Bulletin of Mathematical Biology (2020) 82:6
https://doi.org/10.1007/s11538-019-00686-x

Society for Mathematical Biology

ORIGINAL ARTICLE

Modeling Antibiotic Use Strategies in Intensive Care Units: Comparing De-escalation and Continuation

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Received: 25 August 2018 / Accepted: 2 December 2019 / Published online: 23 December 2019

Abstract
Antimicrobial de-escalation refers to the treatment mechanism of switching from empiric antibiotics with good coverage to alternatives based on laboratory susceptibility test results, with the aim of avoiding unnecessary use of broad-spectrum antibiotics. In a previous study, we have developed multi-strain and multi-drug models in an intensive care unit setting, to evaluate the benefits and trade-offs of de-escalation in comparison with the conventional strategy called antimicrobial continuation. Our simulation results indicated that for a large portion of credible parameter combinations, de-escalation reduces the use of the empiric antibiotic but increases the probabilities of colonization and infections. In this paper, we first simplify the previous models to compare the long-term dynamical behaviors between de-escalation and continuation systems under a two-strain scenario. The analytical results coincide with our previous findings in the complex models, indicating the benefits and unintended consequences of de-escalation strategy result from the nature of this treatment mechanism, not from the complexity of the high-dimensional systems. By extending the models to three-strain scenarios, we find that de-escalation is superior than continuation in preventing outbreaks of invading strains that are resistant to empiric antibiotics. Thus decisions on antibiotic use strategies should be made specifically according to ICU conditions and intervention objectives.

Keywords Antibiotic resistance · Antimicrobial de-escalation · ODE models

Mathematics Subject Classification 92D25 · 92D30 · 34D20 · 34D23

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1 Introduction

Antimicrobial resistance is one of the leading threats in public health, and the rise of this issue could result in life-threatening untreatable infections caused by antimicrobial-resistant pathogens. Due to the limited therapeutic options, antimicrobial stewardship programs (ASPs) have been advocated by public health authorities and implemented in numerous hospitals since late 1990s. ASPs aim to seek for optimal antibiotic use strategies that can preserve the effectiveness of important antibiotics, reduce the cost of health care for infections, and slow down the evolution of antimicrobial resistance. Antimicrobial de-escalation is one of the most recommended strategies and has been commonly practiced by almost all ASP teams (Dellit et al. 2007; Timsit et al. 2014). De-escalation refers to the procedure of stopping unnecessary antibiotic and switching to the "first-line" antibiotics that are older, less expensive, or with a narrower coverage when laboratory test confirms susceptibility. As opposed to de-escalation, the conventional strategy is called continuation (or non-de-escalation), which refers to the continuum use of antibiotics even though the patient can be treated by a "first-line" drug. A lot of clinical and observational studies have been conducted to understand the effects of de-escalation comparing to continuation, but the conclusions varied broadly from study to study (Tabah et al. 2016). For example, no significant change in mortality rate was observed for most of the studies (Tabah et al. 2016), and unintended increases in multi-drug-resistant strains have been observed in the treatment groups following de-escalation (Kim et al. 2012).

Differential equation models have been widely applied in the study of antibiotic use in hospital settings (Spicknall et al. 2013; van Kleef et al. 2013), and strategies such as cycling and informed cycling (Kouyos et al. 2011; zur Wiesch et al. 2014; Tepekule et al. 2017), antibiotic restriction (Obolski et al. 2015), and minimizing treatment duration (Hurford et al. 2012) have been well-studied by constructing complex high-dimensional ODE systems. Realistic models can provide intuitive insights of the mechanisms with credible parameterization methods. Mathematical analysis of the simplified systems can provide parameter thresholds on the outbreak potentials of antimicrobial-resistant pathogens via bifurcation analysis (Webb et al. 2005; D'Agata et al. 2005, 2007; Webb et al. 2009; Webb and Browne 2015; Cen et al. 2017).

To address the varying observations, we have previously developed a novel mathematical model to theoretically compare the impacts of antimicrobial de-escalation and continuation therapies in intensive care units (ICUs) (Hughes et al. 2017). Our simulation results show that de-escalation has advantages at reducing both the use and resistance prevalence of the broad-spectrum antibiotics, but on the other hand, it leads to higher infection and colonization rates in ICUs. However, due to the high dimensionality and complexity of the model, it was rather hard to evaluate the invasion potentials of the drug-resistant strains under each treatment strategy. Further, the model in Hughes et al. (2017) adopts many realistic assumptions (such as the co-circulation of multiple pathogens, the use of multiple drugs, as well as the separation of empiric and definitive therapies), thus we wondered if the benefits and unintended consequences of de-escalation obtained from the simulations are resulted from the complexity of the model system, or the nature of the two treatment strategies.

Motivated by the above, in this paper, we investigate simplified model systems that capture only the key difference between de-escalation and continuation. That is, we consider two ICUs with identical ecological environments but adopt de-escalation and continuation individually as each one's main treatment strategy—the one with de-escalation aims to treat patients with de-escalated antibiotics whenever there is no resistance, while the one with continuation adopts the de-escalated drugs only when the empiric broad-spectrum antibiotics stop working.[1] We will first show, via rigorous analysis, same benefit and unintended consequences of de-escalation can be observed in the simplified systems. Thus, the pros and cons of de-escalation are not caused by the complex model structure in the realistic setting in Hughes et al. (2017), but are due to the difference in nature between the two treatment strategies. Then by computing the invasion reproductive number $\mathcal{R}_0$ of each system, we can compare the abilities possessed by the two strategies in preventing outbreaks of nosocomial infections. We show that de-escalation is advantageous in preventing the pathogens that are resistant to the broad-spectrum antibiotics from invading the ICUs.

This paper involves the analysis and comparison of several model systems, and is organized as follows. In Sect. 2, we introduce the model assumptions and formulation for the two-strain scenario; in Sect. 3, we present the mathematical analysis results of continuation and de-escalation systems, respectively; in Sect. 4, we compare the dynamical behaviors of the two systems both mathematically and numerically; in Sect. 5, we develop the models for the three-strain scenario to investigate the invasion potential of strains resistant to the empiric antibiotic. We organize rigorous mathematical proofs on the stability results of the two-strain systems in the "Appendix," such results are not only useful for comparing the values of steady states between the two systems, but also necessary to guarantee the linearization of the three-strain systems at their corresponding steady states to compute the invasion reproductive numbers in Sect. 5.

2 Model Formulation: Two-Strain Scenario

We consider the co-circulation of two strains of a certain bacterial species—*Pseudomonas aeruginosa*, and two antibiotics that are mostly used as broad-spectrum drug (piperacillin/tazobactam) (American Thoracic Society and Infectious Diseases Society of America 2005; Mermel et al. 2009; Hughes et al. 2016), and the de-escalated drug (ciprofloxacin) (Braykov et al. 2014; Shime et al. 2013; Khasawneh et al. 2014; Kollef et al. 2006; Kaye 2012; Mokart et al. 2014). For simplicity, we label the two strains by numbers 0 and 1, and label the two antibiotics by letters A and B. The patient population in the ICU is then stratified into five classes: uncolonized (S), colonized by strain 0 and 1, respectively, (C_0 and C_1), and infected by strain 0 and 1, respectively, (I_0 and I_1). Specifically, a patient being colonized/infected by strain i, $i = 0, 1$ means that this patient's colonization/infection is dominated by strain i. Coexistence of both strains in one patient is possible, to start with the simplest model, we assume that

[1] Definition of de-escalation from Dellit et al. (2007), Timsit et al. (2014).

patients will majorly transmit, and get colonized/infected by their dominant strains. Our models are based on the following assumptions.

Assumption 1 Strain 0 refers to the susceptible strain, which is susceptible to both drug A and B.

Assumption 2 Strain 1 refers to the resistant strain, which is resistant to drug A but is susceptible to drug B.

Thus, drug A is regarded as the de-escalated antibiotic to treat strain 0 as it has a narrower coverage (such as ciprofloxacin), and drug B is the empiric drug for all infections due to its broad coverage (such as piperacillin/tazobactam).

Assumption 3 Patients are admitted at a constant rate λ into the ICU, with a percentage p of them being uncolonized, and a percentage $(1-p)$ of them being colonized by strain 0.

Here, we assume no patient is colonized by resistant strain upon admission, partly because we consider the ICUs being the epicenter for the transmission of resistance strains, and partly because doing this will facilitate our computation of the invasion reproductive numbers mathematically. In reality, patients already colonized by strain 1 could be admitted into the hospitals, models with such assumptions would be worthwhile to investigate as well.

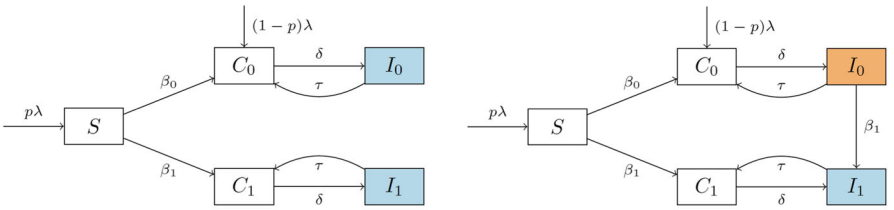
Assumption 4 All patients are removed due to discharge or mortality at a constant rate μ.

We make Assumption 4 based on the following argument: (1) according to clinical studies, the correlation between bacterial resistance and patient mortality is unclear, it was also found that antibiotic resistance had little effect on mortality (Lambert et al. 2011), thus the mortality rates for patients in I_0 and I_1 can be assumed as the same; (2) uninfected patients usually have a lower risk of mortality, thus the mortality rates for classes S, C_0, C_1 should be smaller than I_0, I_1; (3) uninfected patients often have a shorter hospital stay, so the discharge rates for classes S, C_0, C_1 are higher than I_0, I_1; (4) therefore, it is hard to compare the overall removal rates for uninfected and infected patients, and we assume each compartment has the same removal rate for simplification. Indeed, in a more realistic setting, removal rates in each compartment should be different as assumed in Hughes et al. (2017). But as our main purpose of this paper is to investigate the dynamical differences caused by the drug use mechanisms, we leave the more realistic assumption on removal rates for future work.

Assumption 5 Colonized patients could develop infections at a constant rate δ (Hurford et al. 2012; Hughes et al. 2017).

Assumption 6 Infected patients immediately receive effective treatments, and are cured at a constant rate τ.

Here, we simplify the model structure in Hughes et al. (2017) by omitting the empiric therapy and assuming instant diagnosis, since we would like our model to reflect the major difference in the drug use guideline between de-escalation and continuation. The fact that patients have to go through empiric therapy is due to the



(a) Continuation. **(b)** De-escalation

Fig. 1 Compartmental dynamics for antimicrobial continuation and de-escalation models. Compartments colored in blue represent infected patients under treatment of the empiric drug B, and the one colored in orange represents patients under treatment of the de-escalated drug A. When the ICU adopts **continuation** strategy, all infected patients are treated with the broad-spectrum drug B thus there is no strain conversion. When the ICU adopts **de-escalation** strategy, patients in I_0 are receiving drug A and could experience strain conversion via transmissions of strain 1 under the antibiotic selection pressure (Color figure online)

current lack of fast diagnosis technology, which could become available in the future and makes this assumption closer to the reality.

According to the records from our ASP group at Toronto Mount Sinai Hospital, the standard length for antibiotic treatments in ICUs are uniformly fixed regardless of the drug type, such information can be retrieved from the previous publication of the same group (Hurford et al. 2012). So we assume infected patients being cured at a same rate.

Assumption 7 The transmission rates for two strains are assumed to be β_0 and β_1, respectively.

Similar to the assumptions in Hughes et al. (2017), we omit the transmission "vectors" such as health care workers and medical devices, and assume bacteria strains being directly transmitted from patient to patient.

Assumption 8 Patients infected by *P. aeruginosa* usually remain its carriers for 12-25 days (REUSSIR 2001; Murray et al. 2007), which is longer than the normal stay in the ICU (Giantsou et al. 2007; Paskovaty et al. 2015; De Bus et al. 2016). So we assume that infected patients remain colonized for their duration of stay after finishing antibiotic treatments, that is, patients in I_i would recover and move to C_i for $i = 0, 1$.

Assumption 9 Resistant strain can replace dominant sensitive strain given antibiotic selection pressure (Spicknall et al. 2013).

That is, under de-escalation strategy, patients in I_0 are treated with drug A, and it is possible for them to get contaminated by strain 1; then on the individual level, drug A reduces strain 0 but not strain 1; therefore, such patients will have their infection being dominated by the resistant strain 1 under the drug A selection pressure. On the other hand, under continuation strategy, all infected patients are treated with the broad-spectrum drug B which covers both strains; then, no strain conversion could happen. In this way, de-escalation and continuation can result in different treatment mechanisms for ICU patients and the two systems are differed dynamically.

The compartmental dynamics of both de-escalation and continuation scenarios are shown and illustrated in Fig. 1. Model parameters are summarized in Table 1.

Table 1 Parameter table

Parameter	Definition
Parameters for all models	
λ	Patient admission rate
μ	Patient discharge/death rate
p	Percentage of uncolonized patients upon admission
δ	Infection development rate for colonized patients
τ	Infection clearance rate under antibiotic treatments
β_0	Transmission rate of bacteria strain 0
Parameters for multiple strain models	
β_1	Transmission rate of bacteria strain 1
β_2	Transmission rate of bacteria strain 2

The model equations for continuation strategy are shown in (1).

$$\begin{aligned}
\dot{S} &= p\lambda - \beta_0(C_0 + I_0)S - \beta_1(C_1 + I_1)S - \mu S,\\
\dot{C}_0 &= (1-p)\lambda + \beta_0(C_0 + I_0)S + \tau I_0 - (\delta + \mu)C_0,\\
\dot{I}_0 &= \delta C_0 - (\tau + \mu)I_0,\\
\dot{C}_1 &= \beta_1(C_1 + I_1)S + \tau I_1 - (\delta + \mu)C_1,\\
\dot{I}_1 &= \delta C_1 - (\tau + \mu)I_1.
\end{aligned} \tag{1}$$

The model equations for de-escalation strategy are shown in (2).

$$\begin{aligned}
\dot{S} &= p\lambda - \beta_0(C_0 + I_0)S - \beta_1(C_1 + I_1)S - \mu S,\\
\dot{C}_0 &= (1-p)\lambda + \beta_0(C_0 + I_0)S + \tau I_0 - (\delta + \mu)C_0,\\
\dot{I}_0 &= \delta C_0 - (\tau + \mu)I_0 - \beta_1(C_1 + I_1)I_0,\\
\dot{C}_1 &= \beta_1(C_1 + I_1)S + \tau I_1 - (\delta + \mu)C_1,\\
\dot{I}_1 &= \delta C_1 + \beta_1(C_1 + I_1)I_0 - (\tau + \mu)I_1.
\end{aligned} \tag{2}$$

3 Model Analysis: Two-Strain Scenario

When there is no presence of the resistant strain, based on Assumption 6, there is no difference between de-escalation and continuation strategies on the population level in the ICU. Mathematically, it is easy to check that $(S^*, C_0^*, I_0^*, 0, 0)$ is the unique resistant strain-free equilibrium for both system (1) and (2), where

$$S^* = \frac{\frac{\beta_0\lambda}{\mu} + \mu - \sqrt{(\mu + \frac{\beta_0\lambda}{\mu})^2 - 4\beta_0 p\lambda}}{2\beta_0},\ C_0^* = \frac{\mu+\tau}{\mu+\tau+\delta}X_0^*,\ I_0^* = \frac{\delta}{\mu+\tau+\delta}X_0^*,\ X_0^* = \frac{\lambda}{\mu} - S^*.$$

3.1 Continuation System

We aim to analyze the long-term behaviors of system (1). Firstly let $X_0 := C_0 + I_0$ and $X_1 := C_1 + I_1$, system (1) is reduced to a three-dimensional system (3).

$$\begin{aligned} \dot{S} &= p\lambda - \beta_0 X_0 S - \beta_1 X_1 S - \mu S, \\ \dot{X_0} &= (1-p)\lambda + \beta_0 X_0 S - \mu X_0, \\ \dot{X_1} &= \beta_1 X_1 S - \mu X_1. \end{aligned} \tag{3}$$

We therefore have the following positivity and boundedness results.

Proposition 1 *For any initial value $S(0)$, $X_0(0)$, $X_1(0) \geq 0$, the solution to (3) is strictly positive for $S(t)$ and $X_0(t)$, and nonnegative for $X_1(t)$ for all $t > 0$, and is uniformly bounded in $\mathbb{R}^3_+$ for sufficiently large $t \geq 0$. Moreover, for any strictly positive initial condition $(S(0), X_0(0), X_1(0))$, the solution to (3) is strictly positive for all $t \geq 0$.*

We here borrow the concept of invasion reproductive number from ecology (Pugliese 2000) as many other studies (Martcheva et al. 2007; Martcheva 2009; Xiridou et al. 2009) did. The **invasion reproductive number** of strain 1, $\mathcal{R}_1$, is defined as the number of secondary colonization/infections that one individual colonized/infected with strain 1 can produce in the ICU where the strain 0 is already present and at equilibrium.

Note that $(S^*, X_0^*, 0)$ is the resistant strain-free equilibrium of system (3); then, it is locally asymptotically stable for $\mathcal{R}_1 < 1$ and otherwise unstable. Technically, we should calculate $\mathcal{R}_1^{\mathrm{CT}}$ for the continuation system by applying the method in Van Den Driessche and Watmough (2002) to the system linearized at $(S^*, X_0^*, 0)$, and we have $\mathcal{R}_1^{\mathrm{CT}} = \beta_1 S^*/\mu$. The following theorem shows the stability results of system (3).

Theorem 1 *For $\mathcal{R}_1^{CT} < 1$, $(S^*, X_0^*, 0)$ is the unique, globally asymptotically stable equilibrium of system (3). When $\mathcal{R}_1^{CT} > 1$, there exist two equilibria, $(S^*, X_0^*, 0)$ being unstable, and $(\bar{S}, \bar{X_0}, \bar{X_1})$ being globally asymptotically stable with*

$$\bar{S} = \frac{\mu}{\beta_1},\ \bar{X_0} = \frac{1-p}{1-\frac{\beta_0}{\beta_1}} \cdot \frac{\lambda}{\mu},\ \bar{X_1} = \frac{p-\frac{\beta_0}{\beta_1}}{1-\frac{\beta_0}{\beta_1}} \cdot \frac{\lambda}{\mu} - \frac{\mu}{\beta_1}.$$

Proof See "Appendix." □

3.2 De-escalation System

We now analyze system (2). Let $X_1 := C_1 + I_1$, (2) can be reduced to a four-dimensional system (4), and the positivity and boundedness results are as follows:

$$\begin{aligned} \dot{S} &= p\lambda - \beta_0(C_0 + I_0)S - \beta_1 X_1 S - \mu S, \\ \dot{C_0} &= (1-p)\lambda + \beta_0(C_0 + I_0)S + \tau I_0 - (\delta + \mu)C_0, \end{aligned}$$

$$\begin{aligned}\dot{I}_0 &= \delta C_0 - \beta_1 X_1 I_0 - (\tau + \mu) I_0,\\ \dot{X}_1 &= \beta_1 X_1 (S + I_0) - \mu X_1.\end{aligned} \tag{4}$$

Proposition 2 *For any nonnegative initial value* $S(0), C_0(0), I_0(0), X_1(0) \geq 0$*, the solution to system* (4) *is bounded and* $S(t), C_0(t), I_0(t) > 0$ *for all* $t > 0$*. Thus, the flow* Φ_t *generated by the solution to the system is point dissipative.*

Clearly, $(S^*, C_0^*, I_0^*, 0)$ is the resistant strain-free equilibrium of (4), and the invasion reproductive number of strain 1 for the de-escalation system can be computed similarly as $\mathcal{R}_1^{\mathrm{DE}} = \beta_1 (S^* + I_0^*)/\mu$. Under the same set of parameters, we have

$$\mathcal{R}_1^{\mathrm{DE}} > \mathcal{R}_1^{\mathrm{CT}},$$

thus, continuation is always superior in preventing the invasion of the resistant strain 1 than de-escalation.

Further, if the invasion of strain 1 cannot be avoided with either continuation or de-escalation, we would like to determine which of the two strategies can result in less colonized and infected patients. In order to do so, we will need to find the positive equilibrium for system (4). We identify the resistant strain transmission rate β_1 as the bifurcation parameter, and then $\mathcal{R}_1^{\mathrm{DE}} = 1$ corresponds to a threshold for β_1 as stated below.

Definition 1 Denote $\beta_1^\dagger := \mu/(S^* + I_0^*)$, then $\beta_1 > \beta_1^\dagger$ if and only if $\mathcal{R}_1^{\mathrm{DE}} > 1$. Denote $\beta_1^* := \mu/S^*$, then $\beta_1 > \beta_1^*$ if and only if $\mathcal{R}_1^{\mathrm{CT}} > 1$.

3.2.1 Stability Results

We first have the stability result for the resistant strain-free equilibrium.

Theorem 2 *The resistant strain-free equilibrium* $(S^*, C_0^*, I_0^*, 0)$ *for system* (4) *is locally stable for* $\mathcal{R}_1^{DE} < 1$*, and unstable for* $\mathcal{R}_1^{DE} > 1$*.* $(S^*, C_0^*, I_0^*, 0)$ *is globally asymptotically stable when* $\beta_1 < \mu^2/\lambda$*.*

Proof See "Appendix." □

The next theorem investigates the local bifurcation near the resistant strain-free equilibrium $(S^*, C_0^*, I_0^*, 0)$ as β_1 perturbs from $\beta_1^\dagger$, we will show that a resistant strain-prevalent equilibrium bifurcates in the forward direction as β_1 increases. Many studies (Huang et al. 1992; Dushoff et al. 1998; Van Den Driessche and Watmough 2002) have decomposed the center manifold to derive the criteria for the direction of local bifurcation, and our proof follows Theorem 4.1 and Remark 1 by Castillo-Chavez and Song (2004).

Theorem 3 *There exists* $\varepsilon > 0$ *such that system* (4) *has a locally asymptotically stable resistant strain-prevalent equilibrium for* $\beta_1 \in (\beta_1^\dagger, \beta_1^\dagger + \varepsilon)$*.*

Proof See "Appendix." □

3.2.2 Existence of Resistant Strain-Prevalent Equilibrium and Persistence

From now on, we start solving for the resistant strain-prevalent equilibrium that satisfies (5)–(8), and we denote it as $(\widetilde{S}, \widetilde{C}_0, \widetilde{I}_0, \widetilde{X}_1)$ with $\widetilde{X}_1 \neq 0$.

$$p\lambda - \beta_0(C_0 + I_0)S - \beta_1 X_1 S - \mu S = 0, \tag{5}$$
$$(1-p)\lambda + \beta_0(C_0 + I_0)S + \tau I_0 - (\delta + \mu)C_0 = 0, \tag{6}$$
$$\delta C_0 - \beta_1 X_1 I_0 - (\tau + \mu) I_0 = 0, \tag{7}$$
$$\beta_1 X_1 (S + I_0) - \mu X_1 = 0. \tag{8}$$

From (8) we have that $\widetilde{S} + \widetilde{I}_0 = \frac{\mu}{\beta_1}$, and by adding up Eqs. (5)–(8), we have $\widetilde{S} + \widetilde{C}_0 + \widetilde{I}_0 + \widetilde{X}_1 = \frac{\lambda}{\mu}$; hence, $\widetilde{C}_0 + \widetilde{X}_1 = \frac{\lambda}{\mu} - \frac{\mu}{\beta_1}$. Further, calculations yield $\widetilde{C}_0 = \frac{(1-p)\lambda + \beta_0 \widetilde{S}\widetilde{I}_0 + \tau \widetilde{I}_0}{\delta + \mu - \beta_0 \widetilde{S}}$. Now, each component of the positive equilibrium can be represented in terms of $\widetilde{S}$, which is a root of the polynomial (9) with its coefficients in (10).

$$g(S) = S^3 + aS^2 + bS + c \tag{9}$$
$$a = -\tfrac{\lambda}{\mu} - \tfrac{2\mu+\delta+\tau}{\beta_1} + \tfrac{\tau}{\beta_0},\ b = \tfrac{\mu+\delta+\tau}{\mu}\left(\tfrac{\mu}{\beta_1}\right)^2 + \left(\tfrac{\lambda}{\mu} - \tfrac{\tau}{\beta_0}\right)\tfrac{\mu}{\beta_1} + \tfrac{\lambda\delta + p\lambda\mu}{\mu\beta_0},$$
$$c = -p\lambda\tfrac{\delta+\mu}{\beta_0\beta_1}. \tag{10}$$

For $0 < \frac{\mu}{\beta_1} < \frac{\lambda}{\mu}$, $(\widetilde{S}, \widetilde{C}_0, \widetilde{I}_0, \widetilde{X}_1)$ is a positive equilibrium if and only if

$$0 < \widetilde{S} < \tfrac{\mu}{\beta_1} \quad \text{and} \quad 0 < \widetilde{C}_0 = \tfrac{(1-p)\lambda + (\beta_0\widetilde{S} + \tau)(\frac{\mu}{\beta_1} - \widetilde{S})}{\delta + \mu - \beta_0 \widetilde{S}} < \tfrac{\lambda}{\mu} - \tfrac{\mu}{\beta_1}. \tag{11}$$

This is equivalent to

$$0 < \widetilde{S} < \min\left\{\tfrac{\mu}{\beta_1}, \tfrac{\delta+\mu}{\beta_0}\right\} \quad \text{and} \quad \beta_0\widetilde{S}^2 - \left(\tfrac{\lambda}{\mu}\beta_0 - \tau\right)\widetilde{S} + p\lambda + \tfrac{\lambda}{\mu}\delta - \tfrac{\mu}{\beta_1}(\mu + \tau + \delta) > 0, \tag{12}$$

denote $f(S) := S^2 - (\frac{\lambda}{\mu} - \frac{\tau}{\beta_0})S + \frac{p\lambda}{\beta_0} + \frac{\lambda\delta}{\mu\beta_0} - \frac{\mu}{\beta_0\beta_1}(\mu + \tau + \delta)$ we rewrite the above condition as

$$0 < \widetilde{S} < \min\left\{\tfrac{\mu}{\beta_1}, \tfrac{\delta+\mu}{\beta_0}\right\} \quad \text{and} \quad f(\widetilde{S}) > 0. \tag{13}$$

Based on the above discussion, we conclude that finding the resistant strain-prevalent equilibrium is equivalent of finding the roots of polynomial $g(S)$ that satisfies condition (13):

Proposition 3 *For $0 < \beta_1 < \mu^2/\lambda$, system (4) has no resistant strain-prevalent equilibrium. For $\beta_1 > \mu^2/\lambda$, (4) has a resistant strain-prevalent equilibrium $(\widetilde{S}, \widetilde{C}_0, \widetilde{I}_0, \widetilde{X}_1)$ with $\widetilde{X}_1 \neq 0$ if and only if $\widetilde{S}$ is a root of polynomial (9) that satisfies condition (13).*

Observe that

$$g(S) = f(S)\left(S - \tfrac{\mu}{\beta_1}\right) - \tfrac{\mu+\tau+\delta}{\beta_1}\left(S - \tfrac{\mu}{\beta_0}\right)\left(S - \tfrac{\mu}{\beta_1}\right) + (1-p)\tfrac{\lambda\delta}{\beta_0\beta_1} \tag{14}$$

$$= \left(S - \tfrac{\mu}{\beta_1}\right)\left[S^2 - \left(\tfrac{\lambda}{\mu} - \tfrac{\tau}{\beta_0} + \tfrac{\mu+\tau+\delta}{\beta_1}\right)S + \tfrac{p\lambda}{\beta_0} + \tfrac{\lambda\delta}{\mu\beta_0}\right] + (1-p)\tfrac{\lambda\delta}{\beta_0\beta_1}. \tag{15}$$

thus, we can simplify condition (13) further.

Proposition 4 *Condition* (13) *is equivalent to the following condition* (16).

$$\max\{0, h(\beta_1)\} < \widetilde{S} < \min\left\{\tfrac{\mu}{\beta_1}, \tfrac{\delta+\mu}{\beta_0}\right\}, \text{ where} \tag{16}$$

$$h(\beta_1) := \tfrac{1}{2}\Big(\tfrac{\mu}{\beta_0} + \tfrac{\mu}{\beta_1} - \sqrt{\left(\tfrac{\mu}{\beta_0} - \tfrac{\mu}{\beta_1}\right)^2 + \tfrac{4(1-p)\lambda\delta}{\beta_0(\mu+\tau+\delta)}}\Big). \tag{17}$$

Proof See "Appendix." □

Therefore, we can summarize as following.

Proposition 5 *The bifurcation branch of the resistant strain-prevalent equilibrium can be represented by the bifurcation diagram of* $\widetilde{S}$ *in terms of* β_1. *The resistant strain-prevalent equilibrium branch lies in the area*

$$\Gamma := \left\{(\beta_1, \widetilde{S}) : \max\{0, h(\beta_1)\} \le \widetilde{S} \le \min\left\{\tfrac{\mu}{\beta_1}, \tfrac{\delta+\mu}{\beta_0}\right\}\right\}.$$

Further characterization of the region Γ is analyzed in "Appendix," which is of great use on showing the existence results of the positive equilibria $(\widetilde{S}, \widetilde{C_0}, \widetilde{I_0}, \widetilde{X_1})$ as listed below.

Theorem 4 *There exists at least one positive equilibrium of system* (4) *when* $\beta_1 > \beta_1^\dagger$.

1. *If* $\beta_1^\dagger > \beta_0$, *there exists an* $\widetilde{S} < S^*$ *for all* $\beta_1 \in (\beta_1^\dagger, +\infty)$.
2. *If* $\beta_1^\dagger < \beta_0$, *there exists an* $\widetilde{S} > S^*$ *for* $\beta_1 \in (\beta_1^\dagger, \beta_0)$, *and an* $\widetilde{S} < S^*$ *for* $\beta_1 \in (\beta_0, +\infty)$.

Proof See "Appendix." □

With any fixed value β_1, $g(S, \beta_1) = S^3 + aS^2 + bS + c$ in (9)–(10) is a third-order polynomial of S, if the discriminant $\Delta(\beta_1) = 18abc - 4a^3c + a^2b^2 - 4b^3 - 27c^2$ does not change its sign for all $\beta_1 > \beta_1^\dagger$, we should be able to predict the continuation of the bifurcation branch $\widetilde{S}$ and the uniqueness of the resistant strain-prevalent equilibrium. However, the sign of Δ is hard to be checked algebraically, we thus summarize possible cases in the following two corollaries.

Corollary 1 *Assume that the discriminant* $\Delta(\beta_1) = 18abc - 4a^3c + a^2b^2 - 4b^3 - 27c^2 > 0$ *for all* $\beta_1 > \beta_1^\dagger$. *Then, system* (4) *has a continuous bifurcation branch that represents a resistant strain-prevalent equilibrium and*

1. *if* $\beta_1^\dagger > \beta_0$, *the S component of any resistant strain-prevalent equilibrium is less than* S^* *for all* $\beta_1 > \beta_1^\dagger$;
2. *if* $\beta_1^\dagger < \beta_0$, *there exists a continuous bifurcation branch with its S component being greater than* S^* *for* $\beta_1^\dagger < \beta_1 < \beta_0$ *and smaller than* S^* *for* $\beta_1 > \beta_0$.

Proof See "Appendix." □

Corollary 2 *Assume that the discriminant* $\Delta(\beta_1) = 18abc - 4a^3c + a^2b^2 - 4b^3 - 27c^2 < 0$ *for all* $\beta_1 > \beta_1^\dagger$. *Then if* $\beta_1^\dagger > \beta_0$, *there exists a unique resistant strain-prevalent equilibrium with its S component being smaller than* S^* *for all* $\beta_1 > \beta_1^\dagger$.

Proof See "Appendix." □

Remark 1 Note that in Corollary 2, we did not discuss the condition of $\beta_1^\dagger < \beta_0$ as we did in Corollary 1. This is because that $\Delta(\beta_1) < 0$ for all $\beta_1 > \beta_1^\dagger$ and $\beta_1^\dagger < \beta_0$ cannot happen simultaneously: $\Delta(\beta_1) < 0$ implies the uniqueness of the real root $\widetilde{S}$ and from Theorem 4, we know $\widetilde{S} \leq S^*$ for $\beta_1 \in [\beta_0, +\infty)$, but from $(G.5)$ in Lemma 2, we have at least another real root $\frac{\mu+\delta}{\beta_0}$ when $\beta_1 = \beta_0 > \beta_1^\dagger$, which is a contradiction.

The characteristic equation of the Jacobian matrix obtained by linearizing system (4) at the resistant strain-prevalent equilibrium is not easy to compute, thus we do not prove its local stability. Instead, we used Latin hypercube sampling method to numerically validate the uniqueness and local stability of the resistant strain-prevalent equilibrium. This sampling method will be used again and illustrated in detail in the next section.

Next, we provide the result on the persistence of the solution to system (4) when $\beta_1 > \beta_1^\dagger$.

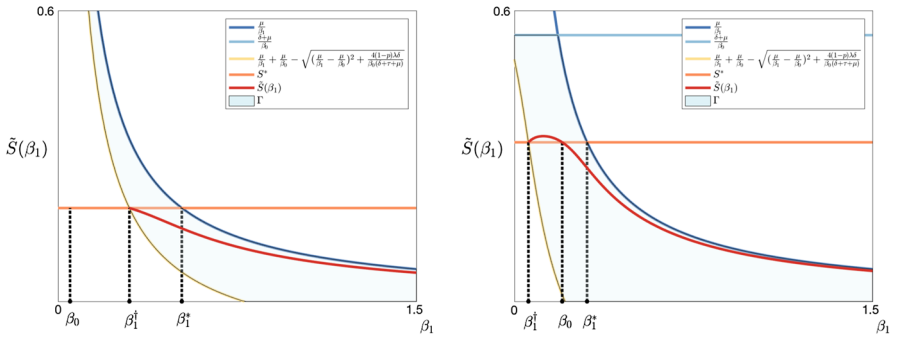
Theorem 5 *When* $\beta_1 > \beta_1^\dagger$, *the flow induced by the solution of system* (4) *with initial value* $x \in \mathbb{X} \setminus \{(S, I_0, C_0, X_1) : X_1 = 0\}$ *is uniformly persistent. That is, there exists* $\eta > 0$ *such that for any nonnegative initial condition* $(S(0), I_0(0), C_0(0), X_1(0))$ *with* $X_1(0) > 0$, *we have* $\liminf_{t \to +\infty} X_1(t) > \eta$.

Proof See "Appendix." □

3.2.3 Understanding the Condition in Theorem 4

Although we are not able to show the global stability of the resistant strain-prevalent equilibrium, the persistence result indicates that strain 1 will be prevalent in the ICU for $\beta_1 > \beta_1^\dagger$. Figure 2 provides two representative bifurcation diagrams of system (4).

Here, we provide an intuitive understanding on why a bump appears in the bifurcation diagram as shown in Fig. 2b and as predicted in Theorem 4. Strain 1 competes with strain 0 for patients once it successfully invades into the ICU. If strain 1 is more virulent than strain 0 (i.e., $\beta_0 < \beta_1^\dagger < \beta_1$), the overall transmission rate of bacteria increases, thus the number of colonized/infected patients increases. If strain 1 is strong enough to invade, but obtains a weaker transmission ability than strain 0 (i.e.,



(a) $\beta_1^\dagger > \beta_0$. **(b)** $\beta_1^\dagger < \beta_0$.

Fig. 2 Bifurcation branch of equilibrium component S under two different conditions for the de-escalation system. **a** $\mu = 0.1$, $\delta = 0.001$, $\tau = 0.25$, $p = 0.1$, $\lambda = 5$, $\beta_0 = 0.05$; **b** $\mu = 0.1$, $\delta = 0.01$, $\tau = 0.25$, $p = 0.66$, $\lambda = 5$, $\beta_0 = 0.2$. This figure can also be used to compare the bifurcation diagrams of system (3) and (4), where the orange curve representing $S = S^*$ together with the lower half of the blue curve representing $S = \frac{\mu}{\beta_1}$ form the bifurcation branch of system (3) (Color figure online)

$\beta_1^\dagger < \beta_1 < \beta_0$), the overall transmission rate of bacteria is then "diluted" and diminishes in general; hence, there will be less colonized/infected patients than the case without strain 1.

Such phenomena do not exist in the continuation scenario, since the strain 1 has to exceed a higher threshold in order to invade successfully, where the threshold (as denoted in Definition 1) β_1^* is always larger than the transmission rate of strain 0. Thus, the overall bacteria transmission rate always increases and leads to more colonized/infected patients.

The following Theorem provides a mathematical support of the above intuitive understanding: there is a threshold of the transmission rate of strain 0 such that β_0 exceeds the threshold if and only if β_0 exceeds the value of $\beta_1^\dagger$.

Theorem 6 *There exists a threshold β_0^*, which is uniquely determined by parameters $\mu, \delta, \tau, \lambda$ and p, such that when $\beta_0 < \beta_0^*$ we have $\beta_1^\dagger > \beta_0$, and when $\beta_0 > \beta_0^*$ we have $\beta_1^\dagger < \beta_0$.*

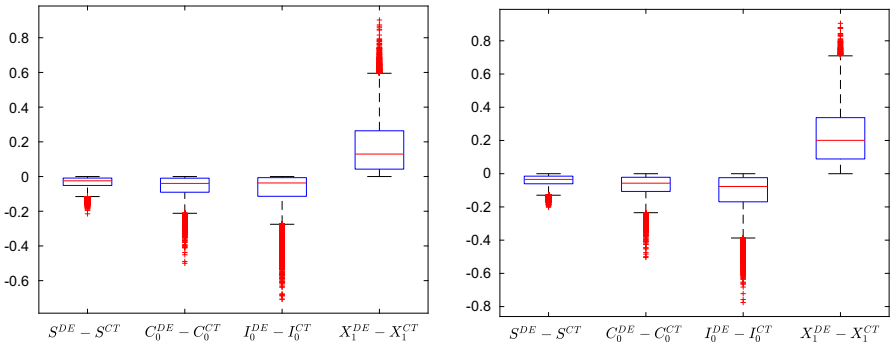
Proof See "Appendix." □

4 Comparison of Two-Strain Scenario

First we use Latin hypercube sampling method to numerically compare the other components of the stable equilibria between de-escalation and continuation systems.

Definition 2 The stable equilibria for systems (3) and (4) are denoted as (S^{CT}, C_0^{CT}, I_0^{CT}, X_1^{CT}) and (S^{DE}, C_0^{DE}, I_0^{DE}, X_1^{DE}), respectively.

For each sampled parameter set, we compute the stable equilibrium values for both systems, and evaluate their differences: $S^{\mathrm{DE}} - S^{\mathrm{CT}}$, $C_0^{\mathrm{DE}} - C_0^{\mathrm{CT}}$, $I_0^{\mathrm{DE}} - I_0^{\mathrm{CT}}$, $X_1^{\mathrm{DE}} - X_1^{\mathrm{CT}}$.



(a) $\beta_1 \in (\beta_1^\dagger, \beta_1^*)$. **(b)** $\beta_1 \in (\beta_1^*, \beta_1^* + 1)$.

Fig. 3 Numerical difference of each component of the stable equilibrium between de-escalation and continuation for the case of $\beta_1^\dagger > \beta_0$. For each figure, approximately 5×10^4 parameter sets are sampled by the Latin hypercube sampling method with $\mu, \delta, \tau, \beta_0, p$ uniformly distributed in $(0, 1)$, λ uniformly distributed in $(0, 5)$, while maintaining the condition $\beta_1^\dagger > \beta_0$. β_1 is uniformly distributed in the interval stated under each condition (Color figure online)

The values of these differences under all sampled parameter combinations are collected in box plots in each figure in Figs. 3 and 4. Similarly, we compute the difference between the use of broad-spectrum drug at the equilibrium values $I_1^{\mathrm{DE}} - (I_0^{\mathrm{CT}} + I_1^{\mathrm{CT}})$ in Fig. 5.

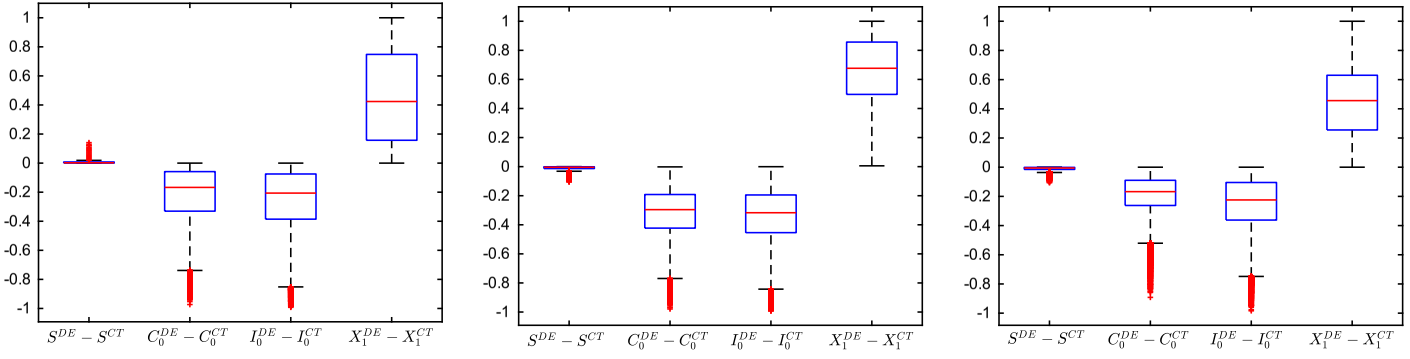
Based on the analytic and numerical results, we conclude that the benefits and trade-offs of de-escalation are consistent with numerical results obtained in the complex model in Hughes et al. (2017). This indicates the benefits and disadvantages of de-escalation are not resulted from the complexity of the treatment procedures that are previously captured, instead, they come from the use of the de-escalated antibiotics and the follow-up selection pressure. We therefore summarize all pros and cons of de-escalation in the two-strain scenario below.

De-escalation Benefit 1 De-escalation results in less use of the broad-spectrum drug B, which is an expected advantage—the initial intention of using de-escalation at the first place is to make less use of the broad-spectrum drugs (Fig. 5).

De-escalation Benefit 2 De-escalation results in less prevalence of the susceptible strain 0, which is a direct benefit of de-escalation judged from the measurement, but the reduction in susceptible strain is paired with an increase in the resistant strain resulted from the strain conversion dynamics in the de-escalation system (Figs. 3 and 4).

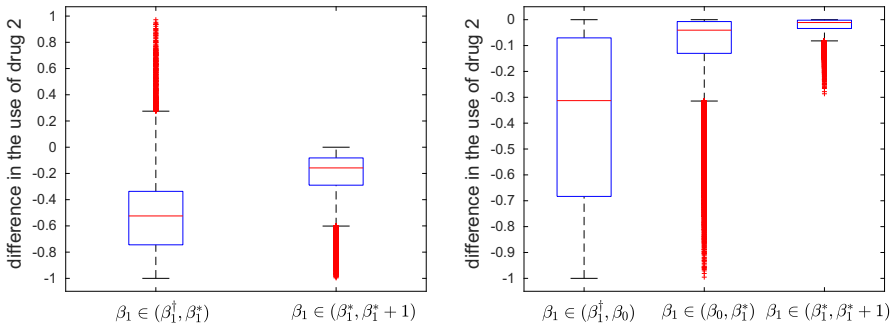
De-escalation Disadvantage 1 De-escalation results in more prevalence of the resistant strain 1, which is a direct result from the fact that de-escalation utilizes more drug A (Figs. 3 and 4).

De-escalation Disadvantage 2 De-escalation results in more colonized and infected patients overall for most of the parameter combinations, this result is observed numer-



(a) $\beta_1 \in (\beta_1^{\dagger}, \beta_0)$. **(b)** $\beta_1 \in (\beta_0, \beta_1^{*})$. **(c)** $\beta_1 \in (\beta_1^{*}, \beta_1^{*} + 1)$.

Fig. 4 Numerical difference of each component of the stable equilibrium between de-escalation and continuation for the case of $\beta_1^{\dagger} < \beta_0$. For each figure, approximately 5×10^4 parameter sets are sampled by the Latin hypercube sampling method with $\mu, \delta, \tau, \beta_0, p$ uniformly distributed in $(0, 1)$, λ uniformly distributed in $(0, 5)$, while maintaining the condition $\beta_1^{\dagger} < \beta_0$. β_1 is uniformly distributed in the interval stated under each condition (Color figure online)



(a) $\beta_1^\dagger > \beta_0$. **(b)** $\beta_1^\dagger < \beta_0$.

Fig. 5 Numerical difference of the use of the broad-spectrum drug B between de-escalation and continuation. Differences are measured by comparing the stable equilibrium values of two systems via $I_1^{\mathrm{DE}} - (I_0^{\mathrm{CT}} + I_1^{\mathrm{CT}})$, parameter values are drawn using the same method illustrated in Figs. 3 and 4 (Color figure online)

ically in Hughes et al. (2017) and our analysis provides a deterministic proof-based confirmation (Fig. 2).

De-escalation Disadvantage 3 De-escalation facilitates potential outbreaks of the resistant strain when susceptible strain is already prevalent ($\mathcal{R}_1^{\mathrm{DE}} > \mathcal{R}_1^{\mathrm{CT}}$).

5 Three-Strain Scenario

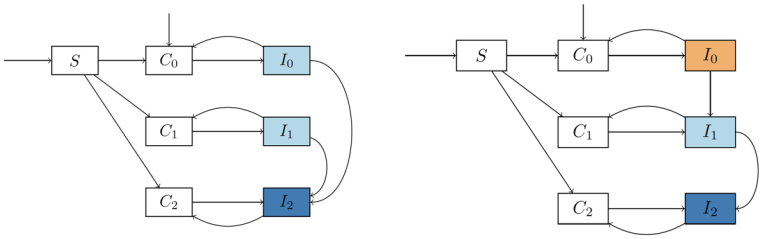
In this section, we are interested in which treatment strategy is superior in preventing the invasion of an additional strain that is resistant to the empiric antibiotic, especially under the worst-case scenario when both strain 0 and 1 inevitably co-circulate. The strain resistant to empiric therapy is denoted as strain 2, with a transmission rate β_2. Assume that some last resort drugs, denoted as drug C, are also available for treatment. In the realistic setting (Hughes et al. 2017), drug A represents ciprofloxacin, drug B represents the empiric antibiotic such as pip-tazo, drug C represents those highly effective antibiotics that are only reserved for severe or high-risk infections, such as carbapenem or aminoglycoside.

5.1 Model Formulation: Three-Strain Scenario

In addition to Assumptions 1–9, we include the following assumptions on the third strain and antibiotic to formulate the de-escalation and continuation systems under the three-strain scenario.

Assumption 10 Strain 0 is susceptible to all three drugs, strain 1 is only resistant to drug A, and strain 2 is only resistant to drug B.

Assumption 11 Patients infected by strain 2 will be treated by drug C under all strategies.



(a) Continuation. **(b)** De-escalation.

Fig. 6 Compartmental dynamics for antimicrobial continuation and de-escalation models under three-strain three-drug scenario. Compartments colored in blue represent infected patients under treatment of the empiric drug B (such as pip-tazo), the one colored in orange represents patients under treatment of the de-escalated drug A (such as ciprofloxacin), and the ones colored in dark blue represents patients under treatment of the last resort drug C (such as carbapenem or aminoglycoside) (Color figure online)

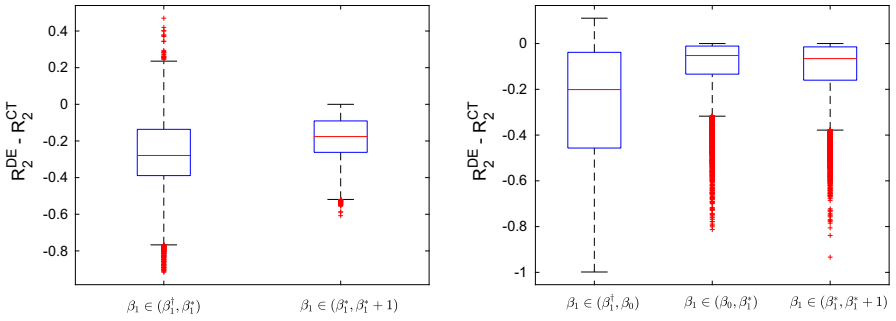
Drug B refers to the empiric broad-spectrum antibiotic that is supposed to be effective for most infections, in practice, since ICU patients are all in severe health conditions, patients showing resistance to the empiric drug usually receive escalated antibiotics for treatment effectiveness.

Assumption 12 Possibilities for strain conversions will follow Assumption 9—patients treated by drug A could have their infection dominated by strain 1; patients treated by drug B could have their infection dominated by strain 2; those treated by drug C will not experience strain conversions as we assume no resistance is present to drug C.

The compartmental dynamics shown in Fig. 6 and equation systems (18)–(19) follow based on the above assumptions.

$$\begin{aligned}
\dot{S} &= p\lambda - \beta_0(C_0 + I_0)S - \beta_1(C_1 + I_1)S - \beta_2(C_2 + I_2)S - \mu S,\\
\dot{C}_0 &= (1-p)\lambda + \beta_0(C_0 + I_0)S + \tau I_0 - (\delta + \mu)C_0,\\
\dot{I}_0 &= \delta C_0 - \beta_2(C_2 + I_2)I_0 - (\tau + \mu)I_0,\\
\dot{C}_1 &= \beta_1(C_1 + I_1)S + \tau I_1 - (\delta + \mu)C_1,\\
\dot{I}_1 &= \delta C_1 - \beta_2(C_2 + I_2)I_1 - (\tau + \mu)I_1,\\
\dot{C}_2 &= \beta_2(C_2 + I_2)S + \tau I_2 - (\delta + \mu)C_2,\\
\dot{I}_2 &= \delta C_2 + \beta_2(C_2 + I_2)(I_0 + I_1) - (\tau + \mu)I_2.
\end{aligned} \tag{18}$$

$$\begin{aligned}
\dot{S} &= p\lambda - \beta_0(C_0 + I_0)S - \beta_1(C_1 + I_1)S - \beta_2(C_2 + I_2)S - \mu S,\\
\dot{C}_0 &= (1-p)\lambda + \beta_0(C_0 + I_0)S + \tau I_0 - (\delta + \mu)C_0,\\
\dot{I}_0 &= \delta C_0 - \beta_1(C_1 + I_1)I_0 - (\tau + \mu)I_0,\\
\dot{C}_1 &= \beta_1(C_1 + I_1)S + \tau I_1 - (\delta + \mu)C_1,\\
\dot{I}_1 &= \delta C_1 - \beta_2(C_2 + I_2)I_1 - (\tau + \mu)I_1,\\
\dot{C}_2 &= \beta_2(C_2 + I_2)S + \tau I_2 - (\delta + \mu)C_2,\\
\dot{I}_2 &= \delta C_2 + \beta_2(C_2 + I_2)I_1 - (\tau + \mu)I_2.
\end{aligned} \tag{19}$$



(a) $\beta_0 < \beta_1^\dagger$. **(b)** $\beta_0 > \beta_1^\dagger$.

Fig. 7 Box plots for $\mathcal{R}_2^{DE} - \mathcal{R}_2^{CT}$. **a** $\mathcal{R}_2^{DE} < \mathcal{R}_2^{CT}$ when strains 0 and 1 are co-circulating in the ICU under both strategies. **b** $\mathcal{R}_2^{DE} < \mathcal{R}_2^{CT}$ whenever the transmission ability of strain 1 is stronger than strain 0. Sampling strategy is the same with Figs. 3 and 4 (Color figure online)

5.2 Invasion Potential of Strain 2

Note that the stable equilibrium of each two-strain system is a strain 2 free equilibrium for the corresponding three-strain system. Thus the *invasion reproductive number of strain* 2, $\mathcal{R}_2$, is denoted as the number of secondary colonization/infections that one individual colonized/infected with strain 2 can produce in the ICU, where strain 0 or both strains 0 and 1 are already present and at equilibrium. By the method in Van Den Driessche and Watmough (2002) and follow the notation in Definition 2, we get the invasion reproductive number of strain 2 as:

$$\mathcal{R}_2^{CT} = \frac{\beta_2}{\mu}\left(S^{CT} + I_0^{CT} + I_1^{CT}\right), \quad \mathcal{R}_2^{DE} = \frac{\beta_2}{\mu}\left(S^{DE} + I_1^{DE}\right).$$

Comparison between the two invasion reproductive numbers of strain 2 is not algebraically obvious, so we check them numerically by Latin hypercube sampling method in Fig. 7, from which we observe that the system with de-escalation has smaller $\mathcal{R}_2$ values for most parameter combinations.

De-escalation Benefit 3 De-escalation is superior in preventing outbreaks of strain 2 when both strain 0 and 1 are prevalent in the ICU.

Figure 7b shows $\mathcal{R}_2^{DE} < \mathcal{R}_2^{CT}$ for all parameter combinations when $\beta_1 > \beta_1^*$ (where both system (3) and (4) have the resistant strain-prevalent equilibria as their stable equilibria).

De-escalation Benefit 4 De-escalation is superior in preventing outbreaks of strain 2 for a majority of parameter combinations even when de-escalation causes the prevalence of strain 1 while continuation does not.

The parameter combinations shown on the first bar plot in Fig. 7a and the first two bar plots in Fig. 7b correspond to the scenario when both strain 0 and 1 become prevalent in the ICU adopting de-escalation while only strain 0 is prevalent in the one adopting continuation.

These results indicate that **De-escalation disadvantage 3** might not be a disadvantage for all the time. Intuitively, patients infected by the susceptible strain are treated by the antibiotic with the least coverage under de-escalation, leaving more antibiotic options for future use of potential resistance development, which results in a lower possibility for conversions to strain 2. That is, patients at primary risks of switching to the resistant strain 2 are those taking the empiric drug B, which refer to patients in I_0 and I_1 under continuation therapy but only patients in I_1 under de-escalation.

6 Discussion

In this paper, we compare de-escalation and continuation under different scenarios with multiple strain and drug combinations. The models analyzed in this paper are simplified versions of those studied in Hughes et al. (2017), which takes into consideration of multiple strains and species and separates the empiric and definitive therapy status. However, the simplified models show similar features as those predicted in the complex models: (1) de-escalation reduces the use of broad-spectrum antibiotics as well as its resistance prevalence; (2) de-escalation increases the overall infection and colonization in the ICU. These indicate that the benefits and unintended consequences of de-escalation strategy observed in Hughes et al. (2017) is not due to the complexity of the model, but resulted from the nature of the strategy differences. Thus, our understanding of the simplified models would provide credible insights into the complicated reality.

The invasion reproductive numbers for strain 2 being calculated in Sect. 5 represent the invasion potential for strain 2 into an ICU when either strain 0 or both 0 and 1 are inevitably prevalent. Technically, the number is calculated by linearizing the three-strain system at the stable equilibrium of the corresponding two-strain system (Martcheva et al. 2007). Thus, the heavy analysis of the steady states for the two-strain systems is necessary for us to determine under which equilibrium should the systems (18) and (19) be linearized in order to calculate the invasion reproductive numbers.

Therefore, we are able to compare the invasion reproductive numbers that represent potentials of invading strain outbreaks. We conclude that de-escalation is superior than continuation in preventing the invasion of the strain that is resistant to the empiric antibiotic, especially when the strain resistant to the de-escalated antibiotic has already become prevalent in the ICU no matter which treatment strategy is being adopted. In reality, the multi-strain de-escalation strategy would depend on the specific drug-bug combination with the coverage of each antibiotic being different from Assumption 10, thus systems (18) and (19) are not unique for three-strain scenarios. Similar analysis can be performed for certain bacterial species and corresponding antibiotics. In general, both de-escalation and continuation possess their own benefits and trade-offs, decisions on strategies should be made specifically according to the conditions of the ICU, and the intervention objectives.

Acknowledgements This research was partially supported by the University of Miami Provost's Research Award (UM PRA 2019-409) and National Science Foundation. The author would like to thank the two

anonymous reviewers and handling editor for their helpful comments and suggestions that helped improve the presentation of the paper.

A Appendix

A.1 Proof of Theorem 1

Proof Sketch of the proof: we can easily get the local stability results by analyzing the eigenvalues of the system linearized at the equilibria. The global stability results can be checked by the LaSalle's invariant principle. When $\mathcal{R}_1^{\mathrm{CT}} < 1$, the Lyapunov function is defined as

$$V_1(S, X_0, X_1) := S - S^* - S^* \ln \frac{S}{S^*} + X_0 - X_0^* - X_0^* \ln \frac{X_0}{X_0^*} + X_1,$$

hence we can get the global stability of $(S^*, X_0^*, 0)$.

For $\mathcal{R}_1^{\mathrm{CT}} > 1$, a routine calculation gives us the unique resistant strain-prevalent equilibrium

$$\bar{S} = \frac{\mu}{\beta_1},\ \bar{X_0} = \frac{1-p}{1-\frac{\beta_0}{\beta_1}} \cdot \frac{\lambda}{\mu},\ \bar{X_1} = \frac{p-\frac{\beta_0}{\beta_1}}{1-\frac{\beta_0}{\beta_1}} \cdot \frac{\lambda}{\mu} - \frac{\mu}{\beta_1},$$

and we can construct the Lyapunov function

$$V_2(S, X_0, X_1) := S - \bar{S} - \bar{S} \ln \frac{S}{\bar{S}} + X_0 - \bar{X_0} - \bar{X_0} \ln \frac{X_0}{\bar{X_0}} + X_1 - \bar{X_1} - \bar{X_1} \ln \frac{X_1}{\bar{X_1}}.$$

to show the global stability of $(\bar{S}, \bar{X_0}, \bar{X_1})$. □

A.2 Proof of Theorem 2

Proof First, we construct a Lyapunov function to show the global stability, we continue using the notation $X_0 := C_0 + I_0$ and define $V_3 : (0, +\infty) \times (0, +\infty) \times (0, +\infty) \times [0, +\infty) \to \mathbb{R}$ where

$$V_3(S, C_0, I_0, X_1) := S - S^* - S^* \ln \frac{S}{S^*} + X_0 - X_0^* - X_0^* \ln \frac{X_0}{X_0^*} + X_1.$$

Proposition 2 guarantees that the function is well-defined, taking the derivative of V_3 along the solution, and we have

$$\begin{aligned}\frac{\mathrm{d}V_3}{\mathrm{d}t}(S, C_0, I_0, X_1) = &- \frac{\mu+\beta_0 X_0^*}{S}(S - S^*)^2 - \frac{\mu-\beta_0 S^*}{X_0}(X_0 - X_0^*)^2 \\ &- X_1(\mu - \beta_1 S^* - \beta_1 \frac{I_0}{X_0} X_0^*)\end{aligned}$$

By the positivity of solution, we have $\frac{I_0}{X_0} = \frac{I_0}{I_0+C_0} \le 1$. Thus, the last item in the above equation can be estimated as $-X_1(\mu - \beta_1 S^* - \beta_1 \frac{I_0}{X_0} X_0^*) \le -X_1(\mu - \beta_1 S^* - \beta_1 X_0^*) =$

$-X_1(\mu - \beta_1\frac{\lambda}{\mu}) \leq 0$ for $\beta_1 < \mu^2/\lambda$. It is also easy to check $\mu - \beta_0 S^* \leq 0$, so $\frac{\mathrm{d}V_3}{\mathrm{d}t}(S, C_0, I_0, X_1) \leq 0$ for $\beta_1 < \mu^2/\lambda$.

Notice that $\frac{\mathrm{d}V_3}{\mathrm{d}t}(S, C_0, I_0, X_1) = 0$ if and only if either $\{S = S^*, X_0 = X_0^*, X_1 = 0\}$ or $\{S = S^*, X_0 = X_0^*, S + I_0 = \frac{\mu}{\beta_1}\}$. Denote the largest invariant set that contains $\{S = S^*, X_0 = X_0^*, X_1 = 0\}$ as $\mathcal{M}_1$. Then for any initial condition $(S(0), C_0(0), I_0(0), X_1(0)) \in \mathcal{M}_1$, we have the corresponding solution to system (4) satisfying $\dot{S}(0) = \dot{X}_0(0) = \dot{X}_1(0) = 0$ so there is no initial rate of change for the three compartments, and we should have $S(t) = S^*$, $X_0(t) = X_0^*$, $X_1(t) = 0$. Therefore, $\mathcal{M}_1 \subset \{S = S^*, X_0 = X_0^*, X_1 = 0\}$, and hence $\mathcal{M}_1 = \{S = S^*, X_0 = X_0^*, X_1 = 0\}$.

Denote the largest invariant set that contains $\{S = S^*, X_0 = X_0^*, S + I_0 = \frac{\mu}{\beta_1}\}$ to be $\mathcal{M}_2$. Then for any initial condition $(S(0), C_0(0), I_0(0), X_1(0)) \in \{S = S^*, X_0 = X_0^*, S + I_0 = \frac{\mu}{\beta_1}\}$, we have the corresponding solution to system (4) satisfying $\dot{S}(0) = \dot{X}_0(0) = \dot{X}_1(0) = 0$, then $S(t) = S^*$, $X_0(t) = X_0^*$, and $X_1(t) = X_1(0)$. As the population in all three compartments are constant, we have $S^* + X_0^* + X_1(0) = \frac{\lambda}{\mu}$, and hence $X_1(0) = 0$; therefore, $\mathcal{M}_2 \subset \mathcal{M}_1$.

For any initial condition $(S(0), C_0(0), I_0(0), X_1(0))$, the system (4) has a unique solution $(S(t), C_0(t), I_0(t), X_1(t))$ such that for any $\varepsilon > 0$, there exists a $t_0 > 0$ and for all $t > t_0$, we have $|C_0(t) + I_0(t) - X_0^*| < \varepsilon$ and $|X_1(t)| < \varepsilon$. And we have the estimation

$$\begin{aligned}&\delta(X_0^* - \varepsilon) - (\varepsilon\beta_1 + \delta + \tau + \mu)I_0(t)\\ &\quad < \dot{I}_0(t) < \delta(X_0^* + \varepsilon) - (-\varepsilon\beta_1 + \delta + \tau + \mu)I_0(t),\end{aligned}$$

thus we have

$$\tfrac{\delta}{\varepsilon\beta_1+\delta+\tau+\mu}(X_0^* - \varepsilon) \leq \lim_{t\to+\infty} I_0(t) \leq \tfrac{\delta}{-\varepsilon\beta_1+\delta+\tau+\mu}(X_0^* + \varepsilon),$$

and since it is for any $\varepsilon > 0$, we know that $\lim_{t\to+\infty} I_0(t) = I_0^*$, and hence $\lim_{t\to+\infty} C_0(t) = C_0^*$. □

A.3 Proof of Theorem 3

Proof System (4) can be framed as a general system of ODEs with the bifurcation parameter β_1:

$$\frac{\mathrm{d}x}{\mathrm{d}t} = f(x, \beta_1), \quad f : \mathbb{R}^4 \times \mathbb{R},\ f \in C^2(\mathbb{R}^4 \times \mathbb{R}).$$

Denote the resistant strain-free equilibrium $(S^*, C_0^*, I_0^*, 0)$ as x^* and we know that

$$f(x^*, \beta_1) = 0 \quad \text{for all} \quad \beta_1 > 0.$$

Next, we verify the assumptions of Theorem 4.1 in Castillo-Chavez and Song (2004). Firstly, the matrix of the linearized system at x^* is

$$A = D_x f(x^*, \beta_1^\dagger) = \begin{bmatrix} -\beta_0 X_0^* - \mu & -\beta_0 S^* & -\beta_0 S^* & -\beta_1^\dagger S^* \\ \beta_0 X_0^* & \beta_0 S^* - \delta - \mu & \beta_0 S^* + \tau & 0 \\ 0 & \delta & -(\tau + \mu) & -\beta_1^\dagger I_0^* \\ 0 & 0 & 0 & 0 \end{bmatrix},$$

and 0 is a simple eigenvalue of A and all the other eigenvalues of A are negative real numbers. Next, we compute the right eigenvector $\mathbf{w} = (w_i)_{i=1}^4$ and have

$$w_1 = \frac{(\mu+\delta-\beta_0 S^*)w_2 - (\beta_0 S^* + \tau)w_3}{\beta_0 X_0^*}, \quad \text{and} \quad w_4 = \frac{\delta w_2 - (\mu+\tau)w_3}{\beta_1^\dagger I_0^*},$$

where we pick

$$w_2 = 1 - \frac{\beta_0 S^* + \tau}{\beta_0 X_0^*} - \frac{\mu+\tau}{\beta_1^\dagger I_0^*} \quad \text{and} \quad w_3 = -1 - \frac{\mu+\delta-\beta_0 S^*}{\beta_0 X_0^*} - \frac{\delta}{\beta_1^\dagger I_0^*}.$$

Simplifying the expressions of w_1 and w_4, we have

$$w_4 = \frac{\mu+\tau+\delta}{\beta_1^\dagger I_0^* X_0^*}\left(\frac{\mu}{\beta_0} + \frac{\lambda}{\mu} - 2S^*\right) > 0, \text{ by knowing that } S^* < \min\left\{\frac{\mu}{\beta_0}, \frac{\lambda}{\mu}\right\},$$
$$w_1 = \left(\frac{\beta_0}{\beta_1^\dagger} - 1\right)\frac{S^*}{\beta_0 X_0^* I_0^*}(\mu + \tau + \delta).$$

Note from the Remark 1 in Castillo-Chavez and Song (2004) w_1, w_2, w_3 are not necessarily positive, but it is crucial to have $w_4 > 0$ as it corresponds to a positive perturbation of the equilibrium x^* on its X_1 component.

Compute the left eigenvector $\mathbf{v} = (v_i)_{i=1}^4$ and we have $v_1 = v_2 = v_3 = 0$, and $v_4 = 1$. We are thus able to calculate the following:

$$a = \sum_{k,i,j=1}^{n} v_k w_i w_j \frac{\partial^2 f_k}{\partial x_i \partial x_j}(x^*, \beta_1^\dagger) = 2\beta_1^\dagger w_4(w_1 + w_3),$$
$$b = \sum_{k,i=1}^{n} v_k w_i \frac{\partial^2 f_k}{\partial x_i \partial \beta_1}(x^*, \beta_1^\dagger) = \frac{\mu}{\beta_1^\dagger} v_4 w_4 > 0.$$

Clearly, $w_3 < 0$ and if $\beta_0 < \beta_1^\dagger$, we have $w_1 < 0$, thus $a < 0$. Otherwise, if $\beta_0 \geq \beta_1^\dagger$, we have

$$w_1 + w_3 = \frac{(\mu+\delta-\beta_0 S^*)w_2 + (\beta_0 X_0^* - \beta_0 S^* - \tau)w_3}{\beta_0 X_0^*}$$
$$= \frac{-\beta_0(\mu+\tau+\delta)(\frac{\mu}{\beta_0} - S^*) - \beta_0\beta_1^\dagger X_0^* I_0^* - \beta_0 I_0^*(\beta_1^\dagger I_0^* + \delta) - \tau I_0^*(\beta_0 - \beta_1^\dagger)}{\beta_0\beta_1^\dagger X_0^* I_0^*} < 0,$$

and thus $a < 0$, which completes the proof. □

A.4 Proof of Proposition 4

Proof From (14), we have

$$g(\widetilde{S})=0 \Longleftrightarrow f(\widetilde{S})\left(\widetilde{S}-\tfrac{\mu}{\beta_1}\right)=\tfrac{\mu+\tau+\delta}{\beta_1}\left(\widetilde{S}-\tfrac{\mu}{\beta_0}\right)\left(\widetilde{S}-\tfrac{\mu}{\beta_1}\right)-(1-p)\tfrac{\lambda\delta}{\beta_0\beta_1}.$$

Then, condition (13) is equivalent to

$$0<\widetilde{S}<\min\left\{\tfrac{\mu}{\beta_1},\tfrac{\delta+\mu}{\beta_0}\right\} \quad \text{and} \quad \widetilde{S}^2-\left(\tfrac{\mu}{\beta_0}+\tfrac{\mu}{\beta_1}\right)\widetilde{S}-(1-p)\tfrac{\lambda\delta}{\beta_0(\mu+\tau+\delta)}+\tfrac{\mu^2}{\beta_0\beta_1}<0,$$

which is equivalent to

$$\begin{aligned}&0<\widetilde{S}<\min\left\{\tfrac{\mu}{\beta_1},\tfrac{\delta+\mu}{\beta_0}\right\} \quad \text{and}\\ &\tfrac{1}{2}\Big(\tfrac{\mu}{\beta_0}+\tfrac{\mu}{\beta_1}-\sqrt{(\tfrac{\mu}{\beta_0}-\tfrac{\mu}{\beta_1})^2+\tfrac{4(1-p)\lambda\delta}{\beta_0(\mu+\tau+\delta)}}\Big)<\widetilde{S}\\ &\quad<\tfrac{1}{2}\Big(\tfrac{\mu}{\beta_0}+\tfrac{\mu}{\beta_1}+\sqrt{(\tfrac{\mu}{\beta_0}-\tfrac{\mu}{\beta_1})^2+\tfrac{4(1-p)\lambda\delta}{\beta_0(\mu+\tau+\delta)}}\Big).\end{aligned}$$

Notice that

$$\begin{aligned}&\tfrac{1}{2}\Big(\tfrac{\mu}{\beta_0}+\tfrac{\mu}{\beta_1}-\sqrt{(\tfrac{\mu}{\beta_0}-\tfrac{\mu}{\beta_1})^2+\tfrac{4(1-p)\lambda\delta}{\beta_0(\mu+\tau+\delta)}}\Big)\\ &\quad<\tfrac{1}{2}\Big(\tfrac{\mu}{\beta_0}+\tfrac{\mu}{\beta_1}-|\tfrac{\mu}{\beta_0}-\tfrac{\mu}{\beta_1}|\Big)<\min\left\{\tfrac{\mu}{\beta_0},\tfrac{\mu}{\beta_1}\right\},\end{aligned}$$

and

$$\begin{aligned}&\tfrac{1}{2}\Big(\tfrac{\mu}{\beta_0}+\tfrac{\mu}{\beta_1}+\sqrt{(\tfrac{\mu}{\beta_0}-\tfrac{\mu}{\beta_1})^2+\tfrac{4(1-p)\lambda\delta}{\beta_0(\mu+\tau+\delta)}}\Big)\\ &\quad>\tfrac{1}{2}\Big(\tfrac{\mu}{\beta_0}+\tfrac{\mu}{\beta_1}+|\tfrac{\mu}{\beta_0}-\tfrac{\mu}{\beta_1}|\Big)>\max\left\{\tfrac{\mu}{\beta_0},\tfrac{\mu}{\beta_1}\right\}.\end{aligned}$$

Thus, condition (13) is equivalent to condition (16). □

A.5 Proof of Theorem 4

Next, we state some facts about the boundaries of region Γ introduced in Proposition 5.

Lemma 1 *The following properties of function h are defined in (17) and S^* are easy to be verified.*

(H.1) $h(\beta_1)$ is a decreasing function for $\beta_1>0$, and $\lim_{\beta_1\to 0^+}h(\beta_1)=\frac{2\mu}{\beta_0}>S^*$;

(H.2) $h(\beta_1)=S^*$ if and only if $\beta_1=\beta_1^\dagger$;

(H.3) $h(\beta_1)<0$ for $\beta_1>\frac{\mu^2(\mu+\tau+\delta)}{(1-p)\lambda\delta}$;

(H.4) $S^*<\frac{\mu+\delta}{\beta_0}$;

(H.5) $\frac{\mu+\delta}{\beta_0}<\frac{\mu}{\beta_1}$ if and only if $\beta_1<\frac{\mu\beta_0}{\mu+\delta}$.

With the above information, the area Γ is illustrated as the shaded areas in Fig. 2. We will need the following Lemma to show the existence of the resistant strain-prevalent equilibria.

Lemma 2 *In the following statements, we begin to regard the function $g(S)$ introduced in (9) with coefficients defined in (10) as a function of two variables, $g(S, \beta_1)$. The following facts about $g(S, \beta_1)$ are true.*

- $(G.1)$ $g(h(\beta_1), \beta_1) < 0$ *for* $\beta_1 > \beta_1^\dagger$, *and* $g(h(\beta_1), \beta_1) = 0$ *when* $\beta_1 = \beta_1^\dagger$ *and* $h(\beta_1^\dagger) = S^*$;
- $(G.2)$ $g(S^*, \beta_1) = 0$ *if and only if* $\beta_1 = \beta_1^\dagger$ *or* $\beta_1 = \beta_0$, $g(S^*, \beta_1) < 0$ *only when* β_1 *lies in between the two roots, otherwise* $g(S^*, \beta_1) > 0$;
- $(G.3)$ $g(\frac{\mu}{\beta_1}, \beta_1) > 0$ *for all* $\beta_1 > 0$;
- $(G.4)$ $g(0, \beta_1) < 0$ *for all* $\beta_1 > 0$.
- $(G.5)$ $g(\frac{\mu+\delta}{\beta_0}, \beta_1) = 0$ *if and only if* $\beta_1 = \beta_0$ *or* $\beta_1 = \frac{\mu(\mu+\delta+\tau)\beta_0}{(\mu+\delta)(\mu+\delta+\tau)-(1-p)\beta_0\lambda}$.
- $(G.6)$ $\frac{\mu}{\beta_0} > \frac{\lambda}{\mu}$ *implies* $\beta_1^\dagger > \beta_0$, *hence* $\beta_1^\dagger < \beta_0$ *implies* $\frac{\mu}{\beta_0} \le \frac{\lambda}{\mu}$.
- $(G.7)$ $g(S, \beta_1^\dagger) = 0$ *has* S^* *as one root, and has no root in* $(S^*, \min\{\frac{\mu+\delta}{\beta_0}, \frac{\mu}{\beta_1^\dagger}\})$ *when* $\beta_1^\dagger < \beta_0$.

Proof $(G.3)-(G.5)$ can be checked either algebraically by hand or symbolically by software Wolfram Mathematica, and we will show the proofs of the other facts.

– *Proof of* $(G.1)$ We first locate the solution β_1 of $g(h(\beta_1), \beta_1) = 0$. From the proof of Proposition 4, we know that $S = h(\beta_1)$ is a root of the following quadratic equation

$$\frac{\mu+\tau+\delta}{\beta_1}(S - \frac{\mu}{\beta_0})(S - \frac{\mu}{\beta_1}) - (1 - p)\frac{\lambda\delta}{\beta_0\beta_1} = 0,$$

hence by (14), $g(h(\beta_1), \beta_1) = f(h(\beta_1), \beta_1)(h(\beta_1) - \frac{\mu}{\beta_1})$. Then $g(h(\beta_1), \beta_1) = 0$ if and only if $f(h(\beta_1), \beta_1) = 0$ since $h(\beta_1) \neq \frac{\mu}{\beta_1}$ for any $\beta_1 > 0$.
Denote the equilibrium we look for as $(h(\beta_1), I_0(\beta_1), C_0(\beta_1), X_1(\beta_1))$, from (11)–(12), we have $f(h(\beta_1), \beta_1) = 0$ if and only if $C_0(\beta_1) = \frac{\lambda}{\mu} - \frac{\mu}{\beta_1}$ and $X_1(\beta_1) = 0$. Thus, we are looking for an equilibrium with its X_1 component being 0. An easy calculation shows that we have either $h(\beta_1) = S_+^*$ (where $S_+^* > S^*$) or $h(\beta_1) = S^*$. As $h(\beta_1)$ is a strictly decreasing function, the solution to $h(\beta_1) = S_+^* > S^*$ is strictly less than $\beta_1^\dagger$. By $(H.2)$ in Lemma 1, $h(\beta_1) = S^*$ yields $\beta_1 = \beta_1^\dagger$. That is, there is no $\beta_1 > \beta_1^\dagger$ such that $g(h(\beta_1), \beta_1) = 0$.
Next we determine the sign of $g(h(\beta_1), \beta_1)$. Observe that $f(h(\beta_1), \beta_1)$ is a continuous function about $\beta_1 > 0$, then by the intermediate value theorem, $f(h(\beta_1), \beta_1)$ will not change its sign for $\beta_1 > \beta_1^\dagger$. Therefore, in order to know the sign of $f(h(\beta_1), \beta_1)$, we only need to test it at a specific β_1 value, which we choose to be $\frac{\mu^2(\mu+\tau+\delta)}{(1-p)\lambda\delta}$ and $h(\frac{\mu^2(\mu+\tau+\delta)}{(1-p)\lambda\delta}) = 0$. An easy calculation yields $f(0, \frac{\mu^2(\mu+\tau+\delta)}{(1-p)\lambda\delta}) = \frac{p\lambda}{\beta_0}(\frac{\delta}{\mu} + 1) > 0$. Also for all $\beta_1 > \beta_1^\dagger$ we have $h(\beta_1) < \frac{\mu}{\beta_1}$, hence $g(h(\beta_1), \beta_1) = f(h(\beta_1), \beta_1)(h(\beta_1) - \frac{\mu}{\beta_1}) < 0$.

– *Proof of* $(G.2)$ By (10), $g(S^*, \beta_1)$ can be seen as a quadratic function about $\frac{\mu}{\beta_1}$ with positive coefficient of the second-order term, it is easy to check that $\frac{\mu}{\beta_0}$ and $\frac{\mu}{\beta_1^\dagger}$ are the two roots for $g(S^*, \beta_1) = 0$, we therefore complete the proof.
– *Proof of* $(G.6)$ Assume $\frac{\mu}{\beta_0} > \frac{\lambda}{\mu}$, notice that $S^* < \min\{\frac{\mu}{\beta_0}, \frac{\lambda}{\mu}\}$, then

$$\frac{\mu}{\beta_1^\dagger} = \frac{\delta}{\mu+\tau+\delta}\frac{\lambda}{\mu} + \frac{\mu+\tau}{\mu+\tau+\delta}S^* < \frac{\mu}{\beta_0}$$

implies $\beta_1^\dagger > \beta_0$.
– *Proof of* $(G.7)$ When $\beta_1 = \beta_1^\dagger$ we have $\frac{\mu}{\beta_1^\dagger} = \frac{\delta}{\mu+\tau+\delta}\frac{\lambda}{\mu} + \frac{\mu+\tau}{\mu+\tau+\delta}S^*$ and rewrite (15) as

$$\begin{aligned} g(S, \beta_1^\dagger) = \left(S - \frac{\mu}{\beta_1^\dagger}\right)\left[S^2 - (\frac{\lambda}{\mu} - \frac{\tau}{\beta_0} + \frac{\lambda\delta}{\mu^2} + \frac{\mu+\tau}{\mu}S^*)S + \frac{p\lambda}{\beta_0} + \frac{\lambda\delta}{\mu\beta_0}\right] \\ +(1-p)\frac{\lambda\delta}{\beta_0\beta_1^\dagger}. \end{aligned}$$

Then, the roots of $g(S, \beta_1^\dagger) = 0$ can be obtained by investigating the intersections between the third-order polynomial $y = P(S) := (S - \frac{\mu}{\beta_1^\dagger})\big[S^2 - (\frac{\lambda}{\mu} - \frac{\tau}{\beta_0} + \frac{\lambda\delta}{\mu^2} + \frac{\mu+\tau}{\mu}S^*)S + \frac{p\lambda}{\beta_0} + \frac{\lambda\delta}{\mu\beta_0}\big]$ and the horizontal line $y = -(1-p)\frac{\lambda\delta}{\beta_0\beta_1^\dagger}$.
Next we look at the roots of the quadratic equation $S^2 - (\frac{\lambda}{\mu} - \frac{\tau}{\beta_0} + \frac{\lambda\delta}{\mu^2} + \frac{\mu+\tau}{\mu}S^*)S + \frac{p\lambda}{\beta_0} + \frac{\lambda\delta}{\mu\beta_0}$. The condition of $\beta_1^\dagger < \beta_0$ is equivalent to

$$\frac{\mu}{\beta_1^\dagger} = \frac{\delta}{\mu+\tau+\delta}\frac{\lambda}{\mu} + \frac{\mu+\tau}{\mu+\tau+\delta}S^* > \frac{\mu}{\beta_0}$$

and equivalent to

$$S^* > \frac{\mu}{\beta_0} - \frac{\delta}{\mu+\tau}(\frac{\lambda}{\mu} - \frac{\mu}{\beta_0}),$$

then we can estimate

$$\frac{\lambda}{\mu} - \frac{\tau}{\beta_0} + \frac{\lambda\delta}{\mu^2} + \frac{\mu+\tau}{\mu}S^* > \frac{\delta+\mu}{\beta_0} + \frac{\lambda}{\mu}.$$

Now, we check the determinant of the quadratic equation

$$\Delta = \left(\frac{\lambda}{\mu} - \frac{\tau}{\beta_0} + \frac{\lambda\delta}{\mu^2} + \frac{\mu+\tau}{\mu}S^*\right)^2 - 4\frac{p\lambda}{\beta_0} - 4\frac{\lambda\delta}{\mu\beta_0} > \left(\frac{\mu+\delta}{\beta_0} - \frac{\lambda}{\mu}\right)^2.$$

Thus, the quadratic equation has two real roots with the bigger one

$$x_1 > \max\{\frac{\mu+\delta}{\beta_0}, \frac{\lambda}{\mu}\},$$

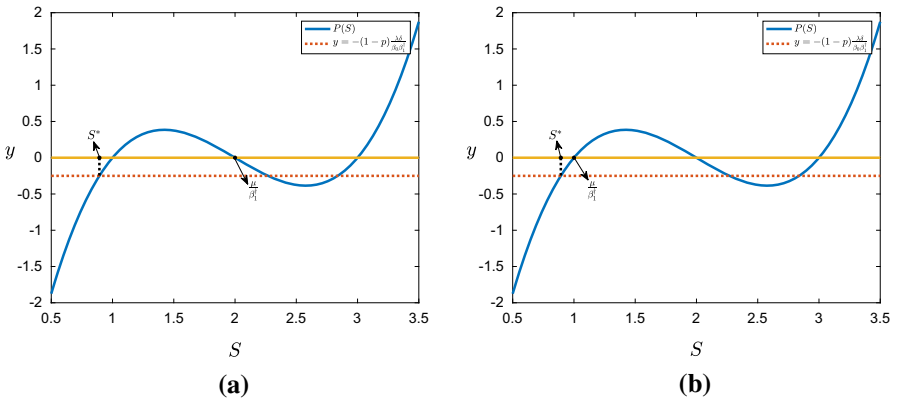


Fig. 8 Auxiliary figure for the proof of $(G.7)$ in Lemma 2 (Color figure online)

it is easy to see that $\frac{\mu}{\beta_1^\dagger} = \frac{\delta}{\mu+\tau+\delta}\frac{\lambda}{\mu} + \frac{\mu+\tau}{\mu+\tau+\delta}S^* < \frac{\lambda}{\mu}$, so we have $x_1 > \frac{\mu}{\beta_1^\dagger}$. Therefore, $\frac{\mu}{\beta_1^\dagger}$ is not the largest root of the third-order polynomial $P(S)$, and the intersections between $y = P(S)$ and line $y = -(1-p)\frac{\lambda\delta}{\beta_0\beta_1^\dagger}$ are illustrated in Fig. 8. In this way, we can see that S^* must be the smallest root of $g(S, \beta_1^\dagger) = 0$ and there is no other root lying in the interval $(S^*, \frac{\mu}{\beta_1^\dagger})$, and there is no other roots lying in the even smaller interval $(S^*, \min\{\frac{\mu+\delta}{\beta_0}, \frac{\mu}{\beta_1^\dagger}\})$.

□

Proof of Theorem 4 We only need to show the existence of an $\widetilde{S}$ that satisfies condition (16). *Proof of 1:* In the case of $\beta_1^\dagger > \beta_0$, for $\beta_1 > \beta_1^\dagger > \beta_0$, we have $\frac{\mu}{\beta_1} < \frac{\mu+\delta}{\beta_0}$; then, condition (16) is reduced to $\max\{0, h(\beta_1)\} < \widetilde{S} < \frac{\mu}{\beta_1}$. By $(G.1)$ and $(G.4)$ in Lemma 2, we have $g(\max\{0, h(\beta_1)\}, \beta_1) < 0$, and by $(G.2)$ and $(G.3)$ in Lemma2, we have $g(\min\{S^*, \frac{\mu}{\beta_1}\}, \beta_1) > 0$. The intermediate value theorem guarantees that $g(\widetilde{S}, \beta_1)$ has a root $\widetilde{S}$ in between $\max\{0, h(\beta_1)\}$ and $\min\{S^*, \frac{\mu}{\beta_1}\}$, and $\widetilde{S} < S^*$.

Proof of 2 We split the proof for the case of $\beta_1^\dagger < \beta_0$ into the following two sub-cases. (1) If $\frac{\mu}{\mu+\delta}\beta_0 < \beta_1^\dagger < \beta_0$, For $\beta_1 > \beta_1^\dagger > \frac{\mu}{\mu+\delta}\beta_0$, we have $\frac{\mu}{\beta_1} < \frac{\mu+\delta}{\beta_0}$; then, condition (16) is reduced to $\max\{0, h(\beta_1)\} < \widetilde{S} < \frac{\mu}{\beta_1}$.

By $(G.1)$ and $(G.4)$ in Lemma 2, we have $g(\max\{0, h(\beta_1)\}, \beta_1) < 0$, and by $(G.2)$ and $(G.3)$ Lemma 2, we have $g(\min\{S^*, \frac{\mu}{\beta_1}\}) > 0$ for $\beta_1 \in (\beta_0, +\infty)$, then the intermediate value theorem guarantees that $g(\widetilde{S}, \beta_1)$ has a root $\widetilde{S}$ in between $\max\{0, h(\beta_1)\}$ and $\min\{S^*, \frac{\mu}{\beta_1}\}$ for $\beta_1 \in (\beta_0, +\infty)$, and $\widetilde{S} < S^*$.

Again by $(G.2)$ in Lemma 2, we have $g(S^*, \beta_1) < 0$ for $\beta_1 \in (\beta_1^\dagger, \beta_0)$, and by $(G.3)$ in Lemma2, the intermediate value theorem guarantees that $g(\widetilde{S}, \beta_1)$ has a root $\widetilde{S}$ in between S^* and $\frac{\mu}{\beta_1}$ for $\beta_1 \in (\beta_1^\dagger, \beta_0)$ and clearly $\widetilde{S} > S^*$.

(2) If $\beta_1^\dagger < \frac{\mu}{\mu+\delta}\beta_0$, we here discuss the existence of $\widetilde{S}$ in three intervals of β_1.

(2a) For $\beta_1 \in (\beta_0, +\infty)$, we have $\frac{\mu}{\beta_1} < \frac{\mu+\delta}{\beta_0}$ and the condition (16) is reduced to $\max\{0, h(\beta_1)\} < \widetilde{S} < \frac{\mu}{\beta_1}$. Follow the same discussion as in case (1), we have the existence of $\widetilde{S} < S^*$.
(2b) For $\beta_1 \in (\frac{\mu}{\mu+\delta}\beta_0, \beta_0)$, we have the condition (16) reduced to

$$\max\{0, h(\beta_1)\} < \widetilde{S} < \frac{\mu}{\beta_1}.$$

By (G.2) and (G.3) in Lemma 2, we can conclude the existence of $\widetilde{S} > S^*$.
(2c) For $\beta_1 \in (\beta_1^\dagger, \frac{\mu}{\mu+\delta}\beta_0)$, we have the condition (16) reduced to

$$\max\{0, h(\beta_1)\} < \widetilde{S} < \frac{\mu+\delta}{\beta_0}.$$

Then in order to prove the conclusion, we only need to show that $g(\frac{\mu+\delta}{\beta_0}, \beta_1) > 0$ for $\beta_1^\dagger \in (\beta_1^\dagger, \frac{\mu}{\mu+\delta}\beta_0)$. From (10), $g(\frac{\mu+\delta}{\beta_0}, \beta_1)$ can be regarded as a quadratic function about $\frac{\mu}{\beta_1}$ with positive coefficient of the second-order term, thus the interval for $g(\frac{\mu+\delta}{\beta_0}, \beta_1) > 0$ is determined by the two zeros of the function which were obtained in (G.5) in Lemma 2. Firstly, if $\frac{\mu(\mu+\delta+\tau)\beta_0}{(\mu+\delta)(\mu+\delta+\tau)-(1-p)\beta_0\lambda} > 0$, it is easy to check that $\frac{\mu}{\mu+\delta}\beta_0 < \frac{\mu(\mu+\delta+\tau)\beta_0}{(\mu+\delta)(\mu+\delta+\tau)-(1-p)\beta_0\lambda}$, and $g(\frac{\mu+\delta}{\beta_0}, \beta_1) > 0$ for $\beta_1 < \frac{\mu}{\mu+\delta}\beta_0$. Secondly, if $\frac{\mu(\mu+\delta+\tau)\beta_0}{(\mu+\delta)(\mu+\delta+\tau)-(1-p)\beta_0\lambda} < 0$, we have $g(\frac{\mu+\delta}{\beta_0}, \beta_1) > 0$ if and only if $\frac{\mu}{\beta_1} > \frac{\mu}{\beta_0}$ or $\frac{\mu}{\beta_1} < \frac{\mu(\mu+\delta+\tau)\beta_0}{(\mu+\delta)(\mu+\delta+\tau)-(1-p)\beta_0\lambda}$ which is equivalent to $\beta_1 < \beta_0$. Thus, we have $g(\frac{\mu+\delta}{\beta_0}, \beta_1) > 0$ for all $\beta_1 \in (\beta_1^\dagger, \frac{\mu}{\mu+\delta}\beta_0)$. □

A.6 Proof of Corollary 1

Proof It is a well-known result that if the discriminant of a third-order polynomial is strictly greater than zero, then the polynomial has three distinct real roots of multiplicity 1, hence each of the real roots S of $g(S, \beta_1) = 0$ is continuously dependent on β_1. As (G.3) and (G.4) in Lemma 2 guarantee the existence of a real root in $(0, \frac{\mu}{\beta_1})$, we denote $S^-(\beta_1)$ as the continuous branch that represents the smallest root in $(0, \frac{\mu}{\beta_1})$, and $S^+(\beta_1)$ as the one that represents the largest root in $(0, \frac{\mu}{\beta_1})$. Then, both $S^-(\beta_1)$ and $S^+(\beta_1)$ are well-defined and continuous for all $\beta_1 > \beta_1^\dagger$.

1. If $\beta_1^\dagger > \beta_0$. For β_1 being sufficiently large, condition (16) is equivalent to $0 < \widetilde{S} < \frac{\mu}{\beta_1}$, hence $S^+(\beta_1)$ stays in the region

$$\Gamma_1 := \left\{(\beta_1, S) : \beta_1 \geq \beta_1^\dagger,\ \max\{0, h(\beta_1)\} \leq S \leq \min\left\{\frac{\mu}{\beta_1}, S^*\right\}\right\}$$

for sufficiently large β_1. By (G.1)−(G.4) in Lemma 2 and that $S^+(\beta_1)$ is a continuous curve, $S^+(\beta_1)$ must stay in region Γ_1 and only touches and crosses the boundary of Γ_1 through the point $(\beta_1^\dagger, S^*)$. Hence, both $S^+(\beta_1)$ and $S^-(\beta_1)$ stay below S^*.

2. $(2a)$: If $\frac{\mu}{\mu+\delta}\beta_0 < \beta_1^\dagger < \beta_0$. By $(G.1)$, $(G.3)$, $(G.4)$, $(G.7)$ in Lemma 2, we know that the curve $S^+(\beta_1)$ stays in region

$$\Gamma_2 := \left\{(\beta_1, S) : \beta_1 \geq \beta_1^\dagger,\ \max\{0, h(\beta_1)\} \leq S \leq \frac{\mu}{\beta_1}\right\}.$$

Then, the bifurcation branch only touches and crosses the boundary of Γ_2 through the point $(\beta_1^\dagger, S^*)$. Also from Theorem 4, there exists a $\widetilde{S} \in (S^*, \frac{\mu}{\beta_1})$ for $\beta_1 \in (\beta_1^\dagger, \beta_0)$, so $S^+(\beta_1)$ must pass through the points $(\beta_1^\dagger, S^*)$ and (β_0, S^*) and stays above S^* for $\beta_1 \in (\beta_1^\dagger, \beta_0)$ and for $\beta_1 > \beta_0$, $S^+(\beta_1) < S^*$.
$(2b)$: If $\beta_1^\dagger < \frac{\mu}{\mu+\delta}\beta_0$. From the proof of $(2c)$ in Theorem 4, the curve $g(S, \beta_1) = 0$ intersects the horizontal line $S = \frac{\mu+\delta}{\beta_0}$ at two points and both of them are outside of the region

$$\Gamma_3 := \left\{(\beta_1, S) : \beta_1 \geq \beta_1^\dagger,\ \max\{0, h(\beta_1)\} \leq S \leq \min\{\tfrac{\mu+\delta}{\beta_0}, \tfrac{\mu}{\beta_1}\}\right\}.$$

By $(G.1)-(G.4)$, $(G.7)$ in Lemma 2, we know that the bifurcation branch $S^+(\beta_1)$ stays in region Γ_3, it only touches and crosses the boundary of Γ_3 through the point $(\beta_1^\dagger, S^*)$, but for $\beta_1 \in (\beta_1^\dagger, \beta_0)$, we have $S^+(\beta_1) > S^*$ and for $\beta_1 > \beta_0$, $S^+(\beta_1) < S^*$. □

A.7 Proof of Corollary 2

Proof If the discriminant of a third-order polynomial is strictly smaller than zero, then the polynomial has only one real root of multiplicity 1, hence $\widetilde{S}$ is unique and continuously dependent on β_1. From Theorem 4, we have that $\widetilde{S} < S^*$. □

A.8 Proof of Theorem 5

We will apply Theorem 1.3.2 in Zhao (2003) to show the uniform persistence, and hence we need to formulate the problem as follows.

Consider the solution space $\mathbb{X} := \{(S, I_0, C_0, X_1) : S, I_0, C_0, X_1 \geq 0\}$, the interior subspace of $\mathbb{X}$: $\mathbb{X}_0 := \{(S, I_0, C_0, X_1) : S, I_0, C_0, X_1 > 0\}$, and the boundary of $\mathbb{X}_0$ in $\mathbb{X}$: $\partial\mathbb{X}_0 := \mathbb{X} \setminus \mathbb{X}_0 = \{(S, I_0, C_0, X_1) : S = 0 \text{ or } I_0 = 0 \text{ or } C_0 = 0 \text{ or } X_1 = 0\}$. We denote $\Phi_t : \mathbb{X} \to \mathbb{X}$, $t \geq 0$ as the semiflow defined by the solution of system (4), and $M_\partial := \{x \in \partial\mathbb{X}_0 : \Phi_t(x) \in \partial\mathbb{X}_0,\ t \geq 0\}$. Denote $d(x, y)$ as the Euclidean distance between two points $x, y \in \mathbb{R}^4$, and $d(x, E) := \inf\{d(x, y) : y \in E\}$ as the distance between a point x and a set $E \subseteq \mathbb{R}^4$. As $\mathbb{X}_0$ is positively invariant, $p(x) := d(x, \partial\mathbb{X}_0)$ can be seen as a generalized distance function for Φ.

Further, we denote the baseline system with only strain 0 as

$$\begin{aligned}\dot{S} &= p\lambda - \beta_0(C_0 + I_0)S - \mu S,\\ \dot{C}_0 &= (1-p)\lambda + \beta_0(C_0 + I_0)S + \tau I_0 - (\delta + \mu)C_0,\end{aligned} \tag{20}$$

$$\dot{I}_0 = \delta C_0 - (\tau + \mu) I_0.$$

Lemma 3 $M_\partial = \{(S, I_0, C_0, X_1) : X_1 = 0\} \cap \partial \mathbb{X}_0$.

Proof If $x \in \{(S, I_0, C_0, X_1) : X_1 = 0\} \cap \partial \mathbb{X}_0$, then $\Phi_t(x)$ is the solution to system (20) and $\Phi_t(x) \in \{(S, I_0, C_0, X_1) : X_1 = 0\} \cap \partial \mathbb{X}_0 \subseteq M_\partial$; hence, $\{(S, I_0, C_0, X_1) : X_1 = 0\} \cap \partial \mathbb{X}_0 \subseteq M_\partial$. For any $x \in M_\partial$, suppose for contradiction that $x \in \{(S, I_0, C_0, X_1) : X_1 > 0\} \cap \partial \mathbb{X}_0$; then, Proposition 2 implies $\Phi_t(x) \in \{(S, I_0, C_0, X_1) : S, I_0, C_0, X_1 > 0\} \nsubseteq \partial \mathbb{X}_0$. Therefore, we have $x \in \{(S, I_0, C_0, X_1) : X_1 = 0\} \cap \partial \mathbb{X}_0$. □

Lemma 4 $\{(S^*, I_0^*, C_0^*, 0)\}$ *is isolated in* $\mathbb{X}$ *for* $\beta_1 > \beta_1^\dagger$.

Proof Choose $\varepsilon = \big(\beta_1(S^* + I_0^*) - \mu\big)/3 > 0$, denote $\mathcal{B}_0$ as the ball centered at $(S^*, I_0^*, C_0^*, 0)$ with radius ε, and denote the maximal invariant set in $\mathcal{B}_0$ as M. For any point $x \in \mathcal{B}_0 \setminus \{(S^*, I_0^*, C_0^*, 0)\}$ and $\Phi_t(x) \in M \subseteq \mathcal{B}_0$ for all $t > 0$, denote $(S(t), I_0(t), C_0(t), X_1(t)) := \Phi_t(x)$, then we have $|S(t) - S^*| < \varepsilon$ and $|I_0(t) - I_0^*| < \varepsilon$ for all $t > 0$. However, from the last equation of system (4), we have $\dot{X}_1(t) = [\beta_1(S(t) + I_0(t)) - \mu] X_1(t) > [\beta_1(S^* + I_0^*) - 2\varepsilon_0 - \mu] X_1(t) = \varepsilon X_1(t)$ for all $t > 0$, then $\dot{X}_1(t) > \varepsilon_1 X_1(t)$ implies $\lim_{t \to +\infty} X(t) = +\infty$ which leads to a contradiction. Therefore, the maximal invariant set in $\mathcal{B}_0$ is the set that contains only the equilibrium $\{(S^*, I_0^*, C_0^*, 0)\}$. □

Proof of Theorem 5 Apply Theorem 1.3.2 in Zhao (2003) to show the uniform persistence. By Proposition 2, $\mathbb{X}_0$ is positively invariant for the semiflow Φ_t generated by the solution to system (4), and Φ_t is compact and point dissipative, hence there is a global attractor for Φ_t.

Let $\{(S^*, I_0^*, C_0^*, 0)\}$ be the finite sequence that only consists of one set, which is obviously disjoint, compact, and from Lemma 4 it is an isolated invariant set in $\partial \mathbb{X}_0$. Next, we check with the following properties.

(a) From Lemma 3, for any $x \in M_\partial$ we know that $\Phi_t(x)$ is the solution to system (20) and by our analysis of the baseline system, we have $\omega(x) = \{(S^*, I_0^*, C_0^*, 0)\}$.
(b) There is apparently no subset of $\{(S^*, I_0^*, C_0^*, 0)\}$ that forms a cycle.
(c) $\{(S^*, I_0^*, C_0^*, 0)\}$ is isolated in $\mathbb{X}$ from Lemma 4.
(d) As stated before, we define $p(x) := d(x, \partial \mathbb{X}_0)$, we need to show that for any $x \in \mathbb{X} \setminus \partial \mathbb{X}_0$, $\lim_{t \to +\infty} d(\Phi_t(x), (S^*, I_0^*, C_0^*, 0)) \neq 0$, and similar argument as the proof in Lemma 4 is sufficient.

It follows from Theorem 1.3.2 in Zhao (2003) that there exists $\eta > 0$ such that for any $x \in \mathbb{X} \setminus M_\partial$, we have $\min_{y \in \omega(x)} p(y) > \eta$. That is,

$$\liminf_{t \to +\infty} S(t) > \eta, \quad \liminf_{t \to +\infty} I_0(t) > \eta, \quad \liminf_{t \to +\infty} C_0(t) > \eta, \quad \liminf_{t \to +\infty} X_1(t) > \eta,$$

for any nonnegative initial condition $(S(0), I_0(0), C_0(0), X_1(0))$ with $X_1(0) > 0$. □

A.9 Proof of Theorem 6

Proof Firstly, we compute the difference between $\beta_1^\dagger$ and β_0:

$$\beta_1^\dagger - \beta_0 = \frac{\mu}{S^*+I_0^*} - \beta_0 = \frac{\mu}{\frac{\lambda}{\mu}\frac{\delta}{\mu+\delta+\tau}+\frac{\mu+\tau}{\mu+\delta+\tau}S^*} - \beta_0.$$

Therefore, $\beta_1^\dagger - \beta_0$ has the same sign with the following function $d(\beta_0)$:

$$d(\beta_0) := \left(\mu - \frac{1}{2}\mu\frac{\mu+\tau}{\mu+\delta+\tau}\right) - \left(\frac{\lambda}{\mu}\frac{\delta}{\mu+\delta+\tau} + \frac{1}{2}\frac{\lambda}{\mu}\frac{\mu+\tau}{\mu+\delta+\tau}\right)\beta_0 + \frac{1}{2}\frac{\mu+\tau}{\mu+\delta+\tau}\sqrt{\left(\frac{\lambda\beta_0}{\mu}+\mu\right)^2 - 4p\lambda\beta_0}.$$

Clearly, $d(0) = \mu > 0$, and

$$\begin{aligned} d(\beta_0) &< \left(\mu - \frac{1}{2}\mu\frac{\mu+\tau}{\mu+\delta+\tau}\right) - \left(\frac{\lambda}{\mu}\frac{\delta}{\mu+\delta+\tau} + \frac{1}{2}\frac{\lambda}{\mu}\frac{\mu+\tau}{\mu+\delta+\tau}\right)\beta_0 + \frac{1}{2}\frac{\mu+\tau}{\mu+\delta+\tau}\left(\frac{\lambda\beta_0}{\mu}+\mu\right) \\ &= \mu - \frac{\lambda}{\mu}\frac{\delta}{\mu+\delta+\tau}\beta_0 \to -\infty \quad \text{as} \quad \beta_0 \to +\infty, \end{aligned}$$

thus $d(\beta_0) < 0$ for β_0 being sufficiently large. Since $d(\beta_0)$ is a continuous function, there exists at least one intersection between its curve and the positive branch of the β_0 axis. Observe that $d(\beta_0) = 0$ has at most two real roots; hence, we can conclude that there exists a unique positive solution to $d(\beta_0) = 0$, and we denote it as β_0^*. So $d(\beta_0) > 0$ on $(0, \beta_0^*)$ and $d(\beta_0) < 0$ on $(\beta_0^*, +\infty)$, which completes the proof. □

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