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*Research article*

# Optimal control for co-infection with COVID-19-Associated Pulmonary Aspergillosis in ICU patients with environmental contamination

**Nandhini Mohankumar[1], Lavanya Rajagopal[1] and Juan J. Nieto[2,*]**

[1] Department of Mathematics, Coimbatore Institute of Technology, Tamilnadu, India

[2] CITMAga, Departamento de Estatística, Análise Matemática e Optimización, Universidade de Santiago de Compostela, 15782 Santiago de Compostela, Spain

* **Correspondence:** Email: juanjose.nieto.roig@usc.es.

**Abstract:** In this paper, we propose a mathematical model for COVID-19-Associated Pulmonary Aspergillosis (CAPA) co-infection, that enables the study of relationship between prevention and treatment. The next generation matrix is employed to find the reproduction number. We enhanced the co-infection model by incorporating time-dependent controls as interventions based on Pontryagin's maximum principle in obtaining the necessary conditions for optimal control. Finally, we perform numerical experiments with different control groups to assess the elimination of infection. In numerical results, transmission prevention control, treatment controls, and environmental disinfection control provide the best chance of preventing the spread of diseases more rapidly than any other combination of controls.

**Keywords:** co-infection; CAPA; hospital environment; reproduction number; optimal control

## 1. Introduction

The world is in the grip of a pandemic triggered by SARS-CoV-2, which has infected more than 24 million people with a mortality rate exceeding 3 percent. There weren't many reports of super infections during the early stages of the current pandemic, but now they seem to be occurring more frequently, specifically secondary fungal diseases [1]. Patients with COVID-19 have been diagnosed with viral, bacterial, and fungal co-infections. Early detection of these co-infections is crucial to implementing an effective antimicrobial regime [2]. COVID-19 patients have suffered from several fatal complications. Invasive pulmonary aspergillosis (IPA) was associated with a poor prognosis, particularly among those experiencing acute respiratory distress syndrome (ARDS) in intensive care units [3].

According to reports, 19 to 35 percent of COVID-19 patients have co-infection with Aspergillus. As

a result, it causes the novel disease phenomenon known as CAPA (COVID-19-Associated Pulmonary Aspergillosis), which can further worsen the prognosis of these patients [4]. Upon infection with SARS-CoV-2, direct damage to the respiratory epithelium allows Aspergillus species to invade the respiratory tract. Patients with CAPA had a high prevalence of chronic cardiovascular disease, renal failure, diabetes mellitus, and corticosteroid use [5]. In COVID-19 patients, CAPA led to a marked increase in mortality, with severity varying depending on the type of treatment [6].

Several early reports indicate that a diagnosis may prove challenging in patients with suspected CAPA. In patients with COVID-19, diagnosing airway-invasive Aspergillosis poses a challenge due to the low prevalence of diagnostic bronchoscopy, a measure to protect healthcare workers from aerosol inhalation, and galactomannan being difficult to detect in serum [7, 8]. Aspergillus commonly appears in upper respiratory tract specimens such as sputum or aspirate. However, it is difficult to distinguish between colonization and invasive infection [9, 10]. Fungus culture and galactomannan tests assist in the diagnosis of early cases, especially in respiratory specimens. The most common species responsible for co-infections among COVID-19 patients was Aspergillus fumigatus and Aspergillus flavus [11]. Patients with severe/critical COVID-19 should continue monitoring for the possibility of Pulmonary Aspergillosis, and aggressive microbiologic testing would also be recommended, along with SARS-CoV-2 [12].

The advent of mathematical models that can be employed to investigate infectious diseases over the last decade led to the development of mathematical epidemiology [13, 14]. Numerous co-infection model for two different diseases has been proposed and analyzed for both co-infection and secondary infection. To the best of our knowledge, this is the first mathematical model to capture the interactions between COVID-19 and Pulmonary Aspergillosis.

The models incorporate COVID-19 with various diseases, such as tuberculosis, bacterial pneumonia, etc, [15, 16] are studied recently. COVID-19-associated Pulmonary Aspergillosis has not been adequately addressed in many of the models. Simulations of co-infection through a population are more realistic when individuals interact with each other and the hospital environment is incorporated into epidemic models. In advance of an outbreak of an epidemic, public health officials can utilize these models to study the epidemic's spread and develop potential response strategies.

This study provides a comprehensive analysis of the dynamics of COVID-19-associated Pulmonary Aspergillosis after taking into consideration the factors outlined in the literature. The present paper contributes to the understanding of co-infections, including COVID-19 and pulmonary aspergillosis. This model is helpful for the prevention and control of emerging secondary infections with COVID-19. In addition, it can be used to study the development of drug-resistant strains such as malaria, tuberculosis, and Methicillin-resistant Staphylococcus aureus (MRSA). The co-dynamics of the COVID-19-Associated Pulmonary Aspergillosis has not been formulated by any of the existing studies within the field. The model is focused on co-infection of CAPA in hospital environment by including the environmental factors in hospital.

In this paper, we incorporate five different control variables into a mathematical model of COVID-

19-Associated Pulmonary Aspergillosis to determine the best approach to controlling the spread of both diseases. The goal of this investigation is to understand dynamics better through further analysis. Accordingly, section 1 provides a model description along with an overview of potential assumptions underlying the model. Section 2 determines the reproduction number based on the next generation matrix. In section 3, a detailed optimal control analysis is performed on the co-infection model. In section 4, we discuss quantitative results obtained by the optimality system.

## 2. Mathematical model

In this section, we present a mathematical model that predicts the dynamics of COVID-19-Associated Pulmonary Aspergillosis among the intensive care unit patients. Accordingly, the total number of patients in ICU counts as the total population and is further divided into $S_p$, susceptible patients in ICU $I_c$, patients who are infected with COVID-19 only $I_a$, patients who have Pulmonary Aspergillosis only $I_{ca}$, patients who have both COVID-19 and Pulmonary Aspergillosis $R_c$, patients who are recovered from COVID-19 $R_a$, patients who have recovered from Pulmonary Aspergillosis $R_{ca}$, patients who have recovered from both COVID-19 and Pulmonary Aspergillosis $F_L$, fungal load in the hospital environment. The following are the assumptions of the model:

1. COVID-19 is not a direct cause of Pulmonary Aspergillosis but the patients receiving severe treatment for the infection are at higher risk.
2. Patients are admitted into the intensive care unit at rate of $A$.
3. Pulmonary Aspergillosis is transmitted through environment and colonized patients.
4. The hospital environment is infected by infected patients and the equipments infected by them.
5. Infected hospital environment is decontaminated using the disinfectants.

The Total human population $N(t)$ is

$$N(t) = S_p + I_c + I_a + I_{ca} + R_c + R_a + R_{ca}$$

The coinfection model is formulated as

$$\begin{aligned}
\frac{dS_p}{dt} &= A - \beta_c S_p I_c - \beta_F S_p F_L - (d' + \mu_p) S_p \\
\frac{dI_c}{dt} &= \beta_c S_p I_c - \beta_h F_L I_c - (d_c + \gamma_c + \mu_p) I_c + \psi_a I_{ca} \\
\frac{dI_a}{dt} &= \beta_F S_p F_L - \beta_a I_c I_a - (d_a + \gamma_a + \mu_p) I_a + \psi_c I_{ca} \\
\frac{dI_{ca}}{dt} &= \beta_h F_L I_c + \beta_a I_c I_a - (\psi_a + \mu_p + \psi_c + \gamma_{ca} + d_{ca}) I_{ca} \\
\frac{dR_c}{dt} &= \gamma_c I_c - \mu_p R_c \\
\frac{dR_a}{dt} &= \gamma_a I_a - \mu_p R_a \\
\frac{dR_{ca}}{dt} &= \gamma_{ca} I_{ca} - \mu_p R_{ca}
\end{aligned} \tag{2.1}$$

$$\frac{dF_l}{dt} = \kappa_F I_a + (\delta_F - \phi_F)F_l$$

Here,
$A$ - admission rate of patients in ICU,
$\beta_c$ - transmission rate of COVID-19 infection from COVID-19 infected patients,
$\beta_F$ - transmission rate of Aspergillus fungal infection from environment,
$\beta_h$ - transmission rate of Aspergillus fungal infection to COVID-19 patients,
$\beta_a$ - transmission rate of COVID-19 infection to Pulmonary Aspergillosis patients,
$d'$ - discharge rate of ICU patients,
$\mu_p$ - death rate of ICU patients,
$d_c$ - disease induced mortality rate of COVID-19 patients,
$d_a$ - disease induced mortality rate of Pulmonary Aspergillosis patients,
$d_{ca}$ - disease induced mortality rate of COVID-19 associated Pulmonary Aspergillosis patients,
$\gamma_c$ - recovery rate of COVID-19 patients,
$\gamma_a$ - recovery rate of Pulmonary Aspergillosis patients,
$\gamma_{ca}$ - recovery rate of COVID-19-Associated Pulmonary Aspergillosis patients,
$\kappa_F$ - rate of use of contaminated medical equipment by Pulmonary Aspergillosis infected patients,
$\delta_F$ - rate of contamination in hospital environment,
$\phi_F$ - disinfection of hospital environment,
$\psi_c$ - co-infected patients who are recovered from COVID-19,
$\psi_a$ - co-infected patients who are recovered from Pulmonary Aspergillosis,

## 3. Basic Reproduction number

Consider the following infected class equations to derive the reproduction number [17].

$$\begin{aligned}
\frac{dI_c}{dt} &= \beta_c S_p I_c - \beta_h F_L I_c - (d_c + \gamma_c + \mu_p)I_c + \psi_a I_{ca} \\
\frac{dI_a}{dt} &= \beta_F S_p F_L - \beta_a I_c I_a - (d_a + \gamma_a + \mu_p)I_a + \psi_c I_{ca} \\
\frac{dI_{ca}}{dt} &= \beta_h F_L I_c + \beta_a I_c I_a - (\psi_a + \mu_p + \psi_c + \gamma_{ca} + d_{ca})I_{ca} \\
\frac{dF_l}{dt} &= \kappa_F I_a + (\delta_F - \phi_F)F_l
\end{aligned} \tag{3.1}$$

The matrix form of (3.1) is decomposed as $F$ and $V$ matrices, where

$$F = \begin{bmatrix} 0 & 0 & \frac{\beta_c A}{\mu_p} & \frac{\beta_c A}{\mu_p} \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix}$$

$$V = \begin{bmatrix} d_c + \gamma_c + \mu_p & 0 & -\psi_a & 0 \\ 0 & d_a + \gamma_a + \mu_p + \rho_a & -\psi_c & 0 \\ 0 & 0 & \psi_a + \mu_p + \psi_c + \gamma_{ca} + d_{ca} & 0 \\ 0 & -\kappa_F & 0 & \phi_F - \delta_F \end{bmatrix}$$

The spectral radius of the $FV^{-1}$ is

$$R_0 = \frac{A\left[\beta_c\left(d_a + \gamma_a + \mu_p + \rho_a\right)(\phi_F - \delta_F) + \beta_F \kappa_F \psi_c\right]}{\mu_p\left(\psi_a + \mu_p + \psi_c + \gamma_{ca} + d_{ca}\right)\left(d_a + \gamma_a + \mu_p + \rho_a\right)(\phi_F - \delta_F)} \tag{3.2}$$

## 4. Optimal control

To minimize the number of infectious patients and increase the number of recovered patients, we reconsider the system (2.1) and use five control variables to reduce the infection spread. Based on the model (2.1), five control measures served as control functions, where $w_1$ represents standard contact precautions implemented in ICU's, $w_2$ represents treatment for COVID-19, $w_3$ represents treatment for Pulmonary Aspergillosis, $w_4$ represents treatment for COVID-19-Associated Pulmonary Aspergillosis, $w_5$ represents HVAC system maintenance that limits the spread of airborne viruses and fungi in the environment. We have revised the model (2.1) by including control variables. The model is structured as follows:

$$\begin{aligned}
\frac{dS_p}{dt} &= A - (1-w_1)\beta_c S_p I_c - (1-w_1)\beta_F S_p F_L - (d' + \mu_p) S_p \\
\frac{dI_c}{dt} &= (1-w_1)\beta_c S_p I_c - (1-w_1)\beta_h F_L I_c - (d_c + \gamma_c + \mu_p + w_2) I_c + \psi_a I_{ca} \\
\frac{dI_a}{dt} &= (1-w_1)\beta_F S_p F_L - (1-w_1)\beta_a I_c I_a - (d_a + \gamma_a + \mu_p + w_3) I_a + \psi_c I_{ca} \\
\frac{dI_{ca}}{dt} &= (1-w_1)\beta_h F_L I_c + (1-w_1)\beta_a I_c I_a - (\psi_a + \mu_p + \psi_c + \gamma_{ca} + d_{ca} + w_4) I_{ca} \\
\frac{dR_c}{dt} &= (\gamma_c + w_2) I_c - \mu_p R_c \\
\frac{dR_a}{dt} &= (\gamma_a + w_3) I_a - \mu_p R_a \\
\frac{dR_{ca}}{dt} &= (\gamma_{ca} + w_4) I_{ca} - \mu_p R_{ca} \\
\frac{dF_l}{dt} &= \kappa_F I_a + (\delta_F - \phi_F - w_5) F_l
\end{aligned} \tag{4.1}$$

We define

$$J(w_1, w_2, w_3, w_4, w_5) = \int_0^T \left[ I_c + I_a + I_{ca} + F_L + \frac{r_1 w_1^2}{2} + \frac{r_2 w_2^2}{2} + \frac{r_3 w_3^2}{2} + \frac{r_4 w_4^2}{2} + \frac{r_5 w_5^2}{2} \right] dt$$

Here, the coefficients $r_1, r_2, r_3, r_4$ and $r_5$ represent balancing costs.

*4.1. Analysis of optimal control*

In order to calculate the objective functional, we use the Hamiltonian constructed from the model system of equations with the necessary adjoint functions. Let $\lambda_{S_p}, \lambda_{I_c}, \lambda_{I_a}, \lambda_{I_{ca}}, \lambda_{R_c}, \lambda_{R_a}, \lambda_{R_{ca}}$ and $\lambda_{F_L}$ be the co-state variables associated with state variables.

$$\begin{aligned} H =& I_c + I_a + I_{ca} + F_L + \frac{r_1 w_1^2}{2} + \frac{r_2 w_2^2}{2} + \frac{r_3 w_3^2}{2} + \frac{r_4 w_4^2}{2} + \frac{r_5 w_5^2}{2} + \lambda_{S_p}\frac{dS_p}{dt} + \lambda_{I_c}\frac{dI_c}{dt} \\ &+ \lambda_{I_a}\frac{dI_a}{dt} + \lambda_{I_{ca}}\frac{dI_{ca}}{dt} + \lambda_{R_c}\frac{dR_c}{dt} + \lambda_{R_a}\frac{dR_a}{dt} + \lambda_{R_{ca}}\frac{dR_{ca}}{dt} + \lambda_{F_L}\frac{dF_L}{dt} \end{aligned} \tag{4.2}$$

Based on Pontryagin's maximum principle, [18, 19] we can derive existence results for the optimal control from [20]. There exist an optimal control $w_1^*, w_2^*, w_3^*, w_4^*, w_5^*$ and associated solutions, $S_p^*, I_c^*, I_a^*, I_{ca}^*, R_c^*, R_a^*, R_{ca}^*$ and $F_L^*$, that minimizes $J(w_1, w_2, w_3, w_4, w_5)$. Additionally, there are adjoint functions, $\lambda_{S_p}, \lambda_{I_c}, \lambda_{I_a}, \lambda_{I_{ca}}, \lambda_{R_c}, \lambda_{R_a}, \lambda_{R_{ca}}$ and $\lambda_{F_L}$, such that

$$\begin{aligned} \frac{d\lambda_{S_p}}{dt} =& (\lambda_{S_p} - \lambda_{I_c})(1-w_1)\beta_c I_c + (\lambda_{S_p} - \lambda_{I_a})(1-w_1)\beta_F F_L + \lambda S_p(d' + \mu_p) \\ \frac{d\lambda_{I_c}}{dt} =& -1 + (\lambda_{S_p} - \lambda_{I_c})(1-w_1)\beta_c S_h + (\lambda_{I_c} - \lambda_{I_{ca}})(1-w_1)\beta_h F_L + (\lambda_{I_a} - \lambda_{I_{ca}}) \\ & (1-w_1)\beta_a I_a + \lambda_{I_c}(d_c + \gamma_c + \mu_p + w_2) - \lambda_{R_c}(\gamma_c + w_2) \\ \frac{d\lambda_{I_a}}{dt} =& -1 + (\lambda_{I_a} - \lambda_{I_{ca}})(1-w_1)\beta_a I_c + \lambda_{I_a}(d_a + \gamma_a + \mu_p + w_3) - \lambda_{R_a}(\gamma_a + w_3) \\ & - \lambda_{F_L}\kappa_F \\ \frac{d\lambda_{I_{ca}}}{dt} =& -1 + (\lambda_{I_{ca}} - \lambda_{I_c})\psi_a + (\lambda_{I_{ca}} - \lambda_{I_a})\psi_c + \lambda_{I_{ca}}(\mu_p + \gamma_{ca} + d_{ca} + w_3) \\ & - \lambda_{R_{ca}}(\gamma_{ca} + w_4) \\ \frac{\lambda_{R_c}}{dt} =& \lambda_{R_c}\mu_p \\ \frac{\lambda_{R_a}}{dt} =& \lambda_{R_a}\mu_p \\ \frac{\lambda_{R_{ca}}}{dt} =& \lambda_{R_{ca}}\mu_p \\ \frac{\lambda_{F_L}}{dt} =& -1 + (\lambda_{S_p} - \lambda_{I_a})(1-w_1)\beta_F S_p + (\lambda_{I_c} - \lambda_{I_{ca}})(1-w_1)\beta_h I_c - \lambda_{F_L}(\delta_F - \phi_F - w_5) \end{aligned}$$

with transversality conditions $\lambda_{S_p}(T) = \lambda_{I_c}(T) = \lambda_{I_a}(T) = \lambda_{I_{ca}}(T) = \lambda_{R_c}(T) = \lambda_{R_a}(T) = \lambda_{R_{ca}}(T) = \lambda_{F_L}(T) = 0$. By Pontryagin's maximum principle, we have evaluated the optimal control and corresponding state variables. By considering the optimality condition and obtaining solution for $w_1^*(t), w_2^*(t), w_3^*(t), w_4^*(t), w_5^*(t)$ gives

$$\begin{aligned}
\frac{dH}{dw_1} =& r_1 w_1 + (\lambda_{S_p} - \lambda_{I_c})\beta_c S_p I_c + (\lambda_{S_p} - \lambda_{I_a})\beta_F S_p F_L + (\lambda_{I_c} - \lambda_{I_{ca}})\beta_h F_L I_c \\
&+ (\lambda_{I_a} - \lambda_{I_{ca}})\beta_a I_c I_a \\
\frac{dH}{dw_2} =& r_2 w_2 + (\lambda_{R_c} - \lambda_{I_c}) I_c \\
\frac{dH}{dw_3} =& r_3 w_3 + (\lambda_{R_a} - \lambda_{I_a}) I_a \\
\frac{dH}{dw_4} =& r_4 w_4 + (\lambda_{R_{ca}} - \lambda_{I_{ca}}) I_{ca} \\
\frac{dH}{dw_5} =& r_5 w_5 - \lambda_{F_L} F_L
\end{aligned}$$

After some manipulations, the optimal control $w_1^*(t)$ is characterised as

$$w_1^*(t) = max\left\{0, min\left\{1, \frac{(\lambda_{I_c} - \lambda_{S_p})\beta_c S_p I_c + (\lambda_{I_a} - \lambda_{S_p})\beta_F S_p F_L + (\lambda_{I_{ca}} - \lambda_{I_c})\beta_h F_L I_c + (\lambda_{I_{ca}} - \lambda_{I_a})\beta_a I_c I_a}{r_1}\right\}\right\} \tag{4.3}$$

Similarly the optimal controls $w_2^*(t), w_3^*(t), w_4^*(t), w_5^*(t)$ are characterised as

$$\begin{aligned}
w_2^* &= max\left\{0, min\left\{1, \frac{(\lambda_{I_c} - \lambda_{R_c})I_c}{r_2}\right\}\right\} \\
w_3^* &= max\left\{0, min\left\{1, \frac{(\lambda_{I_a} - \lambda_{R_a})I_a}{r_3}\right\}\right\} \\
w_4^* &= max\left\{0, min\left\{1, \frac{(\lambda_{I_{ca}} - \lambda_{R_{ca}})I_{ca}}{r_4}\right\}\right\} \\
w_5^* &= max\left\{0, min\left\{1, \frac{\lambda_{F_L} F_L}{r_5}\right\}\right\}
\end{aligned}$$

The state system (4.1), its initial conditions, the adjoint system, the transversality conditions and the optimality conditions (4.3) are compromised by the optimality system.

## 5. Numerical simulation

In this section, we solve the optimality system numerically and evaluate different control strategies according to their sensitivity to the system. By solving the state system forward through time and the adjoint system backward through time, the initial values of the controls are determined, and the optimality conditions are adjusted for subsequent iterations. For the numerical simulation, Table 1 shows the values of the relevant parameters. We propose the following strategies for assessing the effectiveness of control efforts on the system (1):

1. Strategy 1 : Transmission prevention ($w_1$)
2. Strategy 2 : Treatment for COVID-19 ($w_2$)

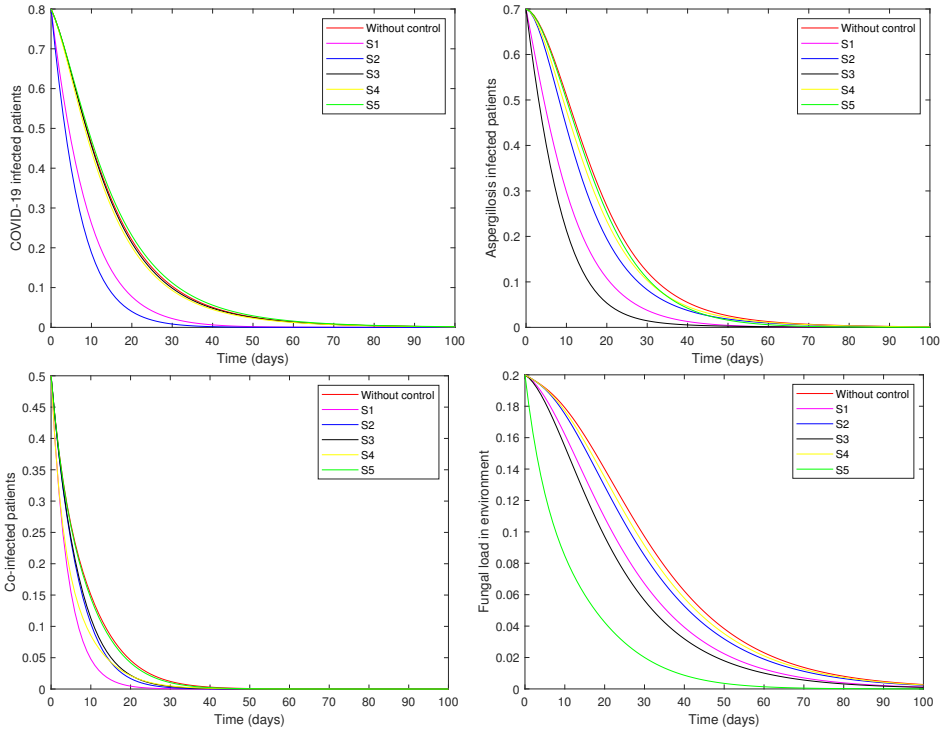


**Figure 1.** State behaviour for Strategies 1 to 5.

3. Strategy 3 : Treatment for Pulmonary Aspergillosis ($w_3$)
4. Strategy 4 : Treatment for COVID-19-Associated Pulmonary Aspergillosis ($w_4$)
5. Strategy 5 : Environmental disinfection ($w_5$)
6. Strategy 6 : ($w_1$)+($w_2$)
7. Strategy 7 : ($w_1$)+($w_3$)
8. Strategy 8 : ($w_1$)+($w_4$)
9. Strategy 9 : ($w_1$)+($w_5$)
10. Strategy 10 : ($w_2$)+($w_3$)
11. Strategy 11 : ($w_2$)+($w_4$)
12. Strategy 12 : ($w_2$)+($w_5$)
13. Strategy 13 : ($w_3$)+($w_4$)
14. Strategy 14 : ($w_3$)+($w_5$)
15. Strategy 15 : ($w_4$)+($w_5$)
16. Strategy 16 : ($w_1$)+($w_2$)+($w_3$)
17. Strategy 17 : ($w_2$)+($w_3$)+($w_4$)
18. Strategy 18 : ($w_3$)+($w_4$)+($w_5$)
19. Strategy 19 : ($w_4$)+($w_5$)+($w_1$)
20. Strategy 20 : ($w_5$)+($w_1$)+($w_2$)
21. Strategy 21 : ($w_1$)+($w_2$)+($w_4$)
22. Strategy 22 : ($w_2$)+($w_3$)+($w_5$)
23. Strategy 23 : ($w_3$)+($w_4$)+($w_1$)
24. Strategy 24 : ($w_3$)+($w_5$)+($w_1$)

**Table 1.** Parameters and its values.

| Parameter | Values | Source |
|---|---|---|
| $A$ | 0.403 | [21] |
| $\beta_c$ | 0.9 | Assumed |
| $\beta_F$ | 0.3 | Assumed |
| $\beta_a$ | 0.67 | Assumed |
| $\beta_h$ | 0.34 | Assumed |
| $d'$ | 0.24 | [22] |
| $\mu_p$ | 0.246 | [23] |
| $d_c$ | 0.416 | [24] |
| $d_{ca}$ | 0.549 | [25] |
| $d_a$ | 0.35 | [26] |
| $\psi_a$ | 0.4 | Assumed |
| $\psi_c$ | 0.6 | Assumed |
| $\gamma_c$ | 0.6 | [27] |
| $\gamma_a$ | 0.474 | [28] |
| $\gamma_{ca}$ | 0.451 | [24] |
| $\kappa$ | 0.15 | [29] |
| $\delta_F$ | 0.2 | [30] |
| $\phi_F$ | 0.7 | [30] |

25. Strategy 25 : $(w_4)+(w_5)+(w_2)$
26. Strategy 26 : $(w_1)+(w_2)+(w_3)+(w_4)$
27. Strategy 27 : $(w_2)+(w_3)+(w_4)+(w_5)$
28. Strategy 28 : $(w_3)+(w_4)+(w_5)+(w_1)$
29. Strategy 29 : $(w_4)+(w_5)+(w_1)+(w_2)$
30. Strategy 30 : $(w_5)+(w_1)+(w_2)+(w_3)$
31. Strategy 31 : $(w_1)+(w_2)+(w_3)+(w_4)+(w_5)$

## 6. Results

### *6.1. Strategies with single control*

Figure 1 shows the behavior of the states under the influence of single control strategies 1 to 5. Without control interventions, we can see that the infected population for COVID-19, Pulmonary Aspergillosis, and COVID-19-associated Pulmonary Aspergillosis increases. In comparison, with control interventions, strategy 2 significantly decreases COVID-19-infected patients, strategy 3 provides a significant reduction in the Pulmonary Aspergillosis patients, strategy 1 effectively reduces the co-infected patients, and strategy 5 is effective in reducing the fungal load in the environment. We can see that the transmission prevention control in strategy 1 achieves a satisfactory drop in all the infected populations and a substantial reduction in the fungal load in the environment. Therefore, the effort of transmission prevention control appears to be the most desirable among the five single control strategies. Although single control strategies are undesirable when considering the overall minimization of infection, we

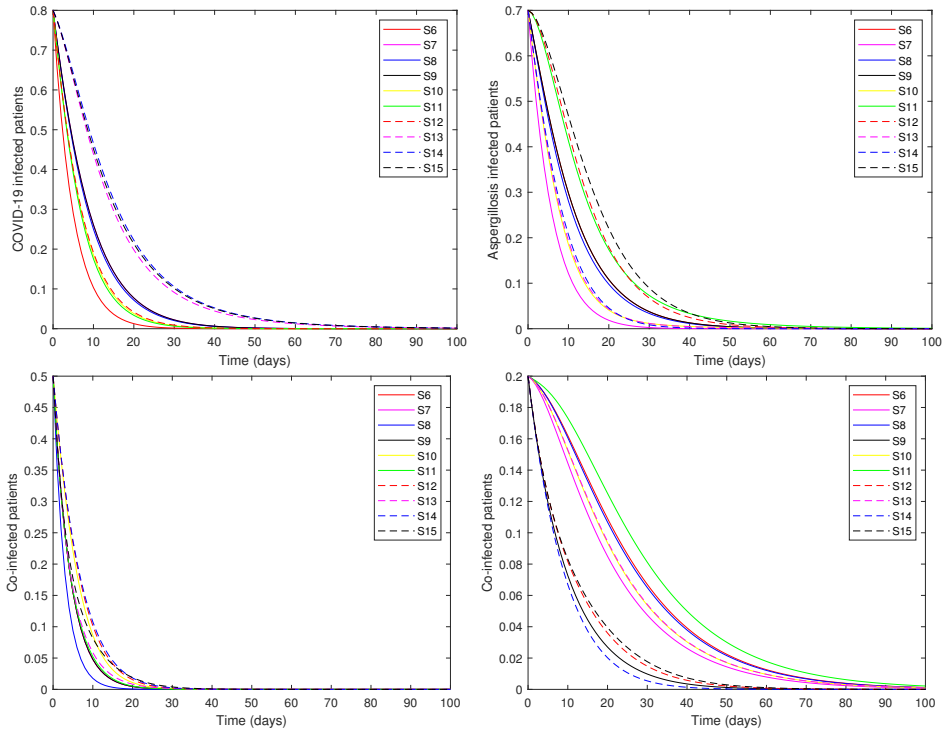


**Figure 2.** State behaviour for Strategies 6 to 15.

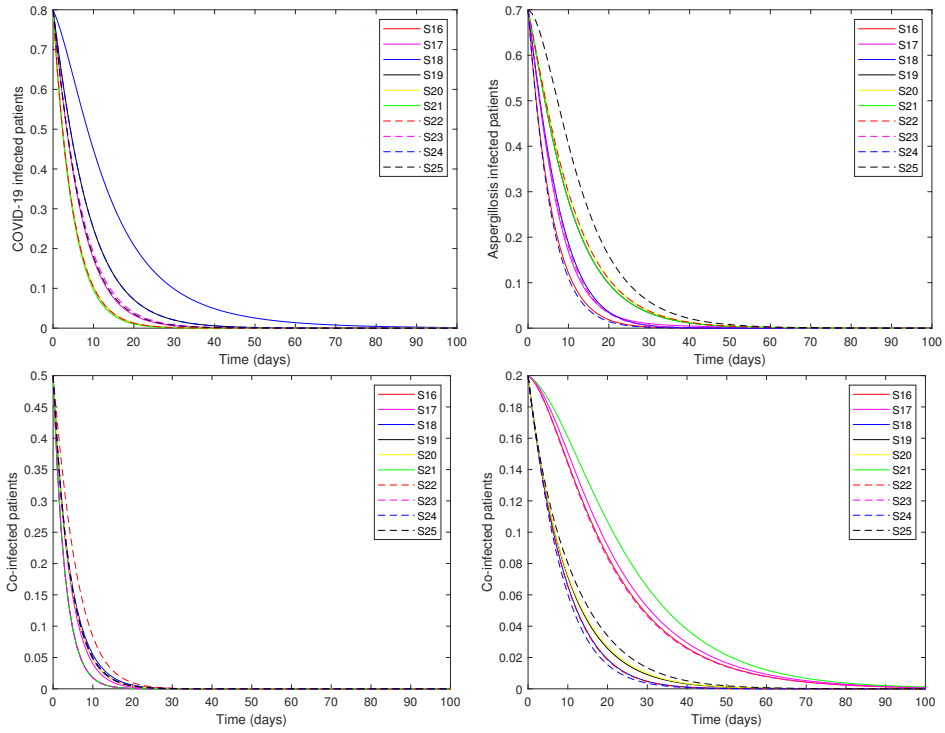


**Figure 3.** State behaviour for Strategies 16 to 25.

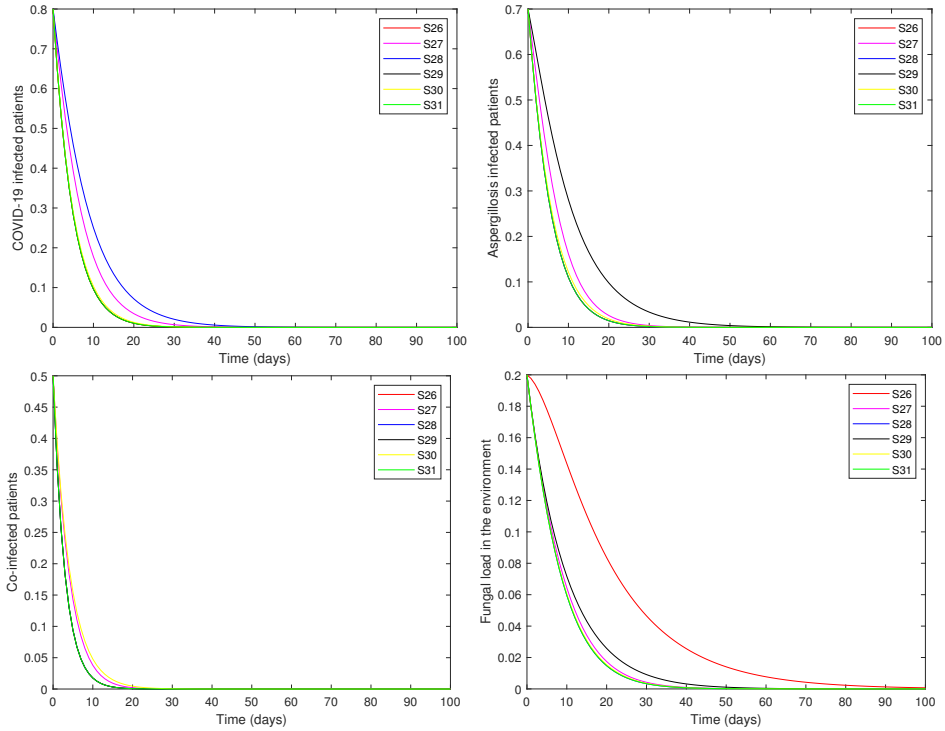


**Figure 4.** State behaviour for Strategies 26 to 31.

can examine two control combinations in the following analysis.

### *6.2. Strategies with double controls*

Figure 2 demonstrates the outcomes of strategies 6 to 15. As we examine the approaches that combine two controls, we observe that strategy 6 (combination of transmission prevention control and treatment for COVID-19 infection) is most effective in reducing COVID-19 infections. In reducing Aspergillosis patients, strategy 7 (combination of transmission prevention control and treatment) is the most effective strategy. To minimize the number of co-infected patients in a short period, strategy 8 (combined transmission prevention control and Aspergillosis treatment) is the most effective combination. It takes relatively fewer days for strategy 14 (combination of Pulmonary Aspergillosis treatment and environment disinfection) to reach the final level since it has the lowest fungal load in the time interval considered. As a result of the reduced fungus load, there would be fewer chances of new patients becoming colonized with the pathogen. The next step is to determine three control combinations to minimize the overall risk of infection.

### *6.3. Strategies with three controls*

Figure 3 illustrates the effects of strategies 16 to 25. Here we examine the three control combinations to reduce the infected patients and the fungal load in the environment. The results show that strategies 20, 21, 22 significantly reduced COVID-19 infected patients. Strategy 24 possesses the ability to reduce the severity of Aspergillosis patients. The goal of curbing co-infected patients is achieved primarily by strategies 21 and 23. Strategy 24 is the most desirable combination to reduce the fungal load in the environment and consistently reduces both the number of Aspergillosis patients and the

amount of fungus contamination.

### *6.4. Strategies with four and five controls*

Based on Figure 5, we can conclude that strategy 31 has a significant impact on reducing the number of infected patients and the fungal load in the environment. Making the effort of five controls, the state population reaches zero in a relatively short number of days.

## 7. Discussions

This work has revealed the dynamic model for co-infection of COVID-19-associated Pulmonary Aspergillosis in the hospital environment. By applying numerical simulations, we endeavor to understand the effect of control interventions under co-infection. In earlier studies [3], the authors have raised awareness of the co-infection of CAPA. Early anti fungal treatment should be administered alongside screening for this grave condition to prevent the co-infection prior, as it infects the immune-compromised patients. In [4], the authors have reported a case and described the assessment of the occurrence and frequency of fungal infections during the pandemic. A case report has been published in [5] highlighting the occurrence of co-infections. Numerous studies have also examined the biological basis of COVID-19-associated Pulmonary Aspergillosis. But, we are the first ones to model COVID-19-associated-Pulmonary Aspergillosis. As a result of this model, emerging secondary infections with COVID-19 can be prevented and controlled.

### *7.1. Contributions*

The highlight of the work is the mathematical formulation, the reproduction number of the model ensures that COVID-19 can infiltrate a vulnerable population where Pulmonary Aspergillosis is already prevalent. As a result, the model is primarily concerned with comprehending the co-dynamics of the spread of COVID-19-associated Pulmonary Aspergillosis in the hospital setting. This model is contributed to investigate the obstructive effects of co-infection of the CAPA with the inclusion of the control interventions.

### *7.2. Implications for practice*

The model - based foundation has been specifically capable of carrying out the Covid-19 and Pulmonary Asperillosis co-transmission, but it can also be used to general epidemiological co-transmitting illnesses with limited hospital facilities. The prediction of epidemic transmission and the development of an early warning system for the limited yet demanding healthcare and volume have been prioritized in epidemiological modeling. It is possible to accomplish this by working and planning in strict accordance with experts and government entities. As a result, it will provide a once-in-a-lifetime opportunity to incorporate novel ideas into demanding healthcare options and planning.

## Conclusions

In this paper, we probe the co-dynamics of the CAPA for the first time and have not yet studied them mathematically. This study focuses on a mathematical approach to investigating the dynamics

of COVID-19-Associated Pulmonary Aspergillosis. The co-occurrence of COVID-19 and Pulmonary Aspergillosis is well formulated using differential equations. The optimal control problem involves five different controls to keep the infection under control. The problem is solved numerically, incorporating different control combinations, and presented in an elaborate simulation. Simulation results are analyzed for each case and show potential limitations to each infection control strategy. After simulating all the controls in the model, we found that prevention, treatment, and environment disinfection are the best ways to minimize CAPA infection.

There have been a number of co-infections of COVID-19 proposed and studied in recent years. Simulations of co-infection through a population are more realistic when individuals interact with each other and the hospital environment is incorporated into epidemic models. Therefore, we formulated the dynamic transmission of COVID-19-associated Pulmonary Aspergillosis in hopsital facility.

The predictions based on the assumptions are taken into consideration. The assumptions can mature over time with the emergence of new evidence. Patients with CAPA have a higher mortality rate than patients without Aspergillosis, so it is crucial to raise awareness and encourage further research. In future work, this model may be modified by examining individual insights into the illness and their developments over time. To aid in mitigating the diseases in the community, we will extend the model to a fractional order derivative form and apply optimal control strategy.

In epidemiological modeling, predictions of epidemic transmission and early warning systems have been prioritized because of the limited yet demanding healthcare and volume. By collaborating closely with experts and government entities, it is possible to accomplish the eradication of disease. Consequently, it is an opportunity to enhance healthcare options and planning in a unique way.

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## Conflict of interest

The authors declare there is no conflict of interest.

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