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AVIAN INFLUENZA OPTIMAL SEASONAL VACCINATION STRATEGY

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Abstract

We present an application of optimal control theory to a simple SIR disease model of avian influenza transmission dynamics in birds. Basic properties of the model, including the epidemic threshold, are obtained. Optimal control theory is adopted to minimize the density of infected birds subject to an appropriate system of ordinary differential equations. We conclude that an optimally controlled seasonal vaccination strategy saves more birds than when there is a low uniform vaccination rate as in resource-limited places.

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1. Introduction

Influenza (flu) is a respiratory infection in mammals and birds caused by an RNA virus in the family Orthomyxoviridae. The virus is divided into three main types (A, B and C), which are distinguished by differences in two major internal proteins [8]. Influenza virus type A is the most significant epidemiologically and the most interesting from an ecological and evolutionary standpoint, because it is found in a wide variety of bird and mammal species and can undergo major shifts in immunological properties. Type B is largely confined to humans and is a significant cause of morbidity. Little is known about type C, which does not cause significant morbidity. Influenza A is further divided into subtypes based on differences in the membrane proteins haemagglutinin (HA) and neuraminidase (NA), which are the most important targets for the immune system. The notation HhNn is used to refer to the subtype comprising the hth discovered HA protein and the nth discovered NA protein. Subtypes of influenza A

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that are currently circulating among people worldwide include H1N1, H1N2 and H3N2 viruses. Subtypes are further divided into strains; each genetically distinct virus isolate is usually considered to be a separate strain.

Avian influenza viruses circulate among birds worldwide. Wild birds are the natural host for all known subtypes of influenza A viruses. Certain birds, particularly water birds, act as hosts for influenza viruses by carrying the virus in their intestines and shedding it in saliva, nasal secretions, and feces [28]. Susceptible birds can become infected with avian influenza virus when they have contact with contaminated nasal, respiratory, or fecal material from infected birds. Fecal-to-oral transmission is the most common mode of spread between birds. Typically, wild birds do not become sick when they are infected with avian influenza A viruses. However, domestic poultry, such as turkeys and chickens, can become very sick and die from avian influenza, and some avian influenza A viruses can also cause serious disease and death in wild birds. Infection with certain avian influenza A viruses (for example, some H5 and H7 strains) can cause widespread disease and death among some species of domesticated birds.

In 2004 H5N1 viruses were isolated from three migratory wild birds in Hong Kong. There was no evidence of H5N1 infection in local or imported poultry, pet birds or captive birds in recreational parks despite major outbreaks of H5N1 avian influenza in the region during 2004. Migratory birds had been traced to the outbreak of H5N1 in parts of Nigeria. The country has many bird sanctuaries along two migratory flight paths that connect with southern Russia, Europe and western Asia [19].

A lot of work has been done in the area of mathematical modelling for influenza in humans (see [8, 9, 20, 21] and references therein). The transmission of avian influenza virus H5N1 was quantified within flocks during the 2004 epidemic in Thailand [26] using flock-level mortality data to estimate the transmission rate parameter and the basic reproduction number. Le Menach *et al.* [17] considered a stochastic model for avian influenza in order to reduce transmission, employing lessons from control of human avian influenza. To evaluate the effectiveness of the control measures, Stegeman *et al.* [25] quantified between-flock transmission characteristics of the virus in two affected areas, using the reproduction ratio. Agusto *et al.* [1] determined the impact of avian influenza vaccine for domestic birds.

The present work is motivated by the availability of avian influenza vaccines and the debate on the source of the H5N1 virus. Some believe that the H5N1 virus is a result of importation of infected poultry, as in the case of the outbreaks in Nigeria [29, 30], Hungary [31] and Korea [32]. Others believe that it is a result of the presence of migratory birds [19], whose flights are seasonal, usually at the advent of winter. Hence, in this work we apply optimal control theory to determine the optimal seasonal vaccination therapy in which vaccination is administered to coincide with bird migration. Using a simple SIR model [12], we view the infection of susceptible birds as a result of coming into contact with infected migratory wild birds.

The model description, basic reproduction number and system stability are presented in the next section. We state the objective function in Section 3 and derive the optimality system which characterizes the optimal control. Some numerical results are illustrated in Section 4.

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2. Model description

The model classifies the bird population into three classes, susceptible, infected and recovered, with population numbers denoted as functions of time by $S(t)$, $I(t)$ and $R(t)$, respectively. The total interacting variable bird population is denoted by $N(t) = S(t) + I(t) + R(t)$. The recruitment rate into the population is denoted by Λ. Susceptible birds are infected by "migratory" birds at a constant rate β. Upon becoming infected with the virus, susceptible birds enter the class of infected birds. The natural death rate of birds is assumed to be proportional to the population number in each class, with rate constant $\mu > 0$. In addition, there is an influenza-induced death in the infected class which is proportional to the population number in that class, with constant $\nu > 0$. Due to the administration of vaccine, the infected move to the recovered class at a constant rate $\gamma > 0$.

The infection rate δ depends on the infection transmission rate α and the proportion of infected birds. The probability of transmission from an infected bird to a susceptible bird is α. Assuming homogeneous mixing,

$$\delta = \frac{\alpha I(t)}{N(t)}. \tag{2.1}$$

Thus we have the following model equations:

$$\begin{aligned} \frac{dS}{dt} &= \Lambda - \delta S - \beta SM - \mu S, \\ \frac{dI}{dt} &= \delta S + \beta SM - (\nu + \mu)I - \gamma I, \\ \frac{dR}{dt} &= \gamma I - \mu R, \end{aligned} \tag{2.2}$$

where the parameters Λ, M, α, β, μ, γ and ν are all positive real numbers. All state variables for the model system (2.2) are assumed to be nonnegative for $t \geq 0$, with initial conditions given by $S_0 \geq 0$, $I_0 \geq 0$ and $R_0 \geq 0$. We consider the region

$$\mathcal{D} = \left\{ (S, I, R) \in \mathbb{R}^3_+ : N \leq \frac{\Lambda}{\mu} \right\}.$$

Solutions of (2.2) starting in $\mathcal{D}$ can be shown to remain in $\mathcal{D}$ for all $t \geq 0$. Thus $\mathcal{D}$ is positively invariant and it is sufficient to consider solutions in $\mathcal{D}$. Existence and continuation results for (2.2) hold in this region. We state and prove Theorem 2.1 for positivity and boundedness of solutions of (2.2) in $\mathcal{D}$.

THEOREM 2.1. *Let the initial data be $S_0 \geq 0$, $I_0 \geq 0$ and $R_0 \geq 0$. Then solutions $S(t)$, $I(t)$ and $R(t)$ of the model system (2.2) are positive for all $t \geq 0$. Moreover, for the model system (2.2), the region $\mathcal{D}$ is positively invariant.*

PROOF. Under the given initial conditions, it is easy to prove that the components of the solutions of (2.2), $S(t)$, $I(t)$ and $R(t)$ are positive for $t \geq 0$. If not, then, using a

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similar approach to Qiu *et al.* [23], we assume for contradiction that there exists a first time t_s such that $S(t_s) = 0$, $S'(t_s) \leq 0$ and $S(t) > 0$, $I(t) > 0$, $R(t) > 0$ for $0 < t < t_s$, or that there exist t_i such that $I(t_i) = 0$, $I'(t_i) \leq 0$ and $I(t) > 0$, $S(t) > 0$, $R(t) > 0$ for $0 < t < t_i$, or that there exist t_j such that $R(t_j) = 0$, $R'(t_j) \leq 0$ and $R(t) > 0$, $S(t) > 0$, $I(t) > 0$ for $0 < t < t_j$. In the first case it follows from (2.2) that

$$S'(t_s) = \Lambda - \delta(t_s)S(t_s) - \beta M S(t_s) - \mu S(t_s) > 0,$$

which is a contradiction. Similarly,

$$I'(t_i) = \delta(t_i)S(t_i) + \beta M S(t_i) - (\nu + \mu)I(t_i) - \gamma I(t_i) > 0$$

for the second case, and

$$R'(t_j) = \gamma I(t_j) - \mu R(t_j) > 0$$

for the third case, which are also contradictions. This implies that $S(t)$, $I(t)$ and $R(t)$ remain positive for all $t > 0$. Since $N(t) \geq I(t)$,

$$\Lambda - (\mu + \nu)N(t) \leq N'(t) \leq \Lambda - \mu N(t)$$

implies that $N(t)$ is bounded and that all solutions starting in the region $\mathcal{D}$ remain in $\mathcal{D}$. The proof is complete. □

2.1. Local stability of the disease-free equilibrium The model system (2.2) has disease-free equilibrium given by

$$\mathcal{E}_0 = (S, I, R) = \left(\frac{\Lambda}{\mu}, 0, 0\right).$$

The basic reproductive number $\mathcal{R}_0$ defines the number of new infections generated by a single infected individual in a completely susceptible population and also governs the linear stability at $\mathcal{E}_0$ [3, 4, 12]. Mathematically, $\mathcal{R}_0$ is defined as the spectral radius [7, 27]. Using the notation in [27] applied to system (2.2), the matrices F and V, for the new infection terms and the remaining transfer terms respectively, are given by

$$F = \begin{pmatrix} \alpha & 0 \\ 0 & 0 \end{pmatrix}, \quad V = \begin{pmatrix} \mu + \nu + \gamma & 0 \\ -\gamma & \mu \end{pmatrix}.$$

It follows that the basic reproduction number is given by

$$\mathcal{R}_0 = \rho(FV^{-1}) = \frac{\alpha}{\mu + \nu + \gamma}. \tag{2.3}$$

Using [27], the following result is established.

LEMMA 2.2. *The disease-free equilibrium of* (2.2) *is locally asymptotically stable if* $\mathcal{R}_0 < 1$ *and unstable if* $\mathcal{R}_0 > 1$.

The basic reproductive number $\mathcal{R}_0$ measures the power of a disease to invade a population under conditions that facilitate maximal growth. Since 1911, control and intervention efforts have been based on the concept of the basic reproductive number, introduced by Ross [24] and in 1927 by Kermack and McKendrick [14].

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2.2. Existence of an endemic equilibrium To find conditions for the existence of an equilibrium, denoted by $\mathcal{E}_1 = (S^{**}, I^{**}, R^{**})$, for which avian influenza is endemic in the population, the equations in (2.2) are solved in terms of the force of infection at steady state (δ^{**}), given by

$$\delta^{**} = \frac{\alpha I^{**}}{N^{**}}, \tag{2.4}$$

where $N^{**} = S^{**} + I^{**} + R^{**}$. Setting the right-hand sides of the model to zero (and noting that $\delta = \delta^{**}$ at equilibrium) gives

$$\begin{aligned} S^{**} &= \frac{\Lambda}{\delta^{**} + \beta M + \mu}, \quad R^{**} = \frac{\gamma}{\mu} I^{**}, \\ I^{**} &= \frac{(\delta^{**} + \beta M) S^{**}}{\mu + \nu + \gamma} \geq \frac{\delta^{**} S^{**}}{\mu + \nu + \gamma} = \frac{\delta^{**} \Lambda}{(\delta^{**} + \beta M + \mu)(\mu + \nu + \gamma)}. \end{aligned} \tag{2.5}$$

Using the above in the expression for δ^{**} in (2.4) shows that the nonzero (endemic) equilibria of the model satisfy

$$a\delta^{**} - c = 0 \tag{2.6}$$

where $a = (\mu + \gamma)$ and $c = \mu(\mu + \nu + \gamma)(\mathcal{R}_0 - 1)$. It is clear that $a > 0$ and if $\mathcal{R}_0 > 1$ we also have $c > 0$. Thus, the linear system (2.6) has a unique positive solution, given by $\delta^{**} = c/a$, whenever $\mathcal{R}_0 > 1$. The components of the endemic equilibrium, $\mathcal{E}_1$, are then determined by substituting $\delta^{**} = c/a$ into (2.5). Note that $\mathcal{R}_0 < 1$ implies that $c < 0$. Thus, for $\mathcal{R}_0 < 1$, the force of infection at steady state (δ^{**}) is negative (which is biologically meaningless). Hence, the model has no positive equilibria in this case. These results are summarized below.

THEOREM 2.3. *The model* (2.2) *has a unique endemic equilibrium whenever* $\mathcal{R}_0 > 1$, *and no endemic equilibrium when* $\mathcal{R}_0 < 1$.

2.3. Local stability of the endemic equilibrium Linearizing (2.2), we have

$$J = \begin{bmatrix} J_{11} & 0 & 0 \\ J_{21} & J_{22} & 0 \\ 0 & J_{32} & J_{33} \end{bmatrix}$$

where $J_{11} = -\delta - \beta M - \mu$, $J_{21} = \delta + \beta M$, $J_{22} = -\nu - \mu - \gamma$, $J_{32} = \gamma$ and $J_{33} = -\mu$. So $J_{11} < 0$, $J_{22} < 0$, $J_{33} < 0$, $J_{12}J_{21} = 0$, $J_{13}J_{31} = 0$, $J_{23}J_{32} = 0$, and hence the equilibrium (S^*, I^*, R^*) of (2.2) is locally asymptotically stable [5]. We have established the following result.

LEMMA 2.4. *The endemic equilibrium of* (2.2) *is locally asymptotically stable.*

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3. Analysis of optimal control

We introduce into (2.2) a time-dependent control uP_Ω, taken to be the vaccination rate, applied seasonally. This yields

$$\begin{aligned}\frac{dS}{dt} &= \Lambda - \delta S - \beta SM - \mu S - SuP_\Omega,\\ \frac{dI}{dt} &= \delta S + \beta SM - (\nu + \mu)I - \gamma I,\\ \frac{dR}{dt} &= \gamma I - \mu R + SuP_\Omega.\end{aligned} \tag{3.1}$$

Adding the equations in the system (3.1) gives

$$\frac{dN}{dt} = \Lambda - \mu N - \nu I.$$

Since R does not appear in the other equations in (3.1), the state equation becomes

$$\begin{aligned}\frac{dS}{dt} &= \Lambda - \delta S - \beta SM - \mu S - SuP_\Omega,\\ \frac{dI}{dt} &= \delta S + \beta SM - (\nu + \mu + \gamma)I,\\ \frac{dN}{dt} &= \Lambda - \mu N - \nu I,\end{aligned} \tag{3.2}$$

with appropriate initial conditions. The control variable $u(t)$ represents the amount of intervention at time t (in years). It has a pair of constraints and it is scaled so that $0 \le u \le 1$. More notably, we only allow the control action to take place during certain times of the year. Connecting back with our motivating situation, we would only allow vaccination in the winter when birds are migrating. Starting the year in the winter, this is taken to occur during the first quarter of each year.

We minimize the objective functional $J(u)$ given by

$$J(u) = \int_0^T (AI(t) + Bu(t)^2 P_\Omega(t))\, dt. \tag{3.3}$$

The $AI(t)$ term represents the density of infected birds and the $Bu^2(t)$ term represents the cost of transmission. The function $P_\Omega(t)$ is a characteristic function of the set Ω given by

$$\Omega = \bigcup_{i=1}^{T} [\sigma_i, \tau_i]$$

with T denoting the total number of years in which the control will be applied and the interval $[\sigma_i, \tau_i]$ being the ith year. Then we see that on the set $[0, T]\backslash\Omega$, the control does not appear in the state equation, which amounts to saying that the control does not

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apply during those time intervals (see [2, 15]). Our goal is to minimize the number of infected birds $I(t)$, while minimizing the cost of the control $u(t)$. We seek an optimal control u^* such that

$$J(u^*) = \min\{J(u) \mid u \in \mathcal{U}\} \tag{3.4}$$

where $\mathcal{U} = \{u \mid u \text{ is measurable}, 0 \leq u \leq 1, t \in [0, T]\}$ is the control set.

The necessary conditions that an optimal control must satisfy come from Pontryagin's maximum principle [22], which converts (3.2)–(3.3) into a problem of minimizing pointwise a Hamiltonian H, with respect to u. The Hamiltonian is formed from the cost functional (3.3) and the governing dynamics (3.2). We obtain

$$\begin{aligned} H = {} & AI + Bu^2 + \lambda_S\left(\Lambda - \frac{\alpha SI}{N} - \beta SM - \mu S - uS\right) \\ & + \lambda_I\left(\frac{\alpha SI}{N} + \beta SM - (\nu + \mu + \gamma)I\right) + \lambda_N(\Lambda - \mu N - \nu I), \end{aligned} \tag{3.5}$$

where λ_S, λ_I, λ_N are the adjoint variables or co-state variables for the states S, I, N. The system of equations governing the adjoint variables is found by taking the appropriate partial derivatives of the Hamiltonian (3.5) with respect to the associated state variable. By applying Pontryagin's maximum principle and the existence result for the optimal control from [10], we obtain the following result.

THEOREM 3.1. *Given an optimal control u^* that minimizes $J(u)$ over $\mathcal{U}$, and solutions I^*, S^*, N^* of the corresponding state system (3.2), there exist adjoint variables λ_S, λ_I, λ_N satisfying*

$$\begin{aligned} -\frac{d\lambda_S}{dt} &= (-\mu - \beta M - u)\lambda_S + \beta M\lambda_I + \frac{\alpha^* I^*}{N}(\lambda_I - \lambda_S), \\ -\frac{d\lambda_I}{dt} &= A - (\nu + \mu + \gamma)\lambda_I - \nu\lambda_N + \frac{\alpha^* S^*}{N}(\lambda_I - \lambda_S), \\ -\frac{d\lambda_N}{dt} &= -\mu\lambda_N - \frac{\alpha^* S^* I^*}{N^2}\lambda_I + \frac{\alpha^* S^* I^*}{N^2}\lambda_S, \end{aligned} \tag{3.6}$$

and with transversality conditions

$$\lambda_I(T) = \lambda_S(T) = \lambda_N(T) = 0. \tag{3.7}$$

Furthermore,

$$u^* = \max\left\{0, \min\left\{1, \frac{S^*\lambda_S}{2B}\right\}\right\}. \tag{3.8}$$

PROOF. Corollary 4.1 of [10] gives the existence of an optimal control due to the convexity of the integrand of J with respect to u, *a priori* boundedness of the state solutions, and the Lipschitz property of the state system with respect to the state variables. The differential equations governing the adjoint variables are obtained by

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differentiation of the Hamiltonian function, evaluated at the optimal control. Then the adjoint system can be written as

$$\begin{aligned}
-\frac{d\lambda_S}{dt} &= \frac{\partial H}{\partial S} = (-\mu - \beta M - u)\lambda_S + \beta M \lambda_I + \frac{\alpha^* I^*}{N}(\lambda_I - \lambda_S),\\
-\frac{d\lambda_I}{dt} &= \frac{\partial H}{\partial I} = A - (\nu + \mu + \gamma)\lambda_I - \nu\lambda_N + \frac{\alpha^* S^*}{N}(\lambda_I - \lambda_S),\\
-\frac{d\lambda_N}{dt} &= \frac{\partial H}{\partial N} = -\mu\lambda_N - \frac{\alpha^* I^* S^*}{N^2}\lambda_I + \frac{\alpha^* I^* S^*}{N^2}\lambda_S,
\end{aligned} \tag{3.9}$$

evaluated at the optimal control and corresponding states, resulting in the stated adjoint system (3.6) and (3.7). Differentiating the Hamiltonian function with respect to the control variables on the interior of the control set gives

$$0 = \frac{\partial H}{\partial u} = 2Bu^* - S^*\lambda_S = 0.$$

Then solving for u, on the interior of the control set, we obtain the optimality conditions (see [2, 18])

$$u^* = \frac{S^*\lambda_S}{2B}. \tag{3.10}$$

By standard control arguments involving the bounds on the controls,

$$u^* = \begin{cases} 0 & \text{if } \dfrac{S^*\lambda_S}{2B} \le 0 \\ \dfrac{S^*\lambda_S}{2B} & \text{if } 0 < \dfrac{S^*\lambda_S}{2B} < 1 \\ 1 & \text{if } \dfrac{S^*\lambda_S}{2B} \ge 1, \end{cases} \tag{3.11}$$

and we conclude that $u^* = \max\{0, \min\{1, S^*\lambda_S/2B\}\}$. □

REMARK 1. Due to the *a priori* boundedness of the state and adjoint functions and the resulting Lipschitz structure of the ordinary differential equations, we obtain the uniqueness of the optimal control for small T. The uniqueness of the optimal control follows from the uniqueness of the optimality system, which consists of (3.2), (3.6) and (3.7) with characterization (3.8). There is a restriction on the length of the time interval in order to guarantee the uniqueness of the optimality system. This restriction is due to the opposite time orientations of (3.2), (3.6) and (3.7); the state problem has initial values and the adjoint problem has final values. This restriction is very common in control problems (see [13, 16]).

Next we discuss numerical solutions of the optimality system and the corresponding optimal control, the parameter choices, and interpretations from various cases.

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TABLE 1. Description of parameters of the avian model (2.2).

Parameter	Description	Baseline value	Reference
Λ	Recruitment rate	3000 per day	[11]
α	Transmission probability within domestic birds	0.00358 per day	[1]
β	Transmission probability between domestic and migratory birds	0.4/20000 per day	[11]
μ	Natural death rate	1/100 per day	[11]
γ	Recovery rate	0.03 per day	[1]
ν	Disease-induced death rate	0.05 per day	[1]

4. Numerical results

In this section, we study numerically an optimal seasonal vaccination strategy for the migratory avian influenza model. The optimal control is obtained by solving the optimality system, consisting of six ordinary differential equations from the state and adjoint equations. An iterative method is used to solve the optimality system. To solve the state equations, we begin with a guess for the controls over the simulated time using the fourth-order Runge–Kutta scheme. Because of the transversality conditions (3.7), the adjoint equations are solved by a backward fourth-order Runge–Kutta scheme using the current iteration of the solutions of the state equation. Then the controls are updated by using a convex combination of the previous controls and the value from the characterization (3.8). This process is repeated and iteration is stopped if the values of the unknowns at the previous iteration are very close to the ones at the current iteration [18].

Numerical results were obtained using MATLAB. We considered four different seasonal vaccination strategies and compared our results with a uniform low vaccination strategy of 35%. We have considered a low vaccination strategy, as this situation is mostly found in countries with limited resources [6]. From the simulation we obtain the following results using the values from Table 1 and initial conditions $M = 100$, $S = 9990$, $I = 10$, $R = 10$.

Minimizing the number of infected birds and utilizing a seasonal vaccination strategy in the first quarter of each year for 10 years (Figure 1(a)), we observed that the number infected over 10 years was more than that obtained from the uniform vaccination strategy, while the number recovered over 10 years was lower than that obtained from uniform vaccination. When seasonal vaccination is applied during the first half of each year for 10 years, equal numbers of infected and recovered birds are observed (Figure 1(b)) for both the uniform and seasonal strategies. When seasonal vaccination is applied in the first three quarters of each year for 10 years, the number infected for seasonal vaccination is lower than for uniform vaccination, while the

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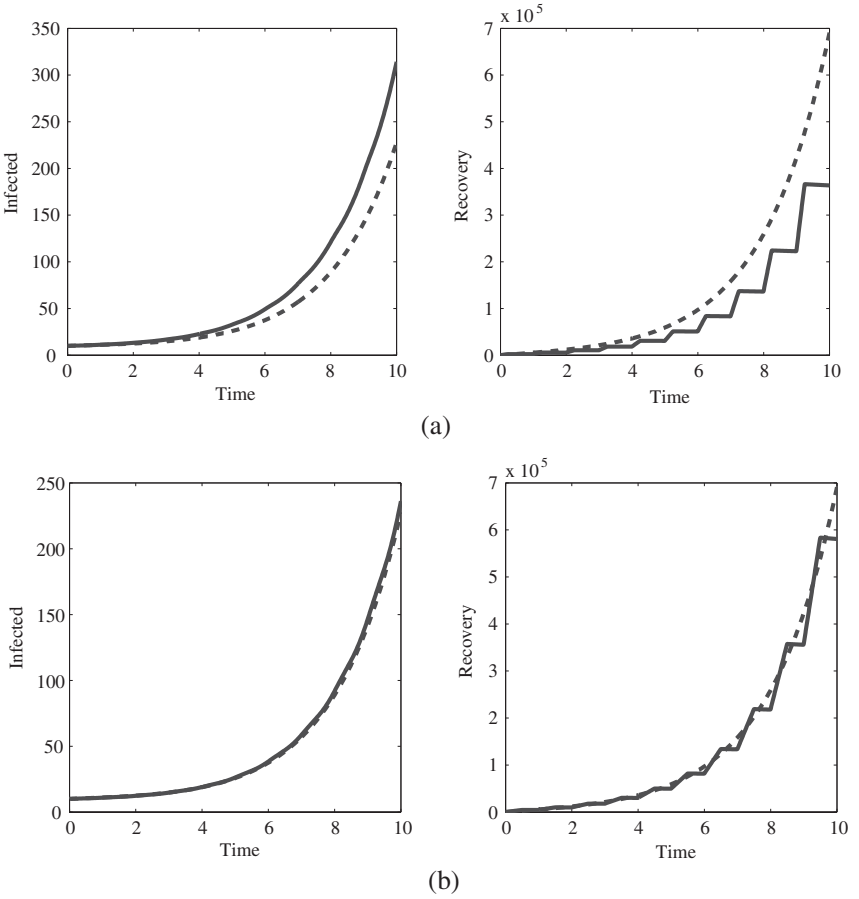

FIGURE 1. Uniform vaccination strategy (dashed lines) and controlled seasonal vaccination strategy (solid lines), with (a) $P_\Omega = \frac{1}{4}$, (b) $P_\Omega = \frac{2}{4}$.

number recovered is higher, as seen in Figure 2(a). This improvement is further boosted when we have a continuous vaccination, as shown in Figure 2(b).

We also considered the objective function (3.3) and observed that implementing a half-yearly optimally controlled vaccination strategy is a lot cheaper than carrying out a continuous optimally controlled vaccination strategy.

5. Summary

We have considered the optimal control for migratory avian influenza dynamics, seeking to minimize infection with a seasonal vaccination strategy and comparing our results with low vaccination rates which often occur in resource-limited places.

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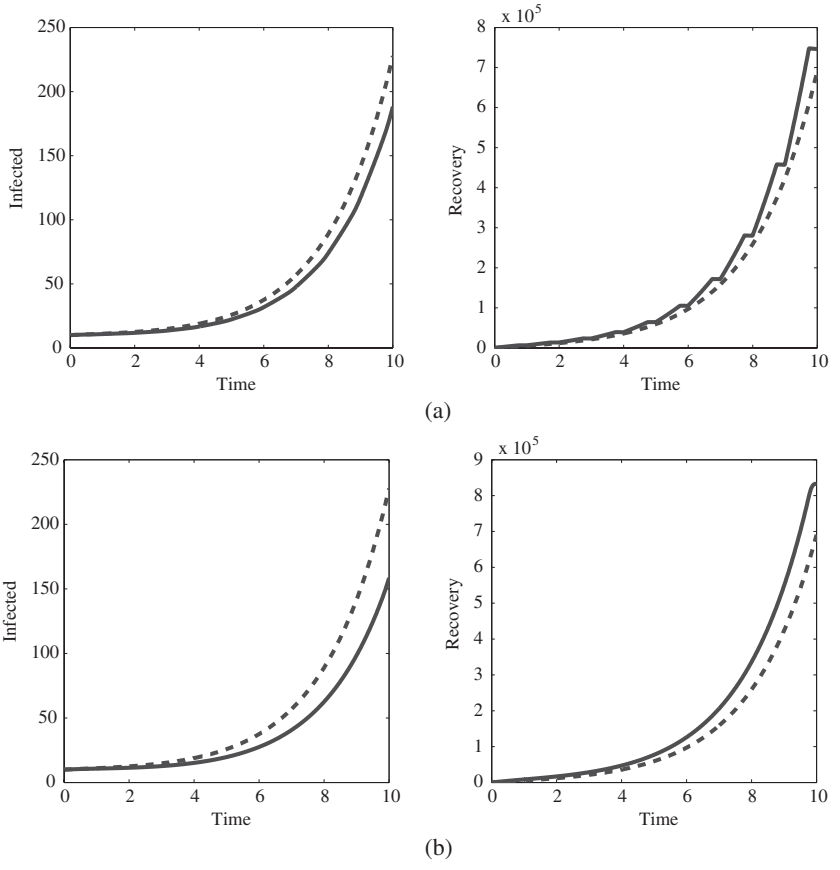

FIGURE 2. Uniform vaccination strategy (dashed lines) and controlled seasonal vaccination strategy (solid lines), with (a) $P_\Omega = \frac{3}{4}$, (b) with $P_\Omega = 1$.

We conclude that an optimally controlled seasonal vaccination strategy saves more birds than when we have a low uniform vaccination strategy. Thus, we recommend that in resource-limited places, seasonal vaccination can be carried out either every half a year or every three quarters of a year.

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