2018-12-03

Modeling the Effect of Seasonality on the Transmission of Antibiotic Resistance Bacteria in Hospitals with Environmental Contamination

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MODELING THE EFFECT OF SEASONALITY ON THE TRANSMISSION OF ANTIBIOTIC-RESISTANT BACTERIA IN HOSPITAL WITH ENVIRONMENTAL CONTAMINATION

By

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A DISSERTATION

Submitted to the Faculty
of the University of Miami
in partial fulfillment of the requirements for
the degree of Doctor of Philosophy

Coral Gables, Florida

December 2018

UNIVERSITY OF MIAMI

A dissertation submitted in partial fulfillment of
the requirements for the degree of
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HUANG, QIMIN (Ph.D., Mathematics)
Modeling the Effect of Seasonality on the Transmission of Antibiotic-Resistant Bacteria in Hospitals with Environmental Contamination (December 2018)

Abstract of a dissertation at the University of Miami.

Dissertation supervised by Professor Shigui Ruan.
No. of pages of text. (108)

Nosocomial infections caused by antibiotic resistant bacteria are a major threat to global public health today. In order to understand the diverse factors contributing to hospital acquired antibiotic resistant infections, we develop some mathematical models and address the theoretical, numerical and stochastic aspects of such models.

In Chapter 2, both deterministic and stochastic mathematical models are developed to explore the roles that antibiotic exposure and environmental contamination play in the transmission dynamics of nosocomial infections in hospitals. Uncolonized patients without or with antibiotic exposure, colonized patients without or with antibiotic exposure, uncontaminated and contaminated health-care workers, and free-living Methicillin-resistant *Staphylococcus aureus* (MRSA) are included in the models. Under the assumption that there is no admission of the colonized patients, the basic reproduction number R_0 is calculated. We prove that when $R_0 < 1$, the infection-free equilibrium is globally asymptotically stable; when $R_0 > 1$, the infection is uniformly persistent. Numerical simulations show that environmental cleaning is the most important intervention. Increasing the stay of colonized patients with antibiotic exposure in hospitals will increase the prevalence of MRSA, which implies to treat patients with antibiotic exposure as efficiently and quickly as possible. Screening and isolating colonized patients at admission, and improving compliance with hand

hygiene are also important control strategies.

In Chapter 3, we extend the deterministic model developed in chapter 2. The extended model with periodic antibiotic prescribing rate is constructed to study the seasonality of Methicillin-resistant *Staphylococcus aureus* (MRSA) infections taking antibiotic exposure and environmental contamination into consideration. The basic reproduction number R_0 for the periodic model is also calculated under the assumption that there are only uncolonized patients with antibiotic exposure at admission. Sensitivity analysis of R_0 with respect to some essential parameters is performed. It is also shown that the infection would go to extinction if the basic reproduction number is less than unity and would persist if it is greater than unity. Numerical simulations indicate that environmental cleaning is the most important intervention to control the infection, which emphasizes the effect of environmental contamination in MRSA infections. It is also important to highlight the importance of effective antimicrobial stewardship programs, to increase active screening at admission and subsequent isolation of positive cases, and to treat patients quickly and efficiently.

In Chapter 4, based on the results obtained from previous chapters, we apply the optimal control theory to the seven-compartment system of ordinary differential equations to minimize the numbers 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 are formulated, and how hospitals should adjust their strategies when different hospital scenarios happen is discussed. Numerical simulations strongly suggest that environmental cleaning rate is key in the control of MRSA infections and hospital should use antibiotics as properly and little as possible. Meanwhile, how to treat colonized patients especially with antibiotic exposure as quickly and efficiently as possible is a

big challenge in controlling MRSA infections. Screening and subsequent isolation can be an effective intervention supplement.

In the last chapter, we summarized the results of the thesis and discuss some future studies.

Acknowledgements

I would first like to express my sincerest thanks to my advisor, Dr. Shigui Ruan, for sharing his knowledge with me, for helping and supporting this project, and for all his encouragements, patience, and guidance throughout my Ph.D. study. It has been an incredible honor to have him as my advisor for these years.

Moreover, I would like to thank my dissertation committee members: Drs. Xi Huo, Chris Cosner, and Don DeAngelis for their invaluable guidance, conversations, and careful reading of the draft. I would also like to thank all the professors and faculty members at the Department of Mathematics, especially, Drs. Steve Cantrell, Bruno de Oliveira, Mingliang Cai, Ilie Grigorescu, and Leticia Oropesa for all the help they offered. Deep thanks are due to Dania Puerto, Toni Taylor, and Sylvia Bacallao for their kind assistance. Thanks to all of you, I have a wonderful time at the University of Miami.

In addition, I would like to thank Drs. Mary Ann Horn, Wandi Ding, Yingke Li, Mingtao Li, Jing Chen, Ping Bi, Jianhua Pang, and Zijian Liu for amazing advice and sharing in the project. Besides, sincere thanks are due to Yekun Xu, Hao Kang, Dan Su, and all my other classmates and friends for their valuable discussions, encouragements and help in any respect during the completion of the project.

Finally, I would like to express my deepest thanks and love to my husband Shuai Xu, my son Shuyi Xu, my parents Chunxiu Zheng, Weican Huang, and my uncle Chenkun Zheng who give me the unbeliveable courage to pursue my dream, and without whom none of this would happen. To them, this dissertation is dedicated.

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Chapter 1

Introduction

Nosocomial infections caused by antibiotic-resistant bacteria are a major threat to global public health today. According to the Centers for Disease Control and Prevention(CDC) [6]: "Each year in the United States, at least 2 million people become infected with bacteria that are resistant to antibiotics and at least 23,000 people die each year as a direct result of these infections." Besides, CDC identifies infections caused by Methicillin-resistant *Staphylococcus aureus* (MRSA), a Gram-positive bacterium, as one of the most common causes of hospital-acquired infections such as serious skin infections, brain abscess (central nervous system infection), endophthalmitis, pneumonia (lung infection), and bloodstream infections, especially in intensive-care units. An observation that patients with MRSA are about 64% more likely to die than patients with a non-resistent form of the infection in hospitals was revealed by a World Health Organization (WHO) report in April 2014 [44]. In fact, MRSA infections result in increased risk of mortality, lengthier stays of patients in hospitals, extra costs of treatment and increased intensive health care [43], [30].

Staph bacteria are usually treated with antibiotics, however, as antibiotics are abused to be prescribed to inhibit these kinds of bacterial infections, so far MRSA has been resistant to many common antibiotics such as methicillin, oxacillin, penicillin, and amoxicillin. Based on a Centers for Disease Control and Prevention (CDC)

report [6], 30-50% of antibiotics patients accepted in hospitals are unnecessary or inappropriate. Even though some antibiotics still work, MRSA is constantly adapting, which makes it difficult for researchers to keep developing new antibiotics. Hence whether a patient has antibiotic exposure or not is kind of important for his or her treatment. There is no wonder that overprescribing and misprescribing lead to the increasing challenges caused by antibiotic-resistant bacteria. In fact, some studies have observed a clear association between antibiotic exposure and MRSA isolation [10], [36], [35]. They prove that patients with history of antibiotic exposure are vulnerable to skin infection and are more likely to be colonized by MRSA, which results in a lengthier duration in hospitals, a higher chance of failed treatment, a larger shedding rate of bacteria to the environment, and even a higher mortality rate. Hence it is necessary to consider antibiotic exposure and use of antibiotics in hospitals as influential factors in the transmission of MRSA.

In order to understand the diverse factors contributing to hospital-acquired antibiotic resistant infections, various models have been proposed [7], [17], [2], [4], [8], [9], [11], [38], [42], [39]. Many of these models show that the direct transmission via the hands of health-care workers (HCWs) is a crucial factor in the transmission of MRSA. In addition, because under certain circumstances MRSA pathogens are capable of surviving for days, weeks or even months on environmental surfaces such as door handles in the unit, healthcare facilities, health-care worker gowns and gloves, environmental contamination is also a necessarily essential factor when we study the transmission of MRSA. Especially, Browne and Webb [5], Wang and Ruan [39] and Wang et al. [42] developed mathematical models to study the effect of environmental contamination on the spread of antibiotic-resistant bacteria in hospitals. Chamchod and Ruan [7] proposed models to investigate the effect of antibiotic exposure on the

transmission of MRSA in hospitals. However, the combined effects of antibiotic exposure and environmental contamination have not been studied. This is one of the motivations of the current study.

The other motivation is that, by analyzing a comprehensive transmission dynamic model of MRSA infections in hospitals both theoretically and numerically, we want to develop optimal cost-effective strategies to help control MRSA infections in hospitals.

Chapter 2

Modeling the effect of antibiotic exposure on the transmission of Methicillin-resistant *Staphylococcus aureus* in hospitals with environmental contamination

2.1 Model Descriptions and Assumptions

The patients, health-care workers (HCWs), and free-living bacteria in the environment in the hospital are divided into the following seven compartments (see Fig. 2.1):

$P_u(t)$=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 Health Care Workers at time t;

$H_c(t)$=Number of contaminated Health Care Workers at time t;

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

(1) We assume that a patient would have antibiotic exposure if he or she has received

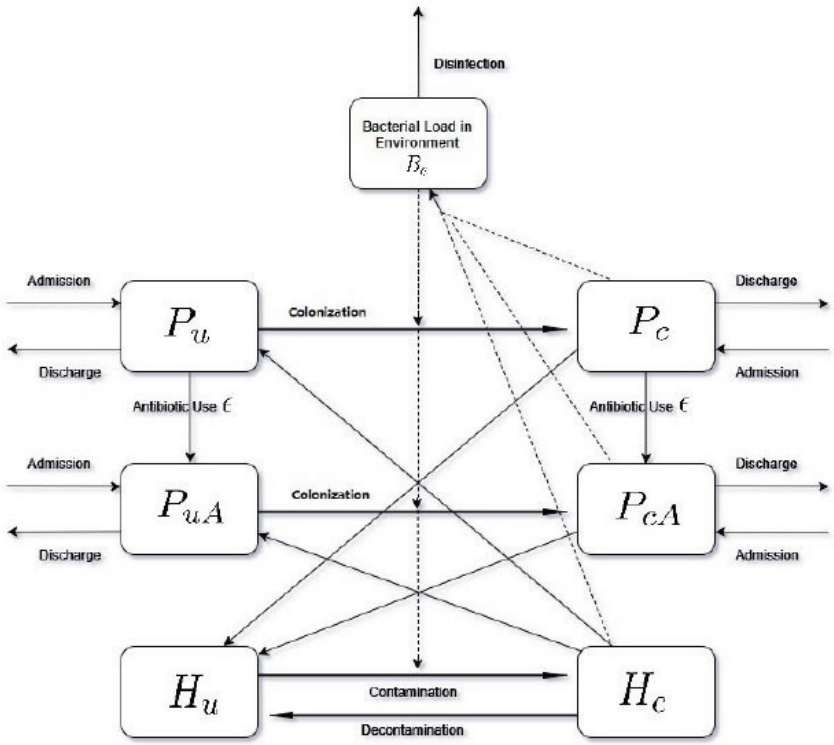

Figure 2.1: Flowchart of the model consisted of uncolonized patients without antibiotic exposure ($P_u(t)$), uncolonized patients with antibiotic exposure ($P_{uA}(t)$), colonized patients without antibiotic exposure ($P_c(t)$), colonized patients with antibiotic exposure ($P_{cA}(t)$), uncontaminated healthcare workers ($H_u(t)$), contaminated healthcare workers ($H_c(t)$), and free-living bacteria in the environment ($B_e(t)$).

antibiotics within the month on admission or is currently receiving antibiotic treatment in the hosptial.

(2) Uncolonized (colonized) patients without antibiotic exposure would move to the uncolonized (colonized) patients with antibiotic exposure at an antibiotic prescribing rate of ϵ per day [15].

(3) The free-living bacteria are uniformly distributed in the environment.

(4) The total number of patients in a unit is a constant N_p. That is equivalent to say that patients are admitted at a total rate $\Omega(t) = \gamma_u P_u + \gamma_c P_c + \gamma_{uA} P_{uA} + \gamma_{cA} P_{cA}$, where $\gamma_u, \gamma_{uA}, \gamma_c$, and γ_{cA} are the corresponding discharge rates of patients from these four compartments. We also denote $\theta_u, \theta_{uA}, \theta_c, \theta_{cA}$ as the corresponding proportion of patients P_u, P_{uA}, P_c, P_{cA} on admission. It was estimated that the fraction of patients with antibiotic exposure of new admissions to be 0.38, i.e., $\theta_{uA} + \theta_{cA}$=0.38 [19] [7].

(5) The total number of health-care workers is a constant N_h.

(6) We assume that the bacterial reproduction cannot occur due to lack of proper conditions in the hospital, even though the free-living bacteria are able to survive in the environment for a long time. As a result, shedding from colonized patients is one of the key transmission of bacteria to contaminate environment $\upsilon_p P_c + \upsilon_{pA} P_{cA}$. υ_p, and υ_{pA} are the shedding rate of bacteria from patients without or with antibiotic exposure, respectively. In addition, when the contaminated HCWs touch the environmental surfaces such as door handles, health facilities, bedding, they leave bacteria there $\upsilon_h H_c$, which is another way to contaminate

the environment. Of course, hospitals always have a standard cleaning rate or disinfection rate γ_b.

(7) We assume that there is no contact between patients, which means that if an uncolonized patient without antibiotic exposure becomes colonized without antibiotic exposure, he/she either contacts contaminated HCWs at rate $\alpha_p\beta_p(1-\eta)P_uH_c$ or touches the contaminated environment at rate $\kappa_pP_uB_e$. A similar process happens when an uncolonized patient with antibiotic exposure becomes colonized with antibiotic exposure at rate $\alpha_p\beta_{pA}(1-\eta)P_{uA}H_c+\kappa_{pA}P_{uA}B_e$. α_p is the contact rate per day, β_p and β_{pA} are the chances of colonization per contact for uncolonized patients without or with antibiotic exposure, respectively, η is the hand hygiene compliance, κ_p and κ_{pA} are the chance of colonization by touching contaminated environment for uncolonized patients without or with antibiotic exposure, respectively.

(8) An uncontaminated HCW becomes contaminated when he/she contacts colonized patients or touches contaminated environmental surfaces at rate $\alpha_p\beta_h(1-\eta)P_cH_u + \alpha_p\beta_{hA}(1-\eta)P_{cA}H_u$, where β_h, β_{hA} are chance of contamination per contact with P_c or P_{cA}, respectively. HCWs have a decontaminated rate μ_c to move from contaminated state to uncontaminated state.

(9) Since antibiotic exposure always results in a higher chance of failure treatment, a lengthier duration of hospital care, a higher probability of colonization and so on, it is reasonable to assume that $\gamma_{cA}^{-1} \geq \gamma_c^{-1} \geq \gamma_{uA}^{-1} \geq \gamma_u^{-1}$, $\upsilon_{pA} \geq \upsilon_p$, $\beta_{pA} \geq \beta_p$, and $\beta_{hA} \geq \beta_h$. In addition, by previous studies [15] [7], we estimate that uncolonized patients with antibiotic exposure P_{uA} is 1.67 times more vulnerable than uncolonized patients without antibiotic exposure P_u, i.e., $\beta_{pA} = 1.6 \times \beta_p$.

Detailed parameter values are listed in Table 2.1. On the basis of the flowchart shown in Fig.2.1 we formulate the system of ordinary differential equations that describes the transition between compartments as follows:

Table 2.1: Parameters and descriptions.

Parameter	Description	Parameter Estimate	Reference
θ_u	proportion of P_u on admission	0.617	[7] [15]
θ_{uA}	proportion of P_{uA}on admission	0.349	[7] [19]
θ_c	proportion of P_c on admission	0.003	[7] [15]
θ_{cA}	proportion of P_{cA}on admission	0.031	[7] [19]
γ_u	discharge rate of P_u	0.2	[7]
γ_{uA}	discharge rate of P_{uA}	0.2	[7]
γ_c	discharge rate of P_c	0.06	[15]
γ_{cA}	discharge rate of P_{cA}	0.055	[7] [15]
γ_b	disinfection rate of environment	0.7	[39]
N_p	total number of patients	23	[39]
N_h	total number of HCWs	23	[39]
α_p	Contact rate	0.0435	[39]
β_p	probability of colonization for P_u after a contact with H_c	0.42	[39]
β_{pA}	probability of colonization for P_{uA} after a contact with H_c	0.42*1.67	[15] [7]
β_h	probability of contamination for HCW after a contact with P_c	0.2	[39] [7]
β_{hA}	probability of contamination for HCW after a contact with P_{cA}	0.25	[7]
η	hand hygiene compliance with HCWs	0.4	[39]
μ_c	decontaminated rate of HCWs	24	[39]
υ_p	contamination(shedding) rate to environment from P_c	235	[39]
υ_{pA}	contamination(shedding) rate to environment from P_{cA}	470	[42] [15]
υ_h	contamination rate to environment by contaminated HCWs	235	[39]
ϵ	antibiotic prescribing rate	0.12	[15] [27]
κ_p	colonization rate from environment for P_u	0.000004	[39]
κ_{pA}	colonization rate from environment for P_{uA}	0.000005	[7] [39]
κ_h	colonization rate from environment for uncontaminated HCWs	0.00001	[39]

$$
\begin{aligned}
\frac{dP_u}{dt} &= \theta_u\Omega(t) - \alpha_p\beta_p(1-\eta)P_uH_c - \kappa_pP_uB_e - \gamma_uP_u - \epsilon P_u,\\
\frac{dP_c}{dt} &= \theta_c\Omega(t) + \alpha_p\beta_p(1-\eta)P_uH_c + \kappa_pP_uB_e - \gamma_cP_c - \epsilon P_c,\\
\frac{dP_{uA}}{dt} &= \theta_{uA}\Omega(t) - \alpha_p\beta_{pA}(1-\eta)P_{uA}H_c - \kappa_{pA}P_{uA}B_e - \gamma_{uA}P_{uA} + \epsilon P_u,\\
\frac{dP_{cA}}{dt} &= \theta_{cA}\Omega(t) + \alpha_p\beta_{pA}(1-\eta)P_{uA}H_c + \kappa_{pA}P_{uA}B_e - \gamma_{cA}P_{cA} + \epsilon P_c,\\
\frac{dH_u}{dt} &= -\alpha_p\beta_h(1-\eta)P_cH_u - \alpha_p\beta_{hA}(1-\eta)P_{cA}H_u - \kappa_hH_uB_e + \mu_cH_c,\\
\frac{dH_c}{dt} &= \alpha_p\beta_h(1-\eta)P_cH_u + \alpha_p\beta_{hA}(1-\eta)P_{cA}H_u + \kappa_hH_uB_e - \mu_cH_c,\\
\frac{dB_e}{dt} &= \upsilon_pP_c + \upsilon_{pA}P_{cA} + \upsilon_hH_c - \gamma_bB_e
\end{aligned}
\tag{2.1.1}
$$

where $\Omega(t) = \gamma_uP_u + \gamma_cP_c + \gamma_{uA}P_{uA} + \gamma_{cA}P_{cA}$, with initial conditions $P_u(0) = P_u^0$,

$P_{uA}(0) = P_{uA}^0,\ P_c(0) = P_c^0,\ P_{cA}(0) = P_{cA}^0,\ H_u(0) = H_u^0,\ H_c(0) = H_c^0,\ B_e(0) = B_e^0$ specified at time 0.

2.2 Mathematical Analysis

In this subsection, we provide detailed mathematical analysis of the model (2.1.1).

Positivity and Invariance of Solutions

Based on the biological background of model (2.1.1), we only consider solutions of model (2.1.1) starting at $t = 0$ with initial values:

$$P_u^0 \geq 0, P_{uA}^0 \geq 0, P_c^0 \geq 0, P_{cA}^0 \geq 0, H_u^0 \geq 0, H_c^0 \geq 0, B_e^0 \geq 0.$$

Lemma 2.1. *If* $P_u^0, P_{uA}^0, P_c^0, P_{cA}^0, H_u^0, H_c^0, B_e^0 \geq 0$, *then* $(P_u(t), P_{uA}(t), P_c(t), P_{cA}(t), H_u(t), H_c(t), B_e(t))$ *the solutions of model* (2.1.1) *are nonnegative for all* $t \geq 0$ *and ultimately bounded. In particular, if* $P_u^0, P_{uA}^0, P_c^0, P_{cA}^0, H_u^0, H_c^0, B_e^0 > 0$, *then the solutions* $(P_u(t), P_{uA}(t), P_c(t), P_{cA}(t), H_u(t), H_c(t), B_e(t))$ *are also positive for all* $t \geq 0$.

Proof. Firstly, by the continuous dependence of solutions with respect to initial values, we only need to prove that when $P_u^0, P_{uA}^0, P_c^0, P_{cA}^0, H_u^0, H_c^0, B_e^0 > 0$, $(P_u(t), P_{uA}(t), P_c(t), P_{cA}(t), H_u(t), H_c(t), B_e(t))$ the solutions are also positive for all $t \geq 0$. That is, the solutions remain in the positive cone if the initial conditions are in the positive cone of $\mathcal{R}^7$. Set

$$m(t) = \min\{P_u(t), P_{uA}(t), P_c(t), P_{cA}(t), H_u(t), H_c(t), B_e(t)\}, \forall t > 0.$$

Clearly, $m(0) > 0$. Assuming that there exists a $t_1 > 0$ such that $m(t_1) = 0$ and $m(t) > 0$ for all $t \in [\, 0, t_1)$.

If $m(t_1) = P_u(t_1)$, from the first equation of model (2.1.1) it follows that $\frac{dP_u}{dt} \geq -(\alpha_p\beta_p(1-\eta)H_c(t)+\kappa_p B_e(t)+\gamma_u+\epsilon)P_u$ for all $t \in [\, 0, t_1)$. Since $H_c(t) > 0, B_e(t) > 0$ for all $t \in [\, 0, t_1)$, we have

$$0 = P_u(t_1) \geq P_u^0 \exp(-\int_0^{t_1} (\alpha_p\beta_p(1-\eta)H_c(s) + \kappa_p B_e(s) + \gamma_u + \epsilon)ds) > 0,$$

which leads to a contradiction. Similar contradictions can be deduced in the cases of $m(t_1) = P_{uA}(t_1), m(t_1) = P_c(t_1), m(t_1) = P_{cA}(t_1), m(t_1) = H_u(t_1), m(t_1) = H_c(t_1), m(t_1) = B_e(t_1)$. Hence, the solutions remain in the positive cone if the initial conditions are in the positive cone $\mathcal{R}^7$.

Secondly, let $T(t) = P_u(t) + P_{uA}(t) + P_c(t) + P_{cA}(t) + H_u(t) + H_c(t) + B_e(t)$. Then

$$\begin{aligned} \frac{dT(t)}{dt} &= \frac{dB_e(t)}{dt} = \upsilon_p P_c + \upsilon_{pA} P_{cA} + \upsilon_h H_c - \gamma_b B_e \\ &\leq \upsilon_p N_p + \upsilon_{pA} N_p + \upsilon_h N_h - \gamma_b B_e(t), \end{aligned}$$

where $N_p = P_u(t) + P_{uA}(t) + P_c(t) + P_{cA}(t)$ and $N_h = H_u(t) + H_c(t)$, which implies that

$$B_e(t) \leq \frac{(\upsilon_p N_p + \upsilon_{pA} N_p + \upsilon_h N_h)}{\gamma_b}(1 - e^{-\gamma_b t}) + B_e^0 e^{-\gamma_b t}.$$

So $B_e(t)$ is bounded by a fixed number

$$M = \frac{(\upsilon_p N_p + \upsilon_{pA} N_p + \upsilon_h N_h)}{\gamma_b} + B_e^0.$$

Let $N = N_p + N_h + M$, we have

$$T(t) = P_u(t) + P_{uA}(t) + P_c(t) + P_{cA}(t) + H_u(t) + H_c(t) + B_e(t) \leq N.$$

Thus, the solutions remain bounded in a positive cone of $\mathcal{R}^7$, and the system induces a global semiflow in the positively invariant set of $\mathcal{R}^7$. This completes the proof. □

Remark 2.2. Denote set G as follows

$$G := \{(P_u, P_{uA}, P_c, P_{cA}, H_u, H_c, B_e) \in \mathcal{R}^7_+ : P_u + P_{uA} + P_c + P_{cA} + H_u + H_c + B_e \leq N)\}.$$

Then Lemma 2.1 implies that G is a positively invariant set with respect to model (2.1.1).

Basic Reproduction Number

When θ_c=0, θ_{cA}=0, that is, there are no colonized patients admitted into hospital, model (2.1.1) has a unique infection-free equilibrium (IFE) which is defined by

$$E_0 = (P_u, P_c, P_{uA}, P_{cA}, H_u, H_c, B_e) = (N^*, 0, N_p - N^*, 0, N_h, 0, 0);$$

$$N^* = \frac{\theta_u \gamma_{uA} N_p}{\theta_{uA}\gamma_u + \theta_u \gamma_{uA} + \epsilon}.$$

We derive the basic reproduction number R_0 for the model (1) by using the techniques in Diekmann et al. [13] and van den Driessche and Watmough [37], which involves linearizing the original nonlinear ordinary differential equations at the infection-free

equilibrium. Re-order the components of E_0 as

$$E_0 = (P_c, P_{cA}, H_c, B_e, P_u, P_{uA}, H_u) = (0, 0, 0, 0, N^*, N_p - N^*, N_h)$$

and set

$$\mathcal{F} = \begin{pmatrix} \alpha_p\beta_p(1-\eta)P_uH_c + \kappa_pP_uB_e \\ \alpha_p\beta_{pA}(1-\eta)P_{uA}H_c + \kappa_{pA}P_{uA}B_e \\ \alpha_p\beta_h(1-\eta)P_cH_u + \alpha_p\beta_{hA}(1-\eta)P_{cA}H_u + \kappa_hH_uB_e \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix},$$

$$\mathcal{V} = \begin{pmatrix} \gamma_cP_c + \epsilon P_c - \theta_c\Omega \\ \gamma_{cA}P_{cA} - [\epsilon P_c + \theta_{cA}\Omega] \\ \mu_cH_c \\ \gamma_bB_e - (\upsilon_pP_c + \upsilon_{pA}P_{cA} + \upsilon_hH_c) \\ \alpha_p\beta_p(1-\eta)P_uH_c + \kappa_pP_uB_e + \gamma_uP_u + \epsilon P_u - \theta_u\Omega \\ \alpha_p\beta_{pA}(1-\eta)P_{uA}H_c + \kappa_{pA}P_{uA}B_e + \gamma_{uA}P_{uA} - [\epsilon P_u + \theta_{uA}\Omega] \\ \alpha_p\beta_h(1-\eta)P_cH_u + \alpha_p\beta_{hA}(1-\eta)P_{cA}H_u + \kappa_hH_uB_e - \mu_cH_c \end{pmatrix},$$

where $\Omega = (\gamma_u P_u + \gamma_c P_c + \gamma_{uA} P_{uA} + \gamma_{cA} P_{cA})$,

$$\mathcal{V}^- = \begin{pmatrix} \gamma_c P_c + \epsilon P_c \\ \gamma_{cA} P_{cA} \\ \mu_c H_c \\ \gamma_b Be \\ \alpha_p \beta_p (1-\eta) P_u H_c + \kappa_p P_u Be + \gamma_u P_u + \epsilon P_u \\ \alpha_p \beta_{pA} (1-\eta) P_{uA} H_c + \kappa_{pA} P_{uA} Be + \gamma_{uA} P_{uA} \\ \alpha_p \beta_h (1-\eta) P_c H_u + \alpha_p \beta_{hA} (1-\eta) P_{cA} H_u + \kappa_h H_u Be \end{pmatrix},$$

$$\mathcal{V}^+ = \begin{pmatrix} \theta_c \Omega \\ \epsilon P_c + \theta_{cA} \Omega \\ 0 \\ \upsilon_p P_c + \upsilon_{pA} P_{cA} + \upsilon_h H_c \\ \theta_u \Omega \\ \epsilon P_u + \theta_{uA} \Omega \\ \mu_c H_c \end{pmatrix}.$$

Since θ_c=0, θ_{cA}=0, then we can derive that

$$F = \begin{pmatrix} 0 & 0 & \alpha_p \beta_p (1-\eta) N^* & \kappa_p N^* \\ 0 & 0 & \alpha_p \beta_{pA} (1-\eta)(N_p - N^*) & \kappa_{pA} (N_p - N^*) \\ \alpha_p \beta_h (1-\eta) N_h & \alpha_p \beta_{hA} (1-\eta) N_h & 0 & \kappa_h N_h \\ 0 & 0 & 0 & 0 \end{pmatrix},$$

$$V = \begin{pmatrix} \gamma_c + \epsilon & 0 & 0 & 0 \\ -\epsilon & \gamma_{cA} & 0 & 0 \\ 0 & 0 & \mu_c & 0 \\ -\upsilon_p & -\upsilon_{pA} & -\upsilon_h & \gamma_b \end{pmatrix}.$$

The basic reproductive number is defined as the spectral radius of FV^{-1}:

$$R_0 = sp(FV^{-1}) = \frac{\alpha_3}{\alpha_1} + \alpha_1 + \alpha_2 \tag{2.2.1}$$

where

$\alpha_1 = (\sqrt{(\frac{\alpha_6^3}{27\mu_c^3\gamma_{cA}^3} + \alpha_5 + \alpha_4)^2 - \alpha_3^3} + \frac{\alpha_6^3}{27\mu_c^3\gamma_{cA}^3} + \alpha_5 + \alpha_4)^{\frac{1}{3}}$,

$\alpha_2 = \frac{\alpha_6}{3\mu_c\gamma_{cA}}$, $\alpha_3 = \frac{\alpha_7}{3\mu_c\gamma_{cA}} + \frac{\alpha_6^2}{9\mu_c^2\gamma_{cA}^2}$, $\alpha_4 = \frac{\alpha_6\alpha_7}{6\mu_c^2\gamma_{cA}^2}$,

$\alpha_5 = \frac{(\beta_p\kappa_{pA} - \beta_{pA}\kappa_p)N^*(N_p - N^*)N_h\alpha_p^2(1-\eta)^2[\ \omega_1\beta_{hA}(\gamma_c+\epsilon) - \omega_2(\beta_h\gamma_{cA} + \beta_{hA}\epsilon)]}{2\mu_c\gamma_{cA}(\gamma_c+\epsilon)}$,

$\alpha_6 = \mu_c\gamma_{cA}(\omega_1\kappa_p N^* + \omega_2\kappa_{pA}(N_p - N^*) + \omega_3\kappa_h N_h)$,

$\alpha_7 = N_h\alpha_p^2(1-\eta)^2[\beta_{hA}\beta_{pA}(N_p - N^*) + \frac{\beta_h\gamma_{cA} + \beta_{hA}\epsilon}{\gamma_c+\epsilon}\beta_p N^*]$

$+(N_p - N^*)N_h\alpha_p(1-\eta)[\omega_2\kappa_h\beta_{pA}\gamma_{cA} + \omega_3\kappa_{pA}\beta_{hA}\mu_c]$

$+N^*N_h\alpha_p(1-\eta)[\omega_1\beta_p\kappa_h\gamma_{cA} + \omega_3\kappa_p\mu_c\frac{\beta_h\gamma_{cA} + \beta_{hA}\epsilon}{\gamma_c+\epsilon}]$.

By Theorem 2 in van den Driessche and Watmough [37], we have the following theorem:

Theorem 2.3. *If $R_0 < 1$, then the infection-free equilibrium E_0 is locally asymptoti-*

cally stable; If $R_0 > 1$, then E_0 is unstable.

Moreover, from the proof of Theorem 2 in van den Driesshce and Watmough [37] or from the proof of Lemma 2.1 in Wang and Zhao [40] , we have the following observation: let

$$J_1 = \begin{pmatrix} -\gamma_c - \epsilon & 0 & \alpha_p\beta_p(1-\eta)N^* & \kappa_p N* \\ \epsilon & -\gamma_{cA} & \alpha_p\beta_{pA}(1-\eta)(N_p - N^*) & \kappa_{pA}(N_p - N^*) \\ \alpha_p\beta_h(1-\eta)N_h & \alpha_p\beta_{hA}(1-\eta)N_h & -\mu_c & \kappa_h N_h \\ \upsilon_p & \upsilon_{pA} & \upsilon_h & -\gamma_b \end{pmatrix}.$$

Let $s(J_1)$ be the maximum real part of the eigenvalues of J_1. Since J_1 is irreducible and has non-negative off-diagonal elements, $s(J_1)$ is a simple eigenvalue of J_1 with a positive eigenvector. Then we have the following corollary:

Corollary 2.4. *There hold two equivalences:*

$$R_0 < 1 \iff s(J_1) < 0; \quad R_0 > 1 \iff s(J_1) > 0.$$

Extinction of Disease.

Theorem 2.5. *If $R_0 < 1$, then the infection-free equilibrium E_0 is globally asymptotically stable.*

Proof. From Theorem 2.3 we know that E_0 is locally asymptotically stable. Now we prove the global attractivity of the infection-free equilibrium E_0.

By the first equation of the model (2.1.1), non-negativity of the solutions and

previous assumptions, we get

$$\frac{dP_u}{dt} \leq \theta_u[\gamma_u P_u + \gamma_{uA}(N_p - P_u)] - \gamma_u P_u - \epsilon P_u.$$

Since $\gamma_{uA} = \max\{\gamma_{uA}, \gamma_c, \gamma_{cA}\}$, it implies that

$$\frac{dP_u}{dt} \leq \theta_u \gamma_{uA} N_p - (-\theta_u\gamma_u + \theta_u\gamma_{uA} + \gamma_u + \epsilon)P_u = \theta_u\gamma_{uA}N_p - (\theta_{uA}\gamma_u + \theta_u\gamma_{uA} + \epsilon)P_u.$$

So $\forall\delta > 0$, there exists $t_1 > 0$, such that $P_u \leq N^* + \delta$, for all $t \geq t_1$.

Similarly, by the third equation of the model (2.1.1), non-negativity of the solutions and previous assumptions, we get

$$\frac{dP_{uA}}{dt} \leq (1-\theta_u)[\gamma_u(N_p - P_{uA}) + \gamma_{uA}P_{uA}] - \gamma_{uA}P_{uA} + \epsilon(N_p - P_{uA}),$$

that is,

$$\frac{dP_{uA}}{dt} \leq (\theta_{uA}\gamma_u + \epsilon)N_p - (\theta_{uA}\gamma_u + \theta_u\gamma_{uA} + \epsilon)P_{uA}.$$

Then $\forall\delta > 0$, there exists $t_2 > 0$, such that $P_{uA} \leq N_p - N^* + \delta$, for all $t \geq t_2$.

Let $T = \max\{t_1, t_2\}$, If $t > T$, since $\theta_c = \theta_{cA} = 0$, then

$$\begin{cases} P_c^{'}(t) \leq \alpha_p\beta_p(1-\eta)(N^* + \delta)H_c + \kappa_p(N^* + \delta)B_e - \gamma_c P_c - \epsilon P_c, \\ P_{cA}^{'}(t) \leq \alpha_p\beta_{pA}(N_p - N^* + \delta)H_c + \kappa_{pA}(N_p - N^* + \delta)B_e - \gamma_{cA}P_{cA} + \epsilon P_c, \\ H_c^{'}(t) \leq \alpha_p\beta_h(1-\eta)N_hP_c + \alpha_p\beta_{hA}(1-\eta)N_hP_{cA} + \kappa_hN_hB_e - \mu_cH_c, \\ B_e^{'}(t) \leq \upsilon_pP_c + \upsilon_{pA}P_{cA} + \upsilon_hH_c - \gamma_bB_e. \end{cases} \tag{2.2.2}$$

Considering the following auxiliary system:

$$\begin{cases} \tilde{P'}_c(t) = \alpha_p\beta_p(1-\eta)(N^*+\delta)\tilde{H}_c + \kappa_p(N^*+\delta)\tilde{B}_e - \gamma_c\tilde{P}_c - \epsilon\tilde{P}_c, \\ \tilde{P'}_{cA}(t) = \alpha_p\beta_{pA}(N_p - N^* + \delta)\tilde{H}_c + \kappa_{pA}(N_p - N^* + \delta)\tilde{B}_e - \gamma_{cA}\tilde{P}_{cA} + \epsilon\tilde{P}_c, \\ \tilde{H'}_c(t) = \alpha_p\beta_h(1-\eta)N_h\tilde{P}_c + \alpha_p\beta_{hA}(1-\eta)N_h\tilde{P}_{cA} + \kappa_h N_h\tilde{B}_e - \mu_c\tilde{H}_c, \\ \tilde{B'}_e(t) = \upsilon_p\tilde{P}_c + \upsilon_{pA}\tilde{P}_{cA} + \upsilon_h\tilde{H}_c - \gamma_b\tilde{B}_e. \end{cases} \tag{2.2.3}$$

Define

$$J_1(\delta) = \begin{pmatrix} -\gamma_c - \epsilon & 0 & \alpha_p\beta_p(1-\eta)(N^*+\delta) & \kappa_p(N*+\delta) \\ \epsilon & -\gamma_{cA} & \alpha_p\beta_{pA}(1-\eta)(N_p - N^* + \delta) & \kappa_{pA}(N_p - N^* + \delta) \\ \alpha_p\beta_h(1-\eta)N_h & \alpha_p\beta_{hA}(1-\eta)N_h & -\mu_c & \kappa_h N_h \\ \upsilon_p & \upsilon_{pA} & \upsilon_h & -\gamma_b \end{pmatrix}.$$

It follows from corollary 2.4 that if $R_0 < 1$, then $s(J_1(0)) < 0$. Since $s(J_1(\delta))$ is continuous for small δ, so there exists δ small enough such that $s(J_1(\delta)) < 0$. Thus there is a negative eigenvalue of $s(J_1(\delta))$ with a positive eigenvector. Obviously if $t \to \infty$, then $\tilde{P}_c, \tilde{P_{cA}}, \tilde{H}_c, \tilde{B}_e \to 0$. Then by the comparison principle we get

$$\lim_{t\to\infty} P_c = 0, \lim_{t\to\infty} P_{cA} = 0, \lim_{t\to\infty} H_c = 0, \lim_{t\to\infty} B_e = 0.$$

Therefore, E_0 is globally attractive when $R_0 < 1$. This completes the proof. □

Uniform Persistence

Let $f : X \to X$ be a continuous map and $X_0 \subset X$ an open set. Define $\partial X_0 := X \backslash X_0$ and $M_\partial := \{x \in \partial X_0 : f^n(x) \in \partial X_0, n \geq 0\}$.

Theorem 2.6 (STRONG REPELLERS, Zhao, 2003 [46]). *Assume that*

1. $f(X_0) \subset X_0$ *and* f *has a global attractor* A;
2. *There exists a finite sequence* $\mathcal{M} = \{M_1, ..., M_k\}$ *of disjoint, compact, and isolated invariant sets in* ∂X_0 *such that:*
   (a) $\cup_{\varphi_0 \in M_\partial} \omega(\varphi_0) \subset \cup_{i=1}^{k} M_i$;
   (b) *no subset of* $\mathcal{M}$ *forms a cycle in* ∂X_0
   (c) M_i *is isolated in* X;
   (d) $W^s(M_i) \cap X_0 = \emptyset$ *for each* $1 \leq i \leq k$.

Then there exists $\delta > 0$ *such that for any compact internally chain transitive set* L *with* $L \not\subset M_i$ *for all* $1 \leq i \leq k$, *we have* $\inf_{x \in L} d(x, \partial X_0) > \delta$.

According to the previous theorem 2.6, we have the following:

Theorem 2.7. *If* $R_0 > 1$, *the model (*2.1.1*) is uniformly persistent.*

Proof. We first define
$X = \{(P_u, P_c, P_{uA}, P_{cA}, H_u, H_c, B_e) : P_u \geq 0, P_c \geq 0, P_{uA} \geq 0, P_{cA} \geq 0, H_u \geq 0, H_c \geq 0, B_e \geq 0\}$,
$X_0 = \{(P_u, P_c, P_{uA}, P_{cA}, H_u, H_c, B_e) \in X : P_c > 0, P_{cA} > 0, H_c > 0, B_e > 0\}$,
$\partial X_0 = X \backslash X_0$.
It can be seen that both X and X_0 are positively invariant with respect to model (2.1.1). Clearly, ∂X_0 is relatively closed in X. Lemma 2.1 implies that the model (2.1.1) is point dissipative, which implies that the solutions of the model (2.1.1) admit

a global attractor. Then we define

$$\begin{aligned} M_\partial &= \{(P_u(0), P_c(0), P_{uA}(0), P_{cA}(0), H_u(0), H_c(0), B_e(0)) : \\ &\quad (P_u(t), P_c(t), P_{uA}(t), P_{cA}(t), H_u(t), H_c(t), B_e(t)) \in \partial X_0, \forall t \geq 0\}. \end{aligned}$$

Now we prove that

$$M_\partial = \{(P_u, 0, P_{uA}, 0, H_u, 0, 0) : P_u \geq 0, P_{uA} \geq 0, H_u = N_h\}.$$

For any point $\varphi_0 = (P_u(0), P_c(0), P_{uA}(0), P_{cA}(0), H_u(0), H_c(0), B_e(0))$ in M_∂, we suppose that one of $P_c(0), P_{cA}(0), H_c(0), B_e(0)$ is not zero, that is to say, $\varphi_0 \notin \{(P_u, 0, P_{uA}, 0, H_u, 0, 0) : P_u \geq 0, P_{uA} \geq 0, H_u = N_h\}$. Without loss of generality, we suppose that $P_c(0) = 0, P_{cA}(0) = 0, H_c(0) = 0, B_e(0) > 0$. By the second, fourth, and sixth equations, we have

$$\frac{dP_c(0)}{dt} \geq \kappa_p P_u(0) B_e(0) > 0; \frac{dP_{cA}(0)}{dt} \geq \kappa_{pA} P_{uA}(0) B_e(0) > 0; \frac{dH_c(0)}{dt} \geq \kappa_h H_u(0) B_e(0) > 0.$$

Thus, there exists $\delta_0 > 0$, if $0 < t < \delta_0$ then $P_c(t) > 0, P_{cA}(t) > 0, H_c(t) > 0, B_e(t) > 0$, which imply that $\varphi_0 \notin \partial X_0$. we will get the similar result for other cases ($P_c(0) > 0$, or $P_{cA}(0) > 0$, or $H_c(0) > 0$). Thus $\varphi_0 \notin M_\partial$. This gives us a contradiction. Hence $\varphi_0 \in \{(P_u, 0, P_{uA}, 0, H_u, 0, 0) : P_u \geq 0, P_{uA} \geq 0, H_u = N_h\}$. So $M_\partial \subseteq \{(P_u, 0, P_{uA}, 0, H_u, 0, 0) : P_u \geq 0, P_{uA} \geq 0, H_u = N_h\}$. Obviously we have $\{(P_u, 0, P_{uA}, 0, H_u, 0, 0) : P_u \geq 0, P_{uA} \geq 0, H_u = N_h\} \subseteq M_\partial$, therefore, $M_\partial = \{(P_u, 0, P_{uA}, 0, H_u, 0, 0) : P_u \geq 0, P_{uA} \geq 0, H_u = N_h\}$. Let φ_0 be an initial value. Clearly there is only one equilibrium $E_0 = (N^*, 0, N_p - N^*, 0, N_h, 0, 0)$ in M_∂,

so $\cup_{\varphi_0 \in M_\partial} \omega(\varphi_0) = E_0$. Therefore, $\{E_0\}$ is a compact and isolated invariant set in ∂X_0.

Next we claim that there exists a positive constant ℓ such that for any solution of model (2.1.1), $\Psi_t(\varphi_0), \varphi_0 \in X_0$, we have

$$\limsup_{t\to\infty} d(\Psi_t(\varphi_0), E_0) \geq \ell,$$

where d is a distant function in X_0. We construct by contradiction so that we suppose the claim is not true. Then $\limsup_{t\to\infty} d(\Psi_t(\varphi_0), E_0) \leq \ell$, for any $\ell > 0$, namely, there exists a positive constant T, such that $N^* - \ell \leq P_u(t) \leq N^* + \ell,\ P_c(t) \leq \ell,\ N_p - N^* - \ell \leq P_{uA}(t) \leq N_p - N^* + \ell,\ P_{cA}(t) \leq \ell,\ N_h - \ell \leq H_u(t) \leq N_h + \ell,\ H_c(t) \leq \ell,\ B_e(t) \leq \ell$, for any $t > T$. While $t > T$, we have,

$$\begin{cases} P_c^{'}(t) \geq \alpha_p\beta_p(1-\eta)(N^* - \ell)H_c + \kappa_p(N^* - \ell)B_e - \gamma_c P_c - \epsilon P_c, \\ P_{cA}^{'}(t) \geq \alpha_p\beta_{pA}(N_p - N^* - \ell)H_c + \kappa_{pA}(N_p - N^* - \ell)B_e - \gamma_{cA}P_{cA} + \epsilon P_c, \\ H_c^{'}(t) \geq \alpha_p\beta_h(1-\eta)(N_h - \ell)P_c + \alpha_p\beta_{hA}(1-\eta)(N_h - \ell)P_{cA} + \kappa_h(N_h - \ell)B_e - \mu_c H_c, \\ B_e^{'}(t) \geq \upsilon_p P_c + \upsilon_{pA}P_{cA} + \upsilon_h H_c - \gamma_b B_e. \end{cases} \tag{2.2.4}$$

Consider the following auxiliary system:

$$\begin{cases} \tilde{P'}_c(t) = \alpha_p\beta_p(1-\eta)(N^*-\ell)\tilde{H}_c + \kappa_p(N^*-\ell)\tilde{B}_e - \gamma_c\tilde{P}_c - \epsilon\tilde{P}_c, \\ \tilde{P'}_{cA}(t) = \alpha_p\beta_{pA}(N_p-N^*-\ell)\tilde{H}_c + \kappa_{pA}(N_p-N^*-\ell)\tilde{B}_e - \gamma_{cA}\tilde{P_{cA}} + \epsilon\tilde{P}_c, \\ \tilde{H'}_c(t) = \alpha_p\beta_h(1-\eta)(N_h-\ell)\tilde{P}_c + \alpha_p\beta_{hA}(1-\eta)(N_h-\ell)\tilde{P_{cA}} + \kappa_h(N_h-\ell)\tilde{B}_e - \mu_c\tilde{H}_c, \\ \tilde{B'}_e(t) = \upsilon_p\tilde{P}_c + \upsilon_{pA}\tilde{P_{cA}} + \upsilon_h\tilde{H}_c - \gamma_b\tilde{B}_e. \end{cases} \tag{2.2.5}$$

we define

$$J_1(\ell) = \begin{pmatrix} -\gamma_c-\epsilon & 0 & \alpha_p\beta_p(1-\eta)(N^*-\ell) & \kappa_p(N*-\ell) \\ \epsilon & -\gamma_{cA} & \alpha_p\beta_{pA}(1-\eta)(N_p-N^*-\ell) & \kappa_{pA}(N_p-N^*-\ell) \\ \alpha_p\beta_h(1-\eta)(N_h-\ell) & \alpha_p\beta_{hA}(1-\eta)(N_h-\ell) & -\mu_c & \kappa_h(N_h-\ell) \\ \upsilon_p & \upsilon_{pA} & \upsilon_h & -\gamma_b \end{pmatrix}.$$

For $R_0 > 1$, by corollary 2.4, we have $s(J_1(0)) > 0$. Since $s(J_1(\ell))$ is continuous for small ℓ, so there exists a positive constant ℓ small enough such that $s(J_1(\ell)) > 0$. Thus, there is a positive eigenvalue of $s(J_1(\delta))$ with a positive eigenvector. It is easy to see if $t \to \infty$, then $\tilde{P}_c, \tilde{P_{cA}}, \tilde{H}_c, \tilde{B}_e \to \infty$. Then by the comparison principle we get

$$\lim_{t\to\infty} P_c = \infty, \lim_{t\to\infty} P_{cA} = \infty, \lim_{t\to\infty} H_c = \infty, \lim_{t\to\infty} B_e = \infty.$$

This contradicts our assumption and completes the proof of the claim.

The claim implies that $\{E_0\}$ is an isolated invariant set in X and $W^s(E_0)\cap X_0 = \emptyset$. Therefore, system (2.1.1) is uniformly persistent if $R_0 > 1$ by Theorem 2.6. This completes the proof. □

2.3 Numerical Simulations

Our deterministic model is simulated for 365 days. With the initial values $(P_u^0, P_{uA}^0, P_c^0, P_{cA}^0, H_u^0, H_c^0, B_e^0) = (4, 6, 7, 6, 17, 6, 1000)$ and parameter values shown in Table 2.1, we estimate the following outcomes : numerical solutions of the deterministic model (2.1.1), prevalences of colonized patients without or with antibiotic exposure, and the basic reproduction number R_0. Simulations are also performed to evaluate the effect of various interventions in changing the prevalence of colonized patients and R_0.

Behavior of the Model

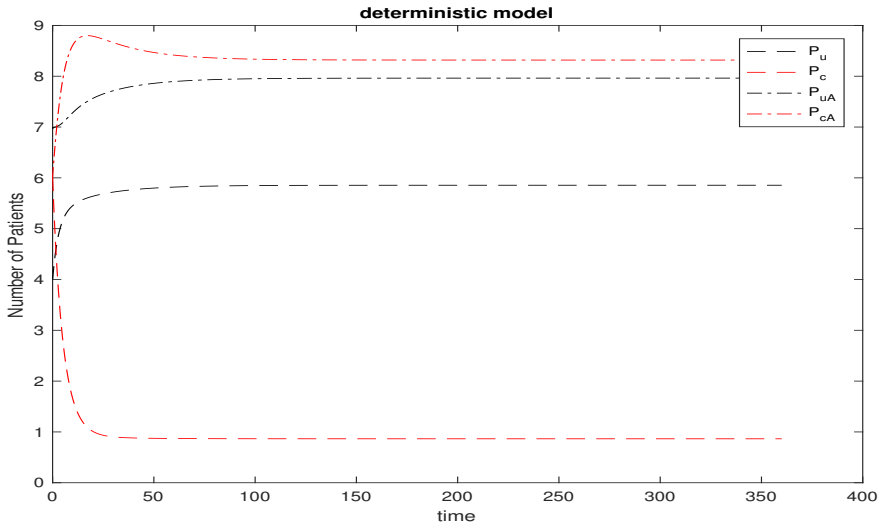

Figure 2.2: Solutions of uncolonized patients without or with antibiotic exposure $(P_u(t), P_{uA}(t))$ and colonized patients without or with antibiotic exposure $(P_c(t), P_{cA}(t))$ of deterministic model (2.1.1) with initial values $(P_u^0, P_{uA}^0, P_c^0, P_{cA}^0, H_u^0, H_c^0, B_e^0) = (4, 6, 7, 6, 17, 6, 1000)$ and $\theta_u = 0.617, \theta_{uA} = 0.349, \theta_c = 0.003, \theta_{cA} = 0.031$ on admission. All parameter values are given in Table 2.1.

Using the baseline parameters in Table 2.1, Figs.2.2,2.3 give the behaviors of solutions to model (2.1.1), which imply that 36% of patients are colonized with MRSA

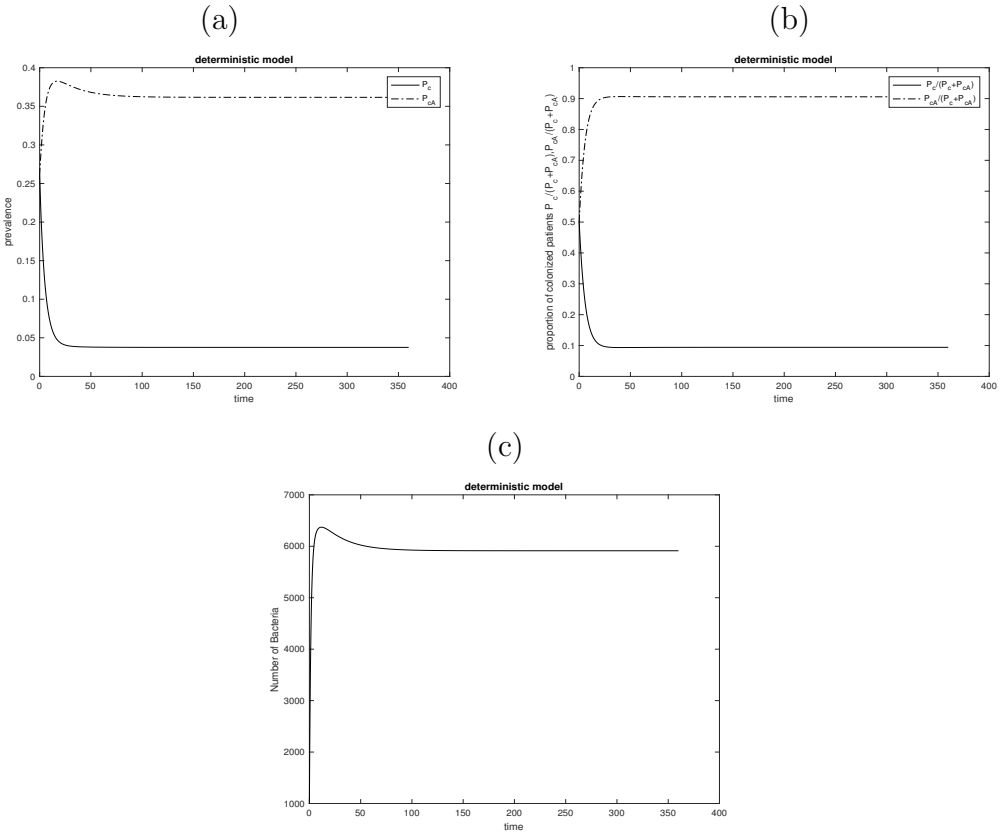

Figure 2.3: (a) Prevalence of colonized patients with or without antibiotic exposure; (b) The proportions of colonized patients with and without antibiotic exposure ; (c) The bacterial load in the environment of deterministic model (2.1.1) with initial values $(P_u^0, P_{uA}^0, P_c^0, P_{cA}^0, H_u^0, H_c^0, B_e^0) = (4, 6, 7, 6, 17, 6, 1000)$ and $\theta_u = 0.617, \theta_{uA} = 0.349, \theta_c = 0.003, \theta_{cA} = 0.031$ on admission.

with antibiotic exposure, and 4% are colonized without antibiotic exposure. While with no admission of MRSA-positive patients ($\theta_c = \theta_{cA} = 0$), Fig.2.4 gives the behaviors of solutions to model (2.1.1), which shows that 21% of patients are colonized with MRSA with antibiotic exposure, and 3% are colonized without antibiotic exposure; While with no admission of patients with history of antibiotic exposure ($\theta_{uA} = \theta_{cA} = 0$), Fig.2.5 indicates that 27% of patients are colonized with MRSA with antibiotic exposure, and 7.5% are colonized without antibiotic exposure; While with no admission of patients with history of antibiotic exposure and MRSA-positive ($\theta_{uA} = \theta_c = \theta_{cA} = 0$), Fig.2.6 says that 14% of patients are colonized with MRSA with antibiotic exposure, and 3.5% are colonized without antibiotic exposure. Hence, to control the hospital infection we may need to reduce the proportion of colonized patients (γ_c, γ_{cA}) at admission by increasing the detection and isolation of the admitted MRSA patients and also reduce the proportion of uncolonized patients with antibiotic exposure (γ_{uA}) by strengthening the public education about how to use antibiotics properly at community.

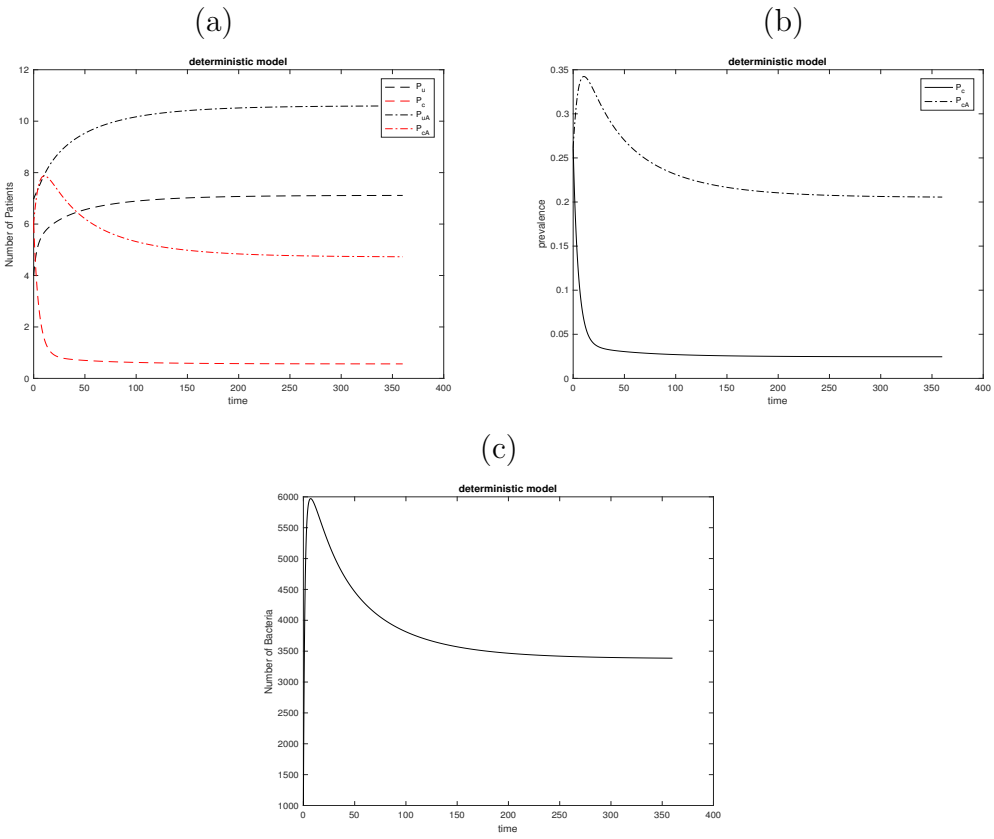

Figure 2.4: (a) Solutions of uncolonized patients without or with antibiotic exposure $(P_u(t), P_{uA}(t))$ and colonized patients without or with antibiotic exposure $(P_c(t), P_{cA}(t))$ of deterministic model (2.1.1) with initial values $(P_u^0, P_{uA}^0, P_c^0, P_{cA}^0, H_u^0, H_c^0, B_e^0) = (4, 6, 7, 6, 17, 6, 1000)$ and $\theta_u = 0.62, \theta_{uA} = 0.38, \theta_c = 0, \theta_{cA} = 0$ on admission; (b) Prevalence of colonized patients with or without antibiotic exposure; (c) The bacterial load in the environment.

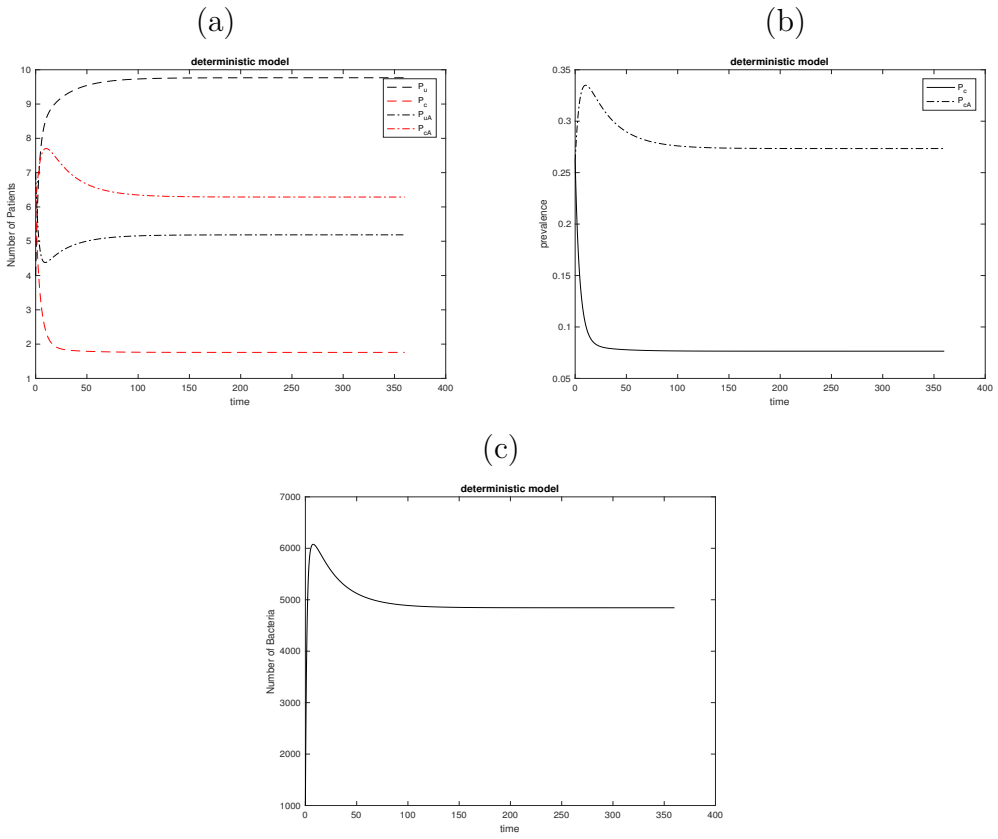

Figure 2.5: (a) Solutions of uncolonized patients without or with antibiotic exposure $(P_u(t), P_{uA}(t))$ and colonized patients without or with antibiotic exposure $(P_c(t), P_{cA}(t))$ of deterministic model (2.1.1) with initial values $(P_u^0, P_{uA}^0, P_c^0, P_{cA}^0, H_u^0, H_c^0, B_e^0) = (4, 6, 7, 6, 17, 6, 1000)$ and $\theta_u = 0.966, \theta_{uA} = 0, \theta_c = 0.034, \theta_{cA} = 0$ on admission; (b) Prevalence of colonozied patients with or without antibiotic exposure; (c) The bacterial load in the environment.

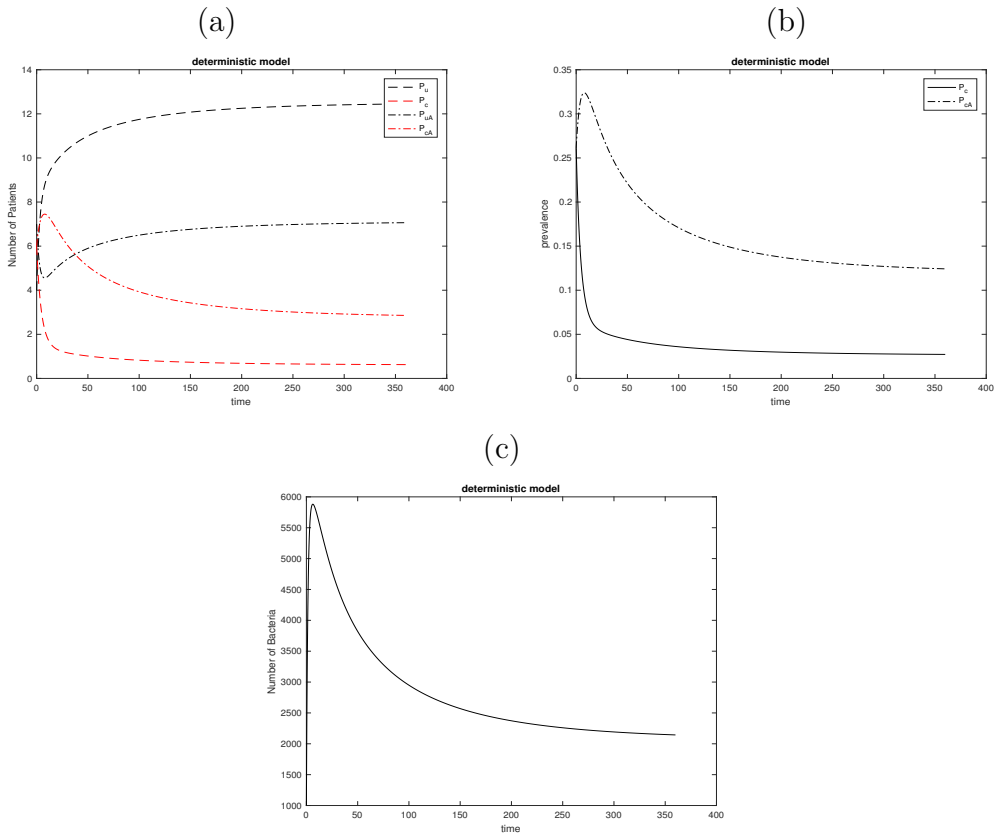

Figure 2.6: (a) Solutions of uncolonized patients without or with antibiotic exposure $(P_u(t), P_{uA}(t))$ and colonized patients without or with antibiotic exposure $(P_c(t), P_{cA}(t))$ of deterministic model (2.1.1) with initial values $(P_u^0, P_{uA}^0, P_c^0, P_{cA}^0, H_u^0, H_c^0, B_e^0) = (4, 6, 7, 6, 17, 6, 1000)$ and $\theta_u = 1, \theta_{uA} = 0, \theta_c = 0, \theta_{cA} = 0$ on admission; (b) Prevalence of colonozied patients with or without antibiotic exposure; (c) The bacterial load in the environment.

The Basic Reproduction Number

In the case where colonized patients are admitted into hospital, the infections will always persist. When $\theta_c = 0, \theta_{cA} = 0$, that is no colonized patients are admitted into hospital, the infection-free equilibrium (IFE) is defined to be $E_0 = (P_u, P_c, P_{uA}, P_{cA}, H_u, H_c, B_e) = (N^*, 0, N_p - N^*, 0, N_h, 0, 0)$ where $N^* = \frac{\theta_u \gamma_{uA} N_p}{\theta_{uA} \gamma_u + \theta_u \gamma_{uA} + \epsilon}$. On the basis of parameters listed in Table 2.1, the basic reproduction number is estimated to be 1.2860, which means that the infections are persistent. We want to

reduce R_0 to below unity by some interventions. Here we perform some simulations to evaluate the effect of the following interventions in reducing the prevalence of colonized patients with or without antibiotic exposure, and R_0: (1) Prescription rate of antibiotics (ϵ); (2) Hand hygiene compliance of HCWS (η); (3) The discharge rate for colonized patients with or without antibiotic exposure (γ_c, γ_{cA}), (i.e., length of stay of colonized patients with or without antibiotic exposure ($\gamma_c^{-1}, \gamma_{cA}^{-1}$); (4) Environmental cleaning rate (γ_b); and (5) Decontamination rate of HCWs (μ_c).

The predicted effects of individual interventions on reducing the prevalence of MRSA and the reproduction number R_0 are shown in Fig.2.7. Fig.2.7A shows that increasing the compliance rate of hand hygiene for HCWs (η) from 0.4 (baseline) to 1, just reduces R_0 from 1.2860 to 1.2197, and reduces the prevalence of colonized patients with and without antibiotic exposure by 4.51% (from 20.56% to 16.04%) and 0.54% (from 2.45% to 1.91%). When antibiotic prescribing rate is reduced from 0.12 (baseline) to 0 (no antibiotic use), we get a result in around 19% reduction in the prevalence of colonized patients with antibiotic exposure, while a little increase and then decrease in the prevalence of colonized patients without antibiotic exposure, and a change from 1.2860 to 0.9251 in R_0 (Fig.2.7B). We investigate the discharge rate (i.e., the reciprocal of the length of stay) of colonized patient without antibiotic exposure (γ_c) and with antibiotic exposure (γ_{cA}), respectively in Fig.2.7C and Fig.2.7D. When the discharge rate of P_c is increased from the baseline 0.06 to 0.2 (i.e., the length of stay of P_c is decreased from 16.6days to 5 days), R_0 reduces to 1.1308, and the prevalence of P_{cA} and P_c reduces by 9.58% (from 21.08% to 11.50%) and 1.72% (from 2.57% to 0.85%). Especially, we notice that if we decrease the discharge rate of P_{cA} a little bit from baseline 0.055, there are dramatic increases in both R_0 and the prevalence of P_{cA}. However, many studies show that colonized patients with an-

tibiotic exposure (P_{cA}) usually lead to a lengthier stay [7], which in turns makes the situation worse. We find out that improving environmental cleaning rate (γ_b) is the most effective intervention from Fig.2.7E. When we increase environmental cleaning rate from 0.7 (baseline) to 1, we are able to decrease the prevalence of P_{cA} and P_c from 20.56% to 1.99% and from 2.45% to 0.21% respectively, and successfully reduce R_0 to below unity. Fig.2.7F shows that decontamination rate of HCWs has little effect.

Observing that individual intervention is hard to reduce R_0 to below unity, we examine the effects of combined interventions (Fig.2.8). When we decrease antibiotic use and in the meantime increase the discharge rate of P_{cA}, we reduce R_0 to below unity efficiently (Fig.2.8b). A similar result happens when combining the increased environmental cleaning rate and decreased discharge rate of P_{cA} (Fig.2.8f).

Sensitivity Analysis

Latin hypercube sampling (LHS) method is used to engage a sensitivity analysis [24] [31]. Partial rank correlation coefficients (PRCCs) are calculated for the following nine parameters against prevalence of colonized patients and R_0 over time: discharge rate for colonized patients with antibiotic exposure (γ_{cA}), environmental cleaning rate (γ_b), probability of colonization for P_{uA} after a contact with a contaminated HCW (β_{pA}), probability of contamination for HCW after a contact with a colonized patient with antibiotic exposure (β_{hA}), hand hygiene compliance rate (η), decontaminated rate of HCWs (μ_c), contamination rate to environment by colonized patients with antibiotic exposure (υ_{pA}), antibiotic prescribing rate (ϵ), contamination rate from environment for uncolonized patient with antibiotic

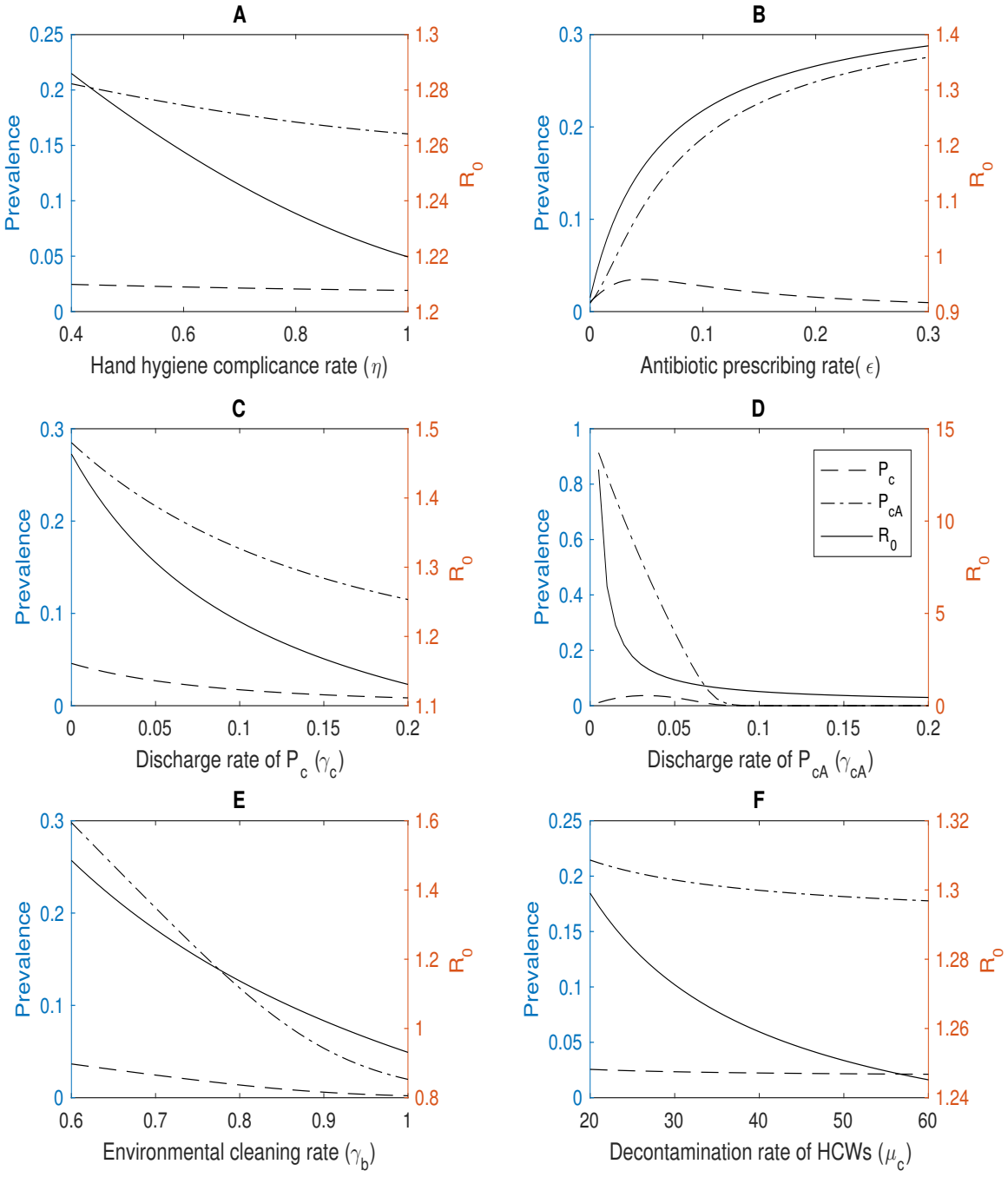

Figure 2.7: Effects of individual interventions on the prevalence of colonized patient with antibiotic exposure (dashed lines), colonized patients without antibiotic exposure (dashed-dot lines) and the basic reproduction number R_0 (solid lines). The following interventions are investigated: compliance with hand hygiene (**A**), antibiotic prescribing rate (**B**), discharge rate of colonized patients without antibiotic exposure P_c (**C**), discharge rate of colonized patients with antibiotic exposure P_{cA} (**D**), environmental cleaning rate (**E**), and decontamination rate of HCWs (**F**).

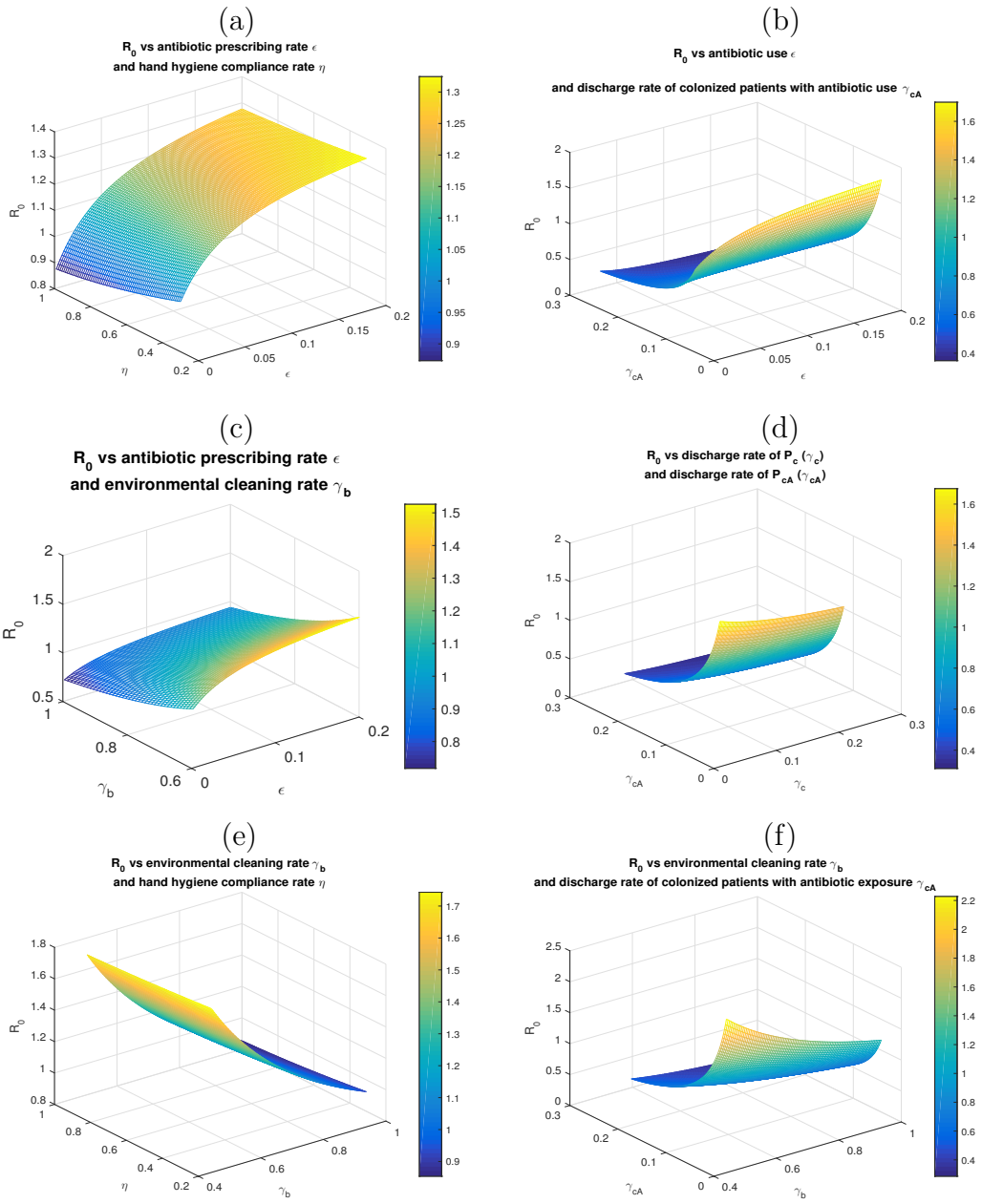

Figure 2.8: Effects of two interventions on the basic reproduction number R_0

exposure (κ_{pA}). We also test for significant PRCCs for the above parameters to evaluate which parameters are essential to our model. Since we find that the PRCC values vary little after about 100 days, it is reasonable and efficient for us to just study the PRCC values on this specific day 100 (Fig.2.9). Fig.2.9(e) implies that the first four parameters have the most impact on the outcome of R_0, which are the environmental cleaning rate γ_b, contamination rate to environment by colonized patient with antibiotic exposure υ_{pA}, contamination rate from environment for uncolonized patient with antibiotic exposure κ_{pA} and antibiotic prescribing rate ϵ. From Figs.2.9(a)-2.9(d), we illustrate the PRCC values of the nine examined parameters and corresponding p-values for the different outcome parameter P_c, P_{cA}, H_c, and B_e. All analysis is done by MATLAB and input parameters are assumed to be normal distributions, due to the lack of present data concerning distribution functions, as shown in Table 2.2.

Table 2.2: Variables evaluated in the sensitivity analysis

Symbol	Distribution	reference
γ_{cA}	$N(0.055, 0.005)$	estimated by [42]
γ_b	$N(0.7, 0.2)$	estimated by [42]
β_{pA}	$N(0.43, 0.1)$	estimated by [42]
β_{hA}	$N(0.2, 0.05)$	estimated by [42]
η	$N(0.4, 0.1)$	estimated by [42]
μ_c	$N(24, 5)$	estimated by [42]
υ_{pA}	$N(470, 150)$	estimated by [42]
ϵ	$N(0.12, 0.02)$	estimated by [42]
κ_{pA}	$N(0.000005, 0.0000006)$	estimated by [42]

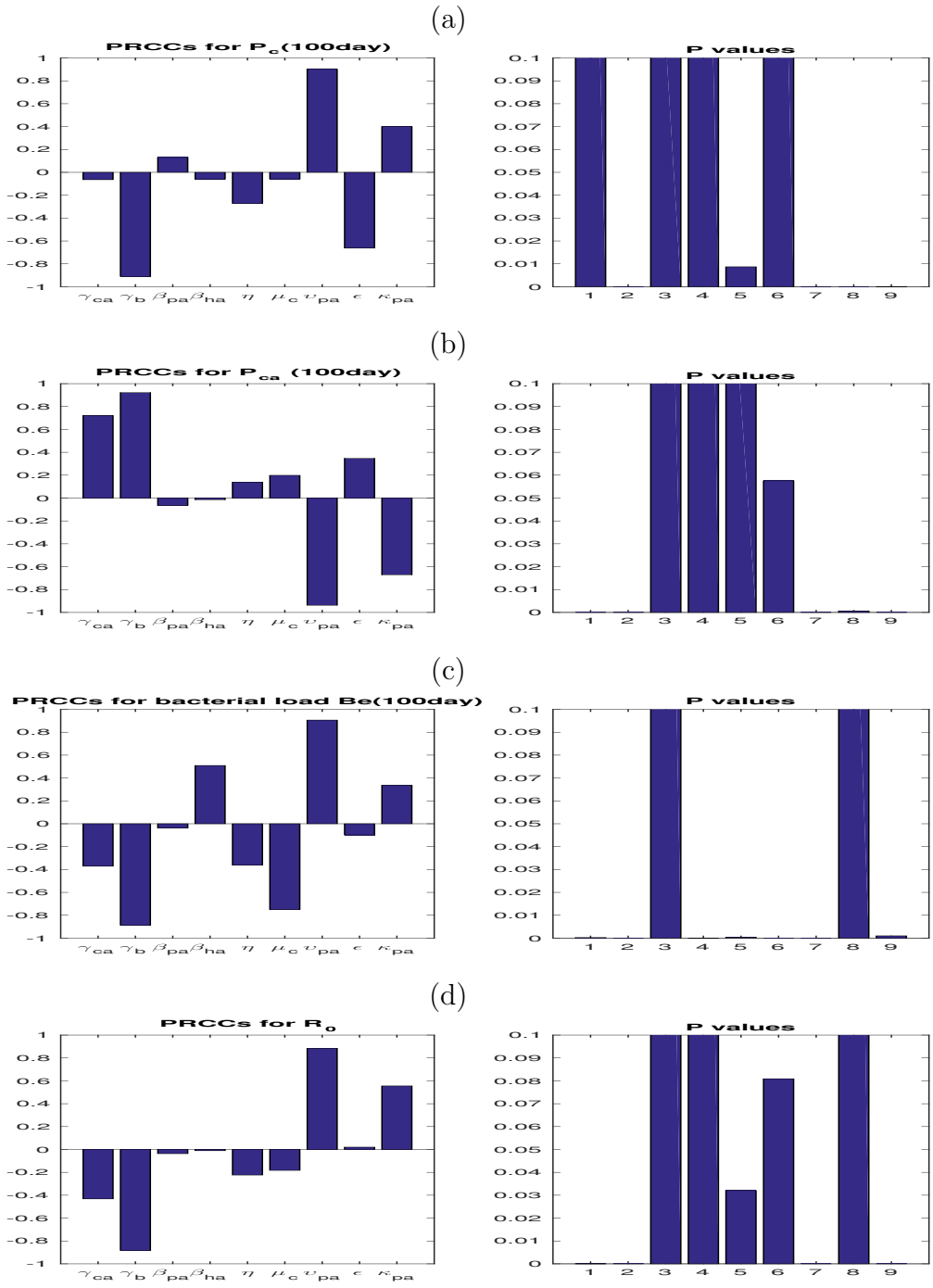

Figure 2.9: (a)-(c) PRCC of the nine parameters for P_c, P_{cA}, B_e whee t=100 day; (e) PRCC for R_0 when $\theta_c = \theta_{cA} = 0$. All the parameters come from Latin Hypercube sampling.

2.4 The Stochastic Model

We know that one disadvantage of deterministic models is that they cannot directly reflect randomness in epidemic events. However, for nosocomial models in hospital subunits, where randomness may matter, there is a need to formulate randomness more precisely. Here we use the techniques introduced in Linda J.S. Allen's book [1] to formulate stochastic epidemic models that relate directly to their deterministic counterparts. According to the underlying assumptions regarding the time and the state variables, stochastic processes usually are described as: 1) discrete time Markov chain (the time and the state variables are discrete), 2) continuous time Markov chain (time is continuous but the state variable is discrete), 3) stochastic differential equation (both the time and the state variables are continuous). Here a continuous-time Markov chain model (CTMC) and a stochastic differential equation model (SDE) are developed ([1], [39]).

2.4.1 Formulation of a CTMC Epidemic model

By the assumption $P_u+P_{uA}+P_c+P_{cA} = N_p, H_u+H_c = N_h, \forall t \geq 0$, we have the process $(P_c, P_{uA}, P_{cA}, H_c, B_e)$ in $\mathcal{R}^5$ with $P_u(t) = N_p - P_{uA} - P_c - P_{cA}$ and $H_u(t) = N_h - H_c$. These five variables have a joint probability denoted by

$$p_{(s,j,k,m,n)}(t) = \Pr(P_c(t) = s, P_{uA}(t) = j, P_{cA}(t) = k, H_c(t) = m, B_e(t) = n)$$

with $s \geq 0, j \geq 0, k \geq 0, 0 \leq s+j+k \leq N_p, 0 \leq m \leq N_h$ and $n \geq 0$. Assume that $\triangle t > 0$ is sufficiently small, the transition probabilities associated with the stochastic

process are defined for a small period of time $\triangle t > 0$ as follows:

$$
\begin{aligned}
&\boldsymbol{p_{(s+i_1,j+i_2,k+i_3,m+i_4,n+i_5);(s,j,k,m,n)}(\triangle t)} \\
&\quad = \Pr[(P_c(t+\triangle t), P_{uA}(t+\triangle t), P_{cA}(t+\triangle t), H_c(t+\triangle t), B_e(t+\triangle t)) = (s+i_1, j+i_2, k+i_3, m+i_4, n+i_5) \\
&\qquad |(P_c(t), P_{uA}(t), P_{cA}(t), H_c(t), B_e(t)) = (s,j,k,m,n)],
\end{aligned}
$$

where $i_1, i_2, i_3, i_4, i_5 \in \{-1, 0, 1\}$, Hence the transition probability is as follow,

$$
\boldsymbol{p_{(s+i_1,j+i_2,k+i_3,m+i_4,n+i_5);(s,j,k,m,n)}(\triangle t)}
$$

$$
= \begin{cases}
\{\theta_c(\gamma_u(N_p - s - j - k) + \gamma_c s + \gamma_{uA} j + \gamma_{cA} k) & \\
+\alpha_p\beta_p(1-\eta)(N_p - s - j - k)m + \kappa_p(N_p - s - j - k)n\}\triangle t & (i_1,i_2,i_3,i_4,i_5) = (1,0,0,0,0) \\
\gamma_c s \triangle t & (i_1,i_2,i_3,i_4,i_5) = (-1,0,0,0,0) \\
\epsilon s \triangle t & (i_1,i_2,i_3,i_4,i_5) = (-1,0,1,0,0) \\
\{\theta_{uA}(\gamma_u(N_p - s - j - k) + \gamma_c s + \gamma_{uA} j + \gamma_{cA} k) + \epsilon(N_p - s - j - k)\}\triangle t & (i_1,i_2,i_3,i_4,i_5) = (0,1,0,0,0) \\
(\kappa_{pA} j n + \gamma_{uA} j)\triangle t & (i_1,i_2,i_3,i_4,i_5) = (0,-1,0,0,0) \\
\alpha_p\beta_{pA}(1-\eta) j m \triangle t & (i_1,i_2,i_3,i_4,i_5) = (0,-1,1,0,0) \\
\{\theta_{cA}(\gamma_u(N_p - s - j - k) + \gamma_c s + \gamma_{uA} j + \gamma_{cA} k) + \kappa_p j n\}\triangle t & (i_1,i_2,i_3,i_4,i_5) = (0,0,1,0,0) \\
\gamma_{cA} k \triangle t & (i_1,i_2,i_3,i_4,i_5) = (0,0,-1,0,0) \\
\{\alpha_p\beta_h(1-\eta)s(N_h - m) + \alpha_p\beta_{hA}(1-\eta)k(N_h - m) + \kappa_h(N_h - m)n\}\triangle t & (i_1,i_2,i_3,i_4,i_5) = (0,0,0,1,0) \\
\mu_c m \triangle t & (i_1,i_2,i_3,i_4,i_5) = (0,0,0,-1,0) \\
(\upsilon_p s + \upsilon_{pA} k + \upsilon_h m)\triangle t & (i_1,i_2,i_3,i_4,i_5) = (0,0,0,0,1) \\
\gamma_b n \triangle t & (i_1,i_2,i_3,i_4,i_5) = (0,0,0,0,-1) \\
0 & otherwise.
\end{cases} \tag{2.4.1}
$$

We must choose the time step $\triangle t$ sufficiently small. In our case it is too complicated to express the transition matrix. Instead, we still are able to express the probabilities $p_{(s,j,k,m,n)}(t+\triangle t)$ by using the Markov property:

$$
\begin{aligned}
&\boldsymbol{p_{(s,j,k,m,n)}(t+\triangle t)} \\
&= p_{(s-1,j,k,m,n)}(t)[\theta_c(\gamma_u(N_p - s + 1 - j - k) + \gamma_c s + \gamma_{uA} j + \gamma_{cA} k) + \alpha_p\beta_p(1-\eta)(N_p - s + 1 - j - k)m \\
&\quad + \kappa_p(N_p - s + 1 - j - k)n]\triangle t + p_{(s+1,j,k,m,n)}(t)\gamma_c(s+1)\triangle t + p_{(s+1,j,k-1,m,n)}(t)\epsilon(s+1)\triangle t \\
&\quad + p_{(s,j-1,k,m,n)}(t)[\theta_{uA}(\gamma_u(N_p - s - j + 1 - k) + \gamma_c s + \gamma_{uA} j + \gamma_{cA} k) + \epsilon(N_p - s - j + 1 - k))]\triangle t \\
&\quad + p_{(s,j+1,k,m,n)}(t)[\kappa_{pA}(j+1)n + \gamma_{uA}(j+1)]\triangle t + p_{(s,j+1,k-1,m,n)}(t)\alpha_p\beta_{pA}(1-\eta)(j+1)m \\
&\quad + p_{(s,j,k-1,m,n)}(t)[\theta_c(\gamma_u(N_p - s - j - k + 1) + \gamma_c s + \gamma_{uA} j + \gamma_{cA}(k+1)) + \kappa_p j n]\triangle t + p_{(s,j,k+1,m,n)}(t)\gamma_{cA}(k+1)\triangle t \\
&\quad + p_{(s,j,k,m-1,n)}(t)[\alpha_p\beta_h(1-\eta)s(N_h - m + 1) + \alpha_p\beta_{hA}(1-\eta)k(N_h - m + 1) + \kappa_h(N_h - m + 1)n]\triangle t \\
&\quad + p_{(s,j,k,m+1,n)}(t)\mu_c(m+1) + p_{(s,j,k,m,n-1)}(t)(\upsilon_p s + \upsilon_{pA} k + \upsilon_h m)\triangle t + p_{(s,j,k,m,n+1)}(t)\gamma_b(n+1)\triangle t + \circ(\triangle t).
\end{aligned}
$$

Naturally, a system of forward Kolmogorov differential equations can be derived:

$$\begin{aligned}
\frac{p_{s,j,k,m,n}}{dt} &= p_{(s-1,j,k,m,n)}[\theta_c(\gamma_u(N_p-s+1-j-k)+\gamma_c s+\gamma_{uA}j+\gamma_{cA}k)+\alpha_p\beta_p(1-\eta)(N_p-s+1-j-k)m \\
&+\kappa_p(N_p-s+1-j-k)n]+p_{(s+1,j,k,m,n)}(t)\gamma_c(s+1)+p_{(s+1,j,k-1,m,n)}(t)\epsilon(s+1) \\
&+p_{(s,j-1,k,m,n)}(t)[\theta_{uA}(\gamma_u(N_p-s-j+1-k)+\gamma_c s+\gamma_{uA}j+\gamma_{cA}k)+\epsilon(N_p-s-j+1-k))] \\
&+p_{(s,j+1,k,m,n)}(t)[\kappa_{pA}(j+1)n+\gamma_{uA}(j+1)]\triangle t+p_{(s,j+1,k-1,m,n)}(t)\alpha_p\beta_{pA}(1-\eta)(j+1)m \\
&+p_{(s,j,k-1,m,n)}(t)[\theta_c(\gamma_u(N_p-s-j-k+1)+\gamma_c s+\gamma_{uA}j+\gamma_{cA}(k+1))+\kappa_p jn] \\
&+p_{(s,j,k+1,m,n)}(t)\gamma_{cA}(k+1)+p_{(s,j,k,m-1,n)}(t)[\alpha_p\beta_h(1-\eta)s(N_h-m+1)+\alpha_p\beta_{hA}(1-\eta)k(N_h-m+1) \\
&+\kappa_h(N_h-m+1)n] \\
&+p_{(s,j,k,m+1,n)}(t)\mu_c(m+1)+p_{(s,j,k,m,n-1)}(t)(\upsilon_p s+\upsilon_{pA}k+\upsilon_h m)+p_{(s,j,k,m,n+1)}(t)\gamma_b(n+1).
\end{aligned}$$

2.4.2 Formulation of a SDE Epidemic Model

We now try to develop a SDE model from the deterministic epidemic model (2.1.1). The system has five variables with a joint probability defined by:

$$p_{(s,j,k,m,n)}(t) = \Pr\{P_c(t)=s, P_{uA}(t)=j, P_{cA}(t)=k, H_c(t)=m, B_e(t)=n\}$$

with $s,j,k=0,...,N_p, m=0...N_h$, and $n\geq 0$, with transition probabilities given in (2.4.1). Let $X(t)=(P_c(t),P_{uA}(t),P_{cA}(t),H_c(t),B_e(t))^T$ with infinitesimal

$$\triangle X(t)=(\triangle P_c(t),\triangle P_{uA}(t),\triangle P_{cA}(t),\triangle H_c(t),\triangle B_e(t))^T,$$

where $\triangle X(t)=X(t+\triangle t)-X(t)$. In addition, we assue that $\triangle X(t)$ has an approximate normal distribution for small $\triangle t$. Hence the random vector $X(t+\triangle t)$ can be

approximated as follows:

$$X(t+\triangle t) = X(t) + \triangle X(t) \approx X(t) + E(\triangle X(t)) + \sqrt{V(\triangle X(t))},$$

where the covariance matrix of $\triangle X(t)$ is

$$V(\triangle X(t)) = E((\triangle X(t))(\triangle X(t))^T) - E(\triangle X(t))E(\triangle X(t))^T \approx E((\triangle X(t))(\triangle X(t))^T)$$

because the elements in the second term are $o([\triangle t]^2)$. So we express the infinitesimal mean matrix $f(X(t),t)$ to order $\triangle t$ as follows:

$$E(\triangle X(t)|X(t)) = \begin{pmatrix} e_c \\ e_{uA} \\ e_{cA} \\ e_h \\ e_b \end{pmatrix} \triangle t = f(X(t),t)\triangle t,$$

where

$e_c = \theta_c(\gamma_u(N_h - P_c - P_{uA} - P_{cA}) + \gamma_c P_c + \gamma_{uA} P_{uA} + \gamma_{cA} P_{cA}) + \alpha_p \beta_p (1-\eta)(N_h - P_c - P_{uA} - P_{cA})H_c + \kappa_p P_u B_e - \gamma_c P_c - \epsilon P_c,$

$e_{uA} = \theta_{uA}(\gamma_u(N_h - P_c - P_{uA} - P_{cA}) + \gamma_c P_c + \gamma_{uA} P_{uA} + \gamma_{cA} P_{cA}) - \alpha_p \beta_{pA}(1-\eta) P_{uA} H_c - \kappa_{pA} P_{uA} B_e - \gamma_{uA} P_{uA} + \epsilon(N_h - P_c - P_{uA} - P_{cA}),$

$e_{cA} = \theta_{cA}(\gamma_u(N_h - P_c - P_{uA} - P_{cA}) + \gamma_c P_c + \gamma_{uA} P_{uA} + \gamma_{cA} P_{cA}) + \alpha_p \beta_{pA}(1-\eta) P_{uA} H_c + \kappa_{pA} P_{uA} Be - \gamma_{cA} P_{cA} + \epsilon P_c,$

$e_h = \alpha_p \beta_h (1-\eta) P_c (N_h - H_c) + \alpha_p \beta_{hA} (1-\eta) P_{cA} (N_h - H_c) + \kappa_h (N_h - H_c) B_e - \mu_c H_c,$

$e_b = \upsilon_p P_c + \upsilon_{pA} P_{cA} + \upsilon_h H_c - \gamma_b B_e.$

and also the infinitesimal variance matrix $\Sigma(X(t)t)$ to order $\triangle t$:

$$
\begin{aligned}
&E(\triangle X(t)(\triangle X(t))^T|X(t)) \\
&= \begin{pmatrix}
\delta_c & 0 & -\epsilon P_c & 0 & 0 \\
0 & \delta_{uA} & -\alpha_p\beta_{pA}(1-\eta)P_{uA}H_c & 0 & 0 \\
-\epsilon P_c & -\alpha_p\beta_{pA}(1-\eta)P_{uA}H_c & \delta cA & 0 & 0 \\
0 & 0 & 0 & \delta_h & 0 \\
0 & 0 & 0 & 0 & \delta_b
\end{pmatrix} \triangle t \\
&= \Sigma(X(t),t)\triangle t,
\end{aligned}
$$

where

$\delta_c = \theta_c(\gamma_u(N_h - P_c - P_{uA} - P_{cA}) + \gamma_c P_c + \gamma_{uA}P_{uA} + \gamma_{cA}P_{cA}) + \alpha_p\beta_p(1-\eta)(N_h - P_c - P_{uA} - P_{cA})H_c + \kappa_p P_u B_e + \gamma_c P_c + \epsilon P_c,$

$\delta_{uA} = \theta_{uA}(\gamma_u(N_h - P_c - P_{uA} - P_{cA}) + \gamma_c P_c + \gamma_{uA}P_{uA} + \gamma_{cA}P_{cA}) + \alpha_p\beta_{pA}(1-\eta)P_{uA}H_c + \kappa_{pA}P_{uA}B_e + \gamma_{uA}P_{uA} + \epsilon(N_h - P_c - P_{uA} - P_{cA}),$

$\delta_{cA} = \theta_{cA}(\gamma_u(N_h - P_c - P_{uA} - P_{cA}) + \gamma_c P_c + \gamma_{uA}P_{uA} + \gamma_{cA}P_{cA}) + \alpha_p\beta_{pA}(1-\eta)P_{uA}H_c + \kappa_{pA}P_{uA}B_e + \gamma_{cA}P_{cA} + \epsilon P_c,$

$\delta_h = \alpha_p\beta_h(1-\eta)P_c(N_h - H_c) + \alpha_p\beta_{hA}(1-\eta)P_{cA}(N_h - H_c) + \kappa_h(N_h - H_c)B_e + \mu_c H_c,$

$\delta_b = \upsilon_p P_c + \upsilon_{pA}P_{cA} + \upsilon_h H_c + \gamma_b B_e.$

It is easy to check that $\delta_c, \delta_{uA}, \delta_{cA}, \delta_h, \delta_b$ are all nonnegative. Hence we have a matrix G satisfying $GG^T = \Sigma$, where G is a 5×12 matrix to order $\triangle t$,

$$
G = \begin{pmatrix}
\sqrt{a_1} & -\sqrt{a_2} & -\sqrt{a_3} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & \sqrt{a_4} & -\sqrt{a_5} & -\sqrt{a_6} & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & \sqrt{a_3} & 0 & 0 & \sqrt{a_6} & \sqrt{a_7} & -\sqrt{a_8} & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \sqrt{a_9} & -\sqrt{a_{10}} & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \sqrt{a_{11}} & -\sqrt{a_{12}}
\end{pmatrix},
$$

where

$a_1 = \theta_c(\gamma_u(N_h - P_c - P_{uA} - P_{cA}) + \gamma_c P_c + \gamma_{uA} P_{uA} + \gamma_{cA} P_{cA}) + \alpha_p \beta_p (1-\eta)(N_h - P_c - P_{uA} - P_{cA}) H_c + \kappa_p P_u Be,$

$a_2 = \gamma_c P_c,$

$a_3 = \epsilon P_c,$

$a_4 = \theta_{uA}(\gamma_u(N_h - P_c - P_{uA} - P_{cA}) + \gamma_c P_c + \gamma_{uA} P_{uA}) + \epsilon(N_h - P_c - P_{uA} - P_{cA}),$

$a_5 = \kappa_{pA} P_{uA} Be + \gamma_{cA} P_{cA},$

$a_6 = \alpha_p \beta_{pA} (1-\eta) P_{uA} H_c,$

$a_7 = \theta_{cA}(\gamma_u(N_h - P_c - P_{uA} - P_{cA}) + \gamma_c P_c + \gamma_{uA} P_{uA} + \gamma_{cA} P_{cA}) + \kappa_{pA} P_{uA} Be,$

$a_8 = \gamma_{cA} P_{cA},$

$a_9 = \alpha_p \beta_h (1-\eta) P_c (N_h - H_c) + \alpha_p \beta_{hA} (1-\eta) P_{cA} (N_h - H_c) + \kappa_h (N_h - H_c) Be,$

$a_{10} = \mu_c H_c,$

$a_{11} = \upsilon_p P_c + \upsilon_{pA} P_{cA} + \upsilon_h H_c,$

$a_{12} = \gamma_b Be.$

Then the stochastic differential equations have the following form:

$$dX(t) = f(X(t), t)dt + G(X(t), t)dW(t).$$

More precisely,

$$\begin{cases} dP_c(t) = e_c dt + \sqrt{a_1} dW_1 - \sqrt{a_2} dW_2 - \sqrt{a_3} dW_3, \\ dP_{uA}(t) = e_{uA} dt + \sqrt{a_4} dW_4 - \sqrt{a_5} dW_5 - \sqrt{a_6} dW_6, \\ dP_{cA}(t) = e_{cA} dt + \sqrt{a_3} dW_3 + \sqrt{a_6} dW_6 + \sqrt{a_7} dW_7 - \sqrt{a_8} dW_8, \\ dH_c t = e_h dt + \sqrt{a_9} dW_9 - \sqrt{a_{10}} dW_{10}, \\ dBe(t) = e_b dt + \sqrt{a_{11}} dW_{11} - \sqrt{a_{12}} dW_{12}. \end{cases} \tag{2.4.2}$$

where $W_1, \cdots, W_{12}$ are twelve independent Wiener processes. Briefly speaking, the Wiener process depends continuously on t, and has stationary independent increments, i.e., the increments $\triangle W$ depend only on $\triangle t$ with

$$\triangle W = W(t + \triangle t) - W(t) \sim N(0, \triangle t).$$

Hence we are able to run stochastic simulations by Matlab [2]. For example, consider

$$P_c(j+1) = P_c(j) + e_c \cdot dt + \sqrt{a_1} \cdot \sqrt{dt} \cdot n_1 - \sqrt{a_2} \cdot \sqrt{dt} \cdot n_2 - \sqrt{a_3} \cdot \sqrt{dt} \cdot n_3$$

where $dt = 0.0001$ is the time step and $n_i, i = 1, 2, 3$ are independent standard normal random variables.

2.4.3 Stochastic Simulations

Using the baseline parameters in Table 2.1, Fig.2.10 gives the behaviors of the model (2.4.2). With no admission of MRSA-positive patients ($\theta_c = \theta_{cA} = 0$), Fig.2.11 shows the behaviors of the model (2.4.2). The simulations are given in Fig.2.12 when there is no admission of patients with history of antibiotic exposure and MRSA-

positive ($\theta_{uA} = \theta_c = \theta_{cA} = 0$). We can see that the stochastic results are roughly consistent with the deterministic results (Figs.2.2-2.6). In Figs.2.13-2.15, we use stochastic models to see the effect of antibiotic prescribing rate ϵ, the discharge rate of colonized patients with antibiotic exposure γ_{cA}, and environmental cleaning rate γ_b on the number of colonized patients, respectively.

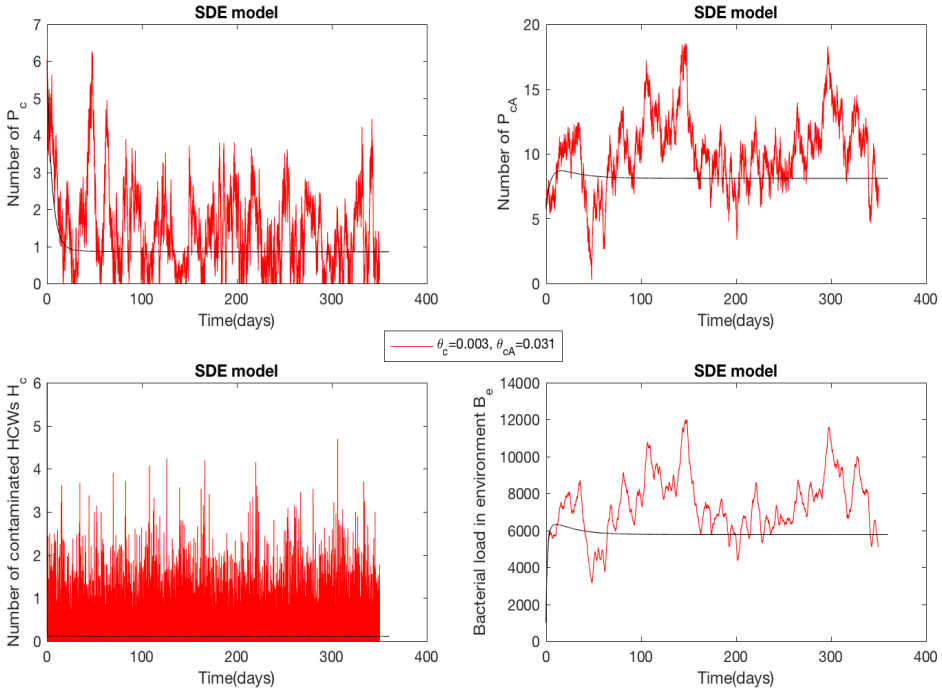

Figure 2.10: Behavior of the SDE model with all the parameter values shown in Table 2.1, especially $\theta_c = 0.003, \theta_{cA} = 0.031$ on admission.

2.5 Discussion

For the deterministic model, numerical simulations were performed to demonstrate the behavior of the solutions and the dependence and sensitivity of the basic reproduc-

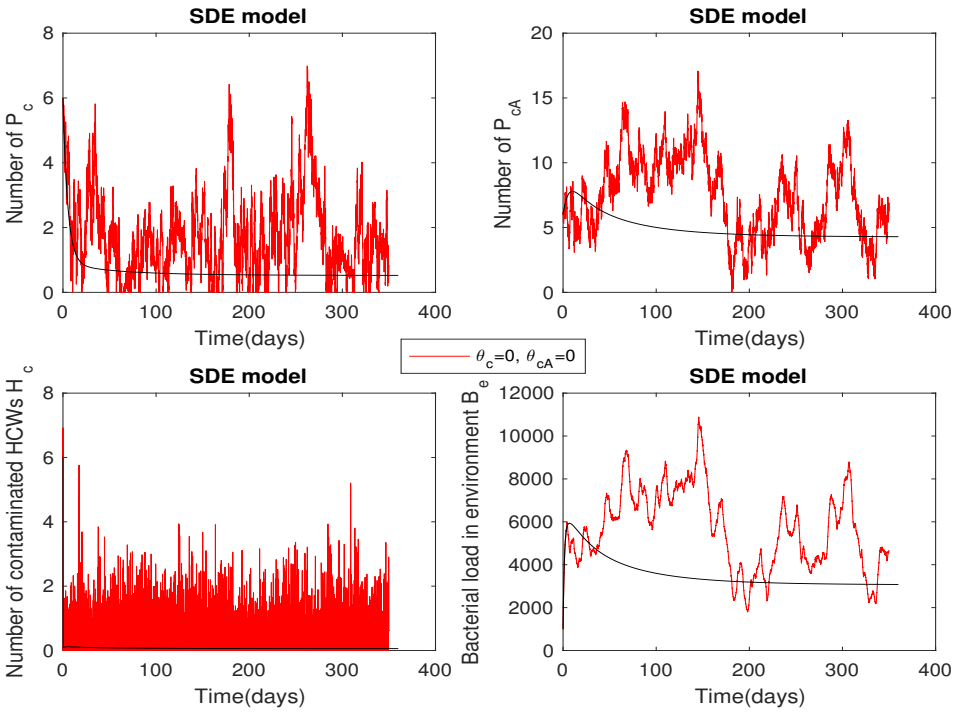

Figure 2.11: Behavior of the SDE model with the parameters shown in Table 2.1 and $\theta_c = \theta_{cA} = 0$ on admission, i.e., there is no admission of MRSA colonized patients.

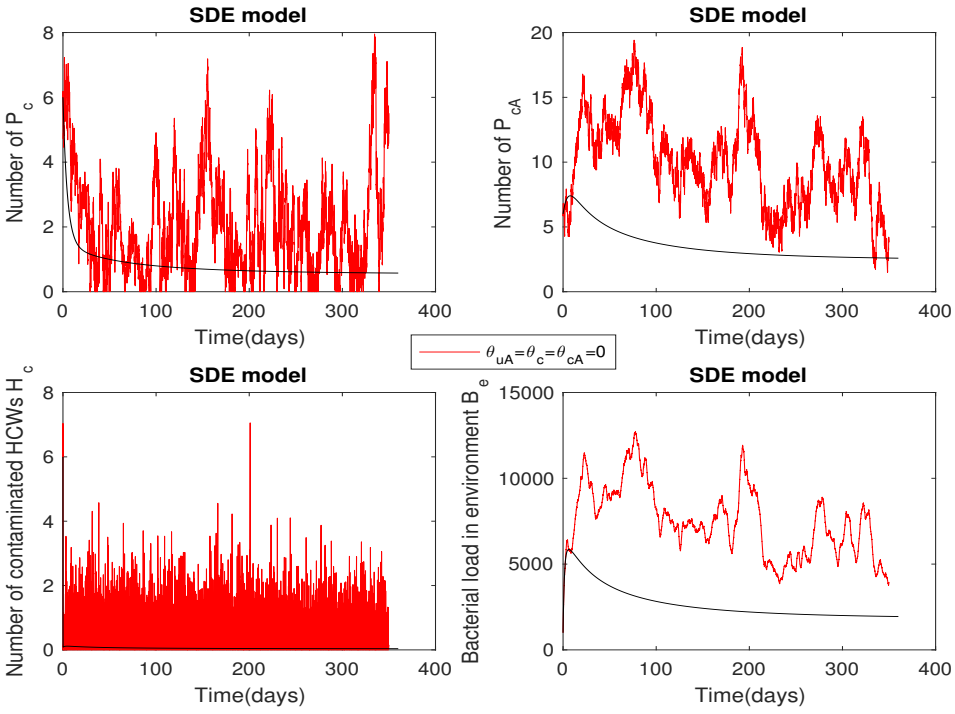

Figure 2.12: When $\theta_{uA} = \theta_c = \theta_{cA} = 0$ on admission, i.e., there is no admission of MRSA colonized patients and no admission of patients with antibiotic exposure, behavior of the SDE model with other parameters shown in Table 2.1.

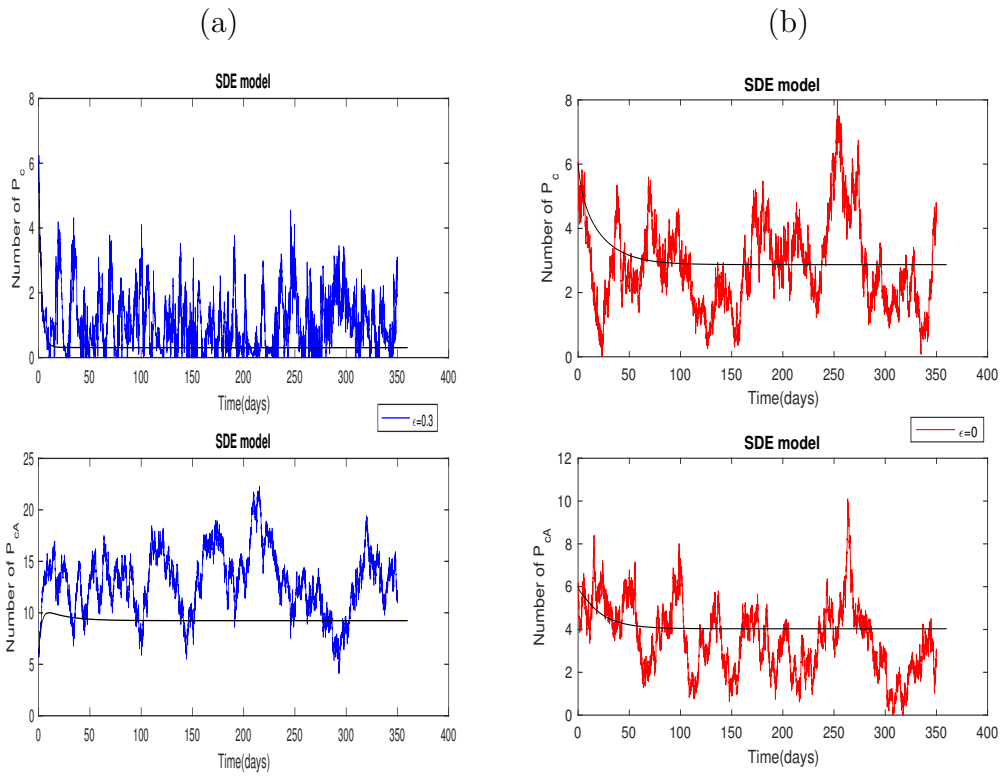

Figure 2.13: (a) When antibiotic prescribing rate ϵ=0.3, the number of colonized patients in stochastic simulations; (b) When antibiotic prescribing rate ϵ=0, the number of colonized patients in stochastic simulations.

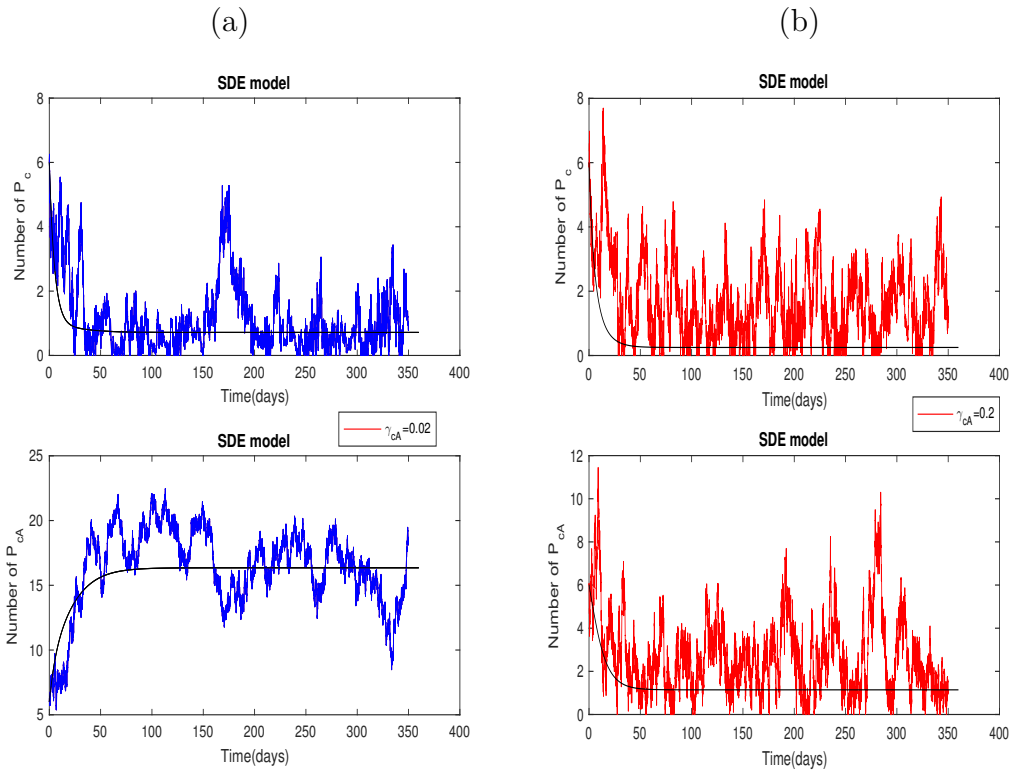

Figure 2.14: (a) When discharge rate of colonized patients with antibiotic exposure γ_{cA}=0.02 (i.e., length of stay in hospital is 50 days for P_{cA}), the number of colonized patients in stochastic simulations; (b) When discharge rate of colonized patients with antibiotic exposure γ_{cA}=0.2 (i.e., length of stay in hospital is 5 days for P_{cA}), the number of colonized patients in stochastic simulations.

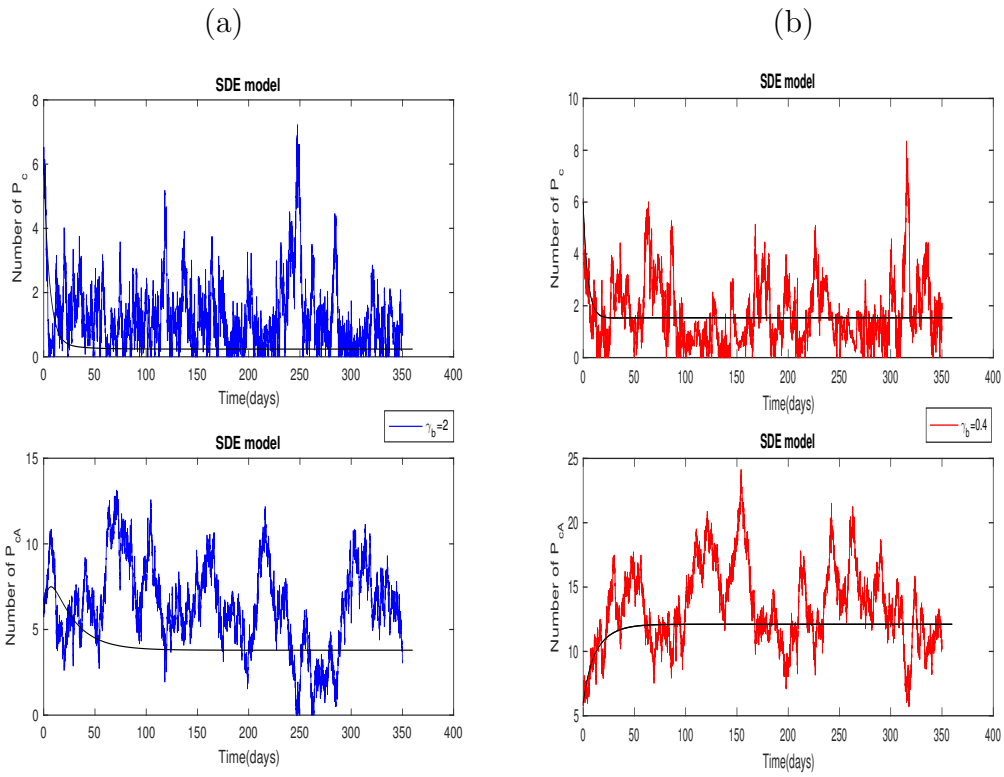

Figure 2.15: (a) When environmental cleaning rate γ_b=2, the number of colonized patients in stochastic simulations; (b) When environmental cleaning rate γ_b=0.4, the number of colonized patients in stochastic simulations.

tion number of various parameters. For the stochastic model, numerical simulations were also carried out to study the effect of antibiotic prescribing rate ϵ, the discharge rate of colonized patients with antibiotic exposure γ_{cA}, and environmental cleaning rate γ_b on the number of colonized patients, respectively.

The simulation results showed that higher discharge rate is associated with lower prevalence of MRSA, which implies that treating patients with antibiotic exposure as quickly and effectively as possible may be an effective strategy. However, on the other hand, patients with antibiotic exposure are more challenging to be treated efficiently and quickly. Hence, this emphasizes the importance of effective antimicrobial stewardship programs in reducing antibiotic usage both in hospital and community. We also found that environmental cleaning is the most efficient intervention. Hospitals should try to use more effective cleaning products, train and monitor the efficacy of cleaning with feedback to cleaning teams. Hand hygiene is also an effective intervention. Finally, screening to reduce admission of colonized patients into the hospital is crucial for the spread and control of MRSA (Figs. 2.4-2.6, 2.10-2.12). Actually, our results suggest that when colonized patients are admitted, MRSA infections always persist in the hospital. Hence, we suggest that active screening at admission and subsequent isolation of positive cases are important to control the infection.

Chapter 3

The extended model of Methicillin-resistant *Staphylococcus aureus* infections in hospitals with environmental contamination

3.1 Background

In recent decades seasonal variation of MRSA infections in the hospital settings has been widely observed, especially in surgical wounds, skin and soft tissue, urine, and respiratory tract in young children [18], [22], [25], [12], [28], [34]. Reasons for this seasonal variation of MRSA infections in hospital are very complicated and still controversial. Previous studies believe that the seasonality involves temperature variation, insect bites, seasonal influenza, community-associated MRSA (CA-MRSA) infection, school season, seasonal community antibiotic use, which may result in a seasonal pattern of antibiotic prescriptions in hospitals. In particular, in the work of Sun et al [34], seasonality in the prescription data was found (see Fig.3.1). Moreover, they performed a seasonal decomposition analysis for the MRSA isolates and found out that both fluoroquinolone prescriptions and the percentage of MRSA isolates that were

resistant to ciprofloxacin peaked in the winter. A similar result was found for both the percentage of MRSA isolates resistant to clindamycin and macrolide/lincosamide prescriptions (see Fig.3.2). Though this does not totally reflect the antibiotic usage in hospitals, it seems likely that the usage of antibiotics in hospitals also fluctuates seasonally [34] [28]. Inspired by their work, we model the antibiotic prescribing rate as a periodic function depending on time t in the transmission of MRSA, which has a period of 365 days and represents that antibiotic prescribing rate increases starting at the beginning of August, reaches a peak in winter and then decreases starting at the beginning of February according to the data shown in Fig.3.2.

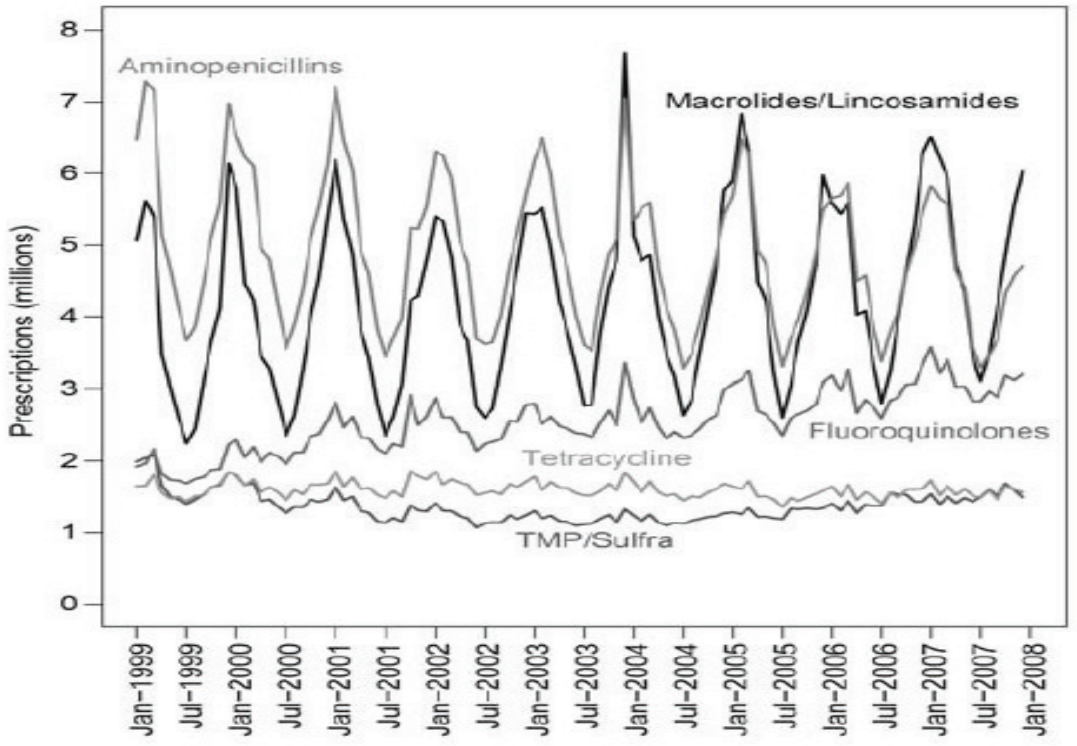

Figure 3.1: Number of prescriptions for antibiotic drug classes, by month. Source: IMS Health, Xponent, 1999-2007. Abbreviation: TMP/Sulfra, trimethoprim/sulfamethoxazole [34].

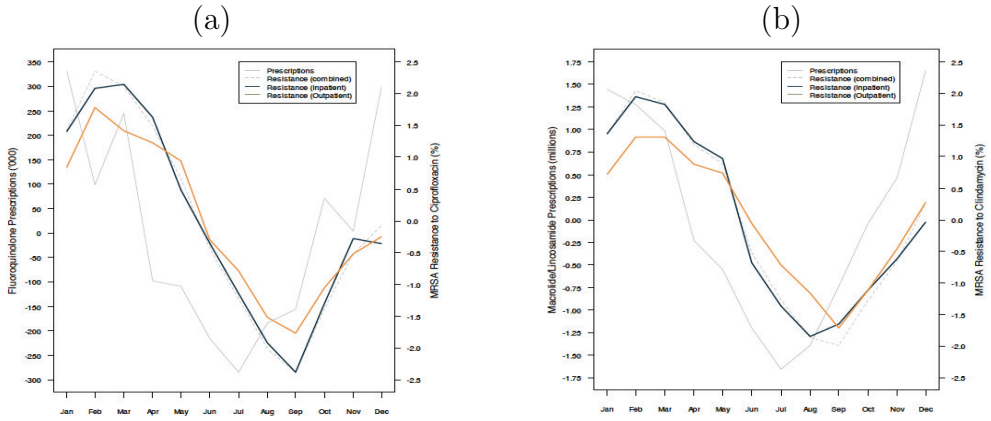

Figure 3.2: (a) Seasonal pattern of fluoroquinolone prescriptions and MRSA isolates resistant to ciprofloxacin; Mean monthly seasonal variation for fluoroquinolone prescriptions and MRSA isolates resistant to clindamycin for inpatient, outpatient and combined isolates as calculated by STL method. Prescription data source: IMS Health, Xponent, 1999-2007; Resistance data source: The Surveillance Network (TSN) Database-USA (Focus Diagnostics, Herndon, VA, USA); (b) Seasonal pattern of macrolide and lincosamide prescriptions and MRSA isolates resistant to ciprofloxacin; Mean monthly seasonal variation for macrolide and lincosamide prescriptions and MRSA isolates resistant to clindamycin for inpatient, outpatient and combined isolates as calculated by STL method. Prescription data source: IMS Health, Xponent, 1999-2007; Resistance data source: The Surveillance Network (TSN) Database-USA (Focus Diagnostics, Herndon, VA, USA) [34].

To the best of our knowledge, no model has been developed to address the seasonality in the transmission of MRSA. However, discussing seasonal variable of MRSA may be helpful in developing effeicient control programs, lowering the long-term health risks, and distributing public resources.

In this chapter, we extend the deterministic model developed in previous chapter to be a periodic mathematical model to describe a comprehensive transmission of MRSA. Boundedness and positivity of solutions, the basic reproduction number, the extinction and uniform persistence of infections are analyzed. Simulations and discussion of the extended model behaviors and sensitive analysis of the basic reproduction number are given.

3.2 The Periodic Deterministic Model

We first denote the patients, health-care workers (HCWS) and free-living bacteria in the environment as the following seven compartments:

$P_u(t)$=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 health care workers at time t.

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

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

The flowchart describing the transmission dynamics of MRSA in hospitals among these seven compartments is given in Fig.2.1.

Based on the seasonal pattern of antibiotic usage found in Sun et al [34], we use a periodic function $\epsilon(t) = \epsilon_0(1 + \epsilon_1 \sin(\frac{2\pi}{365}(t - 240)))$ to describe the antibiotic prescription rate in the hospital. $\epsilon(t)$ has a period of 365 days, and represents that antibiotic prescription rate increases starting at the beginning of August, gains a peak in winter and then decreases starting at the beginning of February according to the data shown in Figs.3.1-3.2. ϵ_0 is the baseline antibiotic prescription rate and ϵ_1 is the magnitude of change.

Detailed parameter values are given in Table 2.1. We hence formulate the periodic mathematical model as follows:

$$\frac{dP_u}{dt} = \theta_u\Omega(t) - \alpha_p\beta_p(1-\eta)P_uH_c - \kappa_pP_uB_e - \gamma_uP_u - \epsilon(t)P_u,$$

$$\frac{dP_c}{dt} = \theta_c\Omega(t) + \alpha_p\beta_p(1-\eta)P_uH_c + \kappa_pP_uB_e - \gamma_cP_c - \epsilon(t)P_c,$$

$$\frac{dP_{uA}}{dt} = \theta_{uA}\Omega(t) - \alpha_p\beta_{pA}(1-\eta)P_{uA}H_c - \kappa_{pA}P_{uA}B_e - \gamma_{uA}P_{uA} + \epsilon(t)P_u,$$

$$\frac{dP_{cA}}{dt} = \theta_{cA}\Omega(t) + \alpha_p\beta_{pA}(1-\eta)P_{uA}H_c + \kappa_{pA}P_{uA}B_e - \gamma_{cA}P_{cA} + \epsilon(t)P_c, \qquad (3.2.1)$$

$$\frac{dH_u}{dt} = -\alpha_p\beta_h(1-\eta)P_cH_u - \alpha_p\beta_{hA}(1-\eta)P_{cA}H_u - \kappa_hH_uB_e + \mu_cH_c,$$

$$\frac{dH_c}{dt} = \alpha_p\beta_h(1-\eta)P_cH_u + \alpha_p\beta_{hA}(1-\eta)P_{cA}H_u + \kappa_hH_uB_e - \mu_cH_c,$$

$$\frac{dB_e}{dt} = \upsilon_pP_c + \upsilon_{pA}P_{cA} + \upsilon_hH_c - \gamma_bB_e,$$

where $\Omega(t) = \gamma_uP_u+\gamma_cP_c+\gamma_{uA}P_{uA}+\gamma_{cA}P_{cA}$, and we denote $\epsilon(t) = \epsilon_0(1+\epsilon_1\sin(\frac{2\pi}{365}(t-240)))$,

with initial conditions $P_u(0) = P_u^0$, $P_{uA}(0) = P_{uA}^0$, $P_c(0) = P_c^0$, $P_{cA}(0) = P_{cA}^0$, $H_u(0) = H_u^0$, $H_c(0) = H_c^0$, $B_e(0) = B_e^0$ at time 0.

3.3 Mathematical Analysis

3.3.1 Basic Reproduction Number

The basic reproduction number R_0 for the periodic deterministic model (3.2.1) is constructed according to the definition in Bacaër and Guenaoui [3] and follows the general calculation procedure in Wang and Zhao [41]. When θ_u=0, θ_c=0, and θ_{cA}=0, that is only uncolonized patients with antibiotic exposure are admitted into hospital, the infection-free infection (IFE) is defined as

$$E_0 = (P_u, P_c, P_{uA}, P_{cA}, H_u, H_c, B_e) = (0, 0, N_p, 0, N_h, 0, 0),$$

We can rewrite the variables of periodic ODE system (3.2.1) as a vector $E_0 = (P_c, P_{cA}, H_c, B_e, P_u, P_{uA}, H_u) = (0, 0, 0, 0, 0, N_p, N_h)$. Following the general calculation procedure in Wang and Zhao [41], we have

$$\mathcal{F} = \begin{pmatrix} \alpha_p\beta_p(1-\eta)P_uH_c + \kappa_pP_uB_e \\ \alpha_p\beta_{pA}(1-\eta)P_{uA}H_c + \kappa_{pA}P_{uA}B_e \\ \alpha_p\beta_h(1-\eta)P_cH_u + \alpha_p\beta_{hA}(1-\eta)P_{cA}H_u + \kappa_hH_uB_e \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix},$$

$$\mathcal{V} = \begin{pmatrix} \gamma_c P_c + \epsilon(t) P_c - \theta_c \Omega \\ \gamma_{cA} P_{cA} - [\epsilon(t) P_c + \theta_{cA} \Omega] \\ \mu_c H_c \\ \gamma_b B_e - (\upsilon_p P_c + \upsilon_{pA} P_{cA} + \upsilon_h H_c) \\ \alpha_p \beta_p (1-\eta) P_u H_c + \kappa_p P_u B_e + \gamma_u P_u + \epsilon(t) P_u - \theta_u \Omega \\ \alpha_p \beta_{pA} (1-\eta) P_{uA} H_c + \kappa_{pA} P_{uA} B_e + \gamma_{uA} P_{uA} - [\epsilon(t) P_u + \theta_{uA} \Omega] \\ \alpha_p \beta_h (1-\eta) P_c H_u + \alpha_p \beta_{hA} (1-\eta) P_{cA} H_u + \kappa_h H_u B_e - \mu_c H_c \end{pmatrix},$$

where $\epsilon(t) = \epsilon_0(1 + \epsilon_1 \sin(\frac{2\pi}{365}(t - 240)))$ and $\Omega(t) = (\gamma_u P_u + \gamma_c P_c + \gamma_{uA} P_{uA} + \gamma_{cA} P_{cA})$. We also have

$$\mathcal{V}^- = \begin{pmatrix} \gamma_c P_c + \epsilon(t) P_c \\ \gamma_{cA} P_{cA} \\ \mu_c H_c \\ \gamma_b B_e \\ \alpha_p \beta_p (1-\eta) P_u H_c + \kappa_p P_u B_e + \gamma_u P_u + \epsilon(t) P_u \\ \alpha_p \beta_{pA} (1-\eta) P_{uA} H_c + \kappa_{pA} P_{uA} B_e + \gamma_{uA} P_{uA} \\ \alpha_p \beta_h (1-\eta) P_c H_u + \alpha_p \beta_{hA} (1-\eta) P_{cA} H_u + \kappa_h H_u B_e \end{pmatrix},$$

$$\mathcal{V}^+ = \begin{pmatrix} \theta_c \Omega \\ \epsilon(t) P_c + \theta_{cA} \Omega \\ 0 \\ \upsilon_p P_c + \upsilon_{pA} P_{cA} + \upsilon_h H_c \\ \theta_u \Omega \\ \epsilon(t) P_u + \theta_{uA} \Omega \\ \mu_c H_c \end{pmatrix}.$$

So we derive that

$$F(t) = \begin{pmatrix} 0 & 0 & 0 & 0 \\ 0 & 0 & \alpha_p\beta_{pA}(1-\eta)N_p & \kappa_{pA}N_p \\ \alpha_p\beta_h(1-\eta)N_h & \alpha_p\beta_{hA}(1-\eta)N_h & 0 & \kappa_h N_h \\ 0 & 0 & 0 & 0 \end{pmatrix},$$

$$V(t) = \begin{pmatrix} \gamma_c + \epsilon(t) & 0 & 0 & 0 \\ -\epsilon(t) & \gamma_{cA} & 0 & 0 \\ 0 & 0 & \mu_c & 0 \\ -\upsilon_p & -\upsilon_{pA} & -\upsilon_h & \gamma_b \end{pmatrix},$$

and

$$M(t) = \begin{pmatrix} -\gamma_u - \epsilon(t) & 0 & 0 \\ \gamma_u + \epsilon(t) & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix}.$$

Let $Y(t,s)$, $t \geq s$ be the evolution operator of the system

$$\frac{dy}{dt} = -V(t)y. \tag{3.3.1}$$

That is, for each $s \in \mathcal{R}$, the 4×4 matrix $Y(t,s)$ satisfies

$$\frac{d}{dt}Y(t,s) = -V(t)Y(t,s), \forall t \geq s, Y(s,s) = I,$$

where I is the 4×4 identity matrix. In order to characterize R_0, we consider the following linear ω-periodic system

$$\frac{dw}{dt} = [-V(t) + \frac{F(t)}{\lambda}]\ \omega, t \in \mathcal{R}_+ \tag{3.3.2}$$

with parameter $\lambda \in (0, \infty)$. Let $W(t, s, \lambda),\ t \geq s$, be the evolution operator of the system (3.3.2) on $\mathcal{R}^4$. Clearly, $\Phi_{F-V} = W(t, 0, 1), \forall t \geq 0$.

According to the method in Wang and Zhao [41], we let ϕ be ω-periodic in s and the initial distribution of infectious individuals. So $F(s)\phi(s)$ is the rate of new infections produced by the infected individuals who were introduced at time s. When $t \geq s,\ Y(t, s)F(s)\phi(s)$ gives the distribution of those infected individuals who were newly infected by $\phi(s)$ and remain in the infected compartments at time t. Naturally,

$$\int_{-\infty}^{t} Y(t, s)F(s)\phi(s)ds = \int_{0}^{\infty} Y(t, t-a)F(t-a)\phi(t-a)da$$

is the distribution of accumulative new infections at time t produced by all those infected individuals $\phi(s)$ introduced at time previous to t.

Let C_ω be the ordered Banach space of all ω-periodic functions from $\mathcal{R}$ to $\mathcal{R}^4$, which is equipped with the maximum norm $\|\cdot\|$ and the positive cone $C_\omega^+ := \{\phi \in C_\omega : \phi(t) \geq 0, \forall t \in \mathcal{R}_+\}$. Then we can define a linear operator $L : C_\omega \to C_\omega$ by

$$(L\phi)(t) \int_{0}^{\infty} Y(t, t-a)F(t, t-a)\phi(t-a)da, \forall t \in \mathcal{R}_+, \phi \in C_\omega,$$

L is called the next infection operator and the spectral radius of L is defined as the basic reproduction number

$$R_0 := \rho(L)$$

for the periodic epidemic model. In order to determine the threshold dynamics, we use Theorems 2.1 and 2.2 in Wang and Zhao [41]. First of all, we need to verify the seven assuptions in the theorems.

(A1)-(A5) The first five conditions can be easily verified by observing $\mathcal{F}$, $\mathcal{V}^+$ and $\mathcal{V}^-$.

(A6) $\rho(\Phi_M(\omega)) < 1$, where $\rho(\Phi_M(\omega))$ is the spectral radius of $\Phi_M(\omega)$. $\Phi_M(t)$ is the monodromy matrix of the linear ω-periodic system $\frac{dq}{dt} = M(t)q$ with

$$M = \begin{pmatrix} -\gamma_u - \epsilon(t) & 0 & 0 \\ \gamma_u + \epsilon(t) & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix}.$$

Hence, we have,

$$\Phi_M(t) = \begin{pmatrix} 0 & 0 & e^{-\int \gamma_u + \epsilon(t)dt} \\ \frac{1}{2} & \frac{1}{2} & -e^{-\int \gamma_u + \epsilon(t)dt} \\ 0 & \frac{1}{2} & 0 \end{pmatrix}.$$

It is obvious that $\rho(\Phi_M(t)) < 1$, since $e^{-\int \gamma_u + \epsilon(t)dt} < 1$ based on $\gamma_u + \epsilon(t) > 0$ in our parameter setting.

(A7) $\rho(\Phi_{-V}(\omega)) < 1$, where $\Phi_{-V}(t)$ is the monodromy matrix of the linear ω-periodic sysstem $\frac{dy}{dt} = -V(t)y$ with

$$-V = \begin{pmatrix} -\gamma_c - \epsilon(t) & 0 & 0 & 0 \\ \epsilon(t) & -\gamma_{cA} & 0 & 0 \\ 0 & 0 & -\mu_c & 0 \\ \upsilon_p & \upsilon_{pA} & \upsilon_h & -\gamma_b \end{pmatrix}.$$

Hence, we have,

$$\Phi_{-V}(t) = \begin{pmatrix} e^{-\int \gamma_u + \epsilon(t)dt} & 0 & 0 & 0 \\ c_1 & e^{-\gamma_{cA}t} & 0 & 0 \\ c_2 & 0 & e^{-\mu_c t} & 0 \\ c_3 & \frac{\upsilon_{pA}}{\gamma_b - \gamma_{cA}} e^{-\gamma_{cA}t} & \frac{\upsilon_h}{\gamma_b - \mu_c} e^{-\mu_c t} & e^{-\gamma_b t} \end{pmatrix},$$

where c_1, c_2 and c_3 do not need to be calculated, even though they can be calculated, since it is a lower triangular matrix with all elements in diagonal being less than one, $\rho(\Phi_{-V}(\omega)) < 1$.

Hence, all assumptions (A1)-(A7) hold, So by (ii) in Theorem 2.1 and Theorem 2.2 in Wang and Zhao [41], we have the following results.

Lemma 3.1. *$R_0 = \lambda$ is the unique solution of $\rho(W(\omega, 0, \lambda)) = 1$, where $W(t, s, \lambda), t \geq s$, is the evolution operator of system (3.3.2).*

Theorem 3.2. *If $R_0 < 1$, then the infection-free equilibrium E_0 is locally asymptotically stable; If $R_0 > 1$, then E_0 is unstable.*

Lemma 3.3. *For the basic reproduction number R_0, we have*

(i)$R_0 = 1$ if and only of $\rho(\Phi_{F-V}(\omega)) = 1$.

(ii)$R_0 > 1$ if and only of $\rho(\Phi_{F-V}(\omega)) > 1$.

(iii)$R_0 < 1$ if and only of $\rho(\Phi_{F-V}(\omega)) < 1$.

Remark 3.4. If $\rho(\Phi_{F-V}(\omega)) < 1$, then the disease-free equilibrium E_0 is locally asymptotically stable; If $\rho(\Phi_{F-V}(\omega)) > 1$, then E_0 is unstable.

In order to characterize R_0, we consider

$$\frac{F(t)}{\lambda} - V(t) = \begin{pmatrix} -(\gamma_c + \epsilon(t)) & 0 & 0 & 0 \\ \epsilon(t) & -\gamma_{cA} & \frac{\alpha_p \beta_{pA}(1-\eta)N_p}{\lambda} & \frac{\kappa_{pA} N_p}{\lambda} \\ \frac{\alpha_p \beta_h (1-\eta) N_h}{\lambda} & \frac{\alpha_p \beta_{hA}(1-\eta)N_h}{\lambda} & -\mu_c & \frac{\kappa_h N_h}{\lambda} \\ \upsilon_p & \upsilon_{pA} & \upsilon_h & -\gamma_b \end{pmatrix},$$

where $\epsilon(t) = \epsilon_0(1+\epsilon_1 \sin(\frac{2\pi}{365}(t-240)))$. We want to calculate the monodromy matrix of the system

$$\frac{dx}{dt} = \left(\frac{F(t)}{\lambda} - V(t)\right) x. \tag{3.3.3}$$

By observing the matrix $\frac{F(t)}{\lambda} - V(t)$, we can see that $x_1(t)$ can be solved directly.

When $x_1(t) = 0$, we have

$$\begin{pmatrix} \dot{x}_2(t) \\ \dot{x}_3(t) \\ \dot{x}_4(t) \end{pmatrix} = A \begin{pmatrix} x_2(t) \\ x_3(t) \\ x_4(t) \end{pmatrix},$$

where

$$A = \begin{pmatrix} -\gamma_{cA} & \frac{\alpha_p \beta_{pA}(1-\eta)N_p}{\lambda} & \frac{\kappa_{pA} N_p}{\lambda} \\ \frac{\alpha_p \beta_{hA}(1-\eta)N_h}{\lambda} & -\mu_c & \frac{\kappa_h N_h}{\lambda} \\ \upsilon_{pA} & \upsilon_h & -\gamma_b \end{pmatrix}$$

is a constant matrix.

When $x_1(t) = -e^{-\int \gamma_u + \epsilon(t)}$, we have

$$\begin{pmatrix} \dot{x}_2(t) \\ \dot{x}_3(t) \\ \dot{x}_4(t) \end{pmatrix} = A \begin{pmatrix} x_2(t) \\ x_3(t) \\ x_4(t) \end{pmatrix} + f(t),$$

where

$$f(t) = \begin{pmatrix} -\epsilon(t) e^{-\int \gamma_u + \epsilon(t)} \\ -\frac{\alpha_p \beta_h (1-\eta) N_h}{\lambda} e^{-\int \gamma_u + \epsilon(t)} \\ -\upsilon_p e^{-\int \gamma_u + \epsilon(t)} \end{pmatrix}.$$

According to the results in Chapter 1 of Perko [26], we are able to find the monodromy matrix of the system (3.3.3). However, the high-dimension of the matrix $\frac{F}{\lambda} - V$ makes the analytical solution for R_0 complicated. Hence, we derive R_0 numerically in next section.

3.3.2 Extinction of Infection

Based on the biological background of the model (3.2.1), we consider solutions of model (3.2.1) with nonnegative initial values:

$$P_u^0 \geq 0, P_{uA}^0 \geq 0, P_c^0 \geq 0, P_{cA}^0 \geq 0, H_u^0 \geq 0, H_c^0 \geq 0, B_e^0 \geq 0.$$

Lemma 3.5. *If $P_u^0, P_{uA}^0, P_c^0, P_{cA}^0, H_u^0, H_c^0, B_e^0 \geq 0$, i.e., the initial values are nonnegative, then the solution of model (3.2.1) is nonnegative for all $t \geq 0$ and ultimately bounded. In particular, if $P_u^0, P_{uA}^0, P_c^0, P_{cA}^0, H_u^0, H_c^0, B_e^0 > 0$, i.e, the initial values are positive, then the solutions of model (3.2.1) is also positive for all $t \geq 0$.*

Proof. According to the continuous dependence of solutions with respect to initial values, we only need to prove that when the initial values are positive, i.e., $P_u^0, P_{uA}^0, P_c^0, P_{cA}^0, H_u^0, H_c^0, B_e^0 > 0$, the solution of model (3.2.1) is also positive for all $t \geq 0$. Let

$$m(t) = \min\{P_u(t), P_{uA}(t), P_c(t), P_{cA}(t), H_u(t), H_c(t), B_e(t)\}, \forall t > 0.$$

By the assumption that the initial values are positive, we clearly have, $m(0) > 0$. So we assume that there exists a $t_1 > 0$ such that $m(t_1) = 0$ and $m(t) > 0$ for all $t \in [\, 0, t_1)$.

If $m(t_1) = P_u(t_1)$, from the first equation of model (3.2.1), it follows that $\frac{dP_u}{dt} \geq -(\alpha_p\beta_p(1-\eta)H_c(t) + \kappa_p B_e(t) + \gamma_u + \epsilon(t))P_u$ for all $t \in [\, 0, t_1)$. Since $H_c(t), B_e(t) > 0, \epsilon(t) = \epsilon_0(1 + \epsilon_1 \sin(\frac{2\pi}{365}(t - 240))) > 0$ for all $t \in [\, 0, t_1)$, we have

$$0 = P_u(t_1) \geq P_u^0 exp(-\int_0^{t_1} (\alpha_p\beta_p(1-\eta)H_c(s) + \kappa_p B_e(s) + \gamma_u + \epsilon(s))ds) > 0,$$

which leads to a contradiction. We can get similar contradictions in the other cases. Hence, the solutions remain in the positive cone if the initial conditions are in the positive cone $\mathcal{R}^7$.

Next, denote $M(t) = P_u(t) + P_{uA}(t) + P_c(t) + P_{cA}(t) + H_u(t) + H_c(t) + B_e(t)$. Then

$$\begin{aligned} \frac{dM(t)}{dt} &= \frac{dB_e(t)}{dt} = \upsilon_p P_c + \upsilon_{pA} P_{cA} + \upsilon_h H_c - \gamma_b B_e \\ &\leq \upsilon_p N_p + \upsilon_{pA} N_p + \upsilon_h N_h - \gamma_b B_e(t), \end{aligned}$$

where $N_p = P_u(t) + P_{uA}(t) + P_c(t) + P_{cA}(t)$ and $N_h = H_u(t) + H_c(t)$, which implies

that

$$B_e(t) \leq \frac{(\upsilon_p N_p + \upsilon_{pA} N_p + \upsilon_h N_h)}{\gamma_b}(1 - e^{-\gamma_b t}) + B_e^0 e^{-\gamma_b t}.$$

So $B_e(t)$ is bounded by a fixed number

$$K = \frac{(\upsilon_p N_p + \upsilon_{pA} N_p + \upsilon_h N_h)}{\gamma_b} + B_e^0.$$

Let $N = N_p + N_h + K$, we have

$$P_u(t) + P_{uA}(t) + P_c(t) + P_{cA}(t) + H_u(t) + H_c(t) + B_e(t) \leq N.$$

Thus, the solution is ultimately bounded. This completes the proof. □

Remark 3.6. Denote

$$G := \{(P_u, P_{uA}, P_c, P_{cA}, H_u, H_c, B_e) \in \mathcal{R}_+^7 : P_u + P_{uA} + P_c + P_{cA} + H_u + H_c + B_e \leq N)\},$$

Lemma (3.5) implies that G is positively invariant set with respect to solutions of model (3.2.1).

Theorem 3.7. *If* $R_0 < 1$, *then the infection-free equilibrium* $E_0 = (0, 0, N_p, 0, N_h, 0, 0)$ *is globally asymptotically stable.*

Proof. According to Theorem 3.2, E_0 is locally asymptotically stable when $R_0 < 1$. According to Lemma 3.3, we know that $R_0 < 1$ is equivalent to $\rho(\Phi_{F-V}(\omega)) < 1$,

where $F - V$ is the defined as

$$F(t) - V(t) = \begin{pmatrix} -\gamma_c - \epsilon(t) & 0 & 0 & 0 \\ \epsilon(t) & -\gamma_{cA} & \alpha_p\beta_{pA}(1-\eta)N_p & \kappa_{pA}N_p \\ \alpha_p\beta_h(1-\eta)N_h & \alpha_p\beta_{hA}(1-\eta)N_h & -\mu_c & \kappa_h N_h \\ \upsilon_p & \upsilon_{pA} & \upsilon_h & -\gamma_b \end{pmatrix}.$$

By the continuity, we can always find a small enough positive constant δ such that

$$\rho(\Phi_{F-V+\delta N}(\omega)) < 1,$$

where

$$N(t) = \begin{pmatrix} 0 & 0 & \alpha_p\beta_p(1-\eta) & \kappa_p \\ 0 & 0 & \alpha_p\beta_{pA}(1-\eta) & \kappa_{pA} \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix}.$$

Now we try to prove the global attractivity of the disease-free equilibrium E_0. By the non-negativity of solutions and the assumption that $\theta_u = \theta_c = \theta_{cA} = 0, \theta_{uA} = 1$, we have the following result from the first equation of the model (3.2.1):

$$\frac{dP_u}{dt} \leq -\gamma_u P_u - \epsilon(t) P_u.$$

Note that $\epsilon(t) = \epsilon_0(1 + \epsilon_1 \sin(\frac{2\pi}{365}(t - 240))) > 0, \forall t$. That is, $\forall \delta > 0$, there exists $t_1 > 0$, such that

$$P_u(t) \leq \delta, \ \forall t \geq t_1.$$

Similarly, by the third equation of the model (3.2.1) and the fact that $\gamma_u =$

$max\{\gamma_u, \gamma_c, \gamma_{cA}\}$, we get

$$\frac{dP_{uA}}{dt} \leq \gamma_u(N_p - P_{uA}) + \gamma_{uA}P_{uA} - \gamma_{uA}P_{uA} + \epsilon(t)(N_p - P_{uA}),$$

that is,

$$\frac{dP_{uA}}{dt} \leq (\gamma_u + \epsilon(t))N_p - (\gamma_u + \epsilon(t))P_{uA}.$$

Then $\forall \delta > 0$, there exists $t_2 > 0$, such that

$$P_{uA}(t) \leq N_p + \delta, \ \forall t \geq t_2.$$

Let $T = \max\{t_1, t_2\}$, If $t > T$, since $\theta_u = \theta_c = \theta_{cA} = 0, \theta_{uA} = 1$, then

$$\begin{cases} P_c^{'}(t) \leq \alpha_p\beta_p(1-\eta)\delta H_c + \kappa_p\delta B_e - \gamma_c P_c - \epsilon(t)P_c, \\ P_{cA}^{'}(t) \leq \alpha_p\beta_{pA}(1-\eta)(N_p+\delta)H_c + \kappa_{pA}(N_p+\delta)B_e - \gamma_{cA}P_{cA} + \epsilon(t)P_c, \\ H_c^{'}(t) \leq \alpha_p\beta_h(1-\eta)N_hP_c + \alpha_p\beta_{hA}(1-\eta)N_hP_{cA} + \kappa_hN_hB_e - \mu_cH_c, \\ B_e^{'}(t) \leq \upsilon_pP_c + \upsilon_{pA}P_{cA} + \upsilon_hH_c - \gamma_bB_e. \end{cases} \tag{3.3.4}$$

Considering the following auxiliary system:

$$\begin{cases} \tilde{P}^{'}{}_c(t) = \alpha_p\beta_p(1-\eta)\delta\tilde{H}_c + \kappa_p\delta\tilde{B}_e - \gamma_c\tilde{P}_c - \epsilon(t)\tilde{P}_c, \\ \tilde{P}^{'}{}_{cA}(t) = \alpha_p\beta_{pA}(1-\eta)(N_p+\delta)\tilde{H}_c + \kappa_{pA}(N_p+\delta)\tilde{B}_e - \gamma_{cA}\tilde{P}_{cA} + \epsilon(t)\tilde{P}_c, \\ \tilde{H}^{'}{}_c(t) = \alpha_p\beta_h(1-\eta)N_h\tilde{P}_c + \alpha_p\beta_{hA}(1-\eta)N_h\tilde{P}_{cA} + \kappa_hN_h\tilde{B}_e - \mu_c\tilde{H}_c, \\ \tilde{B}^{'}{}_e(t) = \upsilon_p\tilde{P}_c + \upsilon_{pA}\tilde{P}_{cA} + \upsilon_h\tilde{H}_c - \gamma_b\tilde{B}_e, \end{cases} \tag{3.3.5}$$

which can be written as,

$$\frac{dx(t)}{dt} = (F(t) - V(t) + \delta N(t))x(t), \quad x(t) = (\tilde{P}_c(t), \tilde{P}_{cA}(t), \tilde{H}_c(t), \tilde{B}_e(t))^T. \quad (3.3.6)$$

Hence, there exists a positive ω-periodic function $f(t) = (f_1(t), f_2(t), f_3(t), f_4(t))^T$ such that $x(t) = e^{\mu t} f(t)$ is a solution of system (3.3.6) where $\mu = \frac{1}{\omega} \ln \rho(\Phi_{F-V+\delta N}(\omega))$, according to the Lemma 2.1 in Zhang and Zhao [45]. Note that $\rho(\Phi_{F-V+\delta N}(\omega)) < 1$, which implies that $\ln \rho(\Phi_{F-V+\delta N}(\omega)) < 0$, that is to say, $\mu < 0$. Then $\lim_{t\to\infty} x(t) = 0$. Let $S(t) = (P_c(t), P_{cA}(t), H_c(t), B_e(t))^T$, by comparison principle, we have $\lim_{t\to\infty} S(t) = 0$, which is equivalent to say that

$$\lim_{t\to\infty} P_c = 0, \lim_{t\to\infty} P_{cA} = 0, \lim_{t\to\infty} H_c = 0, \lim_{t\to\infty} B_e = 0.$$

Therefore, E_0 is globally attractive when $R_0 < 1$. This completes the proof. □

3.3.3 Persistence of Infection

Finally, we prove that the model is uniformly persistent, which implies the the persistence of MRSA infections.

Theorem 3.8. *If $R_0 > 1$, then model (3.2.1) is uniformly persistent.*

Proof. We follow the persistence theory of nonautonomous models given in Zhao [46] to discuss the uniform persistence of model (3.2.1). We first define

$X = \{(P_u, P_c, P_{uA}, P_{cA}, H_u, H_c, B_e) : P_u \geq 0, P_c \geq 0, P_{uA} \geq 0, P_{cA} \geq 0, H_u \geq 0, H_c \geq 0, B_e \geq 0\}$,

$X_0 = \{(P_u, P_c, P_{uA}, P_{cA}, H_u, H_c, B_e) \in X : P_c > 0, P_{cA} > 0, H_c > 0, B_e > 0\}$,

$\partial X_0 = X \backslash X_0$.

Note that both X and X_0 are positively invariant with respect to system (3.2.1), and ∂X_0 is relatively closed in X. Since our model (3.2.1) is ω-periodic ($\omega = 365$ days), the Poincaré map associated with our model (3.2.1) $P : X \to X$ is defined by

$$P(x_0) = \phi(\omega, x_0),\ \forall x_0 \in X,$$

where $x_0 = (P_u(0), P_c(0), P_{uA}(0), P_{cA}(0), H_u(0), H_c(0), B_e(0))$ and $\phi(t, x_0)$ is the unique solution of model (3.2.1) with initial values $\phi(0, x_0) = x_0$. Note that a continuous mapping $f : X \to X$ is said to be compact if f maps any bounded set to a precompact set in X [46]. According to Lemma 2.1, the Poincaré map P is compact and point dissipative on X, which implies that there exists a global attractor by Theorem 1.1.3 in [46].

Define

$$M_\partial = \{x_0 \in \partial X_0 : P^n(x_0) \in \partial X_0,\ n = 1, 2, \cdots\},$$

where $x_0 = (P_u(0), P_c(0), P_{uA}(0), P_{cA}(0), H_u(0), H_c(0), B_e(0))$. We want to verify that

$$M_\partial = \{(P_u, 0, P_{uA}, 0, H_u, 0, 0) : P_u \geq 0, P_{uA} \geq 0, H_u = N_h\}.$$

We first verify that $M_\partial \subseteq \{(P_u, 0, P_{uA}, 0, H_u, 0, 0) : P_u \geq 0, P_{uA} \geq 0, H_u = N_h\}$, which is equivalent to verify that if $x_0 \notin \{(P_u, 0, P_{uA}, 0, H_u, 0, 0) : P_u \geq 0, P_{uA} \geq 0, H_u = N_p\}$, then $x_0 \notin M_\partial$. For any point $x_0 = (P_u(0), P_c(0), P_{uA}(0), P_{cA}(0), H_u(0), H_c(0), B_e(0))$, we suppose that $x_0 \notin \{(P_u, 0, P_{uA}, 0, H_u, 0, 0) : P_u \geq 0, P_{uA} \geq 0, H_u = N_p\}$, that is to say one of $P_c(0), P_{cA}(0), H_c(0), B_e(0)$ is not zero. Without loss of generality, we suppose that $P_c(0) > 0, P_{cA}(0) = 0, H_c(0) = 0, B_e(0) = 0$. By the fourth, sixth and seventh

equations of model (3.2.1), note that $\epsilon(t) > 0\ \forall t$, we have

$$\frac{dP_{cA}(0)}{dt} \geq \epsilon(0)P_c(0) > 0; \frac{dH_c(0)}{dt} \geq \alpha_p\beta_h N_p P_c(0) > 0; \frac{dB_e(0)}{dt} \geq \kappa_p P_c(0) > 0.$$

Thus, there exists $\delta_0 > 0$, if $0 < t < \delta_0$, then $P_c(t) > 0, P_{cA}(t) > 0, H_c(t) > 0, B_e(t) > 0$, which implies that $x_0 \notin \partial X_0$. Other cases ($P_c(0) > 0$, or $P_{cA}(0) > 0$, or $H_c(0) > 0$) can be proved in the similar way. Thus $x_0 \notin M_\partial$. That is to say, for any $x_0 \notin \{(P_u, 0, P_{uA}, 0, H_u, 0, 0) : P_u \geq 0, P_{uA} \geq 0, H_u = N_h\}$, $x_0 \notin M_\partial$. So $M_\partial \subseteq \{(P_u, 0, P_{uA}, 0, H_u, 0, 0) : P_u \geq 0, P_{uA} \geq 0, H_u = N_h\}$.

Obviously we have $\{(P_u, 0, P_{uA}, 0, H_u, 0, 0) : P_u \geq 0, P_{uA} \geq 0, H_u = N_h\} \subseteq M_\partial$, since if $x_0 = (P_u(0), 0, P_{uA}(0), 0, N_p, 0, 0)$, then the solutions $(P_u(t), P_c(t), P_{uA}(t), P_{cA}(t), H_u(t), H_c(t), B_e(t)) \equiv (P_u(t), 0, P_{uA}(t), 0, N_h, 0, 0)$ where $P_u(t) > 0, P_{uA} > 0$. Therefore $M_\partial = \{(P_u, 0, P_{uA}, 0, H_u, 0, 0) : P_u \geq 0, P_{uA} \geq 0, H_u = N_h\}$. There is only one equilibrium $E_0 = (0, 0, N_p, 0, N_h, 0, 0)$ in M_∂, so $\cup_{x_0 \in M_\partial}\omega(x_0) = E_0$. Therefore E_0 is a compact and isolated invariant sets in ∂X_0.

Let $x_0 = (P_u(0), P_c(0), P_{uA}(0), P_{cA}(0), H_u(0), H_c(0), B_e(0)) \in X_0$ be any initial value. Next we claim that there exist a positive constant δ such that

$$\limsup_{n\to\infty} \|P^n(x_0) - E_0\| \geq \delta. \tag{3.3.7}$$

Suppose that claim (3.3.7) is not true, i.e., for any $\delta > 0$, $\limsup_{n\to\infty} \|P^n(x_0) - E_0\| \leq \delta$ for some $x_0 \in X_0$. That is to say, there exists a big enough $n_1 > 0$, for all $n > n_1$, $\|P^n(x_0) - E_0\| \leq \delta$. By the continuity of solution $\phi(t, x_0)$ with respect to the initial values, we know $\forall \ell > 0$, there exists a $\delta > 0$ such that if $\|x_0 - E_0\| \leq \delta$, then $\|\phi(t, x_0) - \phi(t, E_0)\| < \ell,\ \forall t \in [0, \omega]$. Hence we obtain $\|\phi(t, P^n(x_0)) - \phi(t, E_0)\| < \ell$

for all $n > n_1$ and $t \in [0, \omega]$.

Now for any big enough $t \geq 0$, we can rewrite $t = n\omega + \hat{t}$, where $n = [\frac{t}{\omega}]$ is the greatest integer less than or equal to $\frac{t}{\omega}$ and $\hat{t} \in [0, \omega]$. We can always choose t big enough to make sure that $n > n_1$. Hence for big enough t , we have $\|\phi(t, x_0) - \phi(t, E_0)\| = \|\phi(\hat{t}, P^n(x_0)) - \phi(\hat{t}, E_0)\| < \ell$. It follows that $0 \leq P_u(t) \leq \ell,\ P_c(t) \leq \ell,\ N_p - \ell \leq P_{uA}(t) \leq N_p + \ell,\ P_{cA}(t) \leq \ell,\ N_h - \ell \leq H_u(t) \leq N_h + \ell,\ H_c(t) \leq \ell,\ B_e(t) \leq \ell$, for any t big enough. Thus for t big enough, we have

$$\begin{cases} P_c^{'}(t) \geq -\gamma_c P_c - \epsilon(t) P_c, \\ P_{cA}^{'}(t) \geq \alpha_p \beta_{pA}(1-\eta)(N_p - \ell) H_c + \kappa_{pA}(N_p - \ell) B_e - \gamma_{cA} P_{cA} + \epsilon(t) P_c, \\ H_c^{'}(t) \geq \alpha_p \beta_h (1-\eta)(N_h - \ell) P_c + \alpha_p \beta_{hA}(1-\eta)(N_h - \ell) P_{cA} + \kappa_h (N_h - \ell) B_e - \mu_c H_c, \\ B_e^{'}(t) \geq \upsilon_p P_c + \upsilon_{pA} P_{cA} + \upsilon_h H_c - \gamma_b B_e. \end{cases} \tag{3.3.8}$$

Consider the following auxiliary system:

$$\begin{cases} \tilde{P}^{'}{}_c(t) = -\gamma_c \tilde{P}_c - \epsilon(t) \tilde{P}_c, \\ \tilde{P}^{'}{}_{cA}(t) = \alpha_p \beta_{pA}(1-\eta)(N_p - \ell) \tilde{H}_c + \kappa_{pA}(N_p - \ell) \tilde{B}_e - \gamma_{cA} \tilde{P_{cA}} + \epsilon(t) \tilde{P}_c, \\ \tilde{H}^{'}{}_c(t) = \alpha_p \beta_h (1-\eta)(N_h - \ell) \tilde{P}_c + \alpha_p \beta_{hA}(1-\eta)(N_h - \ell) \tilde{P_{cA}} + \kappa_h (N_h - \ell) \tilde{B}_e - \mu_c \tilde{H}_c, \\ \tilde{B}^{'}{}_e(t) = \upsilon_p \tilde{P}_c + \upsilon_{pA} \tilde{P_{cA}} + \upsilon_h \tilde{H}_c - \gamma_b \tilde{B}_e, \end{cases} \tag{3.3.9}$$

which can be written as,

$$\frac{dx(t)}{dt} = (F(t) - V(t) - \ell N(t)) x(t), \quad x(t) = (\tilde{P}_c(t), \tilde{P}_{cA}(t), \tilde{H}_c(t), \tilde{B}_e(t))^T, \tag{3.3.10}$$

where

$$F(t)-V(t)=\begin{pmatrix} -\gamma_c-\epsilon(t) & 0 & 0 & 0 \\ \epsilon(t) & -\gamma_{cA} & \alpha_p\beta_{pA}(1-\eta)N_p & \kappa_{pA}N_p \\ \alpha_p\beta_h(1-\eta)N_h & \alpha_p\beta_{hA}(1-\eta)N_h & -\mu_c & \kappa_hN_h \\ \upsilon_p & \upsilon_{pA} & \upsilon_h & -\gamma_b \end{pmatrix},$$

$$N(t)=\begin{pmatrix} 0 & 0 & 0 & 0 \\ 0 & 0 & \alpha_p\beta_{pA}(1-\eta) & \kappa_{pA} \\ \alpha_p\beta_h(1-\eta) & \alpha_p\beta_{hA}(1-\eta) & 0 & \kappa_h \\ 0 & 0 & 0 & 0 \end{pmatrix}.$$

Hence there exists a positive ω-periodic function $g(t)=(g_1(t),g_2(t),g_3(t),g_4(t))^T$ such that $x(t)=e^{\mu t}g(t)$ is a solution of system (3.3.10) where $\mu=\frac{1}{\omega}\ln\rho(\Phi_{F-V-\ell N}(\omega))$, according to the Lemma 2.1 in Zhang and Zhao [45]. Note that $\rho(\Phi_{F-V-\ell N}(\omega))>1$, which implies that $\ln\rho(\Phi_{F-V-\ell N}(\omega))>0$, that is to say, $\mu>0$. Then $\lim_{t\to\infty}x(t)=\infty$. Let $J(t)=(P_c(t),P_{cA}(t),H_c(t),B_e(t))^T$, by comparison principle, we have $\lim_{t\to\infty}J(t)=\infty$, which is equivalent to say that

$$\lim_{t\to\infty}P_c=\infty,\lim_{t\to\infty}P_{cA}=\infty,\lim_{t\to\infty}H_c=\infty,\lim_{t\to\infty}B_e=\infty.$$

The claim implies that E_0 is an isolated invariant set in X and $W^s(E_0)\cap X_0=\emptyset$. Therefore the Poincaré map P is uniformly persistent with respect to $(X_0,\partial X_0)$ if $R_0>1$ by Theorems 1.3.1 and 3.1.1 in [46]. This completes the proof. □

3.4 Numerical Simulations

The deterministic model with periodic transmission rate is simulated for 1000 days with initial values $(P_u^0, P_{uA}^0, P_c^0, P_{cA}^0, H_u^0, H_c^0, B_e^0) = (4, 6, 7, 6, 17, 6, 1000)$ and detailed parameter values in Table 2.1. The simulated solutions of the model are periodic as shown in Fig.3.3. Based on the seasonal pattern of antibiotic usage observed in Sun et al [34], we assume that antibiotic prescription rate in hospital increases starting at the beginning of August, gains a peak in winter and then decreases starting at the beginning of February according to the data shown in Figs.3.1-3.2, which results in similar pattern of colonized patients with antibiotic exposure in Figs.3.3 and 3.4(a), but with a lag about 15-days. We suggest that there may be a temporal correlation between antibiotic use and resistance. Figs.3.3-3.4 tell us that the prevalence of colonized patients with antibiotic exposure has periodicity between about 34% and 39% and the prevalence of colonized patients without antibiotic exposure is between 4% and 6%, while, when there is no admission of colonized patients, i.e., $\theta_c = \theta_{cA} = 0$, Fig.3.5 implies that the prevalence of colonized patients with antibiotic exposure reduces to between 20% and 23% and the prevalence of colonized patients without antibiotic exposure is between 3% and 5%. This means that detection and isolation of MRSA colonized patients on admission may be a useful intervention to control the hospital infection, while when only uncolonized patients without antibiotic exposure are admitted to hospital, Fig.3.6 indicates that the prevalence of colonized patients with antibiotic exposure is between 12% and 15% and the prevalence of colonized patients without antibiotic exposure is between 3% and 4%. We suggest that in order to control the infection in hospital, it is important to increase the public education about how to use antibiotics properly in community.

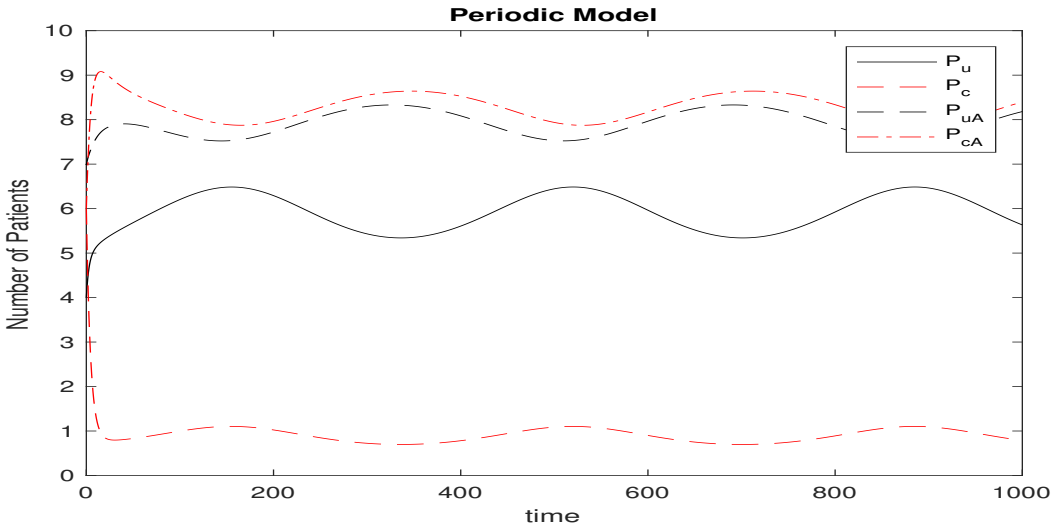

Figure 3.3: Solutions of uncolonized patients without or with antibiotic exposure $(P_u(t), P_{uA})$ and colonized patients without or with antibiotic exposure $(P_c(t), P_{cA})$ of the model (3.2.1) with initial values $(P_u^0, P_{uA}^0, P_c^0, P_{cA}^0, H_u^0, H_c^0, B_e^0) = (4, 6, 7, 6, 17, 6, 1000)$. Parameters are given in Table 2.1.

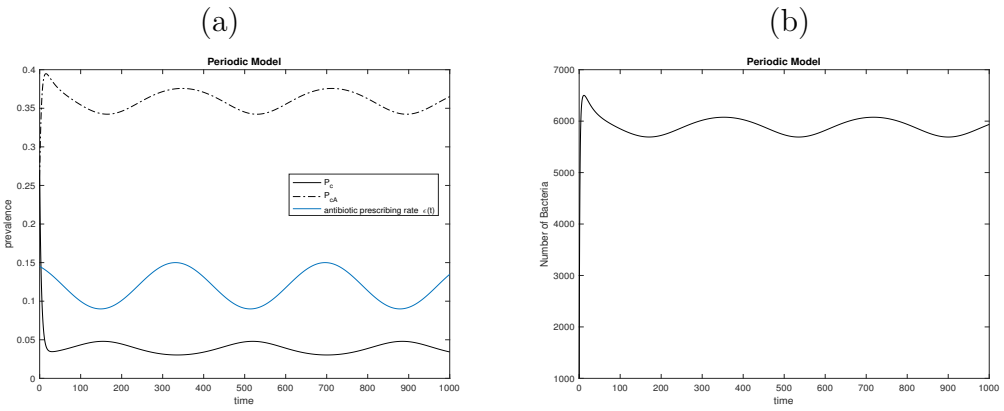

Figure 3.4: (a) Prevalence of colonized patients with or without antibiotic exposure of model (3.2.1) with initial values $(P_u^0, P_{uA}^0, P_c^0, P_{cA}^0, H_u^0, H_c^0, B_e^0) = (4, 6, 7, 6, 17, 6, 1000)$. Parameters are given in Table 2.1. Compared with antibiotic prescribing rate; (b) The free-living bacterial load in the environment.

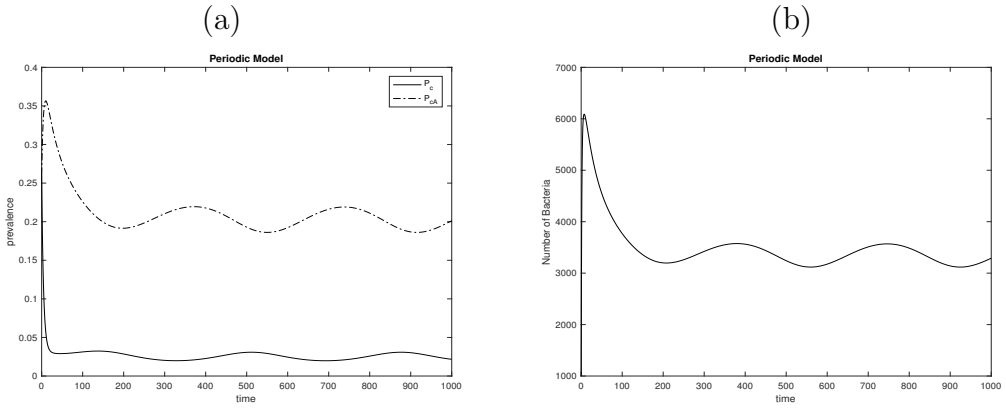

Figure 3.5: (a) Prevalence of colonized patients with or without antibiotic exposure of the model (3.2.1) with initial values $(P_u^0, P_{uA}^0, P_c^0, P_{cA}^0, H_u^0, H_c^0, B_e^0) = (4, 6, 7, 6, 17, 6, 1000)$, $\theta_u = 0.62, \theta_{uA} = 0.38, \theta_c = 0, \theta_{cA} = 0$ and other parameter values given in Table 2.1; (b) The free-living bacterial load in the environment.

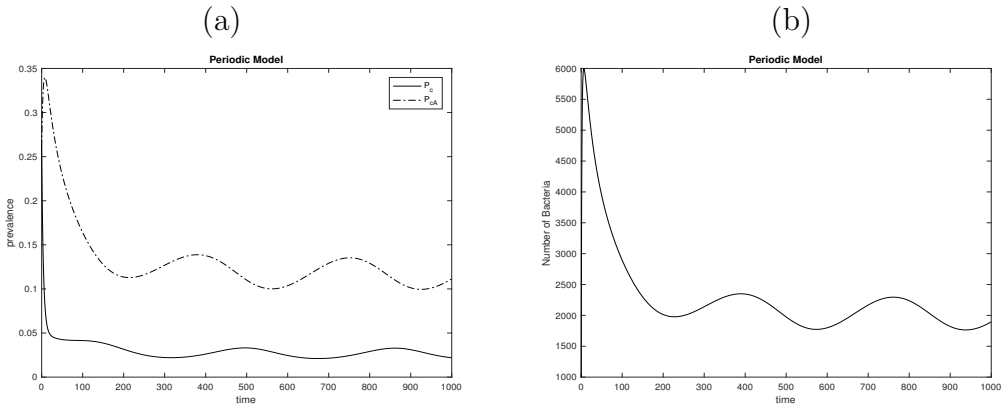

Figure 3.6: (a) Prevalence of colonozied patients with or without antibiotic exposure of modified model (3.2.1) with initial values $(P_u^0, P_{uA}^0, P_c^0, P_{cA}^0, H_u^0, H_c^0, B_e^0) = (4, 6, 7, 6, 17, 6, 1000)$, $\theta_u = 1, \theta_{uA} = 0, \theta_c = 0, \theta_{cA} = 0$ and other parameter values given in Table 2.1; (b) The free-living bacterial load in the environment.

Based on the calculation procedure about the basic reproduction number discussed above, we calculate the basic reproduction number R_0 to be 1.476 with the parameter values in Table 2.1. By Theorem 3.8, we conclude that the infection will persist with the baseline parameter values. In Fig.3.7, we perform some sensitivity analysis to explore the effect of the following parameters on changing the basic reproduction number R_0: (a) The cleaning/disinfection rate of environment γ_b; (b) Shedding rate of bacteria from colonized patients with antibiotic exposure to environment υ_{pA}; (c) The discharge rate of colonized patients with antibiotic exposure γ_{cA}; (d) The hand hygiene compliance with HCWs η; (e) The contact rate between patients and HCWs α_p; (f) The decontaminated rate of HCWs μ_c. Fig. 3.7(a) shows that increasing the environmental cleaning/disinfection rate γ_b from 0.6 to 1 can reduce the basic reproduction number from 1.705 to 1.065, which is the most efficient intervention. Since we assume that the free-living bacteria do not have proper condition to reproduce themselves, shedding bacteria from colonized patients is a crucial factor in environmental contamination, which is verified in Fig. 3.7(b), where, if the shedding rate of colonized patients with antibiotic exposure υ_{pA} is below 300, the basic reproduction number can be below 1. This again emphasizes the importance of environmental cleaning. Fig.3.7(c) indicates that the discharge rate (the inverse of stay in hospital) of colonized patients with antibiotic exposure γ_{cA} greatly increase the basic reproduction number especially when they have a lengthier stay than 18 days (baseline value i.e., 0.055^{-1}). However, it is hard to treat colonized patients with antibiotic exposure efficiently and quickly since they have resistance to many common antibiotics, which usually leads to a lengthier stay to make the situation worse. Hence how to make an efficient and right treatment plan for colonized patients with antibiotic exposure is a challenge and also a key to control the infection. In Fig. 3.7(d), it seems that the

hand hygiene compliance of HCWs (from the baseline value 0.4 to 1) make little difference in changing the basic reproduction number, which is a little surprising, since the hand hygiene is always thought to be an important intervention. We think that this is because the direct transmission through HCWs is well-known, so hospitals have paid enough attention to the hand hygiene of HCWs, while the indirect transmission through contaminated environment lacks our surveillance and is more important than we thought. That is why the environmental cleaning γ_b and the shedding rate γ_{cA} affect greatly the basic reproduction number in our sensitivity analysis Figs.8(a),(b). Hence, we believe that it is necessary to strengthen the surveillance of environmental cleaning with feedback to cleaning team, and try to use more efficient cleaning products. Figs. 3.7(e)-(f) imply how the contact rate α_p and decontaminated rate of HCWs μ_c affect the basic reproduction number.

3.5 Discussion

We presented a comprehensive mathematical model with periodic transmission rate to study MRSA infections in hospitals, including key factors such as environmental contamination and antibiotic exposure. Both the direct transmission via HCWs and the indirect transmission via free-living bacteria in the environment were taken into account. Inspired by the work of Sun et al [34], we modeled the antibiotic prescribing rate as a periodic function depending on time t in the transmission of MRSA, i.e., $\epsilon(t) = \epsilon_0(1 + \epsilon_1 \sin(\frac{2\pi}{365}(t - 240)))$, which has a period of one year (365 days) and implies that antibiotic prescribing rate increases starting at the beginning of August, reaches a peak in winter and then decreases starting at the beginning of February

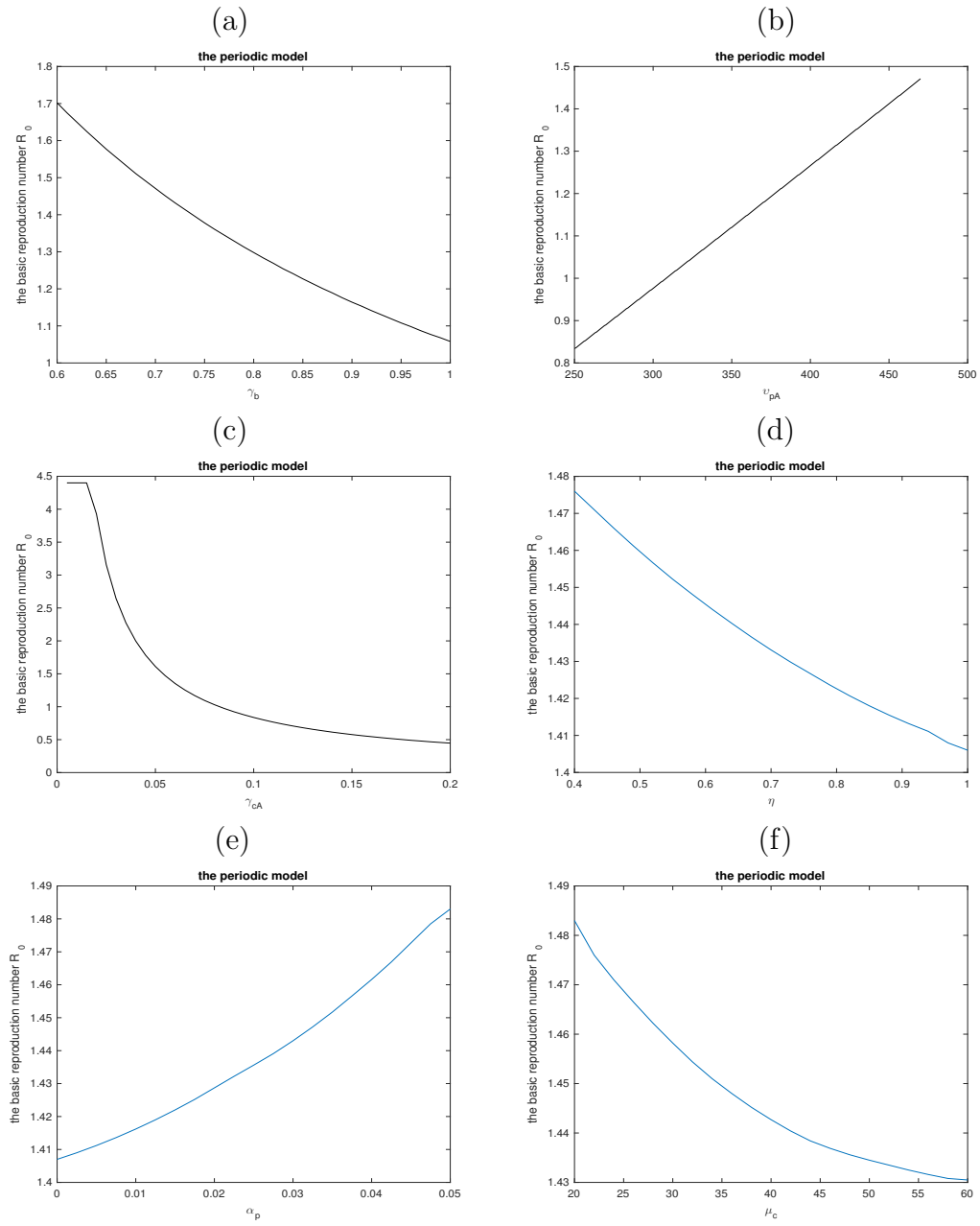

Figure 3.7: Effects of parameters on the basic reproduction number R_0: (a) γ_b, (b) υ_{pA}, (c) γ_{cA}, (d) η, (e) α_p, (f) μ_c. Other parameters values are given in Tabel 2.1.

according to the data shown in Figs.3.1-3.2. Based on the definition in Bacaër and Guenaoui [3] and the calculation procedure in Wang and Zhao [41], we deduced the basic reproduction number R_0 for the periodic deterministic model and carried out some mathematical analysis to prove that the infection would go to extinction if the basic reproduction number is less than unity and would persist if it is greater than unity. On the basis of parameter values given in Table 2.1, the basic reproduction number is estimated to be 1.476, which implies that MRSA infections persist in hospitals. Our simulations suggest that the prevalence of colonized patients with antibiotic exposure has periodicity between about 34% and 39% and the prevalence of colonized patients without antibiotic exposure is between 4% and 6% in Figs.3.3-3.4. In addition, since we observe a lag about 15 days between the pattern of colonized patients with antibiotic exposure and antibiotic prescription rate in Fig. 2.5, we suggest that there may be a temporal correlation between antibiotic use and resistance. By controlling the proportion of patients from four compartments on admission, Figs. 3.5-3.6 imply that the prevalence of colonized patients with or without antibiotic exposure would reduce greatly if only uncolonized patients without antibiotic exposure are admitted. This means that detection and isolation of MRSA colonized patients on admission may be a useful intervention to control the hospital infection, and also strengthens the importance of increasing the public education about how to use antibiotics properly at community.

It follows from the sensitivity analysis that the basic reproduction number is sensitive to the cleaning/disinfection rate of environment γ_b, shedding rate of bacteria from colonized patients with antibiotic exposure to environment υ_{pA}, and the discharge rate of colonized patients with antibiotic exposure γ_{cA}. In particular, environmental cleaning is the most important intervention to control the infection according

to our sensitivity analysis. Fig.3.7(a) shows that increasing the environmental cleaning/disinfection rate γ_b from 0.6 to 1 reduces the basic reproduction number from 1.705 to 1.065. Besides, if the shedding rate of colonized patients with antibiotic exposure υ_{pA} is below 300, the basic reproduction number can be below 1 (Fig.3.7(b)). Because the free-living bacteria do not have proper conditions to reproduce themselves in hospitals, shedding bacteria from colonized patients becomes a key factor in transmission of MRSA. This also indirectly shows the impact of environmental cleaning. We also found that if colonized patients with antibiotic exposure stay in hospitals more than 18 days on average, the basic reproduction number increases dramatically. However, colonized patients with antibiotic exposure usually have resistance to many common antibiotics, which makes it harder and takes longer to treat them. So how to make an efficient and right treatment plan for colonized patients with antibiotic exposure is a challenge to control the infection. We also observed that the hand hygiene compliance of HCWs change little on the basic reproduction number. We guess the reason is that hospitals have paid enough attention to the hand hygiene of HCWs, while still lacking attention on the indirect transmission via contaminated environment that maybe is much more important than we thought. This again explains why the environmental cleaning γ_b and the shedding rate γ_{cA} affect greatly the basic reproduction number in our sensitivity analysis.

Hence, in order to control the infection, we believe it is necessary to strengthen the surveillance of environmental cleaning with feedback to cleaning team, try to use more efficient cleaning products, highlight the necessary of effective antimicrobial stewardship programs, increase active screening on admission and subsequent isolation of positive cases, and treat patients quickly and efficiently.

Chapter 4

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

4.1 Background

In previous chapters, we found that environmental cleaning rate may be the most important intervention to control the MRSA infections, which makes us believe that hospitals still lack attention on the indirect transmission via contaminated environment and also gives us a direction to control the 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 [16].

In this chapter, we aim to develop optimal cost-effective strategies of environmental cleaning and antibiotic use, and also to better understand how environmental

cleaning and antibiotic use affect the transmission and control of MRSA infections in hospitals. We modify the previous seven-compartment system with two control variables incorporated. Our optimal control problem focuses on minimizing the numbers of colonized patients and bacteria in the environment while minimizing the cost associated with environmental cleaning and antibiotic use for a particular time period. By using techniques of optimal control on ordinary differential equations [14] [23] [33] [29], the adjoint equations and the characterizations of optimal control strategies are formulated.

4.2 The State Model

The model in previous chapters was developed to describe the transmission of MRSA in the following seven compartments (see Fig.2.1):

$P_u(t)$=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 health care workers at time t.
$H_c(t)$=number of contaminated health care workers at time t.
$B_e(t)$=number of the free-living bacteria in the environment at time t.

Our goal here is to find optimal cost-effective strategies of environmental cleaning and antibiotic use. Let ϵ_0, γ_b be functions of time, then $\epsilon_0(t)$, $\gamma_b(t)$ are our control

variables, we hence formulate the model as follows:

$$\frac{dP_u}{dt} = \theta_u\Omega(t) - \alpha_p\beta_p(1-\eta)P_uH_c - \kappa_pP_uB_e - \gamma_uP_u - \epsilon_0(t)\phi(t)P_u,$$

$$\frac{dP_c}{dt} = \theta_c\Omega(t) + \alpha_p\beta_p(1-\eta)P_uH_c + \kappa_pP_uB_e - \gamma_cP_c - \epsilon_0(t)\phi(t)P_c,$$

$$\frac{dP_{uA}}{dt} = \theta_{uA}\Omega(t) - \alpha_p\beta_{pA}(1-\eta)P_{uA}H_c - \kappa_{pA}P_{uA}B_e - \gamma_{uA}P_{uA} + \epsilon_0(t)\phi(t)P_u,$$

$$\frac{dP_{cA}}{dt} = \theta_{cA}\Omega(t) + \alpha_p\beta_{pA}(1-\eta)P_{uA}H_c + \kappa_{pA}P_{uA}B_e - \gamma_{cA}P_{cA} + \epsilon_0(t)\phi(t)P_c, \quad (4.2.1)$$

$$\frac{dH_u}{dt} = -\alpha_p\beta_h(1-\eta)P_cH_u - \alpha_p\beta_{hA}(1-\eta)P_{cA}H_u - \kappa_hH_uB_e + \mu_cH_c,$$

$$\frac{dH_c}{dt} = \alpha_p\beta_h(1-\eta)P_cH_u + \alpha_p\beta_{hA}(1-\eta)P_{cA}H_u + \kappa_hH_uB_e - \mu_cH_c,$$

$$\frac{dB_e}{dt} = \upsilon_pP_c + \upsilon_{pA}P_{cA} + \upsilon_hH_c - \gamma_b(t)B_e,$$

subject to initial conditons

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

where $\Omega(t) = \gamma_uP_u(t) + \gamma_cP_c(t) + \gamma_{uA}P_{uA}(t) + \gamma_{cA}P_{cA}(t)$, and we denote $\phi(t) = 1 + \epsilon_1\sin(\frac{2\pi}{365}(t-240))$.

The control set is

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

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:

$$\begin{aligned}\mathcal{J}(u) = \int_0^T [&a_1 P_c(t) + a_2 P_{cA}(t) + a_3 B_e + b_1(\epsilon_0(t)\phi(t))^2 \\ &+ b_2\epsilon_0(t)\phi(t)P_u(t) + b_3\epsilon_0(t)\phi(t)P_c(t) + c_1(\gamma_b(t))^2 + c_2\gamma_b(t)B_e(t)]dt.\end{aligned} \tag{4.2.2}$$

The term $a_1P_c(t) + a_2P_{cA}(t)$ counts the number of colonized patients without or with antibiotic exposure and a_3B_e counts the number of bacteria in the environment. $b_1(\epsilon_0(t)\phi(t))^2$ means the nonlinear cost associated with antibiotic use, while $b_2\epsilon_0(t)\phi(t)P_u(t) + b_3\epsilon_0(t)\phi(t)P_c(t)$ 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, $i = 1, ..., 3$, $j = 1, 2$, are nonnegative, representing weights on the different terms of objective functional. We aim at minimizing 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.

4.3 Optimal Control

In order to use the Pontryagin's Maximum Principle [29], we must first verify the existence of an optimal control [33] [21].

Theorem 4.1. *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 (*4.2.2*).*

Proof. Firstly we can prove that the solutions of system (3.2.1) are nonnegative and uniformly bounded if the initial values are nonnegative [20] [**?**]. It is easily seen that the objective functional values are nonnegative, i.e., the objective funcional 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 uniform boundedness in L^∞, which implies uniformly bounded in $L^2([0,T])$. Since the space $L^2([0,T])$ is reflexive [32], 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 (3.2.1) are uniformly bounded, which gives us uniformaly 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 the system (3.2.1), 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

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

Hence, u^* is an optimal control. □

Theorem 4.2. *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 (3.2.1), there exist*

adjoint variables $\lambda_i(t), i = 1, ..., 7$, *satisfying*

$$\begin{aligned}
\lambda_1' =& - b_2\epsilon_0(t)\phi(t) - \lambda_1[\theta_u\gamma_u - \alpha_p\beta_p(1-\eta)H_c - \kappa_p B_e - \gamma_u - \epsilon_0(t)\phi(t)] \qquad (4.3.1)\\
& - \lambda_2[\theta_c\gamma_u + \alpha_p\beta_p(1-\eta)H_c + \kappa_p B_e] - \lambda_3[\theta_{uA}\gamma_u + \epsilon_0(t)\phi(t)] - \lambda_4\theta_{cA}\gamma_u,\\
\lambda_2' =& - a_1 - b_3\epsilon_0(t)\phi(t) - \lambda_1\theta_u\gamma_c - \lambda_2[\theta_c\gamma_c - \gamma_c - \epsilon_0(t)\phi(t)] - \lambda_3\theta_{uA}\gamma_c \qquad (4.3.2)\\
& - \lambda_4[\theta_{cA}\gamma_c + \epsilon_0(t)\phi(t)] + \lambda_5\alpha_p\beta_h(1-\eta)H_u - \lambda_6\alpha_p\beta_h(1-\eta)H_u - \lambda_7\upsilon_p,\\
\lambda_3' =& - \lambda_1\theta_u\gamma_{uA} - \lambda_2\theta_c\gamma_{uA} - \lambda_3[\theta_{uA}\gamma_{uA} - \alpha_p\beta_{pA}(1-\eta)H_c - \kappa_{pA}B_e - \gamma_{uA}] \qquad (4.3.3)\\
& - \lambda_4[\theta_{cA}\gamma_{uA} + \alpha_p\beta_{pA}(1-\eta)H_c + \kappa_{pA}B_e],\\
\lambda_4' =& - a_2 - \lambda_1\theta_u\gamma_{cA} - \lambda_2\theta_c\gamma_{cA} - \lambda_3\theta_{uA}\gamma_{cA} - \lambda_4[\theta_{cA}\gamma_{cA} - \gamma_{cA}] \qquad (4.3.4)\\
& + \lambda_5\alpha_p\beta_{hA}(1-\eta)H_u - \lambda_6\alpha_p\beta_{hA}(1-\eta)H_u - \lambda_7\upsilon_{pA},\\
\lambda_5' =& \lambda_5[\alpha_p\beta_h(1-\eta)P_c + \alpha_p\beta_{hA}(1-\eta)P_{cA} + \kappa_h B_e] \qquad (4.3.5)\\
& - \lambda_6[\alpha_p\beta_h(1-\eta)P_c + \alpha_p\beta_{hA}(1-\eta)P_{cA} + \kappa_h B_e],\\
\lambda_6' =& \lambda_1\alpha_p\beta_p(1-\eta)P_u - \lambda_2\alpha_p\beta_p(1-\eta)P_u + \lambda_3\alpha_p\beta_{pA}(1-\eta)P_{uA} \qquad (4.3.6)\\
& - \lambda_4\alpha_p\beta_{pA}(1-\eta)P_{uA} - \lambda_5\mu_c + \lambda_6\mu_c - \lambda_7\upsilon_h,\\
\lambda_7' =& - a_3 - c_2\gamma_b(t) + \lambda_1\kappa_p P_u - \lambda_2\kappa_p P_u + \lambda_3\kappa_{pA}P_{uA} - \lambda_4\kappa_{pA}P_{uA} \qquad (4.3.7)\\
& + \lambda_5\kappa_h H_u - \lambda_6\kappa_h H_u + \lambda_7\gamma_b(t),
\end{aligned}$$

with the transversality conditions:

$$\lambda_i(T) = 0, \quad i = 1, ..., 7. \qquad (4.3.8)$$

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

$$\epsilon_0(t)^* = \min\{\max\{m_1, \frac{(\lambda_1 - \lambda_3 - b_2)P_u(t) + (\lambda_2 - \lambda_4 - b_3)P_c(t)}{2b_1\phi(t)}\}, M_1\}, \qquad (4.3.9)$$

$$\gamma_b(t)^* = \min\{\max\{m_2, \frac{(\lambda_7 - c_2)B_e(t)}{2c_1}\}, M_2\}. \tag{4.3.10}$$

Proof. By Pontryagin's Maximum principle, we get the Hamiltonian as follows:

$$\begin{aligned}
\mathcal{H} =& a_1P_c + a_2P_{cA} + a_3B_e + b_1(\epsilon_0(t)\phi(t))^2 + b_2\epsilon_0(t)\phi(t)P_u \\
&+ b_3\epsilon_0(t)\phi(t)P_c + c_1(\gamma_b(t))^2 + c_2\gamma_b(t)B_e(t) \\
&+ \lambda_1[\theta_u\Omega(t) - \alpha_p\beta_p(1-\eta)P_uH_c - \kappa_pP_uB_e - \gamma_uP_u - \epsilon_0(t)\phi(t)P_u,] \\
&+ \lambda_2[\theta_c\Omega(t) + \alpha_p\beta_p(1-\eta)P_uH_c + \kappa_pP_uB_e - \gamma_cP_c - \epsilon_0(t)\phi(t)P_c] \\
&+ \lambda_3[\theta_{uA}\Omega(t) - \alpha_p\beta_{pA}(1-\eta)P_{uA}H_c - \kappa_{pA}P_{uA}B_e - \gamma_{uA}P_{uA} + \epsilon_0(t)\phi(t)P_u] \\
&+ \lambda_4[\theta_{cA}\Omega(t) + \alpha_p\beta_{pA}(1-\eta)P_{uA}H_c + \kappa_{pA}P_{uA}B_e - \gamma_{cA}P_{cA} + \epsilon_0(t)\phi(t)P_c] \\
&+ \lambda_5[-\alpha_p\beta_h(1-\eta)P_cH_u - \alpha_p\beta_{hA}(1-\eta)P_{cA}H_u - \kappa_hH_uB_e + \mu_cH_c] \\
&+ \lambda_6[\alpha_p\beta_h(1-\eta)P_cH_u + \alpha_p\beta_{hA}(1-\eta)P_{cA}H_u + \kappa_hH_uB_e - \mu_cH_c] \\
&+ \lambda_7[\upsilon_pP_c + \upsilon_{pA}P_{cA} + \upsilon_hH_c - \gamma_b(t)B_e],
\end{aligned} \tag{4.3.11}$$

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

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

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

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

with the transversality conditions $\lambda_i(T) = 0,\quad i = 1, ..., 7$. We obtain the characteri-

zation 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

$$2c_1\gamma_b(t) + c_2B_e - \lambda_7 B_e = 0,$$

which implies that

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

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

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

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

□

4.4 Numerical Results

Without any control strategies for 1000 days, Fig.4.1 represents the proportion of uncolonized patients without or with antibiotic exposure, colonized patients without or with antibiotic exposure and number of bacteria in the environment, respectively, based on the parameter values in Table 2.1 and initial condition $(P_u^0, P_{uA}^0, P_c^0, P_{cA}^0, H_u^0, H_c^0, B_e^0) = (4, 6, 7, 6, 17, 6, 1000)$.

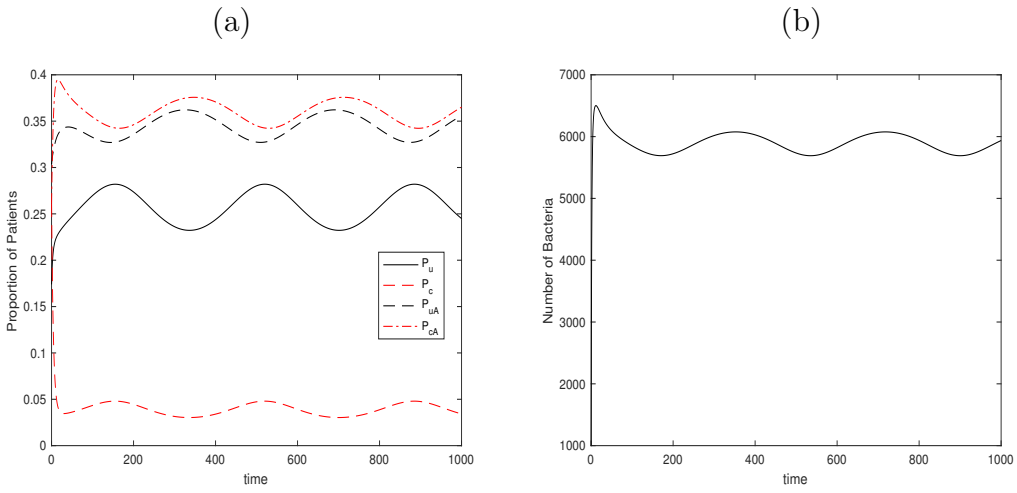

Figure 4.1: Without any control stragies for $T = 1000$ and $(P_u^0, P_{uA}^0, P_c^0, P_{cA}^0, H_u^0, H_c^0, B_e^0) = (4, 6, 7, 6, 17, 6, 1000)$: (a) Proportion of patients, (b) Number of Bacteria in the environment. Parameters values are given in Tabel 2.1.

Next, we introduce optimal control strategies into our system. According to Lenhart and Workman 2007 [23], a Forward-Backward Sweep method is used to solving such optimal control problems numerically. Roughly speaking, we firstly 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 (4.2.1) forward in time with the given initial condition. After that, based on the initial guess of control values, the values of state system solutions we obtained and the transversality conditions of adjoint variables, we can solve the adjoint system (4.3.1-

4.3.7) 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 (4.3.9-4.3.10). Finally, a convergence test is conducted, and the recurrent process will not stop until values converge sufficiently.

By choosing $a_1 = a_2 = 1$, $a_3 = 0.15$, $b_1 = c_1 = 5$, $b_2 = b_3 = 1$, $c_2 = 0.1$, $m_1 = 0.05$, $M_1 = 0, 12$, $m_2 = 0.5$, $M_2 = 10$ in the objective functional, Fig.4.2 gives us the optimal 2-control strategies and how the optimal 2-control strategies change the proportion of $P_u,\ P_{uA},\ P_c,\ P_{cA}$ and the number of bacteria B_e. In particular, the percentage of colonized patients with antibiotic exposure P_{cA} reduces dramatically to between 12.5% and 13.5% and the number of bacteria in the environment also decreases dramatically, with our control strategies. Moreover, according to our observation, 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. Besides, we find that the optimal antibiotic prescription rate is always equal to the minimum we give, i.e., $\epsilon_0(t) = m_1 = 0.05$. We have an intuitive explanation from the construction of our system (4.2.1) and objective functional (4.2.2): when reducing the antibiotic use $\epsilon_0(t)$, $P_u,\ P_c$ increase, $P_{uA},\ P_{cA}$ decrease, but $P_c(t)+P_{cA}(t)$ remain the same, $b_1(\epsilon_0(t)\phi(t))$ decreases, $b_2\epsilon_0(t)\phi(t)P_u(t) + b_3\epsilon_0(t)\phi(t)P_c(t)$ depend, and B_e decreases which leads to the decreasing of $c_1\gamma_b(t) + c_2\gamma_b B_e(t)$. For reasonable weights chosen in objective functional, the smaller the $\epsilon_0(t)$ is, the smaller the values of objective functional are. Hence, there is no wonder in our simulation results the optimal antibiotic prescription rate is always equal to the minimum we give. Therefore, in order to control the MRSA infection in hospitals, we should use antibiotic as proper and little as possible and highlight the importance of effective antimicrobial stewardship programs.

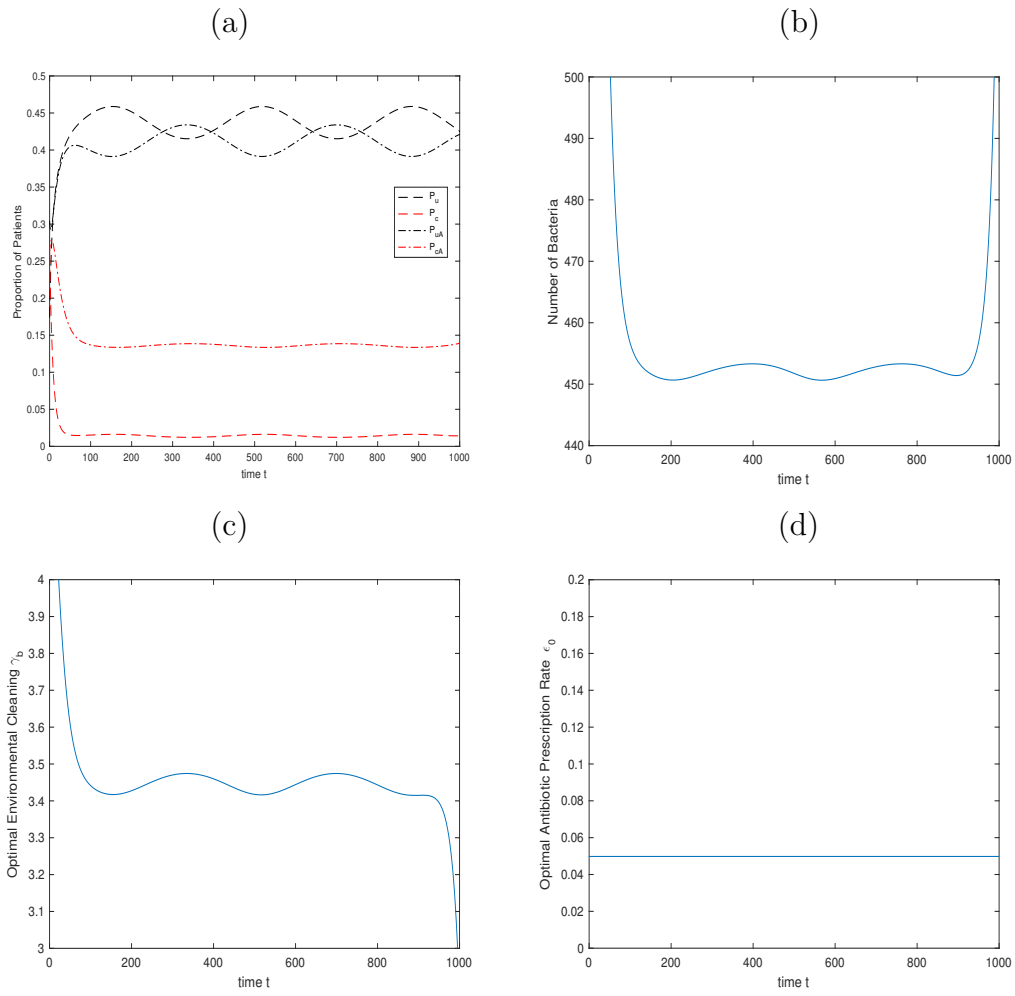

Figure 4.2: Applying optimal 2-control strategies with $c_1 = 5$: (a) Proportion of patients, (b) Number of bacteria in the environment, (c) Optimal environmental cleaning $\gamma_b(t)$, (d) Optimal prescription rate $\epsilon_0(t)$.

When the cost of environmental cleaning is more expensive, i.e., we increase $c_1 = 15$ in Fig.4.3, the corresponding optimal environmental cleaning effort is decreased, but the optimal antibiotic use is still the minimum setting $\epsilon_0(t) = m_1 = 0.05$. Meanwhile, the percentage of P_{cA} increases, as well as the number of bacteria in the environment. When the cost of environmental cleaning is cheaper, i.e., we decrease $c_1 = 1$ in Fig.4.4, the corresponding optimal environmental cleaning effort is increased to around 5.6, and the optimal antibiotic use is the minimum setting $\epsilon_0(t) = m_1 = 0.05$. We observe that the percentage of P_{cA} decreases a little bit compared with Fig.4.2(a).

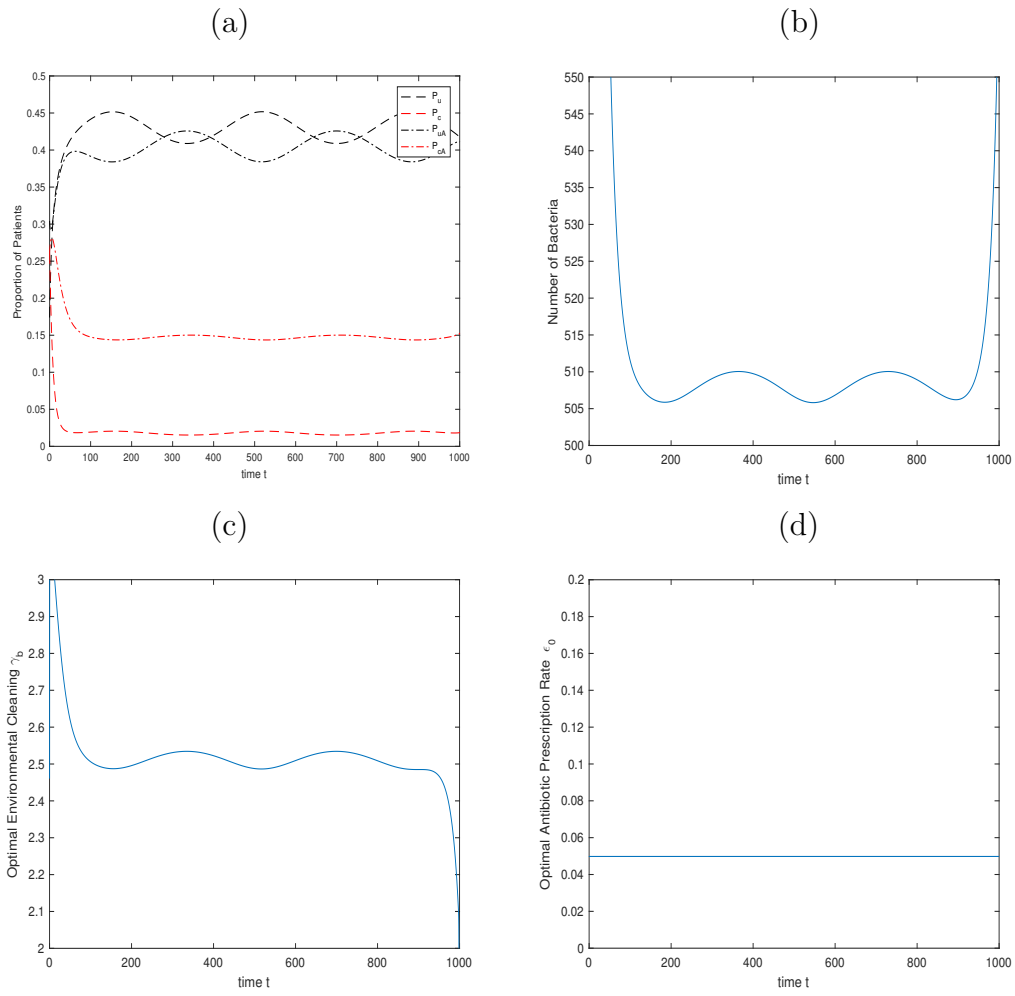

Figure 4.3: Applying optimal 2-control strategies with $c_1 = 15$: (a) Proportion of patients, (b) Number of bacteria in the environment, (c) Optimal environmental cleaning $\gamma_b(t)$, (d) Optimal prescription rate $\epsilon_0(t)$.

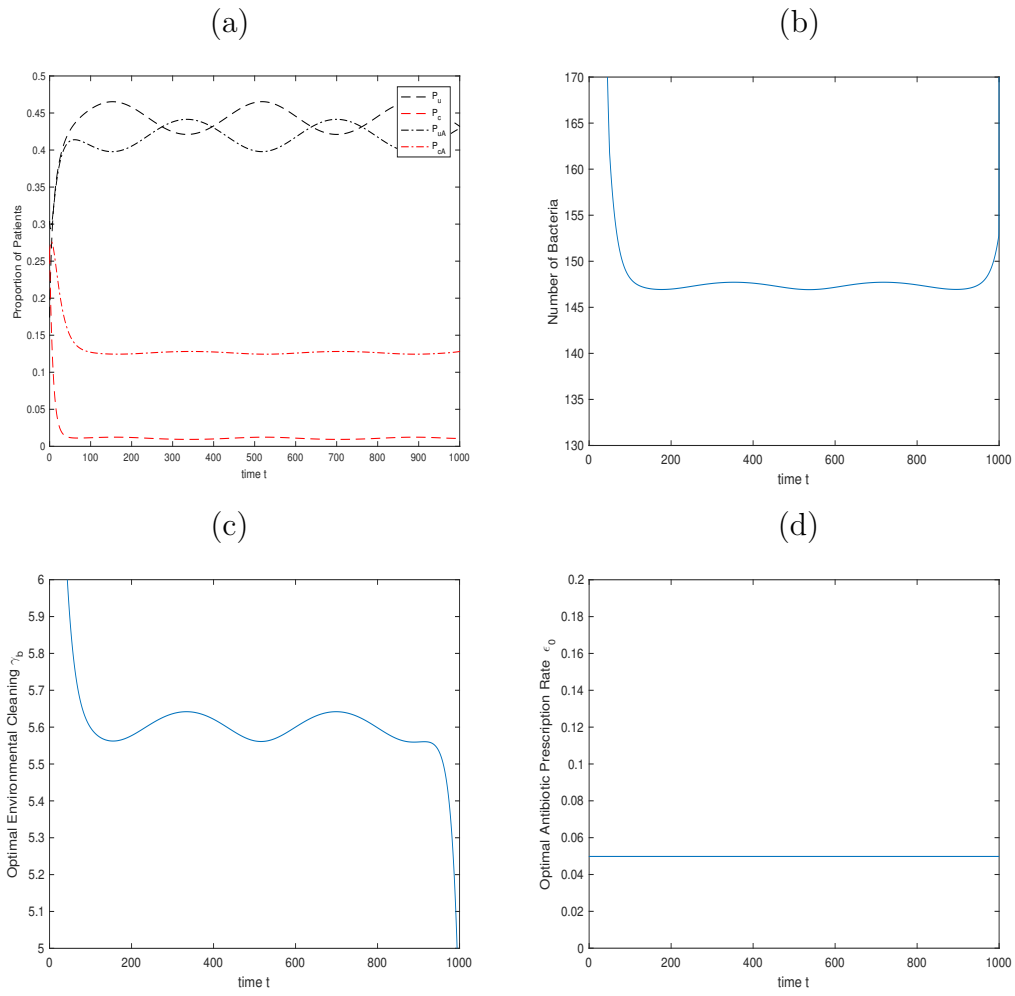

Figure 4.4: Applying optimal 2-control strategies with $c_1 = 1$: (a) Proportion of patients, (b) Number of bacteria in the environment, (c) Optimal environmental cleaning $\gamma_b(t)$, (d) Optimal prescription rate $\epsilon_0(t)$.

Based on the above intuitive explanation about the reason why the optimal antibiotic prescription rate is always equal to the minimum m_1 we set, in the following subsections we focus on exploring how hospitals should adjust their environmental cleaning strategy when different hospital scenarios happen.

4.4.1 Proportion of Patients on Admission

In this subsection, we consider two different cases.

Firstly, we consider the proportion of patients on admission as $\theta_u = 0.617,\ \theta_{uA} = 0.28,\ \theta_c = 0.03,\ \theta_{cA} = 0.1$, where $\theta_{uA} + \theta_{cA}$ is still equal to 0.38, i.e., the fraction of patients with antibiotic exposure of new admission to be 0.38 [19] [7]. Compared with the original proportion of patients on admission as $\theta_u = 0.617,\ \theta_{uA} = 0.349,\ \theta_c = 0.03,\ \theta_{cA} = 0.031$, θ_{cA} is increased since more patients are colonized at community. By choosing the same weight as in Fig.4.2 $a_1 = a_2 = 1$, $a_3 = 0.15$, $b_1 = c_1 = 5$, $b_2 = b_3 = 1$, $c_2 = 0.1$, $m_1 = 0.05$, $M_1 = 0, 12$, $m_2 = 0.5$, $M_2 = 10$ in the objective functional, Fig.4.5(c) suggests that the optimal environmental cleaning rate increases to around 4.2 in compare with around 3.4 in Fig.4.2(c). However, even though hospitals pay more attention to environmental cleaning, in Fig.4.5 the proportion of P_{cA} increases to around 32% from around 13.5% and the number of bacteria in the environment increases as well, compared with Fig.4.2. Hence, it is important to highlight the public education about how to prevend MRSA at 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 [6].

Secondly, we change the proportion of patients on admission to be $\theta_u = 0.617,\ \theta_{uA} = 0.369,\ \theta_c = 0.03,\ \theta_{cA} = 0.011$, where hospitals increase active screening

on admission and subsequent isolation of positive cases so that θ_{cA} reduces to 0.011. Fig.4.6 implies that in this case we only need environmental cleaning effort to be around 2.8 to reduce P_{cA} to be around 6% from around 13.5% in Fig.4.2. Hence, in order to control MRSA infections, active screening on admission and subsequent isolation are important interventions.

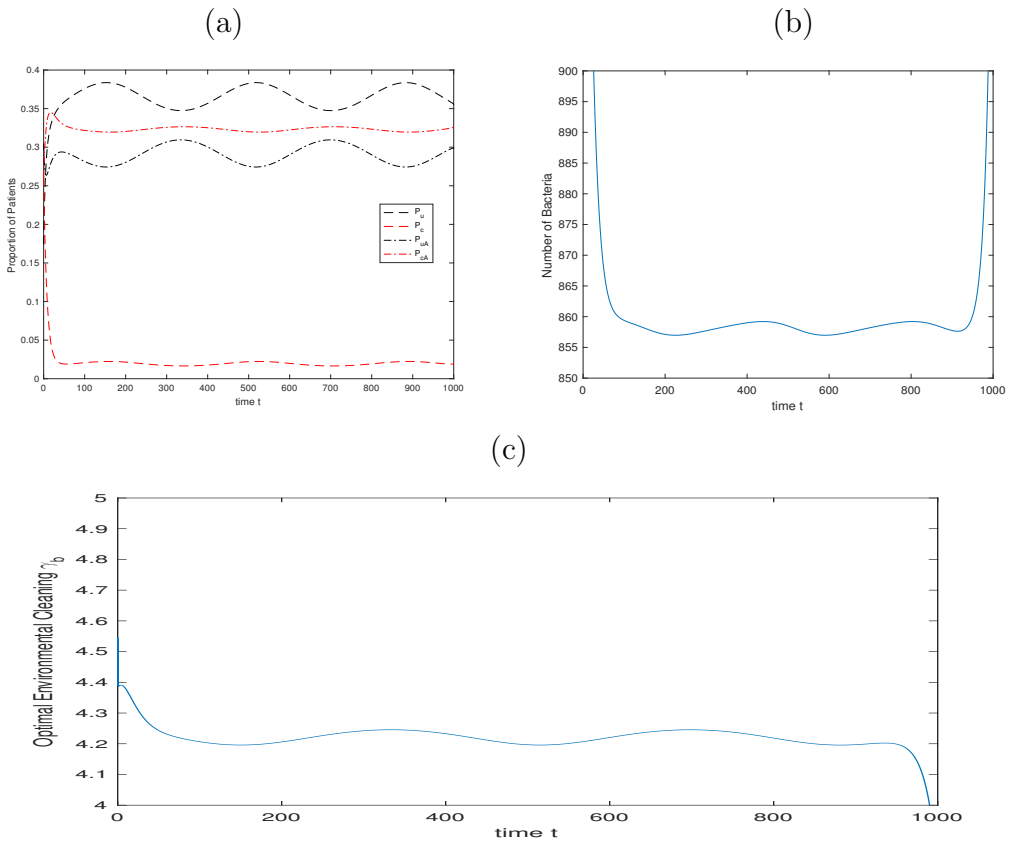

Figure 4.5: Applying optimal 2-control strategies with $\theta_u = 0.617, \theta_{uA} = 0.28, \theta_c = 0.03, \theta_{cA} = 0.1$: (a) Proportion of patients, (b) Number of bacteria in the environment, (c) Optimal environmental cleaning $\gamma_b(t)$.

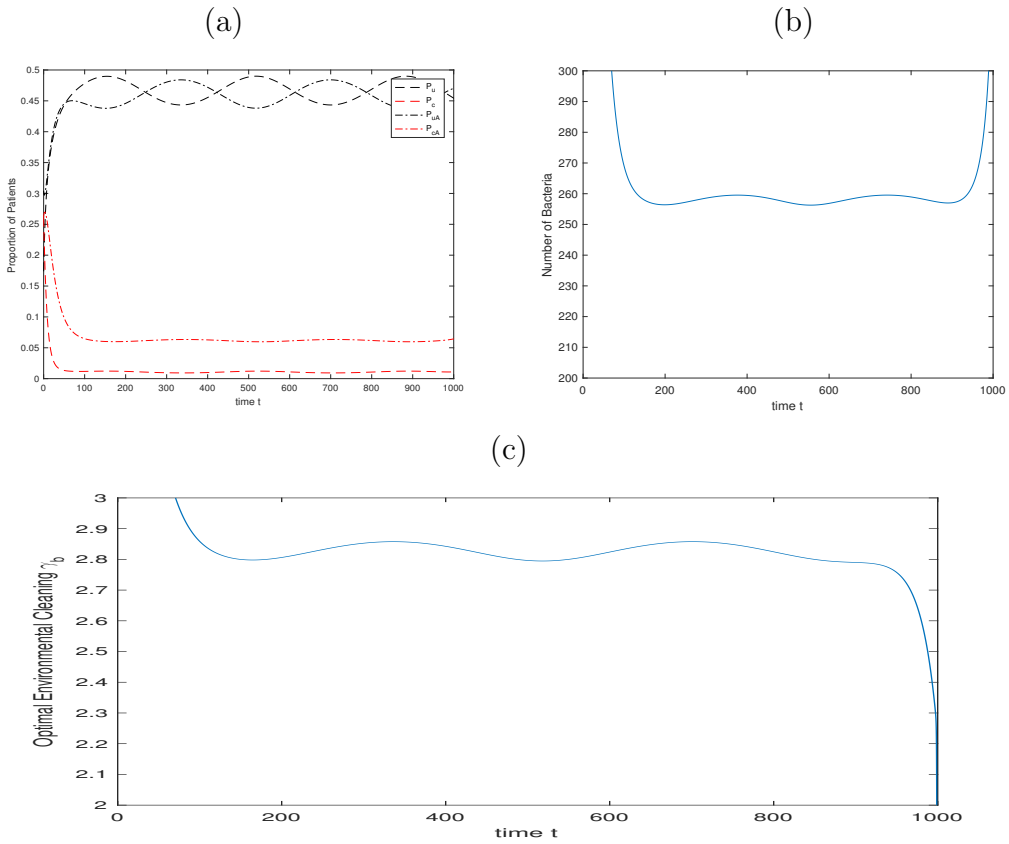

Figure 4.6: Applying optimal 2-control strategies with $\theta_u = 0.617, \theta_{uA} = 0.369, \theta_c = 0.03, \theta_{cA} = 0.011$: (a) Proportion of patients, (b) Number of bacteria in the environment, (c) Optimal environmental cleaning $\gamma_b(t)$.

4.4.2 Length of Stay of Colonized Patients with Antibiotic Exposure P_{cA}

As discussed above, many studies observe that colonized patients with antibiotic exposure tend to have a lengthier duration 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 efficient treatment, say 28 days ($\gamma_{cA} = 0.035$), Other parameter values are shown in Table 1. Still, by choosing the same weight as in Fig.4.2 $a_1 = a_2 = 1$, $a_3 = 0.15$, $b_1 = c_1 = 5$, $b_2 = b_3 = 1$, $c_2 = 0.1$, $m_1 = 0.05$, $M_1 = 0,12$, $m_2 = 0.5$, $M_2 = 10$ in the objective functional, to compare between Fig.4.2, Fig.4.7 shows that hospital should increase the environmental cleaning effort to around 4.1; however, an increase of percentage of P_{cA} and number of bacteria still occurs. Hence, how to treat colonized patients, especially with antibiotic exposure as quickly and efficiently as possible is a big challenge in controlling MRSA infections.

4.5 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 [20] [**?**], numerical simulations strongly suggest that environmental cleaning is the most important intervention to control the MRSA infections, which gives us another way to control the MRSA infections. Hospitals should use more effective products, enhance the monitoring of cleaning by ongoing assessments and feedbacks, and even

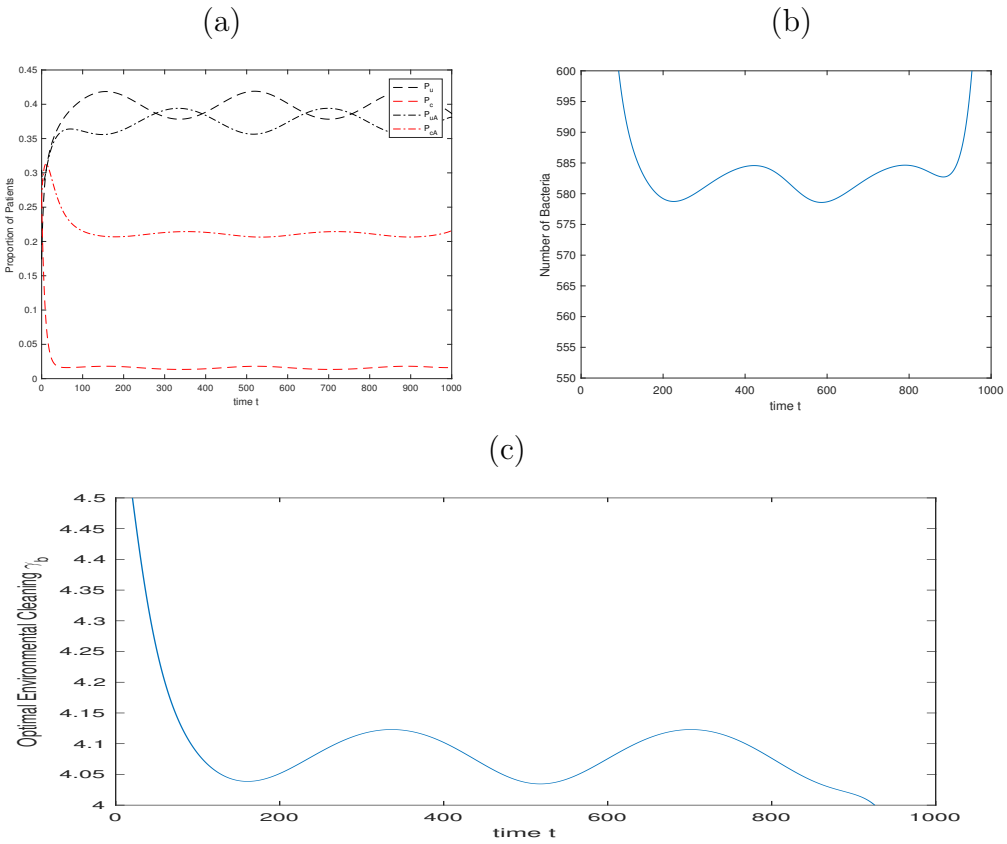

Figure 4.7: Applying optimal 2-control strategies with $\gamma_{cA} = 0.035$: (a) Proportion of patients, (b) Number of bacteria in the environment, (c) Optimal environmental cleaning $\gamma_b(t)$.

use technology (cleaning robots) to supplement the manual cleaning [16]. In order 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 minimize the numbers 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-days time periods since we wanted to observe the seasonality of MRSA infections. Simulation results strongly show that with our control strategies the percentage of colonized patients with antibiotic exposure P_{cA} reduced dramatically in Figs.4.1,4.2. Hence environmental cleaning is key in the control of MRSA infections and hospitals should use antibiotics as properly and as little as possible. 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 bacteria in the environment B_e, which implies that hospitals should be aware of intensifying their cleansing efforts during peak periods.

Furthermore, we discussed how hospitals should adjust their strategies when different hospital scenarios occurs. Firstly, since the cost associated with environmental cleaning is unknown, we tried different cost weights in objective functional to see how the optimal strategies change. Next, we considered a scenario in which the proportion of colonized patients with antibiotic exposure on admission is increased due to increasing colonization cases at the community. We found that even though hospitals increase the optimal environmental cleaning effort, the percentage of P_{cA} in-

creases, as well as the number of bacteria in the environment. Hence it is important to highlight the public education about how to prevent MRSA at 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. Then, we considered screening and subsequent isolation as an effective intervention supplement. Finally, since colonized patients with antibiotic exposure tend to have a lengthier duration in hospitals, our simulations implied that how to treat colonized patients, especially with antibiotic exposure, as quickly and efficiently as possible is a big challenge in controlling MRSA infections.

Chapter 5

Conclusions and Future Work

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 attention to the need to find effective strategies for prevention. In Chapter 2, both deterministic and stochastic mathematical models are developed to study the transmission dynamics of MRSA infections in hospitals, which include uncolonized patients without and with antibiotic exposure, colonized patients without and with antibiotic exposure, uncontaminated and contaminated health-care workers, and free-living MRSA. Under the assumption that there is no admission of the colonized patients, the basic reproduction number R_0 was calculated. It was shown that when $R_0 < 1$ the infection-free equilibrium is globally asymptotically stable, and when $R_0 > 1$ the infection is uniformly persistent. For the deterministic model, numerical simulations were performed to demonstrate the behavior of the solutions and the dependence and sensitivity of the basic reproduction number of various parameters. For the stochastic model, numerical simulations were also carried out to study the effect of antibiotic prescribing rate ϵ, the discharge rate of colonized patients with antibiotic exposure γ_{cA}, and environmental cleaning rate γ_b on the number of colonized patients, respectively.

In Chapter 3, we extended the deterministic model with periodic transmission rate

to study MRSA infections in hospitals, including key factors such as environmental contamination and antibiotic exposure. Inspired by the work of Sun et al [34], we modeled the antibiotic prescribing rate as a periodic function depending on time t in the transmission of MRSA, i.e., $\epsilon(t) = \epsilon_0(1 + \epsilon_1 \sin(\frac{2\pi}{365}(t - 240)))$, which has a period of one year (365 days) and implies that antibiotic prescribing rate increases starting at the beginning of August, reaches a peak in winter and then decreases starting at the beginning of February according to the data shown in Figs.3.1-3.2. Based on the definition in Bacaër and Guenaoui [3] and the calculation procedure in Wang and Zhao [41], we deduced the basic reproduction number R_0 for the periodic deterministic model and carried out some mathematical analysis to prove that the infection would go to extinction if the basic reproduction number is less than unity and would persist if it is greater than unity. On the basis of parameter values given in Table 2.1, the basic reproduction number is estimated to be 1.476, which implies that MRSA infections persist in hospitals.

In Chapter 4, in order to better understand how environmental cleaning and antibiotic use affect the transmission and control of MRSA infections in hospitals, we apply the optimal control theory to the seven-compartment system of ordinary differential equations. Our goal is to minimize the numbers 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 are formulated, and how hospitals should adjust their strategies when different hospital scenarios happen is discussed.

The simulations from Chapter 2-4 strongly suggest that that environmental cleaning is the most important intervention to control the infection, which emphasizes the importance of environmental contamination in the transmission of 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 [16]. It is also necessary to highlight the importance of effective antimicrobial stewardship programs including increasing the public education about how to use antibiotics properly at 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 [6]. Increasing active screening at admission and subsequent isolation of positive cases are important intervention supplement. However, how to treat colonized patients especially with antibiotic exposure as quickly and efficiently as possible is still a big challenge in controlling MRSA infections.

Our project emphasizes many times the importance of incorporating the indirect transmission via free-living bacteria in the environment, where they are assumed to be uniformly distributed. However, bacterial density varies in hospitals. It is more realistic but difficult to take such heterogeneity into consideration in future work. In addition, If it is possible to get data from hospitals, we would be able to get more convincing results in the future.

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