Avian Flu: Modeling and Implications for Control

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November 25, 2013

Abstract

At present H5N1 avian influenza is a zoonotic disease where the transmission to humans occurs from infected domestic birds. Since 2003 more than 500 people have been infected and nearly 60% of them have died. If the H5N1 virus becomes efficiently human-to-human transmittable, a pandemic will occur with potentially high mortality. A mathematical model of avian influenza which involves human influenza is introduced to better understand the complex epidemiology of avian influenza and the emergence of a pandemic strain. Demographic and epidemiological data on birds and humans are used for the parameterization of the model. The differential equation system faithfully projects the cumulative number of H5N1 human cases and captures the dynamics of the yearly cases. The model is used to rank the efficacy of the current control measures used to prevent the emergence of a pandemic strain. We find that culling without re-population and vaccination are the two most efficient control measures each giving 22% decrease in the number of H5N1 infected humans for each 1% change in the affected parameters (μ_b, ν_b for culling and β_b, ν_b for vaccination). Control measures applied to humans, however, such as wearing protective gear, are not very efficient, giving less than 1% decrease in the number of H5N1 infected humans for each 1% decrease in β_Y, the bird-to-human transmission coefficient of H5N1. Furthermore, we find that should a pandemic strain emerge, it will invade, possibly displacing the human influenza virus in circulation at that time. Moreover, higher prevalence levels of human influenza will obstruct the invasion capabilities of the pandemic H5N1 strain. This effect is not very pronounced, as we find that 1% increase in human influenza prevalence will decrease the invasion capabilities of the pandemic strain with 0.006%.

KEYWORDS: avian influenza, H5N1, pandemic, mathematical models, differential equations, reproduction number, invasion reproduction number, control measures, mathematical epidemiology

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AMS Subject Classification: 92D30, 92D40

1 Introduction

Avian influenza (AI) is by far the most dangerous disease linking animal and human wellbeing today. Ten years ago, AI was a disease of poultry and wild birds of limited significance [1, 2]. Today, the emergence of a strain that can infect humans through bird-to-human transmission and kill nearly 60% of those infected [3], has changed this perspective. But the real danger that this pathogen poses to the human health comes from its potential to change into an extremely virulent human-to-human transmittable pandemic strain. Reducing the probability of this happening requires drastic measures for the control of the spread of avian influenza, measures that include culling large numbers of poultry, restrictions on movement and trade of poultry products.

Avian influenza is a very complex disease. The pathogen mutates at a high rate, allowing it to jump species barriers and expand its host range. Various strains of avian influenza have been known to infect a large number of wild bird species, a number of species of domestic birds, a number of species of mammals (such as pigs, dogs and horses) as well as humans. The multi-species conglomerate of hosts, that avian influenza creates, poses serious difficulties for tracing and controlling the disease. Because of this complexity, the efforts are directed to reducing the circulation within the poultry population, as the main animal population responsible for the transmitting the disease to humans. The control strategies currently in place target the domestic bird populations and the humans. In the early 2000s only culling was applied in attempt to reduce the spread of the disease. Large numbers of chickens were destroyed, causing significant hardship and economic loss. Nowadays, multiple control strategies are in place: culling, vaccination of poultry, increasing biosecurity.

Modeling can lead the way into understanding the complex epidemiology of avian influenza and the need for mixed control measures to subdue this zoonotic disease with deadly potential. Mathematical and statistical models have been widely used to describe the transmission of avian influenza and to evaluate the effect of control measures. Early models on avian influenza focused on the humans, investigating the potential impact of a hypothetical pandemic and explored strategies for its possible mitigation [4, 5, 6, 7, 8]. Other models focused on the present status quo centered at infection of domestic birds and current control strategies which primarily target poultry. For example, spatial farm-based model treating poultry-farms as units [9] and SIR models for within-flock transmission of H5N1 [10] were developed. The effects of culling [11, 9, 12] and vaccination [13] were extensively studied. Despite the importance of a number of emergent diseases, many of which arise from spill over infections from animals, few models were developed to involve both animals and humans linked by a pathogen. This situation has been changing recently, particularly in relation to AI. The simplest model that captures birds-to-human transmission pathway of H5N1 involves domestic birds and humans [14].

Recognizing the importance of both birds and humans in the transmission and evolution of AI, a number of models involving domestic birds and humans [14, 15, 16, 17] were developed. Some, more elaborate models, even involve wild birds, as well as domestic birds and humans [11, 18, 19, 20].

In this article we introduce a model of H5N1 avian influenza, human seasonal influenza, and H5N1 pandemic influenza. We address two questions: (1) What is the role of human seasonal influenza in the possible invasion of a H5N1 pandemic strain? (2) What is the efficacy of the control measures, measured as percentage change in H5N1 prevalence in birds and humans, due to 1% change in response parameters? To answer these questions we introduce and investigate a model of avian influenza with human seasonal influenza.

In the next section we introduce our main model. The human part of the model is formulated in two scenarios: (1) Prepandemic scenario model – models the current situation where avian flu infects humans through bird-to-human infection and human flu is endemic. (2) Pandemic scenario model – models a hypothetical scenario in which a pandemic strain emerges and infects humans through human-to-human transmission. In section 3 we introduce the equilibria and reproduction numbers of the model. In section 4 we parameterize the model. The current prepandemic scenario model is parameterized in such a way that the cumulative number of human H5N1 cases agrees with time series data reported by the World Health Organization. The pandemic scenario is parameterized through information from prior pandemics. In section 5 we compute the elasticities of the reproduction number and the prevalence of H5N1 in birds and humans. We use the elasticities to rank the current control measures on avian influenza. Section 6 contains summary of our conclusions and discussion.

2 A model of avian influenza and seasonal human influenza

Low pathogenic avian influenza (LPAI) is endemic in wild birds. More than 100 species of birds grouped in 12 orders are hosts of LPAI viruses [21]. Low pathogenic viruses of the subtypes H5 and H7 have low prevalence in wild birds and are seldom detected by sampling [22, 23]. When low pathogenic strains of the subtypes H5 and H7 are transmitted from wild birds to susceptible domestic birds, such as chicken, ducks and geese, those strains may undergo mutation and become highly pathogenic. The HP H5N1 strains that currently infect poultry, and have started to infect humans, have originated some time in 1996, when highly pathogenic H5N1 virus was isolated from a farmed goose in Guangdong Province, China [24]. Currently, H5N1 HPAI strains are believed to be endemic in the poultry of many Asian countries [25, 11] and outbreaks occur in many countries in Asia, Africa and Europe [26]. One open question about HP H5N1 is whether it is endemic in wild birds, or wild birds become infected with HPAI only through "spill over" infection from the domestic birds.

A model, considering both LPAI and HPAI in domestic birds, was introduced in [11]. The model suggests that LPAI in domestic birds occurs only as a result of transmission from wild birds while HPAI persists in domestic birds populations. Because the domestic bird populations are reservoir of HP H5N1 viruses and a direct source of infection to humans, in this article, we restrict our attention to highly pathogenic H5N1 avian influenza and we include the domestic bird populations only.

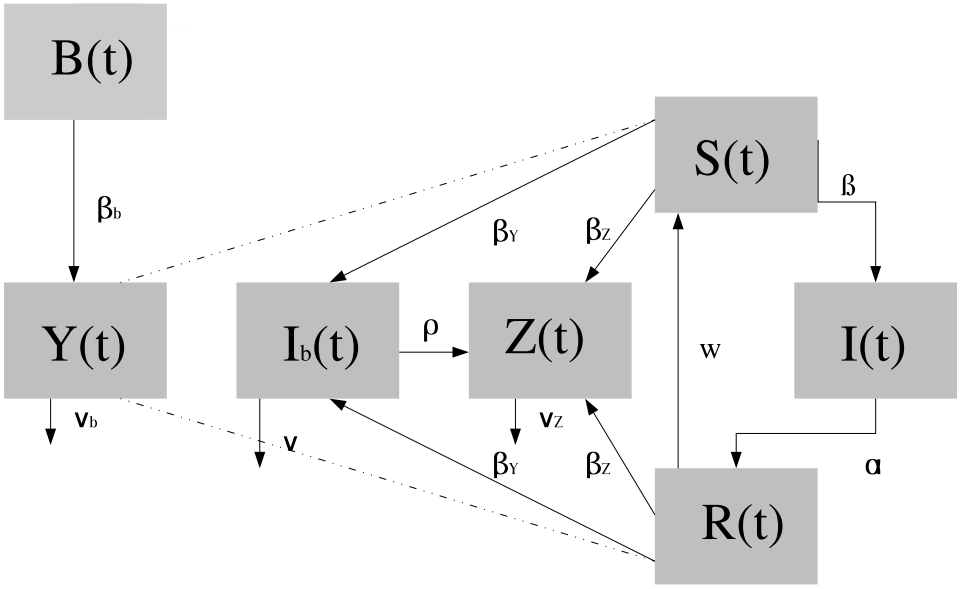

Figure 1: Diagram of the model. Natural birth/recruitment and death rates are omitted as well as the compartment of the jointly infected individuals which is transient.

We will model the epidemic among domestic birds by an SI (Susceptible-Infected) dynamics. Evidence suggest that much of the LPAI transmission occurs through environmental pathways, e.g. contaminated water. The environmental mode of transmission is particularly relevant in the transmission of the LPAI among wild birds (see [27] for associated modeling). However, for the domestic bird populations, who live in restricted spaces, the direct transmission of the HPAI is of primary importance, and it will be the only mode of transmission that we will take into account [28]. Our model assumes no recovery of domestic birds, based on the observed high mortality (90-100%) within 48 hours of infection [29]. Assuming $B(t)$ denotes the number of susceptible domestic birds, and $Y(t)$ denotes the number infected domestic birds (see Table 1) we have the following system for the domestic bird population:

$$\begin{aligned} \frac{dB}{dt} &= \Lambda_b - \beta_b BY - \mu_b B, \\ \frac{dY}{dt} &= \beta_b BY - (\nu_b + \mu_b)Y, \end{aligned} \tag{2.1}$$

where Λ_b is the birth rate of the domestic birds, μ_b is the natural death rate, and ν_b is the disease-induced death rate from HPAI. This model for the domestic birds was introduced by Iwami *et al* [14]. More complex models involving the two-way transmission pattern *wild birds* $\leftrightarrow$ *domestic birds* were considered in [19].

The total domestic poultry population is given by $P(t) = B(t)+Y(t)$. The total avian population satisfies a differential equation obtained from the sum of the two equations above: $P'(t) = \Lambda_b - \mu_b P(t) - \nu_b Y(t)$. This equation is not closed because of the presence of disease-induced mortality.

Notation	Meaning
$B(t)$	number of susceptible birds at time t
$Y(t)$	number of HPAI-infected birds
$P(t)$	total population size of birds
$S(t)$	number of susceptible individuals at time t
$I(t)$	number of individuals infected with seasonal human influenza
$R(t)$	number of recovered individuals from seasonal human influenza
$I_b(t)$	number of humans infected with the bird-to-human transmittable flu strain
$N(t)$	total human population size at time t
$Z(t)$	number of humans infected with pandemic H5N1 strain
$J(t)$	number of humans coinfected with avian and human influenza strains.

Table 1: *List of dependent variables*

Highly pathogenic strains of H5N1 have evolved to infect humans through bird-to-human transmission, thus creating conditions for reassortment with a human strain. Such a reassortment has the potential of creating a highly pathogenic H5N1 strain that is capable of efficient human-to-human transmission. The circulation of seasonal human influenza in the human population has two-fold impact on the creation and invasion of a pandemic H5N1 strain. On the one side, human influenza is expected to provide the genetic material for a hypothetical pandemic strain. Thus the presence and prevalence of human influenza *increases* the probability of emergence of a pandemic strain. On the other side, the human influenza is a competitor of the pandemic strain, and as such it should *impede* its ability to invade. To investigate the impact of human influenza on the ability of pandemic influenza to invade and cause a pandemic, we incorporate human influenza into the model. Regarding the human component of the model we consider two scenarios: (1) a prepandemic scenario, which models the current situation of spill over infection with H5N1 into humans and (2) a hypothetical pandemic scenario in which a human-to-human H5N1 pandemic strain has emerged. We model the two scenarios with two separate models so that the first is nested into the second.

2.1 Prepandemic scenario model

To introduce the prepandemic scenario human model, we denote by $S(t)$ the number of susceptible humans, by $I(t)$ the number of humans infected with human influenza, by $R(t)$ the number of humans recovered from human influenza. Humans can also become infected with HP H5N1 from domestic birds. This class is denoted by $I_b(t)$. The dependent variables are summarized in Table 1. The human epidemic model for the prepandemic scenario takes the form:

$$\begin{aligned} \frac{dS}{dt} &= \Lambda - (\beta I + \beta_Y Y)S - \mu S + wR, \\ \frac{dI}{dt} &= \beta SI - (\alpha + \mu)I, \\ \frac{dR}{dt} &= \alpha I - \beta_Y YR - (\mu + w)R, \\ \frac{dI_b}{dt} &= \beta_Y (S + R)Y - (\mu + \nu)I_b. \end{aligned} \tag{2.2}$$

where Λ is the birth/recruitment rate for humans, μ is the natural death rate, β is the transmission rate for human influenza, α is the recovery rate from human influenza, w is the rate at which immunity wanes, β_Y is the transmission rate of the bird-to-human strain, and ν is the H5N1-induced mortality. We assume that all humans who become infected with bird-to-human transmittable H5N1 exit the system. Summary of the parameters is given in Table 2. The total human population size in the prepandemic scenario is given by $N(t) = S(t) + I(t) + R(t) + I_b(t)$. Adding all equations in system (2.2) we see that the total human population size $N(t)$ satisfies the differential equation $N'(t) = \Lambda - \mu N - \nu I_b$.

Notation	Meaning
Λ_b	birth/recruitment rate into the bird population
μ_b	per capita natural death rate of birds
β_b	transmission coefficient of HP H5N1 strains to susceptible birds
ν_b	disease-induced mortality of birds
Λ	birth/recruitment rate into the population
μ	per capita natural death rate
β	transmission coefficient of human influenza A strains to susceptibles
w	rate of waning of immunity after exposure
β_Y	transmission coefficient of bird-to-human transmittable avian flu strain
β_J	transmission coefficient of bird-to-human transmittable avian flu strain for those infected with human influenza A
α	per capita recovery rate from the class I
ρ	per capita mutation rate of the bird-to-human strain into human-to-human transmittable strain
ν	per capita death rate of infected with bird-to-human flu strain

Table 2: *List of parameters*

2.2 Pandemic scenario model

The highly pathogenic H5N1 strain that currently infects humans through bird-to-human transmission, can cause pandemic among humans if it acquires a highly efficient human-to-human transmission mechanism, while retaining high pathogenicity. This can happen if it exchanges genetic components, a process called *reassortment*, with a human-to-human transmitted strain, such as seasonal human strain or a pandemic H1N1 strain. This scenario is believed to have given rise to the pathogens that caused the 1957, and 1968 pandemics, and possibly the 1918 pandemic. Reassortment may occur if a human strain and an H5N1 strain infect the same individual simultaneously, that is *co-infection* occurs with human and avian influenza strains. The role of pigs, which can be infected by both human and avian flu viruses, as a natural "mixing vessel" for genetic reassortment of flu viruses [30], has been controversial. Reassortment may also occur in humans. To capture the emergence of pandemic strain, we model co-infection [31] in a human host by the avian highly pathogenic H5N1 strain and seasonal human-to-human transmitted flu strain. Such a co-infection may occur for two reasons:

1. Because of the drift human flu strains infect humans repeatedly, sometimes several times in a year.

2. Since 1997, the highly pathogenic H5N1 has been continuously infecting primarily through "spill over" infection to humans in many countries in Asia and Africa.

Several reports have so far been made of possible coinfection of humans with an H5N1 strain and a human strain. One of the co-infection reports was of an Indonesian teen in 2008. The other, of an Egyptian man, suspected of co-infection by H5N1 and the pandemic H1N1 strain in 2009. Both of these reports have not been confirmed in the mainstream medical literature. Although, this far no reliable reports of such co-infection in humans have been made, the risk of reassortment of H5N1 with human flu in a human continues to be significant.

We model this exact, currently hypothetical, scenario in which H5N1 and human flu viruses co-infect a human and create spontaneously a pandemic strain trough *reassortment*. To introduce the pandemic scenario model, let $J(t)$ denote the total number of jointly infected individuals, and $Z(t)$ be the total number of individuals infected with the pandemic H5N1 strain. We assume the emergence of the pandemic H5N1 strain is through reassortment, and hence spontaneous. We model the event with a Dirac delta

function. The human part of the pandemic scenario model takes the form:

$$\begin{aligned}
\frac{dS}{dt} &= \Lambda - (\beta I + \beta_Y Y + \beta_Z Z)S - \mu S + wR,\\
\frac{dI}{dt} &= \beta SI - \beta_J I(t)Y(t) - (\alpha+\mu)I,\\
\frac{dR}{dt} &= \alpha I - \beta_Y YR - \beta_Z R(t)Z(t) - (\mu+w)R,\\
\frac{dI_b}{dt} &= \beta_Y(S+R)Y - (\mu+\nu)I_b,\\
\frac{dJ(t)}{dt} &= \beta_J Y(t)I(t) - (\mu+\nu_J)J(t) - \rho\delta(t-t_1)J(t),\\
\frac{dZ}{dt} &= \rho\delta(t-t_1)J(t) + \beta_Z(S+R)Z - (\mu+\nu_Z)Z.
\end{aligned} \tag{2.3}$$

Parameters introduced in this model in addition to the parameters in model (2.2) include the coefficient β_J which denotes the transmission rate of avian H5N1 infection to individuals infected with human influenza. Individuals, first infected with H5N1 are assumed to be too sick to get subsequently infected with human influenza. Hence, such a term does not exist in the equation for I_b. Parameters ν_J and ν_Z denote the duration of infectiousness of jointly infected and of those infected with pandemic influenza respectively. The spontaneous emergence of a pandemic strain at time t_1 is modeled by Dirac delta function $\delta(t-t_1)$. The mutation rate is ρ.

3 Equilibria and reproduction numbers

Model (2.1)-(2.3) is an extension of the avian influenza model considered by Iwami *et.al.* [15, 16] that includes human influenza. This extention allows for the study of the competition of multiple influenza strains – a typical scenario in which a novel pandemic strain invades.

For the prepandemic scenario, there are two reproduction numbers: the reproduction number of avian influenza, and the reproduction number of human influenza.

$$\mathcal{R}_0^b = \frac{\Lambda_b\beta_b}{\mu_b(\nu_b+\mu_b)} \qquad \mathcal{R}_1 = \frac{\Lambda\beta}{\mu(\nu+\mu)}. \tag{3.1}$$

To interpret the reproduction numbers, observe that in the case of human flu, β gives the number of secondary infections that one infected individual will produce in one unit of time. The fraction $1/(\mu+\nu)$ gives the number of time units this individual stays infected, and Λ/μ gives the number of susceptible individuals. Thus, the reproduction number gives the secondary number of cases one infected individual will generate in an entirely susceptible population during her lifetime as infectious. The system has the disease-free equilibrium $\mathcal{E}_0 = (\frac{\Lambda_b}{\mu_b}, 0, \frac{\Lambda}{\mu}, 0, 0, 0)$ which is locally and globally stable if $\mathcal{R}_0^b < 1$ and $\mathcal{R}_1 < 1$ and unstable if at least one of these inequalities does not hold. The bird model (2.1) is independent of the human models. Avian influenza persists in birds, and humans become infected with H5N1 through bird-to-human transmission, if $\mathcal{R}_0^b > 1$. The endemic equilibrium of the model (2.1) in this case is given by (B^*, Y^*) where

$$B^* = \frac{\nu_b+\mu_b}{\beta_b} \qquad Y^* = \frac{\Lambda_b}{\nu_b+\mu_b}\left(1 - \frac{1}{\mathcal{R}_0^b}\right). \tag{3.2}$$

3.1 Prepandemic scenario

The full system of the prepandemic scenario has three more equilibria besides the disease-free equilibrium: avian influenza dominant equilibrium, human influenza dominant equilibrium, avian and human influenza coexistence equilibrium. The avian influenza dominant equilibrium exists if the reproduction number of avian influenza is greater than one: $\mathcal{R}_0^b > 1$. The equilibrium is given by $\mathcal{E}_b = (B^*, Y^*, S_b^*, 0, 0, I_b^*)$ where B^* and Y^* are defined by the expressions above and

$$S_b^* = \frac{\Lambda}{\beta_Y Y^* + \mu} \qquad I_b^* = \frac{\beta_Y \Lambda Y^*}{(\beta_Y Y^* + \mu)(\mu + \nu)}. \tag{3.3}$$

The avian strain equilibrium is locally stable if the other strains cannot invade it. The total human population size at equilibrium in this case is given by $N^* = S_b^* + I_b^*$. The human influenza dominant equilibrium exists if $\mathcal{R}_1 > 1$ and is given by $\mathcal{E}_1 = (\frac{\Lambda_b}{\mu_b}, 0, S_1^*, I_1^*, R_1^*, 0)$ where

$$S_1^* = \frac{\alpha + \mu}{\beta} \qquad I_1^* = \frac{\Lambda(\mu + w)}{\mu(\mu + \alpha + w)}\left(1 - \frac{1}{\mathcal{R}_1}\right) \qquad R_1^* = \frac{\Lambda\alpha}{\mu(\mu + \alpha + w)}\left(1 - \frac{1}{\mathcal{R}_1}\right). \tag{3.4}$$

The presence of dominance equilibria suggests that avian influenza and human influenza can exist independently of each other in the human population.

RN/ IRN	Explanation
$\mathcal{R}_1$	Reproduction number of humans influenza
$\mathcal{R}_0^b$	reproduction number of bird and bird-to-human influenza
$\hat{\mathcal{R}}$	IRN of human flu at equilibrium of bird flu ($\rho = 0$)

Table 3: *List of reproduction and invasion reproduction numbers and their interpretation*

The current prepandemic scenario where human influenza coexists with the spill-over infection of avian influenza in humans is also captured in this model. What conditions give such a scenario? Because avian influenza circulates in domestic birds populations, and infects humans only through their contact with infected birds, it persists if $\mathcal{R}_0^b > 1$. Avian influenza does not compete with human influenza for susceptibles, as human influenza does not infect domestic birds. Human influenza, however, competes with avian influenza for susceptible humans. Hence, it will persist in the presence of avian influenza, if it can invade the the equilibrium of avian influenza. Human and avian influenza coexist in the human population if $\mathcal{R}_0^b > 1$ and the invasion reproduction number of human influenza at the equilibrium of avian influenza is larger than one, that is, if $\hat{\mathcal{R}} > 1$ [32, 33]. The invasion reproduction number of human influenza is defined as:

$$\hat{\mathcal{R}} = \frac{\Lambda\beta}{(\beta_Y Y^* + \mu)(\beta_J Y^* + \alpha + \mu)}. \tag{3.5}$$

3.2 Pandemic scenario

In the presence of the pandemic strain the human system is a domain of competition of three strains: the H5N1 avian flu strain, the human influenza strain and the H5N1 pandemic influenza strain. Conditions for existence, coexistence and competitive exclusion in the presence of more than two strains are not quite well understood. In addition to the two dominance equilibria in the prepandemic model, there is also a dominance equilibrium of the pandemic strain in the pandemic model (2.3). This equilibrium exists if the reproduction number of the pandemic strain is larger that one, that is $\mathcal{R}_2 > 1$, where the reproduction number of the pandemic strain is given by:

$$\mathcal{R}_2 = \frac{\Lambda\beta_Z}{\mu(\mu+\nu_Z)}. \tag{3.6}$$

When all three strains are present in the system, the conditions for existence and invasion of each strain are complex. Analysis of the present system and derivation of reproduction and invasion reproduction numbers is performed in [32]. Here, we consider the case where the pandemic strain invades into the prepandemic scenario of coexistence of the avian influenza and human influenza strains. Even if the pandemic H5N1 strain successfully invades, it cannot displace the avian H5N1 strain. Given, $\mathcal{R}_0^b > 1$, and the fact that the avian strain persists, there are two possible outcomes of the invasion. The first outcome is that the invasion of the pandemic strain may lead to coexistence of all three strains: the avian, the human, and the pandemic. The second outcome is that the pandemic strain may invade and displace the human influenza strain. For the first outcome to occur, that is for all three strains to coexist, we need all reproduction numbers to be greater than one, the human influenza strain to be able to invade the avian strain $\hat{\mathcal{R}} > 1$ as well as the pandemic strain to be able to invade the avian strain $\hat{\mathcal{R}}_p > 1$. We note that the invasion number of the pandemic strain $\hat{\mathcal{R}}_p$ is defined as follows:

$$\hat{\mathcal{R}}_p = \frac{\Lambda\beta_Z}{(\beta_Y Y^* + \mu)(\mu+\nu_Z)}.$$

Furthermore, for all three strains to coexist we need that the human strain can invade the coexistence equilibrium of the avian and pandemic strains $\hat{\mathcal{R}}_H > 1$, where $\hat{\mathcal{R}}_H = \hat{\mathcal{R}}/\hat{\mathcal{R}}_p$. Finally, we need that the pandemic strain can invade the coexistence equilibrium of the avian and human strains, that is $\hat{\mathcal{R}}_p^H > 1$, where

$$\hat{\mathcal{R}}_p^H = \frac{\beta_Z\Lambda}{\beta_Z I^*(\beta_J Y^* + \mu) + (\beta_Y Y^* + \mu)(\mu+\nu_Z)}. \tag{3.7}$$

In the expression above, I^* is the number of infected individuals with human flu in the coexistence equilibrium of avian flu and human flu, given by

$$I^* = \frac{\Lambda(\beta_Y Y^* + \mu + w)}{(\beta_J Y^* + \mu)(\beta_Y Y^* + \mu + w) + \alpha(\beta_Y Y^* + \mu)}\left(1 - \frac{1}{\hat{\mathcal{R}}}\right).$$

The pandemic reproduction and invasion numbers are summarized in Table 4.

RN/ IRN	Explanation
$\mathcal{R}_2$	Reproduction number of pandemic influenza
$\hat{\mathcal{R}}_p$	IRN of pandemic strain at the equilibrium of avian influenza
$\hat{\mathcal{R}}_H$	IRN of human flu at equilibrium of bird and pandemic flu
$\hat{\mathcal{R}}_p^H$	IRN of pandemic flu at equilibrium of bird and human flu

Table 4: *List of reproduction and invasion reproduction numbers and their interpretation*

The pandemic strain will replace the human strain while invading, if $\hat{\mathcal{R}}_H < 1$, while the remaining reproduction numbers and invasion reproduction numbers remain larger than one. We note that the above reproduction numbers and invasion reproduction numbers are computed with $\rho = 0$. For details we refer to [32].

4 Parameterization of the model

One of the critical components of modeling is selecting biologically relevant values for the parameters. This can be done entirely by fitting the entire model to data as we do in [11, 28]. We use here as a primary source of time series data the cumulative number of human cases of H5N1 reported by the WHO [3]. However, many of the parameters in the system (2.1)-(2.2) may not be identifiable which means that they will exhibit significant sensitivity to small changes in the cumulative number of human H5N1 cases. This is particularly true if we attempt to fit the full model with the pandemic scenario (2.1)-(2.3). Another approach will be to predetermine biologically realistic values for most of the parameters and fit the remaining few to assure the best agreement with the data. We follow this second approach.

4.1 Parameterization of the prepandemic model

Although at present highly pathogenic avian influenza can be found only in avian populations in Europe, Asia, and Africa, we will work with the total population of the world, as in case of pandemic everyone will be affected. First we estimate the parameters associated with the domestic bird population. The Food and Agriculture Organization of the United Nations (FAO) gives statistics on livestock [34]. We present the numbers of the populations of domestic birds for 2008 that we extracted from the web-site in Table 5.

To determine parameters we fix the time unit to be years. Other references use days as time unit. The main data source [3] gives the data in days, however, in days the data exhibit periodicity and autonomous model is not appropriate [11, 28]. We set the world domestic poultry population at 2060×10^7 poultry items. That gives the value of Λ_b/μ_b. The mean lifespan of poultry is 2 years [16] which results in $\Lambda_b = 2060$ where this is in units of 5×10^6 poultry items per year and $\mu_b = 0.5$ years^{-1}. Iwami [16] uses a mean

Type	Population ($\times 10^7$)
Chickens	1839.84
Ducks	110.84
Geese	35.14
Turkeys	48.24
Total	2034.06

Table 5: *World domestic poultry population in 2008. Data taken from [34].*

infectious period for domestic birds of 10 days, that is $\nu_b = 36.5$ years^{-1}.

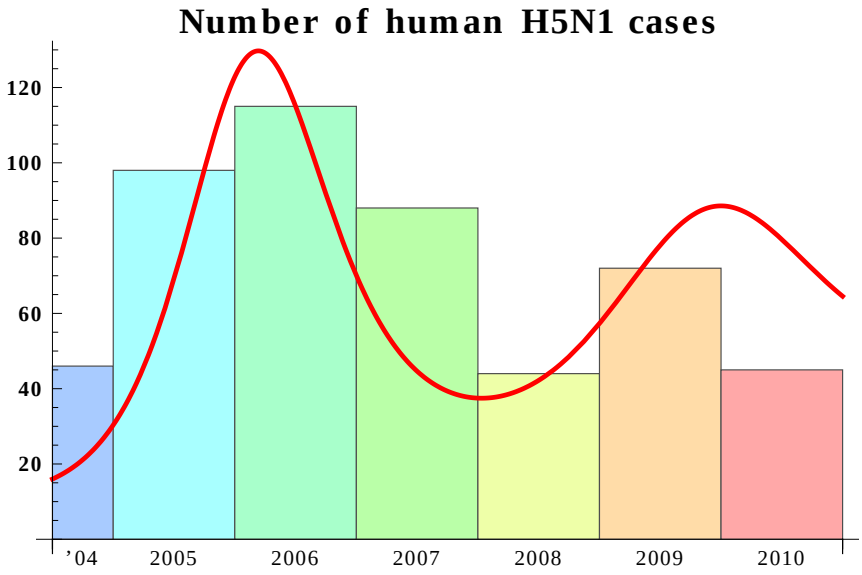

Figure 2: Number of human cases of H5N1 per year as given by WHO [3]. The red curve is the predictions of the model.

Because of the enormous public health concern, there are more data available on human infections that can serve to estimate the parameters in the human part of the model (2.2). Seasonal human influenza has been largely investigated, including with differential equation models [35]. For instance, individuals infected with human influenza shed the virus for a period of 2 to 10 days, which puts α in the range $36.5 - 182.5$ years^{-1}. We take a mean value of 6 days, thus $\alpha = 365/6$ years^{-1}. Loss of immunity in seasonal influenza is assumed to happen in at least one year. Since Smith *et al.* [36] find that antigenically distinct clusters of influenza appear every 2-8 years, we assume that $\omega = 1/2$. Natural lifespan of humans throughout the world varies significantly from country to country. We take an average value of human lifespan to be 65 years [37], therefore $\mu = 1/65$. World human population is approximately 6.5 billion. That gives a value of $\Lambda = 1000$ births per year in units of 10^5 individuals. To estimate the transmission rate β of the seasonal human influenza, we use the fact that Chowell *et*

al. estimate the reproduction number of seasonal influenza to be $\mathcal{R}_1 = 1.3$ [35]. With the values of the other estimated parameters in the reproduction number that gives $\beta \approx 0.00122$.

Notation	Value and Units	Source
Λ_b	2060 $\times 5 * 10^6$ poultry items per year	see text
μ_b	1/2 years^{-1}	[16]
β_b	0.0099 per poultry items per year	fitting
ν_b	365/10 years^{-1}	[16]
Λ	1000 $\times 10^5$ individuals per year	see text
μ	1/65 years^{-1}	[37]
β	0.00122 per individual per year	[35]
w	1/2 years^{-1}	[36]
β_Y	2.28$\times 10^{-9}$ per individual per year	fitting
α	365/6 years^{-1}	[35]
ν	365/10 years^{-1}	[38]

Table 6: *List of parameter values*

Various sources [16, 38] give the mean duration of infectiousness in humans of the bird-to-human avian influenza strain of 10 days which gives $\nu = 36.5$ years^{-1}. The remaining parameters, that is β_b and β_Y, are adjusted so that the cumulative number of human cases visually agrees with the data given by WHO [3] as demonstrated by Figure 2. Estimated parameters are listed in Table 6. Those give a reproduction number of H5N1 $\mathcal{R}_0^b \approx 1.1$, quite consistent with the estimate provided in [39].

We test the predictive capabilities of our model against the yearly number of H5N1 human cases (see Figure 2) and the cumulative number of H5N1 human cases given by the WHO [3]. WHO gives the cumulative number of cases by day. However, the daily data clearly exhibit periodicity, which cannot easily be captured by our autonomous model. We lump the data into half year periods. Each point in the figure contains the number of cases in the period January-June or July-December. The half-year data also exhibit slight periodicity which is averaged by the model. The data that WHO provides is dynamic, that is, as time passes by, WHO adds additional data points to the set. We used the data from January 2005 to December 2010 to estimate the parameters of the model (see Figure 3). Since January 2011 we have been comparing the model predictions with the data coming from WHO. The model is actually capable of predicting the cumulative number of cases on any day – just the position of the day on the time axes has to be computed in years. For instance, WHO gives a cumulative of 553 cases for May 13, 2011. For the end of April 2011, time in years, measured since 01/01/2005, is 6.33. Evaluating the cumulative number of human H5N1 cases at time $t = 6.33$ gives a cumulative number of 560 cases. Thus, at that time the model slightly over-predicts the number of cases.

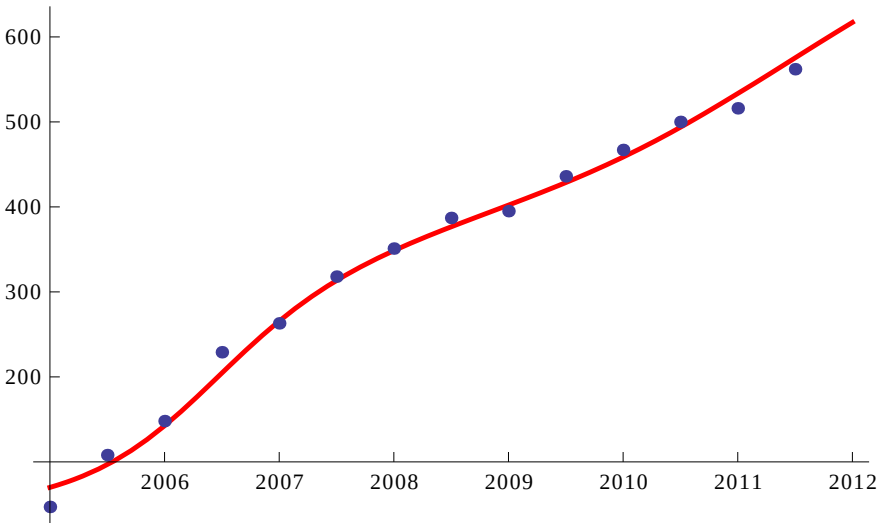

Figure 3: Commutative number of human cases of H5N1 as given by WHO [3]. The red curve is the predictions of the model. Time is measured in years since 01/01/2005. Data points correspond to the cases in the first or second half of year.

4.2 Parameterization of the pandemic model

In the absence of data, the dynamics described by the last two equations of the pandemic scenario model (2.3) are presently hypothetical. One reasonable assumption is to consider the virulence of the evolved human-to-human transmitted pandemic strain to be the same as the bird-to-human transmitted HP H5N1 strain, that is $\nu = \nu_Z$. That will give a value of $\nu_Z = 36.5$ per year. This assumption is likely to over-estimate the virulence of the pandemic strain. The relevant parameters can also be estimated using data on historical pandemics. Considering the 1918 Spanish flu as a worst case scenario we may estimate the infectious period from [40]. Article [40] gives duration of infectiousness of the 1918 pandemic strain of 1-8 days (see supplemental Figure 1) with highest proportion of individuals being infected for 3-4 days and expected mean duration of infectiousness of 4.1 days. That gives virulence rate of the pandemic strain of $\nu_Z = 89$ per year. Furthermore, estimates of the reproduction number of the 1918 pandemic give value of 2-3 [40], while the reproduction number of the novel H1N1 strain that caused the pandemic of 2009 is 1.75 [41].

To understand the variability of model output relative to the variability of the pandemic strain parameters ν_Z, and β_Z, we simulated the model with a variety of parameters, chosen so that $2 \leq \mathcal{R}_2 \leq 3$ and $36.5 \leq \nu_Z \leq 89$ and the remaining parameters taken from Table 6. Our simulations suggested that for any choice of the pandemic parameters from these ranges, the outcome of the dynamic simulation was similar. In all cases the pandemic strain invaded and persisted in the population, while the human influenza strain was eliminated. These numerical observations are confirmed with the values of the reproduction numbers and invasion reproduction numbers for different val-

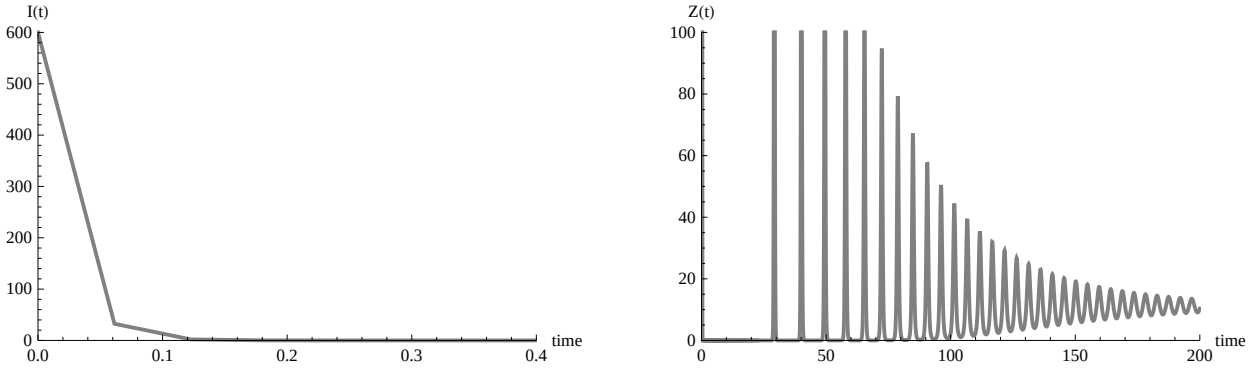

Figure 4: *The left figure shows that the number infected with human influenza tends to zero. The right figure shows that the pandemic strain become established. Parameters are as in Table 6 and* $\beta_Z = 0.00277$, $\nu_Z = 60$, *and* $\mathcal{R}_2 = 3$. *In the above simulation* $\rho = \beta_J = 0$ *and* $Z(0) = 0.00001$, $\nu_J = 0.1 * 365$.

ues of the pandemic strain parameters listed in Table 7. As seen in the table the invasion reproduction number of the human influenza strain is less than one, that is $\hat{\mathcal{R}}_H < 1$, so the human influenza strain cannot invade the equilibrium of the avian and the pandemic strain (which exists because $\hat{\mathcal{R}}_p > 1$). At the same time the invasion reproduction number of the pandemic strain at the equilibrium of the avian and the human strain (this equilibrium exists because $\hat{\mathcal{R}} > 1$) is greater than one, that is $\hat{\mathcal{R}}_p^H > 1$ which suggests that the pandemic strain can invade the equilibrium of avian and human strains. This combination of values implies that the pandemic strain will displace the circulating human influenza strain. We note that if the case was that $\hat{\mathcal{R}}_H > 1$, then human flu would coexist with the pandemic flu. Outcome of the simulations for one parameter set in the case $\hat{\mathcal{R}}_H < 1$ are given in Figure 4.

Notation	$\mathcal{R}_2 = 1.75$	$\mathcal{R}_2 = 2$	$\mathcal{R}_2 = 3$
β_Z	0.000983	0.00274	0.00169
$\hat{\mathcal{R}}$	1.32	1.32	1.32
$\hat{\mathcal{R}}_p$	1.75	2	3
$\hat{\mathcal{R}}_H$	0.755	0.66	0.44
$\hat{\mathcal{R}}_p^H$	1.74	1.99	2.98

Table 7: *List of values of invasion numbers*

5 Sensitivity of reproduction numbers with respect to parameters

Our ultimate goal in developing mathematical models of pandemic influenza is to devise control strategies that may be put in place in case of an emergency. The control measures for H5N1 which is currently a Phase 3 pandemic can be divided into two categories:

A. *Preventive measures*, that is measures that are currently in place to delay or prevent the emergence of a pandemic H5N1 strain. These are measures that we employ now in the prepandemic scenario. These measures currently involve:

   - Vaccination of poultry;
   - Culling/destroying infected and potentially exposed poultry;
   - Reducing contact with poultry by wearing protective gear;
   - Isolation of infected with H5N1 humans and tracing the source of infection of the isolated individual;
   - Increasing biosecurity of poultry rearing;
   - Education of poultry workers and health personnel.

B. *Pandemic control measures*, that is measures that could be/should be put in place in case a human-to-human transmittable strain emerges. Those include:

   - Isolation of infected individuals and quarantine of potential contacts in humans;
   - Social distancing;
   - Vaccination against the pandemic H5N1 strain.

All these measures impact various parameters of the model. In this section we investigate how percentage change in key parameters in the model affect (change) the reproduction numbers, invasion reproduction numbers and prevalence levels of H5N1 at equilibrium. In the prepandemic scenario, the most important parameter to reduce is the reproduction number of avian influenza, $\mathcal{R}_0^b$. If this reproduction number is brought below one, then the H5N1 infection in birds and the resulting "spill over" infection in humans will be eliminated. Even if the reproduction number of avian influenza cannot be brought below one, sensitivity analysis may help determine which parameters, if acted upon, will bring the largest reduction in the number of human infections I_b^*. In the prepandemic scenario, the control measures in place can influence the following parameters: β_b, μ_b, ν_b, β_Y, and others. Vaccination of poultry reduces susceptibility of susceptible poultry, and decreases β_b. It may also decrease the duration of infectiousness in poultry, ν_b. Vaccination is a currently wide spread but rather controversial measure of prevention [42] because it has the potential of masking the disease, and allowing for a widely asymptomatic spread. Spread of HP H5N1 avian influenza among poultry is currently kept in check with culling of infected and exposed birds. That measure affects ν_b and μ_b. Wearing protective clothing when handling poultry, affects the transmission rate from domestic birds to humans, β_Y. Increasing public awareness in the affected countries about the HP H5N1, the dangers of it, and the measures that have to be taken, is a measure that could potentially affect a number of parameters, including β_Y, β_b and ν_b.

Sensitivity indices measure the percentage change of a key quantity, such as the avian influenza reproduction number, in response to a percentage change of a parameter in that quantity. The normalized sensitivity index, also called *elasticity* of the quantity Q with respect to the parameter p, is defined as follows [43]:

$$\varepsilon_p^Q = \frac{\partial Q}{\partial p}\frac{p}{Q} \tag{5.1}$$

Elasticities can be positive or negative. Positive sign says that quantity Q increases with the increase in parameter p, while a negative sign says that quantity Q decreases with increase of parameter p.

5.1 Elasticities of the reproduction numbers and H5N1 prevalence in birds and humans

In this subsection we compute the elasticity indeces of the avian strain reproduction number, as well as the elasticities of the prevalence of H5N1 in birds and humans. The reproduction number $\mathcal{R}_0^b$ is directly proportional to the transmission coefficient β_b. Hence, $\varepsilon_{\beta_b}^{\mathcal{R}_0^b} = 1$. Similarly, the elasticity of the reproduction number with respect to Λ_b is $\varepsilon_{\Lambda_b}^{\mathcal{R}_0^b} = 1$. Next, we can show that

$$\varepsilon_{\nu_b}^{\mathcal{R}_0^b} = -\frac{\nu_b}{\nu_b+\mu_b} = -0.986 \qquad \varepsilon_{\mu_b}^{\mathcal{R}_0^b} = -\frac{\nu_b+2\mu_b}{\nu_b+\mu_b} = -1.01351 \tag{5.2}$$

Several conclusions can be drawn from these formulas. The first, and foremost, is a *conservation law* for the reproduction number. The conservation law for the reproduction number states that the sum of all elasticities of the reproduction number is equal to zero:

$$\varepsilon_{\beta_b}^{\mathcal{R}_0^b} + \varepsilon_{\Lambda_b}^{\mathcal{R}_0^b} + \varepsilon_{\nu_b}^{\mathcal{R}_0^b} + \varepsilon_{\mu_b}^{\mathcal{R}_0^b} = 0 \tag{5.3}$$

The conservation law means that if all parameters in the reproduction number are increased (decreased) by the same percentage, the reproduction number remains unchanged in value. The conservation law will hold for $\mathcal{R}_1$ and $\mathcal{R}_2$, although we would not verify. Conservation law means that the reproduction number is a homogeneous function of degree zero with respect to all its parameters. This property of the reproduction number is not entirely surprising, as the reproduction number remains invariant to change in units.

Second, it is obvious from the values that the reproduction number will experience highest impact with change to poultry natural death rate μ_b. In general acting on any of the parameters produces similar change in the reproduction number.

As the reproduction number of avian influenza is larger than one, and it is well known that the pathogen is endemic in poultry populations in some countries, we investigate what measures may reduce the prevalence of H5N1 among poultry or in humans through spill over infection. Elasticities of the prevalence of infection among domestic birds Y^* and H5N1 in humans I_b^* are given in Table 8.

Parameter	Elasticity of Y^*	Value	Elasticity of I_b^*	Value
Λ_b	$\frac{\mathcal{R}_0^b}{\mathcal{R}_0^b-1}$	11.96	$\frac{\mu}{(\beta_Y Y^*+\mu)}\frac{\mathcal{R}_0^b}{\mathcal{R}_0^b-1}$	11.96
μ_b	$-\frac{\mu_b}{\nu_b+\mu_b}\frac{\mathcal{R}_0^b}{\mathcal{R}_0^b-1}-\frac{1}{\mathcal{R}_0^b-1}$	- 11.12	$-\frac{\mu}{(\beta_Y Y^*+\mu)}\left[\frac{\mu_b}{\nu_b+\mu_b}\frac{\mathcal{R}_0^b}{\mathcal{R}_0^b-1}+\frac{1}{\mathcal{R}_0^b-1}\right]$	-11.12
β_b	$\frac{1}{\mathcal{R}_0^b-1}$	10.96	$\frac{\mu}{(\beta_Y Y^*+\mu)(\mathcal{R}_0^b-1)}$	10.96
ν_b	$-\frac{\nu_b}{\nu_b+\mu_b}\frac{\mathcal{R}_0^b}{\mathcal{R}_0^b-1}$	-11.8	$-\frac{\mu\nu_b\mathcal{R}_0^b}{(\beta_Y Y^*+\mu)(\nu_b+\mu_b)(\mathcal{R}_0^b-1)}$	-11.8
β_Y	–	–	$\frac{\mu}{\beta_Y Y^*+\mu}$	0.99999999
μ	–	–	$-\frac{\mu(\beta_Y Y^*+2\mu+\nu)}{(\beta_Y Y^*+\mu)(\mu+\nu)}$	- 1.00042
ν	–	–	$-\frac{\nu}{\mu+\nu}$	- 0.999579

Table 8: *List of elasticities of Y^* and I_b^**

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It can be verified that the sum of the elasticities with respect to all parameters of both Y^* and I_b^* is zero. In other words, the prevalence of the disease in birds and humans satisfy the conservation law. In particular, we have,

$$\varepsilon_{\Lambda_b}^{Y^*}+\varepsilon_{\mu_b}^{Y^*}+\varepsilon_{\beta_b}^{Y^*}+\varepsilon_{\nu_b}^{Y^*}=0 \tag{5.4}$$

The elasticity of I_b^* with respect to Λ is one, as I_b^* is proportional to Λ. The sum of elasticities of I_b^* with respect to all parameters is zero. Furthermore, the total elasticity with respect to bird parameters only or human parameters only are also zero, that is,

$$\varepsilon_{\Lambda_b}^{I_b^*}+\varepsilon_{\mu_b}^{I_b^*}+\varepsilon_{\beta_b}^{I_b^*}+\varepsilon_{\nu_b}^{I_b^*}=0 \qquad \varepsilon_{\Lambda}^{I_b^*}+\varepsilon_{\mu}^{I_b^*}+\varepsilon_{\beta_Y}^{I_b^*}+\varepsilon_{\nu}^{I_b^*}=0 \tag{5.5}$$

As with the avian influenza reproduction number, the elasticities with respect to all parameters of the the H5N1 prevalence in birds Y^* are fairly similar. The equilibrium prevalence Y^* changes more with respect to duration of infectiousness ν_b compared to the change experienced with respect to β_b. Vaccination replaced culling as a dominant strategy for control of avian influenza in 2005 when novel methods for distinguishing between vaccinated and infected birds became available [44]. Vaccination affects β_b and possibly ν_b, while culling with re-population affects μ_b, ν_b and Λ_b . The prevalence of H5N1 among humans I_b^* changes significantly more with respect to poultry-related parameters β_b, ν_b and μ_b then with respect to the human-related parameters (see Figure 5).

A surprising result from the elasticity analysis of the I_b^* is that the human H5N1 prevalence exhibits relatively low sensitivity to the transmission rate from birds to humans β_Y, which suggests that the use of protective gear has relatively low efficacy. This may be the case since the transmission rate from birds to humans β_Y is estimated to be very small.

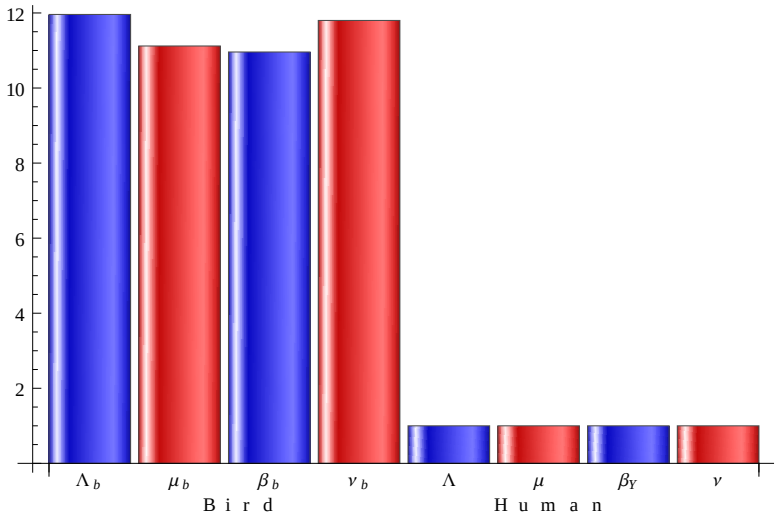

Figure 5: Bar Chart of the sensitivities of I_b^*. Positive sensitivities are in blue, and negative sensitivities are in red. The H5N1 prevalence in humans is far more sensitive to the poultry parameters, rather than to the human parameters.

5.2 Efficacy of control measures

Evaluating the efficacy of multiple control measures, applied in different countries, is a non-trivial task. Key difficulties for direct evaluation involve: (1) Lack of hard-core data of sufficient quality and quantity; (2) Lack of methods or tools to separate the effect of the various control measures on the outcomes; (3) Difficulty in estimating what the status would have been if the control measures were not implemented. Because the direct estimation of the efficacy of the control measures is very hard, indirect methods are often applied. For instance, a study of the efficacy of control measures on avian influenza in a number of developing countries [45] estimates those efficacies based on expert opinions. This approach has the advantage of capturing the predominant view on the control measures but is largely subjective. Here, we apply a different, more objective approach. In this framework, we define the efficacy of control measure A to be given by the combined elasticity of the prevalence of H5N1 in humans I_b^* in response to the key parameters influenced by the control measure A. For instance, culling without re-population affects the average lifespan of poultry $1/\mu_b$ and the average duration of infectiousness $1/\nu_b$. Since both the average lifespan of poultry and the average duration of infectiousness decrease when culling is performed, that means that culling increases μ_b and ν_b. The efficacy of culling without re-population, under this definition, is measured by the combined elasticity of I_b^* to 1% increase in *both* μ_b and ν_b. Thus, adding elasticity of I_b^* with respect to μ_b and the elasticity of I_b^* with respect to ν_b, the efficacy of culling is 22.92% (taken as an absolute value). See Table 8. In other words, if culling increases the death rate of poultry and the disease-induced death rate by 1%, the prevalence of H5N1 in humans I_b^* will decrease by 22.92%. Similarly, vaccination of poultry decreases

infectivity and susceptibility both of which affect β_b. Furthermore, it decreases the duration of infectiousness, that is it increases ν_b. The efficacy of vaccination, under this definition, is measured by the combined elasiticity of I_b^* to 1% decrease in β_b *and* 1% increase in ν_b. From Table 8 we have $-10.96 - 11.8 = -22.76$. Thus the efficacy of vaccination is 22.76%. In other words, if vaccination decreases the transmission rate β_b by 1% and increases the disease-induced death rate by 1%, the prevalence of H5N1 in humans I_b^* will decrease by 22.76%. We can conclude that culling without repopulation is slightly more effective than vaccination. We compare and rank the key control measures based on their efficacies in Table 9.

Control Measure	Affected Parameters	Overall Efficacy	Rank
Culling w/o repopulation	μ_b, ν_b	22.92%	1
Culling with repopulation	Λ_b, μ_b, ν_b	10.96%	3
Vaccination	β_b, ν_b	22.76%	2
Biosecurity	β_b	10.96%	3
Protective gear	β_Y	0.99999%	5
Isolation	ν	0.999579%	6

Table 9: *List of control measures and their efficacies*

Table 9 suggests that culling without immediate repopulation and vaccination are the two most effective control measures in reducing H5N1 prevalence in birds and humans. They are followed by biosecurity and culling with re-population. A surprising outcome of Table 9 is that wearing protective gear while handling poultry is not a very effective control measure in preventing infection of humans. That result may be explained with the very small transmission rate poultry $\longrightarrow$ humans. This approach is not very suitable for evaluating the efficacy of education as the impact of education on the parameters of the model is not very well defined.

Our rankings compare favorably with the efficacy conclusions in [45]. Birol *et al.* also rank culling as one of the most efficacious control measures. Biosecurity comes second, particularly in the case of commercial poultry. Vaccination comes third. Vaccination ranks better than biosecurity for semi-commercial poultry. Overall, culling, vaccination and biosecurity are the three most applied and most efficacious control measures for avian influenza.

5.3 Sesitivities of the invasion reproduction numbers

The capability of the newly formed pandemic strain to invade the prepandemic scenario of coexistence of the avian and human strain is determined by its invasion reproduction number $\hat{\mathcal{R}}_p^H$ which in turn exhibits a complex dependence on nearly all parameters. How each parameter changes the invasion capabilities of the pandemic strain can be learned from the elasticities of $\hat{\mathcal{R}}_p^H$. We focus here on the elasticities of $\hat{\mathcal{R}}_p^H$ with respect to the H5N1 prevalence in birds, Y^*, and the prevalence of human influenza in humans, I^*. We

compute the elasticities of $\hat{\mathcal{R}}_p^H$ using the parameter values in Table 6 and $\beta_Z = 0.00277$, $\nu_Z = 60$, and $\mathcal{R}_2 = 3$. Other parameter values are listed in Table 7.

We first notice that $\hat{\mathcal{R}}_p^H$ depends on the equilibrial prevalences of H5N1 in birds Y^*, and the equlibrial number infected humans with the human influenza strain I^*. The invasion reprodution number of the pandemic strain is a decreasing function of I^*. That means that increase in the number in humans infected by human influenza impedes the invasion of the pandemic strain. The elasticity index will tell how pronounced this effect is. In particular, the elasticity index is given by

$$\frac{\partial \hat{\mathcal{R}}_p^H}{\partial I^*} \cdot \frac{I^*}{\hat{\mathcal{R}}_p^H} = -\frac{\beta_Z^2 \Lambda(\beta_J Y^* + \mu)}{(\beta_Z I^*(\beta_J Y^* + \mu) + (\mu + \nu_Z)(\beta_Y Y^* + \mu))^2} \cdot \frac{I^*}{\hat{\mathcal{R}}_p^H} = -0.00609$$

The dependence of the invasion number of the pandemic strain $\hat{\mathcal{R}}_p^H$ on the prevalence of H5N1 in poultry Y^* appears more complex but it can still be established that $\hat{\mathcal{R}}_p^H$ decreases with increase of Y^*. This observation leads to the somewhat unexpected conclusion that higher prevalence of avian influenza in poultry would impede the invasion of the pandemic strain. This observation was also made by Iwami *et al.* [15, 16], and is a consequence of the fact that the pandemic strain is competing both with the human influenza strain and the avian strain for susceptible humans. To understand the magnitude of this impact we compute the elasticity index for our parameter set

$$\frac{\partial \hat{\mathcal{R}}_p^H}{\partial Y^*} \cdot \frac{Y^*}{\hat{\mathcal{R}}_p^H} = \left[\frac{\partial \hat{\mathcal{R}}_p^H}{\partial I^*} \cdot \frac{\partial I^*}{\partial Y^*} + \frac{\partial \hat{\mathcal{R}}_p^H}{\partial Y^*} \right] \frac{Y^*}{\hat{\mathcal{R}}_p^H} = -0.7 \times 10^{-6}.$$

We see that although such a dependence exists, for realistic parameter values the sensitivity of the invasion number to Y^* is extremely low and this dependence is very weak. The sensitivity of the pandemic strain invasion number with respect to the prevalence of human influenza is more pronounced but still relatively small. In particular, 1% increase of the number of infected with human influenza will decrease the invasion capabilities of the pandemic strain with 0.006%.

6 Discussion

Sixty percent of the emergent pathogens in humans start just as avian influenza is today - as a zoonotic disease at the animal-human interface [46]. Avian influenza is a model of emergent disease, one with deadly potential. If it is studied today, it is so much more likely that a pandemic, should one occur, will be suscessfully mitigated tomorrow.

Avian influenza is a very complex disease, involving multiple species linked by a highly mutable pathogen. There is no unique control strategy that can work in all cases, for all spieces, and in all countries. Detangeling the complexity of avian influenza epidemiology, ecology and control is precisely where mathematical models can be most effective. In particular mathematical models can assist in: (1) providing evaluation of

current measures; (2) investigating hypothetical scenarios, and (3) making predictions based on data and scientific information.

In this article we introduce a mathematical model of avian influenza affecting domestic birds and humans, and seassonal human influenza. We introduce two scenarios: (1) A prepandemic scenario where avian influenza circulates in domestic birds, human influenza circulates in humans, and avian influenza infects humans through bird-to-human transmission. That is the current scenario in place. (2) A pandemic scenario in which a pandemic human-to-human transmittable H5N1 strain invades in the human population.

The parameters of the models are estimated from bird and human demographic and epidemiological data. The transmission parameters of bird-to-bird transmission and bird-to-human transmission of avian influenza are estimated so that the cumulative number of human H5N1 cases, as predicted by the model, agrees with time-series data given by the WHO [3]. The model has the potential for forcasting future human H5N1 cases, at least in the case when the current trend in infections continues.

A major drawback of the models considered here is the lack of consideration of spatial features in the transmission dyamics of avian influenza. Introducing spatial farm-based structure treating poultry-farms as units may have significant effect on the transmission parameters of bird-to-bird transmission and bird-to-human transmission of avian influenza. Such extension of the present models will be interesting to be considered in future endeavors.

The prepandemic scenario model is also used to evaluate current control strategies. The control strategies are ranked based on the elasticity index of the H5N1 prevalence with respect to key parameters whose values are affected by a given control strategy. We find that in general control strategies applied to poultry (such as culling or vaccination) are far more effective in reducing prevalence in humans than control strategies applied to humans (such as wearing protective gear). More specifically, we find that culling without repopulation and vaccination are the two most effective strategies where 1% change in the affected parameters will decrease the H5N1 human prevalence by more than 22%. A surprising result of this analysis is that wearing protective gear is a control measure of very low effectiveness. Presumably this conclusion stems from the fact that the bird-to-human transmission rate is very small – we estimate it in the order of 10^{-9}.

For the pandemic scenario, parameters are hypothetical. We simulated with a range of parameters which give a reproduction number of the pandemic strain between 2-3 and disease-induced mortality rate in the range 36.5-89. The larger than one reproduction number of the pandemic strain does not necessarily mean that it will invade. The outcome of the competition between the seasonal influenza strain and the pandemic strain depends on their invasion numbers. For the range of parameter values that we investigated for the pandemic strain, the outcome always was that the pandemic strain will invade and eliminate the seasonal influenza strain. A more surprising conclusion of this analysis is that the lower the human influenza prevalence in the human population, the higher the chance of the pandemic strain to invade. Our analysis suggests that

this effect is not very pronounced – lowering the prevalence of human influenza by 1% increases the chance of invasion of the pandemic strain by 0.006%. Still, carrying out control measures that lower human influenza prevalence, such as mass seasonal flu vaccination, in the wake of a pandemic strain invasion, seems questionable. Such mass seasonal influenza vaccination was carried out in the fall of 2009, just before the fall wave of the pandemic H1N1 strain. Our results show that such a campaign vaccination makes little sense on epidemiological level. One may argue that on personal level, however, the seasonal influenza vaccination may improve the overall health of individuals and leave them susceptible only to the pandemic strain. In the fall of 2010, however, reports of increased risk of infection with the pandemic H1N1 strain after seasonal flu vaccination also appeared in the literature [47]. So even on personal level obtaining seasonal flu vaccine before a pandemic may increase the risk of acquiring the pandemic strain.

Mathematical models, particularly the ones that are linked to data, can help illucidate the complex ecology, epidemiology and evolution of avian influenza. Such models can assist in evaluating the mutiple control strategies. The model presented here captures the lumped effect accross many countries which have different environmental conditions and apply different mixure of control strategies; however, this model can serve as a starting point for the development of models specific for each geographic region.

Acknowledgments

The author acknowledges partial support from NSF grant DMS-1220342. This article benefitted of discussion the author had with Manojit Roy. The author also thanks two referees for their helpful comments that improved the paper.

References

[1] I. Capua, D.J. Alexander, Animal and human implications of avian and influenza infections, *Biosci. Rep.* **27** (2007), p. 359-372.

[2] I. Capua, D.J. Alexander, Control and prevention of avian influenza in an evolving scenario, *Vaccine* **25** (2007), p. 5645-5652.

[3] World Health Organization, Cumulative Number of Confirmed Human Cases of Avian Influenza A (H5N1) Reported to WHO, http://www.who.int/influenza/human_animal_interface/H5N1_cumulative_table_archives/en/

[4] N.M. Ferguson, D.A.T. Cummings, S. Cauchemez, C. Fraser, S. Riley, A. Meeyai, S. Iamsirithaworn, D.S. Burke, Strategies for containing an emerging influenza pandemic in Southeast Asia, *Nature* **437** (2005), p. 209-214.

[5] T. C. Germann, K. Kadau, I. M. Longini, Jr., C. A. Macken, Mitigation strategies for pandemic influenza in the United States, *PNAS* **103(15)** (2006), p. 5935-5940.

[6] R. F. Grais, J. H. Ellis, G. E. Glass, Assessing the impact of airline travel on the geographic spread of pandemic influenza, *Eur. J. Epidem.* **18** (2003), p. 1065-1072.

[7] I.M. Longini, A. Nizam, S. Xu, K. Ungchusak, W. Hanshaoworakul, D.A.T. Cummings, M.E. Halloran, Containing pandemic influenza at the source, *Science* **309** (2005), p. 1083-1087.

[8] C.E. Mills, J.M. Robins, C.T. Bergstrom, M. Lipsitch, Pandemic influenza: risk of multiple introductions and the need to prepare for them, *PLoS Medicine* **3 (6)** (2006), p. 1-5.

[9] A. Le Menach, E. Vargu, R. F. Grais, D. L. Smith, A. Flahault, Key strategies for reducing spread of avian influenza among commercial poultry holdings: lessons for transmission to humans, *Proc. R. Soc. B* **273** (2006), p. 2467-2475.

[10] T. Tiensin, M. Nielen, H. Vernooij, *et. al*, Transmission of the highly pathogenic avian influenza virus H5N1 within flocks during the 2004 epidemic in Thailand, *JID* **196** (2007), p. 1679-1684.

[11] J. Lucchetti, M. Roy, M. Martcheva, An avian influenza model and its fit to human avian influenza cases, in "Advances in Disease Epidemiology" (J.M. Tchuenche, Z. Mukandavire, eds.), Nova Science Publishers, New York, 2009, p. 1-30.

[12] H. Gulbudak, M. Martcheva, Forward hysteresis and backward bifurcation caused by culling in an avian influenza model, *Math. Biosci.* **246** (2013), p. 202-212.

[13] S. Iwami, T. Suzuki, Y. Takeuchi, Paradox of vaccination: Is vaccination really effective against avian flu epidemics? *PLoS One* **4 (3)** (2009), e4915.

[14] S. Iwami, Y. Takeuchi, X. Liu Avian-human influenza epidemic model, *Math. Biosci.* **207** (2007), p. 1-25.

[15] S. Iwami, Y. Takeuchi, A. Korobeiniov, X. Liu, (2008), Prevention of avian influenza epidemic: What policy should we choose?, *JTB* **252**, p. 732-741.

[16] S. Iwami, Y. Takeuchi, X. Liu, (2009), Avian flu pandemic: Can we prevent it?, *JTB* **257**, p. 181-190.

[17] K.I. Kim, Z. Lin, L. Zhang, Avian-human influenza epidemic model with diffusion, *Nonlin. Analysis: RWA* **11** (2010), p. 313-322.

[18] R. Liu, V.R.S.K. Duvvuri, J. Wu, Spread pattern formation and its implications for control strategies, *Math. Model. Nat. Phenom.* **3(7)** (2008), p. 161-179.

[19] A. B. Gumel, Global dynamics of a two-strain avian influenza model. *Int. J. Comput. Math.***86** (2009), p. 85-108.

[20] F.B. Agusto, A.B. Gumel, Theoretical assessment of avian influenza vaccine, *Dis. Cont. D. Sys. B* **13(1)** (2010), p. 1-25.

[21] D. E. Stallknecht, J. D. Brown, Ecology of avian influenza in wild birds, in "Avian Influenza" (D. E. Swayne, ed.), Blackwell Publishing, Ames, Iowa, 2008, p. 43-58.

[22] USDA, Low Pathogenic "North American" H5N1 Avian Influenza Strain in Wild Birds, http://wildlifedisease.nbii.gov/ai/LPAI-Table.jsp.

[23] A. Wallensten, V. J. Munster, N. Latorre-Margalef *et al.*, Surveillance of influenza A virus in migratory waterfowl in Northern Europe, *Emerging Inf. Dis.* **13 (3)** (2007), p. 404-410.

[24] WHO, H5N1 avian influenza: timeline of major events,
http://www.who.int/csr/disease/avian_influenza/ai_timeline/en/index.html.

[25] Centers for Disease Control and Prevention, Avian Influenza: Current H5N1 Situation, http://www.cdc.gov/flu/avian/outbreaks/current.htm.

[26] OIE, Update on Highly Pathogenic Avian Influenza in Animals (Type H5 and H7), http://www.oie.int/downld/AVIAN%20INFLUENZA/ A_AI-Asia.htm

[27] R. Breban, J. M. Drake, D. E. Stallknecht, P. Rohani, The role of environmental transmission in recurrent avian influenza epidemics, *PLoS Comp. Biol.* **5(4)** (2009), e1000346.

[28] N. Tuncer, M. Martcheva, Modeling Seasonality in Avian Influenza H5N1,*J. Biol. Systems*, (in press).

[29] Centers for Disease Control and Prevention, Key Facts About Avian Influenza (Bird Flu) and Avian Influenza A (H5N1) Virus, http://www.cdc.gov/flu/avian/gen-info/facts.htm

[30] M. R. Castrucci, I. Donatelli, L. Sidoli, G. Barigazzi, Y. Kawaoka, R. G. Webster, Genetic reassortment between avian and human influenza A virusses in Italian pigs, *Virology* **193** (1993), p. 503-506.

[31] R. May, M.A. Nowak, Coinfection and the evolution of parasite virulence, *Proc. R. Soc. Lond. B* **261** (1995), p. 209-215.

[32] M. Martcheva, An evolutionary model of influenza with drift and shift, *J. Biol. Dynamics*, **6 (2)**, 2012, p. 299-332.

[33] M. Martcheva, B. Bolker, R.D. Holt, Vaccine-Induced Pathogen Strain Replacement: What are the Mechanisms?, *J. R. Soc. Interface*, **5** (2008), p. 3-13.

[34] Food and Agriculture Organization, FAO Statistics, CountrySTAT, http://www.fao.org/.

[35] G. Chowell, M. A. Miller, C. Viboud, Seasonal influenza in the United States, France, and Australia: transmission and prospect for control, *Epidemiol. Infect.* **136** (2008), p. 852-864.

[36] D.J. Smith, A.S. Lapedes, J.C. de Jong, T.M. Bestebroer, G.F. Rimmelzwaan, A.D. Osterhaus, R.A. Fouchier, Mapping the antigenic and genetic evolution of influenza virus, *Science* **305(5682)** (2004) p.371-376.

[37] Wikipedia, Life expectancy, http://en.wikipedia.org/wiki/Life_expectancy.

[38] The Writing Committee of the WHO Consultation on Human Influenza A/H5, Avian influenza A (H5N1) infection in humans, *N. Engl. J. Med.* **353 (13)** (2005), p. 1374-1385.

[39] A. Bouma, I. Claassen, K. Natih, D. Klinkenberg, C. A. Donnelly, G. Koch, M. van Boven Estimation of transmission parameters of H5N1 avian influenza virus in chickens, *PLoS Pathogens* **5 (1)** (2009), e1000281.

[40] C.E. Mills, J.M. Robins, M. Lipsitch, Transmissibility of 1918 pandemic influenza *Nature* **432** (2004), p. 904-906.

[41] D. Balcan, H. Hu, B. Goncalves, P. Bajardi, *et. al*, Seasonal transmission potential and activity peaks of the new influenza A(H1N1): a Monte Carlo likelihood analysis based on human mobility, *BMC Medicine* **7 (45)**:29, (2009).

[42] M. H. Cheng, To vaccinate or not to vaccinate?, *Lancet*, **6 (1)** (2006), p. 10-11.

[43] Wikipedia, Elasticity Coefficient, http://en.wikipedia.org/wiki/Elasticity_Coefficient.

[44] D. Butler, Vaccination will work better than culling, say bird flu experts, *Nature* **434** (2005), p. 810.

[45] E. Birol, D. Asare-Marfo, Y. Yakhshilikov, Efficacy and adoption of strategies for avian flu control in developing countries, international Food Policy Research Institute Discussion paper, August 2010.

http://www.ifpri.org/sites/default/files/publications/ifpridp01023.pdf

[46] I. Scoons, The international response to avian influenza, science, policy and politics, in *Avian Influenza: Science, Policy and Politics*, I. Scoons ed., Earthscan, London, Washington DC, 2010.

[47] N. Z. Janjua, D.M. Skowronskii, T.S. Hottles *et. al.*, Seasonal influenza vaccine and increased risk of pandemic A/H1N1-related illness: first detection of the association in British Columbia, Canada, *CID*, **59 (1)** (2010), p. 1017-1027.