Mathematical Modeling for COVID-19 with Focus on Intervention Strategies and Cost-Effectiveness Analysis

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Mathematical modeling for COVID-19 with focus on intervention strategies and cost-effectiveness analysis

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Abstract

The development of appropriate mathematical models and realistic assessments of public health intervention strategies are of great significance to effectively combat the COVID-19 epidemic. In this paper, a novel COVID-19 epidemic model is devised based on the epidemiological states of the individuals and intervention strategies. Some dynamic behaviors of the model, such as forward and backward bifurcation, are analyzed. Specifically, we calibrate the model parameter values using actual COVID-19 data in Brazil by Markov Chain Monte Carlo algorithm such that we can study the effects of interventions on a practical case. Sensitivity analysis shows that non-pharmaceutical interventions are more effective than pharmaceutical interventions in the early stages of the COVID-19 outbreak, and the interventions, namely home isolation, face-mask wearing and media publicity, can effectively reduce the risk of COVID-19 transmission. Based on the new epidemic model, we formulate an optimal control model for studying the control of COVID-19 and then present a cost-effectiveness analysis to unravel the cost and effectiveness of the combination of intervention strategies. The results show that, when taking both the economic cost and the control effectiveness into account, strategy 7 appears to be preferred in inhibiting the COVID-19 outbreak, followed by strategy 5 and strategy 4. By assessing the consequences of these interventions in the real case, we obtain the effective non-pharmaceutical interventions that provide some management implications of controlling COVID-19.

Keywords: COVID-19, Parameter estimation, Bifurcation, Sensitivity analysis, Optimal control, Cost-effectiveness analysis

1 Introduction

The emergence of COVID-19 in 2019 has led to an unprecedented global public health crisis [1]. In the face of this crisis, scientists constantly look for effective intervention strategies for combating the COVID-19 pandemic. Since January 23, 2020, a range of non-pharmaceutical interventions (NPIs) were adopted by the Chinese government, including close contact tracing, quarantine, home isolation, and face-mask wearing. With the implementation of NPIs, there have been few local COVID-19 epidemic outbreaks in the Chinese mainland since March 19th, 2020, which indicates the high effectiveness of these interventions [2]. Similar interventions were implemented by many other countries, but with varying outcomes. Some of these countries failed to prevent the subsequent wave of outbreaks, causing the continuation of the epidemic. According to the WHO [3], as of November 2021, there were reported 249,499,556 cumulative confirmed cases of COVID-19 infection with 5,051,833 deaths worldwide. Therefore, the realistic assessments of proposed public health intervention strategies play a vital role in disease control and the formation of intervention policy.

To explore the COVID-19 pandemic, researchers devised the appropriate mathematical model to assess the course or severity of COVID-19, and focused on characterizing some critical properties of the COVID-19 [4–12]. Due to the adoption of some interventions for inhibiting the COVID-19, the new mathematical models began to consider the impact of interventions to re-estimate the course of COVID-19. Specifically, some models have been devised to explore the practical implications of public health interventions [13–19]. Zhou et al. [20] used a deterministic dynamical model to study the interaction between media publicity and disease progression so as to investigate the effectiveness of media publicity on combating the COVID-19 epidemic. To explore the impact of isolation and contact-tracing strategies on the transmission of COVID-19, Hellewell et al. [21] presented a stochastic model. Eikenberry et al. [22] proposed a model to assess the inhibitory effect of the mask used by the asymptomatic public on COVID-19. Acuña-Zegarra et al. proposed an optimal control problem to explore the optimal vaccination policies [23]. Inspired by the works above, we construct a novel COVID-19 epidemic model, which combines some non-pharmaceutical interventions being implemented in practice (i.e. media publicity, home isolation, vaccination and face-mask wearing). Moreover, our model considers seven-state variables, namely conscious susceptible (S_1), unconscious susceptible (S_2), exposed (E), symptomatic infected (I), asymptomatic infected (A), hospitalized (H) and recovered (R), so as to better describe the realistic transmission dynamics of COVID-19. We explore some basic mathematical properties of this new model in detail. The influential model parameters related to the basic reproduction number are determined by global sensitivity analysis.

Meanwhile, the epidemic optimal control model is employed to suggest the realistic optimal control strategies for combating the COVID-19 epidemic. Asamoah et al. [24] presented a cost-effectiveness analysis based on the work

of Alqarni [25], where they proposed a nonlinear deterministic model to reveal the economic health and cost outcomes associated with COVID-19. Based on our epidemic model, we are motivated to formulate an optimal control model to present a cost-effectiveness analysis of the intervention strategies, where we incorporate the previously determined influential model parameters into the control strategy. We aim to determine the effective non-pharmaceutical interventions to lower the risk of infection by focusing on assessing the consequences of some interventions.

The rest of the paper is organized as follows. The general description and analysis of the proposed model and the existence of backward bifurcation are established in Section 2. Section 3 gives baseline values of model parameters based on the actual infectious data in Brazil. Section 4 decides the influential model parameters which greatly affect the basic reproduction number by global sensitivity analysis. Section 5 presents the formulation and characterization of the optimal control model, and the numerical simulations for seven control strategies. Section 6 estimates the previous control strategies by the cost-effectiveness analysis. Section 7 gives the conclusive remarks.

2 The model formulation

2.1 System description

To explore the dynamic behavior of COVID-19 and identify the key factors that significantly influence the COVID-19 epidemic transmission, a new deterministic model for COVID-19 is formulated. Based on the epidemiological states of the individuals, clinical progression of the disease, and intervention measures, we delineate the realistic transmission dynamics of COVID-19 by extending the classic susceptible–infectious–recovered (SIR) model to the model with seven-state variables, including the conscious susceptible (S_1), the unconscious susceptible (S_2), exposed (E), symptomatic infected (I), asymptomatic infected (A), hospitalized (H) and recovered (R).

We incorporate the main non-pharmaceutical interventions implemented to combat the COVID-19 epidemic into this model, including media publicity, home isolation, vaccination and face-mask wearing. Therefore, we suppose that, p is the transfer rate from S_2 to S_1 reflecting the impact of media publicity, ϵ_1 is the voluntary home isolation rate, ϵ_2 is the face-mask wearing rate, and μ is the vaccination rate. We make the following hypotheses:

(H-1) Only the conscious susceptible individuals choose to be vaccinated, and become vaccinated at μ rate.

(H-2) The recovered individuals return to the conscious susceptible group at ω rate after an immunity period.

(H-3) The unconscious susceptible individuals (S_2) can be transformed into the conscious susceptible group (S_1) at p rate through media publicity.

The COVID-19 transmission dynamics last six months is explored, our model should consider the recruitment and death in the population. The natural mortality rate of the population is represented by d , and all types of people

Fig. 1: Schematic diagram of the proposed model.

have to experience natural death. We hypothesize that the newly recruited individuals enter the susceptible population at rate Λ . The fraction λ of these individuals who are not educated enter S_2 and the remaining $(1 - \lambda)$ individuals will enter S_1 . In conscious susceptible individuals, only the individuals $((1 - \epsilon_1)(1 - \epsilon_2)S_1$, who do not carry out home isolation and do not wear face-mask effectively) will come into contact with infected individuals I and A at the transmission coefficient β_I and β_A , respectively, and get infected. The unconscious susceptible individuals S_2 who do not have self-protection consciousness will unconsciously contact infected individuals I and A with the transmission coefficient β_I and β_A , respectively, and thus get infected. The exposed individuals E will move to I or A after being infected. The symptomatic infected individuals I either recover directly or are sent to the hospital for treatment and then recover, or die at mortality rate d_1 after the treatment fails, whereas the asymptomatic infected individuals A will move to the R group at τ rate after a period of time. Additionally, the recovered individuals R will return to the conscious susceptible group S_1 after an immunity period. The schematic diagram of the model is illustrated in Figure 1, and the descriptions of model parameters are shown in Table 1. The dynamics of these compartments are formulated by model (1):

$$\begin{aligned}
 \frac{dS_1}{dt} &= (1 - \lambda)\Lambda - \frac{(\gamma_I I + \gamma_A A)S_1}{N} - \mu\nu S_1 + pS_2 + \omega R - dS_1, \\
 \frac{dS_2}{dt} &= \lambda\Lambda - pS_2 - \frac{(\beta_A A + \beta_I I)S_2}{N} - dS_2, \\
 \frac{dE}{dt} &= \frac{(\gamma_I I + \gamma_A A)S_1}{N} + \frac{(\beta_A A + \beta_I I)S_2}{N} - (\alpha + d)E, \\
 \frac{dI}{dt} &= \rho\alpha E - (\theta + d)I,
 \end{aligned} \tag{1}$$

$$\begin{aligned}\frac{dA}{dt} &= (1 - \rho)\alpha E - (\tau + d)A, \\ \frac{dH}{dt} &= \kappa\theta I - (\gamma_H + d_1 + d)H, \\ \frac{dR}{dt} &= (1 - \kappa)\theta I + \gamma_H H + \tau A + \mu\nu S_1 - (\omega + d)R,\end{aligned}$$

where, $\gamma_I = \beta_I(1 - \epsilon_1)(1 - \epsilon_2)$, and $\gamma_A = \beta_A(1 - \epsilon_1)(1 - \epsilon_2)$.

Table 1: The descriptions of model parameters

Parameters	Description
Λ	Recruitment rate
λ	Proportion of recruitment with unconscious susceptible individuals S_2
α	Latency rate
d	Natural mortality rate
d_1	Mortality due to illness
τ	Recovery rate of asymptomatic infected individuals
γ_H	Recovery rate of hospitalized individuals
ν	Vaccine efficacy
μ	Vaccination rate
p	The transfer rate from S_2 to S_1 reflecting the impact of media publicity
β_I	Transmission coefficient of the symptomatic infected individuals
β_A	Transmission coefficient of the asymptomatic infected individuals
ϵ_1	The voluntary home isolation rate
ϵ_2	The face-mask wearing rate
ρ	Proportion of symptomatic infected individuals
κ	Proportion of hospitalized individuals
θ	Transition rate from symptomatic infected to recovered or hospitalized
ω	Waning rate of vaccination

2.2 Analysis of the model

Considering that model (1) describes the real-life infectious disease in the population, it is necessary to study on the premise of meeting the ecological significance. Therefore, we need to claim the following results.

2.2.1 Positive invariant region

Theorem 1 *Define the closed set*

$$\mathcal{D} = \{(S_1, S_2, E, I, A, H, R) \in \mathbb{R}_+^7 : S_1, E, I, A, H, R \geq 0, \frac{\Lambda}{d + d_1} \leq N \leq \frac{\Lambda}{d}, 0 \leq S_2 \leq \frac{\lambda\Lambda}{p + d}\}.$$

The solution trajectories of model (1) are bounded, and set $\mathcal{D}$ is positive invariant. Specially, $S_1(t), S_2(t), E(t), I(t), A(t), H(t), R(t)$ are positive for all $t > 0$ if the initial values $S_1(0) > 0, S_2(0) > 0, E(0) > 0, I(0) > 0, A(0) > 0, H(0) > 0$ and $R(0) > 0$.

Proof First, we can get the nonnegativity of the solutions of model (1). Under the initial values $S_1(0) > 0, S_2(0) > 0, E(0) > 0, I(0) > 0, A(0) > 0, H(0) > 0$ and $R(0) > 0$, we define

$$\mathcal{G}(t) = \min\{S_1(t), S_2(t), E(t), I(t), A(t), H(t), R(t)\}, \quad \text{for all } t > 0. \quad (2)$$

It's obviously that $\mathcal{G}(0) > 0$. Suppose there exists a $t_1 > 0$ such that $\mathcal{G}(t_1) = 0$ and $\mathcal{G}(t) > 0$, for all $t \in [0, t_1)$. If $\mathcal{G}(t_1) = S_2(t_1)$, and $S_1(t) \geq 0, E(t) \geq 0, I(t) \geq 0, A(t) \geq 0, H(t) \geq 0$ and $R(t) \geq 0$ for all $t \in [0, t_1]$. Therefore, according to the second equation in model (1), we have

$$\begin{aligned} \frac{dS_2}{dt} &= \lambda\Lambda - pS_2 - \frac{(\beta_A A + \beta_I I)S_2}{N} - dS_2 \\ &\geq -pS_2 - \frac{(\beta_A A + \beta_I I)S_2}{N} - dS_2 \\ &> -pS_2 - \frac{(\beta_A N + \beta_I N)S_2}{N} - dS_2 \\ &> -pS_2 - (\beta_A + \beta_I)S_2 - dS_2, \quad \text{for all } t \in [0, t_1]. \end{aligned} \quad (3)$$

Then, we can obtain

$$S_2(t) > S_2(0)e^{-(p+\beta_A+\beta_I+d)t} > 0, \quad \text{for all } t \in [0, t_1], \quad (4)$$

so, $\mathcal{G}(t_1) = S_2(t_1) > 0$, which contradicts the hypothesis above. Hence, $S_2(t) > 0$ for all $t \geq 0$. Similarly, we have $S_1(t) > 0, E(t) > 0, I(t) > 0, A(t) > 0, H(t) > 0$ and $R(t) > 0$ for all $t \geq 0$.

Second, the uniform and ultimate boundedness of the solution can be proved. From model (1), we have

$$N(t) = S_1(t) + S_2(t) + E(t) + I(t) + A(t) + H(t) + R(t), \quad (5)$$

that is

$$\frac{dN}{dt} = \frac{d(S_1 + S_2 + E + I + A + H + R)}{dt} = \Lambda - dN - d_1H, \quad (6)$$

$$\Lambda - (d + d_1)N \leq \frac{dN}{dt} \leq \Lambda - dN. \quad (7)$$

By a standard comparison theorem, we have

$$N(0)e^{-(d+d_1)t} + \frac{\Lambda}{d+d_1}(1 - e^{-(d+d_1)t}) \leq N(t) \leq N(0)e^{-dt} + \frac{\Lambda}{d}(1 - e^{-dt}), \quad (8)$$

therefore, $N(t)$ is bounded by $\frac{\Lambda}{d+d_1} \leq N(t) \leq \frac{\Lambda}{d}$ as $t \rightarrow \infty$. According to the second equation in model (1), we can obtain

$$\frac{dS_2}{dt} = \lambda\Lambda - pS_2 - \frac{(\beta_A A + \beta_I I)S_2}{N} - dS_2 \leq \lambda\Lambda - (p+d)S_2, \quad (9)$$

that is

$$0 < S_2(t) \leq S_2(0)e^{-(p+d)t} + \frac{\lambda\Lambda}{p+d}(1 - e^{-(p+d)t}), \quad (10)$$

hence, $S_2(t)$ is bounded by $\frac{\lambda\Lambda}{p+d}$ as $t \rightarrow \infty$. The positive invariant set of model (1) can be obtained as

$$\mathcal{D} = \{(S_1, S_2, E, I, A, H, R) \in \mathbb{R}_+^7 : S_1, E, I, A, H, R \geq 0, \frac{\Lambda}{d+d_1} \leq N \leq \frac{\Lambda}{d}, 0 \leq S_2 \leq \frac{\lambda\Lambda}{p+d}\}. \quad (11)$$

□

2.2.2 Disease-free equilibrium (DFE) and the basic reproduction number

The basic reproduction number is an indicator to measure whether an infectious disease is prevalent, to obtain that, it's first necessary to obtain the disease-free equilibrium E_0^* of model (1), so we have

$$\begin{aligned} E_0^* &= (S_1^0, S_2^0, E^0, I^0, A^0, H^0, R^0) \\ &= \left(\frac{\Lambda(\omega + d)(p + d - \lambda d)}{d(p + d)(\mu\nu + \omega + d)}, \frac{\lambda\Lambda}{p + d}, 0, 0, 0, 0, \frac{\mu\nu\Lambda(p + d - \lambda d)}{d(p + d)(\mu\nu + \omega + d)} \right). \end{aligned} \quad (12)$$

Let $X = (E, I, A, H, S_1, S_2, R)^T$. By using the method of next generation matrix proposed in [26], the terms with the new infection $\mathcal{F}$ and the outflow terms $\mathcal{V}$ are defined by

$$\frac{dX}{dt} = \mathcal{F}(X) - \mathcal{V}(X),$$

where

$$\mathcal{F}(X) = \begin{pmatrix} \frac{(\gamma_I I + \gamma_A A)S_1}{N} + \frac{(\beta_A A + \beta_I I)S_2}{N} \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix},$$

$$\mathcal{V}(X) = \begin{pmatrix} (\alpha + d)E \\ -\rho\alpha E + (\theta + d)I \\ -(1 - \rho)\alpha E + (\tau + d)A \\ -\kappa\theta I + (\gamma_H + d_1 + d)H \\ -(1 - \lambda)\Lambda + \frac{(\gamma_I I + \gamma_A A)S_1}{N} + \mu\nu S_1 - pS_2 - \omega R + dS_1 \\ -\lambda\Lambda + pS_2 + \frac{(\beta_A A + \beta_I I)S_2}{N} + dS_2 \\ -(1 - \kappa)\theta I - \gamma_H H - \tau A - \mu\nu S_1 + (\omega + d)R \end{pmatrix}.$$

Hence, the non-negative matrix F of the new infection terms and the non-singular matrix V of the outflow terms are given by

$$F = \begin{pmatrix} 0 & \frac{\gamma_I(\omega + d)(p + d - \lambda d) + \beta_I \lambda d(\mu\nu + \omega + d)}{(p + d)(\mu\nu + \omega + d)} & \frac{\gamma_A(\omega + d)(p + d - \lambda d) + \beta_A \lambda d(\mu\nu + \omega + d)}{(p + d)(\mu\nu + \omega + d)} & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix},$$

$$V = \begin{pmatrix} \alpha + d & 0 & 0 & 0 \\ -\rho\alpha & \theta + d & 0 & 0 \\ -(1 - \rho)\alpha & 0 & \tau + d & 0 \\ 0 & -\kappa\theta & 0 & \gamma_H + d_1 + d \end{pmatrix},$$

where, $\gamma_I = \beta_I(1 - \epsilon_1)(1 - \epsilon_2)$, and $\gamma_A = \beta_A(1 - \epsilon_1)(1 - \epsilon_2)$. Therefore, the basic reproduction number [27] can be obtained as follows

$$\begin{aligned} R_0 &= \rho(FV^{-1}) \\ &= \frac{[(d + \tau)\rho\beta_I + (d + \theta)(1 - \rho)\beta_A] \cdot [\alpha(1 - \epsilon_1)(1 - \epsilon_2)(\omega + d)(p + d - \lambda d) + \alpha\lambda d(\mu\nu + \omega + d)]}{(\alpha + d)(\theta + d)(d + \tau)(p + d)(\mu\nu + \omega + d)} \end{aligned} \quad (13)$$

By using Theorem 2 in [26], the following theorem can be established.

Theorem 2 *The disease-free equilibrium of model (1), given by (12), is locally asymptotically stable whenever $R_0 < 1$, and unstable if $R_0 > 1$.*

2.2.3 The existence of endemic equilibrium

The possible equilibrium solutions of model (1) are defined by

$$\mathbb{E}^* = (S_1^*, S_2^*, E^*, I^*, A^*, H^*, R^*),$$

where $\mathbb{E}^*$ can be considered as any equilibrium of model (1). Furthermore, we let

$$r^* = \frac{\beta_A(1 - \epsilon_1)(1 - \epsilon_2)A^* + \beta_I(1 - \epsilon_1)(1 - \epsilon_2)I^*}{N^*}. \quad (14)$$

Hence, at steady state of model (1), we have

$$\begin{aligned} S_2^* &= \frac{D_5}{r^* + D_4}, \\ S_1^* &= \frac{\delta_1\delta_2D_1[(1 - \lambda)\Lambda r^* + \Lambda D_4 - D_5d] + \lambda\Lambda\omega r^*D_6}{(r^* + D_4)[\delta_1D_1(D_7 + \delta_2r^*) - \omega r^*D_6]}, \\ E^* &= \frac{D_1r^*[\Lambda\delta_2(r^* + D_4) + \lambda\Lambda D_7 - \delta_2D_5d]}{(r^* + D_4)[\delta_1D_1(D_7 + \delta_2r^*) - \omega r^*D_6]}, \\ I^* &= \frac{r^*[\Lambda\delta_2(r^* + D_4) + \lambda\Lambda D_7 - \delta_2D_5d]}{(r^* + D_4)[\delta_1D_1(D_7 + \delta_2r^*) - \omega r^*D_6]}, \\ A^* &= \frac{D_2r^*[\Lambda\delta_2(r^* + D_4) + \lambda\Lambda D_7 - \delta_2D_5d]}{(r^* + D_4)[\delta_1D_1(D_7 + \delta_2r^*) - \omega r^*D_6]}, \\ H^* &= \frac{D_3r^*[\Lambda\delta_2(r^* + D_4) + \lambda\Lambda D_7 - \delta_2D_5d]}{(r^* + D_4)[\delta_1D_1(D_7 + \delta_2r^*) - \omega r^*D_6]}, \\ R^* &= \frac{\mu\nu\delta_1\delta_2D_1[(1 - \lambda)\Lambda r^* + \Lambda D_4 - D_5d] + D_6r^*[\Lambda\delta_2(r^* + D_4) + \lambda\Lambda D_7 - \delta_2D_5d + \lambda\Lambda\mu\nu\omega]}{\delta_2(r^* + D_4)[\delta_1D_1(D_7 + \delta_2r^*) - \omega r^*D_6]}, \end{aligned}$$

where $\delta_1 = \alpha + d$, $\delta_2 = \omega + d$, $\delta_3 = (1 - \epsilon_1)(1 - \epsilon_2)$, $D_1 = \frac{\theta + d}{\rho\alpha}$, $D_2 = \frac{(1 - \rho)(\theta + d)}{\rho(d + \tau)}$, $D_3 = \frac{\kappa\theta}{\gamma_H + d + d_1}$, $D_4 = (p + d)(1 - \epsilon_1)(1 - \epsilon_2)$, $D_5 = \lambda\Lambda(1 - \epsilon_1)(1 - \epsilon_2)$, $D_6 = (1 - \kappa)\theta + \gamma_H D_3 + \tau D_2$, $D_7 = d(\mu\nu + \omega + d)$, and $D_8 = \mu\nu + d$. Substitute

the above expressions of S_1^* , S_2^* , E^* , I^* , A^* , H^* , R^* into equation (14), we can obtain

$$b_0 r^{*2} + b_1 r^* + b_2 = 0, \quad (15)$$

where $b_0 = \zeta_1$, $b_1 = \zeta_2 - \zeta_3$, $b_2 = \zeta_4(1 - R_0)$,

$$\begin{aligned} \zeta_1 &= \Lambda \delta_2 [(1 + D_1 + D_2 + D_3) \delta_2 + D_6] > 0, \\ \zeta_2 &= (\Lambda \delta_2 D_4 + \lambda \Lambda D_7) [(1 + D_1 + D_2 + D_3) \delta_2 + D_6] + (\delta_1 \delta_2 D_1 + \mu \nu \delta_1 D_1) \Lambda \delta_2 \\ &\quad + (\delta_2 (D_5 - \lambda \Lambda) - \lambda \Lambda \mu \nu) (\delta_1 \delta_2 D_1 - \omega D_6), \\ \zeta_3 &= \Lambda \delta_2^2 (\beta_I \delta_3 + \beta_A \delta_3 D_2) + \delta_2 D_5 d [(1 + D_1 + D_2 + D_3) \delta_2 + D_6], \\ \zeta_4 &= \frac{\Lambda}{d} \delta_1 \delta_2 D_1 D_4 D_7 > 0. \end{aligned}$$

The endemic equilibrium exists if the solutions of (15) are positive and real. It's obviously that $b_0 > 0$, since $0 < \rho < 1$, $0 < \kappa < 1$ and all other model parameters are positive. Also, $b_2 < 0$ if and only if $R_0 > 1$ and $b_2 \geq 0$ if and only if $R_0 \leq 1$. Hence, the following theorem can be established as

Theorem 3 *Model (1) has*

- (a) *a unique endemic equilibrium if $b_2 < 0 \Leftrightarrow R_0 > 1$,*
- (b) *a unique endemic equilibrium if $b_1 < 0$, and $b_2 = 0$ or $b_1^2 - 4b_0b_2 = 0$,*
- (c) *two endemic equilibrium if $b_2 > 0$, $b_1 < 0$ and $b_1^2 - 4b_0b_2 > 0$,*
- (d) *no endemic equilibrium otherwise.*

Case (c) of Theorem 3 indicates the existence of backward bifurcation in model (1) provided that $R_0 < 1$. To check that, we set the discriminant $b_1^2 - 4b_0b_2$ to zero, the critical value of R_0 as follows

$$R_0^c = 1 - \frac{b_1^2}{4\zeta_4 b_0}.$$

Based on Theorem 3, we study the occurrence of forward and backward bifurcation with respect to the different parameter β_I . As shown in Figure 2A, the backward bifurcation occurs for the values of R_0 when $0 < R_0^c < R_0 < 1$ with $R_0^c = 0.9775$, at this time, two endemic equilibrium coexist with a locally asymptotically stable disease-free equilibrium. When $R_0 < R_0^c$, there exists a unique locally asymptotically stable disease-free equilibrium, which indicates that there is no outbreak of infectious diseases. The locally asymptotically stable endemic equilibrium coexists with an unstable disease-free equilibrium provided that $R_0 > 1$, which indicates that infectious diseases tend to be stable over time.

As seen in the forward bifurcation diagram of Figure 2B, when $R_0 < 1$, the model has a unique locally stable disease-free equilibrium point; when $R_0 > 1$, there exists a unique locally stable endemic equilibrium point. Hence, we have the following conclusions

Theorem 4 *Model (1) exhibits backward bifurcation when Case (c) of Theorem 3 holds and $R_0^c < R_0 < 1$.*

Fig. 2: Illustration of backward bifurcation and forward bifurcation

The epidemiological significance of the backward bifurcation phenomenon above is that the reproduction threshold (R_0) is less than unity, which is necessary but not sufficient to eliminate the COVID-19 epidemic (since two stable equilibrium points coexist when $R_0^c < R_0 < 1$). In this case, effective disease control or elimination depends on the initial values of the model [28].

3 Baseline values of model parameters

To assign the model parameters with practical meaning and address the proposed model in a real case to verify the rationality of our model, we estimate a group of baseline parameter values by adopting the newly infected data in Brazil from March 18, 2020 to September 18, 2020. The information on cases of COVID-19 is extracted from World Health Organization (WHO) [3]. Note that the data are publicly available.

We mainly concentrate on the newly infected cases and the cumulative infected cases per day in Brazil. The cumulative infected cases can be expressed by

$$\frac{dIC(t)}{dt} = \rho \alpha E(t), \quad (16)$$

where $IC(t)$ indicates the cumulative infected individuals per day. The newly infected cases can be defined as follows

$$I(t) = IC(t) - IC(t-1), \quad (17)$$

where $I(t)$ represents the newly infected individuals.

According to existing data and literature, the fixed initial values and parameters of model (1) can be obtained (see Table 2 for details). Further, we use the MCMC algorithm for 20000 iterations with a burn-in of 5000 times [29–31] to estimate the other unknown parameters and initial conditions. The fitting results of the newly infected cases are shown in Figure 3(a), and the fitting results of the cumulative infected cases are shown in Figure 3(b). Pearson's correlation coefficient between the number of newly infected cases and the number of estimated cases is given in Figure 3(c). The Pearson coefficient is used to measure the correlation between two variables, which is defined as the quotient of the covariance and standard deviation between two variables. The fitting results confirm a good fitting between the actual data and model prediction.

According to the estimated mean values in Table 2, the voluntary home isolation rate, the face-mask wearing rate and the transfer rate through media publicity in Brazil are $\epsilon_1 = 0.01075$, $\epsilon_2 = 0.01181$ and $p = 0.10844$, respectively. These values suggest that, after the COVID-19 epidemic became a pandemic in March 2020, the measures of face-mask wearing and home isolation seem to be ignored by the public in Brazil. In addition, the media's role in publicity and education for COVID-19 is also not obviously adequate. The digital era has facilitated access to information but also magnified the scale of fake news and distorted facts [32]. There is a skepticism emerging in Brazil about the disease as well as the non-pharmaceutical interventions to prevent this pandemic crisis, which leads to the spread of misinformation. Consequently, safe and effective protective measures such as face-mask wearing and home isolation are often ignored by the public.

In order to improve the implementation of the intervention strategies in the public, the key is to eliminate this new skepticism. Therefore, it is more convincing to assess the effectiveness of implementation measures from the perspective of actual infection data, which will be discussed next.

Fig. 3: Curve fitting of the infected cases in Brazil's COVID-19 outbreak. Panel (a) shows the number of newly symptomatic infections per day; Panel (b) represents the cumulative number of symptomatic infections per day. The blue bars represent the number of the symptomatic infected individuals from March 18, 2020 to September 18, 2020, and the pink regions indicate 95% confidence interval (CI). Panel (c) shows the Pearson coefficient of fitting results.

4 Sensitivity analysis and efficacy of interventions

The aim of the global sensitivity analysis is to determine certain significant parameters that have a large impact on R_0 , and some interventions related to these parameters may greatly affect the dynamics of COVID-19. We perform a sensitivity analysis to determine the influence of related parameters on the basic reproduction number by a combination of Partial Rank Correlation Coefficient (PRCC) and Latin Hypercube Sampling (LHS) methods. PRCC is a common method used to measure the nonlinear monotonic relationship between two variables. The analysis shows the PRCC values and the

Table 2: The parameters and initial values of model (1).

Parameters	Mean	STD	95%CI	Source
Λ	7479			Estimated
α	$\frac{1}{5.2}$			[33]
d	0.00629			Estimated
τ	0.14			[34]
γ_H	0.14			[34]
ν	0.83			Estimated
μ	0.08134	0.01030	[0.06115,0.10153]	Fitted
p	0.10844	0.01131	[0.08628,0.13060]	Fitted
β_I	0.13172	0.02235	[0.08792,0.17552]	Fitted
β_A	0.90104	0.04830	[0.80637,0.99571]	Fitted
ϵ_1	0.01075	0.00502	[9.1221e-04,0.02058]	Fitted
ϵ_2	0.01181	0.00267	[0.00657,0.01705]	Fitted
ρ	0.17167	0.02792	[0.11694,0.22640]	Fitted
κ	0.44713	0.14778	[0.15748,0.73678]	Fitted
θ	0.00544	0.00165	[0.00221,0.00867]	Fitted
ω	0.02851	0.00382	[0.02101,0.03601]	Fitted
d_1	0.05802	0.00293	[0.05228,0.06376]	Fitted
λ	0.40474	0.05387	[0.29915,0.51033]	Fitted
$S_1(0)$	6.1339e+06	1.3189e+06	[3.5489e+06,8.7189e+06]	Fitted
$S_2(0)$	6.8427e+07	1.9599e+07	[3.0011e+07,1.0684e+08]	Fitted
$E(0)$	1391	261	[879,1903]	Fitted
$I(0)$	51			From data
$A(0)$	1107	222	[673,1542]	Fitted
$H(0)$	367			[34]
$R(0)$	2			[34]

corresponding p -values, which are used to evaluate the uncertainty level of the certain model parameters. The sign of the PRCC value represents the qualitative relationship between the input and output variables. Generally, the parameters with the highest PRCC value and a corresponding lowest p -value ($p < 0.01$) are considered to take the most influence on the output variable.

The asterisk ($\star$) in Figure 4 highlights the most three influential parameters (i.e the three highest PRCC values) related to R_0 . We summarize the PRCC values of all 14 parameters related to the basic reproduction number and their p -values in Table 3. The voluntary home isolation rate ϵ_1 is the most influential parameter with the leading PRCC value followed by ϵ_2 and p . It implies that improving the implementation of home isolation (i.e. increasing the voluntary home isolation rate ϵ_1) is the most effective in lowering the risk

of COVID-19 transmission. In addition, the face-mask wearing rate ϵ_2 and the transfer rate p are another two sensitive parameters, which indicates that the implementation of the face-mask wearing and the promotion of media publicity are also effective ways to reduce the basic reproduction number and lower the risk of COVID-19 transmission. Therefore, according to the sensitivity analysis, the voluntary home isolation rate (ϵ_1), the face-mask wearing rate (ϵ_2) and the transfer rate (p) are identified as the critical parameters, and the interventions related to these parameters can greatly affect the COVID-19 pandemic. Moreover, these non-pharmaceutical interventions are more effective than pharmaceutical interventions (i.e. related to μ) in the early stages of the COVID-19 outbreak.

Fig. 4: Significance test and PRCCs of model parameters related to R_0 .

Next, we use the baseline parameter values given by fitting the actual data to perform numerical simulations, where we mainly alter the key parameters (i.e. the voluntary home isolation rate (ϵ_1), the face-mask wearing rate (ϵ_2), and the transfer rate (p)), to observe the corresponding effects on the spread of COVID-19.

We examine the variation of COVID-19 progression with the voluntary home isolation rate ϵ_1 and the face-mask wearing rate ϵ_2 , as presented in Figures 5. In panel (a), the other parameters remain the same as the baseline value in Table 2, and ϵ_1 varies ($p = 0.10844$, $\epsilon_2 = 0.01181$). In panel (b), the other parameters remain the same as the baseline value and ϵ_2 varies ($p = 0.10844$, $\epsilon_1 = 0.01075$). The green circular curve is obtained by the baseline values, representing the actual newly infected cases in Brazil. It is found that increasing the parameters ϵ_1 or ϵ_2 (i.e. enhance the implementation of these two non-pharmaceutical interventions), decreases the infected number,

thereby inhibiting the outbreak and the endemic level of COVID-19. Moreover, when the parameter ϵ_1 or ϵ_2 values keep increasing, the number of the infected cases can basically approach to zero.

To explore the impact of media publicity on COVID-19 infections, we examine the effect of the parameter value p on the newly infected cases per day, as shown in Figure 5(c). The other parameters remain the same as the baseline value in Table 2, and p varies ($\epsilon_1 = 0.01075$, $\epsilon_2 = 0.01181$). The red circular curve originates from the baseline values. It demonstrates that as the transfer rate p increases, the number of infected individuals decreases, and the size of the outbreak decreases. It is worthwhile to note that the increase of the parameter value p results in a significant decrease in the number of infected, but with the continuous increase of this value, the number of COVID-19 infections cannot be completely eliminated, which is consistent with the actual situation as the home isolation rate and face-mask wearing rate still keep low levels in this case. Generally speaking, the home isolation rate, the face-mask wearing rate and the transfer rate through media publicity are the dominant factors that affect the dynamics of COVID-19 greatly, which can control the outbreak and the endemic levels of COVID-19.

Table 3: PRCC values of 14 model parameters with corresponding p -values (significant for $p \leq 0.01$)

Parameters	PRCC values	p -values
p	-0.2649	1.7801e-33
β_I	0.1565	1.9452e-12
β_A	0.2167	1.0993e-22
ϵ_1	-0.5511	2.6813e-159
ϵ_2	-0.5113	1.1476e-133
α	0.1976	4.6369e-19
ρ	0.0117	0.5997
v	-0.0468	0.0364
μ	-0.0676	0.0025
ω	0.0342	0.1260
θ	-0.1149	2.5271e-07
τ	-0.2343	2.3906e-26
λ	0.1681	3.8829e-14
d	-0.1224	3.9522e-08

Fig. 5: (a) variation in the newly infected cases per day with different parameters ϵ_1 ; (b) variation in the newly infected cases per day with different parameters ϵ_2 ; (c) variation in the newly infected cases per day with different parameters p .

5 Optimal control analysis

In the previous section, the critical model parameters that affect the dynamics of COVID-19 greatly are given, including the voluntary home isolation rate, ϵ_1 , the face-mask wearing rate, ϵ_2 , and the transfer rate through media publicity, p . Here, we incorporate the following control measures in terms of these three factors into model (1) to study the effective prevention strategy in combating COVID-19:

- u_1 : practising media publicity, and educating unconscious susceptible individuals by media,

- u_2 : practising the voluntary home isolation,
- u_3 : practising the face-mask wearing.

Hence, based on model (1), the optimal control model is given as

$$\begin{aligned}
 \dot{S}_1 &= (1 - \lambda)\Lambda - \frac{(\beta_I I + \beta_A A)(1 - u_2)(1 - u_3)S_1}{N} - \mu\nu S_1 + u_1 S_2 + \omega R - dS_1, \\
 \dot{S}_2 &= \lambda\Lambda - u_1 S_2 - \frac{(\beta_A A + \beta_I I)S_2}{N} - dS_2, \\
 \dot{E} &= \frac{(\beta_I I + \beta_A A)(1 - u_2)(1 - u_3)S_1}{N} + \frac{(\beta_A A + \beta_I I)S_2}{N} - (\alpha + d)E, \\
 \dot{I} &= \rho\alpha E - (\theta + d)I, \\
 \dot{A} &= (1 - \rho)\alpha E - (\tau + d)A, \\
 \dot{H} &= \kappa\theta I - (\gamma_H + d_1 + d)H, \\
 \dot{R} &= (1 - \kappa)\theta I + \gamma_H H + \tau A + \mu\nu S_1 - (\omega + d)R.
 \end{aligned} \tag{18}$$

We need to consider controlling the spread of the epidemic to the greatest extent, and at the same time, we should implement the prevention strategies within a cost-constrained framework, so that the number of infections in the COVID-19 epidemic is the lowest under the cost-constrained conditions. To determine the best strategy based on the possible combination of control measures, we need to minimize the objective function $\mathcal{J}$

$$\mathcal{J}(u_1, u_2, u_3) = \min \int_0^T \left(B_1 E + B_2 I + B_3 A + B_4 H + \frac{1}{2} \sum_{i=1}^3 W_i u_i^2 \right) dt, \tag{19}$$

where T is the terminal time; $B_1, B_2, B_3, B_4 \in \mathcal{R}^+$ are the weight coefficients on the infectious population, and the values of B_1, B_2, B_3, B_4 represent the attention paid to the exposed, symptomatic and asymptomatic infected and hospitalized individuals, respectively. The value of W_i (for $i = 1, 2, 3$) represents the importance of each optimization strategy. We set $B_1 = 0.12, B_2 = 0.28, B_3 = 0.11, B_4 = 3, W_1 = 45000, W_2 = 6000, W_3 = 5000$. The non-empty control set $\mathcal{U}$ can be defined by

$$\mathcal{U} = \{(u_1, u_2, u_3) : u_i \text{ Lebesgue measurable}, 0 \leq u_i \leq u_{imax}, \text{ for } i = 1, 2, 3, t \in [0, T]\}, \tag{20}$$

where $u_{imax}(i = 1, 2, 3)$ are fixed positive constants. Hence, it's important to seek an optimal control $u^* = (u_1^*, u_2^*, u_3^*)$ to make

$$\mathcal{J}(u^*) = \min\{\mathcal{J}(u_1, u_2, u_3) : u_1, u_2, u_3 \in \mathcal{U}\}. \tag{21}$$

5.1 Characterization of the optimal control

The necessary conditions for optimal control are provided by Pontryagin's maximum principle (PMP). According to the PMP, the optimal control problem consisting of the objective function $\mathcal{J}$ (19) and the optimal system (18) is converted into the problem of minimizing a Hamiltonian, defined as $\mathcal{H}$. Hence, the Hamiltonian $\mathcal{H}$ related to the optimal control problem is defined by

$$\begin{aligned} \mathcal{H} = & B_1 E + B_2 I + B_3 A + B_4 H + \frac{1}{2} \sum_{i=1}^3 W_i u_i^2 \\ & + \lambda_{S_1} [(1-\lambda)\Lambda - \frac{(\beta_I I + \beta_A A)(1-u_2)(1-u_3)S_1}{N} - \mu\nu S_1 + u_1 S_2 + \omega R - dS_1] \\ & + \lambda_{S_2} [\lambda\Lambda - u_1 S_2 - \frac{(\beta_A A + \beta_I I)S_2}{N} - dS_2] \\ & + \lambda_E [\frac{(\beta_I I + \beta_A A)(1-u_2)(1-u_3)S_1}{N} + \frac{(\beta_A A + \beta_I I)S_2}{N} - (\alpha + d)E] \\ & + \lambda_I [\rho\alpha E - (\theta + d)I] \\ & + \lambda_A [(1-\rho)\alpha E - (\tau + d)A] \\ & + \lambda_H [\kappa\theta I - (\gamma_H + d_1 + d)H] \\ & + \lambda_R [(1-\kappa)\theta I + \gamma_H H + \tau A + \mu\nu S_1 - (\omega + d)R], \end{aligned} \quad (22)$$

where $\bar{\lambda} = [\lambda_{S_1}, \lambda_{S_2}, \lambda_E, \lambda_I, \lambda_A, \lambda_H, \lambda_R]^T$ are costate variables, and $N = S_1 + S_2 + E + I + A + H + R$.

Theorem 5 *There exists an optimal control $(u_1^*(t), u_2^*(t), u_3^*(t))$, and corresponding solution $x^* = [S_1^*, S_2^*, E^*, I^*, A^*, H^*, R^*]^T$ that minimizes $\mathcal{J}(u_1(t), u_2(t), u_3(t))$ over $\mathcal{U}$. Further, there also exist the adjoint functions, $\lambda_{S_1}, \lambda_{S_2}, \lambda_E, \lambda_I, \lambda_A, \lambda_H$ and λ_R [24], such that*

$$\begin{aligned} \dot{\lambda}_{S_1} = & -\mu\nu\lambda_R + \lambda_{S_1} [\frac{(\beta_I I^* + \beta_A A^*)(1-u_2)(1-u_3)(N^* - S_1^*)}{N^{*2}} + \mu\nu + d] \\ & - \lambda_{S_2} \frac{(\beta_I I^* + \beta_A A^*)S_2^*}{N^{*2}} - \lambda_E [\frac{(\beta_I I^* + \beta_A A^*)(1-u_2)(1-u_3)(N^* - S_1^*)}{N^{*2}} \\ & - \frac{(\beta_I I^* + \beta_A A^*)S_2^*}{N^{*2}}], \\ \dot{\lambda}_{S_2} = & -\lambda_{S_1} [\frac{(\beta_I I^* + \beta_A A^*)(1-u_2)(1-u_3)S_1^*}{N^{*2}} + u_1] \\ & + \lambda_{S_2} [u_1 + d + \frac{(\beta_I I^* + \beta_A A^*)(N^* - S_2^*)}{N^{*2}}] \\ & - \lambda_E [\frac{(\beta_I I^* + \beta_A A^*)(N^* - S_2^*)}{N^{*2}} - \frac{(\beta_I I^* + \beta_A A^*)(1-u_2)(1-u_3)S_1^*}{N^{*2}}], \\ \dot{\lambda}_E = & -B_1 - \lambda_{S_1} \frac{(\beta_I I^* + \beta_A A^*)(1-u_2)(1-u_3)S_1^*}{N^{*2}} - \lambda_{S_2} \frac{(\beta_I I^* + \beta_A A^*)S_2^*}{N^{*2}} - \lambda_A (1-\rho)\alpha \\ & - \lambda_I \rho\alpha + \lambda_E [\alpha + d + \frac{(\beta_I I^* + \beta_A A^*)(1-u_2)(1-u_3)S_1^*}{N^{*2}} + \frac{(\beta_I I^* + \beta_A A^*)S_2^*}{N^{*2}}], \end{aligned}$$

$$\begin{aligned}
\dot{\lambda}_I = & -B_2 - \lambda_{S_1} \left[\frac{(\beta_I I^* + \beta_A A^*)(1-u_2)(1-u_3)S_1^*}{N^{*2}} - \frac{\beta_I(1-u_2)(1-u_3)S_1^*}{N^*} \right] + \lambda_I(\theta + d) \\
& - \lambda_{S_2} \left[\frac{(\beta_I I^* + \beta_A A^*)S_2^*}{N^{*2}} - \frac{\beta_I S_2^*}{N^*} \right] - \lambda_H \kappa \theta - \lambda_R(1-\kappa)\theta \\
& + \lambda_E \left[\frac{(\beta_I I^* + \beta_A A^*)(1-u_2)(1-u_3)S_1^* + (\beta_I I^* + \beta_A A^*)S_2^*}{N^{*2}} \right. \\
& \quad \left. - \frac{\beta_I(1-u_2)(1-u_3)S_1^* + \beta_I S_2^*}{N^*} \right], \\
\dot{\lambda}_A = & -B_3 - \lambda_{S_1} \left[\frac{(\beta_I I^* + \beta_A A^*)(1-u_2)(1-u_3)S_1^*}{N^{*2}} - \frac{\beta_A(1-u_2)(1-u_3)S_1^*}{N^*} \right] \\
& + \lambda_E \left[\frac{(\beta_I I^* + \beta_A A^*)(1-u_2)(1-u_3)S_1^* + (\beta_I I^* + \beta_A A^*)S_2^*}{N^{*2}} \right. \\
& \quad \left. - \frac{\beta_A(1-u_2)(1-u_3)S_1^* + \beta_A S_2^*}{N^*} \right] \\
& - \lambda_{S_2} \left[\frac{(\beta_I I^* + \beta_A A^*)S_2^*}{N^{*2}} - \frac{\beta_A S_2^*}{N^*} \right] - \lambda_R \tau + \lambda_A(\tau + d), \\
\dot{\lambda}_H = & -B_4 - \lambda_{S_1} \frac{(\beta_I I^* + \beta_A A^*)(1-u_2)(1-u_3)S_1^*}{N^{*2}} - \lambda_{S_2} \frac{(\beta_I I^* + \beta_A A^*)S_2^*}{N^{*2}} \\
& + \lambda_E \left[\frac{(\beta_I I^* + \beta_A A^*)(1-u_2)(1-u_3)S_1^*}{N^{*2}} + \frac{(\beta_I I^* + \beta_A A^*)S_2^*}{N^{*2}} \right] \\
& + \lambda_H(\gamma_H + d + d_1) - \lambda_R \gamma_H, \\
\dot{\lambda}_R = & -\lambda_{S_1} \left[\frac{(\beta_I I^* + \beta_A A^*)(1-u_2)(1-u_3)S_1^*}{N^{*2}} + \omega \right] - \lambda_{S_2} \frac{(\beta_I I^* + \beta_A A^*)S_2^*}{N^{*2}} + \lambda_R(\omega + d) \\
& + \lambda_E \left[\frac{(\beta_I I^* + \beta_A A^*)(1-u_2)(1-u_3)S_1^*}{N^{*2}} + \frac{(\beta_I I^* + \beta_A A^*)S_2^*}{N^{*2}} \right].
\end{aligned} \tag{23}$$

With the transversality conditions

$$\lambda_{S_1}(T) = \lambda_{S_2}(T) = \lambda_E(T) = \lambda_I(T) = \lambda_A(T) = \lambda_H(T) = \lambda_R(T) = 0, \tag{24}$$

the following characterization holds

$$u_1^* = \max \left\{ 0, \min \left\{ \frac{\lambda_{S_2} S_2^* - \lambda_{S_1} S_2^*}{W_1}, u_{1 \max} \right\} \right\}, \tag{25}$$

$$u_2^* = \max \left\{ 0, \min \left\{ \frac{(\beta_A A^* + \beta_I I^*)(1-u_3)(\lambda_E S_1^* - \lambda_{S_1} S_1^*)}{W_2 N^*}, u_{2 \max} \right\} \right\}, \tag{26}$$

$$u_3^* = \max \left\{ 0, \min \left\{ \frac{(\beta_A A^* + \beta_I I^*)(1-u_2)(\lambda_E S_1^* - \lambda_{S_1} S_1^*)}{W_3 N^*}, u_{3 \max} \right\} \right\}. \tag{27}$$

Proof According to Pontryagins Maximum Principle, we can give the proof above. By differentiating the Hamiltonian function (22) partially with respect to the state variables S_1 , S_2 , E , I , A , H , R , we can obtain the adjoint state equations (23) as

follows

$$\left\{ \begin{array}{l} \frac{d\lambda_{S_1}}{dt} = -\frac{\partial \mathcal{H}}{\partial S_1}, \quad \lambda_{S_1}(T) = 0, \\ \frac{d\lambda_{S_2}}{dt} = -\frac{\partial \mathcal{H}}{\partial S_2}, \quad \lambda_{S_2}(T) = 0, \\ \frac{d\lambda_E}{dt} = -\frac{\partial \mathcal{H}}{\partial E}, \quad \lambda_E(T) = 0, \\ \frac{d\lambda_I}{dt} = -\frac{\partial \mathcal{H}}{\partial I}, \quad \lambda_I(T) = 0, \\ \frac{d\lambda_A}{dt} = -\frac{\partial \mathcal{H}}{\partial A}, \quad \lambda_A(T) = 0, \\ \frac{d\lambda_H}{dt} = -\frac{\partial \mathcal{H}}{\partial H}, \quad \lambda_H(T) = 0, \\ \frac{d\lambda_R}{dt} = -\frac{\partial \mathcal{H}}{\partial R}, \quad \lambda_R(T) = 0, \end{array} \right. \quad (28)$$

and the optimality condition of control variable is

$$\frac{\partial \mathcal{H}}{\partial u_1} = 0, \quad \frac{\partial \mathcal{H}}{\partial u_2} = 0, \quad \frac{\partial \mathcal{H}}{\partial u_3} = 0, \quad (29)$$

where u_1 needs to satisfy $0 < u_1 < u_{1\max}$. By solving (29), the optimal control u_1^* can be obtained as follows

$$u_1^* = \begin{cases} 0 & \phi_1^* \leq 0 \\ \phi_1^* & 0 \leq \phi_1^* \leq u_{1\max}, \\ u_{1\max} & \phi_1^* \geq u_{1\max} \end{cases} \quad (30)$$

where

$$\phi_1^* = \frac{\lambda_{S_2} S_2 - \lambda_{S_1} S_2}{W_1}, \quad (31)$$

that is

$$u_1^* = \max \left\{ 0, \min \left\{ \frac{\lambda_{S_2} S_2^* - \lambda_{S_1} S_2^*}{W_1}, u_{1\max} \right\} \right\}. \quad (32)$$

By similar arguments, the optimal control u_2^* and u_3^* are characterized as

$$u_2^* = \max \left\{ 0, \min \left\{ \frac{(\beta_A A^* + \beta_I I^*) (1 - u_3) (\lambda_E S_1^* - \lambda_{S_1} S_1^*)}{W_2 N^*}, u_{2\max} \right\} \right\}, \quad (33)$$

$$u_3^* = \max \left\{ 0, \min \left\{ \frac{(\beta_A A^* + \beta_I I^*) (1 - u_2) (\lambda_E S_1^* - \lambda_{S_1} S_1^*)}{W_2 N^*}, u_{3\max} \right\} \right\}. \quad (34)$$

□

5.2 Numerical simulation

Based on the theoretical results in the previous section, in this section, we simulate seven possible combinations of the three intervention strategies (u_1 , u_2 , u_3) through optimization experiments to explore the more effective intervention strategies. our numerical simulations are implemented by system (18) forward in time and an adjoint system (23) backward in time until convergence reaches, which is known as the fourth-order Runge-Kutta forward-backward sweep simulations [24]. We divide the seven possible combinations of strategies into three cases, namely, Case 1 involving the single control, Case 2 involving the dual controls, and Case 3 involving the triple controls.

(1) Case 1 involving the single control measure

- Strategy 1: educating unconscious susceptible individuals by media publicity only ($u_1 \neq 0, u_2 = u_3 = 0$),

- Strategy 2: practising the voluntary home isolation only ($u_2 \neq 0, u_1 = u_3 = 0$),
- Strategy 3: practising the face-mask wearing only ($u_3 \neq 0, u_1 = u_2 = 0$).

(2) Case 2 involving the dual control measures

- Strategy 4: educating unconscious susceptible individuals by media publicity and practising the voluntary home isolation ($u_1 \neq 0, u_2 \neq 0, u_3 = 0$),
- Strategy 5: educating unconscious susceptible individuals by media publicity and practising the face-mask wearing ($u_1 \neq 0, u_2 = 0, u_3 \neq 0$),
- Strategy 6: practising the voluntary home isolation and practising the face-mask wearing ($u_1 = 0, u_2 \neq 0, u_3 \neq 0$).

(3) Case 3 involving the triple control measures

- Strategy 7: educating unconscious susceptible individuals by media publicity, practising the voluntary home isolation, and practising the face-mask wearing ($u_1 \neq 0, u_2 \neq 0, u_3 \neq 0$).

5.2.1 Case 1: implementation of single control measure

Considering the implementation cost of each strategy, and in order to make the implementation rate of each strategy acceptable to the public, we set the maximum implementation rate of each strategy to 0.3. Strategy 1 is the optimal control which considers media publicity only, strategy 2 considers home isolation only, and strategy 3 considers the face-mask wearing only. Figure 6 presents the numerical simulations with the implementation of single control measure. Figure 6A suggests the optimal strategy for strategy 1 over time, Figures 6B and 6C suggest that the optimal strategies for strategy 2 and strategy 3. Figure 6D presents the infections averted per day by three control strategies, where strategy 1 is the most effective during the early stage, followed by constant control, strategy 2, and strategy 3. With the unswerving implementation of strategy 3 and strategy 2, the optimal control effects of strategies 2 and 3 are more effective than strategy 1 during the late stage. In other words, when strategies involving single control are implemented, strategy 1 averts more infections at the beginning, while the long-term benefit of implementing strategies 2 and 3 is observed over time. It can be seen from Figures 6E-F that, whether in terms of the control effect of the cumulative infections averted per day or the objective function, strategy 1 is the most effective. In general, in the implementation of the single control, strategy 1 (i.e. practising media publicity only) is the most realistic and has a significant control effect.

Fig. 6: Simulation results of single control measures. A: Optimal solution of strategy 1; B: Optimal solution of strategy 2; C: Optimal solution of strategy 3; D: Newly infected individuals per day; E: Cumulative infected individuals per day; F: The value of objective function $\mathcal{J}$. No control denoted by the solid blue line means that there is no control measure, and baseline constant control denoted by the solid green line, represents the actual situation of prevention control in Brazil.

5.2.2 Case 2: the implementation of dual control measures

Figure 7 presents the numerical simulations with the implementation of dual control measures. Strategy 4 is the optimal control which considers the combination of media publicity and home isolation at the same time, strategy 5 considers the combination of media publicity and the face-mask wearing,

and strategy 6 considers the combination of home isolation and the face-mask wearing. Figure 7A-C give the suggested optimal controls for strategies 4, 5, 6,

Fig. 7: Simulation results of dual control measures. A: Optimal solution of strategy 4; B: Optimal solution of strategy 5; C: Optimal solution of strategy 6; D: Newly infected individuals per day; E: Cumulative infected individuals per day; F: The value of objective function $\mathcal{J}$. The denotation of No control and baseline constant control is the same as that of Fig. 6.

respectively. The suggested optimal control for strategy 5 is the same as strategy 4. Figure 7D presents the infections averted per day of the various control strategies, where strategy 4 and strategy 5 are the most effective. The constant control is stronger than strategy 6 in the early stage, while with the

unswerving implementation of strategy 6, the optimal control effect of strategy 6 is stronger than constant control (i.e. the actual situation of prevention control in Brazil). Strategy 6 which involves home isolation and face-mask wearing has proved to be significant in a long run, while strategy 4 containing media publicity and home isolation or strategy 5 containing media publicity and face-mask wearing has instant benefit. In Figures 7E-F, we notice that, strategy 4 and strategy 5 also have the highest number of averted cumulative infected individuals and minimum objective function, followed by constant control and strategy 6.

5.2.3 Case 3: the implementation of triple control measures

Fig. 8: Simulation results of triple control measures. A: Optimal solution of strategy 7; B: Newly infected individuals per day; C: Cumulative infected individuals per day; D: The value of objective function $\mathcal{J}$. The denotation of No control and baseline constant control is the same as that of Fig. 6.

Here, we carry out numerical simulations with the implementation of triple control measures simultaneously. Figure 8A presents the suggested optimal strategy for strategy 7, including the control of media publicity, home isolation and face-mask wearing. We notice that, strategy 7 has the best epidemic

prevention and control effect and avoids the largest number of infections in comparison with constant control and the previous strategies. Specifically, with the implementation of strategy 7, the number of infected cases basically approaches to zero.

In order to intuitively evaluate the effectiveness of the seven optimal strategies in restraining the COVID-19 epidemic, we propose a cost-effectiveness analysis based on our control strategy, which is discussed in the next section.

6 Cost-effectiveness analysis

To assess the cost associated with intervention strategies, we propose the Cost-effectiveness analysis. Here, we adopt two indexes, i.e. infection averted ratio (IAR) [35] and average cost-effectiveness ratio (ACER) [24]. Infection averted ratio can be defined by

$$IAR = \frac{\text{Number of infections averted}}{\text{Number of recovered}},$$

where the difference between the total number of disease infections under no control strategy and the total number of infections with the implementation of the control strategy, which is calculated as the number of infections averted. The number of recovered is equal to the total number of individuals who have recovered from disease infection with the implementation of the control strategy. The most cost-effective control strategy usually has the highest ACER value.

Average cost-effectiveness ratio is usually expressed by

$$ACER = \frac{\text{Total cost incurred on the implementation of a particular intervention strategy}}{\text{Total number of infections averted by the intervention strategy}},$$

the most cost-effective control strategy usually has the lowest ACER value, and the total cost of implementing a specific control strategy is estimated as

$$C(u) = \frac{1}{2} \int_0^T \sum_{i=1}^3 W_i u_i^2 dt.$$

6.1 Cost-effectiveness analysis in Case 1

Using the optimal control results as presented in Figure 6, the IAR and ACER among three single control strategies in Case 1 can be calculated. According to the results of IAR in Table 4, strategy 1 (practising educating unconscious susceptible individuals by media publicity only) has the most cost-effectiveness, followed by strategy 2 and strategy 3, both of which are equally cost-effective.

The results of the ACER cost-effectiveness analysis in Table 5 demonstrate

that the single application of control u_1 costs slightly more but is more effective in infections averted than control u_2 and u_3 . Hence, according to the ACER cost-effectiveness analysis, strategy 1 is also considered as the most cost-effective in Case 1, followed by strategy 3 and strategy 2.

Table 4: IAR for Case 1

Strategy	Total infection averted	Total recovered	IAR
Strategy 1 : $u_1(t)$	6.7876e+07	1.9187e+08	0.3538
Strategy 2 : $u_2(t)$	1.0307e+07	1.1821e+08	0.0872
Strategy 3 : $u_3(t)$	1.0307e+07	1.1821e+08	0.0872

Table 5: ACER for Case 1

Strategy	Total infection averted	Cost	ACER
Strategy 1 : $u_1(t)$	6.7876e+07	2.3737e+05	0.0035
Strategy 2 : $u_2(t)$	1.0307e+07	4.9950e+04	0.0048
Strategy 3 : $u_3(t)$	1.0307e+07	4.1625e+04	0.0040

6.2 Cost-effectiveness analysis in Case 2

According to the results obtained from the numerical simulation as presented in Figure 7, we can obtain the IAR and ACER among three dual control strategies in Case 2.

A review of Table 6 indicates that strategies 4 and 5 have the highest IAR. Hence, strategy 4 (which combines educating unconscious susceptible individuals by media publicity and practising the voluntary home isolation) and strategy 5 (which combines educating unconscious susceptible individuals by media publicity and practising the face-mask wearing) are considered as the most cost-effective in Case 2. According to the ACER in Table 7, strategy 5 with the lowest ACER value can be treated as the most cost-effective in Case 2, followed by strategy 4 and strategy 6.

6.3 Cost-effectiveness analysis in Case 3

Using the simulated results of strategy 7 in Case 3 as presented in Figure 8, the cost-effectiveness analysis of this strategy in terms of IAR, ACER is given in Table 8 and Table 9. Besides, we present the sorting IAR and ACER of all the seven strategies in Table 10, Table 11, respectively.

Table 6: IAR for Case 2

Strategy	Total infection averted	Total recovered	IAR
Strategy 4 : $u_1(t) + u_2(t)$	8.8915e+07	1.9497e+08	0.4560
Strategy 5 : $u_1(t) + u_3(t)$	8.8915e+07	1.9497e+08	0.4560
Strategy 6 : $u_2(t) + u_3(t)$	1.9621e+07	1.1938e+08	0.1644

Table 7: ACER for Case 2

Strategy	Total infection averted	Cost	ACER
Strategy 4 : $u_1(t) + u_2(t)$	8.8915e+07	2.0661e+05	0.0023
Strategy 5 : $u_1(t) + u_3(t)$	8.8915e+07	1.9834e+05	0.0022
Strategy 6 : $u_2(t) + u_3(t)$	1.9621e+07	9.1575e+04	0.0047

Table 8: IAR for Case 3

Strategy	Total infection averted	Total recovered	IAR
Strategy 7 : $u_1(t) + u_2(t) + u_3(t)$	9.0035e+07	1.9499e+08	0.4618

From Table 10, we can obtain that strategy 7 is the most effective in inhibiting COVID-19, followed by strategy 5 and strategy 4, so the multi-pronged optimization strategy has a considerable positive impact on epidemic control. From Table 11, strategy 7 also shows the competitive cost advantage as compared to strategies 5, 4, 1. From the perspective of the cost of execution, the cost of strategy 7 is lower than those of strategies 5, 4, 1 but higher than those of strategies 3, 6, and 2. In general, although strategy 7 is not the least expensive to implement, but it averts the highest number of disease infections. Overall, strategy 7 is the most effective in fighting the COVID-19. According to the control recommendations of strategy 7, when media publicity, home isolation, and face-mask wearing are implemented at the same time, in the early stage of the outbreak, it is necessary to pay close attention to the role of media publicity so as to boost home isolation and face-mask wearing measures. In the middle and late stages of the outbreak, home isolation and face-mask wearing should continue to be implemented without laxity.

7 Conclusion

More than a year into the pandemic, COVID-19 accumulates about three hundred million infections worldwide. To lower the risk of COVID-19 transmission, countries have implemented non-pharmaceutical intervention (NPI). The

Table 9: ACER for Case 3

Strategy	Total infection averted	Cost	ACER
Strategy 7 : $u_1(t) + u_2(t) + u_3(t)$	9.0035e+07	1.5133e+05	0.0017

Table 10: The sorting IAR of each strategy

Strategy	Total infection averted	Total recovered	IAR
Strategy 7 : $u_1(t) + u_2(t) + u_3(t)$	9.0035e+07	1.9499e+08	0.4618
Strategy 5 : $u_1(t) + u_3(t)$	8.8915e+07	1.9497e+08	0.4560
Strategy 4 : $u_1(t) + u_2(t)$	8.8915e+07	1.9497e+08	0.4560
Strategy 1 : $u_1(t)$	6.7876e+07	1.9187e+08	0.3538
Strategy 6 : $u_2(t) + u_3(t)$	1.9621e+07	1.1938e+08	0.1644
Strategy 2 : $u_2(t)$	1.0307e+07	1.1821e+08	0.0872
Strategy 3 : $u_3(t)$	1.0307e+07	1.1821e+08	0.0872

Table 11: The sorting ACER of each strategy

Strategy	Total infection averted	Cost	ACER
Strategy 7 : $u_1(t) + u_2(t) + u_3(t)$	9.0035e+07	1.5133e+05	0.0017
Strategy 5 : $u_1(t) + u_3(t)$	8.8915e+07	1.9834e+05	0.0022
Strategy 4 : $u_1(t) + u_2(t)$	8.8915e+07	2.0661e+05	0.0023
Strategy 1 : $u_1(t)$	6.7876e+07	2.3737e+05	0.0035
Strategy 3 : $u_3(t)$	1.0307e+07	4.1625e+04	0.0040
Strategy 6 : $u_2(t) + u_3(t)$	1.9621e+07	9.1575e+04	0.0047
Strategy 2 : $u_2(t)$	1.0307e+07	4.9950e+04	0.0048

transmission dynamics of COVID-19 are influenced to some extent by these NPIs to mitigate COVID-19. To explore the effective non-pharmaceutical interventions in COVID-19, a new COVID-19 epidemic model with consideration of non-pharmaceutical interventions is proposed in this paper. Specifically, we describe the realistic transmission dynamics of infectious disease by extending the SIR model to the new model with seven-state variables.

Some dynamic behaviors of the model, such as forward and backward bifurcation, are analyzed. We then perform a sensitivity analysis to determine the influence of related parameters on the basic reproduction number of our model. The analysis provides that the voluntary home isolation rate, the face-mask wearing rate and the transfer rate are the critical parameters, which greatly affect the COVID-19 pandemic. The non-pharmaceutical interventions

are more effective than pharmaceutical interventions in the early stages of the COVID-19 outbreak. At the same time, numerical simulations also validate the impact of the three measures on the spread of COVID-19.

To obtain effective non-pharmaceutical interventions, an optimal control model is established based on our epidemic model. We conduct optimization simulation experiments and present a cost-effectiveness analysis to unravel the cost and effectiveness of the combination of intervention strategies. Research shows that, strategy 7 appears to be preferred in inhibiting the COVID-19 epidemic, which provides the certain management implications for epidemic prevention and control.

Declarations

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- **Conflict of interest**
The authors declare that they have no conflict of interest.
- **Authors' contributions**
All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Yang Deng, Yi Zhao. The first draft of the manuscript was written by Yang Deng, Yi Zhao, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.
- **Availability of data and materials**
The datasets generated during and/or analysed during the current study are available in WHO (World Health Organization) repository, <https://covid19.who.int/>.

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