J. Math. Biol. (2016) 72:343–361
DOI 10.1007/s00285-015-0887-y

Mathematical Biology

Can treatment increase the epidemic size?

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Received: 30 April 2013 / Revised: 17 February 2014 / Published online: 30 April 2015

Abstract Antiviral treatment is one of the key pharmacological interventions against many infectious diseases. This is particularly important in the absence of preventive measures such as vaccination. However, the evolution of drug-resistance in treated patients and its subsequent spread to the population pose significant impediments to the containment of disease epidemics using treatment. Previous models of population dynamics of influenza infection have shown that in the presence of drug-resistance, the epidemic final size (i.e., the total number of infections throughout the epidemic) is affected by the treatment rate. These models, through simulation experiments, illustrate the existence of an optimal treatment rate, not necessarily the highest possible rate, for minimizing the epidemic final size. However, the conditions for the existence of such an optimal treatment rate have never been found. Here, we provide these conditions for a class of models covered in the literature previously, and investigate the combination effect of treatment and transmissibility of the drug-resistant pathogen strain on the epidemic final size. For the first time, we obtain the final size relations for an epidemic model with two strains of a pathogen (i.e., drug-sensitive and drug-resistant). We also

This work was supported in part by the Natural Sciences and Engineering Research Council of Canada (NSERC), Mathematics of Information Technology and Complex Systems (MITACS), and the Canadian Institutes of Health Research (CIHR).

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discuss this model with specific functional forms of de novo resistance emergence, and illustrate the theoretical findings with numerical simulations.

Keywords Epidemic modelling · Treatment · Drug-resistance · Final size relation · Reproduction numbers

Mathematics Subject Classification 92B05 · 37N25

1 Introduction

In the 1930s, the pioneering work of Kermack and McKendrick established an extremely important principle, stating that the level of susceptibility must exceed a certain threshold in order for an epidemic to occur in a population (Kermak and McKendrick 1927, 1931). This principle was deduced from a simple system of differential equations describing the dynamics of susceptible (S), infected (I), and recovered (R) individuals in a homogeneously mixed population, the so-called classical SIR epidemic model. Since then, many epidemiological models have been developed and studied to address the conditions for disease control (Brauer and Castillo-Chavez 2010; Keeling and Rohani 2008), should the level of susceptibility in the population warrant the occurrence of an epidemic. A key parameter that has been thoroughly investigated in these models is the basic reproduction number, commonly denoted by $\mathscr{R}_0$ (Anderson and May 1992; Diekmann and Heesterbeek 2000, defined (in the epidemiological context) as the average number of secondary infections generated by a single infectious individual introduced into an entirely susceptible population. Translation of the Kermack and McKendrick principle in the context of the basic reproduction number provides the threshold condition $\mathscr{R}_0 > 1$ for an epidemic to take place (Diekmann and Heesterbeek 2000; van den Driessche and Watmough 2002). Naturally, the aim of public health intervention measures is to reduce $\mathscr{R}_0$ below one in order to halt the epidemic spread.

Among disease interventions that have been practiced, antiviral treatment remains a key pharmacological measure to reduce illness, lower disease transmissibility, and therefore reduce $\mathscr{R}_0$ to sufficiently low values to make disease control feasible. In the absence of preventive measures (such as vaccination), antiviral treatment is particularly important for disease management. However, many infectious pathogens can evolve and generate successor strains that confer drug-resistance (Domingo and Holland 1997). The evolution of resistance is generally associated with impaired transmission fitness compared to the drug-sensitive strains of the infectious pathogen (Moghadas 2011). In the absence of treatment, drug-resistant strains may be competitively disadvantaged compared to the drug-sensitive strains and may go extinct. However, treatment prevents the growth and spread of the drug-sensitive strains, and therefore induces a selective pressure that favours the drug-resistant strains to replicate and restore their fitness to a level suitable for successful transmission (Andersson and Levin 1999; Björkman et al. 2000; Maisnier-Patin and Andersson 2004). This phenomenon has been observed in several infectious diseases, in particular for management of influenza infection using antiviral drugs (Rimmelzwaan et al. 2005).

Previous models of influenza epidemics and pandemics have investigated strategies for antiviral treatment in order to reduce the epidemic final size (i.e., the total number of infections throughout the epidemic), while preventing wide spread drug-resistance in the population (Hansen and Day 2011; Lipsitch et al. 2007; Moghadas 2008; Moghadas et al. 2008, 2009). Through computer simulations, these studies have shown that, when the drug-resistant strain is highly transmissible, there is an optimal treatment rate for minimizing the final size (Lipsitch et al. 2007; Moghadas 2008; Moghadas et al. 2008). This optimal treatment rate is not necessarily the highest possible level. Despite the recognition of this optimal treatment rate, no theoretical investigation has been conducted to determine the conditions under which the final size is minimum. In fact, no prior study has expressed the final size relations for epidemic models that contain two strains of a pathogen with different transmissibilities. Here, we develop a model that describes the population dynamics of infections caused by drug-sensitive and drug-resistant strains of a pathogen. We derive the final size relations, and determine conditions under which the epidemic final size decreases with increasing the treatment rate. Our theoretical results, for the first time, formulate the conditions for the existence of an optimal treatment rate within its plausible range, at which the epidemic final size undergoes a local minimum. We discuss the findings for two distinct structures of the model by considering different functional forms for the development of drug-resistance during treatment, and illustrate the results by numerical simulations. Finally we close the paper with some concluding remarks and questions to be addressed in future work.

2 The model

To develop the model with drug-sensitive and drug-resistant pathogen strains (from now on, refered to as resistant strain and sensitive strain, respectively, throughout the paper), we divided a homogeneously mixing population of size $N(t)$ into classes of individuals with epidemiological statuses as susceptible (S), infected with the sensitive strain (I_S), infected with the sensitive strain under treatment (I_T), infected with the resistant strain (I_R), and recovered individuals (R). Since treatment is ineffective against the resistant strain, we combined the two classes of resistance with and without treatment. In the model considered here, susceptible individuals can become infected through contacts with infected individuals in a bilinear mass action incidence. We assume that β is the baseline transmission rate of the sensitive strain; δ_R denotes the relative transmissibility of the resistant strain; δ_T is the relative transmissibility of treated infection with the sensitive strain; η is the rate at which individuals infected with the sensitive strain are treated; and $\gamma_S, \gamma_T, \gamma_R$ are the recovery rates for individuals with the sensitive strain without treatment, sensitive strain with treatment, and resistant strain, respectively; with the initial conditions $S(0) > 0$, $I_S(0) \geq 0$, $I_R(0) \geq 0$, and $I_T(0) = R(0) = 0$. We also assume that treatment reduces the infectiousness, and therefore transmissibility, of the sensitive strain ($\delta_T < 1$) (Halloran et al. 2006). Treatment may also shorten the infectious period ($1/\gamma_T \leq 1/\gamma_S$) (Moghadas et al. 2008). Since resistance generally emerges with compromised transmission fitness (Domingo and Holland 1997), we assume a lower transmissibility of the resistant strain compared to that of the sensitive strain without treatment ($\delta_R < 1$). With these assumptions, the

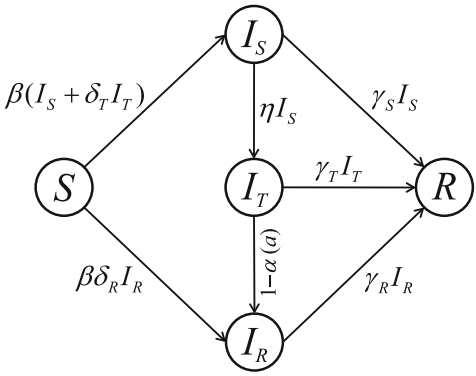

Fig. 1 Model diagram for transitions between subpopulations

model is schematically represented in Fig. 1, and the equations for S and I_S are given by

$$S' = -\beta\left(I_S + \delta_T I_T + \delta_R I_R\right) S,$$
$$I_S' = \beta\left(I_S + \delta_T I_T\right) S - \left(\gamma_S + \eta\right) I_S.$$

The novelty of our model relates largely to the emergence of resistance as a probability function of time since the start of treatment. Experimental studies suggest that the rate of developing resistance increases with time, as resistant mutants in viruses isolated from treated patients were mostly detected several days after the start of treatment (Kiso et al. 2004; Ward et al. 2005). We do not attempt to provide a detailed picture of the resistance development, but assume that resistance emerges in treated individuals at a rate which depends on the time since the onset of treatment. Our primary purpose is to explore how the increase in treatment rate affects the total number of infections (i.e., the epidemic final size).

We define $\alpha(a)$ to be the probability of being in the treated class (I_T) at time a following the initiation of treatment without developing drug-resistance. Thus, $1-\alpha(a)$ represents the probability of developing drug-resistance earlier than time a following the start of treatment. Here, we assume that individuals infected with the sensitive strain may develop drug-resistance after the start of treatment, and therefore $\alpha(0) = 1$. Since the probability of resistance emergence increases with the outgrowth of pathogen replication, it is biologically reasonable to have the following assumption on the probability function α:

(H) $\alpha(a) : [0, \infty) \longrightarrow [0, 1]$ is a non-negative non-increasing, piecewise differentiable function with possibly a finite number of jumps, $\lim_{a\to\infty} \alpha(a) = 0$, and $\int_0^\infty \alpha(a)\,\mathrm{d}a$ is bounded.

Using this assumption and adopting the idea from van den Driessche and Zou (2007), one can easily obtain the total number of treated individuals with the sensitive strain (without developing drug-resistance) at any time t by using

$$I_T(t) = \int_0^t \eta I_S(\xi) e^{-\gamma_T(t-\xi)} \alpha(t-\xi)\,\mathrm{d}\xi. \tag{1}$$

Differentiation of (1) gives

$$I_T'(t) = \eta I_S(t) + \int_0^t \eta I_S(\xi) e^{-\gamma_T (t-\xi)} \alpha'(t-\xi)\, \mathrm{d}\xi - \gamma_T I_T(t),$$

in which, since $\alpha'(a) \leq 0$, the term

$$\int_0^t \eta I_S(\xi) e^{-\gamma_T (t-\xi)} \alpha'(t-\xi)\, \mathrm{d}\xi,$$

represents the flow from I_T to I_R following the emergence of drug-resistance during treatment. Assuming that there are no disease-induced deaths, and neglecting birth and natural death during the epidemic, the total population size remains constant ($N(t) = N$). Since recovered individuals are no longer susceptible to reinfection, we may omit the equation for R without affecting the dynamics of disease transmission in the model. Considering the development of drug-resistance in treated individuals and direct transmission of resistance as influx of the I_R class, the model can be expressed in the form

$$S' = -\beta \left(I_S + \delta_T I_T + \delta_R I_R\right) S, \tag{2}$$

$$I_S' = \beta \left(I_S + \delta_T I_T\right) S - \left(\gamma_S + \eta\right) I_S, \tag{3}$$

$$I_T' = \eta I_S + \int_0^t \eta I_S(\xi) e^{-\gamma_T (t-\xi)} \alpha'(t-\xi)\, \mathrm{d}\xi - \gamma_T I_T, \tag{4}$$

$$I_R' = \delta_R \beta I_R S - \int_0^t \eta I_S(\xi) e^{-\gamma_T (t-\xi)} \alpha'(t-\xi)\, \mathrm{d}\xi - \gamma_R I_R. \tag{5}$$

It is easy to verify that the above model is well-posed with non-negative initial conditions. By using the variation-of-constants formula for the equations for I_S, I_R, R, and considering that $S' = 0$ if $S = 0$, one can deduce that these variables remain non-negative using a contradiction argument. Thus, from (1), it can be seen that $I_T(t) \geq 0$ for all t. Furthermore, the fact that the total population $S + I_S + I_T + I_R + R$ is a positive constant guarantees the boundedness of the model solutions (Brauer and Castillo-Chavez 2010; Xiao and Zou 2013).

Remark The model (2)–(5) can also be derived by the introduction of an age-structured subpopulation and the probability of developing drug-resistance at a certain time. Let $J(t,\, a)$ represent the population size of individuals infected with the sensitive strain at time t, for whom treatment has initiated at time $t - a$. Then

$$\left(\frac{\partial}{\partial t} + \frac{\partial}{\partial a}\right) J(t,\, a) = -\left(p(a) + \gamma_T\right) J(t,\, a),$$

with the boundary condition $J(t,\, 0) = \eta I_S(t)$, and the initial condition $J(0,\, a) = 0$ for $a \geq 0$, where $p(a)$ is the rate at which treated individuals develop drug-resistance at time a. Thus, the total number of infected individuals who develop drug-resistance at time t following the start of treatment is given by

$$Q(t) = \int_0^\infty p(a) J(t,\, a)\, \mathrm{d}a = \int_0^t p(a) J(t-a,\, 0) e^{-\int_0^a \left(\gamma_T + p(s)\right) \mathrm{d}s}\, \mathrm{d}a.$$

Let $\alpha'(a) = -p(a)e^{-\int_0^a p(s)\,\mathrm{d}s}$ be the probability of developing drug-resistance exactly at time a. Using the change of variable $\xi = t - a$, we obtain

$$Q(t) = -\int_0^t \eta I_S(t-a)e^{-\int_0^a \gamma_T\,\mathrm{d}s}\alpha'(a)\,\mathrm{d}a = \int_0^t \eta I_S(\xi)e^{-\gamma_T(t-\xi)}\alpha'(t-\xi)\,\mathrm{d}\xi,$$

which gives the integral term in (4). The remaining parts of the model can then be derived by using our approach described above.

3 Reproduction numbers

In this section, we provide expressions for the reproduction numbers of the model. In the absence of treatment, it can easily be seen that the basic reproduction number for the sensitive strain is $\mathscr{R}_0 = \beta N/\gamma_S$ (Diekmann and Heesterbeek 2000; van den Driessche and Watmough 2002), where N represents the total population size, which is constant in the absence of demographics and disease-induced death. When treatment is applied, $\mathscr{R}_0$ is reduced to a related number, the so-called control reproduction number, denoted by $\mathscr{R}_c$ in our study. Here we provide the expression for $\mathscr{R}_c$ in terms of the model parameters.

Let

$$\alpha^* := \lim_{t\to\infty}\int_0^t e^{-\gamma_T\xi}\alpha(\xi)\,\mathrm{d}\xi, \tag{6}$$

where α^* is the Laplace transform of the function $\alpha(a)$, evaluated at γ_T. Clearly, α^* represents the average time period that an individual infected with the sensitive strain remains in the treatment class before developing drug-resistance. By the properties of $\alpha(a)$ in (H) (i.e., $\alpha(a) \le 1$ for all $a \ge 0$), we have

$$0 < \alpha^* \le \lim_{t\to\infty}\int_0^t e^{-\gamma_T\xi}\,\mathrm{d}\xi = \frac{1}{\gamma_T},$$

and therefore $\gamma_T\alpha^*$ represents the probability that an infected individual will recover during the course of treatment. Thus,

$$\Lambda = -\lim_{t\to\infty}\int_0^t e^{-\gamma_T(t-\xi)}\alpha'(t-\xi)\,\mathrm{d}\xi = 1 - \gamma_T\alpha^*, \tag{7}$$

is the probability that a treated individual will develop drug-resistance. Now, suppose that a single infectious case with the sensitive strain is introduced into a population that is entirely susceptible. When treatment is implemented, the number of secondary cases with the sensitive strain generated by the initial infectious case is given by $\beta N/(\gamma_S+\eta)$ without treatment, and $\delta_T\eta\alpha^*\beta N/(\gamma_S+\eta)$ during treatment before developing drug-resistance. Thus the number of infections with the sensitive strain is given by

$$\mathscr{R}_S = \frac{\beta N}{(\gamma_S+\eta)} + \frac{\delta_T\eta\alpha^*\beta N}{(\gamma_S+\eta)}.$$

From (7), it can be seen that the initial case will also generate a number of secondary (resistant) infections given by $\delta_R \eta(1-\gamma_T\alpha^*)\beta N/(\gamma_R(\gamma_S+\eta))$ after developing drug-resistance during treatment. Thus the total number of new infections generated by a single case of infection with the sensitive strain is given by

$$\mathscr{R}_c^S = \underbrace{\frac{\beta N}{\gamma_S+\eta} + \frac{\eta\delta_T\alpha^*\beta N}{\gamma_S+\eta}}_{\substack{\text{total number of new cases}\\ \text{generated before the}\\ \text{initial infection with the}\\ \text{sensitive strain develops}\\ \text{drug-resistance}}} + \underbrace{\frac{\eta(1-\gamma_T\alpha^*)\delta_R\beta N}{(\gamma_S+\eta)\gamma_R}}_{\substack{\text{total number of new cases}\\ \text{generated after the initial}\\ \text{infection with the sensitive}\\ \text{strain has developed}\\ \text{drug-resistance}}}.$$

Introduction of an individual infected with the resistant strain into the population will result in the generation of only new infections with the resistant strain. The total number of these new cases is given by

$$\mathscr{R}_R = \delta_R\beta N/\gamma_R.$$

The next generation method (van den Driessche and Watmough 2002) gives the control reproduction number for (2)−(5):

$$\mathscr{R}_c = \max\left\{\mathscr{R}_S, \mathscr{R}_R\right\}.$$

In many epidemic modes, the control reproduction number is used to determine whether or not the epidemic will occur. This may be acheived by linearizing the model about the equilibrium point at which no infection is present (i.e., disease-free equilibrium), and evaluating the dominant eigenvalue of the system. This eigenvalue is often referred to the reproduction number, providing a threshold condition for epidemic to occur (when exceeds 1), but does not necessarily correspond to the number of secondary infections generated by a single infectious case.

Remark The next generation method (van den Driessche and Watmough 2002) for computing $\mathscr{R}_c$ disregards the number of infected individuals with the resistant strain caused by an initial infection of the sensitive strain after drug-resistance has developed. To compute this number (i.e., $\mathscr{R}_c^S$), one can use the individual tracing method (Moghadas 2008). In epidemic models considering the demographic structure, $\mathscr{R}_c$ is often used as a threshold for determining the persistence or eradication of the disease. In our model with a short-term epidemic duration, and without demographics (omitting birth and death rates), we focus on the final size of the total infections, which depends not only on $\mathscr{R}_S$ but also $\mathscr{R}_c^S$.

4 Final size relations

In this section, we attempt to provide an expression for the final size relation of the model (2)−(5). We will use the notation $\hat{f}$ to denote $\int_0^\infty f(t)\,\mathrm{d}t$ for an arbitrary non-

negative integrable function, and define the initial conditions $S(0) = S_0$, $I_S(0) = I_{S0}$, $I_R(0) = I_{R0}$, $I_T(0) = 0$, with $S_0 + I_{S0} + I_{R0} = N$. Summation of the Eqs. (2)–(5) gives

$$\left(S + I_S + I_T + I_R\right)' = -\left(\gamma_S I_S + \gamma_T I_T + \gamma_R I_R\right) < 0. \tag{8}$$

Hence, $(S + I_S + I_T + I_R)$ is a decreasing function bounded below by zero, and therefore approaches a limit as $t \to \infty$. Since S is non-negative and decreasing, S approaches a non-negative limit S_∞ as $t \to \infty$. Since $S_0 + I_{S0} + I_{R0} = N$, integration of (8) from 0 to ∞ gives

$$N - S_\infty = \gamma_S \hat{I}_S + \gamma_T \hat{I}_T + \gamma_R \hat{I}_R. \tag{9}$$

Integration of (2) from 0 to ∞ leads to

$$\log \frac{S_0}{S_\infty} = \beta \left[\hat{I}_S + \delta_T \hat{I}_T + \delta_R \hat{I}_R\right]. \tag{10}$$

Integrating Eq. (1), one can easily see (using (6) and the change of variable $t - \xi = u$) that

$$\hat{I}_T = \eta \hat{I}_S \int_0^\infty e^{-\gamma_T u} \alpha(u)\, \mathrm{d}u = \eta \hat{I}_S \alpha^*. \tag{11}$$

Substituting (11) into (9) and (10) gives

$$N - S_\infty = \left(\gamma_S + \gamma_T \eta \alpha^*\right) \hat{I}_S + \gamma_R \hat{I}_R, \tag{12}$$

$$\log \frac{S_0}{S_\infty} = \beta \left[(1 + \delta_T \eta \alpha^*) \hat{I}_S + \delta_R \hat{I}_R\right]. \tag{13}$$

In simple epidemic models, such as the one proposed in Kermak and McKendrick (1927), there are two equations relating S_∞ and $\mathscr{R}_0$ (or $\mathscr{R}_c$) with a single integral term. It is therefore possible to eliminate this integral term and obtain a transcendental equation (the so-called "final size relation"), relating $N - S_\infty$ and the basic reproduction number. However, this is not possible for Eqs. (12) and (13), and we are unable to determine the explicit form of the epidemic final size in the terms of the model parameters. We therefore propose the following approach to understand the effect of treatment rate on the epidemic final size.

Solving (12) and (13) as a system of linear equations for $\hat{I}_R$ and $\hat{I}_S$, we obtain:

$$\left(\mathscr{R}^*(\eta) - \mathscr{R}_R\right) \hat{I}_R = \frac{\mathscr{R}^*(\eta)}{\gamma_R}(N - S_\infty) - \frac{N}{\gamma_R} \log \frac{S_0}{S_\infty}, \tag{14}$$

$$\left(\mathscr{R}_R - \mathscr{R}^*(\eta)\right) \hat{I}_S = \frac{\mathscr{R}_R}{\left(\gamma_S + \gamma_T \eta \alpha^*\right)}(N - S_\infty) - \frac{N}{\left(\gamma_S + \gamma_T \eta \alpha^*\right)} \log \frac{S_0}{S_\infty}, \tag{15}$$

where

$$\mathscr{R}^*(\eta) := \frac{\left(1+\delta_T \eta\alpha^*\right)}{\gamma_S+\gamma_T\eta\alpha^*}\beta N. \tag{16}$$

Remark We may interpret $\mathscr{R}^*(\eta)$ as the total treatment-mediated number of new infections generated by an infectious case with the sensitive strain. This interpretation can be easily obtained by considering

$$\underbrace{\left(\frac{\gamma_S+\gamma_T\alpha^*\eta}{\gamma_S+\eta}\right)}_{\substack{\text{probability that an individual infected}\\ \text{with the sensitive strain remains}\\ \text{sensitive infection before recovery}}}\mathscr{R}^*(\eta) = \underbrace{\left(\frac{\gamma_S}{\gamma_S+\eta}+\frac{\delta_T\eta\gamma_S\alpha^*}{\gamma_S+\eta}\right)\mathscr{R}_0}_{\substack{\text{total number of new cases}\\ \text{generated before the initial}\\ \text{infection with the sensitive strain}\\ \text{develops drug-resistance}}}.$$

A simple calculation yields $\mathscr{R}^*(0)=\mathscr{R}_0$. Since treatment is expected to reduce the infectious period and/or transmissibility of the sensitive strain (i.e., $\delta_T/\gamma_T \le 1/\gamma_S$), we obtain

$$\mathrm{d}\mathscr{R}^*(\eta)/\mathrm{d}\eta = \frac{\alpha^*\left(\gamma_S\delta_T-\gamma_T\right)}{\left(\gamma_S+\gamma_T\eta\alpha^*\right)^2}\beta N \le 0.$$

Therefore, $\mathscr{R}^*(\eta)$ is a decreasing function of η, and $\lim_{\eta\to\infty}\mathscr{R}^*(\eta)=\delta_T\beta N/\gamma_T$.

The behaviour of the system (2)−(5) depends on the values of δ_R/γ_R and δ_T/γ_T. Suppose $\delta_T/\gamma_T < \delta_R/\gamma_R$, indicating that the total number of new cases generated by an infectious case with the sensitive strain under treatment ($\delta_T\beta N/\gamma_T$) is less than the total number of new cases generated by an infectious case with the resistant strain ($\delta_R\beta N/\gamma_R$). In this case, by the properties of $\mathscr{R}^*(\eta)$ and fitness impairment of the resistant strain ($\delta_R/\gamma_R < 1/\gamma_S$), there exists a unique $\eta^*>0$ such that $\mathscr{R}^*(\eta^*)=\mathscr{R}_R$, where

$$\eta^* = \frac{\gamma_S\delta_R-\gamma_R}{\alpha^*\left(\gamma_R\delta_T-\gamma_T\delta_R\right)}.$$

Because $\hat{I}_R$ and $\hat{I}_S$ must be non-negative, we obtain the following final size inequalities from Eqs. (14) and (15):

$$\mathscr{R}_R < \frac{\log\dfrac{S_0}{S_\infty(\eta)}}{\left[1-\dfrac{S_\infty(\eta)}{N}\right]} < \mathscr{R}^*(\eta), \quad \eta<\eta^*, \tag{17}$$

$$\mathscr{R}_R > \frac{\log\dfrac{S_0}{S_\infty(\eta)}}{\left[1-\dfrac{S_\infty(\eta)}{N}\right]} > \mathscr{R}^*(\eta), \quad \eta>\eta^*. \tag{18}$$

For $\eta = \eta^*$, we have the final size relation:

$$\log \frac{S_0}{S_\infty(\eta^*)} = \mathscr{R}_R \left[1 - \frac{S_\infty(\eta^*)}{N}\right]. \tag{19}$$

Note that (17)−(18) do not provide any explicit expression for the final size relation. In order to establish an equality relating the treatment rate and the epidemic final size, we note that the right hand side of (12) represents the epidemic final size in terms of the total number of individuals infected with the resistant strain ($\gamma_R \hat{I}_R$) and the total number of individuals infected with the sensitive strain ($(\gamma_S + \gamma_T \eta \alpha^*)\hat{I}_S$) who do not develop drug-resistance. We define the ratio of these two numbers as a function of η by

$$\lambda(\eta) = \frac{\gamma_R \hat{I}_R}{\left(\gamma_S + \gamma_T \eta \alpha^*\right) \hat{I}_S}.$$

Here, we are considering a specific situation with given parameters and initial values of the subpopulations, so that only the treatment rate η may be varied, and λ is a function of η only. Substitution of $\mathscr{R}^*(\eta)$ and $\lambda(\eta)$ into (12) and (13), gives

$$\log \frac{S_0}{S_\infty(\eta)} = E(\eta)\left(1 - \frac{S_\infty(\eta)}{N}\right), \tag{20}$$

where

$$E(\eta) = \frac{\mathscr{R}^*(\eta) + \mathscr{R}_R \lambda(\eta)}{1 + \lambda(\eta)}. \tag{21}$$

Because the final size depends on the function E which itself depends on the unknown quantities in function $\lambda(\eta)$, it is not possible to express the final size in terms of the model parameters only. To determine the final size in any particular case, it is necessary to perform numerical simulations. However, the Eq. (20) allows us to study the possible behaviour of $E(\eta)$, and the effect of the treatment rate.

We first explore the relation between the final size of the susceptible population and the function $E(\eta)$.

Lemma 1 *Suppose* $0 < S(\eta) \leq N$ *is a solution of the Eq.* (20) *for* $\eta \geq 0$. *Then*

$$S'(\eta)E'(\eta) \leq 0.$$

Proof Implicit differentiation of (20) gives,

$$\left(\frac{E(\eta)}{N} - \frac{1}{S_\infty(\eta)}\right) S'_\infty(\eta) = E'(\eta)\left(1 - \frac{S_\infty(\eta)}{N}\right). \tag{22}$$

Since $1 - S_\infty(\eta)/N > 0$, we need only to show that $S_\infty(\eta) < N/E(\eta)$. From (20), we define the following function

$$G(x) = \log \frac{S_0}{x} - E(\eta)\left(1 - \frac{x}{N}\right),$$

for $x > 0$. From (20) one can see that $S_\infty(\eta)$ is a zero of the function $G(x)$. A simple calculation shows that $G(x) > 0$ for x near zero, and $G(N) < 0$ (since $S_0 < N$); thus there exists x^*, with $0 < x^* < N$, such that $G(x^*) = 0$. Differentiating $G(x)$ with respect to x gives

$$G'(x) = -\frac{1}{x} + \frac{E(\eta)}{N}.$$

If $E(\eta) \leq 1$, then $G'(x) < 0$ for $0 < x \leq N$, which indicates that $x^* = S_\infty(\eta)$ is the only zero of G. Since $x^* < N \leq N/E(\eta)$, it follows that $S_\infty(\eta) < N/E(\eta)$.

Now suppose $E(\eta) > 1$. Since $G'(x) > 0$ for $x > N/E(\eta)$, it follows that $G(x)$ is an increasing function on $[N/E(\eta), N]$. Thus, from $G(N) < 0$ it follows that $G(x)$ has no zero on the interval $[N/E(\eta), N]$. Since $G(S_\infty(\eta)) = 0$, we conclude that $S_\infty(\eta) < N/E(\eta)$. Therefore, we have shown that in both cases ($E(\eta) \leq 1$ and $E(\eta) > 1$), $E(\eta)/N - 1/S_\infty(\eta) < 0$, and consequently $S'(\eta)E'(\eta) \leq 0$. □

We now need to make an assumption about $\lambda(\eta)$, which is the ratio of the total number of infections with the resistant strain to the total number of infections with the sensitive strain. We assume that $\lambda'(\eta)$ is a non-decreasing function of η. Simulations, presented in Sect. 5, indicate that $\lambda'(\eta) \geq 0$ is a plausible assumption. In general, as the treatment rate increases, the total number of infections with the sensitive strain decreases, and the total number of individuals infected with the resistant strain is expected to increase through the development of drug-resistance during treatment or direct transmission of the resistant strain. To further support this assumption, we consider a special case, where $\alpha(0) = 1$ and $\alpha(a) = 0$ for $a > 0$. This effectively means that all treated individuals will develop drug-resistance before recovery. In this case, $\alpha^* = 0$ and the total number of individuals infected with the sensitive strain is given by $\gamma_S \hat{I}_S$. We note that $\mathscr{R}_c^S$ is a decreasing function of η and therefore the total number of new cases generated by an individual infected with the sensitive strain decreases. Hence, increasing the treatment rate decelerates the spread of the sensitive strain, and consequently the rate of decrease in the susceptible class. For this special case, the first term in $\mathscr{R}_c^S$ decreases as η increases. However, the second term in the expression for $\mathscr{R}_c^S$ increases as η increases, giving $\lambda'(\eta) \geq 0$ for $\eta \geq 0$. This assumption is further illustrated by our examples in the model experiments.

With this assumption, we have the following result that describes the relation between the treatment rate and the epidemic final size.

Theorem 1 *Suppose* $\lambda'(\eta) \geq 0$.

1. *If* $\delta_R/\gamma_R \leq \delta_T/\gamma_T$, *then increasing treatment rate reduces the epidemic final size.*
2. *If* $\delta_R/\gamma_R > \delta_T/\gamma_T$, *then either the epidemic final size decreases as the treatment rate increases for* $\eta \geq 0$*; or there exists an* $\eta_0 > 0$ *such that the epidemic final size decreases in the interval of* $0 \leq \eta < \eta_0$, *and has a local minimum at* η_0.

Proof Differentiating $E(\eta)$ in (21) gives

$$E'(\eta) = \frac{[1 + \lambda(\eta)]\,(\mathscr{R}^*(\eta))' + \lambda'(\eta)\left[\mathscr{R}_R - \mathscr{R}^*(\eta)\right]}{(1 + \lambda(\eta))^2}. \tag{23}$$

For case 1, we have $\lim_{\eta\to\infty}\mathscr{R}^*(\eta) \geq \mathscr{R}_R$, and therefore $\mathscr{R}_R - \mathscr{R}^*(\eta) \leq 0$ for $\eta \geq 0$. Since $(\mathscr{R}^*(\eta))' < 0$, the assumption $\lambda'(\eta) \geq 0$ implies that $E'(\eta) < 0$ for $\eta \geq 0$. From Lemma 1, it then follows that $S'_\infty(\eta) \geq 0$. Hence, $S_\infty(\eta)$ is an increasing function of η, and the epidemic final size decreases as η increases.

For case 2, $\eta^* \geq 0$ if $\delta_R/\gamma_R \leq 1/\gamma_S$. Since $\mathscr{R}^*(\eta) \geq \mathscr{R}_R$ for $\eta \leq \eta^*$, it follows that $E'(\eta) < 0$ for $0 \leq \eta \leq \eta^*$. For $\eta > \eta^*$, there are two possibilities: (1) $E'(\eta) < 0$, which leads to the same situation in case 1; (2) there exists at least one $\eta_0 > \eta^*$ such that $E'(\eta_0) = 0$, and $E'(\eta)$ changes the sign at η_0. Considering η_0 as the smallest zero of $E'(\eta)$ greater than η^*, we have $E'(\eta) < 0$ for $0 \leq \eta < \eta_0$. Thus, Lemma 1 implies that $S'_\infty(\eta) \geq 0$ for $0 \leq \eta < \eta_0$, and changes the sign at η_0. From a continuity argument, it follows that $S'_\infty(\eta_0) = 0$, and therefore $S_\infty(\eta)$ exhibits a local maximum at η_0. This shows that the epidemic final size decreases for $0 \leq \eta < \eta_0$, and has a local minimum at η_0.

For case 2, if $\delta_R/\gamma_R > 1/\gamma_S$, then $\eta^* < 0$ and $\mathscr{R}^*(\eta) < \mathscr{R}_R$ for $\eta > 0$. Hence both possibilities exist for $\eta > 0$, and a similar argument applies. □

As a consequence of Theorem 1, one can see that if $\delta_R/\gamma_R > \delta_T/\gamma_T$, then increasing the treatment rate above a certain value can result in an increase in the epidemic final size. This provides a theoretical foundation for previous work that has shown this phenomena by numerical simulations.

Remark The effect of treatment can be included in the model as a reduction of disease transmissibility from the start of treatment but no reduction in infectious period, or a reduction in infectious period but no reduction in the transmissibility, or a combination thereof. In a practical sense, the overall effect of treatment should match the reduction in secondary attack rates observed in household studies (Halloran et al. 2006). When the overall effect is included in the transmissibility, and infectious periods are the same, the conditions in Theorem 1 become $\delta_R \leq \delta_T$ (for case 1), and $\delta_R > \delta_T$ (for case 2).

5 Model experiments

In this section, we illustrate the theoretical findings for two special cases of the model (2)−(5) using numerical simulations.

5.1 Exponential case of de novo resistance

Let $\alpha = e^{-\kappa t}$, where κ represents the rate of de novo resistance in treated individuals. In this case, $\alpha^* = 1/(\kappa + \gamma_T)$, and the model (2)−(5) reduces to a similar model presented in Moghadas (2008):

$$\begin{aligned}
S' &= -\beta\left(I_S + \delta_T I_T + \delta_R I_R\right) S,\\
I'_S &= \beta\left(I_S + \delta_T I_T\right) S - \left(\gamma_S + \eta\right) I_S,\\
I'_T &= \eta I_S - \left(\kappa + \gamma_T\right) I_T,\\
I'_R &= \beta\delta_R I_R S + \kappa I_T - \gamma_R I_R.
\end{aligned}$$

The reproduction number $\mathscr{R}_c^s$ is now given by

$$\mathscr{R}_c^s = \left(\frac{\gamma_S}{\gamma_S+\eta} + \frac{\delta_T \eta \gamma_S}{(\gamma_S+\eta)(\kappa+\gamma_T)}\right)\mathscr{R}_0 + \left(\frac{\eta\kappa}{(\gamma_S+\eta)(\kappa+\gamma_T)}\right)\mathscr{R}_R.$$

The Eq. (12) takes the form

$$N - S_\infty = \left[(\gamma_S+\eta) - \frac{\eta\kappa}{\kappa+\gamma_T}\right]\hat{I}_S + \gamma_R \hat{I}_R.$$

The expressions (14) and (15) for $\hat{I}_S, \hat{I}_R$ are given by

$$\left(\mathscr{R}^*(\eta) - \mathscr{R}_R\right)\hat{I}_R = \frac{\mathscr{R}^*(\eta)}{\gamma_R}(N - S_\infty) - \frac{N}{\gamma_R}\log\frac{S_0}{S_\infty},$$

$$\left(\mathscr{R}_R - \mathscr{R}^*(\eta)\right)\hat{I}_S = \frac{(\kappa+\gamma_T)\mathscr{R}_R}{\gamma_S(\kappa+\gamma_T)+\gamma_T\eta}(N - S_\infty) - \frac{(\kappa+\gamma_T)N}{\gamma_S(\kappa+\gamma_T)+\gamma_T\eta}\log\frac{S_0}{S_\infty},$$

where

$$\mathscr{R}^*(\eta) = \frac{\kappa+\gamma_T+\delta_T\eta}{\gamma_S(\kappa+\gamma_T)+\gamma_T\eta}\beta N.$$

The calculations in the model (2)−(5) following these equations do not contain α^* and remain unchanged.

In order to show our findings for the final size as a function of η, we simulated the model using parameter values for influenza infection published in the literature (Lipsitch et al. 2007; Moghadas 2008). Figure 2a shows the optimal treatment rates at which the final size is minimum for two different levels of drug-resistance transmission. For a relatively low transmissibility of the resistant strain ($\delta_R = 0.65$) above that of the sensitive strain during treatment ($\delta_T = 0.4$), we have $\delta_R/\gamma_R = 2.6 > 1.2 = \delta_T/\gamma_T$, and the optimal rate is $\eta_0 = 0.336$ (red curve). As the transmissibility of drug-resistance increases, the optimal treatment rate decreases. This is shown in Fig. 2a (black curve) for $\delta_R = 0.9$ with $\eta_0 = 0.183$. For a detailed discussion on the variation of the optimal treatment rate, the reader may consult (Moghadas 2008). As illustrated in Fig. 2b, $E(\eta)$ undergoes a local minimum at η_0 for the corresponding scenarios simulated in Fig. 2a. For the scenarios simulated here, Fig. 3a, b show that $\lambda'(\eta) > 0$, and $E'(\eta)$ has a unique zero at η_0 at which the local minimum of the epidemic final size occurs.

5.2 Delay case of de novo resistance

Let

$$\alpha(t) = \begin{cases} 1, & t \le \tau, \\ 0, & t > \tau, \end{cases}$$

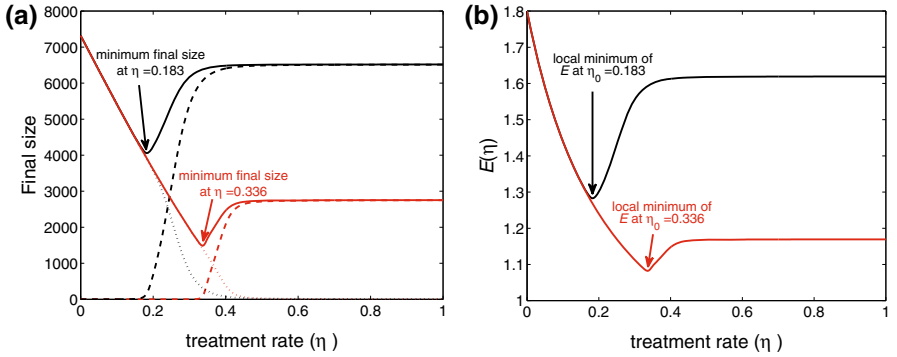

Fig. 2 **a** Final size of the epidemic as a function of the treatment rate. *Solid*, *dotted*, and *dashed curves* correspond to the total number of infections (final size), the total number of untreated and treated infections with the sensitive strain, and the total number of infections with the resistant strain, respectively, for $\delta_R = 0.65$ (*red curves*) and $\delta_R = 0.9$ (*black curves*). **b** Local minimum of $E(\eta)$ for $\delta_R = 0.65$ (*red curve*) and $\delta_R = 0.9$ (*black curve*). Other parameter values are $\mathscr{R}_0 = 1.8$, $\gamma_S = 1/4$ day^{-1}, $\gamma_T = 1/3$ day^{-1}, $\gamma_R = 1/4$ day^{-1}, $\kappa = 10^{-5}$ day^{-1}, and $\delta_T = 0.4$. Initial values of sub-populations are $S_0 = 10^4 - 1$, $I_S(0) = 1$, and $I_T(0) = I_R(0) = 0$

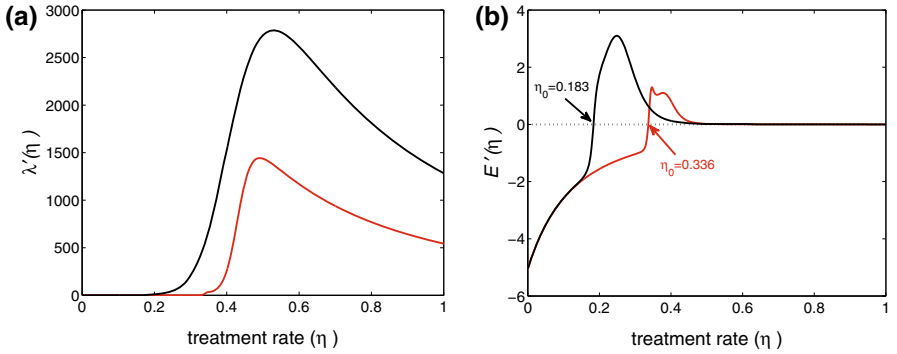

Fig. 3 **a** $\lambda'(\eta)$ as a function of η for the scenarios corresponding to those illustrated in Fig. 2a with $\delta_R = 0.65$ (red curve) and $\delta_R = 0.9$ (*black curve*). **b** $E'(\eta)$ as a function of η for the scenarios corresponding to those illustrated in Fig. 2b with $\delta_R = 0.65$ (*red curve*) and $\delta_R = 0.9$ (*black curve*). Other parameter values are $\mathscr{R}_0 = 1.8$, $\gamma_S = 1/4$ day^{-1}, $\gamma_T = 1/3$ day^{-1}, $\gamma_R = 1/4$ day^{-1}, $\kappa = 10^{-5}$ day^{-1}, and $\delta_T = 0.4$. Initial values of sub-populations are $S_0 = 10^4 - 1$, $I_S(0) = 1$, and $I_T(0) = I_R(0) = 0$

where τ represents the average time to develop de novo resistance in treated individuals (Kiso et al. 2004; Ward et al. 2005). In this case, $\alpha^* = (1 - e^{-\gamma_T \tau})/\gamma_T$, and the model (2)–(5) reduces to the following delay differential equations

$$
\begin{aligned}
S' &= -\beta \left(I_S + \delta_T I_T + \delta_R I_R\right) S, \\
I_S' &= \beta \left(I_S + \delta_T I_T\right) S - \left(\gamma_S + \eta\right) I_S, \\
I_T' &= \eta I_S - \eta I_S(t-\tau) e^{-\gamma_T \tau} - \gamma_T I_T, \\
I_R' &= \delta_R \beta I_R S + \eta I_S(t-\tau) e^{-\gamma_T \tau} - \gamma_R I_R.
\end{aligned}
$$

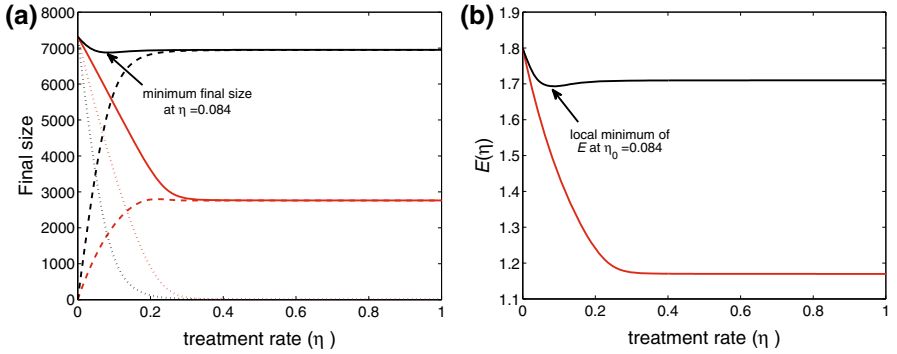

Fig. 4 **a** Final size of the epidemic as a function of the treatment rate. *Solid*, *dotted*, and *dashed curves* correspond to the total number of infections (final size), the total number of untreated and treated infections with the sensitive strain, and the total number of infections with the resistant strain, respectively, for $\delta_R = 0.65$ (*red curves*) and $\delta_R = 0.95$ (*black curves*). **b** Behaviour of $E(\eta)$ for $\delta_R = 0.65$ (*red curve*) and $\delta_R = 0.9$ (*black curve*). Other parameter values are $\mathscr{R}_0 = 1.8$, $\gamma_S = \gamma_T = \gamma_R = 1/4$ day^{-1}, $\tau = 3$ days, and $\delta_T = 0.4$. Initial values of sub-populations are $S_0 = 10^4 - 1$, $I_S(0) = 1$, and $I_T(0) = I_R(0) = 0$

The reproduction number $\mathscr{R}_c^s$ for this model is given by

$$\mathscr{R}_c^s = \left(\frac{\gamma_S}{\gamma_S + \eta} + \frac{\delta_T \gamma_S \eta (1 - e^{-\gamma_T \tau})}{\gamma_S + \eta}\right)\mathscr{R}_0 + \left(\frac{\eta e^{-\gamma_T \tau}}{\gamma_S + \eta}\right)\mathscr{R}_R.$$

The expressions (14) and (15) for $\hat{I}_S$, $\hat{I}_R$ become

$$\left(\mathscr{R}^*(\eta) - \mathscr{R}_R\right)\hat{I}_R = \frac{\mathscr{R}^*(\eta)}{\gamma_R}(N - S_\infty) - \frac{N}{\gamma_R}\log\frac{S_0}{S_\infty},$$

$$\left(\mathscr{R}_R - \mathscr{R}^*(\eta)\right)\hat{I}_S = \frac{\mathscr{R}_R}{\gamma_S + \eta(1 - e^{-\gamma_T \tau})}(N - S_\infty) - \frac{N}{\gamma_S + \eta\left(1 - e^{-\gamma_T \tau}\right)}\log\frac{S_0}{S_\infty},$$

where

$$\mathscr{R}^*(\eta) = \frac{\gamma_T + \delta_T \eta\left(1 - e^{-\gamma_T \tau}\right)}{\gamma_T\left(\gamma_S + \eta(1 - e^{-\gamma_T \tau})\right)}\beta N,$$

and the final size relation is given by (20).

We simulated the delay differential model to illustrate the effect of δ_R and τ on the epidemic final size as the treatment rate changes. For a delay of $\tau = 3$ days in developing drug-resistance, Fig. 4a shows that for $\delta_R = 0.65$ greater than $\delta_T = 0.4$, the epidemic final size decreases as the treatment rate increases (red curve). For a higher transmissibility of the resistant strain ($\delta_R = 0.95$) comparable to that of the sensitive strain, we observed a local minimum for the epidemic final size at $\eta_0 = 0.084$ (Fig. 4a, black curve). Since treated individuals stay for $\tau = 3$ days (on average) in the I_T class, and therefore have a lower transmissibility compared to infected individuals with the resistant strain, the spread of drug-resistance with $\delta_R = 0.65$ is delayed and

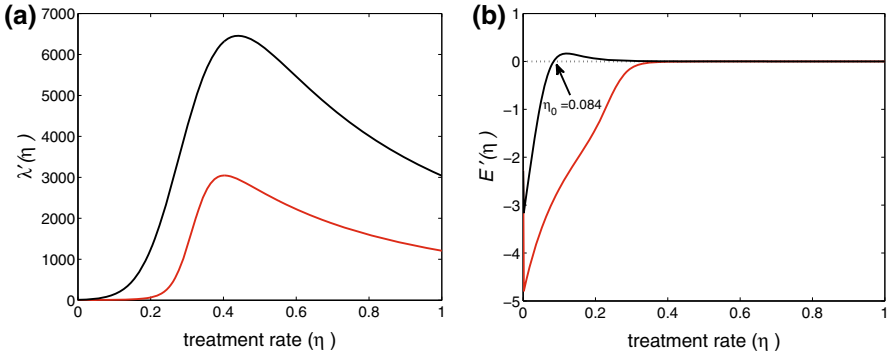

Fig. 5 **a** $\lambda'(\eta)$ as a function of η for the scenarios corresponding to those illustrated in Fig. 2a with $\delta_R = 0.65$ (*red curve*) and $\delta_R = 0.9$ (*black curve*). **b** $E'(\eta)$ as a function of η for the scenarios corresponding to those illustrated in Fig. 2b with $\delta_R = 0.65$ (*red curve*) and $\delta_R = 0.95$ (*black curve*). Other parameter values are $\mathscr{R}_0 = 1.8$, $\gamma_S = \gamma_T = \gamma_R = 1/4$ day^{-1}, $\tau = 3$ days, and $\delta_T = 0.4$. Initial values of sub-populations are $S_0 = 10^4 - 1$, $I_S(0) = 1$, and $I_T(0) = I_R(0) = 0$

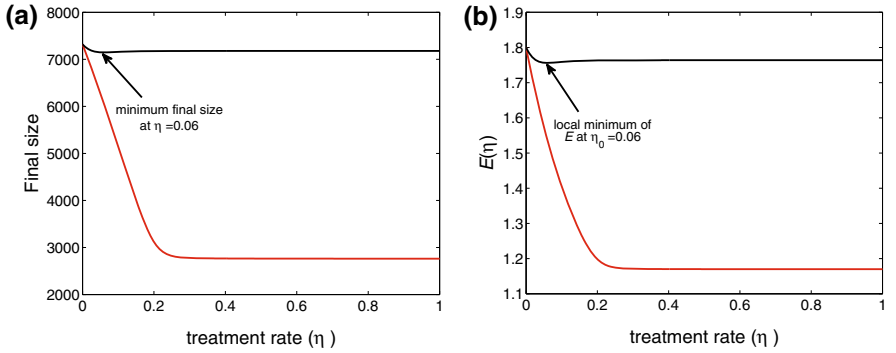

Fig. 6 **a** Final size of the epidemic as a function of the treatment rate for $\delta_R = 0.65$ (*red curve*) and $\delta_R = 0.98$ (*black curve*). **b** Behaviour of $E(\eta)$ for $\delta_R = 0.65$ (*red curve*) and $\delta_R = 0.98$ (*black curve*). Other parameter values are $\mathscr{R}_0 = 1.8$, $\gamma_S = \gamma_T = \gamma_R = 1/4$ day^{-1}, $\tau = 1.5$ days, and $\delta_T = 0.4$. Initial values of sub-populations are $S_0 = 10^4 - 1$, $I_S(0) = 1$, and $I_T(0) = I_R(0) = 0$

requires higher treatment levels compared to $\delta_R = 0.95$ (Fig. 4a, dashed curves). The corresponding simulations for $E(\eta)$ are shown in Fig. 4b, in which the optimal treatment rate is identified at $\eta = 0.084$ when $\delta_R = 0.95$. Figure 5a, b show the behaviour of $\lambda'(\eta)$ and $E'(\eta)$ for the corresponding scenarios with the range of η simulated here.

When treated individuals develop drug-resistance within a shorter period of time following the start of treatment (e.g., an average of $\tau = 1.5$ days), then the resistance spreads more rapidly, and the local minimum of the epidemic final size (when exists) occurs at a lower treatment rate (Fig. 6a, black curve). However, for a sufficiently low transmissibility of drug-resistance ($\delta_R = 0.65$), the epidemic final size decreases as the treatment rate increases (Fig. 6a, red curve). These observation can be described by the fact that for low treatment rates, the sensitive strain has a large competitive

advantage over the resistant strain. However, the presence of a large number of infected individuals with the sensitive strain contributes to the generation of drug-resistance during treatment, and therefore increases the final size of infected individuals with the resistant strain. For high treatment rates, infection caused by the sensitive strain is largely contained, which limits the generation of resistance. When the transmissibility of the resistant strain is significantly lower than that of the sensitive strain, the final size of infected individuals with the drug resistant strain is minimized, and the overall epidemic size decreases. Figure 6b shows the corresponding simulations for $E(\eta)$ with $\tau = 1.5$, where $E'(\eta) < 0$ for all $\eta > 0$ when $\delta_R = 0.65$ (red curve), but has a unique zero at $\eta_0 = 0.06$ when $\delta_R = 0.98$ (black curve).

6 Concluding remarks

In this study, we have focused on determining a final size relation for an epidemic model with two strains of a pathogen. Our theoretical findings demonstrate that if the transmissibility of the resistant strain is sufficiently high, it is possible to have an optimal treatment rate at which the epidemic final size undergoes a local minimum. However, as simulations in the model with delay rate of de novo resistance illustrate, a high transmissibility of the resistance strain is not a sufficient condition for the existence of an optimal treatment rate. We have not been able to show the uniqueness of this optimal rate; however, based on simulation results presented here and in previous work (Lipsitch et al. 2007; Moghadas 2008; Moghadas et al. 2008), we conjecture that the optimal treatment rate is unique.

Based on the findings of this study, the question "Can treatment increase the epidemic size?" may be addressed in two different contexts. Compared to the scenario in which treatment is absent, any level of treatment is useful and will result in a lower epidemic size. This is due to the fact that the transmissibility of the resistant strain cannot exceed that of the sensitive strain, and therefore the disease will be less transmissible even if all treated cases develop drug-resistance. However, comparison of the epidemic sizes for two different treatment rates depends on several parameters including δ_R, δ_T, γ_T, and γ_R as discussed in Theorem 1. While we attempted to address the relation between the treatment rate and the epidemic final size, some questions remain to be addressed. As our simulations show, the optimal treatment rate depends not only on the transmissibility of the resistant strain, but also on the functional form of $\alpha(a)$, representing the probability of developing drug-resistance at time a after the start of treatment. The functional form of α will affect the treatment rate η^*, at which $\mathscr{R}^*(\eta^*) = \mathscr{R}_R$ and the final size relation (19) holds.

Determining the optimal treatment rate in an analytical form based on the model parameters is a difficult task, and would require additional information about $\lambda(\eta)$. We have, however, considered the scenario in which $\lambda(\bar{\eta}) = 1$, for some $\bar{\eta} > 0$. When $\delta_R/\gamma_R > \delta_T/\gamma_T$, if $\bar{\eta}$ exists, then from (20) and (21), it follows that

$$\log \frac{S_0}{S_\infty(\bar{\eta})} = \frac{\mathscr{R}^*(\bar{\eta}) + \mathscr{R}_R}{2} \left(1 - \frac{S_\infty(\bar{\eta})}{N}\right).$$

This final size relation holds at the treatment rate at which the total number of infected individuals with the sensitive strain (untreated and treated) is the same as the total number of infected individuals with the resistant strain. This equality shows that at $\bar{\eta}$, the final size relation is derived from averaging the upper and lower bounds in (18). This relation for averaging the two bounds also holds at η^* at which $\mathscr{R}^*(\eta^*) = \mathscr{R}_R$.

Remark The rate $\bar{\eta}$ provides a threshold above which the final size of infected individuals with the resistant strain dominates that of infected individuals with the sensitive strain. This treatment rate corresponds to the crossing point of dashed and dotted curves of the same color in Figs. 2a and 4a.

The model presented in this work provides a simplified framework for the dynamics of drug-resistance emergence (which depends on time since the onset of treatment) and spread in the population. For epidemics with relatively short duration, such as seasonal or pandemic influenza, this framework could be useful without considering the effect of demographics. Models in which demographics are added to the structure considered here may be analyzed using different methods. For such models, the effect of increasing treatment rate on the epidemic final size may depend on additional demographic parameters. Further study of this type of models is proceeding.

In the present study, we have not explicitly modelled the emergence of drug-resistance, which is a complex process and relies on an error-prone replication mechanism. Although treatment can induce a massive selection presure which favours the growth of the resistant strain (Domingo and Holland 1997; Miller 2011), it is not the sole factor determining the evolution and persistence of drug-resistance (Simonsen et al. 2007). While emergence of drug-resistance poses a significant challenge in the control of several diseases, recent studies suggest important implications for disease control. For example, resistance to mosquito larvicides could benefit malaria control as a result of reduced mosquito adult lifespan, which reduces the chance for the malaria parasite having enough time to complete its development cycle (Liu and Gourley 2012). These considerations suggest that depending on the biological context, treatment and emergence of resistance may have different outcomes.

Acknowledgments The authors would like to thank the reviewers and the editor for their insightful comments that have improved the paper.

References

Anderson R, May R (1992) Infectious diseases of humans. Oxford University Press, Oxford

Andersson D, Levin B (1999) The biological cost of antibiotic resistance. Curr Opinion Microbiol 2(5):489–493

Björkman J, Nagaev I, Berg O, Hughes D, Andersson DI (2000) Effects of environment on compensatory mutations to ameliorate costs of antibiotic resistance. Science 287(5457):1479–1482

Brauer F, Castillo-Chavez C (2010) Mathematical models in population biology and epidemiology, 2nd edn. Springer, New York

Diekmann O, Heesterbeek J (2000) Mathematical epidemiology of infectious diseases. Wiley, Chichester

Domingo E, Holland J (1997) RNA virus mutations and fitness for survival. Ann Rev Microbiol 51:151–178

Halloran M, Hayden F, Yang Y, Longini JI, Monto A (2006) Antiviral effects on influenza viral transmission and pathogenicity: observations from household-based trials. Am J Epidemiol 165(2):212–221

Hansen E, Day T (2011) Optimal antiviral treatment strategies and the effects of resistance. Proc Royal Soc B 278(1708):1082–1089
Keeling M, Rohani P (2008) Modelling infectious diseases in humans and animals. Princeton University Press, Princeton
Kermak W, McKendrick A (1927) A contribution to the mathematical theory of epidemics. Proc Royal Soc A 115(772):700–721
Kermak W, McKendrick A (1931) Contributions to the mathematical theory of epidemics. II. the problem of endemicity. Proc Royal Soc A 138(834):55–83
Kiso M, Mitamura K, Sakai-Tagawa Y, Shiraishi K, Kawakami C, Kimura K, Hayden F, Sugaya N, Kawaoka Y (2004) Resistant influenza A viruses in children treated with oseltamivir: descriptive study. Lancet 364(9436):759–765
Lipsitch M, Cohen T, Murray M, Levin B (2007) Antiviral resistance and the control of pandemic influenza. PLoS Med 4(1):111–121
Liu R, Gourley S (2012) Resistance to larvicides in mosquito populations and how it could benefit malaria control. Eur J Appl Math 24(3):415–436
Maisnier-Patin S, Andersson D (2004) Adaptation to the deleterious effects of antimicrobial drug resistance mutations by compensatory evolution. Res Microbiol 155(5):360–369
Miller R (2011) Controlling the evolution of antibiotic resistance. Ph.D. Thesis
Moghadas S (2008) Management of drug resistance in the population: influenza as a case study. Proc Royal Soc B 275(1639):1163–1169
Moghadas S (2011) Emergence of resistance in influenza with compensatory mutations. Math Popul Stud 18:106–121
Moghadas S, Bowman C, Röst G, Fisman D, Wu J (2009) Post-exposure prophylaxis during pandemic outbreaks. BMC Med 7(73):1–10. doi:10.1186/1741-7015-7-73. http://www.biomedcentral.com/1741-7015/7/73
Moghadas S, Bowman C, Röst G, Wu J (2008) Population-wide emergence of antiviral resistance during pandemic influenza. PLoS One 3(3):e1839
Rimmelzwaan G, Berkhoff E, Nieuwkoop N, Smith D, Fouchier R, Osterhaus A (2005) Full restoration of viral fitness by multiple compensatory comutations in the nucleoprotein of influenza a virus cytotoxic T-lymphocyte escape mutants. J Gen Virol 86(Pt 6):1801–1805
Simonsen L, Viboud C, Grenfell B, Dushoff J, Jennings L, Smit M, Macken C, Hata M, Gog J, Miller M, Holmes E (2007) The genesis and spread of reassortment human influenza A/H3N2 viruses conferring adamantane resistance. Mol Biol Evol 24(8):1811–1820
van den Driessche P, Zou X (2007) Modeling relapse in infectious diseases. Math Biosci 207(1):89–103
van den Driessche P, Watmough J (2002) Reproduction numbers and subthreshold endemic equilibria for compartmental models of disease transmission. Math Biosci 180(1–2):29–48
Ward P, Small I, Smith J, Suter J, Dutkowshi R (2005) Oseltamivir (Tamiflu) and its potential for use in the event of an influenza pandemic. J Antimicrob Chemother 55(Suppl 1):i5–i21
Xiao Y, Zou X (2013) On latencies in malaria infections and their impact on the disease dynamics. Math Biosci Eng 10(2):463–481