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TWO MATHEMATICAL MODELS FOR H1N1 INFLUENZA WITH ANTIVIRAL TREATMENT

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Abstract: In this paper, we establish two mathematical models to study H1N1 influenza transmission dynamics. One model is for the case of concurrent treatment, in which we assume that untreated individuals are detected at random and moved to the treatment compartment at any time of their infected phase, and the other model deals with the case of early diagnosis, in which we assume that with some probability $\sigma \in [0,1]$, individuals are diagnosed at the moment of infection and immediately moved to the treatment compartment. Both models are analyzed including the derivation of the basic and control reproduction numbers, the proof of global stability of disease-free equilibrium points, and demonstrating how the acquired reproduction number can be used to explain the adverse effects associated with antiviral treatment. This effect is also explained using a quantity termed the total control reproduction number. We also compare the differences between the two models in evaluating outcomes of influenza. Numerical simulations are conducted to verify the theoretical analysis results.

Keywords: H1N1 Influenza; antiviral treatment; drug-sensitive strains; drug-resistant strains; reproduction number.

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1. Introduction

Influenza (also known as flu) is a respiratory disease caused by certain RNA viruses of the Orthomyxoviridae family [1]. RNA viruses lack means of correcting errors introduced during replication and influenza has multiple hosts with which mutant and recombinant genotypes may have selective advantage. Influenza viruses have coexisted with humans for centuries and have historically been a cause of excessive morbidity and mortality [2].

H1N1 influenza is a type A flu virus of swine origin that was first detected in April, 2009. The virus infected people and spread from person-to-person, sparking a growing outbreak of flu in the United States [3]. An increasing number of cases are being reported internationally as well. It is well-known that novel influenza A (H1N1) virus spreads in the same way as regular seasonal influenza viruses spread, mainly through coughs and sneezes of people who are infected. At the time of the outbreak in 2009, pandemic H1N1 was a new virus, to which most people did not have immunity, and illness may have been more widespread as a result [4]. There is a need for effective treatment and control strategies in the event of pandemics. The government of China took a series of emergency measures, such as setting up work mechanism to prevent H1N1 influenza from spreading; adopting strict inspection and quarantine measures in the ports of entry and exit; strengthening the management of close contacts; monitoring and reporting infected individuals; and constantly adjusting and improving the diagnosis and treatment of cases.

One of such strategies is treatment of affected patients with antiviral medication. Currently, the drugs for H1N1 influenza are the same as those used for treating seasonal influenza. Two types of antiviral drugs currently available are neuraminidase inhibitors and M2 channel blockers [5]. Neuraminidase inhibitors such as oseltamivir, zanamivir and tamiflu play an important role in inhibiting the virus replication and dissemination. M2 channel blockers such as amantadine and rimantadine can effectively inhibit replication of the virus in infected cells, block the spread of the virus infection. Despite the effectiveness of these drugs in reducing influenza-related morbidity and mortality, the emergence of drug resistance poses a critical limitation on their application. Incidence of viral resistance to M2 channel blockers has been associated with

an increasing rate in seasonal and H1N1 influenza, possibly through widespread or indiscriminate use of the drugs [6]. Neuraminidase inhibitors are less prone to be selected for resistant mutations [7], and therefore offer a better option for pandemic preparedness. However, the emergence of oseltamivir resistance in 2006 has raised concerns about our preparation for an influenza pandemic [8]. Recently, studies show that amantadine and rimantadine do not work among individuals who have suffered drug abuse for a long time. But, oseltamivir, zanamivir and tamiflu can effectively alleviate symptoms in some individuals. This is particularly important for preventing pandemics caused by the emergence of resistant viral mutants. Some individuals who become resistant to single drug may continue to seek treatment with other drugs to alleviate pain. After individuals become resistant to multiple drugs, antiviral treatment will no longer be effective.

In this paper, we formulate two models to study the effect of drug treatment on the prevalence of drug resistance. One considers treatment while ill, and the other considers diagnosis at the moment of infection and immediate treatment with a given probability. We compare the differences between the two models, including their connection to parameters representing treatment strategies and evaluation of the impact of drug treatment on the prevalence of resistance. We examine the role of the acquired reproduction number, in the contribution of treatment failure to the adverse effect of drug treatment.

The paper is organized as follows. Sections 2 and 3 present Model I and Model II, respectively. Analyses of the two models are also included in these sections, including the derivation of the basic and control reproduction numbers, which are shown to determine the stability of equilibria. Section 4 is devoted to numerical simulations, and Section 5 compares the differences between two models. Finally, the findings and conclusions are summarized in Section 6.

2. Model I

The model is based on the transmission dynamics of H1N1 influenza. Assume that, for an individual under treatment with a single drug, if drug resistance has developed, the individual may continue to receive treatment with other drugs. For those individuals, multi-drug resistance

may develop. Let f_1 and f_2 denote the treatment rate of a drug-sensitive individual and individuals who are resistant to a single drug, respectively. Assume that $f_i = p_i k_i (i = 1,2)$, where k_i denote the rate at which an infected patient seeks a doctor, which can happen at any time of the infection, and p_i denote the proportion of patient who receive treatment.

Let N denote the number of the population, which is divided into five subclasses: susceptible S; infected but sensitive to drugs I_{1s}; resistant to a single drug I_{1r}; multi-drug resistant strains I_{2r}; and recovered R. Based on the above assumptions, we establish the following model(called Model I)

$$\begin{cases} \frac{dS}{dt} = \Lambda + \omega R - \beta_{1s}\frac{I_{1s}}{N}S - \beta_{1r}\frac{I_{1r}}{N}S - \beta_{2r}\frac{I_{2r}}{N}S - \mu S, \\ \frac{dI_{1s}}{dt} = \beta_{1s}\frac{I_{1s}}{N}S - \mu I_{1s} - f_1 I_{1s} - \gamma_1 I_{1s}, \\ \frac{dI_{1r}}{dt} = \beta_{1r}\frac{I_{1r}}{N}S + f_1(1-c_1)I_{1s} - \mu I_{1r} - f_2 I_{1r} - \gamma_2 I_{1r}, \\ \frac{dI_{2r}}{dt} = \beta_{2r}\frac{I_{2r}}{N}S + f_2(1-c_2)I_{1r} - \mu I_{2r} - \gamma_3 I_{2r}, \\ \frac{dR}{dt} = f_1 c_1 I_{1s} + \gamma_1 I_{1s} + f_2 c_2 I_{1r} + \gamma_2 I_{1r} + \gamma_3 I_{2r} - \mu R - \omega R. \end{cases} \tag{2.1}$$

Table 1 Definitions of frequently used symbols

Parameters	Description
Λ	Recruitment rate of individuals
β_{1s}	Transmission rate of the drug-sensitive strain
β_{1r}	Transmission rate of strain with resistance to a single drug
β_{2r}	Transmission rate of strains resistant to multiple drugs
$\frac{1}{\mu}$	Average life-span
$f_i (i = 1,2)$	Treatment rate
$c_i (i = 1,2)$	Fraction of treated individuals who recover
$\gamma_i (i = 1,2,3)$	Recovery rate
$\frac{1}{\omega}$	Average immunity period due to infection

Some of the main assumptions made in the formulation of the Model I are as follows:

(i) Homogeneous mixing in the populations;

(ii) Individuals in the I_{1r} class can still receive drug treatment but there is no antiviral drug to treat I_{2r} individuals, and assume that $\beta_{1r} > \beta_{2r}$;

(iii) Transmission rate from individuals in the I_{1r} class is lower than that from individuals in the I_{1s} class due to the antiviral treatment, and so $\beta_{1s} > \beta_{1r}$;

(iv) Disease-induced mortality is ignored.

Note that the total population size

$$N = S + I_{1s} + I_{1r} + I_{2r} + R$$

has the following properties:

$$\frac{dN}{dt} = \Lambda - \mu N, t \to \infty, N \to \frac{\Lambda}{\mu}.$$

It is easy to show that the following biologically-feasible region of Model I

$$\Gamma = \{(S, I_{1s}, I_{1r}, I_{2r}, R) \in R_+^5 : 0 \leq S + I_{1s} + I_{1r} + I_{2r} + R \leq \frac{\Lambda}{\mu}\}$$

is positively-invariant and attracting.

The disease-free equilibrium is $E_{10} = (\frac{\Lambda}{\mu}, 0, 0, 0, 0)$.

2.1. Global stability and reproduction numbers of Model I

We derive the reproduction numbers using the next generation matrix [14]. The three infected variables are I_{1s}, I_{1r}, I_{2r}. Let F and V denote the matrices corresponding to the new infection terms and the transitions between stages, respectively. And for simplicity we introduce the following notations:

$$h_i = \mu + f_i + \gamma_i (i = 1, 2).$$

Note that

$$F = \begin{pmatrix} \beta_{1s} & 0 & 0 \\ 0 & \beta_{1r} & 0 \\ 0 & 0 & \beta_{2r} \end{pmatrix},$$

$$V = \begin{pmatrix} h_1 & 0 & 0 \\ -f_1(1-c_1) & h_2 & 0 \\ 0 & -f_2(1-c_2) & \mu+\gamma_3 \end{pmatrix}.$$

Then

$$FV^{-1} = \begin{pmatrix} \frac{\beta_{1s}}{h_1} & 0 & 0 \\ \frac{\beta_{1r}f_1(1-c_1)}{h_1h_2} & \frac{\beta_{1r}}{h_2} & 0 \\ \frac{\beta_{2r}f_1(1-c_1)f_2(1-c_2)}{h_1h_2(\mu+\gamma_3)} & \frac{\beta_{2r}f_2(1-c_2)}{(\mu+\gamma_3)h_2} & \frac{\beta_{2r}}{\mu+\gamma_3} \end{pmatrix}.$$

The control reproduction number is

$$R_{1c} = \rho(FV^{-1}) = \max\{R_{1sc}, R_{1rc}, R_{1m}\},$$

where,

$$R_{1sc} = \frac{\beta_{1s}}{h_1}, R_{1rc} = \frac{\beta_{1r}}{h_2}, R_{1m} = \frac{\beta_{2r}}{\mu+\gamma_3}.$$

(i) The biological interpretations of these quantities R_{1sc}, R_{1rc} and R_{1m} are as follows. R_{1sc} and R_{1rc} represent the numbers of secondary sensitive cases produced by a drug-sensitive and single drug-resistant strain, respectively, during the period of infection in a susceptible population. While R_{1m} explains the number of secondary multiple drug-resistant cases, during the period of infection in a susceptible population, which is the basic reproduction number for the strain with multi-drug resistance. From the formulation of R_{1sc} and R_{1rc}, we know treatment can reduce infection period.

(ii) In the absence of treatment, i.e., $f_i = 0 (i = 1, 2)$, we can get the basic reproduction number

$$R_{10} = \max\{R_{1s}, R_{1r}, R_{1m}\},$$

where

$$R_{1s} = \frac{\beta_{1s}}{\mu+\gamma_1}, R_{1r} = \frac{\beta_{1r}}{\mu+\gamma_2}, R_{1m} = \frac{\beta_{2r}}{\mu+\gamma_3}.$$

The basic reproduction number R_{r1} of drug-resistant strain can be written as $R_{r1} = \max\{R_{1r}, R_{1m}\}$. R_{1s} denotes the basic reproduction number of drug-sensitive strains.

Theorem 1. *If $R_{1c} < 1$, then the disease-free equilibrium E_{10} is locally asymptotically stable, and unstable if $R_{1c} > 1$.*

Proof. The Jacobian of system (2.1) at E_{10} is

$$J|_{E_{10}} = \begin{pmatrix} -\mu & -\beta_{1s} & -\beta_{1r} & -\beta_{2r} & \omega \\ 0 & h_1(R_{1sc}-1) & 0 & 0 & 0 \\ 0 & f_1(1-c_1) & h_2(R_{1rc}-1) & 0 & 0 \\ 0 & 0 & f_2(1-c_2) & (\mu+\gamma_3)(R_{1m}-1) & 0 \\ 0 & f_1c_1+\gamma_1 & f_2c_2+\gamma_2 & \gamma_3 & -(\mu+\omega) \end{pmatrix}.$$

The eigenvalues are $-\mu, -(\mu+\omega), h_1(R_{1sc}-1) < 0, h_2(R_{1rc}-1) < 0, (\mu+\gamma_3)(R_{1m}-1) < 0$, respectively, that means all eigenvalues of $J|_{E_{10}}$ have negative real parts, hence E_{10} is locally asymptotically stable. □

Recall that total population size $N(t)$ satisfies the equation $\frac{dN}{dt} = \Lambda - \mu N$ and $N(t) \to \frac{\Lambda}{\mu}$ as $t \to \infty$. Using results from Castillo-Chavez and Thieme [15] and Mischaikow et al. [16], we can obtain analytical results by considering the following limiting system

$$\begin{cases} \frac{dS}{dt} = \Lambda + \omega(\frac{\Lambda}{\mu} - S - I_{1s} - I_{1r} - I_{2r}) - \beta_{1s}\frac{\mu}{\Lambda}I_{1s}S - \beta_{1r}\frac{\mu}{\Lambda}I_{1r}S - \beta_{2r}\frac{\mu}{\Lambda}I_{2r}S - \mu S, \\ \frac{dI_{1s}}{dt} = \beta_{1s}\frac{\mu}{\Lambda}I_{1s}S - \mu I_{1s} - h_1 I_{1s}, \\ \frac{dI_{1r}}{dt} = \beta_{1r}\frac{\mu}{\Lambda}I_{1r}S + f_1(1-c_1)I_{1s} - h_2 I_{1r}, \\ \frac{dI_{2r}}{dt} = \beta_{2r}\frac{\mu}{\Lambda}I_{2r}S + f_2(1-c_2)I_{1r} - \mu I_{2r} - \gamma_3 I_{2r}, \\ \frac{dR}{dt} = f_1c_1I_{1s} + \gamma_1 I_{1s} + f_2c_2I_{1r} + \gamma_2 I_{1r} + \gamma_3 I_{2r} - (\mu+\omega)(\frac{\Lambda}{\mu} - S - I_{1s} - I_{1r} - I_{2r}). \end{cases} \tag{2.2}$$

If $R_{1c} < 1$, then $R_{1sc} < 1$ and $R_{1rc} < 1$. From Theorem 2.1, the disease-free equilibrium E_{10} is locally asymptotically stable. In order to verify the global stability of E_{10}, we only need to prove that E_{10} is a global attractor.

From the first equation in (2.2), it follows that

$$S' \leq \frac{(\mu+\omega)\Lambda}{\mu} - (\mu+\omega)S.$$

By the comparison principle, we have $S(t) \leq \frac{\Lambda}{\mu} + (S(0) - \frac{\Lambda}{\mu})e^{-(\mu+\omega)t}$. Without loss of generality, we can assume that $S(t) \leq \frac{\Lambda}{\mu}$. Then it follows from the second and third equations of (2.2) that

$$\begin{cases} I'_{1s} \leq (\beta_{1s} - h_1)I_{1s}, \\ I'_{1r} \leq (\beta_{1r} - h_2)I_{1r} + f_1(1-c_1)I_{1s}. \end{cases}$$

Then by the comparison principle [15], it is easy to show that $I_{1s}(t) \to 0$ and $I_{1r}(t) \to 0$ as $t \to +\infty$ when $R_{1sc} < 1$ and $R_{1rc} < 1$. From the fourth equation of (2.2), we have

$$I'_{2r} \leq (\beta_{2r} - \mu - \gamma_3)I_{2r} + f_2(1-c_2)I_{1r}.$$

Since $I_{1s}(t) \to 0, I_{1r}(t) \to 0$ as $t \to +\infty$ and $R_{1m} < 1$, we have $I_{2r}(t) \to 0$ as $t \to +\infty$. Similarly, from the fifth equation of (2.2) it is easy to obtain that $R(t) \to 0$ as $t \to +\infty$. Substitution of these into the first equation of(2) gives $S(t) \to \frac{\Lambda}{\mu}$ as $t \to +\infty$. This implies that the disease free equilibrium E_{10} is a global attractor. Then we have the following theorem.

Theorem 2. *If $R_{1c} < 1$, the disease-free equilibrium E_{10} is globally asymptotically stable.*

2.2. More on reproduction numbers of Model I

We define R_{1sc} and R_{1rc} as drug-sensitive and single drug-resistant strain control reproduction number, respectively. R_{1m} denotes the basic reproduction number of multi-drug resistant strains. Then we rewrite the expression of R_{1sc} and R_{1rc} as follows

$$R_{1sc} = \frac{\beta_{1s}}{\mu + p_1k_1 + \gamma_1}, R_{1rc} = \frac{\beta_{1r}}{\mu + p_2k_2 + \gamma_2}.$$

Considering the partial derivative of R_{1sc} and R_{1rc} with respect to the proportion $p_i (i = 1,2)$ of patients who receive treatment, which yields

$$\frac{\partial R_{1sc}}{\partial p_1} = \frac{-\beta_{1s}k_1}{(\mu + p_1k_1 + \gamma_1)^2} < 0, \frac{\partial R_{1rc}}{\partial p_2} = \frac{-\beta_{1r}k_2}{(\mu + p_2k_2 + \gamma_2)^2} < 0.$$

Clearly, R_{1sc} and R_{1rc} are decreasing functions of $p_i (i = 1,2)$, that mean the more infected patients to seek antiviral treatment, the easier disease and the epidemic size may be controlled. At the same time, we notice that R_{1m} is independent of $p_i (i = 1,2)$, that implies if drug resistance has developed, antiviral treatment will no longer be effective. But this can not capture the

nonlinear relationship with $p_i (i = 1,2)$, which suggests that more about reproduction number need to be considered. The paper [12] gives a new idea about acquired reproduction number, which can be used to explain the adverse effects associated with antiviral treatment. When a person is infected with H1N1 drug-sensitive strain, the number of secondary cases consists of five components given below:

$$①\frac{S^0}{N^0}(1-p_1)\frac{\beta_{1s}}{\mu+\gamma_1}; ②\frac{S^0}{N^0}p_1c_1\frac{\beta_{1s}}{h_1}; ③\frac{S^0}{N^0}p_1(1-c_1)(1-p_2)\frac{\beta_{1r}}{\mu+\gamma_2};$$

$$④\frac{S^0}{N^0}p_1(1-c_1)p_2c_2\frac{\beta_{1r}}{h_2}; ⑤\frac{S^0}{N^0}p_1(1-c_1)p_2(1-c_2)\frac{\beta_{2r}}{\mu+\gamma_3}.$$

If the total population size N^0 is sufficiently large so that the number of infected cases is relatively small, then $\frac{S(t)}{N(t)}$ can be closely approximated by $\frac{S^0}{N^0}$, and $\frac{S^0}{N^0}$ can be closely approximated 1. The component ① represents the number of new sensitive cases if the person is untreated. The component ② represents the number of new sensitive cases if the person is treated and recover. The component ③ represents the number of cases who have not been cured and do not continue to seek treatment. The component ④ represents the cases of single drug resistant when the person continue to seek treatment and recover. The component ⑤ represents the cases who continue to seek treatment and finally develop multi-drug resistant strains. We denote the sum of components ③, ④ and ⑤ by R_{AR}, which refers to the acquired reproduction number and can be used to explain the adverse effects associated with antiviral treatment. So we get

$$R_{AR} = p_1(1-c_1)(1-p_2)\frac{\beta_{1r}}{\mu+\gamma_2} + p_1(1-c_1)p_2c_2\frac{\beta_{1r}}{h_2} + p_1(1-c_1)p_2(1-c_2)\frac{\beta_{2r}}{\mu+\gamma_3}.$$

Define R_{TC} as the total control reproduction number, which is equal to the sum of both R_{1sc} and R_{AR}, then we have

$$R_{TC} = \frac{\beta_{1s}}{h_1} + p_1(1-c_1)(1-p_2)\frac{\beta_{1r}}{\mu+\gamma_2} + p_1(1-c_1)p_2c_2\frac{\beta_{1r}}{h_2} + p_1(1-c_1)p_2(1-c_2)\frac{\beta_{2r}}{\mu+\gamma_3}.$$

Clearly, $R_{TC} = R_{TC}(p_1, p_2)$. Note that

$$\frac{\partial R_{TC}}{\partial p_1} = -\frac{k_1R_{1sc}}{\mu+p_1k_1+\gamma_1} + (1-c_1)(1-p_2)R_{1r} + (1-c_1)p_2c_2R_{1rc} + (1-c_1)p_2(1-c_2)R_{1m}.$$

From $\frac{\partial R_{TC}}{\partial p_1} = 0$, we obtain

$$p_1^* = \frac{R_{1sc}}{(1-c_1)(1-p_2)R_{1r} + (1-c_1)p_2c_2R_{1rc} + (1-c_1)p_2(1-c_2)R_{1m}} - \frac{\mu+\gamma_1}{k_1},$$

and let

$$p_{1c} = \begin{cases} 0 & p_1^* \leq 0; \\ p_1^* & 0 < p_1^* < 1; \\ 1 & p_1^* \geq 1. \end{cases}$$

Moreover

$$\frac{\partial^2 R_{TC}}{\partial^2 p_1}|_{p_1=p_1^*} = \frac{k_1^2 R_{1sc}}{(\mu + p_1^* + \gamma_1)^2} > 0.$$

Thus, the dependence of R_{TC} on p_1 is nonlinear, and there may be a critical value p_{1c} such that R_{TC} decreases for $0 < p_1 < p_{1c}$ and increases for $p_{1c} < p_1 < 1$. In addition,

$$\frac{\partial R_{TC}}{\partial p_2} = -p_1(1-c_1)R_{1r} + p_1(1-c_1)c_2R_{1rc} - p_1(1-c_1)p_2c_2\frac{k_2R_{1rc}}{\mu+\gamma_2+p_2k_2} + p_1(1-c_1)(1-c_2)R_{1m}.$$

Define

$$p_2^* = \frac{(\mu+\gamma_2)(-R_{1m}c_2 + R_{1rc}c_2 - R_{1r} + R_{1m})}{k_2(R_{1m}c_2 + R_{1r} - R_{1m})},$$

and

$$p_{2c} = \begin{cases} 0 & p_2^* \leq 0; \\ p_1^* & 0 < p_2^* < 1; \\ 1 & p_2^* \geq 1. \end{cases}$$

Moreover

$$\frac{\partial^2 R_{TC}}{\partial^2 p_2}|_{p_2=p_2^*} = \frac{-p_1(1-c_1c_2)k_2(\mu+\gamma_2)R_{1rc}}{(\mu+\gamma_2+p_2^*k_2)^2} < 0.$$

Then, the dependence of R_{TC} on p_2 is nonlinear, there may be a critical value p_{2c} such that R_{TC} increases for $0 < p_2 < p_{2c}$ and decreases for $p_{2c} < p_2 < 1$.

Thus, the dependence of R_{TC} on $p_i (i = 1,2)$ is nonlinear, there may be two critical values p_1^* and p_2^*, such that $\frac{\partial R_{TC}}{\partial p_i} = 0 (i = 1,2)$.

3. Model II

In Model I, k_i(i=1,2) denote the rate at which an infected patient seeks a doctor, that can happen at any time of the infection. Next, we study the model dealing with the case of early diagnosis, in which we assume that with some probability $\sigma \in [0,1]$ individuals are diagnosed at the moment of infection and immediately moved to the treatment compartment. As usual the population is divided into susceptible S, infected I and recovered R. Here, the infected

are further subdivided into untreated individuals I_{1U}, individuals I_{1T} who receive treatment, individuals I_{1r} who are resistant to a single drug and multi-drug resistant strains I_{2r}. Based on the above assumptions, we develop the following model(called Model II)

$$\begin{cases} \frac{dS}{dt} = \Lambda + \omega R - \beta_{1U}\frac{I_{1U}}{N}S - \beta_{1T}\frac{I_{1T}}{N}S - \beta_{1r}\frac{I_{1r}}{N}S - \beta_{2r}\frac{I_{2r}}{N}S - \mu S, \\ \frac{dI_{1U}}{dt} = (1-\sigma)(\beta_{1U}\frac{I_{1U}}{N}S + \beta_{1T}\frac{I_{1T}}{N}S) - \mu I_{1U} - \gamma_1 I_{1U}, \\ \frac{dI_{1T}}{dt} = \sigma\theta_1(\beta_{1U}\frac{I_{1U}}{N}S + \beta_{1T}\frac{I_{1T}}{N}S) - \mu I_{1T} - \gamma_2 I_{1T}, \\ \frac{dI_{1r}}{dt} = \sigma\theta_2(\beta_{1U}\frac{I_{1U}}{N}S + \beta_{1T}\frac{I_{1T}}{N}S) + \beta_{1r}\frac{I_{1r}}{N}S - \mu I_{1r} - \gamma_3 I_{1r}, \\ \frac{dI_{2r}}{dt} = \sigma\theta_3(\beta_{1U}\frac{I_{1U}}{N}S + \beta_{1T}\frac{I_{1T}}{N}S) + \beta_{2r}\frac{I_{2r}}{N}S - \mu I_{2r} - \gamma_4 I_{2r}, \\ \frac{dR}{dt} = \gamma_1 I_{1U} + \gamma_2 I_{1T} + \gamma_3 I_{1r} + \gamma_4 I_{2r} - \mu R - \omega R, \\ \theta_1 + \theta_2 + \theta_3 = 1. \end{cases} \tag{3.1}$$

The meanings of parameters $\mu, \gamma_i (i = 1,2,3)$ are the same as those in Model I.

Note that the total population size

$$N = S + I_{1U} + I_{1T} + I_{1r} + I_{2r} + R$$

has the following properties:

$$\frac{dN}{dt} = \Lambda - \mu N, t \to \infty, N \to \frac{\Lambda}{\mu}.$$

It is easy to show that the following biologically-feasible region of Model II

$$\Gamma = \{(S, I_{1U}, I_{1T}, I_{1r}, I_{2r}, R) \in R_+^6 : 0 \le S + I_{1U} + I_{1T} + I_{1r} + I_{2r} + R \le \frac{\Lambda}{\mu}\}.$$

is positively-invariant and attracting.

The disease-free equilibrium is $E_{20} = (\frac{\Lambda}{\mu}, 0, 0, 0, 0, 0)$.

3.1. Reproduction numbers of Model II

We derive the reproduction numbers using the next generation matrix [9]. The four infected variables are $I_{1U}, I_{1T}, I_{1r}, I_{2r}$, the matrices F and V denote the matrices corresponding to the new infection terms and the transitions between stages, respectively.

Note that

$$F = \begin{pmatrix} (1-\sigma)\beta_{1U} & (1-\sigma)\beta_{1T} & 0 & 0 \\ \sigma\theta_1\beta_{1U} & \sigma\theta_1\beta_{1T} & 0 & 0 \\ \sigma\theta_2\beta_{1U} & \sigma\theta_2\beta_{1T} & \beta_{1r} & 0 \\ \sigma\theta_3\beta_{1U} & \sigma\theta_3\beta_{1T} & 0 & \beta_{2r} \end{pmatrix},$$

$$V = \begin{pmatrix} \mu+\gamma_1 & 0 & 0 & 0 \\ 0 & \mu+\gamma_2 & 0 & 0 \\ 0 & 0 & \mu+\gamma_3 & 0 \\ 0 & 0 & 0 & \mu+\gamma_4 \end{pmatrix}.$$

Then

$$FV^{-1} = \begin{pmatrix} \frac{(1-\sigma)\beta_{1U}}{\mu+\gamma_1} & \frac{(1-\sigma)\beta_{1T}}{\mu+\gamma_2} & 0 & 0 \\ \frac{\sigma\theta_1\beta_{1U}}{\mu+\gamma_1} & \frac{\sigma\theta_1\beta_{1T}}{\mu+\gamma_2} & 0 & 0 \\ \frac{\sigma\theta_2\beta_{1U}}{\mu+\gamma_1} & \frac{\sigma\theta_2\beta_{1T}}{\mu+\gamma_2} & \frac{\beta_{1r}}{\mu+\gamma_3} & 0 \\ \frac{\sigma\theta_3\beta_{1U}}{\mu+\gamma_1} & \frac{\sigma\theta_3\beta_{1T}}{\mu+\gamma_2} & 0 & \frac{\beta_{2r}}{\mu+\gamma_4} \end{pmatrix}.$$

The control reproduction number is

$$R_{2c} = \rho(FV^{-1}) = \max\{R_{2sc}, R_{r2}\}.$$

where

$$R_{2sc} = \frac{\theta_1\sigma\beta_{1T}}{\mu+\gamma_2} + \frac{(1-\sigma)\beta_{1U}}{\mu+\gamma_1}, R_{2r} = \frac{\beta_{1r}}{\mu+\gamma_3}, R_{2m} = \frac{\beta_{2r}}{\mu+\gamma_4},$$

and

$$R_{r2} = \max\{R_{2r}, R_{2m}\}.$$

Here, R_{2m} represents the number of secondary infection cases produced by multi-drug resistant strains during the period of infection in a susceptible population.

Let

$$R_{2U} = \frac{\beta_{1U}}{\mu+\gamma_1}, R_{2T} = \frac{\beta_{1T}}{\mu+\gamma_2}.$$

The biological interpretations of these quantities R_{2U} and R_{2T} are as follows. R_{2U} and R_{2T} represent the numbers of secondary infection cases produced by an untreated and treated case, respectively, during the period of infection in a susceptible population.

3.2. Global stability and more on reproduction numbers of Model II

As discussed in Model I, we consider more about the reproduction number to capture the nonlinear relationship with σ and show that adverse effects associated with antiviral treatment. In some cases, the level of infection may actually get higher when treatment rate is increased. To prove this, we consider the partial derivative of R_{2sc} with respect to σ.

$$\frac{\partial R_{2sc}}{\partial \sigma} = \theta_1 R_{2T} - R_{2U}.$$

From $0 < \theta_1 < 1$ and $\gamma_2 > \gamma_1$, we know that $R_{2T} < R_{2U}$, and hence, $\frac{\partial R_{2sc}}{\partial \sigma} < 0$. Thus, R_{2sc} is a decreasing function of σ. Referring to the expression of R_{r2}, we know that R_{r2} does not depend on σ. Similarly, this can not capture the nonlinear relationship between R_{2sc} and σ, which suggests that more about reproduction number need to be considered [12].

When a person is infected with H1N1 influenza, the number of secondary cases consists of the following four components:

$$①\frac{S^0}{N^0}(1-\sigma)\frac{\beta_{1U}}{\mu+\gamma_1}, ②\frac{S^0}{N^0}\sigma\theta_1\frac{\beta_{1T}}{\mu+\gamma_2}, ③\frac{S^0}{N^0}\sigma\theta_2\frac{\beta_{1r}}{\mu+\gamma_3}, ④\frac{S^0}{N^0}\sigma\theta_3\frac{\beta_{2r}}{\mu+\gamma_4}.$$

If the total population size N^0 is sufficiently large so that the number of infected cases is relatively small, then $\frac{S(t)}{N(t)}$ can be closely approximated by $\frac{S^0}{N^0}$ and closely approximated 1. The component ① represents the cases of new infected H1N1 influenza cases who are untreated. The component ② represents the cases of new infected H1N1 who are treated and do not develop drug resistance. The component ③ represents the cases of new infected H1N1 influenza with drug resistant due to antiviral treatment. The component ④ represents the cases of new infected H1N1 influenza with multi-drug resistant strains due to antiviral treatment. Clearly, the quantity R_{2sc} is the sum of the first two components. Therefore, R_{2sc} underestimates the number of secondary infections by a sensitive case. For ease of reference, we denote the sum of components ③ and ④ by R_{AR}, which refers to the acquired reproduction number, and hence,

$$R_{AR} = \sigma\theta_2\frac{\beta_{1r}}{\mu+\gamma_3} + \sigma\theta_3\frac{\beta_{2r}}{\mu+\gamma_4}.$$

Let R_{TC} denote the sum of both R_{2sc} and R_{AR}, it follows that

$$R_{TC} = \frac{\theta_1\sigma\beta_{1T}}{\mu+\gamma_2} + \frac{(1-\sigma)\beta_{1U}}{\mu+\gamma_1} + \sigma\theta_2\frac{\beta_{1r}}{\mu+\gamma_3} + \sigma\theta_3\frac{\beta_{2r}}{\mu+\gamma_4}.$$

Obviously, R_{TC} is a function of σ. Notice that

$$\frac{\partial R_{TC}}{\partial \sigma} = \theta_1 R_{2T} - R_{2U} + \theta_2 R_{2r} + \theta_3 R_{2m},$$

which is independent of σ. Thus, R_{TC} is a linear function of σ. Furthermore, R_{TC} is always a monotone function of σ. While, paper [12] finds that this relationship can not capture the nonlinear relationship with σ, that suggests that more generations of infections need to be considered.

For the purpose of presentation, denote R_{TC} as the second generation in which new infections are produced. Let $R_{TC}^{[3]}$ denote the number of tertiary infected cases, from the paper of Qiu and Feng [12], we know the expression of $R_{TC}^{[3]}$ as follows

$$R_{TC}^{[3]} = R_{2sc}R_{2sc} + (R_{2sc} + R_{r2})R_{AR},$$

the first and second items in the above expression represent the numbers of tertiary sensitive and resistant cases, respectively, produced in the third generation by a typical sensitive case. The derivative of $R_{TC}^{[3]}$ with respect to σ is
$\frac{\partial R_{TC}^{[3]}}{\partial \sigma} = (\theta_1 R_{2T} - R_{2U})(2\theta_1 \sigma R_{2T} + 2(1-\sigma)R_{2U} + \sigma\theta_2 R_{2r} + \sigma\theta_3 R_{2m}) + (\theta_1 \sigma R_{2T} + (1-\sigma)R_{2U} + R_{r2})(\theta_2 R_{2r} + \theta_3 R_{2m})$.

Let

$$\sigma^* = \frac{(R_{2U} - \theta_1 R_{2T})R_{2U} - (R_{2U} + R_{r2})(\theta_2 R_{2r} + \theta_3 R_{2m})}{(\theta_1 R_{2T} - R_{2U})^2}$$

and

$$\sigma_c = \begin{cases} 0 & \sigma^* \leq 0; \\ \sigma^* & 0 < \sigma^* < 1; \\ 1 & \sigma^* \geq 1. \end{cases}$$

We can show that if

$$\theta_1 R_{2T} - R_{2U} + \theta_2 R_{2r} + R_{2m} < 0,$$

we have

$$\frac{\partial^2 R_{TC}^{[3]}}{\partial^2 \sigma}|_{\sigma=\sigma^*>0},$$

Similarly, if

$$\theta_1 R_{2T} - R_{2U} + \theta_2 R_{2r} + R_{2m} > 0,$$

we get

$$\frac{\partial^2 R_{TC}^{[3]}}{\partial^2 \sigma}|_{\sigma=\sigma^*<0},$$

Thus, the dependence of $R_{TC}^{[3]}$ on σ is nonlinear, there may be a critical value σ_c such that $R_{TC}^{[3]}$ decreases for $0<\sigma<\sigma_c$ and increases for $\sigma_c<\sigma<1$.

The key difference between $R_{TC}^{[3]}$ and R_{TC} in terms of their functional relationships with σ suggests that $R_{TC}^{[3]}$ can provide a more accurate description on how treatment can negatively impact the disease dynamics.

We observe that Model I does not separate untreated and treated individuals, and there are more parameters than that in Model II, and we can not capture the nonlinear relationship of treatment until the second generation. However, Model II separates untreated and treated individuals immediately, and we can not capture the nonlinear relationship of treatment until the tertiary generation. There are some other differences between the two models, which will be given in the section 4.

Now, for convenience we denote $\mu+\gamma_i(i=1,2,3,4)$ by $\mu_i(i=1,2,3,4)$.

Theorem 3. *If $R_{2c}<1$, the disease-free equilibrium E_{20} is locally asymptotically stable, and unstable if $R_{2c}>1$.*

Proof. The Jacobian of system (3.1) at E_{20} is

$$J|_{E_{20}}=\begin{bmatrix} -\mu & -\beta_{1U} & -\beta_{1T} & -\beta_{1r} & -\beta_{2r} & \omega \\ 0 & \mu_1[(1-\sigma)R_{2U}-1] & (1-\sigma)\beta_{1T} & 0 & 0 & 0 \\ 0 & \sigma\theta_1\beta_{1U} & \mu_2(\sigma\theta_1 R_{2T}-1) & 0 & 0 & 0 \\ 0 & \sigma\theta_2\beta_{1U} & \sigma\theta_2\beta_{1T} & \mu_3(R_{2r}-1) & 0 & 0 \\ 0 & \sigma\theta_3\beta_{1U} & \sigma\theta_3\beta_{1T} & 0 & \mu_4(R_{2m}-1) & 0 \\ 0 & \gamma_1 & \gamma_2 & \gamma_3 & \gamma_4 & -(\mu+\omega) \end{bmatrix}.$$

Obviously, we can calculate that four of the eigenvalues are $-\mu,-(\mu+\omega),\mu_3(R_{2r}-1)<0,\mu_4(R_{2m}-1)<0$, and the other two eigenvalues are determined by the following quadratic equation

$$\lambda^2-\{\mu_2(\sigma\theta_1 R_{2T}-1)+\mu_1[(1-\sigma)R_{2U}-1]\}\lambda+\mu_1\mu_2(1-R_{2sc})=0.$$

From

$$\lambda_1+\lambda_2=\mu_2(\sigma\theta_1R_{2T}-1)+\mu_1[(1-\sigma)R_{2U}-1]<0,$$

and

$$\lambda_1\lambda_2=\mu_1\mu_2(1-R_{2sc})>0,$$

we can conclude that both λ_1 and λ_1 have negative real parts, thus all eigenvalues of $J|_{E_{20}}$ have negative real parts, hence E_{20} is locally asymptotically stable. □

The total population size $N(t)$ satisfies the equation $\frac{dN}{dt}=\Lambda-\mu N$ and $N(t)\to\frac{\Lambda}{\mu}$ as $t\to\infty$. Similar to the proof of Theorem 2.2, we can obtain the following limiting system

$$\begin{cases}\frac{dS}{dt}=\Lambda+\omega(\frac{\Lambda}{\mu}-S-I_{1U}-I_{1T}-I_{1r}-I_{2r})-\beta_{1U}\frac{\mu}{\Lambda}SI_{1U}\\ \qquad -\beta_{1T}\frac{\mu}{\Lambda}SI_{1T}-\beta_{1r}\frac{\mu}{\Lambda}SI_{1r}-\beta_{2r}\frac{\mu}{\Lambda}SI_{2r}-\mu S,\\ \frac{dI_{1U}}{dt}=(1-\sigma)(\beta_{1U}\frac{\mu}{\Lambda}SI_{1U}+\beta_{1T}\frac{\mu}{\Lambda}SI_{1T})-\mu_1I_{1U},\\ \frac{dI_{1T}}{dt}=\sigma\theta_1(\beta_{1U}\frac{\mu}{\Lambda}SI_{1U}+\beta_{1T}\frac{\mu}{\Lambda}SI_{1T})-\mu_2I_{1T},\\ \frac{dI_{1r}}{dt}=\sigma\theta_2(\beta_{1U}\frac{\mu}{\Lambda}SI_{1U}+\beta_{1T}\frac{\mu}{\Lambda}SI_{1T})+\beta_{1r}\frac{\mu}{\Lambda}SI_{1r}-\mu_3I_{1r},\\ \frac{dI_{2r}}{dt}=\sigma\theta_3(\beta_{1U}\frac{\mu}{\Lambda}SI_{1U}+\beta_{1T}\frac{\mu}{\Lambda}SI_{1T})+\beta_{2r}\frac{\mu}{\Lambda}SI_{2r}-\mu_4I_{2r},\\ \frac{dR}{dt}=\gamma_1I_{1U}+\gamma_2I_{1T}+\gamma_3I_{1r}+\gamma_4I_{2r}-\mu R-\omega R,\\ \theta_1+\theta_2+\theta_3=1.\end{cases}\tag{3.2}$$

If $R_{2c}<1$, then $R_{2sc}<1$ and $R_{2m}<1$. From Theorem 3.1, the disease-free equilibrium E_{20} is locally asymptotically stable. In the following, we only need to prove that E_{20} is a global attractor.

It follows from the first equation of (4) that

$$S'\le\frac{(\mu+\omega)\Lambda}{\mu}-(\mu+\omega)S.$$

By the comparison principle, we have $S(t)\le\frac{\Lambda}{\mu}+(S(0)-\frac{\Lambda}{\mu})e^{-(\mu+\omega)t}$. Without loss of generality, we can assume that $S(t)\le\frac{\Lambda}{\mu}$. Then it follows from the second and third equations of (3.2) that

$$\begin{cases}I_{1U}'\le[(1-\sigma)\beta_{1U}-\mu_1]I_{1U}+(1-\sigma)\beta_{1T}I_{1T},\\ I_{1T}'\le\sigma\theta_1\beta_{1U}I_{1U}+(\sigma\theta_1\beta_{1T}-\mu_2)I_{1T}.\end{cases}$$

Based on the comparison principle [15], it is easy to show that $I_{1U}(t) \to 0$ and $I_{1T}(t) \to 0$ as $t \to +\infty$ if $R_{2sc} < 1$. From the fourth and fifth equation of (3.2), we get

$$\begin{cases} I'_{1r} \leq \sigma\theta_2(\beta_{1U} + \beta_{1T}) + (\beta_{1r} - \mu_3)I_{1r}, \\ I'_{2r} \leq \sigma\theta_3(\beta_{1U} + \beta_{1T}) + (\beta_{2r} - \mu_4)I_{2r}. \end{cases}$$

Since $I_{1U}(t) \to 0, I_{1T}(t) \to 0$ as $t \to +\infty$ and $R_{2m} < 1$ holds, we obtain $I_{1r}(t) \to 0, I_{2r}(t) \to 0$ as $t \to +\infty$. Similarly, from the sixth equation of (3.2), it is easy to get that $R(t) \to 0$ as $t \to +\infty$. Substitution of these into the first equation of (3.2) gives $S(t) \to \frac{\Lambda}{\mu}$ as $t \to +\infty$. This implies that the disease-free equilibrium E_{20} is a global attractor. Thus, we obtain the following theorem.

Theorem 4. *If $R_{2c} < 1$, the disease-free equilibrium E_{20} is globally asymptotically stable.*

4. Numerical simulations

In this section, we present some numerical simulation results, which confirm or extend the analytic results and illustrate the effect of new infections with sensitive strain and treatment $(f_i(i = 1,2))$ on controlling the infection.

We consider the situation in which the population size has reached the steady-state $\frac{\Lambda}{\mu} = 10^5$. Assume that the life span is $\frac{1}{60}$, then $\mu \approx 0.00005$. According to [13], the immunity obtained from infection about one year, so we choose $\omega = \frac{1}{365} \approx 0.003$. Estimating of the basic reproduction number for H1N1 influenza ranges from 1.75 to 3.96 in 2009-2010 year [14]. In this paper, we set $R_{10} = 1.75$. The baseline transmission coefficient (β_{1s}) for drug-sensitive case can be calculated from the formula for R_{10}, which gives $\beta_{1s} = 0.3$. During H1N1 influenza, several percentage of individuals who receive adamantanamine treatment may develop drug-resistant and when drug-resistant strain develops, some individuals can not recover, they will continue to seek other drugs for treatment, so we choose reasonable c_1 and c_2. We assume an average period of infection to be 6 days, so the recovery rate $\gamma_i(i = 1,2,3) = 0.1667$ [12]. The basic reproduction number of the drug-resistant strain R_{r1} can be either greater or smaller than that of the sensitive strain R_{1s}. Here, we consider the case $\frac{R_{r1}}{R_{1s}} < 1$, and assume $R_{r1} = 0.9 * R_{1s} = 1.5$, those parameter values are summarized in Table 2.

Table 2 Parameter values for system (2.1)

Parameter	Estimated value	Unit	resources
$\frac{\Lambda}{\mu}$	100000	number	[12]
μ	0.00005	day^{-1}	[12]
ω	0.003	day^{-1}	[13]
β_{1s}	0.3	day^{-1}	[14]
β_{1r}	0.25	-	[15]
β_{2r}	Variable	-	[16]
$f_i(i=1,2)$	Variable	-	[12]

Firstly, we only consider the Model I, and perform some simulations.

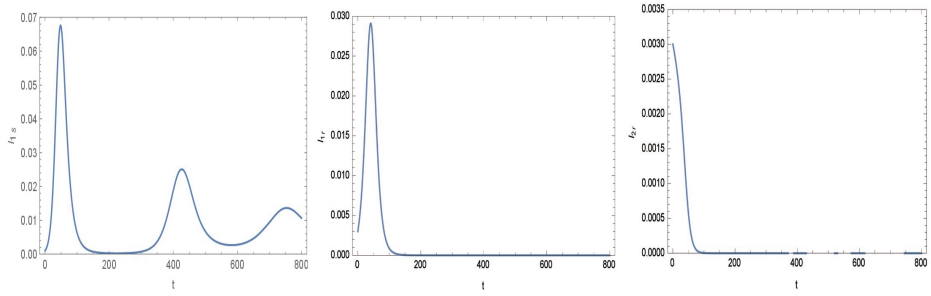

Fig 1: Numerical solutions for I_{1s}, I_{1r}, I_{2r} of Model I, with treatment rate $f_1 = f_2 = 0$.

Fig 1 shows the proportion of sensitive, single and multi-drug resistant cases among total population, respectively, without treatment. Consider the fact that few individuals can develop the multi-drug resistant, hence, we assume $R_{1m} < 1$. From Fig 1, we also note that there appears three peaks, which declines in return, but the disease has long duration. The reason for this phenomenon may be some individuals have immunity for the H1N1 influenza, perhaps they have recovered or they have injected the vaccine of H1N1. There exists only one epidemic peak among single resistant individuals. The time of arriving peak of sensitive cases is almost the same as single resistant cases. Finally, the multi-drug resistant dies out.

When the treatment rate is greater than 0.12, the basic reproduction number is less than one, which implies the control measures can effectively prevent disease outbreaks. So we consider

the case that the treatment rate is less than 0.12. Firstly, we consider $f_2 = 0$ and vary the treatment rate f_1.

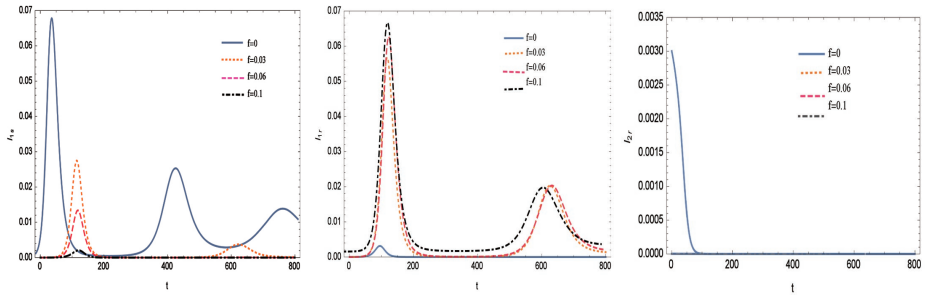

Fig 2: The change of infected drug sensitive, single and multi-drug resistant individuals with different treatment rate f_1.

From the first picture of Fig 2, we find that the rebound phenomenon can vanish, the size of disease can be decreased and the duration of disease becomes shorter with the increase of treatment rate. The arriving of peak can be delayed, which is beneficial for the development of the vaccine. These are the benefits of effective treatments for disease. However, by the second picture of Fig 2, we notice the adverse effects of treatment. With the larger of treatment rate, more individuals become single-drug resistant and when the treatment rate arrived 0.1, the peak time puts forward, which can cause more serious burden to the society. Meanwhile, we calculate the acquired reproduction number and the total control reproduction number, both of them are increasing, which explains the adverse effects on treatment well. Due to $R_{1m} < 1$ and $f_2 = 0$, there is no effect on multi-drug resistant individuals.

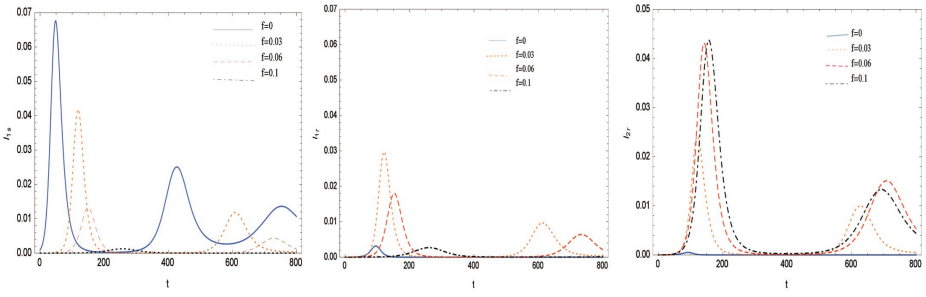

Fig 3: The change of infected drug sensitive, single and multiple drug-resistant individuals with different treatment rate f_2.

Next, fix treatment rate $f_1 = 0.01$ and vary f_2. For the purpose of observing the influence on multi-drug resistant clearly, we consider the case of $R_{1r} > R_{1m} > 1$. We observe the difference

between Fig 2 and Fig 3. Adopting repeated treatment can not eliminate the disease rebound phenomenon in sensitive cases class, but can reduce the size of epidemic disease in single drug resistant cases class. Meanwhile, the adverse effects of treatment is more obvious in multi-drug resistant cases class. Whether taking repeated treatment measures should be considered carefully.

Subsequently, we perform some simulations for Model II. We suppose that Model I and Model II have the same characteristics, such as the basic reproduction number, immunity and recovery rate. Because that the classification of drug sensitive cases from both two model is different, we find that the basic reproduction number is less than one, when the treatment rate exceeds $\sigma = 0.4$, which implies the control measures can effectively prevent disease outbreaks. So we consider the case that the treatment rate is less than 0.4.

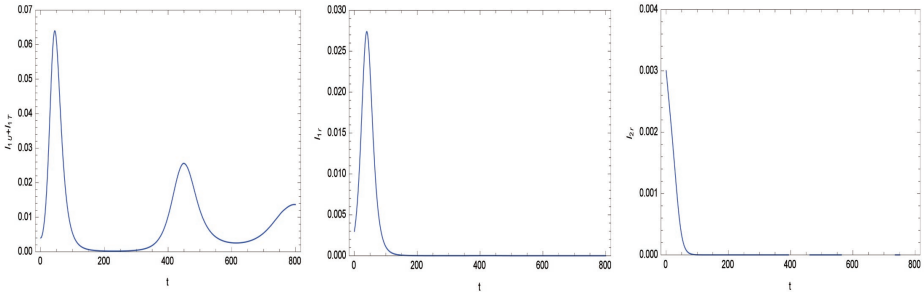

Fig 4: The change of $I_{1U} + I_{1T}$, I_{1r} and I_{2r} with treatment rate $\sigma = 0$.

From Fig 4, we can obtain the same result as that in Model I.

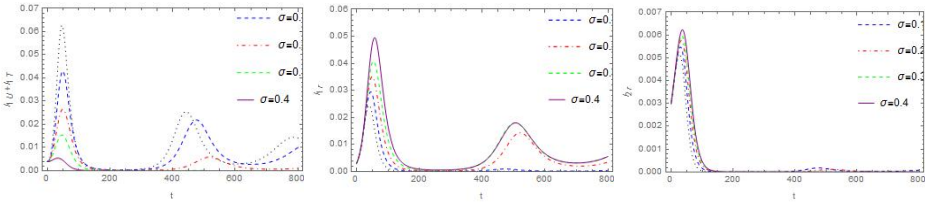

Fig 5: The change of infected drug sensitive, single and multi-drug resistant individuals with different treatment rate σ.

With the increase of treatment rate σ, infected sensitive cases decrease and the time of peak arriving can be delayed. However, both the number of infected single and multi-drug resistant cases increase, that can be explained for adverse effects on treatment. Furthermore, there may appear rebound phenomena among infected multi-drug resistant.

5. Comparison between Model I and Model II

We now discuss the difference between two models.

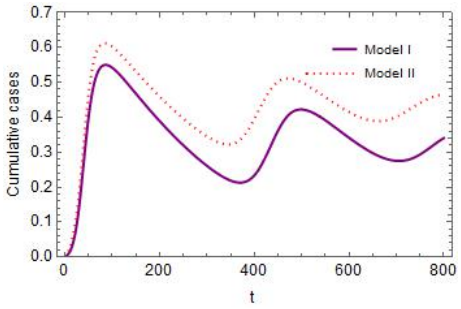

Fig 6: The proportion of cumulative incidence in the total population with treatment rate $\sigma = 0$.

By Fig 6, we notice that the Model II has higher cumulative incidence than Model I in case of without treatment. The reason for this result may include two aspects: one is the time of infected stages, the other is the infected individuals relationship about the treatment. Model I reflecting the average overall time in the I_{1s} compartment is $\frac{1}{\mu+f_1+\gamma_1}$, but in fact, some patients do not seek antiviral treatment, and so the average overall time should be $\frac{1}{\mu+\gamma_1}$. From this perspective, we will shorten the time of natural recovery. The similar conclusion holds for I_{1r} compartment. If the infected individuals, do not immediately seek treatment, but accept treatment and recover later, hence, the overall average time is $\frac{1}{k_1}+\frac{1}{\mu+f_1+\gamma_1}$. Evidently, we have repeated the calculation of the time of treatment. Because $\frac{1}{k_1}$ denotes the time of individuals seeing doctors, and receiving antiviral treatment. Considering that individuals through treatment develop multi-drug resistant strains I_{2r}, Model I imposes the following constrains to balance the times spent in the related stages (e.g., the total time spent from I_{1s} to I_{2r} equals the summation of the times spent from I_{1s} to I_{1r} and from I_{1r} to I_{2r}), which will delay the time of developing I_{2r}.

Model II can avoid the accumulation of time, in which the infected individuals are divided into two parts, including immediately seeking treatment and without treatment. Then, the time is very clear. $\frac{1}{\mu+\gamma_1}$ is the average overall time in the I_{1U} compartment, $\frac{1}{\mu+\gamma_2}$ is the average overall time in the I_{1T} compartment receiving treatment and recovering. Similarly, we can get $\frac{1}{\mu+\gamma_3}$ and $\frac{1}{\mu+\gamma_4}$ is the average overall time in the I_{1r} compartment and I_{2r} compartment, respectively. So Model I is not sufficient to show relationship of time. In order to conquer this, we put forward

Model II. Model I can not distinguish the infected individuals who receive treatment, however, Model II can distinguish well. Which can be identified the force of infection and depict the duration of disease well.

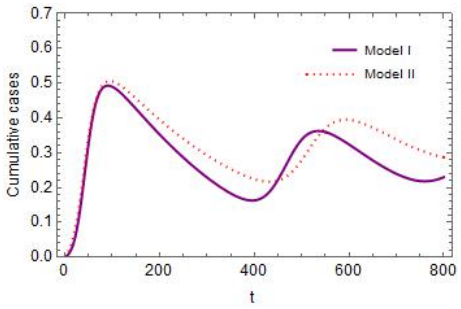

Fig 7: The proportion of cumulative incidence in the total population with treatment rate $\sigma = 0.1$

From Fig 7, we fix $\sigma = 0.1$, and note that the cumulative incidence of Model II is higher than that of Model I. Because when treatment rate arrived 0.1, the basic reproduction number of Model I is less than that of Model II. The arriving time of peak for the second outbreak of Model II is earlier than that of Model I. In our view of this phenomenon, Model II has more accurate time stages than Model I.

6. Discussion and Conclusion

In this paper, we study two mathematical models of H1N1 influenza transmission dynamics, that incorporate drug-sensitive and drug-resistant strains. The main purpose of this study is to examine the impact of antiviral treatment on the prevalence of drug resistance. A detailed stability analysis of the disease-free equilibria, and derivation of the basic and control reproduction number are presented. We also Demonstrate how the acquired reproduction number can be used to explain the adverse effects associated with antiviral treatment. This effect is interpreted using a quantity termed the total control reproduction number.

One of the interesting findings is that, despite the key role that control reproduction numbers play, they do not provide sufficient measures for examining the effect of antiviral treatment or reflect the adverse effects of treatment. To reveal the role of antiviral treatment in controlling H1N1 influenza, we need to consider the acquired reproduction number and the total control reproduction number.

The two models considered in this study have several different features, some of which allow for unique insight into the disease dynamics including the influence of drug resistance on the reproduction numbers. For example, in Model II, we derived the quantity $R_{TC}^{[3]}$ for the control reproduction number, which has different properties than the conventional control reproduction number due to the contribution of acquired resistance R_{AR}. We showed that, under certain conditions, there may exist a threshold value σ^* such that $R_{TC}^{[3]}$ decreases with σ for $\sigma < \sigma^*$ but increases with σ for $\sigma > \sigma^*$. This suggests that the number $R_{TC}^{[3]}$ may provide a better quantity than R_{2sc} for elevating the effect of treatment on the level of infection.

We develop two models with different assumptions about the timing of treatment. It is important to examine the critical assumptions and better understand their possible impact on model outcomes. It often happens that, when a model is formulated, certain assumptions are made without consideration of their consequences. In this paper, we use the exponential waiting time in disease stages. That is, the survival probability is described by a negative exponential function. Due to the memoryless property of exponential distribution, this leads to ODE models that are easy to be analyzed. But models with exponentially distributed infectious stage can result in misleading or incorrect evaluations of effectiveness. In the future, we will pay further attention on the impact of non-exponentially distributed disease stages to epidemic control.

Conflict of Interests

The authors declare that there is no conflict of interests.

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