A two–strain avian–human influenza model with environmental transmission: stability analysis and optimal control strategies

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Abstract

On the basis of the WHO legitimated fear that there will be an avian influenza virus strain capable of mutating once it reaches the human population and sustains human-to-human transmissions, we formulate an "hypothetical" mathematical model which accounts for the mutation of an avian influenza virus having the ability to spill over into the human population and become a highly pathogenic strain. We compute the basic reproduction number of the model and use it to study the existence and stability of equilibrium points. We derive conditions for the global asymptotic stability of any of the three equilibrium. The model is extended to incorporate six relevant time-dependent controls, and use the Pontryagin's maximum principle to derive the necessary conditions for optimal disease control. Finally, the optimal control problem is solved numerically to show the effect of each control parameter and their combination. The incremental cost-effectiveness ratios are calculated to investigate the cost-effectiveness of all possible combinations of the control strategies. This study suggests that quarantine infected humans might be the most cost-effective strategy to control avian influenza transmissions with the virus mutation.

Keywords: Avian influenza, Mutation, Environment transmission, Cost-effectiveness.

1. Introduction

The avian influenza virus (AIV) does not usually infect humans. Avian influenza is caused by several viruses sub-types which can undergo high mutation rate to become harmful to humans. Of the most pathogene, avian influenza viruses H5N1, H7N4, H7N7, H7N9, H9N2 pose a significant potential threat to humans. Infected poultry and their secretions, feces and water contaminated with the virus are the main sources of transmission of avian influenza. In the month of February 2013, 3 persons were infected for the first time, and as of May 31, 132 cases have been discovered, including 37 deaths, and the mortality rate is as high as 30% [1, 2, 3, 4]. At present, human infection with avian influenza A (H7N9) is still sporadic. Sporadic infections almost affect poultry mainly in farms, live poultry markets, wet markets and other areas [5, 6, 7, 8, 9]. In humans, the avian influenza virus causes similar symptoms to those of other types of influenza. These include fever, cough, sore throat, muscle aches, conjunctivitis and, in extreme cases, acute respiratory problems and potentially fatal pneumonia [3, 10]. The incubation time for humans who are infected with the H7N9 influenza virus is about seven days and currently there are drugs to fight this virus [3]. While these antiviral drugs are known to be clinically effective against avian influenza H7N9, there is still a very high death rate from avian influenza H7N9.

It should be noted that poultry are the natural storage hosts of avian influenza virus. Exposed and infected poultry can shed the virus into the environment through their secretions and feces. The

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virus can survive for several weeks to months in feces or contaminated environment under appropriate conditions. Environmental transmission therefore predominates over direct transmission in the spread of influenza virus [11, 12]. The most readily infectious source for humans is virus-carrying poultry, and the primary routes of transmission are poultry-to-human and environment-to-human [3]. Although the H7N9 virus is not thought to have a high capacity to spread efficiently from humans to humans, there is a strong fear that, once the virus infects humans from poultry, it will mutate to a highly pathogenic strain for humans and spreads among them. In this regards, the WHO circular [3] stipulates and I quote "The circulation of certain subtypes of avian viruses, such as A(H5) and A(H7N9) in poultry are a public health concern because these viruses generally cause severe disease in humans and have the capacity to mutate and thus transmit more easily from person to person". This is a sufficient motivation for us to propose a mathematical model which accounts for these features and highlight some recommendations for the future interventions in order to strengthen national and global preparedness and response. Of course, we are not the first researchers to consider this and there are very few existing models taking into the avian influenza vitus mutation to a strain might be highly pathogenic within humans [26, 28, 27].

A number of mathematical modelling studies have been carried out to quantify the potential burden of an influenza pandemic (see, for example, [13, 14, 15, 16]). Although influenza A outbreaks in poultry are generally stopped by a systematic slaughtering of poultry, this practice is economically suicidal, and one should rather focus on affordable preventive measures. This calls for urgent control strategies, at the lowest cost, for the greatest poultry production. With these specific objectives, several mathematical models have been proposed by many researchers. Nunõ and co-workers [17] investigated a model to explore the role of hospital and community control measures, antiviral medicines, and vaccination in controlling an influenza pandemic in a population. In [18, 19, 20] the authors modeled the spread of H7N9 avian influenza with a semilinear and half-saturation incidence rate. In [21] the impacts of both pharmaceutical and non-pharmaceutical control strategies are considered, while the human psychological effect in response to H5N1 avian influenza outbreaks is examined in [22]. In [13], the authors proposed an epidemic model with control, in which they consider the incubation periods of avian influenza A (H7N9) virus with different time delay in the infective avian and human populations. In the same way, a deterministic compartmental eco-epidemiological model with optimal control of Newcastle disease (ND) in Tanzania is proposed and analysed by Hugo and co-workers [23]. Recently, Lee and his collaborators [24] modeled the transmission dynamics and control strategies assessment of H5N6 avian influenza in the Philippines. Jung and co-authors [25] extended the work in [26] by seeking the optimal control strategy for the prevention of the avian influenza pandemic. Similarly, Agusto [27] extended the work of Gumel [28] by monitoring the isolation rate of humans infected with avian and mutant strains.

The current study takes over the work first mathematical model in [26], which considered the virus mutation and the spread of the mutated strain in the human population and extends it to account for the environmental transmissions (from environment to poultry; from environment to humans), mimicking our previous formulation in [11]. In so doing, we extend the above-mentioned models in the following three directions:

(1) We consider a mutation of an avian influenza virus and its spill over to in a highly pathogenic strain in the human population and assume (according to WHO circular [3] and fear) that only the mutated strain spreads the disease from human-to-human.

(2) In order to reduce the number of infected poultry, the number of infected humans, the concentration of avian influenza viruses in the environment, we consider the following six control strategies: The vaccination of poultry; the environmental sanitation; the treatment of infected humans; the quarantine of infected persons; the education campaigns aiming at advising people to avoid contacts with infected poultry and environments.

(3) We design and solve an optimal problem to identify which of the six control strategies or combi-

nation minimizes the number of infected humans.

The model obtained is thoroughly analyzed, both theoretically and computationally.

The following is the layout of the remainder of the paper. After formulating the two-strain avian influenza model and showing its basic properties in Section 2, we present the global analysis of the avian–only model in Section 3. Section 4 focuses on the global analysis of the full model whereas Section 5 provides an analysis of the optimal control model. The theoretical findings are highlighted by numerical simulations in Section 6, and Section 7 deals with the control strategies cost-effectiveness. The last Section is about the conclusion and possible extensions.

2. Two-strain avian influenza model formulation and its basic properties

2.1. Two-strain avian influenza model formulation

There are many dynamic models to describe the spread of infectious diseases. However, an important feature of avian influenza is that not only can it spread between avian and human populations, but, there is also a high mutation rate of the pathogen. That is, humans can be infected by viruses from infected poultry and poultry environment (avian strain) and also by modification of the genetic information in the genome of a human cell (mutant strain). Thus, modelling the dynamic system of the avian and humans population respectively, and combining the two models are appropriate for avian influenza. Furthermore, to place our model derivation in a specific context, we provide the main modeling assumptions.

- Infected poultry remains in the disease state and cannot recover.
- Death due to disease in poultry population is negligible as compared to the natural mortality. This is due to the fact that avian influenza in poultry is low pathogenic.
- Infected humans with the mutant strain can recover and this recovered humans must achieve permanent immunity.
- Since avian influenza is highly pathogenic in humans, the natural death rate in the human population is negligible compared to that due to the disease.
- Since the disease is extremely virulent among humans, those infected with the avian strain cannot recover naturally.

Suppose that the total variable at time t of the poultry population $N_p(t)$ and the human population $N_h(t)$ is divided into two and three sub-populations, respectively, according to disease status. Susceptible poultry and infected poultry are denoted by $S_p(t)$ and $I_p(t)$, respectively. $S_h(t)$ and $R_h(t)$ denote susceptible humans and recovered humans, respectively. The subpopulations $I_{h1}(t)$ and $I_{h2}(t)$ stand for infected humans with the avian strain and mutant strain, respectively. The concentration of the viruses in the environment is denoted by C. It is assumed that all new immigrants and newborns in the poultry and human populations are susceptible.

The above description leads to a model which is symbolically schematized in Figure 1, and from which the following system of highly nonlinear differential equation is derived.

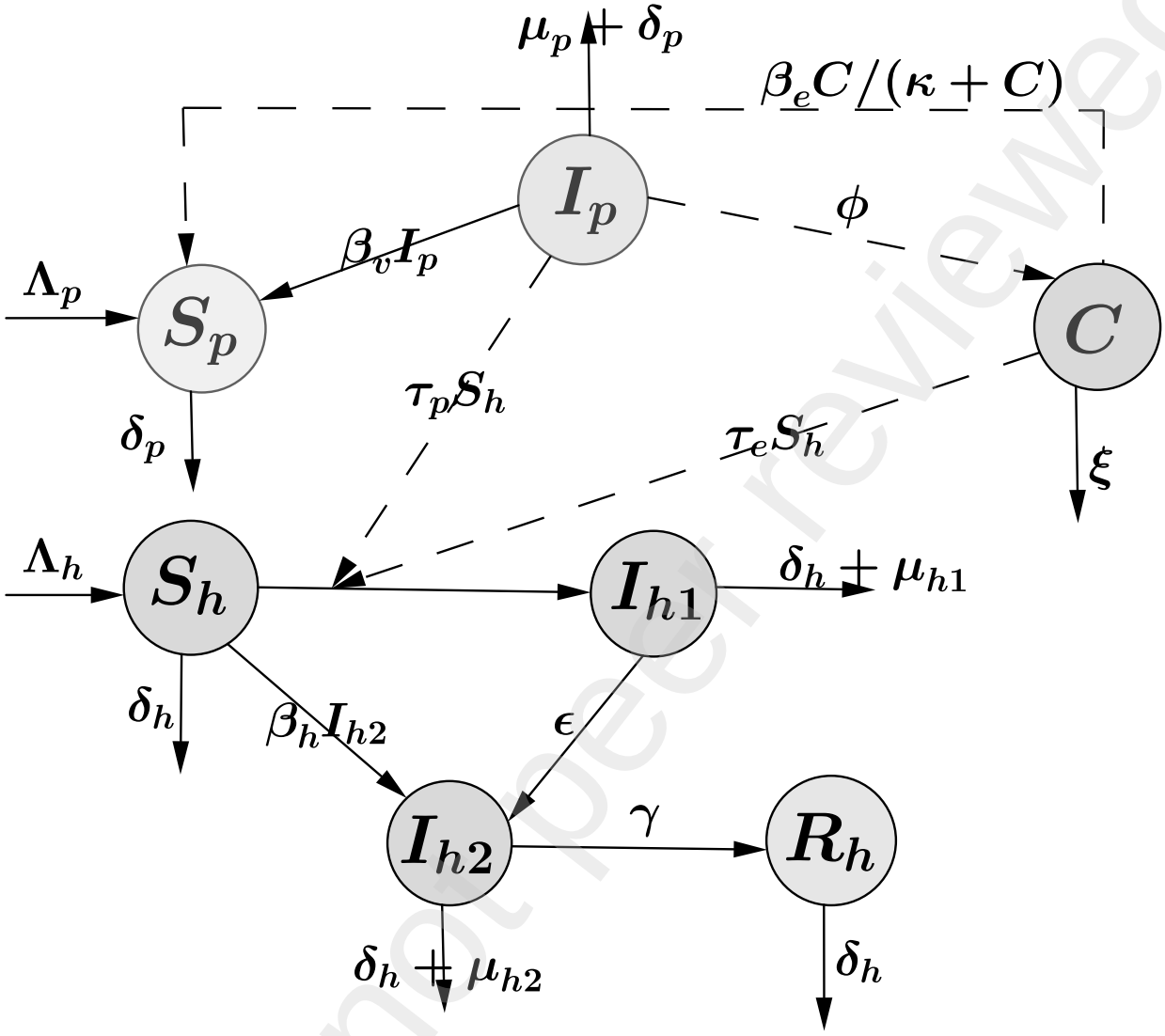

Figure 1: Flowchart of avian influenza transmission of system (2.1).

$$
\begin{cases}
\dfrac{dS_p}{dt} = \Lambda_p - \beta_v S_p I_p - \beta_e \dfrac{S_p C}{C+\kappa} - \delta_p S_p, \\
\dfrac{dI_p}{dt} = \beta_v S_p I_p + \beta_e \dfrac{S_p C}{C+\kappa} - (\delta_p + \mu_p) I_p, \\
\dfrac{dC}{dt} = \phi I_p - \xi C, \\
\dfrac{dS_h}{dt} = \Lambda_h - \tau_p S_h I_p - \tau_e S_h C - \beta_h S_h I_{h2} - \delta_h S_h, \\
\dfrac{dI_{h1}}{dt} = \tau_p S_h I_p + \tau_e S_h C - (\mu_{h1} + \delta_h + \epsilon) I_{h1}, \\
\dfrac{dI_{h2}}{dt} = \beta_h S_h I_{h2} + \epsilon I_{h1} - (\mu_{h2} + \delta_h + \gamma) I_{h2}, \\
\dfrac{dR_h}{dt} = \gamma I_{h2} - \delta_h R_h.
\end{cases}
\tag{2.1}
$$

Every parameter of model (2.1) given in Table 1 is assumed nonnegative and described as follows: Λ_h

Table 1: Biological significance of the model parameters (2.1)–(2.2).

Symbols	Definition	Units
Λ_p	Numbers of imported poultry	ind/week
β_v	Rate at which poultry-to-poultry avian influenza is contracted	$(\text{ ind.week})^{-1}$
μ_{h1}	Death rate in humans due to the avian strain.	week^{-1}
β_e	Rate at which environment-to-poultry avian influenza is contracted	$(\text{ ind.week})^{-1}$
δ_p	Natural death rate of poultry	week^{-1}
μ_p	Disease-related death rate	week^{-1}
Λ_h	Recruitment rate for humans	ind/week
β_h	Rate at which human-to-human avian influenza is contracted	$(\text{ ind.week})^{-1}$
τ_p	Rate at which poultry-to-human avian influenza is contracted	week^{-1}
ϵ	Mutation rate of virus	no unit
δ_h	Natural death rate of humans	week^{-1}
κ	Half-saturation constant for aerosols	$g.m^3$
ξ	Natural mortality rate of virus	week^{-1}
τ_e	Rate at which environment-to-human avian influenza is contracted	ind $/(g.m^3.\text{week})$
ϕ	Emission rate of poultry	$g.m^3/(\text{ind.week})$
μ_{h2}	Human mortality rate induced by the mutant strain	week^{-1}
γ	Recovery rate of humans infected with the mutant strain	week^{-1}

and Λ_p represents the recruitment rate of humans and the numbers of imported poultry, respectively. β_v is the direct contact rate in poultry host such that $\beta_v I_p$ measures the infection force of the infective poultry. In the latter saturated incidence function, β_e denotes the indirect contact rate in poultry host, such that $(\beta_e \gg \beta_v)$; $1/(\kappa + C)$ represents the saturation due to the cleaning of the farm when the concentration of excretion becomes large, and κ is the concentration of avian viruses attached to aerosol particles in the farm with 50% chance of catching the infection. The population of infected poultry is increased by the infection of susceptible poultry at rate $\left(\beta_v I_p + \beta_e C/(\kappa + C)\right) S_p$ and is diminished by natural death at constant rate δ_p and disease death at rate μ_p. The infected poultry infects the farm at constant rate ϕ and the natural death rate of virus is ξ. The susceptible humans decrease due to the spill over of the disease from poultry population and the disease mutation in human population. Then, τ_p is the rate at which poultry-to-human avian strain is contracted, τ_e is the rate at which environment-to-human avian strain is contracted and β_h is the rate at which human-to-human individual mutant strain is contracted. According to Iwami et al [26], it is assumed that humans infected with the avian strain do not infect other humans, so the infected humans with avian strain decrease due to the mutation at rate ϵ, disease-related death at rate μ_{h1} and natural death at rate δ_h. The infected humans with mutant strain diminish due to the recovery of the infected humans with mutant strain at rate γ, disease-related death at rate μ_{h2} and natural death at rate δ_h.

The initial condition for system (2.1) takes the form

$$S_p(0) > 0,\ I_p(0) \geq 0,\ C(0) \geq 0,\ S_h(0) > 0,\ I_{h1}(0) \geq 0,\ I_{h2}(0) \geq 0,\ R_h(0) \geq 0. \tag{2.2}$$

By the fundamental theory of ordinary differential equations [29], we can establish that system (2.1) has a unique solution $(S_p(t), I_p(t), C(t), S_h(t), I_{h1}(t), I_{h2}(t), R_h(t))$ satisfying the initial condition (2.2).

2.2. *The positivity and boundedness of solutions*

This section shows that the solutions of system (2.1) are positive and bounded under the initial condition (2.2).

Theorem 2.1. *All solutions of system (2.1) with initial condition (2.2) are defined on* $(0, \infty)$ *and remain positive for all* $t > 0$.

Proof. See Appendix B.1. ■

Theorem 2.2. *All solutions of system (2.1) with initial condition (2.2) are bounded.*

Proof. See Appendix B.2. ■

From the above discussion, we can conclude that the following set

$$\Omega = \left\{ (S_p, I_p, C, S_h, I_{h1}, I_{h2}, R_h) \in \mathbb{R}_+^7 / S_p + I_p \leq \frac{\Lambda_p}{\delta_p} \; ; \; S_h + I_{h1} + I_{h2} + R_h \leq \frac{\Lambda_h}{\delta_h} \; ; \; C \leq \frac{\phi \Lambda_p}{\delta_p \xi} \right\}$$

is positively invariant for system (2.1).

3. Global analysis of the avian–only model

We first look at the poultry system below, as it decouples from the human system.

$$\begin{cases} \dfrac{dS_p}{dt} = \Lambda_p - \beta_v S_p I_p - \beta_e \dfrac{S_p C}{C + \kappa} - \delta_p S_p, \\ \dfrac{dI_p}{dt} = \beta_v S_p I_p + \beta_e \dfrac{S_p C}{C + \kappa} - (\delta_p + \mu_p) I_p, \\ \dfrac{dC}{dt} = \phi I_p - \xi C. \end{cases} \tag{3.1}$$

3.1. The basic reproduction numbers and feasible equilibria

Two equilibria exist for system (3.1). The first one is the disease-free equilibrium.

$$Z^0 = (S_p^0, 0, 0) \;\text{ where }\; S_p^0 = \frac{\Lambda_p}{\delta_p},$$

which is the state in which infected poultry are absent and the environment is virus-free. The second is a poultry endemic equilibrium $Z^+ = (S_p^+, I_p^+, C^+)$, which represents the state in which infected poultry are found. This is calculated by computing the basic reproduction number of avian influenza in the poultry population, $\mathcal{R}_0^p$. The infected compartments in system (3.1) are I_p and C, ordered (I_p, C). The nonlinear terms with new infection $\mathcal{F}$ and the outflow term $\mathcal{V}$ are given respectively by

$$\mathcal{F} = \begin{pmatrix} S_p \left[\beta_v I_p + \beta_e \dfrac{C}{C + \kappa} \right] \\ 0 \end{pmatrix} \quad \text{and} \quad \mathcal{V} = \begin{pmatrix} (\delta_p + \mu_p) I_p \\ -\phi I_p + \xi C \end{pmatrix}.$$

By evaluating the derivatives of $\mathcal{F}$ and $\mathcal{V}$ at the disease-free equilibrium Z^0, the following matrices are obtained:

$$F = \begin{bmatrix} \beta_v S_p^0 & \dfrac{\beta_e S_p^0}{\kappa} \\ 0 & 0 \end{bmatrix} \text{ and } V = \begin{bmatrix} \delta_p + \mu_p & 0 \\ -\phi & \xi \end{bmatrix}.$$

By applying the next generation approach developed by van den Driessche and Watmough [31], the basic reproduction number of system (3.1) is determined by the spectral radius of FV^{-1}, namely

$$\mathcal{R}_0^p = \frac{\beta_v \Lambda_p}{\delta_p (\mu_p + \delta_p)} + \frac{\beta_e \phi \Lambda_p}{\kappa \delta_p \xi (\mu_p + \delta_p)}.$$

It is straightforward to see that if $\mathcal{R}_0^p > 1$, besides the disease-free equilibrium Z^0, then system (3.1) has an endemic equilibrium Z^+, satisfying

$$C^+ = \frac{\phi}{\xi} I_p^+ \text{ and } S_p^+ = \frac{\Lambda_p \xi}{\beta_e(\phi I_p^+ + \kappa\xi) + \delta_p(\phi I_p^+ + \kappa\xi) + \beta_e \phi I_p^+}, \tag{3.2}$$

where I_p^+ is the positive real root of the following quadratic equation:

$$P(I_p^+) = b_2 {I_p^+}^2 + b_1 I_p^+ + b_0 = 0, \tag{3.3}$$

with

$$\begin{aligned} b_2 &= -\frac{\beta_v \phi(\delta_p + \mu_p)}{\xi}, \\ b_1 &= \frac{\beta_v \Lambda_p \phi}{\xi} - \frac{\beta_e \phi(\delta_p + \mu_p)}{\xi} - \frac{\phi \delta_p(\delta_p + \mu_p)}{\xi} - \beta_v \kappa(\delta_p + \mu_p), \\ b_0 &= \beta_v \Lambda_p \kappa + \frac{\beta_e \Lambda_p \phi}{\xi} - \kappa\delta_p(\delta_p + \mu_p) = \kappa\delta_p(\delta_p + \mu_p)\left(\mathcal{R}_0^p - 1\right). \end{aligned}$$

The solutions of (3.3) must be real and positive for the endemic equilibrium to exist. We note that $b_2 < 0; b_0 < 0 \Leftrightarrow \mathcal{R}_0^p < 1; b_0 \geq 0 \Leftrightarrow \mathcal{R}_0^p \geq 1$. Set $\Delta(\mathcal{R}_0^p) = b_1^2 - 4b_2 b_0$ and $b_1^2 - 4b_2 b_0 = 0$. It follows that $b_1^2 - 4b_2\kappa\delta_p(\delta_p + \mu_p)(\mathcal{R}_0^p - 1) = 0$. Setting $R^* = \mathcal{R}_0^p$ gives

$$R^* = 1 + \frac{b_1^2}{4b_2\kappa\delta_p(\delta_p + \mu_p)}, \text{ that is } R^* = 1 - \frac{\xi b_1^2}{4\beta_v\phi\kappa\delta_p(\delta_p + \mu_p)^2}.$$

The following statements are true:

$$\Delta(\mathcal{R}_0^p) > 0 \Leftrightarrow R^* < \mathcal{R}_0^p;\ \Delta(\mathcal{R}_0^p) = 0 \Leftrightarrow R^* = \mathcal{R}_0^p \text{ and } \Delta(\mathcal{R}_0^p) < 0 \Leftrightarrow \mathcal{R}_0^p < R^*.$$

Different solutions can be obtained depending on the signs of b_1 and b_0. It then follows that :

Theorem 3.1. *System* (3.3)

(i) always has the disease-free equilibrium;

(2i) has a unique endemic equilibrium if $\mathcal{R}_0^p > 1$;

(3i) has a unique endemic equilibrium whenever $\mathcal{R}_0^p = 1$ *and* $b_1 > 0$;

(4i) has a unique endemic equilibrium of multiplicity 2 *when* $\mathcal{R}_0^p = R^*$ *and* $b_1 > 0$;

(5i) has two endemic equilibria, Z_1^+ *and* Z_2^+ *when* $R^* < \mathcal{R}_0^p < 1$ *and* $b_1 > 0$;

(6i) has no endemic equilibria whenever $R^* > \mathcal{R}_0^p$ *or whenever* $R^* < \mathcal{R}_0^p < 1$ *and* $b_1 < 0$ *or whenever* $\mathcal{R}_0^p < 1$ *and* $b_1 < 0$.

Conclusion (5*i*) of Theorem 3.1 indicates that a backward bifurcation may occur when $R^* < \mathcal{R}_0^p < 1$ and $b_1 > 0$ for some parameter values. But in our case, the following Theorem applies.

Theorem 3.2. *The system* (3.1) *presents a trans-critical forward bifurcation at* $\mathcal{R}_0^p = 1$.

Proof. The proof is based on the theoretical results in [30]. The proof is omitted here, but we invite the reader to look at our previous work [11], dealing with a similar case. The forward bifurcation diagram is given in Figure 2 below. ■

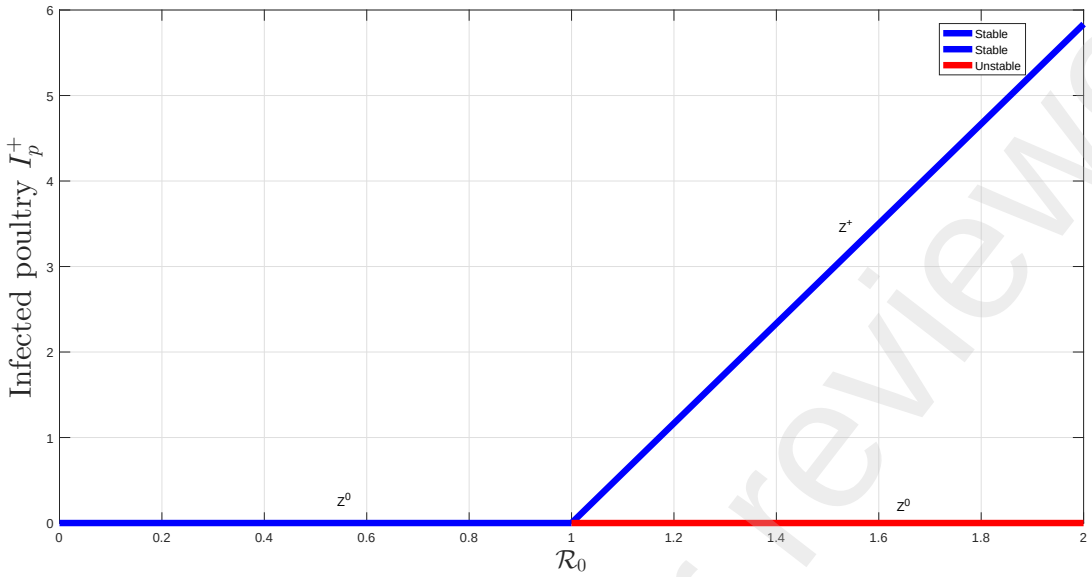

Figure 2: The forward bifurcation curve. The parameter values we used are $\Lambda_p = 50$, $\xi = 500$, $\beta_v = 2$, $\tau_e = 0.1$, $\beta_e = 6$, $\phi = 10^4$, $\delta_p = 5$, $\beta_h = 0.003$, $\Lambda_h = 3$, $\kappa = 10^6$, $\gamma = 0.01$, $\delta_h = 0.015$, $\mu_{h1} = 1$, $\mu_{h2} = 0.06$, $\tau_p = 0.6$, $\mu_p = 1$, $\epsilon = 0.001$.

3.2. Local asymptotic stability

Theorem 3.3. *The disease-free equilibrium Z^0 of the poultry system (3.1) is locally asymptotically stable whenever $\mathcal{R}_0^p < 1$, but unstable when $\mathcal{R}_0^p > 1$.*

Proof. It's straightforward.

■

Theorem 3.4. *The endemic equilibrium Z^+ of the poultry system (3.1) is locally asymptotically stable whenever $\mathcal{R}_0^p > 1$.*

Proof. It is obvious. ■

3.3. Global asymptotic stability

In this section we are interested in the global asymptotic stability of each of the feasible equilibria of system (3.1).

Theorem 3.5. *If $\mathcal{R}_0^p \leq 1$, the disease-free equilibrium Z^0 of the poultry system (3.1) is globally asymptotically stable in Ω.*

Proof. Define the Lyapunov function

$$H_1(t) = S_p - S_p^0 - S_p^0 \ln\left(\frac{S_p}{S_p^0}\right) + I_p + \frac{\beta_e \Lambda_p}{\kappa \delta_p \xi} C.$$

Using the fact that $\Lambda_p = \delta_p S_p^0$, and calculating the derivative of $H_1(t)$ along positive solutions of system (3.1) yields

$$\begin{aligned}
\frac{dH_1(t)}{dt} &= \left(1-\frac{S_p^0}{S_p}\right)\frac{dS_p(t)}{dt} + \frac{dI_p(t)}{dt} + \frac{\beta_e\Lambda_p}{\kappa\delta_p\xi}\frac{dC(t)}{dt},\\
&= \left(1-\frac{S_p^0}{S_p}\right)\left(\Lambda_p - \beta_v S_p I_p - \beta_e S_p\frac{C}{C+\kappa} - \delta_p S_p\right)\\
&\quad + \left(\beta_v S_p I_p + \beta_e S_p\frac{C}{C+\kappa} - (\delta_p+\mu_p)I_p\right) + \frac{\beta_e\Lambda_p}{\kappa\delta_p\xi}(\phi I_p - \xi C),\\
&= -\frac{\delta_p}{S_p}(S_p - S_p^0)^2 + \beta_v S_p^0 I_p + \beta_e S_p^0\frac{C}{C+\kappa} + \frac{\beta_e\phi\Lambda_p}{\kappa\delta_p\xi}I_p\\
&\quad -(\delta_p+\mu_p)I_p - \frac{\beta_e\Lambda_p}{\kappa\delta_p}C.
\end{aligned}$$

Straightforward calculations lead to

$$\frac{dH_1(t)}{dt} \leq -\frac{\delta_p}{S_p}(S_p - S_p^0)^2 + (\delta_p+\mu_p)\left(\mathcal{R}_0^p - 1\right)I_p < 0, \quad \text{when} \quad \mathcal{R}_0^p \leq 1.$$

It is easy to see that the largest invariant subset included in the set $\left\{(S_p, I_p, C) \in \Omega / \frac{dH_1(t)}{dt} = 0\right\}$ is the singleton $\left\{Z^0\right\}$. Thus, by LaSalle's Invariance Principle [32], the disease-free equilibrium Z^0 is globally asymptotically stable in Ω. This completes the proof. ■

Theorem 3.6. *If $\mathcal{R}_0^p > 1$, the endemic equilibrium Z^+ of the poultry system (3.1) is globally asymptotically stable in the interior of Ω.*

Proof. Let $(S_p(t), I_p(t), C(t))$ be any positive solution of system (3.1) with initial condition $(S_p(0), I_p(0), C(0))$. Define

$$H_2(t) = c_3\left[S_p - S_p^+ - S_p^+\ln\left(\frac{S_p}{S_p^+}\right)\right] + c_4\left[I_p - I_p^+ - I_p^+\ln\left(\frac{I_p}{I_p^+}\right)\right] + c_5\left[C - C^+ - C^+\ln\left(\frac{C}{C^+}\right)\right],$$

where the constants c_3, c_4 and c_5 will be determined later.

The derivative of $H_2(t)$ along the positive solutions of the system (3.1) gives

$$\begin{aligned}
\frac{dH_2}{dt} &= c_3\left(1-\frac{S_p^+}{S_p}\right)\frac{dS_p}{dt} + c_4\left(1-\frac{I_p^+}{I_p}\right)\frac{dI_p}{dt} + c_5\left(1-\frac{C^+}{C}\right)\frac{dC}{dt},\\
&= c_3\left(1-\frac{S_p^+}{S_p}\right)\left[\delta_p S_p^+ + \beta_v S_p^+ I_p^+ + \frac{\beta_e S_p^+ C^+}{\kappa+C^+} - \delta_p S_p - \beta_v S_p I_p - \frac{\beta_e S_p C}{\kappa+C}\right]\\
&\quad + c_4\left(1-\frac{I_p^+}{I_p}\right)\left[\beta_v S_p I_p + \frac{\beta_e S_p C}{\kappa+C} - \left(\beta_v S_p^+ + \frac{\beta_e S_p^+ C^+}{I_p^+(\kappa+C^+)}\right)I_p\right]\\
&\quad + c_5\left(1-\frac{C^+}{C}\right)\left[\phi I_p - \frac{\phi I_p^+ C}{C^+}\right],
\end{aligned}$$

$$\begin{aligned}
&= -c_3\frac{\delta_p(S_p - S_p^*)^2}{S_p} + \beta_v S_p^+ I_p^+(c_3+c_4) + \frac{\beta_e S_p^+ C^+}{\kappa+C^+}(c_3+c_4) + \beta_v S_p I_p(c_4-c_3)\\
&\quad + \frac{\beta_e S_p C}{\kappa+C}(c_4-c_3) - \frac{\beta_v {S_p^+}^2 I_p^+}{S_p}c_3 - \frac{\beta_e {S_p^+}^2 C^+}{S_p(\kappa+C^+)}c_3 + \beta_v S_p^+ I_p c_3 + \frac{\beta_e S_p^+ C}{\kappa+C}c_3\\
&\quad - \beta_v S_p^+ I_p c_4 - \frac{\beta_e S_p^+ C^+}{I_p^+(\kappa+C^+)}I_p c_4 - c_4\beta_v S_p I_p^+ - c_4\frac{\beta_e S_p C I_p^+}{I_p(\kappa+C)}\\
&\quad + c_5\phi I_p - c_5\frac{\phi I_p^+ C}{C^+} - c_5\frac{\phi I_p C^+}{C} + \phi I_p^+ c_5.
\end{aligned}$$

By choosing

$$c_3 = c_4 \text{ and } c_5 = \frac{\beta_e S_p^+ C^+}{\phi I_p^+(\kappa + C^+)} c_4,$$

we have

$$\begin{aligned}
\frac{dH}{dt} &= -c_3\frac{(\delta_p+v)(S_p-S_p^+)^2}{S_p} + c_3\beta_v S_p^+ I_p^+\left[2-\frac{S_p^+}{S_p}-\frac{S_p}{S_p^+}\right] \\
&\quad + c_3\frac{\beta_e S_p^+ C^+}{\kappa+C^+}\left[3-\frac{S_p^+}{S_p}+\frac{C(\kappa+C^+)}{C^+(\kappa+C)}-\frac{S_p I_p^+ C(\kappa+C^+)}{S_p^+ I_p C^+(\kappa+C)}-\frac{C}{C^+}-\frac{C^+ I_p}{C I_p^+}\right] \\
&= -c_3\frac{\delta_p(S_p-S_p^+)^2}{S_p} + c_3\beta_v S_p^+ I_p^+\left[2-\frac{S_p^+}{S_p}-\frac{S_p}{S_p^+}\right] \\
&\quad + c_3\frac{\beta_e S_p^+ C^+}{\kappa+C^+}\left[4-\frac{S_p^+}{S_p}-\frac{\kappa+C}{\kappa+C^+}-\frac{S_p}{S_p^+}\frac{I_p^+}{I_p}\frac{\kappa+C^+}{\kappa+C}\frac{C}{C^+}-\frac{C^+}{C}\frac{I_p}{I_p^+}\right] \\
&\quad - c_3\frac{\beta_e S_p^+ C^+}{\kappa+C^+} + c_3\frac{\beta_e S_p^+ C}{\kappa+C} - c_3\frac{\beta_e S_p^+ C}{\kappa+C^+} + c_3\frac{\beta_e S_p^+ C^+(\kappa+C)}{(\kappa+C^+)^2} \\
&= -c_3\frac{\delta_p(S_p-S_p^+)^2}{S_p} + c_3\beta_v S_p^+ I_p^+\left[2-\frac{S_p^+}{S_p}-\frac{S_p}{S_p^+}\right] \\
&\quad + c_3\frac{\beta_e S_p^+ C^+}{\kappa+C^+}\left[4-\frac{S_p^+}{S_p}-\frac{\kappa+C}{\kappa+C^+}-\frac{S_p}{S_p^+}\frac{I_p^+}{I_p}\frac{\kappa+C^+}{\kappa+C}\frac{C}{C^+}-\frac{C^+}{C}\frac{I_p}{I_p^+}\right] \\
&\quad - c_3\frac{\kappa\beta_e S_p^+ C^+(C-C^+)^2}{(\kappa+C)(\kappa+C^+)^2}.
\end{aligned}$$

When $\mathcal{R}_0^p > 1$, it follows from the inequality of arithmetic and geometric means that $H_2'(t) < 0$ for $(S_p(t), I_p(t), C(t)) \neq (S_p^+, I_p^+, C^+)$. Therefore, by LaSalle's Invariance Principle [32], the equilibrium (S_p^+, I_p^+, C^+) is globally asymptotically stable. ■

4. Global analysis of the full model

Now we investigate the full system (2.1).

4.1. *The basic reproduction numbers and feasible equilibria*

System (2.1) has three equilibria. The first one is the full disease free equilibrium

$$F^0 = (S_p^0, 0, 0, S_h^0, 0, 0, 0) \text{ with } S_h^0 = \frac{\Lambda_h}{\delta_h},$$

which represents the state in which the infected poultry with avian strain, infected humans with avian strain and mutant strain are absent and the environment is virus-free.

For other equilibria, we first evaluate the basic reproduction number for mutant strain in the human population. By applying the next generation approach developed by van den Driessche and Watmough [31], the basic reproduction number of system (2.1) is

$$\mathcal{R}_0 = \max\{\mathcal{R}_0^p, \mathcal{R}_0^h\},$$

where

$$\mathcal{R}_0^h = \frac{\beta_h \Lambda_h}{\delta_h(\mu_{h2}+\delta_h+\gamma)}.$$

4.2. *Sensitivity of the basic reproduction number*

To determine the parameters that strongly affect the reproduction number, we use the same methods as [33, 34, 35, 36]. As can be easily observed from sections 3.1 and 4.1, that the reproduction number is a function of the vital parameters of the system dynamics.

Definition 4.1. *The normalized forward sensitivity index of a variable,* Π*, that depends differentially on a parameter,* ω*, is defined as:*

$$\gamma_{\omega}^{\Pi} = \frac{\partial \Pi}{\partial \omega} \times \frac{\omega}{|\Pi|}. \tag{4.1}$$

Now using (4.1), we derive the sensitivity of $\mathcal{R}_0$ to each of the parameters. The sensitivity index of $\mathcal{R}_0$ with respect to β_e, for example, is

$$\gamma_{\beta_e}^{\mathcal{R}_0} = \frac{\partial \mathcal{R}_0}{\partial \beta_e} \times \frac{\beta_e}{\mathcal{R}_0}. \tag{4.2}$$

The detailed indexes of the sensitivity of $\mathcal{R}_0$ resulting from the evaluation of the other model parameters are presented in Table 2 below. A positive (resp. negative) index indicates that an increase in the parameter value results in an increase (resp. decrease) in the $\mathcal{R}_0$ value.

Table 2: Sensitivity indexes for $\mathcal{R}_0$. The parameter values we used are: $\Lambda_p = 50$, $\xi = 500$, $\beta_v = 2$, $\tau_e = 0.1$, $\beta_e = 6$, $\phi = 10^4$, $\delta_p = 5$, $\beta_h = 0.003$, $\Lambda_h = 3$, $\kappa = 10^6$, $\gamma = 0.01$, $\delta_h = 0.015$, $\mu_{h1} = 1$, $\mu_{h2} = 0.06$, $\tau_p = 0.6$, $\mu_p = 1$, $\epsilon = 0.001$.

Parameter	Sensitivity index	Value	Parameter	Sensitivity index	Value
β_v	$\gamma_{\beta_v}^{\mathcal{R}_0}$	0.9999	μ_p	$\gamma_{\mu_p}^{\mathcal{R}_0}$	-0.1667
β_e	$\gamma_{\beta_e}^{\mathcal{R}_0}$	9.9994×10^{-6}	β_h	$\gamma_{\beta_h}^{\mathcal{R}_0}$	1
Λ_p	$\gamma_{\Lambda_p}^{\mathcal{R}_0}$	1	Λ_h	$\gamma_{\Lambda_h}^{\mathcal{R}_0}$	1
ϕ	$\gamma_{\phi}^{\mathcal{R}_0}$	5.9996×10^{-5}	δ_h	$\gamma_{\delta_h}^{\mathcal{R}_0}$	-1.1765
ξ	$\gamma_{\xi}^{\mathcal{R}_0}$	-5.9996×10^{-5}	μ_{h2}	$\gamma_{\mu_{h2}}^{\mathcal{R}_0}$	-0.7059
δ_p	$\gamma_{\delta_p}^{\mathcal{R}_0}$	-1.8333	γ	$\gamma_{\gamma}^{\mathcal{R}_0}$	-0.1176

From Table 2, we can observe that the parameters $\beta_v, \beta_e, \Lambda_p, \phi, \beta_h$ and Λ_h have each a positive influence in the value of $\mathcal{R}_0$. For instance, the biological implication of $\gamma_{\beta_h}^{\mathcal{R}_0} = 1, \gamma_{\Lambda_p}^{\mathcal{R}_0} = 1$ and $\gamma_{\Lambda_h}^{\mathcal{R}_0} = 1$ is that an increase in 100% of β_h, Λ_p and Λ_h results in an increase in 100% in the reproduction number $\mathcal{R}_0$. In reviewing the sensitivity analysis, it is not biologically reasonable and economical to suggest that the mortality rate (poultry or human) be increased in order to control the disease. Other possible sensitive parameters that are important for effective disease control are the recruitment rate (poultry or human) through poultry vaccination and quarantine of infected humans or treatment of infected individuals and sensitisation of humans.

The second equilibrium is the human-endemic equilibrium given by

$$F^{+} = (S_p^0, 0, 0, S_h^{+}, 0, I_{h2}^{+}, R_h^{+}), \text{ where } S_h^{+} = \frac{\delta_h + \mu_{h2} + \gamma}{\beta_h}, \quad I_{h2}^{+} = \frac{\delta_h}{\beta_h}\left(\mathcal{R}_0^h - 1\right), \quad R_h^{+} = \frac{\gamma}{\delta_h} I_{h2}^{+},$$

which corresponds to the state in which poultry and humans infected with the avian strain are absent but humans infected with the mutant strain are present and the environment is free from virus.

The third equilibrium is the full-endemic equilibrium given by

$$F^{*} = (S_p^{+}, I_p^{+}, C^{+}, S_h^{*}, I_{h1}^{*}, I_{h2}^{*}, R_h^{*}), \text{ where } S_h^{*} = \frac{\Lambda_h}{\tau_p I_p^{+} + \tau_e C^{+} + \beta_h I_{h2}^{*} + \delta_h},$$

$$R_h^{*} = \frac{\gamma}{\delta_h} I_{h2}^{*} \text{ and } I_{h1}^{*} = \frac{\tau_p I_p^{+} + \tau_e C^{+}}{\delta_h + \mu_{h1} + \epsilon} S_h^{*},$$

which corresponds to the state in which the poultry and humans are infected with the avian strain and the mutant strain. Here I^*_{h2} is the largest solution of the following equation:

$$H(I^*_{h2}) = \alpha_2 {I^*_{h2}}^2 + \alpha_1 I^*_{h2} + \alpha_0 = 0, \tag{4.3}$$

where

$$\begin{aligned}
\alpha_2 &= \beta_h(\delta_h + \mu_{h1} + \epsilon)(\delta_h + \mu_{h2} + \gamma),\\
\alpha_1 &= (\tau_p I^+_p + \tau_e C^+ + \delta_h)(\delta_h + \mu_{h1} + \epsilon)(\delta_h + \mu_{h2} + \gamma) - \beta_h \Lambda_h(\delta_h + \mu_{h1} + \epsilon),\\
\alpha_0 &= -\epsilon\Lambda_h(\tau_p I^+_p + \tau_e C^+).
\end{aligned}$$

Since $H(0) < 0$ and $\lim_{I^*_{h2}\to\infty} H(I^*_{h2}) = \infty$, F^* is unique if it exists. The following Lemma summarises the above investigation about the existence of equilibria.

Lemma 4.2. *F^0 always exists in Ω. If $\mathcal{R}^h_0 > 1$ and $\mathcal{R}^p_0 < 1$, then F^+ exists in Ω. F^* exists in Ω, if $\mathcal{R}^p_0 > 1$.*

4.3. Local asymptotic stability

The following Theorem is obtained for the local stability of these equilibria.

Theorem 4.3. *If $\mathcal{R}^p_0 < 1$ and $\mathcal{R}^h_0 < 1$, then F^0 is LAS. If $\mathcal{R}^p_0 < 1$ and $\mathcal{R}^h_0 > 1$, then F^+ is LAS. If $\mathcal{R}^p_0 > 1$, then F^* is LAS.*

Proof. See Appendix C.1. ■

4.4. Global asymptotic stability

This section is devoted to the global analysis of the spread of the avian strain and the mutant strain in humans. We denote by ψ_0 the initial value for system (2.1) (that is $\psi_0 = \left(S^0_p, I^0_p, S^0_h, C^0, I^0_{h1}, I^0_{h2}, R^0_h\right)$), and $\omega(\psi_0)$ denotes an ω-limit set of the orbit passing through ψ_0. We need the following Lemmas and Theorems to formulate our global stability Theorem.

Lemma 4.4. *Let $S^\infty_h = \limsup_{t\to\infty} S_h(t)$. Then $S^\infty_h \le S^0_h$.*

Proof. Based on the fourth equality of system (2.1), we have

$$\dot{S}_h = \Lambda_h - \tau_p S_h I_p - \tau_e S_h C - \beta_h S_h I_{h2} - \delta_h S_h \le \Lambda_h - \delta_h S_h.$$

Integrating this inequality over $[0, t]$ we obtain

$$S_h(t) \le S^0_h + |S_h(0) - S^0_h| e^{-\delta_h t}.$$

Given $\epsilon_1 > 0$, we can choose t_1 large enough so that

$$|S_h(0) - S^0_h| e^{-\delta_h t} \le \epsilon_1, \text{ for } t \ge t_1.$$

Hence

$$S_h(t) \le S^0_h + \epsilon_1, \text{ for } t \ge t_1.$$

Thus, for $T_1 \ge t_1$, $\sup_{t\ge T_1} S_h(t) \le S^0_h + \epsilon_1$. Letting $T_1 \to \infty$ we deduce that $S^\infty_h \le S^0_h + \epsilon_1$. Hence as ϵ_1 can be chosen arbitrarily small, $S^\infty_h \le S^0_h$. This completes the proof of Lemma 4.4. ■

As

$$\begin{aligned}
\dot{S}_h + \dot{I}_{h1} + \dot{I}_{h2} + \dot{R}_h &= \Lambda_h - \delta_h(S_h + I_{h1} + I_{h2} + R_h) - \mu_{h1} I_{h1} - \mu_{h2} I_{h2}\\
&\le \Lambda_h - \delta_h(S_h + I_{h1} + I_{h2} + R_h),
\end{aligned}$$

we can easily prove that $S^\infty_h + I^\infty_{h1} + I^\infty_{h2} + R^\infty_h \le S^0_h$, where $I^\infty_{h1} = \limsup_{t\to\infty} I_{h1}(t)$, $R^\infty_h = \limsup_{t\to\infty} R_h(t)$ and $I^\infty_{h2} = \limsup_{t\to\infty} I_{h2}(t)$.

Theorem 4.5. *[26] Assume that X is a subset of $\mathbb{R}^n_+$ and S is a subset of X. Let X be forward invariant. If $\omega(\psi_0) \subset S$ for all $\psi_0 \in X$ and there only exists an equilibrium E such that E is GAS in S and E is LAS in X, then E is GAS in X.*

At present, we are able to prove the GAS of F^0. Let

$$\Omega_0 = \left\{(S_p, I_p, C, S_h, I_{h1}, I_{h2}, R_h) \,/\, S_p > 0,\ I_p = 0, C = 0, S_h > 0,\ I_{h1} = 0,\ I_{h2} = 0, R_h = 0\right\},$$

$$\Omega_1 = \left\{(S_p, I_p, C, S_h, I_{h1}, I_{h2}, R_h) \,/\, S_p > 0,\ I_p \geq 0,\ C \geq 0,\ S_h > 0,\ I_{h1} \geq 0,\ I_{h2} \geq 0,\ R_h \geq 0\right\}.$$

Theorem 4.6. *If $\mathcal{R}_0^p \leq 1$ and $\mathcal{R}_0^h < 1$, then F^0 is GAS in Ω_1.*

Proof. Since $\mathcal{R}_0^p \leq 1$, it follows from Theorem 3.5 that $\lim_{t\to\infty} S_p(t) = S_p^0$, $\lim_{t\to\infty} I_p(t) = 0$ and $\lim_{t\to\infty} C(t) = 0$. Thus

$$\lim_{t\to\infty} I_{h1}(t) = \lim_{t\to\infty} \lambda_1 e^{-(\delta_h + \mu_{h1} + \epsilon)t} = 0,$$

and the following equation holds as $t \to \infty$,

$$\dot{I}_{h2}(t) = (\beta_h S_h(t) - (\mu_{h2} + \delta_h + \gamma))I_{h2}(t).$$

From Lemma 4.4, when $t \to \infty$, we have

$$\dot{I}_{h2} \leq (\beta_h S_h^0 - (\mu_{h2} + \delta_h + \gamma))I_{h2} \leq (\mu_{h2} + \delta_h + \gamma)\left(\mathcal{R}_0^h - 1\right) I_{h2}.$$

Thus

$$\lim_{t\to\infty} I_{h2} \leq \lim_{t\to\infty} \lambda_1 e^{(\mu_{h2}+\delta_h+\gamma)(\mathcal{R}_0^h - 1)} = 0 \ \text{ if and only if } \ \mathcal{R}_0^h < 1.$$

It follows that, for any ψ_0 in Ω_1, $\omega(\psi_0)$ exists in Ω_0. It is obvious that F^0 is GAS in Ω_0. Consequently, we can conclude by Theorem 4.5 that F^0 is GAS on Ω_1. ■

Now we give the following Theorem which proves that F^+ is GAS. Let

$$\Omega_2 = \left\{(S_p, I_p, C, S_h, I_{h1}, I_{h2}, R_h) \in \mathbb{R}^7_+ / S_p > 0,\ I_p = 0, C = 0, S_h > 0,\ I_{h1} = 0,\ I_{h2} > 0,\ R_h > 0\right\},$$

$$\Omega_3 = \left\{(S_p, I_p, C, S_h, I_{h1}, I_{h2}, R_h) \in \mathbb{R}^7_+ / S_p > 0,\ I_p \geq 0,\ C \geq 0,\ S_h > 0,\ I_{h1} \geq 0,\ I_{h2} > 0,\ R_h > 0\right\}.$$

Theorem 4.7. *If $\mathcal{R}_0^p \leq 1$ and $\mathcal{R}_0^h > 1$, then F^+ is GAS in Ω_3.*

Proof. The dynamics of the spread of mutant strain is given by the following system on Ω_2.

$$\begin{cases} \dfrac{dS_p}{dt} = \Lambda_p - \delta_p S_p, \\ \dfrac{dS_h}{dt} = \Lambda_h - \beta_h S_h I_{h2} - \delta_h S_h, \\ \dfrac{dI_{h2}}{dt} = \beta_h S_h I_{h2} - (\mu_{h2} + \delta_h + \gamma) I_{h2}, \\ \dfrac{dR_h}{dt} = \gamma I_{h2} - \delta_h R_h. \end{cases} \tag{4.4}$$

Obviously, the poultry system and the human system are independent. So $\lim_{t\to\infty} S_p(t) = S_p^0$. Let us define

$$\Omega_4 = \left\{(S_p, S_h, I_{h2}, R_h) \in \mathbb{R}^4_+ \,/\, S_p > 0,\ S_h > 0,\ I_{h2} > 0,\ R_h > 0\right\}.$$

To prove Theorem 4.7, the following Lemma is relevant.

Lemma 4.8. *If $\mathcal{R}_0^h > 1$, then $(S_p^0, S_h^+, I_{h2}^+, R_h^+)$ is GAS in Ω_4.*

Proof. Let $N = S_h^+ + I_{h2}^+ + R_h^+$. System (4.4) is dissipative and has a positive equilibrium $(S_p^0, S_h^+, I_{h2}^+, R_h^+)$ if $\mathcal{R}_0^h > 1$. Furthermore, $(S_p^0, S_h^+, I_{h2}^+, R_h^+)$ is LAS (see Theorem 4.3) when $\mathcal{R}_0^h > 1$.

Since system (4.4) is dissipative, positive constants k and K must exist such that $k \leq N \leq K$ for a sufficiently large time. Let us define

$$\Omega_5 = \left\{(S_h, I_{h2}, R_h) \in \mathbb{R}_+^3 \ / \ S_h = S_h^+,\ I_{h2} = I_{h2}^+, R_h \geq 0,\ k \leq N \leq K\right\},$$

$$\Omega_6 = \left\{(S_h, I_{h2}, R_h) \in \mathbb{R}_+^3 \ / \ S_h = S_h^+,\ I_{h2} = I_{h2}^+,\ R_h = 0,\ k \leq N \leq K\right\}.$$

Ω_5 is a compact subset of $\mathbb{R}_+^3$, Ω_6 is a compact subset of Ω_5 and Ω_5 is forward invariant. We define a C^1 function: $P : \Omega_5 \to \mathbb{R}_+$ such that $P(\sigma) = R_h$, which verifies $P(\sigma) = 0$ if and only if $\sigma \in \Omega_6$. On the other hand, $\dot{P}(\sigma) > 0$, $\forall \sigma \in \Omega_6$. Therefore, there exists a positive constant δ such that $\liminf_{t\to\infty} R_h(t) \geq \delta$, $\forall \psi_0 \in \Omega_5 \setminus \Omega_6$ by Appendix A.1. It results that $\omega(\psi_0)$ exists in $\Omega_5 \setminus \Omega_6$, $\forall \psi_0 \in Int\mathbb{R}_+^3$. It is obvious that (S_h^+, I_{h2}^+, R_h^+) is GAS in $\Omega_5 \setminus \Omega_6$. We can now conclude that (S_h^+, I_{h2}^+, R_h^+) is GAS in $Int\mathbb{R}_+^3$ by virtue of Theorem 4.5. ■

It is worth noting that Lemma 4.8 indicates that the mutant strain is endemic in the human population if a human infected with the mutant strain exists and $\mathcal{R}_0^h > 1$.

Thanks to Theorem 3.5, we have $\mathcal{R}_0^p \leq 1$, $\lim_{t\to\infty} S_p(t) = S_p^0, \lim_{t\to\infty} I_p(t) = 0$ and $\lim_{t\to\infty} C(t) = 0$. Therefore, $\lim_{t\to\infty} I_{h1}(t) = 0$. This results in $\omega(\psi_0)$ existing in Ω_2, for all ψ_0 in Ω_3. By virtue of the Lemma 4.8, F^+ is GAS in Ω_2. We therefore deduce that F^+ is GAS in Ω_3 by Theorem 4.5. ■

We next move on to the case where both the avian and mutant strains are spreading among humans.

Definition 4.9. *We say that system (2.1) is permanent if*

$$k_{S_1} \leq \liminf_{t\to\infty} S_p(t) \leq \limsup_{t\to\infty} S_p(t) \leq K_{S_1}$$

$$k_{I_1} \leq \liminf_{t\to\infty} I_p(t) \leq \limsup_{t\to\infty} I_p(t) \leq K_{I_1}$$

$$k_C \leq \liminf_{t\to\infty} C(t) \leq \limsup_{t\to\infty} C(t) \leq K_C$$

$$k_{S_2} \leq \liminf_{t\to\infty} S_h(t) \leq \limsup_{t\to\infty} S_h(t) \leq K_{S_2}$$

$$k_{I_2} \leq \liminf_{t\to\infty} I_{h1}(t) \leq \limsup_{t\to\infty} I_{h1}(t) \leq K_{I_2}$$

$$k_{I_3} \leq \liminf_{t\to\infty} I_{h2}(t) \leq \limsup_{t\to\infty} I_{h2}(t) \leq K_{I_3}$$

$$k_R \leq \liminf_{t\to\infty} R_h(t) \leq \limsup_{t\to\infty} R_h(t) \leq K_R,$$

for any solution of system (2.1) with $\psi_0 \in Int\mathbb{R}_+^7$. The constants k_i and K_i $(i = S_1, I_1, C, S_2, I_1, I_2, R)$ are positive and independent of ψ_0.

Afterwards, we first state and prove the following result which will help us to prove the global stability of the endemic equilibrium F^*.

Theorem 4.10. *If $\mathcal{R}_0^p > 1$, then system (2.1) is permanent, that is, the infected humans with avian strain and mutant strain persist.*

Proof. It is obvious that $K_i; (i = S_1, I_1, C, S_2, I_1, I_2, R)$ exist according to Theorem 2.2. Let's define

$$\Omega_a = \left\{(S_p, I_p, C, S_h, I_{h1}, I_{h2}, R_h) \in \mathbb{R}_+^7 \ / \ S_p \geq k_{S_1}\ ,\ I_p \geq k_{I_1}, C \geq k_C,\ k_1 \leq N_p + N_h \leq K_1\right\},$$

$$\Omega_b = \left\{(S_p, I_p, C, S_h, I_{h1}, I_{h2}, R_h) \in \mathbb{R}_+^7 \ / \ S_p \geq k_{S_1}\ ,\ I_p \geq k_{I_1}, C \geq k_C,\ S_h = 0\ ,\ k_1 \leq N_p + N_h \leq K_1\right\}.$$

Theorems 2.2, 3.5 and 3.6 show that Ω_a is a compact subset of $\mathbb{R}^7_+$, Ω_b is a compact subset of Ω_a and Ω_a is forward invariant (Theorem 3.6 shows that Z^+ is GAS when $\mathcal{R}_0^p > 1$). Consider $P = S_h$. Then $P : \Omega_a \to \mathbb{R}_+$ is C^1 and verifies $P(\sigma) = 0$ if and only if $\sigma \in \Omega_b$. Furthermore, $\dot{P}(\sigma) > 0, \ \forall \sigma \in \Omega_b$. Consequently, there exists a positive constant k_{S_2} such that $\liminf_{t\to\infty} S_h(t) \geq k_{S_2}$, for all ψ_0 in $\Omega_a \setminus \Omega_b$ by Appendix A.1.

Let's now define

$$\Omega_c = \left\{(S_p, I_p, C, S_h, I_{h1}, I_{h2}, R_h)/S_p \geq k_{S_1},\ I_p \geq k_{I_1}, C \geq k_C, S_h \geq k_{S_2},\ I_{h1} = 0,\ k_1 \leq N_p + N_h \leq K_1\right\}.$$

Similarly, a positive constant k_{I_2} exists such that $\liminf_{t\to\infty} I_{h1}(t) \geq k_{I_2}$, for all ψ_0 in $\Omega_a \setminus \Omega_c$. The same goes for all the other state variables. Therefore, we conclude that system (2.1) is permanent. ■

Let us observe that in (2.1), the first three equations do not contain the variables S_h, I_{h1}, I_{h2} and R_h. Also notice that the first three equations of the human system of (2.1) do not contain the variable R_h. Since Z^+ is GAS on $Int\mathbb{R}^3_+$ according to Theorem 3.6, the study of the GAS of F^* can be reduced to the study of the GAS of the equilibrium $(S_h^*, I_{h1}^*, I_{h2}^*)$ of system (4.5) below

$$\begin{cases} \dfrac{dS_h}{dt} = \Lambda_h - \tau_p S_h I_p^+ - \tau_e S_h C^+ - \beta_h S_h I_{h2} - \delta_h S_h, \\ \dfrac{dI_{h1}}{dt} = \tau_p S_h I_p^+ + \tau_e S_h C^+ - (\mu_{h1} + \delta_h + \epsilon) I_{h1}, \\ \dfrac{dI_{h2}}{dt} = \beta_h S_h I_{h2} + \epsilon I_{h1} - (\gamma + \mu_{h2} + \delta_h) I_{h2}. \end{cases} \tag{4.5}$$

From Theorem 4.10 and the boundedness of solutions, it follows that a compact absorbing set exists for system (2.1). Therefore, in Lemma Appendix C.1, both assumptions (H_1) and (H_2) are satisfied for $\mathcal{R}_0^p > 1$.

We now apply Lemma Appendix C.1 to derive the global stability of the endemic equilibrium F^* in the feasible region Ω. So, the following Theorem applies.

Theorem 4.11. *If $\mathcal{R}_0^p > 1$, then the infective equilibriumn F^* of system (2.1) is globally asymptotically stable in the interior of Ω, if the following conditions are satisfied*

$$\begin{aligned} \mu_{h2} + \gamma &\leq \frac{\epsilon k_{I_2}}{K_{I_3}} + \beta_h k_{I_3} + \tau_p I_p^+ + \tau_e C^+ + \delta_h + \mu_{h1} + 2\epsilon, \\ \beta_h K_{I_3} &\leq \frac{\epsilon k_{I_2}}{K_{I_3}} + \delta_h + \mu_{h1} + \epsilon. \end{aligned}$$

Proof. See Appendix C.3. ■

5. Optimal control study

5.1. Optimal control problem formulation

We now extend the two-strain model (2.1) by Introducing vaccination, environmental sanitation, quarantine, education campaigns and treatment. It should be noted that there are two categories of susceptible humans: those in contact with poultry and those in contact with the poultry environment. Improving the response of the susceptible human population through education campaigns is equivalent to changing the behaviour of the susceptible population by providing them with information on the occurrence of the disease. Therefore, disease information can be considered as a possible tool to trigger the responsiveness of susceptible humans. If we consider these response intensities u and w as control variables $(0 \leq u(t), w(t) \leq 1)$, then 0 represents no response and 1 represents a complete response from informed humans.

Therefore, we obtain the following optimal control problem

$$\begin{cases} \dfrac{dS_p}{dt} = \Lambda_p - \beta_v(1-u_1(t))S_pI_p - \beta_e(1-u_1(t))\dfrac{S_pC}{C+\kappa} - \delta_pS_p, \\ \dfrac{dI_p}{dt} = \beta_v(1-u_1(t))S_pI_p + \beta_e(1-u_1(t))\dfrac{S_pC}{C+\kappa} - (\delta_p+\mu_p)I_p, \\ \dfrac{dC}{dt} = \phi I_p - \xi C - u_2(t)C, \\ \dfrac{dS_h}{dt} = \Lambda_h - (1-u_3(t))\tau_pS_hI_p - (1-u_4(t))\tau_eS_hC - (1-u_6(t))\beta_hS_hI_{h2} - \delta_hS_h, \\ \dfrac{dI_{h1}}{dt} = (1-u_3(t))\tau_pS_hI_p + (1-u_4(t))\tau_eS_hC - (\mu_{h1}+\delta_h+\epsilon)I_{h1} - u_5(t)I_{h1}, \\ \dfrac{dI_{h2}}{dt} = (1-u_6(t))\beta_hS_hI_{h2} + \epsilon I_{h1} - (\mu_{h2}+\delta_h+\gamma)I_{h2}, \\ \dfrac{dR_h}{dt} = \gamma I_{h2} + u_5(t)I_{h1} - \delta_hR_h, \end{cases} \tag{5.1}$$

where,

(i) $u_1(t)$ is the control variable based on the poultry vaccination,

(ii) $u_2(t)$ is the control variable based on environmental sanitation,

(iii) $u_3(t)$ is the control variable which is based on the education campaign for humans in contact with poultry,

(iv) $u_4(t)$ is the control variable based on the education campaign for humans in contact with the poultry environment,

(v) $u_5(t)$ is the control variable for measuring the effectiveness of the treatment of infected humans with avian strain,

(vi) $u_6(t)$ is the control variable which is based on the effort to reduce the number of contacts with humans infected with mutant strain.

The functions $u_i(t)$ are assumed to be at least Lebesgue measurable on $[0, t_f]$. The control set is defined as

$$\Omega^c = \left\{ u_i(t) \in L^1(0,t_f) \mid 0 \le u_1(t) \le v_{max},\ 0 \le u_6(t) \le w_{max},\ 0 \le u_i(t) \le 1 \right\}. \tag{5.2}$$

The upper bound w_{max} is determined by the basic reproduction number of mutant strain $\mathcal{R}_0^h$. v_{max} denote the upper bounds for the effort of vaccination. These bounds reflect practical limitations on the maximum rates of controls in a given time period. So we have

$$\mathcal{R}_0^{p*} = \frac{\beta_v(1-u_1^*(t))\Lambda_p}{\delta_p(\mu_p+\delta_p)} + \frac{\beta_e(1-u_1^*(t))\phi\Lambda_p}{\kappa\delta_p(\xi+u_2^*(t))(\mu_p+\delta_p)}; \text{and } \mathcal{R}_0^{h*} = \frac{(1-u_6^*(t)\beta_h\Lambda_h}{\delta_h(\mu_{h2}+\delta_h+\gamma)}.$$

It follows that

$$\mathcal{R}_0^{p*} > 1;\ \text{and } \mathcal{R}_0^{h*} > 1\ \rightarrow v_{max} = 1 - \frac{\kappa\delta_p(\mu_p+\delta_p)(\xi+u_2^*)}{\beta_e\Lambda_p\phi + \kappa\Lambda_p\beta_v(\xi+u_2^*)};\ \text{and } w_{max} = 1 - \frac{1}{\mathcal{R}_0^h}.$$

The existence of time-dependent controls makes the analysis of system (5.1) more involved. Indeed, now the dynamics of the disease depends on the evolution of each control profile. In the sequel, an optimal control analysis of this problem is carried out. We seek to minimise the total number of infections over the time interval $[0, t_f]$; that is, by defining the objective functional

$$J = \int_0^{t_f} \left\{ B_1 I_p + B_2 I_{h1} + B_3 I_{h2} + \frac{A_1}{2} u_1^2 + A_4 u_2 + A_5 u_2^2 + \frac{A_6}{2} u_3^2 + \frac{A_7}{2} u_4^2 + \frac{A_2}{2} u_5^2 + \frac{A_3}{2} u_6^2 \right\} dt,$$

such that

$$J(u_1^*, u_2^*, u_3^*, u_4^*, u_5^*, u_6^*) = \min_{\Omega^c} J(u_1, u_2, u_3, u_4, u_5, u_6). \tag{5.3}$$

In this instance, the parameters, with the appropriate units, define the appropriate costs associated with these controls. The quadratic terms are introduced to indicate the nonlinear costs that can occur at high levels of intervention [37, 38, 39]. The disinfection cost terms, $A_4 u_2(t) + A_5 u_2^2(t)$, are taken from [39]. The minimisation method is subject to the differential system (5.1), henceforth called equations of state.

Our goal is to find optimal controls, $u_i^*(t)$, $\forall i \in \{1, 2, \cdots, 6\}$ such that (5.3) holds.

5.2. *Existence and characterization of the optimal control*

The existence of the finite-time optimal control for system (5.1) is studied here, and the Hamiltonian of the optimal control problem is constructed to derive the first-order necessary conditions for optimal control. For this, we use a result from [40].

Theorem 5.1. *The optimal control* $(u_1^*, u_2^*, u_3^*, u_4^*, u_5^*, u_6^*)$ *and a corresponding optimal state* $(S_p^*, I_p^*, C^*, S_h^*, I_{h1}^*, I_{h2}^*)$ *exist such that expression* (5.3) *holds.*

Proof. The existence of the optimal controls for the problem under consideration is shown by using a result from [40, 41]. We point out that the state and control variables are nonnegative, and that the control set Ω^c, by definition, is closed and bounded. This ensures that the optimal system is bounded, which is necessary for the existence of the optimal control. Moreover, the integrand $B_1 I_p + B_2 I_{h1} + B_3 I_{h2} + \frac{A_1}{2} u_1^2 + A_4 u_2 + A_5 u_2^2 + \frac{A_6}{2} u_3^2 + \frac{A_7}{2} u_4^2 + \frac{A_2}{2} u_5^2 + \frac{A_3}{2} u_6^2$ is convex on the control set Ω^c due to the quadratic character of control variables. Furthermore, a constant $\tau > 1$ and positive numbers $\overline{w}_1$ and $\overline{w}_2$ exist such that

$$B_1 I_p + B_2 I_{h1} + B_3 I_{h2} + \frac{A_1}{2} u_1^2 + A_4 u_2 + A_5 u_2^2 + \frac{A_6}{2} u_3^2 + \frac{A_7}{2} u_4^2 + \frac{A_2}{2} u_5^2 + \frac{A_3}{2} u_6^2 \geq \overline{w}_1 \left(\sum_{i=1}^{6} |u_i|^2 \right)^{\frac{\tau}{2}} - \overline{w}_2.$$

The existence of the optimal control is completed by the boundedness of the state variables. ■

By constructing a Hamiltonian H and applying the Pontryagin's maximum principle [43, 42, 44], the optimal control is characterized in the following Theorem.

Theorem 5.2. *The optimal control variables are* $u_1^*, u_2^*, u_3^*, u_4^*, u_5^*, u_6^*$ *and the corresponding optimal state variables of the control system are* $S_p^*, I_p^*, C^*, S_h^*, I_{h1}^*, I_{h2}^*$. *Consequently, there are adjoint variables* $\lambda_1(t), \lambda_2(t), \lambda_3(t), \lambda_4(t), \lambda_5(t), \lambda_6(t)$

in $\mathbb{R}$ *which satisfy the following adjoint equations:*

$$\begin{aligned}
\frac{d\lambda_1}{dt} &= (\lambda_1-\lambda_2)(1-u_1)\left[\beta_v I_p+\beta_e\frac{C}{\kappa+C}\right]+\delta_p\lambda_1,\\
\frac{d\lambda_2}{dt} &= -B_1+(\lambda_1-\lambda_2)\beta_v S_p(1-u_1)+(\mu_p+\delta_p)\lambda_2-\phi\lambda_3+\tau_p S_h(1-u_3)(\lambda_4-\lambda_5),\\
\frac{d\lambda_3}{dt} &= (\lambda_1-\lambda_2)\frac{(1-u_1)\kappa\beta_e S_p}{(\kappa+C)^2}+(\xi+u_2)\lambda_3+(\lambda_4-\lambda_5)(1-u_4)\tau_e S_h,\\
\frac{d\lambda_4}{dt} &= (\lambda_4-\lambda_5)\left[(1-u_3)\tau_p I_p+(1-u_4)\tau_e C\right]+(\lambda_4-\lambda_6)(1-u_6)\beta_h I_{h2}+\delta_h\lambda_4,\\
\frac{d\lambda_5}{dt} &= -B_2+(\delta_h+\mu_{h1})\lambda_5+\epsilon(\lambda_5-\lambda_6)+u_5\lambda_5,\\
\frac{d\lambda_6}{dt} &= -B_3+(\lambda_4-\lambda_6)(1-u_6)\beta_h S_h+(\delta_h+\mu_{h2}+\gamma)\lambda_6,
\end{aligned} \tag{5.4}$$

and the transversality conditions

$$\lambda_i^*(t_f)=0,\ i=\{1,2,\cdots,6\}. \tag{5.5}$$

In addition, the corresponding optimal controls are as follows:

$$\begin{aligned}
u_1^*(t) &= \max\left\{0,\ \min\left(\frac{(\lambda_2-\lambda_1)\left[\beta_v S_p I_p+\frac{\beta_e S_p C}{\kappa+C}\right]}{A_1},\ v_{max}\right)\right\},\\
u_2^*(t) &= \max\left\{0,\ \min\left(\frac{\lambda_3 C-A_4}{2A_5},\ 1\right)\right\},\\
u_3^*(t) &= \max\left\{0,\ \min\left(\frac{(\lambda_5-\lambda_4)\tau_p S_h I_p}{A_6},\ 1\right)\right\},\\
u_4^*(t) &= \max\left\{0,\ \min\left(\frac{(\lambda_5-\lambda_4)\tau_p S_h C}{A_7},\ 1\right)\right\},\\
u_5^*(t) &= \max\left\{0,\ \min\left(\frac{\lambda_5 I_{h1}}{A_2},\ 1\right)\right\},\\
u_6^*(t) &= \max\left\{0,\ \min\left(\frac{(\lambda_6-\lambda_4)\beta_h S_h I_{h2}}{A_3},\ w_{max}\right)\right\}.
\end{aligned} \tag{5.6}$$

Proof. The Pontryagin's maximum principle [43, 42, 44] is used to solve the optimal control problem by fixing $t_f=365$. It converts (5.1) into a pointwise minimization problem of a Hamiltonian H, with respect to $u_i, i\in\{1,\cdots,6\}$. Here, the Hamiltonian is the integrand of the objective functional coupled to the six right-hand sides of the state equations:

$$\begin{aligned}
H(S_p,I_p,C,S_h,I_{h1},I_{h2},\lambda_i) &= B_1I_p+B_2I_{h1}+B_3I_{h2}+\frac{A_1}{2}u_1^2+A_4u_2(t)+A_5u_2^2+\frac{A_6}{2}u_3^2\\
&+ \frac{A_7}{2}u_4^2+\frac{A_2}{2}u_5^2+\frac{A_3}{2}u_6^2+\textstyle\sum_{i=1}^{6}\lambda_i h_i,
\end{aligned}$$

where h_i is the right-hand side of the differential equation of the i^{th} state variable.

The characteristic function $J_{[a,b]}(t)$ is defined by

$$J_{[a,b]}(t) = \begin{cases} 1, \text{ if } t \in [a;b], \\ \\ 0, \text{ otherwise.} \end{cases} \tag{5.7}$$

For given optimal functions $u_i^*,\ i \in \{1, 2 \cdots, 6\}$, given corresponding optimal state variables $S_p^*, I_p^*, C^*, S_h^*, I_{h1}^*, I_{h2}^*$ of system (5.1), according to the Pontryagin's maximum principle [43, 42, 44], there are adjoint variables $\lambda_1, \lambda_2, \lambda_3, \lambda_4, \lambda_5$ and λ_6 which satisfy the following equations:

$$\frac{d\lambda_1}{dt} = -\frac{\partial H}{\partial S_p}(t),\ \frac{d\lambda_2}{dt} = -\frac{\partial H}{\partial I_p}(t),\ \frac{d\lambda_3}{dt} = -\frac{\partial H}{\partial C}(t),\ \frac{d\lambda_4}{dt} = -\frac{\partial H}{\partial S_h}(t), \tag{5.8}$$

$$\frac{d\lambda_5}{dt} = -\frac{\partial H}{\partial I_{h1}}(t),\ \frac{d\lambda_6}{dt} = -\frac{\partial H}{\partial I_{h2}}(t), \tag{5.9}$$

with transversality requirements $\lambda_i(t_f) = 0; (i = 1, 2, \cdots, 6)$. By substituting the corresponding derivatives into the above inequalities and reorganising them, we obtain the adjoint equations (5.4). According to the optimality condition, we have

$$\frac{\partial H}{\partial u_i} = 0, \quad \text{at } u_i = u_i^*, \forall i \in \{1, 2 \cdots, 6\}. \tag{5.10}$$

Thus (5.6) holds true. According to the properties of the control set (5.2) and the conclusions above, we have for example

$$u_1^* = \begin{cases} 0, \text{ if } \dfrac{(\lambda_1 - \lambda_2)\left[\beta_v S_p I_p + \dfrac{\beta_v S_p C}{\kappa + C}\right]}{A_1} \leq 0, \\ \\ \dfrac{(\lambda_1 - \lambda_2)\left[\beta_v S_p I_p + \dfrac{\beta_v S_p C}{\kappa + C}\right]}{A_1}, \text{ if } 0 < \dfrac{(\lambda_1 - \lambda_2)\left[\beta_v S_p I_p + \dfrac{\beta_v S_p C}{\kappa + C}\right]}{A_1} < v_{max}, \\ \\ v_{max}, \text{ if } \dfrac{(\lambda_1 - \lambda_2)\left[\beta_v S_p I_p + \dfrac{\beta_v S_p C}{\kappa + C}\right]}{A_1} \geq v_{max}, \end{cases}$$

This completes the proof. ■

6. Numerical results

In this section, we numerically study the effects of optimal control strategies such as poultry vaccination, environmental sanitation, education campaigns, quarantine and treatment of infected humans in the spread of avian flu. The numerical solution of the optimal control problem is obtained by solving the optimality and adjoint systems thanks to the forward-backward sweep method. The adjoint systems are numerically solved by a fourth-order Runge-Kutta scheme using the direct solution of the state equations. The optimality condition is satisfied by convex updating of the previous control values. We describe the controls in the following strategies using the parameter values in Table 3 and the following initial condition $(S_p, I_p, C, S_h, I_{h1}, I_{h2}) = (10, 2, 100, 10, 5, 2)$.

Table 3: Parameters and baseline values.

Symbol	Baseline value	Reference	Symbol	Baseline value	Reference
Λ_p	50	Assumed	ξ	500	Assumed
β_v	2	[26]	τ_e	0.1	[11]
β_e	6	Assumed	ϕ	10^4	Assumed
δ_p	5	[26]	β_h	0.003	[26]
Λ_h	3	Assumed	κ	10^6	Assumed
γ	0.01	[26]	δ_h	0.015	[26]
μ_{h1}	1	[26]	μ_{h2}	0.06	[26]
τ_p	0.6	[45]	μ_p	1	Assumed
ϵ	0.001	[26]			

6.1. *Strategy A: control with poultry vaccination (u_1)*

With strategy A, only poultry vaccination u_1 is applied to control the system, with the other controls set to zero. Figure 3 shows the effect of poultry vaccination on the poultry and human populations. The control profile suggests that the u_1 control is at the highest level for about 200 days per year before falling to the lower limit. This result shows that the optimal control measure is effective in both the poultry and human populations and the community will therefore be free of the disease.

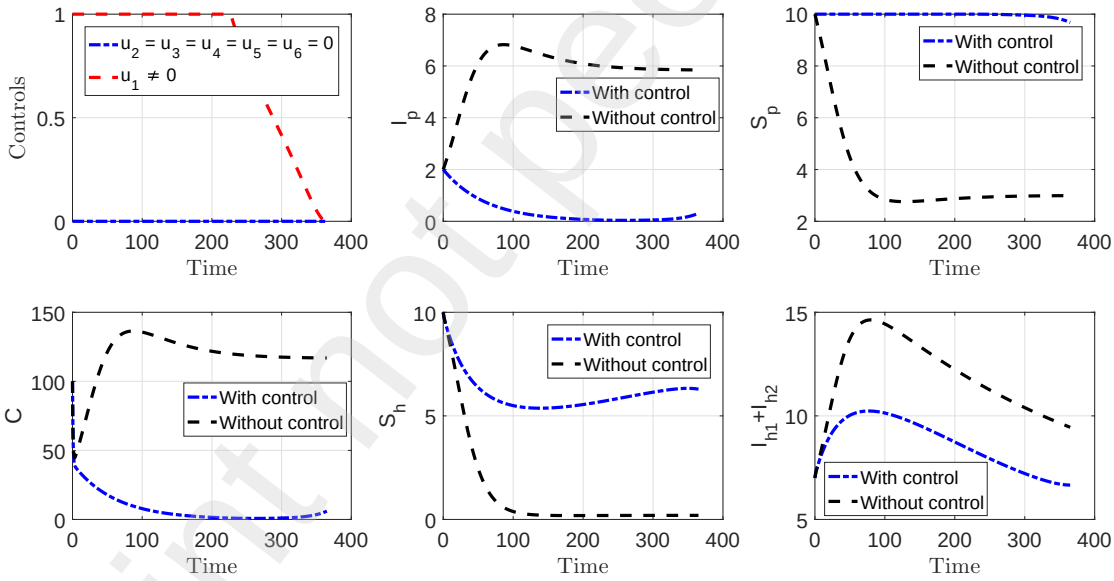

Figure 3: Simulations of model (5.1) showing the effect of poultry vaccination.

6.2. *Strategy B: control with environmental sanitation (u_2)*

Here, only environmental disinfection u_2 is applied to control the system. Figure 4 shows the impact of this control strategy, on the avian and human populations. We do not record any variation in the control profile. Thus, this result illustrates that the use of disinfectants as a control measure is not an optimal solution. It is therefore ineffective in the control of this epizootic.

6.3. *Strategy C: control with education campaign for humans in contact with poultry (u_3)*

Figure 5 describes the effect of implementing an education campaign among humans in contact with poultry and the impact is slightly visible in the human population, while the control profile remains at its upper limit for almost 50 days.

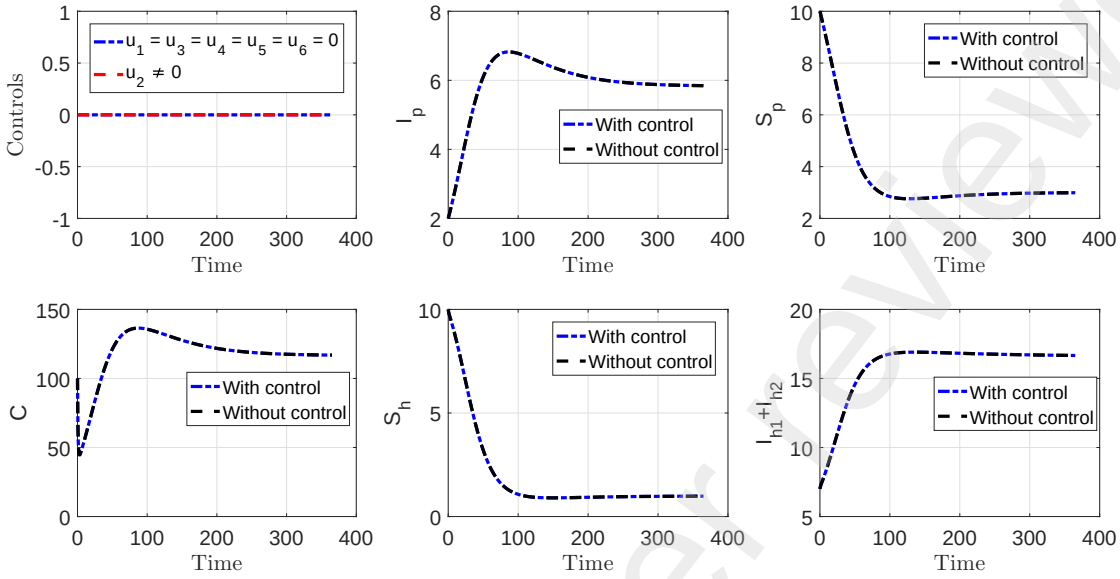

Figure 4: Simulations of model (5.1) showing the effect of environmental sanitation.

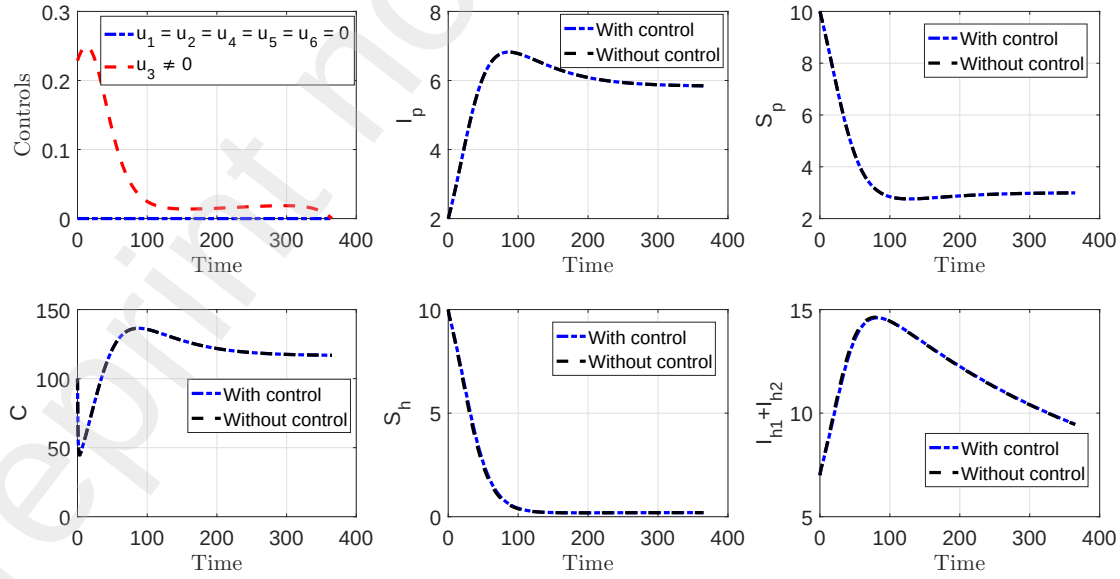

Figure 5: Simulations of model (5.1) showing the effect of education campaign for humans in contact with poultry.

6.4. *Strategy D: control with education campaign for humans in contact with poultry environment* (u_4)

The objective of the education campaign strategy for humans in contact with the poultry environment is to make the community aware of the disease, its mode of transmission, prevention and control measures. When only control u_4 is applied while the others are set to zero, Figure 6 shows a significant effect in human population. This is realistic, as our work [11] shows that the indirect transmission (environment-to-human) is more dominant that the direct transmission (avian-to-human). Moreover, the control profile remains at its upper limit for a long time before gradually decreasing to the lower limit.

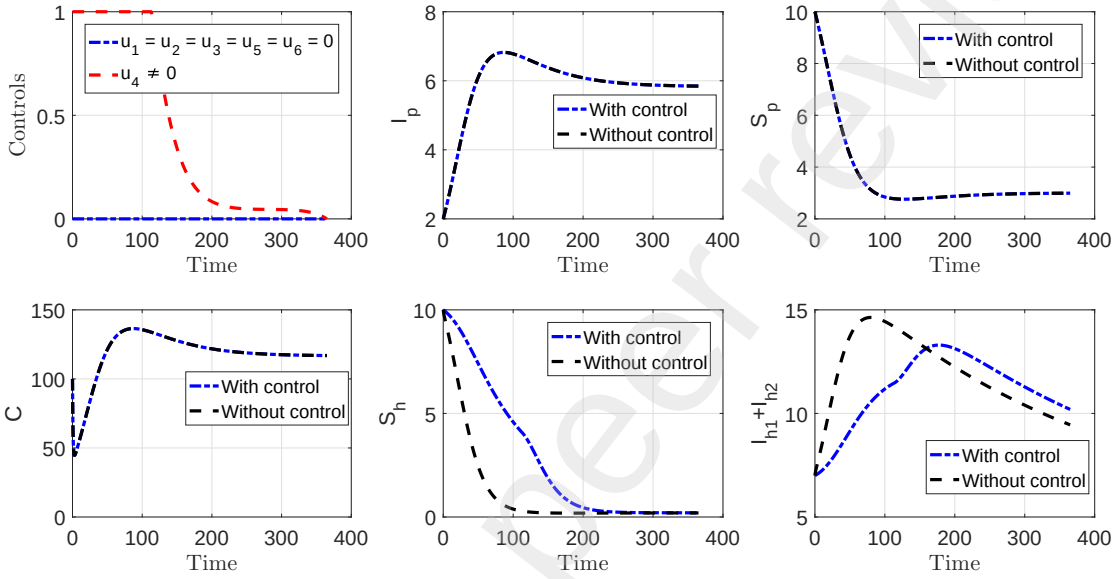

Figure 6: Simulations of model (5.1) showing the effect of education campaign for humans in contact with poultry environment.

6.5. *Strategy E: control with quarantine of infected humans* (u_6)

With strategy E, only quarantine of infected humans u_6 is applied to control the system. Figure 7 shows the impact of quarantine of infected humans on the avian and human populations.

6.6. *Strategy F: control with treatment of infected humans* (u_5)

When only control u_5 is applied while the others are set to zero, the significant effect occurs on the infected humans class (see Figure 8). It should be noted that this treatment control strategy is not effective without vaccination of susceptible poultry and is therefore not preferable for the community as an avian influenza control measure.

6.7. *Strategy G: control with combination of poultry vaccination* (u_1) *and treatment of infected humans* (u_5)

When we use vaccination of poultry and treatment of infected humans as control strategies we see, on Figure 9, a significant impact in both the poultry and human populations. Therefore, this combination can be used as a control strategy against this epidemic.

6.8. *Strategy H: control with combination of poultry vaccination* (u_1) *and education campaign for humans in contact with poultry environment* (u_4)

With strategy H, the combination of vaccination of poultry and sensitisation of humans in contact with the poultry environment is applied to control the epidemic. Figure 10 shows the meaningful effect of using this combination as a control strategy. Thus, it can also be used to eradicate this epizootic.

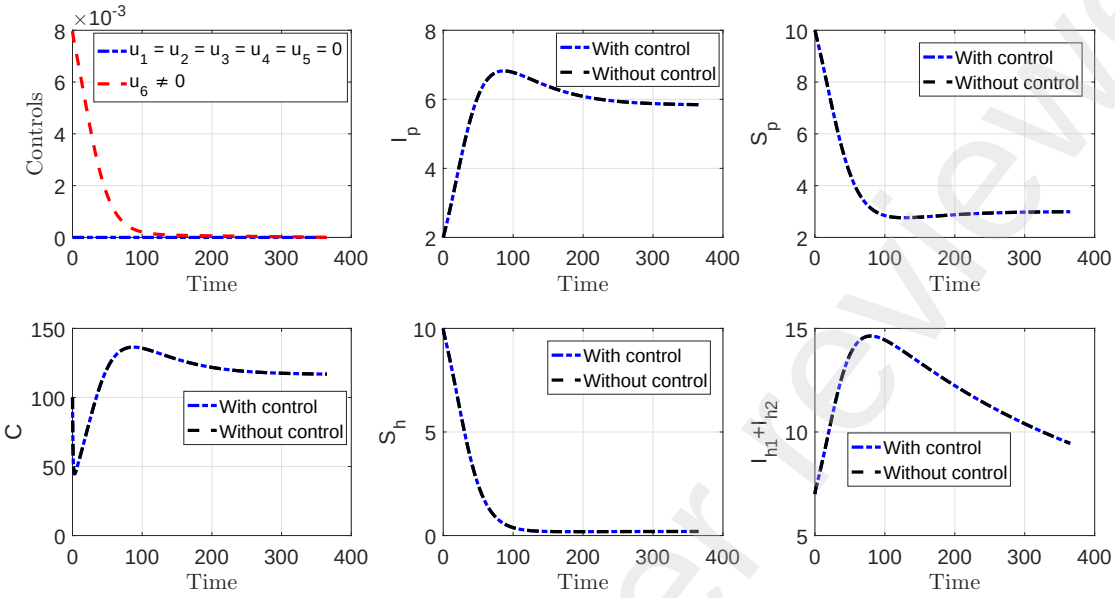

Figure 7: Effect of quarantine of infected humans on model (5.1).

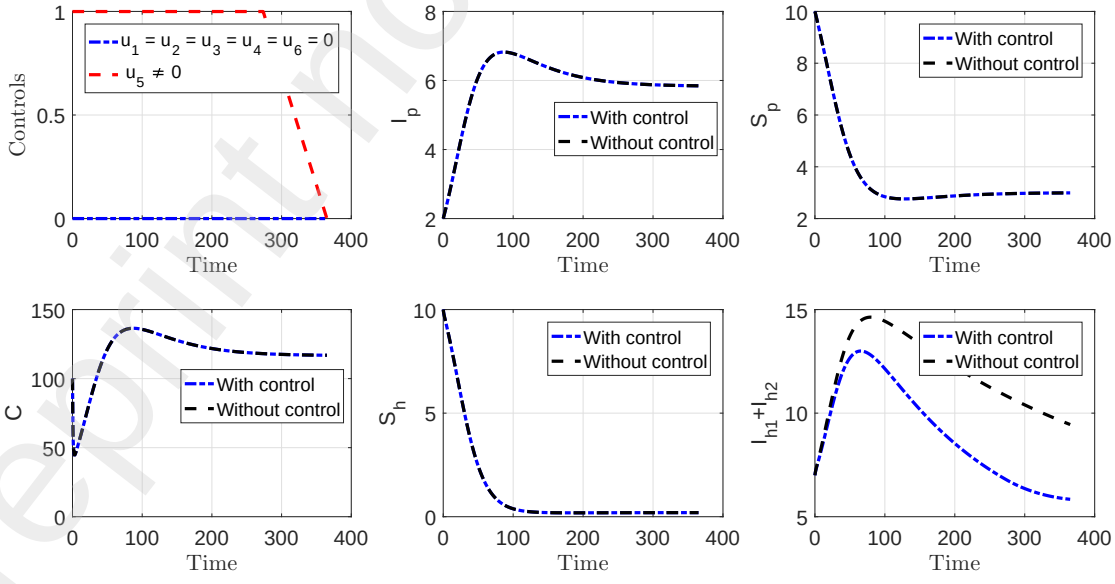

Figure 8: Simulations of model (5.1) showing the effect of therapeutic treatment of infected humans.

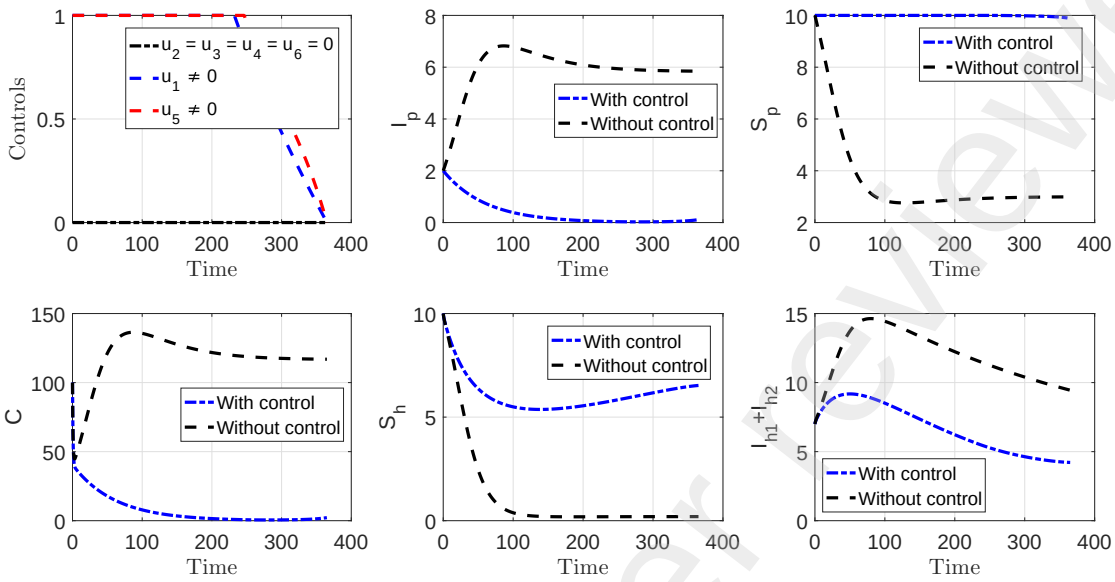

Figure 9: Effect of combination of poultry vaccination and treatment of infected humans on model (5.1).

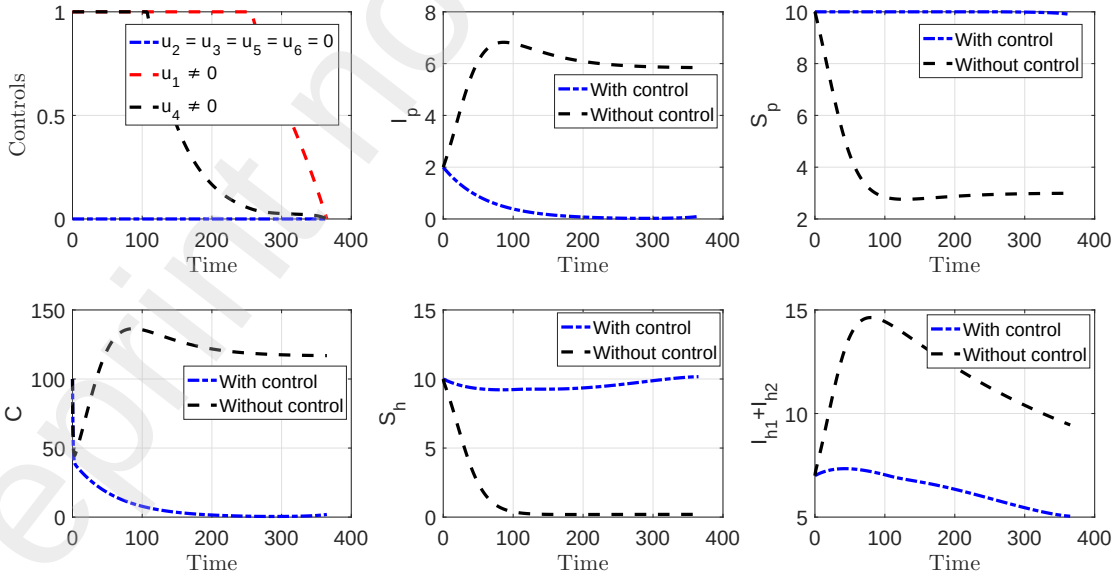

Figure 10: Effect of combination of poultry vaccination and education campaign for humans in contact with poultry environment on model (5.1).

6.9. *Strategy I: control with combination of treatment of infected humans (u_5) and education campaign for humans in contact with poultry environment (u_4)*

By combining the treatment of infected humans with the sensitisation of humans in contact with the poultry environment, an important impact on the human population is shown on Figure 11. Therefore, this strategy can be used to eradicate this epidemic if and only if the poultry population is free of the disease.

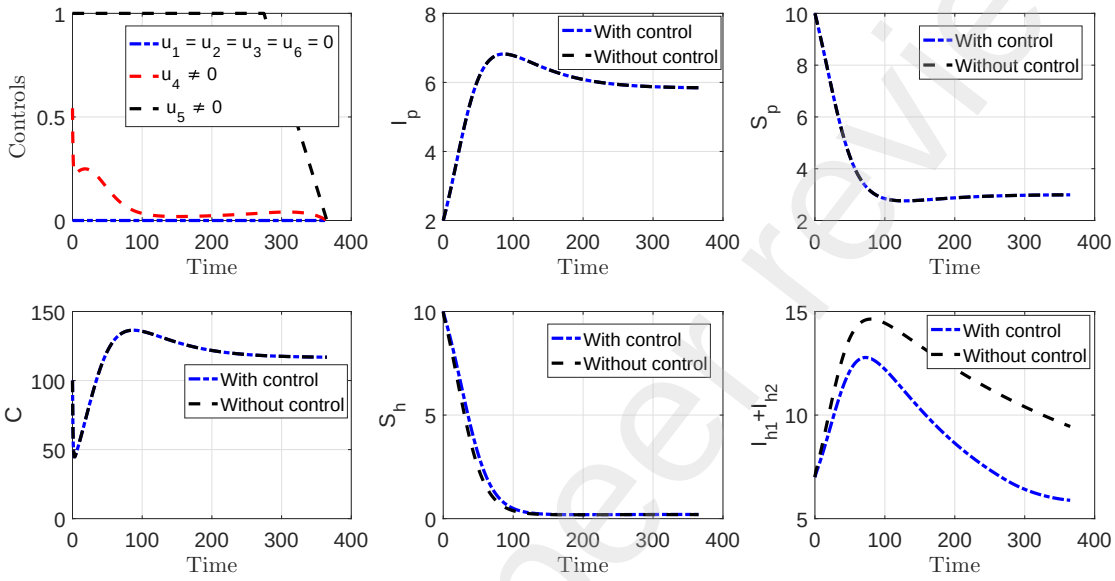

Figure 11: Effect of combination of treatment of infected humans and education campaign for humans in contact with poultry environment on model (5.1).

6.10. *Strategy J: control with combination of poultry vaccination (u_1), treatment of infected humans (u_5) and education campaign for humans in contact with poultry environment (u_4)*

The numerical results show that the human and poultry populations infected and the virus concentration are gradually decreasing, as shown on Figures 12 (b), 12 (d) and 12 (f), while susceptible humans and poultry are increasing (see Figures 12 (b) and 12 (e)). Vaccination, treatment and education campaigns in the community will greatly reduce the spread of the disease. On Figure 12 (a), we see that the control profiles remain at their upper limit for some time and, at the end, they gradually decrease to the lower limit.

7. Cost-effectiveness analysis

To make a decision on which intervention to choose, we evaluate the economic implications of avian influenza control strategies using the CEA technique. CEA helps us identify and propose the most cost-effective strategy to implement with limited resources. We evaluate the costs by using the incremental cost-effectiveness ratios (ICER) to compare the differences in costs and health outcomes of two competing intervention strategies. The infectious averted is computed by taking the absolute value of the difference between the total number of individual species without control and the total number of individual species with control. The control strategies are ranked in order of increasing infection averted as presented in Table 4.

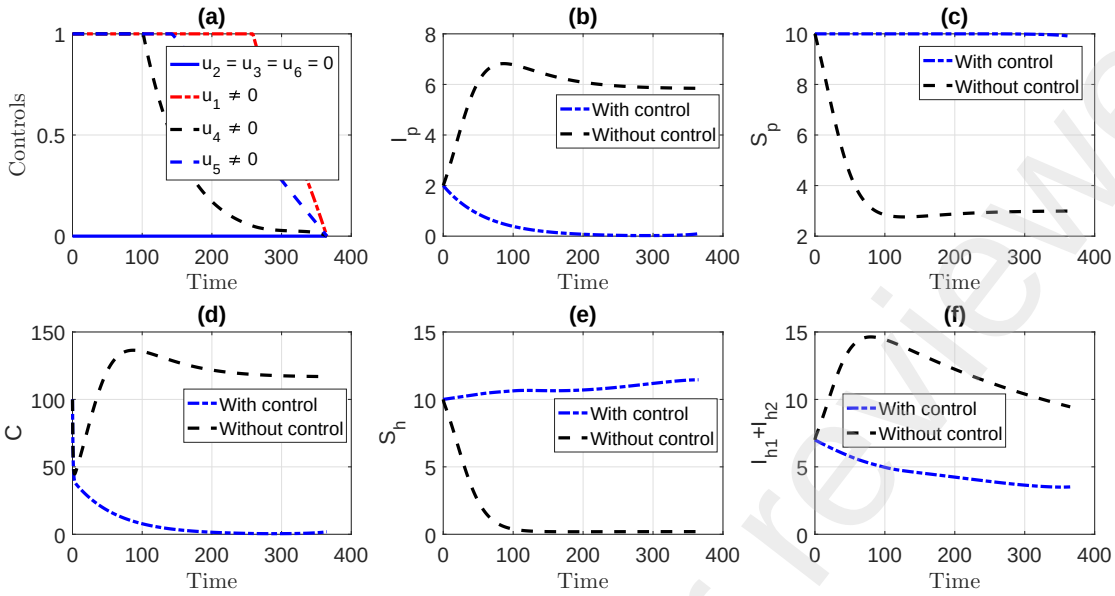

Figure 12: Effect of the three controls on model (5.1).

Table 4: Control strategies in order of increasing infection averted.

Strategies	Total infections averted	Total costs ($)	Objective functional J ($)
Strategy B	0	0	1.3048×10^5
Strategy C	0.0131	275.0413	1.0172×10^5
Strategy E	0.1078	0.5383	1.0883×10^5
Strategy D	0.7359	2.4224×10^3	1.0528×10^5
Strategy A	2.8138	2.8868×10^3	5.8584×10^4
Strategy I	3.5610	2.6921×10^3	8.8885×10^4
Strategy F	3.6060	2.3993×10^3	8.9032×10^4
Strategy H	4.4476	5.7095×10^3	5.1138×10^4
Strategy G	5.2540	4.6109×10^3	5.2637×10^4
Strategy J	5.9817	3.2439×10^3	3.9025×10^4

7.1. Taking into account the quarantine of infected persons (Strategy E is considered)

We see from Table 4 that strategy B (environmental sanitation) cannot be used as a control measure because zero values in Total infections averted and Total costs indicate that no strategy is applied.

$$ICER(C) = \frac{275.0413}{0.0131} = 20995.52, \quad ICER(E) = \frac{0.5383 - 275.0413}{0.1078 - 0.0131} = -2898.66.$$

Now, comparing ICER (C) and ICER (E) using Table 4, a cost saving of −2898.66 is observed for Strategy C over Strategy E. The lower ICER for Strategy E indicates that Strategy C is strongly dominated. That is, Strategy E is more costly and less effective than Strategy E. Therefore, Strategy C is excluded from the set of alternatives so it does not consume limited resources. When we exclude C, we compare strategy E and D, and ICER is recalculated in Table 5 below.

The comparison between strategies E and D indicate that strategy D is strongly dominated and is more costly than strategy E since ICER(E) < ICER(D). Then strategy D is discarded from the set of alternatives. Hence E and A are compared in Table 6.

The comparison shows that ICER(E) < ICER(A); hence strategy A is more costly and excluded from the set of alternatives. We compare strategies E and I in Table 7.

Table 5: Incremental cost-effectiveness ratio in increasing order of total infection averted.

Strategies	Total infections averted	Total costs ($)	ICER
Strategy E	0.1078	0.5383	4.9935
Strategy D	0.7359	2.4224×10^3	3855.85

Table 6: Incremental cost-effectiveness ratio in increasing order of total infection averted.

Strategies	Total infections averted	Total costs ($)	ICER
Strategy E	0.1078	0.5383	4.9935
Strategy A	2.8138	2.8868×10^3	1066.62

Table 7: Incremental cost-effectiveness ratio in increasing order of total infection averted.

Strategies	Total infections averted	Total costs ($)	ICER
Strategy E	0.1078	0.5383	4.9935
Strategy I	3.5610	2.6921×10^3	779.44

The comparison shows that ICER(E) < ICER(I). Therefore, strategy I is excluded from the set of alternatives and we compare strategies E and F in Table 8.

Table 8: Control strategies in order of increasing averted.

Strategies	Total infections averted	Total costs ($)	ICER
Strategy E	0.1078	0.5383	4.9935
Strategy F	3.6060	2.3993×10^3	658.71

Strategy F is strongly dominated and is more costly than strategy E. So, strategy F is excluded from set of alternatives. Thus, strategies E and H need to be compared.

Table 9: Incremental cost-effectiveness ratio in increasing order of total infection averted.

Strategies	Total infections averted	Total costs ($)	ICER
Strategy E	0.1078	0.5383	4.9935
Strategy H	4.4476	5.7095×10^3	1315.49

Strategy H is strongly dominated and is more costly than strategy E. So, strategy H is excluded from set of alternatives. Strategies E and G are now compared in Table 10. As ICER(E) < ICER(G), strategy G

Table 10: Incremental cost-effectiveness ratio in increasing order of total infection averted.

Strategies	Total infections averted	Total costs ($)	ICER
Strategy E	0.1078	0.5383	4.9935
Strategy G	5.2540	4.6109×10^3	895.88

is excluded from the set of alternatives and we compare strategies E and J in Table 11.

Table 11: Incremental cost-effectiveness ratio in increasing order of total infection averted.

Strategies	Total infections averted	Total costs ($)	ICER
Strategy E	0.1078	0.5383	4.9935
Strategy J	5.9817	3.2439×10^3	552.16

Comparison between strategies E and J shows that strategy E is more costly and less effective than strategy J as ICER(E) < ICER(J). Therefore strategy J is discarded from the set of alternatives. Finally, based on the above results, we conclude that strategy E is the most cost-effective among all strategies envisaged for controlling avian influenza.

7.2. *Without taking into account the quarantine of infected persons (Strategy E is not considered)*

$$ICER(C) = \frac{275.0413}{0.0131} = 20995.52, \quad ICER(D) = \frac{2.4224 \times 10^3 - 275.0413}{0.7359 - 0.0131} = 2970.89.$$

Now, comparing ICER (C) and ICER (D) using Table 4, a cost saving of 2970.89 is observed for Strategy C over Strategy D. The lower ICER for Strategy D indicates that Strategy C is strongly dominated. That is, Strategy C is more costly and less effective than Strategy D. Therefore, Strategy C is excluded from the set of alternatives so it does not consume limited resources. When we exclude C, we compare strategy D and A, and ICER is recalculated in Table 12 below.

Table 12: Incremental cost-effectiveness ratio in increasing order of total infection averted.

Strategies	Total infections averted	Total costs ($)	ICER
Strategy D	0.7359	2.4224×10^3	3291.75
Strategy A	2.8138	2.8868×10^3	223.49

The comparison between strategies D and A indicate that strategy D is strongly dominated and is more costly than strategy A since ICER(A) < ICER(D). Then strategy D is discarded from the set of alternatives. Hence A and I are compared in Table 13.

Table 13: Incremental cost-effectiveness ratio in increasing order of total infection averted.

Strategies	Total infections averted	Total costs ($)	ICER
Strategy A	2.8138	2.8868×10^3	1025.94
Strategy I	3.5610	2.6921×10^3	–206.57

The comparison shows that ICER(I) < ICER(A); hence strategy A is more costly and excluded from the set of alternatives. We compare strategies I and F in Table 14.

Table 14: Incremental cost-effectiveness ratio in increasing order of total infection averted.

Strategies	Total infections averted	Total costs ($)	ICER
Strategy I	3.5610	2.6921×10^3	756
Strategy F	3.6060	2.3993×10^3	–6506.67

The negative ICER for strategy F in Table 14 shows that strategy I is more costly and less effective than strategy F. Therefore, strategy I is excluded from the set of alternatives and we compare strategies F and H in Table 15.

Table 15: Control strategies in order of increasing averted.

Strategies	Total infections averted	Total costs ($)	ICER
Strategy F	3.6060	2.3993×10^3	665.36
Strategy H	4.4476	5.7095×10^3	3933.22

Strategy H is strongly dominated and is more costly than strategy F. So, strategy H is excluded from set of alternatives. Thus, strategies F and G need to be compared.

Table 16: Incremental cost-effectiveness ratio in increasing order of total infection averted.

Strategies	Total infections averted	Total costs ($)	ICER
Strategy F	3.6060	2.3993×10^3	665.36
Strategy G	5.2540	4.6109×10^3	1341.99

Table 17: Incremental cost-effectiveness ratio in increasing order of total infection averted.

Strategies	Total infections averted	Total costs ($)	ICER
Strategy F	3.6060	2.3993×10^3	665.36
Strategy J	5.9817	3.2439×10^3	355.52

Strategy G is strongly dominated and is more costly than strategy F. So, strategy G is excluded from set of alternatives. Strategies F and J are now compared in Table 17.

Comparison between strategies F and J shows that strategy F is more costly and less effective than strategy J as ICER(J) < ICER(F). Therefore strategy F is discarded from the set of alternatives. Finally, based on the above results, we conclude that strategy J (combination of poultry vaccination, human education and treatment of infected humans) is the most cost effective among all strategies envisaged for controlling avian influenza. This result agrees quite well with the numbers and costs mentioned in Table 4.

8. Conclusion and discussion

A mathematical model for the dynamic transmission of avian influenza *A* is formulated in this paper, incorporating the following factors: (i) virus mutation and (ii) optimal control strategies. The evaluation of the model was presented in a qualitative manner.

The most striking findings on the long-term dynamics of the system are outlined below.

(1) A disease-free equilibrium was calculated, and the basic reproduction numbers $\mathcal{R}_0^p$ and $\mathcal{R}_0^h$ that determine the outcome of avian influenza *A* in the community were computed.

(2) The disease-free equilibrium was proved to be globally asymptotically stable over a positively invariant region when $\mathcal{R}_0^p \leq 1$ and $\mathcal{R}_0^h < 1$. Furthermore, we have shown that the model has a unique human-endemic and a unique full endemic equilibrium when $\mathcal{R}_0^h > 1$ and $\mathcal{R}_0^p > 1$, respectively. Their global asymptotic stability has been proven.

(3) The Pontryagin's maximum principle was used to derive and analyse the necessary conditions for optimal control strategies (vaccination of poultry, environmental sanitation, education campaigns for susceptible humans and treatment of infected humans). Optimal control thus minimises the population of infected humans.

(4) Numerical results were presented to illustrate the theoretical results. Graphically, strategy (A) shows a significant impact in both poultry and human populations while strategies (C), (D) and (F) have a positive impact on human population. Strategies (B) has almost no effect on both populations.

(5) From the cost-effectiveness analysis, the best way to control transmission or contain an outbreak of avian influenza with virus mutation is to quarantine infected humans. If mutation is not considered, then the best way to contain the outbreak is to combine vaccination of poultry and treatment of infected humans with an education campaign for humans in contact with the poultry environment.

Education campaigns usually have a time delay between the time they are implemented and the time they attract public interest. It is therefore interesting to develop an optimal control problem based on a system of differential equations with multiple delays in the state and control variables. It remains to be seen whether this will represent a significant challenge to the mathematical analysis or whether it will modify the optimal control solution. It is worth noting that, during the cost-effectiveness illustration, we have considered the same cost for all interventions. It would be more realistic to evaluate the outcomes knowing that they actually depend on the choice of the parameters. All these research perspectives will be investigated in our forthcoming work.

Appendix A. Biological permanence

In this part, we present and characterize the concept of biological permanence which is based on the Lyapunov instability Theorem.

We consider the following system of autonomous differential equations:

$$\frac{dx}{dt} = f(x), \tag{A.1}$$

where $x \in \mathbb{R}^n_+$ and $f : \mathbb{R}^n_+ \to \mathbb{R}^n$. Assume that X is a compact subset of $\mathbb{R}^n_+$ and S is a compact subset of X. Let X be forward invariant. Suppose that there exists a C^1 function $P : X \to \mathbb{R}_+$ which satisfies $P(x) = 0$ if and only if $x \in S$. Let " $\cdot$ " denotes differentiation along an orbit and $\pi(x, t)$ the solution of (A.1) and x the initial value.

Theorem Appendix A.1. *[26] If $\dot{P}(\sigma) > 0$, for all σ in S, then there exist a positive constant k and a sufficiently large time T such that $P(\pi(\overline{\psi}_0, t)) > k$, for all $\overline{\psi}_0$ in $X \setminus S$ and $t \geq T$.*

Appendix B. Positivity and boundedness of solutions

Appendix B.1. Proof of Theorems 2.1

Proof. We want to show that the solution variables $(S_p, I_p, S_h, E_h, I_h, C, R_h)$ of system (2.1) corresponding to the initial conditions (2.2) are positive. We define

$$W(t) = \min\left\{S_p(t),\ I_p(t),\ C(t),\ S_h(t),\ I_{h1}(t),\ I_{h2}(t),\ R_h(t)\right\}.$$

It is obvious that $W(0) > 0$. Suppose that there exists $t_1 > 0$ such that $W(t_1) = 0$ and $W(t) > 0$ for all $t \in [0, t_1)$. If $W(t_1) = S_p(t_1)$, then $I_p(t) \geq 0,\ C(t) \geq 0,\ S_h(t) \geq 0,\ I_{h1}(t) \geq 0,\ I_{h2}(t) \geq 0$ and $R_h(t) \geq 0$ for all $t \in [0, t_1]$. According to the first equation of system (2.1), it follows that

$$\frac{dS_p}{dt} = \Lambda_p - \left(\beta_v I_p(t) + \beta_e \frac{C(t)}{C(t) + \kappa} + \delta_p\right) S_p(t),\ t \in [0, t_1]$$

. Hence, we obtain

$$\begin{aligned}\frac{d}{dt}\left[S_p(t) \exp\left\{\delta_p t + \int_0^t \left(\beta_v I_p(s) + \beta_e \frac{C(s)}{C(s) + \kappa}\right) ds\right\}\right] \\ \geq \Lambda_p \exp\left\{\delta_p t + \int_0^t \left(\beta_v I_p(s) + \beta_e \frac{C(s)}{C(s) + \kappa}\right) ds\right\}.\end{aligned}$$

Integrating the above inequality from 0 to t_1 gives

$$\begin{aligned}S_p(t_1) \geq S_p(0) \exp\left\{-\int_0^{t_1} \left(\beta_v I_p(\tau) + \beta_e \frac{C(\tau)}{C(\tau) + \kappa} + \delta_p\right) d\tau\right\} \\ + \exp\left\{-\int_0^{t_1} \left(\beta_v I_p(\tau) + \beta_e \frac{C(\tau)}{C(\tau) + \kappa} + \delta_p\right) d\tau\right\} \\ \times \Lambda_p \int_0^{t_1} \exp\left\{\int_0^s \left(\beta_v I_p(\tau) + \beta_e \frac{C(\tau)}{C(\tau) + \kappa} + \delta_p\right) d\tau\right\} ds > 0.\end{aligned}$$

This contradicts $S_p(t_1) = 0$. Thus we obtain $S_p(t) > 0$, for all $t > 0$. We can also show in the same way that $I_p(t) > 0,\ C(t) > 0,\ S_h(t) > 0,\ I_{h1}(t) > 0,\ I_{h2}(t) > 0$ and $R_h(t) > 0$ for all $t > 0$. ■

Appendix B.2. Proof of Theorems 2.2

Proof. We prove that the total population of poultry and humans at time t, $N_p(t)$ and $N_h(t)$ satisfies the boundedness property $0 < N_p(t) \leq M_1, 0 < N_h(t) \leq M_2$. We also prove that the concentration of virus satisfies the boundedness property $0 \leq C(t) \leq M_3$. We point out that this bound represents the unique equilibrium of the dynamics of the total population in the ideal situation where there is no ongoing infection. It follows from system (2.1) that

$$\begin{cases} \dfrac{dN_p}{dt}(t) = \Lambda_p - \delta_p N_p(t) - \mu_p I_p(t) \leq \Lambda_p - \delta_p N_p(t), \\ \dfrac{dN_h}{dt}(t) = \Lambda_h - \delta_h N_h(t) - \mu_{h1} I_h(t) - \mu_{h2} I_{h2} \leq \Lambda_h - \delta_h N_h(t). \end{cases}$$

Then,

$$\limsup_{t\to\infty} N_p(t) \leq \frac{\Lambda_p}{\delta_p} \text{ and } \limsup_{t\to\infty} N_h(t) \leq \frac{\Lambda_h}{\delta_h}.$$

Hence N_p and N_h are bounded. Thus, for ϵ_1 and ϵ_2 sufficiently small, there exists $T_1 > 0$ such that if $t > T_1$,

$$N_p(t) \leq \frac{\Lambda_p}{\delta_p} + \epsilon_1 \text{ and } N_h(t) \leq \frac{\Lambda_h}{\delta_h} + \epsilon_2.$$

From the third equation of the system (2.1) it follows that, for $t > T_1$,

$$\frac{dC(t)}{dt} \leq \phi\left(\frac{\Lambda_p}{\delta_p} + \epsilon_1\right) - \xi C(t),$$

which leads to

$$\limsup_{t\to\infty} C(t) \leq \frac{\phi\Lambda_p}{\delta_p\xi} + \frac{\phi\epsilon_1}{\xi}.$$

This inequality being true for an arbitrary number of $\epsilon_1 > 0$ sufficiently small, we conclude that

$$\limsup_{t\to\infty} C(t) \leq \frac{\phi\Lambda_p}{\delta_p\xi}.$$

Hence C is bounded. ■

Appendix C. Local and global stability analysis

Appendix C.1. Proof of Theorem 4.3

Proof. The Jacobian of system (2.1) is given by the following matrix

$$\mathcal{J} = \begin{pmatrix} \mathcal{A} & 0 \\ \mathcal{C} & \mathcal{B} \end{pmatrix},$$

with

$$\mathcal{A} = \begin{pmatrix} -\beta_v I_p - \beta_e C - \delta_p & -\beta_v S_p & -\beta_e S_p \\ \beta_v I_p + \beta_e C & \beta_v S_p - (\delta_p + \mu_p) & \beta_e S_p \\ 0 & \phi & -\xi \end{pmatrix},\ C = \begin{pmatrix} 0 & -\tau_v S_h & -\tau_e S_h \\ 0 & \tau_v S_h & \tau_e S_h \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix},$$

$$\mathcal{B} = \begin{pmatrix} -\tau_v I_p - \tau_e C - \beta_h I_{h2} - \delta_h & 0 & -\beta_h S_h & 0 \\ \tau_v I_p + \tau_e C & -(\delta_h + \mu_{h1} + \epsilon) & 0 & 0 \\ \beta_h I_{h2} & \epsilon & \beta_h S_{h2} - (\mu_{h2} + \delta_h + \gamma) & 0 \\ 0 & 0 & \gamma & -\delta_h \end{pmatrix}.$$

Consequently, $\mathcal{J}$ evaluated at equilibrium F^0, F^+, F^* is stable if and only if $\mathcal{A}$ and $\mathcal{B}$ are also stable. By virtue of Theorems 3.3 and 3.4 the submatrix $\mathcal{A}$ evaluated at F^0 or F^+ has only eigenvalues with negative real part if $\mathcal{R}_0^p < 1$. The submatrix $\mathcal{A}$ evaluated at F^* has only eigenvalues with negative real part if $\mathcal{R}_0^p > 1$. Moreover, $\mathcal{B}$ is stable if and only if its first 3×3 block is stable. If we note

$$\overline{B} = \begin{pmatrix} -\tau_v I_p - \tau_e C - \beta_h I_{h2} - \delta_h & 0 & -\beta_h S_h \\ \tau_v I_p + \tau_e C & -(\delta_h + \mu_{h1} + \epsilon) & 0 \\ \beta_h I_{h2} & \epsilon & \beta_h S_{h2} - (\mu_{h2} + \delta_h + \gamma) \end{pmatrix}$$

then, to study the local stability of the equilibria F^0, F^+ and F^* amounts to checking only the eigenvalues of the submatrix $\overline{B}$.

The eigenvalues of $\overline{B}$ at F^0 are

$$\lambda_1 = -\delta_h,\ \lambda_2 = -(\delta_h + \mu_{h1} + \epsilon) \text{ and } \lambda_3 = (\mu_{h2} + \delta_h + \gamma)\left(\mathcal{R}_0^h - 1\right).$$

If $\mathcal{R}_0^h < 1$, then $Re(\lambda_i) < 0,\ \forall i = \{1, 2, 3\}$. Thus F^0 is LAS if $\mathcal{R}_0^p < 1$ and $\mathcal{R}_0^h < 1$.

The characteristic equation for $\overline{B}$ at F^+ is

$$P(\lambda) = (\delta_h + \mu_{h1} + \epsilon - \lambda)\left(\lambda^2 + \delta_h \mathcal{R}_0^h \lambda + \beta_h S_h^+ \delta_h \left(\mathcal{R}_0^h - 1\right)\right) = 0.$$

Therefore, Z^+ is LAS if $\mathcal{R}_0^p < 1$ and $\mathcal{R}_0^h > 1$.

Since

$$\beta_h S_h^* - (\mu_{h2} + \delta_h + \gamma) = -\frac{\epsilon I_{h1}^*}{I_{h2}^*},$$

the characteristic equation for $\overline{B}$ at F^* reads

$$P(\lambda) = \lambda^3 + d_2\lambda^2 + d_1\lambda + d_0 = 0,$$

where

$$\begin{aligned} d_0 &= \beta_h S_h^* \epsilon(\tau_v I_p^+ + \tau_e C^+) + \frac{\epsilon(\delta_h + \mu_{h1} + \epsilon) I_{h1}^*}{I_{h2}^*}(\tau_v I_p^+ + \tau_e C^+ + \beta_h I_{h2}^* + \delta_h) \\ &\quad + \beta_h^2 S_h^* I_{h2}^* (\delta_h + \mu_{h1} + \epsilon), \\ d_1 &= \beta_h^2 S_h^* I_{h2}^* + (\delta_h + \mu_{h1} + \epsilon)(\tau_v I_p^+ + \tau_e C^+ + \beta_h I_{h2}^* + \delta_h) \\ &\quad + \frac{\epsilon I_{h1}^*}{I_{h2}^*}(\tau_v I_p^+ + \tau_e C^+ + \beta_h I_{h2}^* + 2\delta_h + \mu_{h1} + \epsilon), \\ d_2 &= \tau_v I_p^+ + \tau_e C^+ + \beta_h I_{h2}^* + 2\delta_h + \mu_{h1} + \epsilon + \frac{\epsilon I_{h1}^*}{I_{h2}^*}, \end{aligned}$$

$$\begin{aligned} d_2 d_1 - d_0 &= \beta_h^2 S_h^* I_{h2}^* (\tau_v I_p^+ + \tau_e C^+ + \beta_h I_{h2}^* + \delta_h) + \epsilon \beta_h^2 S_h^* I_{h1}^* \\ &\quad + (\delta_h + \mu_{h1} + \epsilon)(\tau_v I_p^+ + \tau_e C^+ + \beta_h I_{h2}^* + \delta_h)^2 \\ &\quad + (\tau_v I_p^+ + \tau_e C^+ + \beta_h I_{h2}^* + \delta_h)(\delta_h + \mu_{h1} + \epsilon)^2 \\ &\quad + \frac{\epsilon I_{h1}^*}{I_{h2}^*}(\tau_v I_p^+ + \tau_e C^+ + \beta_h I_{h2}^* + \delta_h + \delta_h + \mu_{h1} + \epsilon)^2 \\ &\quad + \left(\frac{\epsilon I_{h1}^*}{I_{h2}^*}\right)^2 (\tau_v I_p^+ + \tau_e C^+ + \beta_h I_{h2}^* + \delta_h + \delta_h + \mu_{h1} + \epsilon) - \beta_h S_h^* \epsilon(\tau_v I_p^+ + \tau_e C^+). \end{aligned}$$

Note that $d_i > 0, i = 0, 1, 2$ and $d_1 d_2 - d_0 > 0$. Then, by using Routh-Hurwitz criterion we conclude that the endemic equilibrium Z^* of system (2.1) is locally asymptotically stable. ■

Appendix C.2. Second additive compound matrix

Let n be a positive integer, and A a linear operator on $\mathbb{R}^n$ and also denote its matrix representation with respect to the standard basis of $\mathbb{R}^n$. A canonically induces a linear operator $A^{[2]}$ on $\wedge^2\mathbb{R}^n$. For $u_1, u_2 \in \mathbb{R}^n$, define $A^{[2]}(u_1 \wedge u_2) = A(u_1) \wedge u_2 + u_1 \wedge A(u_2)$ and extend the definition over $\wedge^2\mathbb{R}^n$ by linearity. This is an $\binom{n}{2} \times \binom{n}{2}$ matrix with each entry being a linear expression of the entries of A. When $n = 3$, $A = (a_{ij})$, then the second additive compound matrix $A^{[2]}$ is given by.

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

Detailed information on $A^{[2]}$ can be found in [46, 47]. Let $\mathrm{x} \mapsto \mathrm{f(x)} \in \mathbb{R}^n$ be a C^1 function for x in an open set $\Omega \subset \mathbb{R}^n$. Consider the differential equation

$$\dot{x} = f(x). \tag{C.1}$$

Denote by $x(t, x_0)$, the solution of (C.1) with respect to $x(0, x_0) = x_0$. We make the following two basic assumptions on (C.1):

(H_1) There exists a compact absorbing set $K \subset \Omega$.

(H_2) there exists a unique equilibrium point $\overline{x} \in \Omega$.

Let $\mathrm{x} \mapsto \mathrm{P(x)}$ be an $\binom{n}{2} \times \binom{n}{2}$ matrix-valued function that is C^1 for $x \in \Omega$. Assume that $P^{-1}(x)$ exists and is continuous for $x \in K$. We define a quantity $\overline{q}$ by

$$\overline{q} = \limsup_{t \to +\infty} \sup_{x_0 \in K} \frac{1}{t} \int_0^t \mu(B(x(s, x_0)))ds,$$

where

$$B = P_f P^{-1} + P \frac{\partial f^{[2]}}{\partial x} P^{-1}.$$

The matrix P_f is obtained by replacing each entry p_{ij} of P by its derivative in the direction of f. $\left(\frac{\partial P^*_{ij}}{\partial x}\right) f = \frac{dP_{ij}}{dt} \cdot \frac{\partial f^{[2]}}{\partial x}$ is the second additive compound matrix of the Jacobian matrix $\frac{\partial f}{\partial x}$ of f. $\mu(B)$ is the Lozinskil measure of B with respect to a vector norm $\|.\|$ in $\mathbb{R}^{\binom{n}{2}}$, defined by

$$\mu(B) = \lim_{h \to 0^+} \frac{\|I + hB\| - 1}{h}.$$

It is shown in [46] that if Ω is simply connected, the condition $\overline{q} < 0$ rules out the presence of orbits such as periodic orbits, homoclinic orbits and heteroclinic cycles; and it is robust under C^1 local perturbations of f near any non-equilibrium point that is non-wandering. Now we state the following global stability result from [46].

Lemma Appendix C.1. *Assume that Ω is simply connected and assumptions (H_1) and (H_2) hold. Then the unique equilibrium point $\overline{x}$ of (C.1) is globally stable in Ω if $\overline{q} < 0$.*

Appendix C.3. Proof of Theorem 4.11

Proof. As $\mathcal{R}_0^p > 1$, $(S_p(t), I_p(t), C(t)) \to (S_p^+, I_p^+, C^+)$ when $t \to \infty$ and system (2.1) is permanent. The ω-limit set of system (2.1) lies in $\left\{\left(S_p^+, I_p^+, C^+, S_h, I_{h1}, I_{h2}, R_h\right) : (S_h, I_{h1}, I_{h2}, R_h) \in Int\mathbb{R}_+^4\right\}$. It is enough to consider system (4.5).

The Jacobian matrix A of system (4.5), evaluated at a general solution (S_h, I_{h1}, I_{h2}) is

$$A = \begin{pmatrix} -\delta_h - \beta_h I_{h2} - \tau_p I_p^+ - \tau_e C^+ & 0 & -\beta_h S_h \\ \tau_p I_p^+ + \tau_e C^+ & -(\delta_h + \mu_{h1} + \epsilon) & 0 \\ \beta_h I_{h2} & \epsilon & \beta_h S_h - (\delta_h + \mu_{h2} + \gamma) \end{pmatrix}.$$

Its second additive compound matrix is

$$A^{[2]} = \begin{pmatrix} A_{11} & 0 & \beta_h S_h \\ \epsilon & A_{22} & 0 \\ -\beta_h I_{h2} & \tau_p I_p^+ + \tau_e C^+ & A_{33} \end{pmatrix},$$

where

$$\begin{aligned} A_{11} &= -2\delta_h - \beta_h I_{h2} - \tau_p I_p^+ - \tau_e C^+ - \mu_{h1} - \epsilon, \\ A_{22} &= \beta_h S_h - \beta_h I_{h2} - \tau_p I_p^+ - \tau_e C^+ - 2\delta_h - \mu_{h2} - \gamma, \\ A_{33} &= \beta_h S_h - 2\delta_h - \mu_{h1} - \epsilon - \mu_{h2} - \gamma. \end{aligned}$$

Define the function

$$P(x) = P(S_h, I_{h1}, I_{h2}) = diag\left(\frac{S_h}{I_{h2}}, \frac{S_h}{I_{h2}}, \frac{S_h}{I_{h2}}\right).$$

It holds that

$$P_f P^{-1} = diag\left(\frac{S_h'}{S_h} - \frac{I_{h2}'}{I_{h2}}, \frac{S_h'}{S_h} - \frac{I_{h2}'}{I_{h2}}, \frac{S_h'}{S_h} - \frac{I_{h2}'}{I_{h2}}\right).$$

Moreover,

$$\begin{aligned} B &= P_f P^{-1} + P A^{[2]} P^{-1} \\ &= \begin{pmatrix} \frac{S_h'}{S_h} - \frac{I_{h2}'}{I_{h2}} + A_{11} & 0 & \beta_h S_h \\ \epsilon & \frac{S_h'}{S_h} - \frac{I_{h2}'}{I_{h2}} + A_{22} & 0 \\ -\beta_h I_{h2} & \tau_p I_p^+ + \tau_e C^+ & \frac{S_h'}{S_h} - \frac{I_{h2}'}{I_{h2}} + A_{33} \end{pmatrix} \\ &= \begin{pmatrix} B_{11} & B_{12} \\ B_{21} & B_{22} \end{pmatrix}, \end{aligned}$$

where

$$B_{11} = \frac{S_h'}{S_h} - \frac{I_{h2}'}{I_{h2}} - 2\delta_h - \beta_h I_{h2} - \tau_p I_p^+ - \tau_e C^+ - \mu_{h1} - \epsilon\ ,\ B_{12} = (0, \beta_h S_h)\ ;\ B_{21} = (\epsilon, -\beta_h I_{h2})^T\ ,$$

$$B_{22} = \begin{pmatrix} \frac{S_h'}{S_h} - \frac{I_{h2}'}{I_{h2}} + A_{22} & 0 \\ \tau_p I_p^+ + \tau_e C^+ & \frac{S_h'}{S_h} - \frac{I_{h2}'}{I_{h2}} + A_{33} \end{pmatrix}.$$

Let (u_1, u_2, u_3) be the vectors in $\mathbb{R}^3 \equiv \mathbb{R}^{\begin{pmatrix} 3 \\ 2 \end{pmatrix}}$.

We choose a norm in $\mathbb{R}^3$ as $\|(u_1, u_2, u_3)\| = \sup_i |u_i|$, and $\mu(B) = \sup_i (R_e(b_{ii}) + \sum_{j \neq i} |b_{ij}|)$ denotes the Lozinskil

measure with respect to the norm above. By the method in [47], we have the following estimate:

$$\mu(B) \leq \sup\{g_1; g_2\},$$

where

$$g_1 = \mu_1(B_{11}) + |B_{12}| \quad \text{and} \quad g_2 = \mu_1(B_{22}) + |B_{21}|.$$

$|B_{12}|$ and $|B_{21}|$ are the matrix norms with respect to $l_1 - norm$. μ_1 is the Lozinskil measure with respect to the $l_1 - norm$.

Thus we have

$$\begin{aligned}
\mu_1(B_{11}) &= \frac{S_h^{'}}{S_h} - \frac{I_{h2}^{'}}{I_{h2}} - \beta_h I_{h2} - \tau_p I_p^+ - \tau_e C^+ - 2\delta_h - \mu_{h1} - \epsilon, \\
\mu_1(B_{22}) &= \frac{S_h^{'}}{S_h} - \frac{I_{h2}^{'}}{I_{h2}} + \max\left\{\beta_h S_h - \beta_h I_{h2} - 2\delta_h - \mu_{h2} - \gamma\ ,\ \beta_h S_h - 2\delta_h - \mu_{h1} - \epsilon - \mu_{h2} - \gamma\right\}, \\
|B_{12}| &= \max_j(\textstyle\sum_{i=1}^2 |a_{ij}|) = \beta_h S_h \text{ and } |B_{21}| = \max_j(\textstyle\sum_{i=1}^2 |a_{ij}|) = \epsilon + \beta_h I_{h2}.
\end{aligned}$$

Using the fact that

$$\frac{I_{h2}^{'}}{I_{h2}} = \beta_h S_h + \epsilon\frac{I_{h1}}{I_{h2}} - \delta_h - \mu_{h2} - \gamma,$$

we have

$$\begin{aligned}
g_1 &= \frac{S_h^{'}}{S_h} - \frac{\epsilon I_{h1}}{I_{h2}} - \beta_h I_{h2} - \tau_p I_p^+ - \tau_e C^+ - \delta_h - \mu_{h1} - \epsilon + \mu_{h2} + \gamma, \\
g_2 &= \frac{S_h^{'}}{S_h} + \max\left\{-\delta_h - \frac{\epsilon I_{h1}}{I_{h2}} + \epsilon, -\frac{\epsilon I_{h1}}{I_{h2}} - \delta_h - \mu_{h1} + \beta_h I_{h2}\right\},
\end{aligned}$$

for $t > T$. Because of the uniform persistence (see Theorem 4.10), we can select the constants so that there exists $T > 0$ independent of $(S_p^0, I_p^0, C^0, S_h^0, I_{h1}^0, I_{h2}^0, R_h^0) \in K$ such that $k_{I_2} \leq I_{h1}(t) \leq K_{I_2}$ and $k_{I_3} \leq I_{h2}(t) \leq K_{I_3}$ for $t > T$.

Therefore, setting

$$\begin{aligned}
b_1 &= \frac{\epsilon k_{I_2}}{K_{I_3}} + \beta_h k_{I_3} + \tau_p I_p^+ + \tau_e C^+ + \delta_h + \mu_{h1} + 2\epsilon - \mu_{h2} - \gamma, \\
b_2 &= \frac{\epsilon k_{I_2}}{K_{I_3}} + \delta_h + \mu_{h1} - \beta_h K_{I_3} + \epsilon,
\end{aligned}$$

we have

$$\mu(B) \leq \frac{S_h^{'}}{S_h} + \max\left\{-b_1, -\delta_h - \frac{\epsilon k_{I_2}}{K_{I_3}}, -b_2\right\} = \frac{S_h^{'}}{S_h} - \bar{b},$$

where

$$\bar{b} = \min\left\{b_1, \delta_h + \frac{\epsilon k_{I_2}}{K_{I_3}}, b_2\right\} \text{ with } b_1 \geq 0, b_2 \geq 0.$$

Along each solution $(S_h(t), I_{h1}(t), I_{h2}(t))$ of (4.5) such that $(S_h^0, I_{h1}^0, I_{h2}^0) \in K$ and $t > T$, we have

$$\frac{1}{t}\int_0^t \mu(B)ds \leq \frac{1}{t}\int_0^T \mu(B)ds + \frac{1}{t}\int_T^t\left(\frac{S_h^{'}}{S_h} - \bar{b}\right)ds \leq \frac{1}{t}\int_0^T \mu(B)ds + \frac{1}{t}ln\frac{S_h(t)}{S_h(T)} - \bar{b}\frac{t-T}{t}\ .$$

This implies that $\bar{q} \leq -\frac{\bar{b}}{2} < 0$, if the following conditions hold true:

$$\begin{aligned}
\mu_{h2} + \gamma &\leq \frac{\epsilon k_{I_2}}{K_{I_3}} + \beta_h k_{I_3} + \tau_p I_p^+ + \tau_e C^+ + \delta_h + \mu_{h1} + 2\epsilon, \\
\beta_h K_{I_3} &\leq \frac{\epsilon k_{I_2}}{K_{I_3}} + \delta_h + \mu_{h1} + \epsilon.
\end{aligned}$$

This completes the proof. ■

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