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MATHEMATICAL MODELING ON THE SPREAD OF ZIKA VIRUS INFECTION USING COMPARTMENT MODELS

YUE ZONGMIN



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2024



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MATHEMATICAL MODELING ON THE SPREAD OF ZIKA VIRUS INFECTION
USING COMPARTMENT MODELS

YUE ZONGMIN

THESIS SUBMITTED IN FULFILLMENT OF THE REQUIREMENTS FOR THE
DEGREE OF DOCTOR OF PHILOSOPHY

FACULTY OF SCIENCE AND MATHEMATICS
SULTAN IDRIS EDUCATION UNIVERSITY

2024



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ACKNOWLEDGEMENT

The PhD program is coming to an end. It has been a bittersweet and rewarding period. This period of study has also been an important stage in my life, which has allowed me to rediscover my passion for scientific research after many years. My family and friends have given me a lot of care and help during this period, making it seem like I am starting a new beginning again. I am grateful for all the experiences that I have had.

First of all, I would like to thank my advisor, Dr. Fauzi bin Mohamed Yusof, who has helped me a lot in my studies and life. His rigorous academic attitude and integrity have deeply influenced me. Every time we discussed and exchanged ideas, he had a lot of ideas that always inspired me and opened up new ways of thinking for me. He has an extraordinary passion and tenacity for learning and never stops working, which has impressed us and is a good example for us to follow. I would like to express my most sincere gratitude to Dr. Fauzi bin Mohamed Yusof.

My dear family and parents have always supported me, and my lovely son and daughter have given me great moral strength, which is my motivation to move forward. I am grateful to my friends who supported me and cared about me, which made me feel infinite warmth in a foreign country. Finally, I would like to express my respect and gratitude to the experts who reviewed my thesis, the teachers who participated in the defense, and all the teachers, students and friends who have guided, cared and helped me.

Thank you very much.

ABSTRACT

Zika virus infection is a vector-borne disease transmitted by Aedes mosquitoes, with humans and mosquitoes as primary carriers. This research examines Zika virus transmission patterns and control measures using five mathematical models, employing dynamical systems stability theory, optimal control theory, and ODE45 numerical simulations. It initiates by investigating the effectiveness and details of increased medical investments, restricted access to infection zones and reducing human-mosquito exposure. Findings reveal that none of these measures alone can control the virus spread in the area. The first model is created by introducing a mosquito-harvesting measure, shown to be effective in reducing virus spread. However, caution is needed when applying this measure alone to prevent disproportionate consequences. Next, a Zika virus transmission model incorporating biodiversity dilution is created to analyze its regulatory role. The research findings indicate that biodiversity can suppress the rapid spread of viruses. Maintaining species abundance is beneficial for controlling the Zika virus. Building on this, the third model combines multiple measures in an optimal control framework to identify the best strategies. The fourth model we developed assesses a new infection pathway in Zika virus transmission. The findings reveals a clear enhancement effect in the early stages of transmission that diminishes over time. The fifth Zika virus transmission model focused on immigration, revealing immigration as a fundamental factor for the virus's long-term existence. Screening immigrants is critical for controlling outbreaks during large-scale outbreaks. Dynamic analyses were conducted on all models, identifying conditions and stability of disease-free and endemic equilibrium, emphasizing the critical role of the basic reproduction number in disease-free equilibrium stability. These findings have significant implications for public health strategies, suggesting that a combination of ecological management, immigration control, and targeted medical interventions is essential for controlling Zika virus transmission and informing policy decisions on disease management.

PEMMODELAN MATEMATIK TERHADAP PENYIMPANAN JANGKITAN VIRUS ZIKA MENGGUNAKAN MODEL RUANG

ABSTRAK

Jangkitan virus Zika adalah penyakit yang dijangkiti oleh vektor yang dibawa oleh nyamuk Aedes, dengan manusia dan nyamuk sebagai pembawa utama virus. Kajian ini mengkaji corak penularan virus Zika dan kaedah kawalan menggunakan lima model matematik, menerapkan teori kestabilan sistem dinamik, teori kawalan optimum, dan simulasi numerik ODE45. Ia bermula dengan menyiasat keberkesanan dan butiran pelaburan perubatan yang dipertingkatkan, akses terhad ke zon jangkitan, dan mengurangkan pendedahan manusia-nyamuk. Dapatan menunjukkan bahawa tiada satu kaedah yang boleh mengawal penyebaran virus di kawasan tersebut. Model pertama dicipta dengan memperkenalkan kaedah penuaian nyamuk, di mana analisisnya membuktikan keberkesanan dalam mengurangkan penyebaran virus. Walau bagaimanapun, langkah penjagaan diperlukan apabila menggunakan kaedah ini secara individu untuk mengelakkan kesan yang tidak seimbang. Seterusnya, model penularan virus Zika yang menggabungkan pencairan biodiversiti dicipta untuk menganalisis peranannya dalam mengawal. Dapatan kajian menunjukkan bahawa biodiversiti boleh menyekat penyebaran virus dengan cepat. Menjaga kepelbagaian spesies adalah bagus dalam mengawal virus Zika. Berdasarkan analisis sebelumnya, model ketiga bergabung dengan beberapa kaedah dalam rangka kerja kawalan yang optimum untuk mengenal pasti strategi yang terbaik. Model keempat yang kami bangunkan menilai laluan jangkitan baru dalam penularan virus Zika. Penemuan menunjukkan kesan peningkatan yang jelas pada peringkat awal penularan yang berkurang seiring dengan masa. Model penularan virus Zika kelima menumpukan kepada imigresen, memperlihatkan imigresen sebagai faktor asas bagi kewujudan jangka panjang virus tersebut. Penyaringan imigresen penting untuk mengawal wabak semasa wabak berskala besar. Analisis dinamik dijalankan pada semua model, mengenal pasti keadaan dan kestabilan keseimbangan bebas penyakit dan endemik, menekankan peranan penting bilangan reproduksi asas dalam kestabilan keseimbangan bebas penyakit. Dapatan kajian ini mempunyai implikasi yang signifikan bagi strategi kesihatan awam, menunjukkan bahawa gabungan pengurusan ekologi, kawalan imigresen dan perubatan intervensi yang disasarkan adalah penting untuk mengawal penularan virus Zika dan memaklumkan keputusan dasar mengenai pengurusan penyakit.



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LIST OF ABBREVIATIONS

AGO-B	Autocidal-Gravid-Ovitrap
BG	Biogents' mosquito trap
Bti	Bacillus thuringiensis var. Israelensis
CDC	Centers for Disease Control and Prevention
DDE	Delay Differential Equation
ICER	Incremental Cost-Effectiveness Ratio
IRS	Indoor Residual Spray
LD	Lyme Disease
MERS-CoV	Middle East Respiratory Syndrome Coronavirus
MSEIR	Maternal immunity-SEIR Model
ODE	Ordinary Differential Equation
PDE	Partial Differential Equation
PHEIC	Public Health Emergency of International Concern
PRCC	Partial Rank Correlation Coefficient
SARS	Severe Acute Respiratory Syndrome

SEI	Susceptible-exposed-infectious Model
SEIR	Susceptible-exposed-infectious-removed Model
SEIRS	Susceptible–exposed–infected–recovered–susceptible Model
SIR	Susceptible-infectious-removed Model
SVEIR	Susceptible-vaccinated-exposed-infectious-removed Model
WHO	World Health Organization
WNV	West Nile Virus
ZIKV	Zika Virus

CHAPTER 1

INTRODUCTION

1.1 Introduction

The emergence of infectious diseases has long been a vital threat to human physical and mental health and has had a great impact on human life in various aspects.

Between 1347 and 1352, the Black Death claimed the lives of over 25 million people, which equated to at least one-third of Europe's population at that time, making it one of the most devastating epidemics in human history (Glatter & Finkelman, 2021). In 1920, over 7,500 people died from measles in the United States. In 2019, it is estimated that over 207,500 people died from measles (Sbarra et al., 2023). In the past three centuries, there have been at least 10 global outbreaks of epidemics like this, with the most serious and destructive of the three flu pandemics of the past century being the influenza virus, also known as the Spanish flu. Such influenza began in 1918–1919 and caused 20–50 million deaths worldwide (WHO). In 2002, the severe acute respiratory syndrome (SARS) that shocked the world was first reported in China and spread to

Southeast Asia and other parts of the world. When the epidemic (SARS) ended in July 2003, it had caused more than 8,000 infections and more than 700 deaths worldwide (Wilder-Smith, Chiew, & Lee, 2020). During the First World War, the H1N1 influenza spread globally, with the respective military forces of different countries inadvertently carrying the virus back to their homelands. Due to its high mortality and morbidity rates, this outbreak of illness came to be known as the "Spanish flu pandemic" (Agrawal et al., 2021).

Although sanitary conditions have been remarkably improved, the high effectiveness of antibiotics and the widespread implementation of vaccination programs have brought many infectious diseases under control, we must recognize that there is still a long way for human beings to go to fight against them. The viral mutation and viral transmission are probably carried out for the following reasons: (i) increasing resistance of pathogens to drugs due to their adaptation and evolution in new environments; (ii) invasion of new ecological environment made by humans and other species; (iii) deterioration of climate and environment; (iv) increasing international exchanges and rapid development of economy and trade between countries. Humans are challenged not only by the re-emergence of some originally extinct or tamely controlled infectious diseases (such as malaria, dengue fever, and yellow fever), but also by new infectious diseases such as Middle East Respiratory Syndrome Corona virus (MERS-CoV), Hantavirus, SARS, Ebola, Zika virus, and Convirus-19.

1.2 About Zika virus

Zika virus infection, a vector-borne disease transmitted by *Aedes africanus*, is essentially caused by mosquito bites. Zika virus was initially identified in monkeys in Uganda in 1947(WHO). In 2007, the first case of Zika virus in humans was reported to have occurred on Yap Island (Federated States of Micronesia). It then spread rapidly in Asia, Africa, and the United States (WHO). A large outbreak of Zika virus occurred in 2013 when the virus spread to French Polynesia in the South Pacific. As the largest epidemic outbreak recorded at that time, it had approximately 19,000 suspected cases during the epidemic period (Xu et al., 2022; Salkeld, Hopkins, & Hayman, 2023). In 2015, Brazil officially declared Zika virus transmission occurring locally for the first time (Yakob, 2022). Brazil's Ministry of Health estimated the number of suspected cases at 440,000 to 1,300,000. On February 1, 2016, the Director-General of the World Health Organization (WHO) announced that the outbreak of Zika virus in Latin American countries has become a Public Health Emergency of International Concern (PHEIC) (Goodman, 2020). As of March 9, 2017, 84 countries or territories have experienced moderate transmission of Zika virus (WHO).

Zika virus has an incubation period estimated at 3-14 days. Symptoms of infection are relatively mild. Some infected people may develop a fever and skin rash, whereas some people infected with Zika virus have no symptoms. However, some people may also experience conjunctivitis, muscle and joint pain, and fatigue, and these symptoms usually last 2 - 7 days (Guanche Garcell et al., 2020). Although many

people infected with Zika virus do not appear to become ill, infection during pregnancy can cause severe birth defects (Osorio et al., 2024). On April 13, 2016, the US Centers for Disease Control and Prevention announced that Zika is transmitted from the placenta to the fetus during the mother's pregnancy, which is the leading cause of congenital encephalitis, cerebral palsy, and congenital microcephaly in newborns (Osorio et al., 2024). In addition, some investigations have shown that Guillain-Barré syndrome and a range of other neurological diseases, such as meningitis and myelitis, are associated with Zika virus, and the number of cases of these neurological conditions also exhibited an increasing trend during Zika virus outbreaks (Leonhard et al., 2021; De Almeida Oliveira Evangelista et al., 2021; Osorio et al., 2024).

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People acquire Zika virus primarily through the bite of infected *Aedes* mosquitoes (*Ae. aegypti* and *Ae. albopictus*), which are also important vectors of Dengue and Chikungunya viruses (Jones, Kulkarni, Davidson, RADAM-LAC Research Team, & Talbot, 2020). If one partner is infected with Zika virus, the virus can be transmitted through unprotected sexual activity. A pregnant woman can transmit Zika virus to her fetus during pregnancy. Blood transfusions could be an approach to spread Zika virus. There is research showing that mosquitoes acquire the virus not only by biting previously infected individuals, but also by living in aquatic environments contaminated with Zika virus (e.g., containing urine excreted by infected humans) (Du et al., 2019).

1.3 Dynamics of Infectious Disease and Compartment Model

1.3.1 Dynamics of Infectious Disease

Unfortunately, the outbreak of infectious diseases often serves as the catalyst for people to become aware of their existence and subsequently take necessary measures.

Understanding the newly emerging infectious disease is often imminent people are eager to discover its transmission patterns among infected groups in addition to its viral pathogenesis being analyzed in laboratories. Since infectious diseases are dangerous and destructive, not all experiments can be performed on the human body.

Therefore, the combination of theoretical analysis, numerical simulation, and real data

can replace these dangerous experiments. The characteristics of the spread of diseases

in single and multiple populations and the roles of various internal or external factors

in the development and spread of the disease can be examined. Through the

reproduction of the population itself, the spread of the disease in a single population or

multiple populations, as well as various internal or external factors affecting the

development and spread of the disease, a reasonable mathematical model is established.

This is achieved by employing pertinent theoretical techniques using mathematical

equations like ordinary differential equations (ODEs), partial differential equations

(PDEs), and delay differential equations (DDEs), and others. Then the model is

analyzed by applying the theory of dynamics. To complete the process, numerical



simulations are conducted, often facilitated by software like MATLAB. The analysis approach is called infectious disease dynamics modeling.

Overall, infectious disease dynamics is an appropriate approach that combines clinical case studies with theoretical quantitative research. As an important tool for epidemiological research, it is capable of realizing the efficiency and combination of real-world situations and theories. The main aim is to help investigate different diseases caused by the same or similar pathogen and predict them by abstracting mathematical models from real phenomena. For this purpose, dynamic state analysis, qualitative or quantitative analysis, and numerical simulation are performed to achieve an effective combination of theory and practice. It also enables us to conduct regular research on past diseases and predict the future trend of the disease. Qualitative and quantitative research can be conducted in analyzing the causes and key factors of disease epidemics, and it is more convenient to compare the epidemiological characteristics of various infectious diseases, understand the transmission mechanism of infectious diseases, and propose effective control plans.

Specific mathematical modeling methods and dynamic analysis theory can be readily found in the literature (Xu, Tian, & Gan, 2019; Wang & Cai, 2020). The idea of a mathematical model of infectious diseases was first proposed by Bernoulli (1760) in his investigation on the spread of smallpox in 1760. The complete theoretical system was then methodically formulated in 1911 by the Nobel laureate scientist Ross (1911)





and then applied to malaria and mosquito transmission patterns, examining them with more detail.

Later, many researchers made deep discussions and modifications to this theory. It is worth noting that Kermack and McKendrick first proposed a compartment model for infectious diseases in 1927 (Duclos & Reichert, 2022), which laid a solid foundation for modeling infectious diseases. This technique has been in use by various scholars until now, and the concept of infectious disease threshold was then introduced in 1933 by Kermack and McKendrick (1933). In 2002, Van den Dreessche and Watmough (2002) presented a simple and feasible methodology for calculating the initial reproduction number, which became one of the crucial cornerstones for the dynamic analysis of infectious disease models.



Next, we present the fundamental framework of the compartmental model, upon which the models established in our subsequent research are based.

1.3.2 Compartment Model

The basic concept of the compartment model is to classify the population of a region for a specific type of infectious disease, study the interaction between populations, and employ the rate of change of each population to reflect disease transmission. The law and nature of the world and the model can be combined with real data for analysis, enabling us to conduct quantitative and qualitative research on infectious diseases.



Taking the *SIR* compartment model proposed by Kermack and McKendrick (1927) as an example, the prediction of most infectious diseases closely resembles the observed behavior of infectious diseases. Assuming that the total population of a region remains unchanged, the number of births per unit of time corresponds to the number of natural deaths. Therefore, the model does not consider the increase and decrease of the total population, but only focuses on the flow of people in three different compartments. Based on the principle of uniform mixing, this study divides the population into three groups, namely, *S*, *I*, and *R*, where $S(t)$ represents the number of susceptible individuals at time t , $I(t)$ is the number of infected individuals at time t , and $R(t)$ signifies the population that is recovered by treatment at time t or obtained immune population. It is assumed that the spread of the disease occurs through contact between an infected person and a susceptible person and that the rate of change between members of various groups is relatively simple.

The flowchart of the *SIR* model is suggested as follows

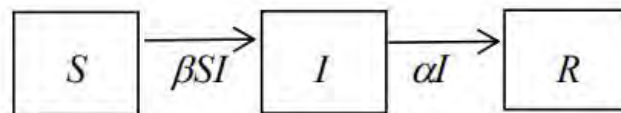


Figure 1.1. The flowchart of the *SIR* model

The governing equations can be stated by:

$$\begin{cases} \frac{dS}{dt} = -\beta SI, \\ \frac{dI}{dt} = \beta SI - \alpha I, \\ \frac{dR}{dt} = \alpha I. \end{cases} \quad (1.1)$$

Assuming that $N(t)$ represents the entire population such that: $N(t) = S(t) + I(t) + R(t)$.

Since the natural birth rate, natural death rate, and death rate are not taken into account,

the total population in such a case is always constant, as mathematically expressed by

$N(t) = S(t) + I(t) + R(t) = C$. The number of susceptible individuals affected by the

disease is commonly proportional to the total value of sensory $S(t)$ in the entire

environment, and its coefficient is denoted by β . Then, the number of newly infected

individuals per unit time at time t would be given by βSI . Let us define α as the

removal rate, and thereby $1/\alpha$ represents the average removal time in infectious

diseases (i.e., the average infectious period).

The basic reproduction number (R_0) is a key factor determining whether an

infectious disease will persist. Given $R_0 = \frac{\beta S_0}{\alpha}$, where S_0 denotes the number of

susceptible people at the initial moment, and R_0 is a threshold value. In the case of

$R_0 > 1$, the infectious disease persists; otherwise, it eventually dies out (Xu et al.,

2019).

Model (1.1) is an early version of the compartmental model, and in recent years, a

series of models have been developed based on the concept of the compartmental

model, with the incorporation of various factors to account for a more detailed



classification of the population (the compartments are further subdivided), the transmission process, and so forth. For instance, the SEIR (Susceptible-Exposed-Infectious-Removed) model takes into consideration the incubation period of the disease; the SEIRS (Susceptible-Exposed-Infected-Recovered-Susceptible) model considers disease recurrence after the patient recovers, with immunity being temporary; the MSEIR model introduces an innate immunity factor; the SVEIR model involves immunization, and so on. The selection of a specific model depends on the characteristics of the corresponding viruses, their influencing factors, and transmission routes.

1.4 Status and Motivation of the Research



A substantial body of literature exists on the study of Zika virus using compartment models, and these studies typically fall into three categories. The first is grounded in actual data, the second is centered around qualitative analysis of the model, and the third focuses on optimal control and evaluating control measures.

(1) Grounded in empirical data

The first type of research relies on data support and requires a large amount of empirical data. For example, Sadeghieh et al. (2021) considered the incubation period of human Zika virus, so an SEIR-based model was developed. They Using data from the 2016 Zika virus outbreak in Brazil and climate data to fit model parameters, predict



future epidemics. Kucharski et al. (2016) employed a compartmental mathematical model similar to the above to analyze the prevalence of the six major archipelagos of French Polynesia in 2013 - 2014, with an estimated range of 2.6 - 4.8 for the basic reproduction number and 94% of the total population infected in six archipelagos. Caminade et al. (2017) conducted a risk estimation analysis for the worldwide Zika virus outbreak using observed gridded temperature and rainfall data sets spanning from 1950 to 2015. Their study focused on examining the influence of seasonal climate variations on Zika virus transmission. It will find that this kind of research requires more extensive data; the authenticity and comprehensiveness of the data directly influence the credibility of the findings.

However, it is difficult for us to obtain real information. One reason is that researchers with primary data usually only present the results and do not share the primary data. Besides, real-time data on Zika virus prevalence and transmission are often unavailable because most people infected with Zika virus do not show signs or symptoms. Additionally, in some countries, reliable reporting and surveillance systems that track transmission of the virus may not be available.

(2) Spotlight on qualitative analysis of model

Many of the inherent laws of disease transmission are implicitly exhibited in the model. For example, why is it that Zika virus will not occur if the basic reproduction number is less than 1? What control parameters are critical to intervene in the case of



an Zika virus outbreak? Do Zika virus eventually become endemic? These questions are often not conceivable with numerical simulations, whereas qualitative research provides a clear understanding of disease dynamics. Hence, the qualitative analysis of the model becomes pivotal for mathematical researchers. These findings allow us to uncover the influence of multi-path transmission on disease propagation, offering insights for long-term virus control strategies.

Illustratively, Bonyah, Khan, Okosun, and Islam (2017) developed a compartment model of Zika virus and demonstrated the threshold characterization of the basic reproduction number by analyzing the stability of the epidemic and disease-free equilibrium points. Augusto, Bewick and Fagan (2017) developed a compartment model focusing on sexual transmission routes, investigated the impact of sexual transmission routes on viral transmission, and identified disease control thresholds that are important for disease transmission. Yamazaki (2019) built on the model originally developed by Augusto et al. (2017) and made an improved by including a diffusion term. Through the study, the importance of the basic reproduction number was emphasized, making it a critical threshold for virus control. It can be seen that determining the threshold of virus transmission is a key issue in this type of research, which can provide a basis for further determining the key factors of transmission, studying control measures, and so on.

While numerous researchers have conducted qualitative studies on models to uncover the infection patterns of Zika virus and ascertain the virus's transmission





threshold, the dynamical behaviors of these models vary. This divergence arises from the distinct factors that each model emphasizes. As a result, the dynamical behavior can become more complex, potentially even diminishing the decisive role of the basic reproduction number. On the other hand, a majority of the current research concentrates primarily on the transmission between humans and mosquitoes, as well as human-to-human transmission, often overlooking the many factors involved in the ecological environment in which the virus and its hosts are found. In reality, multiple factors related to transmission remain understudied. Consider, for example, the effects caused by variables such as immigration, harvesting, biodiversity, and environmental pollution. Notably, environments tainted by infections offer novel pathways for mosquito-borne transmissions. Furthermore, there exists a noticeable gap in the research concerning the influence of biodiversity on Zika virus dynamics.

(3) Navigating optimal control strategies

The third type is more concerned with determining optimal control strategies, aiming to identify the most effective short-term measures for virus control. Optimal control theory is a crucial part of modern control theory, the core of which lies in how to find the optimal control strategy to achieve the extreme value of the system performance index under the conditions of sufficient constraints. For example, Ukanwoke, Okuonghae, and Inyama (2022) analyzed the dynamics of Zika virus in populations featuring two virus strains, utilizing optimal control and cost-effectiveness analyses. Their findings suggest that a combined strategy of promoting effective





condom use alongside vector control using insecticides yields the most significant reduction in disease burden within populations and is deemed the most cost-effective approach. Khan, Shah, Ullah, and Gómez-Aguilar (2019) introduced an optimal control model for asymptomatic vector Zika virus. The model incorporates optimal control strategies, including prevention through mosquito nets, treatment of Zika virus infected individuals, and insecticide spraying. Numerical implementations detail specific programs.

In response to varying transmission routes, spatio-temporal factors, and changes in control strategies, the optimal control model for the Zika virus takes on diverse forms. Nonetheless, within studies of optimal control, there often tends to be a greater emphasis on the outcomes of control measures rather than on delving into the intricacies of their implementation. Hence, before presenting the optimal control model, it's customary to perform a qualitative analysis of the transmission model, considering various factors. This analysis not only helps in determining appropriate control measures based on these findings but also involves a closer examination of the implementation specifics.

This study is motivated by the need to understand Zika virus transmission within the broader environmental context and to address gaps in existing research. We aim to extend previous conclusions by adopting a modeling approach. Specifically, we focus on four intriguing aspects - harvesting, biodiversity, environmental pollution, and immigration - which have not received adequate attention in prior studies. Through



qualitative analysis of the model, we seek to scrutinize the impacts of these factors on Zika virus transmission. Furthermore, our study will offer recommendations for control measures and optimal strategies, highlighting novel insights that may have been overlooked by others.

1.5 Problem Statement

a) Compartmental model and control measures for Zika virus transmission

Based on the characteristics of Zika virus, it is necessary to classify humans as well as categorize mosquitoes in the development of the Zika virus compartmental model. SEIR-SER model is employed in most of the references (Bonyah, Khan, Okosun, & Islam, 2017; Agosto & Bewick, 2017; Agosto, Bewick, & Fagan, 2017; Momoh & Fügenschuh, 2018; Khan, Shah, Ullah, & Gómez-Aguilar, 2019). In contrast, the various models differ in terms of the factors of interest and their coupling being expressed differently in the model, the rate of exposure to infection being expressed differently, the types of employed equations being different, and so on. Control measures for Zika virus transmission are frequently utilized, including increasing medical inputs, reducing mosquito bite rates, restricting population movement, controlling mosquito populations, and so on. These measures can be incorporated into models to examine specific control details. Depending on the different factors we are interested in, we aim to develop a series of relevant compartmental models for Zika virus characterization and to conduct a systematic

theoretical study of Zika virus transmission, infectious disease thresholds and control methods.

b) Control Zika virus by harvesting mosquitoes

In the realm of Zika virus control, the suppression of mosquito populations stands as a crucial strategy. While targeted mosquito control efforts can play a significant role in reducing the transmission of infectious diseases, their impact may vary depending on the effectiveness of the control measures. The precise impact and effectiveness require analysis and assessment through mathematical modeling. In the population dynamics of the harvest model, specific emphasis was placed on the killing or capturing of a particular species by humans. Consequently, the concept of harvesting is integrated into the Zika virus transmission model, where harvesting pertains to the capture of mosquitoes.

It should be noticed that the introduction of harvest control mosquitoes here differs from the models found in most literature associated with the optimal control. Although they both emphasize increasing mosquito mortality, their focus is very different. In optimal control, the most controlling concern is how well a set of control measures can achieve the optimal value of the objective function, such as how well the parameters are capable of achieving the minimum number of patients at a given time. Therefore, this is a short-term investigation. But for the model with harvesting, the



greater concern lies in the long-term impact of harvest on the size of infected individuals. Mosquito killing is thought of as a long-term continuous behavior.

c) Effect of biodiversity

Apart from human interventions in mosquito population control, species diversity can also contribute to the reduction of mosquito populations to a certain degree. While mosquitoes may be considered a nuisance by humans, they play a role in ecosystems as competitors, pollinators, or prey for a variety of species. This introduces a new perspective, known as the "dilution effect" of biodiversity. The "dilution effect" has been corroborated for Lyme disease (LD) and West Nile virus (WNV) (Patil, Kumar, & Bagvandas, 2017), as well as for Hantavirus (Luis, Kuenzi, & Mills, 2018; Heidecke, Lavarello Schettini, & Rocklöv, 2023). The incorporation of dilution effects into a mathematical model can be approached as suggested by Peixoto and Abramson (2006). They proposed considering all organisms sharing resources with rodents as a collective, named "aliens," thus, establishing a competitive relationship between these "aliens" and rodents (vectors of Hantavirus). Drawing inspiration from this, the present study introduces alien species into the Zika virus transmission model, creating an eco-epidemiological model. This model is then employed to investigate the impacts of alien species coexisting within the same ecosystem on disease transmission.

d) An optimal control approach to the spread of Zika virus



Targeted mosquito control, such as the use of insecticides or other interventions to reduce mosquito populations, can indeed reduce the spread of Zika virus. However, heavy use of insecticides can have a range of side effects, such as environmental health problems and drug resistance. Therefore, a complete eradication of Zika virus may require a comprehensive and multifaceted approach that includes vaccination, sanitation, public health campaigns and medical interventions in addition to mosquito control. As a result, here, we intend to consider the optimal control with a biodiversity dilution effect.

e) Effects of the contaminated aquatic environment with Zika virus

As we know, there are several transmission routes for the spread of Zika virus: the bite of an infected Aedes mosquito, unprotected sexual activities, vertical transmission from mother to child, and blood transfusion, among which, biting by mosquitoes is considered as the main transmission route. In recent years, researchers have focused on the aquatic environment that mosquitoes depend on. One study indicated that mosquitoes acquire the virus not only by biting previously infected individuals, but also by living in aquatic environments contaminated with Zika virus (eg, containing urine excreted by infected humans) (Du et al., 2019). Epidemiological investigation reveals that infected blood will contain Zika virus clearly, but the number of live virus particles in the blood of the unit is low. If only a small number of mosquitoes can get the virus by biting an infected person, the typical pathway to spread the epidemic quickly in a short period of time is difficult. Therefore, environmental pollution could

be a crucial factor in the spread of Zika virus. In the present work, we model the transmission dynamics of Zika virus as mosquitoes acquire Zika virus from the aquatic environment. By qualitatively studying the model, we attempt to reveal the influence of this approach on the spread of Zika virus.

f) Effect of immigrants

Human immigration and mobility also promote mosquito breeding and disease transmission in an ecological environment. In human communities, flowerpots, discarded tires, abandoned bottles, and jars provide a breeding ground for mosquitoes with a growing environment once water is accumulated. However, increased migration and delays in infrastructure construction led to improper surface water drainage and the use of unprotected water reservoirs, which also increase mosquito production. Undoubtedly, all the mentioned factors represent potential consequences of population movement. Among them, the most immediate impact is the potential influx of infected individuals through immigration, which may prevent complete eradication of the virus. Duve, Charles, Munyakazi, Lühken, and Witbooi (2023) proposed a malaria transmission model accounting for the immigration. They found that there is no disease-free equilibrium point in the presence of infectious migrant humans. This means that malaria always coexists with humans and eventually forms endemic diseases. For Zika virus, would the same result occur without controlling for migration? By constructing the relevant Zika virus transmission model, we investigate the dynamic behavioral changes induced by immigration factors, the influence of

immigration factors on virus transmission, and assess the feasibility of measures to control immigration. These constitute our fifth area of focus.

1.6 Research Questions

The main problem of our research is to place the spread of Zika virus in an ecological environment, investigate the effects of different facts on disease transmission by qualitative analysis and numerical simulation of models, and provide recommendations on disease control according to different conditions. Specifically, the research questions are as follows:

- Can increasing healthcare investment, limiting population inflows and reducing human-mosquito exposure control the spread of Zika virus? It will be answered in Chapter 4.
- How does the introduction of harvesting affect the dynamic behavior of the model? Compared to the model of Bonyah et al. (2017), what is the difference between the dynamic behavior of these two models? How does killing mosquitoes (or vectors) affect the spread of Zika virus? How to control the virus by controlling the amount of mosquitoes harvested? The answers will be obtained in Chapter 5.
- Assuming that a dilution effect exists, what is the dynamic behavior of the new model? Can this dilution effect (generated by a competitive mechanism between

mosquitoes and exotic organisms) achieve control of Zika virus? The answers will be obtained in Chapter 6.

- Which control measures are selected and how can they be combined to efficiently manage Zika virus within a healthy ecosystem influenced by dilution effects? The answers will be obtained in Chapter 7.
- What is the dynamic behavior of the multi-path transmission model? What is the impact of the new Zika transmission route where mosquitoes get the virus from contaminated water? What are the suggestions for virus control? The answers will be obtained in Chapter 8.
- What is the dynamic behavior of the immigration model? What is the impact of immigration on the spread of Zika virus? What would be the optimal strategy if screening were added to routine control measures? Are screening measures feasible? The answers will be obtained in Chapter 9.

1.7 Objectives of the Research

The main objectives of this thesis are summarized as follows:

- To introduce a Zika virus spread model and its dynamics. Analyze the details and effects of three control measures using numerical methods. It can be find in Chapter 4.

- To establish an extended Zika virus model by coupling mosquito harvesting, and perform a qualitative analysis of the model using dynamical systems stability theory. Conduct numerical experiments to demonstrate the distinct impact of mosquito harvesting. It can be find in Chapter 5.
- To develop an extended Zika virus transmission model by considering biodiversity's dilution effect. Qualitatively analyze its dynamics using dynamical systems stability theory and numerically assess how biodiversity inhibits Zika virus transmission. It can be find in Chapter 6.
- To develop an optimal control model in a biodiversity-rich environment, considering the presence of a dilution effect. Employing optimal control theory, solve the model to identify the optimal control strategy. It can be find in Chapter 7.
- To create a multi-pathway Zika virus model with a new transmission route from contaminated environments. Qualitatively analyze the dynamics of the model using dynamical systems stability theory and numerically assess the impact of the new pathway. It can be find in Chapter 8.
- To develop an extended Zika virus transmission model with the influence of immigrants. Perform a qualitative analysis using dynamical systems stability theory and utilize optimal control modeling to identify combinations of strategies for controlling infected immigrants. Cost analysis will be used to assess the feasibility of the proposed screening measures. It can be find in Chapter 9.

1.8 Structure of the Present Thesis

The thesis is organized as follows:

Chapter 1 presents an overview of Zika virus and the compartmental mathematical model of the disease. The statement of problem, objectives of the study and the research questions are given. Chapter 2 provides a review of Zika virus and related research background, such as modeling developed for Zika virus, mosquito harvesting for Zika virus control, biodiversity effects, Zika virus transmission routes, migratory effects, and optimal control of Zika virus spread. Chapter 3 presents some mathematical methods, theories and theorems. These methods and theorems will be applied in the study of the dynamic behavior of the model, the comparison of the parametric analysis and the numerical simulation of the model in the subsequent chapters. Chapter 4 displays the model of Bonyah et al. (2017) and its analysis. In Chapter 5, we will analyze an Zika virus model with mosquitoes harvesting. The biodiversity is taken into account in Chapter 6. In Chapter 7, we will examine an optimal control model influenced by biodiversity. In Chapter 8, a novel pathway for Zika virus transmission will be included in the basic Zika virus model. A Zika virus transmission model considering immigration will be methodically examined in Chapter 9. In Chapter 10, we will present the research results as well as further research directions to be submitted.

The given chart illustrates how the chapters are linked to each other, whereas the

contributory chapters are presented by green color.

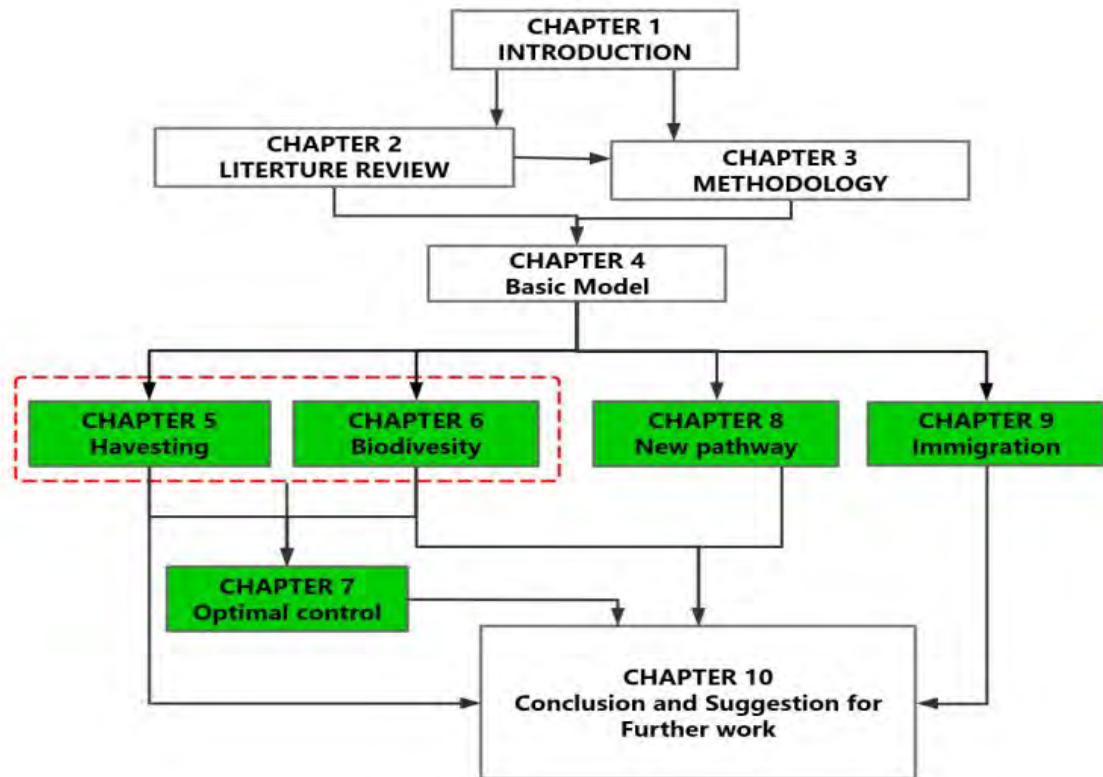


Figure 1.2. Flow chart of the thesis