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	Signed Dated March 23, 2015
A/Prof. Murk J. Bottema,	Dr. Mariusz Bajger,
(Principal Supervisor)	(Co-Supervisor)

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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 biological 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.