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OPTIMAL CONTROL ANALYSIS OF THE EBOLA TRANSMISSION MODEL WITH VACCINATION

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ABSTRACT

Ebola virus disease (EVD) is a deadly disease caused by viruses within the genus Ebolavirus. Over 34,710 people have died from the virus globally, and outbreaks have shown that it spreads rapidly and uncontrollably. This research aims to find the optimal control to prevent the spread of EVD through vaccines. The population is divided into six, namely susceptible (S), vaccinated (V), infectious (I), treated (T), recovered (R), and deceased (D). We construct the model's optimal control parameters using the Pontryagin Principle. Vaccinations are only administered during specific periods. The optimal control interpretation was then obtained using numerical simulations. The results of this study indicate that the natural birth rate and the rate of contact of deceased humans have a much greater impact on the faster spread of the disease. Furthermore, it would be more effective to reduce the spread of EVD by providing vaccination compared to treating infected individuals. In conclusion, vaccination will be more effective if administered every two weeks. This is because it will lower the number of infected individuals significantly and reduce the cost of vaccination.

Keywords: Optimal Control, Ebola, Vaccination, Numerical Simulation.

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PRELIMINARY

Ebola virus disease (EVD) is a deadly disease caused by viruses within the genus Ebolavirus (Centers for Disease Control and Prevention (CDC), 2024). This virus can enter a person's body through cuts in the skin or unprotected mucous membranes with direct contact using the blood or bodily fluids of a person infected with EVD. Each case of EVD has three phases: incubation, early infective, and advanced infective (Jiang et al., 2017). From 2018 to 2020 there are more than 2000 deaths occurred in the Democratic Republic of Congo. The mortality rate in the current EVD outbreak ranges between 55% and 60% (World Health Organization (WHO), 2023). Over 34,710 people have died from the virus globally, and outbreaks have shown that it spreads rapidly and uncontrollably (Tanveer et al., 2024).

To decrease the potential of EVD transmission, we should increase awareness to lower the risk factors for EVD infection owing to human transmission and implement a vaccination or other antiviral medicines that people will take (Rafiq et al., 2020). As a preventive strategy, vaccines and treatment can suppress the number of EVD cases (Walldorf et al., 2019). The EVD vaccine can be used by individuals over 12 months (The United States Government, 2023). People who receive the vaccine should continue to take precautions to avoid exposure to the virus (World Health Organization (WHO), 2020). The Ervebo vaccine was found to be 95 – 100% effective in protecting humans against EVD (Woolsey & Geisbert, 2021). The Democratic Republic of Congo (DRC) found that antibodies were still present in individuals six months after vaccination.

Several obstacles arise in the implementation of vaccination, such as the cost. In 2014, West Africa estimated the cost impact of an EVD outbreak to be between $30 and $50 (Obeng-Kusi et al., 2024). Over four months in 2014, the projected preventive expenditures for EVD in selected organizations in Nigeria were more than 1 billion Naira (Olugasa et al., 2015). Despite these costs, vaccination is a helpful strategy for reducing disease transmission and mortality cases in subsequent outbreaks (Walldorf et al., 2019). The accessibility of vaccines and the ability to combine vaccination with a control strategy are some of the factors affecting vaccination implementation. In addition, we can maximize the vaccination intervention's effect by estimating the vaccination timing.

Vaccination at any time requires more significant costs, so there is a need for a vaccine administration strategy to minimize intervention costs and reduce the number of infected populations more effectively. To solve this problem, we can establish an optimal control model for the spread of EVD to determine a strategy to minimize the cost of vaccination interventions. Mathematical modeling has provided insights into the risk of major epidemics and the impact of public health interventions (Chowell & Nishiura, 2014). This mathematical model will be analyzed and simulated numerically to be interpreted in the real world.

Several studies have been developed to describe the dynamics of EVD transmission using antiviral therapies (Martyushev et al., 2016), isolation of infected and burial of deceased people (Abbas et al., 2024), efficacy and behaviour changes (Kengne & Tadmon, 2024). The studies have explored various control strategies such as treating, quarantining, education campaigns, and increasing sanitary measures controls (Bonyah et al., 2016; Seck et al., 2022). In 2021, Juga et al. found that fear of dying from EVD may help control the disease and lower transmission, but it is insufficient to eradicate it (Juga et al., 2021).

There have been many studies analyzing the spread of the EVD disease using various models and optimal control strategies. However, no one has researched optimal control using vaccination control. Based on this, we analyzed the optimal control model for the spread of EVD with vaccination intervention.

METHODS

This research uses a literature study method from books, journals, or research on optimal control theory. We use the model in (Chasanah et al., 2024) to analyze the optimal vaccination control. In the model used, we assumed that the individual population is constant and closed. Individuals who have recovered cannot be reinfected. Additionally, there is a possibility that individuals who are treated may recover or die. The steps taken to solve the problems related to optimal control theory are as follows:

1. Formulating an objective function J. The objective function used consists of two state variables (I and T) and one control variable (γ). This objective function aims to minimize vaccination costs and the number of people infected with EVD.
2. Constructing the Hamiltonian function H by applying Pontryagin's principle to a problem.
3. Determining the adjoint equation $\left(z_i(t)\right)$ and the transversality condition. Multiply the negative by the partial derivative of the Hamiltonian function H with respect to each state variable to obtain the equation $z_i'(t)$. The transversality condition is satisfied if $z_i(t) = 0, i = 1, \dots, 6$.
4. Determining the optimal condition of vaccination. This condition is obtained by setting the partial derivative of the Hamiltonian function with respect to the control variable equal to 0 $\left(\frac{\partial H}{\partial \gamma(t)} = 0\right)$.
5. Conducting numerical simulations on the infectious subpopulation with strategies without vaccination and vaccination every two, three, and four weeks.

Figure 1. shows the flowchart of the steps taken in this study.

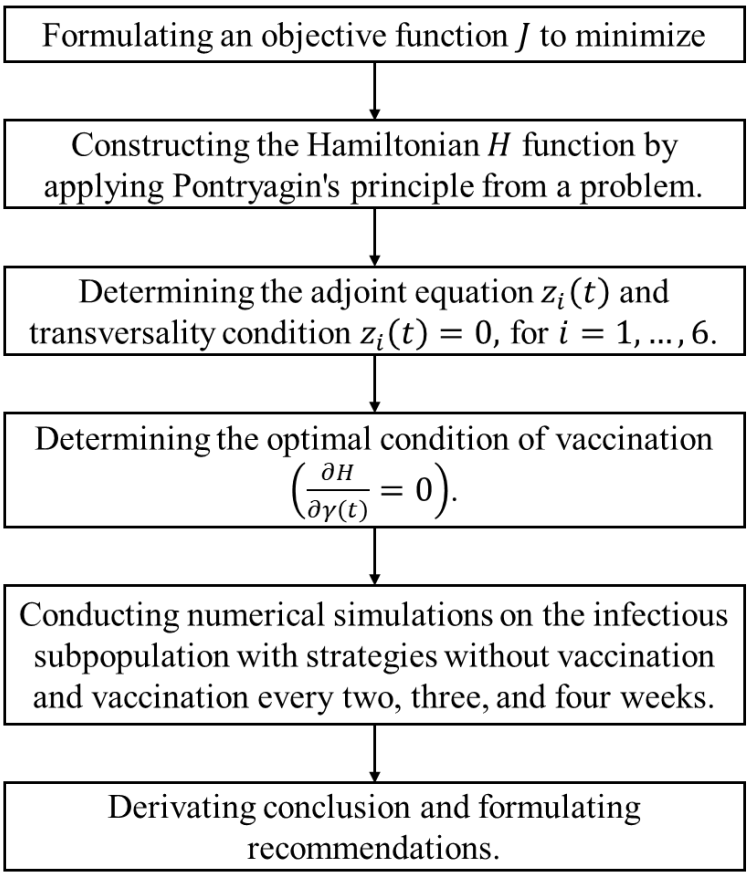

Figure 1. Flowchart the Steps of This Study

RESULT AND DISCUSSION

Mathematical Analysis

This section discusses an analysis, optimal control formulation, numerical simulation, and interpretation of the model. Using the model in (Chasanah et al., 2024), we obtain the equilibrium point, the basic reproduction number, and the local stability of the model. The model uses a deterministic model with the vaccinated compartment. The total population is denoted by N. The population is divided into six compartments, namely, susceptible (S), vaccinated (V), infectious (I), deceased (D), treated (T), and recovered (R). So that,

$$N = S + V + I + D + T + R. \quad (1)$$

This model assumes that a person transmits EVD to another person or person-to-pathogen contact. Based on this, the EVD transmission model was given by

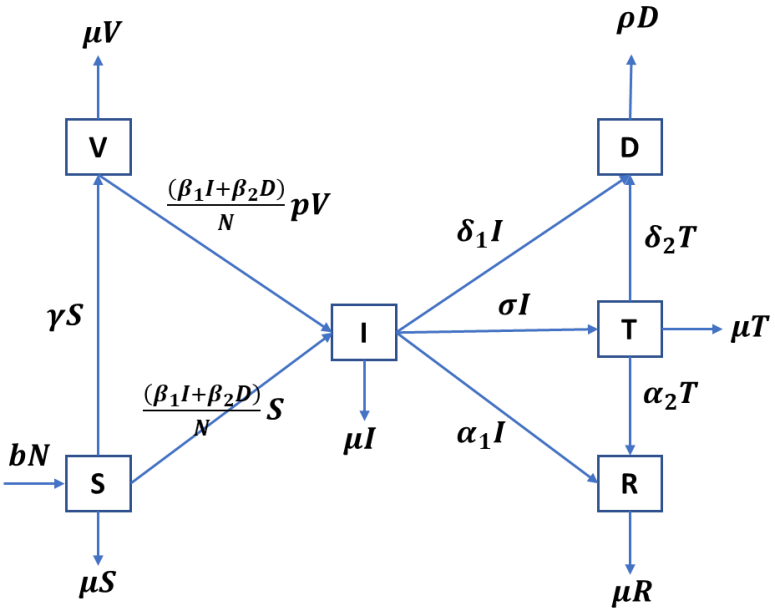

Figure 2. The EVD Transmission Model

Based on the EVD spread model in FIGURE 2., an EVD model that was given by

$$\frac{dS}{dt} = bN - \gamma S - \frac{(\beta_2 D + \beta_1 I)S}{N} - \mu S,$$
$$\frac{dV}{dt} = \gamma S - \frac{(\beta_2 D + \beta_1 I)pV}{N} - \mu V,$$
$$\frac{dI}{dt} = \frac{(\beta_2 D + \beta_1 I)S}{N} + \frac{(\beta_2 D + \beta_1 I)pV}{N} - (\delta_1 + \sigma + \alpha_1 + \mu)I,$$
$$\frac{dT}{dt} = \sigma I - (\delta_2 + \alpha_2 + \mu)T,$$
$$\frac{dR}{dt} = \alpha_1 I + \alpha_2 T - \mu R,$$
$$\frac{dD}{dt} = -D\rho + \delta_1 I + \delta_2 T. \quad (2)$$

Disease-free equilibrium of the model (2) is defined as

$$DFE = (S^*, V^*, I^*, T^*, R^*, D^*) = \left(\frac{bN}{\gamma+\mu}, \frac{\gamma bN}{\mu(\gamma+\mu)}, 0,0,0,0\right) \quad (3)$$

The basic reproduction number is denoted as $\mathcal{R}_0$, indicates how many secondary infections are expected to result from a single infectious case in a fully susceptible population (Delamater et al., 2019). This value is crucial in understanding whether a disease will likely die out or continue spreading within a population (Winarni et al., 2024). When $\mathcal{R}_0$ is less than 1, so each infected individual is, on average, passing the disease to fewer than one person, suggesting that the outbreak will eventually fade. On the other hand, if $\mathcal{R}_0$ is greater than 1, the infection is likely to spread, as each case leads to more than one new

infection (Delamater et al., 2019). We derive the basic reproduction number of the model (2) below.

$$\mathcal{R}_0 = \frac{b(\gamma p + \mu)(\beta_1 \rho B + \beta_2 \delta_1 B + \sigma \beta_2 \delta_2)}{\mu \rho A B(\gamma + \mu)}$$

The disease-free equilibrium point (E_0) is locally stable when the basic reproduction number $\mathcal{R}_0$ is less than 1. Otherwise, it becomes unstable. Additionally, when the endemic equilibrium E_1 exists and $\mathcal{R}_0 > 1$, it is locally stable (Brauer et al., 2019). Figure 3. shows the sensitivity of $\mathcal{R}_0$ influenced by each parameter. Parameters $b, p, \beta_1, \beta_2, \delta_1$, and δ_2 have a positive influence on $\mathcal{R}_0$. This means that the larger the parameter value, the larger the value of $\mathcal{R}_0$. Natural birth rate (b) and the rate of contact of deceased humans (β_2) have a much greater impact on the faster spread of the disease compared to the rate of contact of infectious humans (β_1) and the death rate of the quarantined individual due to EVD (δ_2).

The larger the values of the parameters $\gamma, \mu, \rho, \sigma, \alpha_1$, and α_2, the smaller the value of $\mathcal{R}_0$. Although the rate of treatment of the infectious (σ) and the recovery rate of treatment individual (α_2) did not have a significant impact. The rate of disposal of dead bodies (ρ) is highly sensitive to a decrease in the spread of EVD. It would be more effective to reduce the spread of EVD by providing vaccination compared to treating infected individuals.

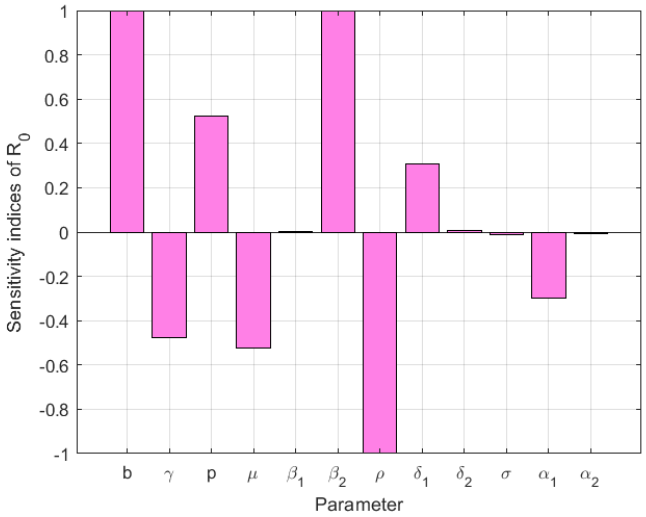

Figure 3. The Sensitivity of Parameters to $\mathcal{R}_0$

We provide an optimal control model based on these dynamics involving an objective function, adjoint equations, and optimization criteria. To perform the simulation, we apply the parameter values listed in Table 1. The resulting numerical analysis illustrates the population dynamics under the influence of vaccination as a control strategy.

Table 1. The Parameter Values of the Model

Parameter	Interpretations	Value
N	Number of population	1000
b	Natural birth rate	$1/(70 \times 52)$
μ	Natural death rate	$1/(70 \times 52)$
γ	Vaccination rate	0.15
β_1	The rate of contact of an infectious human	0.67
β_2	The rate of contact of deceased humans	0.64
p	The percentage of vaccines that cannot protect humans	0.002
δ_1	The death rate of a non-quarantined individual due to EVD	0.75
δ_2	The death rate of a quarantined individual due to EVD	0.3
α_1	The recovery rate of the nontreatment individual	0.33
α_2	The recovery rate of the treatment individual	0.8
σ	The rate of treatment of the infectious	0.019
ρ	The rate of disposal of dead bodies	0.0009

Optimal Control Analysis

In this section, we formulate the model's objective function (2). The objective function depends on three state variables (infectious (I), treated (T), recovered (R), and deceased (D)) and vaccination (γ) as control variables. This function represents the combined cost of managing the infected population and implementing vaccination interventions. Given that the relationship between the number of infections and vaccination efforts is nonlinear, we use a quadratic formulation for both state and control variables. Specifically, the terms $\omega_3 I^2$ and $\omega_4 T^2$ quantify the costs related to infection and treatment. Respectively, $\phi\gamma^2$ captures the cost associated with vaccination, where ϕ denotes the weighting factor. The optimal control strategies are then derived by minimizing the constructed objective function.

$$J(\gamma) = \int_0^T (\omega_3 I^2 + \omega_4 T^2 + \phi\gamma^2)\ dt \tag{4}$$

Then, the Hamiltonian function H is formed using Pontryagin's principle

$$H = \omega_3 I^2 + \omega_4 T^2 + \phi\gamma^2 + \sum_{i=1}^{6} z_i f_i \tag{5}$$

Where function f_i is the right-hand side of the model (2). The adjoint variables z_i for $i = 1, 2, \ldots, 6$ satisfy the following co-state system

$$z_1' = -\frac{\partial H}{\partial S} = z_1\left(\gamma + \frac{(\beta_2 D + \beta_1 I)}{N}\right) - z_2\gamma - z_3\frac{(\beta_2 D + \beta_1 I)}{N},$$

$$z_2' = -\frac{\partial H}{\partial V} = z_2\left(\frac{(\beta_2 D + \beta_1 I)p}{N} + \mu\right) - z_3\frac{(\beta_2 D + \beta_1 I)p}{N},$$

$$z_3' = -\frac{\partial H}{\partial I} = -2\omega_3 I + z_1\frac{\beta_1 S}{N} + z_2\frac{\beta_1 pV}{N} - z_3\left(\frac{\beta_1 S}{N} + \frac{\beta_1 pV}{N} + \delta_1 + \sigma + \alpha_1 + \mu\right) - z_4\sigma - z_5\alpha_1 - z_6\delta_1,$$

$$z_4' = -\frac{\partial H}{\partial T} = -2\omega_4 T + z_4(\delta_2 + \alpha_2 + \mu) - z_5\alpha_2 - z_6\delta_2,$$

$$z_5' = -\frac{\partial H}{\partial R} = -2\omega_5 R + z_5\mu,$$

$$z_6' = -\frac{\partial H}{\partial D} = -2\omega_6 D + z_1\frac{\beta_2 S}{N} + z_2\frac{\beta_2 pV}{N} - z_3\frac{\beta_2 S + \beta_2 pV}{N} + z_6\rho,$$

where the transversality condition $z_i(t) = 0$, for $i = 1, 2, \ldots, 6$.

To obtain the optimal control variable, we solve the partial derivative of a Hamiltonian function (5) concerning the control variable γ^* is equal to zero. Since the control variable is bounded in [0,1] for all $t \in T$, we derive the optimal control variable below.

$$\gamma^* = \begin{cases} 0 & , \text{for } \frac{\partial H}{\partial \gamma(t)} < 0 \\ \frac{S(z_1 - z_2)}{2\phi} & , \text{for } \frac{\partial H}{\partial \gamma(t)} = 0 \\ 1 & , \text{for } \frac{\partial H}{\partial \gamma(t)} > 0 \end{cases}$$

Using the initial condition x_0, we solve the variable state $\dot{x}(t) = \frac{\partial H}{\partial z}$, where $x = (S, V, I, T, R, D)$ and $z = (z_1, z_2, z_3, z_4, z_5, z_6)$, and the co-state system $z(t) = -\frac{\partial H}{\partial x}$ with transversality conditions $z_1(t) = 0$ for $i = 1, 2, \ldots, 6$. We obtain the optimal control γ^* to minimize the cost function $J(\gamma)$ as follows

$$\gamma^* = \max\left\{0, \min\left\{1, \frac{S(z_1 - z_2)}{2\phi}\right\}\right\}. \quad (6)$$

In (6), the control variable is continuous. It means vaccination is given every time. If vaccination is given every few years, we transform (6) into a semi-discrete function with optimal control of the parameter γ^* below.

$$\gamma^*(t) = \sum_{0 \le j \le \frac{T}{h}} \gamma^*(t)\mathbf{1}_{[t_j, t_{j+1}]}$$

where $t_j = jh$, $\mathbf{1}_{[t_j, t_{j+1}]}$ is the function on the interval $[t_j, t_{j+1})$ and $\gamma^*(t)$ (t) is changed every h year.

Numerical Simulation

Numerical simulations were conducted using four vaccination timing strategies: no vaccination, vaccination every two, three, and four weeks. The parameter values and initial population conditions used in this simulation are presented in Tables 1 and 2.

Table 2. Initial Values of Variable

Variable	Value
N	1000
$S(0)$	800
$V(0)$	0
$I(0)$	150
$D(0)$	50
$T(0)$	0
$R(0)$	0

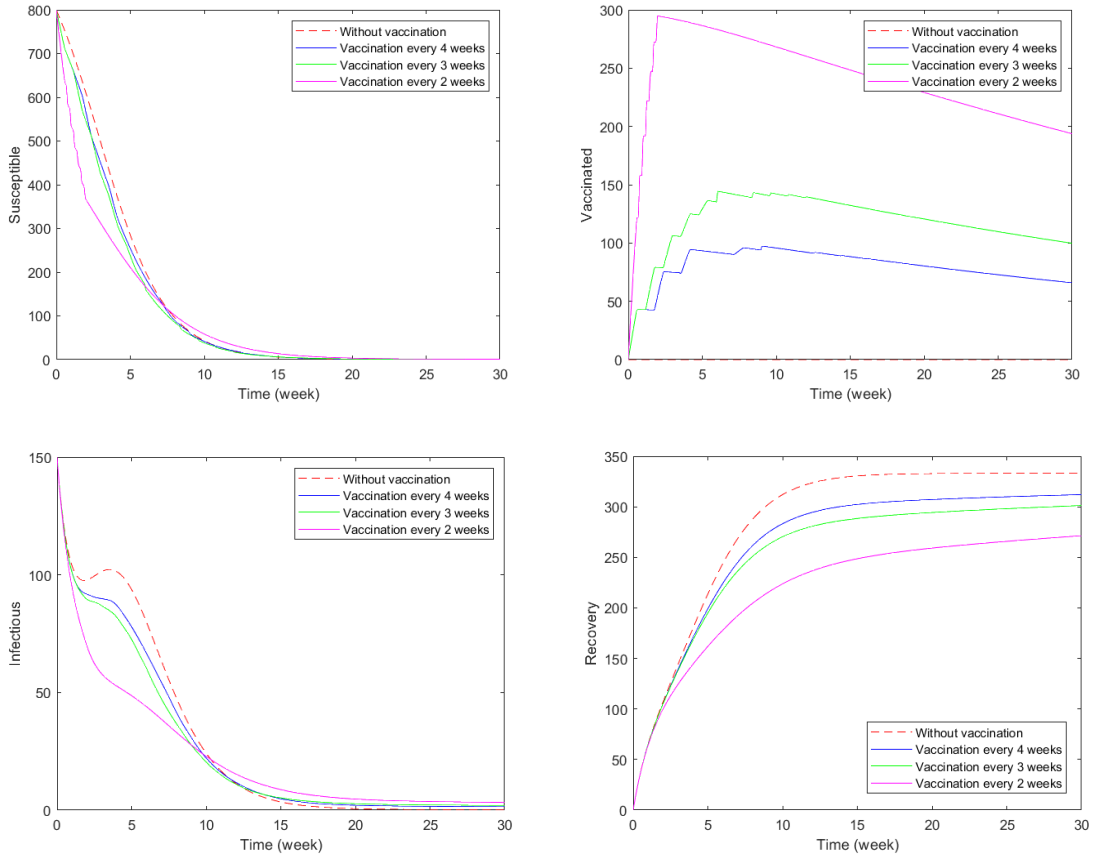

Figure 4. Number of Subpopulations with Several Vaccination Strategies

From Figure 4, implementing a vaccination strategy can reduce the number of infected individuals. The more frequently vaccination is administered, the lower the number of infectious individuals. Without vaccination, the infectious population initially increases before declining in the fifth week. Vaccination administered every four or three weeks produces similar outcomes, whereas a biweekly vaccination schedule yields different results. In this case, infectious individuals significantly decline during the first 15 weeks. Based on this, vaccination activities will be more effective if done every two weeks. Although the cost

is higher compared to vaccination every three or four weeks, the difference in the reduction in the number of infected individuals is quite significant.

CONCLUSION

The study concludes that it would be more effective to reduce the spread of EVD by providing vaccination compared to treating infected individuals. The optimal control to minimize the cost function of vaccination is $\gamma^* = \max\left\{0, \min\left\{1, \frac{S(z_1 - z_2)}{2\phi}\right\}\right\}$. Implementing vaccination can reduce the number of infected individuals in 15 weeks. More frequent vaccination schedules lead to a further decline in EVD cases. However, the improvements are insignificant between vaccinations every three and four weeks. Among the tested intervals, administering vaccination every two weeks proved to be the most effective. This strategy can minimize the infection rate and reduce the overall cost of immunization efforts. Based on the outcomes of this study, the model can be further extended to incorporate more diverse vaccination timing scenarios and to consider additional parameters that may significantly influence the system's outcomes.

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