A STRUCTURED AVIAN INFLUENZA MODEL WITH IMPERFECT VACCINATION AND VACCINE INDUCED ASYMPTOMATIC INFECTION

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Abstract. We introduce a model of avian influenza in domestic birds with imperfect vaccination and age-since-vaccination structure. The model has four components: susceptible birds, vaccinated birds (stratified by vaccination-age), asymptomatically infected birds, and infected birds. The model includes reduction of probability of infection, decreasing severity of disease of vaccinated birds and vaccine waning. The basic reproduction number, $\mathcal{R}_0$, is calculated. The disease-free equilibrium is found to be globally stable under certain conditions when $\mathcal{R}_0 < 1$. When $\mathcal{R}_0 > 1$, existence of an endemic equilibrium is proved (with uniqueness for the ODE case and local stability under stricter conditions) and uniform persistence of the disease is established. The inclusion of reduction in susceptibility of vaccinated birds, reduction in infectiousness of asymptomatically infected birds and vaccine waning can have important implications for disease control. We analytically and numerically demonstrate that vaccination can paradoxically increase the total number of infected, resulting in the "silent spread" of the disease. We also study the effects of vaccine efficacy on disease prevalence and the minimum critical vaccination coverage, a threshold value for vaccination coverage to avoid an increase in total disease prevalence due to asymptomatic infection.
Keywords: mathematical models, vaccination, waning immunity, imperfect vaccine, vaccine efficacy, vaccination coverage, asymptomatic infection, differential equations, reproduction number, culling, H5N1, avian influenza, global stability, local stability.

AMS Subject Classification: 92D30, 92D40

1. Introduction

Vaccination and culling are the main control strategies employed in poultry for eradication of $H5N1$ highly pathogenic avian influenza (HPAI) disease. Culling has proved successful in isolated areas, however, employment of mass culling of poultry has never been a favorable control strategy because of ethical, economical and ecological reasons [1]. Thus, vaccination is employed in the countries where the disease is endemic.

An avian influenza vaccine for poultry produces immune protection for vaccinated birds. This immune protection decreases the probability of infection of vaccinated birds. Besides lowering the chance of infection, a vaccine can also reduce virus shedding and decrease the severity of the disease for an individual. The reduction in virus shedding induced by immune response to the antigen may prevent disease symptoms [10, 12]. Thus, a possible infection after vaccination may lead to asymptomatic infection of poultry birds, in which case vaccinated birds get infected, but do not show symptoms and can still spread the disease to susceptible individuals with a reduction in the probability of successful transmission.

Date: June 25, 2014.
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In general, vaccination does not lead to perfect immunity in populations; instead providing partial immunity which has three parameters to consider: reduction in the susceptibility of vaccinated individuals, reduction in the infectiousness of asymptomatically infected individuals and the rate at which immunity wanes. **The magnitude of these parameters depends on** the time passed after vaccination and the vaccine type. Inactivated whole AI virus vaccines and live recombinant vaccines are currently two types of AI vaccines in use. The minimum onset of immune protection provided by an inactivated vaccine starts 2 weeks after vaccination and can last up to 1 year post vaccination. Recombinant vaccines are able to provide long term protection up to 24 weeks after a single dose in the absence of previous infection with fowlpox virus of poultry [1]. In a field setting, it has also been observed that infection spread to the recently vaccinated birds with low rates of $H5N1$ mortality in poultry when chickens are between 9 and 18 days post-vaccination [11]. Some of the studies also suggest that an earlier infection of poultry with $H9N2$ subtype provides short term partial protective immunity so that it increases the resistance of birds against infection in the early stage of $H5N1$ AI infection [2]. Hemagglutinin (HA)-based AI vaccines are mostly generated from $H5$, $H7$ and $H9$ AI viruses [10]. In the case of vaccination with vaccines generated from $H9N2$ virus, the immunity may last for a shorter duration after vaccination as compared with immunity gained after natural infection [4].

In mathematical models of vaccination, an imperfect vaccine is usually modeled by assuming constant rates of infection and waning for vaccinated individuals [3, 6, 21, 18, 7, 22]. However, the waning immunity and probability of infection after vaccination may have a more general form, and age-since-vaccination structure can capture this complexity. To the best of our knowledge, Arino et al. [6] is the only work that has studied imperfect vaccine in an age-since-vaccination model. The "leaky vaccine" is modeled with a general waning function depending on time passed after vaccination and a reduction in probability of infection. However, Arino et al. assumes that once vaccinated individuals become infected, they have the same infectivity as unvaccinated individuals which become infected. Biologically this may not be a reasonable assumption since vaccine-induced partial immune protection reduces the severity of infection.

In the context of avian influenza, vaccine-induced asymptomatic infection among poultry birds causes difficulties in preventing circulation of virus in co-existing unvaccinated poultry [16]. It weakens the surveillance system, which is an essential component of AI disease control. Detection problems for $H5N1$ HPAI virus in the vaccinated poultry can drastically increase the likelihood of a possible outbreak [8]. Asymptomatically infected birds are capable to spread the disease to healthy unvaccinated birds, which poses a large threat to disease control. Asymptomatic infection in poultry also represents a threat to mamalians including humans.

Mathematical modeling of avian influenza can give important insights on how vaccination affects disease dynamics and prevalence. Iwami et al. considered a differential equation model with a vaccine-sensitive and vaccine-resistant strain of avian influenza, and found that increasing vaccination can increase the total number of infected birds [18]. Even in the absence of a vaccine-resistant strain, vaccination may result in negative outcomes as a result of "silent spread" of the AI virus. Savill et al. [8] considered an individual based model to show how detection problems with asymptomatically infected vaccinated birds can lead to outbreaks when vaccination coverage is not sufficiently large.

However, they do not investigate other mechanisms which can cause negative impact of vaccination, such as increased infectious period of asymptomatic birds, which occurs because previously vaccinated birds do not die due to disease. In addition, individual based models may be sensitive to parameter values, and do not provide general mathematical results and explicit threshold quantities.

In this study we introduce a partial differential equation model of avian influenza in domestic birds with imperfect vaccination and age-since-vaccination structure. The main objective is to understand the epidemiology of $H5N1$ HPAI disease in the context of vaccination and to draw some conclusions about mechanisms causing asymptomatic spread of the virus, an increase in total disease prevalence due to asymptomatic infection. In the terms of epidemiological implications, we derive an explicit threshold value for the minimum critical vaccination coverage and we also study the impact of high and low vaccine efficacy on the critical vaccination coverage and total disease prevalence. In addition, we numerically study culling effect on disease dynamics.

This paper is organized as follows. In the next section we introduce a model of avian influenza in domestic birds with imperfect vaccination and age-since-vaccination structure, which includes reduction of the probability of infection, decreasing severity of disease of vaccinated birds and vaccine waning. We find the basic reproduction number $\mathcal{R}_0$, and investigate the globally stability of disease-free equilibrium when $\mathcal{R}_0 < 1$. We also investigate existence of an endemic equilibrium and show uniform persistence of the disease. In section 3, for further analysis of the model, we consider the ODE version of the model and show uniqueness of the endemic equilibrium. Under certain conditions, we also establish the local stability of the unique endemic equilibrium. In section 4, we analytically study the mechanisms that causes asymptomatic spread and derive some critical vaccination rates including a vaccination rate that indicates the minimum rate of vaccination to avoid asymptomatic spread of the disease. In section 5, we study the impact of vaccine efficacy on the minimum critical vaccination coverage and total disease prevalence. In the last section, we summarize our results and give the conclusion.

2. A model with vaccination and culling

In this section, we introduce a model of avian influenza in domestic birds, with vaccination and age-since-vaccination structure in the vaccinated compartment. We consider a population $N(t)$ whose demography is given by a constant recruitment rate Λ and a natural mortality rate μ. The susceptible domestic bird population $S(t)$ moves to the vaccinated domestic bird compartment with a vaccination rate $\psi S(t)$. The vaccine wanes at a rate dependent upon the age-since-vaccination in order to take into account the loss of protective antibodies over time. Here the waning function $w(a)$ corresponds to the per capita rate at which vaccinated birds with age a (age-since-vaccination) move to the susceptible class. By incorporating age-since-vaccination in the model, we aim to capture possible variable waning $w(a)$ of immunity in the population.

Moreover, infectious birds are separated into two classes: asymptomatic and infected class, denoted by $A(t)$ and $I(t)$, respectively. We assume that vaccinated birds with age a become asymptomatically infected, i.e. move to the $A(t)$ compartment, at the rate $\rho(a)\beta I(t)v(a,t)$, where $v(a,t)$ denotes the density of vaccinated birds and a is time since vaccination. The parameter $\rho(a)$ denotes the reduction in susceptibility of vaccinated domestic birds. The parameter $\rho(a)$ is assumed to be function of vaccination-age

a since the loss of protective antibodies over time can be seen as receding protection against infection. Note that $\rho(a)$ can model decreasing partial immunity offered by the vaccine, whereas the waning rate, $\omega(a)$, describes the complete loss of immunity. **Asymptomatic birds, $A(t)$, recover with a per capita rate γ. Note that immunity is boosted after asymptomatic infection. For simplicity, we assume that the immunity gained after asymptomatic infection is similar to the immune protection generated after vaccination. So with per capita recovery rate γ, asymptomatic birds are added to the vaccinated class in the boundary condition, i.e. their vaccination age is reset to zero.** Also susceptible birds are infected at the total rate $\beta S(t)(I(t) + qA(t))$, where $q < 1$ gives the reduction in the infectivity of asymptomatic individuals for susceptible birds, and move to the infected class $I(t)$. Vaccination increases resistance to infection which leads to reduction in susceptibility of vaccinated individuals against AI disease. Vaccination also reduces virus shedding after a possible infection of vaccinated birds [10]. So asymptomatically infected birds are less infectious to susceptible birds, that is implemented in the model by multiplying the transmission term $\beta A(t)S(t)$ with the reduction constant q. Considering how vaccine works in general and the process of asymptomatic infection of vaccinated birds, it can be more reasonable to assume that asymptomatic birds do not transmit the disease to the vaccinated birds because of reduction in susceptibility of vaccinated birds and reduction in infectiousness of asymptomatic birds.

TABLE 1. Parameters and dependent variable list

Parameter/Variable	Description
$S(t)$	Number of susceptible *birds* at time t
$v(a,t)$	The density of vaccinated *birds* with vaccination age a at time t
$I(t)$	Number of infected *birds* at time t
$A(t)$	Number of asymptomatically infected *birds* at time t
Λ	Constant recruitment rate
β	Transmission rate
μ	Constant per-capita natural death rate
ν	Constant per-capita disease induced death rate
ψ	Constant per-capita vaccination rate
c	Culling coefficient for susceptible and infected birds
$\hat{c}$	Culling coefficient for vaccinated and asymptomatically infected birds
$w(a)$	Per-capita waning rate at vaccination age a
γ	Per-capita recovery rate for asymptomatically infected birds
$\rho(a)$	The reduction in susceptibility of vaccinated birds at vaccination age a
q	The reduction in infectivity of asymptomatic birds

In the model, infected birds leave the compartment with a H5N1 disease-induced death rate ν. Also culling in this model is carried out at a rate proportional to infected poultry to assure that culling is not performed when there is no infection: at a rate cI for susceptible and infected poultry, and at a rate $\hat{c}I$ for vaccinated and asymptomatic poultry. Dependent variables and parameters and their descriptions are listed in Table 1.

The model is formulated as follows:

$$
\begin{cases}
\dfrac{dS}{dt} &= \Lambda - \beta(I+qA)S - (\mu+\psi+cI)S \\
&\qquad\qquad + \displaystyle\int_0^\infty \omega(a)v(a,t)da, \\
\dfrac{\partial v}{\partial t} + \dfrac{\partial v}{\partial a} &= -\rho(a)\beta I v - (\mu+\omega(a)+\hat{c}I)v, \\
v(0,t) &= \psi S + \gamma A, \\
\dfrac{dA}{dt} &= \beta I \displaystyle\int_0^\infty \rho(a)v da - (\mu+\gamma+\hat{c}I)A, \\
\dfrac{dI}{dt} &= \beta(I+qA)S - (\mu+\nu+cI)I
\end{cases}
\tag{2.1}
$$

We assume that all parameters of the model are non-negative, in addition to the following assumptions for the parameters of the model that will be valid through this article:

$$\rho(.),\ \omega(.) \in L^\infty(0,\infty),$$
$$0 \le \rho(a) \le 1,\ \forall a \in (0,\infty).$$

We introduce

$$\phi_I(a,\sigma) = e^{-\int_0^a [\rho(u)\beta I(u+\sigma)+(\mu+w(u)+\hat{c}I(u+\sigma))]du},\ \text{with } a \ge 0,\ \sigma \in R$$

Integrating the second equation of the system (2.1) along the characteristic lines, we obtain

$$
v(a,t) = \begin{cases}
\phi_I(a,t-a)v(0,t-a), & \text{if} \quad t > a \ge 0, \\
\dfrac{\phi_I(a,t-a)}{\phi_I(a-t,t-a)}v(a-t,0), & \text{if} \quad a > t \ge 0,
\end{cases}
\tag{2.2}
$$

where $\phi_I(a,\sigma)$ can be interpreted as the probability of still being in the vaccinated class at vaccination age a having entered the vaccinated stage at time σ (Thieme, 2013 p. 215) [28]. Then

$$\lim_{a\to\infty} v(a,t) = 0,\ \forall\ t \in [0,\infty).$$

Therefore for the vaccinated bird population, we obtain the following ODE :

$$V' = \psi S + \gamma A - \int_0^\infty \rho(a)\beta I v(a,t)da - \int_0^\infty (\mu+\omega(a)+\hat{c}I)v(a,t)da, \tag{2.3}$$

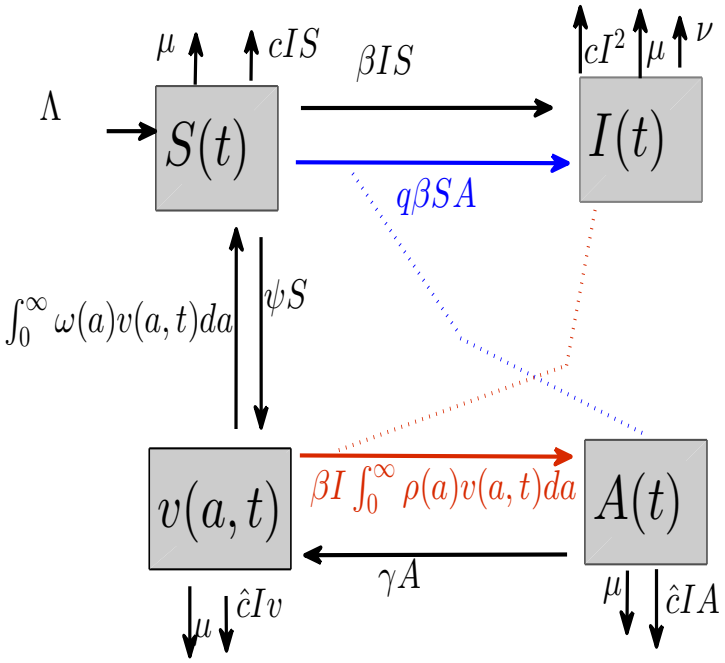


FIGURE 1. *Model structure for asymptomatic infection during a vaccination program:* Susceptible birds (S) become vaccinated (v) with a constant vaccination rate ψ. Some of the vaccinated birds move to the susceptible compartment with waning rate $w(a)$ depending on vaccination age a. After introduction of infection, a portion of vaccinated birds become asymptomatically infected (A) with a reduction $\rho(a)$ in the susceptibility of vaccinated birds. Asymptomatically infected birds recover with a rate γ and moved to the vaccinated compartment because of their previous exposure to the infection and induced partial immunity through vaccination. After getting contact with infected birds, a portion of susceptible birds move to the infected compartment with a rate $\beta(I + qA)$, where q is reduction in the infectiousness of asymptomatically infected birds.

where $V(t) = \int_0^\infty v(a,t)da$. The solutions of the system (2.1) are non-negative for all time t. After adding all equations V', S', A', I' in the system (2.1), we obtain

$$N'(t) \leq \Lambda - \mu N,$$

which implies

$$\limsup_{t\to\infty} N(t) \leq \frac{\Lambda}{\mu}.$$

In the following subsection, we will discuss existence and stability of equilibria, namely infection-free equilibrium and endemic equilibria.

2.1. **Existence and Stability of Equilibria.** The long term behavior of solutions is determined in part by the equilibria that are time-independent solutions of the system (2.1). An equilibrium is called disease-free equilibrium if infected compartments in this equilibrium are zero. Otherwise it is called endemic equilibrium. In this section, we will

investigate existence and stability of equilibria under certain conditions. We will also show that the disease is weakly uniform persistent.

The system (2.1) has a DFE $\mathcal{E}_0 = (S_0, v_0(a), A_0, I_0)$, where

$$S_0 = \frac{\Lambda}{\mu + \psi - \psi \int_0^\infty \omega(a)\phi_0(a)}, \ v_0(a) = \psi S_0 \phi_0(a), \ A_0 = 0, \ I_0 = 0,$$

with $\phi_0(a) = e^{-\int_0^a (\mu + w(u))du}$. Notice that $\int_0^\infty \omega(a)\phi_0(a) < 1$ (by integration by parts) so that the DFE is positive. In addition, $\phi_0(a)$ gives the probability of being in vaccinated compartment at vaccination age a in the absence of disease.
We define the reproduction number as follows:

$$\mathcal{R}_0 = \frac{\beta S_0}{\mu + \nu} + \frac{q\beta S_0}{\mu + \gamma} . \frac{\beta \int_0^\infty \rho(a) v_0(a) da}{(\mu + \nu)}. \tag{2.4}$$

In interpreting this expression, notice that $\frac{1}{\mu + \nu}$, $\frac{1}{\mu + \gamma}$ are the average time spent in the infectious stage and in the asymptomatic stage, respectively. The first term $\frac{\beta S_0}{\mu + \nu}$ is the average number of infected individuals produced by an infected individual during its infectious period among whole susceptible population through direct transmission between infected and susceptible birds. $\frac{\beta \int_0^\infty \rho(a) v_0(a) da}{(\mu + \nu)}$ is the average number of secondary asymptomatically infected birds produced by an infected individual during its infectious period among whole vaccinated bird population. $\frac{q\beta S_0}{\mu + \gamma}$ is the number of secondary infected birds produced by an asymptomatic birds during its asymptomatic infectious period among whole susceptible birds population. Hence the second term in (2.4) is the average number of secondary infected birds produced by an infected individual during its infectious period through indirect transmission, which involves asymptomatically infected birds as a mechanism which causes the transmission of infection for susceptible birds. Hence the total expression in (2.4) represents the average number of infected birds caused by an infected individual during its infectious period among total susceptible and vaccinated bird population. The following theorem gives a condition on local stability of disease free equilibrium:

Theorem 2.1. *If $\mathcal{R}_0 < 1$, then the DFE $\mathcal{E}_0$ is locally asymptotically stable and it is unstable if $\mathcal{R}_0 > 1$.*

Proof. By taking $S(t) = S_0 + x(t), v(a,t) = v_0(a) + y(a,t), A(t) = A_0 + z(t)$ and $I(t) = I_0 + i(t)$, we linearize the system (2.1) about the DFE and look for eigenvalues of the linear operator - that is we look for solutions of the form $x(t) = \overline{x}e^{\lambda t}, y(a,t) = \overline{y}(a)e^{\lambda t}, z(t) = \overline{z}e^{\lambda t}$ and $i(t) = \overline{i}e^{\lambda t}$, where $\overline{x}$, $\overline{y}(a)$, $\overline{z}$, $\overline{i}$ are arbitrary constants at least one of which is non-zero (a function of a in the case of y), but the eigenvalue λ is common. This process results in the following system (the bars have been omitted):

$$
\begin{cases}
\lambda x &= -\beta(i+qz)S_0 - (\mu+\psi)x - ciS_0 \\
&\qquad + \int_0^\infty \omega(a)y(a)da, \\
\lambda y(a) + \dfrac{\partial y(a)}{\partial a} &= -\rho\beta i v_0(a) - \hat{c}i v_0(a) - (\mu+\omega(a))y(a), \\
y(0) &= \psi x + \gamma z, \\
\lambda z &= \beta i \int_0^\infty \rho(a)v_0(a)da - (\mu+\gamma)z, \\
\lambda i &= \beta(i+qz)S_0 - (\mu+\nu)i
\end{cases} \tag{2.5}
$$

By the third equation in (2.5), we obtain

$$
z = \frac{\beta i \int_0^\infty \rho(a)v_0(a)da}{(\lambda+\mu+\gamma)}. \tag{2.6}
$$

By the last equation in (2.5), we also have

$$
(\lambda+\mu+\nu-\beta S_0)i = \beta q z S_0. \tag{2.7}
$$

Substituting (2.6) into (2.7), we obtain the following equation:

$$
(\lambda+\mu+\nu-\beta S_0)i = \beta q S_0 \frac{\beta i \int_0^\infty \rho(a)v_0(a)da}{\lambda+\mu+\gamma}. \tag{2.8}
$$

From the equation above, we derive the following quadratic equation of λ (assuming $i \neq 0$):

$$
\lambda^2 + (\mu+\nu+\mu+\gamma-\beta S_0)\lambda + (\mu+\nu)(\mu+\gamma)(1-\mathcal{R}_0) = 0. \tag{2.9}
$$

Note that when $\mathcal{R}_0 < 1$, then

$$
\mu+\nu-\beta S_0 > \frac{\beta^2 S_0 q \int_0^\infty \rho(a)v_0(a)da}{\mu+\gamma}.
$$

Hence whenever $\mathcal{R}_0 < 1$, we have $\mu+\nu-\beta S_0 > 0$, which also implies $\mu+\nu+\mu+\gamma-\beta S_0 > 0$. Then when $\mathcal{R}_0 < 1$, the quadratic equation (2.9) has two complex roots $\lambda_1,\ \lambda_2$ either with negative real parts or two negative real roots.

Now consider that $i = 0$. Then $z = 0$. Therefore from the equation system (2.5), we obtain

$$
\begin{cases}
\lambda x &= -(\mu+\psi)x + \int_0^\infty \omega(a)y(a)da, \\
\lambda y(a) + \dfrac{\partial y(a)}{\partial a} &= -(\mu+\omega(a))y(a), \\
y(0) &= \psi x,
\end{cases} \tag{2.10}
$$

Solving this equation system, we obtain $\lambda = -\mu + \psi(-1 + \int_0^\infty w(a)e^{-\int_0^a (\mu+w(s)+\lambda)ds}da)$. Notice that the left hand side of the equality above is an increasing function of λ (and at 0, it is zero) and the right hand side of the equation is a decreasing function of λ (and at 0, it is negative since $\int_0^\infty w(a)e^{-\int_0^a (\mu+w(s)+\lambda)ds}da < 1$). So if λ is a real number, these two functions do not intersect on the interval $[0, +\infty)$. However they have to intersect on the interval $(-\infty, 0)$ since as $\lambda \to -\infty$, the left hand side of the equation decreases

and the right hand side of the equation increases.
Now, let λ be a complex number such that $\lambda = \alpha + i\eta$, with $\alpha \geq 0$. Then by rearranging the equality above, we obtain

$$\alpha + \mu + \psi + i\eta = \psi \int_0^\infty w(a) e^{-\int_0^a (\mu + w(s) + \alpha) ds} e^{-i\eta a} da$$

Now taking the absolute value of both sides, we get

$$\alpha + \mu + \psi \leq \psi \int_0^\infty w(a) e^{-\int_0^a (\mu + w(s) + \alpha) ds} da.$$

If $\alpha \geq 0$, this inequality does not hold. Hence, we have a contradiction. Therefore $\alpha < 0$. Considering both cases ($i = 0$ or $i \neq 0$), we can conclude that all eigenvalues λ of the system (2.1) have a negative real part if $\mathcal{R}_0 < 1$. Then when $\mathcal{R}_0 < 1$, the DFE is locally asymptotically stable. However if $\mathcal{R}_0 > 1$, then (2.9) has two real roots with opposite signs in the case of $i \neq 0$. Hence when $\mathcal{R}_0 > 1$, the DFE is unstable.

□

In the following theorem, we show the existence of endemic equilibrium under the condition $\mathcal{R}_0 > 1$, moreover the condition $\gamma = 0$ leads to uniqueness of endemic equilibrium when $\mathcal{R}_0 > 1$.

Theorem 2.2. *When $\mathcal{R}_0 > 1$, the system (2.1) has a positive endemic equilibrium $(S^*, v^*(a), A^*, I^*)$, where*

$$S^* = \frac{\Lambda - (\mu + \nu + cI^*)I^*}{(\mu + \psi + cI^* - \psi(1 + \gamma f(I^*))\Omega(I^*))}, \; v^*(a) = (\psi S^* + \gamma A^*)\phi_I(a), \; A^* = \psi f(I^*) S^*,$$

with

$$f(I^*) = \frac{\beta I^* K(I^*)}{(\mu + \gamma + \hat{c}I^*) - \beta\gamma I^* K(I^*)}, \; \Omega(I^*) = \int_0^\infty \omega(a)\phi_{I^*}(a)da, \; K(I^*) = \int_0^\infty \rho(a)\phi_{I^*}(a)da,$$

and

$$\phi_{I^*}(a) = e^{-\int_0^a [\rho(u)\beta I^* + (\mu + w(u) + \hat{c}I^*)]du}.$$

If $\gamma = 0$, then this equilibrium is unique.

Proof. To compute the steady states of the system (2.1), we set the derivatives with respect to time in the system (2.1) equal zero. In this way we obtain the following system (the stars have been omitted because these are generic values of S, $v(a)$, A and I, not necessarily the equilibrium):

$$\begin{cases} 0 &= \Lambda - \beta(I + qA)S - (\mu + \psi + cI)S \\ & \qquad\qquad + \int_0^\infty \omega(a)v(a)da, \\ \dfrac{\partial v}{\partial a} &= -\rho(a)\beta I v - (\mu + \omega(a) + \hat{c}I)v, \\ v(0) &= \psi S + \gamma A, \\ 0 &= \beta I \int_0^\infty \rho(a) v da - (\mu + \gamma + \hat{c}I)A, \\ 0 &= \beta(I + qA)S - (\mu + \nu + cI)I, \end{cases} \tag{2.11}$$

which includes three algebraic equations and an ODE.
By the third equation (initial condition not counted) in the system (2.11), we have

$$A = \frac{\beta I \int_0^\infty \rho(a)v(a)da}{(\mu + \gamma + \widehat{c}I)}. \tag{2.12}$$

Also by the second equation and boundary condition in the system (2.11), we obtain

$$v(a) = (\psi S + \gamma A)\phi_I(a). \tag{2.13}$$

Then by substituting (2.13) into the equation (2.12), we get

$$A = \frac{\beta I(\psi S + \gamma A)K(I)}{(\mu + \gamma + \widehat{c}I)}. \tag{2.14}$$

($K(I)$, $\Omega(I)$ and $f(I)$ are defined in the statement of Theorem (2.2).)
By arranging the equality (2.14), we obtain

$$A = \psi S \frac{\beta I K(I)}{(\mu + \gamma + \hat{c}I - \beta I \gamma K(I))} \tag{2.15}$$

We note that the denominator is positive since $\beta I K(I) < 1$. Then by the third equality in the system (2.11), we have

$$\beta S(1 + \frac{q\beta\psi S K(I)}{(\mu + \gamma + \hat{c}I - \beta I\gamma K(I))}) = (\mu + \nu + cI) \tag{2.16}$$

By the **fourth** equation in the system (2.11),

$$\beta(I + qA)S = (\mu + \nu + cI)I. \tag{2.17}$$

Substituting the equations (2.13), (2.15), and (2.17) into the first equality in the system (2.11), we obtain

$$S = \frac{\Lambda - (\mu + \nu + cI)I}{(\mu + \psi + cI - \psi(1 + \gamma f(I))\Omega(I))} = F(I). \tag{2.18}$$

Notice that the denominator $D(I)$ of $F(I)$ is positive if

$$(\mu + \psi + cI)\left[(\mu + \gamma + \hat{c}I) - \gamma\beta I K(I)\right] - \psi(\mu + \gamma + \hat{c}I)\Omega(I) > 0. \tag{2.19}$$

By the fact that $0 < (\beta I K(I) + \Omega(I)) < 1$, we can reduce the left hand side of the inequality (2.19) and obtain $D(I) > \mu^2$, which implies $D(I) > 0$ for all $I \geq 0$. Therefore $F(I)$ is a decreasing function of I for all $I \geq 0$ for which $S(I) \geq 0$.

Substituting the equality (2.18) into the equation (2.16) in the system above, we get

$$\beta F(I)(1 + \frac{q\beta\psi F(I)K(I)}{(\mu + \gamma + \hat{c}I - \gamma\beta I K(I))}) = (\mu + \nu + cI) \tag{2.20}$$

Let $G(I) := \beta F(I)(1 + \frac{q\beta\psi F(I)K(I)}{(\mu + \gamma + \hat{c}I - \gamma\beta I K(I))})$ and $L(I) := (\mu + \nu + cI)$. First note that $\exists\ \tilde{I} : F(\tilde{I}) = 0$. So $G(\tilde{I}) = 0$. Also notice that $L(I)$ is an increasing function of I and $G(I)$ is a continuous function of I. Therefore since $G(0) > L(0)$, where $\mathcal{R}_0 = G(0)/L(0)$, then there exists a solution $\hat{I} \in (0, \tilde{I}) : G(\hat{I}) = L(\hat{I})$. Notice that if $\gamma = 0$, then $G(I)$ is a decreasing function of I since $F(I)$ decreases as I increases. So if $\mathcal{R}_0 > 1$, then there is a unique solution I^*, since $L(I)$ increases as I increases (when $\gamma = 0$).

□

In the main model (2.1), we assume that the asymptomatic infected birds recover at a rate γ and move to the vaccinated compartment. In the case of $\gamma = 0$, we establish global extinction of the disease when $\mathcal{R}_0 < 1$.

Theorem 2.3. *Let $\gamma = 0$. If $\mathcal{R}_0 < 1$, then the disease free equilibrium $\mathcal{E}_0 = (S_0, v_0(a), 0, 0)$ is globally asymptotically stable.*

Proof. By the equation (2.2), we have

$$\begin{aligned}
\int_t^\infty v(a,t)da &= \int_t^\infty \frac{\phi_I(a, a-t)}{\phi_I(a-t, t-a)} v(a-t, 0)da \\
&= \int_t^\infty e^{-\int_{a-t}^a [\rho(u)\beta I(u+t-a)+(\mu+w(u)+\hat{c}I(u+t-a))]du} v(a-t,0)da \\
&= e^{-\mu t}\int_t^\infty e^{-\int_{a-t}^a [\rho(u)\beta I(u+t-a)+(w(u)+\hat{c}I(u+t-a))]du} v(a-t,0)da \\
&\leq e^{-\mu t}\int_t^\infty v(a-t,0)da \\
&= e^{-\mu t}\int_0^\infty v(a,0)da
\end{aligned}$$

Then $\lim_{t\to\infty}\int_t^\infty v(a,t)da = 0$, since $v(a,t) \in L^1$. Also by the first equation in the system (2.1), we have

$$S' \leq \Lambda - (\mu+\psi)S + \int_0^\infty w(a)v(a,t)da.$$

Then for $t > 0$ large enough, we obtain

$$\begin{aligned}
S' &\leq \Lambda - (\mu+\psi)S + \int_0^t w(a)v(a,t) + \epsilon \\
&\leq \Lambda - (\mu+\psi)S + \int_0^t w(a)\left[\psi S(t-a) + \gamma A(t-a)\right]\phi_I(a, t-a)da + \epsilon
\end{aligned}$$

Hence by the assumption $\gamma = 0$, we have

$$S' \leq \Lambda - (\mu+\psi)S + \int_0^t w(a)\psi S(t-a)\phi_I(a,t-a)da + \epsilon.$$

Let $S^\infty = \limsup_t S(t)$. Then there exists $\tau > 0$ such that $S(t) \leq S^\infty + \epsilon,\ \forall t \geq \tau$. By the semigroup property, without loss of generality we can assume that $\tau = 0$. Then $S(t) \leq S^\infty + \epsilon,\ \forall t \geq 0$. Therefore

$$S' \leq \Lambda - (\mu+\psi)S + \psi(S^\infty + \epsilon)\int_0^t w(a)\phi_I(a,t-a)da$$

For $x' \leq a - bx$, with constants a, b, we know that $\limsup_t x \leq \frac{a}{b}$. Then by the inequality above, we have

$$S^\infty \leq \frac{\Lambda + \psi(S^\infty + \epsilon)\int_0^\infty w(a)\phi_0(a)da}{\mu + \psi}. \tag{2.21}$$

After rearranging the inequality (2.21), we obtain

$$S^\infty \leq \frac{\Lambda}{\mu + \psi - \psi\int_0^\infty w(a)\phi_0(a)da} + \epsilon\left[\frac{\psi\int_0^\infty w(a)\phi_0(a)da}{\mu + \psi - \psi\int_0^\infty w(a)\phi_0(a)da}\right]$$

Since the inequality above is true for all $\epsilon > 0$ and the second term is bounded, we have

$$S^\infty \leq \frac{\Lambda}{\mu + \psi - \psi\int_0^\infty w(a)\phi_0(a)da} = S_0, \tag{2.22}$$

Also by the last equation in the system (2.1), we have

$$I' \leq \beta\left[(I^\infty + \epsilon) + q(A^\infty + \epsilon)\right](S^\infty + \epsilon) - (\mu + \nu)I.$$

Then by the inequality (2.22) and the similar argument above, we obtain

(2.23)

$$I^\infty \leq \left[\frac{\beta\Lambda}{(\mu+\nu)(\mu + \psi - \psi\int_0^\infty w(a)\phi_0(a)da)}\right] I^\infty + \left[\frac{q\beta\Lambda}{(\mu+\nu)(\mu + \psi - \psi\int_0^\infty w(a)\phi_0(a)da)}\right] A^\infty.$$

Moreover by the third equation in the system (2.1), we have

$$A^\infty \leq \frac{\beta\psi S^\infty I^\infty \int_0^\infty \rho(a)\phi_0(a)da}{\mu}. \tag{2.24}$$

Substituting the equation (2.24) into the equation (2.23) and using the inequality (2.22), we obtain

$$\begin{aligned} I^\infty &\leq \left[\frac{\beta S_0}{(\mu+\nu)} + \frac{q\beta^2 S_0\int_0^\infty \rho(a)v_0(a)da}{(\mu+\nu)\mu}\right] I^\infty \\ &= \mathcal{R}_0 I^\infty. \end{aligned}$$

Then if $\mathcal{R}_0 < 1$, we have $I^\infty = 0$. It also implies $A^\infty = 0$.

□

2.2. **Disease Persistence.** In the presence of a disease, one would like to understand under what conditions the disease will remain endemic for large time. We say the disease is *uniformly weakly endemic* if there exists some $\epsilon > 0$ independent of the initial conditions such that

$$\limsup_{t\to\infty} I(t) > \epsilon, \text{ whenever } I(0) > 0,$$

for all solutions of the model. However the disease is *uniformly strongly endemic* if there exists some $\epsilon > 0$ independent of the initial conditions such that

$$\liminf_{t\to\infty} I(t) > \epsilon, \text{ whenever } I(0) > 0,$$

for all solutions of the model. In the following results, we identify the conditions that result in the prevalence being bounded away from zero.

Proposition 2.1. *If $\mathcal{R}_0 > 1$, then the disease is uniformly weakly endemic.*

Proof. By the way of contradiction, assume that there exists a solution $I(t)$, with $I(0) > 0$, such that

$$\limsup_{t\to\infty} I(t) \leq \epsilon_0,\ \forall\ \epsilon_0 > 0.$$

Fix $\epsilon_0 > 0$ and let $\epsilon_1 > 0$ be given. Then $\exists\ t_0 > 0$: $I(t) \leq \epsilon_0 + \epsilon_1,\ \forall\ t \geq t_0$. Consequently, the semiflow properties of a solution imply that without loss of generality, we have the above inequality valid for all $t \geq 0$.
Next note that

$$\int_0^\infty \rho(a)v(a,t) \leq K$$

for some positive real number K, since $\rho(a) \in [0,1]$ and $\limsup_{t\to\infty} N(t) \leq \dfrac{\Lambda}{\mu}$.

Then by the third equation of the system (2.1),

$$A' \leq \beta\epsilon_2 K - (\mu+\gamma)A, \tag{2.25}$$

with $\epsilon_2 = \epsilon_0 + \epsilon_1$. Then $\limsup_{t\to\infty} A(t) \leq \dfrac{\beta\epsilon_2 K}{(\mu+\gamma)}$. Hence by the inequality above, we have $A(t) \leq \dfrac{\beta\epsilon_2 K}{(\mu+\gamma)} + \delta_0$, for given $\delta_0 > 0$ and $\forall\ t \geq 0$, by **semigroup** property. Then $A(t),\ I(t) \leq \epsilon_3$, where $\epsilon_3 = \dfrac{\beta\epsilon_2 K}{(\mu+\gamma)} + \delta_0 + \epsilon_2,\ \forall\ t \geq 0$, by similar argument above. Let $\epsilon_4 = \epsilon_3 + q\epsilon_3$. Next by the first equation in the system (2.1), we obtain

$$\begin{aligned}
S' &\geq \Lambda - \epsilon_4 S - (\mu+\psi+\hat{c}\epsilon_2)S + \textstyle\int_0^\infty w(a)v(a,t)da,\\
&\geq \Lambda - \epsilon_4 S - (\mu+\psi+\hat{c}\epsilon_2)S + \textstyle\int_0^t w(a)e^{-\int_0^a [\rho(u)\beta\epsilon_2 + w(u) + \mu + \hat{c}\epsilon_2]du}(\psi S(t-a))da,\\
&\geq \Lambda - \epsilon_4 S - (\mu+\psi+\hat{c}\epsilon_2)S\\
&\qquad + (\liminf_{t\to\infty} S(t) - \epsilon_5)\psi \textstyle\int_0^t w(a)e^{-\int_0^a [\rho(u)\beta\epsilon_2 + w(u) + \mu + \hat{c}\epsilon_2]du}da,\\
&\geq \Lambda - \epsilon_4 S - (\mu+\psi+\hat{c}\epsilon_2)S\\
&\qquad + (\liminf_{t\to\infty} S(t) - \epsilon_5)\psi \left[\textstyle\int_0^\infty w(a)e^{-\int_0^a [\rho(u)\beta\epsilon_2 + w(u) + \mu + \hat{c}\epsilon_2]du}da - \delta_1\right],\\
&\geq \Lambda - \epsilon_4 S - (\mu+\psi+\hat{c}\epsilon_2)S\\
&\qquad + (\liminf_{t\to\infty} S(t) - \epsilon_5)\psi \left[\textstyle\int_0^\infty w(a)e^{-\int_0^a [\rho(u)\beta\epsilon_2 + w(u) + \mu + \hat{c}\epsilon_2]du}da - \delta_1\right].
\end{aligned}$$

Notice that we can choose $\delta_1,\ \epsilon_5$ as small as we want. Then

$$S' \geq \Lambda - \epsilon_4 S - (\mu+\psi+\hat{c}\epsilon_2)S + (\liminf_{t\to\infty} S(t))\psi\left[\int_0^\infty w(a)e^{-\int_0^a [\rho(u)\beta\epsilon_2 + w(u) + \mu + \hat{c}\epsilon_2]du}da\right].$$

For the inequality $x'(t) \geq a - bx(t)$, with positive constants $a,\ b$, we have $\liminf_{t\to\infty} x(t) \geq \dfrac{a}{b}$. Then by the inequality above, we obtain

$$\begin{aligned}
\liminf_{t\to\infty} S(t) &\geq \frac{\Lambda}{\epsilon_4 + (\mu+\psi+\hat{c}\epsilon_2) - \psi\int_0^\infty w(a)e^{-\int_0^a [\rho(u)\beta\epsilon_2 + w(u) + \mu + \hat{c}\epsilon_2]du}da}\\
&= S_0^{\epsilon_2}.
\end{aligned}$$

Note that ϵ_4 is a function of ϵ_2 and we can choose ϵ_2 as small as we want (as well as δ_0). By applying Dominated Convergence Theorem, we obtain $\lim_{\epsilon_2\to 0} S_0^{\epsilon_2} = S_0$. Therefore $\liminf_{t\to\infty} S(t) \geq S_0$. Hence for given $\epsilon_6 > 0$, $\exists\ t_1 :\ S(t) \geq S_0 - \epsilon_6,\ \forall\ t \geq t_1$. Again, by semigroup property, without loss of generality, the inequality above is valid for all $t > 0$. Next note that by the third and fourth equation in the system (2.1), we have

$$\begin{cases} A' \geq \psi\beta I \int_0^\infty \rho(a)\phi_0^{\epsilon_2}(a)(S_0-\epsilon_6)da - (\mu+\gamma)A, \\ I' \geq \beta I(S_0-\epsilon_6) + q\beta(S_0-\epsilon_6)A - (\mu+\nu)I, \end{cases} \tag{2.26}$$

where $\phi_0^{\epsilon_2} = e^{-\int_0^a [\rho(u)\beta\epsilon_2 + w(u) + \mu + \hat{c}\epsilon_2]du}$. We can write (2.26) in the following form:

$$\begin{bmatrix} A' \\ I' \end{bmatrix} \geq \begin{bmatrix} -(\mu+\gamma) & \psi\beta\int_0^\infty \rho(a)\phi_0^{\epsilon_2}(a)(S_0-\epsilon_6)da \\ q\beta(S_0-\epsilon_6) & \beta(S_0-\epsilon_6)-(\mu+\nu) \end{bmatrix} \begin{bmatrix} A \\ I \end{bmatrix}. \tag{2.27}$$

Let

$$M =: \begin{bmatrix} -(\mu+\gamma) & \psi\beta\int_0^\infty \rho(a)\phi_0^{\epsilon_2}(a)(S_0-\epsilon_6)da \\ q\beta(S_0-\epsilon_6) & \beta(S_0-\epsilon_6)-(\mu+\nu). \end{bmatrix} \tag{2.28}$$

We have

$$\det M = (\mu+\gamma)(\mu+\nu)\left[1-\mathcal{R}_0^{\epsilon_2}\right] + \epsilon_6\left[\beta(\mu+\gamma) + 2q\beta S_0\psi\beta\int_0^\infty \rho(a)\phi_0^{\epsilon_2}(a)da\right] - \epsilon_6^2\left[q\beta^2\psi\int_0^\infty \rho(a)\phi_0^{\epsilon_2}(a)da\right],$$

where

$$\mathcal{R}_0^{\epsilon_2} = \frac{\beta S_0}{(\mu+\nu)}\left[1 + \frac{q\beta S_0\psi\int_0^\infty \rho(a)\phi_0^{\epsilon_2}(a)da}{(\mu+\gamma)}\right]$$

and $\lim_{\epsilon_2\to 0}\mathcal{R}_0^{\epsilon_2} = \mathcal{R}_0$.
We can choose ϵ_6 as small as we want. Hence when $\mathcal{R}_0^{\epsilon_2} > 1$, we have $\det M < 0$. Then the matrix M has a positive eigenvalue λ, when $\mathcal{R}_0^{\epsilon_2} > 1$. The matrix M is a quasi-positive matrix. Then by Theorem A.43 [Thieme 2003, p.447], its spectral bound (modulus of stability) is an eigenvalue of M associated with a positive eigenvector of M, denoted by $\overrightarrow{V}$, with $\lambda > 0$ an eigenvalue of M. Then $c\overrightarrow{V}$, with a positive constant c, is also an eigenvector of M. Note that $e^{\lambda t}c\overrightarrow{V}$ is a solution of the system $y' = My$. Next taking the constant c sufficiently small, we get

$$c\overrightarrow{V} \leq \begin{bmatrix} A_0 \\ I_0 \end{bmatrix}.$$

Then by the Theorem B.1 [Smith & Waltman 2003, *p.* 261], we obtain

$$e^{\lambda t}c\overrightarrow{V} \leq \begin{bmatrix} A(t) \\ I(t) \end{bmatrix}.$$

for all $t > 0$. Note that left hand side of the inequality goes to infinity as $t \to \infty$, which also implies $A(t),\ I(t)$ go to infinity, as $t \to \infty$. This is a contradiction. □

3. Further Analysis of the Model: The ODE case

In the model (2.1), the waning rate $w(a)$ and the reduction in the susceptibility of vaccinated birds $\rho(a)$ depend on vaccination age a (the time passed post-vaccination). Even though in the avian influenza context, susceptibility of vaccinated birds depends on vaccination age a and vaccine type (for further information, see Introduction section), for the purpose of further analysis of the model (2.1), in this section, we assume waning rate and reduction in the susceptibility of vaccinated birds are constant; i.e. they do not depend on a. Let $\rho(a) = \rho$ and $w(a) = w$, for all $a \geq 0$. Recall that the number of vaccinated birds is $V(t)$ and

$$V(t) = \int_0^\infty v(a,t)da \tag{3.1}$$

Then under the assumptions $\rho(a) = \rho$ and $w(a) = w$ and from the equation (2.3), we obtain

$$\frac{dV}{dt} = \psi S + \gamma A - \rho\beta IV(t) - (\mu + w + \hat{c}I)V(t), \tag{3.2}$$

The resulting ODE model is as follows:

$$\begin{cases} \dfrac{dS}{dt} = \Lambda - \beta(I + qA)S - (\mu + \psi + cI)S + wV, \\ \dfrac{dV}{dt} = \psi S + \gamma A - \rho\beta IV - (\mu + w + \hat{c}I)V, \\ \dfrac{dA}{dt} = \rho\beta IV - (\mu + \gamma + \hat{c}I)A, \\ \dfrac{dI}{dt} = \beta(I + qA)S - (\mu + \nu + cI)I \end{cases} \tag{3.3}$$

The disease-free equilibrium of the ODE system is $\mathcal{E} = (S_0, V_0, 0, 0)$, where $S_0 = \dfrac{\Lambda(\mu + w)}{\mu(\mu + w + \psi)}$ and $V_0 = \dfrac{\Lambda\psi}{\mu(\mu + w + \psi)}$ and the reproduction number for this case is:

$$\mathcal{R}_0 = \frac{\beta S_0}{(\mu + \nu)} + \frac{\rho q \beta^2 S_0 V_0}{(\mu + \nu)(\mu + \gamma)}. \tag{3.4}$$

Notice that the ODE models are the specific case of PDE models. Therefore the results that hold for the PDE version of the model must also hold for the ODE case.

Theorem 3.1. *If $\mathcal{R}_0 < 1$, then the disease-free equilibrium of the system (3.3) is locally asymptotically stable.*

Proof. The proof of Theorem 2.1 also implies the local asymptotical stability of DFE when $\mathcal{R}_0 < 1$. □

In PDE case, it has been difficult to prove uniqueness of the endemic equilibrium without any simplifying assumption though we have shown existence. The following result gives uniqueness of endemic equilibrium in the ODE case.

Theorem 3.2. *If $\mathcal{R}_0 \leq 1$, then the system (3.3) does not have an endemic equilibrium. However, if $\mathcal{R}_0 > 1$, then there is a unique endemic equilibrium.*

Proof. An endemic equilibrium of the system (3.3) must satisfy the following equation system:

$$\begin{cases} 0= \Lambda - \beta(I+qA)S - (\mu+\psi+cI)S + wV, \\ 0= \psi S + \gamma A - \rho\beta IV - (\mu+w+\hat{c}I)V, \\ 0= \rho\beta IV - (\mu+\gamma+\hat{c}I)A, \\ 0= \beta(I+qA)S - (\mu+\nu+cI)I, \end{cases} \tag{3.5}$$

By the third equation in the system (3.5), we have

$$A = \frac{\rho\beta IV}{\mu+\gamma+\hat{c}I}. \tag{3.6}$$

After substituting the equation (3.6) into the second equation in (3.5), we get

$$\psi S = \left[\frac{-\gamma\rho\beta I}{\mu+\gamma+\hat{c}I} + \rho\beta I + \mu + w + \hat{c}I\right] V.$$

Hence

$$V = \frac{\psi S}{\dfrac{\mu+\hat{c}I}{\mu+\gamma+\hat{c}I}\rho\beta I + \mu + w + \hat{c}I} \tag{3.7}$$

By the fourth equation in the system (3.5), we have

$$\beta(I+qA)S = (\mu+\nu+cI)I \tag{3.8}$$

Substituting the equations (3.7) and (3.8) into the first equation in the system (3.5), we obtain

$$\Lambda - (\mu+\nu+cI)I = [\mu+\psi+cI-\psi f(I)]\, S, \tag{3.9}$$

where

$$f(I) = \frac{w}{\dfrac{\mu+\hat{c}I}{\mu+\gamma+\hat{c}I}\rho\beta I + \mu + w + \hat{c}I}.$$

Then

$$S = \frac{\Lambda - (\mu+\nu+cI)I}{\mu+\psi+cI-\psi f(I)} \tag{3.10}$$

Note that $f(I) \in [0,1]$ and it is a decreasing function of I. Hence S is also a nonnegative decreasing function of I for all I, for which $S \geq 0$ (3.10). After substituting (3.6), (3.7), (3.10) into the last equation of the system (3.5) and canceling I from both sides of the equation, we get the following equality:

$$\beta\left[1 + \frac{q\rho\beta}{\mu+\gamma+\hat{c}I}\frac{\psi S}{\dfrac{\mu+\hat{c}I}{\mu+\gamma+\hat{c}I}\rho\beta I + \mu + w + \hat{c}I}\right] S = (\mu+\nu+cI) \tag{3.11}$$

Let $F(I)$ and $G(I)$ be the left and right hand side of the equation (3.11), respectively. Recall that S is a decreasing function of I, $\forall I > 0 : S = S(I) \geq 0$. Hence $F(I)$ is a decreasing function of I. Also note that $G(I)$ is increasing linearly respect to I. Then if

these functions intersect, they must intersect at a unique positive point I.
The endemic equilibrium of the system (3.3) is the constant solution of this system with at least one positive infected component. Hence the intersection point $I > 0$ of the functions $F(I)$ and $G(I)$ is the endemic equilibrium of this system. This system has an equilibrium in R^4_+ with positive infected component $I > 0$ if and only if $F(0) > G(0)$. Notice that $F(0) > G(0)$ if and only if $\mathcal{R}_0 > 1$, where

$$F(0) = \beta\left[1 + \frac{q\rho\beta}{(\mu+\gamma)}\frac{\psi\Lambda}{\mu(\mu+w+\psi)}\right]\frac{\Lambda(\mu+w)}{\mu(\mu+w+\psi)} \qquad = \beta S_0\left[1 + \frac{q\rho\beta}{(\mu+\gamma)}V_0\right]$$

and

$$G(0) = \mu + \nu.$$

□

3.0.1. *The ODE model does not exhibit backward bifurcation.* Vaccination models can exhibit backward bifurcation due to mechanisms such as reinfection, vaccine induced immune waning, vaccine failure, host's disease induced mortality, multiple susceptible groups and host susceptibility after recovery [7, 22, 21]. It seems that our model has these mechanisms. However Theorem (3.2) excludes the existence of backward bifurcation; i.e existence of stable and unstable endemic equilibria when $\mathcal{R}_0 < 1$. The absence of backward bifurcation in this model can be explained with the following argument: The model (3.3) has two susceptible compartments: Susceptible (S) and Vaccinated (V). However in contrast to all vaccination models that exhibit backward bifurcation, the model has multiple infected compartments: Asymptomatic (A) and Infected (I). When susceptible poultry get infected they move to the infected compartment and when vaccinated birds get infected, they become asymptomatically infected. The model does not assume that asymptomatically infected birds move to the infected class. It basically distributes the newly infected individuals to different infected compartments. Therefore the infected individuals do not accumulate in one infected compartment, and this mechanism may exclude the possibility of backward bifurcation.

Even though the non-existence of endemic equilibria when $\mathcal{R}_0 < 1$ is shown in the ODE case, model (3.3), we can only prove global stability of DFE when $\gamma = 0$, as in the general case (Theorem 2.3). The question of global stability of DFE when $\mathcal{R}_0 < 1$ and $\gamma > 0$ seems to be much more difficult. We have attempted proof using comparison arguments, and also standard Lyapunov functions, but the result could not be established when $\gamma > 0$. Thus, the question of global stability of DFE when $\gamma > 0$ and $\mathcal{R}_0 < 1$ remains open, and we cannot rule out oscillations in this case.

The following theorem proves local stability of the endemic equilibrium when $\mathcal{R}_0 > 1$ for a special case of the ODE model (3.3).

Theorem 3.3. *Let $\nu = 0$. Then in the absence of culling; i.e. $c = \hat{c} = 0$, the unique endemic equilibrium of the system (3.3) is locally asymptotically stable when $\mathcal{R}_0 > 1$.*

Proof. Assume $c = \hat{c} = 0$. Then we can analyze the local stability of the unique endemic equilibrium $\mathcal{E}^* = (S^*, V^*, A^*, I^*)$ by investigating the sign of the real part of the

eigenvalues of the the Jocabian matrix $J|_{\mathcal{E}^*}$ of the ODE system evaluated at $\mathcal{E}^*$:

$$J|_{\mathcal{E}^*} = \begin{pmatrix} -\beta(I^* + qA^*) - (\mu + \psi) & w & -q\beta S^* & -\beta S^* \\ \psi & -\rho\beta I^* - (\mu + w) & \gamma & -\rho\beta V^* \\ 0 & \rho\beta I^* & -(\mu + \gamma) & \rho\beta V^* \\ \beta(I^* + qA^*) & 0 & q\beta S^* & \beta S^* - (\mu + \nu) \end{pmatrix}$$

Let $\nu = 0$ and define $M^* := J - \lambda I|_{\mathcal{E}^*}$. Then

$$\det(M^*) = \begin{vmatrix} -\beta(I^* + qA^*) - (\mu + \psi) - \lambda & w & -q\beta S^* & -\beta S^* \\ \psi & -\rho\beta I^* - (\mu + w) - \lambda & \gamma & -\rho\beta V^* \\ 0 & \rho\beta I^* & -(\mu + \gamma) - \lambda & \rho\beta V^* \\ \beta(I^* + qA^*) & 0 & q\beta S^* & \beta S^* - \mu - \lambda \end{vmatrix}$$

(by the row operations: $R_1 + R_4 \mapsto R_1$ and $R_2 + R_3 \mapsto R_2$)

$$= \begin{vmatrix} -(\mu + \psi + \lambda) & w & 0 & -(\mu + \lambda) \\ \psi & -(\mu + w + \lambda) & -(\mu + \lambda) & 0 \\ 0 & \rho\beta I^* & -(\mu + \gamma + \lambda) & \rho\beta V^* \\ \beta(I^* + qA^*) & 0 & q\beta S^* & \beta S^* - (\mu + \lambda) \end{vmatrix}$$

(by the row operation: $R_1 + R_2 \mapsto R_1$)

$$= -(\mu + \lambda) \begin{vmatrix} 1 & 1 & 1 & 1 \\ \psi & -(\mu + w + \lambda) & -(\mu + \lambda) & 0 \\ 0 & \rho\beta I^* & -(\mu + \gamma + \lambda) & \rho\beta V^* \\ \beta(I^* + qA^*) & 0 & q\beta S^* & \beta S^* - (\mu + \lambda) \end{vmatrix}$$

Finally by the column operations $(-1).C_1 + C_i \mapsto C_i$, where $i = 2, 3, 4$, we obtain

$$\det(M^*) = -(\mu + \lambda) \det(N^*),$$

where

$$N = \begin{pmatrix} 1 & 0 & 0 & 0 \\ \psi & -(\mu + w + \psi + \lambda) & -(\mu + \psi + \lambda) & -\psi \\ 0 & \rho\beta I^* & -(\mu + \gamma + \lambda) & \rho\beta V^* \\ \beta(I^* + qA^*) & -\beta(I^* + qA^*) & -\beta(I^* + qA^*) + q\beta S^* & \beta S^* - \beta(I^* + qA^*) - (\mu + \lambda) \end{pmatrix}$$

Then we obtain the following characteristic equation $F(\lambda)$:

$$F(\lambda) = -(\mu + \lambda)(a_3\lambda^3 + a_2\lambda^2 + a_1\lambda + a_0) = 0,$$

where

$a_3 = 1,$

$a_2 = (\mu + \gamma + \mu + w + \psi + \beta(I + qA) + (\mu - \beta S) + \rho\beta I),$

$$a_1 = (\mu + \gamma + \mu + w)(\beta(I + qA) + (\mu - \beta S)) + \psi(\mu - \beta S) + (\mu + w + \psi)(\mu + \gamma) + \rho\beta I(\mu + \psi) + \rho\beta I(\beta(I + qA) + (\mu - \beta S)) - \rho\beta V q\beta S,$$

$$a_0 = (\mu + w)(\mu + \gamma)(\beta(I + qA) + (\mu - \beta S)) + \psi(\mu + \gamma)(\mu - \beta S) + \psi\rho\beta I q\beta S$$
$$+ \rho\beta I\mu(\beta(I + qA) + (\mu - \beta S)) + \rho\beta I\psi(\mu - \beta S)$$
$$- \rho\beta V q\beta S(\mu + w + \psi) + \rho w\beta V\beta(I + qA).$$

By the equilibrium condition derived from the last equation in (3.5), we obtain

$$(\mu - \beta S)I = q\beta AS > 0. \tag{3.12}$$

Also by multiplying both side of the third equation in (3.5) with $q\beta S$ and **dividing by** I, we get

$$-\rho\beta V q\beta S = -(\mu + \gamma)\beta S\frac{qA}{I}. \tag{3.13}$$

Then by the equation (3.12), we have

$$-\rho\beta V q\beta S = -(\mu + \gamma)(\mu - \beta S). \tag{3.14}$$

Now we will show that $a_i > 0$ for all $i \in \{0, 1, 2, 3\}$. By the equation (3.14), we have

$$a_1 = (\mu+\gamma)\beta(I+qA)+(\mu+w)(\beta(I+qA)+(\mu-\beta S))+\psi(\mu-\beta S)+(\mu+w+\psi)(\mu+\gamma)$$
$$+\rho\beta I(\mu + \psi) + \rho\beta I(\beta(I + qA) + (\mu - \beta S)),$$
$$a_0 = (\mu + w)(\mu + \gamma)\beta(I + qA) + \psi\rho\beta I q\beta S$$
$$+\rho\beta I\mu(\beta(I + qA) + (\mu - \beta S)) + \rho\beta I\psi(\mu - \beta S) + \rho w\beta V\beta(I + qA).$$

Notice that by (3.12), we have $(\mu - \beta S) > 0$. Then $\forall\ i \in \{0, 1, 2, 3\}$, we have $a_i > 0$. Now we want to show $a_2a_1 > a_3a_0$. (2nd condition for Routh-Hurwitz Stability Criterion)

By the equation (3.7), we have $V < \dfrac{\psi S}{w}$. Then by the last equality in the system 3.5, we obtain

$$\rho w\beta V\beta(I + qA) < \rho\beta\psi\mu I < \mu\psi\beta I. \tag{3.15}$$

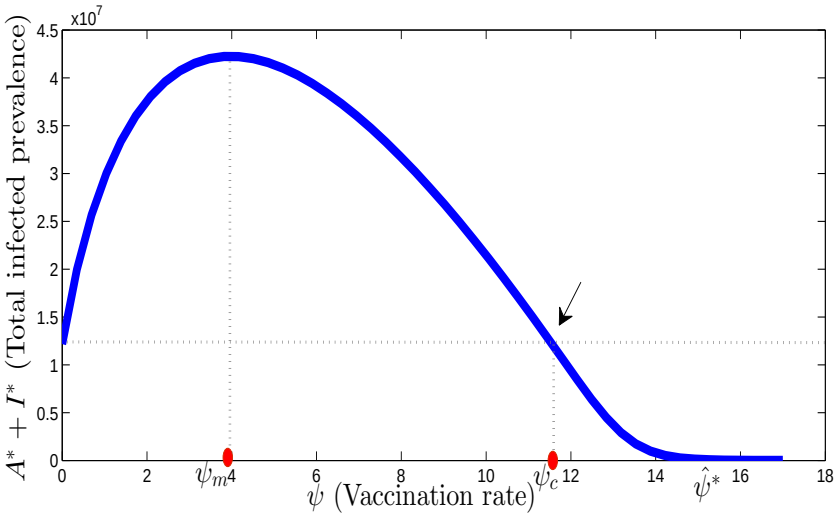
Then
$a_0 < (\mu + w)(\mu + \gamma)\beta(I + qA) + \psi\rho\beta I q\beta S + \rho\beta I\mu(\beta(I + qA) + (\mu - \beta S)) + \rho\beta I\psi(\mu - \beta S) + \mu\psi\beta I$.
Let us define the right hand side of the inequality above as $\widetilde{a}_0$. Then $a_0 < \widetilde{a_0}$. Also it is easy to see that $a_1a_2 - \widetilde{a}_0a_3 > 0$. Then $a_1a_2 - a_0a_3 > 0$. Then by Routh-Hurwitz stability criterion, the endemic equilibrium is locally asymptotically stable whenever the endemic equilibrium exists.

□

4. Asymptomatic Spread caused by Vaccination

Vaccination of poultry has been employed in many regions. However the outbreaks have continued to occur without clear understanding of the mechanisms involved [16, 17]. One of the main objectives of this study is to understand the epidemiology of $H5N1$

a)



b)

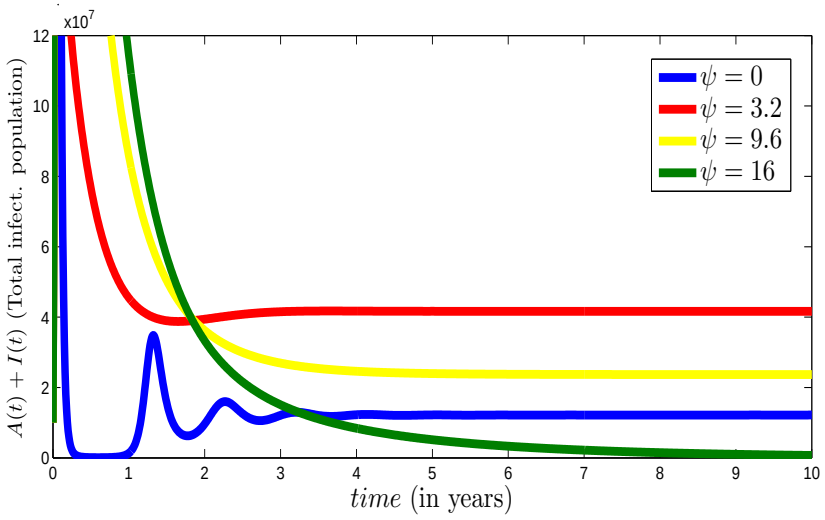


FIGURE 2. a)The total infected and asymptomatic equilibrium with respect to varying vaccination rate ψ. Parameter values are: $\Lambda = 120,\ \mu = 0.5,\ \beta = 1,\ \nu = 365/10,\ \rho = 0.4,\ \gamma = 0.5, q = 0.3, w = 1, c = 1.5, \hat{c} = 1.4$. The initial values are: $S(0) = \Lambda/\mu,\ V(0) = 0,\ A(0) = 0,\ I(0) = 10$. The units for state variables are taken to be 10^7 *birds* in order to reflect the world population of the poultry. b)The total number of infected and asymptomatic birds with respect to time (years) for different vaccination rate values ψ. Parameter values are identical with the parameter values in part (a). Solutions are taken with respect to different ψ values: $\psi = 0$ (blue), $\psi = 3.2$ (red), $\psi = 9.6$ (yellow), $\psi = 16$ (green).

HPAI disease in the context of vaccination and to draw some conclusions about mechanisms causing asymptomatic spread of the virus in domestic bird populations. In this section, under certain simplifications, we derive an explicit condition for asymptomatic spread in poultry population.

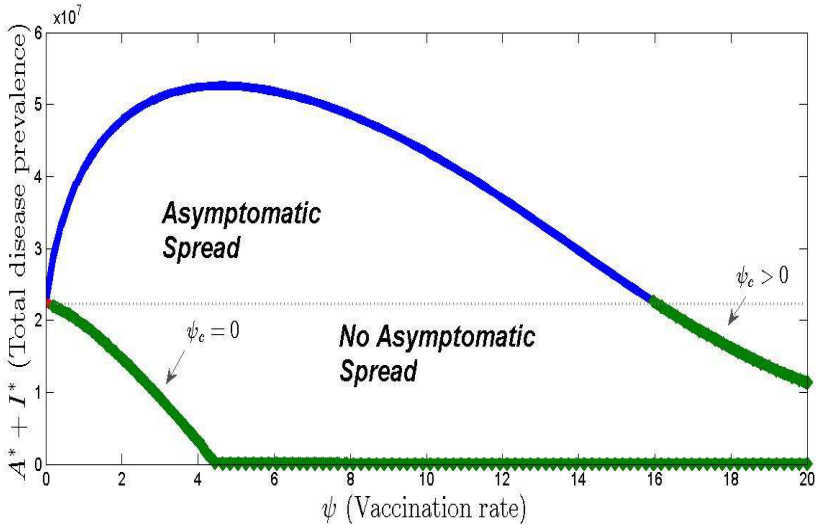


FIGURE 3. In this figure, y-axis shows total disease prevalence $A^* + I^*$ and the x-axis shows vaccination rate ψ. The initial and parameter values are identical to Fig.(2). The different parameter values chosen are: $c = 0.5$, $c1 = 0.1$, $w = 0$, $q = 0$, $\rho = 0.05$. Also for the blue curve, the recovery rate is chosen as $\gamma = 0$ and for the other one, $\gamma = 6$.

4.1. **Derivation under simplifying assumptions.** In this subsection, we will assume that the reduction in infectiousness of asymptomatic birds (q), waning rate w and culling rates $c, \hat{c}$ to be 0. Recall that in the previous section, we showed that when $\mathcal{R}_0(\psi) > 1$, the system (3.3) has a unique endemic equilibrium (S^*, V^*, A^*, I^*); otherwise there is no endemic equilibrium (Theorem 3.2). Under the given simplification, we have

$$\mathcal{R}_0(\psi) = \frac{\beta\Lambda}{(\mu+\nu)(\mu+\psi)}. \tag{4.1}$$

By the last equation in the system (3.5) and under simplifying assumptions, we also obtain $S^* = \dfrac{(\mu+\nu)}{\beta}$. Similarly, by the first equation, we get $S^* = \dfrac{\Lambda}{(\beta I^* + \mu + \psi)}$. By the equality of both equations, we obtain infected equilibrium I^*:

$$I^* = \frac{(\mu+\psi)}{\beta}\left[\mathcal{R}_0(\psi) - 1\right]. \tag{4.2}$$

$\mathcal{R}_0(\psi)$ given by (4.1) is a decreasing function of vaccination rate ψ. By the equation (4.2), we have a critical value $\hat{\psi}^* = \mu(\mathcal{R}_0(0) - 1)$:

$$I^* > 0 \text{ if and only if } \psi \in (0, \hat{\psi}^*) \text{ if and only if } \mathcal{R}_0(\psi) > 1. \tag{4.3}$$

If $\psi \in (0, \hat{\psi}^*)$, then we have the unique endemic equilibrium (S^*, V^*, A^*, I^*), where

$$S^* = \frac{\Lambda}{\beta I^* + \mu + \psi},\ V^* = \frac{\psi S^* + \gamma A^*}{\rho\beta I^* + \mu},\ A^* = \frac{\rho\beta I^* \psi\Lambda}{\mu(\rho\beta I^* + \mu + \gamma)(\beta I^* + \mu + \psi)}, \tag{4.4}$$

with I^* given by (4.2). Notice that the total infected and asymptomatic equilibrium $A^* + I^*$ is differentiable $\forall\ \psi\ \in [0, \infty)$ and $A^* + I^*$ is positive only on the interval $[0, \hat{\psi}^*)$. The next theorem gives a necessary and sufficient condition for existence of a threshold vaccination rate value ψ_m, in which case if $\psi < \psi_m$, then the total disease prevalence increases and it decreases when $\psi > \psi_m$.

Theorem 4.1. *Let $\mathcal{R}_0(\psi) > 1$, where $\mathcal{R}_0(\psi)$ is given by (4.1). If*

$$\mathcal{R}_0(0) > \frac{\mu + \gamma}{\rho\nu} + 1, \tag{4.5}$$

then $A^* + I^*$ has a unique local maximum on the interval $(0, \hat{\psi}^*)$. Otherwise $A^* + I^*$ is a non-increasing function of ψ on the interval $(0, \hat{\psi}^*)$, when $\mathcal{R}_0(\psi) > 1$.

Proof. First note that

$$\frac{\partial I^*}{\partial \psi} = \frac{-1}{\beta}. \tag{4.6}$$

Hence it is a decreasing function of ψ, whenever it exists (i.e. $\mathcal{R}_0(\psi) > 1$).

Claim 4.1. *Let $\mathcal{R}_0(\psi) > 1$. Then A^* has a unique local maximum on the interval $(0, \hat{\psi}^*)$.*

Proof. Notice that A^*, which is given in (4.4) is a differentiable function of ψ. Taking the derivative of A^* respect to the vaccination rate ψ, we obtain

$$\frac{\partial A^*}{\partial \psi} = \Lambda\rho\beta\mu \left[(I^* + \psi\frac{\partial I^*}{\partial \psi})(\rho\beta I^* + \mu + \gamma) - \psi I^* \rho\beta \frac{\partial I^*}{\partial \psi} \right] \frac{1}{[(\rho\beta I^* + \mu + \gamma)^2 \mu^2 (\beta I^* + \mu + \psi)]},$$

Then whenever $\mathcal{R}_0(\psi) > 1$, by (4.2) and (4.6), we have

$$\frac{\partial A^*}{\partial \psi}|_{\psi=0} > 0.$$

Next, we want to show that $A^*(\psi)$ has a unique local maximum on the interval $(0, \hat{\psi}^*)$.

$$\frac{\partial A^*}{\partial \psi} = 0 \Leftrightarrow \left[(I^* + \psi\frac{\partial I^*}{\partial \psi})(\rho\beta I^* + \mu + \gamma) - \psi I^* \rho\beta \frac{\partial I^*}{\partial \psi} \right] = 0.$$

By substituting I^* given by (4.2) in the equation above, we obtain the following quadratic equation of ψ:

$$\psi^2 A + \psi B + C = 0,$$

where $A = \rho(\mu+\nu)^2,\ B = 2\mu A \left[1 - \mathcal{R}_0(0) - \frac{(\mu+\gamma)}{\rho\mu} \right],\ C = \frac{\mu B}{2} \left[1 - \mathcal{R}_0(0) \right]$. The roots of this equation are

$$\psi_{1,2} = \frac{(\mu+\gamma)}{\rho} \left[(1 + \frac{\rho\hat{\psi}^*}{(\mu+\gamma)}) \mp \sqrt{1 + \frac{\rho\hat{\psi}^*}{(\mu+\gamma)}} \right] = \left[\frac{(\mu+\gamma)}{\rho} + \hat{\psi}^* \mp \frac{(\mu+\gamma)}{\rho} \sqrt{1 + \frac{\rho\hat{\psi}^*}{(\mu+\gamma)}} \right]$$

Then, A^* has a unique local maximum at

$$\psi_1 = \left[\frac{(\mu+\gamma)}{\rho} + \hat{\psi}^* - \frac{(\mu+\gamma)}{\rho} \sqrt{1 + \frac{\rho\hat{\psi}^*}{(\mu+\gamma)}} \right] \tag{4.7}$$

on the interval $(0, \hat{\psi}^*)$ since $\psi_2 > \hat{\psi}^*$ ($\psi_2 \notin (0, \hat{\psi}^*)$). Recall that $I^*, A^* > 0$ if and only if $\psi \in (0, \hat{\psi}^*)$. □

In addition, we have

$$\frac{\partial A^*}{\partial \psi} + \frac{\partial I^*}{\partial \psi}|_{\psi=0} = [\rho\mu(\mathcal{R}_0(0) - 1) + \mu + \gamma]\, \mu^2 \mathcal{R}_0(0)\, [\nu\rho(\mathcal{R}_0(0) - 1) - (\mu + \gamma)]$$

Then when $\mathcal{R}_0(\psi) > 1$, we obtain

$$\frac{\partial A^*}{\partial \psi} + \frac{\partial I^*}{\partial \psi}|_{\psi=0} > 0 \Leftrightarrow [\nu\rho(\mathcal{R}_0(0) - 1) - (\mu + \gamma)] > 0$$

Notice that $\lim_{\psi\to\infty} A^* + I^* = 0$. Then the last two argument imply that the function $A^* + I^*$ has a local maximum under the condition

$$\mathcal{R}_0(0) > \frac{\mu + \gamma}{\rho\nu} + 1.$$

In fact it has a unique local maximum by the fact that I^* is a linearly decreasing function of ψ on the interval given and A^*, which is a differentiable function of ψ on the interval $\left[0, \hat{\psi}^*\right]$, has unique local maximum on the same interval. □

When the recovery rate of asymptomatically infected birds is sufficiently small, increasing vaccination rate can actually increase the total disease prevalence, which we call *asymptomatic spread* (4.5). One way to see the reasoning behind this fact is that an extended infectious period in asymptomatically infected birds, i.e. small value of γ due to lower virulence, leads to an accumulation of asymptomatically infected birds. A larger value of γ (faster recovery) will decrease this effect, and for sufficiently large γ, there will not be any asymptomatic spread. We also observe from condition (4.5) that decreasing the value of ρ (reduction in the susceptibility of vaccinated birds), reduces the likelihood of asymptomatic spread. If ρ is sufficiently small, then the total disease prevalence decreases as vaccination rate ψ increases; i.e. vaccination reduces the total disease prevalence. The parameter ρ can be interpreted as the efficacy of the vaccine in preventing infection, with $\rho = 0$ implying complete protection against infection and $\rho = 1$ being the case in which the vaccine has no effect on preventing infection (but it does protect against the severity of infection; in the model, vaccinated birds can only get asymptomatic infection). In the next section we will conduct a deeper analysis on how vaccine efficacy impacts the success of the vaccination program.

Observe in Figure 2(a) that the total disease prevalence keeps increasing as the vaccination rate ψ increases until ψ_m. However, it starts to decrease with respect to vaccination rate ψ once ψ becomes larger than ψ_m. The Figure 2(b) shows the solutions for the total asymptomatically infected and infected bird populations versus time. In the absence of vaccination ($\psi = 0$), the total asymptomatic and infected bird population converges to a low level endemic equilibrium in time. As vaccination rate ψ keeps increasing to $\psi_m = 4.1$, the total disease prevalence also continues to increase. When $\psi = 16$, then the total infected solution eventually decreases and goes to zero; i.e. the disease dies out. Estimates of the parameters Λ, μ, and ν are derived in [18, 23]. In order to consider a country poultry population instead of the world poultry population, we alter the value of Λ compared to the values in [18, 23]. The transmission rate β is chosen in order to have a reasonable reproduction number $\mathcal{R}_0$. For the rest of the

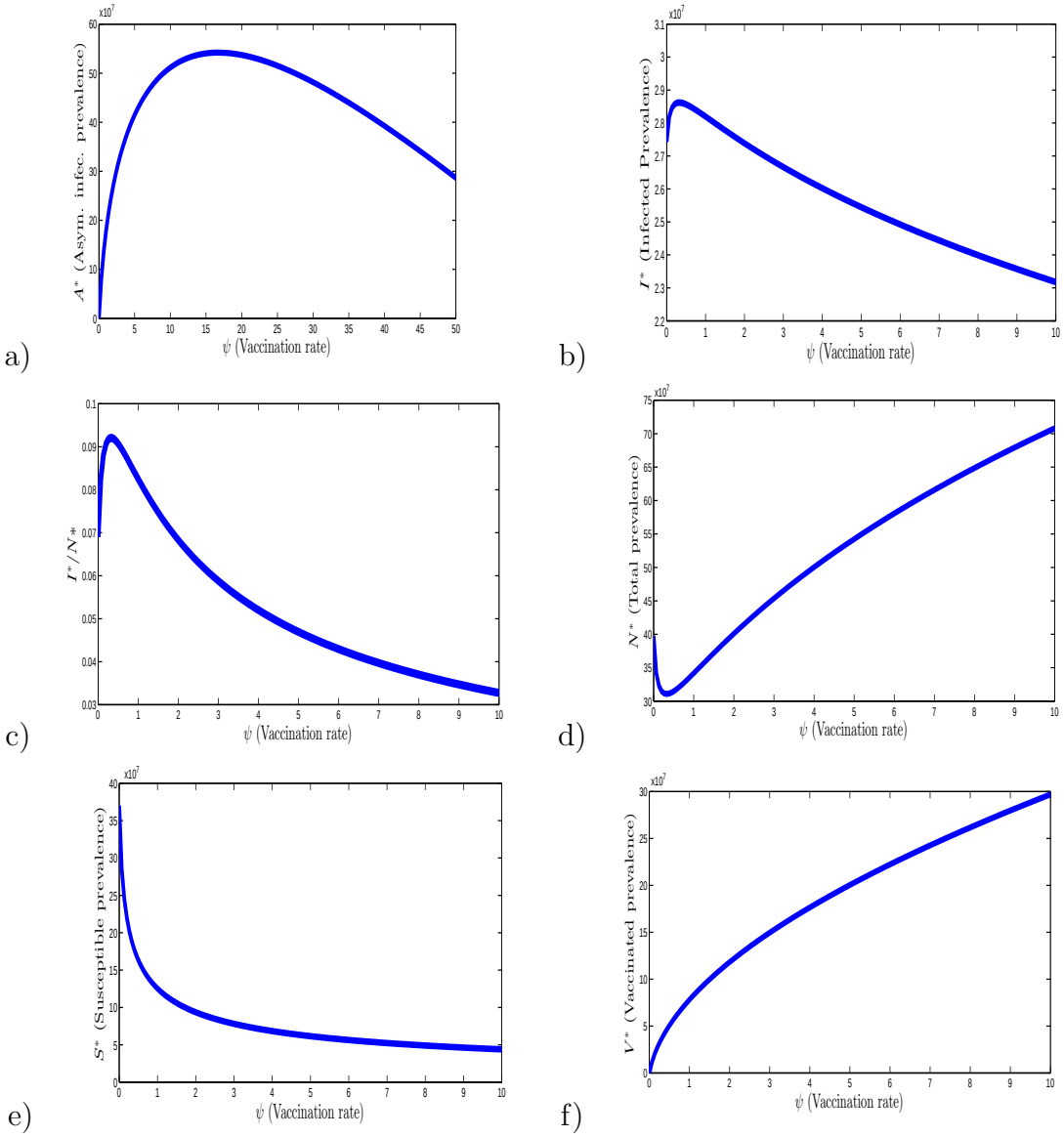


FIGURE 4. Each subfigure shows the disease prevalence (or the fraction I^*/N^*) versus vaccination rate ψ. The common parameter values considered for all subfigures are: $\Lambda = 120,\ \mu = 0.5,\ \beta = 1,\ \nu = 365/10,\ c = 0,\ \hat{c} = 0,\ w = 0.4,\ q = 0.5,\ \rho = 0.5,\ \gamma = 0.5$. The initial values are: $S(0) = \Lambda/\mu,\ V(0) = 0,\ A(0) = 0,\ I(0) = 10$. a)Asymptomatic disease prevalence (A^*)versus vaccination rate ψ. (The only parameter value, which is different than given above is $q = 0.1$) b)Infected disease prevalence (I^*) versus vaccination rate ψ. c)The fraction I^*/N^* versus vaccination rate ψ. d)Total prevalence (N^*) versus vaccination rate ψ. e)Susceptible prevalence (S^*) versus vaccination rate ψ. f)Vaccinated prevalence (V^*) versus vaccination rate ψ.

parameter values, there is insufficient information, and these parameter values will be varied in the simulations.

Analytical and numerical results suggest that even though the prevalence decreases when $\psi > \psi_m$, the prevalence at ψ, where $\psi > \psi_m$, can still be higher than the prevalence in the absence of vaccination; i.e. when $\psi = 0$. It can be seen in Figure 3. In the next section, we will introduce another threshold, namely critical vaccination rate ψ_c, where $(A*+I^*)(\psi) < (A*+I^*)(0)$, when $\psi > \psi_c$ and $(A*+I^*)(\psi) > (A*+I^*)(0)$, when $\psi < \psi_c$.

Numerical results displayed in Figure 4 suggest that in the case of $q > 0$ (asymptomatically infected birds are infectious), if the vaccination rate ψ is not sufficiently large, then $I^*(\psi) > I^*(0)$, i.e. the prevalence of (symptomatic) infected birds obtained with vaccination rate ψ is higher than the prevalence with no vaccination. This increase in infected prevalence can be attributed to the longer infectious period of asymptomatic birds when compared with infected birds, which can die in a short time period (usually within two days of symptom onset), and that the low vaccination coverage allows asymptomatic infected birds to circulate in a relatively large susceptible bird population and cause more infection. However, larger vaccination coverage reduces the amount of the susceptible birds, which are the only class that asymptomatic birds can infect, and I^* decreases below the level obtained with no vaccination. Thus, it is crucial for vaccination coverage to be sufficiently high in order to reduce the number of infected birds. We can observe it from Fig 4(b). Low vaccination coverage also leads to an increase in the proportion of infected in the population at equilibrium, I^*/N^*. However $H5N1$ HPAI virus has a high mortality rate, in which case the increase in the infected bird population decreases the total population size N^*. This can be observed in Fig. 4(c) and in Fig. 4(d).

Despite the fact that asymptomatic birds are less infectious than infected birds, they still pose a significant threat and can lead to the "silent spread" of the disease. Asymptomatically infected birds are difficult to detect and may provide a reservoir for the virus which can cause an outbreak. Thus, it is important to quantify the total number of infected - asymptomatic and (symptomatic) infected - when evaluating a vaccination program. For mathematical models with vaccination, of primary interest has been to assess the potential impact of vaccination program on disease dynamics. R. Smith and S. Blower [19] and Gumel et al. [20] studied HIV vaccination models and addressed perverse outcomes of HIV imperfect vaccination in population-level. They focused on mechanisms that causes an increase in the reproduction number $\mathcal{R}_0(\psi)$. The reproduction number $\mathcal{R}_0(\psi)$ provides an important descriptor of the disease dynamics and the effects of the parameters on $\mathcal{R}_0(\psi)$ can be readily calculated, as we will do for our model in Section 5.4. However, notice that (4.1) and Theorem 4.1 imply that under certain conditions, $\mathcal{R}_0(\psi)$ is a decreasing function of ψ, but $A^* + I^*$ increases with ψ. So our study suggests that reduction in reproduction number due to vaccination may not rule out a possible increase in total disease prevalence $A^* + I^*$. Therefore, investigation of the potential positive and negative outcomes of a vaccination program in the population may require more rigorous arguments than solely considering the reproduction number in order to find possible "silent" reservoirs of the virus in the form of asymptomatic infection.

5. Epidemiological Implications: Vaccine Efficacy and Critical Vaccination Coverage

5.1. **Vaccine Efficacy.** Vaccine efficacy in individual birds can be quantified by the following three parameters: the degree of reduction in susceptibility of vaccinated birds (ρ), the degree of reduction of morbidity and mortality given infection occured ($\gamma,\ \nu$) and the level of reduction in virus shed by infected poultry (q) [14]. In the model (2.1), the parameter q ranges between 0 and 1 and $q = 0$ implies that asymptomatic birds are not **infectious at all, while** $q = 1$ indicates that asymptomatic birds are as infectious as infected birds. The reduction parameter $\rho(a) = 0$ can be interpreted in an analogous way with susceptibility of vaccinated birds to asymptomatic infection.

Vaccine efficacy is an important consideration for the control of AI in poultry [12]. In the previous section, under certain simplifications: $w = q = 0$ and $c = \hat{c} = 0$, we derived a condition (4.5), which suggests that low vaccine efficacy may cause asymptomatic spread of the disease. In this section, we will first derive the minimum critical vaccination coverage and later, in the rest of this section through numerical simulations of the model, we will show how the quantities addressing vaccine efficacy can affect the critical vaccination rate and disease prevalence.

5.2. **Derivation of critical vaccination rate.** In the presence of vaccination, the reproduction number $\mathcal{R}_0(\psi)$ and the total disease prevalence $A^*(\psi) + I^*(\psi)$ depend on the vaccination rate ψ. Under certain conditions, analytical results in section 4.1 suggest that if $\mathcal{R}_0(0) > 1 + \frac{(\mu+\gamma)}{\rho\nu}$, then the total disease prevalence $A^*(\psi) + I^*(\psi)$ is greater than $A^*(0) + I^*(0)$ for some $\psi \in \left(0, \hat{\psi}^*\right)$ (in this interval $\mathcal{R}_0(\psi) > 1$, otherwise $\mathcal{R}_0(\psi) \leq 1$) and have a unique local maximum at $\psi_m \in \left(0, \hat{\psi}^*\right)$. $A^*(0) + I^*(0)$ denotes the disease prevalence in the absence of vaccination when $\mathcal{R}_0(0) > 1$. The critical vaccination rate is given by the vaccination rate ψ_c, which satisfies $(A^* + I^*)(\psi) < (A^* + I^*)(0)$ for all $\psi > \psi_c$ and $(A^* + I^*)(\psi) > (A^* + I^*)(0)$ if $\psi \in [0, \psi_c)$. To find critical vaccination rate ψ_c, we set the following equality:

$$(A^* + I^*)(\psi_c) = (A^* + I^*)(0). \tag{5.1}$$

By the equalities (4.1), (4.2), (4.4), we have

$$A^*(\psi_c) + I^*(\psi_c) = \frac{\rho\Lambda\psi_c\left(\mu(\mathcal{R}_0(0) - 1) - \psi_c\right)}{\mu^2\mathcal{R}_0(0)\left[\rho\mu(\mathcal{R}_0(0) - 1) - \rho\psi_c + \mu + \gamma\right]} + \frac{\mu(\mathcal{R}_0 - 1) - \psi_c}{\beta} \tag{5.2}$$

and

$$A^*(0) + I^*(0) = \frac{\mu(\mathcal{R}_0(0) - 1)}{\beta} \tag{5.3}$$

By (5.1), (5.2) and (5.3), we obtain a quadratic polynomial of ψ_c with roots:

$$\psi_c = 0 \text{ and } \psi_c = \mu(\mathcal{R}_0(0) - (1 + \frac{(\mu + \gamma)}{\rho\nu})).$$

Then the critical vaccination rate is as follows:

$$\psi_c = \mu(\mathcal{R}_0(0) - (1 + \frac{(\mu + \gamma)}{\rho\nu})). \tag{5.4}$$

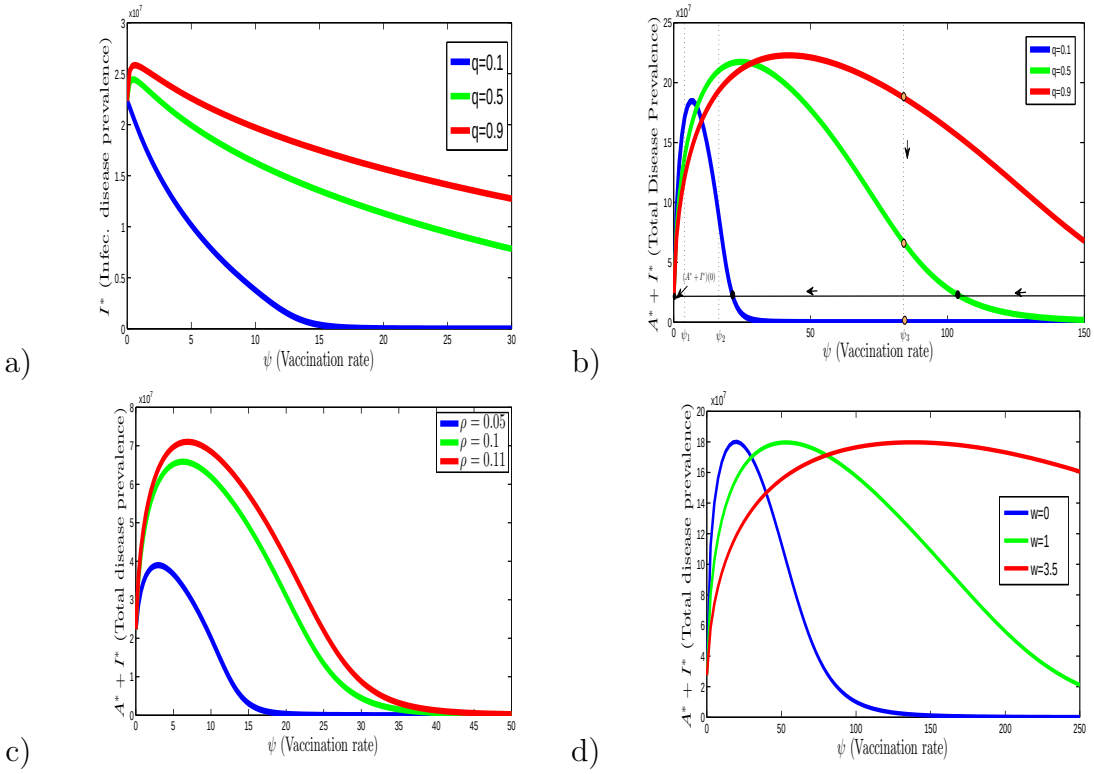


FIGURE 5. In this figure, y axis is as noted and the x-axis shows vaccination rate ψ. In each figure, only one vaccine efficacy parameter (ρ, γ, w, q) is varied to see how the quantities addressing vaccine efficacy changes the total or only infected disease prevalence with respect to increasing vaccination rate. For all figures, fixed parameter values are: $\Lambda = 120$, $\mu = 0.5$, $\beta = 1$, $\nu = 365/10$, $c = 0.5$, $\hat{c} = 0.1$. a) Here, the value of the vaccine efficacy parameter q(the reduction in infectiousness of asymp. infected birds) is varied as $q = 0.1,\ 0.5,\ 0.9$. The other parameters are fixed as: $w = 0$, $\rho = 0.5$, $\gamma = 0.5$. b)Similar to part (a) the efficacy parameter q is varied with the identical parameter values above (part (a)) in $A^* + I^*$. c) The efficacy parameter ρ (the reduction in susceptibility of vaccinated birds) values are taken as $\rho = 0.05,\ 0.1,\ 0.11$ for the total disease prevalence. The other parameters are: $w = 0$, $\rho = 0.5$, $q = 0$. d)The efficacy parameter w (waning rate) is varied as $w = 0,\ 1,\ 3.5$ for the total disease prevalence. The other parameters are: $q = 0$, $\rho = 0.5$, $\gamma = 0.5$.

If $\mathcal{R}_0(0) > (1 + \dfrac{(\mu+\gamma)}{\rho\nu})$ (4.5), then ψ_c is given by (5.4). **Notice that ψ_c is unique** and can be shifted toward zero by taking γ sufficiently large or ρ sufficiently small. This suggests that increasing vaccine efficacy can be crucial for cost-effectiveness of vaccination program in the terms of reducing the scale of minimum vaccination coverage to avoid asymptomatic spread of the disease in the poultry.

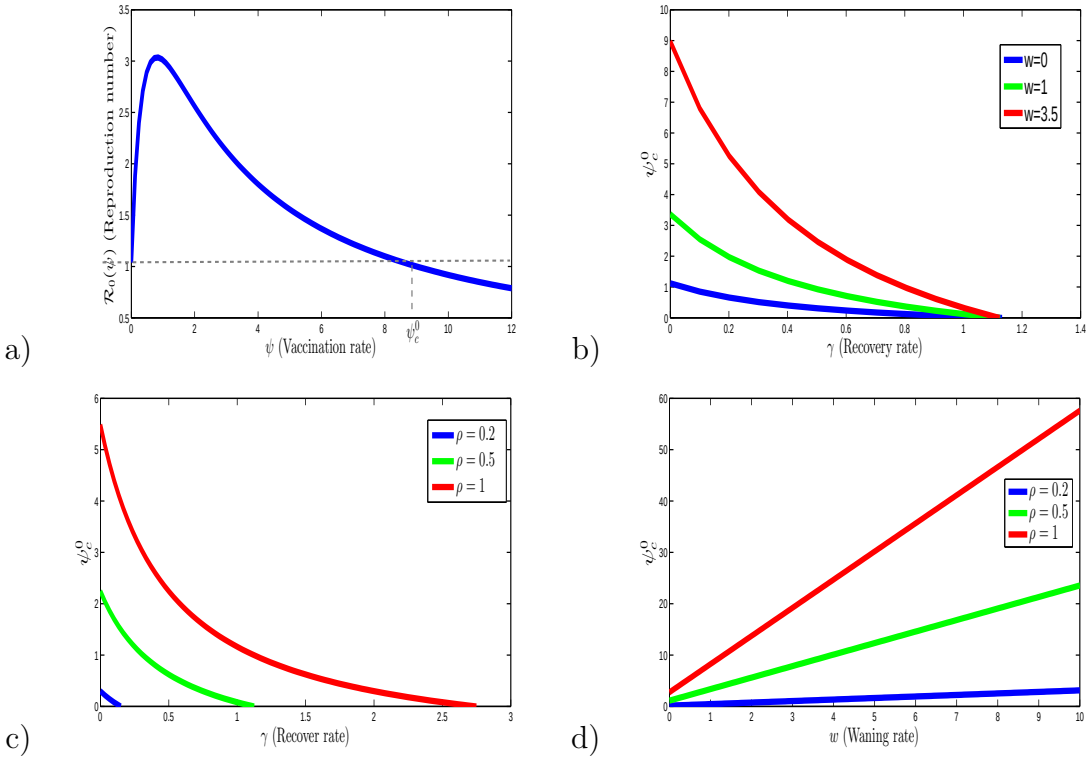


FIGURE 6. In the first subfigure, y-axis shows the reproduction number $\mathcal{R}_0(\psi)$ and x-axis shows vaccination rate ψ (part (a)). In part (b),(c),(d), y-axis shows the critical value ψ_c^0 and x-axis shows waning rate w or ρ along with varying vaccine efficacy parameters. The initial values and parameter values are identical to Fig.(4 with only changes in varying efficacy parameters in blue, green and red curves.

5.3. **The Impact of Vaccine Efficacy on Disease Prevalence and Critical Vaccination Coverage.** In the previous section, we showed that vaccination may cause asymptomatic spread of the disease if the scale of the vaccination is not sufficiently large. Field studies [8] suggest that a sufficiently large-scale vaccination coverage can reduce the total asymptomatic and infected disease prevalence, which mimics our results. **However, how large the vaccination coverage must be is a question** depending on vaccine efficacy. The minimum requirements for the vaccine efficacy are not clearly defined under laboratory experiments. A prediction for the minimum requirements for a vaccine to be efficient in the terms of controlling the disease in the field is still a difficult and open question [1]. In this subsection, through numerical simulations, we will address how the parameters that determine vaccine efficacy increase or decrease the critical vaccination coverage and how these parameters affect disease prevalence.

A successful transmission between infected and susceptible birds depends on the infectiousness of the infected bird and susceptibility of the uninfected bird. An indication for infectiousness is the amount of virus shed by an infected individual [13]. Vaccination reduces the amount of virus shed in (asymptomatically) infected birds, however it does not necessarily provide complete lack of infectivity. Vaccines with high efficacy may reduce the virus shed recognizably and cause low infectiousness of the asymptomatic birds.

As asymptomatically infected birds become more infectious, numerical results displayed in Fig. 5(a) suggest that infected prevalence I^* may increase as the vaccination rate ψ increases. In contrast, when q gets smaller, asymptomatic infection does not cause additional infected prevalence I^* and I^* decreases with increasing vaccination coverage. In Fig.5(b), the critical vaccination rate (for reduction in total disease prevalence $A^* + I^*$) shifts toward zero as asymptomatic birds get less infectious, i.e. as q gets smaller. In the same figure, we also observe that for small vaccination rates ψ, $A^* + I^*$ is a decreasing function of q for the values of q chosen. As the vaccination rate increases, $A^* + I^*$ will begin to decrease for the smaller values of q, but $A^* + I^*$ can keep increasing for larger values of q. Increasing the waning rate w (Fig.5(d)) gives an analogous result to the case of varying q for the parameters utilized in the simulations. These figures show some of the complexities in determining how vaccination coverage, asymptotic infectiousness, and waning, affect the total disease prevalence.

The ultimate goal of a vaccine is to provide immune protection to the birds that completely prevents infection. Numerical simulations illustrated in Fig.5(c) suggest that decreasing ρ (the vaccine-induced reduction in susceptibility to asymptomatic infection) decreases the critical vaccination coverage ψ_c and the total disease prevalence $A^* + I^*$. The remaining vaccine parameter in the model is the recovery rate of asymptomatically infected birds, γ. An extended infectious period (smaller γ) leads to an accumulation of asymptomatically infected birds, which causes an increase in the critical vaccination coverage and in the total disease prevalence. However a larger value of γ (faster recovery) will decrease this effect, and for sufficiently large γ, there will not be any asymptomatic spread (Fig. 3).

In the following section, we also study the imperfect vaccine effect on the epidemiological threshold reproduction number $\mathcal{R}_0$.

5.4. **Reproduction Number and Vaccine Efficacy.**

Proposition 5.1. *Let*

$$\psi_m^0 = \frac{\mu q\beta\Lambda \int_0^\infty \rho(a)\phi_0(a)da + \mu(\mu+\gamma)(\int_0^\infty w(a)\phi_0(a)da - 1)}{(1-\int_0^\infty w(a)\phi_0(a)da)\left[(\mu+\gamma)(1-\int_0^\infty w(a)\phi_0(a)da) + \beta\Lambda q\int_0^\infty \rho(a)\phi_0(a)da\right]}.$$

Then $\mathcal{R}_0(\psi)$ given by (2.4) has a unique local maximum at ψ_m^0 : $\dfrac{d\mathcal{R}_0(\psi)}{d\psi} > 0,\ \forall \psi < \psi_m^0$ and $\dfrac{d\mathcal{R}_0(\psi)}{d\psi} < 0,\ \forall \psi > \psi_m^0$. Notice that $\psi_m^0 > 0$ if and only if

$$1 < \frac{q\beta\Lambda \int_0^\infty \rho(a)\phi_0(a)da}{(\mu+\gamma)(1-\int_0^\infty w(a)\phi_0(a)da)}. \tag{5.5}$$

Proof. Taking derivative of $\mathcal{R}_0(\psi)$ with respect to ψ, we obtain that

$$\frac{d\mathcal{R}_0(\psi)}{d\psi} = 0 \Leftrightarrow \psi = \psi_m. \tag{5.6}$$

Notice that by integration by parts, we have that $(1-\int_0^\infty w(a)\phi_0(a)da) > 0$. Then the denominator of ψ_m^0 is positive. So $\psi_m^0 > 0 \Leftrightarrow$ the condition (5.5) is satisfied. □

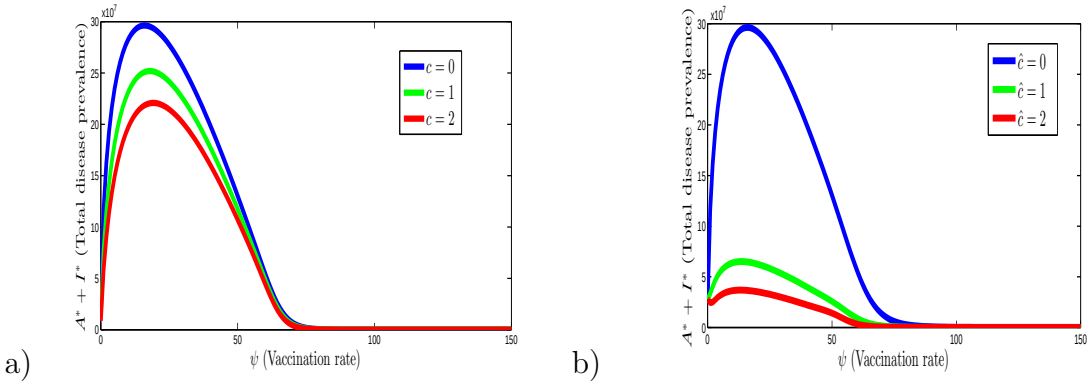


FIGURE 7. In this figure, y-axis shows the total disease prevalence $A^* + I^*$ and x-axis shows vaccination rate ψ. In each figure, we assume that we either only cull infected and susceptible birds with different culling coefficient c (part (a)) or only cull asymptomatically infected and vaccinated birds with distinct culling coefficients $\hat{c}$ (part (b)). The parameters values and initial conditions are identical to the Fig.(4) with exceptions $\rho = q = 0.2$.

For the ODE case, one can obtain the critical vaccination coverage ψ_c^0 by setting $\mathcal{R}_0(\psi_c^0) = \mathcal{R}_0(0)$, where $\mathcal{R}_0(\psi)$ is given by (3.4). We obtain

$$\psi_c^0 = (\mu + w)\left[\frac{(\mu+\nu)}{(\mu+\gamma)}\rho q \mathcal{R}_0(0) - 1\right]. \tag{5.7}$$

Notice that depending on vaccine efficacy parameters ($\rho,\ q,\ w,\ \gamma$), the parameter value ψ_c^0 changes. If ρ or q is sufficiently small, then ψ_c^0 becomes negative; i.e. $\mathcal{R}_0$ decreases as ψ increases. However if γ is sufficiently small, then $\psi_c^0 > 0$ so that $\mathcal{R}_0(\psi) > \mathcal{R}_0(0)$ for all $\psi < \psi_c^0$ and $\mathcal{R}_0(\psi) < \mathcal{R}_0(0)$ when $\psi > \psi_c^0$. Increasing γ, similiarly decreasing ρ or q shifts ψ_c^0 toward zero. Increasing or decreasing waning rate w does not change the sign of ψ_c^0, but the magnitude of it. These can be observed in Figure 6 part (b),(c) and (d).

5.5. **Culling Effect on disease prevalence and critical vaccination coverage.** One of the main control measures applied to poultry is culling, i.e the targeted elimination of a portion of the poultry population in areas affected by avian influenza, to save the rest of the birds and reduce the possibility of further outbreaks. Gulbudak and Martcheva [23] modeled different culling scenarios to understand the dynamics of avian influenza under different culling approaches: mass culling, selective culling and modified culling.

In this study, for simplicity, we consider only mass culling per-capita rate proportional to I. In Fig.7(a), we assume that only infected and susceptible birds are culled at the per-capita rate cI, whereas in Fig.7(b), vaccinated and asymptomatic birds are the only birds culled, which occurs at the per-capita rate $\hat{c}I$. It is not realistic to assume culling only of asymptomatically infected and vaccinated classes and leave out the infected class. However, it can be instructive to know which infected population class is most effective to cull in order to reduce disease prevalence and reduce the minimal critical vaccination coverage to avoid asymptomatic spread. In Fig.7(a), infected and susceptible birds are culled at different culling coefficients $c = 0, 1, 2$. In Fig.7(b), asymptomatically infected

birds and vaccinated birds are culled with again the same varying culling coefficients with part (a). In both cases, culling reduces the total disease prevalence and the minimum critical vaccination coverage. However, numerical simulations suggest that compared to case (a), when only infected and susceptible birds are culled, culling of asymptomatically infected and vaccinated birds can more drastically decrease the disease prevalence and reduce ψ_c. These results show that the detection problems caused by asymptomatic infection can have a negative impact on culling efforts in terms of reducing the total disease prevalence.

6. Discussion

Vaccination of poultry is a powerful tool for control of AI, but there are many factors to consider when evaluating the overall effect of vaccination on disease dynamics. On the individual level, the vaccine generates an immune response protective against AI, however, both the efficacy of the vaccine and the strength and duration of the immune protection can be highly variable. Thus, even though the vaccine provides protection against disease, since it is not a complete protection, vaccinated birds can still become infected and infectious, but their partial immunity will decrease viral shedding, reduce the severity of infection and, often, these birds will be asymptomatic. In the context of such a virulent virus as AI, this asymptomatic infection may actually lead to an extended infectious period and, also, detection of the disease can be compromised. Hence, the population level effects of imperfect vaccination are unclear and it is important to quantify the effectiveness of vaccination. To capture this complexity of vaccination, we analyzed an avian flu model which includes imperfect vaccination, age-since vaccination structure, and asymptomatically infected birds.

Through analysis of our model, the reproduction number $\mathcal{R}_0$, is calculated. The DFE is globally stable when $\mathcal{R}_0 < 1$ and asymptomatic recovery rate, $\gamma = 0$. If $\mathcal{R}_0 > 1$, then there exists endemic equilibrium and it is unique in certain cases (ODE case or $\gamma = 0$) and in ODE case, it is locally asymptotically stable when $\nu = 0$. If $\mathcal{R}_0 > 1$, then the disease is uniformly weakly persistent.

The analytical results also interestingly suggest that spread of the infection through the asymptomatic compartment is possible and vaccination helps eradication of the disease only when vaccination coverage is sufficiently large or vaccine efficacy is high. More specifically, under certain simplifications in ODE case, we analytically and numerically show that insufficient vaccination coverage can cause increase in total infected equilibrium $A^* + I^*$, while sufficiently large-scale vaccination can eradicate the disease. The vaccine efficacy is a vital parameter in determining how a given vaccination coverage affects total disease prevalence. Numerical results also suggest that as asymptomatic birds get more infectious (as q increases), the critical vaccination coverage, which is a threshold for avoiding perversity of vaccination, increases. An improvement in vaccine efficacy can reduce the critical vaccination coverage and even ultimately eradicate the disease.

The detailed description of vaccination in this model can help to more accurately quantify the efficacy of a vaccine and the epidemiological implications of a vaccination program. In future work, we will incorporate data from experimental and observational studies on AI vaccination in order to get reliable estimates for the vaccination parameters in the model. Then, the dynamical consequences of the complex structure induced

by imperfect vaccination can be more fully explored. In addition, we will incorporate multiple patches in the model to see how asymptomatic infection affects spread of the disease through a network of coupled regions with distinct control strategies. In conclusion, the importance and complexity of applying control strategies, such as vaccination, in poultry to control or eradicate AI magnify the need for detailed mathematical models of the impact of control measures. The modeling work contained in this paper can help to understand the effect of vaccination on AI disease dynamics and help to guide policies on strategy for disease control.

Acknowledgments

Maia Martcheva and Hayriye Gulbudak acknowledge partial support from NSF grant DMS-1220342. The authors thank the referees for their helpful suggestions.

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