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 menganggar 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 in 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 divaksinasikan 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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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 km^2. 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.

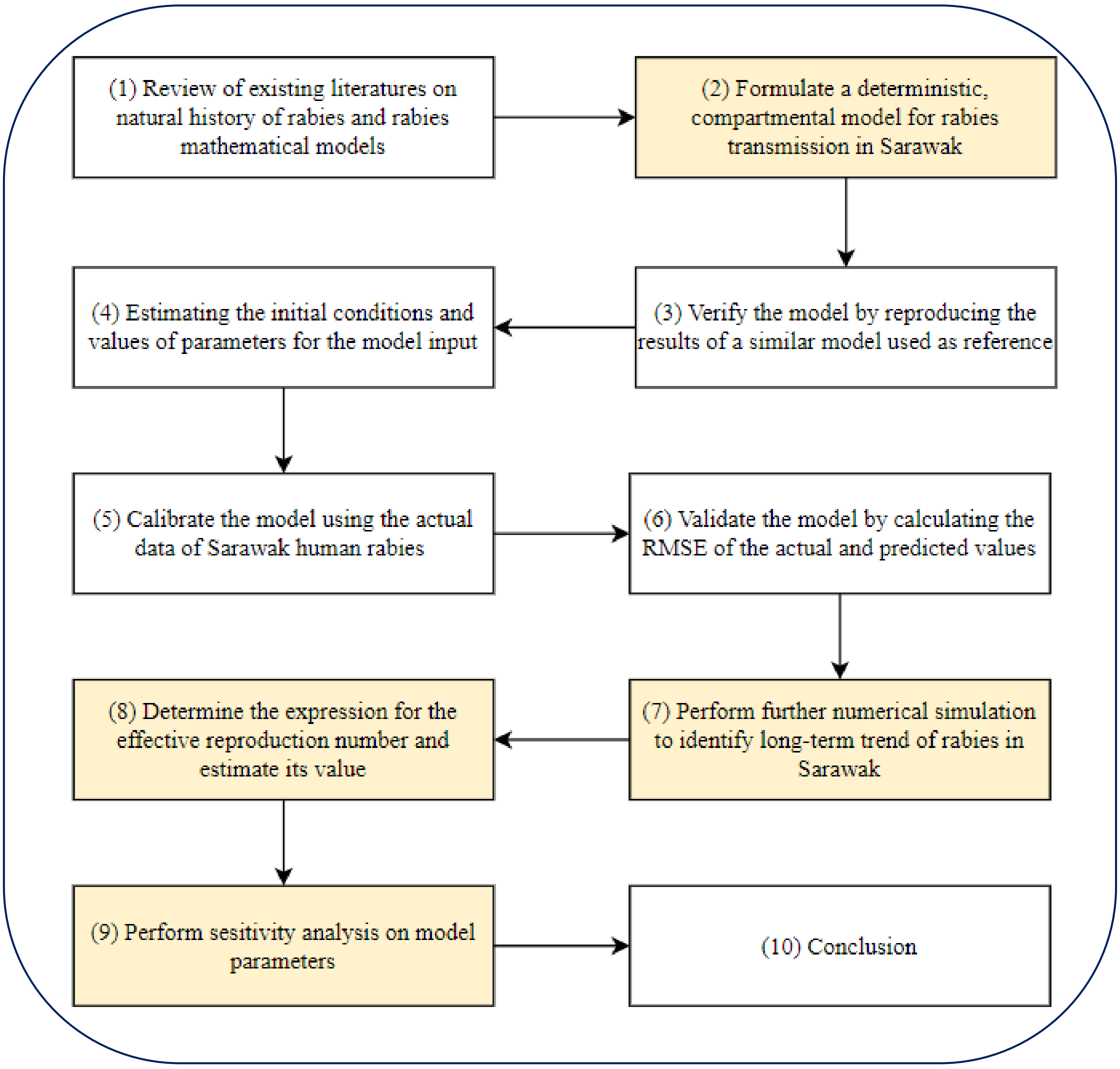

Figure 1.1: Research Procedure

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