Mathematical modeling of Nipah virus transmission

DOCTORAL THESIS

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Dedication

The dissertation is dedicated to my lovely mother *Anju Barua* and beloved father *Chandra Jyoti Barua* who dreamed that their son makes them proud.

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Abbreviations

CDC Centers for Disease Control and Prevention 16

CSF Cerebrospinal Fluid 15

ELISA Enzyme-linked immunosorbent assay 18

HeV Hendra Virus 13

JE Japanese Encephalitis 14, 15

NGM Next Generation Matrix 10

NiV Nipah Virus 1, 2, 13, 15–21

RT-PCR real-time poly- merase chain reaction 17

SARS Severe Acute Respiratory Symptom 6

SEIR Susceptible Exposed Infected Recovered 6, 8, 9

SEIRD Susceptible Exposed Infected Recovered Death 6, 10

SEIRS Susceptible Exposed Infected Recovered Susceptible 9

SIR Susceptible Infected Recovered 6–9

SIRD Susceptible Infected Recovered Dead 10

SIRS Susceptible Infected Recovered Susceptible 6, 9

SIRWS Susceptible Infected Recovered Waned Susceptible 6, 10

SIS Susceptible Infected Susceptible 6

SVIR Susceptible Vaccinated Infected Recovered 10

WHO World Health Organization 13, 16, 18

Chapter 1

Introduction

Throughout history, viral epidemics of variable intensity and frequency created havoc and panic all across the world. Numerous factors, including farming and industrialization, climate change, resource depletion, deforestation, and modifications to natural topography, contribute to viral epidemics. For instance, influenza, smallpox, measles, and yellow fever put an enormous burden on economies [3]. Nipah virus (NiV) is a zoonotic virus meaning that it is transmitted between species from animals to humans and causes outbreaks of fatal disease in humans [4]. After the first identification of the virus in pig-farming villages in Peninsular Malaysia, outbreaks were seen in Singapore, Bangladesh, and India [5, 6, 7]. Nationwide hospitals in Malaysia received more than 200 patients, many of whom passed away. The killing of several pigs to contain the epidemic and the shutdown of farms caused havoc in the pig farming sector. Numerous workers at butcher shops in neighboring Singapore also suffered. Although clinical and epidemiological characteristics first led researchers to assume Japanese encephalitis – a viral encephalitis linked to pigs that are common in Southeast Asia – a separate illness may have been to blame [8, 9, 10]. In South-East Asia, NiV infection has become an alarming threat due to high mortality, periodicity, the unsatisfactory effect of antiviral drugs, and treatment depending on symptomatic patients of the disease [11, 12]. A number of countries including Cambodia, Ghana, Indonesia, Madagascar, the Philippines, and Thailand may be at risk for infection according to WHO [13]. Moreover, WHO has included the Nipah virus in its blueprint list including ten diseases and pathogens to be prioritized for R&D [14]. The animal host reservoir for NiV is the fruit bat (genus name *Pteropus*) also known as the flying fox. Different routes of human transmission include direct transmission from fruit bats, indirect transmission from fruit bats via other animal species, and human-to-human transmission [15, 16, 17, 18]. Fruit partially eaten by bats may be dropped or thrown into pigsties infecting pigs by consuming the contaminated fruit [19]. Pig-to-human transmission mostly results from close contact with sick pigs or their contaminated tissues [13, 20].

Human-to-human transmission was reported in the Malaysian outbreaks in March 1999, especially in families of affected index cases and more than 300 health care workers in the three hospitals that looked after 80% of encephalitis patients [21, 22].

NiV's emergence and dissemination are caused by a number of variables. Different tactics have been developed throughout the infected area to deal with and improve surveillance and awareness, with a focus on personal hygiene. In spite of the threat it poses, up to now, very little mathematical modeling work has been done on Nipah fever transmission. It is also important to note that most of the Nipah models did not consider various important characteristics of the disease, such as transmission from bats and pigs, which, however, play a crucial role in the spread of the disease. Moreover, several of the earlier works did not concentrate on the dynamics of the proposed models but rather considered optimal control problems. To describe the spread of Nipah fever in a more realistic way, in this thesis, we propose two compartmental models considering all possible ways of transmission of NiV among animals and humans: we consider transmission from bats, pigs, and human-to-human transmission. The NiV outbreak is characterized by both periodic and sporadic spillover incidents. To account for this, a compartmental model has been developed to incorporate the periodic nature of the environment in which the outbreak occurs.

1.1 Structure of the dissertation

My thesis is concerned with mathematical models for the spread of Nipah virus disease in constant and periodic environments. In addition, it presents an epidemic model for a zoonotic disease with a general nonlinear incidence, motivated by our model for Nipah transmission. Furthermore, a compartmental model is studied describing the transmission dynamics of some diseases where transmission from corpses of deceased infected is possible – such as in the case of the Nipah virus.

Chapter 2 delves into the fascinating realm of mathematical modeling in epidemiology, offering readers a succinct yet comprehensive overview. This chapter serves as an essential foundation for understanding the subsequent discussions in the next chapters.

Chapter 3 is devoted to introducing the reader to the Nipah virus, providing a concise yet enlightening depiction of the virus itself, its captivating outbreak history, as well as its intricate modes of transmission. Furthermore, this chapter unravels the pathogenic background of the Nipah virus, providing insights into its behavior and impact on human health.

Chapter 4 provides a novel SIRS model to describe the dynamics of Nipah virus transmission, considering human-to-human as well as zoonotic transmission from bats and pigs.

In Chapter 5, motivated by the model described in Chapter 4, we establish and

study an $SIRS$ epidemic model for a zoonotic disease with a general nonlinear incidence rate. We derive a Lyapunov function for the global asymptotic stability of the unique endemic equilibrium.

In Chapter 6, we present a non-autonomous mathematical model for the spread of Nipah virus disease taking into account the periodic nature of various model parameters, such as transmission rate from bats and the bats' birth and death rates.

In Chapter 7, we formulate a compartmental model for the spread of a disease with an imperfect vaccine available, also considering transmission from deceased infected in general. The global dynamics of the system are completely described by constructing appropriate Lyapunov functions. We perform numerical simulations to assess the importance of transmission from the deceased considering the data collected from three infectious disease Ebola virus disease, COVID-19, and Nipah fever to support our analytical results.

Chapter 2

Mathematical modeling in epidemiology

The integration of mathematics into epidemiology has created novel and exciting possibilities for research into the prevalence and causes of disease and illness in communities. To analyze and predict the spread of various diseases, as well as to design effective strategies for their control, researchers and scientists have created an innovative and stimulating field using mathematical tools. A real-world system or phenomenon, typically expressed in terms of mathematical equations like linear and non-linear differential equations can be defined as a mathematical model. Numerous applications of mathematical models include physics, engineering, economics, statistics, and biology.

Compartmental modeling is an effective technique used to depict the movement of individuals between various groups in a population. The population is often divided into different compartments according to criteria like age, health status, and other pertinent attributes in order to apply this modeling technique.

It is firmly established that in modern times diseases are primarily transmitted through contact with viruses or bacteria. However, the idea that unseen living organisms are responsible for causing illness dates back to ancient times, with Aristotle (384 BCE–322 BCE) being among the earliest writers to explore this concept.

John Graunt (1620–1674) was the first scientist who tried to quantify causes of death and provide a method for assessing the relative chances of dying from different conditions, which was published in his book ”Natural and Political Observations made upon the Bills of Mortality” in 1662. The Bills of Mortality were weekly listings of the deceased people in London’s parishes and his analysis led to the foundation of modern epidemiological theory. Dutch scientist Antonie van Leeuwenhoek (1632–1723) utilized microscopes to explore microbes for the first time in the 17th century. The hypothesis regarding the germ of disease, which holds that it is the root cause of many diseases, was initially put forth by German physician Jacob Henle (1809–

1885) in the latter period of the 19th century. This theory was further developed by renowned figures such as Robert Koch (1843–1910), Joseph Lister (1827–1912), and Louis Pasteur (1822–1875) during the late 1800s and early 1900s [23]. Anesthetic and medical hygiene were first attempted by English physician John Snow, whose contribution is highly significant and is regarded as the founding of the science of epidemiology. For the majority of diseases, the method of infection transmission is currently understood. People develop immunity against diseases some disease like influenza, measles, rubella, and chickenpox spread by viral agents, while it is not seen for diseases caused by bacterial pathogens, like tuberculosis, meningitis, and gonorrhea. Certain diseases, such as malaria, employ an indirect transmission method where they are propagated among individuals through the intermediation of vectors. These vectors, often insects, acquire the disease from an infected human and subsequently transmit it to other individuals. Another vector method for HIV/AIDS transmission that involves back-and-forth transmission between males and females is heterosexual transmission [24].

In 1760 Swiss mathematician Bernoulli proposed the first epidemiological mathematical model describing an infectious disease to study the impact of immunization with cowpox upon the expectation of life of the immunized population and discussed the importance of variolation [25, 26]. Smallpox treatment and prevention were major challenges during the time when the disease was still widespread. The idea of using particles from the lesion for smallpox vaccination to acquire immunity was extremely debatable due to the potential harm and fatality associated with it. It was debatable whether the advantages of widespread vaccination outweighed the risks involved. After the first summarized solution to the problem of conflicting hazards, he has done a more thorough examination which was presented in the Royal Academy of Science in Paris and published in 1766. Bernoulli supported the assertion that the benefits of vaccination outweighed the risks of the illness and the associated fatalities. His research offers a thorough comprehension of the smallpox disease's historical significance. The three consecutive works of Kermack and McKendrick's [27, 28, 29] involved creating mathematical models to investigate the transmission of infectious diseases. The reformulation of the Kermack–McKendrick model by Diekmann et al. [30] has reignited interest in epidemic models during the SARS epidemic of 2002–3, the concern about a potential H5N1 influenza epidemic in 2005, the H1N1 influenza pandemic of 2009, and the Ebola outbreak of 2014.

The SIS, SIR, SIRS, SEIR, SEIRD, and SIRWS are typical examples of compartmental models, and the dynamics are described by a system of ordinary differential equations. A brief description of the compartments is given below.

- $S(t)$ is used to represent the individuals who are at risk of developing a particular health condition or disease, or those susceptible to the disease of the population. Various reason for susceptibility includes genetic trend environmental

exposures, lifestyle factors, or a combination of these. Some people may be more susceptible to infectious diseases because of weak immune systems or preexisting health conditions. For instance, for chronic diseases like diabetes or heart disease, some individuals may be more sensitive due to lifestyle choices like food and exercise or hereditary factors.

- $I(t)$ denotes the individuals of the population who have contracted a disease or infection caused by a virus, bacteria, parasite, or other microorganisms. They are capable of spreading the disease through direct contact, airborne transmission, or contaminated objects to those in the susceptible category. Depending on the nature of the infection and the individual's immunity, symptoms may or may not be seen in infected individuals.

- $R(t)$ is the compartment used for the individuals, who have previously been infected with a disease and have returned to a healthy state due to immunization. Individuals may be fully recovered or partially recovered with some residual symptoms influenced by various factors, for example, the severity of the illness, the individual's immune response, and the availability of effective treatments. Partially recovered individuals are able to be infected again or transmit the infection to others.

- $E(t)$ refers to people of the compartment who have come into contact with disease-causing microorganisms and have had the potential for infection. Individuals from this compartment do not necessarily will become infected or develop symptoms, rather it means they have had contact with the infectious agent. Asymptomatic and symptomatic are the two main groups of this compartment depending on the developing symptoms of the disease. Exposed people are important for contact tracing and implementing appropriate measures to prevent the further spread of the disease

- $D(t)$ represents the compartment of those people who have passed away from natural causes or diseases in mathematical epidemiology. This compartment is important in some cases as a corpse can transmit disease.

- $W(t)$ represents a group of individuals whose immunity against a particular disease gradually diminishes over time. This compartment is often included in epidemiological models to capture the dynamics of individuals whose immune protection weakens but can still be boosted upon repeated exposure to the pathogen. This compartment is crucial in studying the long-term effects of immunity and the potential for reinfection within a population.

In 1927, W. O. Kermack and A. G. McKendrick [27] created the SIR model in which they considered a fixed population [31]. This model may be applied to diseases like

diphtheria, typhoid fever, measles, mumps, smallpox, and chickenpox that cause permanent immunity after recovering from the disease [26]. The SIR model must adhere to certain assumptions and limitations, such as boundary conditions, much like every other mathematical model. These limitations specify the conditions under which it is possible to employ the SIR model in real-world applications. The assumptions are discussed below:

(A1) The population size is constant as the population involved in the infection is closed with no additions or leakage of individuals. This presumption may be met by an epidemic that spreads quickly and is short-lived, during which time key events like births, deaths, and migration have little to no impact on the disease's course.

(A2) People in the population encounter one another randomly in that both the probability and the intensity of contact with one another throughout time, regardless of geographic and demographic circumstances, stay constant. For the SIR dynamic system, which is controlled by the same transmission and recovery parameters, and, this is a strong assumption of homogeneity. Such a homogeneity assumption might be conveniently broken in real life. In the literature on infectious diseases, modeling with heterogeneous dynamics of infection is thus a significant and active study subject.

(A3) Only infection can lead to immunity in a susceptible individual; there is no vaccination. In other words, a susceptible compartment has only one exit, the infected compartment, and there is nowhere else that a person at risk could go. The person is no longer susceptible to the virus for the rest of the study period if that individual has been treated, The recovered compartment is the final stage of the infection dynamics because there is no connection between it and the susceptible compartment.

(A4) The infection has no latent phase, meaning that it spreads immediately after exposure. This is a crucial difference between the SIR model and the SEIR model. In actuality, this latency of infection actually refers to the timing of being contagious rather than symptomatic.

(A5) The underlying infection is assumed to evolve in completely neutral environments without any mitigation efforts through external interventions, such as a public health policy of social exclusion, effective medication, or quick testing kits for diagnosis. This is because the SIR model has constant transmission and recovery parameters that are not time-varying.

(A6) The population size is sufficient to support an adequate number of incidences, such as infections, deaths, and recovered patients, enabling the precise and

steady estimation of the SIR model parameters. A well-trained model with trustworthy data is required to not only make an accurate prediction but also to appropriately estimate the prediction uncertainty [32].

Governments often deploy a variety of control measures during an epidemic to slow the disease's spread. The fact that the transmission and recovery rates are no longer stable across time directly results from these outside interventions. Thus, a key generalization of the SIR model is to allow for varying degrees of mitigation actions, such as social exclusion, transit restrictions, the requirement of masks, and city lockdown.

Incorporating seasonality is a property of a transmission rate that is advantageous. It is common knowledge that particular winter months are when infectious diseases spread the quickest. Particularly, seasonal patterns in the behavior of several coronaviruses that cause respiratory infectious illnesses are associated with variations in temperature and humidity [33, 34]. A better long-term prediction of an epidemic would result from the model taking into account such seasonal regularity. Seasonality must be taken into consideration as public awareness of pandemic projection gradually moves from the short term to the long term.

When an epidemic persists for a long time before it is contained, the assumption of a fixed population size is constrictive. For the SIR model's time-varying compartment sizes to be accurately characterized in this situation, natural birth, and death dynamics must be included. In this way, SIR model with vital dynamics can be defined.

In practical applications, the SIR model has some drawbacks. As a result, modifications to this fundamental type that take into consideration various disease mechanisms and presumptions have received a lot of attention in the literature. The commonly used SEIR model includes an exposed compartment between the susceptible and infected compartments to account for an incubation time. One could think of the exposed compartment as a waiting area for virus carriers who are preparing to infect the populace. The essential premise is that those in this exposed group who are not currently contagious but have received the virus will eventually do so. Most infectious disorders that are appropriate for the SIR model in the literature today are thought to fit in the SEIR model.

Long-term immunity to all infectious illnesses does not always develop. After regaining health, people could build immunity for a while before losing it and being susceptible once more. Thus, following a predetermined period of immunity, restored individuals re-enter the susceptible compartment. The SIRS and SEIRS model of disease evolution is a common term. People who touch or come into contact with a corpse from a communicable disease run the risk of contracting the disease. The most dangerous jobs are those that have a lot of interaction with dead bodies. Infected bodies can be safely embalmed and viewed by the grieving, barring a few contagious diseases. Using the proper infection control techniques will help to reduce

the infectious risks that come with dead bodies. So necessarily dead compartment should take into account; in this way, the SIRD or SEIRD model is introduced. The transmission patterns of infectious illnesses for which immunity is transient are captured by SIRS models. A model may incorporate the immune system's strengthening with repeated exposure by adding an additional compartment for people with waning immunity and thus SIRWS model [35] can be formed. Vaccination programs play a vital role to eradicate infectious diseases. Target vaccine coverage that will eradicate an infectious pathogen can be predicted using the straightforward compartmental model. The SVIR model [36] is constructed to determine the vaccination coverage rate necessary to completely eradicate an infection, investigate the effects of vaccine-induced immunity that deteriorates over time, and examine the interactions between vaccine-susceptible and vaccine-resistant strains of infectious agents.

W. H. Hamer [37] postulated that the rate at which infections spread would be determined by two key factors: the number of individuals who are susceptible to the disease and the number of individuals who are already infected. He also introduced the concept of a mass action law, which could be used to quantify the rate at which new infections would occur. This idea of Hamer's has since become a fundamental principle in the development of compartmental models for disease transmission.

Ross [38] developed a basic compartmental model which was the first instance where the concept of the basic reproduction number was introduced and it is worthy to note that this name was given by MacDonald [39] in his work on malaria [23]. The number of secondary cases that one infected individual would generate in an entirely susceptible population is the basic reproduction number and it is commonly denoted by $\mathcal{R}_0$. The length of the infectious period, the likelihood of infecting a susceptible person during one encounter, and the number of additional susceptible people contacted per unit of time all play a role in this. $\mathcal{R}_0$ may thus be significantly different for various infectious diseases as well as for the same disease in various populations [40]. This number has since become a crucial concept in mathematical epidemiology, which is concerned with understanding how infectious diseases spread through populations. Despite being developed many years ago, the concept of the basic reproduction number remains a central idea in modern epidemiology.

The parameters birth rate, infection rate, and recovery rate are used in the estimation of $\mathcal{R}_0$. For the computation of basic reproduction number revolution took place when the Next Generation Matrix (NGM) method was given by Diekmann et al. [30, 41]. One can easily calculate $\mathcal{R}_0$ following the recipe of [30, 41] using NGM with large domain and the NGM with small domain. The threshold value of $\mathcal{R}_0$ is unity. Some conclusions are drawn based on this threshold value, notably that if $\mathcal{R}_0 < 1$, infections are eliminated and if $\mathcal{R}_0 > 1$, the disease is still endemic in the population [42]. Disease control organizations typically aim to lower $\mathcal{R}_0$ until it drops below unity, which can be done by endorsing specific interventions and

developing methods.

Stability analysis comes next when a dynamical system's equilibrium has been established. In order to complete the analysis, the well-known Hartman–Grobman theorem of linearization is used [43, 44]. The stability of equilibria is determined by the theorem using the sign of the real component of each and every eigenvalue of the characteristic polynomial. The qualitative behavior of the solution curves at the equilibrium points can be determined based on the sign. For instance, the solution curves will move in the direction of the equilibrium point is locally asymptotically stable, if every eigenvalue has a negative real portion. Using this theorem, we are able to determine the stability condition of the disease-free equilibrium and endemic equilibrium in terms of $\mathcal{R}_0$. Sometimes it is hard to find out the condition from eigenvalues for stability due to the complexity of the model. The well-known Routh–Hurwitz stability criterion [45, 46] may be used to perform stability analysis of equilibria for higher-order characteristic polynomials of the Jacobian matrix. The criterion does not involve a direct computation of the characteristic polynomial's roots; rather, it analyzes the stability of equilibria by concentrating only on its coefficients.

A general non-autonomous epidemic refers to an infectious disease outbreak that occurs in a population where the transmission dynamics are not constant for the factors influencing the spread of the disease, such as contact rates, population density, and interventions, vary over time. Public health interventions, natural or man-made events, seasonal variations in human behavior or interactions with one another, and other factors all have an impact on non-autonomous epidemics and all these have a significant effect on both the incidence and severity of the disease. In contrast to autonomous epidemics, where the transmission dynamics remain constant throughout the outbreak. Periodic fluctuations are a regular occurrence in the spread of diseases, as is well-known. Determining and computing the basic reproduction numbers of periodic epidemic models is a natural and crucial problem. To understand the effects of recurring contacts or migratory patterns on the spread of disease, the global dynamics of a periodic epidemic model with patch structure are examined by Wang et al. [47] which can be followed by anyone to analyze the periodicity of an epidemic model.

Chapter 3

Nipah virus

Nipah Virus (NiV) is an RNA virus (*Henipavirus* genus, *Paramyxovirinae* subfamily, *Paramyxoviridae* family, order *Mononegavirales*) and a member of *Henipavirus* genus, which also includes the recently discovered Cedar virus and the Hendra Virus (HeV) [1]. Henipaviruses are naturally stored in bats [48]. NiV and HeV are known to induce fatal neurologic and/or respiratory disease, whereas Cedar virus has not been confirmed to be harmful to any animals [49]. Since NiV can cause a wide range of illnesses in both humans and animals, including mild to deadly respiratory illnesses and encephalitis [50], it is one of the diseases on the WHO's priority list of those that need immediate attention in terms of research and development [14]. Due to its zoonotic and human-to-human transmission, NiV is extremely harmful to a variety of mammals and is thought to have pandemic potential [51]. Pteropus bats, the virus's reservoir, are found all over the world and future spillover occurrences are expected to take place in new communities where they live. The latest instance of this is a recent outbreak in a new geographic region in Kerala, India [52]. The comparatively low number of patients and challenges with diagnosis have limited research into this condition. As a virus with a biological safety level 4 (BSL 4) classification, NiV, access to such laboratories is limited in many countries [53].

Nipah virus can endure in some fruit juices or mango fruit for up to three days and at least seven days in date palm sap. In fruit bat urine, the virus has a half-life of 18 hours. In the environment, NiV is comparatively stable and can survive for one hour at 70°C, but viral concentration will be reduced in this case. Heating it for more than 15 minutes at 100°C completely inactivates it [54]. The survivability of the virus in its natural environment may alter based on the various circumstances. Soaps, detergents, and commercially available disinfectants like sodium hypochlorite can easily inactivate NiV [55]. In human NiVs obtained from multiple outbreaks in Malaysia, India, and Bangladesh, a number of variations have been found. Similar to this, distinct genetic variants were found in the NiVs isolated from Chiroptera samples collected in various locations [7, 56, 57]. NiV-B and NiV-M strains have

been found using genomic sequencing, and NiV-B is thought to have greater fatality rates [56, 58]. The outbreaks in diverse regions are brought on by the two NiV strains. It was reported that outbreaks in Malaysia were said to be caused by NiV-M, while epidemics in Bangladesh and India were by NiV-B [56]. Figure 3.1 illustrates the Nipah virus's diagrammatic structure [1].

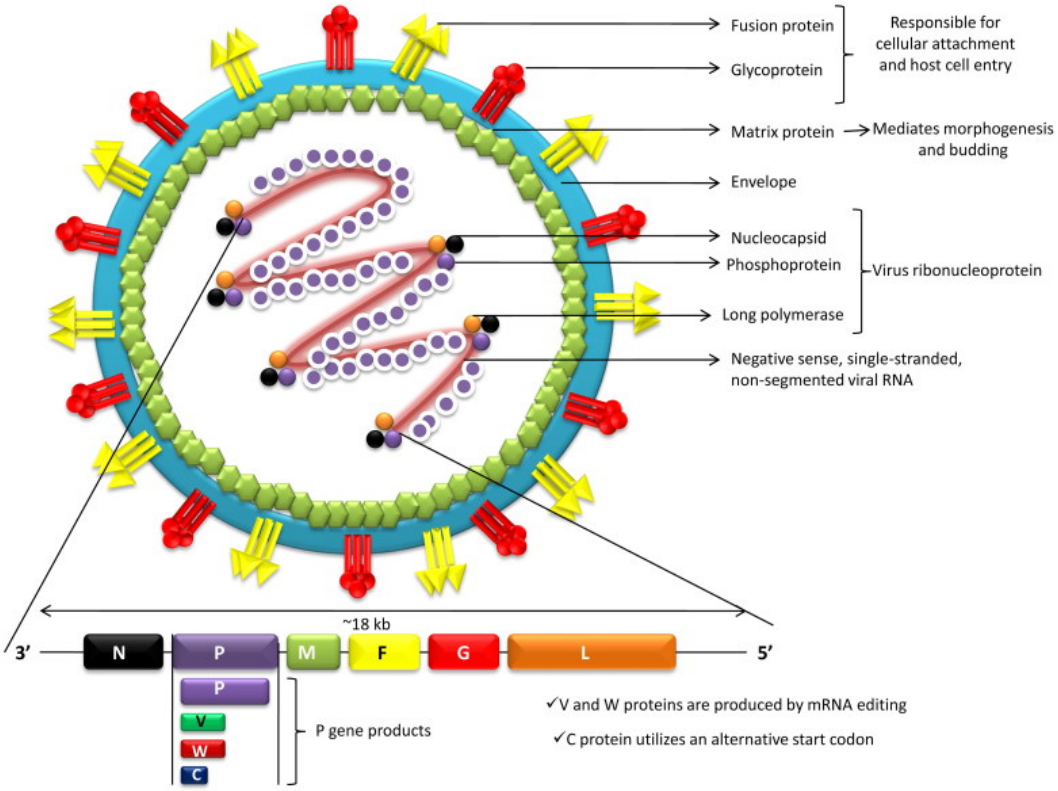


Figure 3.1: *Nipah virus structure [1].*

3.1 History of outbreak

Japanese Encephalitis (JE) is the most common type of viral encephalitis that affects people in Asia and 529 cases including 35 deaths were recorded in Malaysia from 1989 to 1998 with sporadic occurrence [59, 60]. At the end of September 1998, a group of patients were diagnosed with acute febrile encephalitis. These patients were connected to pig farming in the suburb of Ipoh City within the Kinta district of Perak state in Peninsular Malaysia [8, 61]. In the same district, respiratory sickness and encephalitis in pigs occurred prior to the epidemic of febrile encephalitis in humans [62]. Classical swine fever was formerly assumed to be the cause of the pigs' disease. The Institute of Medical Research, Ministry of Health's initial examinations into the

causes of acute encephalitis in 28 individuals in the initial outbreak area suggested that the JE virus was responsible for human mortality [63]. The Ministry of Health proactively implemented a number of control measures based on the management of the JE epidemic to battle the outbreak in the Kinta district and subsequently across the entire nation [64].

3.1.1 Malaysia

The outbreak spread to a town named Sikimat Negeri Sembilan by December 1998, and by February 1999, a similar disease in pigs and humans was observed in the biggest pig-farming region in the Negeri Sembilan state called Sungai Nipah village and Bukit Pelandok [8]. Noted that the spread of the outbreak was associated with the movement of pigs from the Kinta district and between farms [65, 66]. Famous virologists from the University of Malaya discovered the novel paramyxovirus, Nipah Virus (NiV) in early March 1999, was isolated from the Cerebrospinal Fluid (CSF) of an encephalitic patient from Sungai Nipah village and subsequently identified as the aetiological agent responsible for the outbreak [8, 50]. Between September 29, 1998, and December 1999; 283 cases of febrile encephalitis including 109 dead (38.5%) were reported to the Malaysian Ministry of Health, where the state of Negeri Sembilan reported the highest number of cases (231) and fatalities (86), followed by Perak with 28 cases and 15 deaths while Selangor had 24 cases and eight deaths [8]. The mortality rate was close to 40% and 16 days was the mean duration of illness from starting of symptoms to death. Positive viral cultures from the CSF and significant brain-stem involvement were linked to mortality [67]. With the killing of over a million pigs and extensive pig population surveillance, the outbreak in Malaysia was brought to an end [68, 69].

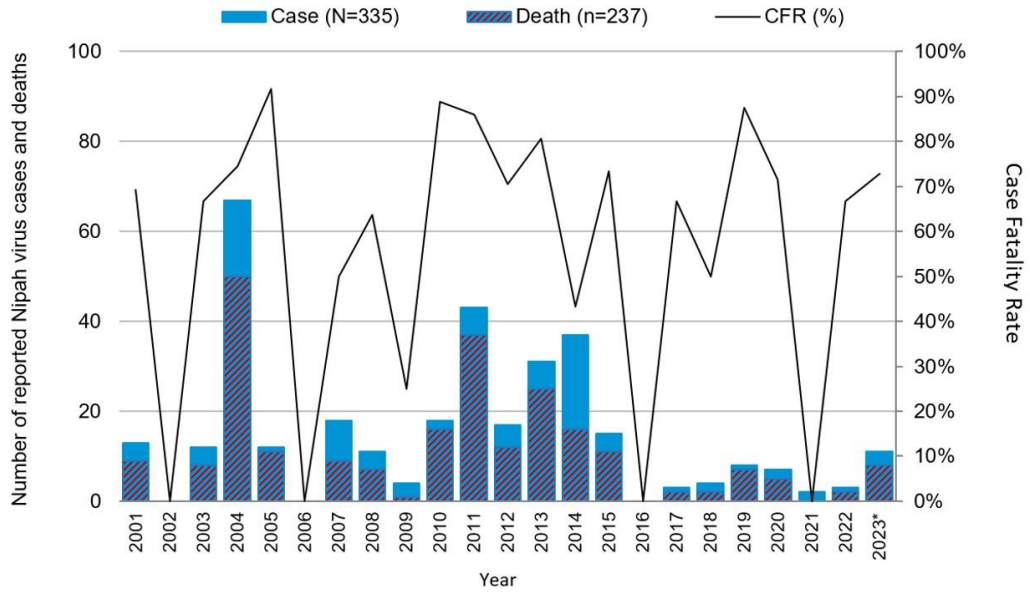
3.1.2 Singapore

During March 13–19, 1999, abattoir workers in Singapore who had contact with pigs from Peninsular Malaysia's epidemic areas were reported to have a cluster of 11 instances of respiratory and encephalitic sickness, with one death. The outbreak in Singapore came to an end after Malaysian pig imports were outlawed on March 19, 1999, and the closure of abattoirs [10, 68].

3.1.3 Bangladesh

The northern and central regions of Bangladesh saw the majority of the Nipah cases and outbreaks occurred from December to May, which is Bangladesh's winter season [6]. In April and May 2001, nine fatal febrile neurologic diseases were reported in the Meherpur District of Bangladesh. Japanese encephalitis, dengue fever,

and malaria were initially ruled out by preliminary investigations by the Ministry of Health, Bangladesh, and the World Health Organization (WHO), but 2 of 42 serum samples collected from village residents in May 2001 revealed reactive antibodies to Nipah virus antigen in tests conducted at the U.S. Centers for Disease Control and Prevention (CDC). However, there was no thorough examination of this outbreak. Eight recorded fatalities and a cluster of febrile illnesses with neurologic symptoms with similar clinical symptoms occurred in January 2003 in nearby villages in Naogaon District, around 150 miles from the village in Meherpur District [70].



Source: Bangladesh Ministry of Health and Family Welfare
**as of 16 February 2023*

Figure 3.2: *Number of reported Nipah virus cases and deaths by year, 1 January 2001 – 13 February 2023, Bangladesh [2].*

Between 2001 and 2007, 17 other NiV transmission cases, ranging from single sporadic human cases to clusters of 2–4 humans were identified in addition to the outbreaks [71]. Despite the fact that incidences of the Nipah virus are generally always reported from seven districts across two divisions in Bangladesh, there have already been 11 cases and eight deaths (fatality rate (73%)) confirmed in 2023, which is rare compared to the previous seven years. The highest cases have been documented since 2015, when there were 15 cases total, including 11 deaths [2]. For the prevention and control of the spread of NiV, the Government of Bangladesh has given some guidelines considering bats to human and human-to-human transmission. These strategies include awareness programs, early case detection through different surveillance, case management, and infection control measures in households, communities, and hospitals [72].

3.1.4 India

In Siliguri, West Bengal, India, during January and February 2001, a febrile disease outbreak connected to altered sensorium was noted. Laboratory examinations failed to identify an infectious agent at the time of the outbreak. Due to Siliguri's proximity to Bangladesh, where NiV infection outbreaks have recently been reported, clinical samples taken during the Siliguri outbreak were retrospectively examined for NiV infection evidence. With a mortality rate of 68%, this catastrophic outbreak claimed the lives of 45 out of 66 confirmed cases. The genuine index patient's information was not available [7]. However, there were no reports of any animal involvement and the dissemination was primarily nosocomial. After that, there was another outbreak took place in the Nadia district, West Bengal in 2007, all five patients who tested positive for the virus perished within 10 days of infection, resulting in a fatality rate of 100% [73]. Surprisingly the third Nipah outbreak was reported in May 2018 in Kerala's Kozhikode and Malappuram districts, which are more than 1,200 km southwest of previous Indian and Bangladeshi outbreaks. There were 17 deaths and 18 confirmed cases as of 1 June 2018 [74].

3.2 Symptoms, diagnosis, and treatment

The incubation time during the Malaysian outbreak ranged from 4 days to 2 months, but it was 10 days in Bangladesh [73, 75]. In Kerala, the incubation period was between 6 and 14 days, with a median of 9.5 days [76]. The onset of this illness starts through respiratory symptoms, including coughing, a sore throat, and respiratory distress, succeeded by a period of 3–14 days characterized by fever and headaches. Following this, the ensuing phase characterized by brain swelling (encephalitis) is marked by common symptoms such as drowsiness, disorientation, and mental confusion. This stage can progress rapidly, leading to a coma within 24-48 hours if left untreated.

Though death may occur in 40–75% of instances however survivors of NiV infection have reported long-term negative effects such as encephalopathy, cerebral atrophy, change in behavior, ocular motor palsies, cervical dystonia, weakness, and facial paralysis. Moreover, there have been reports of infections that manifest symptoms and occasionally even cause death months or even years after contact [13, 77, 78].

Since the initial Nipah virus symptoms are ambiguous, the diagnosis is frequently missed at the time of presentation. This can make it difficult to provide an accurate diagnosis and presents problems with outbreak identification, timely and efficient infection control measures, and activities related to outbreak response. Nipah virus can be detected in two ways. In the primary stage of the illness, real-time polymerase chain reaction (RT-PCR) can be used to detect Nipah virus infection in the

blood, urine, cerebrospinal fluid, and throat and nasal swabs and Enzyme-linked immunosorbent assay (ELISA) for antibody detection is another test during illness and after recovery [79].

Though the Nipah virus is on a priority disease list for the WHO Research and Development Blueprint [14], there are currently no medications or vaccines that are specifically designed to treat Nipah virus infection. For the treatment of severe respiratory and neurologic problems, intensive supportive care is advised [13].

3.3 Reservoir

Bats serve as reservoir hosts for several high-risk pathogens, including Nipah, rabies, and Marbug viruses, furthermore, no significant pathogenic alterations in the bat population are linked to such viruses [80, 81]. They are primarily found in places near farms and orchards, where they eat fruits and nectar, limiting the barrier of spillover of the viruses [82]. The bats are proven to be connected to the NiV epidemics observed in many parts of the world and are indigenous to tropical and subtropical portions of Asia, East Africa, Australian continents, and some oceanic islands [82, 83]. NiV poses a serious threat to both human and animal health due to a number of factors, such as the fact that its bat reservoir hosts are extensively dispersed throughout Asia and are found in areas with dense populations of both people and livestock. This results in frequent outbreaks and widespread spillover occurrences [84]. The main reservoir for henipaviruses in Asia and Australia appears to be a single genus of frugivorous bats called Pteropus also known as fruit bats or flying fox. In several countries in South and Southeast Asia, including Bangladesh, Cambodia, East Timor, Indonesia, India, Malaysia, Papua New Guinea, Vietnam, and Thailand, epidemics of the Nipah viral disease have been linked to the Pteropus bat species [40, 83, 85, 86, 87, 88, 89, 90, 91]. The pig proved to be an effective amplifying host for the virus. Other animals, like the cat, dog, horse, and goat have reportedly displayed signs of illness furthermore, it is thought that diseased pigs were the original hosts for these species and that all other hosts, with the exception of pigs, are essentially ”dead-end” hosts. One victim contracted the ailment from his pet dogs, which later succumbed to the illness [68, 92].

3.4 Nipah virus transmission

Diverse ways are seen to contract either humans or animals with the disease. It is odd how different hosts have multiple paths for transmission that vary based on location due to many factors, such as differing breeding practices and dietary customs [1]. Different routes of human transmission include direct transmission from fruit bats,

indirect transmission from fruit bats via other animal species, and human-to-human transmission [15, 16, 17, 93]. In-depth research is required to comprehend the viral circulation between fruit bats, pigs, and humans along with the processes of NiV transmission from bats to pigs, pigs to humans, and from humans to humans.

3.4.1 Bats to humans and pigs

The main route of bat-to-human transmission was found to be eating fresh date palm sap during investigations into NiV-related outbreaks in Bangladesh [51, 94]. Date palm sap is frequently utilized for fresh consumption and fermenting in Bengali culture. In Bangladesh, the top section of the date palm tree's bark is shaved, allowing the sap to soak into clay pots overnight, that are attached to the tree [95]. *Pteropus* spp. bats are known to regularly consume the shaved bark and commonly contaminate the sap with saliva, urine, and excrement, according to a prior NiV study [96]. It is also known that *Pteropus* spp. bats occasionally excrete and secrete NiV [97, 98]. Additionally, fermented date palm sap is used to create alcoholic beverages known as toddy, tari, and palm wine throughout Asia, Australia, and Africa [99, 100]. Pigs are raised for their economic value, and fruit trees are also grown on farms and in their vicinity for shade. Fruits attract Pteropus spp. bats, and as a result,NiV is spread to pigs and people. When pigs eat fruit that has been bitten by NiV-carrying bats, they become infected and are thought of as biological reservoirs for the disease. Additionally, the data showed that *Pteropus* spp. have a significant seroprevalence of anti-Nipah virus antibodies. This suggests that the virus has evolved sufficiently to allow for transmission among Pteropus bats [1].

3.4.2 Pigs to humans and bats

Humans can catch the illness from infected pigs, which serve as the virus's intermediate host [101]. The biological promiscuity caused by frequent interaction between people and pigs and their excrements is undoubtedly the primary risk factor for transmission in this area. In Malaysia, a large proportion of pigs are raised in pig farms, where the NiV infection can spread between animals. Moreover, slaughterhouses also contribute to the spread of the illness because they are locations where the NiV virus can move from pig to man. Transmission from pigs to bats is not seen in any literature [10, 93]. Because of the transcontinental movement of tainted pig meat, the virus was spread from animals in one region of the world to people in another.

3.4.3 Humans to humans and animal

NiV shed from *Pteropus* spp. may infect one or more people, and the chain of transmission may then continue via person-to-person contact to become an epidemic

[102]. Patient handling and coming into contact with an infected person's excretion are risk factors for infection [103]. It was reported that, during an outbreak in Siliguri, India, in 2001, 45 (75%) of 60 patients, many of whom were medical professionals had a history of hospital exposure to patients infected with Nipah virus [7]. At the same time a case-control study conducted during an outbreak in Meherpur District, Bangladesh, revealed that patients were more likely to have reported touching the secretions of other patients, and their attendants during their illness were more likely to contract the Nipah virus [70]. NiV transmission from humans to animals is not found in any literature.

3.5 Previous modelling studies

Pathological and epidemiological studies of the Nipah virus disease were perceived, but very few mathematical models are available for it which are presented as follows. Biswas [104] proposed a simple SIR model to investigate the disease propagation and control strategy of NiV infections. Numerical simulations have been utilized to depict the dynamics of NiV infections, showcasing the patterns and behavior observed in the spread of the disease. Sultana et al. [11] develop a dynamic model of NiV infections with a population of variable size and two control mechanisms, where raising awareness and providing treatment are seen as controls with the best possible pairing to save costs. We prove the existence of the best controls, and the best controls are described by the Pontryagin maximal principle. An SEIR based on a mathematical model incorporating the quarantine of infectious individuals influenced by the availability of isolation centers and surveillance coverage was formulated and analyzed by Mondal et al. [12]. They assumed birth and death rate are not equal. Among the several possible control parameters, they considered the number of quarantined individuals and the enhanced personal hygiene as a result of the public enlightenment program. A two-layered compartmental model for humans and bats was proposed by Nita et al. [105]. They found that the number of NiV-affected individuals can be reduced by using control on them and bats. Agarwal et al. [106] developed a mathematical model comprising seven compartments, encompassing virus dynamics, flying foxes, and humans. Notably, their model assumes the absence of a cure for this particular disease. Zewdie et al. [107] put forth a SIRD model to examine the influence of unguarded contact with deceased bodies of infected individuals prior to burial or cremation, as well as the rate of disposal, on the dynamics of Nipah virus infection. The model is thoroughly analyzed, and the basic reproduction number is calculated to assess the severity and potential spread of the disease. Raza et al. [108] proposed a stochastic SEIR model for the Nipah virus where they used the non-standard finite difference (NSFD) method for numerical simulation. In this model, they have established that the stochastic NSFD is an efficient, cost-effective

method that accommodates all the desired feasible properties. [109], the authors examined a compartmental model that incorporated bats, humans, and an intermediate host. Most recently, Evergen et al. [110] proposed a SIRD model with Caputo fractional derivative. This paper aims to highlight a numerical model of the Nipah virus (NiV) and its emphasis on investigating the impact of fractional order derivatives on the model's behavior. Specifically, the goal is to assess how the presence of fractional derivatives affects the spread of the NiV disease in terms of memory and heredity effects. In [111], the authors developed a mathematical model comprising a nonlinear fractional-order system of differential equations to examine the dynamics and optimal control strategies for the Nipah virus using the Caputo derivative. Similarly, Baleanu et al. [112] considered a fractional order model that incorporated the potential transmission pathway of unsafe contact with an infectious corpse.

Chapter 4

Global dynamics of a compartmental model for the spread of Nipah virus

Nipah virus, which originated in South-East Asia is a bat-borne virus causing Nipah virus infection in humans. This emerging infectious disease has become one of the most alarming threats to public health due to its periodic outbreaks and extremely high mortality rate. We establish and study a novel SIRS model to describe the dynamics of Nipah virus transmission, considering human-to-human as well as zoonotic transmission from bats and pigs as well as loss of immunity. We determine the basic reproduction number which can be obtained as the maximum of three threshold parameters corresponding to various ways of disease transmission and determine in which of the three species the disease becomes endemic. By constructing appropriate Lyapunov functions, we completely describe the global dynamics of our model depending on these threshold parameters. Numerical simulations are shown to support our theoretical results and assess the effect of various intervention measures.

4.1 Introduction

The Nipah virus is a highly contagious zoonotic pathogen that primarily affects both animals and humans, with fruit bats (specifically, the Pteropus genus) acting as the natural reservoir. Transmission can occur through direct contact with infected bats or through the consumption of fruits contaminated with bat urine or saliva. Furthermore, reports of human-to-human transmission have been made, notably during outbreaks in medical facilities. The symptoms of Nipah virus infection can range from mild to severe and the mortality rate of Nipah virus infection can be significant, with reported rates ranging from 40% to 75% during outbreaks. In South-East Asia, NiV infection has become an alarming threat due to high mortality, periodicity, the unsatisfactory effect of antiviral drugs, and treatment depending on symptomatic patients of the disease [11, 12]. Since there is currently no specific treatment for Nipah virus

infection, so supportive care and management of symptoms are the main approaches employed. Prevention and control measures involve avoiding direct contact with bats or their excreta, practicing good hygiene, implementing infection control measures in healthcare settings, and conducting surveillance and early detection of cases.

To describe the spread of Nipah fever in a more realistic way, in this chapter, we propose a compartmental model considering all possible ways of transmission of NiV among animals and humans: we consider transmission from bats, pigs, and human-to-human transmission. In Section 4.2, we introduce our compartmental model. In Section 4.3, we calculate the basic reproduction number, determine some basic properties of the model, and in Section 4.4 we study the local and global dynamics of the model. In Section 4.5, we perform numerical simulations: we fit the model to data from the 1998–99 outbreak in Malaysia and we assess the effects of changing various disease-related parameters. The chapter is closed by a short discussion of the results in Section 4.6.

4.2 Model formulation

As mentioned in the introduction, our aim is to include disease transmission among three species. More precisely, we develop a compartmental model considering transmission from bats to humans, bats to pigs, bats to bats, pigs to humans, pigs to pigs, and from humans to humans. That is, we do not consider transmission from humans to any of the two animal species and pig-to-bat transmission either as these ways of transmission have a negligible probability.

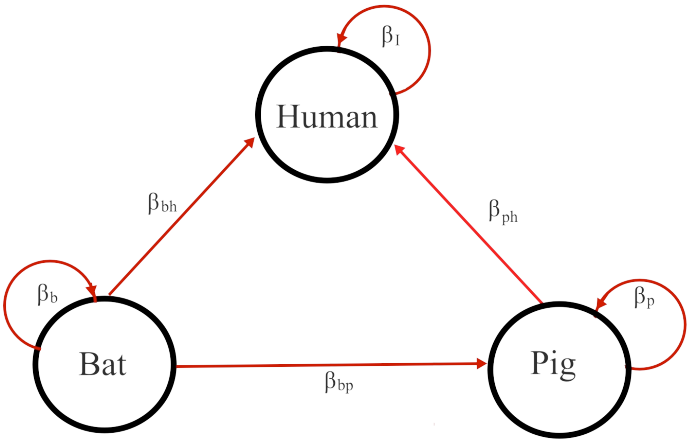


Figure 4.1: *Flow chart of NiV transition. Red arrows indicate NiV transition among Humans, Bats, and Pigs.*

In this work, populations of all three species are divided into susceptibles, infected, and recovered, furthermore, we also include the possibility of immunity loss,

hence, we consider a system consisting of three SIRS models, coupled by intraspecies transmission. The total human population $N(t)$ at time t is divided into susceptibles ($S(t)$), infected ($I(t)$) and recovered $(R(t))$. Hence,

$$N(t) = S(t) + I(t) + R(t).$$

The total pig (intermediate host) population $N_p(t)$ at time t is divided into susceptible ($S_p(t)$), infected ($I_p(t)$) and recovered $(R_p(t))$ individuals, so that

$$N_p(t) = S_p(t) + I_p(t) + R_p(t),$$

similarly the total bat population (host reservoir) $N_b(t)$ at time t is divided into susceptible ($S_b(t)$), infected ($I_b(t)$) and recovered $(R_b(t))$ individuals, such that

$$N_b(t) = S_b(t) + I_b(t) + R_b(t).$$

We denote the birth and death rates of humans by Λ and μ, respectively. There is also a disease-induced death rate, denoted by δ. Rates of human-to-human, pig-to-human and bat-to-human transmission are denoted by β_I, β_{ph} and β_{bh}, respectively. The rate of transmission among bats is denoted by β_b, while that of transmission among pigs by β_p. Transmission from bats to pigs is given by β_{bp}.

Infected humans are transferred to the recovered compartment at the rate γ (i.e. the average duration of the infectious period is $1/\gamma$ days) and θ is the rate of loss of temporary immunity acquired by recovered individuals, meaning that recovered individuals remain immune for $1/\theta$ days on average. We define all other parameters for pigs and bats in an analogous way, for these parameters, we introduce the subscripts p and b, respectively. The transmission diagram of our model is shown in Figure 4.2. A complete description of the model parameters is summarized in Table 4.1.

The system of differential equations established considering the above assump-

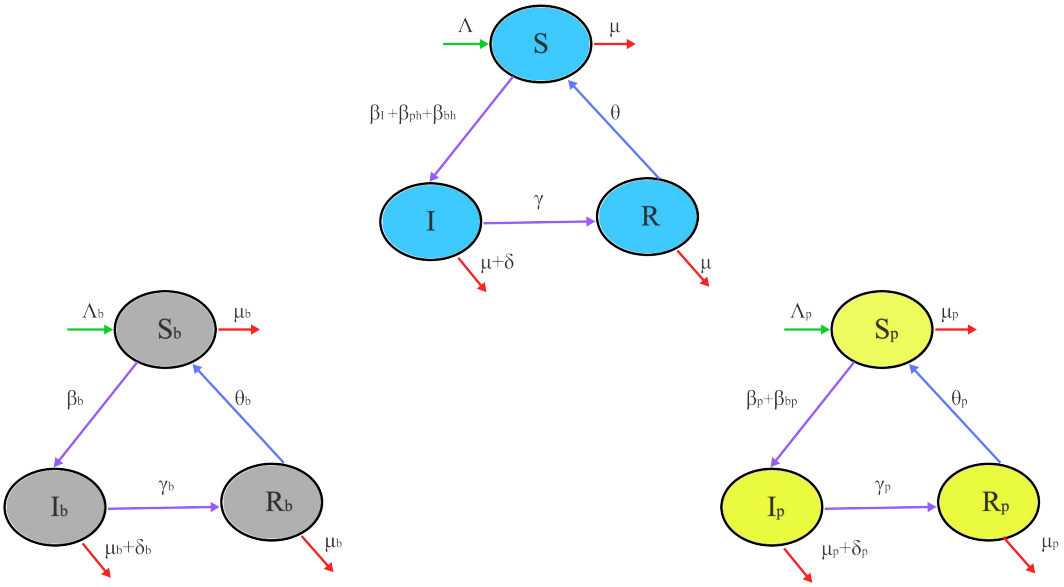


Figure 4.2: *Transmission diagram. Blue arrows indicate the transition from one compartment to another, and green arrows and red arrows indicate new entry and outflow for humans, bats, and pigs respectively. Light blue, gray, and lemon yellow colored ellipses depict compartments for humans, bats, and pigs, respectively.*

tions takes the form

$$\begin{aligned} S'(t) &= \Lambda - \beta_I S(t)I(t) - \beta_{ph} S(t)I_p(t) - \beta_{bh} S(t)I_b(t) - \mu S(t) + \theta R(t), \\ I'(t) &= \beta_I S(t)I(t) + \beta_{ph} S(t)I_p(t) + \beta_{bh} S(t)I_b(t) - (\mu + \delta + \gamma)I(t), \\ R'(t) &= \gamma I(t) - (\mu + \theta)R(t), \end{aligned} \tag{4.1a}$$

$$\begin{aligned} S_p'(t) &= \Lambda_p - \beta_p S_p(t)I_p(t) - \beta_{bp} S_p(t)I_b(t) - \mu_p S_p(t) + \theta_p R_p(t), \\ I_p'(t) &= \beta_p S_p(t)I_p(t) + \beta_{bp} S_p(t)I_b(t) - (\mu_p + \delta_p + \gamma_p)I_p(t), \\ R_p'(t) &= \gamma_p I_p(t) - (\mu_p + \theta_p)R_p(t), \end{aligned} \tag{4.1b}$$

$$\begin{aligned} S_b'(t) &= \Lambda_b - \beta_b S_b(t)I_b(t) - \mu_b S_b(t) + \theta_b R_b(t), \\ I_b'(t) &= \beta_b S_b(t)I_b(t) - (\mu_b + \delta_b + \gamma_b)I_b(t), \\ R_b'(t) &= \gamma_b I_b(t) - (\mu_b + \theta_b)R_b(t), \end{aligned} \tag{4.1c}$$

with nonnegative initial conditions.

It is important to note that due to the asymmetric transmission possibilities among the three species, subsystem (4.1c) can be decoupled from the rest of the equations of (4.1), furthermore, the subsystem consisting of equations (4.1b) and (4.1c) can also be decoupled from the human equations.

Table 4.1: *Description of parameters of model* (4.1).

Parameters	Description
Λ	Recruitment rate for humans
Λ_p, Λ_b	Recruitment rate for pigs, bats respectively
μ	Natural death rate of humans
μ_p, μ_b	Natural death rate of pigs, bats
δ	Disease-induced death rate for humans
δ_p, δ_b	Disease-induced death rate for pigs and bats respectively
γ	Recovery rate for humans
γ_p, γ_b	Recovery rate for pigs and bats respectively
β_I	Transmission rate from infected to susceptible humans
β_p	Transmission rate from infected to susceptible pigs
β_b	Transmission rate from infected to susceptible bats
β_{ph}	Pig-to-human transmission rate
β_{bh}	Bat-to-human transmission rate
β_{bp}	Bat-to-pig transmission rate
$1/\theta$	Average length of immunity for humans
$1/\theta_p, 1/\theta_b$	Average length of immunity for pigs and bats respectively

4.3 Basic properties

4.3.1 Nonnegativity and boundedness

For system (4.1) it is necessary to prove that all the state variables are nonnegative and all the solutions of the system with positive initial conditions have a positive invariant solution. Thus we start with the following lemma.

Lemma 1. *All solutions of model* (4.1) *started from nonnegative initial conditions will remain nonnegative for all forward time and will eventually approach the forward invariant set* $\Gamma = \{S, I, R, S_p, I_p, R_p, S_b, I_b, R_b \in \mathbb{R}^3_+ \times \mathbb{R}^3_+ \times \mathbb{R}^3_+ : 0 < N \leq \Lambda/\mu, 0 < N_p \leq \Lambda_p/\mu_p, 0 < N_b \leq \Lambda_b/\mu_b\}$.

Proof. It can easily be proved that all existing solutions starting from nonnegative initial conditions remain nonnegative for all time $t > 0$. For the total human population $N(t)$ we have

$$N'(t) = S'(t) + I'(t) + R'(t) = \Lambda - \mu N(t) - \delta I(t).$$

Clearly,

$$N'(t) \leq \Lambda - \mu N(t).$$

If the initial value of the total population $N(0) = N_0$, then it follows that

$$N(t) \leq \frac{\Lambda}{\mu} - \left(\frac{\Lambda}{\mu} - N_0\right) e^{-\mu t}.$$

So $N(t) \leq \frac{\Lambda}{\mu}$ as $t > 0$. Applying a similar argumentation as above, we can prove that $N_p(t) \leq \Lambda_p/\mu_p$ and $N_b(t) \leq \Lambda_b/\mu_b$. Hence the region is positively invariant and it attracts all solutions of the equations of the system. □

4.3.2 Derivation of the basic reproduction number

To calculate the basic reproduction number $\mathcal{R}_0$ of (4.1), we follow the general approach established in [30, 42]. For model (4.1) the infectious states are I, I_b and I_p. We can create the transmission vector $\mathcal{F}$ representing the new infections and the transition vector $\mathcal{V}$ which denotes the outflow from the infectious compartments in (4.1) are given by

$$\mathcal{F} = \begin{bmatrix} \beta_I SI + \beta_{ph} SI_p + \beta_{bh} SI_b \\ \beta_p S_p I_p + \beta_{bp} S_p I_b \\ \beta_b S_b I_b \end{bmatrix}, \qquad \mathcal{V} = \begin{bmatrix} (\mu + \delta + \gamma) I \\ (\mu_p + \delta_p + \gamma_p) I_p \\ (\mu_b + \delta_b + \gamma_b) I_b \end{bmatrix}.$$

Model (4.1) has a unique disease-free equilibrium, given by

$$E_0 = \left(S, I, R, S_p, I_p, R_p, S_b, I_b, R_b\right) = \left(\tfrac{\Lambda}{\mu}, 0, 0, \tfrac{\Lambda_b}{\mu_b}, 0, 0, \tfrac{\Lambda_p}{\mu_p}, 0, 0\right).$$

Substituting the value the disease-free equilibrium E_0, we compute the Jacobian F from $\mathcal{F}$ given by

$$F = \begin{bmatrix} \frac{\beta_I \Lambda}{\mu} & \frac{\beta_{ph} \Lambda}{\mu} & \frac{\beta_{bh} \Lambda}{\mu} \\ 0 & \frac{\beta_p \Lambda_p}{\mu_p} & \frac{\beta_{bp} \Lambda_p}{\mu_p} \\ 0 & 0 & \frac{\beta_b \Lambda_b}{\mu_b} \end{bmatrix}$$

and the Jacobian V from $\mathcal{V}$ given by

$$V = \begin{bmatrix} \gamma + \delta + \mu & 0 & 0 \\ 0 & \gamma_p + \delta_p + \mu_p & \\ 0 & 0 & \gamma_b + \delta_b + \mu_b \end{bmatrix},$$

from which the next generation matrix can be calculated as

$$FV^{-1} = \begin{bmatrix} \frac{\beta_I \Lambda}{\mu(\gamma+\delta+\mu)} & \frac{\beta_{ph} \Lambda}{\mu(\gamma_p+\delta_p+\mu_p)} & \frac{\beta_{bh} \Lambda}{\mu(\gamma_b+\delta_b+\mu_b)} \\ 0 & \frac{\beta_p \Lambda_p}{\mu_p(\gamma_p+\delta_p+\mu_p)} & \frac{\beta_{bp} \Lambda_p}{\mu_p(\gamma_b+\delta_b+\mu_b)} \\ 0 & 0 & \frac{\beta_b \Lambda_b}{\mu_b(\gamma_b+\delta_b+\mu_b)} \end{bmatrix}.$$

The eigenvalues of the next generation matrix are $\frac{\beta_I \Lambda}{\mu(\gamma+\delta+\mu)}$, $\frac{\beta_p \Lambda_p}{\mu_p(\gamma_p+\delta_p+\mu_p)}$, $\frac{\beta_b \Lambda_b}{\mu_b(\gamma_b+\delta_b+\mu_b)}$. According to [30, 42], the basic reproduction number $\mathcal{R}_0$ is the spectral radius of FV^{-1}, hence in our model the basic reproduction number is given by

$$\mathcal{R}_0 = \max\left\{\mathcal{R}_0^1, \mathcal{R}_0^2, \mathcal{R}_0^3\right\},$$

where

$$\mathcal{R}_0^1 = \frac{\beta_I \Lambda}{\mu(\gamma+\delta+\mu)},$$
$$\mathcal{R}_0^2 = \frac{\beta_p \Lambda_p}{\mu_p(\gamma_p+\delta_p+\mu_p)},$$
$$\mathcal{R}_0^3 = \frac{\beta_b \Lambda_b}{\mu_b(\gamma_b+\delta_b+\mu_b)}.$$

4.3.3 Existence of endemic equilibria

In this subsection, we will determine the existence of endemic equilibria depending on the parameter values. Due to the asymmetric nature of transmission among the three species, we may have various equilibria corresponding to scenarios where Nipah virus infection is only endemic among the human population, where the disease is endemic in humans and pigs, or where the infection is endemic in all three species.

Lemma 2. *The human-only endemic equilibrium* $\hat{E} := \left(\hat{S}, \hat{I}, \hat{R}, \hat{S}_p, 0, \hat{R}_p, \hat{S}_b, 0, \hat{R}_b, \right)$ *exists if and only if* $\mathcal{R}_0^1 > 1$.

Proof. Let us assume that the disease is not endemic among pigs and bats. In this case, by omitting the terms corresponding to infection from animals to humans we get the system

$$\begin{aligned} S'(t) &= \Lambda - \beta_I S(t) I(t) - \mu S(t) + \theta R(t), \\ I'(t) &= \beta_I S(t) I(t) - (\mu + \delta + \gamma) I(t), \\ R'(t) &= \gamma I(t) - (\mu + \theta) R(t), \end{aligned} \tag{4.2a}$$

$$\begin{aligned} S_p'(t) &= \Lambda_p - \mu_p S_p(t) + \theta_p R_p(t), \\ R_p'(t) &= -(\mu_p + \theta_p) R_p(t), \end{aligned} \tag{4.2b}$$

$$\begin{aligned} S_b'(t) &= \Lambda_b - \mu_b S_b(t) + \theta_b R_b(t), \\ R_b'(t) &= -(\mu_b + \theta_b) R_b(t). \end{aligned} \tag{4.2c}$$

The reduced system (4.2) has the equilibrium $\left(\hat{S}, \hat{I}, \hat{R}, \hat{S}_p, 0, \hat{R}_p, \hat{S}_b, 0, \hat{R}_b\right)$ where

$$\begin{aligned}
\hat{S} &= \tfrac{(\gamma+\delta+\mu)}{\beta_I}, \\
\hat{I} &= \tfrac{(\theta+\mu)(\beta_I\Lambda-\mu(\gamma+\delta+\mu))}{\beta_I(\delta\theta+\gamma\mu+\delta\mu+\theta\mu+\mu^2)} = \tfrac{\mu(\theta+\mu)(\gamma+\delta+\mu)(\mathcal{R}_0^1-1))}{\beta_I(\delta\theta+\gamma\mu+\delta\mu+\theta\mu+\mu^2)}, \\
\hat{R} &= \tfrac{\gamma(\beta_I\Lambda-\mu(\gamma+\delta+\mu))}{\beta_I(\delta\theta+\gamma\mu+\delta\mu+\theta\mu+\mu^2)} = \tfrac{\gamma\mu(\gamma+\delta+\mu)(\mathcal{R}_0^1-1))}{\beta_I(\delta\theta+\gamma\mu+\delta\mu+\theta\mu+\mu^2)}, \\
\hat{S}_p &= \tfrac{\Lambda_p}{\mu_p}, \quad \hat{R}_p = 0, \quad \hat{S}_b = \tfrac{\Lambda_b}{\mu_b}, \quad \hat{R}_b = 0,
\end{aligned}$$

from which it can clearly be seen that this equilibrium exists if and only if $\mathcal{R}_0^1 > 1$. □

Lemma 3. *The human- and pig-endemic equilibrium* $\tilde{E} := \left(\tilde{S}, \tilde{I}, \tilde{R}, \tilde{S}_p, \tilde{I}_p, \tilde{R}_p, \tilde{S}_b, 0, \tilde{R}_b\right)$ *exists if* $\mathcal{R}_0^2 > 1$.

Proof. This case corresponds to the situation when the disease is not endemic among bats, it only affects humans and pigs, hence, in this case, we can omit the terms corresponding to infection from bats from the right-hand sides of model (4.1) to obtain

$$\begin{aligned}
S'(t) &= \Lambda - \beta_I S(t)I(t) - \beta_{ph}S(t)I_p(t) - \mu S(t) + \theta R(t), \\
I'(t) &= \beta_I S(t)I(t) + \beta_{ph}S(t)I_p(t) - (\mu+\delta+\gamma)I(t), \\
R'(t) &= \gamma I(t) - (\mu+\theta)R(t),
\end{aligned} \tag{4.3a}$$

$$\begin{aligned}
S_p'(t) &= \Lambda_p - \beta_p S_p(t)I_p(t) - \mu_p S_p(t) + \theta_p R_p(t), \\
I_p'(t) &= \beta_p S_p(t)I_p(t) - (\mu_p+\delta_p+\gamma_p)I_p(t), \\
R_p'(t) &= \gamma_p I_p(t) - (\mu_p+\theta_p)R_p(t),
\end{aligned} \tag{4.3b}$$

$$\begin{aligned}
S_b'(t) &= \Lambda_b - \mu_b S_b(t) + \theta_b R_b(t), \\
R_b'(t) &= -(\mu_b+\theta_b)R_b(t).
\end{aligned} \tag{4.3c}$$

We let the right-hand side of all eight equations equal to zero. From the subsystem (4.3c) for bats, we again obtain $(\tilde{S}_b, \tilde{R}_b) = (\frac{\Lambda_b}{\mu_b}, 0)$. From the subsystem (4.3b) for pigs, we get

$$\begin{aligned}
\tilde{S}_p &= \tfrac{(\gamma_p+\delta_p+\mu_p)}{\beta_p}, \\
\tilde{I}_p &= \tfrac{(\theta_p+\mu_p)(\beta_p\Lambda_p-\mu_p(\gamma_p+\delta_p+\mu_p))}{\beta_p(\delta_p\theta_p+\gamma_p\mu_p+\delta_p\mu_p+\theta_p\mu_p+\mu_p^2)}, \\
\tilde{R}_p &= \tfrac{\gamma_p(\beta_p\Lambda_p-\mu_p(\gamma_p+\delta_p+\mu_p))}{\beta_p(\delta_p\theta_p+\gamma_p\mu_p+\delta_p\mu_p+\theta_p\mu_p+\mu_p^2)},
\end{aligned}$$

which can be written as

$$\begin{aligned}\tilde{S}_p &= \tfrac{(\gamma_p+\delta_p+\mu_p)}{\beta_p},\\ \tilde{I}_p &= \tfrac{\mu_p(\theta_p+\mu_p)(\gamma_p+\delta_p+\mu_p)(\mathcal{R}_0^2-1)}{\beta_p(\delta_p\theta_p+\gamma_p\mu_p+\delta_p\mu_p+\theta_p\mu_p+\mu_p^2)},\\ \tilde{R}_p &= \tfrac{\gamma_p\mu_p(\gamma_p+\delta_p+\mu_p)(\mathcal{R}_0^2-1)}{\beta_p(\delta_p\theta_p+\gamma_p\mu_p+\delta_p\mu_p+\theta_p\mu_p+\mu_p^2)}.\end{aligned}$$

This implies that $\tilde{I}_p, \tilde{R}_p$ are positive if and only if $\mathcal{R}_0^2 > 1$. Then substituting $\tilde{I}_p$ into the place of $I_p(t)$ in the human equations (4.3a) we obtain

$$\begin{aligned}S'(t) &= \Lambda - \beta_I S(t)I(t) - \beta_{ph}S(t)\tilde{I}_p - \mu S(t) + \theta R(t),\\ I'(t) &= \beta_I S(t)I(t) + \beta_{ph}S(t)\tilde{I}_p - (\mu+\delta+\gamma)I(t),\\ R'(t) &= \gamma I(t) - (\mu+\theta)R(t).\end{aligned} \tag{4.4}$$

To obtain equilibria of the latter system (4.4), we need to solve the algebraic system of equations

$$\begin{aligned}0 &= \Lambda - \beta_I SI - \beta_{ph}S\tilde{I}_p - \mu S + \theta R,\\ 0 &= \beta_I SI + \beta_{ph}S\tilde{I}_p - (\mu+\delta+\gamma)I,\\ 0 &= \gamma I - (\mu+\theta)R.\end{aligned} \tag{4.5}$$

Solving for R in terms of I from the third equation of (4.5) and replacing into the first equation, we get

$$S = \frac{I\gamma\theta + \Lambda(\theta+\mu)}{(\beta_I I + \beta_{ph}\tilde{I}_p + \mu)(\theta+\mu)}. \tag{4.6}$$

Using (4.6), the second equation of (4.5) can be written as

$$\begin{aligned}I^2\beta_I(\gamma\mu + (\delta+\mu)(\theta+\mu)) + I(\beta_{ph}\tilde{I}_p\gamma\mu + (\delta+\mu)(\theta+\mu)\\ + \mu(\gamma+\delta+\mu)(\theta+\mu)(1-\mathcal{R}_0^1)) - \beta_{ph}\tilde{I}_p\Lambda(\theta+\mu) = 0,\end{aligned}$$

a quadratic equation of I. Since the discriminant of this equation is positive and the product of the constant term and that of the leading coefficient is negative, the equation has a unique real positive solution. Hence, a unique equilibrium $\tilde{E}$ with endemicity in humans and pigs exists. □

Lemma 4. *The endemic equilibrium* $E^* := \left(S^*, I^*, R^*, S_p^*, I_p^*, R_p^*, S_b^*, I_b^*, R_b^*\right)$ *with the disease being endemic in all three species exists if and only if* $\mathcal{R}_0^3 > 1$ *and* $\mathcal{R}_0^2 > 1$.

Proof. In this case, we assume that NiV transmission to humans occurs from both animal species. To calculate the endemic equilibrium, we set the right-hand side of

all equations to zero. From the subsystem(4.1c) for bats we get

$$\begin{aligned}
S_b^* &= \frac{(\gamma_b + \delta_b + \mu_b)}{\beta_b}, \\
I_b^* &= \frac{(\theta_b + \mu_b)(\beta_b \Lambda_b - \mu_b(\gamma_b + \delta_b + \mu_b))}{\beta_b(\delta_b\theta_b + \gamma_b\mu_b + \delta_b\mu_b + \theta_b\mu_b + \mu_b^2)} \\
&= \frac{\mu_b(\theta_b + \mu_b)(\gamma_b + \delta_b + \mu_b)(\mathcal{R}_0^3 - 1)}{\beta_b(\delta_b\theta_b + \gamma_b\mu_b + \delta_b\mu_b + \theta_b\mu_b + \mu_b^2)}, \\
R_b^* &= \frac{\gamma_b(\beta_b \Lambda_b - \mu_b(\gamma_b + \delta_b + \mu_b))}{\beta_b(\delta_b\theta_b + \gamma_b\mu_b + \delta_b\mu_b + \theta_b\mu_b + \mu_b^2)} \\
&= \frac{\gamma_b\mu_b(\gamma_b + \delta_b + \mu_b)(\mathcal{R}_0^3 - 1)}{\beta_b(\delta_b\theta_b + \gamma_b\mu_b + \delta_b\mu_b + \theta_b\mu_b + \mu_b^2)}.
\end{aligned}$$

We may substitute the value of I_b^* into the subsystem(4.1b) for pigs. Similarly, as before, the pigs subsystem has a unique fixed point. Substituting the value of I_p^* into the first three equations, we get the following subsystem for humans:

$$\begin{aligned}
S'(t) &= \Lambda - \beta_I S(t)I(t) - \beta_{ph} S(t)I_p^* - \beta_{bh} S(t)I_b^* - \mu S(t) + \theta R(t), \\
I'(t) &= \beta_I S(t)I(t) + \beta_{ph} S(t)I_p^* + \beta_{bh} S(t)I_b^* - (\mu + \delta + \gamma)I(t), \\
R'(t) &= \gamma I(t) - (\mu + \theta)R(t).
\end{aligned} \tag{4.7}$$

Similarly, as in the proof of the previous lemma, we can see that the endemic equilibrium exists if $\mathcal{R}_0^3 > 1$ and $\mathcal{R}_0^2 > 1$. □

4.4 Stability analysis

4.4.1 Local stability of the equilibria

Theorem 5. *The disease-free equilibrium* $E_0\big(\frac{\Lambda}{\mu}, 0, 0, \frac{\Lambda_p}{\mu_p}, 0, 0, \frac{\Lambda_b}{\mu_b}, 0, 0\big)$ *is locally asymptotically stable if* $\mathcal{R}_0^1 < 1, \mathcal{R}_0^2 < 1, \mathcal{R}_0^3 < 1$*, while* E_0 *is unstable if any one of the inequalities altered.*

Proof. The Jacobian of system (4.1) evaluated at the disease-free equilibrium takes

the form

$$\mathcal{J}(E_0) = \begin{bmatrix} -\mu & -\frac{\beta_I\Lambda}{\mu} & \theta & 0 & -\frac{\beta_{ph}\Lambda}{\mu} & 0 & 0 & -\frac{\beta_{bh}\Lambda}{\mu} & 0 \\ 0 & j_{22} & 0 & 0 & \frac{\beta_{ph}\Lambda}{\mu} & 0 & 0 & \frac{\beta_{bh}\Lambda}{\mu} & 0 \\ 0 & \gamma & -\theta-\mu & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & -\mu_p & -\frac{\beta_p\Lambda_p}{\mu_p} & \theta_p & 0 & -\frac{\beta_{bp}\Lambda_p}{\mu_p} & 0 \\ 0 & 0 & 0 & 0 & j_{55} & 0 & 0 & \frac{\beta_{bp}\Lambda_p}{\mu_p} & 0 \\ 0 & 0 & 0 & 0 & \gamma_p & -\theta_p-\mu_p & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & -\mu_b & -\frac{\beta_b\Lambda_b}{\mu_b} & \theta_b \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & j_{88} & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & \gamma_b & -\theta_b-\mu_b \end{bmatrix},$$

while the eigenvalues of $\mathcal{J}(E_0)$ are $-\mu, \theta-\mu, j_{22} = \frac{\beta_I\Lambda-\mu(\gamma+\delta+\mu)}{\mu}, -\mu_p, -\theta_p-\mu_p$, $j_{55} = \frac{\beta_p\Lambda_p-\mu_p(\gamma_p+\delta_p+\mu_p)}{\mu_p}, -\mu_b, -\theta_b-\mu_b, j_{88} = \frac{\beta_b\Lambda_b-\mu_b(\gamma_b+\delta_b+\mu_b)}{\mu_b}$. So the disease-free equilibrium is locally asymptotically stable if $\frac{\beta_I\Lambda-\mu(\gamma+\delta+\mu)}{\mu} = (\gamma+\delta+\mu)(\mathcal{R}_0^1-1) < 0$, $\frac{\beta_p\Lambda_p-\mu_p(\gamma_p+\delta_p+\mu_p)}{\mu_p} = (\gamma_p+\delta_p+\mu_p)(\mathcal{R}_0^2-1) < 0$ and $\frac{\beta_b\Lambda_b-\mu_b(\gamma_b+\delta_b+\mu_b)}{\mu_b} = (\gamma_b+\delta_b+\mu_b)(\mathcal{R}_0^3-1) < 0$. So the disease-free equilibrium is locally asymptotically stable if $\mathcal{R}_0^1 < 1, \mathcal{R}_0^2 < 1$ and $\mathcal{R}_0^3 < 1$. If any of these three altered then that eigenvalue will be positive means the disease-free equilibrium is unstable. This completes our proof. □

4.4.2 Global stability of the equilibria

First, by applying the fluctuation lemma (see for example [113]), we show that the disease free equilibrium is globally asymptotically stable if the basic reproduction number is less than 1. For a bounded function f on $\mathbb{R}_+$, we introduce the notations

$$f^\infty = \limsup_{t\to\infty} f(t) \quad \text{and} \quad f_\infty = \liminf_{t\to\infty} f(t).$$

Theorem 6. *The disease-free equilibrium* $E_0\big(\frac{\Lambda}{\mu}, 0, 0, \frac{\Lambda_p}{\mu_p}, 0, 0, \frac{\Lambda_b}{\mu_b}, 0, 0\big)$ *is globally asymptotically stable* $\Gamma := \{(S(t), I(t), R(t), S_p(t), I_p(t), R_p(t), S_b(t), I_b(t), R_b(t)) \in \mathbb{R}_+^9\}$ *if* $\mathcal{R}_0 < 1$.

Proof. In the previous subsection, we showed that the disease-free equilibrium E_0 is locally asymptotically stable if the basic reproduction number is less than one, hence it is sufficient to prove that E_0 is globally attractive in the positively invariant and attractive set ϕ.

Let $(S_b(t), I_b(t), R_b(t))$ be a solution of the subsystem (4.1c). According to the fluctuation lemma there exists a sequence $\{t_n\}$ such that $t_n \to \infty$ we have $R(t_n) \to$

R^∞, and $R'(t_n) \to 0$ as $n \to \infty$. From the equation for recovered bats we have

$$R_b'(t_n) = \gamma_b I_b(t_n) - (\mu_b + \theta_b) R_b(t_n),$$

then letting $n \to \infty$ implies $0 \leq \gamma_b I_b^\infty - (\mu_b + \theta_b) R_b^\infty$ and hence $R_b^\infty \leq \frac{\gamma_b I_b^\infty}{\mu_b + \theta_b}$. Again by the fluctuation lemma, there exists a sequence $u_n \to \infty$ such that $I_b(u_n) \to I_b^\infty$, and $I_b'(u_n) \to 0$ as $n \to \infty$. From the equation for infected bats, we have

$$I_b'(u_n) = \beta_b S_b(u_n) I_b(u_n) - (\mu_b + \delta_b + \gamma_b) I_b(u_n),$$

which implies $0 \leq \frac{\beta_b \Lambda_b}{\mu_b} I_b^\infty - (\mu_b + \delta_b + \gamma_b) I_b^\infty$ using Lemma 1 and hence $0 \leq (\mathcal{R}_0^3 - 1) I_b^\infty$. Since $\mathcal{R}_0^3 < 1$, we have $I_b^\infty = 0$. It follows that $R_b^\infty = 0$. Applying once again the fluctuation lemma, there exists a sequence $v_n \to \infty$ such that $S(v_n) \to S_\infty$, and $S'(v_n) \to 0$ as $n \to \infty$. From the equation for susceptible bats, we get

$$S_b'(v_n) = \Lambda_b - \beta_b S_b(v_n) I_b(v_n) - \mu_b S_b(v_n) + \theta_b R_b(v_n).$$

Using that $I_b^\infty = 0$ and $R_b^\infty = 0$ and letting $n \to \infty$ we get $(S_b)_\infty = \frac{\Lambda_b}{\mu_b} \geq S_b^\infty$. It follows that $\lim_{t\to\infty} S(t) = \frac{\Lambda_b}{\mu_b}$ if $\mathcal{R}_0^3 < 1$. Hence, for the bats subsystem we have that $\lim_{t\to\infty}(S_b(t), I_b(t), R_b(t)) = \left(\frac{\Lambda_b}{\mu_b}, 0, 0\right)$ holds for all solutions of (4.1c). Applying these results in subsystem (4.1b) for pigs and following a similar calculation, we can prove $\lim_{t\to\infty}(S_p(t), I_p(t), R_p(t)) = \left(\frac{\Lambda_p}{\mu_p}, 0, 0\right)$ if $\mathcal{R}_0^2 < 1$. Finally, for the human subsystem (4.1a) one can prove that $\lim_{t\to\infty}(S(t), I(t), R(t)) = \left(\frac{\Lambda}{\mu}, 0, 0\right)$ if $\mathcal{R}_0^1 < 1$ in an analogous way. Hence, the disease-free equilibrium E_0 is globally asymptotically stable if $\mathcal{R}_0 < 1$. □

Theorem 7. *The human-only endemic equilibrium* $\hat{E} := \left(\hat{S}, \hat{I}, \hat{R}, \hat{S}_p, 0, \hat{R}_p, \hat{S}_b, 0, \hat{R}_b\right)$ *is globally asymptotically stable in*

$$\Gamma := \{(S(t), I(t), R(t), S_p(t), I_p(t), R_p(t), S_b(t), I_b(t), R_b(t)) \in \mathbb{R}_+^9\}$$

if $\mathcal{R}_0^1 > 1$, $\mathcal{R}_0^2 < 1$ *and* $\mathcal{R}_0^3 < 1$.

Proof. In proving the global asymptotic stability of the equilibrium $\hat{E}$, we first take advantage of the fact that if $\mathcal{R}_0^2 < 1$ and $\mathcal{R}_0^3 < 1$ and there is no disease among bats and pigs, then the three species do not affect each other, hence, the subsystems corresponding to each species can be decoupled from the rest of equations. Moreover, the subsystems for bats and pigs can be reduced to the single equations for $S_b'(t)$ and $S_p'(t)$, respectively. That is, we only have to consider the equations

$$S_b'(t) = \Lambda_b - \mu_b S_b(t) \quad \text{and} \quad S_p'(t) = \Lambda_p - \mu_p S_p(t),$$

which clearly have the globally asymptotically stable equilibria $\left(\frac{\Lambda_b}{\mu_b}\right)$ and $\left(\frac{\Lambda_p}{\mu_p}\right)$, re-

spectively. Now, we can turn to the human subsystem consisting of the first three equations of (4.1), however, without transmission from animals. For the convenience of constructing a Lyapunov function, following [114, 115] we consider an equivalent subsystem by letting $N(t) = S(t) + I(t) + R(t)$. Then we can write the subsystem for humans as

$$\begin{aligned} N'(t) &= \Lambda - \mu N(t) - \delta I(t), \\ I'(t) &= \beta_I I(t)(N(t) - I(t) - R(t)) - (\mu + \delta + \gamma) I(t), \\ R'(t) &= \gamma I(t) - (\mu + \theta) R(t), \end{aligned} \tag{4.8}$$

and the equilibrium for humans $\hat{E} \coloneqq \left(\hat{S}, \hat{I}, \hat{R}\right)$ for the system (4.2) gives the boundary equilibrium of (4.7). Clearly, $\hat{N}, \hat{I}$ and $\hat{R}$ satisfy the following equations.

$$\begin{aligned} \Lambda - \mu\hat{N} - \delta\hat{I} &= 0, \\ \beta_I \hat{I}(\hat{N} - \hat{I} - \hat{R}) - (\mu + \delta + \gamma)\hat{I} &= 0, \\ \gamma\hat{I} - (\mu + \theta)\hat{R} &= 0. \end{aligned}$$

We define the Lyapunov function $V(t)$ as

$$V(t) = \frac{\beta_I}{2\delta}(N - \hat{N})^2 + \left(I - \hat{I} - \hat{I}\ln\frac{I}{\hat{I}}\right) + \frac{\beta_I}{2\gamma}(R - \hat{R})^2.$$

Thus the derivative of the Lyapunov function can be computed along the solution of the system of equations (4.7) considering no disease is transmitted from bats and pigs are given by

$$\begin{aligned} V'(t) &= \frac{\beta_I}{\delta}(N - \hat{N})N' + \left(1 - \tfrac{\hat{I}}{I}\right) I' + \tfrac{\beta_I}{\gamma}(R - \hat{R})R' \\ &= \frac{\beta_I}{\delta}(N - \hat{N})(\mu\hat{N} + \delta\hat{I} - \mu N - \delta I) \\ &\quad + \left(1 - \tfrac{\hat{I}}{I}\right)(\beta_I I(N - I - R) - \beta_I I(\hat{N} - \hat{I} - \hat{R})) \\ &\quad - \frac{\beta_I}{\gamma}(R - \hat{R})(\gamma I - \gamma\hat{I} + (\mu + \theta)\hat{R} - (\mu + \theta)R), \\ &= \frac{\beta_I}{\delta}(N - \hat{N})\big[-\mu(N - \hat{N}) - \delta(I - \hat{I})\big] + \beta_I(I - \hat{I})(N - \hat{N} - I + \hat{I} - R + \hat{R}) \\ &\quad + \frac{\beta_I}{\gamma}(R - \hat{R})\big[\gamma(I - \hat{I}) - (\mu + \theta)(R - \hat{R})\big] \\ &\leq -\beta_I(N - \hat{N})(I - \hat{I}) + \beta_I(I - \hat{I})(N - \hat{N}) - \beta_I(I - \hat{I})(R - \hat{R}) \\ &\quad + \beta_I(R - \hat{R})(I - \hat{I}) \\ &= 0. \end{aligned}$$

Furthermore, the equality $V'(t) = 0$ holds only if $N = \hat{N}$, $I = \hat{I}$, and $R = \hat{R}$. Thus, the endemic equilibrium $\hat{E}$, is the only positive invariant set to the system (4.7) contained entirely in $\Gamma := \{(S(t), I(t), R(t), S_p(t), I_p(t), R_p(t), S_b(t), I_b(t), R_b(t)) \in \mathbb{R}^9_+\}$. Therefore, it follows from the Lyapunov method that, since endemic equilibrium for the equivalent system is stable, hence the positive endemic equilibrium for the original system is globally asymptotically stable if $\mathcal{R}_0^1 > 1$. □

Theorem 8. *The equilibrium* $\tilde{E} := \big(\tilde{S}, \tilde{I}, \tilde{R}, \tilde{S}_p, \tilde{I}_p, \tilde{R}_p, \tilde{S}_b, 0, \tilde{R}_b\big)$*, where the disease is endemic among humans and pigs, is globally asymptotically stable in*

$$\Gamma := \{(S(t), I(t), R(t), S_p(t), I_p(t), R_p(t), S_b(t), I_b(t), R_b(t)) \in \mathbb{R}^9_+\}$$

if $\mathcal{R}_0^2 > 1$ *and* $\mathcal{R}_0^3 < 1$.

Proof. In case $\mathcal{R}_0^3 < 1$, there is no disease among bats, then only pig-to-pig, pig-to-human and human-to-human infection occurs. Without bat-to-pig infection, we can first decouple the equations for the pigs from the remaining equations. Similarly to the previous theorem, by letting $N_p(t) = S_p(t) + I_p(t) + R_p(t)$ we may consider an equivalent system for the pigs given as

$$\begin{aligned} N_p'(t) &= \Lambda_p - \mu_p N_p(t) - \delta_p I_p(t), \\ I_p'(t) &= \beta_p I_p(t)(N_p(t) - I_p(t) - R_p(t)) - (\mu_p + \delta_p + \gamma_p) I_p(t), \\ R_p'(t) &= \gamma_p I_p(t) - (\mu_p + \theta_p) R_p(t). \end{aligned} \tag{4.9}$$

We can observe that subsystem (4.9) has the same structure as system (4.8). Following the procedure of Theorem 8 we can show that $(\tilde{S}_p, \tilde{I}_p, \tilde{R}_p)$ is a globally asymptotically stable fixed point of (4.9). Let us now substitute the limiting value $\tilde{I}_p$ of $I_p(t)$ into the human subsystem to obtain

$$\begin{aligned} S'(t) &= \Lambda - \beta_I S(t) I(t) - \beta_{ph} \tilde{I}_p S(t) - \mu S(t) + \theta R(t), \\ I'(t) &= \beta_I S(t) I(t) + \beta_{ph} S(t) I_p(t) + \beta_{bh} S(t) I_b(t) - (\mu + \delta + \gamma) I(t), \\ R'(t) &= \gamma I(t) - (\mu + \theta) R(t). \end{aligned}$$

We note that this system is now different from the reduced pig system and from the reduced human subsystem studied in the previous theorem. Namely, a new type of movement appears from the S compartment to the I compartment, which is given as $S(t)$ multiplied by a constant. By introducing again $N(t) = S(t) + I(t) + R(t)$, we get the equivalent system

$$\begin{aligned} N'(t) &= \Lambda - \mu N(t) - \delta I(t), \\ I'(t) &= (\beta_I I(t) + \beta_{ph} \tilde{I}_p)(N(t) - I(t) - R(t)) - (\mu + \delta + \gamma) I(t), \\ R'(t) &= \gamma I(t) - (\mu + \theta) R(t). \end{aligned} \tag{4.10}$$

We define the Lyapunov function $W(t)$ as

$$W(t) = \frac{1}{2\delta}(N - \tilde{N})^2 + \int_{\tilde{I}}^{I} \frac{u - \tilde{I}}{\beta_I u + \beta_{ph}\tilde{I}_p}\, du + \frac{1}{2\gamma}(R - \tilde{R})^2.$$

The derivative of the Lyapunov function along solutions of system (4.10) is given by

$$\begin{aligned}
W'(t) &= \frac{1}{\delta}(N - \tilde{N})N' + \frac{I - \tilde{I}}{\beta_I I + \beta_{ph}\tilde{I}_p} I' + \frac{1}{\gamma}(R - \tilde{R})R' \\
&= \frac{1}{\delta}(N - \tilde{N})(\mu\tilde{N} + \delta\tilde{I} - \mu N - \delta I) \\
&\quad + (I - \tilde{I})\Bigg[(N - \tilde{N}) - (I - \tilde{I}) - (R - \tilde{R}) \\
&\qquad\qquad - (\mu + \delta + \gamma)\left(\frac{I}{\beta_I I + \beta_{ph}\tilde{I}_p} - \frac{\tilde{I}}{\beta_I \tilde{I} + \beta_{ph}\tilde{I}_p}\right)\Bigg] \\
&\quad + \frac{1}{\gamma}(R - \tilde{R})(\gamma I - \gamma\tilde{I} + (\mu + \theta)\tilde{R} - (\mu + \theta)R) \\
&= \frac{1}{\delta}(N - \tilde{N})\left[-\mu(N - \tilde{N}) - \delta(I - \tilde{I})\right] + (I - \tilde{I})(N - \tilde{N}) - (I - \tilde{I})^2 \\
&\quad - (I - \tilde{I})(R - \tilde{R}) - (I - \tilde{I})\left(\frac{I}{\beta_I I + \beta_{ph}\tilde{I}_p} - \frac{\tilde{I}}{\beta_I \tilde{I} + \beta_{ph}\tilde{I}_p}\right) \\
&\quad + \frac{1}{\gamma}(R - \tilde{R})\left[(\gamma(I - \tilde{I}) - (\mu + \theta)(R - \tilde{R})\right] \\
&\leq - (N - \tilde{N})(I - \tilde{I}) + (I - \tilde{I})(N - \tilde{N}) - (I - \tilde{I})(R - \tilde{R}) \\
&\quad - (I - \tilde{I})\left(\frac{I}{\beta_I I + \beta_{ph}\tilde{I}_p} - \frac{\tilde{I}}{\beta_I \tilde{I} + \beta_{ph}\tilde{I}_p}\right) + (R - \tilde{R})(I - \tilde{I}).
\end{aligned}$$

So $W'(t) \leq 0$ since the function $\frac{I}{\beta_I I + \beta_{ph}\tilde{I}_p}$ is continuous and monotonically increasing in I. i.e. $W(t) < 0$. Furthermore, the equality $W'(t) = 0$ holds only if $N = \tilde{N}, I = \tilde{I}$, and $R = \tilde{R}$. i.e. $W(t) = 0$ Thus, the endemic equilibrium $\tilde{E}$ is the only positive invariant set to the system contained entirely in $\Gamma := \{(S(t), I(t), R(t), S_p(t), I_p(t), R_p(t), S_b(t), I_b(t), R_b(t)) \in \mathbb{R}^9_+\}$. Therefore, it follows from the direct Lyapunov method that, since endemic equilibrium for the equivalent system is stable, hence the endemic equilibrium $\tilde{E}$ of the original system is globally asymptotically stable if $\mathcal{R}_0^2 > 1$ and $\mathcal{R}_0^3 < 1$. □

Theorem 9. *The endemic equilibrium* $E^* := \left(S^*, I^*, R^*, S_p^*, I_p^*, R_p^*, S_b^*, I_b^*, R_b^*\right)$ *is globally asymptotically stable if* $\mathcal{R}_0^3 > 1$.

Proof. Let us now assume that the disease is endemic among bats and pigs, then NiV transmission occurs from both these two species. The subsystem (4.3c) for bats can

be decoupled from the rest of the equations. Similarly to the previous theorems, we consider an equivalent system of (4.3c) by letting $N_b(t) = S_b(t) + I_b(t) + R_b(t)$. Then we get a system for bats that has the same structure as (4.8). Following Theorem 7, it can be shown that the endemic equilibrium (S_b^*, I_b^*, R_b^*) is a globally asymptotically stable equilibrium of the subsystem for bats. Substituting I_b^* into the subsystem (4.3b) for pigs we get a similar subsystem in Theorem 7. Following Theorem 7 we conclude that the endemic equilibrium E^* is globally asymptotically stable if $\mathcal{R}_0^3 > 1$. □

The results concerning the existence and stability of the equilibria are summarized in Table 4.2.

Table 4.2: *Existence and stability properties of equilibria. E_0 denotes disease-free equilibrium, $\hat{E}$ denotes equilibrium where the disease is only endemic among humans, $\tilde{E}$ denotes equilibrium where the disease is only endemic among humans and pigs, E^* denotes equilibrium where the disease is endemic among humans, pigs, and bats.*

Reproduction numbers	E_0	$\hat{E}$	$\tilde{E}$	E^*
$\mathcal{R}_0^1 < 1, \mathcal{R}_0^2 < 1, \mathcal{R}_0^3 < 1$	GAS	-	-	-
$\mathcal{R}_0^1 > 1, \mathcal{R}_0^2 < 1, \mathcal{R}_0^3 < 1$	unstable	GAS	-	-
$\mathcal{R}_0^2 > 1, \mathcal{R}_0^3 < 1$	unstable	unstable	GAS	-
$\mathcal{R}_0^3 > 1$	unstable	unstable	unstable	GAS

4.5 Numerical simulations

In this section, we perform numerical simulations to validate our model and assess the efficiency of various possible intervention strategies. It is important to note that due to the low number and relatively small volume of outbreaks so far, available data on parameters and epidemic spread are rather scarce, hence, it is a difficult task to find data or give precise estimations regarding model parameters. It is worth mentioning that all numerical simulations were performed using *Wolfram Mathematica*.

4.5.1 Fitting to data from the 1998–99 outbreak in Malaysia

We start by fitting our model to real-world data. We have to note that due to the large number of parameters and to the uncertainty of several parameter values, we cannot expect to obtain a single parameter set perfectly fitting the epidemic data. Our aim can rather be only to approximate reasonably well the real scenario and

obtain parameter ranges such that the real parameter values fall into these ranges with a high probability. As an example, we chose the outbreak in early 1999 in the Malaysian state Negeri Sembilan [65]. In fact, the outbreak in Malaysia started in September 1998 and affected the three states Perak, Negeri Sembilan and Selangor inducing 265 cases of acute encephalitis with 105 deaths. However, as most cases occurred in the spring 1999 in Negeri Sembilan, we only consider this period of the outbreak. An interesting characteristic of the epidemic was that the Muslim majority was not affected by the disease as it was mainly transmitted to humans by pigs, hence, we restrict our simulations to the Chinese minority [101, 116].

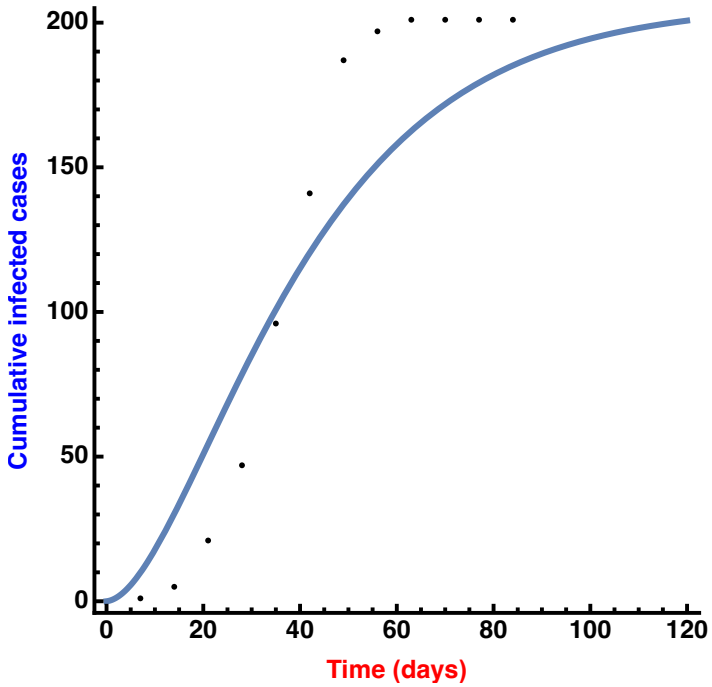


Figure 4.3: *The best fitting solution plotted with 12 weeks data for Negeri Sembilan state, Malaysia started from February 3, 1999*

We use Latin Hypercube Sampling to create a representative sample of parameter values and start a solution of model (4.1) with each of these 10,000 parameter sets. Then we use the least squares method to find the parameter values offering the best fit to real data regarding the cumulative number of infected. Figure 4.3 shows the best fitting solution plotted along with epidemic data.

4.5.2 Sensitivity analysis

We have conducted another analysis using the Latin Hypercube Sampling along with the Partial Rank Correlation Coefficient (PRCC) method with $10,000$ Monte Carlo

simulations per run. Using the variation of parameter values, the PRCC method assists us to quantify the effect of changing the various parameter values on the model's feedback, hence, establish statistical relationships between the input parameters and the outcome value. Note that increasing parameters with positive PRCC values results in the growth of the number of cumulative cases, increasing parameters with negative PRCC will result in a smaller number of cumulative cases. Furthermore, parameters with larger PRCC values are regarded to be most critical for the model.

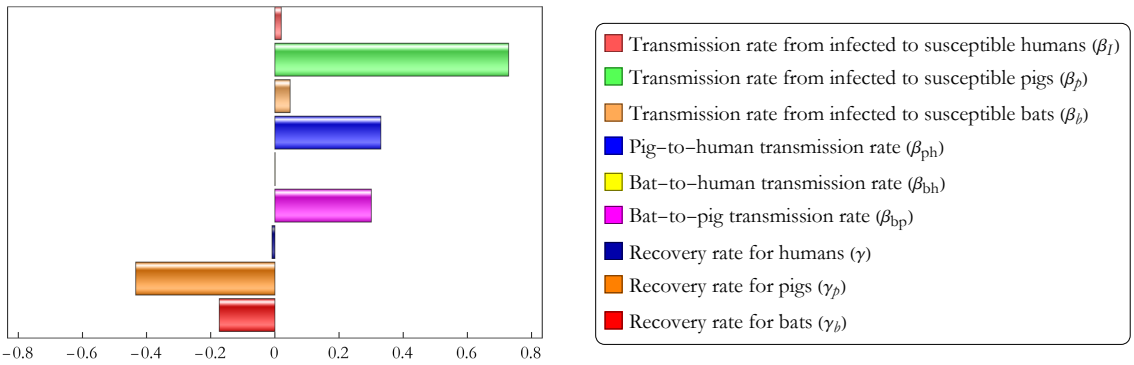


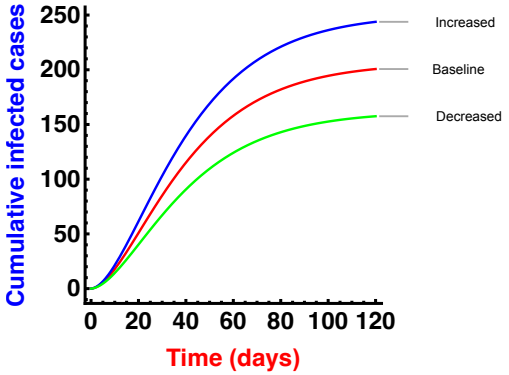
Figure 4.4: *Partial Rank Correlation Coefficients (PRCC).*

The input parameters considered for our PRCC analysis included all transmission rates ($\beta_I, \beta_p, \beta_b, \beta_{ph}, \beta_{bh}, \beta_{bp}$) and recovery rates ($\gamma, \gamma_p, \gamma_b$) while the output parameter was chosen as the cumulative number of infected until the end of the time period under consideration in the fitting. The results obtained and shown in Figure 4.4 demonstrate that the parameters with the largest effect are transmission from infected pigs to susceptible pigs β_p, pigs-to-humans transmission rate β_{ph}, bats-to-pigs transmission rate β_{bp} and recovery rates for pigs γ_p. Hence, parameters related to the intermediate host of NiV, i.e. pigs are seen to be the most important parameters among those that might be subject to control measures.

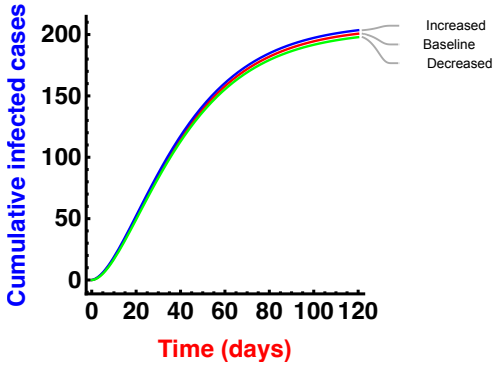
4.5.3 Effect of possible control measures

The PRCC analysis described in the previous section indicates which might be the most efficient tool to reduce the number of infected. In this subsection, we investigate numerically the extent of changes in the number of cases caused by modifying model parameters corresponding to various intervention measures. In Figure 4.5 we plot the cumulative number of infected humans for three different values of selected parameters, while the rest of the parameters are the values obtained in the fitting and shown in Table 4.3. Figure 4.5a suggests that decreasing transmission from pigs to humans may contribute significantly to a decrease in the number of human infections. On the other hand, Figures 4.5b and 4.5c suggest that transmission from

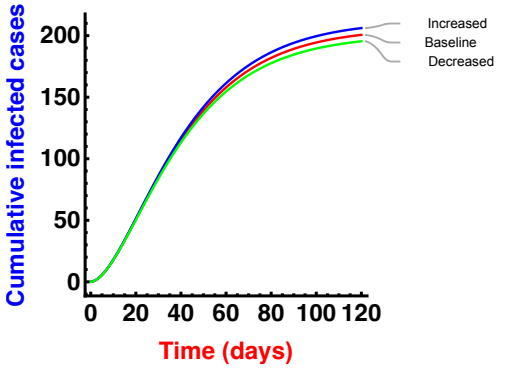
bats and transmission among humans has a smaller importance than transmission from pigs. Finally, Figure 4.5d shows that increasing the pigs' death rate by introducing their culling should also be an efficient tool to prevent further infections among humans.



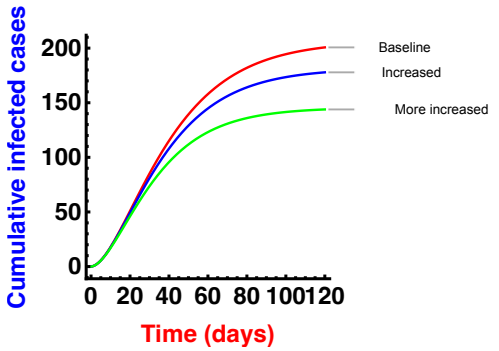
(a) *Number of infected cases for various values of* β_{ph}. *Baseline* $= 4.52495 \times 10^{-6}$, *Increased* $= 5.52495 \times 10^{-6}$, *Decreased* $= 3.52495 \times 10^{-6}$.



(b) *Number of infected cases for various values of* β_{bh}. *Baseline* $= 3.775596 \times 10^{-7}$, *Increased* $= 5.775596 \times 10^{-7}$, *Decreased* $= 1.775596 \times 10^{-7}$



(c) *Number of infected cases for various values of* β_I. *Baseline* $= 1.3989714 \times 10^{-8}$, *Increased* $= 2.3989714 \times 10^{-8}$, *Decreased* $= 0.3989714 \times 10^{-8}$



(d) *Number of infected cases for various values of* μ_p. *Baseline* $= 0.002747$, *Increased* $= 0.005556$, *More increased* $= 0.011111$

Figure 4.5: *Cumulative infected cases for various values of disease parameters.*

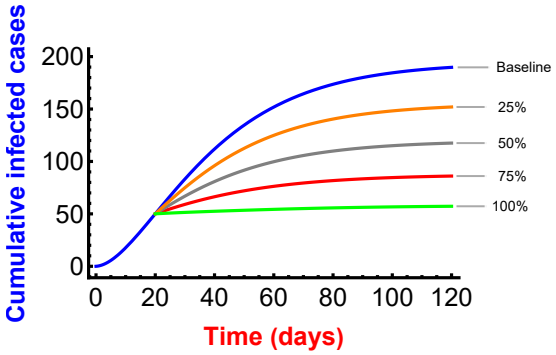
It is important to emphasize, that these results confirming the important role of pigs in disease transmission are not only in accordance with the results of the PRCC analysis but also with observations. Several studies confirm that the primary reason for human Nipah infection during 1998–1999 in Malaysia was the close contact with pigs, especially sick pigs though there might have been secondary exposures by other infected animals, see e.g. [8, 18, 73]. It is noteworthy that the outbreak in Malaysia

was controlled by the culling of more than 1 million pigs in the outbreak area and immediately surrounding areas [69, 92].

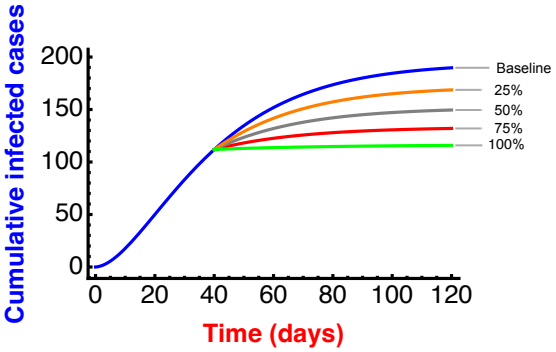
For this reason, we studied the impact of decreasing the number of pigs by culling at different rates (see Figure 4.6. Culling was assumed here to be instantaneous. For this, we have continued our simulation for a given time period (in Figure 4.6a 20 days, in Figure 4.6b 40 days, in Figure 4.6c 60 days from the beginning of the epidemic) and then imposed different rates of culling to see the degree of changes of cumulative infection. Figure 4.6 suggests that culling has a notable influence on reducing disease burden. Figure 4.6 also shows the importance of timely interventions. The effects of interventions in an early period of the epidemic are much more significant than those of control measures introduced later. E.g., a complete culling of pigs may decrease the number of infected by approximately to its quarter if done after 20 days, to its half if done after 40 days, and to three quarters after 60 days. In the latter case, there is only a small difference in the results obtained by culling different fractions of the pig population, while if the interventions are introduced earlier, higher culling rates provide significantly better results in decreasing the cumulative number of infected.

Table 4.3: *Parameters for model* (4.1) *providing the best fit.*

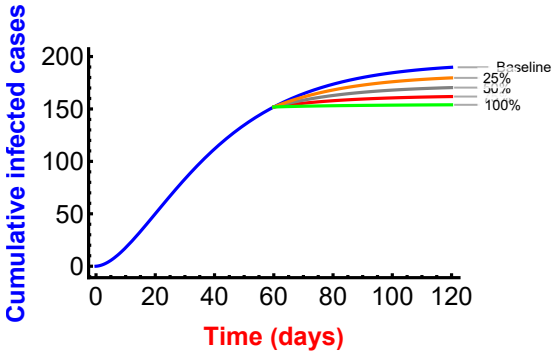
Parameter	Baseline (Range)	Unit	Source
Λ	6.69852	day^{-1}	[117]
Λ_b	0.411	day^{-1}	Assumed
Λ_p	300.3	day^{-1}	[92]
μ	0.0000379	day^{-1}	[117]
μ_b	0.00013699	day^{-1}	Assumed
μ_p	0.002747	day^{-1}	[118]
β_I	$1.39897 \times 10^{-8} (2.0 \times 10^{-9}, 1.0 \times 10^{-7})$	day^{-1}	[107]
β_p	1.20377×10^{-7} $(0.0000000671, 0.000001857)$	day^{-1}	Fitted
β_b	$0.0.0000155344$ $(0.00000671, 0.00001857)$	day^{-1}	[84]
β_{ph}	4.52495×10^{-6} $(2.0 \times 10^{-7}, 2.0 \times 10^{-5})$	day^{-1}	Fitted
β_{bh}	3.7756×10^{-7} $(1.0 \times 10^{-8}, 1.0 \times 10^{-6})$	day^{-1}	Fitted
β_{bp}	1.67739×10^{-6} $(1.0 \times 10^{-7}, 1.0 \times 10^{-5})$	day^{-1}	Fitted
θ	0.00153737 $(0.033, 0.001)$	day^{-1}	Fitted
θ_p	0.000651486 (0.001, 0.00033)	day^{-1}	Fitted
θ_b	0.000444376 (0.001, 0.00033)	day^{-1}	[84]
γ	0.0225626 $(0.015625, 0.03125)$	day^{-1}	[4]
γ_p	0.0692084 $(0.01, 0.1)$	day^{-1}	[13]
γ_b	0.0750248 $(0.01, 0.1)$	day^{-1}	Fitted
δ	0.0436999 $(0.015625, 0.046875)$	day^{-1}	[13]
δ_p	0.000374955 $(0.0001, 0.001)$	day^{-1}	[119]
δ_b	0.000622043 $(0.0001, 0.001)$	day^{-1}	Fitted



(a) *Culling at day 20 of the epidemic.*



(b) *Culling at day 40 of the epidemic.*



(c) *Culling at day 60 of the epidemic.*

Figure 4.6: *Number of cumulative infected cases for various culling rates of pigs and different time of culling.*

4.6 Discussion

In this work, we established a compartmental model to describe the spread of Nipah virus infection, considering the role of the reservoir species fruit bats and the intermediate host pigs as well as loss of immunity of recovered individuals, assuming that intraspecies transmission is only one-directional, from bats to pigs and humans and from pigs to humans. The latter property allowed us to decouple first the equations for bats, then those for pigs, to arrive at a limit equation for humans. Both the limit subsystem for pigs and the one for humans yield us a novel type of model with a linear term describing the movement from susceptibles to infected due to intraspecies transmission.

We determined all possible equilibria of the system and calculated three threshold parameters which determine the global dynamics of the system by determining in which of the three species the disease becomes endemic. By providing appropriate Lyapunov functions, we were able to completely describe the global dynamics of our model. We note that the novel structure of the limit systems mentioned in the previous paragraph demanded the construction of a novel Lyapunov function.

We also performed numerical studies to validate our model, to determine the key parameters regarding disease transmission, and to study the effect of possible intervention measures. Our results suggest that the most important parameters are those related to the intermediate host pigs, which is in accordance with observations during 1998–99 Malaysian outbreak.

Our study certainly has its limitations. For technical reasons, we chose to include only three compartments for each of the three species. A more realistic description of the disease would include an exposed compartment. Temperature, humidity, and climatic conditions may impact Nipah virus survival and transmission. Higher temperatures and increased rainfall can potentially boost virus dissemination, leading to elevated infection rates. Consideration of these environmental parameters might be an element of future studies. The numerical study of the model is made difficult by the limited knowledge of various disease parameters. The study of an extended system and its application to more fully known data might be the subject of a future work.

Chapter 5

Global stability in an SIRS model with zoonotic transmission, nonlinear incidence rate and temporary immunity

We establish and study an $SIRS$ epidemic model for a zoonotic disease with a general nonlinear incidence rate assuming that the animal population has already reached an endemic equilibrium. Due to the zoonotic transmission, there is no disease-free equilibrium and no threshold dynamics can be observed. Using a transformation of variables, we derive a Lyapunov function for the global asymptotic stability of the unique endemic equilibrium.

5.1 Introduction

Zoonotic spillover is the transmission of pathogens from vertebrate animals to humans [120, 121]. The risk of spillover events is related to the interaction of humans with different animal species and pathogens they host, including handling, poaching, and consumption of meat from wild animals [122]. In recent times, there has been an increase in the occurrence rate of novel zoonotic illnesses. Approximately, 60% of known and 75% of emerging human infectious diseases can be spread from animals [123]. Some of the most important zoonotic diseases include Ebola virus disease, many strains of bird flu and swine flu, COVID-19, West Nile fever, Lassa fever, and Nipah fever. Transmission might occur via direct or indirect contact, contaminated food, or vectors. In most of the mathematical models for zoonotic diseases, animals are included by considering analogous compartments as for humans. Our aim is to establish a simple, but general model for zoonotic diseases, incorporating many char-

acteristics of them and assuming that the animal population has already reached an endemic equilibrium, making it possible to only consider human compartments establishing a novel type of model. To formulate and study the proposed model, we are motivated by the recent works [114, 115, 124], where SIR and $SIRS$ type models were introduced with a general nonlinear incidence function.

J. Li et al. [115] introduced a new technique for showing the global asymptotic stability of the endemic equilibrium by introducing a variable transformation and constructing a more general Lyapunov function. A similar method was applied by T. Li et al. [124] for a model with transfer from the infectious to the susceptible class and later by Chen et al. [114] incorporating temporary immunity and relapse. Motivated by these models we derived the Lyapunov function in our model for nonlinear incidence with zoonotic spillover and temporary immunity.

5.2 Model formulation

A simple $SIRS$ model for a zoonotic disease can be established as

$$\begin{aligned} S'(t) &= \Lambda - f(I)S(t) - f_z(I_a(t))S(t) - \mu S(t) + \theta R(t), \\ I'(t) &= f(I)S(t) + f_z(I_a(t))S(t) - (\mu + \delta + \gamma)I(t), \\ R'(t) &= \gamma I(t) - (\mu + \theta)R(t), \end{aligned} \tag{5.1a}$$

$$\begin{aligned} S_a'(t) &= \Lambda_a - f_a(I_a(t))S_a(t) - \mu_a S_a(t) + \theta_a R_a(t), \\ I_a'(t) &= f_a(I_a(t))S_a(t) - (\mu_a + \delta_a + \gamma_a)I_a(t), \\ R_a'(t) &= \gamma_a I_a(t) - (\mu_a + \theta_a)R_a(t), \end{aligned} \tag{5.1b}$$

where S stands for susceptible, I for infected, R for recovered humans. Human-to-human transmission is described by a nonlinear incidence function f and zoonotic transmission by f_z. Human birth and death rates are denoted by Λ and μ respectively. There is also a disease-induced death rate, denoted by δ. Infected humans are transferred to the recovered compartment at the rate γ and θ is the rate of loss of temporary immunity acquired by recovered individuals. Compartments and parameters of the animal subsystem are introduced in an analogous way, with a lower index a. Note that in this work we assume that the disease is only transmitted from animals to humans but not the opposite way as unlike e.g. arthropod-borne diseases, it is typical that animal-to-human transmission occurs via droppings of infected animals or eating fruits contaminated by them, hence, transmission in the other direction does not happen. This way, the animal subsystem (5.1b) can be decoupled from the human subsystem (5.1a). It follows from [114, Theorem 3] that depending on the basic reproduction number, either the disease-free or the unique endemic equilibrium (S_a^*, I_a^*, R_a^*) of the animal subsystem is globally asymptotically stable. In the

present work, we assume that the disease is endemic among animals, hence, all solutions with positive initial conditions tend to the endemic equilibrium. Moreover, we can make the assumption that the animal population has already reached this equilibrium. This way, by substituting the limit value I_a^* of infected animals into the human subsystem (5.1a) and introducing the parameter $\xi := f_z(I_a^*)$, we may rewrite the human subsystem (5.1a) as

$$\begin{aligned} S'(t) &= \Lambda - f(I)S(t) - \xi S(t) - \mu S(t) + \theta R(t), \\ I'(t) &= f(I)S(t) + \xi S(t) - (\mu + \delta + \gamma)I(t), \\ R'(t) &= \gamma I(t) - (\mu + \theta)R(t), \end{aligned} \tag{5.2}$$

with nonnegative initial conditions. Note that the above system differs from the general compartmental epidemiological models for the term $\xi S(t)$ in the first two equations. Such a term is corresponding to direct transmission from susceptibles to infected does not appear in usual models.

5.3 Basic properties and existence of an endemic equilibrium

The following lemma concerning the nonnegativity and boundedness of solutions of (5.2) can easily be shown.

Lemma 10. *All solutions of model 5.2 with nonnegative initial conditions have a positive invariant solution in the region* $\Omega = \{S, I, R \in \mathbb{R}^3_+ : 0 < N \leq \Lambda/\mu\}$.

Proof. It can easily be proved that all solutions started from nonnegative initial conditions remain nonnegative for all time $t > 0$. For the total human population $N(t) = S(t) + I(t) + R(t)$ we have $N'(t) = S'(t) + I'(t) + R'(t) = \Lambda - \mu N(t) - \delta I(t)$. Clearly $N'(t) \leq \Lambda - \mu N(t)$. If the initial value of the total population $N(0) = N_0$, then it follows that $N(t) \leq \frac{\Lambda}{\mu} - \left(\frac{\Lambda}{\mu} - N_0\right)e^{-\mu t}$, hence, $N(t) \leq \frac{\Lambda}{\mu}$ for $t > 0$. This means that the region Ω is positively invariant and it attracts all solutions of the equations of the system. □

Due to the special formulation of the model including a direct transmission from susceptibles to infected corresponding to transmission from animals, unlike most epidemiological models, system (5.2) does not have a disease-free equilibrium. Accordingly, it is not possible to determine a basic reproduction number, and the threshold dynamics usually encountered in epidemiological systems cannot be observed either in the present case. Before we discuss the existence of endemic equilibria, we make some assumptions on the nonlinear incidence function $f(I)S$ following

[114, 115, 124]. The function f is assumed to be a locally Lipschitz function at least on $\mathbb{R}_+ = [0, \infty)$ satisfying

(H1) $f(0) = 0$ and $f(I) > 0$ for $I > 0$;

(H2) $\frac{f(I)}{I}$ is continuous and monotonically nonincreasing for $I > 0$.

Lemma 11. *Model* (5.2) *has a unique endemic equilibrium.*

Proof. To find an endemic equilibrium $E^*\big(S^*, I^*, R^*\big)$ of (5.2), we need to solve the algebraic system of equations given by

$$\begin{aligned} \Lambda - f(I^*)S^* - \xi S^* - \mu S^* + \theta R^* &= 0, \\ f(I^*)S^* + \xi S^* - (\mu + \delta + \gamma)I^* &= 0, \\ \gamma I^* - (\mu + \theta)R^* &= 0. \end{aligned} \tag{5.3}$$

From the last equation of (5.3), we have $R^* = \frac{\gamma I^*}{\mu+\theta}$ and adding the first two equations we get $\Lambda - \mu S^* + \theta R^* - (\mu + \delta + \gamma)I^* = 0$. Now using both of these expressions, we get $S^* = \frac{1}{\mu}\big(\Lambda - \frac{\mu^2+\delta\mu+\gamma\mu+\theta\mu+\delta\theta}{\mu+\theta} I^*\big)$, so S^* will be positive if and only if $I^* < \frac{\Lambda(\mu+\theta)}{\mu^2+\delta\mu+\gamma\mu+\theta\mu+\delta\theta}$. Substituting S^* into the second equation of (5.3) we obtain that for the endemic equilibrium E^*, I^* is a positive root of $\phi(I)$ on the interval $\big(0, \frac{\Lambda(\mu+\theta)}{\mu^2+\delta\mu+\gamma\mu+\theta\mu+\delta\theta}\big)$, where

$$\begin{aligned} \phi(I) &= \frac{f(I) + \xi}{\mu}\left(\Lambda - \frac{\mu^2 + \delta\mu + \gamma\mu + \theta\mu + \delta\theta}{\mu + \theta} I\right) - (\mu + \delta + \gamma)I \\ &= \frac{f(I)}{I}\frac{I}{\mu}\left(\Lambda - \frac{\mu^2 + \delta\mu + \gamma\mu + \theta\mu + \delta\theta}{\mu + \theta} I\right) + \frac{\xi}{\mu}\left(\Lambda - \frac{\mu^2 + \delta\mu + \gamma\mu + \theta\mu + \delta\theta}{\mu + \theta} I\right) \\ &\quad - (\mu + \delta + \gamma)I. \end{aligned}$$

Consider now the function $\bar{\phi}(I) = \frac{\phi(I)}{I}$ which clearly has the same positive zeros as ϕ. By assumption **(H2)**, $\bar{\phi}$ is nonincreasing in the interval $\big(0, \frac{\Lambda(\mu+\theta)}{\mu^2+\delta\mu+\gamma\mu+\theta\mu+\delta\theta}\big)$. So $\lim_{I\to 0^+} \bar{\phi}(I) = \frac{\Lambda\xi}{\mu} > 0$ and $\bar{\phi}\big(\frac{\Lambda(\mu+\theta)}{\mu^2+\delta\mu+\gamma\mu+\theta\mu+\delta\theta}\big) = -(\mu + \delta + \gamma)I < 0$. By the intermediate value theorem, we obtain that $\bar{\phi}$ has a unique positive root in the interval $\big(0, \frac{\Lambda(\mu+\theta)}{\mu^2+\delta\mu+\gamma\mu+\theta\mu+\delta\theta}\big)$. Hence, (5.2) has a unique endemic equilibrium. □

5.4 Global asymptotic stability of the endemic equilibrium

Theorem 12. *The endemic equilibrium E^* is a globally asymptotically stable equilibrium of* (5.2).

Proof. For the convenience of constructing a Lyapunov function consider an equivalent system of (5.2) by letting $N(t) = S(t) + I(t) + R(t)$. Then we can write

$$\begin{aligned} N'(t) &= \Lambda - \mu N(t) - \delta I(t), \\ I'(t) &= (f(I)+\xi)(N(t)-I(t)-R(t)) - (\mu+\delta+\gamma)I(t), \\ R'(t) &= \gamma I(t) - (\mu+\theta)R(t), \end{aligned} \tag{5.4}$$

and the endemic equilibrium $E^* := \left(S^*, I^*, R^*\right)$ for the system (5.2) gives the endemic equilibrium of (5.4) where $N^* = S^* + I^* + R^*$. Moreover, N^*, I^*, and R^* satisfy the following equations,

$$\begin{aligned} \Lambda - \mu N^* - \delta I^* &= 0, \\ (N^* - I^* - R^*) - (\mu+\delta+\gamma)\frac{I^*}{f(I^*)+\xi} &= 0. \\ \gamma I^* - (\mu+\theta)R^* &= 0. \end{aligned} \tag{5.5}$$

Using (5.4) and (5.5) we can write

$$\begin{aligned} N'(t) &= -\mu(N-N^*) - \delta(I-I^*), \\ I'(t) &= (f(I)+\xi)\left[(N-N^*) - (I-I^*) - (R-R^*) - (\mu+\delta+\gamma)\left(\tfrac{I}{f(I)+\xi} - \tfrac{I^*}{f(I^*)+\xi}\right)\right], \\ R'(t) &= \gamma(I-I^*) - (\mu+\theta)(R-R^*). \end{aligned} \tag{5.6}$$

We define the Lyapunov function $V(t)$ for the system (5.6)as

$$V(t) = \frac{1}{2\delta}(N-N^*)^2 + \int_{I^*}^{I} \frac{u-I^*}{f(u)+\xi}\,\mathrm{d}\,u + \frac{1}{2\gamma}(R-R^*)^2.$$

The derivative of the Lyapunov function $V(t)$ along trajectories of (5.6) can be computed as

$$\begin{aligned} V'(t) &= \tfrac{1}{\delta}(N-N^*)N' + \tfrac{I-I^*}{f(I)+\xi}I' + \tfrac{1}{\gamma}(R-R^*)R' \\ &= \tfrac{1}{\delta}(N-N^*)(-\mu(N-N^*) - \delta(I-I^*)) \\ &\quad + (I-I^*)\left[(N-N^*) - (I-I^*) - (R-R^*) - (\mu+\delta+\gamma)\left(\tfrac{I}{f(I)+\xi} - \tfrac{I^*}{f(I^*)+\xi}\right)\right] \\ &\quad + \tfrac{1}{\gamma}(R-R^*)\left(\gamma(I-I^*) - (\mu+\theta)(R-R^*)\right) \\ &\leq -(N-N^*)(I-I^*) + (N-N^*)(I-I^*) - (I-I^*)(R-R^*) \\ &\quad - (\mu+\delta+\gamma)(I-I^*)\left(\tfrac{I}{f(I)+\xi} - \tfrac{I^*}{f(I^*)+\xi}\right) + (I-I^*)(R-R^*) \\ &= -(\mu+\delta+\gamma)\tfrac{(I^*)^2}{f(I^*)+\xi}\left(\tfrac{I}{I^*}-1\right)\left[\tfrac{I(f(I^*)+\xi)}{I^*(f(I)+\xi)} - 1\right]. \end{aligned}$$

So $V'(t) \leq 0$ since the nonlinear incidence function $f(I)$ is continuous and monoton-

ically increasing. Furthermore, the equality $V'(t) = 0$ holds only if $N = N^*, I = I^*$, and $R = R^*$. Therefore, it follows from the direct Lyapunov method that, since the endemic equilibrium for the equivalent system (5.4) is globally asymptotically stable, hence the endemic equilibrium E^* is a globally asymptotically stable equilibrium of the original system (5.2). □

Theorem 12 shows that the endemicity of the disease among animals will result in the disease becoming endemic among humans as well in case of a zoonotic spillover.

5.5 Discussion

In this work, we have introduced a simple novel compartmental model for zoonotic disease. Assuming that the animal population is already in an endemic equilibrium state, we only consider zoonotic transmission as a linear term corresponding to the movement of susceptibles to the infectious class due to transmission from animals, instead of including the usual compartments for the animals as well. Apart from the zoonotic transmission, the model also includes waning immunity of recovered and we consider a general incidence rate. Our new model is related to the $SIRS$ type models studied in [114, 115, 124], however, the appearance of the new term corresponding to zoonotic transmission makes our new model different from those. Furthermore, the global dynamics is different from earlier works as due to the zoonotic transmission, no disease-free equilibrium exists and one cannot observe the usual threshold dynamics determined by the basic reproduction number. Motivated by the above works, we perform a transformation of variables which facilitates us to define a Lyapunov function. This enables us to prove that the unique endemic equilibrium of our model is globally asymptotically stable independently of the parameters. The model can be generalized in various directions, such as including more compartments, first of all, an exposed class, or assuming a periodic behavior of the animal population instead of being in an equilibrium. These ideas are left as a basis of future work.

Chapter 6

A compartmental model for the spread of Nipah virus in a periodic environment

Nipah virus (NiV) is a zoonotic virus that causes outbreaks of fatal disease in humans. Fruit bat also known as the flying fox is the animal host reservoir for NiV. It is known to cause illness in pigs which are considered an intermediate host. In this chapter, we propose a model for Nipah virus disease transmission taking into account all human-to-host animal transmission as well as the loss of immunity in those who have recovered. Furthermore, we take into consideration seasonal effects such as varying transmission rate from bats and birth rate of bats. We studied the existence and uniqueness of a disease-free ω-periodic solution and later deals with the basic reproduction number and stability analysis. To support the analytical results we provide some numerical examples and assess the effect of parameter changes on disease dynamics, which might help to understand how to avoid a yearly periodic recurrence of the disease.

6.1 Introduction

With about 60% of human infections originating from animals [125], zoonotic diseases pose one of the greatest health threats as shown by the recent outbreaks of e.g. Severe Acute Respiratory Syndrome coronavirus (SARS-CoV-2), Ebola virus, Middle East respiratory syndrome coronavirus (MERS-CoV). One of the most menacing emerging zoonotic diseases, Nipah virus disease is highly infectious and spreads in the community via infected animals, infected people or contaminated food and objects, causing severe neurological and respiratory disease with high mortality rates in some instances [53]. Nipah virus, whose animal host reservoir is the fruit bat also known as the flying fox, causes lethal encephalitis in humans and has recently been

reported from Malaysia, Bangladesh, Singapore, and India [5, 6, 20].

Since the outbreak, very few mathematical models are available for the studies of the Nipah virus disease. A basic SIR model with optimal control was presented by Biswas in [104]. A dynamic model of NiV infections with variable size population and two control strategies was formulated by [11]. Incorporating quarantine of infectious individuals, [12] analyzed an SEIR model where birth and death rates were assumed unequal. [105] presented a two-layered model for humans and bats. [106] presented a mathematical model of seven compartments, including virus dynamics, flying foxes, and humans. They considered that this disease has no recovered individuals. The role of deceased individuals who died from Nipah fever and considering no bat population a model was introduced by [107]. [126] concentrated on an optimal control study of some adjustable parameters for a coupled pig-human Nipah virus disease model. Recently, [110] proposed a numerical model of the Nipah virus (NiV) into focus on tracing the fractional order derivative's influence, considering transmission from dead bodies. Barua et al. [127] proposed a three-layered model where transmission from bats and pigs was also considered.

The above literature review demonstrates that despite the threat posed by Nipah virus disease, so far only little research has been done regarding its transmission. Furthermore, most of the models did not consider all important characteristics of the disease and several studies focused on optimal control problems rather than the dynamics of the proposed models. Another important aspect of transmission, which has not been considered in models for Nipah transmission is the periodicity of the environment. The only location where spillover events can be reliably seen annually is Bangladesh, where seasonal patterns of consuming raw date-palm-sap in the "Nipah belt" correlate with outbreak timing and distribution (November to April) [128]. Data from a six-year multidisciplinary research of bats reveal that one of the causes of outbreaks in Pteropus bats is driven by a gradual loss of immunity, culminating in periods of interepizootic activity lasting several years [84]. Furthermore, the bats' reproduction also shows periodicity as studies reported that the bats' mating season occurs from July to October and mothers give birth to one or two newborns from February to March [129].

Motivated by the above, in the present work we propose a model for Nipah virus disease transmission in a periodic environment in which all possible ways of transmission among humans, the reservoir species bats, and the intermediate host pigs are considered. A generalization of the basic reproduction number was defined by Bacaër and Guernaoui [130] as the spectral radius of an integral operator acting on the space of continuous periodic functions. The proof of the existence and stability of the disease-free ω-periodic solution and the periodic solution was first established by Wang and Zhao [47]. The persistence of a class of seasonally forced epidemiological models is investigated by Rebelo et al. [131]. The methods established in the above

papers have since been improved and applied to study the spread of many infectious diseases; see, e.g. [132, 133, 134, 135, 136, 137, 138]. Following them, we study the existence and uniqueness of a disease-free ω-periodic solution in Section 6.3, while Section 6.4 deals with the basic reproduction number and stability analysis. In Section 6.5, we provide some numerical examples to support the analytical results and to assess the effect of parameter changes on disease dynamics, which might help to understand how to avoid a periodic yearly recurrence of the disease. The paper is closed with a short discussion.

6.2 Model formulation

We develop a compartmental model considering all possible transmissions from animals to humans, animals to animals, and from humans to animals with periodicity.

Total human population $N(t)$ at time t is divided into susceptibles ($S(t)$), exposed ($E(t)$), infected ($I(t)$) and recovered $(R(t))$. Hence,

$$N(t) = S(t) + E(t) + I(t) + R(t).$$

The total population of pigs (intermediate host) $N_p(t)$ at time t is divided into susceptible (S_p), exposed ($E_p(t)$), infected ($I_p(t)$) and recovered $(R_p(t))$ individuals, so that

$$N_p(t) = S_p(t) + E_p(t) + I_p(t) + R_p(t).$$

Similarly the total bat population (animal host reservoir) $N_b(t)$ at time t is divided into susceptible (S_b), exposed ($E_b(t)$), infected ($I_b(t)$) and recovered $(R_b(t))$ individuals, such that

$$N_b(t) = S_b(t) + E_b(t) + I_b(t) + R_b(t).$$

We denote the birth and death rates of humans by Π and μ, respectively. There is also a disease-induced death rate, denoted by δ. The force of infection for humans to humans, pigs, and bats for NiV transmission is given by $\beta I, \beta_{hp} I, \beta_p I$ and $\beta_{hb} I$ respectively. Again force of infection for Niv transmission from pigs to humans, pigs, and bats is expressed here as $\beta_{ph} I_p, \beta_p I_p$ and $\beta_{pb} I_p$. Furthermore, the force of infection for Niv transmission from bats to humans, pigs, and bats is expressed here as $\beta_{bh}(t) I_b, \beta_b I_b$ and $\beta_{bp}(t) I_b$. Here the parameters are the effective contact rate of susceptible individuals, who become infected from either humans or animals who became NiV infected.

Here the average duration of the infectious period is $1/\gamma$ days, so infected individuals are transferred to the recovered compartment at the rate γ and θ is the rate of loss of temporary immunity acquired by recovered individuals, meaning that re-

covered individuals remain immune for $1/\theta$ days on average. We define all other parameters for pigs and bats and apply the subscript p and b respectively for them. Note that time-dependent parameters in this model are $\beta_{bh}(t), \beta_{bp}(t)$ and $\Pi_b(t)$.

The transmission diagram of our model is shown in Figure 6.1. A complete description of the model parameters is summarized in Table 6.1. With the above notations, our model takes the form

$$\begin{aligned}
\frac{dS}{dt} &= \Pi - \beta SI - \beta_{ph} SI_p - \beta_{bh}(t) SI_b - \mu S + \theta R, \\
\frac{dE}{dt} &= \beta SI + \beta_{ph} SI_p + \beta_{bh}(t) SI_b - \nu E - \mu E, \\
\frac{dI}{dt} &= \nu E - (\mu + \delta + \gamma) I, \\
\frac{dR}{dt} &= \gamma I - (\mu + \theta) R,
\end{aligned} \tag{6.1a}$$

$$\begin{aligned}
\frac{dS_p}{dt} &= \Pi_p - \beta_p S_p I_p - \beta_{hp} S_p I - \beta_{bp}(t) S_p I_b - \mu_p S_p + \theta_p R_p, \\
\frac{dE_p}{dt} &= \beta_p S_p I_p + \beta_{hp} S_p I + \beta_{bp}(t) S_p I_b - \nu_p E_p - \mu_p E_p, \\
\frac{dI_p}{dt} &= \nu_p E_p - (\mu_p + \delta_p + \gamma_p) I_p, \\
\frac{dR_p}{dt} &= \gamma_p I_p - (\mu_p + \theta_p) R_p,
\end{aligned} \tag{6.1b}$$

$$\begin{aligned}
\frac{dS_b}{dt} &= \Pi_b(t) - \beta_b S_b I_b - \beta_{hb} S_b I - \beta_{pb} S_b I_p - \mu_b S_b + \theta_b R_b, \\
\frac{dE_b}{dt} &= \beta_b S_b I_b + \beta_{hb} S_b I + \beta_{pb} S_b I_p - \nu_b E_b - \mu_b E_b, \\
\frac{dI_b}{dt} &= \nu_b E_b - (\mu_b + \delta_b + \gamma_b) I_b, \\
\frac{dR_b}{dt} &= \gamma_b I_b - (\mu_b + \theta_b) R_b.
\end{aligned} \tag{6.1c}$$

The following initial conditions are associated with the system (6.1), define

$$\phi = (S(0), E(0), I(0), R(0), S_p(0), E_p(0), I_p(0), R_p(0), S_b(0), E_b(0), I_b, R_b(0)),$$

where $S(0) > 0, E(0) \geq 0, I(0) \geq 0, R(0) \geq 0, S_p(0) > 0, E_p(0) \geq 0, I_p(0) \geq 0, R_p(0) \geq 0, S_b(0) > 0, E_b(0) \geq 0, I_b(0) \geq 0, R_b(0) \geq 0$.

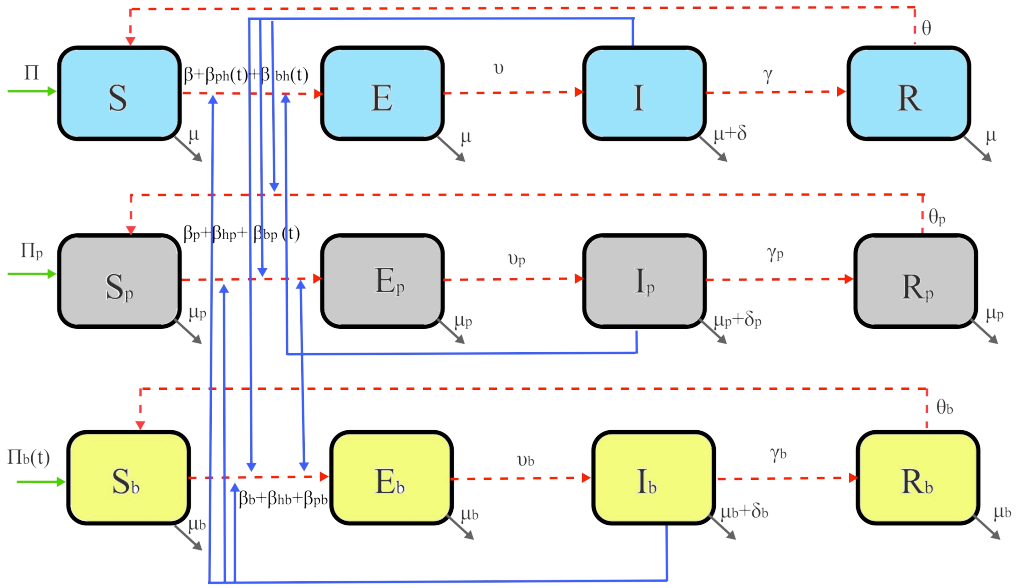


Figure 6.1: *Transmission diagram. Red dashed arrows indicate the transition from one compartment to another. Green arrows and gray indicate new entry and exit for death respectively. The blue arrow represents virus transmission. Light blue, gray, and yellow colored boxes depict compartments for humans, bats, and pigs respectively.*

6.3 The disease-free periodic solution

6.3.1 Existence and uniqueness of the disease-free ω-periodic solution

In this section, we will study the existence and uniqueness of the disease-free periodic solution of system (6.1). For this let us consider the subsystem (6.1a) for humans. For the total human population, we have the linear differential equation

$$N_h'(t) = \Pi - \mu N_h(t) - \delta I(t) \leq \Pi - \mu N_h(t). \tag{6.2}$$

Clearly, $N_h(t)$ is bounded and equation (6.2) has a unique, globally asymptotically stable equilibrium $N_h^* = \Pi/\mu$. Similarly one can prove that the pig subsystem (6.1b) has a unique, globally asymptotically stable equilibrium $N_p^* = \Pi_p/\mu_p$ and $N_p(t)$ is bounded.

Now let us consider the subsystem (6.1c) for bats. To find the disease-free periodic solution of this subsystem, we consider the equation for susceptible bats in case of

Table 6.1: *Description of parameters of model* (6.1).

Parameters	Description
Π	Recruitment rate for humans
$\Pi_b(t), \Pi_p$	Recruitment rate for bats, pigs
μ	Natural death rate of humans
μ_b, μ_p	Natural death rate of bats, pigs
δ	Disease-induced death rate for humans
δ_p, δ_b	Disease-induced death rate for pigs and bats respectively
γ	Recovery rate for humans
γ_p, γ_b	Recovery rate for pigs and bats respectively
β	Human-to-human transmission rate
β_{hp}	Human-to-pig transmission rate
β_{hb}	Human-to-bat transmission rate
β_p	Pig-to-pig transmission rate
β_{ph}	Pig-to-human transmission rate
β_{pb}	Pig-to-bat transmission rate
β_b	Bat-to-bat transmission rate
$\beta_{bh}(t)$	Bat-to-human transmission rate
$\beta_{bp}(t)$	Bat-to-pig transmission rate
$1/\theta$	Average length of immunity for humans
$1/\theta_p, 1/\theta_b$	Average length of immunity for pigs and bats respectively

no disease transmission in the form

$$S_b'(t) = \Pi_b(t) - \mu_b S_b(t), \tag{6.3}$$

with initial condition

$$S_b(0) = S_{b0} \coloneqq \frac{e^{-\mu_b \omega} \int_0^\omega e^{\mu_b \xi} \Pi_b(\xi) d\xi}{1 - e^{-\mu_b \omega}}.$$

For this initial value problem, we have

$$S_b^*(t) = e^{-\mu_b t} \left(S_{b0} + \int_0^t e^{\mu_b \xi} \Pi_b(\xi)\, d\xi \right) > 0,$$

which is globally attractive in $\mathbb{R}_+$. Thus system (6.1) has a unique disease-free periodic solution

$$E^* = (S_h^*, 0, 0, 0, S_p^*, 0, 0, 0, S_b^*(t), 0, 0, 0),$$

where $S_h^* = \Pi/\mu$ and $S_p^* = \Pi_p/\mu_p$.

To introduce the following result, we set $h^L = \sup_{t\in[0,\omega)} h(t)$ for a positive, continuous ω-periodic function $h(t)$.

Lemma 13. *There is* $N_b^* = \frac{\Pi_b^L}{\mu_b} > 0$ *such that each solution in* $\mathbb{R}_+^{12}$ *of* (6.1) *eventually enters*

$$G_{N^*} = \{(S, E, I, R, S_p, E_p, I_p, R_p, S_b, E_b, I_b, R_b) \in \mathbb{R}_+^{12} : \\ N_h \leq N_h^*, N_p \leq N_p^*, N_b \leq N_b^*\},$$

and for each $N_b(t) \geq N_b^*, G_{N^*}$ *is positively invariant for system* (6.1). *Also, we have*

$$\lim_{t \to +\infty} (N_b(t) - S_b^*(t)) = 0.$$

Proof. It can be easily seen from (6.1) that for the bat subsystem, we have

$$N_b'(t) = \Pi_b(t) - \mu_b N_b(t) - \delta_b I_b(t) \leq \Pi_b^L - \mu_b N_b(t) \leq 0, \text{ if } N_b(t) \geq N_b^*,$$

which implies that $G_{N^*}, N_b(t) \geq N_b^*$, is positively invariant and eventually, each forward orbit enters G_{N^*}. To finish the proof, define

$$y(t) = N_b(t) - S_b^*(t), \qquad t \geq 0.$$

Hence, we have $y'(t) = -\mu_b y(t)$ which implies $\lim_{t \to \infty} y(t) = 0$. Hence, the proof is complete. □

6.4 Basic reproduction number and stability analysis

6.4.1 Basic reproduction number

For the numerical approximation of the basic reproduction number in periodic environment let us recall the following theorem from Wang and Zhao [47].

Theorem 14 ([47, Theorem 2.1])**.** *The following statements are valid.*

(i) *If* $\rho(W(\omega, \lambda)) = 1$ *has a positive solution* λ_0*, then* λ_0 *is a eigenvalue of operetor* L*, and hence* $\mathcal{R}_0 > 0$.

(ii) *If* $\mathcal{R}_0 > 0$*, then* $\lambda_0 = \mathcal{R}_0$ *is a unique solution of* $\rho(W(\omega, \lambda)) = 1$.

(iii) $\mathcal{R}_0 = 0$ *if and only if* $\rho(W(\omega, \lambda)) < 1$ *for all* $\lambda > 0$.

Now we will follow the technique introduced by [47], we have the disease-free periodic equilibrium

$$E^* = \Big(\frac{\Pi}{\mu}, 0, 0, 0, \frac{\Pi_p}{\mu_p}, 0, 0, 0, S_b^*(t), 0, 0, 0\Big),$$

of system (6.1) for appropriate parameter values. We introduce the basic reproduction number $\mathcal{R}_0$ for system (6.1) with

$$\mathcal{F}(t,\mathcal{X}(t)) = \begin{bmatrix} \beta SI+\beta_{ph}SI_p+\beta_{bh}(t)SI_b \\ 0 \\ \beta_p S_b I_p+\beta_{hp}S_pI+\beta_{bp}(t)S_pI_b \\ 0 \\ \beta_b S_b I_b+\beta_{hb}S_bI+\beta_{pb}S_bI_p \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix},$$

and

$$\mathcal{V}^-(t,\mathcal{X}(t)) = \begin{bmatrix} (\nu+\mu)E \\ (\mu+\delta+\gamma)I \\ (\nu_p+\mu_p)E_p \\ (\mu_p+\delta_p+\gamma_p)I_p \\ (\nu_b+\mu_b)E_b \\ (\mu_b+\delta_b+\gamma_b)I_b \\ \beta SI+\beta_{ph}SI_p+\beta_{bh}(t)SI_b+\mu S \\ (\mu+\theta)R \\ \beta_p S_pI_p+\beta_{hp}S_pI+\beta_{bp}(t)S_pI_b+\mu_p S_p \\ (\mu_p+\theta_p)R_p \\ \beta_b S_bI_b+\beta_{hb}S_bI+\beta_{pb}S_bI_p+\mu_b S_b \\ (\mu_b+\theta_b)R_b \end{bmatrix}, \quad \mathcal{V}^+(t,\mathcal{X}(t)) = \begin{bmatrix} 0 \\ \nu E \\ 0 \\ \nu_p E_p \\ 0 \\ \nu_b E_b \\ \Pi+\theta R \\ \gamma I \\ \Pi_p+\theta_p R_p \\ \gamma_p I_p \\ \Pi_b(t)+\theta_b R_b \\ \gamma_b I_b \end{bmatrix},$$

where $\mathcal{X} = (E, I, E_p, I_p, E_b, I_b, S, R, S_p, R_p, S_b, R_b)^T$. Here E, I, E_p, I_p, E_b, I_b are the infected compartment and S, R, S_p, R_p, S_b, R_b are the uninfected compartment. Now let us check the conditions (A_1)–(A_5) from [47, p. 701]. System (6.1) is equivalent to

$$\mathcal{X}'(t) = \mathcal{F}(t,\mathcal{X}(t)) - \mathcal{V}(t,\mathcal{X}(t)) = f(t,\mathcal{X}(t)), \tag{6.4}$$

where $\mathcal{V}(t,\mathcal{X}(t)) = \mathcal{V}^-(t,\mathcal{X}(t)) - \mathcal{V}^+(t,\mathcal{X}(t))$. We also introduce here the matrix function $M(t) = (\frac{\partial f_i(t,\mathcal{X}^*(t))}{\partial \mathcal{X}_j})_{(7\le i,j\le 12)}$ where $f_i(t,\mathcal{X}(t))$ is the i-coordinate of $f(t,\mathcal{X}(t))$ and $\mathcal{X}_i$ is the i-th component of $\mathcal{X}$. The function $M(t)$ has the form

$$M(t) = \begin{bmatrix} -\mu & \theta & 0 & 0 & 0 & 0 \\ 0 & -\mu-\theta & 0 & 0 & 0 & 0 \\ 0 & 0 & -\mu_p & \theta_p & 0 & 0 \\ 0 & 0 & 0 & -\mu_p-\theta_p & 0 & 0 \\ 0 & 0 & 0 & 0 & -\mu_b & \theta_b \\ 0 & 0 & 0 & 0 & 0 & -\mu_b-\theta_b \end{bmatrix}. \tag{6.5}$$

We denote $\Phi_M(t)$ as the monodromy matrix of $\frac{dz}{dt} = M(t)z$ and we will use the notation $\rho(\Phi_M(t))$ for the spectral radius of $\Phi_M(\omega)$. Hence, $\rho(\Phi_M(t)) < 1$, which implies that $\mathcal{X}^*(t)$ is a linearly asymptotically stable solution in the disease-free subspace $\mathcal{X} = (0,0,0,0,0,0,0,0,0,S,S_p,S_b) \in R^{12}_+$. This implies that the condition $(A6)$ holds as well.

We introduce the 6×6 matrix functions $F(t)$,$V(t)$ given as $F(t) = \big(\frac{\partial \mathcal{F}_i(t,\mathcal{X}^*(t))}{\partial \mathcal{X}_j}\big)_{1\le i,j\le 6}$ and $V(t) = \big(\frac{\partial \mathcal{V}_i(t,\mathcal{X}^*(t))}{\partial \mathcal{X}_j}\big)_{1\le i,j\le 6}$ with $\mathcal{F}_i$ and $\mathcal{V}_i$ denoting the i-th coordinate of the vec-

tor function $\mathcal{F}$ and $\mathcal{V}$ respectively. The two vector functions can be calculated as

$$F(t) = \begin{bmatrix} 0 & \beta S^* & 0 & \beta_{ph} S^* & 0 & \beta_{bh}(t) S^* \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & \beta_{hp} S_p^* & 0 & \beta_p S_p^* & 0 & \beta_{bp}(t) S_p^* \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & \beta_{hb} S_b^*(t) & 0 & \beta_{pb} S_b^*(t) & 0 & \beta_b S_b^*(t) \\ 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix},$$

and

$$V(t) = \begin{bmatrix} \mu+\nu & 0 & 0 & 0 & 0 & 0 \\ -\nu & \gamma+\delta+\mu & 0 & 0 & 0 & 0 \\ 0 & 0 & \mu_p+\nu_p & 0 & 0 & 0 \\ 0 & 0 & -\nu_p & \gamma_P+\delta_p+\mu_p & 0 & 0 \\ 0 & 0 & 0 & 0 & \mu_b+\nu_b & 0 \\ 0 & 0 & 0 & 0 & -\nu_b & \gamma_b+\delta_b+\mu_b \end{bmatrix}.$$

Note that $F(t)$ is a non-negative matrix function, while $-V(t)$ is cooperative. Suppose $X(t,s)$, $t \geq s$, is the evolution operator of the linear system

$$\frac{dx}{dt} = -V(t)x.$$

Thus, for $s \in \mathbb{R}, X(t,s)$ satisfies the equation

$$\frac{dX(t,s)}{dt} = -V(t)X(t,s), \quad \forall t \geq s, X(s,s) = I,$$

where I denotes the 6×6 identity matrix.

Assume $\psi(s)$ is the distribution of infected, ω-periodic in s. Then, $F(s)\psi(s)$ provides the rate of new cases due to those infected who were introduced at time s. For $t \geq s$, the term $X(t,s)F(s)\psi(s)$ provides us the distribution of the infectious individuals who newly became infected at time s and who are still infected at time t. Therefore,

$$g(t) \coloneqq \int_{-\infty}^{t} X(t,s)F(s)\psi(s)ds = \int_{0}^{\infty} X(t,t-a)F(t-a)\psi(t-a)da,$$

gives the distribution of accumulative new infections at t generated by all infected $\psi(s)$ who was introduced at any time $s \leq t$.

Let us assume that C_ω is the ordered Banach space of ω-periodic functions from $\mathbb{R}$ to $\mathbb{R}^6$, provided with the usual maximum norm $\|\cdot\|_\infty$ and introduce the positive cone

$$C_\omega^+ \coloneqq \{\psi \in C_\omega : \psi(t) \geq 0, \forall t \in \mathbb{R}\}.$$

Define the linear next infection operator $L\colon C_\omega \to C_\omega$ by

$$(L\psi)(t) = \int_{0}^{\infty} X(t,t-a)F(t-a)\psi(t-a)da, \quad \forall t \in \mathbb{R}, \psi \in C_\omega.$$

Then, the basic reproduction number of (6.1) is $\mathcal{R}_0 \coloneqq \rho(L)$, the spectral radius of L

[47]. Let $W(t,\lambda)$ be the monodromy matrix of the linear ω-periodic equation

$$\frac{d\omega}{dt} = \left(-V(t) + \frac{F(t)}{\lambda}\right)\omega, \quad \forall t \in \mathbb{R},$$

with parameter $\lambda \in (0,\infty)$. Now we will apply Theorem 14 to numerically calculate the basic reproduction number of system (6.1).

6.4.2 Local stability of the disease free solution

Based on the results in the previous subsection, we can formulate the following theorem concerning the local stability properties of the disease-free periodic solution E^* of model (6.1). Before we state the main result of this subsection, we recall Theorem 2.2 from [47].

Theorem 15 ([47, Theorem 2.2]). *The following statements are valid:*

(i) $\mathcal{R}_0 = 1$ *if and only if* $\rho(\Phi_{F-V}(\omega)) = 1$*;*

(ii) $\mathcal{R}_0 > 1$ *if and only if* $\rho(\Phi_{F-V}(\omega)) > 1$*;*

(iii) $\mathcal{R}_0 < 1$ *if and only if* $\rho(\Phi_{F-V}(\omega)) < 1$.

Theorem 16. *The disease-free periodic solution* E^* *of* (6.1) *is locally asymptotically stable if* $\mathcal{R}_0 < 1$*, whereas it is unstable if* $\mathcal{R}_0 > 1$.

Proof. The Jacobian matrix of (6.1) calculated at E^* is given by

$$J(t) = \begin{bmatrix} F(t) - V(t) & 0 \\ A(t) & M \end{bmatrix},$$

with $M(t)$ defined in (6.5) and $A(t)$ given by

$$A(t) = \begin{bmatrix} 0 & -\beta S^* & 0 & -\beta_{ph} S^* & 0 & -\beta_{bh}(t) S^* \\ 0 & \gamma & 0 & 0 & 0 & 0 \\ 0 & -\beta_{hp} S_p^* & 0 & -\beta_p S_p^* & 0 & -\beta_{bp}(t) S_p^* \\ 0 & 0 & 0 & \gamma_p & 0 & 0 \\ 0 & -\beta_{hb} S_b^*(t) & 0 & -\beta_{pb} S_b^*(t) & 0 & -\beta_b S_b^*(t) \\ 0 & 0 & 0 & 0 & 0 & \gamma_b \end{bmatrix}.$$

By [139], E^* is a locally asymptotically stable periodic solution if $\rho(\Phi_M(\omega)) < 1$ as well as $\rho(\Phi_{F-V}(\omega)) < 1$ hold. From condition (A_6), we have $\rho(\Phi_M(\omega)) < 1$. It then follows that the stability of E^* is determined by $\rho(\Phi_{F-V}(\omega))$. Hence, E^* is locally asymptotically stable if $\rho(\Phi_{F-V}(\omega)) < 1$, and unstable if $\rho(\Phi_{F-V}(\omega)) > 1$. By using Theorem 15, we complete the proof. □

6.4.3 Global stability of the disease-free solution

We will show the global asymptotic stability of the disease-free periodic solution E^* for $\mathcal{R}_0 < 1$. We will need the following result.

Lemma 17 ([140, Lemma 2.1]). *Let $\mu = \frac{1}{\omega}\ln\rho(\Phi_{A(\cdot)}(\omega))$. Then there exists a positive, ω-periodic function $\nu(t)$ such that $e^{\mu t}\nu(t)$ is a positive solution of $x' = A(t)x$.*

Theorem 18. *The disease-free periodic solution E^* of* (6.1) *is globally asymptotically stable if $\mathcal{R}_0 < 1$ and unstable if $\mathcal{R}_0 > 1$.*

Proof. From Theorem 15, we know that if $\mathcal{R}_0 > 1$, then E^* is unstable and if $\mathcal{R}_0 < 1$, then E^* is locally asymptotically stable. Therefore, it is only left to show that for $\mathcal{R}_0 < 1$, E^* is globally attractive. Because $I(t) \geq 0$, $I_p(t) \geq 0$ and $I_b(t) \geq 0$ from Lemma 13, it can be shown that

$$\begin{aligned} N_h'(t) &= \Pi - \mu N_h(t) - \delta I(t) \\ &\leq \Pi - \mu N_h(t), \end{aligned}$$

$$\begin{aligned} N_p'(t) &= \Pi_p - \mu_p N_p(t) - \delta_p I_p(t) \\ &\leq \Pi_p - \mu N_p(t), \end{aligned}$$

which implies that

$$\limsup_{t\to\infty} N(t) \leq \frac{\Pi}{\mu} = S^*,$$

and

$$\limsup_{t\to\infty} N_p(t) \leq \frac{\Pi_p}{\mu} = S_p^*.$$

Therefore, there exists a $T > 0$ such that $S(t) \leq N_h(t) \leq S^* + \epsilon$, and $S_p(t) \leq N_p(t) \leq S_p^* + \epsilon$, and from Lemma 13, $S_b(t) \leq N_b(t) \leq S_b^*(t) + \epsilon$, for an arbitrary positive ϵ.

Using these estimations for system (6.1), we get

$$\begin{aligned}
\frac{dE}{dt} &\leq (\beta I + \beta_{ph} I_p + \beta_{bh}(t) I_b)(S^* + \epsilon) - \nu E - \mu E,\\
\frac{dI}{dt} &= \nu E - (\mu + \delta + \gamma) I,\\
\frac{dR}{dt} &= \gamma I - (\mu + \theta) R,\\
\frac{dE_p}{dt} &\leq (\beta_p I_p + \beta_{hp} I + \beta_{bp}(t) I_b)(S_p^* + \epsilon) - \nu_p E_p - \mu_p E_p,\\
\frac{dI_p}{dt} &= \nu_p E_p - (\mu_p + \delta_p + \gamma_p) I_p,\\
\frac{dR_p}{dt} &= \gamma_p I_p - (\mu_p + \theta_p) R_p,\\
\frac{dE_b}{dt} &\leq (\beta_b I_b + \beta_{hb} I + \beta_{pb} I_p)(S_b^*(t) + \epsilon) - \nu_b E_b - \mu_b E_b,\\
\frac{dI_b}{dt} &= \nu_b E_b - (\mu_b + \delta_b + \gamma_b) I_b,\\
\frac{dR_b}{dt} &= \gamma_b I_b - (\mu_b + \theta_b) R_b,
\end{aligned} \tag{6.6}$$

for $t > T$. Let $M_\epsilon(t)$ be the 6×6 matrix function defined by

$$\begin{bmatrix}
-\mu - \nu & \beta(S^* + \epsilon) & 0 & \beta_{ph}(S^* + \epsilon) & 0 & \beta_{bh}(t)(S^* + \epsilon)\\
\nu & -\gamma - \delta - \mu & 0 & 0 & 0 & 0\\
0 & \beta_{hp}(S_p^* + \epsilon) & -\mu_p - \nu_p & \beta_p(S_p^* + \epsilon) & 0 & \beta_{bp}(t)(S_p^* + \epsilon)\\
0 & 0 & \nu_p & -\gamma_P - \delta_p - \mu_p & 0 & 0\\
0 & \beta_{hb}(S_b^*(t) + \epsilon) & 0 & \beta_{pb}(S_b^*(t) + \epsilon) & -\mu_b - \nu_b & \beta_b(S_b^*(t) + \epsilon)\\
0 & 0 & 0 & 0 & \nu_b & -\gamma_b - \delta_b - \mu_b
\end{bmatrix}.$$

Let us consider the auxiliary equation

$$\frac{dU(t)}{dt} = M_\epsilon(t) U(t), \tag{6.7}$$

where $U(t) = (E(t), I(t), E_p(t), I_p(t), E_b(t), I_b(t))$. From Theorem 14 we have $\mathcal{R}_0 < 1$ if and only if $\rho(\Phi_{F-V}(\omega)) < 1$. It is clear that $\lim_{\epsilon \to 0} \Phi_{M_\epsilon}(\omega) = \Phi_{F-V}(\omega)$. As $\rho(\Phi_{F-V}(\omega))$ is continuous, we can choose $\epsilon > 0$ small enough such that $\rho(\phi_{M_\epsilon}(\omega)) < 1$. Now following Lemma 17, we have that there is an ω-periodic positive function $p(t)$ such that $p(t)e^{\xi t}$ is a solution of (6.7) and $\xi = \frac{1}{\omega} \ln \rho(\Phi_{M_\epsilon}(\omega)) < 0$. For any $h(0) \in \mathbb{R}^6_+$, we can choose k^* such that $h(0) \leq k^* p(0)$ where $h(t) = (E(t), I(t), E_p(t), I_p(t), E_b(t), I_b(t))^T$. Now applying the comparison principle [141, Theorem B.1], we get $h(t) \leq$

$p(t)e^{\xi t}$ for all $t > 0$, from which we get

$$\lim_{t\to\infty}(E(t), I(t), E_p(t), I_p(t), E_b(t), I_b(t))^T = (0, 0, 0, 0, 0, 0)^T.$$

One can easily find that $N_h(t) \to N_h^*$, $N_p(t) \to N_p^*$, and $N_b(t) \to N_b^*$ as $t \to \infty$. Let $\epsilon > 0$, we can find $t_\epsilon > 0$ such that $I(t) \leqslant \epsilon$, $I_p(t) \leqslant \epsilon$ and $I_b(t) \leqslant \epsilon$ for all $t \geqslant t_\epsilon$. Then, the equation for $R'(t)$, $R_p'(t)$ and $R_b'(t)$ of (6.1) gives

$$\begin{aligned} R'(t) &\leqslant \gamma\epsilon - (\mu + \theta)R(t), \\ R_p'(t) &\leqslant \gamma_p\epsilon - (\mu_p + \theta_p)R_p(t), \\ R_b'(t) &\leqslant \gamma_b\epsilon - (\mu_b + \theta_b)R_b(t), \end{aligned}$$

for large t. From where $R(t) \to 0$, $R_p(t) \to 0$ and $R_p(t) \to 0$ as $t \to +\infty$. Thus the equations for $S'(t), S_p'(t)$ and $S_b'(t)$ in system (6.1) provide that

$$\lim_{t\to\infty} S(t) = S^*, \qquad \lim_{t\to\infty} S_p(t) = S_p^*, \qquad \lim_{t\to\infty}(S_b(t) - S_b^*(t)) = 0.$$

The proof is complete. □

Existence of positive periodic solutions

To show the existence of positive periodic solutions, we first introduce the notations

$$\begin{aligned} X &\coloneqq \left\{(S, E, I, R, S_p, E_p, I_p, R_p, S_b, E_b, I_b, R_b) \in \mathbb{R}_+^{12}\right\}, \\ X_0 &\coloneqq \left\{(S, E, I, R, S_p, E_p, I_p, R_p, S_b, E_b, I_b, R_b) \in X : \begin{matrix} E > 0, I > 0, E_p > 0, \\ I_p > 0, E_b > 0, I_b > 0 \end{matrix}\right\}, \end{aligned}$$

and

$\partial X_0 \coloneqq X \backslash X_0$.

Let us define the Poincaré map $\mathcal{P}\colon \mathbb{R}_+^{12} \to \mathbb{R}_+^{12}$ corresponding to (6.1) as

$$\mathcal{P}(x^0) = u(\omega, x^0), \quad x^0 \in \mathbb{R}_+^{12},$$

where $u(t, x^0)$ is the single solution of (6.1) started with initial condition $x^0 \in \mathbb{R}_+^{12}$. Then,

$$\mathcal{P}^m(x^0) = u(m\omega, x^0), \quad \text{for all } m \geq 0.$$

Proposition 19. *The set X_0 and ∂X_0 are both positively invariant w.r.t. the flow defined in* (6.1).

Proof. Let us consider the initial condition $\phi \in X_0$. By solving (6.1) for all $t > 0$, we

get that

$$
\begin{aligned}
S(t) &= e^{\int_0^t(-\mu-a_1(s))ds}\left(S(0)+\int_0^t e^{\int_0^\xi(\mu+a_1(s))ds}(\Pi+\theta R(\xi))\,d\xi\right)>0,\\
E(t) &= e^{-(\mu+\nu)t}\left(E(0)+\int_0^t e^{(\mu+\nu)s}a_1(s)S(s)ds\right)>0,\\
I(t) &= e^{-(\gamma+\delta+\mu)t}\left(I(0)+\nu\int_0^t e^{(\gamma+\delta+\mu)s}E(s)ds\right)>0,\\
R(t) &= e^{-(\theta+\mu)t}\left(R(0)+\gamma\int_0^t e^{(\theta+\mu)s}I(s)ds\right)>0,\\
S_p(t) &= e^{\int_0^t(-\mu_p-a_2(s))ds}\left(S_p(0)+\int_0^t e^{\int_0^\xi(\mu_p+a_2(s))ds}(\Pi_p+\theta_p R_p(\xi))\,d\xi\right)>0,\\
E_p(t) &= e^{-(\mu_p+\nu_p)t}\left(E_p(0)+\int_0^t e^{(\mu_p+\nu_p)s}a_2(s)S_p(s)ds\right)>0,\\
I_p(t) &= e^{-(\gamma_p+\delta_p+\mu_p)t}\left(I_p(0)+\nu_p\int_0^t e^{(\gamma_p+\delta_p+\mu_p)s}E_p(s)ds\right)>0,\\
R_p(t) &= e^{-(\theta_p+\mu_p)t}\left(R_p(0)+\gamma_p\int_0^t e^{(\theta_p+\mu_p)s}I_p(s)ds\right)>0,\\
S_b(t) &= e^{\int_0^t(-\mu_b-a_3(s))ds}\left(S_b(0)+\int_0^t e^{\int_0^\xi(\mu_b+a_3(s))ds}(\Pi_b(t)+\theta_b R_b(\xi))\,d\xi\right)>0,\\
E_b(t) &= e^{-(\mu_b+\nu_b)t}\left(E_b(0)+\int_0^t e^{(\mu_b+\nu_b)s}a_3(s)S_b(s)ds\right)>0,\\
I_b(t) &= e^{-(\gamma_b+\delta_b+\mu_b)t}\left(I_b(0)+\nu_b\int_0^t e^{(\gamma_b+\delta_b+\mu_b)s}E_b(s)ds\right)>0,\\
R_b(t) &= e^{-(\theta_b+\mu_b)t}\left(R_b(0)+\gamma_b\int_0^t e^{(\theta_b+\mu_b)s}I_b(s)ds\right)>0,
\end{aligned}
$$

where

$$
\begin{aligned}
a_1(t) &= \beta I(t)+\beta_{ph}I_p(t)+\beta_{bh}(t)I_b(t),\\
a_2(t) &= \beta_p I_p(t)+\beta_{hp}I(t)+\beta_{bp}(t)I_b(t),\\
a_3(t) &= \beta_b I_b(t)+\beta_{hb}I(t)+\beta_{pb}I_p(t).
\end{aligned}
$$

Thus X_0 is a positively invariant set. Since X is positively invariant and ∂X_0 is relatively closed in X, then it is clear that ∂X_0 is positively invariant. □

Lemma 20. *If $\mathcal{R}_0 > 1$, then there exists a $\sigma > 0$ such that for any $x^0 \in X_0$, with $\|x^0 - E^*\| < \sigma$ we have*

$$\limsup_{m\to\infty} d(\mathcal{P}^m(x^0), E^*) \geq \sigma.$$

Proof. By Theorem 15 we have $\rho(\Phi_{F-V}(\omega)) > 1$ if $\mathcal{R}_0 > 1$. Then we can choose an

$\eta > 0$ such that $\rho(\Phi_{F-V-M_\eta}(\omega)) > 1$ where the matrix function $M_\eta(t)$ is defined as

$$M_\eta(t) = \begin{bmatrix} 0 & \beta\eta & 0 & \beta_{ph}\eta & 0 & \beta_{bh}(t)\eta \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & \beta_{hp}\eta & 0 & \beta_p\eta & 0 & \beta_{bp}(t)\eta \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & \beta_{hb}\eta & 0 & \beta_{pb}\eta & 0 & \beta_b\eta \\ 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix}.$$

Let us use the notation ϕ for an initial condition of (6.1). The continuous dependence of the solutions on initial values implies that we can find a $\sigma = \sigma(\eta) > 0$ such that for arbitrary $\phi \in X_0$ with $\|\phi - E_0\| \leq \sigma$,

$$\|u(t, \phi) - u(t, E_0)\| \leq \eta, \quad \text{for } 0 \leq t \leq \omega,$$

holds, moreover,

$$\limsup_{m\to\infty} d(\mathcal{P}^m(x^0), E_0) \geq \sigma. \tag{6.8}$$

Indeed, suppose by contradiction that (6.8) is not true, then

$$\limsup_{m\to\infty} d(\mathcal{P}^m(x^0), E_0) < \sigma,$$

hence, it follows from the above that

$$\|u(t, \mathcal{P}^m(\phi)) - u(t, E_0)\| < \eta, \quad \text{for all } m \geq 0, t \in [0, \omega].$$

For an arbitrary $t \geq 0$, let us write t as $t = m\omega + \hat{t}$, where $\hat{t} \in [0, \omega)$ and $m = \left[\frac{t}{\omega}\right]$, the integer part of $\frac{t}{\omega}$. We obtain

$$\|u(t, x^0) - u(t, E_0)\| = \|u(\hat{t}, \mathcal{P}^m(x^0)) - u(\hat{t}, E_0)\| < \eta, \quad \text{for all } t \geq 0.$$

From this, we have

$$S(t) \geq S^* - \eta, \quad S_p(t) \geq S_p^* - \eta, \quad S_b(t) \geq S_b^*(t) - \eta$$

and hence for $\|\phi - E_0\| < \sigma$, we get

$$\begin{aligned} \frac{dE}{dt} &\geq (\beta I + \beta_{ph} I_p + \beta_{bh}(t) I_b)(S^* - \eta) - \nu E - \mu E, \\ \frac{dI}{dt} &= \nu E - (\mu + \delta + \gamma) I, \end{aligned}$$

$$\begin{aligned}
\frac{dR}{dt} &= \gamma I - (\mu + \theta)R,\\
\frac{dE_p}{dt} &\geq (\beta_p I_p + \beta_{hp} I + \beta_{bp}(t) I_b)(S_p^* - \eta) - \nu_p E_p - \mu_p E_p,\\
\frac{dI_p}{dt} &= \nu_p E_p - (\mu_p + \delta_p + \gamma_p) I_p,\\
\frac{dR_p}{dt} &= \gamma_p I_p - (\mu_p + \theta_p) R_p,\\
\frac{dE_b}{dt} &\geq (\beta_b I_b + \beta_{hb} I + \beta_{pb} I_p)(S_b^* - \eta) - \nu_b E_b - \mu_b E_b,\\
\frac{dI_b}{dt} &= \nu_b E_b - (\mu_b + \delta_b + \gamma_b) I_b,\\
\frac{dR_b}{dt} &= \gamma_b I_b - (\mu_b + \theta_b) R_b.
\end{aligned}$$

Introduce now the auxiliary linear system

$$U'(t) = (F(t) - V(t) - M_\eta(t))U(t), \tag{6.9}$$

with $U(t) = (E(t), I(t), E_p(t), I_p(t), E_b(t), I_b(t))$.
Now we have $\rho(F(t) - V(t) - M_\eta(t)) > 1$, while from Lemma 17 we know that there exists a positive, ω-periodic function $p_1(t)$ such that $h(t) = e^{\xi t} p_1(t)$ is a solution of (6.9) and $\xi = \frac{1}{\omega} \ln \rho(\Phi_{F-V} + M_\eta(\omega)) > 0$. Let $t = n\omega$ and n be a non-negative integer, we get

$$h(n\omega) = e^{n\omega\xi} p_1(n\omega) \to (\infty, \infty, \infty, \infty, \infty, \infty, \infty, \infty, \infty)^T.$$

For any $h(0) \in \mathcal{R}_+^9$, we can choose a real number $n_0 > 0$ such that $h(0) \geq n_0 p_1(0)$ where

$$h(0) = (E(t), I(t), R(t), E_p(t), I_p(t), R_p(t), E_b(t), I_b(t), R_b(t))^T.$$

Applying the comparison principle [141, Theorem B.1], we obtain $h(t) \geq p_1(t) e^{\xi t}$ for all $t > 0$, which implies that

$$\lim_{t\to\infty} (E(t), I(t), R(t), E_p(t), I_p(t), R_p(t), E_b(t), I_b(t), R_b(t))^T = (\infty, \infty, \infty, \infty, \infty, \infty, \infty, \infty, \infty)^T.$$

This leads to a contradiction that completes the proof. □

Theorem 21. *Let $\mathcal{R}_0 > 1$. Then system* (6.1) *has at least one positive periodic solution and there exists an $\epsilon_1 > 0$ such that*

$$\liminf_{t\to\infty} (E(t), I(t), R(t), E_p(t), I_p(t), R_p(t), E_b(t), I_b(t), R_b(t))^T \geq (\epsilon_1, \epsilon_1, \epsilon_1, \epsilon_1, \epsilon_1, \epsilon_1, \epsilon_1, \epsilon_1, \epsilon_1)^T,$$

for all $\phi \in X_0$.

Proof. First, we prove that the Poincaré map $\mathcal{P}$ is uniformly persistent with respect to $(X_0, \partial X_0)$, as from this, applying [142, Theorem 3.1.1], it follows that the solution of (6.1) is uniformly persistent with respect to $(X_0, \partial X_0)$. From Proposition 19, we have that both X and X_0 are positively invariant, and ∂X_0 is relatively closed in X. Furthermore, from Lemma 13 it follows that system (6.1) is point dissipative. Let us introduce

$$M_\partial = \{\phi \in \partial X_0 : \mathcal{P}^m(\phi) \in \partial X_0, \forall m \geq 0\}.$$

To apply the theory developed in [142] (see also [140, Theorem 2.3]), we first show that

$$M_\partial = \{(S, 0, 0, S_p, 0, 0, S_b, 0, 0) : S \geq 0, S_p \geq 0, S_b \geq 0\}. \tag{6.10}$$

Let us note that $M_\partial \supseteq (S, 0, 0, S_p, 0, 0, S_b, 0, 0) : S \geq 0, S_p \geq 0, S_b \geq 0$. It is sufficient to prove that $M_\partial \subset \{(S, 0, 0, S_p, 0, 0, S_b, 0, 0) : S \geq 0, S_p \geq 0, S_b \geq 0\}$, i.e., for arbitrary initial condition $\phi \in \partial X_0, E(n\omega) = 0$ or $I(n\omega) = 0$ or $R(n\omega) = 0$ or $E_p(n\omega) = 0$ or $I_p(n\omega) = 0$ or $R_p(n\omega) = 0$ or $E_b(n\omega) = 0$ or $I_b(n\omega) = 0$ or $R_b(n\omega) = 0$ or for all $n \geq 0$.

Assume by contradiction the existence of an integer $n_1 \geq 0$ for which

$$(E(n_1\omega), I(n_1\omega), R(n_1\omega), E_p(n_1\omega), I_p(n_1\omega), R_p(n_1\omega), E_b(n_1\omega), I_b(n_1\omega) \\ R_b(n_1\omega)) > (0, 0, 0, 0, 0, 0, 0, 0, 0).$$

Then, by putting $t = n_1\omega$ into the place of the initial time $t = 0$ in Proposition 19, we get that $S(t) > 0, E(t) > 0, I(t) > 0, R(t) > 0, S_p(t) > 0, E_p(t) > 0, I_p(t) > 0, R_p(t) > 0, S_b(t) > 0, E_b(t) > 0, I_b(t) > 0, R_b(t) > 0$. This is in contradiction with the positive invariance of ∂X_0.

By Lemma 20, $\mathcal{P}$ is weakly uniformly persistent w.r.t. $(X_0, \partial X_0)$. Lemma 1 guarantees the existence of a global attractor of $\mathcal{P}$. Then E^* is an isolated invariant set in X and $W^s(E^*) \cap X_0 = \emptyset$. Each solution in M_∂ tends to E^* and it is clearly acyclic in M_∂.

By [142, Theorem 1.3.1 and Remark 1.3.1], we can deduce that P is uniformly (strongly) persistent w.r.t. $(X_0, \partial X_0)$. Hence, there exists an $\epsilon_1 > 0$ such that

$$\liminf_{t\to\infty}(E(t), I(t), R(t), E_p(t), I_p(t), R_p(t), E_b(t), I_b(t), R_b(t))^T \\ \geq (\epsilon_1, \epsilon_1, \epsilon_1, \epsilon_1, \epsilon_1, \epsilon_1, \epsilon_1, \epsilon_1, \epsilon_1)^T,$$

for all $\phi \in X_0$.

By [142, Theorem 1.3.6], $\mathcal{P}$ has a fixed point $\tilde{\phi} \in X_0$, and hence system (6.1) has at least one periodic solution $u(t, \tilde{\phi})$ with

$$\tilde{\phi} = (\tilde{S}(0), \tilde{E}(0), \tilde{I}(0), \tilde{R}(0), \tilde{S}_p(0), \tilde{E}_p(0), \tilde{I}_p(0), \tilde{R}_p(0)\tilde{S}_b(0), \tilde{E}_b(0), \tilde{I}_b(0), \tilde{R}_b(0)) \in X_0.$$

Now, let us prove that $\tilde{S}(0), \tilde{S}_p(0)$ and $\tilde{S}_b(0)$ are positive. If $(\tilde{S}(0) = 0$, $\tilde{S}_p(0) = 0$, $\tilde{S}_p(0)) = 0$, then we obtain that $\tilde{S}(0) > 0$ and $\tilde{S}_p(0) > 0$ and $\tilde{S}_b(0) > 0$ for all $t > 0$. However, using the periodicity of solution, we have $\tilde{S}(0) = \tilde{S}(n\omega) = 0$, $\tilde{S}_p(0) = \tilde{S}_p(n\omega) = 0$ and$\tilde{S}_b(0) = \tilde{S}_b(n\omega) = 0$, that is a contradiction and hence the statement of the theorem is proved. □

6.5 Numerical simulation

To illustrate our analytical results we perform some numerical simulations. These simulations will also give us suggestions regarding the changes in model parameters which might lead to a yearly periodic recurrence of Nipah virus disease and how to avoid such a recurrence. The periodic transmission rates are described by functions of the form

$$\beta_x \begin{cases} \sin(4t/365 * \Pi) + a, & 0 \leq t \leq 365/4 \qquad \mod 365, \\ a, & 365/4 < t < 365 \qquad \mod 365 \end{cases},$$

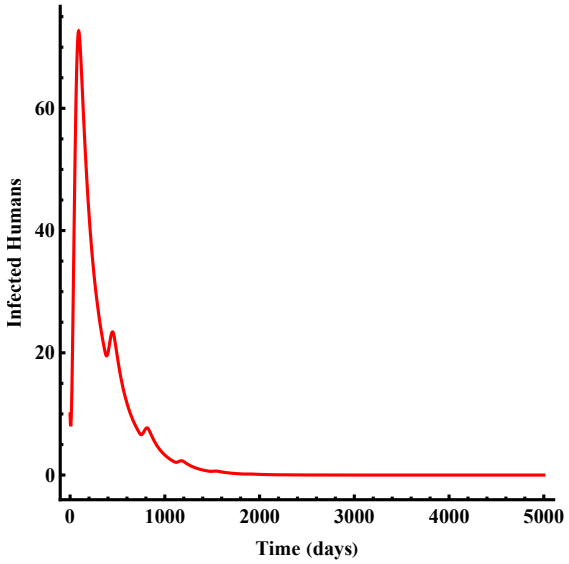
where $x \in bp, bh$, β_x is a baseline value for the transmission rate and a is a positive constant. The periodic function describing the birth rate of bats is defined in a similar way, taking into account the breeding season of the bats.

We show three examples corresponding to different values of the basic reproduction number. To numerically approximate this value, we follow the method described in [143].

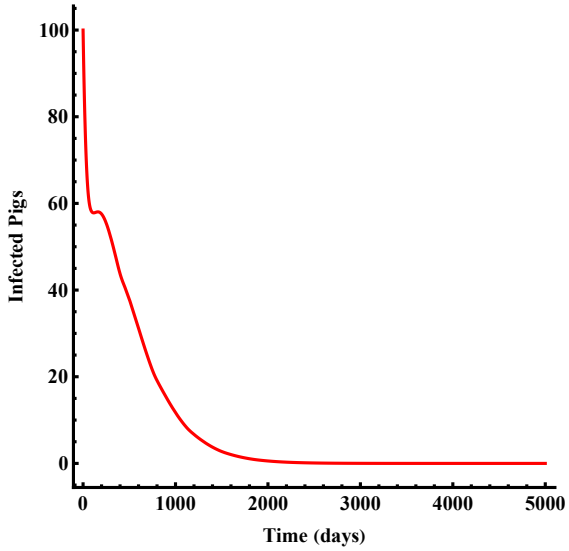
In our first example, the basic reproduction number has the value $\mathcal{R}_0 = 0.85$, i.e. it is significantly smaller than 1. The parameter values corresponding to this example can be found in the first column of Table 6.2, while the number of infected humans, pigs and bats is plotted in Figure 6.2. One can see that – just like expected based on our analytical results – the disease will die out in all three species and the population reaches a (globally asymptotically stable) disease-free steady state.

In Example 2, we consider another set of parameters with which the reproduction number is still below 1, however, in this case, the value $\mathcal{R}_0 = 0.98$ is very close to the threshold value. In this case, one can see that again the disease goes extinct in all three species, as expected from the analytical results. The results of the numerical simulations for the three species are shown in Figure 6.3.

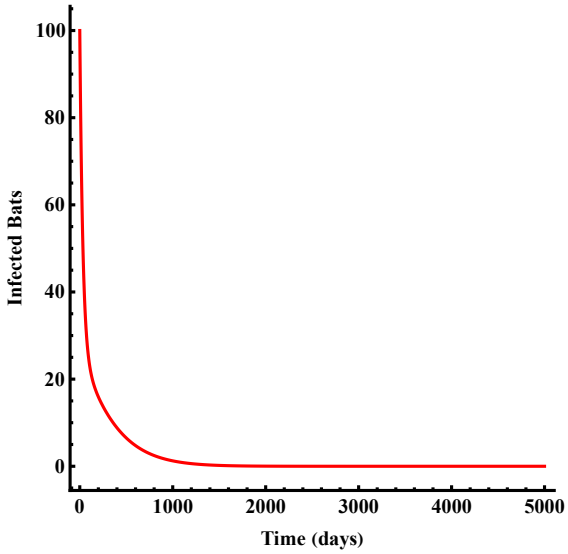
In our last example, shown in Figure 6.4, the applied parameter values (shown in the last column of Table 6.2) result in a basic reproduction number $\mathcal{R}_0 = 3.2$ with value larger than 1. In this case, we can see that the disease persists and the figures suggest that all solutions tend to an endemic periodic solution corresponding to the annual recurrence of the disease. Comparing the parameter values applied in our last example with those of the two previous cases, one can see that a significant increase



(a) *Extinction of infection in humans.*

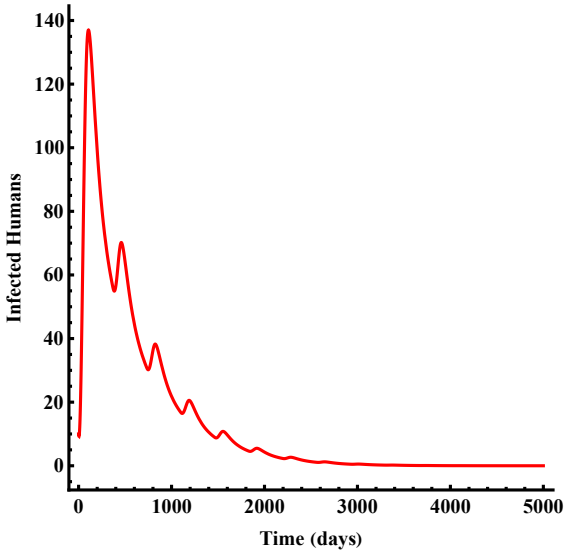


(b) *Extinction of infection in pigs.*

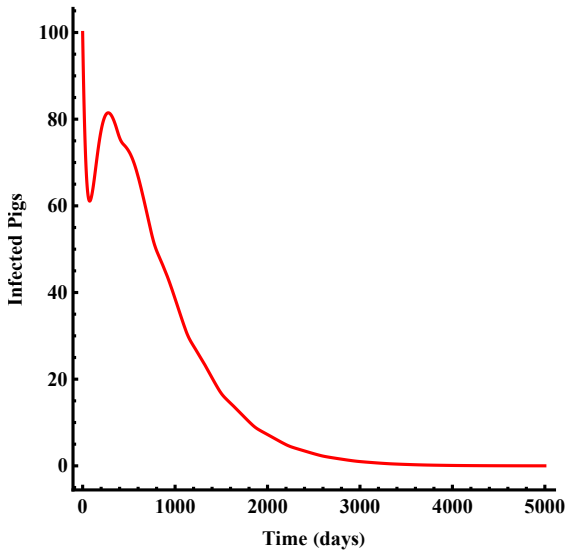


(c) *Extinction of infection in bats.*

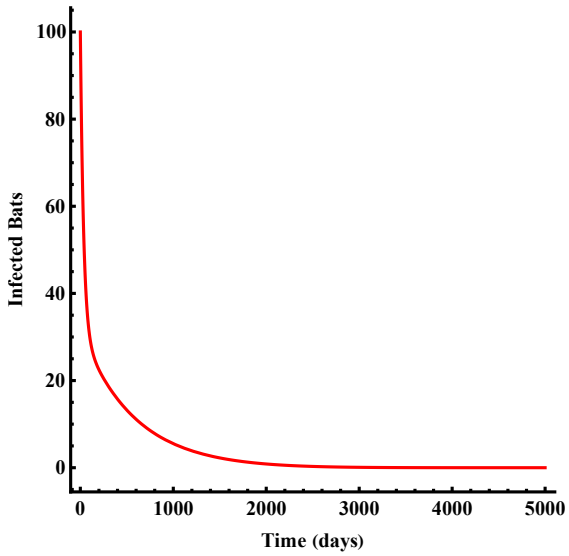
Figure 6.2: *Extinction of NiV when* $\mathcal{R}_0 = 0.85 < 1$ *with parameter values in Table 6.2(Example 1)*



(a) *Extinction of infection in humans.*

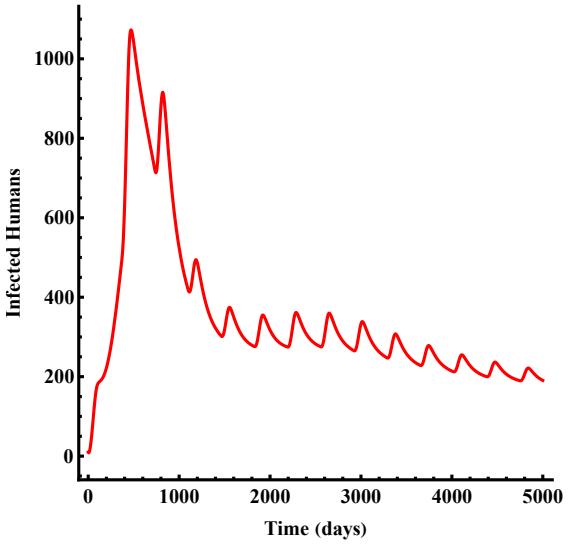


(b) *Extinction of infection in pigs.*

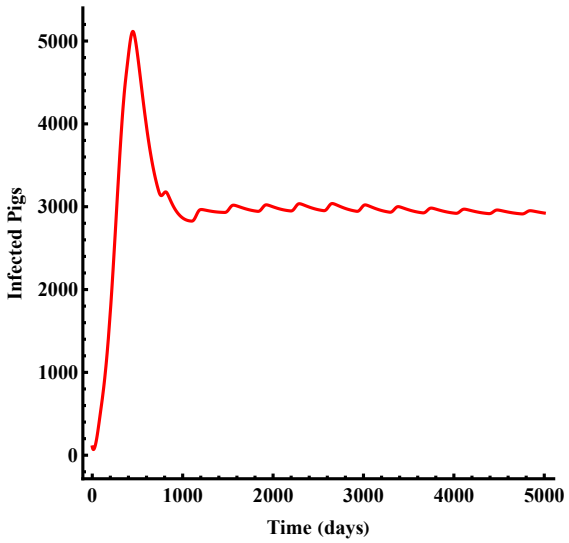


(c) *Extinction of infection in bats.*

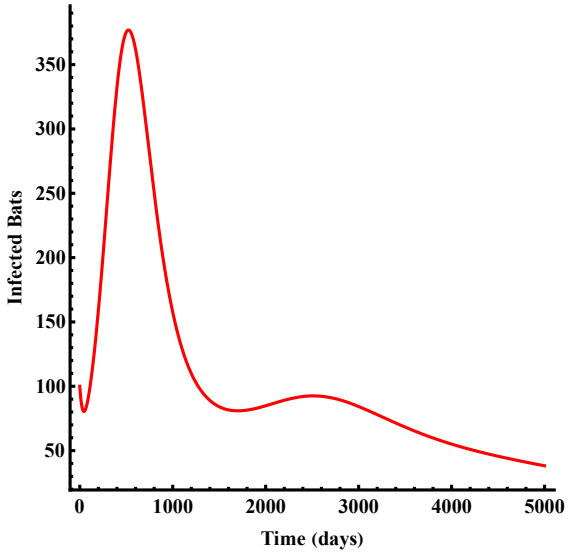
Figure 6.3: *Extinction of NiV when* $\mathcal{R}_0 = 0.98 < 1$ *with parameter values in Table 6.2 (Example 2)*



(a) *Persistence of infection in humans.*



(b) *Persistence of infection in pigs.*



(c) *Persistence of infection in bats.*

Figure 6.4: *Persistence of NiV when* $\mathcal{R}_0 = 3.2 > 1$ *with parameter values in Table 6.2*

Table 6.2: *Parameters for model* (6.1) *providing values for extinction and persistence (unit per days*

Parameter	Value for extinction		Value for persistence	Source
	Example 1	Example 2		
Π	6.69852	6.69852	6.69852	[117]
Π_p	300.3	300.3	300.3	[92]
Π_b	0.411	0.411	0.411	Assumed
μ	0.0000379	0.0000379	0.0000379	[117]
μ_p	0.002747	0.002747	0.002747	[118]
μ_b	0.00013699	0.00013699	0.00013699	Assumed
β	2.28×10^{-9}	2.0×10^{-9}	9.0×10^{-9}	[107]
β_{ph}	1.3×10^{-8}	2.0×10^{-8}	2.0×10^{-8}	Assumed
β_{bh}	1.0×10^{-6}	1.0×10^{-6}	1.04×10^{-6}	Assumed
β_p	6.71×10^{-8}	6.71×10^{-8}	1.32×10^{-6}	Assumed
β_{hp}	7.0×10^{-8}	7.0×10^{-8}	7.0×10^{-8}	Assumed
β_{bp}	1.0×10^{-7}	1.0×10^{-7}	3.01×10^{-6}	Assumed
β_b	6.71×10^{-6}	6.71×10^{-6}	1.88×10^{-5}	[84]
β_{hb}	7.0×10^{-10}	7.0×10^{-10}	7.0×10^{-10}	Assumed
β_{pb}	7.0×10^{-10}	7.0×10^{-10}	7.0×10^{-10}	Assumed
ν	0.01	0.01	0.01	[75]
ν_p	0.01	0.01	0.01	[118]
ν_b	0.01	0.01	0.01	Assumed
θ	0.033	0.033	0.0333	Assumed
θ_p	0.001	0.001	0.000861	Assumed
θ_b	0.0000146	0.000993	0.001	[84]
γ	0.02544	0.015625	0.0177	[4]
γ_p	0.01	0.01	0.0499	[13]
γ_b	0.0225	0.0197	0.01	Assumed
δ	0.04025	0.02065	0.0343	[13]
δ_p	0.00232	0.000325	0.000265	[119]
δ_b	0.000746	0.000575	0.000501	Assumed

in all transmission rates was needed to obtain a situation where the disease remains endemic, along with an increase of the length of the infectious period. On the other hand, the simulations suggest that keeping the transmission rates as low as possible is sufficient to prevent us from huge seasonal outbreaks of the disease.

6.6 Discussion

In this study, we developed a three-species compartmental model to characterize the spread of the Nipah virus infection among bats, pigs, and humans, taking into ac-

count all possible directions of transmission between the three species. To make our model more realistic, we included periodicity in our model considering the periodic birth rate of the reservoir species bats and periodic transmission rates due to the seasonal nature of date palm sap consumption, an important way of disease transmission from bats to humans. We also included the loss of immunity in those who have recovered, as according to studies conducted on bats, one of the factors contributing to outbreaks in Pteropus bats is the gradual loss of immunity over the course of six years.

Using the methods established by Wang and Zhao, we calculated the basic reproduction number ($\mathcal{R}_0$) and determined the existence and uniqueness of a disease-free ω-periodic solution. We showed that this solution is globally asymptotically stable if $\mathcal{R}_0$ is less than 1, while it is unstable otherwise. In the latter case, the disease becomes endemic in the three populations, and we also proved the existence of at least one positive periodic solution. To support the analytical findings and evaluate the impact of parameter changes on disease dynamics, we present several numerical examples. For three values of $\mathcal{R}_0$, we performed numerical simulations to highlight our analytical findings with reference to the NiV disease. When $\mathcal{R}_0 < 1$ and the simulations in the first two examples supported the conclusion that the disease has been eradicated in people, pigs, and bats. This is consistent with the mathematical expectations and points to a disease-free solution. With $\mathcal{R}_0 > 1$, however, the simulations showed sustained disease transmission in the final example, pointing to an endemic periodic solution that corresponds to periodic recurrence. The simulations showed that higher transmission rates and longer infectious periods were necessary for the disease to remain endemic when comparing the parameter values between the examples. On the other hand, simulations showed that reducing transmission rates could successfully stop significant seasonal disease outbreaks. These examples may assist readers understand how to prevent the disease from recurring on an annual basis.

Our work certainly has its limitations. One of the more important is the lack of sufficient data as fortunately, up to now, there have not been any very large-scale Nipah outbreaks in humans. A future better understanding of the characteristics of this disease will contribute to more precise models which might include some additional compartments, i.e. convalescent, infected with relapsed onset, or deceased who may contribute to disease transmission. Temperature, humidity, and climatic conditions can impact the survival and transmission of the Nipah virus, with higher temperatures and increased rainfall that potentially increase virus dissemination and infection rates. Future research should take these environmental aspects into account to fully comprehend the dynamics of disease. Due to the poor understanding of the many disease parameters, the numerical analysis of the model is difficult. Future studies should concentrate on examining an extended system that takes into account other variables and makes use of extensive and well-supported data in or-

der to address this. To improve comprehension, enable more precise predictions, and permit recommendations for disease control and prevention efforts, the model's scope should be expanded and credible data should be included.

Chapter 7

Global dynamics of a compartmental model to assess the effect of transmission from deceased

During several epidemics, transmission from deceased people significantly contributed to disease spread, but mathematical analysis of this transmission has not been seen in the literature numerously. Transmission of Ebola during traditional burials was the most well-known example, however, there are several other diseases such as hepatitis, plague or Nipah virus that can potentially be transmitted from disease victims. This is especially true in the case of serious epidemics when healthcare is overwhelmed and the operative capacity of the health sector is diminished, such as it could be seen during the COVID-19 pandemic. We present a compartmental model for the spread of a disease with an imperfect vaccine available, also considering transmission from deceased infected in general. The global dynamics of the system are completely described by constructing appropriate Lyapunov functions. To support our analytical results, We perform numerical simulations to assess the importance of transmission from the deceased considering the data collected from three infectious disease Ebola virus disease, COVID-19, and Nipah fever.

7.1 Introduction

Several infectious diseases caused by pathogenic microorganisms (e.g. bacteria, viruses, parasites, or fungi) can be spread directly or indirectly, from person to person, however, apart from infection from infectious individuals, also corpses of those deceased due to a given epidemic may pose a risk of transmission, especially under special circumstances like natural disasters [144], an overwhelmed health care system [145], or due to traditional funerary practices [146].

Various examples can be mentioned for this phenomenon. Deaths from diseases such as plague, cholera, typhoid fever, tuberculosis, anthrax, smallpox, and influenza pose a substantial risk to health though most agents do not survive long in the human body after death [147]. Contracting dead bodies from tuberculosis, blood-borne viruses (e.g. hepatitis B and C and HIV), and gastrointestinal infections (e.g. cholera, *E. coli*, hepatitis A, rotavirus diarrhea, salmonellosis, shigellosis, and typhoid/paratyphoid fevers) with persons who are involved in close contact with the dead – such as health care workers, military personnel, rescue workers, volunteers, and others – may be exposed to chronic infectious hazards [144, 148].

Ebola virus disease (EVD or Ebola) is a severe illness in humans that is found primarily in the African continent. EVD can be transmitted between humans through contact with blood, secretions, organs, or other bodily fluids of infected or dead humans or animals, and has become especially known for the role of traditional burials in disease transmission. Some of the early symptoms of this deadly disease are fever, exhaustion, aches and pains, and loss of appetite. People who exhibit Ebola symptoms should seek medical attention right once, and treatment options include hospital-provided medications and oral or intravenous fluids [149, 150, 151]. Influenza remains active in the environment for only one day and HIV remains active in dead bodies kept at 2°C between 6–15 days, therefore corpses can transmit disease and cause death if not handled safely [147]. Recently the world has seen a devastating COVID-19 pandemic and due to the massive transmission of the virus, infection in humans has led to an unexpected situation in global health. Infected individuals with this disease experience mild, moderate, or severe clinical symptoms. Fever, fatigue, dry cough, shortness of breath, etc. are some of its most typical symptoms [152]. It can also be transmitted via human contact or aerial droplets [153]. After postmortem and forensic tests of the corpse, it was observed that the SARS-CoV-2 persists in the human body months after death and should be infectious for weeks (see e.g. [154, 155]). Nipah virus (NiV) is a zoonotic virus that was first identified when a cluster of patients associated with pig farming in Peninsular Malaysia in late September 1998. Close contact with a person who has been infected with the NiV, direct contact with infected animals, such as bats or pigs, or their body fluids (such as their blood, urine, or saliva), eating food products that have been contaminated by the body fluids of infected animals (such as palm sap or fruit contaminated by an infected bat) is the transmission route of this virus. Sporadical outbreaks of NiV have been seen in South and Southeast Asia [50, 156].

Though not strictly the phenomenon studied in our work, it is interesting to mention that during the 14th-century plague pandemic, also known as the 'Black Death' was not only spread from dead bodies but also was used as biological warfare. Namely, the Mongol army hurled plague-infected cadavers into the besieged Crimean city of Caffa. This disease was transmitted to the sieged inhabitants and

fleeing survivors from that area, spreading plague from Caffa to the Mediterranean Basin [157].

Numerous mathematical models are available in literature where a compartment for the deceased can be found, but few of them considered infection transmitted from corpses (see for instance [107, 149, 158, 159, 160, 161]). However, several studies considered pathological phenomena, and review articles on transmission from corpses can be found [162, 163, 164, 165, 166, 167, 168, 169, 170]. For this reason, we are interested to study the transmission of pathogens from the deceased in general. This paper is organized in accordance with the following: formulation of our model and description of the parameters are presented in Section 7.2. In Section 7.3, model analysis and in Section 7.4 the basic reproduction number, equilibrium points, and their stability are presented. Numerical simulations are discussed in Section 7.5. Finally, the overall discussion is presented in Section 7.6 as a conclusion.

7.2 Model formulation

To develop our model, we first divide the total actively-mixing human population (e.g. for EVD, total human population excluding the Ebola-deceased individuals) population, denoted by $N(t)$ at time t, into the following compartments: susceptibles ($S(t)$), vaccinated ($V(t)$), exposed (newly-infected but not infectious) individuals ($E(t)$), infectious individuals with clinical symptoms of the disease ($I(t)$) and recovered ($R(t)$). Hence,

$$N(t) = S(t) + V(t) + E(t) + I(t) + R(t).$$

There is an additional compartment D introduced for deceased humans who passed away due to virus infection and have not been buried yet.

We denote the birth and natural death rates by Λ and μ, respectively. A fraction ρ (with $0 < \rho < 1$) of newborns not vaccinated after birth enter the susceptible compartment, while the remaining fraction enters the vaccinated compartment. The force of infection is given by $\lambda(t) = (\beta_1 I(t) + \beta_2 D(t))$, where the parameter β_1 represents the effective contact rate of susceptible individuals to get an infection from visibly infected individuals and β_2 is the effective unprotected contact rate of susceptible individuals, who become infected from dead bodies. Since vaccines are not fully efficient enough for a disease so we consider vaccine efficiency, which is modeled by introducing the parameter $\eta \in [0, 1]$. Infected individuals progress from the exposed to the infectious compartment at rate σ, and further, they leave the visibly infected compartment at rate γ (i.e. the average duration of the latent period is $1/\sigma$ days and that of the infectious period is $1/\gamma$ days). Disease-induced death affects individuals in the infected compartment. A fraction $0 < \delta < 1$ of those leaving the infectious com-

partment will die due to the infection and arrive in the D class, while the remaining fraction recovers and moves to the recovered compartment R. Infected corpses are buried at the rate α, i.e. the average time until the burial equals $1/\alpha$ days. Besides

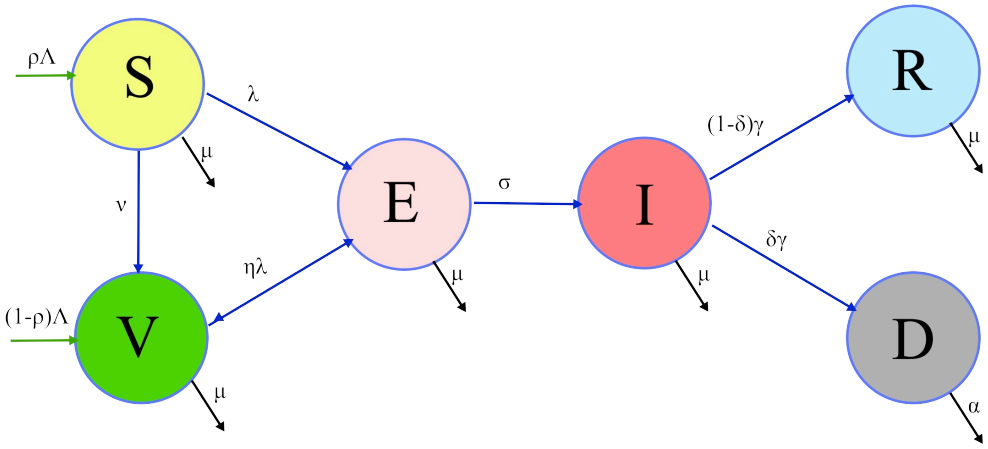


Figure 7.1: *Transmission diagram. Blue arrows indicate the transition from one compartment to another, and green arrows and black arrows indicate new entries and released for death respectively.*

vaccination right after birth, we also consider v as the vaccination rate of adults and with that, susceptible individuals are transferred to the vaccinated compartment. The transmission diagram of our model is shown in Figure 7.1. A complete description of the model parameters is summarized in Table 7.1. With the above notations and assumptions, our model takes the form

$$\begin{aligned}
S'(t) &= \rho\Lambda - (\beta_1 I(t) + \beta_2 D(t))S(t) - vS(t) - \mu S(t),\\
V'(t) &= (1-\rho)\Lambda - \eta(\beta_1 I(t) + \beta_2 D(t))V(t) + vS(t) - \mu V(t),\\
E'(t) &= (\beta_1 I(t) + \beta_2 D(t))(S(t) + \eta V(t)) - (\sigma + \mu)E(t),\\
I'(t) &= \sigma E(t) - (\gamma + \mu)I(t),\\
R'(t) &= (1-\delta)\gamma I(t) - \mu R(t),\\
D'(t) &= \delta\gamma I(t) - \alpha D(t).
\end{aligned} \tag{7.1}$$

The following initial conditions are associated with the system (7.1): $S(0) > 0, V(0) \geq 0, E(0) \geq 0, I(0) \geq 0, R(0) \geq 0, D(0) \geq 0$. We note that system (7.1) is similar to the model studied in [160], where the compartment of low-risk susceptibles corresponds

to our vaccinated compartment. Apart from the main difference, the presence of vaccination of susceptible individuals (i.e. movement from the S class to the V class, which term clearly cannot be present in [160] due to the different meaning of the corresponding compartments), another important difference is that we use mass action incidence, which allows us to prove global asymptotic stability of the endemic equilibrium without additional conditions.

To obtain our analytical results described in Sections 7.3 and 7.4, for technical reasons we will omit vaccination of adults, hence, we study the reduced system

$$\begin{aligned} S'(t) &= \rho\Lambda - (\beta_1 I(t) + \beta_2 D(t))S(t) - \mu S(t), \\ V'(t) &= (1-\rho)\Lambda - \eta(\beta_1 I(t) + \beta_2 D(t))V(t) - \mu V(t), \\ E'(t) &= (\beta_1 I(t) + \beta_2 D(t))(S(t) + \eta V(t)) - (\sigma + \mu)E(t), \\ I'(t) &= \sigma E(t) - (\gamma + \mu)I(t), \\ R'(t) &= (1-\delta)\gamma I(t) - \mu R(t), \\ D'(t) &= \delta\gamma I(t) - \alpha D(t) \end{aligned} \tag{7.2}$$

with the initial conditions $S(0) \geq 0, V(0) \geq 0, E(0) \geq 0, I(0) \geq 0, R(0) \geq 0, D(0) \geq 0$. We note that the assumption of omitting vaccination of older individuals is not merely technical: in the case of several childhood diseases, vaccination almost entirely takes place within a short time after birth and vaccination of older individuals is negligible.

Table 7.1: *Description of parameters of model* (7.1).

Parameters	**Description**
Λ	Recruitment rate
ρ	Fraction of unvaccinated at birth
μ	Natural death rate
β_1	Transmission rate from infectious
β_2	Transmission rate from deceased
η	Vaccination efficiency
$1/\sigma$	Incubation period
$1/\gamma$	Length of infectious period
$1/\alpha$	Average time until burial
δ	Fraction of lethal cases
v	Adult vaccination rate

7.3 Basic properties

7.3.1 Positivity and boundedness of solutions

For system (7.2), it is necessary to prove that all the state variables are non-negative and all the solutions of the system with positive initial conditions have a positive invariant solution. Thus we have the following lemma.

Lemma 22. *All solutions of system* (7.2) *with non-negative initial conditions will enter the invariant region* $\phi = \{S, V, E, I, R, D \in \mathbb{R}^6_+ : 0 < N \leq \Lambda/\mu\}$.

Proof. It can be easily proved that all existing solutions starting from non-negative initial conditions remain non-negative for all time $t > 0$. We already know that the total human population of individuals is $N = S + V + E + I + R$. Then we have

$$N'(t) = S'(t) + V'(t) + E'(t) + I'(t) + R'(t) = \Lambda - \mu N(t) - \delta\gamma I(t),$$

from which

$$N'(t) \leq \Lambda - \mu N(t)$$

follows. If the initial value of the total population $N(0) = N_0$, then we obtain that

$$N(t) \leq \tfrac{\Lambda}{\mu} - \left(\tfrac{\Lambda}{\mu} - N_0\right) e^{-\mu t}.$$

So $N(t) \leq \frac{\Lambda}{\mu}$ as $t > 0$ and this implies $I(t) \leq \frac{\Lambda}{\mu}$. Now we can write the sixth equation of (7.2) as

$$D'(t) \leq \delta\gamma \frac{\Lambda}{\mu} - \alpha D(t),$$

calculating in a similar fashion to the above, we can see that $D(t) \leq \frac{\Lambda\delta\gamma}{\alpha\mu}$ as $t > 0$. Hence the region is positively invariant and attracts all solutions of the equations of the system. □

7.3.2 Derivation of the basic reproduction number

To calculate the basic reproduction number $\mathcal{R}_0$ of (7.2), we follow the general approach established in [30, 42]. In model (7.2), the infectious states are E, I and D. The transmission vector $\mathcal{F}$ representing the new infections and the transition vector

$\mathcal{V}$ denoting the outflow from the infectious compartments in (7.2) are given by

$$\mathcal{F} = \begin{bmatrix} (\beta_1 I + \beta_2 D)(S + \eta V) \\ 0 \\ 0 \end{bmatrix}, \qquad \mathcal{V} = \begin{bmatrix} (\sigma + \mu)E \\ -\sigma E + (\gamma + \mu)I \\ \alpha D - \delta\gamma I \end{bmatrix}.$$

The model (7.2) has a unique disease-free equilibrium, given by

$$E_0 = \left(\tfrac{\rho\Lambda}{\mu}, \tfrac{(1-\rho)\Lambda}{\mu}, 0, 0, 0, 0\right).$$

Substituting the corresponding coordinates of the disease-free equilibrium E_0, we compute the Jacobian F from $\mathcal{F}$ as

$$F = \begin{bmatrix} 0 & \beta_1\left(\tfrac{\rho\Lambda}{\mu} + \eta\tfrac{(1-\rho)\Lambda}{\mu}\right) & \beta_2\left(\tfrac{\rho\Lambda}{\mu} + \eta\tfrac{(1-\rho)\Lambda}{\mu}\right) \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix}$$

and the Jacobian V from $\mathcal{V}$ given by

$$V = \begin{bmatrix} \mu + \sigma & 0 & 0 \\ -\sigma & \gamma + \mu & 0 \\ 0 & -\gamma\delta & \alpha \end{bmatrix},$$

from which the next generation matrix can be calculated as

$$FV^{-1} = \begin{bmatrix} \frac{(\alpha\beta_1+\beta_2\gamma\delta)\Lambda(\eta(1-\rho)+\rho)\sigma}{\alpha\mu(\gamma+\mu)(\mu+\sigma)} & \frac{(\alpha\beta_1+\beta_2\gamma\delta)\Lambda(\eta(1-\rho)+\rho)}{\alpha\mu(\gamma+\mu)} & \frac{\beta_2\Lambda(\eta+\rho-\eta\rho)}{\alpha\mu} \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix}.$$

The eigenvalues of the next generation matrix are $0, 0, \frac{(\alpha\beta_1+\beta_2\gamma\delta)\Lambda(\eta(1-\rho)+\rho)\sigma}{\alpha\mu(\gamma+\mu)(\mu+\sigma)}$. According to [30, 42], the basic reproduction number $\mathcal{R}_0$ is the spectral radius of FV^{-1}, hence we obtain

$$\mathcal{R}_0 = \frac{(\alpha\beta_1 + \beta_2\gamma\delta)\Lambda(\eta(1-\rho)+\rho)\sigma}{\alpha\mu(\gamma+\mu)(\mu+\sigma)}.$$

7.4 Existence of equilibria and stability analysis

7.4.1 Existence of endemic equilibrium

To determine the existence of endemic equilibria, we let the right-hand sides of all equations in (7.2) to be equal to zero. Solving the last three equations we get $E = \frac{I(\gamma+\mu)}{\sigma}$, $R = \frac{I\gamma(1-\delta)}{\mu}$ and $D = \frac{I\gamma\delta}{\alpha}$. Substituting these values in the first three equations,

the system becomes

$$\begin{aligned} S\left(I\left(\beta_1+\frac{\beta_2\gamma\delta}{\alpha}\right)+\mu\right) &= \Lambda\rho, \\ IV\left(\beta_1+\frac{\beta_2\gamma\delta}{\alpha}\right)\eta + V\mu &= \Lambda(1-\rho), \\ \frac{(\gamma+\mu)(\mu+\sigma)}{\sigma} &= \left(\beta_1+\frac{\beta_2\gamma\delta}{\alpha}\right)(S+\eta V). \end{aligned} \tag{7.3}$$

Solving the first two equations of (7.3) for S and V in terms of I, we get $S = \frac{\alpha\Lambda\rho}{I(\alpha\beta_1+\beta_2\gamma\delta)+\alpha\mu}$ and $V = \frac{\alpha\Lambda(1-\rho)}{I(\alpha\beta_1+\beta_2\gamma\delta)\eta+\alpha\mu}$. Substituting these values in the third equation of (7.3) we get the quadratic equation

$$aI^2 + bI + c = 0,$$

where

$$\begin{aligned} a &= (\gamma+\mu)(\mu+\sigma)(\alpha\beta_1+\beta_2\gamma\delta)^2\eta, \\ b &= (\alpha\beta_1+\beta_2\gamma\delta)\left(\alpha\mu(1+\eta)(\gamma+\mu)(\mu+\sigma) - \eta\Lambda\sigma(\alpha\beta_1+\beta_2\gamma\delta)\right), \\ &= (\alpha\beta_1+\beta_2\gamma\delta)\left(\alpha\mu(1+\eta)(\gamma+\mu)(\mu+\sigma) - \Lambda\sigma(\alpha\beta_1+\beta_2\gamma\delta)(\eta+\rho-\eta\rho)\right. \\ &\quad \left. + \Lambda\sigma(\rho-\eta\rho)(\alpha\beta_1+\beta_2\gamma\delta)\right), \\ &= (\alpha\beta_1+\beta_2\gamma\delta)(\alpha\mu\eta(\gamma+\mu)(\mu+\sigma) + \alpha\mu(\gamma+\mu)(\mu+\sigma)(1-\mathcal{R}_0) \\ &\quad + \Lambda\sigma\rho(1-\eta)(\alpha\beta_1+\beta_2\gamma\delta)), \\ c &= -\alpha\mu(\alpha\beta_1+\beta_2\gamma\delta)\Lambda\sigma(\eta(1-\rho)+\rho) + \alpha^2\mu^2(\gamma+\mu)(\mu+\sigma), \\ &= \alpha^2\mu^2(\gamma+\mu)(\mu+\sigma)(1-\mathcal{R}_0). \end{aligned}$$

Clearly, $c < 0$ holds if and only if $\mathcal{R}_0 > 1$. As $a > 0$ independently of the parameters, using Vieta's formulas, we obtain that for $\mathcal{R}_0 \geq 1$, there is exactly one positive solution of the quadratic equation, while if $\mathcal{R}_0 < 1$, there is no positive solution. Therefore, there is no endemic equilibrium if $\mathcal{R}_0 < 1$ and there exists a unique endemic equilibrium if $\mathcal{R}_0 \geq 1$.

7.4.2 Local stability of the equilibria

Theorem 23. *The disease-free equilibrium $E_0\left(\frac{\rho\Lambda}{\mu}, \frac{(1-\rho)\Lambda}{\mu}, 0, 0, 0, 0\right)$ is locally asymptotically stable if $\mathcal{R}_0 < 1$, while E_0 is unstable if the inequality is altered.*

Proof. The Jacobian of system (7.2) evaluated in disease-free equilibrium takes the

form

$$\mathcal{J}(E_0) = \begin{bmatrix} -\mu & 0 & 0 & -\frac{\beta_1\Lambda\rho}{\mu} & 0 & -\frac{\beta_2\Lambda\rho}{\mu} \\ 0 & -\mu & 0 & -\frac{\beta_1\eta\Lambda(1-\rho)}{\mu} & 0 & -\frac{\beta_2\eta\Lambda(1-\rho)}{\mu} \\ 0 & 0 & -\mu-\sigma & \frac{\beta_1\Lambda(\eta+\rho-\eta\rho)}{\mu} & 0 & \frac{\beta_2\Lambda(\eta+\rho-\eta\rho)}{\mu} \\ 0 & 0 & \sigma & -\gamma-\mu & 0 & 0 \\ 0 & 0 & 0 & \gamma-\gamma\delta & -\mu & 0 \\ 0 & 0 & 0 & \gamma\delta & 0 & -\alpha \end{bmatrix},$$

The system is locally asymptotically stable if all the eigenvalues of $\mathcal{J}(E_0)$ have a negative real part. The characteristic equation of $\mathcal{J}(E_0)$ is

$$\Phi(\lambda) \coloneqq (\lambda+\mu)^3(\lambda^3 + C_1\lambda^2 + C_2\lambda + C_3) = 0,$$

where

$$\begin{aligned} C_1 &= \alpha+\gamma+2\mu+\sigma > 0, \\ C_2 &= (\gamma+\mu)(\mu+\sigma)(1-\mathcal{R}_0) + \alpha\sigma + \alpha\gamma + 2\alpha\mu + \frac{\beta_2\Lambda\gamma\delta(\eta(1-\rho)+\rho)}{\alpha\mu}, \\ C_3 &= (\alpha\gamma\mu + \alpha\mu^2 + \alpha\gamma\sigma + \alpha\mu\sigma)(1-\mathcal{R}_0) \end{aligned}$$

Here C_2 and C_3 will be positive if $\mathcal{R}_0 < 1$, Furthermore,

$$\begin{aligned} C_1C_2 - C_3 &= (\alpha+\gamma+\mu+\sigma) \\ &\quad \times \left[(\gamma+\mu)(\mu+\sigma)(1-\mathcal{R}_0) + \alpha\sigma + \alpha\gamma + 2\alpha\mu + \tfrac{\beta_2(\eta\Lambda(1-\rho)+\Lambda\rho)}{\alpha\mu}\right] \\ &\quad - \left[(\alpha\gamma\mu + \alpha\mu^2 + \alpha\gamma\sigma + \alpha\mu\sigma)(1-\mathcal{R}_0)\right] \\ &= \left[(\alpha+\gamma+\mu+\sigma)(\gamma+\mu)(\mu+\sigma) - (\alpha\gamma\mu + \alpha\mu^2 + \alpha\gamma\sigma + \alpha\mu\sigma)\right](1-\mathcal{R}_0) \\ &\quad + (\alpha+\gamma+\mu+\sigma)\left[\alpha\sigma + \alpha\gamma + 2\alpha\mu + \tfrac{\beta_2(\eta\Lambda(1-\rho)+\Lambda\rho)}{\alpha\mu}\right] \\ &= \left[\gamma^2\mu + 2\gamma\mu^2 + \mu^3 + \gamma^2\sigma + 3\gamma\mu\sigma + 2\mu^2\sigma + \gamma\sigma^2 + \mu\sigma^2\right](1-\mathcal{R}_0) \\ &\quad + (\alpha+\gamma+\mu+\sigma)\left[\alpha\sigma + \alpha\gamma + 2\alpha\mu + \tfrac{\beta_2(\eta\Lambda(1-\rho)+\Lambda\rho)}{\alpha\mu}\right] \end{aligned}$$

Again $C_1C_2 - C_3 > 0$ if $\mathcal{R}_0 < 1$. Thus, the Routh–Hurwitz criteria are satisfied if $\mathcal{R}_0 < 1$ and in this case all the eigenvalues of the characteristic equation have negative real parts. Hence, E_0 is stable and is unstable if $\mathcal{R}_0 > 1$. This completes our proof. □

7.4.3 Global stability of the equilibria

In this subsection, we will show the global asymptotic stability of one of the two equilibria, depending on the basic reproduction number. First, we need the following

auxiliary result.

Lemma 24. *For the limit superior of $S(t)$ and $V(t)$, the inequalities*

$$S^{\infty} \leq \frac{\rho\Lambda}{\mu} \quad \textit{and} \quad V^{\infty} \leq \frac{(1-\rho)\Lambda}{\mu}$$

hold.

Proof. According to the fluctuation lemma (see e.g. [113]), there exists a sequence $\{t_n\}$ such that $t_n \to \infty$ we have $S(t_n) \to S^{\infty}$, and $S'(t_n) \to 0$ as $n \to \infty$. Thus, we can say

$$S'(t_n) = \rho\Lambda - (\beta_1 I(t_n) + \beta_2 D(t_n))S(t_n) - \mu S(t_n) \leq \rho\Lambda - \mu S(t_n),$$

which implies

$$0 \leq \rho\Lambda - \mu S^{\infty}$$

and from this

$$S^{\infty} \leq \frac{\rho\Lambda}{\mu}.$$

The other inequality can be shown in an analogous way. □

Theorem 25. *The disease-free equilibrium $E_0\big(\frac{\rho\Lambda}{\mu}, \frac{(1-\rho)\Lambda}{\mu}, 0, 0, 0, 0\big)$ is globally asymptotically stable in $\Gamma := \{(S, V, E, I, R, D) \in \mathbb{R}^6_+\}$ if $\mathcal{R}_0 < 1$.*

Proof. From the calculation of the basic reproduction number for our model, we have the matrices $\mathcal{F}, \mathcal{V}, F$, and V associated with system (7.2). One can easily calculate

$$V^{-1} = \begin{bmatrix} \frac{1}{\mu+\sigma} & 0 & 0 \\ \frac{\sigma}{(\gamma+\mu)(\mu+\sigma)} & \frac{1}{\gamma+\mu} & 0 \\ \frac{\gamma\delta\sigma}{\alpha(\gamma+\mu)(\mu+\sigma)} & \frac{\gamma\delta}{\alpha(\gamma+\mu)} & \frac{1}{\alpha} \end{bmatrix}.$$

Following [171, Theorem 2.1] and using the notations therein, we have the disease compartments $x = (E, I, D)$ and the disease-free compartments $y = (S, V, R)$. Then we define the function $\phi(S, V, E, I, R, D)$ appearing in [171, Theorem 2.1] in the form

$$\begin{aligned} \phi(S, V, E, I, R, D)^T &= (F - V)x - \mathcal{F}(x, y) + \mathcal{V}(x, y) \\ &= \left(\frac{(\beta_1 I + \beta_2 D)(\eta\Lambda(1-\rho) + \Lambda\rho - \mu S - \eta\mu V)}{\mu}, 0, 0 \right). \end{aligned}$$

The function ϕ will be positive if and only if $S + \eta V < \frac{\Lambda\rho}{\mu} + \frac{\Lambda\eta(1-\rho)}{\mu}$ holds. However, from Lemma 3 we know that for any $\epsilon > 0$ there exists a T large enough such

that $S < \frac{\Lambda\rho}{\mu} + \epsilon$ and $V < \frac{\Lambda(1-\rho)}{\mu} + \epsilon$ for all $t > T$. Therefore, the function ϕ will be positive for t large enough. Therefore, each condition mentioned in the above theorem is satisfied, and $\phi > 0$ for $t > T$. Let $\omega^T \geq 0$ be the left eigenvector of the nonnegative matrix $V^{-1}F$ corresponding to $\mathcal{R}_0$. It follows from the theorem that if $\phi \geq 0, F \geq 0, V^{-1} \geq 0$ and $\mathcal{R}_0 \leq 1$ then the function $\omega^T V^{-1}x$, where x stands for the infectious compartments, is a Lyapunov function for the model (7.2). Hence the theorem is proved using LaSalle's invariance principle [172]. □

Theorem 26. *The endemic equilibrium* $E^* := \left(S^*, V^*, E^*, I^*, R^*, D^*\right)$ *is globally asymptotically stable in* $\Gamma := \{(S(t), V(t), E(t), I(t), R(t), D(t)) \in \mathbb{R}^6_+\}$ *if* $\mathcal{R}_0 > 1$.

Proof. Let us define the Lyapunov function $V(t)$ as

$$\begin{aligned} V(t) = {} & \frac{S^*}{E^*}\left(\frac{S}{S^*} - 1 - \ln\frac{S}{S^*}\right) + \frac{V^*}{E^*}\left(\frac{V}{V^*} - 1 - \ln\frac{V}{V^*}\right) + \left(\frac{E}{E^*} - 1 - \ln\frac{E}{E^*}\right) \\ & + \frac{(\beta_1 I^* + \beta_2 D^*)(S^* + \eta V^*)I^*}{\sigma(E^*)^2}\left(\frac{I}{I^*} - 1 - \ln\frac{I}{I^*}\right) \\ & + \frac{\beta_2(S^* + \eta V^*)(D^*)^2}{\delta\gamma I^* E^*}\left(\frac{D}{D^*} - 1 - \ln\frac{D}{D^*}\right) \end{aligned}$$

Consider the function $g\colon \mathbb{R} \to \mathbb{R}$ defined as $g(x) = 1 - x + \ln x$, here $x > 0$ leads to $g(x) \leq 0$, while if $x = 1$ then $g(x) = 0$. So for any $x > 0$ we get $x - 1 \geq \ln x$. The derivative of the Lyapunov function along solutions of system (7.2) can be calculated as

$$\begin{aligned} V'(t) = {} & \tfrac{S^*}{E^*}\tfrac{1}{S^*}\left(1 - \tfrac{S^*}{S}\right)S' + \tfrac{V^*}{E^*}\tfrac{1}{V^*}\left(1 - \tfrac{V^*}{V}\right)V' + \tfrac{1}{E^*}\left(1 - \tfrac{E^*}{E}\right)E' \\ & + \tfrac{(\beta_1 I^* + \beta_2 D^*)(S^* + \eta V^*)I^*}{\sigma(E^*)^2}\tfrac{1}{I^*}\left(1 - \tfrac{I^*}{I}\right)I' + \tfrac{\beta_2(S^* + \eta V^*)(D^*)^2}{\delta\gamma I^* E^*}\tfrac{1}{D^*}\left(1 - \tfrac{D^*}{D}\right)D' \\ = {} & \tfrac{S^*}{E^*}\tfrac{1}{S^*}\left(1 - \tfrac{S^*}{S}\right)\left((\beta_1 I^* + \beta_2 D^*)S^* + \mu S^* - (\beta_1 I + \beta_2 D)S - \mu S\right) \\ & + \tfrac{V^*}{E^*}\tfrac{1}{V^*}\left(1 - \tfrac{V^*}{V}\right)\left(\eta(\beta_1 I^* + \beta_2 D^*)V^* + \mu V^* - \eta(\beta_1 I + \beta_2 D)V - \mu V\right) \\ & + \tfrac{1}{E^*}\left(1 - \tfrac{E^*}{E}\right)\left((\beta_1 I + \beta_2 D)(S + \eta V) - \tfrac{(\beta_1 I^* + \beta_2 D^*)(S^* + \eta V^*)E}{E^*}\right) \\ & + \tfrac{(\beta_1 I^* + \beta_2 D^*)(S^* + \eta V^*)I^*}{\sigma(E^*)^2}\tfrac{1}{I^*}\left(1 - \tfrac{I^*}{I}\right)\left(\sigma E - \tfrac{\sigma E^* I}{I^*}\right) \\ & + \tfrac{\beta_2(S^* + \eta V^*)(D^*)^2}{\delta\gamma I^* E^*}\tfrac{1}{D^*}\left(1 - \tfrac{D^*}{D}\right)\left(\delta\gamma I - \tfrac{\delta\gamma I^* D}{D^*}\right) \\ = {} & \tfrac{S^*}{E^*}\tfrac{1}{S^*}\left(1 - \tfrac{S^*}{S}\right)\left(\beta_1 I^* S^*\left(1 - \tfrac{IS}{I^* S^*}\right) + \beta_2 D^* S^*\left(1 - \tfrac{DS}{D^* S^*}\right) + \mu S^*\left(1 - \tfrac{S}{S^*}\right)\right) \\ & + \tfrac{V^*}{E^*}\tfrac{1}{V^*}\left(1 - \tfrac{V^*}{V}\right)\left(\eta\beta_1 I^* V^*\left(1 - \tfrac{IV}{I^* V^*}\right) + \eta\beta_2 D^* V^*\left(1 - \tfrac{DV}{D^* V^*}\right) + \mu V^*\left(1 - \tfrac{V}{V^*}\right)\right) \\ & + \tfrac{1}{E^*}\left(1 - \tfrac{E^*}{E}\right)\left(\beta_1 I^* S^*\left(\tfrac{IS}{I^* S^*} - \tfrac{E}{E^*}\right) + \beta_2 D^* S^*\left(\tfrac{DS}{D^* S^*} - \tfrac{E}{E^*}\right)\right) \\ & + \tfrac{1}{E^*}\left(1 - \tfrac{E^*}{E}\right)\left(\eta\beta_1 I^* V^*\left(\tfrac{IV}{I^* V^*} - \tfrac{E}{E^*}\right) + \eta\beta_2 D^* V^*\left(\tfrac{DV}{D^* V^*} - \tfrac{E}{E^*}\right)\right) \\ & + \tfrac{(\beta_1 I^* + \beta_2 D^*)(S^* + \eta V^*)I^*}{\sigma(E^*)^2}\tfrac{1}{I^*}\left(1 - \tfrac{I^*}{I}\right)\sigma E^*\left(\tfrac{E}{E^*} - \tfrac{I}{I^*}\right) \\ & + \tfrac{\beta_2(S^* + \eta V^*)(D^*)^2}{\delta\gamma I^* E^*}\tfrac{1}{D^*}\left(1 - \tfrac{D^*}{D}\right)\delta\gamma I^*\left(\tfrac{I}{I^*} - \tfrac{D}{D^*}\right) \end{aligned}$$

$$
\begin{aligned}
&\leq \tfrac{\beta_1 I^* S^*}{E^*}\left(1-\tfrac{S^*}{S}-\tfrac{IS}{I^*S^*}+\tfrac{I}{I^*}\right)+\tfrac{\beta_2 D^* S^*}{E^*}\left(1-\tfrac{S^*}{S}-\tfrac{DS}{D^*S^*}+\tfrac{D}{D^*}\right)\\
&\quad+\tfrac{\eta\beta_1 I^* V^*}{E^*}\left(1-\tfrac{V^*}{V}-\tfrac{IV}{I^*V^*}+\tfrac{I}{I^*}\right)+\tfrac{\eta\beta_2 D^* V^*}{E^*}\left(1-\tfrac{V^*}{V}-\tfrac{DV}{D^*V^*}+\tfrac{D}{D^*}\right)\\
&\quad+\tfrac{\beta_1 I^* S^*}{E^*}\left(\tfrac{IS}{I^*S^*}-\tfrac{E^*IS}{EI^*S^*}-\tfrac{E}{E^*}+1\right)+\tfrac{\beta_2 D^* S^*}{E^*}\left(\tfrac{DS}{D^*S^*}-\tfrac{E^*DS}{ED^*S^*}-\tfrac{E}{E^*}+1\right)\\
&\quad+\tfrac{\eta\beta_1 I^* V^*}{E^*}\left(\tfrac{IV}{I^*V^*}-\tfrac{E^*IV}{EI^*V^*}-\tfrac{E}{E^*}+1\right)+\tfrac{\eta\beta_2 D^* V^*}{E^*}\left(\tfrac{DV}{D^*V^*}-\tfrac{E^*DV}{ED^*V^*}-\tfrac{E}{E^*}+1\right)\\
&\quad+\tfrac{(\beta_1 I^*+\beta_2 D^*)(S^*+\eta V^*)}{E^*}\left(\tfrac{E}{E^*}-\tfrac{I^*E}{IE^*}-\tfrac{I}{I^*}+1\right)\\
&\quad+\tfrac{\beta_2(S^*+\eta V^*)D^*}{E^*}\left(\tfrac{I}{I^*}-\tfrac{D^*I}{DI^*}-\tfrac{D}{D^*}+1\right)\\
&\leq \tfrac{\beta_1 I^* S^*}{E^*}\left(\tfrac{I}{I^*}-\ln\tfrac{I}{I^*}-1-\tfrac{S^*}{S}+\ln\tfrac{S}{S^*}+1-\tfrac{IS}{I^*S^*}+\ln\tfrac{IS}{I^*S^*}+1\right)\\
&\quad+\tfrac{\beta_2 D^* S^*}{E^*}\left(\tfrac{D}{D^*}-\ln\tfrac{D}{D^*}-1-\tfrac{S^*}{S}+\ln\tfrac{S}{S^*}+1-\tfrac{DS}{D^*S^*}+\ln\tfrac{DS}{D^*S^*}+1\right)\\
&\quad+\tfrac{\eta\beta_1 I^* V^*}{E^*}\left(\tfrac{I}{I^*}-\ln\tfrac{I}{I^*}-1-\tfrac{V^*}{V}+\ln\tfrac{V}{V^*}+1-\tfrac{IV}{I^*V^*}+\ln\tfrac{IV}{I^*V^*}+1\right)\\
&\quad+\tfrac{\eta\beta_2 D^* V^*}{E^*}\left(\tfrac{D}{D^*}-\ln\tfrac{D}{D^*}-1-\tfrac{V^*}{V}+\ln\tfrac{V}{V^*}+1-\tfrac{DV}{D^*V^*}+\ln\tfrac{DV}{D^*S^*}+1\right)\\
&\quad+\tfrac{\beta_1 I^* S^*}{E^*}\left(\tfrac{IS}{I^*S^*}-\ln\tfrac{IS}{I^*S^*}-\tfrac{E}{E^*}+\ln\tfrac{E}{E^*}\right)+\tfrac{\beta_2 D^* S^*}{E^*}\left(\tfrac{DS}{D^*S^*}-\ln\tfrac{DS}{D^*S^*}-\tfrac{E}{E^*}+\ln\tfrac{E}{E^*}\right)\\
&\quad+\tfrac{\eta\beta_1 I^* V^*}{E^*}\left(\tfrac{IV}{I^*V^*}-\ln\tfrac{IV}{I^*V^*}-\tfrac{E}{E^*}+\ln\tfrac{E}{E^*}\right)\\
&\quad+\tfrac{\eta\beta_2 D^* V^*}{E^*}\left(\tfrac{DV}{D^*V^*}-\ln\tfrac{DV}{D^*V^*}-\tfrac{E}{E^*}+\ln\tfrac{E}{E^*}\right)\\
&\quad+\tfrac{(\beta_1 I^*+\beta_2 D^*)(S^*+\eta V^*)}{E^*}\left(\tfrac{E}{E^*}-\ln\tfrac{E}{E^*}-\tfrac{I}{I^*}+\ln\tfrac{I}{I^*}\right)\\
&\quad+\tfrac{\beta_2(S^*+\eta V^*)D^*}{E^*}\left(\tfrac{I}{I^*}-\ln\tfrac{I}{I^*}-\tfrac{D}{D^*}+\ln\tfrac{D}{D^*}\right)\\
&\leq \tfrac{\beta_1 S^* I^*}{E^*}\left(\tfrac{I}{I^*}-\ln\tfrac{I}{I^*}-\tfrac{IS}{I^*S^*}+\ln\tfrac{IS}{I^*S^*}\right)+\tfrac{\beta_2 D^* S^*}{E^*}\left(\tfrac{D}{D^*}-\ln\tfrac{D}{D^*}-\tfrac{DS}{D^*S^*}+\ln\tfrac{DS}{D^*S^*}\right)\\
&\quad+\tfrac{\eta\beta_1 V^* I^*}{E^*}\left(\tfrac{I}{I^*}-\ln\tfrac{I}{I^*}-\tfrac{IV}{I^*V^*}+\ln\tfrac{IV}{I^*V^*}\right)\\
&\quad+\tfrac{\eta\beta_2 D^* V^*}{E^*}\left(\tfrac{D}{D^*}-\ln\tfrac{D}{D^*}-\tfrac{DV}{D^*V^*}+\ln\tfrac{DV}{D^*S^*}\right)\\
&\quad+\tfrac{\beta_1 I^* S^*}{E^*}\left(\tfrac{IS}{I^*S^*}-\ln\tfrac{IS}{I^*S^*}-\tfrac{E}{E^*}+\ln\tfrac{E}{E^*}\right)+\tfrac{\beta_2 D^* S^*}{E^*}\left(\tfrac{DS}{D^*S^*}-\ln\tfrac{DS}{D^*S^*}-\tfrac{E}{E^*}+\ln\tfrac{E}{E^*}\right)\\
&\quad+\tfrac{\eta\beta_1 I^* V^*}{E^*}\left(\tfrac{IV}{I^*V^*}-\ln\tfrac{IV}{I^*V^*}-\tfrac{E}{E^*}+\ln\tfrac{E}{E^*}\right)\\
&\quad+\tfrac{\eta\beta_2 D^* V^*}{E^*}\left(\tfrac{DV}{D^*V^*}-\ln\tfrac{DV}{D^*V^*}-\tfrac{E}{E^*}+\ln\tfrac{E}{E^*}\right)\\
&\quad+\tfrac{(\beta_1 I^*+\beta_2 D^*)(S^*+\eta V^*)}{E^*}\left(\tfrac{E}{E^*}-\ln\tfrac{E}{E^*}-\tfrac{I}{I^*}+\ln\tfrac{I}{I^*}\right)\\
&\quad+\tfrac{\beta_2(S^*+\eta V^*)D^*}{E^*}\left(\tfrac{I}{I^*}-\ln\tfrac{I}{I^*}-\tfrac{D}{D^*}+\ln\tfrac{D}{D^*}\right)\\
&= \tfrac{\beta_1 I^* S^*}{E^*}\left(\tfrac{I}{I^*}-\ln\tfrac{I}{I^*}-\tfrac{E}{E^*}+\ln\tfrac{E}{E^*}\right)+\tfrac{\beta_2 D^* S^*}{E^*}\left(\tfrac{D}{D^*}-\ln\tfrac{D}{D^*}-\tfrac{E}{E^*}+\ln\tfrac{E}{E^*}\right)\\
&\quad+\tfrac{\eta\beta_1 I^* V^*}{E^*}\left(\tfrac{I}{I^*}-\ln\tfrac{I}{I^*}-\tfrac{E}{E^*}+\ln\tfrac{E}{E^*}\right)+\tfrac{\eta\beta_2 D^* V^*}{E^*}\left(\tfrac{D}{D^*}-\ln\tfrac{D}{D^*}-\tfrac{E}{E^*}+\ln\tfrac{E}{E^*}\right)\\
&\quad+\tfrac{(\beta_1 I^*+\beta_2 D^*)(S^*+\eta V^*)}{E^*}\left(\tfrac{E}{E^*}-\ln\tfrac{E}{E^*}-\tfrac{I}{I^*}+\ln\tfrac{I}{I^*}\right)\\
&\quad+\tfrac{\beta_2(S^*+\eta V^*)D^*}{E^*}\left(\tfrac{I}{I^*}-\ln\tfrac{I}{I^*}-\tfrac{D}{D^*}+\ln\tfrac{D}{D^*}\right)\\
&= \tfrac{\beta_1 I^*(S^*+\eta V^*)}{E^*}\left(\tfrac{I}{I^*}-\ln\tfrac{I}{I^*}-\tfrac{E}{E^*}+\ln\tfrac{E}{E^*}\right)\\
&\quad+\tfrac{\beta_2 D^*(S^*+\eta V^*)}{E^*}\left(\tfrac{D}{D^*}-\ln\tfrac{D}{D^*}-\tfrac{E}{E^*}+\ln\tfrac{E}{E^*}\right)\\
&\quad+\tfrac{(\beta_1 I^*+\beta_2 D^*)(S^*+\eta V^*)}{E^*}\left(\tfrac{E}{E^*}-\ln\tfrac{E}{E^*}-\tfrac{I}{I^*}+\ln\tfrac{I}{I^*}\right)\\
&\quad+\tfrac{\beta_2(S^*+\eta V^*)D^*}{E^*}\left(\tfrac{I}{I^*}-\ln\tfrac{I}{I^*}-\tfrac{D}{D^*}+\ln\tfrac{D}{D^*}\right)
\end{aligned}
$$

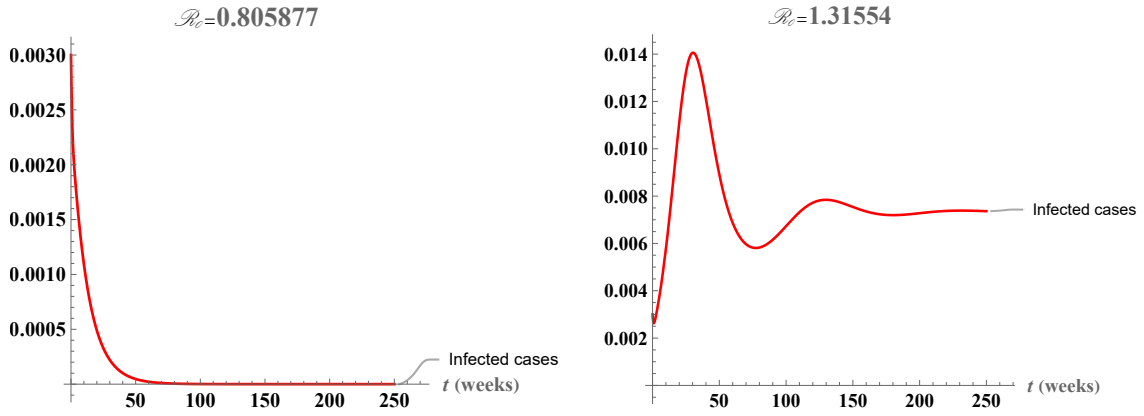
$$
\begin{aligned}
&= \tfrac{\beta_1 I^*(S^*+\eta V^*)}{E^*}\left(\tfrac{I}{I^*} - \ln\tfrac{I}{I^*} - \tfrac{E}{E^*} + \ln\tfrac{E}{E^*}\right) + \tfrac{\beta_2 D^*(S^*+\eta V^*)}{E^*}\left(-\tfrac{E}{E^*} + \ln\tfrac{E}{E^*}\right)\\
&\quad + \tfrac{(\beta_1 I^*+\beta_2 D^*)(S^*+\eta V^*)}{E^*}\left(\tfrac{E}{E^*} - \ln\tfrac{E}{E^*} - \tfrac{I}{I^*} + \ln\tfrac{I}{I^*}\right)\\
&\quad + \tfrac{\beta_2(S^*+\eta V^*)D^*}{E^*}\left(\tfrac{I}{I^*} - \ln\tfrac{I}{I^*}\right)\\
&= 0.
\end{aligned}
$$

From the previous calculation, it is clear that $V'(t) \leq 0$. Furthermore, the equality $V'(t) = 0$ holds only if $S = S^*, V = V^*, E = E^*, I = I^*$, and $D = D^*$. Thus, the endemic equilibrium E^*, is the only positive invariant set to the system (7.2) contained entirely in $\Gamma \coloneqq \{(S(t), V(t), E(t), I(t), R(t), D(t)) \in \mathbb{R}^6_+\}$. Therefore, it follows from LaSalle's invariance principle [172] that every solution of system (7.2) with initial conditions in Γ converges to the endemic equilibrium point, E^*, as $t \to \infty$. Hence, the positive equilibrium is globally asymptotically stable if $\mathcal{R}_0 > 1$. □

To support our analytical results, we present some numerical simulations showing the two possible scenarios concerning the global dynamics of system (7.2). We chose baseline parameter values realistic for Ebola and shown in Table 7.2 with the exception of Λ and μ, which are chose to have the value $\Lambda = \mu = 0.0388$ as, for better visibility of the results, we decided to scale the population to 1 in this simulation. With these parameter values, we obtain $\mathcal{R}_0 = 1.31554$, corresponding to the disease becoming endemic and the the endemic equilibrium being globally asymptotically stable. Changing the values of the two transmission rates to $\beta_1 = 0.273$ and $\beta_2 = 1.226$, the basic reproduction number is decreased to 0.805877, hence, in this case, the disease dies out and the disease-free equilibrium is globally asymptotically stable. The case of the disease dying out is shown in Figure 7.2a, while the situation of the disease becoming endemic in the population is depicted in Figure 7.2b.

7.5 Assessing the effects of transmission by deceased on disease spread

In this section, we perform numerical simulations to assess the effects of disease transmission via contact with the corpses of those deceased due to an infectious disease. Using the baseline values for the available parameter values as listed in Table 7.2, we utilize the Latin Hypercube Sampling method to find the parameter values which provide the best fit to the data. This is a computational technique used in statistics to estimate the simultaneous variation of various model parameters to construct a representative sample set of n-tuples of parameters (n is the number of parameters fitted) taking values from given ranges. The estimated values of the fitted parameters of the model are given in Table 7.2. Although, as mentioned in the introduction, there is a risk of becoming infected this way with several infectious



(a) *Global asymptotic stability of the disease-free equilibrium for* $\mathcal{R}_0 < 1$.

(b) *Global asymptotic stability of the endemic equilibrium for* $\mathcal{R}_0 > 1$.

Figure 7.2: *Global dynamics of model* (7.2) *for different values of* $\mathcal{R}_0$.

diseases, however, the situation might be very different in various cases. Hence, in our simulations, we will consider three infectious diseases with significantly different concerns regarding transmission from the deceased. The three diseases studied in this section are Ebola virus disease, COVID-19, and Nipah fever.

Table 7.2: *Parameters value of the model* (7.2).

Parameters	Ebola and Ref.	COVID-19 and Ref.	Nipah and Ref.
Λ	11826/week [117]	184.83 /day [117]	19.57/day [117]
μ	0.00054/week [117]	0.000033/day [117]	0.00004145/day [117]
β_1	2.375×10^{-8} /week [173]	2.0×10^{-8}/day [174]	5.93×10^{-7}/day [12, 110]
β_2	9.71×10^{-8}/week [158, 161]	3.42×10^{-9}/day [Assumed]	5.08×10^{-7}/day [107, 110]
η	–	0.03 [175]	–
$1/\sigma$	1.498 weeks [176, 177]	5.2 days [178]	8.34 days [179]
$1/\gamma$	0.175 weeks [180]	10 days [181]	11.1 days [12]
$1/\alpha$	0.762 weeks [182]	3 days [Assumed]	1.71 days [Assumed]
δ	0.69 [176, 183]	0.02 [184]	0.76 [107]

The role of transmission from the deceased is widely known in the case of Ebola as during the large outbreak in 2014 outbreak, several articles in the news reported about the traditional funeral ceremonies which included touching and kissing the deceased. For this reason, we chose this disease as our first example, considering a baseline scenario similar to the first weeks of 2014–16 epidemic in Liberia, Sierra Leone, and Guinea.

This situation corresponds to a case where transmission from the deceased highly contributes to the number of new infections, while the total number of infected is moderate with respect to the total population. Furthermore, as there was no vaccine available at the time of the epidemic, we exclude vaccination from our model in this

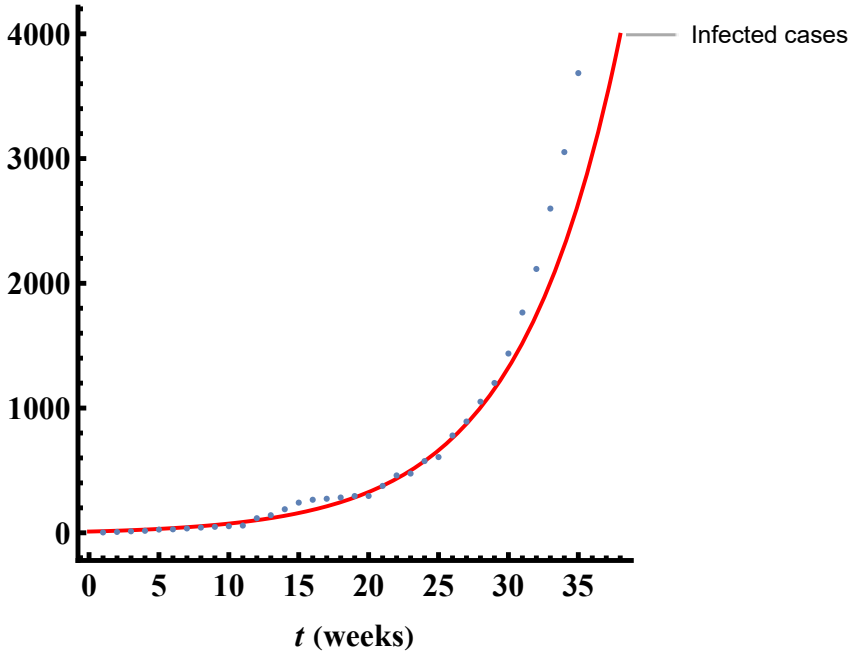
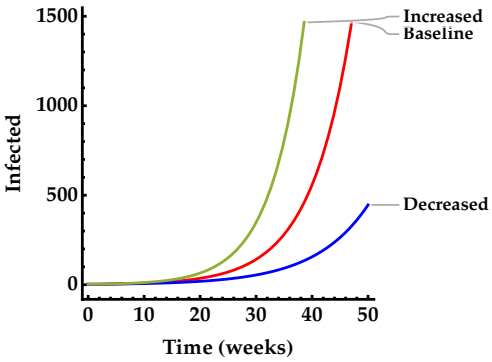


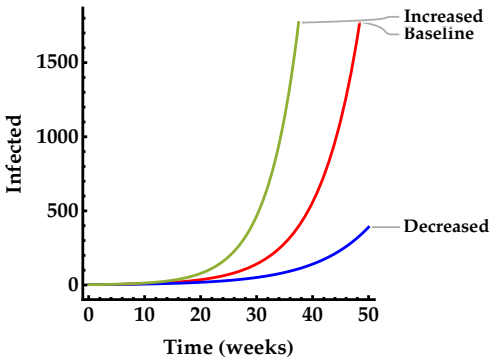
Figure 7.3: *Model* (7.2) *applied to Ebola data of the first 38 weeks of the 2015 epidemic in Guinea, Liberia, and Sierra Leone*

case and use model (7.2) for the simulation. Figure 7.3 shows the solution of model (7.2) with parameters given in Table 7.2 applied to Ebola data of the first 38 weeks of the 2015 epidemic in Guinea, Liberia, and Sierra Leone. Figure 7.4 shows the expected result of changes in parameter values connected to transmission from the deceased. Namely, we consider a change in the transmission rate β_2, corresponding to a reduction of contacts with deceased and decreasing the probability of transmission by increasing hygiene, then a change in the average time until burial, $1/\alpha$, and finally, a parallel change of the two parameters. The three panels of the figure compare the baseline situation to an increase and a decrease of the parameters. The results suggest that the transmission rate from the deceased is a very important parameter in view of the number of infected: an increase of this value can result in much higher numbers of cases, while a successful introduction of an intervention measure affecting this parameter can be very useful in reducing disease burden (see Figure 7.4a). Figure 7.4b suggests that although less impactful than β_2, the time until the burial is also an important parameter, and encouraging fast and safe burials might save plenty of people from infection.

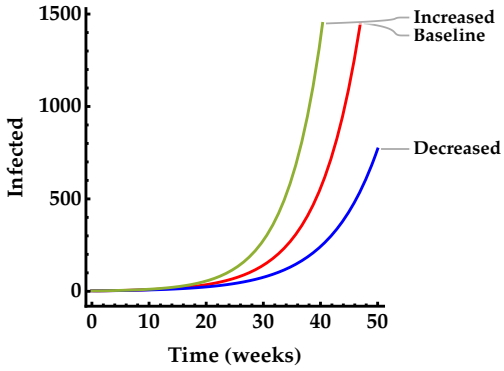
Another recent epidemic where transmission from the deceased is possible is the COVID-19 pandemic [185, 186], for this disease, we take the situation in Finland from 3 Jan 2021 to 21 Nov 2021 [187], after the introduction of vaccination as an example. So we have used model (7.1) for the simulation. Although various reports have confirmed this way of transmission, it is much less important than in the



(a) *Baseline* $\beta_2 = 8.82 \times 10^{-8}$. *Increased* $\beta_2 = 9.82 \times 10^{-8}$. *Decreased* $\beta_2 = 7.82 \times 10^{-8}$.



(b) *Baseline* $\alpha = 1.31$. *Increased* $\alpha = 1.11$. *Decreased* $\alpha = 1.51$.



(c) *Baseline* $\beta_2 = 8.82 \times 10^{-8}, \alpha = 1.31$. *Increased* $\beta_2 = 8.92 \times 10^{-8}, \alpha = 1.21$. *Decreased* $\beta_2 = 8.72 \times 10^{-8}, \alpha = 1.41$.

Figure 7.4: *Number of Ebola virus infected cases for changing* β_2 *and* α *along with their parallel application.*

case of Ebola. One can identify two main possibilities for disease transmission from deceased: one is for those who lived in the same household with the deceased individual, and another way is in health care facilities. The latter is especially crucial in case of a large epidemic when the health system is overwhelmed and it is difficult to handle the corpses. Such situations arose in several countries during the COVID pandemic [167, 188, 189]. Unlike Ebola, in this case, it is not the high transmission rate, but the high number of infections and victims that provide a risk of the occurrence of an elevated number of infections due to contact with the infected deceased. Accordingly, as our simulations shown in Figure 7.6 suggest, in comparison with the total number of infected, infections via contact with victims of the epidemic are relatively small. However, due to the magnitude of the pandemic, even in this case, several cases and deaths can be spared if proper attention is paid to avoiding direct contact

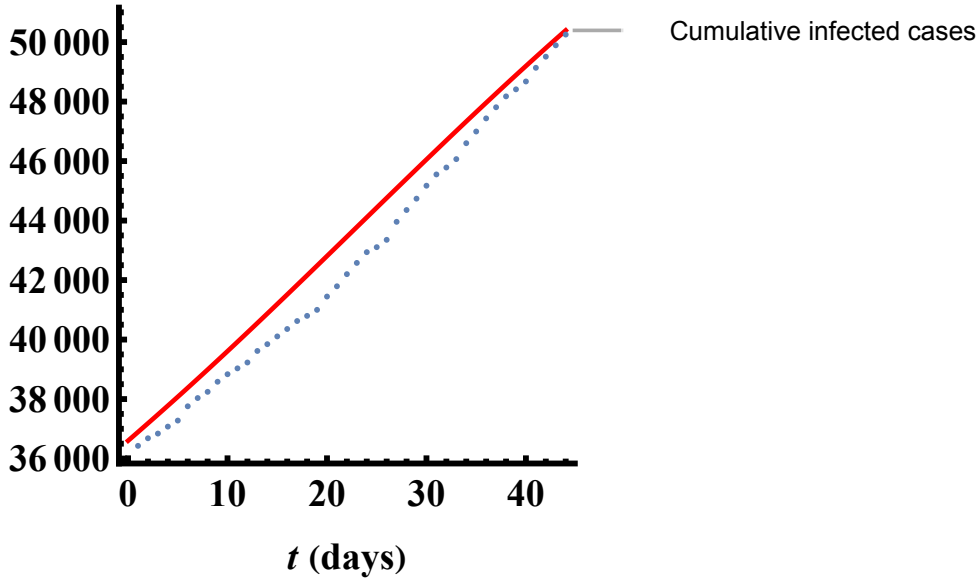


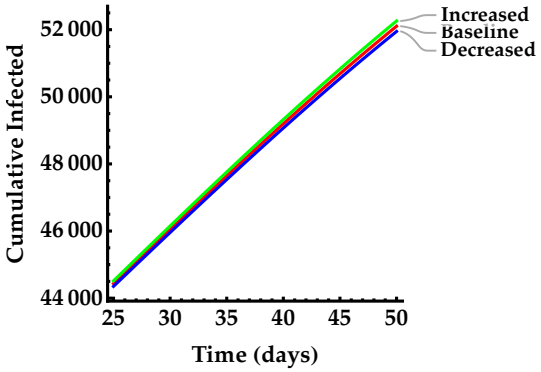
Figure 7.5: *Model* (7.1) *applied to COVID-19 data from spring 2021 in Finland*

with victims of the epidemic.

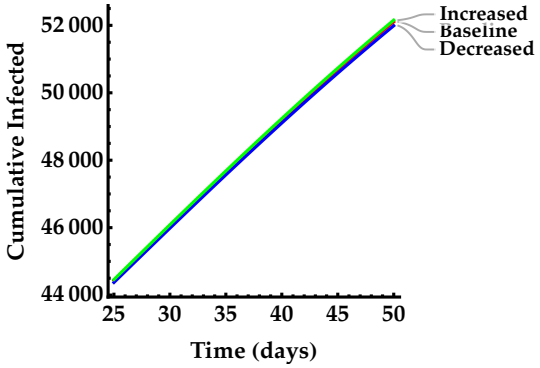
Our third example is Nipah fever, a highly lethal emerging disease that appears in the WHO Blueprint list of epidemic threats needing urgent R&D action [169]. Drinking raw date palm sap, contaminated by Virus from urine or saliva of *Pteropus* fruit bats, is one of the main transmission routes to humans in Bangladesh, however, it was reported that corpse-to-human transmission is also an important way of disease spread due to caregivers being exposed to bodily secretions of infected deceased during ritual bathing of the corps and traditional burial practices [169]. In comparison with the other two diseases, the number of infections is much lower, however, according to various studies (see [107, 110, 169]), transmission from deceased might significantly contribute to new infections, like Ebola, so we have used model (7.2) for simulation. As there is no certified vaccine for NiV, we chose the Siliguri outbreak in early 2001 as an example, a solution approximating data of this epidemic [190] is shown in Figure 7.7. Although less significant than in the case of Ebola, again we can see important changes in the number of infections. Even a small increase in the value of both parameters can increase the number of infected individuals significantly in comparison with the total number of infected.

7.5.1 PRCC analysis

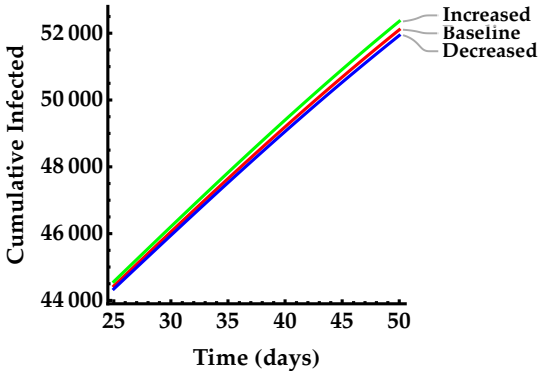
To compare the effects of varying the values of deceased-related parameters with those of other parameters, we performed PRCC analysis, a statistical measure used to determine the strength and direction of the linear relationship between two vari-



(a) *Baseline* $\beta_2 = 3.429 \times 10^{-9}$.
Increased $\beta_2 = 6.429 \times 10^{-9}$.
Decreased $\beta_2 = 0.429 \times 10^{-9}$.



(b) *Baseline* $\alpha = 0.333$.
Increased $\alpha = 0.25$.
Decreased $\alpha = 1$.



(c) *Baseline* $\beta_2 = 3.429 \times 10^{-9}, \alpha = 0.333$.
Increased $\beta_2 = 6.429 \times 10^{-9}, \alpha = 0.25$.
Decreased $\beta_2 = 0.429 \times 10^{-9}, \alpha = 1$.

Figure 7.6: *Number of COVID-19 cumulative infected cases for changing* β_2 *and* α *along with their parallel application.*

ables, while controlling for the effects of other variables. The results for all three epidemics are shown in Figure 7.9. One can see that the PRCC values are in accordance with the results shown in the simulations of the previous subsection. The values show that among the three diseases, it is Ebola for which transmission from deceased contributes the most to the number of infections, while for COVID-19, a very mild effect is shown. The same holds for the average time of burial. As for parameters unrelated to transmission from deceased, we see that transmission from infected has the highest impact, while the length of infectious period is shown to be less important for Ebola, while significant for the other two diseases. Most certainly, the vaccination rate has a very high negative effect on the number of infections in the case of COVID-19.

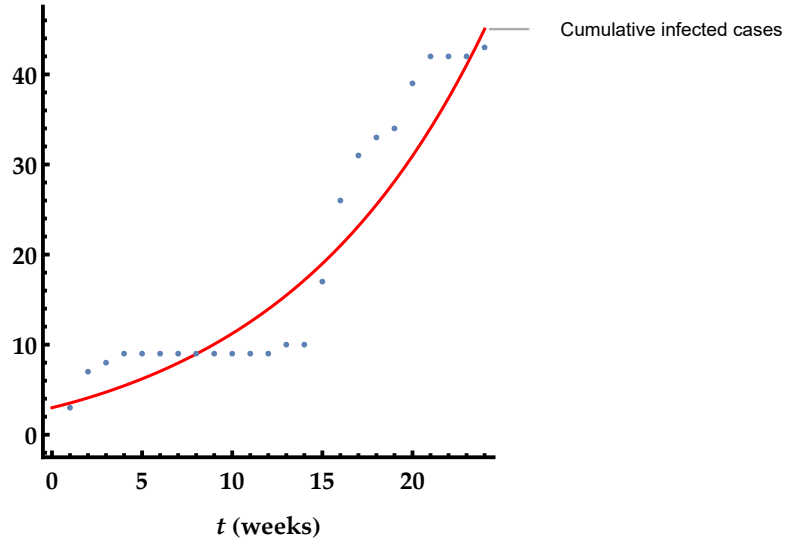
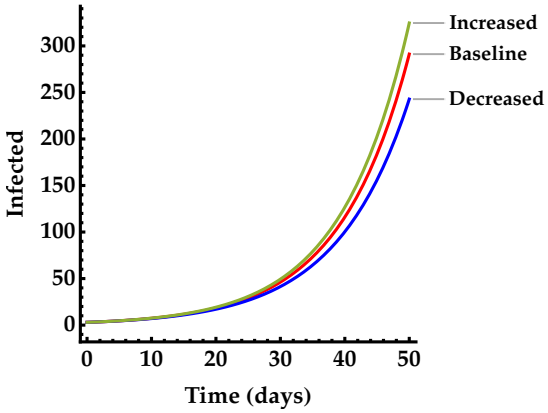


Figure 7.7: *Model* (7.2) *applied to the 2001 Nipah outbreak in Siliguri, India.*

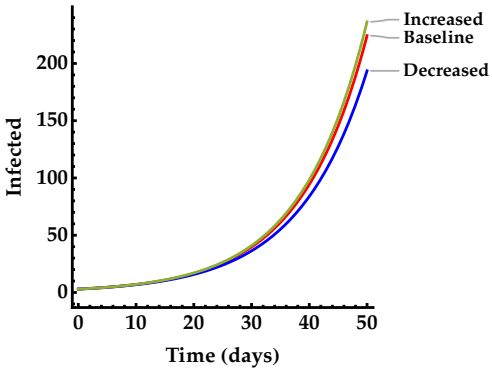
7.6 Conclusions

We established a compartmental model to assess the importance of transmission due to contact with victims of an epidemic, a phenomenon known to occur in many infectious diseases, including Ebola haemorrhagic fever, COVID-19, and plague. The model also includes vaccination, one of the most important tools to protect ourselves from infection. In our work, vaccination is assumed to be imperfect, i.e., those who have received the vaccine can still become infected, however, with a lower probability. We first performed theoretical analysis for a special case of the model, namely, when vaccination takes place after birth and vaccination of adults are neglected. After determining some basic properties of the model and calculating the basic reproduction number, we applied a result by van den Driessche and Shuai to show global asymptotic stability of the disease-free equilibrium in the case $\mathcal{R}_0 < 1$, while constructing an appropriate Lyapunov function allowed us to prove the same for the endemic equilibrium in case $\mathcal{R}_0 > 1$.

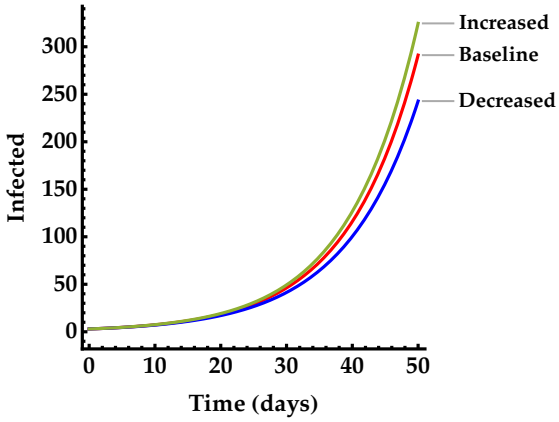
Following the analytical results, we performed numerical simulations to estimate the disease burden due to infection via contact with deceased individuals. To do so, we selected three recent epidemics with different characteristics. The three diseases chosen were Ebola, COVID-19, and Nipah fever. Both Ebola and Nipah fever are known for an important contribution of infections by deceased to the total number of cases. This phenomenon is less typical for COVID-19. For this latter disease, it is the immense number of cases that might result in a significant number of infections caused by contact with deceased infected. On the other hand, up to now, the world has not experienced Ebola or Nipah outbreaks of the scale of the COVID pan-



(a) *Baseline* $\beta_2 = 0.00000051$. *Increased* $\beta_2 = 0.00000057$. *Decreased* $\beta_2 = 0.00000044$.



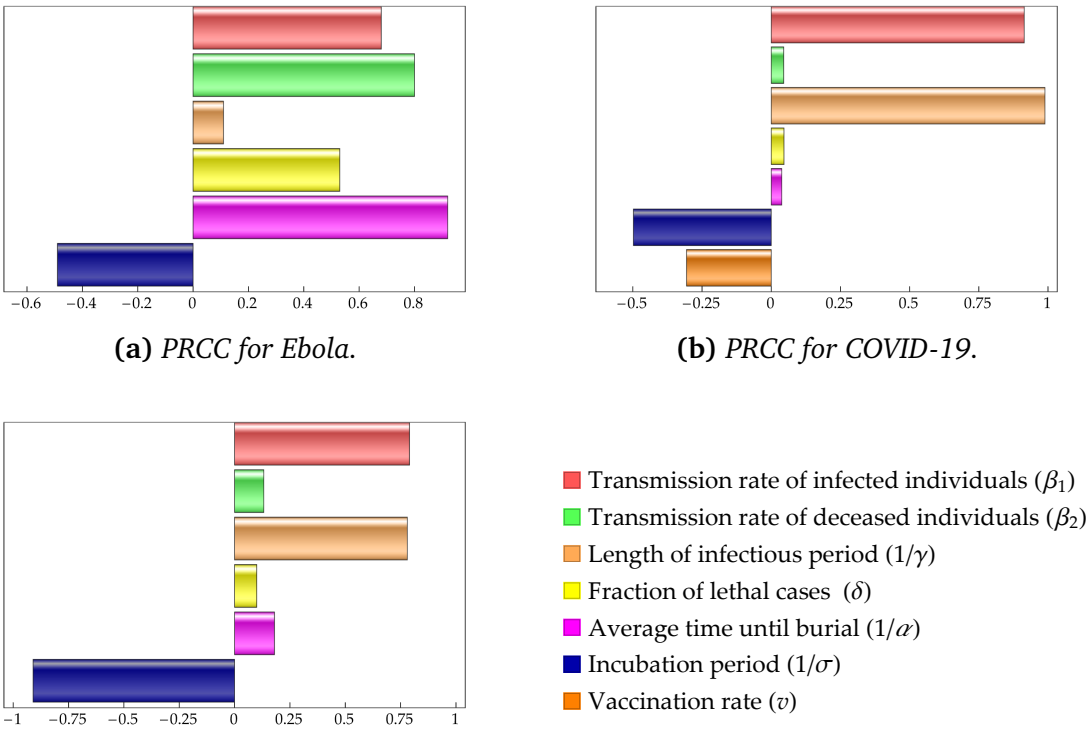
(b) *Baseline* $\alpha = 0.583336$. *Increased* $\alpha = 0.5$. *Decreased* $\alpha = 1$.



(c) *Baseline* $\beta_2 = 0.00000051, \alpha = 0.583336$. *Increased* $\beta_2 = 0.00000057, \alpha = 0.5$. *Decreased* $\beta_2 = 0.00000044, \alpha = 1$.

Figure 7.8: *Number of Nipah virus infected cases for changing* β_2 *and* α *along with their parallel application.*

demic. The numerical results are in accordance with the known characteristics of the diseases and show that in the case of Ebola and Nipah, where traditional funeral ceremonies contribute to transmission from deceased, this way of spread might result in a significant increase of the number of infected. People should keep away from contact with the bodies of people who have died from Ebola and avoid funeral or burial practices that involve touching the body of someone who is suspected or confirmed to have had Ebola disease. At the same time, the simulations suggest that for such epidemics, a very efficient way to reduce the epidemic spread is to diminish this way of transmission as much as possible. On the contrary, generalizing the results of our simulations regarding the COVID-19 epidemic, we may conclude that if corpses are



(a) *PRCC for Ebola.*

(b) *PRCC for COVID-19.*

(c) *PRCC for Nipah.*

Figure 7.9: *Partial Rank Correlation Coefficients (PRCC).*

handled in a safe and adequate way and contact of susceptibles with them is reduced, then even in the case of a large-scale epidemic, one may more or less eliminate the contribution of deceased to disease spread. Furthermore, guidelines from WHO and CDC for an epidemic are to be followed to eradicate the disease.

Our work certainly has its limitations. First of all, we decided to create a general model which might not include some characteristics of a special disease. However, this allowed us to obtain analytical results on the global dynamics of the system which might not be possible in case of a very complex model taking into account all specialties of the given disease. Establishing and studying such more realistic models can be considered a future work.

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Summary

The PhD thesis examines the transmission dynamics of the Nipah virus by using compartmental models, both autonomous and non-autonomous, with time-dependent (periodic) parameters. The basic reproduction number ($\mathcal{R}_0$) describes the dynamics of the system, which has also been demonstrated in our autonomous model to be a threshold parameter with respect to disease extinction or persistence. For periodic compartmental models, $\mathcal{R}_0$ is defined as the spectral radius of an integral operator acting on the space of continuous periodic functions. Our goal is to demonstrate that for $\mathcal{R}_0 < 1$, the disease-free periodic solution of our recently developed models is globally asymptotically stable, whereas, for $\mathcal{R}_0 > 1$, the disease remains endemic and there exists at least one positive ω-periodic solution. Additionally, a modeling analysis to assess the effect of disease transmission from deceased individuals and an $SIRS$ epidemic model for a zoonotic disease with a general nonlinear incidence rate assuming that the animal population has already reached an endemic equilibrium are analyzed in this dissertation.

In Chapter 2, we discuss mathematical modeling in epidemiology. It explores the historical journey of this field, tracing its evolution up to the present day. The chapter covers the fundamentals of various compartmental models used to understand infectious diseases, highlighting their practical applications in different scenarios.

Chapter 3 serves as a comprehensive introduction, which meticulously provides a concise and illuminating description of various aspects related to the Nipah virus, such as its intriguing origin and identification. Within this chapter, the outbreak history associated with this virus and its impact on public health, and its implications for disease management are provided. Symptoms exhibited by individuals infected with the Nipah virus, its clinical manifestations, and diagnosis are described. Lastly, this chapter comes up with the reservoirs of the Nipah virus and an overview of previous studies.

Nipah virus is a serious threat to public health, especially in South-East Asia, and its recurring outbreaks and alarmingly high fatality rate have raised widespread concerns, making it one of the most worrisome infectious diseases in existence. To capture the dynamics of Nipah virus transmission, in Chapter 4 we develop and evaluate a novel SIRS model that takes into account the role of the intermediate host pigs and the reservoir species fruit bats as well as the loss of immunity of recov-

ered individuals, and assuming that interspecies transmission is only one-directional, from bats to pigs and humans and from pigs to humans. With the use of the latter property, we were able to decouple the equations for pigs and bats in order to arrive at an equation for the limit of humans. We obtain a unique type of model with a linear term explaining the transition from susceptibles to infected due to interspecies transmission from both the limit subsystems for pigs and humans.

We identified all possible equilibria of the system and calculated three threshold parameters that, by identifying which of the three species the disease becomes endemic in, define the overall dynamics of the system. We were able to fully explain the overall dynamics of our model by supplying suitable Lyapunov functions. In order to validate our model, identify the critical factors affecting illness transmission, and investigate the impact of potential intervention strategies, we also carried out numerical experiments. Our findings are consistent with observations made during the Malaysian outbreak in 1998–1999 and point to the intermediate host pigs as the most crucial characteristics.

In Chapter 5 we develop a straightforward, innovative compartmental model for zoonotic diseases. We only take into account zoonotic transmission as a linear term corresponding to the movement of susceptibles to the infectious class as a result of transmission from animals, rather than including the typical compartments for the animals as well, presuming that the animal population is already in an endemic equilibrium state. The model takes into account a general incidence rate as well as the declining immunity of recovered patients in addition to zoonotic transmission. Our new model differs from those because a new term μ for zoonotic transmission has emerged. Additionally, the global dynamics differ from past studies in that no disease-free equilibrium occurs as a result of zoonotic transmission, and the typical threshold dynamics indicated by the basic reproduction number cannot be observed. We alter variables in order to define a Lyapunov function, which is inspired by earlier studies. This allows us to demonstrate that our model's singular endemic equilibrium is globally asymptotically stable, regardless of the parameters.

In Chapter 6 we propose a model for Nipah virus disease transmission in a periodic environment, taking into account all human-to-host animal transmission as well as the loss of immunity in those who have recovered. We studied the existence and uniqueness of a disease-free ω-periodic solution and later deal with the basic reproduction number and stability analysis showing that the disease-free periodic solution is globally asymptotically stable if the basic reproduction number is less than 1, while the disease persists in the population otherwise. To support the analytical results we provide some numerical examples and assess the effect of parameter changes on disease dynamics, which might help to understand how to avoid a yearly periodic recurrence of the disease.

In order to evaluate the significance of transmission resulting from contact with

the deceased of an epidemic, a phenomenon known to occur in many infectious diseases, including Ebola haemorrhagic fever, COVID-19, and plague, in Chapter 7 we construct a compartmental model. One of the most crucial methods for preventing illness is included in the model as vaccination. In our research, we consider vaccination to be imperfect, meaning that those who have received the shot still have a chance of contracting the disease. The model's exceptional situation, in which vaccination occurs after birth and adult vaccination is disregarded, was the focus of our initial theoretical investigation. In light of the analytical findings, we ran numerical simulations to calculate the illness burden resulting from interaction with deceased people. To do this, three diseases picked were Nipah fever, COVID-19, and Ebola. It is well known that fatal infections from both Ebola and Nipah fever significantly contribute to the overall number of cases. For COVID-19, this condition is less common. With regard to the latter disease, it is the vast number of cases that could lead to a sizable number of infections brought on by contact with diseased corpses. However, there haven't yet been any Ebola or Nipah epidemics of the same size as the COVID pandemic. People should avoid coming into contact with the remains of Ebola victims and refrain from touching the bodies of those who have either been confirmed or suspected of having the disease during funeral or burial rituals. The simulation also implies that minimizing this method of transmission as much as possible is a highly effective technique to stop the spread of the epidemic. Contrarily, extrapolating from the outcomes of our simulations regarding the COVID-19 epidemic, we may draw the conclusion that, even in the case of a widespread epidemic, one may largely eliminate the contribution of the deceased to the disease if corpses are handled in a safe and appropriate manner and contact with susceptibles with them is minimized.

The dissertation is based on the following four scientific papers, the last three of which are submitted to journals, and the first one is accepted.

(1) Saumen Barua, Attila Dénes. Global dynamics of a compartmental model for the spread of Nipah virus. Accepted in *Heliyon*.

(2) Saumen Barua, Attila Dénes. Global stability in an SIRS model with zoonotic transmission, nonlinear incidence rate and temporary immunity. Submitted.

(3) Saumen Barua, Mahmoud A. Ibrahim, Attila Dénes. A compartmental model for the spread of Nipah virus in a periodic environment. Submitted.

(4) Saumen Barua, Attila Dénes. Global dynamics of a compartmental model to assess the effect of transmission from deceased. Accepted in *Mathematical Biosciences*.

Összefoglalás

A doktori értekezés a Nipah-vírus terjedési dinamikáját vizsgálja autonóm és időfüggő (periodikus) paraméterekkel rendelkező nemautonóm, kompartmentmodellek segítségével. A rendszer dinamikáját a reprodukciós szám ($\mathcal{R}_0$) írja le, amelyről autonóm modellünkben is belátjuk, hogy küszöbparaméterként szolgál a betegség kihalása vagy fennmaradása szempontjából. Periodikus kompartmentmodellek esetén az $\mathcal{R}_0$ a folytonos periodikus függvények terén ható integráloperátor spektrálsugaraként definiálható. Célunk annak bizonyítása, hogy $\mathcal{R}_0 < 1$ esetén az általunk nemrég kifejlesztett modell betegségmentes periodikus megoldása globálisan aszimptotikusan stabil, míg $\mathcal{R}_0 > 1$ esetén a betegség endémiás és legalább egy pozitív ω-periodikus megoldás létezik. Ezen túlmenően a disszertációban egy olyan modellt is vizsgálunk, amelyben a betegségben elhunytak által történő fertőzések hatását tanulmányozzuk, valamint egy általános, nemlineáris incidenciarátával rendelkező zoonotikus betegség $SIRS$ járványmodelljét vizsgáljuk, feltételezve, hogy az állatpopuláció már elérte az endémiás egyensúlyt.

A 2. Fejezetben a matematikai járványtani modellekről nyújtunk rövid áttekintést. Ismertetjük e kutatási terület történetét, nyomon követve fejlődését egészen napjainkig. A fejezet a fertőző betegségek megértéséhez használt különböző kompartmentmodellek alapjait tárgyalja, kiemelve azok gyakorlati alkalmazását különböző szituációkban.

A 3. Fejezet átfogó bevezetésként szolgál, amely részletesen, tömören és világosan ismerteti a Nipah-vírussal kapcsolatos különböző tényeket, például annak érdekes eredetét és leírását. Ebben a fejezetben ismertetjük a Nipah-vírus okozta járványok történetét és a közegészségügyre gyakorolt hatását, valamint a betegség kezelésének lehetőségeit. A Nipah-vírussal fertőzött személyek által mutatott tünetek, a betegség klinikai képe és a diagnózis ismertetése. Végül ez a fejezet a Nipah-vírus számára rezervoárként szolgáló fajok és a korábbi tanulmányok áttekintésével zárul.

A Nipah-vírus komoly veszélyt jelent a közegészségügyre, különösen Délkelet-Ázsiában, és a visszatérő járványok, valamint a riasztóan magas halálozási arány széles körben aggodalmat keltett, így ez az egyik legaggasztóbb fertőző betegség. A Nipah-vírus terjedési dinamikájának leírására a 4. Fejezetben egy új SIRS-modellt dolgozunk ki és vizsgálunk, amely figyelembe veszi a köztes gazda sertések és a rezervoárfaj denevérek szerepét, valamint a gyógyult egyedek immunitásvesztését, és

feltételezi, hogy a fajok közötti terjedés csak egyirányú, a denevérekről a sertésekre és az emberekre, illetve a sertésekről az emberekre. Ez utóbbi tulajdonság felhasználásával sikerült szétválasztani a sertésekre és a denevérekre vonatkozó egyenleteket, hogy az emberekre vonatkozó határegyenlethez jussunk. Egyedülálló típusú modellt kapunk, amelyben a fajok közötti átvitel miatt a fogékonyakból a fertőzöttek osztályába való átmenetet leíró lineáris tag mind a sertésekre, mind az emberekre vonatkozó határérték-alrendszerekből származik.

Az 5. Fejezetben a zoonotikus betegségek egyszerű, innovatív kompartmentmodelljét dolgoztuk ki. A zoonotikus terjedést csak lineáris tagként szerepel, amely a fogékonyaknak az állatokról történő átvitel következtében a fertőző osztályba való átkerülésének felel meg, ahelyett, hogy az állatokra vonatkozó kompartmenteket is figyelembe vennénk, feltételezve, hogy az állatpopuláció már endémiás egyensúlyi állapotban van. A modell a zoonotikus általános incidenciafüggvényt tartalmaz, valamint figyelembe veszi a gyógyult betegek csökkenő immunitását is. Az új modellünk abban különbözik az eddigiektől, hogy a zoonotikus átvitelt egy új μ paraméter írja le. Emellett a globális dinamika annyiban különbözik a korábbi tanulmányoktól, hogy a zoonotikuss átvitel következtében nem alakul ki betegségmentes egyensúly, és nem figyelhető meg a reprodukciós szám által meghatározott tipikus küszöbdinamika. Ahhoz, hogy egy új, korábbi tanulmányok által ihletett Ljapunovfüggvényt konstruálhassunk, a változókat transzformáljuk, ami lehetővé teszi számunkra annak bizonyítását, hogy modellünk egyetlen, endémiás egyensúlya a paraméterektől függetlenül globálisan aszimptotikusan stabil.

A 6. Fejezetben egy, a Nipah-vírus periodikus környezetben történő terjedését leíró modellt adunk meg, amely figyelembe veszi az ember és a gazdaszervezet állatfaj közötti átvitelt, valamint a gyógyult állatok immunitásának csökkenését. Megvizsgáltuk a betegségmentes ω-periodikus megoldás létezését és unicitását, majd meghatároztuk a reprodukciós számot és a rendszer stabilitási tulajdonságait vizsgáltuk, megmutatva, hogy a betegségmentes periodikus megoldás globálisan aszimptotikusan stabil, ha a reprodukciós szám kisebb, mint 1, míg egyébként a betegség fennmarad a populációban. Az analitikus eredmények alátámasztására néhány numerikus példát mutattunk, és vizsgáltuk a paraméterek változásának hatását a betegség dinamikájára, ami segíthet megérteni, hogyan lehet elkerülni a betegség évenkénti periodikus ismétlődését.

A 7. Fejezetben egy kompartmentmodellt állítunk fel annak érdekében, hogy vizsgáljuk a járványban elhunytakkal való érintkezésből eredő átvitel jelentőségét, amely jelenség számos fertőző betegség, többek között az Ebola, a COVID-19 és a pestis esetében ismert. A betegségek megelőzésének egyik legfontosabb módszere, a vakcinálás is szerepel a modellben. Kutatásunkban az oltásról feltesszük, hogy nem nyújt tökéletes védelmet, ami azt jelenti, hogy az oltottak is elkaphatják a betegséget.

Elméleti vizsgálatunk középpontjában a modell speciális esete állt, amelyben az

oltás a születés után történik, és a felnőttkori oltást figyelmen kívül hagyjuk. Az analitikus eredmények fényében numerikus szimulációkat végeztünk az elhunytakkal való interakcióból eredő fertőzések becslésére. Ehhez három betegséget választottunk ki: a Nipah-lázat, a COVID-19-et és az Ebolát. Köztudott, hogy mind az Ebola, mind a Nipah-láz halálos kimenetelű fertőzései jelentősen hozzájárulnak az összes megbetegedés számához. A COVID-19 esetében ez az jelenség kevésbé gyakori. Ami az utóbbi betegséget illeti, az esetek nagy száma az, ami a betegségben elhunytakkal való érintkezésből eredő fertőzések jelentős számához vezethet. A COVID-járványhoz hasonló méretű Ebola- vagy Nipah-járvány azonban még nem volt.

Az embereknek kerülniük kell az Ebolában elhunytakkal való érintkezést, és a temetési szertartások során tartózkodniuk kell az igazoltan vagy gyaníthatóan fertőzöttek testének megérintésétől. Szimulációink arra is utalnak, hogy a járvány terjedésének megállítására rendkívül hatékony módszer, ha az átvitel ezen módját a lehető legkisebbre csökkentjük. Ezzel szemben a COVID-19 járványra vonatkozó szimulációnk eredményeiből levonhatjuk azt a következtetést, hogy még egy széles körű járvány esetén is nagymértékben csökkenthető az elhunytak hozzájárulása a betegséghez, ha a holttesteket biztonságosan és megfelelő módon kezelik, és minimalizálják a velük való érintkezést.

A disszertáció a következő négy tudományos dolgozaton alapul, amelyek közül az utolsó hármat közlésre benyújtottuk különböző folyóiratokhoz, az elsőt pedig közlésre elfogadták.

(1) Saumen Barua, Attila Dénes. Global dynamics of a compartmental model for the spread of Nipah virus. *Heliyon*, közlésre elfogadva.

(2) Saumen Barua, Attila Dénes. Global stability in an SIRS model with zoonotic transmission, nonlinear incidence rate and temporary immunity. Benyújtva.

(3) Saumen Barua, Mahmoud A. Ibrahim, Attila Dénes. A compartmental model for the spread of Nipah virus in a periodic environment. Benyújtva.

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[5] **S. Barua**, B. Das, A. Dénes, A compartmental model for COVID-19 to assess effects of non-pharmaceutical interventions with emphasis on contact-based quarantine. Accepted in *Studia Universitatis Babeș–Bolyai Mathematica*.

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[10] **S. Barua**, B. Das, A. Dénes, A compartmental model for COVID-19 to assess effects of non-pharmaceutical interventions with emphasis on contact-based quarantine. *14th Joint Conference on Mathematics and Computer Science Cluj-Napoca, Romania*, November 24–27, 2022.

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