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# Optimizing multi-drug strategies to prevent antimicrobial quantitative resistance: A nested within- and between-host model

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## Abstract

Antimicrobial resistance (AMR) is a critical global challenge driven by the evolution of bacterial populations that reduce the effectiveness of treatments. This study aims to design an optimal antimicrobial deployment strategy that minimizes both the epidemic size (epidemiological perspective) and the risk of therapeutic failure in the community (evolutionary perspective), particularly in multi-drug treatment settings. Key factors considered include compliance with recommended guidelines, infection duration, treatment initiation delay, and the effectiveness of different drugs. We evaluate the impact of introducing a new antimicrobial, conduct a sensitivity analysis of model parameters on the basic reproduction number and therapeutic failure probability, and explore outcomes of optimal treatment strategies. The approach employs a nested model that explicitly integrates within-host and between-host dynamics. At the within-host scale, the continuous character of AMR is introduced, referred to as quantitative antimicrobial resistance (qAMR). Most models addressing AMR focus on a limited number of resistant strains, often overlooking the potential continuum of resistance, especially as it develops through point mutations. The bacterial dynamics is described by an integro-differential equation, connecting this dynamics to epidemiological parameters such as individual infectiousness, disease-induced mortality, and treatment recovery rates. At the between-host scale, infected individuals are categorized into untreated, treated with compliance to treatment, and treated with non-compliance to treatment. Our results provide insights into AMR dynamics in multi-drug settings, offering a framework for optimizing treatment strategies that balance infection control and resistance prevention. This study contributes to a more effective approach for managing AMR at both individual and population levels.

## Author summary

Antimicrobial resistance (AMR) is a critical global health challenge caused by bacterial evolution that reduces treatment effectiveness. This study develops strategies to optimize antimicrobial use in multi-drug scenarios, balancing infection control (epidemiological perspective) with resistance prevention and treatment efficacy (evolutionary perspective). Our mathematical model integrates bacterial resistance dynamics within individual patients (within-host scale) and community infection spread (between-host scale). Unlike traditional models focused on specific resistant strains, our approach captures a continuum of resistance from mutations. We analyze compliance with treatment guidelines, drug timing, infection duration, and effectiveness, evaluating new antimicrobials and identifying optimal strategies. This framework informs public health policies, improving AMR management.

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**Key words.** Quantitative antimicrobial resistance; Multi-drug treatment; Evolutionary dynamics; Multi-scale nested modelling ; Optimal control; Non-linear system dynamics.

## 1 Introduction

Antimicrobial resistance (AMR) presents one of the critical challenges of modern times [25]. In the context of resistance driven by point mutations, bacterial resistance to a specific antimicrobial is fundamentally a continuous trait, referred to as quantitative antimicrobial resistance (qAMR), at least at the population level. This qAMR is essential for enhancing our understanding of the evolutionary dynamics driving AMR [15]. Most AMR-related models typically focus on the dynamic interaction between a limited number of parasite strains that distinguish from each other by the presence or absence of a small number of resistance genes coding for proteins that inactivates the antibiotic, protects the target or acts as a bypass of the target (e.g., [3, 10, 11, 15, 16, 23, 27, 31, 34–37, 39, 40, 42]). Such models implicitly assume that resistance is primarily driven by resistance genes, rather than arising through mutational processes. In contrast, only a few studies have explored qAMR (e.g., [15, 18, 29]). In these models, bacterial populations are assumed to exhibit phenotypic diversity, characterized by a quantitative descriptor  $x \in \mathbb{R}$ , which represents the resistance level of different bacterial strains. This trait influences various aspects of the bacterial life cycle, such as growth and mortality rates, and also impacts the effectiveness of antimicrobial drugs against the bacterial population. From a theoretical perspective, the properties of the within-host model discussed here are built upon previous analytical findings in [5, 14].

The targeted outcome of an antimicrobial treatment in the clearance of the bacteria from the host. In case of treatment failure, the worse case scenario is when within-host bacterial population has become resistant to treatment (emergence of resistance). Previous analysis ([14]) have shown that intermediate drug concentrations are at the higher risk to lead to treatment failure with emergence of resistance. In the context of multiple drugs used within a community, determining the most effective sustainable strategy to both (i) prevent the emergence of resistant bacterial populations and (ii) control infections within the host population remains a challenge. This issue has been the focus of numerous theoretical studies in recent years, *eg.*, [3, 7, 16, 19, 34–37, 40, 42]. However, none of the aforementioned studies address optimal treatment strategies in the context of qAMR. Furthermore, most of previous modelling work on the topic have considered the epidemiological level only, ignoring the effect of antimicrobial treatment at the individual level (but see e.g., [3, 29, 38]). Building on recent studies [15, 29], we explicitly connect the evolutionary dynamics at both the within-host and between-host levels by treating bacterial resistance as a continuous quantitative trait in a multi-drug setting.

Our goal is to determine the optimal antimicrobial deployment strategy, which involves the allocation of each drug within the treatment framework to simultaneously control the epidemic size and minimize the risk of therapeutic failure in the community. This strategy takes into account crucial factors such as the compliance probability of the host population to recommended guidelines, the time needed for effective infection treatment, the delay before initiating treatment for infected individuals, the community’s treatment rate, and the relative effectiveness of the different antimicrobial drugs introduced in the treatment framework. Compliance to recommended guidelines plays a major role in the development of AMR [2, 6, 24, 26]. Additionally, treatment delays significantly influence patient outcomes and are a major concern in numerous medical studies, including those on HIV, TB, and cancer [8, 9, 20].

At the within-host level, bacterial population dynamics are modeled with an integro-differential equation, as proposed in [15], using the time since an individual is infected as a continuous variable. This variable explicitly links the within- and between-host scales through key parameters such as an individual’s infectiousness, disease-induced mortality, and the recovery rate of treated individuals. Moreover, infected individuals can be either untreated (U), treated with compliance to treatment (C), or treated with non-compliance to treatment (N). Here, compliance (sometimes also called adherence) refers to the extent to which a person correctly follows medical advice, particularly in taking prescribed medications. We assume that compliant individuals effectively clear the infection, while non-compliant or untreated individuals do not. This simplification aids model parameterization but overlooks variability in immune responses, where some infections may clear spontaneously or despite non-compliance. Accounting for such variability presents significant parameterization challenges.

We begin by introducing the nested within- and between-host mathematical model and its parameters, followed by a summary of the mathematical analysis of these dynamics. Next, we present the model’s parameterization and key quantitative variables. We then define the optimal strategy that aims simultaneously to control the epidemic size and to minimize the risk of therapeutic failure in the community. The results section first examines the evolutionary and epidemiological dynamics using a single antimicrobial. We then assess the impact of a newly introduced antimicrobial under various compliance scenarios, perform a global sensitivity analysis of key model parameters on the basic reproduction number and therapeutic failure probability, and explore the outcomes of an

optimal antimicrobial deployment strategy. Finally, we discuss our findings and identify perspectives for future work.

## 2 Model overview

We explicitly link the within-host and between-host levels, treating the magnitude of bacterial resistance to a given antimicrobial as a continuous quantitative trait. Within host, we monitor the progression of infected individuals over time post-infection as a continuous variable. Between hosts, we account for the heterogeneity of antimicrobial treatments, distinguishing between infections treated with a specific antimicrobial and untreated infections. The model proposed is based on the previous framework developed in [15] for the within-host model, and [29] for the nested model. Refer to Figure 1 for a graphical outline of the model.

### 2.1 The within-host model

We focus on a bacterial population that exhibits variation in the magnitude of antimicrobial resistance, characterized by a continuous trait denoted as  $x \in \mathbb{R}$ . This quantitative level of antimicrobial resistance influences multiple aspects of the bacterial population's life cycle, including growth and mortality rates. To capture the dynamics of this bacterial population within a host, we employ an integro-differential equation introduced in [15]. Infected individuals can be untreated or treated and, in the latter case, either with antimicrobial A or B. The bacterial load of untreated infections (U) is denoted as  $b^U(\tau, x)$ , where  $\tau \in (0, +\infty)$  is the time post-infection and  $x$  is the resistance level. We assume that infections treated in compliance with recommended medications result in successful outcomes (i.e., effectively clearing the infection) and are represented by bacterial loads ( $b_A^C(\tau, x)$  or  $b_B^C(\tau, x)$ ). Similarly, we assume that infections treated in non-compliance with recommended medications result in unsuccessful outcomes (i.e., failing to clear the infection) and are represented by bacterial loads  $b_A^N(\tau, x)$  or  $b_B^N(\tau, x)$ . With  $\vartheta \in \{C, N, U\}$  and  $\varrho \in \{A, B\}$ , the within-host model read as

$$\begin{cases} \partial_\tau b_\varrho^\vartheta(\tau, x) = \frac{1}{(1 + B_\varrho^\vartheta(\tau))^\kappa} \int_{\mathbb{R}} J(x-y)p(y)b_\varrho^\vartheta(\tau, y)dy - \xi_\varrho^\vartheta(x)b_\varrho^\vartheta(\tau, x), \\ b_\varrho^\vartheta(0, \cdot) = b_{\varrho 0}^\vartheta(\cdot), \end{cases} \quad (2.1)$$

where  $B_\varrho^\vartheta(\tau) = \int_{\mathbb{R}} b_\varrho^\vartheta(\tau, x)dx$  is the total bacteria load, and  $\kappa$  is a positive parameter that shapes the maintenance of bacterial population homeostasis. Note that a bacterial population with resistance level  $y$  generates offspring with resistance level  $x$  at a per-capita rate of  $J(x-y)p(y)$ , where  $p(y)$  represents the intrinsic growth rate of the bacteria, and  $J(x-y)$  denotes the probability of a bacterial population with resistance level  $y$  mutating to level  $x$  during reproduction. Consequently, the total number of bacteria with resistance level  $x$  produced by a bacterial population  $\tau$ -time post infection can be quantified as  $(1 + \int_{\mathbb{R}} b_\varrho^\vartheta(\tau, x)dx)^{-\kappa} \int_{\mathbb{R}} J(x-y)p(y)b_\varrho^\vartheta(\tau, y)dy$ . The term  $\xi_\varrho^\vartheta(x)$  accounts for the clearance of the bacterial population with resistance level  $x$ , either by the immune system ( $\mu$ ) or by the efficiency of antimicrobial pressure ( $k_\varrho^\vartheta$ ). Thus,  $\xi_\varrho^U(x) = \mu$  for untreated hosts (i.e., no effect of antimicrobial),  $\xi_\varrho^C(x) = \mu + k_\varrho^C(x)$  for successfully treated hosts, and  $\xi_\varrho^N(x) = \mu + k_\varrho^N(x)$  for treated hosts with failure. The mutation kernel  $J \equiv J_\varepsilon$  is assumed a Gaussian distribution  $J_\varepsilon(x) = \frac{1}{\varepsilon\sqrt{2\pi}}e^{-\frac{1}{2}(\frac{x}{\varepsilon})^2}$ , where  $\varepsilon > 0$  is a small parameter that represents the mutation variance within the phenotypic space during a bacterial division.

The dynamical properties of the within-host model (2.1) have been thoroughly examined in [15]. For instance, the within-host basic reproduction number  $\mathcal{N}_\varrho^\vartheta(x)$  for the bacterial population with resistance level  $x$  within an infected individual is calculated as follows

$$\mathcal{N}_\varrho^\vartheta(x) = \frac{p(x)}{\xi_\varrho^\vartheta(x)}, \text{ for } \vartheta \in \{C, N, U\} \text{ and } \varrho \in \{A, B\}.$$

Moreover, Model (2.1) allows to follow evolutionary parameters such as the individual average level of resistance,  $\bar{x}_\varrho^\vartheta(\tau)$ ,  $\tau$ -time post infection :

$$\bar{x}_\varrho^\vartheta(\tau) = \int_{\mathbb{R}} x \frac{b_\varrho^\vartheta(\tau, x)}{B_\varrho^\vartheta(\tau)} dx, \quad \vartheta \in \{C, N, U\} \text{ and } \varrho \in \{A, B\}. \quad (2.2)$$

In [15], the within-host model is shown to converge, within the resistance level space, towards an evolutionary attractor denoted as  $\bar{x}_\varrho^{*\vartheta}$ . This evolutionary attractor characterizes the average level of bacterial resistance at the

equilibrium within an infected host. Notably, it aligns with the local maximum of the basic reproduction number  $\mathcal{N}_\varrho^\vartheta$ , such that

$$\bar{x}_\varrho^{*\vartheta} : \mathcal{N}_\varrho^\vartheta(\bar{x}_\varrho^{*\vartheta}) = \max_x \mathcal{N}_\varrho^\vartheta. \quad (2.3)$$

## 2.2 The between-host model

At the between-hosts scale, the host population is divided into eight states. At any time  $t$ , an individual can be susceptible to infection, denoted as  $S(t)$ , infected, or recovered. Infected individuals are categorized as either untreated, denoted as  $I^U(t, \tau, \bar{x}^U(\tau))$ , or treated with either drug A or B. Treated infections may follow the recommended guidelines, leading to successful outcomes (effectively clearing the infection), denoted as  $I_A^C(t, \tau, \bar{x}_\varrho^C(\tau))$  and  $I_B^C(t, \tau, \bar{x}_\varrho^C(\tau))$ , or they may fail to follow the recommendations, resulting in unsuccessful outcomes (failing to clear the infection), denoted as  $I_A^N(t, \tau, \bar{x}_\varrho^N(\tau))$  and  $I_B^N(t, \tau, \bar{x}_\varrho^N(\tau))$ . Variables  $\tau$  and  $\bar{x}^\vartheta(\tau)$ , with  $\vartheta \in C, N, U$ , respectively represent the time post-infection and the average resistance level of the infected host. It should be noted that each infected individual may harbor multiple bacterial strains, labeled as  $x \in \mathbb{R}$ , with varying frequencies and resistance. Therefore,  $\bar{x}^\vartheta(\tau)$  represents the individual's resistance level quantified by the within-host dynamics (2.2). However, for simplicity and without loss of generality, we will denote  $I^U(t, \tau, \bar{x}^U(\tau))$  as  $I^U(t, \tau)$  and  $I_\varrho^\vartheta(t, \tau, \bar{x}_\varrho^\vartheta(\tau))$  as  $I_\varrho^\vartheta(t, \tau)$ , for  $\vartheta \in \{C, N\}$  and  $\varrho \in \{A, B\}$ . The force of infection induced by infected individuals at time  $t$  is given by

$$\lambda(t) = \int_0^\infty [\beta_A^C(\tau)I_A^C(t, \tau) + \beta_B^C(\tau)I_B^C(t, \tau) + \beta_A^N(\tau)I_A^N(t, \tau) + \beta_B^N(\tau)I_B^N(t, \tau) + \beta^U(\tau)I^U(t, \tau)]d\tau.$$

Here,  $\beta^\vartheta(\tau)$  is the infectiousness of an individual infected  $\tau$  time units ago. Such a transmission rate  $\beta^\vartheta(\tau)$  is linked to the within-host dynamics (2.1) at time  $\tau$ , so is the disease-induced mortality rate  $\alpha^\vartheta(\tau)$  of infected individuals.

Newly infected individuals at time  $t$ , quantified by  $\lambda(t)S(t)$ , can follow one of three paths: (i) they can become untreated infections with a probability of  $(1 - q^T)$ , (ii) they can become treated infections in compliance with recommended medications with a probability of  $q_C q^T$ , or (iii) they can become treated infections in non-compliance with recommended medications with a probability of  $(1 - q_C)q^T$ . Here,  $q^T \in (0, 1)$  represents the proportion of treated infections in the entire host population, while  $q_C \in (0, 1)$  denotes the compliance probability to the recommended guidelines, which is the likelihood that infected hosts follow the recommended prescription. Among the proportion of treated infections  $q^T$  in the whole population, a proportion  $q_A^T$  is treated with drug A, while the remainder,  $q_B^T = 1 - q_A^T$ , is treated with drug B. Consequently, for  $\varrho \in \{A, B\}$ , the dynamics of newly infected individuals (*i.e.*, at  $\tau = 0$ ) given by

$$\begin{cases} I_\varrho^C(t, 0) = q_C q^T q_\varrho^T \lambda(t) S(t), \\ I_\varrho^N(t, 0) = (1 - q_C) q^T q_\varrho^T \lambda(t) S(t), \\ I^U(t, 0) = (1 - q^T) \lambda(t) S(t). \end{cases} \quad (2.4)$$

Moreover, individuals receiving compliant treatment can discontinue it at rates  $\omega_U^{C,\varrho}(\tau)$ , while those receiving noncompliant treatment can stop at rates  $\omega_U^{N,\varrho}(\tau)$ . Untreated individuals, on the other hand, can begin treatment at a rate of  $\omega_T^U(\tau)$ . Importantly, it is expected that compliant individuals do not discontinue treatment, implying  $\omega_U^{C,\varrho} \equiv 0$ . Treated individuals recover from the infection at rate  $\gamma_\varrho^\vartheta(\tau)$ . Susceptible individuals are recruited at a rate of  $\Lambda$ , and the natural mortality rate of the entire population is  $\mu_h$ .

By setting  $\mathbf{I}^C(t, \tau) = (I_A^C(t, \tau), I_B^C(t, \tau))^t$ ,  $\mathbf{I}^N(t, \tau) = (I_A^N(t, \tau), I_B^N(t, \tau))^t$  and  $\mathbf{R}(t) = (R_A(t), R_B(t))^t$ , boundary conditions (2.4) is coupled with the following SIR system (see (C.1) for the detailed formulation)

$$\begin{cases} \dot{S}(t) = \Lambda - S(t)\lambda(t) - \mu_h S(t), \\ (\partial_t + \partial_\tau) \mathbf{I}^C(t, \tau) = -(\boldsymbol{\alpha}^C(\tau) + \boldsymbol{\gamma}^C(\tau) + (1 - \mathbf{q}^T)\boldsymbol{\omega}_U^C(\tau) + \mu_h) \mathbf{I}^C(t, \tau) + q_C \mathbf{q}^T \mathbf{e} \omega_T^U(\tau) I^U(t, \tau), \\ (\partial_t + \partial_\tau) \mathbf{I}^N(t, \tau) = -(\boldsymbol{\alpha}^N(\tau) + \boldsymbol{\gamma}^N(\tau) + (1 - \mathbf{q}^T)\boldsymbol{\omega}_U^N(\tau) + \mu_h) \mathbf{I}^N(t, \tau) + (1 - q_C) \mathbf{q}^T \mathbf{e} \omega_T^U(\tau) I^U(t, \tau), \\ (\partial_t + \partial_\tau) I^U(t, \tau) = -(\alpha^U(\tau) + \gamma^U(\tau) + q^T \omega_T^U(\tau) + \mu_h) I^U(t, \tau) + \mathbf{e}^t (1 - \mathbf{q}^T) (\omega_U^C(\tau) \mathbf{I}^C(t, \tau) + \omega_U^N(\tau) \mathbf{I}^N(t, \tau)), \\ \dot{\mathbf{R}}(t) = \int_0^\infty (\boldsymbol{\gamma}^C(\tau) \mathbf{I}^C(t, \tau) + \boldsymbol{\gamma}^N(\tau) \mathbf{I}^N(t, \tau)) d\tau - \mu_h \mathbf{R}(t), \end{cases} \quad (2.5)$$

with the associated initial conditions

$$S(0) = S_0, \quad \mathbf{R}(0) = \mathbf{R}_0, \quad I^U(0, \tau) = I_0^U(\tau), \quad \mathbf{I}_\varrho^\vartheta(0, \tau) = \mathbf{I}_{\varrho,0}^\vartheta(\tau),$$

and where  $\mathbf{e} = (1, 1)$  and

$$\boldsymbol{\alpha}^\vartheta(\tau) = \text{diag}\left(\alpha_{\text{A}}^\vartheta(\tau), \alpha_{\text{B}}^\vartheta(\tau)\right), \boldsymbol{\omega}_{\text{U}}^\vartheta(\tau) = \text{diag}\left(\omega_{\text{U}}^{\vartheta, \text{A}}(\tau), \omega_{\text{U}}^{\vartheta, \text{B}}(\tau)\right), \boldsymbol{\gamma}^\vartheta(\tau) = \text{diag}\left(\gamma_{\text{A}}^\vartheta(\tau), \gamma_{\text{B}}^\vartheta(\tau)\right), \mathbf{q}^{\text{T}} = q^{\text{T}} \text{diag}\left(q_{\text{A}}^{\text{T}}, q_{\text{B}}^{\text{T}}\right).$$

### 3 Summary of the mathematical analysis results for nested within- and between-host dynamics

For both biological feasibility and technical reasons, the nested model (2.1) and (2.4)-(2.5) is analyzed under natural assumptions, including the positivity and boundedness of parameters. A centered Gaussian distribution is typically used for the mutation kernel  $J$ , though other mutation kernels that satisfy certain general properties can also be applied. Refer to Appendix A for further details on the nested model's assumptions. Furthermore, under these assumptions, the nested model (2.1) and (2.4)-(2.5) is well-posed and there exists a global bounded positive solution. Such a result can be addressed using an integrated semigroup approach and Volterra integral formulation (e.g., see [12, 21, 28, 41]). For details, we refer to [29, Theorem 5.1], where this result is specifically handled.

#### 3.1 The epidemiological basic reproduction number

In the absence of infection, that is  $\mathbf{I}^{\text{N}} = \mathbf{I}^{\text{C}} = \mathbf{I}^{\text{U}} \equiv 0$ , System (2.4)-(2.5) has a disease-free equilibrium (DFE)  $\mathbf{E}^0$  at which the size of susceptible individuals is given by  $S^0 = \Lambda/\mu_h$ . The basic reproduction number, usually denoted  $\mathcal{R}_0$ , is defined as the number of infections arising from one newly infected individual introduced into a healthy (disease-free) host population. Using the next-generation operator approach (eg., [13, 22]), we find that (see [29] for details) the basic reproduction number  $\mathcal{R}_0$  at the between-host scale (2.4)-(2.5) is given by

$$\mathcal{R}_0 = \frac{\Lambda}{\mu_h} \int_0^\infty \langle \boldsymbol{\beta}(\tau), \boldsymbol{\Pi}(\tau, 0)\mathbf{q} \rangle d\tau. \quad (3.1)$$

The term  $\chi(\tau) = \langle \boldsymbol{\beta}(\tau), \boldsymbol{\Pi}(\tau, 0)\mathbf{q} \rangle$  quantifies the infectiousness of all infected individuals  $\tau$ -time post-infection. The parameter  $\mathbf{q}$  represents the landscape status of treated infections. The function  $\boldsymbol{\Pi}(\tau_2, \tau_1)$ , defined for  $0 \leq \tau_1 \leq \tau_2 < \infty$ , represents the evolutionary operator generated by the linearized system of (2.4)-(2.5) around the DFE. It describes the transitions between different infection statuses. Refer to Appendix B for more details.

## 4 Nested model parameterization and quantitative variables

In this section, we briefly describe some useful epidemiological and evolutionary outputs, along with the shape parameters used for simulating the nested model (2.1) and (2.4)-(2.5). All state variables and parameters are summarized in Table 1.

At the within-host level, the intrinsic growth rate function of bacterial population  $p(x)$  is a decreasing function of the resistance level  $x$  (eg., [17]). The function  $p$  is bounded due to physiological constraints, and a strain with no AMR investment is such that  $p(-\infty) := p_m < \infty$ . We also assume that, to the limit, the resistance to an infinite concentration of antimicrobial would require full resource and energy allocation to resistance and none to growth, therefore having  $p(\infty) = 0$ . Using the intrinsic growth rates  $p_0$  and  $p_1$  of the reference 'sensitive' and 'resistant' strains  $x_0$  and  $x_1$  respectively, as in [15], we assume that

$$p(x) = p_m \left[ 1 + \left( \frac{p_m - p_0}{p_0} \right) \left( \frac{p_0}{p_1} \cdot \frac{p_m - p_1}{p_m - p_0} \right)^x \right]^{-1}, \quad (4.1)$$

with  $0 < p_1 < p_0 < p_m$  given in Table 1.

Similarly, the killing rate function  $k_\varrho^\vartheta(x)$ , of a treated infection  $\vartheta \in \{\text{C}, \text{N}\}$  with the antibiotic  $\varrho \in \{\text{A}, \text{B}\}$ , decreases with resistance level  $x$ . We define  $k_\varrho^\vartheta(\cdot)$  using two positive parameters:  $k_{0, \varrho}^\vartheta$  and  $k_{1, \varrho}^\vartheta$ , representing antimicrobial activity against reference strains  $x_0$  and  $x_1$  of the treated infections  $\vartheta$ . Thus,  $k_\varrho^\vartheta(x)$  for a resistance level  $x$  takes the form

$$k_\varrho^\vartheta(x) = k_{0, \varrho}^\vartheta \left( \frac{k_{1, \varrho}^\vartheta}{k_{0, \varrho}^\vartheta} \right)^x. \quad (4.2)$$

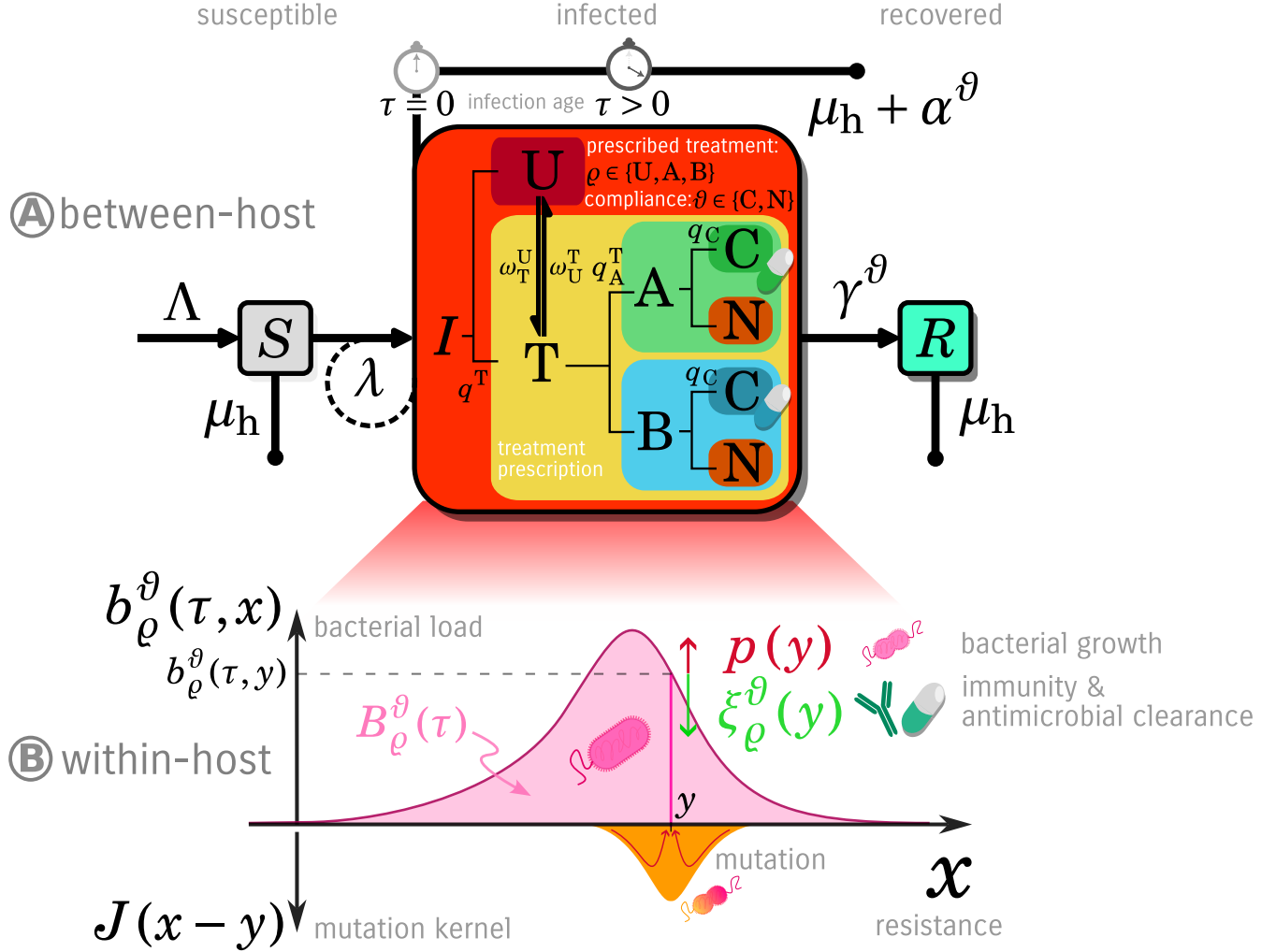


Figure 1: Graphical outline of the model.

**A)** (Top panel) The between-host dynamics are shown as a classical SIR-like flow chart (panel A, top). Note that the infected compartment  $I$  is partitioned according to the treatment status (untreated  $U$ , or treated  $T$ ), and, if treated – either with drug  $A$  or drug  $B$  –, according to compliance (compliant  $C$  or not  $N$ ). The quantities shown along branches of the tree correspond to (constant) the proportions that dichotomize the parent set (the opposite branches having the corresponding probability complementary to 1).

**B)** (Top panel) The within-(infected) host dynamics recapitulates the forces acting over the distribution of the bacterial load  $b$  according to quantitative resistance  $x$ , in a host of infection age  $\tau$ , under treatment  $\varrho$ , with compliance  $\vartheta$ , namely bacterial growth  $p$ , clearance  $\xi$  and mutation  $J$ .

See the model overview section in the main text for details and Table 1 for the meaning of the notations.

Notations		
$t$	Time	
$\tau$	Time since infection	
$x$	Resistance level	
$\varrho$	Antimicrobial treatment, $\varrho \in \{A, B\}$	
$\vartheta$	Infection status: U=untreated, N= treated with failure, C= treated with success.	
Model state variables		
<b>Within-host scale</b>		
$b_\vartheta^\varrho(\tau, x)$	Bacterial density with resistance level $x$ at time $\tau$ , within an individual with infection status $\vartheta$	
<b>Between-host scale</b>		
$S(t)$	Susceptible individual at time $t$	
$I_\vartheta^\varrho(t, \tau)$	Infected individuals at time $t$ , infected since time $\tau$ , and with infection status $\vartheta$	
$R_\vartheta(t)$	Recovered individuals at time $t$	
Variable parameters		
Parameters	Description	Value
$\tau_s$	Delay prior to treatment (days)	{4; 7; 10}
$\tau_r$	Time required for effective treatment (days)	{4; 7; 10}
$q_C$	Proportion of individuals with compliance to recommended guidelines	{0.2; 0.5; 0.7; 0.95}
$r_{\text{eff}}$	Relative effectiveness of antimicrobial B compared to A	{0.1; 0.5; 0.9}
$p^T$	Proportion of treated infections in the entire host population	{0.5; 0.75; 0.95}
$q_B^T$	Proportion of treated infections with antimicrobial B	{0.05; 0.1; 0.5; 0.7; 0.95}
Fixed model parameters		
Parameters	Description (Unit)	Values [Source]
<b>Within-host scale</b>		
$\varepsilon$	Mutation variance within the phenotypic space	0.05 [Assumed]
$J_\varepsilon(x - y)$	Mutation probability from resistance level $x$ to $y$	$G(0, \varepsilon, x - y)^a$
$p(x)$	Intrinsic growth rate of bacterial population with resistance level $x$	defined by (4.1)
$k_\varrho^\vartheta(x)$	Antimicrobial killing rate of bacterial population with resistance level $x$	defined by (4.2)
$\kappa$	Limitation on bacterial growth factor	1
$p_m$	Upper bound of the intrinsic growth rate $p$	10 [15]
$p_0$	Intrinsic growth rate of the reference sensitive strain	$0.95 \times p_m$ [15]
$p_1/p_0$	Reference resistant and sensitive growth rate ratio	0.5 [15]
$k_{0,A}^\vartheta$	Activity of antimicrobial A on the sensitive reference strain (day <sup>-1</sup> )	{15; 3} [15]
$k_{1,A}^\vartheta/k_{0,A}^\vartheta$	Antimicrobial A efficiency ratio of reference resistant and sensitive strains	{0.3; 0.01} [15]
$k_{0,B}^\vartheta$	Activity of antimicrobial B on the sensitive reference strain (day <sup>-1</sup> )	defined by (6.1)
$k_{1,B}^\vartheta/k_{0,B}^\vartheta$	Antimicrobial B efficiency ratio of reference resistant and sensitive strains	defined by (6.1)
$\mathcal{N}_0^0(0)$	The reproduction number of the reference sensitive strain without drug	20 (Assumed)
$m_0$	Size of the initial bacterial population	0.05 [15]
$\sigma_0^2$	Resistance variance of the initial bacterial population	0.05 [15]
$\mu$	Rate of natural clearance of the bacteria population (day <sup>-1</sup> )	$1.81 \times p_0/\mathcal{N}_0^0(0)$ [15]
<b>Between-host scale</b>		
$\beta_\varrho^\vartheta(\tau)$	Transmission rate of infected individuals	defined by (4.3)
$\alpha_\varrho^\vartheta(\tau)$	Disease-induced mortality rate of infected individuals	defined by (4.4)
$\omega_T^U(\tau)$	Rate of treatment initiation for untreated infections	defined by (4.6)
$\omega_U^{\vartheta,\varrho}(\tau)$	Rate of treatment cessation for treated infections	defined by (4.5)
$\gamma_\varrho^\vartheta(\tau)$	Recovery rate of treated infections in the state $\vartheta$	defined by (4.7)-(4.8)
$\Lambda$	Demographic inflow of susceptible individuals	$5 \times 10^4$ [29]
$\mu_h$	Natural death rate	$5.2675 \times 10^{-2}$ [29]
$\beta_0$	Upper bound of the transmission rate	$1.2 \times 10^{-3}$ [29]
$\alpha_0$	Upper bound of virulence (i.e. infection-induced death rate)	$7.5 \times 10^{-2}$ [29]
$r_0$	Half-saturation constant	$9 \times 10^3$

Table 1: Description of the state variables and parameters of the model. <sup>a</sup> The notations  $G(0, \varepsilon, x)$  stand for the normalized density function of the Gaussian distribution with mean 0 and variance  $\varepsilon^2$ .



At the between-host level, the transmission capabilities  $\beta^U$ , and  $\beta_\varrho^\vartheta$  of an infected individuals, either untreated or treated  $\vartheta \in \{C, N\}$  with  $\varrho \in \{A, B\}$ , are defined using Holling-type II functional responses such that

$$\beta^U(\tau) = \frac{\beta_0 B^U(\tau)}{r_0 + B^U(\tau)}, \quad \text{and} \quad \beta_\varrho^\vartheta(\tau) = \frac{\beta_0 B_\varrho^\vartheta(\tau)}{r_0 + B_\varrho^\vartheta(\tau)}, \quad (4.3)$$

where  $\tau$  is the time post-infection,  $\beta_0$  is a scaling constant, and  $r_0$  is the half-saturation constant for the total bacterial load  $B^U(\tau) = \int_{\mathbb{R}} b^U(\tau, x) dx$ ,  $B_\varrho^\vartheta(\tau) = \int_{\mathbb{R}} b_\varrho^\vartheta(\tau, x) dx$ .

Likewise, the disease induced mortality rates of infected individuals  $\alpha^U$ , and  $\alpha_\varrho^\vartheta$  reads as

$$\alpha^U(\tau) = \frac{\alpha_0 B^U(\tau)}{r_0 + B^U(\tau)}, \quad \text{and} \quad \alpha_\varrho^\vartheta(\tau) = \frac{\alpha_0 B_\varrho^\vartheta(\tau)}{r_0 + B_\varrho^\vartheta(\tau)}, \quad (4.4)$$

where  $\alpha_0$  is a scaling constant. Scaling constants  $\alpha_0$ ,  $\beta_0$ , and  $r_0$  are given by Table 1. With the formulations (4.3) and (4.4), infection's transmission and virulence increase monotonically with the within-host bacterial load. However, their increase slows compared to a linear formulation at higher bacterial densities.

Moreover, the treatment  $\vartheta \in \{C, N\}$  with drug  $\varrho \in \{A, B\}$  are stopped the rate  $\omega_{U,\varrho}^\vartheta(\tau)$ ,  $\tau$ -time post infection, such that

$$\omega_{U,\varrho}^\vartheta(\tau) = \begin{cases} 0, & \text{if } B_\varrho^\vartheta(\tau) \leq B_0, \\ c_0, & \text{if } B_\varrho^\vartheta(\tau) > B_0. \end{cases} \quad (4.5)$$

Equation (4.5) assumes that a treated individual ceases the treatment as soon as the total bacterial count starts to increase, eventually reaching the initial bacterial population size,  $B_0$ , observed before the treatment commenced.

The rate  $\omega_T^U(\tau)$ , which describes the transition from an untreated to a treated infection  $\tau$ -time post-infection, is linked to a parameter  $\tau_s$  that represents the delay prior the treatment. Therefore, for a given  $\tau_s$ ,  $\omega_T^U$  is such that

$$\omega_T^U(\tau) = \begin{cases} 0, & \text{if } B^U(\tau) < B^U(\tau_s), \\ c_0, & \text{if } B^U(\tau) > B^U(\tau_s). \end{cases} \quad (4.6)$$

The recovery rate,  $\gamma_\varrho^C$ , of treated individuals in compliance with recommended medications  $\varrho \in \{A, B\}$ , is defined by introducing the parameter  $\tau_r$  that represents the time required for effective recovery *ie.*, the number of days after which the bacterial load becomes undetectable. We then have

$$\gamma_\varrho^C(\tau) = \begin{cases} 0, & \text{if } B_\varrho^C(\tau) > B_\varrho^C(\tau_r), \\ c_0, & \text{if } B_\varrho^C(\tau) \leq B_\varrho^C(\tau_r), \end{cases} \quad \text{with } \varrho \in \{A, B\}. \quad (4.7)$$

Finally, both untreated infections and under-dosed treatment (due to non-compliance) are assumed not to recover from the infections, implying that

$$\gamma^U(\tau) \equiv 0, \quad \text{and} \quad \gamma_\varrho^N(\tau) \equiv 0, \quad \text{for } \varrho \in \{A, B\}. \quad (4.8)$$

The value  $c_0$  is an arbitrary positive parameter that is not strictly significant. For example, consider  $f(\tau) = \exp(-\int_0^\tau \omega_T^U(\sigma) d\sigma)$  the probability of remaining in the untreated state U  $\tau$ -time post-infection. Then, the average delay prior treatment is  $\int_0^\infty f(\tau) d\tau = \tau_s + \frac{1}{c_0}$ . Here we fix,  $c_0 = 100$ , such that  $\int_0^\infty f(\tau) d\tau \approx \tau_s$ . The same reasoning holds for other rates  $\omega, s$  and  $\gamma, s$ .

We introduce two quantitative variables to measure the average resistance level in the host population and the therapeutic failure rate among individuals exposed to antimicrobials. More precisely, the average level of resistance ( $\eta(t)$ ) in the host population at time  $t$  is given by :

$$\eta(t) = \eta_A^T(t) + \eta_B(t)^T + \eta^U(t), \quad (4.9)$$

with

$$\begin{aligned} \eta^U(t) &= \int_0^\infty \bar{x}^U(\tau) \frac{I^U(t, \tau)}{I(t)} d\tau, \\ \eta_A^T(t) &= \int_0^\infty \left( \bar{x}_A^C(\tau) \frac{I_A^C(t, \tau)}{I(t)} + \bar{x}_A^N(\tau) \frac{I_A^N(t, \tau)}{I(t)} \right) d\tau, \\ \eta_B^T(t) &= \int_0^\infty \left( \bar{x}_B^C(\tau) \frac{I_B^C(t, \tau)}{I(t)} + \bar{x}_B^N(\tau) \frac{I_B^N(t, \tau)}{I(t)} \right) d\tau, \end{aligned}$$

and where  $I(t) = \int_0^\infty (I_A^C(t, \tau) + I_B^C(t, \tau) + I_A^N(t, \tau) + I_B^N(t, \tau) + I^U(t, \tau)) d\tau$  is the total infected population at time  $t$ . Note that  $\eta^U(t)$ ,  $\eta_A^T(t)$ , and  $\eta_B^T(t)$  represent the average resistance levels induced by untreated infections, treated infections with drug A, and treated infections with drug B, respectively.

Furthermore, we define therapeutic failures at time  $t$ , denoted  $i^N(t)$ , as the proportion of treated infections in non-compliance with recommended medications among those exposed to the treatment. We then have

$$i^N(t) = \frac{I^N(t)}{I^C(t) + I^N(t) + R(t)},$$

where  $I^C(t) = \int_0^\infty (I_A^C(t, \tau) + I_B^C(t, \tau)) d\tau$ ,  $I^N(t) = \int_0^\infty (I_A^N(t, \tau) + I_B^N(t, \tau)) d\tau$ , and  $R(t) = R_A(t) + R_B(t)$ .

## 5 Optimal deployment of antimicrobials

Our goal is to evaluate the effectiveness of a specified antimicrobial deployment strategy, represented by the pairing  $(q_A^T = 1 - q_B^T, q_B^T)$ , on the epidemiological basic reproduction number  $\mathcal{R}_0$ , given by (3.1), within a given configuration. Quantities  $q_A^T$  and  $q_B^T$  represent the proportion of treated infections with antimicrobial A and B respectively. Any configuration is defined by the set of parameters  $\Delta = (q_C, \tau_r, \tau_s, q^T, r_{\text{eff}})$ , representing the compliance probability to recommended guidelines ( $q_C$ ), the time required for an effective treatment ( $\tau_r$ ), the delay prior to treatment ( $\tau_s$ ), the treatment rate  $q^T$ , and the effectiveness of antimicrobial B compared to A ( $r_{\text{eff}}$ ). It is important to note that antimicrobial B is more effective than A with  $r_{\text{eff}} \in (0, 1)$ , and both antimicrobials are identical for all the other aspects. For the set of parameters  $\Delta$ , we investigate the impact of the deployment strategy, represented by the proportion  $q_B^{*T}$  of antimicrobial B in the treatment landscape, with the remaining proportion  $(1 - q_B^{*T})$  being antimicrobial A. Our focus is on both (i) the epidemic size, measured by the basic reproduction number  $\mathcal{R}_0$ , and (ii) the evolutionary probability of therapeutic failure, measured by  $i^N(\infty)$ . Both the epidemic size and the probability of therapeutic failure are under control as soon as the  $\mathcal{R}_0$  is less than the unity. Our objective is to identify the optimal antimicrobial deployment strategy, represented by the minimum proportion  $q_B^{*T}$  of antimicrobial B, that ensures  $\mathcal{R}_0$  remains below one. Such an objective reads :

$$q_B^{*T}(\Delta) = \min \{q_B^T \in (0, 1) : \mathcal{R}_0(q_B^T, \Delta) < 1\}. \quad (5.1)$$

Note that the optimal deployment strategy  $q_B^{*T} \equiv q_B^{*T}(\Delta)$  depends on the specific configuration defined by the set of parameters  $\Delta$ . Furthermore,  $q_B^{*T}(\Delta)$  may not exist for some configurations of  $\Delta$ .

## 6 Results

At the within-host scale, the initial bacterial population  $b_0^\vartheta(x)$  is assumed to be composed by a bacterial population with an average resistance level  $x = 0$ . Hence, we set  $b_0^\vartheta(x) = m_0 \times \mathcal{N}(0, \sigma_0, x)$ , where  $\mathcal{N}(0, \sigma_0, x)$  stands for the density function of the standard Gaussian distribution at  $x$  with mean 0 and variance  $\sigma_0^2$ . This means that the initial bacterial population mostly comprises the reference sensitive strain  $x_0 = 0$ .

At the between-host scale, the initial susceptible population is  $S_0 = (1 - P_{\text{rev}}) \frac{\Lambda}{\mu_h}$ , and the initial recovered population is  $R_0 = 0$ , where  $P_{\text{rev}} \in (0, 1)$  is the initial prevalence of the infection. Furthermore, the initial distribution of contagious individuals are  $I_0^C(\tau) = 0$ ,  $I_0^N(\tau) = 0$ , and  $I_0^U(\tau) = P_{\text{rev}} \times \frac{\Lambda}{\mu_h} \times L(\tau)$ , for all  $\tau \geq 0$ , and where  $L(\tau) = \gamma_0 e^{-\gamma_0 \tau}$  is the exponential distribution with parameter  $\gamma_0 = 23$ . This parameter is chosen to ensure that the probability of being infected for no more than 6 hours is nearly 100%.

### 6.1 Evolutionary and epidemiological dynamics with one antimicrobial

At the between-host scale, we assume that only antimicrobial A is used initially. Therefore, for successfully treated hosts with drug A, the antimicrobial effect  $k_A^C$  is such that the evolutionary attractor  $\bar{x}_A^{*C}$ , introduced by (2.3), satisfies  $\mathcal{N}_A^C(\bar{x}_A^{*C}) < 1$  (Figure 2,A), resulting in the non-persistence of the infection (Figure 2,B,C). For unsuccessfully treated infections,  $\bar{x}_A^{*N}$  is such that  $\mathcal{N}_A^N(\bar{x}_A^{*N}) > 1$  (Figure 2,D), leading to the within-host infection persistence (Figure 2, E, F). In this latter configuration, the antimicrobial A is initially effective for a certain period as illustrated by the total bacterial load (Figure 2,F). This initial phase is followed by a rebound in bacterial load, which completely escapes the drug efficiency by evolving a higher level of resistance than initially (Figure 2, E, F). Finally, in untreated infections, the absence of drug pressure results in  $\bar{x}^{*U}$  being nearly identical to the average resistance

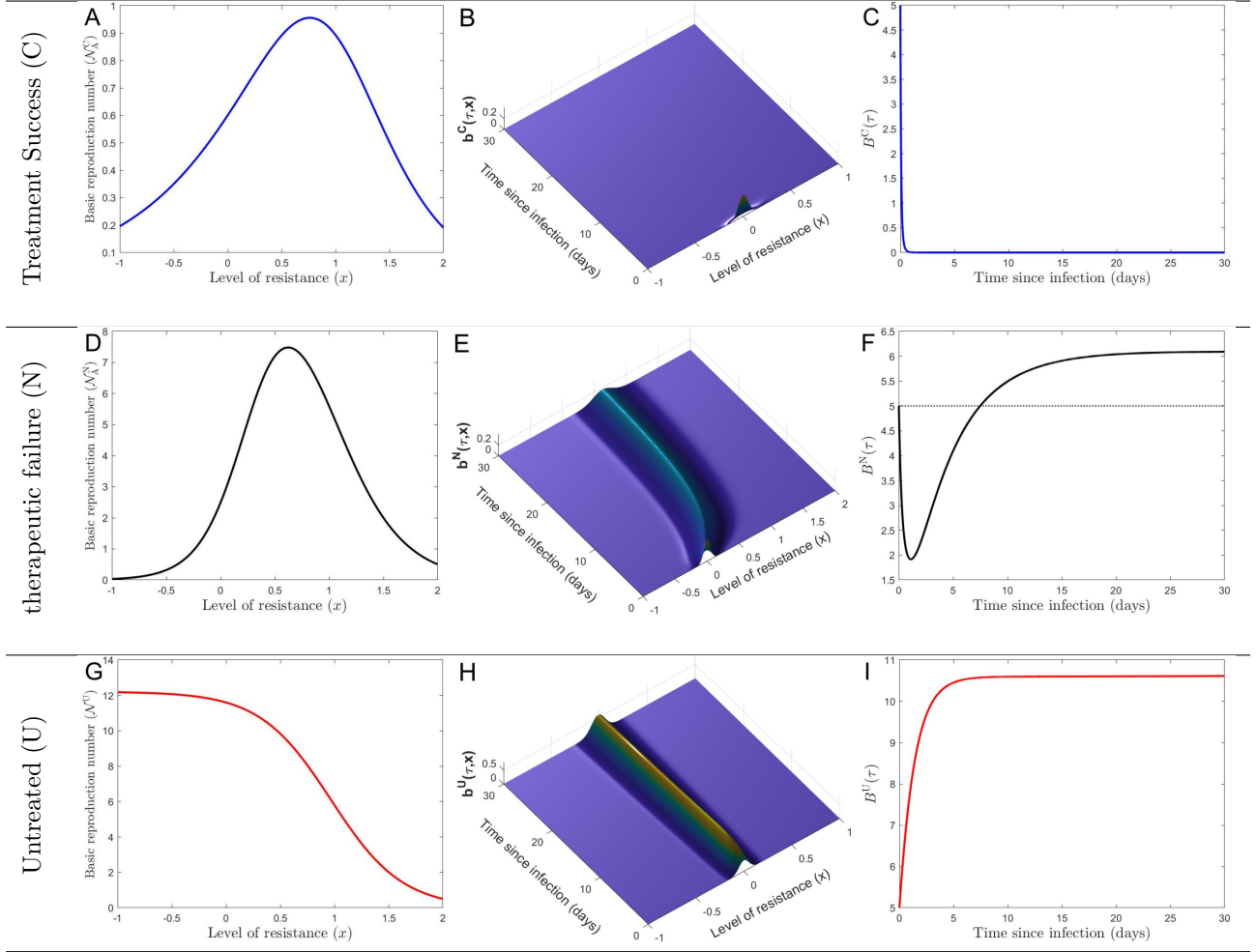


Figure 2: Dynamics of the within-host model. **Row 1.** The basic reproduction number, the dynamics of the bacterial load and the total bacteria load within a successfully treated host (state C). The effect  $k_A^C$  of antimicrobial A defined by (4.2) is such that  $k_{0,A}^C = 15$  and  $k_{1,A}^C/k_{0,A}^C = 0.3$ . **Row 2.** As in Line 1 but within an unsuccessfully treated host (state N). The effect of  $k_A^N$  is such that  $k_{0,A}^N = 3$  and  $k_{1,A}^N/k_{0,A}^N = 0.01$ . **Row 3.** As in row 1 but within an untreated host (state U). The effect of  $k_A^U$  is such that  $k_{0,A}^U = 0$  and  $k_{1,A}^U/k_{0,A}^U = 0$ .

level of the initial bacterial load (Figure 2, H). As a consequence,  $\mathcal{N}^U(\bar{x}^{*U}) > 1$  (Figure 2, G), indicating that the infection persists without the influence of antimicrobial treatment (Figure 2, I).

Moreover, the model proposed here allows for capturing other quantitative parameters such as: the probability of remaining in the untreated compartment  $\tau$ -time post-infection, given by  $e^{-\int_0^\tau \omega_U^U(s) ds}$  (Figure 3A); the probability  $e^{-\int_0^\tau \omega_U^{N,A}(s) ds}$ , of remaining in the treated compartment  $\tau$ -time post infection (Figure 3B); and the probability of remaining in the treated state C  $\tau$ -time post-infection, given by  $e^{-\int_0^\tau \gamma_e^C(s) ds}$  (Figure 3C).

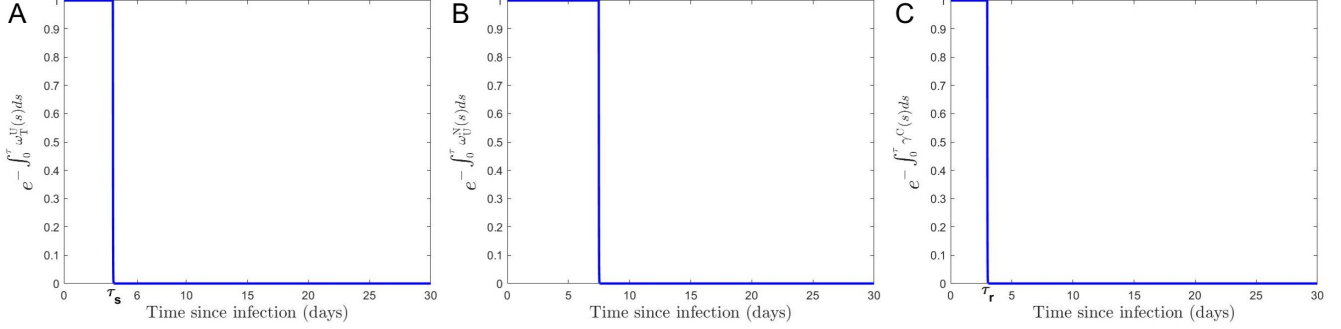


Figure 3: Probabilities of remaining in a compartment  $\tau$ -time post-infection. **(A)** Probability of remaining in the untreated state U  $\tau$ -time post-infection. Time  $\tau_s$  corresponds to the delay prior the treatment. **(B)** Probability of remaining in the treated state N  $\tau$ -time post-infection. **(C)** Probability of remaining in the treated state C  $\tau$ -time post-infection. Time  $\tau_r$  corresponds to the time required for effective treatment.

The associated epidemiological dynamics when only antimicrobial A is used are illustrated by Figure 4. When the compliance probability to recommended guidelines is  $q_C = 50\%$  (Figure 4, line 2), increasing the treatment rate  $q^T$  within the infected population from 50% to 95% slightly improves epidemiological control by reducing the  $\mathcal{R}_0$  from 3.1 to 1.6 (Figure 4D-F). However, this improvement at the epidemiological scale leads to a slight increase in the evolutionary probability of therapeutic failure  $i_A^N$  within the host population (Figure 4D-F), as well as an increase in the average resistance level  $\eta_A^*$  of the host population (Figure 4A-C). A similar configuration occurs when the compliance probability to recommended guidelines is  $q_C = 75\%$  (Figure 4G-I). Although this compliance probability is not sufficient to fully control the infection within the host population, increasing the treatment rate  $q^T$  within the infected population from 50% to 95% substantially improves epidemiological control (Figure 4G-I). Furthermore, the evolutionary probability of therapeutic failure  $i_A^N$  is substantially lower compared to the case  $q_C = 50\%$  (Figure 4, G-I and D-F). Finally, when the compliance probability is sufficiently strong, high treatment rates can definitely control the outbreak within a relatively short period (Figure 4, L).

## 6.2 Evolutionary and epidemiological dynamics with two antimicrobials

We assume that after a period of mono-usage of antimicrobial A until an endemic equilibrium is reached (Figure 4), a proportion  $q_B^T$  of treated infections is replaced by a new antimicrobial B at time  $t = 0$ . Furthermore, at this endemic equilibrium, the infected host population has acquired an average resistance level denoted as  $\eta_A^*$  and defined by (4.9). The antimicrobial B is such that the basic reproduction number  $\mathcal{N}_B^N(\eta_A^*)$  of the bacterial population with resistance level  $\eta_A^*$  is

$$\mathcal{N}_B^N(\eta_A^*) = (1 - r_{\text{eff}}) \mathcal{N}_A^N(\eta_A^*),$$

where the parameter  $r_{\text{eff}} \in (0, 1)$  measures the relative effectiveness of antimicrobial B compared to A. Overall, since the antimicrobial A activity on the sensitive reference strain  $k_{0,A}^\vartheta$  and the ratio of efficiency between the reference resistant and sensitive strains,  $k_{1,A}^\vartheta/k_{0,A}^\vartheta$ , are known (Table 1), constants  $k_{0,B}^\vartheta$  and  $k_{1,B}^\vartheta$  of the killing rate  $k_B^\vartheta$  of antimicrobial B are such that, for  $\vartheta \in \{N, C\}$  :

$$\frac{k_{1,B}^\vartheta}{k_{0,B}^\vartheta} = \frac{k_{1,A}^\vartheta}{k_{0,A}^\vartheta}, \quad \text{and} \quad k_{0,B}^\vartheta = \frac{k_{0,A}^\vartheta + \mu r_{\text{eff}} \left( \frac{k_{1,A}^\vartheta}{k_{0,A}^\vartheta} \right)^{-\eta_A^*}}{1 - r_{\text{eff}}}. \quad (6.1)$$

We illustrate the impact of the newly deployed antimicrobial B on the evolutionary and epidemiological dynamics under various scenarios concerning host population compliance to recommended guidelines ( $q_C$ ). We assume that

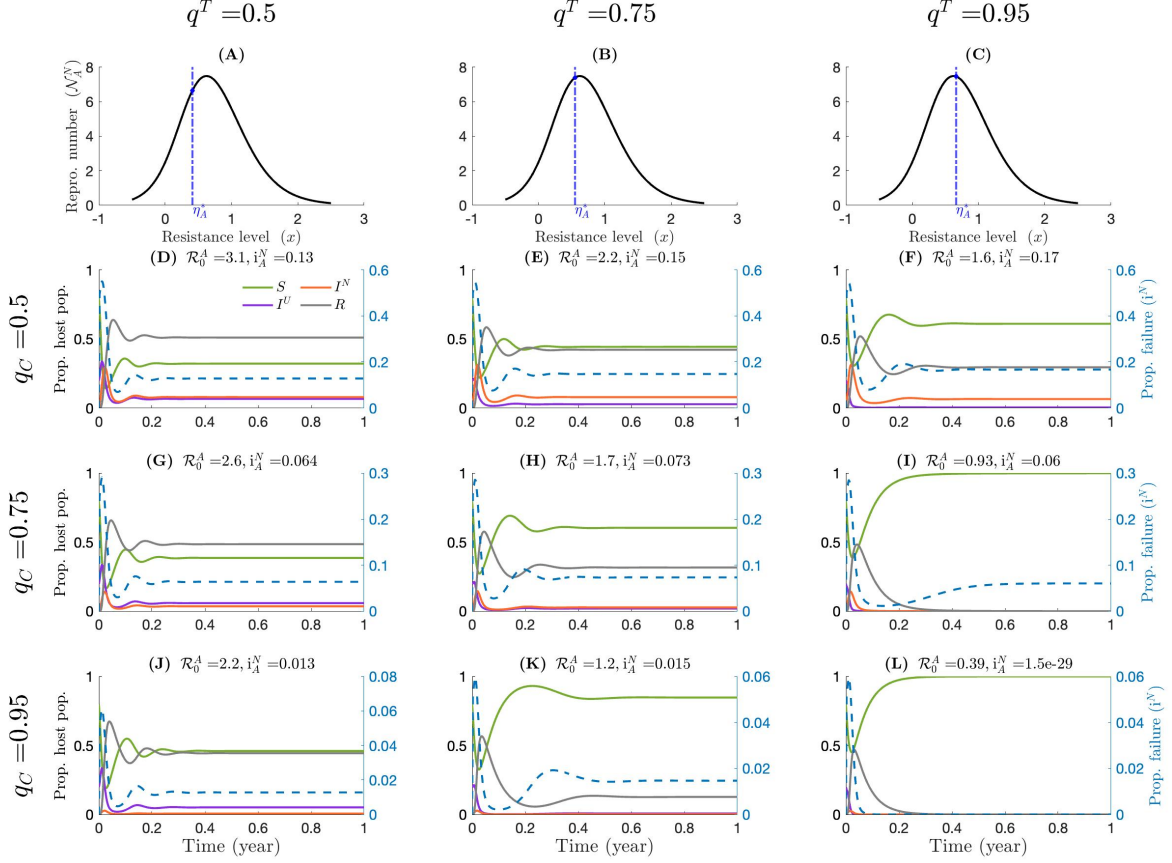


Figure 4: Dynamics of the nested model when only antimicrobial A is used. **Line 1.** The basic reproduction number within an unsuccessfully treated host (state N).  $\eta_A^*$  is the average resistance level within the host population after a period of mono-usage of antimicrobial A with respect to the treatment rate  $q^T$ . **D-F.** The between-host dynamics with respect to the treatment rates when the compliance  $q_C = 0.5$ . **G-I.** same as for D-F, but with  $q_C = 0.75$ . **J-L.** same as for D-F, but with  $q_C = 0.95$ . The other parameter values are default in Table 1,  $\tau_s = 4$  and  $\tau_r = 3$  days. The dashed blue curve represents the proportion of therapeutic failures in the population at time  $t$ .

the relative effectiveness of antimicrobial B compared to A is such that  $r_{\text{eff}} = 0.85$ . In the first scenario, 50% of the host population has a compliance to recommended guidelines (Figure 5). For a low treatment rate  $q^T$  in the host population (Figure 5, column 1), the introduction of antimicrobial B negatively impacts both the epidemic size (as measured by the basic reproduction number  $\mathcal{R}_0$ ) and the evolutionary probability of therapeutic failure (as measured by  $i^N(\infty)$ ). Indeed, increasing the proportion of infections treated with antimicrobial B leads to an increase in the value of the basic reproduction number  $\mathcal{R}_0$  when both A and B are used (denoted as  $\mathcal{R}_0^{\text{AB}}$ ) compared to its value when only A is used (denoted as  $\mathcal{R}_0^{\text{A}}$ ), as shown in Figure 5D,E,F. This configuration is consistent for  $i^N(\infty)$ , with the values  $i_{\text{AB}}^N(\infty)$  always being greater than  $i_{\text{A}}^N(\infty)$ . Similar conclusions hold for intermediate values of the treatment rate  $q^T$  in the host population (Figure 5, column 2). By contrast, for sufficiently high values of the treatment rate  $q^T$  (Figure 5, column 3), introducing antimicrobial B reduces the values of  $\mathcal{R}_0$ . Specifically,  $\mathcal{R}_0^{\text{AB}}$  decreases from 1.6 to 0.96 when the proportion  $q_{\text{B}}^T$  of infections treated with antimicrobial B increases from 0.1 to 0.95 (Figure 5F,I,L). However, although the epidemic size is controlled by increasing the proportion  $q_{\text{B}}^T$ , the presence of antimicrobial B still favors an increase in the evolutionary probability of therapeutic failure  $i^N(\infty)$ .

In the second scenario, 70% of the host population compliant to the recommended guidelines (Figure S1). For a low treatment rates  $q^T$ , the configuration is quite similar to that in Figure (5, column 1), with the introduction of antimicrobial B negatively impacting the evolutionary and epidemiological dynamics (Figure S1, column 1). Intermediate values of the treatment rate  $q^T$  have a slight positive effect on the epidemiological dynamics, resulting in a slight increase in the susceptible population (Figure S1, column 2). In contrast to Figure 5, sufficiently high values of the treatment rate  $q^T$  (Figure S1, column 3) allow for effective epidemic control. Indeed, in such a configuration, when only a small proportion  $q_{\text{B}}^T$  of infections are treated with antimicrobial B, the epidemic is controlled in the relatively short term, even if little effect is observed on the probability of therapeutic failure  $i^N$  (Figure S1F). However, increasing the proportion  $q_{\text{B}}^T$  effectively controls both the epidemic size (measured by  $\mathcal{R}_0$ ) and the evolutionary probability of therapeutic failure (measured by  $i^N$ ), leading to a fully susceptible host population within a relatively short period (Figure S1I and L).

### 6.3 Global sensitivity analysis

We study the sensitivity of the epidemiological basic reproduction number,  $\mathcal{R}_0$ , and the evolutionary probability of therapeutic failure,  $i_{\text{AB}}^N$ , to six parameters: the compliance probability to recommended guidelines ( $q_{\text{C}}$ ), the time required for effective treatment ( $\tau_r$ ), the delay before treatment ( $\tau_s$ ), the treatment rate  $q^T$ , the proportion of treated infection with antimicrobial B ( $q_{\text{B}}^T$ ), and the effectiveness of antimicrobial B compared to A ( $r_{\text{eff}}$ ). The range of variation for these parameters is provided in Table 1. Sensitivity indices are estimated by fitting an ANOVA (Analysis of Variance) linear model, including third-order interactions, to the data generated by simulation. This ANOVA linear model fits well, explaining at least 97% of the variance. For the  $\mathcal{R}_0$ , the sensitivity analysis reveals that  $q^T$ ,  $q_{\text{C}}$ , and  $\tau_s$  are the most influential parameters significantly affecting the epidemiological  $\mathcal{R}_0$ . These parameters account for 29%, 27%, and 24% of the variance, respectively (Figure S2A). These parameters are followed by  $r_{\text{eff}}$ , which explains 5% of the variance. Finally, the importance of  $q_{\text{B}}^T$  and  $\tau_r$  is quite negligible (Figure S2A). For  $i_{\text{AB}}^N$ ,  $q^T$  is the key parameter, explaining 66% of the variance (Figure S2B). It is followed by  $r_{\text{eff}}$  and  $q_{\text{B}}^T$ , which explain 7% and 6% of the variance, respectively. The importance of  $q^T$ ,  $\tau_s$ , and  $\tau_r$  is marginal (Figure S2B).

### 6.4 Optimal intervention

We now investigate the result of implementing an optimal antimicrobial deployment strategy using the objective (5.1). An optimal strategy is determined by the proportion  $q_{\text{B}}^{*\text{T}}$  of antimicrobial B in the treatment landscape, with the remaining proportion ( $q_{\text{A}}^{*\text{T}} = 1 - q_{\text{B}}^{*\text{T}}$ ) being antimicrobial A.

With relatively high values of  $r_{\text{eff}}$  (the effectiveness of antimicrobial B compared to A) and short delay before treatment  $\tau_s$  ( eg.,  $r_{\text{eff}} = 0.85$ , and  $\tau_s = 4$ ), increasing the treatment rate  $q^T$  of infections within the host population significantly reduces the likelihood of failing to control the outbreak using antimicrobials A and B (Figure 6). However, in this scenario, effective epidemic control using antimicrobial drugs A and B is only possible with a sufficiently high treatment rate within the host population (Figure 6A-C). Moreover, increasing the treatment rate  $q^T$  allows for effective epidemic control even when the compliance probability of the host population is relatively weak (Figure 6C). A similar configuration is observed for relatively long delays before treatment (Figure 6D-F). Finally, when the effectiveness of antimicrobial B compared to A,  $r_{\text{eff}}$ , is not strong enough, the use of antimicrobial B is always not recommended, even when the delay before treatment  $\tau_s$  is short and the compliance probability  $q_{\text{C}}$  is high (Figure S3).

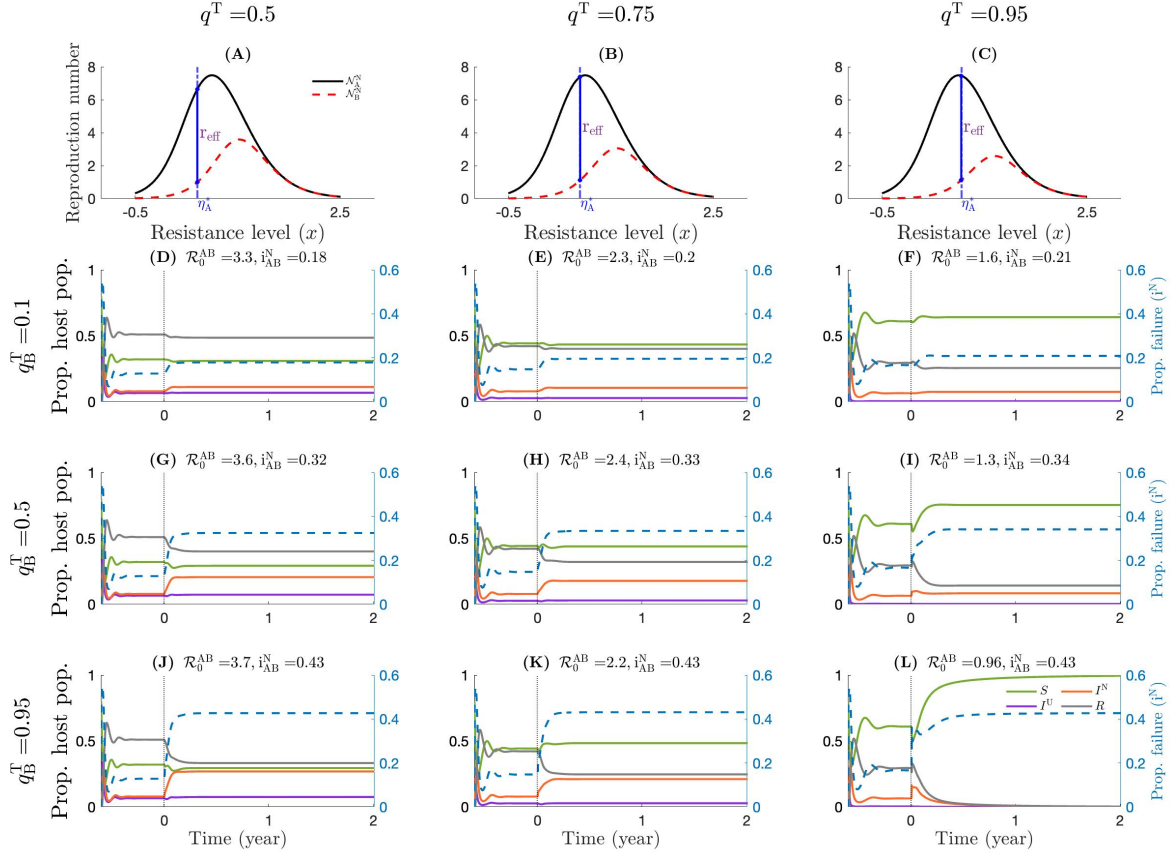


Figure 5: Dynamics of the nested model when the compliance is ( $q_C = 0.5$ ) and the relative effectiveness is ( $r_{\text{eff}} = 0.85$ ). **(A,B,C)** Relative effectiveness of treatment B compared to A within an unsuccessfully treated host (state N). **(D)-(L)** The between-host dynamics with respect to the treatment rates. Parameter values are default in Table 1,  $\tau_s = 4$  and  $\tau_r = 3$  days. The dashed blue curve represents the proportion of therapeutic failures in the population at time  $t$ .

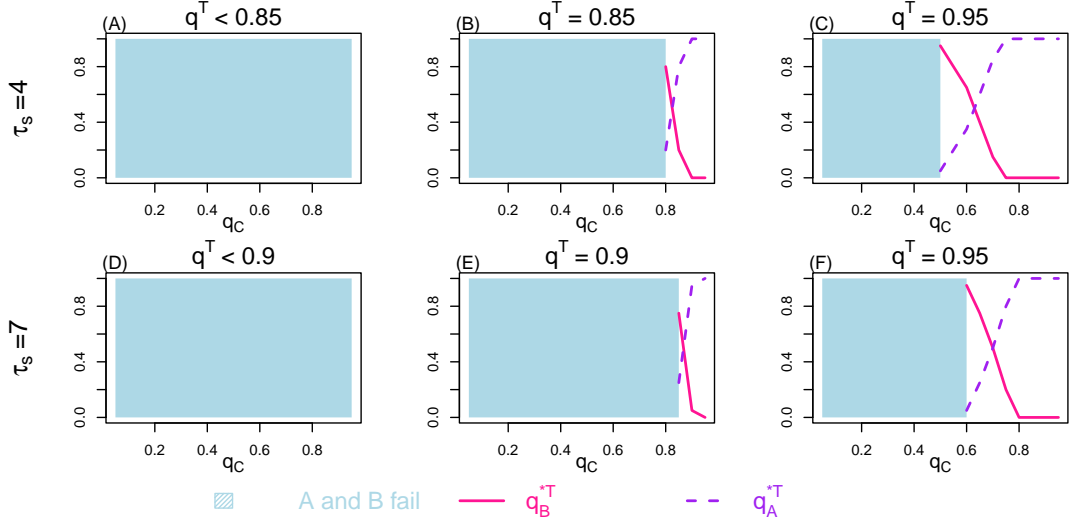


Figure 6: For a given treatment rate  $q^T$  within the host population, the minimum proportion  $q_B^{*T}$  of antimicrobial B, that ensures  $\mathcal{R}_0$  to remain below one is determined with respect to the compliance probability  $q_C$ . The part on treated infections with antimicrobial A is  $q_A^{*T} = 1 - q_B^{*T}$ . **Filled area:**  $q_B^{*T}$  does not exist such that, both antimicrobials A and B fail to clear the outbreak. Here,  $r_{\text{eff}} = 0.85$ ,  $\tau_s = 4$  (line 1) and  $\tau_s = 7$  (line 2), and other parameter values are default in Table 1.

## 7 Discussion

The use of a single antimicrobial can be enough to clear the infection within the host population when (i) the compliance probability of the population to recommended guidelines is sufficiently strong, (ii) the treatment capability of infected individuals by the healthcare system is sufficiently high, and (iii) the time before treatment of infected individuals is sufficiently short (Figure 7). Indeed, in the configuration where the average delay before treatment of infections is 4 days (Figure 7A), at least 90% (*ie.*,  $q^T \geq 0.9$ ) of treated infections by the healthcare system is required to clear the infection within the host population when the compliance probability is high enough (*ie.*,  $q_C \geq 70\%$ ). Furthermore, with relatively long delays before treatment, it becomes quite difficult (in a mono-usage of antimicrobial setting) to ensure the clearance of the infection within the host population even for high values of treatment rates and compliance probabilities (Figure 7B,C).

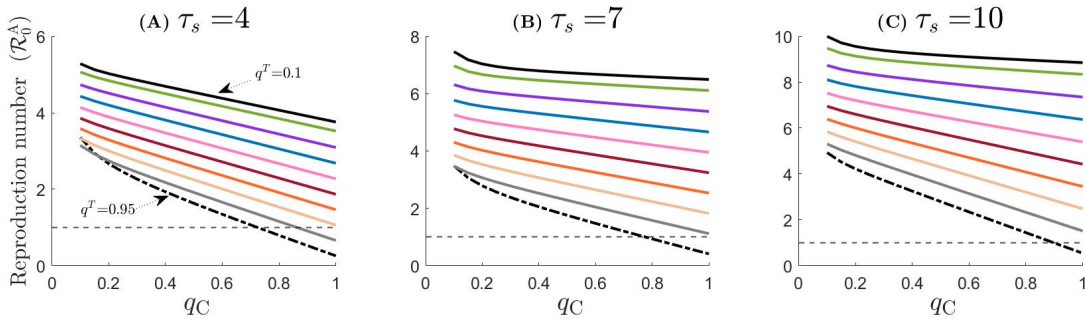


Figure 7: Effect of the compliance probability ( $q_C$ ) and the treatment rate ( $q^T$ ) on the basic reproduction number ( $\mathcal{R}_0^A$ ) when only antimicrobial A is used. Here  $q^T$  varies from 0.1 to 0.95 by step 0.1. From panel A to D we have  $\tau_s = 4, 7$ , and 10 days respectively. The other parameter values are default in Table 1 and  $\tau_r = 3$  days.

As pointed out above, efficient control of the outbreak using only antimicrobial A requires a sufficiently high compliance probability  $q_C$  of the population to recommended guidelines (Figure 7). However, introducing antimicrobial B into the treatment landscape can achieve effective outbreak control when compliance probability is low.

Consider a scenario with a treatment capability of infected individuals by the healthcare system at 95% (*ie.*,  $q^T = 0.95$ ) and an average delay before treatment of about 4 days (*ie.*,  $\tau_s = 4$ ). In a situation where the compliance



probability  $q_C = 0.8$ , using only antimicrobial A is sufficient for effective outbreak control (Figure 8A). However, if the compliance probability is reduced to  $q_C = 0.6$ , this approach fails in controlling the outbreak (Figure 8B). For this moderate compliance value of  $q_C = 0.6$ , by Figure 6C, introducing at least 65% (*ie.*,  $q_B^{*T} = 0.65$ ) of antimicrobial B into the treatment landscape is sufficient to ensure effective outbreak control (Figure 8C). Increasing the proportion of antimicrobial B to 90% more quickly reduces the probability of therapeutic failure within the host population (Figure 8C,D).

Our findings not only recalls that compliance is a key component for the sustainable use of antimicrobial agents but also quantifies its relationships to the other key metrics of bacterial infection control (at both within and between host levels). These results align with other works in the context of drug resistance, *eg.*, [24, 32]. It is, therefore, crucial to explicitly design drug properties that enhance community uptake [4]. However, improving compliance to recommended prescription guidelines is challenging due to its relation to the diversity of external factors, including individual characteristics, population culture, interactions with healthcare providers, and the healthcare system itself that shapes it [30].

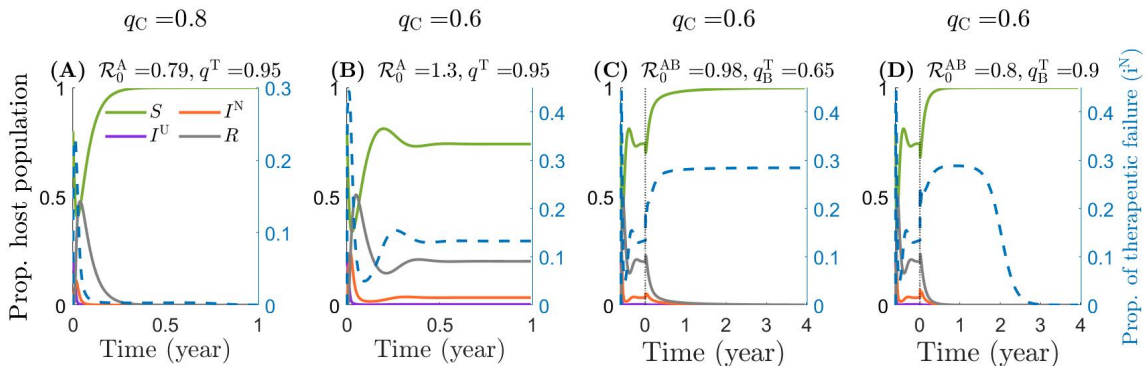


Figure 8: Dynamics of the nested model. **(A-B)** Only antimicrobial A is used and the compliance is  $q_C = 0.8$  for panel A, and 0.6 for panel B. **(C-D)** Both antimicrobials A and B are used in a proportion  $q_B^T = 0.65, q_A^T = 1 - q_B^T$  for panel C, and  $q_B^T = 0.9, q_A^T = 1 - q_B^T$  for panel D. The relative effectiveness is ( $r_{\text{eff}} = 0.85$ ) and the treatment rate within the host population  $q^T = 0.95$ . The other parameter values are default in Table 1 and  $\tau_r = 3$  days.

Caution should be exercised when introducing a new antimicrobial into the healthcare system landscape. The threat of antimicrobial resistance necessitates the sparing use of new drugs, *eg.*, [1, 33]. Even when the relative effectiveness of the new antimicrobial compared to the older one is high, and the compliance probability of the host population is strong, the treatment capability of infected individuals by the healthcare system is a crucial factor for the positive impact of the new antimicrobial on the outbreak size. For instance, the low healthcare system’s treatment capability can contribute to increasing the epidemiological basic reproduction number (*eg.*, Figure S1, line 1). While intermediate treatment capabilities may have a negligible effect on epidemiology, the introduction of a new antimicrobial can negatively impact long-term evolutionary dynamics by increasing the probability of therapeutic failure within the host population (*eg.*, Figure S1, line 2). Furthermore, increasing the treatment capability of the healthcare system lowers the compliance probability threshold to recommended guidelines, below which any antimicrobial strategy would fail to control the epidemic (*eg.*, Figure 6). This may be explained by the fact that failure to sustainably control the infection with a newly introduced antimicrobial (intended to supplement an older antimicrobial under which bacteria are out of control) can lead to the persistence of a bacterial population with a higher average resistance level than initially (*eg.*, Figure 2, line 2).

We assume that treated individuals who comply with recommended medication effectively clear the infection, while non-compliant or untreated individuals fail to do so. However, this represents a potential limitation, as variability in individual immune responses may lead to cases where infected individuals clear the infection without receiving the drug or despite non-compliance with the treatment. The primary reason for this assumption is related to the parameterization purposes of the proposed model. While the model can readily incorporate variability in individual immune responses, parameterizing individual states resulting from such variability (*e.g.*, individuals clearing the infection without receiving the drug or despite non-compliance with the treatment) presents a significant challenge.

## A Assumptions on the nested model (2.1) and (2.4)-(2.5)

**Assumption A.1 (within-host model (2.1))** 1. Functions  $k$ ,  $\xi_\varrho^\vartheta$ , and  $p$  are always positive on  $\mathbb{R}$ , with  $\vartheta \in \{C, N, U\}$  and  $\varrho \in \{A, B\}$ . Furthermore,  $p$  is a bounded function on  $\mathbb{R}$ ,  $\mu > 0$  and  $\kappa > 0$ . Finally, the function  $\frac{p}{\xi_\varrho^\vartheta}$  is continuous on  $\mathbb{R}$  and satisfies  $\frac{p}{\xi_\varrho^\vartheta} > 0$  and  $\lim_{|x| \rightarrow \infty} \frac{p}{\xi_\varrho^\vartheta}(x) = 0$ .

2. The mutation kernel  $J$  is bounded and integrable on  $\mathbb{R}^+$ , positive almost everywhere, and satisfies  $\int_{\mathbb{R}^+} J(x) dx > 0$ ,  $J(-x) = J(x)$ , for all  $x$ .
3. The mutation kernel  $J$  decays rather rapidly towards infinity in the sense that  $J(x) = O\left(\frac{1}{|x|^\infty}\right)$  as  $|x| \rightarrow \infty$ . In other words,  $\lim_{|x| \rightarrow \infty} |x|^n J(x) = 0$ , for all  $n \in \mathbb{N}$ .

**Assumption A.2 (between-host model (2.4)-(2.5))** 1. Recruitment rate  $\Lambda$  and natural death rate  $\mu_h$  are positive constants.

2. The treatment rates  $q^T$ ,  $q_A^T$  and  $q_B^T$  are positive constants.
3. The rates  $\omega_U^{C,e}$ ,  $\omega_U^{N,e}$ ,  $\omega_T^U$  belongs to  $L^\infty(\mathbb{R}_+)$ , with respective essential upper bounds  $\bar{\omega}_U^{C,e}$ ,  $\bar{\omega}_U^{N,e}$ ,  $\bar{\omega}_T^U$  and positive essential lower bounds  $\underline{\omega}_U^{C,e}$ ,  $\underline{\omega}_U^{N,e}$ ,  $\underline{\omega}_T^U$ , with  $\varrho \in \{A, B\}$ .
4. Parameters  $\beta^U$ ,  $\alpha^U$ ,  $\beta_\varrho^\vartheta$ ,  $\alpha_\varrho^\vartheta$  and  $\gamma_\varrho^\vartheta$  ( $\varrho \in \{A, B\}$ ,  $\vartheta \in \{C, N\}$ ) belongs to  $L^\infty(\mathbb{R}_+)$ .
5. The transmission rates  $\beta^U(\cdot)$ ,  $\beta_\varrho^C(\cdot)$ ,  $\beta_\varrho^N(\cdot)$ ,  $s$  ( $\varrho \in \{A, B\}$ ) are Lipschitz continuous almost everywhere on  $\mathbb{R}_+$ .

## B The evolutionary operator $\Pi$

The function  $\Pi(\tau_2, \tau_1)$ , defined for  $0 \leq \tau_1 \leq \tau_2 < \infty$ , represents the evolutionary system generated by the linear operator  $\mathbf{A}$ , which describes the transitions between different infection statuses. It means that  $\Pi$  is generated from the following evolutionary system

$$(\partial_t + \partial_\tau) \mathbf{I}(t, \tau) = \mathbf{A}(\tau) \mathbf{I}(t, \tau), \quad (\text{B.1})$$

where

$$\mathbf{q} = \begin{pmatrix} q_C \mathbf{q}^T \mathbf{e} \\ (1 - q_C) \mathbf{q}^T \mathbf{e} \\ 1 - q^T \end{pmatrix},$$

$$\mathbf{A}(\tau) = \begin{pmatrix} -\Phi^C(\tau) & \mathbf{O}_2 & q_C \mathbf{q}^T \mathbf{e} \omega_T^U(\tau) \\ \mathbf{O}_2 & -\Phi^N(\tau) & (1 - q_C) \mathbf{q}^T \mathbf{e} \omega_T^U(\tau) \\ e^t (1 - \mathbf{q}^T) \omega_U^C(\tau) & e^t (1 - \mathbf{q}^T) \omega_U^N(\tau) & -\Phi^U(\tau) \end{pmatrix},$$

with  $\Phi^C(\tau) = \alpha^C(\tau) + \gamma^C(\tau) + (1 - \mathbf{q}^T) \omega_U^C(\tau) + \mu_h$ ,  $\Phi^N(\tau) = \alpha^N(\tau) + \gamma^N(\tau) + (1 - \mathbf{q}^T) \omega_U^N(\tau) + \mu_h$ , and  $\Phi^U(\tau) = \alpha^U(\tau) + q^T \omega_T^U(\tau) + \mu_h$ .

If, for example, the linear operator  $\mathbf{A}$  is diagonal, we have

$$\mathbf{I}(t, \tau) = \begin{cases} e^{\int_0^\tau \mathbf{A}(\eta) d\eta} \mathbf{I}(t - \tau, 0) = \Pi(\tau, 0) \mathbf{I}(t - \tau, 0); & t > \tau \\ e^{\int_{\tau-t}^\tau \mathbf{A}(\eta) d\eta} \mathbf{I}(0, \tau - t) = \Pi(\tau, \tau - t) \mathbf{I}(0, \tau - t); & t < \tau. \end{cases}$$

In such a configuration we explicitly have  $\Pi(\tau_2, \tau_1) = e^{\int_{\tau_1}^{\tau_2} \mathbf{A}(\eta) d\eta}$ . However, obtaining an explicit expression for  $\Pi$  may not always be straightforward or possible in general. A naive approach would be to solve problem (B.1) as above, but it is well known that such an exponent formula does not give a solution to the problem at hand.

## C Detailed formulation of System (2.4) and (2.5)

$$\left\{ \begin{aligned}
 & \dot{S}(t) = \Lambda - S(t)\lambda(t) - \mu_h S(t), \\
 & (\partial_t + \partial_\tau) I_A^C(t, \tau) = - \left( \alpha_A^C(\tau) + \gamma_A^C(\tau) + (1 - q^T q_A^T) \omega_U^{C,A}(\tau) + \mu_h \right) I_A^C(t, \tau) + q_C q^T q_A^T \omega_U^U(\tau) I^U(t, \tau), \\
 & (\partial_t + \partial_\tau) I_B^C(t, \tau) = - \left( \alpha_B^C(\tau) + \gamma_B^C(\tau) + (1 - q^T q_B^T) \omega_U^{C,B}(\tau) + \mu_h \right) I_B^C(t, \tau) + q_C q^T q_B^T \omega_U^U(\tau) I^U(t, \tau), \\
 & (\partial_t + \partial_\tau) I_A^N(t, \tau) = - \left( \alpha_A^N(\tau) + \gamma_A^N(\tau) + (1 - q^T q_A^T) \omega_U^{N,A}(\tau) + \mu_h \right) I_A^N(t, \tau) + (1 - q_C) q^T q_A^T \omega_U^U(\tau) I^U(t, \tau), \\
 & (\partial_t + \partial_\tau) I_B^N(t, \tau) = - \left( \alpha_B^N(\tau) + \gamma_B^N(\tau) + (1 - q^T q_B^T) \omega_U^{N,B}(\tau) + \mu_h \right) I_B^N(t, \tau) + (1 - q_C) q^T q_B^T \omega_U^U(\tau) I^U(t, \tau), \\
 & (\partial_t + \partial_\tau) I^U(t, \tau) = - \left( \alpha^U(\tau) + q^T \omega_U^U(\tau) + \mu_h \right) I^U(t, \tau) + (1 - q^T q_A^T) \left( \omega_U^{C,A}(\tau) I_A^C(t, \tau) + \omega_U^{N,A}(\tau) I_A^N(t, \tau) \right) \\
 & \quad \quad \quad + (1 - q^T q_B^T) \left( \omega_U^{C,B}(\tau) I_B^C(t, \tau) + \omega_U^{N,B}(\tau) I_B^N(t, \tau) \right), \\
 & \dot{R}_A(t) = \int_0^\infty (\gamma_A^C(\tau) I_A^C(t, \tau) + \gamma_A^N(\tau) I_A^N(t, \tau)) d\tau - \mu_h R_A(t), \\
 & \dot{R}_B(t) = \int_0^\infty (\gamma_B^C(\tau) I_B^C(t, \tau) + \gamma_B^N(\tau) I_B^N(t, \tau)) d\tau - \mu_h R_B(t), \\
 & I_A^C(t, \tau = 0) = q_C q^T q_A^T \lambda(t) S(t), \quad I_B^C(t, \tau = 0) = q_C q^T q_B^T \lambda(t) S(t), \\
 & I_A^N(t, \tau = 0) = (1 - q_C) q^T q_A^T \lambda(t) S(t), \quad I_B^N(t, \tau = 0) = (1 - q_C) q^T q_B^T \lambda(t) S(t), \\
 & I^U(t, \tau = 0) = (1 - q^T) \lambda(t) S(t), \\
 & S(0) = S_0, \quad R_A(0) = R_{A,0}, \quad R_B(0) = R_{B,0}, \quad I^U(0, \tau) = I_0^U(\tau), \quad I_\varrho^\vartheta(0, \tau) = I_{\varrho,0}^\vartheta(\tau), \quad \vartheta \in \{C, N\}, \quad \varrho \in \{A, B\}.
 \end{aligned} \right. \tag{C.1}$$

## D Supplementary figure

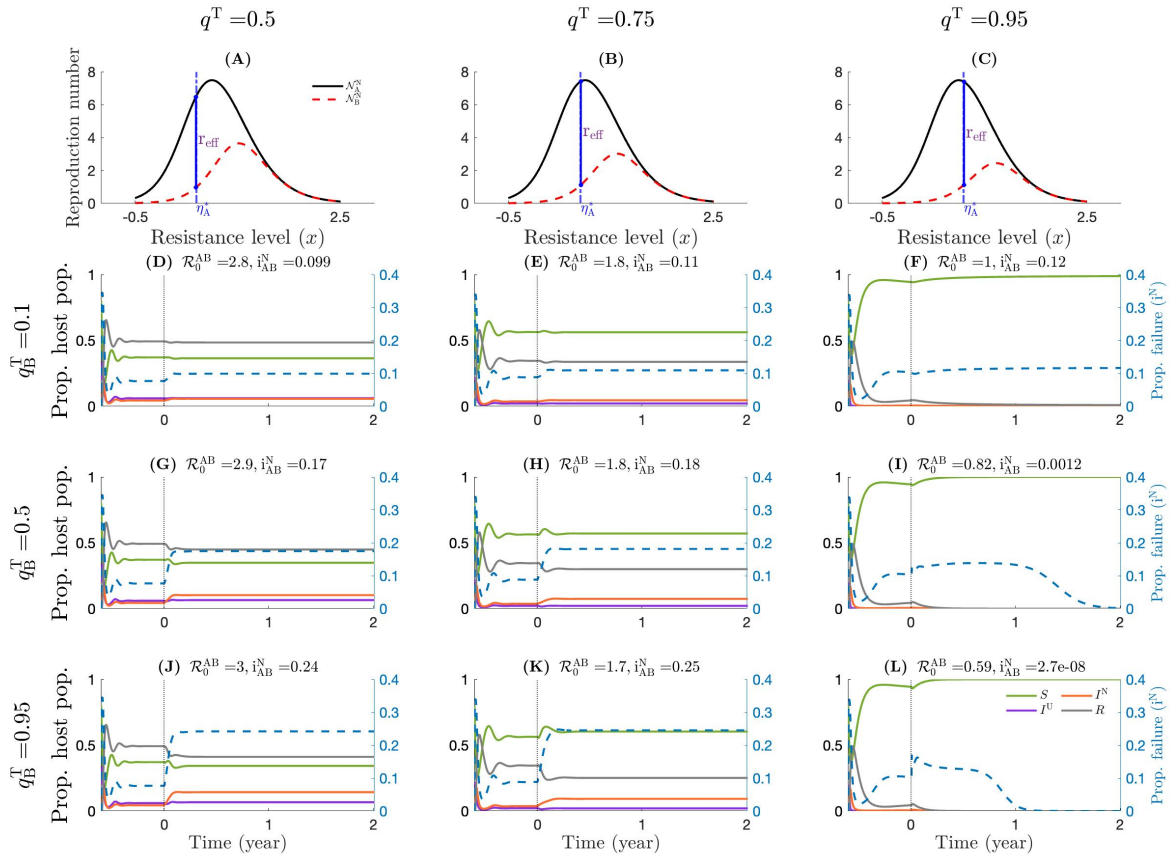


Figure S1: As in Figure 5, but with a compliance probability of  $q_C = 0.7$ .

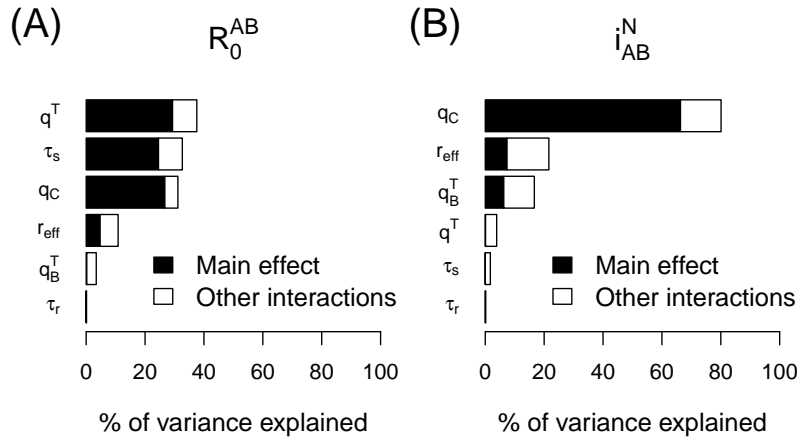


Figure S2: Sensitivity indices for: **(A)** the epidemiological basic reproduction number  $\mathcal{R}_0$ , and **(B)** the evolutionary probability of therapeutic failure  $i_{AB}^N$ . The factors considered are the compliance probability to recommended guidelines ( $q_C$ ), the time required for an effective treatment ( $\tau_r$ ), the delay prior to treatment ( $\tau_s$ ), the treatment rate  $q^T$ , the proportion of treated infection with antimicrobial B ( $q_B^T$ ), and the effectiveness of antimicrobial B compared to A ( $r_{eff}$ ). Main indices show the effect of each factor alone, while total indices show the effect of interactions with other factors.

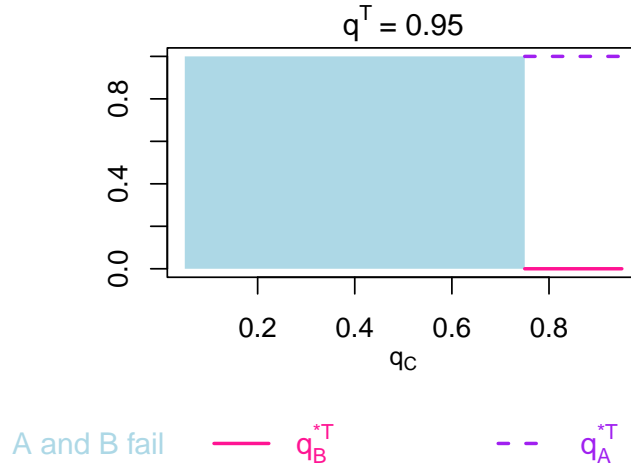


Figure S3: As in Figure 6, but with  $r_{eff} = 0.7$  and  $\tau_s = 4$ .

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