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Avian-Human influenza epidemic model

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Abstract

A mathematical model is proposed to interpret the spread of avian influenza from the bird world to the human world. Our mathematical model warns that two types of the outbreak of avian influenza may occur if the humans do not prevent the spread of avian influenza. Moreover it suggests that we can not feel relieved although the total infected humans are kept at low level. In order to prevent the spread of avian influenza in the human world, we must take the policies not only for the birds infected with avian influenza to exterminate but also for the humans infected with mutant avian influenza to quarantine when mutant avian influenza has already occurred. In particular, the latter policy is shown to be important to stop the second pandemic of avian influenza.

1 Introduction

In 1918, the great pandemic of influenza on modern history had occurred. About 40,000,000 humans died of this pandemic all over the world. After 1918, a pandemic of influenza had occurred twice in 1957 and 1968. Since influenza virus continues always evolving, there exists a menace of pandemic by mutant influenza virus. Influenza virus which infects usually only nonhuman animals sometimes infects humans. The spread of avian influenza in Asia of late years is one of the examples.

In Hong Kong, in 1997, the news that a human was infected with avian influenza from birds was reported. After that, infection to human of avian influenza occurred successively.

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It is known that already 133 humans have been infected in Asia since late 2003 and killed 68. In humans, avian influenza virus causes the similar symptoms as the other types of influenza. These include fever, cough, sore throat, muscle aches, conjunctivitis and, in severe cases, severe breathing problems and pneumonia that may be fatal. The severity of the infection will depend to a large part on the state of the infected human's immune system and if the victims have been exposed to the same kind of virus before, and they have partial immunity.

Since human-cells have receptor for human virus and avian-cells have receptor for avian virus, it was formerly believed that avian influenza virus can not infect humans. Now, it is true that avian influenza virus can infect humans. These cases warn that a pandemic of avian influenza may occur in the human world. Moreover the (highly pathogenic) avian influenza has a high death rate which is about 100 percent for birds and more than 70 percent for humans. This rate is extremely high, since the death rate of influenza virus in 1918 was several percent. Therefore a pandemic of avian influenza may cause the greater influence to the human world than the pandemic of influenza occurred in 1918.

Fortunately, avian influenza can not be transmitted among humans yet. But if avian influenza virus has the affinity for human-cells, it denotes the possibility that avian influenza can be transmitted among humans. It is possible that avian influenza virus may become to have the affinity for human-cells. When avian influenza mutates to be able to be transmitted among humans, it is not clear whether mutant avian influenza will have still high death rate or not. However it is predicted among experts that mutant avian influenza which has the ability to be transmitted among humans will occur.

The World Health Organization (WHO) has warned of a substantial risk of pandemic of avian influenza in the near future. Antiviral drugs "Tamiflu", which can be used for both treatment and prevention, are clinically effective against avian influenza virus and it seems to be our only medicine to fight against the virus. But these drugs are expensive and supplies are limited. Thus it is important to know the mechanism of the spread of avian influenza in the human world. Therefore we construct a mathematical model which interprets the spread of avian influenza from the bird world to the human world. The interested reader is referred to [3] and [4].

2 Model

We construct a mathematical model to interpret the spread of avian influenza from the bird world to the human world with autonomous ordinary differential equations. First we consider the bird system. The (highly pathogenic) avian influenza has the high virulence for birds. Almost all birds infected with avian influenza are dead with the high death rate

or remain infected. Thus we consider the bird system to be the following SI model:

$$\begin{aligned} X' &= c - bX - \omega XY, \\ Y' &= \omega XY - (b+m)Y. \end{aligned} \tag{1}$$

This model describes the interactions among the birds. The population is divided into two classes: susceptible birds, infected birds with avian influenza, with size X and Y, respectively. The parameter c is the rate at which new birds are born. Susceptible and infected birds die at the rate b, $b+m$, respectively, where m is the additional death rate mediated avian influenza. The parameter ω is the rate at which avian influenza is contracted from an average bird individual, provided it is infective. Thus ωXY can be viewed as the force of infection at time t by infected birds with avian influenza.

Next we consider the human system. We assume that the human infected with avian influenza can not infect susceptible humans and this disease also has the high virulence for humans. Thus we consider the following SI model:

$$\begin{aligned} S' &= \lambda - \mu S - \beta_1 SY, \\ B' &= \beta_1 SY - (\mu + d)B. \end{aligned} \tag{2}$$

This model describes the interactions between the birds and humans. The population is divided into two classes: susceptible humans, infected humans with avian influenza, with size S and B, respectively. The parameter λ is the rate at which new humans are born. Susceptible and infected humans die at rate μ, $\mu + d$, respectively, where d is the additional death rate mediated avian influenza. The parameter β_1 is the rate at which avian influenza is contracted from an average bird individual, provided it is infective. Thus $\beta_1 SY$ can be viewed as the force of infection at time t by infected birds with avian influenza.

Moreover we assume that avian influenza can mutate with sufficiently small rate in the human world. That is to say, we assume that the infected human with avian influenza suddenly has the ability to infect a susceptible human with avian influenza when avian influenza mutates in vivo. We call avian influenza which mutates in vivo "mutant avian influenza". That is, the human infected with avian influenza mutates to one with mutant avian influenza at sufficiently small constant rate. In realistic situation, this mutation event must occur stochastically rather than deterministically. But we assume that mutation rate is constant in order to avoid mathematically difficulty. Further we assume that the infected human with mutant avian influenza can infect a susceptible human with mutant avian influenza (and can not infect a human who infected with avian influenza because of immunity against the same kind of virus) and this mutant avian influenza has the lower virulence for human than avian influenza. In addition, the human infected

with mutant avian influenza can recover with eternal immunity against avian influenza and mutant avian influenza. That is to say, avian influenza is spread by infected birds and mutant avian influenza is spread by infected humans in the human world. Thus we consider the human system to be the following SIR model with the mutation process of avian influenza:

$$\begin{aligned} S' &= \lambda - \mu S - \beta_1 SY - \beta_2 SH, \\ B' &= \beta_1 SY - (\mu + d)B - \varepsilon B, \\ H' &= \varepsilon B + \beta_2 SH - (\mu + \alpha)H - \gamma H, \\ R' &= \gamma H - \mu R. \end{aligned} \tag{3}$$

The population is divided into four classes: susceptible human, infected human with avian influenza, infected human with mutant avian influenza, recovered human from mutant avian influenza, with size S, B, H, R, respectively. The parameter ε is the mutation rate, γ is the recovery rate, α is the additional death rate mediated mutant avian influenza, and β_2 is the rate at which mutant avian influenza is contracted from an average human individual, provided it is infective. Thus $\beta_2 SH$ can be viewed as the force of infection at time t by infected humans with mutant avian influenza.

Finally, we consider avian-human influenza epidemic model to be the following SI-SIR model with the mutation process of avian influenza:

$$\begin{aligned} X' &= c - bX - \omega XY, \\ Y' &= \omega XY - (b + m)Y, \\ S' &= \lambda - \mu S - (\beta_1 Y + \beta_2 H)S, \\ B' &= \beta_1 SY - (\mu + d + \varepsilon)B, \\ H' &= \beta_2 SH + \varepsilon B - (\mu + \alpha + \gamma)H, \\ R' &= \gamma H - \mu R. \end{aligned} \tag{4}$$

Remark that all constants are positive and ε is sufficiently small. Moreover b is sufficiently larger than μ ($b \gg \mu$), α is less than d and d is less than m ($m > d > \alpha$) because of the differences of the virulence.

3 Analysis

Firstly, we investigate the bird system (i.e. system (1)). Note that the bird system is independent of the human system. System (1) has two equilibria. The first is the disease free equilibrium:

$$e_0 = (X_0, 0) \quad \text{where} \quad X_0 = \frac{c}{b},$$

which represents the state in which the infected birds with avian influenza are absent.

The second is bird-endemic equilibrium:

$$e_+ = (X^*, Y^*) \text{ where } X^* = \frac{b+m}{\omega},\ Y^* = \frac{c}{b+m} - \frac{b}{\omega},$$

which represents the state in which the infected birds are present.

Here we define the basic reproduction number for avian influenza in the bird world, r_0, which is defined as the number of newly infected birds that are produced from any one infected bird when all birds are susceptible. The rate at which one infected bird gives rise to new infected birds is given by ωX. If all birds are susceptible then $X = c/b$. Since the life-time of an infected bird is $1/(b+m)$, we obtain

$$r_0 = \frac{c\omega}{b(b+m)}.$$

Therefore, there exists e_+ in $\mathbb{R}^2_+$ if and only if $r_0 > 1$. We obtain the following theorem for global stability of the two equilibria. The proof of this theorem is similar to the proof of Theorem 1.1.5 in [2].

Theorem 3.1. *If $r_0 \leq 1$, then e_0 is globally asymptotically stable (GAS) on $\mathbb{R}^2_+$. On the other hand if $r_0 > 1$, then e_+ is GAS on Int $\mathbb{R}^2_+$.*

From Theorem 3.1, we know the following: If $r_0 \leq 1$, then the avian influenza does not spread in the bird world. On the other hand, if $r_0 > 1$, then the avian influenza spreads in the bird world.

Hereafter, we investigate the full system (i.e. system (4)). System (4) has three equilibria. The first is the disease free equilibrium:

$$E_0 = (X_0, 0, S_0, 0, 0, 0) \text{ where } S_0 = \frac{\lambda}{\mu},$$

which represents the state in which the infected birds with avian influenza, humans with avian influenza and mutant avian influenza are absent.

The second is the human-endemic equilibrium (i.e. the boundary equilibrium):

$$E_b = (X_0, 0, \tilde{S}, 0, \tilde{H}, \tilde{R})$$
$$\text{where } \tilde{S} = \frac{\mu+\alpha+\gamma}{\beta_2},\ \tilde{H} = \frac{\lambda}{\mu+\alpha+\gamma} - \frac{\mu}{\beta_2},\ \tilde{R} = \frac{\gamma}{\mu}\tilde{H},$$

which represents the state in which both the birds and humans infected with avian influenza are absent but the infected humans with mutant avian influenza are present.

The third is the full-endemic equilibrium (i.e. the interior equilibrium):

$$E_+ = (X^*, Y^*, S^*, B^*, H^*, R^*)$$
$$\text{where } S^* = \frac{\lambda}{\mu+\beta_1 Y^*+\beta_2 H^*},\ B^* = \frac{\beta_1 Y^*}{\mu+d+\varepsilon}S^*,\ R^* = \frac{\gamma}{\mu}H^*$$

which represents the state in which the infected birds with avian influenza, the infected humans with avian influenza and one with mutant avian influenza are present. Here H^* is the larger root of the following equation:

$$F(H) = \beta_2(\mu+\alpha+\gamma)H^2 + \{(\mu+\beta_1 Y^*)(\mu+\alpha+\gamma) - \beta_2\lambda\}H - \frac{\varepsilon\beta_1\lambda Y^*}{\mu+d+\varepsilon} = 0.$$

Note that $F(H) = 0$ has two real roots and one of them is positive and the other is negative because of $F(0) < 0$. Hence E_+ is unique if it exists.

Let $\mathbf{R}_0$ be the basic reproduction number for mutant avian influenza in the human world where

$$\mathbf{R}_0 = \frac{\beta_2\lambda}{\mu(\mu+\alpha+\gamma)}.$$

Therefore, we obtain the following lemma for the existence of equilibria.

Lemma 3.1. *There always exists E_0 in $\mathbb{R}^6_+$. If $\mathbf{R}_0 > 1$, then there exists E_b in $\mathbb{R}^6_+$. If $r_0 > 1$, then there exists E_+ in $\mathbb{R}^6_+$.*

The Jacobian matrix of system (4) is given as

$$J = \begin{pmatrix} B & 0 \\ C & A \end{pmatrix},$$

where

$$B = \begin{pmatrix} -b-\omega Y & -\omega X \\ \omega Y & \omega X - (b+m) \end{pmatrix},$$

$$A = \begin{pmatrix} -\mu-(\beta_1 Y+\beta_2 H) & 0 & -\beta_2 S & 0 \\ \beta_1 Y & -(\mu+d+\epsilon) & 0 & 0 \\ \beta_2 H & \epsilon & \beta_2 S-(\mu+\alpha+\gamma) & 0 \\ 0 & 0 & \gamma & -\mu \end{pmatrix}.$$

Therefore, J evaluated at equilibrium E_0, E_b, E_+ is stable if and only if so are A and B. From Theorem 3.1, the sub-matrix B evaluated at E_0 and E_b has only the eigenvalues with negative real part if $r_0 < 1$ and one evaluated at E_+ has also only the eigenvalues with negative real part if $r_0 > 1$. Further A is stable if and only if its first 3×3 block is stable. Denote it as $\bar{A}$:

$$\bar{A} = \begin{pmatrix} -\mu-(\beta_1 Y+\beta_2 H) & 0 & -\beta_2 S \\ \beta_1 Y & -(\mu+d+\epsilon) & 0 \\ \beta_2 H & \epsilon & \beta_2 S-(\mu+\alpha+\gamma) \end{pmatrix}.$$

Therefore, when we investigate the stability of the equilibrium E_0, E_b, E_+, we only check the eigenvalues of sub-matrix $\bar{A}$. We obtain the following theorem for the local stability of these equilibria.

Theorem 3.2. *If* $r_0 < 1$ *and* $\mathbf{R}_0 < 1$, *then* E_0 *is LAS. If* $r_0 < 1$ *and* $\mathbf{R}_0 > 1$, *then* E_b *is LAS. If* $r_0 > 1$, *then* E_+ *is LAS.*

In [1], we can get the global results for equilibria and give the detailed explaination for our mathematical results. The interested reader is referred to [1].

4 Simulations

We investigate the spread of avian influenza and mutant avian influenza by numerical simulations. Define

$$\Omega = \{(X, Y, S, B, H, R); X > 0, Y > 0, S > 0, B = 0, H = 0, R = 0\}.$$

Here we are interested in the initial value in Ω. The region Ω denotes that there do not exist the infected humans with avian influenza and mutant avian influenza. Thus the solution with an initial value in Ω predicts the spread of avian influenza and mutant avian influenza in the human world. Thus the intial value is fixed at $X(0) = 10$, $Y(0) = 2$, $S(0) = 100$, $B(0) = 0$, $H(0) = 0$ and $R(0) = 0$.

Firstly, the parameters are fixed at $c = 26.5$, $b = 5$, $\omega = 2$, $m = 5$, $\lambda = 3$, $\mu = 0.015$, $\beta_1 = 0.2$, $\beta_2 = 0.003$, $\varepsilon = 10^{-3}$, $d = 1$, $\alpha = 0.06$ and $\gamma = 0.01$. Hence we are led to $r_0 = 1.06$ and $\mathbf{R}_0 \approx 7.1$ by substituting these parameters to r_0 and $\mathbf{R}_0$. The following figures suggest that the pandemic will occur if the human do not prevent the spread of avian influenza. Fig.1 describes the humans size infected with avian influenza. It interprets that the infected humans with avian influenza appear to be pandemic initially and afterward are kept at low level. Fig.2 describes the humans size infected with mutant avian influenza. This shows that the infected humans with mutant avian influenza suddenly outbreak and afterward keep the relatively high level of the size. Fig.3 describes the total infected humans size. It is clear that the second outbreak is larger than the first one. Moreover it suggests that we can not feel relieved although the total infected humans are kept at low level after the first outbreak. Therefore, our mathematical model warns that the second outbreak by mutant avian influenza will occur if the human do not prevent the spread of avian influenza.

Next, the parameters are fixed at the same as the above example except for $\beta_2 = 0.0015$. That is, the transmission rate of mutant avian influenza is reduced by half. We have $r_0 = 1.06$ and $\mathbf{R}_0 \approx 3.5$. The following figures also suggest that the pandemic will occur if the human do not prevent the spread of avian influenza. Fig.4 describes the humans size infected with avian influenza. It interprets that the infected humans with avian influenza appear to be pandemic again and afterward become endemic. Fig.5

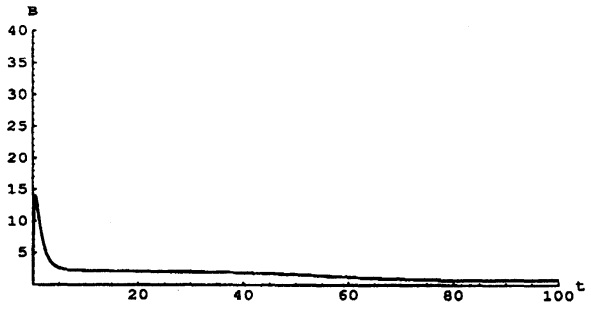

Figure 1: The humans size infected with avian influenza ($r_0 = 1.06$ and $\mathbf{R_0} \approx 7.1$).

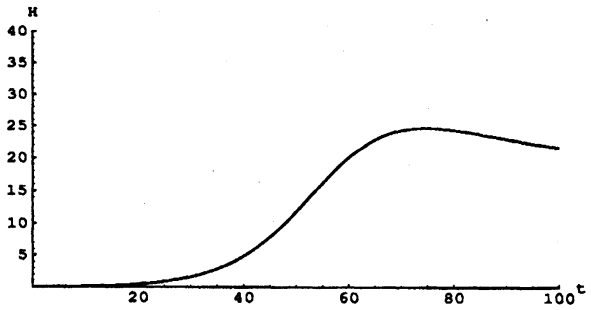

Figure 2: The humans size infected with mutant avian influenza ($r_0 = 1.06$ and $\mathbf{R_0} \approx 7.1$).

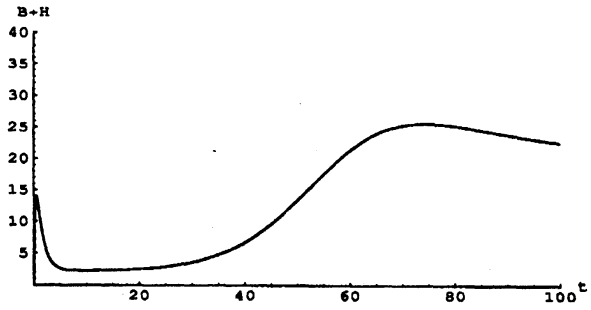

Figure 3: The total infected humans size ($r_0 = 1.06$ and $\mathbf{R_0} \approx 7.1$).

describes the humans size infected with mutant avian influenza. Compare Fig.5 and 2. We find no pandemic of the infected humans with mutant avian influenza in Fig.5. This suggests that we have two types of pandemic, one is due to avian influenza and the other is due to mutant one. When $\mathbf{R}_0$ is relatively high we will have two pandemics (Fig.3) but for small $\mathbf{R}_0$, we have only pandemic of the first type (Fig.6).

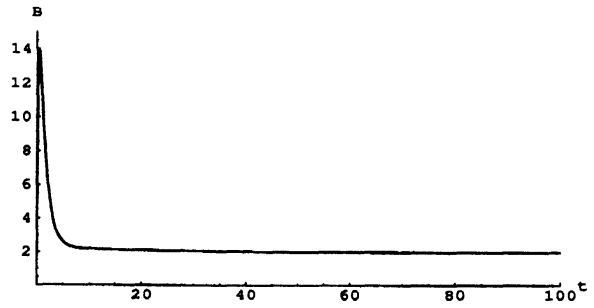

Figure 4: The humans size infected with avian influenza ($r_0 = 1.06$ and $\mathbf{R}_0 \approx 3.5$).

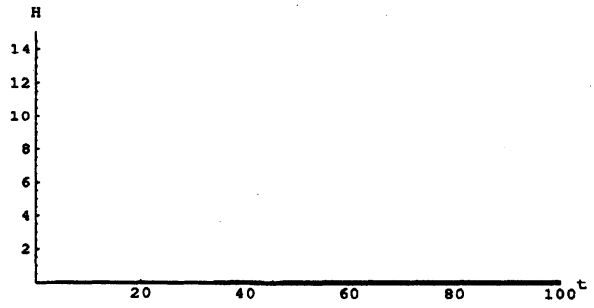

Figure 5: The humans size infected with mutant avian influenza ($r_0 = 1.06$ and $\mathbf{R}_0 \approx 3.5$).

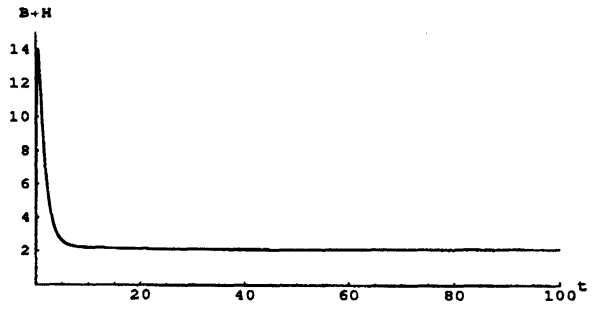

Figure 6: The total infected humans size ($r_0 = 1.06$ and $\mathbf{R}_0 \approx 3.5$).

Finally, the parameters are fixed at the same as the first example exept for $c = 30$ and $\omega = 1.5$. We have now $r_0 = 0.9$ and $\mathbf{R}_0 \approx 7.1$. The following figures suggest that two types of the pandemic will also occur if the humans do not prevent the spread of avian influenza

although all the infected birds and the infected humans with avian influenza were extinct. See Figs 7-9. These figures imply that the second outbreak by mutant avian influenza will occur if the human do not prevent the spread of avian influenza although all the infected birds and the infected humans with avian influenza were extinct.

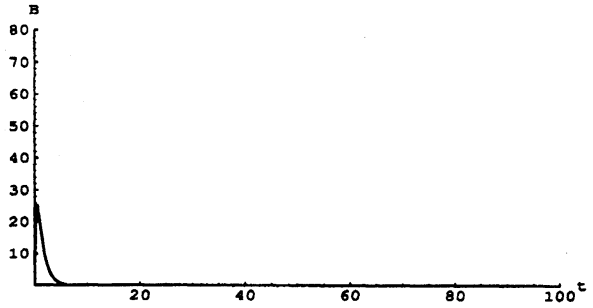

Figure 7: The humans size infected with avian influenza ($r_0 = 0.9$ and $\mathbf{R}_0 \approx 7.1$).

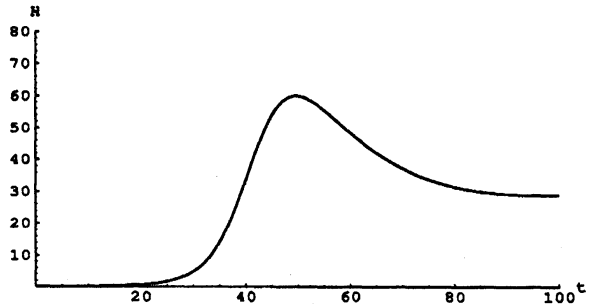

Figure 8: The humans size infected with mutant avian influenza ($r_0 = 0.9$ and $\mathbf{R}_0 \approx 7.1$).

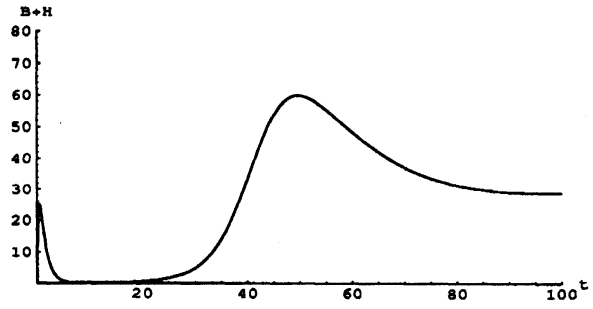

Figure 9: The total infected humans size ($r_0 = 0.9$ and $\mathbf{R}_0 \approx 7.1$).

By comparing Figs 3 and 9, we notice that total number of the infected humans when the infected birds are extinct (Fig.9, $r_0 < 1$) is larger than the number of the infected humans when the infected birds are endemic (Fig.3, $r_0 > 1$). See Figs 1 and 7. The humans infected with avian influenza become extinct for $r_0 < 1$ (Fig.7), but keeps some

posive number for $r_0 > 1$ (Fig.1). The former (Fig.7) situation is more advantageous for the mutant avian influenza. Thus the total number of the infected humans is larger for the case $r_0 < 1$ (Fig.9). It suggests that the extermination of the infected birds with avian influenza is not always the best policy after the incidence of mutant avian influenza in the human world.

However, by comparing Figs 3,9 and Fig.6, we notice that the second outbreak will not occur if $\mathbf{R}_0$ is not large enough (Fig.6). This is because the infected humans with mutant avian influenza do not have the sufficient power to spread mutant avian influenza (see Fig.5). It suggests that to reduce a contact rate for susceptible humans with the infected individuals with mutant avian influenza at low level is a good policy in order to prevent the spread of avian influenza after the incidence of mutant avian influenza in the human world.

5 Discussion

Formerly, it was thought that human can not be infected with avian influenza. But, in Hong Kong, in 1997, the news that a human was infected with avian influenza from a bird was reported. After this, infection to humans of avian influenza have been reported successively. Fortunately, avian influenza can not be transmitted directly from humans to humans yet. However it is said among experts that mutant avian influenza which has the ability to be transmitted among humans will occur.

Therefore we construct a mathematical model to explain the spread of avian influenza and mutant avian influenza. Here we show that mutant avian influenza spreads in the human world when $\mathbf{R}_0 > 1$ or $r_0 > 1$. Moreover our simulations suggest that the second outbreak by mutant avian influenza is larger than the first outbreak by avian influenza when $\mathbf{R}_0 > 1$, $r_0 < 1$ or $\mathbf{R}_0 > 1$, $r_0 > 1$ and we can not feel relieved although the total infected humans are kept at low level after the first outbreak. Further these simulations show that the extermination of the infected birds is not always the best policy in order to prevent the spread of avian influenza in the human world. If mutant avian influenza has already occurred, it is possible that this policy helps to spread mutant avian influenza. On the other hand, to reduce a contact rate for susceptible humans with the individuals infected with mutant avian influenza is a good policy in order to prevent the spread of avian influenza in the human world. Even if mutant avian influenza has already occurred, we can prevent the second outbreak by mutant avian influenza.

Our mathematical model suggests that the spreads of mutant avian influenza are not prevented even if we exterminate the infected birds after the incidence of mutant avian influenza. For example, let us assume that avian influenza and mutant avian influenza

have spread in the human world (i.e. Figs 1-3). Even if we were able to remove all infected birds (i.e. Figs 7-9, $r_0 < 1$), we can not prevent mutant avian influenza spread, and further this policy can help mutant avian influenza spread. But if we can control a rate to come in contact with susceptible humans low (i.e. Figs 4-6, $\mathbf{R}_0$ is not large enough), we can prevent the second outbreak by mutant avian influenza. And it is also effective to treat infected humans with antiviral drug because we can reduce $\mathbf{R}_0$ as a result, even if mutant avian influenza has already occurred. After all the best policy to prevent the spreads of avian influenza in the human world is to exterminate the infected birds earlier than the incidence of mutant avian influenza. If some birds were found to be infected with avian influenza, we should remove all birds at that point because of the rapid spread for avian influenza in the bird world. In order to prevent the spread of avian influenza in the human world, we must take policy not only for infected birds with avian influenza but also for infected humans with mutant avian influenza when mutant avian influenza has already occurred.

It is not far future that mutant avian influenza may occur. From our mathematical model, mutant avian influenza may spread in the human world and the pandemic may occur.

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