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AVIAN INFLUENZA A H7N9 VIRUS HAS BEEN ESTABLISHED IN CHINA

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In March 2013, a novel avian-origin influenza A H7N9 virus was identified among human patients in China and a total of 124 human cases with 24 related deaths were confirmed by May 2013. From November 2013 to July 2017, H7N9 broke out four more times in China. A deterministic model is proposed to study the transmission dynamics of the avian influenza A H7N9 virus between wild and domestic birds and from birds to humans, and is applied to simulate the open data on numbers of the infected human cases and related deaths reported from March to May 2013 and from November 2013 to June 2014 by the Chinese Center for Disease Control and Prevention. The basic reproduction number $\mathcal{R}_0$ is estimated and sensitivity analysis of $\mathcal{R}_0$ in terms of model parameters is performed. Taking into account the fact that it broke out again from November 2014 to June 2015, from November 2015 to July 2016, and from October 2016 to July 2017, we believe that H7N9 virus has been well established in birds and will likely cause regular outbreaks in humans again in the future. Control measures for the future spread of H7N9 include (i) reducing the transmission opportunities between

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wild birds and domestic birds, (ii) closing or monitoring the retail live-poultry markets in the infected areas, and (iii) culling the infected domestic birds in the epidemic regions.

Keywords: Avian Influenza A H7N9 Virus; Transmission Dynamics; Basic Reproduction Number; Seasonal Influenza; Reassortment.

1. Introduction

In March 2013, a novel avian-origin influenza A H7N9 virus was identified among human patients in east China.[1–3] Rapidly it spread to other 10 provinces and municipalities in Mainland China.[4,5] By the beginning of May, a total of 124 human cases of avian influenza A H7N9 virus infection and 24 related deaths were confirmed.[6] There were no reported cases in the summer and fall. However, the virus came again in November 2013. By the end of May 2014, the seasonal outbreak caused 130 human cases with 35 deaths.[7] Moreover, outbreaks of H7N9 virus broke out again from November 2014 to June 2015 with 216 confirmed human cases with 99 deaths, from November 2015 to July 2016 with 114 confirmed human cases and 45 deaths, and from October 2016 to July 2017 with 750 reported human H7N9 cases and 283 deaths, respectively.[7]

Influenza A viruses are divided into subtypes on the basis of their hemagglutinin (H1–H17) and neuraminidase (N1–N10) activities. It is the first time that this H7N9 subtype has infected humans and caused fatal cases. It is confirmed[1–3] that the novel avian influenza A H7N9 virus originated from multiple reassortment events. It has been reported that the H7N9 virus resulted from the recombination of genes between several parent viruses noted in poultry and wild birds in Asia.[8] There was evidence suggesting that the HA gene has its origin in ducks and probably also wild birds. The HA genes were circulating in the East Asian flyway in both wild birds and ducks, while the NA genes were introduced from European lineages and transferred to ducks in China by wild birds through migration along the East Asian flyway.[3] Though the mode of H7N9 virus transmission between avian species remains unknown, various wild birds have been implicated as a source of transmission. Jones *et al.*[9] reported that society finches, zebra finches, sparrows, and parakeets are susceptible to H7N9 virus and shed the virus into water. Jones *et al.*[10] further demonstrated that interspecies transmission of H7N9 virus occurs readily between society finches and bobwhite quail, but only sporadically between finches and chickens, and transmission occurs through shared water. Experimental data of Pantin-Jackwood *et al.*[11] showed that quail and chickens are susceptible to infection, shed large amounts of virus, and are likely important in the spread of the virus to humans, so it is conceivable that passerine birds may serve as vectors for transmission of H7N9 virus to domestic poultry.[10] Data of Bao *et al.*[12] and Chen *et al.*[1] indicate that the novel avian influenza A H7N9 virus was most likely transmitted from the secondary wholesale market to the retail live-poultry market and then to patients.[13] To control the outbreak, from late April to early June in 2013 during the first outbreak, local authorities of the affected provinces

and municipalities, such as Jiangsu, Shanghai, and Zhejiang, closed the retail live-poultry markets, which stopped the transmission of H7N9 for domestic birds and humans immediately and there were no reported human cases till October 2013.

Mathematical modeling is a very useful and important tool in studying the transmission dynamics of infectious diseases,[14,15] and effective prevention and control measures can be designed and evaluated via mathematical analysis and numerical simulations of the model. Due to the high morbidity and mortality in humans and animals, there are plenty of significant works that investigate the transmission dynamics of avian influenza.[16–23] Among them, Tuncer *et al.*[23] studied a model with domestic and wild birds.

Recently, there have been some interesting studies on modeling the outbreaks of the avian influenza A H7N9 virus in China. Chowell *et al.*[24] used a Bayesian approach combined with a SEIR epidemic model fitted to daily case data by provinces and evaluated the impact of live bird market closure in April and May 2013. They estimated that the basic reproduction number for human-to-human transmission as $\mathcal{R}_0 = 0.1$ (95% CI: 0.01–0.49) and predicted a low transmission potential of the avian influenza A (H7N9) virus. In order to determine the original infection source of H7N9 virus, Zhang *et al.*[25] established a dynamical model including migratory birds, resident birds, domestic poultry, and human population. By comparing the data fitting results and the corresponding Akaike Information Criterion values, they concluded that the migrant birds are most likely the original infection source and the basic reproduction number for bird-to-bird transmission was estimated as $\mathcal{R}_0 = 6.02$ (95% CI: 4.60–7.44). Xiao *et al.*[26] proposed and analyzed a deterministic model to access the transmission potential of the avian influenza A (H7N9) virus. By fitting the model to data of the confirmed human cases, they estimated the basic reproduction number for human-to-human transmission as $\mathcal{R}_0 = 0.467$ (95% CI: 0.387–0.651) and concluded that a new outbreak may be possible due to virus mutation and adaption or periodic outbreaks in poultry. Hsieh *et al.*[27] developed a compartmental model for transmissions among (wild and domestic) birds and from birds to humans. Their estimated basic reproduction number for infections among birds is 4.10 and the mean daily number of human infections per infected bird is $3.16 \times 10^{-5}(3.08 \times 10^{-5}, 3.23 \times 10^{-5})$, which indicates minimal risk of widespread bird-to-human infections of H7N9 virus during the outbreak. Liu and Fang[28] constructed a model consisting of both avian and human populations, estimated model parameters using publicly available nationwide surveillance data on animal and human infections, and examined the effectivity of screening and culling infected poultry as a critical measure for preventing human H7N9 infections in the long term. Chong *et al.*[29] used a simple susceptible-infectious (SI) model to analyze the human-to-human transmission rate for the epidemics that occurred between 2013 and 2015 in Zhejiang Province, China. Lin *et al.*[30] developed three different SIRS models to fit the observed human cases between March 2013 and July 2015 in China and found that environmental transmission via viral shedding of infected chickens had contributed to the spread of H7N9 human cases

in China. Guo *et al.*[31] proposed a SE-SEIS avian–human influenza model and discussed the method of controlling the spread of H7N9 avian influenza.

After the outbreaks of the avian influenza A H7N9 virus in 2013 in China, cross-sectional surveys show a high degree of awareness of human–avian influenza in both urban and rural populations, a higher level of proper hygienic practice among urban residents, and in particular a dramatically reduced number of visits to live markets in urban population. Taking into account the psychological effect toward avian influenza in the human population, Liu *et al.*[32] proposed a bird-to-human transmission model in which the avian population exhibits saturation effect and observed that the saturation effect within avian population and the psychological effect in human population cannot change the stability of equilibria but can affect the number of infected humans if the disease is prevalent. Taking into account the incubation periods of avian influenza A virus, Liu *et al.*[33] constructed a bird-to-human transmission model with different time delays in the avian and human populations combining the survival probability of the infective avian and human populations at the latent time, and obtained global asymptotical stability of equilibria of the system. Liu *et al.*[34] studied two avian influenza bird-to-human transmission models with different growth laws of the avian population, one with logistic growth and the other with Allee effect, obtained the threshold value for the prevalence of avian influenza, and investigated the local or global asymptotical stability of each equilibrium of these systems. Moreover, they gave necessary and sufficient conditions for the occurrence of periodic solutions in the avian influenza system with Allee effect of the avian population. Chen *et al.*[35] argued that the lack of understanding of the virus ecology in birds has resulted in the persistent circulating of H7N9 in China. Since the H7N9 virus does not induce clinical signs in poultry and is classified as a low pathogenicity avian influenza virus (Pantin-Jackwood *et al.*[11]), we believe that the population dynamics of avian (both wild and domestic) species contribute significantly to the persistence of the virus in avian as well as human populations.

In this paper, we use an avian–human epidemic model to describe the transmission dynamics of the avian influenza A H7N9 virus infection between wild and domestic birds and from birds to humans. We will estimate the parameters and use the model to simulate the open data for both infected cases and related deaths of the avian influenza A H7N9 virus infection reported by the Chinese Center for Disease Control and Prevention from March to May in 2013 and from November 2013 to May 2014.[6,7] Based on the modeling analysis, data fitting, and sensitivity analysis of the basic reproduction number, we will discuss the transmission dynamics of the avian influenza A H7N9 virus and explore plausible control measures.

2. The Transmission Model

In order to simulate the data on both the infected human cases and the related deaths, we construct an avian–human influenza epidemic model and assume that

all infected individuals are admitted to hospitals because of the high virulence of H7N9 to humans. The total avian population at time t, denoted by $N_a(t)$, is classified into four subclasses: susceptible wild birds $S_w(t)$, susceptible domestic birds $S_d(t)$, infectious wild birds $I_w(t)$, and infectious domestic birds $I_d(t)$, so that $N_a(t) = S_w(t) + S_d(t) + I_w(t) + I_d(t)$. Similarly, the total human population at time t, denoted by $N_h(t)$, is divided into susceptible $S_h(t)$, exposed $E_h(t)$, infected and hospitalized $I_h(t)$, and recovered $R_h(t)$ individuals. Thus, $N_h(t) = S_h(t) + E_h(t) + I_h(t) + R_h(t)$. We adopt a SI structure for both wild and domestic birds and use the classical SEIR model to describe the H7N9 transmission dynamics. The flowchart for the transmission of H7N9 virus between wild and domestic birds and from birds to humans is given in Fig. 1. The model takes the following form:

$$\begin{cases} \dfrac{dS_w}{dt} = \Pi_w - \dfrac{\beta_{ww} I_w + \beta_{wd} I_d}{N_a} S_w - \mu_w S_w, \\ \dfrac{dI_w}{dt} = \dfrac{\beta_{ww} I_w + \beta_{wd} I_d}{N_a} S_w - (\mu_w + \delta_a) I_w, \\ \dfrac{dS_d}{dt} = \Pi_d - \dfrac{\beta_{wd} I_w + \beta_{dd} I_d}{N_a} S_d - \mu_d S_d, \\ \dfrac{dI_d}{dt} = \dfrac{\beta_{wd} I_w + \beta_{dd} I_d}{N_a} S_d - (\mu_d + \delta_a) I_d, \\ \dfrac{dS_h}{dt} = \Pi_h - \dfrac{\beta_{wh} I_w + \beta_{dh} I_d}{N_a} S_h - \mu_h S_h, \\ \dfrac{dE_h}{dt} = \dfrac{\beta_{wh} I_w + \beta_{dh} I_d}{N_a} S_h - (\mu_h + k_h) E_h, \\ \dfrac{dI_h}{dt} = k_h E_h - (\mu_h + \delta_h + \gamma_h) I_h, \\ \dfrac{dR_h}{dt} = \gamma_h I_h - \mu_h R_h. \end{cases} \tag{2.1}$$

The biological meanings of all parameters are given in Table 1.

Note that there is a disease-free equilibrium given by $E_0 = (\Pi_w/\mu_w, 0, \Pi_d/\mu_d, 0, \Pi_h/\mu_h, 0, 0, 0,)$. Following the definition and computation procedure in Diekmann *et al.*[36] and van den Driessche and Watmough,[37] we have

$$FV^{-1} = \begin{pmatrix} \dfrac{\beta_{ww}\Pi_w\mu_d}{(\Pi_w\mu_d + \Pi_d\mu_w)(\mu_w + \delta_a)} & \dfrac{\beta_{wd}\Pi_w\mu_d}{(\Pi_w\mu_d + \Pi_d\mu_w)(\mu_d + \delta_a)} & 0 & 0 \\ \dfrac{\beta_{wd}\Pi_d\mu_w}{(\Pi_w\mu_d + \Pi_d\mu_w)(\mu_w + \delta_a)} & \dfrac{\beta_{dd}\Pi_d\mu_w}{(\Pi_w\mu_d + \Pi_d\mu_w)(\mu_d + \delta_a)} & 0 & 0 \\ \dfrac{\beta_{wh}\Pi_h\mu_d\mu_w}{\mu_h(\Pi_w\mu_d + \Pi_d\mu_w)(\mu_w + \delta_a)} & \dfrac{\beta_{dh}\Pi_h\mu_d\mu_w}{\mu_h(\Pi_w\mu_d + \Pi_d\mu_w)(\mu_d + \delta_a)} & 0 & 0 \\ 0 & 0 & \dfrac{k_h}{\mu_h + k_h} & 0 \end{pmatrix}.$$

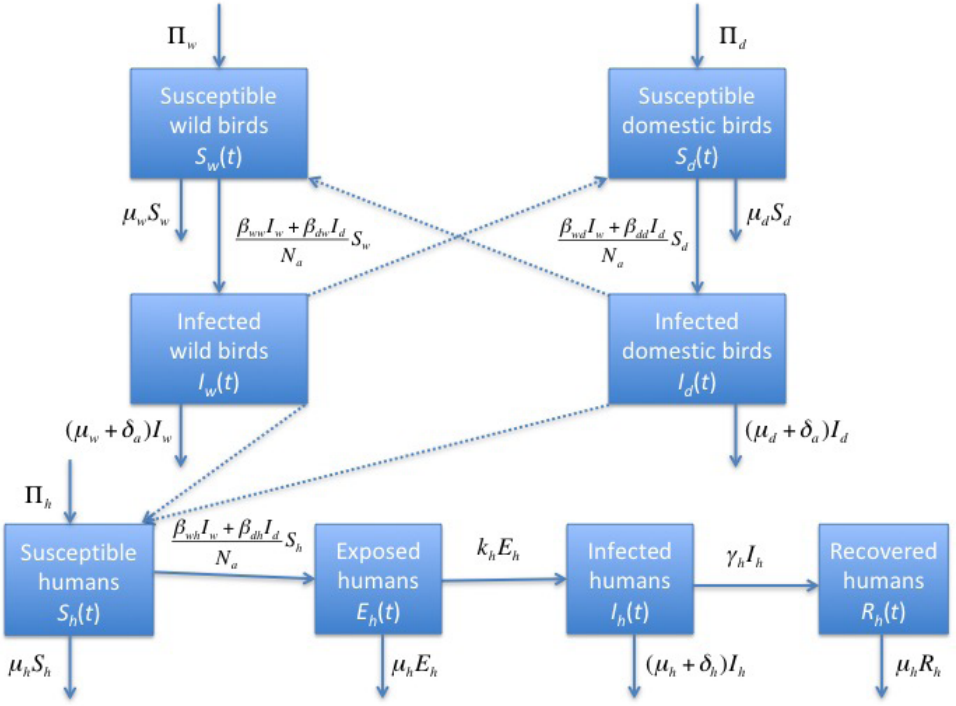


Fig. 1. Flowchart for the transmission of H7N9 virus between wild and domestic birds and from birds to humans.

The basic reproduction number $\mathcal{R}_0$ is defined to be the spectral radius (dominant eigenvalue) of the non-negative matrix FV^{-1}, denoted by $\rho(FV^{-1})$. Thus,

$$\mathcal{R}_0 = \frac{1}{2}(r_1 + r_2 + \sqrt{\Delta}), \tag{2.2}$$

where

$$r_1 = \frac{\beta_{dd}\Pi_d\mu_w}{(\Pi_w\mu_d + \Pi_d\mu_w)(\mu_d + \delta_a)},$$

$$r_2 = \frac{\beta_{ww}\Pi_w\mu_d}{(\Pi_w\mu_d + \Pi_d\mu_w)(\mu_w + \delta_a)},$$

$$\Delta = (r_1 + r_2)^2 - \frac{4\Pi_d\Pi_w(\beta_{ww}\beta_{dd} - \beta_{wd}\beta_{wd})\mu_w\mu_d}{(\Pi_w\mu_d + \Pi_d\mu_w)^2(\mu_w + \delta_a)(\mu_w + \delta_a)}.$$

By the results in van den Driessche and Watmough,[37] it follows that when $\mathcal{R}_0 < 1$, the disease-free equilibrium E_0 is stable, and when $\mathcal{R}_0 > 1$, the disease-free equilibrium E_0 becomes unstable and there exists a positive equilibrium. From the control point of view, the avian influenza A H7N9 virus infection can be controlled if $\mathcal{R}_0 < 1$ and it becomes endemic in the population if $\mathcal{R}_0 > 1$.

3. Results

3.1. *Data sources*

This study uses two sets of data. The first set of data of influenza A H7N9 are on hospitalized cases from March 27 to May 1 in 2013 reported by the Chinese Center for Disease Control and Prevention.[6] A total of 124 infected cases and 24 related deaths were reported in this period. The blue lines in Figs. 2 and 3 represent the

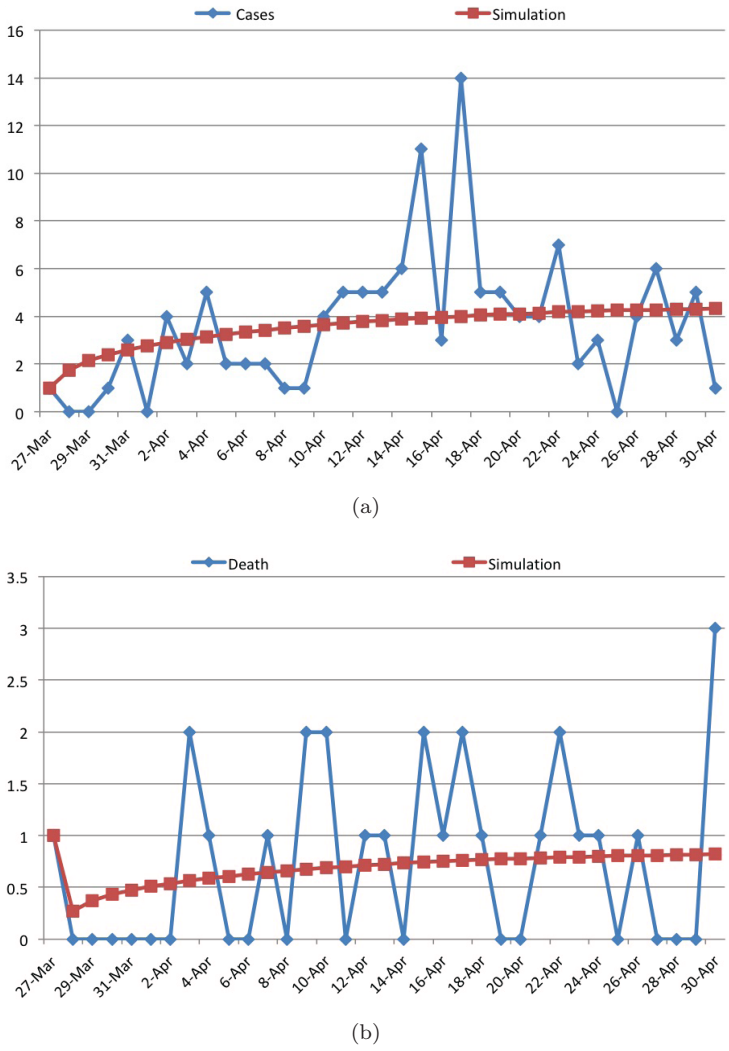
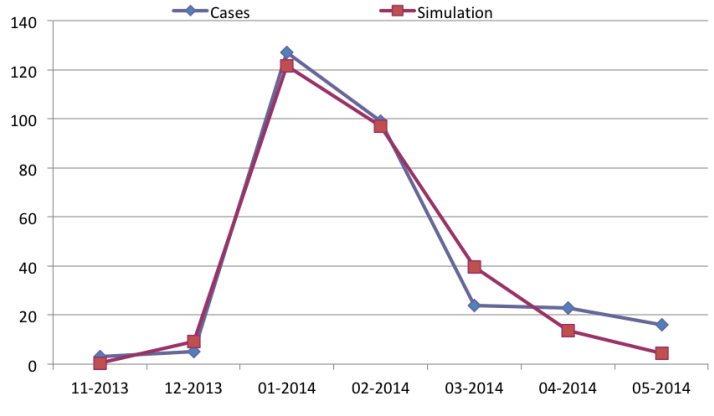
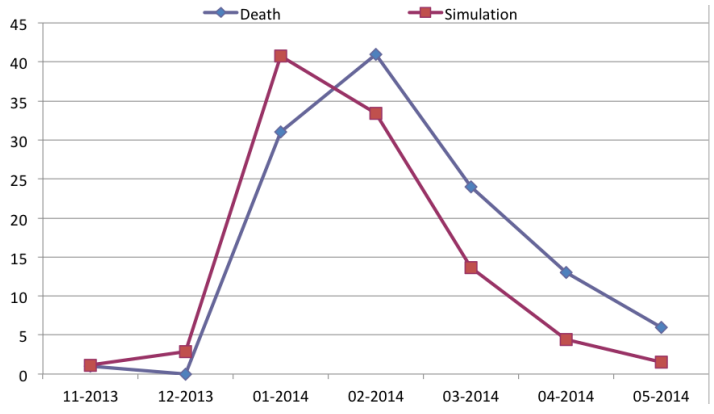


Fig. 2. (a) Comparison of the numerical simulations of the model on the daily number of infected human cases and the reported data on human cases infected by the avian influenza A H7N9 virus from March 27 to May 1, 2013. (b) Comparison of numerical simulations on the number of deaths from the model and the data of deaths caused by the avian influenza A H7N9 virus from March 27 to May 1, 2013. Parameter values are given in Table 1.



(a)



(b)

Fig. 3. (a) Comparison of the numerical simulations of the model on the monthly number of infected human cases and the reported data on human cases infected by the avian influenza A H7N9 virus from November 1, 2013 to May 31, 2014. (b) Comparison of numerical simulations on the number of deaths from the model and the data of deaths caused by the avian influenza A H7N9 virus from November 1, 2013 to May 31, 2014. Parameter values are given in Table 2.

infected human cases and related deaths from March 27 to May 1, 2013, respectively. The second set of data of influenza A H7N9 are on hospitalized cases from November 1, 2013, to May 31, 2014, reported by the National Health and Family Planning Commission of China.[7]

3.2. *Parameter estimation*

We fix the human death rate as $\mu_h = 1/(70 \times 365) \approx 3.91 \times 10^{-5}$ per day. Some initial values of model (2.1) are assumed to be $S_w(0) = S_d(0) = 10^7, S_h(0) = 10^8$, $E_h(0) = 10^3, I_h(0) = R_h(0) = 1$. The initial values $I_w(0)$ and $I_d(0)$ are regarded as parameters.

Table 1. Definition and estimation of parameters with 95% confidence interval for reported data between March 27, 2013 to May 1, 2013. MSS denotes the minimum sum of square.

Parameter	Definition	Source	Value (/day)	95% Interval
Π_w	Recruit rate of wild birds	MSS	134.7973	
Π_d	Recruit rate of domestic birds	MSS	233.3281	
β_{ww}	Transmission rate between wild birds	MSS	1.4003	[1.2936, 1.5113]
β_{dd}	Transmission rate between domestic birds	MSS	0.1745	[0.0001, 0.4281]
β_{wd}	Transmission rate between domestic and wild birds	MSS	0.1431	[1.3508, 1.5172]
μ_w	Natural death rate of wild birds	MSS	0.0011	[0.0003, 0.0027]
μ_d	Death rate of domestic birds	MSS	0.0043	[0.0027, 0.0206]
δ_a	Disease-related death rate of birds	MSS	1.2526	[1.2129, 1.2894]
Π_h	Recruit rate of humans	MSS	115.3615	
β_{wh}	Transmission rate between wild birds and humans	MSS	1.4742	[0.9337, 2.7615]
β_{dh}	Transmission rate between domestic birds and humans	MSS	1.3405	[0.5065, 3.3331]
μ_h	Natural death rate of humans	Fixed	3.91×10^{-5}	
κ_h	Rate of progression to infectious	MSS	0.0019	[0.0017, 0.0023]
γ_h	Recovery rate of humans	MSS	0.6955	[0.5251, 0.8178]
δ_h	Disease-related death rate of humans	MSS	0.1904	[0.0623, 0.3070]
$I_w(0)$	Initial value of infectious wild birds	MSS	7.6489	
$I_d(0)$	Initial value of infectious domestic birds	MSS	5.1075	

Table 2. Definition and estimation of parameters with 95% confidence interval for reported data between November 1, 2013 to May 31, 2014. MSS denotes the minimum sum of squares.

Parameter	Definition	Source	Value (/day)	95% Interval
Π_w	Recruit rate of wild birds	MSS	525.8767	
Π_d	Recruit rate of domestic birds	MSS	98.0552	
β_{ww}	Transmission rate between wild birds	MSS	0.8014	[0.8000,0.8041]
β_{dd}	Trans. rate between domestic birds	MSS	2.1573	[2.1551, 2.1615]
β_{wd}	Trans. rate between domestic and wild birds	MSS	2.396	[2.3951, 2.3977]
μ_w	Natural death rate of wild birds	MSS	0.0006	[0.00057, 0.00066]
μ_d	Death rate of domestic birds		0.0175	[0.01744, 0.01753]
δ_a	Disease-related death rate of birds	MSS	1.5543	[1.5535, 1.5547]
Π_h	Recruit rate of humans	MSS	957.0837	
β_{wh}	Trans. rate between wild birds and humans	MSS	0.0001	[0.000096, 0.000108]
β_{dh}	Trans. rate between domestic birds and humans	MSS	0.0001	[0.000092, 0.00011]
μ_h	Natural death rate of humans	Fixed	3.91×10^{-5}	
κ_h	Rate of progression to infectious	MSS	0.0353	[0.0331 , 0.0385]
γ_h	Recovery rate of humans	MSS	0.9999	[0.9284, 1.0404]
δ_h	Disease-related death rate of humans	MSS	0.3378	[0.2921, 0.3733]
$I_w(0)$	Initial value of infectious wild birds	MSS	0.001	
$I_d(0)$	Initial value of infectious domestic birds	MSS	0.001	

We estimate all unknown parameters by calculating the minimum sum of square (MSS):

$$\text{MSS} = \min \sum [(\text{Cases} - \text{Simulation})^2 + (\text{Death} - \text{Simulation})^2], \tag{3.1}$$

with MATLAB (The Mathworks, Inc.) tool *fminsearch*, which a is part of the optimization toolbox. All parameter values are shown in Tables 1 and 2.

For the parameters in Tables 1 and 2, we assume that the life span of domestic birds is at least one month and at most one year, so that $\mu_d \in [0.0027, 0.0206]$. We assume that the life span of wild birds is at least one year and at most 10 years, that is $\mu_w \in [0.0003, 0.0027]$. The optimal parameters are determined by calculating the Minimum Mean Square Error (MMSE):

$$\min \sum_{i=1}^{n} [(\text{Cases}_i - \text{Simulation}_i)^2/n + (\text{Death}_i - \text{Simulation}_i)^2/n],$$

where n is the number of data points ($n = 35$ for Table 1 and $n = 7$ for Table 2). Then, the Genetic Algorithm (GA) is used to solve the above problem, in order to do so, we give the intervals of parameters as follows:

$$\begin{aligned}
\Pi_w &\in [90, 999], & \Pi_d &\in [0.0001, 2.0], & \beta_{ww} &\in [0.0001, 2.0],\\
\beta_{dw} &\in [0.0001, 2.0], & \beta_{dd} &\in [0.0003, 0.0027], & \mu_w &\in [0.0027, 0.0334],\\
\mu_d &\in [0.0001, 2.0], & \delta_a &\in [90, 999], & \Pi_h &\in [0.0001, 2.0],\\
\beta_{wh} &\in [0.0001, 2.0], & \beta_{dh} &\in [0.0001, 2.0], & \kappa_h &\in [0.0001, 1.0],\\
\gamma_h &\in [0.0001, 1.0], & \delta_h &\in [0.0001, 1.0], & I_w(0) &\in [0.1, 10.0],\\
I_d(0) &\in [0.1, 10.0].
\end{aligned}$$

Population size of 50 and maximum gene of 5000 were chosen, and a crossover probability of 0.55 and mutation probability of 0.44 were chosen to maintain diversity in the population. The mean value and mean variance of 10 optimal MMSE are 5.8001 and 0.0497, respectively. If we regard them as normal distribution, the 95% confidence interval of the MMSE is $[5.4334, 6.1558]$. By the value of 6.1558, we can estimate the 95% confidence interval of the optimal parameter.

3.3. *Simulations*

Figures 2 and 3 represent the numerical simulations of the component $I_h(t)$ in model (2.1) against the number of infected human cases (Figs. 2(a) and 3(a)) and the number of accumulated deaths with the reported data (Figs. 2(b) and 3(b)) from March 27 to May 1, 2013, and from November 1, 2013 to May 31, 2014, respectively.

We would like to point out that the duration for the first dataset (from March 27 to May 1, 2013) was very short and daily, while the second dataset (from November

2013 to May 2014) was a complete set for a whole outbreak and monthly, so there are some differences between the two sets of parameter values.

3.4. *Estimate of the basic reproduction number*

By the expression (2.2) of the basic reproduction number and the optimal parameter values in Tables 1 and 2, we obtain that the value of the basic reproduction number is $\mathcal{R}_0 = 1.0489$ for the first outbreak from March to May in 2013 and $\mathcal{R}_0 = 0.54$ for the second outbreak from November 2013 to May 2014. Notice that the first wave was very short and the data set is daily while the second wave was for the whole outbreak but the data set is monthly, so there are differences between these two estimates. Moreover, once human flu cases were identified, some mandatory control policies such as closing the retail live-poultry markets were taken to control the outbreaks, so the real basic reproduction numbers would be much larger if such control measures were not taken.

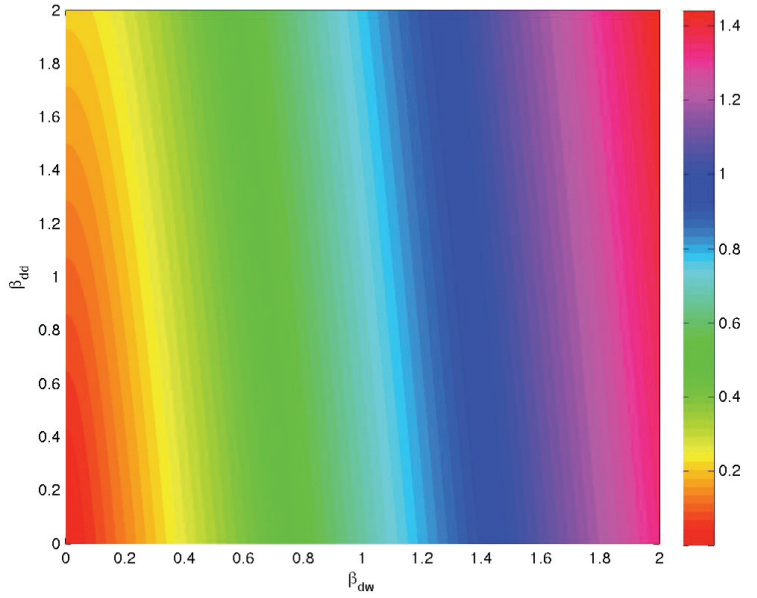
For the Zika outbreak in Barranquilla, Colombia in 2015, Towers *et al.*[38] used data to estimate the basic reproduction number, in particular the basic reproduction number during the initial increase in the infection. In this paper, we used the model to fit data and to estimate the parameters, then the basic reproduction numbers were estimated. Since various control measures had been taken during the outbreaks, what we obtained are in fact *controlled basic reproduction numbers*.

3.5. *Sensitivity analysis*

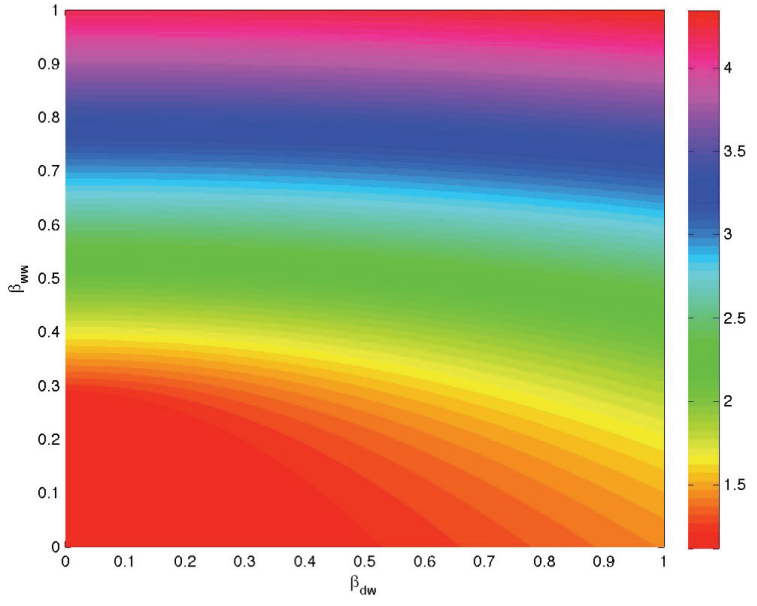
In this section, we carry out some sensitivity analysis of the basic reproduction number on some parameters. If we fix all parameters (as shown in Table 1) except β_{dd} and β_{wd}, the basic reproduction number $\mathcal{R}_0$ increases as either β_{dd} or β_{wd} increases (see Fig. 4(a)). Moreover, when β_{wd} is smaller than 1, $\mathcal{R}_0$ is smaller than 1 even if β_{dd} is as large as 2. Thus, the influence of β_{wd} on $\mathcal{R}_0$ is greater than that of β_{dd}. That is, once β_{dd} is not very large, the control of the cross-infection between wild birds and domestic birds is important. Choose $\beta_{dd} = 1$ in the rest sensitivity analysis. Figure 4(b) shows that $\mathcal{R}_0$ increases as either β_{ww} or β_{wd} increases. Moreover, to make sure that $\mathcal{R}_0 < 1$, we need to reduce β_{ww} and β_{wd} dramatically.

Note that our other study on rabies in China indicates that the initial host size does not influence the number of infected individuals,[39] similar simulations show that initial values do not influence the outcomes, so most initial values were assumed. The initial values of infected wild and domestic birds $I_w(0)$ and $I_d(0)$ were estimated as other parameters by using the datasets in Tables 1 and 2.

Figure 5(a) shows that $\mathcal{R}_0$ decreases as μ_d increases, and to have $\mathcal{R}_0 < 1$, we need to increase μ_d. From Fig. 5(b), it follows that $\mathcal{R}_0$ increases as Π_d decreases and Π_w increases. Therefore, to reduce $\mathcal{R}_0$, we need to (i) reduce the transmission in domestic birds β_{dd} and the transmission between wild birds and domestic birds β_{wd}; (ii) cull the domestic birds to increase the death rate μ_d.

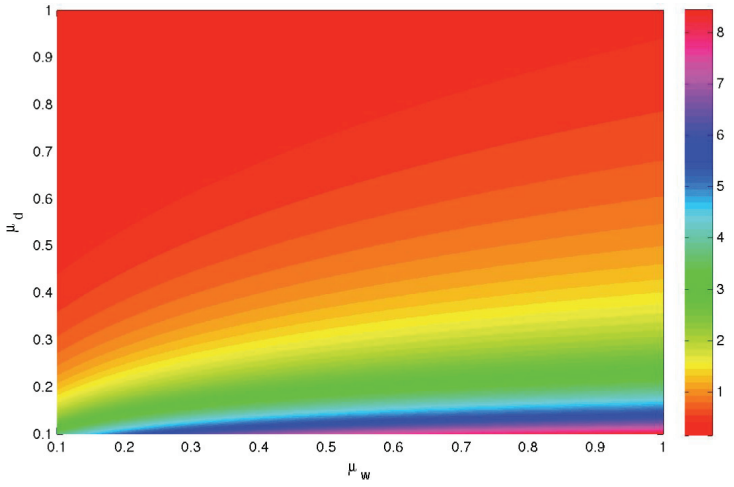


(a)

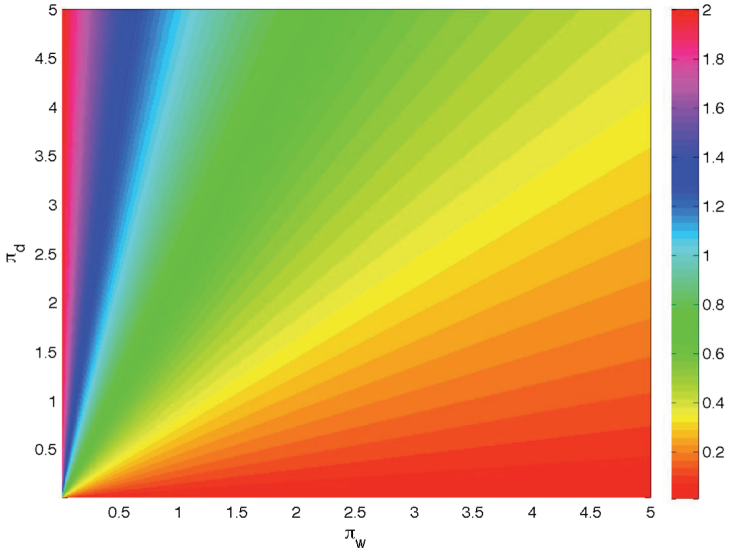


(b)

Fig. 4. The basic reproduction number $\mathcal{R}_0$ in terms of (a) the transmission rates between wild and domestic birds β_{wd} and between domestic birds β_{dd}; (b) the transmission rates between wild and domestic birds β_{wd} and between wild birds β_{ww}. The color bar reflects the value of $\mathcal{R}_0$.



(a)



(b)

Fig. 5. The basic reproduction number $\mathcal{R}_0$ in terms of (a) death rates of domestic birds μ_d and wild birds μ_d; (b) the recruitment rates of domestic birds Π_d and wild birds Π_w. The color bar reflects the value of $\mathcal{R}_0$.

3.6. *Strategies to control the transmission of H7N9*

In order to control the avian influenza, in the middle of April, retail live-poultry markets in the infected areas were closed and very large number of domestic birds were killed. This means that $\Pi_d = 0$ and $S_d(0) = I_d(0) = 0$ in model (2.1). This

strategy can decrease the number of infected human cases and has been proved to be very effective. There were very few new human infected cases at the beginning of June and the retail live-poultry markets were cautiously reopened. However, it might be impossible to eradicate the avian influenza among birds. The most important strategy is to reduce the infection rates β_{wh} and β_{dh} for birds and humans by reducing the contact with both the domestic birds and wild birds.

Based on the experience in 2013 and 2014 outbreaks and the sensitivity analysis in Figs. 4 and 5, we propose the following control measures for the future spread of H7N9: (i) reducing the transmission opportunities between wild birds and domestic birds; (ii) closing or monitoring the retail live-poultry markets in the infected areas; and (iii) culling the infected domestic birds in the epidemic regions.

4. Discussion

In this study, we used a mathematical model to study the transmission dynamics of the avian influenza A (H7N9) virus between wild and domestic birds and from birds to humans. The bird population was divided into four subclasses: susceptible wild birds, infected wild birds, susceptible domestic birds, and infected domestic birds. The human population was classified as susceptible, exposed, infected, and recovered individuals. The deterministic model is described by a set of ordinary differential equations and is applied to simulate the open data for numbers of the infected human cases and related deaths reported by the National Health and Family Planning Commission of China.[7] It is estimated that the basic reproduction number $\mathcal{R}_0 = 1.0489$ for the first outbreak from March to May in 2013 and $\mathcal{R}_0 = 0.54$ for the second outbreak during November 2013–May 2014, respectively.

Sensitivity analysis of $\mathcal{R}_0$ in terms of model parameters demonstrate that the control measures for the spread of avian influenza A (H7N9) virus include (i) reduction of the transmission in domestic birds β_{dd} and the transmission between wild birds and domestic birds β_{wd}; (ii) culling of domestic birds to increase the death rate μ_d; and (iii) reduction of the birth rate of domestic birds. Having learned from the experience on handling the SARS outbreak in 2003, the Chinese Ministry of Health reported the news about H7N9 infection and the data on human infected cases timely and openly, which was helpful to calm down the general public and prevent more infections. Our simulations indicate that closing of the retail live-poultry markets in the infected areas was a very effective measure, probably the most crucial strategy, in controlling further spread of the H7N9 virus to humans.

There are some differences between our model, results and conclusions and some of the above-mentioned studies. First, our model included both wild birds and domestic birds as well as human populations, while the model in Xiao *et al.*[26] did not include wild birds; the model in Hsieh *et al.*[27] included both wild and domestic birds but only a scalar equation was used to represent infected human populations; and the model in Zhang *et al.*[25] contained all components of our model but they focused more on the migratory birds. Second, all these models were used to fit data

only for the first outbreak from March to May in 2013, while we used our model to fit the data not only the first outbreak from March to May in 2013 but also the second outbreak from November 2013 to May 2014.

A key factor that the novel avian influenza A (H7N9) virus did not cause large scale outbreaks in humans is that it has not been able to spread from human to human though there were isolated reported cases.[40] The third outbreak of the avian influenza A (H7N9) virus from November 2014 to June 2015 caused 216 confirmed cases with 99 deaths, the fourth outbreak from November 2015 to July 2016 caused

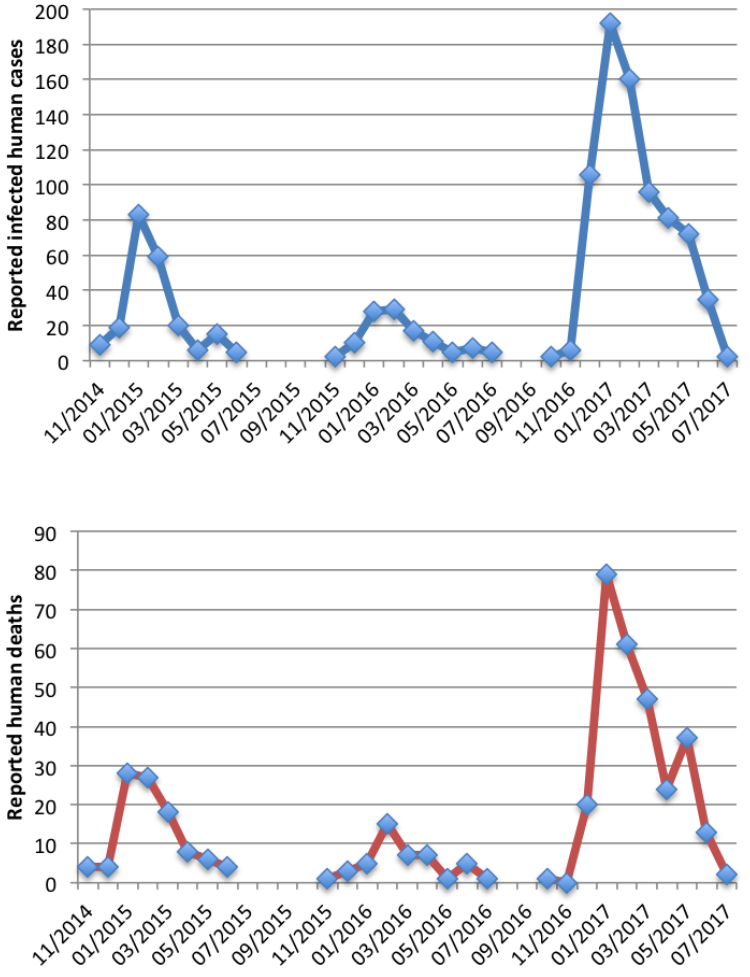


Fig. 6. There were 216 reported human H7N9 cases and 99 deaths from November 2014 to June 2015, 114 reported human H7N9 cases and 45 deaths from November 2015 to July 2016, and 750 reported human H7N9 cases and 283 deaths from October 2016 to July 2017, respectively.

114 confirmed cases with 45 deaths, and the fifth outbreak from November 2016 to July 2017 caused 750 confirmed cases with 283 deaths, respectively (see Fig. 6). We could estimate parameters for each of these outbreaks, use the model to fit the data, and estimate the basic reproduction numbers, the results will be similar to the second wave (from November 2013 to May 2014). This partially confirms our conclusions that H7N9 will persist in both wild and domestic avian species and cause outbreaks in humans again in the future. This also raises more concerns that the time of this outbreak (and the possible future outbreaks) overlaps with the seasonal influenza significantly and there is a greater potential for the avian influenza A (H7N9) virus to cross the species and cause pandemics. Moreover, recent studies show that H7N9 is transmissible in ferrets by respiratory droplet,[41] there were coinfections of H7N9/H9N2 in chickens,[42] and pigs have been shown to be infected with H7N9,[43] the avian influenza A (H7N9) virus has potential in two possible virus reassortments: the coinfection of the avian influenza A (H7N9) virus and the seasonal human influenza A (H3N2, H1N1) viruses[44,45] and the recombination of strains from birds (H7N9), pigs, and humans with pigs acting as "mixing vessels" for avian and human strains.[46,47] Monitoring and surveillance on birds (wild and domestic) and pigs should be enhanced for the avian influenza A (H7N9) virus evolution.

There are some limitations in this study. Firstly, though both wild and domestic birds are included in our model, there were very few data about both bird populations available. We had to use the MSS method to estimate a large number of parameters. Indentifiability analysis might be helpful in estimating parameters. Secondly, the first outbreak of H7N9 from March to May in 2013 was short and the data were very limited, so the simulations in Fig. 2 were not as good as those in Fig. 3 for the second outbreak from November 2013 to June 2014. For such a small set of data for the first outbreak, stochastic simulations might be more suitable. Third, compared to the population size in China, the numbers of infected H7N9 human cases and deaths were small, it would be interesting to study the long-term asymptotic behavior of solutions to the model and the influence of different initial population values. In particular, the updated data certainly indicate the seasonal occurrence of H7N9 infections, it will be interesting to determine if model (2.1) exhibits periodic solutions (see Liu *et al.*[34]) and to simulate the seasonal data.

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