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ORIGINAL ARTICLE

Transmission Dynamics of an Influenza Model with Vaccination and Antiviral Treatment

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Abstract Vaccination and antiviral treatment are two important prevention and control measures for the spread of influenza. However, the benefit of antiviral use can be compromised if drug-resistant strains arise. In this paper, we develop a mathematical model to explore the impact of vaccination and antiviral treatment on the transmission dynamics of influenza. The model includes both drug-sensitive and resistant strains. Analytical results of the model show that the quantities $\mathcal{R}_{SC}$ and $\mathcal{R}_{RC}$, which represent the control reproduction numbers of the sensitive and resistant strains, respectively, provide threshold conditions that determine the competitive outcomes of the two strains. These threshold conditions can be used to gain important insights into the effect of vaccination and treatment on the prevention and control of influenza. Numerical simulations are also conducted to confirm and extend the analytic results. The findings imply that higher levels of treatment may lead to an increase of epidemic size, and the extent to which this occurs depends on other factors such as the rates of vaccination and resistance development. This suggests that antiviral treatment should be implemented appropriately.

Keywords Influenza · Antiviral treatment · Vaccination · Stability · Drug-resistant strains

1. Introduction

Influenza (the flu) is a contagious respiratory illness caused by influenza viruses, which are certain RNA viruses of the *Orthomyxoviridae* family (Lamb, 1989; Earn et al., 2002). In humans, common symptoms of influenza infection are fever, sore throat, muscle pains, severe headache, coughing, and weakness and fatigue. Although it is sometimes confused with the common cold, influenza is a much more severe disease. It has historically been

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a cause of excessive morbidity and mortality. Three influenza pandemics have occurred during the twentieth century and killed tens of millions of people. The most famous and lethal outbreak was the so-called Spanish Flu pandemic (type A influenza, H1N1 subtype), which lasted from 1918 to 1919. Older estimates indicate that 40–50 million people died from the disease, while from current estimates 50–100 million people were killed worldwide. Later flu pandemics were not so devastating. They included the 1957 Asian flu and the 1968 Hong Kong flu, but even these smaller outbreaks killed millions of people. In the 1990s, a deadly avian strain named H5N1 has posed the greatest risk for a new influenza pandemic since it first killed humans in Asia. Because of the high risk for the avian influenza pandemic and large number of deaths associated with influenza, it is imperative to increase our understanding of the influenza disease dynamics. Mathematical models have provided a useful tool to gain insights into the transmission and control of the disease. These insights can potentially help guide us to assess the effectiveness and implications of various preventive and control strategies.

Several recent studies on influenza modeling have focused on the influence of prevention and control measures including vaccination, antiviral use, quarantine, and isolation (see, for example, Ferguson et al., 2003; Alexander et al. 2004, 2007, 2008; Nuño et al., 2005; Regoes and Bonhoeffer, 2006; Lipsitch et al., 2007; McCaw and McVernon, 2007; McCaw et al., 2008). These models have provided useful information about the impact of various control measures in the disease dynamics. However, most of these models have considered either vaccination or antiviral use alone. In this paper, we study a model that includes explicitly both antiviral use and vaccination. We adapt the approach of Lipsitch et al. (2007) for modeling the drug treatment (without prophylaxis). We extend their model by including a vaccinated class and vital dynamics (recruitment and mortality). The new model allows us to examine the effects of antiviral use on the prevalence of both drug-sensitive and drug-resistant strains under the influence of vaccination.

Mathematical properties of the model system are studied both analytically and numerically. It is shown that the system has three possible equilibrium points including an endemic equilibrium at which both strains are present. A detailed analysis of stability and uniform persistence is conducted, which shows that the dynamic behaviors of the system are determined by two quantities, $\mathcal{R}_{SC}(\nu, f)$ and $\mathcal{R}_{RC}(\nu, f)$ (where ν represents the vaccination rate and f represents the treatment rate; see (3)). Results of the bifurcation analysis suggest that the effects of drug treatment on the infection levels of both strains depend not only on the levels of drug use, but also on the rate at which the population is vaccinated. For example, for a given vaccination rate $\nu > 0$ such that $\mathcal{R}_{SC}(\nu, 0) > \mathcal{R}_{RC}(\nu, 0) > 1$, the sensitive strain will be uniformly persistent, while the resistant will be absent. As the treatment rate f increases, the inequality may be reversed such that $1 < \mathcal{R}_{SC}(\nu, f) < \mathcal{R}_{RC}(\nu, f)$, in which case the resistant strain will eliminate the sensitive strain. Moreover, benefits of antiviral use may be compromised in the sense that increasing treatment rate may lead to a higher number of cumulative infection. Whether or not these scenarios are possible and for what values of f they will occur depend on the level of population immunity determined by ν.

Another interesting finding from our model is that we can derive a new epidemiological quantity which represents a measure for the *total* control reproduction number, denoted by $\mathcal{R}_{TC}^{[n]}$, of a sensitive case in the nth generation. We demonstrate that $\mathcal{R}_{TC}^{[n]}$ provides a more suitable measure than the usual control reproduction number $\mathcal{R}_{SC}$ in terms of their capability of detecting a potential negative effect of antiviral use in disease control. More

specifically, we show that $\mathcal{R}_{SC}$ is always a decreasing function of the treatment rate f, whereas $\mathcal{R}_{TC}^{[n]}$ may assume its minimum at an intermediate value $f_c \in (0, 1)$ and become an increasing function of f for $f > f_c$ (see Section 6). This captures the phenomenon we observed about the total number of infections in the numerical simulations of the model. This suggests that the quantity $\mathcal{R}_{TC}^{[n]}$ can serve as a better indicator than $\mathcal{R}_{SC}$ for examining the effect of drug use on the epidemic size.

The analytical results are also used to guide our numerical studies, which illustrate how the combination of vaccination and antiviral use may change the competitive outcomes of the two strains as well as the total infection level, especially in the case when the infection level increases with drug treatment rate.

The paper is organized as follows. Section 2 introduces the new model which is an extension of the model in Lipsitch et al. (2007) by including a vaccinated class and vital dynamics. Threshold conditions for the existence of equilibria are derived in Section 3. Section 4 includes the analysis of stability and uniform persistence, and Section 5 is devoted to numerical simulations. In Section 6, we discuss some issues related to the connection between control reproduction numbers and epidemic sizes. Section 7 summarizes the findings and conclusions.

2. Model description

In Lipsitch et al. (2007), an *SIR* type of epidemic model is proposed to study the effect of prophylaxis and drug treatment on the proportions of sensitive- and resistant-strains of influenza infections. It is assumed that a fraction of infected individuals will receive prophylaxis and that among the individuals who are not prophylaxed a fraction will be treated. It is also assumed that drug-resistant cases may arise as a consequence of antiviral use. Vital dynamics and vaccination are not considered and the transmission rates of the two strains may be different.

The model presented in this paper adopts a similar structure as that in Lipsitch et al. (2007). We introduce a vaccinated class and include vital dynamics. As the main purpose of this model is to look at the interaction between vaccination and drug use, we neglect prophylaxis and consider only drug treatment. Let N denote the total number of the population which is divided into six subclasses: susceptible (S), vaccinated (V), infected with the sensitive strain and untreated (I_{SU}) or treated (I_{ST}), infected with the resistant strain (I_R), and recovered (R). Assume that there is a constant recruitment rate Λ (into the susceptible class) and a per-capita natural death rate μ. A transition diagram between these epidemic classes is shown in Fig. 1. Susceptible individuals are vaccinated at per-capita rate ν and the immunity wanes at per-capita rate σ. The functions $\lambda_S(t)$ and $\lambda_R(t)$ represent the rates at which a susceptible individual becomes infected with the sensitive and resistant strains, respectively. A fraction f of infected individuals with the sensitive strain receives treatment, and with a probability c an individual who received treatment will develop drug resistance. The transmission rate by an individual who received treatment will be reduced by a factor δ. An infected individual in the I_j ($j = ST, SU, R$) class recovers at the rate k_j, and a recovered individual may lose immunity at the rate w ($w = 0$ in the case of permanent immunity). The definitions of all variable and parameters are summarized in Table 1. All parameters are positive except that $0 \le f < 1$ and $0 \le c < 1$.

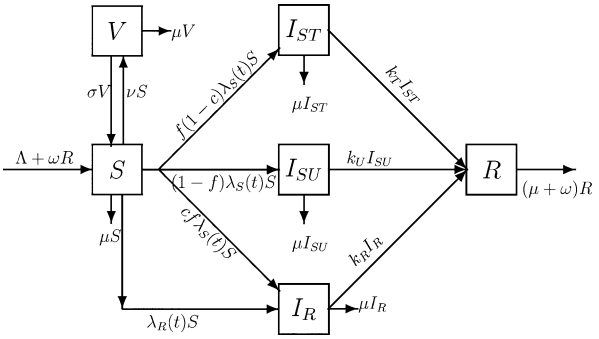

Fig. 1 Diagram of transitions between epidemiological classes.

Table 1 Definitions of frequently used symbols

Parameter	Description
Λ	Recruitment rate of individuals
$\frac{1}{\mu}$	Average life-span
ν	Rate at which susceptible individuals are vaccinated
$\frac{1}{\omega}$	Average time of losing immunity acquired by infection
$\frac{1}{\sigma}$	Average time of losing vaccine-induced immunity
β_S	Transmission coefficient of the untreated infected individuals
β_R	Transmission coefficient of the drug-resistant infected individuals
δ	Reduction factor in infectiousness due to the antiviral treatment
f	Fraction of the new infected cases who are treated
c	Fraction of the treated infected cases who progress to the drug-resistant stage
$\frac{1}{k_U}$	Average infected length of the untreated cases
$\frac{1}{k_T}$	Average infected length of the treated cases
$\frac{1}{k_R}$	Average infected length of the drug-resistant cases

Based on the transition diagram in Fig. 1, the model is described by the following system of differential equations:

$$\begin{cases} \frac{dS}{dt} = \Lambda - (\mu+\nu)S - \lambda_S(t)S - \lambda_R(t)S + \omega R + \sigma V, \\ \frac{dV}{dt} = \nu S - (\sigma+\mu)V, \\ \frac{dI_{SU}}{dt} = (1-f)\lambda_S(t)S - \mu I_{SU} - k_U I_{SU}, \\ \frac{dI_{ST}}{dt} = f(1-c)\lambda_S(t)S - \mu I_{ST} - k_T I_{ST}, \\ \frac{dI_R}{dt} = \lambda_R(t)S + fc\lambda_S(t)S - \mu I_R - k_R I_R, \\ \frac{dR}{dt} = k_T I_{ST} + k_U I_{SU} + k_R I_R - (\mu+\omega)R, \end{cases} \tag{1}$$

where

$$\lambda_S(t) = \beta_S \frac{I_{SU} + \delta I_{ST}}{N}, \qquad \lambda_R(t) = \beta_R \frac{I_R}{N},$$

$N = S + V + I_{SU} + I_{ST} + I_R + R$, and β_S and β_R denote the transmission coefficients for the sensitive and resistant strains, respectively.

3. Steady states and reproduction numbers

Notice that the total population size N satisfies the equation

$$N' = \Lambda - \mu N$$

and that $N(t) \to \frac{\Lambda}{\mu}$ as $t \to +\infty$, we know that the biologically feasible region

$$\Gamma = \left\{ (S, V, I_{SU}, I_{ST}, I_R, R) : 0 \le S, V, I_{SU}, I_{ST}, I_R, R, \right.$$
$$\left. S + V + I_{SU} + I_{ST} + I_R + R \le \frac{\Lambda}{\mu} \right\}$$

is positively invariant for the system (1). Therefore, in what follows, we consider only solutions with initial conditions inside the region Γ, in which the usual existence, uniqueness of solutions and continuation results hold.

The system (1) always has the disease-free equilibrium (DFE)

$$E_0 = \left(S^0, V^0, 0, 0, 0, 0\right),$$

where

$$S^0 = \frac{\sigma + \mu}{\sigma + \mu + \nu} N^0, \qquad V^0 = \frac{\nu}{\sigma + \mu + \nu} N^0, \qquad N^0 = \frac{\Lambda}{\mu} \tag{2}$$

represent the numbers of susceptible, vaccinated, and total populations, respectively, in the absence of infection. The existence of other equilibria are determined by the two quantities, $\mathcal{R}_{SC}$ and $\mathcal{R}_{RC}$, given by

$$\begin{aligned} \mathcal{R}_{SC} &= \frac{\sigma + \mu}{\sigma + \mu + \nu} \left[(1 - f)\mathcal{R}_{SU} + f(1 - c)\mathcal{R}_{ST} \right], \\ \mathcal{R}_{RC} &= \frac{(\sigma + \mu)}{(\sigma + \mu + \nu)} \mathcal{R}_R, \end{aligned} \tag{3}$$

where

$$\mathcal{R}_{SU} = \frac{\beta_S}{\mu + k_U}, \qquad \mathcal{R}_{ST} = \frac{\beta_S \delta}{\mu + k_T}, \qquad \mathcal{R}_R = \frac{\beta_R}{\mu + k_R}. \tag{4}$$

The biological interpretations of these quantities are as follows. $\mathcal{R}_{ST}$ and $\mathcal{R}_{SU}$ represent the numbers of secondary sensitive cases produced by a treated and untreated sensitive case, respectively, during the period of infection in a susceptible population. Notice that each sensitive case may either receive treatment with probability f or remain untreated with probability $1 - f$, and only a fraction $f(1 - c)$ of treated sensitive cases remains

sensitive (the fraction fc becomes resistant). Notice also that $(\sigma+\mu)/(\sigma+\mu+\nu)$ is the fraction of the population that is susceptible. Thus, $\mathcal{R}_{SC}$ (S for sensitive and C for control) represents the number of secondary sensitive cases produced by a typical sensitive case during the period of infection in a population where control measures (vaccination and treatment) are implemented.

Similarly, $\mathcal{R}_R$ in (4) represents the number of secondary resistant cases produced by a resistant case during the period of infection in a completely susceptible population. Thus, $\mathcal{R}_{RC}$ (R for resistant and C for control) represents the number of secondary resistant cases produced by a typical resistant case, i.e., the control reproduction number for the resistant strain, during the period of infection in a population where the fraction of susceptibles is $(\sigma+\mu)/(\sigma+\mu+\nu)$. A detailed derivation of $\mathcal{R}_{SC}$ and $\mathcal{R}_{RC}$ are given in Appendix A.

For ease of presentation, we discuss the cases $f=0$ (no treatment) and $f>0$ separately.

Case 1: $f=0$. Let $\mathcal{R}^0_{SC}=\mathcal{R}_{SC}|_{f=0}=\frac{\sigma+\mu}{\sigma+\mu+\nu}\mathcal{R}_{SU}$. In this case, system (1) has two possible nontrivial boundary equilibria

$$\hat{E}=(\hat{S},\hat{V},0,0,\hat{I}_R,\hat{R}) \quad \text{and} \quad \bar{E}=(\bar{S},\bar{V},\bar{I}_{SU},0,0,\bar{R}), \tag{5}$$

where

$$\begin{aligned} &\hat{S}=\frac{S^0}{\mathcal{R}_{RC}}, \qquad \hat{V}=\frac{V^0}{\mathcal{R}_{RC}},\\ &\hat{I}_R=\frac{(\mu+\omega)N^0}{\mu+\omega+k_R}\left(1-\frac{1}{\mathcal{R}_{RC}}\right), \qquad \hat{R}=N^0-\hat{S}-\hat{V}-\hat{I}_R, \end{aligned} \tag{6}$$

and

$$\begin{aligned} &\bar{S}=\frac{S^0}{\mathcal{R}_{SC}}, \qquad \bar{V}=\frac{V^0}{\mathcal{R}_{SC}},\\ &\bar{I}_{SU}=\frac{(\mu+\omega)N^0}{\mu+\omega+k_U}\left(1-\frac{1}{\mathcal{R}_{SC}}\right), \qquad \hat{R}=N^0-\bar{S}-\bar{V}-\bar{I}_R. \end{aligned} \tag{7}$$

It is clear from (6) and (7) that

(a) $\bar{E}$ exists if and only if $\mathcal{R}_{SC}>1>\mathcal{R}_{RC}$;
(b) $\hat{E}$ exists if and only if $\mathcal{R}_{RC}>1>\mathcal{R}_{SC}$; and
(c) both $\bar{E}$ and $\hat{E}$ exist if and only if $\mathcal{R}_{SC}>\mathcal{R}_{RC}>1$ or $\mathcal{R}_{RC}>\mathcal{R}_{SC}>1$.

Case 2: $0<f<1$. In this case, the boundary equilibrium $\bar{E}$ no longer exists. The reason for this is that when $f>0$, the resistant strain will always present whenever the sensitive strain does due to the *de novo* resistance. The boundary equilibrium $\hat{E}$ still exists and is given by (6). There is also a possible interior equilibria (all components are positive)

$$E^*=(S^*,V^*,I^*_{SU},I^*_{ST},I^*_R,R^*), \tag{8}$$

where

$$
\begin{aligned}
&S^* = \frac{S^0}{\mathcal{R}_{SC}}, \qquad V^* = \frac{V^0}{\mathcal{R}_{SC}},\\
&I^*_{SU} = \frac{(\mu+\omega)(\mathcal{R}_{SC}-1)N^0}{\frac{\sigma+\mu}{\sigma+\mu+\nu}(\beta_S+\beta_R b+\beta_S\delta a)+\omega(1+a+b)\mathcal{R}_{SC}},\\
&I^*_{ST} = aI^*_{SU}, \qquad I^*_R = bI^*_{SU}, \qquad R^* = N^0 - S^* - V^* - I^*_{SU} - I^*_{ST} - I^*_R,
\end{aligned}
\tag{9}
$$

with

$$
a = \frac{f(1-c)(\mu+k_U)}{(1-f)(\mu+k_T)}, \qquad b = \frac{fc(\mu+k_U)}{(1-f)(\mu+k_R)(1-\frac{\mathcal{R}_{RC}}{\mathcal{R}_{SC}})}. \tag{10}
$$

From the expression of $\hat{I}_R$ in (6), it is easy to see that

$$
\hat{I}_R > 0 \quad \text{if and only if} \quad \mathcal{R}_{RC} > 1. \tag{11}
$$

Equation (11) implies that $\hat{E}$ exists if and only if $\mathcal{R}_{RC} > 1$. From (9) and (10), we can see that

$$
\begin{aligned}
&I^*_{SU} > 0 \quad \text{if and only if} \quad \mathcal{R}_{SC} > 1,\\
&I^*_R > 0 \quad \text{if and only if} \quad \mathcal{R}_{RC} < \mathcal{R}_{SC}.
\end{aligned}
\tag{12}
$$

Equation (12) implies that E^* exists if and only if $\mathcal{R}_{SC} > 1$ and $\mathcal{R}_{RC} < \mathcal{R}_{SC}$. Moreover, it is easy to verify that E^* approaches $\bar{E}$ as $f \to 0$.

The above results on the existence of equilibria of system (1) when $0 < f < 1$ are summarized in Theorem 3.1.

Theorem 3.1. *Assume that* $0 < f < 1$. *Let* $\mathcal{R}_{SC}$, $\mathcal{R}_{RC}$ *be defined as in* (3), *and let*

$$
\mathcal{R}_C = \max\{\mathcal{R}_{SC}, \mathcal{R}_{RC}\}. \tag{13}
$$

Then,

(1) *If* $\mathcal{R}_C < 1$, *then only the disease-free equilibrium* E_0 *exists*.
(2) *If* $\mathcal{R}_C > 1$, *then besides* E_0, *system* (1) *has also the resistant-strain-only equilibrium* $\hat{E}$ *when* $\mathcal{R}_{RC} > 1$, *and the coexistence equilibrium* E^* *when* $\mathcal{R}_{SC} > 1$ *and* $\mathcal{R}_{RC} < \mathcal{R}_{SC}$.

The proof of Theorem 3.1 is given in Appendix B.

4. Stability and persistence

The total population size $N(t)$ satisfies the equation $dN/dt = \Lambda - \mu N$ and $N(t) \to \Lambda/\mu$ as $t \to \infty$. Using results from Castillo-Chavez and Thieme (1995) and Mischaikow et al. (1995), we can obtain analytical results by considering the following limiting system

of (1) in which the total population is assumed to be constant $N = \Lambda/\mu$:

$$\begin{cases} \frac{dS}{dt} = \Lambda - (\mu+\nu)S - \frac{\mu\beta_S}{\Lambda}(I_{SU}+\delta I_{ST})S - \frac{\mu\beta_R}{\Lambda}I_R S \\ \qquad + \omega R + \sigma(\frac{\Lambda}{\mu} - S - I_{SU} - I_{ST} - I_R - R), \\ \frac{dI_{SU}}{dt} = (1-f)\frac{\mu\beta_S}{\Lambda}(I_{SU}+\delta I_{ST})S - \mu I_{SU} - k_U I_{SU}, \\ \frac{dI_{ST}}{dt} = f(1-c)\frac{\mu\beta_S}{\Lambda}(I_{SU}+\delta I_{ST})S - \mu I_{ST} - k_T I_{ST}, \\ \frac{dI_R}{dt} = \frac{\mu\beta_R}{\Lambda}I_R S + fc\frac{\mu\beta_S}{\Lambda}(I_{SU}+\delta I_{ST})S - \mu I_R - k_R I_R, \\ \frac{dR}{dt} = k_U I_{SU} + k_T I_{ST} + k_R I_R - (\mu+\omega)R. \end{cases} \tag{14}$$

Notice that the V equation is eliminated from (14) and the variable V (in the S equation) is replaced by $\Lambda/\mu - S - I_{SU} - I_{ST} - I_R - R$. Systems (1) and (14) have the same set of equilibria and the same existence conditions as given in the previous section. For ease of notation, we rearrange the order of variables as $(S, I_R, R, I_{SU}, I_{ST})$, and still use the notation E_0, $\hat{E}$, and E^* (or $\bar{E}$ when $f = 0$) to denote these equilibria. That is, $E_0 = (S^0, 0, 0, 0, 0)$, $\hat{E} = (\hat{S}, \hat{I}_R, \hat{R}, 0, 0)$, and $E^* = (S^*, I_R^*, R^*, I_{SU}^*, I_{ST}^*)$ (which coincides with $\bar{E} = (\bar{S}, 0, \bar{R}, \bar{I}_{SU}, 0)$ when $f = 0$).

4.1. Stability of equilibria

From the derivation of the quantities $\mathcal{R}_{SC}$ and $\mathcal{R}_{RC}$ (see Appendix A) and Theorem 2 of Driessche and Watmough (2002), it follows that the DFE, E_0, is locally asymptotically stable (l.a.s.) if $\mathcal{R}_C < 1$ and unstable if $\mathcal{R}_C > 1$. For the stability of $\hat{E}$, we consider only the case when $\mathcal{R}_{RC} > 1$ as $\hat{E}$ does not exist when $\mathcal{R}_{RC} < 1$.

For $0 \le f < 1$, the Jacobian of system (14) at $\hat{E}$ is

$$J(\hat{S}, \hat{I}_R, \hat{R}, 0, 0) = \begin{pmatrix} A_{11} & A_{12} \\ 0 & A_{22} \end{pmatrix},$$

where

$$A_{11} = \begin{pmatrix} -(\mu+\nu) - \frac{\mu\beta_R}{\Lambda}\hat{I}_R - \sigma & -\frac{\mu\beta_R}{\Lambda}\hat{S} - \sigma & \omega - \sigma \\ \frac{\mu\beta_R}{\Lambda}\hat{I}_R & 0 & 0 \\ 0 & k_R & -(\omega+\mu) \end{pmatrix},$$

$$A_{22} = \begin{pmatrix} (1-f)\frac{\mu\beta_S}{\Lambda}\hat{S} - (\mu+k_U) & (1-f)\frac{\mu\beta_S\delta}{\Lambda}\hat{S} \\ f(1-c)\frac{\mu\beta_S}{\Lambda}\hat{S} & f(1-c)\frac{\mu\beta_S\delta}{\Lambda}\hat{S} - (\mu+k_T) \end{pmatrix},$$

and

$$A_{12} = \begin{pmatrix} -\frac{\mu\beta_S}{\Lambda}\hat{S} - \sigma & -\frac{\mu\beta_S\delta}{\Lambda}\hat{S} - \sigma \\ fc\frac{\mu\beta_S}{\Lambda}\hat{S} & fc\frac{\mu\beta_S\delta}{\Lambda}\hat{S} \\ k_U & k_T \end{pmatrix}.$$

It is shown in Appendix C that all eigenvalues of the matrix A_{11} have negative real parts. Thus, the stability of the equilibrium $\hat{E}$ is determined by the eigenvalues of the matrix A_{22}.

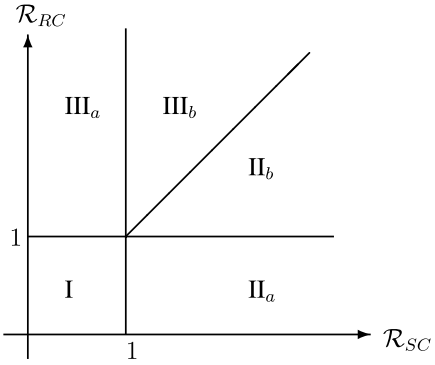

Fig. 2 The bifurcation diagram in $(\mathcal{R}_{SC}, \mathcal{R}_{RC})$ plane. The stability of equilibria in each region is given in Table 2.

Table 2 Existence and stability of equilibria

		E_0	$\hat{E}$	E^* if $0 < f < 1$ (or $\bar{E}$ if $f = 0$)
$\mathcal{R}_C > 1$	I: $\mathcal{R}_C < 1$	LS	DNE	DNE
	II_a: $\mathcal{R}_{SC} > 1 > \mathcal{R}_{RC}$	US	DNE	LS (Simulated)
	II_b: $\mathcal{R}_{SC} > \mathcal{R}_{RC} > 1$	US	US	LS (Simulated)
	III_a: $\mathcal{R}_{RC} > 1 > \mathcal{R}_{SC}$	US	LS	DNE
	III_b: $\mathcal{R}_{RC} > \mathcal{R}_{SC} > 1$	US	LS	E^* DNE ($\bar{E}$ is US for $f = 0$)

DNE: does not exist; US: unstable; LS: locally stable

It is also shown that all eigenvalues of A_{22} have negative real parts if $\mathcal{R}_{SC} < \mathcal{R}_{RC}$ (which includes all points $(\mathcal{R}_{SC}, \mathcal{R}_{RC})$ in the Region III_a and Region III_b in Fig. 2), in which case, $\hat{E}$ is l.a.s. A_{22} has one positive eigenvalue if $\mathcal{R}_{SC} > \mathcal{R}_{RC}$ (see Region II_b in Fig. 2), in which case $\hat{E}$ is unstable.

Although we do not have an analytic result for the stability of E^*, our numerical studies indicate that E^* is globally asymptotically stable whenever it exists, i.e., when $0 < f < 1$, $\mathcal{R}_{SC} > 1$ and $\mathcal{R}_{SC} > \mathcal{R}_{RC}$ (see Region $\mathrm{II} = \mathrm{II}_a \cup \mathrm{II}_b$ in Fig. 2).

Similarly, when $f = 0$, the equilibrium $\bar{E}$ is l.a.s. if $\mathcal{R}_{SC} > \mathcal{R}_{RC}$ and $\mathcal{R}_{SC} > 1$ (see Region II_a and Region II_b in Fig. 2) and unstable if $\mathcal{R}_{RC} > \mathcal{R}_{SC} > 1$ (see Region III_b in Fig. 2).

The stability results for both case 1 ($f = 0$) and case 2 ($f > 0$) can be summarized in the following theorems.

Theorem 4.1. *Assume $f = 0$. Let $\mathcal{R}_C$ be defined as in (13). Then*

(a) *E_0 is locally asymptotically stable if $\mathcal{R}_C < 1$ and unstable if $\mathcal{R}_C > 1$;*
(b) *when $\mathcal{R}_{RC} > 1$, $\hat{E}$ is locally hyperbolically stable if $\mathcal{R}_{SC} < \mathcal{R}_{RC}$ and hyperbolically unstable if $\mathcal{R}_{SC} > \mathcal{R}_{RC}$;*
(c) *when $\mathcal{R}_{SC} > 1$, $\bar{E}$ is locally hyperbolically stable if $\mathcal{R}_{SC} > \mathcal{R}_{RC}$ and hyperbolically unstable if $\mathcal{R}_{SC} < \mathcal{R}_{RC}$.*

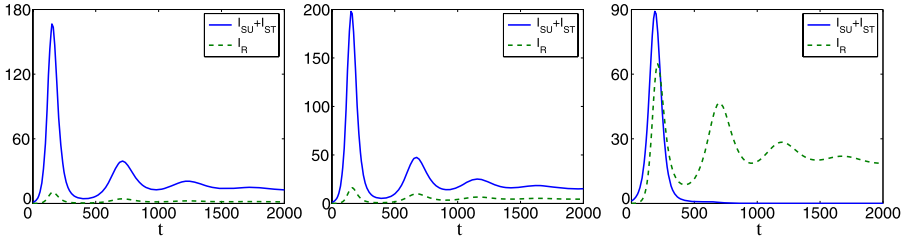

Fig. 3 Numerical solutions for the system (1) when $\mathcal{R}_R = 0.9\mathcal{R}_{SU}$. $I_{SU} + I_{ST}$ is the number of sensitive cases and I_R is the number of resistant cases. (a) $f = 0.13$, $\nu = 0.0017$, which lies in Region II_a; (b) $f = 0.15$, $\nu = 0.001$, which lies in Region II_b; and (c) $f = 0.25$, $\nu = 0.001$,which lies in Region III_b. Initial values are $S(0) = 8000$, $V(0) = 2000$, $I_{SU} = 1$.

Theorem 4.2. *Assume* $0 < f < 1$. *Let* $\mathcal{R}_C$ *be defined as in* (13). *Then*

(a) E_0 *is locally asymptotically stable if* $\mathcal{R}_C < 1$ *and unstable if* $\mathcal{R}_C > 1$;
(b) *when* $\mathcal{R}_{RC} > 1$, $\hat{E}$ *is locally hyperbolically stable if* $\mathcal{R}_{SC} < \mathcal{R}_{RC}$ *and hyperbolically unstable if* $\mathcal{R}_{SC} > \mathcal{R}_{RC}$;
(c) E^* *is stable whenever it exists, i.e., when* $0 < f < 1$, $\mathcal{R}_{SC} > 1$ *and* $\mathcal{R}_{SC} > \mathcal{R}_{RC}$.

Results in Theorems 3.1, 4.1, and 4.2 are also summarized in Table 2 and in the bifurcation diagram shown in Fig. 2. We have conducted extensive simulations to confirm these results, some of which are illustrated in Fig. 3. More detailed explanations of the Fig. 3 are given in Section 5.

4.2. Global stability and uniform persistence

In the special case when the rates of immunity loss from the V and R individuals are equal, i.e., $w = \sigma$, analytical results on the global stability of E_0 and $\hat{E}$ and uniform persistence can be obtained. The simplified system under this assumption is given in Appendix D (see system (D.2)). The results are stated below.

Theorem 4.3. *Consider the limiting system* (D.2) *and assume* $w = \sigma$. *The DFE* E_0 *is globally asymptotically stable if* $\mathcal{R}_C < 1$.

Theorem 4.4. *If* $\mathcal{R}_{RC} > 1 \geq \mathcal{R}_{SC}$, *then the boundary equilibrium* $\hat{E}$ *of system* (D.2) *is globally asymptotically stable.*

In addition, the behavior of the local dynamics near E_0 and $\hat{E}$ as described in Theorem 4.2 implies that system (D.2) is uniformly persistent in $\mathrm{Int}\,\Gamma$ if $\mathcal{R}_{SC} > \mathcal{R}_{RC} > 1$; namely, there exists a constant $\xi > 0$ such that

$$\liminf_{t\to+\infty} S(t) > \xi \quad \text{and} \quad \liminf_{t\to+\infty} I_i(t) > \xi, \quad \text{for } i = SU, ST, R.$$

Here, ξ is independent of initial data in Γ.

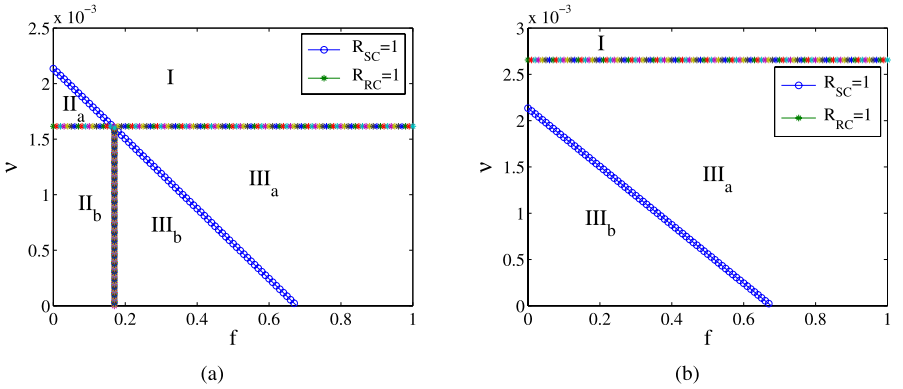

Fig. 4 Bifurcation diagrams in the (ν, f) plane for the cases of $\mathcal{R}_R < \mathcal{R}_{SU}$ (in (a)) and $\mathcal{R}_R > \mathcal{R}_{SU}$ (in (b)). The labeled regions correspond to those in Fig. 2, which is a bifurcation diagram in the $(\mathcal{R}_{SC}, \mathcal{R}_{RC})$ plane. That is, in Region I, $\mathcal{R}_{SC} < 1$ and $\mathcal{R}_{RC} < 1$. In Region II$_a$, $\mathcal{R}_{SC} > 1$ and $\mathcal{R}_{RC} < 1$. In Region II$_b$, $R_{SC} > \mathcal{R}_{RC} > 1$. In Region III$_a$, $\mathcal{R}_{SC} < 1$ and $\mathcal{R}_{RC} > 1$. In Region III$_b$, $R_{RC} > \mathcal{R}_{SC} > 1$.

Theorem 4.5. *Let* $0 < f < 1$ *and* $\mathcal{R}_{SC} > \mathcal{R}_{RC} > 1$. *System* (D.2) *is uniformly persistent.*

The proofs of Theorems 4.3, 4.4, and 4.5 are provided in Appendices D, E, and F, respectively.

Biological implications of the results in Theorems 4.2–4.5 are the following: (i) when $0 < f < 1$ the disease cannot spread if $(\mathcal{R}_{SC}, \mathcal{R}_{RC})$ belongs to Region I in Fig. 2; (ii) both strains will coexist if $(\mathcal{R}_{SC}, \mathcal{R}_{RC})$ is in Region II $=$ II$_a \cup$ II$_b$; and (iii) only the resistant strain will be present if $(\mathcal{R}_{SC}, \mathcal{R}_{RC})$ is in Region III $=$ III$_a \cup$ III$_b$. Notice that when $0 < f < 1$, the resistant strain is always present as long as the disease does not die out. However, the sensitive strain can persist only if its reproduction number is larger than the reproduction number of the resistant restrain $(\mathcal{R}_{SC} > \mathcal{R}_{RC})$. This nonsymmetry between the two strains is a consequence of the *de novo* resistance. Therefore, the use of antiviral drug may generate a significant competitive advantage for the drug-resistant strain even if the reproduction number of the resistant strain is much lower than that of the sensitive strain.

Notice from (3) that $\mathcal{R}_{SC}$ and $\mathcal{R}_{RC}$ are functions of f and/or ν. Thus, the threshold conditions determined by $\mathcal{R}_{SC}$ and $\mathcal{R}_{RC}$ can be rewritten using f and ν, which will make it more transparent to understand the consequence of varying the treatment and vaccination rates. Figure 4 illustrates two bifurcation diagrams in the (ν, f) plane corresponding to two scenarios. Figure 4(a) is for the case when the *basic* reproduction number of the drug-resistant strain is smaller than that of the sensitive strain (i.e., $\mathcal{R}_R < \mathcal{R}_{SU}$), and Fig. 4(b) is for the case when $\mathcal{R}_R > \mathcal{R}_{SU}$. Since the fitness of drug-resistant viruses is not well known, it is relevant to considered both of the cases. In both Fig. 4(a) and Fig. 4(b), the regions represented by the letters correspond to those in the bifurcation diagram in Fig. 2 (which is drawn in the $(\mathcal{R}_{SC}, \mathcal{R}_{RC})$ plane). The stability results in the regions in Fig. 4 are summarized in Table 3. We need to point out that the bifurcation diagram shown in Fig. 4 is produced by fixing all parameter values except ν and f. The set of parameter values used in Fig. 4 is the same as those used in Fig. 3 (see the next section for a more detailed discussion about Fig. 3).

Table 3 Parameter values for system (1)

Parameter	Estimated value	Unit
$\frac{\Lambda}{\mu}$	10000	number
μ	0.00005	day^{-1}
ν	Variable	day^{-1}
ω	0.003	day^{-1}
σ	0.003	day^{-1}
β_S	0.2835	day^{-1}
β_R	Variable	day^{-1}
δ	0.4	–
f	Variable	–
c	0.02	–
k_U	0.1667	day^{-1}
k_T	0.1667	day^{-1}
k_R	0.1667	day^{-1}

Figure 4 can be very helpful for examining the joint effect of treatment and vaccination. For example, consider Fig. 4(a) with $\mathcal{R}_R = 0.9\mathcal{R}_{SU} < \mathcal{R}_{SU}$, and consider three different values of vaccination rates: $\nu = 0.001, 0.0017, 0.0035$. For the smaller value of $\nu = 0.001$, we see from Fig. 4(a) that $(\nu, f) = (0.001, 0)$ lies in Region II$_b$, in which $\bar{E}$ is stable (at $\bar{E}$ the resistant strain is absent as $f = 0$). When f is positive, the coexistence equilibrium E^* begins to emerge. Hence, both the resistant and sensitive strains will persist. As f continuous to increase, (ν, f) moves into Region III$_a$ or III$_b$, in which the sensitive strain is excluded. For the intermediate value of $\nu = 0.0017$, from Fig. 4(a) $(\nu, f) = (0.0017, 0)$ lies in Region II$_a$, in which $\bar{E}$ is stable. When f becomes positive, the coexistence equilibrium E^* emerges and both the resistant and sensitive strains will persist, which is similar to the case of smaller ν. However, as f continuous to increase, (ν, f) will enter Region I, in which both strains will die out. Hence, there is a critical value of treatment rate, f_c, above which the disease can be eliminated. This is clearly different from the case of smaller ν. For the larger value of $\nu = 0.0035$, $(\nu, f) = (0.0035, 0)$ lies in Region I for all f (see Fig. 4(a)). This implies that the disease will not spread. Some simulation results using these three ν values are shown in the next section (see Figs. 5, 6, and 7).

Similar behaviors are observed in Fig. 4(b), in which we assume that $\mathcal{R}_R = 1.1\mathcal{R}_{SU} > \mathcal{R}_{SU}$ with all other parameter values being the same as in Fig. 4(a). The dynamics in various regions shown in Fig. 4(b) are described in Table 2. Some simulation results for this case are also discussed in the next section.

5. Numerical results

In this section, we present some numerical simulation results, which confirm or extend the analytic results and illustrate the effect of two important factors on controlling the infection: the rate at which susceptible individuals are vaccinated (ν) and the fraction of new infections with sensitive strain being treated (f).

We consider the situation in which the population size has reached the steady-state $\Lambda/\mu = 10^4$. Assume that the life span is $1/\mu = 60$ years, i.e., $\mu \approx 0.00005$ (day^{-1}). It

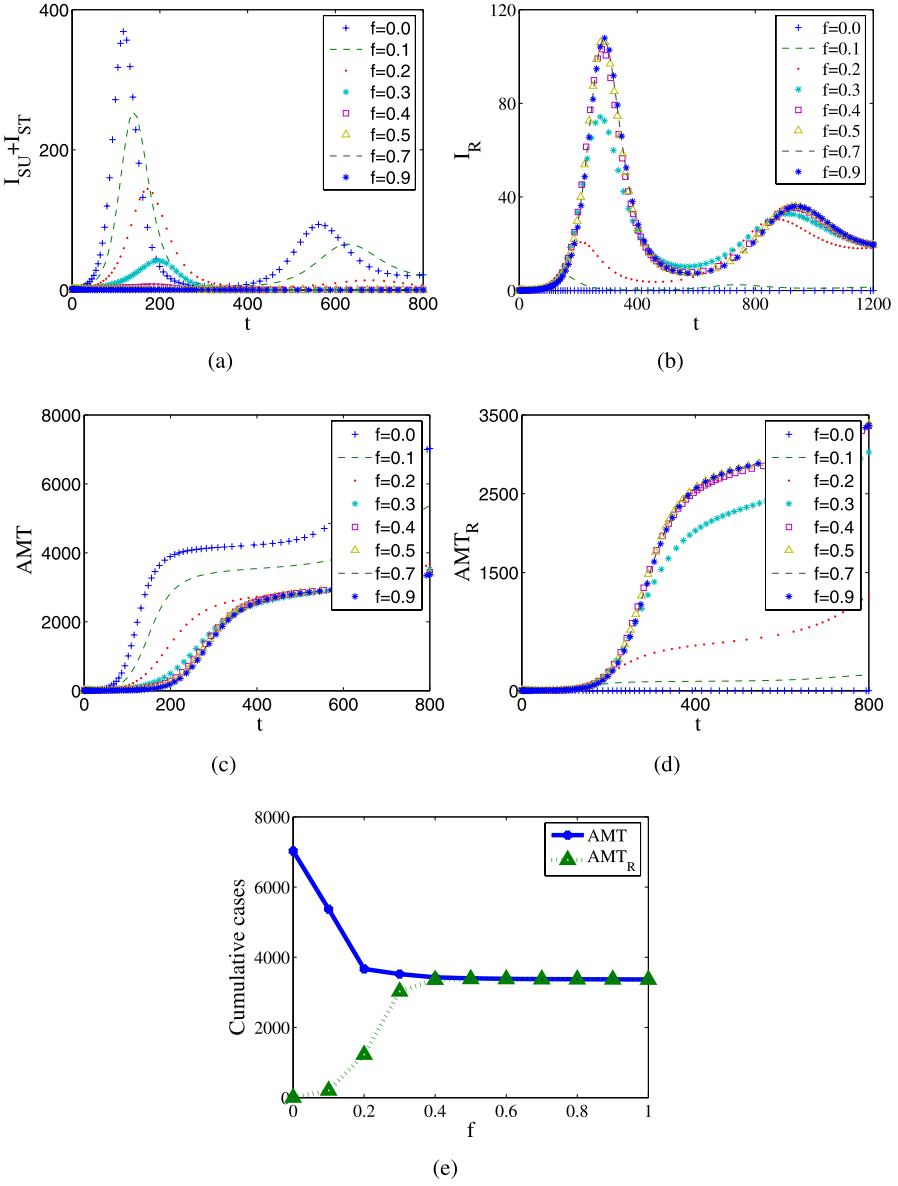

Fig. 5 Simulation results for the case $\mathcal{R}_R = 0.9\mathcal{R}_{SU} < \mathcal{R}_{SU}$ and $\nu = 0.001$. (a), (b), (c), and (d) are time plots of the numbers of sensitive cases $I_{SU}(t)+I_{ST}(t)$, the number of resistant cases, $I_R(t)$, the cumulative infected cases of both strains AMT(t), and the cumulative resistant cases AMT$_R(t)$, respectively. (e) shows the profiles of the cumulative cases vs. treatment rate f at a fixed time $T = 800$. The solid curve in (e) is for the cumulative cases of both strains, AMT(800), and the dashed curve in (e) is for the cumulative resistant cases, AMT$_R$(800). Initial values are $S(0) = 8000$, $V(0) = 2000$, $I(0) = 1$.

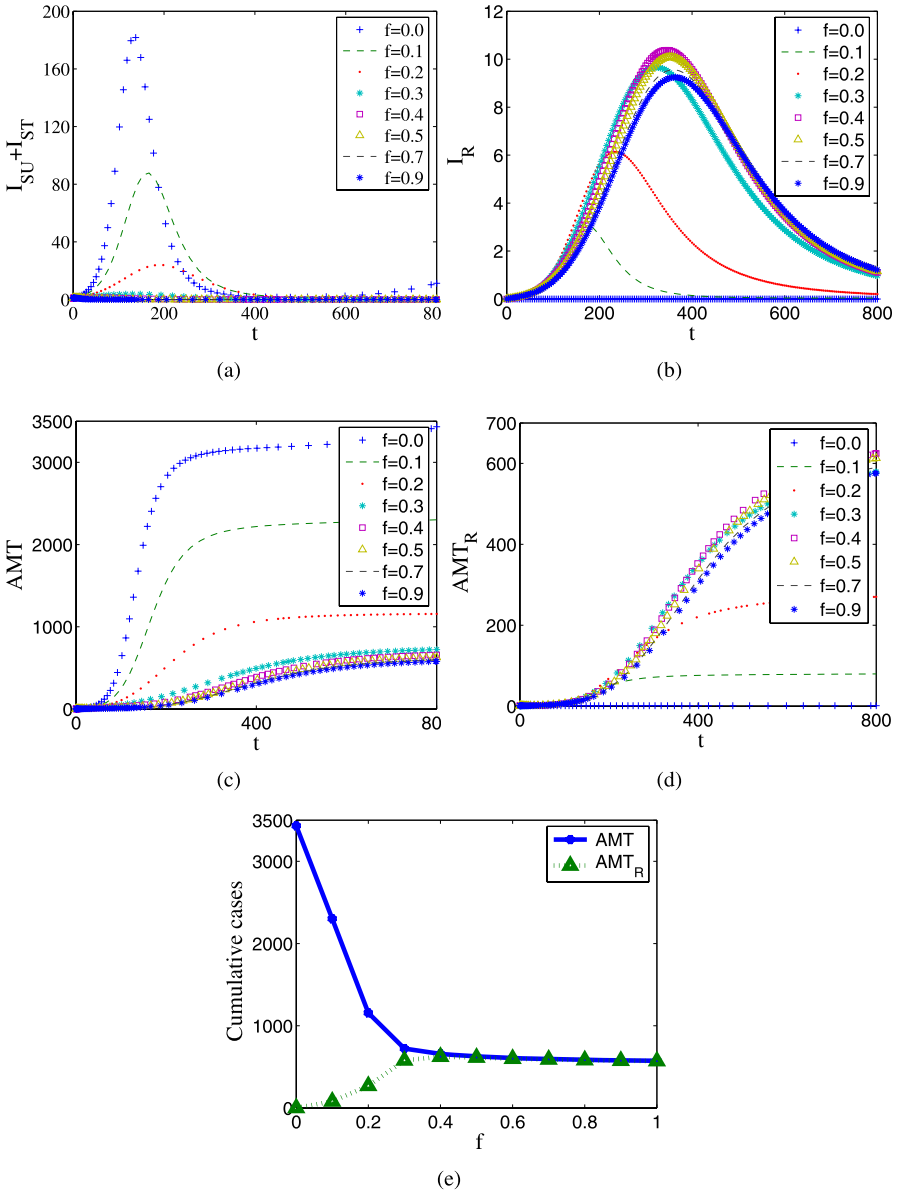

Fig. 6 Similar to Fig. 5 except that $\nu = 0.0017$. All other parameter values are the same as in Fig. 5.

is reported by Fiore et al. (2007) that uncomplicated influenza illness typically resolves after 3–7 days for the majority of persons. Based on this, we assume an average period of infection to be 6 days, i.e., $k_U = k_T = k_R = 0.1667$ (day^{-1}). According to CDC, the protection (immunity) obtained from vaccination lasts about one year (CDC, 2008). As-

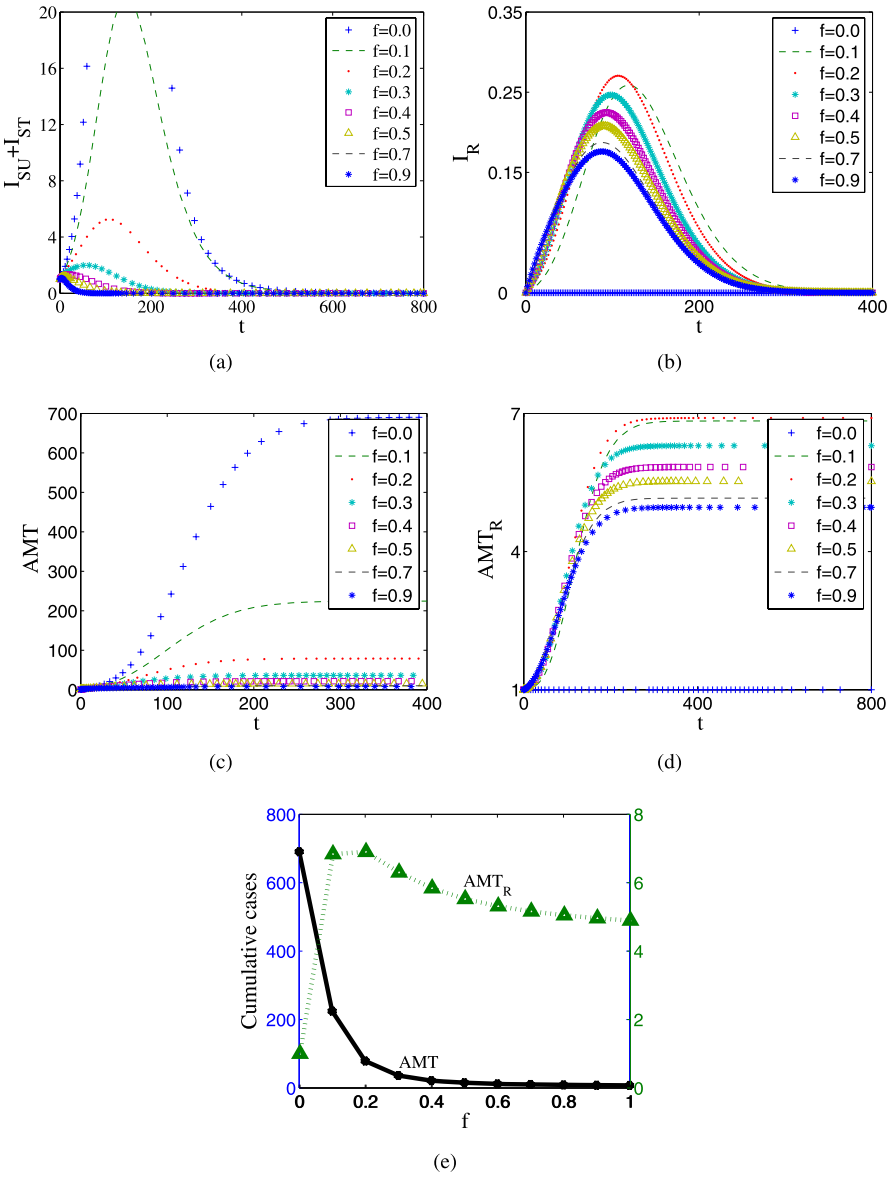

Fig. 7 Similar to Fig. 5 except that $\nu = 0.0035$. All other parameter values are the same as in Fig. 5.

suming that the average length of immunity induced by vaccine (σ) and by infection (ω) are the same, we choose $\sigma = \omega = 0.003$ (day^{-1}) .

Estimates of the basic reproduction number for pandemic influenza vary widely, ranging from 1.68 to 20 (Mills et al., 2004). In this paper, we set $\mathcal{R}_{SU} = 1.7$. The baseline transmission coefficients for untreated sensitive cases (β_S) can be calculated from the for-

mula for $\mathcal{R}_{SU}$ (see (4)), which gives $\beta_S = 0.2835$ (day^{-1}). It is suggested (Kiso et al., 2004) that in normal influenza seasons several percentage of individuals who receive oseltamivir treatment may develop resistance to the drug. From this information, we choose $c = 0.02$. The reduction in transmission rate due to treatment is chosen to be $\delta = 0.4$. The control parameters f and ν can vary. The basic reproduction number of the drug-resistant strain $\mathcal{R}_R$ can be either greater or smaller than that of the sensitive strain $\mathcal{R}_{SU}$. We will consider both the case $\mathcal{R}_R/\mathcal{R}_{SU} < 1$ and the case $\mathcal{R}_R/\mathcal{R}_{SU} > 1$. The parameter values are summarized in Table 3.

We first consider the case $\mathcal{R}_R/\mathcal{R}_{SU} = 0.9 < 1$. In this case, $\mathcal{R}_R = 0.9 \times 1.7 = 1.53$, and using the formula for $\mathcal{R}_R$ in (4) we can get the estimate for $\beta_R = 0.2551$. Figure 3 illustrates some simulation results for (ν, f) in various regions shown in the bifurcation diagram (see Fig. 4(a)). Figure 3(a) is for the case when (ν, f) lies in Region II_a in which $\mathcal{R}_{SC} > 1 > \mathcal{R}_{RC}$, and Fig. 3(b) is for the case when (ν, f) lies in Region II_b in which $\mathcal{R}_{SC} > \mathcal{R}_{RC} > 1$. It shows that in both cases the two strains can coexist, with a higher level of resistant infections in Fig. 3(b). This is because the value of $\mathcal{R}_{RC}$ in Fig. 3(b) is higher. Figure 3(c) is for the case when (ν, f) lies in Region III_b in which $\mathcal{R}_{RC} > \mathcal{R}_{SC} > 1$. It suggests that the boundary equilibrium $\hat{E}$ is a globally attractor. We observe that the simulations shown in this figure confirm the results described in Table 3.

Next, we examine the effect of antiviral treatment on the prevalence of influenza under a given level of vaccination (i.e., for a fixed value of ν). One of the purposes is to look at whether increasing treatment rate will always be beneficial in terms of reducing the infection level. Although the endemic level at E^* can be used as a measure for examining the effects of f and ν, it does not provide detailed information for short-term behaviors. As we are also interested in transient dynamics including epidemic peak size and the time to the peak, the measure we choose to use here is the cumulative number of infected cases (termed cumulative incidence). This quantity is different from the *final* epidemic size for epidemic models without demographics, which have been considered in many recent studies (see, for example, Ma and Earn, 2006; Arino et al., 2007; Feng, 2007). Nevertheless, it provides a reasonable criterion for examining the short-term effect of different control strategies for endemic diseases with demographics.

Let $\mathrm{AMT}(t)$ denote the total cumulative incidence of both strains at time t and let $\mathrm{AMT}_R(t)$ denote the cumulative incidence of the resistant strain at time t. Then these quantities can be calculated by using the following formulas:

$$\mathrm{AMT}(t) = \int_0^t \big(\lambda_S(\tau)S(\tau) + \lambda_R(\tau)S(\tau)\big)\, d\tau,$$

$$\mathrm{AMT}_R(t) = \int_0^t \big(\lambda_R(\tau)S(\tau) + fc\lambda_S(\tau)S(\tau)\big)\, d\tau,$$

where $S(t)$, $\lambda_S(t)$, and $\lambda_R(t)$ are given by the solutions of the system (1).

We consider three fixed values of vaccination rate: $\nu = 0.001, 0.0017, 0.0035$. The simulation results corresponding to these ν values are demonstrated in Figs. 5, 6, and 7, respectively. In all three figures, (a) shows the time plots for the number of sensitive cases $(I_{SU} + I_{ST})$ with various treatment rates (f); (b) shows the time plots for the number of resistant cases (I_R) with various values of f; (c) is the time plot of the total incidence; (d) is the time plot of the total incidence of resistant strain; and (e) plots the total cumulative incidence at an end time T $(= 800)$ as a function of the treatment rate f.

We observe in Figs. 5–7 that for the sensitive strain, as f increases, the peak size for this strain decreases and the time to the peak can be delayed (see (a)). However, for the resistant strain, an increase in f has also increased the peak size for this strain (see (b)). It seems from Figs. 5–6 that a slight increase in vaccination rate ν (from 0.001 and to 0.0017) may dramatically influence the effect of treatment in terms of reducing the peak size for both strains (see (a) and (b)). It seems that the variation in the total incidence between different treatment rates is much smaller in Fig. 5(c) than that in Figs. 6(c), whereas the variation in the total incidence of resistant strain between different treatment rates is much larger in Fig. 5(d) than in Fig. 6(d). This is more easy to see from Figs. 5(e) and 6(e). This suggests again that a slight increase in ν (from 0.001 to 0.0017) can be very helpful for treatment to be more effective. For example, when f is increased from 0.2 to 0.3, the total incidence (AMT) is reduced by 0.75% when $\nu = 0.001$ (see Fig. 5(e)) comparing to 50% when $\nu = 0.0017$ (see Fig. 6(e)), while the total incidence of resistant strain (AMT_R) is increased by 75% when $\nu = 0.001$ comparing to 40% when $\nu = 0.0017$.

We now look at the case $\mathcal{R}_R = 1.1\mathcal{R}_{SU} > \mathcal{R}_{SU}$. For presentation purposes, we choose a different set of values for the vaccinated rates for the simulations: $\nu = 0.001$, 0.0023, and 0.0035. The results are shown in Figs. 8, 9, 10. We observe that the numbers of cases of both strains are significantly reduced with increases vaccination rates ν (see Figs. 8(a–d)–10(a–d)). This clearly demonstrates the important role of vaccination in reducing the infection levels. It is also shown in Figs. 8(e)–10(e) that the variations in the total incidences (AMT) between various treatment rates f are not as large as for the case when $\mathcal{R}_R < \mathcal{R}_{SU}$ (see Figs. 5–7). This is in part due to the fact that the resistant strain has a higher basic reproduction number which can significantly diminish the effect of drug.

The most interesting scenario is the one when $\nu = 0.0035$. From Fig. 10(e), we see that the total incidence (AMT) decreases with f for $f < 0.1$, but it becomes increasing with f when $f > 0.1$. We can also see from Fig. 10(b) that, for large f, the peak size of resistant infections increases with f as well. This shows that increasing treatment rate may potentially have a severe negative impact. Similar effect is also present in the model of Lipsitch et al. (2007). This suggests that it is very important to determine such critical level(s) of treatment rates (in this case $f = 0.1$) so that the benefit of drug treatment will not be compromised. It is equally important to identify the threshold level of vaccination above which negative effects of treatment are likely to occur.

6. More on control reproduction numbers

As discussed in the last section that, in some cases, the level of infection may actually get higher when treatment rate is increased (see Fig. 10(e)). This possibility, however, cannot be reflected by the reproduction numbers $\mathcal{R}_{SC}$ and $\mathcal{R}_{RC}$, which are shown in Section 4 to completely determine the dynamics of the system. To see this, we consider the partial derivative of $\mathcal{R}_{SC}$ (see (3) and (4)):

$$\frac{\partial R_{SC}}{\partial f} = (1-c)\mathcal{R}_{ST} - \mathcal{R}_{SU},$$

which is a constant independent of f. From $0 < c < 1$, $\delta \leq 1$, and $k_T > k_U$, we know that $\mathcal{R}_{ST} < \mathcal{R}_{SU}$, and hence, $\frac{\partial R_{SC}}{\partial f} < 0$. That is, $\mathcal{R}_{SC}$ is a decreasing function of f for a given value of ν. It is clear from (3) and (4) that $\mathcal{R}_{RC}$ does not depend on f.

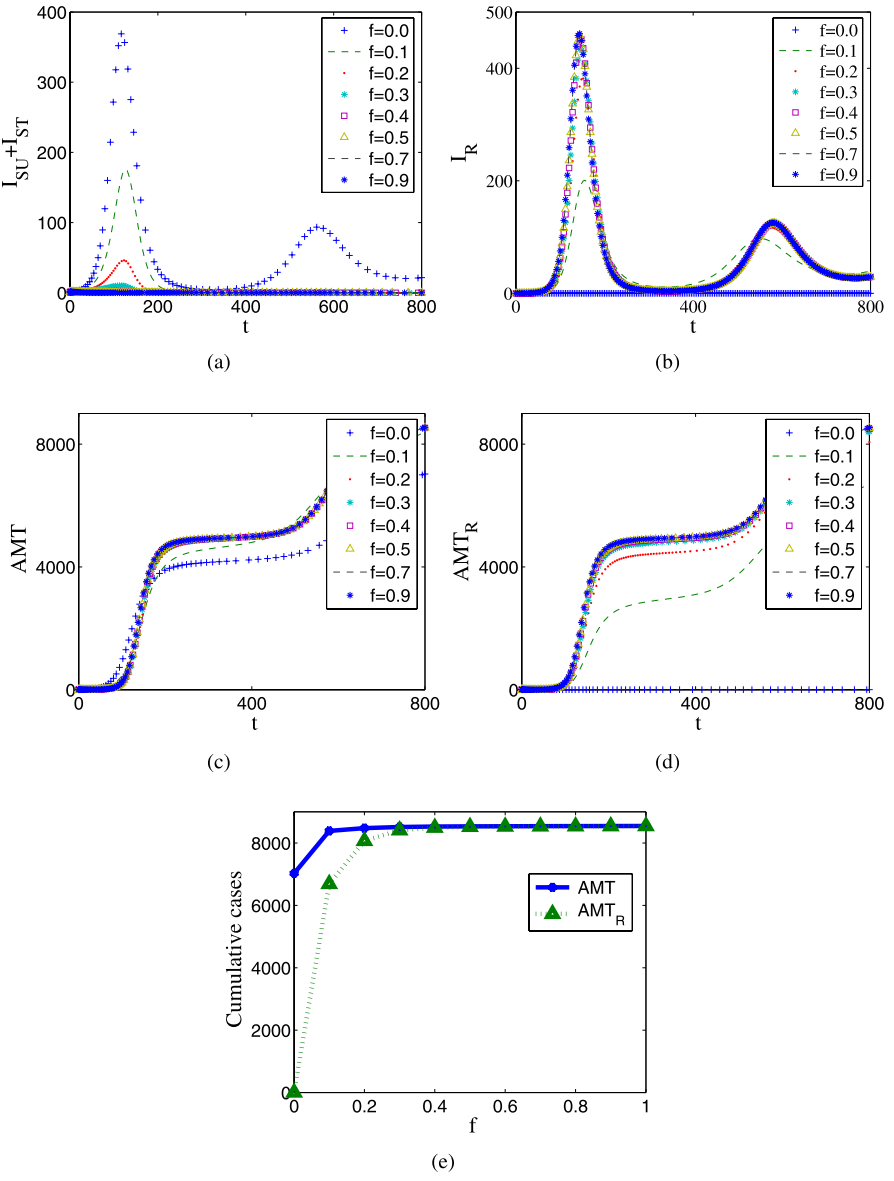

Fig. 8 Similar to Fig. 5 except that $\mathcal{R}_R = 1.1\mathcal{R}_{SU} > \mathcal{R}_{SU}$ and $\nu = 0.001$. All other parameter values are the same as in Fig. 5.

The main reason for this discrepancy between the reproduction numbers ($\mathcal{R}_{SC}$ and $\mathcal{R}_{RC}$) and the epidemic size (AMT), concerning their dependence on drug treatment, can be explained as follows. When a person is infected with the drug-sensitive strain, the

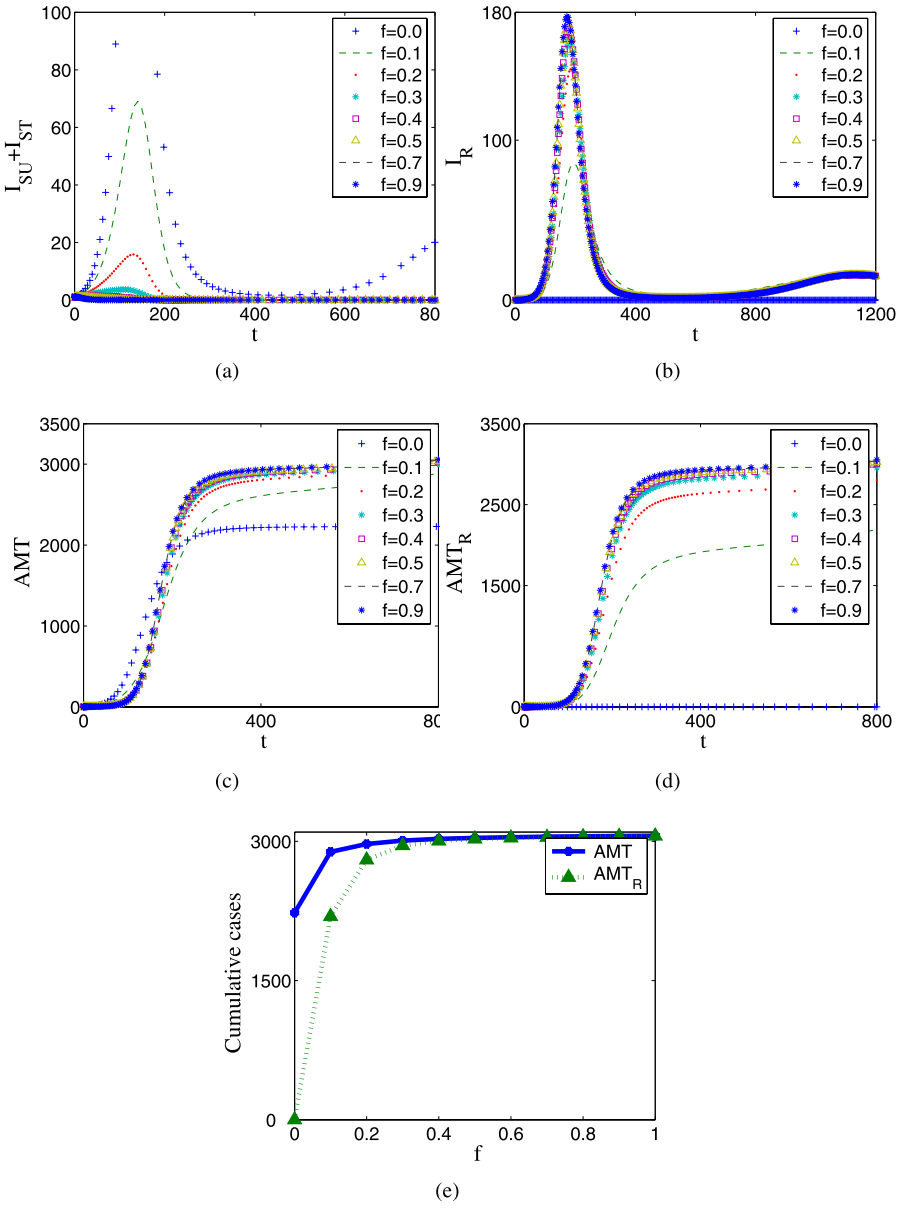

Fig. 9 Similar to Fig. 8 except that $\nu = 0.0023$. All other parameter values are the same as in Fig. 8.

number of secondary cases consist of three components:

$$\text{(i)}\quad \frac{S^0}{N^0}(1-f)\mathcal{R}_{SU}, \qquad \text{(ii)}\quad \frac{S^0}{N^0}f(1-c)\mathcal{R}_{ST}, \qquad \text{(iii)}\quad \frac{S^0}{N^0}fc\mathcal{R}_R.$$

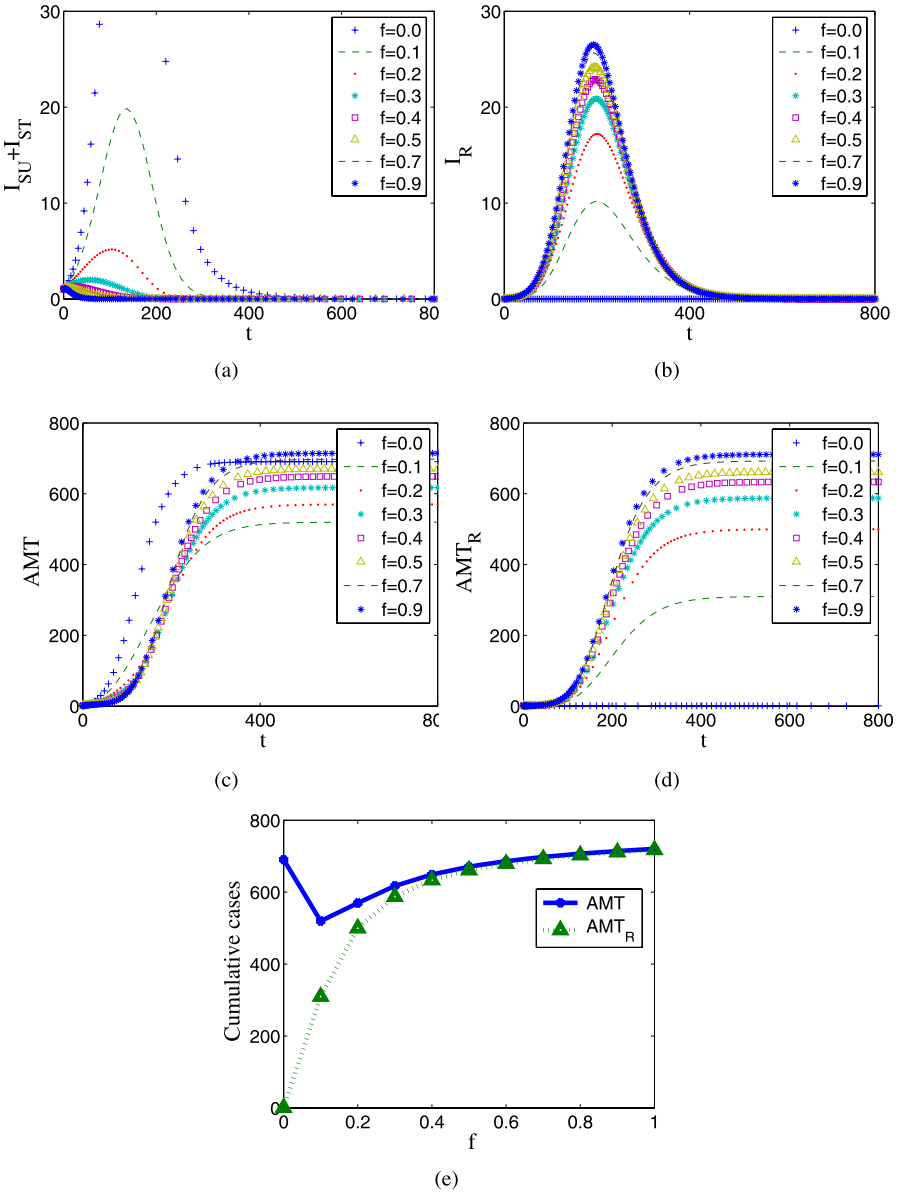

Fig. 10 Similar to Fig. 8 except that $\nu = 0.0035$. All other parameter values are the same as in Fig. 8.

The component (i) represents the number of new sensitive cases if the person is untreated. The component (ii) represents the number of new sensitive cases if the person is treated and did not develop resistance. The component (iii) represents the number of cases with acquired resistance due to antiviral use (*de novo* resistance). Clearly, the quantity $\mathcal{R}_{SC}$ is

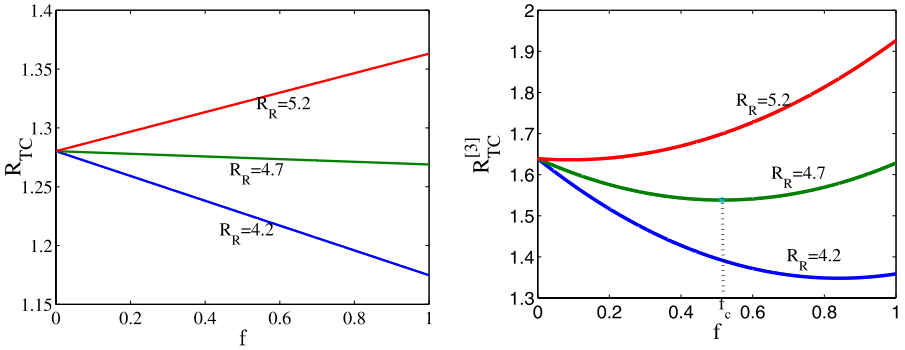

Fig. 11 (a) Plots of $\mathcal{R}_{TC}^{[2]} = \mathcal{R}_{TC}$ vs. treatment rate f for three different values of $\mathcal{R}_R$. It shows that the total control reproduction number in the second generation is a linear function of f. (b) Plots of the total reproduction number in the third generation, $\mathcal{R}_{TC}^{[3]}$, vs. f for three different values of $\mathcal{R}_R$. It shows that $\mathcal{R}_{TC}^{[3]}$ is a nonlinear function of f and can become increasing with f after reaching a minimum at some critical point f_c. Parameter values are $b = 0.003$, $\mu = 0.0005$, $\nu = 0.001$, $c = 0.25$, $\mathcal{R}_{SU} = 1.7$, and $\mathcal{R}_{ST} = 0.68$.

the sum of only the first two components. Therefore, $\mathcal{R}_{SC}$ underestimates the number of secondary infections by a sensitive case. For ease of reference, we denote the component (iii) by $\mathcal{R}_{AR}$ which will be referred to as *acquired* reproduction number (the subscript AR represents acquired resistance), i.e.,

$$\mathcal{R}_{AR} = \frac{S^0}{N^0} f c \mathcal{R}_R = \frac{\sigma + \mu}{\sigma + \mu + \nu} f c \mathcal{R}_R. \tag{15}$$

Let $\mathcal{R}_{TC}$ (T for total and C for control) denote the sum of all three components, i.e.,

$$\mathcal{R}_{TC} = \mathcal{R}_{SC} + \mathcal{R}_{AR}.$$

Clearly, $\mathcal{R}_{TC} = \mathcal{R}_{TC}(\nu, f)$ is also a function of ν and f. Notice that

$$\frac{\partial \mathcal{R}_{TC}}{\partial f} = \frac{\sigma + \mu}{\sigma + \mu + \nu}\big[-\mathcal{R}_{SU} + (1-c)\mathcal{R}_{ST} + c\mathcal{R}_R\big],$$

which is independent of f. Thus, $\mathcal{R}_{TC}$ is a linear function of f (see Fig. 11). Furthermore, for a given value of ν, $\mathcal{R}_{TC}$ is a decreasing function of f if $-\mathcal{R}_{SU} + (1-c)\mathcal{R}_{ST} + c\mathcal{R}_R < 0$, and it is an increasing function of f if $-\mathcal{R}_{SU} + (1-c)\mathcal{R}_{ST} + c\mathcal{R}_R > 0$. Thus, $\mathcal{R}_{TC}$ is always a monotone function of f, and consequently cannot capture the nonlinear relationship with f. This suggests that more generations of infections need to be considered.

For the purpose of presentation, denote $\mathcal{R}_{TC}$ by $\mathcal{R}_{TC}^{[2]}$, where the superscript [2] represents the second generation in which new infections are produced. Let $\mathcal{R}_{TC}^{[3]}$ denote the number of tertiary infected cases (including tertiary sensitive cases and tertiary resistant cases) produced by a sensitive case. (The squared root of $\mathcal{R}_{TC}^{[3]}$ gives the average number of new infection in one generation. To simplify the notation, we will focus on the quantity

without taking the squared root.) 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 $\frac{S^0}{N^0}$. Hence, $\mathcal{R}_{TC}^{[3]}$ can be expressed by

$$\mathcal{R}_{TC}^{[3]} = \mathcal{R}_{SC}\mathcal{R}_{SC} + (\mathcal{R}_{SC} + \mathcal{R}_{RC})\mathcal{R}_{AR}.$$

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 $\mathcal{R}_{TC}^{[3]}$ with respect to f is

$$\begin{aligned}\frac{\partial \mathcal{R}_{TC}^{[3]}}{\partial f} = \left(\frac{\sigma+\mu}{\sigma+\mu+\nu}\right)^2 \big\{&2\big[-\mathcal{R}_{SU} + (1-c)\mathcal{R}_{ST}\big]\big[-\mathcal{R}_{SU} + (1-c)\mathcal{R}_{ST} + c\mathcal{R}_R\big]f \\ &+ c\mathcal{R}_R^2 + \mathcal{R}_{SU}\big[-2\mathcal{R}_{SU} + 2(1-c)\mathcal{R}_{ST} + c\mathcal{R}_R\big]\big\}.\end{aligned}$$

Let

$$f^* = \frac{c\mathcal{R}_R^2 + \mathcal{R}_{SU}[-2\mathcal{R}_{SU} + 2(1-c)\mathcal{R}_{ST} + c\mathcal{R}_R]}{2[-\mathcal{R}_{SU} + (1-c)\mathcal{R}_{ST}][-\mathcal{R}_{SU} + (1-c)\mathcal{R}_{ST} + c\mathcal{R}_R]},$$

and let

$$f_c = \begin{cases} 0, & f^* \le 0; \\ f^*, & 0 < f^* < 1; \\ 1, & f^* \ge 1. \end{cases} \tag{16}$$

We can show that if

$$\big[-\mathcal{R}_{SU} + (1-c)\mathcal{R}_{ST}\big]\big[-\mathcal{R}_{SU} + (1-c)\mathcal{R}_{ST} + c\mathcal{R}_R\big] > 0,$$

then

$$\begin{aligned}&\frac{\partial \mathcal{R}_{TC}^{[3]}}{\partial f} < 0 \quad \text{for } f < f_c, \\ &\frac{\mathcal{R}_{TC}^{[3]}}{\partial f} > 0 \quad \text{for } f > f_c.\end{aligned}$$

Similarly, if

$$\big[-\mathcal{R}_{SU} + (1-c)\mathcal{R}_{ST}\big]\big[-\mathcal{R}_{SU} + (1-c)\mathcal{R}_{ST} + c\mathcal{R}_R\big] < 0,$$

then

$$\begin{aligned}&\frac{\partial \mathcal{R}_{TC}^{[3]}}{\partial f} > 0 \quad \text{for } f < f_c, \\ &\frac{\mathcal{R}_{TC}^{[3]}}{\partial f} < 0 \quad \text{for } f > f_c.\end{aligned}$$

Thus, the dependence of $\mathcal{R}_{TC}^{[3]}$ on f is nonlinear (see Fig. 11(b)). Figure 11(b) shows that there may be a critical value f_c such that $\mathcal{R}_{TC}^{[3]}$ decreases for $0 < f < f_c$ and increases for $f_c < f < 1$.

The key difference between $\mathcal{R}_{TC}^{[3]}$ and $\mathcal{R}_{TC}^{[2]}$ in terms of their functional relationships with f suggest that $\mathcal{R}_{TC}^{[3]}$ can provide a more accurate description on how treatment might negatively impact the disease dynamics. Apparently, it would be desirable to be able to calculate the number of new infections for more generations, which is likely to improve the description more significantly. Let $\mathcal{R}_{TC}^{[n]}$ $(n \geq 2)$ denote the reproduction numbers in nth generation of infections. Then $\mathcal{R}_{TC}^{[n]}$ can be approximately expressed by

$$\begin{aligned}\mathcal{R}_{TC}^{[n]} &= (\mathcal{R}_{SC})^{n-1} + \left(\sum_{i=1}^{n-2} (\mathcal{R}_{SC})^i (\mathcal{R}_{RC})^{n-2-i}\right)\mathcal{R}_{AR} \\ &= \left(\frac{\sigma+\mu}{\sigma+\mu+\nu}\right)^{n-1} \big((1-f)\mathcal{R}_{SU} + f(1-c)\mathcal{R}_{ST}\big)^{n-1} \\ &\quad + \left(\frac{\sigma+\mu}{\sigma+\mu+\nu}\right)^{n-1} fc \sum_{i=1}^{n-2} \big((1-f)\mathcal{R}_{SU} + f(1-c)\mathcal{R}_{ST}\big)^i (\mathcal{R}_R)^{n-1-i}, \\ n &= 4, 5, \ldots. \end{aligned} \tag{17}$$

Although for the case of $n = 3$, we are able to identify analytically the critical value f_c at which $\mathcal{R}_{TC}^{[n]}$ switches its monotonicity (see (16)), it is not easy to do this for general n. Nonetheless, the analytical formula (17) may be helpful for further exploration of more suitable presentations of control reproduction numbers. The definitions of various reproduction numbers are summarized in Table 4.

Table 4 Definition of various reproduction numbers

Quantities	Biological meaning
$\mathcal{R}_{SU}$	The number of secondary sensitive cases produced by a untreated sensitive case in the absence of vaccination and treatment, i.e., the basic reproduction number for the sensitive strains.
$\mathcal{R}_{ST}$	The number of secondary sensitive cases produced by a treated sensitive case in the absence of vaccination and treatment.
$\mathcal{R}_R$	The number of secondary resistant cases produced by a resistant case in the absence of vaccination and treatment, i.e., the basic reproduction number for the resistant strains.
$\mathcal{R}_{SC}$	The number of secondary sensitive cases produced by a sensitive case in the presence of vaccination and treatment.
$\mathcal{R}_{RC}$	The number of secondary resistant cases produced by a resistant case in the presence of vaccination and treatment, i.e., the control reproduction number for the resistant strains.
$\mathcal{R}_{TC}(\mathcal{R}_{TC}^{[2]})$	The number of total secondary cases (including the sensitive cases and the resistant cases) produced by a sensitive case in the presence of vaccination and treatment, i.e., the control reproduction number for the sensitive strains.
$\mathcal{R}_{TC}^{[n]}, n \geq 2$	The number of new infections in the nth generation (including the sensitive cases and the resistant cases) produced by a sensitive case in the presence of vaccination and treatment.

7. Discussion

In this paper, we studied an influenza model that includes both drug sensitive and drug resistant strains and vaccination. The main purposes of this study is to examine the joint impact of vaccination and treatment on the prevalence of the disease influenced by the development of resistance due to drug treatment. A detailed stability and persistence analysis is presented and extensive numerical simulations are conducted using parameter values relevant to influenza. The mathematical results are used to interpret the biological implications of various strategies for disease control and prevention.

Our analysis show that the qualitative behaviors of the model are completely determined by three key quantities: $\mathcal{R}_{SC}$ (the sensitive reproduction number), $\mathcal{R}_{RC}$ (the resistant reproduction number), and $\mathcal{R}_C = \max\{\mathcal{R}_{SC}, \mathcal{R}_{RC}\}$ (see the bifurcation diagram in Fig. 2 and Table 3). More specifically, the disease will die out if $\mathcal{R}_C < 1$, and it will spread if $\mathcal{R}_C > 1$. the competitive outcomes of the two strains are determined by the relative magnitudes of $\mathcal{R}_{SC}$ and $\mathcal{R}_{RC}$. These results are obtained by analyzing the stability of biologically feasible equilibria and the uniform persistence of the system (D.2).

The stability results for E_0 (the disease-free equilibrium) and $\hat{E}$ (the boundary equilibrium at which only the resistant strain is present) are obtained analytically, and the stability of the coexistence equilibrium E^* is obtained via numerical simulations. These results provide important qualitative understanding of the effects of treatment and vaccination on the infection levels of both strains. For example, when $0 < f < 1$, the resistant strain will always persist in the population provided that $\mathcal{R}_{TC} > 1$ even if the reproduction number of the resistant strain $\mathcal{R}_R < 1$ is less than 1. This suggests that antiviral treatment tends to promote persistence of the resistant strain in the sense that the resistant strain can only invade the population in the presence of drug use (since the resistant infection cannot persist in the population alone when $\mathcal{R}_R < 1$).

One of the interesting findings in this paper is that, despite the key role that the reproduction numbers $\mathcal{R}_{SC}$ and $\mathcal{R}_{RC}$ play in determining the qualitative behaviors of the system as mentioned above, they do not provide appropriate measures for examining the effect of antiviral use (described by the treatment rate f) on the level of infection (cumulative cases of both strains). This is because the fact that $\mathcal{R}_{SC}$ is always a decreasing function of f (see (3)) and $\mathcal{R}_{RC}$ does not depend on f, whereas the size of total infection can increase with f in some cases (see Fig. 10). The reason for this discrepancy between reproduction numbers and infection size is that $\mathcal{R}_{SC}$ represents only a fraction of secondary cases produced by one sensitive case. The other fraction of new cases that are resistant (represented by $\mathcal{R}_{AR}$, see (15)) is not accounted for.

To take account of $\mathcal{R}_{AR}$, we derived the new quantity $\mathcal{R}_{TC}^{[n]}$ (the subscript T for total and C for control) which represents the total number of new infections in the nth generation ($n > 2$) produced by one sensitive case. $(\mathcal{R}_{TC}^{[n]})^{1/n}$ gives the average reproduction number by one sensitive case per generation. We showed for $n = 3$ that, under certain conditions, there exists a critical value $f_c \in (0, 1)$ such that $\mathcal{R}_{TC}^{[3]}$ decreases with f for $f < f_c$ but increases with f for $f > f_c$. This suggests that the number $\mathcal{R}_{TC}^{[n]}$ may provide a better quantity than $\mathcal{R}_{SC}$ or $\mathcal{R}_C$ for examining the effect of treatment on the level of infection.

We remark that, since $\mathcal{R}_{TC}^{[3]}$ (and $\mathcal{R}_{TC}^{[n]}$ for all $n > 2$) is a function of both the treatment rate f and the vaccination rate ν, the critical value f_c (above which the benefit of antiviral use can be compromised) varies with ν. Therefore, the critical level of treatment is dependent on the immunity level of the population. Similarly, since $\mathcal{R}_{SC}$ is a function of f and

ν and $\mathcal{R}_{RC}$ is a function of ν, the relative magnitudes of $\mathcal{R}_{SC}$ and $\mathcal{R}_{RC}$ will depend on the levels of antiviral use and vaccination. Hence, the influence of treatment on the prevalence of both strains will also depend on the vaccination level (see Fig. 4 for the bifurcation diagram in the (ν, f) plane). We need to point out that, for demonstration purposes, we have presented our results for the case in which a compromise of antiviral benefits may occur only when the vaccination level is above a threshold. This does not imply that the negative effect of antiviral use will not occur in the absence of vaccine or when vaccination of susceptibles is not available (e.g., in the case of an influenza pandemic), as a similar result has also been shown in models without vaccination (see Lipsitch et al., 2007).

Another contribution of this paper is the derivation of the new epidemiological quantity, $\mathcal{R}_{TC}^{[n]}$. The concept of reproduction numbers have been very useful in the study of disease control and prevention. It has been shown for simple models that the basic and control reproduction numbers are directly linked to the final size of infections in epidemic models without demographics. However, it is not the case in our model which is an endemic model with demographics. Our results suggest that an inverse relationship between the usual reproduction number and the infection level may occur. The main reason for this is that a fraction of new cases produced by an initially sensitive case will be drug-resistant, which will then produce resistant cases at a different rate in the following generation. A consequence of this process is that the traditionally defined reproduction number may not provide an accurate description for changes in the final size of infection affected by antiviral use. This is indeed observed in the numerical simulations of our model, which demonstrated that although in most cases drug treatment may reduce the epidemic size and delay the time to the peak of an epidemic, it may in some cases lead to an increased cumulative incidence and a higher epidemic peak. Therefore, while the reproduction numbers calculated under the traditional definition can provide useful information for the qualitative dynamics, it may not be appropriate for assessing the effect of control measures on the disease prevalence.

The model considered in this paper assumes that individuals in the vaccinated class are completely immune to both strains. This assumption can be relaxed to allow for partial cross-immunity to the resistant strain. The model can also be generalized by including prophylaxis. We have began to study the more generalized model and will publish the results elsewhere.

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Appendix A: Derivation of the quantities $\mathcal{R}_{SC}$ and $\mathcal{R}_{RC}$

Noticing that the model has three infected variables, namely I_{SU}, I_{ST}, and I_R, it follows that, using the notation of Driessche and Watmough (2002), the matrices $\mathcal{F}$ and $\mathcal{V}$ (corresponding to the new infection terms and the remaining transfer terms, respectively) are

given by

$$\mathcal{F} = \frac{\sigma+\mu}{\sigma+\mu+\nu}\begin{pmatrix} (1-f)\beta_S & (1-f)\beta_S\delta & 0 \\ f(1-c)\beta_S & f(1-c)\beta_S\delta & 0 \\ fc\beta_S & fc\beta_S\delta & \beta_R \end{pmatrix},$$
$$\mathcal{V} = \begin{pmatrix} \mu+k_U & 0 & 0 \\ 0 & \mu+k_T & 0 \\ 0 & 0 & \mu+k_R \end{pmatrix}.$$

Thus,

$$\mathcal{F}\mathcal{V}^{-1} = \begin{pmatrix} \mathcal{F}_{11} & 0 \\ \mathcal{F}_{21} & \mathcal{F}_{22} \end{pmatrix},$$

where

$$\mathcal{F}_{11} = \frac{\sigma+\mu}{\sigma+\mu+\nu}\begin{pmatrix} \frac{(1-f)\beta_S}{\mu+k_U} & \frac{(1-f)\beta_S\delta}{\mu+k_T} \\ \frac{f(1-c)\beta_S}{\mu+k_U} & \frac{f(1-c)\beta_S\delta}{\mu+k_T} \end{pmatrix},$$
$$\mathcal{F}_{21} = \frac{\sigma+\mu}{\sigma+\mu+\nu}\left(\frac{fc\beta_S}{\mu+k_U}, \frac{fc\beta_S\delta}{\mu+k_T}\right), \qquad \mathcal{F}_{22} = \frac{(\sigma+\mu)\beta_R}{(\sigma+\mu+\nu)(\mu+k_R)}.$$

Let

$$\mathcal{R}_{SU} = \frac{\beta_S}{\mu+k_U}, \qquad \mathcal{R}_{ST} = \frac{\beta_S\delta}{\mu+k_T}, \qquad \mathcal{R}_R = \frac{\beta_R}{\mu+k_R}.$$

Then we have

$$\begin{aligned} \mathcal{R}_{SC} &= \rho(\mathcal{F}_{11}) \\ &= \frac{\sigma+\mu}{\sigma+\mu+\nu}\left(\frac{(1-f)\beta_S}{\mu+k_U} + \frac{f(1-c)\beta_S\delta}{\mu+k_T}\right) \\ &= \frac{\sigma+\mu}{\sigma+\mu+\nu}\big((1-f)\mathcal{R}_{SU} + f(1-c)\mathcal{R}_{ST}\big), \\ \mathcal{R}_{RC} &= \rho(\mathcal{F}_{22}) = \frac{\beta_R(\sigma+\mu)}{(\sigma+\mu+\nu)(\mu+k_R)} = \frac{(\sigma+\mu)}{(\sigma+\mu+\nu)}\mathcal{R}_R, \end{aligned} \tag{A.1}$$

and

$$\mathcal{R}_C = \rho\big(\mathcal{F}\mathcal{V}^{-1}\big) = \max\{\mathcal{R}_{SC}, \mathcal{R}_{RC}\}, \tag{A.2}$$

where $\rho(M)$ represents the spectral radius of the nonnegative matrix M.

Appendix B: Proof of Theorem 3.1

The equilibria of system (1) are the solutions of the following equations:

$$\begin{cases} \Lambda-(\mu+\nu)S-\frac{\mu\beta_S}{\Lambda}I_{SU}S-\frac{\mu\beta_S\delta}{\Lambda}I_{ST}S-\frac{\mu\beta_R}{\Lambda}I_RS+\omega R+\sigma V=0,\\ \nu S-(\sigma+\mu)V=0,\\ (1-f)\frac{\mu\beta_S}{\Lambda}SI_{SU}+(1-f)\frac{\mu\beta_S\delta}{\Lambda}SI_{ST}-(\mu+k_U)I_{SU}=0,\\ f(1-c)\frac{\mu\beta_S}{\Lambda}SI_{SU}+f(1-c)\frac{\mu\beta_S\delta}{\Lambda}SI_{ST}-(\mu+k_T)I_{ST}=0,\\ \frac{\mu\beta_R}{\Lambda}I_RS+fc\frac{\mu\beta_S}{\Lambda}SI_{SU}+fc\frac{\mu\beta_S\delta}{\Lambda}SI_{ST}-(\mu+k_R)I_R=0,\\ k_TI_{ST}+k_UI_{SU}+k_RI_R-(\mu+\omega)R=0. \end{cases} \tag{B.1}$$

In order to solve the algebraic Eqs. (B.1), we consider three cases as follows.

Case 1: $I_R=0$. In this case, from the fifth equation of (B.1) and the fact that $S>0$ and $0<f<1$, we have $I_{SU}=I_{ST}=0$. Substitution of $I_R=I_{SU}=I_{ST}=0$ in (B.1) yields that

$$S=\frac{(\sigma+\mu)\Lambda}{\mu(\sigma+\mu+\nu)}:=S^0,\qquad V=\frac{\nu\Lambda}{\mu(\sigma+\mu+\nu)}:=V^0,\qquad R=0.$$

Case 2: $I_R>0$ and $I_{ST}=0$. In this case, it follows from the fourth and fifth equations of (B.1) that $I_{SU}=0$ and $S=\frac{S^0}{\mathcal{R}_{RC}}:=\hat{S}$. Substitution of $I_{ST}=0$, $I_{SU}=0$, $S=\hat{S}$ in (B.1) gives

$$\begin{cases} \Lambda-(\mu+\nu)\hat{S}-\frac{\mu\beta_R}{\Lambda}I_R\hat{S}+\omega R+\sigma V=0,\\ \nu\hat{S}-(\sigma+\mu)V=0,\\ k_RI_R-(\mu+\omega)R=0. \end{cases} \tag{B.2}$$

Solving the linear algebraic equations (B.2), we obtain

$$V=\frac{V^0}{\mathcal{R}_{RC}}:=\hat{V},\qquad I_R=\frac{(\mu+\omega)N^0}{(\mu+\omega+k_R)}\left(1-\frac{1}{\mathcal{R}_{RC}}\right):=\hat{I}_R,$$
$$R=N^0-\hat{S}-\hat{V}-\hat{I}_R:=\hat{R}.$$

Case 3: $I_R>0$ and $I_{ST}>0$. It follows from the third and fourth equations of (B.1) that

$$\begin{cases} ((1-f)\frac{\mu\beta_S}{\Lambda}S-(\mu+k_U))I_{SU}+(1-f)\frac{\mu\beta_S\delta}{\Lambda}SI_{ST}=0,\\ f(1-c)\frac{\mu\beta_S}{\Lambda}SI_{SU}+(f(1-c)\frac{\mu\beta_S\delta}{\Lambda}S-(\mu+k_T))I_{ST}=0. \end{cases} \tag{B.3}$$

The fact that $I_{ST}>0$ implies that

$$\begin{vmatrix} ((1-f)\frac{\mu\beta_S}{\Lambda}S-(\mu+k_U)) & (1-f)\frac{\mu\beta_S\delta}{\Lambda}S\\ f(1-c)\frac{\mu\beta_S}{\Lambda}S & (f(1-c)\frac{\mu\beta_S\delta}{\Lambda}S-(\mu+k_T)) \end{vmatrix}=0. \tag{B.4}$$

Solving (B.4) gives

$$S=\frac{(\mu+k_U)(\mu+k_T)\Lambda}{(\mu+k_U)f(1-c)\beta_S\mu\delta+(\mu+k_T)(1-f)\beta_S\mu}=\frac{S^0}{\mathcal{R}_{SC}}:=S^*.$$

Substitution of $S = S^*$ in (B.1) yields that

$$\begin{cases} \Lambda - (\mu+\nu)S^* - \frac{\mu\beta_S}{\Lambda} I_{SU} S^* - \frac{\mu\beta_S\delta}{\Lambda} I_{ST} S^* - \frac{\mu\beta_R}{\Lambda} I_R S^* + \omega R + \sigma V = 0, \\ \nu S^* - (\sigma+\mu)V = 0, \\ (1-f)\frac{\mu\beta_S}{\Lambda} S^* I_{SU} + (1-f)\frac{\mu\beta_S\delta}{\Lambda} S^* I_{ST} - (\mu+k_U) I_{SU} = 0, \\ \frac{\mu\beta_R}{\Lambda} I_R S^* + fc\frac{\mu\beta_S}{\Lambda} S^* I_{SU} + fc\frac{\mu\beta_S\delta}{\Lambda} S^* I_{ST} - (\mu+k_R) I_R = 0, \\ k_T I_{ST} + k_U I_{SU} + k_R I_R - (\mu+\omega) R = 0. \end{cases} \tag{B.5}$$

After extensive algebraic calculations, the solution of the linear algebraic equations (B.5) is

$$V = \frac{V^0}{\mathcal{R}_{SC}} := V^*,$$

$$I_{SU} = \frac{(\mu+\omega)(\mathcal{R}_{SC}-1)N^0}{\frac{\sigma+\mu}{\sigma+\mu+\nu}(\beta_S + \beta_R b + \beta_S\delta a) + \omega(1+a+b)\mathcal{R}_{SC}} := I_{SU}^*,$$

$$I_{ST} = a I_{SU}^* := I_{ST}^*, \qquad I_R = b I_{SU}^* := I_R^*,$$

$$R = N^0 - S^* - V^* - I_{SU}^* - I_{ST}^* - I_R^* := R^*,$$

where $a = \frac{f(1-c)(\mu+k_U)}{(1-f)(\mu+k_T)}$ and $b = \frac{fc(\mu+k_U)}{(1-f)(\mu+k_R)(1-\frac{\mathcal{R}_{RC}}{\mathcal{R}_{SC}})}$.

From the above analysis, it follows that the system (B.1) has three possible nonnegative solutions. Therefore, the system (1) has three possible equilibria E_0, $\hat{E}$, and E^*. From the expression of $\hat{I}_R$, it is easy to see that $\hat{I}_R > 0$ if and only if $\mathcal{R}_{RC} > 1$. Similarly, we can easily see that $I_{SU}^* > 0$ if and only if $\mathcal{R}_{SC} > 1$, and $I_R^* > 0$ if and only if $\mathcal{R}_{RC} < \mathcal{R}_{SC}$. When $\mathcal{R}_C < 1$, i.e., $\mathcal{R}_{SC} \le 1$ and $\mathcal{R}_{RC} \le 1$, it follows that either $\hat{I}_R < 0$ and $I_{SU}^* < 0$, or $\hat{I}_R < 0$ and $I_R^* < 0$. Thus, system (1) has only one equilibrium E_0. When $\mathcal{R}_{RC} > 1$, it follows that the resistant-strain-only equilibrium $\hat{E}$ exists. This implies that the system (1) has two nonnegative equilibria, E_0 and $\hat{E}$. When $\mathcal{R}_{SC} > \mathcal{R}_{RC}$ and $\mathcal{R}_{SC} > 1$, it is easy to see that the coexistence equilibrium E^* exists. This completes the proof of Theorem 3.1.

Appendix C: Proof of the stability of the matrix A_{11}

Let $\lambda_j(A_{11})$, $j = 1, 2, 3$, be the eigenvalues of the matrix A_{11} with $\Re(\lambda_1(A_{11})) \le \Re(\lambda_2(A_{11})) \le \Re(\lambda_3(A_{11}))$. Direct calculation yields that $\mathrm{Det}(A_{11}) = -\frac{\mu\beta_R}{\Lambda}\hat{I}_R(\sigma+\mu)(k_R+\mu+\omega) < 0$. It then follows that $\lambda_1(A_{11})\lambda_2(A_{11})\lambda_3(A_{11}) < 0$. This means that either $\Re(\lambda_i(A_{11})) < 0$ for $i = 1, 2, 3$, or $\Re(\lambda_1(A_{11})) < 0 < \Re(\lambda_2(A_{11})) \le \Re(\lambda_3(A_{11}))$. Since $\mathrm{Tr}(A_{11}) = -(\mu+\nu+\frac{\mu\beta_R}{\Lambda}\hat{I}_R+\sigma) < 0$, we know that $\Re(\lambda_1(A_{11}) + \lambda_2(A_{11})) < 0$ and $\Re(\lambda_1(A_{11}) + \lambda_3(A_{11})) < 0$. Now let us consider the second additive compound (Li and Muldowney, 1995; Arino et al., 2003) of the matrix A_{11}:

$$A_{11}^{[2]} = \begin{pmatrix} -(\mu+\nu) - \frac{\mu\beta_R}{\Lambda}\hat{I}_R - \sigma & 0 & -\omega+\sigma \\ k_R & -(\mu+\nu) - \frac{\mu\beta_R}{\Lambda}\hat{I}_R - \sigma - (\omega+\mu) & -\frac{\mu\beta_R}{\Lambda}\hat{S} - \sigma \\ 0 & \frac{\mu\beta_R}{\Lambda}\hat{I}_R & -(\omega+\mu) \end{pmatrix}.$$

Straightforward calculations yield that

$$\begin{aligned}\operatorname{Det} A_{11}^{[2]} = &-\left(\mu+\nu+\frac{\mu\beta_R}{\Lambda}\hat{I}_R+\sigma\right)\left(\mu+\nu+\frac{\mu\beta_R}{\Lambda}\hat{I}_R+\sigma+\omega+\mu\right)(\omega+\mu)\\ &-\omega k_R\frac{\mu\beta_R}{\Lambda}\hat{I}_R+\sigma k_R\frac{\mu\beta_R}{\Lambda}\hat{I}_R\\ &-\left(\frac{\mu\beta_R}{\Lambda}\hat{S}+\sigma\right)\frac{\mu\beta_R}{\Lambda}\hat{I}_R\left(\mu+\nu+\frac{\mu\beta_R}{\Lambda}\hat{I}_R+\sigma\right)<0.\end{aligned}$$

The conditions $\frac{\mu\beta_R}{\Lambda}\hat{S}=(\mu+k_R)$ and $\sigma k_R\frac{\mu\beta_R}{\Lambda}\hat{I}_R<(\frac{\mu\beta_R}{\Lambda}\hat{S}+\sigma)\frac{\mu\beta_R}{\Lambda}\hat{I}_R(\mu+\nu+\frac{\mu\beta_R}{\Lambda}\hat{I}_R+\sigma)$ are used in the last step. The eigenvalues of $A_{11}^{[2]}$ are $\lambda_i(A_{11})+\lambda_j(A_{11})$, $1\le i<j\le 3$. It then follows that

$$\begin{aligned}-1&=\operatorname{sgn}\big(\det(A_{11}^{[2]})\big)\\ &=\operatorname{sgn}\big(\Re\big(\lambda_1(A_{11})+\lambda_2(A_{11})\big)\Re\big(\lambda_1(A_{11})+\lambda_3(A_{11})\big)\Re\big(\lambda_2(A_{11})+\lambda_3(A_{11})\big)\big)\\ &=\operatorname{sgn}\big(\big(\Re\big(\lambda_2(A_{11})+\lambda_3(A_{11})\big)\big)\big).\end{aligned}$$

This together with $\Re(\lambda_1(A_{11})+\lambda_2(A_{11}))<0$ and $\Re(\lambda_1(A_{11})+\lambda_3(A_{11}))<0$, implies that $\Re(\lambda_i(A_{11}))<0$ for all $i=1,2,3$, i.e., the matrix A_{11} is stable.

Appendix D: Proof of Theorem 4.3

Let $W=V+R$, then system (1) can be written as

$$\begin{cases}S'=\Lambda-(\mu+\nu)S-\lambda_S(t)S-\lambda_R(t)S+\sigma W,\\ I_{SU}'=(1-f)\lambda_S(t)S-\mu I_{SU}-k_U I_{SU},\\ I_{ST}'=f(1-c)\lambda_S(t)S-\mu I_{ST}-k_T I_{ST},\\ I_R'=\lambda_R(t)S+fc\lambda_S(t)S-\mu I_R-k_R I_R,\\ W'=\nu S+k_T I_{ST}+k_U I_{SU}+k_R I_R-(\mu+\sigma)W.\end{cases}\tag{D.1}$$

The limiting system of (D.1) is

$$\begin{cases}S'=\Lambda-(\mu+\nu)S-\frac{\mu\beta_S}{\Lambda}(I_{SU}+\delta I_{ST})S-\frac{\mu\beta_R}{\Lambda}I_RS\\ \qquad\quad+\sigma(\frac{\Lambda}{\mu}-S-I_{SU}-I_{ST}-I_R),\\ I_{SU}'=(1-f)\frac{\mu\beta_S}{\Lambda}(I_{SU}+\delta I_{ST})S-\mu I_{SU}-k_U I_{SU},\\ I_{ST}'=f(1-c)\frac{\mu\beta_S}{\Lambda}(I_{SU}+\delta I_{ST})S-\mu I_{ST}-k_T I_{ST},\\ I_R'=\frac{\mu\beta_R}{\Lambda}I_RS+fc\frac{\mu\beta_S}{\Lambda}(I_{SU}+\delta I_{ST})S-\mu I_R-k_R I_R.\end{cases}\tag{D.2}$$

If $\mathcal{R}_C<1$, then $\mathcal{R}_{SC}<1$ and $\mathcal{R}_{RC}<1$. From Theorem 4.2, E_0 is locally asymptotically stable. In the following, we only need to prove that the DFE E_0 is a global attractor.

From the first equation in (D.2), it follows that

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

By the comparison principle, we have $S(t) \le \frac{\sigma+\mu}{\sigma+\mu+\nu}\frac{\Lambda}{\mu} + (S(0) - \frac{\sigma+\mu}{\sigma+\mu+\nu}\frac{\Lambda}{\mu})e^{-(\sigma+\mu+\nu)t}$. Without loss of generality, we can assume that $S(t) \le \frac{\sigma+\mu}{\sigma+\mu+\nu}\frac{\Lambda}{\mu}$. Then it follows from the second and third equations of (D.2) that

$$\begin{cases} I'_{SU} \le (\frac{\sigma+\mu}{\sigma+\mu+\nu}(1-f)\beta_S - \mu - k_U)I_{SU} + \frac{\sigma+\mu}{\sigma+\mu+\nu}(1-f)\beta_S\delta I_{ST}, \\ I'_{ST} \le \frac{\sigma+\mu}{\sigma+\mu+\nu}f(1-c)\beta_S I_{SU} + (\frac{\sigma+\mu}{\sigma+\mu+\nu}f(1-c)\beta_S\delta - \mu - k_T)I_{ST}. \end{cases} \tag{D.3}$$

Then by the comparison principle (Smith, 1995), it is easy to show that $I_{SU}(t) \to 0$ and $I_{ST}(t) \to 0$ as $t \to +\infty$ if $\mathcal{R}_{SC} < 1$. From the fourth equation of (D.2), we have

$$I'_R \le \left(\frac{\sigma+\mu}{\sigma+\mu+\nu}\beta_R - \mu - k_R\right)I_R + \frac{\sigma+\mu}{\sigma+\mu+\nu}fc\beta_S I_{SU} + \frac{\sigma+\mu}{\sigma+\mu+\nu}fc\delta I_{ST}.$$

Since $I_{SU}(t) \to 0$, $I_{ST}(t) \to 0$ as $t \to +\infty$ and $\mathcal{R}_{RC} < 1$, we have $I_R(t) \to 0$ as $t \to +\infty$. Similarly, from the fifth equation in (14) it is easy to see that $R(t) \to 0$ as $t \to +\infty$. Substitution of these into the first equation in (14) gives $S(t) \to S^0$ as $t \to +\infty$. This implies that the DFE E_0 is a global attractor. The proof of Theorem 4.3 is completed.

Appendix E: Proof of Theorem 4.4

Using a similar argument as in the proof of Theorem 4.3, we can show that $I_{SU}(t) \to 0$ and $I_{ST}(t) \to 0$ as $t \to +\infty$ if $\mathcal{R}_{SC} < 1$. Then the limiting system of (D.2) is

$$\begin{cases} S' = \Lambda - (\mu+\nu)S - \frac{\mu\beta_R}{\Lambda}I_R S + \sigma(\frac{\Lambda}{\mu} - S - I_R), \\ I'_R = \frac{\mu\beta_R}{\Lambda}I_R S - \mu I_R - k_R I_R. \end{cases} \tag{E.1}$$

Let (F, G) be the vector field defined by system (E.1). Then for the Dulac function $D(S, I_R) = \frac{1}{SI_R}$, there holds

$$\frac{\partial DF}{\partial S} + \frac{\partial DG}{\partial I_R} = -\frac{\Lambda}{S^2 I_R} - \frac{\sigma(\frac{\Lambda}{\mu} - I_R)}{S^2 I_R} < 0.$$

Thus, (E.1) does not have a limit cycle. Therefore, the local stability of $\hat{E}$ implies the global stability in Int Γ. This completes the proof of Theorem 4.4.

Appendix F: Proof of Theorem 4.5

Define

$$\begin{aligned} X &= \{(S, I_{SU}, I_{ST}, I_R) : S \ge 0, I_{SU} \ge 0, I_{ST} \ge 0, I_R \ge 0\}, \\ X_0 &= \{(S, I_{SU}, I_{ST}, I_R) : S > 0, I_{SU} > 0, I_{ST} > 0, I_R > 0\}, \\ \partial X_0 &= X \setminus X_0. \end{aligned} \tag{F.1}$$

It then suffices to show that (D.2) is uniformly persistent with respect to $(X_0, \partial X_0)$ (see Wang and Zhao, 2004). From (D.2), it follows that both X and X_0 are positively invariant. Clearly, ∂X_0 is relatively closed in X and system (D.2) is point dissipative. Consider the following set using solutions $(S(t), I_{SU}(t), I_{ST}(t), I_R(t))$ of system (D.2)

$$M_\partial = \big\{(S(0), I_{SU}(0), I_{ST}(0), I_R(0)) : (S(t), I_{SU}(t), I_{ST}(t), I_R(t)) \in \partial X_0, \forall t \geq 0\big\}.$$

We can show that

$$M_\partial = \big\{(S, I_{SU}, I_{ST}, I_R) \in \partial X : I_{SU} = 0, I_{ST} = 0\big\} \tag{F.2}$$

if $0 < f < 1$. Assume that $(S(0), I_{SU}(0), I_{ST}(0), I_R(0)) \in M_\partial$. It suffices to show that $I_{SU}(t) = 0$ and $I_{ST}(t) = 0$ for all $t \geq 0$. Suppose not. Then there exists a $t_0 \geq 0$ such that $I_{SU}(t_0) > 0$ or $I_{ST}(t_0) > 0$ and $I_R(t_0) = 0$. Since $0 < f < 1$, we have

$$I_R'(t_0) = fc\frac{\mu\beta_S}{\Lambda}\big(I_{SU}(t_0) + \delta I_{ST}(t_0)\big) > 0.$$

It follows that there is an ε_0 such that $I_R(t) > 0$ for $t_0 < t < t_0 + \varepsilon_0$. This means that $(S(t), I_{SU}(t), I_{ST}(t), I_R(t)) \notin \partial X_0$ for $t_0 < t < t_0 + \varepsilon_0$, which contradicts the assumption that $(S(0), I_{SU}(0), I_{ST}(0), I_R(0)) \in M_\partial$. Thus, (F.2) holds. Just as in the proof of Theorem 4.4, we can easily prove that $\hat{E}$ is globally asymptotically stable in Int M_∂. Moreover, $\bigcup_{x\in M_\partial} \omega(x) = \{E_0, \hat{E}\}$. By Theorem 4.6 of Thieme (1993), we only need to show that $W^s(E_0) \cap X_0 = \emptyset$, $W^s(\hat{E}) \cap X_0 = \emptyset$ if $\mathcal{R}_{RC} > 1$ and $\mathcal{R}_{SC} > 1$.

Since $\mathcal{R}_{RC} > 1$, we can choose an $\eta > 0$ small enough such that $\mathcal{R}_{RC} - \frac{\mu\beta_R}{\Lambda(\mu+k_R)}\eta > 1$. Assume that $W^s(E_0) \cap X_0 \neq \emptyset$. Then there exists a positive solution $(\bar{S}(t), \bar{I}_{SU}(t), \bar{I}_{ST}(t), \bar{I}_R(t))$ with $(\bar{S}(0), \bar{I}_{SU}(0), \bar{I}_{ST}(0), \bar{I}_R(0))) \in X_0$, such that $(\bar{S}(t), \bar{I}_{SU}(t), \bar{I}_{ST}(t), \bar{I}_R(t)) \to E_0$ as $t \to +\infty$. Thus, when t is sufficiently large, we have $S^0 - \eta < \bar{S}(t) < S^0 + \eta$ and $\bar{I}_R(t) \to 0$. From the fourth equation of system (D.2) , it follows that

$$\bar{I}_R' \geq \frac{\mu\beta_R}{\Lambda}(S^0 - \eta)\bar{I}_R - (\mu + k_R)\bar{I}_R. \tag{F.3}$$

By the comparison principle (Smith, 1995), we have that $\bar{I}_R(t) \to +\infty$ when t is sufficiently large. This contradicts $\bar{I}_R(t) \to 0$ as $t \to +\infty$. Thus, we must have $W^s(E_0) \cap X_0 = \emptyset$.

In the following, we prove that $W^s(\hat{E}) \cap X^0 = \emptyset$. Assume the contrary, that is, $W^s(\hat{E}) \cap X^0 \neq \emptyset$. Then there exists a positive solution $(\tilde{S}(t), \tilde{I}_{SU}(t), \tilde{I}_{ST}(t), \tilde{I}_R(t))$ with $(\tilde{S}(0), \tilde{I}_{SU}(0), \tilde{I}_{ST}(0), \tilde{I}_R(0)) \in X_0$, such that $(\tilde{S}(t), \tilde{I}_{SU}(t), \tilde{I}_{ST}(t), \tilde{I}_R(t)) \to \hat{E}$ as $t \to +\infty$. Since $\mathcal{R}_{SC} > \mathcal{R}_{RC} > 1$, we can choose a $\rho > 0$ small enough such that

$$\frac{(1-f)\mu\beta_S(\hat{S} - \rho)}{\Lambda(\mu + k_U)} + \frac{f(1-c)\mu\beta_S\delta(\hat{S} - \rho)}{\Lambda(\mu + k_T)} > 1.$$

Thus, when t is sufficiently large, we have $\hat{S} - \rho \leq \tilde{S}(t) \leq \hat{S} + \rho, 0 \leq \tilde{I}_{SU}(t) \leq \rho, 0 \leq \tilde{I}_{ST}(t) \leq \rho, \hat{I}_R - \rho \leq \tilde{I}_R(t) \leq \hat{I}_R + \rho$ and

$$\begin{cases} \tilde{I}_{SU}' \geq (((1-f)\frac{\mu\beta_S}{\Lambda})(\hat{S} - \rho) - \mu - k_U)\tilde{I}_{SU} + (1-f)\frac{\mu\beta_S}{\Lambda}\delta(\hat{S} - \rho)\tilde{I}_{ST}, \\ \tilde{I}_{ST}' \geq f(1-c)\frac{\mu\beta_S}{\Lambda}(\hat{S} - \rho)\tilde{I}_{SU} + (f(1-c)\frac{\mu\beta_S}{\Lambda}\delta(\hat{S} - \rho) - \mu - k_T)\tilde{I}_{ST}. \end{cases}$$

By the comparison principle (Smith, 1995), we have $\tilde{I}_{SU}(t) \to +\infty$, $\tilde{I}_{ST}(t) \to +\infty$ as $t \to +\infty$. This contradicts $\tilde{I}_{SU}(t) \to 0$, $\tilde{I}_{ST}(t) \to 0$ as $t \to +\infty$. The above assertion is thus proved, i.e., $W^s(\hat{E}) \cap X_0 = \emptyset$.

Since $W^s(E_0) \cap X_0 = \emptyset$, $W^s(\hat{E}) \cap X_0 = \emptyset$, and $\{E_0, \hat{E}\}$ are acyclic in ∂X_0, by Theorem 4.6 of Thieme (1993) we are able to conclude that the system (1) is uniformly persistent with respect to $(X_0, \partial X_0)$. This completes the proof of Theorem 4.5.

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