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Optimal control of environmental cleaning and antibiotic prescription in an epidemiological model of methicillin-resistant *Staphylococcus aureus* infections in hospitals

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ABSTRACT

We consider a deterministic model of Methicillin-resistant *Staphylococcus aureus* infections in hospitals with seasonal oscillations of the antibiotic prescription rate. The model compartments consist of uncolonized patients with or without antibiotic exposure, colonized patients with or without antibiotic exposure, uncontaminated or contaminated healthcare workers, and free-living bacteria in the environment. We apply optimal control theory to this seven-compartment periodic system of ordinary differential equations to reduce the number of colonized patients and density of bacteria in the environment while minimizing the cost associated with environmental cleaning and antibiotic use in a particular time period. Characterizations of optimal control strategies are formulated and the ways hospitals should adjust these strategies for different scenarios are discussed. Numerical simulations strongly suggest that environmental cleaning is essential in the control of MRSA infections and antibiotic usage is suggested to be maintained at the least possible level. Screening, isolating, and shortening the extremely lengthened stays of colonized patients with antibiotic use history are all effective intervention strategies.

1. Introduction

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a type of staph bacteria considered as one of the most common causes of hospital-acquired infections, especially in intensive care units. Infections caused by staph bacteria are usually treated by antibiotics. However, a report released by the Centers for Disease Control and Prevention (CDC) in 2017 stated that 30–50% of the antibiotic treatments in hospitals are unnecessary or inappropriate [5]. As a result of the overuse of antibiotics in recent decades, MRSA is now resistant to multiple commonly used antibiotics, which makes MRSA infections harder to be treated and even causes life-threatening cases in intensive care units. According to a WHO report [33], patients infected by MRSA are 64% more possible to die compared to those infected by non-resistant bacteria in hospitals.

The spread of MRSA has been widely studied in [1,3,4,6–9,11,29–31]. Direct contact between healthcare workers (HCWs) and patients is believed to be the major transmission route of MRSA in hospitals. Until recently, strategies for controlling MRSA infections focus on improving HCW-patient hygiene measures, such as enhancing hand hygiene compliance with HCWs, screening and decolonizing colonized patients, and isolating positive cases. However, less attention has been paid to reducing the environmental contamination levels. It is found that MRSA has the ability to survive for weeks in environments such as healthcare facilities, doors, and sinks, which means that indirect transmission via environmental contamination is also crucial. In addition, some studies show that patients with antibiotic exposure are more likely to be colonized by MRSA, which leads to lengthier hospital stays, higher chances of failed or delayed treatments, more expensive costs, and even higher death rates [6,10,27,28]. Thus the pattern of antibiotic prescription rates in hospitals could also influence the spread of MRSA, and in the work of Sun et al. [26], seasonal oscillations of antibiotic prescription rates have been observed. Inspired by the above findings, Huang et al. [17] developed a deterministic model that considered both periodic antibiotic prescribing rates and environmental contaminations and found that environmental cleaning may be the most important intervention to control nosocomial MRSA infections, which corresponds to the suggestions on enhancing the environmental hygiene standard by better monitoring strategies, and using technology (cleaning robots) to supplement the cleaning manuals [14].

In this paper, we aim to seek for optimal and cost-effective strategies of environmental cleaning and antibiotic use, and also to better understand how environmental cleaning and antibiotic use would affect the transmission and control of MRSA infections in hospitals. In

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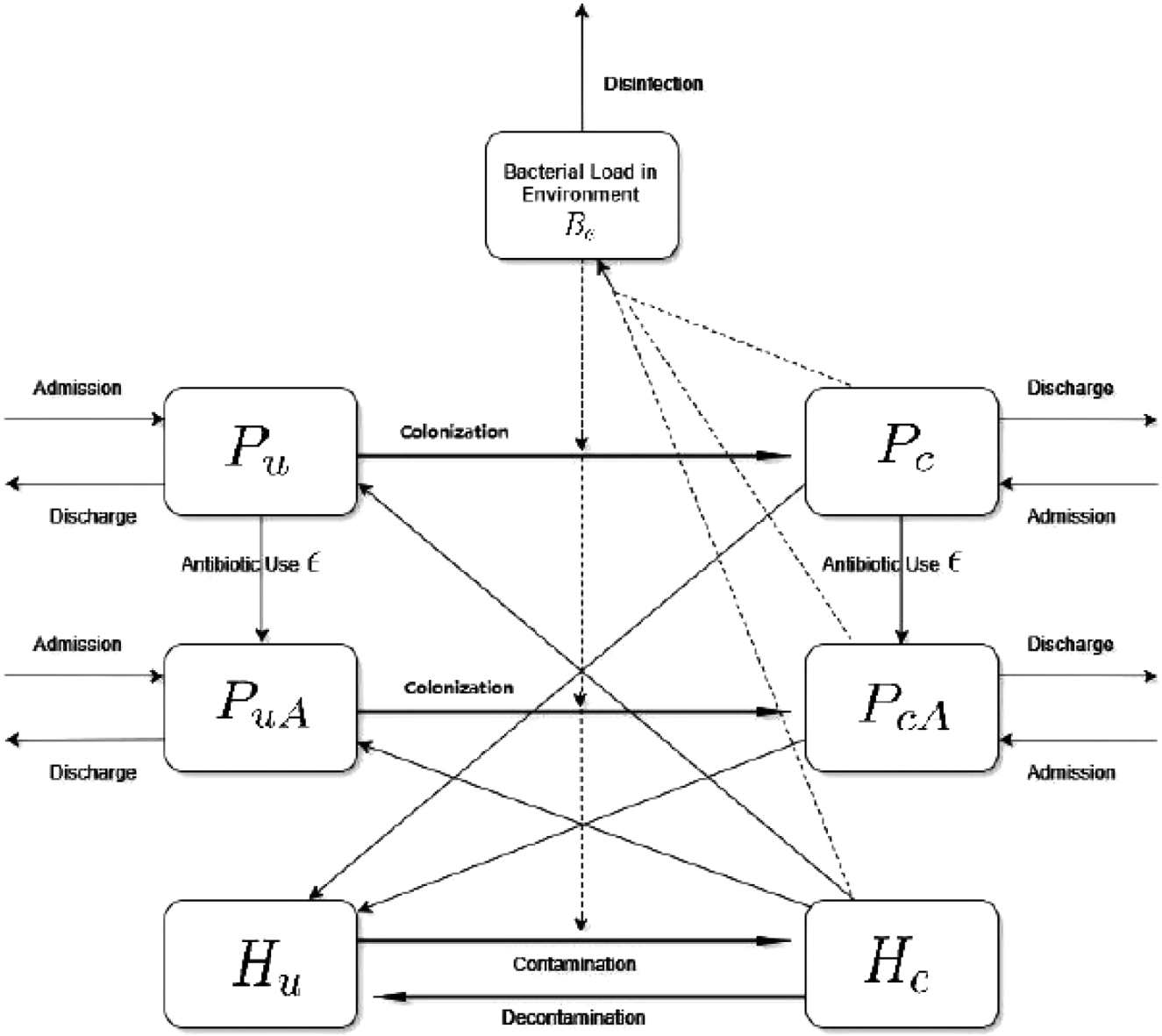

Fig. 1. Transmission flowchart of MRSA among patients, health-care works and the environment in hospitals [17].

Section 2, we present our seven-compartment periodic system and introduce the objective functionals and the two control variables. We aim to minimize the number of colonized patients, the density of bacteria in the environment, and the cost associated with environmental cleaning and antibiotic use for a particular time period. In Section 3, we develop the adjoint equations and formulate the characterization of optimal control strategies by applying the optimal control theory [12,20,23,25]. In Section 4, we present simulation results and discussions on the optimized strategies.

2. The model

The model in [17] was developed to describe the transmission of MRSA in the following seven compartments (see Fig. 1):

$P_u(t)$ = number of uncolonized patients without antibiotic exposure at time t.

$P_{uA}(t)$ = number of uncolonized patients with antibiotic exposure at time t.

$P_c(t)$ = number of colonized patients without antibiotic exposure at time t.

$P_{cA}(t)$ = number of colonized patients with antibiotic exposure at time t.

$H_u(t)$ = number of uncontaminated healthcare workers at time t.

$H_c(t)$ = number of contaminated healthcare workers at time t.

$B_e(t)$ = density of the free-living bacteria of a ward in the environment at time t.

Patients are divided as uncolonized without or with antibiotic exposure, colonized without or with antibiotic exposure, where a patient is said to be with antibiotic exposure if he or she has received antibiotics within the month on admission or is currently receiving antibiotic treatment in the hospital. Healthcare workers are categorized regarding their contamination status. Environmental contamination is

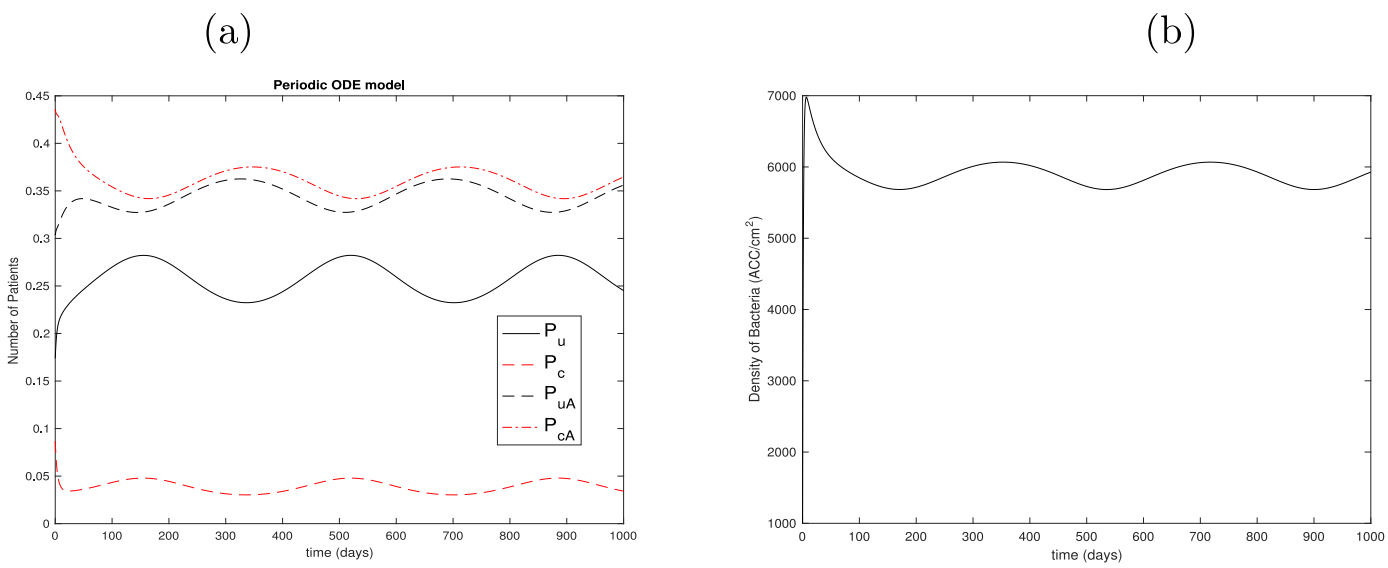

Fig. 2. Baseline model without control. Simulations are based on the fixed parameters in Table 1. (a) Proportion of patients; (b) environmental bacteria density.

Table 1
Parameters and descriptions [17].

Symbol	Description	Value	References
ϵ_0	Antibiotic prescription rate (day^{-1})	0.12 (varied)	[13,22]
ϵ_1	Magnitude of change of antibiotic prescription rate (no dimension)	0.25	[26]
θ_u	Proportion of P_u on admission (day^{-1})	0.617	[6,13]
θ_{uA}	Proportion of P_{uA} on admission (day^{-1})	0.349	[6,15]
θ_c	Proportion of P_c on admission (day^{-1})	0.003	[6,13]
θ_{cA}	Proportion of P_{cA} on admission (day^{-1})	0.031	[6,15]
γ_u	Discharge rate of P_u (day^{-1})	0.2	[6]
γ_{uA}	Discharge rate of P_{uA} (day^{-1})	0.2	[6]
γ_c	Discharge rate of P_c (day^{-1})	0.06	[13]
γ_{cA}	Discharge rate of P_{cA} (day^{-1})	0.055	[6,13]
γ_b	Disinfection (cleaning) rate of environment (day^{-1})	0.7 (varied)	[30]
α_p	Contact rate (day^{-1} person^{-1})	0.0435	[30]
β_p	Probability of colonization for P_u after a contact with H_c (no dimension)	0.42	[30]
β_{pA}	Probability of colonization for P_{uA} after a contact with H_c (no dimension)	0.42 × 1.67	[6,13]
β_h	Probability of contamination for HCWs after a contact with P_c (no dimension)	0.2	[6,30]
β_{hA}	Probability of contamination for HCWs after a contact with P_{cA} (no dimension)	0.25	[6]
η	Hand hygiene compliance with HCWs (no dimension)	0.4	[30]
μ_c	Decontamination rate of HCWs (day^{-1})	24	[30]
υ_p	Shedding rate to environment from P_c (day^{-1} person^{-1} ACC/cm^2)	235	[30]
υ_{pA}	Shedding rate to environment from P_{cA} (day^{-1} person^{-1} ACC/cm^2)	470	[13,31]
υ_h	Contamination rate to environment by H_c (day^{-1} person^{-1} ACC/cm^2)	235	[30]
κ_p	Colonization rate from environment for P_u (day^{-1} (ACC/cm^2)$^{-1}$)	0.000004	[30]
κ_{pA}	Colonization rate from environment for P_{uA} (day^{-1} (ACC/cm^2)$^{-1}$)	0.000005	[6,30]
κ_h	Colonization rate from environment for H_u (day^{-1} (ACC/cm^2)$^{-1}$	0.00001	[30]
N_p	Total number of patients	23	[30]
N_h	Total number of HCWs	23	[30]

assumed to be homogeneous, that is, the free-living bacteria are uniformly distributed in the environment. Patients are admitted to the hospital at a total rate $\Omega(t)$ from any of these four compartments with the corresponding fractions θ_u, θ_{uA}, θ_c, θ_{cA}, respectively, and have an average length of stay γ_u^{-1}, γ_{uA}^{-1}, γ_c^{-1}, γ_{cA}^{-1}, respectively. By assuming that the total number of patients in a unit is a constant N_p, we set $\Omega(t) = \gamma_u P_u + \gamma_c P_c + \gamma_{uA} P_{uA} + \gamma_{cA} P_{cA}$. Moreover, uncolonized patients without antibiotic exposure can move to colonized patients without antibiotic exposure either by contacting contaminated HCWs, $\alpha_p \beta_p (1-\eta) P_u H_c$, or by touching the contaminated environment, $\kappa_p P_u B_e$. A similar process occurs when uncolonized patients with antibiotic exposure become colonized patients with antibiotic exposure, $\alpha_p \beta_{pA} (1-\eta) P_{uA} H_c + \kappa_{pA} P_{uA} B_e$. α_p is the contact rate, η is the compliance rate with the hand hygiene, β_p and β_{pA} are the probabilities of colonization for P_u and P_{uA} after a contact with H_c, respectively, κ_p and κ_{pA} are the colonization rates from contaminated environment for P_u and P_{uA}, respectively. To model the seasonal use of antibiotics in hospitals, we assume that patients without antibiotic exposure become patients with antibiotic exposure at a rate of $\epsilon_0(1 + \epsilon_1 \sin(\frac{2\pi}{365}(t - 240)))$, which has a period of 365 days, and this rate increases from the beginning of

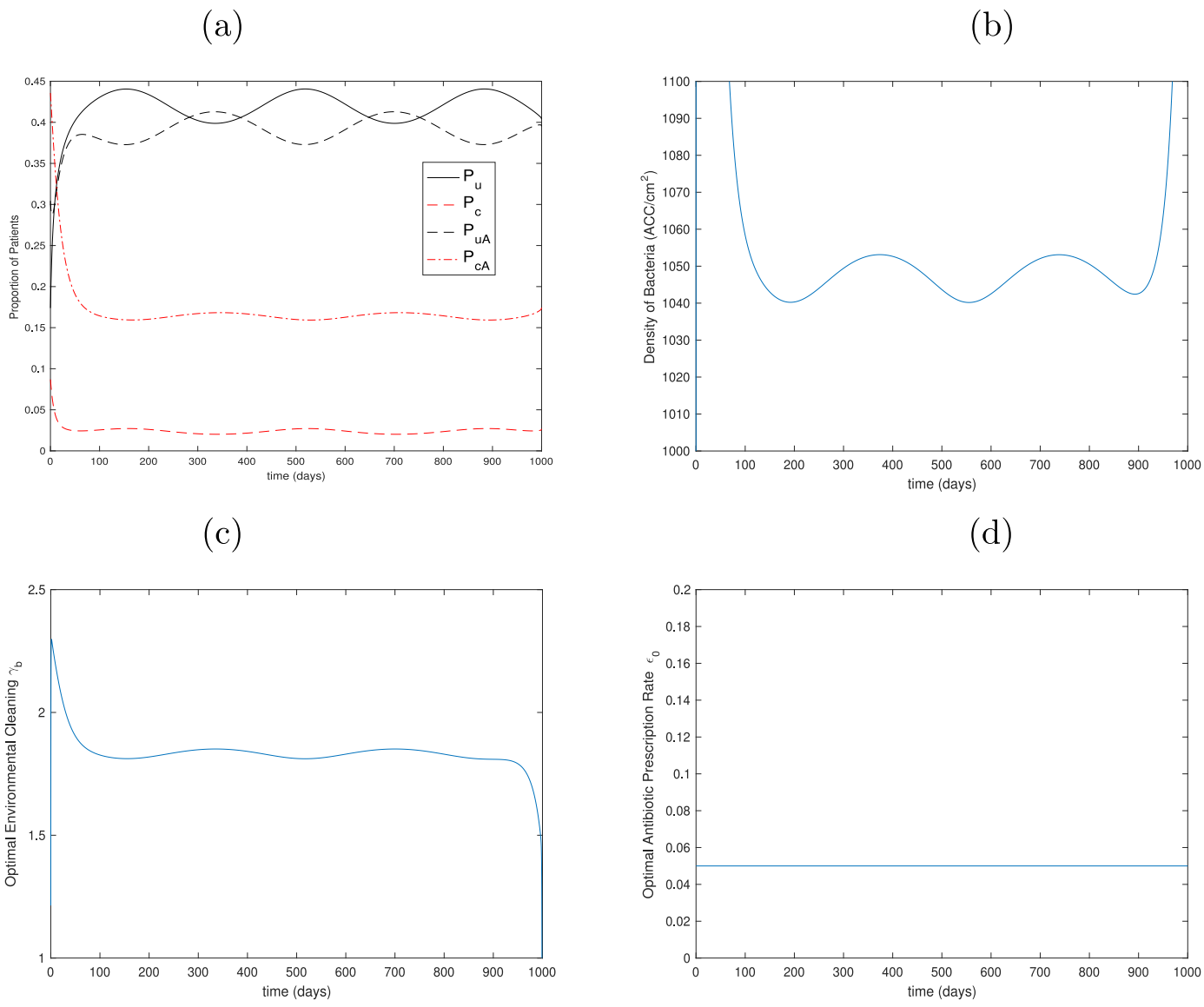

Fig. 3. Baseline model simulations with optimal two-control strategies. (a) Proportion of patients; (b) environmental bacteria density; (c) optimal environmental cleaning rate; (d) optimal antibiotic prescription rate.

August, peaks in winter and decreases from the beginning of February according to the data shown in [26]. ϵ_0 is the baseline antibiotic prescription rate and ϵ_1 is the magnitude of change. Besides, uncontaminated HCWs become contaminated HCWs either by contacting colonized patients or by touching contaminated environmental surfaces, $\alpha_p\beta_h(1-\eta)P_cH_u + \alpha_p\beta_{hA}(1-\eta)P_{cA}H_u$. β_h and β_{hA} are the probability of contamination for HCWs after a contact with P_c and P_{cA}, respectively. Contaminated HCWs have a decontamination rate μ_cH_c every day. The total number of HCWs is also a constant $N_h = H_u + H_c$. In addition, colonized patients shed bacteria at a rate of $\upsilon_pP_c + \upsilon_{pA}P_{cA}$, where υ_p and υ_{pA} are the bacteria shedding rate of patients without and with antibiotic exposure, respectively. Contaminated HCWs touching environmental surfaces is another way of environmental contamination, which happens at a rate of υ_hH_c. We denote γ_b as the environmental disinfection rate.

The model in [16,17] strongly suggests that environmental cleaning is the most important intervention and antibiotic usage is also necessary for the control of MRSA infections. Our goal here is to find optimal cost-effective strategies of environmental cleaning and antibiotic use. Therefore, we identify ϵ_0, γ_b as functions of time, then $\epsilon_0(t)$, $\gamma_b(t)$ are our control variables, we hence formulate the model as follows [17]:

$$\frac{dP_u}{dt} = \theta_u\Omega(t) - \alpha_p\beta_p(1-\eta)P_uH_c - \kappa_pP_uB_e - \gamma_uP_u - \epsilon_0(t)\left(1+\epsilon_1\sin\left(\frac{2\pi}{365}(t-240)\right)\right)P_u, \tag{1}$$

$$\begin{aligned}
\frac{dP_c}{dt} &= \theta_c\Omega(t) + \alpha_p\beta_p(1-\eta)P_uH_c + \kappa_pP_uB_e - \gamma_cP_c - \epsilon_0(t)\left(1+\epsilon_1\sin\left(\frac{2\pi}{365}(t-240)\right)\right)P_c,\\
\frac{dP_{uA}}{dt} &= \theta_{uA}\Omega(t) - \alpha_p\beta_{pA}(1-\eta)P_{uA}H_c - \kappa_{pA}P_{uA}B_e - \gamma_{uA}P_{uA}\\
&\quad + \epsilon_0(t)\left(1+\epsilon_1\sin\left(\frac{2\pi}{365}(t-240)\right)\right)P_u,\\
\frac{dP_{cA}}{dt} &= \theta_{cA}\Omega(t) + \alpha_p\beta_{pA}(1-\eta)P_{uA}H_c + \kappa_{pA}P_{uA}B_e - \gamma_{cA}P_{cA}\\
&\quad + \epsilon_0(t)\left(1+\epsilon_1\sin\left(\frac{2\pi}{365}(t-240)\right)\right)P_c,\\
\frac{dH_u}{dt} &= -\alpha_p\beta_h(1-\eta)P_cH_u - \alpha_p\beta_{hA}(1-\eta)P_{cA}H_u - \kappa_hH_uB_e + \mu_cH_c,\\
\frac{dH_c}{dt} &= \alpha_p\beta_h(1-\eta)P_cH_u + \alpha_p\beta_{hA}(1-\eta)P_{cA}H_u + \kappa_hH_uB_e - \mu_cH_c,\\
\frac{dB_e}{dt} &= \upsilon_pP_c + \upsilon_{pA}P_{cA} + \upsilon_hH_c - \gamma_b(t)B_e,
\end{aligned} \tag{2}$$

subject to initial values

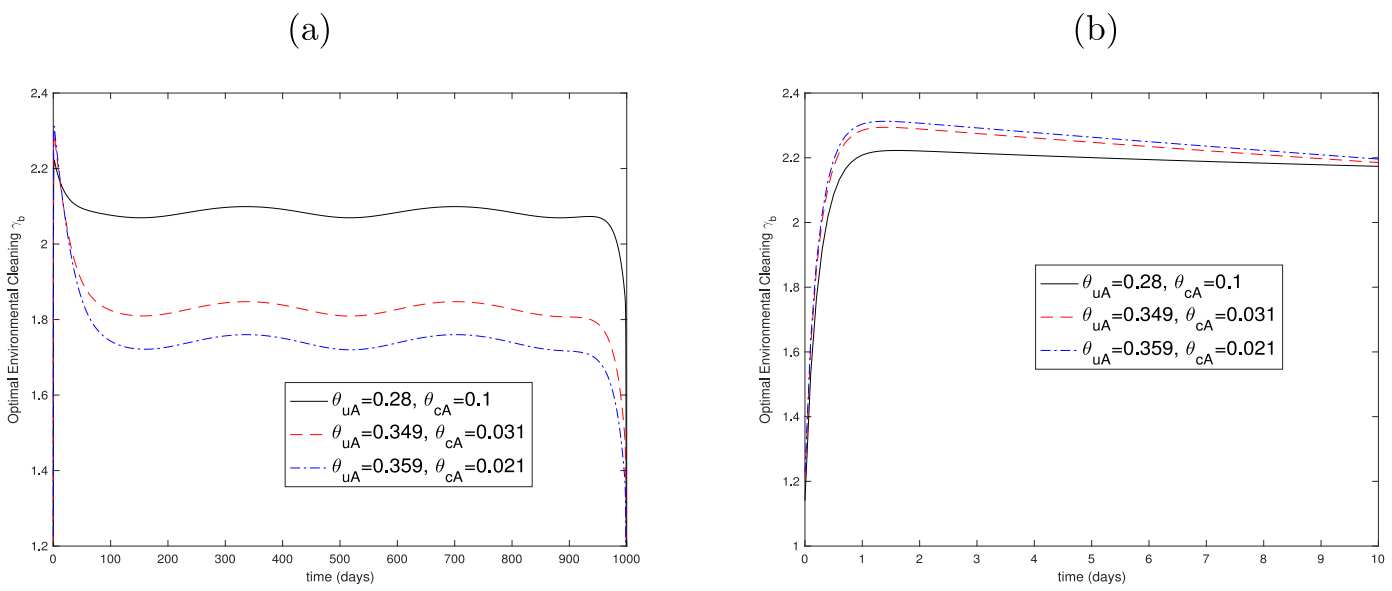

Fig. 4. Optimal control strategies with various colonization ratios upon admission. (a) Optimal environmental cleaning in 1000 days; (b) optimal environmental cleaning in initial 10 days.

$P_u(0) = P_u^0$, $P_{uA}(0) = P_{uA}^0$, $P_c(0) = P_c^0$, $P_{cA}(0) = P_{cA}^0$, $H_u(0) = H_u^0$, $H_c(0) = H_c^0$, $B_e(0) = B_e^0$,

where $\Omega(t) = \gamma_u P_u(t) + \gamma_c P_c(t) + \gamma_{uA} P_{uA}(t) + \gamma_{cA} P_{cA}(t)$ and $\phi(t) = 1 + \epsilon_1 \sin(\frac{2\pi}{365}(t - 240))$. Parameter interpretations and values are listed in Table 1.

The control set is

$$U := \{u = (\epsilon_0(t), \gamma_b(t)) \mid m_1 \le \epsilon_0(t) \le M_1,\ \ m_2 \le \gamma_b(t) \le M_2,\ \ \textit{Lebesgue measurable}\},$$

where the constants M_1, M_2 (m_1, m_2) are the maximum (mimimum) control efforts for antibiotic prescription rate and disinfection/cleaning rate of environment, respectively.

Our goal is to minimize the objective functional:

$$\begin{aligned}\mathcal{J}(u) = \int_0^T [&a_1 P_c(t) + a_2 P_{cA}(t) + a_3 B_e(t) + b_1(\epsilon_0(t)\phi(t))^2 \\ &+ b_2 \epsilon_0(t)\phi(t) P_u(t) + b_3 \epsilon_0(t)\phi(t) P_c(t) + c_1(\gamma_b(t))^2 \\ &+ c_2 \gamma_b(t) B_e(t)]dt. \end{aligned} \tag{3}$$

The term $a_1 P_c(t) + a_2 P_{cA}(t)$ counts the number of colonized patients without or with antibiotic exposure and $a_3 B_e$ counts the density of bacteria in the environment. $b_1(\epsilon_0(t)\phi(t))^2$ means the nonlinear cost associated with antibiotic use, and $b_2\epsilon_0(t)\phi(t)P_u(t) + b_3\epsilon_0(t)\phi(t)P_c(t)$ represents the linear cost associated with antibiotic use. Similarly, $c_1(\gamma_b(t))^2$ and $c_2\gamma_b(t)B_e(t)$ represent the nonlinear and linear cost of environmental cleaning, respectively. All the coefficients a_i, b_i, and c_j, $i = 1, \ldots, 3$, $j = 1, 2$, are nonnegative, representing weights on the different terms of objective functional. We aim at minimizing the numbers of colonized patients, the density of bacteria in the environment, and the cost associated with environmental cleaning and antibiotic use in a particular time period.

3. Optimal control

In order to use the Pontryagin's Maximum Principle [23], we must first verify the existence of an optimal control [18,25].

Theorem 3.1. *There exists an optimal control vector $u^* = (\epsilon_0^*, \gamma_b^*) \in U$ with the corresponding state solutions $x^* = (P_u^*, P_{uA}^*, P_c^*, P_{cA}^*, H_u^*, H_c^*, B_e^*)$ that minimizes the objective functional $\mathcal{J}(u)$ in (3).*

Proof. Firstly we can prove that the solutions of system (2) are nonnegative and uniformly bounded if the initial values are nonnegative [16,17]. It is easily seen that the objective functional values are nonnegative, i.e., the objective functional is bounded below. So there exists a minimizing sequence of controls $u^k = (\epsilon_0^k, \gamma_b^k) \in U$ such that

$$\lim_{k\to\infty} \mathcal{J}(u^k) = \inf_{u\in U} \mathcal{J}(u).$$

The controls in U are uniformly bounded in L^∞, which implies uniform boundedness in $L^2([0, T])$. Since the space $L^2([0, T])$ is reflexive [24], there exists $u^* = (\epsilon_0^*, \gamma_b^*) \in U$ such that on a subsequence,

$$\epsilon_0^k \rightharpoonup \epsilon_0^*,\ \ \gamma_b^k \rightharpoonup \gamma_b^* \text{ weakly in } L^2([0, T]) \text{ as } k \to \infty.$$

Next, it is obvious that the state sequence $x^k = (P_u^k, P_{uA}^k, P_c^k, P_{cA}^k, H_u^k, H_c^k, B_e^k)$ corresponding to the minimizing sequence of controls u^k is also uniformly bounded. Moreover, the right-hand sides of system (2) are uniformly bounded, which gives us uniformly bounded derivatives for x^k. Hence the corresponding state sequence x^k is equicontinuous. According to the Arzelà-Ascoli Theorem, there exists $x^* = (P_u^*, P_{uA}^*, P_c^*, P_{cA}^*, H_u^*, H_c^*, B_e^*)$ such that on a subsequence,

$$x^k \to x^* \text{ uniformly on } [0, T].$$

Finally, by choosing the proper subsequence and passing the limit to system (2), we are able to obtain that x^* is the state solution corresponding to the control u^*. Based on the lower semi-continuity of the L^2 − norm with respect to L^2 weak convergence, we have

$$\inf_{u\in U} \mathcal{J}(u) = \lim_{k\to\infty} \mathcal{J}(u^k) \ge \mathcal{J}(u^*).$$

Hence, u^* is an optimal control. □

Theorem 3.2. *Given an optimal control vector $u^* = (\epsilon_0^*, \gamma_b^*) \in U$ and the corresponding state solutions $x^* = (P_u^*, P_{uA}^*, P_c^*, P_{cA}^*, H_u^*, H_c^*, B_e^*)$ in system (2), there exist adjoint variables $\lambda_i(t)$, $i = 1, \ldots, 7$, satisfying*

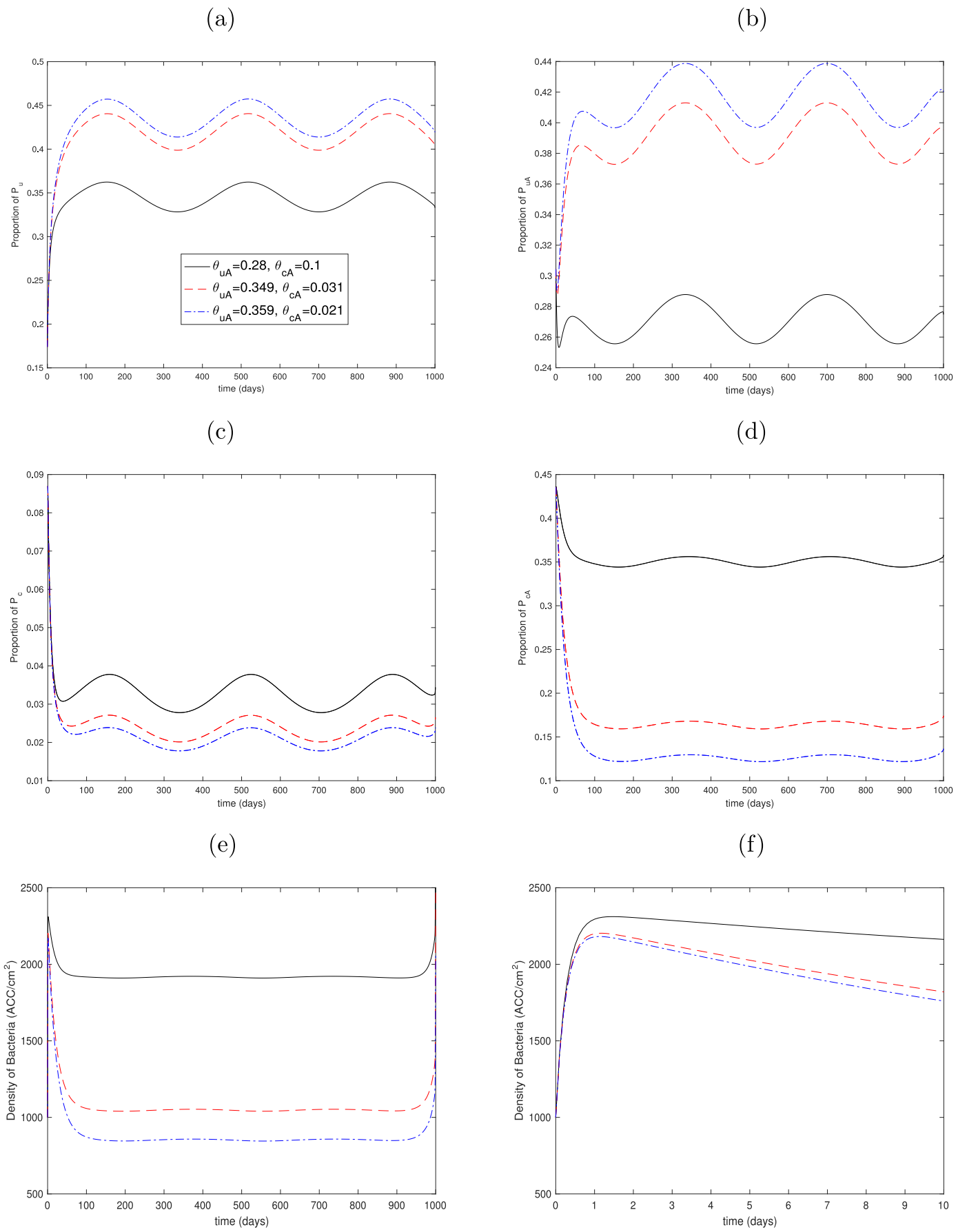

Fig. 5. Control results with various colonization ratios upon admission corresponding to optimal control strategy shown in Fig. 4. (a) Proportion of uncolonized patients without antibiotic exposures; (b) proportion of uncolonized patients with antibiotic exposures; (c) proportion of colonized patients without antibiotic exposures; (d) proportion of colonized patients with antibiotic exposures; (e) density of bacteria in 1000 days; (f) density of bacteria in initial 10 days.

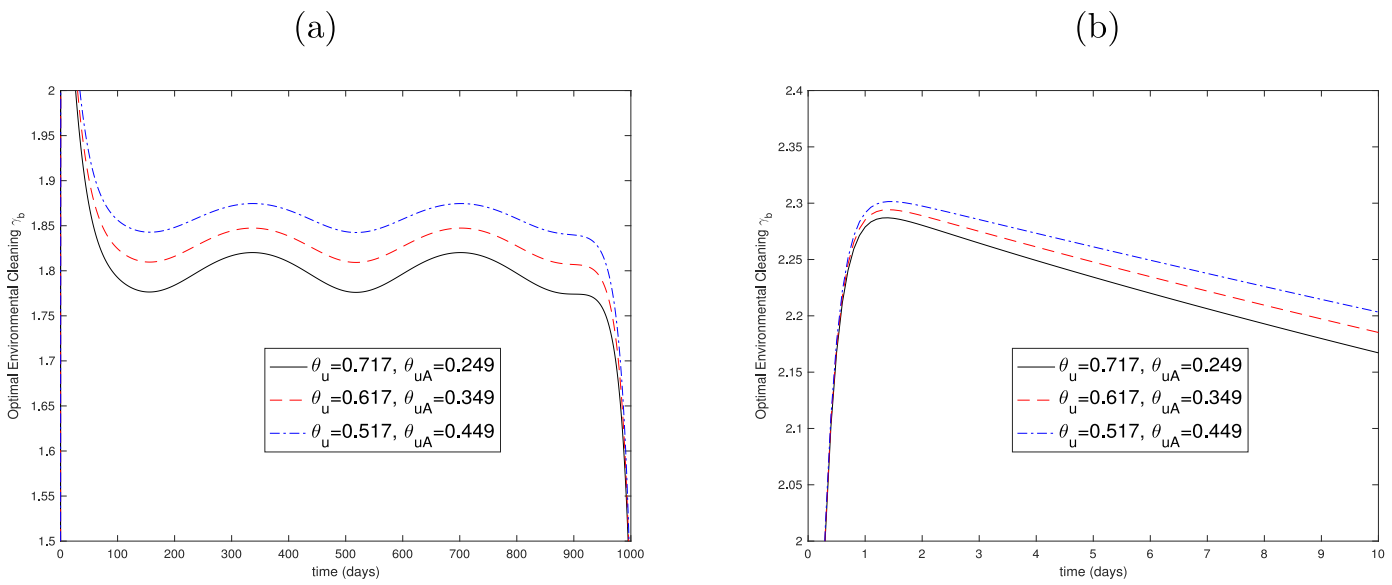

Fig. 6. Optimal control strategies with various antibiotic exposure ratios upon admission. (a) Optimal environmental cleaning in 1000 days; (b) optimal environmental cleaning in initial 10 days.

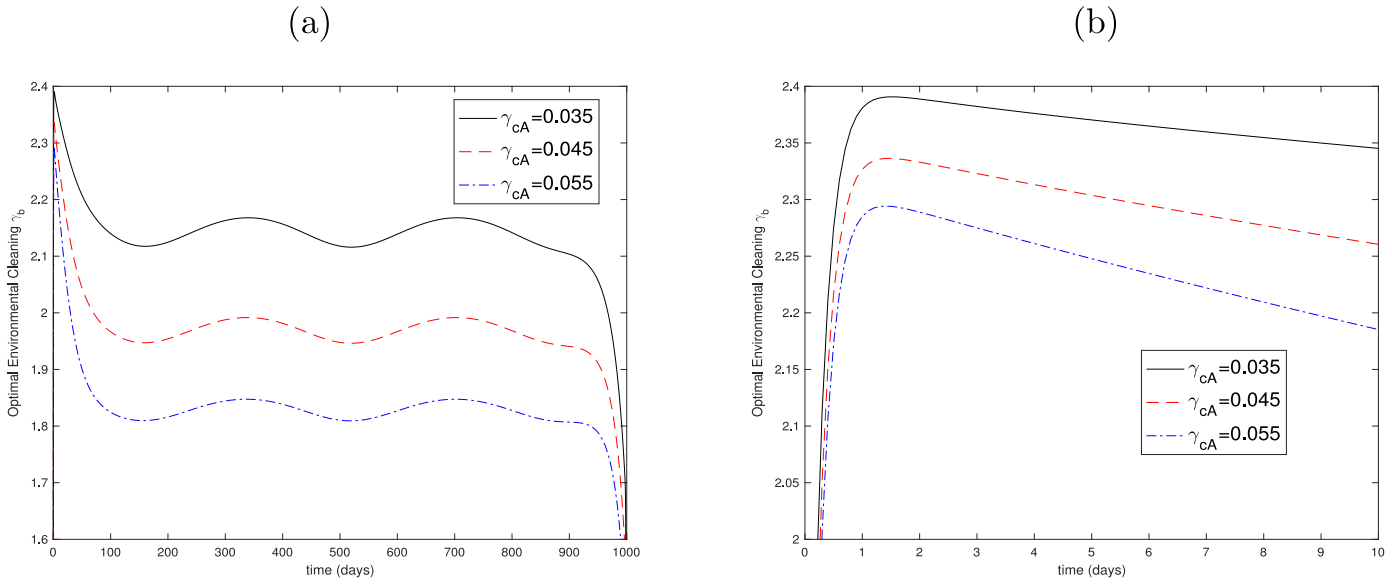

Fig. 7. Optimal control strategies with various discharge rates for colonized patients with antibiotic exposures. (a) Optimal environmental cleaning in 1000 days; (b) optimal environmental cleaning in initial 10 days.

$$\begin{aligned}\lambda_1' &= -b_2\epsilon_0(t)\phi(t) - \lambda_1[\theta_u\gamma_u - \alpha_p\beta_p(1-\eta)H_c - \kappa_pB_e - \gamma_u - \epsilon_0(t)\phi(t)] \\ &\quad - \lambda_2[\theta_c\gamma_u + \alpha_p\beta_p(1-\eta)H_c + \kappa_pB_e] - \lambda_3[\theta_{uA}\gamma_u + \epsilon_0(t)\phi(t)] \\ &\quad - \lambda_4\theta_{cA}\gamma_u,\end{aligned} \tag{4}$$

$$\begin{aligned}\lambda_2' &= -a_1 - b_3\epsilon_0(t)\phi(t) - \lambda_1\theta_u\gamma_c - \lambda_2[\theta_c\gamma_c - \gamma_c - \epsilon_0(t)\phi(t)] - \lambda_3\theta_{uA}\gamma_c \\ &\quad - \lambda_4[\theta_{cA}\gamma_c + \epsilon_0(t)\phi(t)] + \lambda_5\alpha_p\beta_h(1-\eta)H_u - \lambda_6\alpha_p\beta_h(1-\eta)H_u \\ &\quad - \lambda_7\upsilon_p,\end{aligned} \tag{5}$$

$$\begin{aligned}\lambda_3' &= -\lambda_1\theta_u\gamma_{uA} - \lambda_2\theta_c\gamma_{uA} - \lambda_3[\theta_{uA}\gamma_{uA} - \alpha_p\beta_{pA}(1-\eta)H_c - \kappa_{pA}B_e - \gamma_{uA}] \\ &\quad - \lambda_4[\theta_{cA}\gamma_{uA} + \alpha_p\beta_{pA}(1-\eta)H_c + \kappa_{pA}B_e],\end{aligned} \tag{6}$$

$$\begin{aligned}\lambda_4' &= -a_2 - \lambda_1\theta_u\gamma_{cA} - \lambda_2\theta_c\gamma_{cA} - \lambda_3\theta_{uA}\gamma_{cA} - \lambda_4[\theta_{cA}\gamma_{cA} - \gamma_{cA}] \\ &\quad + \lambda_5\alpha_p\beta_{hA}(1-\eta)H_u - \lambda_6\alpha_p\beta_{hA}(1-\eta)H_u - \lambda_7\upsilon_{pA},\end{aligned} \tag{7}$$

$$\begin{aligned}\lambda_5' &= \lambda_5[\alpha_p\beta_h(1-\eta)P_c + \alpha_p\beta_{hA}(1-\eta)P_{cA} + \kappa_hB_e] \\ &\quad - \lambda_6[\alpha_p\beta_h(1-\eta)P_c + \alpha_p\beta_{hA}(1-\eta)P_{cA} + \kappa_hB_e],\end{aligned} \tag{8}$$

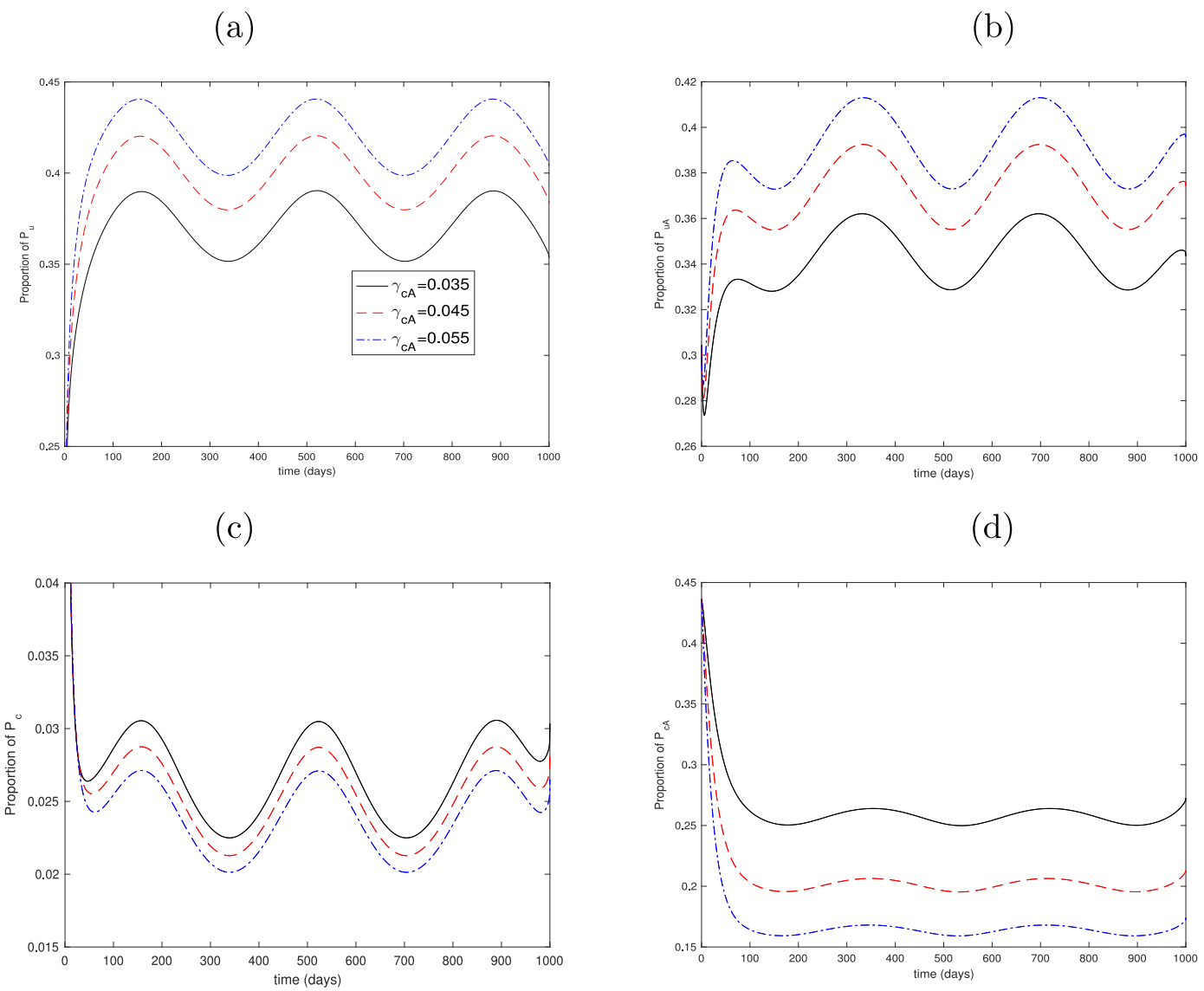

Fig. 8. Control results with various discharge rates for colonized patients with prior antibiotic exposures corresponding to optimal control strategy shown in Fig. 7. (a) Proportion of uncolonized patients without antibiotic exposures; (b) proportion of uncolonized patients with antibiotic exposures; (c) proportion of colonized patients without antibiotic exposures; (d) proportion of colonized patients with antibiotic exposures.

$$\begin{aligned}\lambda_6' &= \lambda_1\alpha_p\beta_p(1-\eta)P_u - \lambda_2\alpha_p\beta_p(1-\eta)P_u + \lambda_3\alpha_p\beta_{pA}(1-\eta)P_{uA}\\ &\quad - \lambda_4\alpha_p\beta_{pA}(1-\eta)P_{uA} - \lambda_5\mu_c + \lambda_6\mu_c - \lambda_7\upsilon_h,\end{aligned} \tag{9}$$

$$\begin{aligned}\lambda_7' &= -a_3 - c_2\gamma_b(t) + \lambda_1\kappa_p P_u - \lambda_2\kappa_p P_u + \lambda_3\kappa_{pA}P_{uA} - \lambda_4\kappa_{pA}P_{uA}\\ &\quad + \lambda_5\kappa_h H_u - \lambda_6\kappa_h H_u + \lambda_7\gamma_b(t)\end{aligned} \tag{10}$$

with the transversality conditions:

$$\lambda_i(T) = 0, \quad i = 1, \ldots, 7. \tag{11}$$

Furthermore, the optimal control vector is given by $u^* = (\epsilon_0(t)^*, \gamma_b(t)^*)$, *where*

$$\epsilon_0(t)^* = \min\left\{\max\left\{m_1, \frac{(\lambda_1-\lambda_3-b_2)P_u(t) + (\lambda_2-\lambda_4-b_3)P_c(t)}{2b_1\phi(t)}\right\}, M_1\right\}, \tag{12}$$

$$\gamma_b(t)^* = \min\left\{\max\left\{m_2, \frac{(\lambda_7-c_2)B_e(t)}{2c_1}\right\}, M_2\right\}. \tag{13}$$

Proof. By the Pontryagin's Maximum Principle, we obtain the Hamiltonian as follows:

$$\begin{aligned}\mathcal{H} = {} & a_1P_c + a_2P_{cA} + a_3B_e + b_1(\epsilon_0(t)\phi(t))^2 + b_2\epsilon_0(t)\phi(t)P_u\\ & + b_3\epsilon_0(t)\phi(t)P_c + c_1(\gamma_b(t))^2 + c_2\gamma_b(t)B_e(t)\\ & + \lambda_1[\theta_u\Omega(t) - \alpha_p\beta_p(1-\eta)P_uH_c - \kappa_pP_uB_e - \gamma_uP_u - \epsilon_0(t)\phi(t)P_u,\ ]\\ & + \lambda_2[\theta_c\Omega(t) + \alpha_p\beta_p(1-\eta)P_uH_c + \kappa_pP_uB_e - \gamma_cP_c - \epsilon_0(t)\phi(t)P_c]\\ & + \lambda_3[\theta_{uA}\Omega(t) - \alpha_p\beta_{pA}(1-\eta)P_{uA}H_c - \kappa_{pA}P_{uA}B_e - \gamma_{uA}P_{uA}\\ & \quad + \epsilon_0(t)\phi(t)P_u]\\ & + \lambda_4[\theta_{cA}\Omega(t) + \alpha_p\beta_{pA}(1-\eta)P_{uA}H_c + \kappa_{pA}P_{uA}B_e - \gamma_{cA}P_{cA}\\ & \quad + \epsilon_0(t)\phi(t)P_c]\\ & + \lambda_5[-\alpha_p\beta_h(1-\eta)P_cH_u - \alpha_p\beta_{hA}(1-\eta)P_{cA}H_u - \kappa_hH_uB_e + \mu_cH_c]\\ & + \lambda_6[\alpha_p\beta_h(1-\eta)P_cH_u + \alpha_p\beta_{hA}(1-\eta)P_{cA}H_u + \kappa_hH_uB_e - \mu_cH_c]\\ & + \lambda_7[\upsilon_pP_c + \upsilon_{pA}P_{cA} + \upsilon_hH_c - \gamma_b(t)B_e],\end{aligned} \tag{14}$$

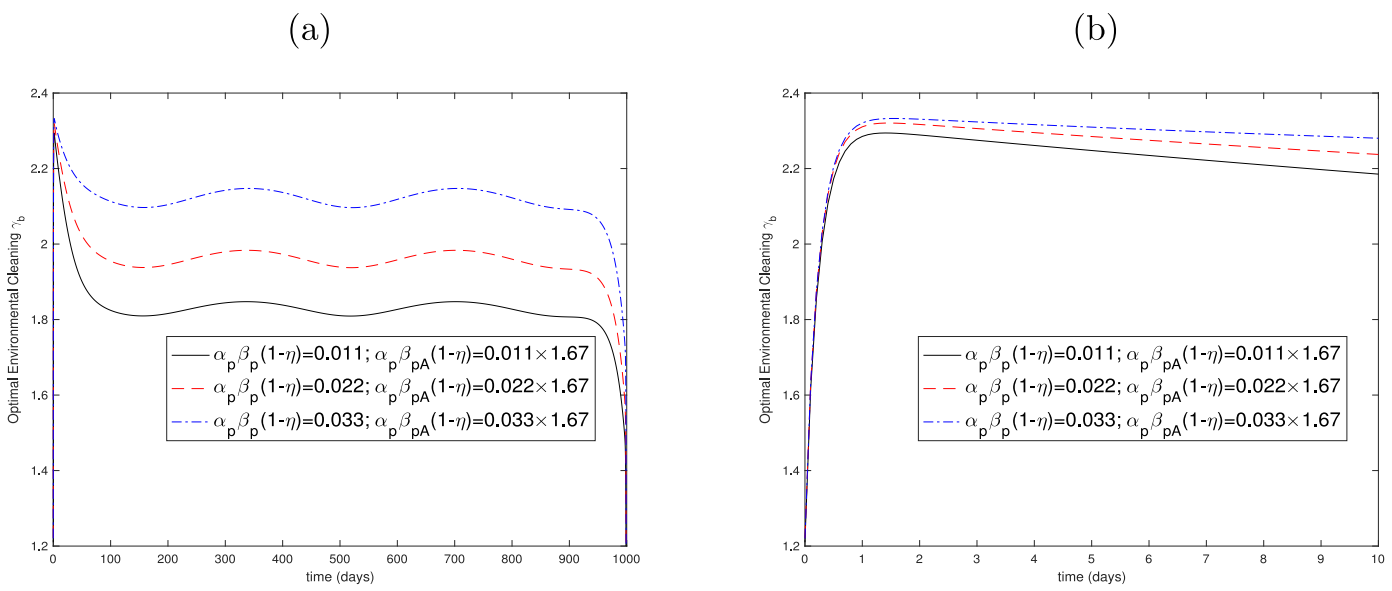

Fig. 9. Optimal control strategies with various transmission rates. (a) Optimal environmental cleaning in 1000 days; (b) optimal environmental cleaning in initial 10 days.

where $\phi(t) = 1 + \epsilon_1 \sin(\frac{2\pi}{365}(t - 240))$ and $\Omega(t) = \gamma_u P_u(t) + \gamma_c P_c(t) + \gamma_{uA} P_{uA}(t) + \gamma_{cA} P_{cA}(t)$.

We define adjoint variables $\lambda_i(t)$, $i = 1, \ldots, 7$, by:

$$\lambda_1' = -\frac{\partial \mathcal{H}}{\partial P_u}, \quad \lambda_2' = -\frac{\partial \mathcal{H}}{\partial P_c}, \quad \lambda_3' = -\frac{\partial \mathcal{H}}{\partial P_{uA}}, \quad \lambda_4' = -\frac{\partial \mathcal{H}}{\partial P_{cA}},$$

$$\lambda_5' = -\frac{\partial \mathcal{H}}{\partial H_u}, \quad \lambda_6' = -\frac{\partial \mathcal{H}}{\partial H_c}, \quad \lambda_7' = -\frac{\partial \mathcal{H}}{\partial B_e}$$

with the transversality conditions $\lambda_i(T) = 0, \quad i = 1, \ldots, 7$. We obtain the characterization of optimal controls by letting:

$$\frac{\partial \mathcal{H}}{\partial \epsilon_0(t)} = 0, \quad \frac{\partial \mathcal{H}}{\partial \gamma_b(t)} = 0.$$

From $\partial \mathcal{H}/\partial \epsilon_0(t) = 0$, we have

$$2b_1(\phi(t))^2\epsilon_0(t) + b_2\phi(t)P_u + b_3\phi(t)P_c - \lambda_1\phi(t)P_u - \lambda_2\phi(t)P_c + \lambda_3\phi(t)P_u + \lambda_4\phi(t)P_c = 0,$$

which implies that

$$\epsilon_0(t) = \frac{(\lambda_1 - \lambda_3 - b_2)P_u(t) + (\lambda_2 - \lambda_4 - b_3)P_c(t)}{2b_1\phi(t)},$$

where $\phi(t) = 1 + \epsilon_1 \sin(\frac{2\pi}{365}(t - 240))$ would never be 0 for all t. From $\partial \mathcal{H}/\partial \gamma_b(t) = 0$, we have

$$2c_1\gamma_b(t) + c_2 B_e - \lambda_7 B_e = 0,$$

which implies that

$$\gamma_b(t) = \frac{(\lambda_7 - c_2)B_e(t)}{2c_1}.$$

By taking the upper and lower bounds for $\epsilon_0(t)$ and $\gamma_b(t)$ into account, we have the following characterization of the optimal controls:

$$\epsilon_0(t)^* = \min\left\{\max\left\{m_1, \frac{(\lambda_1 - \lambda_3 - b_2)P_u(t) + (\lambda_2 - \lambda_4 - b_3)P_c(t)}{2b_1\phi(t)}\right\}, M_1\right\},$$

$$\gamma_b(t)^* = \min\left\{\max\left\{m_2, \frac{(\lambda_7 - c_2)B_e(t)}{2c_1}\right\}, M_2\right\}.$$

This completes the proof. □

4. Numerical results

Without any control strategies for 1000 days, Fig. 2 represents the proportions of uncolonized patients without or with antibiotic exposure, colonized patients without or with antibiotic exposure and density of bacteria in the environment, respectively, based on the parameter values in Table 1 and initial values $(P_u^0, P_{uA}^0, P_c^0, P_{cA}^0, H_u^0, H_c^0, B_e^0) = (4, 2, 7, 10, 17, 6, 1000)$.

Next, we introduce optimal control strategies into our system. According to Lenhart and Workman [20], a Forward-Backward Sweep method is used to solve such optimal control problems numerically. Roughly speaking, we first divide the time interval $[0, T]$ into equal parts and make an initial guess for control values. By using a Runge-Kutta 4 (RK4) routine, we are able to solve the state system in (2) forward in time with the given initial values. After that, based on the initial guess of control values, the values of state system solutions obtained and the transversality conditions of adjoint variables, we can solve the adjoint system (3)-(9) backward in time by RK4. Then, we update our control value by entering the new state and adjoint values into the characterization of the control in (11)(12). Finally, a convergence test is conducted and the recurrent process will not stop until values converge sufficiently.

4.1. Optimal control with baseline control parameters

Since we do not have enough data on the detailed cost, we choose the values of our weighted coefficients, a_i $(i = 1, 2, 3)$, b_i $(i = 1, 2, 3)$, c_i $(i = 1, 2)$, by comparing the relative size of each term without being multiplied by the corresponding values of their weighted coefficients in the objective functional (3). In particular, by observing that the linear cost associated with environmental cleaning, given as $\gamma_b(t)B_e$, and the density of bacteria, B_e, are relatively large in comparison to the other

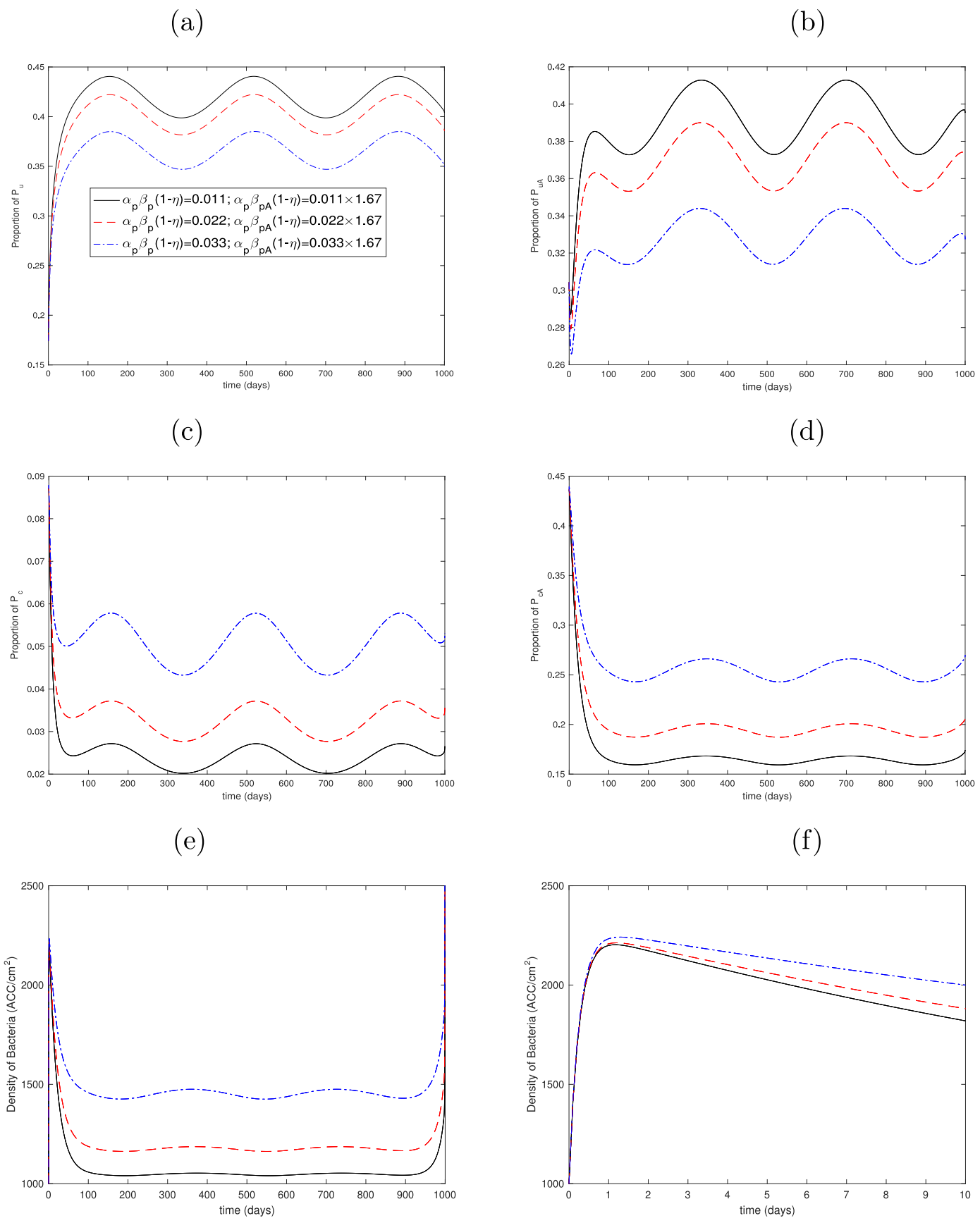

Fig. 10. Control results with various transmission rates corresponding to optimal 2-control strategies shown in Fig. 9. (a) Proportion of uncolonized patients without antibiotic exposures; (b) proportion of uncolonized patients with antibiotic exposures; (c) proportion of colonized patients without antibiotic exposures; (d) proportion of colonized patients with antibiotic exposures; (e) density of bacteria in 1000 days; (f) density of bacteria in initial 10 days.

terms, we choose their weighted coefficients, a_3 and c_2, to be relatively small in comparison to the remaining coefficients. Similarly, we choose b_1, b_2 and b_3 to be relatively large in comparison to the remaining coefficients. We believe that, once the detailed data is known, it can be incorporated into the appropriate values of control parameters to get a more realistic result. Therefore, we choose $a_1 = a_2 = 1$, $a_3 = 0.015$, $c_1 = 5$, $b_1 = 50$, $b_2 = b_3 = 10$, $c_2 = 0.01$ as the baseline weights in the objective functional (3). We choose the upper and lower bounds of the cleaning rate and antibiotic prescription rate based on their baseline values in Table 1: $m_1 = 0.05$, $M_1 = 0.12$, $m_2 = 0.5$, $M_2 = 10$.

Fig. 3 gives us the results of optimal two-control strategies. Comparing to the case with no control as shown in Fig. 2, the percentage of colonized patients with antibiotic exposure P_{cA} is reduced from 35% ~ 40% to 15% ~ 20%, as well as the density of bacteria in the environment. Moreover, we observe that the optimal environmental cleaning rate $\gamma_b(t)$ has a similar seasonal pattern as P_{cA} and B_e, which implies that hospitals should be aware of intensifying their cleansing efforts during the peak period of antibiotic prescription. In the following subsections, we focus on exploring how hospitals should adjust their environmental cleaning strategy when different hospital and community scenarios happen. Justification of control parameters and initial values is presented in the Appendix.

4.2. Impacts of community situations on control strategies

First, we investigate the impacts of the colonization level in the community. To do this, we increase the fraction of colonized patients with antibiotic exposure on admission, θ_{cA}, and decrease the fraction of uncolonized patients with antibiotic exposure on admission, θ_{uA}, with $\theta_{uA} + \theta_{cA} = 0.38$, i.e., the fraction of patients with antibiotic exposure of new admission is always equal to 0.38 [6,15]. That is to say, antibiotic use in the community does not change, but more patients with antibiotic exposure are colonized in the community. Figs. 4 and 5 show that hospitals should pay more attention to the environmental cleaning when the colonization ratio is higher in the community level. However, optimized cleaning would not reduce the proportion of P_{cA} and the density of bacteria in the environment to levels comparable with those lower colonized communities. Hence, even though environmental cleaning is the most effective intervention as suggested in [17], it is not enough to only consider environmental cleaning. To reduce θ_{cA}, one way is to highlight the public education about how to prevent MRSA infections in the community, such as maintaining good hand and body hygiene especially after exercise, avoiding sharing personal items such as towels and razors, keeping scrapes and wounds clean and covered until healed [5], the other way is to increase active screening on admission and isolation of positive cases.

Second, we study the influences of community-level antibiotic prescription rates. We increase the fraction of uncolonized patients with antibiotic exposure on admission, θ_{uA}, and decrease the fraction of uncolonized patients without antibiotic exposure on admission, θ_u, with θ_c and θ_{cA} fixed. That is to say, the number of colonized patients in the community does not change, while, more antibiotics are used in the community. Fig. 6 implies that enhanced cleaning efforts are needed for communities with high prescription rates.

4.3. Impacts of lengthened hospital stays on control strategies

As discussed above, it was observed in many studies that colonized patients with antibiotic exposure tend to have a lengthier stay in hospitals. Our baseline value $\gamma_{cA} = 0.055$ implies that P_{cA} stay in hospitals for about 18 days ($\gamma_{cA}^{-1} = 18.18$). In this subsection, we explore what can happen if P_{cA} have a lengthier stay in hospitals due to lack of the efficient treatment, say 22 days ($\gamma_{cA} = 0.035$), and 28 days ($\gamma_{cA} = 0.035$). Figs. 7 and 8 show that hospitals should increase the environmental cleaning effort corresponding to the lengthier stay of P_{cA}. However, an increase of the percentage of P_{cA} and density of bacteria still occurs, even with an increase of effort to environmental cleaning. Hence, rapid diagnosis and efficient treatment of colonized patients, especially those with prior antibiotic exposures, is also essential in controlling MRSA infections.

4.4. Impacts of transmission rate between patients and HCWs on control strategies

Another scenario we consider is an increase in the transmission rate between patients and HCWs, $\alpha_p\beta_p(1-\eta)$ and $\alpha_p\beta_{pA}(1-\eta)$. Such an increase occurs for many reasons, one of which being an understaffed hospital where HCWs may not follow proper rules such as adequate washing of hands and wearing of gloves when necessary. Fig. 9 shows how such an increase in $\alpha_p\beta_p(1-\eta)$ and $\alpha_p\beta_{pA}(1-\eta)$ affects the optimal environmental cleaning, where $\alpha_p\beta_p(1-\eta) = 0.011$ and $\alpha_p\beta_{pA}(1-\eta) = 0.011 \times 1.67$ are our original choices. As expected, we should increase the environmental cleaning rate. The resulting solutions are illustrated in Fig. 10 for the increased transmission rate. In particular, the proportions of P_c, P_{cA} and density of bacteria increase even though an increase of environmental cleaning is applied. Hence, preventing the direct transmission between HCWs and patients is also crucial in the control of MRSA infections.

5. Conclusion and discussion

As one of the most common causes of hospital-acquired infections, especially in intensive care units, MRSA, which is resistant to multiple commonly used antibiotics, calls for attention to find effective strategies for prevention. In our previous work [16,17], numerical simulations strongly suggest that environmental cleaning is the most important intervention to control MRSA infections, which gives us another way to control MRSA infections. Hospitals should use more effective products, enhance the monitoring of cleaning by ongoing assessments and feedbacks, and even use technology (cleaning robots) to supplement the manual cleaning [14]. To better understand how environmental cleaning and antibiotic use affect the transmission and control of MRSA infections in hospitals, we applied the optimal control theory to a seven-compartment system of ordinary differential equations. Our goal was to reduce the number of colonized patients and bacteria in the environment while minimizing the cost associated with environmental cleaning rate and antibiotic use in a particular time period. Characterizations of optimal control strategies were formulated.

Our simulations considered 1000-day time periods since we wanted to observe the seasonality of MRSA infections. Simulation results strongly showed that with our control strategies the percentage of colonized patients with antibiotic exposure P_{cA} reduced dramatically. Hence environmental cleaning is key in the control of MRSA infections. Moreover, according to our observation, the optimal environmental cleaning rate $\gamma_b(t)$ has a similar seasonal pattern as the number of colonized patients with antibiotic exposure, P_{cA}, and the density of bacteria in the environment, B_e, which implies that hospitals should be aware of intensifying their cleansing efforts during peak periods.

Further, we discussed how other hospital and community factors would impact the optimal control strategies and outcomes. On the community level, reducing the MRSA colonization ratio and antibiotic prescription rates will relieve the burden of cleaning efforts in the hospitals regarding controlling nosocomial MRSA transmissions and infections. Upon admission of new patients, screening, decolonization,

and isolation are also considered as effective intervention strategies. Inside the hospital, it is essential to shorten the lengthened stays of colonized patients, especially those who have prior exposures to antibiotics, which implies the importance of rapid diagnosis and efficient treatments.

Last but not least, our model can be enhanced to capture other important features about nosocomial transmissions of bacteria. For the sake of simplicity, we assumed uniformly distributed bacteria density, however, environmental heterogeneity should be considered to make the model assumptions more realistic. To do so, clinical studies on the correlations about bacteria density of different surfaces in the hospitals will be helpful in subdividing the environment into further categories [19,21]. We also assumed constant ratios for different patient status upon admission and related such ratios to the community factors, in reality, this is usually a stochastic process, and we investigated this possibility by using stochastic models in another study [16]. Furthermore, real data on the costs of treating infections, environmental cleaning, as well as penalties on overdosing antibiotics will be helpful in applying the methods of this study to provide cost-effectiveness analysis for certain nosocomial infection containment and antibiotic stewardship programs.

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Appendix. Justification of control parameters and initial values

In order to justify our choice of the control parameters, we vary the value for each control parameter while keeping the values of all others. Firstly, we observe that the optimal antibiotic prescription rate is always equal to the lowest prescription rate, i.e., $\epsilon_0(t) = m_1$, no matter how we

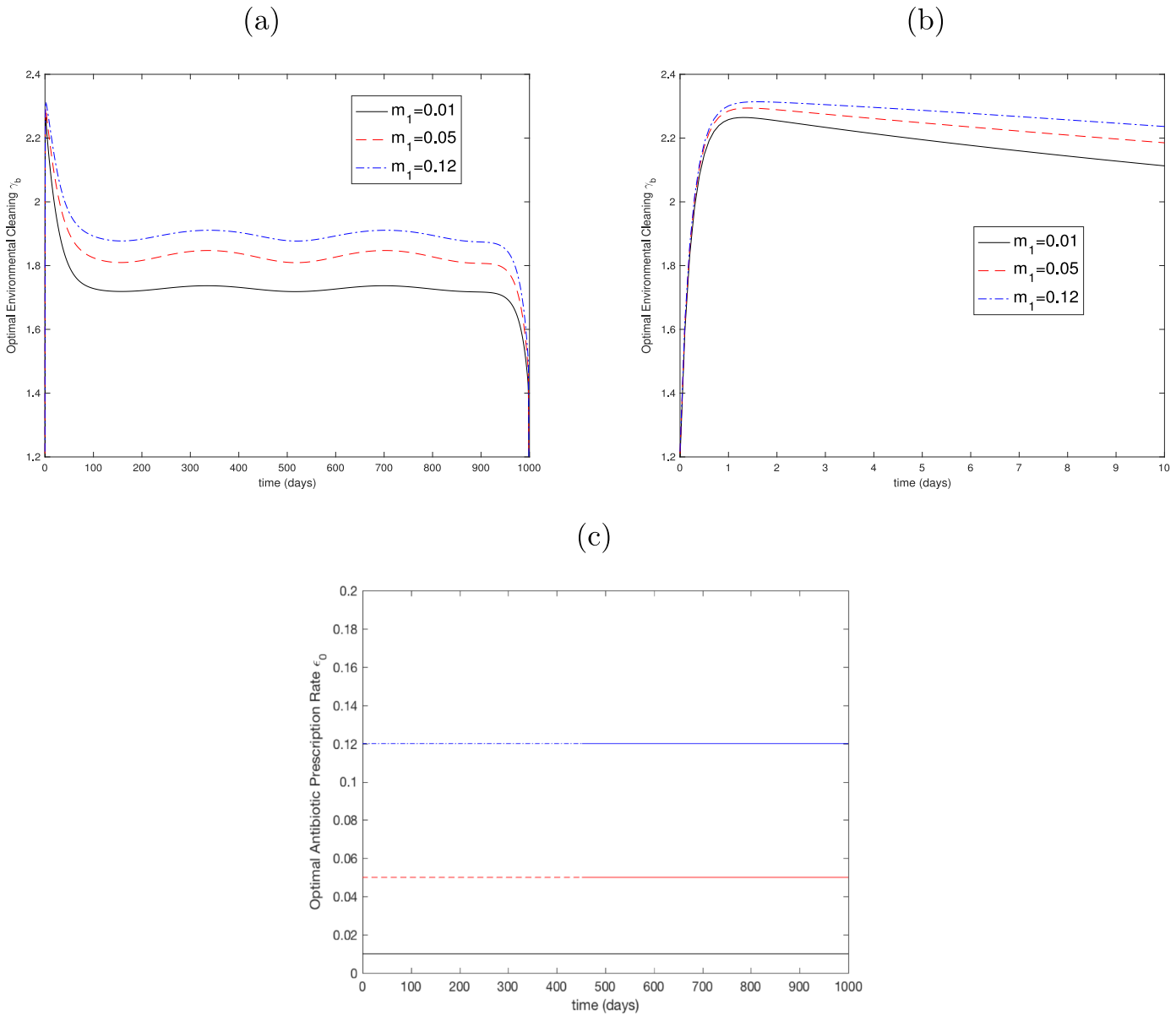

Fig. 11. Optimal control strategies with various m_1 values. (a) Optimal environmental cleaning in 1000 days; (b) optimal environmental cleaning in initial 10 days; (c) optimal antibiotic prescription rate.

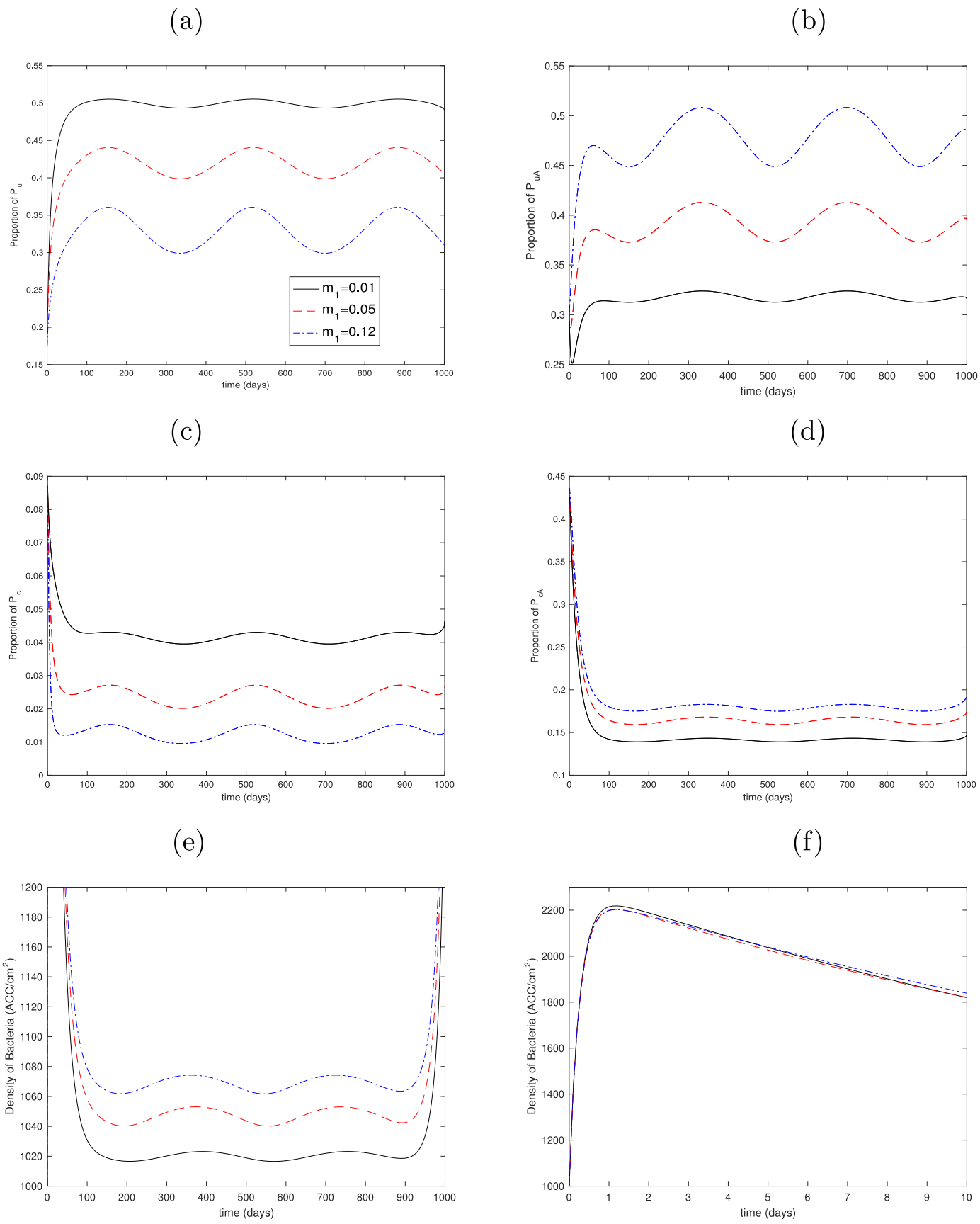

Fig. 12. Control results with various m_1 values corresponding to optimal 2-control strategies shown in Fig. 11. (a) Proportion of uncolonized patients without antibiotic exposures; (b) proportion of uncolonized patients with antibiotic exposures; (c) proportion of colonized patients without antibiotic exposures; (d) proportion of colonized patients with antibiotic exposures; (e) density of bacteria in 1000 days; (f) density of bacteria in initial 10 days.

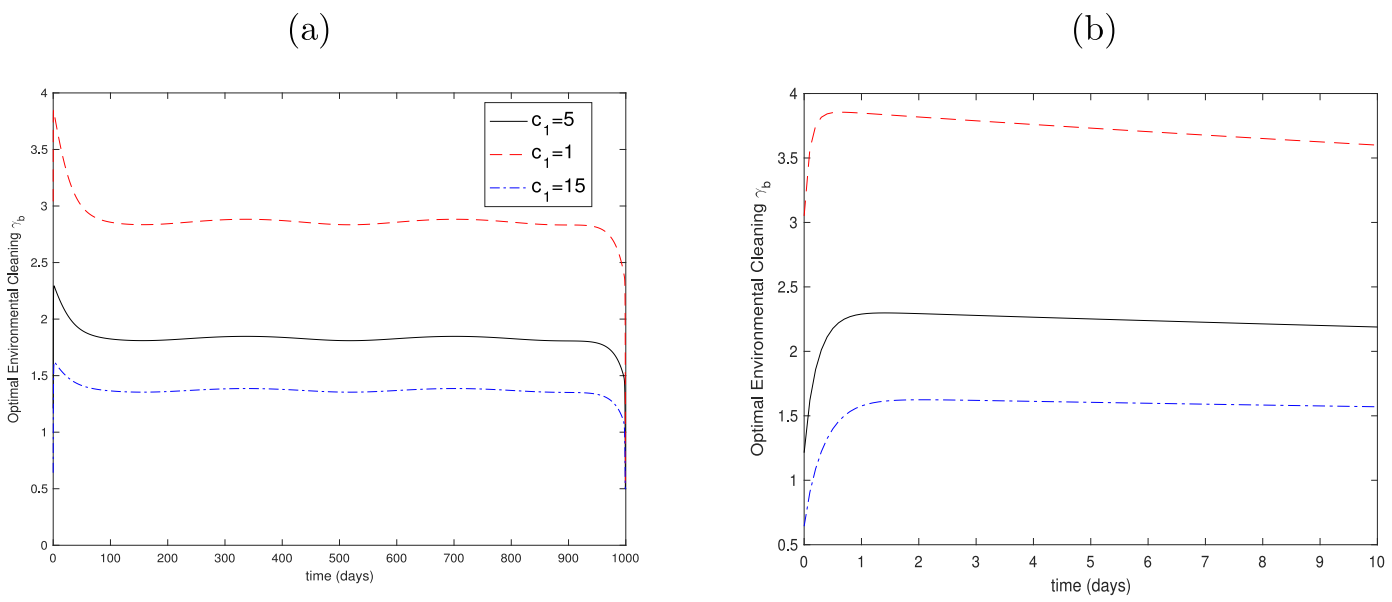

Fig. 13. Optimal control strategies with various c_1 values. (a) Optimal environmental cleaning in 1000 days; (b) optimal environmental cleaning in initial 10 days.

choose m_1. This is not a surprising result: lower antibiotic prescription rate $\epsilon_0(t)$ always leads to increased P_u and P_c, decreased B_e, P_{uA} and P_{cA}, and unchanged $P_c + P_{cA}$, thus all items in the objective functional (3) yield lower values except for $b_2\epsilon_0(t)\phi(t)P_u(t)$ and $b_3\epsilon_0(t)\phi(t)P_c(t)$. Our experimental results show that, except for extremely large weights on b_2 and b_3 (as large as 5,000 with the other weights being their baseline values), smaller $\epsilon_0(t)$ would always lead to smaller objective functional values. Intuitively speaking, our model assumes that a higher prescription rate leads to a higher patient colonization rate, a lengthier hospital stay, and a higher bacteria shedding rate to the environment, so a low prescription rate always help on reducing the value of the cost function. We present some simulations with various m_1 values in Figs. 11 and 12, where we see that the lower antibiotic prescription rate would not only require smaller optimal environmental cleaning rate but also yield less colonized patients and lower cost. Therefore, maintaining the use of antibiotics at the least possible level is essential in the control of MRSA infections.

Secondly, we justify the choices of the key weighted parameters c_1, c_2 and a_3. We vary each of them in a significantly large range around the baseline value, with $c_1 \in [1,\ 15]$, $c_2 \in [0.01,\ 1]$, and $a_3 \in [0.005,\ 0.15]$, and plot the optimal control results with representative values in Figs. 13–17(a), in which no qualitative change in the optimal control results is observed. Thus we consider the control results as robust under reasonable variations of the baseline weighted parameters. Further, in Fig. 17(b), we gradually increase the lower bound for environmental cleaning (m_2) from the baseline value of 0.5 to 2. We observe that there is no difference in the optimal control strategy for m_2 being as large as 1, but the optimal cleaning rate is suggested to be maintained at the least possible value when m_2 exceeds 2, which means that no extra cleaning is needed if the minimum cleaning effort is already good enough. Besides, our optimal control results are still robust under small variations of the minimum cleaning effort as we set our baseline m_2 to be 0.5.

Lastly, we justify our choice of $(P_u^0,\ P_{uA}^0,\ P_c^0,\ P_{cA}^0,\ H_u^0,\ H_c^0,\ B_e^0) = (4,\ 2,\ 7,\ 10,\ 17,\ 6,\ 1000)$ as the initial conditions upon the implementation of the control efforts. The initial bacteria density $B_e^0 = 1000$ is based on data from clinical hygiene evaluation studies in [2,32], and we choose the initial patient and HCW distributions randomly while keeping the total number of patients and HCWs being both 23 to reflect the situation in Beijing Tongren Hospital [29]. We modify our initial distributions of patients and HCWs, as well as bacteria density to generate several other initial conditions and we observe that the optimal control results only differ during the initial period of enforcement and coincide for the long-term period as shown with some representative cases in Fig. 18.

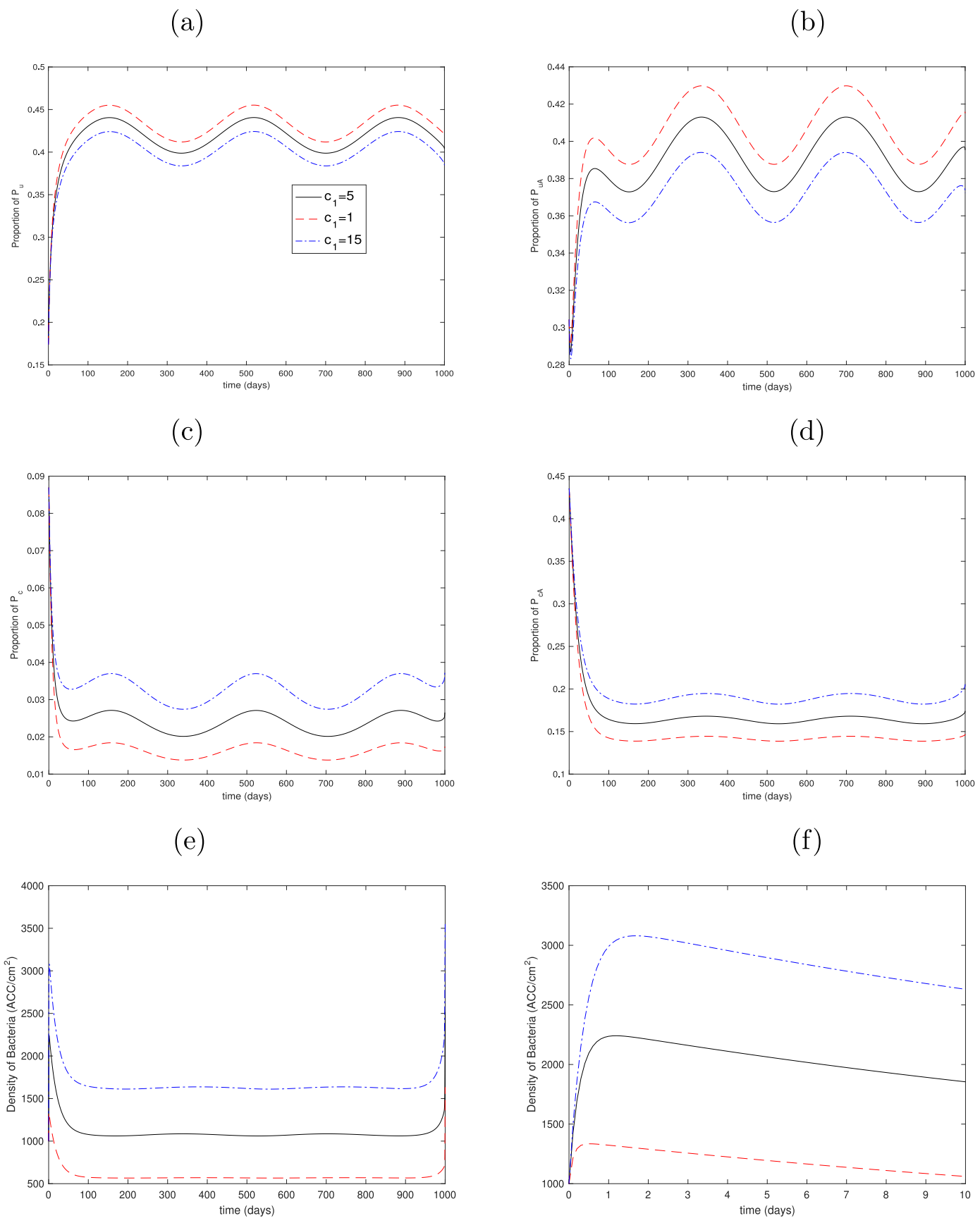

Fig. 14. Control results with various c_1 values corresponding to optimal control strategies shown in Fig. 13. (a) Proportion of uncolonized patients without antibiotic exposures; (b) proportion of uncolonized patients with antibiotic exposures; (c) proportion of colonized patients without antibiotic exposures; (d) proportion of colonized patients with antibiotic exposures; (e) density of bacteria in 1000 days; (f) density of bacteria in initial 10 days.

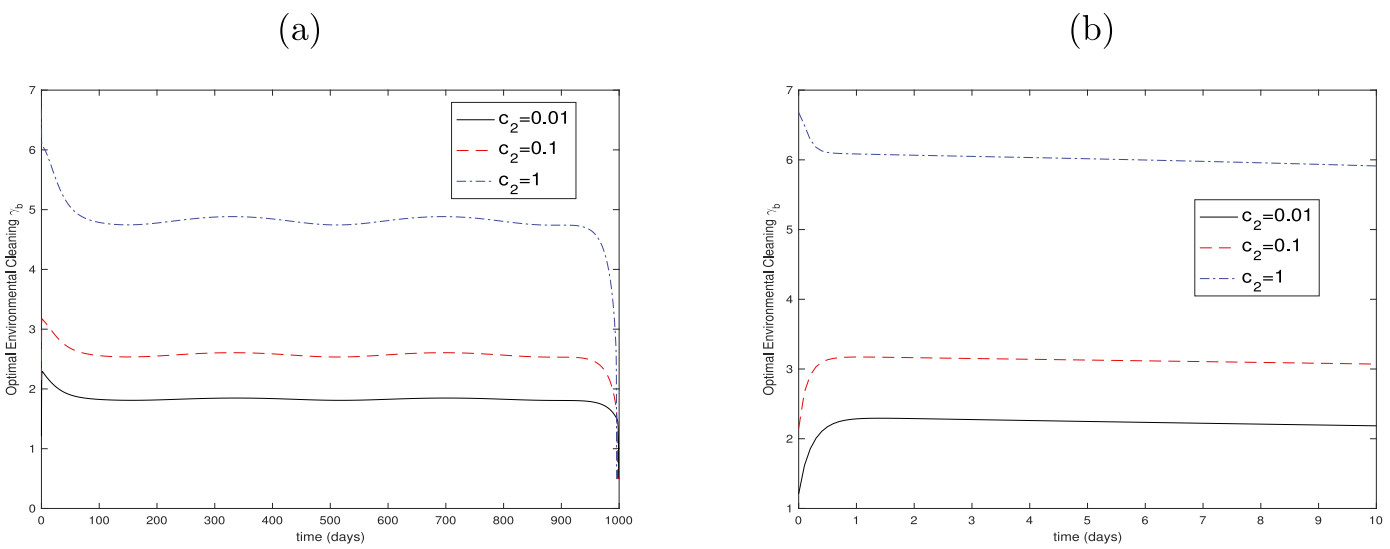

Fig. 15. Optimal control strategies with various c_2 values. (a) Optimal environmental cleaning rate in 1000 days; (b) optimal environmental cleaning in initial 10 days.

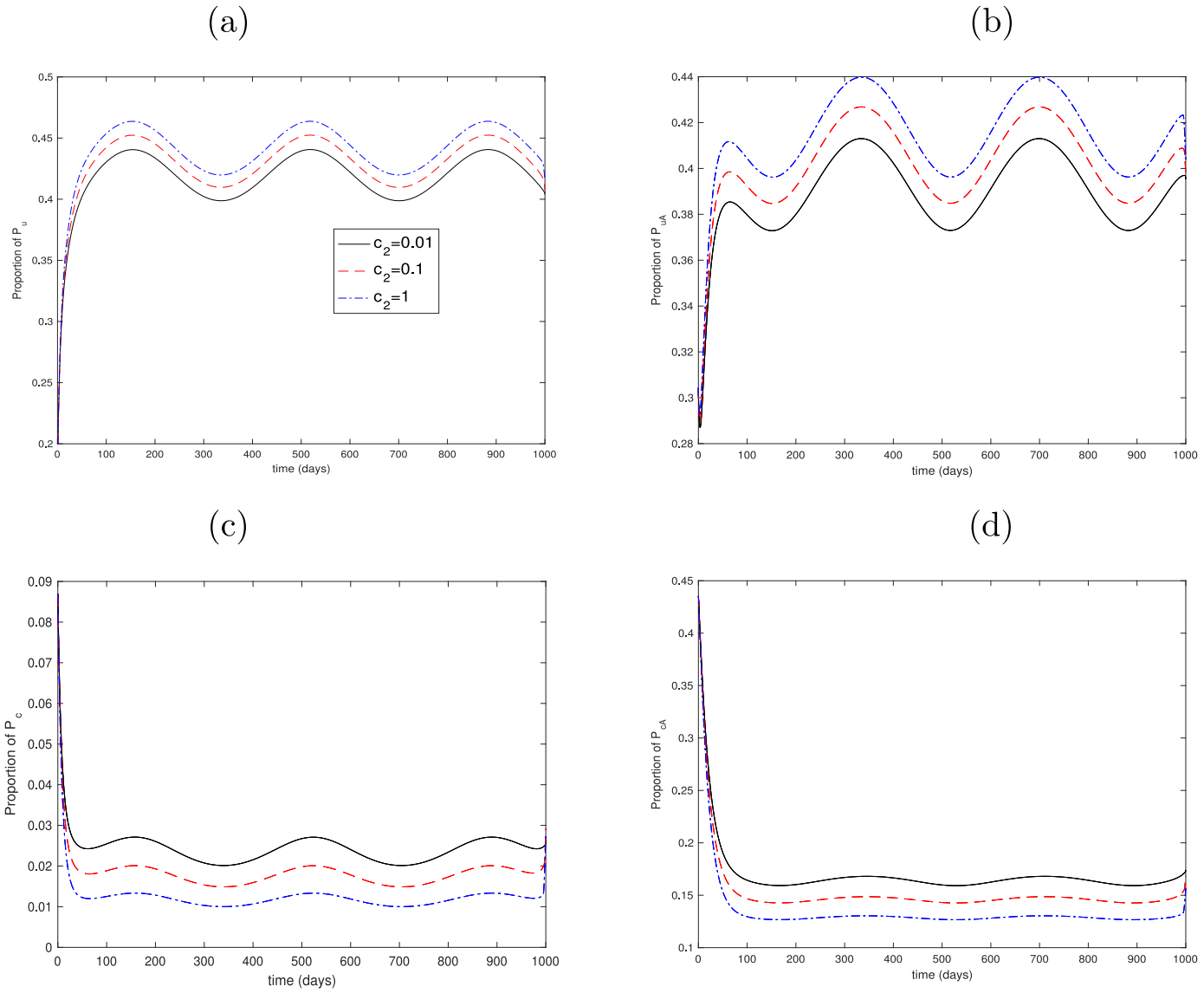

Fig. 16. Control results with various c_2 values corresponding to optimal control strategies shown in Fig. 15. (a) Proportion of uncolonized patients without antibiotic exposures; (b) proportion of uncolonized patients with antibiotic exposures; (c) proportion of colonized patients without antibiotic exposures; (d) proportion of colonized patients with antibiotic exposures.

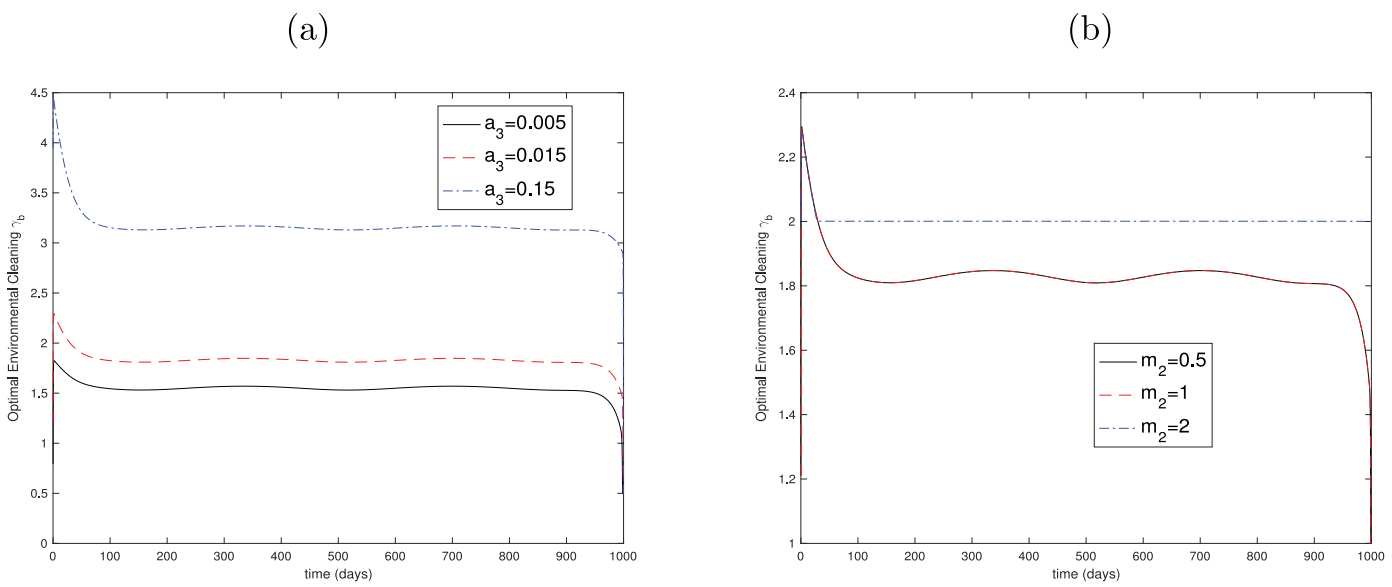

Fig. 17. Optimal control strategies with various a_3 and m_2 values. (a) Optimal environmental cleaning with various a_3 values; (b) optimal environmental cleaning with various m_2 values.

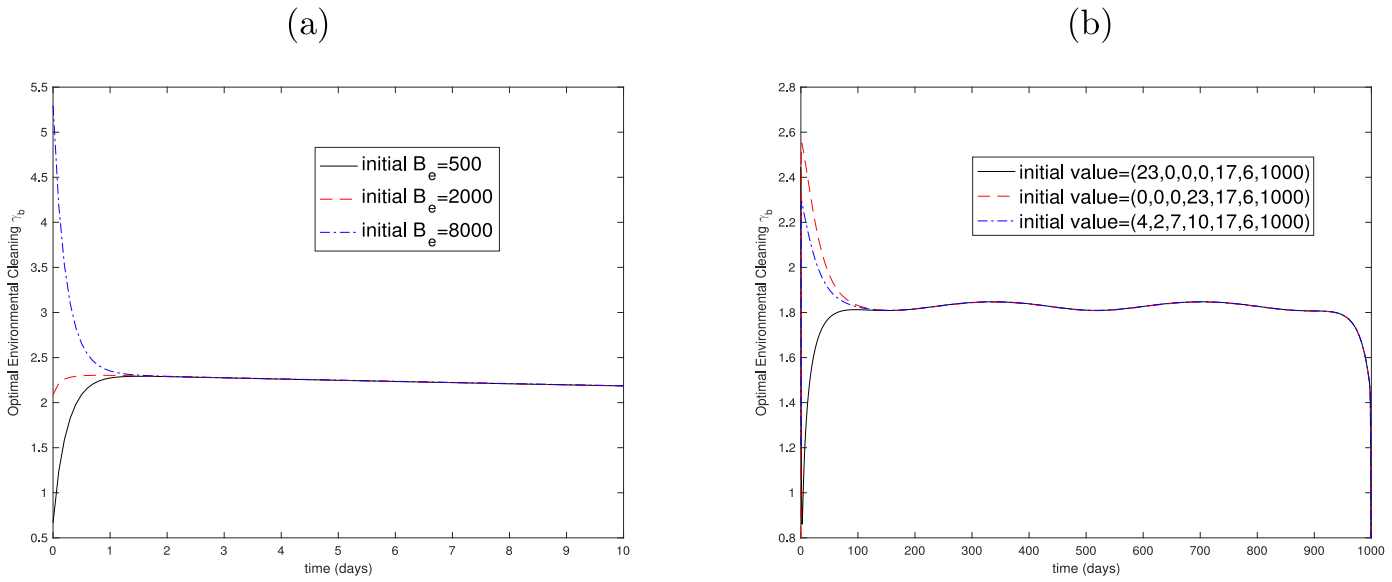

Fig. 18. Optimal control strategies with various initial conditions. (a) Optimal environmental cleaning rate with various initial bacteria density; (b) optimal environmental cleaning rate with various initial patient status distributions.

Supplementary material

Supplementary material associated with this article can be found, in the online version, at 10.1016/j.mbs.2019.01.013.

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