A model of highly pathogenic avian influenza with environmental reservoir
and vaccine intervention in broilers in an all-in-all-out housing system

by

Meagan Coffey

A Thesis
presented to
The University of Guelph

In partial fulfilment of requirements
for the degree of
Masters of Science
in
Biophysics

Guelph, Ontario, Canada

©Meagan Coffey, January, 2018
ABSTRACT

A MODEL OF HIGHLY PATHOGENIC AVIAN INFLUENZA IN BROILERS WITH ENVIRONMENTAL RESERVOIR AND VACCINE INTERVENTION IN AN ALL-IN-ALL-OUT HOUSING SYSTEM

Meagan Coffey advisors: Hermann Eberl, Amy Greer
University of Guelph, 2017

Avian influenza is a subtype of the influenza A virus which emerged as a highly infectious disease in the 1980’s and has caused mass fatalities throughout the poultry industry. Domesticated birds, and specifically broilers, which are birds raised for meat consumption, can become infected and spread the pathogen rapidly due to the birds genetics and environment. The objective of this project was to develop an original model to study highly pathogenic avian influenza (HPAI) in broilers and to analyze the effects such as interventions. An SIR model was developed with the addition of an environmental reservoir to better study the spread of the influenza pathogen. The model was then extended to include the addition of an imperfect vaccine. The model and vaccination model were analyzed for stability and sensitivity of parameters. Economic values play a large role in the poultry industry and have a large influence on decision-making. An economic analysis was done to determine the monetary impact of an imperfect vaccine versus no vaccine intervention.
ACKNOWLEDGEMENTS

First I would like to thank my advisory committee, Drs Hermann Eberl and Amy Greer. Hermann has played a role in my life beyond advisor and mentor. I absorb everything he says and apply it to my life both in and out of the school environment. Amy has been able to reel me in and keep me on track when things began to get overwhelming. I’m thankful for her strong head and ability to help me get where I need to go. The yin and yang of their mentor-ship has helped me through this thesis in an enjoyable and productive manner.

I would also like to thank my fellow graduate students and officemates who have dealt with my pestering questions and long-winded stories for seven semesters. Without them this process would have been far less enjoyable and certainly much quicker. I would also like to thank my friends and family, with particular thanks to Jeff, Meghan, and my parents. Their support has brought me through the highs and lows of this thesis and have made me a better person with their guidance.
# Table of Contents

## List of Tables

<table>
<thead>
<tr>
<th>No.</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>vii</td>
<td>vii</td>
<td></td>
</tr>
</tbody>
</table>

## List of Figures

<table>
<thead>
<tr>
<th>No.</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>viii</td>
<td>viii</td>
<td></td>
</tr>
</tbody>
</table>

## 1 Background

1.1 Emerging Infectious Diseases .................................. 1  
1.2 Avian Influenza Biology ....................................... 2  
1.3 Avian Influenza Vaccine ........................................ 3  
1.4 Zoonosis .................................................................. 4  
1.5 Domestic Poultry .................................................. 5  
1.6 Economic Considerations ......................................... 6  
1.7 Mathematical Modelling .......................................... 7  
1.8 Model Literature .................................................. 9  
1.9 Objectives ................................................................ 14  
1.10 Outline of Thesis ................................................. 14  

## 2 Mathematical Model

2.1 Assumptions ......................................................... 15  
2.1.1 Basic Assumptions ............................................... 15  
2.1.2 Vaccine Intervention ........................................... 17  
2.1.3 Economic Analysis .............................................. 18  
2.2 Model Structure .................................................... 20  
2.2.1 Base Model ....................................................... 20  
2.2.2 Vaccine Intervention ........................................... 21  
2.3 Parameter Values ................................................... 24  
2.4 Outcome of Interest ................................................. 25  
2.5 Methods of Analysis ............................................... 25  
2.5.1 Steady State Analysis ......................................... 25  
2.5.2 Sensitivity Analysis ............................................ 27  
2.5.3 Economic Analysis .............................................. 28
3 Results
3.1 Illustrative Simulation
3.2 Stability Analysis
3.3 Sensitivity Analysis
3.4 Economic Analysis

4 Discussion
4.1 Stability Analysis
4.2 Sensitivity Analysis
4.3 Economic Analysis

5 Conclusions
5.1 Conclusions
5.2 Future Work

References
List of Tables

1.1 Summary table of model literature from references ......................... 10

2.1 Parameters and their default values used in our simulations, with references 24

2.2 Estimated parameter values for economic analysis equations ............. 30

3.1 Population size of all consumable birds at time 30 days predicted by the model for small and large variations in parameters with $N = 30000$ and $P = 0.001$ .......................................................... 39

3.2 Population size of all consumable birds at time 40 days predicted by the model for small and large variations in parameters with $N = 30000$ and $P = 0.001$ .......................................................... 39
List of Figures

2.1 Compartment model where solid lines represent direct movement of birds and dotted lines represent movement of pathogen between hosts and environment, $P$. $S$ represents susceptible birds able to get the infection, $E$ represents exposed birds who are infected but asymptomatic, $I$ represents infected birds who are infected and symptomatic, and $P$ represents pathogen in the environment ......................................................... 17

2.2 Compartment model where solid lines represent direct movement and dotted lines represent movement of pathogen between hosts and environment. $S$ represents susceptible birds able to get the infection, $E$ represents exposed birds who are infected but asymptomatic, $I$ represents infected birds who are infected and symptomatic, $S_v$ represents incompletely vaccinated susceptible individuals who are able to get the infection, $E_v$ represents incompletely vaccinated exposed individuals who are infected but asymptomatic, $R_v$ represents completely vaccinated individuals who are unable to get the infection, and $P$ represents pathogen in the environment ......................................................... 19

2.3 Weight of birds in lbs based on age in days, represented by $\kappa(t)$ .................................. 29

3.1 Illustrative simulation of initial model, equations (2.1) - (2.4), with initial conditions (30000, 0, 0, 0.001) over 40 days .................................................. 34

3.2 Illustrative simulation of vaccine model with 33% efficacy, equations (2.9) - (2.15), with initial conditions (10000, 0, 0, 0.001, 10000, 0, 10000) over 40 days .................................................. 35

3.3 Sensitivity analysis of infection rate parameter, $\gamma$, with 1% and 10% change in parameter value. Compartmental population sizes of birds (S,E,I) and pathogen(P) are plotted over 40 days to compare the difference due to parameter size. .................................................. 43

3.4 Sensitivity analysis of infection rate parameter, $\gamma$, with 10% and 50% change in parameter value. Compartmental population sizes of birds (S,E,I) and pathogen(P) are plotted over 40 days to compare the difference due to parameter size. .................................................. 44
3.5 Sensitivity analysis of incubation parameter, $\lambda$, with 1% and 10% change in parameter value. Compartmental population sizes of birds (S,E,I) and pathogen(P) are plotted over 40 days to compare the difference due to parameter size. ................................................................. 45

3.6 Sensitivity analysis of incubation parameter, $\lambda$, with 10% and 50% change in parameter value. Compartmental population sizes of birds (S,E,I) and pathogen(P) are plotted over 40 days to compare the difference due to parameter size. ................................................................. 46

3.7 Sensitivity analysis of death rate parameter, $\delta$, with 1% and 10% change in parameter value. Compartmental population sizes of birds (S,E,I) and pathogen(P) are plotted over 40 days to compare the difference due to parameter size. ................................................................. 47

3.8 Sensitivity analysis of death rate parameter, $\delta$, with 10% and 50% change in parameter value. Compartmental population sizes of birds (S,E,I) and pathogen(P) are plotted over 40 days to compare the difference due to parameter size. ................................................................. 48

3.9 Sensitivity analysis of shedding rate parameter, $\beta$, with 1% and 10% change in parameter value. Compartmental population sizes of birds (S,E,I) and pathogen(P) are plotted over 40 days to compare the difference due to parameter size. ................................................................. 49

3.10 Sensitivity analysis of shedding rate parameter, $\beta$, with 10% and 50% change in parameter value. Compartmental population sizes of birds (S,E,I) and pathogen(P) are plotted over 40 days to compare the difference due to parameter size. ................................................................. 50

3.11 Financial loss per bird versus efficacy at day 25 with no vaccination cost . . . 52

3.12 Financial loss per bird versus efficacy at day 30 with no vaccination cost . . . 53

3.13 Financial loss per bird versus efficacy at day 35 with no vaccination cost . . . 54

3.14 Financial loss per bird versus efficacy at day 40 with no vaccination cost . . . 55

3.15 Financial loss per bird versus efficacy at day 40 with vaccination cost $e^2$ . . 56

4.1 Simulation of low pathogen avian influenza with initial conditions (10000, 0, 0, 0.001) over 40 days where $\gamma = 0.2$, $\lambda = 0.7$, $\delta = 0.03$, $\alpha = 0.15$, $\beta = 0.1$, $\nu = 0.3$ ................................................................. 59
Chapter 1

Background

1.1 Emerging Infectious Diseases

An emerging infectious disease (EID) is a disease that has recently emerged or that is increasing in incidence over time [31]. Emerging infectious diseases pose a large problem as there is often a lack of information regarding their biology and natural history making it difficult to predict the possible outcomes for both animal and human health [25]. Zoonotic diseases are diseases that are transmissible to humans through an animal host or vice-versa [40]. These diseases are especially difficult to control when one or more of the host species exhibit asymptomatic or mildly symptomatic infections [31].
1.2 Avian Influenza Biology

Avian influenza is a subtype of the influenza A virus and is an emerging infectious disease that developed as a highly pathogenic infectious disease in the 1980’s causing mass mortalities in the poultry industry [9]. Both domesticated and wild birds can become infected with avian influenza with varying degrees of clinical severity. The virus is zoonotic and therefore can spread from domesticated and wild avian hosts to humans as well as other mammals, such as swine. Avian influenza viruses are comprised of sixteen different haemagglutinin subtypes (H1-H16), which represent low, mild, or highly pathogenic subtypes of the virus [29]. Strains of low pathogen avian influenza (LPAI) cause mild clinical symptoms in birds, such as decreased appetite and egg production, or can be completely asymptomatic with no disease induced mortality [6]. In contrast, strains of highly pathogenic avian influenza show moderate to severe clinical symptoms (i.e. swelling, coughing, sneezing, and diarrhoea) and have a varied mortality rate ranging from 5% to 100% [26]. Of all of the haemagglutinin subtypes, H5 and H7 have been shown to have the highest pathogenicity and in turn to be the most fatal to domestic poultry [26, 35]. For H5 and H7 subtypes, case fatality can range from 20-100% of birds that become infected, causing it to be one of the most important infections in the poultry industry [3, 9]. Wild birds such as gulls, ducks, and geese are able to act as reservoirs for the pathogen and carry the pathogen asymptptomatically or with minimal clinical symptoms [3]. When wild bird hosts come in contact with domesticated poultry species opportunities exist for transmission of the pathogen into the poultry population where it causes more significant clinical
illness and disease [9]. Once the disease has entered the domestic bird population there is a chance that the pathogen could acquire genetic mutations that would allow for spillover to the human population and possibly sustained person to person transmission in the human population [9]. Zoonotic strains that have acquired the ability for sustained person to person transmission represent an important pandemic risk for the human population [40]. Avian influenza outbreaks in North America have cost over two billion dollars due to product loss and government intervention, thus research should be focused in this area [38].

1.3 Avian Influenza Vaccine

The avian influenza vaccine is a tool that can be used to help decrease the presence of avian influenza pathogens in the environment (i.e. barn) and decrease the number of infected individuals in a domestic bird population [14]. The main goals of an avian influenza vaccine are to protect against clinical symptoms and death, and reduce pathogen shedding by infected individuals [34].

The avian influenza vaccines have a variety of strains for different vaccines, just as with the virus itself. The vaccine strain is dependent on the haemagglutinin subtype (H1-H16) of the influenza virus and can provide approximately 88% protection with it’s use, depending on the strain [34]. It is suggested to be used with additional preventative measures such as biosecurity practices, education, and selective culling of sick animals [14]. Most vaccinations can be supplied on the first day of a birds life and animals that are vaccinated are safe
for consumption after approximately 2 weeks of time, depending on the vaccine strain [14].

These measures have shown to have better economic favour than the previous stamping out method where all domestic birds in a surrounding area were culled in the event of an avian influenza outbreak [17].

### 1.4 Zoonosis

Spillover of avian influenza into human populations can happen when there is a high prevalence of infection in wild and/or domestic bird populations, there is significant interaction between birds and humans, and when there is a high probability of infection given an effective contact [25]. The likelihood of contact between humans and domestic birds (e.g. poultry) changes based on location and lifestyle.

Live bird markets are a common way to sell poultry and other bird species in many Asian countries, as well as in some parts of the United States [32]. The contents of these markets can consist of chicken, turkey, duck, quail, and a variety of other bird types [32]. These markets are common in parts of the world that have experienced many deadly outbreaks of the highly pathogenic avian influenza virus due to the close contact between humans and birds [38]. Consumption of birds infected with avian influenza that have not been cooked to a high enough temperature can also lead to human infections [6]. Humans are dead end hosts for most strains of avian influenza and human to human transmission is rare [3]. In some instances, the virus mutates such that sustained human to human transmission
becomes possible and the risk of a pandemic increases [25].

1.5 Domestic Poultry

Domestic poultry in North America are considered to be layer chickens, broiler chickens, and turkeys that are reared for food consumption either through egg or meat production [6]. Turkeys and chickens exhibit different clinical manifestations of the disease and immunological responses to infection [4]. Each different type of poultry also have unique housing systems and the housing characteristics can directly influence the disease dynamics within the population.

In North American farming practices, egg laying female birds, particularly chickens, are most commonly kept in caged farming systems [13]. These systems keep a small number of birds in one cage, with many cages in a room. Birds are typically the same age in each cage but not necessarily between cages. This also means that the birds are entering the population and leaving at different times [6].

Broiler is a term used to describe chickens being raised for meat consumption [13]. In North America, these birds are most often kept in open housing systems where all birds are free to roam anywhere in an enclosed barn [13]. Due to the short lifespan of these birds, typically between 30 and 45 days [6], most production systems use an all-in-all-out strategy. This means that all birds enter an empty barn at day 0 and leave the barn for processing at the same time, depending on weight [13]. Since these birds are free to roam...
anywhere, all birds are able to interact with each other. The population dynamics of these broiler chickens are very unnatural due to their short lifespan and housing system and are therefore seldom studied in relation to disease dynamics. There is a need to study these birds to help control the spread of low and high pathogen avian influenza among broilers.

### 1.6 Economic Considerations

In the poultry industry, economics play a key role in guiding practices and regulations. The loss of a flock can be financially devastating to a farmer and/or an agricultural company. Highly and lowly pathogenic strains of avian influenza are considered to be very detrimental to domestic poultry flocks [12]. Prevention measures such as biosecurity practices and vaccinations can also be very costly to individual farmers, so the long term economic benefit is small, especially if the chance of avian influenza infection is small. Disease outbreaks play an important role in the financial viability of a poultry farm, but even the public knowledge of the presence of a pathogen such as avian influenza may lead to a profit loss and erode consumer confidence in poultry products [6].

Before an outbreak, preventative measures can be put into place to reduce the likelihood of pathogen introduction and subsequent spread in the poultry flock. These preventative measures can include cleaning, biosecurity practices (i.e. sanitizing, limited entry, proper disposal of infected birds), vaccination, and education. Many farmers are apprehensive to implement these preventative measures due to their upfront expense, but they have
been shown to reduce economic losses overall [21]. Although mass culling is the quickest method to eradicate disease after it has been detected within a poultry flock, it raises significant animal welfare concerns and is economically very expensive for farmers and taxpayers [7]. Only removing birds who show signs of infection is referred to as selective culling and has been shown to have better economic outcomes than mass culling [10]. Improved economic outcomes are likely due to a combination of factors related to negative public perceptions regarding poultry after mass culling activities have been undertaken due to avian influenza [6]. The implementation of prevention and control strategies before and during an avian influenza outbreak in poultry play a crucial role in preventing the introduction and subsequent spread of the disease which has significant economic implications for poultry farmers.

1.7 Mathematical Modelling

Epidemiological disease modelling has been studied since the early 1900’s but has gained further attention since 1990 [8] as a method for computationally exploring the spread of a pathogen within a population. Compartment models can act as organizational frameworks for integrating information on disease natural history and host population dynamics in order to quantify the spread of an infection through a population [19]. For immunizing infections (that confer immunity after individuals have recovered from their infection) the compartments of a model are generally represented as susceptible-infected-
recovered/removed (SIR). This represents groups of individuals in a population who are “susceptible” to infection, “infected” and able to transmit the pathogen to others, and “recovered”/”removed” and unable to become reinfected [25]. Individuals within the model are considered to be in one of three mutually exclusive health states and the rate of transition between the states describes the disease dynamics within the population as a whole. Modifications to the base model structure can also be made to better capture the biology of the host-pathogen dynamics. This can be done by adding (or removing) compartments to represent vaccination, immunity, latency period, and asymptomatic states [8].

After the compartments have been described, the interactions between them can be described mathematically. This can be done using deterministic or stochastic implementation of the model. Deterministic models have initial inputs and conditions that are static and describe the average behaviour of the described host-pathogen system. These models must be large enough to allow continuous modelling and give an average outcome to identify trends in the disease dynamics which are much simpler to study analytically [19]. They can be described by differential equations, which use continuous time, or difference equations, which use discrete time. In terms of computational analysis, it is very straightforward with deterministic models. These models represent the average movement of disease based on initial parameters, therefore differences in parameters can be easily compared. Stochastic models incorporate some inherent randomness to better capture the variability in possible model parameters and the associated model outcomes. These stochastic models typically incorporate probability distributions and each model run utilizes a different parameter value
drawn from the specified distribution. These can be run with very small population sizes. In this case, the model needs to be run many times in order to fully capture the range of possible outcomes given the uncertainty of model inputs [5]. This makes stochastic models much more complex to study than deterministic models.

1.8 Model Literature

A very heavily researched area of high pathogen avian influenza modelling has been focused on human-bird interaction. Due to this interaction, only strains of avian influenza that are transmissible to humans are looked at, which are the highly pathogenic H5N1 and H7N9 strains [22, 41]. These papers use very simple models (e.g. SIS) for the avian portion of the model, as their priority is looking at the human dynamics component of the model [18, 22]. This overly simplifies the model by not taking into account important dynamics such as a latency period and how the disease spreads in the poultry populations. Human transmission of avian influenza is also very rare [25], but these models take the possibility into account. Studies that look into the human-avian dynamics of avian influenza are often based on the original model by Iwami et. al. [22]. This paper uses an SI-SIR model to model the avian-human spread of the disease. There is no distinction between the wild and domestic birds and the model assumes they have the same dynamics. This simplified approach is an excellent baseline but the models overlook some of the important complexities of avian transmission. Gumel [18] models two-strains of avian influenza virus looking at
<table>
<thead>
<tr>
<th>Author</th>
<th>Humans in Model</th>
<th>Bird Type</th>
<th>Model Type</th>
<th>Location</th>
<th>Intervention</th>
<th>Economic Analysis</th>
<th>Time Frame</th>
<th>Frame Type</th>
<th>Analytical Type</th>
<th>Location</th>
<th>Model Type</th>
<th>Type in Model</th>
<th>Type in Model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iwami et al.</td>
<td>Yes</td>
<td>Combined</td>
<td>SI-SIR</td>
<td>Japan</td>
<td>Isolation</td>
<td>None</td>
<td>Infinite</td>
<td>Direct and Indirect and Direct</td>
<td>Vaccination and Culture</td>
<td>Vaccination and Culture</td>
<td>Wild and Wild and</td>
<td>Wahl and Wahl and</td>
<td></td>
</tr>
<tr>
<td>Gumel</td>
<td>Yes</td>
<td>Wild and Domestic</td>
<td>SI-SI</td>
<td>Canada</td>
<td>Isolation</td>
<td>None</td>
<td>Infinite</td>
<td>Direct</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>SIR</td>
<td>SIR</td>
</tr>
<tr>
<td>Chong et al.</td>
<td>Yes</td>
<td>Combined</td>
<td>SI-SIR</td>
<td>China</td>
<td>Isolation and Vaccination</td>
<td>None</td>
<td>Thailand</td>
<td>Direct</td>
<td>Vaccination and Culture</td>
<td>Vaccination and Culture</td>
<td>Vaccination and Culture</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Xiao et al.</td>
<td>Yes</td>
<td>Domestic</td>
<td>SIR</td>
<td>China</td>
<td>Isolation</td>
<td>None</td>
<td>Infinite</td>
<td>Direct</td>
<td>Vaccination and Culture</td>
<td>Vaccination and Culture</td>
<td>Vaccination and Culture</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Chong and Smith</td>
<td>No</td>
<td>Domestic</td>
<td>SIR</td>
<td>China</td>
<td>Isolation</td>
<td>None</td>
<td>Infinite</td>
<td>Direct</td>
<td>Vaccination and Culture</td>
<td>Vaccination and Culture</td>
<td>Vaccination and Culture</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Gulbudak and Martcheva</td>
<td>No</td>
<td>Domestic</td>
<td>SIR</td>
<td>USA</td>
<td>Culling</td>
<td>None</td>
<td>Infinite</td>
<td>Direct and Indirect</td>
<td>Vaccination and Culture</td>
<td>Vaccination and Culture</td>
<td>None</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Zhai et al.</td>
<td>No</td>
<td>Combined</td>
<td>SIR</td>
<td>China</td>
<td>Isolation</td>
<td>None</td>
<td>Infinite</td>
<td>Direct</td>
<td>Vaccination and Culture</td>
<td>Vaccination and Culture</td>
<td>Vaccination and Culture</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Vaidya et al.</td>
<td>No</td>
<td>Wild</td>
<td>SIR</td>
<td>Canada</td>
<td>Vaccination</td>
<td>None</td>
<td>Infinite</td>
<td>Direct and Indirect</td>
<td>Vaccination and Culture</td>
<td>Vaccination and Culture</td>
<td>None</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Guliubak and Martcheva</td>
<td>No</td>
<td>Domestic</td>
<td>SI-SEIR</td>
<td>USA</td>
<td>Vaccination and Culling</td>
<td>None</td>
<td>Infinite</td>
<td>Direct</td>
<td>Vaccination and Culture</td>
<td>Vaccination and Culture</td>
<td>Vaccination and Culture</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Nickbakhsh et al.</td>
<td>No</td>
<td>Domestic</td>
<td>SIR</td>
<td>UK</td>
<td>Metapopulation</td>
<td>None</td>
<td>SIS</td>
<td>Direct and Indirect</td>
<td>Vaccination and Culture</td>
<td>Vaccination and Culture</td>
<td>None</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Marchevara et al.</td>
<td>No</td>
<td>Domestic</td>
<td>SIR</td>
<td>USA</td>
<td>Vaccination</td>
<td>None</td>
<td>Infinite</td>
<td>Direct and Indirect</td>
<td>Vaccination and Culture</td>
<td>Vaccination and Culture</td>
<td>None</td>
<td>None</td>
<td></td>
</tr>
</tbody>
</table>

Table 1.1: Summary table of model literature from references
the human and avian dynamics. Gumel extends Iwami et. al.’s [22] model by introducing different model structures for domestic and wild type birds and analyzes the bird dynamics alone before introducing the human transmission model. The model introduces human strains with analysis and introduction of control measures, such as isolation of infected birds, to help decrease an endemic equilibrium. Chong et. al. [11] also used the Iwami et. al. [22] paper as the basis for their model where they used the simplest SI model for the birds, with a more complex SIR model for the human strains. The addition of a hyperbolic force of infection in the bird model creates a more complex and realistic approach to disease spread and allows for management introductions that cannot be modelled with linear interactions. Xiao et. al. [41] developed a similar SI-SEIR model. The birds are again grouped together with simple SI interaction. Overall, the model and results of all of these models are very similar. The simplicity works well when focusing on the spread of disease in humans, but to control and model the spread of disease in birds more complex models should be introduced.

Domestic birds pose the biggest issues when it comes to modelling avian influenza because their housing conditions are very unnatural compared to humans or wild birds, which can amplify transmission. These birds may be kept on farms in a room with no ability to roam outside or interact with other populations. The complexity of these models comes from the variety of conditions poultry can be kept in depending on their country, what they are being raised for, and the biosecurity measures in effect. Many avian influenza studies are focused on Asian countries such as China and Thailand. The country where the
birds are raised defines the type of housing system the bird will be raised in. The type of domestic bird being looked at also plays a large role. Turkeys have a unique housing system compared to layer chickens, raised for eggs, and to broiler chickens, raise for meat. The main type of housing system in Asian countries such as Thailand and China is open barns with birds having the freedom to roam outside. These birds are often brought to live bird markets where birds from different places can spread avian influenza to other birds as well as to humans. This is where human and bird interaction can play an important role. Chong [10] examined a SIR model that included the culling of infected birds. Chong [10, 11] has looked at the human-bird interaction as well as bird movement controls as a way of controlling the virus. When all the birds are together in the bird market, there is a chance of infection to all the birds. Thiuthad et. al. [36] looked at the spread of highly pathogenic H5N1 in Thailand using a simple SIS model with population diffusion to mimic highly populous human areas. In Western countries, poultry handling is much more regulated and controlled. For chickens, layers are typically kept in battery caged housing where cages of a few hundred birds, varied in age, are stacked in rooms for rearing. Broilers are typically kept in an all-in-all-out free range styled housing system. These birds are able to roam in a large open room until rearing. All birds enter the barn on day 1 and leave the barn at the time of rearing, thus they are all the same age. This type of housing system has not been modelled to the extent other systems have, though it is important to understand.

The introduction of a vaccine to the model causes a large change in dynamics. This is because the current avian influenza vaccines available don’t always provide complete
immunity to all birds, birds can be asymptotically infected, and the pathogen can survive in the environment without a host for a period of time [12, 17]. Gulbaduk and Martcheva [17] looked at domestic poultry populations with imperfect vaccination and infection with highly pathogenic avian influenza. Their findings demonstrate that the vaccination is only effective at eradicating the disease if the vaccine is used in a wide spread population or if the vaccine efficacy is very high. They show that while culling would be best to eradicate the disease, vaccination can help play a key role in significantly reducing infectious birds. Lee and Suarez [24] discuss the importance of vaccination, not due to its ability to perfectly protect all birds, but instead to reduce the amount of virus that is in circulation in the environment and to help prevent clinical cases of the disease. Vaccination can be a highly valuable tool in managing avian influenza and the incorporation of the vaccine into a model has important implications for model stability analysis and suppression of the virus.

A summary of the peer-reviewed literature is represented in table 1.1. In terms of modelling, the wild bird and human populations are well studied, particularly in Asian countries. A lot of information is also available on the direct transmission of the pathogen. There is a need to research specific domestic poultry populations without over-simplifying the model. It is also important to look at realistic time-frames and not just long term behaviour.
1.9 Objectives

The objective of this thesis project was to develop an original model to study highly pathogenic avian influenza in a broiler chicken population with an all in-all out housing system. Once the model was specified it was analysed. A control measure of poultry vaccination will then be added to the model and solutions will be obtained to identify the control strategies and their costs for this host-pathogen system. This model will then be translated to economic applications to determine if vaccine use is optimal in any cases.

1.10 Outline of Thesis

The second Chapter of this thesis will introduce the SIR model and parameters. This model will be extended to include vaccination intervention and analyzed for stability and parameter sensitivity. An economic analysis will also be introduced and explained for analysis.

The third Chapter of this thesis will summarize the results of models in Chapter 2. The model simulations will be discussed along with their stability and sensitivity results. The economic analysis will also be explained.

The fourth Chapter of this thesis will discuss the results of analyses and how these results connect to the information already known in the peer-reviewed literature.

The fifth and final Chapter will discuss the concluding remarks. Possible future directions of this project will also be discussed.
Chapter 2

Mathematical Model

2.1 Assumptions

2.1.1 Basic Assumptions

A disease model was defined using the biology as described in section 1.2 and the SIR dynamics described in section 1.7. In addition, the following assumptions have been made to assist in describing the natural history of the disease.

1. The poultry farm system includes thousands of birds, making the population size large enough to be modelled using ordinary differential equations (ODE).

2. There is complete mixing in the population and all broilers are free to roam within a room/building Therefore, all birds have an equal likelihood of contacting any other bird.
3. Each broiler is in one of the following disease states; susceptible (able to get infection), exposed (infected but asymptomatic), or infected (infected and symptomatic) and only one of those classes at any given time, in accordance with traditional SEIR dynamics. The birds move through each class in accordance with the dynamics that are described in section 2.2.1.

4. All broilers that enter the barn at day 0 are the same age. No broilers are introduced into the population after initial time (t=0) and no other broilers die naturally. Broiler death by natural causes typically accounts for less than 1% of the population, thus it is neglected in the model [6].

5. Broilers can only become infected through contact with the pathogen in the reservoir (in this case, the environment). A reservoir is created as a result of the shedding of the pathogen into the environment by infected birds [37]. Bird to bird contact may cause transmission but more commonly, transmission occurs due to contact with infected respiratory droplets, mucus, saliva, and faeces and not by other direct means [17].

6. Birds contact the pathogen in the environmental reservoir which causes infection at some rate [37].

7. Exposed and infected individuals shed the pathogen at different rates, through bodily fluids, that contribute to the reservoir [37].

8. The pathogen will lose viability in the reservoir at some rate when not in a host, e.g. pathogen decay in the environment [35].
2.1. ASSUMPTIONS

CHAPTER 2. MATHEMATICAL MODEL

Figure 2.1: Compartment model where solid lines represent direct movement of birds and dotted lines represent movement of pathogen between hosts and environment, $P$. $S$ represents susceptible birds able to get the infection, $E$ represents exposed birds who are infected but asymptomatic, $I$ represents infected birds who are infected and symptomatic, and $P$ represents pathogen in the environment

Based on the assumptions, a compartment model was constructed as shown in Figure 2.1.

2.1.2 Vaccine Intervention

As an extension of the disease model, vaccine intervention was introduced. This intervention used the following additional assumptions:

9. If broilers are vaccinated, the entire flock is vaccinated upon entering the barn at day 1 ($t=0$) and no birds are vaccinated after this time [13].

10. If vaccinated, a broiler is in one of the classes of incomplete susceptible ($S_V$), incomplete exposed ($E_V$), or complete vaccination ($R_V$) at any given time, otherwise they are considered nonvaccinated.
11. Infection rates are the same for susceptible ($S$) and incomplete susceptible ($S_V$) individuals to enter their respective exposed classes [6].

12. The introduction of a vaccine allows broilers to be vaccinated at some rate of effectiveness [33].

13. If a broiler is imperfectly vaccinated, such that the bird can still acquire the pathogen, and becomes exposed, they will shed the disease at a lesser rate than the unvaccinated counterpart [6].

The compartmental model with included vaccination is shown in Figure 2.2.

2.1.3 Economic Analysis

An analysis of the economic viability of vaccine made the following assumptions:

14. The upfront costs to maintain a poultry barn/farm are the same, regardless of poultry population size.

15. Food is measured daily only for surviving birds [13].

16. The cost of vaccine varies depending on efficacy.

17. All birds who do not show signs of infection are consumable to the public and are sold by live weight to the abattoir for some profit [6].

18. Of the birds that have successful vaccination, an equal number of birds are incompletely vaccinated ($S_V$) and completely vaccinated ($V$).
Figure 2.2: Compartment model where solid lines represent direct movement and dotted lines represent movement of pathogen between hosts and environment. S represents susceptible birds able to get the infection, E represents exposed birds who are infected but asymptomatic, I represents infected birds who are infected and symptomatic, $S_v$ represents incompletely vaccinated susceptible individuals who are able to get the infection, $E_v$ represents incompletely vaccinated exposed individuals who are infected but asymptomatic, $R_v$ represents completely vaccinated individuals who are unable to get the infection, and P represents pathogen in the environment.
2.2 Model Structure

2.2.1 Base Model

Based on the assumptions and compartment model of section 2.1.1, an ODE mathematical model has been created using an adapted version of the SEIR system. The removed compartment, $R$ in this case is redundant and not included, it is comprised of the birds leaving the infected compartment, $I$, at rate $\delta$. First, there are susceptible, $S$, young broilers who can become exposed at some rate $\gamma$ as a result of interaction with the pathogen reservoir ($P$), as correlated to assumption 2.1.1. This interaction is not linear but is dependent on the population size and how much pathogen is shed into the environment by the infected birds. The infected birds move into the exposed class, $E$ where the infection multiplies in their system for about a week, at rate $\lambda$, before they are infected and more infective to the birds around them, $I$. Both the exposed and infected broilers contribute infection to the reservoir through shedding of the pathogen, as per assumption 2.1.1. Exposed birds shed the pathogen at rate $\beta$ and the infected birds shed the pathogen at rate $\alpha$ into the environment, $P$. With highly pathogenic avian influenza, these birds then die at some rate $\delta$. The birds become infected as a result of interaction with the pathogen reservoir, as per assumption 2.1.1. This is represented by infected birds shedding the infection into the environment through faeces, saliva, mucus, etc. Infection can be removed from the reservoir through degradation of the infection due to a reduction in the host population and their ability to shed pathogen, as per assumption 2.1.1. The system of four differential
equations is represented with the following set of equations.

\[
\begin{align*}
\frac{dS}{dt} &= -\frac{\gamma PS}{1 + P} \quad (2.1) \\
\frac{dE}{dt} &= \frac{\gamma PS}{1 + P} - \lambda E \quad (2.2) \\
\frac{dI}{dt} &= \lambda E - \delta I \quad (2.3) \\
\frac{dP}{dt} &= \alpha I + \beta E - \nu P \quad (2.4)
\end{align*}
\]

In all cases we assume all birds are initially in the susceptible class with no exposed or infected birds. There is a small amount of pathogen in the environment \((p)\). This is represented with the following initial conditions.

\[
\begin{align*}
S(0) &= N \quad (2.5) \\
E(0) &= 0 \quad (2.6) \\
I(0) &= 0 \quad (2.7) \\
P(0) &= p \quad (2.8)
\end{align*}
\]

### 2.2.2 Vaccine Intervention

The avian influenza vaccine is never perfectly matched to control for an individual outbreak and strain mismatch can cause reduced effectiveness [14]. If all broilers are vac-
2.2. MODEL STRUCTURE

Cinated on day 1, prior to entering the barn, some birds will be protected from contracting the virus. Some of these birds will have strong protection and will be fully immune to the pathogen, i.e. they will enter the compartment \( R_v \). This is the class of birds with perfect vaccine protection. Some birds will have incomplete vaccine protection, i.e. they will be in the compartment \( S_v \), as noted in assumption 2.1.2. These birds become exposed to the pathogen in the environment at the same rate as the fully susceptible birds, as per assumption 2.1.2, but have a reduced chance of becoming infected. These birds will enter an incomplete exposed class, \( E_v \). There is also a possibility that a birds immune system will not generate an immune response and will not be protected from the virus. Despite vaccination, they will remain in the compartment \( S \). These birds will remain in the basic SEIR model.

Model equations and parameters are also dependent on vaccine use and effectiveness within the population. Some fraction of the population has a vaccine used on it with some degree of effectiveness, represented by \( \xi \). Of the rest of the population \( (1 - \xi_S - \xi_R) \), the vaccine was used and had no effect on the broilers’s immune system. If the vaccine used on the broiler has worked with perfect coverage, these birds are represented by \( \xi_R \) and will have no change in infectivity through their life period. If the vaccine used on the broiler has worked with incomplete coverage, these birds are represented by \( \xi_S \) and can become exposed to the virus and shed at some rate but remain asymptomatic. The total vaccinated population \( \xi_S \) and \( \xi_R \) is equal to \( \xi \). The population fractions in each of the three initial values must add to one.
This gives us the following set of differential equations:

\[
\begin{align*}
\frac{dS}{dt} &= -\frac{\gamma PS}{1+P} \\
\frac{dE}{dt} &= \frac{\gamma PS}{1+P} - \lambda E \\
\frac{dI}{dt} &= \lambda E - \delta I \\
\frac{dP}{dt} &= \alpha I + \beta (E + E_v) - \nu P \\
\frac{dS_v}{dt} &= -\frac{\gamma PS_v}{1+P} \\
\frac{dE_v}{dt} &= \frac{\gamma PS_v}{1+P} \\
\frac{dR_v}{dt} &= 0
\end{align*}
\] (2.9) (2.10) (2.11) (2.12) (2.13) (2.14) (2.15)

The initial conditions of the model as used in computational results are as follows.
Table 2.1: Parameters and their default values used in our simulations, with references

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Units</th>
<th>Definition</th>
<th>Value</th>
<th>Citation</th>
</tr>
</thead>
<tbody>
<tr>
<td>γ</td>
<td>day$^{-1}$</td>
<td>Infection Rate</td>
<td>0.4</td>
<td>[18]</td>
</tr>
<tr>
<td>λ</td>
<td>day$^{-1}$</td>
<td>Incubation Period</td>
<td>1.4</td>
<td>[6]</td>
</tr>
<tr>
<td>δ</td>
<td>day$^{-1}$</td>
<td>Death Rate</td>
<td>0.06</td>
<td>[22]</td>
</tr>
<tr>
<td>α</td>
<td>day$^{-1}$</td>
<td>Infectious Shedding Rate</td>
<td>0.3</td>
<td>[37]</td>
</tr>
<tr>
<td>β</td>
<td>day$^{-1}$</td>
<td>Exposed Shedding Rate</td>
<td>0.2</td>
<td>[6]</td>
</tr>
<tr>
<td>ν</td>
<td>day$^{-1}$</td>
<td>Cleaning/Degredation Rate</td>
<td>varied</td>
<td>assumed</td>
</tr>
</tbody>
</table>

$$S(0) = (1 - \xi_S - \xi_R)N \quad (2.16)$$

$$E(0) = 0 \quad (2.17)$$

$$I(0) = 0 \quad (2.18)$$

$$P(0) = p \quad (2.19)$$

$$S_v(0) = \xi_S N \quad (2.20)$$

$$E_v(0) = 0 \quad (2.21)$$

$$R_v(0) = \xi_R N \quad (2.22)$$

### 2.3 Parameter Values

Parameter values used in the model were taken from the peer-reviewed literature. These parameter values were either found through lab experimentation [6, 37] or through analysis of previously described data [18, 22]. The parameters are presented in Table 2.1.
2.4 Outcome of Interest

The outcome of interest is the bird population suitable for sale to the abattoir after a finite time $T$ before termination of life and entrance into the food industry. This is the group of birds that can be used for consumption by the general population. Another outcome of interest is the profit at the end of the finite time period. The financial aspect of vaccination cost and profit of birds is also an outcome of interest.

2.5 Methods of Analysis

2.5.1 Steady State Analysis

In order to assess whether the disease can establish itself in the population or not, we carry out a steady state analysis of the disease free equilibrium. We consider an $n$-dimensional autonomous differential equation

$$\dot{x} = f(x)$$  \hspace{2cm} (2.23)

where $f : \mathbb{R}^n \to \mathbb{R}^n$ is differentiable and $x = x(t) \in \mathbb{R}^n$.

**Definition 1** Let $x^* \in \mathbb{R}^n$ be such that $f(x^*) = 0$. Then $x^*$ is called an equilibrium (steady state) of (2.23).

**Corollary 2** The constant solutions of (2.23) are its equilibria.
Definition 3 [23] An equilibrium $x^*$ of (2.23) is **stable** if for any $\epsilon > 0$ there exists a corresponding $\delta > 0$ such that every solution $x(t)$ that satisfies $\|x(0) - x^*\| < \delta$ also satisfies $\|x(t) - x^*\| < \epsilon$ for all $t \geq 0$. If $x^*$ is not stable, it is called **unstable**.

A criterion to test for stability is obtained by linearization.

Theorem 4 [39] Let $x^*$ be an equilibrium of (2.23) and let $J(x^*)$ be the Jacobian of $f$ evaluated in $x^*$ with eigenvalues $\lambda_1, \ldots, \lambda_n \in \mathbb{C}$. Define $\hat{\lambda} := \max \{\Re \lambda_i, i = 1, \ldots, n\}$. If $\hat{\lambda} < 0$, then $x^*$ is stable. If $\hat{\lambda} > 0$, then $x^*$ is unstable. If $\hat{\lambda} = 0$, then $x^*$ is stable under the linearized system if and only if for all eigenvalues with $\lambda_i$ with $\Re \lambda = 0$ the algebraic multiplicity and the geometric multiplicity are the same.

A useful tool to test for stability is Gershgorin’s theorem.

Theorem 5 [20] Let $A \in \mathbb{C}^{n \times n}$ and define

$$R_i := \sum_{j=1, j \neq i}^{n} |a_{ij}|, \quad i = 1, \ldots, n \quad (2.24)$$

and

$$D_i := \{z \in \mathbb{C} : |z - a_{ii}| \leq R_i\}, \quad i = 1, \ldots, n. \quad (2.25)$$

Then the set of all eigenvalues of $A$, $\sigma(A) := \{\lambda_1, \ldots, \lambda_n\}$ lies in

$$\sigma(A) \subset \bigcup_{i=1}^{n} D_i. \quad (2.26)$$

Another useful result to test for stability is the Routh-Hurwitz criterion.
Theorem 6 [27] Let $A \in \mathbb{R}^{n \times n}$ with characteristic polynomial

$$P(\lambda) = \lambda^n + a_1 \lambda^{n-1} + \ldots + a_n = 0,$$  \hspace{1cm} (2.27)

where coefficients $a_i, i = 0, \ldots, n$, are real and $a_n > 0$. We define $a_i = 0$ for $i > n$. The following conditions are necessary and sufficient for all eigenvalues of $A$ to have negative real parts

$$D_1 = a_1 > 0, \quad D_2 = \begin{vmatrix} a_1 & a_3 \\ 1 & a_2 \end{vmatrix} > 0, \quad D_3 = \begin{vmatrix} a_1 & a_3 & a_5 \\ 1 & a_2 & a_4 \\ 0 & a_1 & a_3 \end{vmatrix} > 0,$$

$$D_k = \begin{vmatrix} a_1 & a_3 & \cdots & \cdots \\ 1 & a_2 & a_4 & \cdots \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \cdots & a_k \end{vmatrix} > 0, \quad k = 1, \ldots, n.$$

2.5.2 Sensitivity Analysis

In order to assess model sensitivity with respect to the parameters, we perform a sensitivity analysis. We consider a parameter, $a$, in a model. The model is considered sensitive with respect to $a$ if when $a$ is varied, we observe a significant difference in the model outcome of interest. If the results are not significantly changed, the model is considered not sensitive with respect to $a$. 
Sensitivity analysis was done using the software program R and the packages ggplot and deSolve [15]. Each parameter was varied in small intervals to look at local sensitivity of the parameter and large intervals to look at global sensitivity of the parameter with respect to the model. Models were also tested at large and small population sizes to determine if there was a difference in model sensitivity across a range of population sizes.

Sensitivity of economic parameters was not done as it is an analysis done post processing and does not affect the model outcome.

### 2.5.3 Economic Analysis

An economic analysis was performed to investigate the financial benefits and costs to using a vaccination program. A function was created to model the financial loss, $L$, to a farm or farmer with a broiler chicken population infected with avian influenza. Initially, there is some cost to raising a flock, represented by $\Omega$. These costs are independent of flock size and include the costs of a building, electricity, farm hands, etc. There is an additional cost of food for the birds which is dependent on population size ($N$). In cases of death, these birds do not need to be fed. Broilers are on a strict food plan and food intake is heavily monitored. The cost of food is represented by $\varphi$ and is presented as a cost per day, based on the population size of living birds as represented in the epidemic model. If vaccination is implemented, there is a cost to vaccinate each bird. The cost of vaccination is dependent on efficacy based on the equation $v(e)$. Finally, the surviving and healthy birds can be sold into the market at some profit to the farm or farmer. This profit is dependent
Figure 2.3: Weight of birds in lbs based on age in days, represented by $\kappa(t)$

on weight and the number of surviving birds. The weights of the birds dependent on day is
represented by values in Figure 2.3 and $\kappa(t)$ based on average daily gain of birds [13]. The
profit per lb is represented by $\rho$. All parameters and their values are represented in table
2.2. Overall the equation to represent loss is as follows:

$$L(N, e, t) = \Omega + \varphi \int_0^t (N - R) d\tau + N(v(e)) - \rho \kappa(t)(N - R - I)$$  \hspace{1cm} (2.28)
Table 2.2: Estimated parameter values for economic analysis equations

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Units</th>
<th>Definition</th>
<th>Value</th>
<th>Citation</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\Omega$</td>
<td>dollars</td>
<td>Upfront Costs</td>
<td>5000</td>
<td>[1]</td>
</tr>
<tr>
<td>$\varphi$</td>
<td>dollars/bird*day</td>
<td>Food Cost</td>
<td>1.49</td>
<td>[1]</td>
</tr>
<tr>
<td>$\rho$</td>
<td>dollars/lb</td>
<td>Profit</td>
<td>1.11</td>
<td>[6]</td>
</tr>
<tr>
<td>$v(e)$</td>
<td>dollars/bird</td>
<td>Vaccine Cost</td>
<td>unknown</td>
<td>assumed</td>
</tr>
<tr>
<td>$\kappa(t)$</td>
<td>lbs</td>
<td>Bird Weight</td>
<td>Figure 2.3</td>
<td>[13]</td>
</tr>
</tbody>
</table>

2.6 Software Used

For all our simulations we used the software program R and its software packages deSolve and ggplot [15]. To aid in the stability analysis we used the computer algebra system wxmaxima [2].
Chapter 3

Results

3.1 Illustrative Simulation

Based on the model described in section 2.2.1 and the initial conditions described in section 2.2.2, an illustrative simulation was run and is shown in Figure 3.1. With the addition of the vaccination, as described in section 2.2.2, another simulation was run and shown in Figure 3.2.

In the base model without the introduction of vaccination, Figure 3.1, the parameters are as described in section 2.3 and \( \beta = 0.2, \nu = 0.3 \). The susceptible compartment is monotonically decreasing from 30000 birds to 0 by day 21. Over half of the population is removed from the susceptible compartment by day 3. The exposed compartment is increasing until it reaches its peak of 4843 exposed individuals at day 3, then is decreasing until the population reaches 0 at day 25. The infected compartment increases at a lower rate of
the exposed compartment until it reaches its peak of approximately 21259 on day 7 and decreases after that. The infected class population reaches 3379 by the 40th day. The environmental potential compartment increases and decreases similarly to that of the infected individuals compartment, only slightly delayed. The environmental reservoir amount increases and reaches a peak of 19136 on day 11 and from there is decreasing until day 40 where it reaches a value of 4223.

In the model that includes the vaccination intervention (Figure 3.2), the parameters are as described in section 2.3 and $\beta = 0.2, \nu = 0.3, \xi_s = \xi_R = \frac{1}{3}$. Initial bird population size of the poultry is 30000, the same as the model without vaccine intervention. The susceptible, exposed, and infected compartments have similar results to that of the unvaccinated model. The susceptible compartment is monotonically decreasing from 10000 birds to 0 by day 18. Over half of the population is removed from the susceptible bird population by day 3. The exposed compartment is increasing until it reaches it’s peak of 1626 exposed individuals at day 3, then is decreasing until the population reaches 0 at day 21. The infected compartment increases at a lower rate of the exposed compartment until it reaches its peak of approximately 7088 on day 7 and decreases after that. The infected class population reaches 1129 by the 40th day. The environmental potential also has a similar result to the unvaccinated model. The main difference is that after the peak, the reservoir value decreases at a lower rate in the vaccinated model. The potential increases and reaches a lower peak of 12377 on day 13 and decreases until day 40 where it reaches a value of 8077. The vaccinated susceptible individuals, $S_V$, have the same result to the susceptible individ-
3.2 Stability Analysis

The model (2.1) - (2.4) possesses a disease free steady state at \((S_0, 0, 0, 0)\). With the criterion in Theorem 4 it is stable if all its eigenvalues have negative real parts. The Jacobian of (2.1) - (2.4) is obtained as

\[
J = \begin{bmatrix}
-\frac{\gamma P}{1+P} & 0 & 0 & -\frac{\gamma S}{(1+P)^2} \\
\frac{\gamma P}{1+P} & -\lambda & 0 & \frac{\gamma S}{(1+P)^2} \\
0 & \lambda & -\delta & 0 \\
0 & \beta & \alpha & -\nu 
\end{bmatrix}.
\]

In the extinction equilibrium, \((0, 0, 0, 0)\), this reduces to
Figure 3.1: Illustrative simulation of initial model, equations (2.1) - (2.4), with initial conditions (30000, 0, 0, 0.001) over 40 days
Figure 3.2: Illustrative simulation of vaccine model with 33% efficacy, equations (2.9) - (2.15), with initial conditions (10000, 0, 0, 0.001, 10000, 0, 10000) over 40 days
3.2. **STABILITY ANALYSIS**  

\[ J(S_0, 0, 0, 0) = \begin{bmatrix} 0 & 0 & 0 & 0 \\ 0 & -\lambda & 0 & 0 \\ 0 & \lambda & -\delta & 0 \\ 0 & \beta & \alpha & -\nu \end{bmatrix} . \]

No eigenvalue is positive. One eigenvalue is 0 and three are negative. This suggests that it is not unstable, i.e. close to extinction the disease can not be eradicated.

In the disease free equilibrium, \((S_0, 0, 0, 0)\), the Jacobian reduces to

\[ J(S_0, 0, 0, 0) = \begin{bmatrix} 0 & 0 & 0 & -\gamma S_0 \\ 0 & -\lambda & 0 & \gamma S_0 \\ 0 & \lambda & -\delta & 0 \\ 0 & \beta & \alpha & -\nu \end{bmatrix} . \]

One eigenvalue of this matrix is zero. The remaining three eigenvalues are the eigenvalues of the lower 3 \times 3 submatrix, i.e. the roots of

\[ z^3 + (\delta + \lambda + \nu)z^2 + (\lambda \delta + \delta \nu + \lambda \nu - \gamma \beta S_0)z + (\lambda \delta \nu - \lambda \alpha \gamma S_0 - \gamma \beta S_0) = 0 \]

The eigenvalues of this 3 \times 3 submatrix are too involved for insightful analysis so alternative methods are used.
Gershgorin’s Theorem 5 immediately implies that the inequalities

\[ \gamma S_0 < \lambda < \delta \]
\[ \beta + \alpha < \nu \]

are sufficient for the three eigenvalues to be negative.

The first inequality states that the infection rate should be smaller than the rate of E to I. This makes sense because if birds are being infected too slowly the disease will die out before more birds become infected. The second part states that the rate of E to I should be less than the death rate. This also makes sense because if those infected are dying out faster than they are entering the infected class and in turn faster than they are becoming infected, then obviously the disease will not persist.

The second inequality states that the combination of the two shedding rates should be less than the degradation rate. This also makes sense as if pathogen is being cleaned out of the environment faster than it is being created, there is no chance for susceptible individuals to become infected.

A stronger, but more involved, necessary and sufficient stability condition can be obtained with the Routh-Hurwitz criterion 6. This requires the following inequalities

\[ D_1 = \delta + \lambda + \nu > 0 \]
\[ D_2 = \begin{vmatrix} \delta + \lambda + \nu & \lambda \delta \nu - \lambda \alpha \gamma S_0 - \delta \beta \gamma S_0 \\ 1 & \lambda \delta + \delta \nu + \lambda \nu - \gamma \beta S_0 \end{vmatrix} > 0 \]

\[ \lambda \delta \nu - \lambda \alpha \gamma S_0 - \delta \beta \gamma S_0 > 0 \]

The first inequality is unconditionally satisfied. The other inequalities can be simplified to

\[ (\delta + \lambda + \nu)(\lambda \delta + \delta \nu + \lambda \nu - \gamma \beta S_0) > (\lambda \delta \nu - \lambda \alpha \gamma S_0 - \gamma \beta \delta S_0) > 0 \]

The first part of the inequality shows that if \( \nu \) is sufficiently large that the system will be stable. It also shows that if \( \alpha \) is sufficiently large that the system will be stable. This is the cleaning rate, so if pathogen can be cleaned out fast enough, it will not be there to cause infection. If \( \alpha \gg \beta \) then the system is stable, which is true by the parameter definitions which state the shedding rate of \( I \) is larger than the shedding rate for \( E \). The second part of the inequality states that if \( \gamma \) is sufficiently small the system will be stable. This is the infection rate so it makes sense in the system. It also shows again that if \( \nu \) is sufficiently large that the system will also be stable.
3.3 Sensitivity Analysis

A sensitivity analysis was performed in Rstudio using ggplot and deSolve. The model without vaccine intervention was run initially with no parameter changes. Each parameter was then varied at ±1%, ±10%, and ±50% individually while keeping all other parameters at the base level to determine local sensitivity and global sensitivity. The initial population was set to 30000 and simulations were run for a 40 day period. Final population sizes (i.e., birds in compartments $S, E, I$) were recorded at day 30 and 40. Both of these times were chosen to show a difference in culling time on population size. These final population sizes are represented in table 3.1 and table 3.2.

Based on the final population sizes shown in tables 3.1 and 3.2, all of the parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Population Remaining</th>
<th>-50%</th>
<th>-10%</th>
<th>-1%</th>
<th>1%</th>
<th>10%</th>
<th>50%</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\gamma = 0.4$</td>
<td>6158</td>
<td>5805</td>
<td>6058</td>
<td>6147</td>
<td>6169</td>
<td>6284</td>
<td>7470</td>
</tr>
<tr>
<td>$\lambda = 1.4$</td>
<td>6158</td>
<td>6067</td>
<td>6133</td>
<td>6155</td>
<td>6161</td>
<td>6189</td>
<td>6447</td>
</tr>
<tr>
<td>$\delta = 0.06$</td>
<td>6158</td>
<td>2823</td>
<td>5265</td>
<td>6062</td>
<td>6255</td>
<td>7205</td>
<td>13544</td>
</tr>
<tr>
<td>$\beta = 0.3$</td>
<td>6158</td>
<td>6159</td>
<td>6158</td>
<td>6158</td>
<td>6158</td>
<td>6158</td>
<td>13544</td>
</tr>
<tr>
<td>$\alpha = 0.2$</td>
<td>6158</td>
<td>6181</td>
<td>6165</td>
<td>6158</td>
<td>6158</td>
<td>6151</td>
<td>6147</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Base Population</th>
<th>-50%</th>
<th>-10%</th>
<th>-1%</th>
<th>1%</th>
<th>10%</th>
<th>50%</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\gamma = 0.4$</td>
<td>3379</td>
<td>3186</td>
<td>3324</td>
<td>3373</td>
<td>3386</td>
<td>3449</td>
<td>4116</td>
</tr>
<tr>
<td>$\lambda = 1.4$</td>
<td>3379</td>
<td>3329</td>
<td>3366</td>
<td>3378</td>
<td>3381</td>
<td>3396</td>
<td>3538</td>
</tr>
<tr>
<td>$\delta = 0.06$</td>
<td>3379</td>
<td>1147</td>
<td>2721</td>
<td>3307</td>
<td>3453</td>
<td>4198</td>
<td>10033</td>
</tr>
<tr>
<td>$\beta = 0.3$</td>
<td>3379</td>
<td>3379</td>
<td>3379</td>
<td>3379</td>
<td>3379</td>
<td>3379</td>
<td>3380</td>
</tr>
<tr>
<td>$\alpha = 0.2$</td>
<td>3379</td>
<td>3373</td>
<td>3378</td>
<td>3379</td>
<td>3379</td>
<td>3381</td>
<td>3392</td>
</tr>
</tbody>
</table>
are considered not sensitive except for death rate, \( \delta \). Death rate is sensitive to parameter changes and can effect the population size immensely. Sensitivity of parameters was based on final population sizes at day 30 and 40, which is compartments \( S, E, \) and \( I \). Death rate is highly variable between strains of avian influenza and will affect the prevalence of the disease in a population. We can be confident with our parameter choices of all other parameters that they are reasonable to use in our analyses. Even though some of the parameters have larger differences in their peaks, the final population size is most important for this analysis. For the parameters that are considered not sensitive, the final population sizes are less varied from the base case than the initial parameter is varied. Due to the sensitivity of the death rate, \( \delta \), all analyses should consider the death rate parameter chosen to account for the differences that may be in the values due to this sensitivity. Also note that these graphs and table values were calculated based on an initial population of 30000 birds. Simulations were also run with a population of 5000 birds to determine if there would be a difference in the sensitivity, but there was no difference in terms of ratios and trends.

In Figure 3.3 the infection rate parameter, \( \gamma \), is measured at local sensitivity. Each compartment follows the same trend as the initial parameters and reaches the same equilibrium. There is a notable difference in the transients of the exposed compartment, \( E \), and the infected compartment, \( I \). In Figure 3.4 the infection rate parameter, \( \gamma \), is measured at global sensitivity. Each compartment follows the same trend as the initial parameters and they reach a similar equilibrium. There is a notable difference in the transients of the susceptible, \( S \), exposed, \( E \), and infected, \( I \), compartments as an increase in the parameter
causes an increase of the maximums in \( E \) and \( I \) and a decrease in time to reach the equilibrium. In Figure 3.5 the incubation parameter, \( \lambda \), is measured at local sensitivity. Each compartment follows the same trend as the initial parameters and reach the same equilibrium. There is a notable difference in the exposed compartment, \( E \), where a decrease in the parameter causes an increase in the maximum of the transient. In Figure 3.6 the incubation parameter, \( \lambda \), is measured at global sensitivity. Each compartment follows the same trend as the initial parameters and reaches the same equilibrium. There is a notable difference in the exposed compartment, \( E \), where a decrease in the parameter causes an increase in the maximum of the transient and the length it takes to reach equilibrium. In Figure 3.7 the death rate parameter, \( \delta \), is measured at local sensitivity. Each compartment follows the same trend as the initial parameters and reach a similar equilibrium. There is a significant difference in the infected compartment, \( I \), where a decrease in the parameter increases the maximum at the transient and increases the time it takes to reach equilibrium. There is also an increase of the environmental potential, \( P \), with a decrease in the parameter. In Figure 3.8 the death rate parameter, \( \delta \), is measured at global sensitivity. Each compartment follows the same trend as the initial parameters and reach the same equilibrium, except for the infected class, \( I \), and the environmental potential, \( P \). There is a significant difference in the infected compartment, \( I \), where a decrease in the parameter increases the maximum at the transient and increases the time it takes to reach equilibrium. There is also an increase of the environmental potential, \( P \), with a decrease in the parameter. These results are significant when looking at total population size or infected class size but not when
looking only at the consumable bird population, $S$ and $E$. In Figure 3.9 the shedding rate parameter, $\beta$, is measured at local sensitivity. Each compartment follows the same trend as the initial parameters and reach the same equilibrium. There is a notable difference in the environmental potential, $P$, where an increase in the parameter causes an increase in the environmental potential. This does not, however, have an effect on the other compartments. In Figure 3.10 the shedding rate parameter, $\beta$, is measured at global sensitivity. Each compartment follows the same trend as the initial parameters and reach the same equilibrium. There is a notable difference in the environmental potential, $P$, where an increase in the parameter causes an increase in the environmental potential. This does not, however, have an effect on the other compartments.

### 3.4 Economic Analysis

The results of the economic equation 2.28 are represented in Figures (3.11) - (3.14). These graphs represented do not account for the vaccination cost per bird, $v(e)$. All of the graphs show the same trends with their main differences being the slopes of the lines. This is accounted for by the cost to feed the birds versus the amount of profit at the time of slaughter. With the results of these graphs and looking back at the initial simulations, Fig-
Figure 3.3: Sensitivity analysis of infection rate parameter, $\gamma$, with 1% and 10% change in parameter value. Compartmental population sizes of birds (S,E,I) and pathogen(P) are plotted over 40 days to compare the difference due to parameter size.
Figure 3.4: Sensitivity analysis of infection rate parameter, \( \gamma \), with 10% and 50% change in parameter value. Compartmental population sizes of birds (S,E,I) and pathogen(P) are plotted over 40 days to compare the difference due to parameter size.
3.4. ECONOMIC ANALYSIS

CHAPTER 3. RESULTS

Figure 3.5: Sensitivity analysis of incubation parameter, $\lambda$, with 1% and 10% change in parameter value. Compartmental population sizes of birds (S,E,I) and pathogen(P) are plotted over 40 days to compare the difference due to parameter size.
Figure 3.6: Sensitivity analysis of incubation parameter, $\lambda$, with 10% and 50% change in parameter value. Compartmental population sizes of birds (S,E,I) and pathogen(P) are plotted over 40 days to compare the difference due to parameter size.
Figure 3.7: Sensitivity analysis of death rate parameter, $\delta$, with 1% and 10% change in parameter value. Compartmental population sizes of birds (S,E,I) and pathogen(P) are plotted over 40 days to compare the difference due to parameter size.
Figure 3.8: Sensitivity analysis of death rate parameter, $\delta$, with 10% and 50% change in parameter value. Compartmental population sizes of birds (S,E,I) and pathogen(P) are plotted over 40 days to compare the difference due to parameter size.
Figure 3.9: Sensitivity analysis of shedding rate parameter, $\beta$, with 1% and 10% change in parameter value. Compartmental population sizes of birds (S,E,I) and pathogen(P) are plotted over 40 days to compare the difference due to parameter size.
Figure 3.10: Sensitivity analysis of shedding rate parameter, $\beta$, with 10% and 50% change in parameter value. Compartmental population sizes of birds (S,E,I) and pathogen(P) are plotted over 40 days to compare the difference due to parameter size.
ures 3.1 and 3.2, it is apparent that all birds die of the disease before the time of slaughter. Thus only the birds with vaccination contribute to the economic model. Since the initial population data based on efficacy is linearly related, the economic results also show a linear relationship. When looking at the relationship of population size on loss, it appears that the loss function will converge to some maximum linear relationship, despite an increase in population.

Vaccination cost can range from $0.50 to $3.40 [30], but the relationship with efficacy is not well known. The result of the economic equation (2.28) with inclusion of vaccination cost per bird, $v(e) = e^2$ is represented in Figure 3.15. When this graph is compared to Figure 3.12, which both look at results of culling at day 30, you can see that the y-intercepts are the same for both. The main difference is the curve of the line that is associated with a quadratic relationship of vaccine efficacy. It can be seen that the vaccine efficacy relationship only plays a minor role in the economic equation and the main results are due to the portions of the equation that do not include this relationship. Since the relationship of the efficacy vs cost is not well known for HPAI in broilers, it is important to look at the results of the other parts of the equation. These Figures have a 1:1 ratio of poultry in compartments $S_V$ and $R_V$ through the initial conditions, but it is important to note that when the ratio was switched to 2:0 or 0:2 that the results did not change.
Figure 3.11: Financial loss per bird versus efficacy at day 25 with no vaccination cost
3.4. ECONOMIC ANALYSIS

Figure 3.12: Financial loss per bird versus efficacy at day 30 with no vaccination cost

Figure 3.12: Financial loss per bird versus efficacy at day 30 with no vaccination cost
3.4. ECONOMIC ANALYSIS  

CHAPTER 3. RESULTS

Figure 3.13: Financial loss per bird versus efficacy at day 35 with no vaccination cost
Figure 3.14: Financial loss per bird versus efficacy at day 40 with no vaccination cost
3.4. ECONOMIC ANALYSIS

CHAPTER 3. RESULTS

Figure 3.15: Financial loss per bird versus efficacy at t=30 with vaccination parameter

Figure 3.15: Financial loss per bird versus efficacy at day 40 with vaccination cost $e^2$
Chapter 4

Discussion

4.1 Stability Analysis

In the linear stability analysis, there are zero eigenvalues that pose difficulty in finding complete stability results. Instead, we obtained partial results which gave conditions at which there is instability. For the disease free steady state, we know the disease has the ability to establish itself. There are specific parameters in the model that can have an effect on the ability of the virus to become established. These parameters can be controlled through operational strategies or are affected by the strain of avian influenza.

The parameters $\alpha$, $\beta$, $\gamma$, and $\delta$ are determined by the strain of the disease. $\alpha$ and $\beta$ are the shedding rates of an exposed or infected individual. The shedding of pathogen contributes to the environmental potential and thus the spread of disease. If these rates are significantly small, and significantly smaller than the degradation rate $\nu$, there is no
instability. If the infection rate parameter $\gamma$ is sufficiently small, there is no instability. If the death rate parameter $\delta$ is significantly large, there is also no instability. If the death rate is large enough, the infected individuals will die before they have the ability to shed the pathogen and spread the disease.

The parameter $\nu$ is the removal or degradation rate. This could in part be controlled by the disease in the viability of the virus outside of a host. If this viability is very small, the disease would be unable to establish itself in the population. $\nu$ can also have an operational strategy role. This can be represented as a cleaning or removal parameter. If the barn is cleaned (i.e. shovel shavings) well enough and often enough, the disease may not establish in a population. It is important to note that cleaning will come at some cost that will have an effect on the economic analysis of the model.

As an addition to the results, a quick simulation was run to determine the qualitative behaviour of a lower pathogenic strain. All parameters were halved and the vaccine-free case was run. The results are represented in Figure 4.1, where all the default parameters were halved for the simulation. This shows that with low pathogen avian influenza (LPAI), there is the possibility of an endemic equilibrium in the population and that more work should be done looking into this case.

Through this stability analysis we can see that the population reaches equilibrium very quickly. The pathogen does not reach equilibrium as quickly as the populations but still reaches equilibrium in a short time. This trend may not necessarily be true for lower pathogenic strains of avian influenza. It would be interesting to study the time it takes to
Figure 4.1: Simulation of low pathogen avian influenza with initial conditions (10000, 0, 0, 0.001) over 40 days where $\gamma = 0.2$, $\lambda = 0.7$, $\delta = 0.03$, $\alpha = 0.15$, $\beta = 0.1$, $\nu = 0.3$
reach equilibrium and how different parameter values affect the equilibrium of the model.

4.2 Sensitivity Analysis

In the sensitivity analysis, it was determined that the model was only sensitive to the death rate parameter, $\delta$. The death rate parameter significantly decreased the population size of the infected compartment as death rate increased. Death rate is highly variable between strains of avian influenza and can have a major impact on the population.

The model was not considered sensitive to any of the other parameter values. Many of these parameters, however, were sensitive in the transient periods of the populations. Since the model reaches equilibrium very quickly, these transient values do not play a role in the sensitivity of the model. If we were to study this model with lower pathogenic avian influenza, it is possible that the point of culling could take place during this transition. These parameters then may have a major impact on the sensitivity of the model.

4.3 Economic Analysis

In the economic analysis, it was determined that under specific assumptions, vaccination in a population at some efficacy can lead to a profit. This is largely dependent on the cost of the vaccination. This cost is not currently known, particularly in relation to the efficacy of the vaccine. With further research into this relationship, an idea of how vaccination can affect profit could be better determined. In the efficacy, there is also a fixed relationship...
we assumed. It is possible that different relationships between efficacy will give different results. Also due to the wide range of vaccine costs, different costs of vaccine will also give different results. These different relationships can either support the use of vaccine or not.

This analysis looked specifically at vaccination in a single population where there was a guarantee of infection. It may not always make sense to introduce vaccination into a population where the probability of disease is very low. For some likelihood of infection, \( p \), and some number of flocks, \( M \), a formula can be created to analyze the financial loss over multiple flocks:

\[
L = (1 - p)M \times \text{Loss}_{\text{uninfected}} + pM \times \text{Loss}_{\text{infected}}
\]  

(4.1)

In this formula, the loss values are calculated through the loss function in the economic analysis. This can be analyzed for flocks that are vaccinated or unvaccinated, i.e. 0% vaccine efficacy. The equation for each can be set equal to determine the probability of infection needed to turn a profit (or negative loss) from vaccinating flocks.

The economic analysis focused on highly pathogenic avian influenza. It is possible that for lower pathogenicities the cost of the vaccination may outweigh the benefits. Further studies into this idea should be looked at in the future.
Chapter 5

Conclusions

5.1 Conclusions

In this thesis, a system of ordinary differential equations was presented to model the spread of avian influenza in a broiler chicken population and environment. The model and subsequent analysis is able to conclude the following:

• The outcome of the model is not sensitive to parameters in the range of highly pathogenic avian influenza values. This is because the point of termination occurs after the equilibrium on the consumable birds is reached. This is to say that all birds who will not enter the consumer food system are not viable much earlier than culling would occur.

• The cost of vaccination per bird can be substantial compared to other costs and profit per bird. In cases of highly pathogenic avian influenza outbreaks, vaccination can
turn financial loss into profit. For situations in which the possibility of an avian influenza outbreak is unknown, the cost of the vaccination may outweigh the possible benefits of its use.

- The results of the economic analysis are heavily dependent on the efficacy of the vaccination and its cost. The relationship between these two parameters is not well understood. Therefore, for our analysis, we had to introduce simplifying assumptions.

- The economic analysis equation and results presented in this thesis consider a single infected flock. These results could be used in a risk analysis of operations with several flocks, which have a certain likelihood of infection.

## 5.2 Future Work

To better understand the results provided in this thesis, more work should be done. First, the standard linearization process did not give a full result of stability. Other methods should be looked into to help fully understand the stability. The initial conditions are also meaningful to the stability and to other results. They should be emphasized and incorporated into the stability analysis. This work can be computationally difficult and may not give results that are intuitive to parameters.

As previously discussed, an analysis of lower pathogenic cases of avian influenza should be looked into. Specifically how the model changes, the differences of cost and the likeli-
hood of vaccine use, and the sensitivity of model parameters. If termination occurs in the transient stage, all of these areas will vary to what was presented in this thesis. This can be done by looking at parameter values associated with lower pathogenicities and similar analyses can be done.

The relationship between vaccine cost and efficacy is heavily dependent on assumption and is limited in research. More work should be done to better define this relationship and look into the breakdown of the definition of efficacy. This should be done through lab trials and on-farm trials. These will be associated with high financial costs to run and animal ethics issues.

As previously discussed, the risk analysis of multiple flocks should be looked into. The financial gains and losses in one flock with guaranteed infection will differ from many flocks with only some probability of infection. This can first be done through analysis of an equation with many different flock sizes and probabilities of infection. This can also be performed in an on-farm trial to determine the real life application of the vaccine over time for a farmer.
References


[38] Walden, G., and Pallone, F. USDA has taken actions to reduce risks but needs a plan to evaluate its efforts. USA Government Accountability Office, 2017.

