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Optimal Control and Cost-Effectiveness Analysis in an Epidemic Model with Viral Mutation and Vaccine Intervention

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ABSTRACT

The existence of viral mutations in various infectious diseases can make it difficult to overcome outbreaks caused by these viruses. In this paper, we introduce an optimal control problem in a two-strain SIR epidemic model with viral mutation and vaccine administration. The purpose of this study was to investigate the efficacy and cost-effectiveness of two disease prevention strategies, namely restriction of community mobility to prevent disease transmission and vaccine intervention. We consider the time-dependent control case, and we use Pontryagin's Maximum Principle to derive necessary conditions for the optimal control of the disease. We also calculate the Average Cost-Effectiveness Ratio (ACER) and the Incremental Cost-Effectiveness Ratio (ICER) to investigate the cost-effectiveness of all possible strategies of the control measures. The results of this study indicate that the most cost-effective disease control strategy is a combination of mobility restriction and vaccination.

Keywords: Epidemic Model; Cost-Effectiveness Analysis; Numerical Simulation; Optimal Control; Viral Mutation

INTRODUCTION

Epidemiological modeling is a field of mathematical modeling that studies the causes, patterns, and effects of disease on health in a population. The SIR (susceptible, infected, recovered) compartment model that Kermack-McKendrick first introduced in 1927 became the basis for developing models of the spread of infectious diseases. According to the characteristics of the disease, different epidemic models by adding or modifying compartments have been developed and studied. Among them by adding a compartment vaccination [1],[2],[3], treatment [4], quarantine [5], viruses or bacteria that cause disease[6], disease-carrying vectors [7], and others.

In various types of infectious diseases caused by viruses, viruses mutations make the epidemic difficult to overcome immediately. The emergence of new variants of this virus increased the length of the epidemic period. Such conditions are also currently happening in various parts of the world, namely the COVID-19 pandemic. Especially in

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Indonesia, after experiencing a decline in cases for about nine months since the beginning of the pandemic in March 2020, the number of positive COVID-19 cases again increased in mid-June 2021. The Government has taken various policies to be able to end the spread of this COVID-19 disease immediately. Beside targeting vaccinations, the Government is currently implementing Community Activity Restrictions (PPKM) to control the spread of the COVID-19 outbreak. Many mathematical models of COVID-19 have also been developed, as in [5], [8]–[12].

In the last few decade, optimal control theory has developed rapidly, and its diverse applications are widely used in various scientific and engineering fields. This theory has proven to be effective in mathematical epidemiology when it comes to determining how to remove or reduce the number of cases at the lowest possible cost. The optimal control theory has been utilized to capture intervention strategies in many research, see for example [5], [7], [10], [13]–[16] Optimal control models involving vaccination strategies have also been developed, as in [3], [16], [17]. However, these models did not consider the presence of viral mutations that were presumed to be more virulent in the pre-mutated viruses. As in 12 states across the United States, the more easily transmissible strain of SARS-CoV-2, B.1.1.7, has been found [18]. In this article, we will discuss the SIR epidemic model by considering the presence of viral mutations. We are also considering vaccine intervention as one of prevention against diseases. Motivated by this, in this article, we intend to modify the epidemic model with virus mutation and vaccine interventions studied in Adi et al. [19]. Instead of constant parameters of the intervention strategy, we use a control function to express the intervention strategy in this model. The goal is to find the best function for a given control measure by applying Pontryagin's maximum principle [20]. This study also observes which control strategy is the most cost-effective, which is determined through the Average Cost-Effectiveness Ratio (ACER) and the Incremental Cost-Effectiveness Ratio (ICER), as defined in [21]–[24]. Besides being applied to the spread of COVID-19, the model can also be used for other diseases involving viral mutations.

This paper's structure is as follows. The methodologies used in our research are discussed in the following section. After then, the model's analysis was discussed. Finally, we will provide a brief summary of our work.

METHODS

The optimal control problem is analyzed by performing the following steps:

1. We consider a modified SIR epidemic model taking into account the presence of viral mutations and vaccine intervention.
2. Considering a time-dependent constant case-control and using Pontryagin's Maximum Principle to obtain the necessary conditions for optimal disease control.
3. Demonstrating the numerical result of the existence of the optimal control by implementing the forward-backward fourth-order Runge-Kutta method.
4. Computing the Average Cost-Effectiveness Ratio (ACER) and Additional Cost-Effectiveness Ratio (ICER) to investigate the cost-effectiveness of all possible control action strategies.

RESULTS AND DISCUSSION

Formulation of the optimal control problem

Modifying the standard SIR model, Adi et al. [19] have developed an epidemic model taking into account the presence of viral mutations and vaccine interventions. Mutations are recorded in terms that transfer an individual infected with one strain to an individual infected with another strain. The populations subdivided into five classes, which are; Susceptible (S), Infected by strain one (I_1), Infected by strain two (I_2), Vaccinated (V), and Recovered (R). The model is given in (1) below.

$$\begin{aligned}
\frac{dS}{dt} &= \Lambda - \beta_1 S I_1 - \beta_2 S I_2 - \gamma S - \mu S,\\
\frac{dI_1}{dt} &= \beta_1 S I_1 - (\omega + \alpha_1 + c + \mu) I_1,\\
\frac{dI_2}{dt} &= \beta_2 S I_2 + \omega I_1 + (1-\varepsilon) V I_2 - (\alpha_2 + d + \mu) I_2,\\
\frac{dV}{dt} &= \gamma S - (1-\varepsilon) V I_2 - \mu V,\\
\frac{dR}{dt} &= \alpha_1 I_1 + \alpha_2 I_2 - \mu R.
\end{aligned} \tag{1}$$

The first four equations in the system (1) do not depend on R, so to analyze the dynamics of the model, the fifth Equation is neglected. Please refer to [19] for details. Next, paying attention only to the first four equations, we introduce a time-dependent control in the system (1). The purpose is to control the spread of disease and study strategies to eradicate epidemics in a community. We introduce two control functions, $u_1(t)$ and $u_2(t)$, which represent attempts to prevent disease transmission from both viral strains and vaccinations, respectively. The corresponding state system is given by:

$$\begin{aligned}
\frac{dS}{dt} &= \Lambda - (1-u_1(t))(\beta_1 I_1 + \beta_2 I_2) S - u_2(t) S - \mu S,\\
\frac{dI_1}{dt} &= (1-u_1(t))\beta_1 S I_1 - (\omega + \alpha_1 + c + \mu) I_1,\\
\frac{dI_2}{dt} &= (1-u_1(t))\beta_2 S I_2 + \omega I_1 + (1-\varepsilon) V I_2 - (\alpha_2 + d + \mu) I_2,\\
\frac{dV}{dt} &= u_2(t) S - (1-\varepsilon) V I_2 - \mu V,
\end{aligned} \tag{2}$$

where $u_1(t)$ is a control strategy that maintains the state of the uninfected population in the susceptible class and reduces the rate at which individuals leave the susceptible class to the infected class, either by strain one or by strain two, and $u_2(t)$ is a control strategy to increase the number of individuals vaccinated. Medically, considering that both strategies have many limitations so that they are not fully effective, it is realistic to assume that $0 \le u_{i\,max} < 1, i = 1,2$. Hence, the bounded Lebesgue measurable set of admissible control is represented as

$$\Omega = \left\{ \left(u_1(t), u_2(t)\right) | 0 \le u_i(t) \le u_{i\,max}, i = 1,2, t \in [0,T] \right\}. \tag{3}$$

The aim is to gain the optimal value u_i^* of the control $u_i(t)$ in the time interval $[0,T]$, such that the associate state trajectories $X^* = (S^*, I_1^*, I_2^*, V^*)$ are solutions of the system (2) in the interval $[0,T]$ with the initial conditions:

$$S(0) \geq 0, I_1(0) \geq 0, I_2(0) \geq 0, V(0) \geq 0, \tag{4}$$

and u_i^* maximizes the objective function given by:

$$J(u_1, u_2) = \int_0^T \left[w_1 S(t) + w_2 V(t) - w_3 I_1(t) - w_4 I_2(t) - \frac{C_1 u_1^2(t)}{2} - \frac{C_2 u_2^2(t)}{2} \right] dt, \tag{5}$$

with $w_1, w_2, w_3, w_4, C_1, C_2$ are positive weight constant where we want to maximize the susceptibles $S(t)$, and vaccinated individuals $V(t)$, and to minimize both infected individuals by strain one $I_1(t)$ and by strain two $I_2(t)$ (negative sign means maximizing) while keeping prevention cost $u_1(t)$ and vaccination cost $u_2(t)$ low. The cost of the prevention program could come from the implementation of the restriction of citizen mobilization, quarantine, or local lockdowns. At the same time, the cost of vaccination comes from everything needed to implement the vaccination program.

Our optimal control problem is to determining (S^*, I_1^*, I_2^*, V^*) related to an admissible control u_i^* on the time interval $[0, T]$ satisfying Equation (2) and the initial condition of (4) and maximizing the cost functional of Equation (5) such that

$$J(u_1^*, u_2^*) = \max_{\Omega} J(u_1, u_2). \tag{6}$$

Here, we consider that the objective function as a function of u_1 and u_2, so it is concave with respect to the control u_i. From this property and noting that the control system also satisfies the Lipschitz property corresponding to the state variables (S, I_1, I_2, V), it is ensured that the optimal control u of the optimal control problem in Equation (4) exists. Hence, the maximum value can be obtained [25]–[27].

Characteristic of the optimal controls

In order to take advantage the Pontryagin's maximal principle, the system (4) and the objective functional (5) need to be converted into a pointwise Hamiltonian, $\mathcal{H}$ with respect to (u_1, u_2), and we get

$$\begin{aligned} \mathcal{H} &= w_1 S(t) + w_2 V(t) - w_3 I_1(t) - w_4 I_2(t) - \frac{C_1 u_1^2}{2} - \frac{C_2 u_2^2}{2} \\ &+ \lambda_1[\Lambda - (1-u_1)(\beta_1 I_1 + \beta_2 I_2)S - u_2 S - \mu S] \\ &+ \lambda_2[(1-u_1)\beta_1 S I_1 - (\omega + \alpha_1 + c + \mu) I_1] \\ &+ \lambda_3[(1-u_1)\beta_2 S I_2 + \omega I_1 + (1-\varepsilon) V I_2 - (\alpha_2 + d + \mu) I_2] \\ &+ \lambda_4[u_2 S - (1-\varepsilon) V I_2 - \mu V]. \end{aligned} \tag{7}$$

where $\lambda_1, \lambda_2, \lambda_3, \lambda_4$ are the costate variables or adjoint variables associated with the state variables S, I_1, I_2, V. We summarize the necessary conditions for the optimal control $u_i^*, i = 1,2$ in Theorem 1 below.

Theorem 1. *There is an optimal control $u_i^*, i = 1,2$ corresponding to the optimal solution (S^*, I_1^*, I_2^*, V^*) that maximizes the objective functional $J(u_1, u_2)$ over Ω. Moreover, there exist costate variables or adjoint variables, $\lambda_j, j = 1,2,3,4$ that satisfies $\frac{d\lambda_j}{dt} = -\frac{\partial \mathcal{H}}{\partial X}$ with transversality condition $\lambda_j(T) = 0, j = 1,2,3,4$. Furthermore, the associated optimal control $u_i^*, i = 1,2$ are given by*

$$u_1^* = \min\left\{\max\left\{0, \frac{(\lambda_1-\lambda_2)\beta_1 I_1^* S^* + (\lambda_1-\lambda_3)\beta_2 I_2^* S^*}{C_1}\right\}, u_{1\,max}\right\},$$
$$u_2^* = \min\left\{\max\left\{0, \frac{(\lambda_4-\lambda_1)S^*}{C_2}\right\}, u_{2\,max}\right\}. \quad (8)$$

Proof. The adjoint system is derived by taking the partial derivative of the Hamiltonian $\mathcal{H}$ with respect to the associated state variables so that

$$\begin{aligned}
\frac{d\lambda_1}{dt} &= -\frac{\partial \mathcal{H}}{\partial S} = -w_1 + (\lambda_1-\lambda_2)(1-u_1)\beta_1 I_1 + (\lambda_1-\lambda_3)(1-u_1)\beta_2 I_2 \\
&\quad +(u_2+\mu)\lambda_2 - \omega\lambda_3, \\
\frac{d\lambda_2}{dt} &= -\frac{\partial \mathcal{H}}{\partial I_1} = w_3 + (\lambda_1-\lambda_2)(1-u_1)\beta_1 S + (\omega+\alpha_1+c+\mu)\lambda_2 - \omega\lambda_3, \\
\frac{d\lambda_3}{dt} &= -\frac{\partial \mathcal{H}}{\partial I_2} = w_4 + (\lambda_1-\lambda_3)(1-u_1)\beta_2 S + (\alpha_2+d+\mu)\lambda_3 \\
&\quad +(\lambda_4-\lambda_3)(1-\varepsilon)V, \\
\frac{d\lambda_4}{dt} &= -\frac{\partial \mathcal{H}}{\partial V} = -w_2 + (\lambda_4-\lambda_3)(1-\varepsilon)I_2 + \mu\lambda_4,
\end{aligned} \quad (9)$$

along with the transversality conditions $\lambda_j(T) = 0, j = 1,2,3,4$. Then, the optimal control u_i^* are defined by solving $\frac{\partial \mathcal{H}}{\partial u_i} = 0$. This lead to the condition of optimal controls

$$\frac{\partial \mathcal{H}}{\partial u_1} = -C_1 u_1 + (\lambda_1-\lambda_2)\beta_1 I_1^* S^* + (\lambda_1-\lambda_3)\beta_2 I_2^* S^* = 0,$$
$$\frac{\partial \mathcal{H}}{\partial u_2} = -C_2 u_2 + (\lambda_4-\lambda_1)S^* = 0.$$

Hence, we have

$$u_1 = \frac{(\lambda_1-\lambda_2)\beta_1 I_1^* S^* + (\lambda_1-\lambda_3)\beta_2 I_2^* S^*}{C_1},$$
$$u_2 = \frac{(\lambda_4-\lambda_1)S^*}{C_2}. \quad (10)$$

Since $u_i^*, i = 1,2$ must belong to Ω, we get

$$u_1^* = \begin{cases} 0 & , \text{if } u_1 \le 0 \\ \dfrac{(\lambda_1-\lambda_2)\beta_1 I_1^* S^* + (\lambda_1-\lambda_3)\beta_2 I_2^* S^*}{C_1} & , \text{if } 0 < u_1 < u_{1\,max} \\ u_{1\,max} & , \text{if } u_1 \ge u_{1\,max} \end{cases},$$

$$u_2^* = \begin{cases} \dfrac{(\lambda_4-\lambda_1)S^*}{C_2} & , \text{if } u_2 \le 0 \\ & , \text{if } 0 < u_2 < u_{2\,max} \\ & , \text{if } u_2 \ge u_{2\,max} \end{cases}.$$

which can also be characterized by

$$u_1^* = \min\left\{\max\left\{0, \frac{(\lambda_1-\lambda_2)\beta_1 I_1^* S^* + (\lambda_1-\lambda_3)\beta_2 I_2^* S^*}{C_1}\right\}, u_{1\,max}\right\}, \quad (11)$$

$$u_2^* = \min\left\{\max\left\{0, \frac{(\lambda_4 - \lambda_1)S^*}{C_2}\right\}, u_{2\,max}\right\}.$$

This completes the proof.

The following section provides numerical simulations of the optimality system, the control profile, and discussions.

Numerical results and discussion

We observe the optimal trajectories of the optimal system through some numerical simulations. We applied the forward-backward sweep method described in [20], which is very commonly used in the literature of optimal control problems, as in the literature [9], [14], [23]. For numerical simulation, we use a set of parameter values as in [19] and take the weight factor w_1, w_2, w_3, w_4, equal to one $C_1 = 2$, and $C_2 = 2$ due to the lack of the available literature and data. It should be noted that the weight values selected for the simulation are only for the theoretical sense to describe the control strategy proposed in this model. For the maximum control, we set u_1, $u_{1\,max} = 0.5$ under the assumption that it is difficult to maintain community discipline in implementing prevention of disease transmissions such as restrictions on community interaction/mobilization, local lockdown, and quarantine. As for the control with vaccination, $u_{1\,max} = 0.7$ was taken based on the assumption that the vaccine was not yet fully effective and the lack of awareness of the individual to be vaccinated. We will focus on comparing the three control strategies.

- Strategy I: Combination of prevention of disease transmission and vaccination. In this case u_1 and u_2 are defined as control variables.
- Strategy II: Use restrictions on community interaction/mobilization as a control. In this case, only u_1 is taken as a control variable.
- Strategy III: Vaccine intervention as the only control, so only u_2 as the control variable.

Figure 1 shows the impact of implementing various strategies on the population size of $S(t)$ (Fig. 1a) and $V(t)$ (Fig. 1b) for 50 days. It can be seen that without implementing the control strategy, the number of susceptible individuals and vaccinated individuals is lower than if the control strategy is applied. With optimal control strategies, most susceptible individuals will be protected or vaccinated against the virus, thus leading to higher individuals in the vaccinated class (Fig. 1b) and ultimately resulting in fewer individuals being infected by either strain one or strain two see Figure 2.

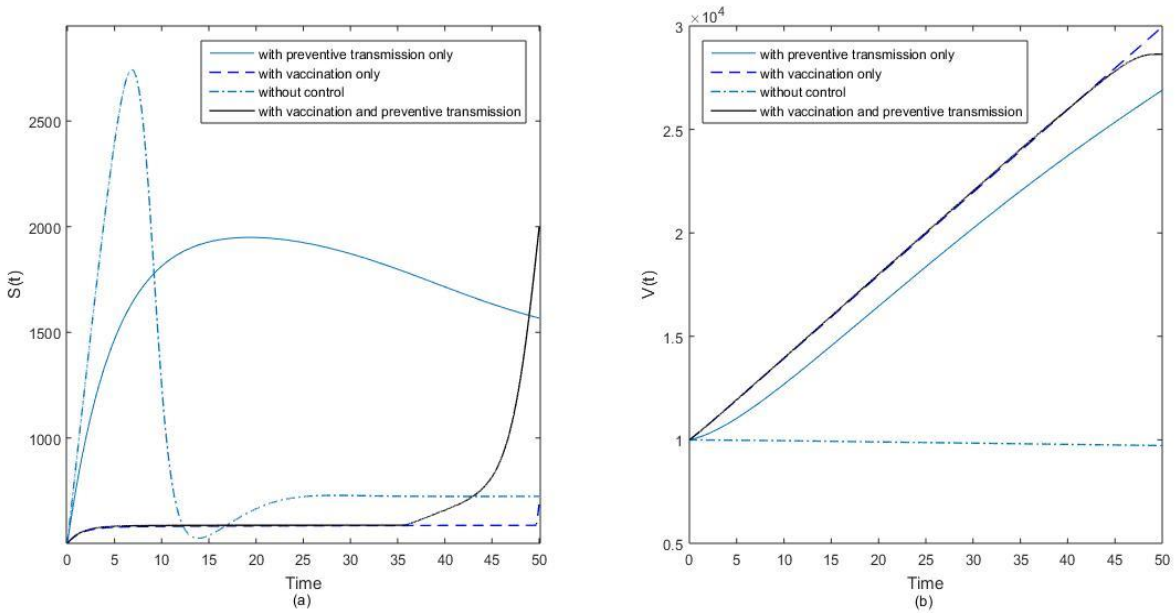
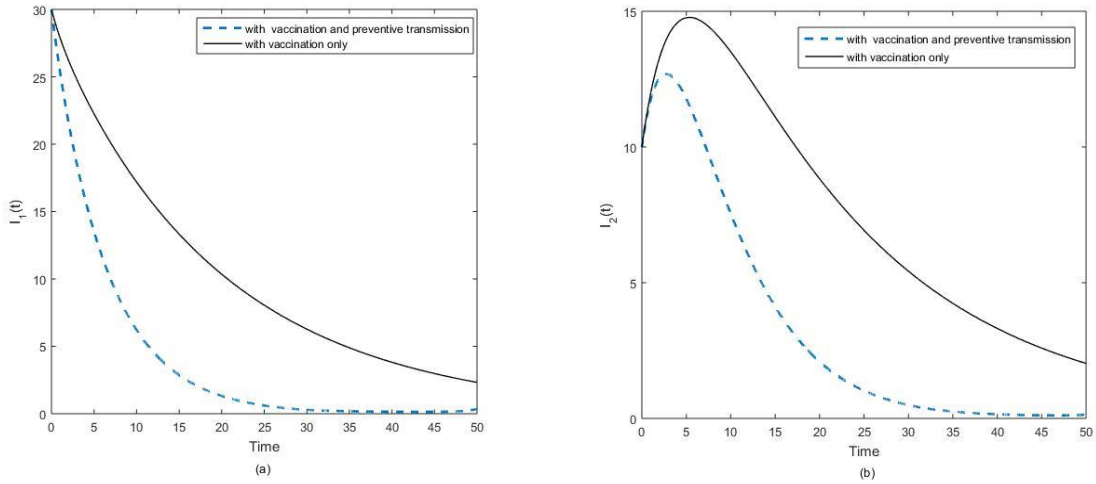


Figure 1. Simulation results without and with the implementation of various control strategies. (a) Susceptible individuals, (b) Vaccinated individuals.

In Figures 2(a) - 2(d), we show the impact of using optimal control strategies on the number of individuals infected by strain one and strain two. This suggests that disease in infectious populations can be reduced more rapidly when both controls are applied (Strategy I) compared to the situation without control or by using a single control, i.e., prevention of transmission only (Strategy II) or vaccination only (Strategy III). From the simulation results, the trajectories of optimal control show that the combination of two control strategies can lead to desired disease control. Fig. 2(a) – 2(b) show a comparison of the number of individuals infected by strains one and by strain two using Strategy I and Strategy III. Figures 2(c) - 2(d) show the situation of individuals infected by strain one and strain two by implementing strategy II and without control strategy. Based on the number of infected individuals, it appears that strategy I is the best strategy that can be applied to end the spread of the disease immediately. The corresponding time-dependent controls $u_1(t)$ and $u_2(t)$ are depicted in Figure 3.



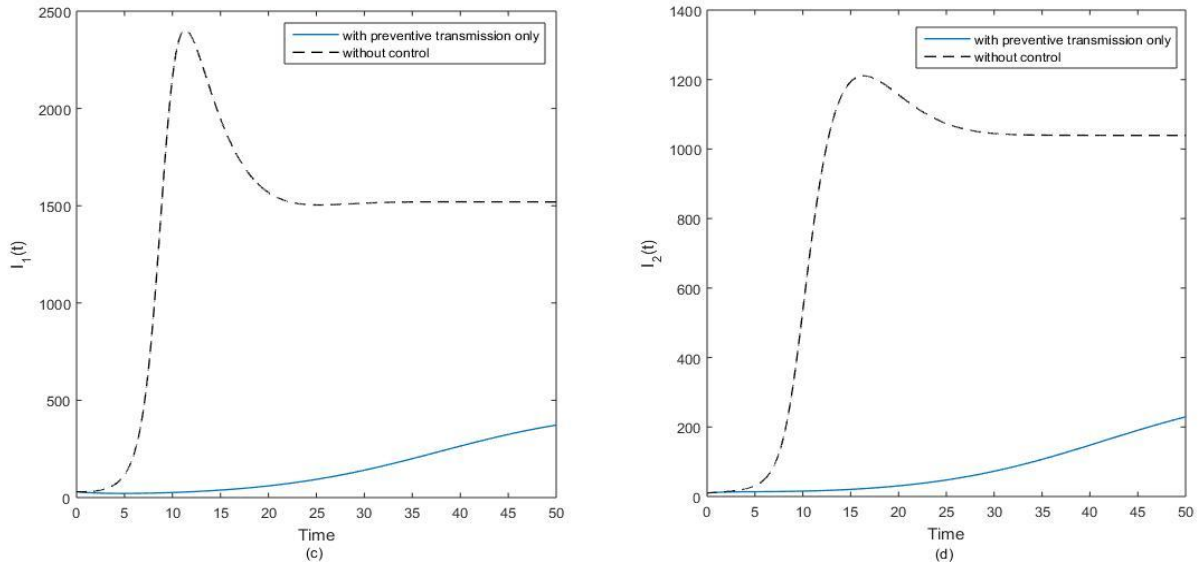
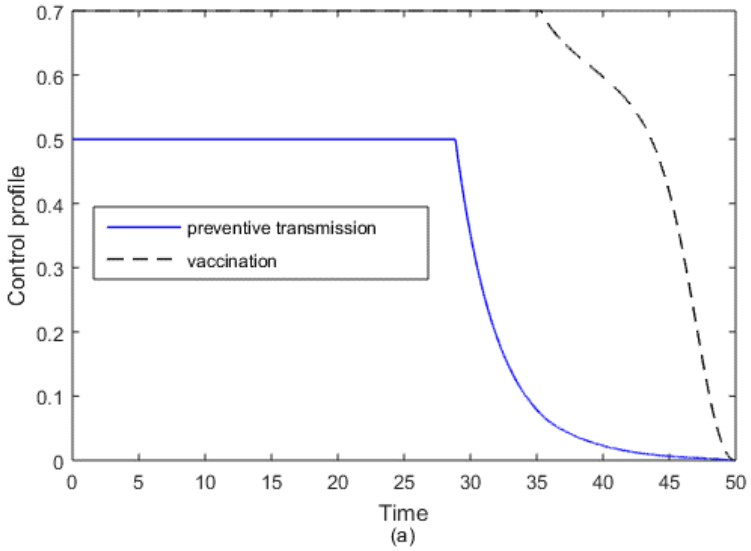


Figure 2. Simulation results for individuals infected by strain one (a), (c) and infected individuals by strain two (b), (d) without and with the implementation of various control strategies.

Figure 3(a) tells us that strategy I can be implemented by maintaining preventive transmission control $u_1(t)$ and vaccination $u_2(t)$ at their upper bounds for about 30 days and 35 days, respectively, and gradually decreasing to their lower bounds. Figure 3(b) illustrates the implementation of Strategy II, which shows that the control $u_1(t)$ is kept at its upper bound over time. While Figure 3(c) shows that if Strategy III is implemented, then the control $u_2(t)$ should be maintained at its upper bound most of the time. When these controls are implemented on a broad scale, it is also critical to adopt an approach that provides optimal cost, i.e., less cost. As a result, we will look at the cost-effectiveness of these controls in the next section.



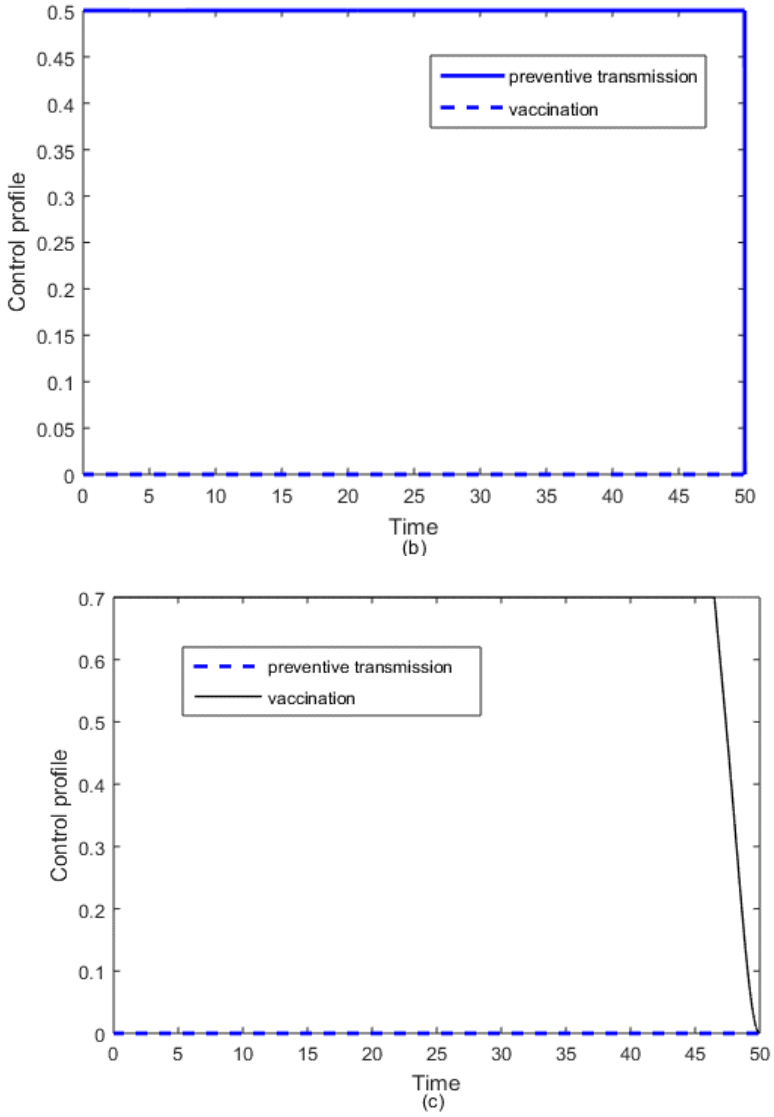


Figure 3. Control profile for each strategy. (a) Strategy I, (b) Strategy II, (c) Strategy III.

Cost-effectiveness analysis

In this section, we use the Average Cost-Effectiveness Ratio (ACER) and the Incremental Cost-Effectiveness Ratio (ICER) to carry out the cost-effectiveness analysis. The average cost-effective ratio (ACER) is calculated as follows [21]:

$$\text{ACER} = \frac{\text{The total cost } (\text{T}_\text{c})}{\text{Total number of infections averted } (\text{T}_\text{a})}. \tag{12}$$

The total number of individuals infected averted during the intervention period T is obtained by using

$$\text{T}_\text{a} = \int_0^T (I_1^* + I_2^*)dt - \int_0^T (I_1 + I_2)dt, \tag{13}$$

where I_1^*, I_2^* are the solution of infected classes by strain one and the infected classes by strain two without controls and I_1, I_2 are the optimal solution with controls. The total

cost implemented during the period T is calculated as follows:

$$\mathrm{T}_c = \int_0^T \frac{1}{2}(C_1 u_1^2 + C_2 u_2^2)dt.$$

Based on this cost analysis, the most cost-effective strategy is the one with the smallest ACER value [23]. Now, we calculate the total cost invested and total infected averted in each strategy to analyze the cost-effectiveness. Using the formula (12), we find that Strategy I has the smallest ACER value and Strategy II has the largest ACER value, as seen in Figure 4. The results are also given in Table 1. Thus, according to the ACER value, the most effective intervention strategy is Strategy I.

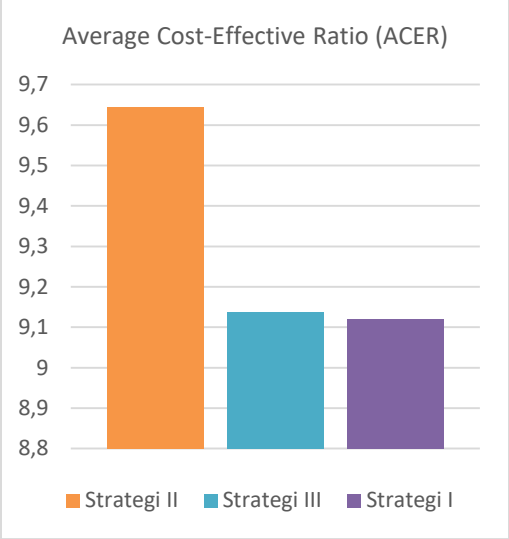


Figure 4. Average cost-effectiveness ratio (ACER) results for Strategy I – III

The ICER, on the other hand, is calculated by dividing the cost difference between two feasible interventions by the difference in their effects. Mathematically, it is expressed as [22], [24]:

$$\mathrm{ICER} = \frac{\text{Difference in costs produced by strategies i and j}}{\text{Difference in the total number of infection averted in strategies i and j}}. \quad (14)$$

The difference between the total number of infected individuals without controls and the total number of infected individuals with controls is used to compute the total number of averted infections. Furthermore, we employed the cost functions $\frac{C_1}{2}u_1^2$ and $\frac{C_2}{2}u_2^2$ across time to calculate the total cost of the implemented strategies. We also used the parameter values from the preceding section to calculate the total cost and total infections averted, as shown in Table 1, with total averted infections are ranked according to their increasing in order. Then, the ICER is calculated using the formula in (14). First, we computed for the competing strategies II and III as follows:

$$\mathrm{ICER\ (II)} = \frac{989{,}582.93 - 0}{102{,}599{,}77 - 0} = 9.6451,$$
$$\mathrm{ICER\ (III)} = \frac{1{,}026{,}524.16 - 989{,}582.93}{112{,}334.16 - 102{,}599{,}77} = 3.7949.$$

The results of the ICER computation (as shown in Table 1) show that strategy II has a

higher ICER value than strategy III. As a result, implementing prevention transmission control u_1 alone is more expensive and ineffective than using Vaccine intervention control u_2. As a result, Strategy II is removed from the list of possible control strategies. The ICER for Strategies III and I now need to be recalculated. The calculation is as follows:

$$\text{ICER (III)} = \frac{1{,}026{,}524.16}{112{,}334.16} = 9.1381,$$

$$\text{ICER (I)} = \frac{1{,}029{,}506.04 - 1{,}026{,}524.16}{112{,}886.09 - 112{,}334.16} = 5.4026.$$

Table 2 summarizes the results of the calculations.

Table 1. Strategies I – III in order of increasing number of averted infected

Strategy	Total infected averted	Total cost	ACER	ICER
Strategy II	102,599.77	989,582.93	9.6451	9.6451
Strategy III	112,334.16	1,026,524.16	9.1381	3.7949
Strategy I	112,886.09	1,029,506.04	9.1199	-

Table 2. Comparison between Strategies III and I

Strategy	Total infected averted	Total cost	ICER
Strategy III	112,334.16	1,026,524.16	9.1381
Strategy I	112,886.09	1,029,506.04	5.4026

It is clearly shown from Table 2 that Strategy III has an ICER value greater than Strategy I. Therefore, due to its cost-effectiveness and health benefits, Strategy I, that combination of prevention of disease transmission and vaccination, is the best of all possible options.

CONCLUSIONS

This paper has presented and analyzed a modified SIR epidemic model considering a time-dependent constant control that includes two control variables. The two control variables considered in this model are prevention of disease transmission, such as by restricting community interactions and administering vaccines. Numerical simulation of the optimal control problem was carried out using three strategies. Strategy I, a combination of prevention of disease transmission and vaccination, Strategy II, only prevention of disease transmission by restriction community interaction is taken as a control variable, and Strategy III, if the vaccine intervention is the only intervention carried out. All strategies show control profiles adjusted for the number of infected individuals in the community. Stronger interventions are needed to substantially reduce the number of infected individuals and the cost of implementing the strategy. Furthermore, analysis to determine the most cost-effective strategy was carried out using ACER and ICER. Based on calculating ACER and ICER, we found that using both controls simultaneously was the most cost-effective method and vaccination was the most cost-effective method in a single intervention. When only one intervention is applied, our simulations reveal that vaccination is the best single intervention strategy. However, the combination of vaccination and the restriction of community interactions, i.e., Strategy I, gave the best results in reducing the number of infected individuals with the cheapest cost compared to a single intervention strategy. We think that our work

will serve as a foundation for mathematical models that examine cost-effectiveness analyses using real-world data, especially on an epidemic model which considers viral mutation and vaccination.

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