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Drug resistance in tuberculosis—a reinfection model

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Abstract

There is increasing recognition that reinfection is an important component of TB transmission. Moreover, it has been shown that partial immunity has significant epidemiological consequences, particularly in what concerns disease prevalence and effectiveness of control measures. We address the problem of drug resistance as a competition between two types of strains of *Mycobacterium tuberculosis*: those that are sensitive to anti-tuberculosis drugs and those that are resistant. Our objective is to characterise the role of reinfection in the transmission of drug-resistant tuberculosis. The long-term behaviour of our model reflects how reinfection modifies the conditions for coexistence of sensitive and resistant strains. This sets the scene for discussing how strain prevalence is affected by different control strategies. It is shown that intervention effectiveness is highly sensitive to the baseline epidemiological setting.

Keywords: Reinfection; Drug resistance; Tuberculosis; Control strategies; Coexistence; Stability; Mathematical models

1. Introduction

Tuberculosis (TB) is a disease caused by infection with *Mycobacterium tuberculosis*, which most frequently affects the lungs (pulmonary TB). It is one of the most common infectious diseases with two billion people (one-third of the world's population) currently infected. Nine million new cases of active disease develop each year, resulting in two million deaths, mostly in developing countries. Despite intensive control efforts, recent data show that global incidence is increasing, largely due to an association with human immunodeficiency virus (HIV) (World Health Organization, 2005). Treatment efficacy is decreasing due to the emergence of multi-drug resistant strains (Dye et al., 2002).

According to a recent report of the World Health Organization (WHO) (WHO/IUATLD, 2004), the overall prevalence of drug resistance ranges from 0% (Andorra, Iceland and Malta) to 63.9% (Karakalpakstan, Uzebekistan) with a median of 10.4%. The WHO distinguishes between two types of resistance: acquired resistance—resistance among previously treated patients; and primary resistance—resistance among new cases (WHO/IUATLD, 1998). In all regions studied, prevalence of acquired resistance is higher than prevalence of primary resistance, but the size of this difference varies between regions (WHO/IUATLD, 2004).

Treatment of TB consists of a combination of different drugs to avoid acquisition of resistance. Despite these precautions, drug resistance continues to emerge being favoured by the long duration of treatment and improper use of the antibiotics (Crofton et al., 1997). Drug resistant TB has higher rates of treatment failure and longer periods of infectiousness in part due to the time lapse between TB diagnosis and obtaining drug-sensitivity test results (Espinal et al., 2000). Most worrisome is resistance to the two first line drugs, isoniazid and rifampicin, defined as multi-drug resistance (MDR). Geographical distribution of MDR is very heterogeneous: it is highly prevalent in several areas of the former Soviet Union and in Israel, Ecuador and some Provinces of China, but it is absent or present with

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very low prevalence in a significant number of countries. Prevalence of MDR TB ranges from 0% to 26.8%, with a median of 1.7% (WHO/IUATLD, 2004).

Mathematical models have addressed the transmission dynamics of antibiotic resistance in general (Austin et al., 1997; Bonhoeffer, 2002; Boni and Feldman, 2005). More specifically to TB, a number of mathematical models have also been proposed (Blower and Chou, 2004; Blower and Gerberding, 1998; Blower et al., 1996; Castillo-Chavez and Feng, 1997; Cohen and Murray, 2004; Dye and Espinal, 2001; Dye and Williams, 2000). Overall these models assume that resistant strains are less transmissible, reflecting a trade-off between fitness and resistance. Combined results demonstrate that the relative fitness between resistant and sensitive strains is a crucial parameter: for some values it is predicted that second-line drugs would be needed to prevent future epidemics (Dye and Espinal, 2001), whereas for other values it appears as a local problem that can be managed through proper implementation of strategies currently recommended by the WHO (Dye and Williams, 2000). Moreover, Cohen and Murray (2004) find that even when resistant strains have, on average, a lower transmissibility a small subpopulation of a relatively fit MDR strain may outcompete both the drug-sensitive strains and the less fit MDR strains. ~~The~~relation between resistance acquisition and fitness cost as well as its epidemiological consequences in *M. tuberculosis* is, however, under discussion (Cohen et al., 2003; Gagneux et al., 2006).

Although it is recognised that reinfection is an important component of TB transmission (Chiang and Riley, 2005), few modellers take it into consideration. It has been shown that for infectious diseases where immunity acquired by individuals after exposure is not totally protective, allowing for reinfection to occur at a reduced rate, the equilibrium prevalence of infection is highly sensitive to a threshold other than the epidemic threshold. This has been named the 'reinfection threshold' and marks a critical transmission rate above which reinfection processes are dominant (Gomes et al., 2004, 2005a,b; Breban and Blower, 2005). The reinfection threshold has strong implications on epidemiological reasoning, particularly in what respects the effectiveness of interventions.

For the case of resistant TB, a few models have considered reinfection (Blower and Chou, 2004; Castillo-Chavez and Feng, 1997; Cohen and Murray, 2004; Dye and Williams, 2000) but the implementations vary significantly. Blower and Chou (2004) and Dye and Williams (2000) incorporate reinfection at a reduced rate (partial immunity) applying to latent individuals only. Blower and Chou (2004) assume that recovered individuals have either total protection against reinfection (if treated), or no protection at all (if self-cured). By contrast, Dye and Williams (2000) assume that self-cured individuals have a high relapse but cannot be reinfected. Castillo-Chavez and Feng (1997) neglect exogenous reinfection of latent individuals and assume superinfection but only by resistant strains. Cohen and Murray (2004) consider that latent and recovered individuals benefit from partial immunity and have identical susceptibilities to reinfection. Reinfection can happen with different strains and the new strain always replaces the previous one. The model characterises strains by both fitness and resistance status reaching a level of complexity that limits its analysis in what reinfection is concerned.

We extend previous work by devoting special care to the implementation of reinfection and analysis of its consequences to the spread of drug-resistant TB. The model is based on a reinfection framework for the transmission of TB (Gomes et al., 2004), and extended to describe the competition between two types of strains: sensitive and resistant to drugs. Model extension is made in steps permitting intermediate analysis in a systematic way. We describe how coexistence is shaped by reinfection dynamics and by the outcome of mixed infection. The model predicts that coexistence is common for highly endemic settings due to the greater relative importance of reinfection. Long-term effectiveness of different control measures is considered, and shows important sensitivity to the baseline epidemiological setting.

2. Model construction

2.1. Exogenous reinfection and endogenous reactivation

The model is based on the TB transmission framework proposed in Gomes et al. (2004). The host population is divided into different categories based on the individual history of infection. Three classes characterise the host population: susceptible (S), who have never been exposed to the *mycobacterium*; latent (L), who are infected but not infectious; and infectious (I) with active disease (see the diagram in Fig. 1). Population size is assumed constant over time. Susceptible individuals are infected at a rate proportional to the prevalence of active TB and may develop active disease (progress to I) or maintain a latent infection (enter L). Individuals who recover from active disease by treatment with antibiotics or self-cure are transferred from I back to L. Infected individuals acquire some immunity as a result of infection, which reduces the risk of subsequent infection but does not fully prevent it.

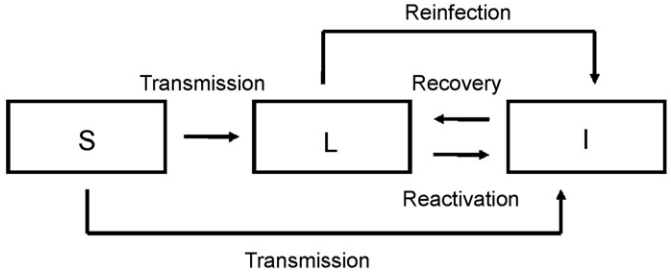

Fig. 1. TB model.

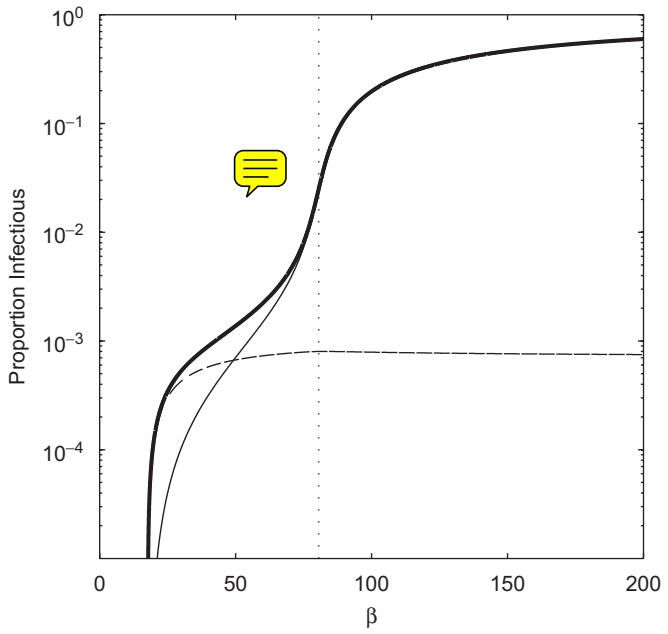

Fig. 2. Equilibrium curve: heavy black line represents all TB cases. Thin dashed and full lines represent primary and reinfection cases, respectively. Vertical line marks the reinfection threshold.

Finally, latent individuals can progress to active TB due to endogenous reactivation or exogenous reinfection.

Fig. 2 shows the equilibrium curve for the proportion of active infections and illustrates the reinfection threshold (Gomes et al., 2004). Above this threshold most TB cases are due to reinfection. Thinner lines in this figure trace the equilibrium proportion of cases resulting from primary infection and reinfection, respectively.

2.2. Drug resistance

The model is extended to include two strains with different sensitivities to antibiotics (see diagram in Fig. 3). We specify drug-resistant and drug-sensitive strains by adding subscripts r and s to model variables and parameters.

Resistant cases may emerge when individuals are infected with a resistant strain (primary resistance) or as a result of treatment failure (acquired resistance). We assume that a fraction, γ, of infectious individuals with active sensitive TB (I_s) progresses into the infectious class of resistant strains (I_r) due to treatment failure. These correspond to cases of acquired resistance.

2.3. Strain interactions

Molecular epidemiological studies suggest that mixed infections (infections with more than one strain) are common (Warren et al., 2004), and that once an individual is infected with both sensitive and resistant strains, a differential selection pressure will be imposed by treatment (van Rie et al., 2004). Moreover, an individual infected with

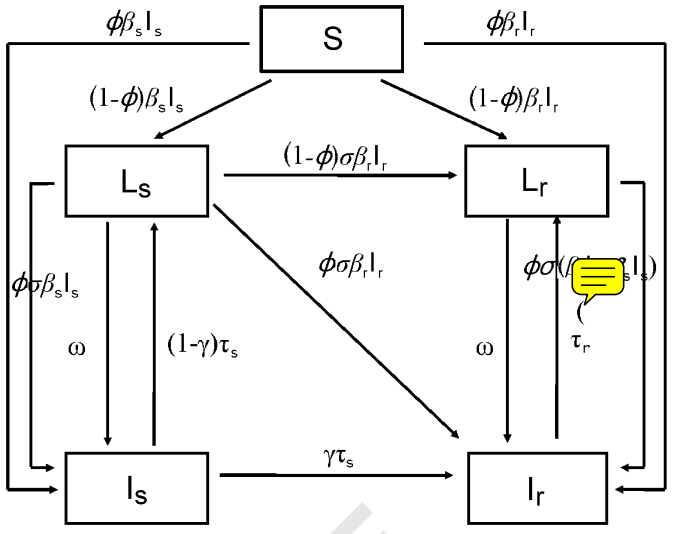

Fig. 3. Two-strain TB model.

both resistant and sensitive strains may have two alternative progressions: (i) develop resistant TB if treated with the drugs to which one of the strains is resistant; or (ii) develop sensitive TB if untreated or if treated with a regimen set as to overcome the specific resistance pattern.

Initially we assume that when an individual is infected with both resistant and sensitive strains there will be a preferential activation (and transmission) of resistant strains—scenario (i) above. This corresponds to a worse case scenario where the treatment regimen available is not totally effective and selects for resistance. Later, in Section 5, we show that the results essentially extend to a more general implementation of mixed infection—scenario (ii) above.

The two-strain model can be represented as the system of differential equations:

$$\begin{cases} \dfrac{dS}{dt} = b - (\beta_s I_s + \beta_r I_r + \mu)S, \\ \dfrac{dL_s}{dt} = (1-\phi)\beta_s I_s S - (\omega + \phi\sigma\beta_s I_s + \sigma\beta_r I_r + \mu)L_s \\ \qquad +(1-\gamma)\tau_s I_s, \\ \dfrac{dL_r}{dt} = (1-\phi)\beta_r I_r S + (1-\phi)\sigma\beta_r I_r L_s \\ \qquad -(\omega + \phi\sigma\beta_s I_s + \phi\sigma\beta_r I_r + \mu)L_r + \tau_r I_r, \\ \dfrac{dI_s}{dt} = \phi\beta_s I_s S + (\omega + \phi\sigma\beta_s I_s)L_s - (\tau_s + \mu + \delta)I_s, \\ \dfrac{dI_r}{dt} = \phi\beta_r I_r S + \phi\sigma\beta_r I_r L_s + (\omega + \phi\sigma\beta_s I_s + \phi\sigma\beta_r I_r)L_r \\ \qquad +\gamma\tau_s I_s - (\tau_r + \mu + \delta)I_r. \end{cases} \quad (1)$$

Parameter values are given and described in Table 1. Parameters that refer to sensitive TB take values as in Gomes et al. (2004). Reactivation rate is considered the same for sensitive and resistant infections. Individuals reactivate at a low rate so that a majority never progress to

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Table 1
Two-strain model parameters

Symbol	Definition	Value
β_s, β_r	Transmission coefficient	Variable
μ	Death rate and birth rate	$1/70\,\mathrm{yr}^{-1}$
δ	Death rate associated to TB	$0.2\,\mathrm{yr}^{-1}$
ϕ	Proportion of individuals that develop active TB (the remaining $1-\phi$ have latent sensitive TB)	0.1
σ	Factor reducing the risk of infection as a result of acquired immunity to a previous infection with sensitive and resistant TB	0.25
ω	Rate of endogenous reactivation of latent TB	$0.0002\,\mathrm{yr}^{-1}$
τ_s, τ_r	Rate of treatment of active sensitive and resistant TB	$2, 1.5\,\mathrm{yr}^{-1}$
γ	Proportion of sensitive TB treatment failure acquiring resistance	0.003 (or $\gamma = 0$)

active disease (Gomes et al., 2004; Vynnycky and Fine, 1997). Different assumptions can be found in the literature that discriminate related mechanisms such as relapse of self-cured individuals or of treated patients, chronic infections and successive treatment failures (Blower and Chou, 2004; Dye et al., 1998; Castillo-Chavez and Feng, 1997; Dye and Williams, 2000, respectively). We assume the rate of mortality associated to TB as in Dye and Espinal (2001). Birth rate b compensates for disease-induced and background mortality to keep the population size constant over time, so $b = \mu + \delta(I_s + I_r)$. The proportion acquiring resistance, γ, is on the lower bound of ranges considered in Cohen and Murray (2004) and Dye and Espinal (2001). We assume that the period of infectiousness of a resistant TB case is, on average, two months longer than that of a sensitive case. There is evidence that an individual infected with a resistant strain stays longer in the infectious state due to either improper regimen, late identification of the resistance phenotype, or lower efficacy of treatment (Espinal et al., 2000). The factor reducing the risk of infection as a result of acquiring immunity, σ, is the same for both resistant and sensitive strains. Differences in transmission rates are explored by continuously varying the strain-specific transmission coefficients β_s and β_r.

3. Equilibria and stability

For system (1) the simplex

$$\mathbb{S} := \{(S, L_s, L_r, I_s, I_r) \in (\mathbb{R}_0^+)^5 : S + L_s + L_r + I_s + I_r = 1\}$$

is a positively invariant set, and thus we restrict the study of the solutions of the system to $\mathbb{S}$. By the fundamental theory of ODE's, we know that (1) defines a dynamical system on $\mathbb{S}$ as uniqueness, global existence and continuous dependence of solutions on initial data is guaranteed when initial values are in $\mathbb{S}$.

3.1. Basic reproduction number, R_0

We calculate the basic reproduction number, R_0, using the next generation approach, developed in van den Driessche and Watmough (2002). The basic reproduction number is defined as the dominant eigenvalue of the next generation matrix,

$$R_0 = \max\{R_{0s}, R_{0r}\},$$

where R_{0s} and R_{0r} are the two eigenvalues (see Appendix A.1 for details):

$$R_{0s} = \frac{\beta_s(\omega + \phi\mu)}{(\mu+\omega)(\mu+\delta+\tau_s) - (1-\gamma)\tau_s\omega},$$

$$R_{0r} = \frac{\beta_r(\omega + \phi\mu)}{(\mu+\omega)(\mu+\delta+\tau_r) - \omega\tau_r}. \quad (2)$$

We can also interpret R_{0s} and R_{0r} as the average number of secondary infectious cases that an infectious individual (with a sensitive or a resistant strain, respectively) would generate in a totally susceptible host population. A threshold condition for endemicity is given by $R_0 = 1$: the disease dies out if $R_0 < 1$, and becomes endemic if $R_0 > 1$.

3.2. Steady states

System (1) has one disease-free equilibrium, $E_0 = (1, 0, 0, 0, 0)$ and two endemic equilibria of the form $E_r = (S^r, 0, L_r^r, 0, I_r^r)$ and $E_{rs} = (S^*, L_s^*, L_r^*, I_s^*, I_r^*)$, corresponding, respectively, to states where only resistant strains, or both types of strains are present.

The bifurcation diagram in Fig. 4(a) divides the (R_{0s}, R_{0r})-space into three regions as characterised by the long-term epidemiological outcomes, each corresponding to a stable steady state of the system: disease eradication (I), persistence of only drug-resistant TB (II) or coexistence i.e., persistence of both drug-sensitive and drug-resistant TB (III).

Note that, infectious cases with sensitive strains give rise to new cases of resistant strains at a constant rate $\gamma > 0$, due the acquisition of resistance through treatment failure. It is, therefore, not possible to have an equilibrium where only sensitive strains are present. However, this equilibrium exists in the limit $\gamma = 0$, which corresponds to no acquired resistance. The resulting equilibrium has the form $E_s = (S^s, L_s^s, 0, I_s^s, 0)$ and in Fig. 4(b) we can see the corresponding stability region (marked as IV). We explore this limit

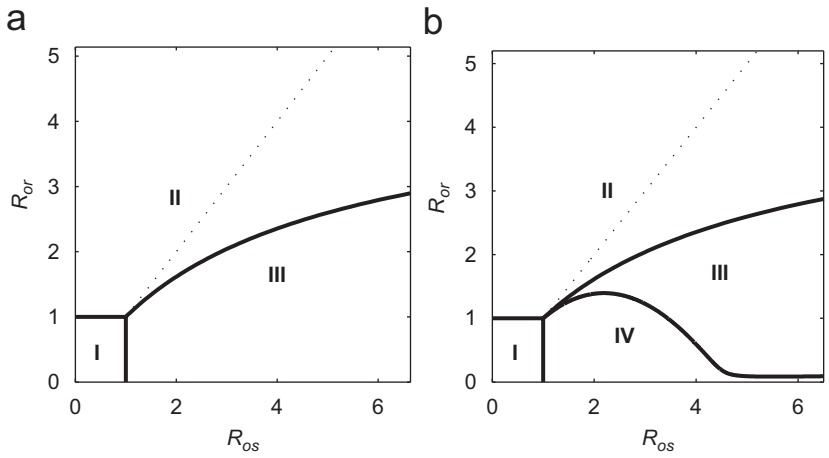

Fig. 4. Long-term epidemiological outcome: (a) $\gamma > 0$; (b) $\gamma = 0$. I—disease eradication; II—persistence drug-resistant TB only; III—coexistence. IV—persistence drug-sensitive TB only. The dotted line corresponds to the model without reinfection $\sigma = 0$.

case in more detail in Section 3.5, but otherwise we consider $\gamma > 0$.

3.3. Stability of the disease-free equilibrium

The stability properties of the disease-free equilibrium (trivial equilibrium) E_0, corresponding to the threshold condition for endemicity are given by Theorem 1, stated below and proved in Appendix A.2.

Theorem 1. *The disease-free equilibrium E_0 of system* (1) *is locally asymptotically stable, if $R_0 < 1$, i.e., if $R_{0s} < 1$ and $R_{0r} < 1$, and it is unstable for $R_0 > 1$.*

Remark 1. Numerical results suggest that the disease-free equilibrium is in fact globally asymptotically stable for $R_0 < 1$.

3.4. Stability of boundary and coexistence equilibria

The existence of an equilibrium for which only resistant strains persist is given by Theorem 2, stated below and proved in Appendix A.3.

Theorem 2. *System* (1) *has exactly one non-trivial boundary equilibrium, $E_r = (S^r, 0, L_r^r, 0, I_r^r)$, for $R_{0r} > 1$.*

In order to derive an expression for the region of stability of the boundary equilibrium we measure the capacity of sensitive TB strains to invade and persist in a population where resistant TB is at equilibrium. In this context, $E_r = (S^r, 0, L_r^r, 0, I_r^r)$ corresponds to an equilibrium free of sensitive TB. Applying the methods in van den Driessche and Watmough (2002) once again we find the basic reproduction number of the sensitive strains in a population where resistant strains are fixed (see Appendix A.3 for details):

$$R_{0s}(E_r) = \frac{S^r \beta_s (\phi(\mu + \sigma\beta_r I_r^r) + \omega)}{(\mu + \sigma\beta_r I_r^r + \omega)(\mu + \delta + \tau_s) - (1-\gamma)\tau_s\omega}.$$

This formalism permits the derivation of a threshold condition for coexistence, now equivalent to a threshold condition for sensitive TB endemicity in a population where resistant strains are at equilibrium, $R_{0s}(E_r) = 1$: only resistant TB persists for $R_{0s}(E_r) < 1$, while for $R_{0s}(E_r) > 1$ sensitive strains can invade a population where resistant strains are fixed, that is, to say coexistence is possible.

Theorem 3 below expresses this result in terms of stability for the equilibrium E_r. The proof is in Appendix A.3.

Theorem 3. *If $R_{0r} > 1$ the equilibrium E_r of system* (1) *is stable for $R_{0s}(E_r) < 1$ and unstable for $R_{0s}(E_r) > 1$.*

Remark 2. The curve that defines the coexistence region is given by the following relation (see Fig. 4):

$$R_{0s}(E_r) = 1 \Longleftrightarrow \beta_s = f(\beta_r) = \frac{(\mu + \sigma\beta_r I_r^r)(\mu + \delta + \tau_s) + \omega(\mu + \delta + \gamma\tau_s)}{S^r(\phi(\mu + \sigma\beta_r I_r^r) + \omega)}. \quad (3)$$

Remark 3. Numerical results support that below the curve defined by f in the (R_{0s}, R_{0r})-space both types of strains will persist.

Relation (3) reveals that persistence of sensitive strains depends on the reinfection process. The expression of $R_{0s}(E_r)$ is similar to that for R_{0s} in (2) with an additional term, $\sigma\beta_r I_r^r$. This term corresponds to ~~reinfection~~ by resistant strains of latent individuals infected with sensitive TB. Contrasting with the case where reinfection is not considered, $\sigma = 0$ (dotted line in Fig. 4), reveals that persistence of only resistant strains is now possible even when these have lower transmissibility $R_{0r} < R_{0s}$. Coexistence is no longer governed solely by the invasion capacities of each strain (R_{0s} and R_{0r}) but also by the ability of sensitive strains to overcome the reinfection pressure exerted by resistant strains. In particular, our results can be compared to the analysis of Blower and Gerberding (1998) (see Fig. 2 and Table 1 within), which does not consider reinfection. The model developed by

these authors has the same possible outcomes (I,II,III) but these are fully determined by a linear relation between pathogen fitness as measured by the respective R_0: disease eradication (I) if $R_{0s}<1$ and $R_{0r}<1$; persistence of only resistant TB (II) if $R_{0r}>1$ and $R_{0r}>R_{0s}$; of both drug sensitive and drug-resistant TB (III) if $R_{0s}>1$ and $R_{0s}>R_{0r}$.

3.5. Limit case: $\gamma = 0$

The limit case $\gamma = 0$ is equivalent to assuming that there is no acquisition of drug resistance through treatment failure. Analysis of this limit case reveals regions where the elimination of drug-resistant strains may result from prevention of acquired resistance alone.

For $\gamma = 0$, the system has three non-trivial equilibria corresponding to the presence of each type of strains alone and coexistence (Fig. 4(b)). The existence of the first two is given by Theorem 4, stated below and proved in Appendix A.4.

Theorem 4. *For $\gamma = 0$, system (1) has exactly two non-trivial boundary equilibria: $E_r = (S^r, 0, L_r^r, 0, I_r^r)$ for $R_{0r}>1$ and $E_s = (S^s, L_s^s, 0, I_s^s, 0)$ for $R_{0s}>1$.*

Two coexistence thresholds must be calculated: the first separates the region where only sensitive TB persists from the region of coexistence; the second marks the shift from coexistence to persistence of resistant TB alone.

Regarding the second threshold, it can be verified that the threshold condition is the same as when $\gamma>0$, i.e., $R_{0s}(E_r) = 1$. Moreover, the stability results pertaining the equilibrium E_{sr} (Theorem 3) can be extended to the case $\gamma = 0$. To compute the first threshold we use the same reasoning as before. We consider resistant TB as the phenotype invading a population where sensitive TB is already endemic. Then, $E_s = (S^s, L_s^s, 0, I_s^s, 0)$ corresponds to the equilibrium free of resistant TB. In this case the coexistence threshold is given by

$$R_{0r}(E_s) = \frac{(S^s + \sigma L_s^s)\beta_r(\phi\mu + \phi\sigma\beta_s I_s^s + \omega)}{(\mu + \phi\sigma\beta_s I_s^s + \omega)(\mu + \delta + \tau_r) - (\omega + \phi\sigma\beta_s I_s^s)\tau_r} = 1$$

as derived in Appendix A.4. Resistant strains can invade a population where sensitive strains are fixed when $R_{0r}(E_s)>1$.

The corresponding result for the stability of the boundary equilibrium is expressed by Theorem 5, stated below and proved in Appendix A.4.

Theorem 5. *Consider system (1) with $\gamma = 0$. When $R_{0r}>1$, the equilibrium E_r is stable if $R_{0s}(E_r)<1$ and unstable if $R_{0s}(E_r)>1$. When $R_{0s}>1$, the equilibrium E_s is stable for $R_{0r}(E_s)<1$ and unstable for $R_{0r}(E_s)>1$.*

Again we emphasise the dependence of the coexistence threshold on reinfection. Susceptible and latent individuals infected with sensitive strains are susceptible to (re)infection with resistant strains at rates $\beta_r I_r$ (infection) and $\sigma\beta_r I_r$ (superinfection), respectively. The result is the non-linear curve in Fig. 4(b).

4. Fitness impact on the coexistence region

Drug resistance among *M. tuberculosis* isolates is caused by point mutations in the bacterial genome that affect anti-mycobacterial drug activity. If a mutation that confers drug resistance can exert a cost to the parasite we may expect these strains to be less transmissible than the drug sensitive. To explore the epidemiological consequences of resistance cost we fix the relative transmission coefficient, $\alpha = \beta_r/\beta_s$, and explore the system behaviour by varying a parameter β such that

$$\beta_s := \beta, \quad \beta_r := \alpha\beta.$$

As such, $\alpha<1$ means that the resistant strains have lower transmissibility than the sensitive. Despite being less likely, the possibility $\alpha>1$ is also considered since this topic is still open to discussion (Cohen et al., 2003; Gagneux et al., 2006). Fig. 5 shows the bifurcation diagrams obtained for two values of α. When $\alpha = 0.5$ (full line) low values of β_s lead to coexistence, but only resistant strains persist for high rates of transmission, where reinfection prevails. In this scenario it is possible to induce coexistence of sensitive and resistant strains by reducing the disease transmission rate. In turn, coexistence improves the chance of controlling drug-resistance prevalence. For $\alpha = 1.1$ (dashed line) β_s and β_r lie in regions I and II thus, only resistant strains may persist.

We derive a critical value for α below which a reduction in the overall transmission can open the possibility for coexistence:

$$\alpha_C = \frac{\mu(\mu + \delta + \tau_r) + \omega(\mu + \delta)}{\mu(\mu + \delta + \tau_s) + \omega(\mu + \delta + \gamma\tau_s)}.$$

Note that, for the choice of parameters as in Table 1, $\alpha_C \approx 0.7745<1$ (dotted line in Fig. 5(a)). The critical value α_C will be later used to compare the impact of different control measures on the coexistence region.

In the case illustrated by $\alpha = 0.5$, as the transmission coefficient, β, increases, the system evolves from dominance of the sensitive strain to dominance of the resistant. This can be interpreted as follows. The minimal transmissibility above which resistant strains can be sustained in the population where sensitive strains are endemic, without the contribution of acquired resistance ($\gamma = 0$), is given by the condition $R_{0r}(E_s) = 1$. This marks a threshold in transmission above which superinfection of sensitive by resistant strains occurs. This superinfection threshold is marked in Fig. 6. Below the threshold, resistant strains are outcompeted by the sensitive due to the higher transmission coefficient of the latter (recall that $\alpha<1$). In this regime, resistant cases can only be maintained due to acquired resistance ($\gamma>0$).

Disease prevalence exhibits a new steep increase, for sufficiently high transmission rates. This is given by the

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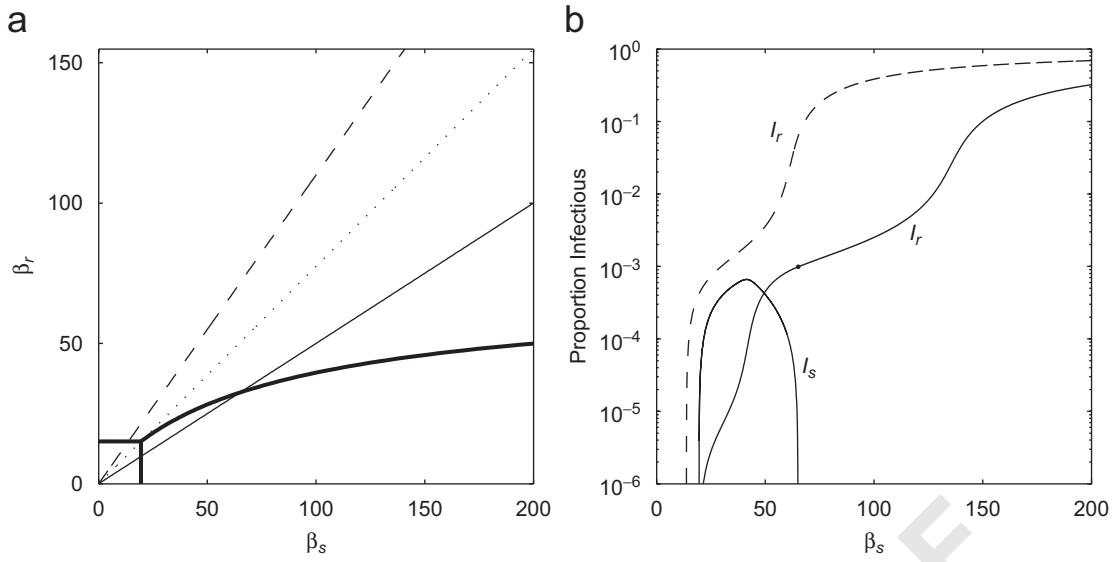

Fig. 5. Decreased transmission: (a) Bifurcation diagram: Straight lines correspond to $\beta_r = \alpha\beta_s$ for different values of α : $\alpha = 1.1$ dashed line, $\alpha = 0.5$ full line, and $\alpha = \alpha_C$ dotted line. (b) Corresponding equilibrium curves: $\alpha = 1.1$ dashed line, $\alpha = 0.5$ full lines (only stable equilibria represented).

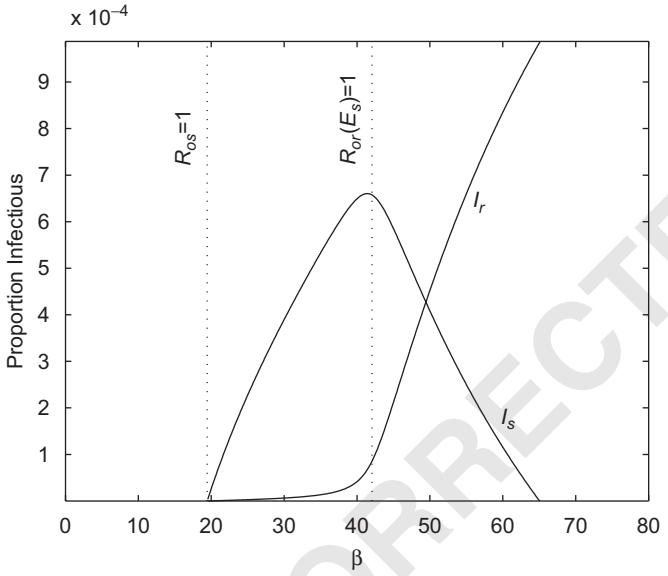

Fig. 6. Equilibrium curves for $\alpha = 0.5$ (linear scale). The vertical dotted lines mark the epidemic threshold of sensitive strains and the super-infection threshold of resistant strains.

reinfection threshold for the resistant strains, ~~RT_r~~, and marks the shift in dominance from primary infections to reinfections. Since sensitive strains are no longer circulating in the population, this threshold is simply $R_{0r} = 1/\sigma$ (with $\omega = 0$, see Gomes et al., 2006, for a derivation).

5. Model extensions—mixed infections

In the model presented in Section 2 we assumed that active TB resulting from a mixed infection would always express the resistant phenotype. Now we relax this assumption by also allowing individuals with a mixed infection to progress to sensitive TB (scenario (ii) in Section 2.3). Molecular studies suggest several possible outcomes for mixed infections (van Rie et al., 2004): sensitive TB may develop in untreated individuals carrying mixed infections due to the faster replication of sensitive strains; sensitive strains may prevail when treatment matches drug regimen to the resistance pattern specific to each case; resistant strains may emerge when treating with first line anti-tuberculosis drugs. Moreover, fitness trade-offs may favour sensitive strains when competition takes place during the latent stage but, this will only have impact on transmission once individuals progress to the disease stage. Although the possible outcomes we describe here are intuitive and expected, they are the product of different and complex mechanisms. These mechanisms are still, quantitatively and qualitatively, unclear from the molecular point of view.

We extend the two-strain model by introducing a mixed latent class, L_m, representing the proportion of individuals with a latent infection that combines both resistant and sensitive strains—mixed infection. When individuals with mixed infections progress to active TB, either by endogenous reactivation or exogenous reinfection, a fraction θ will manifest resistant TB entering I_{mr} while the remainder will develop sensitive TB progressing into I_{ms}. The model is represented diagrammatically by Fig. 7 and corresponds to the system of equations:

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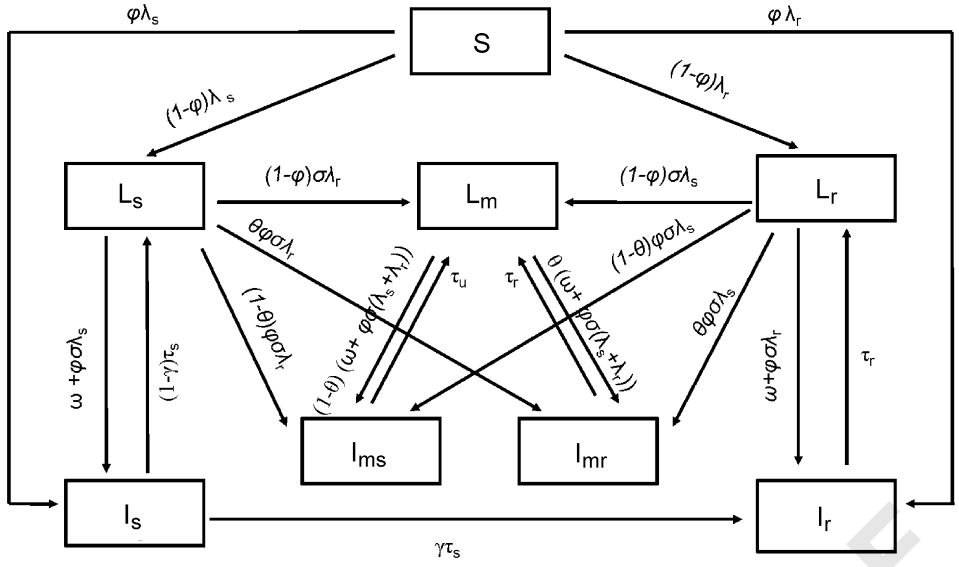

Fig. 7. Mixed infections model.

$$
\begin{cases}
\dfrac{dS}{dt} = b - (\lambda_s + \lambda_r + \mu)S, \\
\dfrac{dL_s}{dt} = (1-\phi)\lambda_s S - (\omega + \phi\sigma\lambda_s + \sigma\lambda_r + \mu)L_s + (1-\gamma)\tau_s I_s, \\
\dfrac{dI_s}{dt} = \phi\lambda_s S + (\omega + \phi\sigma\lambda_s)L_s - (\tau_s + \mu + \delta)I_s, \\
\dfrac{dL_m}{dt} = (1-\phi)\sigma\lambda_r L_s - (\omega + \phi\sigma(\lambda_s + \lambda_r) + \mu)L_m \\
\qquad + \tau_s I_{ms} + \tau_r I_{mr} + (1-\phi)\sigma\lambda_s L_r, \\
\dfrac{dI_{ms}}{dt} = (1-\theta)\phi\sigma\lambda_r L_s + (1-\theta)(\omega + \phi\sigma(\lambda_s + \lambda_r))L_m \\
\qquad - (\tau_s + \mu + \delta)I_{ms} + (1-\theta)\phi\sigma\lambda_s L_r, \\
\dfrac{dI_{mr}}{dt} = \theta\phi\sigma\lambda_r L_s + \theta(\omega + \phi\sigma(\lambda_s + \lambda_r))L_m \\
\qquad -(\tau_r + \mu + \delta)I_{mr} + \theta\phi\sigma\lambda_s L_r, \\
\dfrac{dL_r}{dt} = (1-\phi)\lambda_r S - (\omega + \sigma\lambda_s + \phi\sigma\lambda_r + \mu)L_r + \tau_r I_r, \\
\dfrac{dI_r}{dt} = \phi\lambda_r S + \gamma\tau_s I_s + (\omega + \phi\sigma\lambda_r)L_r - (\tau_r + \mu + \delta)I_r,
\end{cases}
\tag{4}
$$

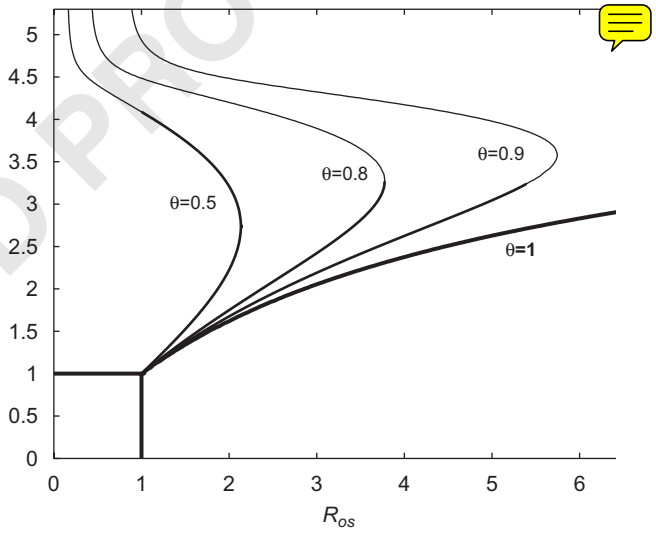

Fig. 8. Long-term epidemiological outcome: bifurcation diagram on R_{0s} and R_{0r}. Curves separate coexistence region from persistence of only resistant strains for different values of parameter θ. For $\theta = 1$ we have the same curve as in Fig. 4.

where $\lambda_s = \beta_s(I_s + I_{ms})$ and $\lambda_r = \beta_r(I_r + I_{mr})$ represent the force of infection of the two types of TB. The parameters are the same as before with exception of θ and the birth rate, b, that we consider in such a way that the population size is constant over time, so $b = \mu + \delta(I_s + I_{ms} + I_r + I_{mr})$. Parameter θ summarises all mechanisms that determine the prevailing strain in a mixed infection. It can be varied to explore different scenarios, depending on the relative contribution of each mechanism to the overall situation. Note that with $\theta = 1$ we recover the two-strain model presented in Section 2.

Fig. 8 shows the long-term behaviour of the mixed infection model when we change parameter θ. Notably, the coexistence region increases as the percentage of mixed infections that progress to sensitive active-TB increases. The limit case ($\theta = 1$) is, in fact, the worst case scenario. Moreover, coexistence again depends on the transmission coefficients of both types of strains in a non-linear manner.

A more subtle result is that coexistence is possible for high transmission levels of drug-resistant strains even when sensitive strains have low transmissibility. This is related to the assumption that individuals never succeed in fully clearing TB bacteria and therefore, mixed infections are very frequent when either or both strains are highly transmissible. Under the current assumption, a fraction $\theta(<1)$ of these infections will progress to resistant TB and the remaining will progress to sensitive TB, thus forcing

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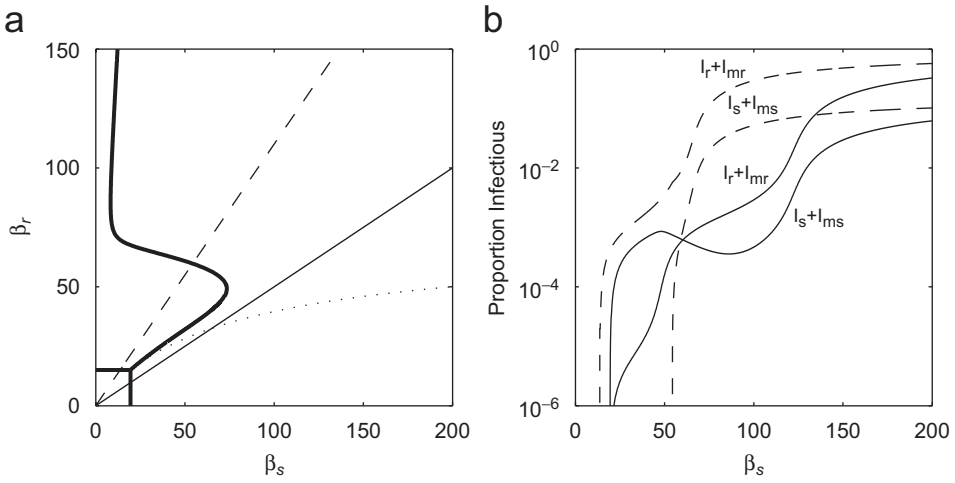

Fig. 9. Mixed infections case $\theta = 0.8$: (a) Bifurcation diagram: straight lines correspond to $\beta_r = \alpha\beta_s$ for different values of α : $\alpha = 1.1$ dashed line, $\alpha = 0.5$ full line. Dotted line corresponds to $\theta = 1$. (b) Corresponding equilibrium curves: $\alpha = 1.1$ dashed line, $\alpha = 0.5$ full lines (only stable equilibria represented).

coexistence. In contrast, all mixed infections will develop into resistant TB when $\theta = 1$.

Let us again explore what happens when the transmission rate of resistant and sensitive strains have a linear association: $\beta_r = \alpha\beta_s$. Parameter α thus expresses the impact of resistance on pathogen fitness. In Fig. 9(a) straight lines exemplify two contrasting cases: drug resistance has an associated cost ($\alpha = 0.5$, full lines) or resistant strains have a higher transmission rate ($\alpha = 1.1$, dashed lines). When $\alpha = 0.5$, resistant and sensitive strains coexist for all possible values of β_s. If transmission (β_s) increases, resistant strains start to dominate. But inversely to the case $\theta = 1$ (two-strain model) this does not drive sensitive strains to extinction because some mixed infections develop sensitive cases (compare Fig. 9(b) with Fig. 5(b), full lines). Above a certain transmission level, mixed infections represent almost the totality of TB infections, and the proportionof resistant TB in the total TB burden is then driven by θ.

6. Control strategies

The World Health Organization (WHO) has two major control programs for TB: DOTS, Directly Observed Treatment Short-course, consisting of standardised short-course treatment of TB cases given under direct obsrvation to ensure treatment adequacy and compliance; and DOTS-plus, an extension of DOTS specifically designed for controlling multi-drug resistant TB. DOTS-plus uses more effective, but also more expensive and toxic drugs. It is not always clear what should be the strategy of choice to manage resistant TB in a given setting (Dye et al., 2002; Pablos-Méndez et al., 2002): is DOTS enough or should it be extended to DOTS-plus?

Knowing that reinfection can have strong consequences on the effectiveness of interventions (Gomes et al., 2004) we explore how our model behaves under these two strategies. These control measures are designed to fight different processes: DOTS prevents the acquisition of resistance due to treatment failure by ensuring compliance; whereas DOTS-plus reduces transmission of resistant strains by adapting the treatment regimen to better suit resistant cases. Therefore, we model DOTS by reducing the proportion of failed treatments that leads to acquired resistance, i.e., lowering γ. DOTS-plus is modelled by reducing the time during which individuals infected with resistant strains are infectious, i.e., increasing the rate of recovery from active disease with resistant strains, τ_r.

We will focus on the case $\theta = 1$ which corresponds to the two-strain TB model (1). However, the mixed-infection model has similar results as we will discuss.

6.1. Coexistence region

In Section 4 we fixed $\alpha = \beta_r/\beta_s$ and described a trend of strain coexistence at low transmission and dominance of the resistant strain at high transmission. This trend is verified when α is below a critical value, α_C. Above this critical value, resistance is always dominant irrespective of the transmission intensity. Therefore, the impact of control strategies on α_C gives an indication of its effect on the extent of the coexistence region. We evaluate the sensitivity and elasticity of α_C to the two parameters, γ and τ_r, manipulated by DOTS and DOTS-plus, respectively. Using the terminology from mathematical demography in (Caswell, 2001), we introduce the partial derivatives

$$s_p = \frac{\partial \alpha_C}{\partial p} \quad \text{and} \quad e_p = \frac{p}{\alpha_C}\frac{\partial \alpha_C}{\partial p} = \frac{\partial \ln \alpha_C}{\partial \ln p}$$

to define, respectively, the sensitivity and elasticity of α_C to a parameter p, where p is γ or τ_r. Note that, since equal increments on a logarithmic scale correspond to equal proportions on an arithmetic scale, we can say that elasticity measures proportional sensitivity.

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Table 2
Sensitivity and elasticity of α_C to γ and τ_r

p	Initial value (1)	Change $\frac{1}{3}$ (2)	Sensitivity (3)	Elasticity (4)	Abs. variation in α_C (5) $\approx$ (2) · (3)	New α_C $\alpha_C + (5)$	% Variation in α_C $\frac{(2)}{(1)} \cdot (4) \cdot 100$
γ	0.003	−0.001	−0.0098	-3.7883×10^{-5}	9.7797×10^{-6}	0.7745	0.0013
τ_r	1.5	0.5	0.4510	0.8735	0.2255	1.0000	29.1157

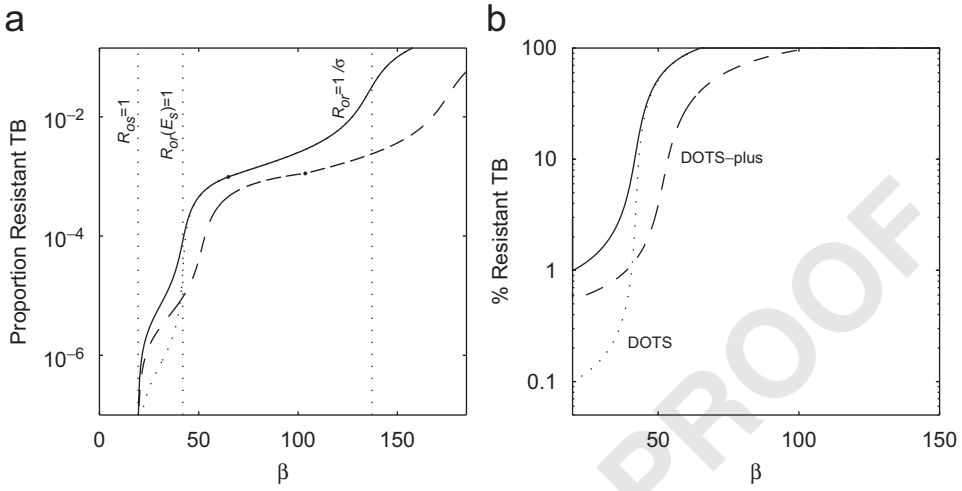

Fig. 10. Impact of different control measures on resistant TB (case with $\alpha = 0.5$): (a) Proportion of resistant TB in total population; (b) Percentage of resistant phenotype in total TB cases. Full line corresponds to baseline proportion (no intervention), dotted line represents a DOTS like intervention ($\gamma = 0.0003$) and dashed line represents a DOTS-plus like intervention ($\tau_r = 2$).

Table 2 shows the sensitivities and elasticities of α_C to changes in γ and τ_r for the case of $\frac{1}{3}$ of change in each parameter. Both changes increase α_C which implies an improvement on conditions to coexistence. Elasticity is approximately -3.7883×10^{-5} for γ and 0.8735 for τ_r, corresponding to a variation of approximately 0.001% and 29%, respectively. Thus, for the case of γ the improvement is almost undetectable.

More generally, we can compare the elasticity of α_C to the two parameters γ and τ_r, by looking to the quotient between absolute value of the elasticities:

$$\left|\frac{e_{\tau_r}}{e_\gamma}\right| = \frac{\mu\tau_r}{\omega\tau_s\gamma}\frac{1}{\alpha_C}. \quad (5)$$

Since the rate of endogenous reactivation of latent TB, ω is several orders of magnitude smaller than the death rate, μ, the rates of recovery under treatment, τ_r and τ_s are of the same order of magnitude and $\gamma\alpha_C$ is small, we conclude that the quotient is greater than one.

These results show that α_C is more sensitive to changes in the infectious period than in the proportion of sensitive TB treatment failure acquiring resistance. Therefore, the impact on the coexistence region is greatest for the DOTS-plus strategy.

6.2. Prevalence of infection

A complementary way to assess the effectiveness of the two control measures is to compare the equilibrium prevalence of resistant TB before and after the intervention. Interventions affect both the prevalence of resistant active TB cases in the population and the percentage of active TB cases that carry the resistant phenotype (Fig. 10(a) and (b), respectively).

DOTS-plus like interventions decrease not only the percentage of resistant TB in the coexistence region but also the overall prevalence of drug-resistant strains at all transmission potentials. As the results of the sensitivity analysis suggest, DOTS-plus can significantly increase the coexistence region which, by itself, inhibits the transmission of resistance due to strain competition. Moreover, this control strategy, shifts to the right the superinfection and reinfection thresholds of resistant strains ($R_{0r}(E_s) = 1$ and $R_{0r} = 1/\sigma$) delaying the predominance of drug resistance (see Fig. 10(b)).

We can also observe that a DOTS like intervention has impact at low transmissibility. In fact, Fig. 10(a) shows that DOTS is not effective above the superinfection threshold of resistant strains, $R_{0r}(E_s) = 1$. As we have stressed before, above this threshold the sensitive strains start to decline and the resistant strains become dominant. Therefore, any

intervention that depends on the incidence of sensitive TB, I_s, has negligible impact. Indeed, above the superinfection threshold, the contribution of acquired drug resistance through treatment failure ($\gamma\tau_s I_s$) is minimum compared to cases caused by transmission of resistant strains. When the transmission potential is below this threshold, on the contrary, DOTS is the most effective strategy, both in relative and absolute terms. Moreover, in the limit case $\gamma = 0$, system (1) has another equilibrium, E_s, corresponding to the presence of only sensitive TB. Below the superinfection threshold of resistant strains, i.e., for $R_{0r}(E_s) < 1$, this equilibrium is stable (region IV in Fig. 4 (b)). This means that if acquired drug resistance could be completely blocked ($\gamma = 0$) drug-resistant strains would be eradicated.

The control strategies modelled here have the same qualitative outcome in the mixed infection model as in the particular case $\theta = 1$. DOTS causes a decrease in resistant TB prevalence only below the superinfection threshold of resistant strains, whereas DOTS-plus forces a decrease in resistant TB prevalence for all endemic scenarios (results not shown).

Consequently, DOTS-plus may benefit regions of high endemic prevalence where infection with resistant strains wipes out the impact of DOTS. By contrast, DOTS is only effective for low endemic settings and in such scenarios it is, in fact, more suitable than DOTS-plus.

7. Discussion

By using simple models with reinfection we describe how thresholds in transmission shape the conditions for coexistence of resistant and sensitive TB strains and how this affects resistant TB prevalence and control.

First, we assumed that individuals carrying at least one resistant strain always manifest and transmit resistant TB. This simplification is justifiable by the fact that standard regimens confer a selection advantage to resistant strains, while the availability of treatment regimens that are recommended to combat resistance is limited. However, other possibilities can and should be considered. In van Rie et al. (2004), the authors conclude that treatment and adherence determine which strains are dominant in a mixed infection with sensitive and resistant strains. They find that treatment with second-line drugs leads to re-emergence of drug-sensitive strains. Furthermore, within-host competition may also favour drug-sensitive strains during latency.

We extended the first model by implementing two alternative progressions of mixed infections into active disease: a proportion θ activates resistant TB; while the remaining $(1-\theta)$ activates sensitive TB. When $\theta = 1$ (original model) coexistence is only observed at low transmissibility. By contrast, when $\theta < 1$ (mixed infection model) coexistence extends to higher transmissibility. A reinfection threshold marks the endemic level above which the majority of individuals harbour mixed infections. The fact that mixed infections can result in sensitive or resistant active infections, favours coexistence.

The results obtained are significantly different from those found in models where reinfection is not considered (Blower and Gerberding, 1998; Dye et al., 2002). For R_0 near 1, the system is governed by primary transmission and coexistence is only possible when resistant strains are comparatively less transmissible (Austin et al., 1997; Boni and Feldman, 2005). However, as we move away from $R_0 = 1$ reinfection starts to play a greater role. When the majority of individuals harbour mixed infections, the outcome of within-host competition shapes the frequency of resistance in the population and may sustain coexistence in the community.

The mechanisms that determine which phenotype prevails in mixed infections (during latency or active disease) are still poorly understood. And even if different pathways have been described (van Rie et al., 2004), little is known about their frequency in the population. More epidemiological studies are needed to clarify this issue so that explicit, detailed models can be constructed and used to explore different interventions.

Reinfection also has implications on the effectiveness of different control strategies. A DOTS like intervention is ineffective against resistance in regions where primary resistance is common—above the superinfection threshold by resistant strains. It is precisely in those populations that a switch from DOTS to DOTS-plus can have the greatest impact. However, DOTS should continue to be the strategy of choice in populations where superinfection is rare. Even though DOTS and DOTS-plus interventions are much more complex than considered here, our work already highlights fundamental differences in outcome between the two strategies. Although coexistence results for $\theta = 1$ differ from those obtained with $\theta < 1$, results concerning intervention efficacy are qualitatively the same.

In conclusion, primary resistance plays a fundamental role on the outcome of competition between sensitive and resistant strains in the host population. The strategy of choice to counteract the spread of resistance depends critically on the superinfection threshold of resistant strains.

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Appendix A

Numeric calculations and some analytical manipulations were obtained using MATLAB 6.5®. Equilibrium curves were computed with MATCONT continuation package of MATLAB 6.5® (Dhooge et al., 2003).

A.1. Calculation of the basic reproduction number for system (1)

In order to compute the basic reproduction number it is important to distinguish new infections from all other class transitions in population. The infected classes are L_s, L_r, I_s and I_r. Following van den Driessche and Watmough (2002), we can write system (1) as

$$\dot{X} = f(X) \Leftrightarrow \dot{X} = \mathscr{F}(X) - \mathscr{V}(X) = \mathscr{F}(X) - (\mathscr{V}^-(X) - \mathscr{V}^+(X)), \tag{6}$$

where $X = (L_s, L_r, I_s, I_r, S)$, $\mathscr{F}$ is the rate of appearance of new infections in each class; $\mathscr{V}^+$ is the rate of transfer into each class by all other means and $\mathscr{V}^-$ is the rate of transfer out of each class. Hence,

$$\mathscr{F} = ((1-\phi)\beta_s I_s S, (1-\phi)\beta_r I_r S, \phi\beta_s I_s S, \phi\beta_r I_r S, 0)^{\mathrm{T}},$$

and the disease-free equilibrium is $X_0 = (0,0,0,0,1)$.

Derivatives $D\mathscr{F}(X_0)$ and $D\mathscr{V}(X_0)$ can be partitioned as

$$D\mathscr{F}(X_0) = \begin{bmatrix} F & 0 \\ 0 & 0 \end{bmatrix}, \quad D\mathscr{V}(X_0) = \begin{bmatrix} V & 0 \\ J_3 & J_4 \end{bmatrix},$$

where F and V correspond to the derivatives of $\mathscr{F}$ and $\mathscr{V}$ with respect to the infected classes:

$$F = \begin{bmatrix} 0 & 0 & (1-\phi)\beta_s & 0 \\ 0 & 0 & 0 & (1-\phi)\beta_r \\ 0 & 0 & \phi\beta_s & 0 \\ 0 & 0 & 0 & \phi\beta_r \end{bmatrix}, \quad V = \begin{bmatrix} \mu+\omega & 0 & -(1-\gamma)\tau_s & 0 \\ 0 & \mu+\omega & 0 & \tau_r \\ -\omega & 0 & \mu+\delta+\tau_s & 0 \\ 0 & -\omega & \gamma\tau_s & \mu+\delta+\tau_r \end{bmatrix}.$$

The basic reproduction number is defined, following van den Driessche and Watmough (2002), as the spectral radius of the next generation matrix, FD^{-1}:

$$R_0 = \max\{R_{0s}, R_{0r}\},$$

where R_{0s} and R_{0r} are the two eigenvalues:

$$R_{0s} = \frac{\beta_s(\omega+\phi\mu)}{(\mu+\omega)(\mu+\delta+\tau_s)-(1-\gamma)\tau_s\omega} \quad \text{and} \quad R_{0r} = \frac{\beta_r(\omega+\phi\mu)}{(\mu+\omega)(\mu+\delta+\tau_r)-\tau_r\omega}.$$

A.2. Disease-free equilibrium

Proof of Theorem 1. By Theorem 2 in van den Driessche and Watmough (2002) it is sufficient to prove conditions:

(A1) if $X \geqslant 0$, then $\mathscr{F}, \mathscr{V}^+, \mathscr{V}^- \geqslant 0$,
(A2) if $X_i = 0$ then $\mathscr{V}_i^- = 0$ (where i refers to a vector component),
(A3) $\mathscr{F}_i = 0$ for the components that correspond to uninfected classes,
(A4) if X^* is a disease-free equilibrium then $\mathscr{F}_i(X^*) = 0$ and $\mathscr{V}_i^+(X^*) = 0$ for the components that correspond to uninfected classes,
(A5) if $\mathscr{F}$ is set to zero then all eigenvalues of $Df(X_0)$ have negative real parts.

The verification of (A1)–(A4) is straightforward.

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The Jacobian of f at X_0 with $\mathscr{F}$ set to zero, as

$$Df_{(\mathscr{F}=0)}(X_0) = \begin{bmatrix} -(\omega+\mu) & 0 & (1-\gamma)\tau_s & 0 & 0 \\ 0 & -(\omega+\mu) & 0 & \tau_r & 0 \\ \omega & 0 & -(\mu+\delta+\tau_s) & 0 & 0 \\ 0 & \omega & \gamma\tau_s & -(\mu+\delta+\tau_r) & 0 \\ 0 & 0 & \delta-\beta_s & \delta-\beta_r & -\mu \end{bmatrix}.$$

The eigenvalues are: $-\mu$ and the solutions of equation

$$p_1(\lambda)p_2(\lambda) = 0,$$

where $p_1(\lambda) = \lambda^2 - a_1\lambda + a_0$ and $p_2(\lambda) = \lambda^2 - b_1\lambda + b_0$ and

$$-a_1 = 2\mu + \delta + \tau_r + \omega,$$

$$a_0 = \mu(\mu+\delta+\tau_r) + \omega(\mu+\delta),$$

$$-b_1 = 2\mu + \delta + \tau_s + \omega,$$

$$b_0 = \mu(\mu+\delta+\tau_s) + \omega(\mu+\delta+\gamma\tau_s).$$

Since $-a_1, a_0$ and $-b_1, b_0$ are positive, all eigenvalues have negative real part and the result follows. □

A.3. Boundary and coexistence equilibria

Proof of Theorem 2. From the first, second and third equations of system (1) at equilibrium, we get a relation between S, L_s, L_r and I_s, I_r:

$$S = \frac{\mu+\delta I_s+\delta I_r}{\mu+\beta_s I_s+\beta_r I_r} = F(I_s, I_r),$$

$$L_s = I_s\frac{(1-\phi)\beta_s S+(1-\gamma)\tau_s}{\mu+\omega+\phi\sigma\beta_s I_s+\sigma\beta_r I_r} = I_s\frac{(1-\phi)\beta_s F(I_s,I_r)+(1-\gamma)\tau_s}{\mu+\omega+\phi\sigma\beta_s I_s+\sigma\beta_r I_r} = G(I_s,I_r)I_s,$$

$$L_r = I_r\frac{(1-\phi)\beta_r(S+\sigma L_s)+\tau_r}{\mu+\omega+\phi\sigma(\beta_s I_s+\beta_r I_r)} = I_r\frac{(1-\phi)\beta_r(F(I_s,I_r)+\sigma G(I_s,I_r)I_s)+\tau_r}{\mu+\omega+\phi\sigma(\beta_s I_s+\beta_r I_r)} = H(I_s,I_r)I_r.$$

Suppose that $I_s = 0$ (and subsequently $L_s = 0$). If I_r is non-zero, from the fifth equation of system (1) we get

$$\phi\beta_r F(0,I_r) + (\omega+\phi\sigma\beta_r I_r)H(0,I_r) - (\mu+\delta+\tau_r) = 0. \tag{7}$$

We can write this as follows:

$$\frac{P(I_r)}{Q(I_r)} = 0,$$

where P and Q are polynomials of second degree such that

$$Q(I_r) = (\mu+\beta_r I_r)(\mu+\omega+\phi\sigma\beta_r I_r) > 0,$$

$$P(I_r) = \mu(p_2(\beta_r)I_r^2 + p_1(\beta_r)I_r + p_0(\beta_r)),$$

where

$$p_2(\beta_r) = -\phi\sigma\beta_r^2 < 0,$$

$$p_1(\beta_r) = \phi\sigma\beta_r^2 - (\tau_r+\omega+\mu+(1-\phi)\delta+\phi\sigma(\mu+\delta))\beta_r,$$

$$p_0(\beta_r) = \beta_r(\omega+\phi\mu) - (\mu(\mu+\tau_r+\delta)+\omega(\mu+\delta)).$$

If

$$\beta_r > \frac{\mu(\mu+\delta+\tau_r)+\omega(\mu+\delta)}{\phi\mu+\omega} \iff R_{0r} > 1,$$

then $p_0(\beta_r) > 0$ and we have exactly one positive solution of $P(I_r)$.

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If

$$\beta_r \leqslant \frac{\mu(\mu+\delta+\tau_r)+\omega(\mu+\delta)}{\phi\mu+\omega} \Leftrightarrow R_{0r} \leqslant 1,$$

then $p_0(\beta_r) \leqslant 0$ but also $p_1(\beta_r) \leqslant 0$, since $0<\phi,\sigma<1$. So there are no positive solutions of $P(I_r)$. □

A.3.1. Calculation of the coexistence threshold when $\gamma>0$

Consider the case only when the sensitive TB is transmissible, in a population where resistant TB is at equilibrium. The infected compartments are L_s and I_s. Following van den Driessche and Watmough (2002), we write system (1) as in (6) where $X=(L_s, I_s, S, L_r, I_r)$ and

$$\mathscr{F} = ((1-\phi)\beta_s I_s S,\ \phi\beta_s I_s S, 0, 0, 0)^{\mathrm{T}}.$$

The disease (sensitive-TB)-free equilibrium is $(0, 0, S^r, L_r^r, I_r^r)$.

We can compute F and V that correspond to the derivatives at X_0 with respect to the infected classes of $\mathscr{F}$ and $\mathscr{V}$, respectively:

$$F = \begin{bmatrix} 0 & (1-\phi)\beta_s \\ 0 & \beta_s \end{bmatrix}, \quad V = \begin{bmatrix} \mu+\omega+\sigma\beta_r I_r^r & -(1-\gamma)\tau_s \\ -\omega & \mu+\delta+\tau_s \end{bmatrix}.$$

The basic reproduction number of the sensitive strains in a population where resistant strains are fixed is then the spectral radius of the next generation matrix, FV^{-1}:

$$R_{0s}(E_r) = \frac{S^r\beta_s(\phi(\mu+\sigma\beta_r I_r^r)+\omega)}{(\mu+\sigma\beta_r I_r^r+)(\mu+\delta+\tau_s)-(1-\gamma)\tau_s\omega}.$$

Remark 4. *Note that this is still valid for $R_{0r}<1$. In this case the disease-free equilibrium is $E_0=(1,0,0,0,0)$ and we restore the endemicity threshold.*

Proof of Theorem 3. By Theorem 2 in van den Driessche and Watmough (2002) it is sufficient to prove conditions (A1)–(A5). Once more, conditions (A1)–(A4) are of trivial verification. To prove the remaining condition (A5) we write the Jacobian of f at X_0, with $\mathscr{F}$ set to zero, ordering coordinates as (S, L_r, I_r, L_s, I_s). Then, the Jacobian has the form

$$Df_{(\mathscr{F}=0)}(S^r, L_r^r, I_r^r, 0, 0) = \begin{bmatrix} G_1 & G_2 \\ 0 & G_4 \end{bmatrix},$$

where

$$G_1 = \begin{bmatrix} -(\mu+\beta_r I_r^r) & 0 & \delta-\beta_r S^r \\ (1-\phi)\beta_r I_r^r & -(\mu+\omega+\phi\sigma\beta_r I_r^r) & (1-\phi)\beta_r S^r-\phi\sigma\beta_r L_r^r+\tau_r \\ \phi\beta_r I_r^r & \omega+\phi\sigma\beta_r I_r^r & \phi\beta_r(S^r+\sigma L_r^r)-(\mu+\delta+\tau_r) \end{bmatrix}$$

and

$$G_4 = \begin{bmatrix} -(\mu+\omega+\sigma\beta_r I_r^r) & (1-\gamma)\tau_s \\ \omega & -(\tau_s+\mu+\delta) \end{bmatrix}.$$

Therefore, the eigenvalues of the Jacobian are given by the eigenvalues of G_1 and G_4.

For G_1 the eigenvalues are $-\mu$ and the roots of the polynomial

$$p_1(\lambda) = (\lambda^2 - a_1\lambda + a_0)$$

where

$$-a_1 = -(\phi S^r+\phi\sigma L_r^r)\beta_r + (1+\phi\sigma)I_r^r\beta_r + (2\mu+\delta+\tau_r+\omega),$$

$$a_0 = \phi\sigma\beta_r^2 I_r^{r2} + [-\phi\sigma\beta_r^2(S^r+L_r^r)+\beta_r(\tau_r+\omega+\mu+(1-\phi)\delta + \phi\sigma(\mu+\delta))]I_r^r + \mu(\mu+\delta+\tau_r)+\omega(\mu+\delta)-\beta_r((\omega+\phi\mu)S^r-\phi\sigma\mu L_r^r).$$

From equation five of system (1) at the equilibrium E_r we get

$$(\phi S^r+\phi\sigma L_r^r)\beta_r I_r^r = (\mu+\delta+\tau_r)-\omega L_r^r$$

so $-a_1 I_r^r = \omega L_r^r + (\mu+\omega)I_r^r + (1+\phi\sigma)I_r^{r2}\beta_r > 0$. Since $I_r^r>0$, $-a_1>0$. From the proof of result 2 we know that I_r^r is the only positive solution of $P(I_r)=\mu(p_2(\beta_r)I_r^2+p_1(\beta_r)I_r+p_0(\beta_r))$. We can write a_0 as

$$a_0 = -p_2(\beta_r)I_r^{r2} - p1(\beta_r)I_r^r + \phi\sigma\beta_r^2 I_r^r - \phi\sigma\beta_r^2(S^r + L_r^r)I_r^r - p_0(\beta_r) + \beta_r(\omega + \phi\mu) - \beta_r((\omega + \phi\mu)S^r - \phi\sigma\mu L_r^r),$$

Now using the fact that $1 = S^r + L_r^r + I_r^r$ we get

$$a_0 = \phi\sigma\beta_r^2 I_r^r(1 - S^r - L_r^r) + \beta_r(\omega + \phi\mu)(1 - S^r - L_r^r) + \beta_r(\omega + \phi\mu)L_r^r - \beta_r\phi\sigma\mu L_r^r = \phi\sigma\beta_r^2 I_r^{r2} + \beta_r(\omega + \phi\mu)I_r^r + \beta_r(\omega + \phi\mu(1 - \sigma))L_r^r > 0.$$

Since $-a_1$ and a_0 are positive for all possible values of $\beta_r > \dfrac{\mu(\mu + \delta + \tau_r) + \omega(\mu + \delta)}{\phi\mu + \omega}$ all eigenvalues of $G1$ have negative real part.

For G_4 the characteristic polynomial is

$$p_2(\lambda) = \lambda^2 - b_1\lambda + b_0,$$

where

$$b_0 = (\mu + \sigma\beta_r I_r^r)(\mu + \delta + \tau_s) + \omega(\mu + \delta + \gamma\tau_s),$$
$$-b_1 = 2\mu + \delta + \tau_s + \omega + \sigma\beta_r I_r^r.$$

Since $b_0 > 0$ and $-b_1 > 0$ are both positive we conclude that all eigenvalues of G_4 have negative real part. □

Remark 5. From the proof of this result we conclude that stability of E_r is equivalent to stability of the endemic equilibrium of the sub-system with only resistant strains and simultaneously stability of the sensitive TB-free equilibrium.

A.4. Limit case $\gamma = 0$

Proof of Theorem 4. To show the existence of E_r we just have to repeat the calculations in the proof of result 2 with $\gamma = 0$.

Suppose now that $I_r = 0$ (and subsequently $L_r = 0$). If I_r is non-zero, from the fourth equation of system (1) we get

$$\phi\beta_s F(I_s, 0) + (\omega + \phi\sigma\beta_s I_s)G(I_s, 0) - (\mu + \delta + \tau_s) = 0, \tag{8}$$

where F and G are the same functions as in the proof of result 2. Note that $F(I_s, 0), G(I_s, 0)$ have the same expression as $F(0, I_r), H(0, I_r)$, respectively, if we just change the subscripts s, r. Moreover, Eq. (8) will be the same as Eq. (7) if we just change the subscripts s, r. Therefore, we conclude that for $R_{0s} > 1$ we have exactly one positive solution of $P(I_s)$, that corresponds to E_s. □

A.4.1. Calculus of the coexistence threshold for $\gamma = 0$, $R_{0r}(E_s)$

Assume $\gamma = 0$. In what concerns the coexistence threshold for the resistant strains invasion of a population where sensitive TB is at equilibrium, let us assume that only resistant TB is considered disease. Therefore, the infected compartments are L_r and I_r and following (van den Driessche and Watmough, 2002), we can write system (1) as in (6) with $X = (L_r, I_r, S, L_s, I_s)$ and

$$\mathscr{F} = ((1 - \phi)\beta_s I_s S, \phi\beta_s I_s S, 0, 0, 0)^{\mathrm{T}}.$$

The disease (resistant-TB)-free equilibrium is then $X_0 = (0, 0, S^r, L_r^r, I_r^r)$. Let us compute F and V corresponding to the derivatives at X_0, with respect to the infected classes, of $\mathscr{F}$ and $\mathscr{V}$, respectively:

$$F = \begin{bmatrix} 0 & (1 - \phi)\beta_r(S^s + \sigma L_s^s) \\ 0 & \phi\beta_r(S^s + \sigma L_s^s) \end{bmatrix}, \quad V = \begin{bmatrix} \mu + \omega + \phi\sigma\beta_s I_s^s & -\tau_r \\ -(\omega + \phi\sigma\beta_s I_s^s) & \mu + \delta + \tau_r \end{bmatrix}.$$

The basic reproduction number of the resistant strains, in a population where the sensitive strains are fixed, is the spectral radius of the next generation matrix, FV^{-1}:

$$R_{0r}(E_s) = \frac{(S^s + \sigma L_s^s)\beta_r(\phi\mu + \omega + \phi\sigma\beta_s I_s^s)}{(\mu + \omega + \phi\sigma\beta_s I_s^s)(\mu + \delta + \tau_r) - (\omega + \phi\sigma\beta_s I_s^s)\tau_r}.$$

Proof of Theorem 5. In what matters the stability of E_r we can repeat the calculations in the proof of result 3 with $\gamma = 0$.

For the case of equilibrium $E_s = (S^s, L_s^s, 0, I_s^s, 0)$ by the Theorem 2 in van den Driessche and Watmough (2002) is sufficient to prove conditions (A1)–(A5) for the system as we described above. It is straightforward to check (A1)–(A4).

Let us prove condition (A5). For simplicity of calculations let us write the Jacobian of f, with $\mathscr{F}$ set to zero, at X_0 with the following order in the coordinates (S, L_s, I_s, L_r, I_r). Then the Jacobian can be written in the following way:

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$$Df_{(\mathscr{F}=0)}(S, L_s^s, I_s^s, 0, 0) = \begin{bmatrix} H_1 & H_2 \\ 0 & H_4 \end{bmatrix},$$

where

$$H_1 = \begin{bmatrix} -(\beta_r I_s^s + \mu) & 0 & \delta - \beta_s S^s \\ (1-\phi)\beta_s I_s^s & -(\mu + \omega + \phi\sigma\beta_s I_s^s) & (1-\phi)\beta_s S^s - \phi\sigma\beta_s L_s^s + \tau_s \\ \phi\beta_s I_s^s & \omega + \phi\sigma\beta_s I_s^s & \phi\beta_s(S^s + \sigma L_s^s) - (\mu + \delta + \tau_s) \end{bmatrix}$$

and

$$H_4 = \begin{bmatrix} -(\mu + \omega + \phi\sigma\beta_s I_s^s) & \tau_r \\ \omega + \phi\sigma\beta_s I_s & -(\tau_r + \mu + \delta) \end{bmatrix}.$$

Therefore, the eigenvalues of the Jacobian are given by the eigenvalues of H_1 and H_4.

Note that H_1 is similar to G_1 in the proof of ~~result~~ 3 if we just replace the subscript r by s. So we conclude that all eigenvalues of H_1 have negative real part.

For H_4 the characteristic polynomial is

$$p_2(\lambda) = \lambda^2 - b_1\lambda + b_0,$$

where

$$b_0 = (\mu + \sigma\beta_s I_s^s)(\mu + \delta + \tau_r) + \omega(\mu + \delta),$$

$$-b_1 = (2\mu + \delta + \tau_r + \omega + \sigma\beta_s I_s^s).$$

Since both $b_0 > 0$ and $-b_1 > 0$ all eigenvalues of H_4 have negative real parts. □

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