รายงานวิจัยฉบับสมบูรณ์

แบบจำลองคณิตศาสตร์ของโรคอหิวาสำหรับการแพร่ระบาดที่เกิดจากการย้ายถิ่นฐานของผู้ติดเชื้อ

ดร.ชัยรัตน์ มดนาค

พฤษภาคม 2559

สัญญาเลขที่ R2559C143

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ภาควิชาคณิตศาสตร์ คณะวิทยาศาสตร์

กองทุนวิจัยมหาวิทยาลัยนเรศวร

บทคัดย่อ

งานวิจัยนี้ได้ศึกษาเกี่ยวกับการระบาดของโรคอหิวาและการควบคุม โดยผู้ศึกษาเน้นเรื่องการแบ่งกลุ่มสุ่มเสี่ยงออกเป็นสองกลุ่ม โดยกลุ่มแรกมีความสุ่มเสี่ยงสูงต่อการติดเชื้อและสามารถแพร่เชื้อโรคไปสู่กลุ่มคนอื่นได้อย่างรวดเร็ว ส่วนอีกกลุ่มคือกลุ่มที่มีความสุ่มเสี่ยงน้อยต่อการติดเชื้อ ดังนั้นการแบ่งคนออกเป็นกลุ่มๆจึงมีประโยชน์ต่อการวางแผนการควบคุมโดยใช้วัคซีน ซึ่งผลการศึกษาพบว่าวัคซีนสามารถลดจำนวนผู้ติดเชื้อโรคอหิวาลงได้ถ้ามีการวางแผนที่ดี

คำสำคัญ : โรคอหิวา การรักษาด้วยการฉีดวัคซีน การหาค่าเหมาะสม การควบคุมโรค

Abstract

In this study, we presented several Cholera mathematical models. Our model formulation is based on SIR model and is modified from the model proposed by Jin Wang and Chairat Modnak. The epidemic and endemic analysis including the calculation of the reproductive number are conducted. Optimal vaccination plan for two different clusters of Susceptibles, $S1$ and $S2$, are investigated. The results show that with a well vaccination plan, the number of infections for both group can be reduced and eventually an outbreak will be stopped. We will extend to multigroup for our future work.

Keyword: Cholera model, Disease control, Stability, Optimal control, Multigroup

Executive Summary

1. ความสำคัญและที่มาของปัญหาที่ทำการวิจัย

โรคอหิวาเป็นโรคร้ายแรง ผู้ติดเชื้อที่ปราศจากการรักษาอย่างถูกต้อง สามารถเสียชีวิตได้อย่างเฉียบพลัน การระบาดของโรคอหิวาเกิดได้หลายสาเหตุ อย่างเช่น การดื่มน้ำที่ปนเปื้อนเชื้อแบคทีเรียสายพันธ์ Vibrio Cholerae หรืออาหารดิบๆสุกๆซึ่งมีเชื้อแบคทีเรียสายพันธ์นี้ปนเปื้อน ส่วนการแพร่ระบาดของโรคจากคนสู่คนไม่ค่อยพบเห็นมากนัก

ไม่นานมานี้ เราจะเห็นว่ายังมีข่าวการแพร่ระบาดของโรคนี้ทั่วโลก และจะเห็นว่าจำนวนครั้งที่เกิดเพิ่มมากขึ้นทุกๆปี ครั้งล่าสุดในปี 2010-2011 ในประเทศ Haiti เป็นการกลับมาระบาดครั้งยิ่งใหญ่ของโรคนี้อีกครั้งในยุคสมัยใหม่นี้ และเป็นครั้งที่ร้ายแรงที่สุด โดยจากรายงานพบว่า มีผู้ติดเชื้อมากกว่า 530,000 ราย และเสียชีวิตมากกว่า 7,000 ราย [1] การระบาดของโรคครั้งสำคัญๆที่มีผู้เสียชีวิตเป็นจำนวนมากยังพบเห็นได้ในหลายประเทศ อาทิเช่น Sierra Leone ในปี 2012, Nigeria ในปี 2010, Vietnam ในปี 2009, Zimbabwe ในปี 2008 และประเทศอินเดียในปี 2007 สำหรับประเทศไทยยังพบผู้ติดเชื้อโรคอหิวาทุกปี โดยข้อมูลจากสำนักระบาดวิทยา กรมควบคุมโรค พบว่า ตั้งแต่วันที่ 1 มกราคม – 18 กันยายน 2555 ได้รับรายงานผู้ป่วยยืนยันอหิวาตกโรค จำนวน 29 ราย โดยมีรายงานจาก 10 จังหวัด ได้แก่ จังหวัดตาก 13 ราย ยะลา 5 ราย กรุงเทพ 4 ราย เชียงใหม่ ประจวบคีรีขันธ์ ตราด สุพรรณบุรี นครราชสีมา ภูเก็ต ระนอง จังหวัดละ 1 ราย [2]

มีการศึกษาโดยใช้แบบจำลองคณิตศาสตร์มากมายสำหรับโรคอหิวา เพื่อทำความเข้าใจเกี่ยวกับโรค พฤติกรรมของการแพร่ระบาดของโรค รวมทั้งการควบคุมการแพร่ระบาด ในปี 2009 Mukandavire [3] เสนอแบบจำลองทางคณิตศาสตร์ที่ไม่ซับซ้อนมากนัก ง่ายต่อการเข้าใจ และมีความซับซ้อนในการหาผลเฉลยทางตัวเลขน้อย ซึ่งเป็นแบบจำลองที่ผู้วิจัยมากมายนำไปต่อยอด โดยที่โมเดลคือ

$$\frac{dS}{dt} = \mu N - \beta_e S \frac{B}{k+B} - \beta_h SI - \mu S$$

$$\frac{dI}{dt} = \beta_e S \frac{B}{k+B} + \beta_h SI - (\gamma + \mu) I$$

$$\frac{dR}{dt} = \gamma I - \mu R$$

$$\frac{dB}{dt} = \varepsilon I - \delta B$$

โดยที่ S คือ กลุ่มสุ่มเสี่ยงของผู้ติดเชื่อ I คือ กลุ่มผู้ติดเชื้อ R คือ กลุ่มผู้ที่ได้รับการรักษาหายแล้ว และ B คือ กลุ่มประชากรของแบคทีเรีย โดยที่พารามิเตอร์อื่นๆคือค่าคงตัวต่างๆ

2. **วัตถุประสงค์**

เพื่อสร้างแบบจำลองทางคณิตศาสตร์ในการอธิบายการระบาดของโรคอหิวาโดยการศึกษาการแบ่งกลุ่มประชากร

3. **ระเบียบวิธีวิจัย**

3.1 ศึกษาแบบจำลองทางคณิตศาสตร์ต้นแบบที่นำเสนอโดย Mukandavire

3.2 ศึกษาแบบจำลองทางคณิตศาสตร์อื่นๆที่เกี่ยวข้องกับโรคอหิวาเพื่อเป็นประโยชน์ต่อการขยายโมเดล

3.3 สร้างแบบจำลองทางคณิตศาสตร์ขั้นสูงสำหรับโรคอหิวาโดยการแบ่งกลุ่มประชากร

3.4 ตรวจสอบความถูกต้องของโมเดล

3.5 ศึกษาความเป็นไปได้ในการขยายแบบจำลองทางคณิตศาสตร์เพื่องานวิจัยในอนาคตและการประยุกต์ใช้

3.6 สรุปและเขียนงานวิจัย เพื่อตีพิมพ์ในวารสารและรายงานไปยังเจ้าของทุนวิจัย

4. แผนการดำเนินงานวิจัย

กิจกรรม	เดือนที่											
	1	2	3	4	5	6	7	8	9	10	11	12
1. ศึกษาแบบจำลองทางคณิตศาสตร์ต้นแบบที่นำเสนอโดย Mukandavire												
2. ศึกษาแบบจำลองทางคณิตศาสตร์อื่นๆที่เกี่ยวข้องกับโรคอหิวาเพื่อเป็นประโยชน์ต่อการขยายโมเดล												
3. สร้างแบบจำลองทางคณิตศาสตร์ขั้นสูงสำหรับโรคอหิวาสำหรับการแบ่งกลุ่มประชากร และตรวจสอบความถูกต้อง												
4. ศึกษาความเป็นไปได้ในการขยายแบบจำลองทางคณิตศาสตร์เพื่องานวิจัยในอนาคตและการประยุกต์ใช้												
5. สรุปและเขียนงานวิจัย เพื่อตีพิมพ์ในวารสารและรายงานไปยังเจ้าของทุนวิจัย												

5. ตัวชี้วัดเพื่อการเมินผลสำเร็จของโครงการ

5.1 ตีพิมพ์ในวารสารระดับนานาชาติที่มีค่า Impact Factor **จำนวน 1 เรื่อง**

เนื้อหางานวิจัย

(ดูรายระเอียดทั้งหมดดังเอกสารแนบหน้าถัดไป)

LIST OF CONTENTS

Chapter 1

Introduction

Key facts

- Cholera is an acute diarrhoeal disease that can kill within hours if left untreated.
- There are an estimated 3–5 million cholera cases and 100,000–120,000 deaths due to cholera every year.
- Up to 80% of cases can be successfully treated with oral rehydration salts.
- Effective control measures rely on prevention, preparedness and response.
- Provision of safe water and sanitation is critical in reducing the impact of cholera and other waterborne diseases.
- Oral cholera vaccines are considered an additional means to control cholera, but should not replace conventional control measures.

Cholera is an acute diarrhoeal infection caused by ingestion of food or water contaminated with the bacterium Vibrio cholerae. Every year, there are an estimated 3–5 million cholera cases and 100 000–120 000 deaths due to cholera. The short incubation period of two hours to five days, enhances the potentially explosive pattern of outbreaks.

Symptoms

Cholera is an extremely virulent disease. It affects both children and adults and can kill within hours. About 75% of people infected with V. cholerae do not develop any symptoms, although the bacteria are present in their faeces for 7–14 days after infection and are shed back into the environment, potentially infecting other people.

Among people who develop symptoms, 80% have mild or moderate symptoms, while around 20% develop acute watery diarrhoea with severe dehydration. This can lead to death if untreated.

People with low immunity – such as malnourished children or people living with HIV – are at a greater risk of death if infected.

History

During the 19th century, cholera spread across the world from its original reservoir in the Ganges delta in India. Six subsequent pandemics killed millions of people across all continents. The current (seventh) pandemic started in South Asia in 1961, and reached Africa in 1971 and the Americas in 1991. Cholera is now endemic in many countries.

Vibrio cholerae strains

Two serogroups of V. cholerae – O1 and O139 – cause outbreaks. V. cholerae O1 causes the majority of outbreaks, while O139 – first identified in Bangladesh in 1992 – is confined to South-East Asia.

Non-O1 and non-O139 V. cholerae can cause mild diarrhoea but do not generate epidemics.

Recently, new variant strains have been detected in several parts of Asia and Africa. Observations suggest that these strains cause more severe cholera with higher case fatality rates. Careful epidemiological monitoring of circulating strains is recommended.

The main reservoirs of V. cholerae are people and aquatic sources such as brackish water and estuaries, often associated with algal blooms. Recent studies indicate that global warming creates a favourable environment for the bacteria.

Risk factors and disease burden

Cholera transmission is closely linked to inadequate environmental management. Typical at-risk areas include peri-urban slums, where basic infrastructure is not available, as well as camps for internally displaced people or refugees, where minimum requirements of clean water and sanitation are not met.

The consequences of a disaster – such as disruption of water and sanitation systems, or the displacement of populations to inadequate and overcrowded camps – can increase the risk of cholera transmission should the bacteria be present or introduced. Epidemics have never arisen from dead bodies.

Cholera remains a global threat to public health and a key indicator of lack of social development. Recently, the re-emergence of cholera has been noted in parallel with the ever-increasing size of vulnerable populations living in unsanitary conditions.

The number of cholera cases reported to WHO continues to rise. For 2011 alone, a total of 589 854 cases were notified from 58 countries, including 7816 deaths. Many more cases were unaccounted for due to limitations in surveillance systems and fear of trade and travel sanctions. The true burden of the disease is estimated to be 3–5 million cases and 100 000–120 000 deaths annually.

Prevention and control

A multidisciplinary approach based on prevention, preparedness and response, along with an efficient surveillance system, is key for mitigating cholera outbreaks, controlling cholera in endemic areas and reducing deaths.

Treatment

Cholera is an easily treatable disease. Up to 80% of people can be treated successfully through prompt administration of oral rehydration salts (WHO/UNICEF ORS standard sachet). Very severely dehydrated patients require administration of intravenous fluids. Such patients also require appropriate antibiotics to diminish the duration of diarrhoea, reduce the volume of rehydration fluids needed, and shorten the duration of V. cholerae excretion. Mass administration of antibiotics is not recommended, as it has no effect on the spread of cholera and contributes to increasing antimicrobial resistance.

In order to ensure timely access to treatment, cholera treatment centres (CTCs) should be set up among the affected populations. With proper treatment, the case fatality rate should remain below 1%.

Outbreak response

Once an outbreak is detected, the usual intervention strategy is to reduce deaths by ensuring prompt access to treatment, and to control the spread of the disease by providing safe water, proper sanitation and health education for improved hygiene and safe food handling practices by the community. The provision of safe water and sanitation is a formidable challenge but remains the critical factor in reducing the impact of cholera.

Oral cholera vaccines

There are two types of safe and effective oral cholera vaccines currently available on the market. Both are whole-cell killed vaccines, one with a recombinant B-sub unit, the other without. Both have sustained protection of over 50% lasting for two years in endemic settings.

Both vaccines are WHO-prequalified and licensed in over 60 countries. Dukoral has been shown to provide short-term protection of 85–90% against V. cholerae O1 among all age groups at 4–6 months following immunization.

The other vaccine (Shanchol) provides longer-term protection against V. cholerae O1 and O139 in children under five years of age.

Both vaccines are administered in two doses given between seven days and six weeks apart. The vaccine with the B-subunit (Dukoral) is given in 150 ml of safe water.

Chapter 2

Basic Concepts

In this chapter, we will present some interesting mathematical models that describes the cholera dynamics. We will start with an early compartmental model that includes only a few state equations. The more complicated Cholera model then will be studied. Finally, we will present and carefully study a model proposed by Jin Wang and Chairat Modnak. Then, we will extend the model and explore strategies to control an cholera outbreak.

Basic Model

Kermack and Mckendrick proposed the following model in 1927

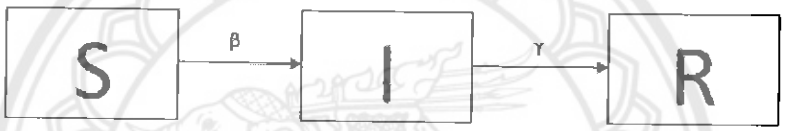

Figure 2.1: The SIR model.

$$\begin{aligned} \frac{dS}{dt} &= -\beta SI, \\ \frac{dI}{dt} &= -\beta SI - \gamma I, \\ \frac{dR}{dt} &= \gamma I, \end{aligned}$$

where

- S is the susceptible state.
- I is the infected state.
- R is the recovered from the disease state.
- βN is the appropriate contact sufficient to transmit in transmit.
- γ is the infectives recover rate.

Basic SIS model

This next simple model is

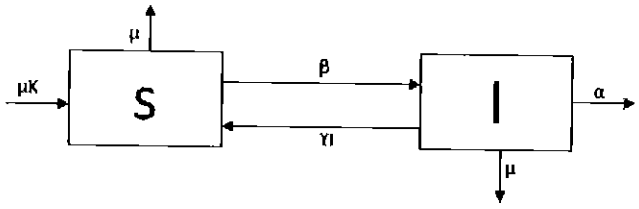

Figure 2.2: The SIS model.

$$\frac{dS}{dt} = -\beta SI + \mu(K\text{-}S) + \gamma I$$
$$\frac{dI}{dt} = \beta SI - (\alpha + \mu + \gamma)I$$

where

- S is the susceptible state.
- I is the infected state.
- N is the total population size.
- μ is natural death rate.
- K is birth rate.
- γ is the rate of recovered individuals are removed from the infective class.
- α is the disease-related death rate from infective class.
- β is the contact rate.

Basic SIR model

The first SIR type model was proposed by H.E. Soper. He assumed that the total population size is constant and the birth rate and death rate are constant. His model is

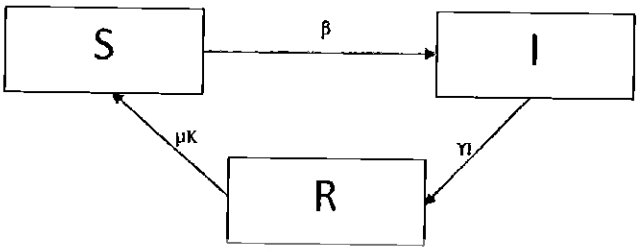

Figure 2.3: The basic SIR model.

$$\begin{aligned} \frac{dS}{dt} &= -\beta SI + \mu k \\ \frac{dI}{dt} &= \beta SI - \gamma I \\ \frac{dR}{dt} &= \gamma I + \mu k \end{aligned}$$

where

- S is the susceptible state.
- I is the infected state.
- R is the recovered from the disease state.
- β is the contact rate.
- γ is recovery.
- μ is natural death rate.
- μk is is birth rate.

The modified SIR model proposed by Jin Wang and Chirat Modnak

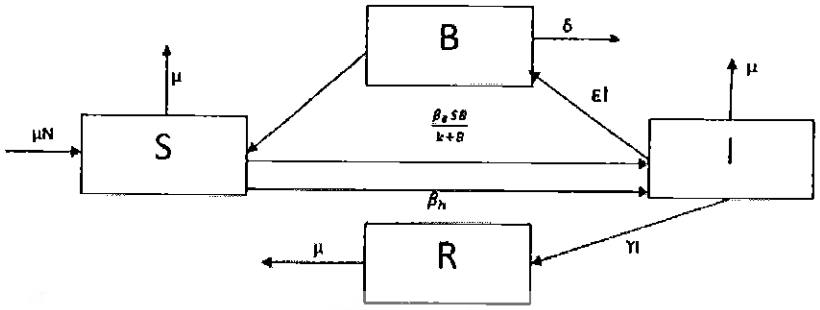

Figure 2.4: The modified SIR model.

$$\begin{aligned}
\frac{dS}{dt} &= \mu N - \frac{\beta_e SB}{k+B} - \beta_h SI - \mu S \\
\frac{dI}{dt} &= \frac{\beta_e SB}{k+B} + \beta_h SI - (\gamma + \mu)I \\
\frac{dB}{dt} &= \varepsilon I - \delta B \\
\frac{dR}{dt} &= \gamma I - \mu R
\end{aligned}$$

where

- S is the susceptible state.
- I is the infected state.
- B is the concentration of the vibrios in the environment state.
- R is the recovered human population state.
- N is the total population state.
- μ natural human birth/death rate.
- ε is the rate of human contribution (e.g.,shedding) to V.cholerae.
- δ is the natural death rate of V.cholerae.
- γ is the rate of recovery from cholera.

. k is the pathogen concentration that yields 50% chance of catching cholera.

. β_e and β_h represent rates of ingesting vibrios from the contaminated water and through human-to-human interaction.

The SVIS model

Let us now consider a SIS type disease when a vaccination program is in effect and there is a constant flow of incoming immigrants.

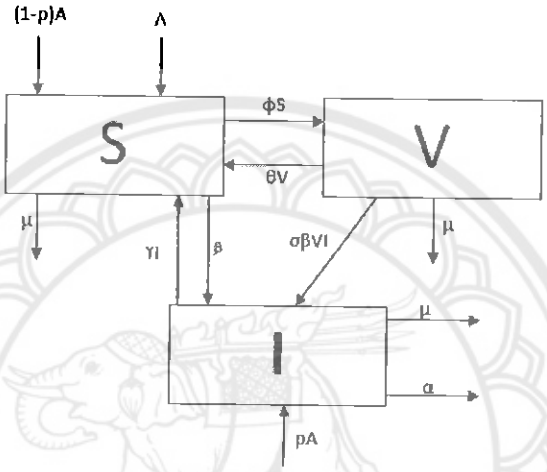

Figure 2.5: The SVIS model.

$$\begin{aligned}
\frac{dS}{dt} &= (1-p)A + \Lambda - \beta SI - (\mu+\phi)S + \gamma I + \theta V \\
\frac{dI}{dt} &= pA + \beta SI + \sigma\beta VI - (\mu+\gamma+\alpha)I \\
\frac{dv}{dt} &= \phi S - \sigma\beta VI - (\mu+\theta)V
\end{aligned}$$

where

. S is the susceptible state.

. I is the infected state.

. V is the vaccinated state.

. R is the recovered human population state.

. A is the number of immigrants.

- p is the portion of infectives among immigrants.
- Λ is the birth rate.
- β is is the contact rate.
- γ is the recovery rate.
- ϕ is the vaccination rate.
- σ is the factor by which the vaccine reduces infection.
- θ is the rate at which the vaccine wears off.
- μ is the natural related death rate.
- α is the disease related death rate.
- R_0 is the basic reproductive number.
- $R_\phi$is vaccination reproductive number.

Cholera Model with Immigrants

Case Study

In this study we will extend a model prosed by including an immigrant state. We assume that the immigration rate is a constant, however, the number of population in total is not a constant.The immigrants can become infected individuals with the probability of p and the rest becomes the risk group of being infected. Now, our model contains six differential equations as follows:

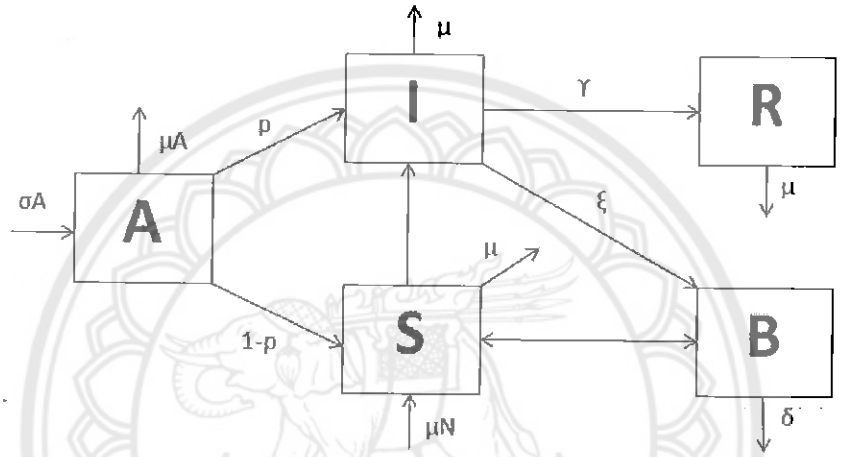

Figure 2.6: The Cholera Mathematical Model with Immigrants by Nattawud Sornsomrit

$$
\begin{aligned}
\frac{dS}{dt} &= \mu(N+(1-p)A) - \beta_h SI - \mu S - \frac{\beta_e SB}{k+B} \\
\frac{dA}{dt} &= \sigma A - p\beta_h AI - (1-p)A - \mu A \\
\frac{dI}{dt} &= p\beta_h AI + \beta_h SI + \frac{\beta_e SB}{k+B} - (\gamma+\mu)I \\
\frac{dB}{dt} &= \xi I - \delta B \\
\frac{dR}{dt} &= \gamma I - \mu R
\end{aligned}
$$

where

. S is the susceptible state

. I is the infected state

- B is the concentration of the vibrios in the environment state
- R is the recovered human population state
- N is the total population state
- A is the immigrants
- p is the portion of infectives among immigrants
- μ natural human birth/death rate
- ξ is the rate of human contribution (e.g.,shedding) to V.cholerae
- δ is the natural death rate of V.cholerae
- γ is the rate of recovery from cholera
- k is the pathogen concentration that yields 50% chance of catching cholera
- β_e and β_h represent rates of ingesting vibrios from the contaminated water and through human-to-human interaction.
- σA is the rate of immigration.

From this case study shows that with different immigration rates, the number of infections changed. We can conclude that in order to prevent an outbreak of Cholera, precauion in immigrants should be considered.

In the next Chapter, we will extend some previous models and verify the model by dynamics analyses and also numerical simulations.

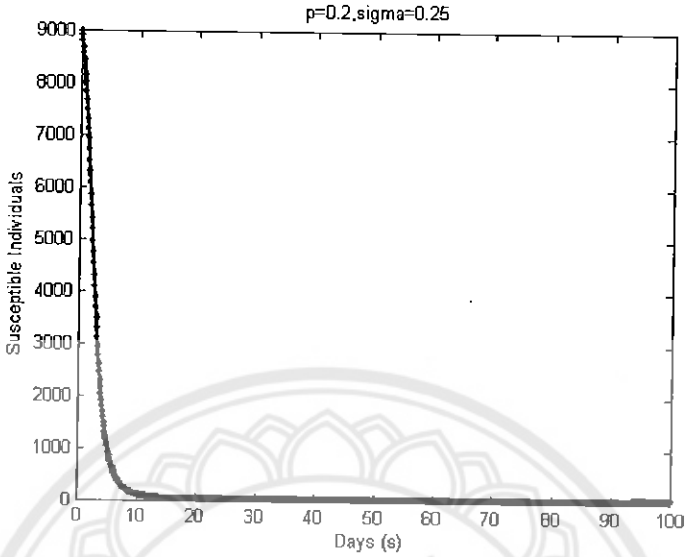

Figure 2.7: First Case:σ =0.25

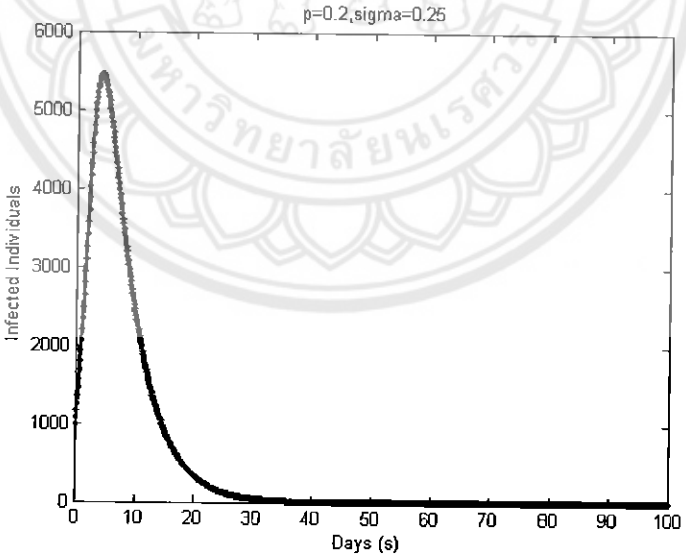

Figure 2.8: First Case:σ =0.25

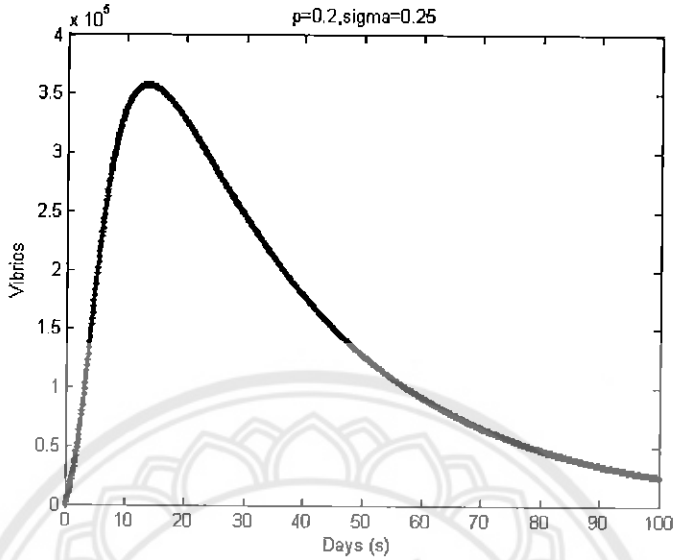

Figure 2.9: First Case:σ =0.25

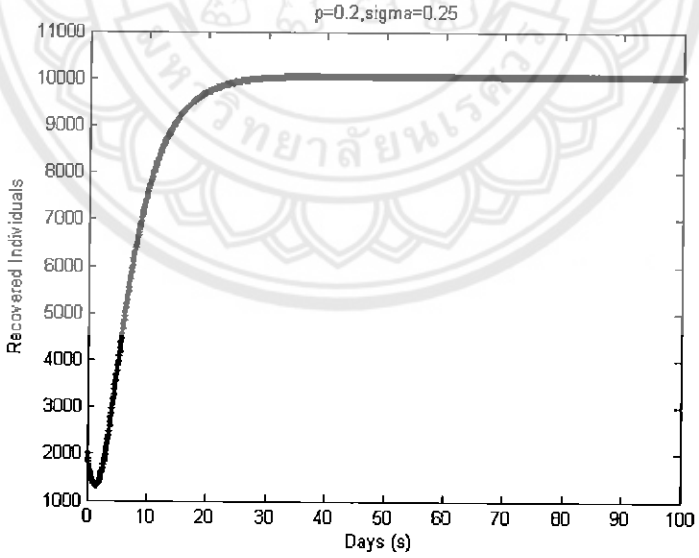

Figure 2.10: First Case:σ =0.25

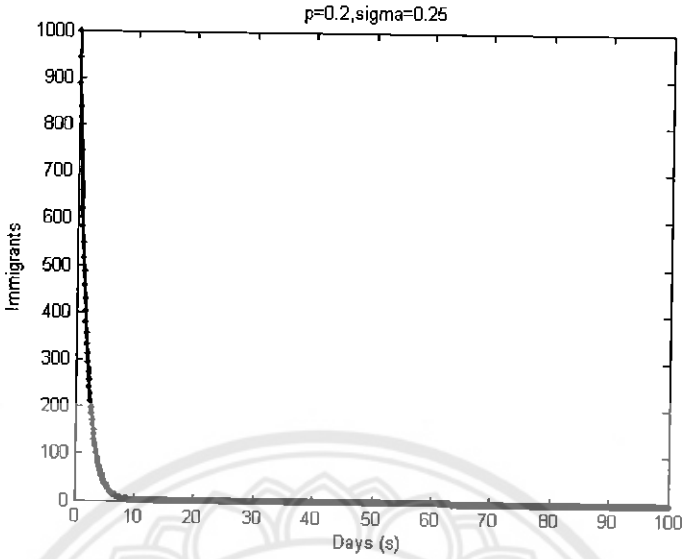

Figure 2.11: First Case:σ =0.25

Chapter 3

Methodology and Results

In this chapter, we will extend the model we have presented in Chapter 2. The modification will be based on SIR model proposed by Jin Wang and Chairit Modnak. The study will focus on two groups of humman populations, low-risk individuals (S_2) and hig-risk individuals (S_1). They will be vacciuated with rates of ϕ_1 for high-risk group and ϕ_2 for low-risk group. A high-risk group is a cluster of those who live nearby rivers or hospitals or never had vaccine and a low-risk group is a group of human populations who live in a well-infrastructued community; they have clean water and food and have good health care plan and they have been vaccinated or have experienced with the disease.

The infective class is put into two different classes.One is a low-infectious state (I_2) and another is a high-infection state (I_1). The low-infectious individuals have low ability to transmit the disease and high ability for the high-infectious individuals. We assume that they live in a distinct place and they will not have a close contact to each other. The concentration of vibrios (the cholera pathogen) in contaminated water is deuoted by B.

In conclusion, we consider a human population which is divided into four classes:the susceptibles(S_1 and S_2) the vaccinated (V), the infected (I_1 and I_2) and the recovered (R).We assume the total population remains a constant, N.

We thus obtain the following system of differential equations describing the cholera dynamics with vaccination:

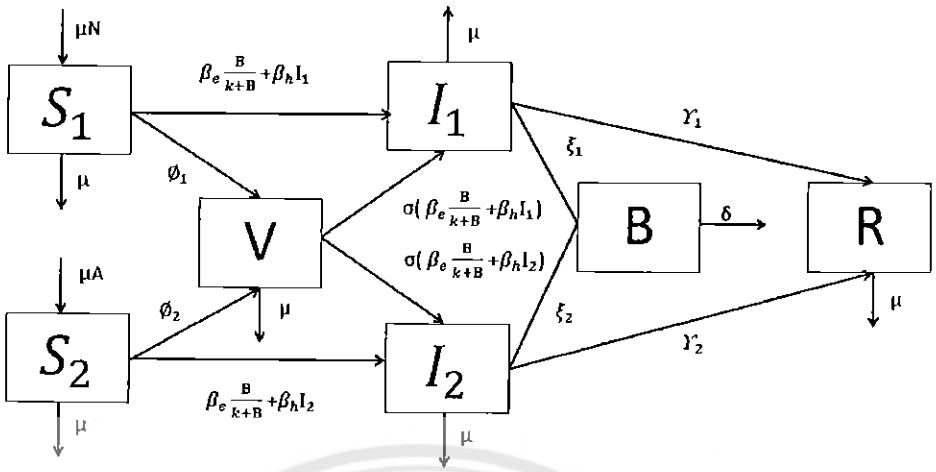

Figure 3.1: The cholera mathematical model of a risk-structured two-group model and controls by Nattawud Sornsomrit

$$
\begin{aligned}
\frac{dS_1}{dt} &= \mu N - (\beta_e \frac{B}{k+B} + \beta_h I_1)S_1 - (\phi_1 + \mu)S_1 \\
\frac{dS_2}{dt} &= \mu A - (\beta_e \frac{B}{k+B} + \beta_h I_2)S_2 - (\phi_2 + \mu)S_2 \\
\frac{dV}{dt} &= \phi_1 S_1 + \phi_2 S_2 - \sigma(\beta_e \frac{B}{k+B} + \beta_h I_1)V - \sigma(\beta_e \frac{B}{k+B} + \beta_h I_2)V - \mu V \\
\frac{dI_1}{dt} &= (\beta_e \frac{B}{k+B} + \beta_h I_1)S_1 + \sigma(\beta_e \frac{B}{k+B} + \beta_h I_1)V - (\gamma_1 + \mu)I_1 \\
\frac{dI_2}{dt} &= (\beta_e \frac{B}{k+B} + \beta_h I_2)S_2 + \sigma(\beta_e \frac{B}{k+B} + \beta_h I_2)V - (\gamma_2 + \mu)I_2 \\
\frac{dB}{dt} &= \xi_1 I_1 + \xi_2 I_2 - \delta B \\
\frac{dR}{dt} &= \gamma_1 I_1 + \gamma_2 I_2 - \mu R
\end{aligned}
$$

where

- S_1 is represents individuals group1. They never contanct with the disease or have had vaccine,therefore,they are considered as a high-risk group
- S_2 is represents individuals group2. They have experienced with the disease or have been vaccinated,,therefore,they are considered as a low-risk group
- I_1 is represents infected individuals from group1.

. I_2 is represents infected individuals from group2.

. B is the concentration of the vibrios in the environment state.

. R is the recovered from the disease state.

. β_e and β_h represent rates of ingesting vibrios from the contaminated water and through human-to-human interaction.

. γ_1 and γ_2 is recovery.

. μ is natural death rate.

. δ is the natural death rate of V.cholerae.

. ξ_1 and ξ_2 is the rate of human contribution (e.g.,shedding) to V.cholerae.

. σ is adegree of protection, σ= (1-ε),where ε is the vaccine efficacy.

. ϕ_1 and ϕ_2 is the vaccination rate.

. V is the vaccinated class.

3.1 The disease-free-equiliibrium

From our model formulation, we next will conduct the epidemic and endemic analysis. At the disease-free-equiliibrium (DFE), all the states are zeros. we set a $I_1 = I_2 = B = R = 0$ and find S_1 and S_2 from the model. There fore , the DFE will have nonzero states S_1, S_2 and V says $\varepsilon_0 = (S_1, S_2, V, 0, 0, 0, 0)$.

By stting $\frac{dS_1}{dt}, \frac{dS_2}{dt}$ and $\frac{dV}{dt}$ equal to zero, we can find S_1, S_2 and V:

$$\varepsilon_0 = (S_1, S_2, 0, 0, 0, 0)$$

$$\begin{aligned}
\frac{dS_1}{dt} : \mu N - (\phi_1 + \mu)S_1 &= 0 \\
\mu N &= (\phi_1 + \mu)S_1 \\
\frac{\mu N}{\phi_1 + \mu} &= S_1 \\
\frac{dS_2}{dt} : \mu A - (\phi_2 + \mu)S_2 &= 0 \\
\mu A &= (\phi_2 + \mu)S_2 \\
\frac{\mu A}{\phi_2 + \mu} &= S_2 \\
\frac{dV}{dt} : \phi_1 S_1 + \phi_2 S_2 - \mu V &= 0 \\
-\mu V &= -(\phi_1 S_1 + \phi_2 S_2) \\
\frac{\phi_1 S_1 + \phi_2 S_2}{\mu} &= V
\end{aligned}$$

Thus now we have the DFE:

$$\varepsilon_0 = (\frac{\mu N}{\phi_1 + \mu}, \frac{\mu A}{\phi_2 + \mu}, \frac{\phi_1 S_1 + \phi_2 S_2}{\mu}, 0, 0, 0, 0)$$

or

$$\varepsilon_0 = (\frac{\mu N}{\phi_1 + \mu}, \frac{\mu A}{\phi_2 + \mu}, \frac{\phi_1(\frac{\mu N}{\phi_1+\mu}) + \phi_2(\frac{\mu A}{\phi_2+\mu})}{\mu}, 0, 0, 0, 0).$$

3.2 Epidemic dynamics

One of the most important concerned about any infectious disease is its ability to invade a population.The basic reproduction number, R_0, is a measure of the potential for disease spread in a population. It represents the average number of secondary in cases generated by any in fected individual if introduced into a susceptible population with no immunity to the disease in the absence of interventions to control the infection. If $R_0 < 1$,then on average, an infected individual produces less then one newly infected individual over the course of his infection period.In this case, the infection may die out in the long run. Conversely, if $R_0 > 1$,each infected individual produes, on averag more than one new infection,the infection will be ableb to spreed in a population. A large value of R_0 may indicate the possibility of a major epidemic. We first compute the baic reproduction number for this model using the method of van den Driessche and Watmough. Here, the associated next generation matrices are given by

$$\mathcal{F} = \begin{bmatrix} (\beta_e \frac{B}{k+B} + \beta_h I_1)S_1 + \sigma(\beta_e \frac{B}{k+B} + \beta_h I_1)V \\ (\beta_e \frac{B}{k+B} + \beta_h I_2)S_2 + \sigma(\beta_e \frac{B}{k+B} + \beta_h I_2)V \\ 0 \end{bmatrix}$$

$$F = \begin{bmatrix} \frac{\partial \mathcal{F}}{\partial I_1} & \frac{\partial \mathcal{F}}{\partial I_2} & \frac{\partial \mathcal{F}}{\partial B} \\ \frac{\partial \mathcal{F}}{\partial I_1} & \frac{\partial \mathcal{F}}{\partial I_2} & \frac{\partial \mathcal{F}}{\partial B} \\ \frac{\partial \mathcal{F}}{\partial I_1} & \frac{\partial \mathcal{F}}{\partial I_2} & \frac{\partial \mathcal{F}}{\partial B} \end{bmatrix}$$

$$F = \begin{bmatrix} \beta_h S_1 + \sigma\beta_h V & 0 & (\frac{\beta_e k S_1}{(k+B)^2}) + (\frac{\sigma\beta_e k V}{(k+B)^2}) \\ 0 & \beta_h S_2 + \sigma\beta_h V & (\frac{\beta_e k S_2}{(k+B)^2}) + (\frac{\sigma\beta_c k V}{(k+B)^2}) \\ 0 & 0 & 0 \end{bmatrix}$$

$$\mathcal{V} = \begin{bmatrix} (\gamma_1 + \mu)I_1 \\ (\gamma_2 + \mu)I_2 \\ -\xi_1 I_1 - \xi_2 I_2 + \delta B \end{bmatrix}$$

$$V = \begin{bmatrix} \frac{\partial \mathcal{V}}{\partial I_1} & \frac{\partial \mathcal{V}}{\partial I_2} & \frac{\partial \mathcal{V}}{\partial B} \\ \frac{\partial \mathcal{V}}{\partial I_1} & \frac{\partial \mathcal{V}}{\partial I_2} & \frac{\partial \mathcal{V}}{\partial B} \\ \frac{\partial \mathcal{V}}{\partial I_1} & \frac{\partial \mathcal{V}}{\partial I_2} & \frac{\partial \mathcal{V}}{\partial B} \end{bmatrix}$$

$$V = \begin{bmatrix} \gamma_1 + \mu & 0 & 0 \\ 0 & \gamma_2 + \mu & 0 \\ -\xi_1 & -\xi_2 & \delta \end{bmatrix}$$

The basic reproductive number is then determined as the spectral radius of FV^{-1} ,which yields

$$V^{-1} = \frac{1}{(\gamma_1+\mu)(\gamma_2+\mu)\delta}\begin{bmatrix} (\gamma_2+\mu)\delta & 0 & 0 \\ 0 & (\gamma_1+\mu)\delta & 0 \\ (\gamma_2+\mu)\xi_1 & (\gamma_1+\mu)\xi_2 & (\gamma_1+\mu)(\gamma_2+\mu) \end{bmatrix}$$

$$= \begin{bmatrix} \frac{1}{\gamma_1+\mu} & 0 & 0 \\ 0 & \frac{1}{\gamma_2+\mu} & 0 \\ \frac{\xi_1}{(\gamma_1+\mu)\delta} & \frac{\xi_2}{(\gamma_2+\mu)\delta} & \frac{1}{\delta} \end{bmatrix}$$

$$FV^{-1} = \begin{bmatrix} \beta_h(\frac{\mu N}{\phi_1+\mu}) + \sigma\beta_h(\frac{\phi_1(\frac{\mu N}{\phi_1+\mu})+\phi_2(\frac{\mu A}{\phi_2+\mu})}{\mu}) & 0 \\ 0 & \beta_h(\frac{\mu N}{\phi_2+\mu}) + \sigma\beta_h(\frac{\phi_1(\frac{\mu N}{\phi_1+\mu})+\phi_2(\frac{\mu A}{\phi_2+\mu})}{\mu}) \\ 0 & 0 \end{bmatrix}$$

$$\begin{bmatrix} (\frac{\beta_c k(\frac{\mu N}{\phi_1+\mu})}{(k^2}) + (\frac{\sigma\beta_c k(\frac{\phi_1(\frac{\mu N}{\phi_1+\mu})+\phi_2(\frac{\mu A}{\phi_2+\mu})}{\mu})}{k^2}) \\ (\frac{\beta_c k(\frac{\mu A}{\phi_2+\mu})}{k^2}) + (\frac{\sigma\beta_c k(\frac{\phi_1(\frac{\mu N}{\phi_1+\mu})+\phi_2(\frac{\mu A}{\phi_2+\mu})}{\mu})}{k^2}) \\ 0 \end{bmatrix}$$

$$\cdot \begin{bmatrix} \frac{1}{\gamma_1+\mu} & 0 & 0 \\ 0 & \frac{1}{\gamma_2+\mu} & 0 \\ \frac{\xi_1}{(\gamma_1+\mu)\delta} & \frac{\xi_2}{(\gamma_2+\mu)\delta} & \frac{1}{\delta} \end{bmatrix}$$

$$
\begin{aligned}
a_{11} &= \left[\beta_h\left(\frac{\mu N}{\phi_1+\mu}\right)+\sigma\beta_h\left(\frac{\phi_1\left(\frac{\mu N}{\phi_1+\mu}\right)+\phi_2\left(\frac{\mu A}{\phi_2+\mu}\right)}{\mu}\right)\right]\cdot\frac{1}{\gamma_1+\mu}+ \\
&\quad \left[\left(\frac{\beta_e k\left(\frac{\mu N}{\phi_1+\mu}\right)}{k^2}\right)+\left(\frac{\sigma\beta_e k\left(\frac{\phi_1\left(\frac{\mu N}{\phi_1+\mu}\right)+\phi_2\left(\frac{\mu A}{\phi_2+\mu}\right)}{\mu}\right)}{k^2}\right)\right]\cdot\frac{\xi_1}{(\gamma_1+\mu)\delta} \\
a_{12} &= \left[\left(\frac{\beta_e k\left(\frac{\mu N}{\phi_1+\mu}\right)}{k^2}\right)+\left(\frac{\sigma\beta_e k\left(\frac{\phi_1\left(\frac{\mu N}{\phi_1+\mu}\right)+\phi_2\left(\frac{\mu A}{\phi_2+\mu}\right)}{\mu}\right)}{k^2}\right)\right]\cdot\frac{\xi_2}{(\gamma_2+\mu)\delta} \\
a_{13} &= \left[\left(\frac{\beta_e k\left(\frac{\mu N}{\phi_1+\mu}\right)}{k^2}\right)+\left(\frac{\sigma\beta_e k\left(\frac{\phi_1\left(\frac{\mu N}{\phi_1+\mu}\right)+\phi_2\left(\frac{\mu A}{\phi_2+\mu}\right)}{\mu}\right)}{k^2}\right)\right]\cdot\frac{1}{\delta} \\
a_{21} &= \left[\left(\frac{\beta_e k\left(\frac{\mu A}{\phi_2+\mu}\right)}{k^2}\right)+\left(\frac{\sigma\beta_e k\left(\frac{\phi_1\left(\frac{\mu N}{\phi_1+\mu}\right)+\phi_2\left(\frac{\mu A}{\phi_2+\mu}\right)}{\mu}\right)}{k^2}\right)\right]\cdot\frac{\xi_1}{(\gamma_1+\mu)\delta} \\
a_{22} &= \left[\beta_h\left(\frac{\mu A}{\phi_2+\mu}\right)+\sigma\beta_h\left(\frac{\phi_1\left(\frac{\mu N}{\phi_1+\mu}\right)+\phi_2\left(\frac{\mu A}{\phi_2+\mu}\right)}{\mu}\right)\right]\cdot\frac{1}{\gamma_2+\mu}+ \\
&\quad \left[\left(\frac{\beta_e k\left(\frac{\mu A}{\phi_2+\mu}\right)}{k^2}\right)+\left(\frac{\sigma\beta_e k\left(\frac{\phi_1\left(\frac{\mu N}{\phi_1+\mu}\right)+\phi_2\left(\frac{\mu A}{\phi_2+\mu}\right)}{\mu}\right)}{k^2}\right)\right]\cdot\frac{\xi_2}{(\gamma_2+\mu)\delta} \\
a_{23} &= \left[\left(\frac{\beta_e k\left(\frac{\mu A}{\phi_2+\mu}\right)}{k^2}\right)+\left(\frac{\sigma\beta_e k\left(\frac{\phi_1\left(\frac{\mu N}{\phi_1+\mu}\right)+\phi_2\left(\frac{\mu A}{\phi_2+\mu}\right)}{\mu}\right)}{k^2}\right)\right]\cdot\frac{1}{\delta} \\
a_{31} &= 0 \\
a_{32} &= 0 \\
a_{33} &= 0
\end{aligned}
$$

$$
FV^{-1}=\begin{bmatrix} a_{11} & a_{12} & a_{13} \\ a_{21} & a_{22} & a_{23} \\ a_{31} & a_{32} & a_{33} \end{bmatrix}
$$

$$
\begin{aligned}
det(\lambda I - FV^{-1}) &= \begin{vmatrix} \lambda - a_{11} & -a_{12} & -a_{13} \\ -a_{21} & \lambda - a_{22} & -a_{23} \\ -a_{31} & -a_{32} & \lambda - a_{33} \end{vmatrix} \\
&= (\lambda - a_{11})(\lambda - a_{22})\lambda - (\lambda(-a_{21}) - (-a_{12})) \\
&= (\lambda - a_{11})(\lambda - a_{22})\lambda - a_{21}a_{12}\lambda.
\end{aligned}
$$

We set $\det(\lambda I - FV^{-1})$ equal to zero to fine eigenvalues. Thus

$$
\begin{aligned}
&[(\lambda - a_{11})(\lambda - a_{22}) - a_{21}a_{12}]\lambda = 0 \\
&\lambda = 0; (\lambda - a_{11})(\lambda - a_{22}) - a_{21}a_{12} = 0 \\
&\lambda^2 - a_{22}\lambda - a_{11}\lambda + a_{11}a_{22} - a_{21}a_{12} = 0 \\
&\lambda^2 - (a_{22} + a_{11})\lambda + a_{11}a_{22} - a_{21}a_{12} = 0
\end{aligned}
$$

We will use the guadratic formular ;

$$x = \frac{-b \pm \sqrt{b^2 - 4ac}}{2a}$$

to solve

$$\lambda^2 - (a_{22} + a_{11})\lambda + a_{11}a_{22} - a_{21}a_{12} = 0$$

Thus, we have the solutions,

$$\lambda_{1,2} = \frac{-(-(a_{22} + a_{11})) \pm \sqrt{(a_{22} + a_{11})^2 - 4(1)(a_{11}a_{22} - a_{21}a_{12})}}{2(1)}$$

or

$$\lambda_{1,2} = \frac{(a_{22} + a_{11}) \pm \sqrt{(a_{22} + a_{11})^2 - 4(a_{11}a_{22} - a_{21}a_{12})}}{2}$$

Let's consider terms inside the square root.

We will show that

$$
\begin{aligned}
& (a_{22}+a_{11})^2 - 4(a_{11}a_{22} - a_{21}a_{12}) \\
= \; & a_{22}^2 + 2a_{22}a_{11} + a_{11}^2 - 4a_{11}a_{22} + 4a_{21}a_{12} \\
= \; & a_{22}^2 - 2a_{11}a_{22} + a_{11}^2 + 4a_{21}a_{12} \\
= \; & (a_{22}-a_{11})^2 + 4a_{21}a_{12} > 0
\end{aligned}
$$

Since all a_{ij} for i,j=1,2 are positive, therefore, the inequality holds.

That is

$$\lambda_{1,2} = \frac{(a_{22}+a_{11}) \pm \sqrt{(a_{22}+a_{11})^2 - 4(a_{11}a_{22} - a_{21}a_{12})}}{2}$$

are real numbers. Hence,

$$
\begin{aligned}
R_0 &= \rho(Fv^{-1}) \\
&= max\left\{ \frac{(a_{22}+a_{11}) \pm \sqrt{(a_{22}+a_{11})^2 - 4(a_{11}a_{22} - a_{21}a_{12})}}{2} \right\}
\end{aligned}
$$

where

$$
\begin{aligned}
a_{11} &= \left[\frac{(\beta_h)(\mu N)(\phi_2+\mu) + \sigma\beta_h[(\phi_1 N)(\phi_2+\mu) + (\phi_2 A)(\phi_1+\mu)]}{(\phi_1+\mu)(\phi_2+\mu)} \right] \cdot \frac{1}{\gamma_1+\mu} + \\
&\quad \left[\frac{(\beta_e)(\mu N)(\phi_2+\mu) + \sigma\beta_e[(\phi_1 N)(\phi_2+\mu) + (\phi_2 A)(\phi_1+\mu)]}{k(\phi_1+\mu)(\phi_2+\mu)} \right] \cdot \frac{\xi_1}{(\gamma_1+\mu)\delta} \\
a_{12} &= \left[\frac{(\beta_e)(\mu N)(\phi_2+\mu) + \sigma\beta_e[(\phi_1 N)(\phi_2+\mu) + (\phi_2 A)(\phi_1+\mu)]}{k(\phi_1+\mu)(\phi_2+\mu)} \right] \cdot \frac{\xi_2}{(\gamma_2+\mu)\delta} \\
a_{21} &= \left[\frac{(\beta_e)(\mu A)(\phi_2+\mu) + \sigma\beta_e[(\phi_1 N)(\phi_2+\mu) + (\phi_2 A)(\phi_1+\mu)]}{k(\phi_1+\mu)(\phi_2+\mu)} \right] \cdot \frac{\xi_1}{(\gamma_1+\mu)\delta} \\
a_{22} &= \left[\frac{(\beta_h)(\mu A)(\phi_2+\mu) + \sigma\beta_h[(\phi_1 N)(\phi_2+\mu) + (\phi_2 A)(\phi_1+\mu)]}{(\phi_1+\mu)(\phi_2+\mu)} \right] \cdot \frac{1}{\gamma_2+\mu} + \\
&\quad \left[\frac{(\beta_e)(\mu A)(\phi_2+\mu) + \sigma\beta_e[(\phi_1 N)(\phi_2+\mu) + (\phi_2 A)(\phi_1+\mu)]}{k(\phi_1+\mu)(\phi_2+\mu)} \right] \cdot \frac{\xi_2}{(\gamma_2+\mu)\delta}
\end{aligned}
$$

Theorem 3.1. *The disease-free equilibrium of the model is locally asymptotically stable if* $R_0 < 1$, *and unstable if* $R_0 > 1$.

We mention that the basic reproduction number can also be derived by the next generation matrix analysis.

To study the global asymptotic stabillity of DFE, one common approach is to construct an appropriate Lyapunov function. We have found, however, that it is simpler to apply the following result introduced by Castilli-Chavez et al.

$$F(X_1,0) = \begin{bmatrix} \mu N-(\phi_1+\mu)S_1 \\ \mu A-(\phi_2+\mu)S_2 \\ \phi_1 S_1+\phi_2 S_2-\mu V \\ -\mu R \end{bmatrix}$$

$$F(X_1,0) = \begin{bmatrix} \mu N-\mu S_1 \\ \mu A-S_2 \\ -\mu V \\ -\mu R \end{bmatrix}$$

For R:

$$\begin{aligned} \frac{dR}{dt} &= -\mu R \\ \frac{dR}{dt}+\mu R &= 0 \\ R^{'}+\mu R &= 0 \\ R(t) &= R(0)e^{-\mu t} \end{aligned}$$

For V:

$$\begin{aligned} \frac{dV}{dt} &= -\mu V \\ \frac{dV}{dt}+\mu V &= 0 \\ V^{'}+\mu V &= 0 \\ V(t) &= V(0)^{e-\mu t} \end{aligned}$$

For S_1:

$$\begin{aligned} e^{\mu t}\frac{dS_1}{dt}+e^{\mu t}\mu S_1 &= e^{\mu t}\mu N \\ \frac{d}{dt}(e^{\mu t}\cdot S_1) &= e^{\mu t}\mu N \\ \int \frac{d}{dt}(e^{\mu t}S_1)dt &= \int e^{\mu t}\mu N dt \\ e^{\mu t}\cdot S_1 &= \frac{\mu N}{\mu}e^{\mu t}+C \\ S_1(t) &= N+Ce^{-\mu t} \end{aligned}$$

When $t = 0$, we have

$$S_1(0) = N + C.$$

Thus

$$C = S_1(0) - N.$$

Hence

$$S_1(t) = N + (S_1(0) - N)e^{-\mu t}.$$

For S_2:

$$\begin{aligned} e^{\mu t}\frac{dS_2}{dt} + e^{\mu t}\mu S_2 &= e^{\mu t}\mu A \\ \frac{d}{dt}(e^{\mu t} \cdot S_2) &= e^{\mu t}\mu A \\ \int \frac{d}{dt}(e^{\mu t}S_2)dt &= \int e^{\mu t}\mu A dt \\ e^{\mu t} \cdot S_2 &= \frac{\mu A}{\mu}e^{\mu t} + C \\ S_2(t) &= A + Ce^{-\mu t}. \end{aligned}$$

When $t = 0$, we have

$$S_2(0) = A + C,$$

thus

$$C = S_2(0) - A.$$

Hence

$$S_2(t) = A + (S_2(0) - A)e^{-\mu t}.$$

Clearly, $R(t) \to 0, V(t) \to 0, S_1(t) \to N$ and $S_2(t) \to A$ as $t \to \infty$, regardless of the values of $R(0)$ and $S(0)$. Thus $X_1^* = (N, A, 0, 0)$. is globally asymptotically stable.

Next consider that

$$G(X_1, X_2) = \begin{bmatrix} (\beta_e \frac{B}{k+B} + \beta_h I_1)S_1 + \sigma(\beta_e \frac{B}{k+B} + \beta_h I_1)V - (\gamma_1 + \mu)I_1 \\ (\beta_e \frac{B}{k+B} + \beta_h I_2)S_2 + \sigma(\beta_e \frac{B}{k+B} + \beta_h I_2)V - (\gamma_2 + \mu)I_2 \\ \xi_1 I_1 + \xi_2 I_2 - \delta B \end{bmatrix}.$$

We can then obtain

$$\begin{aligned} U &= \begin{bmatrix} S_1\beta h + -(\gamma_1 + \mu) & 0 & \frac{S_1\beta_e}{k} \\ 0 & S_2\beta_h - (\gamma_2 + \mu) & \frac{S_2\beta_e}{k} \\ \xi_1 & \xi_2 & -\delta \end{bmatrix}, \\ &= \begin{bmatrix} N\beta h + -(\gamma_1 + \mu) & 0 & \frac{N\beta_e}{k} \\ 0 & A\beta_h - (\gamma_2 + \mu) & \frac{A\beta_e}{k} \\ \xi_1 & \xi_2 & -\delta \end{bmatrix}. \end{aligned}$$

Thus,

$$\begin{aligned} \hat{G}(X_1, X_2) &= UX_2 - G(X_1, X_2) \\ &= \begin{bmatrix} N\beta h + -(\gamma_1 + \mu) & 0 & \frac{N\beta_e}{k} \\ 0 & A\beta_h - (\gamma_2 + \mu) & \frac{A\beta_e}{k} \\ \xi_1 & \xi_2 & -\delta \end{bmatrix} \cdot \begin{bmatrix} I_1 \\ I_2 \\ B \end{bmatrix} - \\ &\quad \begin{bmatrix} (\beta_e \frac{B}{k+B} + \beta_h I_1)S_1 + \sigma(\beta_e \frac{B}{k+B} + \beta_h I_1)V - (\gamma_1 + \mu)I_1 \\ (\beta_e \frac{B}{k+B} + \beta_h I_2)S_2 + \sigma(\beta_e \frac{B}{k+B} + \beta_h I_2)V - (\gamma_2 + \mu)I_2 \\ \xi_1 I_1 + \xi_2 I_2 - \delta B \end{bmatrix} \\ &= \begin{bmatrix} [N\beta h + -(\gamma_1 + \mu)]I_1 + [\frac{N\beta_e}{k}]B \\ [A\beta_h - (\gamma_2 + \mu)]I_2 + [\frac{A\beta_e}{k}]B \\ \xi_1 I_1 + \xi_2 I_2 - \delta B \end{bmatrix} - \\ &\quad \begin{bmatrix} (\beta_e \frac{B}{k+B} + \beta_h I_1)S_1 + \sigma(\beta_e \frac{B}{k+B} + \beta_h I_1)V - (\gamma_1 + \mu)I_1 \\ (\beta_e \frac{B}{k+B} + \beta_h I_2)S_2 + \sigma(\beta_e \frac{B}{k+B} + \beta_h I_2)V - (\gamma_2 + \mu)I_2 \\ \xi_1 I_1 + \xi_2 I_2 - \delta B \end{bmatrix} \\ &= \begin{bmatrix} N\beta_h I_1 + [\frac{N\beta_e}{k}]B - (\beta_e \frac{B}{k+B} + \beta_h I_1)S_1 + \sigma(\beta_e \frac{B}{k+B} + \beta_h I_1)V \\ A\beta_h I_2 + [\frac{A\beta_e}{k}]B - (\beta_e \frac{B}{k+B} + \beta_h I_2)S_2 + \sigma(\beta_e \frac{B}{k+B} + \beta_h I_2)V \\ 0 \end{bmatrix} \end{aligned}$$

First,we consider row one of the matrix $\hat{G}$.

$$\begin{aligned}
& N\beta_h I_1 + [\frac{N\beta_e}{k}]B - (\beta_e \frac{B}{k+B} + \beta_h I_1)S_1 + \sigma(\beta_e \frac{B}{k+B} + \beta_h I_1)V \\
= \; & N\beta_h I_1 + \frac{N\beta_e B}{k} - \frac{\beta_B S_1}{k+B} - \beta_h I_1 S_1 - \frac{\sigma V \beta_e B}{k+B} - \sigma\beta_h I_1 V \\
= \; & \beta_h I_1(N - S_1 - \sigma V) + \frac{(N\beta_e B)(k+B) - \beta_e B S_1 k - \sigma V \beta_e B k}{k(k+B)} \\
= \; & \beta_h I_1(N - S_1 - \sigma V) + \frac{(N\beta_e B k) + (N\beta_e B^2) - \beta_e B S_1 k - \sigma V \beta_e B k}{k(k+B)} \\
= \; & \beta_h I_1(N - S_1 - \sigma V) + \frac{\beta_e B k(N - S_1 - \sigma V) + N\beta_e B^2}{k(k+B)}.
\end{aligned}$$

Similarly,row two of the matrix is

$$\begin{aligned}
& A\beta_h I_2 + [\frac{A\beta_e}{k}]B - (\beta_e \frac{B}{k+B} + \beta_h I_2)S_2 + \sigma(\beta_e \frac{B}{k+B} + \beta_h I_2)V \\
= \; & A\beta_h I_2 + \frac{A\beta_e B}{k} - \frac{\beta_B S_2}{k+B} - \beta_h I_2 S_2 - \frac{\sigma V \beta_e B}{k+B} - \sigma\beta_h I_2 V \\
= \; & \beta_h I_2(A - S_2 - \sigma V) + \frac{(A\beta_e B)(k+B) - \beta_e B S_2 k - \sigma V \beta_e B k}{k(k+B)} \\
= \; & \beta_h I_2(A - S_2 - \sigma V) + \frac{(A\beta_e B k) + (A\beta_e B^2) - \beta_e B S_2 k - \sigma V \beta_e B k}{k(k+B)} \\
= \; & \beta_h I_2(A - S_2 - \sigma V) + \frac{\beta_e B k(A - S_2 - \sigma V) + A\beta_e B^2}{k(k+B)}.
\end{aligned}$$

Now we can write the matrix in the form

$$\hat{G}(X_1, X_2) = \begin{bmatrix} \beta_h I_1(N - (S_1 + \sigma V)) + \frac{\beta_e B k(N - (S_1 + \sigma V)) + N\beta_e B^2}{k(k+B)} \\ \beta_h I_2(A - (S_2 + \sigma V)) + \frac{\beta_e B k(A - (S_2 + \sigma V)) + A\beta_e B^2}{k(k+B)} \\ 0 \end{bmatrix}$$

Since $0 \leq S_1 + \sigma V \leq N$and $0 \leq S_2 + \sigma V \leq A$,it's obvious that

$\hat{G}(X, Z) \geq 0$

3.3 Endemic Equillibrium Points

When the disease is present in the population, $I^* \neq 0$, there may be several critical points where $I^* \neq 0$, which are the endemic equilibrium points (EEP) of the model. These points will be denoted as $E_e = (S_1^*, V^*, I_1^*, S_2^*, I_2^*, B^*, R^*)^T$ which are determined from the model as follows.We begin with setting the equations to zero.

$$\mu N - (\beta_e \frac{B^*}{k + B^*} + \beta_h I_1^*) S_1^* - (\phi_1 + \mu) S_1^* = 0 \tag{3.1}$$

$$\mu A - (\beta_e \frac{B^*}{k + B^*} + \beta_h I_2^*) S_2^* - (\phi_2 + \mu) S_2^* = 0 \tag{3.2}$$

$$\phi_1 S_1^* + \phi_2 S_2^* - \sigma(\beta_e \frac{B^*}{k + B^*} + \beta_h I_1^*) V^* - \sigma(\beta_e \frac{B^*}{k + B^*} + \beta_h I_2^*) V^* - \mu V^* = 0 \tag{3.3}$$

$$(\beta_e \frac{B^*}{k + B^*} + \beta_h I_1^*) S_1^* + \sigma(\beta_e \frac{B^*}{k + B^*} + \beta_h I_1^*) V^* - (\gamma_1 + \mu) I_1^* = 0 \tag{3.4}$$

$$(\beta_e \frac{B^*}{k + B^*} + \beta_h I_2^*) S_2^* + \sigma(\beta_e \frac{B^*}{k + B^*} + \beta_h I_2^*) V^* - (\gamma_2 + \mu) I_2^* = 0 \tag{3.5}$$

$$\xi_1 I_1^* + \xi_2 I_2^* - \delta B^* = 0$$

$$\gamma_1 I_1^* + \gamma_2 I_2^* - \mu R^* = 0$$

We will solve the EEP from these equations.

It is easy to see that we have

$$\begin{aligned}
B^* &= \frac{\xi_1 I_1^* + \xi_2 I_2^*}{\delta} \\
S_1^* &= \frac{\mu N}{\beta_e \frac{(\frac{\xi_1 I_1^* + \xi_2 I_2^*}{\delta})}{k+(\frac{\xi_1 I_1^* + \xi_2 I_2^*}{\delta})} + \beta_h I_1^* + (\phi_1 + \mu)} \\
&= \frac{\mu N}{\beta_e \frac{(\frac{\xi_1 I_1^* + \xi_2 I_2^*}{\delta})}{(\frac{k\delta+(\xi_1 I_1^* + \xi_2 I_2^*)}{\delta})} + \beta_h I_1^* + (\phi_1 + \mu)} \\
S_1^* &= \frac{\mu N}{\beta_e \frac{\xi_1 I_1^* + \xi_2 I_2^*}{k\delta+(\xi_1 I_1^* + \xi_2 I_2^*)} + \beta_h I_1^* + (\phi_1 + \mu)} \\
S_2^* &= \frac{\mu A}{\beta_e \frac{(\frac{\xi_1 I_1^* + \xi_2 I_2^*}{\delta})}{k+(\frac{\xi_1 I_1^* + \xi_2 I_2^*}{\delta})} + \beta_h I_2^* + (\phi_2 + \mu)} \\
&= \frac{\mu A}{\beta_e \frac{(\frac{\xi_1 I_1^* + \xi_2 I_2^*}{\delta})}{(\frac{k\delta+(\xi_1 I_1^* + \xi_2 I_2^*)}{\delta})} + \beta_h I_2^* + (\phi_2 + \mu)} \\
S_2^* &= \frac{\mu A}{\beta_e \frac{\xi_1 I_1^* + \xi_2 I_2^*}{k\delta+(\xi_1 I_1^* + \xi_2 I_2^*)} + \beta_h I_2^* + (\phi_2 + \mu)}
\end{aligned}$$

Next we combine the equations (3.1),(3.2),(3.3),(3.4) and (3.5) together and thus we have

$$\begin{aligned}
&\mu N + \mu A - \mu S_1^* - \mu S_2^* - \mu V^* - (\gamma_1 + \mu) I_1^* - (\gamma_2 + \mu) I_2^* = 0 \\
&(\gamma_1 + \mu) I_1^* - (\gamma_2 + \mu) I_2^* = muN + \mu A - \mu S_1^* - \mu S_2^* - \mu V^* \\
&(\gamma_1 + \mu) I_1^* - (\gamma_2 + \mu) I_2^* = \mu(N + A - S_1^* - S_2^* - V^*) \\
&N + A - (\frac{(\gamma_1 + \mu) I_1^* - (\gamma_2 + \mu) I_2^*}{\mu}) = S_1^* + S_2^* + V^*.
\end{aligned}$$

Let

$$\tau_1 = \frac{(\gamma_1 + \mu)}{\mu}$$

and

$$\tau_2 = \frac{(\gamma_2 + \mu)}{\mu}$$

Then

$$N + A - (\tau_1 I_1^* - \tau I_2^*) = S_1^* + S_2^* + V^* \tag{3.6}$$

First consider S_1^* :

$$S_1^* = \frac{\mu N}{\beta_e \frac{\xi_1 I_1^* + \xi_2 I_2^*}{k\delta+(\xi_1 I_1^* + \xi_2 I_2^*)} + \beta_h I_1^* + (\phi_1 + \mu)}$$

We next will simplify the denominator.That is

$$\begin{aligned}
&\beta_e \frac{\xi_1 I_1^* + \xi_2 I_2^*}{k\delta + (\xi_1 I_1^* + \xi_2 I_2^*)} + \beta_h I_1^* + (\phi_1 + \mu) \\
= \;& \frac{\beta_e \xi_1 I_1^* + \beta_e \xi_2 I_2^* + (\beta_h I_1^* + (\phi_1 + \mu))(k\delta + (\xi_1 I_1^* + \xi_2 I_2^*)}{k\delta + (\xi_1 I_1^* + \xi_2 I_2^*)} \\
= \;& (\beta_e \xi_1 I_1^* + \beta_e \xi_2 I_2^* + \beta_h I_1^* k\delta + \phi_1 k\delta + \mu k\delta + \beta_h I_1^* \xi_1 I_1^* + \phi_1 \xi_1 I_1^* \\
& + \mu \xi_1 I_1^* + \beta_h I_1^* \xi_1 I_2^* + \phi_1 \xi_2 I_2^* + \mu \xi_2 I_2^*) \div (k\delta + (\xi_1 I_1^* + \xi_2 I_2^*)) \\
= \;& (\beta_h \xi_1) I_1^{*2} + (\beta_e \xi_1 + \beta_h k\delta + \phi_1 \xi_1 + \mu \xi_1 + \beta_h \xi_2 I_2^*) I_1^* + (\beta_e \xi_2 \\
& \phi_1 \xi_2 + \mu \xi_2) I_2^* + (\phi_1 k\delta + \mu k\delta) \div (k\delta + (\xi_1 I_1^* + \xi_2 I_2^*)).
\end{aligned}$$

Let

$$\begin{aligned}
A_1 &= \beta_h \xi_1 \\
B_1 &= \beta_e \xi_1 + \beta_h k\delta + \phi_1 \xi_1 + \mu \xi_1 + \beta_h \xi_2 I_2^* \\
C_1 &= (\beta_e \xi_2 + \phi_1 \xi_2 + \mu \xi_2) I_2^* \\
D_1 &= \phi_1 k\delta + \mu k\delta
\end{aligned}$$

where

$$Q_1 = \frac{A_1 I_1^{*2} + B_1 I_1^* + C_1 I_2^* + D_1}{k\delta + (\xi_1 I_1^* + \xi_2 I_2^*)}.$$

Hence

$$S_1^* = \frac{\mu N}{Q_1}.$$

Then

$$S_1^* = \frac{\mu N}{\frac{A_1 I_1^{*2} + B_1 I_1^* + C_1 I_2^* + D_1}{k\delta + (\xi_1 I_1^* + \xi_2 I_2^*)}}.$$

Second consider S_2^* :

$$S_2^* = \frac{\mu A}{\beta_e \frac{\xi_1 I_1^* + \xi_2 I_2^*}{k\delta + (\xi_1 I_1^* + \xi_2 I_2^*)} + \beta_h I_2^* + (\phi_2 + \mu)}$$

and the denominator can be simplified as

$$\begin{aligned}
&\beta_e\frac{\xi_1 I_1^* + \xi_2 I_2^*}{k\delta + (\xi_1 I_1^* + \xi_2 I_2^*)} + \beta_h I_2^* + (\phi_2 + \mu) \\
= \;& \frac{\beta_e\xi_1 I_1^* + \beta_e\xi_2 I_2^* + (\beta_h I_2^* + (\phi_2 + \mu))(k\delta + (\xi_1 I_1^* + \xi_2 I_2^*)}{k\delta + (\xi_1 I_1^* + \xi_2 I_2^*)} \\
= \;& (\beta_e\xi_1 I_1^* + \beta_e\xi_2 I_2^* + \beta_h I_2^* k\delta + \phi_2 k\delta + \mu k\delta + \beta_h I_2^*\xi_1 I_1^* + \phi_2\xi_1 I_1^* + \mu\xi_1 I_1^* \\
& + \beta_h I_2^*\xi_2 I_2^* + \phi_2\xi_2 I_2^* + \mu\xi_2 I_2^*) \div (k\delta + (\xi_1 I_1^* + \xi_2 I_2^*)) \\
= \;& (\beta_h\xi_2) I_2^{*2} + (\beta_e\xi_1 + \phi_2\xi_1 + \mu\xi_1 + \beta_h\xi_1 I_2^*) I_1^* + (\beta_e\xi_2 + \beta_h k\delta + \phi_2\xi_2 \\
& + \mu\xi_2) I_2^* + (\phi_2 k\delta + \mu k\delta) \div (k\delta + (\xi_1 I_1^* + \xi_2 I_2^*)).
\end{aligned}$$

Let

$$\begin{aligned}
A_2 &= \beta_h\xi_2 \\
B_2 &= \beta_e\xi_1 + \phi_2\xi_1 + \mu\xi_1 + \beta_h\xi_1 I_2^* \\
C_2 &= \beta_e\xi_2 + \beta_h k\delta + \phi_2\xi_2 + \mu\xi_2 \\
D_2 &= \phi_2 k\delta + \mu k\delta
\end{aligned}$$

where

$$Q_2 = \frac{A_2 I_2^{*2} + B_2 I_1^* + C_2 I_2^* + D_2}{k\delta + (\xi_1 I_1^* + \xi_2 I_2^*)}.$$

Hence

$$S_2^* = \frac{\mu A}{Q_2}.$$

Then

$$S_2^* = \frac{\mu A}{\frac{A_2 I_2^{*2} + B_2 I_1^* + C_2 I_2^* + D_2}{k\delta + (\xi_1 I_1^* + \xi_2 I_2^*)}}.$$

Next, we turn to V^* that is

$$\begin{aligned}
V^* &= \frac{(\gamma_1 + \mu) I_1^* - (\beta_e\frac{B^*}{k + B^*} + \beta_h I_1^*) S_1^*}{\sigma(\beta_e\frac{B^*}{k + B^*} + \beta_h I_1^*)} \\
&= \frac{(\gamma_1 + \mu) I_1^* - (\beta_e\frac{\frac{\xi_1 I_1^* + \xi_2 I_2^*}{\delta}}{k + \frac{\xi_1 I_1^* + \xi_2 I_2^*}{\delta}} + \beta_h I_1^*)\frac{\mu N}{\frac{A_1 I_1^{*2} + B_1 I_1^* + C_1 I_2^* + D_1}{k\delta + (\xi_1 I_1^* + \xi_2 I_2^*)}}}{\sigma(\beta_e\frac{\frac{\xi_1 I_1^* + \xi_2 I_2^*}{\delta}}{k + \frac{\xi_1 I_1^* + \xi_2 I_2^*}{\delta}} + \beta_h I_1^*)}
\end{aligned}$$

Consider that

$$\begin{aligned}
&\beta_e \frac{\frac{\xi_1 I_1^* + \xi_2 I_2^*}{\delta}}{k + \frac{\xi_1 I_1^* + \xi_2 I_2^*}{\delta}} + \beta_h I_1^* \\
= \;& \beta_e \frac{\xi_1 I_1^* + \xi_2 I_2^*}{k\delta + (\xi_1 I_1^* + \xi_2 I_2^*)} + \beta_h I_1^* \\
= \;& \frac{\beta_e \xi_1 I_1^* + \beta_e \xi_2 I_2^* + \beta_h k\delta I_1^* + \beta_h \xi_1 I_1^* + \beta_h \xi_2 I_2^*}{k\delta + (\xi_1 I_1^* + \xi_2 I_2^*)} \\
= \;& \frac{(\beta_e \xi_1 + \beta_h k\delta + \beta_h \xi_1) I_1^* + (\beta_e \xi_2 + \beta_h \xi_2) I_2^*}{k\delta + (\xi_1 I_1^* + \xi_2 I_2^*)}.
\end{aligned}$$

Let

$$\begin{aligned}
A_3 &= \beta_e \xi_1 + \beta_h k\delta + \beta_h \xi_1 \\
B_3 &= \beta_e \xi_2 + \beta_h \xi_2.
\end{aligned}$$

where

$$Q_3 = \frac{A_3 I_1^* + B_3 I_2^*}{k\delta + (\xi_1 I_1^* + \xi_2 I_2^*)}.$$

Hence

$$V^* = \frac{(\gamma_1 + \mu) I_1^* - (Q_3) \frac{\mu N}{\frac{A_1 I_1^{*2} + B_1 I_1^* + C_1 I_2^* + D_1}{k\delta + (\xi_1 I_1^* + \xi_2 I_2^*)}}}{\sigma(Q_3)}.$$

Thus

$$\begin{aligned}
V^* &= \frac{(\gamma_1 + \mu) I_1^* - \frac{A_3 I_1^* + B_3 I_2^*}{k\delta + (\xi_1 I_1^* + \xi_2 I_2^*)} \frac{\mu N}{\frac{A_1 I_1^{*2} + B_1 I_1^* + C_1 I_2^* + D_1}{k\delta + (\xi_1 I_1^* + \xi_2 I_2^*)}}}{\sigma \frac{A_3 I_1^* + B_3 I_2^*}{k\delta + (\xi_1 I_1^* + \xi_2 I_2^*)}} \\
&= \frac{(\gamma_1 + \mu) I_1^* - \frac{\mu N (A_3 I_1^* + B_3 I_2^*)}{A_1 I_1^{*2} + B_1 I_1^* + C_1 I_2^* + D_1}}{\sigma \frac{A_3 I_1^* + B_3 I_2^*}{k\delta + (\xi_1 I_1^* + \xi_2 I_2^*)}} \\
&= \left[\left((\gamma_1 + \mu) A_1 I_1^{*3} + (\gamma_1 B_1 + \mu B_1) I_1^{*2} + (\gamma_1 C_1 I_2^* + \gamma_1 D_1 + \mu C_1 I_2^* \right. \right. \\
&\quad \left. + \mu D_1 - \mu N A_3) I_1^* + (-\mu N B_3) I_2^* \right) \div \left(A_1 I_1^{*2} + B_1 I_1^* + C_1 I_2^* \right. \\
&\quad \left. \left. + D_1 \right) \right] \div \left[\sigma \frac{A_3 I_1^* + B_3 I_2^*}{k\delta + (\xi_1 I_1^* + \xi_2 I_2^*)} \right].
\end{aligned}$$

Let

$$\begin{aligned}
E_1 &= (\gamma_1 + \mu) A_1 \\
E_2 &= \gamma_1 B_1 + \mu B_1 \\
E_3 &= \gamma_1 C_1 I_2^* + \gamma_1 D_1 + \mu C_1 I_2^* + \mu D_1 - \mu N A_3 \\
E_4 &= -\mu N B_3.
\end{aligned}$$

Then

$$V^* = \frac{\frac{E_1 I_1^{*3} + E_2 I_1^{*2} + E_3 I_1^* + E_4 I_2^*}{A_1 I_1^{*2} + B_1 I_1^* + C_1 I_2^* + D_1}}{\frac{\sigma A_3 I_1^* + \sigma B_3 I_2^*}{k\delta + (\xi_1 I_1^* + \xi_2 I_2^*)}}.$$

Let's consider the risht handside of equation(3.6).We have $S_1^* + S_2^* + V^* =$

$$\frac{\mu N}{\frac{A_1 I_1^{*2} + B_1 I_1^* + C_1 I_2^* + D_1}{k\delta + (\xi_1 I_1^* + \xi_2 I_2^*)}} + \frac{\mu A}{\frac{A_2 I_2^{*2} + B_2 I_1^* + C_2 I_2^* + D_2}{k\delta + (\xi_1 I_1^* + \xi_2 I_2^*)}} + \frac{\frac{E_1 I_1^{*3} + E_2 I_1^{*2} + E_3 I_1^* + E_4 I_2^*}{A_1 I_1^{*2} + B_1 I_1^* + C_1 I_2^* + D_1}}{\frac{\sigma A_3 I_1^* + \sigma B_3 I_2^*}{k\delta + (\xi_1 I_1^* + \xi_2 I_2^*)}}, \quad (3.7)$$

Consider the first term. We have its numerator

$$\begin{aligned} & \mu N \cdot \frac{A_2 I_2^{*2} + B_2 I_1^* + C_2 I_2^* + D_2}{k\delta + (\xi_1 I_1^* + \xi_2 I_2^*)} \cdot \frac{\sigma A_3 I_1^* + \sigma B_3 I_2^*}{k\delta + (\xi_1 I_1^* + \xi_2 I_2^*)} \\ = \; & \big(\mu N A_2 \sigma A_3 I_2^{*2} I_1^* + \mu N A_2 \sigma B_3 I_2^{*3} + \mu N B_2 \sigma A_3 I_1^{*2} + \mu N B_2 \sigma B_3 I_1^* I_2^* + \\ & \mu N C_2 \sigma A_3 I_2^* I_1^* + \mu N C_2 \sigma B_3 I_2^{*2} + \mu N D_2 \sigma A_3 I_1^* + \mu N D_2 \sigma B_3 I_2^*\big) \\ & \div \big(k\delta + (\xi_1 I_1^* + \xi_2 I_2^*)\big)^2, \end{aligned}$$

and the numerator of the second term is

$$\begin{aligned} & \mu A \cdot \frac{A_1 I_1^{*2} + B_1 I_1^* + C_1 I_2^* + D_1}{k\delta + (\xi_1 I_1^* + \xi_2 I_2^*)} \cdot \frac{\sigma A_3 I_1^* + \sigma B_3 I_2^*}{k\delta + (\xi_1 I_1^* + \xi_2 I_2^*)} \\ = \; & \big(\mu A A_1 \sigma A_3 I_1^{*3} + \mu A A_1 \sigma B_3 I_1^{*2} I_2^* + \mu A B_1 \sigma A_3 I_1^{*2} + \mu A B_1 \sigma B_3 I_1^* I_2^* + \\ & \mu A C_1 \sigma A_3 I_2^* I_1^* + \mu A C_1 \sigma B_3 I_2^* + \mu A D_1 \sigma A_3 I_1^* + \mu A D_1 \sigma B_3 I_2^*\big) \\ & \div \big(k\delta + (\xi_1 I_1^* + \xi_2 I_2^*)\big)^2. \end{aligned}$$

and the numerator of the third term is

$$\begin{aligned} & \frac{E_1 I_1^{*3} + E_2 I_1^{*2} + E_3 I_1^* + E_4 I_2^*}{k\delta + (\xi_1 I_1^* + \xi_2 I_2^*)} \cdot \frac{A_1 I_1^{*2} + B_1 I_1^* + C_1 I_2^* + D_1}{k\delta + (\xi_1 I_1^* + \xi_2 I_2^*)} \\ & \cdot \frac{A_2 I_2^{*2} + B_2 I_1^* + C_2 I_2^* + D_2}{k\delta + (\xi_1 I_1^* + \xi_2 I_2^*)} \\ = \; & \big(E_1 A_2 I_1^{*5} + E_1 B_2 I_1^{*4} + E_1 C_2 I_1^{*3} I_2^* + E_1 D_2 I_1^{*3} + E_2 A_2 I_1^{*4} + E_2 B_2 I_1^{*3} \\ & + E_2 C_2 I_1^{*2} I_2^* + E_3 A_2 I_1^{*3} + E_3 B_3 I_1^{*2} + E_3 C_2 I_1^* I_2^* + E_3 D_2 I_1^* + E_4 A_2 I_1^{*2} I_2^* \\ & + E_4 B_2 I_1^* I_2^* + E_4 C_2 I_2^{*2} + E_4 D_2 I_2^*\big) \div \big(k\delta + (\xi_1 I_1^* + \xi_2 I_2^*)\big)^2 \end{aligned}$$

Then the equation (3.7) becomes

$$\begin{aligned} = & \left[(E_1A_2)I_1^{*5} + (E_1B_2 + E_2A_2)I_1^{*4} + (\mu AA_1\sigma A_3 + E_1C_2I_2^* + E_1D_2 \right. \\ & + E_3B_2 + E_3A_2)I_1^{*3} + (\mu NB_2\sigma A_3 + \mu AA_1\sigma B_3I_2^* + \mu AB_1A_3 + E_2C_2I_2^* \\ & + E_2D_2 + F_3B_3 + E_4A_2I_2^*)I_1^{*2} + (\mu NA_2\sigma A_3I_2^{*2} + \mu NB_2\sigma B_3I_2^* \\ & + \mu NC_2\sigma A_3I_2^* + \mu ND_2\sigma A_3 + \mu AB_1B_3I_2^* + \mu AC_1\sigma A_3I_2^* + \mu AD_1\sigma A_3 \\ & + E_3C_2I_2^* + E_3D_2 + E_4B_2I_2^*)I_1^* + (\mu NA_2\sigma B_3)I_2^{*3} + (\mu NC_2\sigma B_3 \\ & \left. + E_4C_2)I_2^{*2} + (\mu ND_2\sigma B_3 + \mu AC_1\sigma B_3 + \mu AD_1\sigma B_3 + E_4D_2)I_2^* \right] \\ & \div \left[k\delta + (\xi_1I_1^* + \xi_2I_2^*)\right]^2. \end{aligned}$$

Let

$$\begin{aligned} F_1 &= E_1A_2 \\ F_2 &= E_1B_2 + E_2A_2 \\ F_3 &= \mu AA_1\sigma A_3 + E_1C_2I_2^* + E_1D_2 + E_3B_2 + E_3A_2 \\ F_4 &= \mu NB_2\sigma A_3 + \mu AA_1\sigma B_3I_2^* + \mu AB_1A_3 + E_2C_2I_2^* + E_2D_2 + E_3B_3 \\ &\quad + E_4A_2I_2^* \\ F_5 &= \mu NA_2\sigma A_3I_2^{*2} + \mu NB_2\sigma B_3I_2^* + \mu NC_2\sigma A_3I_2^* + \mu ND_2\sigma A_3 \\ &\quad + \mu AB_1B_3I_2^* + \mu AC_1\sigma A_3I_2^* + \mu AD_1\sigma A_3 + E_3C_2I_2^* + E_3D_2 + E_4B_2I_2^* \\ F_6 &= \mu NA_2\sigma B_3 \\ F_7 &= \mu NC_2\sigma B_3 + E_4C_2 \\ F_8 &= \mu ND_2\sigma B_3 + \mu AC_1\sigma B_3 + \mu AD_1\sigma B_3 + E_4D_2 \end{aligned}$$

Then the numerator of the above equation becomes

$$\frac{F_1(I_1^{*5}) + F_2(I_1^{*4}) + F_3(I_1^{*3}) + F_4(I_1^{*2}) + F_5(I_1^*) + F_6(I_2^{*3}) + F_7(I_2^{*2}) + F_8(I_2^*)}{\left[k\delta + (\xi_1I_1^* + \xi_2I_2^*)\right]^2}$$

Next we will consider the denominator of equation (3.7). We have

$$\begin{aligned}
&\big[A_2A_1\sigma A_3I_2^{*2}I_1^{*3} + A_2B_1\sigma A_3I_2^{*2}I_1^{*2} + A_2C_1\sigma A_3I_2^{*3}I_1^{*} + A_2D_1\sigma A_3I_2^{*2}I_1^{*} + \\
&A_2A_1\sigma B_3I_2^{*3}I_1^{*2} + A_2B_1\sigma B_3I_2^{*3}I_1^{*} + A_2C_1\sigma B_3I_2^{*4} + A_2D_1\sigma B_3I_2^{*3} + \\
&B_2A_1\sigma A_3I_2^{*4} + B_2B_1\sigma A_3I_1^{*3} + B_2C_1\sigma A_3I_2^{*}I_1^{*2} + B_2D_1\sigma A_3I_1^{*2} + \\
&B_2A_1\sigma B_3I_2^{*}I_1^{*3} + B_2B_1\sigma B_3I_2^{*}I_1^{*2} + B_2C_1\sigma B_3I_2^{*2}I_1^{*} + B_2D_1\sigma B_3I_1^{*}I_2^{*} + \\
&C_2A_1\sigma A_3I_2^{*}I_1^{*3} + C_2B_1\sigma A_3I_2^{*}I_1^{*2} + C_2C_1\sigma A_3I_2^{*2}I_1^{*} + C_2D_1\sigma A_3I_2^{*}I_1^{*} + \\
&C_2A_1\sigma B_3I_2^{*2}I_1^{*2} + C_2B_1\sigma B_3I_2^{*2}I_1^{*} + C_2C_1\sigma B_3I_2^{*3} + C_2D_1\sigma B_3I_2^{*2} + \\
&D_2A_1\sigma A_3I_1^{*3} + D_2B_1\sigma A_3I_1^{*2} + D_2C_1\sigma A_3I_2^{*}I_1^{*} + D_2D_1\sigma A_3I_1^{*} + \\
&D_2A_1\sigma B_3I_2^{*}I_1^{*2} + D_2B_1\sigma B_3I_2^{*}I_1^{*} + D_2C_1\sigma B_3I_2^{*2} + D_2D_1\sigma B_3I_2^{*}\big] \div \\
&\big[k\delta + (\xi_1I_1^{*} + \xi_2I_2^{*})\big]^3.
\end{aligned}$$

Rearrange terms,we have

$$\begin{aligned}
= \ &\big[(B_2A_1\sigma A_3)I_1^{*4} + (A_2A_1\sigma I_2^{*2} + B_2B_1\sigma A_3 + B_2A_1\sigma B_3I_2^{*} + C_2A_1\sigma A_3I_2^{*} \\
&+D_2A_1\sigma A_3)I_1^{*3} + (A_2B_1\sigma A_3I_2^{*2} + B_2C_1\sigma A_3I_2^{*} + B_2D_1\sigma A_3 + B_2B_1\sigma B_3I_2^{*} \\
&+C_2B_1\sigma A_3I_2^{*} + C_2A_1\sigma B_3I_2^{*2} + A_2A_1\sigma B_3I_2^{*3} + D_2B_1\sigma A_3 + D_2A_1\sigma B_3I_2^{*}) \\
&I_1^{*2} + (A_2C_1\sigma A_3I_2^{*3} + A_2D_1\sigma A_3I_2^{*2} + A_2B_1\sigma B_3I_2^{*3} + B_2C_1I_2^{*2} \\
&+B_2D_1\sigma B_3I_2^{*} + C_2C_1\sigma A_3I_2^{*} + C_2D_1\sigma A_3I_2^{*} + C_2B_1\sigma B_3I_2^{*2} + D_2C_1\sigma A_3I_2^{*} \\
&+D_2D_1\sigma A_3 + D_2B_1\sigma B_3I_2^{*})I_1^{*} + (A_2C_1\sigma B_3)I_2^{*4} + (A_2D_1\sigma B_3 \\
&+C_2C_1\sigma B_3)I_2^{*3} + (C_2D_1\sigma B_3 + D_2C_1\sigma B_3)I_2^{*2} + (D_2D_1\sigma B_3)I_2^{*}\big] \\
&\div\big[k\delta + (\xi_1I_1^{*} + \xi_2I_2^{*})\big]^3.
\end{aligned}$$

Let

$$
\begin{aligned}
G_1 &= B_2A_1\sigma A_3 \\
G_2 &= A_2A_1\sigma I_2^{*2} + B_2B_1\sigma A_3 + B_2A_1\sigma B_3I_2^* + C_2A_1\sigma A_3I_2^* + D_2A_1\sigma A_3 \\
G_3 &= A_2B_1\sigma A_3I_2^{*2} + B_2C_1\sigma A_3I_2^* + B_2D_1\sigma A_3 + B_2B_1\sigma B_3I_2^* + C_2B_1\sigma A_3I_2^* \\
&\quad C_2A_1\sigma B_3I_2^{*2} + A_2A_1\sigma B_3I_2^{*3} + D_2B_1\sigma A_3 + D_2A_1\sigma B_3I_2^* \\
G_4 &= A_2C_1\sigma A_3I_2^{*3} + A_2D_1\sigma A_3I_2^{*2} + A_2B_1\sigma B_3I_2^{*3} + B_2C_1I_2^{*2} + B_2D_1\sigma B_3I_2^* \\
&\quad + C_2C_1\sigma A_3I_2^* + C_2D_1\sigma A_3I_2^* + C_2B_1\sigma B_3I_2^{*2} + D_2C_1\sigma A_3I_2^* + D_2D_1\sigma A_3 \\
&\quad + D_2B_1\sigma B_3I_2^* \\
G_5 &= A_2C_1\sigma B_3 \\
G_6 &= A_2D_1\sigma B_3 + C_2C_1\sigma B_3 \\
G_7 &= C_2D_1\sigma B_3 + D_2C_1\sigma B_3 \\
G_8 &= D_2D_1\sigma B_3.
\end{aligned}
$$

Then the denominator of the equation above becomes

$$\frac{G_1(I_1^{*4}) + G_2(I_1^{*3}) + G_3(I_1^{*2}) + G_4(I_1^*) + G_5(I_2^{*4}) + G_6(I_2^{*3}) + G_7(I_2^{*2}) + G_8(I_2^*)}{\left[k\delta + (\xi_1 I_1^* + \xi_2 I_2^*)\right]^3}.$$

Therefore now equation (3.6) becomes

$$N + A - (\tau_1 I_1^* - \tau I_2^*) = S_1^* + S_2^* + V^*$$

$$N + A - (\tau_1 I_1^* - \tau I_2^*) = \frac{\frac{F_1(I_1^{*5}) + F_2(I_1^{*4}) + F_3(I_1^{*3}) + F_4(I_1^{*2}) + F_5(I_1^*) + F_6(I_2^{*3}) + F_7(I_2^{*2}) + F_8(I_2^*)}{\left[k\delta + (\xi_1 I_1^* + \xi_2 I_2^*)\right]^2}}{\frac{G_1(I_1^{*4}) + G_2(I_1^{*3}) + G_3(I_1^{*2}) + G_4(I_1^*) + G_5(I_2^{*4}) + G_6(I_2^{*3}) + G_7(I_2^{*2}) + G_8(I_2^*)}{\left[k\delta + (\xi_1 I_1^* + \xi_2 I_2^*)\right]^3}}$$

$$N + A - (\tau_1 I_1^* - \tau I_2^*) = \left[\left(F_1(I_1^{*5}) + F_2(I_1^{*4}) + F_3(I_1^{*3}) + F_4(I_1^{*2}) + F_5(I_1^*) + F_6(I_2^{*3}) + F_7(I_2^{*2}) + F_8(I_2^*)\right) \div \left(G_1(I_1^{*4}) + G_2(I_1^{*3}) + G_3(I_1^{*2}) + G_4(I_1^*) + G_5(I_2^{*4}) + G_6(I_2^{*3}) + G_7(I_2^{*2}) + G_8(I_2^*)\right)\right] \cdot \left[k\delta + (\xi_1 I_1^* + \xi_2 I_2^*)\right]$$

$$NG_1I_1^{*4} + NG_2I_1^{*3} + NG_3I_1^{*2} + NG_4I_1^* + NG_5I_2^{*4} + NG_6I_2^{*3} + NG_7I_2^{*2}$$
$$+NG_8I_2^* + AG_1I_1^{*4} + AG_2I_1^{*3} + AG_3I_1^{*2} + AG_4I_1^* + AG_5I_2^{*4} + AG_6I_2^{*3}$$
$$+AG_7I_2^{*2} + AG_8I_2^* - \tau_1G_1I_1^{*5} - \tau_1G_2I_1^{*4} - \tau_1G_3I_1^{*3} - \tau_1G_4I_1^{*2} - \tau_1G_5I_2^{*4}I_1^*$$
$$-\tau_1G_6I_2^{*3}I_1^* - \tau_1G_7I_2^{*2}I_1^* - \tau_1G_8I_2^*I_1^* - \tau_2G_1I_1^{*4}I_2^* - \tau_2G_2I_1^{*3}I_2^* - \tau_2G_3I_1^{*2}I_2^*$$
$$-\tau_2G_4I_1^*I_2^* - \tau_2G_5I_2^{*5} - \tau_2G_6I_2^{*4} - \tau_2G_7I_2^{*3} - \tau_2G_8I_2^{*2}$$
$$= F_1k\delta I_1^{*5} + F_2k\delta I_1^{*4} + F_3k\delta I_1^{*3} + F_4k\delta I_1^{*2} + F_5k\delta I_1^* + F_6k\delta I_2^{*3} + F_7k\delta I_2^{*2} + F_8k\delta I_2^*$$
$$+F_1\xi_1I_1^{*6} + F_2\xi_1I_1^{*5} + F_3\xi_1I_1^{*4} + F_4\xi_1I_1^{*3} + F_5\xi_1I_1^{*2} + F_6\xi_1I_2^{*3}I_1^* + F_7\xi_1I_2^{*2}I_1^*$$
$$+F_8\xi_1I_2^*I_1^* + F_1\xi_2I_1^{*5}I_2^* + F_2\xi_2I_1^{*4}I_2^* + F_3\xi_2I_1^{*3}I_2^* + F_4\xi_2I_1^{*2}I_2^* + F_5\xi_2I_1^*I_2^*$$
$$+F_6\xi_2I_2^{*4} + F_7\xi_1I_2^{*3} + F_8\xi_2I_2^{*2},$$

$$(F_1\xi_1)I_1^{*6} + (F_1k\delta + F_2\xi_1 + F_1\xi_2I_2^* + \tau_1G_1)I_1^{*5} + (F_2k\delta + F_3\xi_1 + F_2\xi_2I_2^*$$
$$+\tau_1G_2 + \tau_2G_1I_2^* - NG_1 - AG_1)I_1^{*4} + (F_3k\delta + F_4\xi_1 + F_3\xi_2I_2^* + \tau_1G_3$$
$$+\tau_2G_2I_2^* - NG_2 - AG_2)I_1^{*3} + (F_4k\delta + F_5\xi_1 + F_4\xi_2I_2^* + \tau_1G_4 + \tau_2G_3I_2^*$$
$$-NG_3 - AG_3)I_1^{*2} + (F_5k\delta + F_6\xi_1I_2^{*3} + F_7\xi_1I_2^{*2} + F_8\xi I_2^{*2} + F_5\xi_2I_2^*$$
$$+\tau_1G_5I_2^{*4} + \tau_1G_6I_2^{*3} + \tau_1G_7I_2^{*2} + \tau_1G_8I_2^* + \tau_2G_4I_2^* - NG_4 - AG_4)I_1^*$$
$$+(\tau_2G_5)I_2^{*5} + (F_6\xi_2 - NG_5 + \tau_2G_6 - AG_5)I_2^{*4} + (F_7\xi_2 + F_6k\delta + \tau_2G_7$$
$$-NG_6 - AG_6)I_2^{*3} + (F_8\xi_2 + F_7k\delta + \tau_2G_8 - NG_7 - AG_7)I_2^{*2} + (F_8k\delta$$
$$-NG_8 - AG_8)I_2^* = 0.$$

Let

$$\begin{aligned}
H_1 &= F_1\xi_1 \\
H_2 &= F_1k\delta + F_2\xi_1 + F_1\xi_2 I_2^* + \tau_1 G_1 \\
H_3 &= F_2k\delta + F_3\xi_1 + F_2\xi_2 I_2^* + \tau_1 G_2 + \tau_2 G_1 I_2^* - NG_1 - AG_1 \\
H_4 &= F_3k\delta + F_4\xi_1 + F_3\xi_2 I_2^* + \tau_1 G_3 + \tau_2 G_2 I_2^* - NG_2 - AG_2 \\
H_5 &= F_4k\delta + F_5\xi_1 + F_4\xi_2 I_2^* + \tau_1 G_4 + \tau_2 G_3 I_2^* - NG_3 - AG_3 \\
H_6 &= F_5k\delta + F_6\xi_1 I_2^{*3} + F_7\xi_1 I_2^{*2} + F_8\xi I_2^{*2} + F_5\xi_2 I_2^* + \tau_1 G_5 I_2^{*4} \\
&\quad + \tau_1 G_6 I_2^{*3} + \tau_1 G_7 I_2^{*2} + \tau_1 G_8 I_2^* + \tau_2 G_4 I_2^* - NG_4 - AG_4 \\
H_7 &= \tau_2 G_5 \\
H_8 &= F_6\xi_2 - NG_5 + \tau_2 G_6 - AG_5 \\
H_9 &= F_7\xi_2 + F_6k\delta + \tau_2 G_7 - NG_6 - AG_6 \\
H_{10} &= F_8\xi_2 + F_7k\delta + \tau_2 G_8 - NG_7 - AG_7 \\
H_{11} &= F_8k\delta - NG_8 - AG_8 \\
H_{12} &= H_7 + H_8 + H_9 + H_{10}.
\end{aligned}$$

Then the equation above becomes

$$H_1 I_1^{*6} + H_2 I_1^{*5} + H_3 I_1^{*4} + H_4 I_1^{*3} + H_5 I_1^{*2} + H_6 I_1^* + H_{12} = 0$$

ROUTH'S STABILITY CRITERION

Consider a closed-loop transfer function

$$H(s) = \frac{b_0 s^m + b_1 s^{m-1} + \ldots + b_{m-1}s + b_m}{a_0 s^n + a_1 s^{n-1} + \ldots + a_{n-1}s + a_n} = \frac{B(s)}{A(s)}$$

where the a_i's and b_i's are real constants and $m \leq n$. An alternative to factoring thr denominator, Routh's stability, criterion, determines the mumber of closedloop poles in the right-half s plane.

Algorithm for applying Routh's stability criterion The algorithm described below, like the stability criterion, requirion, requires the order of $A(s)$ to be finite.

1. Factor out any roots at the origin to obtain the polynomial, and multiply by -1 if necessary, to obtain

$$a_0 s^n + a_1 s^{n-1} + \ldots + a_{n-1}s + a_n = 0$$

where $a_0 \neq 0$ and $a_n < 0$.

2.If the order of the resulting polynomial is at least two and any coefficcient a_i is zero

or negative, the polynomaial has at one root with nonnegative real part. To obtain the precise number of roots with nooegative real part, procrrd as follows. Arrange thr coefficents of the the polynomial, and values subsequently calculated from them as shown below:

$$\begin{array}{lccccc} s^n & a_0 & a_2 & a_4 & a_6 & \ldots \\ s^{n-1} & a_1 & a_3 & a_5 & a_7 & \ldots \\ s^{n-2} & b_1 & b_2 & b_3 & b_4 & \ldots \\ s^{n-3} & c_1 & c_2 & c_3 & c_4 & \ldots \\ s^{n-4} & d_1 & d_2 & d_3 & d_4 & \ldots \\ \vdots & \vdots & \vdots & & & \\ s^2 & e_1 & e_2 & & & \\ s^1 & f_1 & & & & \\ s^0 & g_0 & & & & \end{array}$$

where the coefficients b_i are

$$\begin{aligned} b_1 &= \frac{a_1 a_2 - a_0 a_3}{a_1} \\ b_2 &= \frac{a_1 a_4 - a_0 a_5}{a_1} \\ b_3 &= \frac{a_1 a_6 - a_0 a_7}{a_1} \\ &\vdots \end{aligned}$$

generated until all subsequent coefficients are zero. Similarly, cross multiply thr coefficents of the two previous rows to obtain the c_i, d_i,etc.

$$
\begin{aligned}
c_1 &= \frac{b_1 a_3 - a_1 b_2}{b_1} \\
c_2 &= \frac{b_1 a_5 - a_1 a_3}{b_1} \\
c_3 &= \frac{b_1 a_7 - a_1 b_4}{b_1} \\
&\vdots \\
d_1 &= \frac{c_1 b_2 - b_1 c_2}{c_1} \\
d_2 &= \frac{c_1 b_3 - b_1 c_3}{c_1} \\
&\vdots
\end{aligned}
$$

until the nth row of thearray has been completed[1] Missing coefficients are replaced by zeros. The resulting array is called the Routh array. The powers of s are not considered to be part of the array. We can think of them as labels. The column beginning with a_0 is considered to be the first columm of the array.

The Routh array is seen to be truangular. Ii can be shown that multiplying a row by a positive number to simplify the calculation of the next row does not affect the outcomr of the application of the Routh criterion.

3. Count the number of sign changes in the first columm of the array. It can be shown that a necessary and sufficient for all roots of (2) to be located in the left-half plane is that all the ai are positive and all of the coefficients in the first column be positive.

Examples

Given a system with characteristic equation

$$a_2 s^2 + a_1 s + a_0 = 0$$

determine which values of will make the system and which will make the system unstable. Arranged in matrix form, the coefficients are

$$
\begin{array}{ccc}
s^2 & a_2 & a_0 \\
s & a_1 & \\
1 & a_1 a_0 / a_2 &
\end{array}
$$

The Routh-Hurwitz criterion states that all of thr coefficients in the first column of coefficients must be positive, so for this case we must have $a_2 > 0$ and $a_1 > 0$. Since a_2 and a_1, a_0 must be greater than 0 as well.

As another example, consider the system with characteristic equation

$$s^3 + s^2 + 2s + 24 = 0$$

Arranged in matrix form, the coefficents are

$$\begin{array}{cc} s^3 & 1 & 2 \\ s^2 & 1 & 24 \\ s & -22 & a_0 \\ 1 & 24 \end{array}$$

Since at least one of the coefficients (-22) is less than zero, this system is unstem is unstable. In fact, it has two roots in the right half-plane.

As a final example, consider the system with characteristic equation

$$s^5 + 2s^4 + 2s^3 + 4s^2 + 11s + 10 = 0$$

We construct the matrix as in the other examples,

$$\begin{array}{cccc} s^5 & 1 & 2 & 11 \\ s^4 & 2 & 4 & 10 \\ s^3 & 0 & 6 & 0 \end{array}$$

At this point, we cannot continue since we have a 0 in the first column. We are interested only in the sign of the coefficients, so the workaround is to replace the 0 with a small, positive number, call it E. Then we have

$$\begin{array}{cccc} s^5 & 1 & 2 & 11 \\ s^4 & 2 & 4 & 10 \\ s^3 & E & 6 & 0 \\ s^2 & c_1 & 10 \\ s^1 & d_1 & 10 \\ 1 & 10 \end{array}$$

Let $a_0 = H_1, a_1 = H_2, a_2 = H_3, a_3 = H_4, a_4 = H_5, a_5 = H_6, a_6 = H_{12}$

$$
\begin{aligned}
b_1 &= \frac{a_1a_2 - a_0a_5}{a_1} \\
&= \frac{H_2H_3 - H_1H_4}{H_2} \\
b_2 &= \frac{a_1a_4 - a_0a_5}{a_1} \\
&= \frac{H_2H_5 - H_1H_6}{H_2} \\
b_3 &= \frac{a_1a_6 - a_0(0)}{a_1} \\
&= \frac{H_2H_{12} - H_1(0)}{H_2} \\
&= H_{12} \\
c_1 &= \frac{b_1a_3 - a_1b_2}{b_1} \\
&= \frac{(\frac{H_2H_3 - H_1H_4}{H_2})H_4 - H_2(\frac{H_2H_5 - H_1H_6}{H_2})}{\frac{H_2H_3 - H_1H_4}{H_2}} \\
&= \frac{(H_2H_3 - H_1H_4)H_4 - H_2(H_2H_5 - H_1H_6)}{H_2H_3 - H_1H_4} \\
&= H_4H_2(\frac{H_2H_5 - H_1H_6}{H_2H_3 - H_1H_4}) \\
c_2 &= \frac{b_1a_5 - a_1b_3}{b_1} \\
&= \frac{(\frac{H_2H_3 - H_1H_4}{H_2})H_6 - H_1(\frac{H_2H_{12}}{H_2})}{(\frac{H_2H_3 - H_1H_4}{H_2})} \\
&= (H_6 - H_1)(\frac{H_2H_{12}}{H_2H_3 - H_1H_4})
\end{aligned}
$$

$$
\begin{aligned}
d_1 &= \frac{c_1b_2 - b_2c_2}{c_1} \\
&= \left[(H_4H_2(\frac{H_2H_5 - H_1H_6}{H_2H_3 - H_1H_4})) \cdot (\frac{H_2H_5 - H_1H_6}{H_2}) - (\frac{H_2H_5 - H_1H_6}{H_2}) \right. \\
&\quad \left. \cdot((H_6 - H_1)(\frac{H_2H_{12}}{H_2H_3 - H_1H_4}))\right] \div \left[H_4H_2(\frac{H_2H_5 - H_1H_6}{H_2H_3 - H_1H_4})\right] \\
&= (\frac{H_2H_5 - H_1H_6}{H_2}) - \left[(\frac{H_2H_5 - H_1H_6}{H_2}) \cdot ((H_6 - H_1)(\frac{H_2H_{12}}{H_2H_3 - H_1H_4}))\right] \\
&\quad \div \left[H_4H_2(\frac{H_2H_5 - H_1H_6}{H_2H_3 - H_1H_4})\right] \\
d_2 &= \frac{c_1b_3 - b_1c_3}{c_1} \\
&= \frac{(H_4H_2(\frac{H_2H_5 - H_1H_6}{H_2H_3 - H_1H_4}))(H_{12}) - (\frac{H_2H_3 - H_1H_4}{H_2})(0)}{H_4H_2(\frac{H_2H_5 - H_1H_6}{H_2H_3 - H_1H_4})} \\
&= H_{12} \\
e_1 &= \frac{d_1c_2 - c_1d_2}{d_1} \\
&= c_2 - \frac{c_1d_2}{d_1} \\
&= (H_6 - H_1)(\frac{H_2H_{12}}{H_2H_3 - H_1H_4}) - (H_{12})\left[H_4H_2(\frac{H_2H_5 - H_1H_6}{H_2H_3 - H_1H_4})\right] \div \\
&\quad \left[(\frac{H_2H_5 - H_1H_6}{H_2}) - \left[(\frac{H_2H_5 - H_1H_6}{H_2}) \cdot ((H_6 - H_1)(\frac{H_2H_{12}}{H_2H_3 - H_1H_4}))\right]\right. \\
&\quad \left. \div \left[H_4H_2(\frac{H_2H_5 - H_1H_6}{H_2H_3 - H_1H_4})\right]\right] \\
f_0 &= \frac{e_1d_2 - d_1e_2}{e_1} \\
&= \frac{e_1H_{12} - d_1(0)}{e_1} \\
&= H_{12}
\end{aligned}
$$

Numerically, We have the values of these unknow us as follows:

I_1^{*6}	1.9366×10^{-6}	1.0196×10^3	1.9918×10^4	0.0031
I_1^{*5}	0.3098	2.7118×10^4	27.6067	0
I_1^{*4}	1.0194×10^3	1.9918×10^4	0.0031	0
I_1^{*3}	2.7112×10^4	27.6067	0	
I_1^{*2}	1.9898×10^4	0.0031		
I_1^{*1}	2.7112×10^4	0		
I_1^{*0}	0.0031			

Form the ROUTH'S STABILITY CRITERION, we conclude that there exists a unigne positive epuillibrium point.

Theorem 3.5. *The positive endemic equilibrium exists and is unique if and only if* $R_0 > 1$.

Theorem 3.6. *When* $R_0 > 1$, *the positive endemic equilibrium of system is locally asymptotically stable*

Proof. Consider the Jacobian at the endemic equilibrium. To make the algebraic manipulation simpler, we set

$$G = \frac{\beta_e B^*}{k + B^*} + \beta_h I_1^*, \quad F = \frac{\beta_e B^*}{k + B^*} + \beta_h I_2^*, \quad H = \sigma(\frac{\beta_e B^*}{k + B^*} + \beta_h I_1^*)$$

$$I = \sigma(\frac{\beta_e B^*}{k + B^*} + \beta_h I_2^*), \quad J = \frac{S_1^* k \beta_e}{(k + B^*)^2}, \quad M = \frac{S_2^* k \beta_e}{(k + B^*)^2}$$

$$N = \frac{\sigma k \beta_e V^*}{(k + B^*)^2}, \quad P = \beta_h S_1^*, \quad Q = \beta_h S_2^*, \quad R = \sigma \beta_h V^*$$

Note thet $G, F, H, I, J, M, N, P, Q$ and R are all positive. The Jacobian matrix then becomes

$$J_B^* = \begin{bmatrix} -G-(\phi_1+\mu) & 0 & 0 & -P & 0 & -J & 0 \\ 0 & -F-(\phi_2+\mu) & 0 & 0 & -Q & -M & 0 \\ \phi_1 & \phi_2 & -H-I-\mu & -R & -R & -2N & 0 \\ G & 0 & H & P+R-\mu-\gamma_1 & 0 & J+N & 0 \\ 0 & F & I & 0 & Q+R-\mu-\gamma_2 & M+N & 0 \\ 0 & 0 & 0 & \xi_1 & \xi_2 & -\delta & 0 \\ 0 & 0 & 0 & \gamma_1 & \gamma_2 & 0 & -\mu \end{bmatrix}$$

Since for this undergraduate project we have a very limit of time to study and to complete the positive definite proof, we will aproximate the eigenvalues of the 7×7 matrix numerically. In order to have the EEP stable, we need to have negative real parts of all eigenvalues. We conducted a few numerical approximations with different time sets (100, 500, 1000, 4000, 8000 days) resulting all eigenvalues have negative real parts. Therefore, numerically, we conclude that there exists a unique positive solution and it is locally asymptotically stable.

For T=100:

$$e_{100} = \begin{bmatrix} -0.0001 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & -0.0440 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & -0.0553+0.0178i & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & -0.0322 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & -0.3958 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & -0.2238 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & -0.932 \end{bmatrix}$$

For T=500:

$$e_{500} = \begin{bmatrix} -0.0001 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & -0.1575 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & -0.1967 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & -0.0311 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & -0.0173 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & -0.0099 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & -0.0045 \end{bmatrix}$$

For T=1000:

$$e_{1000} = \begin{bmatrix} -0.0001 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & -0.1709 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & -0.1942 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & -0.0322 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & -0.0031 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & -0.0023 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & -0.0010 \end{bmatrix}$$

For T=4000:

$$e_{4000} = \begin{bmatrix} -0.0001 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & -0.1715 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & -0.1740 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & -0.0313 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & -0.0001 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & -0.0001 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & -0.0001 \end{bmatrix}$$

For T=8000:

$$e_{8000} = \begin{bmatrix} -0.0001 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & -0.1702 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & -0.1461 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & -0.0293 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & -0.0001 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & -0.0001 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & -0.0001 \end{bmatrix}$$

3.4 Optimal control study

3.4.1 The Basic Problem and Necessary Conditions

In our basic optimal control problem for ordinary differential equations, we use u(t) for the control and x(t) for the state. The state variable satisfies a differential equation which depends on the control variable:

$$x'(t) = g(t, x(t), u(t)).$$

As the control function is changed, the solution to the differential equation will change. Thus we can view the control-to-state relationship as a map $u(t) \mapsto x = x(u)$ (of course, x is really a function of the independent variable t; we write x(u) simply to remind us of the dependence on u). Our basic optimal control problem consists of finding a piecewise continuous control $u(t)$ and the associated state variable $x(t)$ to maximize the given objective functional, i.e.,

$$\max_u \int_{t_0}^{t_1} f(t, x(t), u(t))dt.$$

subject to $x'(t) = g(t, x(t), u(t)), \quad x(t_0) = x_0 \, and \, x(t_1)$ free.

Such a maximizing control is called an optimal control. By $x(t_1)$ free, it is meant that the value of $x(t_1)$ is unrestricted. For our purposes, f and g will always be continuously differentiable functions in all three arguments. Thus, as the control(s) will always be piecewise continuous, the associated states will always be piecewise differentiable.

The principle technique for such an optimal control problem is to solve a set of ``necessary conditions" that an optimal control and corresponding state must satisfy. It is important to understand the logical difference between necessary conditions and sufficient conditions of solution sets.

Necessary Conditions : If $u^*(t), x^*(t)$ are optimal, then the following conditions hold ...

Sufficient Conditions : If $u^*(t), x^*(t)$ satisfy the following conditions ..., then $u^*(t), x^*(t)$ are optimal.

We will discuss sufficient conditions in the next chapter. For now, let us derive the necessary conditions. Express our objective functional in terms of the control:

$$J(u) = \int_{t_0}^{t_1} f(t, x(t), u(t))dt,$$

where $x = x(u)$ is the corresponding state.

The necessary conditions that we derive were developed by Pontryagin and his co-workers

in Moscow in the 1950's. Pontryagin introduced the idea of ``adjoint" functions to append the differential equation to the objective functional. Adjoint function have a similar purpose as Lagrange multipliers in multivariate calculus, which append constraints to the function of several variable to be maximized or minimized. Thus, we begin by finding appropriate conditions that the adjoint function should satisfy. Then, by differentiating the map from the control to the objective functional, we will derive a characterization of the optimal control in terms of the optimal state and corresponding adjoint. So do not feel as if we are ``pulling a rabbit out of the hat" when we define the adjoint equation.

3.4.2 Pontryagin's Maximum Principle

These conclusions can be extended to a version of Pontryagin's Maximum Principle.

Theorem 3.7. *If $u^*(t)$ and $x^*(t)$ are optimal for problem (3.4.1), then there exists a piecewise differentiable adjoint variable $\lambda(t)$ such that*

$$H(t, x^*(t), u(t), \lambda(t)) \leq H(t, x^*(t), u^*(t), \lambda(t))$$

for all control u at each time t, where the Hamiltonian H is

$$H = f(t, x(t), u(t)) + \lambda(t) g(t, x(t), u(t)),$$

and

$$\lambda'(t) = -\frac{\partial H(t, x^*(t), u^*(t), \lambda(t))}{\partial x}, \lambda(t_1) = 0$$

Theorem 3.8. *Suppose that $f(t, x, u)$ and $g(t, x, u)$ are both continuously differentiable functions in thier three arguments and concave in u. Suppose u^* is an optimal control for problem (3.4.1), with associated state x^*, and λ a piecewise differentiable function with $\lambda \geq 0$ for all t. Suppose for all $t_0 \leq t \leq t_1$*

$$0 = H_u(t, x^*(t), u^*(t), \lambda(t)).$$

Then for all controls u and each $t_0 \leq t \leq t_1$, we have

$$H(t, x^*(t), u(t), \lambda(t)) \leq H(t, x^*(t), u^*(t), \lambda(t)).$$

Now we turn to the more general model with time-dependent control v(t). We consider the system on a time interval [0,T]. The function v(t) is assumed to be at least Lebesgue measurable on [0,T]. The control set is defined as

$$\Omega = \{v(t) | 0 \leq v(t) \leq v_{max}\}$$

where v_{max} denotes the upper bounds for the effort of vaccination. The bound reflects practical limitation on the maximum rate of control in given time period.

The presence of time-dependent controls makes the analysis of our system difficult. In fact, the disease dynamics now depend on the evolution of control. In what follows we perform an optimal control study on this problem. We aim to minimize the total number of infections and the costs of control over the time interval $[0, T]$; i.e.,

$$\min_{(\phi_{1,2})\in\Omega} \int_0^T [I_1(t) + I_1(t) + c_{11}\phi_1(t)S_1(t) + c_{12}\phi_2(t)S_2] \\ c_{21}\phi_1(t)^1 + c_{22}\phi_2(t)^2]dt \tag{3.8}$$

Here, the parameters c_{11} ,c_{22} , c_{21} and c_{22} with appropriate units, define the appropriate costs associated with these controls. Quadratic terms are introduced to indicate nonlinear costs potentially arising at high intervention level. The minimization process is subject to the differential equation of our system, which are now referred to as the state equations. Correspondingly, the unknows S_1, S_2, I_1, I_2, V and B are now called the state variables, in contrast to the control variables ϕ_1 and ϕ_2. Our goal is to determine the optimal controls $\phi_1^*(t)$ and $\phi_2^*(t)$,so as to minimize the objective functional in (3.8).

We first establish the following theorem on the existence of optimal control.

Theorem 3.9. *There exists $v^*(t) \in \Omega$ such that the objective functional in (3.8) is minimized.*

Proof. Note that the control set Ω is closed and convex, and the integrand of the objective functional in (3.8) is convex. Hence, based on the standard optimal control theorems in [2] the conditions for the existence of the optimal control are satisfied, as our model is linear in the control variables. Indeed, the optimal control is also unique for small T due to the Lipschitz structure of the state equations and the boundedness of the state variables[2, 3].

We will follow the method described in [4],[5] to seek the optimal control solution. This method is based on Pontryagin's Maximum Principle [6] which introduces the adjoint functions and represents an optimal control in terms of the state and adjoint functions. Essentially, this approach transfers the problem of minimizing the objective functional (under the constraint of

the state equations) into minimizing the Hamiltonian with respect to the controls.

$$\begin{aligned}
\frac{dS_1}{dt} &= \mu N - (\beta_e \frac{B}{k+B} + \beta_h I_1)S_1 - (\phi_1 + \mu)S_1 \\
\frac{dS_2}{dt} &= \mu A - (\beta_e \frac{B}{k+B} + \beta_h I_2)S_2 - (\phi_2 + \mu)S_2 \\
\frac{dV}{dt} &= \phi_1 S_1 + \phi_2 S_2 - \sigma(\beta_e \frac{B}{k+B} + \beta_h I_1)V - \sigma(\beta_e \frac{B}{k+B} + \beta_h I_2)V - \mu V \\
\frac{dI_1}{dt} &= (\beta_e \frac{B}{k+B} + \beta_h I_1)S_1 + \sigma(\beta_e \frac{B}{k+B} + \beta_h I_1)V - (\gamma_1 + \mu)I_1 \\
\frac{dI_2}{dt} &= (\beta_e \frac{B}{k+B} + \beta_h I_2)S_2 + \sigma(\beta_e \frac{B}{k+B} + \beta_h I_2)V - (\gamma_2 + \mu)I_2 \\
\frac{dB}{dt} &= \xi_1 I_1 + \xi_2 I_2 - \delta B \\
\frac{dR}{dt} &= \gamma_1 I_1 + \gamma_2 I_2 - \mu R
\end{aligned}$$

Let us first define the adjoint functions $\lambda_{S_1}, \lambda_{S_2}, \lambda_{I_1}\lambda_{I_2}, \lambda_V$ and λ_B associated with the state equations for S_1, S_2, I_1, I_2, V amd B, respectively. We then form the Hamiltonian, H, by corresponding state equations, and adding each of these products to the integrand of the objective functional. As a result, we obtain

$$\begin{aligned}
H &= I_1 + I_2 + c_{11}\phi_1 S_1 t + c_{12}\phi_2 S_2 t + c_{21}\phi_1^2 + c_{22}\phi_1^2 \\
&\quad + \lambda_{S_1}\left[\mu N - (\frac{\beta_e B}{k+B} + \beta_h I_1)S_1\right] \\
&\quad + \lambda_{S_2}\left[\mu A - (\frac{\beta_e B}{k+B})S_2 + (\phi_2 + \mu)S_2)\right] \\
&\quad + \lambda_V\left[\phi_1 S_1 + \phi_2 S_2 - \sigma(\beta_e \frac{B}{k+B} + \beta_h I_1)V - \sigma(\beta_e \frac{B}{k+B} + \right. \\
&\quad \left. \beta_h I_2)V - \mu V\right] \\
&\quad + \lambda_{I_1}\left[\beta_e \frac{B}{k+B} + \beta_h I_1)S_1 + \sigma(\beta_e \frac{B}{k+B} + \beta_h I_1)V - (\gamma_1 + \mu)I_1\right] \\
&\quad + \lambda_{I_2}\left[\beta_e \frac{B}{k+B} + \beta_h I_2)S_2 + \sigma(\beta_e \frac{B}{k+B} + \beta_h I_2)V - (\gamma_2 + \mu)I_2\right] \\
&\quad + \lambda_B\left[\xi_1 I_1 + \xi_2 I_2 - \delta B\right]
\end{aligned}$$

To achieve the optimal control, the adjoint functions must satisfy

$$\begin{aligned}
\frac{d\lambda_{S_1}}{dt} &= -\frac{\partial H}{\partial S_1} = -c_{11}\phi_1(t) + \lambda_S\Big[\frac{\beta_e B}{k+B} + \beta_h I_1 + (\phi_1+\mu)\Big] \\
&\quad - \lambda_v\big[\phi_1\big] - \lambda\Big[\frac{\beta_e B}{k+B} + \beta_h I_1\Big] \\
\frac{d\lambda_{S_2}}{dt} &= -\frac{\partial H}{\partial S_2} = -c_{12}\phi_2(t) + \lambda_S\Big[\frac{\beta_e B}{k+B} + \beta_h I_2 + (\phi_2+\mu)\Big] \\
&\quad - \lambda_v\big[\phi_2\big] - \lambda\Big[\frac{\beta_e B}{k+B} + \beta_h I_2\Big] \\
\frac{d\lambda_V}{dt} &= -\frac{\partial H}{\partial B} = \lambda_v\Big[\sigma\big(\frac{\beta_e B}{k+B} + \beta_h I_1\big) + \sigma\big(\frac{\beta_e B}{k+B} + \beta_h I_2\big) + \mu\Big] \\
&\quad - \lambda_{I_1}\Big[\sigma\big(\frac{\beta_e B}{k+B} + \beta_h I_1\big)\Big] - \lambda_{I_2}\Big[\sigma\big(\frac{\beta_e B}{k+B} + \beta_h I_2\big)\Big] \\
\frac{d\lambda_{I_1}}{dt} &= -\frac{\partial H}{\partial I_1} = -1 + \lambda_{S_1}\big[\beta_h S_1\big] - \lambda_V\big[-\sigma\beta_h V\big] \\
&\quad - \lambda_{I_1}\big[\beta_h S_1 + \sigma\beta_h V - (\gamma_1+\mu)\big] - \lambda_B\big[\xi_1\big] \\
\frac{d\lambda_{I_2}}{dt} &= -\frac{\partial H}{\partial I_2} = -1 + \lambda_{S_2}\big[\beta_h S_2\big] - \lambda_V\big[-\sigma\beta_h V\big] \\
&\quad - \lambda_{I_2}\big[\beta_h S_2 + \sigma\beta_h V - (\gamma_2+\mu)\big] - \lambda_B\big[\xi_2\big] \\
\frac{d\lambda_B}{dt} &= -\frac{\partial H}{\partial B} = \lambda_{S_1}\Big[\frac{S_1\beta_e k}{(k+B)^2}\Big] - \lambda_{S_2}\Big[-\frac{S_2\beta_e k}{(k+B)^2}\Big] \\
&\quad - \lambda_V\Big[-\frac{2\sigma V\beta_2 k}{(k+B)^2}\Big] - \lambda_{I_1}\Big[\frac{S_1\beta_e k}{(k+B)^2} + \frac{\sigma V\beta_e k}{(k+B)^2}\Big] \\
&\quad - \lambda_{I_2}\Big[\frac{S_2\beta_e k}{(k+B)^2} + \frac{\sigma V\beta_e k}{(k+B)^2}\Big] - \lambda_B\big[-\delta\big]
\end{aligned}$$

with transversality conditions (or final time conditions):

$$\lambda_{S_1}(T) = 0, \lambda_{S_2}(T) = 0, \qquad \lambda_{I_1}(T) = 0, \lambda_{I_2}(T) = 0,$$

$$\lambda_V(T) = 0, \lambda_B(T) = 0$$

The characterization of the optimal control $\phi_1^*(t)$ and $\phi_2^*(t)$ based on the condition

$$\frac{\partial H}{\partial \phi_1} = 0, \qquad \frac{\partial H}{\partial \phi_2} = 0$$

respectively, subject to the constraint $0 \le \phi_1 \le \phi_{1max}$ and $0 \le \phi_2 \le \phi_{2max}$.Specifically, we have

$$\phi_1^*(t) = max[0, min(\phi_1(t), \phi_{1max})]$$

$$\phi_2^*(t) = max[0, min(\phi_2(t), \phi_{2max})]$$

where

$$\phi_1(t) = [(\lambda_{S_1} S_1 - \lambda_V S_1 - c_{11}) S_1(t)]/(2c_{21})$$
$$\phi_2(t) = [(\lambda_{S_2} S_2 - \lambda_V S_2 - c_{12}) S_2(t)]/(2c_{22})$$

The following graphs show that with vaccination in the model, the number of infections are reduced to lower than that of the original. This study shows that in order to control an outbreak, vaccination plan should be deployed in the early of outbreak.

Table 3.1: Cholera model parameters and values.

Parameter	Symbol	Value	References
Total population Group 1	N	2,000	[11]
Total population Group 2	A	1,000	[11]
Natural human birth and death rate	μ	$(43.5yr)^{-1}$	[11]
Rate of recovery from cholera Group 1	γ_1	$(5day)^{-1}$	[11]
Rate of recovery from cholera Group 2	γ_2	$(5day)^{-1}$	[11]
Rate of human contribution to V. *cholerae* Group 1	ξ_1	10 cells/ml-day	[11]
Rate of human contribution to V. *cholerae* Group 2	ξ_2	18 cells/ml-day	[11]
Ingestion rate through human-human interaction	β_h	0.00011/day	[11]
Bacteria death rate	δ	$(30day)^{-1}$	[11]
Half saturation constant (less-inf.)	k	10^6 cells/ml	[11]
Ingestion rate (hyperinf.)	β_e	0.075/day	[11]

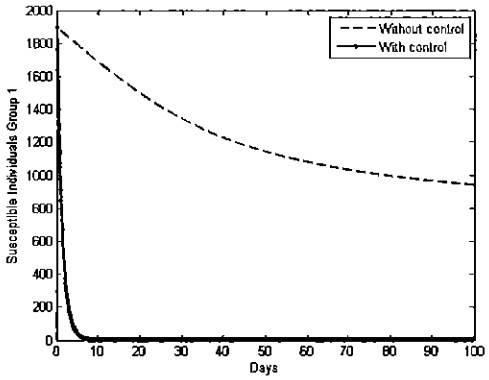

Figure 3.2: Susceptible Individuals Group 1 VS Days

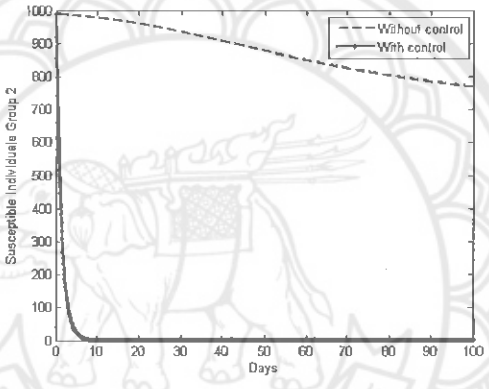

Figure 3.3: Susceptible Individuals Group 2 VS Days

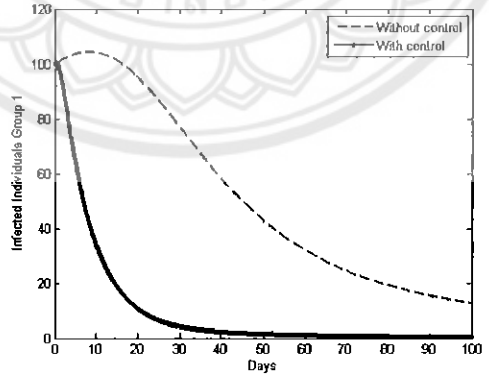

Figure 3.4: Infected Individuals Group 1 VS Days

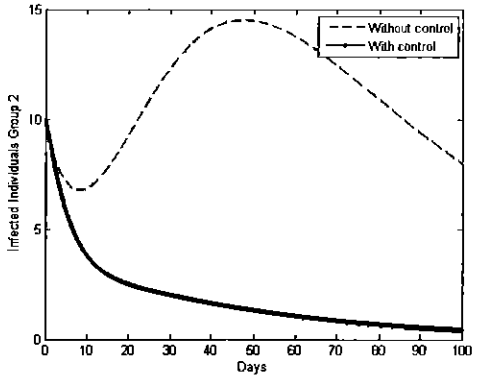

Figure 3.5: Infected Individuals Group 2 VS Days

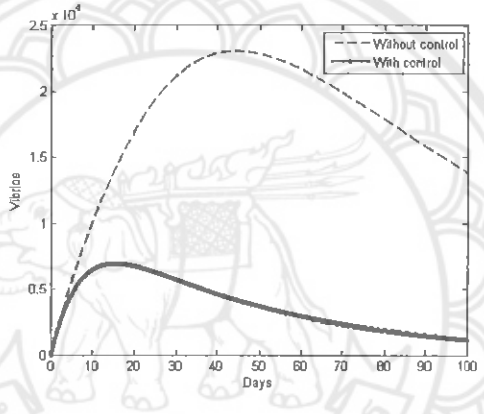

Figure 3.6: Vibrios VS Days

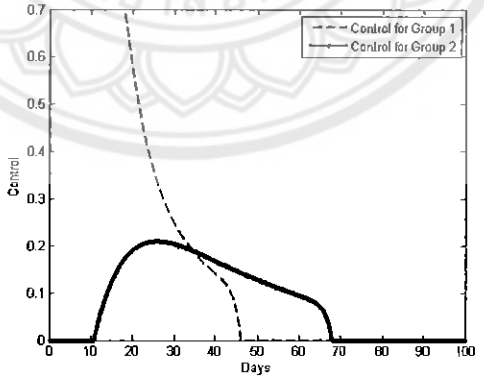

Figure 3.7: Control for Group 1 and Control for Group 2 VS Days

According to our numerical simulations, the infected plots show that the numbers of infections for both group are not surprise. With vaccination for both group, the dark line,the numbers of infections are lower than those without vaccination. Thus, with a good vaccination plan,when an outbreak occurs it will be a good strategy to control or stop the disease from spreading. In addition, isolating susceptibles at early of an outbreak helps in planning to deploy vaccine in optimal costs.

Chapter 4

Conclusions

In this study, we have explored several Cholera mathematical models. We also presented the important of optimal control theory applied to a biological model. Our interest in this study is that dividing human populations into two clusters; low-risk and hi-risk of being infected from the disease. S_1 and S_2 represent a high-risk and a low-risk susceptibles, respectively. With some rates, S_1 and S_2 are infected and become infectious individuals; I_1 and I_2 respectively.The infected populations are isolated, therefore, they will not have a close contact to each other. As a result, they are considered as two different clusters.We have explored vaccination strategies to these two clusters and found that with a good vaccination plan, an outbreak can be stopped and the plan should be deployed immediately after the outbreak. Optimal control theory is very important in this study to gain optimal control solution; optimal vaccination cost. This would be benefit to some countries that lag of funds for having a mass vaccination plan.

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A multigroup model for cholera dynamics and control

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We propose a general multigroup model for cholera dynamics that involves both direct and indirect transmission pathways and that incorporates spatial heterogeneity. Under biologically feasible conditions, we show that the basic reproduction number R_0 remains a sharp threshold for cholera dynamics in multigroup settings. We verify the analysis by numerical simulation results. We also perform an optimal control study to explore optimal vaccination strategy for cholera outbreaks.

Keywords: Cholera epidemics; multigroup models; optimal control.

Mathematics Subject Classification 2010: 92D30, 34A34

1. Introduction

Cholera epidemics continue to devastate impoverished populations with limited access to clean water and sanitation resources. Cholera, an infectious waterborne disease caused by the bacterium *Vibrio cholerae*, can spread rapidly and lead to death within days or hours if left untreated. Recent years witnessed an increasing number of cholera outbreaks worldwide, including one of the largest cholera epidemics in modern history that took place in Haiti from 2010–2012 with more than 530,000 reported cases [22]. Major cholera outbreaks also include those in Sierra Leone (2012), Ghana (2011), Nigeria (2010), Vietnam (2009), Zimbabwe (2008), and India (2007), among others. These outbreaks have increased in frequency, severity,

and duration, implying that current knowledge in cholera dynamics and public health guidelines to control the disease are not adequate.

A major limitation of current quantitative studies (e.g. [3, 8, 9, 15, 18, 21]) on cholera transmission and control is that spatial heterogeneity and dispersal are not sufficiently addressed, resulting in poor understanding of the spread of cholera infection. In paper [12], basic reproduction numbers were estimated for the 10 provinces in Zimbabwe. The results were highly heterogeneous, showing that the underlying transmission pattern varied widely throughout the country. Similarly, in the work of Tuite *et al.* [19], very different basic reproduction numbers were established for the 10 administrative departments of Haiti. Although relatively simple mathematical models were used in these studies, they did imply that spatial heterogeneity takes an essential role in cholera transmission and the design of control strategies. Consequently, the effects of dispersal and movement among different spatial regions, including the communication of human populations and dispersal of vibrios, are critical in shaping the global epidemics and endemism of cholera.

One of the most successful approaches to investigate spatial heterogeneity in mathematical epidemiology is the multigroup modeling [7, 17], where the entire population is divided into $n(n \geq 2)$ distinct groups and disease transmission occurs both within the same group and between different groups, reflecting the movement of human hosts and/or the pathogen from one region to another. In this paper, we construct a general multigroup modeling framework for cholera, based on which the complex dynamics and the control strategy of cholera can be carefully investigated. This work is based on a recent study by Wang and Liao [21] where a general cholera model was proposed that incorporates general incidence and pathogen functions and unifies many of the existing cholera models. However, one weakness for the model in [21] is that spatial homogeneity was assumed; i.e. the entire population being studied must exist under the same conditions in the same environment. In this paper, we make a significant extension of the model in [21] to a heterogeneous environment with arbitrary number of groups representing different spatial regions. We analyze the essential dynamical properties of the model, including local and global stabilities of the epidemic and endemic equilibria, with an emphasis on the interaction among the multiple transmission pathways of cholera and the interaction between within-group and inter-group dynamics. We present numerical simulation results to validate our analysis. In particular, we conduct an optimal control simulation to highlight the design strategy of cholera controls based on spatial heterogeneity.

The remainder of the paper is organized as follows. In Sec. 2, we introduce the multigroup cholera model and present necessary (and biologically reasonable) assumptions. We then derive the basic reproduction number in Sec. 3 and prove the global stability of the disease-free equilibrium (DFE) in Sec. 4. The existence of the endemic equilibrium is established and its global stability is analyzed in Sec. 5. Then, we conduct numerical simulation and optimal control study in Sec. 6. Finally, conclusions are drawn in Sec. 7.

2. Mathematical Model

The total population N is divided into n distinct groups each partitioned into a susceptible compartment S, an infectious compartment I, and a recovered compartment R, where the population in each group is assumed to be a constant and given by $N_i = S_i + I_i + R_i$, for $i = 1, \ldots, n$. Since the case fatality rates for cholera are typically pretty low (at or below 1%) [22], we assume cholera-induced mortality can be neglected in this work. Once an infected individual enters the recovered compartment, the newly recovered individual no longer influences the dynamics of the system. Also, since $R_i = N_i - S_i - I_i$, we can remove the recovered compartments from the system. The pathogen concentration in the contaminated water is denoted by B_i for each group $i = 1, \ldots, n$.

The incidence function is given in the form $\sum_{j=1}^{n} f_j(I_j, B_j)$, where susceptible individuals can be infected either by interacting with infectious individuals (human-to-human direct transmission) or by ingesting contaminated water (environment-to-human indirect transmission). The rate of change for the pathogen concentration in each group is denoted by the function $h_i(I_i, B_i)$ for $i = 1, \ldots, n$.

Based on these conditions and building on the cholera model in [21], a general multigroup model can be formulated as the following system:

$$\frac{dS_i}{dt} = bN_i - \sum_{j=1}^{n} S_i f_j(I_j, B_j) - bS_i, \tag{1}$$

$$\frac{dI_i}{dt} = \sum_{j=1}^{n} S_i f_j(I_j, B_j) - (\gamma_i + b)I_i, \quad i = 1, \ldots, n, \tag{2}$$

$$\frac{dB_i}{dt} = h_i(I_i, B_i), \tag{3}$$

where the parameter b represents the natural human birth and death rate and γ_i represents the rate of recovery from cholera in each group. We assume that $f_i(I_i, B_i)$ and $h_i(I_i, B_i)$ satisfy the following biologically sensible properties for $i = 1, \ldots, n$:

(A1) $f_i(0, 0) = h_i(0, 0) = 0$.

(A2) $f_i(I_i, B_i) \geq 0$ and f_i only vanishes at $(0, 0)$.

(A3)

$$\frac{\partial f_i}{\partial I_i}(I_i, B_i) \geq 0, \quad \frac{\partial f_i}{\partial B_i}(I_i, B_i) \geq 0, \quad \frac{\partial h_i}{\partial I_i}(I_i, B_i) \geq 0, \quad \frac{\partial h_i}{\partial B_i}(I_i, B_i) \leq 0.$$

(A4) $f_i(I_i, B_i)$ and $h_i(I_i, B_i)$ are both concave; i.e. the matrices

$$D^2 f_i = \begin{bmatrix} \dfrac{\partial^2 f_i}{\partial I_i^2} & \dfrac{\partial^2 f_i}{\partial I_i \partial B_i} \\ \dfrac{\partial^2 f_i}{\partial I_i \partial B_i} & \dfrac{\partial^2 f_i}{\partial B_i^2} \end{bmatrix} \quad \text{and} \quad D^2 h_i = \begin{bmatrix} \dfrac{\partial^2 h_i}{\partial I_i^2} & \dfrac{\partial^2 h_i}{\partial I_i \partial B_i} \\ \dfrac{\partial^2 h_i}{\partial I_i \partial B_i} & \dfrac{\partial^2 h_i}{\partial B_i^2} \end{bmatrix}$$

are negative semidefinite everywhere.

It follows from (A1) that the model admits a unique DFE, denoted by

$$P_0 = \left(S_1^0, I_1^0, B_1^0, \ldots, S_n^0, I_n^0, B_n^0\right) = (N_1, 0, 0, \ldots, N_n, 0, 0), \tag{4}$$

and (A2) guarantees a non-negative force of infection. The inequalities in (A3) respectively state that the rate of new infection increases with rises in infectious population size or bacterial concentration, increased infection population also leads to a higher growth rate for the pathogen, and the vibrio cannot independently thrive in the absence of the inflow from contaminated sewage [3, 8]. Finally, assumption (A4) is based on the saturation effect. We mention that another multigroup cholera model was recently proposed in [16], yet our model is more general in both the incidence representation and the pathogen dynamics.

Under these assumptions, Eq. (3) yields

$$\frac{dB_i}{dt} = h_i(I_i, B_i) \leq \frac{\partial h_i}{\partial I_i}(0,0)I_i + \frac{\partial h_i}{\partial B_i}(0,0)B_i \leq \frac{\partial h_i}{\partial I_i}(0,0)N_i + \frac{\partial h_i}{\partial B_i}(0,0)B_i,$$

which implies that

$$0 \leq B_i \leq \omega_i N_i \quad \text{with} \quad \omega_i = -\frac{(\partial h_i/\partial I_i)(0,0)}{(\partial h_i/\partial B_i)(0,0)}.$$

Therefore, the feasible region is given by

$$\Gamma \equiv \big\{(S_1, I_1, B_1, \ldots, S_n, I_n, B_n) \in \mathbb{R}^{3n} : 0 \leq S_i + I_i \leq N_i, 0 \leq B_i \leq \omega_i N_i, i = 1, \ldots, n\big\} \tag{5}$$

and it is positively invariant in $\mathbb{R}^{3n}$.

3. Basic Reproduction Number

Following the next-generation matrix theory [20], the basic reproduction number, R_0, is mathematically defined as the spectral radius of the next-generation matrix. In order to determine the next-generation matrix of our model, we first consider the compartmentalized infectious subsystem:

$$\begin{bmatrix} dI_1/dt \\ \vdots \\ dI_n/dt \\ dB_1/dt \\ \vdots \\ dB_n/dt \end{bmatrix} = \begin{bmatrix} \sum_{i=1}^{n} S_1 f_i(I_i, B_i) \\ \vdots \\ \sum_{i=1}^{n} S_n f_i(I_i, B_i) \\ 0 \\ \vdots \\ 0 \end{bmatrix} - \begin{bmatrix} (\gamma_1 + b)I_1 \\ \vdots \\ (\gamma_n + b)I_n \\ -h_1(I_1, B_1) \\ \vdots \\ -h_n(I_n, B_n) \end{bmatrix} = \mathcal{F} - \mathcal{V}, \tag{6}$$

where $\mathcal{F}$ denotes the rate of appearance of new infections, and $\mathcal{V}$ denotes the rate of transfer of individuals into or out of each compartment. For convenience, let:

$$\frac{\partial f_i}{\partial I_i}(0,0) \equiv p_i,$$

$$\frac{\partial f_i}{\partial B_i}(0,0) \equiv q_i,$$

$$\frac{\partial h_i}{\partial I_i}(0,0) \equiv r_i,$$

$$\frac{\partial h_i}{\partial B_i}(0,0) \equiv u_i,$$

for $i = 1, \ldots, n$. Then, the $2n \times 2n$ Jacobian matrices evaluated at P_0, the DFE, are given by:

$$F = D\mathcal{F}(P_0) = \begin{bmatrix} N_1p_1 & \cdots & N_1p_n & N_1q_1 & \cdots & N_1q_n \\ \vdots & \ddots & \vdots & \vdots & \ddots & \vdots \\ N_np_1 & \cdots & N_np_n & N_nq_1 & \cdots & N_nq_n \\ 0 & \cdots & 0 & 0 & \cdots & 0 \\ \vdots & \ddots & \vdots & \vdots & \ddots & \vdots \\ 0 & \cdots & 0 & 0 & \cdots & 0 \end{bmatrix}, \tag{7}$$

$$V = D\mathcal{V}(P_0) = \begin{bmatrix} \gamma_1 + b & 0 & \cdots & \cdots & \cdots & \cdots & \cdots & \cdots & \cdots & 0 \\ 0 & \gamma_2 + b & 0 & \cdots & \cdots & \cdots & \cdots & \cdots & \cdots & 0 \\ \vdots & \ddots & \ddots & \ddots & \cdots & \cdots & \cdots & \cdots & \cdots & \vdots \\ \vdots & \ddots & \ddots & \ddots & \ddots & \cdots & \cdots & \cdots & \cdots & \vdots \\ 0 & \cdots & \cdots & 0 & \gamma_n + b & 0 & \cdots & \cdots & \cdots & 0 \\ -r_1 & 0 & \cdots & \cdots & 0 & -u_1 & 0 & \cdots & \cdots & 0 \\ 0 & -r_2 & 0 & \cdots & \cdots & 0 & -u_2 & 0 & \cdots & 0 \\ \vdots & \ddots & \ddots & \ddots & \cdots & \ddots & \ddots & \ddots & \ddots & \vdots \\ \vdots & \cdots & \ddots & \ddots & \ddots & \cdots & \ddots & \ddots & \ddots & 0 \\ 0 & \cdots & \cdots & 0 & -r_n & 0 & \cdots & \cdots & 0 & -u_n \end{bmatrix}. \tag{8}$$

Hence, the next-generation matrix is defined as

$$FV^{-1} = \begin{bmatrix} \frac{N_1}{\gamma_1+b}\left(p_1 - \frac{q_1 r_1}{u_1}\right) & \cdots & \frac{N_1}{\gamma_n+b}\left(p_n - \frac{q_n r_n}{u_n}\right) & -N_1\frac{q_1}{u_1} & \cdots & -N_1\frac{q_n}{u_n} \\ \frac{N_2}{\gamma_1+b}\left(p_1 - \frac{q_1 r_1}{u_1}\right) & \cdots & \frac{N_2}{\gamma_n+b}\left(p_n - \frac{q_n r_n}{u_n}\right) & -N_2\frac{q_1}{u_1} & \cdots & -N_2\frac{q_n}{u_n} \\ \vdots & & \vdots & \vdots & \vdots & \vdots \\ \frac{N_n}{\gamma_1+b}\left(p_1 - \frac{q_1 r_1}{u_1}\right) & \cdots & \frac{N_n}{\gamma_n+b}\left(p_n - \frac{q_n r_n}{u_n}\right) & -N_n\frac{q_1}{u_1} & \cdots & -N_n\frac{q_n}{u_n} \\ 0 & \cdots & 0 & 0 & \cdots & 0 \\ \vdots & & \vdots & \vdots & \vdots & \vdots \\ 0 & \cdots & 0 & 0 & \cdots & 0 \end{bmatrix}. \tag{9}$$

To find the spectral radius of FV^{-1}, we proceed to determine its characteristic equation. For convenience, let

$$A_k = \frac{1}{\gamma_k + b}\left(p_k - \frac{q_k r_k}{u_k}\right).$$

Then,

$$\det(\lambda I - FV^{-1}) = \lambda^n \begin{vmatrix} \lambda - N_1 A_1 & \cdots & -N_1 A_n \\ \vdots & \ddots & \vdots \\ -N_n A_1 & \cdots & \lambda - N_n A_n \end{vmatrix}.$$

Denote

$$X_1 = \begin{bmatrix} N_1 A_1 & N_1 A_2 & \cdots & N_1 A_n \\ N_2 A_1 & N_2 A_2 & \cdots & N_2 A_n \\ \vdots & \vdots & \ddots & \vdots \\ N_n A_1 & N_n A_2 & \cdots & N_n A_n \end{bmatrix}.$$

Claim.

$$\det(\lambda I - FV^{-1}) = \lambda^{2n-1}\left(\lambda - \sum_{i=1}^{n} N_i A_i\right), \tag{10}$$

or, equivalently,

$$\det(\lambda I - X_1) = \lambda^{n-1}\left(\lambda - \sum_{i=1}^{n} N_i A_i\right).$$

Proof of claim. We prove the claim by induction. When $n = 2$, it can be easily verified that (10) holds. Now, assume (10) is true for n. Let us test the case $n + 1$.

Then, we have

$$\det(\lambda I - FV^{-1}) = \lambda^{n+1}\det(\lambda I - X_1)$$
$$= \lambda^{n+1}\begin{vmatrix} \lambda - N_1A_1 & \cdots & -N_1A_n & -N_1A_{n+1} \\ \vdots & \ddots & \vdots & \vdots \\ -N_nA_1 & \cdots & \lambda - N_nA_n & -N_nA_{n+1} \\ -N_{n+1}A_1 & \cdots & -N_{n+1}A_n & \lambda - N_{n+1}A_{n+1} \end{vmatrix}.$$

Let us split up the last column so that the determinant can be written as the sum of two determinants,

$$\det(\lambda I - X_1) = \begin{vmatrix} \lambda - N_1A_1 & \cdots & -N_1A_n & 0 \\ \vdots & \ddots & \vdots & \vdots \\ -N_nA_1 & \cdots & \lambda - N_nA_n & 0 \\ -N_{n+1}A_1 & \cdots & -N_{n+1}A_n & \lambda \end{vmatrix}$$
$$+ \begin{vmatrix} \lambda - N_1A_1 & \cdots & -N_1A_n & -N_1A_{n+1} \\ \vdots & \ddots & \vdots & \vdots \\ -N_nA_1 & \cdots & \lambda - N_nA_n & -N_nA_{n+1} \\ -N_{n+1}A_1 & \cdots & -N_{n+1}A_n & -N_{n+1}A_{n+1} \end{vmatrix}$$
$$\equiv |Y_1| + |Z_1|.$$

From our assumption on n, it is clear that the first determinant is the following

$$|Y_1| = \lambda\left[\lambda^{n-1}\left(\lambda - \sum_{i=1}^{n} N_iA_i\right)\right]$$
$$= \lambda^n\left(\lambda - \sum_{i=1}^{n} N_iA_i\right).$$

For the second determinant $|Z_1|$, note that the elementary row operation $(C_i \leftarrow C_i - (A_i/A_{n+1}) \cdot C_{n+1}), i = 1, \ldots, n$, yields:

$$\begin{vmatrix} \lambda & \cdots & 0 & -N_1A_{n+1} \\ \vdots & \ddots & \vdots & \vdots \\ 0 & \cdots & \lambda & -N_nA_{n+1} \\ 0 & \cdots & 0 & -N_{n+1}A_{n+1} \end{vmatrix} = \lambda^{n-1}\begin{vmatrix} \lambda & -N_nA_{n+1} \\ 0 & -N_{n+1}A_{n+1} \end{vmatrix} = -\lambda^n N_{n+1}A_{n+1}.$$

Therefore,

$$\begin{aligned}\det(\lambda I - X_1) &= |Y_1| + |Z_1| \\ &= \lambda^n \left(\lambda - \sum_{i=1}^{n} N_i A_i\right) - \lambda^n N_{n+1} A_{n+1} \\ &= \lambda^n \left(\lambda - \sum_{i=1}^{n+1} N_i A_i\right).\end{aligned}$$

Thus,

$$\det(\lambda I - FV^{-1}) = \lambda^{2(n+1)-1} \left(\lambda - \sum_{i=1}^{n+1} N_i A_i\right)$$

and the claim holds. □

Hence, the basic reproduction number is given by

$$\begin{aligned}R_0 &= \rho(FV^{-1}) \\ &= \sum_{i=1}^{n} \frac{N_i}{\gamma_i + b} \left(p_i - \frac{q_i r_i}{u_i}\right) \\ &= \sum_{i=1}^{n} \frac{N_i}{\gamma_i + b} \left\{\frac{\partial f_i}{\partial I_i}(0,0) - \frac{\partial f_i}{\partial B_i}(0,0) \left(\frac{\partial h_i}{\partial B_i}(0,0)\right)^{-1} \frac{\partial h_i}{\partial I_i}(0,0)\right\}. \qquad (11)\end{aligned}$$

Note that $\frac{\partial h_i}{\partial B_i} \leq 0$ from assumption (A3). Equation (11) clearly shows that the basic reproduction number R_0 for the entire system is the summation of individual reproduction numbers from all the n groups. Within each group, the reproduction number consists of two parts: one is the contribution from the direct (or, human-to-human) transmission, $\frac{N_i}{\gamma_i + b} \frac{\partial f_i}{\partial I_i}(0,0)$; the other is the contribution from the indirect (or, environment-to-human) transmission, $\frac{N_i}{\gamma_i + b} \frac{\partial f_i}{\partial B_i}(0,0)(-\frac{\partial h_i}{\partial B_i}(0,0))^{-1} \frac{\partial h_i}{\partial I_i}(0,0)$.

Based on the work of [20], we immediately obtain the following result on the local stability of the DFE.

Theorem 1. *Let R_0 be defined as* (11)*, then the DFE P_0 of the system* (1)–(3) *is locally asymptotically stable if $R_0 < 1$, and unstable if $R_0 > 1$.*

4. Global Stability of DFE

Indeed we can establish a stronger result below regarding the stability of the DFE.

Lemma 2. *Assume* (A1)–(A4)*. If $R_0 \leq 1$, then the DFE P_0 is globally asymptotically stable in Γ. Additionally, if $R_0 > 1$, the system* (1)–(3) *is uniformly persistent.*

Proof. Let

$$\begin{bmatrix} w_1 & \cdots & w_n & w_{n+1} & \cdots & w_{2n} \end{bmatrix} = \begin{bmatrix} p_1 & \cdots & p_n & q_1 & \cdots & q_n \end{bmatrix} V^{-1}. \qquad (12)$$

$$= \sum_{i=1}^{n} N_i w_i [p_1 \quad \cdots \quad p_n \quad q_1 \quad \cdots \quad q_n] \begin{bmatrix} I_1 \\ \vdots \\ I_n \\ B_1 \\ \vdots \\ B_n \end{bmatrix}$$

$$- [p_1 \quad \cdots \quad p_n \quad q_1 \quad \cdots \quad q_n] \begin{bmatrix} I_1 \\ \vdots \\ I_n \\ B_1 \\ \vdots \\ B_n \end{bmatrix}$$

$$= \left\{ \left(\sum_{i=1}^{n} N_i w_i \right) - 1 \right\} [p_1 \quad \cdots \quad p_n \quad q_1 \quad \cdots \quad q_n] \begin{bmatrix} I_1 \\ \vdots \\ I_n \\ B_1 \\ \vdots \\ B_n \end{bmatrix}.$$

That is,

$$L' \leq (R_0 - 1)[p_1 \quad \cdots \quad p_n \quad q_1 \quad \cdots \quad q_n] \begin{bmatrix} I_1 \\ \vdots \\ I_n \\ B_1 \\ \vdots \\ B_n \end{bmatrix}. \tag{15}$$

Now, note that $L' = 0$ if and only if either:

(a) $R_0 < 1$ and $I_1 = B_1 = \cdots = I_n = B_n = 0$, or
(b) $R_0 = 1$ and $S_i = N_i$ for $i = 1, \ldots, n$.

Let K be the largest compact invariant subset of

$$G = \{(S_1, I_1, B_1, \ldots, S_n, I_n, B_n) \in \Gamma : L' = 0\}.$$

In case (a), each solution in K satisfies $S_i' = bN_i - bS_i$ for $i = 1, \ldots, n$, and obviously the solution converges to $S_i = N_i$ for $i = 1, \ldots, n$. In case (b), note that $S_i = N_i$

satisfies

$$S_i' = bN_i - \sum_{j=1}^{n} S_i f_j(I_j, B_j) - bS_i$$

which implies

$$\sum_{j=1}^{n} f_j(I_j, B_j) = 0.$$

Hence, from assumption (A2), it is obvious that $I_1 = B_1 = \cdots = I_n = B_n = 0$. Therefore, all solutions in Γ converge to the DFE; that is, the largest compact invariant set where $L' = 0$ is the singleton $\{P_0\}$. By LaSalle's Invariance Principle, P_0 is globally asymptotically stable in Γ if $R_0 \leq 1$.

If $R_0 > 1$, then $L' > 0$ in a neighborhood of P_0 in the interior of Γ. Thus, solutions in the interior of Γ sufficiently close to P_0 move away from P_0, implying that P_0 is unstable. Consequently, the instability of P_0 (which is on the boundary of the domain Γ) implies uniform persistence of the system [5]. □

5. Endemic Equilibrium

The dynamics of the system (1)–(3) when $R_0 < 1$ has been completely described by Theorem 1 and Lemma 2. Now, we conduct an endemic analysis when $R_0 > 1$. The following theorem shows the existence and uniqueness of the endemic equilibrium.

Theorem 3. *For the system* (1)–(3), *if* $R_0 > 1$, *there exists a unique positive endemic equilibrium, and if* $R_0 < 1$, *there is no positive endemic equilibrium.*

Proof. Under assumption (A3), the equation $h_i(I_i, B_i) = 0$ implicitly defines a function $B_i = g_i(I_i)$ with $g_i'(I_i) \geq 0$, for $i = 1, \ldots, n$. In addition, differentiating $h_i(I_i, B_i) = 0$ twice with respect to I_i yields

$$[1, g_i'(I_i)] \begin{bmatrix} \dfrac{\partial^2 h_i}{\partial I_i^2} & \dfrac{\partial^2 h_i}{\partial I_i \partial B_i} \\ \dfrac{\partial^2 h_i}{\partial I_i \partial B_i} & \dfrac{\partial^2 h_i}{\partial B_i^2} \end{bmatrix} \begin{bmatrix} 1 \\ g'(I_i) \end{bmatrix} + \frac{\partial h_i}{\partial B_i} g_i''(I_i) = 0.$$

Using assumption (A4), we can readily see that $g_i''(I_i) \leq 0$, for $i = 1, \ldots, n$.

Then, setting the right-hand sides of Eqs. (1)–(3) to zero, we obtain:

$$S_k = \frac{bN_k}{b + \sum_{i=1}^{n} f_i(I_i, g_i(I_i))}, \tag{16}$$

$$I_k = \frac{bN_k}{\gamma_k + b} \left\{ \frac{\sum_{i=1}^{n} f_i(I_i, g_i(I_i))}{b + \sum_{i=1}^{n} f_i(I_i, g_i(I_i))} \right\}, \tag{17}$$

$$B_k = g_k(I_k). \tag{18}$$

In particular, from Eq. (17), it follows that

$$\frac{I_k}{I_1} = \frac{bN_k}{\gamma_k + b} \cdot \frac{\gamma_1 + b}{bN_1} = \frac{\gamma_1 + b}{\gamma_k + b} \cdot \frac{N_k}{N_1}, \quad k = 1, \ldots, n,$$

implying that

$$I_k = \frac{\gamma_1 + b}{\gamma_k + b} \cdot \frac{N_k}{N_1} \cdot I_1 \equiv c_k \cdot I_1, \quad k = 1, \ldots, n. \tag{19}$$

Note that $c_k > 0$ and thus $I_1 > 0$ implies that $I_k > 0$ for all $k = 1, \ldots, n$. Also, it is clear that $c_1 \equiv 1$.

Let us define the following

$$H(I_1) \equiv I_1 = \frac{bN_1}{\gamma_1 + b}\left\{\frac{f_1(I_1, g_1(I_1)) + f_2(c_2 I_1, g_2(c_2 I_1)) + \cdots + f_n(c_n I_1, g_n(c_n I_1))}{b + f_1(I_1, g_1(I_1)) + f_2(c_2 I_1, g_2(c_2 I_1)) + \cdots + f_n(c_n I_1, g_n(c_n I_1))}\right\}. \tag{20}$$

Note that $H(0) = 0$ and $H(I_1) \geq 0$ for all $I_k \geq 0$ with $k = 1, \ldots, n$. Denote:

$$\begin{aligned} P_1(I_1) &\equiv f_1(I_1, g_1(I_1)), \\ P_2(I_1) &\equiv f_2(c_2 I_1, g_2(c_2 I_1)), \\ &\vdots \\ P_n(I_1) &\equiv f_n(c_n I_1, g_n(c_n I_1)). \end{aligned}$$

Then we have,

$$H(I_1) = \frac{bN_1}{\gamma_1 + b}\left\{\frac{P_1(I_1) + P_2(I_1) + \cdots + P_n(I_1)}{b + P_1(I_1) + P_2(I_1) + \cdots + P_n(I_1)}\right\} \tag{21}$$

and taking the derivative we find that

$$H'(I_1) = \frac{bN_1}{\gamma_1 + b}\left\{\frac{b(P_1'(I_1) + P_2'(I_1) + \cdots + P_n'(I_1))}{(b + P_1(I_1) + P_2(I_1) + \cdots + P_n(I_1))^2}\right\}, \tag{22}$$

where

$$P_k'(I_1) = c_k\left\{\frac{\partial f_k}{\partial I_k}(c_k I_1, g_k(c_k I_1)) + \frac{\partial f_k}{\partial B_k}(c_k I_1, g_k(c_k I_1)) \cdot g_k'(c_k I_1)\right\} \geq 0, \tag{23}$$

for $k = 1, \ldots, n$. Therefore, $H'(I_1) \geq 0$ for $I_1 \geq 0$. In particular, note that

$$\begin{aligned} H'(0) &= \frac{N_1}{\gamma_1 + b}(P_1'(0) + P_2'(0) + \cdots + P_n'(0)) \\ &= \frac{N_1}{\gamma_1 + b}\left\{\sum_{k=1}^{n} c_k\left(\frac{\partial f_k}{\partial I_k}(0,0) + \frac{\partial f_k}{\partial B_k}(0,0) \cdot g_k'(0)\right)\right\} \end{aligned}$$

$$= \frac{N_1}{\gamma_1 + b} \left\{ \sum_{k=1}^{n} \frac{\gamma_1 + b}{\gamma_k + b} \cdot \frac{N_k}{N_1} \left(\frac{\partial f_k}{\partial I_k}(0,0) + \frac{\partial f_k}{\partial B_k}(0,0) \cdot g_k'(0) \right) \right\}$$

$$= \frac{N_1}{\gamma_1 + b} \left\{ \frac{\partial f_1}{\partial I_1}(0,0) + \frac{\partial f_1}{\partial B_1}(0,0) \cdot g_1'(0) \right\} + \frac{N_1}{\gamma_1 + b} \left(\frac{\gamma_1 + b}{\gamma_2 + b} \cdot \frac{N_2}{N_1} \right)$$
$$\times \left\{ \frac{\partial f_2}{\partial I_2}(0,0) + \frac{\partial f_2}{\partial B_2}(0,0) \cdot g_2'(0) \right\} + \cdots + \frac{N_1}{\gamma_1 + b} \left(\frac{\gamma_1 + b}{\gamma_n + b} \cdot \frac{N_n}{N_1} \right)$$
$$\times \left\{ \frac{\partial f_n}{\partial I_n}(0,0) + \frac{\partial f_n}{\partial B_n}(0,0) \cdot g_n'(0) \right\}$$

$$= \frac{N_1}{\gamma_1 + b} \left\{ \frac{\partial f_1}{\partial I_1}(0,0) + \frac{\partial f_1}{\partial B_1}(0,0) \cdot g_1'(0) \right\}$$
$$+ \frac{N_2}{\gamma_2 + b} \left\{ \frac{\partial f_2}{\partial I_2}(0,0) + \frac{\partial f_2}{\partial B_2}(0,0) \cdot g_2'(0) \right\}$$
$$+ \cdots + \frac{N_n}{\gamma_n + b} \left\{ \frac{\partial f_n}{\partial I_n}(0,0) + \frac{\partial f_n}{\partial B_n}(0,0) \cdot g_n'(0) \right\}$$

$$= \sum_{k=1}^{n} \frac{N_k}{\gamma_k + b} \left\{ \frac{\partial f_k}{\partial I_k}(0,0) + \frac{\partial f_k}{\partial B_k}(0,0) \cdot g_k'(0) \right\}$$

$$= R_0. \tag{24}$$

Next, we have

$$H''(I_1) = \frac{b^2 N_1}{\gamma_1 + b} \left\{ \frac{\begin{array}{c}(P_1''(I_1) + \cdots + P_n''(I_1))(b + P_1(I_1) + \cdots + P_n(I_1)) \\ -2(P_1'(I_1) + \cdots + P_n'(I_1))^2\end{array}}{(b + P_1(I_1) + \cdots + P_n(I_1))^3} \right\}, \tag{25}$$

where

$$P_k''(I_1) = c_k^2 \left\{ \frac{\partial^2 f_k}{\partial I_k^2}(c_k I_1, g_k(c_k I_1)) + 2 \cdot g_k'(c_k I_1) \cdot \frac{\partial^2 f_k}{\partial I_k \partial B_k}(c_k I_1, g_k(c_k I_1)) \right.$$
$$\left. + (g_k'(c_k I_1))^2 \cdot \frac{\partial^2 f_k}{\partial B_k^2}(c_k I_1, g_k(c_k I_1)) + \frac{\partial f_k}{\partial B_k}(c_k I_1, g_k(c_k I_1)) \cdot g_k''(c_k I_1) \right\}$$

$$= c_k^2 \cdot \begin{bmatrix} 1 & g_k'(c_k I_1) \end{bmatrix} \begin{bmatrix} \frac{\partial^2 f_k}{\partial I_k^2}(c_k I_1, g_k(c_k I_1)) & \frac{\partial^2 f_k}{\partial I_k \partial B_k}(c_k I_1, g_k(c_k I_1)) \\ \frac{\partial^2 f_k}{\partial I_k \partial B_k}(c_k I_1, g_k(c_k I_1)) & \frac{\partial^2 f_k}{\partial B_k^2}(c_k I_1, g_k(c_k I_1)) \end{bmatrix}$$
$$\times \begin{bmatrix} 1 \\ g_k'(c_k I_1) \end{bmatrix} + c_k^2 \cdot \frac{\partial f_k}{\partial B_k} \cdot g_k''(c_k I_1), \tag{26}$$

for $k = 1, \ldots, n$. From assumption (A4) and the fact $g_k''(I_k) \leq 0$, it follows that $P_k''(I_1) \leq 0$ for $k = 1, \ldots, n$. And therefore, $H''(I_1) \leq 0$ for $I_1 \geq 0$. That is, the function $H(I_1)$ is increasing and concave on $(0, \infty)$ with $H'(0) = R_0$. If $H'(0) = R_0 > 1$, there is a unique positive fixed point I_1^* for $H(I_1)$, and thus, from Eq. (19), unique positive fixed points $I_2^*, \ldots, I_n^*$. Furthermore, with $I_k > 0$ for $k = 1, \ldots, n$ and Eqs. (16) and (18), it follows that there exists a unique endemic equilibrium denoted by

$$P^* = \left(S_1^*, I_1^*, B_1^*, \ldots, S_n^*, I_n^*, B_n^*\right). \tag{27}$$

In contrast, if $H'(0) = R_0 < 1$, there is no positive fixed point for $H(I_1)$ and thus no endemic equilibrium. □

We proceed to show the global asymptotic stability of the endemic equilibrium. By Theorem 3, the endemic equilibrium $P^* = \left(S_1^*, I_1^*, B_1^*, \ldots, S_n^*, I_n^*, B_n^*\right)$ exists and is unique when $R_0 > 1$. Note that $S_1^*, I_1^*, B_1^*, \ldots, S_n^*, I_n^*, B_n^*$ are positive and satisfy the following equilibrium equations:

$$bN_k = \sum_{j=1}^{n} S_k^* f_j\left(I_j^*, B_j^*\right) + bS_k^*, \tag{28}$$

$$(\gamma_k + b) = \sum_{j=1}^{n} S_k^* f_j\left(I_j^*, B_j^*\right) \cdot \frac{1}{I_k^*}, \tag{29}$$

$$h_k\left(I_k^*, B_k^*\right) = 0, \tag{30}$$

for $k = 1, \ldots, n$.

To study the endemic global dynamics, we introduce another assumption here. We assume that the solutions to the system (1)–(3) implicitly define a function $B_j = B_j(I_j)$ with $B_j'(I_j) \geq 0$ and $B_j''(I_j) \leq 0$, for $j = 1, \ldots, n$. Biologically, this means that the bacterial concentration will increase with the rise of the infected human population, but the rate of the increase will slow down when the infected population is high due to saturation. Let us denote

$$Q_j(I_j) = f_j(I_j, B_j(I_j)), \quad j = 1, \ldots, n.$$

Then we have

$$Q_j'(I_j) = \frac{\partial f_j}{\partial I_j} + \frac{\partial f_j}{\partial B_j} B_j'(I_j) \geq 0 \tag{31}$$

and

$$Q_j''(I_j) = \begin{bmatrix} 1 & B_j'(I_j) \end{bmatrix} \begin{bmatrix} \dfrac{\partial f_j}{\partial I_j^2} & \dfrac{\partial f_j}{\partial I_j \partial B_j} \\ \dfrac{\partial f_j}{\partial I_j \partial B_j} & \dfrac{\partial f_j}{\partial B_j^2} \end{bmatrix} \begin{bmatrix} 1 \\ B_j'(I_j) \end{bmatrix} + \frac{\partial f_j}{\partial B_j} B_j''(I_j) \leq 0, \tag{32}$$

$$= G_k(I_k) - G_j(I_j) + \Phi\left(\frac{S_k^*}{S_k}\right) + \Phi\left(\frac{S_k f_j(I_j, B_j)}{S_k^* f_j(I_j^*, B_j^*)} \cdot \frac{I_k^*}{I_k}\right)$$

$$+ \Phi\left(\frac{f_j(I_j^*, B_j^*)}{f_j(I_j, B_j)} \cdot \frac{I_j}{I_j^*}\right) + \left(\frac{f_j(I_j, B_j)}{f_j(I_j^*, B_j^*)} - 1\right)\left(1 - \frac{f_j(I_j^*, B_j^*)}{f_j(I_j, B_j)} \cdot \frac{I_j}{I_j^*}\right)$$

$$\leq G_k(I_k) - G_j(I_j), \tag{37}$$

where

$$G_k(I_k) = -\frac{I_k}{I_k^*} + \ln \frac{I_k}{I_k^*}. \tag{38}$$

Note that

$$D_k' = \sum_{j=1} a_{kj} F_{kj}(S_k, I_k, B_k, I_j, B_j) \quad \text{and}$$

$$F_{kj}(S_k, I_k, B_k, I_j, B_j) = G_k(I_k) - G_j(I_j),$$

if and only if

$$\left(1 - \frac{S_k^*}{S_k}\right)(S_k^* - S_k) = 0, \quad \left(1 - \frac{B_k^*}{B_k}\right) h_k(I_k, B_k) = 0,$$

$$\left(\frac{f_j(I_j, B_j)}{f_j(I_j^*, B_j^*)} - 1\right)\left(1 - \frac{f_j(I_j^*, B_j^*)}{f_j(I_j, B_j)} \cdot \frac{I_j}{I_j^*}\right) = 0.$$

Let $A = [a_{kj}]$ and c_k be as given in [16, Proposition 3.1] for the weighted digraph $(\mathcal{G}, A)$; see also Appendix A. For $k = 1, \ldots, n$,

$$d^-(k) = d^+(k) = n - 1.$$

Then, for $n > 2$,

$$D' = \sum_{k=1}^{n} c_k D_k' \leq \sum_{k=1}^{n} \sum_{j=1}^{n} c_k a_{kj} F_{kj}$$

$$\leq \sum_{k=1}^{n} \sum_{j=1}^{n} c_k a_{kj} [G_k(I_k) - G_j(I_j)]$$

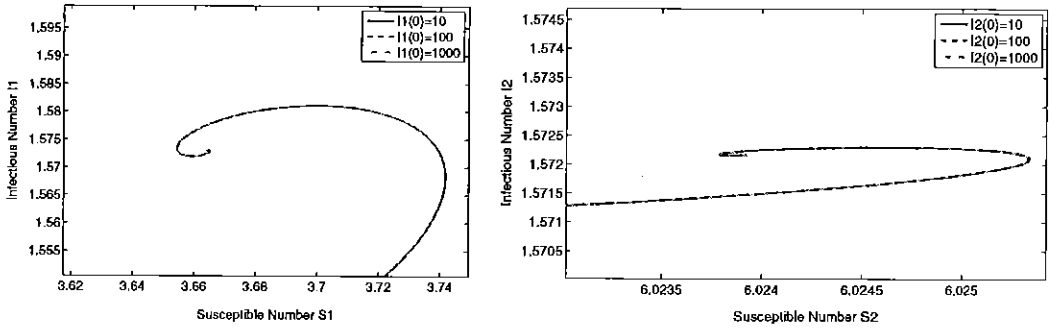
$$= \sum_{k=1}^{n} \sum_{j=1}^{n} c_k a_{kj} \left(-\frac{I_k}{I_k^*} + \ln \frac{I_k}{I_k^*} + \frac{I_j}{I_j^*} - \ln \frac{I_j}{I_j^*}\right)$$

$$= 0.$$

Hence, D is a Lyapunov function.

Now, suppose $n = 2$. Since $d^+(k) = n - 1 = 1$ for $k = 1, 2$, by [16, Theorem 3.3],

$$c_k a_{kj} = \sum_{i=1}^{2} c_j a_{ji}; \quad \text{that is,} \quad c_k = \sum_{i=1}^{2} c_j a_{ji}/a_{kj}.$$



(a) (b)

Fig. 1. Phase portraits (zoomed-in) for the two-group cholera model with different initial conditions, and $R_0 > 1$. (a) I_1 vs. S_1. All the curves converge to the endemic equilibrium with $I_1^* \approx 1.572$, $S_1^* \approx 3.664$. (b) I_2 vs. S_2. All the curves converge to the endemic equilibrium with $I_2^* \approx 1.572$, $S_2^* \approx 6.024$.

will consider vaccination as the only control measure. It is worth mentioning that the World Health Organization (WHO) recently emphasized and recommended the use of vaccines in cholera endemic places and pre-emptively during outbreaks and emergency settings [2].

We assume that susceptible individuals in groups 1 and 2 are vaccinated, respectively, at rates $u_1(t)$ and $u_2(t)$. Correspondingly, the equations for the susceptibles in system (39) are modified as:

$$\frac{dS_1}{dt} = \mu_1 N_1 - (\lambda_{11} S_1 B_1 + \lambda_{12} S_1 B_2) - (\beta_{11} S_1 I_1 + \beta_{12} S_1 I_2) - \mu_1 S_1 - u_1(t) S_1, \tag{40}$$

$$\frac{dS_2}{dt} = \mu_2 N_2 - (\lambda_{21} S_2 B_1 + \lambda_{22} S_2 B_2) - (\beta_{21} S_2 I_1 + \beta_{22} S_2 I_2) - \mu_2 S_2 - u_2(t) S_2 \tag{41}$$

and there are no changes to other equations in the model.

In our optimal control study, we aim to minimize the total number of infections and the (linear) costs of vaccination for both groups over a time domain $[0, T]$; i.e.

$$\min_{(u_1(t),\, u_2(t))} \int_0^T (I_1(t) + c u_1(t) S_1(t) + I_2(t) + c u_2(t) S_2(t)) dt, \tag{42}$$

where c denotes the unit cost of the cholera vaccines. We refer to this as a *global control strategy*. The control set is defined as

$$\{(u_1(t), u_2(t)) \,|\, 0 \le u_1(t) \le u_{1_{\max}}, 0 \le u_2(t) \le u_{2_{\max}}\}, \tag{43}$$

where $u_{1_{\max}}$ and $u_{2_{\max}}$ denote the upper bounds for the effort of vaccination in groups 1 and 2, respectively. These bounds reflect practical limitation of resources to implement the controls in a given time period.

Existence of the optimal control solution directly follows the standard optimal control theorems [4], by noting that the control set is closed and convex, the integrand of the objective functional in (42) is also convex, and the model is linear in the control variables u_1 and u_2. Furthermore, the optimal control is unique for small T due to the Lipschitz property of the state equations and the boundedness of the state variables [4]. Then, following Pontryagin's Maximum/Minimum Principle [13, 14], we introduce the adjoint functions and represent the optimal control in terms of the state and adjoint functions. Essentially, this approach transfers the problem of minimizing the objective functional (under the constraint of the state equations) into minimizing the Hamiltonian with respect to the controls.

Let us first define the adjoint functions λ_{S_i}, λ_{I_i} and λ_{B_i} $(i = 1, 2)$ associated with the state equations for S_i, I_i and B_i, respectively. We then form the Hamiltonian, H, by multiplying each adjoint function with the right-hand side of its corresponding state equation, and adding each of these products to the integrand of the objective functional in (42). As a result, we obtain

$$\begin{aligned}
H &= I_1(t) + cu_1(t)S_1(t) + I_2(t) + cu_2(t)S_2(t) + \lambda_{S_1}\left(\frac{dS_1}{dt}\right) + \lambda_{S_2}\left(\frac{dS_2}{dt}\right) \\
&\quad + \lambda_{I_1}\left(\frac{dI_1}{dt}\right) + \lambda_{I_2}\left(\frac{dI_2}{dt}\right) + \lambda_{B_1}\left(\frac{dB_1}{dt}\right) + \lambda_{B_2}\left(\frac{dB_2}{dt}\right) \\
&= I_1(t) + cu_1(t)S_1(t) + I_2(t) + cu_2(t)S_2(t) \\
&\quad + \lambda_{S_1}[\mu_1 N_1 - (\lambda_{11}S_1B_1 + \lambda_{12}S_1B_2) - (\beta_{11}S_1I_1 + \beta_{12}S_1I_2) - \mu_1 S_1 - u_1(t)S_1] \\
&\quad + \lambda_{S_2}[\mu_2 N_2 - (\lambda_{21}S_2B_1 + \lambda_{22}S_2B_2) - (\beta_{21}S_2I_1 + \beta_{22}S_2I_2) - \mu_2 S_2 - u_2(t)S_2] \\
&\quad + \lambda_{I_1}[(\lambda_{11}S_1B_1 + \lambda_{12}S_1B_2) + (\beta_{11}S_1I_1 + \beta_{12}S_1I_2) - (\mu_1 + \gamma_1)I_1] \\
&\quad + \lambda_{I_2}[(\lambda_{21}S_2B_1 + \lambda_{22}S_2B_2) + (\beta_{21}S_2I_1 + \beta_{22}S_2I_2) - (\mu_2 + \gamma_2)I_2] \\
&\quad + \lambda_{B_1}[\xi_1 I_1 - \delta_1 B_1] + \lambda_{B_2}[\xi_2 I_2 - \delta_2 B_2].
\end{aligned}$$

To achieve the optimal control, those adjoint functions must satisfy

$$\frac{d\lambda_{S_1}}{dt} = -\frac{\partial H}{\partial S_1}, \quad \frac{d\lambda_{S_2}}{dt} = -\frac{\partial H}{\partial S_2}, \quad \frac{d\lambda_{I_1}}{dt} = -\frac{\partial H}{\partial I_1} \tag{44}$$

and

$$\frac{d\lambda_{I_2}}{dt} = -\frac{\partial H}{\partial I_2}, \quad \frac{d\lambda_{B_1}}{dt} = -\frac{\partial H}{\partial B_1}, \quad \frac{d\lambda_{B_2}}{dt} = -\frac{\partial H}{\partial B_2}. \tag{45}$$

For example,

$$\begin{aligned}
\frac{d\lambda_{S_1}}{dt} = -\frac{\partial H}{\partial S_1} &= -cu_1 + \lambda_{S_1}(\lambda_{11}B_1 + \lambda_{12}B_2 + \beta_{11}I_1 + \beta_{12}I_2 + \mu_1 + u_1) \\
&\quad - \lambda_{I_1}(\lambda_{11}B_1 + \lambda_{12}B_2 + \beta_{11}I_1 + \beta_{12}I_2).
\end{aligned}$$

and

$$u_2^* = u_{2_{\max}} \quad \text{if} \quad \frac{\partial H}{\partial u_2} < 0; \quad u_2^* = 0 \quad \text{if} \quad \frac{\partial H}{\partial u_2} > 0. \tag{49}$$

In our numerical tests, we have found that the values of the switching functions $\frac{\partial H}{\partial u_i}$ $(i = 1, 2)$ are never zero on a non-empty time interval. Hence, singular control does not occur in our optimal control study.

Based on this optimal control model, we have performed several runs in numerical simulation. In particular, we have chosen cross transmission rates in such a way that $\beta_{12} > \beta_{21}$ and $\lambda_{12} > \lambda_{21}$, while keeping other transmission parameters the same between the two groups: $\xi_1 = \xi_2 = \xi, \lambda_{11} = \lambda_{22} = \lambda, \mu_1 = \mu_2 = \mu, \gamma_1 = \gamma_2 = \gamma, \delta_1 = \delta_2 = \delta, \beta_{11} = \beta_{22} = \beta$. See Table 1 for all these parameter values. This simple setting allows us to investigate the impact of human and pathogen dispersal (through distinct cross transmission rates) on the optimal control strategy for each group. In addition, we set the time period $T = 100$ days. The results for this scenario are presented in Fig. 2. As can be naturally expected, the higher disease transmission from group 2 to group 1 (than that in converse route) results in higher levels of infection and pathogen concentration in group 1, which necessitates longer duration of vaccination in group 1. Note that we have set the maximum vaccination

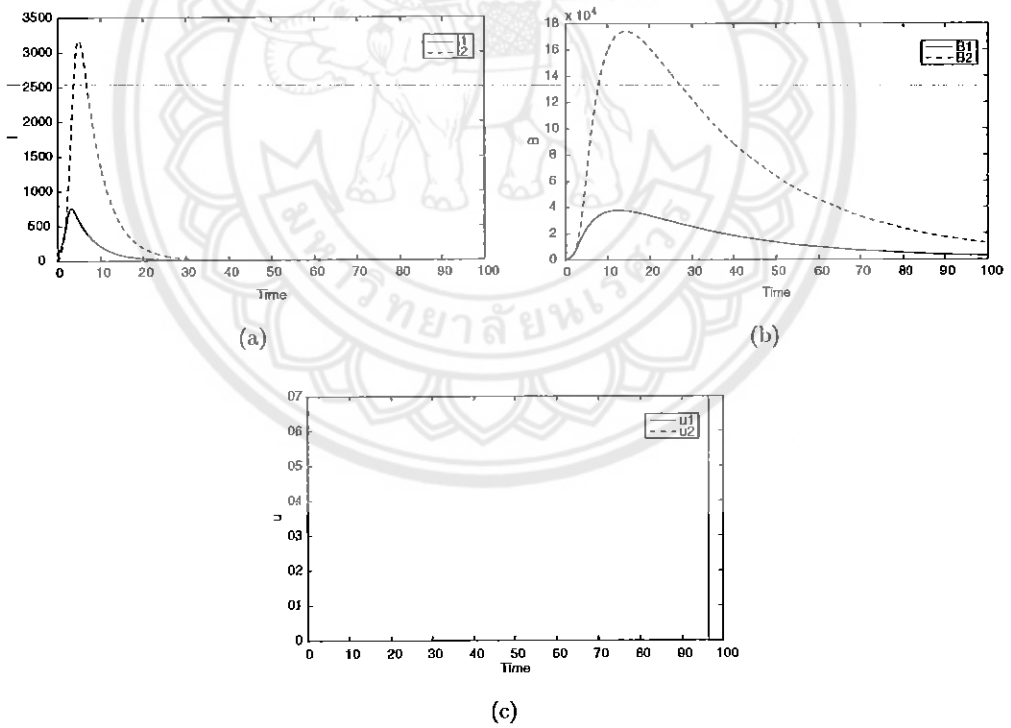


Fig. 3. Results for the two-group cholera model with optimal control on group 1 only: (a) infected populations I_1 and I_2; (b) vibrio concentrations B_1 and B_2; (c) optimal control profiles u_1 and $u_2 = 0$.

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