ORIGINAL ARTICLE

Optimal Control Theory Applied to Rabies Epidemiological Model with Time-dependent Vaccination in Davao City, Mindanao Island, Philippines

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ABSTRACT

Background and Objective. Rabies continues to be a challenge in Davao City despite the efforts of the city's local government to vaccinate primarily the non-stray dog population. Meanwhile, studies have shown that time-dependent vaccination strategy is considered a prime factor for a cost-effective rabies control strategy. Hence, this study aims to provide information that will determine the optimal vaccination strategy targeted to the stray dog population that minimizes the rabies-infected dog population and vaccination costs using optimal control theory (OCT).

Methods. OCT is used to identify the optimal level of key rabies control, i.e., vaccination. Here, OCT was applied to a modified Susceptible-Exposed-Infectious-Vaccinated (SEIV) compartmental model. The study's key parameters were derived from published articles on rabies in Davao City and similar regions, along with the city's rabies reports.

Results. The findings revealed that while rabies remains endemic in the city, it is possible to reduce the number of cases through consistent implementation of vaccination programs to the exposed and susceptible dog populations. Nevertheless, the feasibility of these findings relies to the effective targeting of vaccine coverage for the dog population. From the simulations performed, the exposed dog population (i.e., pre-rabid dogs) was able to reach zero observation when the transmission rate (β) is 0.001 for all values of anti-rabies vaccine coverages for exposed (α) and susceptible (b) dog populations and β = 0.01 only when α = 0.7 and b = 0.7, α = 0.7 and b = 0.5, and α = 0.5 and b = 0.7. Consequently, the number of infectious dogs will thereby decrease. Moreover, a nonlinear correspondence was also observed in all scenarios between the vaccination rate and the number of rabies-exposed dogs such that the reduction in the incidence of rabies cases becomes apparent only when the vaccination rate is at least 0.9995.

Conclusion. In high rabies transmissibility scenarios, a time-dependent vaccination strategy demonstrated a reduction in the number of rabies-infected dogs. However, this approach involves a trade-off, limiting the period during which monthly vaccinations can be relaxed.

** Dejell Anne M. Satur and Zython Paul T. Lachica contributed equally to this work.*

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Consequently, a robust and timely vaccination program for dogs is crucial to manage high rabies transmission rates. Lastly, the model simulation underscores the importance of initiating monthly vaccinations.

Keywords: optimal control theory, optimization, rabies, SEIV model, time-dependent vaccination

INTRODUCTION

Rabies has been known to be one of the oldest and most lethal diseases, killing people and animals.[1] In the Philippines, the rabies virus kills at least 200 to 300 Filipinos annually.[2] In response to the persisting rabies cases, the Anti-Rabies Act of 2007 (or the Republic Act 9482) was enacted, establishing the National Rabies Control Program (NRCP) that aims to control and eliminate rabies across the country[3] through strategies such as mass dog vaccination, establishment of central database system for registered and vaccinated dogs, impounding of stray and unvaccinated dogs, conduct of information and education campaign on the prevention and control of rabies and dog population control through neutering.[4]

Dogs continue to be the dominant transmitters of the rabies virus.[5,6] Specifically, stray or ownerless dogs are more susceptible to rabies infection due to their free-roaming state and more prone to contact with other rabid animals. Vaccination is an effective strategy for eliminating rabies, and its implementation in the stray dog population dramatically mitigates the risk of human rabies.[7,8] Ending the rabies epidemic is also a priority among the many global health concerns confronting humankind today,[9,10] which calls to review and either adapt or re-design evidence-based rabies interventions, and create context-specific implementation plans to effectively deploy these interventions. Although the budgetary requirements for such a move may appear to be substantially high, it can be potentially offset by the number of prevented rabies-attributed deaths.

Davao City, the largest city in the Philippines by geographical area, had an estimated dog population of roughly 178,000 in 2020, based on the 1,776,949 human population as recorded by the Philippine Statistics Authority (PSA)[11] and an average observed dog-to- human ratio of 1:10[12,13]. With the increase in the human population, the dog population is anticipated to increase as well. Moreover, findings from the City Veterinarian's Office (CVO) indicates an increase in rabies cases over the past years.[14,15] These conditions present a significant obstacle to achieving the rabies-free Philippines goal. Retrospectively, the CVO has implemented four stepped-up rabies control strategies in response to the 2007 Anti-Rabies Act, namely (1) mass vaccination of dogs, (2) impounding of dogs, i.e., catching free-roaming and stray dogs and placing them in the city pound, (3) castration, i.e., surgical removal of the male dog's testicles, and (4) information and education campaign (IEC) sessions since 2011.[16] Although impounding free-roaming or stray dogs has been found to reduce cases, the CVO has faced significant logistical challenges, such as shortages of impounding vehicles, manpower, and scheduling difficulties.[14,17] This instance may illustrate the World Health Organization's (WHO) recommendation of vaccination as the most cost-effective method for eradicating rabies in dogs.[18] Particular to Davao City, mass dog vaccination and IEC campaigns happens simultaneously. Dog owners bring their dogs for free vaccination and the CVO personnel hand out flyers or pamphlets to the dog owners as form of the IEC.[17] Additionally, informative videos on the ways to avoid rabies exposure and infection as well as the physical manifestation of rabies infection when post-exposure prophylaxis vaccine is not promptly administered are also played during the vaccination drive.[18] Although while the vaccination strategy has been stepped up, the vaccine coverage against canine rabies in Davao City from 2011 to 2018 were most of the time less than 70%.[14,17] Therefore, there is a need to increase the anti-rabies vaccine coverage in the city to amplify the impact of the rabies control program.

Rabies can be viewed as a dynamical system due to its complex interactions and dynamics involved in its spread within host populations.[19,20] This perspective draws on insights from epidemiological modeling, particularly the Susceptible-Exposed-Infectious-Recovered (SEIR) framework, which has been applied to various infectious diseases to understand their dynamics.[21] Several studies have applied SEIR modeling techniques to rabies epidemiology to understand its dynamics and control. For instance, the SEIR framework was used to assess the economic impact of different control strategies on rabies transmission in dog populations.[22,23] Another relevant SEIR-based study simulated the transmission dynamics of dog rabies with indirect interspecies transmission from jackals, highlighting how the disease can persist and spread in wildlife populations.[24] These models account for the interplay between susceptible, exposed, infectious, and recovered dogs, showcasing how rabies dynamics evolve over time, respond to interventions, and exhibit nonlinear behaviors, which are all characteristics of dynamical systems.

Optimization methods are used to determine the optimal solution for system design and operational policy variables,[25] and because this research is centered on the dynamics of a population over time, the approaches considered must account for the system's nonlinearity, i.e., the population value for each subpopulation. The method presented in this study was derived from optimal control theory (OCT) and applied to a mathematical model of rabies transmission, with vaccination serving as a control. OCT is concerned with determining control strategies for dynamical systems, as well as taking into account the extent of control over time.[26,27] The objective of OCT is to determine the control signals that will cause a process to satisfy the physical constraints and, at the same time, maximize/minimize some performance criteria.[28] For instance, application of OCT in finding the optimal distribution of vaccine evaluated through an SEIR model characterizing the population dynamics of a rabies epidemic in raccoons with seasonal birth pulse.[29]

In this work, OCT was applied in a rabies epidemic model and the model dynamics was studied in the presence of a time-dependent vaccination. The standard SEIV (Susceptible-Exposed-Infectious-Vaccinated) epidemiological model was used to consider a compartment for vaccinated dogs 30 in recasting the problem as an optimal control problem and then used as a basis for the objective function of the OCT.[31] The constraints included were the rates of change in the varying sorts of stray dog populations, as defined by the SEIV framework. The simulation findings were achieved using the Forward-Backward Sweep method. The initial conditions were calibrated using dog rabies reports in Davao City from 2011 to 2017.

OBJECTIVES

The objective of this study is to aid in the development of an optimal vaccination strategy by providing an overview and analysis of several rabies epidemic scenarios.

Specifically, this research aims to (1) develop a modified SEIV model of rabies transmission in a stray dog population with vaccination as a control strategy; (2) compare various scenarios of a rabies epidemic in a stray dog population utilizing optimal control theory; and (3) aid in determining the optimal vaccination strategy that minimizes the number of infectious stray dogs and vaccination costs. The model simulations provided an overview of the sub-various population's dynamic behavior under the model assumptions and parameters. Furthermore, this work discussed the particular scenarios that aid in understanding how these populations grow and shrink over time with time-dependent vaccination.

MATERIALS AND METHODS

Study Area

The study area was in Davao City, Philippines, a highly urbanized city with a household population of 1.77 million distributed across its 182 barangays.[11] In terms of rabies landscape, an alarmingly increasing trend in animal rabies cases has been documented by the city's annual reports over five years, with recorded cases escalating from 12 in 2015 to 15 in 2016, 21 in 2017, 51 in 2018, and subsequently declining to 29 in 2019.[15] However, from 2022 to 2023, approximately 300 to 350 dog-bite victims per day sought post-exposure prophylaxis vaccinations and consultations. Notably, during the same period, 16 rabies-induced human deaths were recorded.[32]

Study Design

Vaccination has been known to be a cost-effective strategy for rabies control.[33] Mathematical modeling is useful in determining the necessary number of dogs to be vaccinated by simulating potential outcomes, such as the number of rabies-infected dogs and the time required to reduce the incidence of rabies. Hence, mathematical modelling with optimal control theory was employed in this paper to identify a dog vaccination strategy that yields the lowest number of rabies-infected dogs through model simulation. Additionally, the model assumptions and initial conditions, detailed in the following sections, were established to ensure the reliability of the model simulations.

Model Formulation

The compartmental model used in this study is a Susceptible-Exposed-Infectious-Vaccinated (SEIV) epidemiological model, which consists of four compartments, namely: (1) susceptible, (2) exposed, (3) infectious, and (4) vaccinated.[34] It describes the dynamics of rabies transmission through time and focuses primarily on a stray dog population, with vaccination as a proposed control strategy. The susceptible (S) compartment comprises the dog population that either has not been exposed to the virus and does not have any immunity against it or dogs with waned vaccine-induced immunity a year after receiving vaccination. Susceptible dogs that are infected by rabies virus remains latent for some time before becoming infectious are considered under the exposed (E) compartment, i.e., dogs that are infected but not yet infectious. Meanwhile, the infectious (I) compartment comprises the virus-infected dog population that are able to transmit the disease. Lastly, the vaccinated (V) compartment comprises the dog population that has been vaccinated against rabies, keeping them from getting infected and contagious for a certain period. These population compartments are measured over time. Hence, they are functions of time t in months, i.e., $S(t)$, $E(t)$, $I(t)$, and $V(t)$. The model has the following assumptions:

1. The population within each compartment is well-mixed (i.e., any two dogs interact with the same probability).
2. A portion of the dog population gives birth to a new generation with rate A, which becomes part of the susceptible population. A proportion of the susceptible population becomes part of the exposed population when a susceptible dog interacts with an infected dog. It becomes exposed due to transmission rate $^{\beta}$, where N is the N total of all populations such that $N(t) = S(t) + E(t) + I(t) + V(t)$. Exposed dogs are dogs have contracted (i.e., bitten by other rabid dogs) but are not yet infectious.
3. Exposed dogs become infectious at an incubation rate σ.
4. Vaccinated dogs become susceptible to rabies due to the rate of loss of vaccination immunity, θ.
5. When a proportion of the rabies-exposed dogs α and a proportion of the susceptible dogs b are given the same vaccination treatments at the same rate, these proportions become part of the vaccinated dog population. These dogs are vaccinated at rate $k(t)$ at time t.

6. Dogs from the susceptible, exposed, and vaccinated populations can still die regardless of disease due to natural mortality at a rate m.
7. Once a dog is considered part of the infectious population, it can never be vaccinated. These dogs are assumed to never recover and die due to the disease at rate μ.

The movements and interactions of compartments and the corresponding parameters are depicted in Figure 1. The mathematical model, which describes the dynamics of the population compartments over time, is derived from the schematic diagram in Figure 1.

The rate of change for each compartment is specified by a system of ordinary differential equations:

$$\frac{dS}{dt} = A + \theta V - \frac{\beta SI}{N} - mS - bk(t)S, \quad [1]$$

$$\frac{dE}{dt} = \frac{\beta SI}{N} - mE - ak(t)E - \sigma E, \quad [2]$$

$$\frac{dI}{dt} = \sigma E - \mu I, \quad [3]$$

$$\frac{dV}{dt} = ak(t)E - \theta V + bk(t)S - mV, \quad [4]$$

$$\frac{dN}{dt} = A - mS - mE - \mu I - mV, \quad [5]$$

under the following initial conditions:

$$S(t), E(t), I(t), V(t), N(t) \geq 0 \quad [6]$$

where the description of the parameters is in Table 1.

Model Parameterization

The parameters used in the model and their corresponding values are listed in Table 1. The monthly inflow of stray dogs in Davao City, A, is estimated using the dog-household ratio.[11,12] The range of values assumes a long-term incidence of rabies to observe the effect of the vaccination rate on reducing the incidence of the disease.[35] The assigned values for α and b are vaccine coverages based on the WHO recommendation.[36] These parameters were chosen particularly to illustrate the significance of the varying values utilized to compare the simulated results. The remaining parameter values were based from other rabies study.[37]

Optimal Control Problem Formulation

With the formulated SEIV model, we use OCT to determine the optimal vaccination strategy that minimizes the number of infectious stray dogs and vaccination costs.

Objective Function

We reformulate the SEIV model into an optimal control problem with vaccination rate $k(t)$ as the control. The objectives are to (1) minimize the infectious dog population as well as (2) the vaccination cost incurred by the end of a given time period $[0, T]$. The objective function is shown in equation [7] where each objective weighting factor was all set to one to signify the relative importance of each objective,[38,39] and the state functions as constraints, along with their corresponding initial conditions, are shown in equations [8]-[12]. The control variable $k(t)$ was set to be nonlinear to consider higher costs when increasing the coverage of the intended population of the intervention.[26,34]

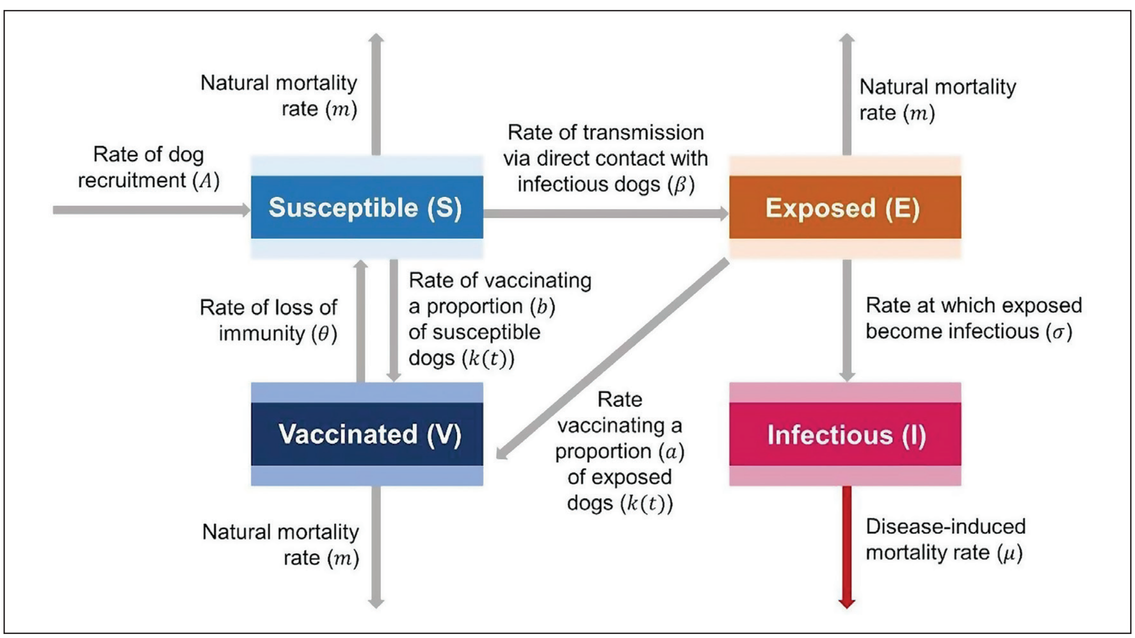

Figure 1. ***Schematic Diagram of the SEIV Model.*** The rectangles signify the four compartments: S, E, I, and V; the arrows indicate the dynamics among the compartments.

Table 1. Definition and Values of the Parameters Used in the Model Simulation

Parameters	Value/s	Unit	Description	Source
$k(t)$	[0,1]	month^{-1}	Vaccination rate at time t	Loucks et al., 2017
$A*$	0 500 1000 1500 2000	$\frac{\text{dogs}}{\text{month}}$	Monthly inflow of stray dogs in Davao City	Assumption
m	$\frac{1}{150}$	month^{-1}	Natural mortality rate of stray dogs	Zhang et al., 2011
μ	$\frac{1}{12}$	month^{-1}	Death rate due to disease	Zhang et al., 2011
$\beta*$	10^{-3} 10^{-2} 10^{-1} 1	month^{-1}	Transmission rate of rabies virus	Assumption
σ	0.5	month^{-1}	Rate at which exposed becomes infectious	Zhang et al., 2011
θ	$\frac{1}{12}$	month^{-1}	Rate of loss of vaccination immunity	Zhang et al., 2011
$a*$	0.5 0.7	N/A	Proportion of exposed population to vaccinate	Assumption
$b*$	0.5 0.7	N/A	Proportion of susceptible population to vaccinate	Assumption

**The simulation involved varying the values of these parameters.*

$$\min_k \int_0^T (I(t) + [k(t)]^2)dt, \quad [7]$$

subject to

$$S'(t) = A + \theta V - \frac{\beta SI}{N} - mS - bk(t)S, \qquad S(0) = S_0 \geq 0, \quad [8]$$

$$E'(t) = \frac{\beta SI}{N} - mE - ak(t)E - \sigma E, \qquad E(0) = E_0 \geq 0, \quad [9]$$

$$I'(t) = \sigma E - \mu I, \qquad I(0) = I_0 \geq 0, \quad [10]$$

$$V'(t) = ak(t)E - \theta V + bk(t)S - mV, \qquad V(0) = V_0 \geq 0, \quad [11]$$

$$N'(t) = A - mS - mE - \mu I - mV, \qquad N(0) = N_0 \geq 0, \quad [12]$$

where

$$0 \leq k(t) \leq 1. \quad [13]$$

Initialization

A 24-month interval was chosen for this study (i.e., $T = 24$) for the optimal control simulation. The 24-month time frame was chosen to strike a balance between observing medium-term impacts and providing a window of opportunity to change strategies if needed, that allows a thorough evaluation of the program's effectiveness in controlling rabies and enabling data-driven decision-making for ongoing efforts.

In 2011, the CVO initiated the Intensified Rabies Control Program in Davao City with the primary objective of effectively curbing the incidence of rabies in the city. This program placed a significant emphasis on the systematic implementation of mass dog vaccination. In that year, CVO recorded two positive dog rabies cases. So, at t_0=January 2011, the initial value set for $I(t_0)$ is two. The initial value for $S(t_0)$ is an estimate based on the dog-household ratio.[12,13] The initial values of $E(t_0)$ and $V(t_0)$ are estimates from the recorded number of unvaccinated dogs and vaccinated dogs, respectively. The initial values for the functions $S(t_0)$, $E(t_0)$, $I(t_0)$, and $V(t_0)$ are shown in Table 2.

Table 2. Initial Values of the Variables

Variables	Description	Values
$S(t_0)$	Initial value of the susceptible population	2000
$E(t_0)$	Initial value of the exposed population	5000
$I(t_0)$	Initial value of the infectious population	2
$V(t_0)$	Initial value of the vaccinated population	5000

Algorithm and Numerical Tool

The Forward-Backward Sweep method, one of the several approaches evolved from optimum control theory, was used to solve the formulated optimal control problem.[31] The method was performed through MATLAB® R2021b.

Methods of Analysis

Among the parameters involved in the system, those that were varied were A, β, α, and b. A study substantiated that a change on the inflow rate in susceptible population constitute a significant and most sensitive factor contributing to the documented cases of canine rabies in Davao City.[34] By varying the transmission rate of the disease (β) within the assigned range, the impact of the vaccination rate on the decrease of disease incidence was observed. The study compared scenarios when the percentage of the exposed dog population vaccinated (α) is 50% and the percentage of the susceptible population vaccinated (*b*) is 70% – and vice versa. The study also compared scenarios when both percentages of the exposed and susceptible populations vaccinated are equal – both (α) and (*b*) are either 50% or 70%.

The transversality conditions for optimality were derived using the Pontryagin's Maximum Principle.[40] In this study, the final time in intervals will be T = 24 months, such that the transversality conditions will be represented as $\lambda_i(24) = 0$, i = 1, 2, 3, 4. With this, the transversality conditions represented by the adjoint functions, are as follows. Refer to Appendix A for the derivation of adjoint functions.

$$\lambda'_1 = \lambda_1 m + \frac{\beta I}{N}(\lambda_1 - \lambda_2) + bk(\lambda_1 - \lambda_4), \qquad \lambda_1(24) = 0, \qquad [14]$$

$$\lambda'_2 = \lambda_2 m + \sigma(\lambda_2 - \lambda_3) + ak(\lambda_2 - \lambda_4), \qquad \lambda_2(24) = 0, \qquad [15]$$

$$\lambda'_3 = \lambda_3 \mu + \frac{\beta S}{N}(\lambda_1 - \lambda_2) - 1, \qquad \lambda_3(24) = 0, \qquad [16]$$

$$\lambda'_4 = \theta(\lambda_4 - \lambda_2) + \lambda_4 m \qquad \lambda_4(24) = 0, \qquad [17]$$

Simulation

The resulting control function and state functions correspond to the varied values of the monthly inflow of stray dogs (*A*), transmission rate (β), the proportion of exposed dogs vaccinated (α), and the proportion of susceptible dogs vaccinated (*b*). In the implementation, different parameter settings were defined according to the varied parameters, *A*, β, α, and *b*. There were 32 scenarios chosen to be simulated. Refer to Appendix B for the details of each scenario.

The possible scenarios were characterized into sets to observe in terms of how each affects a population over a chosen period of time. Analyzing these parameters in this manner is essential because it provides a more elaborated interpretation of whether or not a parameter has a significant effect on the dynamics and the size of a population over time. Table 3 shows the 12 sets of scenarios formed and studied.

RESULTS

The observations and analyses gathered from these sets provide significant information that helps in finding the optimal vaccination strategy that minimizes the infectious population and the cost of vaccination efforts. Although some of these observations include specific and exact values, it should be noted that these do not actually represent the scenarios in the real world and can only be used for comparison reasons. The dynamics of the control function, $k(t)$, the state functions, $E(t)$, and $I(t)$ for over a simulation period of 24 months are presented in this section. Some of the results for each set is presented in the succeeding figures.

The exposed populations in Figure 2 had a swift decrease from the start of the simulation to approximately by the 8th or 9th month, then had a gradual increase up to the 24th month. These populations behave at a similar pace over time. It was observed that since the 5th month, the size of each population showed extremely slight differences between each other. These slight differences remained evident until reaching the final time. The resulting exposed population reached to a minimum value at around the 15th to 17th month.

The sizes of the infectious populations in Figure 2 were observed to be equal with each other. These vary at a similar

Table 3. Scenarios Categorized into Sets

Set	Scenarios	Monthly inflow of stray dogs (A)	Proportion of exposed (α) and susceptible (b) dog to be vaccinated	Disease transmission rate (β)	Description
I	1, 2, 3, 4, 5	500, 1000, 1500, 2000, 0	(0.5, 0.5)	10^{-3}	Exploring the confounding effect of the monthly inflow of stray dogs A with a slow disease transmission rate β
II	6, 7, 8, 9, 10	500, 1000, 1500, 2000, 0	(0.7, 0.5)	10^{-3}	
III	11, 12, 13, 14, 15	500, 1000, 1500, 2000, 0	(0.5, 0.7)	10^{-3}	
IV	16, 17, 18, 19, 20	500, 1000, 1500, 2000, 0	(0.7, 0.7)	10^{-3}	
V	1, 21, 22, 23	500	(0.5, 0.5)	10^{-3}, 10^{-2}, 10^{-1}, 1	Exploring the confounding effect of disease transmission rate β with a low monthly inflow of stray dogs A
VI	6, 24, 25, 26	500	(0.7, 0.5)	10^{-3}, 10^{-2}, 10^{-1}, 1	
VII	11, 27, 28, 29	500	(0.5, 0.7)	10^{-3}, 10^{-2}, 10^{-1}, 1	
VIII	16, 30, 31, 32	500	(0.7, 0.7)	10^{-3}, 10^{-2}, 10^{-1}, 1	
IX	1, 6, 11, 16	500	(0.5,0.5), (0.7,0.5), (0.5,0.7), (0.7, 0.7)	10^{-3}	Exploring the effect of vaccine coverages (α, b) at a low monthly inflow of stray dogs A with varying disease transmission rates β
X	21, 24, 27, 30	500	(0.5,0.5), (0.7,0.5), (0.5,0.7), (0.7, 0.7)	10^{-2}	
XI	22, 25, 28, 31	500	(0.5,0.5), (0.7,0.5), (0.5,0.7), (0.7, 0.7)	10^{-1}	
XII	23, 26, 29, 32	500	(0.5,0.5), (0.7,0.5), (0.5,0.7), (0.7, 0.7)	1	

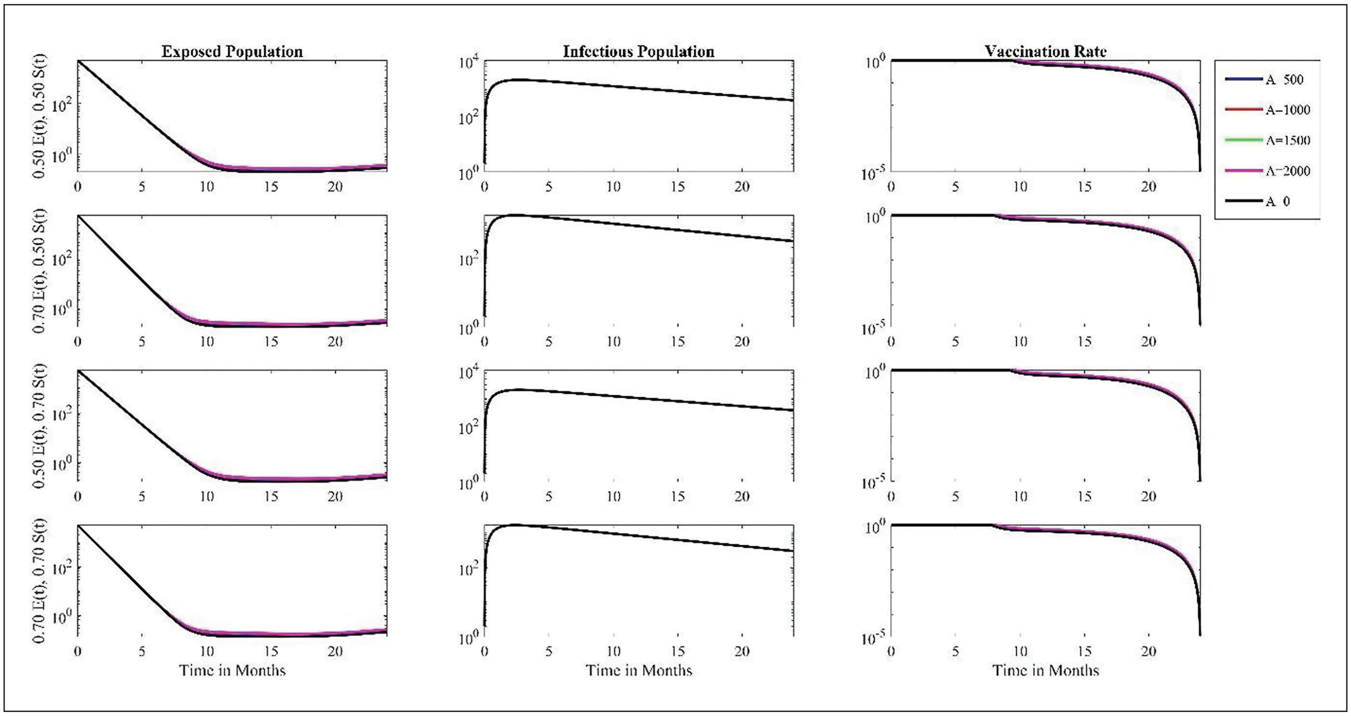

Figure 2. Exploring the confounding effect of the monthly inflow of stray dogs *A* with a slow disease transmission rate (β = 10^{-3}). The labels in the y-axis correspond the vaccine coverage to the target dog population.

pace over time. This population first increased up to an average maximum of approximately 1844 dogs between the 2nd and 3rd month.

Immediately after reaching the maximum point, the infectious population began to decrease and reached a final population size of approximately 342 dogs.

Based on the simulation, it was estimated that the time-dependent vaccination rate should have a starting value of approximately 0.9995. It should be noted that the vaccination rate quantifies how often dogs from the susceptible compartment move towards the vaccinated compartment. In the context of this paper, the movement of dogs from susceptible to the vaccinated compartment is through mass dog vaccination campaigns.

Thus, a vaccination rate of approximately 0.9995 indicates an implementation of monthly vaccination. For a transmission rate β of 0.001, the vaccination rate can be slowed down on the 7th and 8th month following the first month of vaccine implementation (i.e., t = 1) regardless the monthly inflow of stray dogs.

The scenarios illustrated in Figure 3 showed that when β is higher, it increases the size of exposed population. It was observed that all exposed populations had decreased to their minimum points i.e., Scenario 6 (blue) at 16th month, Scenario 24 (red) at 19th month, Scenario 25 (green) at 22nd month, Scenario 26 (magenta) at 23rd month, and had a gradual increase up to the 24th month. These populations behave at a similar pace over time with slight differences between each other specifically with low transmission rates of β = 0.001 and β = 0.01 that reached minimum values lesser than 1.

The resulting infectious populations were observed to increase rapidly from the origin to different maximum points, before decreasing steadily until the 24th month. This population first increased up to an average maximum of approximately 2214 dogs between the 2nd and 3rd month. By the 24th month, it showed that the population with higher transmission rate resulted to higher infectious population size. Although these population decreased until the final time, no population had reached a size of zero.

Similar to the previous result, monthly vaccination was deemed necessary to be performed since the time-dependent vaccination rate was estimated to be at approximately 0.9995. However, compared to the previous scenario, the slowing down of the vaccination rate was observed one month later (8th and 9th months). For a transmission rate at β = 0.01 (i.e., 10 times faster than β = 0.001), the vaccination rate can be slowed down between 18th and 19th month. At a transmission rate of β = 0.1, the vaccination rate can be slowed down between 22nd to 23rd month. Finally, when the transmission rate is at β = 1, a monthly vaccination program should be initiated and continued until the 24th month from its commencement. However, these timings of vaccination were observed if 70% of the susceptible and exposed dog populations were vaccinated.

In Figure 4, the exposed population had a swift decrease from the start of the simulation to approximately by the 16th or 17th month, then had a gradual increase up to the 24th month.

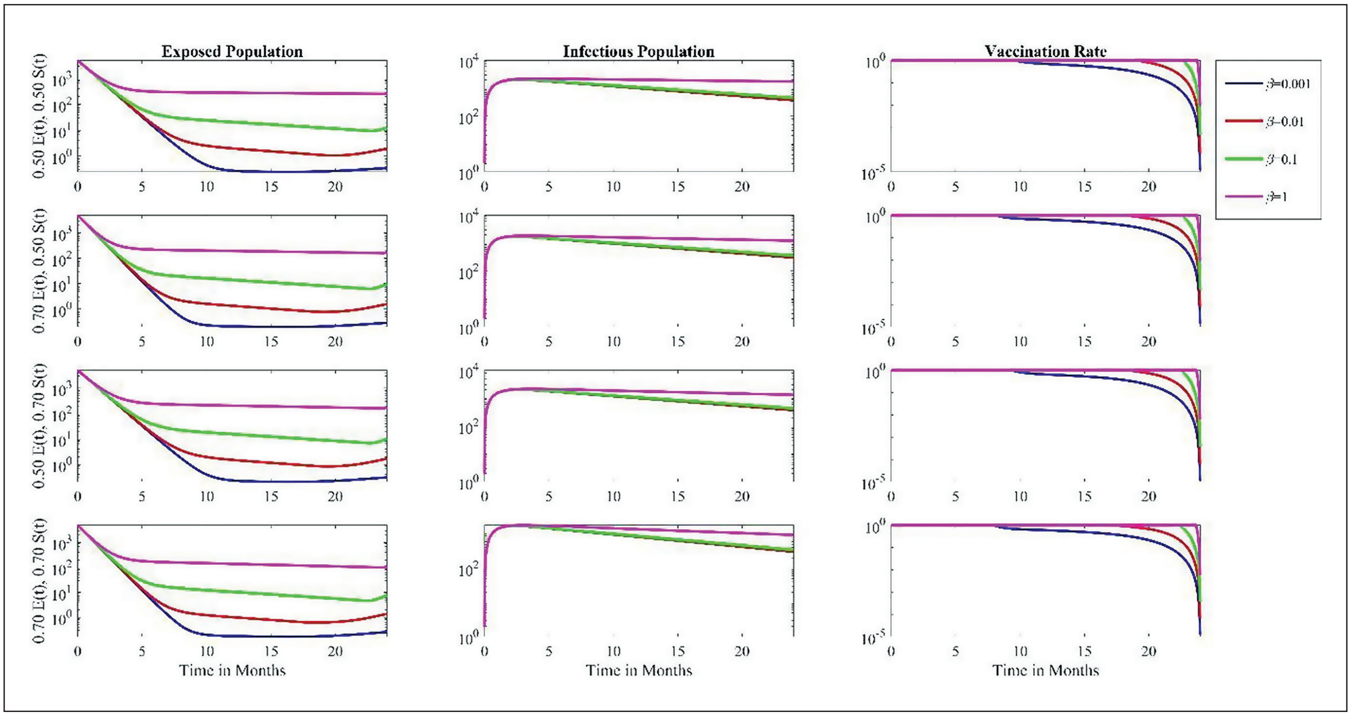

Figure 3. Exploring the confounding effect of disease transmission rate β with a low monthly inflow of stray dogs (A = 500). The labels in the y-axis correspond the vaccine coverage to the target dog population.

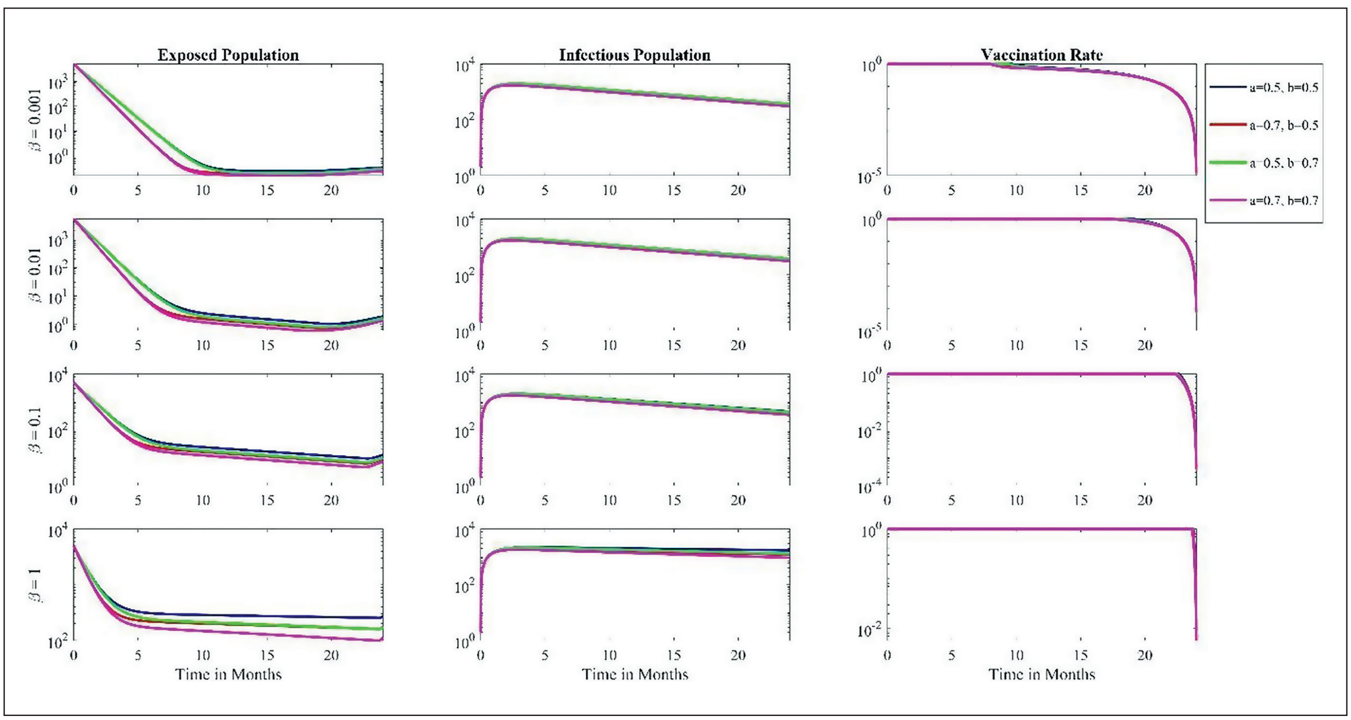

Figure 4. Exploring the effect of vaccine coverages (a, b) at a low monthly inflow of stray dogs (A = 500) with varying disease transmission rates β. The labels in the y-axis correspond the vaccine coverage to the target dog population.

These populations behave at a similar pace over time with slight differences in population sizes. All exposed population has size that ranged from approximately 0.25 to 0.35 until the 24th month.

The sizes of the infectious populations in Figure 4 were observed to be equal with each other. These vary at a similar pace over time. This population first increased up to an average maximum of approximately 1844 dogs at between the 2nd and 3rd month.

Immediately after reaching the maximum point, the infectious population began to decrease and reached a final population size of approximately from 302 to 1742 dogs.

Finally, monthly vaccinations remain a prudent measure regardless of whether vaccination coverages are at 50% or 70%, transmission rates, and even at a low inflow of stray dogs into the system. Observations indicate that when the transmission rate is at $\beta = 0.001$, the vaccination rate can be slowed down between 7th and 8th month following the first month of vaccine implementation. For a transmission rate at $\beta = 0.01$, the vaccination campaign need not be conducted monthly after the 17th and 18th months. When the transmission rate is at $\beta = 0.1$, the decline is observed between 22nd to 23rd month. Finally, when the transmission rate is at $\beta = 1$, a monthly vaccination program should be implemented and maintained for a duration of 24 months from its start date.

DISCUSSION

Rabies remains one of the many health problems considered in the Philippines. As a low-to-middle income country, the inefficient allocation of financial resources in inadequately planned vaccination campaigns will be costly. Hence in the planning of the vaccination deployment, it is necessary to consider analytical methods that can minimize the infectious population while ensuring a low-cost vaccination drive over time. This study applied the optimal control theory to provide information that will be able to explain and describe how populations behave with time-dependent vaccination over a chosen interval.

The goal was to minimize the infectious stray dog population with minimal costs. We formulated a closed system with varying values to observe possible trends and fluctuations in the presence or absence of control intervention. The results of this study described how the dynamics of a population move over time under different scenarios chosen according to the parameters varied – i.e., the entering population A, the proportion of exposed that were vaccinated α, the proportion of susceptible that were vaccinated b, and the transmission rate of rabies β. By comparing these scenarios, the effects and impacts of each varied parameter on the dynamics of a population over time, were further proved and explained.

Focusing on the infectious dog population, the decrease in the population was observed with lower disease transmission (β) values. Although among varying β's there were differences between sizes, the differences were not considered high.

When both portions of the vaccinated exposed and susceptible dog population are at its highest, the decrease of the vaccination and the infectious dog population become faster. In general, for the resulting vaccination rates, when β is at its lowest, the vaccination rate has the lowest value. Its decrease begins at the earliest possible point, making the vaccination rate under the higher β value decreases later in time. It was observed that when the exposed dog population decreased, the vaccination rate began to decline as well. Hence, a nonlinear correspondence between the exposed dog population and the vaccination rate is present for all scenarios but at different times.

The modeling results suggest a potential interruption in the transmission of rabies.

While this interruption is evident in the simulated exposed populations, it is not as pronounced in the simulated infectious populations.[41,42] The simulation result aligns with the known efficacy of rabies vaccines as effective immunizing agents against the rabies virus. The vaccine functions by prompting the body to generate its own antibodies against the rabies virus.[43] However, some model simulations illustrate the persistence of the exposed population and is tantamount to say that it sustains the virus transmission. Additionally, since the infectious population is assumed to be non-recoverable, reducing their numbers through vaccination may appear less impactful. Nonetheless, isolating and possibly culling infected populations are recommended strategies to curb transmission.

The scenarios highlighted the critical role of the time-dependent vaccination rate.

The consistent vaccination efforts led to a noticeable reduction in rabies transmission, evidenced by the decreased number of exposed dogs. This reduction in transmission rate is a positive indicator for effective disease management and control. However, it is important to note that these results are based on the assumption that at least 50% of the target dog population (for the purposes of the simulation) are vaccinated. Essentially, dog vaccine coverage is determined by the dog population size especially in aiming to achieve the 70% herd immunity target. Biennial dog population censuses conducted by the Davao CVO may not accurately reflect the actual dog population, as they often count only dogs vaccinated during mass campaigns. Moreover, many dog owners do not adhere to the recommended annual vaccinations.[44,45] These accumulated issues hinder the achievement of the herd immunity. Investing in an animal registry system, along with vaccinations, can help ensure vaccination targets are achieved effectively.[46] Additionally, while this paper indicated considerably high vaccination efforts for the first of the implementation time, this would be cost-effective in the long run. With a consistent rate of time-dependent vaccination, rabies will be eliminated at the earliest possible point in time, and vaccination will no longer be necessary.

Additionally, a local study by Lachica and colleagues[47] on rabies epidemiology found a correlation between rabies cases and the temperature, suggesting that vaccination should ideally occur before the hot season, when more dogs are mobile. Building on this, a promising area for future research would be to conduct an optimal control theory (OCT) study incorporating weather-dependent and time-varying transmission rates. Such research could identify optimal windows for vaccination campaigns by aligning them with peak rabies transmission periods, potentially enhancing the effectiveness of these efforts. Moreover, it has been documented that children are at risk of rabies exposure,[48] therefore, there is potential in creating an OCT with an SEIV rabies epidemiological model that encompasses humans. This could explore lowering of disease burden attributed to rabies by optimizing the vaccination programs on both humans and animals.

CONCLUSION

This paper has provided a baseline information on the potential of a time-dependent vaccination strategy in the epidemiological rabies context of Davao City, Philippines. Even on scenarios with high rabies transmissibility, time-dependent vaccination strategy still works but trades off on the time where monthly vaccination can be relaxed. Moreover, since the model analysis focuses solely on vaccination, incorporating additional interventions, such as dog impounding as implemented by the CVO, could potentially demonstrate the elimination of dog rabies cases, though the temporal aspect for achieving this outcome remains a good area of investigation.

In conclusion, a robust and timely vaccination program for dogs is essential to manage high rabies transmission rates. Our simulation suggests the importance of initiating monthly vaccinations, with a vaccination rate of approximately 0.9995. The time required to relax the monthly vaccination schedule varies depending on the transmission rate and other factors. For a transmission rate of around 0.001 and a low inflow of stray dogs (approximately 500), it would take seven to nine months to relax the monthly vaccinations, even with only 50% vaccine coverage. For a transmission rate of 0.01, the monthly vaccinations need to be prolonged to 18 to 19 months, and for a transmission rate of 0.1, at least 24 months of monthly vaccinations are necessary. This study underscores the need for sustained and potentially intensified vaccination efforts to effectively control rabies transmission, especially in highly transmissible scenarios.

Meanwhile, this study primarily focuses on canine rabies dynamics based on significant incidents reported within the city. Future research should consider including other potential hosts, such as feline populations, which can also serve as sources of rabies exposure. This broader approach could enhance the development of optimal control strategies or validate the robustness of strategies that currently only consider dogs. Moreover, exploring the efficacy of combining rabies vaccines of varying effectiveness can also be explored. This area presents a valuable opportunity for future research particularly in mass dog vaccination programs, aimed at optimizing the timing and deployment strategies of rabies vaccines.

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Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure

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APPENDICES

Appendix A. Derivation for adjoint functions and optimality condition

The objective functional with its constraints is given by equations [7]-[13]. These were used in creating the Hamiltonian function which will be used in solving for the adjoint functions and the optimality condition. The Hamiltonian function, H, was first constructed in order to find the adjoint functions, λi's (i = 1, 2, 3, 4), and the optimality condition, $k*$.

$$H = I + k^2 + \lambda_1[A + \theta V - mS - \frac{\beta SI}{N} - b(k)S] + \lambda_2[\frac{\beta SI}{N} - mE - \sigma E - a(k)E] + \lambda_3(\sigma E - \mu I) + \lambda_1[b(k)S] + a(k)E - \theta V - mV \quad [14]$$

The optimality condition, k^*, was obtained by solving for the partial derivative of H with respect to k, and equating it to 0.

$$\frac{\partial H}{\partial k} = 0 \text{ at } k* \Rightarrow 2k* - Sb\lambda_1 - Ea\lambda_2 + \lambda_4 (Sb + Ea) = 0$$

$$k* = \frac{Sb\lambda_1 - Sb\lambda_4 \pm Ea\lambda_2 - Ea\lambda_4}{2} \quad [15]$$

The adjoint functions, λi's ($i = 1, 2, 3, 4$), were then obtained by solving for the negative of the partial derivative of H with respect to each of S, E, I, and V.

$$\lambda'_1 = -\frac{\partial H}{\partial S}$$

$$\lambda'_1 = \lambda_1 [-m - \frac{\beta I}{N} - bk] + \lambda_2 \frac{\beta I}{N} + \lambda_4 (bk)$$

$$\lambda'_1 = \lambda_1 m + [\frac{\beta I}{N}(\lambda_1 - \lambda_2)] + bk(\lambda_1 - \lambda_4) \quad [16]$$

$$\lambda'_2 = -\frac{\partial H}{\partial E}$$

$$\lambda'_2 = -[\lambda_2(-m - \sigma - ak) + \lambda_3(\sigma) + \lambda_4(ak)]$$

$$\lambda'_2 = \lambda_2 m + \sigma(\lambda_2 - \lambda_3) + ak(\lambda_2 - \lambda_4) \quad [17]$$

$$\lambda'_3 = \frac{\partial H}{\partial I}$$

$$\lambda'_3 = -[1 + \lambda_1 (-\frac{\beta S}{N}) + \lambda_2(\frac{\beta S}{N}) + \lambda_3 (-\mu)]$$

$$\lambda'_3 = \lambda_2 \mu + (\frac{\beta S}{N})(\lambda_1 - \lambda_2) - 1 \quad [18]$$

$$\lambda'_4 = -\frac{\partial H}{\partial V}$$

$$\lambda'_4 = -[\lambda_1(\theta) + \lambda_4(-\theta - m)]$$

$$\lambda'_4 = \theta(\lambda_4 - \lambda_1) + \lambda_4 m \quad [19]$$

Appendix B. Parameter settings for each of the 32 scenarios

Scenario	A	a	b	β
1	500	0.5	0.5	10^{-3}
2	1000	0.5	0.5	10^{-3}
3	1500	0.5	0.5	10^{-3}
4	2000	0.5	0.5	10^{-3}
5	0	0.5	0.5	10^{-3}
6	500	0.7	0.5	10^{-3}
7	1000	0.7	0.5	10^{-3}
8	1500	0.7	0.5	10^{-3}
9	2000	0.7	0.5	10^{-3}
10	0	0.7	0.5	10^{-3}
11	500	0.5	0.7	10^{-3}
12	1000	0.5	0.7	10^{-3}
13	1500	0.5	0.7	10^{-3}
14	2000	0.5	0.7	10^{-3}
15	0	0.5	0.7	10^{-3}
16	500	0.7	0.7	10^{-3}
17	1000	0.7	0.7	10^{-3}
18	1500	0.7	0.7	10^{-3}
19	2000	0.7	0.7	10^{-3}
20	0	0.7	0.7	10^{-3}
21	500	0.5	0.5	10^{-2}
22	500	0.5	0.5	10^{-1}
23	500	0.5	0.5	1
24	500	0.7	0.5	10^{-2}
25	500	0.7	0.5	10^{-1}
26	500	0.7	0.5	1
27	500	0.5	0.7	10^{-2}
28	500	0.5	0.7	10^{-1}
29	500	0.5	0.7	1
30	500	0.7	0.7	10^{-2}
31	500	0.7	0.7	10^{-1}
32	500	0.7	0.7	1