AN AVIAN INFLUENZA MODEL AND ITS FIT TO HUMAN AVIAN INFLUENZA CASES

JOSEPH LUCCHETTI, MANOJIT ROY, AND MAIA MARTCHEVA*

Abstract. Low Pathogenic Avian Influenza (LPAI) virus, which circulates in wild bird populations in mostly benign form, is suspected to have mutated into a highly pathogenic (HPAI) strain after transmission to the domestic birds. HPAI has recently garnered worldwide attention because of the "spillover" infection of this strain from domestic birds to humans - primarily those in poultry industry - causing significant human fatality and thus creating potentially favorable conditions for another flu pandemic. We use an ordinary differential equation model to describe this complex dynamics of the HPAI virus, which epidemiologically links a number of species in a multi-species community. We include the wild bird population as a periodic source feeding infection to the coupled domestic bird-human system. We also account for mutation between the low and high pathogenic strains. Finally, we fit our model to the actual number of human avian influenza cases obtained from WHO, and estimate the relevant reproduction numbers. We discuss open questions and problems in modeling the complex epidemiology of avian influenza.

Keywords: avian influenza, low-pathogenic avian influenza, high-pathogenic avian influenza, strains, competitive coexistence exclusion, human cases, data fitting.

AMS Subject Classification: 92D30, 92D40

1. The Ecology and Epidemiology of Avian Influenza

Influenza viruses belong to the family *Orthomyxoviridae* (Greek *orthos* means straight, and *myxo* means mucus, implying a disease with respiratory symptoms), and are made up of segmented, negative sense, single stranded RNA genomes [1]. Orthomyxoviridae family currently consists of five distinct genera: *Influenzavirus A*, *Influenzavirus B*, *Influenzavirus C* (also known as Influenza virus types A, B and C – those that cause influenza in vertebrate animals including birds), *Thogotovirus* (tick–borne viruses that can also infect mammals) and *Isavirus* (a viral disease of Atlantic salmon). Among them, only the viruses of Influenza A genus are known to cause Avian Influenza (AI) infection in birds. The RNA genome of these viruses is made up of eight sections corresponding to the proteins they encode, and is encapsulated by a lipid bilayer obtained from host cells. Studding this outer shell are hemagglutinin (HA) and neuraminidase (NA) proteins, which play key roles in fusion of the viral envelope to host cells. Sixteen sufficiently distinct HA molecules (H1–H16) and nine NA molecules (N1–N9) have been observed in influenza A viruses that allow their further classification into subtypes. For example, the most recent AI outbreaks are due to the H5N1 subtype, whereas the previous three major outbreaks that led to pandemics were attributed to H1N1 ("Spanish Influenza", during

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*author for correspondence.

1918–20), H2N2 ("Asian Influenza" of 1957–58) and H3N2 ("Hong Kong Influenza" of 1968–69) subtypes [7].

As of October 22, 2008, there are 387 total reported cases of H5N1 infection in humans worldwide, which has resulted in 245 deaths – a case fatality rate of over 60% [8]. When compared with the death toll in the three pandemics mentioned above (an estimated 40–100 million dead in Spanish Flu, over 4 million in Asian Flu and over 1 million in Honk Kong Flu [16]), the number of H5N1 related cases to date seems miniscule. This is in part due to the timeliness and scale of control measures that are being implemented (for instance, prompt quarantine and large–scale culling of domestic birds after initial infection is detected), but also largely because the virus appears to be quite inefficient in human–to–human transmission, an essential requirement to trigger a pandemic. With a few exceptions of probable limited person–to–person transmission in very close quarters [9, 10, 11, 12, 13, 14], humans seem to get infected only after handling live poultry or consuming severely undercooked poultry products such as raw duck blood [15]. Though it is likely that domestic poultry are often infected due to trafficking of live birds and their by-products, trade alone does not seem sufficient to justify the global spread of the disease. It is expected that migratory birds play a role in the transmission of the disease to domestic birds on the global scale.

1.1. **The role of wild birds.** In the past avian influenza was found primarily in wild birds. All sixteen H subtypes and nine N subtypes are routinely detected in wild bird populations, and are particularly common in Charadriiformes (gulls and shorebirds) and Anseriformes (waterfowl such as ducks, geese and swans) [2, 3]. Until recently, all strains of AI have been either asymptomatic or have caused mild respiratory problems in wild birds [3]. These strains are therefore known as low pathogenic AI (LPAI) strains, and wild birds are their natural reservoirs [3]. Prior to 2002, there was only a single reported case of highly pathogenic AI (HPAI) outbreak in wild birds; this occurred in 1961 in South Africa where some 1300 common terns died from a strain of influenza A virus of subtype H5N3 [4]. Post 2002 there have been several outbreaks of AI in wild birds accompanied by high mortality rates. Still, relative to the prevalence of AI in wild birds or the number of AI cases in domestic birds, the instances of wild bird deaths from HPAI infection is quite small [5].

This relatively low frequency of outbreaks in wild birds is one of the characteristics that makes HPAI potentially dangerous. For example, if a strain of H5N1 that is highly pathogenic in domestic birds or humans are asymptomatic (or only mildly symptomatic) in migratory wild birds even for a short duration, the virus could be carried across the globe along migratory pathways [17, 18, 19, 20]. Moreover, direct long–distance movements may not be necessary, and viruses may also spread by sequential contacts among wild birds along their migration routes, and via environmental reservoirs [2, 5, 42, 43]. There are two recent HPAI outbreaks in wild birds that tend to indicate such may be the case: Qinghai Lake outbreak in Western China [21] and Lake Towada outbreak in Japan [43].

In 2005, approximately 6000 wild birds, mostly bar-headed geese, were found dead around Qinghai Lake [21]. While typical such HPAI outbreaks occur in the vicinity of domestic poultry farms, thereby indicating that these may be due to "spillover" infection from domestic to wild birds, this particular outbreak occurred in the Qinghai Lake Natural Protection Zone, far away from any such farm. Phylogenetic analysis of

isolates of viruses from outbreaks in Europe [39] and Africa [40] in 2006 revealed that the Qinghai Lake virus was their likely ancestor. However, among the 390 strains of H5N1 isolated from poultry farms and bird markets in Southern China in 2005 and 2006, only one was found to be genetically similar to the Qinghai Lake virus [41]. These observations provide compelling evidence that migratory birds might have been the cause of transmission. Similarly, on April 21, 2008, four whooper swans were found dead in Lake Towada in Japan, all infected with H5N1 strains [43]. Though there have been poultry outbreaks of H5N1 across Japan, there was none since the beginning of 2008, and phylogenetic analysis indicated that the viruses that killed these swans are genetically distinct from the earlier domestic strains [43]. Limited outbreaks of H5N1 in Australia further suggest that migration may play a role in the transmission of AI, since many of the birds that migrate to Australia do so over regions with high H5N1 activity [44].

The hypothesis that wild birds, and in particular migratory birds, are a significant contributor to the global spread of HPAI is, however, not without scrutiny. Feare [5] analyzes several outbreaks between 2002 and 2007, and notes that many of these do not follow migratory paths nor do they occur during the season when birds typically migrate. The case at Towada Lake appears to lend support to Feare's argument, since the migratory pattern of whooper swans indicates they might have already been in Japan several months prior to their death. The most likely explanation is that other wild birds infected these swans while they were residing in Japan [43], an apparent case of sequential infection mentioned earlier. Further, even though H5N1 strains that are highly pathogenic to poultry and humans are found to be non-pathogenic in some wild birds in laboratory experiments [45, 46, 47, 48], there is insufficient evidence that this will remain so in the field. The few times such HPAI H5N1 infection in apparently healthy migratory birds have been reported, for instance at Poyang Lake in China [22] and Lake Chany in Russia [23], the methodology and sampling employed in these works are questioned [24]. Moreover, the physiologically demanding task of long-distance flight appears to induce immunosuppression in wild birds, whose migratory performance is thereby compromised by HPAI infection [25]. Thus, it seems unlikely that wild birds can remain asymptomatic to HPAI infection long enough to spread the viruses over long distances.

From these observations, a scenario seems to be emerging where the migratory birds perform at least a moderately important role in the geographic distribution of HPAI virus. Because they are natural reservoirs of, and therefore mostly asymptomatic to, the LPAI strains, there is little doubt that they have been carrying these strains during migration. Recent phylogenetic analysis of LPAI isolates collected in Alaska from the northern pintail ducks, a species that migrate between North America and Alaska, shows significantly high frequency (45%) of intercontinental genetic exchange between Asian and North American virus lineages, nearly 7× larger than previously reported [26] (the authors suspect this may still be an underestimate). This is an important observation given that northern pintails are one of the rare east–west transcontinental migrants, and from this finding it is possible that eventual point mutations of these North American HPAI strains may retain substantial genetic similarity to their Asian counterparts.

1.2. **The role of domestic birds.** Domestic poultry play several crucial roles in the evolutionary dynamics and transmission of HPAI. Studies seem to indicate that HPAI

strains have evolved by point mutations from the LPAI strains after their spillover infection to domestic birds from the wild birds [1, 3]. Before the first outbreak of human cases of H5N1 in 1997, it was determined that amino acid changes in AI viruses did not cause selective benefits in wild birds. This indicated that AI in the wild may have been at an evolutionary equilibrium [2, 49]. This is most likely not the case for domestic poultry, which are novel hosts to many subtypes of AI. This allows selective pressures to act, possibly creating highly pathogenic strains. Because of the spillover infection of these HPAI strains from domestic birds back to the wild bird populations (which are also novel hosts to these evolved strains), studies have shown that many strains of AI are currently under positive selective pressure [40, 50]. The processes that trigger such point mutations of LPAI strains are not yet well known. In some cases the mutations appeared to have happened soon after introduction of the LPAI strains into domestic birds, whereas in others the LPAI viruses circulated in poultry for months before mutating into HPAI [1]. Even though it is impossible to predict if and when this mutation will occur, it seems clear that the longer and wider LPAI circulates in poultry, the higher the chance that mutation to HPAI will occur [1].

Once mutant strains of AI arise, domestic birds play a further role in the maintenance and spatial transmission of the virus. One of the most interesting developments in the analysis of AI in domestic birds occurred in 2005 when Hulse-Post et al. [45] investigated the pathogenicity of H5N1 in ducks. It is widely known that some strains of H5N1 that are fatal in chickens can be asymptomatic in ducks. However, there are many strains of H5N1 that cause high mortality rates in ducks. Hulse-Post et al. found that if a duck is infected with a strain that eventually causes mortality, the virus that is shed by the infected duck during the late stages of infection can exhibit low pathogenicity to other ducks, while still being highly pathogenic to chickens and mice. This suggests that ducks may play a crucial role in maintaining and transmitting mutant strains of AI that are highly pathogenic to poultry and humans [45].

The role of ducks in transmission of AI is further explored by a study of the spatial spread of outbreaks in Thailand during 2004 and 2005. It was found that these outbreaks were strongly correlated with the prevalence of free-grazing ducks. Such duck rotate through recently harvested rice paddy fields every few days, carrying any pathogens they may be infected with to new fields. These fields are also a source of food for many migratory birds [51]. These observations, taken in conjunction with Hulse-Post et al.'s findings and the previous hypothesis that wild birds may transmit HPAI, suggest a complex picture for the spread of AI via inter–specific interactions. One possible scenario is that wild birds carry AI either short or long distances and infect ducks, which convert the highly virulent strain of AI into a form that is asymptomatic in other ducks. These ducks could then freely infect chickens and humans without being overburdened by the disease themselves.

Anthropogenic factors, such as movement of poultry, poultry manure (as agriculture and aquaculture fertilizers), poultry by–products, accidental transfer of infected material from poultry farms (*e.g.* contaminated water, straw, or soil in vehicles during tarnsfer), legal and illegal trades of live animals etc. are also linked to many AI outbreaks all over the world, particularly in South–East Asia [22]. For example, a multivariate analysis of risk factors associated with H5N1 outbreaks in individual farms in China during 2002 identified one of the strong factors as whether a farm had been visited by someone from a

live bird market [52]. Even though poultry are not transferred from live bird markets to farms, bird buyers, catchers, trucks and cages all could carry the virus in that direction [52].

1.3. **Transmission to humans and control measures.** Because all HA and NA influenza subtypes are found in wild birds and have the potential to add new virulent mutations and combinations to the existing human flu arsenal, a high degree of human infection risk from avian influenza remains. However, the lack of direct interaction between wild birds and humans (their ecological habitats do not often overlap) creates an epidemiological bottleneck that the infectious strains must first pass through domestic bird populations, before they can reach human populations; that is, humans are at the end of the interaction chain *wild birds* $\rightarrow$ *domestic birds* $\rightarrow$ *humans*. While the mechanisms of bird–to–bird transmission of LPAI and HPAI strains follow complex interaction pathways between wild and domestic birds and are still poorly understood [1, 3], most human infections with HPAI viruses have occurred from direct and prolonged cotact with poultry. The likely pathways are proximity to contaminated air or water, inhalation of infectious aerosol droplets, exposure to infected poultry and butchering of birds, and consumption of duck's blood or undercooked poultry, even though the relative efficiency of these different routes have not been determined [15]. The first known example of the direct transmission of HPAI from domestic birds to humans was recorded in Hong Kong in 1997, when 18 people were infected with H5N1 strains, six of whom died [27]. Since then, human cases have been reported mainly in China, Thailand, Indonesia, and Vietnam; almost all of them are from poultry–related infection. There have also been occasional instances where such bird–to–human transmission were observed outside mainland Asia. For example, in 2003 poultry workers in the Netherlands contracted viral conjunctivitis, after being infected with the HP H7N7 strain from poultry flocks [28]. Timely intervention of international authorities, including the OIE, resulted in its successful eradication. However, in Southeast Asia, livestock husbandry practices that include housing domestic birds in close proximity to humans and the use of live–bird markets makes it a high–risk place for human infection with HPAI strains.

Judging from the available data, no case of casual transmission via nasal aerosols has been confirmed, risks to health care workers appear to be minimal, and blood tests of persons in contact with human AI–infected patients have been negative [29]. These facts seem to suggest that the virus has not yet evolved into becoming broadly transmissible from human to human [30]. There are, however, instances where probable person–to–person transmission have been reported among humans in very close quarters, for example within family clusters [9, 10, 11, 12, 13, 14]. For instance, the 2003 H7N7 outbreak in the Netherlands appeared to have caused secondary human–to–human transmission between poultry workers and their immediate families in at least 30 households [12, 31]. From December 2005 to January 2006, a cluster of 8 confirmed cases, belonging to 3 households within 1.5km of each other, was detected in eastern Turkey [13]. In 2006, a cluster of 8 human cases, all members of the same extended family of a 37–year old woman who originally became infected with HPAI H5N1, was detected in northern Sumatra [32]. However, none of these reported human–to–human transmission cases seem to be definitive, and moreover, their frequency is still much smaller than the confirmed bird–to–human transmission cases.

Control of AI outbreaks in domestic birds typically involves mass culling and quarantine of infected poultry. Globally several hundred million birds have been destroyed so far, causing economic damage estimated at over US$10 billion in Asian poultry sector alone [33]. In 2004, more than 62 million birds were either killed from HP H5N1 infection or culled in Thailand, whereas Vietnam saw culling of over 50 million birds since 2004 [33]. In the 2003 Dutch H7N7 outbreak, a total of 255 flocks became infected during a period of nine weeks, and more than 30 million birds were culled as a control measure [34]. Besides mass culling, vaccination of flocks against HPAI infection is now also adopted as an effective, and popular, alternative strategy [35]. Several vaccination initiatives have been implemented in Mexico, Italy, The Netherlands, and different places in Asia [33, 36, 37]. However, vaccinating poultry can make monitoring and surveillance difficult, and using a single vaccine strain may drive evolution of AI strains into new genetic variants [38]. These issues apart, AI vaccination appears to be here to stay and promises to be effective in reducing HPAI outbreaks [3].

1.4. **Epidemiological models of avian influenza.** The models developed to describe the dynamics of avian influenza fall into two basic categories: stochastic and deterministic. With the exception of one in depth paper, all of the stochastic models surveyed are intended to describe the spatial spread of H5N1 after its hypothetical mutation into a strain that can efficiently transmit from human to human. Germann et al.[53] used a stochastic model to show that if a human–to–human transmittable form of AI starts at a single location and has a low basic reproduction number ($R_0 < 1.9$), early detection and preventive measures (most importantly vaccination and restricting mobility of people) are likely to work in all but a small portion of the population. Further, for such values of R_0 the study concludes that vaccination alone will be able to eradicate any pandemic if sufficient stockpiles of vaccine (55 million courses for $R_0 = 1.8$) exist. This is in agreement with an earlier study by Longini et al.[54] that concluded that, for small values of R_0 (< 1.4) containment with 100,000 courses of vaccine could be sufficient to control the pandemic, whereas larger values of R_0 (> 1.7) will likely require restricting the mobility of the population in order to control the spread of the disease if only limited stockpiles of vaccine are available. Mills et al. [55] disagrees with this mode of analysis. Indeed, given the way that AI spreads through wild and domestic birds, it is unlikely that human–to–human transmission will occur only once or even several times. Such control measures will only prolong the time until a control measure fails. Rao et al. [56] instead run stochastic simulations assuming that human–to–human transmission is not yet efficient, and focus their model on wild and domestic birds. They conclude that without an efficient human–to–human transmission, it is very improbable that a large pandemic would occur.

The second class of models are deterministic, typically based on differential or difference equations. Relatively little seems to have been done for this class of models. The model that seems to be most relevant to our work here is due to Iwami et al. [57]. Their model is a basic SIR model with the following additional features: 1) compartments are provided for susceptible and infected domestic birds, 2) mutation is allowed to occur within the human population that causes the virus to become human–to–human transmittable, and 3) the model assumes that infection with either strain of the virus results in permanent immunity from both strains. However, once such mutant viruses are created, the model assumes that it stays within the human population. The authors

are able to obtain reasonable definitions of the basic reproduction numbers for the bird virus strain as well as the human virus strain and obtain global stability of the appropriate equilibria. In a later paper [58], the authors analyze the model's predicted effect of human quarantine and culling of domestic birds. While quarantine is found to be always beneficial, culling is detrimental for certain values of the parameters. However, since this model neglects to take into account the complicated wild bird-domestic bird dynamics and does not allow for the possible transmission of mutant viruses in bird populations, it is unclear how realistic the conclusions are.

1.5. **Structure and organization of this article.** The chapter is organized as follows. In section 2, we introduce our deterministic (ODE–based) model of AI transmission dynamics, incorporating the epidemiological interactions between wild and domestic birds and humans, which include LPAI→HPAI mutation within the domestic bird population. Section 3 presents a preliminary analysis of the model and describes some of its mathematical properties. This section derives the reproduction numbers of LPAI and HPAI in domestic birds, as well as the invasion reproduction number of LPAI. Invasion of HPAI may occur only in the case when there is no LPAI→HPAI mutation, and the respective invasion reproduction number is also derived in this case. In section 4, we describe the curve fitting algorithm using MATLAB software package, and use it to fit the human HPAI infection data obtained from WHO database. We discuss the possibility for projections of the cumulative number of cases based on model introduced in section 2. We conclude the chapter in section 5 with a discussion of some open questions and problems in AI modeling.

2. The Model

2.1. **Description.** We introduce an ordinary differential equation model for the wild bird→domestic bird→human pathway of avian influenza transmission. The main objective of our model is to capture the epidemiology of domestic bird–human interaction dynamics, where wild birds serve only as a background source of LPAI injection into domestic bird populations. Therefore, we model the number of LPAI–infected wild birds as a constant, denoted by I_w. Transmission of LPAI virus to domestic birds (from infected wild birds) occurs at a rate $\beta_{L_w} I_w$, where β_{L_w} is the transmission coefficient; likewise, β_{L_d} denotes the transmission coefficient for transmission from LPAI–infected domestic birds. Because LPAI is typically mild in domestic birds and very rarely causes mortality, in the model we assume that for LPAI–infected birds there is no disease–induced death. Domestic birds recover from LPAI infection at a rate α_d.

From the available evidence discussed earlier, we include the possibility that LPAI strains can mutate into HPAI strains within domestic bird populations at a per capita rate m. By definition, domestic birds suffer a high mortality rate from infection with HPAI strain; we denote this rate by $\mu_{I_{H_d}}$. Both susceptible and LPAI-infected domestic birds are infected by HPAI strains with the transmission coefficient β_{H_d}.

The most favored control strategy adopted today consists of destroying all birds in the entire farm whenever HPAI infection is detected. The very high mortality from HPAI together with mass culling cause very few domestic birds to survive HPAI. Accordingly, our model does not incorporate recovery from HPAI infection. Furthermore, we will assume that the rate at which culling of the domestic bird population takes place is

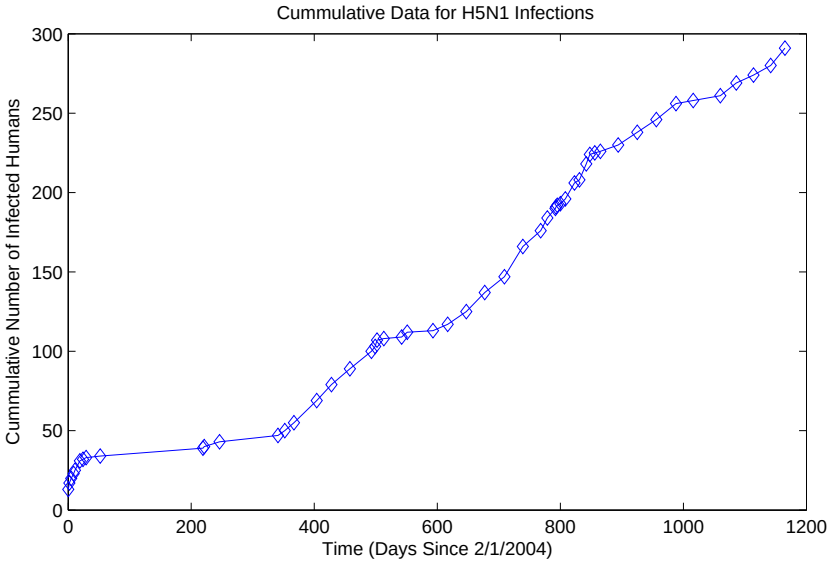

FIGURE 1. Graph of the cumulative number of human infections. Data taken from WHO's web-site.

proportional to the number of birds that are infected with either LPAI or HPAI, and that birds from all disease classes are culled at the same per capita rate $\mu_{cull}(I_{L_d} + I_{H_d})$.

Humans appear to contract only HPAI, and primarily through contact with infected domestic poultry. We denote the corresponding transmission coefficient by β_{H_u}. Around 40% of humans do recover (presumably because of health care), and we denote the per capita recovery rate of humans by α_{H_u}. Since there are very few confirmed cases of human–to–human transmission of H5N1 so far, we do not consider human-to-human transmission dynamics in our model. We model the 60% human case fatality (from cumulative WHO data) by incorporating a disease-induced death rate $\mu_{I_{H_u}}$. Thus, we use a standard SIR model for the human epidemiology with the modification that susceptible humans are infected at a rate proportional to the number of HPAI–infected domestic birds, rather than the number of infected humans.

Figure 1 shows the cumulative number of human cases of H5N1 infection as provided by WHO. One objective of our model is to find values of the model parameters (described above) that best fit this data in the least squared sense. A glance at the plot in Figure 1 shows that the rate of new infections appears to oscillate with a period very close to 365 days (one year). The model as described below may not be capable of intrinsically generating such cycles. Therefore, we introduce an external periodic forcing to the dynamics, in terms of a periodic LPAI injection into the domestic bird population from infected wild birds. There is a strong biological justification for such a periodic forcing, as explained below.

We model LPAI transmission from wild to susceptible domestic birds as the per capita rate $\beta_{L_w} I_w(\sin((t+\omega) * \frac{2\pi}{365})c_1 + c_2)$, where $c_1 \leq 1$ and $c_2 \geq 1$ affect how strongly this periodic function affects the transmission rate (the condition $c_2 \geq c_1$ prevents negative values for a density function). This periodic transmission may be interpreted as due to either a periodicity in the infected wild bird population size, $I_w sin((t+\omega) * \frac{2\pi}{365})c_1 + c_2)$,

or a periodicity in the transmission term, $\beta_{L_w} sin((t+\omega) * \frac{2\pi}{365})c_1 + c_2)$. The first type of periodicity may be a result of the seasonal breeding patterns of migratory wild birds, which seasonally boosts the number of susceptible wild birds that in turn leads to a surge in the number if LPAI-infected wild birds. The second type of periodicity may arise in the periodically enhanced contact rates between wild and domestic birds during seasonal migration of the former.

2.2. **Summary of simplifying assumptions.** Modeling the complex interactions involving wild bird species, domestic bird species and humans requires introducing a large number of parameters, few of which are known or even easily determined from available information. Therefore, we must make several assumptions in order to reduce the number of parameters. This in turn will reduce the number of parameters to be estimated through fitting.

(1) Because the initial period of time over which we fit the data is fairly small (<2.5 years), we ignore human birth and (natural) death. However, as more data become available and fitting can be performed over larger periods of time, human demography may need to be incorporated.
(2) Wild bird dynamics are ignored in our model, because we assume wild birds are infected only by LPAI. This assumption may appear drastic but reflects our current understanding of the role of wild birds in the distribution and transmission of HPAI strains. There is definitive evidence that they can acquire HPAI and die from it. The question of whether they can carry HPAI viruses long distances via migration and spread them globally remains unclear, and we effectively assume such distribution is not significant. Thus wide birds enter into the model only via their infected number I_w, which we assume either constant or periodic.
(3) We assume that LPAI mutates into HPAI (within domestic bird populations) continuously at a constant per capita mutation rate m. However, it is believed that the appropriate LPAI→HPAI mutation occurred only once in the mid 1990s [59]. This hypothesis seems supported by the results of our fitting, which lead to an extremely small value of m. Our assumption of continuous mutation is driven by the need for simplicity.
(4) We assume that HPAI strains can super-infect LPAI–infected domestic birds. The transmission coefficient of super-infection is assumed to be the same as that of the original HPAI infection of susceptible domestic birds (β_{H_d}). This assumption is based on the justifiable premise that LPAI may be so benign that LPAI-infected birds may have similar susceptibility to HPAI strains as naive birds. Besides, this assumption also reduces the number of fitted parameters by one.
(5) We assume that the per capita rate of culling of domestic birds is proportional of the infected domestic birds (by both LPAI and HPAI strains). Since typically all birds in the farm, including infected and uninfected ones, are destroyed (and sometimes even those in neighboring farms), we assume that susceptible, infected and recovered domestic birds are destroyed at the same per capita culling rate.

The resulting model is schematically shown in Figure 2.

2.3. **Differential Equations.** From the diagram in Figure 2 and above assumptions, we obtain the following system of ordinary differential equations for the domestic bird

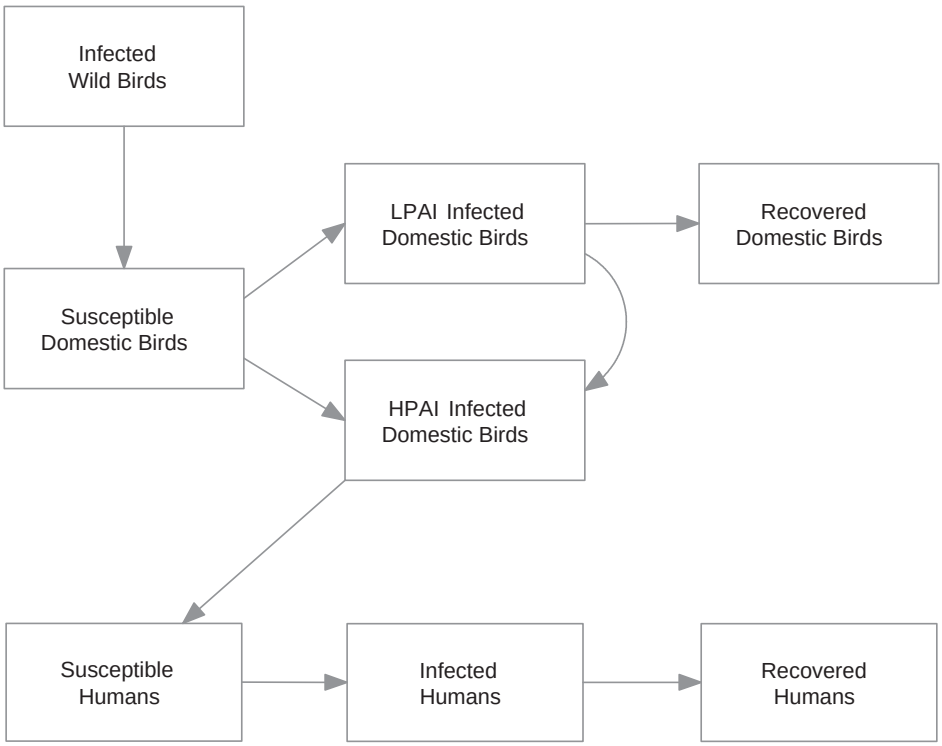

FIGURE 2. Diagram of model.

population. Below, $S_d(t)$ denotes the number of susceptible domestic birds at time t, $I_{L_d}(t)$ denotes the number of domestic birds infected with LPAI at time t, $R_d(t)$ denotes the number of birds in the LPAI recovered class at time t, and $I_{H_d}(t)$ denotes the number of domestic birds infected with HPAI at time t.

$$
\begin{cases}
\frac{dS_d}{dt} = \Lambda_d - (\mu_{cull}(I_{H_d} + I_{L_d}) + \mu_d)S_d - \beta_{H_d} I_{H_d} S_d \\
\qquad\qquad - S_d(\beta_{L_d} I_{L_d} + I_w \beta_{L_w}(\sin((t+\omega)\frac{2\pi}{365})c_1 + c_2)) \\
\frac{dI_{L_d}}{dt} = S_d(\beta_{L_d} I_{L_d} + I_w \beta_{L_w}(\sin((t+\omega)\frac{2\pi}{365})c_1 + c_2)) - (\mu_{cull}(I_{H_d} + I_{L_d}) + \mu_d)I_{L_d} \\
\qquad\qquad - mI_{L_d} - \alpha_d I_{L_d} - \beta_{H_d} I_{H_d} I_{L_d} \\
\frac{dR_d}{dt} = \alpha_d I_{L_d} - (\mu_d + \mu_{cull}(I_{H_d} + I_{L_d}))R_d \\
\frac{I_{H_d}}{dt} = \beta_{H_d} I_{H_d}(S_d + I_{L_d}) + mI_{L_d} - (\mu_{cull}(I_{H_d} + I_{L_d}) + \mu_d + \mu_{I_{H_d}})I_{H_d} \\
S_d(0) = S_{d_0}, R_d(0) = R_{d_0}, I_{L_d}(0) = I_{L_{d_0}}, I_{H_d}(0) = I_{H_{d_0}}
\end{cases} \tag{2.1}
$$

Similarly, we obtain the following system of ordinary differential equations for the human population.

Variable	Meaning
I_w	Number of infected wild birds (assumed constant)
Λ_d	Growth rate of domestic birds
μ_d	Natural death rate of domestic birds
β_{H_d}	Transmission coefficient of HPAI among domestic birds
β_{L_d}	Transmission coefficient of LPAI among domestic birds
β_{L_w}	Transmission coefficient of LPAI from wild to domestic birds
m	Rate at which LPAI mutates into HPAI
α_d	Recovery rate of domestic birds infected with LPAI
$\mu_{I_{H_d}}$	Death rate of domestic birds due to HPAI
μ_{cull}	Per infected bird death rate of domestic birds due to culling
ω	Phase shift of sine wave
c_1	A measure of the strength of migration on LPAI transmission from wild to domestic birds
c_2	Similar to c_1
β_{Hu}	Incidence rate of HPAI from domestic birds to humans
$\mu_{I_{Hu}}$	Death rate of humans due to HPAI
α_{Hu}	Recovery rate of humans with HPAI
S_d	Number of susceptible domestic birds
I_{L_d}	Number of LPAI infected domestic birds
R_d	Number of recovered domestic birds
I_{H_d}	Number of HPAI infected domestic birds
S_{Hu}	Number of susceptible humans
I_{Hu}	Number of infected humans
R_{Hu}	Number of recovered humans
I_{total}	Cumulative number of infected humans

TABLE 1. The meaning of the parameters and state variables.

$$
(2.2)\qquad \begin{cases} \frac{dS_{Hu}}{dt} = -\beta_{Hu} I_{H_d} S_{Hu} \\ \frac{dI_{Hu}}{dt} = -\mu_{I_{Hu}} I_{Hu} - \alpha_{Hu} I_{Hu} + \beta_{Hu} I_{H_d} S_{Hu} \\ \frac{dR_{Hu}}{dt} = \alpha_{Hu} I_{Hu} \\ \frac{dI_{total}}{dt} = \beta_{Hu} I_{H_d} S_{Hu} \\ S_{Hu}(0) = S_{Hu_0}, I_{Hu}(0) = I_{Hu_0}, R_{Hu}(0) = R_{Hu_0}, I_{total}(0) = I_{total_0} \end{cases}
$$

Here, $S_{Hu}(t)$ denotes the number of susceptible humans at time t, $I_{Hu}(t)$ denotes the number of humans infected with AI at time t, $R_{Hu}(t)$ is the number of humans recovered from AI at time t, and $I_{total}(t)$ is the cumulative number of infected humans through time t. The meaning of all model variables and parameters used in this chapter are summarized in Table 1.

3. Basic Mathematical Properties of the Model

3.1. **Persistence of LPAI and HPAI in the full model.** The model (2.1)-(2.2) is a non-autonomous system of differential equations with external source of infection coming from the wild bird population. If $N_d(t)$ denotes the total population size of domestic birds, then the number of the domestic birds is given by

$$N_d(t) = S_d(t) + I_{L_d}(t) + R_d(t) + I_{H_d}(t).$$

The total domestic bird population size satisfies the following inequality:

$$N_d'(t) \leq \Lambda_d - \mu_d N_d(t)$$

From this inequality one can infer that the total domestic bird population size is a bounded function of time. The following inequality holds for all time

$$N_d(t) \leq \frac{\Lambda_d}{\mu_d}$$

provided that the initial condition satisfies this relationship. If the initial condition does not satisfy the above inequality, then we still have

$$\limsup_t N_d(t) \leq \frac{\Lambda_d}{\mu_d}.$$

The external source term guarantees that the disease is persistent in the domestic bird population. There are various types of persistence but the one satisfied in this model is the uniform strong persistence. We will say that the LPAI is *uniformly strongly persistent* if there exists $\eta > 0$ such that

$$\liminf_t I_{L_d}(t) \geq \eta \qquad \text{for all} \qquad I_{L_d}(0) > 0.$$

Similarly, we will say that the HPAI is *uniformly strongly persistent* if there exists $\eta > 0$ such that

$$\liminf_t I_{H_d}(t) \geq \eta \qquad \text{for all} \qquad I_{H_d}(0) > 0$$

Uniform strong persistence says that if the initial number of domestic birds infected with LPAI is positive, the number of domestic birds infected with LPAI will remain positive and long term will not approach zero. To see the uniform strong persistence, notice that the number of susceptible domestic birds satisfy the following inequality

$$S_d' \geq \Lambda_d - p_d S_d$$

where p_d denotes the following constant: $p_d = \mu_{cull}\frac{\Lambda_d}{\mu_d} + \mu_d + (\beta_{H_d} + \beta_{L_d})\frac{\Lambda_d}{\mu_d} + (c_1 + c_2) I_w \beta_{L_w}$. The above inequality implies the persistence of the susceptible population, a result that would hold independently of the presence of the external source:

$$\liminf_t S_d(t) \geq \frac{\Lambda_d}{p_d} > 0.$$

The second equation in (2.1) leads to the following inequality for the number of domestic birds infected with LPAI:

$$I_{L_d}'(t) \geq \Lambda_{L_d} - p_{L_d} I_{L_d}(t)$$

where $p_{L_d} = \mu_{cull}\frac{\Lambda_d}{\mu_d} + \mu_d + m + \alpha_d + \beta_{H_d}\frac{\Lambda_d}{\mu_d}$ and $\Lambda_{L_d} = c_2\beta_{L_w}I_w\frac{\Lambda_d}{2p_d}$. We note that Λ_{L_d} is positive only in the case when I_w is positive. The above inequality implies the persistence of the LPAI:

$$\liminf_t I_{L_d}(t) \geq \frac{\Lambda_{L_d}}{p_{L_d}} > 0.$$

LPAI would persist in the domestic bird population without additional conditions only in the case when the wild bird population is a constant external source of the pathogen. Similar reasoning applied to the fourth equation in (2.1) gives

$$I'_{H_d}(t) \geq m\frac{\Lambda_{L_d}}{2p_{L_d}} - p_{H_d}I_{H_d}(t)$$

which leads to persistence

$$\liminf_t I_{H_d}(t) \geq \frac{m\Lambda_{L_d}}{2p_{L_d}p_{H_d}} > 0.$$

HPAI persists in the domestic bird population without additional conditions, only in the case when mutation of LPAI into HPAI takes place on continuous bases and the wild bird population is an external source of LPAI.

Since system (2.1)-(2.2) has a periodic forcing term, it may be possible to establish that it has one (or more) periodic solution(s) of the same period as the source term. Most simulations result in solution that converges to a periodic solution.

None of the human epidemiological classes in system (2.2) is persistent in any sense. A continuous infection process coming from a persistent infection in the domestic bird population depletes the pool of susceptible humans. Because the model assumes no birth, the number of susceptible humans, and hence the number of infected and recovered humans, decline in time to zero. This means that the human component of our model is only valid short term.

3.2. **Avian influenza in the domestic bird-human system.** Strains of LPAI were first introduced to the domestic bird populations from the wild bird populations. However, sampling for LPAI H5N1 strains in wild bird populations, particularly in North America, shows very low prevalence [61]. We would like to investigate whether the LPAI and HPAI strains can persist in the domestic bird-human system if there is no continuous inflow from the wild bird population. Because we estimate the transmission rate of LPAI strains from wild to domestic birds as very small (see Table 2), and this transmission rate can be made even smaller through control measures, we set $\beta_{L_w} = 0$. In this case the system becomes closed (there is no influx) and autonomous. We can define the reproduction numbers of the LPAI as

$$\mathcal{R}_L = \frac{\beta_{L_d}\Lambda_d}{\mu_d(\mu_d + m + \alpha_d)}$$

and the HPAI as

$$\mathcal{R}_H = \frac{\beta_{H_d}\Lambda_d}{\mu_d(\mu_d + \mu_{I_{H_d}})}.$$

The reproduction numbers measure the number of secondary cases of LPAI (HPAI respectively) that one infected domestic bird with LPAI (HPAI respectively) will produce

in an entirely susceptible bird population. With our least-squared estimated parameters in Table 2 we have

$$\mathcal{R}_L = 1.42857, \qquad \mathcal{R}_H = 2.71781.$$

Recall that these are reproduction numbers in the absence of external infection source. Typically, LPAI would persist in the absence of HPAI if $\mathcal{R}_L > 1$. Similarly, HPAI would persist in the absence of LPAI if $\mathcal{R}_H > 1$, as in each case each infected bird replaces itself with more than one new infected bird. We need both reproduction numbers to be larger than one so that strains of both kinds may persist, if we assume no mutation of LPAI into HPAI. Since we assume continuous mutation (although very small) of the LPAI into the HPAI, we only need $\mathcal{R}_L > 1$ to guarantee persistence of both LPAI and HPAI in the domestic bird population. In other words, if LPAI persists in the domestic bird population and continuously mutates into the HPAI, the HPAI will also persist. All those observations can be rigorously established mathematically as we did before about the non-autonomous system but will be omitted.

System (2.1) with $\beta_{L_w} = 0$ controls the behavior of system (2.2). Avian flu will persist in the human population if it persists in the domestic bird population. We focus on system (2.1) to understand the behavior of the solutions. Ordering the variables in the order of the equations in system (2.1), System (2.1) has a disease-free equilibrium where there are only susceptible birds but no pathogen of any kind. The disease-free equilibrium is given by $\mathcal{E}_0 = (\frac{\Lambda_d}{\mu_d}, 0, 0, 0)$. Concerning the endemic equilibria, since our estimated value of the mutation rate m is very small, it is worth considering two cases which lead to somewhat different equilibria of the LPAI and HPAI. In this section we continue with the case $m \neq 0$. The case $m = 0$ will be taken up in the next section.

In the case $m \neq 0$ there is no equilibrium of the LPAI alone. That is, we cannot have non-zero numbers of infected individuals with LPAI but zero infected individuals with HPAI. This is in agreement with our previous observation that persistence of LPAI in the presence of continuous mutation leads to persistence of HPAI as well. Thus, single-strain equilibria are only of the HPAI. This means that HPAI can be present in the domestic bird population whether LPAI is present or not. Any HPAI–only equilibrium has the form $\mathcal{E}_H = (S_d^*, 0, 0, I_{H_d}^*)$ where (we omit the stars)

$$S_d = \frac{\mu_{cull} I_{H_d} + \mu_d + \mu_{I_{H_d}}}{\beta_{H_d}}$$

and I_{H_d} is the solution of the following equation

$$\frac{\mu_{cull} I_{H_d} + \mu_d + \mu_{I_{H_d}}}{\beta_{H_d}} = \frac{\Lambda_d}{\beta_{H_d} I_{H_d} + \mu_{cull} I_{H_d} + \mu_d} \tag{3.1}$$

The above equation has a positive solution if and only if $\mathcal{R}_H > 1$. The solution, if it exists, is necessarily unique, since the left hand side above is an increasing function of I_{H_d} while the right hand side is a decreasing function of I_{H_d}. This gives a unique equilibrium $\mathcal{E}_H$ of HPAI alone. It can be shown that this endemic equilibrium is locally asymptotically stable.

It can also be shown that if $\mathcal{R}_L < 1$ and $\mathcal{R}_H < 1$ then both LPAI and HPAI will disappear from the domestic bird population. The invasion reproduction number of the

LPAI at the equilibrium of the HPAI is given by

$$\hat{\mathcal{R}}_L = \frac{\beta_{L_d} S_d^*}{\mu_{cull} I_{H_d}^* + \beta_{H_d} I_{H_d}^* + \mu_d + m + \alpha_d}$$

If $\mathcal{R}_H > 1$ and LPAI can invade the equilibrium of HPAI, that is $\hat{\mathcal{R}}_L > 1$ (and that implies that $\mathcal{R}_L > 1$) then we expect that the two AI strains coexist. In fact, it should be possible to establish uniform strong persistence of both LPAI and HPAI. In this case the endemic equilibrium $\mathcal{E}_H$ for HPAI should be unstable. If $\mathcal{R}_H > 1$ and LPAI cannot invade the equilibrium of HPAI, that is $\hat{\mathcal{R}}_L < 1$, then the expectation is that HPAI persists but LPAI dies out, even if $\mathcal{R}_L > 1$. This last statement is not easy to show, and more complex scenarios might be possible. The biological significance of this last scenario is that HPAI can displace (competitively exclude) LPAI strain in domestic birds. The value of $\hat{\mathcal{R}}_L$ that corresponds to the parameter estimate that are listed in Table 2 is $\hat{\mathcal{R}}_L = 0.501173$. This value suggests that in the absence of external inflow of LPAI from the wild bird population, HPAI will displace and eliminate LPAI in the domestic bird population.

We note that culling as a control strategy in model (2.1) does not affect the reproduction number $\mathcal{R}_H$ because we assume that the per capita culling rate is proportional to the number of infected birds. In other words, in a completely susceptible bird population, there is no culling (this is equivalent to the fact that culling is not needed if infection is not detected). So culling has no effect on the reproduction number. There are other types of reproduction numbers, such as the effective reproduction number. The effective reproduction number depends on the number of susceptible birds at time t, and will depend on culling:

$$\mathcal{R}_H(t) = \frac{\beta_{H_d} S_d(t)}{\mu_d + \mu_{I_{H_d}}}.$$

Looking at equation (3.1) one can see that the equilibrium number of HPAI infected domestic birds $I_{H_d}^*$ declines as μ_{cull} increases. The maximum number of infected birds which occurs with $\mu_{cull} = 0$ is given by:

$$I_{H_d}^{max} = \frac{\mu_d(\mathcal{R}_H - 1)}{\beta_{H_d}}.$$

The dependence of S_d^* and the invasion reproduction number $\hat{\mathcal{R}}_L$ on the culling rate μ_{cull} seems non-monotone, and possibly complex.

3.3. **Invasion of HPAI. The case m = 0.** Wild bird populations are reservoir of LPAI strains. It is currently believed that strains of the H5N1 AI underwent antigenic drift in the mid-1990's and became adapted to domestic birds. The HPAI occurred as a result of reassortment in the domestic birds, and now is spreading among the domestic bird population [6]. It appears that continuous mutation from LPAI to HPAI does not occur – a scenario which seems to agree with our estimates on m which are nearly zero. In this subsection we consider the mathematically distinct case $m = 0$ and address the question under what conditions a newly emerged HPAI strain can invade the domestic bird population.

In this case the reproduction numbers of LPAI and HPAI are given by the same expressions as before with $m = 0$. In the case $m = 0$, besides the disease-free equilibrium

$\mathcal{E}_0$ that we found with $m \neq 0$, there is a unique LPAI-only equilibrium and a unique HPAI-only equilibrium. The HPAI exclusive equilibrium exists if an only if $\mathcal{R}_H > 1$ and is $\mathcal{E}_H = (S_d^H, 0, 0, I_{H_d}^*)$ with values of the non-zero quantities given by the expressions in the case $m \neq 0$. In addition to the HPAI exclusive equilibrium, in the case $m = 0$ there is also an LPAI exclusive equilibrium which exists if and only if $\mathcal{R}_L > 1$ and is given by $\mathcal{E}_L = (S_d^L, I_{L_d}^*, R^*, 0)$. The non-zero values in that equilibrium are

$$S_d^L = \frac{\mu_{cull} I_{L_d}^* + \mu_d + \alpha_d}{\beta_{L_d}}$$

and $I_{L_d}^*$ is the unique positive solution of the equation:

$$\frac{\Lambda_d}{\beta_{L_d} I_{L_d}^* + \mu_{cull} I_{L_d}^* + \mu_d} = \frac{\mu_{cull} I_{L_d}^* + \mu_d + \alpha_d}{\beta_{L_d}}$$

which exists if and only if $\mathcal{R}_L > 1$. The value of R^* is given by

$$R^* = \frac{\alpha_d I_{L_d}^*}{\mu_{cull} I_{L_d}^* + \mu_d}$$

The invasion capabilities of an emergent HPAI strain are measured by the HPAI invasion reproduction number at the equilibrium of LPAI. The HPAI invasion reproduction number is given by

$$\hat{\mathcal{R}}_H = \frac{\beta_{H_d}(S_d^L + I_{L_d}^*)}{\mu_{cull} I_{L_d}^* + \mu_d + \mu_{I_{H_d}}} \tag{3.2}$$

It can be rigorously established that if $\mathcal{R}_L > 1$ so that the equilibrium $\mathcal{E}_L$ exists and if $\hat{\mathcal{R}}_H > 1$, that is HPAI can invade the equilibrium of LPAI, then HPAI persists in the domestic bird population. Depending on the invasion reproduction number of LPAI the following options are possible:

(1) If $\mathcal{R}_L > 1$ and $\hat{\mathcal{R}}_H > 1$, and if, in addition, $\mathcal{R}_H > 1$ so that the equilibrium $\mathcal{E}_H$ exists and if $\hat{\mathcal{R}}_L < 1$, so that HPAI cannot invade the equilibrium of HPAI, then the expectation is that $I_{L_d}(t) \to 0$ as $t \to \infty$, while $I_{H_d}(t) \to I_{H_d}^*$ as $t \to \infty$. This global result is not easy to establish.
(2) If $\mathcal{R}_L > 1$ and $\hat{\mathcal{R}}_H > 1$, and if, in addition, $\mathcal{R}_H > 1$ so that the equilibrium $\mathcal{E}_H$ exists and if $\hat{\mathcal{R}}_L > 1$, so that LPAI can also invade the equilibrium of HPAI, then there is a coexistence equilibrium $\mathcal{E}^* = (\bar{S}_d, \bar{I}_{L_d}, \bar{R}, \bar{I}_{H_d})$.

To see this last statement, we set the derivatives equal to zero. From the first equation in (2.1) we have

$$S_d^* = \frac{\Lambda_d}{\mu_{cull}(I_{L_d} + I_{H_d}) + \beta_{H_d} I_{H_d} + \beta_{L_d} I_{L_d} + \mu_d}.$$

The right-hand side of the expression above is a function of I_{H_d} and I_{L_d} which we denote by $\mathcal{S}(I_{L_d}, I_{H_d})$. The function $\mathcal{S}$ is a decreasing function of each of its arguments when the other argument is held fixed. From the second and forth equation in (2.1) we get the system:

$$\begin{cases} F(I_{L_d}, I_{H_d}) = 1 \\ G(I_{L_d}, I_{H_d}) = 1 \end{cases} \tag{3.3}$$

where the two functions F and G are given by

$$\begin{cases} F(I_{L_d}, I_{H_d}) = \dfrac{\beta_{L_d}\mathcal{S}}{\mu_{cull}(I_{L_d}+I_{H_d})+\beta_{H_d}I_{H_d}+\alpha_d+\mu_d} \\ \\ G(I_{L_d}, I_{H_d}) = \dfrac{\beta_{H_d}(\mathcal{S}+I_{L_d})}{\mu_{cull}(I_{L_d}+I_{H_d})++\mu_{I_{H_d}}+\mu_d} \end{cases} \tag{3.4}$$

The function F is a decreasing function of both I_{L_d} and I_{H_d}. The function G is a decreasing function of I_{H_d} when I_{L_d} is held fixed. For each fixed I_{L_d} the equation $F(I_{L_d}, I_{H_d}) = 1$ has a unique solution. Since the derivative of F with respect to its second argument is strictly positive for non-negative values of the arguments, the implicit function theorem implies that there is a continuous, differentiable function $I_{H_d} = f(I_{L_d})$. Define $H(I_{H_d}) = G(I_{L_d}, f(I_{L_d}))$. If $\hat{I}_{H_d}$ is the unique solution of $F(0, \hat{I}_{H_d}) = 1$, then $\hat{I}_{H_d} = f(0)$. We note that $\hat{I}_{H_d} > I^*_{H_d}$. The function $G(I_{L_d}, I_{H_d})$ is a decreasing function of I_{H_d} and therefore, $1 = G(0, I^*_{H_d}) > G(0, \hat{I}_{H_d}) = H(0)$. On the other hand, since $F(I^*_{L_d}, 0) = 1$, then $f(I^*_{L_d}) = 0$. Consequently,

$$H(I^*_{L_d}) = \frac{\beta_{H_d}(\mathcal{S}(I^*_{L_d}, 0) + I^*_{L_d})}{\mu_{cull}I^*_{L-d} + \mu_d + \mu_{I_{H_d}}} = \hat{\mathcal{R}}_H > 1.$$

This implies that the equation $H(I_{L_d}) = 1$ has a solution $\bar{I}_{L_d}$ satisfying $O < \bar{I}_{L_d} < I^*_{L_d}$ and $\bar{I}_{H_d} = f(\bar{I}_{L_d})$ with $0 < \bar{I}_{H_d} < \hat{I}_{H_d}$. That establishes the existence of a coexistence equilibrium. The coexistence equilibrium that occurs when both invasion reproduction numbers are larger than one, is usually locally asymptotically stable.

We now move on to fitting our differential equation model to the cumulative number of human case data of AI as given by WHO [8]. Fitting a dynamic model to data has a three-fold purpose: (1) Validation of the model, (2) Estimating the parameters, and (3) Projection of future number of cases. We address all three purposes, but first we describe our fitting procedure.

4. Fitting Model to Data

4.1. **General Method.** The model fitting is implemented using MATLAB's *lsqcurvefit* function. Cumulative HPAI infection data for humans are obtained from the WHO database [8]. We discard data points between the days from January 28 through October 25, 2004, because of lack of precision in reporting (and also their seeming mismatch with the rest of the data – see Figure 1). All points near the beginning and end of the apparent period (time unit=500 and time unit=850 in Figure 1) are included as the outbreak pattern seems to change rapidly near it. For the remainder of the days between January 7, 2005 (time unit=341), and April 11, 2007 (time unit=1165), roughly one point per month is selected from the available data whenever possible. We carried out our initial curve fitting shortly after April 11, 2007, based on the data points available upto that time. Data from April 11, 2007, to September 10, 2008 (most recent data available at the time of writing this article) was later collected from the updated WHO database, and used to determine the predictive capabilities of the model.

We fitted our model to the data using initial guesses for all model parameter values, and obtained better estimates of the same parameters from the fit. The function that

MATLAB fit to the data was the numerical solution of the model (2.1)–(2.2). That is, MATLAB computed the numerical solution of the model with a different set of parameters every time lsqcurvefit evaluated the function with which it was attempting to fit data. Unfortunately, MATLAB's curve fitting procedures are not particularly good at determining global minima, so one must manually determine reasonable values of the parameters. If the initial guesses for the parameters are poor, MATLAB will find a local minimum for the least squared error that is far from the global minimum. Once sufficiently good estimates of the parameters were determined, a script was run which iteratively executed lsqcurvefit. After each execution, one or several parameters were perturbed in order to attempt to find alternative smaller local minima near the previous best-fit parameters.

4.2. **Specific MATLAB Code.** Before the curve fitting can begin, MATLAB must be supplied with the model. To code a basic system of differential equations in MATLAB, one creates a function that takes as parameters a real number (the time variable) and an array (which specifies the value of each state variable). The function should then generate an array that specifies the value of the derivative of each of the state variables. [1] Further, since the model's parameters will be changing within the program, this function should also take in an array which specifies the value of each parameter. Suppose that AI_model(t,x,c) is such a function, where t is the time variable, x is the array which specifies a value for each state variable (say x=$[S_d, I_{L_d}, R_d, I_{H_d}, S_{Hu}, I_{Hu}, R_{Hu}, I_{total}]$) and c is the array of parameters.

Now, this function is neither what the differential equation solver expects as input (since it requires an array of parameters to be supplied), nor is it what lsqcurvefit expects (since it is the model itself, not the model's solution). So, we need another function that fills this gap. This function should take as input an array of values of the independent variable and an array of parameters. It should return as output an array whose i^{th} entry is the numerical solution of the model using the specified array of parameters evaluated at the i^{th} entry of the array of the independent variable. In particular, the model will be fit to data that was obtained for I_{total}, so the 8^{th} coordinate of the numerical solution should be returned. The following function performs this task:

```
function output=call_AI_model(c,tdata)
%Input    -  c      : An array of parameters for the model
%            tdata  : An array of data points of the independent variable
%Output   -
%   The numerical solution to AI_model evaluated at times specified by tdata

x0=[c(15),c(16),c(17),c(18),c(19),0,13,47];
AI_model_constants=@(z0,z1)(AI_model(z0,z1,c));
[t,s]=ode15s(AI_model_constants, tdata, x0);
output=s(:,8);
```

lsqcurvefit can call this function since it takes in the proper variables and generates the proper array as output. It calls ode15s (one of MATLAB's numerical ODE solvers) to

[1] If the system of differential equations is of the form $x\prime = f(x,t)$, then f is exactly the function that MATLAB expects.

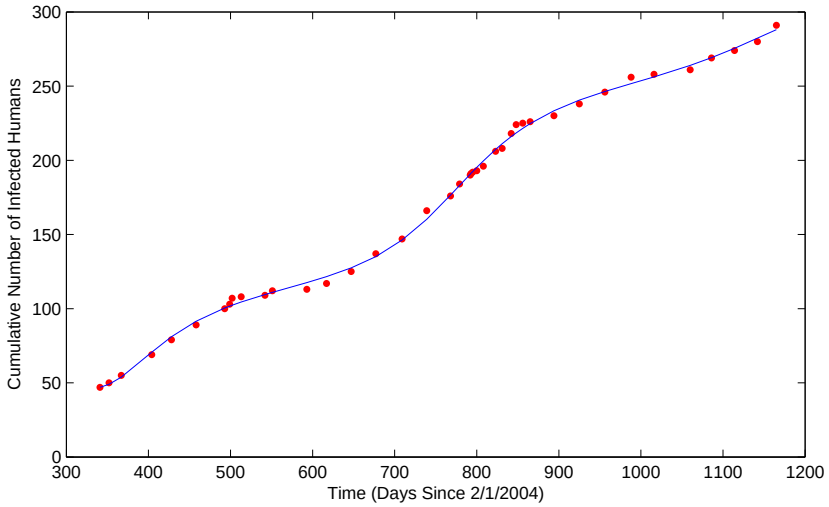

FIGURE 3. The curve that resulted from the curve fitting plotted alongside the WHO data.

solve AI_model with parameters coming from c. So, we can now use lsqcurvefit to call this function using the following command:

[new_params,error] = lsqcurvefit(@call_AI_model,initial_params,
tdata, Infected_data, param_lower_bound, param_upper_bound)

We then place this command into a couple of embedded loops which slightly perturb the new parameters after each execution of lsqcurvefit.

4.3. **Results from the fitting. Extending the fit.** As mentioned before, we fitted the model (2.1)-(2.2) in April, 2007, to the then available data on the cumulative number of human cases. We will call this set of data our *calibration data set*. This calibration data set consists of a total of 41 data points. The main criterion used for the goodness of fit to the calibration set of data was minimizing the least squared error E_c^2. The smallest least squared error that we obtained with our fit at that time had a value 283.08 across the 41 data points. The results of our original fit are presented in Figure 3.

The initial fit was performed with all parameters left free for MATLAB to determine them from the best fit. Our main thrust was that a better fit will be obtained if MATLAB's optimization routines have more degrees of freedom. MATLAB obtained the following values for the parameters from that fit (Table 2).

One problem with this method is that for those parameters whose values can be independently obtained from elsewhere (e.g. available literature), the fitted estimates computed by MATLAB may not agree well with these values. For example, one parameter whose value can be obtained from the literature is the lifespan of poultry, which for chickens is 5 to 10 years when kept under favorable conditions. We estimate $\mu_d = 0.001678$ day^{-1} which corresponds to a lifespan of 1.6 years. Similarly, WHO [8] data on the mortality of humans infected with avian influenza give a mean case-fatality proportion (CFP) [62] of approximately 0.6. That is, about 60% of the infected humans die from avian influenza. The probability of dying when infected with avian influenza, as given

Variable	Value	Units	Variable	Value	Units
Λ_d	1.7711	individuals $\cdot$ day^{-1}	μ_d	0.001678	day^{-1}
$\mu_{I_{H_d}}$	0.08912	day^{-1}	μ_{cull}	0.001207	individual$^{-1}\cdot$day^{-1}
β_{H_d}	0.0002338	individual$^{-1}\cdot$day^{-1}	β_{L_d}	4.9575e-005	individual$^{-1}\cdot$day^{-1}
β_{L_w}	3.1599e-007	individual$^{-1}\cdot$day^{-1}	m	6.6097e-009	day^{-1}
α_d	0.03495	day^{-1}	β_{Hu}	0.001098	individual$^{-1}\cdot$day^{-1}
$\mu_{I_{Hu}}$	0.2845	day^{-1}	c_1	0.8517	*unitless*
ω	7.1453	days	c_2	1.0490	*unitless*
α_{Hu}	0.2669	day^{-1}	I_w	80.7456	individuals
S_{d_0}	746.0352	individuals	$I_{L_{d_0}}$	14.1744	individuals
$I_{H_{d_0}}$	0.3384	individuals	S_{Hu_0}	357.9811	individuals

TABLE 2. Parameters determined via the original curve fit of the model.

by the model, is

$$P_d = \frac{\mu_{I_{H_u}}}{\mu_{I_{H_u}} + \alpha_{H_u}},$$

while the probability of recovery is

$$P_r = \frac{\alpha_{H_u}}{\mu_{I_{H_u}} + \alpha_{H_u}}.$$

Based on CFP, $P_d \approx 0.6$ and $P_r \approx 0.4$, whereas Table 2 gives $P_d = 0.52$ and $P_r = 0.48$. Thus, a value of $P_d = 0.52$ underestimates the observed probability of human death. (Better estimate of the disease-induced death rate $\mu_{I_{H_u}}$ may be obtained if we fit the cumulative number of dead individuals as reported by WHO [8].)

Despite the fact that Table 2 underestimates the poultry lifespan and the probability of human death from infection, these estimates are still reasonably close to the observed values. MATLAB optimization routines have the ability to keep a parameter fixed at a predefined value, or search for an optimal value of the parameter in a predefined range. Using these options would guarantee that known parameters have values within expected ranges. The least squared errors obtained from a fit when some parameters are kept fixed, or within range, are expected to be larger.

In November 2008 we revisited the problem. WHO has continued to collect and update its database on the cumulative number of human HPAI infection cases. We will call this new data set between April 2007 and November 2008 the *test data set*. The main question that we asked was: If we use the model developed in April 2007 to predict this recent test data, how good would our predictions be? We extrapolated the best fit curve obtained from the model (2.1)-(2.2), with the estimated parameters from Table 2, upto November 2008 and compared it to our test data. In this early attempt (not shown here) the model appears to seriously *underestimate* the observed number of human cases.

For our initial fit to the calibration data set, we chose the model with the smallest least squared error E_c^2, which appears to have done poorly with the new test data set. We refitted the model to the calibration data starting with larger numbers of susceptible humans and allowing for larger error E_c^2. In Figure 4 we show the results of our fit to the calibration data (red dots), with least squares error E_c^2 of 370. The projection of the

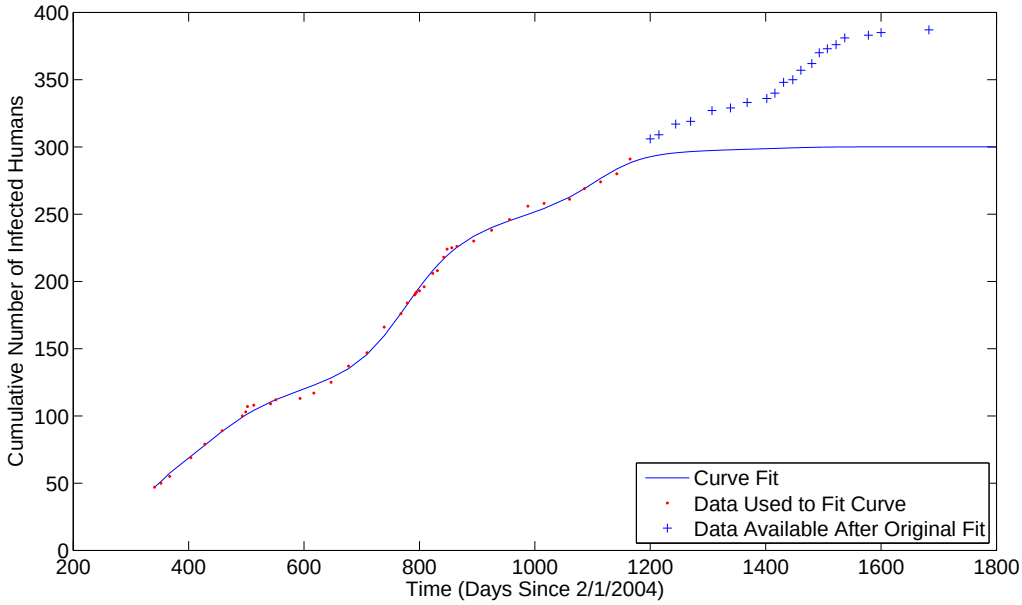

FIGURE 4. The curve that resulted from the curve fitting the calibration set of data with least squares error of 370, extended to November 2008 and plotted alongside the WHO data.

fit to the present day (blue line) as well as the new test data set from WHO (blue stars) are also shown for comparison. As can be seen, the model continues to underestimate the recently observed number of human cases between April 2007 and November 2008.

Figure 5 presents another attempt at predicting the test data set using an initial fit with even larger least squared error: $E_c^2 = 574$. This time the model does a far better job of capturing the recent patterns of human cases. We show a sample of the model's fit to the calibration data set, and its prediction of the test data set, in Table 3.

Of course, in future if we use the model with least squared error of 574 (Figure 5) to predict the cumulative number of human HPAI cases after November 2008, our model would likely underestimate this future data as well. From the requirement of starting with higher and higher initial susceptible humans for better fit with future data sets, it appears that one likely reason for the underestimation is the absence of a recruitment term for susceptible humans in our model. However, continuing to increase the number of susceptible humans would lead to an even larger least squared error over the calibration set. Moreover, there are now nearly four years worth of WHO data on the human cases of avian influenza. Any model that fits those and predicts into the future would have to run over a period of 4+ years. This is no longer short enough period so that human demography can be totally ignored. Our next step will be to incorporate human births and natural deaths and refit the model.

We close this section with some reflections on our curve fitting procedure. One of the problems with this method is that MATLAB's routines assume that the function one is trying to fit the data to is continuous. That is, MATLAB assumes that the solution

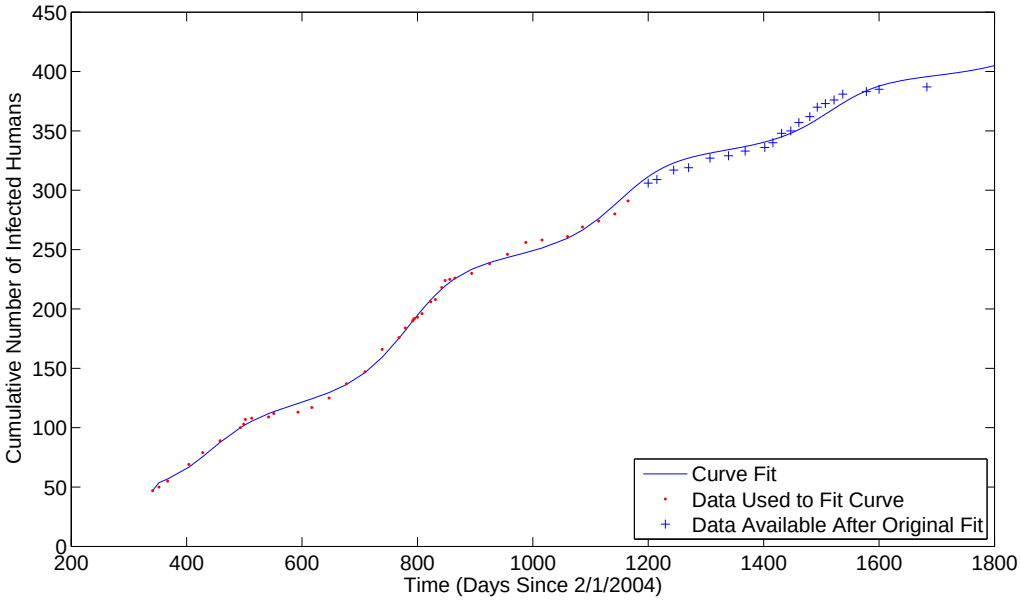

FIGURE 5. The curve that resulted from the curve fitting the calibration set of data with least squares error of 574, extended to November 2008 and plotted alongside the WHO data.

of the model is continuous in its parameters. One explanation for why some trial and error was required to find good values of the parameters is just that this continuity requirement is not satisfied. However, lsqcurvefit did in general perform reasonably well at some points.

The fit we obtained is, however, far from perfect. Consider the behavior of the points in Figure 3 near time unit=500 and time unit=850. The data points immediately before and after these times lie below the curve, whereas those at these times lie above the curve. Further, consider Figure 4, especially in the interval from 500 to 850 days. It looks as though this curve is typically increasing except at the beginning/end of this period.

We believe a slight modification on the model (2.1)-(2.2) would result in a better fit. For instance, instead of our assumption that the death rate (of domestic birds) due to culling is simply proportional the the number of infected domestic birds, it seems as though they should have a more complex non-linear relationship. This is because an HPAI infection is not typically noticed immediately after it has occurred, and instead only once the infection becomes noticeable is culling implemented. Also, our model ignores vaccination as an alternative control measure. However, as noted in the beginning, vaccination is increasingly being employed in many places. Future efforts should focus on determining appropriate functional forms for these various effects.

5. DISCUSSION

We developed an ordinary differential equation model to describe the complex epidemiology of the LPAI and HPAI strains, involving multi–species interaction of wild

	Date	Days (Since 2/1/2004)	Predicted CN (Dates Used for Fitting)	Projected CN	Observed CN
As Originally Fit	January 7, 2005	341	47.00		47
	February 2, 2005	367	56.85		55
	March 11, 2005	404	66.76		69
	April 4, 2005	428	75.672		79
	May 4, 2005	458	87.658		89
	June 8, 2005	493	99.919		100
	July 27, 2005	542	111.84		109
	August 5, 2005	551	113.51		112
	September 16, 2005	593	120.45		113
	October 10, 2005	617	124.28		117
	November 9, 2005	647	129.62		125
	December 9, 2005	677	136.37		137
	January 10, 2006	709	146.33		147
	February 9, 2006	739	159.32		166
	March 10, 2006	768	175.30		176
	April 3, 2006	792	189.88		190
	May 4, 2006	823	207.66		206
	June 6, 2006	856	222.41		225
	July 14, 2006	894	233.38		230
	August 14, 2006	925	239.08		238
	September 14, 2006	956	243.38		246
	October 16, 2006	988	247.42		256
	November 13, 2006	1016	251.29		258
	December 27, 2006	1060	259.45		261
	January 22, 2007	1086	266.36		269
	February 19, 2007	1114	276.09		274
	March 19, 2007	1142	287.79		280
	April 11, 2007	1165	297.85		291
Extended Prediction	May 16, 2007	1200		311.43	306
	June 29, 2007	1244		322.90	317
	July 25, 2007	1270		327.10	319
	August 31, 2007	1307		331.26	327
	October 2, 2007	1339		334.17	329
	December 4, 2007	1402		340.63	336
	January 2, 2008	1431		344.96	348
	February 1, 2008	1461		351.12	357
	March 4, 2008	1493		359.77	370
	April 2, 2008	1522		368.74	376
	May 28, 2008	1578		383.74	383
	June 19, 2008	1600		387.69	385
	September 10, 2008	1683		395.63	387

Table 3. Results of curve fit.

bird, domestic bird and human populations. Our model particularly focused on how the HPAI strain, after having mutated from the LPAI strain within domestic birds, is passed on to humans. We assumed wild birds to be a periodic source feeding seasonally pulsed LPAI infection to the domestic birds, in order to incorporate the approximately 1-year period oscillation observed in the cumulative human HPAI infection cases (the assumption of an external periodic forcing is biologically justifiable because of the seasonal migratory behavior of the wild birds, which may change their population size during breeding season, and/or increase their contact rates with domestic birds during migration). Our model further incorporates a continuous mutation of the LPAI virus into HPAI strain within the domestic bird population, a feature again rooted on strong biological footing (to our knowledge, previous AI models have not taken such mutation into account). We mathematically analyzed the persistence and co-existence of the LPAI and HPAI strains within the domestic bird population under different conditions, by deriving

the appropriate reproduction numbers. Because there is no recruitment of humans in our model, all human disease classes approach zero asymptotically. Finally, we carried out a least-squared fit of our model to the cumulative human cases of HPAI infection obtained from the WHO database, and estimated the model parameters, including the reproduction numbers, from the best fitted model.

The interacting bird–human system of transmission of avian influenza seems ideal for developing and testing mathematical models of complex epidemiological systems that have predictive properties. The fact that WHO provides regularly updated cumulative number of human cases can help modelers (such as us) to fine–tune our models, and thereby increase their predictive powers. The examples shown here illustrate some of the challenges involved in this endeavor of model fitting. Based on the real–time updating of the WHO data, one can calibrate the model using the data available until this moment, and use this calibrated model to predict future cases. Later on, one can revisit the model and compare its predictions with the actual new set of data as reported by WHO. Prediction using these complex epidemic systems is uncertain and inherently risky. One can expect even models with good predictive powers to work over only small periods of time. The best strategy appears to be to fit the model to the known set of data, and predict future occurrences over short time windows. As new data become available, the model has to be refitted and fine-tuned, and possibly used again for the following short-term prediction.

One of the most pressing concerns today is the possibility that the HPAI strain can genetically recombine with the human influenza (HI) strain (that causes year–round mild flu symptoms in humans) within a co–infected host, such as pigs or humans that have similar cellular receptors for both flu strains and also often live in close proximity to domestic poultry [3, 60]. Such a recombination process can create a new subtype that has both the high pathogenicity of HPAI and high human–to–human transmissibility of HI. Because human immunity against such a novel strain will be minimal, a global pandemic with a high level of mortality could then occur. Indeed, a recent conservative estimate suggests a 3.9% probability of a flu pandemic occurring in any given year, with a 95% support interval of 0.7% – 7.6% (see Figure 1, [60]). Given this persistent threat, an urgent focus of the modeling efforts should be in understanding the dynamics of such a co–infection of, for example, the human hosts. This would require extending the model (2.1)–(2.2) to include the HI strain co–infecting humans that are simultaneously infected with HPAI strains (from birds), and a recombination process that creates the evolved strain within a human host. The model by Iwami et al. [57] considers human infection by a "mutant" AI strain that originates from point mutation of the original HPAI strain, and therefore ignores the biological realism of genetic recombination within a co–infected host as the more likely source of this novel strain. Developing suitable models for the next possible flu pandemic is a task for the future.

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Department of Mathematics, University of Florida, 358 Little Hall, PO Box 118105, Gainesville, FL 32611–8105
E-mail address: jbl@math.ufl.edu

Department of Botany and Zoology, University of Florida, 358 Little Hall, PO Box 118105, Gainesville, FL 32611
E-mail address: rdholt@zoo.ufl.edu

Department of Mathematics, University of Florida, 358 Little Hall, PO Box 118105, Gainesville, FL 32611–8105
E-mail address: maia@math.ufl.edu