Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Efficacy of limited antiviral treatment, testing, hospitalization, and social distancing for COVID-19 pandemic

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ABSTRACT

The control measures of a pandemic must be cautiously evaluated, especially when resources are "limited". A model of COVID-19 transmission dynamics is applied to assess the impact of antiviral treatment, testing, hospitalization, and social distancing. Under the assumption of "unlimited" resources, five control strategies involving social distancing, testing, hospitalization, and antiviral treatment are tested. Then these "optimal" policies are sought in the case of limited resources on behalf of a COVID-19 pandemic scenario. The amplitude of peak epidemics will often be minimized by executing strategies from the beginning of a pandemic, spreading the epidemics' greatest impact over a longer time frame. Therefore, the timing and potency of control measures can reduce the pressure on the system during the top of the epidemic through the pandemic, decreasing the pressure on the healthcare infrastructure. In case of limited access to antiviral supplies, the role of testing, hospitalization, and social distancing strategies is emphasized in this study.

1. Introduction

Extensive simulation and analysis with the aid of a mathematical framework and appropriate sub-models can strengthen the identification, evaluation, and implementation of effective worldwide COVID-19 pandemic mitigation plans. The preparation plan to deal with the distribution of antiviral drugs must consider a variety of factors, including the virulence of the pathogen (defined according to the case mortality rate in the population), which plays a crucial part in evaluating the antiviral drug stock size for a community [1]. When the supply of antiviral drugs is insufficient, these assessment levels have new meanings. Therefore, the use of non-pharmaceutical interventions or treatments [2] must also be considered in the preparation process, including the availability of masks and ventilator distribution plans [3].

In emergencies (such as the emergency generated by the SARS-CoV-2 virus in 2019), the world's inadequate potency to manufacture antiviral drugs and vaccines (especially the vaccine of COVID-19) has caused many worries [4,5]. Throughout the pandemic moment, stocks of antiviral medicine (and COVID-19 vaccine) have prospected to be held by developed countries. Countries with large populations and no facilities for quality healthcare services, such as Bangladesh, Pakistan, and/or India [6], do not have the base to produce antiviral drugs to fulfill the requirements of such emergencies. Developing nations have not got enough drug stocks, equipment, or vaccine supplies that people consider the least in time. The abnormal level of morbidity and fatality among young people has caused more concern [7]. Who gets the vaccine first?- the elderly, the young, women expecting childbirth, or emergency worker? The usefulness of the WHO definition of a pandemic is now being questioned, as the severity of this pandemic seems to be higher compared with the past SARS pandemic (2003).

For many decades, optimal control theory and intervention strategies have been applying in engineering, economic and mathematical topics. In the recent decade, it has become popular in epidemiology as well. But all the existing researches are usually limited to 3 or 4 controls which motivated us to extend that limit. In our paper, for the first time, we have introduced 11 controls in a model that arrived from Ref. [8], which

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makes our research more challenging and effective.

This paper focuses on determining "optimal" control strategies to lessen the COVID-19 pandemic effect through the wise use of limited antiviral drug supplies, testing (contact tracing), hospitalization, and social distancing policies (SDPs). The parameters that are used in our dynamic model are initially calibrated using data of the COVID-19 pandemic [8] baseline scenario. The intervention efficacy substitutes that involve the distribution of antiviral drugs, testing, hospitalization, and social distancing are explored. In our analysis, we used optimal control (OC) theory [9] as a primary tool, which has a history of successful applications in industrial, biological, and medical problems.

In Section 2, we describe the model, including eleven control functions. Comparison of the five scenarios numerical simulation results and discussion are introduced in Section 3. We summarized our thoughts and conclusions in Section 4.

2. COVID-19 pandemic model with controls

To inspect the influence of antiviral treatment (improved treatment methods and gaining immunity against the virus), testing (mandatory mass contact tracing, testing activities [10,11] and testing subsidies), hospitalization (appropriate treatment in the ICU), and SDPs (for instance, school closure, working remotely, lockdown, quarantine, isolation) in a simulated situation similar to the COVID-19 pandemic [8], OC theory is used. We set up our model using parameter estimates related to the deadliest SARS virus pandemic on record [8,12]. The intervention strategies are modeled by the functions $u_i(t)\ \left(i = 1, 11\right)$ which control externally the number of asymptomatic (both undetected and detected) and clinical (both undetected and detected) cases within a given limited time frame. The underlying dynamic model categorizes individuals as susceptible (S), undetected asymptomatic or paucisymptomatic infectious (A_U), detected asymptomatic infectious (A_D), undetected clinically ill (symptomatic) and infectious (I_U), detected clinically ill (symptomatic) and infectious (I_D), detected infectious with life-threatening symptoms/serious morbidity (I_D^C), recovered (R) and death (D). At time t, the entire population is N. The disease dynamics are modeled by the following system of nonlinear ordinary differential equations (ODEs) [8]:

$$
\begin{cases}
\dot{S}(t) = \dfrac{-[(1-\epsilon_8 u_8(t))\alpha A_U + (1-\epsilon_9 u_9(t))\beta A_D + (1-\epsilon_{10}u_{10}(t))\gamma I_U + (1-\epsilon_{11}u_{11}(t))\delta I_D]S}{N},\\
\dot{A}_U(t) = \dfrac{[(1-\epsilon_8 u_8(t))\alpha A_U + (1-\epsilon_9 u_9(t))\beta A_D + (1-\epsilon_{10}u_{10}(t))\gamma I_U + (1-\epsilon_{11}u_{11}(t))\delta I_D]S}{N}\\
\qquad -((\epsilon+\epsilon_5 u_5(t)) + \varsigma + (\lambda+\epsilon_1 u_1(t)))A_U,\\
\dot{A}_D(t) = (\epsilon+\epsilon_5 u_5(t))A_U(t) - (\eta + (\rho+\epsilon_2 u_2(t)))A_D,\\
\dot{I}_U(t) = \varsigma A_U - ((\theta+\epsilon_6 u_6(t)) + \mu + (k+\epsilon_3 u_3(t)))I_U,\\
\dot{I}_D(t) = \eta A_D + (\theta+\epsilon_6 u_6(t))I_U - (\upsilon + (\xi+\epsilon_4 u_4(t)))I_D,\\
\dot{I}_D^C(t) = \mu I_U + \upsilon I_D - (\tau + (\sigma+\epsilon_7 u_7(t)))I_D^C,\\
\dot{R}(t) = (\lambda+\epsilon_1 u_1(t))A_U + (\rho+\epsilon_2 u_2(t))A_D + (k+\epsilon_3 u_3(t))I_U\\
\qquad +(\xi+\epsilon_4 u_4(t))I_D + (\sigma+\epsilon_7 u_7(t))I_D^C,\\
\dot{D}(t) = \tau I_D^C,\\
N(t) = S + A_U + A_D + I_U + I_D + I_D^C + R + D.
\end{cases}
\tag{1}
$$

Because of contact between a susceptible subject and an undetected asymptomatic, a detected asymptomatic, an undetected symptomatic, or a detected symptomatic subject, the transmission rate (disease transmission probability in a single contact multiplied by the average number of contacts per person) are α, β, γ and δ respectively. ϵ and θ denote the detection probability relative to asymptomatic and symptomatic cases, respectively. ς and η respectively represent the probability of clinically relevant symptoms in asymptomatic subjects (unaware and aware of being infected, respectively), and they are comparable without specific treatment. μ and υ represent the rate of life-threatening symptoms in undiscovered and discovered infected individuals, respectively. τ means the mortality rate for infected cases with life-threatening symptoms. λ, k, ξ, ρ and σ indicate the five types of infected subjects recovery rate.

The controlling efforts $u_1(t)$, $u_2(t)$, $u_3(t)$ and $u_4(t)$ alter the number of asymptomatic infectious (undetected) ($\epsilon_1 A_U(t)$), asymptomatic infectious (detected) ($\epsilon_2 A_D(t)$), symptomatic infectious (undetected) ($\epsilon_3 I_U(t)$) and symptomatic infectious (detected) ($\epsilon_4 I_D(t)$) cases receiving antivirals per unit of time. As for A_U individuals, since they are not aware of being infected, they will only try to gain immunity against the virus by proper nutrition, taking no medications. Assume that when the control is equal to 1, each control reaches the maximum per capita efficacy antiviral rate.

The controlling efforts $u_5(t)$ and $u_6(t)$ alters the number of undetected asymptomatic ($\epsilon_5 A_U(t)$) and symptomatic infectious ($\epsilon_6 I_U(t)$) cases receiving test per unit of time. Assume that when each control is equal to 1, each control reaches the maximum per capita efficacy testing rate.

The controlling effort $u_7(t)$ alters the number of detected infectious cases with life-threatening symptoms by being hospitalized per unit of time. Since the number of infected individuals is high, we are only taking into ICU those in critical conditions. Assume that when the control is equal to 1, the control has reached the highest per capita efficiency.

The social distancing rate-adjusting controlling factors, $(1-\epsilon_8 u_8(t))$, $(1-\epsilon_9 u_9(t))$, $(1-\epsilon_{10} u_{10}(t))$ and $(1-\epsilon_{11} u_{11}(t))$ quantifies the prevention or restriction of the speed of interaction between a susceptible subject and an undetected asymptomatic, a detected asymptomatic, an undetected symptomatic or a detected symptomatic subject, because of external effort. Hence, in $(1-\epsilon_8 u_8(t))\alpha S(t)A_U(t)$, $(1-\epsilon_9 u_9(t))\beta S(t)A_D(t)$, $(1-\epsilon_{10}u_{10}(t))\gamma S(t)I_U(t)$ and $(1-\epsilon_{11}u_{11}(t))\delta S(t)I_D(t)$ the parameter α, β, γ and δ denotes the maximum transmission rate per susceptible individuals and per undetected asymptomatic, per detected asymptomatic, per undetected symptomatic or per detected symptomatic individuals with $(1-\epsilon_8 u_8(t))$, $(1-\epsilon_9 u_9(t))$, $(1-\epsilon_{10} u_{10}(t))$ and $(1-\epsilon_{11} u_{11}(t))$ denoting the reduction in α, β, γ and δ

respectively generated by the external social distancing control; ϵ_8, ϵ_9, ϵ_{10} and ϵ_{11} measures the effectiveness of $u_8(t)$, $u_9(t)$, $u_{10}(t)$ and $u_{11}(t)$ respectively $(\epsilon_i\left(i=8,11\right)\in(0,1)$ *and* $u_i(t)\left(i=8,11\right)\in[0,1])$. The case when $\epsilon_i u_i(t)\approx 1\ \left(i=8,11\right)$ corresponds to the ideal situation, that is, when contacts between susceptible and undetected asymptomatic, detected asymptomatic, undetected symptomatic or detected symptomatic individuals are completely avoided (prevented by effective SDPs), the total transmission rate is effectively reduced to zero. Assuming the baseline contact rate of each community member and the infected individual is the same, and the parameters ϵ_8, ϵ_9, ϵ_{10} and ϵ_{11} reduce the contact rate between infected individuals which simulate the effect of SDPs on undetected asymptomatic, detected asymptomatic, undetected symptomatic and detected symptomatic individuals. Hospitalization and effective SDPs are not standard because effective social distancing of infected persons is expensive and requires special facilities. As the number of cases increases, the availability of such specialized facilities will be limited; this is rare in countries with limited resources. When it comes to infectious class, people expect some form of social distancing, which may affect transmission. It is as effective as the large-scale SDPs implemented in New Zealand, but it is costly for a relatively low pandemic severity. Therefore, here, we focus on the recognized cost of SDPs.

In the absence of control strategies, the dynamics of Model (1) is determined by the basic reproduction number R_0 (an average measure of the number of secondary cases of primary infections during the entire infection period in a fully susceptible population [13]). When control measures $\left(u_i(t)=0,\ i=1,11\right)$ are absent, the R_0 of Model (1) is given by the equation

$$R_0=\frac{1}{\epsilon+\varsigma+\lambda}\left[\left(\alpha+\frac{\beta\epsilon}{\eta+\rho}+\frac{\gamma\varsigma}{\theta+\mu+k}\right)+\frac{\delta}{\upsilon+\xi}\left(\frac{\eta\epsilon}{\eta+\rho}+\frac{\varsigma\theta}{\theta+\mu+k}\right)\right]$$

This dimensionless measure indicates the number of secondary cases generated by five groups: the undetected asymptomatic (A_U), detected asymptomatic (A_D), undetected clinically ill and infectious (I_U), detected clinically ill and infectious (I_D), detected infected with life-threatening symptoms (I_D^C), respectively [8]. Although various parameters are used to find the basic reproduction number R_0, we only focus on the value of R_0 to guess the scenario of the disease. For the values of various parameters, we collect data from medical resources. Whenever $R_0=1$, each existing infection will cause a new infection. The disease will continue to exist and remain stable, but it will not break out or spread. When $R_0>1$, an epidemic will show up, and the infection spreads in the population. And finally, the epidemic eventually disappears if $R_0<1$ [14]. The estimated maximum value of R_0 for the pandemic COVID-19 is 4.5 [15].

The parameter definitions and assumptions lead to Model (1) involving a system of nonlinear ODEs and eleven controls. Through simulations of Model (1) parameterized in the context of the COVID-19 pandemic, controls influence is explored. The objective functional $\mathcal{F}$ proposes the optimization problem of interest, determining the most effective strategy. The overall pre-selected objective involves minimizing the number of asymptomatic and clinically infected individuals within a limited time interval of [0, T] with minimal cost. The objective functional $\mathcal{F}$ is given

$$\mathcal{F}(u_1,u_2,u_3,u_4,u_5,u_6,u_7,u_8,u_9,u_{10},u_{11})=\int_0^T\left[C_1A_U+C_2A_D+C_3I_U+C_4I_D+C_5I_D^C+\sum_{i=1}^{11}\frac{W_i}{2}u_i^2\right]dt \tag{2}$$

Constants C_i $(i=1,5)$ and W_i $(i=1,11)$ are measures of the relative cost of interventions on [0, T]. We model the control efforts through a linear combination of quadratic terms, $u_i^2(t)$ $(i=1,11)$. The OC problem is to find optimal control functions $u_i^*(t)$ $(i=1,11)$, such that

Table 1
Definition of parameters and their corresponding baseline values used in numerical simulations [8,16].

Parameter	Definition	Value
A	Transmission rate due to contacts between a susceptible and an undetected asymptomatic subject (days^{-1})	0.057 – 0.57
B	Transmission rate due to contacts between a susceptible and a detected asymptomatic subject (days^{-1})	0.005 – 0.011
Γ	Transmission rate due to contacts between a susceptible and an undetected symptomatic subject (days^{-1})	0.057 – 0.456
Δ	Transmission rate due to contacts between a susceptible and a detected symptomatic subject (days^{-1})	0.005 – 0.011
ϵ	Detection probability rate, relative to asymptomatic cases	0.143 – 0.6
θ	Detection probability rate, relative to symptomatic cases	0.371
ς	Probability rate at which an asymptomatic subject (unaware of being infected) develops clinically relevant symptoms	0.025 – 0.125
η	Probability rate at which an asymptomatic subject (aware of being infected) develops clinically relevant symptoms	0.025 – 0.125
μ	Rate at which undetected symptomatic subjects develop life-threatening symptoms	0.008 – 0.017
υ	Rate at which detected symptomatic subjects develop life-threatening symptoms	0.015 – 0.027
τ	Mortality rate	0.01
λ	Recovery rate for an asymptomatic subject (unaware of being infected) (days^{-1})	0.08 – 0.034
ρ	Recovery rate for an asymptomatic subject (aware of being infected) (days^{-1})	0.017 – 0.034
k	Recovery rate of for a symptomatic subject (unaware of being infected) (days^{-1})	0.017 – 0.02
ξ	Recovery rate for a symptomatic subject (aware of being infected) (days^{-1})	0.017 – 0.02
σ	Recovery rate for a symptomatic subject (aware of being infected) with life-threatening symptoms (days^{-1})	0.01 – 0.017
ϵ_1	Efficacy of antiviral treatment on undetected asymptomatic individuals	0.5
ϵ_2	Efficacy of antiviral treatment on detected asymptomatic individuals	0.5
ϵ_3	Efficacy of antiviral treatment on undetected clinically ill and infectious individuals	0.5
ϵ_4	Efficacy of antiviral treatment on detected clinically ill and infectious individuals	0.5
ϵ_5	Efficacy of testing on undetected asymptomatic individuals	0.5
ϵ_6	Efficacy of testing on undetected clinically ill and infectious individuals	0.5
ϵ_7	Efficacy of hospitalization on detected symptomatic subjects with life-threatening symptoms	0.5
ϵ_8	Efficacy of social distancing between a susceptible and an undetected asymptomatic subject	0.5
ϵ_9	Efficacy of social distancing between a susceptible and a detected asymptomatic subject	0.5
ϵ_{10}	Efficacy of social distancing between a susceptible and an undetected symptomatic subject	0.5
ϵ_{11}	Efficacy of social distancing between a susceptible and a detected symptomatic subject	0.5
T	Total simulation duration (days)	200
C_i	Weight constants on A_U, A_D, I_U, I_D and I_D^C classes ($i=1,5$)	1
W_i	Weight constants on controls ($i=1,11$)	50
$N(0)$	Initial number of total population size	60000000
$S(0)$	Initial number of susceptible individuals	59999777
$A_U(0)$	Initial number of undetected asymptomatic or pauci-symptomatic individuals	200
$A_D(0)$	Initial number of detected asymptomatic or pauci-symptomatic individuals	20
$I_U(0)$	Initial number of undetected clinically ill and infectious individuals	1
$I_D(0)$	Initial number of detected clinically ill and infectious individuals	2

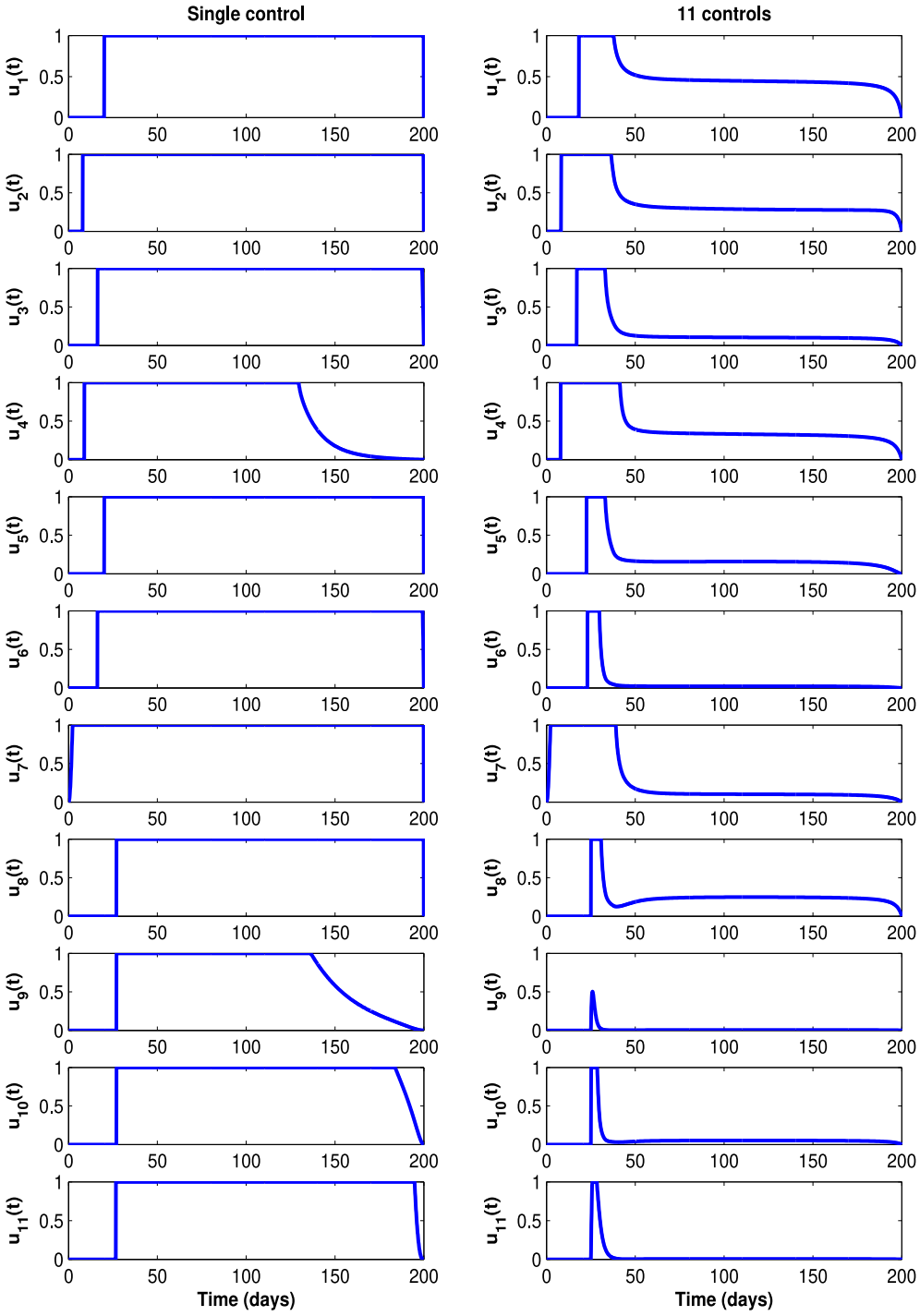

Fig. 1. Top left eleven graphs show the OC functions computed for Strategies 1–5 using only one control function, respectively. Eleven OC functions implemented for Strategy 5 are shown in top right graphs. Parameter values are given in Table 1 when $R_0 = 2.38$.

$$\mathcal{F}\left(u_1^*, u_2^*, u_3^*, u_4^*, u_5^*, u_6^*, u_7^*, u_8^*, u_9^*, u_{10}^*, u_{11}^*\right) = \min_{\Omega} \mathcal{F}(u_1, u_2, u_3, u_4, u_5, u_6, u_7, u_8, u_9, u_{10}, u_{11}),$$

where, $\Omega = \left\{ u_i(t) \middle\| \; 0 \le u_i(t) \le 1, \; t \in [0, T], \forall i = 1, 11 \right\}$,

subject to the system (1) with initial conditions. To solve this OC problem, Pontryagin's Maximum Principle is applied, and A explains the necessary conditions for its application.

Five different control strategies are explored. This approach can be used to test various options. Here, however, we only look at the following five alternatives:

- Strategy 1: Antiviral treatment controls on undetected asymptomatic, detected asymptomatic, undetected clinical and detected clinical cases (controls $u_1(t)$, $u_2(t)$, $u_3(t)$ and $u_4(t)$).
- Strategy 2: Testing controls on undetected asymptomatic and undetected clinical cases (controls $u_5(t)$ and $u_6(t)$).
- Strategy 3: Hospitalization control on detected infectious with life-threatening symptoms cases (control $u_7(t)$ alone).
- Strategy 4: Social distancing controls on undetected asymptomatic, detected asymptomatic, undetected clinical and detected clinical cases (controls $u_8(t)$, $u_9(t)$, $u_{10}(t)$ and $u_{11}(t)$).

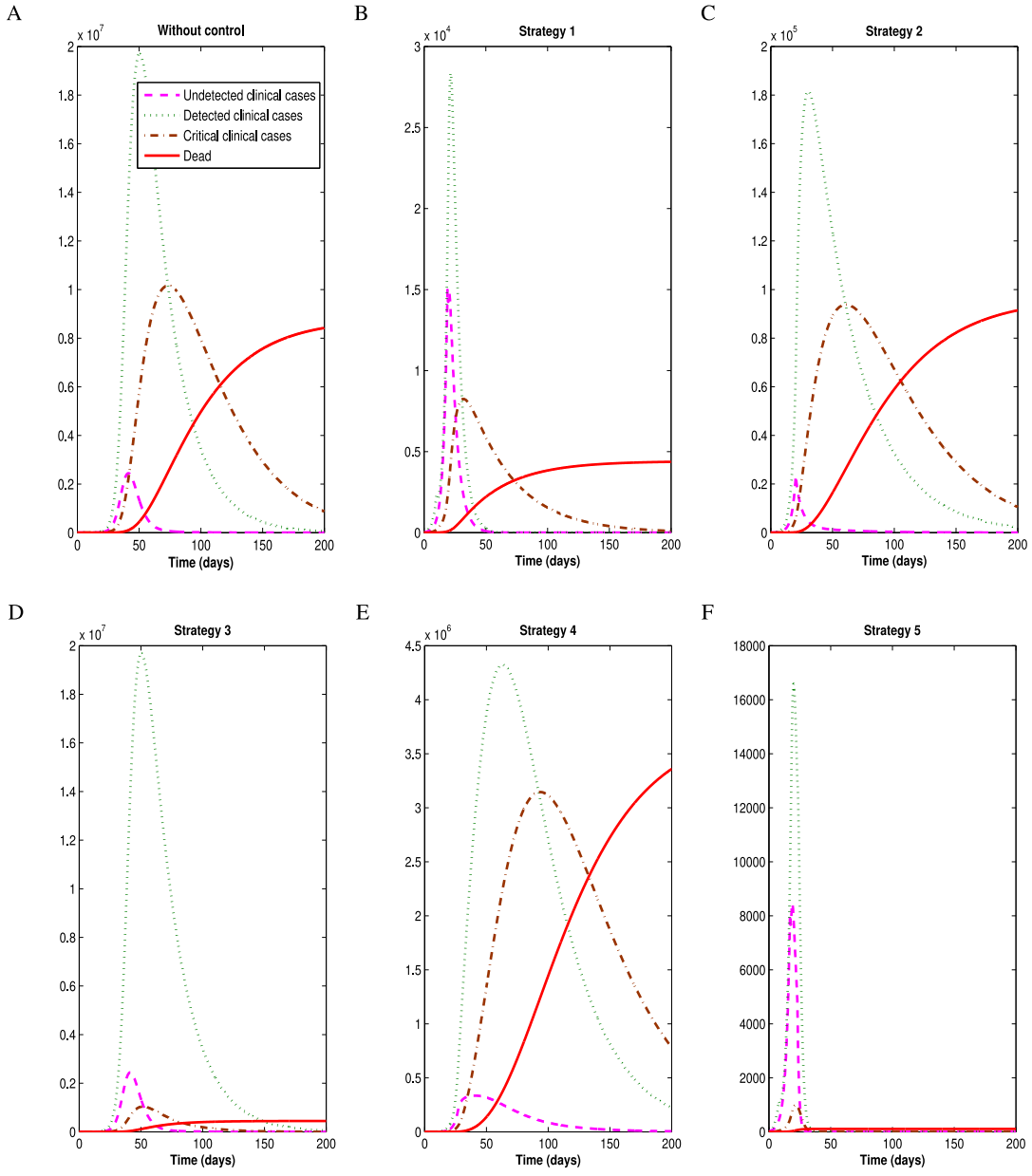

Fig. 2. The graphs (A–F) illustrate the comparisons of the corresponding daily incidence in clinical and disease-induced deaths under no controls with those generated with Strategies 1–5. Parameter values are given in Table 1 when $R_0 = 2.38$.

- Strategy 5: Four antiviral treatment controls on undetected asymptomatic, detected asymptomatic, undetected clinical, and detected clinical cases. Two testing controls on undetected asymptomatic and undetected clinical cases. One hospitalization control on detected infectious with life-threatening symptoms cases. Four social distancing controls on undetected asymptomatic, detected asymptomatic, undetected clinical and detected clinical cases (controls $u_i(t)$, $i = 1, 11$).

Strategies 1–5 use the objective functionals (3–7), respectively.

$$\mathcal{F}(u_1, u_2, u_3, u_4) = \int_0^T \left[C_1 A_U + C_2 A_D + C_3 I_U + C_4 I_D + \sum_{i=1}^{4} \frac{W_i}{2} u_i^2 \right] dt \tag{3}$$

$$\mathcal{F}(u_5, u_6) = \int_0^T \left[C_1 A_U + C_3 I_U + \sum_{i=5}^{6} \frac{W_i}{2} u_i^2 \right] dt \tag{4}$$

$$\mathcal{F}(u_7) = \int_0^T \left[C_5 I_D^C + \frac{W_7}{2} u_7^2 \right] dt \tag{5}$$

$$\mathcal{F}(u_8, u_9, u_{10}, u_{11}) = \int_0^T \left[C_1 A_U + C_2 A_D + C_3 I_U + C_4 I_D + \sum_{i=8}^{11} \frac{W_i}{2} u_i^2 \right] dt \tag{6}$$

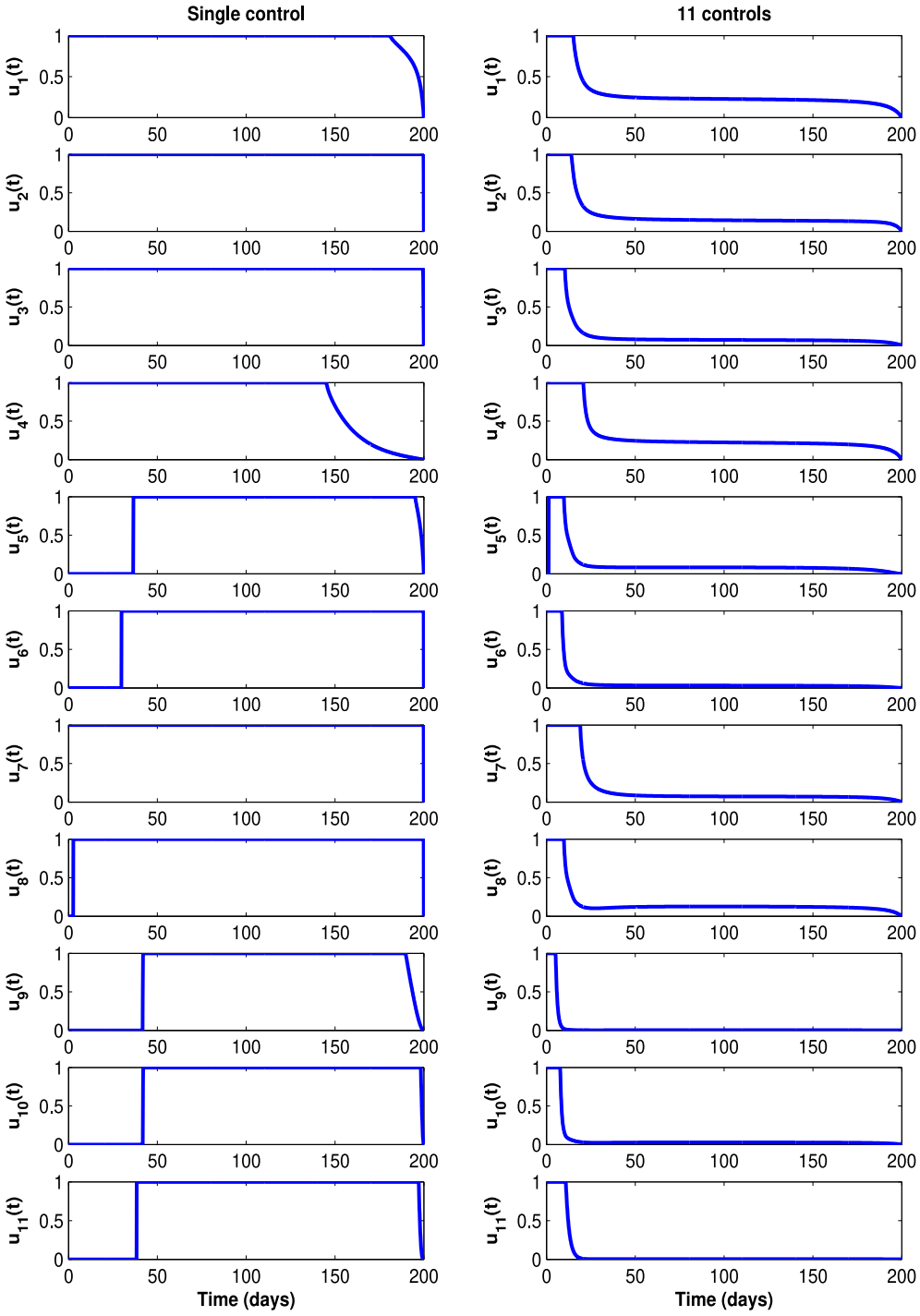

Fig. 3. Top left graphs show the OC functions computed for Strategies 1–5 using only one control function, respectively. Eleven OC functions implemented for Strategy 5 are plotted in top right. Parameter values are given in Table 1 when $R_0 = 1.5$.

$$\mathcal{F}(u_1, u_2, u_3, u_4, u_5, u_6, u_7, u_8, u_9, u_{10}, u_{11})$$

$$= \int_0^T \left[C_1 A_U + C_2 A_D + C_3 I_U + C_4 I_D + C_5 I_D^C + \sum_{i=1}^{11} \frac{W_i}{2} u_i^2 \right] dt \tag{7}$$

The outputs are calculated numerically of a single strategy or integrated strategy. Strategies are applied from the related optimal system results, consisting of a nonlinear ODEs system involving state equation (1) and adjoint equations (A.2). The state equations are solved using the forward Euler method with given initial conditions for the state variables (1). The corresponding adjoint system (A.2) is solved using the backward Euler method with the transversality conditions (A.3). Previously and currently calculated controls convex combination results in updated controls using the optimality equations (A.4). In Table 1, the initial conditions and model parameters default values are given where units are per day for all rates, and baseline values are used throughout the report unless otherwise stated.

3. Results and discussion

In the case of unlimited and limited resources, simulation results generated by the numerical implementation of the intervention strategy

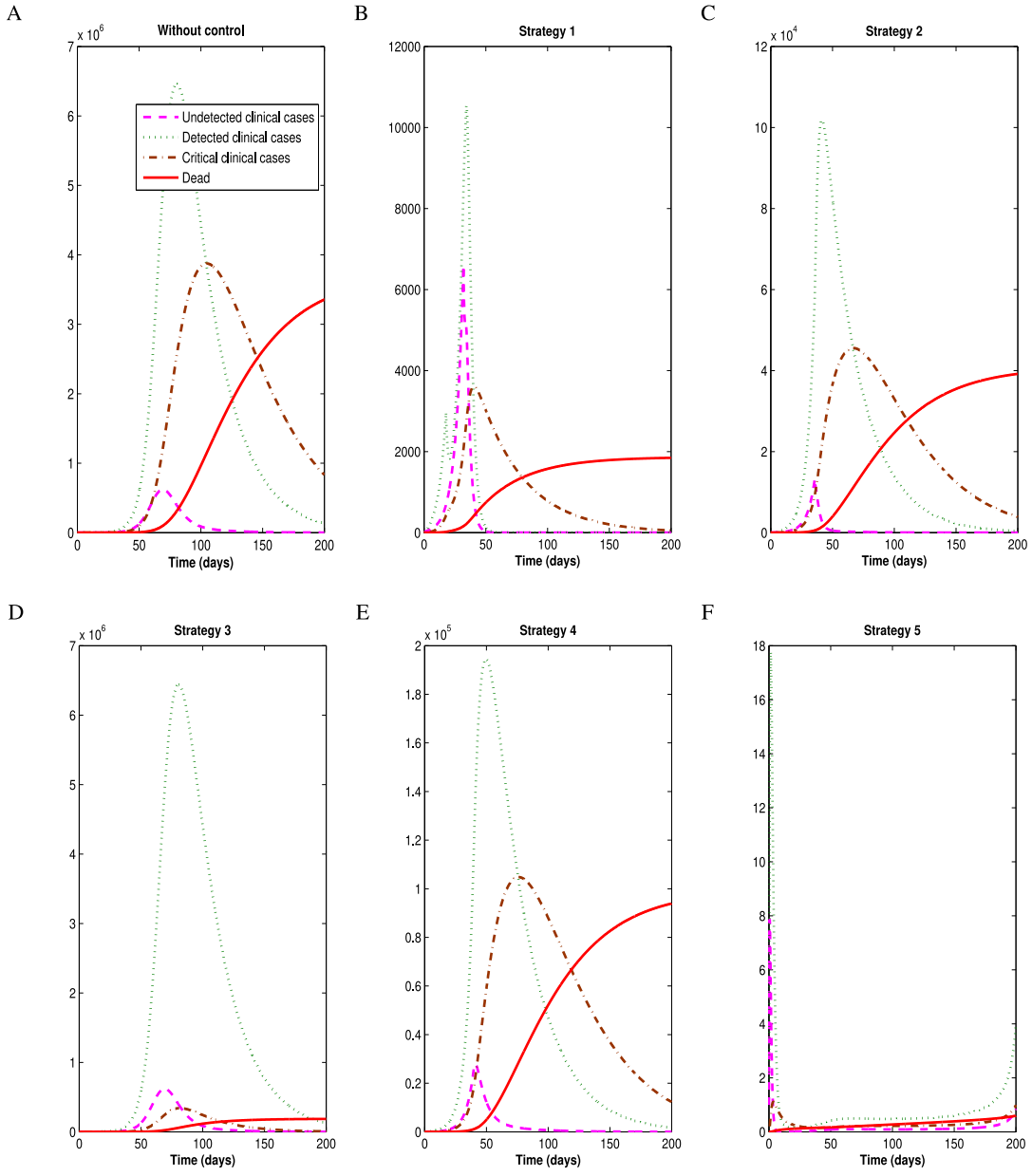

Fig. 4. The graphs (A–F) show the comparisons of the corresponding daily incidence in clinical and COVID-19 related deaths under no controls with those generated with Strategies 1–5. Parameter values are given in Table 1 when $R_0 = 1.5$.

described in Section 2 are presented. The sensitivity analysis results of some model parameters in System 1 are given in Subsection 3.2. The sensitivity analyses related to unlimited antiviral drugs, testing kits, ICU resources are reported only.

3.1. Strategies implementations

To ensure that our model works or not, we have taken the basic reproduction number R_0 as a norm. The detailed description of R_0 is already given in Section 2. The impact of the antiviral treatment, testing, hospitalization, and SDPs on the COVID-19 pandemic dynamics is evaluated at different transmission levels, measured by R_0; first, consider that we have an unlimited supply of antiviral drugs, testing kits, ICU facilities. The graphs of the eleven OCs calculated under strategies 1–5 are shown in Fig. 1 (In Table 1 parameter values used are provided with $R_0 = 2.38$). The top left eleven graphs in Fig. 1 depict the OC functions computed for Strategies 1–5 (single control strategies). The top right eleven graphs in Fig. 1 illustrate the results of implementing eleven control efforts simultaneously for Strategy 5.

Usually, high reproduction numbers ($R_0 > 2$) produce epidemics that have high epidemic peaks. Fig. 2 shows the comparison of the impact of each strategy on the uncontrolled epidemic state variables when $R_0 = 2.38$. These graphs show the number of clinical cases (undetected, detected, and critical) and deaths that occurred each day under no controls and Strategies 1–5. The Fig. 2(A) epidemic curves (under no interventions) show the difference from those generated by implementing the optimal strategies. Strategy 5 (Fig. 2(F)) shows that all four epidemics are significantly reduced. In contrast, Strategy 1 (Fig. 2(B)), Strategy 2 (Fig. 2(C)), Strategy 3 (Fig. 2(D)) and Strategy 4 (Fig. 2(E)) produce slightly fewer reductions (compared with the no intervention situation). Strategy 1 performs better than Strategy 2, 3, and 4. The use of integrated control Strategies (1, 2, 4, and 5) require a lot of effort at the beginning of an outbreak (top right eleven graphs in Fig. 1) and then suddenly dropped throughout the epidemic (most probably for the high reduction in

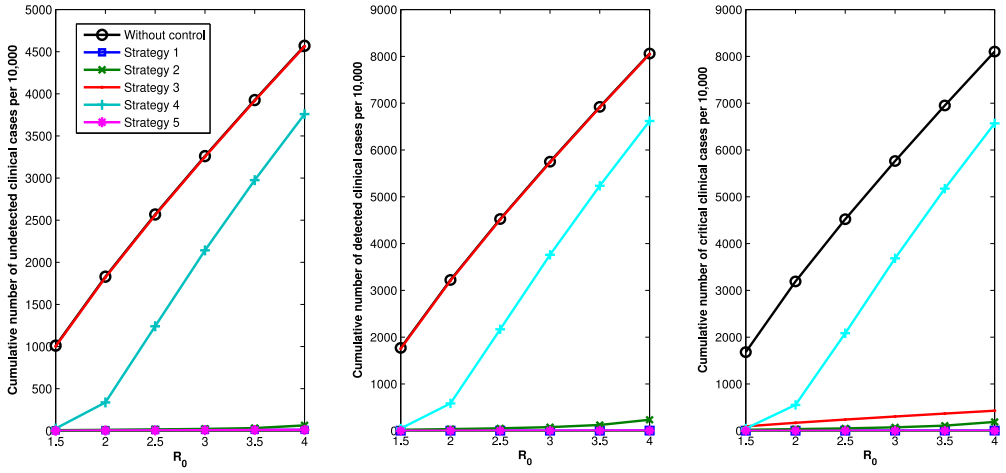

Fig. 5. The cumulative clinical cases under no control and Strategies 1–5 as a function of R_0.

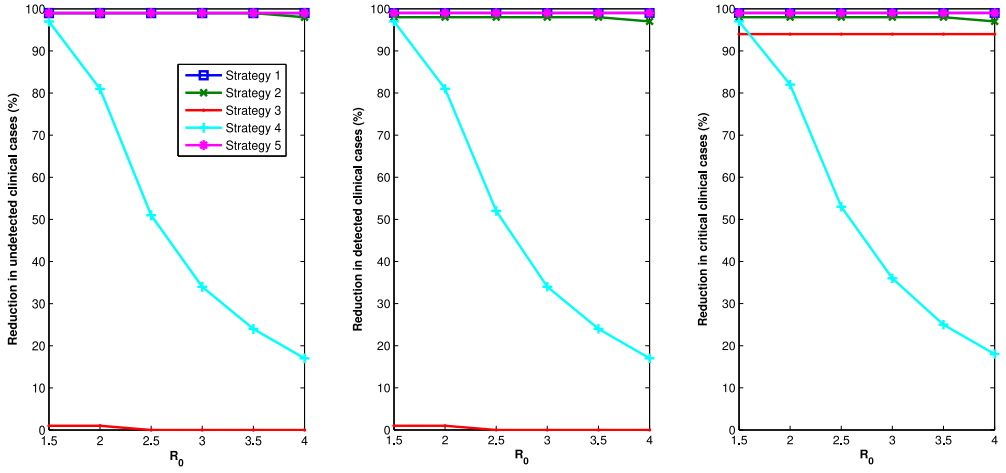

Fig. 6. The reduction of the clinical cases concerning the baseline scenario without interventions.

the population susceptibility level). The single control optimal strategies (Strategy 3) requires high-level efforts from the beginning (top left eleven graphs in Fig. 1) and must be maintained for a certain period, more extended than it would be necessary for strategies (Strategies 1, 2, 4 and 5).

Naturally, the optimal strategy is an implicit function of R_0 where the values of $R_0 > 2$ will cause an outbreak for which the OC requires immediate execution with full efforts. In Strategy 3, it is necessary to keep maintaining the efforts for a long time because the large $R_0's$ quickly reduces the susceptible population. On the contrary, using a single OC will not significantly impact; using integrated multiple strategies is more effective. In the case of Strategy 5 (integrated control strategy), the time distribution of the OCs is different because executing multiple controls simultaneously cannot eliminate the possibility of an outbreak. However, this distribution can still reduce the intensity of the COVID-19 epidemic peak by distributing the infection cases in a broad time frame. When hospital resources (beds and personnel) are limited, it is indispensable to allocate the burden of COVID-19 cases over a more extended period.

The low $R_0's$ ($R_0 < 2$) situation can be best handled by implementing the initial total effort and then steadily reducing the effort during the remaining epidemic duration (compare Figs. 1 and 2 for $R_0 = 2.38$ with Figs. 3 and 4 for $R_0 = 1.5$ respectively). The usefulness of the control, in the long run, comes from the following fact: for the "low" values of R_0 (in this case, $R_0 < 2$) there are still plenty of susceptible individuals available for controls to have an impact (reducing generations in secondary cases).

COVID-19 epidemics (no outbreak takes place) can effectively be controlled by Strategy 5 for low but realistic R_0 values (for example, $R_0 = 1.5$ in Figs. 3 and 4). The panels in Fig. 2 show that despite this, even under strategy 5, the use of OC cannot prevent the outbreak of the epidemic (see the increase in the number of cases for $R_0 = 2.38$). A reliable estimate of R_0 as early as possible helps evaluate the OC policy's effectiveness. Knowing the estimated R_0 value helps to assess the limitations of optimal policies in the rapidly spreading infectious diseases presence (such as COVID-19).

The optimal Strategies 1–5 on the cumulative clinical (undetected, detected, and critical) cases as a R_0 function is displayed in Fig. 5. Besides, Fig. 5 shows the comparisons between the cumulative undetected, detected, and critical clinical cases (without interventions) and the cumulative number generated according to Strategies 1–5 as a R_0 function. Compared with Strategy 3 developed using a single control, the combined control Strategies 1, 2, 4, and 5 can significantly reduce clinical infection cases.

Compared with the no-intervention situation, the effectiveness of all strategies is evaluated by the percentage reduction of the cumulative

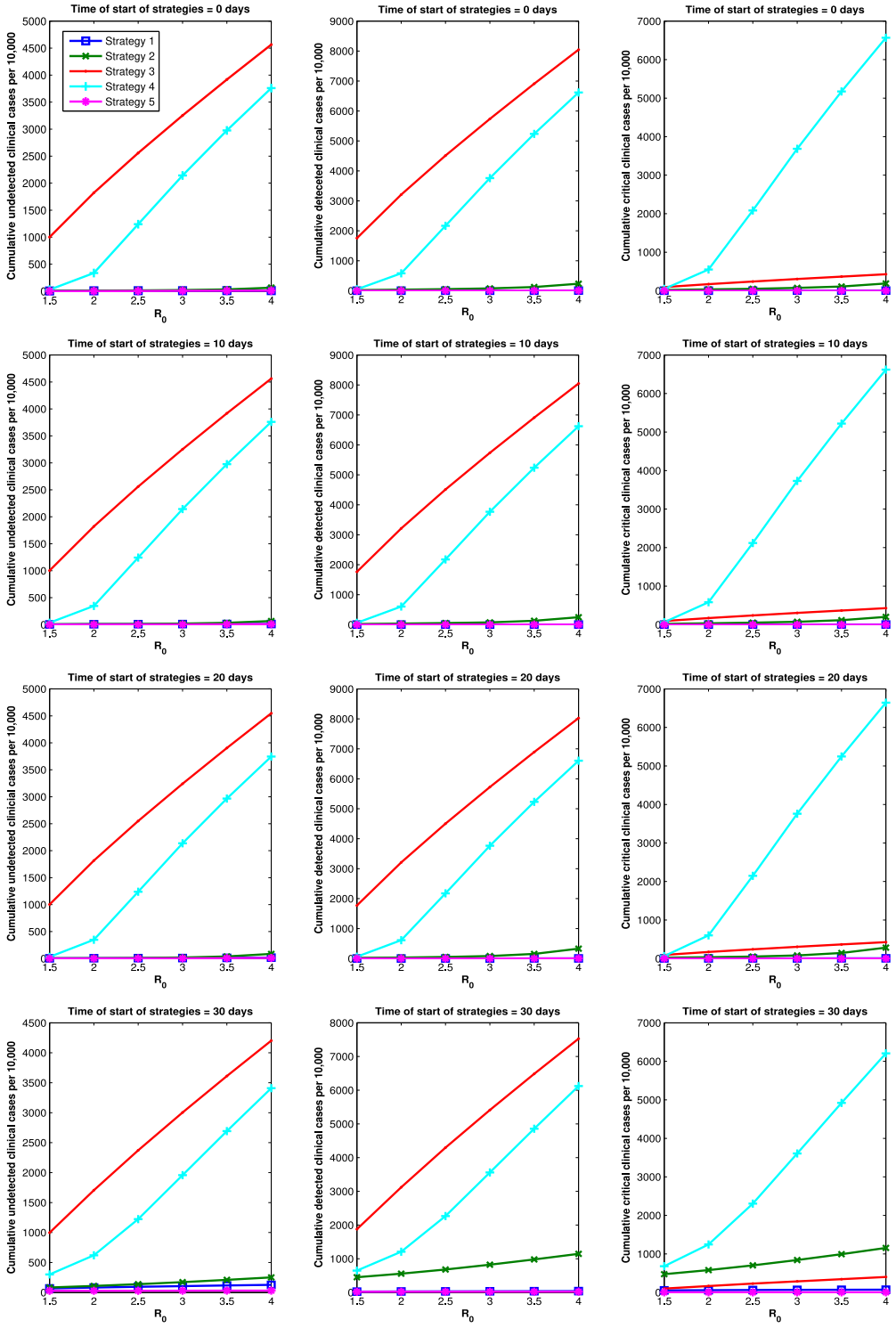

Fig. 7. The cumulative clinical cases are plotted as a function of R_0 for Strategies 1–5, where the strategies start at 0, 10, 20, 30 days after the pandemic onset.

clinical infections, which is calculated based on the relative difference between the results with no-intervention and under Strategies 1–5. This reduction is illustrated as a R_0 function in Fig. 6. Regardless of the strategy adopted, it displays a high reduction for low reproduction numbers. The integrated strategies produce 90% or more reductions when $R_0 = 1.5$ and also try to maintain this reduction when R_0 increases. For instance, Strategies 1, 2, and 5 generate improvements over the entire R_0 values range.

Relative to the start time of the pandemic, the beginning of antiviral treatment is naturally essential. At the end of the pandemic, the impact of the time delay is assessed based on the cumulative number of clinical cases. Under four different starting times of antiviral treatments, testing, hospitalization, and SDPs (0, 10, 20, and 30 days after the epidemic), the OC for each delayed case is recalculated. These situations are used to assess the impact of delayed intervention strategies relative to the pandemic's start. Fig. 7 shows the relationship between the cumulative

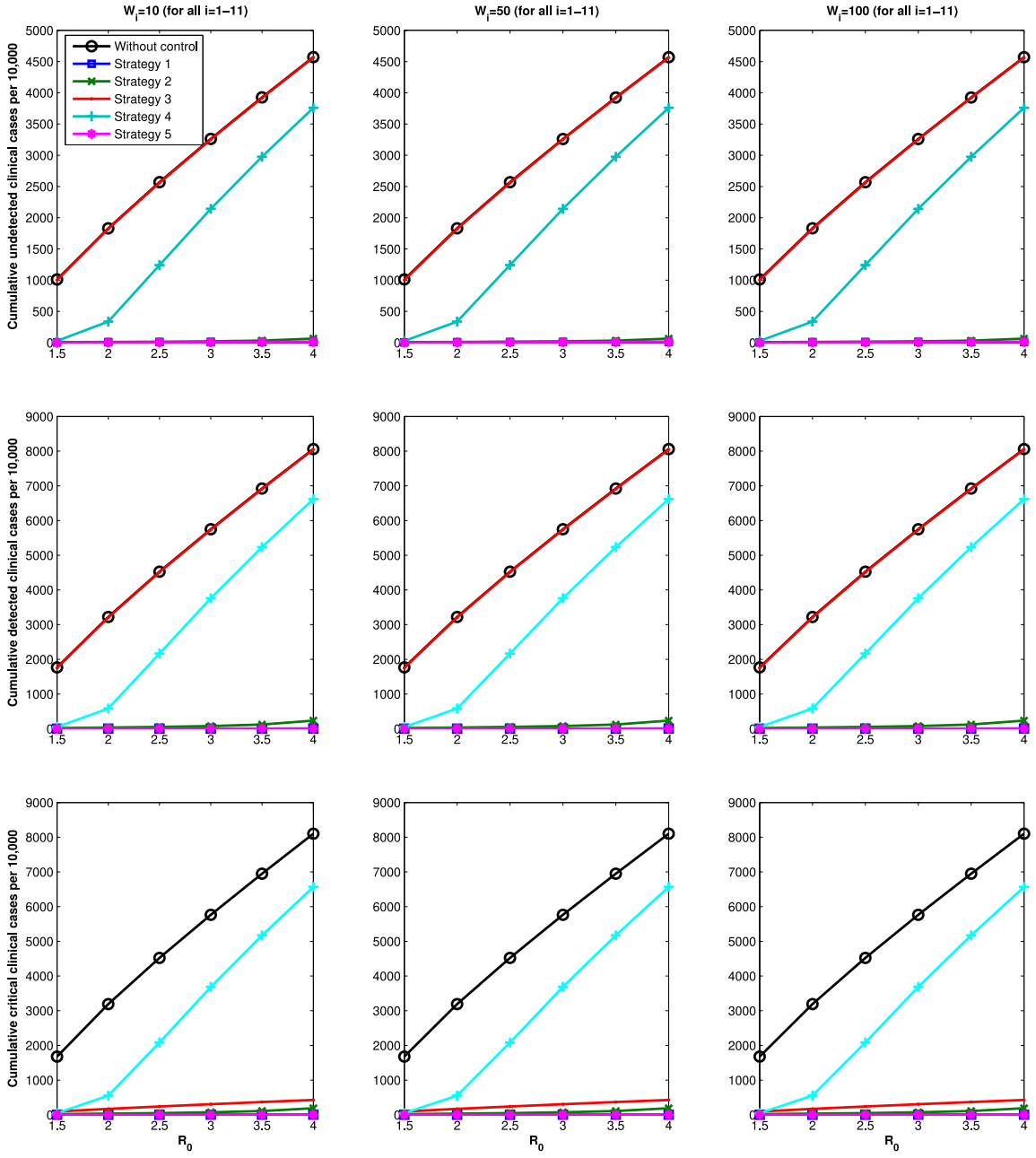

Fig. 8. The cumulative clinical (undetected, detected and critical) cases are plotted as functions of R_0 for three different values of weight constants, $W_i = 10,\ 50,\ 100\ (i = 1, 11)$.

clinical cases of strategies 1–5 and R_0. In these simulations, antiviral treatment, testing, hospitalization, and SDPs start at time t = 0, 10, 20, and 30 days respectively after the pandemic began (for each time delay, the OCs under all strategies are recalculated). If applied earlier (t = 0 days), all strategies are most effective. Under all strategies (compared to the case of no intervention), delays in the availability of antiviral treatment, testing, hospitalization, and SDPs will assist in an increase in the number of clinical infections. Strategies 1 and 5 perform better than all selected strategies. Besides, if executed immediately (t = 0 days), both strategies are very effective for the range of $R_0 = 1.5 - 4$. As the initial time of antiviral treatment, testing, hospitalization, and SDPs increases, the range of R_0 where OCs are effective, gets smaller. For example, if the start date of antiviral treatment, testing, hospitalization, and SDPs is $t =$ 30 days after the pandemic begins, there is no effective control strategy. This last observation focuses on the significance of worldwide inspection in real-time [17] and enhances the importance of the open approach embraced by Italian public health officials in dealing with COVID-19. Besides, the preliminary handling of the SARS-CoV-2 epidemic in 2019 (see Ref. [8] and its references) still has many shortcomings.

3.2. Sensitivity analyses

Sensitivity analyses evaluate the quantitative impact of model parameter changes on the cumulative clinical (undetected, detected, and critical) cases to study the model parameter changes impact. The weight constants sensitivity to the control group (parameters W_i $(i = 1, 11)$) and the efficacy of antiviral treatment, testing, hospitalization and SDPs (parameters ϵ_i $(i = 1, 11)$) has been evaluated through extensive simulations. Figs. 8 and 9 give a glimpse of the effect of changes in these parameters in terms of the cumulative clinically infectious cases. The situations of no interventions versus controls generated scenarios are presented.

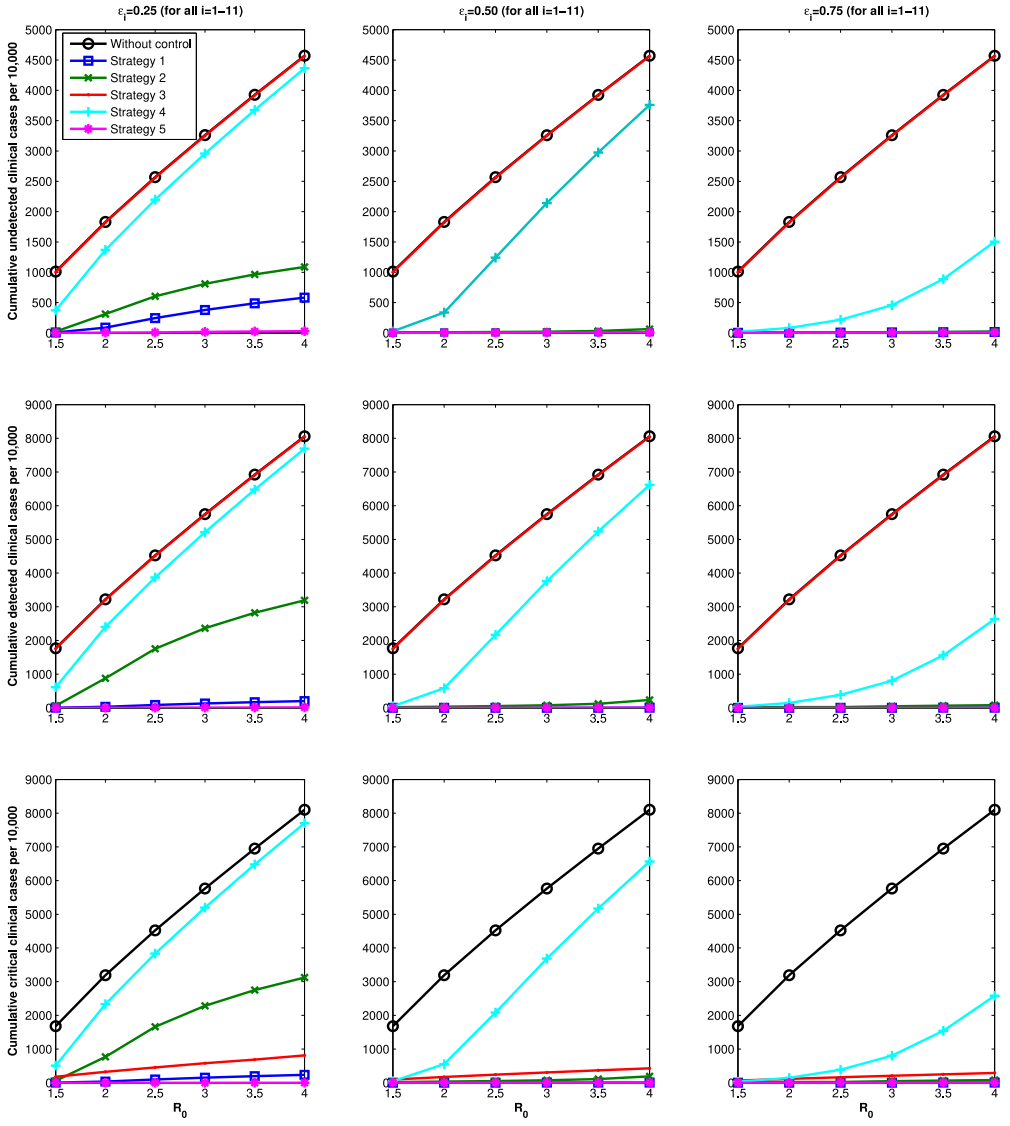

Fig. 9. The cumulative clinical cases are plotted as a function of R_0 for three different values of efficacy, $\epsilon_i = 0.25,\ 0.50,\ 0.75\ (i = 1, 11)$.

3.2.1. *Weight constants impact on controls*

Five selected strategies are compared using different objective functionals (specified in 2). The weight constants role in all five strategies is studied. Still, detailed information of the analyses is not included because the results are not very sensitive to significant changes in these weights. Instead, this lack of sensitivity to weight changes is explained by selected cases. This paper focuses on the role of relative costs because the exact prices are not always known. Fig. 8 illustrates the cumulative clinical cases (under no interventions and all strategies) as a R_0 function using three different weight constants $W_i = 10,\ 50,\ 100\ (i = 1, 11)$. The general shapes of the curves are similar, but the amplitude is slightly changed. As we increase the weight constants, increase the cost of antiviral treatment, testing, hospitalization, and social distancing efforts, the total clinical cases have increased due to reduced intensity in implementing the interventions. When $W_i\ (i = 1, 11)$ changes in the range of 1 − 100, the differences in cumulative numbers of I_U, I_D, and I_D^C are not significant. The weights of Strategy 5 ($C_i\ (i = 1, 5)$) are also analyzed for sensitivity, keeping the cost between 1 and 100. We found that the impact of these changes on the cumulative number of individuals in the I_U, I_D, and I_D^C categories is not that significant.

3.2.2. *Impact of control efficacy*

The effectuality of antiviral treatment, testing, hospitalization, and SDPs is discussed in the range of 0.25–0.75. The parameters $\epsilon_i\ (i = 1, 4)$ respectively quantify the relative efficacy of antiviral treatment for undetected asymptomatic, detected asymptomatic, undetected clinically ill, and detected clinically ill. ϵ_5 and ϵ_6 respectively quantify the relative efficacy of detecting undetected asymptomatic and undetected clinical disease cases while ϵ_7 quantifies the relative effectiveness of hospitalization for critical clinical patients. The parameter $\epsilon_i\ (i = 8, 11)$ quantifies the relative efficacy of social distancing. Fig. 9 illustrates the simulation results of various efficacy measures. The greater the effectiveness, the stronger the influence of the control strategies on reducing the asymptomatic and clinical cases. For $\epsilon_i = 0.75\ (i = 1, 11)$, even at higher R_0 levels, Strategies 1, 2 and 5 support significant reductions. The performance of Strategies 1–5 with each other changes with the effective changes of antiviral treatment, testing, hospitalization, and social distance (Fig. 9).

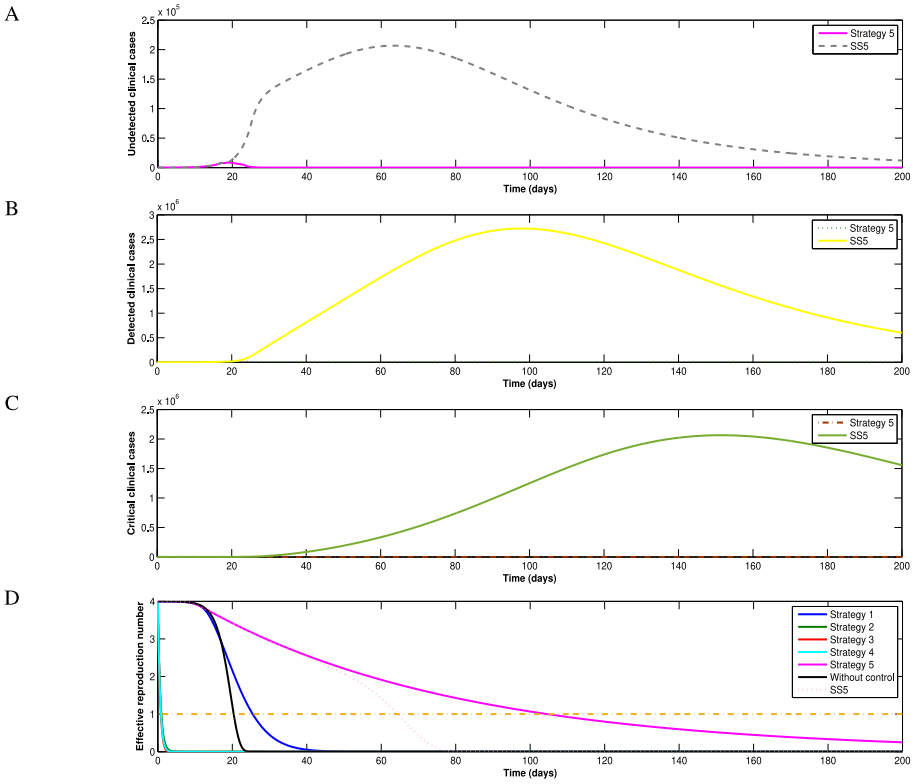

Fig. 10. A, B, C: Daily number of clinical cases are compared for the full optimal (Strategy 5) and corresponding one suboptimal strategy (SS5). D: The effective reproduction numbers are plotted for the full optimal (Strategies 1–5), without optimal and one suboptimal strategy (SS5).

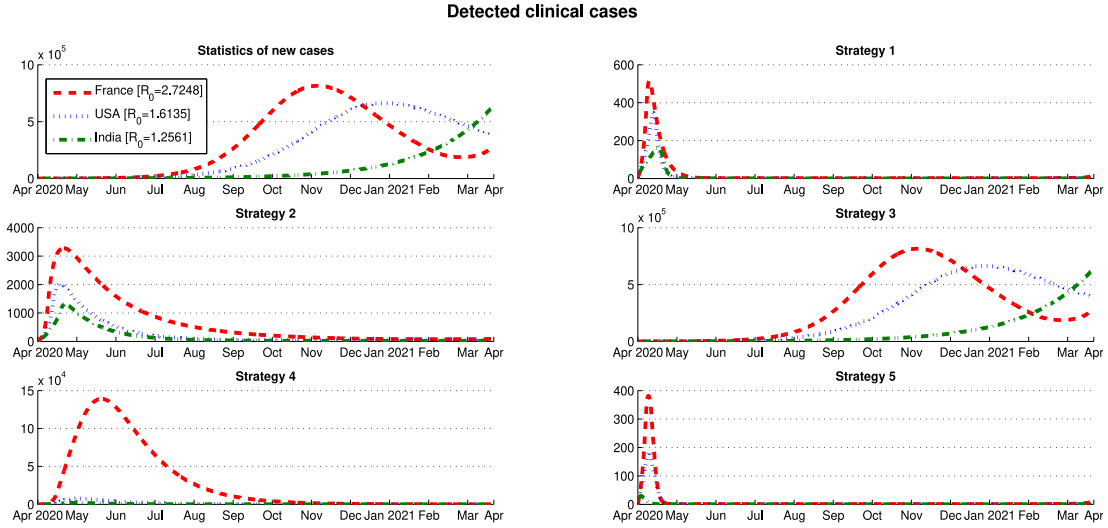

Fig. 11. Comparison of detected clinical cases (I_D) in France, USA, and India, with the impact of control strategies 1, 2, 3, 4, and 5.

3.3. Suboptimal strategies with limited antiviral drugs, ICU resources, testing kits supplies

The expected number of antiviral drugs, testing kits, and ICU resources that can be used for pandemic control are limited worldwide, especially in developing countries. They are almost unavailable in the poorest countries. In introducing limited antiviral drug inventory and testing kits for testing, ICU resources can be implemented in the framework described in this paper. The rest of this section focuses on situations where there are a limited number of antiviral drugs, testing kits, and ICU resources, sufficient to provide antiviral drugs, testing kits, and ICU resource coverage between 5 and 30%. One suboptimal strategy is considered, which involves using antiviral drugs, testing kits, and ICU resources in the clinical infection category. This suboptimal strategy is defined in terms of OC solutions generated without restrictions (Section 3.1). Suboptimal Strategy 5 (SS5) (maximum workload) is constructed based on the optimal solution in the subinterval $[0, T']$ (where $T' \leq T$) and jumps to zero at T', when antiviral drugs, testing kits, ICU resources are consumed. We set the controls to zero in this limited resource situation and solve the state system forward in time for the remaining epidemic duration (when $t > T'$).

Fig. 10 shows the results produced under the full OC and one suboptimal approach (SS5) for Strategy 5. The following expression gives the effective reproduction number

$$\mathcal{R}(t) = \frac{S(t)}{N(t)(\epsilon+\varsigma+\lambda)}\left[\left(\alpha + \frac{\beta\epsilon}{\eta+\rho} + \frac{\gamma\varsigma}{\theta+\mu+k}\right) + \frac{\delta}{\upsilon+\xi}\left(\frac{\eta\epsilon}{\eta+\rho} + \frac{\varsigma\theta}{\theta+\mu+k}\right)\right]$$

which captures the effect of the fraction of susceptible individuals in the population that changes over time $S(t)/N(t)$. To track the impact of the controls, we evaluated the effective reproduction number over time in the control's presence. The curves exhibiting the changes in the effective reproduction numbers as a time function are plotted in Fig. 10(D) under the optimal (unlimited antiviral drugs, testing kits, ICU resources coverage), without optimal and the one suboptimal strategy (limited antiviral drugs, testing kits, ICU resources coverage). With limited antiviral drugs, testing kits, and ICU resources reserve, SS5 reduces the peak size of the epidemic and delays its occurrence. Naturally, early implementation of potent antiviral drugs, testing kits, and ICU resources (with best efforts) can reduce the overall impact of the pandemic.

3.4. Comparative analysis for different R_0

To understand the impact of the presented study, a comparative analysis of three countries, namely France, the USA, and India, with different basic reproduction numbers R_0 [18,19] are depicted in Fig. 11. A cursory glance is enough to clarify that a nation observes an epidemic peak month sooner than other countries if R_0 is higher. Here, France with $R_0 = 2.7248$ faced the peak in November.

After applying all the five strategies, different phenomena can be observed in Fig. 11. Integrated Strategy 5 performs better than the other single strategies 1, 2, 3, and 4. Here, Strategy 3 is not working well because it only works for individuals with severe morbidity (I_D^C). As for Strategies 1, 2, and 4, Strategy 1 is superior to others since the medication is the only source to eradicate an outbreak. In a new disease scenario, someone cannot expect it at the initial stage of the pandemic. As for alternate ways, testing and social distancing strategies (Strategy 2 and 4 respectively) are preferable options.

3.5. Discussion

A year ago, every aspiring individual worldwide wanted to mitigate the effects and spread of the ongoing COVID-19 (SARS-CoV-2) pandemic. The COVID-19 news reporting spread rate even exceeds the extension rate of the worldwide COVID-19 news series [20]. The distinctive, age-related transmission, morbidity, and fatality patterns observed worldwide increase the level of uncertainty inherent in health emergencies [7].

During the outbreak, the major problem is that not all infectious cases are diagnosed. Besides, even if effective diagnostic tools are available, an appropriate response cannot be established quickly enough to reduce the COVID-19 global extend. Even in the wealthiest countries, medical services do not effectively counter the COVID-19 pandemic within the time frame of interest. Public health policy must consider the time delay adverse effects on multiple levels (time interval between the first appearance of symptoms and diagnosis; delayed reporting; emergency facilities limited capacity and presence of antiviral drugs, test kits, and ICU facilities and delay of vaccine access). In the existence of multiple limiting factors, mathematical models provide a feasible, fast, cheap, and effective method to count the impact of local decision-making on disease dynamics at numerous organization levels. Mathematical models can be applied to establish model-ordered questions and answers series. For example, what effect does the time of intervention start on morbidity and fatality? Will using a single control intervention strategy or a comprehensive control intervention strategy make a substantial quantitative difference? Is there a quick and productive way to measure the potential "severity" or spread of an emergency disease? Also, when policies seem to perform poorly, is the situation caused by the timing of the interventions? Even if certain infectious diseases can be effectively implemented, can the dynamic productiveness of the best strategy be easily derailed? Or how do developing countries respond to health emergencies?

Estimating the basic reproduction number R_0 is the first step in evaluating the control interventions' potential impact. Current data shows that the estimated R_0′s value of the ongoing COVID-19 pandemic is within a feasible range; hence timely optimal control measures implementation may significantly differ. However, the gap between theory and application is still significant. Many affected countries cannot obtain sufficient antiviral drugs, testing reagent stocks, and adequate social evacuation facilities. The delay in distributing the appropriate minimum COVID-19 vaccines (in countries with enough funds to purchase these vaccines) means their impact will not be much effective.

Our studies have guided us to some patterns. The simulation outcomes manifest that treating clinical cases in the community (must choose among the strategies presented in this paper) can significantly reduce the incidence of pandemics compared with focusing antiviral resources on hospitalized patients. Model simulations of reasonable "pandemic" R_0 values reveal that quantitatively speaking, using integrated mitigation strategies is much better than using a single strategy instead of when $R_0 > 2$, there is not much that can be done to lessen the impact of the COVID-19 pandemic. The final observation may be crucial for policymakers (they should not promise items that cannot be delivered). Decision-makers should routinely use the estimated value of R_0 to determine the planned diminution measures anticipated impact.

Testing, hospitalization, and social distancing strategies are effective, especially when antiviral drugs are limited or rare. Therefore, the real-time monitoring methods improvement is crucial because the intervention timing is the most sensitive factor in restraining the expansion of COVID-19. If we are to respond to worldwide health threats of this nature effectively, other cost-effective measures must be grasped. A recent article [21] emphasized the tremendous impact that systematic use of face shields and masks can have in reducing the expansion of the pandemic.

The high value of the basic reproduction number R_0 is a terrible message because, in that situation, our "only" hope is to perform the OC strategy immediately. Moreover, in that case, the most effective control strategy is to apply strict SDPs (Strategy 4). To ensure the SDPs properly, the government can introduce a mobile network GPS tracking system [22,23] through which infected individuals can be taken into strict surveillance more effectively. Applying this procedure, Hong Kong already has obtained magnificent outcomes [24].

Epidemics with relatively low R_0 values are most likely to greet control estimations delivered within a "reasonable" time window. Obviously, in both cases, the sooner the control strategy is implemented, the better.

We have determined the delivery patterns of OC strategies. At the beginning of the epidemic, the application of a single control measure (Strategy 3) requires the most significant sustained effort (OC measure). The implementation of comprehensive mitigation strategies (Strategies 1, 2, 4, 5) required a high level of action initially and then suddenly reduced control efforts during the epidemic. Using a single strategy (especially when R_0 is large) cannot prevent epidemic peaks (if symptoms are severe, it is a nightmare for medical institutions). When R_0 is high, the susceptible population must be lower than the critical mass to maintain the outbreak. Compared with a single control strategy, integrated control methods help keep the susceptible population below the critical mass required to maintain an epidemic. The "longer" time window can be conducted in time, thereby reducing the possibility of a prominent epidemic peak. In a longer time frame, the presence of a pool of available susceptible individuals means that control is still feasible, as there are still infections that require to refrain. Compared with the strategies of providing antiviral treatment to infected persons, the usage of SDPs with higher effectiveness is more operative in reducing the transmission rate.

The improvement of policies when resources are short benefits from our research on "immense" resource scenarios. A "sub-optimal" strategy is presented, whose impact is explored under five pre-selected strategies. We observe that under this protocol (maximum) intensified antiviral treatment, testing, ICU facilities implemented at the initial state of the outbreak managed to lessen the outbreak while delaying the peak of the pandemic. Predictions manifest that as the number of available antiviral resources increases, the pandemic's effect is significantly reduced, mainly if the distribution of such antiviral drugs is performed out in conjunction with testing, hospitalization, and social distancing strategy. Moreover, the point should be noted that our model can give a better outcome if implemented correctly; however, a potential drawback of the dynamic models related to epidemics is that it does not focus on age groups or genders. It focuses on the entire population.

4. Conclusion

The nucleus of this research is to determine the benefits of implementing a pandemic COVID-19 mitigation policy that combines pharmacological and non-pharmacological interventions with limited and unlimited resources. Efforts to reduce the COVID-19 pandemic impact may be successful, especially if the R_0 is not an outlier. If the implementation of the intervention is "fast" enough and the policy involves the use of multiple OC strategies (a comprehensive management approach), it can be alleviated. Unless there are minimal resources available, no plan is reasonable. The impact of early intervention on any country will benefit the world. It should be noted that in the COVID-19 pandemic, oxygen supply plays a vital role. However, in the current study, we did not include it in the control model. We will consider it in future research.

Authorship

The International Committee of Medical Journal Editors (ICMJE) recommends that authorship be based on the following four criteria:

Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND.

Drafting the work or revising it critically for important intellectual content; AND.

Final approval of the version to be published; AND.

Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Declaration of competing interest

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

Appendix A

The purpose is to reduce the number of asymptomatic and clinically infected individuals throughout the outbreak of the COVID-19 pandemic within a limited time interval [0, T] with minimum cost. In Eq. (2) the objective functional $\mathcal{F}$ is defined. Our target is to obtain OCs, $u_i^*(t)\ (i=1,11)$, such that

$$\mathcal{F}\left(u_1^*,u_2^*,u_3^*,u_4^*,u_5^*,u_6^*,u_7^*,u_8^*,u_9^*,u_{10}^*,u_{11}^*\right)=\min_{\Omega}\mathcal{F}(u_1,u_2,u_3,u_4,u_5,u_6,u_7,u_8,u_9,u_{10},u_{11}), \tag{A.1}$$

where, $\Omega=\left\{u_i(t)\middle\|\ 0\le u_i(t)\le 1,\ t\in[0,T],\forall i=1,11\right\}$ subject to the system (1) with initial conditions. Given the regularity of criterion (2) and system (1), the standard results in control theory [25] can ensure the existence of OCs. The necessary conditions that optimal solutions must meet come from Pontryagin's Maximum Principle [9]. This principle converts the problem (A.1) into the problem of minimization of Hamiltonian H given by

$$\begin{aligned}
H &= C_1A_U + C_2A_D + C_3I_U + C_4I_D + C_5I_D^C + \sum_{i=1}^{11}\frac{W_i}{2}u_i^2\\
&+\lambda_1(t)\left[-\frac{((1-\epsilon_8u_8)\alpha A_U+(1-\epsilon_9u_9)\beta A_D+(1-\epsilon_{10}u_{10})\gamma I_U+(1-\epsilon_{11}u_{11})\delta I_D)}{N}S\right]\\
&+\lambda_2(t)\left[\frac{((1-\epsilon_8u_8)\alpha A_U+(1-\epsilon_9u_9)\beta A_D+(1-\epsilon_{10}u_{10})\gamma I_U+(1-\epsilon_{11}u_{11})\delta I_D)}{N}S\right.\\
&\left.-((\epsilon+\epsilon_5u_5)+\varsigma+(\lambda+\epsilon_1u_1))A_U\right]\\
&+\lambda_3(t)[(\epsilon+\epsilon_5u_5)A_U-(\eta+(\rho+\epsilon_2u_2))A_D]\\
&+\lambda_4(t)[\varsigma A_U-((\theta+\epsilon_6u_6)+\mu+(k+\epsilon_3u_3))I_U]\\
&+\lambda_5(t)[\eta A_D+(\theta+\epsilon_6u_6)I_U-(\upsilon+(\xi+\epsilon_4u_4))I_D]\\
&+\lambda_6(t)\left[\mu I_U+\upsilon I_D-(\tau+(\sigma+\epsilon_7u_7))I_D^C\right]
\end{aligned}$$

From this Pontryagin's Maximum Principle [9] and Hamiltonian, we obtain.

Theorem 1. *There exist OCs $u_i^*(t)\ (i=1,11)$ and corresponding solutions, S^*, A_U^*, A_D^*, I_U^*, I_D^*, $I_D^{C^*}$, R^*, D^* that minimizes $\mathcal{F}$ over Ω. For the above statement to be true, there must exist continuous functions $\lambda_i(t)$ such that*

$$\begin{cases} \dot{\lambda}_1(t) = (\lambda_1 - \lambda_2)\dfrac{[(1-\epsilon_8 u_8)\alpha A_U + (1-\epsilon_9 u_9)\beta A_D + (1-\epsilon_{10}u_{10})\gamma I_U + (1-\epsilon_{11}u_{11})\delta I_D]}{N}, \\ \dot{\lambda}_2(t) = -C_1 + \dfrac{(\lambda_1-\lambda_2)(1-\epsilon_8 u_8)\alpha S}{N} + (\lambda_2-\lambda_3)(\epsilon+\epsilon_5 u_5) \\ \qquad +(\lambda_2-\lambda_4)\varsigma + \lambda_2(\lambda+\epsilon_1 u_1), \\ \dot{\lambda}_3(t) = -C_2 + \dfrac{(\lambda_1-\lambda_2)(1-\epsilon_9 u_9)\beta S}{N} + (\lambda_3-\lambda_5)\eta + \lambda_3(\rho+\epsilon_2 u_2), \\ \dot{\lambda}_4(t) = -C_3 + \dfrac{(\lambda_1-\lambda_2)(1-\epsilon_{10}u_{10})\gamma S}{N} + (\lambda_4-\lambda_5)(\theta+\epsilon_6 u_6) \\ \qquad +(\lambda_4-\lambda_6)\mu + \lambda_4(k+\epsilon_3 u_3), \\ \dot{\lambda}_5(t) = -C_4 + \dfrac{(\lambda_1-\lambda_2)(1-\epsilon_8 u_8)\delta S}{N} + (\lambda_5-\lambda_6)\upsilon + \lambda_5(\xi+\epsilon_4 u_4), \\ \dot{\lambda}_6(t) = -C_5 + \lambda_6(\tau + (\sigma+\epsilon_7 u_7)), \end{cases} \tag{A.2}$$

with transversality conditions,

$$\lambda_i(T) = 0,\ i = 1,6 \tag{A.3}$$

Also,

$$\begin{cases} u_1^*(t) = \min\left\{\max\left\{0, \epsilon_1 A_U \dfrac{\lambda_2}{W_1}\right\}, 1\right\}, \\ u_2^*(t) = \min\left\{\max\left\{0, \epsilon_2 A_D \dfrac{\lambda_3}{W_2}\right\}, 1\right\}, \\ u_3^*(t) = \min\left\{\max\left\{0, \epsilon_3 I_U \dfrac{\lambda_4}{W_3}\right\}, 1\right\}, \\ u_4^*(t) = \min\left\{\max\left\{0, \epsilon_4 I_D \dfrac{\lambda_5}{W_4}\right\}, 1\right\}, \\ u_5^*(t) = \min\left\{\max\left\{0, \epsilon_5 A_U \dfrac{\lambda_2-\lambda_3}{W_5}\right\}, 1\right\}, \\ u_6^*(t) = \min\left\{\max\left\{0, \epsilon_6 I_U \dfrac{\lambda_4-\lambda_5}{W_6}\right\}, 1\right\}, \\ u_7^*(t) = \min\left\{\max\left\{0, \epsilon_7 I_D^C \dfrac{\lambda_6}{W_7}\right\}, 1\right\}, \\ u_8^*(t) = \min\left\{\max\left\{0, \epsilon_8 \alpha A_U S \dfrac{\lambda_2-\lambda_1}{NW_8}\right\}, 1\right\}, \\ u_9^*(t) = \min\left\{\max\left\{0, \epsilon_9 \beta A_D S \dfrac{\lambda_2-\lambda_1}{NW_9}\right\}, 1\right\}, \\ u_{10}^*(t) = \min\left\{\max\left\{0, \epsilon_{10} \gamma I_U S \dfrac{\lambda_2-\lambda_1}{NW_{10}}\right\}, 1\right\}, \\ u_{11}^*(t) = \min\left\{\max\left\{0, \epsilon_{11} \gamma I_D S \dfrac{\lambda_2-\lambda_1}{NW_{11}}\right\}, 1\right\} \end{cases} \tag{A.4}$$

Proof. The following can be acquired from the Pontryagin's Maximum Principle [9]:

$$\dot{\lambda}_1(t) = -\frac{\partial H}{\partial S},\ \dot{\lambda}_2(t) = -\frac{\partial H}{\partial A_U},\ \dot{\lambda}_3(t) = -\frac{\partial H}{\partial A_D},$$

$$\dot{\lambda}_4(t) = -\frac{\partial H}{\partial I_U},\ \dot{\lambda}_5(t) = -\frac{\partial H}{\partial I_D},\ \dot{\lambda}_6(t) = -\frac{\partial H}{\partial I_D^C},$$

with $\lambda_i(T) = 0,\ i = 1,6$ assessed at the OCs and corresponding states, which outcomes the adjoint system (A.2). The Hamiltonian H is minimized with respect to the controls at the OCs, so we differentiate H with respect to $u_i\left(i = 1,11\right)$ on the set Ω, respectively:

$$\frac{\partial H}{\partial u_1} = W_1 u_1 - \epsilon_1 A_U \lambda_2 = 0 \qquad at\ u_1 = u_1^*,$$

$$\frac{\partial H}{\partial u_2} = W_2 u_2 - \epsilon_2 A_D \lambda_3 = 0 \qquad at\ u_2 = u_2^*,$$

$$\frac{\partial H}{\partial u_3} = W_3 u_3 - \epsilon_3 I_U \lambda_4 = 0 \qquad at\ u_3 = u_3^*,$$

$$\frac{\partial H}{\partial u_4} = W_4 u_4 - \epsilon_4 I_D \lambda_5 = 0 \qquad at\ u_4 = u_4^*,$$

$$\frac{\partial H}{\partial u_5} = W_5 u_5 - \epsilon_5 A_U (\lambda_2 - \lambda_3) = 0 \qquad at\ u_5 = u_5^*,$$

$$\frac{\partial H}{\partial u_6} = W_6 u_6 - \epsilon_6 I_U (\lambda_4 - \lambda_5) = 0 \qquad at\ u_6 = u_6^*,$$

$$\frac{\partial H}{\partial u_7} = W_7 u_7 - \epsilon_7 I_D^C \lambda_6 = 0 \qquad at\ u_7 = u_7^*,$$

$$\frac{\partial H}{\partial u_8} = W_8 u_8 - \epsilon_8 \alpha A_U S \frac{\lambda_2 - \lambda_1}{N W_8} = 0 \qquad at\ u_8 = u_8^*,$$

$$\frac{\partial H}{\partial u_9} = W_9 u_9 - \epsilon_9 \beta A_D S \frac{\lambda_2 - \lambda_1}{N W_9} = 0 \qquad at\ u_9 = u_9^*,$$

$$\frac{\partial H}{\partial u_{10}} = W_{10} u_{10} - \epsilon_{10} \gamma I_U S \frac{\lambda_2 - \lambda_1}{N W_{10}} = 0 \quad at\ u_{10} = u_{10}^*,$$

$$\frac{\partial H}{\partial u_{11}} = W_{11} u_{11} - \epsilon_{11} \gamma I_D S \frac{\lambda_2 - \lambda_1}{N W_{11}} = 0 \quad at\ u_{11} = u_{11}^*.$$

Solving for $u_i^*\left(i = 1, 11\right)$ we obtain

$$u_1^* = \epsilon_1 A_U \frac{\lambda_2}{W_1},\ u_2^* = \epsilon_2 A_D \frac{\lambda_3}{W_2},\ u_3^* = \epsilon_3 I_U \frac{\lambda_4}{W_3},$$

$$u_4^* = \epsilon_4 I_D \frac{\lambda_5}{W_4},\ u_5^* = \epsilon_5 A_U \frac{\lambda_2 - \lambda_3}{W_5},\ u_6^* = \epsilon_6 I_U \frac{\lambda_4 - \lambda_5}{W_6},$$

$$u_7^* = \epsilon_7 I_D^C \frac{\lambda_6}{W_7},\ u_8^* = \epsilon_8 \alpha A_U S \frac{\lambda_2 - \lambda_1}{W_8},\ u_9^* = \epsilon_9 \beta A_D S \frac{\lambda_2 - \lambda_1}{W_9},$$

$$u_{10}^* = \epsilon_{10} \gamma I_U S \frac{\lambda_2 - \lambda_1}{W_{10}},\ u_{11}^* = \epsilon_{11} \gamma I_D S \frac{\lambda_2 - \lambda_1}{W_{11}}.$$

The properties (A.4) are obtained through standard variation arguments with the control ranges.

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