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Assessing different interventions against Avian Influenza A (H7N9) infection by an epidemiological model

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ABSTRACT

This paper aims at evaluating the effectiveness of different intervention measures against the infection of avian influenza A (H7N9) by using an epidemiological model. The model formulates the intrinsic interactions of domestic poultry (DP), H7N9 virus and humans by ordinary differential equations and couples the essential roles of various interventions (including culling, vaccinating, screening, disinfecting, and reducing contact rate, etc). Qualitative analysis indicates that when the recruiting poultry is virus-free, there is a transmission threshold denoted by basic reproduction number which can determine the invasion of H7N9; and there is always a stable H7N9 endemic in case of persistent import of virus-carrying poultry, under which only complete vaccination or cutting off poultry-to-poultry/human contacts can stop H7N9 transmission. By performing numerical analysis of the model with biological background parameters, the intervention outcomes against H7N9 infection are further quantified. It is found that (1) reducing poultry-human/poultry interaction and per-contact infection probability, as well as culling DP, are highly effective in diminishing the infections of humans and DP; (2) the disease is prevented when larger than $(1 - 0.1\lambda_p)$ proportion of DP is vaccinated, where λ_p is the DP-to-DP transmission rate; (3) cleaning and disinfecting environment play limited role in reducing the risk of infection; and (4) screening imported poultry is quite important for stopping disease diffusion, but it works little when local epidemic is prevailing. Combing these measures with real situations would be necessary for controlling H7N9 epidemics and reaching one health purpose.

1. Introduction

Since the first report of human infections with avian influenza A (H7N9) virus (referred to as H7N9 hereafter) in eastern China in March 2013, fives waves of H7N9 infection have occurred in China by February 2021, recording a total of 1568 human infections with 616 deaths [1]. This novel virus is not only posing potential threats to public health, but also causing huge economic losses to poultry industry. How to effectively control its transmission and minimize economic loss is an urgent scientific issue to be tackled.

As the detection of H7N9 virus and the occurrence of human infection with H7N9, many intervention measures were attempted and implemented [2–6]. These interventions mainly target the interaction of H7N9 virus, poultry and human (which is the key dynamics of H7N9 transmission), encompassing culling, screening and vaccinating domestic poultry (DP), cleaning and disinfecting environment, as well as reducing poultry-human/poultry contacts (see Fig. 1). Their control effects were also evaluated by many researchers [2–10]. According to recent studies, the closure of live poultry markets (LPMs) has been shown to be highly effective in reducing the positive rates in the environment and the incidence of human infections [2,3,7–11]. Yet it seems that many other interventions (e.g., environmental disinfection, screening and culling of poultry) exhibit different control effects, with geographic heterogeneity [2,11,12]. The primary analysis technologies of existing studies are epidemiological investigations and statistical models, by comparing the outcomes before and after the implementation of certain intervention method against H7N9 [2–6,12,13]. Further mechanism analysis on various interventions as a whole may help reasonably to compare their impacts and to find optimal strategies.

To this end, this paper attends to establish a new epidemiological model for comprehensively evaluating the combined intervention effects. The model takes into account the intrinsic patterns of H7N9 virus transmission among DP and humans, in which various intervention methods (including culling, vaccinating, screening DP, reducing

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contact, cleaning and disinfecting the environment) are taken into account by modifying the model parameters based on their practical effects. The analysis mode is divided into two situations: with or without constant input of infected poultry. The transmission dynamics are further investigated, including the expression of epidemic threshold and the conditions for disease prevails or not. Combining with sensitivity analysis and numerical simulations, comprehensive and systematic comparisons of intervention results are carried out, in which scientific control strategies against H7N9 are provided.

2. Model formulation

For evaluating the effectiveness of different interventions against H7N9, many techniques were developed, such as Bayesian principle [3,7], ordinary differential equation (ODEs) [2,4,5], sequence alignment and phylogenetic approach [8,9], epidemiological surveys [10]. Inspired by recent compartmental modeling framework [2–6,12,13], this section proposes a new dynamical system to simulate H7N9 transmission process. Based on the compartmental principle and H7N9 epidemiology, the following assumptions are proposed for model formulation.

(1) The total number of DP, humans and viral loads in surrounding are denoted by N_p, N_h and V, respectively. DP population is classified into two subclasses: the susceptible and the infected, denoted by S_p and I_p, respectively. Human population is classified into four subclasses: the susceptible, the exposed, the infected and the recovered, denoted by S_h, E_h, I_h and R_h, respectively. Human individuals can be infected through two paths: direct contact with infected poultry, or indirect infection through exposure to the environment contaminated by I_p [12,14].

(2) The specific transmission process is as follows. Susceptible poultry and people are infected at rates λ_p and λ_h by contacting infectious poultry, and are also infected at rates β_p and β_h by exposing to H7N9 virus in surrounding, respectively. Here the transmission rates (λ_p and λ_h) equal the product of contact rate and per-contact probability of infection. If infected, poultry becomes infectious immediately until death, and human individual falls ill after going through an incubation period of $1/\omega$ and finally recovers or dies. Here H7N9 virus in surrounding is released by infected poultry at rate r and then is removed at rate d_v.

(3) The intervention measures are taken into account in the following ways. First, culling will directly reduce the numbers of susceptible and infected DP at rate α_p. Second, vaccination will change parts of susceptible DP into immune DP, that is, the total susceptible poultry S_p becomes $(1-\eta)S_p$ due to vaccination. Third, screening will reduce the importation of infected DP. If without screening, the proportion q of imported DP carries virus. Fourth, LPM closure and quarantine will cut down DP-DP/human contacts and reduce infection probability, hence leading to small values of transmission rates λ_p and λ_h. Fifth, cleaning and disinfecting the environment will accelerate the elimination of virus in surrounding, which is inflected by increasing the removal rate d_v. The implementation of these interventions correspond to the changes of related parameters.

Accordingly, the transfer flowchart of H7N9 transmission and its intervention project are outlined in Fig. 1, The corresponding dynamical model with the coupling of interventions is described by the following ODEs.

$$\begin{cases} S_{p'} = A(1-q) - \lambda_p \dfrac{I_p}{N_p}(1-\eta)S_p - \beta_p(1-\eta)S_pV - (d_p+\alpha_p)S_p, \\ I_{p'} = qA + \lambda_p \dfrac{I_p}{N_p}(1-\eta)S_p + \beta_p(1-\eta)S_pV - (d_p+\alpha_p)I_p, \\ V' = rI_p - d_vV, \\ S_{h'} = B - \lambda_h \dfrac{I_p}{N_p}S_h - \beta_hS_hV - d_hS_h, \\ E_{h'} = \lambda_h \dfrac{I_p}{N_p}S_h + \beta_hS_hV - d_hE_h - \omega E_h, \\ I_{h'} = \omega E_h - (d_h+\alpha_h)I_h - \delta I_h, \\ R_{h'} = \delta I_h - d_hR_h. \end{cases} \tag{1}$$

The detailed interpretations of the variables and parameters are shown in Table 1. All variables and parameters are set to be nonnegative due to biological significance. Direct computation yields that the

Table 1
Description of model parameters, in which time unit is week or per week.

Parameter	Definition	Value	Source
A	Recruitment rate of DP	Variable	
B	Recruitment rate of humans	Variable	
q	Proportion of imported DP carrying virus	Variable	
λ_p	Transmission rate from I_p to S_p	Variable	
λ_h	Transmission rate from I_p to S_h	Variable	
β_p	Transmission rate from V to S_p	Variable	
β_h	Transmission rate from V to S_h	Variable	
α_p	Culling rate of DP	Variable	
η	Vaccinated proportion of DP	Variable	
d_p	Slaughter rate of DP	1/8	[13]
α_h	Disease-related death rate of I_h	0.36	[13]
d_v	Natural mortality rate of virus	0.7	[5]
ω	Reciprocal of the incubation period	7/3.3	[13]
δ	Recovery rate of I_h	2	[12]
r	Discharging concentration of H7N9 virus by I_p	4.5	[12]
d_h	Natural death rate of human	$1/(77\times 52)$	

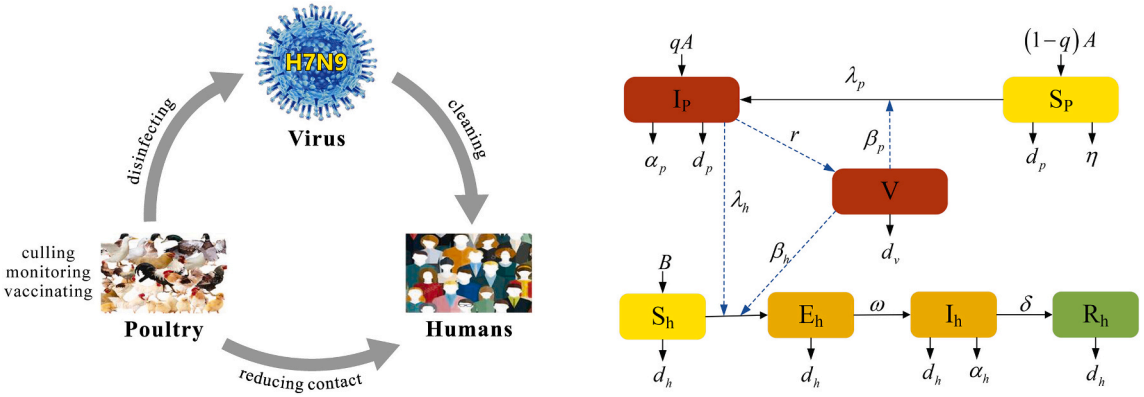

Fig. 1. Intervention strategies towards domestic poultry (DP), H7N9 virus and human beings during H7N9 transmission (left), and the flowchart of H7N9 transmission among DP and from DP to human beings (right).

solutions of model (1) always stay in its attractive region:

$$\Omega = \left\{ \left(S_p, I_p, V, S_h, E_h, I_h, R_h\right) \in R_+^7 \middle| 0 \le S_p, I_p \le \frac{A}{d_p+\alpha_p}; 0 \le V \le \frac{Ar}{d_v\left(d_p+\alpha_p\right)}, 0 \le S_h, E_h, I_h, R_h \le \frac{B}{d_h} \right\}$$

(1) has a unique positive equilibrium $E_1 = (S_p^1, I_p^1, V^1, S_h^1, E_h^1, I_h^1, R_h^1)$, where

Theorem 3.1. (i) When $R_0 < 1$, the disease-free equilibrium E_0 is locally asymptotically stable; (ii) When $R_0 > 1$, the positive equilibrium

$$I_p^1 = \frac{A(R_0-1)}{\left(d_p+\alpha_p\right)R_0}, S_p^1 = N_p^1 - I_p^1, V^1 = \frac{rI_p^1}{d_v}, S_h^1 = \frac{BN_p^1}{\lambda_h I_p^1 + N_p^1\left(\beta_h V^1 + d_h\right)}, E_h^1 = \frac{\lambda_h I_p^1 S_h^1 + \beta_h S_h^1 V^1 N_p^1}{(d_h+\omega)N_p^1},$$
$$R_h^1 = \frac{\delta I_h^1}{d_h}, I_h^1 = \frac{B\omega\left[R_0 - 1 + \sqrt{(R_0-1)^2}\right]\left(d_v\lambda_h\left(d_p+\alpha_p\right) + A\beta_h r\right)}{(d_h+\alpha_h+\delta)(d_h+\omega)\left\{\left[R_0 - 1 + \sqrt{(R_0-1)^2}\right]\left(d_v\lambda_h\left(d_p+\alpha_p\right) + A\beta_h r\right) + 2d_v d_h\left(d_p+\alpha_p\right)R_0\right\}}. \quad (3)$$

In the following, the effectiveness of the interventions are evaluated systematically by digging the dynamics of the model (1) in mathematical and numerical approaches.

3. Mathematical dynamics

Since the proposed model (1) is a high-dimensional nonlinear ODE system, it is impossible to obtain its analytical solutions. This section will analyze the model dynamics mathematically, in which (1) the basic reproduction number is calculated, which is a critical measure of the transmissibility, acting as an epidemic threshold in epidemiology; and (2) the stability of the model equilibria is verified, for showing the long-term evolutions of the model solutions and the robustness of model solutions to initial condition. By doing so, one can formulate the regulation mechanism of interventions in disease transmission, and acquire the conditions under which the disease will die out or persist.

In view of that the import and export of DP would potentially cause local outbreaks and spatiotemporal spread of H7N9, just like the large diffusion situation of H7N9 infection in China in 2017, the following analysis is divided into two cases: with or without the input of infected poultry, corresponding to $q = 0$ or $q \neq 0$. Moreover, note that humans do not involve the circulation of H7N9 virus, and the last fourth equations are linear ODEs for given variables (S_p, I_p, V). The following mathematical analysis is mainly focused on the first three equations of system (1).

3.1. $q = 0$ (Import of virus-free poultry)

It is clear that system (1) always has a disease-free equilibrium $E_0 = (N_p^1, 0, B/d_h, 0, 0, 0,)$, where $N_p^1 = A/(d_p+\alpha_p)$. Decomposing this system by next-generation matrix [15] and linearizing it at the disease-free equilibrium E_0 gives the basic reproduction number as:

$$R_0 = \frac{\lambda_p(1-\eta)}{d_p+\alpha_p} + \frac{A\beta_p r(1-\eta)}{\left(d_p+\alpha_p\right)^2 d_v}. \quad (2)$$

These two parts of R_0 is contributed separately by poultry and environmental virus. Direct computation yields that when $R_0 > 1$ system

Proof. (i)The characteristic polynomial of the Jacobian matrix at E_0 is $(\lambda + d_p + \alpha_p)f_0(\lambda) = 0$, where

$$f_0(\lambda) = \lambda^2 + \left[d_v + \left(d_p + \alpha_p - \lambda_p(1-\eta)\right)\right]\lambda + d_v\left(d_p + \alpha_p - \lambda_p(1-\eta)\right) - \frac{A\beta_p r(1-\eta)}{d_p+\alpha_p}.$$

Since $\Delta = [d_v - (d_p + \alpha_p - \lambda_p(1-\eta))]^2 + 4A\beta_p r(1-\eta)/(d_p+\alpha_p) > 0$, the eigenvalues of $f_0(\lambda)$ are all real numbers, that is, $\lambda_i = 0.5\left(d_v + d_p + \alpha_p - \lambda_p(1-\eta)\right) \pm 0.5\sqrt{\Delta}$ for $i = 2, 3$. It follows from $R_0 < 1$ that $-\left(d_v + \left(d_p + \alpha_p - \lambda_p(1-\eta)\right)\right) + \sqrt{\Delta} < 0$. Hence, when $R_0 < 1$, all eigenvalues have negative real parts, yielding that the disease-free equilibrium E_0 is locally asymptotically stable.

(ii)The characteristic polynomial of Jocabian matrix at E_1 is $(\lambda + d_p + \alpha_p)(\lambda^2 + a_1\lambda + a_2) = 0$, where

$$a_1 = d_v + \frac{\lambda_p(1-\eta)(R_0-1)}{R_0} + \frac{A\beta_p r(1-\eta)}{d_v\left(d_p+\alpha_p\right)}, a_2 = \frac{\lambda_p d_v(1-\eta)(R_0-1)}{R_0} + \frac{A\beta_p r(1-\eta)(R_0-1)}{\left(d_p+\alpha_p\right)}.$$

It follows from $R_0 > 1$ that $a_1 > 0$, $a_2 > 0$ and all eigenvalues have negative real parts, which completers the proof.

Theorem 3.2. (i) When $R_0 < 1$, the disease-free equilibrium E_0 is globally asymptotically stable; (ii) When $R_0 > 1$, the positive equilibrium E_1 is globally asymptotically stable.

Proof. (i) Substituting $S_p = N_p^1 - I_p$ into the first three equations of model (1), it is obtained its limited system:

$$\begin{cases} I_{p'} = \left[\lambda_p\frac{I_p}{N_p^1}(1-\eta) + \beta_p V(1-\eta)\right]\left(N_p^1 - I_p\right) - \left(d_p+\alpha_p\right)I_p, \\ V' = rI_p - Vd_v. \end{cases} \quad (4)$$

Define a Lyapunov function as $L(t) = (d_p+\alpha_p)I_p(t)/(A\beta_p) + (1-\eta)V(t)/d_v$. Differentiating L along the solutions of (4) yields

$$L'(t) = \frac{d_p+\alpha_p}{A\beta_p}\left(\lambda_p\frac{I_p}{N_p^1}(1-\eta)\left(N_p^1 - I_p\right) + \beta_p V(1-\eta)\left(N_p^1 - I_p\right) - \left(d_p+\alpha_p\right)I_p\right) + \frac{(1-\eta)}{d_v}\left(rI_p - Vd_v\right),$$
$$< (R_0-1)\frac{\left(d_p+\alpha_p\right)^2 I_p}{A\beta_p}.$$

If $R_0 < 1$, then $L'(t) < 0$. According to LaSalle's invariance principle, E_0 is globally asymptotically stable.

(ii) When $R_0 > 1$, system (1) has a unique positive equilibrium E_1. Given a Dulac function $D(I_p, V) = 1/I_p$, let the right-hand sides of system (4) to be P and Q. It follows that

$$\frac{\partial(DP)}{\partial I_p} + \frac{\partial(DQ)}{\partial V} = -\frac{\lambda_p(1-\eta)}{N_p^1} - \frac{\beta_p(1-\eta)N_p^1 V}{I_p^2} - \frac{d_v}{I_p} < 0.$$

Hence, the Bendixson-Dulac theorem shows that there is no closed orbit, yielding that the positive equilibrium E_1 is globally asymptotically stable when $R_0 > 1$.

3.2. $q \neq 0$ (Import of virus-carrying poultry)

It is first clarified the existence of equilibrium in (1). Let the right-hand side of the equations in (1) to be zero and combine them into one expression. It is obtained a unique positive solution of I_p and I_h, that is

$$I_p^* = \frac{(R_0 - 1) + \sqrt{(R_0 - 1)^2 + 4qR_0}}{2(d_p + \alpha_p)R_0/A},$$

$$I_h^* = \frac{B\omega\left[R_0 - 1 + \sqrt{(R_0 - 1)^2 + 4qR_0}\right]\left(d_v\lambda_h(d_p + \alpha_p) + A\beta_h r\right)}{(d_h + \alpha_h + \delta)(d_h + \omega)\left\{\left[R_0 - 1 + \sqrt{(R_0 - 1)^2 + 4qR_0}\right]\left(d_v\lambda_h(d_p + \alpha_p) + A\beta_h r\right) + 2d_v d_h(d_p + \alpha_p)R_0\right\}}.$$

Direct calculation yields that system (1) has a unique equilibrium $E^* = (S_p^*, I_p^*, V^*, S_h^*, E_h^*, I_h^*, R_h^*)$, corresponding to the endemic state. There is no disease-free equilibrium of system (1) in case of persistent import of poultry carrying virus. The specific expressions of E^* is similar to the formulas in (3), which only needs to replacing I_p^1 and I_h^1 by I_p^* and I_h^*, respectively. The long-term evolution dynamics of system (1) is verified in the following.

Theorem 3.3. When $q \neq 0$, the endemic equilibrium point E^* is globally asymptotically stable.

Proof. The characteristic polynomial of the system (1) at the endemic equilibrium E^* is

$$H(\lambda) = (\lambda + d_h)(\lambda + d_h + \alpha_h + \delta)(\lambda + d_h + w)\left(\lambda + \lambda_h I_p^* \Big/ N_p^* + \beta_h V^* + d_h\right)$$
$$(\lambda + d_p + \alpha_p)F(\lambda) = 0,$$

where $F(\lambda) = \lambda^2 + a_1\lambda + a_2 = 0$, with

$$a_1 = (d_p + \alpha_p) + d_v + \beta_p(1-\eta)V^* + \lambda_p(1-\eta)\left(I_p^* - S_p^*\right)\Big/ N_p^*,$$
$$a_2 = \lambda_p d_v(1-\eta)\left(I_p^* - S_p^*\right)\Big/ N_p^* + \beta_p d_v(1-\eta)V^* + (\alpha_p + d_p)d_v - \beta_p r(1-\eta)S_p^*.$$

It is obvious that the first five eigenvalues of $H(\lambda)$ is negative. The other two eigenvalues are determined by $F(\lambda)$. Since $\Delta_1 = a_1 > 0$ and $\Delta_2 = a_1 a_2 > 0$, it follows from the Routh-Hurwitz conditions that the endemic equilibrium E^* is locally asymptotically stable.

Moreover, it is chosen Dulac function as $B(I_p, V) = 1/I_p$ for the the limited system of the first three equations of model (1). Direct calculation derives that

$$\frac{\partial}{\partial I_p}\left(\frac{I_p'}{I_p}\right) + \frac{\partial}{\partial V}\left(\frac{V'}{I_p}\right) = -\frac{qA}{I_p^2} - \frac{\beta_p(1-\eta)N_p V}{I_p^2} - \frac{\lambda_p(1-\eta)}{N_p} - \frac{d_v}{I_p} < 0.$$

It follows from the Bendixson-Dulac theorem that there is no closed orbit for this two-dimensional system, which concludes this theorem.

4. Quantifying assessment of interventions

To evaluating the effectiveness of different interventions, some assumptions about the model parameters are made as follows. (1) The stable number of human population is set to be 1 million, all of which are susceptible at initial time, i.e., $N_h = S_h(0) = 1{,}000{,}000$. (2) The population ratio of humans and DP is based on the data in Guangdong Province, China, since it is regarded as a high-risk area for avian influenza A (H7N9) transmission and it accounts for about 10% of DP industry [14]. Accordingly, this ratio is $\xi = 6.16$ by week, and the number of DP is $N_p = N_h/\xi = 162{,}243$. (3) The average life expectancy is 77 years old in Guangdong, hence the natural mortality rate of human is $d_h = 1/(77 \times 52) = 0.00025$, and the weekly recruitment rate of humans is $B =$

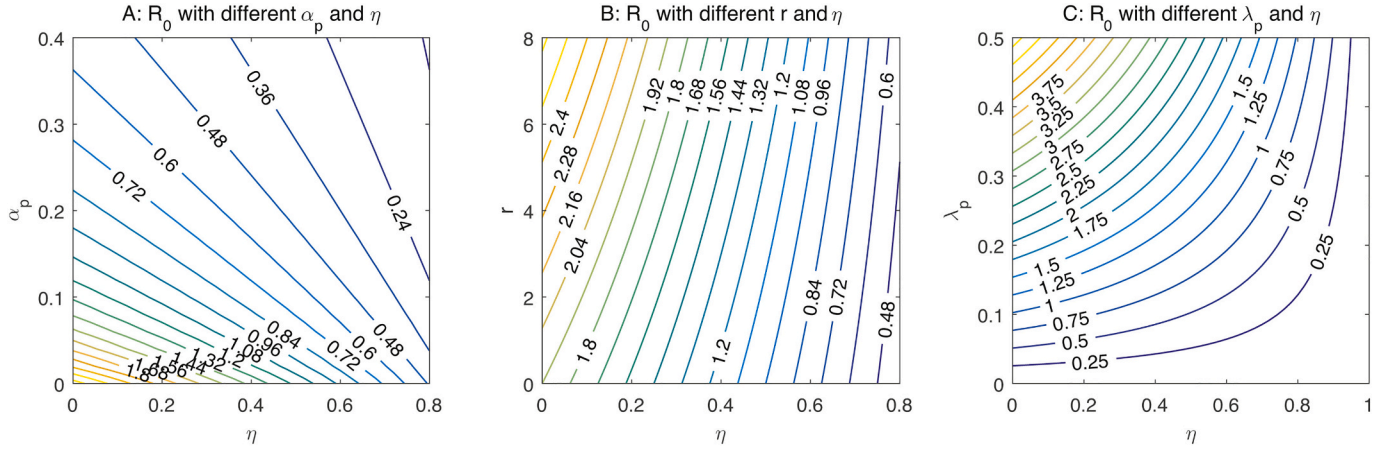

Fig. 2. Impacts of culling (α_p), vaccination (η), viral loads in surrounding (r) and transmission rate (λ_p) on the basic reproduction number R_0.

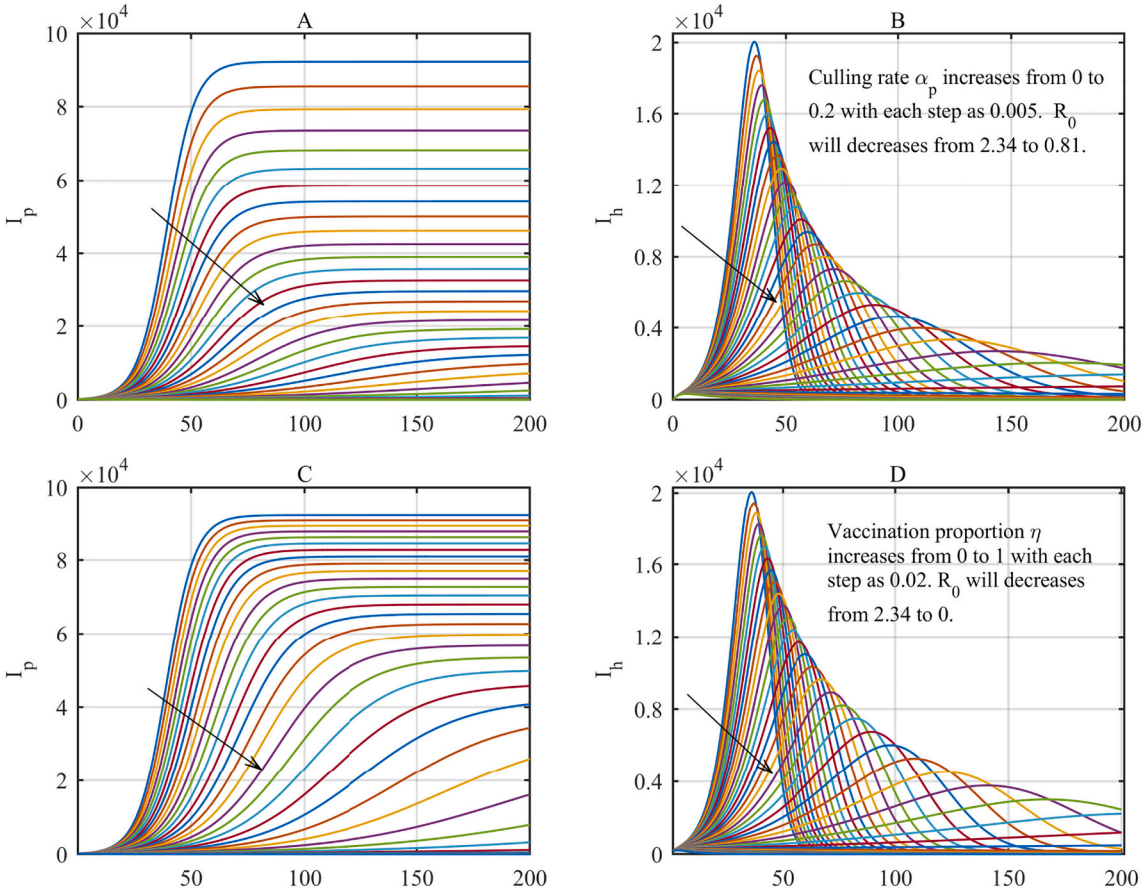

Fig. 3. Impacts of culling poultry (A and B) and vaccination poultry (C and D) on the emergence of H7N9 infections.

$N_h d_h = 250$. (4) The feeding period of DP is 8 weeks, hence the the weekly recruitment rate of DP is $A = N_p d_p = 20{,}280$. (5) Taking into account that the ratio of direct and indirect infection with avian influenza virus is 82/18 [16], it is assumed that $\beta_p = 18\lambda_p d_v/82rN_p$ and $\beta_h = 18\lambda_h d_v/82rN_p$. (6) If not specified, the baseline values of some parameters are set to be $\alpha_p = q = \eta = 0$, $\lambda_p = \lambda_h = 0.24$. The descriptions of parameters can be found in Table 1. Based on the above information, the intervention outcomes are quantified by simulating model (1) with Matlab software.

Fig. 2 shows the impacts of various interventions on the basic reproduction number R_0. It is observed that R_0 decreases rapidly in case of increasing culling rate α_p and vaccination proportion η, as well as reducing the transmission rate λ_p. For reducing R_0 less than 1, either one of the following conditions is met: (1) over 57% DP has to be vaccinated if without culling; (2) when the culling rate α_p increases from 0.05 to 0.1, vaccinated proportion η can decrease from 41% to 26%; (3) when the transmission rate increase from 0.2 to 0.3, vaccinated proportion η should increase from 48% to 67%; (4) no vaccination is needed if the culling rate α_p is larger than 0.17 or the transmission rate λ_p is less than 0.1. However, it seems that the discharging rate of H7N9 virus in surrounding r plays a minor in modifying R_0. When r increases from 0 to 6, R_0 increases from 1.92 to 2.47 if without vaccination, or R_0 increases from 1.58 to 1.98 if the vaccinated proportion is $\eta = 0.2$.

Fig. 3 shows the effectiveness of culling and vaccination on H7N9 transmission. It is observed that both interventions can mitigate infection promptly and efficiently, in which increasing culling rate or vaccination proportion can largely reduce infection number but also prolong epidemic period at low incidence rate. Numerical simulations show that when culling 1%, 2% and 3% DP in each week, the total number of human infections could decrease by 3.9%, 5.0% and 7.4%, respectively, compared to the situation without intervention. The reduction rates for the total number of DP infections would be 8.6%, 17.1% and 25.5%, respectively. In case of vaccinating 10%, 20% and 30% DP, the total number of human infections and DP infections would be reduced by 5.0%, 16.9%, 52.0%, and 12.3%, 27.5%, 46.8%, respectively. Particularly, when the culling rate of DP satisfies $\alpha_p > 0.14$ or the vaccination proportion of DP satisfies $\eta > 57\%$, then $R_0 < 1$ and the disease will eventually die out.

Fig. 4 shows the effectiveness of screening and cleaning/disinfection. It is found that reducing the recruitment rate of infected DP and accelerating the elimination of virus in environment can alleviate infection burden to some extent. Such effectiveness is more prominent when the corresponding parameters increase from small values, but the control effect is gradually stable as these parameters keep increase. The simulation results show that no infection occurs when $q = 0$. In contrast, when q increases tinily from 0.02 to 0.06, the total number of human infections and DP infections would increase by 1.6% and 8.4%, respectively. When q vastly increases from 0.8 to 1, the infections just increase by 0.2%, and 7.0%, respectively. The simulation results also show that when d_v dropped slightly from 0.3 to 0.1, the total number of human infections and DP infections would increase by 14.4% and 23.3%, respectively. When d_v greatly reduces from 6 to 4, the infections just increase by 0.7% and 1.9%, respectively. For different values of q and d_v, it always has $R_0 > 1$, along with high risk of H7N9 transmission.

Fig. 5 shows the infection process with different transmission rates. It is found that reducing the per-contact probability of infection, or the interactions among poultry, between poultry and humans could dramatically inhibit the incidences. When the transmission rates λ_p and λ_h increase from 0.11 to 0.13, the total number of human infections and DP infections would quickly increase by 5.46 times and 15.8 times, respectively. When $\lambda_h > 0.1$ and $\lambda_p = 0.24$, nearly all people would be infected, but with no change in DP infections. Particularly, when DP-to-

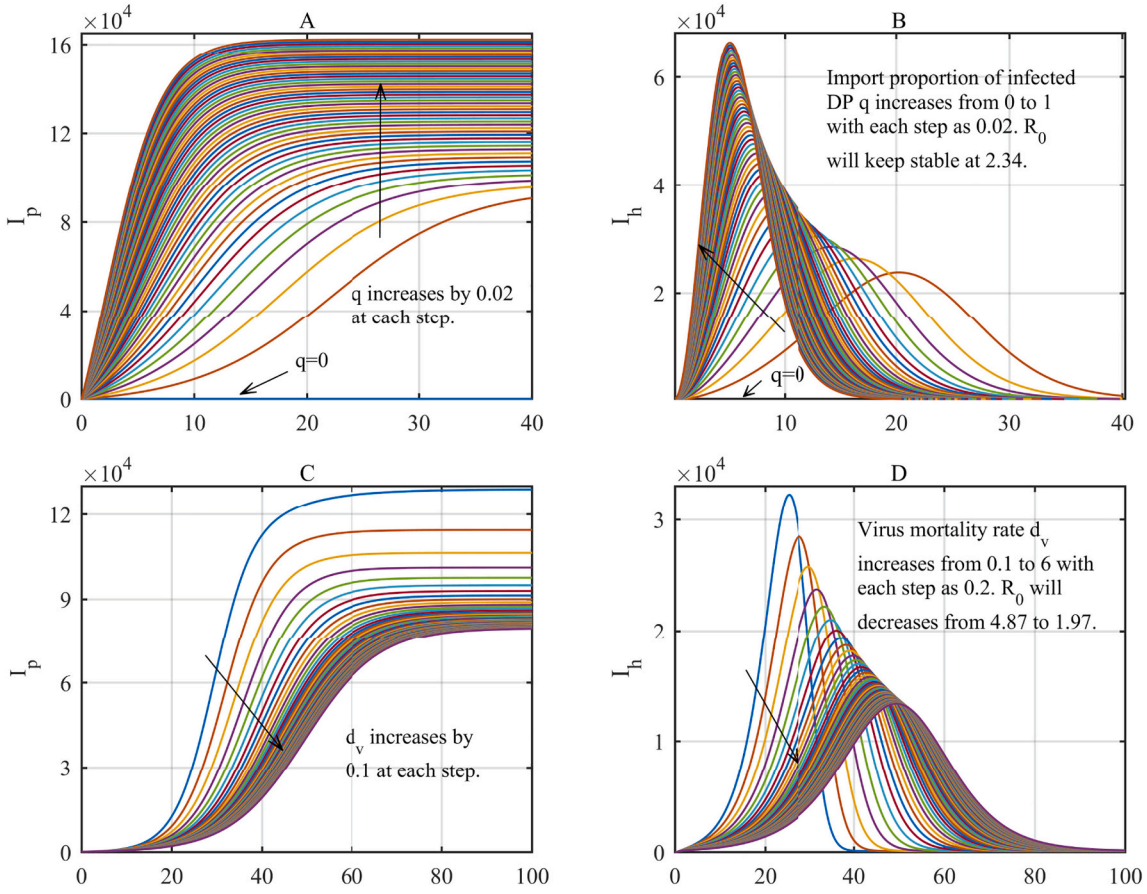

Fig. 4. Impacts of the virus-carrying rate of imported DP (A and B) and mortality rate of environmental virus (C and D) on the emergence of H7N9 infections.

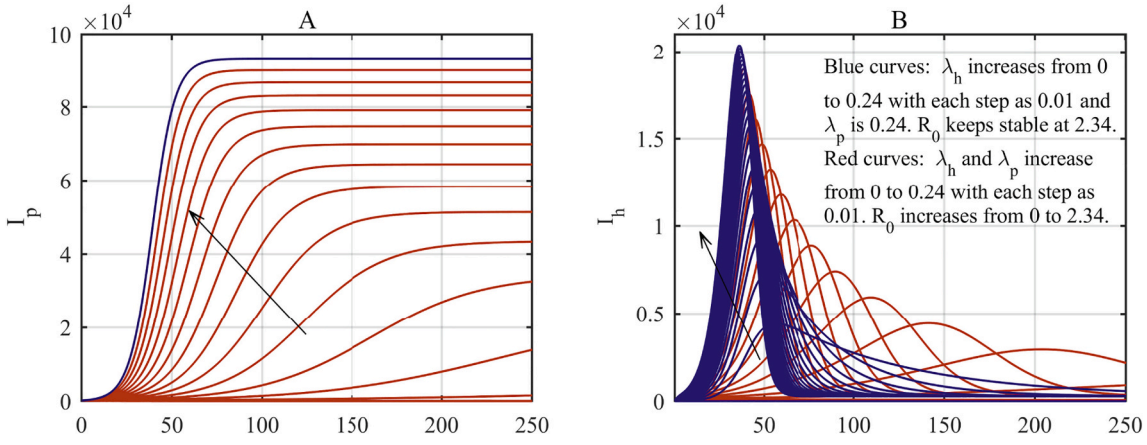

Fig. 5. Impacts of modifying the transmission rates among poultry (λ_p), between poultry and humans (λ_p) on the emergence of H7N9 infections.

DP transmission rate satisfies $\lambda_p < 0.1$, then $R_0 < 1$ and hence the incidence rate will slow down and the disease will eventually die out.

Fig. 6 shows the sensitivity indices of the basic reproduction number R_0 and the endemic equilibrium point I_h^* to model parameters with their baseline values. Here the sensitivity index of R_0 to parameter θ is calculated by using formula $\frac{\partial R_0}{\partial \theta}\frac{\theta}{R_0}$ derived from [17]. It is found that the most sensitive parameter for R_0 is the mortality rate of poultry ($d_p + \alpha_p$), followed by the vaccination rate of poultry (η) and the DP-to-DP transmission rate(λ_p). The magnitude of the sensitivity index of I_h^* shows similar results, in which I_h^* is most sensitive to the proportion of imported poultry with virus (q), followed by η and λ_p. It seems that R_0 and I_h^* are not very sensitive to the parameters related to environmental virus (i.e.,r, d_v, β_p and β_h).

Fig. 7 compares the effectiveness of various interventions by computing the cumulative human infections in case of implementing these interventions with different intensities. It is found that either increasing poultry culling rate or reducing transmission rate can rapidly minimize human infections. Particularly, slight increase of DP-to-DP/human transmission rates λ_p and λ_h from zero can cause large number of human infections. When $\lambda_h = 0.05$, about 76% people are infected. When λ_h is larger than 0.1 or λ_p is larger than 0.25, almost all people are infected. Yet the control effect is not significant when only a small part of DP are vaccinated. Furthermore, little change of the infection number

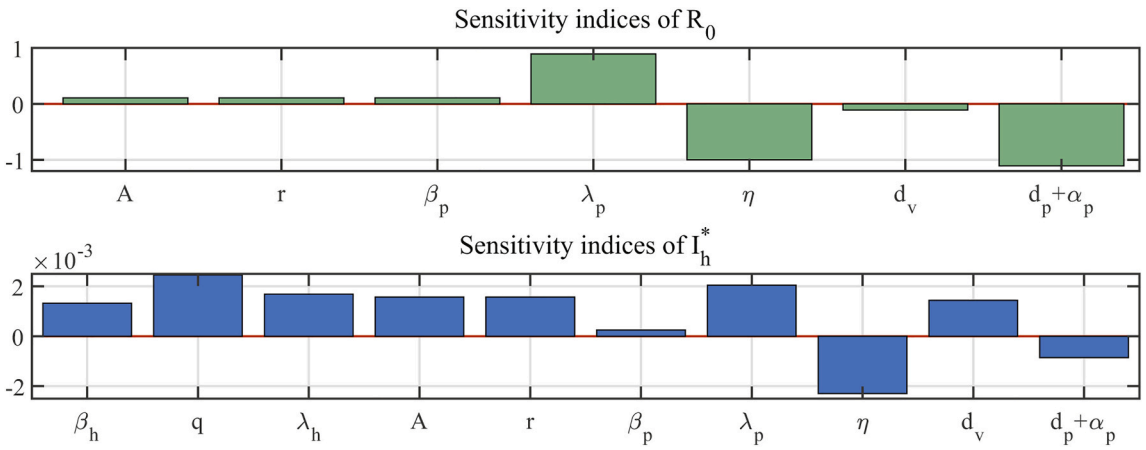

Fig. 6. The histogram of sensitivity indices of R_0 and I_h^* to model parameters.

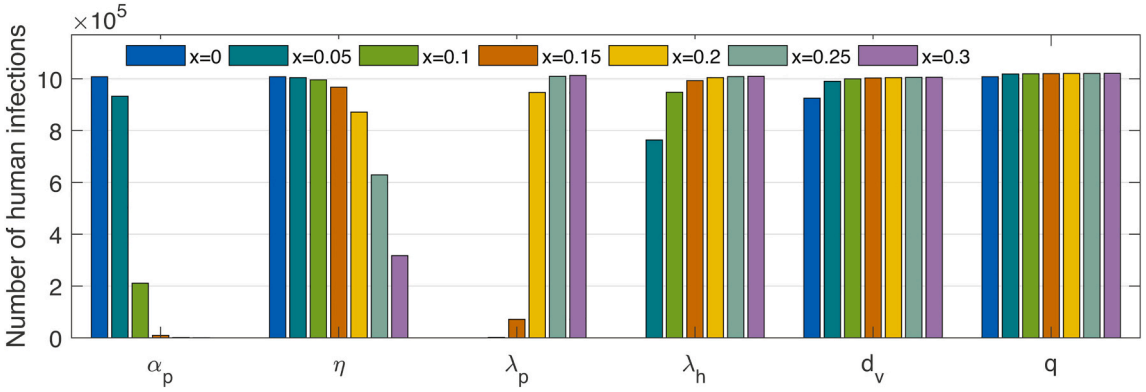

Fig. 7. Impact of different intensities of various interventions on the cumulative number of human infections. Here x corresponds the value of the single intervention parameter in abscissa with other parameters equal to their baseline values.

is observed in case of different strength of cleaning/disinfection and immigration of infected poultry (when there is autochthonous transmission).

5. Discussion

This paper has developed a new modeling framework for evaluating the control effects of different interventions on the epidemic of H7N9. In the form of a deterministic ODE system with biological significance, the proposed model describe the essential transmission process of virus evolution among DP and humans, with compartmental framework as SI (poultry)-V-SEIR (humans). Compared with related existing studies, such as exploring the outcomes of LPM closure and" 1110″ policy by using a SI (poultry)-SEIR (humans) model [2]; quantifying the effect of LPM closure by using Bayesian models [3,7]; estimating vaccination and seasonal effects by using a SI (birds)-SVI (poultry)-SIR (humans) model [4]; evaluating the time-dependent optimal prevention between elimination and quarantine by a using SI (birds)-SI (humans) model [6]; and revealing the impacts of LPM closure on virus activity and human infections by using phylogenetic analysis and epidemiological surveys [8–10]; the present study takes into account more intervention measures by incorporating the intrinsic interactions between disease prevalence and intervention functions, which allows for clarifying the control mechanism of these interventions. Specifically, the effects of culling, vaccination, screening, disinfection and LPM closure are reflected by model parameters, that is, they will modify the culling rate, vaccination proportion, proportion of imported DP carrying virus, elimination rate of environmental virus, and transmission rate, respectively.

Mathematical analyses are first performed to clarify the transmission dynamics with intervention disturbance. Two situations are considered: whether the recruitment DP carries virus or not. In case of consistent recruitment of infected DP, there will always exist a globally stable endemic, and it is impossible for intervention measures to prevention H7N9 transmission, unless implementing complete vaccination or cutting off poultry-to-poultry/human contacts. In case of that all recruitment DP is susceptible, there exists a reproduction number R_0, which is the critical threshold to determine the disease outbreak. If $R_0 < 1$, no matter how many DP are initially infected, H7N9 epidemic will quickly die out. Otherwise, the disease will spread out and become an endemic. Such R_0 is a nonlinear combination of the model parameters accounting for the virus circulation among DP and environment under the regulation of the interventions. Yet R_0 has nothing to do with human-infection parameters, since there is no evidence for human-to-human transmission of H7N9. Further analysis reveals that R_0 is highly dependent on the DP-to-DP transmission rate, vaccination proportion and culling rate, indicating their critical roles acting on H7N9 propagation.

The following insights derived from this study can provide scientific clues for evaluating the intervention strategies against H7N9 infection.

- Screening should be the first line of defence against H7N9 transmission. Strict monitor of imported poultry can stop the invading of H7N9 virus in virgin place. Otherwise, if there is consistent recruitment of infected DP, only complete vaccination or cutting off poultry-to-poultry/human contacts can stop further infection. Therefore, the import of virus-carrying DP acts as a trigger for local infection, and monitoring imported poultry during the early stages of an outbreak is significant for prevention. Once the disease becomes endemic, more

efforts are needed for local control.

- Vaccinating DP is highly effective in reducing transmission risk and infection burden. It is noted that vaccinating a small part of DP does not work, and the necessary proportion of DP to be vaccinated depends on other transmission parameters, that is

$$\eta > 1 - \frac{(d_p + \alpha_p)^2 d_v}{\lambda_p d_v (d_p + \alpha_p) + A\beta_p r}.$$

In present study, it is estimated that for different DP-to-DP transmission rate λ_p, H7N9 infection can be prevented when $\eta > 1 - 0.1\lambda_p$. This result is parallel to the current circumstance in China: since the heavy use of the H5/H7 vaccine in DP in the autumn of 2017, there have been almost no reports of human H7N9 infection [18].

- Limiting DP-DP/humans contacts or reducing per-contact infection probability can quickly weaken infectivity and efficiently protect population health against infection. Their roles are reflected by transmission rates λ_p and λ_h, which equal the product of contact rate and per-contact infection probability. Under the assumption of this paper, H7N9 could not spread if the weekly transmission rates satisfy $\lambda_p < 0.1$ or $\lambda_h = 0$. Such efforts correspond to zero poultry stock overnight, personal hygiene and LPM closure, which were the most commonly used measures in five waves of outbreaks in China during 2013–2017. Similarly to our results, such interventions were verified to be quite effective in preventing human infections [2,3,7,10,11].

- Poultry culling is an effective measure for rapidly reducing transmission risk and infection number. In practice, this intervention was adopted targeting the whole hennery where H7N9 virus was detected. Noting that it is difficult to differentiate whether DP is infected or not, health DP in the same hennery may also be culled when implementing this intervention (which is also for the sake of risk reduction). That would cause high economic loss to DP industry. For example, to reduce the basic reproduction number less than one, the weekly culling rate should increase to $\alpha_p = 0.14$, and then the total number of DP would fall 53%.

- Cleaning and disinfecting environment can accelerate the elimination of environmental virus, and thus alleviates the intensity of H7N9 transmission to some extent. Yet it could not eradicate the risk of H7N9 infection, as that basic reproduction number is usually larger than one if only implementing this intervention. That is probably because indirect transmission only accounts for 18% of the total human infections [16]. The result is consistent to our previous finding [2]. Hence only implementing this measure is not enough to prevent H7N9 transmission. Combining it with other interventions can perform much better for the control.

In summary, this paper provides a modeling framework to evaluate the effectiveness of various intervention against H7N9. Base on our results, all of these interventions (i.e., culling, vaccinating, screening, disinfecting and reducing contact) play certain roles in preventing H7N9 transmission. To prevention H7N9 epidemic and release economic burden, these strategies should be taken into account with real situation: vaccinating a majority of DP should be the first strategy under consideration; If without vaccination, it should strengthen the monitoring of imported poultry, and must keep humans away from poultry; and it could be better to regularly clean and disinfect the surroundings. The analyses of control strategies also can be applied to against other avian influenzas.

This paper has the following limitations that need further discussion. (1) The roles of interventions are quantified by model parameters. Data supports from related experiments and epidemiological survey would may the results more reliable. (2) The proposed model is a simplification of practical issue, which does not incorporate all potential factors, such as absolute humidity (that is verified to be negatively associated with H7N9 infection [2]) and age structure (most patients are elderly people). (3) Some interventions may have multiple effects and may couple together, which needs further check. For example, cleaning and disinfecting environment may also reduce the per-contact infection probability and hence leads to low transmission rate. In this case, their roles may be underestimated. However, the present study clarifies the dynamics of the widely-employed interventions by a epidemiological model, providing confident output for application.

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Declaration of Competing Interest

The authors declare no conflicts of competing interest.

References

[1] Food and Agriculture Organization of the United Nations, H7N9 situation update, RUL, http://www.fao.org/ag/againfo/programmes/en/empres/H7N9/situation_update.html, 2017.
[2] G. Zhu, M. Kang, X. Wei, T. Tang, T. Liu, et al., Different intervention strategies toward live poultry markets against avian influenza A (H7N9) virus: model-based assessment, Environ. Res. 198 (2021) 110465.
[3] J. Lu, W. Liu, R. Xia, Q. Dai, C. Bao, F. Tang, et al., Effects of closing and reopening live poultry markets on the epidemic of human infection with avian influenza A virus, J. Biomed. Res. 30 (2016) 112–119.
[4] J. Zhang, Y. Li, Z. Jin, H. Zhu, Dynamics analysis of an avian influenza A (H7N9) epidemic model with vaccination and seasonality, Complexity 4161287 (2019) 1–15.
[5] Jung Eunok, Iwami Shingo, et al., Optimal control strategy for prevention of avian influenza pandemic, J. Theor. Biol. 260 (2009) 220–229.
[6] G. Fournie, D.U. Pfeiffer, Can closure of live poultry markets halt the spread of H7N9, Lancet 383 (9916) (2014) 496–497.
[7] H. Yu, J.T. Wu, B.J. Cowling, et al., Effect of closure of live poultry markets on poultry-to-person transmission of avian influenza A H7N9 virus: an ecological study, Lancet 383 (9916) (2014) 541–548.
[8] J. Wu, Lu Jing, N.R. Faria, et al., Effect of live poultry market interventions on influenza A(H7N9) virus, Guangdong, China, Emerg. Infect. Dis. 22 (12) (2016) 2104–2112.
[9] J. Yuan, E.H.Y. Lau, K. Li, et al., Effect of live poultry market closure on Avian Influenza A(H7N9) virus activity in Guangzhou, China, 2014, Emerg. Infect. Dis. 21 (10) (2015) 1784–1793.
[10] P. Wu, H. Jiang, J.T. Wu, et al., Poultry market closures and human infection with influenza A(H7N9) virus, China, 2013-14, Emerg. Infect. Dis. 20 (11) (2014) 1891–1894.
[11] V. Offeddu, B.J. Cowling, J.S.M. Peiris, Interventions in live poultry markets for the control of avian influenza: a systematic review, One Health 2 (2016) 55–64.
[12] Y. Xing, L. Song, G. Sun, Z. Jin, J. Zhang, Assessing reappearance factors of H7N9 avian influenza in china, Appl. Math. Comput. 309 (2017) 192–204.
[13] J. Zhang, Z. Jin, G. Sun, X. Sun, Y. Wang, B. Huang, Determination of original infection source of H7N9 avian influenza by dynamical model, Sci. Rep. 4 (2014) 4846.
[14] P. Zhou, J. Ma, A. Lai, G.C. Gray, S. Su, S. Li, Avian influenza A(H7N9) virus and mixed live poultry-animal markets in Guangdong province: A perfect storm in the making? Emerg. Microbes Infec. 4 (10) (2015), e63.
[15] P. van den Driessche, J. Watmough, Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission, Math. Biosci. 180 (2002) 29–48.
[16] Q. Li, L. Zhou, M. Zhou, Z. Chen, F. Li, H. Wu, Z. Feng, Epidemiology of human infections with avian influenza A(H7N9) virus in China, N. Engl. J. Med. 370 (2014) 520–532.
[17] N. Chitnis, J.M. Hyman, J.M. Cushing, Determining important parameters in the spread of malaria through the sensitivity analysis of a mathematical model, Bull. Math. Biol. 70 (5) (2018) 1272–1296.
[18] X. Zeng, G. Tian, J. Shi, G. Deng, C. Li, H. Chen, Vaccination of poultry successfully eliminated human infection with H7N9 virus in China, Sci. China Life Sci. 61 (2018) 1465–1473.