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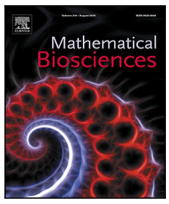

Original Research Article

Optimal control strategies for mitigating antibiotic resistance: Integrating virus dynamics for enhanced intervention design

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ABSTRACT

Given the global increase in antibiotic resistance, new effective strategies must be developed to treat bacteria that do not respond to first or second line antibiotics. One novel method uses bacterial phage therapy to control bacterial populations. Phage viruses replicate and infect bacterial cells and are regarded as the most prevalent biological agent on earth. This paper presents a comprehensive model capturing the dynamics of wild-type bacteria (S), antibiotic-resistant bacteria (R), and virus-infected (I) bacteria population, incorporating virus inclusion. Our model integrates biologically relevant parameters governing bacterial birth rates, death rates, mutation probabilities and incorporates infection dynamics via contact with a virus. We employ an optimal control approach to study the influence of virus inclusion on bacterial population dynamics. Through numerical simulations, we establish insights into the stability of various system equilibria and bacterial population responses to varying infection rates. By examining the equilibria, we reveal the impact of virus inclusion on population trajectories, describe a medical intervention for antibiotic-resistant bacterial infections through the lense of optimal control theory, and discuss how to implement it in a clinical setting. Our findings underscore the necessity of considering virus inclusion in antibiotic resistance studies, shedding light on subtle yet influential dynamics in bacterial ecosystems.

1. Introduction

Bacteria are microorganisms that are composed of a single cell. They are widely distributed in nature and cause a range of infections and also play an essential role in human health [1]. Beneficial bacteria can be found in the gastrointestinal tract, where they support the digestive system and aid healthy development of the immune system. *Bifidobacteria* and *E. coli* are examples of healthy bacteria found in the intestine which break down complex carbohydrates and also improve gut health [2]. Mutations in the deoxyribonucleic acid (DNA) of a bacteria may occur due to mistakes when bacterial cells undergo binary fission [1,3] and can sometimes alter the functioning of its genes, leading to changes in their phenotype. These mutations facilitate the emergence of diversity within its population, which may improve the capacity of the bacteria to adapt to its changing environment [4–7]. When mutations occur in bacteria important for human health, harmful infections could arise. Typical treatment for such pathogenic bacterial infection involves antibiotics. However, some mutations render bacteria antibiotic-resistant, making it difficult to treat infections. Other mutations make bacteria more virulent or more easily transmissible [8–10].

Antibiotic resistance in bacteria is a growing problem in public health, as it is increasingly harder to treat infections caused by mutant antibiotic-resistant bacteria [3,11]. The scourge of antibiotic-resistant genes among microbial pathogens poses a serious threat to the effectiveness of current antimicrobial treatments, particularly for severe bacterial infections leading to sepsis [12]. The progressive emergence of antimicrobial resistance (AMR) has been driven by the use of anti-infection treatments in humans, animals, and food production [10,13]. This has been further compounded by the inadequacy of measures designed to curtail the infections [13]. According to the World Health Organization (WHO), antibiotic resistance has significant economic cost implications as a result of prolonged illnesses and longer hospital stays which could lead to death or disability [14]. Two central factors that drive antimicrobial resistance are the volume of antimicrobials used and the spread of resistant micro-organisms and genes encoding for resistance [15]. These factors can both be controlled through preventative measures. A central goal of infection bacteriology is thus to identify aspects of bacterial ecology to mitigate infection and develop novel treatments.

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Mathematical models have been historically successful in capturing essential features of infective microbes to predict infection dynamics. These models have significantly advanced our understanding of infectious diseases, their transmission, and the development of new treatments. Jenner et al. [16] and Xavier et al. [17] both highlight the crucial role of innovative mathematical and computational modeling techniques in predicting disease outbreaks and designing containment strategies. Mathematical models have also been used to study the evolution of infectious microbes, including their adaptation to host immune systems and the emergence of new strains [18], which has helped to inform the development of new vaccines and drugs. Several authors have considered the mathematical modeling of antimicrobial resistance with different objectives. For example, Ibargüen-Mondragón et al. [19] proposed an ordinary differential equation (ODE) model for the concurrent acquisition of resistance to bactericidal and bacteriostatic antibiotics, where resistance is generated by specific changes in bacterial DNA sequence and plasmid transmission. The model showed that applying appropriate therapies and stimulating the immune system is the best way to eliminate progression to resistance for many bacterial infections. Alavez-Ramírez et al. [20] presented a model for the emergence of resistance of *Mycobacterium tuberculosis* bacteria to antibiotics to assess the efficiency of administering one or two drugs for controlling latent tuberculosis infection considering its dependence on strengths of the immune system. Regarding AMR control, a number of studies have established results for the optimal control strategies for mitigating bacterial resistance. For managing bacterial populations with persister dynamics, Leenheer and Cogan [21] applied the amount of antimicrobial as the control variable to predict the optimal timing and duration of antibiotic treatment. Ibargüen-Mondragón et al. [22] formulated an optimal control problem to minimize the bacterial population with plasmid-mediated antibiotic resistance, considering the action of both antibiotic treatment and immune system to combat bacterial infections. Gutiérrez et al. [23] developed an approach for managing bacterial populations with persistent dynamics. They offer a completely automated, high-throughput approach that combines in-the-moment measurements with computer-controlled optogenetic manipulation of bacterial growth to perform precise and reliable compositional control of a two-strain *E. coli* community.

From a deterministic perspective, we can single out other research focused on the acquisition of antibiotic resistance: the causal factors underlying bacterial resistance is given in [24], analysis of bacterial behavior in response to various antibiotic treatments in [25–27], optimum antibiotic use in [28], and modeling of the acquisition of resistance from external sources in [29]. Both deterministic and stochastic models have been used to study bacterial resistance mathematically. The interaction between antibiotic-sensitive and antibiotic-resistant bacteria was mathematically studied by Mena et al. [30]. They formulated an optimal control problem for an unperturbed and a perturbed system, where the control variable is prophylaxis. Merdan et al. [31] compared mathematical models of bacterial resistance under random conditions with a deterministic model including immune system response and antibiotic therapy. In [32], the authors applied a stochastic population model to investigate the effect of resistance, persistence, and hypermutation on antibiotic treatment failure and found that the relative impact of these factors depends on the antibiotic concentration and the infection time scale.

In this paper, we will focus on the use of viruses to mitigate bacterial infection. Roach and Donovan [33] explored the therapeutic applications of bacteriophage-derived proteins, such as endolysins and peptidoglycan hydrolases, in animal models of bacterial infection. The potential of targeting bacterial virulence and the use of bacteriophage-based approaches was highlighted in [34–36], as alternative strategies to combat antibiotic resistance and control bacterial infections. Mekalanos et al. [37] explored how bacteriophages can influence the dynamics of cholera outbreaks. The research showed that lytic bacteriophages, which specifically target and destroy virulent strains of cholera-causing bacteria (*Vibrio cholerae*), can significantly reduce the severity of cholera outbreaks. Furthermore, in their study on bacteriophage-resistant and bacteriophage-sensitive bacteria, Han and Smith [38] explored the population dynamics within a chemostat. They found that while resistant bacteria may survive phage attacks, they are less efficient at competing for nutrients compared to sensitive bacteria. This trade-off significantly influences their population dynamics and persistence.

Mathematical modeling has been instrumental in understanding the dynamics and control of viral infections, including the use of viruses to control bacterial infections [39]. Clifton et al. [40] demonstrated that antibiotic-induced proviruses can play a role in controlling bacterial populations, expanding the understanding of phage-antibiotic synergy. Bacteriophages, viruses that only replicate in and infect bacterial cells, are regarded as the most prevalent biological agent on earth and are found everywhere in the environment. Styles et al. [41] emphasized the need for realistic mathematical models to improve the understanding of bacteriophage, bacteria, and eukaryotic interactions, which is crucial for the development of phage therapy. These studies collectively underscore the importance of mathematical modeling in exploring the use of viruses to control bacterial infections. One challenge with phage therapy is that phages, like other pathogens, are construed as "outsiders" by the human immune system and are eliminated in due time [42,43]. Thus, if phage therapy is unsuccessful once, the same phage therapy cannot be used to treat a given infected individual. Using virotherapy to completely eliminate a given infection is possible but with a low chance of success. However, this can be circumvented by using phages in combination with other antibacterial agents [43,44].

Here, we hope to explore phage therapy with a mathematical model in a different capacity. Rather than completely eliminating an infection, we seek to understand if introducing virus-infected bacteria can help mitigate an infection indefinitely. We borrow from the concept in ecology known as apparent competition, wherein the presence of multiple prey with a common predator prevents any single prey from being eliminated [45]. If we consider wild-type bacteria and antibiotic-resistant bacteria as prey for a bacteriophage, the theory of apparent competition stipulates that the antibiotic-resistant bacteria will not outgrow the wild-type bacteria. Thus, infection may not be completely removed, but it can be controlled. In this paper, we describe the dynamics of the interactions of antibiotic-sensitive and antibiotic-resistant bacteria with a user-controlled viral infection. To this end, we formulate a mathematical model that consists of a nonlinear system of three ordinary differential equations. These equations describe the interaction between populations of bacteria sensitive to and resistant to antibiotics, along with the viral infection. With the goal of minimizing the population of antibiotic resistant bacteria, we formulate an optimal control problem where the control variable is a proxy for introducing virus-infected bacteria near the region of bacterial infection. The infection is user-controlled as a mechanism to mitigate undesirable antibiotic resistant bacteria.

The study introduces a framework for understanding and optimizing control interventions in bacterial ecosystems. By integrating optimal control techniques, dynamically exploring control strategies, quantitatively assessing control impact, and elucidating long-term system behavior, we provide a holistic approach to tackling antibiotic resistance and advancing our understanding of complex ecological dynamics with the goal of reducing the antibiotic resistant population. Our work lays the foundation for progressing treatment of antibiotic-resistant bacterial infection.

2. Model formulation

Our model consists of three different bacterial strain populations: wild-type, antibiotic-resistant, and the virus-infected bacterial strains, it describes the interactions between them (see Fig. 1). Analyzing this model will provide insight into which biophysical parameters are

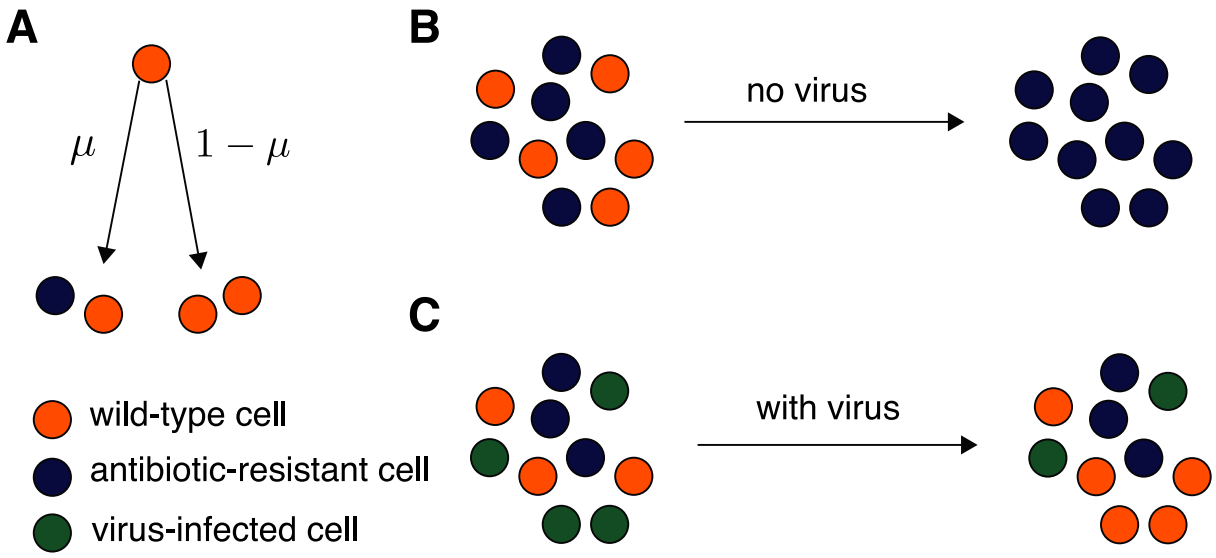

Fig. 1. Schematic of our model. (A) Wild-type cells undergo fission and with a probability μ produce antibiotic-resistant mutants. (B) If these arise, then they will eventually dominate the population. This is undesirable. (C) We hypothesize that adding viral infection promotes the ability for coexistence between the wild-type and antibiotic-resistant strains.

key to affecting model output. Let $S(t)$, $R(t)$ and $I(t)$ be the populations $(S, R, I > 0)$ of wild-type bacteria, antibiotic-resistant bacteria, and virus-infected bacteria respectively. We represent the interactions between them with the following model:

$$\begin{aligned}\frac{dS}{dt} &= \lambda S\left(1-\frac{S+R+I}{K}\right)(1-\mu)-\beta IS-\delta_s S\\ \frac{dR}{dt} &= \lambda S\left(1-\frac{S+R+I}{K}\right)\mu+\gamma R\left(1-\frac{S+R+I}{K}\right)-\beta IR-\delta_m R\\ \frac{dI}{dt} &= \beta IS+\beta IR-\delta_i I+\alpha(t),\end{aligned} \tag{1}$$

where μ is the probability that a wild-type bacterial division results in an antibiotic-resistant mutation. We assume μ depends on R: As R increases, the likelihood of horizontal gene transfer increases, yielding more mutants. We therefore take μ to be an increasing function of R that saturates as $R \to \infty$. We represent this with a Hill function:

$$\mu = \mu_0 + (1-\mu_0)\frac{R}{Z+R+I}.$$

We assume a basal mutation probability μ_0, which is the inherent likelihood of a mutation occurring independent of the number of the antibiotic-resistant bacteria. The parameter Z is the half-activation population. The birth rate and death rate of wild-type bacteria are λ and δ_s respectively, and K is the carrying capacity. We set $K = 1$ for simplicity in the rest of the paper. This effectively normalizes S, R, and I so that they now represent fractions of K that each subpopulation occupies. We assume a logistic growth described by $S(1-S-R-I)$. Note that the death rates are not explicitly required since the logistic term accounts for death as well. We include this term to make the model amenable for future modifications, such as including antibiotic treatment. For the antibiotic-resistant population, the birth rate and death rate are characterized by γ and δ_m respectively. Mutation of wild-type bacteria leading to new resistant bacteria is represented with $S(1-S-R-I)\mu$. Our model forgoes explicit virus dynamics and models infection via contact with infected bacteria. The rate at which we inject virus-infected bacteria into the system is time-dependent and described by $\alpha(t)$, and β quantitates the infectivity of the viral infection. We assume infection is a stronger contributor to infective cell growth than division—our model thus does not include a term for virus-infected cell birth [46,47]. Including such a term does not qualitatively affect our results. The death rate of virus-infected cells is characterized by δ_i. Here, we assume all the model parameters λ, γ, β, δ_s, δ_m, δ_i are positive and that all the initial conditions of model system (1) satisfy $0 \le S(0), R(0), I(0) \le 1$. Parameter values are given in Table 1. Unless otherwise noted, these are the values used throughout the paper. We use α and $\alpha(t)$ interchangeably throughout the remainder of the paper, explicitly including time dependence whenever necessary.

We note that Eq. (1) can be derived systematically from a lattice-based microscopic spatial stochastic model of bacterial dynamics. In such a model, each lattice site is occupied by a wild-type, antibiotic-resistant, or virus-infected bacterial cell or is vacant. Division and infection events characterize the reactions that describe the stochastic evolution of the microscopic configurations of the lattice. By invoking a mean field approximation and a macroscopic limit, one can derive Eq. (1) [7,48]. We will explore this stochastic lattice model in detail as a subject of future work.

To understand what biophysical parameters promote reaching desirable stationary states, we next compute the equilibria of Eq. (1) and determine their stability in the absence of the control α ($\alpha(t) \equiv 0$). Then, using α as our control variable, we will apply optimal control to the system to determine how to tune α in time to minimize the antibiotic-resistant bacterial population while maintaining the wild-type bacterial population.

3. Model analysis

This section explores the dynamics of bacterial populations as the infection rate increases. It includes simulations of the bacterial population under two conditions: one without any control measures and no initial infection = and the other with an increased infection rate and an initial infection present. These analyses highlight how varying infection rates and initial conditions affect population trajectories, providing insights into the effectiveness of infection control strategies.

To examine these various circumstances, we compute the equilibria of Eq. (1) and determine their respective stability. We begin by proving that solutions to Eq. (1) are non-negative.

Table 1
Description of parameters used.

Parameters	Description	Value	Source
λ	Growth rate of the antibiotic-wild-type bacteria S	1.6 d^{-1}	[49]
γ	Growth rate of antibiotic-resistant bacteria R	0.8 d^{-1}	[50]
μ_0	The rate of mutation of S bacteria cells into R	10^{-8} d^{-1}	[51]
$\alpha(t)$	The rate of injection of virus-infected bacteria into the system	[0, 1] conc d^{-1}	Assumed
β	Infection rate of virus-infected bacteria I	1.96 d^{-1}	[52]
δ_s	Death rate of S	0.312 d^{-1}	[53]
δ_m	Death rate of R	0.312 d^{-1}	[53]
δ_i	Death rate of I	2.5 d^{-1}	Assumed

3.1. Non-negativity of solutions

Here we establish non-negativity of solutions for Eq. (1). To do this, we demonstrate that the vector field,

$$\mathbf{F} \equiv \left\langle \frac{dS}{dt}, \frac{dR}{dt}, \frac{dI}{dt} \right\rangle,$$

does not point outward relative to the positive orthant along the planes $S = 0$, $R = 0$, and $I = 0$. We assume that $0 \le S(0), R(0), I(0) \le 1$. For this proof, we use the fundamental fact that for any two vectors $\mathbf{a}, \mathbf{b} \in \mathbb{R}^n$:

1. $\mathbf{a} \cdot \mathbf{b} > 0$ means $\mathbf{a}, \mathbf{b}$ point into the same half-space
2. $\mathbf{a} \cdot \mathbf{b} < 0$ means $\mathbf{a}, \mathbf{b}$ point into opposite half-spaces
3. $\mathbf{a} \cdot \mathbf{b} = 0$ means $\mathbf{a}, \mathbf{b}$ are orthogonal

Theorem 1. *Solutions to Eq. (1) with $S(0) \in [0, 1]$, $R(0) \in [0, 1]$, and $I(0) \in [0, 1]$ are non-negative.*

Proof. *(a)* $S = 0$. Along the plane $S = 0$, the outward pointing normal is $\mathbf{n}_S = \langle -1, 0, 0 \rangle$. We compute

$$\mathbf{F} \cdot \mathbf{n}_S = -\frac{dS}{dt}\Big|_{S=0} = 0.$$

Thus, the flow of the dynamical system governed by Eq. (1) is orthogonal to the outward pointing normal. A trajectory of the system confined to the $S = 0$ plane will thus not become negative. Indeed, the plane $S = 0$ is an invariant set of Eq. (1).

(b) $I = 0$. Along the plane $I = 0$, the outward pointing normal is $\mathbf{n}_I = \langle 0, 0, -1 \rangle$. As before, we compute

$$\mathbf{F} \cdot \mathbf{n}_I = -\frac{dI}{dt}\Big|_{I=0} = -\alpha(t) \le 0.$$

Thus, the flow of the dynamical system is into the positive orthant.

(c) $R = 0$. Along the plane $R = 0$, the outward pointing normal is $\mathbf{n}_R = \langle 0, -1, 0 \rangle$. As before we compute

$$\mathbf{F} \cdot \mathbf{n}_R = -\frac{dR}{dt}\Big|_{R=0} = -\lambda S\,(1 - (S + I)) \le 0,$$

for $0 \le S(0), I(0) \le 1$. Hence, the flow of $\mathbf{F}$ is again into the positive orthant. Note in particular that the only way to make $\frac{dR}{dt} < 0$ is to have $S + I > 1$, but if $0 \le S(0), I(0) \le 1$, this will never occur since along the line $S + I = 1$, $\frac{dR}{dt} = 0$ when $R = 0$. □

This establishes that solutions beginning in the positive orthant of $\mathbb{R}^3$ never leave it. Thus, solutions are non-negative.

We next examine the equilibria and stability properties of Eq. (1).

3.2. Linear stability analysis

We find the equilibria of system (1) by setting the temporal derivatives on the left hand side to zero and solving the resulting algebraic equations.

No virus case. In the absence of virus and control ($\beta = 0, \alpha = 0, I(0) = 0$), Eq. (1) is reduced to a planar system and two equilibria manifest. One equilibrium ($S = 0, R = 0$) represents an extinction scenario where no bacteria are present. The eigenvalues of the corresponding linearization are

$$\theta_1 = \lambda(1 - \mu_0) - \delta_s \quad \text{and} \quad \theta_2 = \gamma - \delta_m.$$

The instability of this state for our parameter values, indicated by the positive eigenvalues in the linearization (see Table 2), suggests that any small perturbation away from this equilibrium will cause the population to move away from extinction towards an alternative equilibrium. Consequently, the bacteria strains rapidly proliferate, but a significant concern arises if the antibiotic-resistant population begins to grow faster than the wild-type population. This scenario would result in the resistant strains becoming predominant, posing a significant challenge for treatment and control of infections.

We observed this exact occurrence manifest as the other equilibrium point from Eq. (1). The extermination of wild-type bacteria by the resistant strain ($S = 0, R = 1 - \frac{\delta_m}{2\gamma}$) occurs as a stable equilibrium (see Table 2, Fig. 2A), with eigenvalues corresponding to the linearization,

$$\theta_1 = \frac{-\delta_s(Z+1)\gamma - \delta_m\Big(\lambda(\mu_0 - 1)Z - \delta_s\Big)}{(Z+1)\gamma - \delta_m} \quad \text{and} \quad \theta_2 = \delta_m - \gamma,$$

being negative for our parameter values. Thus, any small perturbation away from this state will return to the equilibrium, which characterizes the dominance of the antibiotic-resistant population. This outcome is undesirable because it implies that the antibiotic-resistant bacteria have become the predominant strain, making it difficult to control infections.

The proliferation of resistant bacteria highlights the critical need for the development of new antimicrobial treatments and the implementation of rigorous infection control measures. Addressing this issue is essential to prevent the rise of untreatable bacterial infections and safeguard public health. These findings underscore the urgency of implementing optimal control measures to prevent the growth of resistant strains and to manage existing populations effectively.

Adding virus-infected bacteria. To ascertain if imputing a viral intervention in system dynamics allows for resistant population mitigation, we next introduce a virus-infected population into our system and determine the stability of various equilibria from Eq. (1). Following a similar process applied to the no virus case summarized in Table 2, we obtain the equilibria and the eigenvalues for the model when the virus infected population is added. In this scenario, analytical results for the equilibria and eigenvalues are not obtainable. As such, we present numerical results for our parameter set.

Four equilibria result: extinction, antibiotic-resistant population dominance, non wild type coexistence, and coexistence (see Table 3):

1. Extinction: The linearization around the extinction scenario ($S = 0, R = 0, I = 0$) yields eigenvalues with positive real part. Thus, it is unstable. This suggests that both bacterial strains and virus-infected population could proliferate rapidly when pushed away from extinction. The one caveat to this is the existence of the stable manifold of the extinction equilibrium corresponding to θ_3 (see Table 3) in the direction of the eigenvector corresponding to θ_3. Along this invariant manifold, solutions converge to extinction as $t \to \infty$. However, a perturbation yielding a position on the stable manifold is unlikely, so we do not consider it a generic perturbation from extinction. There are two possibilities that emerge from this instability: (1) The antibiotic-resistant bacteria again dominate or (2) the virus-infected bactera facilitate coexistence.

Table 2
Equilibria and stability analysis when β =0, α =0 and no virus-infected bacteria present.

Equilibrium point	State variables	Eigenvalues	Stability
Extinction	$S = 0, \quad R = 0$	$\theta_1 = 0.488, \quad \theta_2 = 1.288$	Unstable
Antibiotic-Resistant Population Dominance	$S = 0, \quad R = 0.610$	$\theta_1 = -0.488, \quad \theta_2 = -0.224$	Stable

Table 3
Equilibria and stability when $\beta > 0$, $\alpha = 0$, and $I > 0$. Here, $j = \sqrt{-1}$.

Equilibrium point	State variables	Eigenvalues	Stability
Extinction	$S = 0, \quad R = 0, \quad I = 0$	$\theta_1 = 0.488$ $\theta_2 = 1.288$ $\theta_3 = -2.500$	Unstable
Antibiotic-Resistant Population Dominance	$S = 0, \quad R = 0.610, \ I = 0.0$	$\theta_1 = -0.488$ $\theta_2 = -0.224$ $\theta_3 = 15.800$	Unstable
Non Wild Type Coexistence	$S = 0, \ R = 0.083, \ I = 0.014$	$\theta_1 = 0.111$ $\theta_2 = -0.0333 + 1.0258j$ $\theta_3 = -0.0333 - 1.0258j$	Unstable
Coexistence	$S = 0.042, \ R = 0.041, \ I = 0.025$	$\theta_1 = -0.0617$ $\theta_2 = -0.0639 + 1.4389j$ $\theta_3 = -0.0639 - 1.4389j$	Stable

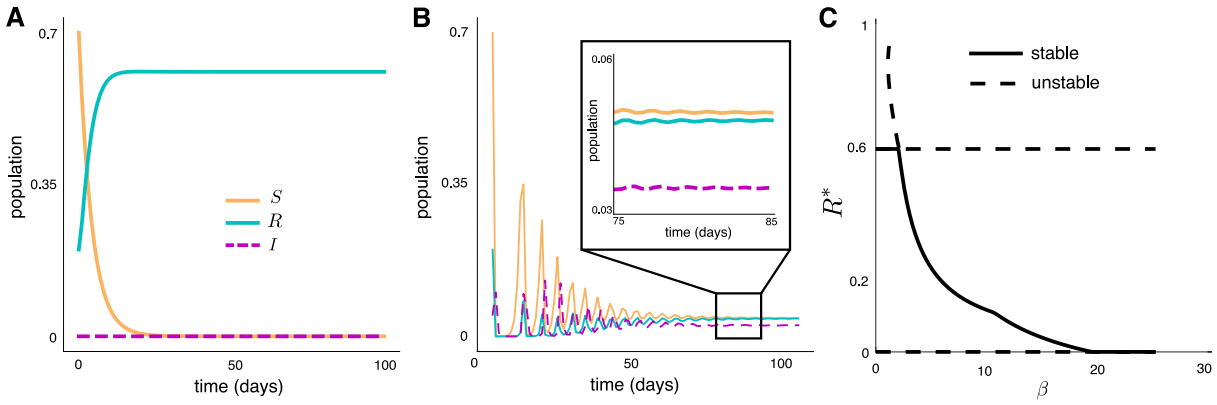

Fig. 2. Simulation results of Eq. (1): (A) bacteria population in the absence of virus-infected bacteria $\alpha = 0$, $\beta = 0$ and $I(0) = 0$, (B) bacteria population in the presence of virus-infected bacteria $\alpha = 0$, $\beta = 15$ and $I(0) > 0$, and (C) a bifurcation diagram showing the impact of virus infectivity on equilibrium of the antibiotic-resistant population.

2. Antibiotic-Resistant Population Dominance: The possibility of strict dominance by antibiotic-resistant bacteria is nullified in the presence of virus-infected bacteria because the mutant dominant equilibrium is unstable. This instability suggests that the introduction of the virus can alter the system dynamics, leading to the growth of the bacteria strains over time. Although there exists a 2D submanifold of phase space generated by the eigendirections of the negative eigenvalues θ_1, θ_2 wherein contraction to the dominant antibiotic-resistant bacteria equilibrium occurs, we do not consider this as a generic perturbation away from this equilibrium. This highlights the impact of the virus in mitigating the dominance of antibiotic resistance in the bacterial populations.
3. Non Wild Type Coexistence: This equilibrium represents a case where antibiotic-resistant bacteria coexist with virus-infected bacteria and the wild type bacteria have gone extinct. The eigenvalues indicate instability, suggesting that small disturbances will cause the populations to deviate from this delicate balance. The instability of this equilibrium will support the growth of the wild-type bacteria population. The instability implies that both antibiotic-resistant and virus infected bacterial populations could grow faster than the wild-type strains, potentially leading to their dominance. This outcome is undesirable, necessitating the implementation of effective control measures to prevent the unchecked proliferation of antibiotic-resistant and virus-infected bacterial strains.
4. Coexistence: In this scenario, all bacterial strains coexist. Importantly, this equilibrium is stable as indicated by the negative real parts of all eigenvalues in the linearization. Furthermore, in this case with our parameters, the model predicts that the wild-type strain outnumbers the mutant, which is desirable (see Fig. 2B). This ensures a level of control and mitigation of the risks associated with bacterial coexistence and resistance emergence.

Thus, we have established that the presence of virus mitigates the antibiotic-resistant population. To further embellish this point, we show a bifurcation diagram in Fig. 2C depicting how the equilibrium of the antibiotic-resistant population decreases as a function of virus infectivity (β). For low infectivities, the antibiotic-resistant population is able to maintain its dominance. However, at a critical infectivity, a transcritical bifurcation occurs and stabilizes the coexistence state. In principle, introducing a highly infective virus will completely exterminate the antibiotic-resistant population. This is desirable, but a high infectivity will eventually eliminate all bacterial population, which is not desirable.

Although simply introducing virus-infected bacteria helps mitigate antibiotic-resistant bacterial infection, the persistence of antibiotic-resistant population at levels similar to wild-type population is problematic. Furthermore, the stable equilibrium suggests coexistence, but

the vast majority of the compartment is vacant ($1-S^*-R^*-I^* = 0.892$). Thus we must determine if it is possible to attain a situation where the wild-type population outnumbers the antibiotic-resistant population significantly and populates much of the compartment. To that end, we implement optimal control theory on Eq. (1).

4. Optimal control

The integration of optimal control techniques in studying bacterial dynamics, particularly in the context of antibiotic resistance and virus inclusion, is motivated by the urgent need for effective strategies to combat bacterial infections. Optimal control methods offer a powerful framework for designing and implementing interventions that optimize the use of available resources, such as antibiotics and vaccines, to minimize the emergence and transmission of antibiotic-resistant population while preserving the efficacy of existing treatments. Recent studies have highlighted the potential of optimal control in guiding decision-making processes and informing policy interventions aimed at controlling antibiotic resistance [54–56]. By incorporating virus inclusion into the model, our study further extends this framework to elucidate the complex interplay between bacteria and viruses and to explore avenues for combating antibiotic resistance.

For the purposes of mitigating antibiotic-resistant bacteria, consider the objective function

$$J(\alpha) = \int_0^T \left(AR(t) - PS(t) + C\alpha(t)^2 \right) dt, \tag{2}$$

subject to

$$\begin{aligned}
\frac{dS}{dt} &= \lambda S\,(1-(S+R+I))\,(1-\mu) - \beta IS - \delta_s S \\
\frac{dR}{dt} &= \lambda S\,(1-(S+R+I))\,\mu + \gamma R\,(1-(S+R+I)) - \beta IR - \delta_m R \\
\frac{dI}{dt} &= \beta IS + \beta IR - \delta_i I + \alpha(t),
\end{aligned}$$

with

$$\begin{aligned}
S(0) &= S_0 \in [0,1], \\
R(0) &= R_0 \in [0,1], \\
I(0) &= I_0 \in [0,1].
\end{aligned} \tag{3}$$

The constants A, P and C are weights applied on $S(t)$, $R(t)$ and the control variable $\alpha(t)$ (the virus infected bacteria infusion rate), respectively. We employ a standard quadratic term for the control variable α in Eq. (2) following [57]. Using a quadratic term facilitates onset of continuous control, whereas employing a linear term results in discontinuous bang–bang control.

The goal is to minimize the objective functional $J(\alpha)$ in order to find the optimal values of α such that the antibiotic-susceptible bacteria population S is maximized while the antibiotic-resistant bacteria population R is minimized. The objective of minimizing the virus-infected population and the cost of control can be achieved through proper implementation of the control over a time interval given by $[0,T]$. Therefore, we seek a Lebesgue integrable optimal control $\alpha^*(t)$ such that

$$J(\alpha^*) = \min_{\alpha(t)}\{J(\alpha)\}. \tag{4}$$

4.1. Existence of optimal control

First, we need to characterize our admissible controls and ascertain the existence of an optimal control. Let $\mathcal{L}^0$ denote the set of Lebesgue integrable functions between $[0,T]$ and $[0,1]$. This is the set of admissible controls. That is, $\alpha(t) \in \mathcal{L}^0$. Then, the optimal control α^* satisfies

$$J(\alpha^*) = \min_{\alpha\in\mathcal{L}^0} J(\alpha).$$

To ensure the existence of α^*, the state variables S, R, I must be bounded for $t \in [0,T]$. Because S, R, I are confined to the tetrahedron $\mathcal{T}$, where

$$\mathcal{T} = \{(S,R,I) | S \geq 0 \wedge R \geq 0 \wedge I \geq 0 \wedge S+R+I \leq 1\},$$

S, R, and I are uniformly bounded. That is, $0 \leq S \leq 1$, $0 \leq R \leq 1$, and $0 \leq I \leq 1$.

Theorem 2. *There exists an optimal control $\alpha^* \in \mathcal{L}^0$ which minimizes $J(\alpha)$ subject to Eq. (1).*

Proof. Because $\alpha(t)$ is bounded by definition and S, R, and I are uniformly bounded, $\min[J(\alpha)]$ is finite. Let $\{\alpha_n(t)\}_{n\in\mathbb{N}}$ be the minimizing sequence for J, and let $\{S_n(t)\}$, $\{R_n(t)\}$, and $\{I_n(t)\}$ be the corresponding sequence of state variable trajectories. Since $S_n(t)$, $R_n(t)$, and $I_n(t)$ are uniformly bounded, their temporal derivatives are also uniformly bounded. This follows from the right-hand sides of Eq. (1) being rational functions. As a result, $S_n(t)$, $R_n(t)$, and $I_n(t)$ are Lipschitz continuous. Therefore, they are equicontinuous. By the Arzela–Ascoli theorem [58], the sequences of controls and state functions have convergent subsequences $\{S_{n_k}\}$, $\{R_{n_k}\}$, $\{I_{n_k}\}$, and $\{\alpha_{n_k}\}$ with $k \in \mathbb{N}$ satisfying

$$S_{n_k} \to S^* \quad R_{n_k} \to R^* \quad I_{n_k} \to I^* \quad \alpha_{n_k} \to \alpha^*$$

as $k \to \infty$.

Next we establish that S^*, R^*, and I^* are solutions to Eq. (1). We show this for S, and the arguments are completely analogous for R and I. Assuming that initial data for all functions $S_{n_k}(t)$ are identical, we have

$$S_{n_k}(t) = S(0) + \int_0^t \left[\lambda S_{n_k}(1-S_{n_k}-R_{n_k}-I_{n_k})(1-\mu_{n_k}) - \beta S_{n_k} I_{n_k} - \delta_S S_{n_k}\right] ds,$$

where

$$\mu_{n_k} = \mu_0 + (1-\mu_0)\frac{R_{n_k}}{Z + R_{n_k} + I_{n_k}}.$$

Taking $k \to \infty$ and switching order of integration and limits yields

$$S^*(t) = S(0) + \int_0^t \left[\lambda S^*(1-S^*-R^*-I^*)(1-\mu^*) - \beta S^* I^* - \delta_S S^*\right] ds,$$

where

$$\begin{aligned}
\mu^* &= \lim_{k\to\infty} \mu_{n_k} = \lim_{k\to\infty} \left(\mu_0 + (1-\mu_0)\frac{R_{n_k}}{Z+R_{n_k}+I_{n_k}} \right) \\
&= \mu_0 + (1-\mu_0)\frac{R^*}{Z+R^*+I^*}.
\end{aligned}$$

The limit passes through the integral and the nonlinearity due to Lebesgue integrability of the functions. Thus, $S^*(t)$, $R^*(t)$, and $I^*(t)$ are solutions to the dynamical system.

Finally,

$$\begin{aligned}
\min_{\alpha\in\mathcal{L}^0} J(\alpha) &= \lim_{k\to\infty} J(\alpha_{n_k}) \\
&= \lim_{k\to\infty} \int_0^T \left[AR_{n_k}(t) - PS_{n_k}(t) + C\alpha_{n_k}(t)^2 \right] dt \\
&\geq \int_0^T \left[AR^*(t) - PS^*(t) + C\alpha^*(t)^2 \right] dt \\
&= J(\alpha^*).
\end{aligned}$$

Because $J(\alpha^*)$ cannot be strictly less than $\min_{\alpha\in\mathcal{L}^0} J(\alpha)$, we have

$$\min_{\alpha\in\mathcal{L}^0} J(\alpha) = J(\alpha^*)$$

□

Next we employ Pontryagin's Maximum Principle [57] to determine α^*. This principle converts Eqs. (2)–(3) into a problem of minimizing the associated Hamiltonian H pointwise with respect to α.

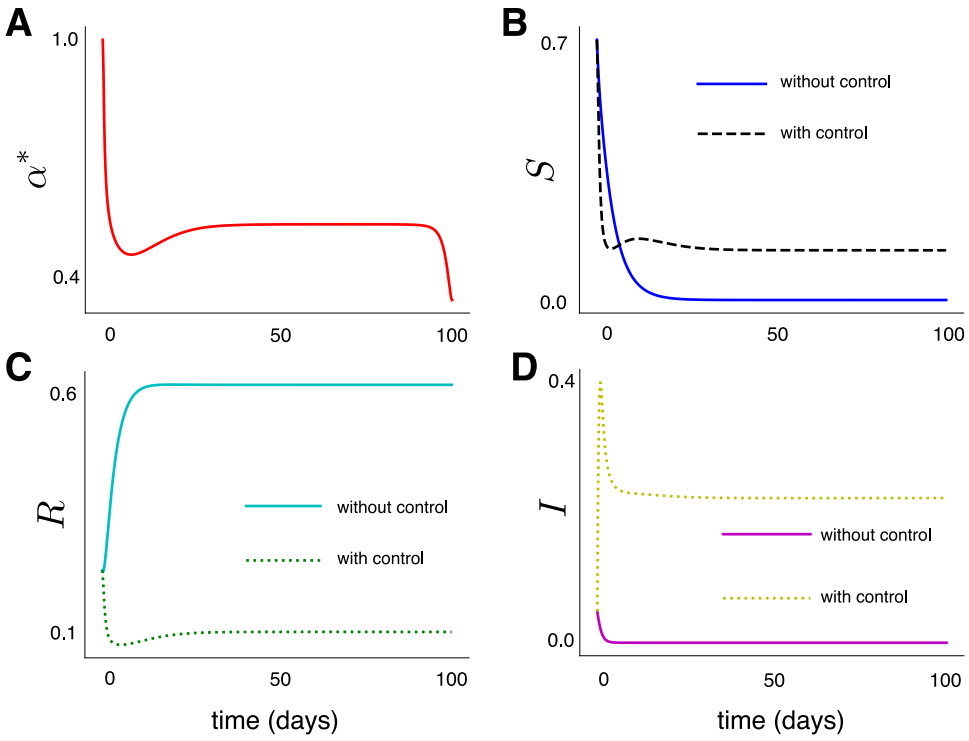

Fig. 3. Simulation results of Eq. (1) with optimal control obtained from solving Eq. (4). (A) the optimal profile for the control variable α, (B) the corresponding wild type bacteria population S, (C) the corresponding antibiotic-resistant bacteria population R, and (D) the corresponding virus infected bacteria population I. Here, $A = 10$, $P = 0.01$, and $C = 1$.

4.2. Determining the optimal control

We define the Hamiltonian for this problem by

$$\begin{aligned} H &= \left(AR(t) - PS(t) + C\alpha^2\right) + \Lambda_S\left(\frac{dS}{dt}\right) + \Lambda_R\left(\frac{dR}{dt}\right) + \Lambda_I\left(\frac{dI}{dt}\right) \\ &= AR(t) - PS(t) + C\alpha^2 + \Lambda_S\left(\lambda S(1-S-R-I)(1-\mu) - \beta IS - \delta_s S\right) \\ &+ \Lambda_R\left(\lambda S(1-S-R-I)\mu + \gamma R(1-S-R-I) - \beta IR - \delta_m R\right) \\ &+ \Lambda_I\left(\beta IS + \beta IR - \delta_i I + \alpha\right) \end{aligned}$$

where $\Lambda_S(t)$, $\Lambda_R(t)$, and $\Lambda_I(t)$ are the corresponding adjoint or co-state variables to be determined by applying Pontryagin's Maximum Principle with the following transversality conditions

$$\Lambda_S(T) = 0,$$

$$\Lambda_R(T) = 0,$$

$$\Lambda_I(T) = 0.$$

Using the optimality condition $\frac{\partial H}{\partial \alpha} = 0$, we solve for the optimal injection rate of the virus infected bacteria α,[1]

$$\alpha^* = \frac{-\Lambda_I}{2C}.$$

We solve the optimal control problem employing the forward–backward sweep method [57].

[1] Technically, we should have $\alpha^*(t) = \min(1, \max(0, -\frac{\Lambda_I}{2C}))$ because we need to check if the boundaries optimize our objective functional. However, in our model analysis, $0 < \alpha^*(t) < 1$ so we are not required to do so. See [57] for further details.

4.3. Results

We implemented the optimal control over a period of $T = 100$ days and observed the resulting dynamics of the bacterial population state variables. Fig. 3A shows the optimal trajectory of the control variable α to obtain our desired results. It predominantly maintains a constant value with sharp declines near the start and end of the time interval of interest. The effect of this control upon the bacterial strain populations is shown in Figs. 3B-D. For comparison, we also present the analogous bacterial populations in the absence of control. Fig. 3A shows that the wild-type bacteria population is significantly higher with control present than without it. Conversely, the antibiotic-resistant bacteria population R (see Fig. 3B) decreased drastically in the presence of control. This finding underscores the intricate relationships between viruses and bacteria, as well as the potential for exploiting viral therapy to combat antibiotic resistance. The population dynamics when optimal control strategies are applied and its effect on the bacteria population provide insights into the dynamics of wild-type and antibiotic-resistant bacteria populations under different control scenarios, facilitating the evaluation and optimization of control strategies to manage antibiotic resistance effectively.

A clinically plausible implementation. The following results are motivated by the difficulty of clinically realizing the exact control profile in Fig. 3A for the rate of infusion of the virus into the system. Although the optimal control profile facilitated the onset of a state where wild-type bacteria significantly dominate mutant strains, implementing such a tightly regulated control is not feasible clinically. However, because the control profile is predominantly constant, we seek to determine a constant injection rate $\hat{\alpha}$ such that

$$\hat{\alpha}T = \int_0^T \alpha^*(t)\, dt.$$

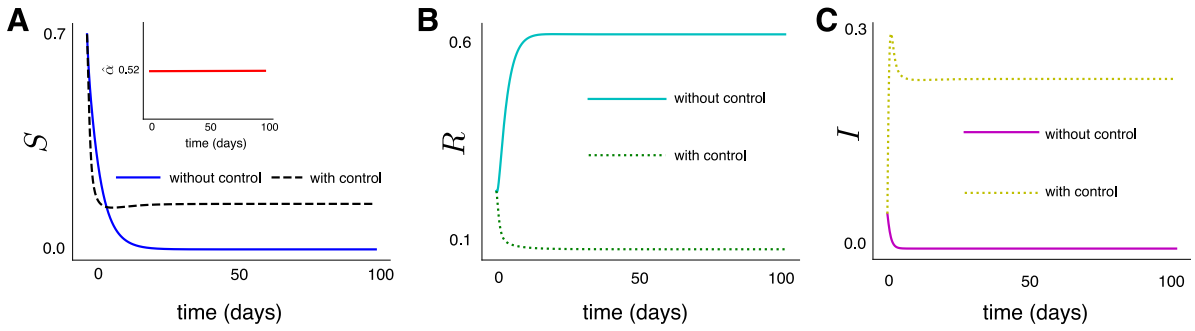

Fig. 4. Simulation results from Eq. (1) with a constant virus infusion rate $\hat{\alpha}$ as obtained from Eq. (5) (A) Wild type population in response to the constant control profile. Inset: the constant control profile. (B) Antibiotic-resistant bacteria population R and (C) Virus infected bacteria population I.

Table 4
Comparison of the objective functional of the optimal and the constant control profile.

Control profile	Objective functional
Optimal: $\alpha^* = [0, 1]$	$J(\alpha^*) = 87.6903$
Constant: $\hat{\alpha} = 0.5200$	$J(\hat{\alpha}) = 90.3541$

That is, we determine a constant injection rate $\hat{\alpha}$ such that the total virus injected over the time interval $[0, T]$ is equal to the total amount injected with the optimal control profile. This yields the simple equation for $\hat{\alpha}$:

$$\hat{\alpha} = \frac{1}{T}\int_0^T \alpha^*(t)\, dt \tag{5}$$

This constant rate of virus injection is applied into our system to see the effect on the dynamics of S, R, and I. Success in reducing antibiotic resistant bacteria with constant injection rate imputes stability in intervention measures while offering predictability.

Fig. 4A-B illustrate the changes in the populations of S and R, respectively, reflecting the effect of the constant rate of viral infusion (Fig. 4A inset) on the population in the bacterial community. The resulting dynamics of the bacterial populations are similar to Fig. 3, indicating that system dynamics are not overtly sensitive to the control profile. In this clinically feasible injection protocol, desirable reduction in antibiotic resistant bacterial population is achieved when compared with the absence of control case.

How far from optimality is the constant control profile implementation? In Table 4 we compare the objective functional J for the different scenarios of α (Optimal vs Constant). The objective functional value for $J(\hat{\alpha})$ is reasonably close to $J(\alpha^*)$, with approximately a 4% difference in value. Thus, implementing a constant viral infusion is a clinically feasible protocol that is near optimality for mitigating antibiotic-resistant mutant bacterial infection.

5. Conclusion

This study focused on modeling the interplay between wild type bacteria, antibiotic-resistant bacteria, and virus-infected bacteria populations, with the specific aim of understanding how antibiotic-resistant bacterial infections may be treated or controlled in the presence of a viral infection. We found that the simple introduction of a virus facilitates the desirable outcome of wild-type bacteria outcompeting antibiotic resistant bacteria. However, the presence of virus vastly diminished the total bacterial population. This motivated the implementation of optimal control upon the viral infusion rate. In the presence of control, wild-type bacteria vastly overcome antibiotic resistant bacteria. Although the optimal infusion profile is not realistically realizable in a clinical setting, we showed that using a constant profile approximation of the optimal infusion rate is sufficient to reduce antibiotic resistant bacteria and maximize wild type bacteria population.

Importantly, we did *not* seek to *eliminate* antibiotic-resistant bacteria completely. Our goal was simply to mitigate antibiotic-resistant bacteria population. This removed the need for unnecessarily strong interventions—such as the ones that facilitated onset of antibiotic-resistant bacterial population. Rather, we modified a standard dynamical system of bacterial dynamics in infections and allowed the intrinsic dynamics to result in desirable outcome of diminished mutant population.

The findings of this study have significant implications for curbing antibiotic resistance. Our strategy not only reduces the population of antibiotic-resistant bacteria but also maximizes the presence of wild-type bacteria, which are more susceptible to antibiotics. This dual benefit highlights the potential of using viral infections as a complementary tool in the fight against antibiotic resistance. Moreover, our study underscores the importance of considering the broader ecological and evolutionary dynamics in the design of treatment strategies. By not aiming to eliminate antibiotic-resistant bacteria completely, we avoid the selective pressures that often lead to the emergence of even more resistant strains. Instead, our approach seeks to balance the bacterial ecosystem, promoting a more sustainable and long-term solution to antibiotic resistance.

There are a number of issues to explore in future work. First, our work here demonstrates that viral infection could be a measure used to mitigate antibiotic-resistant bacterial infection, but it clearly overlooks aspects of bacterial infection. For example, our model overlooks the effect of including spatial dynamics. It would be interesting to use dispersion theory to characterize the biophysical parameters that affect viral infection of resistant bacteria and to inform optimal control in space. Another important question in spatial systems is how do we incorporate viral dynamics? We can simply proceed as we did in this manuscript and track infected bacterial cells or we could explicitly model viral dynamics and their infection process of bacteria, leading to a complex multiscale modeling paradigm. Finally, as we noted in the body of manuscript, Eq. (1) can be derived systematically from a stochastic lattice model. It would be interesting to implement stochastic optimal control theory and see what wrinkles including noise brings to the dynamics.

CRediT authorship contribution statement

Zainab O. Dere: Writing – review & editing, Writing – original draft, Software, Investigation, Formal analysis. **N.G. Cogan:** Writing – review & editing, Supervision, Investigation, Conceptualization. **Bhargav R. Karamched:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper

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Appendix

A.1. Adjoint equations

The adjoint equations for the optimal control are given by

$$
\begin{aligned}
\lambda_S'(t) &= -\frac{\partial H}{\partial S} = -\Bigg[-P + \Lambda_S \Bigg((\lambda - 2\lambda S - \lambda R - \lambda I)\Big(1 - \Big(\mu_0 + (1-\mu_0) \\
&\quad \times \frac{R}{Z+R+I} \Big)\Big) - \beta I - \delta_s \Bigg) \\
&\quad + \Lambda_R \Big((\lambda - 2\lambda S - \lambda R - \lambda I)\big(\mu_0 + (1-\mu_0)\frac{R}{Z+R+I}\big) - \gamma R \Big) + \Lambda_I(\beta I) \Bigg] \\
\lambda_R'(t) &= -\frac{\partial H}{\partial R} = -\Bigg[A + \Lambda_S \Bigg(-\lambda S\big(1 - \big(\mu_0 + (1-\mu_0)\frac{R}{Z+R+I}\big)\big) \\
&\quad + (\lambda S - \lambda S^2 - \lambda S R \\
&\quad - \lambda S I)\frac{(Z+R+I)(\mu_0-1) - (\mu_0-1)R}{(Z+R+I)^2} \Bigg) \\
&\quad + \Lambda_R \Bigg((-\lambda S)\big(\mu_0 + (1-\mu_0)\frac{R}{Z+R+I}\big) \\
&\quad + \big(\lambda S - \lambda S^2 - \lambda S R - \lambda S I\big)\frac{(Z+R+I)(\mu_0-1) - (\mu_0-1)R}{(Z+R+I)^2} \\
&\quad + \gamma - \gamma S - 2\gamma R - \gamma I \\
&\quad - \beta I - \delta_m \Bigg) + \Lambda_I(\beta I) \Bigg] \\
\lambda_I'(t) &= -\frac{\partial H}{\partial I} = -\Bigg[\Lambda_S \Big((\lambda S - \lambda S^2 - \lambda S R - \lambda S I)\big(\frac{(1-\mu_0)R}{(Z+R+I)^2}\big) \Big) \\
&\quad - \lambda S \Big(1 - (\mu_0 \\
&\quad + (1-\mu_0)\frac{R}{Z+R+I}) - \beta S \Big) + \Lambda_R \Bigg(-\lambda S\big(\mu_0 + (1-\mu_0)\frac{R}{Z+R+I}\big) \\
&\quad + (\lambda S - \lambda S^2 - \lambda S R \\
&\quad - \lambda S I)\frac{(1-\mu_0)R}{(Z+R+I)^2} - \gamma R - \beta R \Bigg) + \Lambda_I\big(\beta S + \beta R - \delta_i\big) \Bigg]
\end{aligned}
\tag{6}
$$

Data availability

Data will be made available on request.

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