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Mathematical analysis of a two-strain disease model with amplification

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ABSTRACT

We investigate a two-strain disease model with amplification to simulate the prevalence of drug-susceptible (s) and drug-resistant (m) disease strains. Drug resistance first emerges when drug-susceptible strains mutate and become drug-resistant, possibly as a consequence of inadequate treatment, i.e. amplification. In this case, the drug-susceptible and drug-resistant strains are coupled. We perform a dynamical analysis of the resulting system and find that the model contains three equilibrium points: a disease-free equilibrium; a mono-existent disease-endemic equilibrium at which only the drug-resistant strain persists; and a co-existent disease-endemic equilibrium where both the drug-susceptible and drug-resistant strains persist. We found two basic reproduction numbers: one associated with the drug-susceptible strain (R_{0s}); the other with the drug-resistant strain (R_{0m}), and showed that at least one of the strains can spread in a population if $\max[R_{0s}, R_{0m}] > 1$. Furthermore, we also showed that if $R_{0m} > \max[R_{0s}, 1]$, the drug-susceptible strain dies out but the drug-resistant strain persists in the population (mono-existent equilibrium); however if $R_{0s} > \max[R_{0m}, 1]$, then both the drug-susceptible and drug-resistant strains persist in the population (co-existent equilibrium). We conducted a local stability analysis of the system equilibrium points using the Routh-Hurwitz conditions and a global stability analysis using appropriate Lyapunov functions. Sensitivity analysis was used to identify the key model parameters that drive transmission through calculation of the partial rank correlation coefficients (PRCCs). We found that the contact rate of both strains had the largest influence on prevalence. We also investigated the impact of amplification and treatment/recovery rates of both strains on the equilibrium prevalence of infection; results suggest that poor quality treatment/recovery makes coexistence more likely and increases the relative abundance of resistant infections.

1. Introduction

Many pathogens have several circulating strains. The presence of drug-resistant strains of a pathogen often follows soon after a new treatment becomes available. This can be due to sub-therapeutic drug levels which may efficiently kill drug-susceptible pathogens whilst allowing drug-resistant sub-populations to grow [1]. This acquired resistance, which can result from incorrect treatment, poor adherence or malabsorption, is called amplification [2–4]. One of the major challenges in preventing the spread of infectious diseases is to control the genetic variations of pathogens through proper treatment regimens [5,6].

Mathematical models can improve our understanding of genetic variations of infectious pathogens as well as those components that are significant to infectious disease diagnosis, and treatment [7–13]. Mathematical models can also be used to improve health policy and infectious disease monitoring plans by identifying thresholds which must be reached in order to achieve elimination [13–15]. For example, analytical solutions, numerical solutions and stability analyses of mathematical models can identify

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regions in the parameter space where the various asymptotic states are stable or unstable, thus allowing us to predict the long-term behaviour of the system [13,14,16]. Further, sensitivity analysis of a mathematical model allows us to discover the parameters that have the greatest influence on the model outputs [14,17].

The growing threat of drug-resistant pathogen strains presents a significant challenge throughout the world, particularly in developing countries and those with lower socio-economic status [18]. Once drug-resistant strains have emerged in a population, primary transmission of these strains may also contribute to the disease burden (in addition to amplification) [19]. Recent studies [20–24] have shown that drug-resistant strains can in some cases possess higher virulence to transmit disease than drug-susceptible strains, and those individuals infected with a drug-resistant strain have the highest mortality rate, e.g. tuberculosis and HIV [25,26].

To examine the threat posed by genetic variations of pathogens, we present a two-strain (drug-susceptible, and drug-resistant) Susceptible-Infected-Recovered (SIR) epidemic model with coupled infectious compartments and use it to investigate the emergence and spread of mutated strains of infectious diseases. We consider the possibility that an individual's position changes from drug-susceptible at initial presentation to resistant at follow-up. This is the mode by which drug resistance first emerges in a population and is designed to reproduce the phenotypic phenomenon of amplification. The model can be applied to investigate the co-existent or competitive exclusive phenomena among the strains. We choose the SIR model in this study in order to model the many diseases that have a protracted infectious period with treatment–including hepatitis C and HIV. Here the removed compartment "R" is to be applied broadly to those people who are neither infectious nor susceptible, including people in treatment, isolation, no longer contacting others or dead. In this way, we believe that our model captures many of the infectious agents that are traditionally modelled by Susceptible (S) to Infected (I) models.

Explicitly, in this paper we perform a rigorous analytical and numerical analysis of the proposed two- strain model properties and solutions from both the mathematical and biological viewpoints. For each, we use the next-generation matrix method to determine analytic expressions for the basic reproduction numbers of the drug-susceptible and drug-resistant strains and find that these are important determinants for regulating system dynamics. With a focus on the early and late-time behaviour of the system, we outline the required conditions for disease fade-out, infection mono-existence, and co-existence.

To supplement and validate the analytic analysis, we use numerical techniques to solve the model equations and explore the epidemic trajectory for a range of possible parameter values and initial conditions. The local stability of the three system equilibria is examined using the Routh-Hurwitz conditions and the global stability of the disease-free equilibrium and mono-existent disease-endemic equilibrium is examined using appropriate Lyapunov functions. Following this, we perform a sensitivity analysis to investigate the model parameters that have the greatest influence on disease prevalence.

The remainder of this paper is constructed as follows: in section 2 we present the two-strain SIR model with differential infectivity and amplification, and verify the boundedness and positivity of solutions as well as the existence of several equilibria. Local and global stability analyses of the equilibria are presented in section 3. In section 4 we discuss a sensitivity analysis of the model outputs. We then provide numerical simulations to support analytic results in section 5. Finally, in section 6, we provide a summary of our outcomes, discuss their importance for public health policy and propose guidelines for future disease management efforts.

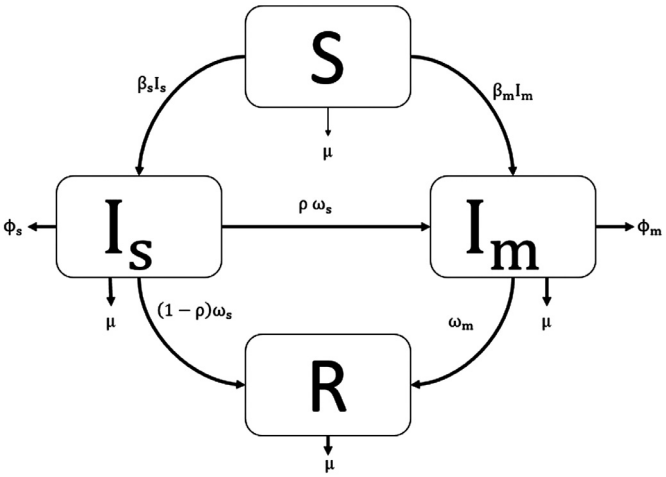

Fig. 1. Flow chart of the two-strain SIR model showing the four infection states, and the per-capita transition rates in and out of each state (not shown: the constant recruitment rate Λ into the susceptible compartment S). Subscripts s and m denote drug-susceptible and drug-resistant quantities respectively.

2. Model description and analysis

Model equations:

We developed a dynamic two-strain SIR model for the transmission of drug-susceptible and drug-resistant infections, where the total population is divided into four subclasses: S– susceptible individuals; I_s – individuals infected with the drug-susceptible strain; I_m – individuals infected with the drug-resistant strain; and R–recovered individuals, who are assumed to have immunity against both strains. Thus the total population number N(t) at time t is

$$N(t) = S(t) + I_s(t) + I_m(t) + R(t). \quad (1)$$

We also introduced the following parameters: Λ – constant recruitment rate into the susceptible class through birth or immigration[1]; μ–natural per-capita death rate across the entire population; β_s (β_m) – effective contact rate between individuals with drug-susceptible (drug-resistant) infection and susceptibles; ω_s (ω_m)–per-capita treatment/recovery rate for drug-susceptible (drug-resistant) infected individuals; ϕ_s (ϕ_m)–disease-related per-capita death rate for drug-susceptible (drug-resistant) infected individuals; ρ–proportion of individuals who amplify from the drug-susceptible strain to the drug-resistant strain during treatment/recovery. We assumed the proportion of individuals who amplify–due to incomplete treatment or lack of compliance in the use of first-line drugs–move directly from the drug-susceptible compartment I_s into the drug-resistant compartment I_m. The model structure is illustrated in Fig. 1.

From the aforementioned, the populations in each disease state are determined by the following system of nonlinear ordinary differential equations:

$$\dot{S} = \Lambda - \mu S - \beta_s I_s S - \beta_m I_m S, \quad (2)$$

$$\dot{I}_s = \beta_s I_s S - (\omega_s + \phi_s + \mu) I_s, \quad (3)$$

$$\dot{I}_m = \rho\omega_s I_s + \beta_m I_m S - (\omega_m + \phi_m + \mu) I_m, \quad (4)$$

[1] Data strongly suggest that the absolute number of births globally has been approximately constant for the last 30 years and is predicted to remain constant for the next 30 years. Therefore, within the timescale of an SIR-type infection it is reasonable to assume a constant growth rate (https://population.un.org/wpp/Graphs/900).

$$\dot{R} = (1-\rho)\omega_s I_s + \omega_m I_m - \mu R. \quad (5)$$

Given non-negative initial conditions for the system above, it is straightforward to show that each of the state variables remain non-negative for all $t > 0$. Moreover, summing equations (2)–(5) we find that the size of the total population, N(t), satisfies

$$\dot{N}(t) \leq \Lambda - \mu N(t).$$

Integrating this inequality we find

$$N(t) \leq \frac{\Lambda}{\mu} + N(0)e^{-\mu t}.$$

This shows that the total population size N(t) is bounded in this case and that it naturally follows that each of the compartment states $(S,\ I_s, I_m, R)$ are also bounded.

Note that equations (2)–(4) are independent of the size of the recovered population R(t); therefore, if we only wish to track disease incidence and prevalence, we can focus our attention on the following reduced system (6)–(8):

$$\dot{S} = \Lambda - \mu S - \beta_s I_s S - \beta_m I_m S, \quad (6)$$

$$\dot{I}_s = (\beta_s S - \chi_s) I_s, \quad (7)$$

$$\dot{I}_m = \rho\omega_s I_s + \beta_m I_m S - \chi_m I_m \quad (8)$$

where $\chi_s = \omega_s + \phi_s + \mu$ and $\chi_m = \omega_m + \phi_m + \mu$ represent the total removal rates from the respective infectious compartments.

Given the positivity and boundedness of the system solutions, we find that the feasible region for equations (6)–(8) is given by

$$D = \left\{ (S,\ I_s,\ I_m) \in \mathbb{R}^3_+ : S + I_s + I_m \leq \frac{\Lambda}{\mu} \right\} \quad (c)$$

where D is positively invariant. Therefore, in this study we consider the system of equations (6)–(8) in the set D.

2.1. Basic reproduction number

Here we estimate the basic reproduction number of the model (6)–(8). In an epidemic model, the basic reproduction number is the expected number of secondary cases created by a single infectious case introduced into a totally susceptible population. If the basic reproduction number is greater than one, the number of infected individuals grows and the infection typically shows persistent behaviour. Conversely, if the basic reproduction number is less than one, the number of infective individuals typically tends to zero [12,27,28]. Here we use the next-generation matrix technique to estimate the basic reproduction number(s) of our system [28].

The reduced model (6)–(8) has two infected states: I_s; and I_m, and one uninfected state: S. At the infection-free steady state $I_s^* = I_m^* = 0$. Hence, from (6), in the absence of infection $S^* = \frac{\Lambda}{\mu}$.

Linearizing the system about the infection-free equilibrium, we find that equations (3)–(4) are closed, such that the linearized infection sub-model becomes

$$\dot{I}_s = (\beta_s S^* - \chi_s) I_s, \quad (9)$$

$$\dot{I}_m = \rho\omega_s I_s + \beta_m I_m S^* - \chi_m I_m. \quad (10)$$

Here, the ODEs (9) and (10) describe the production of newly infected individuals and changes in the states of already infected individuals.

By setting $\mathbf{x}^T = (I_s,\ I_m)^T$, where T denotes transpose, the infection subsystem can be written in the following form:

$$\dot{\mathbf{x}} = (T + \Sigma)\mathbf{x}. \quad (11)$$

The matrix T contains the transmission component of equations (9) and (10) (i.e. the arrival of susceptible individuals into the infected compartments I_s and I_m) and the matrix Σ contains transitions between, and out of the infected states (i.e. recovery, amplification and death).

For the subsystem (9)–(10), these components are given respectively by

$$T = \begin{pmatrix} \beta_s S^* & 0 \\ 0 & \beta_m S^* \end{pmatrix} \text{ and } \Sigma = \begin{pmatrix} -\chi_s & 0 \\ \rho\omega_s & -\chi_m \end{pmatrix}.$$

The next-generation matrix, K, is then given by [27]

$$K = -T\Sigma^{-1} = \begin{pmatrix} \frac{S^*\beta_s}{\chi_s} & 0 \\ \frac{S^*\beta_m\omega_s\rho}{\chi_s\chi_m} & \frac{S^*\beta_m}{\chi_m} \end{pmatrix}.$$

The dominant eigenvalues of K are the basic reproduction numbers for the drug-susceptible and drug-resistant strains; they represent the average number of new infections from each strain produced by one infected individual. The lower triangular structure of K allows us to immediately read off the basic reproduction numbers for the drug-susceptible and drug-resistant strains respectively as:

$$R_{0s} = \frac{S^*\beta_s}{\chi_s} = \frac{\Lambda\ \beta_s}{\mu\chi_s} \quad (a)$$

and

$$R_{0m} = \frac{S^*\beta_m}{\chi_m} = \frac{\Lambda\ \beta_m}{\mu\chi_m}. \quad (b)$$

Interestingly we find that the basic reproduction numbers $\mathbf{R_{0s}}$ and $\mathbf{R_{0m}}$ are both independent of the amplification rate $\boldsymbol{\rho}$ [29].

2.1.1. Strain replacement

To investigate the relative magnitude of R_{0s} and R_{0m}, which is anticipated to strongly influence the system dynamics (see below), we introduce the parameters c and $\in$ which we respectively define as the fitness cost exacted on the transmissibility of strain m relative to that of strain s, and the reduction in treatment rate of strain m relative to that of strain s. More specifically, we let

$$\beta_m = (1-c)\beta_s$$

and

$$\omega_m = (1-\in)\omega_s.$$

If we assume that both R_{0s} and R_{0m} are greater than 1, then the condition for resistant infections to replace sensitive infections is given by,

$$R_{0m} > R_{0s}.$$

Substituting the formulae (a) and (b) for the basic reproduction numbers gives:

$$\frac{\beta_m}{\omega_m + \phi_m + \mu} > \frac{\beta_s}{\omega_s + \phi_s + \mu}.$$

Assuming that $\mu \approx 0$ (since it is very slow compared to the other rates) and that $\phi_m \approx \phi_s$ yields the condition

$$\frac{(1-c)\beta_s}{(1-\in)\omega_s + \phi_s} > \frac{\beta_s}{\omega_s + \phi_s},$$

which we can rearrange to obtain

$$\in > \frac{c(\omega_s + \phi_s)}{\omega_s}.$$

The above relation shows that the resistant strain can outcompete the susceptible strain if the resistance level $\in$ is high (which may be the case for drug-resistant individuals). Alternatively, the resistant strain will be fitter than the susceptible one if the fitness cost c is sufficiently low.

2.2. System properties

2.2.1. Existence of equilibria

It is clear from equations (6)–(8) that a disease-free equilibrium (denoted by E^*) always exists:

$$E^* = (S^*,\ I_s^*,\ I_m^*) = \left(\frac{\Lambda}{\mu},\ 0,\ 0\right). \tag{12}$$

From equation (6)–(8) we can also derive the mono-existent endemic equilibrium point (denoted by $E^{\#}$) at which the drug-resistant strain persists and the drug-susceptible strain dies out:

$$E^{\#} = \left(S^{\#}, 0, I_m^{\#}\right),$$

where

$$\begin{aligned} S^{\#} &= \frac{S^*}{R_{0m}} = \frac{\Lambda}{\mu R_{0m}}, \\ I_s^{\#} &= 0,\ I_m^{\#} = \frac{\mu(R_{0m}-1)}{\beta_m}. \end{aligned} \tag{13}$$

Inspecting (13) we see that the mono-existent endemic equilibrium $E^{\#} = (S^{\#}, 0, I_m^{\#}) \in D$ (i.e. exists) if, and only if $R_{0m} \geq 1$.

Finally, the co-existent endemic equilibrium of the system (6)–(8) (denoted by $E^{\dagger}$) is given by

$$E^{\dagger} = (S^{\dagger}, I_s^{\dagger}, I_m^{\dagger}),$$

where

$$\begin{aligned} S^{\dagger} &= \frac{\Lambda}{\mu R_{0s}} = S^*/R_{0s}, \\ I_s^{\dagger} &= \frac{\mu\ (R_{0s}-1)}{\beta_s}\ \Psi, \\ I_m^{\dagger} &= \frac{\rho R_{0s}\omega_s \mu\ (R_{0s}-1)}{\beta_s\ \chi_m\ (R_{0s}-R_{0m}) + \rho R_{0s}\omega_s \beta_m}, \\ &= \frac{\rho\omega_s R_{0s}}{\chi_m (R_{0s}-R_{0m})}\ \frac{\mu\ (R_{0s}-1)}{\beta_s}\ \Psi. \end{aligned} \tag{14}$$

The variable Ψ in equation (14) is defined as

$$\Psi = \left(1 + \frac{\rho\omega_s R_{0s}\beta_m}{\beta_s \chi_m\ (R_{0s}-R_{0m})}\right)^{-1} = \left(1 + \frac{\rho\omega_s\ R_{0m}}{\chi_s\ (R_{0s}-R_{0m})}\right)^{-1}, \tag{d}$$

and $0 < \Psi < 1$ for $R_{0s} > R_{0m}$. Therefore, equation (14) shows that the co-existent endemic equilibrium $E^{\dagger} = (S^{\dagger},\ I_s^{\dagger},\ I_m^{\dagger}) \in D$ (i.e. exists) if, and only if $R_{0s} > \max[R_{0m},\ 1]$.

3. Stability analysis

Since equations (2)–(4) are independent of equation (5) (i.e. the evolution of S, I_s and I_m are independent of $R(t)$), we can focus our attention on the reduced system (6)–(8) to study the persistence of the infection. To investigate stability of the equilibria of equations (6)–(8), the following results are established:

3.1. Infection-free equilibrium

Lemma 1. If $R_0 = \max[R_{0s},\ R_{0m}] < 1$, the disease-free equilibrium E^* of (6)–(8) is locally and globally asymptotically stable; if, however, $R_0 = \max[R_{0s},\ R_{0m}] > 1$, E^* is unstable.

Proof. : We consider the Jacobian of the system (6)–(8) which is given by

$$J = \begin{pmatrix} -\beta_s I_s - \beta_m I_m - \mu & -\beta_s S & -\beta_m S \\ \beta_s I_s & \beta_s S - \chi_s & 0 \\ \beta_m I_m & \rho\omega_s & \beta_m S - \chi_m \end{pmatrix}.$$

At the infection-free equilibrium point, E^*, this reduces to

$$J^* = \begin{pmatrix} -\mu & -\beta_s S^* & -\beta_m S^* \\ 0 & \chi_s(R_{0s}-1) & 0 \\ 0 & \rho\omega_s & \chi_m(R_{0m}-1) \end{pmatrix}.$$

The structure of J^* allows us to immediately read off the three eigenvalues, λ_i, as

$$\lambda_1 = -\mu,\ \lambda_2 = \chi_s(R_{0s}-1) \text{and } \lambda_3 = \chi_m(R_{0m}-1). \tag{15}$$

It is easy to verify that all the eigenvalues (15) have negative real parts for $R_{0s} < 1$ and $R_{0m} < 1$. Hence, the disease-free equilibrium E^* of (6)–(8) is locally asymptotically stable for $R_{0s} < 1$ and $R_{0m} < 1$. If $R_{0s} > 1$ or $R_{0m} > 1$, at least one of the eigenvalues (15) has a positive real part and E^* is unstable.

Now the global stability of the disease-free equilibrium E^* for $R_{0s} < 1$ and $R_{0m} < 1$ can be investigated. First, from equation (7), we have

$$\dot{I}_s = (\beta_s S - \chi_s) I_s,$$

which can be integrated to give

$$I_s(t) = I_s(0) e^{\int_0^t \beta_s\ S(\tau) d\tau - \chi_s\ t} \tag{16}$$

for all $t \geq 0$.

Substituting in the upper bound $S(t) \leq \frac{\Lambda}{\mu} = S^*$, which follows immediately from the definition of D (equation (c)), we obtain

$$\begin{aligned} I_s(t) &\leq I_s(0) e^{(\beta_s S^* - \chi_s)t}, \\ &\leq I_s(0) e^{\chi_s (R_{0s}-1)t}. \end{aligned}$$

It follows then that if $R_{0s} < 1$ we have $I_s(t) \to 0$ as $t \to \infty$. Hence the hyperplane $I_s = 0$ attracts all solutions of (6)–(8) originating in D whenever $R_{0s} < 1$.

Since $I_s(t) \to 0$ as $t \to \infty$ for $R_{0s} < 1$, it follows that $\rho\ \omega_s I_s(t) \to 0$ such that equation (8) reduces to

$$\dot{I}_m = \beta_m I_m S - \chi_m I_m.$$

Following the same strategy for I_m as we used above for I_s yields

$$I_m(t) \leq I_m(0) e^{\chi_m (R_{0m}-1)t}.$$

Similarly, if $R_{0m} < 1$, $I_m(t) \to 0$ as $t \to \infty$ and the hyperplane $I_m = 0$ attracts all solutions of (6)–(8) originating in D. Finally, it is straightforward to show that if $I_s \to 0$, and $I_m \to 0$, then $S \to S^*$. Therefore E^* is globally asymptotically stable when $R_0 = \max[R_{0s}, R_{0m}] < 1$.

3.2. Mono-existent endemic equilibrium

Lemma 2. If the boundary equilibrium $E^{\#} = (S^{\#}, 0, I_m^{\#})$ of the equations (6)–(8) exists and $R_{0m} > \max[1, R_{0s}]$, $E^{\#}$ is locally and globally asymptotically stable.

Proof. : We consider the Jacobian of the system (6)–(8) at the mono-existent endemic equilibrium point $E^{\#}$ which is given by

$$J^{\#} = \begin{pmatrix} -\beta_m I_m^{\#} - \mu & -\beta_s S^{\#} & -\beta_m S^{\#} \\ 0 & -\frac{\chi_s (R_{0m}-R_{0s})}{R_{0m}} & 0 \\ \beta_m I_m^{\#} & \rho\omega_s & 0 \end{pmatrix}.$$

The structure of $J^{\#}$ allows us to immediately read off the first eigenvalue, $\lambda_1 = -\chi_s \frac{(R_{0m}-R_{0s})}{R_{0m}}$ which is negative whenever $R_{0m} > R_{0s}$. The remaining eigenvalues can be calculated as the roots of the following equation

$$\left(\lambda^2 + a_1\lambda + a_2\right) = 0 \tag{17}$$

where

$a_1 = \beta_m I_m^{\#} + \mu = \mu R_{0m}$,

$a_2 = \beta_m^2 I_m^{\#} S^{\#} = \mu\chi_m(R_{0m} - 1)$.

For local stability we must ensure that the Routh-Hurwitz criteria [30] are satisfied:

$a_1 > 0$, and
$a_2 > 0$, which holds whenever $R_{0m} > 1$.

Thus, by the Routh-Hurwitz criteria, the boundary equilibrium $E^{\#}$ is locally asymptotically stable whenever $R_{0m} > \max[1, R_{0s}]$. Conversely, for $E^{\#} \in D$, it is unstable when $R_{0m} < R_{0s}$.

Now we prove $E^{\#}$ is globally asymptotically stable if $R_{0m} > \max[1, R_{0s}]$. Considering equation (7) and (8), we have

$$\dot{I}_s = (\beta_s S - \chi_s)I_s, \tag{18}$$

$$\dot{I}_m = \rho\omega_s I_s + \beta_m I_m S - \chi_m I_m. \tag{19}$$

Following [31], first we divide equation (18) and (19) through by I_s and I_m respectively to obtain

$$\frac{d\log I_s}{dt} = \beta_s S - \chi_s, \tag{20}$$

$$\frac{d\log I_m}{dt} = \beta_m S - \chi_m + \rho\omega_s \frac{I_s}{I_m}. \tag{21}$$

Rearranging equations (20) and (21) to solve for S we get

$$S = \frac{1}{\beta_s}\frac{d\log I_s}{dt} + \frac{\chi_s}{\beta_s} = \frac{1}{\beta_m}\frac{d\log I_m}{dt} + \frac{\chi_m}{\beta_m} - \frac{\rho\omega_s}{\beta_m}\frac{I_s}{I_m} \tag{22}$$

which immediately leads to the following inequality:

$$\frac{1}{\beta_s}\frac{d\log I_s}{dt} + \frac{\chi_s}{\beta_s} \le \frac{1}{\beta_m}\frac{d\log I_m}{dt} + \frac{\chi_m}{\beta_m}.$$

Integrating both sides of the equation above gives

$$\left(\frac{I_s(t)}{I_s(0)}\right)^{\frac{1}{\beta_s}} e^{\frac{\chi_s}{\beta_s}t} \le \left(\frac{I_m(t)}{I_m(0)}\right)^{\frac{1}{\beta_m}} e^{\frac{\chi_m}{\beta_m}t}$$

which we can rearrange to obtain

$$\left(\frac{I_s(t)}{I_s(0)}\right)^{\frac{1}{\beta_s}} \le \left(\frac{I_m(t)}{I_m(0)}\right)^{\frac{1}{\beta_m}} e^{\left(\frac{\chi_m}{\beta_m} - \frac{\chi_s}{\beta_s}\right)t}.$$

Next, we use equations (a) and (b) for the basic reproduction numbers, to rewrite this inequality as

$$\left(\frac{I_s(t)}{I_s(0)}\right)^{\frac{1}{\beta_s}} \le \left(\frac{I_m(t)}{I_m(0)}\right)^{\frac{1}{\beta_m}} e^{S^*\left(\frac{1}{R_{0m}} - \frac{1}{R_{0s}}\right)t}.$$

Finally, since both $I_s(t)$ and $I_m(t)$ are bounded, as we take the limit as $t \to \infty$ we find:

$$\lim_{t\to\infty}\left(\frac{I_s(t)}{I_s(0)}\right)^{\frac{1}{\beta_s}} \le \lim_{t\to\infty}\left(\frac{I_m(t)}{I_m(0)}\right)^{\frac{1}{\beta_m}} e^{S^*\left(\frac{1}{R_{0m}} - \frac{1}{R_{0s}}\right)t} \to 0 \text{ for } R_{0m} > R_{0s}.$$

Hence the hyperplane $I_s = 0$ attracts all solutions of (6)–(8) when $R_{0m} > R_{0s}$.

To complete the global stability proof, we show the endemic equilibrium $E^{\#}$ is globally asymptotically stable on the hyperplane $I_s = 0$ by constructing the following Lyapunov function [32]:

$$V^{\#} = S - S^{\#}\ln S + I_m - I_m^{\#}\ln I_m + C$$

where

$$C = -\left(S^{\#} - S^{\#}\ln S^{\#} + I_m^{\#} - I_m^{\#}\ln I_m^{\#}\right).$$

Taking the derivative of $V^{\#}(t)$ along system trajectories yields

$$\begin{aligned}
\dot{V}^{\#} &= \left(1 - \tfrac{S^{\#}}{S}\right)\dot{S} + \left(1 - \tfrac{I_m^{\#}}{I_m}\right)\dot{I}_m,\\
&= \left(1 - \tfrac{S^{\#}}{S}\right)(\Lambda - \mu S - \beta_m I_m S) + \left(1 - \tfrac{I_m^{\#}}{I_m}\right)(\beta_m I_m S - \chi_m I_m),\\
&= \Lambda - \mu S - \beta_m I_m S - \Lambda\tfrac{S^{\#}}{S} + \mu S^{\#} + \beta_m I_m S^{\#} + \beta_m I_m S - \chi_m I_m\\
&\quad -\beta_m I_m^{\#} S + \chi_m I_m^{\#}.
\end{aligned}$$

First, we substitute in the identity

$$\Lambda = \mu S^{\#} + \beta_m I_m^{\#} S^{\#},$$

to obtain

$$\begin{aligned}
\dot{V}^{\#} &= \mu S^{\#} + \beta_m I_m^{\#} S^{\#} - \mu S - \mu S^{\#}\frac{S^{\#}}{S} - \beta_m I_m^{\#} S^{\#}\frac{S^{\#}}{S} + \mu S^{\#}\\
&\quad +\beta_m I_m S^{\#} - \chi_m I_m - \beta_m I_m^{\#} S + \chi_m I_m^{\#},\\
&= \mu S^{\#}\left(2 - \frac{S}{S^{\#}} - \frac{S^{\#}}{S}\right) + \beta_m I_m^{\#} S^{\#} - \beta_m I_m^{\#} S^{\#}\frac{S^{\#}}{S} + \beta_m I_m S^{\#}\\
&\quad -\chi_m I_m - \beta_m I_m^{\#} S + \chi_m I_m^{\#}
\end{aligned}$$

We can simplify this expression further by substituting in the identity $\beta_m S^{\#} = \chi_m$ to get

$$\begin{aligned}
\dot{V}^{\#} &= \mu S^{\#}\left(2 - \frac{S}{S^{\#}} - \frac{S^{\#}}{S}\right) + \chi_m I_m^{\#} - \chi_m I_m^{\#}\frac{S^{\#}}{S} + \chi_m I_m - \chi_m I_m\\
&\quad -\chi_m I_m^{\#}\tfrac{S}{S^{\#}} + \chi_m I_m^{\#},\\
&= \mu S^{\#}\left(2 - \frac{S}{S^{\#}} - \frac{S^{\#}}{S}\right) + \chi_m I_m^{\#}\left(2 - \frac{S}{S^{\#}} - \frac{S^{\#}}{S}\right),\\
&= \left(\mu S^{\#} + \chi_m I_m^{\#}\right)\left(2 - \frac{S}{S^{\#}} - \frac{S^{\#}}{S}\right).
\end{aligned}$$

Since the arithmetic mean is greater than or equal to the geometric mean, we obtain $\dot{V}^{\#} \le 0$.

Therefore, the mono-existent endemic equilibrium $E^{\#}$ is globally asymptotically stable if $R_{0m} > 1$.

3.3. Co-existent endemic equilibrium

Lemma 3. If the endemic equilibrium $E^{\dagger} = (S^{\dagger}, I_s^{\dagger}, I_m^{\dagger})$ of equations (6)–(8) exists, $E^{\dagger}$ is locally asymptotically stable.

Proof. : We consider the Jacobian of the system (6)–(8) at the co-existent endemic equilibrium point $E^{\dagger}$ which is given by

$$J^{\dagger} = \begin{pmatrix} -\beta_s I_s^{\dagger} - \beta_m I_m^{\dagger} - \mu & -\beta_s S^{\dagger} & -\beta_m S^{\dagger}\\ \beta_s I_s^{\dagger} & \beta_s S^{\dagger} - \chi_s & 0\\ \beta_m I_m^{\dagger} & \rho\omega_s & \beta_m S^{\dagger} - \chi_m \end{pmatrix}.$$

To simplify this expression, we use the following identities

$$-\beta_s I_s^{\dagger} - \beta_m I_m^{\dagger} - \mu = -\mu\ R_{0s},$$

$$-\beta_s S^{\dagger} = -\frac{R_{0s}\ \chi_s}{S^*}\ \frac{S^*}{R_{0s}} = -\chi_s,$$

$$-\beta_m S^{\dagger} = -\frac{R_{0m}\ \chi_m}{S^*}\ \frac{S^*}{R_{0s}} = -\chi_m\frac{R_{0m}}{R_{0s}},$$

$$\beta_s I_s^{\dagger} = \beta_s\ \frac{\mu\ (R_{0s} - 1)}{\beta_s}\ \Psi = \mu(R_{0s} - 1)\Psi,$$

$$\beta_m I_m^{\dagger} = \frac{\rho\omega_s}{\chi_s}\ \frac{R_{0m}}{(R_{0s} - R_{0m})}\ \mu\ (R_{0s} - 1)\Psi,$$

$$\beta_s S^{\dagger} - \chi_s = \chi_s\left(\frac{\beta_s S^*}{R_{0s}\chi_s} - 1\right) = \chi_s\left(\frac{R_{0s}}{R_{0s}} - 1\right) = \chi_s(1 - 1) = 0,$$

$$\beta_m S^\dagger - \chi_m = \chi_m\left(\frac{\beta_m S^*}{\chi_m R_{0s}} - 1\right) = \frac{\chi_m}{R_{0s}}\,(R_{0m} - R_{0s})$$

where in the fourth line we have substituted in the definition of Ψ given in equation (d). This allows us to rewrite the matrix $J^\dagger$ in the following form:

$$J^\dagger = \begin{pmatrix} -\mu R_{0s} & -\chi_s & -\chi_m \frac{R_{0m}}{R_{0s}} \\ \mu\,(R_{0s}-1)\Psi & 0 & 0 \\ \mu\,(R_{0s}-1)(1-\Psi) & \rho\ \omega_s & \chi_m \frac{(R_{0m}-R_{0s})}{R_{0s}} \end{pmatrix}.$$

To determine the stability of this matrix we use the Routh-Hurwitz criteria, which state that the real parts of the roots of the characteristic polynomial associated with a three by three matrix $J^\dagger$ are negative if $A_1 > 0,\ A_2 > 0,\ A_3 > 0$, and $A_1A_2 > A_3$, where $A_1 = -\text{trace}(J^\dagger)$, A_2 represents the sum of the two by two principal minors of $J^\dagger$ and $A_3 = -\det(J^\dagger)$.

Condition 1: For the matrix $J^\dagger$, we have

$$A_1 = -\text{trace}\left(J^\dagger\right) = \mu\ R_{0s} + \frac{\chi_m\ (R_{0s} - R_{0m})}{R_{0s}}.$$

Hence, $A_1 > 0$ if $R_{0s} > R_{0m}$.

Condition 2:

$$\begin{aligned} A_2 &= \begin{vmatrix} 0 & 0 \\ \rho\ \omega_s & \frac{\chi_m\ (R_{0m}-R_{0s})}{R_{0s}} \end{vmatrix} + \begin{vmatrix} -\mu R_{0s} & -\chi_m \frac{R_{0m}}{R_{0s}} \\ \mu\ (R_{0s}-1)(1-\Psi) & \chi_m \frac{(R_{0m}-R_{0s})}{R_{0s}} \end{vmatrix} \\ &\quad + \begin{vmatrix} -\mu R_{0s} & -\chi_s \\ \mu(R_{0s}-1)\Psi & 0 \end{vmatrix}, \\ &= \mu\chi_m\ (R_{0s} - R_{0m}) + \mu\chi_m \tfrac{R_{0m}}{R_{0s}}(R_{0s}-1)(1-\Psi) + \mu\chi_s(R_{0s}-1)\Psi. \end{aligned}$$

Recalling that $0 < \Psi < 1$ for $R_{0s} > R_{0m}$, we see that $A_2 > 0$ is satisfied whenever $R_{0s} > 1$ and $R_{0s} > R_{0m}$.

Condition 3:

$$\begin{aligned} A_3 &= \det\left(J^\dagger\right), \\ &= -\mu\ (R_{0s}-1)\Psi \begin{vmatrix} -\chi_s & \chi_m \frac{R_{0m}}{R_{0s}} \\ \rho\ \omega_s & \chi_m \frac{(R_{0m}-R_{0s})}{R_{0s}} \end{vmatrix}, \\ &= -\mu\ (R_{0s}-1)\Psi\ \left[\tfrac{\chi_s\chi_m\ (R_{0s}-R_{0m})}{R_{0s}} + \tfrac{\rho\ \omega_s\chi_m R_{0m}}{R_{0s}}\right], \\ &= \mu\ (R_{0s}-1)\Psi\ \frac{\chi_s\chi_m\ (R_{0s}-R_{0m})}{R_{0s}}\ \left[1 + \tfrac{\rho\ \omega_s R_{0m}}{\chi_s\ (R_{0s}-R_{0m})}\right], \\ &= \mu\ (R_{0s}-1)\ \frac{\chi_s\chi_m\ (R_{0s}-R_{0m})}{R_{0s}}\ \frac{\Psi}{\Psi}, \\ &= \frac{\mu\ \chi_s\chi_m}{R_{0s}}\ (R_{0s}-1)(R_{0s}-R_{0m}) \end{aligned}$$

where in the fifth line we have substituted in the definition of Ψ given in equation (d). The condition $A_3 > 0$ is true if $R_{0s} > 1$ and $R_{0s} > R_{0m}$.

Finally, if we multiply the expressions for A_1 and A_2 it is straightforward to show that the condition $A_1A_2 > A_3$ is satisfied when $R_{0s} > 1$ and $R_{0s} > R_{0m}$. Thus, by the Routh-Hurwitz criteria, the co-existent endemic equilibrium $E^\dagger$ is locally asymptotically stable when $R_{0s} > 1$ and $R_{0s} > R_{0m}$.

4. Sensitivity analysis

Recognizing the relative importance of the various risk factors responsible for the transmission of infectious diseases is essential. The progression of the drug-resistant strain and its incidence and prevalence must be understood in order to determine how best to decrease disease burden. For this purpose, we calculated the partial rank correlation coefficients (PRCCs)–which is a global sensitivity analysis technique using Latin Hypercube Sampling (LHS)–of several key output variables. In each case we assigned a uniform distribution from 0 to 3 times the baseline value for each input parameter to generate a total of 100,000,000 computations of each

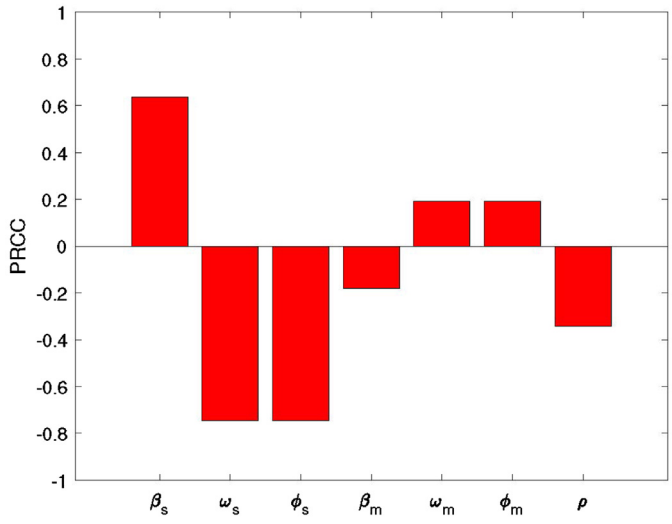

Fig. 2. PRCC values depicting the sensitivities of the model output I_s with respect to the input parameters β_s, ω_s, ϕ_s, β_m, ω_m, ϕ_m and ρ, when $R_{0s} > \max[R_{0m}, 1]$ (i.e. co-existent endemic equilibrium $E^\dagger$).

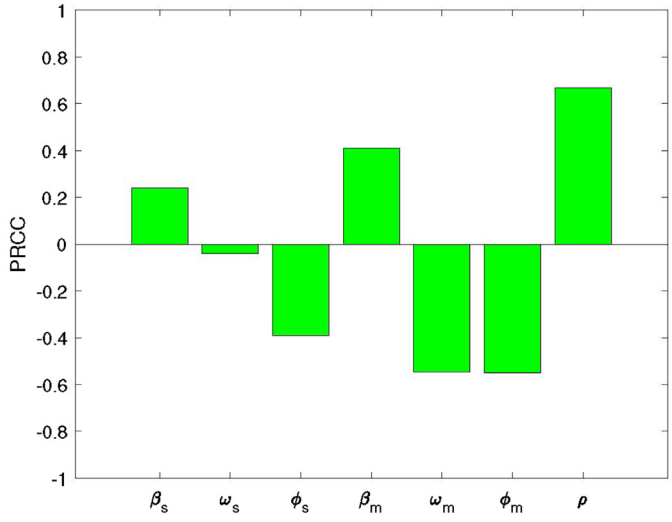

Fig. 3. PRCC values depicting the sensitivities of the model output I_m with respect to the input parameters β_s, ω_s, ϕ_s, β_m, ω_m, ϕ_m and ρ, when $R_{0s} > \max[R_{0m}, 1]$] (i.e. co-existent endemic equilibrium $E^\dagger$).

output variable of interest. Here the model outputs we consider are the number of infectious individuals I_s and I_m and their total sum $(I_s + I_m)$ at equilibrium. Note that PRCC values lie between -1 and +1. Positive (negative) values imply a positive (negative) correlation to the model parameter and outcomes. The bigger (smaller) the absolute value of the PRCC, the greater (lesser) the correlation of the parameter to the model outcome.

Figs 2–4 display the correlation between I_s, I_m and $(I_s + I_m)$ and the corresponding parameters β_s, ω_s, ϕ_s, β_m, ω_m, ϕ_m and ρ when $R_{0s} > \max[R_{0m}, 1]$, that is, at the co-existent endemic equilibrium. From Figs 2–4, it is easy to perceive that I_s and $(I_s + I_m)$ have a strong positive correlation with β_s and I_m has a weaker positive correlation with β_s, implying that a positive change of β_s will increase I_s, $(I_s + I_m)$ and I_m. Parameters ω_s and ϕ_s have a negative correlation with I_s, I_m and $(I_s + I_m)$. In addition β_m has a negative correlation with I_s and $(I_s + I_m)$ but a strong positive correlation with I_m. Parameters ω_m and ϕ_m have a positive correlation with I_s and $(I_s + I_m)$ but strong negative correlation with I_m.

Table 1
Description of model parameters

Parameters	Description	Estimated value	References
Λ	A demographic parameter which represents the recruitment rate into the population	1	
μ	Per-capita death rate	$\frac{1}{70}$ per year	[33]
β_s	The effective contact rate per unit time between susceptible and drug-susceptible infective individuals	variable	–
β_m	The effective contact rate per unit time between susceptible and drug-resistant infective individuals	variable	–
ω_s	The per-capita rate at which the drug-susceptible infected population progress to the recovery stage per unit time as a result of treatment	0.290 per year	[34]
ω_m	The per-capita rate at which the drug-resistant infected population progress to the recovery stage per unit time as a result of treatment	0.145 per year	Assume
ρ	The proportion of amplification due to treatment default on first-line drug therapy	0.035	[35]
φ_s	The per-capita rate at which the drug-susceptible infected population die from infection per unit time	0.37 over 3 years	[35]
φ_m	The per-capita rate at which the drug-resistant infected population die from infection per unit time	0.37 over 3 years	[35]

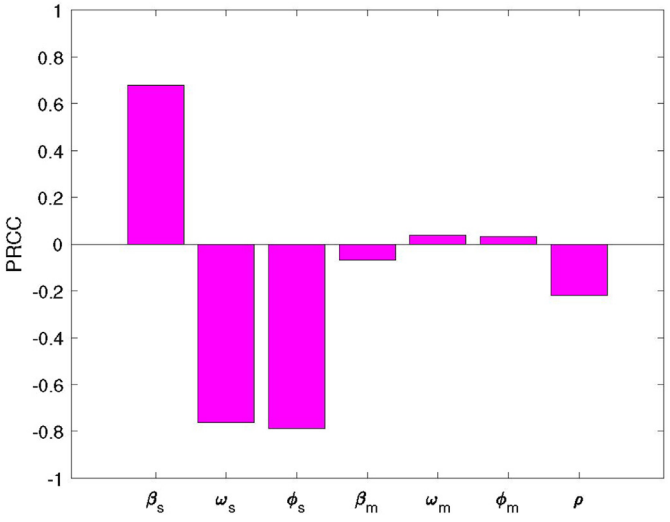

Fig. 4. PRCC values depicting the sensitivities of the model output $I_s + I_m$ with respect to the input parameters $\beta_s, \omega_s, \phi_s, \beta_m, \omega_m, \phi_m$ and ρ, $R_{0s} > \max[R_{0m}, 1]]$ (i.e. co-existent endemic equilibrium $E^{\dagger}$).

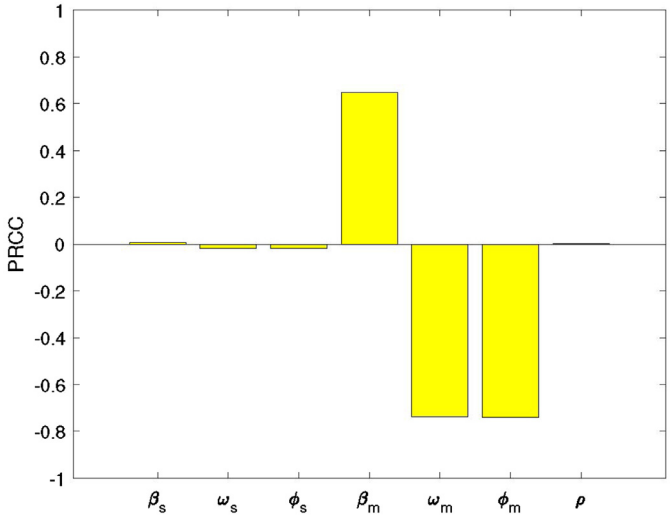

Fig. 5. PRCC values depicting the sensitivities of the model output I_m with respect to the input parameters $\beta_s, \omega_s, \phi_s, \beta_m, \omega_m, \phi_m$ and ρ, when $R_{0m} > R_{0s}$ and $R_{0m} > 1$] (i.e. mono-existent endemic equilibrium $E^{\#}$).

Further, parameter ρ has a negative correlation with I_s and $(I_s + I_m)$ but a strong positive correlation with I_m. Fig. 5 represents the correlation between the equilibrium value of I_m and the corresponding model parameters β_s, ω_s, ϕ_s, β_m, ω_m, ϕ_m and ρ when $R_{0m} > R_{0s}$ and $R_{0m} > 1$ (i.e. at the mono-existent endemic equilibrium). Parameters β_s, β_m and ρ (small value not showing)

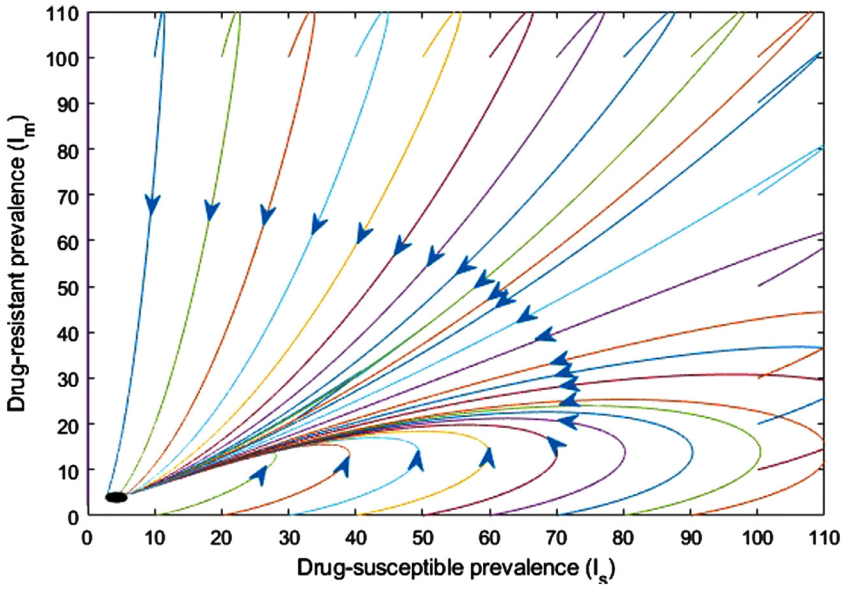

Fig. 6. Co-existent endemic equilibrium: $R_{0s} > \max[R_{0m}, 1]$. In this case both the drug-susceptible infection and drug-resistant infection persist in the population (black dot). All parameter values assume their baseline values given in Table 1.

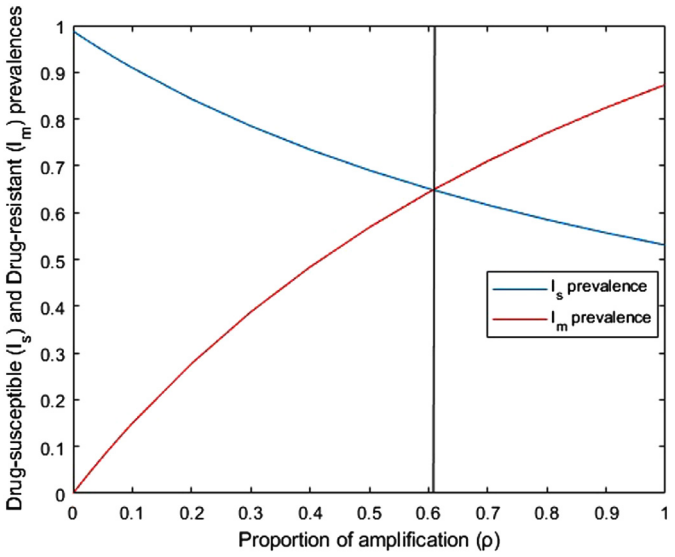

Fig. 7. Effect of amplification (ρ) on the drug-susceptible (I_s) prevalence and drug-resistant prevalence (I_m). All parameter values assume their baseline values given in Table 1.

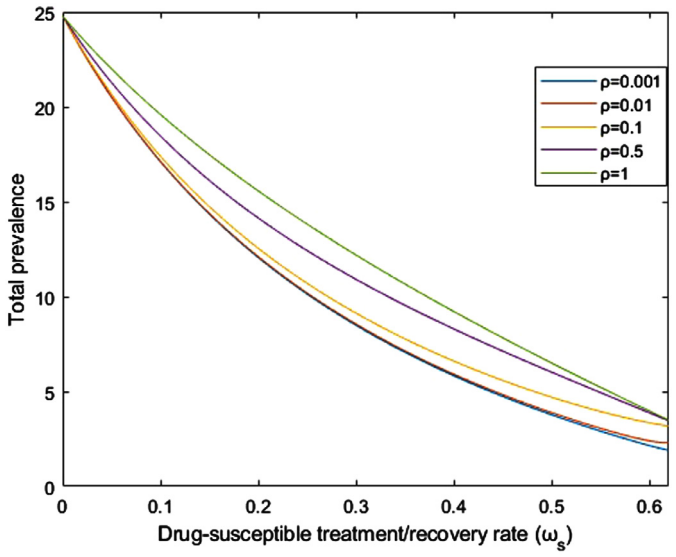

Fig. 8. Effect of drug-susceptible treatment/recovery rate (ω_s) on the equilibrium level of total prevalence when both infectious rates (β_s, β_m) are fixed to their baseline values. All remaining parameter values assume their baseline values given in Table 1.

have positive PRCC values, implying that a positive change in these parameters will increase I_m. In contrast, ω_s, ϕ_s, ω_m and ϕ_m have negative PRCC values and, thus, increasing theses parameters will consequently decrease I_m.

5. Numerical simulations

In this section, we carry out detailed numerical simulations (using the Matlab programming language) to support the analytic results and to assess the impact of amplification and the drug-susceptible treatment/recovery rate on equilibrium levels of total prevalence and drug-resistant prevalence. For illustration we have chosen baseline parameter values consistent with tuberculosis infection and transmission [33–35]. In accordance with the analytic results we found three equilibrium points: the disease-free equilibrium E^*; a mono-existent endemic equilibrium $E^{\#}$; and a co-existent endemic equilibrium $E^{\dagger}$. We used different initial conditions for both strains of all populations and found that if both basic reproduction numbers are less than one (i.e. $\max[R_{0s}, R_{0m}] < 1$) then the disease-free equilibrium is locally and globally asymptotically stable. If $R_{0m} > \max[R_{0s}, 1]$, the drug-susceptible strain dies out but the drug-resistant strain persists in the population. Furthermore, if $R_{0s} > \max[R_{0m}, 1]$, then both the drug-susceptible and drug-resistant strains persist in the population.

Fig. 6 illustrates the stability of the co-existent endemic equilibrium (i.e. when $R_{0s} > \max[R_{0m}, 1]$) by depicting system trajectories through the I_s vs I_m plane originating from different initial conditions. In this system both strains (I_s and I_m) persist because of the amplification pathway from the drug-susceptible strain to the drug-resistant strain. Fig. 7 depicts the effect of amplification (ρ) on equilibrium levels of drug-susceptible prevalence and drug-resistant prevalence and shows that in the first region ($\rho \lesssim 0.6$) the drug-susceptible prevalence is initially dominant but that the drug-resistant prevalence rises with increasing ρ. Eventually, for $\rho \gtrsim 0.6$, the drug-resistant strain becomes dominant courtesy of the amplification pathway.

Fig. 8, and Fig. 9 show the effect of the drug-susceptible strain treatment/recovery rate on the equilibrium level of total prevalence, and drug-resistant prevalence when both infection rates (β_s, β_m) are fixed. If we increase the proportion of amplification,

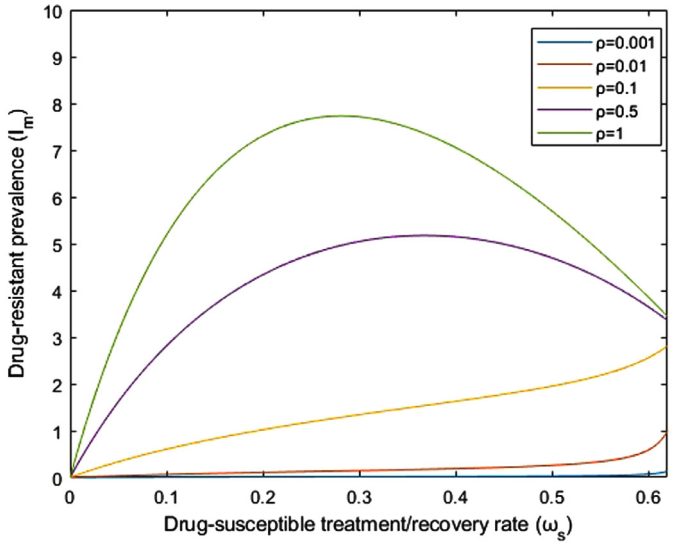

Fig. 9. Effect of drug-susceptible treatment/recovery rate (ω_s) on the equilibrium level of the drug-resistant strain when both infectious rates (β_s, β_m) are fixed to their baseline values. All remaining parameter values assume their baseline values given in Table 1.

both the total prevalence and drug-resistant prevalence also increase.

However, Fig. 9 shows that for high amplification, the drug-resistant prevalence increased when the treatment/recovery rate of the drug-susceptible strain moved from zero to around 0.25 to 0.30, then declined to a common point. For lower amplification values, the drug-resistant proportion only increased up to the common point. This point is the drug-resistant only equilibrium and occurs when the effective reproduction number of the drug-susceptible strain becomes lower than the basic reproduction number of drug-resistant strain. Numerical simulations show that for sufficiently high amplification, the prevalence of the drug-resistant strain will exceed that of its inherent equilibrium value (that is, the resistant-only equilibrium) when the drug-susceptible strain exists and is being treated.

6. Discussion and conclusion

In this study, we formulated a two-strain SIR non-constant population model with amplification and investigated its dynamic behaviour. We considered amplification as the process by which an individual infected with a drug-susceptible strain acquires infection with a drug-resistant strain. Using the next-generation matrix, we obtained the basic reproduction number of each strain, namely R_{0s} for drug-susceptible cases and R_{0m} for drug-resistant cases. We found that the basic reproduction numbers determine the equilibrium states of the system and their stability. Specifically if R_{0m} is greater than R_{0s} and unity, only the drug-resistant strain will remain, whereas if R_{0s} is larger than R_{0m} and unity, a coexistence is likely. We also found that both basic reproduction numbers are independent of the amplification rate, which indicates that the reproductive capacity of each strain is autonomous of the amplification rate between them.

We also found that the drug-susceptible strain is not necessarily the most prevalent at equilibrium even if it has the highest basic reproduction number. This is a consequence of the fact that the drug-susceptible strain persists purely on direct transmission whereas the drug-resistant strain prevalence is driven by a combination of direct transmission and amplification. These results explain in part the rise in drug-resistant strain prevalence when the drug-susceptible strain is treated.

Lastly, we explored the effect of the drug-susceptible treatment rate on the equilibrium level of total prevalence and drug-resistant prevalence. We found that if we increase the drug-susceptible treatment rate, the total prevalence will decline. However, the response of the drug-resistant strain prevalence is non-monotonic, increasing for a certain period and then declining at a particular threshold point. This finding has important implications for choosing the proper intervention or treatment strategies. From a microbiological viewpoint, resistance first occurs by a genetic mutation in a micro-organism that leads to resistance to a treatment, modelled by reducing the treatment rate. Therefore, one could question whether it is prudent to risk the emergence of drug-resistant strains by increasing the treatment rate of the drug-susceptible strain. However, at least initially, such resistance-conferring mutations typically exact a “fitness cost” whereby drug-resistant organisms reproduce at a lower rate and are often less transmissible than their drug-susceptible counterparts [36]. Nevertheless, the selective pressure applied by antibiotic treatment permits drug-resistant mutants to become the dominant strain in a patient infected with disease on first-line therapy and allows for further mutations with selection for fitness. Therefore, increasing drug-susceptible treatment rates may increase the likelihood of emergence of an even more prolific strain which also has drug resistance.

In conclusion, this study has concentrated on a two-strain coupled SIR epidemic model and performed a rigorous analytical analysis of the system properties and solutions, for understanding infectious disease genetic variation and the rising threat of antibiotic resistance or inadequate treatment. These results help inform the practice of drug treatment in the setting of drug resistance and emergent strains, such as is occurring in tuberculosis and other bacterial pathogens. This work shows theoretically that treatment of drug-susceptible strains of an infectious disease can drive the emergence of the drug-resistant strain, even if that strain has reduced fitness, such that the reproduction number is less than one. Further, under these circumstances, our analysis shows that this emergence of drug resistance will be overcome if the treatment rate is sufficient to eliminate the drug-susceptible strain from the population. Hence, we recommend that for problematic drug-resistant pathogens, estimates of the reproduction numbers of the susceptible and resistant strains be made along with the risk of amplification, to ensure optimal levels of treatment be used to minimise the risk of emergence of the resistant strains. Future modelling studies could focus on specific pathogens (and their associated parameters) and whether treatment may lead to unintended threats to infection control such as an increase in resistant strains.

Credit Authors statement

Md Abdul Kuddus initiated the concept of the study, wrote the manuscript, developed the model, analysed the data, wrote code for model, and acted as corresponding author.

Emma S. McBryde assisted with the development of the model, proof read and critically reviewed the manuscript.

Adeshina I. Adekunle critically reviewed the manuscript

Lisa J. White proof read and critically reviewed the manuscript

Michael T. Meehan assisted with the development of the model, analysis of the data, proof read and critically reviewed the manuscript.

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Declaration of Competing Interest

None.

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