Mathematical Models for the Spread and Control of Multi-strain Influenza-A Viruses in Indonesia

by

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SUMMARY

Indonesia has the highest number outbreaks of avian flu in poultry and the greatest number of human casualties due to avian flu. It has also been speculated that the country poses the biggest threat for a future epidemic caused by a mutated virus resulting from recombination between avian flu and other strains of influenza-A. Work to mitigate the impact of avian flu and control the spread of disease in Indonesia, where millions of poor people rely on poultry for their livelihoods, is very important. A synthesis of available best practice in emergency response is needed to advise the country in capacity building, surveillance methods, and approaches for coping with new introductions of avian flu as well as future emerging disease threats. Several important issues in the control and impact of avian flu in Indonesia are little understood.

Indonesia has difficulties in containing avian flu due to enormous and complex problems. Four main non medical factors in the spread and control of the disease are domestic farming practices, the prominence of wet markets, lack of government coordination on disease prevention, and economic constraints. This thesis addresses the problems of modeling the effects of these factors to the spread and control of avian flu and possible mutated viruses. It is assumed that a mutated virus, referred to here as mutant-avian-flu, emerges as a result of a rare virus recombination between avian flu and swine flu.

More specifically, it is assumed that avian flu, swine flu and mutant-avian flu are spreading among linked populations of poultry and humans. The populations are characterized by their disease states. The dynamics of the disease states are described as deterministic processes and modeled in the form of well defined initial value problems (IVPs) and optimal control problems (OCPs). The basic reproduction numbers are defined for avian flu transmission among birds, swine flu transmission among humans and mutant-avian flu transmission among humans. The equilibrium points of the systems are given as functions of the basic reproduction numbers. Stability analysis of the equilibrium points are given. Some are globally asymptotically stable (GAS), and others are locally asymptotically stable (LAS). Disease controls are defined as functions of the basic reproduction numbers. The disease controls describe the effort to reduce the effectiveness of the force of infection.

The models do not attempt to match observations in high detail but are intended to capture the main features of the disease dynamics under certain assumptions. As analytical tools, the models and methods developed in this study help to better understand the dynamic behavior of avian flu, swine flu and mutant-avian flu among linked populations of poultry and humans in Indonesia. The models presented in this thesis are intended to demonstrate the feasibility of constructing a model-based tool to inform decision making bodies in Indonesia regarding the management of future epidemics.

CERTIFICATION

I certify that this thesis does not incorporate without acknowledgment any material previously submitted for a degree or diploma in any university; and that to the best of my knowledge and belief it does not contain any material previously published or written by another person except where due reference is made in the text.

Signed Dated March 23, 2015

Wuryatmo Sidik

We believe that this thesis is properly presented, conform to the specifications for the thesis and this is of sufficient standard to be, *prima facie*, worthy of examination.

Signed Dated March 23, 2015

A/Prof. Murk J. Bottema,

(Principal Supervisor)

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(Co-Supervisor)

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CONTENTS

Summary ii

Certification iii

Acknowledgments iv

Table of Contents viii

List of Figures xii

List of Tables xiii

List of Acronyms xiv

Preface xv

1. INTRODUCTION 1

1.1 Motivation of the study 1

1.2 Tipar: A case study of an isolated village 8

1.3 Rationale and aims of the study 9

1.4 Scope of the study 12

1.5 Outcomes and limitations 13

2. LITERATURE REVIEW 14

2.1 Basic science of influenza-A 14

2.2 Scope of mathematical modeling of influenza-A 17

2.2.1 Number of virus strains 18

2.2.2 Transmissibility 18

2.2.3 Risk of epidemic 19

2.2.4 Disease controls . . . 19
2.2.5 Global scale models . . . 20
2.2.6 Population dispersal . . . 21
2.2.7 Cross species models . . . 21
2.3 Modeling approaches . . . 22
2.3.1 Compartmental models . . . 23

3. DETERMINISTIC MODELS . . . 28
3.1 Euclidean Space $\mathbb{R}^n$ . . . 28
3.2 A class of deterministic compartmental models . . . 29
3.3 Characterizing the stability of a disease state equilibrium . . . 32
3.3.1 Local stability . . . 32
3.3.2 Global stability . . . 33
3.4 The limiting systems . . . 36
3.5 The method for biological permanence . . . 36
3.6 Reproduction number and stability . . . 38
3.7 Disease control problem . . . 42

4. DISEASE DYNAMICS IN A SINGLE REGION . . . 45
4.1 Modeling choices and assumptions . . . 45
4.1.1 Virus strains . . . 45
4.1.2 Population assumptions . . . 45
4.1.3 Avian flu dynamic among the bird population . . . 46
4.1.4 Disease dynamic among humans . . . 47
4.2 Diseases transmission model for a single region . . . 48
4.3 Reproduction numbers . . . 51
4.4 Disease state equilibria . . . 53
4.4.1 Disease state equilibria among poultry birds . . . 53
4.4.2 Disease state equilibria for the full system . . . 54
4.5 Stability analysis of disease state equilibria . . . 60
4.5.1 Stability analysis of disease state equilibria among birds . . . 61
4.5.2 Stability analysis of disease state equilibria for the full systems . 63

4.5.3 Stability analysis of disease free equilibrium 64
4.5.4 Stabilty analysis of swine flu epidemic equilibrium 67
4.5.5 Stabilty analysis of mutant-avian flu epidemic equilibrium 70
4.5.6 Stability analysis of avian-flu epidemic equilibrium (among birds and humans) 73
4.5.7 Stability analysis of avian flu epidemic among birds and humans combined with mutant avian flu epidemic among humans 76
4.6 Disease persistence among humans 79
4.7 Simulation 81
4.7.1 Epidemic Parameters: Tipar case 81
4.7.2 Sensitivity Analysis 89
4.8 Discussion 92

5. DISEASE DYNAMICS IN MULTI-REGIONS 94
5.1 Modeling choices and assumptions 94
5.2 Diseases transmission model for multi-regions 95
5.3 Diseases transmission model for two identical regions 97
5.4 Reproduction numbers 99
5.5 Disease state equilibria 101
5.5.1 Disease state equilibria among poultry birds 101
5.5.2 Disease state equilibria for the full system 104
5.6 Stability analysis of disease state equilibria 108
5.6.1 Stability analysis of the disease free equilibrium 111
5.6.2 Stability analysis of swine flu epidemic equilibrium in both regions 112
5.6.3 Stabilty analysis of mutant-avian flu epidemic equilibrium 113
5.6.4 Stability analysis of avian-flu epidemic equilibrium. 114
5.6.5 Stability analysis of avian flu epidemic among birds and humans combined with mutant avian flu epidemic among humans 118
5.7 Simulation 121
5.8 Discussion 122

6. BORDER SCREENING 126
6.1 Modeling choices and assumptions 127
6.2 Border screening: the full model 128
6.3 Disease dynamics in two identical regions: the effect of border screening 129
6.4 Reproduction numbers 130
6.5 Disease state equilibria 132
6.5.1 Disease state equilibria among birds 132
6.5.2 Disease state equilibria for the full system 134
6.6 Stability analysis of disease state equilibria 138
6.6.1 Stability analysis of the disease free equilibrium 141
6.6.2 Stability analysis of swine flu epidemic equilibrium in both regions 142
6.6.3 Stabilty analysis of mutant-avian flu epidemic equilibrium 143
6.6.4 Stability analysis of avian-flu epidemic equilibrium. 145
6.6.5 Stability analysis of avian flu epidemic among birds and humans combined with mutant avian flu epidemic among humans 151
6.7 Simulation 153
6.8 Discussion 154

7. CONTROLLING THE SPREAD OF DISEASE 158
7.1 Uncontrolled system 158
7.2 Designing the disease controls 159
7.3 Optimal disease control problem 160
7.4 Necessary conditions for the optimality of the disease controls 161
7.5 Simulation 163
7.5.1 Algorithm 163
7.5.2 Estimation of disease transmission parameters 166
7.6 Discussion 167

8. CONCLUSION 170
8.1 Discussion 170
8.2 Conclusion 173
8.3 A vision and the directions for the future 174

Bibliography 176

LIST OF FIGURES

1.1 Map of Indonesia: 1539 Outbreak at Ternate island (red dot). 3

1.2 Avian flu outbreaks among poultry in Indonesia during 2005-2007 2008, [1] 5

1.3 Tipar, Cikelet. An isolated village having twelve human cases of avian flu. It surrounded by hills and a mountain 9

1.4 Typical house of Cikelet villagers. The wooden floor is raised about fifty centimeters to house free range chickens resting during the nights 10

1.5 Location of human cases of Avian flu by Province in Indonesia per May 2007. 11

2.1 Pandemic Generation. 17

4.1 Compartments of humans and bird populations. The red line is avian flu transmission, the yellow line is swine flu transmission, the brown line is mutant-avian flu transmission. 49

4.2 The effect of varying the number of effective contacts between an infectious bird and susceptible birds, κ_p, on the dynamics of the avian flu in the bird world. The vertical axis shows the proportion of birds with avian flu. The horizontal axis shows the time in days. Green, blue, red and black lines are the dynamics of avian flu among birds when κ_p equals to 2, 3, 4 and 5, respectively 83

4.3 The effect of varying the number of effective contacts between an infectious bird and susceptible birds, κ_p, on the dynamics of diseases in human world. The vertical axes show the proportion of humans with the diseases. (a) Proportion of infected human with swine flu. (b) Proportion of infected human with avian flu but asymptomatic. (c) Proportion of infected human with avian flu and symptomatic. (d) Proportion of infected human with mutant-avian flu. Green, blue, red and black lines are the dynamics of the diseases when κ_p is equal to 2, 3, 4 and 5, respectively. The horizontal axes show the time in days. 84

4.4 The effect of varying the number of effective contacts between an infectious bird and susceptible human, κ_{ph}, on the dynamics of the diseases in human world. The vertical axes show the proportion of humans with the diseases. The horizontal axes show the time in days. Green, blue, red and black lines are the dynamics of the diseases when κ_{ph} is equal to 1, 2, 3 and 4, respectively. (a) Proportion of infected human with swine flu. (b) Proportion of infected human with avian flu but asymptomatic. (c) Proportion of infected human with avian flu and symptomatic. (d) Proportion of infected human with mutant-avian flu. 85

4.5 The effect of varying the number of effective contacts between an infectious human with swine flu and susceptible human, κ_{sh}, on the dynamics of the diseases in human world. The vertical axes show the proportion of humans with the diseases. The horizontal axes show the time in days. Green, blue, red and black lines are the dynamics of the diseases when κ_{sh} is equal to 1, 2, 3 and 4, respectively. (a) Proportion of infected human with swine flu. (b) Proportion of infected human with avian flu but asymptomatic. (c) Proportion of infected human with avian flu and symptomatic. (d) Proportion of infected human with mutant-avian flu. The horizontal axes show the time in days. 86

4.6 The effect of varying the number of effective contacts between an infectious human with swine flu and humans infected with avian flu but asymptomatic,κ_{sa}, on the dynamics of the diseases in human world. The vertical axes show the proportion of humans with the diseases. The horizontal axes show the time in days. Green, blue, red and black lines are the dynamics of the diseases when κ_{sa} is equal to $1, 2, 3$ and 4, respectively. (a) Proportion of infected human with swine flu. (b) Proportion of infected human with avian flu but asymptomatic. (c) Proportion of infected human with avian flu and symptomatic. (d) Proportion of infected human with mutant-avian flu. 87

4.7 The effect of varying the number of effective contacts between an infectious human with mutant-avian flu and susceptible humans ,κ_{mh}, on the dynamics of the diseases in human world. The vertical axes show the proportion of humans with the diseases. Green, blue, red and black lines are the dynamics of the diseases when κ_{mh} is equal to $1, 2, 3$ and 4, respectively. (a) Proportion of infected human with swine flu. (b) Proportion of infected human with avian flu but asymptomatic. (c) Proportion of infected human with avian flu and symptomatic. (d) Proportion of infected human with mutant-avian flu. The horizontal axes show the time in days. 88

4.8 Tornado plot of SRCCs, indicating the importance of each parameter's uncertainty in contributing to the variability in the time to the basic reproduction number R_p. Brown bars are SRCCs when $\kappa_p = 3$ and $R_p = 0.82$. Blue bars are SRCCs when $\kappa_p = 4$ and $R_p = 1.32$ 91

4.9 Tornado plot of partial rank correlation coefficients, indicating the importance of each parameter's uncertainty in contributing to the variability in the time to the basic reproduction number R_{sh} 92

4.10 Tornado plot of partial rank correlation coefficients, indicating the importance of each parameter's uncertainty in contributing to the variability in the time to the basic reproduction number R_{mh} 93

5.1 Compartments of humans and poultry bird populations in two regions. Solid red lines represent local avian flu transmission, dashed red lines represent avian flu transmission due to transporting of birds, yellow lines represent swine flu transmission, brown lines represent transmission of mutant-avian flu. 96

5.2 The proportion of infected birds in the provinces. The horizontal axis is time in days. (a), (b), (c), (d) and (e) are the proportion of infected birds in Central Java, West Java, Jakarta, Banten and Lampung respectively. 122

5.3 Sum of proportions of infected birds in the provinces of Central Java, West Java, Jakarta, Banten and Lampung. 123

5.4 The proportion of human cases (infected humans with avian flu) in the five provinces. The horizontal axis is time in days. (a), (b), (c), (d) and (e) are the proportion of human case in Central Java, West Java, Jakarta, Banten and Lampung respectively. 124

5.5 The proportion of infected human with Mutant avian-flu in the provinces. The horizontal axis is time in days. (a), (b), (c), (d) and (e) are the proportion of infectious humans with Mutant avian-flu in Central Java, West Java, Jakarta, Banten and Lampung respectively. 125

6.1 The proportion of culled birds in the provinces as a result of the implementation of screening and subsequent culling policies with $\sigma_3 = 0.5$ at east borders of Jakarta. The horizontal axis is time in days. (a), (b), (c), (d) and (e) are the proportion of infected birds in Central Java, West Java, Jakarta, Banten and Lampung respectively. 154

6.2 The proportion of infectious birds in the provinces as a result of the implementation of screening and subsequent culling policies with $\sigma_3 = 0.5$ at the East borders of Jakarta. The horizontal axis is time in days. (a), (b), (c), (d) and (e) are the proportion of infected birds in Central Java, West Java, Jakarta, Banten and Lampung respectively. 155

6.3 The proportion of human cases in the five provinces as a result of the implementation of screening and subsequent culling policies with $\sigma_3 = 0.5$ at the East borders of Jakarta. The horizontal axis is time in days. (a), (b), (c), (d) and (e) are the proportion of human case in Central Java, West Java, Jakarta, Banten and Lampung respectively. 156

6.4 The proportion of infected human with Mutant avian-flu in the five provinces as a result of the implementation of screening and subsequent culling policies with $\sigma_3 = 0.5$ at the East borders of Jakarta. The horizontal axis is time in days. (a), (b), (c), (d) and (e) are the proportion of infectious humans with Mutant avian-flu in Central Java, West Java, Jakarta, Banten and Lampung respectively. 157

7.1 Proportion of infectious poultry birds. The horizontal axis is time in days. Uncontrolled in blue, controlled in red 166

7.2 Proportion of infected human with avian flu. (a) Asymptomatic. (b)Symptomatic. The horizontal axis is time in days. Uncontrolled in blue, controlled in red168

7.3 (a) proportion of infectious humans with swine flu. (b) proportion of infectious humans with mutant-avian flu. The horizontal axis is time in days. Uncontrolled in blue, controlled in red 169

LIST OF TABLES

1.1 Cumulative number of human cases as of 12 April 2012 7

1.2 Human cases of avian flu in Indonesia by province as of December 2007. The percentages refer to the percent of the total confirmed or suspected cases. 8

1.3 Human cases of avian flu in Tipar, Cikelet from June to August 2006 . . 9

4.1 The Spearman Rank Correlation Coefficients for R_p and related epidemic parameters. For every parameter, there are two rows. The first row corresponds to SRCC values when $\kappa_p = 3$ and $R_p = 0.82$. The second row corresponds to SRCC values when $\kappa_p = 4$ and $R_p = 1.32$. 90

4.2 The p-values of SRCCs for R_p and its epidemic parameters. The p-values of SRCCs when $\kappa_p = 3$ and $R_p = 0.82$ are given in the top rows. The below rows show the p-values of SRCCs when $\kappa_p = 4$ and $R_p = 1.32$ . . 91

4.3 The Spearman Rank Correlation Coefficients for R_{sh} and its epidemic parameters 91

4.4 The p-values of SRCCs for R_{sh} and its epidemic parameters 92

4.5 The Spearman Rank Correlation Coefficients for R_{mh} and its epidemic parameters 92

4.6 The p-values of SRCCs for R_{mh} and its epidemic parameters 93

LIST OF ACRONYMS

HPAI Highly Pathogenic Avian Influenza 2

H1N1 swine-origin influenza-A 15

H2N2 Asian flu 15

H3N2 Hong Kong flu 15

H5N1 avian-origin influenza-A 14

WHO World Health Organization 15

FAO Food and Agriculture Organization 16

LAS locally asymptotically stable 32

GAS globally asymptotically stable 32

IVP initial value problem 30

DDP disease dynamics problem 170

ODCP optimal disease control problem xvi

PREFACE

This thesis can be classified as a mathematical epidemiology of infectious disease caused by multi-strain influenza-A viruses. It contains models and methods for the solutions of some problems on analyzing the disease transmission dynamics of avian flu, swine flu and mutant-avian flu. The mutant-avian flu is a hypothetical virus to model the threat of a future epidemic due to recombination between avian flu and swine flu. The work herein is an analytical study; simulations are carried out to visualize some of the results only. Even though the study addresses the specific circumstances in Indonesia, the models and methods may be applicable to other under-resourced countries which have similar problems to Indonesia.

Chapters 1, 2, and 3 provide background information. Chapters 4, 5, 6, and 7 present the original contributions of the thesis. Chapter 8 provides concluding remarks of the thesis.

Chapter 1 serves as an introduction to the thesis. It states the motivation, rationale and aims of the study. It also describes the material and methods used and lists the outcomes of the study.

Chapter 2 reviews existing literature on biological and mathematical aspects of the spread and control of multi-strain influenza-A. Section 2.1 provides some information on the basic science of influenza-A viruses from biological and medical points of view. Section 2.2 reviews existing mathematical models of the viruses. The review focuses on the scope of the models and the modeling approaches used. The reviewed models differ both in terms of the aspects of influenza-A outbreak considered and in terms of the mathematical setting. The choice of mathematical setting is influenced by the aspect of influenza-A outbreaks addressed in the study. Section 2.3 discusses modeling approaches and in particular compartmental models. The discussion leads to a justification that deterministic modeling is a suitable approach to tackle problems considered in this study.

Chapter 3 gives some theoretical background on the basic ideas and techniques for modeling infectious diseases. Section 3.1 describes a class of deterministic compartmental models considered in the study. Section 3.2 provides methods for characterizing the local and global stability of a disease state equilibria. It includes the Salle's invariance principle and the Poincaré Bendixon theorem. Section 3.3 discusses the limiting system. It provides a stability theorem for the limiting system and the method of bi-

ological permanence. Section 3.4 derives a method to calculate the basic reproduction number and its relation to the stability analysis. Section 3.5 describes optimal disease control problems for the epidemic models. This section includes methods for designing disease control and solving the optimal disease control problems.

Chapter 4 presents models for analyzing the effect of human behavior on the dynamics of the diseases caused by avian flu, swine flu and mutant avian flu in a single isolated region. Section 4.1 discusses the modeling choices and assumptions made. A well defined epidemic model is derived in Section 4.2. In Section 4.3, three reproduction numbers are defined as the threshold values of the disease transmissions. Section 4.5 provides stability analysis of six disease state equilibria. Numerical simulations are given in Section 4.7. Epidemic parameters are taken from a case study of Tipar, a small isolated village in the sub-district of Cikelet, West Java. Tipar has the largest number of human cases in West Java. The sensitivity analysis of reproduction numbers is given in Section 4.7.2. Section 4.8 discusses the analytical and numerical results and draws some conclusions.

Chapter 5 presents models for analyzing the effects of bird trading to the dynamics of the diseases in the bird and human world. Section 5.1 discusses the modeling choices taken. The effect of bird trading on the spread of disease and control of disease is modeled by transport-related infection and border-screening. A well defined epidemic model is derived in Section 5.2. Section 5.3 discusses the disease transmission model in two identical regions. Reproduction numbers are defined in Section 5.4. Disease state equilibria and their stability analysis are given in Sections 5.5 and 5.6, respectively. Section 5.7 provides some simulation results. The last section discusses the study results and draws some conclusions.

Chapter 6 presents models for analyzing the effects of border screening for infected birds on the dynamics of the diseases in the bird and human worlds. Section 6.1 discusses the modeling choices and assumptions made. A well defined epidemic model is derived in Section 6.2. Section 6.3 discusses the disease transmission model in two identical regions. Reproduction numbers are defined in Section 6.4. Disease state equilibria and their stability analysis are given in Section 6.5. Section 6.7 provides some simulation results. The last section discusses the study results and draws some conclusions.

Chapter 7 presents models for analyzing the economic trade-off between the spread and control of disease in an isolated region and the problem of designing optimal disease controls. The first section recalls the disease dynamic with no control. Section 7.3 outlines a disease control problem. The necessary condition for the existence of an optimal control is given in Section 7.4. Finally, Section 7.6 discusses some results of the study. Section 7.5 outline an Indirect method algorithm for solving the optimal disease control problem (ODCP) in the simulation study. Section 7.6 discusses some results of the study and draws some conclusions.

Chapter 8 serves as the concluding chapter of the thesis. This chapter summarizes the study results and provides an overview of the new knowledge discovered during the study followed by some implications of the study and future research directions.

1. INTRODUCTION

This chapter serves as an introduction to this thesis. The first section introduces the motivation for the study. Section 1.3 states the rationale and the aims of the study. Section 1.4 states the assumptions and approaches used to develop models and the method of analysis. The outcomes and limitations of the study are listed in Section 1.5.

1.1 Motivation of the study

Indonesia has a long history of epidemics caused by influenza-A viruses. In 1539, the island of Ternate in the Maluku archipelago (red dot in Figure 1.1) was hit by a disease outbreak that rapidly destroyed healthy birds and soon after by a disease of similar lethality in humans. As a result of the disease many places in the region were depopulated [2].

Not all evidence points to avian-origin influenza-A (H5N1) or avian flu as being responsible for the 1539 outbreak. Nevertheless, there is a lesson to be learned from the outbreak. Features of the outbreak have some similarity to avian influenza of the 21^{st} century. The disease was consistent with a *zoonosis* (an infectious disease that can be transmitted from animals to humans), supporting the idea of transmission from poultry to humans. The zoonosis appears to have been an emerging infectious disease, not seen before by the indigenous people or by the Portuguese. Also, throughout the island, the illness seems to have affected poultry before affecting humans [2].

The 1539 outbreak was prevented from spreading by the isolation of the region. The isolation was due to a trading practices policy imposed on the region by Portuguese colonists at that time [2]. This acted as an unintentional public health measure.

The second epidemic was the Spanish flu which occurred between 1918-1919. It claimed 1.5 million out of 30 million lives in Indonesia (Dutch East Indies) [3], [4], [5]. The virus was believed to be derived from influenza-A [6] , [7], [8], [9]. The disease spread from Hong Kong and Singapore to Indonesia through sea ports [3], [4], [5]. The first case was reported on the east coast of Sumatra in July 1918. In the same month, the disease spread to Java and Kalimantan and then Bali and Sulawesi, reaching as far as the eastern part of the archipelago in Maluku and Timor. The second wave came in October 1918 and was more widespread and brought the most deaths. In Tana Toraja,

10 percent of the population reportedly died from the disease [3]. In Lombok island, the disease claimed 36,000 lives or 5.9 percent of the island's population.

Attempts to control the influenza pandemic were implemented in 1920 by ordering regional authorities, schools, sea craft, and seaports to raise a special flag called the Influenza Flag [4]. Posters on disease prevention were published in tribal languages to educate the people. Often, posters were in the form of a dialog between characters from puppet shows which were popular at the time.

Highly Pathogenic Avian Influenza (HPAI) is the most recent and globally important of such emerging disease problems. This disease harms the livelihood of poor farmers as well as commercial poultry producers. It infects humans and has the potential to evolve into a human pandemic. In Indonesia, avian flu first appeared in Pekalongan in Central Java in August 2003 and by January 2004 it had spread across Java and into Bali, Kalimantan and southern Sumatra. In 2005, the disease reached Sulawesi, North Sumatra, and Aceh, and in 2006, Papua. At the end of June 2006, 27 of 33 provinces were affected [10] and by the end of 2007, nearly all provinces reported outbreaks (Figure 1.2).

Initial outbreaks of avian flu are thought to have been in the commercial poultry sector, resulting from imports of live birds as breeding stock from China [10]. Phylogenetic analysis suggests that the Indonesian outbreak originated from a single introduction [11]. The rapid spread is most commonly explained as the result of transporting infected commodities including commercial chickens [12]. The prevalence rate of the disease among poultry varies between regions (Figure 1.2).

The avian flu epidemic among birds has raised some concern about poultry production, marketing and consumption in Indonesia. Between August 2003 and January 2004, at least 600,000 chickens reportedly died of the flu in 17 of Central Java's 35 regencies. Some 10.5 million birds were reportedly lost in 2004 due to the disease and culling. During peaks of infection in February/March 2005 and 2006, recorded monthly poultry deaths were 530,453 and 647,832 respectively. The losses due to disease or culling are estimated to have been between 15% and 20% of all poultry stock. In 2004, the combined effect of 50% to 60% lower prices and 40% lower sales volumes meant income reductions of 70% to 80% for traders [13]. Employment opportunities dropped by 40% at large poultry farms. During outbreaks, there was a drop in poultry product demand by $45 - 60\%$. The industry operated at just a third of its full capacity [13]. The economic loss resulting from avian flu epidemic from 2004 to June 2008 reached $32.4 million [14].

Fig. 1.1: Map of Indonesia: 1539 Outbreak at Ternate island (red dot).

In 2003 there were three cases of avian flu among humans in Vietnam and one in Cambodia, all resulting in deaths. From 2005 to 2008, Indonesia had more deaths from the disease than any other country and, at the time of writing this thesis, had the highest number of total deaths (Table 1.1). By April 12, the cumulative number of human cases in the country was 156 deaths out of 188 human cases [15].

The distribution of avian flu among humans in Indonesia has not been uniform. Ninety seven percent occurred on Java and Sumatera (Table 1.2). The majority of human cases in Indonesia occurred in Jakarta Province (25.2%) followed by two neighboring provinces Banten (20.6%) and West Java (16.8%). Statistical analysis showed that the confirmed cases were geographically clustered within an area on Java island covered by eight districts along the border of three neighboring provinces of Jakarta, West Java, and Banten [1] (Figure 1.5) .

There were the 113 sporadic and 26 cluster outbreaks detected between July 2005 and July 2009 [16], [17]. Opinions vary as to whether human H5N1 virus infections in Indonesia have a cluster pattern. All human H5N1 cases have been among blood relatives, suggesting a possible genetic predisposition toward susceptibility to H5N1 virus infection. A small cluster of eight cases of which seven were fatal, has been identified in Karo, North Sumatra [10], [18], [19]. Whether the virus is capable of sustaining human to human transmission is still unproven.

Indonesia has difficulties in containing avian flu due to enormous and complex problems. Four main non-medical factors in the spread and control of the disease are domestic farming practices, the prominence of wet markets, lack of government coordination and economic constraints.

Poultry farming in the country is predominantly a rural or backyard enterprise. Domestic poultry production has been identified as a key element in poverty alleviation in rural areas. The problem is that most poor households have limited knowledge about human and animal health. They do not understand the bio-security and health issues at stake. In this case, the bio-security is understood to mean the protection of food supply from contamination and threat. People raise birds and other animals such as ducks and pigs in very close proximity, facilitating the spread of illnesses. Not only do these people live close to their poultry, they also live close to each other, often sharing farm tools without thorough cleaning between uses.

Wet markets, also called live bird markets, are common throughout Indonesia. Wet markets typically consist of a hodge-podge of stalls selling pet birds, ornamental birds, chickens, ducks, pigeons and many other types of birds. While the emphasis is on birds, many of these markets also sell other animals such as cats, dogs, hamsters, mice, and many more species. Among the stalls selling live birds and animals there are stalls selling food and stalls where birds are de-feathered, slaughtered and cooked.

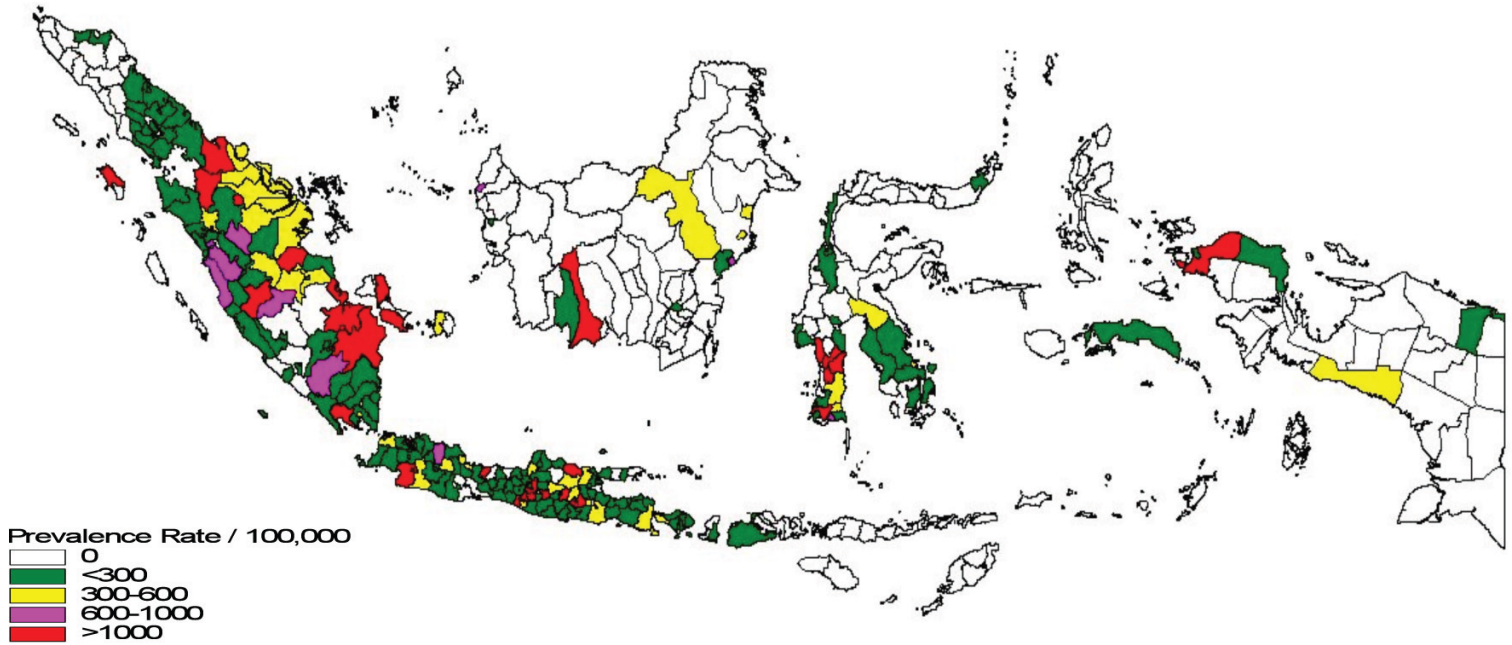

Fig. 1.2: Avian flu outbreaks among poultry in Indonesia during 2005-2007 2008, [1]

Often the sanitation is poor and stalls seldom have their own water supplies, relying instead on water fetched in buckets from a common source. Grey waste water is usually just poured out on the ground. There is little awareness among farmers, bird sellers, and consumers on how diseases such as avian flu are spread and there are no procedures in place to manage emergencies. It has been suggested that the mixture of species, the lack of management, and multiple suppliers are all features that make the markets potential hot spots for spreading viruses [20]. It is thought that poultry trading contributes to the spread of the disease across the country [10], [18].

Most human cases in Indonesia have acquired avian flu infection from poultry and live bird markets [10], [18]. Handling of sick or dead poultry during the week before the onset of illness is the most commonly recognized risk factor[10], [18].

Both domestic farming practice and wet markets raise concern of possible virus mutation through re-assortment or recombination between avian flu and other influenza-A viruses such as swine flu [10], [18]. A mutation might result in a new virus with a epidemic potential among humans [21], [22], [23], [24]. However, unlike the 2009 swine flu pandemic which was caused by a low pathogenic virus, a future epidemic caused by a new mutant-avian flu could become one of the worst in history if it is highly pathogenic [22], [25].

The third reason for the persistence of the disease and its spread in the country is the lack of government coordination. Countrywide action and cooperation is essential in combating a virus such as avian flu. This type of response becomes very challenging in the presence of a decentralized government. From 1998, the Indonesian government has undergone significant reforms moving from a highly centralized model to a more decentralized one.

The local branches of government hold most of the power. As a result, it has been very difficult to mount a united defense against the flu even for implementing border screening and culling policies.

The fourth reason for the persistence of the disease and its spread in the country is economic constraint. The country has little capacity, or regulatory enforcement power, to implement control of even basic bio-security measures. The World Health Organization has recommended the culling of infected birds and any bird which may have come in contact with an infected bird. A lack of initial action and ineffective procedures, however, has prevented these measures from being fully implemented. When culling was utilized, few incentives were provided to the public to participate. The subsidy offered by the government was less than the market value for chickens. The low level of financial compensation from the government for bird depopulation does not provide incentive for the farmers to cooperate [10].

Tab. 1.1: Cumulative number of human cases as of 12 April 2012

Country	**2003**		**2004**		**2005**		**2006**		**2007**		**2008**		**2009**		**2010**		**2011**		**2012**		**Total**	
	C	D	C	D	C	D	C	D	C	D	C	D	C	D	C	D	C	D	C	D	C	D
Azerbaijan	0	0	0	0	0	0	8	5	0	0	0	0	0	0	0	0	0	0	0	0	8	5
Bangladesh	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	2	0	3	0	6	0
Cambodia	0	0	0	0	4	4	2	2	1	1	1	0	1	0	1	1	8	8	2	2	20	18
China	1	1	0	0	8	5	13	8	5	3	4	4	7	4	2	1	1	1	1	1	42	28
Djubouti	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0
Egypt	0	0	0	0	0	0	18	10	25	9	8	4	39	4	29	13	39	15	9	5	167	80
Indonesia	0	0	0	0	20	13	55	45	42	37	24	20	21	19	9	7	12	10	5	5	188	156
Iraq	0	0	0	0	0	0	3	2	0	0	0	0	0	0	0	0	0	0	0	0	3	2
Lao PDR	0	0	0	0	0	0	0	0	2	2	0	0	0	0	0	0	0	0	0	0	2	2
Myanmar	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1	0
Nigeria	0	0	0	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	1	1
Pakistan	0	0	0	0	0	0	0	0	3	1	0	0	0	0	0	0	0	0	0	0	3	1
Thailand	0	0	17	12	5	2	3	3	0	0	0	0	0	0	0	0	0	0	0	0	25	17
Turkey	0	0	0	0	0	0	12	4	0	0	0	0	0	0	0	0	0	0	0	0	12	4
Vietnam	3	3	29	20	61	19	0	0	8	5	6	5	5	5	7	2	0	0	4	2	123	61
Total	4	4	46	32	98	43	115	79	88	59	44	33	73	32	48	24	62	34	24	15	602	355

- C is number of cases, D is number of deaths
- WHO reports only laboratory cases
- Source: WHO/GIP, data in HQ as 12 April 2012

Tab. 1.2: Human cases of avian flu in Indonesia by province as of December 2007. The percentages refer to the percent of the total confirmed or suspected cases.

Province	**Island**	**Population density/km^2**	**Confirmed number (%)**	**Suspected number (%)**
DKI Jakarta	Java	13,400	27 (25.2)	153 (50.7)
Banten	Java	1,016	22 (20.6)	51 (16.9)
West java	Java	1,033	18 (16.8)	0 (0)
Central Java	Java	951	9 (8.4)	0 (0)
North Sumatra	Sumatra	158	8 (7.5)	0 (0)
East Java	Java	726	7 (6.5)	87 (28.8)
Riau	Sumatra	52	7 (6.5)	0 (0)
West Sumatra	Sumatra	100	3 (2.8)	0 (0)
Lampung	Sumatra	197	2 (1.9)	0 (0)
Bali	Bali	599	2 (1.9)	0 (0)
South Sumatra	Sumatra	59	1 (0.9)	11 (3.6)
South Sulawesi	Sulawesi	133	1 (0.9)	0 (0)
		Total	107(26.2)	302 (73.8)

1.2 Tipar: A case study of an isolated village

West Java has had eighteen human cases of avian flu (Table 1.2), eleven of which were located in Tipar, a small village in the sub-district of Ciketet, Kabupaten Garut, West Java. The outbreak in Tipar is anomalous in that most other cases occurred in areas with a large poultry industry or areas involved in the transport of poultry. Tipar is an isolated village of 556 households comprising an area of about 60 acres surrounded by hills and a mountain (Fig. 1.3). A typical household raises 15-20 chickens for domestic consumption but there is no poultry industry and the village in not part of a trade network in poultry. Houses are built about 50 cm above ground and chickens use this space for shelter (Fig. 1.4). Chickens roam about the village freely.

During the day, men work the fields and women and children stay near the house and tend the chickens. This is significant since most cases were among women and children. A study showed that among housewives in Tipar, 62.4% had no knowledge of avian flu and 79.2% have never had social support from the government [26].

The first human case of avian flu in Tipar occurred in June 2006. Some people from Pameungpeuk, a village close to Tipar, brought chickens to a village function. The chickens died the next day and some the villages own chickens died shortly afterward. No one associated the death of the chickens with avian flu and the chickens were consumed. Soon afterward, on June 16, 2006, a villager died after symptoms of high fever. The local puskesmas (health care clinics) did not become aware of the outbreak until three people died. The regional government of Garut only took action after five people had died. The village was isolated and the villagers were vaccinated. The local government reported 12 cases of suspected and confirmed avian flu (Table 1.3).

Fig. 1.3: Tipar, Cikelet. An isolated village having twelve human cases of avian flu. It surrounded by hills and a mountain

Tab. 1.3: Human cases of avian flu in Tipar, Cikelet from June to August 2006

No	Name	Age	Feel Sick	Case	Status
1	Rahmat Hidayat	1	June 4	Suspected	Dead, June 16
2	Satria	4	July 19	Suspected	Dead, July 31
3	Robiah	13	July 28	Suspected	Dead, August 1
4	Misbah binti Sukmaji	20	July 28	Suspected	Dead, August 6
5	Umar bin Aup	17	July 28	Confirmed	Survive
6	Euis Lina	35	July 19	Confirmed	Dead, August 10
7	Ai Siti Amanah binti Ade	2	August 3	Confirmed	Dead, August 15
8	Santi bin Iwan	6	August 3	Suspected	Survive
9	Yana	60	August 15	Suspected	Survive
10	Iswahati binti Pendi	5	August 15	Suspected	Survive
11	Kuraesin	35	August 17	Suspected	Survive
12	Osin Gil	14	August 20	Suspected	Survive

Pasir Gambir and Pameungpeuk are two villages close to Tipar which also have had a few human cases of avian flu. These villages are separated by a big river. Therefore, the most likely mode of transmission of avian flu was through trading of chickens.

1.3 Rationale and aims of the study

Efforts were made by many institutions to track HPAI, develop vaccines and control the disease in endemic countries to prevent a global pandemic but many of these were not implemented in Indonesia. This work is of great importance in the context of trans-boundary animal diseases, particularly those arising in developing countries such as Indonesia whose scarce resources and capacity in disease control could lead to the spread of diseases harmful to animal and human health in other regions around the

Fig. 1.4: Typical house of Cikelet villagers. The wooden floor is raised about fifty centimeters to house free range chickens resting during the nights

globe.

Work to mitigate the impact of HPAI in Indonesia, where many millions of poor people rely on poultry for their livelihoods, is very important. A synthesis of available best practices in emergency response is needed to advise the country in capacity building, surveillance methods and approaches for coping with new introductions of HPAI as well as future emerging disease threats. Several important issues in the control and impact of HPAI in Indonesia are little understood.

Mathematical models have been developed and used to understand the spread and control of influenza-A viruses. The review of existing models given in Chapter 2 shows that models have been developed based on the premise of ideal situations of bio-security and un-limited resources for disease surveillance and containing the pandemic. Such models may be applicable for developed countries but not for developing countries such as Indonesia. No published work could be found which models the spread and control of avian flu and the threat of a future epidemic in Indonesia.

There are lessons to learn from the three previous pandemics in Indonesia. Government regulations and propaganda programs for disease prevention are key factors for disease prevention and eradication. Therefore, in order to mitigate further spread of avian flu and anticipate future pandemics, a model is needed that demonstrates the likely patterns of the spread of disease and allows for comparison between possible control measures.

Fig. 1.5: Location of human cases of Avian flu by Province in Indonesia per May 2007.

In modeling control, the realities of Indonesian culture and economic state discussed in Section 1.1 must be taken into account. For example, simply asking rural people to cull their chickens is not viable as people will choose the threat of disease over certain poverty. Compensating family farmers for their losses is not economically feasible and resources do not exist to implement comprehensive preventative measures. This study provides work toward a model for the spread and control of avian flu that is realistic for Indonesia.

1.4 Scope of the study

Field studies show that human infection of avian flu is influenced by, and may even depend on, host genetic susceptibility [17], [27], [28]. There is no evidence of human to human transmission of avian flu [29], [30], [31], [32]. Therefore, it is assumed in this study that avian flu rarely infects humans but is not communicable among humans.

Genome studies provide strong genetic evidence that new future strains could be mixing and mutating in the tropics [33], [34]. A likely plausible scenario is that a new virus results from recombination between avian-origin influenza-A (H5N1) and swine flu [35], [36], [37], [38], [39]. The emergence of such a hypothetical virus is included in this study and is referred to as mutant-avian flu.

This study is concerned with the development of new mathematical models and methods for analyzing the disease spread and control of avian flu, swine flu and mutant-avian flu among linked populations of birds and humans in Indonesia. It is assumed that the three influenza-A virus strains cause five disease transmissions, namely (i) avian flu transmission among birds. (ii) avian flu transmission from infected birds to humans. (iii) swine flu transmission from infectious humans with swine flu to susceptible humans. (iv) swine flu transmission from infectious humans with swine flu to humans having swine flu but who are asymptomatic. (v) mutant-avian flu transmission among humans. The disease transmissions are modeled by using the mass action incident assumption.

The linked populations of poultry birds and humans are characterized by their disease-states. The dynamics of the disease states are described by deterministic processes and modeled in the form of well-defined systems of differential equations. The models and methods developed in this study are justified theoretically.

This thesis is an analytical study. In addition, simulations were carried out but only to visualize some results. The epidemic parameters used for simulations were taken from available literature on the 1918-1919 Spanish flu, the 2004-2009 avian flu epidemics among birds, the 2004-2009 avian flu cases among humans and the 2009 swine flu pandemic.

Extensive algebraic manipulations were carried out by using the symbolic computation package of Maple 16©. Simulations were performed by using MATLAB R2010b©.

1.5 Outcomes and limitations

The models do not attempt to match observations in high detail but are intended to capture the main features of the disease dynamics under certain assumptions. As analytical tools, the models and methods developed in this study help to better understand the dynamic behavior of avian flu, swine flu and mutant-avian flu among linked population of poultry and humans in Indonesia.

The thesis outcomes are useful for modeling and analyzing the current and future situations of disease spread and control of influenza-A in Indonesia. The models are able to track the disease dynamics among birds and humans simultaneously. Specific outcomes include:

- In Chapter 4, models are presented to analyze the dynamics of avian flu, swine flu and mutant-avian flu in human and poultry populations.
- In Chapter 5, models are presented to study the effect of the transportation of birds to the dynamics of the diseases in the bird and human worlds.
- In Chapter 6, models are presented to study the effect of border screening for infected birds to the dynamic of the diseases in the bird and human worlds.
- In Chapter 7, models are presented to analyze economic trade-off between the spread and control of the diseases.

Even though the work herein addresses the specific circumstances of Indonesia, the models and methods may be applicable to other under resourced countries which have similar conditions to Indonesia.

There are limitations to the models developed. One limitation is that precise knowledge of epidemic parameters in particular disease transmission of mutant-avian flu is unknown and is difficult to measure. Unfortunately, this is a key parameter that yields the force of infection or transmission of the disease. It is a source of important non linearity of the models and can make the difference between regular cyclic variations of incidence and chaos. Another limitation of the models is the difficulty in running the full model over all regions of interest in Indonesia. Therefore, the models cannot to be used as prediction tools. The scope of the thesis is laying the mathematical foundation for a model.Despite these limitations, the models can help interpret observed epidemiological trends, guide the collection of data towards further understanding, and assist the design of programs for the control of the diseases. The models can help gain insight into the factors controlling the disease persistence and stability of disease transmission within large human communities.

2. LITERATURE REVIEW

The purpose of this chapter is to review existing literature on biological and mathematical aspects of the spread and control of multi-strain influenza-A. Section 2.1 provides some information on influenza-A viruses from biological and medical points of view. Section 2.2 reviews existing mathematical models of influenza-A viruses including the scope of the models and modeling approaches that have appeared in the literature. The reviewed models differ both in terms of the aspects of the disease outbreak considered and in terms of the mathematical setting. The choice of mathematical setting is often influenced by the aspect of the disease outbreaks addressed in the study. The compartmental model is the most popular and the basic compartmental model is described in Section 2.3. A discussion leads to the conclusion that deterministic models are suitable for addressing the problems posed in Chapter 1.

2.1 Basic science of influenza-A

The various types of influenza-A viruses can broadly be categorized as low and high pathogenic viruses. The cycle of a low pathogenic virus among waterfowl and wild birds is genetically stable [40]. It persist in water [41], is capable of surviving more than 100 days at 17^oC and uses ice as its reservoir [42], [43], [44]. Direct disease transmission among birds is through a fecal-oral route [45]. Low pathogenic influenza may evolve into high pathogenic virus [46], [47], [48].

Avian flu can be maintained, amplified, and disseminated in live-poultry markets [45][49]. Once avian flu has developed in poultry birds, it can transmit horizontally among poultry birds with a mortality rate of 60% [40], [47]. The interaction of migratory wild birds and domestic poultry has sustained avian flu, but the importance of migrating wild birds as an ecological reservoir is uncertain [49].

Influenza A virus of different subtypes infect many other species, in particular mammals such as domestic cats [29], [30], [31], [50], dogs [32], mice [51], [52], ferrets [53], [54], cynomolgous (monkeys) [55] and swine [35]. The pathogenic level of the virus depends on its hosts. The differences in the surface proteins prevent these viruses from jumping across species barriers and causing infection in humans [24]. The highly pathogenic avian-origin influenza-A (H5N1) virus has succeeded in crossing the species barrier and has started infecting humans [36], [56], [57], [58]. The virus is less pathogenic in mam-

mals generally, but is highly pathogenic to ferrets [59] and humans. The mortality rate in humans is about 60% [60], [61], [62].

Human cases of avian flu acquire the virus by direct transmission from infectious birds [24], [47], [56], [60], [61], [62], [63] although the exact mode and sites of the virus acquisition in the respiratory tract are not completely understood [64]. There is no conclusive evidence of human to human transmission of avian flu [29], [30], [31], [32], but there is a possibility that this might have happened [65], [56]. Clusters of human avian flu illness with at least two epidemiological linked cases have been identified in 10 countries and have accounted for approximately one quarter of cases.

The 20th century witnessed three pandemics caused by influenza-A viruses namely the Spanish flu which occurred between 1918 and 1919, Asian flu (H2N2) occurred 40 years later (1957-1958) and the Hong Kong flu (H3N2) 1968 to 1969. The first influenza A pandemic of the 21st century was marked by the spread of Swine flu, a new strain of swine-origin influenza-A (H1N1).

The Spanish flu pandemic has been described as "the greatest medical holocaust in history" [66]. The global mortality rate of the disease is not known, but it is estimated that 10% to 20% of those who were infected died [67]. With about a third of the world population infected, this case-fatality ratio means that 3% to 6% of the entire global population died [9]. Phylogenetic analyses of the complete genome of the 1918 influenza virus suggest that the 1918 virus was derived from an avian source[6]. It is a bird flu that learned how to spread among humans.

Asian flu was identified first in Guizhou, China in February 1957. It spread quickly to Singapore in the same month, reached Hong Kong by April, and the US by June [68]. It caused approximately two million deaths worldwide.

Hong Kong flu was detected first in Hong Kong in early 1968. The pandemic infected an estimated 500,000 Hong Kong residents, 15% of the population [69]. It arrived in the United States in September 1968 and became widespread in December 1968. Deaths peaked in December 1968 and January 1969 with the elderly being hit hardest. The virus returned in 1970 and 1972. Total deaths were approximately 33,800, making it a mild pandemic [69].

Swine flu was first identified in Mexico in April 2009 and soon spread worldwide. The disease is communicable among humans with a mortality rate similar to seasonal flu, around one percent [70], [71]. In May of 2009, the World Health Organization (WHO) announced that there had been 30,000 confirmed cases of swine flu influenza, but the same day, the Centers for Disease Control and Prevention (CDC) estimated around a million cases [72]. In November of 2011, WHO reported that the global swine flu pandemic included more than 18 thousand deaths and that the virus was still circulating, though at much reduced levels compared to those in 2009. Swine flu vaccination programs have been effective in halting the disease spreading further [73].

The programs might be optimized by giving the vaccine to a targeted population only [74], [75], [76], [77].

The spread of avian flu among birds appear to be principally related to the movement of poultry and poultry products [47], [62], [78], [79]. Poultry markets, in particular live bird markets, are the most risky places for disease transmission [63], [78]. A bird is most likely to get infected if the bird resides within a radius of one km from an outbreak area (26.2%). The second largest possibility to get infected is during transport (21.3%). A bird may also get infected by indirect transmission from poultry workers and their tools (9.4%) and in the slaughter house (8.5%). Only a small proportion (1.0%) of poultry birds get infected by a direct transmission from wild birds in nature [79].

The WHO has warned that the threat of a new influenza pandemic has been aggravated with the appearance of highly pathogenic avian flu [80]. The Food and Agriculture Organization (FAO) has estimated that avian flu has led to the death or destruction of more than 200 million birds worldwide, resulting in economic losses of over 20 billion dollars [81]. Experts claim that the next flu pandemic could become one of the worst in history, not because it has killed many people yet but because of its potential [22], [25].

The threat of a mutated version of avian flu causing pandemic is real. Simultaneous infection of humans by avian flu and other influenza A viruses could theoretically generate novel influenza viruses with pandemic potential [36], [82], [83]. The lesson to learn is that of the 2009 swine flu pandemic. The virus is thought to be a mutation, more specifically, a recombination of four known strains of influenza A virus subtype H1N1, one endemic in humans, one endemic in birds, and two endemic in pigs [71], [84].

A virus mutation process could be in the form of antigenic shift or antigenic drift. Antigenic shift is the process by which two or more different strains of a virus combine to form a new subtype having a mixture of the surface antigens of the original strains. Antigenic drift describes small and gradual changes in the surface proteins (antigens) of the virus through random mutational processes [23], [85].

Figure 2.1 depicts a possible scenario of future pandemic generation. A virus recombination can occur when avian flu (which can live in birds with 2-3 receptors) from birds and swine flu (which can live in mammals and human with 2-6 and 2-3 receptors) from human recombine to become more infectious and then infect the human population [35], [36], [37], [38], [39]. These molecular-biological and genomic studies are important to unfold in advance possible new strains which may have pandemic potential [83]. The new strains found could then be utilized to support the development of vaccine or other disease control planning processes [36], [83].

Hybrid viruses have the potential to express surface antigens from avian flu to

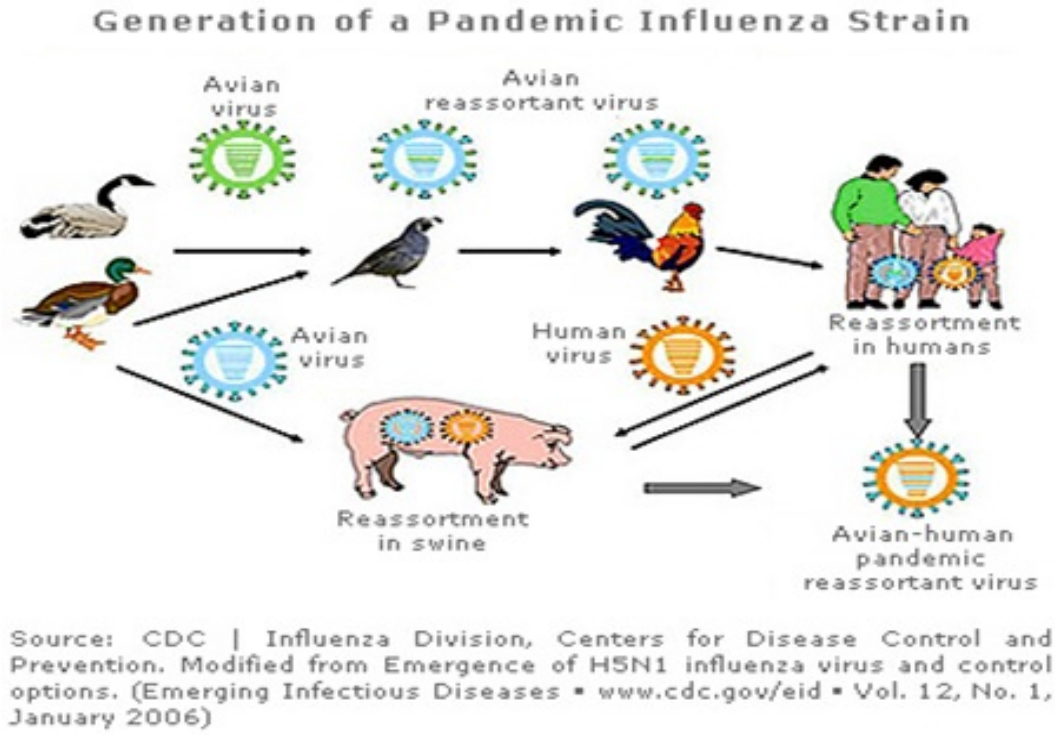

Fig. 2.1: Pandemic Generation.

which the human population has no preexisting immunity [25]. Therefore, it has been suggested that the virus may only need to change slightly to become communicable among humans [22], [56], [65], [25]. The process for a pandemic can be triggered by three stages of virus mutation[21]. First, an incremental increase in the ability of the virus to move from birds or animals to humans. Second, an incremental increase in the virulence of virus. Third, an incremental increase in the contagiousness of the virus between humans.

2.2 Scope of mathematical modeling of influenza-A

The foundations of mathematical epidemiology were laid in the late nineteenth and early twentieth centuries by public-health physicians and biological scientists [86], [87], [88], [89], [90]. The concept of differential mortality was used to estimate the rate of deaths attributable to a given disease such as the 1918 influenza pandemic. A discrete chain binomial was used to model the spread of infection in a susceptible population [86], [91].

A disease control model was first developed by R. A. Ross in his work on malaria, which earned him the second Nobel prize in Medicine in 1902. His model showed that the spread of malaria in a region can be controlled by reducing the mosquito population [87]. The result was generalized later for larger classes of diseases by introducing the concept of reproduction numbers [88], [89], [90].

The reproduction number is the number of secondary infections caused by a single infective introduced into a homogeneous population made up entirely of susceptible individuals over the course of the infection of this single infective [88], [89], [90], [92], [93]. A non homogeneous population is considered as a multi state population. The reproduction number of a multi state population based on age classes and types of individuals are referred to as *state-reproduction number* [94] and *type reproduction number* [95], respectively.

Models have been developed for understanding the spread and control of avian influenza. Various issues have been considered in influenza epidemic and pandemic models such as the number of virus strains, the population of study, transmissibility, disease control measures, effect of spatial demographics, delay, and virus mutation. The following subsections (2.2.1 to 2.2.7) review the existing models based on the scope of models.

2.2.1 Number of virus strains

Most of the existing models consider a single influenza-A virus strain spread among birds populations only [60], [62], [96] or among human population only [61], [71], [97], [98], [99], [100]. Only few consider multi strain influenza-A viruses circulating in both bird and human populations [101], [102], [103], [104].

2.2.2 Transmissibility

A main focus of modeling infectious diseases has been in the understanding and computation of the basic reproduction number [105], [106], [107], [108], [109], [110], [111], [112], [113]. If the value of reproduction number is less than or equal to one, then the disease free equilibrium is locally asymptotically stable and therefore the disease cannot invade the population. If it is greater than one, the disease free equilibrium is unstable and the disease may invade the population.

Transmissibility of avian flu in poultry birds has been estimated. The disease latency period among birds varies from 0.20 days to 0.44 days. The mean infectious period varies from 1.3 days to 2.5 days and the reproduction number varies from 0.99 to 2.0 [114]. These estimated reproduction numbers are slightly lower than those based on a field observation of 2.0 to 3.5 [17], [115].

In humans, avian flu transmission due to direct transmission from infectious birds is very rare [103], [104]. The resampling-based test was used to detect person-to-person transmission of avian flu among humans [17], [116], [117]. Studies show that there is no evidence of transmissibility of avian flu virus among humans.

2.2.3 Risk of epidemic

The risk of a future avian flu epidemic among human populations has been modeled and analyzed. Most of the existing models are based on the underlying assumption that the disease is already communicable among humans such as 1918 (Spanish) flu [98], [99], swine flu [61], [71], and 1957 (Asian) flu [100].

Some assumed that avian flu has a high risk of causing an imminent pandemic such as in the Spanish (1918) flu pandemic. In these models, epidemic parameters based on 1918 Spanish pandemic where used [7], [8]. The reproduction numbers were estimated between 2 to 3 [7] or 1.49 (spring wave) and 3.75 (autumn wave) [118]. These reproduction numbers are higher than the reproduction number of Asian flu (H2N2) which was estimated to be between $1.6 - 1.8$ [33], [100]. The reproduction number of Spanish flu is also higher than the reproduction number of the Hong Kong flu (H3N2) pandemics which where estimated as $1.06 - 2.06$ [119]. These models ignore the complexities of cross species infection processes. Only a few consider virus mutation when modeling the risk of an avian flu epidemic among human [103], [104].

2.2.4 Disease controls

The basic reproduction number may also be considered to be the control effort needed to eliminate the infection from a homogeneous host population [120]. Feasible intervention strategies both biomedical and behavioral have been modeled and analyzed. The control policies can be categorized into two groups. The first group of control policies aims to reduce the effectiveness of the force of disease transmissions. In this category the disease control could constitute vaccination [79], antiviral agents [121], social distancing policies such as school closure [100], [122], travel restrictions [46], [79] or a combination of these [123], [124]. The second group of control policies aims to manage the disease out break such as screening for infectious individuals followed by quarantine [98], public health measures [8], [97], bird culling [125] and cleaning the environment [96].

Disease control by vaccination

Theoretically, a pandemic with a reproduction number of 2 to 4 could be prevented by vaccinating or administering antiviral prophylaxis to $50-75\%$ of the population [7]. For highly contagious viruses (i.e. a reproductive rate of 2.3 or higher), the use of the vaccine for approximately 20% of the population leaves $30\% - 50\%$ of the population infected [126]. Given enough drugs for 50% of the population, household-based prophylaxis coupled with reactive school closure could reduce clinical attack rates by $40 - 50\%$. More widespread prophylaxis might reduce attack rates by over 75% [126].

Vaccine stockpiled in advance of a pandemic could significantly reduce attack rates even if the efficacy is low [127]. Vaccine production capacity and antiviral medication

stockpiles are insufficient to provide for broad coverage, even in wealthy countries. Therefore, optimal distribution strategies are very important [128]. Shifting vaccination resources away from the high-risk groups to the high-activity groups will result in improved herd immunity in both the high-risk group and the population as whole [129]. Targeted layered containment is important for resource efficiency [130]. Targeted use of antivirals would be sufficient to contain an outbreak with reproduction number below 1.4, as long as the intervention is applied within the first 21 days of the outbreak [121]. Incentives are necessary for voluntary vaccine programs to be the successful [131], [132]. Vaccination, however, is considered to be too expensive to be a practical control in Indonesia. Therefore, vaccination is not included in the models presented in this thesis.

Disease control by social distancing

Disease control measures that generally reduce contacts between individuals may be the most powerful protection against a pandemic until adequate vaccine and antiviral medicines can be produced [8]. Effective isolation measures in hospital clinics at best would only ensure control with probability 0.87 while reducing the transmission rate by greater than 76.5% guarantees stopping an epidemic [99].

Behavioral interventions such as closing schools, quarantining infected individuals or imposing travel restrictions have been modeled and analyzed for effectiveness. Prolonged school closures could reduce the cumulative number of influenza cases by 13 to 17% [122]. It has been suggested that household quarantine could be more effective than closing schools [127].

Some combination of behavioral and biomedical interventions are more effective for containing the pandemic [128], [131], [132]. In the case of the 1918 (Spanish) flu; time-limited public health interventions reduced total mortality only moderately (perhaps $10-30\%$). The impact of intervention was limited because interventions were implemented too late and lifted too early [8]. The effectiveness of human quarantine varies depending on when the limitation on travel between communities is implemented and how long it lasts, and a policy of introducing quarantine at the earliest possible time may not always lead to the greatest reduction in cases of a disease [98].

2.2.5 Global scale models

The worldwide spread of a pandemic and its possible containment strategy at a global level have been modeled. Migratory birds may spread avian flu viruses to new geographic regions [60], [133]. There is a pattern to the spread of avian flu among birds from Asia into Alaska [60], [96]. The inclusion of air transportation is crucial in the assessment of the occurrence probability of global outbreaks [126]. A global cooperative strategy, including countries that make part of their resources available for global

use, has proven to be effective for containing the disease [84], [96], [134]. It has been suggested that a pandemic could be effectively contained if one country donates some of their stockpiled antivirals to other countries in need [126]. Spatial demographic and delay both have effect on the spread of disease [135], [136] . It has been suggested that extensive air travel restrictions would not delay spread of a pandemic by more than a few weeks [127], [136].

2.2.6 Population dispersal

There have been many investigations concerning the effect of population dispersal on the spread of a disease. Epidemic models have been considered to describe the dynamics of disease spread between two or more patches and study the threshold dynamics [137], [138], [139], [140], [141]. Also the effect of population dispersal on the spread of a disease have been investigated [137], [138], [139]. The movement of susceptible or infected individuals can enhance or suppress the spread of disease, depending on the heterogeneity and connectivity of the spatial environment [139], [140]. All these investigations ignored the possibility that individuals become infective during travel. Transport-related infection models for two identical regions were investigated [142]. The study shows that transport-related infection can make the disease endemic even if two isolated regions are disease free [142]. Furthermore, restricting travel of infected individuals in the form of border screening [143] [144] is important for disease eradication since this allows the possibility to eradicate the component of the disease driven by transport-related infection.

2.2.7 Cross species models

The models for the spread and control of disease listed above have been developed for a single strain such as seasonal flu [97], 1918 (Spanish) flu [98], [99], swine flu [61], [71] or 1957 (Asian) flu [100]. They may not be suitable for describing epidemics generated by strains that emerge due to recombination of species-specific strains and subsequent cross-species transmission. Interaction between birds and humans results in a different scenario for the spread and control of disease than for a single population of birds or humans [101], [102], [103], [104].

It has been suspected that confined animal feeding operations serve as amplifiers of influenza. A study showed that when the workers comprised $15-45\%$ of the community, human influenza cases increased by $42-86\%$. Successful vaccination of at least 50% of the workers canceled the amplification [101].

It was pointed out in Section 2.1 that a virus mutation process can be modeled by a drift or shift mechanism [23], [85]. There are only few published studies to consider the effect of a virus mutation [102], [103], [145], [125], [104], [146]. The drift evolution in

seasonal influenza was first modeled as an evolutionary model [102]. The model assumes that the susceptible class is continually replenished because the pathogen changes genetically, and hence immunologically, from one epidemic to the next, causing previously immune hosts to become susceptible. The inter-epidemic period, and the probability that a host will become reinfected, depend on the rate of amino acid substitution in the pathogen.

On the other hand, interaction between infectious birds and infectious humans may also result in a virus mutation of avian flu. Shift mechanisms have been used to model the effect of avian-human [103] and swine-human [101] cross species virus mutations. An avian-human cross species model considered a hypothetical mutant virus as a shift virus mutation of avian flu [103]. The results show that when mutant influenza-A has already occurred, the spread of avian flu in the human world can be prevented only by a combination of culling infected birds and quarantining the infected humans. Reducing the contact rate between susceptible humans and the individuals infected with mutant influenza-A also helps to prevent the occurrence of a pandemic [135]. The quarantine policy can effectively reduce both human morbidity and mortality but a bird culling policy can increase human morbidity or mortality in a worst case situation [125].

Further, a model that incorporates both drift and shift as evolution mechanisms of influenza was proposed in [104]. As in [102], the drift evolution of influenza was modeled by the total number of the amino-acid substitutions during the strain circulating time. The study showed that amino-acid substitution structure of human influenza can destabilize the human influenza equilibrium and sustained oscillations are possible. For low levels of infection in domestic birds, these oscillations persist, inducing oscillations in the number of humans infected with the avian flu strain.

2.3 Modeling approaches

When modeling a complex system such as the spread and and control of influenza-A viruses, there is a trade off between a model's degree of abstraction and its usefulness. Each model has its own approach and set of assumptions. Most existing models reviewed in the previous section are based on simulation studies.

At the microscopic level for virus mutation, bio-informatics methods have been used to predict antigenic variants of avian flu virus. These methods predict the emergence of a new strain of influenza-A with human to human transmission capability. A simulation study showed that a new influenza-A pandemic might happen as a result of recombination of avian flu and swine flu. A human already infected with avian flu might become infected with swine flu [36], [37]. Readers who are interested in simulation studies for virus mutations may refer to [147], [148], [149], [150], [151], [152].

Some models have been proposed for detecting person-to-person transmission in closed social contact networks. The models assumed that each individual has a finite

set of contacts to whom they can pass infection. The ensemble of all such contacts forms a mixing network. Knowledge of the structure of the network allows models to compute the epidemic dynamics at the population scale from the individual-level behavior of infections [153], [117], [116]. There is still much to be done in validating the simulation results and relating them to the theory. Readers who are interested in studying epidemics using social networks may refer to [153], [154], [155], [156]. There is also reference to the use of bond percolation for infectious disease prediction and control [157]. Network theory also has been used for predicting outbreak diversity [156], [158], [159].

Most of models discussed in the previous sections partition the population of interest according their disease states. Such models are referred to as *compartmental models*. compartmental models are very important in mathematical epidemiology of infectious diseases due to analytical properties of the models. The following subsection reviews the description and development of simple compartmental models.

2.3.1 Compartmental models

Compartmental models assume that population groups are fully-mixed, so every individual has an equal chance of spreading the disease to any other member. Compartmental models are identified by a string of letters that provides information about the structure of the model. A compartmental model with disease states of susceptible (S), infectious (I) and (R) recovered is referred to as a SIR model. The model becomes SEIR if the infection transmission has an *exposed* (E, infected but not infectious) period. SIR models become SIS (or SIRS) if susceptibility returns after infection (or after immunity).

Let $S(t), I(t)$ and $R(t)$ be random variables representing compartmental measurements of susceptible, infective and recovered individuals, respectively. The measurement can be a cumulative number or a ratio. $S(t), I(t)$ and $R(t)$ are the disease state variables and they may be discrete or continuous. A disease state variable may be modelled as a continuous variable if its rate of change is small compared to the number of individuals. Epidemic models can be classified according the type of their disease state variables. If the transition of disease states are probabilistic in nature, the disease state variables are probabilistic and the model is referred to as a *stochastic epidemic model*, otherwise the model is a *deterministic epidemic model*.

The transition rate from the compartment of susceptible individuals to the compartment of infectious individuals is modeled by the *force of infection*, which is the rate (in deterministic models) or probability (in stochastic models) at which susceptible individuals become infected. The force of infection is proportional to the *transmission rate*, the effective number of contacts per unit time and the proportion of infectious individuals. The transmission rate or *contact rate* is the average number of adequate

contacts per day of an infected individual with susceptible individuals which may result in disease transmission.

Stochastic models are used to estimate the probabilistic quantities for the outcome events, such as the probability distribution of extinction time, the probability distribution of final epidemic size, the associate mean and so on. Consider first a simple SIR stochastic model. It has two independent discrete probabilistic random variables $S(t)$ and $I(t)$ since the random variable $R(t)$ can be found by $R(t) = N - I(t) - S(t)$. The bi-variate process $\{(S(t), I(t))\}_{t=0}^{\infty}$ has a joint probability function

$$p_{s,i}(t) = Prob\left[S(t) = s, I(t) = i\right],$$

and it has the Markov property and is time-homogeneous.

Let $\Delta S = S(t+\Delta t) - S(t)$ and $\Delta I = I(t+\Delta t) - I(t)$. The probability of a transition is denoted as

$$p_{(s+k,i+j),(s,i)}(\Delta t) = Prob\left((\Delta S, \Delta I) = (k, j) | (S(t), I(t)) = (s, i)\right).$$

At a disease state $(S(t), I(t)) = (s, i)$, there are five possible outcomes in a near future time $t + \Delta t$: a new infection, a death, a birth, or a recovery, no change (stationary). Assume that the probability that there will be an additional infectious individual is $b(i) = \frac{\alpha\beta i\, s}{N}\Delta t$, where α is the effective number of contacts per unit time and β is the transmission rate. The formulation $\frac{\beta I(t)}{N}$ is the so-called *true mass-action model* and includes the mixing process, i.e. the individuals in the population will be totally mixed and the probability of contact with an infected member will decrease as population size increases. Another approach, the *pseudo mass-action* with *infection force* $\beta I(t)$ assumes a constant probability of contact with an infected member is independent of population size (i.e. the number of contacts increases with population size) [160]. The probability that the number of infectious individuals is reduced by one due to of a death and recovery are $d(i) = \gamma\, i\Delta t$ and $r(i) = b\,(N - s - i)\Delta t$, respectively. The probability that the disease state remains the same is $1 - \frac{\alpha\beta i\, s}{N}\Delta t - (\gamma i + b(N - s))\,\Delta t$. Therefore, the transition probabilities can be defined as a six valued function representing six possible outcomes, [110]

$$p_{ji}(\Delta t) = \begin{cases} \frac{\alpha\beta is}{N}\Delta t & \text{if } (k, j) = (-1, 1) \\ \gamma i\Delta t & \text{if } (k, j) = (0, -1) \\ b\, i\Delta t & \text{if } (k, j) = (1, -1) \\ b(N - s - i)\Delta t & \text{if } (k, j) = (1, 0) \\ 1 - \frac{\alpha\beta i\, s}{N}\Delta t - (\gamma i + b(N - s))\,\Delta t & \text{if } (k, j) = (0, 0) \\ 0 & \text{if otherwise.} \end{cases} \tag{2.1}$$

These transitions represent all possible changes in the state i during the time interval Δt, which must be chosen small enough such that the transition probabilities lie in the interval $[0, 1]$ and the sum of them is equal to one.

Applying the Markov property that the future state of the processes depends only on the current state and not on the past and the preceding transition probabilities, the probabilities p_i at time $t + \Delta t$ can be calculated based on $p_i(t)$ [105],

$$\begin{aligned} p_{(s,i)}(t+\Delta t) &= p_{(s+1,i-1)}(t)\frac{\alpha\beta}{N}(i-1)(s+1)\Delta t + p_{(s,i+1)}(t)\gamma(i+1)\Delta t \\ &+ p_{(s-1,i+1)}b(i+1)\Delta t + p_{(s-1,i)}(t)b(n-s+1-i)\Delta t) \\ &+ p_{(s,i)}(t)\left(1-\left(\frac{\alpha\beta}{N}i\,s+\gamma i+b(N-s)\right)\Delta t\right). \end{aligned} \tag{2.2}$$

In matrix form (2.2) can be written as

$$p(t+\Delta t) = P(\Delta t)p(t) = P^{n+1}(\Delta t)p(0) \tag{2.3}$$

where $t = n\Delta t$ and $P(\Delta t) = (p_{ij}(\Delta t))$ is the *transition matrix*. When the transition probability is independent of time, the process is referred to as *time homogeneous*, and is equivalent to an *autonomous* system in a deterministic model. The epidemic process $\{I(t)\}_{t=0}^{\infty}$ is completely formulated by (2.2) or (2.3).

Often, time in the epidemic equation (2.2) or (2.3) is treated as a discrete variable in which case the *Markov Chain* property (the current state depends only on the previous state) is typically invoked. Such a model is referred to as a *discrete time Markov chain*. A discrete time Markov chain is suitable for modeling an epidemic with disease states which are changing relatively slowly in time such that time can be discretised. If disease states are changing so fast such that the time can not be discretised, the models are referred to as a *continuous time Markov chain* [110], [161], [162].

Comparing corresponding deterministic and stochastic models, one can say in general that if the model is linear, the deterministic equations are the same as the equations for the means of the stochastic model and the two have the same solutions [105], [163], [164]. That is not true for nonlinear models. For example, in a stochastic SIS model the expected number of infectious individuals is calculated by

$$E(I(t)) = \sum_{i=0}^{N} i p_i(t).$$

As $t \to 0$, one easily has [110]

$$\frac{E(I(t))}{dt} \leq \frac{\beta}{N}[N - E(I(t))]E(I(t)) - (b+\gamma)E(I(t)).$$

This is the rate of change of the expected number of infectious individuals. If the tran-

sition of disease states are deterministic in nature then the disease state variables are deterministic and $E(I(t)) = I(t)$. Consequently, the number of infectious individuals in the final time is calculated by

$$\frac{dI(t)}{dt} = \frac{\beta}{N}[N - I(t)]I(t) - (b + \gamma)I(t).$$

These show that the final mean number of infected individuals in the stochastic SIS model is less than the final number of infected individuals in the deterministic SIS model.

Simple SIS and SIR stochastic models discussed in the literature review show that they do capture the variability of the disease transmission, recovery, birth, and death processes at the individual level. Stochastic models have several advantages. More specifically, they allow follow-up of each individual in the population on a chance basis. There are some disadvantages in using the stochastic approach.

The first disadvantage is that there is a problem regarding the reproduction number used for describing the properties of disease free equilibria in the population [88], [89], [90], [92], [93]. In a stochastic model, the disease free equilibrium may be independent of a reproduction number. For example, recall the discrete time Markov chain for SIS model is (2.2). The set of disease states $S = \{0, 1, 2, .., N\}$ can be partitioned into the set of recurrent states R and the set of transient states T. A disease state z_i is said to be *transient* if, for a given starting disease state z_i, there is a non-zero probability that it will never return to z_i; otherwise it is a *recurrent*. (2.2) has $R = \{0\}$ and $T = \{1, 2, .., N\}$. The zero state $\{0\}$ is an *absorbing state*, no other state can be reached from the zero state. Let $P^n = (p_{ij}^{(n)})$, where $p_{ij}^{(n)}$ is the (i, j) element of the nth power of transition matrix, $P^{(n)}$, then for any state $i \in S$ and any transient state $i \in T$

$$\lim_{n\to\infty} p_{ij}^{(n)} = 0.$$

In matrix form, the transition probability is given by (2.3). By using the Markov chain condition, [110], [165]

$$\lim_{t\to\infty} p(t) = (1, 0, \ldots, 0)^T,$$

where $t = n\Delta t$. Therefore the population approaches a disease free equilibrium regardless of the reproduction number. The average time to reach a disease free equilibrium depends on the initial condition and the epidemic parameter values, but it can be extremely long. The absence of a reproduction number in disease free equilibrium is not really expected, as a reproduction number is the central point of epidemiology modeling [88], [89], [90], [92], [93].

The second disadvantage is regarding the complexity of designing the transition probabilities. For a simple SIR model with only two variables S, I (where R can be

found by $R = N - S - I$ under a constant population assumption), the transition probabilities are defined as a six valued function (2.1). Increasing the number of disease states in the model will increase the model complexity exponentially. By contrast, the complexity of a deterministic model increases only linearly with the number of disease states.

The third disadvantage is the use of a stochastic model for large populations. In a large population, the variability of the disease state variables are very small and many transitions are needed to model small changes. These models can become mathematically very complex and do not lend themselves to an explanation of the dynamic.

For the reasons listed above, stochastic modeling will not be pursued further in this work. Stochastic models are not suitable for this study. Useful references include [110], [112], [113], [161], [162], [166].

3. DETERMINISTIC MODELS

The purpose of this chapter is to provide background on the basic ideas, theories and techniques used in this thesis. Section 3.2 describes a class of deterministic models considered in the study. Characteristics of these epidemic models, in particular for the uniqueness of solution and stability of the disease equilibrium states are given. Section 3.3 provides methods for characterizing local and global stability. Mathematical results on the stability analysis for the models are presented in this section. Section 3.6 derives a method for calculating the reproduction number. Section 3.7 describes optimal disease control problems for the epidemic models. Methods for designing disease control and solving the optimal disease control problems are also given.

3.1 Euclidean Space $\mathbb{R}^n$

The n-dimensional linear space over reals $\mathbb{R}^n$ is the vector space used throughout the thesis. $\mathbb{R}^n$ equipped with a *scalar product* is referred to as Euclidean Space. The scalar product is a function $(\boldsymbol{x}, \boldsymbol{y}) : \mathbb{R}^n \times \mathbb{R}^n \to \mathbb{R}$ satisfying condition

i $(\boldsymbol{x}, \boldsymbol{x}) \geq 0$;

ii $(\boldsymbol{x}, \boldsymbol{x}) = 0$ if only if $\boldsymbol{x} = \boldsymbol{0}$;

iii $(\boldsymbol{x}, \boldsymbol{y}) = (\boldsymbol{y}, \boldsymbol{x})$;

iv for any $t \in \mathbb{R}$, $(t\boldsymbol{x}, \boldsymbol{y}) = t(\boldsymbol{x}, \boldsymbol{y})$;

v $(\boldsymbol{x} + \boldsymbol{y}, \boldsymbol{z}) = (\boldsymbol{x}, \boldsymbol{z}) + (\boldsymbol{y}, \boldsymbol{z})$.

If $\{e_1, ..., e_n\}$ is a basis in $\mathbb{R}^n$, and $\boldsymbol{x} = \sum x_i e_i$, $\boldsymbol{y} = \sum y_j e_j$ then $(\boldsymbol{x}, \boldsymbol{y}) = \sum_{i,j} x_i y_j (e_i e_j)$. In particular if $\{e_1, ..., e_n\}$ is an orthonormal basis in $\mathbb{R}^n$, then $(\boldsymbol{x}, \boldsymbol{y}) = \sum x_i y_i$. The *length* (or the *Euclidean norm*) of the vector is $|\boldsymbol{x}| = \sqrt{(\boldsymbol{x}, \boldsymbol{x})}$ which satisfies the following properties:

(a) $|\boldsymbol{x}| > 0$ for $\boldsymbol{x} \neq 0$;

(b) $|t\boldsymbol{x}| = |t||\boldsymbol{x}|$ for $t \in \mathbb{R}$ and $\boldsymbol{x} \in \mathbb{R}^n$;

(c) $|\boldsymbol{x} + \boldsymbol{y}| \leq |\boldsymbol{x}| + |\boldsymbol{y}|$.

Definition 3.1. *A set $A \subset \mathbb{R}^n$ is open, if for each $\boldsymbol{a} \in A$ there is an open ball $B(\boldsymbol{a}, r) = \{\boldsymbol{x} \in \mathbb{R}^n : |\boldsymbol{x} - \boldsymbol{a}| < r,\ r \in \mathbb{R}\}$ such that $B \subset A$. A set $X \subset \mathbb{R}^n$ is closed if its complement $X^c = \mathbb{R}^n \setminus X$ is open .*

A sequence $\{\boldsymbol{x}^m\} \subset \mathbb{R}^n$ converge to $\boldsymbol{x}$ if $\lim_{k\to\infty} |\boldsymbol{x}^k - \boldsymbol{x}| = 0$

Definition 3.2. *A set $K \subset \mathbb{R}^n$ is compact, if any sequence $\{\boldsymbol{x}^m\} \subset K$ has a subsequence $\{\boldsymbol{x}^{m_j}\}$ convergent to a point from K.*

Theorem 3.3. *A set $K \subset \mathbb{R}^n$ is compact if only if it is closed and bounded.*

3.2 A class of deterministic compartmental models

In a deterministic compartmental model, individuals in the population are assigned to different subgroups or compartments, each representing a specific disease state. The disease states are assumed to be uniformly distributed throughout space.

Suppose there are n disease states. Let

$$\boldsymbol{z}(t) = (z_1(t), \ldots, z_n(t))$$

be the vector of disease state variables. The independent variable $t \in \mathbb{R}^1_+$ is referred to as time. Let $\Omega \subseteq \mathbb{R}^n_+$ be the set of all disease states

$$\Omega = \{\boldsymbol{z}(t) \,|\, 0 \le t \le \infty\}.$$

Let

$$Q = \{\, \boldsymbol{q} \,|\, \boldsymbol{q} = (q_1, \ldots, q_k)\} \subseteq \mathbb{R}^k_+$$

be a set of epidemic parameters. It is an open set $\mathbb{R}^k_+$. For a given set of epidemic parameters $\boldsymbol{q} \in Q$, the dynamics of the disease states is described by

$$\boldsymbol{z}' = \boldsymbol{f}(\boldsymbol{z}; \boldsymbol{q}), \tag{3.1a}$$

$$\boldsymbol{z}(0) = \boldsymbol{z}_0 \in \Omega. \tag{3.1b}$$

Here $\boldsymbol{z}'$ is the first derivative of $\boldsymbol{z}$ with respect to time t,

$$\boldsymbol{f} \colon \mathbb{R}_+ \times \mathbb{R}^n_+ \longrightarrow \mathbb{R}^n_+.$$

and $\boldsymbol{z}(0)$ is an initial disease state.

In the following, some definitions and terminology are introduced which will be used in later discussions on the qualitative behavior of the disease dynamics. A solution of

(3.1a), $\boldsymbol{z} = \boldsymbol{z}(t; \boldsymbol{q}) \in \mathbb{R}^n_+$ is a map, $\boldsymbol{z}$, from some interval $I \in \subset \mathbb{R}^1$ into $\mathbb{R}^n$

$$\boldsymbol{z} : I \to \mathbb{R}^n,$$
$$t \to \boldsymbol{z}(t),$$

which satisfies (3.1a),

$$\boldsymbol{z}'(t) = \boldsymbol{f}(t, \boldsymbol{z}(t); \boldsymbol{q}).$$

The map $\boldsymbol{z}(t; \boldsymbol{q})$ has a geometrical interpretation as a curve in $\mathbb{R}^n$ and (3.1a) gives the tangent vector at each point of the curve. For this reason, $\boldsymbol{f}$ is referred to as a *vector field*. The space of dependent variables of (3.1a) (*i.e*, $\mathbb{R}^n$) is referred to as the *phase space* of (3.1a). A solution curve that passes through an initial state (3.1b)

$$\boldsymbol{z}(t_0, \boldsymbol{z}_0; \boldsymbol{q}) = \boldsymbol{z}_0.$$

is referred to as the solution of initial value problem (IVP) (3.1a), (3.1b).

It is assumed that new infections can only happen by means of interaction between susceptible individuals with infectious individuals (horizontal transmission). It is possible to have more than one disease in the transmission model. However, it is assumed that there is no double infection of the same disease. A double infection may happen for two or more different diseases. Each disease transmission results in a change of disease state.

Let $\boldsymbol{z} = (\boldsymbol{y}, \boldsymbol{x})$ where $\boldsymbol{y} = (z_1, z_2 \ldots, z_d)$ is the vector corresponding to infected compartments and $\boldsymbol{x} = (z_{d+1}, \ldots, z_n)$ is the vector corresponding to susceptible compartments. The set of disease free states, $\mathcal{D} \subset \Omega$ can be written as

$$\mathcal{D} = \{\boldsymbol{z} = (\boldsymbol{y}, \boldsymbol{x}) | \boldsymbol{z} \in \Omega,\ \boldsymbol{y} = \boldsymbol{0}\}.$$

This study considers a class of deterministic epidemic models with a polynomial vector field $\boldsymbol{f}(t, \boldsymbol{z}; \boldsymbol{q})$ satisfying the following conditions.

(C_1) . The set of all disease states Ω is positively invariant for the the vector field $\boldsymbol{f}(\boldsymbol{z}; \boldsymbol{q})$. That is, for any initial value $\boldsymbol{z}_0 \in \Omega$ the disease states $\boldsymbol{z}(t)$ remains in Ω for all $t > 0$. It is assumed that Ω is a $\mathbf{C}^r$ *positively invariant manifold* with $r \geq 1$. Here $\mathbf{C}^r$ refers to the set of continuously differentiable functions of order r.

(C_2) . The subspace of disease free states $\mathcal{D}$ is positively invariant for the vector field $\boldsymbol{f}(\boldsymbol{z}; \boldsymbol{q})$.

(C_3) . In the absence of the disease, the population has a stable equilibrium.

For a given set of disease parameters $\boldsymbol{q} \in Q$ and initial disease state $\boldsymbol{z}_0 \in \Omega$, the problem of finding the *disease propagation*, i.e. disease state over time, is equivalent to the problem of finding solutions to the IVP (3.1a), (3.1b).

The existence and uniqueness of $\boldsymbol{z}(t; \boldsymbol{q}, \boldsymbol{z}_0) \in \mathbb{R}^n$ is guaranteed by the following theorem.

Theorem 3.4. *For a given set of disease parameter $\boldsymbol{q} \in Q$ and initial condition $\boldsymbol{z}_0 \in \Omega$, the IVP (3.1a), (3.1b) has a unique non negative solution $\boldsymbol{z}(t; \boldsymbol{q}, \boldsymbol{z}_0)$.*

Proof. By conditions (C_1) and (C_2) the existence of a solution is guaranteed. For the proof of the uniqueness of the solution can be referred to [167], [168], [169]. □

Furthermore, the solution can be extended to a compact set containing the initial condition $\boldsymbol{z}_0$.

Theorem 3.5. *The solution of (3.1a), (3.1b), $\boldsymbol{z}(t; p, \boldsymbol{z}_0)$, can be extended up to the boundary of a compact set containing the initial condition $\boldsymbol{z}_0$.*

Proof. By Condition (C_1), the set of all disease states Ω is positively invariant for the the vector field $\boldsymbol{f}(t, \boldsymbol{z}; \boldsymbol{q})$, is closed and bounded. By Theorem 3.3, Ω is compact. For a complete proof,see [169]. □

Corollary 3.6. *The solution of (3.1a), (3.1b), $\boldsymbol{z}(t; \boldsymbol{q}, \boldsymbol{z}_0)$, is bounded above. There are positive numbers K_i, such that $z_i(t) \leq \limsup_{t\to\infty} z_i(t) \leq K_i$ for $i = 1, \ldots, n$.*

The problem of understanding the qualitative behavior of the disease dynamics governed by IVP (3.1a), (3.1b) is in general a very hard problem. The important starting point in understanding the disease dynamics is to find the *equilibria* of (3.1a), (3.1b). Many key questions regarding the progress of an epidemic can be studied by analyzing the disease equilibrium states. For example, whether the introduction of a few infective individuals results in an epidemic or not.

The propagation of the disease starting from an initial disease state $\boldsymbol{z}_0$ is depicted by a graph $\boldsymbol{z}(t, \boldsymbol{z}_0)$ over t which is also referred to as an *integral curve*

$$\boldsymbol{z}(t, \boldsymbol{z}_0) = \{(\boldsymbol{z}, t) \in \mathbb{R}^n_+ \times \mathbb{R}^1_+ | \boldsymbol{z}' = \boldsymbol{f}(\boldsymbol{z}; \boldsymbol{q}),\ \boldsymbol{z}(0) = \boldsymbol{z}_0,\ t \in [0, t_F]\}$$

where t_T is the final time. A disease state is said to be in *equilibrium*, denoted as $\boldsymbol{z}^* \in \mathbb{R}^n_+$, if its does not change with time. Since $(3.1a)$ is an *autonomous* or *independent of time* ordinary differential equation, the equilibrium points the system of differential equations in IVP (3.1a), (3.1b) can be found using the following theorem

Theorem 3.7. *$\boldsymbol{z}^*$ is an equilibrium point of IVP (3.1a), (3.1b) if only if $f_1(\boldsymbol{z}^*; \boldsymbol{q}) = \cdots = f_n(\boldsymbol{z}^*; \boldsymbol{q}) = 0$.*

It is of interest to see in the long run ($t \to \infty$) whether the disease will be eliminated or if it will exist in the population indefinitely. $\boldsymbol{z} = (\boldsymbol{y}, \boldsymbol{x})$ where $\boldsymbol{y} = (z_1, z_2 \ldots, z_d)$ is the vector corresponding to infected compartments and $\boldsymbol{x} = (z_{d+1}, \ldots, z_n)$ is the vector corresponding to susceptible compartments. A disease state in which the population remains in the absence of disease is referred to as a disease free equilibrium. A disease state equilibrium in which infected individuals remain present is referred to as *disease endemic equilibrium.*

Definition 3.8. *The system (3.1a), (3.1b) is disease permanent if and only if there is one or more disease endemic equilibrium stat es. i.e. if there exist a lower bound* $k_i, > 0$ *such that*

$$k_i \leq \liminf_{t \to \infty} y_i(t)$$

for at least one i*. Such disease state variables correspond to infected compartments.*

Let $\varphi(t, \boldsymbol{z}_0)$ denote the solution of IVP (3.1a), (3.1b) under the initial condition $\boldsymbol{z}_0$. The equilibrium disease state $\boldsymbol{z}^*$ is an *attractor* of (3.1a), (3.1b) if $\lim_{t\to\infty} \varphi(t, \boldsymbol{z}_0) = \boldsymbol{z}^*$ for all $\boldsymbol{z}_0$ in some open set containing $\boldsymbol{z}_0$. Let N be the maximal open set of initial disease states $\boldsymbol{z}_0$ satisfying the above condition. N is referred to as *basin attraction* of $\boldsymbol{z}^*$. N is the stable manifold of $\boldsymbol{z}^*$. In case $N = \Omega$, $\boldsymbol{z}^*$ is a global attractor.

3.3 Characterizing the stability of a disease state equilibrium

Roughly speaking, an equilibrium state $\boldsymbol{z}^*$ of $\varphi(t, \boldsymbol{z}_0)$ is *stable* if for any other disease state that is "close" enough to $\boldsymbol{z}^*$ at a given time will remain close to $\boldsymbol{z}^*$ for all later time. Formally,

Definition 3.9. *(Lyapunov Stability) An equilibrium state* $\boldsymbol{z}^*$ *is said to be stable (or Lyapunov stable) if given* $\epsilon > 0$*, there exists a* $\delta = \delta(\epsilon) > 0$ *such that for any other solution,* $\boldsymbol{y}(t)$*, of (3.1a) satisfying* $|\boldsymbol{z}^*(t') - \boldsymbol{y}(t')| < \delta$ *then* $|\boldsymbol{z}^*(t) - \boldsymbol{y}(t)| < \epsilon$ *for* $t > t'$*,* $t' \in \mathbb{R}$*. When* $\boldsymbol{z}^*$ *is not stable it is called unstable.*

Definition 3.10. *(Asymptotic Stability) An equilibrium state* $\boldsymbol{z}^*$ *is said to be asymptotically stable if it is Lyapunov stable and for any other solution,* $\boldsymbol{y}(t)$*, of (3.1a), there exists a constant* $b > 0$ *such that, if* $|\boldsymbol{z}^*(t_0)\boldsymbol{y}(t_0)| < b$*, then* $\lim_{t\to\infty} |\boldsymbol{z}^*(t_0)\boldsymbol{y}(t_0)| = 0$*. Therefore* $\boldsymbol{z}^*$ *is an attractor. The equilibrium state* $\boldsymbol{z}^*$ *is said to be a locally asymptotically stable (LAS) or globally asymptotically stable (GAS) if it is a local or global attractor, respectively.*

3.3.1 Local stability

To determine the local stability a disease state equilibrium $\boldsymbol{z}^* = (\boldsymbol{z}_i^*)_{i=1\ldots n}$, it is necessary to understand the nature of the solution near $\boldsymbol{z}^*$. Let $N_{\boldsymbol{z}^*}$ be the set of disease

states near the disease state equilibrium $\boldsymbol{z}^*$. $N_{\boldsymbol{z}^*}$ is referred to as a *neighborhood* of $\boldsymbol{z}^*$. The notion of nearness may be specified by defining $N_{\boldsymbol{z}^*}$ explicitly as dependent on a parameter $\delta > 0$, by

$$N_{\boldsymbol{z}^*} = \{\boldsymbol{z} \in \mathbb{R}_+^n \mid |\boldsymbol{z} - \boldsymbol{z}^*| \leq \delta, \} \tag{3.2}$$

where $|.|$ denotes the Euclidean norm on $\mathbb{R}^n$.

Consider the disease states in the neighborhood $N_{\boldsymbol{z}^*}$. If δ is sufficiently small, then the evolution of the disease state $\boldsymbol{z}$ can be approximated by the linearized system [170], [171]

$$\boldsymbol{z}' = J_{\boldsymbol{f}}(\boldsymbol{z}^*)(\boldsymbol{z} - \boldsymbol{z}^*) \tag{3.3}$$

where $J_{\boldsymbol{f}}(\boldsymbol{z}^*) = \left[\frac{\partial f_i}{\partial z_j}\right]_{\boldsymbol{z}=\boldsymbol{z}^*}$, the *Jacobian matrix* of the vector field $\boldsymbol{f}$ evaluated at the disease state equilibrium $\boldsymbol{z}^*$. The local stability of the disease state equilibrium of (3.1a), (3.1b) can be characterized by the following theorem [170], [171].

Theorem 3.11. *$\boldsymbol{z}^*$, a disease state equilibrium of (3.1a), (3.1b), is LAS if and only if all eigenvalues of the Jacobian matrix $J_{\boldsymbol{f}}(\boldsymbol{z}^*)$ have a negative real part.*

The spectrum of $J_{\boldsymbol{f}}(\boldsymbol{z}^*)$ is given by the roots of its characteristic polynomial. Let

$$a_n\lambda^n + a_{n-1}\lambda^{n-1} + ... + a_1\lambda + a_0 = 0$$

be the characteristic polynomial of $J_{\boldsymbol{f}}(\boldsymbol{z}^*)$. A disease state equilibrium of (3.1a), (3.1b), is LAS if and only if all roots of corresponding characteristic polynomial λ_i for $i = 1, 2, \ldots n$ have a negative real part.

3.3.2 Global stability

The fact that all the eigenvalues of the Jacobian matrix $J_{\boldsymbol{f}}(\boldsymbol{z}^*)$ have a negative real part is in general not enough to ensure the global asymptotic stability in Ω [172]. The main approach used to deal with such a problem is to resort to *Lyapunov functions* which are defined as follows [172].

Definition 3.12. *Let $G \subseteq \Omega \subset \mathbb{R}_+^n$ be a set of disease states generated the vector field $\boldsymbol{f} = (f_1, f_2, \ldots, f_n)$ in (3.1a), (3.1b) and $\boldsymbol{z}^* \in \Omega$ be an equilibrium state. A continuous map $\mathcal{F} : G \to \mathbb{R}_+$ is a Lyapunov function for $\boldsymbol{f}$ on Ω if*

- $\mathcal{F}(\boldsymbol{z}^*) = 0$
- $\mathcal{F}(\boldsymbol{z}) > 0 \quad \boldsymbol{z} \in G \setminus \{\boldsymbol{z}^*\}$
- $\mathcal{L}_{\boldsymbol{f}}\mathcal{F} \leq 0$ *for* $\boldsymbol{z} \in G$,

where $\mathcal{L}_{\boldsymbol{f}}$ is the *Lie derivative* associated to vector field $\boldsymbol{f}$, $\mathcal{L}_f\varphi = \sum f_i \partial z_i \varphi$.

The global stability can be characterized by the following theorem [170], [171], [172].

Theorem 3.13. *The equilibrium state $\boldsymbol{z}^*$ of (3.1a), (3.1b) is a GAS if and only if there exists a Lyapunov function $\mathcal{F} : N_{\boldsymbol{z}^*} \to \mathbb{R}$.*

The idea of the sets of ω-limit and α-limit is used to characterize the global stability of a disease state equilibria. These are defined as follows [170].

Definition 3.14. *A disease state $\hat{\boldsymbol{z}}$ is called an ω-limit point, denoted as $\omega(\hat{\boldsymbol{z}})$, if there exists a sequence $\{t_i\}$, $t_i \to \infty$, such that $\varphi(t_i, \boldsymbol{z}) \to \hat{\boldsymbol{z}}$. A disease state $\hat{\boldsymbol{z}}$ is called an α-limit point, denote $\alpha(\hat{\boldsymbol{z}})$, if there exists a sequence $\{t_i\}$, $t_i \to -\infty$, such that $\varphi(t_i, \boldsymbol{z}) \to \hat{\boldsymbol{z}}$. The sets of all ω-limit points is called the ω-limit set. The sets of all α-limit points is called the α-limit set.*

The global stability is characterized by the following theorem, which is a version of the *LaSalle's invariance* principle in [172].

Theorem 3.15. *Let $\boldsymbol{f} = (f_1, f_2, \ldots, f_n)$ be the vector field $\boldsymbol{f}$ in (3.1a), (3.1b) and let $\boldsymbol{z}$ be disease state generated by $\boldsymbol{f}$. Let G be a closed subset of $\mathbb{R}^n$ and assume that f has a Lyapunov function $\mathcal{F} : G \to \mathbb{R}$. Let $\mathcal{J}$ be the largest invariant set for $\boldsymbol{f}$ contained in $\{\boldsymbol{z} \in G \mid \mathcal{L}_{\boldsymbol{f}}\mathcal{F}(\boldsymbol{z}) = 0\}$. Then the following statements hold.*

- *For any $\boldsymbol{z} \in G$ such that $\boldsymbol{z}(t) \in G$ for all t there exist $w(\boldsymbol{z}) \subset \mathcal{J}$.*
- *If $\mathcal{J}$ is a singleton, say $\boldsymbol{z}^*$, then it is an equilibrium of $\boldsymbol{f}$. If moreover G is compact then any solution $\boldsymbol{z} \in G$ tends to $\boldsymbol{z}^*$ as $t \to \infty$. In particular, if G is compact and positively invariant then $\boldsymbol{z}^*$ is globally asymptotically stable in G.*

Proof. See [172]. □

Similar results from a more geometric approach are obtained by creating a *Dulac function* defined as follows [171], [173].

Definition 3.16. *Let $\Omega \subset \mathbb{R}^n$ be an open set and $\varphi : \Omega \to \mathbb{R}$ a C^1 function. φ is a Dulac function of (3.1a), (3.1b) on Ω if $\varphi(\boldsymbol{z}) \geq 0, \forall \boldsymbol{z} \in \Omega$ and $\varphi(\boldsymbol{z}) = 0$ implies $\boldsymbol{f}(\boldsymbol{z}) = \boldsymbol{0}$.*

It is very important to understand the key feature of a dynamical system. Periodic orbits can be used to understand the orbit evolution from the distant past (i.e. as $\to -\infty$) to the distant future (i.e. as $\to \infty$). The entire course of the evolution is determined by knowledge over a finite time interval, i.e., the period.

When the dimension of (3.1a), (3.1b) is two, the global stability can be characterized by the following *Bendixson-Dulac* theorem [171], [173]. Let two dimensional autonomous system

$$\dot{\boldsymbol{x}} = \boldsymbol{f} \;\Leftrightarrow\; \begin{bmatrix} \dot{x} \\ \dot{y} \end{bmatrix} = \begin{bmatrix} f_1(x,y) \\ f_2(x,y) \end{bmatrix} \tag{3.4}$$

where f_1 and f_2 are at least $\mathcal{C}^1$.

Theorem 3.17. *(Bendixson's criterion) If on a simply connected region $D \subset \mathbb{R}^2$ (i.e., D has no holes in it) $\Delta.(\varphi \boldsymbol{f}) \neq 0$ and does not change sign, then (3.4) has no closed orbits lying entirely in D.*

Proof. Using (3.4) and applying the chain rule,

$$\int_\Gamma f_1(x,y)dy - f_2(x,y)dx = 0$$

for a closed orbit Γ. By Green's theorem this implies

$$\int_S \left(\frac{\partial f_1}{\partial x} + \frac{\partial f_2}{\partial y} \right) dxdy = 0$$

where S is the interior bounded by Γ. But if $\frac{\partial f_1}{\partial x} + \frac{\partial f_2}{\partial y} \neq 0$ and doesn't change the sign, then this can't be true. Therefore, there must be no closed orbit in D. □

The criterion was generalized as follow

Theorem 3.18. *(Bendixson-Dulac) If there exists a $\mathcal{C}^1$ function $\varphi(x,y)$, the Dulac function, such that $\Delta.(\varphi \boldsymbol{f}) \neq 0$ in a simply connected region $\mathcal{R}$ of the plane then (3.4) has no periodic solutions lying entirely in $\mathcal{R}$.*

The following theorem is refereed to as the Poincaré-Bendixson theorem [170].

Theorem 3.19. *(Poincaré-Bendixson) Let a finite set of disease states $M \subset \Omega \subset \mathbb{R}^n$ be positively invariant for the vector field $\boldsymbol{f}$ of (3.1a), (3.1b). Let a disease state equilibrium $\boldsymbol{z}^* \in M$. If there is $\omega(\boldsymbol{z}^*)$ then the following possibilities holds*

i) $\omega(\boldsymbol{z}^*)$ is a fixed point;

ii) $\omega(\boldsymbol{z}^*)$ is a closed orbit;

iii) $\omega(\boldsymbol{z}^*)$ consist of a finite number of fixed points $q_1, \ldots q_n$ and orbits γ with $\omega_-(\gamma) = q_i$ and $\omega(\gamma) = q_j$

Proof. To proof the theorem, the following lemma [170] is required.

Lemma 3.20. *If $\omega(p)$ does not contain fixed points, then $\omega(p)$ is a closed orbit.*

If $\omega(p)$ contains only fixed points, then it must consist of a unique fixed point, since the number of fixed points in M is finite and $\omega(p)$ is a connected set. If $\omega(p)$ contains no fixed points, then, by Lemma 3.20, it must be a closed orbit. Suppose that $\omega(p)$ contains fixed points and nonfixed points (sometimes called regular points). Let γ be a trajectory in $\omega(p)$ consisting of regular points. Then $\omega(\gamma)$ and $\alpha(\gamma)$ must be fixed points since, if they were not, then, by Lemma 3.20, $\omega(\gamma)$ and $\alpha(\gamma)$ would be closed orbits, which is absurd, since $\omega(p)$ is connected and contains fixed points. It is shown that every regular point in $\omega(p)$ has a fixed point for an α and γ limit set. This proves iii) and completes the proof of Theorem 3.19 (Poincare-Bendixson). □

3.4 The limiting systems

The disease dynamic (3.1a), (3.1b) can be qualitatively determined by those of the limiting system under some conditions [103]. Define $\boldsymbol{y}_0$ as an initial disease state of disease dynamic (3.1a), (3.1b) and let $\omega(\boldsymbol{y}_0)$ denote an ω-limit set of the orbit through $\boldsymbol{y}_0$. Recall that with the initial condition $\boldsymbol{y}_0$ and the state of all disease states $\Omega \subset \mathbb{R}^n_+$ is forward invariant for the the vector field $\boldsymbol{f}(\boldsymbol{y}_0\ \boldsymbol{q})$. Let $G \subset \Omega$.

Theorem 3.21. *If $\omega(\boldsymbol{y}_0) \subset G$ for all $\boldsymbol{y}_0 \in \Omega$ and there exists exactly one equilibrium point E such that E is GAS on G and E is LAS on Ω, then E is GAS on Ω*

Proof. It s required to show that $E \in \omega(\tilde{\boldsymbol{y}}_0)$ for all $\tilde{\boldsymbol{y}} \in \Omega \backslash G$ Since Ω is forward invariant and $\omega(\tilde{\boldsymbol{y}}_0) \subset G$ for $\forall \tilde{\boldsymbol{y}}_0 \in \Omega \setminus G$. $\omega(\tilde{\boldsymbol{y}}_0)$ must include some element $\sigma \in G$. (i.e $\exists \sigma \in G$ such as $\sigma \in \omega(\tilde{\boldsymbol{y}}_0)$. Since E is GAS on G and $\omega(\tilde{\boldsymbol{y}}_0)$ is an invariant set, it is concluded that $E \in \omega(\tilde{\boldsymbol{y}}_0)$ for all $\tilde{\boldsymbol{y}} \in \Omega \setminus G$. Thus, E is GAS on Ω because E is LAS on Ω. □

3.5 The method for biological permanence

Recall the system (3.1a), (3.1b)

$$\boldsymbol{z}' = \boldsymbol{f}(\boldsymbol{z}; \boldsymbol{q}),$$
$$\boldsymbol{z}(0) = \boldsymbol{z}_0 \in \Omega.$$

where $\boldsymbol{z} = (z_1, z_2 \ldots) \in \mathbb{R}^n_+$ and $\boldsymbol{f} : \mathbb{R}^n_+ \to \mathbb{R}^n$. $\boldsymbol{z} = (\boldsymbol{y}, \boldsymbol{x})$ where $\boldsymbol{y} = (z_1, z_2 \ldots, z_d)$ is the vector corresponding to infected compartments and $\boldsymbol{x} = (z_{d+1}, \ldots, z_n)$ is the vector corresponding to susceptible compartments. By Definition 3.8), the system (3.1a), (3.1b) is *disease permanent* if and only if there is one or more disease endemic equilibrium states.

It is consider here the subject of biological permanence, i.e., the study of the long-term survival of each disease state. If there is is difficulty to predict an asymptotic behaviour such as an equilibrium, it is necessary to examine the condition for permanence, which require that all solution eventually enter and remain in a region with non-zero distance from the boundary [174]. The system will be called permanent if there exists a compact subset in the interior of the state space where all orbits starting from the interior eventually end up [175].

Theorem 3.2 guarantee the solution set of IVP (3.1a), (3.1b), $\boldsymbol{z}(t;\boldsymbol{p},\boldsymbol{z}_0)$ can be extended into a compact set containing the initial solution $\boldsymbol{z}_0$. Assume that V is a compact subset of $\mathbb{R}^n_+$ and W is a compact subset of V. Let V be forward invariant. Suppose that there exists a $\mathcal{C}^1$ function $P : V \to \mathbb{R}_+$ which satisfies $P(\boldsymbol{z}) = 0$ if and only if $\boldsymbol{z} \in V$. Let "." denote differentiation along an orbit and $\pi(\boldsymbol{z}_0, t)$ denote the solution of (3.1a) and $\boldsymbol{z}_0$ is the initial value (3.1b).

Theorem 3.22. *If $\dot{P}(w) > 0$ for all $w \in W$, then there exist some positive constant k and sufficiently large time T such that $P(\pi(\tilde{\xi}_0, t)) > k$ for all $\tilde{\xi}_0 \in V \setminus W$ and $\forall t \geq T$.*

Proof. Proof of this theorem appear in [103], given here for completeness. Since W is compact and $\dot{P}(\xi_0)$ is continuous on V, There exists $\inf \dot{P}(\xi_0)$ on W. Define $\dot{P}(\xi_0) = \tilde{c}$ and $c = \tilde{c}/2$. Since $\dot{P}(\xi_0)$ is continuous on V and $\dot{P}(w) > 0\ \forall w \in W$.

$$\forall w \in W,\ \exists \rho > 0,\ \forall u \in W :\ |w - u| < \rho \Rightarrow \dot{P}(u) > c.$$

Thus, define the neighborhood $N(w)\ \forall w \in W$ such that

$$N(w) = \{u \in V\ :\ |w - u| < \rho\},$$

and $N(w)$ for $w \in W$ forms an open cover of W ($i.e. W \subset \cup_{w \in W} N(w)$). Since W is compact, there is a finite sub-cover $N_1(w_1), N_2(w_2) \ldots N_n(w_n)$ such that $W \subset \cup_{k=1}^{n} N_k(w_k$. In addition let $U = \bigcup_{k=1}^{n} N_k(w_k$ then U is a subset of V i.e, $(V \setminus W \bigcap U \neq \emptyset)$ such that $\dot{P}(\xi_0)$. Since $t_P(w) > 0$ for all $w \in W$. Since $V \setminus W$ is a compact set, there is some $r^* = inf P(\tilde{\xi}_0)\ \forall \tilde{\xi}_0 \in V \setminus U$. Thus there exists some positive constants $r_2 < r_1 < r^*$ such that

$$U_1 = \{\xi \in U : P(\xi \leq r_1,\ U_2 = \{\xi \in U : P(\xi \leq r_2 \text{ and W} \subset \text{U}_1 \subset \text{U}_2 \subset \text{U}.$$

It is assumed that there exists some $t_2 \geq t_0$ such that $P(\pi(\tilde{\xi}_0, t_2)) \leq r_2$ (i.e. $\pi(\tilde{\xi}_0, t) \in U_2)\ \forall \tilde{\xi}_0 \in V \setminus W$. Then there exists some $t_1 < t_2$ such that $\pi(\tilde{\xi}_0, t_1) \in U_1 \setminus U_2$ because $\pi(\tilde{\xi}_0, t)$ is continuous in t. Since $P(\pi(\tilde{\xi}_0, t_1)) > P(\pi(\tilde{\xi}_0, t_2))$, then there must exists some $\hat{t} \in [t_1, t_2]$ such that $\dot{P}(\pi(\tilde{\xi}_0, \hat{t})) < 0$ and $\pi(\tilde{\xi}_0, \hat{t}) \in U$. However, $\dot{P}(u) > c\ \forall \tilde{\xi}_0 \in U \setminus V$ goes out from U. On the other hand, there exists some $\tilde{t}$ such that $\pi(\tilde{\xi}_0, \tilde{t})\ \forall \tilde{\xi}_0 \in U \setminus V$ goes out from U. In the similar manner, there does not exists

$t_3 > \tilde{t}$ such as $\pi(\tilde{\xi}_0, t_3) \in U_2$. Thus, there exists sufficiently large time T such that $\forall \tilde{\xi}_0 \in V \setminus W,\ \forall t \geq T,\ \pi(\tilde{\xi}_0, \tilde{t}) \cap U_2 = \emptyset$. It is clear that $P(\pi(\tilde{\xi}_0, t)) > r_2\ \forall t \geq T$. □

3.6 Reproduction number and stability

Stability analysis of disease state equilibria for a class of epidemic models governed by (3.1a), (3.1b) satisfying conditions $(C_1), (C_2)$ and (C_3) were given in the previous sections. The state variables in an epidemiological model represent fractions of the population and so they should remain nonnegative as time goes forward.

The condition (C_1) assumes that the solution space is a positively invariant manifold. The nonnegative cone $\mathbb{R}^n_+$ is positively invariant for the family $\boldsymbol{f}(\boldsymbol{z}, \boldsymbol{q})$. Only the positive cone $\mathbb{R}^n_+$ of the epidemic parameters space $\mathbb{R}^n_+$ is of interest. The condition is equivalent to the following.

$(C_1)'$ Write each $f_i(\boldsymbol{z}, \boldsymbol{q})$ uniquely in the form $f_i(\boldsymbol{z}, \boldsymbol{q}) = f_{i,1}(\boldsymbol{z}, \boldsymbol{q}) + x_i f_{i,2}(\boldsymbol{z}, \boldsymbol{q})$ where $f_{i,1}$ does not depend on x_i. to requiring for each i that

$$\forall \boldsymbol{q} \geq 0\ \forall \boldsymbol{z},\quad f_{i,1}(\boldsymbol{z}; \boldsymbol{q}) \geq 0.$$

The condition (C_2) assume that the disease free subspace is positively invariant. This condition is equivalent to the following statement.

$(C_2)'$ The subspace V of $\mathbb{R}^n$ defined by $z_1 = \ldots = z_d = 0$, where $d < n$, is invariant for the family $\boldsymbol{f}(\boldsymbol{z}, \boldsymbol{q})$. Let us write $\boldsymbol{z} = \boldsymbol{y}, \boldsymbol{x}$ with $\boldsymbol{y} = z_1, \ldots, z_d$ and $\boldsymbol{x} = z_{d+1}, \ldots, z_n$. This condition is equivalent to requiring that

$$\forall i = 1, \ldots, d, f_i(0, \boldsymbol{x}, \boldsymbol{q}) = 0.$$

The LaSalle's invariance principle in Theorem 3.15 and Theorem 3.19 (Poincare-Bendixson) however are very hard to implement. In particular it is impossible to provide generic Lyapunov and ω_+-limit functions for epidemic models with three or more disease state variables. Therefore, the additional condition (C_3) states that in the absence of the disease, the population has a stable equilibrium. Given a disease free equilibrium $(0, \psi(\boldsymbol{q}))$ such that $\psi(\boldsymbol{q})$ is locally asymptotically stable for the family of vector fields $h(\boldsymbol{x}, \boldsymbol{q})$. For the considered family of vector fields $\boldsymbol{f}(\boldsymbol{z}, \boldsymbol{q})$, the condition (C_3) is equivalent to the following statement.

$(C_3)'$ There exists a smooth map $\psi : U\mathbb{R}^{nd}$ such that $\psi(\boldsymbol{q})$ is a hyperbolic locally asymptotically stable equilibrium of $h(\boldsymbol{x}, \boldsymbol{q})$.

Condition $(C_3)'$ is reasonable from a biological perspective and is useful from a mathematical perspective because of Theorem 3.25 below. To set up the theorem

however, it is necessary to recall two class of matrices namely, Z-matrices and M-matrices which are used in the theorem.

A real matrix is called nonnegative if all its entries are nonnegative. It is called a $Z-$matrix if all its off-diagonal entries are nonpositive (i.e less or equal to zero). A matrix $A = (a_{ij})$ is called a $Z-$Matrix if $a_{ij} \leq 0,\ i \neq j$. A matrix $A = (a_{ij})$ is called an M-Matrix if $a_{ij} \leq 0$ whenever $i \neq j$ and all principal minors of A are positive. An M matrix is a Z-matrix with eigen-values whose real parts are positive. These two classes of matrices are useful in spectral analysis of certain classes of matrices [176]. A matrix A with nonpositive off-diagonal elements is an M-matrix if and only if A is non singular and A^{-1} is nonnegative [176]. A $d \times d$ matrix A is an M-matrix if and only if it may be written in the form $A = sI_dB$, where B is nongenative and $s > \rho(B)$. Here $\rho(.)$ stands for the *spectral radius*.

Recall also that a square matrix A is called *reducible* if there exists a permutation matrix P such that PAP^t is block triangular, where P^t denotes matrix transpose of P. Otherwise, it is called *irreducible*. A fundamental result concerning nonnegative matrices is the following theorem known as the Perron-Frobenius theorem.

Theorem 3.23. *(Perron-Frobenius) Let A be a real $d \times d$ irreducible matrix. Then $\rho(A)$ is a simple eigenvalue of A. Moreover, it has an eigen-vector w with positive entries, i.e., $w_i > 0$ for $i = 1, \ldots, d$.*

The following lemma gives two characterizations of M-matrices [172].

Lemma 3.24. *Let $A = (a_{i,j})$ be a $d \times d$ real Z-matrix and let D be the diagonal matrix whose i^{th} diagonal entry is $a_{i,i}$. Then the following properties are equivalent.*

i) A is an M-matrix.

ii) All the diagonal entries of A are positive and $\rho\left(I_d - D^{-1}A\right) < 1$.

iii) All the leading principal minors of A are positive.

A classical approach for the study of the local asymptotic stability of the system (3.1a)

$$\boldsymbol{z}' = \boldsymbol{f}(\boldsymbol{z}; \boldsymbol{q})$$

near an equilibrium $\boldsymbol{z}^*$ consists in considering the linear differential system

$$\boldsymbol{w}' = \partial_{\boldsymbol{z}}\boldsymbol{f}(\boldsymbol{z}^*; \boldsymbol{q}).\boldsymbol{w} \tag{3.5}$$

where $\partial_{\boldsymbol{z}}\boldsymbol{f}(\boldsymbol{z}^*; \boldsymbol{q})$ stands for the Jacobian matrix, with respect to $\boldsymbol{z}$, of $\boldsymbol{f}$ at $\boldsymbol{z}^*$. The flow generated by the differential system (3.5) is nothing but $\exp(t\partial_{\boldsymbol{z}}\boldsymbol{f}(\boldsymbol{z}^*; \boldsymbol{q})).\boldsymbol{w} =$

$\partial_{\boldsymbol{z}}\boldsymbol{l}(\boldsymbol{z}^*, t; \boldsymbol{q}).\boldsymbol{w}$. In particular, the origin $\boldsymbol{0}$ which is an equilibrium of the system (3.5) is asymptotically stable if and only if all the eigenvalues of the matrix $\partial_{\boldsymbol{z}}\boldsymbol{f}(\boldsymbol{z}^*; \boldsymbol{q})$ have a negative real part.

Theorem 3.25. . *Consider the class of epidemic models in (3.1a), (3.1b) where $\boldsymbol{f}(\boldsymbol{z}; \boldsymbol{q})$ satisfies the conditions $(C_1)'$ and $(C_2)'$. Let us write $\boldsymbol{z} = (\boldsymbol{y}, \boldsymbol{x})$ where $\boldsymbol{y} = (z_1, z_2 \ldots, z_d)$ is the vector corresponding to infected compartments and $\boldsymbol{x} = (z_{d+1}, \ldots, z_n)$ is the vector corresponding to susceptible compartments and let $\psi : P \to \mathbb{R}^{n-d}$ be a smooth map, where $P \subset \mathbb{R}^k_+$ is an open set. Let*

$$g(\boldsymbol{y}; \boldsymbol{q}) = (f_1(\boldsymbol{y}, \psi(\boldsymbol{q}); \boldsymbol{q}), \ldots, f_d(\boldsymbol{y}, \psi(\boldsymbol{q}); \boldsymbol{q}))$$

and

$$h(\boldsymbol{x}; \boldsymbol{q}) = (f_{d+1}(0, \boldsymbol{x}; \boldsymbol{q}), ..., f_n(0, \boldsymbol{x}; \boldsymbol{q})).$$

Then the following properties are satisfied:

i) The Jacobian matrix, $\partial_{\boldsymbol{z}} f(0, \psi(\boldsymbol{q}); \boldsymbol{q})$, of $\boldsymbol{f}$ at $(0, \psi(\boldsymbol{q}))$ has the form

$$\begin{pmatrix} \partial_{\boldsymbol{y}} g(0; \boldsymbol{q}) & 0 \\ B & \partial_{\boldsymbol{x}} h(\psi(\boldsymbol{q}); \boldsymbol{q}) \end{pmatrix}$$

and $\partial_y g(0; \boldsymbol{q})$ is a Z-matrix.

ii) The point $(\psi(0, \boldsymbol{q})$ is a hyperbolic locally asymptotically stable equilibrium of $\boldsymbol{f}(\boldsymbol{z}; \boldsymbol{q})$ if and only if the point $\psi(\boldsymbol{q})$ for the vector field $h(\boldsymbol{x}; \boldsymbol{q})$ and $\partial_{\boldsymbol{y}} g(0; \boldsymbol{q})$ is an M-matrix.

Proof. The vector field $h(\boldsymbol{y}, \boldsymbol{q})$, which is the restriction of $\boldsymbol{f}(\boldsymbol{z}, \boldsymbol{q})$ to the disease free subspace, governs the behavior of the population in the absence of the disease.

i) Clearly, $\partial_{y_i} f(0, \psi(\boldsymbol{q}); \boldsymbol{q}) = \partial_{\boldsymbol{y}} g(0; \boldsymbol{q})$ and $\partial_{x_j} f(0, \psi(\boldsymbol{q}); \boldsymbol{q}) = \partial_{x_j} h(\psi(\boldsymbol{q}); \boldsymbol{q})$

$$\begin{pmatrix} \partial_{\boldsymbol{y}} g(0; \boldsymbol{q}) & C \\ B & \partial_{\boldsymbol{x}} h(\psi(\boldsymbol{q}); \boldsymbol{q}) \end{pmatrix}.$$

By an assumption of satisfying condition $(C_2)'$ each $f_i(\boldsymbol{y}, \boldsymbol{x}; \boldsymbol{q}), i = 1, ..., d$ can be written in the form $f_i(\boldsymbol{y}, \boldsymbol{x}; \boldsymbol{q}) = \sum_1^d v_k(\boldsymbol{y}, \boldsymbol{x}; \boldsymbol{q}) y_k$. This gives $\partial_{x_i} f_i(0, \psi(\boldsymbol{q}); \boldsymbol{q}) = 0$ and so $C = 0$. On the other hand, By assumption (C_1) $f_i(\boldsymbol{y}, \boldsymbol{x}; \boldsymbol{q}) \geq 0$ for any $x \geq 0$ and any $y \geq 0$ such that $y_i = 0$. In particular, for $x = \psi(\boldsymbol{q})$ and $i = 1, ..., d$ $f_i(\boldsymbol{y}, \psi(\boldsymbol{q}); \boldsymbol{q}) = g_i(\boldsymbol{y}; \boldsymbol{q}) \geq 0$ for any $y \geq 0$ such that $y_i = 0$. This shows that $\mathbb{R}^n_+$ is positively invariant for the family of vector fields $g(\boldsymbol{y}; \boldsymbol{q})$, and since 0 is an equilibrium of $g(\boldsymbol{y}; \boldsymbol{q})$ it follows from Lemma 4.1 that $\partial_y g(0; \boldsymbol{q})$ is a *Z-matrix*.

ii) Clearly, $(0, \psi(\boldsymbol{q}))$ is an equilibrium of $f(\boldsymbol{y}, \boldsymbol{x}; \boldsymbol{q})$ if and only if so is $\psi(\boldsymbol{q})$ for $h(\boldsymbol{x}; \boldsymbol{q})$. Moreover, the triangular structure of the matrix $\partial_{\boldsymbol{z}} f(0, \psi(\boldsymbol{q}); \boldsymbol{q})$ implies that its characteristic polynomial is the product of the characteristic polynomials of $\partial_{\boldsymbol{y}} g(0; \boldsymbol{q})$ and $\partial_{\boldsymbol{x}} h(\psi(\boldsymbol{q}); \boldsymbol{q})$ This shows that $(0, \psi(\boldsymbol{q}))$ is hyperbolic and stable, i.e., all the eigenvalues of $\partial_{\boldsymbol{x}} h(\psi(\boldsymbol{q}); \boldsymbol{q})$ have a negative real part, if and only if so is $\psi(\boldsymbol{q}$ for $\partial_{\boldsymbol{y}} g(0; \boldsymbol{q})$ is an *M-matrix*.

□

The following corollary holds for the class of epidemic models satisfying conditions $(C_1)'$-$(C_3)'$.

Corollary 3.26. *Consider the class of epidemic models (3.1a), (3.1b) where $f(\boldsymbol{z}; \boldsymbol{q})$ satisfies the conditions $(C_1)'$-$(C_3)'$. Then the following properties are equivalent.*

i) The equilibrium $(0, \psi(\boldsymbol{q}))$ of $\boldsymbol{f}(\boldsymbol{z}, \boldsymbol{q})$ is hyperbolic and locally asymptotically stable.

ii) All the diagonal entries of the matrix $\partial_y g(0; \boldsymbol{q})$ are negative and $\rho(I_d - D^{-1}\partial_y g(0; \boldsymbol{q})) \leq 1$, where D is the diagonal matrix having the same diagonal as $\partial_y g(0; \boldsymbol{q})$.

iii) All the leading principal minors of the matrix $\partial_y g(0; \boldsymbol{q})$ are positive

where I_d is the identity matrix of dimension $d \times d$.

Proof. By Theorem 3.25 and assumption $(C_3)'$, $(0, \psi(p))$ is hyperbolic and locally asymptotically stable if and only if $\partial_y g(0; \boldsymbol{q})$ is an M-matrix. The fact that *i*) is equivalent to *ii*) and *iii*) is then a direct consequence of Lemma 3.24. □

This result means $\rho(I_d - D^{-1}\partial_y g(0; \boldsymbol{q}))$ is a threshold value to justify whether an equilibrium $(0, \psi(\boldsymbol{q}))$ of $\boldsymbol{f}(\boldsymbol{z}, \boldsymbol{q})$ is hyperbolic and locally asymptotically stable or not. If $\rho(I_d - D^{-1}\partial_y g(0; \boldsymbol{q})) \leq 1$ then $(0, \psi(\boldsymbol{q}))$ is hyperbolic and locally asymptotically stable, otherwise unstable. The spectral radius of matrix $I_d - D^{-1}\partial_y g(0; \boldsymbol{q})$ is less than one if and only if all the leading principal minors of the matrix $\partial_y g(0; \boldsymbol{q})$ are positive.

The threshold value $\rho(I_d - D^{-1}\partial_y g(0; \boldsymbol{q}))$ is referred to as *basic reproduction number* [93], [177], or *basic reproduction ratio* [92], and is denoted by R_o. Thus

Definition 3.27.

$$R_o = \rho(I_d - D^{-1}\partial_y g(0; \boldsymbol{q})). \tag{3.6}$$

Matrix $I_d - D^{-1}\partial_y g(0; \boldsymbol{q})$ is referred to as *next generation matrix* [92] for the class of epidemic models (3.1a), (3.1b) satisfying conditions $(C_1)'$-$(C_3)'$ and can be thought of as the number of cases one case generates on average over the course of its infectious

period, in an otherwise uninfected population. R_o is useful because it helps determine whether or not an infectious disease can spread through a population. When $R_0 \leq 1$ the infection will die out in the long run. But if $R_0 > 1$, the infection will be able to remain in the population indefinitely.

3.7 Disease control problem

An important motivation behind mathematical modelling the spread of infectious diseases is evaluation of alternative control policies. One approach to this is *via* optimal control theory. Let us define the disease control set

$$\Phi = \{\phi(t) = (\phi_1(t), \ldots, \phi_m(t)) |\, a \leq \phi_j(t) \leq b,\ 0 \leq t \leq t_F\}$$

for $a, b, t_F > 0$. $\phi(t)$ represents a set of policies to control the diseases from an initial time $t = 0$ to a final time t_F .

It is assumed that the dynamics of diseases are modeled by

$$\boldsymbol{z}'(t) = f(t, \boldsymbol{z}, \phi; p) \tag{3.7a}$$

$$\boldsymbol{z}(0) = \boldsymbol{z}_0, \boldsymbol{z}_0 \in \Omega \tag{3.7b}$$

where

$$f = (f_1, \ldots, f_n) : \mathbb{R}_+ \times \mathbb{R}_+^n \times \mathbb{R}_+^m \longrightarrow \mathbb{R}_+^n$$

is continuous and has continuous first order partial derivatives with respect to $\boldsymbol{z}$ and u. The f_i are continuous functions and the first derivatives with respect to z_i, ϕ_j and t for all $i = 1, \ldots, n$ and $j = 1, \ldots, m$ are also continuous functions. Setting $\phi_j = 0, \forall j = 1, \ldots, m$ reduces (3.7) into the disease dynamics without control (3.7).

It is assumed that the disease control $\phi(t) = (\phi_j(t))$ for $j = 1, \ldots, m$ are Lebesgue measurable functions. The existence of solutions to the initial value problem (3.7) is guaranteed by the following theorem

Theorem 3.28. *Starting from an initial value $\boldsymbol{z}_0 \in \Omega$ IVP, (3.7) has bounded solutions $\boldsymbol{z}(t, \phi; \boldsymbol{z}_0) \in \mathbb{R}_+^n$ passing through the initial condition.*

Proof. Since the disease controls $\phi_j(t)$ $j = 1, \ldots, m$ are Lebesgue measurable functions, the right hand side of differential equations in (3.7) is continuous in the disease state variable $\boldsymbol{z}(t)$ but only measurable in t for fixed $\boldsymbol{z}$. The existence of solutions is guaranteed by results in [178], [179]. □

The problem of designing optimal disease control policies is equivalent to the prob-

lem of finding *optimal policies* $\boldsymbol{z}^*(t, \phi^*(t)) \in \Omega \subseteq \mathbb{R}^n_+$ such that

$$J[\phi^*] = \max_{\phi \in \Phi} J[\phi], \tag{3.8}$$

where

$$J[\phi] = \int_a^{t_F} g(t, \boldsymbol{z}, u; p) + \Upsilon(\boldsymbol{z}(\boldsymbol{z}_F))\,\mathrm{d}x. \tag{3.9}$$

Here $\Upsilon(\boldsymbol{z}(\boldsymbol{z}_F))$ is the value of disease states at the final time t_F. The problem of solving (3.7), (3.8), (3.9) is referred as an optimal disease control problem (ODCP).

Instead of searching an optimal solution in the solution domain Ω, there are sufficient and necessary conditions for an optimal solution for the ODCP (3.7), (3.8), (3.9). In the case of $\Upsilon(\boldsymbol{z}(x_F)) = 0$ the sufficient condition for existence of an optimal control for the optimal control problem is guaranteed by the following theorem

Theorem 3.29. *Let* $M > 0$ *and* $D^+ = \{(y^o, y) \,|\, \exists v \in U, y = g(t, z, u; p),\, y^o \geq g(t, z, u; p)\}$. *If*

- $\exists M > 0$, $|z(t, u)| \leq M$ *for all* $u \in U$ *and* $t \in [0, t_F]$
- g *is lower semi-continuous, (ie.,* $\liminf_{z \to z_*} g(\boldsymbol{z}) \geq g(\boldsymbol{z}_*)$*),* $\quad \boldsymbol{z}_* \in \Omega$,
- D^+ *is convex for* $(t, \boldsymbol{z}) \in [0, \boldsymbol{z}_F] \times \{|x| \leq M\}$

then there exists an optimal control $u^* \in U$.

For $\Upsilon(\boldsymbol{z}(x_F)) \neq 0$, the necessary condition for the existence of an optimal solution for the optimal control problem is referred to as Pontryagins maximum principle [180], [181], [182], [183].

Theorem 3.30. *Let* $u^* \in U$ *be an optimal control of the ODCP (3.7), (3.8), (3.9). Then there exists a set of adjoint functions* $\lambda = (\lambda_i).\lambda_i : \mathbb{R} \longrightarrow \mathbb{R}^n$ *such that* $\boldsymbol{z}(t, u^*), u^*, \lambda_i$ *satisfy the state system*

$$\boldsymbol{z}'(t) = f(t, \boldsymbol{z}, u^*; p), \tag{3.10a}$$

$$\boldsymbol{z}(0) = \boldsymbol{z}_0, \boldsymbol{z}_0 \in \Omega \tag{3.10b}$$

and the adjoint system

$$\lambda'(t) = -\frac{\partial L}{\partial \boldsymbol{z}} = -\left(g_{\boldsymbol{z}}(t, \boldsymbol{z}, u^*; p) + \lambda^T.f_{\boldsymbol{z}}(t, \boldsymbol{z}, u^*; p)\right) \tag{3.11}$$

with transversality condition

$$\lambda(t_F) = \Upsilon'(\boldsymbol{z}(t_F)) \tag{3.12}$$

where L is referred to as the Hamiltonian functional

$$L(t, \boldsymbol{z}, u) = f(t, \boldsymbol{z}, u; p) + \lambda^T . g(t, \boldsymbol{z}, u; p), \tag{3.13}$$

and where T denotes the transpose.

4. DISEASE DYNAMICS IN A SINGLE REGION

This chapter presents models for analyzing the dynamics of diseases caused by multi strain influenza-A viruses among poultry and human populations in a single region. Based on modeling choices and assumptions taken in Section 4.1, a mathematical model is developed in Section 4.2. The model captures the dynamic of diseases caused by multi strain influenza-A. The model also captures a mutation process due to genetic assortment between avian flu and swine flu. In Section 4.3, three reproduction numbers are defined as the threshold value of three disease transmissions. In Section 4.4, disease state equilibria of the model are derived. The ordinates of each equilibria are presented and associated to the reproduction numbers. Section 4.5 provides stability analysis of disease state equilibria. Section 4.6 discusses disease persistence among humans. Numerical simulations are given in Section 4.7. Section 4.8 discusses the analytical and numerical results and draws some conclusions.

4.1 Modeling choices and assumptions

4.1.1 Virus strains

This study considers three influenza viruses that are spreading among linked populations of poultry and humans. The first virus, avian flu, is transmissible between birds, transmissible from birds to humans, but not between humans. The second virus, swine flu, spreads and is communicable among humans but does not infect birds. The third virus is a hypothetical virus that results from a rare mutation process in the form of recombination of avian flu and swine flu viruses [36], [37], [38], [39]. This virus is referred to as mutant-avian flu virus. The mutant virus is assumed to be able to spread among humans with epidemic potential similar to swine flu. An epidemic caused by the mutant-avian flu could become severe because of the potential to combine the ability of swine flu to spread between humans and the virulence of avian flu [22], [25].

4.1.2 Population assumptions

Only populations of poultry birds are considered in the model. While wild birds may contribute to the onset of flu among poultry birds, interactions between poultry and wild birds are not likely to contribute significantly to spread of avian flu among poultry

birds [49]. Wild birds are extremely unlikely to contribute to the spread of avian flu among humans [49].

Populations of birds and humans change over time due to births, deaths, migration and other means of movements. However, the net of change in total population is assumed to be negligibly small over the time interval over which the model is applied (a few weeks or a few months). Here, total bird and human populations are assumed to be constant.

It is assumed that individuals in the interrelated population of poultry birds (or birds for short) and humans are assigned to compartments, each representing a specific disease stage. Each sub population in any compartment is assumed to be homogeneous in the sense that individuals have the same infectious periods, immunity periods, and contact rates with individuals in other sub populations. Disease transmissions among birds and humans are modeled on the mass action incident assumption, where the number of effective contacts is constant.

An infection is transmitted through contacts between the infectious and the susceptible individuals (horizontal transmission). Therefore, it is assumed that all newborns are susceptible.

4.1.3 Avian flu dynamic among the bird population

Let $S_p(t)$ be the compartment for susceptible poultry birds. It is assumed that susceptible bird offspring and the restocking of birds result in population growth of $\eta_p S_p(t)$. Death among susceptible birds removes birds at a rate of $\delta_p S_p(t)$. It is assumed that η_p and δ_p are independent of time t.

Let $I_p(t)$ be the compartment of infectious birds. A susceptible bird becomes infectious at the rate of $\alpha_p \kappa_p \, I_p(t) S_p(t)$, where α_p is the avian flu transmission rate from infectious birds to susceptible birds and κ_p is the number of effective contacts between an infectious bird and susceptible birds per unit time. Avian influenza is highly pathogenic among birds. Death among infected birds however, may be caused by natural incidence or by the disease. Infected birds are removed at a rate of $(\delta_p + m_p) I_p(t)$. Here, m_p can be considered as the avian flu virulence in the bird population. It is assumed that α_p, κ_p, m_p are independent of time t. Thus, the bird system follows a simple SI model

$$S_p' = \eta_p - \delta_p \, S_p - \alpha_p \kappa_p I_p S_p \tag{4.1a}$$

$$I_p' = \alpha_p \kappa_p I_p S_p - (\delta_p + m_p) I_p. \tag{4.1b}$$

4.1.4 Disease dynamic among humans

Let $S_h(t)$ denote the compartment for susceptible humans. Human offspring are assumed to be susceptible to the diseases. It is assumed that human offspring and susceptible immigrants enter the population at a rate of η_h. Death removes susceptible humans at a rate $\delta_h S_h(t)$.

Human infection by avian flu occurs by means of direct virus transmission from infectious birds to humans [24]. Susceptible humans become infected by avian flu at a rate of $\alpha_{ph}\,\kappa_{ph}\,I_p(t)S_h(t)$, where α_{ph} is the avian flu transmission rate from infectious poultry birds to susceptible human and κ_{ph} is the number of effective contacts between an infectious bird and susceptible humans per unit time.

Existing models of the disease spread and control of avian flu among humans, such as in [103],[104], consider one infected disease state only. Here, infected humans with avian flu are classified as asymptomatic and symptomatic. Let $I_a(t)$ and $I_b(t)$ be the compartments for asymptomatic or symptomatic humans with avian flu, respectively. This partition is important, since individuals in these groups are treated differently. Asymptomatic individuals are usually still active while symptomatic individuals are very sick and are usually isolated [16], [17], [28]. Since the mutations considered here require further infection of swine flu and hence contact with swine flu infected humans, only asymptomatic individuals are modeled as having the potential to host a virus mutation.

A human infected with avian flu may be asymptomatic with probability γ and symptomatic with probability $1-\gamma$. Therefore susceptible humans move to the states of asymptomatic at a rate of $\gamma\alpha_{ph}\,\kappa_{ph}\,I_p(t)S_h(t)$ and move to the states of symptomatic at a rate of $(1-\gamma)\alpha_{ph}\,\kappa_{ph}\,I_p(t)S_h(t)$,

Death among infected humans with avian flu may be caused by a natural incidence or by the disease. They are removed at a rate of $(\delta_h + m_a)I_a(t)$ and $(\delta_h + m_b)I_b(t)$, where m_a and m_b can be considered as avian flu virulence on asymptomatic humans and symptomatic humans, respectively.

Consider a second virus, swine flu, which is spreading and communicable among humans with a transmission rate of α_{sh}. Let $I_s(t)$ denote the compartment of humans infected by swine flu. A susceptible human becomes infectious with swine flu at the rate of $\alpha_{sh}\,\kappa_{sh}\,I_s(t)S_h(t)$, where κ_{sh} is the effective number of contacts among humans per unit time in normal circumstance. Humans infected by swine flu are removed at a rate of $(\delta_h + m_s)I_s(t)$. Here, m_s can be considered as the swine flu virulence in the human population.

It is assumed here that a pandemic threat posed by avian flu virus mutation is a result of re-combination between avian flu and swine flu. It is assumed that a double virus co-infection happens only when an infected but asymptomatic human with avian flu is

subsequently infected by swine flu. Suppose the co-infection happens at the rate of α_{sa}. Therefore $\alpha_{sa}\,\kappa_{sa}\,I_s(t)I_a(t)$ can be considered as the *transmission of co-infection*, where κ_{sa} is the effective number of contacts between infected but asymptomatic humans of avian flu and infectious humans with swine flu.

It is assumed that the virus re-combination of avian flu and swine flu mutate *in vivo* into a new avian flu virus strain with a probability of mutation μ. The virus is referred to as mutant-avian flu virus. It is assumed that the virus has the ability to transmit between humans at a rate of α_{mh}. Let $I_m(t)$ be the compartment for infectious humans with mutant-avian flu. A susceptible human becomes infectious with mutant-avian flu at the rate of $\alpha_{mh}\,\kappa_{mh}\,I_m(t)S_h(t)$.

Based on the above assumptions, the dynamic of the diseases among humans can be modeled as

$$S_h' = \eta_h - \delta_h\,S_h - \alpha_{ph}\kappa_{ph}I_pS_h - \alpha_{sh}\kappa_{sh}I_sS_h - \alpha_{mh}\kappa_{mh}I_mS_h \tag{4.2a}$$

$$I_s' = \alpha_{sh}\kappa_{sh}I_sS_h - (\delta_h + m_s)\,I_s \tag{4.2b}$$

$$I_a' = \gamma\alpha_{ph}\kappa_{ph}I_pS_h - \mu\alpha_{sa}\kappa_{sa}I_sI_a - (\delta_h + m_a)\,I_a \tag{4.2c}$$

$$I_b' = (1-\gamma)\alpha_{ph}\kappa_{ph}I_pS_h - (\delta_h + m_b)\,I_b \tag{4.2d}$$

$$I_m' = \mu\alpha_{sa}\kappa_{sa}I_sI_a + \alpha_{mh}\kappa_{mh}I_mS_h - (\delta_h + m_m)\,I_m. \tag{4.2e}$$

4.2 Diseases transmission model for a single region

It is obvious from (4.1a, 4.1b) and (4.2a − 4.2e) that disease dynamics among birds are independent of the disease dynamics among humans. However the disease dynamics among humans does depend on the disease dynamics in the bird world. Figure 4.1 shows a schematic diagram of the compartments of the bird and human populations.

Let $Z(t)$ be the vector of disease state variables for the linked population of birds and humans.

$$Z(t) = (S_p(t), I_p(t), S_h(t), I_s(t), I_a(t), I_b(t), I_m(t))$$

and $\Omega_1 \subseteq \mathbb{R}_+^7$ be the set of all disease states

$$\Omega = \{Z(t)\,|\,0 \le t < \infty\}.$$

For a given set of epidemic parameters $q \in Q_1 \subseteq \mathbb{R}_+^{21}$

$$\begin{aligned} Q_1 =&\{q|q = (q_j),\ q_j = \eta_p, \eta_h, \delta_p, \delta_h, \alpha_p, \alpha_{sh}, \alpha_{ph}, \mu, \alpha_{sa}, \alpha_{mh}, \kappa_p, \kappa_{sh}, \kappa_{ph}, \kappa_{sa}, \kappa_{mh},\\ &m_p, m_a, m_b, m_s, m_m, \gamma\} \end{aligned}$$

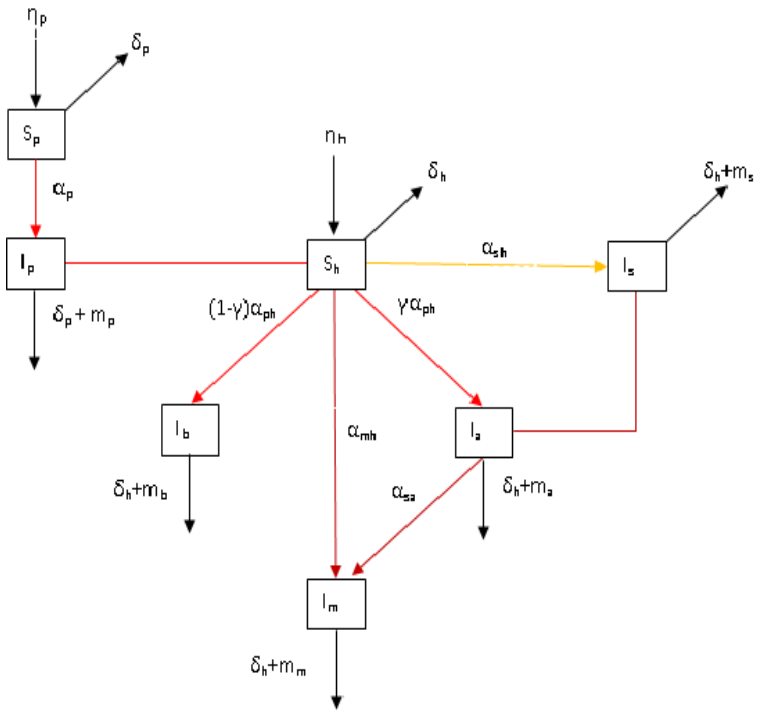

Fig. 4.1: Compartments of humans and bird populations. The red line is avian flu transmission, the yellow line is swine flu transmission, the brown line is mutant-avian flu transmission.

and an initial disease state

$$Z(0) = Z_0,\ Z_0 = (S_{p_0}, I_{p_0}, S_{h_0}, I_{s_0}, I_{a_0}, I_{b_0}, I_{m_0}) \in \Omega,$$

the dynamics of the disease state $Z(t)$ is described by the initial value problem (IVP)

$$S_p' = \eta_p - \delta_p S_p - \alpha_p \kappa_p I_p S_p \tag{4.3a}$$
$$I_p' = \alpha_p \kappa_p I_p S_p - (\delta_p + m_p) I_p \tag{4.3b}$$
$$S_h' = \eta_h - \delta_h S_h - \alpha_{ph} \kappa_{ph} I_p S_h - \alpha_{sh} \kappa_{sh} I_s S_h - \alpha_{mh} \kappa_{mh} I_m S_h \tag{4.3c}$$
$$I_s' = \alpha_{sh} \kappa_{sh} I_s S_h - (\delta_h + m_s) I_s \tag{4.3d}$$
$$I_a' = \gamma \alpha_{ph} \kappa_{ph} I_p S_h - \mu \alpha_{sa} \kappa_{sa} I_s I_a - (\delta_h + m_a) I_a \tag{4.3e}$$
$$I_b' = (1-\gamma) \alpha_{ph} \kappa_{ph} I_p S_h - (\delta_h + m_b) I_b \tag{4.3f}$$
$$I_m' = \mu \alpha_{sa} \kappa_{sa} I_s I_a + \alpha_{mh} \kappa_{mh} I_m S_h - (\delta_h + m_m) I_m, \tag{4.3g}$$
$$Z(0) = Z_0,\ Z_0 \in \Omega. \tag{4.3h}$$

The existence of a solution for IVP $(4.3a) - (4.3g)$ and (4.3h) is guaranteed by the following lemma.

Lemma 4.1. *For a given set of disease parameter $q \in Q_1$ and initial condition $Z_0 \in \Omega_1$,*

there is a solution, $Z(t; q, Z_0)$, for the IVP $(4.3a) - (4.3g)$ and (4.3h).

Proof. The disease state variable Z has a mixed structure between infected and uninfected. It is convenient to group the disease state variables into infected and uninfected compartments. For this reason, the state variable will be reordered so that the first five elements of the new state variable correspond to infected sub-populations. The disease state vector becomes $\bar{Z} = (I_p, I_s, I_a, I_b, I_m, S_p, S_h)$. Under the ordered variable $\bar{Z}$, the right hand side of system of differential equations $(4.3a) - (4.3g)$ can be written as

$$f = \hat{f} + \breve{f} \tag{4.4}$$

where

$$\hat{f} = \begin{bmatrix} \alpha_p \kappa_p I_p S_p \\ \alpha_{sh} \kappa_{sh} I_s S_h \\ \gamma \alpha_{ph} \kappa_{ph} I_p S_h - \mu \alpha_{sa} \kappa_{sa} I_s I_a \\ (1-\gamma) \alpha_{ph} \kappa_{ph} I_p S_h \\ \mu \alpha_{sa} \kappa_{sa} I_s I_a + \alpha_{mh} \kappa_{mh} I_m S_h \\ -\alpha_p \kappa_p I_p S_p \\ -\alpha_{ph} \kappa_{ph} I_p S_h - \alpha_{sh} \kappa_{sh} I_s S_h - \alpha_{mh} \kappa_{mh} I_m S_h \end{bmatrix}, \quad \breve{f} = \begin{bmatrix} -(\delta_p + m_p) I_p \\ -(\delta_h + m_s) I_s \\ -(\delta_h + m_a) I_a \\ -(\delta_h + m_b) I_b \\ -(\delta_h + m_m) I_m \\ \eta_p - \delta_p S_p \\ \eta_h - \delta_h S_h \end{bmatrix}.$$

The component $\hat{f}$ models the rate of new infections, while the component $\breve{f}$ models the rates of transfer due to births, deaths, disease mortality. The system described $(4.3a) - (4.3g)$ is an *autonomous* system, because f does not depend on time. Therefore, if $\bar{Z}(t; q)$ is a solution of the system on interval $t \in (t_1, t_2)$ then for any real number $\tau \in \Re^1$, the function $\bar{Z}(t - \tau; q)$ is a solution of the system on interval $(t_1 + \tau, t_2 + \tau)$. Thus, given an initial condition $\bar{Z}_0$ as a solution at initial time $t_0 \in T$, the existence of a solution at a future time $t > t_0$ is guaranteed. □

Furthermore, the solution is unique and non-negative. This is formalized in the following theorem.

Theorem 4.2. *For a given set of disease parameter $q \in Q_1$ and initial condition $Z_0 \in \Omega_1$, the IVP $(4.3a) - (4.3g)$ and (4.3h) has a unique non negative solution $Z(t; q, Z_0)$.*

Proof. The reordered disease state variable $\bar{Z}$ can be written as

$$\bar{Z} = (V, W)$$

where $V = (I_p, I_s, I_a, I_b, I_m)$ and $W = (S_p, S_h)$. The set of disease states becomes

$$\Omega_1 = \{\bar{Z} = (V, W) : \bar{Z} \geq 0\}.$$

Note that the reordered disease states variable $\bar{Z}$ only been used in a section that is required to define a reproduction number. Let

$$D_1 = \{\bar{Z} = (V, W) : V = (0, 0, 0, 0, 0)\}$$

be the set of disease free states. All disease parameters, $q_i \geq 0$ for all $q_i \in Q$, for any initial disease state $\bar{Z}(0)$, Ω_1 and D_1 are positively invariant under f. Therefore, the uniqueness of the solution is guaranteed by Theorem 3.4 in Section 3.2.

Let $K \subset \Omega$ be a compact set containing the initial condition $(\bar{Z}(0))$. Since $(4.3a) - (4.3g)$ is an autonomous system, the solution $\bar{Z}(t, t_0, \bar{Z}(0); q)$ can be uniquely extended forward in time t up to the boundary of D_1, (Theorem 1.1.9 of [170]). □

4.3 Reproduction numbers

In Section 2.2, the reproduction number was defined as the expected number of secondary infections produced in a completely susceptible population by a typical infected individual during the individuals entire period of infection. If the reproduction number is less than or equal to one then the disease free equilibrium is locally asymptotic stable and so the disease cannot invade the population. But if the reproduction number is greater than one, then the a disease free equilibrium is unstable and the disease may invade the population.

In the reordered notation of the disease state variable, $\bar{Z}$, the disease state equilibria Z_i^* can be written as $\bar{Z}_i^* = (V_i^*, W_i^*)$, where V_i^* corresponds to infected compartments $V_i^* = (I_{p_1}^*, I_{s_1}^*, I_{a_1}^*, I_{b_1}^*, I_{m_1}^*)$ and $W_1^* = (S_{p_1}^*, S_{h_1}^*)$. The disease free equilibrium state Z_1^* has five disease free compartments,

$$V^* = (I_{p_1}^*, I_{s_1}^*, I_{a_1}^*, I_{b_1}^*, I_{m_1}^*) = (0, 0, 0, 0, 0).$$

Therefore, using the decomposition of f in (4.4), only the first five elements are considered, and so $f_1 = \hat{f}_1 + \breve{f}_1$ becomes

$$f_1 = \begin{bmatrix} \alpha_p \kappa_p I_p S_p \\ \alpha_{sh} \kappa_{sh} I_s S_h \\ \gamma \alpha_{ph} \kappa_{ph} I_p S_h - \mu \alpha_{sa} \kappa_{sa} I_s I_a \\ (1-\gamma) \alpha_{ph} \kappa_{ph} I_p S_h \\ \mu \alpha_{sa} \kappa_{sa} I_s I_a + \alpha_{mh} \kappa_{mh} I_m S_h \end{bmatrix} + \begin{bmatrix} -(\delta_p + m_p) I_p \\ -(\delta_h + m_s) I_s \\ -(\delta_h + m_a) I_a \\ -(\delta_h + m_b) I_b \\ -(\delta_h + m_m) I_m \end{bmatrix}$$

The Jacobian matrices of $\hat{f}_1$ and $\breve{f}_1$ are

$$J_{\hat{f}_1} = \begin{bmatrix} \alpha_p\kappa_p S_p & 0 & 0 & 0 & 0 \\ 0 & \alpha_{sh}\kappa_{sh}S_h & 0 & 0 & 0 \\ \gamma\alpha_{ph}\kappa_{ph}S_h & -\mu\alpha_{sa}\kappa_{sa}I_a & -\mu\alpha_{sa}\kappa_{sa}I_s & 0 & 0 \\ (1-\gamma)\alpha_{ph}\kappa_{ph}S_h & 0 & 0 & 0 & 0 \\ 0 & \mu\alpha_{sa}\kappa_{sa}I_a & \mu\alpha_{sa}\kappa_{sa}I_s & 0 & \alpha_{mh}\kappa_{mh}S_h \end{bmatrix}$$

and

$$J_{\breve{f}_1} = \begin{bmatrix} -(\delta_p + m_p) & 0 & 0 & 0 & 0 \\ 0 & -(\delta_h + m_s) & 0 & 0 & 0 \\ 0 & 0 & -(\delta_h + m_a) & 0 & 0 \\ 0 & 0 & 0 & -(\delta_h + m_b) & 0 \\ 0 & 0 & 0 & 0 & -(\delta_h + m_m) \end{bmatrix},$$

respectively. Substituting Z_1^* into $J_{\hat{f}_1}$ and $J_{\breve{f}_1}$ results in

$$\hat{F}_1 = \begin{bmatrix} \frac{\eta_p\alpha_p\kappa_p}{\delta_p} & 0 & 0 & 0 & 0 \\ 0 & \frac{\eta_h\alpha_{sh}\kappa_{sh}}{\delta_h} & 0 & 0 & 0 \\ \frac{\gamma\alpha_{ph}\kappa_{ph}\eta_h}{\delta_h} & 0 & 0 & 0 & 0 \\ \frac{(1-\gamma)\alpha_{ph}\kappa_{ph}\eta_h}{\delta_h} & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & \frac{\eta_h\alpha_{mh}\kappa_{mh}}{\delta_h} \end{bmatrix}$$

and

$$\breve{F}_1 = \begin{bmatrix} -(\delta_p + m_p) & 0 & 0 & 0 & 0 \\ 0 & -(\delta_h + m_s) & 0 & 0 & 0 \\ 0 & 0 & -(\delta_h + m_a) & 0 & 0 \\ 0 & 0 & 0 & -(\delta_h + m_b) & 0 \\ 0 & 0 & 0 & 0 & -(\delta_h + m_m \end{bmatrix}.$$

$\hat{F}_1 \cdot \breve{F}_1^{-1}$ (where $\breve{F}_1^{-1}$ is the inverse matrix of $\breve{F}_1$) is referred to as the *next generation matrix* (Section 3.6). The characteristic polynomial of the matrix is

$$\mathcal{C}_1 = \lambda^2 \left(\lambda - \frac{\eta_p\,\alpha_p\kappa_p}{\delta_p\,(\delta_p + m_p)}\right)\left(\lambda - \frac{\eta_h\,\alpha_{sh}\kappa_{sh}}{\delta_h\,(\delta_h + m_s)}\right)\left(\lambda - \frac{\eta_h\,\alpha_{mh}\kappa_{mh}}{\delta_h\,(\delta_h + m_m)}\right). \tag{4.5}$$

Based on Theorem 3.25 and Corollary 3.26 in Section 3.6, the basic reproduction numbers for the epidemic model $(4.3a) - (4.3g)$ are defined as the spectral radius of the

next generation matrices. Therefore

$$R_p = \frac{\eta_p\, \alpha_p \kappa_p}{\delta_p\ (\delta_p + m_p)}, \tag{4.6}$$

$$R_{sh} = \frac{\eta_h\, \alpha_{sh} \kappa_{sh}}{\delta_h\, (\delta_h + m_s)} \tag{4.7}$$

and

$$R_{mh} = \frac{\eta_h\, \alpha_{mh} \kappa_{mh}}{\delta_h\, (\delta_h + m_m)}. \tag{4.8}$$

R_p is the basic reproduction number for the transmission of avian flu among birds, R_{sh} is the basic reproduction number for the transmission of swine flu among humans, and R_{mh} is the basic reproduction number for the transmission of mutant-avian flu among humans.

4.4 Disease state equilibria

4.4.1 Disease state equilibria among poultry birds

Since humans do not infect birds, avian flu dynamics among birds is independent of the dynamics of diseases among humans. The bird dynamical system (4.1a) - (4.1b) can be treated as a stand alone system. It is assumed there is no infected poultry, $I_p = 0$. For equilibrium it is required that $S_p' = 0$. Having $I_p = 0$, (4.1b) becomes $\eta_p - \delta_p\, S^*_{p_0} = 0$,

$$S^*_{p_0} = \frac{\eta_p}{\delta_p}.$$

The pair

$$e^*_0 = (S^*_{p_0}, 0) \tag{4.9}$$

is referred to as the bird disease free state.

In an endemic situation $I_p \neq 0$. For an endemic equilibrium, it is required

$$I_p' = 0 \;\; \Leftrightarrow \;\; \left[\alpha_p \kappa_p S^*_{p_+} - (\delta_p + m_p)\right] I^*_{p_+} = 0.$$

Since $I^*_{p_+} \neq 0$ then $\alpha_p \kappa_p S^*_{p_+} - (\delta_p + m_p) = 0$. Therefore,

$$\begin{aligned} S^*_{p_+} &= \frac{\delta_p + m_p}{\alpha_p \kappa_p} \\ &= \frac{\eta_p}{\delta_p} \frac{1}{R_p}. \end{aligned}$$

Given $\eta_p\alpha_p\kappa_p - \delta_p\left(\delta_p + m_p\right) > 0$,

$$\begin{aligned} I^*_{p_+} &= \frac{\eta_p\alpha_p\kappa_p - \delta_p\left(\delta_p + m_p\right)}{\alpha_p\kappa_p\left(\delta_p + m_p\right)}, \\ &= \frac{\eta_p}{\delta_p + m_p} - \frac{\delta_p}{\alpha_p\kappa_p} \\ &= \frac{\eta_p}{\delta_p + m_p}(1 - \frac{1}{R_p}). \end{aligned}$$

The bird system has an endemic state

$$e^*_+ = (S^*_{p_+}, I^*_{p_+}). \tag{4.10}$$

4.4.2 Disease state equilibria for the full system

The dynamics of the diseases among humans does depend on the dynamics of avian flu among birds. The influence of the bird populations on the human populations may be modeled as a time dependent external source. Another possibility is to combine the human and bird populations into a single system. The advantage of the latter is that the system remains autonomous. Therefore, to study the dynamic of the diseases among humans, it is convenient to consider the full dynamical system $(4.3a) - (4.3g)$, (4.3h). It has five disease state equilibria

$$Z_i = (S^*_{p_i}, I^*_{p_i}, S^*_{h_i}, I^*_{s_i}, I^*_{a_i}, I^*_{b_i}, I^*_{m_i}),\ i = 1, \ldots, 5.$$

The first three happen when there is disease free in the bird world $I^*_{p_i} = 0,\ i = 1, 2, 3$ and last two happen when the disease is endemic among birds, $I^*_{p_i} \neq 0,\ i = 4, 5$.

Consider first when there is no infected poultry, $I^*_p = 0$. In this case, the full system $(4.3a) - (4.3g)$, (4.3h) has at most three equlibria points. Let Z^*_i denote an equilibrium point.

$$Z^*_i = (S^*_{p_i}, 0, S^*_{h_i}, I^*_{s_i}, I^*_{a_i}, I^*_{b_i}, I^*_{m_i}).$$

At Z^*_i the equilibrium requires

$$S'_p = 0 \ \Leftrightarrow\ \eta_p - \delta_p S^*_{p_i} = 0 \tag{4.11a}$$

$$S'_h = 0 \ \Leftrightarrow\ \eta_h - \left[\delta_h - \alpha_{sh}\kappa_{sh}I^*_{s_i} - \alpha_{mh}\kappa_{mh}I^*_{m_i}\right] S^*_{h_i} = 0 \tag{4.11b}$$

$$I'_s = 0 \ \Leftrightarrow\ \left[\alpha_{sh}\kappa_{sh}S^*_{h_i} - (\delta_h + m_s)\right] I^*_{s_i} = 0 \tag{4.11c}$$

$$I'_a = 0 \ \Leftrightarrow\ (-1)\left[\mu\alpha_{sa}\kappa_{sa}I^*_{s_1} - (\delta_h + m_a)\right] I^*_{a_i} = 0 \tag{4.11d}$$

$$I'_b = 0 \ \Leftrightarrow\ (-1)\left[(\delta_h + m_b)\right] I^*_{b_i} = 0 \tag{4.11e}$$

$$I'_m = 0 \ \Leftrightarrow\ \mu\alpha_{sa}\kappa_{sa}I^*_{s_i}I^*_{a_i} + \left[\alpha_{mh}\kappa_{mh}I^*_{m_i}S^*_{h_1} - (\delta_h + m_m)\right] I^*_{m_i} = 0, \tag{4.11f}$$

From (4.11a)

$$S^*_{p_i} = S^*_{p0} = \frac{\eta_p}{\delta_p}\ i = 1, 2, 3.$$

Since $\mu\alpha_{sa}\kappa_{sa}I^*_{s_i} \geq (\delta_h + m_a) > 0$ it follows from (4.11d) that

$$I^*_{a_i} = 0,\ i = 1, 2, 3.$$

Now (4.11e) implies that

$$I^*_{b_i} = 0,\ i = 1, 2, 3,$$

and hence (4.11f) gives

$$S^*_{h_i} = \frac{\delta_h + m_m}{\alpha_{mh}\kappa_{mh}} \text{ or } \mathrm{I}^*_{\mathrm{m_i}} = 0.$$

In the case of the former alternative then

$$\alpha_{mh}\kappa_{mh}I^*_{m_i}S^*_{h_i} - (\delta_h + m_m) \neq 0$$

and so (4.11c) gives

$$I^*_{s_i} = 0.$$

Thus from (4.11b),

$$\eta_h - \left[\delta_h - \alpha_{sh}\kappa_{sh}I^*_{s_i} - \alpha_{mh}\kappa_{mh}I^*_{m_i}\right]\frac{\delta_h + m_m}{\alpha_{mh}\kappa_{mh}} = 0$$

and hence provided $\eta_h\alpha_{sh}\kappa_{sh} - \delta_h + m_m > 0$ there is an equilibrium coordinate

$$I^*_{m_i} = \frac{\eta_h}{\delta_h + m_m} - \frac{\delta_h}{\alpha_{mh}\kappa_{mh}} > 0.$$

In the case of the latter alternative then (4.11c) gives the further alternative

$$S^*_{h_i} = \frac{\delta_h + m_s}{\alpha_{sh}\kappa_{sh}} \text{ or } \mathrm{I}^*_{\mathrm{s_i}} = 0.$$

In the case of the former of the further alternatives then (4.11b) gives

$$\eta_h - \left[\delta_h - \alpha_{sh}\kappa_{sh}I^*_{s_i} - \alpha_{mh}\kappa_{mh}I^*_{m_i}\right]\frac{\delta_h + m_s}{\alpha_{sh}\kappa_{sh}} = 0$$

and provided $\eta_h\alpha_{sh}\kappa_{sh} - \delta_h(\delta_h + m_s) > 0$, there is an equilibrium coordinate

$$I^*_{s_1} = \frac{\eta_h}{\delta_h + m_s} - \frac{\delta_h}{\alpha_{sh}\kappa_{sh}}.$$

In the case of the latter of the further alternatives, (4.11b) shows that

$$S^*_{h_i} = S^*_{h_0} = \frac{\eta_h}{\delta_h}.$$

Thus, in the case of no infected birds, $I^*_p = 0$, the full system $(4.3a) - (4.3g)$, (4.3h) has three equlibria points. First, the disease free equilibrium is

$$Z^*_1 = (S^*_{p_1}, 0, S^*_{h_1}, 0, 0, 0, 0), \tag{4.12}$$

$$S^*_{p_1} = S^*_{p_0} = \frac{\eta_p}{\delta_p},$$
$$S^*_{h_1} = \frac{\eta_h}{\delta_h}.$$

Second, the swine flu epidemic equilibrium is

$$Z^*_2 = (S^*_{p_2}, 0, S^*_{h_2}, I^*_{s_2}, 0, 0, 0) \tag{4.13}$$

where

$$S^*_{p_2} = S^*_{p_0} = \frac{\eta_p}{\delta_p},$$

$$S^*_{h_2} = \frac{\delta_h + m_s}{\alpha_{sh}\kappa_{sh}},$$
$$= \frac{\eta_h}{\delta_h}\frac{1}{R_{sh}}$$

$$I^*_{s_2} = \frac{\eta_h\,\alpha_{sh}\kappa_{sh} - \delta_h(\delta_h + m_s)}{\alpha_{sh}\kappa_{sh}\,(\delta_h + m_s)}$$
$$= \frac{\eta_h}{\delta_h + m_s}(1 - \frac{1}{R_{sh}})$$

Z^*_2 is the state in which there are no birds or humans infected by avian flu and no human infected by mutant-avian flu but there are humans infected by swine flu.
Third, the mutant-avian flu epidemic equilibrium is

$$Z^*_3 = (S^*_{p_3}, 0, S^*_{h_3}, 0, 0, 0, I^*_{m_3}) \tag{4.14}$$

where

$$S^*_{p3} = S^*_{p0} = \frac{\eta_p}{\delta_p},$$

$$\begin{aligned} S^*_{h3} &= \frac{\delta_h + m_m}{\alpha_{mh}\kappa_{mh}} \\ &= \frac{\eta_h}{\delta_h}\frac{1}{R_{mh}} \end{aligned}$$

$$\begin{aligned} I^*_{m3} &= \frac{\eta_h\,\alpha_{mh}\kappa_{mh} - \delta_h(\delta_h + m_m)}{\alpha_{mh}\kappa_{mh}\,(\delta_h + m_m)} \\ &= \frac{\eta_h}{\delta_h + m_m}(1 - \frac{1}{R_{mh}}) \end{aligned}$$

Z^*_3 is the state in which there are no birds or humans infected by avian flu and no humans infected by swine flu but there are humans infected by mutant-avian flu. Z^*_1, Z^*_2 and Z^*_3 are disease equilibria of the full system $(4.3a) - (4.3g)$, (4.3h) when there is no avian-flu epidemic in the bird world.

In the case of an endemic situation in the bird world, $I_p \neq 0$, the full system $(4.3a) - (4.3g)$, (4.3h) has at most two equlibria points

$$Z_i = (S^*_{p_i}, I^*_{p_i}, S^*_{h_i}, I^*_{s_i}, I^*_{a_i}, I^*_{b_i}, I^*_{m_i}),\ i = 4, 5. \tag{4.15}$$

The first,

$$Z_4 = (S^*_{p_4}, I^*_{p_4}, S^*_{h_4}, 0, I^*_{a_4}, I^*_{b_4}, 0) \tag{4.16}$$

is the avian flu epidemic equilibrium state among birds and humans. The equilibrium requires

$$S'_p = 0 \Leftrightarrow \eta_p - \delta_p\, S^*_{p_4} - \alpha_p\kappa_p I^*_{p_4} S^*_{p_4} = 0 \tag{4.17a}$$
$$I'_p = 0 \Leftrightarrow \alpha_p\kappa_p I^*_{p_4} S^*_{p_4} - (\delta_p + m_p) I^*_{p_4} = 0 \tag{4.17b}$$
$$S'_h = 0 \Leftrightarrow \eta_h - \delta_h S^*_{h_4} - \alpha_{ph}\kappa_{ph} S^*_{s_4} = 0 \tag{4.17c}$$
$$I'_a = 0 \Leftrightarrow \gamma\alpha_{ph}\kappa_{ph} I^*_{p_4} S^*_{h_4} - (\delta_h + m_a)\, I^*_{a_4} = 0 \tag{4.17d}$$
$$I'_b = 0 \Leftrightarrow (1-\gamma)\alpha_{ph}\kappa_{ph} I^*_{p_4} S^*_{h_4} - (\delta_h + m_b)\, I^*_{b_4} = 0. \tag{4.17e}$$

$I^*_{p_4} > 0$ and the condition $I'_p = 0$ implies

$$\begin{aligned} S^*_{p_4} &= \frac{\delta_p + m_p}{\alpha_p\kappa_p} \\ &= \frac{\eta_p}{\delta_p}\frac{1}{R_p} \end{aligned}$$

$S^*_{p_4} = S^*_{p_+}$. Now $I'_p = 0$ gives

$$\begin{aligned} I^*_{p_4} &= \frac{\eta_p}{\delta_p + m_p} - \frac{\delta_p}{\alpha_p \kappa_p} \\ &= \frac{\eta_p}{\delta_p + m_p}\left[1 - \frac{\delta_p(\delta_p + m_p)}{\eta_p \alpha_p \kappa_p}\right] \\ &= \frac{\eta_p}{\delta_p + m_p}(1 - \frac{1}{R_p}) \end{aligned}$$

$I^*_{p_4} = I^*_{p_+}$. The condition $S'_h = 0$ gives

$$\begin{aligned} S^*_{h_4} &= \frac{\eta_h}{\delta_h + \alpha_{ph}\kappa_{ph} I^*_{p_4}} \\ &= \frac{\eta_h}{\delta_h + \alpha_{ph}\kappa_{ph}\frac{\eta_p}{\delta_p + m_p}\left(1 - \frac{1}{R_p}\right)} \\ &= \frac{\frac{\eta_h}{\delta_h}}{1 + \frac{\alpha_{ph}\kappa_{ph}\eta_p}{\eta_h\,(\delta_p + m_p)}\left(1 - \frac{1}{R_p}\right)} \end{aligned}$$

$S^*_{h_4}$ also can be written as

$$S^*_{h_4} = \frac{\frac{\eta_h}{\delta_h}}{1 + r_{ph}}$$

where r_{ph} is defined as

$$r_{ph} = \frac{\alpha_{ph}\kappa_{ph}\eta_p}{\eta_h\ (\delta_p + m_p)}\left(1 - \frac{1}{R_p}\right). \tag{4.18}$$

The derivation of $I^*_{a_4}$ and $I^*_{b_4}$ are as follows. Since $I^*_{s_4} = 0$ the equation (4.17d) implies

$$I^*_{a_4} = \frac{\gamma \alpha_{ph}\kappa_{ph} I^*_{p_4} S^*_{h_4}}{\delta_h + m_a}.$$

Since $I^*_{m_4} = 0$ and from (4.17c) gives $\alpha_{ph}\kappa_{ph} I^*_{p_4} = \eta_h - \delta_h S^*_{h_4}$ and so the above expression becomes

$$\begin{aligned} I^*_{a_4} &= \frac{\gamma \alpha_{ph}\kappa_{ph} I^*_{p_4} S^*_{h_4}}{\delta_h + m_a} \\ &= \frac{\gamma}{\delta_h + m_a}(\eta_h - \delta_h S^*_{h_4}) \\ &= \frac{\gamma \eta_h}{\delta_h + m_a}\left(1 - 1 - \frac{1}{1 + r_{ph}}\right). \end{aligned}$$

A similar derivation using (4.17e) gives

$$\begin{aligned} I^*_{b_4} &= \frac{(1-\gamma)\alpha_{ph}\kappa_{ph}I^*_{p4}S^*_{h_4}}{\delta_h + m_b} \\ &= \frac{(1-\gamma)}{\delta_h + m_b}(\eta_h - \delta_h S^*_{h_4}) \\ &= \frac{(1-\gamma)\eta_h}{\delta_h + m_b}\left(1 - 1 - \frac{1}{1+r_{ph}}\right). \end{aligned}$$

The last equilibrium disease state

$$Z^*_5 = (S^*_{p_5}, I^*_{p_5}, S^*_{h_5}, 0, I^*_{a_5}, I^*_{b_5}, I^*_{m_5}), \tag{4.19}$$

is the disease state equilibrium in which there are avian flu epidemics among birds and humans and also an epidemic of mutant-avian flu among humans.

$$S^*_{p_5} = S^*_{p_+} = \frac{\delta_p + m_p}{\alpha_p\kappa_p} = \frac{\eta_p}{\delta_p}\frac{1}{R_p}$$

$$I^*_{p_5} = I^*_{p_+} = \frac{\eta_p}{\delta_p + m_p} - \frac{\delta_p}{\alpha_p\kappa_p} = \frac{\eta_p}{\delta_p + m_p}(1 - \frac{1}{R_p})$$

The derivation of $S^*_{h_5}, I^*_{a_4}, I^*_{b_5}$ and $I^*_{m_5}$ are as follows. The relevant equilibrium equations are

$$S'_p = 0 \;\Leftrightarrow\; S'_{p_5} = \eta_p - \delta_p S_{p_5} - \alpha_p\kappa_p I_{p_5} S_{p_5} = 0 \tag{4.20a}$$

$$I'_p = 0 \;\Leftrightarrow\; \alpha_p\kappa_p I_{p_5} S_{p_5} - (\delta_p + m_p) I_{p_5} = 0 \tag{4.20b}$$

$$S'_h = 0 \;\Leftrightarrow\; \eta_h - \delta_h S_{h_5} - \alpha_{ph}\kappa_{ph} I_{p_5} S_{h_5} - \alpha_{sh}\kappa_{sh} I_{s_5} S_{h_5} - \alpha_{mh}\kappa_{mh} I_{m_5} S_{h_5} = 0 \tag{4.20c}$$

$$I'_a = 0 \;\Leftrightarrow\; \gamma\alpha_{ph}\kappa_{ph} I_{p_5} S_{h_5} - \mu\alpha_{sa}\kappa_{sa} I_{s_5} I_{a_5} - (\delta_h + m_a) I_{a_5} = 0 \tag{4.20d}$$

$$I'_b = 0 \;\Leftrightarrow\; (1-\gamma)\alpha_{ph}\kappa_{ph} I_{p_5} S_{h_5} - (\delta_h + m_b) I_{b_5} = 0 \tag{4.20e}$$

$$I'_m = 0 \;\Leftrightarrow\; \mu\alpha_{sa}\kappa_{sa} I_{s_5} I_{a_5} + \alpha_{mh}\kappa_{mh} I_m S_{h_5} - (\delta_h + m_m) I_{m_5} = 0. \tag{4.20f}$$

Suppose $I^*_{s_5} = 0$ and $I^*_{m_5} > 0$ the condition $I'_m = 0$ gives

$$S^*_{h_5} = \frac{\delta_h + m_m}{\alpha_{mh}\kappa_{mh}} = \frac{\eta_h}{\delta_h}\frac{1}{R_{mh}}$$

The condition (4.20c), $S'_h = 0$, now implies

$$\begin{aligned} I^*_{m_5} &= \frac{\eta_h - \left(\delta_h + \alpha_{ph}\kappa_{ph} I^*_{p_5}\right) S^*_{h_5}}{\alpha_{mh}\kappa_{mh} S^*_{h_5}} \\ &= \frac{\eta_h - \left[\delta_h + \alpha_{ph}\kappa_{ph}\frac{\eta_p}{\delta_h + m_m}(1 - \frac{1}{R_p})\right]\frac{\delta_h + m_m}{\alpha_{mh}\kappa_{mh}}}{\delta_h + m_m} \\ &= \frac{\delta_h}{\alpha_{mh}\kappa_{mh}}\left[\frac{\alpha_{mh}\kappa_{mh}\eta_h}{\delta_h(\delta_p + m_m)} - 1 - \frac{\alpha_{ph}\kappa_{ph}\eta_h}{\delta_h(\delta_p + m_p)}(1 - \frac{1}{R_p})\right] \\ &= \frac{\delta_h}{\alpha_{mh}\kappa_{mh}}\left[R_{mh} - (1 + r_{ph})\right]. \end{aligned}$$

where r_{ph} is defined by (4.38)

$$r_{ph} = \frac{\alpha_{ph}\kappa_{ph}\eta_p}{\eta_h\ (\delta_p + m_p)}\left(1 - \frac{1}{R_p}\right).$$

The final equilibrium equations (4.20d) and (4.20e) give $I'_a = 0$ and $I'_b = 0$. Hence,

$$\begin{aligned} I^*_{a_5} &= \frac{\gamma\alpha_{ph}\kappa_{ph} I^*_{p_5} S^*_{h_5}}{\delta_h + m_a} \\ &= \frac{\gamma\alpha_{ph}\kappa_{ph}\frac{\eta_p}{\delta_p + m_p}(1 - \frac{1}{R_p})\frac{\delta_h + m_m}{\alpha_{mh}\kappa_{mh}}}{\delta_h + m_a} \\ &= \frac{\gamma\eta_h r_{ph}}{(\delta_h + m_a)R_{mh}} \end{aligned}$$

and

$$\begin{aligned} I^*_{b_5} &= \frac{(1-\gamma)\alpha_{ph}\kappa_{ph} I^*_{p_5} S^*_{h_5}}{\delta_h + m_b} \\ &= \frac{(1-\gamma)\alpha_{ph}\kappa_{ph}\frac{\eta_p}{\delta_p + m_p}(1 - \frac{1}{R_p})\frac{\delta_h + m_m}{\alpha_{mh}\kappa_{mh}}}{\delta_h + m_b} \\ &= \frac{(1-\gamma)\eta_h r_{ph}}{(\delta_h + m_b)R_{mh}}. \end{aligned}$$

4.5 Stability analysis of disease state equilibria

The following subsections (4.5.3 to 4.5.7) analyze the local and global stability of the disease state equilibrium points. The Poincaré-Bendixon theorem (Theorem 3.19 in Section 3.3) is used to prove global stability of disease state equilibria, namely that for any initial disease state Z_0, there will always exist $\omega(Z_0)$, the ω-limit set of orbits through Z_0 in Ω.

4.5.1 Stability analysis of disease state equilibria among birds

Recall that the bird system (4.1a, 4.1b) has two disease state equilibria; e_0 and e_+, where e_0 and e_+ are respectively given by (4.9)

$$e_0 = (S^*_{p_0}, 0) \text{ where } \mathrm{S}^*_{\mathrm{p_0}} = \frac{\eta_{\mathrm{p}}}{\delta_{\mathrm{p}}},$$

and (4.10)

$$e_+ = (S^*_{p_+}, I^*_{p_+})$$

where

$$S^*_{p_+} = \frac{\eta_p}{\delta_p}\frac{1}{R_p}$$

and

$$I^*_{p_+} = \frac{\eta_p}{\delta_p + m_p}(1 - \frac{1}{R_p}).$$

The stability analysis of these disease equilibria are well known, see for example [177] [103], but are given here for completeness.

Theorem 4.3. *If $R_p \leq 1$ then e_0 is GAS on $\mathbb{R}^2_+$. On the other hand, if $R_p > 1$ then e_+ is GAS on $Int(\mathbb{R}^2_+)$.*

Proof. The Jacobian matrix for the bird system (4.1a, 4.1b) is

$$J = \begin{bmatrix} -\delta_p - \alpha_p\kappa_p I_p & -\alpha_p\kappa_p S_p \\ \alpha_p\kappa_p I_p & \alpha_p\kappa_p S_p - (\delta_p + m_p) \end{bmatrix}. \tag{4.21}$$

(4.21) evaluated at $(S^*_{p_0}, 0)$ is

$$J(e_0) = \begin{bmatrix} -\delta_p & -(\delta_p + m_p) R_p \\ 0 & (\delta_p + m_p)(R_p - 1) \end{bmatrix}. \tag{4.22}$$

The eigenvalues of this Jacobian matrix are $-\delta_p$ and $(\delta_p + m_p)(R_p - 1)$. Both eigen values are negative if $R_p < 1$. Therefore, e_0 is locally stable on $\mathbb{R}^2_+$.

To justify that $S_p \to \frac{\eta_p}{\delta_p}$ and $I_p \to 0$ as $t \to \infty$, the LaSalle's invariance principle is used. First construct a Lyapunov function $\mathcal{L}$. The most common types of Lyapunov functions for infectious disease transmission models are quadratic and Volterra type of functions [184], [185]. Following [103], let

$$\mathcal{L} = \frac{1}{2}(S_p - S_{p_0})^2 + S_{p_0} I_p,$$

where $S^*_{p0} = \frac{\eta_p}{\delta_p}$. Differentiating along the orbit results in

$$\begin{aligned}
\dot{\mathcal{L}} &= (S_p - S_{p_0})(\eta_p - \delta_p S_p - \alpha_p \kappa_p) + S_{p_0}\left[\alpha_p \kappa_p I_p S_p - (\delta_p + m_p) I_p\right] \\
&= (I_p - S_{p_0})\left[-\delta_p (S_p - S_{p_0}) - \alpha_p \kappa_p I_p (S_p - S_{p_0}) - \alpha_p \kappa_p I_p S_{p_0}\right] \\
&+ S_{p_0}\left[\alpha_p \kappa_p I_p S_p - (\delta_p + m_p) I_p\right] \\
&= -(\delta_p + \alpha_p \kappa_p I_p)(S_p - S_{p_0})^2 + S_{p_0}(\delta_p + m_p)(R_p - 1).
\end{aligned}$$

If $R_p \leq 1$ then $\dot{\mathcal{L}} \leq 0$. Meanwhile the largest invariant subset of $\dot{\mathcal{L}} = 0$ is the singleton $\{(\frac{\eta_p}{\delta_p}, 0)\}$. Therefore, the use of the LaSalle invariance principle in Section 3.3, results in $S_p \to \frac{\eta_p}{\delta_p}$ and $I_p \to 0$ whenever $R_p \leq 1$ and $t \to \infty$. Therefore, e_0 is globally stable on $\mathbb{R}^2_+$.

The Jacobian matrix (4.21) evaluated at $(S^*_{p_+}, I^*_{p_+})$ is

$$J(e_+) = \begin{bmatrix} -\delta_p R_p & -(\delta_p + m_p) \\ \delta_p (R_p - 1) & 0 \end{bmatrix} \tag{4.23}$$

with its characteristic polynomial

$$\mathcal{C}_b(\lambda) = \lambda^2 + \delta_\lambda R_p \lambda + (R_p - 1)\,\delta_p\,(\delta_p + m_p)\,.$$

For $R_p > 1$, the linear coefficient and constant coefficient of the characteristic equation are positive. That is $\delta_p R_p > 0$ and $(R_p - 1)\,\delta_p\,(\delta_p + m_p) > 0$. Therefore the roots of the characteristic equation have negative real parts.

Let the right hand side of (4.3a) and (4.3b) be denoted as $\psi(S_p, I_p)$ and $\chi(S_p, I_p)$

$$\dot{\mathbf{x}} = \mathbf{f} \quad \Leftrightarrow \quad \begin{bmatrix} \dot{x} \\ \dot{y} \end{bmatrix} = \begin{bmatrix} \psi(S_p, I_p) \\ \chi(S_p, I_p) \end{bmatrix}.$$

By using Theorem 3.18 (Bendixson-Dulac), define a positive Dulac function as

Let the right hand side of (4.3a, 4.3b) be denoted by the vector

$$\boldsymbol{f} = \begin{bmatrix} \psi(S_p, I_p) \\ \chi(S_p, I_p) \end{bmatrix}$$

and define a Dulac function

$$\Psi = \frac{1}{S_p I_p}.$$

Then

$$\begin{aligned}\Delta.(\Psi \boldsymbol{f}) &= \frac{\partial(\Psi\psi)}{\partial S_p} + \frac{\partial(\Psi\chi)}{\partial I_p} \\ &= \frac{\partial}{\partial S_p}\left[\frac{\eta_p}{S_p I_p} - \frac{\delta_p}{I_p} - \alpha_p\kappa_p\right] + \frac{\partial}{\partial I_p}\left[\alpha_p\kappa_p - \frac{\delta_p + m_p}{S_p}\right] \\ &= -\frac{\eta_p}{S_p^2 I_p}\end{aligned}$$

since $S_p > 0$, $I_p > 0$ and $\eta_p > 0$. Hence, the first two equations of the disease transmission model $(4.3a) - (4.3g)$ does not have a limit cycle in $G \subset R^2$. Hence the Dulac criterion implies that there is no periodic solution in $\mathbb{R}^2_+$. Applying the Poincaré Bendixon theorem (Theorem 3.19 in Section 3.3), for $R_p > 1$ gives $\lim_{t\to\infty} S_p(t) = \frac{\eta_p}{\delta_p}\frac{1}{R_p}$ and $\lim_{t\to\infty} I_p(t) = \frac{\eta_p}{\delta_p + m_p}(1 - \frac{1}{R_p})$). Therefore, e_+ is globally stable on $Int\mathbb{R}^2_+$. □

4.5.2 *Stability analysis of disease state equilibria for the full systems*

In the following subsections, the full system $(4.3a) - (4.3g)$ will be used to study the stability of equilibria. The Jacobian matrix of the system is given by

$$\mathcal{J} = \begin{bmatrix} J_1 & O \\ J & J_2 \end{bmatrix}, \tag{4.24}$$

where J is given by (4.21), the Jacobian matrix of the bird system (4.1a, 4.1b)

$$J_1 = \begin{bmatrix} -\delta_p - \alpha_p\kappa_p I_p & -\alpha_p\kappa_p S_p \\ \alpha_p\kappa_p I_p & \alpha_p\kappa_p S_p - (\delta_p + m_p) \end{bmatrix}, \tag{4.25}$$

$$O = \begin{bmatrix} 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{bmatrix},\ J = \begin{bmatrix} 0 & j_{3,2} \\ 0 & 0 \\ 0 & j_{5,2} \\ 0 & j_{6,2} \\ 0 & 0 \end{bmatrix},$$

and

$$J_2 = \begin{bmatrix} j_{3,3} & j_{3,4} & 0 & 0 & j_{3,7} \\ j_{4,3} & j_{4,4} & 0 & 0 & 0 \\ j_{5,3} & j_{5,4} & j_{5,5} & 0 & 0 \\ j_{6,3} & 0 & 0 & j_{6,6} & 0 \\ j_{7,3} & j_{7,4} & j_{7,5} & 0 & j_{7,7} \end{bmatrix}, \tag{4.26}$$

where $j_{3,2} = -\alpha_{ph}\kappa_{ph}S_h$, $j_{3,3} = -\delta_h - \alpha_{ph}\kappa_{ph}I_p - \alpha_{sh}\kappa_{sh}I_s - \alpha_{mh}\kappa_{mh}I_m$, $j_{3,4} = -\alpha_{sh}\kappa_{sh}S_h$, $j_{3,7} = -\alpha_{mh}\kappa_{mh}S_h$, $j_{4,3} = -\alpha_{sh}\kappa_{sh}I_s$, $j_{4,4} = \alpha_{sh}\kappa_{sh}S_h - \delta_h - m_s$, $j_{5,2} = \gamma_a\alpha_{ph}\kappa_{ph}S_h$, $j_{5,3} = \gamma_a\alpha_{ph}\kappa_{ph}I_p$, $j_{5,4} = -\mu\,\alpha_{sa}\kappa_{sa}I_a$, $j_{5,5} = -\mu\,\alpha_{sa}\kappa_{sa}I_s - (\delta_h + m_a)$, $j_{6,2} = (1-\gamma_a)\alpha_{yh}\kappa_{ph}S_h$, $j_{6,3} = (1-\gamma_a)\alpha_{yh}\kappa_{ph}I_p$, $j_{6,6} = -(\delta_h + m_b)$, $j_{7,3} = \alpha_{mh}\kappa_{mh}I_m$, $j_{7,4} = \mu\,\alpha_{sa}\kappa_{sa}I_a$, $j_{7,5} = \mu\,\alpha_{sa}\kappa_{sa}I_s$, $j_{7,7} = \alpha_{mh}\kappa_{mh}S_h - (\delta_h + m_m)$.

J and J_2 are referred to as *key Jacobian matrices* or *principal minors*. The Jacobian matrix (4.24) is stable at an equilibrium point z^* if and only if the key Jacobian matrices $J(z^*)$ and $J_2(z^*)$ are stable (by Corollary 3.26).

4.5.3 Stability analysis of disease free equilibrium

The stability behavior of the disease free equilibrium Z_1^* is analyzed as follows.

Lemma 4.4. *If $R_p \leq 1$, $R_{sh} \leq 1$ and $R_{mh} \leq 1$ then $Z_1^* = (\frac{\eta_p}{\delta_p}, 0, \frac{\eta_h}{\delta_h}, 0, 0, 0, 0)$ is LAS.*

Proof. At $Z_1^* = (S_{p_1}^*, 0, S_{h_1}^*, 0, 0, 0)$

$$S_{p_1}^* = \frac{\eta_p}{\delta_p} > 0 \text{ and } \mathrm{S}_{\mathrm{h}_1}^* = \frac{\eta_{\mathrm{h}}}{\delta_{\mathrm{h}}} > 0.$$

At Z_1^* the key Jacobian matrices (4.25) and (4.26) becomes

$$J_{11} = \begin{bmatrix} j_{1,1} & j_{1,2} \\ 0 & j_{2,2} \end{bmatrix} \tag{4.27}$$

and

$$J_{12} = \begin{bmatrix} j_{3,3} & j_{3,4} & 0 & 0 & j_{3,7} \\ 0 & j_{4,4} & 0 & 0 & 0 \\ 0 & 0 & j_{5,5} & 0 & 0 \\ 0 & 0 & 0 & j_{6,6} & 0 \\ 0 & 0 & 0 & 0 & j_{7,7} \end{bmatrix} \tag{4.28}$$

respectively, where $j_{1,1} = (-1)\delta_p, \quad j_{1,2} = -\alpha_p\kappa_p S^*_{p_2}, \quad j_{2,2} = -\alpha_p\kappa_p S^*_{p_2} - (\delta_p + m_p)$, $j_{3,3} = -\delta_h, \quad j_{3,4} = (-1)\alpha_{sh}\kappa_{sh}S^*_{h_1}, \quad j_{3,7} = (-1)\alpha_{mh}\kappa_{mh}S^*_{h_1}, \quad j_{4,4} = \alpha_{sh}\kappa_{sh}S^*_{h_1} - (\delta_h + m_s), \quad j_{5,5} = (-1)(\delta_h - m_a), \quad j_{6,6} = (-1)(\delta_h - m_b), \quad j_{7,7} = \alpha_{mh}\kappa_{mh}S^*_{h_1} - (\delta_h + m_m)$.

The characteristic polynomial for the first key Jacobian matrix, J, is

$$\begin{aligned}|\lambda I - J_{11}| &= (\lambda + \delta_p)\left[\lambda - \alpha_p\kappa_p S^*_{p_1} + (\delta_p + m_p)\right] \\ &= (\lambda + \delta_p)\left[\lambda - \frac{\alpha_p\kappa_p\eta_p}{\delta_p} + (\delta_p + m_p)\right]\end{aligned}$$

and hence J_{11} is stable provided

$$\alpha_p\kappa_p S^*_{p_1} - (\delta_p + m_p) \leq \frac{\alpha_p\kappa_p\eta_p}{\delta_p} - (\delta_p + m_p) \leq 0 \Leftrightarrow R_p \leq 1.$$

The characteristic polynomial for the second key Jacobian matrix, J_{12}, is

$$|\lambda I - J_{12}| = \begin{bmatrix} \lambda - j_{3,3} & -j_{3,4} & 0 & 0 & j_{3,7} \\ 0 & \lambda - j_{4,4} & 0 & 0 & 0 \\ 0 & 0 & \lambda - j_{5,5} & 0 & 0 \\ 0 & 0 & 0 & \lambda - j_{6,6} & 0 \\ 0 & 0 & 0 & 0 & \lambda - j_{7,7} \end{bmatrix}$$

J_{12} is stable provided

$$\alpha_{sh}\kappa_{sh}S^*_{h_1} - (\delta_h + m_s) \leq 0 \Leftrightarrow \frac{\alpha_{sh}\kappa_{sh}\eta_h}{\delta_h} - (\delta_h + m_s) \leq 0 \Leftrightarrow R_{sh} \leq 1$$

and

$$\alpha_{mh}\kappa_{mh}S^*_{h_1} - (\delta_h + m_m) \leq 0 \Leftrightarrow \frac{\alpha_{mh}\kappa_{mh}\eta_h}{\delta_h} - (\delta_h + m_m) \leq 0 \Leftrightarrow R_{mh} \leq 1.$$

Therefore $Z^*_1 = (\frac{\eta_p}{\delta_p}, 0, \frac{\eta_h}{\delta_h}, 0, 0, 0, 0)$ is well defined and stable if $R_p \leq 1, R_{sh} \leq 1$ and $R_{mh} \leq 1$.

□

In the following, the Poincaré-Bendixon theorem (Theorem 3.19 in Section 3.3) is used to prove that Z^*_1 is also globally stable; for any initial disease state Z_0 there will always exist $\omega(Z_0)$, ω-limit set of orbit through Z_0.

Starting from any initial disease state Z_0, the final disease state when $t \to \infty$ is subject to the following lemma,

Lemma 4.5. *Let* $S^\infty_h = \limsup_{t\to\infty} S_h(t)$. *Then* $S^\infty_h \leq S^*_{h_1}$

Proof. Equation (4.3c) gives

$$S_h' = \eta_h - \delta_h S_h - \alpha_{ph}\kappa_{yh} I_p S_h - \alpha_{sh}\kappa_{sh} I_s S_h - \alpha_{mh}\kappa_{mh} I_m S_h \leq \eta_h - \delta_h S_h.$$

Integrating the inequality over $[0, t]$ results in

$$S_h(t) \leq S_{h_1}^* + |S_h(0) - S_{h_1}^*| e^{-\delta_h t}.$$

Therefore $\forall \epsilon > 0, \exists t_1$ such that $|S_h(0) - S_{h_1}^*| e^{-\delta_h t} \leq \epsilon$ for any $t > t_1$.
Hence $S_h(t) \leq S_{h_1}^* + \epsilon$ for $t \geq t_1$. Thus for $T_1 \geq t_1, \limsup_{t \geq T_1} S_h(t) \leq S_{h_1}^* + \epsilon$.
Letting for $T_1 \to \infty$, results in $S_h^\infty \leq S_{h_1}^* + \epsilon$, $S_h^\infty \leq S_{h_1}^*$ for $\epsilon > 0$. □

The global stability behavior of Z_1^* is analyzed as follows. For $Z = (S_p, I_p, S_h, I_s, I_a, I_b, I_m)$, let

$$\Omega_1 = \{Z | S_p > 0, I_p \geq 0, S_h > 0, I_s \geq 0, I_a \geq 0, I_b \geq 0, I_m \geq 0\}$$
$$G_1 = \{Z | S_p > 0, I_p = 0, S_h > 0, I_s = 0, I_a = 0, I_b = 0, I_m = 0\}.$$

Theorem 4.6. *If $R_p \leq 1, R_{sh} < 1$ and $R_{mh} < 1$ then $Z_1^* = (S_{p_1}^*, 0, S_{h_1}^*, 0, 0, 0, 0)$ is GAS on Ω_1.*

Proof. Since $S_p' + \delta_p S_p = \eta_p$ is a linear first order differential equation can be solved exactly to give $S_p(t) = \eta_p/\delta_p + (S_{p_0}^* - \eta_p/\delta_p) e^{-\delta_p t} \to \eta_p/\delta_p$ as $t \to \infty$. Having $I_p = 0$ in equation (4.3f) and integrating over $[0, \infty]$ results in $\lim_{t\to\infty} I_b(t) = 0$.

By using Lemma 4.5, equation (4.3d) becomes

$$I_s' \leq \left[\alpha_{sh}\kappa_{sh} S_{h_1}^* - (\delta_h + m_s)\right] I_s$$

or

$$I_s' \leq (\delta_h + m_s)(R_{sh} - 1)\, I_s.$$

Since $R_{sh} < 1$, $\lim_{t\to\infty} I_s(t) = 0$. Hence, $\lim_{t\to\infty} I_a(t) = 0$. Therefore, as $t \to \infty$ equation (4.3g) becomes

$$I_m' \leq \alpha_{mh}\kappa_{mh} I_m S_{h_1}^* - (\delta_h + m_m)\, I_m$$

or

$$I_m' \leq (\delta_h + m_m)\,(R_{mh} - 1)\; I_m.$$

Since $R_{mh} < 1$, $\lim_{t\to\infty} I_m(t) = 0$. These imply that for any initial disease state $Z_0 \in \Omega_1$ there will always exist ω-limit set of orbit through Z_0, $\omega(Z_0) \in G_1$. Therefore

Z_1^* is GAS on G_1. Since $G_1 \subset \Omega_1$ and Z_1^* is LAS on Ω_1(by Lemma 4.4), hence Z_1^* is GAS on Ω_1. □

4.5.4 Stabilty analysis of swine flu epidemic equilibrium

The swine flu epidemic equilibrium, Z_2^*, corresponds to the situation in which there are no birds or humans infected by avian flu and no humans infected mutant-avian flu but there are humans infected by swine flu. By using the definitions of the basic reproduction numbers in Section 4.3,

$$Z_2^* = (S_{p_2}^*, 0, S_{h_2}^*, I_{s_2}^*, 0, 0, 0) \tag{4.29}$$

where

$$\begin{aligned} S_{p_2}^* &= S_{p_0}^* = \frac{\eta_p}{\delta_p}, \\ S_{h_2}^* &= \frac{\eta_h}{\delta_h}\frac{1}{R_{sh}}, \\ I_{s_2}^* &= \frac{\eta_h}{\delta_h + m_s}(1 - \frac{1}{R_{sh}}). \end{aligned}$$

Lemma 4.7. *If $R_p \leq 1$ and $R_{sh} > \max\{R_{mh}, 1\}$ then $Z_2^* = (S_{p_2}^*, 0, S_{h_2}^*, I_{s_2}^*, 0, 0, 0)$ is LAS.*

Proof. At Z_2^* ${}^*_{p_2} = \frac{\eta_p}{\delta_p} > 0$ $S_{h_2}^* = \frac{\delta_h + m_s}{\alpha_{sh}\kappa_{sh}}$ Note that

$$I_{s_2}^* = \frac{\eta_h}{\delta_h + m_s}\left(1 - \frac{1}{R_{sh}}\right) > 0 \Leftrightarrow R_{sh} > 1$$

and so $I_{s_2}^* > 0$ provided $R_{sh} > 1$.

At Z_2^* the key Jacobian matrices (4.25) and (4.26) becomes

$$J_{21} = \begin{bmatrix} j_{1,1} & j_{1,2} \\ 0 & j_{2,2} \end{bmatrix} \tag{4.30}$$

and

$$J_{22} = \begin{bmatrix} j_{3,3} & j_{3,4} & 0 & 0 & j_{3,7} \\ j_{4,3} & 0 & 0 & 0 & 0 \\ 0 & 0 & j_{5,5} & 0 & 0 \\ 0 & 0 & 0 & j_{6,6} & 0 \\ 0 & 0 & j_{7,5} & 0 & j_{7,7} \end{bmatrix}, \tag{4.31}$$

respectively, where $j_{1,1} = (-1)\delta_p$, $j_{1,2} = -\alpha_p\kappa_p S^*_{p_2}$, $j_{2,2} = -\alpha_p\kappa_p S^*_{p_2} - (\delta_p + m_p)$, $j_{3,3} = (-1)(\delta_h + \alpha_{sh}\kappa_{sh}I^*_{s_2})$, $j_{3,4} = (-1)\alpha_{sh}\kappa_{sh}S^*_{h_2}$, $j_{37} = (-1)\alpha_{mh}\kappa_{mh}S^*_{h_2}$, $j_{4,3} = (-1)\alpha_{sh}\kappa_{sh}I^*_{s_2}$, $j_{5,5} = (-1)\left[\mu\alpha_{sh}\kappa_{sh}I^*_{s_2} + (\delta_h + m_a)\right]$, $j_{6,6} = (-1)(\delta_h + m_b)$, $j_{7,5} = (-1)[\mu\alpha_{sa}\kappa_{sa}I^*_{s_2}$, $j_{7,7} = \alpha_{mh}\kappa_{mh}S^*_{h_2} + (\delta_h + m_m)$.

The key Jacobian matrix J_{21} is stable if $R_p \leq 1$ because $J_{21} = J_{11}$ and J_{11} is stable if $R_p \leq 1$. The characteristic polynomial of the key Jacobian matrix (4.31) is

$$|\lambda I - J_{22}| = \begin{bmatrix} \lambda - j_{3,3} & -j_{3,4} & 0 & 0 & j_{3,7} \\ j_{4,3} & \lambda & 0 & 0 & 0 \\ 0 & 0 & \lambda - j_{5,5} & 0 & 0 \\ 0 & 0 & 0 & \lambda - j_{6,6} & 0 \\ 0 & 0 & j_{7,5} & 0 & \lambda - j_{7,7} \end{bmatrix}$$

or

$$\begin{aligned} |\lambda I - J_{22}| &= (\lambda - j_{5,5})(\lambda - j_{6,6})(\lambda - j_{7,7}) \begin{bmatrix} \lambda - j_{3,3} & j_{3,4} \\ -j_{4,3} & \lambda \end{bmatrix} \\ &= (\lambda - j_{5,5})(\lambda - j_{6,6})(\lambda - j_{7,7})(\lambda^2 + b\lambda + c) \end{aligned}$$

where $b = -j_{3,3}$ and $c = -j_{4,3}j_{3,4}$. Since $j_{5,5} = (-1)\left[\mu\alpha_s\kappa_s I^*_{s_2} + (\delta_h + m_a)\right]$ and $j_{6,6} = (-1)(\delta_h + m_b) < 0$ the matrix J_2 is stable if

$$j_{7,7} = \frac{\alpha_{mh}\kappa_{mh}(\delta_h + m_s)}{\alpha_{sh}\kappa_{sh}} \leq 0 \Leftrightarrow R_{mh} \leq R_{sh}$$

and the roots of the quadratic $\lambda^2 + b\lambda + c$ have negative real parts. Since

$$b = -j_{3,3} = \delta_h + \alpha_{sh}\kappa_{sh}I^*_{s_2} = \frac{\alpha_{sh}\kappa_{sh}\eta_h}{\delta_h + m_s} > 0$$

it follows that the roots of the quadratic have negative real parts if

$$c = -j_{4,3}j_{3,4} = \alpha^2_{sh}\kappa^2_{sh}I^*_{s_2}S^*_{h_2} = \left(\frac{\alpha_{sh}\kappa_{sh}\eta_h}{\delta_h + m_s} - \delta_h\right)(\delta_h + m_s) \geq 0 \Leftrightarrow R_{sh} \geq 1.$$

Hence Z^*_2 is well-defined and stable if $R_p \leq 1$ and $R_{sh} > \max\{R_{mh}, 1\}$. It is interesting to consider the slightly stronger condition $j_{7,7} = -\epsilon_m < 0$. If $S_h = S^*_{h_2}$ and $I^*_{a_2} = 0$ then the final system equation becomes

$$I'_m(S^*_{h_2}, 0)(t) = -\epsilon_m I_m(S^*_{h_2}, 0)(t)$$

and so if $I_m(S^*_{h_2}, 0)(t) > 0$ then $I_m(S^*_{h_2}, 0)(t) \downarrow I^*_{m_2} = 0$ as $t \to \infty$. Hence the condition $j_{7,7} \leq 0 \Leftrightarrow R_{mh} \leq R_{sh}$ is effectively a stability condition on the coordinate I_m at the point $I^*_{m_2} = 0$. □

For $Z = (S_p, I_p, S_h, I_s, I_a, I_b, I_m)$, let

$$\Omega_2 = \{Z | S_p > 0, I_p \geq 0, S_h > 0, I_s > 0, I_a \geq 0, I_b \geq 0, I_m \geq 0\}$$
$$G_2 = \{Z | S_p > 0, I_p = 0, S_h > 0, I_s > 0, I_a = 0, I_b = 0, I_m = 0\}.$$

The global stability of Z_2^* on Ω_2 is analyzed as follow. In relation to the equilibrium at the point Z_2^*, by setting $I_p = 0, I_a = 0, I_b = 0$ and $I_m = 0$, the full system is simplified to

$$S_p' = \eta_p - \delta_p S_p \tag{4.32a}$$
$$S_h' = \eta_h - \delta_h S_h - \alpha_{sh}\kappa_{sh} I_h S_h \tag{4.32b}$$
$$I_s' = \alpha_{sh}\kappa_{sh} I_s S_h - (\delta_h + m_s) I_s. \tag{4.32c}$$

Lemma 4.8. *If $R_{sh} > 1$ then $Y_2^* = (S_{p_2}^*, S_{h_2}^*, I_{s_2}^*)$ is LAS for the simplified system (4.32a)-(4.32c).*

Proof. It is important to understand that the variables S_p, S_h and I_s are conditionally independent of the remaining variables I_p, I_a, I_b only if these neglected variables are guaranteed at the nominated zero values. The coordinates for the equilibrium point $Y_2^* = (S_{p_2}^*, S_{h_2}^*, I_{s_2}^*)$ in the simplified system (4.32a)-(4.32c)

$$S_{p_2}^* = \frac{\eta_p}{\delta_p},\ S_{h_2}^* = \frac{\delta_p + m_s}{\alpha_{sh}\kappa_{sh}}, I_{s_2}^* = \frac{\eta_h}{\delta_h + m_s} - \frac{\delta_h}{\alpha_{sh}\kappa_{sh}}.$$

These coordinates are well-defined and positive provided $I_{s_2}^* > 0 \Leftrightarrow R_{sh} > 1$. Now the Jacobian matrix at Y_2^* is

$$H = \begin{bmatrix} -\delta_p & 0 & 0 \\ 0 & -\frac{\alpha_{sh}\kappa_{sh}\eta_h}{\delta_h + m_s} & -(\delta_h + m_s) \\ 0 & \frac{\alpha_{sh}\kappa_{sh}\eta_h}{\delta_h + m_s} - \delta_h & 0 \end{bmatrix}$$

and so the characteristic polynomial is

$$|\lambda I - H| = (\lambda + \delta_p)\left(\lambda^2 + \frac{\alpha_{sh}\kappa_{sh}\eta_h}{\delta_h + m_s}\lambda + \alpha_{sh}\kappa_{sh}\eta_h - \delta_h(\delta_h + m_s)\right).$$

The condition $R_{sh} > 1$ ensures that the constant coefficient of the quadratic factor is nonnegative. Since the two remaining coefficients in the quadratic factor are also positive it follows that the two roots of the quadratic have negative real parts. Since the remaining root of the characteristic polynomial is negative it follows that the simplified system is stable at Y_2^*. □

Lemma 4.8 applies to the simplified system (4.32a)-(4.32c)and the projected point

$Y_2^* = (S_{p_2}^*, S_{h_2}^*, I_{s_2}^*)$ and does not apply to the full system (4.3a)-(4.3g) and the point $Z_2^* = (S_{p_2}^*, 0, S_{h_2}^*, I_{s_2}^*, 0, 0, 0)$. In terms of convergence it can be seen that $Z_2(t) \to Z_2^*$ implies $Y_2(t) \to Y_2^*$ but the reverse implication is not true.

Theorem 4.9. *If $R_p \leq 1$ and $R_{sh} \geq \max\{R_{mh}, 1\}$ then $Z_2^* = (S_{p_2}^*, 0, S_{h_2}^*, I_{s_2}^*, 0, 0, 0)$ is GAS on Ω_2.*

Proof. Since $S_p' + \delta_p S_p = \eta_p$ is a linear first order differential equation can be solved exactly to give $S_p(t) = \eta_p/\delta_p + (S_{p_0}^* - \eta_p/\delta_p)e^{-\delta_p t} \to \eta_p/\delta_p$ as $t \to \infty$. Having $I_p = 0$ in equation (4.3f) and integrating it over $[0, \infty]$ results in $\lim_{t\to\infty} I_b(t) = 0$. By Lemma 4.5, $S_h^\infty \leq S_{h_1}^*$. Since $R_{mh} \leq 1$, $\lim_{t\to\infty} I_m(t) = 0$. Hence, $\lim_{t\to\infty} I_a(t) = 0$. Therefore, as $t \to \infty$ equation (4.3g) becomes

$$I_m' \leq \alpha_{mh}\kappa_{mh} I_m S_{h_2}^* - (\delta_h + m_m)\, I_m$$

or

$$I_m' \leq (\delta_h + m_m)\,(R_{mh} - 1))\; I_m.$$

Since $R_{mh} \leq 1$, $\lim_{t\to\infty} I_m(t) = 0$. These imply that for any initial disease state, Z_0, there will always exist an ω-limit set of orbit through Z_0, $\omega(Z_0) \in G_2$. By Lemma 4.8, Z_2^* is GAS on G_2. Since $G_2 \subset \Omega_2$ and Z_2^* is LAS on Ω_2 then Z_2^* is GAS on Ω_2.

□

4.5.5 Stabilty analysis of mutant-avian flu epidemic equilibrium

The mutant avian flu epidemic equilibrium, Z_3^*, corresponds to the situation in which there are no birds or humans infected by avian flu and no humans infected by swine flu but there are humans infected by mutant-avian flu. By using the definitions of the basic reproduction numbers in Section 4.3,

$$Z_3^* = (S_{p_3}^*, 0, S_{h_3}^*, 0, 0, 0, I_{m_3}^*), \tag{4.33}$$

where

$$\begin{aligned} S_{p_3}^* &= S_{p_0}^* = \frac{\eta_p}{\delta_p} \\ S_{h_3}^* &= \frac{\eta_h}{\delta_h}\frac{1}{R_{mh}}, \\ I_{m_3}^* &= \frac{\eta_h}{\delta_h + m_m}(1 - \frac{1}{R_{mh}}). \end{aligned}$$

Lemma 4.10. *If $R_p \leq 1$ and $R_{mh} > \max\{R_{sh}, 1\}$ then $Z_3^* = (S_{p_3}^*, 0, S_{h_3}^*, 0, 0, 0, I_{m_3}^*)$ is LAS.*

Proof.

$$S^*_{p_3} = S^*_{p_0} = \frac{\eta_p}{\delta_p},\ S^*_{h_3} = \frac{\delta_h + m_m}{\alpha_{mh}\kappa_{mh}}, I^*_{m_3} = \frac{\eta_h}{\delta_h + m_m} - \frac{\delta_h}{\alpha_{mh}\kappa_{mh}}.$$

Note that

$$\frac{\eta_h}{\delta_h + m_m} - \frac{\delta_h}{\alpha_{mh}\kappa_{mh}} > 0 \Leftrightarrow \frac{\eta_h}{\delta_h + m_m}\left(1 - \frac{1}{R_{mh}}\right) > 0 \Leftrightarrow R_{mh} > 1$$

and so $I^*_{m_3} > 0$ provided $R_{mh} > 1$.

At Z^*_3 the key Jacobian matrices (4.25) and (4.26) becomes

$$J_{31} = J_{11} = \begin{bmatrix} j_{1,1} & j_{1,2} \\ 0 & j_{2,2} \end{bmatrix} \tag{4.34}$$

and

$$J_{32} = \begin{bmatrix} j_{3,3} & j_{3,4} & 0 & 0 & j_{3,7} \\ 0 & j_{4,4} & 0 & 0 & 0 \\ 0 & 0 & j_{5,5} & 0 & 0 \\ 0 & 0 & 0 & j_{6,6} & 0 \\ j_{7,5} & 0 & 0 & 0 & j_{7,7} \end{bmatrix} \tag{4.35}$$

respectively, where $j_{1,1} = (-1)\delta_p$, $j_{1,2} = -\alpha_p\kappa_p S^*_{p_2}$, $j_{2,2} = -\alpha_p\kappa_p S^*_{p_2} - (\delta_p + m_p)$, $j_{3,3} = (-1)(\delta_h + \alpha_{mh}\kappa_{mh}I^*_{m_3})$, $j_{3,4} = (-1)\alpha_{sh}\kappa_{sh}S^*_{h_3}$, $j_{3,7} = (-1)\alpha_{mh}\kappa_{mh}S^*_{h_3}$, $j_{4,4} = (-1)\alpha_{sh}\kappa_{sh}S^*_{h_3} - (\delta_h + m_s)$, $j_{5,5} = (-1)(\delta_h + m_a)$, $j_{6,6} = (-1)(\delta_h + m_b)$, $j_{7,3} = (-1)\alpha_{mh}\kappa_{mh}I^*_{m_3}$, $j_{7,7} = \alpha_{mh}\kappa_{mh}S^*_{h_3} - (\delta_h + m_m)$.

The key Jacobian matrix J_{31} is stable if $R_p \leq 1$ because $J_{31} = J_{11}$ and J_{11} is stable if $R_p \leq 1$.

$$|\lambda I - J_{32}| = (\lambda - j_{4,4})(\lambda - j_{5,5})(\lambda - j_{6,6})(\lambda^2 + b\lambda + c)$$

where $b = (-1)j_{3,3}$ and $c = -j_{7,3}j_{3,7}$. The roots $j_{5,5} < 0$ and $j_{6,6} < 0$

$$j_{4,4} \leq 0 \Leftrightarrow \frac{\alpha_{sh}\kappa_{sh}}{\alpha_{mh}\kappa_{mh}} - (\delta_h + m_s) \leq 0 \Leftrightarrow R_{mh} \geq R_{sh}.$$

Hence it follows that the matrix J_2 will be stable if the roots of the quadratic $\lambda^2 + b\lambda + c$ have negative real parts. Since $b = (-1)j_{3,3} > 0$ the stability is assumed provided

$$c = \alpha^2_{mh}\kappa^2_{mh}I^*_{m_3}S^*_{h_3} = \left(\frac{\alpha_{mh}\kappa_{mh}\eta_h}{\delta_h + m_m} - \delta_h\right)(\delta_h + m_m) \geq 0 \Leftrightarrow R_{mh} \geq 1.$$

Hence Z^*_3 is well-defined and stable if $R_p \leq 1$ and $R_{mh} > \max\{R_{sh}, 1\}$.

□

The global stability of the disease free equilibrium Z_3^* is analyzed as follows. For $Z = (S_p, I_p, S_h, I_s, I_a, I_b, I_m)$, let

$$\Omega_3 = \{Z | S_p > 0, I_p \geq 0, S_h > 0, I_s \geq 0, I_a \geq 0, I_b \geq 0, I_m > 0\},$$
$$G_3 = \{Z | S_p > 0, I_p = 0, S_h > 0, I_s = 0, I_a = 0, I_b = 0, I_m > 0\}.$$

In domain G_3 , $(4.3a) - (4.3g)$ reduces to

$$S_p' = \eta_p - \delta_p S_p \tag{4.36a}$$
$$S_h' = \eta_h - \delta_h S_h - \alpha_{sh}\kappa_{sh} I_h S_h \tag{4.36b}$$
$$I_m' = \alpha_{mh}\kappa_{mh} I_m S_h - (\delta_h + m_m) I_m. \tag{4.36c}$$

Lemma 4.11. *If $R_{mh} > 1$ then $Y_3^* = (S_{p_3}^*, S_{h_3}^*, I_{m_3}^*)$ is LAS for the simpified system (4.36a)-(4.36c).*

Proof. The variables S_p, S_h and I_m are conditionally independent of the remaining variables I_p, I_a, I_b only if these neglected variables are guaranteed at the nominated zero values. The coordinates for the equilibrium point $Y_3^* = (S_{p_3}, S_{h_3}, I_{s_3})$ in the simplified system (4.36a)-(4.36c)

$$S_{p_3}^* = \frac{\eta_p}{\delta_p},\ S_{h_3}^* = \frac{\delta_p + m_m}{\alpha_{mh}\kappa_{mh}}, I_{m_2}^* = \frac{\eta_h}{\delta_h + m_m} - \frac{\delta_h}{\alpha_{mh}\kappa_{mh}}.$$

These coordinates are well-defined and positive provided $I_{m_3}^* > 0 \Leftrightarrow R_{mh} > 1$. Now the Jacobian matrix at Y_3^* is

$$H = \begin{bmatrix} -\delta_p & 0 & 0 \\ 0 & -\frac{\alpha_{mh}\kappa_{mh}\eta_h}{\delta_h + m_m} & -(\delta_h + m_m) \\ 0 & \frac{\alpha_{mh}\kappa_{mh}\eta_h}{\delta_h + m_m} - \delta_h & 0 \end{bmatrix}$$

and so the characteristic polynomial is

$$|\lambda I - H| = (\lambda + \delta_p)\left(\lambda^2 + \frac{\alpha_{mh}\kappa_{mh}\eta_h}{\delta_h + m_m}\lambda + \alpha_{mh}\kappa_{mh}\eta_h - \delta_h(\delta_h + m_m)\right).$$

The condition $R_{mh} > 1$ ensures that the constant coefficient of the quadratic factor is nonnegative. Since the two remaining coefficients in the quadratic factor are also positive it follows that the two roots of the quadratic have negative real parts. Since the remaining root of the characteristic polynomial is negative it follows that the simplified system is stable at Y_3^*. □

Lemma 4.11 applies to the simplified system (4.36a)-(4.36c)and the projected point $Y_3^* = (S_{p_3}^*, S_{h_3}^*, I_{m_3}^*)$ and does not apply to the full system (4.3a)-(4.3g) and the point $Z_3^* = (S_{p_3}^*, 0, S_{h_3}^*, 0, 0, 0, I_{m_3}^*)$. In terms of convergence it can be seen that $Z_3(t) \to Z_3^*$ implies $Y_3(t) \to Y_3^*$ but the reverse implication is not true.

Theorem 4.12. *If $R_p \leq 1$ and $R_{mh} \geq \max\{R_{sh}, 1\}$ then $Z_3^* = (S_{p_3}^*, 0, S_{h_3}^*, 0, 0, 0, I_{m_3}^*)$ is GAS on Ω_3.*

Proof. Since $S_p' + \delta_p S_p = \eta_p$ is a linear first order differential equation can be solved exactly to give $S_p(t) = \eta_p/\delta_p + (S_p(0) - \eta_p/\delta_p)e^{-\delta_p t} \to \eta_p/\delta_p$ as $t \to \infty$. Having $I_p = 0$ in equation (4.3f) and integrating over $[0, \infty]$ results in $\lim_{t\to\infty} I_b(t) = 0$.

By using Lemma 4.5, $S_h^\infty \leq S_{h_1}^*$. Since $R_{mh} \leq 1$, $\lim_{t\to\infty} I_m(t) = 0$. Hence, $\lim_{t\to\infty} I_a(t) = 0$. Therefore, at $t \to \infty$ equation (4.3d) becomes

$$I_s' \leq (\delta_h + m_s)\left(\alpha_{sh}\kappa_{sh}S_{h_3}^* - 1)\right) I_s,\ t \to \infty$$

or

$$I_s' \leq (\delta_h + m_s)\left(R_{sh} - 1)\right) I_s.$$

Since $R_{sh} \leq 1$, $\lim_{t\to\infty} I_s(t) = 0$. These imply that for any initial disease state Z_0, there will always exist $\omega(Z_0)$, the ω-limit set of orbit through Z_0 in $\mathcal{D}_3$. By Lemma 4.11, Z_3^* is GAS on G_3. Since Z_3^* is LAS on Ω_3, Z_3^* is GAS on Ω_3. □

4.5.6 *Stability analysis of avian-flu epidemic equilibrium (among birds and humans)*

Z_4^* coresponds to the situation in which there are avian flu epidemics among birds and humans. By using the definitions of the basic reproduction numbers, the disease state when there are avian flu epidemics among birds and humans, Z_4^*, becomes

$$Z_4^* = (S_{p_4}^*, I_{p_4}^*, S_{h_4}^*, 0, I_{a_4}^*, I_{b_4}^*, 0). \tag{4.37}$$

$$S_{p_4}^* = \frac{\eta_p}{\delta_p}\frac{1}{R_p} > 0,$$

$$I_{p_4}^* = \frac{\eta_p}{\delta_p + m_p}(1 - \frac{1}{R_p}),$$

$$S_{h_4}^* = \frac{\frac{\eta_h}{\delta_h}}{1 + \frac{\alpha_{ph}\kappa_{ph}\eta_p}{\eta_h(\delta_p + m_p)}\left(1 - \frac{1}{R_p}\right)}$$

or

$$S^*_{h_4} = \frac{\frac{\eta_h}{\delta_h}}{1 + r_{ph}}$$

where r_{ph} is defined as

$$r_{ph} = \frac{\alpha_{ph}\kappa_{ph}\eta_p}{\eta_h\ (\delta_p + m_p)} \left(1 - \frac{1}{R_p}\right). \tag{4.38}$$

$S^*_{h_4} > 0 \Leftrightarrow R_p > 1$

$$I^*_{a_4} = \frac{\gamma\eta_h}{\delta_h + m_a} \left(1 - \frac{1}{1 + r_{ph}}\right) > 0$$

and

$$I^*_{b_4} = \frac{(1-\gamma)\eta_h}{\delta_h + m_b} \left(1 - \frac{1}{1 + r_{ph}}\right) > 0$$

The condition $R_p > 1$ means $r_{ph} > 0$ and hence guarantees that $I^*_{p_4} > 0, S^*_{h_4} > 0, I^*_{a_4} > 0$ and $I^*_{b_4} > 0$.

Theorem 4.13. *If $R_p > 1$ and $\max\{R_{sh}, R_{mh}\} < 1 + r_{ph}$ then $Z^*_4 = (S^*_{p_4}, I^*_{p_4}, S^*_{h_4}, 0, I^*_{a_4}, I^*_{b_4}, 0)$ is LAS.*

Proof. At Z^*_4 the key Jacobian matrices (4.25) and (4.26) becomes

$$J_{41} = \begin{bmatrix} j_{1,1} & j_{1,2} \\ j_{2,1} & 0 \end{bmatrix} \tag{4.39}$$

and

$$J_{42} = \begin{bmatrix} j_{3,3} & j_{3,4} & 0 & 0 & j_{3,7} \\ 0 & j_{4,4} & 0 & 0 & 0 \\ j_{5,3} & j_{5,4} & j_{5,5} & 0 & 0 \\ j_{6,3} & 0 & 0 & j_{6,6} & 0 \\ 0 & j_{7,4} & 0 & 0 & j_{7,7} \end{bmatrix} \tag{4.40}$$

respectively, where $j_{1,1} = (-1)\delta_p(\alpha_p\kappa_p I^*_{p_4})$, $j_{1,2} = -\alpha_p\kappa_p S^*_{p_4}$, $j_{2,1} = \alpha_p\kappa_p I^*_{p_4} - (\delta_p + m_p)$,, $j_{2,2} = \alpha_p\kappa_p S^*_{p_4} - (\delta_p + m_p)$, $j_{3,3} = (-1)(\delta_h + \alpha_{ph}\kappa_{ph} I^*_{p_4})$, $j_{3,4} = (-1)\alpha_{sh}\kappa_{sh} S^*_{h_4}$, $j_{3,7} = (-1)\alpha_{mh}\kappa_{mh} S^*_{h_4}$, $j_{4,4} = (-1)\alpha_{sh}\kappa_{sh} S^*_{h_4} - (\delta_h + m_s)$, $j_{5,3} = \gamma\alpha_{ph}\kappa_{ph} I^*_{p_4}$, $j_{5,4} = (-1)\mu\alpha_{sa}\kappa_{sa} I^*_{a_4}$, $j_{5,5} = (-1)(\delta_h + m_a)$, $j_{6,3} = (1-\gamma)\alpha_{ph}\kappa_{ph} I^*_{p_4}$, $j_{6,6} = (-1)(\delta_h + m_b)$, $j_{7,4} = \mu\alpha_{sa}\kappa_{sa} I^*_{a_4}$, $j_{7,7} = \alpha_{mh}\kappa_{mh} S^*_{h_4} + (\delta_h + m_m)$.

It follows that

$$\begin{aligned}|\lambda I - J_{41}| &= (\lambda - j_{1,1})\lambda - j_{1,2}j_{2,1} \\ &= \lambda^2 - j_{1,1}\lambda - j_{1,2}j_{2,1} \\ &= \lambda^2 - b\lambda - c\end{aligned}$$

where the formulæfor $S^*_{p_4}$ and $I^*_{p_4}$ can be used to see that

$$b = -j_{1,1} = \alpha_p \kappa_p I^*_{p_4} = \frac{\mu_p \alpha_p \kappa_p}{\delta_p + m_p} > 0$$

and

$$c = -j_{1,2}j_{2,1} = \alpha_p^2 \kappa_p^2 S^*_{p_4} I^*_{p_4} > 0.$$

Hence if the root are real they are both negative. If the root are complex conjugates then the real part is negative. In either case J_{41} is stable. Next

$$\begin{aligned}|\lambda I - J_{42}| &= (\lambda - j_{6,6}) \begin{bmatrix} \lambda - j_{3,3} & -j_{3,4} & 0 & j_{3,7} \\ 0 & \lambda - j_{4,4} & 0 & 0 \\ -j_{5,3} & -j_{5,4} & \lambda - j_{5,5} & 0 \\ 0 & j_{7,4} & 0 & \lambda - j_{7,7} \end{bmatrix} \\ &= (\lambda - j_{6,6})(\lambda - j_{5,5}) \begin{bmatrix} \lambda - j_{3,3} & -j_{3,4} & -j_{7,7} \\ 0 & \lambda - j_{4,4} & 0 \\ 0 & \lambda - j_{7,7} & 0 \end{bmatrix}\end{aligned}$$

or

$$\begin{aligned}|\lambda I - J_{42}| &= (\lambda - j_{6,6})(\lambda - j_{5,5})(\lambda - j_{4,4})(\lambda - j_{7,7}) \begin{bmatrix} \lambda - j_{3,3} & -j_{7,7} \\ 0 & \lambda - j_{7,7} \end{bmatrix} \\ &= \Pi_{k=3}^{7} (\lambda - j_{k,k}) \\ &= 0\end{aligned}$$

if $\lambda = j_{k,k}$ for each $k = 3, \ldots, 7$. Clearly $j_{3,3}, j_{5,5}$ and $j_{6,6}$ are all negative. $j_{4,4} < 0$ if $\alpha_{sh}\kappa_{sh}S^*_{h_4} - (\delta_h - m_s) < 0$ and $j_{7,7} < 0$ if $\alpha_{mh}\kappa_{mh}S^*_{h_4} - (\delta_h - m_m) < 0$. Hence the matrix J_{42} is stable if $\alpha_{sh}\kappa_{sh}S^*_{h_4} - (\delta_h - m_s) = -\epsilon_s < 0$ and $\alpha_{mh}\kappa_{mh}S^*_{h_4} - (\delta_h - m_m) = -\epsilon_s < 0$. These conditions are interesting because when $S_h = S^*_{h_4}$

$$I'_s(S^*_{h_4}, t) = \left[\alpha_{sh}\kappa_{sh}S^*_{h_4} - (\delta_h - m_s)\right] I_s(S^*_{h_4}, t) = \epsilon_s I_s(S^*_{h_4}, t)$$

and so $I_s(S^*_{h_4}, t) > 0$ then $I_s(S^*_{h_4}, 0, t) \downarrow 0$ as $t \uparrow \infty$. Is $I^*_{s_4} = 0$ and $S_h = S^*_{h_4}$ then

$$I'_m(S^*_{h_4}, 0, t) = \left[\alpha_{mh}\kappa_{mh}S^*_{h_4} - (\delta_h - m_m)\right] I_m(S^*_{h_4}, t) = \epsilon_m I_m(S^*_{h_4}, t)$$

and so if $I_m(S^*_{h_4}, 0, t_0) > 0$ then $I_m(S^*_{h_4}, 0, t) \downarrow 0$ as $t \uparrow \infty$. Hence these conditions are essentially stability conditions on $I^*_{s_4} = 0$ and $I^*_{m_4} = 0$ respectively. Note that

$$\alpha_{sh}\kappa_{sh}\frac{\frac{\eta_h}{\delta_h}}{1 + r_{ph}} - (\delta_h - m_s) < 0 \Leftrightarrow \frac{\eta_h\alpha_{sh}\kappa_{sh}}{\delta_h(\delta_h - m_s)} < 1 + r_{ph} \Leftrightarrow R_{sh} < 1 + r_{ph}$$

and

Hence Z^*_4 well-defined and stable if $R_p > 1$ and $\max\{R_{sh}, R_{mh}\} < 1 + r_{ph}$. Therefore Z^*_4 is LAS. □

4.5.7 *Stability analysis of avian flu epidemic among birds and humans combined with mutant avian flu epidemic among humans*

The disease state equilibrium point Z^*_5 corresponds to the situation in which there are avian flu epidemic among birds and humans combined with mutant avian flu epidemic among humans,

$$Z^*_5 = (S^*_{p_5}, I^*_{p_5}, S^*_{h_5}, 0, I^*_{a_5}, I^*_{b_5}, I^*_{m_5}). \tag{4.41}$$

$$S^*_{p_5} = \frac{\eta_p}{\delta_p}\frac{1}{R_p} > 0.$$

From (4.20a) it follows that

$$I^*_{p_5} = \frac{\eta_p}{\delta_p + m_p}(1 - \frac{1}{R_p})$$

Hence for $I^*_{p_5} > 0$ it is required that $R_p > 1$. it follows from (4.20f)

$$S^*_{h_5} = \frac{\delta_h + m_m}{\alpha_{mh}\kappa_{mh}} > 0.$$

Now (4.20c) gives

$$I^*_{m_5} = \frac{\delta_h}{\alpha_{mh}\kappa_{mh}}\left[R_{mh} - (1 + r_{ph})\right].$$

where r_{ph} is defined by (4.38)

$$r_{ph} = \frac{\alpha_{ph}\kappa_{ph}\eta_p}{\eta_h\ (\delta_p + m_p)}\left(1 - \frac{1}{R_p}\right)$$

Therefore for $I^*_{m_5} > 0$ it is necessary that $R_{mh} > 1 + r_{ph}$. Finally (4.20d) and (4.20e) give

$$I^*_{a_5} = \frac{\gamma\eta_h r_{ph}}{(\delta_h + m_a)R_{mh}} > 0$$

and

$$I^*_{b_5} = \frac{(1-\gamma)\eta_h r_{ph}}{(\delta_h + m_b)R_{mh}} > 0$$

The condition $R_p > 1$ and $R_{mh} > 1 + r_{ph}$ guarantees that $I^*_{p_5} > 0, I^*_{a_5} > 0, I^*_{b_5} > 0$ and $I^*_{m_5} > 0$.

Theorem 4.14. *If $R_p > 1$ and $R_{mh} > \max\{R_{sh}, 1 + r_{ph}\}$ then $Z^*_5 = (S^*_{p_5}, I^*_{p_5}, S^*_{h_2}, 0, I^*_{a_5}, I^*_{b_5}, I^*_{m_5})$ is LAS.*

Proof. At Z^*_5 the key Jacobian matrices (4.25) and (4.26) becomes

$$J_{51} = \begin{bmatrix} j_{1,1} & j_{1,2} \\ j_{2,1} & 0 \end{bmatrix} \tag{4.42}$$

and

$$J_{52} = \begin{bmatrix} j_{3,3} & j_{3,4} & 0 & 0 & j_{3,7} \\ 0 & j_{4,4} & 0 & 0 & 0 \\ j_{5,3} & j_{5,4} & j_{5,5} & 0 & 0 \\ j_{6,3} & 0 & 0 & j_{6,6} & 0 \\ j_{7,3} & j_{7,4} & 0 & 0 & j_{77} \end{bmatrix} \tag{4.43}$$

respectively. where $j_{1,1} = (-1)\delta_p(\alpha_p\kappa_p I^*_{p_5})$, $j_{1,2} = -\alpha_p\kappa_p S^*_{p_5}$, $j_{2,1} = \alpha_p\kappa_p I^*_{p_5} - (\delta_p + m_p)$, $j_{2,2} = \alpha_p\kappa_p S^*_{p_5} - (\delta_p + m_p) = 0$, $j_{3,3} = (-1)(\delta_h + \alpha_{ph}\kappa_{ph}I^*_{p_5} + \alpha_{mh}\kappa_{mh}I^*_{m_5})$, $j_{3,4} = (-1)\alpha_{sh}\kappa_{sh}S^*_{h_5}$, $j_{3,7} = (-1)\alpha_{mh}\kappa_{mh}S^*_{h_5}$, $j_{4,4} = (-1)\alpha_{sh}\kappa_{sh}S^*_{h_5} - (\delta_h + m_s)$, $j_{5,3} = \gamma\alpha_{ph}\kappa_{ph}I^*_{p_5}$, $j_{5,4} = (-1)\mu\alpha_{sa}\kappa_{sa}I^*_{a_5}, j_{5,5} = (-1)(\delta_h + m_a)$, $j_{6,3} = (1-\gamma)\alpha_{ph}\kappa_{ph}I^*_{p_5}$, $j_{6,6} = (-1)(\delta_h + m_b)$, $j_{7,3} = \alpha_{mh}\kappa_{mh}I^*_{m_5}$, $j_{7,4} = \mu\alpha_{sa}\kappa_{sa}I^*_{a_4}$, $j_{7,7} = \alpha_{mh}\kappa_{mh}S^*_{h_4} + (\delta_h + m_m)$.

The key Jacobian matrix J_{51} is stable if $R_p \geq 1$ because $J_{51} = J_{41}$ and J_{41} is stable

if $R_p > 1$. The characteristic polynomial of the second key Jacobian matrix J_{52} is

$$
\begin{aligned}
|\lambda I - J_{52}| &= (\lambda - j_{6,6}) \begin{bmatrix} \lambda - j_{3,3} & -j_{3,4} & 0 & j_{3,7} \\ 0 & \lambda - j_{4,4} & 0 & 0 \\ -j_{5,3} & -j_{5,4} & \lambda - j_{5,5} & 0 \\ j_{7,3} & -j_{7,4} & \lambda - j_{7,7} & \end{bmatrix} \\
&= (\lambda - j_{6,6})(\lambda - j_{5,5}) \begin{bmatrix} \lambda - j_{3,3} & -j_{3,4} & -j_{7,7} \\ 0 & \lambda - j_{4,4} & 0 \\ j_{7,3} & \lambda - j_{7,7} & 0 \end{bmatrix} \\
&= (\lambda - j_{6,6})(\lambda - j_{5,5})(\lambda - j_{4,4})(\lambda - j_{7,7}) \begin{bmatrix} \lambda - j_{3,3} & -j_{7,7} \\ -j_{7,7} & \lambda - j_{7,7} \end{bmatrix} \\
&= \left[\Pi_{k=3}^{7} (\lambda - j_{k,k})\right] [\lambda^2 + b\lambda + c] \\
&= 0
\end{aligned}
$$

where $b = (-1)(j_{3,3} + j_{7,7})$ and $c = j_{3,3}j_{7,7} - j_{7,3}j_{3,7}$. Hence $|\lambda I - J_2| = 0$ if and only if $\lambda = j_{k,k}$ for each $k = 4, 5, 6$ or if $\lambda^2 + b\lambda + c = 0$. Now

$$
\begin{aligned}
b &= 2\delta_h + m_m + \alpha_{ph}\kappa_{ph} I^*_{p_5} - \alpha_{mh}\kappa_{mh} S^*_{h_5} + \alpha_{mh}\kappa_{mh} I^*_{m_5} \\
&= 2\delta_h + m_m + \alpha_{ph}\kappa_{ph} \left(\frac{\eta_p}{\delta_p + m_p} - \frac{\delta_p}{\alpha_p \kappa_p} \right) - \alpha_{mh}\kappa_{mh} \frac{\delta_h + m_m}{\alpha_{mh}\kappa_{mh}} \\
&+ \alpha_{mh}\kappa_{mh} \left(\frac{\eta_h}{(\delta_h + m_m)} - \frac{\delta_h}{\alpha_{mh}\kappa_{mh}} - \frac{\alpha_{ph}\kappa_{ph}\eta_p}{\alpha_{mh}\kappa_{mh}(\delta_p + m_p)} + \frac{\alpha_{ph}\kappa_{ph}\delta_p}{\alpha_{mh}\kappa_{mh}\alpha_p\kappa_p} \right) \\
&= \frac{\alpha_{mh}\kappa_{mh}\eta_h}{\delta_h + m_m} \\
&> 0
\end{aligned}
$$

and

$$
\begin{aligned}
c &= (-1)(\delta_h + \alpha_{ph}\kappa_{ph} I^*_{p_5} + \alpha_{mh}\kappa_{mh} I^*_{m_5})[\alpha_{mh}\kappa_{mh} S^*_{h_5} - \delta_h + m_m] \\
&+ \alpha_{mh}\kappa_{mh} I^*_{m_5} \alpha_{mh}\kappa_{mh} S^*_{h_5} \\
&= -\delta_h \alpha_{mh}\kappa_{mh} \frac{\delta_h + m_m}{\alpha_{mh}\kappa_{mh}} - \alpha_{ph}\kappa_{ph} \left(\frac{\eta_p}{\delta_p + m_p} - \frac{\delta_p}{\alpha_p\kappa_p} \right) (\delta_h + m_m) \\
&+ \alpha_{mh}\kappa_{mh} I^*_{m_5} \alpha_{mh}\kappa_{mh} S^*_{h_5} \\
&= \alpha_{mh}\kappa_{mh} I^*_{m_5} \alpha_{mh}\kappa_{mh} S^*_{h_5} \\
&> 0
\end{aligned}
$$

Since $b > 0$ and $c > 0$ it follows that the roots of the equation $\lambda^2 + b\lambda + c = 0$ are complex conjugates with negative real parts or else they are both real and negative.

The roots $j_{5,5}$ and $j_{6,6}$ are both negative. It follows that J_{52} is stable if and only if $j_{4,4} = \alpha_{sh}\kappa_{sh}S^*_{h_5} - \delta_h + m_s = \epsilon_s < 0$. This is an interesting condition because when $S_h = S^*_{h_5}$,

$$I'(S^*_{h_5}, t) = \left[\alpha_{sh}\kappa_{sh}S^*_{h_5} - \delta_h + m_s\right](I^*_{h_5}, t) = -\epsilon_s I(S^*_{h_5}, t).$$

If $I(S^*_{h_5}, t) > 0$ then $I(S^*_{h_5}, t) \downarrow 0$ as $t \uparrow \infty$. Hence this is effectively a stability condition for the coordinate $I^*_{s_5} = 0$. Since

$$\alpha_{sh}\kappa_{sh}S^*_{h_5} - (\delta_h + m_s) < 0 \Leftrightarrow \alpha_{sh}\kappa_{sh}\frac{(\delta_h + m_m)}{\alpha_{mh}\kappa_{mh}} - (\delta_h + m_s) < 0 \Leftrightarrow R_{sh} < R_{mh}.$$

Therefore, Z^*_5 is well-defined and stable if $R_p > 1$ and $R_{mh} > \max\{R_{sh}, 1 + r_{ph}\}$. □

4.6 Disease persistence among humans

If avian flu is epidemic among birds then the disease persists among humans. When $R_p > 1$, non-zero lower bounds for each of the human disease states are guaranteed by following theorem.

Lemma 4.15. *If $R_p(t) > 1$ then there are positive lower bounds k_i for I_a, I_b, I_s, I_m.*

Proof. For $Z = (S_p, I_p, S_h, I_s, I_a, I_b, I_m) \in \mathbb{R}^7_+$, let

$$\Omega_+ = \{Z | S_p \geq k_x, I_p \geq k_y, k \leq n + N \leq K\},$$
$$D_h = \{Z = (S_p, I_p, S_h, I_s, I_a, I_b, I_m) \in \mathbb{R}^7_+ : S_p \geq k_x, I_p \geq k_y, H = 0, k \leq n + N \leq K\}.$$

Theorem 4.2 guarantees the existence of a unique solution of the full system $(4.3a) - (4.3g)$. Ω_+ is a compact subset of $\mathbb{R}^7_+$ and D_h is a compact subset of Ω_+. On the other hand, the bird system (4.1a, 4.1b), which is independent of (eq: HumanSingle Ch41,4.2e), has a globally stable epidemic state on $Int\mathbb{R}^2_+$ (by Theorem 4.3). Therefore Ω_+ is forward invariant.

Consider ξ as a function of t, $\xi : \Omega_+ \to \mathbb{R}_+$ is a continuously differentiable function satisfying

- $\xi(\epsilon) = 0$ if only if $\epsilon \in D_h$
- $\dot{\xi}(\epsilon) > 0$ for all $\epsilon \in D_h$,

where "." denotes differentiation along an orbit.

Thus, based on Theorem 3.22, for the initial disease state $Z_0 \in \Omega_+ \setminus D_h$ there exists some positive constant k_h such that

$$\liminf_{t\to\infty} S_h(t) \geq k_h.$$

Next, define

$$D_s = \{Z = (S_p, I_p, S_h, I_s, I_a, I_b, I_m) \in \mathbb{R}^7_+ : S_p \geq k_x, I_p \geq k_y, S_h \geq k_h, I_s = 0, k \leq n + N \leq K\}.$$

By using a similar method, it is easy to show that there are positive constants k_s, k_a, k_b, k_m such that

$$\begin{aligned}
&\liminf_{t\to\infty} I_s(t) \geq k_s,\\
&\liminf_{t\to\infty} I_a(t) \geq k_a,\\
&\liminf_{t\to\infty} I_b(t) \geq k_b,\\
&\liminf_{t\to\infty} I_m(t) \geq k_m,
\end{aligned}$$

where

$$\begin{aligned}
D_s = &\quad \{Z = (S_p, I_p, S_h, I_s, I_a, I_b, I_m) \in \mathbb{R}^7_+ : S_p \geq k_x, I_p \geq k_y, I_s = 0, k \leq n + N \leq K\},\\
D_a = &\quad \{Z = (S_p, I_p, S_h, I_s, I_a, I_b, I_m) \in \mathbb{R}^7_+ : S_p \geq k_x, I_p \geq k_y, I_a = 0, k \leq n + N \leq K\},\\
D_b = &\quad \{Z = (S_p, I_p, S_h, I_s, I_a, I_b, I_m) \in \mathbb{R}^7_+ : S_p \geq k_x, I_p \geq k_y, I_b = 0, k \leq n + N \leq K\},\\
D_m = &\quad \{Z = (S_p, I_p, S_h, I_s, I_a, I_b, I_m) \in \mathbb{R}^7_+ : S_p \geq k_x, I_p \geq k_y, I_m = 0, k \leq n + N \leq K\}.
\end{aligned}$$

□

Theorems 4.13 and 4.14 show that Z_4^* and Z_5^* are LAS. Lemma 4.15 shows that the swine flu, avian flu and mutant-avian flu exist persistently in the human world even though there is no more avian flu among birds. Thus, the uniqueness of Z_4^* and Z_5^* suggests that these equlibria are GAS. The proof for GAS seem to follow similarly to proving GAS for other disease equilibria but the size of the problem is so large that the computations have not been completed. However, the following corollaries would justify the use of the lower bounds (4.16) and for (4.17) in solving the optimal disease control problems addressed in Chapter 7.

Corollary 4.16. *If* $R_p > 1$, $R_{sh} > 1$, $R_{mh} > 1$, $R_{mh} > R_{sh}$, $r_{sa} \leq 1$ *then* $S_p(t) \geq S^*_{p_+}, I_p(t) \geq I^*_{p_+}, S_h(t) \geq S^*_{h_4}, I_a(t) \geq I^*_{a_4}$, $I_b(t) \geq I^*_{b_4}$

and

Corollary 4.17. *If* $R_p > 1$, $R_{sh} > 1$, $R_{mh} > 1$, $R_{mh} > R_{sh}$, $r_{sa} \leq 1$ *then* $S_p(t) \geq S^*_{p_+}, I_p(t) \geq I^*_{p_+}, S_h(t) \geq S^*_{h_2}, I_a(t) \geq I^*_{a_5}$, $I_b(t) \geq I^*_{b_5}$, $I_m(t) \geq I^*_{m_5}$.

4.7 Simulation

4.7.1 Epidemic Parameters: Tipar case

The epidemic parameters used in the following simulation are based on the case study of the Tipar village in Cikelet, West Java, described in Section 1.2. There is no swine flu in Tipar and no mutant avian flue has yet appeared in Tipar. Parameters for these aspects of the simulation are taken from available literature.

The chicken population of Tipar is about 10,000 and so this is the value taken for N_p. In a year, a typical hen produces two broods of about ten hatchlings each. Some are sold, eaten or die of natural causes leaving about six new chickens per hen, per year. With an average of about 10 hens per household and 556 households, the recruitment rate per day is taken as $\eta_p = 90$.

The mean life span of chickens is two years [13], [186], [187], [188]. The rate of natural death daily is $\frac{1}{2*365} = 0.001369863$. Hence, $\delta_p = 0.001369863$.

As free-range poultry, the chickens spread unrestricted trough the village by day and shelter underneath houses at night. Thus the assumptions of even contact rates and well mixing of the population are well satisfied by healthy birds. However, sick birds are less mobile. The effective contact rate between infectious chickens and susceptible chickens is taken as two or three per day. Thus, values for κ_p are set at 2 or 3, $\kappa_p = 2, 3$. The transmission rate of avian flu among birds is estimated to be 0.2 with a mean infectious period (incubation period) of four days [10], [16]. Therefore, the daily transmission rate is 0.2, $\alpha_p = 0.2$. An infected chicken will die in about four days and so the mortality among chickens due to avian flu is taken as $m_p = 0.25$.

The total population of Tipar is 2010 and so $S_h = N_h(0) = 2010$. The mean lifespan of villagers is about 60 years. The rate of natural death daily is $\frac{1}{60*365} \approx 0.00005$. Hence, $\delta_h = 0.00005$. Tipar is an isolated village and so there is no daily immigration or emigration. Since $S_h = N_h(0) = \frac{\eta_h}{\delta_h} = 2010$, the birth rate for humans is $\eta_h = 0.092$.

Every day the villagers have contact with chickens. A population member has equal change to have contact with chickens. It is assumed that the number of effective contacts between an infectious bird and susceptible humans is 2 per day. The estimated transmission rate of avian influenza from infected birds to susceptible humans in Indonesia is 2.0×10^{-4} [28], [17]. The estimated mean infectious period of humans with avian influenza is about nine days [189], [28], [17]. The estimated mean infectious period is about 10 days. Since $\frac{1}{m_p} = 10$, the mortality rate of avian flu among human is $m_p = 0.1$. Table 1.3 shows that out of twelve human cases in Tipar: six died while six survived; nine are suspected (without symptom) and three are confirmed (with symptom). There is no report to say that a survivor became infected again. In the simulation it is assumed that a survivor can remain infected but is not infectious. In this study, the proportion of asymptomatic case is assumed to be $\gamma = 3/4$.

The estimated transmission rate of swine flu from infectious humans with swine flu to susceptible humans is 1.82×10^{-4} [61] [190][191]. Virulence among infectious humans with swine flu is 0.01 per day [61]. Therefore, $\alpha_{sh} = 1.82 \times 10^{-4}$ and $\frac{1}{m_s} = 14$ or $m_s = 0.07$ per day.

The number of effective contacts between an infectious human with swine flu and susceptible humans per day is one, $\kappa_{sh} = 1$. Otherwise, if swine flu is epidemic $\kappa_{sh} = 0.1$. It is assumed that $\kappa_{mh} = 1$ if the mutant-avian flu is epidemic otherwise $\kappa_{mh} = 0.1$. It is assumed that $\kappa_{sa} = 0.1$ if the swine flu epidemic otherwise $\kappa_{sa} = 0.01$.

It is estimated that the virulence of the mutant-avian flu as a result of virus recombination between avian flu and swine flu viruses is lower than avian flu but much higher than swine flu. It is assumed that the future epidemic due to mutant-avian flu is comparable with the severe situation of the 1918 pandemic [189]. Estimated transmission rates of the 1918 Spain pandemic vary very widely, ranging from 1.2 to 20 [99], [192], [7], [193]. It is assumed that the probability of mutation as a result of virus recombination of avian flu and swine flu is 4.125×10^{-4} per day, $\mu = 0.0004$. This is two thirds of the probability of virus mutation for the "sole" mutation of 5.50×10^{-4} per day [125]. Following [125], it is assumed here that transmission rate of mutant-avian influenza is 2.8×10^{-4} per day with an estimated mean infectious period of about 14 days for humans with swine flu. Therefore, $\alpha_{mh} = 2.8 \times 10^{-4}$ and $\frac{1}{m_m} = 14$ or $m_p = 0.07$ per day.

Simulation studies show that the spread of avian flu in the human world appears later than that in the bird world. Mutant influenza-A has a bigger magnitude than avian flu in terms of the proportion of individuals acquiring the disease. Variation in the number of effective contacts between susceptible and infectious individuals has significant effects on the spread of disease.

Variation on the number of effective contacts between an infectious individual and susceptible individuals have significant effects to the spread of disease. Figure 4.2 shows the effect of variation of the number of effective contacts between an infectious bird and susceptible birds, κ_p, on the disease transmission among birds. There is no epidemic if κ_p is three or less. When $\kappa_p = 3$ there is a small outbreak in the second day, but then disappear. Avian flu is epidemic among birds if $\kappa_p \geq 4$. The first outbreak happens in the second day and will be followed by another outbreak about one month later. Increasing κ_p will increase the concavity of the corresponding graphs. The red and black lines intersect at about fourth and tenth days.

Figure 4.3 shows the effect of the variation of κ_p on disease transmission among humans. Increasing κ_p will also increase the spread of the diseases among humans except the swine flu. Figure 4.3 (a) shows increasing κ_p will decrease the spread of the swine flu. The decrease on the proportion of human infectious with swine flu is due to double co-infection with avian flu. Comparing Figure 4.3 (a) (b), (c) and (d)

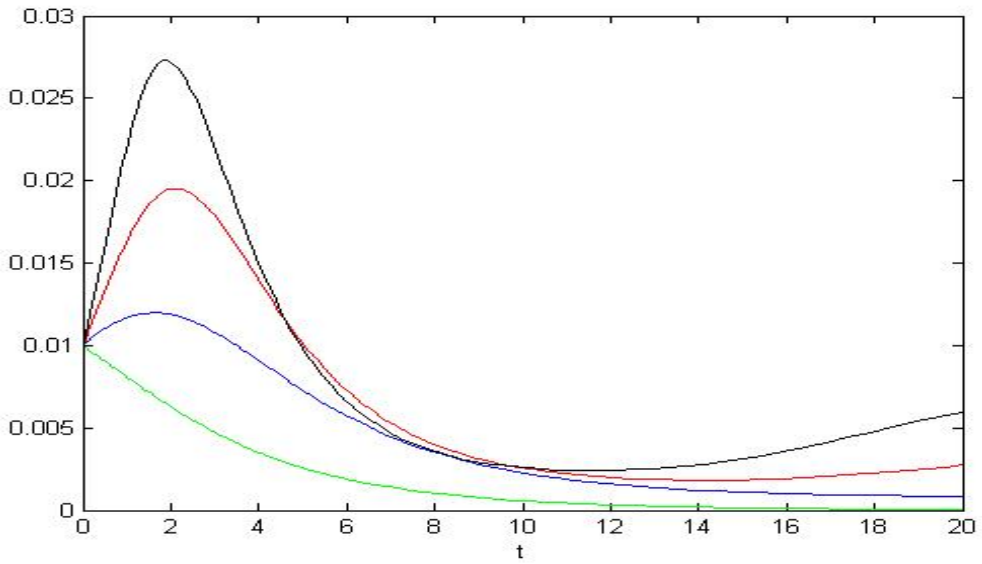

Fig. 4.2: The effect of varying the number of effective contacts between an infectious bird and susceptible birds, κ_p, on the dynamics of the avian flu in the bird world. The vertical axis shows the proportion of birds with avian flu. The horizontal axis shows the time in days. Green, blue, red and black lines are the dynamics of avian flu among birds when κ_p equals to 2, 3, 4 and 5, respectively

shows that the outbreak of avian flu in the human world happens just after the time of outbreak in the bird world. The time of outbreak of swine flu is independent to the time of outbreak of avian flu in the bird world. The outbreak of mutant avian flu happens just after the time of outbreak of avian flu and swine in the human world. Comparing Figure 4.3 (a) and (b), the proportion of human infected with avian flu but asymptomatic is higher than that of symptomatic. This is in line with reports by World Health Organization (WHO) that the number of human cases (infected humans with avian flu) is higher than that of being reported in [15].

Variations in $\kappa_{ph}, \kappa_{sh}, \kappa_{sa}$ and κ_{mh} have no effect to the dynamics of avian flu among birds. They all all have significant effects on the spread of diseases among humans (Figures 4.4 - 4.7). As expected, the effective number of contacts between an infectious bird and humans for spreading avian flu from birds to humans (κ_{ph}) effects the proportion of humans with avian flu (both symptomatic and asymptomatic) more than the proportion of people with mutant-avian flu (Figure 4.4). The number of effective contacts between humans for spreading swine flu between humans(κ_{sh}) effects all human groups severely (Figure 4.5) while the the number effective contacts between a human with swine flu and asymptomatic humans with avian flu (κ_{sa}) influences the mutant avian flu group most, as expected (Figure 46). The number of effective contacts between humans for spreading the mutant avian flu (κ_{mh}) obviously has greatest influence on the proportion of humans with mutant avian flu (Figure 4.7).

Figures 4.2 - 4.7 demonstrate that the effects of the number of effective contacts

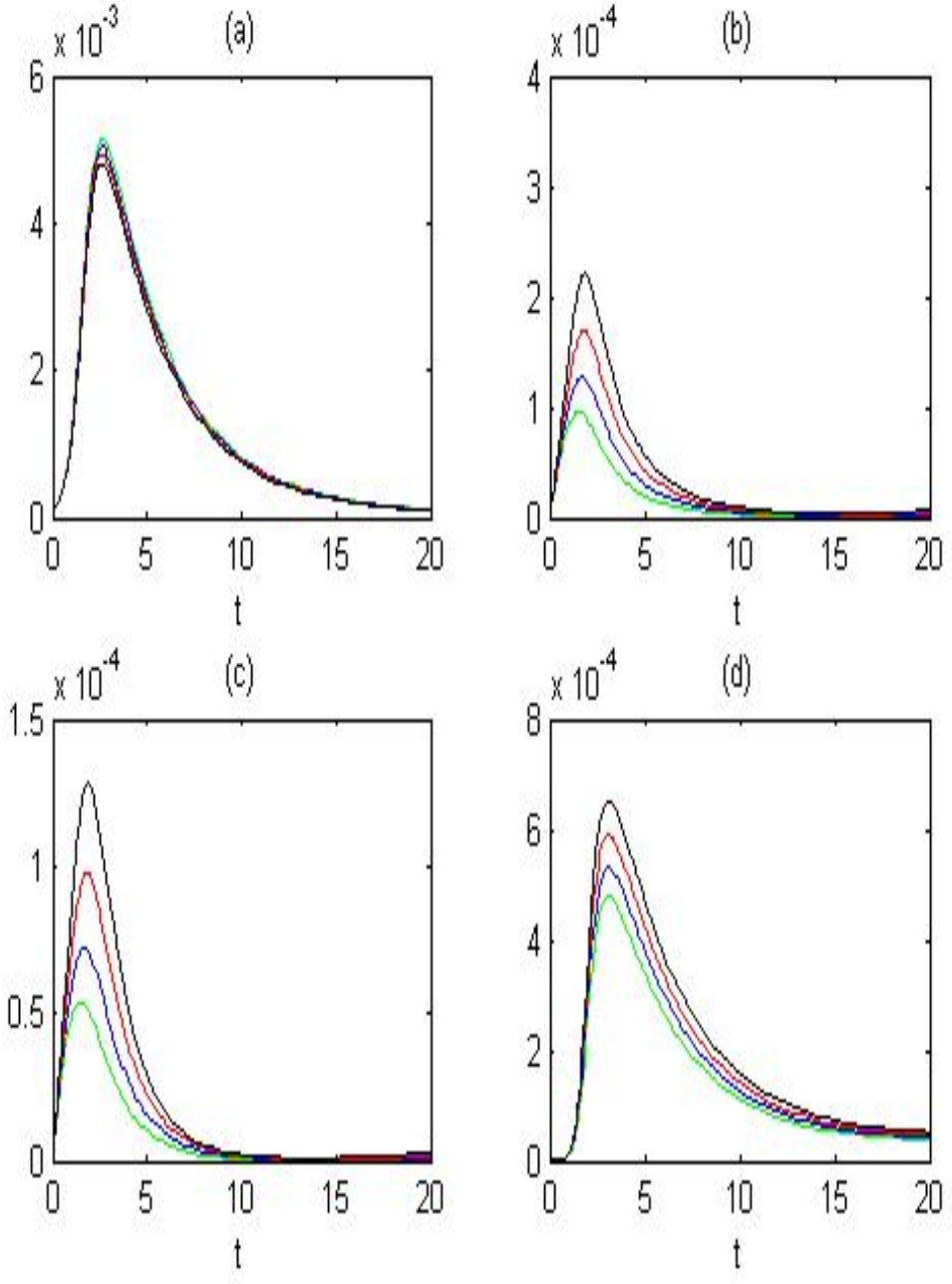

Fig. 4.3: The effect of varying the number of effective contacts between an infectious bird and susceptible birds, κ_p, on the dynamics of diseases in human world. The vertical axes show the proportion of humans with the diseases. (a) Proportion of infected human with swine flu. (b) Proportion of infected human with avian flu but asymptomatic. (c) Proportion of infected human with avian flu and symptomatic. (d) Proportion of infected human with mutant-avian flu. Green, blue, red and black lines are the dynamics of the diseases when κ_p is equal to 2, 3, 4 and 5, respectively. The horizontal axes show the time in days.

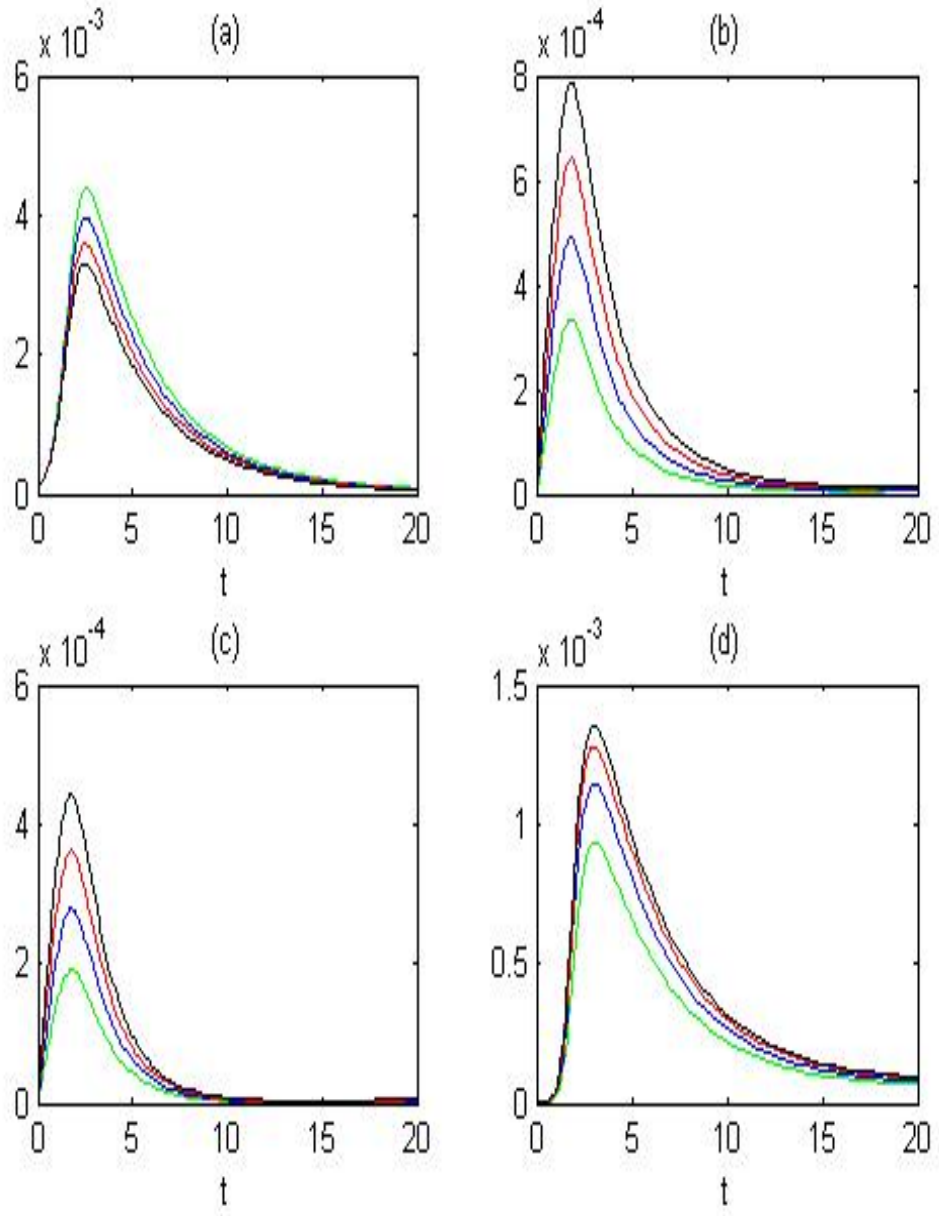

Fig. 4.4: The effect of varying the number of effective contacts between an infectious bird and susceptible human, κ_{ph}, on the dynamics of the diseases in human world. The vertical axes show the proportion of humans with the diseases. The horizontal axes show the time in days. Green, blue, red and black lines are the dynamics of the diseases when κ_{ph} is equal to 1, 2, 3 and 4, respectively. (a) Proportion of infected human with swine flu. (b) Proportion of infected human with avian flu but asymptomatic. (c) Proportion of infected human with avian flu and symptomatic. (d) Proportion of infected human with mutant-avian flu.

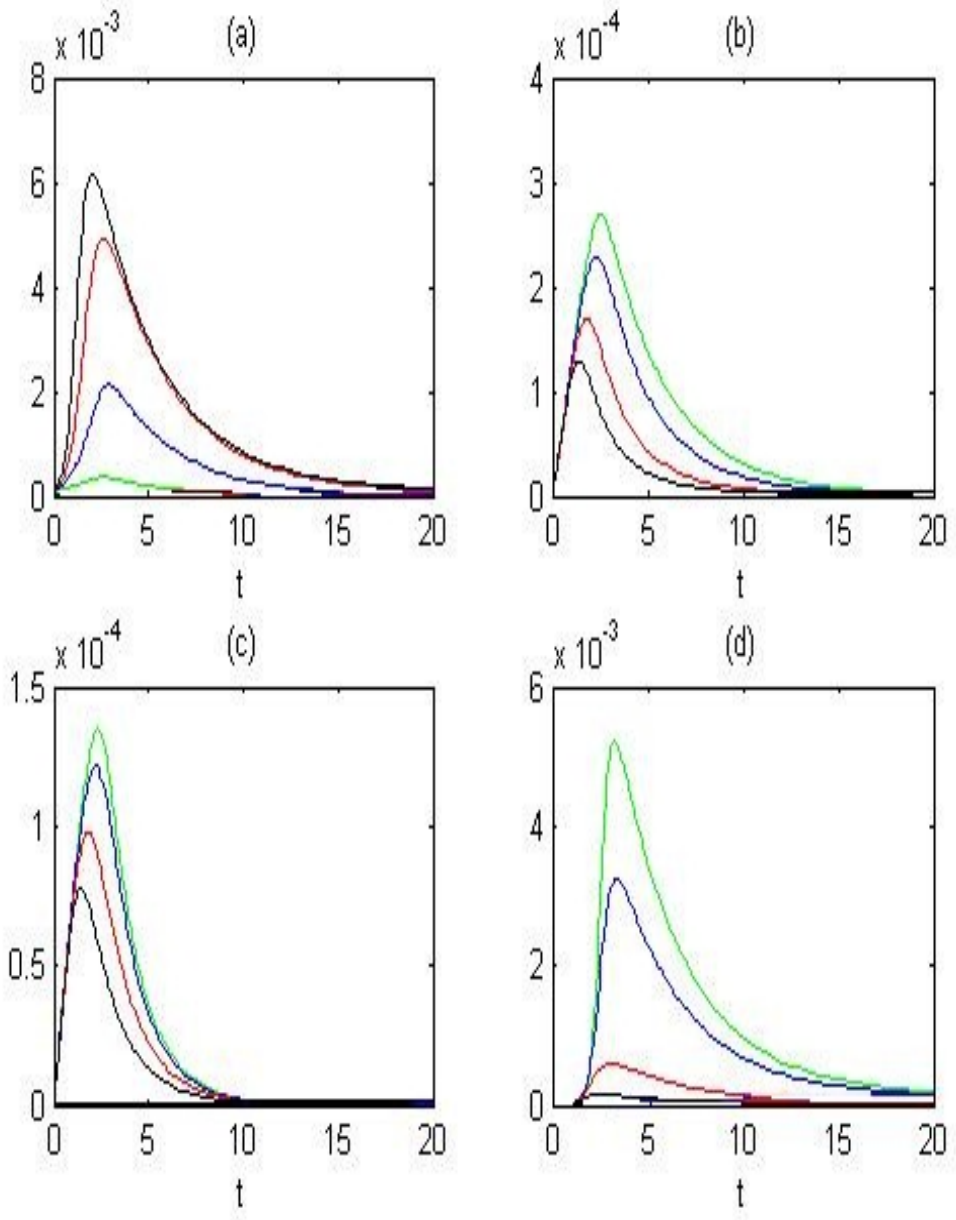

Fig. 4.5: The effect of varying the number of effective contacts between an infectious human with swine flu and susceptible human, κ_{sh}, on the dynamics of the diseases in human world. The vertical axes show the proportion of humans with the diseases. The horizontal axes show the time in days. Green, blue, red and black lines are the dynamics of the diseases when κ_{sh} is equal to 1, 2, 3 and 4, respectively. (a) Proportion of infected human with swine flu. (b) Proportion of infected human with avian flu but asymptomatic. (c) Proportion of infected human with avian flu and symptomatic. (d) Proportion of infected human with mutant-avian flu. The horizontal axes show the time in days.

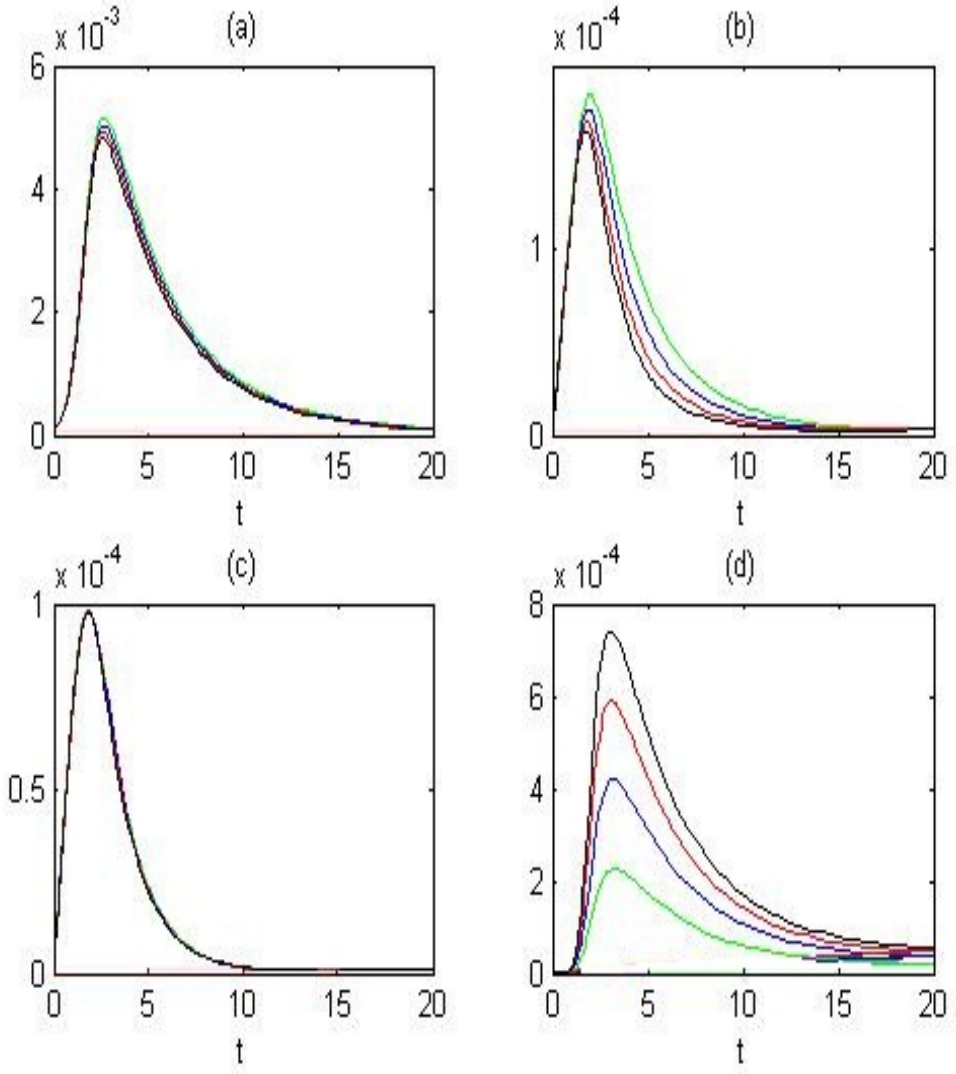

Fig. 4.6: The effect of varying the number of effective contacts between an infectious human with swine flu and humans infected with avian flu but asymptomatic,κ_{sa}, on the dynamics of the diseases in human world. The vertical axes show the proportion of humans with the diseases. The horizontal axes show the time in days. Green, blue, red and black lines are the dynamics of the diseases when κ_{sa} is equal to $1, 2, 3$ and 4, respectively. (a) Proportion of infected human with swine flu. (b) Proportion of infected human with avian flu but asymptomatic. (c) Proportion of infected human with avian flu and symptomatic. (d) Proportion of infected human with mutant-avian flu.

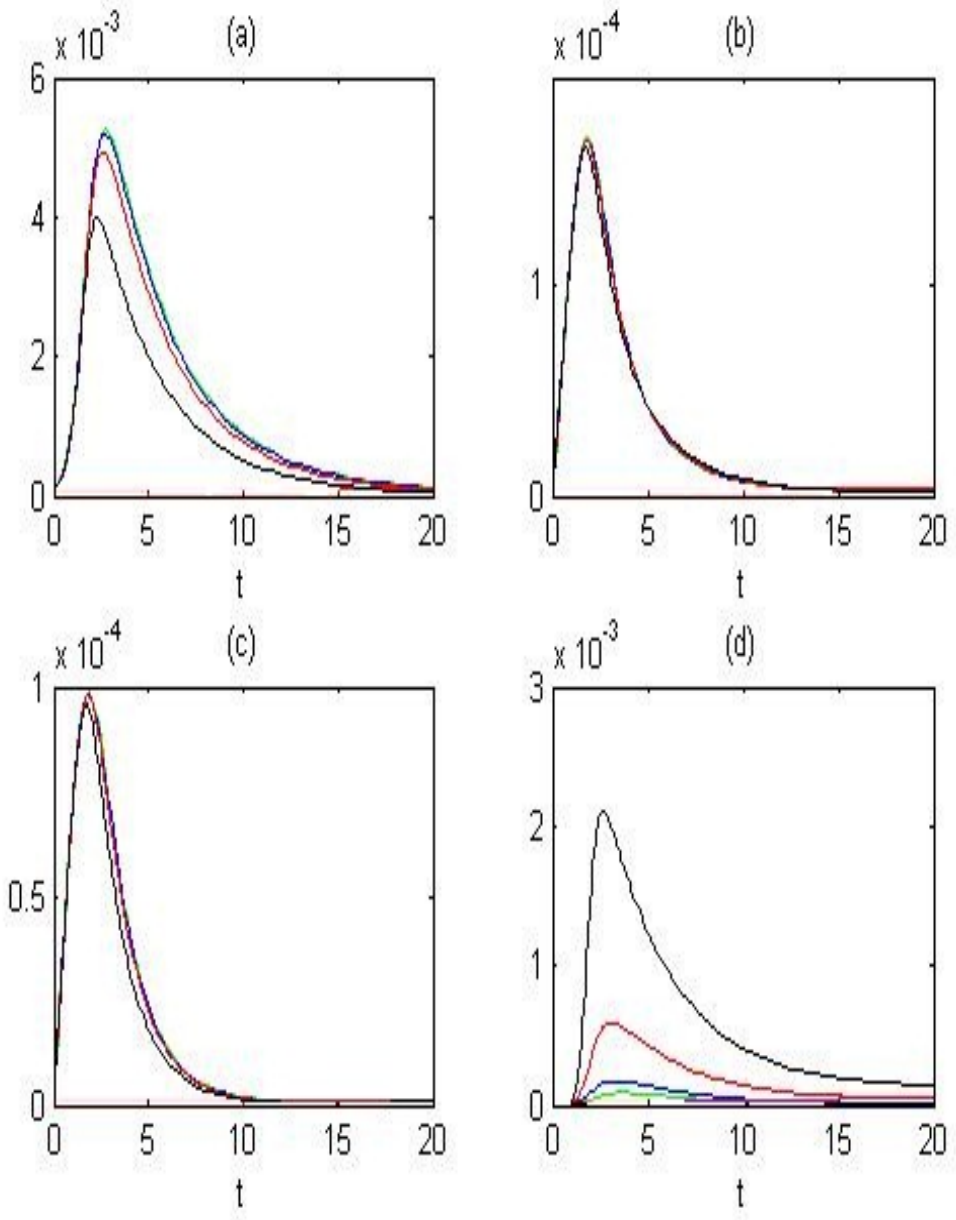

Fig. 4.7: The effect of varying the number of effective contacts between an infectious human with mutant-avian flu and susceptible humans ,κ_{mh}, on the dynamics of the diseases in human world. The vertical axes show the proportion of humans with the diseases. Green, blue, red and black lines are the dynamics of the diseases when κ_{mh} is equal to $1, 2, 3$ and 4, respectively. (a) Proportion of infected human with swine flu. (b) Proportion of infected human with avian flu but asymptomatic. (c) Proportion of infected human with avian flu and symptomatic. (d) Proportion of infected human with mutant-avian flu. The horizontal axes show the time in days.

between susceptible and infectious individuals may be substantial even for κ_p which does not involve humans directly.

4.7.2 Sensitivity Analysis

There are uncertainties in the values of the epidemic parameters. Sampling methods and sensitivity analysis are used to determine the degree of uncertainty in the basic reproduction numbers that is due to uncertainty in the epidemic parameters.

Each of the reproduction numbers (4.6), (4.7) (4.7) and (4.8) were simulated by sampling a single value from each epidemic parameter's distribution. The Latin Hypercube Sampling method [194] was used. For each epidemic parameter, the method defines and stratifies a probability density function into N serial intervals with equivalent probability. A single value is then selected randomly from every interval and this is done for every parameter. In this way, an input value from each sampling interval is used only once in the analysis but the entire parameter space is equitably sampled in an efficient manner [195], [194] [196].

There is little information in the literature regarding distributions of the parameters in the model. In absence of other information, each distribution was taken to be normal centered at the parameter value used in the simulations above and with standard deviation given by approximately one tenth of the value or 1 for discrete parameters such as the numbers of effective contacts per unit time. The specific distributions are as follows.

- $\delta_p \sim N(0.1, 0.01), \quad \delta_h \sim N(0.1, 0.01),$
- $\alpha_p \sim N(0.041, 0.001), \quad \alpha_{ph} \sim N(0.00041, 0.000041),$
- $\alpha_{sh} \sim N(0.000182, 0.00001), \quad \alpha_{mh} \sim N(0.2, 0.009)$
- $\kappa_p \sim N(3, 1)$ or $\alpha_p \sim N(2, 1),$
- $\kappa_{sh} \sim N(3, 1)$ or $\kappa_{sh} \sim N(2, 1),$
- $\kappa_{mh} \sim N(3, 1)$ or $\kappa_{mh} \sim N(2, 1),$
- $m_p \sim N(0.8, 0.1), m_s \sim N(0.07, 0.001), m_m \sim N(0.2, 0..9),$
- $R_p \sim N(\mu_p, \sigma_p), \quad R_{sh} \sim N(\mu_{sh}, \sigma_{sh}), \quad R_{mh} \sim N(\mu_{mh}, \sigma_{mh})$
- $\mu \sim N(0.001, 0.0001).$

The model was run 1000 times with different parameter sets sampled from the distributions above.

Equations for the basic reproduction numbers (4.6), (4.7) and (4.8) are non-linear. Therefore it is appropriate to use the Spearman Rank Correlation Coefficients (SRCCs) for sensitivity analysis of the basic reproduction numbers. The calculation of SRCCs are useful for ranking the importance of the correlation between epidemic parameters and the basic reproduction numbers.

Table 4.1 shows the SRCCs for the epidemic parameters $\eta_p, \delta_p, \alpha_p, m_p, \kappa_p$ and the basic reproduction number R_p. The first row corresponds to SRCC values when $\kappa_p = 3$ and $R_p = 0.82$. The second row corresponds to SRCC values when $\kappa_p = 4$ and $R_p = 1.32$. The table shows that κ_p has the biggest SRCCs to the basic reproduction number

Tab. 4.1: The Spearman Rank Correlation Coefficients for R_p and related epidemic parameters. For every parameter, there are two rows. The first row corresponds to SRCC values when $\kappa_p = 3$ and $R_p = 0.82$. The second row corresponds to SRCC values when $\kappa_p = 4$ and $R_p = 1.32$.

SRCCs	η_p	δ_p	α_p	m_p	κ_p
η_p	1	0.012591	-0.029300	-0.003100	0.027533
	1	-0.020150	-0.030360	0.026735	-0.062570
δ_p	0.012591	1	-0.021170	-0.017610	-0.002330
	-0.020150	1	0.060087	0.024298	0.001436
α_p	-0.029300	-0.021170	1	-0.013320	-0.031380
	-0.030360	0.060087	1	-0.060480	-0.015940
m_p	-0.003100	-0.017610	-0.013320	1	0.047320
	0.026735	0.024298	-0.060480	1	0.013221
κ_p	0.027533	-0.002330	-0.031380	0.047320	1
	-0.062570	0.001436	-0.015940	0.013221	1
R_p	0.209705	-0.201080	0.023493	-0.118070	0.931383
	0.194453	-0.288710	0.041830	-0.218570	0.865198

R_p. The corresponding p-values for the SRCCs are given in Table 4.2 below. The first row corresponds to the p-values of SRCC when $\kappa_p = 3$ and $R_p = 0.82$. The second row corresponds to the p-values of SRCC when $\kappa_p = 4$ and $R_p = 1.32$. Table 4.2 shows that the p-values of SRCCs for κ_p to R_p are zero, κ_p is the most significant contributor to R_p. Therefore R_p is the most sensitive to κ_p. Furthermore, the Tornado plot in Figure 4.8 shows the importance of the uncertainty of each epidemic parameter in contributing to that the variability of epidemic parameters to the basic reproduction number R_p . Brown bars are SRCCs when $\kappa_p = 3$ and $R_p = 0.82$. Blue bars are SRCCs when $\kappa_p = 4$ and $R_p = 1.32$. κ_p is the most important contributor to the variability of R_p.

In the following, sensitivity analysis is carried out to determine the degree of uncertainty for the basic reproduction numbers R_{sh} and R_{mh}. Table 4.3 shows that κ_{sh} has the biggest SRCCs to the basic reproduction number R_{sh}. Table 4.4 shows that κ_{sh} is the most significant contributor to R_{sh}. Therefore R_{sh} is the most sensitive to κ_{sh}. The Tornado plot in Figure 4.9 shows that the variability of κ_{sh} is the most important contributor to the variability of R_{sh}.

Table 4.5 below shows that κ_{mh} has the biggest SRCCs to the basic reproduction

Tab. 4.2: The p-values of SRCCs for R_p and its epidemic parameters. The p-values of SRCCs when $\kappa_p = 3$ and $R_p = 0.82$ are given in the top rows. The below rows show the p-values of SRCCs when $\kappa_p = 4$ and $R_p = 1.32$

p-values	η_p	δ_p	α_p	m_p	κ_p
η_p	0	0.690809	0.354568	0.921958	0.384377
	0	0.524409	0.337388	0.398316	0.047937
δ_p	0.690809	0	0.503639	0.577920	0.941381
	0.524409	0	0.057514	0.442714	0.963809
α_p	0.354568	0.503639	0	0.673935	0.321523
	0.337388	0.057514	0	0.055881	0.614659
m_p	0.921958	0.577920	0.673935	0	0.134805
	0.398316	0.442714	0.055881	0	0.676204
κ_p	0.384377	0.941381	0.321523	0.134805	0
	0.047937	0.963809	0.614659	0.676204	0
R_p	<0.000001	<0.000001	0.457976	0.000184	0
	<0.000001	<0.000001	0.186237	<0.000001	0

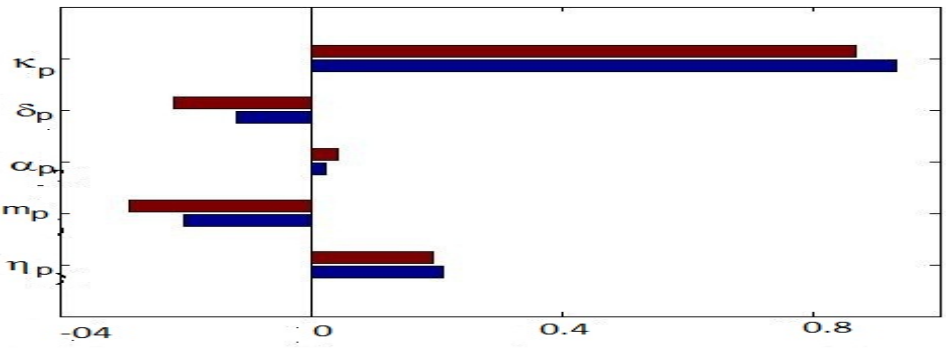

Fig. 4.8: Tornado plot of SRCCs, indicating the importance of each parameter's uncertainty in contributing to the variability in the time to the basic reproduction number R_p. Brown bars are SRCCs when $\kappa_p = 3$ and $R_p = 0.82$. Blue bars are SRCCs when $\kappa_p = 4$ and $R_p = 1.32$

.

Tab. 4.3: The Spearman Rank Correlation Coefficients for R_{sh} and its epidemic parameters

SRCCs	η_h	δ_h	α_{sh}	m_s	κ_{sh}
η_h	1	-0.003490	-0.000590	-0.021520	0.095111
δ_h	-0.003490	1	0.010101	0.002796	-0.05293
α_{sh}	-0.000590	0.010101	1	0.009823	0.024352
m_s	-0.021520	0.002796	0.009823	1	0.010505
κ_{sh}	0.095111	-0.052930	0.024352	0.010505	1
R_{sh}	0.261014	-0.293140	0.105717	-0.587900	0.674317

Tab. 4.4: The p-values of SRCCs for R_{sh} and its epidemic parameters

p-values	η_h	δ_h	α_{sh}	m_s	κ_{sh}
η_h	0	0.912295	0.985099	0.496549	0.002616
δ_h	0.912295	0	0.749662	0.929624	0.094334
α_{sh}	0.985099	0.749662	0	0.756334	0.441684
m_s	0.496549	0.929624	0.756334	0	0.740006
κ_{sh}	0.002616	0.094334	0.441684	0.740006	0
R_{sh}	<0.000001	<0.000001	0.000818	0	0

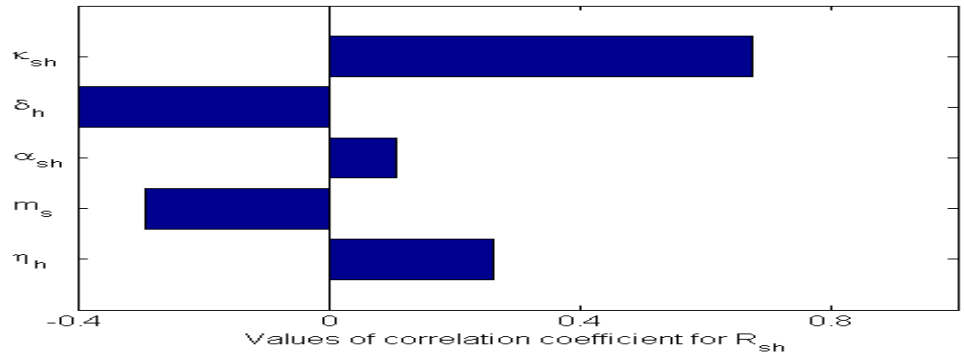

Fig. 4.9: Tornado plot of partial rank correlation coefficients, indicating the importance of each parameter's uncertainty in contributing to the variability in the time to the basic reproduction number R_{sh}

number R_{mh}. Table 4.6 shows that κ_{mh} is the most significant contributor to R_{mh}. Therefore R_{mh} is the most sensitive to κ_{mh}. The Tornado plot in Figure 4.10 shows that the variability of κ_{mh} is the most important contributor to the variability of R_{mh}.

4.8 Discussion

(a) $Z_1^* = (\frac{\eta_p}{\delta_p}, 0, \frac{\eta_h}{\delta_h}, 0, 0, 0, 0)$ is well defined and stable if $R_p \leq 1, r_{sh} \leq 1$ and $r_{mh} \leq 1$.

(b) $Z_2^* = (S_{p_2}^*, 0, S_{h_2}^*, I_{s_2}^*, 0, 0, 0)$ is well defined and stable if $R_p \leq 1, r_{sh} > \max\{r_{mh}, 1\}$.

Tab. 4.5: The Spearman Rank Correlation Coefficients for R_{mh} and its epidemic parameters

SRCCs	η_h	δ_h	α_{mh}	m_m	κ_{mh}
η_h	1	0.025510	-0.078980	-0.009650	-0.064610
δ_h	0.025510	1	-0.035470	0.019286	0.049140
α_{mh}	-0.078980	-0.035470	1	-0.036180	-0.040490
m_m	-0.009650	0.019286	-0.036180	1	-0.037050
κ_{mh}	-0.064610	0.049140	-0.040490	-0.037050	1
R_{mh}	0.138857	-0.228870	0.076889	-0.642560	0.654698

Tab. 4.6: The p-values of SRCCs for R_{mh} and its epidemic parameters

p-values	η_h	δ_h	α_{mh}	m_m	κmh
η_h	0	0.420288	0.012499	0.760521	0.041098
δ_h	0.420288	0	0.262380	0.542353	0.120421
α_{mh}	0.012499	0.262380	0	0.252957	0.200725
m_m	0.760521	0.542353	0.252957	0	0.241731
κ_{mh}	0.041098	0.120421	0.200725	0.241731	0
R_{mh}	<0.000001	<0.000001	0.015033	0	0

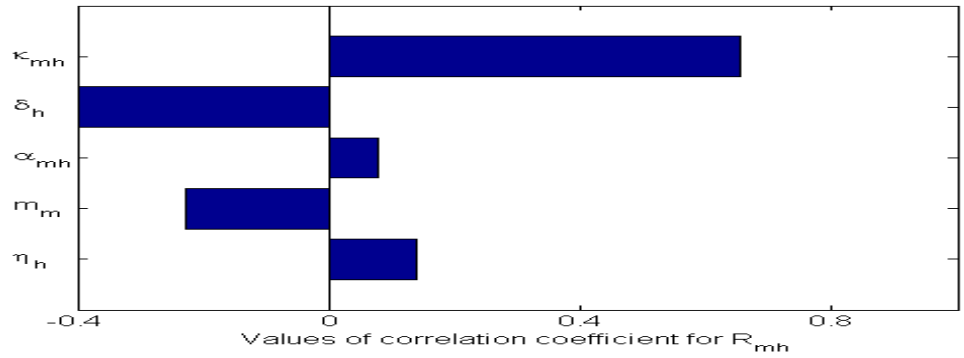

Fig. 4.10: Tornado plot of partial rank correlation coefficients, indicating the importance of each parameter's uncertainty in contributing to the variability in the time to the basic reproduction number R_{mh}

(c) $Z_3^* = (S_{p_3}^*, 0, S_{h_3}^*, 0, 0, 0, I_{m_3}^*)$ is well defined and stable if $R_p \leq 1, r_{sh} > \max\{r_{sh}, 1\}$.

(d) $Z_4^* = (S_{p_4}^*, I_{p_4}^*, S_{h_4}^*, 0, I_{a_4}^*, I_{b_4}^*, 0)$ is well defined and stable if $R_p \leq 1, r_{sh} > \max\{r_{sh}, r_{mh}\} < 1 + r_{ph}$.

(e) $Z_6^* = (S_{p_6}^*, I_{p_6}^*, S_{h_6}^*, 0, I_{a_6}^*, I_{b_6}^*, I_{m_6}^*)$ is well defined and stable if $R_p \leq 1, r_{mh} > \max\{r_{sh}, 1 + r_{ph}\}$.

The results above hold under the assumption that there is no external source of infection. An external source of infection may result in different disease dynamics behavior. The next chapter discusses the effect of bird trading to the disease dynamics and how to devise a screening policy to control the spread of the diseases.

5. DISEASE DYNAMICS IN MULTI-REGIONS

Jakarta is the biggest consumers of chicken in the country, but only a small number of chickens are raised in the city. Chickens from Central Java are transported to West Java and Jakarta. Some chicken in Jakarta markets are re-transported to Banten and then to Lampung in Sumatra. On the other hand, Table 1.2 shows that DKI Jakarta has the highest number of human cases. Nationally, the city has 50.7% of all suspected avian flu and 25% confirmed of avian flu. This indicates that the spread of the disease is largely due to the transport of chickens.

It has been suspected that bird transportation enhances the spread of the diseases and may result in different dynamic behaviors of the diseases. This chapter develops models for analyzing and interpreting the effect of bird trading on the spread of avian flu, swine flu and mutant-avian flu.

This chapter is organized as follow. Section 5.1 describes modeling choices and assumptions. Section 5.2 formulates a model to describe the effect of transporting birds to the dynamics of the diseases. A model for a special case of two identical regions is given in Section 5.3. Analytical analysis for the model is given in Sections 5.4, 5.5 and 5.6. Numerical simulations for $n \geq 2$ regions are given in Section 5.7. Section 5.8 discusses the analytical and numerical results and draws some conclusions.

5.1 Modeling choices and assumptions

Demographically, the domain of the study comprises several regions which have different characteristics in terms population, mobility, disease transmission and capability to administer disease controls.

The modeling choices and assumptions of Chapter 4 are adopted here. The same notation is used for compartments and epidemic parameters, but with subscript i referring to region i. Poultry birds may move from one region to another region as a result of bird trading. It is assumed that there is no hatching or restocking during travel. Let θ_{ji} denote the rate of transfer of poultry birds from region j to region i. Not all incoming susceptible birds successfully reach the destination region in the state of susceptible; some become infected during travel. Let $\beta_{p_{ji}}$ and $\varkappa_{p_{ji}}$ denote the transmission rate of avian flu and the number of effective contacts between an infectious bird and susceptible birds during travel from region i to region j, respectively. Due to conditions

during the transportation of the birds, the infection rate and the effective number of contacts between an infectious bird and susceptible birds per unit time may be higher during transport than in the normal circumstance. It is assumed that $\beta_{p_{ji}} \geq \alpha_{p_i}$ and $\beta_{p_{ji}} \geq \alpha_{p_j}$. While $\varkappa_{p_{ji}} \geq \varkappa_{p_i}$ and $\varkappa_{p_{ji}} \geq \varkappa_{p_j}$. The incoming birds are assumed to fully mix with the destination compartments of the same disease states.

The dynamics of the disease states among birds is described by

$$\begin{aligned} S'_{p_i}(t) =&\eta_{p_i} - (\delta_{p_i} + \sum_{j\neq i}\theta_{ij})S_{p_i} - \alpha_{p_i}\kappa_{p_i}I_{p_i}S_{p_i} + \sum_{j\neq i}\theta_{ji}(1-\beta_{p_{ji}}\varkappa_{p_{ji}}I_{p_j})\,S_{p_j} \\ I'_{p_i}(t) =&\alpha_{p_i}\kappa_{p_i}I_{p_i}S_{p_i} - (\delta_{p_i} + m_{p_i} + \sum_{j\neq i}\theta_{ij})I_{p_i} + \sum_{j\neq i}\theta_{ji}(1+\beta_{p_{ji}}\varkappa_{p_{ji}}S_{p_j})\,I_{p_j}. \end{aligned} \tag{5.1}$$

The incoming birds are assumed to fully mix with the destination compartments of the same disease states. An incoming infected bird is mixed with local infected birds, an incoming susceptible bird is mixed with susceptible birds. It is assumed that humans do not move, they remain in the same region. Therefore, a human is infected by local infectious chickens only. The dynamics of the disease states among humans in region i is described by

$$\begin{aligned} S'_{h_i}(t) =&\eta_{h_i} - \delta_{h_i}S_{h_i} - \alpha_{ph_i}\kappa_{ph_i}I_{p_i}S_{h_i} - \alpha_{sh_i}\kappa_{sh_i}I_{s_i}S_{h_i} - \alpha_{mh_i}\kappa_{mh_i}I_{m_i}S_{h_i}, \\ I'_{s_i}(t) =&\alpha_{sh_i}\kappa_{sh_i}I_{s_i}S_{h_i} - (\delta_{h_i} + m_{s_i})\,I_{s_i}, \\ I'_{a_i}(t) =&\gamma_i\alpha_{ph_i}\kappa_{ph_i}I_{p_i}S_{h_i} - \mu_i\alpha_{sa_i}\kappa_{sa_i}I_{s_i}I_{a_i} - (\delta_{h_i} + m_{a_i})\,I_{a_i}, \\ I'_{b_i}(t) =&(1-\gamma_i)\alpha_{ph_i}\kappa_{ph_i}I_{p_i}S_{h_i} - (\delta_{h_i} + m_{b_i})\,I_{b_i}, \\ I'_{m_i}(t) =&\mu_i\alpha_{sa_i}\kappa_{sa_i}I_{s_i}I_{a_i} + \alpha_{mh_i}\kappa_{mh_i}I_{m_i}S_{h_i} - (\delta_{h_i} + m_{m_i})\,I_{m_i}. \end{aligned} \tag{5.2}$$

5.2 Diseases transmission model for multi-regions

Figure 5.1 shows a schematic diagram of the compartments of bird and human populations in two regions. The disease dynamics among birds in any region is independent of the disease dynamics among humans. Due to transportation, an infectious bird from a region may infect humans in any region. Therefore, the disease dynamics among humans is dependent on the disease dynamics in the bird world. Let $Q_n \subseteq \mathbb{R}_+^{27n}$ be the set of disease parameters

$$\begin{aligned} Q_n =\{&q = (q_i)|\, q_i = \eta_{p_i}, \eta_{h_i}, \delta_{p_i}, \delta_{h_i}, \alpha_{p_i}, \alpha_{sh_i}, \alpha_{ph_i}, \alpha_{sa_i}, \alpha_{mh_i}, \kappa_{p_i}, \kappa_{sh_i}, \\ &\kappa_{ph_i}, \kappa_{sa_i}, \kappa_{mh_i}, \mu, m_{p_i}, m_{a_i}, m_{b_i}, m_{s_i}, m_{m_i}, \gamma_i, \theta_{ij}, \beta_{p_{ij}}, \varkappa_{p_{ij}},\ i = 1, \ldots, n\}. \end{aligned}$$

Let $\Omega_n \subseteq \mathbb{R}_+^{7n}$ be the set of all disease states

$$\Omega_n = \{Z(t) = (Z_i(t))_{i=1,\ldots,n} | Z_i(t) = (S_{p_i}(t), I_{p_i}(t), S_{h_i}(t), I_{s_i}(t), I_{a_i}(t), I_{b_i}(t), I_{m_i}(t))\}.$$

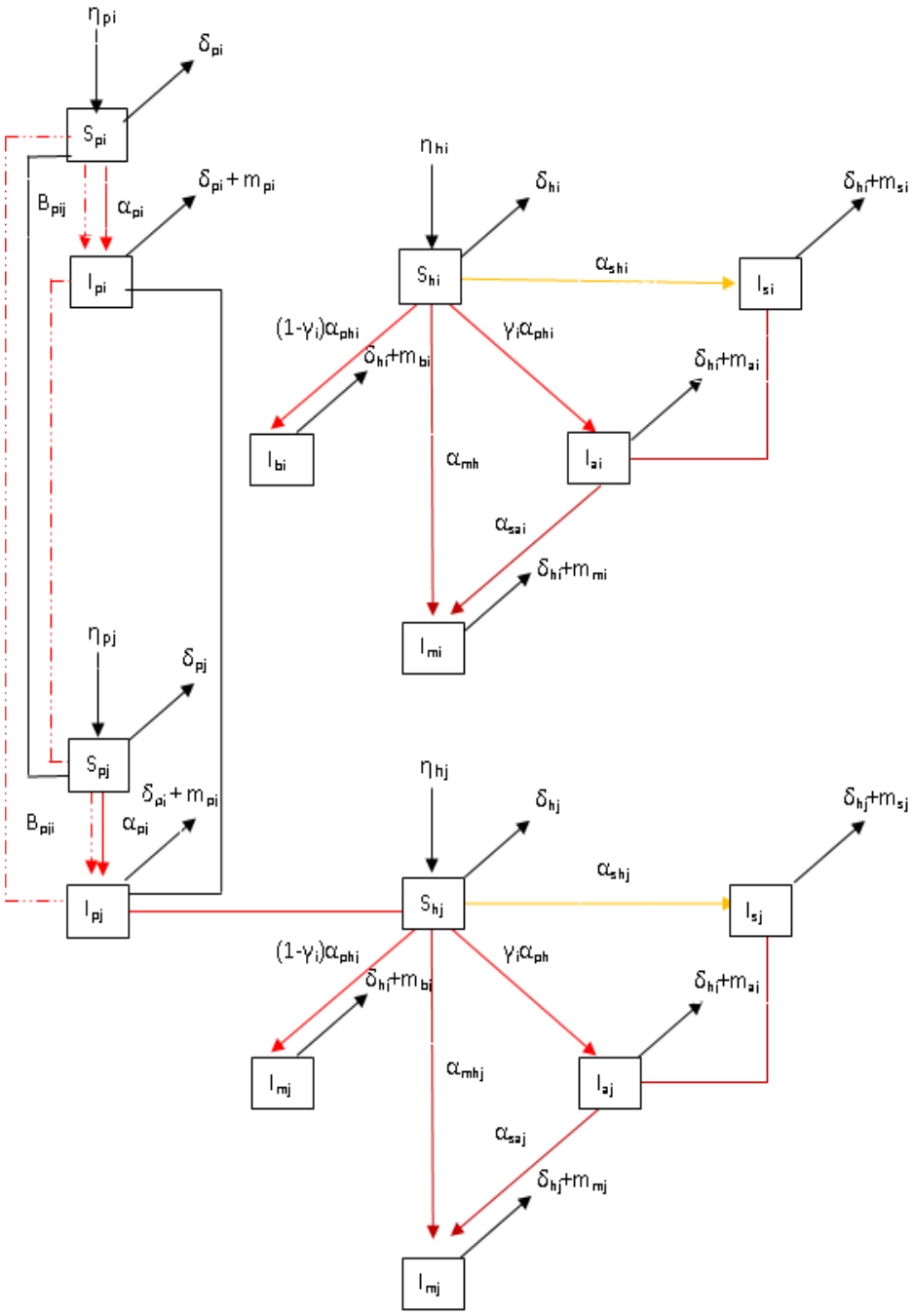

Fig. 5.1: Compartments of humans and poultry bird populations in two regions. Solid red lines represent local avian flu transmission, dashed red lines represent avian flu transmission due to transporting of birds, yellow lines represent swine flu transmission, brown lines represent transmission of mutant-avian flu.

For a given set of epidemic parameters $q \in Q_n$ and an initial disease state $Z_0 \in \Omega_n$ the dynamics of the disease state $Z(t)$ is modeled by

$$S'_{p_i} i(t) = \eta_{p_i} - (\delta_{p_i} + \sum_{j \neq i} \theta_{ij}) S_{p_i} - \alpha_{p_i} \kappa_{p_i} I_{p_i} S_{p_i} + \sum_{j \neq i} \theta_{ji} (1 - \beta_{p_{ji}} \varkappa_{p_{ji}} I_{p_j}) S_{p_j} \tag{5.3a}$$

$$I'_{p_i}(t) = \alpha_{p_i} \kappa_{p_i} I_{p_i} S_{p_i} - (\delta_{p_i} + m_{p_i} + \sum_{j \neq i} \theta_{ij}) I_{p_i} + \sum_{j \neq i} \theta_{ji} (1 + \beta_{p_{ji}} \varkappa_{p_{ji}} S_{p_j}) I_{p_j}, \tag{5.3b}$$

$$S'_{h_i}(t) = \eta_{h_i} - \delta_{h_i} S_{h_i} - \alpha_{ph_i} \kappa_{ph_i} I_{p_i} S_{h_i} - \alpha_{sh_i} \kappa_{sh_i} I_{s_i} S_{h_i} - \alpha_{mh_i} \kappa_{mh_i} I_{m_i} S_{h_i}, \tag{5.3c}$$

$$I'_{s_i}(t) = \alpha_{sh_i} \kappa_{sh_i} I_{s_i} S_{h_i} - (\delta_{h_i} + m_{s_i}) I_{s_i}, \tag{5.3d}$$

$$I'_{a_i}(t) = \gamma_i \alpha_{ph_i} \kappa_{ph_i} I_{p_i} S_{h_i} - \mu_i \alpha_{sa_i} \kappa_{sa_i} I_{s_i} I_{a_i} - (\delta_{h_i} + m_{a_i}) I_{a_i}, \tag{5.3e}$$

$$I'_{b_i}(t) = (1 - \gamma_i) \alpha_{ph_i} \kappa_{ph_i} I_{p_i} S_{h_i} - (\delta_{h_i} + m_{b_i}) I_{b_i}, \tag{5.3f}$$

$$I'_{m_i}(t) = \mu_i \alpha_{sa_i} \kappa_{sa_i} I_{s_i} I_{a_i} + \alpha_{mh_i} \kappa_{mh_i} I_{m_i} S_{h_i} - (\delta_{h_i} + m_{m_i}) I_{m_i}, \tag{5.3g}$$

$$Z(0) = Z_0,\ Z_0 \in \Omega_n. \tag{5.3h}$$

If $\theta_{ij} = 0$ for all $i, j = 1, \ldots, n$, then (5.3a)-(5.3g) becomes n copies of (4.3a)-(4.3g) while Ω_n becomes Ω_1 for each n. Therefore, the IVP (5.3a)-(5.3h) becomes n copies of the IVP (4.3a)-(4.3h).

The existence of a unique solution for IVP (5.3a)-(5.3h) is guaranteed by the following theorem.

Theorem 5.1. *For any non negative initial condition $Z_0 \in \Omega_n$, (5.3a)-(5.3g) has a unique and bounded solution passing through the initial condition (5.3h).*

Proof. (5.3a)-(5.3g) is an autonomous system. It is easy to show that the set of all disease states Ω_n and its subspace of disease free states are positively invariant under f, the vector field (right hand side) of the system of differential equations (5.3a)-(5.3g). Therefore, the uniqueness of the solution of IVP (5.3a), (5.3h) is guaranteed by Theorem 3.4 in Section 3.2. □

5.3 Diseases transmission model for two identical regions

To be able to analyze the dynamics of the diseases analytically, consider two identical regions, i.e., with epidemic parameters the same for each region. Denote the first region as region 1 and the second region as region 2.

Avian flu dynamics among birds is independent of the dynamic of diseases among

humans. The dynamics of avian flu among birds in two identical regions is

$$S'_{p_1}(t) = \eta_p - (\delta_p + \theta)S_{p_1} - \alpha_p\kappa_p I_{p_1} S_{p_1} + \theta(1 - \beta_p \varkappa_p I_{p_2})\, S_{p_2}, \tag{5.4a}$$
$$I'_{p_1}(t) = \alpha_p\kappa_p I_{p_1} S_{p_1} - (\delta_p + m_p + \theta)\, I_{p_1} + \theta(1 + \beta_p \varkappa_p S_{p_2})\, I_{p_2}, \tag{5.4b}$$
$$S'_{p_2}(t) = \eta_p - (\delta_p + \theta)S_{p_2} - \alpha_p\kappa_p I_{p_2} S_{p_2} + \theta(1 - \beta_p \varkappa_p I_{p_1})S_{p_1}, \tag{5.4c}$$
$$I'_{p_2}(t) = \alpha_p\kappa_p I_{p_2} S_{p_2} - (\delta_p + m_p + \theta)\, I_{p_2} + \theta(1 + \beta_p \varkappa_p S_{p_1})I_{p_1}, \tag{5.4d}$$
$$W(t) = W_0,\ W_0 \in \Omega_{2B}, \tag{5.4e}$$

where $W_0 \in \Omega_{2B}$ is an initial disease state and

$$\Omega_{2B} = \{W = (W_1, W_2) : W_1 = (S_{p_1}, I_{p_1}), W_2 = (S_{p_2}, I_{p_2})\}.$$

The difference between two identical regions and one region is the inclusion of the transportation terms.

The full system (5.3a)-(5.3h) is reduced to

$$S'_{p_1}(t) = \eta_p - (\delta_p + \theta)S_{p_1} - \alpha_p\kappa_p I_{p_1} S_{p_1} + \theta(1 - \beta_p \varkappa_p I_{p_2})\, S_{p_2}, \tag{5.5a}$$
$$I'_{p_1}(t) = \alpha_p\kappa_p I_{p_1} S_{p_1} - (\delta_p + m_p + \theta)\, I_{p_1} + \theta(1 + \beta_p \varkappa_p S_{p_2})\, I_{p_2}, \tag{5.5b}$$
$$S'_{h_1}(t) = \eta_h - \delta_h S_{h_1} - \alpha_{ph}\kappa_{ph} I_{p_1} S_{h_1} - \alpha_{sh}\kappa_{sh} I_{s_1} S_{h_1} - \alpha_{mh}\kappa_{mh} I_{m_1} S_{h_1}, \tag{5.5c}$$
$$I'_{s_1}(t) = \alpha_{sh}\kappa_{sh} I_{s_1} S_{h_1} - (\delta_h + m_s)\, I_{s_1}, \tag{5.5d}$$
$$I'_{a_1}(t) = \gamma\alpha_{ph}\kappa_{ph} I_{p_1} S_{h_1} - \mu\alpha_{sa}\kappa_{sa} I_{s_1} I_{a_1} - (\delta_h + m_a)\, I_{a_1}, \tag{5.5e}$$
$$I'_{b_1}(t) = (1 - \gamma)\alpha_{ph}\kappa_{ph} I_{p_1} S_{h_1} - (\delta_h + m_b)\, I_{b_1}, \tag{5.5f}$$
$$I'_{m_1}(t) = \mu\alpha_{sa}\kappa_{sa} I_{s_1} I_{a_1} + \alpha_{mh}\kappa_{mh} I_{m_1} S_{h_1} - (\delta_h + m_m)\, I_{m_1}, \tag{5.5g}$$
$$S'_{p_2}(t) = \eta_p - (\delta_p + \theta)S_{p_2} - \alpha_p\kappa_p I_{p_2} S_{p_2} + \theta(1 - \beta_p \varkappa_p I_{p_1})S_{p_1}, \tag{5.5h}$$
$$I'_{p_2}(t) = \alpha_p\kappa_p I_{p_2} S_{p_2} - (\delta_p + m_p + \theta)\, I_{p_2} + \theta(1 + \beta_p \varkappa_p S_{p_1})I_{p_1}, \tag{5.5i}$$
$$S'_{h_2}(t) = \eta_h - \delta_h S_{h_2} - \alpha_{ph}\kappa_{ph} I_{p_2} S_{h_2} - \alpha_{sh}\kappa_{sh} I_{s_2} S_{h_2} - \alpha_{mh}\kappa_{mh} I_{m_2} S_{h_2}, \tag{5.5j}$$
$$I'_{s_2}(t) = \alpha_{sh}\kappa_{sh} I_{s_2} S_{h_2} - (\delta_h + m_s)\, I_{s_2}, \tag{5.5k}$$
$$I'_{a_2}(t) = \gamma\alpha_{ph}\kappa_{ph} I_{p_2} S_{h_2} - \mu\alpha_{sa}\kappa_{sa} I_{s_2} I_{a_2} - (\delta_h + m_a)\, I_{a_2}, \tag{5.5l}$$
$$I'_{b_2}(t) = (1 - \gamma)\alpha_{ph}\kappa_{ph} I_{p_2} S_{h_2} - (\delta_h + m_b)\, I_{b_2}, \tag{5.5m}$$
$$I'_{m_2}(t) = \mu\alpha_{sa}\kappa_{sa} I_{s_2} I_{a_2} + \alpha_{mh}\kappa_{mh} I_{m_2} S_{h_2} - (\delta_h + m_m)\, I_{m_2}, \tag{5.5n}$$
$$Z(0) = Z_0,\ Z_0 \in \Omega_2, \tag{5.5o}$$

where $Z_0 \in \Omega_2$ is an initial disease state and

$$\Omega_2 = \{Z = (Z_i) : Z_i = (S_{p_i}, I_{p_i}, S_{h_i}, S_i, I_{s_i}, I_{a_i}, I_{b_i}, I_{m_i}),\ i = 1, 2\}.$$

5.4 Reproduction numbers

The following basic reproduction numbers of the spread of the diseases in two identical regions are defined by using procedures similar to those in Section 4.3. The basic reproduction numbers for the disease dynamics among birds, (5.4a) - (5.4d), is derived by using the same methods as in Chapter 4.

The disease state variables $Y = (S_{p_1}, I_{p_1}, S_{p_2}, I_{p_2})$ are grouped into infected and uninfected compartments. For this reason, the state variable will be reordered so that the first five elements of the new state variable correspond to infected sub-populations. The disease state vector becomes $\bar{Y} = (I_{p_1}, I_{p_2}, S_{p_1}, S_{p_2})$. Under the ordered variable $\bar{Y}$, the right hand side of system of differential equations (5.4a) - (5.4d) can be written as

$$f = \hat{f} + \breve{f}$$

where

$$\hat{f} = \begin{bmatrix} \alpha_p \kappa_p I_{p_1} S_{p_1} + \theta \beta_p \varkappa_p I_{p_2} S_{p_2} \\ \alpha_p \kappa_p I_{p_2} S_{p_2} + \theta \beta_p \varkappa_p I_{p_1} S_{p_1} \\ -\alpha_p \kappa_p I_{p_1} S_{p_1} + \theta \beta_p \varkappa_p I_{p_2} S_{p_2} \\ -\alpha_p \kappa_p I_{p_1} S_{p_2} + \theta \beta_p \varkappa_p I_{p_1} S_{p_1} \end{bmatrix}$$

and

$$\breve{f} = \begin{bmatrix} -(\delta_p + m_p) I_{p_1} + \theta I_{p_2} \\ -(\delta_p + m_p) I_{p_2} + \theta I_{p_1} \\ \eta_p - \delta_p S_{p_1} + \theta S_{p_2} \\ \eta_p - \delta_p S_{p_2} + \theta S_{p_1}. \end{bmatrix}.$$

The component $\hat{f}$ models the rate of new infections, while the component $\breve{f}$ models the rates of transfer due to births, deaths, disease mortality.

In the reordered notation of the disease state variable, $\bar{Y}$, a disease state equilibria Y_i^* can be written as (V_i^*, W_i^*), where V_i^* corresponds to infected compartments $V_i^* = (I_{p_1}^*, I_{p_2}^*)$ and $W_1^* = (S_{p_1}^*, S_{p_2}^*)$. The disease free equilibrium state has two disease free compartments,

$$V^* = (I_{p_1}^*, I_{p_2}^*) = (0, 0).$$

Only the first two elements are considered, and so

$$f_1 = \hat{f}_1 + \breve{f}_1$$

where

$$\hat{f}_1 = \begin{bmatrix} \alpha_p \kappa_p I_{p_1} S_{p_1} + \theta \beta_p \varkappa_p I_{p_2} S_{p_2} \\ \alpha_p \kappa_p I_{p_2} S_{p_2} + \theta \beta_p \varkappa_p I_{p_1} S_{p_1} \end{bmatrix}$$

and

$$\breve{f}_1 = \begin{bmatrix} -(\delta_p + m_p) I_{p_1} + \theta I_{p_2} \\ -(\delta_p + m_p) I_{p_2} + \theta I_{p_1}. \end{bmatrix}.$$

The Jacobian matrices of $\hat{f}_1$ and $\breve{f}_1$ are

$$J_{\hat{f}_1} = \begin{pmatrix} \alpha_p \kappa_p S_p & \theta \beta_p \varkappa_p S_p \\ \theta \beta_p \varkappa_p S_p & \alpha_p \kappa_p S_p \end{pmatrix}$$

and

$$J_{\breve{f}_1} = \begin{pmatrix} (\delta_p + m_p) + \theta & -\theta \\ -\theta & (\delta_h + m_s) + \theta \end{pmatrix}$$

respectively. It is assumed there is no infected poultry, $I_p = 0$. For equilibrium it is required that $S'_p = 0$. Having $I_p = 0$ and omitting the index i (5.4a) and (5.4a) become $\eta_p - \delta_p S^*_{p_0} = 0$,

$$S^*_{p_0} = \frac{\eta_p}{\delta_p}.$$

At $Y^*_1 = (S^*_{p_0}, 0, S^*_{p_0}, 0) = (\frac{\eta_p}{\delta_p}, 0, \frac{\eta_p}{\delta_p}, 0)$, the Jacobian matrices $J_{\hat{f}_1}$ and $J_{\breve{f}_1}$ at Y^*_1 become

$$\hat{F}_1 = \begin{pmatrix} \frac{\eta_p \alpha_p \kappa_p}{\delta_p} & \frac{\eta_p \theta \beta_p \kappa_p}{\delta_p} \\ \frac{\eta_p \theta \beta_p \kappa_p}{\delta_p} & \frac{\eta_h \alpha_{sh} \kappa_{sh}}{\delta_h} \end{pmatrix}$$

and

$$\breve{F}_1 = \begin{pmatrix} (\delta_p + m_p) + \theta & -\theta \\ -\theta & (\delta_p + m_p) + \theta, \end{pmatrix}$$

respectively. The next generation matrix is $\hat{F}_1 \cdot \breve{F}_1^{-1}$ (where $\breve{F}_1^{-1}$ is the inverse matrix

of $\breve{F}_1$). The characteristic polynomial of the matrix is

$$\mathcal{C}_1 = \lambda \left(\lambda - \frac{\eta_p \left(\alpha_p \kappa_p + \theta \beta_p \varkappa_p \right)}{\delta_p \left(\delta_p + m_p \right)} \right). \tag{5.6}$$

Therefore the basic reproduction number for avian flu transmission among birds is

$$R_{p\theta} = \frac{\eta_p \left(\alpha_p \kappa_p + \theta \beta_p \varkappa_p \right)}{\delta_p \left(\delta_p + m_p \right)}, \tag{5.7}$$

or

$$R_{p\theta} = R_p + R_{p\beta}, \tag{5.8}$$

where R_p is the basic reproduction number due to "local" avian flu transmission among birds which is defined by (4.6)

$$R_p = \frac{\eta_p \, \alpha_p \kappa_p}{\delta_p \left(\delta_p + m_p \right)} \tag{5.9}$$

and $R_{p\beta}$ is the basic reproduction number avian flu transmission among birds during transport

$$R_{p\beta} = \frac{\eta_p \, \theta \beta_p \varkappa_p}{\delta_p \left(\delta_p + m_p \right)}. \tag{5.10}$$

Since a human becomes infected with avian flu virus by local infectious chickens only and becomes infected with swine flu and mutant-avian flu viruses by local infectious humans only, the reproduction for swine flu transmission among humans and the reproduction for mutant-avian flu transmission among humans are remain the same as for an isolated region discussed in Chapter 4. Recall from (4.7)

$$R_{sh} = \frac{\eta_h \, \alpha_{sh} \kappa_{sh}}{\delta_h \left(\delta_h + m_s \right)} \tag{5.11}$$

and from (4.8)

$$R_{mh} = \frac{\eta_h \, \alpha_{mh} \kappa_{mh}}{\delta_h \left(\delta_h + m_m \right)} \tag{5.12}$$

respectively.

5.5 Disease state equilibria

5.5.1 Disease state equilibria among poultry birds

Since humans do not infect birds, avian flu dynamics among birds is independent of the dynamics of diseases among humans. The bird dynamical system (5.4a) - (5.4d) can be

treated as a stand alone system. Consider first, a situation when there is no infected poultry in either region, so that $I_{p_1} = I_{p_2} = 0$. For an equilibrium it is required that $S'_{p_i} = 0,\ i = 1, 2$. Having $I_{p_1} = 0$, (5.4a) and (5.4c) become

$$\begin{aligned} S'_{p_1} = 0 \ &\Leftrightarrow \eta_p - (\delta_p + \theta)\, S^*_{p_1} + \theta S^*_{P_2} = 0, \\ S'_{p_2} = 0 \ &\Leftrightarrow \eta_p - (\delta_p + \theta)\, S^*_{p_2} + \theta S^*_{P_1} = 0. \end{aligned}$$

Adding these equations, results

$$2\eta_p - \delta_p(S^*_{p_1} + S^*_{p_2}) = 0 \ \Leftrightarrow (S^*_{p_1} + S^*_{p_2}) = 2\frac{\eta_p}{\delta_p} \ \Leftrightarrow S^*_{p_i} = \frac{\eta_p}{\delta_p}, i = 1, 2.$$

therefore

$$S^*_{p_i} = S^*_{p_0} = \frac{\eta_p}{\delta_p}.$$

The disease state

$$E^*_0 = (S^*_{p_0}, 0, S^*_{p_0}, 0) \tag{5.13}$$

is referred to as the disease free state of the bird world.

In an endemic situation $I_{p_i} \neq 0,\ i = 1, 2$. For an endemic equilibrium, it is required from (5.4b) and (5.4d),

$$\begin{aligned} I'_{p_1} = 0 \ &\Leftrightarrow \ \left[\alpha_p \kappa_p S^*_{p_1} - (\delta_p + m_p + \theta)\right] I^*_{p_1} + \theta \left[1 + \beta_p \varkappa_p S^*_{p_2}\right] I^*_{p_2} = 0 \\ I'_{p_2} = 0 \ &\Leftrightarrow \ \left[\alpha_p \kappa_p S^*_{p_2} - (\delta_p + m_p + \theta)\right] I^*_{p_2} + \theta \left[1 + \beta_p \varkappa_p S^*_{p_1}\right] I^*_{p_1} = 0 \end{aligned}$$

Adding these equations result in

$$(\alpha_p \kappa_p + \theta \beta_p \varkappa_p I^*_{p_1}) S^*_{p_1} + (\alpha_p \kappa_p + \theta \beta_p \varkappa_p I^*_{p_2}) S^*_{p_2} - (\delta_p + m_p)(I^*_{p_1} + I^*_{p_2}) = 0.$$

Only balanced equilibria are reported in this study. They are well behaved and asymptotically stable. Their impact to the spread of the diseases in human world are measurable. Therefore, it is assumed here that, $S^*_{p_1} = S^*_{p_1} = S^*_{p_\oplus}$ and $I^*_{p_1} = I^*_{p_1} = I^*_{p_\oplus}$. At a disease state equilibria

$$E^*_\oplus = (S^*_{p_\oplus}, I^*_{p_\oplus}, S^*_{p_\oplus}, I^*_{p_\oplus}),$$

it is required that

$$(\alpha_p \kappa_p + \theta \beta_p \varkappa_p) S^*_{p_\oplus} I^*_{p_\oplus} - (\delta_p + m_p) I^*_{p_\oplus} = 0.$$

Since $I^*_{p_\oplus} \neq 0$,

$$(\alpha_p\kappa_p + \theta\beta_p\varkappa_p)S^*_{p_\oplus} - (\delta_p + m_p) = 0 \quad \Leftrightarrow \quad .S^*_{p_\oplus} = \frac{(\delta_p + m_p)}{(\alpha_p\kappa_p + \theta\beta_p\varkappa_p)}$$

$$S^*_{p_i} = S^*_{p_\oplus} = \frac{(\delta_p + m_p)}{(\alpha_p\kappa_p + \theta\beta_p\varkappa_p)} = \frac{\eta_p}{\delta_p}\frac{1}{R_{p\theta}}, \;\; i = 1, 2.$$

Given $\eta_p(\alpha_p\kappa_p + \theta\beta_p\varkappa_p) - \delta_p\,(\delta_p + m_p) > 0$,

$$\begin{aligned} I^*_{p_\oplus} &= \frac{\eta_p(\alpha_p\kappa_p + \theta\beta_p\varkappa_p) - \delta_p\,(\delta_p + m_p)}{(\alpha_p\kappa_p + \theta\beta_p\varkappa_p)\,(\delta_p + m_p)}, \\ &= \frac{\eta_p}{\delta_p + m_p} - \frac{\delta_p}{(\alpha_p\kappa_p + \theta\beta_p\varkappa_p)} \\ &= \frac{\eta_p}{\delta_p + m_p}\left[1 - \frac{\delta_p(\delta_p + m_p)}{\eta_p(\alpha_p\kappa_p + \theta\beta_p\varkappa_p)}\right] \\ &= \frac{\eta_p}{\delta_p + m_p}(1 - \frac{1}{R_{p\theta}}), \; i = 1, 2. \end{aligned}$$

The system dynamic (5.4a) - (5.4d) has an endemic state

$$E^*_\oplus = (S^*_{p_\oplus}, I^*_{p_\oplus}, S^*_{p_\oplus}, I^*_{p_\oplus}), \tag{5.14}$$

where

$$\begin{aligned} S^*_{p_\oplus} &= \frac{\eta_p}{\delta_p}\frac{1}{R_{p\theta}}, \\ I^*_{p_\oplus} &= \frac{\eta_p}{\delta_p + m_p}(1 - \frac{1}{(R_{p\theta} - 1)}). \end{aligned}$$

In the case of $\theta = 0$, there is no movement of poultry birds, the endemic disease equilibrium (5.14) becomes

$$E^*_+ = (e^*_+, e^*_+) \tag{5.15}$$

where

$$e^*_+ = (S^*_{p_+}, I^*_{p_+})$$

with

$$\begin{aligned} S^*_{p_+} &= \frac{\delta_p + m_p}{\alpha_p\kappa_p} = \frac{\eta_p}{\delta_p}\frac{1}{R_p}, \\ I^*_{p_+} &= \frac{\eta_p}{\delta_p + m_p} - \frac{\delta_p}{\alpha_p\kappa_p} = \frac{\eta_p}{\delta_p + m_p}(1 - \frac{1}{(R_p - 1)}). \end{aligned}$$

is the endemic equilibrium of single isolated region (4.1a)-(4.1a).

Consider the initial disease states $S_{p_i}(0) \geq 0$ and $I_{p_i}(0) \geq 0$ for $i = 1, 2$. It is assumed that $0 \leq \theta \leq 1$. The last term in equation (5.4a) and (5.4c) satisfy

$$\theta S_{p_i} - \theta\beta_p\kappa_p I_{p_i} S_{p_i} \geq 0,\ i = 1, 2$$

for any $S_{p_i} \geq 0$ and $I_{p_i} \geq 0$ when $0 \leq \theta \leq 1$. This is reasonable from a biological point of view, since the first term θS_{p_i} represents the susceptible poultry birds leaving region i and the second denotes poultry birds in $\theta\beta_p\kappa_p I_{p_i} S_{p_i}$ becoming infected during travel from region i to j. Hence, the number (or proportion) of infected poultry birds during travel is at most the same as the number (or proportion) of susceptible birds who travel.

5.5.2 Disease state equilibria for the full system

The dynamics of the diseases among humans does depend on the dynamics of avian flu among birds. Therefore, to study the dynamics of the diseases among humans, it is convenient to consider the full dynamical system (5.3a)-(5.3h). It has five disease state equilibria

$$Z^*_{i\theta} = (Z^*_{it}, Z^*_{it}),\ i = 1, \ldots 5$$

where

$$Z^*_{it} = (S^*_{p_{i\theta}}, I^*_{p_{i\theta}}, S^*_{h_{i\theta}}, I^*_{s_{i\theta}}, I^*_{a_{i\theta}}, I^*_{b_{i\theta}}, I^*_{m_{i\theta}}).$$

The first three happen when there is disease free in bird world $I^*_{p_{i\theta}} = 0,\ 1, 2, 3$ and last two happen when there is disease endemic among birds, $I^*_{p_{i\theta}} \neq 0,\ i = 4, 5$.

Consider first when there is disease free in bird world $I^*_{p_{i\theta}} = 0,\ 1, 2, 3$. By omitting index i, for equilibrium it is required that $S'_p = 0$. Having $I_p = 0$, (5.5a) and (5.5h) become $\eta_p - \delta_p\, S^*_{p_0} = 0$, therefore

$$S^*_{p_0} = \frac{\eta_p}{\delta_p}.$$

For an equilibrium, it is required that $S'_{h_i} = 0\ i = 1, 2$. Having $I_{s_i} = I_{a_i} = I_{b_i} = I_{m_i} = 0$ and by omitting index i, f (5.5b) and (5.5j) become $\eta_h - \delta_p\, S^*_{h_0} = 0$, therefore

$$S^*_{h_0} = \frac{\eta_h}{\delta_h}.$$

$$Z^*_{1\theta} = (Z^*_{1t}, Z^*_{1t}) \tag{5.16}$$

where Z_{1t}^* is given by

$$Z_{1t}^* = (S_{p_{1\theta}}^*, 0, S_{h_{1\theta}}^*, 0, 0, 0, 0),$$

where

$$S_{p_{1\theta}}^* = S_{p_0}^* = \frac{\eta_p}{\delta_p},$$
$$S_{h_{1\theta}}^* = \frac{\eta_h}{\delta_h}.$$

Z_{1t}^* is the disease free equilibrium in each region and $Z_{1\theta}^*$ is referred to as the bird disease free state of (5.3a)-(5.3h). Second, the swine flu epidemic equilibrium is

$$Z_{2\theta}^* = (Z_{2t}^*, Z_{2t}^*). \tag{5.17}$$

$Z_{2t}^* = Z_2^*$, where Z_2^* is the swine flu epidemic equilibrium in each region given in (4.29). Hence,

$$Z_{2t}^* = (S_{p_{2\theta}}^*, 0, S_{h_{2\theta}}^*, I_{s_{2\theta}}^*, 0, 0, 0, 0), \tag{5.18}$$

where

$$S_{p_{2\theta}}^* = S_{p_0}^* = \frac{\eta_p}{\delta_p},$$
$$S_{h_{2\theta}}^* = \frac{\eta_h}{\delta_h}\frac{1}{R_{sh}},$$
$$I_{s_{2\theta}}^* = \frac{\eta_h}{\delta_h + m_s}(1 - \frac{1}{R_{sh}}).$$

Third, the mutant-avian flu epidemic equilibrium is

$$Z_{3\theta}^* = (Z_{3t}^*, Z_{3t}^*). \tag{5.19}$$

$Z_{3t}^* = Z_3^*$, where Z_3^* is the mutant-avian flu epidemic equilibrium in each region given in (4.33). Hence,

$$Z_{3t}^* = (S_{p_{3\theta}}^*, 0, S_{h_{3\theta}}^*, 0, 0, 0, I_{m_{3\theta}}^*)$$

is the mutant-avian flu epidemic equilibrium in each region. Here

$$S_{p_{3\theta}}^* = S_{p_0}^* = \frac{\eta_p}{\delta_p},$$
$$S_{h_{3\theta}}^* = \frac{\eta_h}{\delta_h}\frac{1}{R_{mh}},$$
$$I_{m_{3\theta}}^* = \frac{\eta_h}{\delta_h + m_m}(1 - \frac{1}{R_{mh}}).$$

When $R_{p\theta} > 1$ (avian flu is epidemic among birds) there are two disease state equilibria, $Z^*_{4\theta}$ and $Z^*_{5\theta}$.

$$Z^*_{4\theta} = (Z^*_{4t}, Z^*_{4t}) \tag{5.20}$$

where

$$Z^*_{4t} = Z^*_4 = (S^*_{p_{4\theta}}, I^*_{p_{4\theta}}, S^*_{h_{4\theta}}, 0, I^*_{a_{4\theta}}, I^*_{b_{4\theta}}, 0). \tag{5.21}$$

Z^*_4 is the disease equilibrium state of each region when there are avian flu epidemics among birds and humans. Here

$$\begin{aligned} S^*_{p_{4\theta}} &= S^*_{p_\otimes} = \frac{\eta_p}{\delta_p}\frac{1}{R_{p\theta}}, \\ I^*_{p_{4\theta}} &= I^*_{p_\otimes} = \frac{\eta_p}{\delta_p + m_p}(1 - \frac{1}{R_{p\theta}}). \end{aligned}$$

$$\begin{aligned} S^*_{h_{4\theta}} &= \frac{\eta_h}{\delta_h + \alpha_{ph}\kappa_{ph}I^*_{p_{4\theta}}} \\ &= \frac{\eta_h}{\delta_h + \alpha_{ph}\kappa_{ph}\frac{\eta_p}{\delta_p+m_p}\left(1 - \frac{1}{R_{p\theta}}\right)} \\ &= \frac{\frac{\eta_h}{\delta_h}}{1 + \frac{\alpha_{ph}\kappa_{ph}\eta_p}{\eta_h\,(\delta_p+m_p)}\left(1 - \frac{1}{R_{p\theta}}\right)} \\ &= \frac{\frac{\eta_h}{\delta_h}}{1 + r_{ph\theta}} \end{aligned}$$

where $r_{ph\theta}$ is defined as

$$r_{ph\theta} = \frac{\alpha_{ph}\kappa_{ph}\eta_p}{\eta_h\ (\delta_p + m_p)}\left(1 - \frac{1}{R_{p\theta}}\right). \tag{5.22}$$

$$\begin{aligned} I^*_{a_{4\theta}} &= \frac{\gamma\alpha_{ph}\kappa_{ph}I^*_{p_4}S^*_{h_{4\theta}}}{\delta_h + m_a} \\ &= \frac{\gamma}{\delta_h + m_a}(\eta_h - \delta_h S^*_{h_{4\theta}}) \\ &= \frac{\gamma\eta_h}{\delta_h + m_a}\left(1 - \frac{1}{1 + r_{ph}}\right) > 0 \end{aligned}$$

and

$$\begin{aligned} I^*_{b_{4\theta}} &= \frac{(1-\gamma)\alpha_{ph}\kappa_{ph}I^*_{p_{4\theta}}S^*_{h_{4\theta}}}{\delta_h + m_b} \\ &= \frac{(1-\gamma)}{\delta_h + m_b}(\eta_h - \delta_h S^*_{h_4}) \\ &= \frac{(1-\gamma)\eta_h}{\delta_h + m_b}\left(1 - \frac{1}{1+r_{ph}}\right) > 0 \end{aligned}$$

The condition $R_{p\theta} > 1$ means $r_{ph\theta} > 0$ and hence guarantees that $I^*_{p_{4\theta}} > 0, S^*_{h_{4\theta}} > 0, I^*_{a_{4\theta}} > 0$ and $I^*_{b_{4\theta}} > 0$.

The fifth equilibrium state is

$$Z^*_{5\theta} = (Z^*_{5t}, Z^*_{5t}) \tag{5.23}$$

where

$$Z^*_{5t} = Z^*_5 = (S^*_{p_{5\theta}}, I^*_{p_{5\theta}}, S^*_{h_{5\theta}}, 0, I^*_{a_{5\theta}}, I^*_{b_{5\theta}}, I^*_{m_{5\theta}}). \tag{5.24}$$

Z^*_5 is the disease state equilibrium of each region when there are avian flu epidemics among birds and humans and also an epidemic of mutant-avian flu among humans. Here

$$\begin{aligned} S^*_{p_{5\theta}} &= S^*_{p_\otimes} = \frac{\eta_p}{\delta_p}\frac{1}{R_{p\theta}}, \\ I^*_{p_{5\theta}} &= I^*_{p_\otimes} = \frac{\eta_p}{\delta_p + m_p}(1 - \frac{1}{R_{p\theta}}). \end{aligned}$$

Hence for $I^*_{p_{5\theta}} > 0$ it is required that $R_{p\theta} > 1$. It follows from (4.20f)

$$S^*_{h_{5\theta}} = \frac{\delta_h + m_m}{\alpha_{mh}\kappa_{mh}} > 0.$$

Now (4.20c) gives

$$\begin{aligned} I^*_{m_{5\theta}} &= \frac{\eta_h - \left(\delta_h + \alpha_{ph}\kappa_{ph}I^*_{p_{5\theta}}\right)S^*_{h_{5\theta}}}{\alpha_{mh}\kappa_{mh}S^*_{h_{5\theta}}} \\ &= \frac{\eta_h - \left[\delta_h + \alpha_{ph}\kappa_{ph}\frac{\eta_p}{\delta_h + m_m}(1 - \frac{1}{R_{p\theta}})\right]\frac{\delta_h + m_m}{\alpha_{mh}\kappa_{mh}}}{\delta_h + m_m} \\ &= \frac{\delta_h}{\alpha_{mh}\kappa_{mh}}\left[\frac{\alpha_{mh}\kappa_{mh}\eta_h}{\delta_h(\delta_p + m_m)} - 1 - \frac{\alpha_{ph}\kappa_{ph}\eta_h}{\delta_h(\delta_p + m_p)}(1 - \frac{1}{R_{p\theta}})\right] \\ &= \frac{\delta_h}{\alpha_{mh}\kappa_{mh}}\left[R_{mh} - (1 + r_{ph})\right]. \end{aligned}$$

where $r_{ph\theta}$ is defined by (4.38)

$$r_{ph\theta} = \frac{\alpha_{ph}\kappa_{ph}\eta_p}{\eta_h\ (\delta_p + m_p)} \left(1 - \frac{1}{R_{p\theta}}\right).$$

Therefore for $I^*_{m_{5\theta}} > 0$ it is necessary that $R_{mh} > 1 + r_{ph\theta}$. Finally (4.20d) and (4.20e) give

$$\begin{aligned} I^*_{a_{5\theta}} &= \frac{\gamma\alpha_{ph}\kappa_{ph}I^*_{p_{5\theta}}S^*_{h_{5\theta}}}{\delta_h + m_a} \\ &= \frac{\gamma\alpha_{ph}\kappa_{ph}\frac{\eta_p}{\delta_p+m_p}(1 - \frac{1}{R_{p\theta}})\frac{\delta_h+m_m}{\alpha_{mh}\kappa_{mh}}}{\delta_h + m_a} \\ &= \frac{\gamma\eta_h r_{ph}}{(\delta_h + m_a)R_{mh}} > 0 \end{aligned}$$

and

$$\begin{aligned} I^*_{b_{5\theta}} &= \frac{(1-\gamma)\alpha_{ph}\kappa_{ph}I^*_{p_{5\theta}}S^*_{h_{5\theta}}}{\delta_h + m_b} \\ &= \frac{(1-\gamma)\alpha_{ph}\kappa_{ph}\frac{\eta_p}{\delta_p+m_p}(1 - \frac{1}{R_{p\theta}})\frac{\delta_h+m_m}{\alpha_{mh}\kappa_{mh}}}{\delta_h + m_b} \\ &= \frac{(1-\gamma)\eta_h r_{ph}}{(\delta_h + m_b)R_{mh}} > 0 \end{aligned}$$

Following the previous result on disease persistence in human world, Lemma 4.15 in Section 4.6, a disease free state among birds in region 1 would not necessarily stop the disease from spreading among humans; the disease among humans in region 1 may disappear (disease free in both bird and human world), there could be a swine flu epidemic, a mutant-avian flu epidemic, or epidemics of all human diseases except avian flu.

5.6 Stability analysis of disease state equilibria

Reorder disease state variables

$$Z = (S_{p_1}, I_{p_1}, S_{h_1}, I_{s_1}, I_{a_1}, I_{b_1}, I_{m_1}, S_{p_2}, I_{p_2}, S_{h_2}, I_{s_2}, I_{a_2}, I_{b_2}, I_{m_2})$$

into

$$\bar{Z} = (S_{p_1}, I_{p_1}, S_{p_2}, I_{p_2}, S_{h_1}, I_{s_1}, I_{a_1}, I_{b_1}, I_{m_1}, S_{h_2}, I_{s_2}, I_{a_2}, I_{b_2}, I_{m_2}).$$

In this new variable, (5.5a)-(5.5n) becomes

$$S'_{p_1}(t) = \eta_p - (\delta_p + \theta)S_{p_1} - \alpha_p\kappa_p I_{p_1} S_{p_1} + \theta(1 - \beta_p \varkappa_p I_{p_2})\, S_{p_2}, \tag{5.25a}$$
$$I'_{p_1}(t) = \alpha_p\kappa_p I_{p_1} S_{p_1} - (\delta_p + m_p + \theta)\, I_{p_1} + \theta(1 + \beta_p \varkappa_p S_{p_2})\, I_{p_2}, \tag{5.25b}$$
$$S'_{p_2}(t) = \eta_p - (\delta_p + \theta)S_{p_2} - \alpha_p\kappa_p I_{p_2} S_{p_2} + \theta(1 - \beta_p \varkappa_p I_{p_1})S_{p_1}, \tag{5.25c}$$
$$I'_{p_2}(t) = \alpha_p\kappa_p I_{p_2} S_{p_2} - (\delta_p + m_p + \theta)\, I_{p_2} + \theta(1 + \beta_p \varkappa_p S_{p_1})I_{p_1}, \tag{5.25d}$$
$$S'_{h_1}(t) = \eta_h - \delta_h S_{h_1} - \alpha_{ph}\kappa_{ph} I_{p_1} S_{h_1} - \alpha_{sh}\kappa_{sh} I_{s_1} S_{h_1} - \alpha_{mh}\kappa_{mh} I_{m_1} S_{h_1}, \tag{5.25e}$$
$$I'_{s_1}(t) = \alpha_{sh}\kappa_{sh} I_{s_1} S_{h_1} - (\delta_h + m_s)\, I_{s_1}, \tag{5.25f}$$
$$I'_{a_1}(t) = \gamma\alpha_{ph}\kappa_{ph} I_{p_1} S_{h_1} - \mu\alpha_{sa}\kappa_{sa} I_{s_1} I_{a_1} - (\delta_h + m_a)\, I_{a_1}, \tag{5.25g}$$
$$I'_{b_1}(t) = (1 - \gamma)\alpha_{ph}\kappa_{ph} I_{p_1} S_{h_1} - (\delta_h + m_b)\, I_{b_1}, \tag{5.25h}$$
$$I'_{m_1}(t) = \mu\alpha_{sa}\kappa_{sa} I_{s_1} I_{a_1} + \alpha_{mh}\kappa_{mh} I_{m_1} S_{h_1} - (\delta_h + m_m)\, I_{m_1},, \tag{5.25i}$$
$$S'_{h_2}(t) = \eta_h - \delta_h S_{h_2} - \alpha_{ph}\kappa_{ph} I_{p_2} S_{h_2} - \alpha_{sh}\kappa_{sh} I_{s_2} S_{h_2} - \alpha_{mh}\kappa_{mh} I_{m_2} S_{h_2}, \tag{5.25j}$$
$$I'_{s_2}(t) = \alpha_{sh}\kappa_{sh} I_{s_2} S_{h_2} - (\delta_h + m_s)\, I_{s_2}, \tag{5.25k}$$
$$I'_{a_2}(t) = \gamma\alpha_{ph}\kappa_{ph} I_{p_2} S_{h_2} - \mu\alpha_{sa}\kappa_{sa} I_{s_2} I_{a_2} - (\delta_h + m_a)\, I_{a_2}, \tag{5.25l}$$
$$I'_{b_2}(t) = (1 - \gamma)\alpha_{ph}\kappa_{ph} I_{p_2} S_{h_2} - (\delta_h + m_b)\, I_{b_2}, \tag{5.25m}$$
$$I'_{m_2}(t) = \mu\alpha_{sa}\kappa_{sa} I_{s_2} I_{a_2} + \alpha_{mh}\kappa_{mh} I_{m_2} S_{h_2} - (\delta_h + m_m)\, I_{m_2}, \tag{5.25n}$$

The Jacobian matrix of (5.25a)-(5.25n) at $\bar{Z}_{i\theta} \forall i = 1, \ldots, 5$ is given by

$$\mathcal{J}_{i\theta} = \begin{bmatrix} J_{i\theta 1} & O_1 & O_1 \\ J_4 & J_{i\theta 2} & O_3 \\ J_5 & O_3 & J_{i\theta 3} \end{bmatrix} \quad \text{fori} = 1, \ldots, 5. \tag{5.26}$$

$$J_{i\theta 1} = \begin{bmatrix} j_{1,1} & j_{1,2} & j_{1,3} & j_{1,4} \\ j_{2,1} & j_{2,2} & j_{2,3} & j_{2,4} \\ j_{3,1} & j_{3,2} & j_{3,3} & j_{3,4} \\ j_{4,1} & j_{4,2} & j_{4,3} & j_{4,4} \end{bmatrix}, \tag{5.27}$$

where $j_{1,1} = -\delta_p - \theta - \alpha_p\kappa_p I_{p_1}$, $j_{1,2} = -\alpha_p\kappa_p S_{p_1}$, $j_{1,3} = \theta(1 - \beta_p\varkappa_p I_{p_2})$, $j_{1,4} = -\theta\beta_p\varkappa_p S_{p_2}$, $j_{2,1} = \alpha_p\kappa_p I_{p_1}$, $j_{2,2} = \alpha_p\kappa_p S_{p_1} - (\delta_p + m_p) - \theta$, $j_{2,3} = \theta\beta_p\varkappa_p I_{p_2}$, $j_{2,4} = \theta(1 + \beta_p\varkappa_p S_{p_2})$, $j_{3,1} = \theta(1 - \beta_p\varkappa_p I_{p_1})$, $j_{3,2} = -\theta\beta_p\varkappa_p S_{p_1}$, $j_{3,3} = -\delta_p - \theta - \alpha_p\kappa_p I_{p_2}$, $j_{3,4} = -\alpha_p\kappa_p S_{p_2}$, $j_{4,1} = \theta\beta_p\varkappa_p I_{p_1}$, $j_{4,2} = \theta(1 + \beta_p\varkappa_p S_{p_1})$, $j_{4,3} = \alpha_p\kappa_p I_{p_2}$,

$j_{4,4} = \alpha_p \kappa_p I_{p_2} - (\delta_p + m_p) - \theta(1 + \beta_p \varkappa_p S_{p_1})$.

$$J_{i\theta 2} = \begin{bmatrix} j_{5,5} & j_{5,6} & 0 & 0 & j_{5,9} \\ j_{6,5} & j_{6,6} & 0 & 0 & 0 \\ j_{7,5} & j_{7,6} & j_{7,7} & 0 & 0 \\ j_{8,5} & 0 & 0 & j_{8,8} & 0 \\ j_{9,5} & j_{9,6} & j_{9,7} & 0 & j_{9,9} \end{bmatrix}, \tag{5.28}$$

$$J_{i\theta 3} = \begin{bmatrix} j_{10,10} & j_{10,11} & 0 & 0 & j_{10,14} \\ j_{11,10} & j_{11,11} & 0 & 0 & 0 \\ j_{12,10} & j_{12,11} & j_{12,12} & 0 & 0 \\ j_{13,10} & 0 & 0 & j_{13,13} & 0 \\ j_{14,10} & j_{14,11} & j_{14,12} & 0 & j_{14,14} \end{bmatrix}, \tag{5.29}$$

where $j_{5,5} = j_{10,10} = -\delta_h - \alpha_{ph}\kappa_{ph} I_{p_1} - \alpha_{sh}\kappa_{sh} I_s - \alpha_{mh}\kappa_{mh} I_m$, $j_{5,6} = j_{10,11} = -\alpha_{sh}\kappa_{sh} S_{h_1}$, $j_{5,9} = j_{10,14} = -\alpha_{mh}\kappa_{mh} S_{h_1}$, $j_{6,5} = j_{11,10} = -\alpha_{sh}\kappa_{sh} I_s$, $j_{6,6} = j_{11,11} = \alpha_{sh}\kappa_{sh} S_{h_1} - (\delta_h + m_s)$, $j_{7,5} = j_{12,10} = \gamma_a \alpha_{ph}\kappa_{ph} I_{p_1}$, $j_{7,6} = j_{12,11} = -\mu\, \alpha_{sa}\kappa_{sa} I_a$, $j_{7,7} = j_{12,12} = -\mu\, \alpha_{sa}\kappa_{sa} I_{s_1} - (\delta_h + m_a)$, $j_{8,5} = j_{13,10} = (1 - \gamma_a)\alpha_{yh}\kappa_{ph} I_{p_1}$, $j_{8,8} = j_{13,13} = -(\delta_h + m_b)$, $j_{9,5} = j_{14,10} = \alpha_{mh}\kappa_{mh} I_{m_1}$, $j_{9,6} = j_{14,11} = \mu\, \alpha_{sa}\kappa_{sa} I_a$, $j_{9,7} = j_{14,12} = \mu\, \alpha_{sa}\kappa_{sa} I_{s_1}$, $j_{9,9} = j_{14,14} = \alpha_{mh}\kappa_{mh} S_{h_1} - (\delta_h + m_m)$.

$$J_4 = \begin{bmatrix} 0 & j_{5,2} & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & j_{7,2} & 0 & 0 \\ 0 & j_{8,2} & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix}, \; J_5 = \begin{bmatrix} 0 & 0 & 0 & j_{10,4} \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & j_{12,4} \\ 0 & 0 & 0 & j_{13,4} \\ 0 & 0 & 0 & 0 \end{bmatrix},$$

where $j_{5,2} = j_{10,4} = -\alpha_{ph}\kappa_{ph} S_{h_1}$, $j_{7,2} = j_{12,4} = \gamma_a \alpha_{ph}\kappa_{ph} S_{h_1}$, $j_{8,2} = j_{13,4} = (1 -$

$\gamma_a)\alpha_{yh}\kappa_{ph}S_{h_1}$. O_1, O_2 and O_3 are zero matrices

$$O_1 = \begin{bmatrix} 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{bmatrix}, \; O_2 = \begin{bmatrix} 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{bmatrix}.$$

J_1, J_2 and J_3 are the key Jacobian matrices or principal minors of the Jacobian matrix $\mathcal{J}$ given in (5.26). The Jacobian matrix is stable at an equilibrium point $Z^*_{i\theta},\ i = 1, \ldots 6$ if and only if the key Jacobian matrices are stable at $Z^*_{i\theta}$ (by Corollary 3.26).

5.6.1 Stability analysis of the disease free equilibrium

The first disease equilibrium ($i = 1$) is the disease free equilibrium, $Z^*_{1\theta} = (Z^*_{1t}, Z^*_{1t})$ where $Z^*_{1t} = (\frac{\eta_p}{\delta_p}, 0, \frac{\eta_h}{\delta_h}, 0, 0, 0, 0)$. Stability analysis of $Z^*_{1\theta} = (Z^*_{1t}, Z^*_{1t})$ is given as follows.

Theorem 5.2. *If $R_{p\theta} < 1$, $R_{sh} \leq 1$, $R_{mh} \leq 1$, $r_{ph} \leq 1$, then $Z^*_{1\theta}$ is LAS.*

Proof. At $E^*_0 = (\frac{\eta_p}{\delta_p}, 0, \frac{\eta_p}{\delta_p}, 0,)$, first key Jacobian matrix is

$$J_{1\theta 1} = J_1(E^*_0) = \begin{bmatrix} j_{1,1} & j_{1,2} & j_{1,3} & j_{1,4} \\ 0 & j_{2,2} & 0 & j_{2,4} \\ 0 & j_{3,2} & j_{3,3} & j_{3,4} \\ 0 & j_{4,2} & 0 & j_{4,4} \end{bmatrix},$$

where $j_{1,1} = -\delta_p - \theta$, $j_{1,2} = -\alpha_p\kappa_p\frac{\eta_p}{\delta_p}$, $j_{1,3} = \theta$, $j_{1,4} = -\theta\beta_p\varkappa_p\frac{\eta_p}{\delta_p}$, $j_{2,1} = 0$, $j_{2,2} = \alpha_p\kappa_p\frac{\eta_p}{\delta_p} - (\delta_p + m_p) - \theta$, $j_{2,3} = 0$, $j_{2,4} = \theta(1 + \beta_p\varkappa_p\frac{\eta_p}{\delta_p})$, $j_{3,1} = \theta$, $j_{3,2} = -\theta\beta_p\varkappa_p\frac{\eta_p}{\delta_p}$, $j_{3,3} = -\delta_p - \theta$, $j_{3,4} = -\alpha_p\kappa_p\frac{\eta_p}{\delta_p}$, $j_{4,1} = 0$, $j_{4,2} = \theta(1 + \beta_p\varkappa_p\frac{\eta_p}{\delta_p})$, $j_{4,3} = 0$, $j_{4,4} = -(\delta_p + m_p) - \theta(1 + \beta_p\varkappa_p\frac{\eta_p}{\delta_p})$.

The characteristic polynomial of $J_{1\theta 1}$ is

$$\mathcal{C}_{1\theta} = (\lambda - m_p(R_0 - 1))^2 (\lambda + \delta_p)(\lambda + (\delta_p + 2\theta))$$

Hence, the key Jacobian matrix $J_{1\theta 1}$ is stable if $R_{0\theta} < 1$. The key Jacobian matrix $J_{1\theta 2}$

and $J_{1\theta 3}$ are the same as the key Jacobian matrix (4.28),

$$J_{1\theta 2} = J_{1\theta 2} = J_{12} = \begin{bmatrix} j_{3,3} & j_{3,4} & 0 & 0 & j_{3,7} \\ 0 & j_{4,4} & 0 & 0 & 0 \\ 0 & 0 & j_{5,5} & 0 & 0 \\ 0 & 0 & 0 & j_{6,6} & 0 \\ 0 & 0 & 0 & 0 & j_{7,7} \end{bmatrix},$$

where $j_{3,3} = -\delta_h$, $j_{3,4} = (-1)\alpha_{sh}\kappa_{sh}S^*_{h_{1\theta}}$, $j_{3,7} = (-1)\alpha_{mh}\kappa_{mh}S^*_{h_{1\theta}}$, $j_{4,4} = \alpha_{sh}\kappa_{sh}S^*_{h_{1\theta}} - (\delta_h + m_s)$, $j_{5,5} = (-1)(\delta_h - m_a)$, $j_{6,6} = (-1)(\delta_h - m_b)$, $j_{7,7} = \alpha_{mh}\kappa_{mh}S^*_{h_{1\theta}} - (\delta_h + m_m)$, $j_{8,1} = -\delta_p$, $j_{8,2} = -(\delta_p + m_p)R_{p\theta}$, $j_{9,2} = j_{9,9} = (\delta_p + m_p)(R_{p\theta} - 1)$. Recall some results from Sub-section 4.5.3 that J_{11} is proven to be stable if $R_p \leq 1$ and J_{12} is proven to be stable if $R_{sh} \leq 1$ and $R_{mh} \leq 1$. Since $J_{1\theta 1} = J_{11}$ and $R_p \leq R_{p\theta}$, therefore $J_{1\theta 1}$ is stable if $R_{p\theta} \leq$. Since $J_{1\theta 2} = J_{1\theta 2} = J_{12}$ therefore $J_{1\theta 2} = J_{1\theta 2}$ are stable if $R_{sh} \leq 1$ and $R_{mh} \leq 1$. Therefore $Z^*_{1\theta}$ is well defined and stable if $R_p < 1, R_{sh} \leq 1$ and $R_{mh} \leq 1$. □

This result means that disease eradication is possible for a sufficient small parameter β_p when the both regions are disease free without traveling (that is, $R_{p\theta}$ for small β_p when $R_p < 1$). From 5.8, if $\beta_p = 0$ and $R_p < 1$ holds, then infectious diseases should disappear in both regions. However, the disease free state among birds does not guarantee a disease free state among humans. The following are three possible disease equilibria.

5.6.2 *Stability analysis of swine flu epidemic equilibrium in both regions*

The swine flu epidemic equilibrium is (5.17)

$$Z^*_{2\theta} = (Z^*_{2t}, Z^*_{2t})$$

where

$$Z^*_{2t} = (S^*_{p_{2\theta}}, 0, S^*_{h_{2\theta}}, I^*_{s_{2\theta}}, 0, 0, 0, 0),$$

is the swine flu epidemic equilibrium in each region. Here

$$S^*_{p_{2\theta}} = S^*_{p_0} = \frac{\eta_p}{\delta_p},$$
$$S^*_{h_{2\theta}} = \frac{\eta_h}{\delta_h}\frac{1}{R_{sh}},$$
$$I^*_{s_{2\theta}} = \frac{\eta_h}{\delta_h + m_s}(1 - \frac{1}{R_{sh}}).$$

Theorem 5.3. *If $R_{p\theta} < 1$ and $R_{sh} > \max\{R_{mh}, 1\}$ then the swine flu epidemic equilibrium $Z^*_{2\theta}$ is LAS.*

Proof. At $\bar{Z}^*_{2\theta}$ the Jacobian matrix (5.26) becomes

$$\mathcal{J}_{2\theta} = \mathcal{J}(\bar{Z}^*_{2\theta}) = \begin{bmatrix} J_{2\theta 1} & O_1 & O_1 \\ J_4 & J_{2\theta 2} & O_3 \\ J_5 & O_3 & J_{2\theta 3} \end{bmatrix}.$$

$J_{2\theta 1} = J_{1\theta 1}$, so from the last Sub-section, $J_{2\theta 1}$ is table if and only if $R_{p\theta} < 1$.

The second and third key Jacobian matrices $J_{2\theta 2} = J_{2\theta 3}$, are the same as the key Jacobian matrix given in (4.31)

$$J_{2\theta 2} = J_{2\theta 3} = J_{12} = \begin{bmatrix} j_{3,3} & j_{3,4} & 0 & 0 & j_{3,7} \\ j_{4,3} & 0 & 0 & 0 & 0 \\ 0 & 0 & j_{5,5} & 0 & 0 \\ 0 & 0 & 0 & j_{6,6} & 0 \\ 0 & 0 & j_{7,5} & 0 & j_{7,7} \end{bmatrix}$$

where $j_{3,3} = (-1)(\delta_h + \alpha_{sh}\kappa_{sh}I^*_{s_{2\theta}})$, $j_{3,4} = (-1)\alpha_{sh}\kappa_{sh}S^*_{h_{2\theta}}$, $j_{37} = (-1)\alpha_{mh}\kappa_{mh}S^*_{h_{2\theta}}$, $j_{4,3} = (-1)\alpha_{sh}\kappa_{sh}I^*_{s_{2\theta}}$, $j_{5,5} = (-1)\left[\mu\alpha_{sh}\kappa_{sh}I^*_{s_{2\theta}} + (\delta_h + m_a)\right]$, $j_{6,6} = (-1)(\delta_h + m_b)$, $j_{7,5} = (-1)[\mu\alpha_{sa}\kappa_{sa}I^*_{s_{2\theta}}$, $j_{7,7} = \alpha_{mh}\kappa_{mh}S^*_{h_{2\theta}} + (\delta_h + m_m)$.

Recall some results from Sub-section 4.5.4 that J_{21} is proven to be stable if $R_p \leq 1$ and J_{12} is proven to be stable if $R_{sh} > \max\{R_{mh}, 1\}$. Since $J_{2\theta 1} = J_{21}$ and $R_p \leq R_{p\theta}$, then $J_{2\theta 1}$ is stable if $R_{p\theta} \leq 1$ Since $J_{2\theta 2} = J_{1\theta 3} = J_{22}$ therefore $J_{2\theta 2} = J_{1\theta 3}$ are stable if $R_{sh} > \max\{R_{mh}, 1\}$. □

5.6.3 Stabilty analysis of mutant-avian flu epidemic equilibrium

The mutant avian flu epidemic equilibrium, $Z^*_{3\beta}$, corresponds to the situation in which there are no birds or humans infected by avian flu and no humans infected by swine flu but there are humans infected by mutant-avian flu. By using the definitions of the basic reproduction numbers in Section 4.3,

$$Z^*_{3\theta} = (Z^*_{3t}, Z^*_{3t}), \tag{5.30}$$

with

$$Z^*_{3t} = (S^*_{p_{3\theta}}, 0, S^*_{h_{3\theta}}, 0, 0, 0, I^*_{m_{3\theta}}),$$

where

$$S^*_{p3\theta} = S^*_{p0} = \frac{\eta_p}{\delta_p}$$
$$S^*_{h3\theta} = \frac{\eta_h}{\delta_h}\frac{1}{R_{mh}},$$
$$I^*_{m3\theta} = \frac{\eta_h}{\delta_h + m_m}(1 - \frac{1}{R_{mh}}).$$

Theorem 5.4. *If $R_{p\theta} < 1$ and $R_{mh} > \max\{R_{sh}, 1\}$ then $Z^*_{3\theta}$ is LAS.*

Proof. At $\bar{Z}^*_{3\theta}$ the Jacobian matrix (5.26) becomes

$$\mathcal{J}_{3\theta} = \mathcal{J}(\bar{Z}^*_{3\theta}) = \begin{bmatrix} J_{3\theta 1} & O_1 & O_1 \\ J_4 & J_{3\theta 2} & O_3 \\ J_5 & O_3 & J_{3\theta 3} \end{bmatrix}.$$

$J_{3\theta 1} = J_{1\theta 1}$, so $J_{3\theta 1}$ is table if and only if $R_{p\theta} < 1$.

The second and third key Jacobian matrices $J_{3\theta 2} = J_{3\theta 3}$, are the same as J_{32}, the key Jacobian matrix given in (4.40),

$$J_{3\theta 2} = J_{3\theta 3} = J_{32} = \begin{bmatrix} j_{3,3} & j_{3,4} & 0 & 0 & j_{3,7} \\ 0 & j_{4,4} & 0 & 0 & 0 \\ 0 & 0 & j_{5,5} & 0 & 0 \\ 0 & 0 & 0 & j_{6,6} & 0 \\ j_{7,5} & 0 & 0 & 0 & j_{7,7} \end{bmatrix}, \text{for} k = 1, \ldots, 4,$$

where $j_{1,1} = (-1)\delta_p$, $j_{1,2} = -\alpha_p\kappa_p S^*_{p3\theta}$ $j_{2,2} = -\alpha_p\kappa_p S^*_{p3\theta} - (\delta_p + m_p)$, $j_{3,3} = (-1)(\delta_h + \alpha_{mh}\kappa_{mh}I^*_{m_3})$, $j_{3,4} = (-1)\alpha_{sh}\kappa_{sh}S^*_{h3\theta}$, $j_{3,7} = (-1)\alpha_{mh}\kappa_{mh}S^*_{h_3}$, $j_{4,4} = (-1)\alpha_{sh}\kappa_{sh}S^*_{h3\theta} - (\delta_h + m_s)$, $j_{5,5} = (-1)(\delta_h + m_a)$, $j_{6,6} = (-1)(\delta_h + m_b)$, $j_{7,3} = (-1)\alpha_{mh}\kappa_{mh}I^*_{m3\theta}$, $j_{7,7} = \alpha_{mh}\kappa_{mh}S^*_{h3\theta} - (\delta_h + m_m)$.

Recall some results from Sub-section 6.6.3 that J_{31} is proven to be stable if $R_{p\theta}1$ and J_{32} is proven to be stable if $R_{mh} > \max\{R_{sh}, 1\}$. Since $J_{3\theta 1}$ and $R_p \leq R_{p\theta} < 1$ therefore $J_{3\theta 1}$ are stable if $R_{p\theta} < 1$. Since $J_{3\theta 2} = J_{3\theta 3} = J_{32}$ therefore $J_{3\theta 2}$ and $J_{3\theta 3}$ are stable if $R_{mh} > \max\{R_{sh}, 1\}$. □

5.6.4 Stability analysis of avian-flu epidemic equilibrium.

The disease state when there are avian flu epidemics among birds and humans, $Z^*_{4\theta}$, is

$$Z^*_{4\theta} = (Z^*_{4t}, Z^*_{4t}) \tag{5.31}$$

with

$$Z^*_{4t} = (S^*_{p_{4\theta}}, I^*_{p_{4\theta}}, S^*_{h_{4\theta}}, 0, I^*_{a_{4\theta}}, I^*_{b_{4\theta}}, 0),$$

where

$$S^*_{p_{4\theta}} = \frac{\delta_p + m_p}{\alpha_p \kappa_p} = \frac{\eta_p}{\delta_p}\frac{1}{R_p} > 0$$
$$I^*_{p_{4\theta}} = \frac{\eta_p}{\delta_p + m_p}(1 - \frac{1}{R_{p\theta}})$$
$$S^*_{h_{4\theta}} = \frac{\frac{\eta_h}{\delta_h}}{1 + r_{ph}}$$

where r_{ph} is defined as (4.38),

$$r_{ph\theta} = \frac{\alpha_{ph}\kappa_{ph}\eta_p}{\eta_h\ (\delta_p + m_p)}\left(1 - \frac{1}{R_{p\theta}}\right). \tag{5.32}$$

$$I^*_{a_4} = \frac{\gamma\eta_h}{\delta_h + m_a}\left(1 - \frac{1}{1 + r_{ph\theta}}\right),$$

and

$$I^*_{a_b} = \frac{(1-\gamma)\eta_h}{\delta_h + m_b}\left(1 - \frac{1}{1 + r_{ph\theta}}\right).$$

Theorem 5.5. *If* $R_{p\theta} > 1,\ R_{p\theta} \leq 2R_p$ *and* $\max\{R_{sh}, R_{mh}\} < 1 + r_{ph}$ *then* $Z^*_{4\theta} = (Z^*_{4t}, Z^*_{4t})$ *is LAS.*

Proof. At $\bar{Z}^*_{4\theta}$ the Jacobian matrix (5.26) becomes

$$\mathcal{J}_{4\theta} = \mathcal{J}(\bar{Z}^*_{4\theta}) = \begin{bmatrix} J_{4\theta 1} & O_1 & O_1 \\ J_4 & J_{4\theta 2} & O_3 \\ J_5 & O_3 & J_{4\theta 3} \end{bmatrix}.$$

From (5.33)

$$J_{4\theta 1} = \begin{bmatrix} j_{1,1} & j_{1,2} & j_{1,3} & j_{1,4} \\ j_{2,1} & j_{2,2} & j_{2,3} & j_{2,4} \\ j_{3,1} & j_{3,2} & j_{3,3} & j_{3,4} \\ j_{4,1} & j_{4,2} & j_{4,3} & j_{4,4} \end{bmatrix},$$

where $j_{1,1} = -\delta_p - \theta - \alpha_p\kappa_p I_{p_{4\theta}}$, $j_{1,2} = -\alpha_p\kappa_p S_{p_{4\theta}}$, $j_{1,3} = \theta(1 - \beta_p\varkappa_p I_{p_2})$, $j_{1,4} = -\theta\beta_p\varkappa_p S_{p_2}$, $j_{2,1} = \alpha_p\kappa_p I_{p_{4\theta}}$, $j_{2,2} = \alpha_p\kappa_p S_{p_{4\theta}} - (\delta_p + m_p) - \theta$, $j_{2,3} = \theta\beta_p\varkappa_p I_{p_2}$, $j_{2,4} =$

$\theta(1+\beta_p\varkappa_p S_{p_{4\theta}})$, $j_{3,1}=\theta(1-\beta_p\varkappa_p I_{p_{4\theta}})$, $j_{3,2}=-\theta\beta_p\varkappa_p S_{p_{4\theta}}$, $j_{3,3}=-\delta_p-\theta-\alpha_p\kappa_p I_{p_{4\theta}}$, $j_{3,4}=-\alpha_p\kappa_p S_{p_{4\theta}}$, $j_{4,1}=\theta\beta_p\varkappa_p I_{p_1}$, $j_{4,2}=\theta(1+\beta_p\varkappa_p S_{p_{4\theta}})$, $j_{4,3}=\alpha_p\kappa_p I_{p_2}$, $j_{4,4}=\alpha_p\kappa_p I_{p_{4\theta}}-(\delta_p+m_p)-\theta(1+\beta_p\varkappa_p S_{p_{4\theta}})$.

Denote the partition matrix $J_{4\theta 1}$ as

$$J_{4\theta 1}=\begin{bmatrix} A & B \\ B & A \end{bmatrix} \tag{5.33}$$

where

$$A=\begin{bmatrix} -\delta_p-\theta-\alpha_p\kappa_p I_{p_{4\theta}} & -\alpha_p\kappa_p S_{p_{4\theta}} \\ \alpha_p\kappa_p I_{p_{4\theta}} & \alpha_p\kappa_p S_{p_{4\theta}}-(\delta_p+m_p)-\theta \end{bmatrix}$$

and

$$B=\begin{bmatrix} \theta(1-\beta_p\varkappa_p I_{p_{4\theta}}) & -\theta\beta_p\varkappa_p S_{p_{4\theta}} \\ \theta\beta_p\varkappa_p I_{p_{4\theta}} & \theta(1+\beta_p\varkappa_p S_{p_{4\theta}}) \end{bmatrix}$$

At $E^*_{\oplus}$

$$S^*_{p_{4\theta}}=S^*_{p_\otimes}=\frac{\eta_p}{\delta_p}\frac{1}{R_{p\theta}},$$
$$I^*_{p_{4\theta}}=I^*_{p_\otimes}=\frac{\eta_p}{\delta_p+m_p}(1-\frac{1}{R_{p\theta}})$$

$$A=\begin{bmatrix} -\delta_p-\theta-\alpha_p\kappa_p\frac{\eta_p}{(\delta_p+m_p)}(1-\frac{1}{R_{p\theta}}) & -\alpha_p\kappa_p\frac{\eta_p}{\delta_p}\frac{1}{R_{p\theta}} \\ \alpha_p\kappa_p\frac{\eta_p}{(\delta_p+m_p)}(1-\frac{1}{R_{p\theta}}) & \alpha_p\kappa_p\frac{\eta_p}{\delta_p}\frac{1}{R_{p\theta}}-(\delta_p+m_p)-\theta \end{bmatrix}$$
$$=\begin{bmatrix} -\delta_p-\theta-\frac{R_p}{\delta_p}(1-\frac{1}{R_{p\theta}}) & -\frac{R_p}{(\delta_p+m_p)}\frac{1}{R_{p\theta}} \\ \frac{R_p}{\delta_p}(1-\frac{1}{R_{p\theta}}) & \frac{1}{(\delta_p+m_p)}\frac{R_p}{R_{p\theta}}-(\delta_p+m_p)-\theta \end{bmatrix}$$

and

$$B=\begin{bmatrix} \theta(1-\beta_p\varkappa_p\frac{\eta_p}{(\delta_p+m_p)}(1-\frac{1}{R_{p\theta}})) & -\theta\beta_p\varkappa_p\frac{\eta_p}{\delta_p}\frac{1}{R_{p\theta}} \\ \theta\beta_p\varkappa_p\frac{\eta_p}{(\delta_p+m_p)}(1-\frac{1}{R_{p\theta}}) & \theta(1+\beta_p\varkappa_p\frac{\eta_p}{\delta_p}\frac{1}{R_{p\theta}}) \end{bmatrix}$$
$$=\begin{bmatrix} \theta-\frac{R_{p\beta}}{\delta_p}(1-\frac{1}{R_{p\theta}}) & -\frac{R_{p\beta}}{(\delta_p+m_p)}\frac{1}{R_{p\theta}} \\ \frac{R_p}{\delta_p}(1-\frac{1}{R_{p\theta}}) & \theta+\frac{R_p}{(\delta_p+m_p)}\frac{1}{R_{p\theta}}) \end{bmatrix}.$$

At $E^*_{\oplus}$, the eigen-values of matrix $J_{4\theta 1}$ is identical to those $A_1 + A_2$ and $A_1 - A_2$ where

$$A + B = \begin{bmatrix} -\delta_p - \frac{R_{p\theta}}{\delta_p}(1 - \frac{1}{R_{p\theta}}) & -\frac{1}{(\delta_p + m_p)} \\ \frac{2R_p}{\delta_p}(1 - \frac{1}{R_{p\theta}}) & \frac{2}{(\delta_p + m_p)}\frac{R_p}{R_{p\theta}} - (\delta_p + m_p) \end{bmatrix}$$

and

$$A - B = \begin{bmatrix} -\delta_p - 2\theta - \frac{(R_{p\beta} - R_p)}{\delta_p}(1 - \frac{1}{R_{p\theta}}) & -\frac{(R_{p\beta} - R_p)}{(\delta_p + m_p)}\frac{1}{R_{p\theta}} \\ 0 & -2\theta - (\delta_p + m_p) \end{bmatrix}.$$

First, consider the matrix $A + B$. Trivially $tr(A + B) < 0$. From (5.7),

$$(\eta_p (\alpha_p \kappa_p + \theta \beta_p \varkappa_p))\frac{1}{R_{p\theta}} - \delta_p (\delta_p + m_p) = 0.$$

Since $R_{p\theta} > 1$, hence

$$(\eta_p (\alpha_p \kappa_p + \theta \beta_p \varkappa_p))\frac{1}{R^2_{p\theta}} - \delta_p (\delta_p + m_p) < 0. \tag{5.34}$$

. Therefore the determinant of $A + B$

$$det(A + B) > 0.$$

Hence the eigen values of matrix $A + B$ have negative real parts. Since $0 \leq \beta \leq 1$, $0 \leq \varkappa \leq 1$ and $R_{p\theta} > 1$, (5.34) results in

$$tr(A - B) < \left((\alpha_p \kappa_p - \theta \beta_p \varkappa_p)\frac{1}{R^2_{p\theta}} - m_p \right) < 0.$$

In addition $det(A - B) > 0$ when $R_{p\theta} \leq 2R_p$. Therefore, the eigen values of matrix $A - B$ have negative real parts. Since the eigen values of matrices $A + B$ and $A - B$ have negative real parts at $E^*_{4\theta} = (S^*_{p4\theta}, I^*_{p4\theta}, S^*_{p4\theta}, I^*_{p4\theta})$, the key Jacobian matrix $J_{4\theta 1}$ is stable when $R_{p\theta} \leq 2R_p$.

The second and third key Jacobian matrices

$$J_{4\theta 2} = J_{4\theta 3} = \begin{bmatrix} j_{3,3} & j_{3,4} & 0 & 0 & j_{3,7} \\ 0 & j_{4,4} & 0 & 0 & 0 \\ j_{5,3} & j_{5,4} & j_{5,5} & 0 & 0 \\ j_{6,3} & 0 & 0 & j_{6,6} & 0 \\ 0 & j_{7,4} & 0 & 0 & j_{7,7} \end{bmatrix} \text{ for k} = 1, \ldots 4$$

where $j_{1,1} = (-1)\delta_p(\alpha_p\kappa_p I^*_{p_{4\theta}})$, $j_{1,2} = -\alpha_p\kappa_p S^*_{p_{4\theta}}$, $j_{2,1} = \alpha_p\kappa_p I^*_{p_{4\theta}} - (\delta_p + m_p)$, $j_{2,2} = \alpha_p\kappa_p S^*_{p_{4\theta}} - (\delta_p + m_p) = 0$, $j_{3,3} = (-1)(\delta_h + \alpha_{ph}\kappa_{ph} I^*_{p_{4\theta}})$, $j_{3,4} = (-1)\alpha_{sh}\kappa_{sh} S^*_{h_{4\theta}}$, $j_{3,7} = (-1)\alpha_{mh}\kappa_{mh} S^*_{h_{4\theta}}$, $j_{4,4} = (-1)\alpha_{sh}\kappa_{sh} S^*_{h_{4\theta}} - (\delta_h + m_s)$, $j_{5,3} = \gamma\alpha_{ph}\kappa_{ph} I^*_{p_{4\theta}}$, $j_{5,4} = (-1)\mu\alpha_{sa}\kappa_{sa} I^*_{a_{4\theta}}$, $j_{5,5} = (-1)(\delta_h + m_a)$, $j_{6,3} = (1-\gamma)\alpha_{ph}\kappa_{ph} I^*_{p_{4\theta}}$, $j_{6,6} = (-1)(\delta_h + m_b)$, $j_{7,4} = \mu\alpha_{sa}\kappa_{sa} I^*_{a_{4\theta}}$, $j_{7,7} = \alpha_{mh}\kappa_{mh} S^*_{h_{4\theta}} + (\delta_h + m_m)$.

Next for the other key Jacobian matrices, B_{4k}, $k = 1, \ldots, 4$. Results from Subsection 4.5.6 show that

$$|\lambda I - J_{4\theta 2}| = |\lambda I - J_{4\theta 3}| = \Pi_{k=3}^{7}(\lambda - j_{k,k}) = 0$$

with $j_{k,k}$, $i = 1, \ldots 7$ are all real negatives. Furthermore, the matrix $J_{4\theta 2}$ and $J_{4\theta 3}$ are stable if

$$\alpha_{sh}\kappa_{sh}\frac{\frac{\eta_h}{\delta_h}}{1 + r_{ph\theta}} - (\delta_h - m_s) < 0 \Leftrightarrow \frac{\eta_h\alpha_{sh}\kappa_{sh}}{\delta_h(\delta_h - m_s)} < 1 + r_{ph\theta}$$
$$\Leftrightarrow R_{sh} < 1 + r_{ph\theta}$$

and

$$\alpha_{mh}\kappa_{sh}\frac{\frac{\eta_h}{\delta_h}}{1 + r_{ph\theta}} - (\delta_h - m_m) < 0 \Leftrightarrow \frac{\eta_h\alpha_{mh}\kappa_{mh}}{\delta_h(\delta_h - m_m)} < 1 + r_{ph\theta}$$
$$\Leftrightarrow R_{mh} < 1 + r_{ph\theta}.$$

Therefore $Z^*_{4\theta}$ well-defined and stable if $R_{p\theta} > 1$ and $\max\{R_{sh}, R_{mh}\} < 1 + r_{ph\theta}$. Therefore Z^*_4 is LAS. □

5.6.5 *Stability analysis of avian flu epidemic among birds and humans combined with mutant avian flu epidemic among humans*

The disease state equilibrium point Z^*_5 corresponds to the situation in which there are avian flu epidemic among birds and humans combined with mutant avian flu epidemic among humans,

$$Z^*_{5\theta} = (Z^*_{5t}, Z^*_{5t}) \tag{5.35}$$

with

$$Z^*_{5t} = (S^*_{p_{5\theta}}, I^*_{p_{5\theta}}, S^*_{h_{5\theta}}, 0, I^*_{a_{5\theta}}, I^*_{b_{5\theta}}, I^*_{m_{5\theta}}),$$

where

$$S^*_{p_{5\theta}} = \frac{\eta_p}{\delta_p}\frac{1}{R_{p\theta}}.$$

From (4.20a) it follows that

$$I^*_{p_{5\theta}} = \frac{\eta_p}{\delta_p + m_p}(1 - \frac{1}{R_{p\theta}}),$$
$$S^*_{h_{5\theta}} = \frac{\delta_h + m_m}{\alpha_{mh}\kappa_{mh}}$$

Now (4.20c) gives

$$I^*_{m_{5\theta}} = \frac{\delta_h}{\alpha_{mh}\kappa_{mh}} \left[R_{mh} - (1 + r_{ph\theta})\right].$$

where $r_{ph\theta}$ is defined by (5.32)

$$r_{ph\theta} = \frac{\alpha_{ph}\kappa_{ph}\eta_p}{\eta_h\ (\delta_p + m_p)} \left(1 - \frac{1}{R_{p\theta}}\right).$$

Therefore for $I^*_{m_{5\theta}} > 0$ it is necessary that $R_{mh} > 1 + r_{ph\theta}$. Finally (4.20d) and (4.20e) give

$$I^*_{a_{5\theta}} = \frac{\gamma\eta_h r_{ph}}{(\delta_h + m_a)R_{mh}} > 0$$

and

$$I^*_{b_{5\theta}} = \frac{(1-\gamma)\eta_h r_{ph}}{(\delta_h + m_b)R_{mh}}.$$

The condition $R_{p\theta} > 1$ and $R_{mh} > 1 + r_{ph}$ guarantees that $I^*_{p_{5\theta}} > 0, I^*_{a_{5\theta}} > 0, I^*_{b_{5\theta}} > 0$ and $I^*_{m_{5\theta}} > 0$.

Theorem 5.6. *If $R_{p\theta} > 1$, $R_{p\theta} \leq 2R_p$ and $R_{mh} > \max\{R_{sh}, 1 + r_{ph}\}$ then $Z^*_{5\theta} = (Z^*_{5t}, Z^*_{5t})$ is LAS.*

Proof. At $\bar{Z}^*_{5\theta}$ the Jacobian matrix (5.26) becomes

$$\mathcal{J}_{5\theta} = \mathcal{J}(\bar{Z}^*_{5\theta}) = \begin{bmatrix} J_{5\theta 1} & O_1 & O_1 \\ J_4 & J_{5\theta 2} & O_3 \\ J_5 & O_3 & J_{5\theta 3} \end{bmatrix}.$$

The first key Jacobian matrix is given by (5.33)

$$J_{5\theta 1} = \begin{bmatrix} A & B \\ B & A \end{bmatrix}$$

Results from the last section show that at $E^*_{\oplus}$ the key Jacobian matrix $J_{5\theta 1}$ is stable

when $R_{p\theta} \leq 2R_p$. and

$$J_{4\theta 2} = J_{4\theta}3 = \begin{bmatrix} j_{3,3} & j_{3,4} & 0 & 0 & j_{3,7} \\ 0 & j_{4,4} & 0 & 0 & 0 \\ j_{5,3} & j_{5,4} & j_{5,5} & 0 & 0 \\ j_{6,3} & 0 & 0 & j_{6,6} & 0 \\ j_{7,3} & j_{7,4} & 0 & 0 & j_{77} \end{bmatrix} \text{ for } k = 1, \ldots, 4$$

where $j_{1,1} = (-1)\delta_p(\alpha_p\kappa_p I^*_{p_{5\theta}})$, $j_{1,2} = -\alpha_p\kappa_p S^*_{p_{5\theta}}$, $j_{2,1} = \alpha_p\kappa_p I^*_{p_{5\theta}} - (\delta_p + m_p)$, $j_{2,2} = \alpha_p\kappa_p S^*_{p_5} - (\delta_p + m_p)$, $j_{3,3} = (-1)(\delta_h + \alpha_{ph}\kappa_{ph} I^*_{p_5} + \alpha_{mh}\kappa_{mh} I^*_{m_{5\theta}})$, $j_{3,4} = (-1)\alpha_{sh}\kappa_{sh} S^*_{h_{5\theta}}$, $j_{3,7} = (-1)\alpha_{mh}\kappa_{mh} S^*_{h_{5\theta}}$, $j_{4,4} = (-1)\alpha_{sh}\kappa_{sh} S^*_{h_{5\theta}} - (\delta_h + m_s)$, $j_{5,3} = \gamma\alpha_{ph}\kappa_{ph} I^*_{p_{5\theta}}$, $j_{5,4} = (-1)\mu\alpha_{sa}\kappa_{sa} I^*_{a_{5\theta}}$, $j_{5,5} = (-1)(\delta_h + m_a)$, $j_{6,3} = (1-\gamma)\alpha_{ph}\kappa_{ph} I^*_{p_{5\theta}}$, $j_{6,6} = (-1)(\delta_h + m_b)$, $j_{7,3} = \alpha_{mh}\kappa_{mh} I^*_{m_{5\theta}}$, $j_{7,4} = \mu\alpha_{sa}\kappa_{sa} I^*_{a_{5\theta}}$, $j_{7,7} = \alpha_{mh}\kappa_{mh} S^*_{h_{5\theta}} + (\delta_h + m_m)$.

A result from Sub-section 5.6.4 show that the key jacobian matrix $J_{4\theta 1}$ is stable at $E^*_{\oplus}$ when $R_{p\theta} \leq 2R_p$. Hence, the key jacobian matrix $J_{5\theta 1}$ is stable at $E^*_{\oplus}$) when $R_{p\theta} \leq 2R_p$.

Next for the other key Jacobian matrix, $J_{5\theta 2}$. Results from Sub-section 4.5.6 show that

$$|\lambda I - J_{5\theta 2}| = |\lambda I - J_{5\theta 3}| = \left[\Pi_{k=3}^{7}(\lambda - j_{k,k})\right][\lambda^2 + b\lambda + c] = 0$$

where

$$b = \frac{\alpha_{mh}\kappa_{mh}\eta_h}{\delta_h + m_m} > 0$$

and

$$c = \alpha_{mh}\kappa_{mh} I^*_{m_5}\alpha_{mh}\kappa_{mh} S^*_{h_5} > 0$$

If $I(S^*_{h_{5\theta}}, t) > 0$ then $I(S^*_{h_{5\theta}}, t) \downarrow 0$ as $t \uparrow \infty$. Hence this is effectively a stability condition for the coordinate $I^*_{s_{5\theta}} = 0$. Since

$$\alpha_{sh}\kappa_{sh} S^*_{h_{5\theta}} - (\delta_h + m_s) < 0 \Leftrightarrow \alpha_{sh}\kappa_{sh}\frac{(\delta_h + m_m)}{\alpha_{mh}\kappa_{mh}} - (\delta_h + m_s) < 0 \Leftrightarrow R_{sh} < R_{mh},$$

Therefore, $Z^*_{5\theta}$ is well-defined and stable if $R_p > 1$ and $R_{mh} > \max\{R_{sh}, 1 + r_{ph\theta}\}$. □

A small transmission rate β_p is harmful to disease eradication since $R_{p\theta} > R_p$ for $\beta_p > 0$. The following stability analysis is for disease state equilibria when $R_{p\theta} > 1$ that leads to an endemic situation in both regions. If infected birds can travel and there is

transport-related infection such that $R_{p\theta} > 1$ and $R_{p\theta} \leq 2R_p$, then the endemic steady state appears in two regions and becomes stable.

5.7 Simulation

Theorems 5.2, 5.3, 5.4, 5.5 and 5.6 show that the disease dynamics of (5.5a)-(5.5n) is dependent on the values of reproduction numbers $R_{p\theta}, R_{sh}$ and R_{mh}.

Similar to sensitivity analysis in Section 4.7,

- $R_{p\theta}$ is most sensitive to the change of $\alpha_p, \kappa_p, \beta_p, \varkappa_p$,
- R_{sh} is most sensitive to the change of α_{sh}, κ_{sh},
- R_{mh} is most sensitive to the change of α_{mh}, κ_{mh}.

The effect of disease transmission during transport due to bird trading is analyzed. In relation with avian flu, Central Java, West Java, Jakarta, Banten and Lampung are five most prominent provinces in Indonesia [197]. Chickens from Central Java are transported by trucks to West Java, Jakarta and banten. Some chickens in Jakarta markets are re-transported to Lampung in Sumatra which is separated from Java by Sunda strait. All destination can be reached in a day except Lampung.

Figure 5.2 shows that the outbreak starts in Central Java then West Java, Jakarta, Banten and Lampung, respectively. Jakarta has the most infected birds due to the fact that Jakarta is the biggest consumer of poultry birds and the transport of birds is focused on supplying Jakarta.

The proportion of infected birds in Central Java and West Java increased in the beginning then decreasing in the end. Meanwhile the proportion of infected birds in Jakarta and Banten are increasing even though these regions initially have a very small proportion of infected birds.

The sum of all the infectious birds over the five provinces Central Java, West Java, Jakarta, Banten and Lampung clearly reflects the timing and magnitude of the contributions from each province (Fig. 5.3). The initial increase is the contribution from Central Java. By Fig. 5.2(a), the maximum is reached in the first day but the sum now increases slowly due to the initial contributions from West Java, Jakarta and Banten. The combined increase is then very rapid as the outbreak takes hold strongly in these provinces and starts to diminish at about day 3. However the outbreak in Lampung then dominates to push the sum to its final maximum at around day 4.

The proportion of human cases of avian flu in each provinces follows the trend of the proportion of infected birds in the provinces. Fig. 5.4 shows that West Java, Jakarta and Banten have higher proportion of infected humans with mutant-avian flu. This is confirmed in Table 1.2. The mutant-avian flu outbreak in each region appears later than avian flu but has a greater proportional magnitude than avian flu (Fig. 5.5)

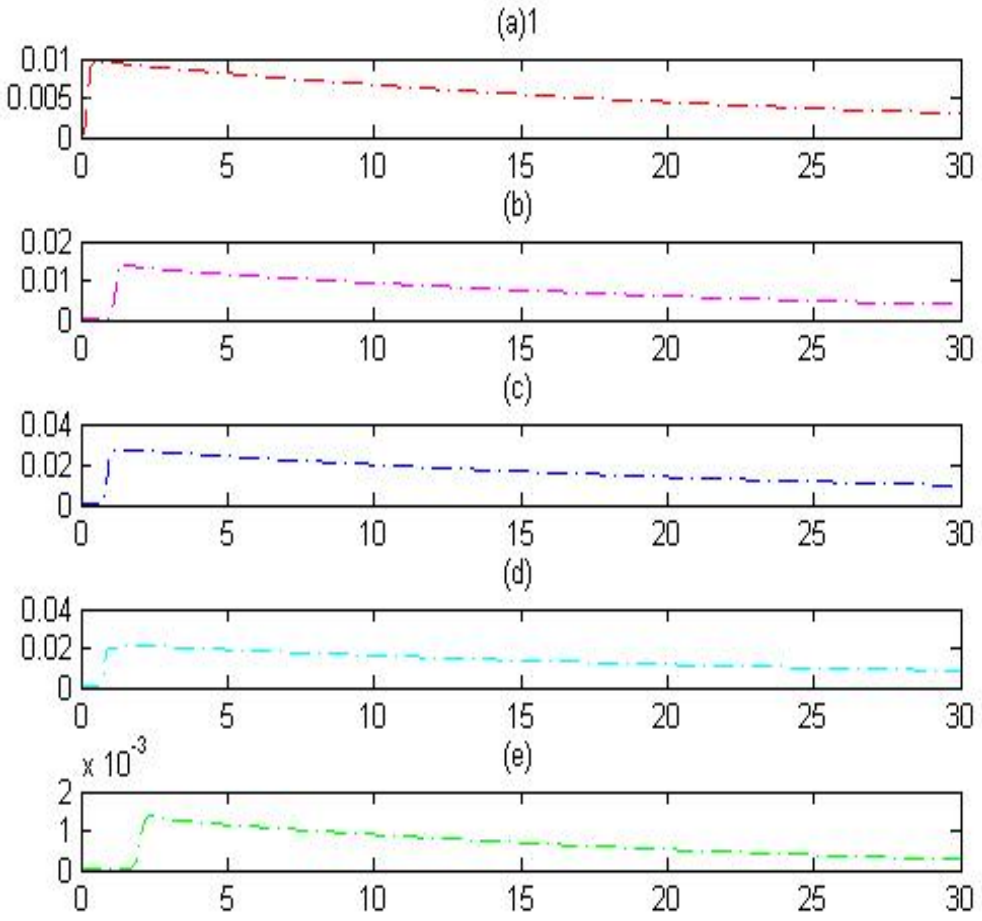

Fig. 5.2: The proportion of infected birds in the provinces. The horizontal axis is time in days. (a), (b), (c), (d) and (e) are the proportion of infected birds in Central Java, West Java, Jakarta, Banten and Lampung respectively.

5.8 Discussion

Equation (5.8) shows that even a small transmission rate $\beta_p > 0$ is harmful to disease eradication since $R_{p\theta} > R_p$ for $0 < \beta_p \leq 1$. On the contrary, the transmission rate $\beta_p > 1$ leads to an endemic situation in both regions. In fact, if $\beta_p = 0$ and $R_p < 1$ holds, then the infectious diseases should disappear in both regions.

The following are all possible combination values of $R_p, R_{p\theta}$ and their implication to avian flu dynamics among birds in both regions.

- If $R_{p\theta} < 1, R_p < 1$ then birds in both regions eventually become free of avian flu.
- If $R_{p\theta} > 1$ but $R_p < 1$ then birds remain free of avian flu when both regions are isolated. However, transport-related infection will lead to the disease becoming endemic at both regions.

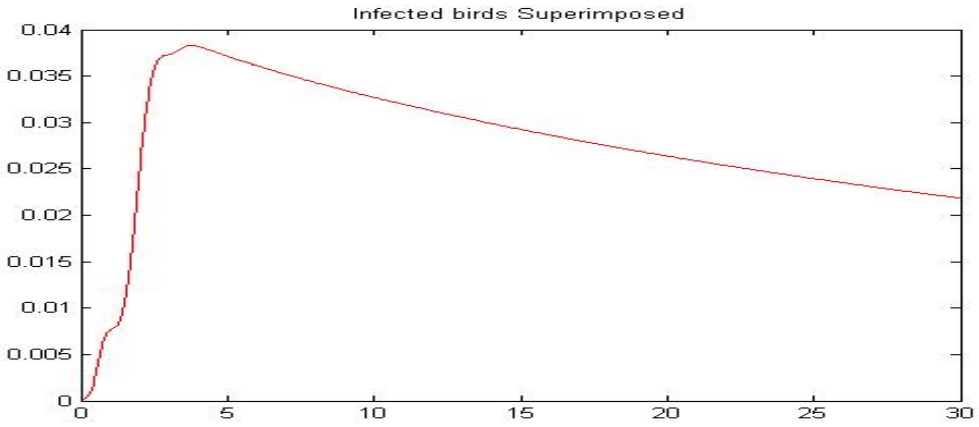

Fig. 5.3: Sum of proportions of infected birds in the provinces of Central Java, West Java, Jakarta, Banten and Lampung.

- If $R_{p\theta} > 1$ and $R_p > 1$ then avian flu will be endemic among birds even if both regions are isolated. Transport-related infection will increase the magnitude of avian flu endemic if the regions are not isolated.

Bird transport is a significant factor for the spread of the diseases not only in the bird world but also in the human world. Bird transport may cause epidemics among birds and humans even in a region which is initially disease free. If avian flu is already endemic among birds in both regions, then bird trading will intensify the spread of the diseases among bird and humans.

Consider the disease state $Z^*_{4\beta}$ as a function of β_p.

$$S^*_{p_\otimes} \to S^*_{p_\oplus} \text{ and } I^*_{p_\otimes} \to I^*_{p_\oplus} \text{ as } \beta_p \to 0.$$

Since $\frac{\partial S^*_{p_\otimes}}{\partial \beta_p} < 0$ and $\frac{\partial I^*_{p_\otimes}}{\partial \beta_p} > 0$, hence

$$S^*_{p_\otimes} < S_{p_\oplus},\ I^*_{p_\otimes} > I_{p_\oplus} \text{ when } \beta_p > 0,$$
$$S^*_{p_\otimes} = S_{p_\oplus},\ I_{p_\otimes} = I_{p_\oplus} \text{ when } \beta_p = 0.$$

This implies that at a steady state, the total proportion of susceptible birds in the both regions decreases with the increase of β_p, while the proportion of infected birds increases with increases of β_p. Furthermore

$$\frac{\partial}{\partial \beta_p}(S_{p_\otimes} + I_{p_\otimes}) < 0 \text{ when } m_p > \delta_p$$

and

$$S_{p_\otimes} + I_{p_\otimes} \leq S_{p_\oplus} + I_{p_\oplus}.$$

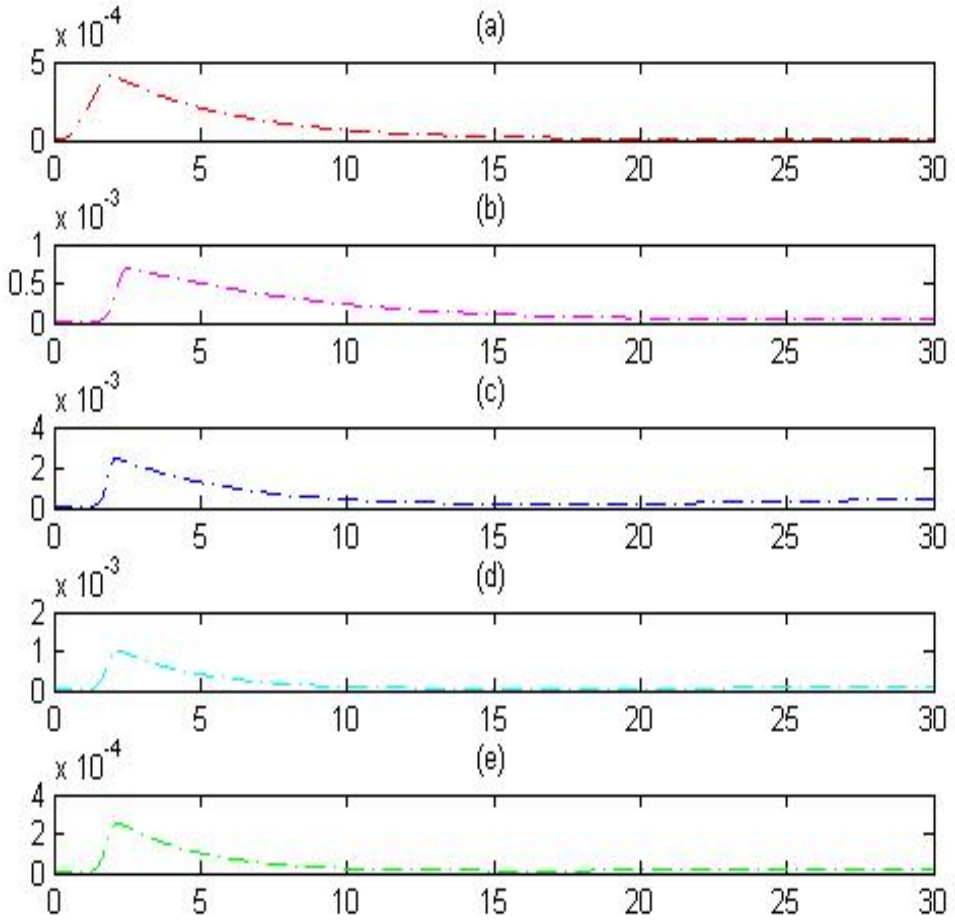

Fig. 5.4: The proportion of human cases (infected humans with avian flu) in the five provinces. The horizontal axis is time in days. (a), (b), (c), (d) and (e) are the proportion of human case in Central Java, West Java, Jakarta, Banten and Lampung respectively.

Hence the final size of bird populations decreases with the increase of β_p. Finally,

$$\frac{\partial}{\partial \beta_p}\left(\frac{I^*_{p_\otimes}}{S_{p_\otimes} + I_{p_\otimes}}\right) > 0,$$

the proportion of the infected birds increases with the increase of β_p. On the contrary, the proportion of the susceptible birds decreases with the increase of β_p. Increasing $I^*_{p_\otimes}$ (the proportion of infected birds) will decrease $S^*_{h_4}$ (the proportion of susceptible humans) and increase $I^*_{a_4}$ and $I^*_{b_4}$ (the proportions of infected humans having avian flu without symptom and with symptom, respectively). Similar analysis of $Z^*_{5\theta}$ shows that increasing β_p will decrease the proportion of susceptible humans and increase the proportion of infected humans with avian flu and mutant-avian flu. This suggests that infection due to bird transport increases the potential of epidemics among birds and

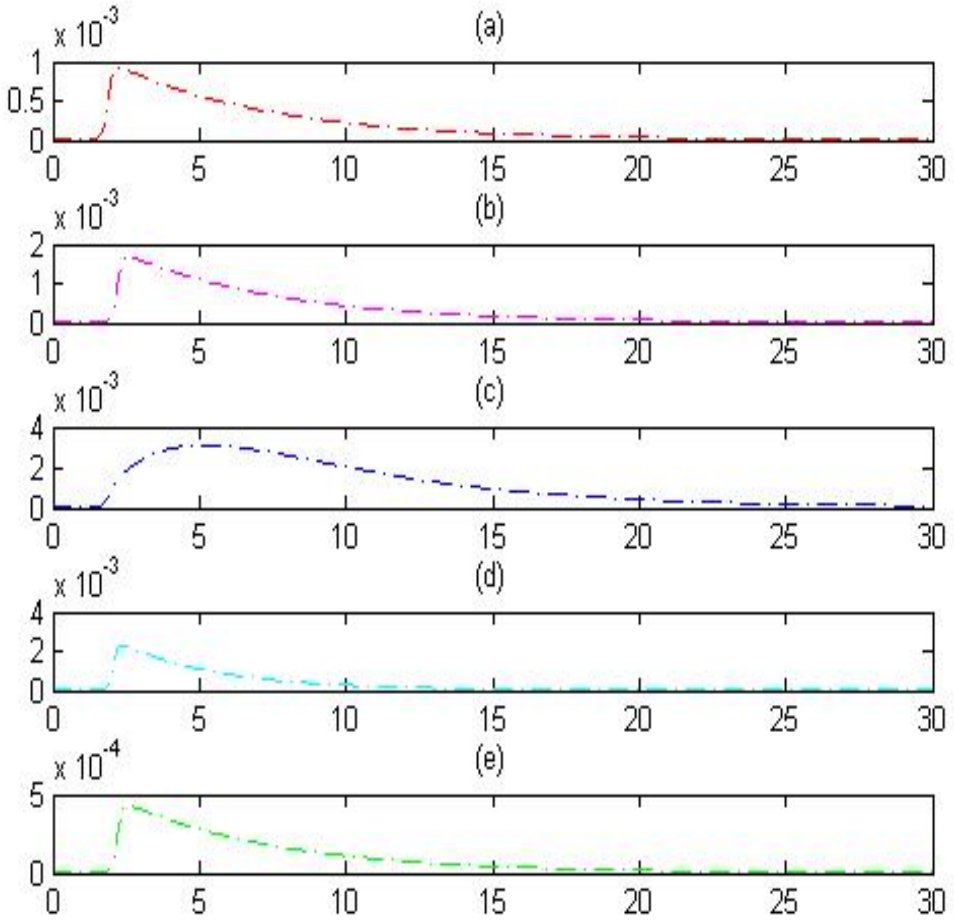

Fig. 5.5: The proportion of infected human with Mutant avian-flu in the provinces. The horizontal axis is time in days. (a), (b), (c), (d) and (e) are the proportion of infectious humans with Mutant avian-flu in Central Java, West Java, Jakarta, Banten and Lampung respectively.

therefore increases the spread of the disease among humans.

On the contrary, the transmission rate β leads to an endemic situation in both cities. In fact, if $\beta = 0$ and $R_p < 1$ hold then infectious disease should disappear in both cities from (5.8). Further, if infected birds can travel and there is transport-related infection such that $R_{p\theta} > 1$ and $R_{p\theta} \leq 2R_p$ then the endemic steady state Z^* appears in two cities become stable.

6. BORDER SCREENING

Border screening and subsequent culling of diseased birds is an attractive option for managing avian flu in Indonesia. This conclusion results from four important considerations developed in this thesis.

First, avian flu does not seem to spread between humans. This was discussed in Section 2.2.2. Thus preventing outbreaks or mitigating outbreaks requires reducing the effective contacts between infected poultry and humans.

Second, culling birds generally is unacceptable because so many poor Indonesian families rely heavily on raising a few chickens or other poultry. Large scale treatment of infected birds is impractical and much too expensive. Large scale screening programs applied to family poultry flocks across the nation are also impractical and too expensive. These cultural and economic aspects were described in Chapter 1.

Third, the analysis in Section 4.7 shows that the effective rates of transmission are important to the spread of the diseases.

Fourth, the results in Chapter 5 indicate that transporting poultry contributes substantially to the rate of transmission of avian flu among birds and subsequently to humans and hence to the likelihood of mutations causing possible highly virulent and contagious mutant-avian flu in humans.

Border screening of poultry focuses screening to a limited number of major transportation arteries and so becomes practical to install. Sick birds could be culled without severe impact on the family poultry stock. Since this takes place in a few specific locations, setting up proper infrastructure for disposing of culled birds is also feasible.

This chapter develops models for analyzing and interpreting the effect of border screening and the culling of infected birds to the spread and control of the diseases among humans.

This chapter is organized as follows. Section 6.1 describes modeling choices and assumptions taken. Section 6.2 formulates a general border screening model. The model is described and analyzed with regard to the effect of border screening and culling of infected birds to the dynamics of the diseases. For the special case of two identical regions, analysis on the effect of border screening to the dynamics of diseases among birds and humans are given in Section 6.3. Numerical simulations for $n \geq 2$ regions are given in Section 6.7. Section 6.8 discusses the analytical and numerical results and draws some conclusions.

6.1 Modeling choices and assumptions

The modeling choices and assumptions of Chapter 5 are adopted here. The same notation is used for compartments and epidemic parameters. In addition, it is assumed that screening procedures are taken after the transported birds arrive at the destination region i. Let σ_i denote the probability of successful border screening at region i. It is assumed that the screening processes never falsely identify a susceptible individual as being infected (no false positives) but some sick birds are not detected (false negatives). When an incoming infected bird is identified, it will be isolated. Let C_i denotes the isolated poultry birds in region i. The quarantine birds are treated with recovery rate r_p and some are culled and disposed with a rate of c_p. The dynamics of the disease state among birds is described by

$$\begin{aligned}
S'_{p_i}(t) =& \eta_{p_i} - (\delta_{p_i} + \sum_{j\neq i}\theta_{ij})S_{p_i} - \alpha_{p_i}\kappa_{p_i}I_{p_i}S_{p_i} \\
&+ \sum_{j\neq i}\theta_{ji}(1-\beta_{p_{ji}}\varkappa_{p_{ji}}I_{p_j})\,S_{p_j} + r_c C_{p_i} \\
I'_{p_i}(t) =& \alpha_{p_i}\kappa_{p_i}I_{p_i}S_{p_i} - (\delta_{p_i} + m_{p_i} + \sum_{j\neq i}\theta_{ij})I_{p_i} + \sum_{j\neq i}(1-\sigma_i)\theta_{ji} \\
&\times (1+\beta_{p_{ji}}\varkappa_{p_{ji}}S_{p_j})\,I_{p_j}, \\
C'_{p_i}(t) =& \sum_{j\neq i}\sigma_i\theta_{ji}(1+\beta_{p_{ji}}\varkappa_{p_{ji}}S_{p_j})\,I_{p_j} - (r_p + m_c)C_{p_i}
\end{aligned} \tag{6.1}$$

As in Chapter 5, it is assumed that the movement of humans between regions is negligible. The dynamics of the disease states among humans is described by (5.2),

$$\begin{aligned}
S'_{h_i}(t) &= \eta_{h_i} - \delta_{h_i}S_{h_i} - \alpha_{ph_i}\kappa_{ph_i}I_{p_i}S_{h_i} - \alpha_{sh_i}\kappa_{sh_i}I_{s_i}S_{h_i} - \alpha_{mh_i}\kappa_{mh_i}I_{m_i}S_{h_i}, \\
I'_{s_i}(t) &= \alpha_{sh_i}\kappa_{sh_i}I_{s_i}S_{h_i} - (\delta_{h_i} + m_{s_i})\,I_{s_i}, \\
I'_{a_i}(t) &= \gamma_i\alpha_{ph_i}\kappa_{ph_i}I_{p_i}S_{h_i} - \mu_i\alpha_{sa_i}\kappa_{sa_i}I_{s_i}I_{a_i} - (\delta_{h_i} + m_{a_i})\,I_{a_i}, \\
I'_{b_i}(t) &= (1-\gamma_i)\alpha_{ph_i}\kappa_{ph_i}I_{p_i}S_{h_i} - (\delta_{h_i} + m_{b_i})\,I_{b_i}, \\
I'_{m_i}(t) &= \mu_i\alpha_{sa_i}\kappa_{sa_i}I_{s_i}I_{a_i} + \alpha_{mh_i}\kappa_{mh_i}I_{m_i}S_{h_i} - (\delta_{h_i} + m_{m_i})\,I_{m_i}.
\end{aligned} \tag{6.2}$$

The disease dynamics among birds in any region is independent of the disease dynamics among humans. However, the disease dynamics among humans is dependent to disease dynamics in the bird world.

6.2 Border screening: the full model

The set of disease parameters becomes $\in Q_{n\sigma} \subseteq \mathbb{R}_+^{32n}$ for the full system becomes

$$\begin{aligned} Q_{n\sigma} = \quad & \{q = (q_i) |\, q_i = \eta_{p_i}, \eta_{h_i}, \delta_{p_i}, \delta_{h_i}, \alpha_{p_i}, r_{p_i}, m_{c_i}, \alpha_{sh_i}, \alpha_{ph_i}, \alpha_{sa_i}, \alpha_{mh_i}, \kappa_{p_i}, \kappa_{sh_i}, \kappa_{ph_i}, \\ & \kappa_{sa_i}, \kappa_{mh_i}, \mu_i, m - p_i, m_{a_i}, m_{b_i}, m_{s_i}, m_{m_i}, \gamma_i, \theta_{ij}, \sigma_i, \beta_{p_{ij}}, \varkappa_{p_{ij}},\ i = 1, \ldots, n\}. \end{aligned}$$

Let $Z(t) \in \Omega_n \subseteq \mathbb{R}_+^{8n}$ be the set of all disease states

$$\begin{aligned} \Omega_{n\sigma} = & \{Z(t) = (Z_i(t)) : Z_i(t) = (S_{p_i}(t), I_{p_i}(t), C_{p_i}(t), S_{h_i}(t), I_{s_i}(t), I_{a_i}(t), I_{b_i}(t), \\ & I_{m_i}(t)),\ i = 1, \ldots, n\}. \end{aligned}$$

For a given set of epidemic parameters $q \in Q_{n\sigma}$, the dynamics of the disease state $Z(t)$ is described by the IVP

$$\begin{aligned} S'_{p_i}(t) = & \eta_{p_i} - (\delta_{p_i} + \sum_{j \neq i} \theta_{ij}) S_{p_i} - \alpha_{p_i} \kappa_{p_i} I_{p_i} S_{p_i} + \sum_{j \neq i} \theta_{ji} (1 - \beta_{p_{ji}} \varkappa_{p_{ji}} I_{p_j})\, S_{p_j} \\ & + r_p C_{p_i}, \qquad (6.3a) \\ I'_{p_i}(t) = & \alpha_{p_i} \kappa_{p_i} I_{p_i} S_{p_i} - (\delta_{p_i} + m_{p_i} + \sum_{j \neq i} \theta_{ij}) I_{p_i} \\ & + \sum_{j \neq i} (1 - \sigma_i) \theta_{ji} (1 + \beta_{p_{ji}} \varkappa_{p_{ji}} S_{p_j})\, I_{p_j}, \qquad (6.3b) \\ C'_{p_i}(t) = & \sum_{j \neq i} \sigma_i \theta_{ji} (1 + \beta_{p_{ji}} \varkappa_{p_{ji}} S_{p_j})\, I_{p_j} - (r_p + m_c) C_{p_i}, \qquad (6.3c) \\ S'_{h_i}(t) = & \eta_{h_i} - \delta_{h_i} S_{p_i} - (p_{a_i} + p_{b_i}) \alpha_{ph_i} \kappa_{ph_i} I_{p_i} S_{h_i} - \alpha_{sh_i} \kappa_{sh_i} I_{s_i} S_{h_i} \\ & - \alpha_{mh_i} \kappa_{mh_i} I_{m_i} S_{h_i}, \qquad (6.3d) \\ I'_{s_i}(t) = & \alpha_{sh_i} \kappa_{sh_i} I_{s_i} S_{h_i} - (\delta_{h_i} + m_{s_i})\, I_{s_i}, \qquad (6.3e) \\ I'_{a_i}(t) = & p_{a_i} \alpha_{ph_i} \kappa_{ph_i} I_{p_i} S_{h_i} - \mu_i \alpha_{sa_i} \kappa_{sa_i} I_{s_i} I_{a_i} - (\delta_{h_i} + m_{a_i})\, I_{a_i}, \qquad (6.3f) \\ I'_{b_i}(t) = & (1 - \gamma_i) \alpha_{ph_i} \kappa_{ph_i} I_{p_i} S_{h_i} - (\delta_{h_i} + m_{b_i})\, I_{b_i}, \qquad (6.3g) \\ I'_{m_i}(t) = & \mu_i \alpha_{sa_i} \kappa_{sa_i} I_{s_i} I_{a_i} + \alpha_{mh_i} \kappa_{mh_i} I_{m_i} S_{h_i} - (\delta_{h_i} + m_{m_i})\, I_{m_i}, \qquad (6.3h) \\ Z(0) = & Z_0,\ Z_0 \in \Omega_{n\sigma}. \qquad (6.3i) \end{aligned}$$

If $\sigma_i = 0$ for all $i = 1, \ldots, n$, then (6.3a)-(6.3i) becomes (5.3a)-(5.3h) and $\Omega_{n\sigma}$ becomes Ω_n. Therefore, the IVP (6.3a)-(6.3i) becomes (5.3a)-(5.3h).

The existence of a unique solution for IVP (6.3a)-(6.3i) is guaranteed by the following theorem.

Theorem 6.1. *For any nonnegative initial condition $Z_0 \in \Omega_{n\sigma}$, (6.3a)-(6.3h) has a unique and bounded solution satisfying the initial condition (6.3i).*

Proof. Comparing between (6.3a)-(6.3i) and (5.3a)-(5.3h), σ is the only additional pa-

rameter and C_i are the additional disease states. The state of all disease states $\Omega_{n\sigma}$ and its subspace of disease free states are positively invariant under f, the vector field (right hand side) of the system of differential equations (6.3a)-(6.3h). Therefore, the uniqueness of the solution is guaranteed by Theorem 3.4 in Section 3.2. □

6.3 Disease dynamics in two identical regions: the effect of border screening

Avian flu dynamics among birds is independent of the dynamics of diseases among humans. For an initial disease state $W_0 \in \Omega_{2B}$, the dynamics of avian flu among birds in two identical regions is

$$\begin{aligned}
S'_{p_1}(t) =& \eta_p - (\delta_p + \theta)S_{p_1} - \alpha_p\kappa_p I_{p_1} S_{p_1} + \theta(1 - \beta_p\varkappa_p I_{p_2})\, S_{p_2} + r_p C_{p_1}, && \text{(6.4a)}\\
I'_{p_1}(t) =& \alpha_p\kappa_p I_{p_1} S_{p_1} - (\delta_p + m_p + \theta)\, I_{p_1} + (1-\sigma)\theta(1 + \beta_p\varkappa_p S_{p_2})\, I_{p_2}, && \text{(6.4b)}\\
C'_{p_1}(t) =& \sigma\theta(1 + \beta_p\varkappa_p S_{p_2})\, I_{p_2} - (r_p + m_c)C_{p_1}, && \text{(6.4c)}\\
S'_{p_2}(t) =& \eta_p - (\delta_p + \theta)S_{p_2} - \alpha_p\kappa_p I_{p_2} S_{p_2} + \theta(1 - \beta_p\varkappa_p I_{p_1})S_{p_1} + r_p C_{p_2}, && \text{(6.4d)}\\
I'_{p_2}(t) =& \alpha_p\kappa_p I_{p_2} S_{p_2} - (\delta_p + m_p + \theta)\, I_{p_2} + (1-\sigma)\theta(1 + \beta_p\varkappa_p S_{p_1})I_{p_1}, && \text{(6.4e)}\\
C'_{p_2}(t) =& \sigma\theta(1 + \beta_p\varkappa_p S_{p_1})\, I_{p_1} - (r_p + m_c)C_{p_2}, && \text{(6.4f)}\\
W(0) =& W_0,\ Z_0 \in \Omega_{2B}, && \text{(6.4g)}
\end{aligned}$$

where

$$\Omega_{2B} = \{W = (W_1, W_2) : W_1 = (S_{p_1}, I_{p_1}, C_{p_1}), W_2 = (S_{p_2}, I_{p_2}, C_{p_2})\}.$$

The full system (6.3a), (6.3i) is reduced to

$$\begin{aligned}
S'_{p_1}(t) =& \eta_p - (\delta_p + \theta)S_{p_1} - \alpha_p\kappa_p I_{p_1} S_{p_1} + r_p C_{p_1} + \theta(1 - \beta_p\varkappa_p I_{p_2})\, S_{p_2}, && \text{(6.5a)}\\
I'_{p_1}(t) =& \alpha_p\kappa_p I_{p_1} S_{p_1} - (\delta_p + m_p + \theta)\, I_{p_1} + (1-\sigma)\theta(1 + \beta_p\varkappa_p S_{p_2})\, I_{p_2}, && \text{(6.5b)}\\
C'_{p_1}(t) =& \sigma\theta(1 + \beta_p\varkappa_p S_{p_2})\, I_{p_2} - (r_p + m_c)C_{p_1}, && \text{(6.5c)}\\
S'_{h_1}(t) =& \eta_h - \delta_h S_{h_p} - (p_a + p_b)\alpha_{ph}\kappa_{ph} I_{p_1} S_{h_1} - \alpha_{sh}\kappa_{sh} I_{s_1} S_{h_1}\\
& - \alpha_{mh}\kappa_{mh} I_{m_1} S_{h_1}, && \text{(6.5d)}\\
I'_{s_1}(t) =& \alpha_{sh}\kappa_{sh} I_{s_1} S_{h_1} - (\delta_h + m_s)\, I_{s_1}, && \text{(6.5e)}\\
I'_{a_1}(t) =& p_a\alpha_{ph}\kappa_{ph} I_{p_1} S_{h_1} - \mu\alpha_{sa}\kappa_{sa} I_{s_1} I_{a_1} - (\delta_h + m_a)\, I_{a_1}, && \text{(6.5f)}\\
I'_{b_1}(t) =& p_b\alpha_{ph}\kappa_{ph} I_{p_1} S_{h_1} - (\delta_h + m_b)\, I_{b_1}, && \text{(6.5g)}\\
I'_{m_1}(t) =& \mu\alpha_{sa}\kappa_{sa} I_{s_1} I_{a_1} + \alpha_{mh}\kappa_{mh} I_{m_1} S_{h_p} - (\delta_h + m_m)\, I_{m_1}, && \text{(6.5h)}\\
S'_{p_2}(t) =& \eta_p - (\delta_p + \theta)S_{p_2} - \alpha_p\kappa_p I_{p_2} S_{p_2} + r_p C_{p_2} + \theta(1 - \beta_p\varkappa_p I_{p_1})S_{p_1}, && \text{(6.5i)}\\
I'_{p_2}(t) =& \alpha_p\kappa_p I_{p_2} S_{p_2} - (\delta_p + m_p + \theta)\, I_{p_2} + (1-\sigma)\theta(1 + \beta_p\varkappa_p S_{p_1})I_{p_1}, && \text{(6.5j)}
\end{aligned}$$

$$C'_{p_2}(t) = \sigma\theta(1+\beta_p\varkappa_p S_{p_1})\, I_{p_1} - (r_p + m_c)C_{p_2}, \tag{6.5k}$$

$$S'_{h_2}(t) = \eta_h - \delta_h S_{h_s} - (p_a + p_b)\alpha_{ph}\kappa_{ph} I_{p_2} S_{h_2} - \alpha_{sh}\kappa_{sh} I_{s_2} S_{h_2} - \alpha_{mh}\kappa_{mh} I_{m_2} S_{h_2}, \tag{6.5l}$$

$$I'_{s_2}(t) = \alpha_{sh}\kappa_{sh} I_{s_2} S_{h_2} - (\delta_h + m_s)\, I_{s_2}, \tag{6.5m}$$

$$I'_{a_2}(t) = p_a\alpha_{ph}\kappa_{ph} I_{p_2} S_{h_2} - \mu\alpha_{sa}\kappa_{sa} I_{s_2} I_{a_2} - (\delta_h + m_a)\, I_{a_2}, \tag{6.5n}$$

$$I'_{b_2}(t) = p_b\alpha_{ph}\kappa_{ph} I_{p_2} S_{h_2} - (\delta_h + m_b)\, I_{b_2}, \tag{6.5o}$$

$$I'_{m_2}(t) = \mu\alpha_{sa}\kappa_{sa} I_{s_2} I_{a_2} + \alpha_{mh}\kappa_{mh} I_{m_2} S_{h_2} - (\delta_h + m_m)\, I_{m_2} \tag{6.5p}$$

$$Z(0) = Z_0,\ Z_0 \in \Omega_2, \tag{6.5q}$$

where $Z_0 \in \Omega_2$ is an initial disease state and

$$\Omega_2 = \{Z = (Z_i) : Z_i = (S_{p_i}, I_{p_i}, C_{p_i}, S_{h_i}, I_{s_i}, I_{a_i}, I_{b_i}, I_{m_i}),\ i = 1, 2\}.$$

6.4 Reproduction numbers

The following basic reproduction numbers for the spread of the diseases in two identical regions are defined by using procedures similar to those in Sections 4.3 and 5.3.

$$\hat{F}_1 = \begin{pmatrix} \frac{\eta_p\alpha_p\kappa_p}{\delta_p} & 0 & (1-\sigma)\frac{\eta_p\theta\beta_p\kappa_p}{\delta_p} & 0 \\ 0 & 0 & \sigma\frac{\eta_p\theta\beta_p\kappa_p}{\delta_p} & 0 \\ (1-\sigma)\frac{\eta_p\theta\beta_p\kappa_p}{\delta_p} & 0 & \frac{\eta_h\alpha_{sh}\kappa_{sh}}{\delta_h} & 0 \\ \frac{\eta_p\sigma\beta_p\kappa_p}{\delta_p} & 0 & 0 & 0 \end{pmatrix}$$

and

$$\breve{F}_1 = \begin{pmatrix} (\delta_p + m_p) + \theta & 0 & -(1-\sigma)\theta & 0 \\ 0 & r_p + c_p & -\sigma\theta & 0 \\ -(1-\sigma)\theta & 0 & (\delta_p + m_p) + \theta & 0 \\ -\sigma\theta & 0 & 0 & r_p + c_p \end{pmatrix}$$

respectively. The next generation matrix $\hat{F}_1 \cdot \breve{F}_1^{-1}$ (where $\breve{F}_1^{-1}$ is the inverse matrix of $\breve{F}_1$). The characteristic polynomial of the matrix is

$$\mathcal{C}_1 = \lambda^3 \left(\lambda - \frac{\eta_p\left(\alpha_p\kappa_p + (1-\sigma)\theta\beta_p\varkappa_p\right)}{\delta_p\ (\delta_p + m_p + \sigma\theta)} \right). \tag{6.6}$$

Therefore the basic reproduction number for the avian flu transmission among birds is

The basic reproduction number for the spread of avian flu among birds is

$$R_{p\theta\sigma} = \frac{\eta_p \left(\alpha_p \kappa_p + (1-\sigma)\theta\beta_p \varkappa_p\right)}{\delta_p \left(\delta_p + m_p + \sigma\theta\right)}, \tag{6.7}$$

In the case of $\sigma = 0$ (there is no border screening), the basic reproduction number in (6.7) becomes (5.10)

$$R_{p\theta} = R_p + R_{p\beta}, \tag{6.8}$$

where $R_{p\beta}$ is the basic reproduction number during transport which is defined by (5.10),

$$R_{p\beta} = \frac{\eta_p \, \theta\beta_p \varkappa_p}{\delta_p \left(\delta_p + m_p\right)}. \tag{6.9}$$

and R_p is the basic reproduction number for "local" avian flu transmission among birds in an isolated region which is defined by (4.6)

$$R_p = \frac{\eta_p \, \alpha_p \kappa_p}{\delta_p \left(\delta_p + m_p\right)}. \tag{6.10}$$

Comparing (6.7) and (6.8), $R_{p\theta\sigma} = R_{p\theta}$ when $\sigma = 0$. Furthermore, since $\frac{\partial R_{p\theta\sigma}}{\partial \sigma} < 0$, entry screening σ for $0 < \sigma \leq 1$ decreases the basic reproduction number. Therefore culling is beneficial for disease eradication.

Since a human is infected avian flu virus by local infectious chickens only and is infected swine flu and mutant-avian flu viruses by local infectious humans only, the reproduction for swine flu transmission among humans and the reproduction for mutant-avian flu transmission among humans remain the same as for an isolated region discussed in Chapter 4. Recall from (4.7)

$$R_{sh} = \frac{\eta_h \, \alpha_{sh} \kappa_{sh}}{\delta_h \left(\delta_h + m_s\right)} \tag{6.11}$$

and from (4.8)

$$R_{mh} = \frac{\eta_h \, \alpha_{mh} \kappa_{mh}}{\delta_h \left(\delta_h + m_m\right)} \tag{6.12}$$

respectively.

6.5 Disease state equilibria

6.5.1 Disease state equilibria among birds

Consider first a situation when there is no infected poultry at both regions $I_{p_1} = I_{p_2} = 0$. For an equilibrium it is required that $S'_{p_i} = C'_{p_i} = 0\ i = 1, 2$, such that

$$S'_{p_1} = 0 \ \Leftrightarrow \eta_p - (\delta_p + \theta)S_{p_1} + r_p C_{p_1} + \theta S_{p_2} = 0, \tag{6.13a}$$
$$C'_{p_1}(t) = 0 \ \Leftrightarrow -(r_p + m_c)C_{p_1} = 0, \tag{6.13b}$$
$$S'_{p_2} = 0 \ \Leftrightarrow \eta_p - (\delta_p + \theta)S_{p_2} + r_p C_{p_2} + \theta S_{p_1} = 0, \tag{6.13c}$$
$$C'_{p_2}(t) = 0 \ \Leftrightarrow -(r_p + m_c)C_{p_2} = 0, \tag{6.13d}$$
$$\tag{6.13e}$$

Since $(r_p + m_c) \neq 0$ then $C_{p_1} = C_{p_2} = 0$, adding equations (6.13a) and (6.13c) results

$$2\eta_p - \delta_p(S^*_{p_1} + S^*_{p_2}) = 0 \ \Leftrightarrow (S^*_{p_1} + S^*_{p_2}) = 2\frac{\eta_p}{\delta_p} \ \Leftrightarrow S^*_{p_i} = \frac{\eta_p}{\delta_p},\ i = 1, 2.$$

therefore

$$S^*_{p_i} = S^*_{p_0} = \frac{\eta_p}{\delta_p},\ i = 1, 2.$$

$$E^*_0 = (S^*_{p_0}, 0, 0, S^*_{p_0}, 0, 0) \tag{6.14}$$

is referred to as the disease free state of bird world.

In endemic situation $I_{p_i} \neq 0,\ i = 1, 2$. For endemic equilibrium, it is required

$$S'_{p_1} = 0 \ \Leftrightarrow \ \eta_p - (\delta_p + \theta)S_{p_1} - \alpha_p\kappa_p I_{p_1} S_{p_1} + \theta(1 - \beta_p\varkappa_p I_{p_2})\, S_{p_2} + r_p C_{p_1}, \tag{6.15a}$$
$$I'_{p_1} = 0 \ \Leftrightarrow \ \alpha_p\kappa_p I_{p_1} S_{p_1} - (\delta_p + m_p + \theta)\, I_{p_1} + (1 - \sigma)\theta(1 + \beta_p\varkappa_p S_{p_2})\, I_{p_2} = 0, \tag{6.15b}$$
$$C'_{p_1} = 0 \ \Leftrightarrow \ \sigma\theta(1 + \beta_p\varkappa_p S_{p_2})\, I_{p_2} - (r_p + m_c)C_{p_1} = 0, \tag{6.15c}$$
$$S'_{p_1} = 0 \ \Leftrightarrow \ \eta_p - (\delta_p + \theta)S_{p_2} - \alpha_p\kappa_p I_{p_2} S_{p_2} + \theta(1 - \beta_p\varkappa_p I_{p_1})S_{p_1} + r_p C_{p_2} = 0, \tag{6.15d}$$

$$I'_{p_2} = 0 \ \Leftrightarrow \ \alpha_p\kappa_p I_{p_2} S_{p_2} - (\delta_p + m_p + \theta)\, I_{p_2} + (1 - \sigma)\theta(1 + \beta_p\varkappa_p S_{p_1})I_{p_1} = 0, \tag{6.15e}$$
$$C'_{p_2} = 0 \ \Leftrightarrow \ \sigma\theta(1 + \beta_p\varkappa_p S_{p_1})\, I_{p_1} - (r_p + m_c)C_{p_2} = 0, . \tag{6.15f}$$

Adding equations (6.15b) and (6.15e) results in

$$(\alpha_p\kappa_p + \theta\beta_p\varkappa_p I^*_{p1})S^*_{p1} + (\alpha_p\kappa_p + (1-\sigma)\theta\beta_p\varkappa_p I^*_{p2})S^*_{p2} - (\delta_p + m_p)(I^*_{p1} + I^*_{p2}) = 0.$$

Only balanced equilibria are reported in this study. They are well behaved and asymptotically stable. So their impact to the spread of the diseases in human world is measurable. Therefore, it is assumed here that $S^*_{p1} = S^*_{p1} = S^*_{p\otimes}$, $I^*_{p1} = I^*_{p1} = I^*_{p\otimes}$ and $C^*_{p1} = C^*_{p1} = C^*_{p\otimes}$. At a disease state equilibria

$$E^*_\otimes = (S^*_{p\otimes}, I^*_{p\otimes}, C^*_{p\otimes}, S^*_{p\otimes}, I^*_{p\otimes}, C^*_{p\otimes}),$$

it is required that

$$(\alpha_p\kappa_p + (1-\sigma)\theta\beta_p\varkappa_p)S^*_{p\otimes}I^*_{p\otimes} - (\delta_p + m_p)I^*_{p\otimes} = 0.$$

Since $I^*_{p\otimes} \neq 0$, hence

$$(\alpha_p\kappa_p + (1-\sigma)\theta\beta_p\varkappa_p)S^*_{p\otimes} - (\delta_p + m_p) = 0$$
$$\Leftrightarrow \quad .S^*_{p\otimes} = \frac{(\delta_p + m_p)}{(\alpha_p\kappa_p + (1-\sigma)\theta\beta_p\varkappa_p)}$$

Therefore, by using the definition of the basic reproduction number $R_{p\theta\sigma}$ in (6.7)

$$S^*_{p_i} = S^*_{p\otimes} = \frac{(\delta_p + m_p)}{(\alpha_p\kappa_p + (1-\sigma)\theta\beta_p\varkappa_p)} = \frac{\eta_p}{\delta_p}\frac{1}{R_{p\theta\sigma}}, \quad i = 1, 2.$$

Given $\eta_p(\alpha_p\kappa_p + (1-\sigma)\theta\beta_p\varkappa_p) - \delta_p(\delta_p + m_p) > 0$,

$$\begin{aligned} I^*_{p_i} = I^*_{p\otimes} &= \frac{\eta_p(\alpha_p\kappa_p + (1-\sigma)\theta\beta_p\varkappa_p) - \delta_p(\delta_p + m_p)}{(\alpha_p\kappa_p + (1-\sigma)\theta\beta_p\varkappa_p)(\delta_p + m_p)}, \\ &= \frac{\eta_p}{\delta_p + m_p} - \frac{\delta_p}{(\alpha_p\kappa_p + (1-\sigma)\theta\beta_p\varkappa_p)} \\ &= \frac{\eta_p}{\delta_p + m_p}\left[1 - \frac{\delta_p(\delta_p + m_p)}{\eta_p(\alpha_p\kappa_p + (1-\sigma)\theta\beta_p\varkappa_p)}\right] \\ &= \frac{\eta_p}{\delta_p + m_p}(1 - \frac{1}{R_{p\theta\sigma}}), \ i = 1, 2. \end{aligned}$$

Substituting $S^*_{p_i}$ and $I^*_{p_i}$ into (6.15c) or (6.15f) results in

$$\begin{aligned} C_{p_i} &= \frac{\sigma\theta(1+\beta_p\varkappa_p S_{p_i})\, I_{p_i}}{(r_p+m_c)}, \\ &= \frac{\sigma\theta(1+\beta_p\varkappa_p \frac{\eta_p}{\delta_p}\frac{1}{R_{p\theta\sigma}})\,\frac{\eta_p}{\delta_p+m_p}(1-\frac{1}{R_{p\theta\sigma}})}{(r_p+m_c)}, \\ &= \frac{\sigma\theta}{(r_p+m_c)} + \frac{\eta_p}{(r_p+m_c)}\frac{R_{p\beta}}{R_{p\theta\sigma}}(1-\frac{1}{R_{p\theta\sigma}}), \end{aligned}$$

The system dynamic (6.4a) - (6.4f) has an endemic state

$$\mathcal{E}^*_{\otimes} = (S^*_{p_\otimes}, I^*_{p_\otimes}, C^*_{p_\otimes}, S^*_{p_\otimes}, I^*_{p_\otimes}, C^*_{p_\otimes}), \tag{6.16}$$

where

$$\begin{aligned} S^*_{p_\otimes} &= \frac{\eta_p}{\delta_p}\frac{1}{R_{p\theta\sigma}}, \\ I^*_{p_\otimes} &= \frac{\eta_p}{\delta_p+m_p}(1-\frac{1}{R_{p\theta\sigma}}) \\ C^*_{p_\otimes} &== \frac{\sigma\theta}{(r_p+m_c)} + \frac{\eta_p}{(r_p+m_c)}\frac{R_{p\beta}}{R_{p\theta\sigma}}(1-\frac{1}{R_{p\theta\sigma}}) \end{aligned}$$

where $R_{p\theta\sigma}$ is given in (6.7),

$$R_{p\theta\sigma} = \frac{\eta_p\,(\alpha_p\kappa_p + (1-\sigma)\theta\beta_p\varkappa_p)}{\delta_p\;(\delta_p+m_p+\sigma\theta)}.$$

and $R_{p\beta}$ is given in (6.9)

$$R_{p\beta} = \frac{\eta_p\,\theta\beta_p\varkappa_p}{\delta_p\;(\delta_p+m_p)}.$$

6.5.2 Disease state equilibria for the full system

The disease dynamic (6.5a)-(6.27n) has five disease steady states equilibria

$$Z^*_{i\theta\sigma} = (Z^*_{is}, Z^*_{is})$$

where

$$Z^*_{is} = (S^*_{p_{i\sigma}}, I^*_{p_{i\sigma}}, C^*_{p_{i\sigma}}, S^*_{h_{i\sigma}}, I^*_{s_{i\sigma}}, I^*_{a_{i\sigma}}, I^*_{b_{i\sigma}}, I^*_{m_{i\sigma}}),\ i = 1, \ldots 5,$$

of which three happen when there is a disease free bird world $I^*_{p_{i\sigma}} = 0,\ 1, 2$ and the other two happen when there is disease endemic among birds, $I^*_{p_{i\sigma}} \neq 0,\ 1, 2$. First, the disease free equilibrium in which there are no epidemics among birds or humans in

either regions

$$Z^*_{1\sigma} = (Z^*_{1s}, Z^*_{1s}) \tag{6.17}$$

where Z^*_{1s} is the disease free equilibrium in each region. Z^*_{1s} is given by

$$Z^*_{1s} = (S^*_{p_{1\sigma}}, 0, 0, S^*_{h_{1\sigma}}, 0, 0, 0, 0),$$

where

$$S^*_{p_{1\sigma}} = S^*_{p_0} = \frac{\eta_p}{\delta_p},$$
$$S^*_{h_{1\sigma}} = S^*_{h_1}\frac{\eta_h}{\delta_h}.$$

Second, the swine flu epidemic equilibrium

$$Z^*_{2\sigma} = (Z^*_{2s}, Z^*_{2s}) \tag{6.18}$$

where

$$Z^*_{2s} = (S^*_{p_{2\sigma}}, 0, 0, S^*_{h_{2\sigma}}, I^*_{s_{2\sigma}}, 0, 0, 0), \tag{6.19}$$

is the swine flu epidemic equilibrium in each region. Here

$$S^*_{p_{2\sigma}} = S^*_{p_0} = \frac{\eta_p}{\delta_p}$$
$$S^*_{h_{2\sigma}} = \frac{\eta_h}{\delta_h}\frac{1}{R_{sh\sigma}},$$
$$I^*_{s_{2\sigma}} = \frac{\eta_h}{\delta_h + m_s}(1 - \frac{1}{R_{sh}}).$$

Third, the mutant-avian flu epidemic equilibrium

$$Z^*_{3\sigma} = (Z^*_{3s}, Z^*_{3s}) \tag{6.20}$$

where

$$Z^*_{3s} = (S^*_{p_{3\sigma}}, 0, 0, S^*_{h_{3\sigma}}, 0, 0, 0, I^*_{m_{3\sigma}}) \tag{6.21}$$

is the mutant-avian flu epidemic equilibrium in each region. Here

$$S^*_{p_{3\sigma}} = S^*_{p_0} = \frac{\eta_p}{\delta_p}$$
$$S^*_{h_{3\sigma}} = \frac{\eta_h}{\delta_h}\frac{1}{R_{mh}},$$
$$I^*_{m_{3\sigma}} = \frac{\eta_h}{\delta_h + m_m}(1 - \frac{1}{R_{mh}}).$$

When $R_{p\theta\sigma} > 1$ (avian flu epidemic is epidemic among birds) there are two disease state equilibria, $Z^*_{4\sigma}$ and $Z^*_{5\sigma}$.

$$Z^*_{4\sigma} = (Z^*_{4s}, Z^*_{4s}) \tag{6.22}$$

where

$$Z^*_{4s} = (S^*_{p_{4\sigma}}, I^*_{p_{4\sigma}}, C^*_{p_{4\sigma}}, S^*_{h_{4\sigma}}, 0, I^*_{a_{4\sigma}}, I^*_{b_{4\sigma}}, 0), \tag{6.23}$$

is the disease equilibrium state of each region when there are avian flu epidemics among birds and humans. Here

$$\begin{aligned}
S^*_{p_{4\sigma}} &= S^*_{p_\otimes} = \frac{\eta_p}{\delta_p}\frac{1}{R_{p\theta\sigma}},\\
I^*_{p_{4\sigma}} &= I^*_{p_\otimes} = \frac{\eta_p}{\delta_p + m_p}(1 - \frac{1}{R_{p\theta\sigma}}),\\
C^*_{p_{4\sigma}} &= C^*_{p_\otimes} = \frac{\sigma\theta}{(r_p + m_c)} + \frac{\eta_p}{(r_p + m_c)}\frac{R_{p\beta}}{R_{p\theta\sigma}}(1 - \frac{1}{R_{p\theta\sigma}}),
\end{aligned}$$

$$\begin{aligned}
S^*_{h_{4\sigma}} &= \frac{\eta_h}{\delta_h + \alpha_{ph}\kappa_{ph}I^*_{p_{4\sigma}}} =\\
&= \frac{\eta_h}{\delta_h + \alpha_{ph}\kappa_{ph}\frac{\eta_p}{\delta_p + m_p}\left(1 - \frac{1}{R_{p\theta\sigma}}\right)}\\
&= \frac{\frac{\eta_h}{\delta_h}}{1 + \frac{\alpha_{ph}\kappa_{ph}\eta_p}{\eta_h\,(\delta_p + m_p)}\left(1 - \frac{1}{R_{p\theta\sigma}}\right)}\\
&= \frac{\frac{\eta_h}{\delta_h}}{1 + r_{p\theta\sigma}}
\end{aligned}$$

where $r_{p\theta\sigma}$ is defined as

$$r_{p\theta\sigma} = \frac{\alpha_{ph}\kappa_{ph}\eta_p}{\eta_h\,(\delta_p + m_p)}\left(1 - \frac{1}{R_{p\theta\sigma}}\right). \tag{6.24}$$

$$\begin{aligned}
I^*_{a_{4\sigma}} &= \frac{\gamma\alpha_{ph}\kappa_{ph}I^*_{p_4}S^*_{h_{4\sigma}}}{\delta_h + m_a}\\
&= \frac{\gamma}{\delta_h + m_a}(\eta_h - \delta_h S^*_{h_{4\sigma}})\\
&= \frac{\gamma\eta_h}{\delta_h + m_a}\left(1 - \frac{1}{1 + r_{ph}}\right) > 0
\end{aligned}$$

and

$$I^*_{b_{4\sigma}} = \frac{(1-\gamma)\alpha_{ph}\kappa_{ph}I^*_{p_{4\sigma}}S^*_{h_{4\sigma}}}{\delta_h + m_b}$$
$$= \frac{(1-\gamma)}{\delta_h + m_b}(\eta_h - \delta_h S^*_{h_4})$$

$$I^*_{b_{4\sigma}} = \frac{(1-\gamma)\eta_h}{\delta_h + m_b}\left(1 - \frac{1}{1+r_{ph}}\right) > 0$$

The condition $R_{p\theta\sigma} > 1$ means $r_{p\theta\sigma} > 0$ and hence guarantees that $I^*_{p_{4\sigma}} > 0, S^*_{h_{4\sigma}} > 0, I^*_{a_{4\sigma}} > 0$ and $I^*_{b_{4\sigma}} > 0$.

The fifth,

$$Z^*_{5\sigma} = (Z^*_{5s}, Z^*_{5s}) \tag{6.25}$$

where

$$Z^*_{5s} = (S^*_{p_{5\sigma}}, I^*_{p_{5\sigma}}, S^*_{h_{5\sigma}}, 0, I^*_{a_{5\sigma}}, I^*_{b_{5\sigma}}, I^*_{m_{5\sigma}}), \tag{6.26}$$

is the disease state equilibrium of each region when there are avian flu epidemics among birds and humans and also an epidemic of mutant-avian flu among humans. Here

$$S^*_{p_{5\sigma}} = S^*_{p_\otimes} = \frac{\eta_p}{\delta_p}\frac{1}{R_{p\theta\sigma}},$$
$$I^*_{p_{5\sigma}} = I^*_{p_\otimes} = \frac{\eta_p}{\delta_p + m_p}(1 - \frac{1}{R_{p\theta\sigma}}),$$
$$C^*_{p_{4\sigma}} = C^*_{p_\otimes} = \frac{\sigma\theta}{(r_p + m_c)} + \frac{\eta_p}{(r_p + m_c)}\frac{R_{p\beta}}{R_{p\theta\sigma}}(1 - \frac{1}{R_{p\theta\sigma}}),$$

$$S^*_{p_{5\sigma}} = \frac{\delta_p + m_p}{\alpha_p\kappa_p} = \frac{\eta_p}{\delta_p}\frac{1}{R_{p\theta\sigma}} > 0.$$

From (4.20a) it follows that

$$I^*_{p_{5\sigma}} = \frac{\eta_p}{\delta_p + m_p} - \frac{\delta_p}{\alpha_p\kappa_p} = \frac{\eta_p}{\delta_p + m_p}\left[1 - \frac{\delta_p(\delta_p + m_p)}{\eta_p\alpha_p\kappa_p}\right] = \frac{\eta_p}{\delta_p + m_p}(1 - \frac{1}{R_{p\theta\sigma}})$$

Hence for $I^*_{p_{5\sigma}} > 0$ it is required that $R_{p\theta\sigma} > 1$. It follows from (4.20f)

$$S^*_{h_{5\sigma}} = \frac{\delta_h + m_m}{\alpha_{mh}\kappa_{mh}} > 0.$$

Now (4.20c) gives

$$\begin{aligned} I^*_{m_{5\sigma}} &= \frac{\eta_h - \left(\delta_h + \alpha_{ph}\kappa_{ph} I^*_{p_{5\sigma}}\right) S^*_{h_{5\sigma}}}{\alpha_{mh}\kappa_{mh} S^*_{h_{5\sigma}}} \\ &= \frac{\eta_h - \left[\delta_h + \alpha_{ph}\kappa_{ph}\frac{\eta_p}{\delta_h+m_m}(1-\frac{1}{R_{p\theta\sigma}})\right]\frac{\delta_h+m_m}{\alpha_{mh}\kappa_{mh}}}{\delta_h + m_m} \\ &= \frac{\delta_h}{\alpha_{mh}\kappa_{mh}}\left[\frac{\alpha_{mh}\kappa_{mh}\eta_h}{\delta_h(\delta_p+m_m)} - 1 - \frac{\alpha_{ph}\kappa_{ph}\eta_h}{\delta_h(\delta_p+m_p)}(1-\frac{1}{R_{p\theta\sigma}})\right] \\ &= \frac{\delta_h}{\alpha_{mh}\kappa_{mh}}\left[R_{mh} - (1+r_{ph})\right]. \end{aligned}$$

where $r_{p\theta\sigma}$ is defined by (4.38)

$$r_{p\theta\sigma} = \frac{\alpha_{ph}\kappa_{ph}\eta_p}{\eta_h\ (\delta_p + m_p)}\left(1 - \frac{1}{R_{p\theta\sigma}}\right).$$

Therefore for $I^*_{m_{5\sigma}} > 0$ it is necessary that $R_{mh} > 1 + r_{p\theta\sigma}$. Finally (4.20d) and (4.20e) give

$$\begin{aligned} I^*_{a_{5\sigma}} &= \frac{\gamma\alpha_{ph}\kappa_{ph} I^*_{p_{5\sigma}} S^*_{h_{5\sigma}}}{\delta_h + m_a} \\ &= \frac{\gamma\alpha_{ph}\kappa_{ph}\frac{\eta_p}{\delta_p+m_p}(1-\frac{1}{R_{p\theta\sigma}})\frac{\delta_h+m_m}{\alpha_{mh}\kappa_{mh}}}{\delta_h + m_a} \\ &= \frac{\gamma\eta_h r_{ph}}{(\delta_h+m_a)R_{mh}} > 0 \end{aligned}$$

and

$$\begin{aligned} I^*_{b_{5\sigma}} &= \frac{(1-\gamma)\alpha_{ph}\kappa_{ph} I^*_{p_{5\sigma}} S^*_{h_{5\sigma}}}{\delta_h + m_b} \\ &= \frac{(1-\gamma)\alpha_{ph}\kappa_{ph}\frac{\eta_p}{\delta_p+m_p}(1-\frac{1}{R_{p\theta\sigma}})\frac{\delta_h+m_m}{\alpha_{mh}\kappa_{mh}}}{\delta_h + m_b} \\ &= \frac{(1-\gamma)\eta_h r_{ph}}{(\delta_h+m_b)R_{mh}} > 0 \end{aligned}$$

6.6 Stability analysis of disease state equilibria

Let reorder disease state variables

$$Z = (S_{p_1}, I_{p_1}, C_{p_1}, S_{h_1}, I_{s_1}, I_{a_1}, I_{b_1}, I_{m_1}, S_{p_2}, I_{p_2}, C_{p_2}, S_{h_2}, I_{s_2}, I_{a_2}, I_{b_2}, I_{m_2})$$

into

$$\bar{Z} = (S_{p_1}, I_{p_1}, C_{p_1}, S_{p_2}, I_{p_2}, C_{p_2}, S_{h_1}, I_{s_1}, I_{a_1}, I_{b_1}, I_{m_1}, S_{h_2}, I_{s_2}, I_{a_2}, I_{b_2}, I_{m_2}).$$

In this new variable, (6.5a)-(6.27p) becomes

$$S'_{p_1}(t) = \eta_p - (\delta_p + \theta)S_{p_1} - \alpha_p\kappa_p I_{p_1}S_{p_1} + r_p C_{p_1} + \theta(1 - \beta_p\varkappa_p I_{p_2})\, S_{p_2}, \tag{6.27a}$$

$$I'_{p_1}(t) = \alpha_p\kappa_p I_{p_1}S_{p_1} - (\delta_p + m_p + \theta)\, I_{p_1} + (1-\sigma)\theta(1 + \beta_p\varkappa_p S_{p_2})\, I_{p_2}, \tag{6.27b}$$

$$C'_{p_1}(t) = \sigma\theta(1 + \beta_p\varkappa_p S_{p_2})\, I_{p_2} - (r_p + m_c)C_{p_1}, \tag{6.27c}$$

$$S'_{p_2}(t) = \eta_p - (\delta_p + \theta)S_{p_2} - \alpha_p\kappa_p I_{p_2}S_{p_2} + r_p C_{p_2} + \theta(1 - \beta_p\varkappa_p I_{p_1})S_{p_1}, \tag{6.27d}$$

$$I'_{p_2}(t) = \alpha_p\kappa_p I_{p_2}S_{p_2} - (\delta_p + m_p + \theta)\, I_{p_2} + (1-\sigma)\theta(1 + \beta_p\varkappa_p S_{p_1})I_{p_1}, \tag{6.27e}$$

$$C'_{p_2}(t) = \sigma\theta(1 + \beta_p\varkappa_p S_{p_1})\, I_{p_1} - (r_p + m_c)C_{p_2}, \tag{6.27f}$$

$$\begin{aligned} S'_{h_1}(t) =& \eta_h - \delta_h S_{h_p} - (p_a + p_b)\alpha_{ph}\kappa_{ph}I_{p_1}S_{h_1} - \alpha_{sh}\kappa_{sh}I_{s_1}S_{h_1} \\ & - \alpha_{mh}\kappa_{mh}I_{m_1}S_{h_1}, \end{aligned} \tag{6.27g}$$

$$I'_{s_1}(t) = \alpha_{sh}\kappa_{sh}I_{s_1}S_{h_1} - (\delta_h + m_s)\, I_{s_1}, \tag{6.27h}$$

$$I'_{a_1}(t) = p_a\alpha_{ph}\kappa_{ph}I_{p_1}S_{h_1} - \mu\alpha_{sa}\kappa_{sa}I_{s_1}I_{a_1} - (\delta_h + m_a)\, I_{a_1}, \tag{6.27i}$$

$$I'_{b_1}(t) = p_b\alpha_{ph}\kappa_{ph}I_{p_1}S_{h_1} - (\delta_h + m_b)\, I_{b_1}, \tag{6.27j}$$

$$I'_{m_1}(t) = \mu\alpha_{sa}\kappa_{sa}I_{s_1}I_{a_1} + \alpha_{mh}\kappa_{mh}I_{m_1}S_{h_p} - (\delta_h + m_m)\, I_{m_1}, \tag{6.27k}$$

$$\begin{aligned} S'_{h_2}(t) =& \eta_h - \delta_h S_{h_s} - (p_a + p_b)\alpha_{ph}\kappa_{ph}I_{p_2}S_{h_2} - \alpha_{sh}\kappa_{sh}I_{s_2}S_{h_2} \\ & - \alpha_{mh}\kappa_{mh}I_{m_2}S_{h_2}, \end{aligned} \tag{6.27l}$$

$$I'_{s_2}(t) = \alpha_{sh}\kappa_{sh}I_{s_2}S_{h_2} - (\delta_h + m_s)\, I_{s_2}, \tag{6.27m}$$

$$I'_{a_2}(t) = p_a\alpha_{ph}\kappa_{ph}I_{p_2}S_{h_2} - \mu\alpha_{sa}\kappa_{sa}I_{s_2}I_{a_2} - (\delta_h + m_a)\, I_{a_2}, \tag{6.27n}$$

$$I'_{b_2}(t) = p_b\alpha_{ph}\kappa_{ph}I_{p_2}S_{h_2} - (\delta_h + m_b)\, I_{b_2}, \tag{6.27o}$$

$$I'_{m_2}(t) = \mu\alpha_{sa}\kappa_{sa}I_{s_2}I_{a_2} + \alpha_{mh}\kappa_{mh}I_{m_2}S_{h_2} - (\delta_h + m_m)\, I_{m_2}. \tag{6.27p}$$

The Jacobian matrix of (5.25a)-(5.25n) at $\bar{Z}_{i\theta} \forall i = 1, \ldots, 5$ is given by

$$\mathcal{J}_{i\theta} = \begin{bmatrix} J_{i\theta 1} & O_1 & O_1 \\ J_4 & J_{i\theta 2} & O_3 \\ J_5 & O_3 & J_{i\theta 3} \end{bmatrix} \quad \text{fori} = 1, \ldots, 5. \tag{6.28}$$

$$J_{i\theta 1} = \begin{bmatrix} j_{1,1} & j_{1,2} & j_{1,3} & j_{1,4} & j_{1,5} & 0 \\ j_{2,1} & j_{2,2} & 0 & j_{2,4} & j_{2,5} & 0 \\ 0 & 0 & j_{3,3} & j_{3,4} & j_{3,5} & 0 \\ j_{4,1} & j_{4,2} & 0 & j_{4,4} & j_{4,5} & j_{4,6} \\ j_{5,1} & j_{5,2} & 0 & j_{5,4} & j_{5,5} & 0 \\ j_{6,1} & j_{6,2} & 0 & 0 & 0 & j_{6,6} \end{bmatrix}, \tag{6.29}$$

where $j_{1,1} = -\delta_p - \theta - \alpha_p\kappa_p I_{p_{i\sigma}}$, $j_{1,2} = -\alpha_p\kappa_p S_{p_{i\sigma}}$, $j_{1,3} = r_p$, $j_{1,4} = \theta(1-\beta_p\varkappa_p I_{p_{i\sigma}})$, $j_{1,5} = -\theta\beta_p\varkappa_p S_{p_{i\sigma}}$, $j_{2,1} = \alpha_p\kappa_p I_{p_{i\sigma}}$, $j_{2,2} = \alpha_p\kappa_p S_{p_{i\sigma}} - (\delta_p + m_p) - \theta$, $j_{2,4} = (1-\sigma)\theta\beta_p\varkappa_p I_{p_{i\sigma}}$, $j_{2,5} = (1-\sigma)\theta(1+\beta_p\varkappa_p S_{p_{i\sigma}})$, $j_{3,3} = -(r_p + m_c)$, $j_{3,4} = \sigma\theta\beta_p\varkappa_p I_{p_{i\sigma}}$, $j_{3,5} = \sigma\theta(1+\beta_p\varkappa_p S_{p_{i\sigma}})$, $j_{4,1} = \theta(1-\beta_p\varkappa_p I_{p_{i\sigma}})$, $j_{4,2} = -\theta\beta_p\varkappa_p S_{p_{i\sigma}}$, $j_{4,4} = -\delta_p - \theta - \alpha_p\kappa_p I_{p_{i\sigma}}$, $j_{4,5} = -\alpha_p\kappa_p S_{p_{i\sigma}}$, $j_{4,6} = r_p$, $j_{5,1} = (1-\sigma)\theta\beta_p\varkappa_p I_{p_{i\sigma}}$, $j_{5,2} = (1-\sigma)\theta(1+\beta_p\varkappa_p S_{p_{i\sigma}})$, $j_{5,4} = \alpha_p\kappa_p I_{p_{i\sigma}}$, $j_{5,5} = -(\delta_p + m_p + \theta)$, $j_{6,1} = \sigma\theta\beta_p\varkappa_p I_{p_2}$, $j_{6,2} = \sigma\theta(1+\beta_p\varkappa_p S_{p_{i\sigma}})$, $j_{6,6} = -(r_p + m_c)$.

$$J_{i\theta 2} = \begin{bmatrix} j_{7,7} & j_{7,8} & 0 & 0 & j_{7,11} \\ j_{8,7} & j_{8,8} & 0 & 0 & 0 \\ j_{9,7} & j_{9,8} & j_{9,9} & 0 & 0 \\ j_{10,7} & 0 & 0 & j_{10,10} & 0 \\ j_{11,7} & j_{11,8} & j_{11,9} & 0 & j_{11,11} \end{bmatrix}, \tag{6.30}$$

$$J_{i\theta 3} = \begin{bmatrix} j_{12,12} & j_{12,13} & 0 & 0 & j_{12,16} \\ j_{13,12} & j_{13,13} & 0 & 0 & 0 \\ j_{14,12} & j_{14,13} & j_{14,14} & 0 & 0 \\ j_{15,12} & 0 & 0 & j_{15,15} & 0 \\ j_{16,12} & j_{16,13} & j_{16,14} & 0 & j_{16,16} \end{bmatrix}, \tag{6.31}$$

where $j_{7,7} = j_{12,12} = -\delta_h - \alpha_{ph}\kappa_{ph}I_{p_{i\sigma}} - \alpha_{sh}\kappa_{sh}I_s - \alpha_{mh}\kappa_{mh}I_{m_{i\sigma}}$, $j_{7,8} = j_{12,13} = -\alpha_{sh}\kappa_{sh}S_{h_1}$, $j_{7,11} = j_{12,16} = -\alpha_{mh}\kappa_{mh}S_{h_{i\sigma}}$, $j_{8,7} = j_{13,12} = -\alpha_{sh}\kappa_{sh}I_{s_{i\sigma}}$, $j_{8,8} = j_{13,13} = \alpha_{sh}\kappa_{sh}S_{h_{i\sigma}} - (\delta_h + m_s)$, $j_{9,7} = j_{14,12} = \gamma_a\alpha_{ph}\kappa_{ph}I_{p_1}$, $j_{9,8} = j_{14,13} = -\mu\,\alpha_{sa}\kappa_{sa}I_a$, $j_{9,9} = j_{14,14} = -\mu\,\alpha_{sa}\kappa_{sa}I_{s_{i\sigma}} - (\delta_h + m_a)$, $j_{10,7} = j_{15,12} = (1-\gamma_a)\alpha_{yh}\kappa_{ph}I_{p_{i\sigma}}$, $j_{10,10} = j_{15,15} = -(\delta_h + m_b)$, $j_{11,17} = j_{16,12} = \alpha_{mh}\kappa_{mh}I_{m_{i\sigma}}$, $j_{11,8} = j_{16,13} = \mu\,\alpha_{sa}\kappa_{sa}I_{a_{i\sigma}}$, $j_{11,9} = j_{16,14} = \mu\,\alpha_{sa}\kappa_{sa}I_{s_{i\sigma}}$, $j_{11,11} = j_{16,16} = \alpha_{mh}\kappa_{mh}S_{h_1} - (\delta_h + m_m)$.

$$J_4 = \begin{bmatrix} 0 & j_{7,2} & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & j_{9,2} & 0 & 0 & 0 & 0 \\ 0 & j_{10,2} & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix}, \; J_5 = \begin{bmatrix} 0 & 0 & 0 & 0 & j_{12,5} & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & j_{14,5} & 0 \\ 0 & 0 & 0 & 0 & j_{15,5} & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix},$$

where $j_{7,2} = j_{12,5} = -\alpha_{ph}\kappa_{ph}S_{h_1}$, $j_{9,2} = j_{14,5} = \gamma_a\alpha_{ph}\kappa_{ph}S_{h_1}$, $j_{10,2} = j_{15,5} = (1-\gamma_a)\alpha_{yh}\kappa_{ph}S_{h_1}$. O_1, O_2 and O_3 are zero matrices

$$O_1 = \begin{bmatrix} 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{bmatrix}, \; O_2 = \begin{bmatrix} 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{bmatrix}.$$

J_1, J_2 and J_3 are the key Jacobian matrices or principal minors of the Jacobian matrix $\mathcal{J}$ given in (5.26). The Jacobian matrix is stable at an equilibrium point $Z^*_{i\theta}$, $i = 1, \ldots 6$ if and only if the key Jacobian matrices are stable at $Z^*_{i\theta}$ (by Corollary 3.26).

6.6.1 Stability analysis of the disease free equilibrium

The first disease equilibrium ($i = 1$) is the disease free equilibrium, $Z^*_{1\sigma} = (Z^*_{1s}, Z^*_{1s})$ where $Z^*_{1s} = (\frac{\eta_p}{\delta_p}, 0, \frac{\eta_h}{\delta_h}, 0, 0, 0, 0)$. Stability analysis of $Z^*_{1\sigma} = (Z^*_{1s}, Z^*_{1s})$ is given as follows.

Theorem 6.2. *If $R_{p\theta\sigma} < 1$, $R_{sh} \leq 1$, $R_{mh} \leq 1$, $r_{ph} \leq 1$, then $Z^*_{1\sigma}$ is LAS.*

Proof. At $\bar{Z}^*_{1\sigma}$ the Jacobian matrix (5.26) becomes

$$\mathcal{J}_{1\sigma} = \mathcal{J}(\bar{Z}^*_{1\sigma}) = \begin{bmatrix} J_{1\sigma 1} & O_1 & O_1 \\ J_4 & J_{1\sigma 2} & O_3 \\ J_5 & O_3 & J_{1\sigma 3} \end{bmatrix}. \tag{6.32}$$

At $E^*_0 = (\frac{\eta_p}{\delta_p}, 0, 0, \frac{\eta_p}{\delta_p}, 0, 0)$, first key Jacobian matrix is

$$J_{1\theta 1} = \begin{bmatrix} j_{1,1} & j_{1,2} & j_{1,3} & j_{1,4} & j_{1,5} & 0 \\ 0 & j_{2,2} & 0 & 0 & j_{2,5} & 0 \\ 0 & 0 & j_{3,3} & 0 & j_{3,5} & 0 \\ 0 & j_{4,2} & 0 & j_{4,4} & j_{4,5} & j_{4,6} \\ 0 & j_{5,2} & 0 & 0 & j_{5,5} & 0 \\ 0 & j_{6,2} & 0 & 0 & 0 & j_{6,6} \end{bmatrix}, \tag{6.33}$$

where $j_{1,1} = -\delta_p - \theta$, $j_{1,2} = -\alpha_p\kappa_p\frac{\eta_p}{\delta_p}$, $j_{1,3} = r_p$, $j_{1,4} = \theta$, $j_{1,5} = -\theta\beta_p\varkappa_p\frac{\eta_p}{\delta_p}$, $j_{2,2} = \alpha_p\kappa_p\frac{\eta_p}{\delta_p} - (\delta_p + m_p) - \theta$, $j_{2,5} = (1-\sigma)\theta(1+\beta_p\varkappa_p\frac{\eta_p}{\delta_p})$, $j_{3,3} = -(r_p + m_c)$, $j_{3,5} = \sigma\theta(1+\beta_p\varkappa_p\frac{\eta_p}{\delta_p})$, $j_{4,2} = -\theta\beta_p\varkappa_p\frac{\eta_p}{\delta_p}$, $j_{4,4} = -\delta_p - \theta$, $j_{4,5} = -\alpha_p\kappa_p\frac{\eta_p}{\delta_p}$, $j_{4,6} = r_p$,

$j_{5,2} = (1-\sigma)\theta(1+\beta_p \varkappa_p \frac{\eta_p}{\delta_p})$, $j_{5,5} = -(\delta_p + m_p + \theta)$, $j_{6,2} = \sigma\theta(1+\beta_p \varkappa_p \frac{\eta_p}{\delta_p})$, $j_{6,6} = -(r_p + m_c)$.

The characteristic polynomial of $J_{1\sigma 1}$ is

$$\mathcal{C}_{1\sigma} = (\lambda - m_p(R_0 - 1)^2 (\lambda + \delta_p)(\lambda + (\delta_p + 2\theta))$$

Hence, the key Jacobian matrix $J_{1\sigma 1}$ is stable if $R_{0\sigma} < 1$. The key Jacobian matrix $J_{1\sigma 2}$ and $J_{1\sigma 3}$ are the same as the key Jacobian matrix (12 Ch4),

$$J_{1\sigma 2} = J_{1\sigma 2} = J_{12} = \begin{bmatrix} j_{3,3} & j_{3,4} & 0 & 0 & j_{3,7} \\ 0 & j_{4,4} & 0 & 0 & 0 \\ 0 & 0 & j_{5,5} & 0 & 0 \\ 0 & 0 & 0 & j_{6,6} & 0 \\ 0 & 0 & 0 & 0 & j_{7,7} \end{bmatrix},$$

where $j_{3,3} = -\delta_h$, $j_{3,4} = (-1)\alpha_{sh}\kappa_{sh}S^*_{h_{1\sigma}}$, $j_{3,7} = (-1)\alpha_{mh}\kappa_{mh}S^*_{h_{1\sigma}}$, $j_{4,4} = \alpha_{sh}\kappa_{sh}S^*_{h_{1\sigma}} - (\delta_h + m_s)$, $j_{5,5} = (-1)(\delta_h - m_a)$, $j_{6,6} = (-1)(\delta_h - m_b)$, $j_{7,7} = \alpha_{mh}\kappa_{mh}S^*_{h_{1\sigma}} - (\delta_h + m_m)$, $j_{8,1} = -\delta_p, j_{8,2} = -(\delta_p + m_p) R_{p\theta\sigma}, j_{9,2} = j_{9,9} = (\delta_p + m_p)(R_{p\theta\sigma} - 1)$ Recall some results from Sub-section 4.5.3 that J_{11} is proven to be stable if $R_p \leq 1$ and J_{12} is proven to be stable if $R_{sh} \leq 1$ and $R_{mh} \leq 1$. Since $J_{1\sigma 1} = J_{11}$ and $R_p \leq R_{p\theta\sigma}$, therefore $J_{1\sigma 1}$ is stable if $R_{p\theta\sigma} \leq$. Since $J_{1\sigma 2} = J_{1\sigma 2} = J_{12}$ therefore $J_{1\sigma 2} = J_{1\sigma 2}$ are stable if $R_{sh} \leq 1$ and $R_{mh} \leq 1$. Therefore $Z^*_{1\sigma}$ is well defined and stable if $R_p < 1, R_{sh} \leq 1$ and $R_{mh} \leq 1$. □

This result means that disease eradication is possible for a sufficient small parameter β_p when the both regions are disease free without traveling (that is, $R_{p\theta\sigma}$ for small β_p when $R_p < 1$). From 5.8, if $\beta_p = 0$ and $R_p < 1$ holds, then infectious diseases should disappear in both regions. However, the disease free state among birds does not guarantee a disease free state among humans. The following are three possible disease equilibria.

6.6.2 Stability analysis of swine flu epidemic equilibrium in both regions

The swine flu epidemic equilibrium is (5.17)

$$Z^*_{2\sigma} = (Z^*_{2t}, Z^*_{2t})$$

where

$$Z^*_{2t} = (S^*_{p_{2\sigma}}, 0, 0, S^*_{h_{2\sigma}}, I^*_{s_{2\sigma}}, 0, 0, 0, 0),$$

is the swine flu epidemic equilibrium in each region. Here

$$S^*_{p_{2\sigma}} = S^*_{p0} = \frac{\eta_p}{\delta_p},$$
$$S^*_{h_{2\sigma}} = \frac{\eta_h}{\delta_h}\frac{1}{R_{sh}},$$
$$I^*_{s_{2\sigma}} = \frac{\eta_h}{\delta_h + m_s}(1 - \frac{1}{R_{sh}}).$$

Theorem 6.3. *If $R_{p\theta\sigma} < 1$ and $R_{sh} > \max\{R_{mh}, 1\}$ then the swine flu epidemic equilibrium $Z^*_{2\sigma}$ is LAS.*

Proof. At $\bar{Z}^*_{2\sigma}$ the Jacobian matrix (6.32) becomes

$$\mathcal{J}_{2\sigma} = \mathcal{J}(\bar{Z}^*_{2\sigma}) = \begin{bmatrix} J_{2\sigma 1} & O_1 & O_1 \\ J_4 & J_{2\sigma 2} & O_3 \\ J_5 & O_3 & J_{2\sigma 3} \end{bmatrix}.$$

$J_{2\sigma 1} = J_{1\sigma 1}$, so from the last Sub-section, $J_{2\sigma 1}$ is table if and only if $R_{p\theta\sigma} < 1$.

The second and third key Jacobian matrices $J_{2\sigma 2} = J_{2\sigma 3}$, are the same as the key Jacobian matrix given in (4.31)

$$J_{2\sigma 2} = J_{2\sigma 3} = J_{12} = \begin{bmatrix} j_{3,3} & j_{3,4} & 0 & 0 & j_{3,7} \\ j_{4,3} & 0 & 0 & 0 & 0 \\ 0 & 0 & j_{5,5} & 0 & 0 \\ 0 & 0 & 0 & j_{6,6} & 0 \\ 0 & 0 & j_{7,5} & 0 & j_{7,7} \end{bmatrix}$$

where $j_{3,3} = (-1)(\delta_h + \alpha_{sh}\kappa_{sh}I^*_{s_{2\sigma}})$, $j_{3,4} = (-1)\alpha_{sh}\kappa_{sh}S^*_{h_{2\sigma}}$, $j_{37} = (-1)\alpha_{mh}\kappa_{mh}S^*_{h_{2\sigma}}$, $j_{4,3} = (-1)\alpha_{sh}\kappa_{sh}I^*_{s_{2\sigma}}$, $j_{5,5} = (-1)\left[\mu\alpha_{sh}\kappa_{sh}I^*_{s_{2\sigma}} + (\delta_h + m_a)\right]$, $j_{6,6} = (-1)(\delta_h + m_b)$, $j_{7,5} = (-1)[\mu\alpha_{sa}\kappa_{sa}I^*_{s_{2\sigma}}$, $j_{7,7} = \alpha_{mh}\kappa_{mh}S^*_{h_{2\sigma}} + (\delta_h + m_m)$.

Recall some results from Sub-section 4.5.4 that J_{21} is proven to be stable if $R_p \leq 1$ and J_{12} is proven to be stable if $R_{sh} > \max\{R_{mh}, 1\}$. Since $J_{2\sigma 1} = J_{21}$ and $R_p \leq R_{p\theta\sigma}$, then $J_{2\sigma 1}$ is stable if $R_{p\theta\sigma} \leq 1$ Since $J_{2\sigma 2} = J_{1\sigma 3} = J_{22}$ therefore $J_{2\sigma 2} = J_{1\sigma 3}$ are stable if $R_{sh} > \max\{R_{mh}, 1\}$. □

6.6.3 Stabilty analysis of mutant-avian flu epidemic equilibrium

The mutant avian flu epidemic equilibrium, $Z^*_{3\beta}$, corresponds to the situation in which there are no birds or humans infected by avian flu and no humans infected by swine flu but there are humans infected by mutant-avian flu. By using the definitions of the

basic reproduction numbers in Section 4.3,

$$Z^*_{3\sigma} = (Z^*_{3t}, Z^*_{3t}), \tag{6.34}$$

with

$$Z^*_{3t} = (S^*_{p_3}, 0, 0, S^*_{h_3}, 0, 0, 0, I^*_{m_3}),$$

where

$$\begin{aligned} S^*_{p_{3\sigma}} &= S^*_{p_0} = \frac{\eta_p}{\delta_p} \\ S^*_{h_{3\sigma}} &= \frac{\eta_h}{\delta_h}\frac{1}{R_{mh}}, \\ I^*_{m_{3\sigma}} &= \frac{\eta_h}{\delta_h + m_m}(1 - \frac{1}{R_{mh}}). \end{aligned}$$

Theorem 6.4. *If $R_{p\theta\sigma} < 1$ and $R_{mh} > \max\{R_{sh}, 1\}$ then $Z^*_{3\sigma}$ is LAS.*

Proof. At $\bar{Z}^*_{2\sigma}$ the Jacobian matrix (5.26) becomes

$$\mathcal{J}_{3\sigma} = \mathcal{J}(\bar{Z}^*_{3\sigma}) = \begin{bmatrix} J_{3\sigma 1} & O_1 & O_1 \\ J_4 & J_{3\sigma 2} & O_3 \\ J_5 & O_3 & J_{3\sigma 3} \end{bmatrix}.$$

$J_{3\sigma 1} = J_{1\sigma 1}$, so $J_{3\sigma 1}$ is table if and only if $R_{p\theta\sigma} < 1$.

The second and third key Jacobian matrices $J_{3\sigma 2} = J_{3\sigma 3}$, are the same as J_{32}, the key Jacobian matrix given in (4.40),

$$J_{3\sigma 2} = J_{3\sigma 3} = J_{32} = \begin{bmatrix} j_{3,3} & j_{3,4} & 0 & 0 & j_{3,7} \\ 0 & j_{4,4} & 0 & 0 & 0 \\ 0 & 0 & j_{5,5} & 0 & 0 \\ 0 & 0 & 0 & j_{6,6} & 0 \\ j_{7,5} & 0 & 0 & 0 & j_{7,7} \end{bmatrix}, \text{for k} = 1, \ldots, 4,$$

where $j_{1,1} = (-1)\delta_p$, $j_{1,2} = -\alpha_p\kappa_p S^*_{p_{3\sigma}}$ $j_{2,2} = -\alpha_p\kappa_p S^*_{p_{3\sigma}} - (\delta_p + m_p)$, $j_{3,3} = (-1)(\delta_h + \alpha_{mh}\kappa_{mh} I^*_{m_{3\sigma}})$, $j_{3,4} = (-1)\alpha_{sh}\kappa_{sh} S^*_{h_{3\sigma}}$, $j_{3,7} = (-1)\alpha_{mh}\kappa_{mh} S^*_{h_{3\sigma}}$, $j_{4,4} = (-1)\alpha_{sh}\kappa_{sh} S^*_{h_{3\sigma}} - (\delta_h + m_s)$, $j_{5,5} = (-1)(\delta_h + m_a)$, $j_{6,6} = (-1)(\delta_h + m_b)$, $j_{7,3} = (-1)\alpha_{mh}\kappa_{mh} I^*_{m_{3\sigma}}$, $j_{7,7} = \alpha_{mh}\kappa_{mh} S^*_{h_{3\sigma}} - (\delta_h + m_m)$.

Recall some results from Sub-section 6.6.3 that J_{31} is proven to be stable if $R_{p\theta\sigma}1$ and J_{32} is proven to be stable if $R_{mh} > \max\{R_{sh}, 1\}$. Since $J_{3\sigma 1}$ and $R_p \leq R_{p\theta\sigma} < 1$ therefore $J_{3\sigma 1}$ are stable if $R_{p\theta\sigma} < 1$. Since $J_{3\sigma 2} = J_{3\sigma 3} = J_{32}$ therefore $J_{3\sigma 2}$ and $J_{3\sigma 3}$

are stable if $R_{mh} > \max\{R_{sh}, 1\}$. □

6.6.4 Stability analysis of avian-flu epidemic equilibrium.

The disease state when there are avian flu epidemics among birds and humans, $Z^*_{4\sigma}$, is

$$Z^*_{4\sigma} = (Z^*_{4t}, Z^*_{4t}) \tag{6.35}$$

with

$$Z^*_{4t} = (S^*_{p_{4\sigma}}, I^*_{p_{4\sigma}}, C^*_{p_{4\sigma}}, S^*_{h_{4\sigma}}, 0, I^*_{a_{4\sigma}}, I^*_{b_{4\sigma}}, 0),$$

where

$$\begin{aligned}
S^*_{p_{4\sigma}} &= S^*_{p_\otimes} = \frac{\eta_p}{\delta_p}\frac{1}{R_{p\theta\sigma}} > 0 \\
I^*_{p_{4\sigma}} &= I^*_{p_\otimes} = \frac{\eta_p}{\delta_p + m_p}(1 - \frac{1}{R_{p\theta\sigma}}) > 0 \\
C^*_{p_{4\sigma}} &= C^*_{p_\otimes} == \frac{\sigma\theta}{(r_p + m_c)} + \frac{\eta_p}{(r_p + m_c)}\frac{R_{p\beta}}{R_{p\theta\sigma}}(1 - \frac{1}{R_{p\theta\sigma}}) \\
S^*_{h_4} &= \frac{\frac{\eta_h}{\delta_h}}{1 + r_{p\theta\sigma}}
\end{aligned}$$

where r_{ph} is defined as (4.38),

$$r_{p\theta\sigma} = \frac{\alpha_{ph}\kappa_{ph}\eta_p}{\eta_h\ (\delta_p + m_p)}\left(1 - \frac{1}{R_{p\theta\sigma}}\right). \tag{6.36}$$

$$I^*_{a_{4\sigma}} = \frac{\gamma\eta_h}{\delta_h + m_a}\left(1 - \frac{1}{1 + r_{p\theta\sigma}}\right),$$

and

$$I^*_{b_{4\sigma}} = \frac{(1-\gamma)\eta_h}{\delta_h + m_b}\left(1 - \frac{1}{1 + r_{p\theta\sigma}}\right).$$

Theorem 6.5. *If $R_{p\theta\sigma} > 1$ and $\max\{R_{sh}, R_{mh}\} < 1 + r_{ph}$ then $Z^*_{4\sigma} = (Z^*_{4t}, Z^*_{4t})$ is LAS.*

Proof. At $\bar{Z}^*_{4\sigma}$ the Jacobian matrix (5.26) becomes

$$\mathcal{J}_{4\sigma} = \mathcal{J}(\bar{Z}^*_{4\sigma}) = \begin{bmatrix} J_{4\sigma 1} & O_1 & O_1 \\ J_4 & J_{4\sigma 2} & O_3 \\ J_5 & O_3 & J_{4\sigma 3} \end{bmatrix}.$$

At $\bar{Z}^*_{4\sigma}$ the Jacobian matrix (5.26) becomes

$$\mathcal{J}_{4\sigma} = \mathcal{J}(\bar{Z}^*_{4\sigma}) = \begin{bmatrix} J_{4\sigma 1} & O_1 & O_1 \\ J_4 & J_{4\sigma 2} & O_3 \\ J_5 & O_3 & J_{4\sigma 3} \end{bmatrix}.$$

From (6.37)

$$J_{i\theta 1} = \begin{bmatrix} j_{1,1} & j_{1,2} & j_{1,3} & j_{1,4} & j_{1,5} & 0 \\ j_{2,1} & j_{2,2} & 0 & j_{2,4} & j_{2,5} & 0 \\ 0 & 0 & j_{3,3} & j_{3,4} & j_{3,5} & 0 \\ j_{4,1} & j_{4,2} & 0 & j_{4,4} & j_{4,5} & j_{4,6} \\ j_{5,1} & j_{5,2} & 0 & j_{5,4} & j_{5,5} & 0 \\ j_{6,1} & j_{6,2} & 0 & 0 & 0 & j_{6,6} \end{bmatrix}, \tag{6.37}$$

where $j_{1,1} = -\delta_p - \theta - \alpha_p\kappa_p I_{p_1}$, $j_{1,2} = -\alpha_p\kappa_p S_{p_{4\sigma}}$, $j_{1,3} = r_p$, $j_{1,4} = \theta(1 - \beta_p\varkappa_p I_{p_{4\sigma}})$, $j_{1,5} = -\theta\beta_p\varkappa_p S_{p_{4\sigma}}$, $j_{2,1} = \alpha_p\kappa_p I_{p_{4\sigma}}$, $j_{2,2} = \alpha_p\kappa_p S_{p_1} - (\delta_p + m_p) - \theta$, $j_{2,4} = (1-\sigma)\theta\beta_p\varkappa_p I_{p_{4\sigma}}$, $j_{2,5} = (1-\sigma)\theta(1 + \beta_p\varkappa_p S_{p_{4\sigma}})$, $j_{3,3} = -(r_p + m_c)$, $j_{3,4} = \sigma\theta\beta_p\varkappa_p I_{p_{4\sigma}}$, $j_{3,5} = \sigma\theta(1+\beta_p\varkappa_p S_{p_{4\sigma}})$, $j_{4,1} = \theta(1-\beta_p\varkappa_p I_{p_{4\sigma}})$, $j_{4,2} = -\theta\beta_p\varkappa_p S_{p_{4\sigma}}$, $j_{4,4} = -\delta_p - \theta - \alpha_p\kappa_p I_{p_{4\sigma}}$, $j_{4,5} = -\alpha_p\kappa_p S_{p_{4\sigma}}$, $j_{4,6} = r_p$, $j_{5,1} = (1-\sigma)\theta\beta_p\varkappa_p I_{p_{4\sigma}}$, $j_{5,2} = (1-\sigma)\theta(1 + \beta_p\varkappa_p S_{p_{4\sigma}})$, $j_{5,4} = \alpha_p\kappa_p I_{p_{4\sigma}}$, $j_{5,5} = -(\delta_p + m_p + \theta)$, $j_{6,1} = \sigma\theta\beta_p\varkappa_p I_{p_{4\sigma}}$, $j_{6,2} = \sigma\theta(1 + \beta_p\varkappa_p S_{p_2})$, $j_{6,6} = -(r_p + m_c)$.
At $\mathcal{E}^*_\otimes = (S^*_{p_\otimes}, I^*_{p_\otimes}, C^*_{p_\otimes}, S^*_{p_\otimes}, I^*_{p_\otimes}, C^*_{p_\otimes})$, the key Jacobian matrix $J_{4\sigma 1}$ can be written as

$$J_{4\sigma 1} = \begin{bmatrix} A & B \\ B & A \end{bmatrix} \tag{6.38}$$

where

$$A = \begin{bmatrix} a_{1,1} & a_{1,2} & r_p \\ a_{2,1} & a_{2,2} & 0 \\ 0 & 0 & a_{3,3} \end{bmatrix}, \quad B = \begin{bmatrix} b_{1,1} & b_{1,2} & 0 \\ b_{2,1} & b_{2,2} & 0 \\ b_{3,1} & b_{3,2} & 0 \end{bmatrix}$$

where

$$a_{1,1} = -\delta_p - \theta - \alpha_p\kappa_p I^*_{p_4} = -\delta_p - \theta - \alpha_p\kappa_p \frac{\eta_p}{\delta_p + m_p}(1 - \frac{1}{R_{p\theta\sigma}})$$

$$a_{1,2} = -\alpha_p\kappa_p S^*_{p_4} = -\alpha_p\kappa_p \frac{\eta_p}{\delta_p}\frac{1}{R_{p\theta\sigma}}$$

$$a_{1,3} = r_p$$

$$a_{2,1} = \alpha_p\kappa_p I^*_{p_4} = \alpha_p\kappa_p \frac{\eta_p}{\delta_p + m_p}(1 - \frac{1}{R_{p\theta\sigma}})$$

$$a_{2,2} = \alpha_p\kappa_p S^*_{p_4} - (\delta_p + m_p) - \theta = \alpha_p\kappa_p \frac{\eta_p}{\delta_p}\frac{1}{R_{p\theta\sigma}} - (\delta_p + m_p) - \theta$$

$$a_{3,3} = -(r_p + m_c)$$

$$b_{1,1} = \theta(1 - \beta_p\varkappa_p I^*_{p_4}) = \theta(1 - \beta_p\varkappa_p \frac{\eta_p}{\delta_p + m_p}(1 - \frac{1}{R_{p\theta\sigma}})$$

$$b_{1,2} = -\theta\beta_p\varkappa_p S^*_{p_4} = -\theta\beta_p\varkappa_p \frac{\eta_p}{\delta_p}\frac{1}{R_{p\theta\sigma}}$$

$$b_{2,1} = (1-\sigma)\theta\beta_p\varkappa_p I^*_{p_4} = (1-\sigma)\theta\beta_p\varkappa_p \frac{\eta_p}{\delta_p + m_p}(1 - \frac{1}{R_{p\theta\sigma}})$$

$$b_{2,2} = (1-\sigma)\theta(1 + \beta_p\varkappa_p S^*_{p_4}) = (1-\sigma)\theta(1 + \beta_p\varkappa_p \frac{\eta_p}{\delta_p}\frac{1}{R_{p\theta\sigma}}$$

$$b_{3,1} = \sigma\theta\beta_p\varkappa_p I^*_{p_4} = \sigma\theta\beta_p\varkappa_p \frac{\eta_p}{\delta_p + m_p}(1 - \frac{1}{R_{p\theta\sigma}})$$

$$b_{3,2} = \sigma\theta\left(1 + \beta_p\varkappa_p S^*_{p_4}) = \sigma\theta(1 + \beta_p\varkappa_p \frac{\eta_p}{\delta_p}\frac{1}{R_{p\theta\sigma}}\right)$$

At $E^*_\times$, the eigen-values of matrix $J_{4\sigma 1}$ is identical to those $C = A + B$ and $D = A - B$

$$C = \begin{bmatrix} c_{1,1} & c_{1,2} & c_{1,3} \\ c_{2,1} & c_{2,2} & 0 \\ a_{3,1} & a_{3,2} & a_{3,3} \end{bmatrix}, \quad D = \begin{bmatrix} d_{1,1} & d_{1,2} & d_{1,3} \\ d_{2,1} & d_{2,2} & 0 \\ d_{3,1} & d_{3,2} & d_{3,3} \end{bmatrix}$$

where

$$
\begin{aligned}
c_{1,1} &= -\delta_p - \theta - \alpha_p\kappa_p\frac{\eta_p}{\delta_p+m_p}(1-\frac{1}{R_{p\theta\sigma}}) + \theta\left(1-\beta_p\varkappa_p\frac{\eta_p}{\delta_p+m_p}(1-\frac{1}{R_{p\theta\sigma}})\right)\\
&= -\delta_p - \frac{R_{p\theta}}{\delta_P}(1-\frac{1}{R_{p\theta\sigma}}),\\
c_{1,2} &= -\alpha_p\kappa_p\frac{\eta_p}{\delta_p}\frac{1}{R_{p\theta\sigma}} - \theta\beta_p\varkappa_p\frac{\eta_p}{\delta_p}\frac{1}{R_{p\theta\sigma}} = \frac{R_{p\theta}}{(\delta_P+m_p)}\frac{1}{R_{p\theta\sigma}},\\
c_{1,3} &= r_p,\\
c_{2,1} &= \alpha_p\kappa_p\frac{\eta_p}{\delta_p+m_p}(1-\frac{1}{R_{p\theta\sigma}}) + (1-\sigma)\theta\beta_p\varkappa_p\frac{\eta_p}{\delta_p+m_p}\left(1-\frac{1}{R_{p\theta\sigma}}\right),\\
&= \frac{1}{\delta_p}(R_p - R_{p\beta})(1-\frac{1}{R_{p\theta\sigma}}),\\
c_{2,2} &= \alpha_p\kappa_p\frac{\eta_p}{\delta_p}\frac{1}{R_{p\theta\sigma}} - (\delta_p+m_p) - \theta + (1-\sigma)\theta\left(1+\beta_p\varkappa_p\frac{\eta_p}{\delta_p}\frac{1}{R_{p\theta\sigma}}\right)
\end{aligned}
$$

$$
\begin{aligned}
c_{3,1} &= \sigma\theta\beta_p\varkappa_p\frac{\eta_p}{\delta_p+m_p}(1-\frac{1}{R_{p\theta\sigma}}) = \sigma\frac{R_{p\beta}}{\delta_p}\left(1-\frac{1}{R_{p\theta\sigma}}\right),\\
c_{3,2} &= \sigma\theta\left(1+\beta_p\varkappa_p\frac{\eta_p}{\delta_p}\frac{1}{R_{p\theta\sigma}}\right) = \sigma\left(\theta+\frac{R_{p\beta}}{\delta_p+m_p}\frac{1}{R_{p\theta\sigma}}\right)\\
c_{3,3} &= -(r_p+m_c)
\end{aligned}
$$

and

$$
\begin{aligned}
d_{1,1} &= -\delta_p - \theta - \alpha_p\kappa_p\frac{\eta_p}{\delta_p+m_p}(1-\frac{1}{R_{p\theta\sigma}}) - \theta\left(1-\beta_p\varkappa_p\frac{\eta_p}{\delta_p+m_p}(1-\frac{1}{R_{p\theta\sigma}})\right)\\
&= -\delta_p - 2\theta - \frac{1}{\delta_p}(R_p - R_{p\beta})(1-\frac{1}{R_{p\theta\sigma}}),\\
d_{1,2} &= -\alpha_p\kappa_p\frac{\eta_p}{\delta_p}\frac{1}{R_{p\theta\sigma}} + \theta\beta_p\varkappa_p\frac{\eta_p}{\delta_p}\frac{1}{R_{p\theta\sigma}}\\
&= -\frac{1}{(\delta_p+mp)}(R_p - R_{p\beta})(1-\frac{1}{R_{p\theta\sigma}}),\\
d_{1,3} &= r_p\\
d_{2,1} &= \alpha_p\kappa_p\frac{\eta_p}{\delta_p+m_p}(1-\frac{1}{R_{p\theta\sigma}}) - (1-\sigma)\theta\beta_p\varkappa_p\frac{\eta_p}{\delta_p+m_p}\left(1-\frac{1}{R_{p\theta\sigma}}\right)\\
&= -\frac{1}{\delta_p}(\sigma R_{p\theta} - R_{p\beta})(1-\frac{1}{R_{p\theta\sigma}}),\\
d_{2,2} &= \alpha_p\kappa_p\frac{\eta_p}{\delta_p}\frac{1}{R_{p\theta\sigma}} - (\delta_p+m_p) - \theta - (1-\sigma)\theta\left(1+\beta_p\varkappa_p\frac{\eta_p}{\delta_p}\frac{1}{R_{p\theta\sigma}}\right)\\
&= \theta(\sigma-2)\frac{1}{(\delta_p+m_p)}(R_{p\theta} - R_{p\beta})\frac{1}{R_{p\theta\sigma}},\\
d_{3,1} &= -\sigma\theta\beta_p\varkappa_p\frac{\eta_p}{\delta_p+m_p}\left(1-\frac{1}{R_{p\theta\sigma}}\right) = -\sigma\frac{R_{p\beta}}{\delta_p}\left(1-\frac{1}{R_{p\theta\sigma}}\right),\\
d_{3,2} &= -\sigma\theta\left(1+\beta_p\varkappa_p\frac{\eta_p}{\delta_p}\frac{1}{R_{p\theta\sigma}}\right) = -\sigma\left(\theta+\frac{R_{p\beta}}{\delta_p+m_p}\frac{1}{R_{p\theta\sigma}}\right)\\
d_{3,3} &= -(r_p+m_c).
\end{aligned}
$$

Note that matrices A and B have the same form as following

$$
M = \begin{bmatrix} m_{1,1} & m_{1,2} & m_{1,3}\\ m_{2,1} & m_{2,2} & 0\\ m_{3,1} & m_{3,2} & m_{3,3}\end{bmatrix}.
$$

For this kind of matrix, the following Routh-Hurwitz theorem is stated as follows,

Theorem 6.6. *Routh-Hurwitz. Let $\chi_1 = -tr(M)$, $\chi_2 = M_1 + M_2 + M_3$ and $\chi_3 = det(M)$, where $M_1 = m_{1,1}m_{2,2} - m_{2,1}m_{1,2}$, $M_2 = m_{1,1}m_{3,3} - m_{3,1}m_{1,3}$ and $M_1 = m_{2,2}m_{3,3}$. Then M is stable (i.e each of eigen value of M has negative real part) if and only if the following conditions hold:*

(i) $\chi_1 > 0$,

(ii) $\chi_3 > 0$,

(iii) $\chi_1\chi_2 - \chi_3 > 0$.

Here $det(M)$ is the determinant of matrix M and $tr(M)$ is the trace of matrix M, it is the sum of the diagonal elements of M.

First, consider the matrix $C = A + B$. It is required to show that $\chi_1 = tr(C) > 0$. Given $0 \leq \theta \leq 1$, $R_{p\theta\sigma} > 1$. It is obvious that the diagonal elements are all negative. $C_{1,1} = -\delta_p - \frac{R_{p\theta}}{\delta_P}(1 - \frac{1}{R_{p\theta\sigma}}) < 0$, $c_{2,2} = \alpha_p\kappa_p\frac{\eta_p}{\delta_p}\frac{1}{R_{p\theta\sigma}} - (\delta_p + m_p) - \theta + (1-\sigma)\theta\left(1 + \beta_p\varkappa_p\frac{\eta_p}{\delta_p}\frac{1}{R_{p\theta\sigma}}\right) < 0$ and $c_{3,3} = -(r_p + m_c) < 0$. Hence, $tr(M) = C_{1,1} + C_{2,2} + C_{3,3} < 0$ and $\chi_1 = -tr(M) > 0$. $c_{2,1} > 0, c_{3,2} \geq 0, c_{1,3} > 0$. It is ease to show that $M_i > 0$ for all $i = 1, 2, 3$. Therefore, by Theorem 6.6, matrix $C = A + B$ is stable. Similarly, it is ease to proof that matrix $D = A - B$ is stable. Hence, at $\mathcal{E}^*_{4\sigma} = (S^*_{p4\sigma}, I^*_{p4\sigma}, S^*_{p4\sigma}, I^*_{p4\sigma})$ the key Jacobian matrix $J_{4\theta 1}$ is stable.

The second and third key Jacobian matrices

$$J_{4\sigma 2} = J_{4\sigma 3} = \begin{bmatrix} j_{3,3} & j_{3,4} & 0 & 0 & j_{3,7} \\ 0 & j_{4,4} & 0 & 0 & 0 \\ j_{5,3} & j_{5,4} & j_{5,5} & 0 & 0 \\ j_{6,3} & 0 & 0 & j_{6,6} & 0 \\ 0 & j_{7,4} & 0 & 0 & j_{7,7} \end{bmatrix} \text{ for k} = 1, \ldots 4$$

where $j_{1,1} = (-1)\delta_p(\alpha_p\kappa_p I^*_{p_{4\sigma}})$, $j_{1,2} = -\alpha_p\kappa_p S^*_{p_{4\sigma}}$, $j_{2,1} = \alpha_p\kappa_p I^*_{p_\sigma} - (\delta_p + m_p)$, $j_{2,2} = \alpha_p\kappa_p S^*_{p_{4\sigma}} - (\delta_p + m_p) = 0$, $j_{3,3} = (-1)(\delta_h + \alpha_{ph}\kappa_{ph} I^*_{p_{4\sigma}})$, $j_{3,4} = (-1)\alpha_{sh}\kappa_{sh} S^*_{h_4}$, $j_{3,7} = (-1)\alpha_{mh}\kappa_{mh} S^*_{h_4}$, $j_{4,4} = (-1)\alpha_{sh}\kappa_{sh} S^*_{h_{4\sigma}} - (\delta_h + m_s)$, $j_{5,3} = \gamma\alpha_{ph}\kappa_{ph} I^*_{p_{4\sigma}}$, $j_{5,4} = (-1)\mu\alpha_{sa}\kappa_{sa} I^*_{a_{4\sigma}}$, $j_{5,5} = (-1)(\delta_h + m_a)$, $j_{6,3} = (1-\gamma)\alpha_{ph}\kappa_{ph} I^*_{p_{4\sigma}}$, $j_{6,6} = (-1)(\delta_h + m_b)$, $j_{7,4} = \mu\alpha_{sa}\kappa_{sa} I^*_{a_{4\sigma}}$, $j_{7,7} = \alpha_{mh}\kappa_{mh} S^*_{h_{4\sigma}} + (\delta_h + m_m)$.

Next for the other key Jacobian matrices, B_{4k}, $k = 1, \ldots, 4$. Results from Subsection 4.5.6 show that

$$|\lambda I - J_{4\sigma 2}| = |\lambda I - J_{4\sigma 3}| = \Pi_{k=3}^{7}(\lambda - j_{k,k}) = 0$$

with $j_{k,k}$, $i = 1, \ldots 7$ are all real negatives. Furthermore, the matrix $J_{4\sigma 2}$ and $J_{4\sigma 3}$ stable if

$$\alpha_{sh}\kappa_{sh}\frac{\frac{\eta_h}{\delta_h}}{1 + r_{p\theta\sigma}} - (\delta_h - m_s) < 0 \Leftrightarrow \frac{\eta_h\alpha_{sh}\kappa_{sh}}{\delta_h(\delta_h - m_s)} < 1 + r_{p\theta\sigma}$$
$$\Leftrightarrow R_{sh} < 1 + r_{p\theta\sigma}$$

and

$$\alpha_{mh}\kappa_{sh}\frac{\frac{\eta_h}{\delta_h}}{1 + r_{p\theta\sigma}} - (\delta_h - m_m) < 0 \Leftrightarrow \frac{\eta_h\alpha_{mh}\kappa_{mh}}{\delta_h(\delta_h - m_m)} < 1 + r_{p\theta\sigma}$$
$$\Leftrightarrow R_{mh} < 1 + r_{p\theta\sigma}$$

Therefore $Z^*_{4\sigma}$ well-defined and stable if $R_{p\theta\sigma} > 1$ and $\max\{R_{sh}, R_{mh}\} < 1 + r_{p\theta\sigma}$. Therefore $Z^*_{4\sigma}$ is LAS. □

6.6.5 *Stability analysis of avian flu epidemic among birds and humans combined with mutant avian flu epidemic among humans*

The disease state equilibrium point Z^*_5 corresponds to the situation in which there are avian flu epidemic among birds and humans combined with mutant avian flu epidemic among humans,

$$Z^*_{5\sigma} = (Z^*_{5t}, Z^*_{5t}) \tag{6.39}$$

with

$$Z^*_{5t} = (S^*_{p_{5\sigma}}, I^*_{p_{5\sigma}}, C^*_{p_{5\sigma}}, S^*_{h_{5\sigma}}, 0, I^*_{a_{5\sigma}}, I^*_{b_{5\sigma}}, I^*_{m_{5\sigma}}),$$

where

$$S^*_{p_{5\sigma}} = S^*_{p_\otimes} = \frac{\eta_p}{\delta_p}\frac{1}{R_{p\theta\sigma}} > 0$$
$$I^*_{p_{5\sigma}} = I^*_{p_\otimes} = \frac{\eta_p}{\delta_p + m_p}(1 - \frac{1}{R_{p\theta\sigma}}) > 0$$
$$C^*_{p_{5\sigma}} = C^*_{p_\otimes} == \frac{\sigma\theta}{(r_p + m_c)} + \frac{\eta_p}{(r_p + m_c)}\frac{R_{p\beta}}{R_{p\theta\sigma}}(1 - \frac{1}{R_{p\theta\sigma}})$$

$$S^*_{p_{5\sigma}} = \frac{\delta_p + m_p}{\alpha_p\kappa_p} = \frac{\eta_p}{\delta_p}\frac{1}{R_{p\theta\sigma}}$$

Now (4.20c) gives

$$I^*_{m_{5\sigma}} = \frac{\delta_h}{\alpha_{mh}\kappa_{mh}}\left[R_{mh} - (1 + r_{p\theta\sigma})\right].$$

where $r_{p\theta\sigma}$ is defined by (5.32)

$$r_{ph} = \frac{\alpha_{ph}\kappa_{ph}\eta_p}{\eta_h\ (\delta_p + m_p)}\left(1 - \frac{1}{R_{p\theta\sigma}}\right).$$

Therefore for $I^*_{m_5} > 0$ it is necessary that $R_{mh} > 1 + r_{ph}$. Finally (4.20d) and (4.20e) give

$$I^*_{a_{5\sigma}} = \frac{\gamma\eta_h r_{ph}}{(\delta_h + m_a)R_{mh}} > 0$$

and

$$I^*_{b_{5\sigma}} = \frac{(1-\gamma)\eta_h r_{ph}}{(\delta_h + m_b)R_{mh}}.$$

Theorem 6.7. *If $R_{p\theta\sigma} > 1$ and $R_{mh} > \max\{R_{sh}, 1 + r_{ph}\}$ then $Z^*_{5\sigma} = (Z^*_{5t}, Z^*_{5t})$ is LAS.*

Proof. At $\bar{Z}^*_{5\sigma}$ the Jacobian matrix (6.32) becomes

$$\mathcal{J}_{5\sigma} = \mathcal{J}(\bar{Z}^*_{5\sigma}) = \begin{bmatrix} J_{5\sigma 1} & O_1 & O_1 \\ J_4 & J_{5\sigma 2} & O_3 \\ J_5 & O_3 & J_{5\sigma 3} \end{bmatrix}.$$

The first key Jacobian matrix is given by (6.38)

$$J_{5\sigma 1} = \begin{bmatrix} A & B \\ B & A \end{bmatrix}$$

Result from the last section show that at $E^*_{\oplus}$ the key Jacobian matrix $J_{5\sigma 1}$ is stable. and

$$J_{5\sigma 2} = J_{4\sigma}3 = \begin{bmatrix} j_{3,3} & j_{3,4} & 0 & 0 & j_{3,7} \\ 0 & j_{4,4} & 0 & 0 & 0 \\ j_{5,3} & j_{5,4} & j_{5,5} & 0 & 0 \\ j_{6,3} & 0 & 0 & j_{6,6} & 0 \\ j_{7,3} & j_{7,4} & 0 & 0 & j_{77} \end{bmatrix} \text{ fork} = 1, \ldots, 4$$

where $j_{1,1} = (-1)\delta_p(\alpha_p\kappa_p I^*_{p_{5\sigma}})$, $j_{1,2} = -\alpha_p\kappa_p S^*_{p_{5\sigma}}$, $j_{2,1} = \alpha_p\kappa_p I^*_{p_{5\sigma}} - (\delta_p + m_p)$, $j_{2,2} = \alpha_p\kappa_p S^*_{p_{5\sigma}} - (\delta_p + m_p)$, $j_{3,3} = (-1)(\delta_h + \alpha_{ph}\kappa_{ph} I^*_{p_{5\sigma}} + \alpha_{mh}\kappa_{mh} I^*_{m_{5\sigma}})$, $j_{3,4} = (-1)\alpha_{sh}\kappa_{sh} S^*_{h_{5\sigma}}$, $j_{3,7} = (-1)\alpha_{mh}\kappa_{mh} S^*_{h_{5\sigma}}$, $j_{4,4} = (-1)\alpha_{sh}\kappa_{sh} S^*_{h_{5\sigma}} - (\delta_h + m_s)$, $j_{5,3} = \gamma\alpha_{ph}\kappa_{ph} I^*_{p_{5\sigma}}$, $j_{5,4} = (-1)\mu\alpha_{sa}\kappa_{sa} I^*_{a_{5\sigma}}$, $j_{5,5} = (-1)(\delta_h + m_a)$, $j_{6,3} = (1-\gamma)\alpha_{ph}\kappa_{ph} I^*_{p_{5\sigma}}$, $j_{6,6} = (-1)(\delta_h + m_b)$, $j_{7,3} = \alpha_{mh}\kappa_{mh} I^*_{m_{5\sigma}}$, $j_{7,4} = \mu\alpha_{sa}\kappa_{sa} I^*_{a_{5\sigma}}$, $j_{7,7} = \alpha_{mh}\kappa_{mh} S^*_{h_{5\sigma}} + (\delta_h + m_m)$.

A result from Sub-section 5.6.4, the key jacobian matrices c is stable at $E^*_{\otimes}$). Hence, the key jacobian matrix $J_{5\sigma 1}$ is stable at $E^*_{\otimes}$).

Results from Sub-section 4.5.6 show that

$$|\lambda I - J_{5\sigma 2}| = |\lambda I - J_{5\sigma 3}| = \left[\Pi_{k=3}^{7}(\lambda - j_{k,k})\right][\lambda^2 + b\lambda + c] = 0$$

where

$$b = \frac{\alpha_{mh}\kappa_{mh}\eta_h}{\delta_h + m_m} > 0$$

and

$$c = \alpha_{mh}\kappa_{mh}I^*_{m_5}\alpha_{mh}\kappa_{mh}S^*_{h_5} > 0$$

If $I(S^*_{h_{5\sigma}}, t) > 0$ then $I(S^*_{h_{5\sigma}}, t) \downarrow 0$ as $t \uparrow \infty$. Hence this is effectively a stability condition for the coordinate $I^*_{s_{5\sigma}} = 0$. Since

$$\alpha_{sh}\kappa_{sh}S^*_{h_5} - (\delta_h + m_s) < 0 \Leftrightarrow \alpha_{sh}\kappa_{sh}\frac{(\delta_h + m_m)}{\alpha_{mh}\kappa_{mh}} - (\delta_h + m_s) < 0$$
$$\Leftrightarrow R_{sh} < R_{mh}.$$

Therefore, $Z^*_{5\sigma}$ is well-defined and stable if $R_p > 1$ and $R_{mh} > \max\{R_{sh}, 1 + r_{ph}\}$. □

6.7 Simulation

The estimated values of the epidemiological parameters and the population parameters used in the numerical simulation are adopted from Chapters 4 and 5. The variation on screening probability represent the commitment of each region on preventing the spread of disease from outside. When an infected bird is identified, it will be culled and disposed. As expected, the probability of successful border screening affects the proportion culled birds. Increasing the probability of successful border screening that is implemented at the entry point of a region i, σ_i, will increase the proportion of culled birds at the region i.

Following the scenario was developed in Chapter 4, poultry chickens from Central Java are transported to West Java and Jakarta. Some chicken in Jakarta markets are re-transported to Banten and then to Lampung in Sumatra. To see the effect of screening and subsequent culling policies, it is assumed that the set of policies is implemented in the entry points to Jakarta to prevent the spread of avian flu from Central and West Java.

In the simulation, the probability of successful border screening at east entry points of Jakarta is assumed to be 0.5, $\sigma_3 = 0.5$. Fig. 6.1 shows the dynamics of culled birds in the provinces. Since the set of policies is implemented at the east border of Jakarta only, there are no culled birds in Central Java, West Java, Banten and Lampung except Jakarta. The policy implemented at the East border of Jakarta affects the proportion of infected birds outside Jakarta, Banten and Lampung. Figure 6.1 shows that the policies do not affect the disease dynamics in Central and West Java, but it does affect the disease dynamics in Jakarta, Banten and Lampung. In these provinces, the

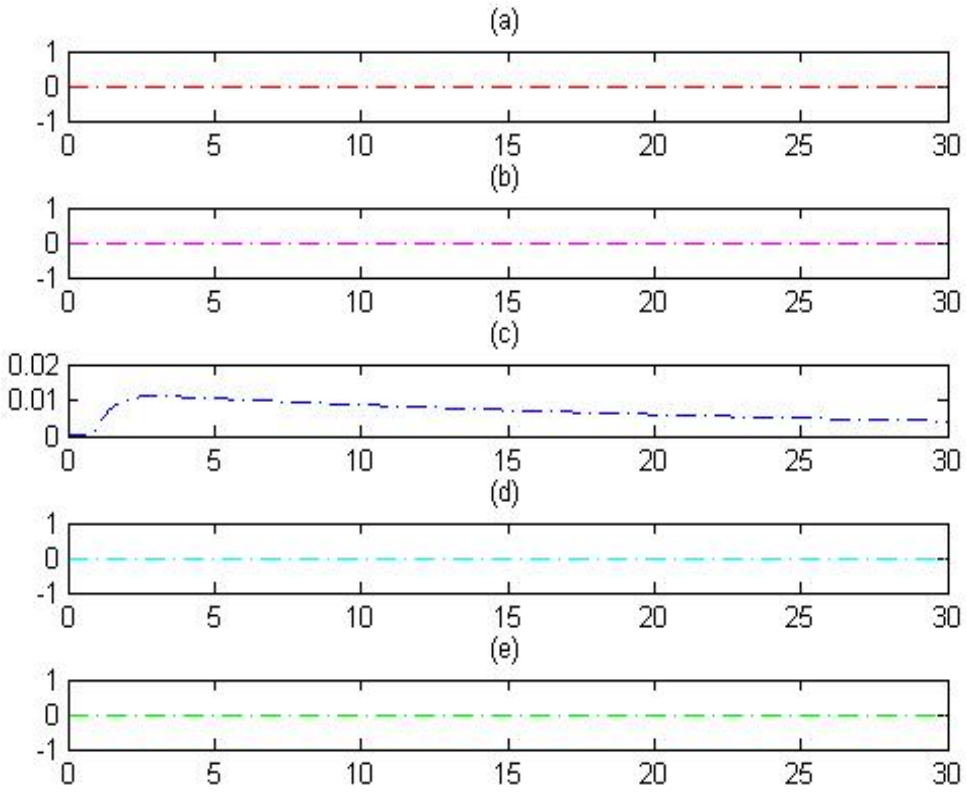

Fig. 6.1: The proportion of culled birds in the provinces as a result of the implementation of screening and subsequent culling policies with $\sigma_3 = 0.5$ at east borders of Jakarta. The horizontal axis is time in days. (a), (b), (c), (d) and (e) are the proportion of infected birds in Central Java, West Java, Jakarta, Banten and Lampung respectively.

proportion of infected birds are reduced.

The policy implemented at the East border of Jakarta also affects the dynamics of diseases of humans in Jakarta, Banten and Lampung. Variations in σ_3 have no effect to the dynamics of human diseases in Central Java and West Java. It has significant effects on the spread of diseases among humans in Jakarta, Banten and Lampung (Figures 6.3 - 4.4).

6.8 Discussion

Implementing entry screening policies for infectious birds entering a region is effective in reducing the spread of disease among birds and humans in the region. Increasing the probability of successful screening of birds entering a region will decrease the magnitude of disease among birds and humans in the region at the expense of increased costs of screening and culling.

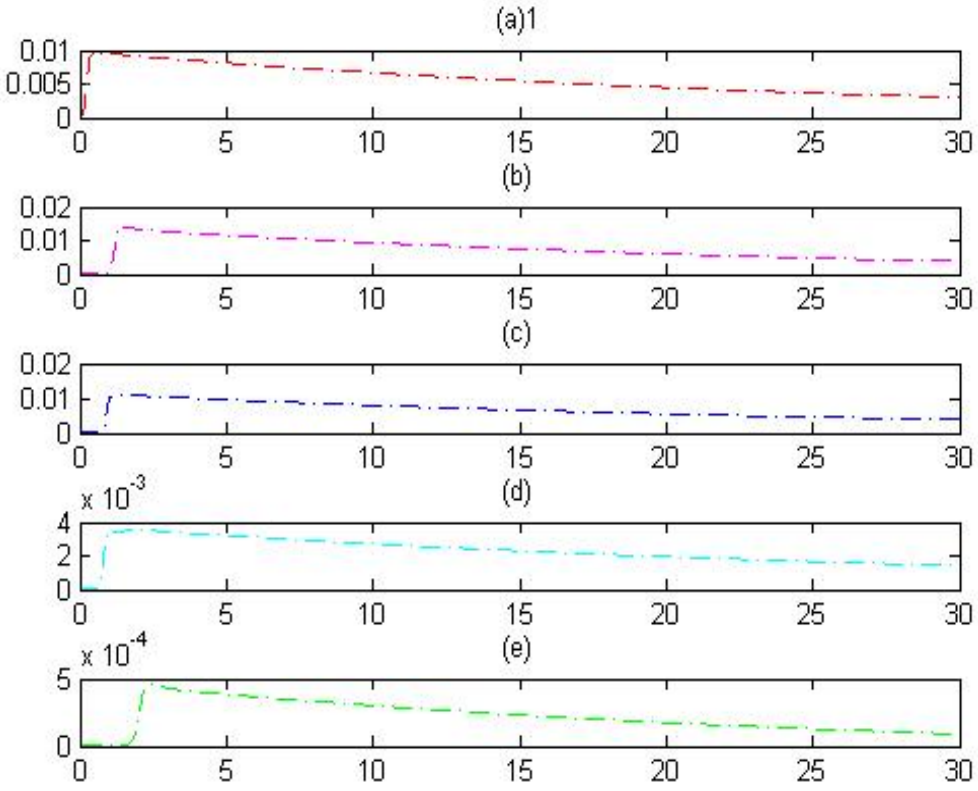

Fig. 6.2: The proportion of infectious birds in the provinces as a result of the implementation of screening and subsequent culling policies with $\sigma_3 = 0.5$ at the East borders of Jakarta. The horizontal axis is time in days. (a), (b), (c), (d) and (e) are the proportion of infected birds in Central Java, West Java, Jakarta, Banten and Lampung respectively.

By Theorem 5.2 disease eradication among birds and humans in both regions is possible. Theorems 5.3, 5.4, 5.5 and 5.6 however, show that the disease free states among birds does not guarantee disease free states among humans.

In the case of $R_{p\sigma\sigma} > 1$ avian flu is endemic among birds in both regions. In this case there are two possible endemic states; avian flu is endemic among birds and humans or avian flu is endemic among birds and humans but with mutant-avian flu present in humans. The disease will be endemic among birds and humans in both regions in the sense of permanence, which means that the number of infected birds and humans will be bounded below by positive constants which are independent of initial values.

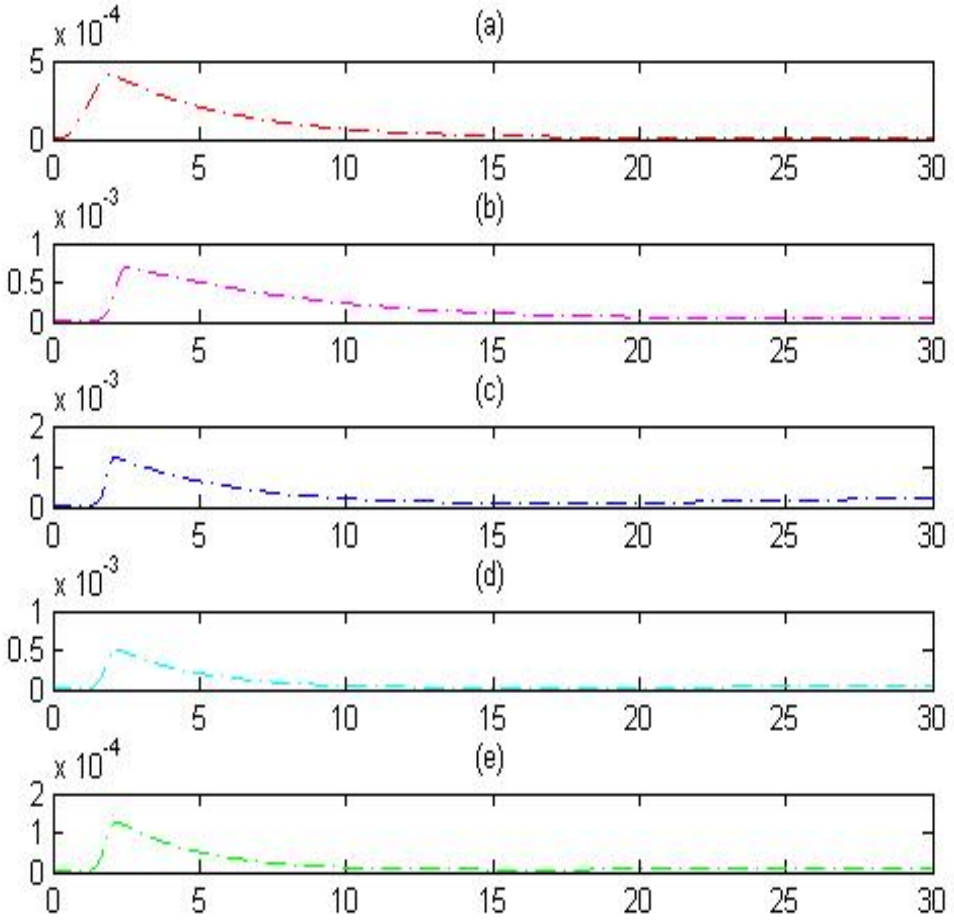

Fig. 6.3: The proportion of human cases in the five provinces as a result of the implementation of screening and subsequent culling policies with $\sigma_3 = 0.5$ at the East borders of Jakarta. The horizontal axis is time in days. (a), (b), (c), (d) and (e) are the proportion of human case in Central Java, West Java, Jakarta, Banten and Lampung respectively.

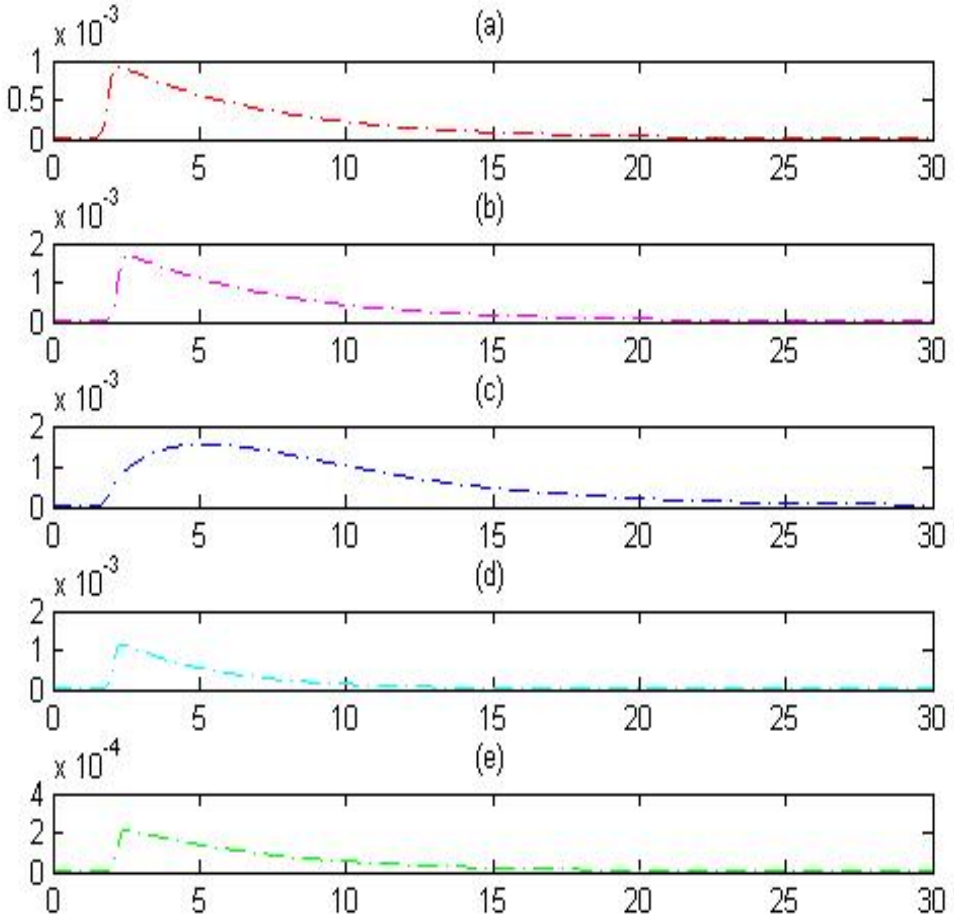

Fig. 6.4: The proportion of infected human with Mutant avian-flu in the five provinces as a result of the implementation of screening and subsequent culling policies with $\sigma_3 = 0.5$ at the East borders of Jakarta. The horizontal axis is time in days. (a), (b), (c), (d) and (e) are the proportion of infectious humans with Mutant avian-flu in Central Java, West Java, Jakarta, Banten and Lampung respectively.

7. CONTROLLING THE SPREAD OF DISEASE

Studies of uncontrolled systems in Chapter 4 showed that, even if there are disease free equilibria, it usually takes a long time for the disease to disappear. Therefore, the disease may cause a large number of casualties among birds and humans.

Results in Chapter 6 show that implementing screening policies for infectious birds entering a region is effective for reducing the spread of disease among birds and humans in the region. Increasing the probability of successful screening of birds entering a region will decrease the impact of the disease among birds and humans in the region at the expense of increased costs of screening and culling. This indicates some trade-off is required between the level of screening and the impact of the disease. This is particularly important in Indonesia where resources for screening and culling programs and other forms in intervention are limited. Therefore, it is of interest to devise disease control policies such that the disease can be contained in a relatively short period of time possibly with some economic trade-off.

This chapter develops models for analyzing and interpreting the effect of the implementation of control policies in order to develop a strategy that is optimal subject to limited resources.

The screening of birds discussed in Chapter 6 is a control measure but was presented as a fixed program over time and and was not optimized in any way. The control measures discussed in this chapter are time dependent. The key question is given limited resources for implementing a control measure, what should the level of control be, viewed as a function of time, so as to maximize the effect of the control measure.

Section 7.3 outlines a disease control problem. The necessary condition for the existence of an optimal control is given in Section 7.4. Finally, Section 7.6 discusses some results of the study. Section 7.5 outlines an indirect method algorithm for solving the optimal disease control problem (ODCP) in the simulation study.

7.1 Uncontrolled system

Recall from Chapter 4 that the disease dynamics in a single region is governed by the initial value problem (IVP) (4.3a)-(4.3h)

$$S_p' = \eta_p - \delta_p S_p - \alpha_p \kappa_p I_p S_p \tag{7.1a}$$

$$I_p' = \alpha_p \kappa_p I_p S_p - (\delta_p + m_p)\, I_p \tag{7.1b}$$

$$S_h' = \eta_h - \delta_h\, S_h - \alpha_{ph}\kappa_{ph} I_p S_h - \alpha_{sh}\kappa_{sh} I_s S_h - \alpha_{mh}\kappa_{mh} I_m S_h \tag{7.1c}$$

$$I_s' = \alpha_{sh}\kappa_{sh} I_s S_h - (\delta_h + m_s)\, I_s \tag{7.1d}$$

$$I_a' = \gamma\alpha_{ph}\kappa_{ph} I_p S_h - \mu\alpha_{sa}\kappa_{sa} I_s I_a - (\delta_h + m_a)\, I_a \tag{7.1e}$$

$$I_b' = (1-\gamma)\alpha_{ph}\kappa_{ph} I_p S_h - (\delta_h + m_b)\, I_b \tag{7.1f}$$

$$I_m' = \mu\alpha_{sa}\kappa_{sa} I_s I_a + \alpha_{mh}\kappa_{mh} I_m S_h - (\delta_h + m_m)\, I_m, \tag{7.1g}$$

$$Z(0) = Z_0,\ Z_0 \in [0,T] \times \mathbb{R}^7. \tag{7.1h}$$

Where the set of epidemic parameters $Q_1 \subseteq \mathbb{R}_+^{21}$

$$\begin{aligned} Q_1 \quad = \quad & \{\, \eta_p, \eta_h, \delta_p, \delta_h, \alpha_p, \alpha_{sh}, \alpha_{ph}, \mu, \alpha_{sa}, \alpha_{mh}, \kappa_p, \kappa_{sh}, \kappa_{ph}, \kappa_{sa}, \kappa_{mh}, \\ & m_p, m_a, m_b, m_s, m_m, \gamma \} \end{aligned}$$

are defined in Section 4.1. The basic reproduction numbers of avian flu transmission in the bird world is given by (4.6) as

$$R_p = \frac{\eta_p\, \alpha_p \kappa_p}{\delta_p\ (\delta_p + m_p)}. \tag{7.2}$$

The basic reproduction number of swine flu transmission among humans is given by (4.7) as

$$R_{sh} = \frac{\eta_h\, \alpha_{sh}\kappa_{sh}}{\delta_h\, (\delta_h + m_s)}. \tag{7.3}$$

the basic reproduction number of mutant-avian flu transmission among humans is given by (4.8) as

$$R_{mh} = \frac{\eta_h\, \alpha_{mh}\kappa_{mh}}{\delta_h\, (\delta_h + m_m)} \tag{7.4}$$

7.2 Designing the disease controls

The sensitivity analysis of the basic reproduction numbers R_p, R_{sh} and R_{mh} in Section 4.7.2 shows that R_p is the most sensitive to κ_p, R_{sh} is the most sensitive to κ_{sh} and R_{mh} is the most sensitive to κ_{mh}. These results show that the contact intensities between infected and susceptible individuals, κ_p, κ_{sh} and κ_{mh} are the most feasible parameters to be controlled for reducing the transmission of the diseases.

Let $\varphi_p(t)$ be the disease control function that aims to reduce the transmission of avian flu among birds. In principle, the control functions could have been defined to target different control strategies. For example $\varphi_p(t)$ could been chosen to target farming methods that influence the level of contact between families and their poultry and the control measures $\varphi_{sh}(t)$ and $\varphi_{mh}(t)$ could have been defined to target social

distancing programs. These were not developed further in light of the discussions at the beginning or this chapter and the beginning of the previous chapter.

The disease control functions $\varphi_p(t)$ is implemented into the system in such a way that the rates of change of infected humans are modeled using relatively simple extensions of the uncontrolled system (7.1a)-(7.1g). In order to increase the number of susceptible birds, (7.1a) is modified into

$$S_p' = \eta_p - \delta_p S_p - \alpha_p \kappa_p (1 - \varphi_p) I_p S_p,$$

In order to decrease the number of infected birds, (7.1b) is modified into

$$I_p' = \alpha_p \kappa_p (1 - \varphi_p) I_p S_p - (\delta_p + m_p) I_p,$$

. $\varphi_{sh}(t), \varphi_{ph}(t)$ and $\varphi_{mh}(t)$ are implanted into the system in a similar way.

7.3 Optimal disease control problem

The problem of designing optimal disease control policies is equivalent to the problem of finding *optimal policies* $\varphi^*(t) = (\varphi_p^*(t), \varphi_{sh}^*(t), \varphi_{mh}^*(t))$ such that

$$J^*(\varphi) = \min_{\varphi \in \Phi} J(\varphi) \tag{7.5}$$

where

$$J(\varphi) = \int_a^{t_F} \left(\frac{C_p}{2} \varphi_p^2 + \frac{C_{sh}}{2} \varphi_{sh}^2 + \frac{C_{mh}}{2} \varphi_{mh}^2 - S_p(t) - S_h(t) \right) \mathrm{d}t. \tag{7.6}$$

subject to the disease state constraints

$$S_p' = \eta_p - \delta_p S_p - \alpha_p \kappa_p (1 - \varphi_p) I_p S_p, \tag{7.7a}$$
$$I_p' = \alpha_p \kappa_p (1 - \varphi_p) I_p S_p - (\delta_p + m_p) I_p, \tag{7.7b}$$
$$S_h' = \eta_h - \delta_h S_h - \alpha_{ph} \kappa_{ph} I_p S_h - \alpha_{sh} \kappa_{sh} (1 - \varphi_{sh}) I_s S_h \tag{7.7c}$$
$$- \alpha_{mh} \kappa_{mh} (1 - \varphi_{mh}) I_m S_h, \tag{7.7d}$$
$$I_s' = \alpha_{sh} \kappa_{sh} (1 - \varphi_{sh}) I_s S_h - (\delta_h + m_s) I_s, \tag{7.7e}$$
$$I_a' = \gamma \alpha_{ph} \kappa_{ph} I_p S_h - \mu \alpha_{sa} \kappa_{sa} I_s I_a - (\delta_h + m_a) I_a, \tag{7.7f}$$
$$I_b' = (1 - \gamma) \alpha_{ph} \kappa_{ph} I_p S_h - (\delta_h + m_b) I_b \tag{7.7g}$$
$$I_m' = \mu \alpha_{sa} \kappa_{sa} I_s I_a + \alpha_{mh} \kappa_{mh} (1 - \varphi_{mh}) I_m S_h - (\delta_h + m_m) I_m \tag{7.7h}$$

and the control constraints

$$0 \leq \varphi_p \leq \varphi_p^U \leq 1, \tag{7.8a}$$
$$0 \leq \varphi_{sh} \leq \varphi_{sh}^U \leq 1, \tag{7.8b}$$
$$0 \leq \varphi_{mh} \leq \varphi_{mh}^U \leq 1. \tag{7.8c}$$

The problem of finding an optimal policy $\varphi^*(t) = (\varphi_p^*(t), \varphi_{sh}^*(t), \varphi_{mh}^*(t))$ is referred to as optimal disease control problem (ODCP).

7.4 Necessary conditions for the optimality of the disease controls

In this section the emphasis is on setting the necessary conditions for optimality of the ODCP based on Theorem 3.30, the Pontryagins maximum principle. Consider the Hamiltonian function

$$\begin{aligned}
\mathcal{H} &= (-1)\left[\frac{C_p}{2}\varphi_p^2 + \frac{C_{sh}}{2}\varphi_{sh}^2 + \frac{C_{mh}}{2}\varphi_{mh}^2 - S_p(t) - S_h(t)\right] \\
&+ \zeta_p[\eta_p - \delta_p S_p - \alpha_p\kappa_p(1-\varphi_p)I_p S_p] \qquad (7.9)\\
&+ \xi_p[\alpha_p\kappa_p(1-\varphi_p)I_p S_p - (\delta_p + m_p)I_p] \\
&+ \zeta_h[\eta_h - \delta_h S_h - \alpha_{ph}\kappa_{ph}I_p S_h \qquad (7.10)\\
&- \alpha_{sh}\kappa_{sh}(1-\varphi_{sh})I_s S_h] \\
&+ \xi_s[\alpha_{sh}\kappa_{sh}(1-\varphi_{sh})I_s S_h - (\delta_h + m_s)I_s] \\
&+ \xi_a[\gamma\alpha_{ph}\kappa_{ph}I_p S_h - \mu\alpha_{sa}\kappa_{sa}I_s I_a - (\delta_h + m_a)I_a], \\
&+ \xi_b[(1-\gamma)\alpha_{ph}\kappa_{ph}I_p S_h - (\delta_h + m_b)I_b] \\
&+ \xi_m[\mu\alpha_{sa}\kappa_{sa}I_s I_a + \alpha_{mh}\kappa_{mh}(1-\varphi_{mh})I_m S_h - (\delta_h + m_m)I_m] \qquad (7.11)
\end{aligned}$$

where the adjoint variables $\zeta_p, \xi_p, \zeta_h, \xi_s, \xi_a, \xi_b, \xi_m$ are defined by the linear differential equations

$$\zeta_p' = -1 + [\delta_p + \alpha_p\kappa_p(1-\varphi_p)I_p]\zeta_p - \alpha_p\kappa_p(1-\varphi_p)I_p\xi_p, \tag{7.12a}$$
$$\begin{aligned}
\xi_p' &= \alpha_p\kappa_p(1-\varphi_p)S_p\zeta_p - \alpha_p\kappa_p(1-\varphi_p)S_p\xi_p - \gamma\alpha_{ph}\kappa_{ph}S_h\xi_a \\
&- (1-\gamma)\alpha_{ph}\kappa_{ph}S_h\xi_b,
\end{aligned} \tag{7.12b}$$
$$\begin{aligned}
\zeta_h' &= -1 + [\delta_h + \alpha_{ph}\kappa_{ph}I_p + \alpha_{sh}\kappa_{sh}(1-\varphi_{sh})I_s \\
&+ \alpha_{mh}\kappa_{mh}(1-\varphi_{mh})I_m]\xi_h - \alpha_{sh}\kappa_{sh}(1-\varphi_{sh})I_s\xi_s, \\
&- \gamma\alpha_{ph}\kappa_{ph}I_p\xi_a - (1-\gamma)\alpha_{ph}\kappa_{ph}I_p\xi_b - \alpha_{mh}\kappa_{mh}I_m\xi_m,
\end{aligned} \tag{7.12c}$$
$$\xi_s' = \alpha_{sh}\kappa_{sh}(1-\varphi_{sh})S_{sh}\zeta_h + [-\alpha_{sh}\kappa_{sh}(1-\varphi_{sh})I_s + (\delta_h + m_s)]\xi_s \tag{7.12d}$$

$$+\mu\alpha_{sa}\kappa_{sa}I_a\xi_a - \mu\alpha_{sa}\kappa_{sa}I_a\xi_m, \tag{7.12e}$$

$$\xi_a' = [\mu\alpha_{sa}\kappa_{sa}I_s + (\delta_h + m_a)]\xi_a - \mu\alpha_{sa}\kappa_{sa}I_s\xi_m \tag{7.12f}$$

$$\xi_b' = (\delta_h + m_b)\xi_b \tag{7.12g}$$

$$\xi_m' = \alpha_{mh}\kappa_{mh}(1-\varphi_{mh})S_h\xi_h + [-\alpha_{mh}\kappa_{mh}(1-\varphi_{mh})S_h, \\ +(\delta_h + m_m)]\xi_m. \tag{7.12h}$$

In order to maximize the Hamiltonian subject to the given control constraints. Consider the Lagrangian function

$$\mathcal{L} = \mathcal{H}+\nu_p\varphi_p+\vartheta_p(\varphi_p^U-\varphi_p)+\nu_{sh}\varphi_{sh}+\vartheta_{sh}(\varphi_{sh}^U-\varphi_{sh})+\nu_{mh}\varphi_{mh}+\vartheta_{mh}(\varphi_{mh}^U-\varphi_{mh}) \tag{7.13}$$

where $\nu_p, \vartheta_p, \nu_{sh}, \vartheta_{sh}, \nu_{mh}, \vartheta_{mh}$ are nonnegative Lagrange multipliers for the control constraints. Set the relevant partial derivatives equal to zero and apply the Karush-Kuhn-Tucker conditions to obtain

$$\frac{\partial\mathcal{L}}{\partial\varphi_p} = 0 \Rightarrow -C_p\varphi_p + (\zeta_p - \xi_p)\alpha_p\kappa_p I_p S_p + \nu_p - \vartheta_p = 0 \tag{7.14a}$$

$$\frac{\partial\mathcal{L}}{\partial\varphi_{sh}} = 0 \Rightarrow -C_{sh}\varphi_{sh} + (\zeta_{sh} - \xi_{sh})\alpha_{sh}\kappa_{sh}I_{sh}S_{sh} + \nu_{sh} - \vartheta_{sh} = 0 \tag{7.14b}$$

$$\frac{\partial\mathcal{L}}{\partial\varphi_{mh}} = 0 \Rightarrow -C_{mh}\varphi_{mh} + (\zeta_{mh} - \xi_{mh})\alpha_{mh}\kappa_{mh}I_{mh}S_{mh} + \nu_{mh} - \vartheta_{mh} = 0 \tag{7.14c}$$

and $\nu_p\varphi_p = 0, \vartheta_p(\varphi_p^U - \varphi_p) = 0, \nu_{sh}\varphi_{sh} = 0, \vartheta_{sh}(\varphi_{sh}^U - \varphi_{sh}) = 0, \nu_{mh}\varphi_{mh} = 0$ and $\vartheta_{mh}(\varphi_{mh}^U - \varphi_{mh}) = 0$. It follows that

$$\varphi_p = \begin{cases} 0 & \text{if } \zeta_p < \xi_p \\ \frac{(\zeta_p-\xi_p)\alpha_p\kappa_p I_p S_p}{C_p} & \text{if } 0 \le \frac{(\zeta_p-\xi_p)\alpha_p\kappa_p I_p S_p}{C_p} < \varphi_p^U \\ \varphi_p^U & \text{if } \varphi_p^U \le \frac{(\zeta_p-\xi_p)\alpha_p\kappa_p I_p S_p}{C_p} \end{cases} \tag{7.15a}$$

$$\varphi_{sh} = \begin{cases} 0 & \text{if } \zeta_{sh} < \xi_{sh} \\ \frac{(\zeta_{sh}-\xi_{sh})\alpha_{sh}\kappa_{sh} I_{sh} S_{sh}}{C_{sh}} & \text{if } 0 \le \frac{(\zeta_{sh}-\xi_{sh})\alpha_{sh}\kappa_{sh} I_{sh} S_{sh}}{C_{sh}} < \varphi_{sh}^U \\ \varphi_{sh}^U & \text{if } \varphi_{sh}^U \le \frac{(\zeta_{sh}-\xi_{sh})\alpha_{sh}\kappa_{sh} I_{sh} S_{sh}}{C_{sh}} \end{cases} \tag{7.15b}$$

$$\varphi_{mh} = \begin{cases} 0 & \text{if } \zeta_{mh} < \xi_{mh} \\ \frac{(\zeta_{mh}-\xi_{mh})\alpha_{mh}\kappa_{mh} I_{mh} S_{mh}}{C_{mh}} & \text{if } 0 \le \frac{(\zeta_{mh}-\xi_{mh})\alpha_{mh}\kappa_{mh} I_{mh} S_{mh}}{C_{mh}} < \varphi_{mh}^U \\ \varphi_{mh}^U & \text{if } \varphi_{mh}^U \le \frac{(\zeta_{mh}-\xi_{mh})\alpha_{mh}\kappa_{mh} I_{mh} S_{mh}}{C_{mh}} \end{cases} \tag{7.15c}$$

Note that $\vartheta_p = 0$ and $\nu_p = (\zeta_p - \xi_p)\alpha_p\kappa_p I_p S_p > 0$ when $\varphi_p = 0$ and $\nu_p = 0$ and $\vartheta_p = -C_p\varphi_p^U + (\zeta_p - \xi_p)\alpha_p\kappa_p I_p S_p > 0$ when $\varphi_p = \varphi_p^U$. Since $0 < \varphi_p < \varphi_p^U$, hence $\nu_p = \vartheta_p = 0$. Similar remarks apply to the Lagrange multipliers for the other two

control variables. The optimality conditions are given as follow

$$\varphi_p^*(t) = min\left\{max\left\{0, \phi_p(t)\right\}, \varphi_p^U\right\},\ t \in [t_0, t_F], \tag{7.16a}$$
$$\varphi_{sh}^*(t) = min\left\{max\left\{0, \phi_{sh}(t)\right\}, \varphi_{sh}^U\right\}, t \in [t_0, t_F], \tag{7.16b}$$
$$\varphi_{nh}^*(t) = min\left\{max\left\{0, \phi_{mh}(t)\right\}, \varphi_{mp}^U\right\}, t \in [t_0, t_F]. \tag{7.16c}$$

where

$$\begin{aligned}\phi_p(t) &= \frac{(\zeta_p(t) - \xi_p(t))\alpha_p\kappa_p I_p(t)S_p(t)}{C_p} \\ &= \left(\frac{\zeta_p(t) - \xi_p(t)}{C_p}\right)\left(\frac{\delta_p(\delta_p + m_p)}{\eta_p}\right) R_p I_p(t)S_p(t)\end{aligned} \tag{7.17a}$$
$$\begin{aligned}\phi_{sh}(t) &= \frac{(\zeta_{sh}(t) - \xi_{sh}(t))\alpha_{sh}\kappa_{sh} I_{sh}(t)S_{sh}(t)}{C_{sh}} \\ &= \left(\frac{\zeta_{sh}(t) - \xi_{sh}(t)}{C_{sh}}\right)\left(\frac{\delta_h(\delta_h + m_s)}{\eta_h}\right) R_{sh} I_s(t)S_h(t)\end{aligned} \tag{7.17b}$$
$$\begin{aligned}\phi_{mh}(t) &= \frac{(\zeta_{mh}(t) - \xi_{mh}(t))\alpha_{mh}\kappa_p I_{mh}(t)S_{mh}(t)}{C_{mh}} \\ &= \left(\frac{\zeta_{mh}(t) - \xi_p(sh)}{C_{mh}}\right)\left(\frac{\delta_h(\delta_h + m_m)}{\eta_h}\right) R_{mh} I_m(t)S_h(t)\end{aligned} \tag{7.17c}$$

7.5 Simulation

In practice it may be convenient to assume that the controls are piecewise constant. For each given value of the constants can be found local numerical solutions to the state equations. Since the adjoint system is a system of linear differential equations with variable coefficients defined in terms of the known state variables it can be found a local analytic solution for the adjoint variables. Of course the fundamental matrix for the adjoint system will be expressed in terms of the numerical functions found for the state variables.

7.5.1 Algorithm

The steps for implementing control are as follow.

1. Subdivide the interval $[t_0, t_F]$ into N equal subintervals. For $t \in [t_k, t_{k+1}]$ and $k = 0, 1, \ldots, N-1$ assume piecewise-constant control functions

$$\begin{aligned}\varphi_p^{(0)}(t) &= \varphi_p^{(0)}(t_k), \\ \varphi_{sh}^{(0)}(t) &= \varphi_{sh}^{(0)}(t_k), \\ \varphi_{mh}^{(0)}(t) &= \varphi_{mh}^{(0)}(t_k).\end{aligned}$$

2. Apply the assumed controls $\varphi_p^{(i)}, \varphi_{sh}^{(i)}$ and $\varphi_{mh}^{(i)}$ to integrate the state equations (7.7a)-(7.7h) from an initial time t_0 to a final time t_F with the given initial conditions $Z_0 \in [0,T] \times \mathbb{R}^7$ and store the disease state trajectory

$$Z^{(i)} = \left(S_p^{(i)}, I_p^{(i)}, S_h^{(i)}, S^{(i)}, I_a^{(i)}, I_b^{(i)}, I_m^{(i)}\right).$$

3. Applying $\varphi_p^{(i)}, \varphi_{sh}^{(i)}$ and $\varphi_{mh}^{(i)}$ and the disease state $Z^{(i)}$ to integrate co-state equations (7.12a)-(7.12h) backward, i.e., from $[t_F, t_0]$. The starting value $\lambda_{(j)}^{(i)}(t_F)$ can be obtained by the transversality conditions

$$\begin{aligned}
&\zeta_p^{(i)(i)}(t_F) = \zeta_p(t_F),\\
&\xi_p^{(i)}(t_F) = \xi_p(t_F),\\
&\zeta_h^{(i)}(t_F) = \zeta_h(t_F),\\
&\xi_s^{(i)}(t_F) = \xi_s(t_F),\\
&\xi_a^{(i)}(t_F) = \xi_a(t_F),\\
&\xi_b^{(i)}(t_F) = \xi_b(t_F),\\
&\xi_m^{(i)}(t_F) = \xi_m(t_F).
\end{aligned}$$

Store the values $\zeta_p^{(i)}, \xi_p^{(i)}, \zeta_h^{(i)}, \xi_s^{(i)}, \xi_a^{(i)}, \xi_b^{(i)}$ and $\xi_m^{(i)}$

4. Let

$$\begin{aligned}
\phi_p^{(i)} &= \left(\frac{\zeta_p^{(i)} - \xi_p^{(i)}}{C_p}\right)\left(\frac{\delta_p(\delta_p + m_p)}{\eta_p}\right) R_p I_p^{(i)}(t) S_p^{(i)}(t)\\
\phi_{sh}^{(i)} &= \left(\frac{\zeta_{sh}^{(i)} - \xi_{sh}^{(i)}}{C_{sh}}\right)\left(\frac{\delta_h(\delta_h + m_s)}{\eta_h}\right) R_{sh} I_s^{(i)}(t) S_h^{(i)}(t)\\
\phi_{mh}^{(i)} &= \left(\frac{\zeta_{mh}^{(i)} - \xi_p^{(i)}}{C_{mh}}\right)\left(\frac{\delta_h(\delta_h + m_m)}{\eta_h}\right) R_{mh} I_m^{(i)}(t) S_h^{(i)}(t)
\end{aligned}$$

5. Based on the optimality criteria (7.16a), (7.16b), (7.16c), check the values of $\phi_p^{(i)}, \phi_{sh}^{(i)}$ and $\phi_{mh}^{(i)}$.

   (a) Checking the value of ϕ_p
      i. If $\phi_p^{(i)} > 0$ then let $\varphi_p^{(i)} = \phi_p^{(i)}$ otherwise $\varphi_p^{(i)} = 0$ go to Step 7.
      ii. If $\phi_p^{(i)} < \varphi_p^U$ then let $\varphi_p^{(i)} = \phi_p^{(i)}$ otherwise $\varphi_p^{(i)} = \varphi_p^U$ go to Step 5.

   (b) Checking the value of ϕ_{sh}
      i. If $\phi_{sh}^{(i)} > 0$ then let $\varphi_{sh}^{(i)} = \phi_{sh}^{(i)}$ otherwise $\varphi_{sh}^{(i)} = 0$ go to Step n7.
      ii. If $\phi_{sh}^{(i)} < \varphi_{sh}^U$ then let $\varphi_{sh}^{(i)} = \phi_{sh}^{(i)}$ otherwise $\varphi_{sh}^{(i)} = \varphi_{sh}^U$ go to Step 5.

   (c) Checking the value of ϕ_{mh}
      i. If $\phi_{mh}^{(i)} > 0$ then let $\varphi_{mh}^{(i)} = \phi_{mh}^{(i)}$ otherwise $\varphi_{mh}^{(i)} = 0$ go to Step 7.

ii. If $\phi_{mh}^{(i)} < \varphi_p^U$ then let $\varphi_{mh}^{(i)} = \phi_{mh}^{(i)}$ otherwise $\varphi_{mh}^{(i)} = \varphi_{mh}^U$ go to Step 7.

6. Let

$$\varphi^{(*)} = \left(\varphi_p^{(*)}, \varphi_{sh}^{(*)}, \varphi_{mh}^{(*)}\right)$$

where

$$\begin{aligned}
\varphi_p^{(*)} &= \varphi_p^{(i)}, \\
\varphi_{sh}^{(*)} &= \varphi_{sh}^{(i)}, \\
\varphi_{mh}^{(*)} &= \varphi_{mh}^{(i)}
\end{aligned}$$

and

$$Z^{(*)} = \left(S_p^{(*)}, I_p^{(*)}, S_h^{(*)}, I_s^{(*)}, I_a^{(*)}, I_b^{(*)}, I_m^{(*)}\right)$$

where

$$\begin{aligned}
S_p^{(*)} &= S_p^{(i)}, \\
I_p^{(*)} &= I_p^{(i)}, \\
S_h^{(*)} &= S_h^{(i)}, \\
I_s^{(*)} &= I_s^{(i)}, \\
I_a^{(*)} &= I_a^{(i)}, \\
I_b^{(*)} &= I_b^{(i)}, \\
I_m^{(*)} &= I_m^{(i)}.
\end{aligned}$$

7. For $k = 0, 1, \ldots, N-1$ and a step size τ adjust the piecewise-constant control functions by

$$\begin{aligned}
\varphi_p^{(i+1)}(t_k) &= \varphi_p^{(i)}(t_k) - \tau\phi_p^{(i)}(t_k), \\
\varphi_{sh}^{(i+1)}(t_k) &= \varphi_{sh}^{(i)}(t_k) - \tau\phi_{sh}^{(i)}(t_k), \\
\varphi_{mh}^{(i+1)}(t_k) &= \varphi_{mh}^{(i)}(t_k) - \tau\phi_{mh}^{(i)}(t_k).
\end{aligned}$$

Let

$$\begin{aligned}
\varphi_p^{(i)}(t_k) &= \varphi_p^{(i+1)}(t_k), \\
\varphi_{sh}^{(i)}(t_k) &= \varphi_{sh}^{(i+1)}(t_k), \\
\varphi_{mh}^{(i)}(t_k) &= \varphi_{mh}^{(i+1)}(t_k)
\end{aligned}$$

and return to step 2.

Figure 7.1 shows that the optimal control is effective in reducing the proportion of infected birds with avian flu in the beginning. Increasing proportion of infected birds in the end is caused by low balancing cost factor for controlling avian flu among birds.

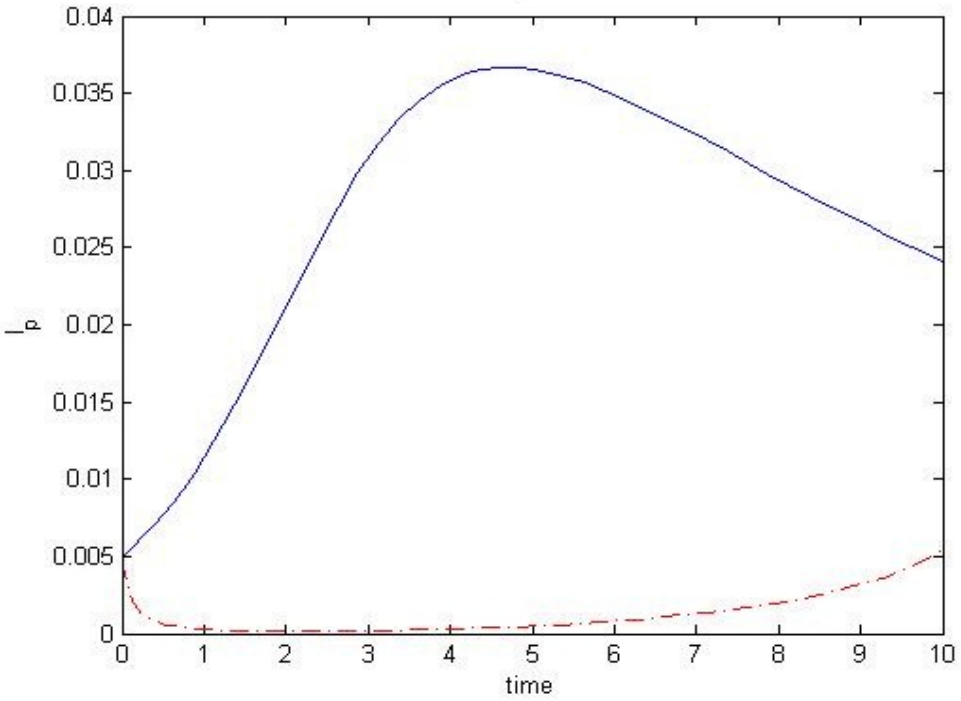

Fig. 7.1: Proportion of infectious poultry birds. The horizontal axis is time in days. Uncontrolled in blue, controlled in red

Figure 7.2 shows that the optimal control is effective in reducing the proportion of infected humans with avian flu in the beginning. Figure 7.3 shows that the optimal control is effective in reducing the proportion of infected human with avian flu.

7.5.2 Estimation of disease transmission parameters

In uncontrolled systems such as in Chapter 4, equations (4.6), (4.7) and (4.8) estimate the basic reproduction numbers for the disease transmissions for estimated epidemiological parameter values given in Section 4.7 and a given a set of population parameters.

For a controlled system however, the problem is slightly different. For a given set of values of basic reproduction numbers and population parameters, it is necessary to determine the rate at which the disease spreads in order to control the disease. The population parameters $(\eta_p, \eta_h, \delta_p, \delta_h, \kappa_p, \kappa_{ph}, \kappa_{sh}, \kappa_{sa}, \kappa_{mh})$ used in the numerical simulation are adopted from Chapter 4.

Estimated basic reproduction numbers of avian influenza transmission among poultry birds in Indonesia during 2004-2009 vary between 1.8 to 4.00 [198], [28], [17]. There-

fore it is reasonable to take 1.86 as the estimate of the basic reproduction of avian flu among birds [125]. The transmission rate among birds is estimated by using the basic reproduction number formula (4.6).

The basic reproduction number of swine flu among humans is estimated to be 1.6 [61] ($R_{sh} = 1.6$). The estimated mean infectious period of infected humans with swine flu is about 14 days [61]. Swine flu virulence among infectious humans is 0.01 [61] ($m_s = 0.01$). The transmission rate of swine from humans infectious with swine flu to susceptible humans is estimated by using the basic reproduction number formula (4.7), 1.82×10^{-4} per-day (i.e. $\alpha_{sh} = 1.82 \times 10^{-4}$).

7.6 Discussion

Analysis showed that the cost of disease controls plays the most important factor in the optimal control strategy. The quarantine policy is better than the culling policy during the spread of disease, even if the unit execution cost of the quarantine policy is more than that of the culling policy. Also the change of the unit execution cost does affect the total cumulative cost of the optimal prevention policies but does not affect the relative frequency of each cumulative execution cost. Furthermore, it shows that an optimal strategy to reduce the number of total infected humans might increase the chance of containing the mutant influenza.

Controlling the contact intensity between susceptible and infectious birds is effective in reducing the number of infected birds and humans. The execution costs committed to the control policies affects the optimal strategy of prevention policies. The quarantine policy is considered more important compared to the social distancing policy during the disease spread, even if the unit execution cost of the quarantine policy is more expensive than that of the social distancing policy. Also, the change of the unit execution cost does affect the total cumulative cost of the optimal prevention policies but does not affect the relative frequency of each cumulative execution cost. Furthermore, interestingly, it shows that an optimal strategy to reduce the number of total infected humans might increase a chance of invasion by a mutant influenza.

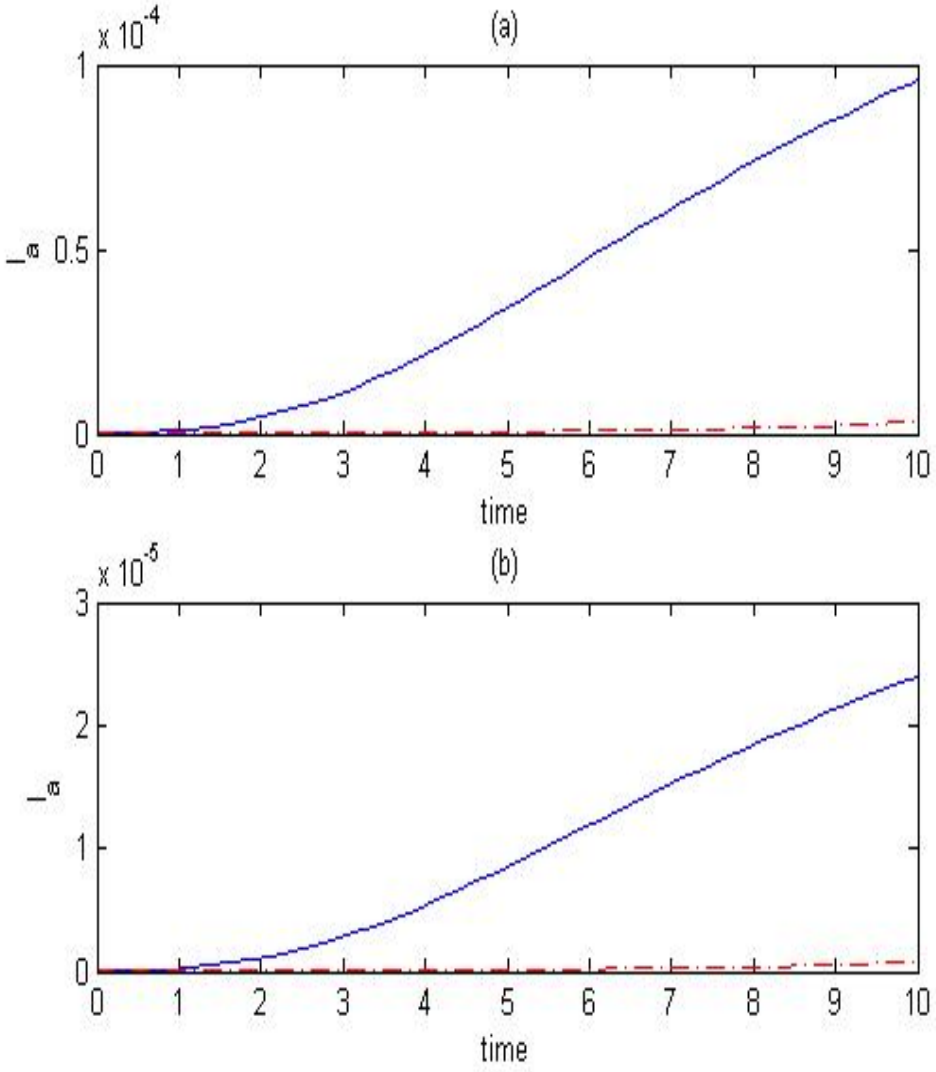

Fig. 7.2: Proportion of infected human with avian flu. (a) Asymptomatic. (b)Symptomatic. The horizontal axis is time in days. Uncontrolled in blue, controlled in red

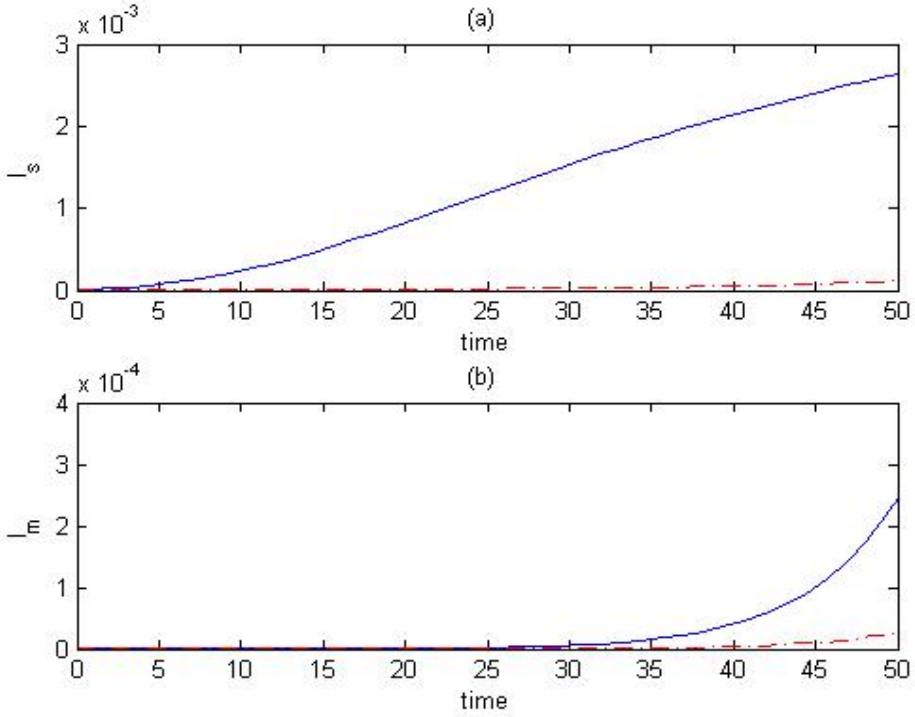

Fig. 7.3: (a) proportion of infectious humans with swine flu. (b) proportion of infectious humans with mutant-avian flu. The horizontal axis is time in days. Uncontrolled in blue, controlled in red

8. CONCLUSION

This thesis has addressed some problems of modeling, analyzing and interpreting the spread of disease and control of multi-strain influenza-A viruses (i.e. avian flu, swine flu and mutant-avian flu) among linked populations of birds and humans in Indonesia. Mutant-avian flu is a hypothetical mutated virus resulting from virus recombination between of avian flu and swine flu.

The dynamics of the disease states were described as deterministic processes. Seven disease states were considered for a single region problem and $7n$ disease states for the problems of n regions. An additional disease state (culled birds) is used to address the effect of border screening.

The dynamics of the diseases is modeled in the form of well-defined disease dynamics problem (DDP)s and optimal disease control problems ODCPs. Models and methods developed in this study are justified theoretically. Analytical results were presented in theorems and corollaries. Simulations were presented to visualize the dynamic of the diseases and the economic trade-off between the spread and control of the diseases.

8.1 Discussion

In the case of a single region, the variability of seven disease states were modeled by the DDP (4.3a)- (4.3h). The existence of a unique solution is guaranteed Lemma 4.1. Three reproduction numbers were defined for the transmission of the diseases by (4.6), (4.7) and (4.8). The sensitivity analysis on the reproduction numbers shows that the reproduction numbers are most sensitive towards the effective number of contacts of susceptible to infectious individuals. These indicate that the effective number of contacts of susceptible to infectious individuals is the best option to be controlled.

The disease dynamic model (4.3a)-(4.3h) has five equilibria, one disease free equilibrium and four epidemic equilibria. The four epidemic equilibria were expressed as the functions of the reproduction numbers in (4.29), (4.33),(4.37) and (4.41). The asymptotic analysis showed that three are globally asymptotically stable and the other two are locally asymptotically stable. Three human epidemic equilibria namely, (4.29), (4.33) and (4.37) happen when there is no epidemic in the bird world. The stability analysis are given in Theorems 4.6, 4.9, 4.12, 4.13 and 4.14. Numerical analysis show that:

(i) The spread of avian flu in the human world appears later than that in the bird world.

(ii) Containing avian flu in the bird world does not stop the spread of the implicated diseases in the human world.

(iii) The spread of mutant-avian-flu has a greater magnitude than avian flu in terms of the proportion of individuals acquiring the disease.

(iv) Reducing the contact among poultry birds will reduce the spread of avian flu but not swine flu and mutant-avian-flu.

(v) Social distancing programs reduce the number of human casualties.

The disease dynamics problem (DDP) (4.3a)-(4.3h) is an extension of the model proposed in [103] in some ways. Swine flu was considered as an additional source of infection and the mutant influenza-A is considered as a recombination of avian flu and swine flu. These model extensions are necessary to capture more accurately (for a biological point of view) the pandemic generation scenario that has been suggested [84],[71].

The effect of bird trading on the dynamics of the diseases in a set of n-regions was modeled by the DDP (5.3a)-(5.3h). For two identical regions, the model becomes (5.5a)-(5.5o). For the two identical regions model, three reproduction numbers were defined by (5.7), (5.11) and (5.12). These reproduction numbers are dependent on α and β (the rates of disease transmission due to transport related infection). The analysis shows that if $R_{p\alpha\beta} < 1, R_{p\alpha} < 1$ then birds in both regions are free of avian flu. If $R_{p\alpha\beta} > 1$ but $R_{p\alpha} < 1$ then birds remain free of avian flu when both regions are isolated. But the transport-related infection will lead to the disease becoming endemic at both regions. If $R_{p\alpha\beta} > 1$ and $R_{p\alpha} > 1$ then the avian flu is endemic among birds even if both regions are isolated. The transport-related infection will increase the magnitude of avian flu endemic.

In addition to the 'local' disease-state equilibria in each region there are disease state equilibria due to transport-related infection. These disease equilibria will determine which region will have an epidemic and which ones will not. The stability of the disease-state equilibria corresponding to the DDP (4.3a)-(4.3h) is preserved in the DDP (5.3a)-(5.3h). The stability analysis are given in Theorems 5.2, 5.3, 5.4, 5.5 and 5.6. Numerical analysis shows that:

(vi) Bird trading is a significant factor for the spread of diseases not only in the bird world but also in the human world.

(vii) Bird trading may result in an epidemic among birds and humans even in a region which is initially disease free.

(viii) If avian flu is already endemic among birds in both regions, then bird trading will intensify the spread of the diseases among bird and humans.

The IVP (5.5a), (5.5o) is an extension of transport-related infection models for a single species and single disease transmission and appeared in [138], [139], [142], [143] in some ways namely, number of species, number of disease transmissions. The model also extends knowledge in the sense of its ability to analyze the effect of transport-related infection of a species to the disease dynamics of other species. The analysis on the effects of bird trading to the disease dynamics in the bird world confirm the similar results for a single species population considered in [142]. This study presents results on the effects of birds trading to the dynamics of the diseases among humans. It extends knowledge about the effects of transport related infection and screening of a species to the dynamics of (more than one) diseases of another species.

The effect of border screening to the dynamics of the diseases was modeled by the DDP (6.3a)-(6.3i) and (6.5a)-(6.5q). For the two identical regions model (6.5a)-(6.5q), three reproduction numbers were defined by (6.7), (6.11) and (6.12). These reproduction numbers are dependent on α, β and σ (the probability for screening infected birds). Analysis shows that:

(ix) Border screening has the potential to eliminate avian flu transmission during bird transportation.

(x) Increasing the probability of successful screening of birds entering a region will decrease the magnitude of spread of disease among birds and humans in the region at the expense of increased costs of screening and culling. This indicates some economic trade-off between screening policy implementation and spread of disease.

The DDP (6.5a), (6.5q) is an extension of transport-related infection models for a single species and single disease transmission that have appeared in [143] in some ways, namely, the number of species and the number of disease transmissions. The model also extends these studies in the sense of its ability to analyze the effect of transport-related infection and border-screening of a species to the disease dynamics of other species. The analysis on the effects of birds trading to the disease dynamics in the bird world confirm similar results for a single species population considered in [143]. This study presents results on the effects of border screening to the dynamics of the diseases among humans. It extends knowledge about the effects of transport related infection and border screening of a species to the dynamics of (more than one) diseases of another species. The analysis on the effects of birds trading on the disease dynamics in the bird world confirms the similar results for a single species population considered in [143]. It extends knowledge about the effects of transport related infection and screening of a species to the dynamics of (more than one) diseases of another species.

The problems of modeling and analyzing the economic trade-off between spread of disease and control was modeled by minimizing the objective function (7.6) subject to disease state constraints (7.7a)-(7.7a) and the control constraints (7.8a)-(7.8a). The necessary conditions for optimality of the ODCP, (7.16a)-(7.16a), were derived based on Theorem 3.30, the Pontryagins maximum principle. Three disease controls were aimed to reduce the effectiveness of three disease transmissions. The control functions are defined by the equations (7.17a), (7.17b), (7.17c). An indirect algorithm for finding optimal disease control policies is given in Sub-section 7.5.1.

Analysis showed that the cost of disease controls plays the most important factor in the optimal control strategy. The quarantine policy is better than the culling policy during the spread of disease, even if the unit execution cost of the quarantine policy is more expensive than that of the culling policy. Also, the change of the unit execution cost does affect the total cumulative cost of the optimal prevention policies but does not affect the relative frequency of each cumulative execution cost. Furthermore, it shows that an optimal strategy to reduce the number of total infected humans might increase a chance of containing the mutant influenza.

The ODCP (7.5)-(7.8c) is an extension of the disease control model proposed in [146] in some ways. This extends the previous studies for the prevention of the pandemic influenza to evaluate the time-dependent optimal prevention policies that are associated with culling policy and quarantine policy, considering its execution cost. The execution cost affects the optimal strategy of prevention policies and the prevention of the spread of disease.

8.2 Conclusion

The long range goal of this work is to provide a tool to be used by government officials in Indonesia for making decisions concerning strategies for managing epidemics. There was no intention of delivering such a tool in the course of this thesis study. The objective was to provide the mathematical setting and demonstrate the feasibility of such a tool, in principle.

The theoretical aspects of the work demonstrate that the long term behaviour of diseases and their effects on linked populations of birds and humans may be understood qualitatively by studying equilibria of a dynamical system. The demonstration of the stability of these equilibria justifies numerical computations. The numerical computations provide the details of the evolution of the disease states over time that will be of primary interest in predicting impacts on populations.

Of course, merely predicting the effects of the disease is of limited benefit. A major feature of a future tool will be the capacity to determine optimal intervention strategies. Should resources be used to maximum capacity at the onset of an epidemic or should

these be spread out over time – and if so, what level of intervention, viewed as a function of time, is optimal. This work shows that these questions may be addressed by implementing methods from the control theory. This work also shows that the potential benefits of optimizing interventions may be substantial.

Although the models presented here reflect the recent situation with bird flu in Indonesia, the final tool will be designed to be more general. The theoretical aspects of the work are already quite general and are likely to apply as is or with only minor adjustments. The implementation depends on knowing parameters related to the diseases and populations involved. The final tool will allow users to redefine such parameters as necessary in future scenarios. The tool has the potential to facilitate this step too. Sensitivity analysis is useful in understanding which parameters of the diseases and the populations are the most important to determine. Thus the user may use the tool to decide if resources are better spent on carefully determining transmission rates or effective contact rates, for example.

One important aspect of building the tool has not been addressed in this thesis, namely the human-computer interaction aspect. The tool will be most useful if officials with little scientific or technical knowledge are able to understand output of the model as well the scope and limitation of the predictions. Even if the official is not the person who actually runs the model, he or she must be able to digest the results. This will require careful consideration of the presentation of results in terms of graphs and figures, and text. Human-computer interaction is a separate topic and could be addressed in the future.

This thesis has provided the core theoretical foundation for building a tool that is useful for managing epidemics. Sensitivity analysis and the inclusion of control aspects demonstrate that a practical tool is feasible. Numerical computations demonstrate the potential benefit of using the model in determining strategies for intervention.

8.3 A vision and the directions for the future

Not withstanding the development of a user friendly shell for the model, the model itself is also subject to improvement. Some directions for future work are as follow.

The models developed in this study capture the variability of disease states at the population level, but do not capture the variability inherent at the individual level. The mutation process was assumed to be homogeneous throughout the population and modeled by shift evolution. One direction to improve the models is by considering a drift evolution. Let $\mu(\tau)$ be the probability of virus mutation due to virus recombination between swine flu and avian flu, where τ is time since the virus recombination took place. The quantity $\tau(\mu, t)$ represents the density of humans developing mutant-avian

flu. The cumulative number of humans develop mutant avian flu at time t is

$$\int_{a_0}^{a_1} \tau(\mu, t)$$

In the case of an isolated region, the variability of disease states among birds and humans is denoted by $z(t) = (S_p(t), I_p(t), S_h(t), I_s(t), I_a(t), I_b(t), I_m(t))$. The disease dynamics in a single region is modeled by

$$\dot{z}(t) = f_1(z(t); \alpha, p), \quad z(0) = z_0, \tag{8.1}$$

where $f_1 : \Omega_1 \times \Psi_1 \times Q_1 \to \Re_+$ and $z(t), z_0 \in \Omega_1 \subseteq \mathbb{R}_+^7$. $\alpha \in \Psi_1 \subset \mathbb{R}_+^5$ is the vector of five disease transmission parameters. $q \in Q_1 \subset \mathbb{R}_+^{19}$ is the vector of nineteen disease parameters other than transmission parameters.

By introducing the additional disease state τ, the variability of disease states among birds and humans is $Z(t) = (z(t), \tau(t))$ and the disease dynamics become

$$\dot{Z}(t) = f_1(Z(t); \alpha, p), \quad Z(0) = Z_0, \tag{8.2}$$

where $f_1 : \Omega_1 \times \Psi_1 \times Q_1 \to \Re_+$ and $Z(t), Z_0 \in \Omega_{1\tau} \subset \mathbb{R}_+^8$. Comparing (8.1) and (8.2), the former is a system of differential equations, while the later is a system of stochastic differential equations. Analyzing the latter model will be much harder due to stochastic differential terms in the model.

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