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Mathematical Modelling of an Avian Influenza: Optimal Control Study for Intervention Strategies

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Abstract: Avian influenza, caused by influenza A viruses, has drawn attention from scientists worldwide to study its epidemic dynamics. In this paper, we study the spread of bird flu or avian influenza and optimal control theory for intervention strategies from SIR-based model. In addition, we divide human population into five states; Susceptible (S), Vaccinated (V), Exposed (E), Infective (I) and Recovered (R). Equilibrium analysis to investigate the dynamics of the model is carefully derived. We further study the optimal control to seek cost effective for control and treatment strategies. Numerical results show that strategically deployed vaccination and medical treatment can significantly reduce the numbers of exposed and infectious persons.

Keywords: Avain influenza, Optimal control, Epidemic model, Infectious disease, Intervention strategies

1 Introduction

Avian influenza is caused by type A strains of the influenza virus. These viruses are carried by aquatic birds and can infect local poultry, birds and other animal species. There are, in general, two categories of influenza A virsus 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 condtions, LPAI mutates and evolves into HPAI that causes illness in birds and leads to 90-100 percent of death rates within 48 hours. When LPAI outbreaks occur in poultry, culling method is usually carried out and that causes the economic impact.

Influenza A viruses can spread from infected birds to susceptible humans which there has been a report from such transmission documented on the Centers for Disease Control and Prevention website. Humans infected by avian influenza show symptoms such as fever, cough, sore throat, acute respiratory distress, and respiratory failure. Avian influenza subtype HPAI H5N1 has been endemic in Asia and several other places, according to the data on CDC website. The latest data as of 19 July 2016 reported by World Health Organization (WHO) shows that the disease is still considered as a likely possible threat in near future to humans. According to the data reported to WHO from Azerbaijan, Bangladesh, Cambodia, Canada, China, Djibouti, Egypt, Indonesia, Iraq, Lao People's Democratic Republic, Myanmar, Nigeria, Pakistan, Thailand, Viet Nam, from 2003-2016, there were 854 cases; among these, 450 individuals have been fatal. In addition, WHO has published outbreak factsheets of human infection with avain influenza A(H7N9) virus in China and the data shows that from 24 June - 29 July 2016, there were five cases of laboratory-confirmed human infection with avain influenza A(H7N9);two of the five cases reported exposure to live poultry. In January 2016, a report of an HPAI(H7N8) outbreak in Indiana, North America, was confirmed in a commercial turkey flock in Dubois County. Also, LPAI(H7N8) was detected in eight nearby turkey flocks. However, there was no report in human infection from this incidence. Human infections with the influenza virus A(H7N9) need to be monitored since the changes in the virus and its transmission dynamic to humans can cause a serious problem to public health.

There have been many mathematical models (see, e.g., [2,4,10,13,16,17,18,19,24]) published for the transmission of the influenza A viruses and the spread of the infection among birds. However, in this study, birds are not included in our model since we are interested in

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only optimal control study in human dynamics when outbreaks occur. Similarly, a number of studies have proposed with a focus only on humans and the impact of hypothetical pandemics(see, e.g., [8,9,12,25,27,29,30,31,32]). Meanwhile, there are only a few studies conducted optimal control theory to gain more guidelines for human vaccination and other control measures to prevent avian influenza pandemics among humans. In 2009, Eunok Jung et al. [19] formulated an optimal control mathematical model for prevention of avain influenza pandemic based on the assumptions that the infection is fatal and the study was interested in the quarantine control and the effort of reducing the number of infected birds or elimination control. The results of their study shows that screening of the infected humans and restriction of their movement help reducing the number of infectious persons. In 2016, there were a few studies on an optimal control of an SIR epidemic model with a saturated treatment which they were very general and not useful to predict and to control an outbreak of avian influenza.

Most (if not all) of the current mathematical studies of avian influenza utilize an SIR model for human disease transmission. Some of these studies have applied the optimal control theory to seek cost-effective vaccination and treatment strategies. However, they have assumed that vaccination confers lifetime immunity and the recovered individuals have temporary immunity so that they will not move into susceptible class. In reality, however, the recovered or vaccinated class may lose immunity over time and re-enter the susceptible class and become re-infected individuals.

The main contribution of the present work is a modeling framwork that incorporates the vaccinated class of humans and the control strategies; vaccination and medical treatment. Adding the vaccinated class of humans 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 vaccination and medical treatment will provide useful information for public health administrations in the prevention of an avian influenza outbreak.

The organization of this paper is 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) in Section 3. The global stability of the DFE for the system is also established. Section 4 is devoted to the analysis of the endemic dynamics. An optimal control model for vaccination and medical treatment is constructed and analyzed in Section 5. Finally, conclusions are drawn and some discussion is presented in Section 6.

2 Mathematical model with constant controls

We describe the avian influenza dynamics using a system of five differential equations. The human population is divided into five classes: susceptible (S), vaccinated (V), exposed (E), infectious (I), and recovered (R). A diagram of the model is presented in Figure 1.

We use an SVEIRS model to represent the disease dynamics of humans and we assume that individuals are born and die at an average rate μ. We further assume that susceptible individuals are vaccinated at a rate $\phi_1(t)$, where t is the time variable, with a vaccine that has a degreee of protection $\sigma = (1-\varepsilon)$, where ε is the vaccine efficacy. Infected individuals are treated at a rate $\phi_2(t)$, and some recover naturally at a rate γ into the recovered class. Susceptible and some of vaccinated humans, once infected, will first enter the exposed class E, and then become infectious after an incubation period, $1/\kappa$; here κ is the progression rate from exposed to infectious. The recovered individuals can lose immunity and return to the susceptible class at a rate of δ. In case there is no disease related mortality, $N = S+E+I+R$ and they represent the (constant) total population. Thus, our model take the form below:

$$\frac{dS}{dt} = \mu N - \beta IS - (\phi_1(t)+\mu)S + \delta R, \tag{1}$$

$$\frac{dV}{dt} = \phi_1(t)S - \sigma\beta IV - \mu V, \tag{2}$$

$$\frac{dE}{dt} = \sigma\beta IV + \beta IS - \kappa E - \mu E, \tag{3}$$

$$\frac{dI}{dt} = \kappa E - (\alpha+\mu+\gamma+\phi_2(t))I, \tag{4}$$

$$\frac{dR}{dt} = \phi_2(t)I + \gamma I - \mu R - \delta R. \tag{5}$$

In general, $\phi_1(t)$ and $\phi_2(t)$ are functions of t, representing non-uniform and time-dependent controls. For the special case when the rates of all the two controls are positive constants, i.e.,

$$\phi_1(t) = \phi_1 > 0 \text{ and } \phi_2(t) = \phi_2 > 0 \tag{6}$$

the model (1)-(5) is reduced to an autonomous system. This allow us to conduct a careful equilibrium analysis.

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 $\mathbf{X} = (S,V,E,I,R)^T$.

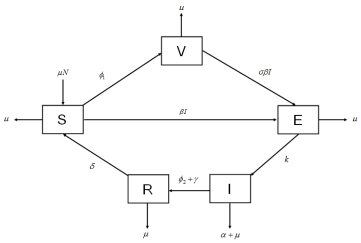

Fig. 1: Diagram of the model.

3 Disease-free equilibrium

With constant controls, the disease-free equilibrium (DFE) of the system (1)-(5) is given by

$$\varepsilon_0 = \left(\frac{\mu N}{\phi_1+\mu}, \frac{\phi_1 N}{\phi_1+\mu}, 0, 0, 0\right) \tag{8}$$

To compute the basic reproduction number, we use the well-known method of van den Driessche and Watmough [6], with the associated next-generation matraces

$$F = \begin{bmatrix} 0 & \sigma\beta V + \beta S \\ 0 & 0 \end{bmatrix} \text{ and } V = \begin{bmatrix} \kappa+\mu & 0 \\ -\kappa & \alpha+\mu+\gamma+\phi_2 \end{bmatrix}. \tag{9}$$

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

$$R_0 = \frac{\kappa\sigma\beta\phi_1 N + \kappa\beta\mu N}{(\phi_1+\mu)(\kappa+\mu)(\alpha+\mu+\gamma+\phi_2)}. \tag{10}$$

Consequently, based on work in [6], we immediately obtain the result below:

Theorem 3.1. The disease-free equilibrium of the model (1)-(5) 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 3.2. Consider a model system written in the form

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

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.

Theorem 3.3. The disease-free equilibrium of the model is globally asymptotic stable if $R_0 < 1$ provided $\delta = 0$.
Proof. We show that the conditions (H1) and (H2) hold when $R_0 < 1$. In our ODE system (1)-(5), $X_1 = (S, V, R), X_2 = (E, I)$, and $X_1^* = \left(\frac{\mu N}{\phi_1+\mu}, \frac{\phi_1 N}{\phi_1+\mu}, 0\right)$. We note that

$$\frac{dX_1}{dt} = F(X_1, 0) = \begin{bmatrix} \mu N - \phi_1 S - \mu S \\ \phi_1 S - \mu V \\ -\mu R \end{bmatrix}$$

is a linear and its solution can be found as

$$R(t) = R(0)e^{-\mu t},$$
$$S(t) = \frac{\mu N}{\phi_1+\mu} + \left[(S(0) - \frac{\mu N}{\phi_1+\mu}\right] \cdot e^{-(\phi_1+\mu)t}$$

and

$$\begin{aligned} V(t) = {} & \frac{\phi_1 N}{\phi_1+\mu} + R(0)e^{-\mu t} + V(0)e^{-\mu t} \\ & + C_1\frac{e^{-\mu t}}{\phi_1} - \frac{\phi_1 N}{\phi_1+\mu}e^{-\mu t} \\ & - \frac{\phi_1(R(0))}{\phi_1+\mu}e^{-\mu t} + C_1\frac{e^{-\mu t}}{\phi_1} - C_1\frac{e^{-(\mu+\phi_1)t}}{\phi_1}. \end{aligned}$$

Clearly, $R(t) \to 0, S(t) \to \frac{\mu N}{\phi_1+\mu}$ and $V(t) \to \frac{\phi_1 N}{\phi_1+\mu}$ as $t \to \infty$, regardless of the values of $R(0), V(0)$ and $S(0)$. Thus $X_1^* = \left(\frac{\mu N}{\phi_1+\mu}, \frac{\phi_1 N}{\phi_1+\mu}, 0\right)$ is globally asymptotically stable.

Next, we have

$$G(X_1, X_2) = \begin{bmatrix} \sigma\beta IV + \beta IS - (\kappa+\mu)E \\ \kappa E - (\alpha+\mu+\gamma+\phi_2)I \end{bmatrix}$$

We can then obtain

$$A = \begin{bmatrix} -(\kappa+\mu) & \sigma\beta\frac{\phi_1 N}{\phi_1+\mu} + \beta\frac{\mu N}{\phi_1+\mu} \\ \kappa & -(\alpha+\mu+\gamma+\phi_2) \end{bmatrix}$$

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

$$\hat{G}(X_1,X_2) = \begin{bmatrix} -(\kappa+\mu) & \sigma\beta\frac{\phi_1 N}{\phi_1+\mu}+\beta\frac{\mu N}{\phi_1+\mu} \\ \kappa & -(\alpha+\mu+\gamma+\phi_2) \end{bmatrix} \begin{bmatrix} E \\ I \end{bmatrix} - \begin{bmatrix} \sigma\beta IV+\beta IS-(\kappa+\mu)E \\ \kappa E-(\alpha+\mu+\gamma+\phi_2)I \end{bmatrix}, = \begin{bmatrix} \sigma\beta I\left(\frac{\phi_1 N}{\phi_1+\mu}-V\right)+\beta I\left(\frac{\mu N}{\phi_1+\mu}-S\right) \\ 0 \end{bmatrix}.$$

Since $0 \le V \le \frac{\phi_1 N}{\phi_1+\mu}$ and $0 \le S \le \frac{\mu N}{\phi_1+\mu}$. Therefore, the DFE $X_0 = (X_1^*,0)$ is globally asymptotically stable. □

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 model.

4.1 Endemic equilibrium

We first examine the existence of the positive endemic equilibrium. Denote the endemic equilibrium of the model by $\varepsilon^* = (S^*,V^*,E^*,I^*,R^*)$. From equations (1)-(5) we obtain

$$\frac{dS^*}{dt} = \mu N-\beta I^*S^*-(\phi_1+\mu)S^*+\delta R^*, \tag{11}$$
$$\frac{dV^*}{dt} = \phi_1 S^*-\sigma\beta I^*V^*-\mu V^*, \tag{12}$$
$$\frac{dE^*}{dt} = \sigma\beta I^*V^*+\beta I^*S^*-(\kappa+\mu)E^*, \tag{13}$$
$$\frac{dI^*}{dt} = kE^*-(\alpha+\mu+\gamma+\phi_2)I^*, \tag{14}$$
$$\frac{dR^*}{dt} = \phi_2 I^*+\gamma I^*-\mu R^*-\delta R^*. \tag{15}$$

With some algebraic manipulations, we have

$$S^* = \frac{\mu NQ_1+\delta Q_3 I^*}{(\beta I^*+Q_2)Q_1}, \tag{16}$$
$$V^* = \frac{\phi_1 S^*}{\sigma\beta I^*+\mu}, \tag{17}$$
$$E^* = \frac{a_1 I^*}{\kappa}, \tag{18}$$
$$R^* = \frac{Q_3 I^*}{Q_1} \tag{19}$$

where $a_1 = \alpha+\mu+\gamma+\phi_2, Q_1 = \mu+\delta, Q_2 = \phi_1+\mu$, and $Q_3 = \phi_2+\gamma$.

We substitute S^*,V^* and E^* into equation (13) to obtain

$$\left(\frac{\sigma\phi_1+\sigma\beta I^*+\mu}{\sigma\beta I^*+\mu}\right)\left(\frac{\mu NQ_1+\delta Q_3 I^*}{(\beta I^*+Q_2)Q_1}\right) = \left(\frac{\kappa+\mu}{\kappa\beta}\right)a_1.$$

This equation, after some algebra, yields a quadratic equation

$$A_1 I^{*^2}+B_1 I^*+C_1 = 0, \tag{20}$$

where

$$A_1 = \sigma\beta\delta Q_3-\left(\frac{\kappa+\mu}{\kappa\beta}\right)a_1 Q_1\sigma\beta^2,$$
$$B_1 = (\sigma\phi_1+\mu)\delta Q_3+\sigma\beta\mu NQ_1-\left(\frac{\kappa+\mu}{\kappa\beta}\right)a_1(\sigma\beta Q_2+\mu\beta)Q_1,$$
$$C_1 = (\sigma\phi_1+\mu)\mu NQ_1-\left(\frac{\kappa+\mu}{\kappa\beta}\right)a_1\mu Q_2 Q_1.$$

The roots of equation (20) have to satisfy

$$I_1^*I_2^* = \frac{C_1}{A_1} \text{ and } I_1^*+I_2^* = -\frac{B_1}{A_1}.$$

Consider that C_1 can be rewritten as

$$C_1 = \frac{(\mu+\delta)\mu}{\kappa\beta(\kappa+\mu)(\alpha+\mu+\gamma+\phi_2)(\phi_1+\mu)}(R_0-1).$$

When $R_0 > 1$, it is clearly seen that $C_1 > 0$. Meanwhile we have

$$A_1 = \sigma\beta\delta(\phi_2+\gamma)-\left(\frac{\kappa+\mu}{\kappa}\right)(\alpha+\mu+\gamma+\phi_2)(\mu+\delta)\sigma\beta, = \sigma\beta\left(\delta(\phi_2+\gamma)-\left(\frac{\kappa+\mu}{\kappa}\right)(\alpha+\mu+\gamma+\phi_2)(\mu+\delta)\right) < 0.$$

Thus $I_1^*I_2^* < 0$; that is, the two roots of equation (20) 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)-(5) exists and is unique provided $R_0 > 1$.

4.2 Local stability

In this section we proceed to analyze the local stability of the endemic equilibrium. First we establish the following result.

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

Proof. The Jacobian of the system (1)-(5) at ε^* is given by

$$J(\varepsilon^*) = \begin{bmatrix} -\beta I^*-(\phi_1+\mu) & 0 & 0 & -\beta S^* \\ \phi_1 & -\sigma\beta I^*-\mu & 0 & -\sigma\beta V^* \\ \beta I^* & \sigma\beta I^* & -\kappa-\mu & \sigma\beta_1 V^*+\beta S^* \\ 0 & 0 & \kappa & -a_1 \end{bmatrix}$$

where $a_1 = \alpha+\mu+\gamma+\phi_2$.
The characteristic equation of the matrix $J(\varepsilon^*)$ is

$$\begin{aligned}
0 &= \det(\lambda I - J(\varepsilon^*)) \\
&= \lambda^4 + (\kappa+3\mu+\sigma+\beta I^*+\beta I^*+\phi_1+a_1)\lambda^3 \\
&+ (\kappa\sigma\beta I^* + 2\mu\sigma\beta I^* + 2\mu\kappa + 3\mu^2 + \kappa\beta I^* + 2\mu\beta I^* \\
&+ \kappa\phi_1 + 2\mu\phi_1 + \sigma\beta^2 I^{*2} + \phi_1\sigma\beta I^* + a_1\kappa + a_1\phi_1 \\
&+ 3a_1\mu + a_1\sigma\beta I^* + a_1\beta I^* - \kappa\sigma\beta V^* - \kappa\beta S^*)\lambda^2 \\
&+ (\kappa\sigma\beta^2 I^{*2} + \mu\sigma\beta^2 I^{*2} + \kappa\mu\beta I^* + \mu^2\beta I^* + \kappa\phi_1\sigma\beta I^* \\
&+ \mu\phi_1\sigma\beta I^* + \kappa\mu\phi_1 + \mu^2\phi_1 + \kappa\mu\sigma\beta I^* + \mu^2\sigma\beta I^* \\
&+ \mu^2\kappa + \mu^3 + a_1\kappa\sigma\beta I^* + a_1\mu\sigma\beta I^* + 2a_1\mu\kappa + 3a_1\mu^2 \\
&+ 2a_1\mu\phi_1 + a_1\kappa\beta I^* + 2a_1\mu\beta I^* + a_1\sigma\beta^2 I^{*2} + a_1\mu\sigma\beta I^* \\
&+ a_1\phi_1\sigma\beta I^* - \kappa\sigma\beta^2 I^* S^* + a_1\kappa\phi_1 - 2\kappa\mu\sigma\beta V^* \\
&- 2\kappa\mu\beta S^* - \kappa\sigma\beta^2 I^* V^* - \kappa\phi_1\beta S^* - \kappa\phi_1\sigma\beta V^*)\lambda \\
&+ (a_1\kappa\sigma\beta^2 I^{*2} + a_1\mu\sigma\beta^2 I^{*2} + a_1\kappa\mu\beta I^* + a_1\mu^2\beta I^* \\
&+ a_1\mu^2\kappa + a_1\kappa\phi_1\sigma\beta I^* + a_1\mu\phi_1\sigma\beta I^* + a_1\kappa\mu\phi_1 \\
&+ a_1\mu^2\phi_1 + a_1\kappa\mu\sigma\beta I^* + a_1\mu^3 + a_1\mu^2\sigma\beta I^* \\
&- \kappa\mu\sigma\beta^2 I^* V^* - \kappa\phi_1\mu\sigma\beta V^* - \kappa\phi_1\mu\beta S^* \\
&- \kappa\mu\sigma\beta^2 I^* S^* - \kappa\mu^2\sigma\beta V^* - \kappa\mu^2\beta S^*). \qquad (21)
\end{aligned}$$

Equation (21) can be put into a quartic equation of the form

$$A_4\lambda^4 + A_3\lambda^3 + A_2\lambda^2 + A_1\lambda + A_0 = 0, \qquad (22)$$

where

$$\begin{aligned}
A_4 &= 1, \\
A_3 &= \kappa+3\mu+\sigma+\beta I^*+\beta_1 I^*+\phi_1+a_1, \\
A_2 &= \kappa\sigma\beta I^* + 2\mu\sigma\beta I^* + 2\mu\kappa + 3\mu^2 + \kappa\beta I^* + 2\mu\beta I^* \\
&+ \kappa\phi_1 + 2\mu\phi_1 + \sigma\beta^2 I^{*2} + \phi_1\sigma\beta I^* + a_1\kappa + 3a_1\mu \\
&+ a_1\sigma\beta I^* + a_1\beta I^* + a_1\phi_1 - \kappa\sigma\beta V^* - \kappa\beta S^*, \\
A_1 &= \kappa\sigma\beta^2 I^{*2} + \mu\sigma\beta^2 I^{*2} + \kappa\mu\beta I^* + \mu^2\beta I^* + \kappa\phi_1\sigma\beta I^* \\
&+ \mu\phi_1\sigma\beta I^* + \kappa\mu\phi_1 + \mu^2\phi_1 + \kappa\mu\sigma\beta I^* + \mu^2\sigma\beta I^* \\
&+ \mu^2\kappa + \mu^3 + a_1\kappa\sigma\beta I^* + a_1\mu\sigma\beta I^* + 2a_1\mu\kappa + 3a_1\mu^2 \\
&+ a_1\kappa\beta I^* + 2a_1\mu\beta I^* + a_1\kappa\phi_1 + 2a_1\mu\phi_1 + a_1\sigma\beta^2 I^{*2} \\
&+ a_1\mu\sigma\beta I^* + a_1\phi_1\sigma\beta I^* - \kappa\sigma\beta^2 I^* S^* - 2\kappa\mu\sigma\beta V^* \\
&- 2\kappa\mu\beta S^* - \kappa\sigma\beta^2 I^* V^* - \kappa\phi_1\beta S^* - \kappa\phi_1\sigma\beta V^*, \\
A_0 &= a_1\kappa\sigma\beta^2 I^{*2} + a_1\mu\sigma\beta^2 I^{*2} + a_1\kappa\mu\beta I^* + a_1\mu^2\beta I^* \\
&+ a_1\mu^2\kappa + a_1\kappa\phi_1\sigma\beta I^* + a_1\mu\phi_1\sigma\beta I^* \\
&+ a_1\kappa\mu\phi_1 + a_1\mu^2\phi_1 + a_1\kappa\mu\sigma\beta I^* + a_1\mu^2\sigma\beta I^* + a_1\mu^3 \\
&- \kappa\mu\sigma\beta^2 I^* V^* - \kappa\phi_1\mu\sigma\beta V^* - \kappa\mu^2\beta S^* - \kappa\phi_1\mu\beta S^* \\
&- \kappa\mu\sigma\beta^2 I^* S^* - \kappa\mu^2\sigma\beta V^*.
\end{aligned}$$

We clearly see that $A_4 > 0$ and $A_3 > 0$. Using equations (14) and (15), we have

$$\kappa a_1 + \mu a_1 - \kappa\sigma\beta V^* - \kappa\beta S^* = 0.$$

Thus A_2 yields

$$\begin{aligned}
A_2 &= \kappa\sigma\beta I^* + 2\mu\sigma\beta I^* + 2\mu\kappa + 3\mu^2 + \kappa\beta I^* + 2\mu\beta I^* \\
&+ \kappa\phi_1 + 2\mu\phi_1 + \sigma\beta^2 I^{*2} + \phi_1\sigma\beta I^* + a_1\kappa + 3a_1\mu \\
&+ a_1\sigma\beta I^* + a_1\beta I^* + a_1\phi_1 - \kappa\sigma\beta V^* - \kappa\beta S^*, \\
&= \kappa\sigma\beta I^* + 2\mu\sigma\beta I^* + 2\mu\kappa + 3\mu^2 + \kappa\beta I^* + 2\mu\beta I^* \\
&+ \kappa\phi_1 + 2\mu\phi_1 + \sigma\beta^2 I^{*2} + \phi_1\sigma\beta I^* + 2a_1\mu + a_1\sigma\beta I^* \\
&+ a_1\beta I^* + a_1\phi_1, \\
&> 0.
\end{aligned}$$

Hence $A_2 > 0$. Meanwhile, from equations (14) and (15), with some manipulation, we find

$$\phi_1\kappa a_1 + \phi_1\mu a_1 - \phi_1\kappa\sigma\beta V^* - \phi_1\kappa\beta S^* = 0,$$

and

$$\sigma\beta\kappa a_1 I^* + \sigma\beta\mu a_1 I^* - \kappa\sigma^2\beta^2 I^* V^* - \sigma\kappa\beta^2 I^* S^* = 0.$$

Thus A_1 yields

$$\begin{aligned}
A_1 &= \kappa\sigma\beta^2 I^{*2} + \mu\sigma\beta^2 I^{*2} + \kappa\mu\beta I^* + \mu^2\beta I^* + \kappa\phi_1\sigma\beta I^* \\
&+ \mu\phi_1\sigma\beta I^* + \kappa\mu\phi_1 + \mu^2\phi_1 + \kappa\mu\sigma\beta I^* + \mu^2\sigma\beta I^* \\
&+ \mu^2\kappa + \mu^3 + a_1\kappa\sigma\beta I^* + a_1\mu\sigma\beta I^* + 2a_1\mu\kappa \\
&+ 3a_1\mu^2 + a_1\kappa\beta I^* + 2a_1\mu\beta I^* + a_1\kappa\phi_1 + 2a_1\mu\phi_1 \\
&+ a_1\sigma\beta^2 I^{*2} + a_1\mu\sigma\beta I^* + a_1\phi_1\sigma\beta I^* - \kappa\sigma\beta^2 I^* S^* \\
&- 2\kappa\mu\sigma\beta V^* - 2\kappa\mu\beta S^* - \kappa\sigma\beta^2 I^* V^* - \kappa\phi_1\beta S^* \\
&- \kappa\phi_1\sigma\beta V^* \\
&= \kappa\sigma\beta^2 I^{*2} + \mu\sigma\beta^2 I^{*2} + \kappa\mu\beta I^* + \mu^2\beta I^* + \kappa\phi_1\sigma\beta I^* \\
&+ \mu\phi_1\sigma\beta I^* + \kappa\mu\phi_1 + \mu^2\phi_1 + \kappa\mu\sigma\beta I^* + \mu^2\sigma\beta I^* \\
&+ \mu^2\kappa + \mu^3 + a_1\mu\kappa + 2a_1\mu^2 + a_1\kappa\beta I^* \\
&+ 2a_1\mu\beta_1 I^* + a_1\mu\phi_1 + a_1\sigma\beta^2 I^{*2} + a_1\mu\sigma\beta I^* \\
&+ a_1\phi_1\sigma\beta I^* \\
&> 0 .
\end{aligned}$$

Hence $A_1 > 0$. Similarly, equations (14) and (15) give

$$\begin{aligned}
\mu\sigma\beta\kappa a_1 I^* + \sigma\beta\mu^2 a_1 I^* - \mu\kappa\sigma^2\beta^2 I^* V^* - \mu\sigma\kappa\beta^2 I^* S^* = 0, \\
\mu^2\kappa a_1 + \mu^3 a_1 - \mu^2\kappa\sigma\beta V^* - \mu^2\kappa\beta S^* = 0,
\end{aligned}$$

and

$$\phi_1\mu\kappa a_1 + \phi_1\mu^2 a_1 - \phi_1\mu\kappa\sigma\beta V^* - \phi_1\mu\kappa\beta S^* = 0.$$

Hence

$$\begin{aligned}
A_0 &= a_1\kappa\sigma\beta^2 I^{*2} + a_1\mu\sigma\beta^2 I^{*2} + a_1\kappa\mu\beta I^* + a_1\mu^2\beta I^* \\
&+ a_1\mu^2\kappa + a_1\kappa\phi_1\sigma\beta I^* + a_1\mu\phi_1\sigma\beta I^* + a_1\kappa\mu\phi_1 \\
&+ a_1\mu^2\phi_1 + a_1\kappa\mu\sigma\beta I^* + a_1\mu^2\sigma\beta I^* + a_1\mu^3 \\
&- \kappa\mu\sigma\beta^2 I^* V^* - \kappa\phi_1\mu\sigma\beta V^* - \kappa\mu^2\beta S^* - \kappa\phi_1\mu\beta S^* \\
&- \kappa\mu\sigma\beta^2 I^* S^* - \kappa\mu^2\sigma\beta V^* \\
&= a_1\kappa\sigma\beta^2 I^{*2} + a_1\mu\sigma\beta^2 I^{*2} + a_1\kappa\mu\beta I^* + a_1\mu^2\beta I^* \\
&+ a_1\kappa\phi_1\sigma\beta I^* + a_1\mu\phi_1\sigma\beta I^* + a_1\kappa\mu\sigma\beta I^*.
\end{aligned}$$

Thus $A_0 > 0$. To ensure that all roots of equation (22) have negative real parts, the Routh-Hurwitz stability criterion [20] requires A_0, A_1, A_2, A_3 and A_4 all to be positive, and additional conditions $A_3A_2 > A_1$ and $A_3A_2A_1 > A_3^2A_0 + A_1^2$ must satisfy. By simple algebra and comparing terms, the conditions are satistied. This completes the proof. □

5 Optimal control

Now we turn to more general model (1)-(5) with a time-dependent vaccination profile, $\phi_1(t)$, and treatment profile, $\phi_2(t)$, and conduct an optimal control study. Optimal control theory has been used in many works (see, e.g., [21,34]). We consider the system on a time interval [0,T]. The functions $\phi_1(t)$ and $\phi_2(t)$ are assumed to be at least Lebesgue measurable on [0,T]. The control set is defined as

$$\Gamma = \{(\phi_1(t), \phi_2(t))|\ 0 \le \phi_1(t) \le \phi_{1max}, \\ 0 \le \phi_2(t) \le \phi_{2max}\}, \quad (23)$$

where $\phi_{1_{max}}$ and $\phi_{2_{max}}$ denote the upper bounds for the effort of vaccination and treatment, respectively. These bounds reflect practical limitations on the maximum rates of controls that can be implemented in a given time period.

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

$$\min_{\phi_1,\phi_2\in\Gamma} \int_0^T [I(t) + c_1\phi_1(t)S(t) + c_2\phi_2(t)I(t) \\ + c_3\phi_1(t)^2 + c_4\phi_2(t)^2]dt. \quad (24)$$

where c_1 , c_2 , c_3 and c_4 are appropriate units defined the appropriate costs associated with the control.

Let us first define the adjoint functions $\lambda_S, \lambda_V, \lambda_E, \lambda_I$ and λ_R associated with the state equations for S, V, E, I and R, respectively. We then from 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

$$\begin{aligned} H &= I(t) + c_1\phi_1(t)S(t) + c_2\phi_2(t)I(t) + c_3\phi_1(t)^2 + c_4\phi_2(t)^2 \\ &+ \lambda_S(\mu N - \beta IS - (\phi_1(t) + \mu)S + \delta) \\ &+ \lambda_V(\phi_2(t)S - \sigma\beta IV - \mu V) \\ &+ \lambda_E(\sigma\beta IV + \beta IS - \kappa E - \mu E) \\ &+ \lambda_I(\kappa E - (\alpha + \mu + \gamma + \phi_2(t))) \\ &+ \lambda_R(\phi_2(t)I + \gamma I - \mu R - \delta R). \end{aligned}$$

To achieve the optimal control, the adjoint functions must satisfy

$$\frac{d\lambda_S}{dt} = -\frac{\partial H}{\partial S}, \frac{d\lambda_V}{dt} = -\frac{\partial H}{\partial V}, \frac{d\lambda_E}{dt} = -\frac{\partial H}{\partial E}, \frac{d\lambda_I}{dt} = -\frac{\partial H}{\partial I}, \\ \frac{d\lambda_R}{dt} = -\frac{\partial H}{\partial R}.$$

Thus, we have

$$\begin{aligned} \frac{d\lambda_S}{dt} &= -c_1\phi_1(t) + \lambda_S(\beta I + \phi_1(t) + \mu) - \lambda_V\phi_1(t) - \lambda_E\beta I, \\ \frac{d\lambda_V}{dt} &= \lambda_V\sigma\beta I + \lambda_V\mu - \lambda_E\sigma\beta I, \\ \frac{d\lambda_E}{dt} &= \lambda_E(\kappa + \mu) - \lambda_I\kappa, \\ \frac{d\lambda_I}{dt} &= -1 - C_2\phi_2(t) + \lambda_S\beta S + \lambda_V\sigma\beta V - \lambda_E(\sigma\beta_1 V + \beta S) \\ &+ \lambda_I(\alpha + \mu + \gamma + \phi_2(t)) - \lambda_R(\phi_2(t) + \gamma), \\ \frac{d\lambda_R}{dt} &= -\lambda_S\delta + \lambda_R(\mu\delta), \end{aligned}$$

with the final-time conditions $\lambda_S(T) = 0$, $\lambda_V(T) = 0$, $\lambda_E(T) = 0$, $\lambda_I(T) = 0$, and $\lambda_R(T) = 0$. The characterizations of the optimal controls $\phi_1^*(t)$ and $\phi_2^*(t)$ are based on the conditions

$$\frac{\partial H}{\partial \phi_1} = 0 \text{ and } \frac{\partial H}{\partial \phi_2} = 0 \quad (25)$$

respectively, subject to the constraints $0 \le \phi_1(t) \le \phi_{1_{max}}$ and $0 \le \phi_2(t) \le \phi_{2max}$. Thus we have

$$\phi_1^*(t) = \max[0, \min(\phi_1(t), \phi_{1\max})], \quad (26)$$

$$\phi_2^*(t) = \max[0, \min(\phi_2(t), \phi_{2\max})], \quad (27)$$

where

$$\phi_1(t) = \frac{S(t)(\lambda_S - \lambda_V - c_1)}{2c_3} \text{ and } \phi_2(t) = \frac{I(t)(\lambda_I - \lambda_R - c_2)}{2c_4}. \quad (28)$$

The optimal control system, consisting of the state equations, the adjoint equations and the optimality condition (25), 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 vaccination and treatment strategies can significantly bring down the number of infectious individuals. Some typical results are presented in Figures 2 and 3.

In addition, the dynamics of the exposed individuals can be observed from Figure 3. Without vaccination and treatment, 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 $t \approx 12$ days. With optimal vaccination and treatment, 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.

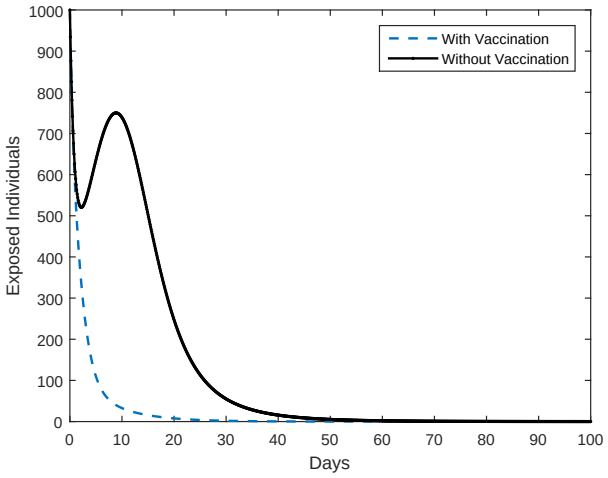

Fig. 2: Exposed individuals: similary, we can see that the number of exposed population is reduced due to the combination of vaccination and treatment in the model.

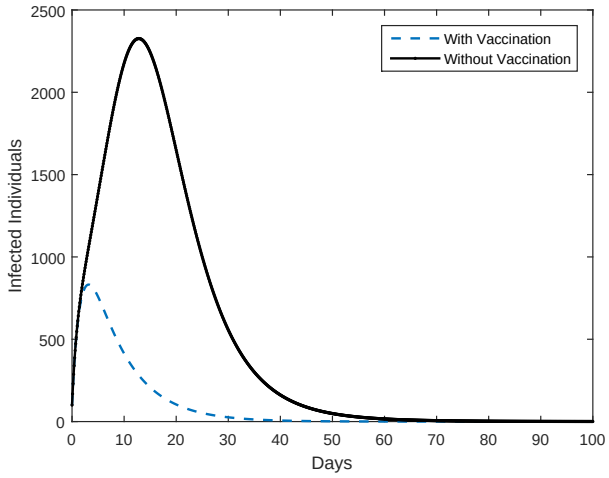

Fig. 3: The acute avian influenza infection population : it shows that with vaccination and treatment in the model can reduce the number of acute avian influenza infection group.

Table 1: Parameter values and symbols.

Parameter	Symbol	Value
Total human population	N	8,000
Birth and death rate	μ	$(70*365^{-1})/\text{day}$
Contract avian influenza rate	β	0.5/N/day
The loss of immunity period	σ	$0.699/\text{day}$
Rate of vaccination	ϕ_1	$0.7/\text{day}$
Rate of treatments	ϕ_2	$0.7/\text{day}$
Duration of immunity loss	δ	0.01
The recovery rate for E	κ	0.00015
The recovery rate for I	γ	0.36
Death rate due to disease	α	0.03
Appropriate cost	c_1	0.3
Appropriate cost	c_2	0.7
Appropriate cost	c_3	0.5
Appropriate cost	c_4	0.4

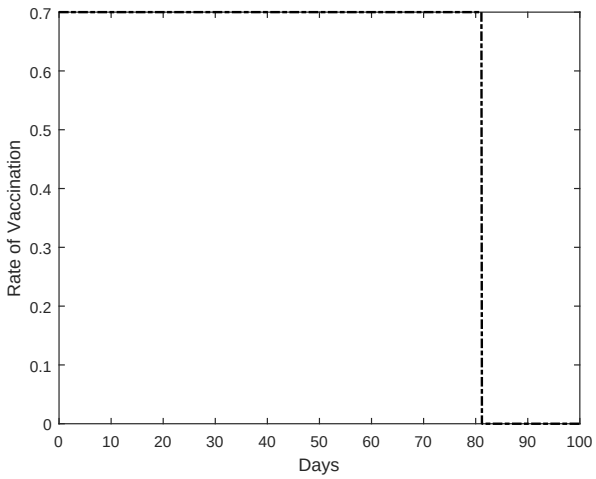

Fig. 4: Rate of vaccination (ϕ_1) vs. time (days) with $\phi_{1max} = 0.7$, $\mu = (70*365^{-1})$, $\beta = 0.5$, $\sigma = 0.699$, $\delta = 0.01$, $\kappa = 0.00015$, $\gamma = 0.36$, $\alpha = 0.03$, $c_1 = 0.3$, $c_2 = 0.7$, $c_3 = 0.5$ and $c_4 = 0.4$. The result shows that the vaccination rate stays at the maximum rate about 81 day and reduces to almost zero within 83 day.

6 Conclusions

We have presented a mathematical model for the spread of Avian Influenza that involves with the effects of vaccination and medical treatment. We have done this work by studying in both theoretical and numerical ways. In order to observe the effects 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 susceptibles are vaccinated with the rate ϕ_1 and thus they became a vaccinated class and assumed that humans are treated with the rate ϕ_2 and thus they became a recovered class. According to our study, it shows that with a good vaccination plan combined with a medical treatment, when strategically deployed, can significantly reduce the numbers of exposed and infectious people and help eradicate the disease outbreak. Throughout the paper, we

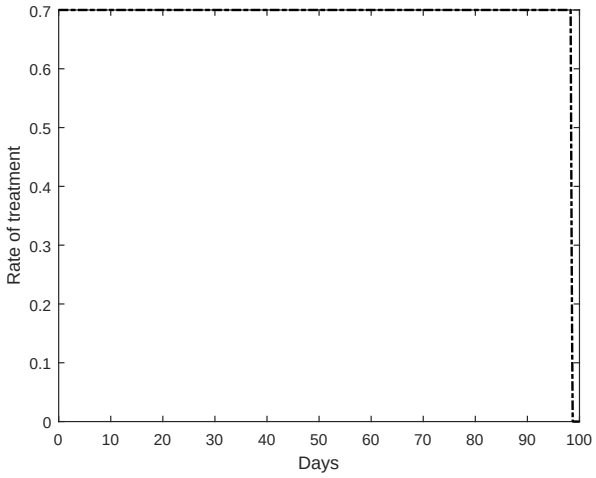

Fig. 5: Rate of treatment (ϕ_2) vs. time (days) with $\phi_{2max} = 0.7$, $\mu = (70 * 365^{-1})$, $\beta = 0.5$, $\sigma = 0.699$, $\delta = 0.01$, $\kappa = 0.00015$, $\gamma = 0.36$, $\alpha = 0.03$, $c_1 = 0.3$, $c_2 = 0.7$, $c_3 = 0.5$ and $c_4 = 0.4$. The result shows that the treatment rate stays at the maximum rate about 98 day and reduces to almost zero within 100 day.

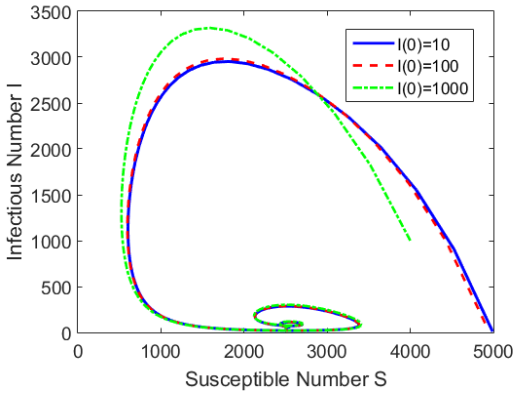

Fig. 6: Phase portraits for our model with different initial conditions and $R_0 > 1$. All the curves converge to the endemic equilibrium with $I^* \approx 20$, $S^* \approx 2600$.

have utilized both analytical and numerical means so as to gain deeper insight into the disease dynamics.

In this study we have conducted the local stability of the endemic equilibrium, however, the global asymptotic stability of the endemic equilibrium is not investigated due to the complexity of the system which we hope to overcome in future work. 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 for more careful investigation of the disease mechanism.

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