Final Report

Project Title Modeling an avian influenza dynamics with controls

By Dr.Chairat Modnak

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Abstract

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ในงานวิจัยนี้ ผู้วิจัยมีความสนใจในการสร้างแบบจำลองทางคณิตศาสตร์เพื่ออธิบายการแพร่ระบาดของโรคไข้หวัดนกสายพันธ์ใหม่และศึกษาการรักษาและควบคุมการแพร่ระบาดอย่างเหมาะสม เพื่อลดจำนวนของผู้ติดเชื้อและป้องกันการแพร่ระบาดต่อไป ซึ่งในงานวิจัยนี้ ผู้วิจัยได้ศึกษางานวิจัยต่างๆมากมายที่เกี่ยวข้องและค้นคว้าหาข้อมูลจากเว็บไซต์ที่สาคัญต่างๆเพื่อนำข้อมูลมาประกอบในการทางานวิจัยในครั้งนี้ ซึ่งแบบจำลองที่ผู้วิจัยได้สร้างขึ้น สามารถอธิบายการแพร่ระบาดของโรคไข้หวัดนกสายพันธ์ใหม่ได้ดีและมีเสถียรภาพในการนำไปใช้งาน ซึ่งสามารถยืนยันได้จากบทพิสูจน์ทางคณิตศาสตร์และผลวิเคราะห์เชิงตัวเลข การหาค่าเหมาะสมในการรักษาด้วยยาต่อต้านไวรัสได้รวมในงานวิจัยนี้ด้วยเช่นเดียวกัน เพื่อเป็นประโยชน์ต่อการวางแผนในการรักษาผู้ป่วยอย่างเหมาะสม

In this work we have studied the spread of bird flu or avian influenza by first we considered the spread from birds to humans and to have simpler model we have considered only human-human transmission for our second model. The latter makes analysis easier for global stability. For both models, we have determined the reproductive numbers of both epidemic and endemic equilibrium points. The numerical simulations are used to verify our analyzes and optimal solutions are computed by optimal control study.

Keywords : Optimal control study, avian influenza, infectious disease.

Executive summary

In this research, we have studied several avian influenza mathematical models and we found that many of them have not included treatment strategies to control the disease outbreaks. Therefore, in our study, we have presented a mathematical model for avian influenza that involves both bird and human populations and that incorporates the effects of latency and vaccination for humans, using a system of six nonlinear differential equations. Our model employs an SI model for birds and an SEIRS model for humans, and both bird-to-human and human-to-human transmission routes are included in the system. We have analyzed the epidemic and endemic dynamics of the combined model; particularly, we have established the local and global stabilities based on the basic reproductive numbers. In addition, we have performed an optimal control study to explore the optimal vaccination strategy in order to contain the disease outbreak in humans. Our results show that human vaccination, when strategically deployed, can signifficantly reduce the numbers of exposed and infectious people and help eradicate the disease outbreak. Throughout the paper, we have utilized both analytical and numerical means so as to gain deeper insight into the disease dynamics. There are several limitations in this study which we hope to overcome in future work. We have assumed that vaccination confers lifetime immunity, though, more realistically, we could consider imperfect vaccination. In such a case, a new compartment representing the vaccinated class can be added into the model, where vaccinated individuals can lose immunity over time and re-enter the susceptible class. For simplicity, we have only considered bi-linear incidence in this work. Similar modeling and analysis techniques can be extended to other types of incidences (such as half saturation) for more careful investigation of the disease mechanism. In addition, differentiating LPAI and HPAI dynamics and incorporating the mutation of virus strains into our model will allow more detailed study, and possibly lead to deeper understanding of avian influenza.

Objectives

1. We will study and investigate several avian mathematical models.
2. We will formulate an avian mathematical model with controls.
3. We will conduct numerical simulations to verify our results.
4. We will conclude our resutls and provide some suggestions.

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Chapter 1

Introduction

Avian influenza is an infectious viral disease of birds especially wild water fowl such as ducks and geese, often causing no apparent signs of illness. Avian Influenza viruses can sometimes spread to domestic poultry and cause large-scale outbreaks of serious disease. Some of these Avian Influenza viruses have also been reported to cross the species barrier and cause disease or subclinical infections in humans and other mammals. Avian Influenza viruses are divided into 2 groups based on their ability to cause disease in poultry: high pathogenicity or low pathogenicity. Highly pathogenic viruses result in high death rates (up to 100% mortality within 48 hours) in some poultry species. Low pathogenicity viruses also cause outbreaks in poultry but are not generally associated with severe disease.

The H5N1 virus subtype, a highly pathogenic Avian Influenza virus, first infected humans in 1997 during a poultry outbreak in Hong Kong SAR, China. Since its widespread re-emergence in 2003 and 2004, this avian virus has spread from Asia to Europe and Africa and has become entrenched in poultry in some countries, resulting in millions of poultry infections, several hundred human cases, and many human deaths. Outbreaks in poultry have seriously impacted livelihoods, the economy and international trade in affected countries.

The H7N9 virus subtype, a low pathogenic Avian Influenza virus, first infected 3 humans 2 residents of the city of Shanghai and 1 resident of Anhui province in March 2013. No cases of H7N9 outside of China have been reported. Containment measures, including the closure of live bird markets for several months, have impacted the agriculture sectors of affected countries and international trade. Continued surveillance for H7N9 will be necessary to detect and control the spread of the virus.

THE CAUSE OF THE AVIAN INFLUENZA DISEASE

Bird flu can be transmitted from livestock to wild birds and also to pet birds, and vice-versa. The virus spreads through infected birds, via their saliva, nasal secretions, feces, and feed. Birds become infected when they are in contact with contaminated

excrements or secretions, or tainted surfaces. Domesticated poultry becomes infected via direct contact with infected waterfowl, other infected livestock, or tainted surfaces of cages and other farming equipment and installations.

There are three types of influenza viruses: A, B and C. Wild aquatic birds particularly certain wild ducks, geese, swans, gulls, shorebirds and terns are the natural hosts for all known influenza type A viruses. Influenza A viruses are divided into subtypes on the basis of two proteins on the surface of the virus: hemagglutinin (H) and neuraminidase (N). For example, an "H7N2 virus" designates an influenza A virus subtype that has an H 7 protein and an N 2 protein. Similarly an "H5N1" virus has an H 5 protein and an N 1 protein. There are 18 known H subtypes and 11 known N subtypes. Many different combinations of HA and N proteins are possible. All known subtypes of influenza A viruses can infect birds, except subtypes H17N10 and H18N11, which have only been found in bats. Only two influenza A virus subtypes i.e. H1N1 and H3N2 are currently in general circulation among people. Some subtypes are found in other infected animal species. For example, H7N7 and H3N8 virus infections can cause illness in horses, and H3N8 virus infection can also cause illness in dogs. Three prominent subtypes of avian influenza A viruses are known to infect both birds and people.

RISK FACTORS FOR HUMAN INFECTION

The primary risk factor for human infection appears to be direct or indirect exposure to infected live or dead poultry or contaminated environments, such as live bird markets. Controlling circulation of the (H5N1) and (H7N9) viruses in poultry is essential to reducing the risk of human infection. Given the persistence of the (H5N1) and (H7N9) viruses in some poultry populations, control will require long-term commitments from countries and strong coordination between animal and public health authorities. Although avian influenza A viruses usually do not infect humans, rare cases of human infection with these viruses have been reported. Most human infections with avian influenza A viruses have occurred following direct or close contact with infected poultry. Illness in humans has ranged from mild to severe.

The spread of avian influenza A viruses from one ill person to another has been reported very rarely, and has been limited, inefficient and not sustained. However, because of the possibility that avian influenza A viruses could change and gain the ability to spread easily between people, monitoring for human infection and person-to-person

transmission is extremely important for public health.

SYMPTOMS

The reported signs and symptoms of low pathogenic avian influenza A virus infections in humans have ranged from conjunctivitis to influenza-like illness e.g. fever, cough, sore throat, muscle aches to lower respiratory disease (pneumonia) requiring hospitalization. Highly pathogenic avian influenza A virus infections in people have been associated with a wide range of illness from conjunctivitis only, to influenza-like illness, to severe respiratory illness e.g. shortness of breath, difficulty breathing, pneumonia, acute respiratory distress, viral pneumonia, respiratory failure with multi-organ disease, sometimes accompanied by nausea, abdominal pain, diarrhea, vomiting and sometimes neurologic changes (altered mental status, seizures). H7N9 and Asian H5N1 have been responsible for most human illness worldwide to date, including the most serious illnesses and deaths.

TREATMENT

Treatment of patients with severe influenza e.g. those requiring hospitalization presents multiple challenges. The effect of specific antiviral strategies in serious or life-threatening influenza is not established from clinical trials conducted to support licensure of oseltamivir and zanamivir, as those studies were conducted primarily among previously healthy outpatients with uncomplicated illness. However, a number of more recent observational studies have reported that oseltamivir treatment up to 96 hours after illness onset of patients hospitalized with suspected or confirmed influenza is associated with lower risk for severe outcomes. For this reason, recommendations in this report do not necessarily represent FDA-approved uses of antiviral products but are based on published observational studies and expert opinion and are subject to change as the developmental status of investigational products and the epidemiologic and virologic features of influenza change over time. Initiation of antiviral treatment as early as possible is recommended for hospitalized patients. However, antiviral treatment might be effective in reducing morbidity and mortality in hospitalized patients even if treatment is not started until more than 48 hours after onset of illness. Data from observational studies indicates the benefit of antiviral treatment for hospitalized persons even when treatment is delayed. Careful attention to ventilator and fluid management and to the prevention and treatment of secondary bacterial pneumonia also is critical for severely ill patients.

PREVENTION

Currently, there is no disease bird flu vaccine that has been allowed to be used in General, but in the near future is expected to test the vaccine in people. Best flu vaccine used in the vaccine is a mixture of H1N1 and H3N2 strains B, which should be injected in the Group at risk like a professional involved with chicken, duck, goose, all poultry and birds quail farmers who end salvage staffing medical patient care bird flu. In the area of medicine influenza and bird flu are only 2 – 3 types. For Thailand We use the drug oseltamivir, which is used to eat. And the first phase, in the disease. However, this type of medication should have surveillance because it was originally reported to be drug resistant, such as reports from Japan found infections influenza drugs oseltamivir to anti-malarial 18 percent, so those who are in high risk groups should get a vaccination flu prevention. Medical personnel have the opportunity to bird flu infection. Although it does not happen very often but I do work with caution, according to the international standard (universal precaution).

Chapter 2

Basic Concepts

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

Dr.Chairat Modnak and Dr. Jin Wang : SEIR Model[25]

They let N_h and N_b represent the population of humans and birds, respectively. The population of birds is divided into two groups: S_b and I_b, where S_b represents the susceptible and I_b represents the infected birds. The population of humans is classified into three classes, susceptible (S_h), exposed (E), infective (I_h), and recoverd (R). We let ϕ_h represents for vaccination control. The recovered individuals can move to the susceptible class due to the temporary immunity disapperance. Thus, their purpose model takes the from below:

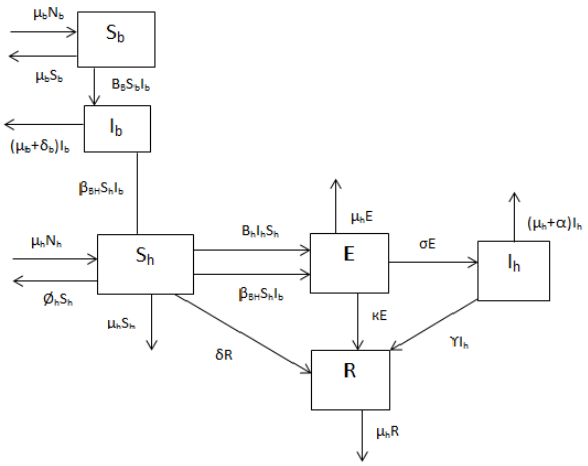

Figure 2.1: The SEIR Model

$$
\begin{aligned}
\frac{dS_b}{dt} &= \mu_b N_b - \mu_b S_b - \beta_B S_b I_b, \\
\frac{dI_b}{dt} &= \beta_B S_b I_b - (\mu_b + \delta_b) I_b, \\
\frac{dS_h}{dt} &= \mu_h N_h - \beta_h I_h S_h - \beta_{BH} S_h I_b + \delta R - \mu_h S_h - \phi_h S_h, \\
\frac{dE}{dt} &= \beta_h I_h S_h + \beta_{BH} S_h I_b - (\mu_h + \sigma + \kappa) E, \\
\frac{dI_h}{dt} &= \sigma E - (\mu_h + \alpha + \gamma) I_h, \\
\frac{dR}{dt} &= \kappa E + \gamma I_h - \mu_h R - \delta R,
\end{aligned}
$$

Table 1 Biological meaning of all parameters and state variables.

Parameter	Biological meaning
N_b	Total population of birds
N_h	Total population of humans
S_b	Susceptible birds
S_h	Susceptible humans
I_b	Infected birds
I_h	Infected humans
E	Exposed individuals
R	Recovered individuals
μ_b	Natural death and birth rates of birds
β_b	Rate at which birds contract avian influenza
δ_b	Additional disease death rate due to avian strain in birds
β_h	Transmission coefficient of the disease
β_{BH}	Rate at which bird-to-human avian influenza is contracted
σ	The loss of immunity period
μ_h	Natural death and birth rates of humans
κ	The recovery rate for exposed popution
γ	The recovery rate for infected population
α	The disease induced morality rate

Md.Samsuzzoha : SEIRS Model[7]

In this model, the population under study is divided into four groups: susceptible (those at risk of contracting the disease),exposed (those who are infected but not yet infectious), infective (those who are infectious and capable of transmitting the disease), and recovered (those who have not attained permanent immunity). It has been assumed that only susceptible populations are affected by the infectious populations. Since recovery does not give immunity, individuals move from the susceptible- exposed-infectious class to the susceptible class upon recovery when the temporary immunity disappears. The model consists of the following system of ordinary differential equations:

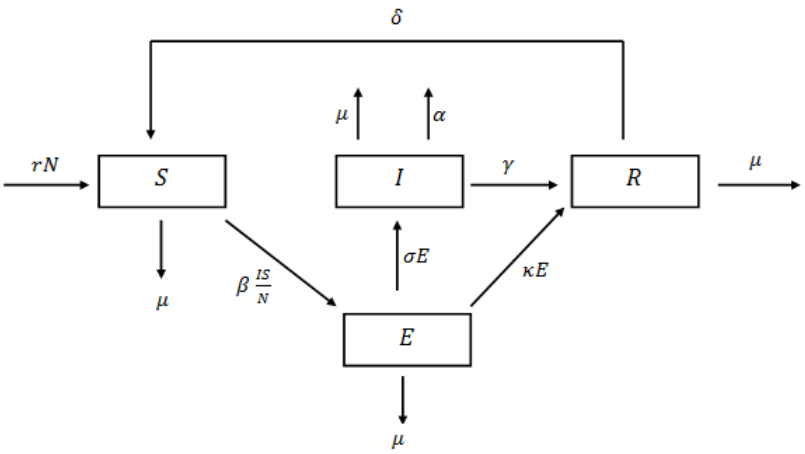

Figure 2.2: The SEIRS Model

$$
\begin{aligned}
\frac{dS}{dt} &= -\beta\frac{IS}{N} - \mu S + rN + \delta R, \\
\frac{dE}{dt} &= \beta\frac{IS}{N} - (\mu + \sigma + \kappa)E, \\
\frac{dI}{dt} &= \sigma E - (\mu + \alpha + \gamma)I, \\
\frac{dR}{dt} &= \kappa E + \gamma I - \mu R - \delta R,
\end{aligned}
$$

and $S + E + I + R = N$ where the variables S, E, I and R represent the proportion of the populations in each of the four categories: susceptible individuals, exposed individuals, infected individuals and recovered individuals, respectively. Here N represents the total population. The parameters representation is as: β, the transmission coefficient of the disease; μ, the natural mortality rate; r, the birth rate;σ^{-1} , the incubation period; κ and γ, the recovery rate for both exposed and infected populations; α, the disease induced morality rate and δ^{-1}, the loss of immunity period.

Table 2 Parameters used in the numerical solution.

Parameter	Biological meaning	Value	Source
β_0	Transmission coefficient	0.514000000	[?]
σ^{-1}	Mean duration of latency (days)	2.000000000	[?]
γ^{-1}	Mean recovery time for clinically ill (days)	5.000000000	[?]
δ^{-1}	Duration of immunity loss(days)	365.0000000	[?]
μ	Natural mortality rate per day	5.500×10^{-8}	[?]
r	Birth rate per day	7.140×10^{-5}	[?]
κ	Recovery rate of latents per day	1.857×10^{-4}	[?]
α	Flu induced mortality rate per day	9.300×10^{-6}	[?]
ε	Degree ofseasonality	0.500000000	[?]

Md.Samsuzzoha : SVEIRS Model[8]

The SVEIRS model for influenza proposed of the following system of nonlinear ordinary differential equations:

$$\frac{dS}{dt} = -\beta\beta_E\frac{ES}{N} - \beta\beta_I\frac{IS}{N} - \phi S - \mu S + \delta R + \theta V + rN,$$
$$\frac{dV}{dt} = -\beta\beta_E\beta_V\frac{EV}{N} - \beta\beta_I\beta_V\frac{IV}{N} - \mu V - \theta V + \phi S,$$
$$\frac{dE}{dt} = \beta\beta_E\frac{ES}{N} + \beta\beta_I\frac{IS}{N} + \beta\beta_E\beta_V\frac{EV}{N} + \beta\beta_I\beta_V\frac{IV}{N} - (\mu + \kappa + \sigma)E,$$
$$\frac{dI}{dt} = \sigma E - (\mu + \alpha + \gamma)I,$$
$$\frac{dR}{dt} = \kappa E + \gamma I - \mu R - \delta R,$$

The diagram of this model is represented as follows:

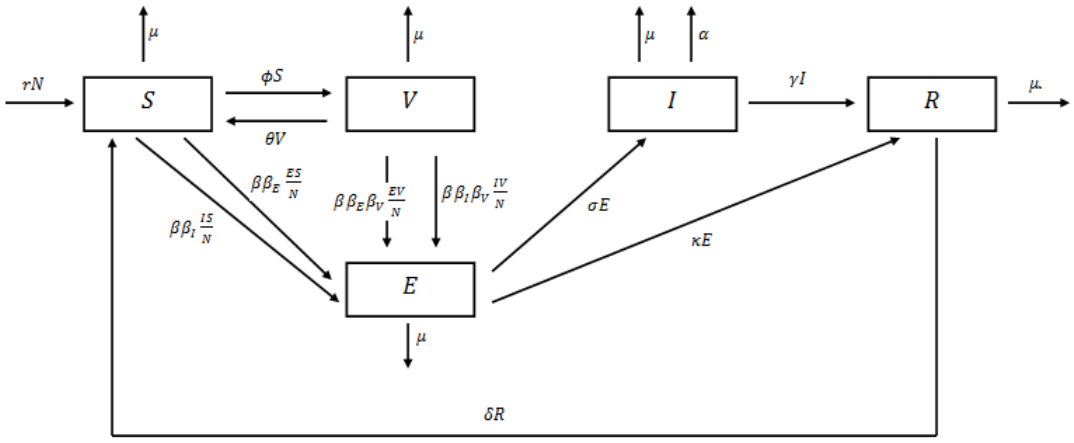

Figure 2.3: The SVEIRS Model

Table 3 Biological meaning of all parameters and state variables.

Parameter	Biological meaning
β	Contact rate
β_E	Ability to cause exposed by exposed individuals
β_I	Ability to cause infection by exposed individuals
$1-_{\beta_V}$	Factor by which the vaccine reduces infection
σ^{-1}	Mean duration of latency
γ^{-1}	Mean recovery time for clinically ill
δ^{-1}	Duration of immunity loss
μ	Natural mortality rate
r	Birth rate
κ	Recovery rate of latents
α	Flu induced mortality rate
θ^{-1}	Duration of vaccine-induced immunity loss
ϕ	Rate of vaccination
State variables and their biological meaning	
S	Proportion of susceptible population
V	Proportion of vaccinated population
E	Proportion of exposed population
I	Proportion of infective population
R	Proportion of recovered population
N	Total population
S_0	Number of susceptible population at time t = 0
V_0	Number of vaccinated population at time t = 0
E_0	Number of exposed population at time t = 0
I_0	Number of infective population at time t = 0
R_0	Number of recovered population at time t = 0

Table 4 Estimated parameters value for $SEIRS$ Model.

Parameter	Value(First)[1]	Value (Second wave)[1]	Source
β	0.502000	0.5000000	Estimated
σ	0.6990000	1.0000000	Estimated
γ	0.3600000	0.3400000	Estimated
δ	0.0027400	0.0027400	...
μ	0.0003671	0.0003671	...
r	0.0006762	0.0006762	...
κ	0.0001500	0.0001500	Estimated
α	0.0300000	0.0300000	Estimated
S_0	4865.0000	3982.0000	Estimated
E_0	9.0000000	10.000000	Estimated
I_0	68.000000	79.000000	Estimated
R_0	0.0000000	0.0000000	...

[1] Unit per day where applicable.

Nyuk Sian Chong Model[11]

The population of birds and humans are represented by $N_b(t)$ and $N_h(t)$, respectively, at time t. The bird population is divided into two sub-populations: susceptible (S_b) and infected (I_b) birds. The number of susceptibles for the bird population is increased by new recruitment (birth), but reduced through natural death and infection (moving to class I_b). On the other hand, the infected bird population is increased by the infection of susceptible birds whereas reduction is caused by natural mortality and death due to avian influenza. The total bird population at time t is formulated by $N_b = S_b + I_b$. The human population is subdivided into those who are susceptible (S_h), infected with avian strain (I_a), infected with mutant strain (I_m), and recovered from avian and mutant strains (R_h). The total population of humans at time t is given by $N_h = S_h + I_a + I_m + R_h$. The number of susceptibles for the human population is increased by recruitment, but diminished by infection (moving to class I_a or I_m) and natural death. The number of infected humans with the avian strain is increased by the infection of susceptible humans and reduced through mutation (moving to class I_m), recovery from the disease (moving to class R_h), natural death and disease death. The growth of the population of infected

humans with mutant strain is caused by the infection of susceptible humans and mutation of infected humans with the avian strain, but reduced by recovery from the disease (moving to class R_h), natural death and disease death.

A schematic flowchart of this model is depicted in Figure 2.4. The descriptions of the variables and associated parameters are given in Table 4.

Considering the above formulations and the flow diagram, we have the following system of nonlinear ordinary differential equations:

$$\begin{aligned}
\frac{dS_b}{dt} &= \Lambda_b - \mu_b S_b - \frac{\beta_b S_b I_b}{H_b + I_b}, \\
\frac{dI_b}{dt} &= \frac{\beta_b S_b I_b}{H_b + I_b} - (\mu_b + \delta_b) I_b, \\
\frac{dS_h}{dt} &= \Lambda_h - \mu_h S_h - \frac{\beta_a S_h I_a}{H_a + I_a} - \frac{\beta_m S_h I_m}{H_m + I_m} - \frac{\beta_{bh} S_h I_b}{H_{bh} + I_b}, \\
\frac{dI_a}{dt} &= \frac{\beta_{bh} S_h I_b}{H_{bh} + I_b} + \frac{\beta_a S_h I_a}{H_a + I_a} - (\mu_h + d + \varepsilon + \gamma_a) I_a, \\
\frac{dI_m}{dt} &= \frac{\beta_m S_h I_m}{H_m + I_m} + \varepsilon I_a - (\mu_h + \alpha + \gamma_m) I_m, \\
\frac{dR_h}{dt} &= \gamma_a I_a + \gamma_m I_m - \mu_h R_h,
\end{aligned}$$

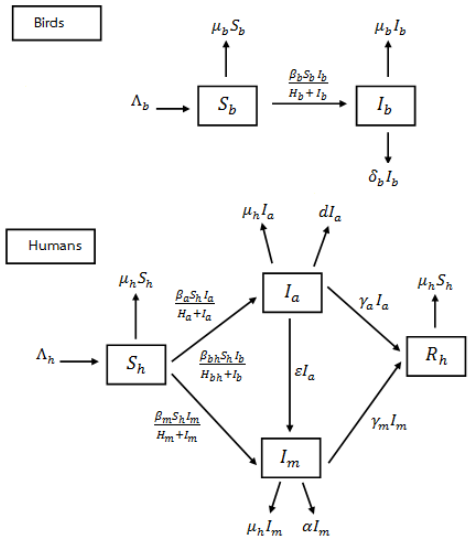

Figure 2.4: Flowchart of the model

Table 5 Description of the variables and associated parameters.

Symbol	Description
$S_b(t)$	Susceptible birds
$I_b(t)$	Infected birbs
$S_h(t)$	Susceptible humans
$I_a(t)$	Infected humans which avian strain
$I_m(t)$	Infected humans which mutant strain
$R_h(t)$	Recovered humans from avian and mutant strains
$N_b(t)$	Total bird population
$N_h(t)$	Total human population
$\Lambda_b(t)$	Bird inflow
$\Lambda_h(t)$	Human recruitment rate
$\mu_b(t)$	Natural death rate of birds
$\mu_h(t)$	Natural death rate of humans
$\beta_a(t)$	Rate at which human-to-human avian influenza is contracted
$\beta_m(t)$	Rate at which human-to-human mutant influenza is contracted
$\beta_{bh}(t)$	Rate at which bird-to-human avian influenza is contracted
$\beta_b(t)$	Rate at which birds contract aviav influenza
$H_a(t)$	Half-saturation contant for human with avian strain
$H_m(t)$	Half-saturation contant for human with mutant strain
$H_b(t)$	Half-saturation contant for birds with avian strain
α	Additional death rate mediated by mutant strain
S_0	Number of susceptible population at time $t = 0$
V_0	Number of vaccinated population at time $t = 0$
E_0	Number of exposed population at time $t = 0$
I_0	Number of infective population at time $t = 0$
R_0	Number of recovered population at time $t = 0$

Table 6 Model parameters

Parameter	Sample value	References	Range
Λ_b	$1,000$ per day	Bowman et al. (2005)	$[100, 2,000]$
Λ_h	30 per day	Bowman et al. (2005)	$[1.30]$
μ_b	$\frac{1}{100}$ per day	Gumel (2009)	$[0.0005, 0.1]$
μ_h	$\frac{1}{70\times365}$ per day	Bowman et al.	$\left[\frac{1}{75\times365}, \frac{1}{65\times365}\right]$
β_a	0.4 per day	Gumel (2009)	$[0.05, 2.5]$
β_m	$0.3 \times \beta_a$ per day	Gumel (2009)	[0.01,0.5]
H_a	$150,000$ intdividuals	Assumed	$[10,000, 500,000]$
H_m	$150,000$ intdividuals	Assumed	$[10,000, 500,000]$
α	0.06 per day	Iwami et al. (2007)	$[0.01, 0.1]$
ε	0.01 per day	Gumel (2009)	$[0.005, 0.05]$
d	1 per day	Iwami et al. (2007)	$(0.05, 2.5)$
δ_b	5 per day	Iwami et al. (2007)	$[1, 10]$
γ_a	0.05 per day	Gumel (2009)	$[0.01, 0.1]$
γ_m	0.01 per day	Gumel (2009)	$[0.005, 0.05]$
β_b	0.4 per day	Gumel (2009)	$[0.05, 2.5]$
H_b	$180,000$ individuals	Assumed	$[10,000, 500,000]$
β_{b_h}	0.2 per day	Iwami et al. (2007)	N/A
H_{b_h}	$120,000$ individuals	Assumed	N/A

Chapter 3

Research methodology

3.1 Our first proposed model

From our model formulation, we next will conduct the epidemic and endemic analysis. At the disease-free equilibrium state we have absence of infection. We let N_h and N_b represent the population of humans and birds, respectively. The population of birds is divided into two groups: S_b and I_b, where S_b represents the susceptible and I_b represents the infected birds. The population of humans is classified into three classes,susceptible (S_h), exposed (E), infective (I_h), and recovered (R). We let ϕ_h represents for vaccination control. The recovered individuals can move to the susceptible class due to the temporary immunity disappearance. Thus, our purpose model takes the form below: A diagram to illustrate our model is presented in Figure 3.1

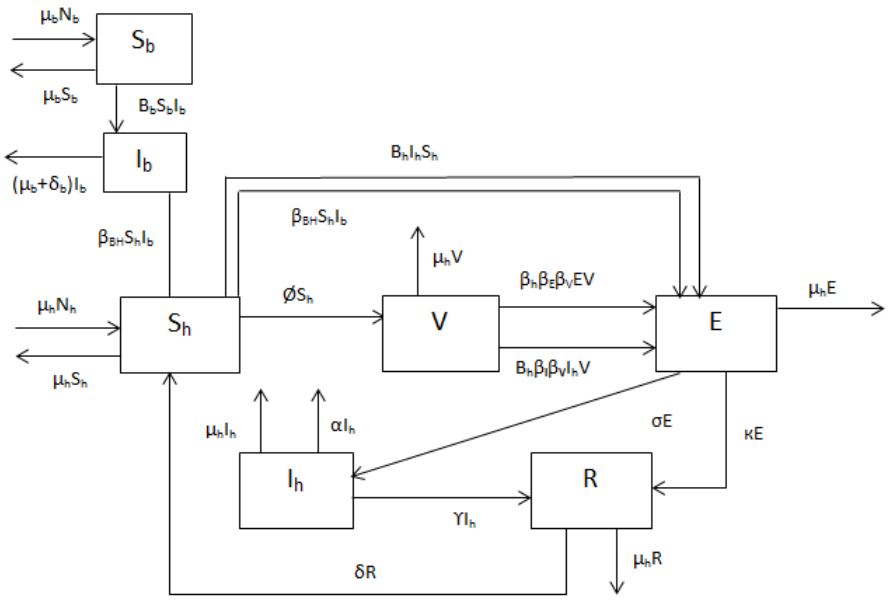

Figure 3.1: Diagram of the model.

$$\frac{dS_b}{dt} = \mu_b N_b - \mu_b S_b - \beta_B S_b I_b \tag{3.1}$$
$$\frac{dI_b}{dt} = \beta_B S_b I_b - (\mu_b + \delta_b) I_b \tag{3.2}$$
$$\frac{dS_h}{dt} = \mu_h N_h - \beta_h I_h S_h - \beta_{BH} S_h I_b - \mu_h S_h - \phi S_h + \delta R \tag{3.3}$$
$$\frac{dV}{dt} = \phi S_h - \beta_h \beta_E \beta_V E V - \beta_h \beta_I \beta_V I_h V - \mu_h V \tag{3.4}$$
$$\frac{dE}{dt} = \beta_h I_h S_h + \beta_{BH} S_h I_b + \beta_h \beta_E \beta_V E V + \beta_h \beta_I \beta_V I_h V - (\sigma + \mu_h + \kappa) E \tag{3.5}$$
$$\frac{dI_h}{dt} = \sigma E - (\alpha + \mu_h + \gamma) I_h \tag{3.6}$$
$$\frac{dR}{dt} = \kappa E + \gamma I_h - \mu_h R - \delta R \tag{3.7}$$

Written in a vector from, the above equations become

$$\frac{dX}{dt} = F(X) \tag{3.8}$$

with

$$X = (S, V, E, I, R)^T$$

Table 7: Parameter symbols

Symbol	Parameter
N_b	Total birds population
N_h	Total humans population
S_b	Susceptible birds
S_h	Susceptible humans
V	Vaccinated population
E	Exposed individuals
R	Recovered individuals
I_b	Infected birbs
I_h	Infected humans
μ_b	Natural death and birth rates of birds
μ_h	Natural death and birth rates of humans
β_B	Rate at which birds contract avian influenza
β_E	Ability to cause infection by exposed individuals
β_I	Ability to cause infection by infectious individuals
β_V	Factor by which the vaccine reduces infection
β_h	Transmission coefficient of the disease
β_{BH}	Rate at which bird-to-human avian influenza is contracted
δ_b	Additional disease death rate due to avian strain in birds
δ	Duration of immunity loss
σ	The loss of immunity period
κ	The recovery rate for exposed population
γ	The recovery rate for infected population
α	Flu induced mortality rate
ϕ	Rate of vaccination

3.2 Epidemic analysis

In this section, we will provide the epidemic analysis which will be conducted into two parts: for birds and for humans.

3.2.1 Epidemic analysis for birds

The disease-free equilibrium (DFE):

$$\mu_b N_b - \beta_B S_b I_b - \mu_b S_b = 0 \tag{3.9}$$

$$N_b = S_b \tag{3.10}$$

and the DFE for birds is denoted by

$$\epsilon_b = (N_b, 0). \tag{3.11}$$

We first compute the basic reproduction number for this model using the method of van den Driessche and Watmough. Here for birds, the associated next generation matrices are given by

$$F = [\beta_B N_b] \quad \text{and} \quad V = [\mu_b + \delta_b]$$

Thus,

$$FV^{-1} = \frac{1}{\mu_b + \delta_b}[\beta_B N_b] = \frac{\beta_B N_b}{\mu_b + \delta_b}$$

The basic reproduction number is then determined as the spectral radius of FV^{-1}. Consider:

$$\det(FV^{-1} - \lambda I) = 0 \tag{3.12}$$

Thus,

$$\lambda = 0 \quad \text{or} \quad \lambda = \frac{\beta_B N_b}{\mu_b + \delta_b} \tag{3.13}$$

Therefore the reproduction number for birds is denoted by

$$R_0^b = \frac{\beta_B N_b}{\mu_b + \delta_b} \tag{3.14}$$

Next, we will determine the reproduction for humans.

3.2.2 Epidemic analysis for humans:

The disease-free equilibrium (DFE):

$$\mu_h N_h - \mu_h S_h - \phi S_h = 0$$

$$S_h = \frac{\mu_h N_h}{\mu_h + \phi}$$

and

$$\phi S_h - \beta_h \beta_E \beta_V E V - \beta_h \beta_I \beta_V I_h V - \mu_h V = 0$$

$$V = \frac{\phi S_h}{\mu_h}$$

$$= \frac{\phi N_h}{\mu_h + \phi}$$

That is the DFE for humans is denoted by

$$\epsilon_h = (\frac{\mu_h N_h}{\mu_h + \phi_h}, \frac{\phi N_h}{\mu_h + \phi}, 0, 0, 0). \tag{3.15}$$

We first compute the basic reproduction number for this model using the method of van den Driessche and Watmough. Here for humans, the associated next generation matrices are given by

$$\mathcal{F} = \begin{bmatrix} \beta_h I_h S_h + \beta_h \beta_E \beta_V E V + \beta_h \beta_I \beta_V I_h V \\ 0 \end{bmatrix}$$

$$F = \begin{bmatrix} \frac{\partial \mathcal{F}_{11}}{\partial E} & \frac{\partial \mathcal{F}_{11}}{\partial I} \\ \frac{\partial \mathcal{F}_{21}}{\partial E} & \frac{\partial \mathcal{F}_{21}}{\partial I} \end{bmatrix}$$

$$F = \begin{bmatrix} \beta_h \beta_E \beta_V V & \beta_h S_h + \beta_h \beta_I \beta_V V \\ 0 & 0 \end{bmatrix}$$

and

$$\mathcal{V} = \begin{bmatrix} (\mu_h + \sigma + \kappa) E \\ -\sigma E + (\mu_h + \alpha + \gamma) I_h \end{bmatrix}$$

$$V = \begin{bmatrix} \frac{\partial \mathcal{V}_{11}}{\partial E} & \frac{\partial \mathcal{V}_{11}}{\partial I_h} \\ \frac{\partial \mathcal{V}_{21}}{\partial E} & \frac{\partial \mathcal{V}_{21}}{\partial I_h} \end{bmatrix}$$

$$V = \begin{bmatrix} \mu_h + \sigma + \kappa & 0 \\ -\sigma & \mu_h + \alpha + \gamma \end{bmatrix}$$

At the DFE point, we have

$$F(\epsilon_0) = \begin{bmatrix} \frac{\beta_h \beta_E \beta_V \phi N_h}{\mu_h + \phi} & \beta_h S_h + \frac{\beta_h \beta_I \beta_V \phi N_h}{\mu_h + \phi} \\ 0 & 0 \end{bmatrix}$$

The basic reproduction number is then determined as the spectral radius of FV^{-1}. Consider

$$
\begin{aligned}
V(\epsilon_0) &= \begin{bmatrix} \mu_h+\sigma+\kappa & 0 \\ -\sigma & \mu_h+\alpha+\gamma \end{bmatrix} \\
\det V &= (\mu_h+\sigma+\kappa)(\mu_h+\alpha+\gamma) - 0 \\
&= (\mu_h+\sigma+\kappa)(\mu_h+\alpha+\gamma) \\
\text{adj.}V &= \begin{bmatrix} C_{11} & C_{12} \\ C_{21} & C_{22} \end{bmatrix}^T \\
&= \begin{bmatrix} \mu_h+\alpha+\gamma & \sigma \\ 0 & \mu_h+\sigma+\kappa \end{bmatrix}^T \\
&= \begin{bmatrix} \mu_h+\alpha+\gamma & 0 \\ \sigma & \mu_h+\sigma+\kappa \end{bmatrix}
\end{aligned}
$$

and hence,

$$
\begin{aligned}
V^{-1} =& \frac{1}{detV} \cdot adj.V, \\
=& \frac{1}{g_1 g_2} \times \begin{bmatrix} g_2 & 0 \\ \sigma & g_1 \end{bmatrix}, \\
=& \begin{bmatrix} \frac{1}{g_1} & 0 \\ \frac{\sigma}{g_1 g_2} & \frac{1}{g_2} \end{bmatrix}.
\end{aligned}
$$

Let $g_1 = \mu_h+\sigma+\kappa$, $g_2 = \mu_h+\alpha+\gamma$, $g_3 = \frac{\beta_h \beta_E \beta_V \phi N_h}{\mu_h+\phi}$ and $g_4 = \beta_h S_h + \frac{\beta_h \beta_I \beta_V \phi N_h}{\mu_h+\phi}$. Thus

$$
\begin{aligned}
FV^{-1} &= \begin{bmatrix} g_3 & g_4 \\ 0 & 0 \end{bmatrix} \begin{bmatrix} \frac{1}{g_1} & 0 \\ \frac{\sigma}{g_1 g_2} & \frac{1}{g_2} \end{bmatrix} \\
&= \begin{bmatrix} \frac{g_3}{g_1} + \frac{\sigma g_4}{g_1 g_2} & \frac{g_4}{g_2} \\ 0 & 0 \end{bmatrix}
\end{aligned}
$$

and

$$
det(FV^{-1} - \lambda I) = \left[\frac{g_3}{g_1} + \frac{\sigma g_4}{g_1 g_2} - \lambda \right] (-\lambda) = 0.
$$

$$\lambda = \left[\frac{g_3}{g_1} + \frac{\sigma g_4}{g_1 g_2}, 0\right]$$

Thus,

$$R_0^h = \lambda = \frac{g_3}{g_1} + \frac{\sigma g_4}{g_1 g_2}.$$

The basic reproduction number is then determined as the spectral radius of FV^{-1} and it is easy to see that the reproduction number for humans is given by

$$R_0^h = \frac{\beta_h \beta_E \beta_V \phi N_h(\mu_h + \alpha + \gamma) + \sigma \beta_h S_h(\mu_h + \phi) + \sigma \beta_h \beta_I \beta_V \phi N_h}{(\mu_h + \phi)(\mu_h + \sigma + \kappa)(\mu_h + \alpha + \gamma)} \tag{3.16}$$

and hence the basic reproduction number for our model is

$$R_0 = \max\{R_0^b, R_0^h\}. \tag{3.17}$$

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

We mention that the basic reproduction number, given in equations (3.17), can also be derived by the next generation matrix analysis.

To study the global asymptotic stabillity of DFE, we will apply the following result introduced by Castilli-Chavez et al.

Lemma 3.2. *Consider a model system written in the form*

$$\begin{aligned} \frac{dX_1}{dt} &= F(X_1, X_2), \\ \frac{dX_2}{dt} &= G(X_1, X_2), G(X_1, 0) = 0 \end{aligned}$$

where $X_1 \in \mathbb{R}^m$ denotes (its components) the number of uninfected individuals and $X_2 \in \mathbb{R}^n$ denotes (its components) the number of infected individuals including latent, infections, etc; $X_0 = (X_1^*, 0)$ denotes the disease-free equilibrium of the system.
Also assume the conditions $(H1)$ and $(H2)$ below:

(H1) For $\frac{dX_1}{dt} = F(X_1, 0)$,$X_1^*$ is globally asymptotically stable;

(H2) $G(X_1, X_2) = AX_2 - \hat{G}(X_1, X_2)$, $\hat{G}(X_1, X_2) \geq 0$ for $(X_1, X_2) \in \Omega$, where the Jacobian $A = \frac{\partial G}{\partial X_2}(X_1^*, 0)$ is an M-matrix (the off diagonal elements of A are non-negative) and Ω is the region where the model makes biological sense.
Then the DFE $X_0 = (X_1^*, 0)$ is globally asymptotically stable provided that $R_0 < 1$.

Theorem 3.3. *The disease-free equilibrium of the model is globally asymptotic stable if* $R_0 < 1$.

$Proof$ We only need to show that the condition (H1) and (H2) hold when $R_0 < 1$. In our ODE system, $X_1 = (S_h, V, R)$, $X_2 = (E, I_h)$, and $X_1^* = (\frac{\mu_h N_h}{\mu_h + \phi}, \frac{\phi N_h}{\mu_h + \phi}, 0)$. We note that the system

$$\frac{dX_1}{dt} = F(X_1, 0) = \begin{bmatrix} \mu_h N_h - \mu_h S_h - \phi S_h + \delta R \\ \phi S_h - \mu_h V \\ -\mu_h R - \delta R \end{bmatrix}$$

The system is linear and its solution can be easily found as
For R:

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

For S:

$$\begin{aligned} \frac{dS_h}{dt} &= \mu_h N_h - \mu_h S_h - \phi S_h + \delta R \\ \frac{dS_h}{dt} + \mu_h S_h + \phi S_h &= \mu_h N_h + \delta R \\ \frac{dS_h}{dt} + (\mu_h + \phi) S_h &= \mu_h N_h + \delta (R(0)) e^{-(\mu_h + \delta)t} \\ e^{(\mu_h + \phi)t} \frac{dS_h}{dt} + e^{(\mu_h + \phi)t} (\mu_h + \phi) S_h &= e^{(\mu_h + \phi)t} \mu_h N_h + e^{(\mu_h + \phi)t} \delta (R(0)) e^{-(\mu_h + \delta)t} \\ \frac{d}{dt} (e^{(\mu_h + \phi)t} \cdot S_h) &= e^{(\mu_h + \phi)t} \mu_h N_h + e^{(\phi - \delta)t} \delta (R(0)) \\ \int \frac{d}{dt} (e^{(\mu_h + \phi)t} \cdot S_h) dt &= \int e^{(\mu_h + \phi)t} \mu_h N_h dt + \int e^{(\phi - \delta)t} \delta (R(0)) dt \\ e^{(\mu_h + \phi)t} \cdot S_h &= \mu_h N_h \cdot \frac{e^{(\mu_h + \phi)t}}{\mu_h + \phi} + \delta (R(0)) \cdot \frac{e^{(\phi - \delta)t}}{\phi - \delta} + C_1 \\ S_h(t) &= \frac{\mu_h N_h}{\mu_h + \phi} + \delta (R(0)) \frac{e^{(\phi - \delta)t}}{\phi - \delta} \cdot e^{-(\mu_h + \phi)t} + C_1 e^{-(\mu_h + \phi)t} \end{aligned}$$

For V:

$$\begin{aligned}
\frac{dV}{dt} &= \phi S_h - \mu_h V \\
\frac{dV}{dt} + \mu_h V &= \phi S_h \\
\frac{dV}{dt} + \mu_h V &= \frac{\phi\mu_h N_h}{\mu_h+\phi} + \phi\delta(R(0))\frac{e^{(\phi-\delta)t}}{\phi-\delta}\cdot e^{-(\mu_h+\phi)t} + \phi C_1 e^{-(\mu_h+\phi_h)t} \\
e^{\mu_h t}\frac{dV}{dt} + e^{\mu_h t}\mu_h V &= e^{\mu_h t}\frac{\phi\mu_h N_h}{\mu_h+\phi} + e^{\mu_h t}\phi\delta(R(0))\frac{e^{(\phi-\delta)t}}{\phi-\delta}\cdot e^{-(\mu_h+\phi)t} + \phi C_1 e^{-\phi t} \\
\frac{d}{dt}(e^{\mu_h t}\cdot V) &= e^{\mu_h t}\frac{\phi\mu_h N_h}{\mu_h+\phi} + e^{\mu_h t}\phi\delta(R(0))\frac{e^{(\phi-\delta)t}}{\phi-\delta}\cdot e^{-(\mu_h+\phi)t} + \phi C_1 e^{-\phi t}
\end{aligned}$$

$$\begin{aligned}
\int \frac{d}{dt}(e^{\mu_h t}\cdot V)dt &= \int e^{\mu_h t}\frac{\phi\mu_h N_h}{\mu_h+\phi} + \int e^{\mu_h t}\phi\delta(R(0))\frac{e^{(\phi-\delta)t}}{\phi-\delta}\cdot e^{-(\mu_h+\phi)t} + \int \phi C_1 e^{-\phi t}dt \\
e^{\mu t}\cdot V &= \frac{\frac{\phi\mu_h N_h}{\mu_h+\phi}\cdot e^{\mu_h t}}{\mu_h} + \frac{\frac{\phi\delta(R(0))}{\phi-\delta}\cdot e^{-\delta t}}{-\delta} + C_2 - C_1\frac{e^{-\phi t}}{\phi} \\
V(t) &= \frac{\phi N_h}{\mu_h+\phi} + \frac{\phi(R(0))e^{-\delta t}}{\phi-\delta}\cdot e^{-\mu_h t} + C_2 e^{-\mu_h t} - C_1\frac{e^{-(\mu_h+\phi)t}}{\phi}
\end{aligned}$$

when $t=0$, we have

$$\begin{aligned}
S_h(0) &= \frac{\mu_h N_h}{\mu_h+\phi} + \delta(R(0))\frac{e^{(\phi-\delta)(0)}}{\phi-\delta}\cdot e^{-(\mu_h+\phi)(0)} + C_1 e^{-(\mu_h+\phi)(0)} \\
&= \frac{\mu_h N_h}{\mu_h+\phi} + \frac{\delta(R(0))}{\phi-\delta} + C_1 \\
C_1 &= S_h(0) - \frac{\mu_h N_h}{\mu_h+\phi} - \frac{\delta(R(0))}{\phi-\delta}
\end{aligned}$$

Let C_1 be as above in S_h,

$$\begin{aligned}
S_h(t) &= \frac{\mu_h N_h}{\mu_h+\phi} + \delta(R(0))\frac{e^{(\phi-\delta)t}}{\phi-\delta}\cdot e^{-(\mu_h+\phi)t} + \left[S(0) - \frac{\mu_h N_h}{\mu_h+\phi} - \frac{\delta(R(0))}{\phi-\delta}\right]e^{-(\mu_h+\phi)t} \\
&= \frac{\mu_h N_h}{\mu_h+\phi} + \delta(R(0))\frac{e^{(\phi-\delta)t}}{\phi-\delta}\cdot e^{-(\mu_h+\phi)t} + S(0)e^{-(\mu_h+\phi)t} \\
&- \frac{\mu_h N_h}{\mu_h+\phi}e^{-(\mu_h+\phi)t} - \delta(R(0))\frac{e^{-(\mu_h+\delta)t}}{\phi-\delta}
\end{aligned}$$

When $t = 0$, we have

$$\begin{aligned} V(0) &= \frac{\phi N_h}{\mu_h + \phi} + \frac{\phi(R(0))e^{-\delta(0)}}{\phi - \delta} \cdot e^{-\mu_h(0)} + C_2 e^{-\mu_h(0)} \\ &\quad - C_1 \frac{e^{-(\mu_h+\phi)(0)}}{\phi} \\ &= \frac{\phi N_h}{\mu_h + \phi} + \frac{\phi(R(0))}{\phi - \delta} + C_2 - \frac{C_1}{\phi} \\ C_2 &= V(0) - \frac{\phi N_h}{\mu_h + \phi} - \phi\frac{(R(0))}{\phi - \delta} + \frac{C_1}{\phi} \end{aligned}$$

Let C_2 be as above in V,

$$\begin{aligned} V(t) &= \frac{\phi N_h}{\mu_h + \phi} + \phi(R(0))\frac{e^{-\delta t}}{\phi - \delta} \cdot e^{-\mu_h t} + \left[V(0) - \frac{\phi N_h}{\mu_h + \phi} - \frac{\phi(R(0))}{\phi - \delta} + \frac{C_1}{\phi}\right] e^{-\mu_h t} \\ &\quad - C_1 \frac{e^{-(\mu_h+\phi)t}}{\phi} \\ V(t) &= \frac{\phi N_h}{\mu_h + \phi} + \phi(R(0))\frac{e^{-(\mu_h+\delta)t}}{\phi - \delta} e^{-\mu_h t} + V(0)e^{-\mu_h t} - \frac{\phi N_h}{\mu_h + \phi} e^{-\mu_h t} \\ &\quad - \phi(R(0))\frac{e^{-\mu_h t}}{\phi - \delta} + C_1 \frac{e^{-\mu_h t}}{\phi} - C_1 \frac{e^{-(\mu_h+\phi)t}}{\phi} \end{aligned}$$

Clearly, $R(t) \to 0$, $S_h(t) \to \frac{\mu_h N_h}{\mu_h + \phi}$ and $V(t) \to \frac{\phi N_h}{\mu_h + \phi}$ as $t \to \infty$, regardless of the values of R(0), V(0) and S(0). Thus $X_1^* = (\frac{\mu_h N_h}{\mu_h + \phi}, \frac{\phi N_h}{\mu_h + \phi}, 0)$ is globally asymptotically stable.

Next, we have

$$\frac{dX_2}{dt} = G(X_1, X_2) = \begin{bmatrix} \beta_h I_h S_h + \beta_{BH} S_h I_b + \beta_h \beta_E \beta_V EV + \beta_h \beta_I \beta_V I_h V \\ -(\mu_h + \sigma + \kappa)E \\ \sigma E - (\mu_h + \alpha + \gamma)I_h \end{bmatrix}$$

$$\frac{\partial G}{\partial X_2}(X_1, 0) = A = \begin{bmatrix} \beta_h \beta_E \beta_V V - (\mu_h + \sigma + \kappa) & \beta_h S_h + \beta_h \beta_I \beta_V V \\ \sigma & -(\mu_h + \alpha + \gamma) \end{bmatrix}$$

$$\frac{\partial G}{\partial X_2}(X_1^*, 0) = A = \begin{bmatrix} \beta_h \beta_E \beta_V \frac{\phi N_h}{\mu_h + \phi} - (\mu_h + \sigma + \kappa) & \beta_h \frac{\mu_h N_h}{\mu_h + \phi} + \beta_h \beta_I \beta_V \frac{\phi N_h}{\mu_h + \phi} \\ \sigma & -(\mu_h + \alpha + \gamma) \end{bmatrix}$$

Thus,

$$\begin{aligned}
G(X_1, X_2) =& AX_2 - \hat{G}(X_1, X_2) \\
\hat{G}(X_1, X_2) =& AX_2 - G(X_1, X_2) \\
&= \begin{bmatrix} \beta_h\beta_E\beta_V V - (\mu_h + \sigma + \kappa) & \beta_h S_h + \beta_h\beta_I\beta_V V \\ \sigma & -(\mu_h + \alpha + \gamma) \end{bmatrix} \begin{bmatrix} E \\ I_h \end{bmatrix} \\
&\quad - \begin{bmatrix} \beta_h\beta_E\beta_V EV + \beta_h\beta_I\beta_V I_h V - (\mu_h + \sigma + \kappa)E \\ \sigma E - (\mu_h + \alpha + \gamma)I_h \end{bmatrix} \\
&= \begin{bmatrix} \beta_h S_h I_h \\ 0 \end{bmatrix}
\end{aligned}$$

which is clearly an M-matrix. Meanwhile, we find

$$\therefore \hat{G}(X_1, X_2) = [\beta_h S_h I_h, 0]^T$$

It is obvious that $\hat{G}(X_1, X_2) \geq 0$.

The stability at the DFE determines the short-term epidemics of the disease, where as its dynamics over a longer period of time is characterized by the stability at the endemic equilibrium. In this section we will analyze the endemic properties of our avian influenza model.

3.3 Endemic analysis

The stability at the DFE determines the short-term epidemics of the disease, where as its dynamics over a longer period of time is characterized by the stability at the endemic equilibrium. In this section we will analyze the endemic properties of our avian influenza model.

3.3.1 Endemic equilibrium

We first examine the existence of the positive endemic equilibrium. Denote the endemic equilibrium of the model by $\epsilon^* = (S_b^*, I_b^*, S_h^*, V^*, I_h^*, R^*)$. From equations (3.1) - (3.7)

we obtain

$$\frac{dS_b^*}{dt} = \mu_b N_b - \mu_b S_b^* - \beta_B S_b^* I_b^* \tag{3.18}$$
$$\frac{dI_b^*}{dt} = \beta_B S_b^* I_b^* - (\mu_b + \delta_b) I_b^* \tag{3.19}$$
$$\frac{dS_h^*}{dt} = \mu_h N_h - \beta_h I_h^* S_h^* - \beta_{BH} S_h^* I_b^* - \mu_h S_h^* - \phi S_h^* + \delta R^* \tag{3.20}$$
$$\frac{dV^*}{dt} = \phi S_h^* - \beta_h \beta_E \beta_V E^* V^* - \beta_h \beta_I \beta_V I_h^* V^* - \mu_h V^* \tag{3.21}$$
$$\frac{dE^*}{dt} = \beta_h I_h^* S_h^* + \beta_{BH} S_h^* I_b^* + \beta_h \beta_E \beta_V E^* V^* + \beta_h \beta_I \beta_V I_h^* V^* - (\sigma + \mu_h + \kappa) E^* \tag{3.22}$$
$$\frac{dI_h^*}{dt} = \sigma E^* - (\alpha + \mu_h + \gamma) I_h^* \tag{3.23}$$
$$\frac{dR^*}{dt} = \kappa E^* + \gamma I_h^* - \mu_h R^* - \delta R^* \tag{3.24}$$

First, we find S_b^* :

$$\beta_B S_b^* I_b^* - (\mu_b + \delta_b) I_b^* = 0,$$
$$S_b^* = \frac{\mu_b + \delta_b}{\beta_B}.$$

Then, the equation (3.18) becomes

$$\mu_b N_b - \mu_b S_b^* - \beta_B S_b^* I_b^* = 0,$$
$$\mu_b \Big(\frac{N_b}{\mu_b + \delta_b} - \frac{1}{\beta_B} \Big) = I_b^*.$$

Next, we substitute I_b^* into equation (3.22) and obtain

$$\beta_h I_h^* S_h^* + \beta_{BH} S_h^* \mu_b (\frac{N_b}{\mu_b + \delta_b} - \frac{1}{\beta_B}) + \beta_h \beta_E \beta_V E^* V^* + \beta_h \beta_I \beta_V I_h^* V^* - (\sigma + \mu_h + \kappa) E^* = 0 \tag{3.25}$$

From (3.23), we solve for E^* and we have

$$E^* = \frac{(\mu_h + \alpha + \gamma) I_h^*}{\sigma} \tag{3.26}$$

Thus

$$
\begin{aligned}
R^* &= Q_2 I_h^* \\
E^* &= Q_1 I_h^* \\
S_h^* &= \frac{\mu_h N_h + \delta Q_2 I_h^*}{\beta_h I_h^* + Q_3} \\
V^* &= \phi \frac{(\mu_h N_h + \delta Q_2 I_h^*)}{(\beta_h I_h^* + Q_3)(Q_4 Q_1 I^* h + Q_5 I_h^* + \mu_h)}
\end{aligned}
$$

$$
\begin{aligned}
Q_1 &= \frac{\mu_h + \alpha + \gamma}{\sigma} \\
Q_2 &= \frac{kQ_1 + \gamma}{\mu_h + \delta} \\
Q_3 &= \beta_{BH} I_b^* + \mu_h + \phi \\
Q_4 &= \beta_h \beta_E \beta_V \\
Q_5 &= \beta_h \beta_I \beta_V
\end{aligned}
$$

Now we find I_h^* from ;

$$
\begin{aligned}
N &= S_h^* + V^* + E^* + I_h^* + R^* \\
&= \frac{\mu_h N_h + \delta Q_2 I_h^*}{\beta_h I_h^* + Q_3} + \phi \frac{(\mu_h N_h + \delta Q_2 I_h^*)}{(\beta_h I_h^* + Q_3)(Q_4 Q_1 I_h^* + Q_5 I_h^* + \mu_h)} + Q_1 I_h^* + I_h^* + Q_2 I_h^* \\
&= \frac{(\mu_h N_h + \delta Q_2 I_h^*)(Q_4 Q_1 I_h^* + Q_5 I_h^* + \mu_h) + \phi(\mu_h N_h + \delta Q_2 I_h^*)}{(\beta_h I_h^* + Q_3)(Q_4 Q_1 I_h^* + Q_5 I_h^* + \mu_h)} \\
&+ \frac{Q_1 I_h^* (\beta_h I_h^* + Q_3)(Q_4 Q_1 I_h^* + Q_5 I_h^* + \mu_h) + I_h^* (\beta_h I_h^* + Q_3)(Q_4 Q_1 I_h^* + Q_5 I_h^* + \mu_h)}{(\beta_h I_h^* + Q_3)(Q_4 Q_1 I_h^* + Q_5 I_h^* + \mu_h)} \\
&+ \frac{Q_2 I_h^* (\beta_h I_h^* + Q_3)(Q_4 Q_1 I_h^* + Q_5 I_h^* + \mu_h)}{(\beta_h I_h^* + Q_3)(Q_4 Q_1 I_h^* + Q_5 I_h^* + \mu_h)} \\
0 &= T_1 I_h^{*3} + T_2 I_h^{*2} + T_3 I_h^* + T_4
\end{aligned}
$$

where

$$T_1 = \frac{Q_4Q_1^2\beta_h + Q_1Q_5\beta_h + Q_4Q_1\beta_h + Q_5\beta_h + Q_1Q_2Q_4\beta_h + Q_2Q_5\beta_h}{Q_4Q_1\beta_hI_h^{*2} + Q_5\beta_hI_h^{*2} + \mu_h\beta_hI_h^* + Q_4Q_1Q_3I_h^* + Q_3Q_5I_h^* + \mu_hQ_3}$$

$$T_2 = \frac{Q_4Q_1Q_2\delta + Q_5Q_2\delta + Q_1\beta_h\mu_h + Q_4Q_1^2Q_3 + Q_1Q_3Q_5 + \beta_h\mu_h + Q_4Q_1Q_3 + Q_5Q_3}{Q_4Q_1\beta_hI_h^{*2} + Q_5\beta_hI_h^{*2} + \mu_h\beta_hI_h^* + Q_4Q_1Q_3I_h^* + Q_3Q_5I_h^* + \mu_hQ_3}$$
$$+ \frac{Q_2\beta_h\mu_h + Q_1Q_2Q_3Q_4 + Q_2Q_3Q_5}{Q_4Q_1\beta_hI_h^{*2} + Q_5\beta_hI_h^{*2} + \mu_h\beta_hI_h^* + Q_4Q_1Q_3I_h^* + Q_3Q_5I_h^* + \mu_hQ_3}$$

$$T_3 = \frac{Q_4Q_1\mu_hN_h + Q_5\mu_hN_h + Q_2\mu_h\delta + Q_2\phi\delta + Q_1Q_3\mu_h + Q_3\mu_h + Q_2Q_3\mu_h}{Q_4Q_1\beta_hI_h^{*2} + Q_5\beta_hI_h^{*2} + \mu_h\beta_hI_h^* + Q_4Q_1Q_3I_h^* + Q_3Q_5I_h^* + \mu_hQ_3}$$

$$T_4 = \frac{\mu_h^2N_h + \phi\mu_hN_h}{Q_4Q_1\beta_hI_h^{*2} + Q_5\beta_hI_h^{*2} + \mu_h\beta_hI_h^* + Q_4Q_1Q_3I_h^* + Q_3Q_5I_h^* + \mu_hQ_3}$$

which our endemic equilibrium point is

$$(S_h^*, V^*, E^*, I_h^*, R^*)$$

Theorem 3.4. *The positive endemic equilibrium ϵ^* of the system $(3.1) - (3.7)$ exists and unique if $R_0 > 1$, and there is no positive endemic equilibrium if $R_0 < 1$.*

3.3.2 Local stabilities

We proceed to analyze the stability properties of the endemic equilibrium. First we establish the following result regarding the local stability.

Theorem 3.5. *When $R_0 > 1$, the endemic equilibrium ϵ^* is locally asymptotically stable.*

$Proof$ The jacobian of the system $(3.1) - (3.7)$ at ϵ^* is given by

$$J(\epsilon)^* = \begin{bmatrix} -g_5 - g_6 & 0 & 0 & -g_7 & \delta \\ \phi & -g_8 - \mu_h & g_9 & -g_9 & 0 \\ g_5 & g_8 & g_9 - g_1 & g_7 + g_{10} & 0 \\ 0 & 0 & \sigma & -g_2 & 0 \\ 0 & 0 & \kappa & \gamma & -g_{11} \end{bmatrix}$$

where

$$
\begin{aligned}
g_1 &= \mu_h + \sigma + \kappa, \\
g_2 &= \mu_h + \alpha + \gamma, \\
g_3 &= \frac{\beta_h \beta_E \beta_V \phi N_h}{\mu_h + \phi}, \\
g_4 &= \beta_h S_h^* + \frac{\beta_h \beta_I \beta_V \phi N_h}{\mu_h + \phi} \\
g_5 &= \beta_h I_h^* + \beta_{BH} I_b^* \\
g_6 &= \mu_h + \phi \\
g_7 &= \beta_h S_h^* \\
g_8 &= \beta_h \beta_E \beta_V E^* + \beta_h \beta_I \beta_V I_h^* \\
g_9 &= \beta_h \beta_E \beta_V V^* \\
g_{10} &= \beta_h \beta_I \beta_V V^* \\
g_{11} &= \mu_h + \delta,
\end{aligned}
$$

The characteristic equation of the matrix $J(\varepsilon^*)$ is

$$
\begin{aligned}
0 &= |\lambda I - J(\varepsilon^*)| \\
&= (\lambda + g_5 + g_6)[(\lambda + g_8 + \mu_h)(\lambda - g_9 + g_1)(\lambda + g_2)(\lambda + g_{11}) \\
&+ \sigma(-g_7 - g_{10})(\lambda + g_{11}) + g_9 g_8 (\lambda + g_2)(\lambda + g_{11}) + g_{10} g_8 \sigma(\lambda + g_{11})] - g_7[-g_8 \sigma \phi \lambda \\
&- g_8 g_{11} \sigma \phi - g_5 \sigma \lambda^2 - g_5 g_{11} \sigma \lambda - g_5 g_8 g_{13} \sigma - g_5 \sigma \mu_h \lambda - g_5 g_{11} \sigma \mu_h] \\
&- \delta[g_8 \phi \gamma \sigma + g_8 \phi \kappa \lambda + g_8 \phi \kappa g_2 + g_5 \sigma \gamma \lambda + g_5 g_8 \sigma \gamma + g_5 \mu_h \sigma \gamma + g_5 \kappa \lambda^2 \\
&+ g_5 g_8 \kappa \lambda + g_5 \mu_h \kappa \lambda + g_5 g_2 \kappa \lambda + g_5 g_8 g_2 \kappa + g_5 g_2 \kappa \mu_h]
\end{aligned}
$$

$$= \lambda^5 + [g_8 - g_9 + g_1 + \mu_h + g_2 + g_{11} + g_5 + g_6]\lambda^4 + [g_8 g_1 - g_8 g_9 - g_9 \mu_h$$
$$+ g_1 \mu_h - g_9 g_2 + g_8 g_2 + g_1 g_2 + g_2 \mu_h - g_9 g_{11} + g_8 g_{11} + g_1 g_{11} + g_{11} \mu_h$$
$$+ g_2 g_{11} - g_5 g_9 + g_5 g_8 + g_5 g_1 + g_5 \mu_h + g_5 g_2 + g_5 g_{11} - g_6 g_9 + g_6 g_8 + g_6 g_1$$
$$+ g_6 \mu_h + g_6 g_2 + g_6 g_1]\lambda^3 + [g_8 g_1 g_2 - g_8 g_9 g_2 - g_9 g_2 \mu_h$$
$$+ g_1 g_2 \mu_h - g_8 g_9 g_{11} + g_8 g_1 g_{11} - g_9 g_{11} \mu_h + g_1 g_{11} \mu_h$$
$$- g_9 g_2 g_{11} + g_8 g_2 g_{11} + g_1 g_2 g_{11} + g_2 g_{11} \mu_h - g_5 g_8 g_9$$
$$+ g_5 g_8 g_1 - g_5 g_9 \mu_h + g_5 g_1 \mu_h - g_5 g_9 g_2 + g_5 g_8 g_2 + g_5 g_1 g_2$$
$$+ g_5 g_2 \mu_h - g_5 g_9 g_{11} + g_5 g_8 g_{11} + g_5 g_1 g_{11} + g_5 g_{11} \mu_h$$
$$+ g_5 g_2 g_{11} - g_6 g_8 g_9 + g_6 g_8 g_1 - g_6 g_9 \mu_h + g_6 g_1 \mu_h - g_6 g_9 g_2 + g_6 g_8 g_2$$
$$+ g_6 g_1 g_2 + g_6 g_2 \mu_h - g_6 g_9 g_{11} + g_6 g_8 g_{11} + g_6 g_1 g_{11}$$
$$+ g_6 g_{11} \mu_h + g_6 g_2 g_{11} + g_6 g_2 g_{11} + g_5 g_7 \sigma - \delta \kappa g_5]\lambda^2 + [g_8 g_1 g_2 g_{11} - g_8 g_9 g_2 g_{11}$$
$$- g_9 g_2 g_{11} \mu_h + g_1 g_2 g_{11} \mu_h + g_1 g_2 g_{11} \mu_h - g_5 g_8 g_9 g_2$$
$$+ g_5 g_8 g_1 g_2 - g_5 g_9 g_2 \mu_h + g_5 g_1 g_2 \mu_h - g_5 g_8 g_9 g_{11} + g_5 g_8 g_{11} g_{11} - g_5 g_9 g_{11} \mu_h + g_5 g_1 g_{11} \mu_h$$
$$- g_5 g_9 g_2 g_{11} + g_5 g_8 g_2 g_{11} + g_5 g_1 g_2 g_{11} + g_5 g_2 g_{11} \mu_h - g_6 g_8 g_9 g_2 + g_6 g_8 g_1 g_2 - g_6 g_9 g_2 \mu_h$$
$$+ g_6 g_1 g_2 \mu_h - g_6 g_8 g_9 g_{11} + g_6 g_8 g_1 g_{11} - g_6 g_9 g_{11} \mu_h + g_6 g_1 g_{11} \mu_h - g_6 g_9 g_2 g_{11} + g_6 g_8 g_2 g_{11}$$
$$+ g_6 g_1 g_2 g_{11} + g_6 g_2 g_{11} \mu_h + g_7 g_8 \sigma \phi + g_5 g_7 g_{11} \sigma + g_5 g_7 g_8 \sigma + g_5 g_7 \sigma \mu_h - g_8 \delta \phi \kappa - g_5 \delta \sigma \gamma$$
$$- g_5 g_8 \delta \kappa - g_5 \delta \mu_h \kappa - g_5 g_2 \delta \kappa]\lambda - g_5 g_8 g_9 g_2 g_{11} + g_5 g_8 g_1 g_2 g_{11} - g_5 g_9 g_2 g_{11} \mu_h + g_5 g_1 g_2 g_{11} \mu_h$$
$$- g_6 g_8 g_9 g_2 g_{11} + g_6 g_8 g_1 g_2 g_{11} - g_6 g_9 g_2 g_{11} \mu_h + g_6 g_1 g_2 g_{11} \mu_h + g_7 g_8 g_{11} \sigma \phi + g_5 g_7 g_8 g_{11} \sigma$$
$$+ g_5 g_7 g_{11} \sigma \mu_h - g_8 \delta \phi \gamma \sigma - g_8 g_2 \delta \phi \kappa - g_5 g_8 \delta \sigma \gamma - g_5 \delta \mu_h \sigma \gamma - g_5 g_8 g_2 \delta \kappa - g_5 g_2 \delta \kappa \mu_h = 0$$

Now the equation can be put into the equation of the form

$$z_0 \lambda^5 + z_1 \lambda^4 + z_2 \lambda^3 + z_3 \lambda^2 + z_4 \lambda + z_5 = 0 \tag{3.27}$$

where

$$z_0 = 1$$

$$z_1 = g_8 - g_9 + g_1 + \mu_h + g_2 + g_{11} + g_5 + g_6$$

$$\begin{aligned} z_2 = {} & g_8 g_1 - g_8 g_9 - g_9 \mu_h + g_1 \mu_h - g_9 g_2 + g_8 g_2 + g_1 g_2 + g_2 \mu_h \\ & - g_9 g_{11} + g_8 g_{11} + g_1 g_{11} + g_{11} \mu_h + g_2 g_{11} - g_5 g_9 + g_5 g_8 + g_5 g_1 + g_5 \mu_h + g_5 g_2 \\ & + g_5 g_{11} - g_6 g_9 + g_6 g_8 + g_6 g_1 + g_6 \mu_h + g_6 g_2 + g_6 g_1 \end{aligned}$$

$$\begin{aligned} z_3 = {} & g_8 g_1 g_2 - g_8 g_9 g_2 - g_9 g_2 \mu_h + g_1 g_2 \mu_h - g_8 g_9 g_{11} + g_8 g_1 g_{11} - g_9 g_{11} \mu_h + g_1 g_{11} \mu_h - g_9 g_2 g_{11} \\ & + g_8 g_2 g_{11} + g_1 g_2 g_{11} + g_2 g_{11} \mu_h - g_5 g_8 g_9 + g_5 g_8 g_1 - g_5 g_9 \mu_h + g_5 g_1 \mu_h - g_5 g_9 g_2 + g_5 g_8 g_2 \\ & + g_5 g_1 g_2 + g_5 g_2 \mu_h - g_5 g_9 g_{11} + g_5 g_8 g_{11} + g_5 g_1 g_{11} + g_5 g_{11} \mu_h + g_5 g_2 g_{11} - g_6 g_8 g_9 \\ & + g_6 g_8 g_1 - g_6 g_9 \mu_h + g_6 g_1 \mu_h - g_6 g_9 g_2 + g_6 g_8 g_2 + g_6 g_1 g_2 + g_6 g_2 \mu_h - g_6 g_9 g_{11} \\ & + g_6 g_8 g_{11} + g_6 g_1 g_{11} + g_6 g_{11} \mu_h + g_6 g_2 g_{11} + g_6 g_2 g_{11} + g_5 g_7 \sigma - \delta \kappa g_5 \end{aligned}$$

$$\begin{aligned} z_4 = {} & [g_8 g_1 g_2 g_{11} - g_8 g_9 g_2 g_{11} - g_9 g_2 g_{11} \mu_h + g_1 g_2 g_{11} \mu_h \\ & + g_1 g_2 g_{11} \mu_h - g_5 g_8 g_9 g_2 + g_5 g_8 g_1 g_2 - g_5 g_9 g_2 \mu_h + g_5 g_1 g_2 \mu_h - g_5 g_8 g_9 g_{11} \\ & + g_5 g_8 g_{11} g_{11} - g_5 g_9 g_{11} \mu_h + g_5 g_1 g_{11} \mu_h - g_5 g_9 g_2 g_{11} + g_5 g_8 g_2 g_{11} \\ & + g_5 g_1 g_2 g_{11} + g_5 g_2 g_{11} \mu_h - g_6 g_8 g_9 g_2 + g_6 g_8 g_1 g_2 - g_6 g_9 g_2 \mu_h + g_6 g_1 g_2 \mu_h \\ & - g_6 g_8 g_9 g_{11} + g_6 g_8 g_1 g_{11} - g_6 g_9 g_{11} \mu_h + g_6 g_1 g_{11} \mu_h - g_6 g_9 g_2 g_{11} + g_6 g_8 g_2 g_{11} \\ & + g_6 g_1 g_2 g_{11} + g_6 g_2 g_{11} \mu_h + g_7 g_8 \sigma \phi + g_5 g_7 g_{11} \sigma + g_5 g_7 g_8 \sigma + g_5 g_7 \sigma \mu_h \\ & - g_8 \delta \phi \kappa - g_5 \delta \sigma \gamma - g_5 g_8 \delta \kappa - g_5 \delta \mu_h \kappa - g_5 g_2 \delta \kappa \end{aligned}$$

$$\begin{aligned} z_5 = {} & -g_5 g_8 g_9 g_2 g_{11} + g_5 g_8 g_1 g_2 g_{11} - g_5 g_9 g_2 g_{11} \mu_h + g_5 g_1 g_2 g_{11} \mu_h \\ & - g_6 g_8 g_9 g_2 g_{11} + g_6 g_8 g_1 g_2 g_{11} - g_6 g_9 g_2 g_{11} \mu_h + g_6 g_1 g_2 g_{11} \mu_h + g_7 g_8 g_{11} \sigma \phi + g_5 g_7 g_8 g_{11} \sigma \\ & + g_5 g_7 g_{11} \sigma \mu_h - g_8 \delta \phi \gamma \sigma - g_8 g_2 \delta \phi \kappa - g_5 g_8 \delta \sigma \gamma - g_5 \delta \mu_h \sigma \gamma - g_5 g_8 g_2 \delta \kappa - g_5 g_2 \delta \kappa \mu_h \end{aligned}$$

Let $a_0 = z_0, a_1 = z_1, a_2 = z_2, a_3 = z_3, a_4 = z_4, a_5 = z_5$
Thus the routh-hurwitz criterion requires.

$$b_1 = \frac{a_1 a_2 - a_0 a_3}{a_1} \geq 0,$$
$$b_2 = \frac{a_1 a_4 - a_0 a_5}{a_1} \geq 0,$$
$$c_1 = \frac{b_1 a_3 - a_1 b_2}{b_1} \geq 0,$$
$$c_2 = \frac{b_1 a_5 - a_1 a_3}{b_1} \geq 0,$$

It's not easy to solve for this equation, therefore, we omit it here.

3.4 Optimal treatments

The Basic Problem and Necessary Conditions

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

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

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

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

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

Such a maximizing control is called an optimal control. By $x(t_1)$ free, it is meant that

the value of $x(t_1)$ is unrestricted. For our purposes, f and g will always be continuously differentiable functions in all three arguments. Thus, as the control(s) will always be piecewise continuous, the associated states will always be piecewise differentiable.

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

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

First, let us derive the necessary conditions. Express our objective functional in terms of the control:

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

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

The necessary conditions that we derive were developed by Pontryagin and his coworkers in Moscow in the 1950's. Pontryagin introduced the idea of "adjoint" functions to append the differential equation to the objective functional. Adjoint function have a similar purpose as Lagrange multipliers in multivariate calculus, which append constraints to the function of several variable to be maximized or minimized. Thus, we begin by finding appropriate conditions that the adjoint function should satisfy. Then, by differentiating the map from the control to the objective functional, we will derive a characterization of the optimal control in terms of the optimal state and corresponding adjoint.

Pontryagin's Maximum Principle

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

Theorem 3.6. *If $u^*(t)$ and $x^*(t)$ are optimal for problem (3.1)-(3.5), then there exists a piecewise differentiable adjoint variable $\lambda(t)$ such that*

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

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

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

and

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

Theorem 3.7. *Suppose that $f(t, x, u)$ and $g(t, x, u)$ are both continuously differentiable functions in thier three arguments and concave in u. Suppose u^* is an optimal control for problem (3.1)-(3.5), with associated state x^*, and λ a piecewise differentiable function with $\lambda \geq 0$ for all t. Suppose for all $t_0 \leq t \leq t_1$*

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

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

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

Now we turn to the more general model (3.1-3.7) with time-dependent controls $\phi(t)$ .We consider the system on a time interval [0,T]. The functions $\phi(t)$ are assumed to be at least lebesgue measurable on [0,T]. The control set is defined as

$$\Omega = \left\{\phi(t) | 0 \leq \phi(t) \leq \phi_{max}\right\} \tag{3.28}$$

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

In this study, we perform an optimal control study to minimize the total numbers of infections as the cost of control over the time interval [0,T];i.e.

$$\min_{\phi \in \Omega} \int_0^T [I_h(t) + c_{21}\phi(t)S_h(t) + c_{22}\phi(t)^2]dt.$$

where c_{21} and c_{22} are appropriate units defined the appropriate costs associated with the control.

Let us first define the adjoint functions $\lambda_{S_h}, \lambda_V, \lambda_E, \lambda_{I_h}$ and λ_R associated with the state equations for S_h,V,E,I_h and R, respectively.We then from Hamiltionian, H, by multiplying each adjoint function with the right-hand side of its corresponding state equation, and adding each of these products to the integrand of the objective functional.

As a result, we obtain

$$\begin{aligned}H = I_h(t) &+ c_{21}\phi(t)S_h(t) + c_{22}\phi(t)^2 \\ &+ \lambda_{S_h}[\mu_h N_h - \beta_h I_h S_h - \beta_{BH} S_h I_b - \mu_h S_h - \phi(t)S_h + \delta R] \\ &+ \lambda_V[\phi(t)S_h - \beta_h\beta_E\beta_V EV - \beta_h\beta_I\beta_V I_h V - \mu_h V] \\ &+ \lambda_E[\beta_h I_h S_h + \beta_{BH} S_h I_b + \beta_h\beta_E\beta_V EV + \beta_h\beta_I\beta_V I_h V - (\mu_h + \sigma + \kappa)E] \\ &+ \lambda_{I_h}[\sigma E - (\mu_h + \alpha + \gamma)I_h] \\ &+ \lambda_R[\kappa E + \gamma I_h - \mu_h R - \delta R]\end{aligned}$$

To achieve the optimal control, the adjoint functions must satisfy

$$\begin{aligned}\frac{d\lambda_{S_h}}{dt} &= -\frac{\partial H}{\partial S_h}, \\ \frac{d\lambda_V}{dt} &= -\frac{\partial H}{\partial V}, \\ \frac{d\lambda_E}{dt} &= -\frac{\partial H}{\partial E}, \\ \frac{d\lambda_{I_h}}{dt} &= -\frac{\partial H}{\partial I_h}, \\ \frac{d\lambda_R}{dt} &= -\frac{\partial H}{\partial R},\end{aligned}$$

Thus, we have

$$\begin{aligned}\frac{d\lambda_{S_h}}{dt} &= -c_{21}\phi(t) + \lambda_{S_h}(\beta_h I_h + \beta_{BH} I_b + \mu_h + \phi(t)) - \lambda_V\phi(t) - \lambda_E\beta_h I_h - \lambda_E\beta_{BH} I_b, \\ \frac{d\lambda_V}{dt} &= \lambda_V(\beta_h\beta_E\beta_V E + \beta_h\beta_I\beta_V I_h + \mu_h) - \lambda_E(\beta_h\beta_E\beta_V E + \beta_h\beta_I\beta_V I_h), \\ \frac{d\lambda_E}{dt} &= \lambda_V(\beta_h\beta_E\beta_V V) - \lambda_E(\beta_h\beta_E\beta_V V) + \lambda_E(\mu_h + \sigma + \kappa) - \lambda_{I_h}(\sigma) - \lambda_R(\kappa), \\ \frac{d\lambda_{I_h}}{dt} &= -1 + \lambda_{S_h}(\beta_h S_h) + \lambda_V\beta_h\beta_I\beta_V V - \lambda_E(\beta_h S_h + \beta_h\beta_I\beta_V V) + \lambda_{I_h}(\gamma + \mu_h + \alpha) - \lambda_R(\gamma), \\ \frac{d\lambda_R}{dt} &= \lambda_{S_h}(\delta) + \lambda_R(\mu_h + \delta),\end{aligned}$$

with the final-time conditions $\lambda_{S_h}(T) = 0, \lambda_V(T) = 0, \lambda_E(T) = 0,$ and $\lambda_{I_h}(T) = 0, \lambda_R(T) = 0,$ The characterization of the optimal control $\phi^*(t)$ in then based on the condition

$$\frac{\partial H}{\partial \phi} = 0$$

respectively, subject to the constraint $0 \leq \phi \leq \phi_{max}$.Consider $\frac{\partial H}{\partial \phi}$, which gives

$$\frac{\partial H}{\partial \phi} = S_h \frac{(\lambda_{S_h} - c_{21} - \lambda_V)}{2c_{22}}$$

Due to the presence of both initial conditions (for the state equations) and final time conditions (for the adjoint equations), and the fact that most models of our interest are nonlinear, the optimal control system has to be solved numerically. We will use the Forward-Backward Sweep Method to conduct the numerical simulation.
Assume that $u = u(t, x, \lambda)$ can be found explicitly from the optimality condition.

- Step 1. Make an initial guess for u (usually 0) on the entire domain.
- Step 2 Using the initial condition $x(0) = a$ and the values for u, solve x forward in time over the domain.
- Step 3. Using the transversality condition $\lambda(T) = b$ (usually 0) and the values for u and x, solve λ backward in time.
- Step 4 Update u by the new x and λ values. We use the optimality condition to update control u at this step.
- Step 5. Check convergence. If values in this iteration and the last one are negligibly close, output the current values as solutions; otherwise, return to Step 2.

Next,we conduct numerical simulation to verify some of our analytical results. Optimal control theory is applied to the model to seek for optimal vaccination strategies, The numerical solution show that with a well planned of vaccination can reduce a number of infections.

Table 8: Parameter values and symbols

Parameter	Symbol	Value
Total human population	N_h	10,000
Total bird population	N_b	$2 * N_h$
Natural human birth and death rate	μ_h	$(70 * 365^{-1})/day$
Natural bird birth and death rate	μ_b	$(100^{-1})/day$
Rate at which birds contract avian influenza	β_B	$0.4/200,000/day$
Rate at which bird-to-human avian influenza is contracted	β_{BH}	$0.2/(N_b * 100)/day$
Ability to cause infection by exposed individuals	β_E	$0.5/N_h/day$
Ability to cause infection by infectious individuals	β_I	$0.5/N_h/day$
Factor by which the vaccine reduces infection	β_V	$0.5/N_h/day$
Additional disease death rate due to avian strain in birds	δ_b	$5/day$
Duration of immunity loss in human	δ	$5/day$
The loss of immunity period	σ	$0.699/day$
Rate of vaccination	ϕ	$0.7/day$
The recovery rate for exposed population	κ	0.00015
The recovery rate for infected population	γ	0.36
The disease induced morality rate	α	0.03
Assuming that there are costs of group β_V	c_{21}	0.01
Assuming that there are costs of group β_V	c_{22}	0.5

First we let $(1-\beta_V) = 0.1$ which is a vaccine efficacy of 90%. The numerical simulations are shown below:

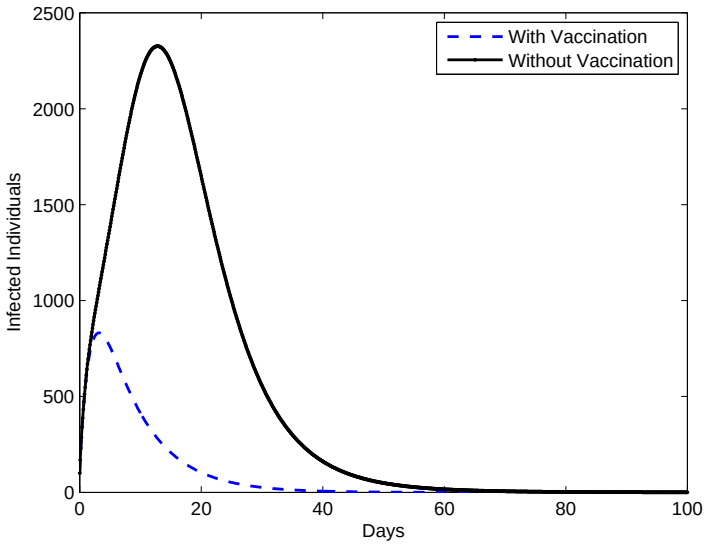

Figure 3.2: The acute avian influenza infection population : it shows that with medications in the model can reduce the number of acute avian influenza infection group.

Figure 3.2 shows the infection curves for the model with vaccine (solid line) and that without the optimal control of vaccination (dashed line). It is clearly seen the infection level has been reduced due to the incorporation of vaccine. In addition, the dynamics of exposed population is shown in Figure 3.3 similarly the exposed population to the disease in our model with vaccine cooperated is approaching to zero faster than that without vaccine.

This result shows that applying vaccine to susceptible humans reduces the infection due to the avian influenza A viruses and the number of exposed humans to the disease is reduced versus time.

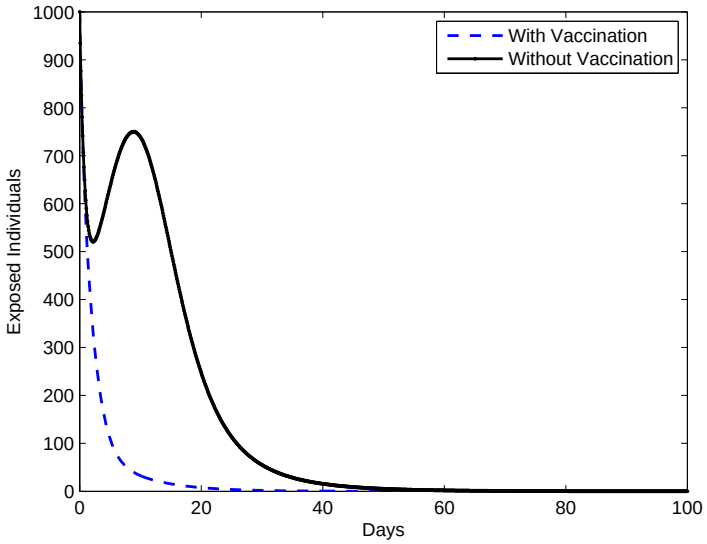

Figure 3.3: Clinical latency exposed individuals of the modified model : Similary, we can see that the number of clinical latency state is reduced with medications in the model.

The second we let $(1 - \beta_V) = 0.5$ which is a vaccine efficacy of 50%. The numerical simulations are shown below:

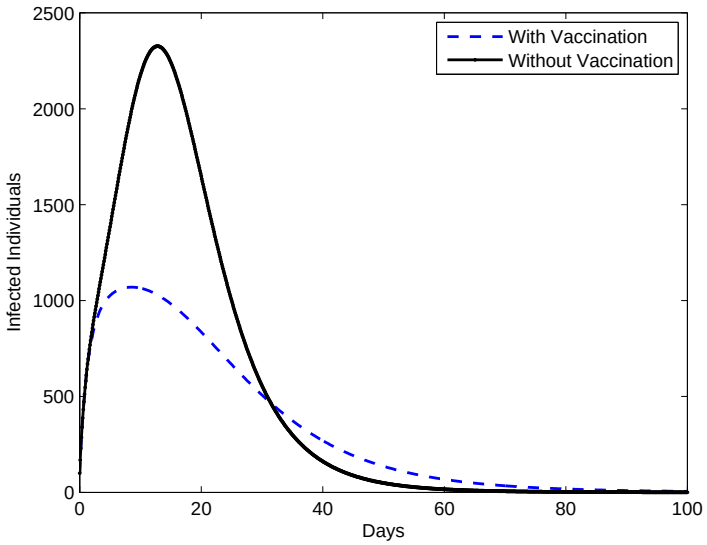

Figure 3.4: The acute avian influenza infection population : it shows that with medications in the model can reduce the number of acute avian influenza infection group.

Figure 3.4 shows the infection curves for the model with vaccine (solid line) and that without the optimal control of vaccination (dashed line). It is clearly seen the infection level has been reduced due to the incorporation of vaccine.

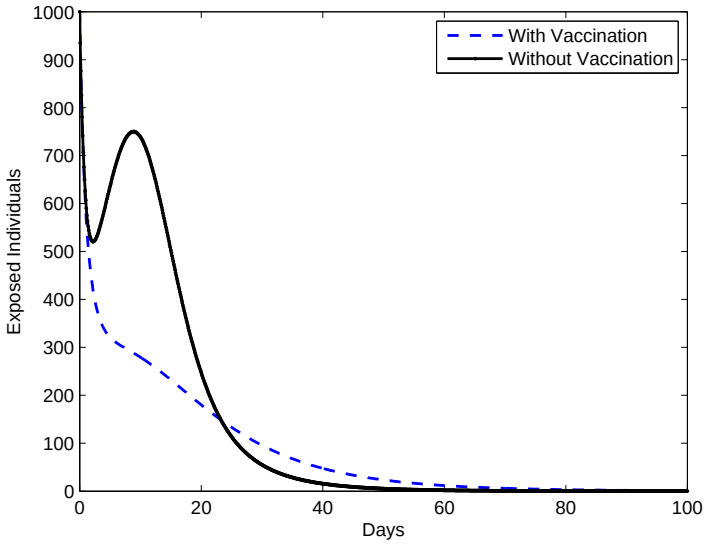

Figure 3.5: Clinical latency exposed individuals of the modified model : Similary, we can see that the number of clinical latency state is reduced with medications in the model.

The third we let $(1 - \beta_V) = 0.7$ which is a vaccine efficacy of 30%. The numerical simulations are shown below:

Figure 3.6 shows the infection curves for the model with vaccine (solid line) and that without the optimal control of vaccination (dashed line). It is clearly seen the infection level has been reduced due to the incorporation of vaccine but not much.

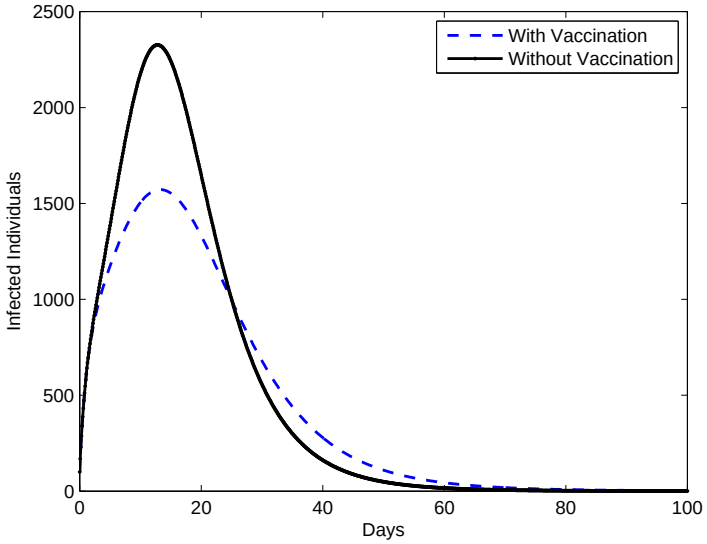

Figure 3.6: The acute avian influenza infection population : it shows that with medications in the model can reduce the number of acute avian influenza infection group.

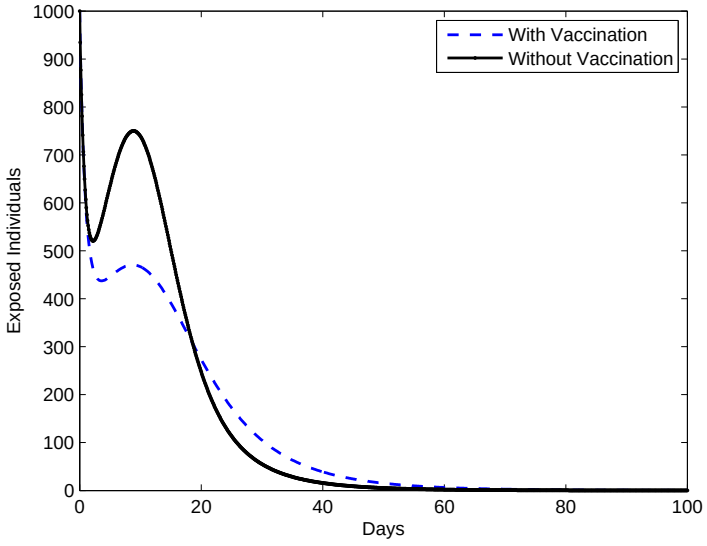

Figure 3.7: Clinical latency exposed individuals of the modified model : Similary, we can see that the number of clinical latency state is reduced with medications in the model.

3.5 Our second proposed model

We describe the avian influenza dynamics using a system of four differential equations. The population of humans is compartmentalized into four classes: susceptible (S), exposed (E), infectious (I), and recovered (R). A diagram to illustrate our model is presented in Figure 3.5

We find a unique disease-free equilibrium (DFE) by setting $E = I = R = 0$ and find S from the model. Therefore, the DFE will have nonzero states S says $\varepsilon_0 = (S, 0, 0, 0)$

By setting $\frac{dS}{dt}$ equal to zero, we can find S:

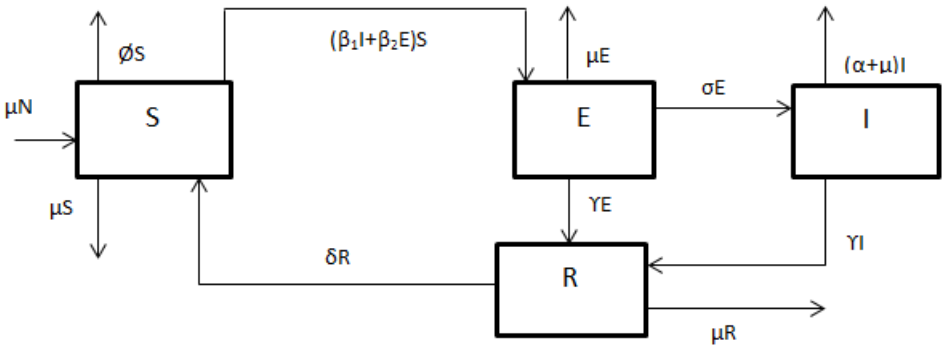

Figure 3.8: Diagram of the model.

We use an SEIR model to represent the disease dynamics. Since incubation period is not given in an exact interval, therefore, we assume that susceptible individuals can be infected from both exposed (late incubation period) and infectious people with rates of β_1 and β_2 , respectively. Susceptible humans, once infected, will first enter the exposed class E, and then become infectious after an incubation period, $1/\sigma$; here σ is the progression rate from exposed to infectious. Both the exposed and infectious people may recover from the disease.

We assume the natural birth and death rates are the same, and denoted by μ. We also denote the disease caused death rates by α. In addition, we represent the influx rates for the population by the constant Γ. For convenience of discussion, we write

$\Gamma = \mu N$, where N can be interpreted as the respective time-averaged population. In case there is no disease related mortality, $N = S + E + I + R$ and it represents the (constant) total population. Finally, we incorporate antiviral drug treatments into the exposed and infectious as disease control measures with rates of ϕ_1 and ϕ_2, respectively. Our model thus takes the form below:

$$\frac{dS}{dt} = \mu N - (\beta_1 I + \beta_2 E)S - \mu S - \phi S + \delta R \tag{3.29}$$

$$\frac{dE}{dt} = (\beta_1 I + \beta_2 E)S - (\sigma + \mu + \gamma)E \tag{3.30}$$

$$\frac{dI}{dt} = \sigma E - (\alpha + \mu + \gamma)I \tag{3.31}$$

$$\frac{dR}{dt} = \gamma E + \gamma I - \mu R - \delta R \tag{3.32}$$

where

- S is the susceptible state.
- E is the exposed state.
- I is the infected state.
- R is the recovered human population sets.
- N is the total population.
- μ is the natural human birth and death rates.
- σ is the transition rate from exposure to infection.
- γ is the recovery rate.
- α is the disease related death rate.
- ϕ is the vaccination rate.
- δ is progression rate.
- β_1 is transmission coefficient of the infectious initially.
- β_2 is transmission coefficient of the infectious severe.

The definition and numerical values of all the model parameters are provided in Table 2. Written in a vector from, the above equations become

$$\frac{dX}{dt} = F(X) \tag{3.33}$$

with $X = (S, E, I, R)^T$

3.6 Epidemic analysis

We start our analysis of the model by studying the disease-free equilibrium (DEF) and calculating the basic reproduction numbers.It is straightforward to obtain the DFE for our system:

$$\mu N - \mu S - \phi S = 0$$
$$S = \frac{\mu N}{\mu + \phi}$$

Now we have the DFE:

$$\varepsilon_0 = \left(\frac{\mu N}{\mu + \phi}, 0, 0, 0 \right).$$

Next we will compute the basic reproductive number, R_0, for this model using the method of van den Driessche and Watmough. Here the associated next generation matrices

$$\mathcal{F} = \begin{bmatrix} (\beta_1 I + \beta_2 E)S \\ 0 \end{bmatrix}$$
$$F = \begin{bmatrix} \frac{\partial \mathcal{F}_{11}}{\partial E} & \frac{\partial \mathcal{F}_{11}}{\partial I} \\ \frac{\partial \mathcal{F}_{21}}{\partial E} & \frac{\partial \mathcal{F}_{21}}{\partial I} \end{bmatrix}$$
$$F = \begin{bmatrix} \beta_2 S & \beta_1 S \\ 0 & 0 \end{bmatrix}$$

and

$$\mathcal{V} = \begin{bmatrix} (\sigma+\mu+\gamma)E \\ -\sigma E + (\alpha+\mu+\gamma)I \end{bmatrix}$$

$$V = \begin{bmatrix} \frac{\partial \mathcal{V}_{11}}{\partial E} & \frac{\partial \mathcal{V}_{11}}{\partial I} \\ \frac{\partial \mathcal{V}_{21}}{\partial E} & \frac{\partial \mathcal{V}_{21}}{\partial I} \end{bmatrix}$$

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

At the DFE point, we have

$$F(\epsilon_0) = \begin{bmatrix} \frac{\beta_2 \mu N}{\mu+\phi} & \frac{\beta_1 \mu N}{\mu+\phi} \\ 0 & 0 \end{bmatrix}$$

The basic reproduction number is then determined as the spectral radius of FV^{-1}. Consider

$$V(\epsilon_0) = \begin{bmatrix} \sigma+\mu+\gamma & 0 \\ -\sigma & \alpha+\mu+\gamma \end{bmatrix}$$

$$\begin{aligned} \det V &= (\sigma+\mu+\gamma)(\alpha+\mu+\gamma) - 0 \\ &= (\sigma+\mu+\gamma)(\alpha+\mu+\gamma) \end{aligned}$$

$$\begin{aligned} \text{adj.}V &= \begin{bmatrix} C_{11} & C_{12} \\ C_{21} & C_{22} \end{bmatrix}^T \\ &= \begin{bmatrix} \alpha+\mu+\gamma & \sigma \\ 0 & \sigma+\mu+\gamma \end{bmatrix}^T \\ &= \begin{bmatrix} \alpha+\mu+\gamma & 0 \\ \sigma & \sigma+\mu+\gamma \end{bmatrix} \end{aligned}$$

and hence,

$$\begin{aligned} V^{-1} &= \frac{1}{detV} \cdot adj.V, \\ &= \frac{1}{a_1 a_2} \times \begin{bmatrix} a_2 & 0 \\ \sigma & a_1 \end{bmatrix}, \\ &= \begin{bmatrix} \frac{1}{a_1} & 0 \\ \frac{\sigma}{a_1 a_2} & \frac{1}{a_2} \end{bmatrix}. \end{aligned}$$

Let $a_1 = \sigma + \mu + \gamma$ and $a_2 = \alpha + \mu + \gamma$.

Thus

$$FV^{-1} = \begin{bmatrix} \beta_2 S & \beta_1 S \\ 0 & 0 \end{bmatrix} \begin{bmatrix} \frac{1}{a_1} & 0 \\ \frac{\sigma}{a_1 a_2} & \frac{1}{a_2} \end{bmatrix}$$
$$= \begin{bmatrix} \frac{\beta_2 S}{a_1} + \frac{\beta_1 S\sigma}{a_1 a_2} & \frac{\beta_1 S}{a_2} \\ 0 & 0 \end{bmatrix}$$

and

$$det(FV^{-1} - \lambda I) = \left(\frac{\beta_2 S}{a_1} + \frac{\beta_1 S\sigma}{a_1 a_2} - \lambda\right)(-\lambda) = 0$$

$$\lambda = \left[\frac{\beta_2 \mu N}{(\mu+\phi)(\sigma+\mu+\gamma)} + \frac{\beta_1 \mu N\sigma}{(\sigma+\mu+\gamma)(\gamma+\mu+\alpha)(\mu+\phi)}, 0\right]$$

Thus,

$$R_0 = \lambda = \frac{\beta_2 \mu N}{(\mu+\phi)(\sigma+\mu+\gamma)} + \frac{\beta_1 \mu N\sigma}{(\sigma+\mu+\gamma)(\gamma+\mu+\alpha)(\mu+\phi)}.$$

Based on the work in [18] , we immediately obtain the result below :

Theorem 3.8. *when $R_0 < 1$, the DFE, ε_0 , is locally asymptotically stable; when $R_0 > 1$, ε_0 is unstable.*

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

Lemma 3.9. *Consider a model system written in the form*

$$\begin{aligned} \frac{dX_1}{dt} &= F(X_1, X_2), \\ \frac{dX_2}{dt} &= G(X_1, X_2), \qquad G(X_1, 0) = 0 \end{aligned}$$

where $X_1 \in \mathbb{R}^m$ denotes (its components) the number of uninfected individuals and $X_2 \in \mathbb{R}^n$ denotes (its compnents) the number of infected individuals including latent, infectious, etc; $X_0 = (X_1^*)$ denotes the disease-free equilibrium of the system.
Also assume the conditions $(H1)$ and $(H2)$ below:

(H1) For $\frac{dX_1}{dt} = F(X_1, 0), X_1^*$ is globally asymptotically stable;

(H2) $G(X_1, X_2) = AX_2 - \hat{G}(X_1, X_2)$, $\hat{G}(X_1, X_2) \geq 0$ for $(X_1, X_2) \in \Omega$, where the Jacobian $A = \frac{\partial G}{\partial X_2}(X_1^*, 0)$ is an M-matrix (the off diagonal elements of A are non-negative) and Ω is the region where the model makes biological sense.
Then the DFE $X_0 = (X_1^*, 0)$ is globally asymptotically stable provided that $R_0 < 1$.

Theorem 3.10. *The disease-free equilibrium of the model is globally asymptotic stable if* $R_0 < 1$.

Proof. We only need to show that the condition (H1) and (H2) hold when $R_0 < 1$.
In our ODE system, $X_1 = (S, R)$, $X_2 = (E, I)$, and $X_1^* = (\frac{\mu N}{\mu+\phi}, 0)$.
We note that the system

$$\frac{dX_1}{dt} = F(X_1, 0) = \begin{bmatrix} \mu N - \mu S + \delta R - \phi S \\ -\mu R - \delta R \end{bmatrix}$$

is linear and its solution can be easily found as
For R:

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

For S:

$$\begin{aligned} \frac{dS}{dt} &= \mu N - \mu S + \delta R - \phi S \\ \frac{dS}{dt} + \mu S + \phi S &= \mu N + \delta R \\ \frac{dS}{dt} + (\mu + \phi)S &= \mu N + \delta(R(0))e^{-(\mu+\delta)t} \\ e^{(\mu+\phi)t}\frac{dS}{dt} + e^{(\mu+\phi)t}(\mu + \phi)S &= e^{(\mu+\phi)t}\mu N + e^{(\mu+\phi)t}\delta(R(0))e^{-(\mu+\delta)t} \\ \frac{d}{dt}(e^{(\mu+\phi)t} \cdot S) &= e^{(\mu+\phi)t}\mu N + e^{(\phi-\delta)t}\delta(R(0)) \\ \int \frac{d}{dt}(e^{(\mu+\phi)t} \cdot S)dt &= \int e^{(\mu+\phi)t}\mu N dt + \int e^{(\phi-\delta)t}\delta(R(0))dt \\ e^{(\mu+\phi)t} \cdot S &= \mu N \cdot \frac{e^{(\mu+\phi)t}}{\mu+\phi} + \delta(R(0)) \cdot \frac{e^{(\phi-\delta)t}}{\phi-\delta} + C_1 \\ S(t) &= \frac{\mu N}{\mu+\phi} + \delta(R(0))\frac{e^{(\phi-\delta)t}}{\phi-\delta} \cdot e^{-(\mu+\phi)t} + C_1 e^{-(\mu+\phi)t} \end{aligned}$$

Clearly, $R(t) \to 0$, $S(t) \to \frac{\mu N}{\mu+\phi}$ as $t \to \infty$, regardless of the values of $R(0)$ and $S(0)$. Hence $X_1^* = (\frac{\mu N}{\mu+\phi}, 0)$ is globally asymptotically stable and condition $H1$ holds.

Next, we have

$$\frac{dX_2}{dt} = G(X_1, X_2) = \begin{bmatrix} (\beta_1 I + \beta_2 E)S - (\mu + \sigma + \gamma)E \\ \sigma E - (\mu + \alpha + \gamma)I \end{bmatrix}$$

$$\frac{\partial G}{\partial X_2}(X_1, 0) = A = \begin{bmatrix} \beta_2 S - (\mu + \sigma + \gamma) & \beta_1 S \\ \sigma & -(\mu + \alpha + \gamma) \end{bmatrix}$$

$$\frac{\partial G}{\partial X_2}(X_1^*, 0) = A = \begin{bmatrix} \frac{\beta_2 \mu N}{\mu+\phi} - (\mu + \sigma + \gamma) & \frac{\beta_1 \mu N}{\mu+\phi} \\ \sigma & -(\mu + \alpha + \gamma) \end{bmatrix}$$

Thus,

$$\begin{aligned} G(X_1, X_2) =& AX_2 - \hat{G}(X_1, X_2) \\ \hat{G}(X_1, X_2) =& AX_2 - G(X_1, X_2) \\ =& \begin{bmatrix} \frac{\beta_2 \mu N}{\mu+\phi} - (\mu + \sigma + \gamma) & \frac{\beta_1 \mu N}{\mu+\phi} \\ \sigma & -(\mu + \alpha + \gamma) \end{bmatrix} \begin{bmatrix} E \\ I \end{bmatrix} \\ & - \begin{bmatrix} (\beta_1 I + \beta_2 E)E - (\mu + \sigma + \gamma)E \\ \sigma E - (\mu + \alpha + \gamma)I \end{bmatrix} \\ =& \begin{bmatrix} (\frac{\beta_2 \mu N}{\mu+\phi} - (\mu + \sigma + \gamma))E + (\frac{\beta_1 \mu N}{\mu+\phi})I \\ \sigma E + -(\mu + \alpha + \gamma)I \end{bmatrix} \\ & - \begin{bmatrix} (\beta_1 I + \beta_2 E)S - (\mu + \sigma + \gamma)E \\ \sigma E - (\mu + \alpha + \gamma)I \end{bmatrix} \\ =& \begin{bmatrix} \beta_2 E(\frac{\mu N}{\mu+\phi} - S) + \beta_1 I(\frac{\mu N}{\mu+\phi} - S) \\ 0 \end{bmatrix} \end{aligned}$$

which is clearly an M-matrix. Meanwhile, we find

$$\therefore \hat{G}(X_1, X_2) = \left[\beta_2 E(\frac{\mu N}{\mu + \phi} - S) + \beta_1 I(\frac{\mu N}{\mu + \phi} - S), 0)\right]^T$$

Since $0 \leq S \leq \frac{\mu N}{\mu+\phi} \leq N$ it is obvious that $\hat{G}(X_1, X_2) \geq 0$.

3.7 Endemic dynamics

The stability at the DFE determines the short-term epidermics of the disease, where as its dynamics over a longer period of time is characterized by the stability at the endemics equilibrium. In this section we will analyze the endemic properties of our avian influenza model.

3.7.1 Endemic equilibrium

We first examine the existence of the positive endemic equilibrium. Denote the endemic equilibrium of the model by $\varepsilon^* = (S^*, E^*, I^*, R^*)$. From equations (3.29) and (3.30) we obtain

$$S^* = \frac{\mu N + \delta R^* - a_1 E^*}{\mu + \phi} \tag{3.34}$$

where $a_1 = \sigma + \mu + \gamma$. From equation (3.31), we have

$$E^* = \frac{a_2 I^*}{\sigma}$$

where $a_2 = \alpha + \mu + \gamma$. Hence equation (3.32) becomes

$$R^* = \frac{(\gamma a_2 + \gamma\sigma) I^*}{\sigma(\mu + \delta)}$$

Thus, equation (3.30) gives

$$\begin{aligned}
0 &= (\beta_1 I^* + \beta_2 E^*) S^* - \frac{a_1 a_2 I^*}{\sigma}, \\
0 &= \beta_1 I^* S^* + \frac{\beta_2 a_2 I^* S^*}{\sigma} - \frac{a_1 a_2 I^*}{\sigma}, \\
0 &= I^* \big(\beta_1 S^* + \frac{\beta_2 a_2 S^*}{\sigma} - \frac{a_1 a_2}{\sigma}\big), \\
0 &= I^* \left[\beta_1 \left(\frac{\mu N}{\mu + \phi} - \frac{a_1 a_2 I^*}{\sigma(\mu + \phi)} + \frac{\delta R^*}{\mu + \phi}\right) + \frac{\beta_2 a_2}{\sigma}\left(\frac{\mu N}{\mu + \phi}\right.\right. \\
&\quad \left.\left. - \frac{a_1 a_2 I^*}{\sigma(\mu + \phi)} + \frac{\delta R^*}{\mu + \phi}\right) - \frac{a_1 a_2}{\sigma}\right], \\
0 &= \left(\frac{\beta_1 \mu \sigma N}{a_1 a_2(\mu + \phi)} + \frac{\beta_2 \mu N}{a_1(\mu + \phi)} + \frac{\beta_2 \delta \gamma (a_2 + \sigma)}{a_1 \sigma(\mu + \phi)(\mu + \delta)} - 1 - \frac{I^*}{\mu + \phi}\right. \\
&\quad \left. + \frac{\beta_1 \delta \gamma (a_2 + \sigma) I^*}{a_1 a_2(\mu + \phi)(\mu + \delta)} - \frac{\beta_2 a_2 I^*}{\sigma(\mu + \phi)(\mu + \delta)}\right), \\
I^* &= \frac{t_1 t_3}{t_2}
\end{aligned}$$

Since all parameters are positive, thus we have

$$R_0 = \frac{\beta_2 \mu N}{(\mu + \phi)(\sigma + \mu + \gamma)} + \frac{\beta_1 \mu N \sigma}{(\sigma + \mu + \gamma)(\gamma + \mu + \alpha)(\mu + \phi)}$$

Hence if $R_0 > 1$, we have

$$\frac{\beta_2 \mu N}{(\mu+\phi)(\sigma+\mu+\gamma)} + \frac{\beta_1 \mu N \sigma}{(\sigma+\mu+\gamma)(\gamma+\mu+\alpha)(\mu+\phi)} > 1.$$

where

$$\begin{aligned} t_1 &= \frac{\beta_1 \mu \sigma N}{a_1 a_2 (\mu+\phi)} + \frac{\beta_2 \mu N}{a_1(\mu+\phi)} + \frac{\beta_2 \delta \gamma (a_2+\sigma)}{a_1 \sigma (\mu+\phi)(\mu+\delta)}, \\ t_2 &= a_1 a_2 \sigma(\mu+\delta) + \beta_2 a_2^2 a_1 - \beta_1 \delta \gamma \sigma (a_2+\sigma), \\ t_3 &= a_1 a_2 (\mu+\phi)(\mu+\delta), \end{aligned}$$

Thus, it is obvious that $I^* > 0$.

Theorem 3.11. *The positive endemic equilibrium ϵ^* of the system (3.21)-(3.24) exists and is unique if $R_0 > 1$, and there is no positive endemic equilibrium if $R_0 < 1$.*

3.7.2 Local and global stabilities

We proceed to analyze the stability properties of the endemic equilibrium. First we establish the following result regarding the local stability. For simplicity, we assume that $\delta = 0$

Theorem 3.12. *When $R_0 > 1$, the endemic equilibrium ϵ^* is locally asymptotically stable.*

Proof. The Jacobian of the system (3.21)-(3.24) at ϵ^* is given by

$$J_= \begin{bmatrix} -(\beta_1 I + \beta_2 E) - \mu - \phi & -\beta_2 S & -\beta_1 S \\ \beta_1 I + \beta_2 E & \beta_2 S - \mu - \sigma - \gamma & \beta_1 S \\ 0 & \sigma & -(\mu+\alpha+\gamma) \end{bmatrix}$$

at ϵ^* is given by

$$J_\epsilon^* = \begin{bmatrix} -(\beta_1 I^* + \beta_2 E^*) - \mu - \phi & -\beta_2 S^* & -\beta_1 S^* \\ \beta_1 I^* + \beta_2 E^* & \beta_2 S^* - \mu - \sigma - \gamma & \beta_1 S^* \\ 0 & \sigma & -(\mu+\alpha+\gamma) \end{bmatrix}$$

The characteristic equation of the matrix $J(\epsilon^*)$ is

$$\begin{aligned}
0 =&|\lambda I - J(\epsilon^*)| \\
=&(\lambda + (\beta_1 I^* + \beta_2 E^* + \mu))(\lambda - (\beta_2 S^* - a_1))(\lambda + a_2) + \beta_1 S^*(\beta_1 I^* + \beta_2 E^*)\sigma \\
=&\lambda^3 + [(\beta_1 I^* + \beta_2 E^* + \mu) - (\beta_2 S^* - a_1) + a_2]\lambda^2 \\
&+ [a_2(\beta_1 I^* + \beta_2 E^* + \mu) - (\beta_1 I^* + \beta_2 E^* + \mu)(\beta_2 S^* - a_1) - a_2(\beta_2 S^* - a_1) - \sigma\beta_1 S^* \\
&+ (\beta_1 I^* + \beta_2 E^*)\beta_2 S^*]\lambda \\
&+ [\beta_1 S^*(\beta_1 I^* + \beta_2 E^*)\sigma - a_2(\beta_1 I^* + \beta_2 E^* + \mu)(\beta_2 S^* - a_1) \\
&- \sigma\beta_1 S^*(\beta_1 I^* + \beta_2 E^* + \mu) + a_2(\beta_1 I^* + \beta_2 E^*)\beta_2 S^*]
\end{aligned}$$

From matrix $J(\epsilon^*)$ can be put into a cubic equation of the form

$$A_3\lambda^3 + A_2\lambda^2 + A_1\lambda + A_0 \tag{3.35}$$

where

$$\begin{aligned}
A_3 &= 1, \\
A_2 &= (\beta_1 I^* + \beta_2 E^* + \mu) - (\beta_2 S^* - a_1) + a_2, \\
A_1 &= a_2(\beta_1 I^* + \beta_2 E^* + \mu) - (\beta_1 I^* + \beta_2 E^* + \mu)(\beta_2 S^* - a_1) \\
&\quad - a_2(\beta_2 S^* - a_1) - \sigma\beta_1 S^* + (\beta_1 I^* + \beta_2 E^*)\beta_2 S^*, \\
A_0 &= \beta_1 S^*(\beta_1 I^* + \beta_2 E^*)\sigma - a_2(\beta_1 I^* + \beta_2 E^* + \mu)(\beta_2 S^* - a_1) \\
&\quad - \sigma\beta_1 S^*(\beta_1 I^* + \beta_2 E^* + \mu) + a_2(\beta_1 I^* + \beta_2 E^*)\beta_2 S^*
\end{aligned}$$

Note that at the endemic equilibruim, the right-hand side of equation (3.22) become 0, which yield

$$\frac{\beta_1 I^* S^*}{E^*} = a_1 - \beta_2 S^*$$

Since all parameters are positive, we have $a_1 - \beta_2 S^* > 0$. Thus,

$$A_2 = \beta_1 I^* + \beta_2 E^* + \mu + a_2 + a_1 - \beta_2 S^* > 0. \tag{3.36}$$

Now rewrite A_1 as

$$A_1 = a_2(\beta_1 I^* + \beta_2 E^* + \mu) + (\beta_1 I^* + \beta_2 E^* + \mu)(a_1 - \beta_2 S^*) \tag{3.37}$$

$$+ a_2(a_1 - \beta_2 S^*) - \sigma\beta_1 S^* + (\beta_1 I^* + \beta_2 E^*)\beta_2 S^* \tag{3.38}$$

From equation (3.38), consider terms

$$\begin{aligned} a_2(a_1 - \beta_2 S^*) - \sigma\beta_1 S^* =& a_1 a_2 - \beta_2 a_2 S^* - \sigma\beta_1 S^* \\ =& a_1 a_2 - (\beta_2 a_2 + \sigma\beta_1) S^* \\ =& (\beta_2 a_2 + \sigma\beta_1)\left[\frac{a_1 a_2}{\beta_2 a_2 + \sigma\beta_1} - S^*\right] \end{aligned}$$

and when $R_0 > 1$, we have

$$\begin{aligned} \frac{\beta_2 \mu N}{(\mu a_1 + \phi a_1)} + \frac{\sigma\beta_1\mu N}{a_1 a_2(\mu + \phi)} &> 1 \\ a_2\beta_2\mu N + \sigma\beta_1\mu N &> a_1 a_2(\mu + \phi) \\ N(a_2\beta_2\mu + \sigma\beta_1\mu) &> a_1 a_2(\mu + \phi) \\ N &> \frac{a_1 a_2(\mu + \phi)}{\beta_2 a_2 \mu + \sigma\beta_1\mu}. \end{aligned}$$

Hence it is obvious that $A_1 > 0$ since $a_1 - \beta_2 S^* > 0$ and $R_0 > 1$. Next we consider A_0:

$$\begin{aligned} A_0 &= \beta S^*(\beta_1 I^* + \beta_2 E^*)\sigma - a_2(\beta_1 I^* + \beta_2 E^* + \mu)(\beta_2 S^* - a_1) \\ &\quad - \sigma\beta_1 S^*(\beta_1 I^* + \beta_2 E^* + \mu) + a_2(\beta_1 I^* + \beta_2 E^*)\beta_2 S^* \\ &= \beta_1 S^*(\beta_1 I^* + \beta_2 E^*)\sigma + (\beta_1 I^* + \beta_2 E^* + \mu)[a_1 a_2 - a_2\beta_2 S^* - \sigma\beta_1 S^*] \\ &\quad + a_2(\beta_1 I^* + \beta_2 E^*)\beta_2 S^*. \end{aligned}$$

We have $a_1 a_2 - a_2\beta_2 S^* - \sigma\beta_1 S^* > 0$ from equation (3.41), since $N > \frac{a_1 a_2(\mu+\phi)}{\beta_2 a_2 \mu + \sigma\beta_1\mu}$ when $R_0 > 1$. Thus, $A_0 > 0$ Next we consider the Routh-Hurwitz table

λ^3	A_3	A_1
λ^2	A_2	A_0
λ^1	B_1	0
λ^0	C_1	0

where

$$B_1 = \frac{A_2 A_1 - A_0 A_3}{A_2}, C_1 = A_0. \tag{3.39}$$

To ensure that all roots of equation (3.34) have negative real parts, the Routh-Hurwitz stability criterion requires A_0, A_1, A_2, A_3, B_1 and C_1 all to be positive. It is straightforward to observe that $A_2 A_1 > A_0 A_3$; i.e., $B_1 > 0$. To that end, we let $Q_1 = \beta_1 I^* + \beta_2 E^* + \mu$

and $Q_2 = \beta_1 I^* + \beta_2 E^*$. Hence

$$A_1 A_2 = [Q_1 + (a_1 - \beta_2 S^*) + a_2][a_2 Q_1 + Q_1(a_1 - \beta_2 S^*) \tag{3.40}$$

$$+ (a_1 a_2 - a_2 \beta_2 S^* - \sigma \beta_1 S^*) + Q_2 \beta_2 S^*] \tag{3.41}$$

and

$$A_0 = \beta_1 S^* Q_2 \sigma + Q_1[a_1 a_2 - a_2 \beta_2 S^* - \sigma \beta_1 S^*] + a_2 Q_2 \beta_2 S^*. \tag{3.42}$$

Since a_1 - $\beta_2 S^* > 0$, $A_1 > 0$, $A_2 > 0$ and $A_0 > 0$, it is obvious that $A_1 A_2 > A_0 A_3$. This completes the proof.

Next, we will follow the geometric approach originally proposed by Li and Muldowney [37,22] to investigate the global asymptotic stability of the endemic equilibrium. To that end, we first present the following result based on the geometric approach.

Lemma 3.13. *Consider a dynamical system $\frac{dx}{dt} = f(x)$,where $f : D \mapsto \mathbb{R}^n$ is a C^1 function and $D \subset \mathbb{R}^n$ is a simply connected domain. Assume that there exists a compact absorbing set $K \subset D$ and the system has a unique equilibrium point X^* in D. Then X^* is globally asymptotically stable in D if $\bar{q_2} < 0$, where*

$$\bar{q_2} = \limsup_{t \to \infty} \sup_{X_0 \in K} \frac{1}{t} \int_0^t m(P(X(s, X_0)))ds. \tag{3.43}$$

In equation (3.38) , P is a Matrix-valued function defined as

$$P = Q_f Q^{-1} + Q J^{[2]} Q^{-1}, \tag{3.44}$$

where $Q(X)$ is a $\binom{n}{2} \times \binom{n}{2}$ matrix-valued C^1 function in D, Q_f is the derivative of Q (entry-wise) along the direction of f, and $J^{[2]}$ is the second additive compound matrix of the Jacobian $J(\mathbf{X}) = \mathbf{Df}(\mathbf{X})$. Meanwhile, $m(P)$ is the Lozinski measure of P with respect to a matrix norm; i.e.,

$$m(P) = \lim_{h \to 0^+} \frac{|\amalg + hP| - 1}{h}, \tag{3.45}$$

where $\amalg$ represents the identity matrix.

To show the global stability of the endemic equilibrium for the system (3.21)-(3.24), we consider a simplified case of our model by assuming $\phi = 0$;i.e.,

no treatment and no disease caused mortality,and apply the geometric approach summarized in Lemma 3.11 Then $S+E+I+R=N$ is a constant which allows us to drop equation (3.24) and consider a three-dimensional system (3.21)-(3.23), written as

$$\frac{dS}{dt} = \mu N - (\beta_1 I + \beta_2 E)S - \mu S \tag{3.46}$$

$$\frac{dE}{dt} = (\beta_1 I + \beta_2 E)S - (\sigma + \mu + \gamma)E \tag{3.47}$$

$$\frac{dI}{dt} = \sigma E - (\alpha + \mu + \gamma)I \tag{3.48}$$

on the feasible domain

$$\Omega = (S, E, I) | 0 \leq S + E + I \leq N.$$

Let us define

$$Q(S,E,I) = \begin{bmatrix} 1 & 0 & 0 \\ 0 & \frac{E}{I} & 0 \\ 0 & 0 & \frac{E}{I} \end{bmatrix}$$

Then

$$Q_f Q^{-1} = \begin{bmatrix} 0 & 0 & 0 \\ 0 & (\frac{I}{E})(\frac{E}{I})_f & 0 \\ 0 & 0 & \frac{I}{E}(\frac{E}{I})_f \end{bmatrix}$$

where $\frac{I}{E}(\frac{E}{I})_f = \frac{E'}{E} - \frac{I'}{I}$ based on equations (3.21) and (3.22)
The Jacobian of the system (3.48)-(3.49) is

$$J = \begin{bmatrix} -(\beta_1 I + \beta_2 E) - \mu & -\beta_2 S & -\beta_1 S \\ \beta_1 I + \beta_2 E & \beta_2 S - a_1 & 0 \\ 0 & \sigma & -a_2 \end{bmatrix}$$

where $a_1 = \sigma + \mu + \gamma$ and $a_2 = \alpha + \mu + \gamma$ and thus the second additive compound matrix associated with the Jacobian is,

$$J^{[2]} = \begin{bmatrix} a_{11} + a_{22} & a_{23} & -a_{13} \\ a_{32} & a_{11} + a_{33} & a_{12} \\ -a_{31} & a_{21} & a_{22} + a_{33} \end{bmatrix}$$

$$J^{[2]} = \begin{bmatrix} -(\beta_1 I + \beta_2 E) - \mu + \beta_2 S - a_1 & 0 & -\beta_1 S \\ \sigma & -(\beta_1 I + \beta_2 E) - \mu - a_2 & -\beta_2 S \\ 0 & \beta_1 I + \beta_2 E & \beta_2 S - a_1 - a_2 \end{bmatrix}$$

Thus we have

$$QJ^{[2]}Q^{-1} = \begin{bmatrix} 1 & 0 & 0 \\ 0 & \frac{E}{I} & 0 \\ 0 & 0 & \frac{E}{I} \end{bmatrix} \begin{bmatrix} \ J^{[2]} \ \end{bmatrix} \begin{bmatrix} 1 & 0 & 0 \\ 0 & \frac{I}{E} & 0 \\ 0 & 0 & \frac{I}{E} \end{bmatrix}$$

$$= \begin{bmatrix} -(\beta_1 I + \beta_2 E) - \mu + \beta_2 S - a_1 & \frac{\beta_1 SI}{E}\beta_1 S & \frac{\beta_1 SI}{E} \\ \frac{E\sigma}{I} & -(\beta_1 I + \beta_2 E) - \mu - a_2 & -\beta_2 S \\ 0 & \beta_1 I + \beta_2 E & \beta_2 S - a_1 - a_2 \end{bmatrix}$$

Where

$$\frac{I}{E}\left(\frac{E}{I}\right)_f = \frac{E'}{E} - \frac{I'}{I}$$

Hence

$$P = Q_f Q^{-1} + QJ^{[2]}Q^{-1} = \begin{bmatrix} P_{11} & P_{12} \\ P_{21} & P_{22} \end{bmatrix} \tag{3.49}$$

with

$$P_{11} = -(\beta_1 I + \beta_2 E) - \mu + \beta_2 S - a_1,$$
$$P_{12} = [\ \frac{\beta_1 SI}{E} \quad \frac{\beta_1 SI}{E}\ ],$$
$$P_{21} = \begin{bmatrix} \frac{E\sigma}{I} \\ 0 \end{bmatrix},$$
$$P_{22} = \begin{bmatrix} \frac{I}{E}(\frac{E}{I})_f - (\beta_1 I + \beta_2 E) - \mu - a_2 & -\beta_2 S \\ \beta_2 I + \beta_2 E & \frac{I}{E}(\frac{E}{I})_f + \beta_2 S - a_1 - a_2 \end{bmatrix}$$

Let us choose the vector norm | | in $\mathbb{R}^3$ as

$$|(x_1, x_2, x_3)| = \max\left\{|x_1|, |x_2| + |x_3|\right\}$$

we need to verify the condition $\mu(p) < 0$.We have

$$\mu(p) \leq \left\{sup(g_1, g_2)\right\},$$

where

$$\begin{aligned} g_1 &= \mu_1(P_{11}) + |P_{12}| \\ &= -\beta_1 I - \beta_2 E - \mu + \beta_2 S - a_1 + \frac{\beta_1 SI}{E} \\ g_2 &= |P_{11}| + \mu_1(P_{12}) \\ &= \frac{E\sigma}{I} + \max\left\{ \frac{I}{E}\Big(\frac{E}{I}\Big)_f - \mu - a_2 \right\} \leq \frac{E\sigma}{I} + \frac{I}{E}\Big(\frac{E}{I}\Big)_f - \mu - a_2 \end{aligned}$$

Provided that $\mu < a_1 = \sigma + \mu + \gamma$ or $0 < \sigma + \gamma$ which is always true.
Using

$$\begin{aligned} \frac{E'}{E} &= \frac{\beta_1 SI}{E} + \beta_2 S - a_1, \\ \frac{I'}{I} &= \frac{\sigma E}{I} - a_2 \end{aligned}$$

Since

$$\frac{I}{E}\Big(\frac{E}{I}\Big)_f = \frac{E'}{E} - \frac{I'}{I}$$

We obtain

$$\begin{aligned} g_2 &\leq \frac{E\sigma}{I} + \frac{I}{E}\Big(\frac{E}{I}\Big)_f - \mu - a_2 \\ &= \frac{\sigma E}{I} + \frac{E'}{E} - \frac{I'}{I} - \mu - a_2 \\ &= \frac{E'}{E} - \mu \qquad\qquad , \mu > 0 \end{aligned}$$

and

$$g_1 = -\beta_1 I - \beta_2 E - \mu + \beta_2 S - a_1 + \frac{\beta_1 SI}{E}$$

from

$$\begin{aligned} g_1 &= -\beta_1 I - \beta_2 E - \mu + \beta_2 S - a_1 + \frac{\beta_1 SI}{E} \\ &= \frac{E'}{E} - \frac{E'}{E} - \beta_1 I - \beta_2 E - \mu + \beta_2 S - a_1 + \frac{\beta_1 SI}{E} \\ &= \frac{E'}{E} - \mu - (\beta_1 I + \beta_2 E) \\ &\leq \frac{E'}{E} - \mu \end{aligned}$$

This implies that

$$\mu(p) \leq \frac{E'}{E} - \mu$$

By the uniform persistence ,there exist $\epsilon > 0$ and $T > 0$
such that when $t > T$, we have

$$E(t) \geq \epsilon, \qquad \frac{\log E(t)}{t} < \frac{\mu}{2}$$

Thus

$$\begin{aligned} \frac{1}{t}\int_0^1 \mu(p)dt &< \frac{\log E(t)}{t} - \mu \\ &< \frac{\mu}{2} - \mu = -\frac{\mu}{2}, \end{aligned}$$

which implies $\bar{q_2} < 0$.Hence, we have estabished the following result:

Theorem 3.14. *The endemic equilibrium of the system (3.47)-(3.48) is globally asymptotically stable.*

From Theorem 3.14, we obtain the global asymptotically stability of the endemic equilibrium for the original system (3.29)-(3.32) under the assumptions of no treatments and disease related mortality.

Chapter 4

Results

Optimal treatments Now we turn to the more general model with time-dependent controls $\phi(t)$ .We consider the system on a time interval [0,T]. The functions $\phi(t)$ are assumed to be at least lebesgue measurable on [0,T]. The control set is defined as

$$\Omega = \left\{\phi(t)|0 \leq \phi(t) \leq \phi_{max}\right\} \tag{4.1}$$

where ϕ_{max} denotes the upper bounds for the effort of treatments. The bound reflects practical limitation on the maximum rate of controls in a given time period.

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

$$\min_{\phi\in\Omega} \int_0^T [I(t) + c_{21}\phi(t)S(t) + c_{22}\phi(t)^2]dt. \tag{4.2}$$

The cost parameters are associated with the controls and defined by c_{21} and c_{22}.Quadratic terms are introduced to indicate nonlinear costs potentially arising at high intervention levels.

We note that our model is linear in the control variables ϕ, and the control set Ω is closed and convex. Meanwhile, the integrand of the objective functional in (3.53) is also convex. Hence, standard optimal control teory [7,21] yields the following result:

Theorem 4.1. *There exist $\phi^* \in \Omega$ such that the objective functional in (3.53) is minimized.*

Indeed, the optimal control solution is also unique for small T due to the Lipschitz structure of the model equations and the boundedness of the state variables. To proceed, we apply Pontryagin's minimum principle to determine the optimal control. We first define the adjoint function λ_S,λ_E and λ_I associated with the state equations for

S, E and I, respectively. We then form the Hamiltonian,H, by multiplying each adjoint function with the right-hand side of its corresponding state equation, and adding each of these products to the integrand of the objective functional. As a result, we obtain

$$\begin{aligned} H = I(t) &+ c_{21}\phi(t)S(t) + c_{22}\phi(t)^2 \\ &+ \lambda_S[\mu N - (\beta_1 I + \beta_2 E)S - \mu S - \phi(t)S + \delta R] \\ &+ \lambda_E[(\beta_1 I + \beta_2 E)S - (\mu + \sigma + \gamma)E] \\ &+ \lambda_I[\sigma E - (\mu + \alpha + \gamma)I] \\ &+ \lambda_R[\gamma E + \gamma I - \mu R - \delta R] \end{aligned}$$

To achieve the optimal control, the adjoint functions must satisfy $\frac{d\lambda_S}{dt} = -\frac{\partial H}{\partial S}$, $\frac{d\lambda_E}{dt} = -\frac{\partial H}{\partial E}$, $\frac{d\lambda I}{dt} = -\frac{\partial H}{\partial I}$ and $\frac{d\lambda_R}{dt} = -\frac{\partial H}{\partial R}$. Thus, we have

$$\begin{aligned} \frac{d\lambda_S}{dt} &= -c_{21}\phi(t) + \lambda_S(\beta_1 I + \beta_2 E + \mu + \phi) - \lambda_E(\beta_1 I + \beta_2 E), \\ \frac{d\lambda_E}{dt} &= \lambda_S(\beta_2 S) - \lambda_E(\beta_2 S + \sigma + \mu + \gamma) - \lambda_I(\sigma) - \lambda_R(\gamma), \\ \frac{d\lambda_I}{dt} &= -1 + \lambda_S(\beta_1 S) - \lambda_E(\beta_1 S) + \lambda_I(\gamma + \mu + \alpha) - \lambda_R(\gamma), \\ \frac{d\lambda_R}{dt} &= -\lambda_S(\delta) + \lambda_R(\mu + \delta), \end{aligned}$$

with the final-time conditions $\lambda_S(T) = 0, \lambda_V(T) = 0, \lambda_E(T) = 0,\ and\ \lambda_I(T) = 0, \lambda_R(T) = 0$, The characterization of the optimal control $\phi^*(t)$ in then based on the condition

$$\frac{\partial H}{\partial \phi} = 0 \tag{4.3}$$

subject to the constraints $0 \leq \phi \leq \phi_{max}$.Specifically, we have

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

where

$$\phi^*(t) = \frac{[(\lambda_S S - c_{21}S(t))]}{2c_{22}}$$

Due to the presence of both initial conditions (for the state equations) and final time conditions (for the adjoint equations), and the fact that most models of our interest

are nonlinear, the optimal control system has to be solved numerically. We will use the Forward-Backward Sweep Method to conduct the numerical simulation.
Assume that $u = u(t, x, \lambda)$ can be found explicitly from the optimality condition.

- Step 1. Make an initial guess for u (usually 0) on the entire domain.
- Step 2 Using the initial condition $x(0) = a$ and the values for u, solve x forward in time over the domain.
- Step 3. Using the transversality condition $\lambda(T) = b$ (usually 0) and the values for u and x, solve λ backward in time.
- Step 4 Update u by the new x and λ values. We use the optimality condition to update control u at this step.
- Step 5. Check convergence. If values in this iteration and the last one are negligibly close, output the current values as solutions; otherwise, return to Step 2.

The optimal control system, consisting of the state equations, the adjoint equations and the optimality condition (3.48), has to be solved numerically. We have conducted numerical simulation using various choices of cost parameters and time intervals, and have observed a unique solution in each case. The numerical results clearly demonstrate that an optimal treatment strategy can significant bring down the number of exposed and infectious individuals, thus reducing the burden of an avian influenza outbreak. Some typical results are presented below.

Table 9: Parameter values and symbols

Parameter	Symbol	Value	References
Total population	N	10,000	
The vaccination rate	ϕ	0.07	[28]
Transmission coefficien of the infectious intially	β_1	$0.5/N/day$	[4]
Transmission coefficien of the infectious severe	β_2	$0.5/N/day$	[4]
Nutural human birth and death rates	μ	$(70 * 365^{-1})/day$	[4]
Disease related death rate	α	0.012	[28]
The progression rate	δ	0.01	[8]
Transmission rate from exposure to infection	σ	$0.699/day$	[28]
Recovery rate	γ	0.15	[28]

Assumming that there are costs $c_{21} = 0.2$ and $c_{22} = 0.5$

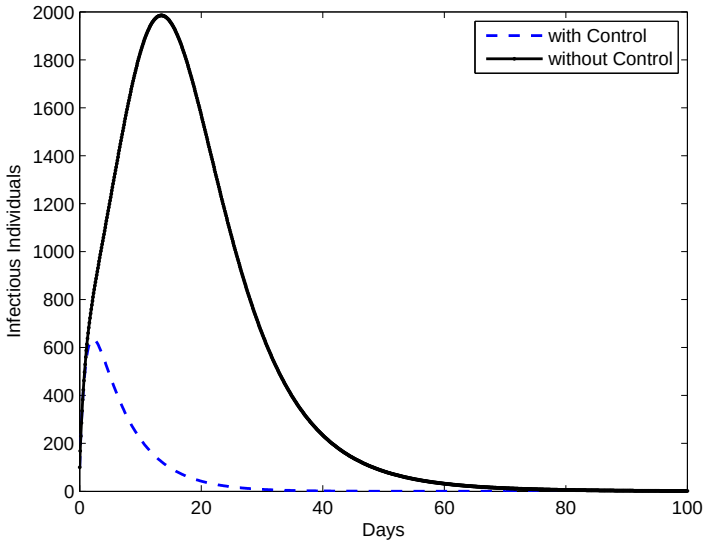

Figure 4.1: Number of infectious individuals.

Figure 3.9 depicts the infectious individuals for the case without treatments (solid line) and that with optimal treatments (dashed line). The reduction, in both the infection level and the outbreak period, due to the incorporation of treatments is significant. Figure 3.10 shows the dynamics of the exposed individuals. Without treatments, the exposed population (E) attains very high values immediately after the onset of the outbreak. As S decreases,E goes down for a short period of time.Then with the increase of infectious individuals (I), the exposed population starts increasing again and reaches a peak at

$t \approx 10$ days (not that the peak of E occurs before that of I; compare Figures 3.9 and 3.10). With optimal treatments, however,E continues decreasing until reaching and settling at a value close to zero, which,consequently,leads to a very low infection level for I.

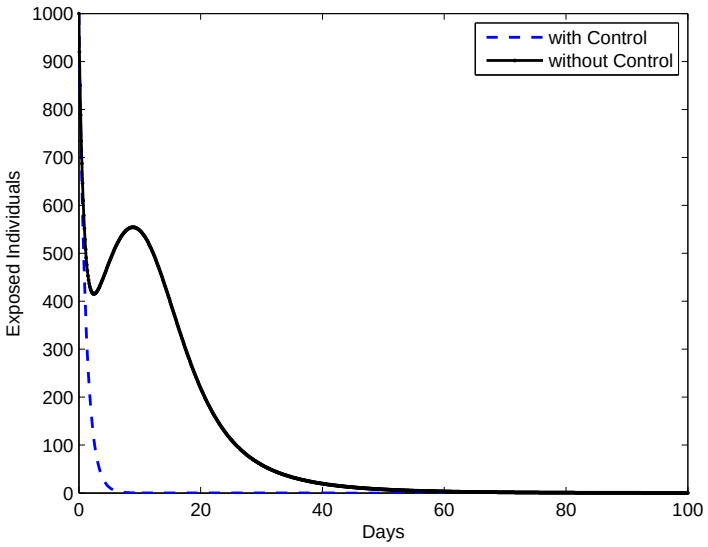

Figure 4.2: Number of exposed individuals.

Chapter 5

Conclusions and Discussions

In this study, we have presented a mathematical model for the spread of Avian Influenza that involves with the effect of latency and medical treatments. We have done this work by studying in both theoretical and numerical ways. In order to observe the effect of rate of vaccination and vaccine efficiency on the spread of disease and find ways to control the outbreak of the bird flu disease, we use the optimal control study. The model exhibits two feasible points of equilibrium, namely, the disease-free equilibrium and the endemic equilibrium. The stability of these two feasible points of equilibrium are controlled by the threshold number R_0. If R_0 is less than one, then the disease dies out and the disease-free equilibrium is stable. If R_0 is greater than one, then the disease persists and the disease free equilibrium is unstable. We have the values is based on the theory of R_0. We assumed that humans are vaccinated with the rate $\phi(t)$ and thus they became a vaccinated class. According to our study, it shows that with a good vaccination plan, when strategically deployed, can significantly reduce the numbers of exposed and infectious people and help eradicate the disease outbreak. Throughout the paper, we have utilized both analytical and numerical means so as to gain deeper insight into the disease dynamics.

ภาคผนวก

In this Chapter we will include our final version of our research paper (output) which is attached the whole paper in the next page. This version has sent to the Dynamical Systems: An International Journal to have the review.

August 7, 2015

Editor
Dynamical Systems: An International Journal

Dear Editor:

On behalf of my co-author, Chairat Modnak, I am pleased to submit this article, "An avian influenza model with latency and vaccination", for original publication in **Dynamical Systems: An International Journal**. In this paper, we formulate a dynamical system model for avian influenza that includes bird-human interaction and that incorporates the effects of infection latency and human vaccination. We investigate the essential dynamics of the model through a careful mathematical analysis. Meanwhile, we explore effective vaccination strategy to control avian influenza outbreaks using optimal control theory. Our results show that strategically deployed human vaccination can significantly reduce the numbers of exposed and infectious persons.

In accordance with the journal guidelines, we acknowledge that this manuscript is not currently considered nor already published elsewhere.

Thank you very much for your consideration. We look forward to hearing from you.

Sincerely,

Jin Wang, Professor

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An avian influenza model with latency and vaccination

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Abstract Avian influenza, caused by influenza A viruses, has received worldwide attention over recent years. The viruses can spread from birds to humans as well as through the human-to-human transmission route. In this study, we formulate a mathematical model for avian influenza that includes bird-human interaction and that incorporates the effects of infection latency and human vaccination. We investigate the essential dynamics of the model through an equilibrium analysis. Meanwhile, we explore effective vaccination strategy to control avian influenza outbreaks using optimal control theory. Our results show that strategically deployed human vaccination can significantly reduce the numbers of exposed and infectious persons.

1 Introduction

Avian influenza is caused by influenza A viruses. These viruses are naturally carried by wild aquatic birds such as ducks, geese, swarms, or seagulls, and can infect local poultry and other bird and animal species [37]. It is known that there are two categories of influenza A viruses that may cause illness in birds: low pathogenic avian influenza (LPAI) and high pathogenic avian influenza (HPAI). Wild birds usually spread LPAI viruses to domestic birds and, under suitable conditions, LPAI undergoes mutation and evolves into HPAI that causes failure of internal organs and leads to 90-100 percent of death rates among domestic birds within 48

hours. A recent HPAI outbreak among birds in the United States was reported by the US Department of Agriculture in 2014.

Influenza A viruses can spread from infected birds to humans. Meanwhile, person-to-person transmission of such viruses has also been documented [37]. Humans infected by avian influenza exhibit symptoms such as fever, cough, sore throat, muscle aches, and in severe cases can have breathing difficulty, pneumonia, acute respiratory distress, and respiratory failure. Avian influenza subtype H5N1 has been endemic in Asia and several other places, with 777 laboratory-confirmed human infections; among these 428, or 55.1 percent, have been fatal [38]. The world's first three human cases of avian influenza subtype H7N9 were reported in China in 2013. From 2014 to February 2015, 227 deaths from 602 human H7N9 cases have been claimed. Severe human infections of other subtypes of avian influenza (H7N3, H7N7, etc.) have also been reported [38]. If the situation continues without effective control, an avian influenza pandemic could occur among humans with potentially high mortality rates.

There have been many mathematical models (see, e.g., [2,10,13,18,33]) published for the transmission of the influenza A viruses and the spread of the infection among birds. Several avian influenza models have also been proposed with a focus on humans and the impact of hypothetical pandemics (see, e.g., [8, 9, 26, 28]). Meanwhile, quite a few studies have been conducted to link birds and humans in avian influenza epidemics. For example, Chong et al. [4] proposed a model in 2014 for coupled bird-human dynamics with half-saturated incidence and mutation of virus strains. Liu et al. [25] investigated avian influenza with psychological effect and utilized an SI (Susceptible-Infected) model for birds and an SIR (Susceptible-Infected-Recovered) model for humans, where disease transmission in humans is solely contributed by infected birds. Gumel [12] analyzed the global dynamics of an avian influenza model with two virus strains. Iwami and co-workers [16, 17, 19] proposed bird-human interaction models to analyze potential avian flu pandemics and the control strategy. Martcheva and co-workers [30–32] studied low and high pathogenic avian influenza and the impact of seasonality on disease dynamics. Other related work can be found in recent reviews [1, 27] and references therein.

Most (if not all) of the current mathematical studies of avian influenza utilize an SIR model for human disease transmission. In reality, however, there is generally an incubation (or, latent) period for avian influenza that has been clinically observed as ranging from 2 to 8 days, with an average of 5 days, and possibly as long as 17 days [15, 39]. It is also found that the latency of avian influenza is typically longer than that for normal seasonal influenza (which is around 2 to 3 days). This latent period could have important implications on the length, frequency and severity of avian influenza outbreaks among humans, as well as on the surveillance of patients and the control of disease epidemics, yet very little attention has been placed on its mathematical modeling. Meanwhile, although bird/poultry vaccination has been widely adopted in containing the influenza and investigated in several studies (e.g., [11,13,18]), human vaccines for avian influenza are only recently available (FDA licensed the first H5N1 vaccine in 2007) and are still used in small-scale clinical tests. More guidelines for human vaccination and other control measures are thus urgently needed to prevent avian influenza pandemics among humans.

The main contribution of the present work is a new modeling framework that couples the bird and human populations and that incorporates the disease incubation period and the human vaccination. Representing the latency in the model necessitates the addition of another compartment, i.e., the exposed individuals, and increases the dimension of the whole system which makes the analysis more challenging. We will utilize both analytical and numerical means so as to gain deeper insight into the disease dynamics. Meanwhile, our analysis and simulation results regarding the human vaccination will provide useful information for public health administrations in the prevention and intervention of an avian influenza outbreak.

The remainder of this paper is organized as follows. Details of our avian influenza mathematical model is provided in Section 2, followed by a careful analysis of the disease-free equilibria (DFE) for both the bird and human populations in Section 3. The global stability of the DFE for the entire system is also established. Section 4 is devoted to the analysis of the endemic dynamics. In particular, the global asymptotic stability of the endemic equilibrium is investigated using the geometric approach [6, 22, 23]. An optimal control model for human vaccination is constructed and analyzed in Section 5. Finally, conclusions are drawn and some discussion is presented in Section 6.

2 Mathematical model

We describe the avian influenza dynamics using a system of six differential equations. The population of birds is divided into two compartments: S_b and I_b, where S_b represents the susceptible birds and I_b represents the infected birds. The population of humans is compartmentalized into four classes: susceptible (S_h), exposed (E), infectious (I_h), and recovered (R). A diagram to illustrate our model is presented in Figure 1.

We use an SI model to represent the disease dynamics among birds. Susceptible birds are infected through contacts (at a rate of β_B) with infected ones. The infected birds then transmit the disease to human hosts at a contact rate β_{BH}. Meanwhile, the infection also spreads among the human population through the person-to-person pathway with a transmission rate β_h. Susceptible humans, once infected, will first enter the exposed class E, and then become infectious after an incubation period, $1/\sigma$; here σ is the progression rate from exposed to infectious. Both the exposed and infectious people may recover from the disease, and recovered individuals can lose immunity and return to the susceptible class at a rate of δ. Hence, an SEIRS (Susceptible-Exposed-Infectious-Recovered-Susceptible) model is employed here to describe the human disease dynamics.

We assume the natural birth and death rates are the same, and denote that by μ_b and μ_h for birds and humans, respectively. We also denote the disease caused death rates by δ_b and α, respectively, for birds and humans. In addition, we represent the influx rates for these two populations by the constants Γ_b and Γ_h. For convenience of discussion, we write

$$\Gamma_b = \mu_b N_b \,, \qquad \Gamma_h = \mu_h N_h \,,$$

where the two constants, N_b and N_h, can be interpreted as the respective time-averaged population for birds and humans. In case there is no disease related mortality, $N_b = S_b + I_b$ and $N_h = S_h + E + I_h + R$ and they represent the (constant) total populations for birds and humans. Finally, we incorporate vaccination into the susceptible human population as a disease control measure; we assume that the vaccine will confer permanent immunity and that vaccinated individuals are removed from the susceptible class at a rate of ϕ_h.

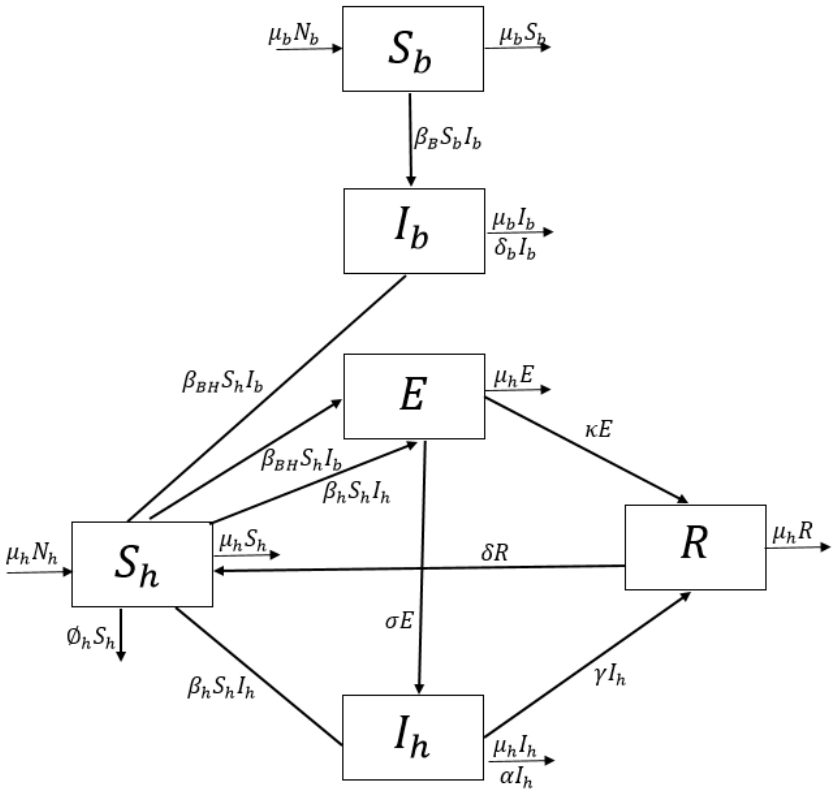


Figure 1: Diagram of the model.

Our model thus takes the form below:

$$\frac{dS_b}{dt} = \mu_b N_b - \mu_b S_b - \beta_B S_b I_b, \tag{1}$$

$$\frac{dI_b}{dt} = \beta_B S_b I_b - (\mu_b + \delta_b) I_b, \tag{2}$$

$$\frac{dS_h}{dt} = \mu_h N_h - \beta_h I_h S_h - \beta_{BH} S_h I_b + \delta R - \mu_h S_h - \phi_h S_h, \tag{3}$$

$$\frac{dE}{dt} = \beta_h I_h S_h + \beta_{BH} S_h I_b - (\mu_h + \sigma + \kappa) E, \tag{4}$$

$$\frac{dI_h}{dt} = \sigma E - (\mu_h + \alpha + \gamma) I_h, \tag{5}$$

$$\frac{dR}{dt} = \kappa E + \gamma I_h - \mu_h R - \delta R. \tag{6}$$

The definition and numerical values of all the model parameters are provided in Table 1. Written in a vector form, the above equations become

$$\frac{d\mathbf{X}}{dt} = \mathbf{F}(\mathbf{X}) \tag{7}$$

with $\mathbf{X} = (S_b, I_b, S_h, E, I_h, R)^T$.

3 Epidemic analysis

We start our analysis of the model by studying the disease-free equilibrium (DFE) and calculating the basic reproduction numbers. Since our model contains two populations: birds and humans, it is best that we first investigate the bird subsystem, represented by equations (1) and (2), and then proceed to the human subsystem that consits of equations (3)-(6). We will follow the same strategy when analyzing the endemic equilibrium as well.

It is straightforward to obtain the DFE for the bird subsystem:

$$\epsilon_b = (N_b, 0). \tag{8}$$

Consequently, the basic reproduction number for birds can be easily determined as

$$R_0^b = \frac{\beta_B N_b}{\mu_b + \delta_b}. \tag{9}$$

We have the following result:

Proposition 3.1. When $R_0^b < 1$, the DFE, ϵ_b, for the bird subsystem is locally asymptotically stable; when $R_0^b > 1$, ϵ_b is unstable.

The DFE for the human subsystem is given by

$$\epsilon_h = (\frac{\mu_h N_h}{\mu_h + \phi_h}, 0, 0, 0). \tag{10}$$

To compute the basic reproduction number for humans, we use the well-known method of van den Driessche and Watmough [34], with the associated next-generation matrices

$$F = \begin{bmatrix} 0 & \beta_h \frac{\mu_h N_h}{\mu_h + \phi_h} \\ 0 & 0 \end{bmatrix} \quad \text{and} \quad V = \begin{bmatrix} \mu_h + \sigma + \kappa & 0 \\ -\sigma & \mu_h + \alpha + \gamma \end{bmatrix}.$$

The basic reproductive number is then determined as the spectral radius of FV^{-1}; thus we obtain

$$R_0^h = \frac{\sigma \beta_h \mu_h N_h}{(\mu_h + \phi_h)(\mu_h + \sigma + \kappa)(\mu_h + \alpha + \gamma)}. \tag{11}$$

Consequently, we have the following result:

Proposition 3.2. When $R_0^h < 1$, the DFE, ϵ_h, for the human subsystem is locally asymptotically stable; when $R_0^h > 1$, ϵ_h is unstable.

Constructing the next-generation matrices for the entire model, equations (1)-(6), we can easily obtain the basic reproduction number for the combined system:

$$R_0 = \max\{R_0^b, R_0^h\}. \tag{12}$$

This expression indicates that both the bird and human subsystems will contribute to the threshold dynamics of the full system. Based on the work in [34], we immediately obtain the result below:

Theorem 3.3. *The disease-free equilibrium of the full model (1)-(6) is locally asymptotically stable if $R_0 < 1$, and unstable if $R_0 > 1$.*

Next we examine the global asymptotic stability of the DFE. To that end we state the following result introduced by Castillo-Chavez et al. [3].

Lemma 3.4. Consider a model system written in the form

$$\begin{aligned} \frac{dX_1}{dt} &= F(X_1, X_2), \\ \frac{dX_2}{dt} &= G(X_1, X_2), \quad G(X_1, 0) = 0 \end{aligned}$$

where $X_1 \in \mathbb{R}^m$ denotes (its components) the number of uninfected individuals and $X_2 \in \mathbb{R}^n$ denotes (its components) the number of infected individuals including latent, infectious,

etc; $X_0 = (X_1^*, 0)$ denotes the disease-free equilibrium of the system. Also assume the two conditions (H1) and (H2) below:
(H1) For $\frac{dX_1}{dt} = F(X_1, 0)$, X_1^* is globally asymptotically stable;
(H2) $G(X_1, X_2) = AX_2 - \hat{G}(X_1, X_2)$, $\hat{G}(X_1, X_2) \geq 0$ for $(X_1, X_2) \in \Omega$, where the off-diagonal elements of the Jacobian matrix $A = \frac{\partial G}{\partial X_2}(X_1^*, 0)$ are non-negative, and Ω is the region where the model makes biological sense.

Then the DFE $X_0 = (X_1^*, 0)$ is globally asymptotically stable provided that $R_0 < 1$.

We now apply this lemma to our model, under the assumption that $\delta = 0$; i.e., recovery from the disease will confer lifetime immunity. Then from equation (3), we observe that $dS_h/dt \leq \mu_h N_h - (\mu_h + \phi_h)S_h$, which yields $S_h \leq \frac{\mu_h N_h}{\mu_h + \phi_h}$.

Theorem 3.5. *When $R_0 < 1$, the disease-free equilibrium of the model (7) is globally asymptotic stable provided that $\delta = 0$.*

Proof. We show that the conditions (H1) and (H2) hold when $R_0 < 1$. In our ODE system (1)-(6), $X_1 = (S_b, S_h, R)$, $X_2 = (I_b, E, I_h)$, and $X_1^* = (N_b, \frac{\mu_h N_h}{\mu_h + \phi_h}, 0)$. We note that

$$\frac{dX_1}{dt} = F(X_1, 0) = \begin{bmatrix} \mu_b N_b - \mu_b S_b \\ \mu_h N_h + \delta R - \mu_h S_h - \phi_h S_h \\ -\mu_h R - \delta R \end{bmatrix}$$

is linear and its solution can be easily found as

$$R(t) = R(0)e^{-(\mu_h + \delta)t}, \qquad S_b(t) = N_b + (S_b(0) - N_b)e^{-\mu_b t}$$

and

$$S_h(t) = \frac{\mu_h}{\mu_h + \phi_h} N_h + \frac{\delta}{\phi_h - \delta} R(0)e^{-(\mu_h + \delta)t} + \Big(S_h(0) - \frac{\mu_h N_h}{\mu_h + \phi_h} - \frac{\delta}{\phi_h - \delta} R(0)\Big)e^{-(\mu_h + \phi_h)t}.$$

Clearly, $R(t) \to 0$, $S_b(t) \to N_b$ and $S_h(t) \to \frac{\mu_h}{\mu_h + \phi_h} N_h$ as $t \to \infty$, regardless of the values of $R(0)$, $S_b(0)$ and $S_h(0)$. Hence, $X_1^* = (N_b, \frac{\mu_h}{\mu_h + \phi_h} N_h, 0)$ is globally asymptotically stable for the subsystem $dX_1/dt = F(X_1, 0)$.

Next, we have

$$G(X_1, X_2) = \begin{bmatrix} \beta_B S_b I_b - (\mu_b + \delta_b) I_b \\ \beta_h S_h I_h + \beta_{BH} S_h I_b - (\mu_h + \sigma + \kappa) E \\ \sigma E - (\mu_h + \alpha + \gamma) I_h \end{bmatrix}.$$

We can then obtain

$$A = \begin{bmatrix} \beta_B N_b - (\mu_b + \delta_b) & 0 & 0 \\ \frac{\beta_{BH}\mu_h}{\mu_h + \phi_h} N_h & -(\mu_h + \sigma + \kappa) & \frac{\beta_h \mu_h}{\mu_h + \phi_h} N_h \\ 0 & \sigma & -(\mu_h + \alpha + \gamma) \end{bmatrix}$$

with all non-negative off-diagonal elements. Meanwhile, we find

$$\hat{G}(X_1, X_2) = \begin{bmatrix} \beta_B I_b(N_b - S_b) \\ (\beta_{BH} I_b + \beta_h I_h)(\frac{\mu_h N_h}{\mu_h + \phi_h} - S_h) \\ 0 \end{bmatrix}$$

Since $0 \leq S_b \leq N_b$ and $0 \leq S_h \leq \frac{\mu_h N_h}{\mu_h + \phi_h}$, it is obvious that $\hat{G} \geq 0$. □

We conclude this section by making another comment on the expression of R_0 in equation (12). Practically, the bird/poultry population (N_b) is much larger than the human population (N_h) in a typical place of an avian influenza outbreak, while the transmission rates for the birds and humans are normally of the same order [4,29]. As a result, $R_0^b > R_0^h$ usually holds, which leads to $R_0 = R_0^b$. Indeed, our analysis in what follows highlights the essential role of R_0^b in shaping the disease endemic dynamics of the coupled bird-human system.

4 Endemic analysis

The stability at the DFE determines the short-term epidemics of the disease, whereas its dynamics over a longer period of time is characterized by the stability at the endemic equilibrium. In this section we will analyze the endemic properties of our avian influenza model.

4.1 Endemic equilibrium

We first examine the existence of the positive endemic equilibrium. Denote the endemic equilibrium of the full model by

$$\epsilon^* = (S_b^*, I_b^*, S_h^*, E^*, I_h^*, R^*).$$

From equations (1) and (2) we obtain

$$S_b^* = \frac{\mu_b + \delta_b}{\beta_B} \quad \text{and} \quad I_b^* = \mu_b\Big(\frac{N_b}{\mu_b + \delta_b} - \frac{1}{\beta_B}\Big),$$

where $I_b^* > 0$ as long as $R_0^b > 1$.

Next, we substitute I_b^* into equation (4) to obtain

$$\beta_h I_h^* S_h^* + \beta_{BH} S_h^* \mu_b\Big(\frac{N_b}{\mu_b + \delta_b} - \frac{1}{\beta_B}\Big) - (\mu_h + \sigma + \kappa)E^* = 0. \tag{13}$$

From equation (5), we have

$$E^* = \frac{(\mu_h + \alpha + \gamma)I_h^*}{\sigma}. \tag{14}$$

With some algebraic manipulations, equations (13) and (14) yield

$$S_h^* = \frac{(\mu_h + \sigma + \kappa)(\mu_h + \alpha + \gamma)}{\sigma\Big(\beta_h I_h^* + \beta_{BH}\mu_b\Big(\frac{N_b}{\mu_b + \delta_b} - \frac{1}{\beta_B}\Big)\Big)} I_h^*.$$

Now we substitute E^*, I_b^* and S_h^* into equation (3) to obtain

$$\mu_h N_h - \frac{(\mu_h+\sigma+\kappa)(\mu_h+\alpha+\gamma)}{\sigma} I_h^* \frac{1}{\beta_h I_h^* + \beta_{BH}\mu_b\Big(\frac{N_b}{\mu_b+\delta_b} - \frac{1}{\beta_B}\Big)} \cdot$$

$$\Big(\beta_h I_h^* + \beta_{BH}\mu_b\Big(\frac{N_b}{\mu_b+\delta_b} - \frac{1}{\beta_B}\Big) + \mu_h + \phi_h\Big) + \frac{\kappa\Big(\frac{\mu_h+\alpha+\gamma}{\sigma}\Big) I_h^* + \gamma I_h^*}{\mu_h+\delta}\delta = \ 0.$$

This equation, after some algebra, yields a quadratic equation

$$A_1 {I_h^*}^2 + B_1 I_h^* + C_1 = 0, \tag{15}$$

where

$$A_1 = (b-a)\beta_h, \quad B_1 = \mu_h N_h \beta_h - ac - a\mu_h - a\phi_h + bc, \quad C_1 = c\mu_h N_h,$$

and where

$$a = \frac{(\mu_h+\sigma+\kappa)(\mu_h+\alpha+\gamma)}{\sigma}, \quad b = \frac{\kappa\Big(\frac{\mu_h+\alpha+\gamma}{\sigma}\Big)+\gamma}{\mu_h+\delta}\delta, \quad c = \beta_{BH}\mu_b\Big(\frac{N_b}{\mu_b+\delta_b} - \frac{1}{\beta_B}\Big).$$

The roots of equation (15) have to satisfy

$$I_{h_1}^* I_{h_2}^* = \frac{C_1}{A_1} \qquad \text{and} \qquad I_{h_1}^* + I_{h_2}^* = -\frac{B_1}{A_1}.$$

When $R_0^b > 1$, we have $C_1 > 0$. Meanwhile we have

$$\begin{aligned} A_1 &= (b-a)\beta_h \\ &= \beta_h\Big[\frac{\kappa\Big(\frac{\mu_h+\alpha+\gamma}{\sigma}\Big)+\gamma}{\mu_h+\delta}\delta - \frac{(\mu_h+\sigma+\kappa)(\mu_h+\alpha+\gamma)}{\sigma}\Big] \\ &= \frac{-\beta_h}{\sigma(\mu_h+\delta)}\Big[\mu_h^3 + \mu_h^2(\alpha+\gamma+\sigma+\kappa+\delta) + \mu_h(\alpha\sigma+\sigma\gamma+\kappa\alpha+\kappa\gamma+\delta\alpha\delta\gamma+\delta\sigma) + \delta\sigma\alpha\Big] \\ &< 0. \end{aligned}$$

Thus $I_{h_1}^* I_{h_2}^* < 0$; that is, the two roots of equation (15) are both real: one must be positive and the other must be negative. Consequently, we have the result below:

Theorem 4.1. *The positive endemic equilibrium ϵ^* of the system (1)-(6) exists and is unique provided that $R_0^b > 1$.*

In addition, we note that if $I_b^* = 0$ (i.e., no infection persistent in birds, and thus no disease contribution to the humans), then $c = C_1 = 0$, and equation (15) is reduced to

$$I_h^*(A_1 I_h^* + B_1) = 0\,. \tag{16}$$

In this case, $A_1 < 0$ still holds, and

$$B_1 = \mu_h\beta_h N_h - a(\mu_h + \phi_h) = \mu_h\beta_h N_h\big(1 - \frac{1}{R_0^h}\big) > 0$$

if and only if $R_0^h > 1$. Consequently, equation (16) has two biologically feasible roots $I_{h_1}^* = 0$ and $I_{h_2}^* = -B_1/A_1 > 0$ when $R_0^h > 1$, and only one biologically meaningful root $I_{h_1}^* = 0$ when $R_0^h < 1$.

These analytical findings show that in the absence of birds, the human subsystem (3)-(6) is reduced to a normal SEIRS model whose threshold dynamics are determined by the human reproduction number R_0^h. In contrast, when the bird-human interaction is included, the endemic dynamics of the combined system are characterized by the bird reproduction number R_0^b, a somehow surprising result. We observe, however, that the infected birds (I_b) directly contribute to a positive growth of the exposed and infectious humans in our model. Hence, the implication is that an avian influenza outbreak among birds (where $R_0^b > 1$) will always lead to disease outbreak and persistence in a *completely susceptible* human population. Using vaccination to reduce the number of susceptible individuals in the human population, therefore, would be an important control measure to protect humans against the infection and to contain the disease outbreak.

4.2 Local and global stabilities

We proceed to analyze the stability properties of the endemic equilibrium. First we establish the following result regarding the local stability.

Theorem 4.2. *When $R_0^b > 1$, the endemic equilibrium ϵ^* is locally asymptotically stable.*

Proof. The Jacobian of the system (1)-(6) at ϵ^* is given by

$$J(\epsilon^*) = \begin{bmatrix} -(\beta_h I_h + \beta_{BH} I_b^*) - (\mu_h - \phi_h) & 0 & -\beta_h S_h^* & \delta \\ \beta_h I_h^* + \beta_{BH} I_b^* & -(\mu_h + \sigma + \kappa) & \beta_h S_h^* & 0 \\ 0 & \sigma & -(\mu_h + \alpha + \gamma) & 0 \\ 0 & \kappa & \gamma & -(\mu_h + \delta) \end{bmatrix}.$$

The characteristic equation of the matrix $J(\epsilon^*)$ is

$$\begin{aligned} 0 =& \det|\lambda I - J(\epsilon^*)| \\ =& (\lambda + [(\beta_h I_h^* + \beta_{BH} I_b^*)])[(\lambda + (\mu_h + \sigma + \kappa))(\lambda + (\mu_h + \alpha + \gamma))(\lambda + (\mu_h + \delta)) \\ & - (\lambda + (\mu_h + \delta))\sigma\beta_h S_h^*] \\ & + (\beta_h I_h^* + \beta_{BH} I_b^*)[\delta\sigma\gamma - \kappa\delta(\lambda + (\mu_h + \alpha + \gamma)) + \sigma\beta_h S_h^*(\lambda + (\mu_h + \delta))]. \end{aligned} \tag{17}$$

Let $Q = \beta_h I_h^* + \beta_{BH} I_b^*$. Equation (17) can be put into a quartic equation of the form

$$a_4\lambda^4 + a_3\lambda^3 + a_2\lambda^2 + a_1\lambda + a_0, \tag{18}$$

where

$$
\begin{aligned}
a_4 &= 1,\\
a_3 &= (\mu_h+\sigma+\kappa)+(\mu_h+\sigma+\kappa)+Q+2\mu_h+\delta+\phi_h,\\
a_2 &= (\mu_h+\sigma+\kappa)(\mu_h+\alpha+\gamma)-\sigma\beta_h S_h^*\\
&\quad +(Q+2\mu_h+\delta+\phi_h)(2\mu_h+\alpha+\gamma+\sigma+\kappa)\\
&\quad +Q(\mu_h+\delta)+(\mu_h+\phi_h)(\mu_h+\delta),\\
a_1 &= (Q+2\mu_h+\delta+\phi_h)[(\mu_h+\sigma+\kappa)(\mu_h+\alpha+\gamma)-\sigma\beta_h S_h^*]\\
&\quad +[Q(\mu_h+\delta)+(\mu_h+\phi_h)(\mu_h+\delta)][(\mu_h+\alpha+\gamma)+(\mu_h+\sigma+\kappa)],\\
a_0 &= [Q(\mu_h+\delta)+(\mu_h+\phi_h)(\mu_h+\delta)][(\mu_h+\sigma+\kappa)(\mu_h+\alpha+\gamma)-\sigma\beta_h S_h^*].
\end{aligned}
$$

Using equation (5), at the endemic equilibrium we have $I_h^* = \frac{\sigma E^*}{\mu_h+\alpha+\gamma}$. Thus equation (4) yields

$$(\mu_h+\sigma+\kappa)(\mu_h+\alpha+\gamma)-\beta\sigma S_h^* = \frac{(\mu_h+\alpha+\gamma)\beta_{BH}S_h^*I_b^*}{E^*} > 0$$

as long as $R_0^b > 1$. Therefore, we obtain $a_i > 0$ for $0 \le i \le 4$. Next we consider the Routh-Hurwitz table [20]

λ^4	a_4	a_2	a_0
λ^3	a_3	a_1	0
λ^2	b_1	b_2	0
λ^1	c_1	0	0
λ^0	d_1	0	0

where

$$b_1 = \frac{a_3a_2-a_1a_4}{a_3}, \quad b_2 = \frac{a_0a_3}{a_3} = a_0, \quad c_1 = \frac{a_1b_1-a_3b_2}{b_1}, \quad d_1 = \frac{b_2c_1}{c_1} = b_2.$$

To ensure that all roots of equation (18) have negative real parts, the Routh-Hurwitz stability criterion [20] requires b_1, b_2, c_1 and d_1 all to be positive.

It is straightforward to observe that $a_3a_2 > a_1a_4$; i.e., $b_1 > 0$. Since $a_0 > 0$, we have $b_2 > 0$ and $d_1 > 0$. For c_1, we note that

$$a_1b_1-a_3b_2 = a_1\Big[\frac{a_3a_2-a_1a_4}{a_3}\Big]-a_3a_0 = \frac{a_1a_2a_3-(a_1^2+a_3^2a_0)}{a_3}.$$

We proceed to show that $a_1a_2a_3 > a_1^2+a_3^2a_0$. For ease of comparison, we denote $A = Q+2\mu_h+\delta+\phi_h$, $B = (\mu_h+\sigma+\kappa)(\mu_h+\alpha+\gamma)-\sigma\beta_hS_h^*$, $C = Q(\mu_h+\delta)+(\mu_h+\phi_h)(\mu_h+\delta)$, and $D = (\mu_h+\alpha+\gamma)+(\mu+\sigma+\kappa)$. Note that $A, B, C, D > 0$. Then we can write

$$a_1a_2a_3 = (AB+CD)(B+AD+C)(D+A)$$

and

$$a_1^2 + a_3^2 a_0 = (AB + CD)^2 + (D + A)^2 CB.$$

Simple algebra then yields $a_1 a_2 a_3 > a_1^2 + a_3^2 a_0$; i.e., $c_1 > 0$. This completes the proof. □

Next, we will follow the geometric approach originally proposed by Li and Muldowney [6, 22, 23] to investigate the global asymptotic stability of the endemic equilibrium. To that end, we first present the following result based on the geometric approach.

Lemma 4.3. Consider a dynamical system $\frac{dX}{dt} = f(X)$, where $f : D \mapsto \mathbb{R}^n$ is a C^1 function and $D \subset \mathbb{R}^n$ is a simply connected domain. Assume that there exists a compact absorbing set $K \subset D$ and the system has a unique equilibrium point X^* in D. Then X^* is globally asymptotically stable in D if $\bar{q_2} < 0$, where

$$\bar{q_2} = \limsup_{t\to\infty} \sup_{X_0 \in K} \frac{1}{t} \int_0^t m\big(P(X(s, X_0))\big)\, ds\,. \tag{19}$$

In equation (19), P is a matrix-valued function defined as

$$P = Q_f Q^{-1} + Q J^{[2]} Q^{-1}\,,$$

where $Q(X)$ is a $\binom{n}{2} \times \binom{n}{2}$ matrix-valued C^1 function in D, Q_f is the derivative of Q (entry-wise) along the direction of f, and $J^{[2]}$ is the second additive compound matrix of the Jacobian $J(X) = Df(X)$. Meanwhile, $m(P)$ is the Lozinskiĭ measure of P with respect to a matrix norm; i.e.,

$$m(P) = \lim_{h\to 0^+} \frac{|\mathbb{I} + hP| - 1}{h}\,,$$

where $\mathbb{I}$ represents the identity matrix.

We start our global stability analysis by considering the bird-only subsystem. The following result can be easily established:

Theorem 4.4. *When $R_0^b > 1$, the endemic equilibrium (S_b^*, I_b^*) of the bird-only subsystem is globally asymptotically stable.*

Proof. Let us rewrite equations (1) and (2) as

$$\frac{dS_b}{dt} = \mu_b N_b - \mu_b S_b - \beta_B S_b I_b \triangleq f_1(S_b, I_b),$$
$$\frac{dI_b}{dt} = \beta_B S_b I_b - (\mu_b + \delta_b) I_b \triangleq f_2(S_b, I_b).$$

We already know that when $R_0^b > 1$, the disease-free equilibrium $(N_b, 0)$ is unstable and the endemic equilibrium (S_b^*, I_b^*) exists and is unique. Let $h(S_b, I_b) = \frac{1}{I_b}$ which is positive and smooth on the domain $\mathbb{R}^2_+ \triangleq \{(S_b, I_b) \big| S_b > 0, I_b > 0\}$.
Then $\frac{\partial}{\partial S_b}(f_1 h) + \frac{\partial}{\partial I_b}(f_2 h) = -\frac{\mu_b}{I_b} - \beta_b < 0$ throughout the domain $\mathbb{R}^2_+$. Based on the Bendixson-Dulac criteria, there is no closed orbit in the region $\mathbb{R}^2_+$. Hence (S_b^*, I_b^*) is globally asymptotically stable. □

Now, to show the global stability of the endemic equilibrium for the full system (1)-(6), we only need to consider the subsystem (3)-(6) with the bird components already at the endemic steady state [25]. Still, the subsystem (3)-(6) is four-dimensional and challenging to analyze in general. In what follows, we consider a simplified case of our model by assuming $\phi_h = \alpha = 0$; i.e., no vaccination and no disease caused mortality, and apply the geometric approach summarized in Lemma 4.3. Then $S_h + E + I_h + R = N_h$ is a constant which allows us to drop equation (6) and consider a three-dimensional system (3)-(5), written as

$$\frac{dS_h}{dt} = \mu_h N_h - \beta_h I_h S_h - (\mu_h + \beta_{BH} I_b^*) S_h + \delta(N_h - S_h - E - I_h), \tag{20}$$

$$\frac{dE}{dt} = \beta_h I_h S_h - (\mu_h + \sigma + \kappa) E + \beta_{BH} I_b^* S_h, \tag{21}$$

$$\frac{dI_h}{dt} = \sigma E - (\mu_h + \gamma) I_h, \tag{22}$$

on the feasible domain

$$\Omega = \{(S_h, E, I_h) \,\big|\, 0 \le S_h + E + I_h \le N_h\}.$$

We shall mention that although the system (20)-(22) is slightly simpler than the original system (3)-(6), it is still an SEIRS model with an additional, but essential, incidence term (contributed by the infected birds). It is thus different from a typical SEIR model analyzed in the literature. When $R_0^b > 1$, the disease-free equilibrium of the system (20)-(22), located on the boundary of the domain Ω, is unstable. This implies that the disease is uniformly persistent. It then follows from the compactness of the domain and the uniform persistence of the system that there exists a compact absorbing set in Ω. By the geometric approach, it remains to verify the generalized Bendixson criterion $\bar{q}_2 < 0$, where $\bar{q}_2$ is defined in equation (19).

Let us define

$$Q(S_h, E, I_h) = \begin{bmatrix} 1 & 0 & 0 \\ 0 & \frac{E}{I_h} & 0 \\ 0 & 0 & \frac{E}{I_h} \end{bmatrix}.$$

Then

$$Q_f Q^{-1} = \begin{bmatrix} 0 & 0 & 0 \\ 0 & \frac{I_h}{E}(\frac{E}{I_h})_f & 0 \\ 0 & 0 & \frac{I_h}{E}(\frac{E}{I_h})_f \end{bmatrix},$$

where $\frac{I_h}{E}(\frac{E}{I_h})_f = \frac{E'}{E} - \frac{I_h'}{I_h}$ based on equations (3) and (4).

The Jacobian of the subsystem (20)-(22) is

$$J = \begin{bmatrix} -\beta_h I_h - d_1 - \delta & -\delta & -\beta_h S_h - \delta \\ \beta_h I_h + d_3 & -d_2 & \beta_h S_h \\ 0 & \sigma & -d_4 \end{bmatrix},$$

where

$$d_1 = \mu_h + \beta_{BH} I_b^*, \quad d_2 = \mu_h + \sigma + \kappa, \quad d_3 = \beta_{BH} I_b^*, \quad \text{and} \quad d_4 = \mu_h + \gamma,$$

and the second additive compound matrix associated with the Jacobian is given by

$$J^{[2]} = \begin{bmatrix} j_{11} & \beta_h S_h & \beta_h S_h + \delta \\ \sigma & j_{22} & -\delta \\ 0 & \beta_h I_h + \beta_{BH} I_b^* & j_{33} \end{bmatrix},$$

where

$$\begin{aligned} j_{11} &= -\beta_h I_h - \delta - 2\mu_h - \sigma - \kappa - \beta_{BH} I_b^*, \\ j_{22} &= -\beta_h I_h - \delta - 2\mu_h - \gamma - \beta_{BH} I_b^*, \\ j_{33} &= -2\mu_h - \sigma - \kappa - \gamma. \end{aligned}$$

We thus have

$$QJ^{[2]}Q^{-1} = \begin{bmatrix} 1 & 0 & 0 \\ 0 & \frac{E}{I_h} & 0 \\ 0 & 0 & \frac{E}{I_h} \end{bmatrix} \begin{bmatrix} j_{11} & \beta_h S_h & \beta_h S_h + \delta \\ \sigma & j_{22} & -\delta \\ 0 & \beta_h I_h + \beta_{BH} I_b^* & j_{33} \end{bmatrix} \begin{bmatrix} 1 & 0 & 0 \\ 0 & \frac{I_h}{E} & 0 \\ 0 & 0 & \frac{I_h}{E} \end{bmatrix}$$

$$= \begin{bmatrix} -\beta_h I_h - \delta - 2\mu_h - \sigma - \kappa - \beta_{BH} I_b^* & \beta_h S_h \frac{I_h}{E} & \frac{I_h}{E}(\beta_h S_h + \delta) \\ \sigma \frac{E}{I_h} & -(\beta_h I_h + \delta + 2\mu_h + \gamma + \beta_{BH} I_b^*) & -\delta \\ 0 & \beta_h I_h + \beta_{BH} I_b^* & -(2\mu_h + \sigma + \kappa + \gamma) \end{bmatrix}$$

Hence

$$P = Q_f Q^{-1} + QJ^{[2]}Q^{-1} = \begin{bmatrix} p_{11} & p_{12} \\ p_{21} & p_{22} \end{bmatrix},$$

with

$$\begin{aligned} p_{11} &= -\beta_h I_h - \delta - 2\mu_h - \sigma - \kappa - \beta_{BH} I_b^*, \\ p_{12} &= \left[\beta_h \frac{S_h I_h}{E}, \frac{(\beta_h S_h + \delta) I_h}{E} \right], \\ p_{21} &= \begin{bmatrix} \sigma \frac{E}{I_h} \\ 0 \end{bmatrix}, \end{aligned}$$

and

$$p_{22} = \begin{bmatrix} \frac{I_h}{E}(\frac{E}{I_h})_f - \beta_h I_h - \delta - 2\mu_h - \gamma - \beta_{BH} I_b^* & -\delta \\ \beta_h I_h + \beta_{BH} I_b^* & \frac{I_h}{E}(\frac{E}{I_h})_f - 2\mu_h - \sigma - \kappa - \gamma \end{bmatrix}.$$

Let us choose the vector norm $|\cdot|$ in $\mathbb{R}^3$ as

$$|(x_1, x_2, x_3)| = \max\{|x_1|, |x_2| + |x_3|\}.$$

One can then verify that the Lozinskiĭ measure $m(P)$ with respect to this norm can be estimated as

$$m(P) \leq \sup\{g_1, g_2\},$$

where

$$\begin{aligned} g_1 &= m_1(p_{11}) + |p_{12}|, \\ g_2 &= |p_{21}| + m_1(p_{22}). \end{aligned}$$

Here $|p_{12}|$ and $|p_{21}|$ are matrix norms induced by the L_1 vector norm, and m_1 denotes the Lozinskiĭ measure with respect to the L_1 norm. We thus obtain

$$\begin{aligned} g_1 &= -\beta_h I_h - \delta - 2\mu_h - \sigma - \kappa - \beta_{BH} I_b^* + \frac{(\beta_h S_h + \delta) I_h}{E}, \\ g_2 &= \sigma \frac{E}{I_h} + \max\Big\{ \frac{I_h}{E}\Big(\frac{E}{I_h}\Big)_f - \delta - 2\mu_h - \gamma,\ \ \frac{I_h}{E}\Big(\frac{E}{I_h}\Big)_f - 2\mu_h - \delta - \kappa - \gamma + \delta \Big\} \\ &\leq \frac{I_h}{E}\Big(\frac{E}{I_h}\Big)_f - \delta - 2\mu_h - \gamma + \sigma \frac{E}{I_h}, \end{aligned}$$

provided that $2\delta < \sigma + \kappa$. Using

$$\begin{aligned} \frac{E'}{E} &= \beta_h \frac{I_h S_h}{E} + \beta_{BH} I_b^* \frac{S_h}{E} - (\mu_h + \sigma + \kappa), \\ \frac{I_h'}{I_h} &= \sigma \frac{E}{I_h} - (\mu_h + \gamma), \\ \frac{I_h}{E}\Big(\frac{E}{I_h}\Big)_f &= \frac{E'}{E} - \frac{I_h'}{I_h}, \end{aligned}$$

we obtain

$$\begin{aligned} g_1 &\leq \frac{E'}{E} - \delta - \mu_h + \max\Big\{ \frac{\delta}{E} - \beta_h,\ 0 \Big\}, \\ g_2 &\leq \frac{E'}{E} - \delta - \mu_h \,. \end{aligned}$$

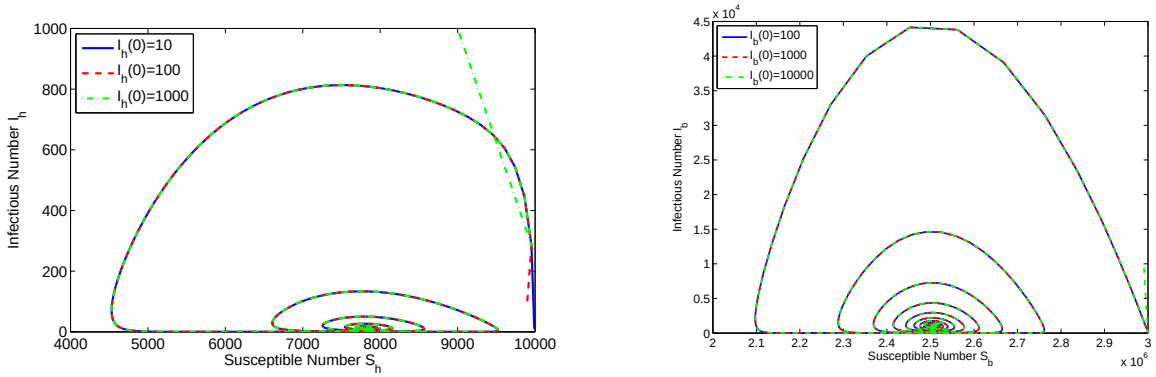
By the uniform persistence of the system, there exist $\epsilon > 0$ and $T > 0$ such that when $t > T$, we have $E \geq \epsilon$, and $\frac{\log E(t)}{t} < \frac{\delta + \mu_h}{2}$. If $\delta < \epsilon\beta_h$, then $\frac{\delta}{E} - \beta_h < 0$ when $t > T$, and

$$\frac{1}{t}\int_0^t m(P)dt < \frac{\log E(t)}{t} - (\delta + \mu_h) < -\frac{\delta + \mu_h}{2}\,,$$

which implies $\bar{q_2} < 0$. Hence, we have established the following result:

Theorem 4.5. *When $R_0^b > 1$, the endemic equilibrium of the system (20)-(22) is globally asymptotically stable provided that $\delta < \min\Big(\frac{\sigma+\kappa}{2},\ \epsilon\beta_h\Big)$.*

Combining the results in Theorems 4.4 and 4.5, we obtain the global asymptotic stability of the endemic equilibrium for the original system (1)-(6) under the assumptions of no vaccination and disease related mortality as well as small immunity loss. A numerical illustration of this global endemic stability result is provided in Figure 2.



(a) (b)

Figure 2: Phrase portraits for $R_0 > 1$ with different initial conditions. (a) I_h vs. S_h. All the curves converge to the endemic equilibrium with $I_h^* \approx 4.01, S_h^* \approx 7799.9$. (b) I_b vs. S_b. All the curves converge to the endemic equilibrium with $I_b^* \approx 988, S_b^* \approx 2.5 \times 10^6$.

5 Optimal vaccination

Now we turn to the more general model (1)-(6) with a time-dependent vaccination profile $\phi_h(t)$, and conduct an optimal control study. We consider the system on a time interval $[0, T]$. The function $\phi_h(t)$ is assumed to be at least Lebesgue measurable on $[0, T]$. The control set is defined as

$$\Lambda = \{\phi_h(t) \,|\, 0 \leq \phi_h(t) \leq \phi_{max}\},$$

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

Our optimal control study aims to minimize the total numbers of infectious people and the cost of control over the time interval $[0, T]$; i.e.,

$$\min_{\phi_h \in \Lambda} \int_0^T \left[I_h(t) + c_1 \phi_h(t) S_h(t) + c_2 \phi_h^2(t) \right] dt \,, \tag{23}$$

where the linear and quadratic terms are introduced to account for the costs at different intervention levels [36], and c_1 and c_2 are cost parameters (with appropriate units) associated with the control.

We note that our model is linear in the control variable ϕ_h and that the control set Λ is closed and convex. Meanwhile, the integrand of the objective functional in (23) is also convex. Hence, standard optimal control theory [7, 21] yields the following result:

Theorem 5.1. *There exists a $\phi_h^* \in \Lambda$ such that the objective functional in (23) is minimized.*

Indeed, the optimal control solution is also unique for small T due to the Lipschitz structure of the model equations and the boundedness of the state variables [7]. To proceed, we apply Pontryagin's minimum principle to determine the optimal control. We first define the adjoint functions $\lambda_{S_h}, \lambda_E, \lambda_{I_h}$ and λ_R associated with the state equations for S_h, E, I_h and R, respectively. We then from the Hamiltonian, H, by multiplying each adjoint function with the right-hand side of its corresponding state equation, and adding each of these products to the integrand of the objective functional. As a result, we obtain

$$\begin{aligned} H = {} & I_h(t) + c_1\phi_h(t)S_h(t) + c_2\phi_h^2(t) \\ & + \lambda_{S_h}\Big[\mu_h N_h - \beta I_h S_h - \beta_{BH} S_h I_b + \delta R - \mu_h S_h - \phi_h S_h\Big] \\ & + \lambda_E\Big[\beta I_h S_h + \beta_{BH} S_h I_b - (\mu_h + \sigma + \kappa)E\Big] \\ & + \lambda_{I_h}\Big[\sigma E - (\mu_h + \alpha + \gamma)I_h\Big] \\ & + \lambda_R\Big[\kappa E + \gamma I_h - \mu_h R - \delta R\Big]. \end{aligned}$$

To achieve the optimal control, the adjoint functions must satisfy $\frac{d\lambda_{S_h}}{dt} = -\frac{\partial H}{\partial S_h}$, $\frac{d\lambda_E}{dt} = -\frac{\partial H}{\partial E}$, $\frac{d\lambda_{I_h}}{dt} = -\frac{\partial H}{\partial I_h}$, and $\frac{d\lambda_R}{dt} = -\frac{\partial H}{\partial R}$. Thus, we have

$$\frac{d\lambda_{S_h}}{dt} = -c_1\phi_h(t) + \lambda_{S_h}(\beta I_h + \beta_{BH} I_b + \mu_h + \phi_h) - \lambda_E(\beta I_h + \beta_{BH} I_b), \tag{24}$$

$$\frac{d\lambda_E}{dt} = \lambda_E(\mu_h + \sigma + \kappa) - \lambda_{I_h}\sigma - \lambda_R\kappa, \tag{25}$$

$$\frac{d\lambda_{I_h}}{dt} = -1 + \lambda_{S_h}\beta S_h - \lambda_E\beta S_h + \lambda_{I_h}(\mu_h + \alpha + \gamma) - \lambda_R\gamma, \tag{26}$$

$$\frac{d\lambda_R}{dt} = -\lambda_{S_h}\delta + \lambda_R(\mu_h + \delta), \tag{27}$$

with the final-time conditions $\lambda_{S_h}(T) = 0$, $\lambda_{I_h}(T) = 0$, $\lambda_E(T) = 0$, and $\lambda_R(T) = 0$. The characterizations of the optimal control $\phi_h(t)$ is then based on the condition

$$\frac{\partial H}{\partial \phi_h} = 0 \tag{28}$$

subject to the constraint $0 \leq \phi_h \leq \phi_{max}$.

The optimal control system, consisting of the state equations, the adjoint equations and the optimality condition (28), has to be solved numerically. We have conducted numerical

Table 1: Model parameters and values

Parameter	Symbol	Value	Source
Averaged human population	N_h	$10,000$	Assumed
Averaged bird population	N_b	$300 * N_h$	Assumed
Natural birth and death rate of humans	μ_h	$(70 * 365)^{-1}$ /day	[4]
Natural birth and death rate of birds	μ_b	$(100)^{-1}$/day	[4]
Contact rate for birds	β_B	0.4/200,000/day	[4]
Bird-to-human transmission rate	β_{BH}	$0.2/(N_b * 100)$/day	[4]
Human-to-human transmission rate	β_h	$0.5/N_h$ /day	[4]
Disease related death rate for birds	δ_b	5/day	[4]
Disease related death rate for humans	α	0.03/day	[29]
Rate of immunity loss	δ	0.699/day	[29]
Transition rate from exposure to infection	σ	0.2/day	[15]
Recovery rate for exposed people	κ	0.00015/day	[29]
Recovery rate for infected people	γ	0.16/day	[29]

simulation using various choices of cost parameters and time intervals, and have observed a unique solution in each case. The numerical results clearly demonstrate that an optimal vaccination strategy can significantly bring down the number of exposed and infectious human individuals, thus reducing the burden of an avian influenza outbreak. Some typical results are presented below.

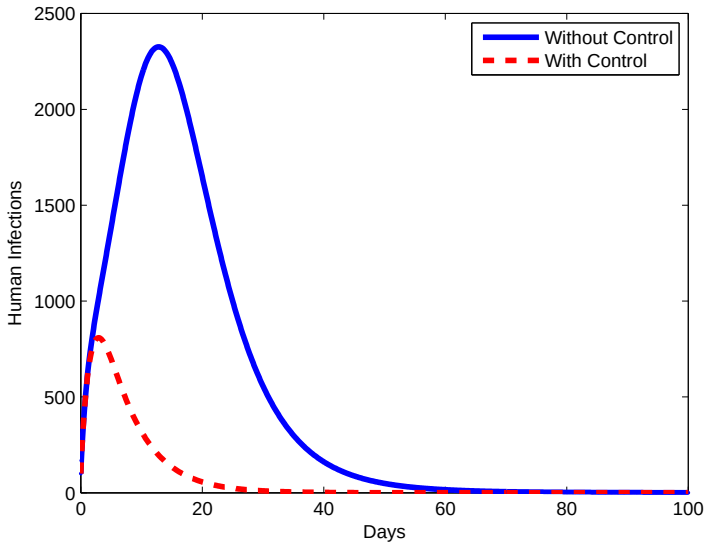


Figure 3: Number of infectious humans.

Figure 3 depicts the infectious humans for the case without vaccination (solid line) and that with optimal vaccination (dashed line). The reduction, in both the infection level and the outbreak period, due to the incorporation of vaccination is significant. Figure 4 shows the dynamics of the infectious human population for a much longer period of time. We observe that when vaccination is not deployed, the infection curve, after several epidemic oscillations (with decaying magnitudes), eventually approaches a positive endemic state. In contrast, with an optimal vaccination strategy, the infection is quickly reduced to a level very close to zero, and stays there for all the time afterwards.

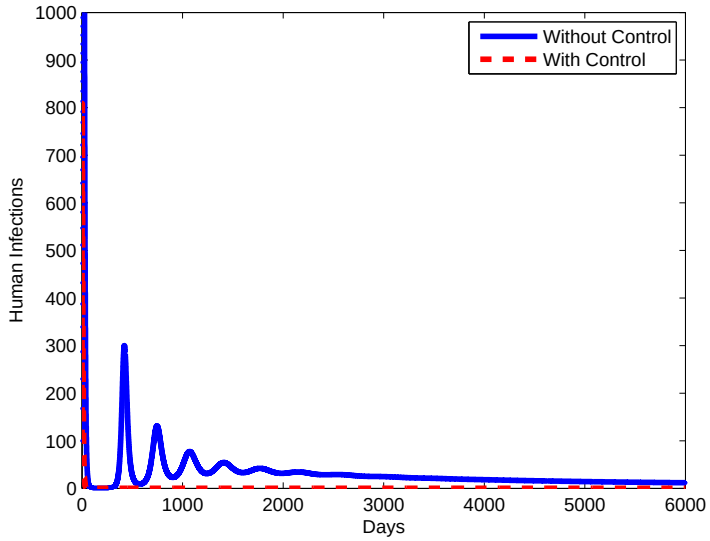


Figure 4: Number of infectious humans for a long term.

In addition, the dynamics of the exposed humans can be observed from Figure 5. Without vaccination, the exposed population (E) attains very high values immediately after the onset of the outbreak, mainly due to the contribution from the infected birds (I_b). As I_b and S_h decrease, E goes down for a short period of time. Then with the increase of infectious humans (I_h), the exposed population starts increasing again and reaches a peak at $t \approx 10$ days (note that the peak of E occurs before that of I_h; compare Figures 3 and 5). With optimal vaccination, however, E continues decreasing until reaching and settling at a value close to zero, which, consequently, leads to a very low infection level for I_h.

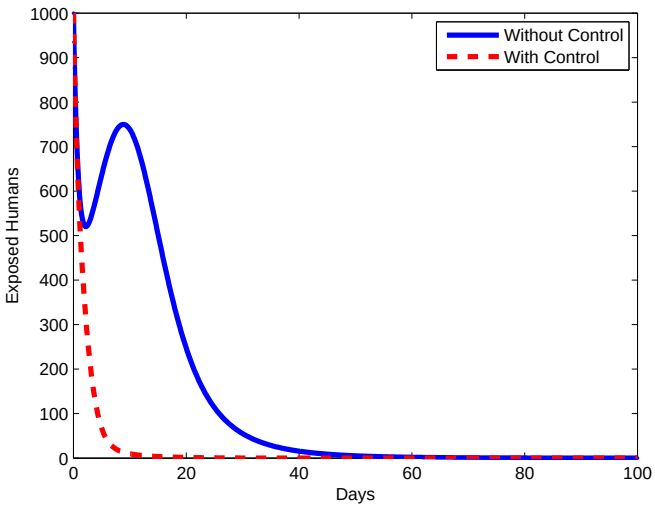


Figure 5: Number of exposed humans.

6 Conclusions

We have presented a mathematical model for avian influenza that involves both bird and human populations and that incorporates the effects of latency and vaccination for humans, using a system of six nonlinear differential equations. Our model employs an SI model for birds and an SEIRS model for humans, and both bird-to-human and human-to-human transmission routes are included in the system. We have analyzed the epidemic and endemic dynamics of the combined model; particularly, we have established the local and global stabilities based on the basic reproductive numbers. In addition, we have performed an optimal control study to explore the optimal vaccination strategy in order to contain the disease outbreak in humans. Our results show that human vaccination, when strategically deployed, can significantly reduce the numbers of exposed and infectious people and help eradicate the disease outbreak. Throughout the paper, we have utilized both analytical and numerical means so as to gain deeper insight into the disease dynamics.

There are several limitations in this study which we hope to overcome in future work. We have assumed that vaccination confers lifetime immunity, though, more realistically, we could consider imperfect vaccination. In such a case, a new compartment representing the vaccinated class can be added into the model, where vaccinated individuals can lose immunity over time and re-enter the susceptible class. For simplicity, we have only considered bi-linear incidence in this work. Similar modeling and analysis techniques can be extended to other types of incidences (such as half saturation) for more careful investigation of the disease mechanism. In addition, differentiating LPAI and HPAI dynamics and incorporating the mutation of virus strains into our model will allow more detailed study, and possibly lead to deeper understanding of avian influenza.

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