



Research article

Thresholds and control in a multiscale epidemic model

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Abstract: We formulated a multiscale epidemic model linking within-host viral dynamics to population transmission under resistance-mediated loss of treatment efficacy. The within-host subsystem tracked target cells, infected cells, viral load, and immune effectors, while an SEIR model represents population spread, vaccination, and recovery. We established positivity and invariance, derived a quasi-steady population model through singular perturbation, and provided a finite-horizon reduction error estimate that included the effects of initial conditions and changes in control. For constant controls and frozen efficacy, a next-generation matrix yielded a control reproduction number and local and global disease-free stability thresholds. A finite-horizon control problem compared vaccination and treatment schedules under progressive efficacy decay, using numerically optimized open-loop policies and explicitly defined baseline controls. In 180-day full-model simulations at baseline resistance, the computed policy had a composite cost of 8623.88, compared with 9638.97 for constant maximal control, while cumulative incidence was 0.240 versus 0.221. A cost-component analysis and a comparison without the explicit viral-load penalty revealed how the objective weights affect these rankings. Under active treatment, resistance influences cumulative incidence, and a synthetic negative-binomial fit reproduces weekly exposure means.

Keywords: multiscale epidemic model; within-host dynamics; SEIR; numerical control; resistance-aware intervention

1. Introduction

A central challenge in infectious-disease modeling is to reconcile processes that occur on markedly different time scales. Within a host, pathogen replication, immune response, and therapeutic action evolve over hours to days and determine viral burden and shedding. At the population level, contact

structure, latency, recovery, and interventions shape transmission over weeks to months. From a biological standpoint, the mechanistic link between these scales is infectiousness: individuals transmit in proportion to pathogen load and its temporal profile, while population-level control policies (e.g., vaccination and treatment deployment) feed back into within-host selection pressures and hence treatment efficacy. Mathematical frameworks that couple within-host and between-host dynamics are therefore useful both for clarifying threshold mechanisms and for designing interventions grounded in measurable biological quantities.

Classical compartmental models in the Kermack–McKendrick lineage provide a tractable setting for epidemic threshold analysis and control design [1–4]. In these models, the basic or control reproduction number summarizes transmission potential and yields stability criteria for disease-free equilibria, commonly via next-generation operator constructions [5–7]. Heterogeneous stage durations and alternative infection-age structures can materially shift inferred transmission potential and intervention impact [8–10]. Furthermore, within-host viral dynamics have been successfully modeled by systems capturing target-cell limitation, viral production and clearance, and immune-mediated control, with extensions incorporating therapeutic effects and time-scale separation [11–16]. These within-host models motivate biologically interpretable coupling laws in which transmission depends on viral load, often in a saturating manner reflecting dose–response or contact-limited effects, consistent with early within-host–between-host links in influenza and related systems [17–19]. Multiscale surveys emphasize that such couplings can substantially modify population-level thresholds and the predicted impact of interventions [20].

A further biological feature relevant to intervention design is treatment efficacy decay driven by resistance emergence or waning effectiveness. Even when a population model includes a treatment control, it is not straightforward to represent resistance in a mechanistically consistent way without embedding at least a reduced within-host description. This motivates us for this study: we couple a fast within-host infection–immunity subsystem to a slow SEIR transmission model through a viral-load-dependent transmission coefficient, and we incorporate resistance-aware therapy through a decaying efficacy profile.

The main methodological contribution is the combination of a phenomenological efficacy-decay law with a conditional finite-horizon reduction estimate that accounts for control switching. Standard SEIR dynamics, saturating transmission, next-generation thresholds, and direct numerical control transcription are established tools and are not claimed as new.

Our focus is on mathematically verifiable properties that support biological interpretability and control design. First, we establish positivity and forward invariance of the feasible region, ensuring the model is well posed in the biologically relevant state space. Second, we exploit an explicit fast–slow structure to derive a reduced epidemic model in which the population dynamics are driven by a quasi-steady within-host viral load. The reduction is justified under explicit uniform Lyapunov conditions by a finite-horizon error bound that includes the accumulated slow-state effect of initial and switching layers. Third, for constant controls, we derive a control reproduction number for the reduced system and prove a threshold stability theorem for the disease-free equilibrium. This yields an analytically transparent criterion that links vaccination intensity and resistance-modulated treatment efficacy to epidemic control.

In addition to analysis, we examine finite-horizon intervention design by formulating an optimal control problem for vaccination and treatment intensity. The optimization objective penalizes population

burden and within-host viral load alongside intervention effort, reflecting the multiscale nature of the biological goals and standard approaches to epidemic optimal control [21–23]. Numerical experiments examine resistance-mediated efficacy decay using numerically optimized feasible policies, without a claim of global optimality. The fast–slow reduction and error estimates rely on standard singular-perturbation techniques for time-scale separated systems [24].

The remainder of the paper is organized as follows: In Section 2, we introduce the model and establish well-posedness; In Section 3, we develop the conditional fast–slow reduction and frozen threshold analysis; In Section 4, we define the control algorithms and reproducible numerical methods; In Section 5, we report the numerical experiments; and in Section 6, we discuss limitations and extensions.

2. Multiscale model formulation

As illustrated in Figure 1, the multiscale framework couples the within-host viral dynamics with the population-level SEIR system through the viral-load-dependent transmission rate $\beta_p(V_h)$. The control variables $\epsilon(t)$ and $u(t)$ act at the within-host and population levels, respectively.

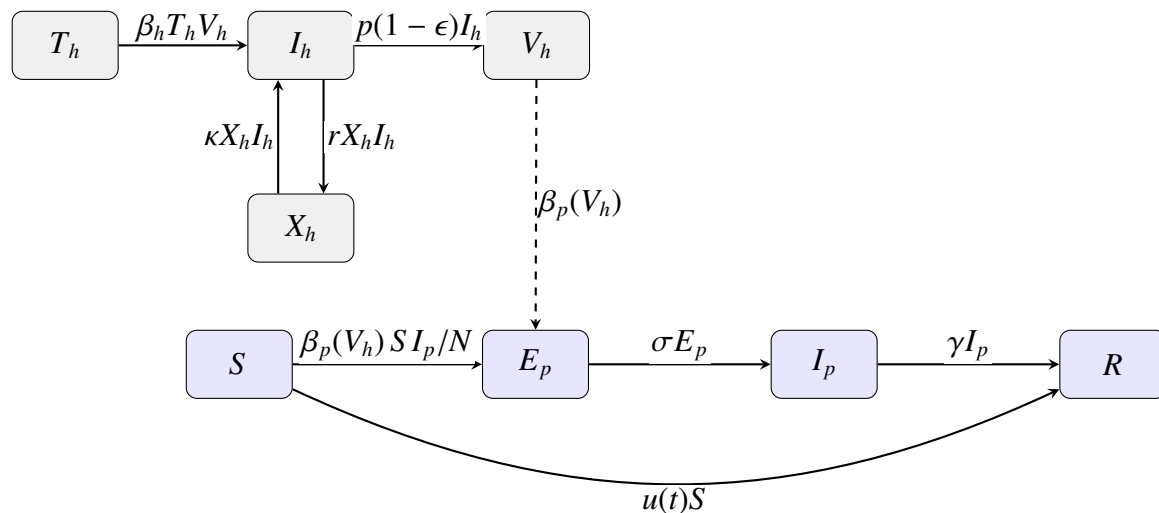


Figure 1. Multiscale flow diagram. The within-host subsystem (gray) couples to the population SEIR system (blue) through the viral-load-dependent transmission coefficient $\beta_p(V_h)$. Treatment efficacy $\epsilon(t)$ modulates viral production, while vaccination $u(t)$ moves susceptible individuals to the recovered class.

2.1. Within-host subsystem (fast scale)

Let (T_h, I_h, V_h, X_h) denote healthy target cells, infected cells, viral load, and immune effector cells, respectively. All kinetic coefficients $\lambda, d_T, \beta_h, d_I, \kappa, p, c, r, d_X, \mu, \sigma, \gamma, \beta_0, K$ are positive, and $u_{\max} \geq 0$. We introduce a small parameter $\eta \in (0, 1]$ to encode time-scale separation (fast within-host, slow population):

$$\eta \dot{T}_h = \lambda - d_T T_h - \beta_h T_h V_h, \quad (2.1)$$

$$\eta \dot{I}_h = \beta_h T_h V_h - d_I I_h - \kappa X_h I_h, \quad (2.2)$$

$$\eta \dot{V}_h = p(1 - \epsilon(t)) I_h - c V_h, \quad (2.3)$$

$$\eta \dot{X}_h = r X_h I_h - d_X X_h. \quad (2.4)$$

The treatment efficacy is resistance-aware, with $0 < \epsilon_{\max} < 1$ and $\alpha \geq 0$:

$$\epsilon(t) = \epsilon_{\max} a(t) e^{-\alpha t}, \quad 0 \leq a(t) \leq 1. \quad (2.5)$$

To motivate this form, let $s(t) \in [0, 1]$ denote the residual sensitivity of the within-host viral population to treatment, normalized by $s(0) = 1$. Over a finite treatment horizon, we approximate the loss of sensitivity by the first-order law

$$\dot{s}(t) = -\alpha s(t), \quad s(0) = 1, \quad (2.6)$$

whose solution is $s(t) = e^{-\alpha t}$. The effective inhibition is then the product of the maximum pharmacodynamic efficacy $\epsilon_{\max}$, the administered treatment intensity $a(t)$, and the remaining drug sensitivity $s(t)$, which gives Eq (2.5). This closure is consistent with the approximately exponential early expansion of a fitter resistant subpopulation under drug selection and with classical viral-dynamics models that distinguish drug-sensitive and resistant variants [25, 26]. Here, α has units day^{-1} and is a lumped *rate of efficacy erosion*, not a mutation rate: It summarizes the combined effects of pre-existing resistant variants, de novo mutation, their selective advantage during therapy, and any unmodeled gradual loss of effective drug susceptibility. The associated efficacy half-life is $t_{1/2} = \log(2)/\alpha$. When $\alpha = 0$, efficacy remains constant, while larger values of α indicate more rapid resistance-mediated treatment failure.

The exponential law is therefore a parsimonious phenomenological approximation based on a constant proportional rate of sensitivity loss, rather than a complete evolutionary model. In particular, Eq (2.5) assumes that the resistance pressure represented by α is approximately constant over the modeled horizon. If resistance is assumed to accumulate only during treatment exposure, a natural extension is $s(t) = \exp\{-\alpha \int_0^t a(\tau) d\tau\}$; alternatively, explicit sensitive- and resistant-virus compartments can represent mutation, fitness costs, and competitive replacement mechanistically [25, 26]. We retain the simpler form here to preserve analytical tractability while allowing the control analysis to capture progressive loss of treatment benefit. Time is measured in days; fast-system coefficients are scaled by $1/\eta$ in physical time, whereas population and efficacy-decay rates act directly on that time scale.

2.2. Population subsystem (slow scale)

Let (S, E_p, I_p, R) denote susceptible, exposed, infectious, and recovered populations, with $N = S + E_p + I_p + R > 0$. The coupling uses a saturating transmission coefficient

$$\beta_p(V_h) = \beta_0 \frac{V_h}{V_h + K}, \quad \beta_0 > 0, \quad K > 0. \quad (2.7)$$

We interpret β_0 as the upper limit on the effective transmission rate set by contact opportunities and other population-level constraints, and $V_h/(V_h + K)$ as the viral-load-dependent probability that an otherwise effective contact produces sufficient exposure for transmission. Thus, at low viral load, $\beta_p(V_h) \approx (\beta_0/K)V_h$, so infectiousness increases approximately in proportion to shedding, whereas at high viral load $\beta_p(V_h) \rightarrow \beta_0$, because further increases in virus cannot create more effective contacts and have diminishing effects on the probability of infection per contact. Parameter K is consequently the half-saturation viral load, since $\beta_p(K) = \beta_0/2$. Mathematically, this is the Hill dose-response

law with Hill exponent one (equivalently, a Michaelis–Menten-type closure), chosen as the simplest monotone map satisfying $\beta_p(0) = 0$, a linear low-load response, and a finite upper bound. Saturating Hill relations have been used to connect viral load to infectiousness in HIV models [27], and broader within-host–between-host analyses identify such nonlinear dose–response maps as a standard coupling device [20, 28]. Empirical and data-calibrated studies likewise find that higher viral load is associated with greater infectiousness but that the increase is sublinear or exhibits diminishing returns [29, 30]. These findings motivate saturation, but they do not uniquely select the exponent-one form; Eq (2.7) is therefore a parsimonious closure rather than a pathogen-universal law. Moreover, if sufficiently resolved transmission-pair data are available, it can be replaced by the more flexible Hill form $\beta_0 V_h^q / (V_h^q + K^q)$ and q estimated jointly with K . A single representative within-host state sets the calendar-time transmission coefficient for every infectious individual, regardless of time since infection. This closure can be useful for a synchronized or approximately homogeneous infectious cohort, but it does not describe a general mixture of infection ages. In particular, reducing this one viral trajectory reduces the infectiousness of the infectious population simultaneously; predicted treatment benefits are conditional on this strong approximation. An age-structured extension and its implications are discussed in Section 6. The population dynamics are

$$\dot{S} = \mu N - \beta_p(V_h) \frac{S I_p}{N} - \mu S - u(t)S, \quad (2.8)$$

$$\dot{E}_p = \beta_p(V_h) \frac{S I_p}{N} - (\sigma + \mu)E_p, \quad (2.9)$$

$$\dot{I}_p = \sigma E_p - (\gamma + \mu)I_p, \quad (2.10)$$

$$\dot{R} = \gamma I_p - \mu R + u(t)S, \quad (2.11)$$

where $u(t)$ is the vaccination control.

2.3. Admissible controls and optimization target

We define the admissible set

$$\mathcal{U} = \{(u, a) : [0, T] \rightarrow \mathbb{R}^2 \mid 0 \leq u(t) \leq u_{\max}, 0 \leq a(t) \leq 1, \text{ measurable}\}. \quad (2.12)$$

To match the computational objective, let $b(t) = \beta_p(V_h(t))S(t)I_p(t)/N$ denote the rate of new exposures and define

$$\begin{aligned} J(u, a) = \int_0^T & (w_C b(t) + w_I I_p(t) + w_V V_h(t) + \tfrac{1}{2} c_u u(t)^2 \\ & + \tfrac{1}{2} c_a a(t)^2 + w_{\text{res}} \alpha a(t)^2) \, dt + w_T I_p(T). \end{aligned} \quad (2.13)$$

The additional $w_{\text{res}} \alpha a^2$ term is a policy penalty for resistance-associated treatment effort, not a dynamically modeled resistant-strain burden.

2.4. Basic well-posedness

Define the feasible region

$$\Omega = \{(T_h, I_h, V_h, X_h, S, E_p, I_p, R) \in \mathbb{R}_+^8 : S + E_p + I_p + R = N\}.$$

Proposition 2.1 (Positivity and invariance). Assume $(u, a) \in \mathcal{U}$ and nonnegative initial data with $S(0) + E_p(0) + I_p(0) + R(0) = N$. Then the systems (2.1)–(2.11) admit a unique global solution, all state variables remain nonnegative for $t \geq 0$, and the population simplex is invariant:

$$S(t) + E_p(t) + I_p(t) + R(t) = N \quad \text{for all } t \geq 0.$$

Proof. **Step 1: Existence and uniqueness (Carathéodory).** Fix $\eta > 0$ and $(u, a) \in \mathcal{U}$. The control functions are measurable and bounded, so $\epsilon(t) = \epsilon_{\max} a(t)e^{-\alpha t}$ is measurable and bounded. The vector field in (2.1)–(2.11) is measurable in t and locally Lipschitz in the state variables on the open set $V_h > -K$, which contains the nonnegative state space (the denominator satisfies $V_h + K \geq K > 0$ there on nonnegative states). Therefore, by the Carathéodory existence theorem, for every initial condition, there exists a unique maximal absolutely continuous solution on some interval $[0, t_{\max})$.

Step 2: Positivity (forward invariance of $\mathbb{R}_+^8$). We show that the nonnegative orthant is forward invariant. Consider any component $X(t)$ of the state. If at some time τ we have $X(\tau) = 0$ and all other components are nonnegative, then the corresponding right-hand side is nonnegative, so the trajectory cannot cross into negative values.

Concretely, at the boundary:

$$\begin{aligned} \eta \dot{T}_h|_{T_h=0} &= \lambda > 0, & \eta \dot{I}_h|_{I_h=0} &= \beta_h T_h V_h \geq 0, & \eta \dot{V}_h|_{V_h=0} &= p(1 - \epsilon(t))I_h \geq 0, \\ \eta \dot{X}_h|_{X_h=0} &= 0, & \dot{S}|_{S=0} &= \mu N > 0, & \dot{E}_p|_{E_p=0} &= \beta_p(V_h) \frac{S I_p}{N} \geq 0, \\ \dot{I}_p|_{I_p=0} &= \sigma E_p \geq 0, & \dot{R}|_{R=0} &= \gamma I_p + u(t)S \geq 0. \end{aligned}$$

Hence each coordinate hyperplane is inward pointing, and by standard boundary invariance arguments (e.g., Nagumo's theorem for orthants), all variables remain nonnegative on $[0, t_{\max})$.

Step 3: Invariance of the population simplex. Let $N_p(t) := S(t) + E_p(t) + I_p(t) + R(t)$. Summing (2.8)–(2.11) yields

$$\dot{N}_p(t) = \mu N - \mu N_p(t).$$

Solving this linear ODE gives

$$N_p(t) = N + (N_p(0) - N)e^{-\mu t}.$$

With the assumption $N_p(0) = N$, we obtain $N_p(t) \equiv N$ for all t , so the simplex constraint is invariant.

Step 4: Global existence (no finite-time blow-up). It remains to show $t_{\max} = \infty$. By positivity, it suffices to derive a priori bounds on all components.

Within-host bounds. Let $U(t) := T_h(t) + I_h(t)$. Adding (2.1) and (2.2) gives

$$\eta \dot{U} = \lambda - d_T T_h - d_I I_h - \kappa X_h I_h \leq \lambda - d_{\min} U, \quad d_{\min} := \min\{d_T, d_I\}.$$

By comparison with $\eta \dot{U} = \lambda - d_{\min} U$,

$$0 \leq U(t) \leq U_{\max} := \max \left\{ U(0), \frac{\lambda}{d_{\min}} \right\} \quad \text{for all } t \in [0, t_{\max}).$$

In particular, $0 \leq T_h(t) \leq U_{\max}$ and $0 \leq I_h(t) \leq U_{\max}$.

Next, since $0 \leq 1 - \epsilon(t) \leq 1$, from (2.3) we obtain

$$\eta \dot{V}_h \leq pI_h - cV_h \leq pU_{\max} - cV_h,$$

so by comparison,

$$0 \leq V_h(t) \leq V_{\max} := \max \left\{ V_h(0), \frac{pU_{\max}}{c} \right\}.$$

Finally, (2.4) can be written as

$$\eta \dot{X}_h = X_h (rI_h - d_X) \leq X_h (rU_{\max} - d_X),$$

hence

$$0 \leq X_h(t) \leq X_h(0) \exp \left(\frac{(rU_{\max} - d_X)t}{\eta} \right) \quad \text{for all } t \in [0, t_{\max}).$$

Thus, all within-host variables remain finite on every finite time interval.

Population bounds. On the invariant simplex, $0 \leq S, E_p, I_p, R \leq N$.

Therefore, the full state remains bounded on every finite interval. By the continuation theorem for Carathéodory ODEs, the maximal existence time must be $t_{\max} = \infty$. This completes the proof. $\square$

3. Singular-perturbation reduction and threshold theorem

3.1. Fast-slow reduction

Let $z = (T_h, I_h, V_h, X_h)$ and $y = (S, E_p, I_p, R)$. The system can be written as

$$\eta \dot{z} = f(z; \epsilon(t)), \quad (3.1)$$

$$\dot{y} = F(y, z; u(t)). \quad (3.2)$$

The formal quasi-steady reduction sets $f(z; \epsilon(t)) = 0$ and selects an attracting frozen-efficacy equilibrium $z^*(\epsilon(t))$. Its validity requires uniform attraction over the range of efficacy values visited.

Assumption 3.1 (Uniform Lyapunov tracking conditions). *Let $\mathcal{I} \subset [0, \epsilon_{\max}]$ be a compact efficacy interval. The map $z^* : \mathcal{I} \rightarrow \mathbb{R}_+^4$ is continuously differentiable with bounded derivative and satisfies $f(z^*(e); e) = 0$. All fast trajectories under consideration, including trajectories following control switches, stay in a compact neighborhood where there exists a continuously differentiable function $W(w, e)$ and positive constants m_1, m_2, k, G, H , independent of η , such that*

$$m_1 \|w\|^2 \leq W(w, e) \leq m_2 \|w\|^2, \quad (3.3)$$

$$\nabla_w W(w, e) \cdot f(z^*(e) + w; e) \leq -kW(w, e), \quad (3.4)$$

$$\|\nabla_w W(w, e)\| \leq G \|w\|, \quad |\partial_e W(w, e)| \leq HW(w, e). \quad (3.5)$$

The same neighborhood and constants apply throughout $\mathcal{I}$.

Assumption 3.1 provides the moving-equilibrium estimate needed under switching, which a frozen spectral gap alone does not. A sufficient local construction is available if the selected smooth branch has a uniformly Hurwitz Jacobian $A(e) = D_z f(z^*(e); e)$ on $\mathcal{I}$. For this polynomial vector field, solve

$A(e)^T P(e) + P(e)A(e) = -I$ and set $W(w, e) = w^T P(e)w$; compactness and smoothness give uniform positive bounds on P and bounded P' , and a uniformly small neighborhood makes the nonlinear remainder satisfy (3.4). The trajectory-containment requirement must also be checked: This construction is local and does not establish attraction of all biologically admissible states.

Write $q(e) = p(1 - e)$ and

$$\mathcal{R}_h(e) = \frac{\beta_h \lambda q(e)}{d_T d_I c}.$$

The infection-free frozen equilibrium is $(\lambda/d_T, 0, 0, 0)$. The immune-free infected equilibrium, when $\mathcal{R}_h(e) > 1$, is

$$T_h^* = \frac{cd_I}{\beta_h q}, \quad I_h^* = \frac{\lambda}{d_I} - \frac{cd_T}{\beta_h q}, \quad V_h^* = \frac{qI_h^*}{c}, \quad X_h^* = 0.$$

Immune invasion is excluded on this branch when $rI_h^* < d_X$. The immune-positive candidate is

$$I_h^* = \frac{d_X}{r}, \quad V_h^* = \frac{qd_X}{cr}, \quad T_h^* = \frac{\lambda}{d_T + \beta_h V_h^*}, \quad X_h^* = \frac{\beta_h T_h^* V_h^* / I_h^* - d_I}{\kappa},$$

provided $X_h^* > 0$. For the infection-free branch, the eigenvalues $-d_T$ and $-d_X$ accompany the infected-cell/virus block with characteristic polynomial $\xi^2 + (d_I + c)\xi + d_I c(1 - \mathcal{R}_h(e))$; hence, a compact interval with $\mathcal{R}_h(e) \leq 1 - \delta$, $\delta > 0$ gives a uniform local spectral gap. For the immune-free infected branch, put $L = d_T + \beta_h V_h^*$ and $H_0 = \beta_h V_h^* > 0$; the three-state characteristic polynomial is $\xi^3 + (L + d_I + c)\xi^2 + L(d_I + c)\xi + cd_I H_0$. Its coefficients are positive and $(L + d_I + c)L(d_I + c) > cd_I H_0$ because $L > H_0$ and $(d_I + c)^2 > cd_I$, so the Routh–Hurwitz criterion gives stability of that block. The fourth eigenvalue is $rI_h^* - d_X$; hence, a compact efficacy range with $\mathcal{R}_h \geq 1 + \delta$ and $rI_h^* \leq d_X - \delta_X$, for positive margins, is another explicit uniformly locally stable regime. For infected branches, the Jacobian to be checked is

$$A(e) = \begin{pmatrix} -d_T - \beta_h V_h^* & 0 & -\beta_h T_h^* & 0 \\ \beta_h V_h^* & -d_I - \kappa X_h^* & \beta_h T_h^* & -\kappa I_h^* \\ 0 & q(e) & -c & 0 \\ 0 & rX_h^* & 0 & rI_h^* - d_X \end{pmatrix}.$$

The thresholds $\mathcal{R}_h = 1$ and $rI_h^* = d_X$ must be avoided, and distance from these thresholds is not a substitute for verifying the remaining eigenvalues and trajectory containment. With the nominal numerical parameters, $\mathcal{R}_h(e) = 4(1 - e)$ and the efficacy range $[0, 0.95]$ crosses $e = 0.75$, where the spectral gap vanishes. Therefore, the full-range numerical experiments below are integrations of the full model, not a validation or an application of the uniform reduction theorem across that bifurcation.

Theorem 3.2 (Finite-horizon reduction with switching layers). *Suppose that Assumption 3.1 holds. Let u be bounded and measurable, and let ϵ take values in $\mathcal{I}$, be Lipschitz on each of finitely many intervals, and have switches $0 < t_1 < \dots < t_L < T$. The partition and the interval Lipschitz bounds are independent of η . Define*

$$d_0 = \|z(0) - z^*(\epsilon(0^+))\|, \quad D = \operatorname{ess\,sup}_{t \notin \{t_j\}} \left\| \frac{d}{dt} z^*(\epsilon(t)) \right\|, \quad \delta_j = \|z^*(\epsilon(t_j^+)) - z^*(\epsilon(t_j^-))\|.$$

Let $\bar{y}$ solve

$$\dot{\bar{y}} = F(\bar{y}, z^*(\epsilon(t)); u(t)), \quad \bar{y}(0) = y(0). \quad (3.6)$$

For all sufficiently small $\eta > 0$, there are constants $C_L, \nu > 0$, independent of η , such that (with right-hand values at switches)

$$\|z(t) - z^*(\epsilon(t))\| \leq C_L \left(e^{-\nu t/\eta} d_0 + \eta D + \sum_{t_j \leq t} e^{-\nu(t-t_j)/\eta} \delta_j \right), \quad (3.7)$$

$$\sup_{0 \leq t \leq T} \|y(t) - \bar{y}(t)\| \leq C_{T,L} \eta \left(d_0 + TD + \sum_{j=1}^L \delta_j \right). \quad (3.8)$$

The constants may depend on the fixed horizon, the number of switches, the Lyapunov constants, and the control regularity bounds. In particular, bounded initial mismatch and a fixed finite switch schedule give an $O(\eta)$ slow-state error; uniformity is not claimed when the number of switches grows as $\eta \rightarrow 0$.

Proof. On one continuity interval let $w = z - z^*(\epsilon(t))$ and $h = \sqrt{W(w, \epsilon(t))}$. Since

$$\dot{w} = \eta^{-1} f(z^*(\epsilon) + w; \epsilon) - \frac{d}{dt} z^*(\epsilon(t)),$$

(3.3)–(3.5) imply, where $h > 0$,

$$\dot{h} \leq \left(-\frac{k}{2\eta} + \frac{H|\dot{\epsilon}|}{2} \right) h + \frac{G}{2\sqrt{m_1}} \left\| \frac{d}{dt} z^*(\epsilon(t)) \right\|.$$

The inequality extends through $h = 0$ by the upper Dini derivative, or by regularizing $\sqrt{W}$ and taking a limit. Let L_ϵ bound $|\dot{\epsilon}|$ on all intervals. For $\eta H L_\epsilon \leq k/2$, comparison gives

$$\|w(t)\| \leq B e^{-\nu(t-s)/\eta} \|w(s)\| + B\eta D, \quad \nu = k/4, \quad (3.9)$$

on every such interval, with a common $B \geq 1$. The physical fast state is continuous at t_j , whereas

$$w(t_j^+) = w(t_j^-) - (z^*(\epsilon(t_j^+)) - z^*(\epsilon(t_j^-))).$$

Consequently $\|w(t_j^+)\| \leq \|w(t_j^-)\| + \delta_j$. Concatenating (3.9) across the finitely many intervals proves (3.7), with a constant that can absorb at most $L + 1$ factors of B . This accounts separately for the initial layer and every switch-induced layer.

On the population simplex and the assumed compact fast-state set, F is uniformly Lipschitz in y, z , with constants L_y, L_z . Since $y(0) = \bar{y}(0)$, the integral form of Grönwall's inequality gives

$$\|y(t) - \bar{y}(t)\| \leq L_z \int_0^t e^{L_y(t-s)} \|w(s)\| \, ds.$$

Using (3.7), $e^{L_y(t-s)} \leq e^{L_y T}$, and

$$\int_{t_j}^t e^{-\nu(s-t_j)/\eta} \, ds \leq \eta/\nu, \quad \int_0^t \eta D \, ds \leq \eta TD,$$

proves (3.8). The contribution of an initial or switching layer to the slow state is accumulated and of order η ; it is not an exponentially decaying slow-state error. $\square$

3.2. Reduced SEIR model and control reproduction number

Under the conditions of Theorem 3.2, the effective transmission coefficient is

$$\beta^*(t) = \beta_0 \frac{V_h^*(\epsilon(t))}{V_h^*(\epsilon(t)) + K}. \quad (3.10)$$

For constant vaccination and treatment controls, the following autonomous reduced system holds when efficacy is also frozen at $\bar{\epsilon}$ (or when $\alpha = 0$). Constant a alone does not make efficacy constant if $\alpha > 0$.

$$\dot{S} = \mu N - \beta^* \frac{S I_p}{N} - (\mu + \bar{u})S, \quad (3.11)$$

$$\dot{E}_p = \beta^* \frac{S I_p}{N} - (\sigma + \mu)E_p, \quad (3.12)$$

$$\dot{I}_p = \sigma E_p - (\gamma + \mu)I_p, \quad (3.13)$$

$$\dot{R} = \gamma I_p - \mu R + \bar{u}S. \quad (3.14)$$

The disease-free equilibrium (DFE) is

$$\mathcal{E}_0 = (S^*, E_p^*, I_p^*, R^*) = \left(\frac{\mu N}{\mu + \bar{u}}, 0, 0, \frac{\bar{u}N}{\mu + \bar{u}} \right). \quad (3.15)$$

We derive the control reproduction number by the next-generation matrix construction [5,6]; practical extensions to structured populations are discussed in [31,32]. For infected compartments (E_p, I_p) , the new-infection and transition matrices at the frozen DFE are

$$F = \begin{pmatrix} 0 & \beta^* S^*/N \\ 0 & 0 \end{pmatrix}, \quad V = \begin{pmatrix} \sigma + \mu & 0 \\ -\sigma & \gamma + \mu \end{pmatrix},$$

$$FV^{-1} = \begin{pmatrix} \frac{\beta^* \sigma S^*}{N(\sigma + \mu)(\gamma + \mu)} & \frac{\beta^* S^*}{N(\gamma + \mu)} \\ 0 & 0 \end{pmatrix}.$$

Its spectral radius gives the control reproduction number

$$\mathcal{R}_c(\bar{u}, \bar{a}) = \rho(FV^{-1}) = \frac{\beta^*(\bar{a}) \sigma}{(\sigma + \mu)(\gamma + \mu)} \cdot \frac{\mu}{\mu + \bar{u}}. \quad (3.16)$$

Theorem 3.3 (Threshold stability of the reduced DFE). *Consider the reduced systems (3.11)–(3.14) under constant controls $(\bar{u}, \bar{a})$ and frozen efficacy, with nonnegative initial data with $S + E_p + I_p + R = N$. Then:*

(i) *The DFE $\mathcal{E}_0$ is locally asymptotically stable if $\mathcal{R}_c(\bar{u}, \bar{a}) < 1$, and unstable if $\mathcal{R}_c(\bar{u}, \bar{a}) > 1$.*

(ii) *If $\mathcal{R}_c(\bar{u}, \bar{a}) < 1$, then $\mathcal{E}_0$ is globally asymptotically stable in the feasible region.*

Proof. We work on the invariant simplex $\{(S, E_p, I_p, R) \in \mathbb{R}_+^4 : S + E_p + I_p + R = N\}$.

(i) **Local stability/instability.** Under constant controls, β^* is constant and the DFE is

$$\mathcal{E}_0 = (S^*, 0, 0, R^*), \quad S^* = \frac{\mu N}{\mu + \bar{u}}, \quad R^* = \frac{\bar{u}N}{\mu + \bar{u}}.$$

Linearizing the infected subsystem (E_p, I_p) at $\mathcal{E}_0$ yields

$$\begin{bmatrix} \dot{E}_p \\ \dot{I}_p \end{bmatrix} = A \begin{bmatrix} E_p \\ I_p \end{bmatrix}, \quad A := \begin{bmatrix} -(\sigma + \mu) & \beta^* S^*/N \\ \sigma & -(\gamma + \mu) \end{bmatrix}.$$

The trace is $\text{tr}(A) = -(\sigma + \mu) - (\gamma + \mu) < 0$. The determinant is

$$\det(A) = (\sigma + \mu)(\gamma + \mu) - \sigma\beta^* \frac{S^*}{N}.$$

Hence, $\det(A) > 0$ if and only if

$$\sigma\beta^* \frac{S^*}{N} < (\sigma + \mu)(\gamma + \mu) \iff \frac{\beta^* \sigma}{(\sigma + \mu)(\gamma + \mu)} \cdot \frac{S^*}{N} < 1.$$

Using $S^*/N = \mu/(\mu + \bar{u})$, this is exactly $\mathcal{R}_c(\bar{u}, \bar{a}) < 1$. For a 2×2 matrix, $\text{tr}(A) < 0$ and $\det(A) > 0$ is equivalent to both eigenvalues having negative real part, so the infected subsystem is locally asymptotically stable when $\mathcal{R}_c < 1$. If $\mathcal{R}_c > 1$, then $\det(A) < 0$ and A has one positive eigenvalue, so the DFE is unstable.

(ii) Global asymptotic stability when $\mathcal{R}_c < 1$. Assume $\mathcal{R}_c(\bar{u}, \bar{a}) < 1$. First note that from (3.11),

$$\dot{S} = \mu N - (\mu + \bar{u})S - \beta^* \frac{S I_p}{N} \leq \mu N - (\mu + \bar{u})S.$$

Solving the comparison equation $\dot{s} = \mu N - (\mu + \bar{u})s$ gives

$$S(t) \leq S^* + (S(0) - S^*)e^{-(\mu + \bar{u})t},$$

hence $\limsup_{t \rightarrow \infty} S(t) \leq S^*$. Convergence of S itself is established only after $E_p, I_p \rightarrow 0$ below. Thus, for any $\delta > 0$ there exists t_δ such that

$$S(t) \leq S^* + \delta \quad \text{for all } t \geq t_\delta.$$

Choose $\delta > 0$ small enough so that

$$\frac{\beta^* \sigma}{(\sigma + \mu)(\gamma + \mu)} \cdot \frac{S^* + \delta}{N} < 1. \quad (3.17)$$

This is possible because the left-hand side is continuous in δ and equals $\mathcal{R}_c(\bar{u}, \bar{a}) < 1$ at $\delta = 0$.

For $t \geq t_\delta$, the infected variables satisfy the differential inequalities

$$\dot{E}_p = \beta^* \frac{S(t)}{N} I_p - (\sigma + \mu) E_p \leq \beta^* \frac{S^* + \delta}{N} I_p - (\sigma + \mu) E_p,$$

$$\dot{I}_p = \sigma E_p - (\gamma + \mu) I_p.$$

Consider the linear cooperative system

$$\dot{\tilde{E}} = \beta^* \frac{S^* + \delta}{N} \tilde{I} - (\sigma + \mu) \tilde{E}, \quad \dot{\tilde{I}} = \sigma \tilde{E} - (\gamma + \mu) \tilde{I},$$

with initial data $(\tilde{E}(t_\delta), \tilde{I}(t_\delta)) = (E_p(t_\delta), I_p(t_\delta))$. By the comparison theorem for cooperative systems, we have

$$0 \leq E_p(t) \leq \tilde{E}(t), \quad 0 \leq I_p(t) \leq \tilde{I}(t) \quad \text{for all } t \geq t_\delta.$$

The matrix of the linear system is

$$A_\delta = \begin{bmatrix} -(\sigma + \mu) & \beta^*(S^* + \delta)/N \\ \sigma & -(\gamma + \mu) \end{bmatrix}.$$

Its trace is negative and its determinant satisfies

$$\det(A_\delta) = (\sigma + \mu)(\gamma + \mu) - \sigma\beta^* \frac{S^* + \delta}{N} > 0$$

by (3.17). Hence, A_δ is Hurwitz and $(\tilde{E}(t), \tilde{I}(t)) \rightarrow (0, 0)$ exponentially as $t \rightarrow \infty$. By comparison, $(E_p(t), I_p(t)) \rightarrow (0, 0)$ as well.

Finally, since $S + E_p + I_p + R = N$ is invariant and $E_p, I_p \rightarrow 0$, we have $R(t) = N - S(t) + o(1)$. Moreover, the equation for S can be written as

$$\dot{S} = \mu N - (\mu + \bar{u})S + \xi(t), \quad \xi(t) := -\beta^* \frac{S(t)I_p(t)}{N} \rightarrow 0,$$

and the stable linear system with vanishing input implies $S(t) \rightarrow S^*$. Therefore, $R(t) \rightarrow N - S^* = R^*$, completing the proof of global asymptotic stability. $\square$

Theorem 3.3 is an autonomous frozen-coefficient threshold statement. It does not guarantee finite-horizon suppression under time-varying efficacy or from a highly susceptible initial state, and Theorem 3.2 applies only on efficacy ranges meeting its uniform tracking conditions.

4. Control formulation and computational method

4.1. Finite-horizon control problem

We minimize the composite objective (2.13) over admissible controls $(u, a) \in \mathcal{U}$ subject to the full multiscale dynamics (2.1)–(2.11) on $[0, T]$. The controls are parametrized as piecewise-constant functions on a uniform partition,

$$0 = t_0 < t_1 < \cdots < t_M = T, \quad u(t) = u_j, \quad a(t) = a_j \quad (t_j \leq t < t_{j+1}).$$

This gives the finite-dimensional nonlinear program

$$\min_{\{u_j, a_j\}} \hat{J} \quad \text{subject to} \quad 0 \leq u_j \leq u_{\max}, \quad 0 \leq a_j \leq 1, \quad (4.1)$$

where $\hat{J}$ denotes (2.13) evaluated at the piecewise-constant controls. Here, $M = 12$ and $T = 180$ days, so each control interval lasts 15 days. The computed policies are numerically optimized feasible open-loop controls; random restarts do not certify global optimality, uniqueness, or continuous-time optimality.

4.2. Threshold-guided heuristic (reference policy)

We define the comparator operationally using the candidate grids $U_g = \{ku_{\max}/8 : k = 0, \dots, 8\}$ and $A_g = \{k/10 : k = 0, \dots, 10\}$, with target $\rho_{\text{tar}} = 0.95$. At the start t_j of every interval, the following steps determine the applied pair independently of the previously applied controls:

- (1) For every $(u, a) \in U_g \times A_g$, calculate $e_j(a) = \epsilon_{\max} a e^{-at_j}$ and the biologically admissible frozen within-host equilibrium using the explicit branches in Section 3.1.
- (2) Compute $\mathcal{R}_{c,j}(u, a)$ from (3.16), with $V_h^* = V_h^*(e_j(a))$ and susceptible fraction $\mu/(\mu + u)$ at the corresponding vaccination DFE.
- (3) Among candidates with $\mathcal{R}_{c,j} \leq 0.95$, choose the pair minimizing $c_u u^2 + c_a a^2$. If none is feasible, minimize $\mathcal{R}_{c,j} + 10^{-4}(c_u u^2 + c_a a^2)$ instead. Break ties by increasing u and then increasing a .
- (4) Hold the selected controls on $[t_j, t_{j+1})$, while efficacy continues to decay according to (2.5). Recompute the candidate scores at t_{j+1} using the updated calendar time.

The procedure defines a frozen-equilibrium threshold diagnostic over the stated control grid. The rule uses the disease-free equilibrium susceptible fraction rather than the current susceptible fraction. It is a weak baseline for short-horizon control because it can achieve its threshold at very low vaccination intensity while the population remains largely susceptible. The grid search can therefore select a small vaccination rate that makes the eventual DFE stable while enabling a substantial transient epidemic from an initially almost fully susceptible population. Two additional transparent baselines are no control, $(u, a) = (0, 0)$, and constant maximal control, $(u, a) = (u_{\max}, 1)$, throughout the horizon.

4.3. Numerically optimized open-loop policy

Each objective evaluation integrates the full eight-state model separately on every control interval, restarting the solver at the exact switch time with the continuous terminal state from the preceding interval. LSODA uses relative tolerance 10^{-8} and absolute tolerance 10^{-10} . The four strictly positive within-host states are integrated in logarithmic coordinates, avoiding state clipping or a numerical absorbing zero for infected cells and virus. Three auxiliary ODE variables integrate new exposures, the running objective, and viral burden; the terminal penalty is added to the integrated running cost. Population states are integrated directly, and their sum and nonnegativity are checked on the output trajectories.

For L-BFGS-B, vaccination is rescaled to $u_j/u_{\max} \in [0, 1]$, so both control types have unit box bounds. Four starts are used at each resistance value: the heuristic, constant maximal control, maximal treatment without vaccination, and a uniform random vector on $[0, 1]^{2M}$. The six optimization seeds are 100, ..., 105 in increasing resistance order. The algorithm uses forward finite differences of size 10^{-5} in the scaled variables, a maximum of 40 iterations and 3500 objective evaluations per start, $\text{ftol} = 10^{-10}$, $\text{gtol} = 10^{-5}$, and at most 30 line-search steps. The solver minimizes $J/10^4$ for numerical scaling; the reported cost remains J . The lowest evaluated feasible cost among returned candidates and initial policies is retained, and the termination status of every start is recorded in the repository.

The computed policy is open-loop: The control sequence is computed once using nominal parameters and then applied without reoptimization. Fixed-policy evaluation at perturbed parameters measures sensitivity of these particular computed schedules; it does not establish performance of an adaptive controller.

4.4. Frozen threshold diagnostic and numerical verification

The quantity $\mathcal{R}_{c,j}$ is a frozen-equilibrium diagnostic, not a finite-horizon or nonautonomous stability guarantee. In particular, $\mathcal{R}_{c,j} < 1$ during most intervals does not establish elimination from the actual initial condition, and changing efficacy can violate the uniform attraction assumption in Theorem 3.2. For each computed resistance-specific schedule, we repeat the full simulation with tighter LSODA tolerances (10^{-10} , 10^{-12}) and with Radau (10^{-9} , 10^{-11}), comparing objective values and prevalence trajectories. These checks test numerical integration for fixed controls; they do not certify a global control optimum or the biological validity of the representative-host approximation.

4.5. Observation model and parameter-perturbation evaluation

The synthetic observation model uses weekly new exposures, $b(t) = \beta_p(V_h(t))S(t)I_p(t)/N$. For a reporting population $N_{\text{obs}} = 200,000$, let $m_k = N_{\text{obs}} \int_{t_{k-1}}^{t_k} b(s) ds$, with a final partial interval ending at day 180. Observed counts satisfy

$$Y_k \sim \text{NB}(r_{\text{nb}}, p_k), \quad p_k = \frac{r_{\text{nb}}}{r_{\text{nb}} + m_k}, \quad \mathbb{E}Y_k = m_k, \quad \text{Var}(Y_k) = m_k + \phi m_k^2, \quad \phi = \frac{1}{r_{\text{nb}}}.$$

Thus, ϕ is the quadratic overdispersion coefficient, and its asymptotic coefficient of variation is $\sqrt{\phi}$. Calibration uses $\phi = 0.10$ ($r_{\text{nb}} = 10$), with independent counts and seed 42. Counts of new exposures are synthetic, not observed reported diagnoses, and a pathogen-specific study would need a delay and reporting model.

The heatmap uses $q \in \{0.05, 0.10, 0.20\}$ as a parameter-perturbation amplitude, not negative-binomial observation noise. For each resistance value and q , six independent parameter draws are evaluated for the fixed heuristic, constant maximal control, and computed schedule. Starting from the uncertainty distribution in Section 4.8, we additionally multiply β_0 by $1 + Z_\beta$, $Z_\beta \sim N(0, (0.05 + q)^2)$, and α by $1 + Z_\alpha$, $Z_\alpha \sim N(0, q^2)$, clipping the latter to $[0.001, 0.1]$; the seed is $\text{round}(10^5 \alpha) + 100q$. All realized transmission draws are positive, and all individual draws and outcomes are available in the repository. Because the controls do not respond to observations, this experiment cannot establish robustness to surveillance noise.

4.6. Synthetic calibration and its limits

Synthetic calibration checks the estimation workflow in a specified model-generated setting; it does not validate structural or practical identifiability. The generating parameters are $(\alpha, \beta_0, K) = (0.010, 1.25, 80)$, with constant controls $(u, a) = (0.0015, 0.5)$, so that treatment is active. The three parameters are estimated by minimizing the actual negative-binomial negative log-likelihood with known dispersion. Bounds are $\alpha \in [0.001, 0.08]$, $\beta_0 \in [0.8, 2]$, and $K \in [20, 220]$; the scaled variables use divisors $(0.01, 1.25, 80)$. Four starting vectors are $(0.004, 1.0, 50)$, $(0.025, 1.5, 120)$, $(0.050, 1.1, 180)$, and $(0.015, 1.7, 100)$. Likelihood minimization uses L-BFGS-B with finite-difference step 10^{-4} in scaled variables, at most 80 iterations and 1200 evaluations, $\text{ftol} = 10^{-10}$, $\text{gtol} = 10^{-5}$, and 30 line-search steps; the likelihood is divided by the number of observation intervals for scaling.

Forty parametric bootstrap datasets are generated from the fitted negative-binomial model with seed 11 and refitted from the fitted vector, using at most 60 iterations per replicate. Only successful refits enter the pointwise 2.5th–97.5th percentile interval for the fitted mean curve, and the number

retained is reported. This is a conditional fitted-mean uncertainty interval, not a Bayesian posterior or a predictive interval for future noisy counts. We also report the dispersion of estimates across the four starts and singular values of the local mean-response Jacobian, weighted by the inverse observation standard deviation and scaled by the nominal parameter values. These descriptive diagnostics can reveal weak information or near-collinearity but do not constitute a complete identifiability analysis.

4.7. Global sensitivity analysis

Six independent uniform inputs are used: $\alpha \in [0.001, 0.05]$, $\beta_0 \in [0.9, 1.6]$, $K \in [40, 140]$, $\gamma \in [1/14, 1/4]$, $\sigma \in [1/8, 1/3]$, and $\epsilon_{\max} \in [0.70, 0.99]$. The response is cumulative new exposures over 180 days.

4.7.1. Partial rank correlation coefficients

A Latin hypercube of 250 vectors (seed 1) is evaluated for the threshold heuristic and for a second, fixed treatment-active policy $(u, a) = (0.0015, 0.8)$. PRCC is the correlation of parameter and response ranks after regression on the other five parameter ranks. Two-sided approximate p -values use $t = r\sqrt{(n-d-1)/(1-r^2)}$ with $n-d-1 = 243$ degrees of freedom ($n = 250, d = 6$). The comparison of policies distinguishes absence of treatment exposure from resistance sensitivity when treatment is administered.

4.7.2. Sobol' indices

For the heuristic, two independent input blocks A, B are drawn from one 12-dimensional scrambled Sobol sequence with $N_S = 256$ points (seed 2), giving $N_S(d+2) = 2048$ model evaluations. For $A_B^{(j)}$, replace column j of A by column j of B ; writing $Y_A, Y_B, Y_{AB,j}$ for their responses, use

$$\widehat{S}_{1,j} = \frac{N_S^{-1} \sum_i (Y_{B,i} - \bar{Y})(Y_{AB,j,i} - Y_{A,i})}{\widehat{\text{Var}}(Y)}, \quad \widehat{S}_{T,j} = \frac{(2N_S)^{-1} \sum_i (Y_{A,i} - Y_{AB,j,i})^2}{\widehat{\text{Var}}(Y)}.$$

The mean and sample variance use the pooled Y_A, Y_B vectors; confidence half-widths are 1.96 times the bootstrap standard deviation from 1000 paired-row resamples (seed 3). Finite-sample estimates are not clipped to $[0, 1]$, and precision is judged from the reported uncertainty rather than treating point estimates as exact rankings.

4.8. Fixed-policy Monte Carlo analysis

For each of the six resistance values, 12 parameter vectors are generated with independent multipliers: $\beta_0, \gamma, \sigma, \alpha$ use $U(0.9, 1.1)$; K uses $U(0.85, 1.15)$; and $\epsilon_{\max}$ uses $U(0.95, 1.05)$ followed by clipping to $[0.65, 0.99]$. The perturbed α is clipped to $[0.001, 0.1]$, and the common random generator has seed 123. Nominal policies are held fixed under each draw, preserving paired comparisons with the heuristic and constant maximal control. We record

$$\Delta J_B = 100 \frac{J_B - J_{\text{numerical}}}{J_B}, \quad B \in \{\text{heuristic, constant maximal}\}.$$

For each resistance value and comparator, 2000 bootstrap resamples of the 12 paired relative improvements produce a percentile interval for the mean, using seeds 1000, $\dots$, 1005. The two-sided

exact Wilcoxon signed-rank test is applied separately to paired cost differences against the heuristic and constant maximal policy. With twelve nonzero paired differences, its minimum possible two-sided p -value is $2/2^{12} = 0.000488$, attained when all differences have the same sign; this does not quantify the effect size or broad policy robustness.

4.9. Nominal values and reproducibility

The numerical study is a methodological demonstration rather than a calibration to one named pathogen. Within-host states use model-scale units; the coefficients in the fast equations correspond to physical relaxation rates divided by η , so, for example, the physical infected-cell and virion turnover times are η/d_I and η/c . Population compartments are fractions ($N = 1$), whereas N_{obs} is a separate count scale used only for synthetic observations. Tables 1 and 2 specify all nominal model coefficients, initial states, objective weights, and control bounds. The six resistance values are exactly 0.0030, 0.0104, 0.0178, 0.0252, 0.0326, and 0.0400 day^{-1} ; the baseline is 0.0252. The accompanying script, run manifest, optimizer logs, synthetic data, bootstrap results, sensitivity samples, fixed-policy perturbation draws, and integration checks document the computations for every numerical figure and table. No empirical efficacy, cost, or pathogen-specific interpretation is inferred from these nominal choices.

Table 1. Nominal coefficients and initial conditions for the full-model experiments.

Quantity	Value	Interpretation
η	0.05	Time-scale ratio
λ, d_T, β_h	10, 0.01, 2×10^{-4}	Target-cell supply, loss, infection
d_I, κ, p, c	0.5, 0.002, 50, 5	Infected-cell loss, killing, production, clearance
r, d_X	10^{-4} , 0.1	Immune expansion and loss
ϵ_{max}	0.95	Maximum inhibition
α (baseline)	0.0252	Efficacy erosion rate
β_0, K	1.25, 80	Maximum transmission and half-saturation
μ, σ, γ	$1/(70 \cdot 365)$, 1/5, 1/7	Demography, progression, recovery
N, T	1, 180	Population normalization and horizon (days)
$(T_h, I_h, V_h, X_h)(0)$	(1000, 0.05, 5, 1)	Positive within-host initial states
$(S, E_p, I_p, R)(0)$	(0.999, 0.0005, 0.0005, 0)	Population initial fractions

Table 2. Objective and control settings; observation settings apply only to calibration.

Quantity	Value	Quantity	Value
w_C	800	w_I	150
w_V	0.35	w_T	900
c_u	900	c_a	25
w_{res}	2	u_{max}	0.012
a_{max}	1	M	12
ϕ, r_{nb}	0.10, 10	N_{obs}	200,000

5. Numerical experiments

5.1. Policy comparison under baseline resistance

We compare no control, the explicitly defined threshold heuristic, constant maximal control, and a numerically optimized open-loop policy at $\alpha = 0.0252 \text{ day}^{-1}$ over 180 days (Figure 2; Table 3). The heuristic selects $u_j = 0.0015$ and $a_j = 0$ in every interval, with cumulative new exposures 0.952195 and peak infectious prevalence 0.268170. Its frozen no-control reproduction number is approximately 5.704, whereas the selected vaccination rate gives $\mathcal{R}_c \approx 0.145$, evaluated at $S^*/N = \mu/(\mu + 0.0015) \approx 0.0254$. The actual initial susceptible fraction is 0.999, giving a frozen transmission potential of approximately 5.698 when the quasi-steady untreated viral load is used. Vaccination takes roughly $1/(\mu + 0.0015) \approx 650$ days to approach its demographic DFE in the absence of infection; the small equilibrium susceptible fraction is therefore not reached before the transient epidemic wave. The numerically optimized policy attains $J = 8623.88$, a 24.72% reduction relative to the heuristic, with cumulative incidence 0.240026 and peak prevalence 0.034011. Because the heuristic costs only 0.71% less than no control (11,455.80 versus 11,537.81), it is a weak practical comparator. Against constant maximal control the computed schedule costs 10.53% less (8623.88 versus 9638.97), but has higher cumulative incidence (0.240026 versus 0.221115). For this schedule, the prevalence peak occurs near day 101.8; treatment is maximal for the first three intervals and then declines, while vaccination is maximal for the first nine intervals and then decreases. The representative viral load reaches a very small positive minimum (approximately 7.1×10^{-16}) before rebounding to about 150 by the end of the horizon. Thus, suppression is transient and is not viral clearance or population elimination. Relative to constant maximal control, the optimized schedule trades a slightly higher epidemic burden for lower treatment effort under the stated weights.

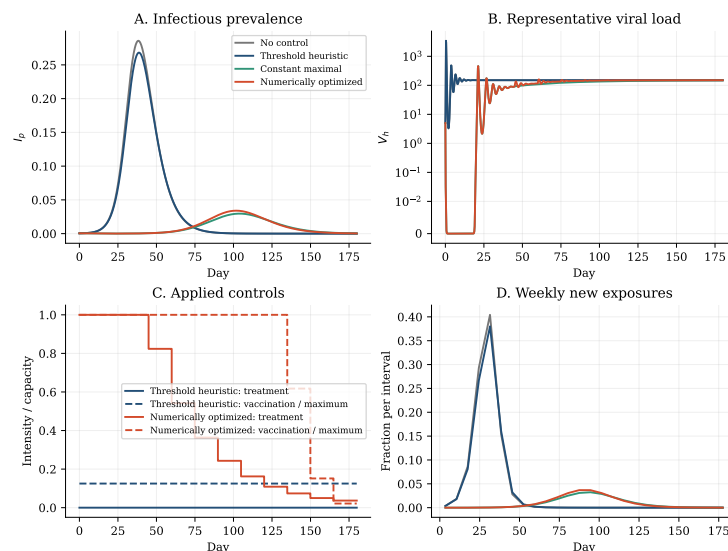


Figure 2. Full-model policy comparison at $\alpha = 0.0252 \text{ day}^{-1}$: (A) infectious prevalence for four policies; (B) representative viral load on a symlog scale, including rebound; (C) heuristic and numerically optimized controls, with vaccination normalized by $u_{\max}$; and (D) weekly new-exposure fractions, with the final interval truncated at day 180.

Table 3. Four-policy comparison at baseline resistance; all entries use the full-model integration and the stated objective.

Policy	J	Cumulative new exposures	Peak I_p
No control	11,537.81	0.996636	0.285707
Weak DFE heuristic	11,455.80	0.952195	0.268170
Constant maximal	9638.97	0.221115	0.029644
Numerically optimized	8623.88	0.240026	0.034011

At baseline resistance, the direct viral-load component is 9693.48 (about 84.0% of J) without control, 9693.48 under the heuristic, and 7377.19 under the computed schedule. Table 4 separates the seven cost contributions; a large direct viral-load penalty arises even in the absence of population cases because it integrates one representative-host trajectory.

Table 4. Seven contributions to the baseline composite objective at $\alpha = 0.0252 \text{ day}^{-1}$. Each row combines the corresponding upper and lower panels; the entries sum to J up to rounding.

Policy	New exposures	Prevalence	Viral load	Vaccination
No control	797.31	1047.03	9693.48	0.00
Weak DFE heuristic	761.76	1000.38	9693.48	0.18
Constant maximal	176.89	232.64	6958.39	11.66
Numerically optimized	192.02	252.53	7377.19	9.14

Policy	Treatment	Resistance penalty	Terminal	J
No control	0.00	0.00	0.00	11,537.81
Weak DFE heuristic	0.00	0.00	0.00	11,455.80
Constant maximal	2250.00	9.07	0.32	9638.97
Numerically optimized	789.53	3.18	0.28	8623.88

With $w_V = 0$, the four original schedules have costs 1844.33 (no control), 1762.32 (heuristic), 2680.58 (constant maximal), and 1246.69 (computed schedule). The computed schedule remains less costly than each of the three fixed comparators under this altered objective, while the newly optimized policy is evaluated separately in Table 5.

Table 5. Baseline policy comparison without the explicit viral-load penalty ($w_V = 0$), retaining all other weights and the same 180-day horizon; the original computed schedule is distinguished from a new schedule optimized under this objective.

Policy	J with $w_V = 0$	Cumulative new exposures	Peak I_p
No control	1844.33	0.996636	0.285707
Weak DFE heuristic	1762.32	0.952195	0.268170
Constant maximal	2680.58	0.221115	0.029644
Original computed schedule	1246.69	0.240026	0.034011
Reoptimized for $w_V = 0$	921.07	0.287329	0.044931

5.2. Sensitivity of policy performance to resistance rate

Across the six resistance values (Figure 3), the untreated and heuristic trajectories are identical because neither applies treatment, so efficacy decay has no effect on their state equations. For the computed policies, cumulative incidence increases from 5×10^{-7} at $\alpha = 0.0030$ to 0.404856 at $\alpha = 0.0400$, while objective cost increases from 2455.54 to 9450.87. The apparent 17.50%–78.57% cost improvement is relative to the weak DFE heuristic; against constant maximal control the six nominal cost savings range from 0.47% to 13.38%. Constant maximal control achieves slightly lower cumulative incidence than the computed policy at each tested resistance value, while the computed policy achieves a lower composite cost. These finite computations show a resistance-dependent trade-off; they do not prove a globally optimal schedule or a universal monotone law. Of the 24 optimization starts, 22 report convergence and 2 stop at the iteration limit; every termination status is recorded in the repository. The selected baseline candidate is from a converged start, but this still does not establish global optimality.

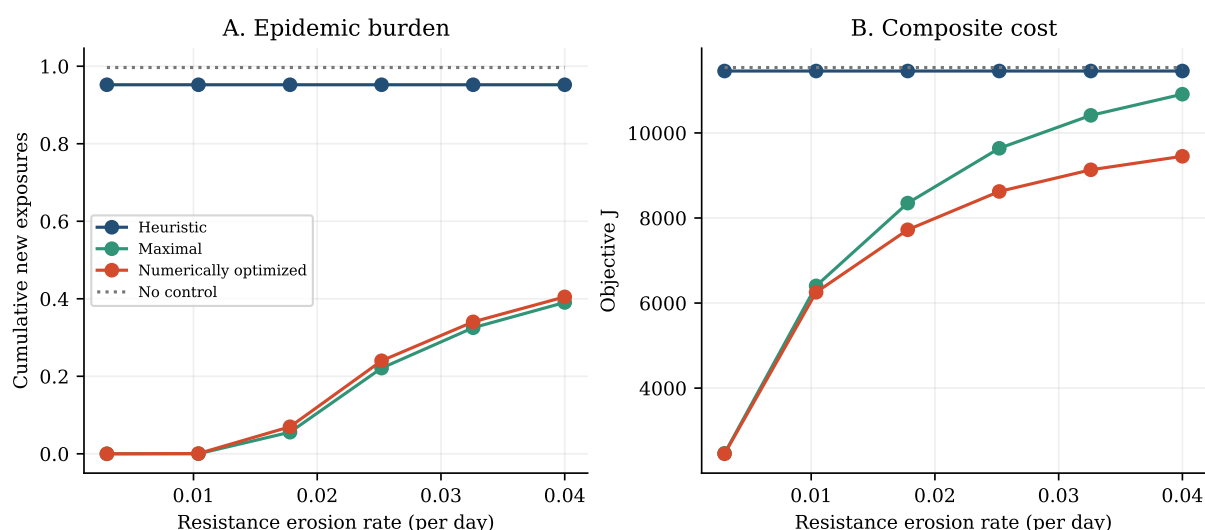


Figure 3. Resistance sweep for all four policies: (A) cumulative new exposures; and (B) composite objective cost. The heuristic has no treatment and is independent of α , while the treatment-active schedules permit rebound as efficacy erodes.

5.3. Joint parameter-perturbation evaluation

Figure 4 reports the 18 cell means under identical perturbations for the weak heuristic (16.86%–78.29%) and constant maximal control (0.45%–13.74%). Each cell is based on only six draws, so its annotated mean is a small-sample simulation summary. The horizontal axis uses the exact six resistance values, and the vertical axis is the parameter-perturbation amplitude q , which is separate from negative-binomial overdispersion ϕ . No noisy observations are fed back to either policy; this figure cannot establish surveillance-noise robustness or adaptive policy performance.

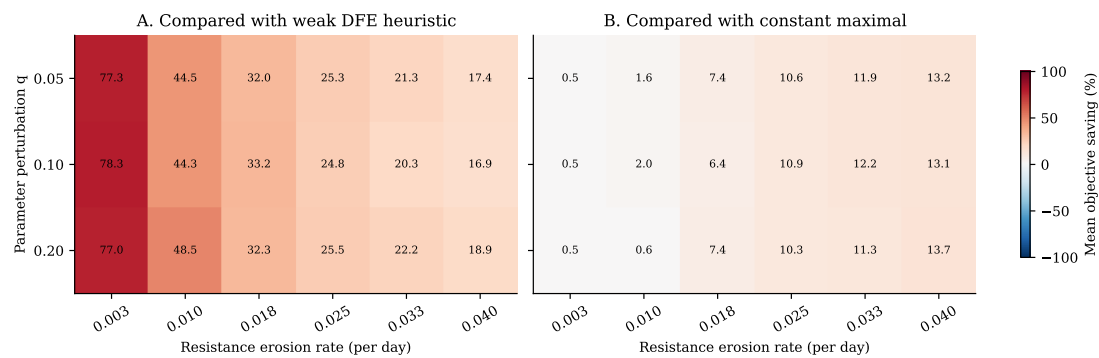


Figure 4. Paired mean cost savings (%) for the fixed numerically optimized schedules under resistance and parameter perturbations: (A) relative to the weak DFE heuristic; and (B) relative to constant maximal control. Each cell uses the same six draws; q denotes parameter perturbations.

5.4. Synthetic data calibration

Figure 5 shows the synthetic negative-binomial calibration results. The synthetic calibration uses nonzero constant treatment and synthetic weekly new-exposure counts under a negative-binomial observation model, with true $(\alpha, \beta_0, K) = (0.010, 1.25, 80)$. The lowest returned negative-log-likelihood candidate has $(\hat{\alpha}, \hat{\beta}_0, \hat{K}) = (0.02208, 1.9736, 220.00)$, rather than exact recovery of the generating values. Only one of the four initial runs reports convergence; the other three terminate abnormally, and the lowest-likelihood returned candidate is not certified as a maximum-likelihood estimate. The candidate reaches the upper bound for K , and nearby candidates from different starts have similar likelihoods but different parameter values. The scaled weighted local mean-response Jacobian has condition number approximately 4.5×10^2 ; this is a descriptive local sensitivity diagnostic, with additional limitations at a boundary estimate. Of 40 parametric bootstrap refits, 25 satisfy the optimizer success criterion and enter the displayed fitted-mean interval; the remaining refits are reported as failures, excluded from the interval. Conditioning on successful refits can bias the interval, and forty requested replicates are insufficient for a precise coverage claim. The generating and fitted models are identical, dispersion is known, and no reporting misspecification or empirical heterogeneity is present; this exercise therefore does not validate structural or real-world practical identifiability. A fitted mean can resemble the synthetic curve despite weakly determined parameters; further work requires more informative treatment designs, joint viral-load and population observations, profile likelihoods, and repeated datasets.

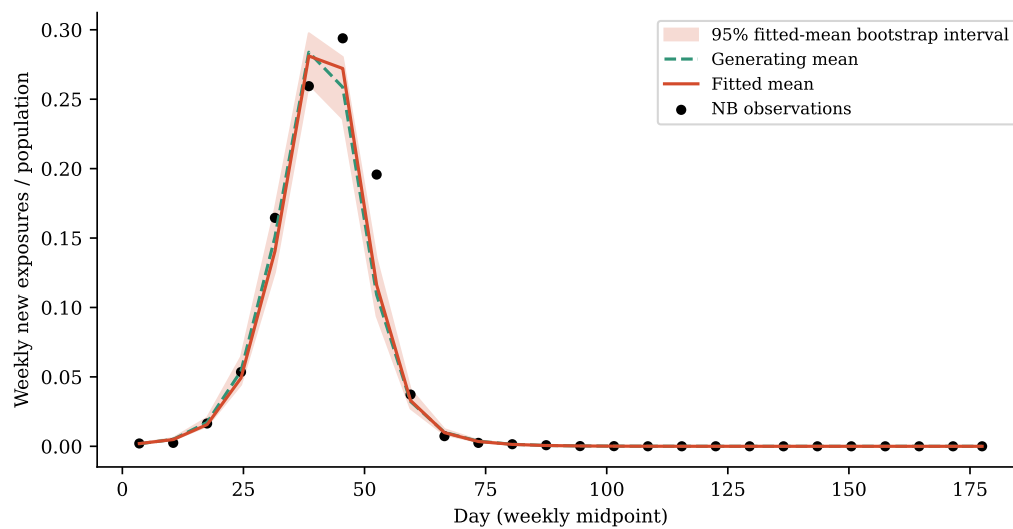


Figure 5. Synthetic negative-binomial calibration under $(u, a) = (0.0015, 0.5)$: observed weekly fractions, generating mean, lowest returned likelihood candidate, and pointwise interval from successful parametric-bootstrap refits. Curve agreement does not establish parameter identifiability; the band excludes future count noise and failed refits.

5.5. Global sensitivity analysis

Under the heuristic, recovery, transmission, and saturation dominate the cumulative-incidence response (Figure 6; Table 6). For all vectors in the stated sensitivity ranges, the cheapest threshold-feasible grid pair is $u = 0.0015, a = 0$; therefore α and $\epsilon_{\max}$ are absent from the governing state equations in this experiment. Their Sobol indices are zero, while their small or marginal sample PRCC associations reflect sampling and rank residualization, not treatment-mediated effects. Under the separate fixed treatment-active policy $(u, a) = (0.0015, 0.8)$, resistance has PRCC 0.804 and maximum efficacy has PRCC -0.384 (both approximate $p < 10^{-8}$); recovery remains strongly negative (PRCC -0.908). Thus, the resistance motivation is conditional on treatment exposure: Lack of sensitivity in an untreated experiment cannot establish that resistance is unimportant under treatment. The nonlinear and policy-specific response also limits interpretations of rank correlations as universal causal rankings.

Table 6. Sobol sensitivity indices for the heuristic ($N_S = 256$); confidence entries are approximate 95% half-widths from paired-row bootstrap resampling.

Parameter	S_1	Half-width	S_T	Half-width
α	0.000	0.000	0.000	0.000
β_0	0.282	0.134	0.388	0.106
K	0.177	0.119	0.215	0.061
γ	0.352	0.133	0.582	0.181
σ	0.015	0.026	0.022	0.007
$\epsilon_{\max}$	0.000	0.000	0.000	0.000

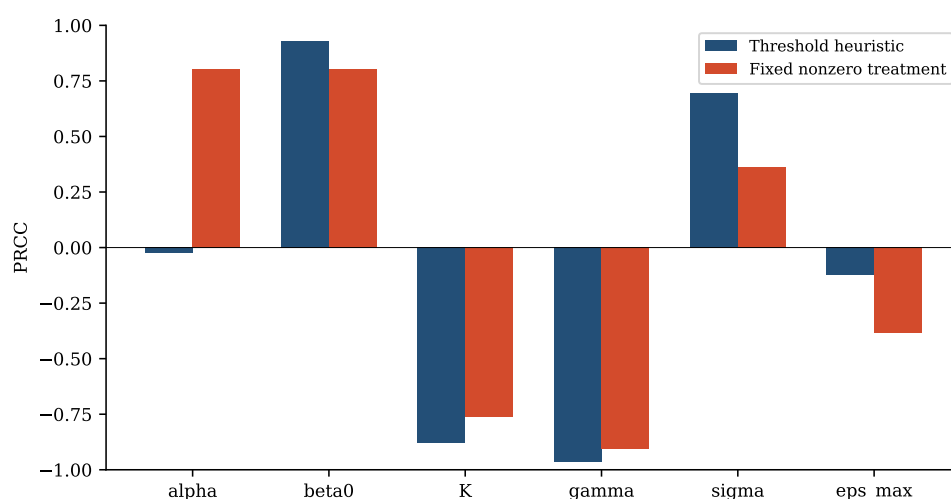


Figure 6. PRCC for cumulative new exposures using the same 250-point Latin hypercube under the threshold heuristic and fixed treatment-active policy $(u, a) = (0.0015, 0.8)$; the heuristic's efficacy parameters have no structural effect because its treatment intensity is zero.

5.6. Robustness of objective improvement under parameter uncertainty

For 12 paired parameter draws at each resistance value, mean relative cost savings are 17.72%–77.65% versus the weak heuristic and 0.46%–13.34% versus constant maximal control (Figure 7; Table 7). For each comparator, the percentile intervals and paired test results must be interpreted at the stated twelve-draw resolution. These are conditional fixed-policy comparisons over a narrow, prespecified uncertainty distribution and a small ensemble; they are not guarantees against unmodeled uncertainty, observation noise, or infection-age heterogeneity.

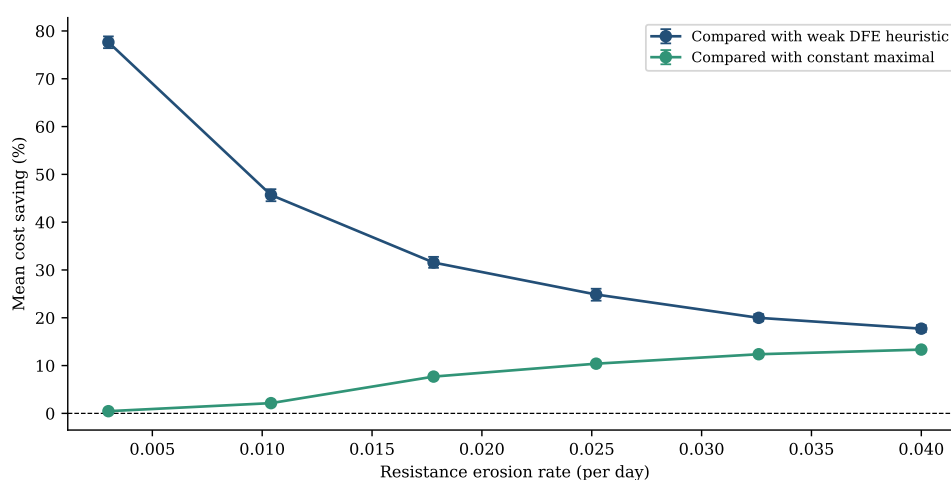


Figure 7. Paired mean cost savings of fixed numerically optimized schedules against the weak DFE heuristic and constant maximal control under 12 common parameter draws at each resistance value; error bars are percentile bootstrap intervals for the simulated mean.

Table 7. Fixed-policy Monte Carlo comparisons using the same 12 parameter draws for both comparators. The two-sided exact Wilcoxon minimum $p = 2/2^{12} = 0.000488$ records only twelve paired differences with the same sign.

A. Compared with weak DFE heuristic				
α	Mean (%)	95% interval (%)	p	n_+
0.0030	77.65	76.40–78.87	0.000488	12
0.0104	45.68	44.38–46.90	0.000488	12
0.0178	31.56	30.45–32.75	0.000488	12
0.0252	24.86	23.57–26.07	0.000488	12
0.0326	19.99	19.27–20.76	0.000488	12
0.0400	17.72	16.99–18.46	0.000488	12
B. Compared with constant maximal control				
α	Mean (%)	95% interval (%)	p	n_+
0.0030	0.46	0.43–0.48	0.000488	12
0.0104	2.14	1.90–2.43	0.000488	12
0.0178	7.69	7.36–8.00	0.000488	12
0.0252	10.40	10.13–10.65	0.000488	12
0.0326	12.37	12.18–12.56	0.000488	12
0.0400	13.34	13.16–13.53	0.000488	12

5.7. Integration checks

Tighter LSODA and independent Radau simulations of the six computed schedules have maximum relative objective difference 1.4×10^{-8} and maximum absolute prevalence difference 3.7×10^{-9} on the common output grid. The largest population-mass discrepancy in these checks is 1.1×10^{-14} ; complete solver results are available in the repository. These checks support numerical integration of the stated positive-state model; they do not validate the representative-host closure, certify parameter identifiability, or establish global control optimality.

6. Discussion and conclusions

The main methodological contribution is an efficacy-decay closure coupled to a conditional fast–slow reduction with an explicit finite-horizon error bound that includes accumulated initial and switching layers. The frozen SEIR threshold and the next-generation matrix construction are standard; their role is to clarify eventual autonomous DFE stability, not to guarantee short-horizon epidemic suppression from an almost fully susceptible initial population. Uniform fast attraction must hold on the selected efficacy range and along the considered trajectories, and it fails at the nominal branch crossing; the full-model experiments are therefore distinct from the regime of the uniform reduction theorem. The positivity-preserving full-model simulation shows that very small positive viral loads can rebound when efficacy decays; transient suppression does not establish eradication. The computed schedules reduce the stated composite objective relative to the weak DFE heuristic and constant maximal control at the tested nominal values; constant maximal control has lower incidence in the resistance sweep. The 17%–78% heuristic-relative savings largely compare with an almost untreated baseline, whereas maximal-control

comparisons represent an active-intervention alternative. The cost weights, parameter ranges, time horizon, and deployment capacities are illustrative policy choices, so these rankings are conditional and are not pathogen-specific recommendations. The resistance sensitivity result depends on exposure: The untreated heuristic cannot reveal a treatment-resistance effect, whereas the fixed treatment-active sensitivity experiment can. Neither finding implies that resistance universally dominates epidemic outcomes or that the exponential law represents explicit resistant-strain evolution. The closure also permits efficacy erosion during untreated periods; treatment-exposure-dependent erosion or explicit sensitive and resistant strains would be more mechanistic extensions. A strong limitation is the shared representative-host trajectory: All infectious individuals experience the same calendar-time viral load, so suppressing it simultaneously suppresses their transmission coefficient. The separate $w_V \int_0^T V_h(t) dt$ term assigns a cost to that single representative trajectory, not a measured population viral-load total; viral load also affects new exposures through $\beta_p(V_h)$, so this is an additional, partly overlapping preference for virological suppression. At baseline, it contributes about 84.0% of no-control cost; even with full initial treatment, efficacy $0.95e^{-0.0252t}$ crosses the within-host threshold 0.75 after approximately 9.4 days, permitting later viral rebound. Under $w_V = 0$, the original computed schedule still has the lowest composite cost among the four original schedules, while the new objective requires its own separate numerical optimization. These policy rankings remain conditional on the illustrative weights and the representative-host closure. A concrete structured extension replaces I_p by an infectious-age density $i(t, \xi)$, with age ξ measured from entry into the infectious class, satisfying

$$\partial_t i + \partial_\xi i = -(\gamma + \mu)i, \quad i(t, 0) = \sigma E_p(t), \quad I_p(t) = \int_0^\infty i(t, \xi) d\xi. \quad (6.1)$$

$$b_{\text{age}}(t) = \frac{S(t)}{N} \int_0^\infty \beta_0 \frac{v(t, \xi)}{v(t, \xi) + K} i(t, \xi) d\xi. \quad (6.2)$$

Here, $v(t, \xi)$ is the cohort-specific viral trajectory under calendar-time treatment, requiring a within-host initial-state distribution at infectious entry; a formulation with age since infection must additionally represent the latent stage. Replacing new-exposure incidence by b_{age} in the population equations prevents one representative trajectory from instantaneously controlling every infection age. We have not simulated this extension and do not claim that the quantitative benefits or policy rankings persist under it. Synthetic calibration also remains a limitation: Near-equivalent fits, boundary estimates, optimizer failures, and a conditional bootstrap do not support exact recovery or real-world identifiability. Empirical use requires matched within-host and population observations, reporting and delay models, informative treatment designs, and formal identifiability diagnostics. In future work, researchers should examine age-structured coupling, explicit resistance evolution, resource and treatment-budget constraints, feedback control, discretization refinement, and adjoint-based optimization.

Data and code availability

The code and numerical data are publicly available at <https://github.com/shiralikadyrov/MBE-8705-multiscale-epidemic-model>.

Use of AI tools declaration

ChatGPT (OpenAI) was used to assist with manuscript editing, mathematical revision, computational-code revision, and $\text{\LaTeX}$ preparation. The authors remain responsible for checking and approving all mathematical statements, numerical analyses, references, and final text.

Conflict of interest

The authors declare no conflict of interest.

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