



Faculty of Computer Science and Information Technology

Modelling the Rabies Transmission Dynamics and Control in Sarawak

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Modelling the Rabies Transmission Dynamics and Control in Sarawak

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DECLARATION

I declare that the work in this thesis was carried out in accordance with the regulations of Universiti Malaysia Sarawak. Except where due acknowledgements have been made, the work is that of the author alone. The thesis has not been accepted for any degree and is not concurrently submitted in candidature of any other degree.



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ABSTRACT

In July 2017, the historically rabies-free Sarawak notified its first-ever case of rabies involving two children from the Serian district. As of 2022, rabies is still ongoing in Sarawak and all of the human cases have been classified as dog-mediated rabies. However, modelling studies of rabies in Sarawak are still scarce despite the evolving epidemic in the state. Hence, this research aims to fill the research gap by developing the first mathematical model for the transmission dynamics of rabies among the human population and dog population in Malaysia, in particular Sarawak, and further explore the long-term trend of the disease. By employing the Next Generation Matrix approach, this study will also be the first to determine and estimate the effective reproduction number of rabies in Sarawak. Other objective includes identifying the most influential parameters in the disease dynamics by performing local sensitivity analysis on the model parameters. In this study, data on human rabies in Sarawak were mainly collected from the official online press statement made by the Director-General of Health Malaysia, which include information such as bite cases, number of confirmed cases, post-exposure prophylaxis treatment, and rabies onset date. We have formulated a deterministic, compartmental Susceptible-Exposed-Infected-Vaccinated (SEIV) model that incorporates the dynamics of dog-to-dog and dog-to-human rabies transmission in Sarawak. To scale it to a local context, this model considers the intervention measures conducted by the Sarawak State Health Department and the Department of Veterinary Services Sarawak. In a long run, the model has predicted that the rabies cases in Sarawak would continue to decline, before experiencing a slight bump after 100 months from the initial outbreak in July 2017. Whereas the effective reproduction number for Sarawak rabies is estimated to be 3.06, further model analysis have shown that the disease-free equilibrium point is generally stable and this result has enabled us to ascertain that

Sarawak can be rabies-free. Consequently, we have estimated the value of the herd immunity threshold to be 0.67. Thus, approximately 70% of the dog population in Sarawak should be vaccinated annually in order to achieve herd immunity. Apart from intensifying the mass dog vaccination campaigns, mobile vaccine units can be deployed to increase vaccination coverage, while oral rabies vaccination can be an alternative for the free-roaming dog population. Also, our sensitivity analysis revealed the significance of dog population management as a mainstay in any rabies control programmes. In conclusion, towards achieving the goal of zero dog-mediated rabies deaths by 2030, the Sarawak authorities should strengthen their efforts in reducing the dog population through the implementation of humane interventions such as the Trap-Neuter-Vaccinate-Relocate (TNVR) method, targeted removal of strays, chemical sterilisation and surgical sterilisation for dogs.

Keywords: Rabies, deterministic, compartmental, modelling, Sarawak

Pemodelan Dinamik Penularan dan Kawalan Jangkitan Rabies di Sarawak

ABSTRAK

Pada Julai 2017, Sarawak yang bebas rabies dalam sejarah memaklumkan kes rabies pertamanya yang melibatkan dua kanak-kanak dari daerah Serian. Setakat tahun 2022, rabies masih berterusan di Sarawak dan semua kes manusia telah diklasifikasikan sebagai kes rabies yang berkaitan dengan gigitan anjing. Walau bagaimanapun, kajian pemodelan rabies di Sarawak masih amat terhad walaupun wabak rabies semakin berkembang di negeri itu. Oleh itu, penyelidikan ini bertujuan untuk mengisi jurang penyelidikan tersebut dengan merumus model matematik bagi mengkaji dinamik penyebaran dan penularan jangkitan rabies dalam populasi manusia dan anjing di Malaysia, khususnya di negeri Sarawak, serta meneroka trend jangka panjang wabak ini. Dengan menggunakan kaedah “Next Generation Matrix”, kajian ini juga adalah kajian yang pertama di Malaysia yang merumus dan mengangkar nilai “effective reproduction number” bagi wabak rabies di Sarawak. Objektif lain adalah seperti mengenal pasti parameter yang paling berpengaruh bagi dinamik penularan wabak rabies di Sarawak dengan menggunakan analisa sensitiviti tempatan terhadap parameter model. Dalam kajian ini, data bagi kes rabies dalam kalangan manusia telah dikumpul dari sumber kenyataan akhbar rasmi oleh Ketua Pengarah Kesihatan Malaysia, yang termasuk informasi berkaitan kes gigitan anjing, bilangan kes rabies yang telah disahkan,, rawatan profilaksis rabies dan tarikh gejala simptom. Kami telah merumuskan suatu model “Susceptible-Exposed-Infected-Vaccinated (SEIV)” yang bersifat deterministik dan kompartmental, dan model ini merangkumi dinamik bagi penyebaran wabak rabies dalam kalangan anjing dan manusia di Sarawak. Bagi menuruti konteks tempatan, model ini juga merangkumi langkah-langkah campur tangan kerajaan seperti Jabatan Kesihatan Negeri Sarawak dan Jabatan Perkhidmatan Veterinar Sarawak. Dalam

jangka masa panjang, model kami telah meramal kemerosotan bilangan kes rabies di Sarawak, sebelum kes mula sedikit meningkat setelah 100 bulan selepas kes pertama yang dikesan pada July 2017. Nilai “effective reproduction number” telah dianggarkan berjumlah 3.06. Melalui analisis model, kami juga telah menunjukkan bahawa “disease-free equilibrium point” bagi model in adalah stabil dan hal ini menjelaskan kemampuan Sarawak untuk bebas rabies. Kemudian, kami juga menganggar nilai imuniti kelompok bagi rabies di Sarawak berjumlah 0.67. Hal ini bermaksud anggaran 70% populasi anjing di Sarawak hendaklah divaksinasi bagi mencapai imuniti kelompok. Selain daripada mempergiatkan kempen suntikan vaksin anti-rabies bagi anjing, unit vaksin bergerak juga hendaklah dikerah bagi mempertingkatkan liputan vaksinasi. Vaksin rabies oral juga boleh dijadikan alternatif untuk diberi kepada populasi anjing liar. Hasil kajian analisis sensitiviti kami juga menunjukkan bahawa kawalan populasi anjing adalah tunjang utama dalam mana-mana program kawalan rabies. Kesimpulannya, untuk mencapai sasaran sifar kematian rabies menjelang tahun 2030, kerajaan Sarawak perlu mempertingkatkan usaha bagi mengurangkan populasi anjing seperti dengan melaksanakan kaedah “Trap-Neuter-Vaccinate-Relocate (TNVR)”, penyingkiran anjing liar yang disasar, pensterilan kimia, dan pembedahan pensterilan anjing.

Kata kunci: *Rabies, deterministik, kompartmental, pemodelan, Sarawak*

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LIST OF ABBREVIATIONS

CFR	Case-to-Fatality Ratio
DFE	Disease-Free Equilibrium
MLE	Maximum Likelihood Estimator
NPI	Non-Pharmaceutical Intervention
ODE	Ordinary Differential Equation
PEP	Post-Exposure Prophylaxis
RIG	Rabies-Immunoglobulin
RMSE	Root-Mean-Square-Error
RNA	Ribonucleic Acid
SEI	Susceptible-Exposed-Infectious
SEIR	Susceptible-Exposed-Infectious-Recovered
SEIV	Susceptible-Exposed-Infectious-Vaccinated
SEIVR	Susceptible-Exposed-Infectious-Vaccinated-Recovered
SIR	Susceptible-Infected-Recovered
TNVR	Trap-Neuter-Vaccinate-Relocate
WAHIS	World Animal Health Information System
WHO	World Health Organization
WOAH	World Organisation for Animal Health

CHAPTER 1

INTRODUCTION

1.1 Overview

Rabies is a viral zoonosis that is widespread throughout the world, with only Antarctica and a few island territories considered rabies-free. Globally, over 95% of human rabies cases are caused by dogs as the principal source. In terms of the global disease burden, the World Health Organization (WHO), in 2020, reported around 59000 human rabies mortality estimates per annum in over 150 countries and territories, whereby Africa and Asia accounting for 95% of all cases. As rabies is grossly underreported, the figure would be an underestimate, with the rural poor populations bearing a disproportionate share of the burden.

In Malaysia, the incidences of rabies were first documented in 1924 and by the year 1999, Malaysia has successfully eliminated the disease. However, multiple rabies outbreaks occurred in the states of Perlis, Kedah, and Penang in July 2015, and were resolved by November 2015. In July 2017, Malaysia announced its first rabies-related human death in two decades, following the emergence of the disease in the state of Sarawak. With the increasing burden of rabies disease worldwide, the World Health Organization (WHO) and World Organisation for Animal Health (WOAH) have issued a global call to action in 2015 to collaborate and pool resources to eradicate dog-transmitted human rabies by year 2030. As rabies is highly fatal once exposed, Malaysia will need to take proactive measures and coordinate collaborations between multiple sectors to prevent cases of both human and canine rabies in order to achieve the WHO 2030 goal of canine-mediated rabies elimination.

1.2 Background of Study

Rabies remains a significant public health problem in the majority of developing nations including Malaysia. In July 2017, the historically rabies-free Sarawak notified its first-ever case of rabies after two children from Serian succumbed to the disease. Serian is a district in the state of Sarawak, Malaysia with a population of 110577 and an area of 2405 km². The Serian district shares a political border with the rabies-endemic Kalimantan, Indonesia and a 2019 study has reported that the rabies virus isolated in Sarawak shared a 99% homology similarity with the Indonesian lineage. This proves that rabies in Sarawak was actually originated from the neighbouring country, highly likely via the free movement of rabid dog through the Sarawak-Kalimantan porous border. The unprecedented outbreak in 2017 prompted the Sarawak government to set up a rabies task force committee which oversees the implementation of various rabies control measures including dog mass vaccination campaign and the targeted removal of the stray dog population. According to Sarawak Disaster Information (2019), there has been a total of 140000 owned dogs vaccinated and a targeted removal of 22698 stray dogs, whereas 13024 rabies-exposed victims have been treated with the post-exposure prophylaxis (PEP) in 2019. Despite being a vaccine-preventable disease, the Sarawak rabies outbreak has recorded an alarming figure by year 2020, with 31 confirmed human cases of dog-mediated rabies in total, including 30 deaths and a lone survivor who is in a vegetative state.

Over the past decades, mathematical modelling has become an increasingly popular tool used by epidemiologists to understand how diseases will evolve over time in a population. Complex epidemiological processes can be simplified and quantified by defining the rules that describe the interactions between individuals or populations, and converting these rules into a system of mathematical equations. Besides, one of the key metrics in

epidemiology that can be extracted through modelling is the effective reproduction number. This metric represents the number of susceptible people that can get infected from a single infective in a specific area over a period of time. Ultimately, the modelling results and insights can be used to predict the effects of an intervention and forecast emerging outbreaks.

1.3 Research Problem

Since 2015, numerous studies have been conducted to study the rabies outbreaks in Malaysia. However, these research efforts were mainly focused on phylogenetic analysis and situational analysis of rabies in Malaysia, specifically canine rabies. Modelling studies of rabies in Sarawak in particular, are still scarce despite the evolving epidemic in the state. Hence, this work aims to fill the research gap by developing a deterministic, compartmental model for the transmission dynamics of rabies for both human and dog populations in Sarawak. Apart from that, although the rabies outbreak in Sarawak has been ongoing since 2017, there is no study yet that attempts to compute the effective reproduction number of Sarawak rabies despite it being a critical epidemic threshold for disease persistence. Therefore, this study will determine the effective reproduction number for rabies in the context of Sarawak. After the model has been calibrated, this research will also analyse the effects of parameter changes in order to identify the most influential parameters for rabies in the state of Sarawak via sensitivity analysis.

1.4 Research Objectives

The following set of objectives motivates this research:

- i. To formulate a mathematical model that captures the dynamics of transmission of rabies in Sarawak.
- ii. To identify the long-term trend of human rabies in Sarawak.

- iii. To obtain the expression for the effective reproduction number and its value in the context of Sarawak rabies outbreak.
- iv. To determine the effects of parameter changes in terms of the disease dynamics in Sarawak in order to identify the most influential parameters.

1.5 Research Procedure

The flowchart in Figure 1.1 shows the 10-step action plan for conducting this research. In Figure 1.1, the yellow highlighted boxes pinpoint the major steps that would accomplish our research objectives.

In the first step, literature review is done to gain knowledge on the natural history of rabies and identify the techniques used in developing a rabies epidemic model. In the second step, the mathematical model for Sarawak rabies transmission is formulated by incorporating the interactions among the human and dog populations and considering the different control strategies taken by the Sarawak government. This step accomplishes our first research objective. The third step is the model verification stage, whereby a model from a similar study will be reproduced. Next is to gather the initial conditions and parameters values in the context of Sarawak rabies either through estimation, assumptions or sourced from literatures. Then, the model is calibrated using actual human rabies data in Sarawak and parameters will be re-adjusted if required. After that, the Sarawak rabies model will be validated by calculating the Root-Mean-Square-Error (RMSE) between the actual and simulated values. In the seventh step, further numerical simulation of our rabies epidemic model will be performed in order to explore the long-term trend of the disease in Sarawak. We are interested to observe if the disease would persist or die-out in the long run. This step accomplishes our second research objective. In the eighth step, the expression for the

effective reproduction number for Sarawak rabies is determined and its value will be estimated. This particular step accomplishes our third research objective. In the next step, sensitivity analysis is performed in order to identify the influential parameters of rabies transmission in Sarawak. This step accomplishes our final research objective. In the last step, public health insights are generated from the modelling results and the sensitivity analysis study.

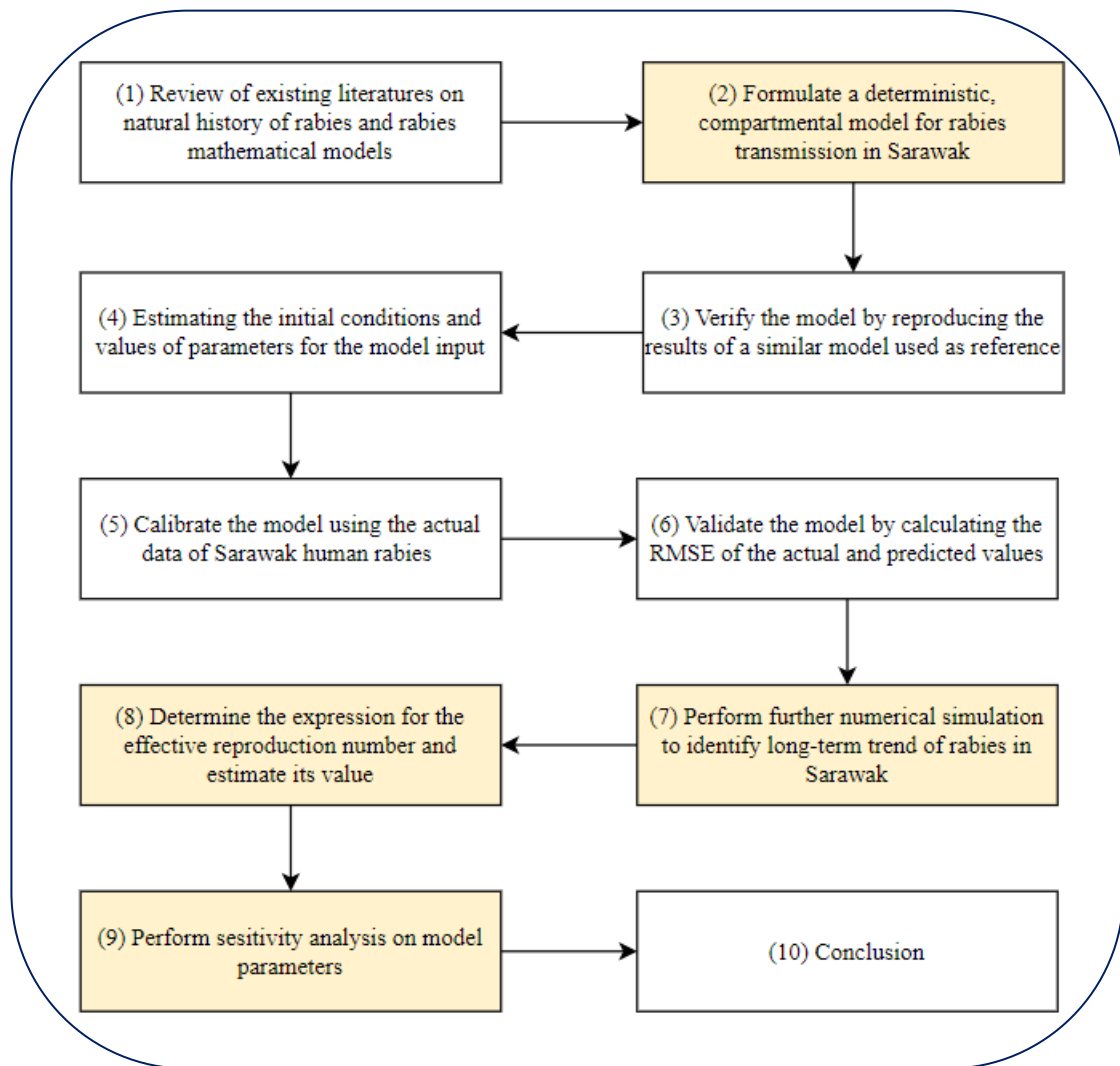


Figure 1.1: Research Procedure

1.6 Chapter Summary

This thesis constitutes six chapters. Chapter 1 contains the problem statement, objectives of the study and the research procedures. Chapter 2 provides a review of literatures related to rabies disease and epidemiological modelling. Also, reviews on the important epidemic thresholds such as the effective reproduction number and herd immunity will be discussed. Chapter 3 includes the formulation of the epidemic model and the estimation of parameters as well as the initial conditions. In Chapter 4, the result of the numerical simulation of the epidemic model is presented as well as model verification, model calibration and model validation. Chapter 5 covers the effective reproduction number, herd immunity threshold and the steady state analysis of the model system by finding the disease-free equilibrium (DFE) and analyses its local stability. The chapter also provides sensitivity analysis of the model parameters and identify the most influential parameter. Chapter 6 is the conclusion of the study whereby the summary, contribution of the study and future work will be discussed.

CHAPTER 2

LITERATURE REVIEW

2.1 Overview

This chapter presents the literature reviews that would eventually assist in the formulation of our Sarawak rabies model. The chapter begins with the natural history of rabies in Section 2.2 which includes its mode of transmission, clinical symptoms of rabies in human and the available rabies treatment and control. Section 2.3 covers the reviews on mathematical modelling in epidemiology and its history, the usage and steps to find the key metrics in epidemiology such as the effective reproduction number and herd immunity threshold and discusses the Root-Mean-Square-Error (RMSE) as the model performance metric. Then, Section 2.4 and Section 2.5 provide the reviews on mathematical modelling of wildlife rabies and canine rabies, respectively. Lastly, Section 2.6 will summarise how these reviews would support our decision in the formulation of the Sarawak rabies epidemic model.

2.2 Natural History of Rabies

The causative rabies virus (RABV) is an enveloped single-stranded RNA virus of the genus *Lyssavirus* in the family *Rhabdoviridae* (Susilawathi et al., 2012) that can infect almost every mammal. RABV is transmitted to human when open wounds on the skin are exposed to saliva from infected animals following a deep bite or scratch that involves penetration of the skin. Once inside the body, the virus travels along the peripheral nerves and spinal cord until it reaches the brain, where it replicates rapidly, causing acute encephalitis and eventually death of the host.

Rabies is highly deadly with a case-to-fatality ratio (CFR) of nearly 100% and extremely rare cases of recovery (Adedeji et al., 2010). Rabies has a 1 - 3 months of average incubation period, but the incubation period might also be longer than a year (Bleck & Rupprecht, 2009). Early prodromal symptoms include fever, headache, insomnia and numbness or pain at the bite site that could last from 20 to 60 days. This is followed by the furious stage presenting classic rabies symptoms such as violent behaviour, hallucinations, hypersalivation, hydrophobia and aerophobia.

Following an animal bite, all wounds should be cleaned immediately with soap under running water for 15 minutes. After that, post-exposure prophylaxis (PEP) vaccine and rabies-immunoglobulin (RIG) will be administered to prevent progression into a full-blown rabies symptom in humans. Nevertheless, the effectiveness of PEP would depend on the time of vaccine administration as well as the location of the bite. Pre-exposure prophylaxis in human is also available especially to those occupational groups with high risk of contracting rabies; case in point, the veterinarians, veterinary students, rabies laboratory workers and animal control officers. As rabies can only be transmitted by animals, common control measures include animal vaccination prior to exposure and reducing the number of susceptible animals via culling. Despite being preventable via vaccination and prompt post-exposure treatment, the disease is nearly always fatal once clinical symptoms are allowed to fully develop.

2.3 Mathematical Epidemiology

The history of mathematical modelling in epidemiology can be traced back to Daniel Bernoulli in 1760 with the invention of the first compartmental model for smallpox (Bacaër, 2011). According to Bernoulli's model with age-dependent parameters, human population

can be partitioned into two sub-classes; namely the susceptible compartment and the recovered compartment (Dietz, 2002). The compartmental model is a modelling technique commonly used in the field of epidemiological modelling.

2.3.1 Compartmental Model

In epidemiological modelling, compartmental model is a technique whereby the population of interest is divided according to the disease status. The model can either be a deterministic or stochastic, equation-based or agent-based model.

- i. **Deterministic:** The outcome of interest always output the same values for every given value of the input variable.
- ii. **Stochastic:** An element of chance is considered as to whether an infection actually occurs.
- iii. **Equation-based:** The model captures the variability over time using a set of ordinary differential equations (ODEs), or over time and space using partial differential equations (PDEs). It assumes homogeneity and is continuous.
- iv. **Agent-based:** The model captures the behaviour of a system using a set of agents that encapsulate the interactions and actions appropriate to the system. It assumes heterogeneity and is discrete.

One of the first compartmental models was the deterministic, compartment-based model known as the Susceptible-Infected-Recovered (SIR) model developed by Kermack and McKendrick in 1927 (Brauer, 2017). An SIR model is considered as a dynamical systems model as it is built in such a way that individuals belong to discrete states or

compartments – either susceptible, infected or recovered, and the number of individuals in these compartments can change over time.

- i. **Susceptible compartment:** Refers to individuals who are healthy and can get infected.
- ii. **Infected compartment:** Refers to individuals who are infected with the pathogen and can transmit the disease to other susceptibles.
- iii. **Recovered compartment:** Refers to individuals who had recovered from the disease with naturally acquired active immunity.

In epidemiology, the term “incidence” refers to the number of new infected cases, therefore the rate of change of the susceptible compartment (S) can be regarded as;

$$\frac{dS}{dt} = - \text{incidence}.$$

By using the Law of Mass-Action, “incidence” can be represented as the product of the force of infection $\lambda(t)$ and the number of susceptible individuals $S(t)$ at time t , thus

$$\text{incidence} = \lambda(t)S(t),$$

where the force of infection is assumed to be proportional to the size of infected population i.e., $\lambda(t) = \beta I(t)$ and the constant of proportionality β is known as the disease transmission rate. The rate of change of the susceptible individuals moving into the infected compartment becomes:

$$\frac{dS}{dt} = -\beta IS.$$

The rate of change of the infected compartment is given by:

$$\frac{dI}{dt} = \beta IS - \alpha I,$$

where α is the recovery rate and αI refers to the number of recovered individuals. So, the infected individuals who recover will transition to the recovered compartment.

$$\frac{dR}{dt} = \alpha I.$$

Hence, the SIR model consists of a system of three coupled ordinary differential equations (ODEs) below that mimics the change in the number of susceptible $S(t)$, infective $I(t)$ and recovered individuals $R(t)$ at time t in a given host population (Franc et al., 2014). Schematically, the Kermack-McKendrick SIR model can be described by the transmission diagram Figure 2.1.

$$\frac{dS}{dt} = -\beta IS,$$

$$\frac{dI}{dt} = \beta IS - \alpha I,$$

$$\frac{dR}{dt} = \alpha I.$$

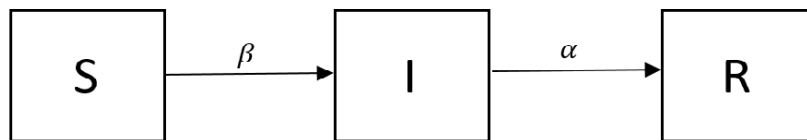


Figure 2.1: Transmission Diagram of the Kermack-McKendrick SIR Model

The basis of the work of Kermack and McKendrick has been used in numerous models for epidemics. The typical SIR model is usually extended to include a multitude of other epidemiological parameters such as the incubation period, natural births and deaths, or incorporating non-pharmaceutical interventions (NPIs) such as lockdown, isolation and social distancing, as well as pharmaceutical interventions such as vaccination and anti-viral medications. The inclusion of these parameters and assumptions led to various additional compartments such as:

- i. Exposed: Refers to persons who have contracted the disease but are still in the incubation period and cannot yet spread it.
- ii. Vaccinated: Refers to individuals who gained active immunity through vaccines.
- iii. Quarantined: Refers to individuals who are isolated from society in order to stop the spread of the disease.

2.3.2 Effective Reproduction Number (R_e)

The effective reproduction number R_e is inarguably one of the most sought-after parameters in public health and epidemiology. In the context of our study, R_e describes the dog-to-person transmissibility of a rabies virus. It represents the expected number of secondary cases in a partially susceptible population generated by one infected dog over the entire course of its infectious period, as opposed to the basic reproduction number, R_0 whereby transmissibility is determined within a completely susceptible population with no interventions.

Furthermore, R_e indicates whether the invasion of the rabies virus would give rise to an exponentially growing epidemic. Specifically, $R_e = 1$ indicates an epidemic threshold. Whenever $R_e < 1$, then on average one infected dog cannot infect more than one person and

consequently the chain of disease transmission will die out without exponential growth in a long run. Conversely, the range of $\mathbf{R}_e > 1$ would lead to an exponentially growing epidemic and result in an outbreak.

The steps to obtain the effective reproduction number $\mathbf{R}_e$ follows the approach by Diekmann, Heesterbeek and Metz (1990) and Asamoah et al. (2017). The authors mathematically defined the effective reproduction number $\mathbf{R}_e$ as the spectral radius of a positive linear operator known as the Next Generation matrix (G). The process of evaluating the eigenvalues of the Next Generation matrix, G involves solving the characteristic equation of matrix G : $|G - \lambda I| = 0$, where λ is the eigenvalue. Following Asamoah et al. (2017), the effective reproduction number can be determined by finding the spectral radius (dominant eigenvalue) of the Next Generation matrix G , denoted by $\rho(G)$ as it gives the fastest growth of the infected population.

2.3.3 Herd Immunity Threshold

Another key metric in epidemiology is the herd immunity threshold. According to Saunders (1994), herd immunity is described as a phenomenon in which susceptible individuals are automatically protected from a disease due to a certain proportion of immunized individuals within the population. So, in other words, when a sufficiently large proportion of the population are vaccinated, it would be difficult for an epidemic to occur, much less to spread, due to the induced herd immunity phenomenon that breaks the chain of transmission. In 1952, Macdonald (1952) quantified the herd immunity as a measurable critical threshold value and expressed it as a function in terms of the effective reproduction number $\mathbf{R}_e$. Hence, the formula for the herd immunity threshold (H) is

$$H = 1 - \frac{1}{R_e}. \quad (2.1)$$

2.3.4 Root-Mean-Square-Error (RMSE)

Root-Mean-Square-Error (RMSE) is a metric commonly used in model validation (Chae et al., 2018). RMSE measures the residual difference between the predicted value and the actual value. According to Li et al. (2018), the two values are close and comparable when the RMSE value is less than 2.0, which alludes that the epidemic model provides good forecasts. This measure of error is expressed as below:

$$RMSE = \sqrt{\frac{\sum_{i=1}^n (\hat{y}_i - y_i)^2}{n}}, \quad (2.2)$$

where y_i is the actual values, $\hat{y}_i$ is the predicted values, and n is the total number of data. In this study, the actual values y_i are the actual monthly human rabies active cases in a 26-month period reported from the first outbreak in June 2017 to July 2019 in Sarawak, while the predicted values $\hat{y}_i$ are represented by the number of infected humans simulated from the model. In summary, the evaluation metric RMSE is used in this study to discern how far off the simulated number of infected humans would be from the actual cases, whereby 2.0 is taken as the benchmark value.

2.4 Mathematical Modelling of Wildlife Rabies

Wildlife rabies has been a major public health problem in several countries. For example, rabies in Europe and North America mainly involves foxes, raccoons and bats while other wildlife hosts for rabies virus include African wild dogs in Africa and ferret badger in China. Mathematical modelling has become crucial in comprehending the transmission and progression of rabies in wildlife over the past decades.

Back in 1981, Anderson et al. (1981) introduced a deterministic compartmental model for fox rabies in Europe which spearheaded numerous other rabies models today. The fox population in Europe was divided into three subclasses namely the susceptible, the infected but not yet infectious, and the infectious. Consequently, the behaviour and interactions amongst these different populations are mathematically characterised by a system of coupled ordinary differential equations (ODEs). The simple model was the SEI model, whereby S, E and I represented the population densities of susceptible, exposed and infectious fox, respectively. Suppose that K_T is the minimum threshold density for persistence of an epidemic, the model predicted three possible population dynamical behaviours when rabies is introduced into an initially stable healthy population: (1) rabies would eventually disappear when the carrying capacity of fox habitat, K is below K_T , (2) damped oscillations in fox population and rabies prevalence approaching a steady state when K is slightly larger than K_T and (3) limit cycle behaviour when K is significantly larger than K_T . Results also suggested a 3 to 5-year cycles of rabies outbreak. Furthermore, the model provided a criterion to determine the precise level of control (whether vaccination, culling or mixture of both) required to eradicate rabies in either a favourable fox habitat (large K) or poor fox habitats (small K). Culling seemed to be the recommended method in a habitat where density of fox population is low.

Extending the work of the previously mentioned authors, Coyne, Smith, and McAllister (1989) introduced the class of recovered individuals who acquired natural immunity for rabies among raccoons in the mid-Atlantic region in the United States. Raccoons that are immune were put into the recovered class and the exposed animals were subdivided into the infected but not infectious, and those exposed that eventually gain immunity naturally. The model estimated that rabies could be eradicated when more than

32% of raccoon population is culled yearly or when 99% of the susceptible are given annual vaccination. The method of either culling only or vaccination only was recommended as either one would always be the control strategy with the cheapest cost. A mixture of both methods would be cheaper than the method of culling alone only when the per capita vaccination cost is 20% or less than that of culling cost.

Childs et al. (2000) reanalysed the work of Coyne, Smith, and McAllister (1989) by utilising a more extensive database from a surveillance network that stretched over two decades and involving 35,387 rabid raccoons reported within counties of mid-Atlantic and north-eastern states in the United States. The work suggested that the immunity level of raccoon population must be updated, from the previously estimated 20% by Coyne, Smith, and McAllister (1989), to only as low as 1% to 5%. The work also identified a 48-month periodicity in rabies outbreaks that was not detected by Coyne, Smith, and McAllister (1989). The works mentioned above however, only considers a spatially uniform situation.

Smith and Cheeseman (2002) made use of a simple compartmental model to study the efficacy of different control strategies for rabies in foxes including vaccination, culling, as well as temporary sterilisation by using abortifacient and permanent sterilisation by using immunocontraceptive. The study noted that culling would be the more effective control method as compared to vaccination, given equal efficacy of control. This is due to the fact that vaccinated foxes could still reproduce and thus increasing the number of susceptible to above the critical threshold density.

Asano, Gross, Lenhart and Real (2008) first introduced optimal control applied to a model for rabies transmission in raccoons. The authors employed optimal control in a meta-population SIR model in which a population was divided into subpopulations connected by

movement via immigration and emigration. The model used consists of a system of 27 ODEs with three state variables and nine subpopulations each. Simulations with time period of 15 days were done to explore the optimal vaccination distribution strategy over a short period following an outbreak detection. Results showed that regardless of the distance from the origin of the spread, rate of rabies transmission was higher in a population with large susceptible; and that rapid vaccination at a higher rate should be given to the larger population.

Clayton et al. (2010) included birth pulse function in the state equations, whereby organisms are added into the population during seasonal births at a very specific time interval. In order to make the model more realistic, the authors also added a dynamics equation for the vaccination level. The work concluded that the closer the outbreak detection is to the beginning of the seasonal birth pulse, the longer the period of time at which vaccine needs to be distributed.

2.5 Mathematical Modelling of Canine Rabies

The studies mentioned above solely focused on modelling rabies in wildlife animals such as fox and raccoon. However, modelling of canine rabies is imperative as dogs are still the main source of human rabies transmission (WHO, 2020).

Hampson et al. (2007) collated a 30-year dog rabies annual surveillance data from 1971 to 2000 from nine countries across Africa and a simple model was created which includes the susceptible compartment, exposed compartment, infectious compartment and vaccinated compartment, along with the rabies intervention parameters. The work noted a 3- to 6-year periodicity of canine rabies epidemics and subsequently found significant synchrony between the outbreaks over large spatial scale attributable to combination of both

large-scale intervention efforts and dog dispersal. The basic reproduction number $R_0 = 1.2$ for rabies transmission among dogs in Africa was also estimated.

Carroll et al. (2010) was the first to investigate canine rabies control method by using immunocontraception alongside rabies vaccination. Immunocontraceptives are single-shot vaccine injections delivered to the animal that induce infertility in the animal for several years. The continuous, compartmental model in Anderson et al. (1981) and Hampson et al. (2007) was adapted in order to compare the effects of three canine rabies control methods: vaccination, vaccination plus fertility control (immunocontraceptives), and culling, when applied at varying rates and duration. In the SEIV model, dog population was divided into four classes: susceptible individuals, exposed individuals, infectious individuals and vaccinated individuals. The model predicted that culling 35% of the dog population within a month could eradicate rabies better than vaccination alone, however achieving the percentage might not be feasible. The work also highlighted the addition of fertility control in reducing the required vaccination coverage for rabies eradication down to only 30% as opposed to the normal 70% target vaccination coverage. This is possible as fertility control helps to control dog birth rate in a long run thus lowering the number of susceptible animals to below the minimum threshold density for disease transmission.

Zinsstag et al. (2009) was the first to incorporate both canine population and human population in a dynamical modelling for the spread of rabies. The deterministic model took into account four compartments for each of the human and canine populations in the city of Chad, Africa: the susceptible, the exposed, the infectious, and the recovered. The behaviour and interactions amongst these populations were mathematically characterised by a system of coupled ODEs. The value of the estimated effective reproductive ratio was $R_e \approx 1$, which

further supported the observed low level stable endemic transmission of rabies in the city. According to Zinsstag et al. (2009), the observed synchrony of rabies cycles Hampson et al. (2007) could be due to a surveillance bias as rabies diagnosis with laboratory confirmation was only available in major cities and not in the rural or suburban areas. The work concluded that the more cost-effective control strategy would be to combine human post-exposure prophylaxis (PEP) with dog mass vaccination.

Wiraningsih et al. (2010) proposed a deterministic, compartmental model to study the optimal control problem involving optimal vaccine distribution for the canine-to-human rabies spread. In the SEIR model, only individuals with active immunity from pre-exposure vaccination were considered in the recovered compartment. The basic reproduction number was derived and the objective functional was formulated which seek to minimize the infected dogs and humans while maximizing the number of susceptible.

Zhang et al. (2011) modelled rabies transmission dynamics in China using the SEIR framework and concluded that the disease cannot be eradicated with the ongoing control strategies. Model simulation showed a steady decline in the number of human rabies cases in the next 7 or 8 years. The number of cases will rise again to a peak before eventually become stable. Sensitivity analysis on the number of human rabies cases in terms of model parameters highlighted that lowering dog births combined with increasing dog vaccination rate would be the best approach to control human rabies in China. Hou, Jin and Ruan (2012) constructed a deterministic susceptible-exposed-infectious-vaccinated (SEIV) model for the dog-human rabies transmission in which both strays and owned dogs are taken into account. The model fit considerably well with the reported data on human rabies cases in the province of Guangdong, China from 2006 to 2010 and predicted that the number of human cases

would decrease steadily for several years before rising slightly afterwards. This finding revealed that even with the existing disease control and management measures, rabies will remain in Guangdong province. Furthermore, the work also stated that the more effective control measure would be to increase the rate of vaccination and culling rate of domestic dogs rather than the stray dogs.

Following the fact that the cases of human rabies in China are notably higher in the summer and autumn season, Zhang et al. (2012a) built a seasonal rabies model and described the disease transmission rates among dogs and from dog to human as periodic functions. The model was utilized for the purpose of predicting the monthly incidences of human rabies within the period of year 2004 to year 2010, and the subsequent estimation of the basic reproduction number of $R_0 = 1.03$ proved that rabies in China cannot be eliminated with the current control measures. Sensitivity analysis of some parameters on the value of R_0 further showed that rabies in China can only be eliminated when the dog birth is drastically reduced. Furthermore, R_0 is significantly affected by the change in the baseline contact rates, therefore stray dog management is very important in order to minimise the possibility of interaction and contact between dogs.

Fitzpatrick et al. (2014) formulated a multi-host deterministic compartmental SEIV model that included the dog population and wildlife population in Ngorongoro and Serengeti, Tanzania whereby only the dogs can be in the vaccinated compartment. Through sensitivity analysis, the authors have determined that the optimal coverage for dog vaccination in Serengeti should be 70%.

Agaba (2014) slightly modified the SEIR model from Zhang et al. (2011) by considering the pre-exposure prophylaxis for humans in the model. Results from model

simulation showed a significant decrease in the number of infected humans in comparison to the model with only human post-exposure prophylaxis. The work suggested the use of human pre-exposure prophylaxis as one of the control measures for rabies transmission apart from culling and dog vaccination. The pre-exposure vaccination of human should be given to those with potential occupational health hazards including veterinarians, veterinary students, veterinary technicians, animal control officers and laboratory worker as this group of people will have a higher risk of exposure to zoonotic diseases such as rabies.

Eti Dwi Wiraningsih et al. (2015) developed a deterministic SEIR model describing the spread of rabies in stray dog populations, domestic dog populations, and human populations, taking into account the impact of vaccination and culling in dogs. They studied the stability analysis for the equilibria of the model to determine the basic reproduction number and then separately analysed the equilibria stability of the disease-free and endemic states for the stray dog population and domestic dog population.

Wera, Mourits, Siko and Hogeveen (2016) evaluated the cost-effectiveness of alternative mass vaccination strategies for rabies control in Flores Island and developed a deterministic model for rabies transmission dynamics in Flores Island that included the dog population dynamics in a representative village. Results implied that implementing a yearly mass vaccination for dogs with a long-acting vaccine coverage rate of 70% can reduce the outbreak durations, making this the most cost-effective strategy for Flores Island.

Fitzpatrick et al. (2016) evaluated the cost-effectiveness of various rabies management measures in Tamil Nadu and adapted a compartmental transmission model parameterised using actual data for rabies in Tamil Nadu. The author suggested it would be

more cost-effective to vaccinate at least 13% of the stray dog population in Tamil Nadu in order to reduce the number of human rabies cases by up to 90%.

Bilinski et al. (2016) extended the multi-host compartmental SEIV model by Fitzpatrick et al. (2014) to include the human population in Ngorongoro and Serengeti, Tanzania. The study evaluated the cost-effectiveness of several dog rabies vaccination regimens in the two districts with different coverage and frequency. The authors have determined that if the rabies reintroduction risk is minimal, the most cost-effective method to manage the rabies transmission in Ngorongoro and Serengeti, Tanzania would be to conduct semi-annual dog vaccination programmes.

Asamoah, Oduro, Bonyah and Seidu (2017) explored the use of pre-exposure prophylaxis for both dogs and human population and their impacts on the transmission of rabies. The work proposed an optimal control modelling and simulation approach in order to study the effects comparison between three intervention methods: culling, pre-exposure prophylaxis and post-exposure prophylaxis when implemented at varied rates. The SEIR model employed by Zhang et al. (2011) was modified and the non-effectiveness of pre- and post-exposure prophylaxis was considered in the model. Findings indicated that when both prophylaxes are equally expensive, the optimal method for rabies eradication would be the greater usage of pre-exposure vaccination in both dogs and human.

Wera, Mourits and Hogeveen (2017) developed a deterministic, compartmental SEIVR model depicting the rabies transmission dynamics between canines and humans on Flores Island. Then, they estimated the ratio of cost-effectiveness for the different mass dog vaccination strategies in Flores Island. Findings showed that the consolidated efforts of

yearly mass dog vaccination at 70% coverage with a long-acting vaccine and human PEP could eradicate all human rabies deaths, but at a somewhat higher cost-effectiveness ratio.

By utilizing a deterministic SEIR model for canine and canine-mediated rabies transmission in East Africa via the RabiesEcon spreadsheet tool, Borse et al. (2018) opined that in a high disease transmission scenario, a threshold of 70% immunisation coverage in the canine population would break the chain of transmission of rabies for a minimum duration of two decades. In a low rabies transmission level, however, it was more cost-effective to vaccinate 20% of the East African dog population semi-annually or 50% annually. Id et al. (2019) determined the threshold of vaccination coverage to pre-empt canine rabies re-establishment within a post-elimination context by adopting a customised version of RabiesEcon to simulate different rabies reintroduction scenarios. Results suggested vaccination free-ranging dogs with immunisation coverage of approximately 38% to 56% in order to impede canine rabies reintroduction in the areas where it has been successfully eradicated.

Although dogs remain the primary source of rabies infection, accounting for more than 95% of total human rabies cases, the number of cases of the human rabies originated from Chinese ferret badgers has been increasing in China. From 1994 to 2008, more than 50 cases of human rabies due to Chinese ferret badgers were recorded in Zhejiang Province. Therefore, Huang, Ruan, Shu and Wu (2019) constructed an SEIR model with multiple host to capture the dynamical transmission of rabies among the populations of dogs, Chinese ferret badgers and human in the Zhejiang province. The study stressed the importance of including data collection on wildlife animals such as Chinese ferret badgers, bats and wolves

in the national rabies surveillance as wildlife-originated human rabies cases have been reported more frequently in several parts of China.

By using a deterministic compartmental SIR model, Musaili and Chepkwony (2020) has captured the transmission dynamics of rabies among dogs in Makueni and studied the impact of public health education as one of the rabies eradication control measures in Makueni. Findings showed that the public health education on the need of canine pre- and post-exposure prophylaxis and highlighting the responsible pet ownership commitment decreased the cases of canine rabies significantly in Makueni, Kenya.

2.6 Summary

In summary, rabies is a fatal zoonotic viral disease that can be transmitted to human when open wounds on the skin are exposed to saliva from infected animals, predominantly dogs. Despite being preventable via dog vaccination and prompt post-exposure treatment in humans, the disease is nearly always fatal once clinical symptoms are allowed to fully develop. As human rabies cases and rabies-related deaths are primarily due to canine rabies, we will need to formulate our epidemic model to incorporate both the dog population and human population. Based on the reviews, our model will also need to consider multiple rabies control measures, such as dog culling, dog rabies vaccination and the post-exposure prophylaxis (PEP) in humans.

As outbreak management and interventions rely heavily on the ability to predict the dynamics of a disease, the use of epidemiological models should not be overlooked. Basically, epidemiological models utilise coupled differential equations, and this type of modelling technique is typically known as dynamical systems modelling. Dynamical systems model requires state variables, and in the context of infectious diseases, these state

variables refer to the three main compartments of Susceptible, Infected and Recovered. Based on our reviews, epidemiological models for both wildlife rabies and canine rabies have the same mathematical foundation. Since rabies recovery cases are very rare, rabies epidemiological model usually employs the Susceptible-Exposed-Infected (SEI) framework as its most basic compartments or state variables. Due to the fact that all human rabies cases in Sarawak were transmitted from the dog population, canine rabies models will serve as the primary reference point in the development of our model in Chapter 3.

Over the past decades, there have been numerous rabies epidemiological models proposed to model wildlife rabies as well as canine rabies that consider demographic factors and various intervention parameters. Despite various research on rabies modelling mentioned in the earlier sections, nonetheless, scarcity of study on rabies virus transmission dynamics in Malaysia particularly in the state of Sarawak remains. Based on our literature reviews, we propose to develop a Susceptible-Exposed-Infected-Vaccinated (SEIV) model, as this framework is best suited to capture the rabies transmission dynamics in Sarawak, which includes local government interventions such as post-exposure treatment for humans and several canine rabies control methods.

Sensitivity analysis will be conducted to investigate the effect of changes in the intervention parameters on the value of the effective reproduction number (R_e). The effective reproduction number (R_e) has a threshold of one and it can be used to identify the key transmission parameter. The expression for R_e can be determined by finding the largest eigenvalue of the Next Generation Matrix (G). Other countries have reported the values of R_e to be in the range of 1.03 – 1.2. Hence, we aim to estimate the value of the effective reproduction number for Sarawak rabies from our formulated epidemic model in the context

of Sarawak, and then compare these values with other reported estimates. Another key metrics in epidemiology is the herd immunity threshold (H) and it is simply an expression in terms of R_e . By and large, past studies have shown that herd immunity can only be attained when the vaccination coverage for canine rabies is at least 70%, meaning when a 70% vaccination coverage is achieved, it would halt further transmission of rabies. Therefore, this value serves as the benchmark for our estimation of the Sarawak's herd immunity threshold for rabies in Chapter 4. Lastly, as a model performance metric, the RMSE will be calculated in this study to discern how far off the simulated values from our SEIV model would be from the actual data, whereby 2.0 is taken as the benchmark value.

CHAPTER 3

MODEL FORMULATION

3.1 Overview

This chapter will focus on the formulation of the Susceptible-Exposed-Infectious-Vaccinated (SEIV) rabies transmission model in the context of Sarawak. The discussion on model verification is given in Section 3.3. Next, Section 3.4 provides the data collection method and the model input used for calibration. The chapter also covers the estimation of the model parameters and initial conditions in Section 3.5 and Section 3.6, respectively. Lastly, Section 3.7 presents the summary of the chapter.

3.2 Formulation of the SEIV Rabies Model

In order to develop the model for rabies transmission with demography, disease mortality and interventions, we consider two interacting population of dogs and humans. In accordance to their disease status, we partition the population into four exclusive compartments: (i) susceptible, (ii) exposed, (iii) infected and (iv) vaccinated. Each individual cannot be in more than one single compartment at a given time, however they can transition into different compartments as they progress in the disease.

3.2.1 Compartment for the Dog Population

We divide the dog population size at time t into four compartments: (i) susceptible dogs $S_d = S_d(t) > 0$, (ii) exposed dogs $E_d = E_d(t) \geq 0$, (iii) infectious dogs $I_d = I_d(t) \geq 0$ and (iv) the vaccinated dogs $V_d = V_d(t) \geq 0$.

The susceptible compartment (S_d) belongs to healthy dogs who do not have immunity, therefore can still get infected by rabies virus. As no immigration is considered, the entry of new susceptible individuals into the dog population is via birth at a recruitment rate of A , while the removal of susceptible dogs is possible via natural death at a rate of m_d . The product of the number of susceptible and infectious dogs, denoted by $S_d I_d$, represents the total number of contacts or interactions between a susceptible individual and an infectious individual; the rate of transmission, β_d , is the proportion of effective contacts between the susceptible and infectious dogs that will give rise to new infection. Thus, the fraction of susceptible dogs (S_d) transitioning into the exposed compartment (E_d) at a rate of β_d is denoted by the term $\beta_d S_d I_d$ —famously known as the mass action incidence. In Sarawak, as dog vaccination is only given to healthy susceptible dogs before rabies exposure, hence, $k_d S_d$, where k_d is the rate of vaccination for dogs, refers to the number of susceptible dogs who acquired immunity via vaccination and moved into the vaccinated compartment. The term λ_d denotes the rate of dog immunity loss and $\lambda_d V_d$ represents the number of vaccinated dogs who have lost immunity and become susceptible again. Furthermore, the Sarawak government has implemented culling as one of the mitigation measures to reduce dog population in Sarawak. Aside from the vaccinated dogs, dogs in other compartments may be subjected to culling. Hence, susceptible dogs can also be removed from the susceptible class due to culling at a rate of c_d .

Figure 3.1 below shows the interaction within the susceptible dog compartment which can be expressed into a differential equation as:

$$\frac{dS_d}{dt} = A + \lambda_d V_d - \beta_d S_d I_d - (m_d + k_d + c_d) S_d.$$

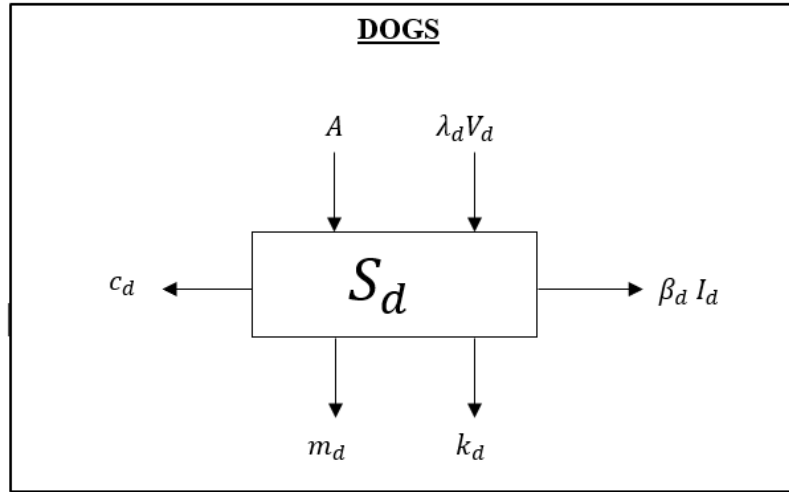


Figure 3.1: Susceptible Compartment for Dog Population

Dogs in the exposed compartment (E_d) are those who have acquired the pathogen but are not yet capable of spreading the infection further as they are still in the latency period. The susceptible dogs (S_d) who interacts with the infectives enter the exposed compartment (E_d) at a rate of β_d , while the removal of exposed dogs is possible via natural death at a rate of m_d . As discussed in Section 2.2, rabies has an epidemiologically long incubation period which may be longer than a year, hence the Exposed compartment (E_d) is required to represent dogs that are infected but not yet infectious. Since infected dogs are not immediately infectious, the reciprocal of the dog latent period (σ_d) gives the rate of progression of exposed dogs to infectious dog (I_d); hence $\sigma_d E_d$ refers to the number of exposed dogs that develops clinical signs of rabies and consequently capable of virus transmission. Aside from the vaccinated dogs, dogs in other compartments may be subjected to culling. Hence, exposed dogs can also be removed from the exposed class due to culling at a rate of c_d .

Figure 3.2 below shows the interaction within the exposed dog compartment which can be expressed into a differential equation as:

$$\frac{dE_d}{dt} = \beta_d S_d I_d - (m_d + \sigma_d + c_d)E_d.$$

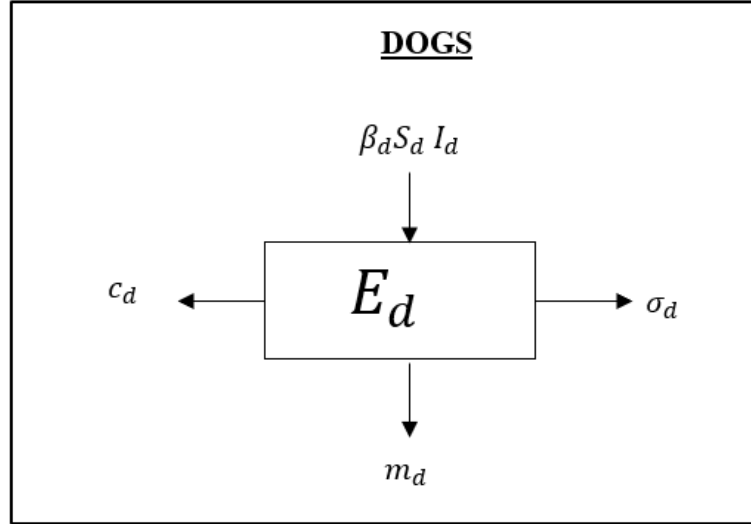


Figure 3.2: Exposed Compartment for Dog Population

Dogs in the infectious compartment (I_d) are those having both the pathogen as well as the capability of transmission. Exposed dogs develop clinical signs of rabies, become infectious and enter the infectious compartment at a rate of σ_d . The infectious dogs may die due to natural causes at a rate of m_d or due to rabies-related death at a rate of μ_d , whereby $\mu_d I_d$ represents the number of infected dogs died due to rabies. Aside from the vaccinated dogs, dogs in other compartments may be subjected to culling. Hence, infectious dogs can also be removed from the exposed class due to culling at a rate of c_d .

Figure 3.3 below shows the interaction within the infectious dog compartment which can be expressed into a differential equation as:

$$\frac{dI_d}{dt} = \sigma_d E_d - (m_d + \mu_d + c_d)I_d.$$

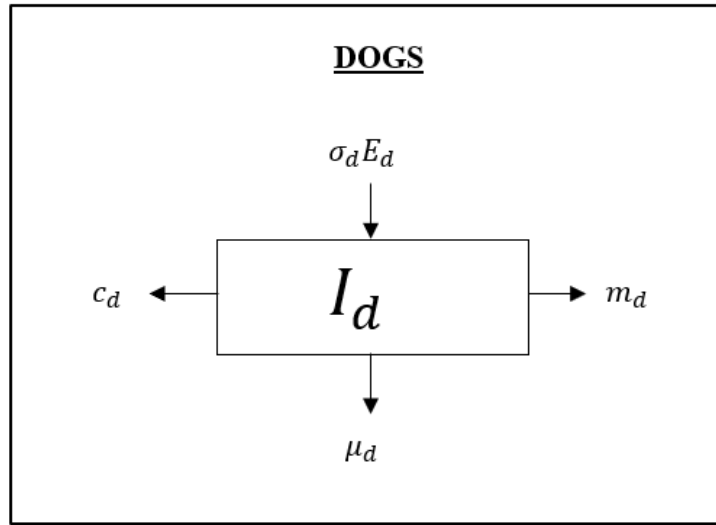


Figure 3.3: Infectious Compartment for Dog Population

Lastly, dogs that are actively immune to rabies due to vaccination make up the vaccinated class V_d . The susceptible dogs who acquired immunity via vaccination moves into the vaccinated compartment at a dog vaccination rate of k_d . The term λ_d denotes the rate of dog immunity loss and $\lambda_d V_d$ represents the number of vaccinated dogs who have lost immunity and become susceptible again. The vaccinated dogs may also die due to natural causes at a rate of m_d .

Figure 3.4 below shows the interaction within the vaccinated dog compartment which can be expressed into a differential equation as:

$$\frac{dV_d}{dt} = k_d S_d - (m_d + \lambda_d) V_d.$$

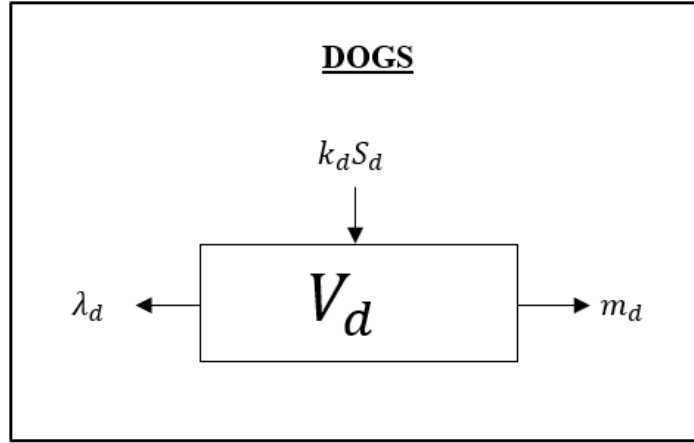


Figure 3.4: Vaccinated Compartment for Dog Population

3.2.2 Compartment for the Human Population

Similarly, the human population size at time t is divided into four classes: (i) the susceptible humans $S_h = S_h(t) > 0$, (ii) exposed humans $E_h = E_h(t) \geq 0$, (iii) infected humans $I_h = I_h(t) \geq 0$ and (iv) vaccinated humans $V_h = V_h(t) \geq 0$.

The susceptible compartment (S_h) belongs to healthy individuals who can still get infected by the rabies virus. As no immigration is considered, the entry of new susceptible individuals into the human population is via birth at a recruitment rate of B , while the removal of susceptible human is possible via natural death at a rate of m_h . As β_h is the rate of dog-to-human rabies transmission, thus $\beta_h S_h I_d$ is the number of new human rabies cases due to exposure to rabid dogs. As λ_h is the rate of human immunity loss, thus, $\lambda_h V_h$ represents the number of vaccinated humans who have lost immunity and transition into the susceptible compartment again.

Figure 3.5 shows the interaction within the susceptible human compartment which can be expressed into a differential equation as below:

$$\frac{dS_h}{dt} = B + \lambda_h V_h - \beta_h S_h I_d - m_h S_h.$$

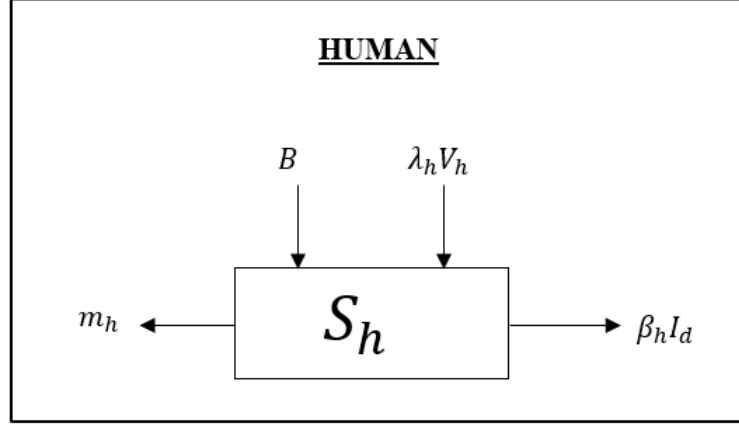


Figure 3.5: Susceptible Compartment for Human Population

In the context of human, the exposed compartment (E_h) refers to the infected humans in their incubation period who are yet to show any clinical signs of rabies. Due to exposure to rabid dogs (I_d), susceptible human (S_h) can progress into the exposed compartment (E_h) at a rate of $\beta_h I_d$. The removal of exposed dogs can occur via natural death at a rate of m_h . Humans with rabies exposure will require immediate treatment via post-exposure prophylaxis (PEP) and $k_h E_h$ refers to the number of exposed humans who received immunity via PEP; where k_h is denoted as the rate of vaccination for humans. The reciprocal of the human incubation period (σ_h) prior to the onset of rabies symptoms represents the rate of progression from exposed human to infected human. Thus $\sigma_h E_h$ is the number of exposed humans who leaves the incubation period and develops rabies clinical symptoms.

Figure 3.6 below shows the interaction within the exposed human compartment which can be expressed into a differential equation as:

$$\frac{dE_h}{dt} = \beta_h S_h I_d - (m_h + \sigma_h + k_h) E_h.$$

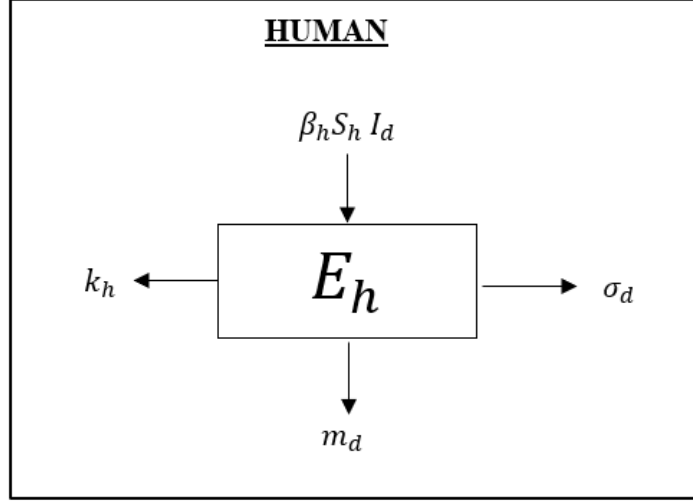


Figure 3.6: Exposed Compartment for Human Population

Human infected compartment (I_h) refers to the infected individuals showing clinical symptoms of rabies. Exposed humans develop clinical signs of rabies and enter the infected compartment at a rate of σ_h . The infected human may die due to natural causes at a rate of m_h or due to rabies disease-induced mortality at a rate of μ_h , whereby $\mu_h I_h$ represents the number of infected humans died due to rabies.

Figure 3.7 below shows the interaction within the infected human compartment which can be expressed into a differential equation as:

$$\frac{dI_h}{dt} = \sigma_h E_h - (m_h + \mu_h) I_h.$$

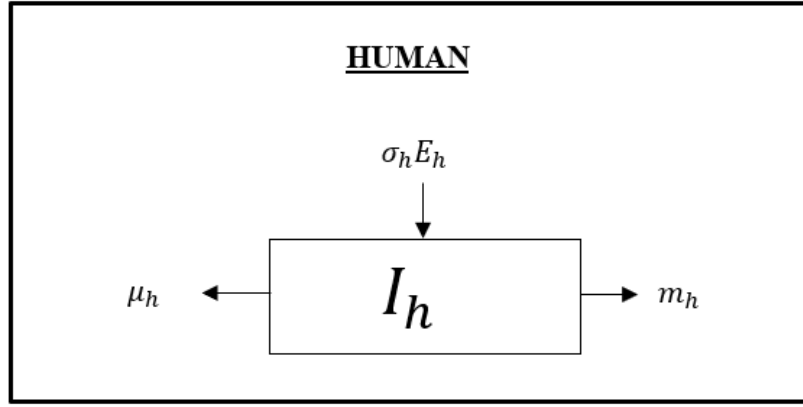


Figure 3.7: Infectious Compartment for Human Population

Finally, V_h makes up the compartment for human who receives the post-exposure prophylaxis (PEP)—a treatment given to patients following dog bite incident. $k_h E_h$ refers to the number of exposed humans who received immunity via PEP; where k_h denoted as the rate of vaccination for humans. The term λ_h denotes the rate of human immunity loss and $\lambda_h V_h$ represents the number of vaccinated humans who have lost immunity and move back to the exposed compartment. The vaccinated human may also die due to natural causes at a rate of m_d .

Figure 3.8 shows the interaction within the vaccinated human compartment which can be expressed into a differential equation as below:

$$\frac{dV_h}{dt} = k_h E_h - (m_h + \lambda_h) V_h.$$

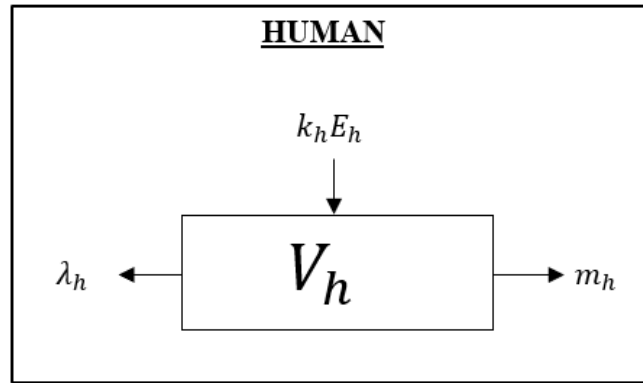


Figure 3.8: Vaccinated Compartment for Human Population

3.2.3 Model Assumptions

The SEIV disease transmission model is derived by assuming several assumptions as described in the previous section.

- i. All populations are sufficiently large and mix homogeneously.
- ii. All populations are closed as no migration is considered.
- iii. All individuals are born equally susceptible to rabies and subjected to natural mortality.
- iv. All infected dogs are equally infectious.
- v. Transmission of rabies virus within and between populations is only possible via direct contact with infected dogs.
- vi. All bites from infectious dogs lead to virus transmission.
- vii. Without vaccination, all bites from infectious dog will lead to the development of rabies clinical symptoms.

- viii. Vaccine efficacy is at 100%, whereby vaccinated dogs or humans will be completely protected against rabies but rabies vaccination does not confer lifelong immunity.
- ix. After clinical symptoms have developed, fatality due to rabies is 100% for both dogs and humans.

3.2.4 System of Equations and Parameter Description

The corresponding mathematical equations that describe the dynamics of Sarawak rabies transmission based on the aforementioned assumptions are given by a system of coupled ODEs (3.1) with 15 parameters as shown in the transmission diagram (Figure 3.9).

$$\begin{aligned}
 \frac{dS_d}{dt} &= A + \lambda_d V_d - \beta_d S_d I_d - (m_d + k_d + c_d) S_d, \\
 \frac{dE_d}{dt} &= \beta_d S_d I_d - (m_d + \sigma_d + c_d) E_d, \\
 \frac{dI_d}{dt} &= \sigma_d E_d - (m_d + \mu_d + c_d) I_d, \\
 \frac{dV_d}{dt} &= k_d S_d - (m_d + \lambda_d) V_d, \\
 \frac{dS_h}{dt} &= B + \lambda_h V_h - \beta_h S_h I_d - m_h S_h, \\
 \frac{dE_h}{dt} &= \beta_h S_h I_d - (m_h + \sigma_h + k_h) E_h, \\
 \frac{dI_h}{dt} &= \sigma_h E_h - (m_h + \mu_h) I_h, \\
 \frac{dV_h}{dt} &= k_h E_h - (m_h + \lambda_h) V_h,
 \end{aligned} \tag{3.1}$$

with $S_d > 0$, $E_d \geq 0$, $I_d \geq 0$, $V_d \geq 0$, $S_h > 0$, $E_h \geq 0$, $I_h \geq 0$, and $V_h \geq 0$.

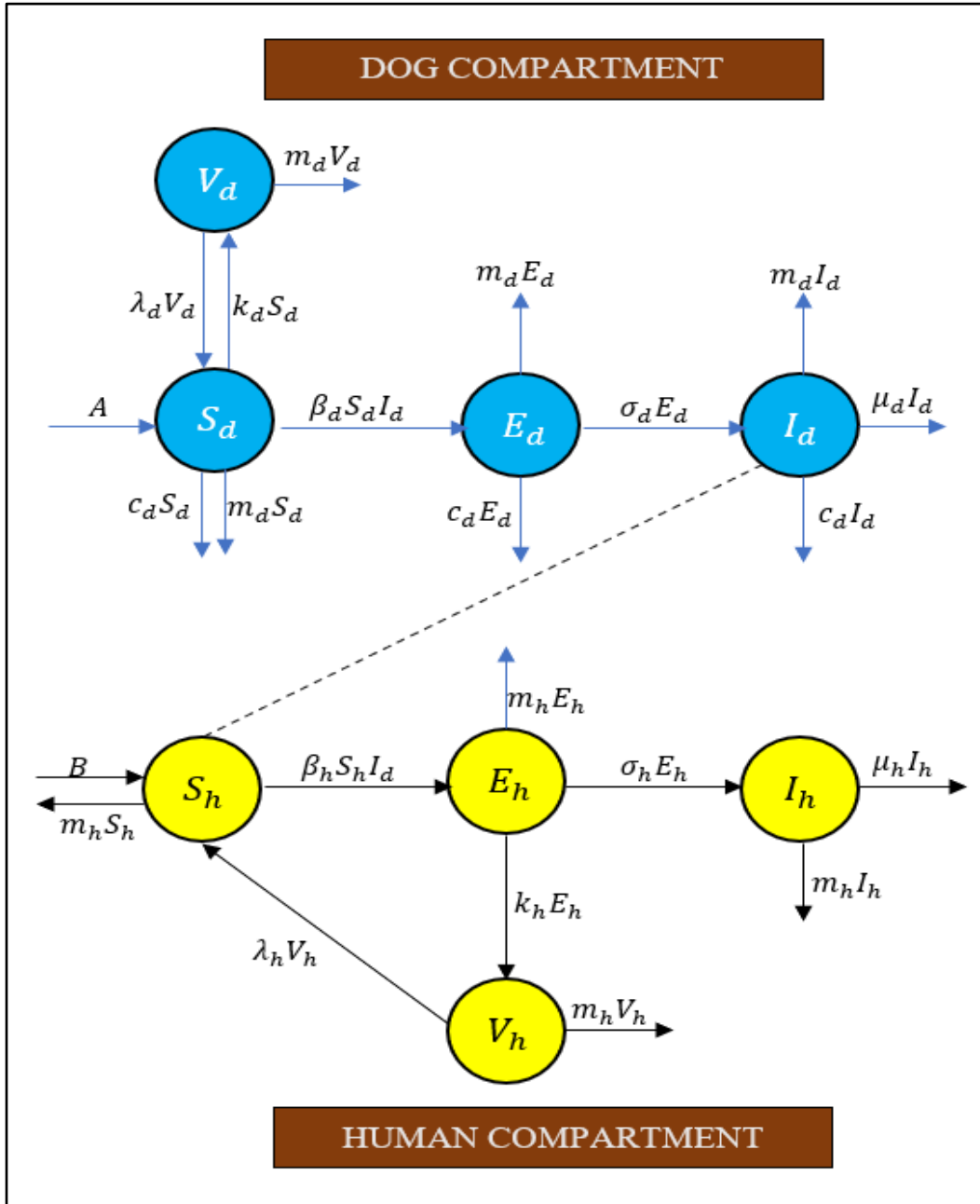


Figure 3.9: Rabies Transmission Diagram for the Dog and Human Population

Furthermore, the summary of the parameter descriptions is given in Table 3.1.

Table 3.1: Dog and Human Parameter Description

Parameter	Description
A	Monthly number of new born dogs
β_d	Rate of dog-to-dog transmission
σ_d	Reciprocal of the dog incubation period
μ_d	Dog rabies-related death rate
m_d	Dog natural mortality rate
c_d	Rate of dog culling
k_d	Rate of dog vaccination
λ_d	Rate of dog immunity loss
B	Monthly human birth rate
β_h	Rate of dog-to-human transmission
σ_h	Reciprocal of the human incubation period
μ_h	Human disease-induced death rate
m_h	Human natural mortality rate
k_h	Rate of human PEP vaccination
λ_h	Rate of human immunity loss

3.3 Model Verification

Next, we are interested to reproduce the model simulation from the paper Analysis of Rabies in China: Transmission Dynamics and Control (Zhang et al., 2011) due to the fact that our rabies model (3.1) is similar to and is actually an extension of the model from Zhang et al. (2011). One of the major differences is that the model in Zhang et al. (2011) incorporates dog post-exposure vaccination and no culling, while our model (3.1) includes

the pre-exposure vaccination for dogs and targeted culling; in-line with the intervention measures conducted by the Sarawak Department of Veterinary Services. Moreover, our model (3.1) presumes that all rabies exposures without post-exposure prophylaxis (PEP) would lead to clinical symptoms in humans, as opposed to the assumption in Zhang et al. (2011).

Both the dog and human populations are included in the deterministic, compartmental model in Zhang et al. (2011). For the dog population, the susceptible, exposed, infected and vaccinated compartments are denoted as S_d, E_d, I_d and V_d , respectively. For the human population, the susceptible, exposed, infected and vaccinated compartments are denoted as S_h, E_h, I_h and V_h , respectively. The susceptible-exposed-infected-vaccinated (SEIV) rabies model in Zhang et al. (2011) is a system of eight ordinary differential equations with 16 parameters:

$$\frac{dS_d}{dt} = A + \lambda_d V_d + \sigma_d(1 - \gamma_d)E_d - \beta_d S_d I_d - (m_d + k_d)S_d,$$

$$\frac{dE_d}{dt} = \beta_d S_d I_d - (m_d + \sigma_d + k_d)E_d,$$

$$\frac{dI_d}{dt} = \sigma_d \gamma_d E_d - (m_d + \mu_d)I_d,$$

$$\frac{dV_d}{dt} = k_d(S_d + E_d) - (m_d + \lambda_d)V_d,$$

$$\frac{dS_h}{dt} = B + \lambda_h V_h + \sigma_h(1 - \gamma_h)E_h - \beta_h S_h I_d - m_h S_h,$$

$$\frac{dE_h}{dt} = \beta_h S_h I_d - (m_h + \sigma_h + k_h)E_h,$$

$$\frac{dI_h}{dt} = \sigma_h \gamma_h E_h - (m_h + \mu_h) I_h,$$

$$\frac{dV_h}{dt} = k_h E_h - (m_h + \lambda_h) V_h.$$

The description of parameters is listed in Table 3.2 below.

Table 3.2: Parameter values and initial conditions in Zhang et al. (2011)

	Description	Value (/year)
Parameters		
A	Annual number of new born dogs	3×10^6
β_d	Rate of dog-to-dog transmission	1.58×10^{-7}
σ_d	Reciprocal of the dog incubation period	6
μ_d	Dog rabies-related death rate	1
m_d	Dog natural mortality rate	0.08
γ_d	Rate of clinical outcome of exposed dogs	0.4
k_d	Rate of dog vaccination	0.09
λ_d	Rate of dog immunity loss	1
B	Annual number of human births	1.54×10^7
β_h	Rate of dog-to-human transmission	2.29×10^{-12}
σ_h	Reciprocal of the human incubation period	6
μ_h	Human disease-induced death rate	1
m_h	Human natural mortality rate	0.0066
k_h	Rate of human PEP vaccination	0.54
λ_h	Rate of human immunity loss	1

Table 3.2 continued

γ_h	Rate of clinical outcome of exposed humans	0.4
Initial conditions		
$S_d(0)$	Initial number of susceptible dogs	3.5×10^7
$E_d(0)$	Initial number of exposed dogs	2×10^5
$I_d(0)$	Initial number of infected dogs	1×10^5
$V_d(0)$	Initial number of vaccinated dogs	2×10^5
$S_h(0)$	Initial number of susceptible humans	1.29×10^9
$E_h(0)$	Initial number of exposed humans	250
$I_h(0)$	Initial number of infected humans	89
$V_h(0)$	Initial number of vaccinated humans	2×10^5

3.4 Data Collection

After we verify the formulated rabies model, we will then attempt to model the Sarawak rabies transmission dynamics. In this study, secondary data collection on human rabies in Sarawak are collated from the official online press statement announced periodically by the Director-General of Health Malaysia (Abdullah, 2019), which include information that is crucial for parameter estimation purposes such as bite cases, number of confirmed cases, PEP treatment, and rabies onset date. Apart from the publicly available materials, information gathering pertaining the details on Sarawak rabies prevention and control measures are complemented by an informal meeting in 2019 with several delegates from the Sarawak State Health Department and the Institute of Health and Community Medicine, Universiti Malaysia Sarawak. In addition, other information required for parameter estimation such as the number of dogs culled, number of dogs vaccinated and the

Sarawak dog demography is extracted from the World Animal Health Information System (WAHIS) database (WAHIS, 2019), the official website for Sarawak Disaster Information (Sarawak Disaster Information, 2019) and online news.

For model calibration purpose, we will fit the model (3.1) to the actual monthly number of human rabies active cases in Sarawak. Hence, the data of human rabies active cases in a 26-month period starting from the first outbreak in June 2017 to July 2019 is extracted from the official online press statements released by the Director-General of Health Malaysia (Abdullah, 2019). In this research, a rabies case is considered as active when the person is currently having rabies clinical symptoms. Therefore, from the time when the clinical symptoms begin to develop up until the time the victim dies or recovered, the case is considered as active case. Hence, we define a rabies case as active by considering the patient's onset date until the date of death or recovery. We extract this information manually from the Director-General's online press releases (Abdullah, 2019) whereby the onset date and the date of death were published.

3.5 Parameter Estimation

Generally, several parameters are estimated from actual data in Sarawak while some are derived through model fitting or sourced from literature. The Sarawak rabies data is extracted from official online press statements made by the Director-General of Health Malaysia, the World Animal Health Information System (WAHIS) database, the official website for Sarawak Disaster Information, and online news source.

3.5.1 Monthly number of new born dogs

We approximate the total dog population in Sarawak to be 200000 according to online press release (Dayak Daily, 2019). Also, we assume the crude annual dog birth rate

per 100 population to be 11 puppies/dog (New et al., 2004), so that the monthly number of new born dogs (A) can be calculated as

Annual number of new born dogs

$$= \frac{\text{total number of dogs}}{100} \times \text{crude annual dog birth rate per 100 population}$$

$$= \frac{200000}{100} \times 11 = 22000.$$

So,

monthly number of new born dogs (A) = (annual number of new born dogs) $\div$ 12 month

$$A = 22000 \div 12 \approx 1800.$$

3.5.2 Rate of dog culling

We define the dog culling rate (c_d) as the proportion of monthly average number of dogs culled and the total population of dogs. A total of 15509 dogs was culled in the period of July 2017 to February 2019 based on the Sarawak Disaster Information website (Sarawak Disaster Information, 2019). Again, by assuming that the total dog population in Sarawak to be 200000 (Dayak Daily, 2019), we estimate the rate of dog culling, c_d as below:

Monthly average number of dogs culled

$$= (\text{total number of dogs culled between July 2017 to February 2019}) \div 20 \text{ months}$$

$$= \frac{15509}{20}.$$

$$c_d = \frac{\text{monthly average number of dogs culled}}{\text{total population of dogs}},$$

$$c_d = \frac{\frac{15509}{20}}{200000} \approx 0.004 \text{ per month}$$

3.5.3 Rate of dog vaccination

We define the dog vaccination rate (k_d) as the ratio of monthly average of vaccinated dogs to the total population of dogs. A total of 103166 vaccinated dogs was reported in the period of July 2017 to February 2019 based on the database of the World Animal Health Information System (WAHIS, 2019). Again, by assuming that the total dog population in Sarawak to be 200000 (Dayak Daily, 2019), we estimate the rate of dog vaccination, k_d as below:

Monthly average number of dogs vaccinated

= (total number of dogs vaccinated between July 2017 to February 2019) $\div$ 20 months

$$= \frac{103166}{20}.$$

$$k_d = \frac{\text{monthly average number of dogs vaccinated}}{\text{total population of dogs}},$$

$$k_d = \frac{\frac{103166}{20}}{200000} \approx 0.02 \text{ per month.}$$

3.5.4 Monthly human birth rate

The Sarawak human population and the crude annual human birth rate in 2017 are obtained from the Department of Statistics Malaysia (DOSM, 2019). We are specifically interested in the values for the year 2017 as it was the year of the first rabies outbreak. The crude birth rate can be defined as the number of births per 1000 population per year. It is mentioned in the official website of the Malaysian Statistics Department, that the human population in 2017 was 2.77 million and the crude annual human birth rate was 13.6 per 1000 population per year (DOSM, 2019). Hence, the monthly human birth rate, B can be calculated as:

Annual number of new born humans

$$= \frac{\text{total number of humans}}{1000} \times \text{crude annual human birth rate per 1000 population}$$

$$= \frac{2770000}{1000} \times 13.6 = 37672.$$

So,

monthly number of new born human (B) = (annual number of new born humans) $\div$ 12 month

$$A = 37672 \div 12 \approx 3139.$$

3.5.5 Human rabies-related death rate

In the span of 12 months from the first outbreak in June 2017, Sarawak has reported a total of 10 human deaths from a total of 11 rabies positive cases (Abdullah, 2019), bringing the human death rate due to rabies up to an approximate 91%. I.e.,

$$\mu_h = \frac{10}{11} \approx 0.91.$$

Therefore, we have approximated the human rabies mortality rate (μ_h) to be 0.91.

3.5.6 Reciprocal of the human incubation period

By measuring the duration between the time of exposure with the rabies virus to the time the patient becoming symptomatic, we calculate the incubation period mean of the eight positive cases of human rabies and estimated it to be two and a half months (refer Appendix A). The estimated value of human rabies incubation period is also close to the that chosen in Zhang et al. (2011) which is 2 months. Therefore, the reciprocal of human incubation period (σ_h) becomes

$$\sigma_h = \frac{1}{2.5} = 0.4.$$

3.5.7 Rate of human PEP vaccination

The human vaccination rate (k_h) is estimated as the proportion of exposed individuals getting treated; that is the number of patients receiving PEP out of the total number of individuals exposed with the rabies virus, in which half of the frequency of dog bite cases is taken as proxy (Tepsumethanon et al., 2004). As a result, we estimate the monthly rate of human vaccination (k_h) by calculating the proportion of the monthly average number of human vaccinated and half of the entire frequency of bite cases between July 2017 to March 2021. Both information are available at the Sarawak Disaster Information official website (Sarawak Disaster Information, 2020).

Monthly average number of humans vaccinated

= (total number of humans vaccinated between July 2017 to March 2021) ÷ 44 months

$$= \frac{18369}{44}.$$

Half of the total frequency of bite cases between July 2017 to March 2021 = $\frac{55491}{2}$.

$$k_h = \frac{\text{monthly average number of humans vaccinated}}{\text{half of the total frequency of bite cases between July 2017 to March 2021'}}$$

$$k_h = \frac{\frac{18369}{44}}{\frac{55491}{2}} = 0.015 \approx 0.02.$$

3.5.8 Dog natural mortality rate

The natural mortality rate for dogs, m_d is obtained from Asamoah et al. (2017) whereby the dog mortality rate per year was stated as 0.056/year. Since all parameters in this work are taken as monthly rates, the dog natural mortality rate, m_d is converted as:

$$m_d = 0.056 \text{ per 1 year,}$$

$$= 0.056 \text{ per 12 months,}$$

$$= \frac{0.056}{12} \text{ per month.}$$

3.5.9 Human natural mortality rate

The human crude death rate is obtained from the Department of Statistics Malaysia (DOSM, 2019). The crude death rate can be defined as the number of deaths per 1000 population per year. Again, we are only interested in the value of the Sarawak crude death rate for the year 2017 as it was the year of the first rabies outbreak. According to the Malaysian Statistics Department, the crude death rate in 2017 for the Sarawak state was 4.7 per 1000 population per year (DOSM, 2019). Hence, we calculate the monthly human natural mortality rate, m_h as:

$$m_h = \frac{4.7}{1000} \text{ per 1 year,}$$

$$= 0.0047 \text{ per 12 months,}$$

$$= \frac{0.0047}{12} \text{ per month.}$$

3.5.10 Reciprocal of dog incubation period

As stated by Zhang et al. (2011), the reciprocal of dog incubation period is assumed to be 6 per year. Therefore, we convert the reciprocal of dog incubation period, σ_d into monthly rate:

$$\sigma_d = 6 \text{ per year} = 6 \text{ per 12 months} = 0.5 \text{ per month.}$$

3.5.11 Rate of dog immunity loss and rate of human immunity loss

According to Zhang et al. (2011), the rates of vaccination immunity loss for both dogs and humans are presumed to be one per year. Hence, the rates of dog immunity loss, λ_d and human immunity loss, λ_h can be calculated as:

$$\lambda_d = \lambda_h = 1 \text{ per year} = 1 \text{ per 12 months} = \frac{1}{12} \text{ per month.}$$

3.5.12 Dog rabies-related death rate

The rabies mortality rate for dogs is taken as probability of one per year based on Zhang et al. (2011). Hence, in terms of probability, the monthly rate is as below:

$$\mu_d = 1 \text{ per year} = 1 \text{ per month.}$$

3.5.13 Dog-to-dog transmission rate and dog-to-human transmission rate

Through model calibration, we will fit the curve for the simulated monthly number of infected humans with the actual human positive rabies cases for a 26-month period starting from the first outbreak in June 2017 to July 2019. We select a range of starting values for these dog-to-dog transmission rate and dog-to-human transmission rate parameters based on past literatures for the initial simulation prior to model calibration.

3.6 Initial Conditions

The initial values of the four compartments for both the dog and human populations are either estimated or arbitrarily assumed. There were no immunization programs for dogs implemented at the early phase of the outbreak so $V_d(0) = 0$. As the first case of rabies in Sarawak was detected in humans, this implies that the virus has been circulating within the dog population for some time before the spillover event happened. Hence, we assume that the initial number of exposed dogs to be 300 and the initial number of infectious dogs to be

200. According to online news (Dayak Daily, 2019), the Sarawak dog population is estimated to be 200000. Hence, the initial number of susceptible dogs would be $S_d(0) = 200000 - E_d(0) - I_d(0) - V_d(0) = 200000 - 300 - 200 = 199500$.

Three victims were infected with rabies during the first month of the outbreak and no PEP vaccination was given at the time, so $I_h(0) = 3$ and $V_h(0) = 0$. As of 2 July 2017, the first affected district, Serian, had reported a total of 34 dog bite cases (Borneo Post, 2017). Similar to the estimation of human PEP vaccination rate in the previous Section 3.5.7, we will take half of the frequency of dog bite cases as proxy to the total number of exposed humans (Tepsumethanon et al., 2004). Hence, we approximate $E_h(0) = 20$ based on this assumption. According to the Malaysian Statistics Department, the Sarawak human population in 2017 was 2.77 million. Therefore, the initial number of susceptible humans would be $S_h(0) = 2770000 - E_h(0) - I_h(0) - V_h(0) = 2770000 - 20 - 3 = 2769977$.

3.7 Summary

We have formulated a system of eight ordinary differential equations (3.1) with 15 parameters that considers two interacting population of dogs and humans to describe the dynamics of Sarawak rabies transmission. The compartment model follows the Susceptible-Exposed-Infected-Vaccinated (SEIV) framework that incorporates the dynamics of dog-to-dog and dog-to-human rabies transmission in Sarawak. To scale it to a local context, this model incorporates immunity in the form of post-exposure prophylaxis for humans and pre-exposure vaccination for dogs, as well as targeted dog culling; in-line with the intervention measures conducted by the Sarawak State Health Department and the Department of Veterinary Services. In summary, the transmission and progression of rabies virus between the two populations of dog and human, which are governed by several epidemiological non-

negative parameters, can be visualised in the simplified schematic diagrams in Figure 3.10 and Figure 3.11 shown in the next page.

The China rabies model from Zhang et al. (2011) was selected for model verification purpose as our Sarawak rabies model is actually an extension of the Zhang et al. (2011) model. To simulate the rabies transmission dynamics in Sarawak, we collect data on Sarawak rabies for parameter estimations primarily from online sources such as the Director-General of Health official press release statements.

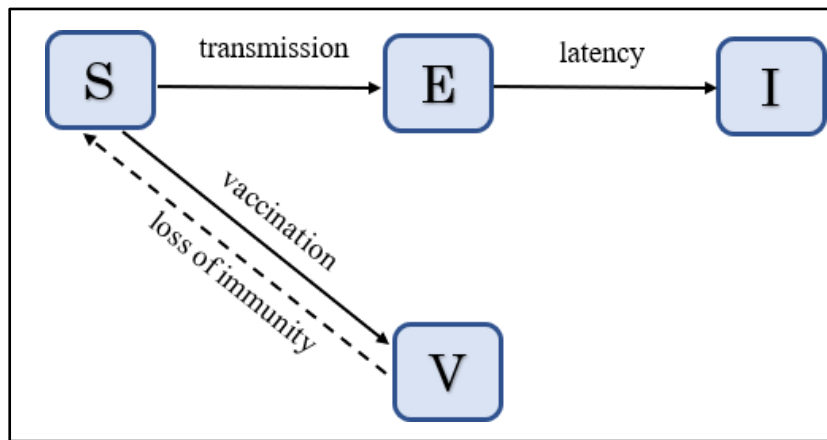


Figure 3.10: Schematic Diagram of the Dog Compartmental SEIV Model

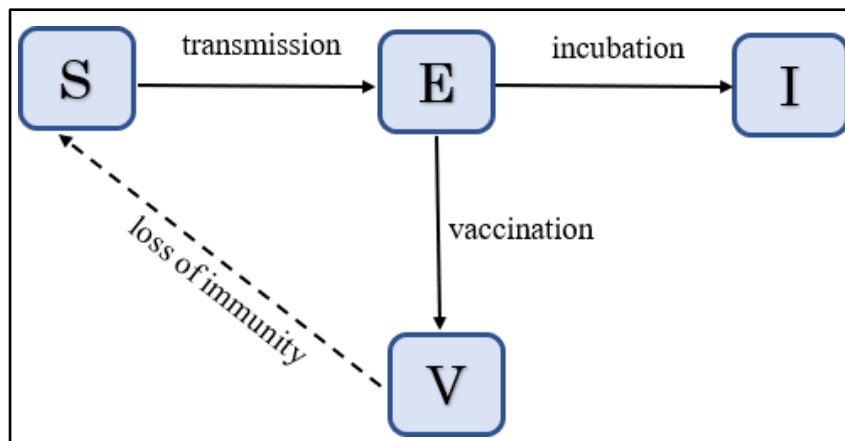


Figure 3.11: Schematic Diagram of the Human Compartmental SEIV Model

To summarize, we have estimated eight model parameters from the actual data in Sarawak, while five were sourced from literature and another two parameters will be derived through model fitting. Similarly, five initial conditions were estimated using Sarawak data, and three initial conditions were presumed. For those parameters that can only be estimated during model fitting, we select a range of starting values based on past literatures for the initial simulation prior to model calibration. The values of these parameters and initial conditions are listed in Table 3.3 – Table 3.5 below:

Table 3.3: Dog Parameter Description and Values

Parameter	Description	Value (/month)	Source
A	Monthly number of new born dogs	1800	estimated
β_d	Rate of dog-to-dog transmission	TBD	fitting
σ_d	Reciprocal of the dog incubation period	0.5	Zhang et al., (2011)
μ_d	Dog rabies-related death rate	1	Zhang et al., (2011)
m_d	Dog natural mortality rate	0.056/12	(Asamoah et al., 2017)
c_d	Rate of dog culling	0.004	estimated
k_d	Rate of dog vaccination	0.02	estimated
λ_d	Rate of dog immunity loss	1/12	Zhang et al., (2011)

*TBD – To be determined

Table 3.4: Human Parameter Description and Values

Parameter	Description	Value (/month)	Source
B	Monthly human birth rate	3139	estimated
β_h	Rate of dog-to-human transmission	TBD	fitting
σ_h	Reciprocal of the human incubation period	0.4	estimated
μ_h	Human disease-induced death rate	0.91	estimated
m_h	Human natural mortality rate	0.0047/12	estimated
k_h	Rate of human PEP vaccination	0.02	estimated
λ_h	Rate of human immunity loss	1/12	Zhang et al., (2011)

*TBD – To be determined

Table 3.5: Initial conditions

Parameter	Description	Value	Source
$S_d(0)$	Initial number of susceptible dogs	199500	assumption
$E_d(0)$	Initial number of exposed dogs	300	assumption
$I_d(0)$	Initial number of infected dogs	200	assumption
$V_d(0)$	Initial number of vaccinated dogs	0	estimated
$S_h(0)$	Initial number of susceptible humans	2769977	estimated
$E_h(0)$	Initial number of exposed humans	20	estimated
$I_h(0)$	Initial number of infected humans	3	estimated
$V_h(0)$	Initial number of vaccinated humans	0	estimated

*TBD – To be determined

CHAPTER 4

NUMERICAL RESULT

4.1 Overview

This chapter presents the numerical results obtained in this research. First, Section 4.2 is the reproduction of the simulation in Zhang et al. (2011) as model verification. Then, Section 4.3 presents the model calibration to estimate some parameter values and initial condition through model fitting. Using the updated parameter values from model calibration, Section 4.4 gives the Sarawak rabies model validation using the actual number of monthly active cases of human rabies in Sarawak and calculates the Root-Mean-Square-Error (RMSE). Section 4.5 provides the numerical simulation of the SEIV rabies model in the context of Sarawak. Lastly, Section 4.6 provides the summary of the entire chapter.

4.2 Model Verification

Only the plot of infected humans against time is presented in the article by Zhang et al. (2011). Therefore, we have reproduced the same simulation in R using the exact values of parameters and initial conditions (see Table 3.5) as in Zhang et al. (2011). Then, the two plots of infected humans are placed side-by-side for comparison.

Both plots indicate that after 10 years, the first wave of human rabies outbreak will reach its peak with almost 3500 people infected with rabies. The number of humans infected will continue to decline and rise again after the 20th year and the second wave of outbreak will reach its peak around the 30th and 40th year. The peak of the second outbreak however is significantly reduced to only less than 200 infected people. It can be observed that the two plots are in agreement with each other. Hence, it is possible to reproduce this simulation and extend from the Zhang et al. (2011) model.

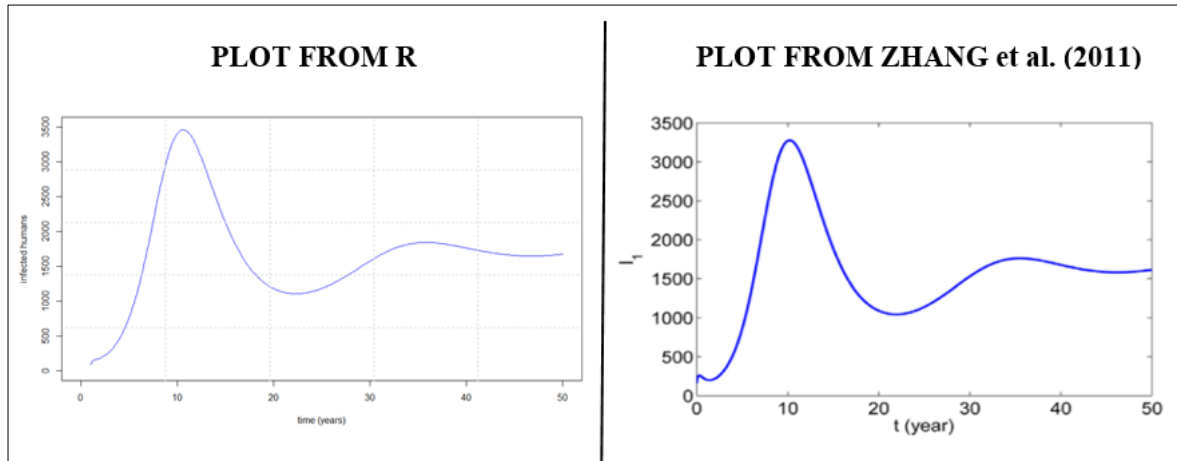


Figure 4.1: Plot of Infected Humans Against Time

4.3 Model Calibration

For model calibration purpose, the system of equations in model (3.1) is solved numerically using the parameter values and initial conditions from Table 3.3 – Table 3.5, and simulated for 26 months using *ode* function in the package *deSolve* in R. The values for some parameters and initial conditions will be re-adjusted during this process.

Figure 4.2 below shows the plot on the simulation of infected human using our SEIV model (3.1) and the actual data of monthly human rabies active cases in a 26-month period starting from the first outbreak in June 2017 to July 2019 extracted from the online press release of the Director-General of Health Malaysia (Abdullah, 2019). The solid blue line represents our simulation while the red dots represent the actual monthly human rabies cases.

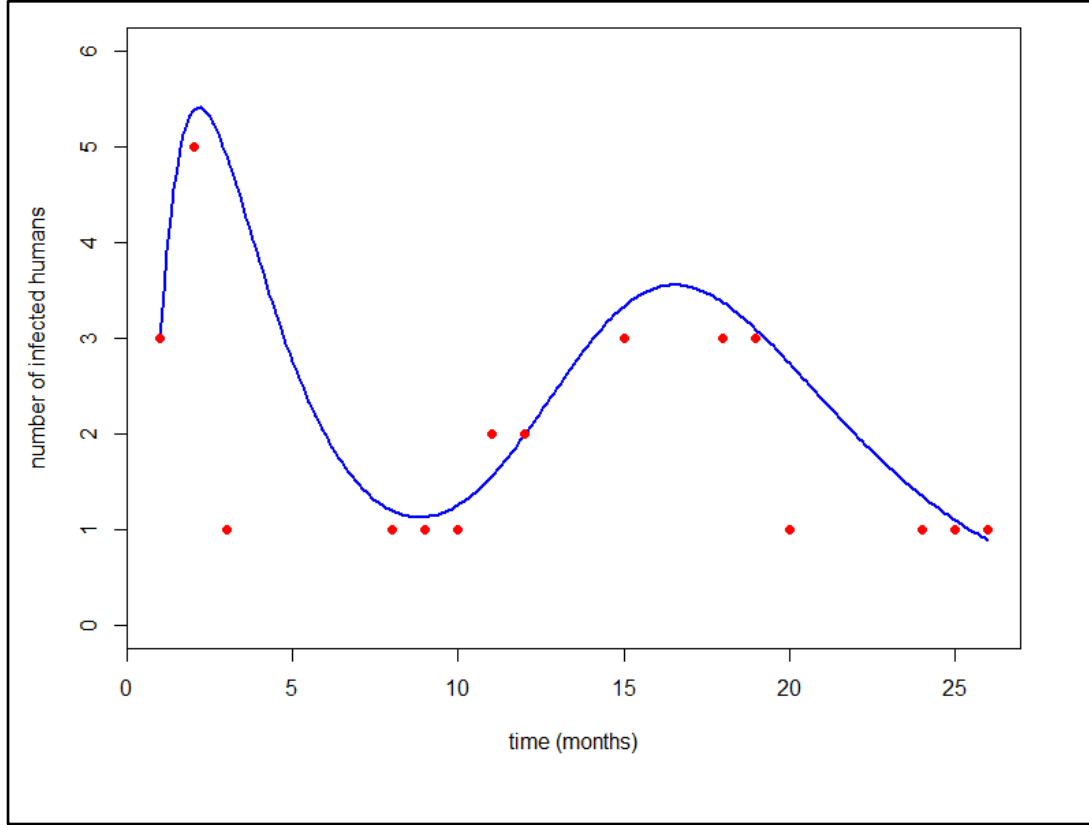


Figure 4.2: Plot of the Number of Human Rabies Cases Against Time

Through heuristics methods via “eyeballing” and visual inspection, the dog-to-dog transmission rate (β_d) and dog-to-human transmission rate (β_h) are found to be 0.000017 per year and 6×10^{-11} per year, respectively. Also, we determined the initial value of exposed humans, $E_h(0)$ to be 20 while the initial values of exposed dogs, $E_d(0)$ and infected dogs, $I_d(0)$ is found to be 300 and 200, respectively.

Hence, after the re-adjustment of some parameter values through model fitting, we summarize these values in the Table 4.1 and Table 4.2 shown in the next page.

Table 4.1: Dog Parameter Description and Values After Calibration

Parameter	Description	Value (/month)	Source
A	Monthly number of new born dogs	1800	estimated
β_d	Rate of dog-to-dog transmission	0.000017	fitting
σ_d	Reciprocal of the dog incubation period	0.5	Zhang et al., (2011)
μ_d	Dog rabies-related death rate	1	Zhang et al., (2011)
m_d	Dog natural mortality rate	0.056/12	(Asamoah et al., 2017)
c_d	Rate of dog culling	0.004	estimated
k_d	Rate of dog vaccination	0.02	estimated
λ_d	Rate of dog immunity loss	1/12	Zhang et al., (2011)

Table 4.2: Human Parameter Description and Values After Calibration

Parameter	Description	Value (/month)	Source
B	Monthly human birth rate	3139	estimated
β_h	Rate of dog-to-human transmission	8×10^{-11}	fitting
σ_h	Reciprocal of the human incubation period	0.4	estimated
μ_h	Human disease-induced death rate	0.91	estimated
m_h	Human natural mortality rate	0.0047/12	estimated
k_h	Rate of human PEP vaccination	0.02	estimated

Table 4.2 continued

λ_h	Rate of human immunity loss	1/12	Zhang et al., (2011)
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4.4 Model Validation

We have fitted the SEIV model (3.1) with the actual Sarawak rabies incidences in human from the period of June 2017 to July 2019 by varying the values of several parameters and initial conditions. It can be observed from Figure 4.2 that the model is able to capture well the first and second outbreak of human rabies in Sarawak. Overall, the trend of the simulated number of infected humans is similar to the actual human rabies cases reported. They both peaked initially at the second month and the second peak can be seen right after the 15th month. In this study, we will use RMSE as a model performance metric to discern how far off the simulated number of infected humans would be from the actual cases.

4.4.1 Root-Mean-Square-Error (RMSE)

The differences between the actual and simulated values are presented in the last column of Table 4.3. The positive sign indicates that the simulated number of infected humans are more than the actual human rabies case, while the negative sign indicates that the simulated number of infected humans are less than the actual human rabies case. Using the formula (2.2) for calculating RMSE shown in Chapter 2, the Root-Mean-Square-Error (RMSE) is found to be 1.9556. As the RMSE value is less than 2.0 (Li et al., 2018), it can be concluded that within the period of study between June 2017 to July 2019, the model (3.1) reflects the dynamics of human rabies in Sarawak quite reasonably well due to the small RMSE.

Table 4.3: Differences Between the Simulated and Actual Rabies Incidences

No.	Month	Number of cases	Simulation	Differences
1	June 2017	3	3.0000	0.000
2	July 2017	5	5.3796	-0.3796
3	August 2017	1	4.9098	-3.9098
4	September 2017	0	3.7963	-3.7963
5	October 2017	0	2.7582	-2.7582
6	November 2017	0	1.9787	-1.9787
7	December 2017	0	1.4678	-1.4678
8	January 2018	1	1.9142	-0.9142
9	February 2018	1	1.1292	-0.1292
10	March 2018	1	1.2541	-0.2541
11	April 2018	2	1.5501	0.4499
12	May 2018	2	1.9815	0.0185
13	June 2018	0	2.4825	-2.4825
14	July 2018	0	2.9625	-2.9625
15	August 2018	3	3.3311	-0.3311
16	September 2018	0	3.5271	-3.5271
17	October 2018	0	3.5337	-3.5337
18	November 2018	3	3.3733	-0.3733
19	December 2018	3	3.0915	-0.0915
20	January 2019	1	2.7395	-1.7395
21	February 2019	0	2.3625	-2.3625
22	March 2019	0	1.9939	-1.9939

Table 4.3 continued

23	April 2019	0	1.6547	-1.6547
24	May 2019	1	1.3559	-0.3559
25	June 2019	1	1.1009	-0.1009
26	July 2019	1	0.8883	0.1117

4.5 Numerical Simulation of SEIV Model

By using the parameter values and initial conditions from Table 3.5, Table 4.1 and Table 4.2, the system of equations in model (3.1) is solved numerically and simulated for 150 months using ode function in the package *deSolve* in R. The objective of this simulation is to observe and investigate the long-term trend of the human population when rabies virus is introduced into the population in Sarawak.

Figure 4.3 is the plot of susceptible humans against time. The number of susceptible humans can be seen increasing continuously mainly due to birth. Since human rabies PEP is only given to dog-bite victims who have been exposed to possible rabid dogs, a large number of people would still remain susceptible as they won't become immune due to vaccination.

Figure 4.4 is the plot of exposed humans against time. The number of exposed humans initially decreases before increasing and reaching a peak between the 15th and 20th month. The number of exposed humans would then decrease and remain low for a long period of time. This could be due to low risk of contact between human and infected dogs as various intervention measures are being conducted; such as culling and mass dog vaccination, which break the chain of transmission of rabies from dogs to humans.

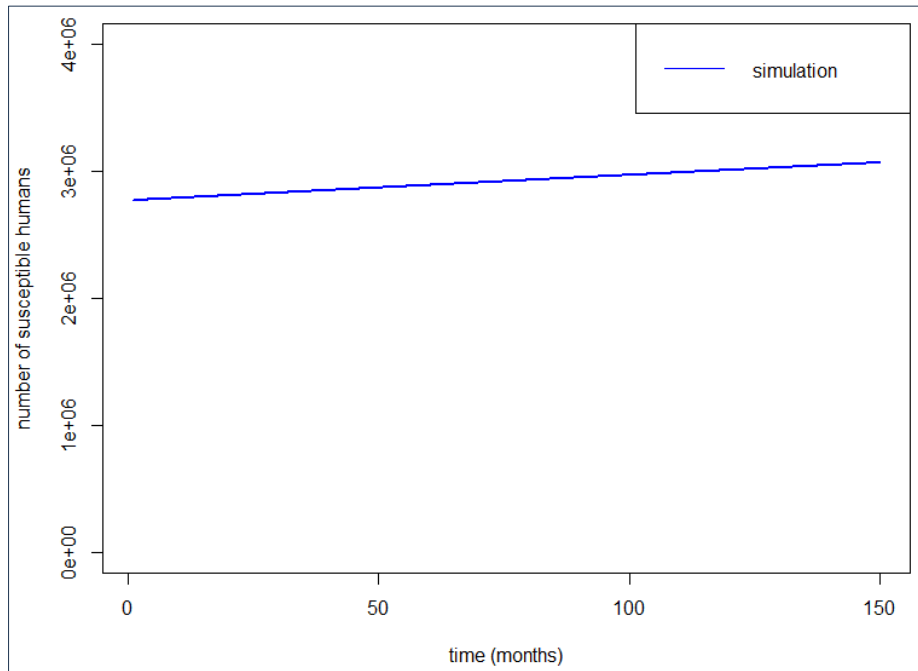


Figure 4.3: Plot of Susceptible Humans Population Over Time

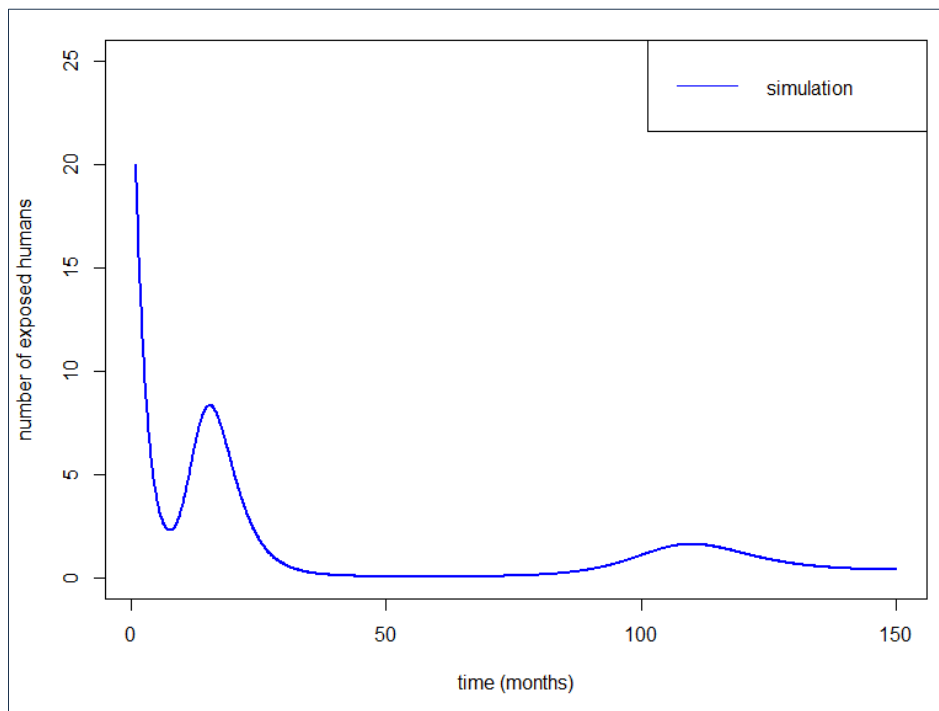


Figure 4.4: Plot of Exposed Humans Population Over Time

Figure 4.5 is the plot of infected humans against time. The number of infected humans increases and reaches a peak in a span of less than five months while the second peak of the outbreak is between the 15th and 20th month. After that, the model also predicts that the cases would continue to decline most likely due to the intervention measures implemented by the Sarawak government before experiencing a slight bump after 100 months.

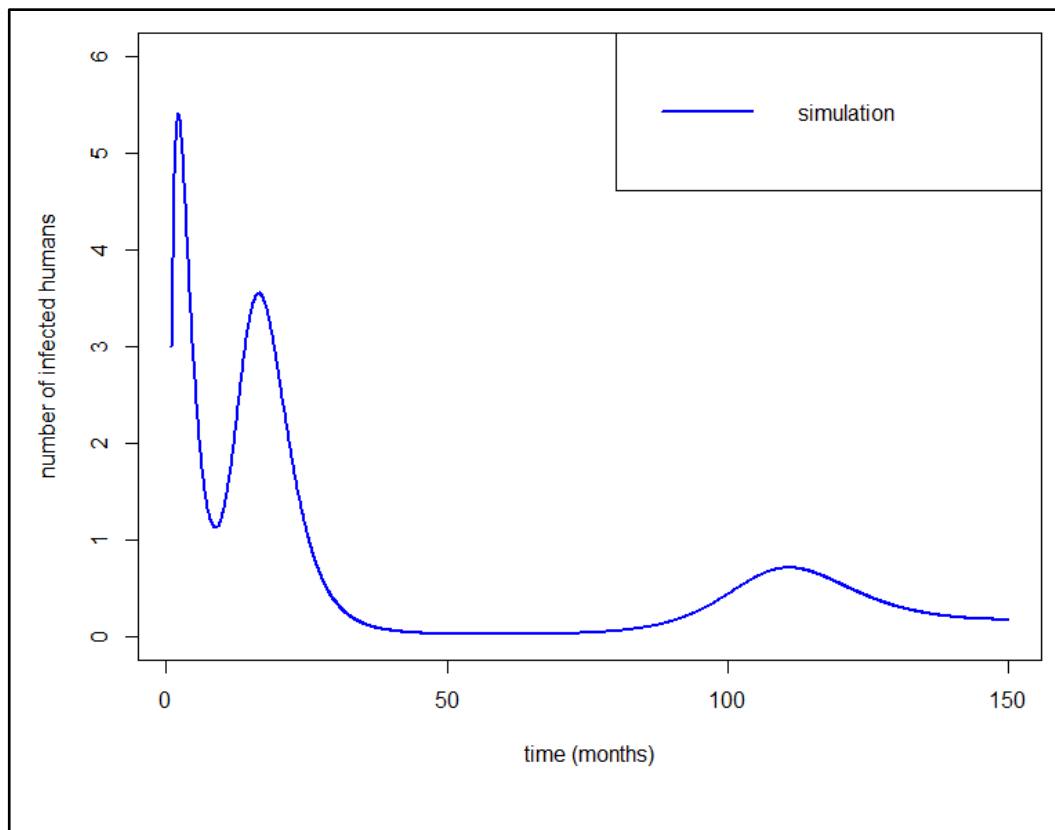


Figure 4.5: Plot of Infected Humans Population Over Time

Figure 4.6 is the plot of vaccinated humans against time. The number of vaccinated humans initially increases and reaches a peak at the 25th month. The trend seems to decrease before increasing back after the 100th month mark. This pattern of vaccination is aligned

with the trend on exposed humans in Figure 4.3 since human rabies vaccination is given as prophylaxis.

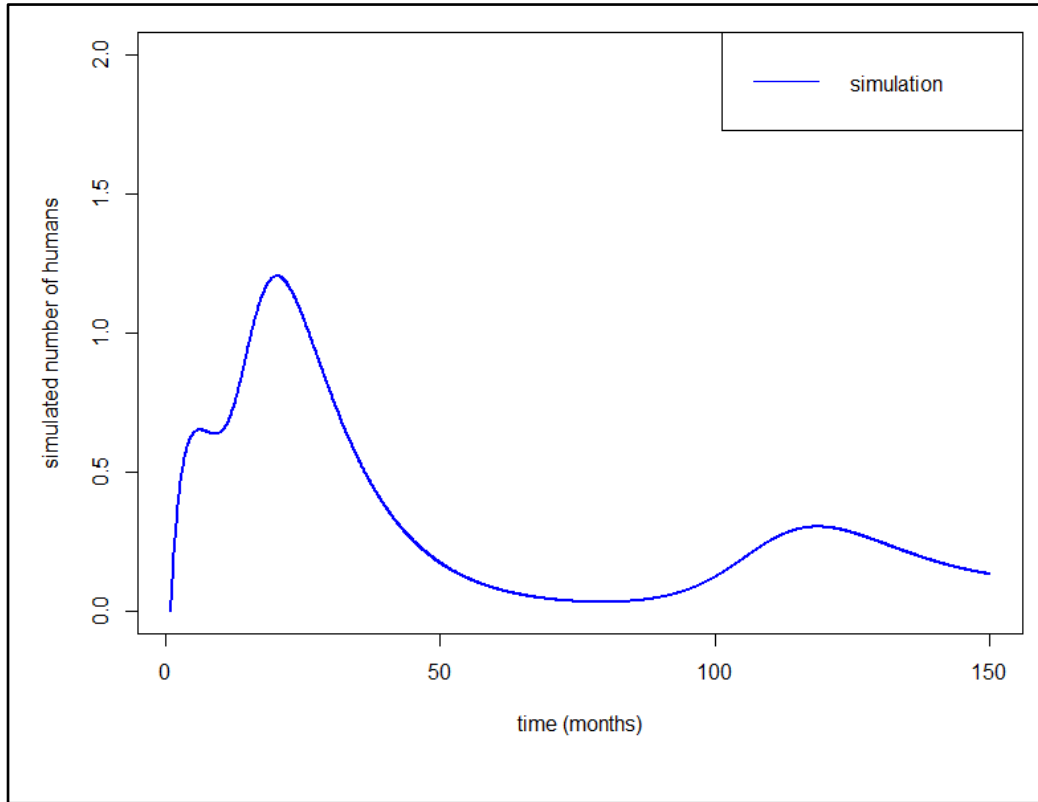


Figure 4.6: Plot of Vaccinated Humans Population Over Time

4.6 Summary

In summary, we have successfully verified the formulated rabies epidemic model by reproducing the simulation results from the Zhang et al. (2011) model. For model calibration purpose, the system of equations in model (3.1) is solved numerically using the parameter values and initial conditions from Table 3.3 – Table 3.5 and simulated for 26 months. After the re-adjustment of some parameter values through model fitting, we summarise these updated values in Table 4.1 and Table 4.2. It can be concluded that within the period of study between June 2017 to July 2019, the model (3.1) portrays the dynamics of human rabies in Sarawak quite reasonably well due to the small RMSE values computed in Table 4.4.

After model validation, numerical simulation was performed again for 150 months using the updated parameter values and initial conditions in Table 3.5, Table 4.1 and Table 4.2 to observe and investigate the long-term trend of human population when rabies virus is introduced in Sarawak. From the simulation, the number of infected humans can be seen increasing and reaching a peak within 5 months, while the second peak of the outbreak is between the 15th and 20th month. Lastly, the model also predicts that the cases would continue to decline, most likely due to the intervention measures implemented by the Sarawak government, before experiencing a slight bump after 100 months from the initial outbreak.

CHAPTER 5

MODEL ANALYSIS AND DISCUSSION

5.1 Overview

This chapter covers the steady state analysis of the epidemic model system by finding the disease-free equilibrium (DFE) and analyses its local stability. It is important to study the behaviour of solutions near the equilibrium point DFE—or rather, the steady state. This is because, in the context of epidemiology, when the DFE is locally asymptotically stable, this means that it is possible to achieve a state free of rabies in the population. Section 5.2 also determines the effective reproduction number by using the Next Generation Matrix approach. Evaluating the effective reproduction number is crucial as it is a key metric to perform the sensitivity analysis in the following Section 5.3. Findings from the sensitivity analysis will enable the identification of the most influential parameters for rabies transmission in Sarawak and the best control strategies for rabies eradication will be discussed in Section 5.4. Lastly, Section 5.5 provides the summary of the entire chapter.

5.2 Steady State Analysis of SEIV Model

At equilibrium, we have steady rates of individuals moving into and out of each compartment; and since the rates are exactly balanced, they cancelled out each other. In other words, the rate of change of the number of individuals entering and leaving a compartment becomes zero. That being so, at the equilibrium point, we can equate the left-hand side of model system (3.1) to zero:

$$\begin{aligned}
0 &= A + \lambda_d V_d - \beta_d S_d I_d - (m_d + k_d + c_d) S_d, \\
0 &= \beta_d S_d I_d - (m_d + \sigma_d + c_d) E_d, \\
0 &= \sigma_d E_d - (m_d + \mu_d + c_d) I_d, \\
0 &= k_d S_d - (m_d + \lambda_d) V_d, \\
0 &= B + \lambda_h V_h - \beta_h S_h I_d - m_h S_h, \\
0 &= \beta_h S_h I_d - (m_h + \sigma_h + k_h) E_h, \\
0 &= \sigma_h E_h - (m_h + \mu_h) I_h, \\
0 &= k_h E_h - (m_h + \lambda_h) V_h.
\end{aligned} \tag{5.1}$$

5.2.1 Disease Free Equilibrium

The disease-free equilibrium ($\mathbf{E}_0$) is an equilibrium state where infection is absent. Assuming there are no infected individuals in both populations, i.e, $E_d = 0, I_d = 0, E_h = 0, I_h = 0$, so the equation system (5.1) becomes

$$\begin{aligned}
A + \lambda_d V_d - (m_d + k_d + c_d) S_d &= 0, \\
k_d S_d - (m_d + \lambda_d) V_d &= 0, \\
B + \lambda_h V_h - m_h S_h &= 0, \\
-(m_h + \lambda_h) V_h &= 0.
\end{aligned} \tag{5.2}$$

After we proceed to solve for the values of S_d, V_d, S_h , and V_h from (5.2), the model system (3.1) has a disease-free equilibrium

$$\mathbf{E}_0 = (S_d^0, E_d^0, I_d^0, V_d^0, S_h^0, E_h^0, I_h^0, V_h^0) = (S_d^0, 0, 0, V_d^0, S_h^0, 0, 0, V_h^0)$$

Hence,

$$\mathbf{E}_0 =$$

$$\left(\frac{A(m_d + \lambda_d)}{(m_d + k_d + c_d)(m_d + \lambda_d) - \lambda_d k_d}, 0, 0, \frac{k_d A}{(m_d + k_d + c_d)(m_d + \lambda_d) - \lambda_d k_d}, \frac{B}{m_h}, 0, 0, 0 \right). \quad (5.3)$$

5.2.2 Effective Reproduction Number ($\mathbf{R}_e$)

In order to obtain the effective reproduction number $\mathbf{R}_e$ for model (3.1), the Next Generation Matrix approach and notations hereafter follow heavily from Diekmann, Heesterbeek and Metz (1990) and Asamoah et al. (2017). Now, by considering the infected classes; i.e., E_d, I_d, E_h and I_h , we set $f_1 = \frac{dE_d}{dt}$, $f_2 = \frac{dI_d}{dt}$, $f_3 = \frac{dE_h}{dt}$ and $f_4 = \frac{dI_h}{dt}$ which gives:

$$\left. \begin{aligned} f_1(S_d, E_d, I_d) &= \beta_d S_d I_d - (m_d + \sigma_d + c_d) E_d, \\ f_2(E_d, I_d) &= \sigma_d E_d - (m_d + \mu_d + c_d) I_d, \\ f_3(S_h, E_h, I_h) &= \beta_h S_h I_h - (m_h + \sigma_h + k_h) E_h, \\ f_4(E_h, I_h) &= \sigma_h E_h - (m_h + \mu_h) I_h. \end{aligned} \right\} \quad (5.4)$$

We evaluate the Jacobian matrix (J) by taking partial derivatives of the equations in (5.4) with respect to E_d, I_d, E_h and I_h to get

$$J = \begin{pmatrix} \frac{\partial f_1}{\partial E_d} & \frac{\partial f_1}{\partial I_d} & \frac{\partial f_1}{\partial E_h} & \frac{\partial f_1}{\partial I_h} \\ \frac{\partial f_2}{\partial E_d} & \frac{\partial f_2}{\partial I_d} & \frac{\partial f_2}{\partial E_h} & \frac{\partial f_2}{\partial I_h} \\ \frac{\partial f_3}{\partial E_d} & \frac{\partial f_3}{\partial I_d} & \frac{\partial f_3}{\partial E_h} & \frac{\partial f_3}{\partial I_h} \\ \frac{\partial f_4}{\partial E_d} & \frac{\partial f_4}{\partial I_d} & \frac{\partial f_4}{\partial E_h} & \frac{\partial f_4}{\partial I_h} \end{pmatrix},$$

which then yields

$$J = \begin{pmatrix} -(m_d + \sigma_d + c_d) & \beta_d S_d & 0 & 0 \\ \sigma_d & -(m_d + \mu_d + c_d) & 0 & 0 \\ 0 & \beta_h S_h & -(m_h + \sigma_h + k_h) & 0 \\ 0 & 0 & \sigma_h & -(m_h + \mu_h) \end{pmatrix}.$$

Suppose that the Next Generation matrix (G) is given as $G = FV^{-1}$, we let $J = F - V$ which gives F and V matrices at the disease-free equilibrium point, E_0 :

$$F(E_0) = \begin{pmatrix} 0 & \beta_d S_d^0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & \beta_h S_h^0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix},$$

$$V(E_0) = \begin{pmatrix} m_d + \sigma_d + c_d & 0 & 0 & 0 \\ -\sigma_d & m_d + \mu_d + c_d & 0 & 0 \\ 0 & 0 & m_h + \sigma_h + k_h & 0 \\ 0 & 0 & -\sigma_h & m_h + \mu_h \end{pmatrix}.$$

After computing the inverse of matrix V by partitioning the matrix into four 2×2 sub-matrices and evaluating the concomitant inverses, the Next Generation matrix, $G = FV^{-1}$ is determined.

$$G = FV^{-1} = \begin{pmatrix} \frac{\sigma_d \beta_d S_d^0}{(m_d + \sigma_d + c_d)(m_d + \mu_d + c_d)} & \frac{\beta_d S_d^0}{m_d + \mu_d + c_d} & 0 & 0 \\ 0 & 0 & 0 & 0 \\ \frac{\sigma_d \beta_h S_h^0}{(m_d + \sigma_d + c_d)(m_d + \mu_d + c_d)} & \frac{\beta_h S_h^0}{m_d + \mu_d + c_d} & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix}.$$

The process of evaluating the eigenvalues of the Next Generation matrix, G involves solving the characteristic equation of matrix G : $|G - \lambda I| = 0$, where λ is the eigenvalue. We first form the characteristic equation:

$$|G - \lambda I| = \begin{vmatrix} \frac{\sigma_d \beta_d S_d^0}{(m_d + \sigma_d + c_d)(m_d + \mu_d + c_d)} - \lambda & \frac{\beta_d S_d^0}{m_d + \mu_d + c_d} & 0 & 0 \\ 0 & -\lambda & 0 & 0 \\ \frac{\sigma_d \beta_h S_h^0}{(m_d + \sigma_d + c_d)(m_d + \mu_d + c_d)} & \frac{\beta_h S_h^0}{m_d + \mu_d + c_d} & -\lambda & 0 \\ 0 & 0 & 0 & -\lambda \end{vmatrix} = 0.$$

By finding the determinant, the characteristic equation becomes

$$\lambda^3 \left(\frac{\sigma_d \beta_d S_d^0}{(m_d + \sigma_d + c_d)(m_d + \mu_d + c_d)} - \lambda \right) = 0. \quad (5.5)$$

Following Asamoah et al. (2017), the controlled reproduction number can be determined by finding the spectral radius (dominant eigenvalue) of the Next Generation matrix G , denoted by $\rho(G)$, as it gives the fastest growth of the infected population. Solving (5.5), we get the eigenvalues of the Next Generation matrix G : $\lambda = 0, \lambda = 0, \lambda = 0, \lambda =$

$$\frac{\beta_d S_d^0 \sigma_d}{(m_d + \sigma_d + c_d)(m_d + \mu_d + c_d)}.$$

Hence, we have the effective reproduction number $\mathbf{R_e}$ expressed as:

$$\mathbf{R_e} = \frac{\beta_d S_d^0 \sigma_d}{(m_d + \sigma_d + c_d)(m_d + \mu_d + c_d)},$$

$$\mathbf{R_e} \quad (5.6)$$

$$= \frac{\beta_d \sigma_d A(m_d + \lambda_d)}{(m_d + \sigma_d + c_d)(m_d + \mu_d + c_d)[(m_d + k_d + c_d)(m_d + \lambda_d) - \lambda_d k_d]}.$$

Next, the value of $\mathbf{R_e}$ in the context of Sarawak is calculated by inserting the dog parameter values (refer Table 4.1) used in the simulation of model (3.1) into the equation (5.6).

When the above parameter values were inserted into the R_e expression (5.6), the value of is found to be $R_e = 3.06$. In this study, R_e represents the average number of humans that can be infected by one infected dog over the entire course of its infectious period. As the calculated R_e is greater than one, this indicate that one rabid dog could potentially cause three new human rabies cases in Sarawak.

5.2.3 Herd Immunity Threshold

In the context of this study where immunity is incorporated into the model, the herd immunity threshold (2.1) will be expressed in terms of the effective reproduction number. Therefore, the herd immunity threshold (H) is calculated to be:

$$H = 1 - \frac{1}{R_e} = 1 - \frac{1}{3.06} = 0.6732.$$

This means that approximately 70% of the dog population in Sarawak should be vaccinated in order to break the chain of transmission of rabies and protect those who are not immunised. Also, our vaccination target is in agreement with the recommendation by WHO (Leung & Davis, 2017).

5.2.4 Local Stability of Disease-free Equilibrium

In our study, the equilibrium point to be tested for stability is the steady-state disease-free equilibrium E_0 in (5.3). We approach this problem by using the Lyapunov's Indirect Method. A necessary and sufficient condition for an equilibrium point to be locally asymptotically stable is that the real part of all eigenvalues of the Jacobian matrix must be of negative value (Martcheva, 2013). We first set the right-hand side of the system of differential equations (3.1) to be

$$\begin{aligned}
h_1 &= A + \lambda_d V_d - \beta_d S_d I_d - (m_d + k_d + c_d) S_d, \\
h_2 &= \beta_d S_d I_d - (m_d + \sigma_d + c_d) E_d, \\
h_3 &= \sigma_d E_d - (m_d + \mu_d + c_d) I_d, \\
h_4 &= k_d S_d - (m_d + \lambda_d) V_d, \\
h_5 &= B + \lambda_h V_h - \beta_h S_h I_d - m_h S_h, \\
h_6 &= \beta_h S_h I_d - (m_h + \sigma_h + k_h) E_h, \\
h_7 &= \sigma_h E_h - (m_h + \mu_h) I_h, \\
h_8 &= k_h E_h - (m_h + \lambda_h) V_h.
\end{aligned} \tag{5.7}$$

Therefore, we linearise at the disease-free equilibrium (DFE) point $\mathbf{E}_0$ of equation (5.7) to obtain the Jacobian matrix evaluated at $\mathbf{E}_0$, $J_{\mathbf{E}_0}$:

$$J_{\mathbf{E}_0} = \begin{pmatrix} \frac{\partial h_1}{\partial S_d} & \frac{\partial h_1}{\partial E_d} & \frac{\partial h_1}{\partial I_d} & \frac{\partial h_1}{\partial V_d} & \frac{\partial h_1}{\partial S_h} & \frac{\partial h_1}{\partial E_h} & \frac{\partial h_1}{\partial I_h} & \frac{\partial h_1}{\partial V_h} \\ \frac{\partial h_2}{\partial S_d} & \frac{\partial h_2}{\partial E_d} & \frac{\partial h_2}{\partial I_d} & \frac{\partial h_2}{\partial V_d} & \frac{\partial h_2}{\partial S_h} & \frac{\partial h_2}{\partial E_h} & \frac{\partial h_2}{\partial I_h} & \frac{\partial h_2}{\partial V_h} \\ \frac{\partial h_3}{\partial S_d} & \frac{\partial h_3}{\partial E_d} & \frac{\partial h_3}{\partial I_d} & \frac{\partial h_3}{\partial V_d} & \frac{\partial h_3}{\partial S_h} & \frac{\partial h_3}{\partial E_h} & \frac{\partial h_3}{\partial I_h} & \frac{\partial h_3}{\partial V_h} \\ \frac{\partial h_4}{\partial S_d} & \frac{\partial h_4}{\partial E_d} & \frac{\partial h_4}{\partial I_d} & \frac{\partial h_4}{\partial V_d} & \frac{\partial h_4}{\partial S_h} & \frac{\partial h_4}{\partial E_h} & \frac{\partial h_4}{\partial I_h} & \frac{\partial h_4}{\partial V_h} \\ \frac{\partial h_5}{\partial S_d} & \frac{\partial h_5}{\partial E_d} & \frac{\partial h_5}{\partial I_d} & \frac{\partial h_5}{\partial V_d} & \frac{\partial h_5}{\partial S_h} & \frac{\partial h_5}{\partial E_h} & \frac{\partial h_5}{\partial I_h} & \frac{\partial h_5}{\partial V_h} \\ \frac{\partial h_6}{\partial S_d} & \frac{\partial h_6}{\partial E_d} & \frac{\partial h_6}{\partial I_d} & \frac{\partial h_6}{\partial V_d} & \frac{\partial h_6}{\partial S_h} & \frac{\partial h_6}{\partial E_h} & \frac{\partial h_6}{\partial I_h} & \frac{\partial h_6}{\partial V_h} \\ \frac{\partial h_7}{\partial S_d} & \frac{\partial h_7}{\partial E_d} & \frac{\partial h_7}{\partial I_d} & \frac{\partial h_7}{\partial V_d} & \frac{\partial h_7}{\partial S_h} & \frac{\partial h_7}{\partial E_h} & \frac{\partial h_7}{\partial I_h} & \frac{\partial h_7}{\partial V_h} \\ \frac{\partial h_8}{\partial S_d} & \frac{\partial h_8}{\partial E_d} & \frac{\partial h_8}{\partial I_d} & \frac{\partial h_8}{\partial V_d} & \frac{\partial h_8}{\partial S_h} & \frac{\partial h_8}{\partial E_h} & \frac{\partial h_8}{\partial I_h} & \frac{\partial h_8}{\partial V_h} \end{pmatrix}$$

$$= \begin{pmatrix} C_1 & 0 & -\beta_d S_d^0 & \lambda_d & 0 & 0 & 0 & 0 \\ 0 & C_2 & \beta_d S_d^0 & 0 & 0 & 0 & 0 & 0 \\ 0 & \sigma_d & C_3 & 0 & 0 & 0 & 0 & 0 \\ k_d & 0 & 0 & C_4 & 0 & 0 & 0 & 0 \\ 0 & 0 & -\beta_h S_h^0 & 0 & -m_h & 0 & 0 & \lambda_h \\ 0 & 0 & \beta_h S_h^0 & 0 & 0 & C_5 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & \sigma_h & C_6 & 0 \\ 0 & 0 & 0 & 0 & 0 & k_h & 0 & C_7 \end{pmatrix}$$

where

$$C_1 = -(m_d + k_d + c_d), C_2 = -(m_d + \sigma_d + c_d),$$

$$C_3 = -(m_d + \mu_d + c_d), C_4 = -(m_d + \lambda_d),$$

$$C_5 = -(m_h + \sigma_h + k_h), C_6 = -(m_h + \mu_h),$$

$$C_7 = -(m_h + \lambda_h).$$

Next, we evaluate the characteristic equation of the Jacobian matrix, $|J_{E_0} - \lambda I| = 0$, by multiplying J_{E_0} with a 8×8 identity matrix and subtracting the diagonal elements with the eigenvalue λ . We then take the determinant of the whole expression and lastly equate it to zero in order to get the characteristic equation as:

$$|J_{E_0} I - \lambda| = 0,$$

$$\begin{vmatrix} C_1 - \lambda & 0 & -\beta_d S_d^0 & \lambda_d & 0 & 0 & 0 & 0 \\ 0 & C_2 - \lambda & \beta_d S_d^0 & 0 & 0 & 0 & 0 & 0 \\ 0 & \sigma_d & C_3 - \lambda & 0 & 0 & 0 & 0 & 0 \\ k_d & 0 & 0 & C_4 - \lambda & 0 & 0 & 0 & 0 \\ 0 & 0 & -\beta_h S_h^0 & 0 & -m_h - \lambda & 0 & 0 & \lambda_h \\ 0 & 0 & \beta_h S_h^0 & 0 & 0 & C_5 - \lambda & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & \sigma_h & C_6 - \lambda & 0 \\ 0 & 0 & 0 & 0 & 0 & k_h & 0 & C_7 - \lambda \end{vmatrix} = 0.$$

By eliminating the fifth row and column of $|J_{E_0}I - \lambda|$, the equation becomes:

$$(-m_h - \lambda) \begin{vmatrix} C_1 - \lambda & 0 & -\beta_d S_d^0 & \lambda_d & 0 & 0 & 0 \\ 0 & C_2 - \lambda & \beta_d S_d^0 & 0 & 0 & 0 & 0 \\ 0 & \sigma_d & C_3 - \lambda & 0 & 0 & 0 & 0 \\ k_d & 0 & 0 & C_4 - \lambda & 0 & 0 & 0 \\ 0 & 0 & \beta_h S_h^0 & 0 & C_5 - \lambda & 0 & 0 \\ 0 & 0 & 0 & 0 & \sigma_h & C_6 - \lambda & 0 \\ 0 & 0 & 0 & 0 & k_h & 0 & C_7 - \lambda \end{vmatrix} = 0.$$

Next, we proceed to eliminate the seventh row and column, so the equation becomes:

$$(-m_h - \lambda)(C_6 - \lambda) \begin{vmatrix} C_1 - \lambda & 0 & -\beta_d S_d^0 & \lambda_d & 0 & 0 \\ 0 & C_2 - \lambda & \beta_d S_d^0 & 0 & 0 & 0 \\ 0 & \sigma_d & C_3 - \lambda & 0 & 0 & 0 \\ k_d & 0 & 0 & C_4 - \lambda & 0 & 0 \\ 0 & 0 & \beta_h S_h^0 & 0 & C_5 - \lambda & 0 \\ 0 & 0 & 0 & 0 & k_h & C_7 - \lambda \end{vmatrix} = 0.$$

As the sixth column contains only diagonal element, we eliminate the sixth row and column so that the equation can be reduced to:

$$(-m_h - \lambda)(C_6 - \lambda)(C_7 - \lambda) \begin{vmatrix} C_1 - \lambda & 0 & -\beta_d S_d^0 & \lambda_d & 0 \\ 0 & C_2 - \lambda & \beta_d S_d^0 & 0 & 0 \\ 0 & \sigma_d & C_3 - \lambda & 0 & 0 \\ k_d & 0 & 0 & C_4 - \lambda & 0 \\ 0 & 0 & \beta_h S_h^0 & 0 & C_5 - \lambda \end{vmatrix} = 0.$$

Eliminating the fifth row and column as the fifth column contains only diagonal element, we get:

$$(-m_h - \lambda)(C_6 - \lambda)(C_7 - \lambda)(C_5 - \lambda) \begin{vmatrix} C_1 - \lambda & 0 & -\beta_d S_d^0 & \lambda_d \\ 0 & C_2 - \lambda & \beta_d S_d^0 & 0 \\ 0 & \sigma_d & C_3 - \lambda & 0 \\ k_d & 0 & 0 & C_4 - \lambda \end{vmatrix} = 0.$$

Next, the equation can be further reduced and expressed as:

$$(-m_h - \lambda)(C_6 - \lambda)(C_7 - \lambda)(C_5 - \lambda)[(C_1 - \lambda)(C_4 - \lambda) - \lambda_d k_d] \begin{vmatrix} C_2 - \lambda & \beta_d S_d^0 \\ \sigma_d & C_3 - \lambda \end{vmatrix} = 0$$

Hence, six separate equations can be formed from the characteristic equation of the linearised system; where equations (5.8)–(5.11) produce one eigenvalue each while equations (5.12)–(5.13) give two eigenvalues each.

$$-m_h - \lambda = 0 \quad (5.8)$$

$$C_6 - \lambda = 0 \quad (5.9)$$

$$C_7 - \lambda = 0 \quad (5.10)$$

$$(C_5 - \lambda) = 0 \quad (5.11)$$

$$(C_1 - \lambda)(C_4 - \lambda) - \lambda_d k_d = 0 \quad (5.12)$$

$$\begin{vmatrix} C_2 - \lambda & \beta_d S_d^0 \\ \sigma_d & C_3 - \lambda \end{vmatrix} = 0 \quad (5.13)$$

From the equations (5.8) – (5.13), the analysis of all eight eigenvalues, $\lambda_n, n = 0, 1, 2, 3, 4, 5, 6, 7, 8$, in terms of their signs are discussed below:

a. $-m_h - \lambda$

$$-m_h - \lambda = 0$$

$$\lambda_1 = -m_h.$$

Since $m_h > 0$, then the value of λ_1 is always negative. Hence, the eigenvalue λ_1 is stable.

b. $C_6 - \lambda$

$$C_6 - \lambda = 0,$$

$$-(m_h + \mu_h) - \lambda = 0,$$

$$\lambda_2 = -(m_h + \mu_h).$$

Since $m_h > 0$ and $\mu_h > 0$, then the value of λ_2 is always negative. Hence, the eigenvalue λ_2 is stable.

c. $C_7 - \lambda$

$$C_7 - \lambda = 0,$$

$$-(m_h + \lambda_h) - \lambda = 0,$$

$$\lambda_3 = -(m_h + \lambda_h).$$

Since $m_h > 0$ and $\lambda_h > 0$, then the value of λ_3 is always negative. Hence, the eigenvalue λ_3 is stable.

d. $C_5 - \lambda$

$$(C_5 - \lambda) = 0,$$

$$-(m_h + \sigma_h + k_h) - \lambda = 0,$$

$$\lambda = -(m_h + \sigma_h + k_h).$$

Since $m_h > 0$, $\sigma_h > 0$ and $k_h > 0$, then the value of λ_4 is always negative. Hence, the eigenvalue λ_4 is stable.

e. $(C_1 - \lambda)(C_4 - \lambda) - \lambda_d k_d = 0$

$$(C_1 - \lambda)(C_4 - \lambda) - \lambda_d k_d = 0,$$

$$C_1 C_4 - C_1 \lambda - C_4 \lambda + \lambda^2 - \lambda_d k_d = 0. \quad (5.14)$$

Rearranging the equation (5.14) as:

$$\lambda^2 + (-C_1 - C_4)\lambda + (C_1 C_4 - \lambda_d k_d) = 0 \quad (5.15)$$

The eigenvalues λ_5 and λ_6 can be found by solving the above quadratic equation (5.15) in standard form. However, for the purpose of this stability analysis, we are only interested to show that the real part of the two eigenvalues λ_5 and λ_6 is negative and distinct. This can be proven only if we have (i) positive coefficient of λ , (ii) a positive constant term and (iii) a positive discriminant.

The first condition holds true always since all parameters are positive, so $-C_1 - C_4 = -[-(m_d + k_d + c_d)] -[-(m_d + \lambda_d)] = 2m_d + k_d + c_d + \lambda_d > 0$. However, for the second condition the constant term is only positive $C_1 C_4 - \lambda_d k_d = (m_d + k_d + c_d)(m_d + \lambda_d) - \lambda_d k_d > 0$ when $(m_d + k_d + c_d)(m_d + \lambda_d) > \lambda_d k_d$. However, it can be seen that that the second condition is always true as all parameters are positive in $(m_d + k_d + c_d)(m_d + \lambda_d) > \lambda_d k_d$:

$$(m_d + k_d + c_d)(m_d + \lambda_d) > \lambda_d k_d$$

$$m_d^2 + m_d \lambda_d + m_d k_d + \lambda_d k_d + m_d c_d + c_d \lambda_d - \lambda_d k_d > 0$$

$$m_d^2 + m_d \lambda_d + m_d k_d + m_d c_d + c_d \lambda_d > 0$$

Lastly, the third condition only holds true provided that the discriminant $(-C_1 - C_4)^2 - 4(C_1 C_4 - \lambda_d k_d) > 0$. Equivalently, the discriminant can be expressed as

$(2m_d + k_d + c_d + \lambda_d)^2 > 4((m_d + k_d + c_d)(m_d + \lambda_d) - \lambda_d k_d)$. Therefore, the two eigenvalues λ_5 and λ_6 are stable as long as we have

$$(2m_d + k_d + c_d + \lambda_d)^2 > 4((m_d + k_d + c_d)(m_d + \lambda_d) - \lambda_d k_d).$$

$$\mathbf{f.} \quad \begin{vmatrix} C_2 - \lambda & \beta_d S_d^0 \\ \sigma_d & C_3 - \lambda \end{vmatrix}$$

$$\begin{vmatrix} C_2 - \lambda & \beta_d S_d^0 \\ \sigma_d & C_3 - \lambda \end{vmatrix} = 0$$

$$(C_2 - \lambda)(C_3 - \lambda) - \beta_d S_d^0 \sigma_d = 0,$$

$$C_2 C_3 - C_2 \lambda - C_3 \lambda + \lambda^2 - \beta_d S_d^0 \sigma_d = 0. \quad (5.16)$$

We rearrange equation (5.16) further in order to form the characteristic equation

$$\lambda^2 - (C_2 + C_3)\lambda + (C_2 C_3 - \beta_d S_d^0 \sigma_d) = 0. \quad (5.17)$$

In equation (5.17), the term $(C_2 + C_3)$ is known as the trace matrix of the Jacobian, $\text{Tr}(J_{E_0})$, while the constant term $(C_2 C_3 - \beta_d S_d^0 \sigma_d)$ is the determinant of the Jacobian, $\text{Det}(J_{E_0})$ (Martcheva, 2013). Furthermore, Martcheva (2013) stated that for a 2×2 matrix, the two eigenvalues formed are real and negative if and only if (i) $\text{Tr}(J_{E_0})$ is negative and (ii) $\text{Det}(J_{E_0})$ is positive. The first condition is always true as all parameters are positive, thus $C_2 + C_3 = -(m_d + \sigma_d + c_d) - (m_d + \mu_d + c_d) < 0$. For the second condition to become true, we need

$$C_2 C_3 - \beta_d S_d^0 \sigma_d > 0,$$

$$\beta_d S_d^0 \sigma_d < C_2 C_3,$$

$$\beta_d S_d^0 \sigma_d < (m_d + \sigma_d + c_d)(m_d + \mu_d + c_d). \quad (5.18)$$

By dividing both sides of the inequality (5.18) by the term $(m_d + \sigma_d + c_d)(m_d + \mu_d + c_d)$, we have

$$\frac{\beta_d S_d^0 \sigma_d}{(m_d + \sigma_d + c_d)(m_d + \mu_d + c_d)} < 1,$$

which is simply $\mathbf{R_e} < 1$ as $\mathbf{R_e} = \frac{\beta_d S_d^0 \sigma_d}{(m_d + \sigma_d + c_d)(m_d + \mu_d + c_d)}$

In conclusion, we have proven that all eigenvalues of the Jacobian matrix are real and negative. Additionally, we have shown that the effective reproduction number $\mathbf{R_e}$ (5.4) is of importance in determining the stability of the disease-free equilibrium (DFE). This is evident as we have obtained the condition which states that the DFE of system (3.1) is locally asymptotically stable if and only if $\mathbf{R_e} < 1$.

5.3 Sensitivity Analysis of the Effective Reproduction Number

In order to determine the parameters that contribute most to the rabies transmission in Sarawak, we opted for the normalised forward sensitivity index— a local sensitivity analysis technique. Local sensitivity analysis addresses sensitivity relative to a change of a single parameter value (Hoops et al., 2016). Generally, local sensitivity analysis is simpler and faster. However, calibrated parameters are required prior to applying a local sensitivity analysis.

5.3.1 Effects of Changing Parameter Values on R_e

As the value of R_e from equation (5.6) is dependent on the model parameters, we analysed the effect of varying parameters values on the value of R_e . Again, only the eight dog parameters will be involved in the analysis.

a. Monthly Number of New Born Dogs, A

The estimated value of A inserted into the expression of R_e was 1800. The values of this parameter are varied between 500 to 2000 (refer to Figure 5.1).

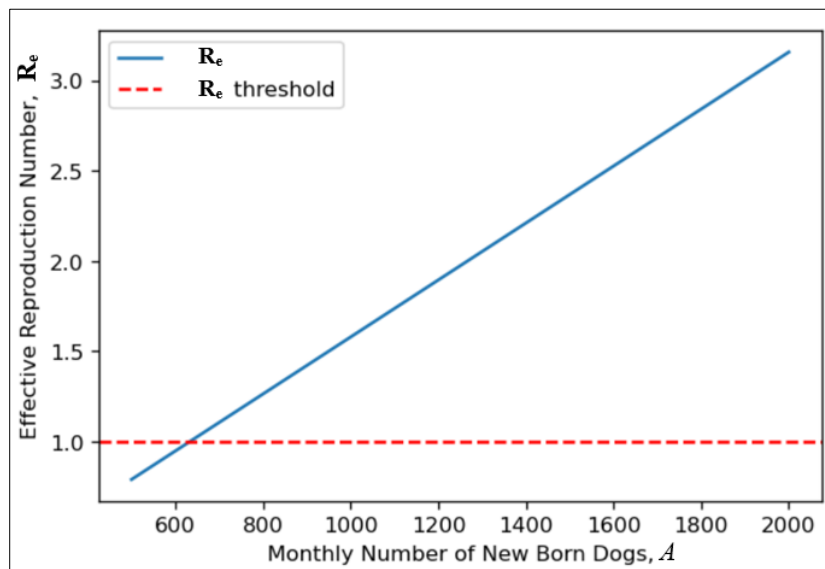


Figure 5.1: Plot of R_e Against Monthly Number of New Born Dogs

b. Rate of Dog-to-dog Transmission, β_d

The estimated value of β_d inserted into the expression of R_e was 0.000017. The values of this parameter are varied between 0 to 0.00002 (refer to Figure 5.2).

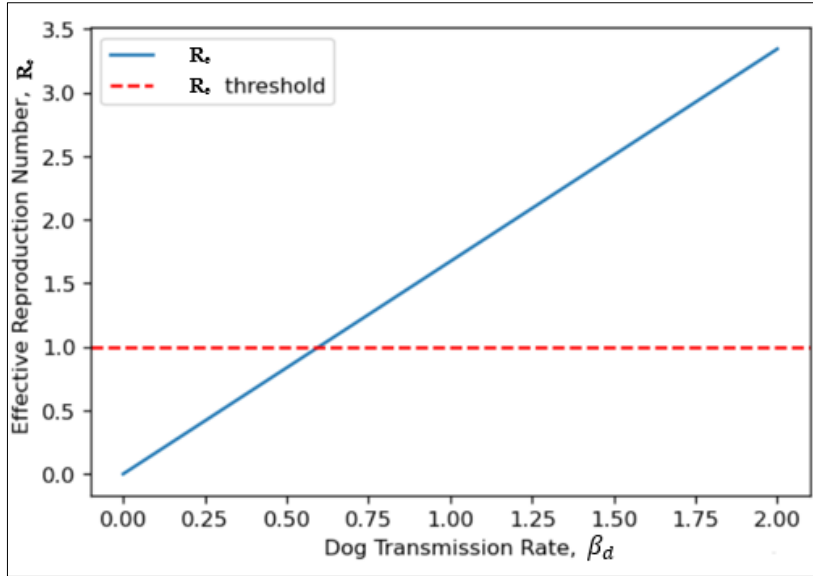


Figure 5.2: Plot of R_e Against Rate of Dog-to-dog Transmission

c. Reciprocal of the dog incubation period, σ_d

The estimated value of σ_d inserted into the expression of R_e was 0.5. The values of this parameter are varied between 0.3 to 0.6 (refer to Figure 5.3).

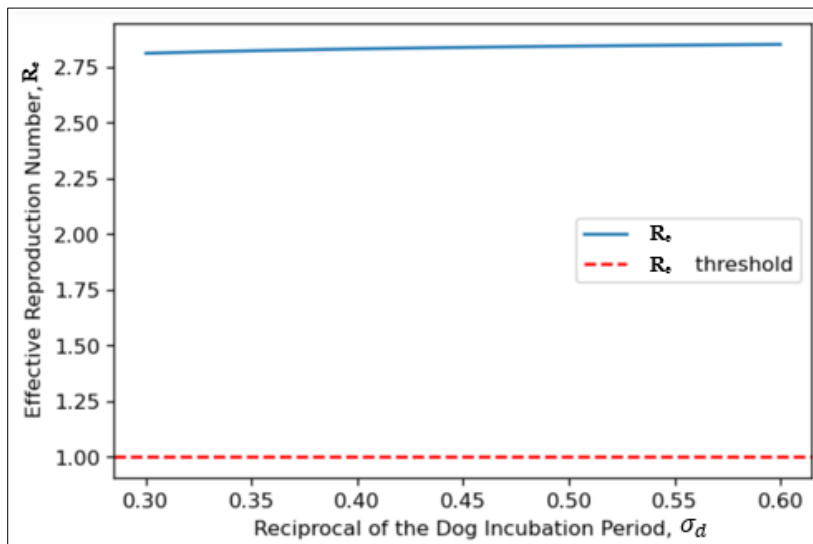


Figure 5.3: Plot of R_e Against Reciprocal of the Dog Incubation Period

d. Dog Rabies-related Death Rate, μ_d

The estimated value of μ_d inserted into the expression of $\mathbf{R_e}$ was 1. The values of this parameter are varied between 0.25 to 1 (refer to Figure 5.4).

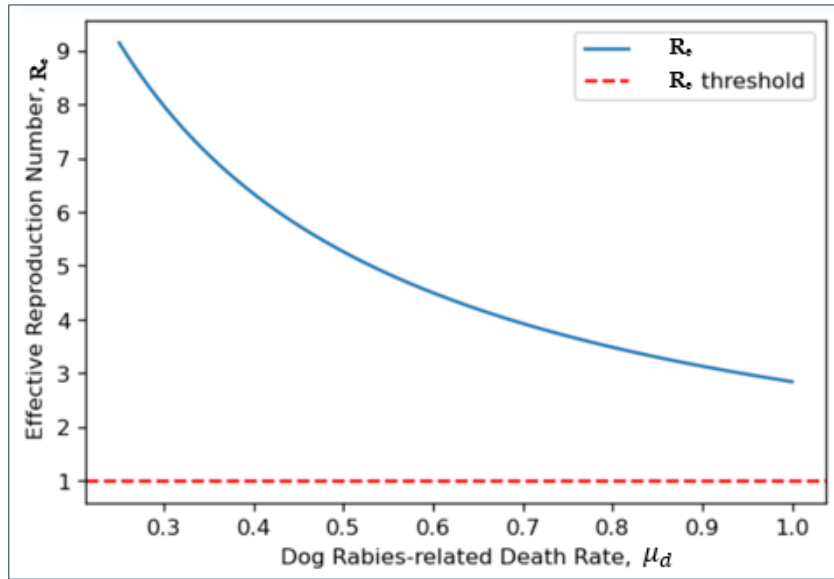


Figure 5.4: Plot of $\mathbf{R_e}$ Against Dog Rabies-related Death Rate

e. Dog Natural Mortality Rate, m_d

The estimated value of m_d inserted into the expression of $\mathbf{R_e}$ was $0.056/12 \approx 0.0047$. The values of this parameter are varied between 0.001 to 0.03 (refer to Figure 5.5).

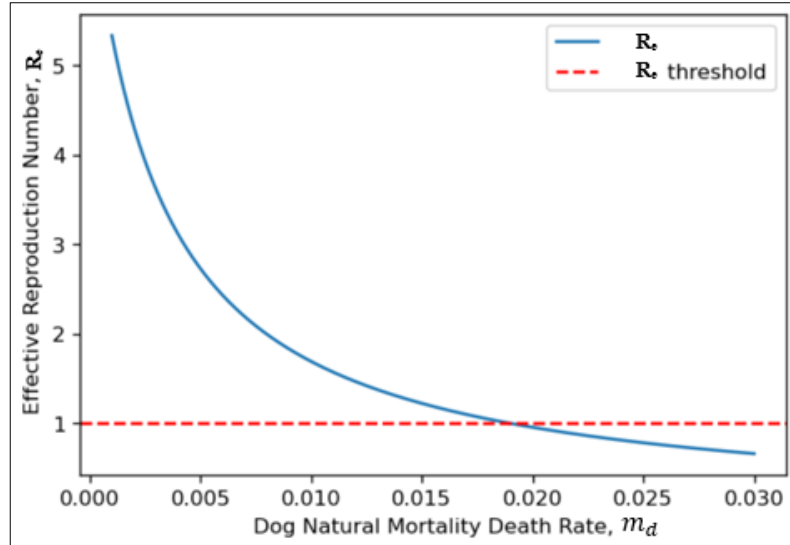


Figure 5.5: Plot of R_e Against Dog Natural Mortality Rate

f. Rate of Dog Culling, c_d

The estimated value of c_d inserted into the expression of R_e was 0.004. The values of this parameter are varied between 0.002 to 0.005 (refer to Figure 5.6).

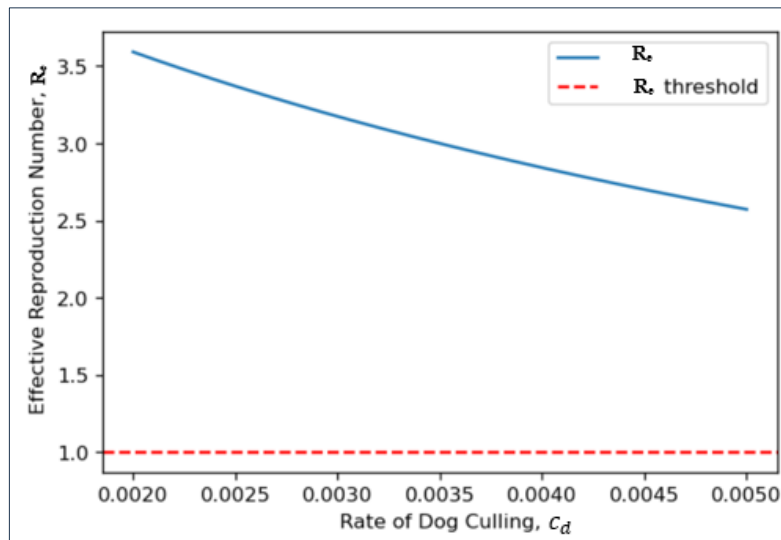


Figure 5.6: Plot of R_e Against Rate of Dog Culling

g. Rate of Dog Vaccination, k_d

The estimated value of k_d inserted into the expression of R_e was 0.02. The values of this parameter are varied between 0.01 to 0.04 (refer to Figure 5.7).

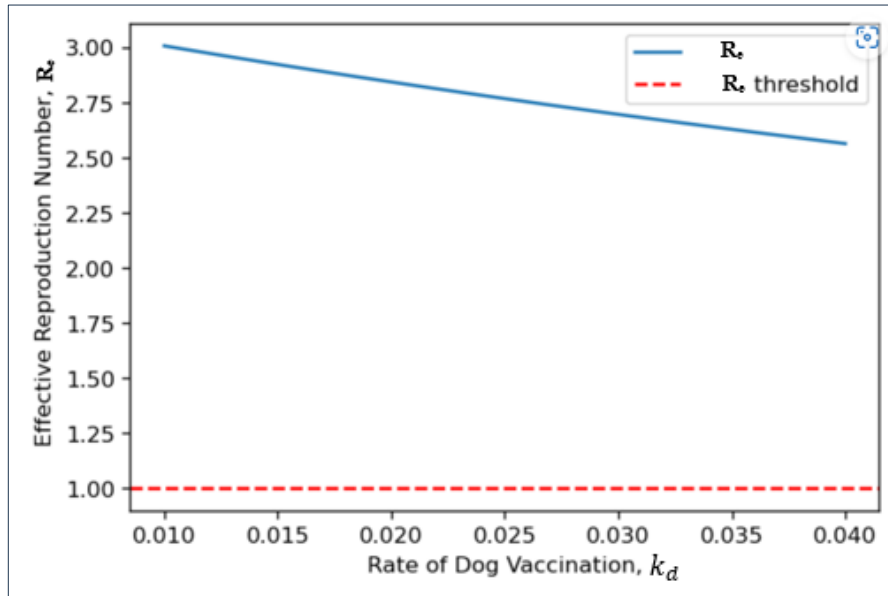


Figure 5.7: Plot of R_e Against Rate of Dog Vaccination

h. Rate of Dog Immunity Loss, λ_d

The estimated value of λ_d inserted into the expression of R_e was $1/12 \approx 0.083$. The values of this parameter are varied between 0.06 to 0.09 (refer to Figure 5.8).

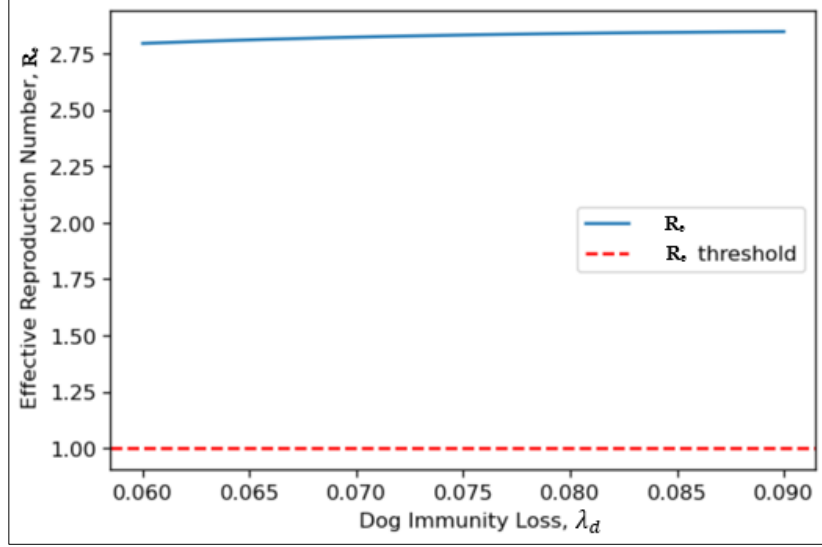


Figure 5.8: Plot of R_e Against Rate of Dog Immunity Loss

5.3.2 Normalised Forward Sensitivity Index

Under local sensitivity analysis, the normalised forward sensitivity index is a partial derivative-based method as long as the variable is a differentiable function of the parameter (Zamir et al., 2016). The normalised forward sensitivity index of R_e is the ratio of the relative change in R_e to the relative change in the model parameter.

The effective reproduction number R_e (5.6) is a function of eight parameters where

$$R_e = \frac{\beta_d \sigma_d A(m_d + \lambda_d)}{(m_d + \sigma_d + c_d)(m_d + \mu_d + c_d)[(m_d + k_d + c_d)(m_d + \lambda_d) - \lambda_d k_d]} \lambda_d$$

A small perturbation Δ_ρ to the parameter ρ and the corresponding change in R_e is as

Δ_{R_e} is given by

$$\Delta_{R_e} = R_e(\rho + \Delta_\rho) - R_e(\rho),$$

$$\Delta_{R_e} = \frac{R_e(\rho + \Delta\rho) - R_e(\rho)}{\Delta\rho} \cdot \Delta\rho,$$

$$\Delta_{R_e} \approx \Delta\rho \frac{\partial R_e}{\partial \rho}.$$

Then, as the normalised forward sensitivity index of $\mathbf{R_e}$ is the ratio of the relative change in $\mathbf{R_e}$ to the relative change in the model parameter, then the normalised sensitivity index is defined by

$$\Gamma_\rho = \frac{\frac{\Delta R_e}{R_e}}{\frac{\Delta \rho}{\rho}} = \frac{\Delta R_e}{R_e} \times \frac{\rho}{\Delta \rho} = \frac{\rho}{R_e} \frac{\partial R_e}{\partial \rho}.$$

According to the parameter values in Table 4.1, the normalised forward sensitivity indices for the eight parameters give the following values and nature of the signs.

$$\begin{aligned} \Gamma_{R_e}^{\beta_d} &= \frac{\beta_d}{R_e} \frac{\partial R_e}{\partial \beta_d} \\ &= \frac{\beta_d(m_d + \sigma_d + c_d)(m_d + \mu_d + c_d)((m_d + k_d + c_d)(m_d + \lambda_d) - \lambda_d k_d)}{A\beta_d\sigma_d(m_d + \lambda_d)} \\ &\quad \times \frac{A\sigma_d(m_d + \lambda_d)}{(m_d + \sigma_d + c_d)(m_d + \mu_d + c_d)((m_d + k_d + c_d)(m_d + \lambda_d) - \lambda_d k_d)}, \\ &= 1. \end{aligned}$$

$$\Gamma_{R_e}^A = \frac{A}{R_e} \frac{\partial R_e}{\partial A}$$

$$\begin{aligned}
&= \frac{A(m_d + \sigma_d + c_d)(m_d + \mu_d + c_d)((m_d + k_d + c_d)(m_d + \lambda_d) - \lambda_d k_d)}{A\beta_d \sigma_d (m_d + \lambda_d)} \\
&\times \frac{\beta_d \sigma_d (m_d + \lambda_d)}{(m_d + \sigma_d + c_d)(m_d + \mu_d + c_d)((m_d + k_d + c_d)(m_d + \lambda_d) - \lambda_d k_d)}, \\
&= 1.
\end{aligned}$$

$$\begin{aligned}
\Gamma_{R_e}^{\sigma_d} &= \frac{\sigma_d}{R_e} \frac{\partial R_e}{\partial \sigma_d} \\
&= \frac{\sigma_d(m_d + \sigma_d + c_d)(m_d + \mu_d + c_d)[(m_d + k_d + c_d)(m_d + \lambda_d) - \lambda_d k_d]}{A\beta_d \sigma_d (m_d + \lambda_d)} \\
&\times \frac{A\beta_d (m_d + \lambda_d)(m_d + \lambda_d)}{(m_d + \sigma_d + c_d)^2 (m_d + \mu_d + c_d)[(m_d + k_d + c_d)(m_d + \lambda_d) - \lambda_d k_d]}, \\
&= \frac{m_d + c_d}{m_d + \sigma_d + c_d} = 0.02120718.
\end{aligned}$$

$$\begin{aligned}
\Gamma_{R_e}^{\mu_d} &= \frac{\mu_d}{R_e} \frac{\partial R_e}{\partial \mu_d} \\
&= \frac{\mu_d(m_d + \sigma_d + c_d)(m_d + \mu_d + c_d)[(m_d + k_d + c_d)(m_d + \lambda_d) - \lambda_d k_d]}{A\beta_d \sigma_d (m_d + \lambda_d)} \\
&\times \left(-\frac{A\beta_d \sigma_d (m_d + \lambda_d)}{(m_d + \sigma_d + c_d)(m_d + \mu_d + c_d)^2 [(m_d + k_d + c_d)(m_d + \lambda_d) - \lambda_d k_d]} \right), \\
&= -\frac{\mu_d}{m_d + \mu_d + c_d} = -0.9914078.
\end{aligned}$$

$$\Gamma_{R_e}^{m_d} = \frac{m_d}{R_e} \frac{\partial R_e}{\partial m_d}$$

$$\begin{aligned}
& \frac{m_d(m_d + \sigma_d + c_d)(m_d + \mu_d + c_d)[(m_d + k_d + c_d)(m_d + \lambda_d) - \lambda_d k_d]}{A\beta_d \sigma_d(m_d + \lambda_d)} \\
& \times \left[\frac{A\beta_d \sigma_d}{(m_d + \sigma_d + c_d)(m_d + \mu_d + c_d)[(m_d + k_d + c_d)(m_d + \lambda_d) - \lambda_d k_d]} \right. \\
& - \frac{A\beta_d \sigma_d(m_d + \lambda_d)}{(m_d + \sigma_d + c_d)^2(m_d + \mu_d + c_d)[(m_d + k_d + c_d)(m_d + \lambda_d) - \lambda_d k_d]} \\
& - \frac{A\beta_d \sigma_d(m_d + \lambda_d)}{(m_d + \sigma_d + c_d)(m_d + \mu_d + c_d)^2[(m_d + k_d + c_d)(m_d + \lambda_d) - \lambda_d k_d]} \\
& \left. - \frac{A\beta_d \sigma_d(m_d + \lambda_d)(2m_d + \lambda_d + k_d + c_d)}{(m_d + \sigma_d + c_d)(m_d + \mu_d + c_d)[(m_d + k_d + c_d)(m_d + \lambda_d) - \lambda_d k_d]^2} \right] \\
& = m_d \left[\frac{1}{m_d + \lambda_d} - \frac{1}{m_d + \sigma_d + c_d} - \frac{1}{m_d + \mu_d + c_d} \right. \\
& \quad \left. - \frac{2m_d + \lambda_d + k_d + c_d}{(m_d + k_d + c_d)(m_d + \lambda_d) - \lambda_d k_d} \right]
\end{aligned}$$

$$= -0.5990487$$

$$\begin{aligned}
\Gamma_{R_e}^{k_d} &= \frac{\partial \mathbf{R}_e}{\partial k_d} \frac{k_d}{\mathbf{R}_e} \\
&= \frac{k_d(m_d + \sigma_d + c_d)(m_d + \mu_d + c_d)[(m_d + k_d + c_d)(m_d + \lambda_d) - \lambda_d k_d]}{A\beta_d \sigma_d(m_d + \lambda_d)} \\
&\times \left(- \frac{m_d A\beta_d \sigma_d(m_d + \lambda_d)}{(m_d + \sigma_d + c_d)(m_d + \mu_d + c_d)[(m_d + k_d + c_d)(m_d + \lambda_d) - \lambda_d k_d]^2} \right), \\
&= - \frac{k_d m_d}{(m_d + k_d + c_d)(m_d + \lambda_d) - \lambda_d k_d} = -0.2645125.
\end{aligned}$$

$$\Gamma_{R_e}^{c_d} = \frac{c_d}{\mathbf{R}_e} \frac{\partial \mathbf{R}_e}{\partial c_d},$$

$$\begin{aligned}
&= \frac{c_d(m_d + \sigma_d + c_d)(m_d + \mu_d + c_d)[(m_d + k_d + c_d)(m_d + \lambda_d) - \lambda_d k_d]}{A\beta_d \sigma_d (m_d + \lambda_d)} \cdot A\beta_d \sigma_d (m_d \\
&+ \lambda_d) \left[-\frac{2m_d + 2c_d + \mu_d + \sigma_d}{(m_d + \sigma_d + c_d)^2 (m_d + \mu_d + c_d)^2 [(m_d + k_d + c_d)(m_d + \lambda_d) - \lambda_d k_d]} \right. \\
&\quad \left. - \frac{m_d + \lambda_d}{(m_d + \sigma_d + c_d)(m_d + \mu_d + c_d)[(m_d + k_d + c_d)(m_d + \lambda_d) - \lambda_d k_d]^2} \right], \\
&= c_d \left[-\frac{2m_d + 2c_d + \mu_d + \sigma_d}{(m_d + \sigma_d + c_d)(m_d + \mu_d + c_d)} - \frac{m_d + \lambda_d}{(m_d + k_d + c_d)(m_d + \lambda_d) - \lambda_d k_d} \right] \\
&= -0.4345818.
\end{aligned}$$

$$\begin{aligned}
\Gamma_{R_e}^{\lambda_d} &= \frac{\lambda_d}{R_e} \frac{\partial R_e}{\partial \lambda_d} \\
&= \frac{\lambda_d(m_d + \sigma_d + c_d)(m_d + \mu_d + c_d)[(m_d + k_d + c_d)(m_d + \lambda_d) - \lambda_d k_d]}{A\beta_d \sigma_d (m_d + \lambda_d)} \\
&\quad \times \left[\frac{A\beta_d \sigma_d}{(m_d + \sigma_d + c_d)(m_d + \mu_d + c_d)[(m_d + k_d + c_d)(m_d + \lambda_d) - \lambda_d k_d]} \right. \\
&\quad \left. - \frac{A\beta_d \sigma_d (m_d + \lambda_d)(m_d + c_d)}{(m_d + \sigma_d + c_d)(m_d + \mu_d + c_d)[(m_d + k_d + c_d)(m_d + \lambda_d) - \lambda_d k_d]^2} \right], \\
&= \lambda_d \left[\frac{1}{m_d + \lambda_d} - \frac{m_d + c_d}{(m_d + k_d + c_d)(m_d + \lambda_d) - \lambda_d k_d} \right], \\
&= 0.1032521.
\end{aligned}$$

Table 5.1: Sensitivity Indices of R_e to the Parameters

Parameter (ρ_i)	Description	Sensitivity Index ($\Gamma_{R_e}^{\rho_i}$)
β_d	Rate of dog-to-dog transmission	+1.0000
A	Monthly number of new born dogs	+1.0000

Table 5.1 continued

σ_d	Reciprocal of the dog incubation period	+0.0212
μ_d	Disease-induced death rate	−0.9914
m_d	Dog natural mortality rate	−0.5990
k_d	Rate of dog vaccination	−0.2645
c_d	Rate of dog culling	−0.4345
λ_d	Rate of dog immunity loss	+0.1032

The plus and minus signs in Table 5.1 denote the positive influence and negative influence of the parameters on $\mathbf{R_e}$, respectively. Consequently, the reduction in the values of the parameters μ_d, m_d, k_d, c_d and the increase in the values of $\beta_d, A, \sigma_d, \lambda_d$ will cause a rise in the number of secondary infections. The sensitivity indices of $\mathbf{R_e}$ with respect to the model parameters in Table 5.1 also allow us to measure the corresponding percentage change in the value of $\mathbf{R_e}$ with the change in the parameters. For example, $\mathbf{I}_{R_e}^{\beta_d} = +1$ means that the increase (or decrease) in the dog-to-dog transmission rate (β_d) by 5% may increase (or decrease) the number of secondary infections by $1 \times 5\% = 5\%$. Hence, β_d is one of the highly sensitive parameters as even a slight variation in its value could trigger a change in the value of $\mathbf{R_e}$. On the other hand, $\mathbf{I}_{R_e}^{m_d} = -0.5990$, means that increasing (or decreasing) the values of dog mortality rate (m_d) by 10% decreases (or increases) the value of R_e by $0.5990 \times 10\% \approx 6\%$. The computed sensitivity indices indicate the most influential parameters affecting $\mathbf{R_e}$ are found to be the dog-to-dog transmission rate (β_d), the rate of newborn dogs (A), dog disease-related death rate (μ_d), dog culling rate (c_d) and dog natural death rate (m_d). Our result agrees with the findings from 5.2.1 as well as another rabies modelling study

(Asamoah et al., 2017) whereby dog transmission rate and the rate of new born dogs had the greatest impact on the reproductive number.

5.4 Control Strategies to Eradicate Rabies

From the result of the first part of the sensitivity analysis (refer Figure 5.1 – Figure 5.8), it can be seen that the values of R_e varies greatly even when there is a slight increment in the value of A , β_d , μ_d , and m_d . This indicates that the monthly number of new born dogs, rate of dog-to-dog transmission, dog rabies-related death rate and dog natural mortality rate highly affect the value of the effective reproduction number, R_e . Other than that, the computed values of the sensitivity indices (refer Table 5.1) suggested that the most influential parameters are found to be the dog-to-dog transmission rate (β_d), the rate of newborn dogs (A), dog culling rate (c_d), dog disease-related death rate (μ_d) and dog natural death rate (m_d).

The sensitivity analysis has highlighted that dog population management forms the cornerstone in any rabies control strategies. Therefore, rabies awareness campaigns should be intensified to educate the community and emphasise the significance of minimising the number of newborn dogs. Neutering or spaying of domestic dogs would bring down the number of newborn puppies introduced into the susceptible dog population. Nonetheless, since the immunity for dog rabies vaccine is temporary and lasts only for one year, deploying vaccination teams annually that target pet dogs would be ineffective in achieving herd immunity when the dog birth remains uncontrolled especially among the free-roaming dog population. Hence, targeted removal of strays within a rabies hotspot area can be implemented in lieu of mass culling. Apart from that, the city council and the veterinary department should look into implementing the Trap-Neuter-Vaccinate-Relocate (TNVR)

method as a collaborative effort to humanely manage the free-roaming dog population especially the urban strays (Roebeling et al., 2014). Trap-Neuter-Vaccinate-Relocate (TNVR) is a method in which free-roaming dogs are humanely captured, surgically sterilised, vaccinated against rabies, and then returned to their natural habitat. Unlike culling, TNVR will not result in a vacuum effect since no new dogs will move to replace the void left by the culled dogs. Hence, the TNVR method can help to minimise dog population turnover and size, as the dogs would only die due to natural causes, making it easier to achieve and maintain the targeted rabies immunity threshold and vaccination coverage.

In addition to rabies vaccination, chemical sterilisation methods, such as immunocontraceptives, can substitute the costly and time-consuming surgical sterilisation process. (Carroll et al., 2010). Immunocontraceptive is a form of chemical birth control in which parenteral injections given in conjunction with rabies immunisations render the dog sterile for years; therefore, it can be utilised easily on a large-scale during mass vaccination efforts for population control. However, more studies on the side effects of immunocontraceptive should be carried out prior to its application in dogs.

Other than that, since highly connected roaming dogs might lead to effective contact rates and dog-to-dog rabies transmission rates (Hudson et al., 2019), public education regarding dog roaming habits, importance of dog containment and the promotion of responsible pet ownership (Mpolya, 2019) could significantly control rabies spread by reducing the contact between the owned dogs and infected free-roaming dogs.

Lastly, based on the computed herd immunity threshold of approximately 70% in Section 5.2.3, we recommend that community-based mass dog vaccination campaigns for rabies should be conducted more frequently to rapidly increase population immunity. As vaccines for canine rabies should be made more accessible to those in isolated rural regions

of Sarawak, mobile vaccine units can be deployed as opposed to a fixed-location vaccination point to rapidly reach more population (Castillo-Neyra et al., 2019). Besides, rabies control strategies depend on the local landscape such as the dog population type and dog interaction or behaviour. For example, in reality, many free-roaming dogs in Sarawak actually have owners. Hence, oral rabies vaccinations (ORVs) can be used as an alternative to parenteral vaccination in order to target the free-roaming dog population. The feasibility of ORVs with community empowerment has been proven successful in Bangladesh (Bonwitt et al., 2020) and India (Yale et al., 2022). As larger groups of dogs can make it more difficult for vaccinators to reach the individual animals, well cooperation from the community who knows the dog behaviour better will be required to increase accessibility of the free-roaming dogs. The elimination of rabies is possible if canine vaccination efforts are strengthened to achieve a vaccine coverage goal of at least 70%.

5.5 Summary

In summary, this chapter determined the disease-free equilibrium (DFE) point, which is an important equilibrium in epidemiology. In order to understand the long-term behaviour of an epidemic system, we investigated the stability of the disease-free equilibrium (DFE) point. Eigenvalues are used as indicators to determine the stability of the DFE in the epidemic system (3.1). As seen in previous section, we have shown that all eigenvalues of the Jacobian matrix are real and negative when $\mathbf{R}_e < 1$, which means that the DFE is locally asymptotically stable under this condition. Hence, this theoretically proves that it is possible to arrive at a state free of rabies within Sarawak population if the threshold condition is met.

Apart from that, the effective reproduction number for Sarawak rabies is determined by finding the largest eigenvalue in the Next Generation Matrix (G) and the value is calculated to be $\mathbf{R}_e = 3.06$. This implies that, in Sarawak, one rabid dog could potentially

cause three new human rabies cases on average. Consequently, with the value of R_e , we have estimated the value of the herd immunity threshold to be 0.67. Thus, we opined that around 70% of the dog population in Sarawak should be vaccinated in order to break the chain of transmission of rabies and protect those who are not immunised. Also, our vaccination target is in agreement with the recommendation by WHO (Leung & Davis, 2017). Hence, we suggest that rabies immunisations for dogs be made more accessible to those in isolated rural regions of Sarawak in order to achieve a vaccine coverage goal of greater than 70%.

The sensitivity analysis has indicated that the monthly number of new born dogs, rate of dog-to-dog transmission, dog rabies-related death rate and dog natural mortality rate highly affect the value of the effective reproduction number, R_e . Besides analysing the changes in the values of R_e , we computed the sensitivity indices via the normalised forward sensitivity index formula. The values of the sensitivity indices (refer Table 5.1) suggested that the most influential parameters are found to be the dog-to-dog transmission rate (β_d), the rate of newborn dogs (A), dog culling rate (c_d), dog disease-related death rate (μ_d) and dog natural death rate (m_d). Hence, this sensitivity analysis revealed the significance of dog population management in reducing rabies transmission and serves as the mainstay in any control programmes for rabies elimination.

CHAPTER 6

CONCLUSION

6.1 Summary

Ever since the first outbreak of canine and human rabies in 2017, there is still a dearth of research into rabies transmission dynamics in Sarawak. Hence, the actual burden of the disease in Sarawak is still under-explored. In this thesis, we have developed Malaysia's first deterministic, compartmental model of rabies transmission for both dog and human populations, in the context of Sarawak. The compartment model follows the Susceptible-Exposed-Infected-Vaccinated (SEIV) framework that incorporates the dynamics of dog-to-dog and dog-to-human rabies transmission in Sarawak.

As mentioned in Chapter 1, the model development is motivated by several research goals including to identify the influential parameters in controlling rabies spread by analysing the effect of varying parameters values on the value of the effective reproduction number R_e as well as through a theoretical strategy exploration using the Normalised Forward Sensitivity Index approach. The SEIV model is an extension of the model from Zhang et al. (2011) and consists of a system of eight differential equations with 15 parameters as shown in Chapter 3. The model is initially formulated based on the natural history of rabies and then incorporated with parameters related to rabies interventions and control strategies in Sarawak such as dog culling, human rabies PEP and dog rabies vaccination. Chapter 3 provides detailed information on the parameter estimation and initial conditions used in the SEIV model.

In Chapter 4, the model parameters are calibrated using data on human rabies incidence in Sarawak between June 2017 to July 2019 by varying the values of several

parameters. Overall, the trend of the simulated number of infected humans is similar to the actual human rabies cases reported in Sarawak within the period of study. Furthermore, the Root-Mean-Square-Error (RMSE) is found to be 1.9556 and hence, between June 2017 to July 2019, the SEIV model portrays the human rabies cases in Sarawak quite reasonably due to the small RMSE value.

Although the rabies outbreak in Sarawak has been ongoing since 2017, there is no study yet that attempts to compute the effective reproduction number R_e of Sarawak rabies. Hence, Chapter 5 analyses the steady state of the model specifically the local stability of the disease-free equilibrium (DFE) and the formula for the effective reproduction number R_e is also obtained using the Next Generation Matrix approach. From the stability analysis of the disease-free equilibrium (DFE), we have proven that R_e is an important epidemic threshold for Sarawak rabies spread and that there exists a state whereby rabies infection is totally absent when the effective reproduction number less than one. As the R_e is estimated to be 3.06, this indicates that one rabid dog could potentially cause three new human rabies cases and the disease will continue to persist in Sarawak. Apart from the effective reproduction number, the herd immunity threshold for Sarawak rabies is approximately 0.67. Thus, roughly 70% of the dog population in Sarawak should be vaccinated in order to achieve herd immunity. Other than intensifying mass dog vaccination campaigns, mobile vaccines unit can be deployed to target hard-to-reach areas in Sarawak rural regions, while oral rabies vaccinations (ORVs) can be used as an alternative to parenteral vaccination for free-roaming dogs.

Local sensitivity analysis of model parameters on the effective reproduction number R_e found that the monthly number of newborn puppies is the most important parameter in rabies spread in Sarawak. The findings from the sensitivity analysis in Chapter 5 improved

understanding that dog population management heavily affects the number of human exposures to rabies and the effectiveness of rabies control strategies. Since dog population management forms the cornerstone in any rabies control programmes, the Sarawak authorities should prioritise and focus on reducing the dog population through the implementation of interventions such as the Trap-Neuter-Vaccinate-Relocate (TNVR) method, targeted removal of strays, and surgical sterilisation for dogs. Also, the use of chemical sterilisation method such as immunocontraceptive can be considered alongside mass rabies vaccination campaigns. However, more studies on the side effects of immunocontraceptive must be carried out prior to its application in dogs. Other than that, public education regarding dog roaming habits, importance of dog containment and the promotion of responsible pet ownership should be intensified to prevent human exposure to the infected dogs.

6.2 Contribution of Study

Rabies is an ongoing, evolving outbreak in the state of Sarawak. Research efforts on rabies in Sarawak, specifically modelling studies, are still limited despite the burden of disease has worsened ever since the first case reported in July 2017.

Based on the first objective, this work attempts to fill the research gap by successfully developing the first deterministic, compartmental model for the transmission dynamics of rabies virus in Malaysia, in particular Sarawak. The model is adopted from Zhang et. al. (2011) and modified to incorporate local demography factors and the government rabies interventions in the context of Sarawak. Moreover, the model parameters and initial conditions were estimated and calibrated using Sarawak data. The numerical simulation provided a long-term trend and look-ahead forecasts of rabies cases in Sarawak, which can

be used by the Sarawak public health officials to take a more proactive measure, because it is always better to predict to mitigate an outbreak rather than react to contain it.

From our Sarawak rabies epidemic model (3.1), the estimated value of the effective reproduction number for Sarawak rabies has been computed for the first time. This is a significant contribution to the body of knowledge in the field of epidemiology and infectious diseases since the effective reproduction number is an important epidemiological threshold and a key indicator to quantify how fast a disease spreads. The estimated effective reproduction number can be used to make comparisons with other country studies, and then to gauge the rabies situation in Sarawak when scaled to our local context, as the dynamics of the disease may differ depending on geographical area.

The final objective of this research is to identify the most influential parameters affecting the rabies disease dynamics in Sarawak. Sensitivity analysis of the effective reproduction number has revealed the importance of dog population management in curtailing rabies transmission. The result clearly demonstrates that the Sarawak government must strengthen its collective preparedness and intervention to fight the ongoing rabies epidemic. Due to the fact that rabies is a zoonotic disease, we opined that a coordinated multiple-level communications and strong inter-sectoral collaboration among stakeholders, multi-agency and multidisciplinary cooperation would be required and interventions should be deployed in a timely manner. Unless preparedness improves, rabies epidemics in Sarawak are inevitable and will be very costly.

In conclusion, the findings of this study undeniably increased the knowledge on rabies transmission and eradication in Sarawak that is crucial to achieve the “Zero by 30” goal, which is a WHO global strategic plan, aimed at eliminating human rabies deaths by 2030.

6.3 Future Work

This study mainly analysed the temporal dynamics of rabies transmission of rabies in Sarawak. Hence, it would be useful for future work to include the spatial dynamics of rabies as well. We would also like to note would like to note that this study has a certain limitation, most notably the paucity of data on canine and human rabies. To precisely estimate the model parameter values, future research should consider employing a richer dataset. Thus, a more comprehensive dog demographic data should be collected and dog ecological studies in Sarawak should be emphasised since the effectiveness of rabies intervention efforts highly depends on the dog demographic processes (Gsell et al., 2012), as well as the knowledge about the dog's natural and rabies-induced death rates, as indicated in our previous analysis. Availability of additional data on Sarawak rabies in the future will allow for a more accurate calculation of the model parameters. Other than that, a better estimation of the model parameters can be done using numerical optimisation technique such as the Maximum Likelihood Estimator (MLE). Finally, as the frequency of feline rabies cases in Sarawak rises, the present rabies model can be adjusted to accommodate other potential hosts, particularly the cat population.

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APPENDICES

Appendix A: Estimation of human rabies incubation period in Sarawak.

We calculated the incubation period mean of eight positive cases of human rabies in Sarawak. The incubation period is determined by calculating the difference between the date of symptom onset and the date of the dog bite case (date of exposure). Hence, between 1 July 2017 to 19 January 2019, we only take the first eight cases of human rabies whereby the exact dates of symptom onset and dog bite were available and have been disclosed by the Director-General of Health Malaysia in the online press release.

Case	Date of Death	Date of Bite Case	Date of Onset	Incubation Period (month)
1	4 Jul 2017	15 Apr 2017	5 June 2017	1.7
2	4 Jul 2017	15 Apr 2017	5 June 2017	1.7
3	4 Feb 2018	27 Nov 2017	20 Jan 2018	1.8
4	3 Apr 2018	23 Dec 2017	29 Mar 2018	3.2
5	31 May 2018	20 Apr 2018	20 May 2018	1
6	21 Aug 2018	13 Jan 2018	6 Aug 2018	6.8
7	5 Dec 2018	4 Oct 2018	21 Nov 2018	1.6
8	11 Dec 2018	15 Sep 2018	27 Nov 2018	2.4
Total				20.26

Hence, the mean incubation period can be calculated as:

$$\text{Mean incubation period} = \frac{20.26}{8} \approx 2.5 \text{ months.}$$

Appendix B: Data on monthly human rabies active cases in Sarawak.

Below are the monthly number of human rabies active cases in Sarawak for a period of 26-month starting from the first outbreak in June 2017 to July 2019 collected from the online press release of the Director-General of Health Malaysia.

Year	Month	Number of active cases
2017	July	3
	August	5
	September	1
	October	0
	November	0
	December	0
2018	January	0
	February	1
	March	1
	April	1
	May	2
	June	2
	July	0
	August	0
	September	3

	October	0
	November	0
	December	3
2019	January	3
	February	1
	March	0
	April	0
	May	0
	June	1
	July	1
	August	1
Total		29

Appendix C: Publications as part of this research.

Below is the table of publications produced as part of this study:

No.	Title of publication	Type	Journal	Year
	Published			
1	Model simulation for the spread of rabies in Sarawak, Malaysia	Original research	International Journal on Advanced Science, Engineering and Information Technology (IJASEIT)	2019
2	A Scoping Review of the Effectiveness of Control Interventions of Human and Canine Rabies in an Effort to Rationalise the One Health Approach	Review paper	Borneo Epidemiology Journal (BEJ)	2020
3	Sensitivity Analysis of the Effective Reproduction Number in a Sarawak Rabies Epidemic Model	Original research	Proceedings of the International Conference on Future Trends in Smart Communities	2022