Dynamics of Low and High Pathogenic Avian Influenza in Bird Populations

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Avian influenza H5N1 is at present the most dangerous zoonotic disease infecting wild and domestic birds. Avian influenza (AI) H5N1 exists in two forms: Low pathogenic (LPAI) and high pathogenic (HPAI). LPAI is a mild infection in chicken, much like human flu in humans. HPAI is a systemic infection in chicken. It infects multiple organs and results in death in 48 hours [1]. It is HPAI H5N1 that currently infects humans mostly through domestic bird-to-human transmission. World Health Organization has reported more than 650 human cases. From these infected individuals more than 60% have died [2].

The HPAI H5N1 is dangerous because it can mutate to become effectively human-to-human transmissible. The emergence of a pandemic HPAI H5N1 strain may happen in one of two ways: (1) reassortment and (2) mutation. Even if the mortality of the pandemic strain is much smaller than the one of the current bird-to-human transmittable strains, it will kill millions of people. Because of its importance to public health, AI has been extensively modeled. The first few articles were published by Iwami *et al.* [6, 7, 8]. The authors introduced a simple domestic birds-humans model, in which the current circulating HPAI H5N1 strain mutates into a human-to-human transmittable strain. They conclude that continuing culling of H5N1-infected domestic birds in the face of the emergence of a pandemic strain will increase the chance of that pandemic strain and will result of higher prevalence of pandemic strain infected humans. Using H5N1 human case data, Martcheva [10] shows that the interference that the bird-to-human strain exercises over the pandemic strain is very low and should not influence the decision to continue culling.

HPAI usually evolves from LPAI in domestic birds. However, it is the HPAI that is dangerous and deadly both for humans and for poultry. Prior

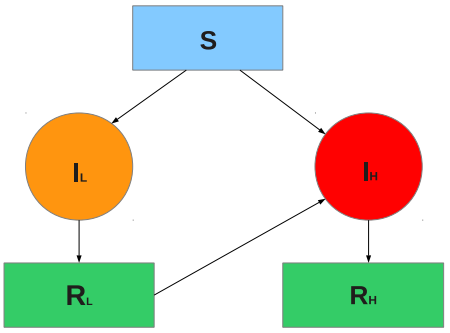
exposure to LPAI both for domestic and for wild birds can make a subsequent infection with HPAI much more mild and even asymptomatic. This property is called cross-immunity, that is LPAI provides partial protection and cross-immunity to HPAI. Several articles have studied the interaction between LPAI and HPAI. Lucchetti *et al* [9] show that HPAI persists in poultry but LPAI can be found in poultry only because of spill-over infection from wild birds. Bourouiba *et al* [3] investigates the impact of cross-immunity on the two types of AI.

Mathematical Model. To understand the interplay between LPAI and HPAI we introduce a simple mathematical model of cross-immunity between LPAI and HPAI. To build the model, we assume:

- Infected birds with HPAI can recover. That assumption is valid for wild birds and may hold for vaccinated poultry
- Infected birds with LPAI can recover
- Recovered from LPAI birds can get infected with HPAI but not vice versa, that is, we assume that once infected with HPAI the bird exits the system.
- Recovered birds from LPAI can get infected with HPAI at a lower probability. We do not keep track of the recovery rate of birds infected with HPAI which have been priorly infected with LPAI.

The flow-chart of the model is shown in Figure 1. In the flowchart, S is the

Figure 1. Flow-Chart of the Model



number of susceptible birds, I_L is the number of birds infected with LPAI,

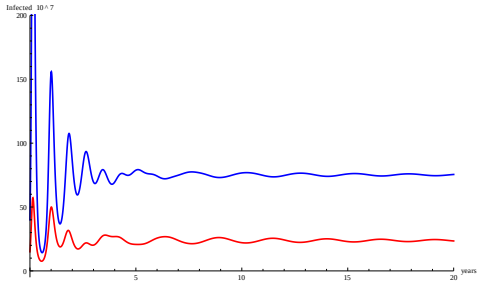
I_H is the number of birds infected with HPAI, R_L is the number of birds recovered from LPAI, R_H is the number of birds recovered from HPAI. The model takes the form.

$$\begin{cases} S' = \Lambda - \beta_L I_L S - \beta_H I_H S - \mu S, \\ I'_L = \beta_L I_L S - (\mu + \alpha_L) I_L, \\ R'_L = \alpha_L I_L - q\beta_H I_H R_L - \mu R_L, \\ I'_H = \beta_H I_H S + q\beta_H I_H R_L - (\mu + \alpha_H + \nu_H) I_H, \\ R'_H = \alpha_H I_H - \mu R_H \end{cases} \tag{1}$$

Here β_L and β_H are the transmission rates of LPAI and HPAI respectively, α_L and α_H are the recovery rates of LPAI and HPAI, ν_H is the disease-induced mortality of HPAI and q is the reduced susceptibility when priorly infected with LPAI birds get infected with HPAI. Λ is the recruitment rate and μ is the death rate of birds. A model of this type with

The Competition between LPAI and HPAI. Dynamically, long-term, there are four options for the LPAI and HPAI: (1) Both LPAI and HPAI decline to zero; (2) LPAI persists, HPAI declines to zero; (3) HPAI persists, LPAI declines to zero; (4) Both LPAI and HPAI persist. This last scenario, called coexistence, is illustrated in Figure 2. The prevalence of LPAI is larger than the prevalence of HPAI, which is the case in wild birds in nature.

Figure 2. Coexistence of LPAI and HPAI in wild birds. Red line is HPAI, blue line is LPAI.



These outcomes correspond to four types of equilibria of model (1). The first type is the Disease-Free Equilibrium (DFE), $\mathcal{E}_0 = (\Lambda/\mu, 0, 0, 0, 0)$. This equilibrium corresponds to the case when both LPAI and HPAI die out long term. The stability of this equilibrium depends on the reproduction

numbers of LPAI and HPAI:

$$\mathcal{R}_L = \frac{\Lambda\beta_L}{\mu(\mu+\alpha_L)} \qquad \mathcal{R}_H = \frac{\Lambda\beta_H}{\mu(\mu+\alpha_H)} \tag{2}$$

The reproduction number of LPAI (HPAI) gives the number of secondary infections one infected with LPAI(HPAI) bird will produce in an entirely susceptible bird population. It can be shown [11] that if $\mathcal{R}_L < 1$ and $\mathcal{R}_H < 1$ then the DFE is locally asymptotically stable. If $\mathcal{R}_L > 1$ or $\mathcal{R}_H > 1$, then it is unstable. Moreover, it can be shown that if $\mathcal{R}_L < 1$ and $\mathcal{R}_H < 1$ then the DFE is globally asymptotically stable. Ideally, through control measures we would like to push the reproduction numbers of both LPAI and HPAI below one. However, that may be difficult in practice.

Furthermore, we find that the systems has LPAI-only equilibrium and HPAI-only equilibrium. The LPAI-only equilibrium is given by $\mathcal{E}_L = (S^*, I_L^*, R_L^*, 0, 0)$ where

$$S^* = \frac{\mu+\alpha_L}{\beta_L}, \qquad I_L^* = \frac{\mu}{\beta_L}(\mathcal{R}_L - 1), \qquad R_L^* = \frac{\alpha_L}{\beta_L}(\mathcal{R}_L - 1).$$

Clearly the LPAI-only equilibrium exists if and only if $\mathcal{R}_L > 1$. The HPAI-only equilibrium is given by $\mathcal{E}_H = (S^\circ, 0, 0, I_H^\circ, R_H^\circ)$ where

$$S^\circ = \frac{\mu+\alpha_H+\nu_H}{\beta_H}, \qquad I_H^\circ = \frac{\mu}{\beta_H}(\mathcal{R}_H - 1), \qquad R_H^\circ = \frac{\alpha_H}{\beta_H}(\mathcal{R}_H - 1).$$

Clearly the HPAI-only equilibrium exists if and only if $\mathcal{R}_H > 1$.

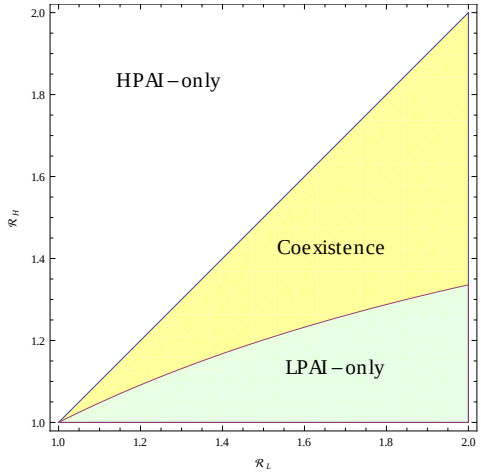
The stability of the semi-trivial equilibria and, therefore, the outcome of the competition between LPAI and HPAI is given by the invasion reproduction numbers. The invasion reproduction number of LPAI (HPAI) at the equilibrium of HPAI (LPAI), denoted by $\mathcal{R}_L^*$ ($\mathcal{R}_H^*$), gives the number of secondary cases one LPAI-infected (HPAI-infected) bird will produce in a population in which the HPAI (LPAI) is at equilibrium. The values of the invasion numbers are given below:

$$\mathcal{R}_L^* = \frac{\mathcal{R}_L}{\mathcal{R}_H} \qquad \mathcal{R}_H^* = \frac{\mathcal{R}_H}{\mathcal{R}_L}\left(1 + \frac{q\alpha_L}{\mu(\alpha_L+\mu)}(\mathcal{R}_L - 1)\right)$$

Furthermore, the LPAI dominance equilibrium $\mathcal{E}_L$ is locally asymptotically stable if $\mathcal{R}_H^* < 1$, that is if the HPAI cannot invade the equilibrium of the LPAI. The LPAI equilibrium is unstable if $\mathcal{R}_H^* > 1$. Similarly, the HPAI dominance equilibrium $\mathcal{E}_H$ is locally asymptotically stable if $\mathcal{R}_L^* < 1$, that is if the LPAI cannot invade the equilibrium of the HPAI. The HPAI equilibrium is unstable if $\mathcal{R}_L^* > 1$.

Furthermore, it can be shown that if both invasion numbers are greater than one, $\mathcal{R}_H^* > 1$ and $\mathcal{R}_L^* > 1$, then a unique coexistence equilibrium exists, $\mathcal{E}^{**} = (S^{**}, I_L^{**}, R_L^{**}, I_H^{**}, R_H^{**})$. To get a better idea of the parameter space where LPAI-only exists, HPAI-only exists or the two coexist, in the $(\mathcal{R}_L, \mathcal{R}_H)$-plane, we plot the regions of coexistence and dominance. These regions are given by the equalities $\mathcal{R}_L^* = 1$ and $\mathcal{R}_H^* = 1$. The resulting figure is given as Figure 3.

Figure 3. Regions of dominance and coexistence of LPAI and HPAI.

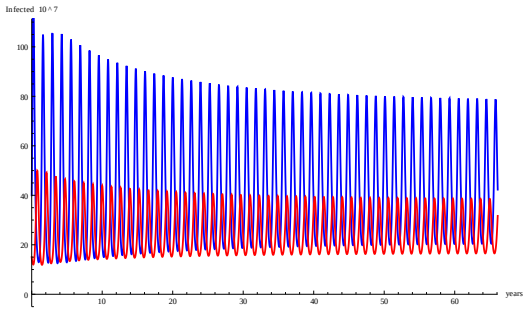


Examining Figure 3, we can make several interesting conclusions. First, we may notice that region of parameter space for which HPAI persist is much larger. Thus, HPAI is present for more values of $\mathcal{R}_L$ and $\mathcal{R}_H$. Second, the presence of LPAI actually increases the area where HPAI persists. That is visible from the coexistence area. Third, simulations suggests that the larger the q, the larger the coexistence area and the smaller the area where LPAI persists alone. If $q = 0$ then there will not be coexistence but competitive exclusion between the LPAI and HPAI. In this case we call cross-immunity a coexistence mechanism because its presence leads to coexistence. When competitive exclusion is the only possible outcome, that is in the case $q = 0$, then the whether LPAI persists or HPAI persists is determined by their reproduction numbers. The AI with the larger reproduction number will persists as long as this reproduction number is above one.

In the late 1980's Carlos-Castillo-Chavez *et al* investigated the question

whether cross-immunity may be responsible for the oscillations observed in influenza dynamics. They concluded the a simple ODE model with cross-immunity cannot produce sustained oscillations. Surprisingly, this is not the case for model (1). We find that the coexistence equilibrium can be destabilized through Hopf bifurcation. In this case oscillations in which both LPAI and HPAI persist occur. This destabilization seems to need $q \approx 1$, that is it occurs in the case when LPAI provides nearly no protection against HPAI. The oscillations are shown in Figure 4.

Figure 4. Coexistence of LPAI and HPAI in the form of sustained oscillations.



Summary. We introduce an LPAI and HPAI model which describes well the transmission of the two pathogen variants both in wild and domestic birds. The model has a unique DFE which is globally stable if the two reproduction numbers are below one. The model has LPAI and HPAI dominance equilibria which exist when the LPAI (HPAI) reproduction number is above one. The LPAI (HPAI) dominance equilibrium is locally asymptotically stable if the invasion reproduction number of the HPAI (LPAI) is below one. The model has a unique coexistence equilibrium if both invasion numbers are above one. The coexistence equilibrium can become unstable and persistence of LPAI and HPAI is possible in the form of sustained oscillations. LPAI and HPAI compete for susceptible individuals: Increasing prevalence of LPAI decreases prevalence of HPAI. This may explain why higher prevalence of LPAI leads to lower prevalence of HPAI in wild birds and vice versa in domestic birds.

About the authors: *Necibe Tuncer* is an Assistant Professor at University of Tulsa. She got her Ph.D. degree in 2007 in Applied Mathematics from Auburn University. Her Ph.D. dissertation focuses on developing and

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