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OPTIMAL CONTROL ON MATHEMATICAL MODEL OF MPOX DISEASE SPREAD

Putri Nabila Ikhsani [1], Tarmizi Usman[2*], Muhammad Ikhwan[3]

[1]*Mathematics Graduate Program, Universitas Syiah Kuala*
Jln. T. Syech Abdur Rauf No.3, Banda Aceh, 23111, Indonesia

[2,3]*Department of Mathematics, Faculty of Mathematics and Natural Sciences, Universitas Syiah Kuala*
Jln. T. Syech Abdur Rauf No.3, Banda Aceh, 23111, Indonesia

*Corresponding author's e-mail: * **tarmiziusman@usk.ac.id***

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ABSTRACT

The Global emergency related to mpox infection outside endemic areas occurred in 2022. The United States is one of the areas that has been significantly impacted by the mpox virus. To reduce the number of infection cases, it is essential to control the spread of the disease. This can be achieved through optimal control. The intervention provided to combat the dynamic spread of mpox can be represented in the form of a mathematical model. This model comprises the animal population (SEI) and the human population (SEIR). Furthermore, the model that has been formed also divides humans into high-risk and low-risk populations. The classification is based on the risk of complications and death caused by infection. The model will be analyzed in order to ascertain its disease-free and endemic stability. The spread of mpox is then controlled by healthy living behaviors and antiviral administration to reduce the number of infection cases. To this end, numerical simulations were conducted to visualize the spread of mpox with and without the function of control variables so that optimal results were obtained. The results of the numerical simulation demonstrate that a reduction in infection cases by 64.62% can be achieved by implementing an average rate of healthy living behaviors of 93.15% and distributing an average rate of antivirus at 75.11%.

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1. INTRODUCTION

Mpox is one of the *zoonotic* infectious diseases caused by viruses of the *Orthopoxvirus* in the *Poxviridae* family [1]. In terms of *zoonotic*, mpox can be transmitted between animals and humans. The disease is endemic in tropical rainforest regions, particularly Central Africa and West Africa, where natural agents of the spread, such as the African Striped Squirrel (*Funisciurus sp*), Chamca Baboon (*Papio ursinus*), chimpanzees (*Pan troglodytes*), and others mostly live in [2]. In non-endemic regions such as The United States and The United Kingdom, domestic pets are identified as potential carriers of the virus. Animals that are at risk or talented as agents of virus transmission include prairie dogs (*Cynomys ludovicianus*), squirrels, rats, chinchillas, marmots and groundhogs, giant-pouched rats, hedgehogs, and shrews [3]. Transmission of the mpox virus from animals to humans can occur through scratches, bites, and direct contact with body fluids from infected animals. Meanwhile, human-to-animal transmission can occur through direct contact such as hugging, petting, kissing, and sharing bedding and food with pets. The spread of mpox between humans can occur through close contact with lesions of infected individuals, splashing fluid or saliva, sexual contact, and direct contact with a contaminated environment [4], [5].

In terms of prevention, there is currently no vaccine that has been specifically formulated to deal with the spread of mpox. Consequently, the vaccine that is currently in use is the smallpox vaccine. The vaccine has received approval for circulation in several regions in 2019. However, global availability remains very limited, so mass vaccination is not currently recommended [4], [6]. Mpox is similar to smallpox in general; therefore, sufferers can recover without medical intervention. However, this does not apply to several groups, including children under the age of eight, pregnant women, individuals with immune disorders, and those with comorbidities [6]. In these groups, mpox can cause a range of complications, including pneumonia, corneal infection, brain inflammation, and even death [4]. There have been documented cases of severe illness and fatalities from May 10, 2022, to March 7, 2023. There are 38 deaths (1.3 per 1,000 mpox cases) among individuals with probable or confirmed mpox that were reported to the CDC and classified as mpox-related. Of the 33 individuals with available clinical data, 93.9% (31 of 33) were immunocompromised, primarily due to HIV infection. Among the two immunocompromised decedents without HIV, one was presumed to have been immunocompromised due to undiagnosed diabetes; this individual presented with diabetic ketoacidosis, a severe and life-threatening complication of diabetes, at the time of mpox diagnosis [7].

The risks and complications associated with mpox infection are not solely a concern for those residing in endemic areas; the entire global population is affected. On 23 July 2022, the World Health Organization (WHO) designated mpox as a global emergency disease due to the exponential increase in cases, which had reached over 87,000 in 110 non-endemic countries [5]. The increase in positive cases in 2022 has prompted the development of research related to the spread of mpox disease, both from the medical and mathematical perspectives. In the medical field, some post-infection antiviral therapies that have been developed to treat orthopoxvirus infection are brincidofovir and tecovirimat. The antiviral brincidofovir was approved by the FDA in June 2021 for use in either adult humans or neonates infected with mpox. Meanwhile, the antiviral tecovirimat was approved for use in adults and children weighing at least 13 kg by the FDA in July 2018, followed by the EMA in June 2021. The use of tecovirimat has been carried out as an adjunct to treatment in certain groups with smallpox, mpox, cowpox, and other infectious diseases due to infection with the Poxviridae virus. In the field of mathematics, the spread of mpox can be described by the formation of a mathematical model. Several studies have been conducted on the spread of mpox, including research [8], which discusses the transmission of mpox in Nigeria by grouping humans into groups that experience clinical symptoms after infection. Furthermore, research [9] proposed the application of optimal control to the mpox spread model. The model divides humans into high-risk and low-risk populations. The risk grouping is based on habitual, hygienic, and environmental conditions that are considered to make individuals more susceptible to disease. In the study, the interventions given were the strategy of administering vaccines to susceptible humans and the strategy of giving tecovirimat antivirals to quarantine populations to accelerate the healing process of infection. The results showed that the number of exposed, quarantined, and infected humans decreased when the intervention was given to the population. Moreover, several mathematical models related to the spread of mpox were also discussed in research [10]–[13].

This article will discuss the development of a mathematical model of the spread of mpox based on various studies related to the spread of mpox that have been carried out previously. The model will divide the proportion of humans into high-risk and low-risk populations. In contrast to the previous research [9], the risk factor under consideration is the likelihood of complications and mortality resulting from the disease in question. An individual is considered to be at high risk if they belong to one of the following groups: children

under the age of eight, pregnant women, individuals with immune deficiency, and those with comorbidities such as HIV/AID and diabetic ketoacidosis [4], [7]. This study applies optimal control within a mathematical model of mpox transmission, targeting interventions in the infected human to minimize infection cases. This objective is achieved by reducing the exposed and infected subpopulations among both animals and humans. The intervention carried out is in the form of curative measures given to infected humans to accelerate the occurrence of recovery, which results in a smaller chance of interaction between infected and susceptible humans. Consequently, the implementation of this control measure can potentially reduce the incidence of future infection cases. Infected individuals will be intervened upon through the implementation of healthy living behaviors and the administration of tecovirimat antivirals. Healthy living behaviors, which may be considered supportive therapy, involve the adoption of beneficial habits such as balanced nutrition, adequate hydration, and the intake of supplements that can alleviate symptoms resulting from infection. Meanwhile, tecovirimat antivirals are administered to high-risk individuals infected to accelerate healing and minimize post-infection complications.

2. RESEARCH METHODS

This study employs a quantitative descriptive methodology, adopting a quantitative approach to describe the event. The first step in this study is a literature study by collecting references such as books, journals, and relevant information as the basis for theory and reference materials to construct a mathematical model for the spread of mpox disease. The references are closely related to the differential equation system, equilibrium and stability, optimal control theory, the mpox virus, and treatment of infected individuals through supportive therapy (healthy living behavior) and antiviral administration. The subsequent stage of the study involves the collection of data on mpox infection cases and parameter values. The deployment data was obtained from the CDC in the United States and utilized as the initial values in the simulation stage. Meanwhile, the parameter value data was sourced from previous research and information provided by several official websites in the United States.

The next step is to identify and establish model assumptions for the construction of the model. At this stage, a mathematical model of the mpox spread is formed by involving two populations: the animal population and the human population. This model divides the human population into high and low risk based on clinical conditions and their risk of death and complications. The animal population is divided into three categories: susceptible animals ($\boldsymbol{S_r}$), exposed animal ($\boldsymbol{E_r}$), and infected animals ($\boldsymbol{I_r}$). The mathematical model constructed for the human population follows the SEIR (Susceptible, Exposed, Infected, Recovered), comprising the following subpopulations: susceptible humans ($\boldsymbol{S_h}$), low-risk exposed humans ($\boldsymbol{E_1}$), high-risk exposed humans ($\boldsymbol{E_2}$), low-risk infected humans ($\boldsymbol{I_1}$), high-risk infected humans ($\boldsymbol{I_2}$), and recovered humans ($\boldsymbol{R}$). In the exposed human group, risk factors are reflected by differential progression rates to infection. Specifically, low-risk exposed human ($\boldsymbol{E_1}$) exhibit partial immunity, resulting in a prolonged incubation period relative to high-risk exposed humans ($\boldsymbol{E_2}$). Similarly, low-risk infected humans ($\boldsymbol{I_1}$), have a lower mortality risk than high-risk infected humans ($\boldsymbol{I_2}$), leading to a higher natural recovery rate in $\boldsymbol{I_1}$ compared to $\boldsymbol{I_2}$. The existence of exposure groups in both animals and humans is based on the virus's incubation period, which ranges from 5-21 days. Furthermore, the model will be analyzed to identify the equilibrium point and stability criteria.

Moreover, the model will be provided with controls in the form of healthy living behavior ($\boldsymbol{u_1}$) and antiviral administration ($\boldsymbol{u_2}$) to see how these intervention actions can minimize cases of mpox infection. The rates of healthy behaviors ($\boldsymbol{u_1}$) and antiviral administration ($\boldsymbol{u_2}$) are expressed as percentages of infected individuals who engage in healthy behaviors and receive antivirals, respectively. Therefore, the values of $\boldsymbol{u_1}$ and $\boldsymbol{u_2}$ are constrained to the interval $[\boldsymbol{0}, \boldsymbol{1}]$. This stage is part of optimal control. At this stage, an objective function will be formulated with the aim of reducing factors that could facilitate the spread of the virus, such as minimizing the number of individuals who are both exposed and infected. The optimal control problem that has been formulated will be solved using the Potryagin Minimum Principle. The results obtained will then be simulated numerically to obtain a visual representation. The numerical method used is the fourth-order Runge-Kutta method with a forward sweep approach for the state equation and a backward sweep for the costate equation. The results obtained will be visualized and interpreted to reach a conclusion. The following is a picture of the method used in the research,

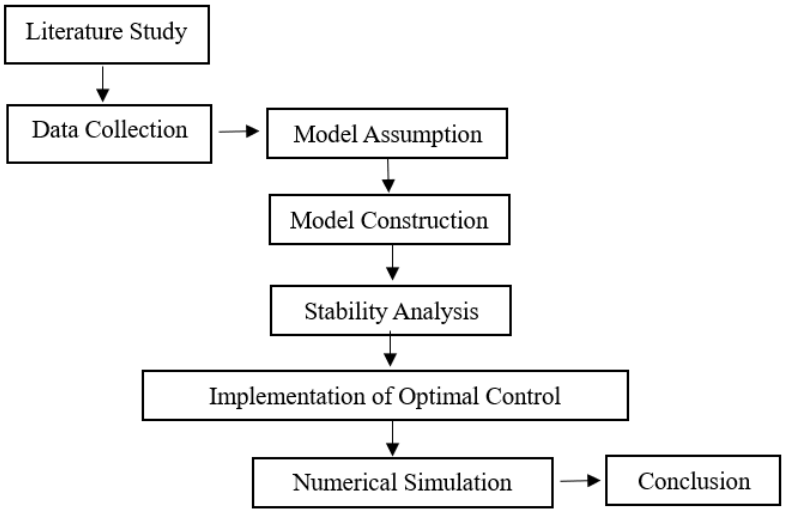


Figure 1. Research Method

3. RESULTS AND DISCUSSION

3.1 Mathematical Model

The mathematical model presented in this study is constructed based on a set of assumptions. These assumptions are derived by considering a range of deployment factors. The following assumptions are provided to delineate the boundaries of the model:

The animal population is divided into three subpopulations: susceptible animals (S_r), exposed animal (E_r), and infected animals (I_r). Therefore, the total animal population at the time t is $N_r(t) = S_r(t) + E_r(t) + I_r(t)$.

a. The human population is divided into six subpopulations: susceptible humans (S_h), exposed low-risk humans (E_1), exposed high-risk humans (E_2), infected low-risk humans (I_1), infected high-risk humans (I_2), and recovered humans (R). Therefore, the total human population at the time t is $N_h(t) = S_h(t) + E_1(t) + E_2(t) + I_1(t) + I_1(t) + R(t)$.
b. Animal and human mortality rates consist of natural mortality and infectious mortality.
c. Human and animal populations are both open, with different rates of birth and death.
d. Susceptible animals (S_r) will be exposed to mpox (E_r) if there is contact with infected animals (I_r). Following this initial contact, an incubation period will elapse before the animals become infected.
e. An individual is considered to be at high risk if they belong to one of the following groups: children under the age of eight, pregnant women, individuals with immune deficiency, and those with comorbidities.
f. High-risk individuals are acutely aware of the dangers of mpox to their clinical condition, so they limit their interactions with animals. As a result, this group becomes exposed (E_2) when interacting with infected humans.
g. Healthy susceptible can be exposed to the mpox virus (E_1) if there is contact between infected humans and susceptible humans (S_h) or contact between infected animals (I_r) and susceptible humans (S_h).
h. Individuals with no underlying health conditions (low risk) who are exposed to mpox (E_1) will experience mpox disease with a low risk of death and complications (I_1), but at any time also have the potential to become a high-risk infection group (I_2) that is also influenced by the incubation period.
i. It is important to note that individuals who have recovered from an infection will move to the group of recovered individuals (R) at a different rate based on their risk factors. Furthermore, it is possible for individuals who have been cured to become susceptible again, as it is not guaranteed that they will remain permanently immune to infection.

The initial phase of animal-to-animal transmission of the disease begins with interactions between susceptible (S_r) and infected animals (I_r). This interaction results in the animal's exposure to mpox, which will become infected at a rate influenced by the incubation period of the virus, hygienic factors, and others. Conversely, humans may also become infected with mpox if they come into contact with both infected animals (I_r) and infected humans. In this case, individuals exposed to mpox are classified according to risk group, resulting in the formation of two exposed subpopulations, designated as (E_1) and (E_2). The infection rate varies between subpopulations. In this case, high-risk exposed humans (E_2) are assumed to have a shorter incubation period, allowing them to become infected (I_2) with the virus rapidly. Low-risk humans who are exposed (E_1) can also become infected with high risk (I_2) due to the potential emergence of clinical factors that manifest during the virus incubation period occurs, allowing E_1 to transition to either I_1 or I_2. Once the infection period has concluded, infected humans can be designated as cured (R). This recovery is contingent upon the natural human recovery rate, which varies depending on the specific risk factors involved. The mpox deployment model is illustrated in **Figure 2**.

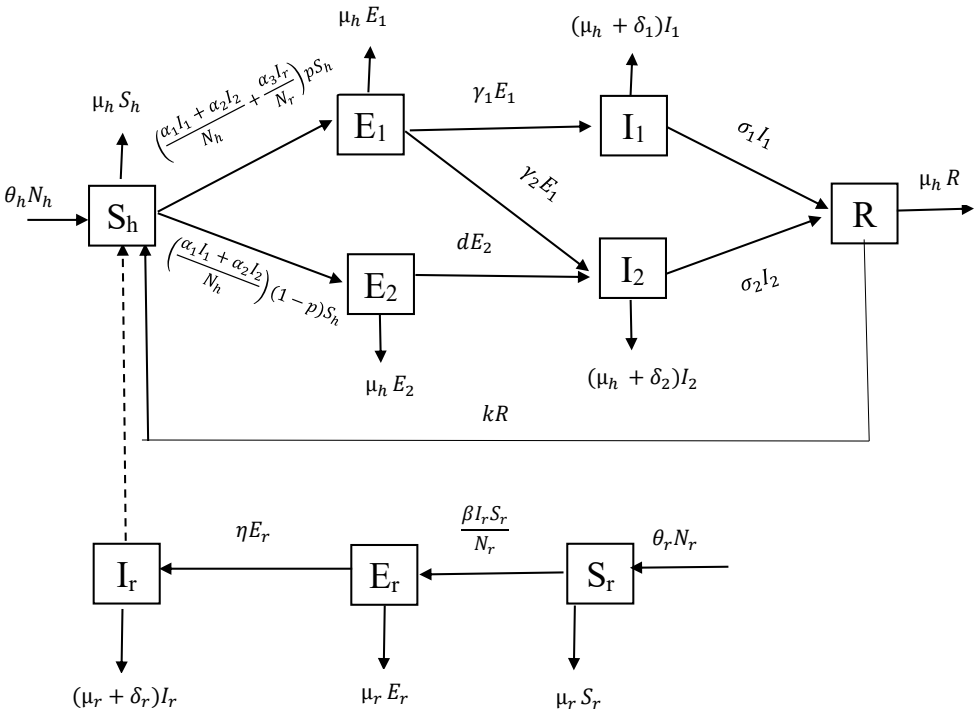


Figure 2. Mpox Spread Diagram

Based on **Figure 2**, the following system of differential equations is obtained

$$
\begin{aligned}
\frac{dS_r}{dt} &= \theta_r N_r - \frac{\beta I_r S_r}{N_r} - \mu_r S_r \\
\frac{dE_r}{dt} &= \frac{\beta I_r S_r}{N_r} - (\eta + \mu_r) E_r \\
\frac{dI_r}{dt} &= \eta E_r - (\mu_r + \delta_r) I_r \\
\frac{dS_h}{dt} &= \theta_h N_h - \left(\frac{\alpha_1 I_1 + \alpha_2 I_2}{N_h} + \frac{\alpha_3 I_r}{N_r}\right) p S_h - \left(\frac{\alpha_1 I_1 + \alpha_2 I_2}{N_h}\right)(1-p) S_h - \mu_h S_h + kR \\
\frac{dE_1}{dt} &= \left(\frac{\alpha_1 I_1 + \alpha_2 I_2}{N_h} + \frac{\alpha_3 I_r}{N_r}\right) p S_h - (\gamma_1 + \gamma_2 + \mu_h) E_1 \\
\frac{dE_2}{dt} &= \left(\frac{\alpha_1 I_1 + \alpha_2 I_2}{N_h}\right)(1-p) S_h - (d + \mu_h) E_2 \\
\frac{dI_1}{dt} &= \gamma_1 E_1 - (\mu_h + \delta_1 + \sigma_1) I_1 \\
\frac{dI_2}{dt} &= \gamma_2 E_1 + d E_2 - (\mu_h + \delta_2 + \sigma_2) I_2 \\
\frac{dR}{dt} &= \sigma_1 I_1 + \sigma_2 I_2 - (k + \mu_h) R
\end{aligned}
\tag{1}
$$

The parameters used in this study are shown in the following **Table 1**,

Table 1. Parameter Value

Parameter	Description	Unit	Value	References
θ_r	Growth rate of animal population	Year	0.2	[11]
θ_h	Growth rate of human population	Year	0.012	[14]
μ_r	Natural death rate in animals	Year	0.2	[11]
μ_h	Natural death rate in humans	Year	0.0091	[15]
δ_r	Death rate in animals due to infection	Year	0.5	[16]
δ_1	Death rate in low-risk humans due to infection	Day	$0.13\ x\ 10^{-6}$	[11]
δ_2	Death rate in high-risk humans is due to infection	Day	0.0009	Assume
p	Proportion of low-risk humans susceptible	Year	0.55	Assume
β	Contact rate between infected animal and susceptible animal	Day	0.0007	Assume
α_1	Contact rate between infected low-risk humans and susceptible humans	Day	0.0032	[8]
α_2	Contact rate between infected high-risk humans and susceptible humans	Year	0.1	Assume
α_3	Contact rate between infected animals and susceptible humans	Year	0.00025	[16]
η	Progression rate from exposed to infected in animals	Day	0.0773	[17]
γ_1	Progression rate from exposed to infected in low-risk humans	Day	0.004	[11]
γ_2	Progression rate from exposed low-risk humans to infected at high-risk	Day	0.009	Assume
d	Progression rate from exposed to infected in high-risk groups	Day	0.014	Assume
σ_1	Natural recovery rate in infected healthy humans	Week	0.3432	[17]
σ_2	Natural recovery rate in high-risk infected humans	Week	0.15	Assume
k	The rate of reinfection cases in human	Day	$1.75\ x\ 10^{-7}$	[18]

As can be observed in **Table 1**, certain parameter values are based on assumptions. The occurrence of assumed parameter values is a consequence of the limited data available regarding the dissemination of mpox in individuals at high risk. Consequently, the estimated value of the parameter is based on the value observed in low-risk humans. The assumed values assigned to parameters, such as the natural recovery rate for high-risk infected individuals (σ_2), are estimated to be lower than those for low-risk individuals (σ_1). This adjustment reflects the impact of risk factors that slow the healing process in high-risk cases [4].

The solution obtained from this model is the number of individuals in all subpopulations, so the solution obtained must be non-negative. The initial value given to the subpopulation is non-negative [19],

$S_r(0) > 0,\ E_r(0) \geq 0,\ I_r(0) \geq 0,$
$S_h(0) > 0,\ E_1(0) \geq 0,\ E_2(0) \geq 0,\ I_1(0) \geq 0,\ I_2(0) \geq 0, R(0) \geq 0.$

Theorem 1. *If a non-negative initial condition is given in* **Equation (1)**, *then the solution obtained for the system is positive in* $\mathbb{R}_9^+ \cup 0_9$ *for all* $t > 0$.

Proof. Based on **Equation (1)** where the initial value is non-negative for all subpopulations, then each variable has the following bounds,

$$\begin{aligned}
\frac{dS_r}{dt}|_{(S_r=0,E_r\geq 0,I_r\geq 0,S_h>0,E_1\geq 0,E_2\geq 0,I_1\geq 0,I_2\geq 0,R\geq 0)} &= \theta_r N_r > 0\\
\frac{dE_r}{dt}|_{(S_r>0,E_r=0,I_r\geq 0,S_h>0,E_1\geq 0,E_2\geq 0,I_1\geq 0,I_2\geq 0,R\geq 0)} &= \frac{\beta I_r S_r}{N_r} \geq 0\\
\frac{dI_r}{dt}|_{(S_r>0,E_r\geq 0,I_r=0,S_h>0,E_1\geq 0,E_2\geq 0,I_1\geq 0,I_2\geq 0,R\geq 0)} &= \eta E_r \geq 0\\
\frac{dS_h}{dt}|_{(S_r>0,E_r\geq 0,I_r\geq 0,S_h>0,E_1=0,E_2\geq 0,I_1\geq 0,I_2\geq 0,R\geq 0)} &= \theta_h N_h + kR \geq 0\\
\frac{dE_1}{dt}|_{(S_r>0,E_r\geq 0,I_r\geq 0,S_h>0,E_1=0,E_2\geq 0,I_1\geq 0,I_2\geq 0,R\geq 0)} &= \left(\frac{\alpha_1 I_1 + \alpha_2 I_2}{N_h} + \frac{\alpha_3 I_r}{N_r}\right) pS_h \geq 0\\
\frac{dE_2}{dt}|_{(S_r>0,E_r\geq 0,I_r\geq 0,S_h>0,E_1\geq 0,E_2=0,I_1\geq 0,I_2\geq 0,R\geq 0)} &= \left(\frac{\alpha_1 I_1 + \alpha_2 I_2}{N_h}\right)(1-p)S_h \geq 0\\
\frac{dI_1}{dt}|_{(S_r>0,E_r\geq 0,I_r\geq 0,S_h>0,E_1\geq 0,E_2\geq 0,I_1=0,I_2\geq 0,R\geq 0)} &= \gamma_1 E_1 \geq 0\\
\frac{dI_2}{dt}|_{(S_r>0,E_r\geq 0,I_r\geq 0,S_h>0,E_1\geq 0,E_2\geq 0,I_1\geq 0,I_2=0,R\geq 0)} &= \gamma_2 E_1 + dE_2 \geq 0\\
\frac{dR}{dt}|_{(S_r>0,E_r\geq 0,I_r\geq 0,S_h>0,E_1\geq 0,E_2\geq 0,I_1\geq 0,I_2\geq 0,R=0)} &= \sigma_1 I_1 + \sigma_2 I_2 \geq 0
\end{aligned} \tag{2}$$

By substituting the parameter values in **Table 1**, it can be shown that the rate of change of each variable in **Equation (2)** is non-negative at $\mathbb{R}_9^+ \cup 0_9$. Therefore, the solution of **Equation (1)** will always be non-negative if the initial conditions are satisfied. ■

3.2 Model Analysis

The mpox spread model will be analyzed by simplifying the model in **Equation (1)** into a non-dimensional form. This will be achieved by transforming all subpopulation compartments in the form of the proportion of the number of individuals in the subpopulation to the total population. The following model is obtained:

$$\begin{aligned}
\frac{ds_r}{dt} &= \theta_r - (\beta i_r + \mu_r)s_r\\
\frac{de_r}{dt} &= \beta i_r s_r - (\eta + \mu_r)e_r\\
\frac{di_r}{dt} &= \eta e_r - (\mu_r + \delta_r)i_r\\
\frac{ds_h}{dt} &= \theta_h - (\alpha_1 i_1 + \alpha_2 i_2 + \alpha_3 i_r)ps_h - (\alpha_1 i_1 + \alpha_2 i_2)(1-p)s_h - \mu_h s_h + kr\\
\frac{de_1}{dt} &= (\alpha_1 i_1 + \alpha_2 i_2 + \alpha_3 i_r)ps_h - (\gamma_1 + \gamma_2 + \mu_h)e_1\\
\frac{de_2}{dt} &= (\alpha_1 i_1 + \alpha_2 i_2)(1-p)s_h - (d + \mu_h)e_2\\
\frac{di_1}{dt} &= \gamma_1 e_1 - (\mu_h + \delta_1 + \sigma_1)i_1\\
\frac{di_2}{dt} &= \gamma_2 e_1 + de_2 - (\mu_h + \delta_2 + \sigma_2)i_2\\
\frac{dr}{dt} &= \sigma_1 i_1 + \sigma_2 i_2 - (k + \mu_h)r
\end{aligned} \tag{3}$$

3.2.1 Equilibrium Points

An equilibrium point is a condition where a system is not affected by time **[20]**. The following equilibrium point values are obtained,

a. A disease-free equilibrium point is a condition where there are no cases of infection, so there are only susceptible humans in the subpopulation. The disease-free equilibrium point is expressed by $E_0 = (s_r, e_r, i_r, s_h, e_1, e_2, i_1, i_2, r)$,

$$E_0 = \left(\frac{\theta_r}{\mu_r}, 0, 0, \frac{\theta_h}{\mu_h}, 0, 0, 0, 0, 0\right). \quad (4)$$

b. Endemic equilibrium point is a condition where there is mpox infection in the population. The endemic equilibrium point is expressed by $E^* = (s_r^*, e_r^*, i_r^*, s_h^*, e_1^*, e_2^*, i_1^*, i_2^*, r^*)$,

$$s_r^* = \frac{\theta_r}{\beta i_r^* + \mu_r}, \qquad e_r^* = \frac{\beta i_r^* s_r^*}{\eta + \mu_r},$$
$$i_r^* = \frac{\eta e_r^*}{\delta_r + \mu_r}, \qquad s_h^* = \frac{\theta_h + k r^*}{\alpha_1 i_1^* + \alpha_2 i_2^* + \alpha_3 i_r^* p + \mu_h}$$
$$e_1^* = \frac{(\alpha_1 i_1^* + \alpha_2 i_2^* + \alpha_3 i_r^*) p s_h^*}{(\gamma_1 + \gamma_2 + \mu_h)}, \qquad e_2^* = \frac{(\alpha_1 i_1^* + \alpha_2 i_2^*)(1-p) s_h^*}{(d + \mu_h)},$$
$$i_1^* = \frac{\gamma_1 e_1^*}{(\mu_h + \delta_1 + \sigma_1)}, \qquad i_2^* = \frac{\gamma_2 e_1^* + d e_2^*}{(\mu_h + \delta_2 + \sigma_2)}, \qquad r^* = \frac{\sigma_1 i_1^* + \sigma_2 i_2^*}{(k + \mu_h)} \quad (5)$$

3.2.2 Stability Analysis

Stability analysis is done by forming the Jacobian matrix of the system in **Equation (3)**. There are two equilibrium points that will be examined for stability criteria: disease-free and endemic stability. By substituting the disease-free equilibrium point in **Equation (4)** into the Jacobian matrix, the following eigenvalues are obtained:

$$\lambda_1 = -\mu_r$$
$$\lambda_2 = -\eta - \mu_h$$
$$\lambda_3 = -\mu_h$$
$$\lambda_4 = -(\gamma_1 + \gamma_2 + \mu_h)$$
$$\lambda_5 = -d - \mu_h$$
$$\lambda_6 = -k - \mu_h$$
$$\lambda_7 = \frac{-(\delta_r + \eta + 2\mu_r) + \sqrt{\delta_r^2 - 2\delta_r\eta + \eta^2 + 8\delta_r\mu_r + 8\mu_r^2 + 4\eta\beta\left(\frac{\theta_r}{\mu_r}\right)}}{2}$$
$$\lambda_8 = \frac{-(\gamma_1 + \gamma_2 + \delta_1 + \sigma_1 + 2\mu_h) - \sqrt{(\gamma_1 + \gamma_2 - \delta_1 - \sigma_1)^2 + 4\gamma_1\alpha_2 p\left(\frac{\theta_r}{\mu_r}\right)}}{2}$$

Furthermore, the value of λ_9 is obtained by finding the root of the following polynomial

$$\lambda^4 + A\lambda^3 + B\lambda^2 + C\lambda + D = 0$$

where,

$$A = \gamma_1 + \gamma_2 + \delta_1 + \delta_2 + \sigma_1 + \sigma_2 + d + 4\mu_h$$
$$B = (\gamma_1 + \gamma_2 + \mu_h)(d + \mu_h) + (\delta_1 + \delta_2 + \sigma_1 + \sigma_2 + 2\mu_h)(\gamma_1 + \gamma_2 + d + 2\mu_h) + (\delta_2 + \sigma_2 + \mu_h)(\delta_1 + \sigma_1 + \mu_h) - \frac{\theta_h}{\mu_h}(\alpha_1\gamma_1 p + \alpha_2 d(1-p) + \alpha_2\gamma_2 p)$$
$$C = (\delta_1 + \delta_2 + \sigma_1 + \sigma_2 + 2\mu_h)(\gamma_1 + \gamma_2 + \mu_h)(d + \mu_h) + (\delta_2 + \sigma_2 + \mu_h)(\delta_1 + \sigma_1 + \mu_h)(\gamma_1 + \gamma_2 + d + 2\mu_h) - \left[\frac{p\theta_h}{\mu_h}\left(\alpha_1\gamma_1(d + \delta_2 + \sigma_2 + 2\mu_h) + \alpha_2\gamma_2(d + \delta_1 + \sigma_1 + 2\mu_h)\right) + \frac{(1-p)\theta_h\alpha_2 d}{\mu_h}(\gamma_1 + \gamma_2 + \delta_1 + \sigma_1 + 2\mu_h)\right]$$

By substituting the parameter values in **Table 1**, all eigenvalues obtained are negative. Based on this, the system is asymptotically stable at the disease-free equilibrium point. Furthermore, the stability criteria at the endemic equilibrium point can be obtained by substituting **Equation (5)** into the Jacobian matrix. At this stage, eigenvalues are obtained using MatlabR2017a. The results obtained show that all eigenvalues obtained are negative. Consequently, the system is also stable in the endemic state. However, we also obtained this result by determining the value of the reproduction number **[19]**. In this case, the results obtained with the reproduction number show that the obtained system is stable. The number of compartments is certainly a consideration when choosing a stability analysis method, given the complexity of the model.

3.3 Optimal Control

The main objective of optimal control is the control to reduce the cases of mpox infecting healthy living behavior (u_1) and antiviral administration (u_2). This control strategy is implemented as a curative measure directed at individuals infected with mpox. In alignment with this objective, the formulation of the objective function is presented as follows:

$$Z(u_1, u_2,) = \int_{t_0}^{t_f} \left(E_r + I_r + E_1 + E_2 + I_1 + I_2 + \frac{A_1}{2} u_1^2 + \frac{A_2}{2} u_2^2 \right) dt \tag{6}$$

Meanwhile, the formulation of the constraint function can be done by intervening in the mathematical model in **Equation (1)** with the given control. In an effort to minimize future cases of infection, infected humans are given control in the form of healthy living behavior and antiviral administration to accelerate healing in such a way as to minimize the chance of infected humans interacting with susceptible humans. In this case, low-risk infected humans (I_1) and high-risk infected humans (I_2) will apply healthy living behavior as one of the supportive therapies that can accelerate healing. With the presence of risk factors and deaths in the high-risk group, high-risk infected humans (I_2) will receive additional antiviral tecovirimat treatment to accelerate healing and avoid complications that arise after infection. Therefore, the following constraint function is obtained.

$$\begin{aligned}
\frac{dS_r}{dt} &= \theta_r N_r - \frac{\beta I_r S_r}{N_r} - \mu_r S_r \\
\frac{dE_r}{dt} &= \frac{\beta I_r S_r}{N_r} - (\eta + \mu_r) E_r \\
\frac{dI_r}{dt} &= \eta E_r - (\mu_r + \delta_r) I_r \\
\frac{dS_h}{dt} &= \theta_h N_h - \left(\frac{\alpha_1 I_1 + \alpha_2 I_2}{N_h} + \frac{\alpha_3 I_r}{N_r} \right) p S_h - \left(\frac{\alpha_1 I_1 + \alpha_2 I_2}{N_h} \right) (1-p) S_h - \mu_h S_h + kR \\
\frac{dE_1}{dt} &= \left(\frac{\alpha_1 I_1 + \alpha_2 I_2}{N_h} + \frac{\alpha_3 I_r}{N_r} \right) p S_h - (\gamma_1 + \gamma_2 + \mu_h) E_1 \\
\frac{dE_2}{dt} &= \left(\frac{\alpha_1 I_1 + \alpha_2 I_2}{N_h} \right) (1-p) S_h - (d + \mu_h) E_2 \\
\frac{dI_1}{dt} &= \gamma_1 E_1 - (\mu_h + \delta_1 + (1+u_1)\sigma_1) I_1 \\
\frac{dI_2}{dt} &= \gamma_2 E_1 + d E_2 - (\mu_h + \delta_2 + (1+u_1+u_2)\sigma_2) I_2 \\
\frac{dR}{dt} &= (1+u_1)\sigma_1 I_1 + (1+u_1+u_2)\sigma_2 I_2 - (k + \mu_h) R
\end{aligned} \tag{7}$$

with the description as shown in **Table 2**

Table 2. Control Parameter

Parameter	Description
u_1	Healthy living behavior rate
u_2	Antiviral administration rate
A_1	Weight on healthy living behavior control
A_2	Weight on antivirus administration control

The objective function in **Equation (6)** shows that the objective of optimal control is to minimize the spread of mpox. This can be done by minimizing populations that can accelerate the spread of disease such as animals and humans exposed to and infected with mpox. In addition, healthy living behavior is also minimized with weight A_1 due to the costs incurred for several supportive measures such as fulfilling balanced nutrition, providing supplements, using pain relievers, and other measures that require costs **[21]**. In addition, antiviral administration is also minimized with weight A_2 due to the cost and risks posed after antiviral administration **[6], [22]**. The results of providing control on the system can be obtained using Pontryagin minimum principle condition **[23]** with the following steps:

Step 1: The Hamilton function is formed by summing the integrand of the objective function in **Equation (6)** and the right-hand side of the constraint function in **Equation (7)** which has been multiplied by the costate variable **(λ).**

$$
\begin{aligned}
H &= E_r + I_r + E_1 + E_2 + I_1 + I_2 + \frac{A_1}{2}u_1^2 + \frac{A_2}{2}u_2^2 \\
&+\lambda_1\left[\theta_r N_r - \frac{\beta I_r S_r}{N_r} - \mu_r S_r\right] + \lambda_2\left[\frac{\beta I_r S_r}{N_r} - (\eta + \mu_r)E_r\right] \\
&+\lambda_3[\eta E_r - (\mu_r + \delta_r)I_r] \\
&+\lambda_4\left[\theta_h N_h - \left(\frac{\alpha_1 I_1 + \alpha_2 I_2}{N_h} + \frac{\alpha_3 I_r}{N_r}\right)pS_h - \left(\frac{\alpha_1 I_1 + \alpha_2 I_2}{N_h}\right)(1-p)S_h - \mu_h S_h + kR\right] \\
&+\lambda_5\left[\left(\frac{\alpha_1 I_1 + \alpha_2 I_2}{N_h} + \frac{\alpha_3 I_r}{N_r}\right)pS_h - (\gamma_1 + \gamma_2 + \mu_h)E_1\right] + \lambda_6\left[\left(\frac{\alpha_1 I_1 + \alpha_2 I_2}{N_h}\right)(1-p)S_h - (d + \mu_h)E_2\right] \\
&+\lambda_7[\gamma_1 E_1 - (\mu_h + \delta_1 + (1+u_1)\sigma_1)I_1] + \lambda_8[\gamma_2 E_1 + dE_2 - (\mu_h + \delta_2 + (1+u_1+u_2)\sigma_2)I_2] \\
&+\lambda_9[(1+u_1)\sigma_1 I_1 + (1+u_1+u_2)\sigma_2 I_2 - (k + \mu_h)R]
\end{aligned} \tag{8}
$$

Step 2: Determine the stationary condition of the Hamiltonian function with respect to all control variables, i.e., the first partial derivative of **Equation (8)** with respect to the control variables u_1 and u_2.

$$\frac{\partial H}{\partial u_1} = 0, \qquad \frac{\partial H}{\partial u_2} = 0$$

the following optimal conditions for u_1 and u_2 are obtained

$$u_1 = \frac{(\lambda_7 - \lambda_9)\sigma_1 I_1 + (\lambda_8 - \lambda_9)\sigma_2 I_2}{A_1}, \qquad u_2 = \frac{(\lambda_8 - \lambda_9)\sigma_2 I_2}{A_2}.$$

Then, by ensuring that the value of u obtained is always in the interval [0,1], the optimal value for each control is formulated,

$$
\begin{aligned}
u_1^* &= min\left\{max\left\{0, \frac{(\lambda_7 - \lambda_9)\sigma_1 I_1 + (\lambda_8 - \lambda_9)\sigma_2 I_2}{A_1}\right\}, 1\right\}, \\
u_2^* &= min\left\{max\left\{0, \frac{(\lambda_8 - \lambda_9)\,\sigma_2 I_2}{A_2}\right\}, 1\right\},
\end{aligned}
$$

Step 3: Substitute u_1^* and u_2^* into **Equation (8)** to obtain the optimal condition of the Hamilton (H^*).

Step 4: Determine the state equation in the optimal state,

$$\frac{dx^*(t)}{dt} = \frac{\partial H^*}{\partial \lambda}$$

Thus, the following state equation is obtained:

$$
\begin{aligned}
\dot{S_r^*} &= \frac{\partial H^*}{\partial \lambda_1} = \theta_r N_r - \frac{\beta I_r S_r}{N_r} - \mu_r S_r \\
\dot{E_r^*} &= \frac{\partial H^*}{\partial \lambda_2} = \frac{\beta I_r S_r}{N_r} - (\eta + \mu_r)E_r \\
\dot{I_r^*} &= \frac{\partial H^*}{\partial \lambda_3} = \eta E_r - (\mu_r + \delta_r)I_r \\
\dot{S_h}^* &= \frac{\partial H^*}{\partial \lambda_4} = \theta_h N_h - \left(\frac{\alpha_1 I_1 + \alpha_2 I_2}{N_h} + \frac{\alpha_3 I_r}{N_r}\right)pS_h - \left(\frac{\alpha_1 I_1 + \alpha_2 I_2}{N_h}\right)(1-p)S_h - \mu_h S_h + kR \\
\dot{E_1^*} &= \frac{\partial H^*}{\partial \lambda_5} = \left(\frac{\alpha_1 I_1 + \alpha_2 I_2}{N_h} + \frac{\alpha_3 I_r}{N_r}\right)pS_h - (\gamma_1 + \gamma_2 + \mu_h)E_1 \\
\dot{E_2}^* &= \frac{\partial H^*}{\partial \lambda_6} = \left(\frac{\alpha_1 I_1 + \alpha_2 I_2}{N_h}\right)(1-p)S_h - (d + \mu_h)E_2 \\
\dot{I_1^*} &= \frac{\partial H^*}{\partial \lambda_7} = \gamma_1 E_1 - (\mu_h + \delta_1 + (1+u_1^*)\sigma_1)I_1
\end{aligned}
$$

$$\dot{I}_2^* = \frac{\partial H^*}{\partial \lambda_8} = \gamma_2 E_1 + dE_2 - (\mu_h + \delta_2 + (1 + u_1^* + u_2^*)\sigma_2) I_2$$

$$\dot{R}^* = \frac{\partial H^*}{\partial \lambda_9} = (1 + u_1^*)\sigma_1 I_1 + (1 + u_1^* + u_2^*)\sigma_2 I_2 - (k + \mu_h) R.$$

Step 5: Determine the costate equation in the optimal state,

$$\frac{d\lambda^*(t)}{dt} = -\frac{\partial H^*}{\partial x}$$

Thus, the following costate equation is obtained:

$$\dot{\lambda}_1^* = -\frac{\partial H^*}{\partial S_r} = (\lambda_1 - \lambda_2)\frac{\beta I_r}{N_r} + \mu_r \lambda_1$$

$$\dot{\lambda}_2^* = -\frac{\partial H^*}{\partial E_r} = (\lambda_2 - \lambda_3)\eta + \mu_r \lambda_2$$

$$\dot{\lambda}_3^* = -\frac{\partial H^*}{\partial I_r} = (\lambda_1 - \lambda_2)\frac{\beta S_r}{N_r} + (\lambda_4 - \lambda_5)\frac{\alpha_3 p S_h}{N_r} + (\mu_r + \delta_r)\lambda_3$$

$$\dot{\lambda}_4^* = -\frac{\partial H^*}{\partial S_h} = \big(\lambda_4 - \lambda_5 p - \lambda_6(1-p)\big)\frac{(\alpha_1 I_1 + \alpha_2 I_2)}{N_h} + (\lambda_4 - \lambda_5)\frac{\alpha_3 p I_r}{N_r} + \mu_h \lambda_4$$

$$\dot{\lambda}_5^* = -\frac{\partial H^*}{\partial E_1} = -1 + (\lambda_5 - \lambda_7)\gamma_1 + (\lambda_5 - \lambda_8)\gamma_2 + \mu_h \lambda_5$$

$$\dot{\lambda}_6^* = -\frac{\partial H^*}{\partial E_2} = -1 + (d + \mu_h)\lambda_6 - d\lambda_8$$

$$\dot{\lambda}_7^* = -\frac{\partial H^*}{\partial I_1} = -1 + (\lambda_4 - \lambda_5 p - (1-p)\lambda_6)\frac{\alpha_1 S_h}{N_h} + (\mu_h + \delta_1)\lambda_7 + (\lambda_7 - \lambda_9)(1 + u_1^*)\,\sigma_1$$

$$\dot{\lambda}_8^* = -\frac{\partial H^*}{\partial I_2} = -1 + (\lambda_4 - \lambda_5 p - (1-p)\lambda_6)\frac{\alpha_2 S_h}{N_h} + (\mu_h + \delta_2)\lambda_8 + (\lambda_8 - \lambda_9)(1 + u_1^* + u_2^*)\,\sigma_2$$

$$\dot{\lambda}_9 = -\frac{\partial H}{\partial R} = (\lambda_9 - \lambda_4)k + \mu_h \lambda_9 .$$

With the transversal condition that $\lambda_i(t_f) = 0$ for $i = 1,2, \dots ,9$

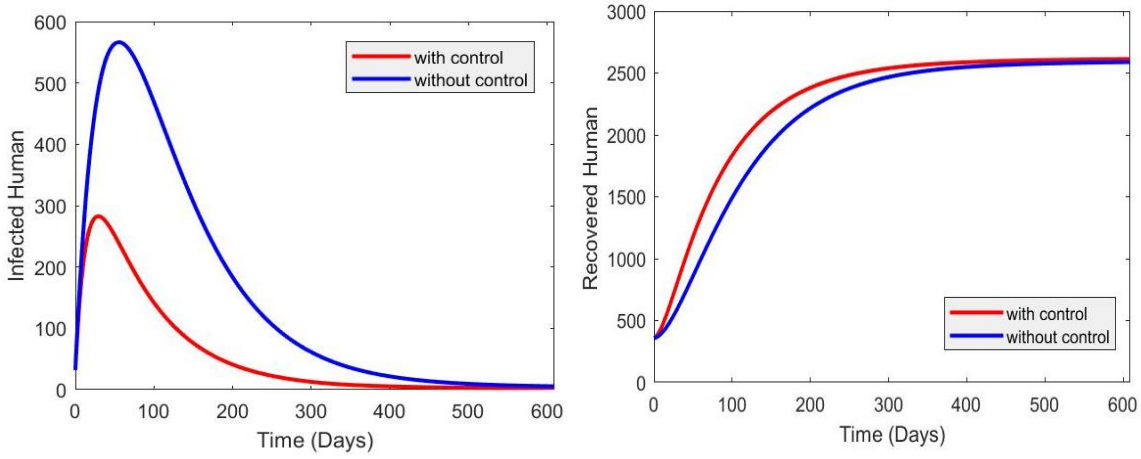
3.4 Numerical Simulation

To produce a visualization that can represent the behavior of mpox spread, simulations are carried out using MATLAB software. In addition to parameter values, this simulation requires the weight value of the control variable and the initial value of each subpopulation. The cost weight of implementing control measures u_1 and u_2 is represented by the parameters $A_1$and A_2. The weight values given for each control are $A_1 = 0.25$ and $A_2 = 0.5$. The value of $A_2 > A_1$ indicates that the priority of minimizing the costs and side effects of antiviral administration is more prioritized than the costs incurred for healthy living behavior. In addition, the following initial values are also given;

Table 3. Initial Conditions of Subpopulation

Variables	Description	Initial Values	References
S_r	Susceptible animal	50,000	Data Fitted
E_r	Exposed animal	20,000	Assume
I_r	Infected animal	30,000	Assume
S_h	Susceptible human	333,202,915	Data Fitted
E_1	Exposed low-risk human	1,200	Assume
E_2	Exposed high-risk human	1,000	Assume
I_1	Infected low-risk human	20	[24]
I_2	Infected high-risk human	12	[24]
R	Recovered human	358	[7]
N_r	Total population of animals	100,000	Assume
N_h	Total population of humans	333,205,505	[25]

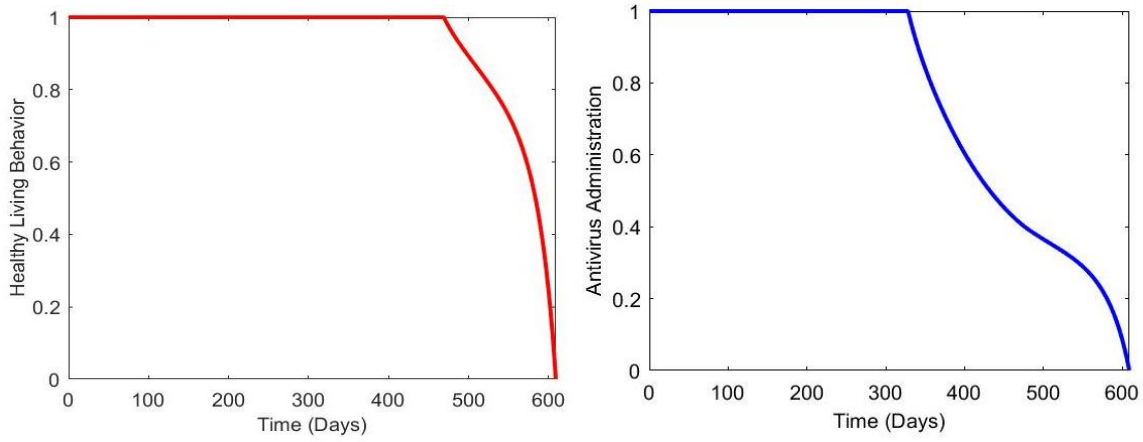
The initial value provided for the total number of animals that serve as virus-carrying agents is based on an analysis of research findings and information reported by the CDC. In the study **[11],** the ratio of the total population of animals and humans was 11:100. However, based on information from **[3]**, it can be inferred that the number of animals, both natural agents and animals that have the potential to spread the virus, is very low in the United States. Consequently, the ratio of total disease-carrying animals and total humans is presumed to be smaller, given the potential interactions between humans and endemic disease-carrying animals in the United States are quite difficult to occur. Some initial values for the human subpopulation were also assumed by estimating infection cases reported by the CDC and population density in the region **[24]**, **[25]**.



(a) **(b)**

Figure 3. Comparison of Changes in Population Size without and with Control
(a) Infected Human, (b) Recovered Human

The simulation results in **Figure 3** show that there are changes in the number of infected and recovered individuals when control is given. In the figure, the number of infected individuals is simulated as a whole by summing low-risk infected individuals (I_1) and high-risk infected individuals (I_2). The results obtained show that the number of infected people decreased by 64.62% after implementing healthy living behaviors and receiving antiviral treatment, as shown in **Figure 3(a)**. Meanwhile, the change in the total number of recovered individuals in **Figure 3(b)** shows that the application of healthy living behaviors and antiviral drugs can increase the number of individuals by 5.59%. Simulation results suggest that control measures effectively reduce infection cases over time, but infections may increase again if controls are lifted while rates remain elevated. To reduce the number of infected individuals and increase the cure rate, the rate at which the control should be administered at each time is shown in the following figure,



(a) **(b)**

Figure 4. Control Providing Rate
(a) Healthy Living Behavior, (b) Antiviral Administration

The simulation shown in **Figure 4** is the control rate given each time. The average rate of healthy behaviors (u_1) that must be applied to the infected human group is 93.15%. Meanwhile, the average antiviral

rate (u_2) that should be distributed to high-risk infected humans is 75.11%. In **Figure 4**, it can be seen that the controls given initially are constant before changing every day. The rate of change in the level of control is able to show the conditions of spread that occur. In this case, giving a high percentage of control at the beginning of the simulation gives a drastic decrease in the number of infected humans, so that the provision of control over time decreases as fewer cases of infection occur. The healthy living behavior provided is in supportive therapy, which includes the encouragement of habits that can facilitate the healing process. This differs from the natural habits of humans. One example of supportive therapy that can be intervened in cases of mpox infection is the administration of supplements and pain relievers to alleviate the symptoms of the infection **[21]**. The administration of antivirals represents a medical intervention whose distribution is regulated based on the patient's condition **[7]**.

In regulatory practice, changes in the control rate that occur within a short period of time (days) make it difficult for the government to use the results in designing a regulation. A constant control rate over time would give different results in terms of infection case reduction but could show the rate of control provision in general. However, a constant control rate is also not effective and efficient for some types of interventions, such as antiviral administration, in which case the rate of antiviral administration should decrease along with the decrease in infection cases. Based on the results obtained, any given control rate should take into account the risks of both costs and side effects of the interventions performed. Thus, any given control rate also has limits and is not excessive.

4. CONCLUSIONS

In this study, we have demonstrated that healthy living behavior and antiviral administration significantly minimize the spread of mpox in the United States. Numerical simulation results show that to reduce infection cases by 64.62% and increase the number of cured individuals by 5.59%, the average rate of healthy living behavior that must be implemented is 93.15%, and the rate of antivirus that must be distributed is 75.11%. Based on the simulation results, the number of infected individuals is constantly decreasing, indicating a lower risk of infection cases in 2024 This conclusion is also supported by data reported by the Centers for Disease Control and Prevention (CDC). However, it should be noted that the dynamics of infectious disease spread can also increase at any time. This study used the average rate of control to indicate the percentage of intervention in general. Providing constant control may have a different impact on reducing infection cases. Therefore, further research needs to be conducted so that the application of control can be done effectively in every situation without short-term changes.

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