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Modeling Environmental Contamination of Antibiotic-Resistant Bacteria in Hospitals

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MODELING ENVIRONMENTAL CONTAMINATION OF ANTIBIOTIC-RESISTANT BACTERIA IN HOSPITALS

By

Lei Wang

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Methicillin-resistant *Staphylococcus aureus* (MRSA) is a bacterium that causes infections in different parts of the body. It is tougher to treat than most strains of *Staphylococcus aureus* or staph, because it is resistant to some commonly used antibiotics. In this work, we investigate the role of environmental contamination on the clinical epidemiology of antibiotic-resistant bacteria in hospitals. A compartmental model is constructed to describe the transmission characteristics of MRSA in hospital setting. The deterministic epidemic model includes five compartments: colonized and uncolonized patients, contaminated and uncontamincated health care workers (HCWs), and bacterial load in environment. Basic reproduction number R_0 is calculated, and its numerical and sensitivity analysis has been performed to study the asymptotic behavior of our model, and to help identify factors responsible for observed patterns of infection. A stochastic epidemic model with stochastic simulations is also presented to supply a comprehensive analysis of its behavior. The purpose of this study is to provide theoretical guidance for designing efficient control measures, such as increasing the hand hygiene compliance of HCWs and disinfection rate of environment, and decreasing the transmission rate between environment and patients and HCWs.

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Contents

Chapter 1

Introduction

The emergence and spread of antimicrobial-resistant bacteria (ARB) is one of the most serious public health threats. Bacteria such as vancomycin-resistant enterococci (VRE) and glycopeptide-intermediate sensitive *Staphylococcus aureus* present hospitals with the prospect of a postantibiotic era, in which few if any therapeutic antimicrobial agents remain effective.[33] Compared to infections caused by susceptible strains, infections caused by antibiotic-resistant organisms are more likely to prolong hospitalization, to increase the risk of death, and to require treatment with more toxic or more expensive antibiotics.[10] Patients admitted to healthcare institutions are the main reservoirs of ARB. It is estimated that $5 - 10\%$ of patients develop an infection directly related to their hospitalization, resulting in over 90,000 deaths per year in the US. Infections that are acquired in hospitals, and are favored by a hospital environment, referred to by the technical term 'nosocomial' have been a big threat to the public health. This situation is even more severe in China. A high percentage of hospital-acquired infections are caused by highly resistant bacteria such as methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant ente-

rococci. In particular, methicillin-resistant *Staphylococcus aureus* (MRSA) is associated with considerable morbidity and mortality among inpatients,[7, 8] and accounts for $35 - 80\%$ of total staphylococcal infection in China.[29] Patients colonized with MRSA are more likely to develop infection.[22, 23] Considerable quantitative research has been dedicated into the study of infection control strategies. However, to gain a complete understanding of the numerous interrelated variables that contribute to the spread of ARB, mathematical modeling has a particularly successful record of applications to the epidemiology of infectious diseases. This is especially true for the description of the transmission dynamics of diseases ranging from measles and pertussis to gonorrhea and in the prediction of the effects of public health interventions such as treatment and vaccination on these dynamics.[16] Mathematical modeling has provided a means to study the transmission dynamics of nosocomial pathogens in hospitals, including investigations of patient and health care worker contact patterns, and HCW-and patient-mediated transmission.

Much evidence has been proposed to show that environmental contamination is an important factor in the transmission of MRSA.[5] Environmental contamination may contribute to transmission of health care pathogens when health care workers contaminate their hands or gloves by touching contaminated surfaces, or when patients come into direct contact with contaminated surfaces. Transmission of MRSA from environmental surfaces to gloves or hands of HCWs has been documented by several investigators.[4] However, little is known about the role of environmental infection in the transmission dynamics of MRSA, and this provides the motivation of our research.

To investigate the transmission pattern of nosocomial infection in hospitals, we first introduce a compartmental model of the transmission dynamics of MRSA in Bei-

jing Tongren Hospital with patients, HCWs and volunteers.[30] The hospital provided patient data collected from Emergence Ward (EW) that we will use in the analysis of our model. Based on this research, we establish a mathematical model with patients, HCWs and bacteria in the environment. I used a combination of numerical and sensitivity analysis to analyze the deterministic model, which concentrates on the interactions between environmental infection and patients and HCWs. A stochastic epidemic model and its simulations are also introduced to check the essential features that are not well described in the deterministic model.

To control the nosocomial infection with environmental infection in hospitals, we give suggestions on control strategies as follows. First, increasing the disinfection rate of environment will help to control the transmission dynamic of MRSA in the hospital. Meanwhile, it is essential to control the contamination rates between the environment and patients and HCWs. Finally, we should give priority to controlling the contamination rate between the environment and patients rather than that of the environment and HCWs.

Chapter 2

Modeling the transmission dynamics of methicillin-resistant *Staphylococcus aureus* in Beijing Tongren Hospital

2.1 Purpose

We consider the semi-professional volunteers who work in many tertiary care hospitals in China to be healthcare assistants. These volunteers have less training than HCWs[27, 35], care for patients on a one-to-one basis, and are known to be less compliant with handwashing than HCWs. The daily work of volunteers includes taking care of patients' daily lives, helping patients transfer from one unit to another, reporting irregular results to doctors, etc. They do not usually share work stations with HCWs. It is not clear whether the current infection control measures are effective to control MRSA transmission on wards with volunteers. Hence, it is important to assess the role of volunteers in MRSA transmission in order to identify reasonable infection control programs for the whole hospital setting.

Most studies have used deterministic differential equation models which aggregate

patient and HCW populations into compartments such as colonized or uncolonized patients, and contaminated or uncontaminated HCWs, and employ the Ross-Macdonald model structure for vector-borne diseases.[2, 17] A stochastic version of such a model has also been proposed to study the transmission of MRSA in an intensive care unit.[19] Following a similar modeling structure, the authors constructed a compartmental model to describe the transmission characteristics of MRSA in the emergency ward (EW) and respiratory intensive care unit (RICU) for volunteers in Beijing Tongren Hospital, Beijing, China. The aim of this study was to analyze the transmission dynamics of MRSA in wards with both professional HCWs and volunteers, and to assess various infection prevention programmes to improve the control of MRSA and other multi-drug-resistant bacteria infections in similar hospitals.

This study was conducted in Beijing Tongren Hospital, a 1600-bed university-affiliated teaching hospital. Seventy volunteers worked at the hospital, distributed over various wards, and all were managed by the Hospital Administration Centre of Nursing Workers. Our study was focused on two wards: the emergency ward (EW) and the respiratory intensive care unit (RICU). Twenty-three volunteers worked in the EW, and two worked on the RICU. As the majority of patients admitted to the EW are critically ill and are usually transferred to other units, the prevention of MRSA transmission is particularly important. There are 23 beds in the EW and 7 beds in the RICU. Our study of the environmental infection will use the patient data collected from the EW.

2.2 Model description and assumptions

The patients were divided into two groups: uncolonized $P_U(t)$ and colonized $P_C(t)$. No distinction was made between colonized and infected patients. The HCWs and volunteers were also grouped into two subpopulations: uncontaminated HCWs $H_U(t)$ and contaminated HCWs $H_C(t)$, and uncontaminated volunteers $V_U(t)$ and contaminated volunteers $V_C(t)$, respectively. It was assumed that patients are admitted to the hospital at rate λ, and a portion ϕ were already colonized with MRSA before entering. δ_U and δ_C represent the discharge rates for uncolonized and colonized patients, respectively. Patients can become colonized through contact with contaminated HCWs and volunteers, respectively, according to a mass-action law: $(1-\eta)\beta_{PH}P_U(t)H_C(t)$ and $(1-\xi)\beta_{PV}P_U(t)V_C(t)$, where η describes the hand hygiene of HCWs, and ξ describes the hand hygiene of volunteers. It was assumed that the transmission rate for volunteers (β_{PV}) was lower than the transmission rate for HCWs (β_{PH}) as volunteers only care for one patient at a time. HCWs can become contaminated through contact with colonized patients, $\beta_{PH}P_C(t)H_U(t)$, as can volunteers, $\beta_{PV}P_C(t)V_U(t)$. $1/\gamma_H$ and $1/\gamma_V$ represent the durations of contamination of HCWs and volunteers, respectively. Figure 2.1 shows a schematic illustration of the mathematical compartments.

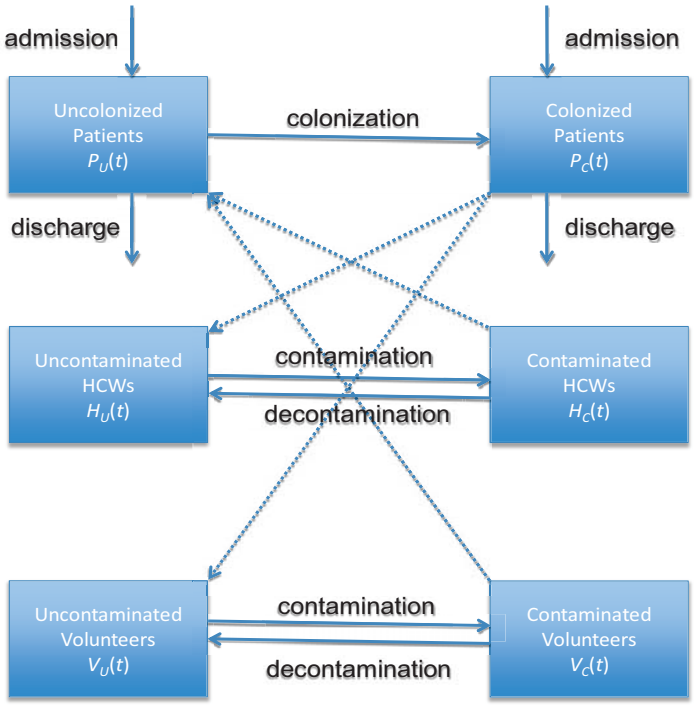

Figure 2.1: *A compartmental model of transmission dynamics of methicillin-resistant Staphylococcus aureus among patients, healthcare workers (HCWs) and volunteers in Beijing Tongren Hospital*

The deterministic model is a system of six ordinary differential equations as follows:

$$\begin{cases} \frac{dP_U}{dt} = \lambda(1-\phi) - \left[\frac{(1-\eta)}{N}\beta_{PH}H_C(t) + \frac{(1-\xi)}{N}\beta_{PV}V_C(t)\right]P_U(t) - \delta_U P_U(t) \\ \frac{dP_C}{dt} = \lambda\phi + \left[\frac{(1-\eta)}{N}\beta_{PH}H_C(t) + \frac{(1-\xi)}{N}\beta_{PV}V_C(t)\right]P_U(t) - \delta_C P_C(t) \\ \frac{dH_U}{dt} = -\frac{(1-\eta)}{N}\beta_{PH}P_C(t)H_U(t) + \gamma_H H_C(t) \\ \frac{dH_C}{dt} = \frac{(1-\eta)}{N}\beta_{PH}P_C(t)H_U(t) - \gamma_H H_C(t) \\ \frac{dV_U}{dt} = -\frac{(1-\xi)}{N}\beta_{PV}P_C(t)V_U(t) + \gamma_V V_C(t) \\ \frac{dV_C}{dt} = \frac{(1-\xi)}{N}\beta_{PV}P_C(t)V_U(t) - \gamma_V V_C(t); \end{cases} \tag{2.1}$$

2.3 Parameter estimation

An investigator observed the daily care activities of HCWs and volunteers over three 1-h periods (9:00-10:00 am, 12:30-13:30 pm, 23:00-24:00pm), repeated on three different days, including compliance with handwashing and other infection control measures, and patient care activities. Contact plate sampling was employed to detect MRSA colonies on the hands of HCWs/volunteers before and after medical care of MRSA-positive patients. HCWs/volunteers were asked to wash their hands thoroughly before contact with patients. MRSA was transferred to the hands of HCWs/volunteers in 19 out of 207 observed contacts with patients or their local environment $(19/207, 9.2\%)$. Therefore, δ was estimated to be 0.09. Handwashing compliance rates of volunteers were 20.7%(25/121) on the EW and 23.1%(30/130) on the RICU. Corresponding figures for HCWs were 41.0%(50/122) and 45.6%(57/125). Note that $\beta_{PH} = \delta \times \theta_{PH}$

Table 1: Baseline parameters values and estimates for the transmission of MRSA in the Emergency Ward (EW) and respiratory intensive care unit (RICU).

Parameter	Symbol	Baseline value		Sources
		EW	RICU	
Total number of beds	N	23	7	Tongren
Total number of HCWs	H	23	14	Tongren
Total admissions per day	λ	0.79	0.33	Tongren
Fraction of admissions per day				
Colonized patients	θ	0.067	0.165	Tongren
Length of stay (days)				
Uncolonized patients	$1/\delta_U$	13	7	Tongren
Colonized patients	$1/\delta_C$	20	13	Tongren
Hand hygiene compliance (0 to 1)				
HCWs	η	0.41	0.46	Observed
Volunteers	ξ	0.2	0.23	Observed
Transmission probability per contact	δ	0.09		Observed
Transmission rate				
Colonized patients to HCWs	β_{PH}	0.72		Estimated
Colonized patients to volunteers	β_{PV}	0.20		Estimated
Duration of contamination (days)				
HCWs	$1/\gamma_H$	1/24	1/24	Austin *et al.*
volunteers	$1/\gamma_V$	1/12	1/12	Tongren

(contact rate, patients-HCWs), where θ_{PH} = number of patients $\times$ (total number of contacts between HCWs and patients per day)/(total number of patients $\times$ total number of HCWs in the ward). $\beta_{PV} = \delta \times \theta_{PV}$ (contact rate, patients-volunteers), where θ_{PV} = number of patients $\times$ (total number of contacts between volunteers and patients per day)/(total number of patients $\times$ total number of volunteers in the ward). Only 'effective contacts' between patients and volunteers were calculated, which were composed of two parts: contacts that occurred when a volunteer had contacts with other patients in the ward, and effective contacts between a volunteer and his/her dedicated patient. Baseline parameters and their estimates are listed in Table 1.

2.4 Results

Basic Reproduction number

In epidemiology, the basic reproduction number (sometimes called basic reproductive rate, or basic reproductive ratio and denoted R_0) of an infection is defined as the expected number of secondary cases produced by a single (typical) infection in a completely susceptible population. Since the actual number of secondary cases produced by an infected individual is an integer that can vary depending on their contacts and they can be random factors that affect the chance of disease transmission after a contact, the number of secondary cases aring from a single infection should really be viewed as a random variable. R_0 can be interpreted as its expected value. Thus, since R_0 represents the expected value (that is, the mean) of a random variable, it is not necessarily an integer. R_0 is very important and useful because it helps in most cases determine whether or not an infectious disease can spread through a population. Generally, larger R_0 implies it is harder to control the epidemic. To be more specific, when $R_0 < 1$, the disease would die out eventually; when $R_0 > 1$, the disease will be endemic. Once we have the expression of R_0, it is possible to do a sensitivity analysis, which would be helpful in leading to an optimal control strategy. In this study, R_0 represents the number of patients who are colonized with MRSA by an index case patient at the beginning of the epidemic. From the point of view of infection control, the infection and spread of MRSA can be controlled in a hospital if $R_0 < 1$, whereas if $R_0 > 1$, MRSA has become endemic in the hospital. This study aimed to determine factors that affect the spread and control of MRSA in the hospital by analyzing the dependence of R_0 on various model parameters (i.e. sensitivity

analysis). An explicit expression for R_0 is derived in the case of $\phi = 0$ (i.e. when no colonized patients are admitted to hospital). Sensitivity analysis of R_0 was undertaken in terms of the model parameters, such as transmission rate between patients and volunteers, length of hospital stay for uncolonized and colonized patients, and the duration of contamination of HCWs and volunteers.

We may find R_0 by its definition directly from the model. More specifically: $R_0 = \tau \cdot \bar{c} \cdot d$, [14] where τ is the transmissibility (i.e., probability of infection given contact between a susceptible and infected individual), $\bar{c}$ is the average rate of contact between susceptible and infected individuals, and d is the duration of infectiousness. But for other cases, it is not easy to obtain it from the model in such a straightforward manner. The usual way to calculate R_0 is due to van den Driessche and Watmough.[28] Their paper and notes have given a precise definition and algorithm for obtaining R_0 for a general compartmental ordinary differential equation model of disease transmission. In this work, we will use this method to find the basic reproduction number R_0 of our model. The details of this method we adapt from van den Driessche and Watmough are as follows.[28]

Consider a heterogeneous population whose individuals are distinguishable by age, behaviour, spatial position and/or stage of disease, but which can be grouped into n homogeneous compartments. Let $x = (x_1, ..., x_n)^t$, with each $x_i \geqslant 0$, being the number of individuals in each compartment. For clarity we sort the compartments so that the first m compartments correspond to infected individuals. The distinction between infected and uninfected compartments must be determined from the epidemiological interpretation of the model and cannot be deduced from the structure of the equations

alone. We define X_s to be the set of all disease free states. That is

$$\mathbf{X}_s = \{x \geqslant 0 | x_i = 0, i = 1, ..., m\}.$$

In order to compute R_0, it is important to distinguish new infections from all other changes in population. Let $\mathscr{F}_i(x)$ be the rate of appearance of new infections in compartment i, $\mathscr{V}_i^+(x)$ be the rate of transfer of individuals into compartment i by all other means, and $\mathscr{V}_i^-(x)$ be the rate of transfer of individuals out of compartment i. It is assumed that each function is continuously differentiable at least twice in each variable. The disease transmission model consists of nonnegative initial conditions together with the following system of equations:

$$\dot{x}_i = f_i(x) = \mathscr{F}_i(x) - \mathscr{V}_i(x), \qquad i = 1, ..., n, \tag{2.2}$$

where $\mathscr{V}_i = \mathscr{V}_i^- - \mathscr{V}_i^+$ and the functions satisfy assumptions (A1)-(A5) described below.

(A1) if $x \geqslant 0$, then $\mathscr{F}_i, \mathscr{V}_i^+, \mathscr{V}_i^- \geqslant 0$ for $i = 1, ..., n$.

(A2) if $x_i = 0$ then $\mathscr{V}_i^- = 0$. In particular, if $x \in \mathbf{X}_s$ then $\mathscr{V}_i^- = 0$ for $i = 1, ..., m$.

(A3) $\mathscr{F}_i = 0$ if $i > m$.

(A4) if $x \in \mathbf{X}_s$ then $\mathscr{F}_i(x) = 0$ and $\mathscr{V}_i^+(x) = 0$ for $i = 1, ..., m$.

(A5) if $\mathscr{F}(x)$ is set to zero, then all eigenvalues of $Df(x_0)$ have negative real parts, where $Df(x_0)$ is the derivative $[\partial f_i / \partial x_j]$ evaluated at the disease free equilibrium (DFE) x_0 (i.e. the Jacobian Matrix).

The conditions listed above allow us to partition the matrix $Df(x_0)$ as shown by the following lemma.

Lemma 2.1. *If x_0 is a DFE of (2.2) and $f_i(x)$ satisfies (A1)-(A5), then the derivatives $D\mathscr{F}(x_0)$ and $D\mathscr{V}(x_0)$ are partitioned as*

$$D\mathscr{F}(x_0) = \begin{pmatrix} F & 0 \\ 0 & 0 \end{pmatrix}, \qquad D\mathscr{V}(x_0) = \begin{pmatrix} V & 0 \\ J_3 & J_4 \end{pmatrix},$$

where F and V are the $m \times m$ matrices defined by

$$F = \left[\frac{\partial \mathscr{F}_i}{\partial x_j}(x_0)\right] \quad \textit{and} \quad V = \left[\frac{\partial \mathscr{V}_i}{\partial x_j}(x_0)\right] \quad \textit{with} \quad 1 \leqslant i, j \leqslant m.$$

Further, F is non-negative, V is a non-singular M-matrix and all eigenvalues of J_4 have positive real part.

Note that part of derivative $D\mathscr{V}(x_0)$ does not contribute to the calculation of R_0, we simply denote it as J_3, J_4. Following Diekmann et al.[9], we call FV^{-1} the next generation matrix for the model and set

$$R_0 = \rho\left(FV^{-1}\right),$$

where $\rho(A)$ denotes the spectral radius of a matrix A. To be more specific, R_0 is the largest eigenvalue of the matrix FV^{-1}.

When $\phi = 0$, that is no colonized patients are admitted into the hospital, then the disease-free steady state is obtained:

$$E_0 = (P_U, P_C, H_U, H_C, V_U, V_C) = \left(\frac{\lambda}{\delta_U}, 0, 1, 0, 1, 0\right).$$

The infected compartments are colonized patients P_C, contaminated HCWs H_C and

contaminated volunteers V_C; the uninfected compartments are uncolonized patients P_U, uncontaminated HCWs H_U and uncontaminated volunteers V_U. Thus, for this mode, $n = 6, m = 3$. After rearrangement, we denote

$$x = (P_C, H_C, V_C, P_U, H_U, V_U)^t, \quad x_0 = (0, 0, 0, \frac{\lambda}{\delta_U}, 1, 1),$$

and

$$\dot{x_i} = f_i(x) = \mathscr{F}_i(x) - (\mathscr{V}_i^-(x) - \mathscr{V}_i^+(x)), \qquad i = 1, ..., 6,$$

with

$$\mathscr{F}(x) = \begin{pmatrix} \mathscr{F}_1(x) \\ \mathscr{F}_2(x) \\ \mathscr{F}_3(x) \\ \mathscr{F}_4(x) \\ \mathscr{F}_5(x) \\ \mathscr{F}_6(x) \end{pmatrix} = \begin{pmatrix} \frac{(1-\eta)}{N}\beta_{PH}P_U H_C + \frac{(1-\xi)}{N}\beta_{PV}P_U V_C \\ \frac{(1-\eta)}{N}\beta_{PH}P_C H_U \\ \frac{(1-\xi)}{N}\beta_{PV}P_C V_U \\ 0 \\ 0 \\ 0 \end{pmatrix},$$

and

$$\mathscr{V}^-(x) = \begin{pmatrix} \delta_C P_C \\ \gamma_C H_c \\ \gamma_V V_C \\ \left[\frac{(1-\eta)}{N}\beta_{PH}H_C + \frac{(1-\xi)}{N}\beta_{PV}V_C\right] P_U + \delta_U P_U \\ \frac{(1-\eta)}{N}\beta_{PH}P_C H_U \\ \frac{(1-\xi)}{N}\beta_{PV}P_C V_U \end{pmatrix}, \mathscr{V}^+(x) = \begin{pmatrix} 0 \\ 0 \\ 0 \\ \lambda \\ \gamma_H H_C \\ \gamma_V V_C \end{pmatrix}.$$

It is easy to check that (A1)-(A5) are satisfied. For $1 \leqslant i, j \leqslant 3$,

$$\begin{aligned} F &= \left[\frac{\partial \mathscr{F}_i}{\partial x_j}(x_0)\right] \\ &= \begin{pmatrix} 0 & \frac{(1-\eta)}{N}\beta_{PH}P_U & \frac{(1-\xi)}{N}\beta_{PV}P_U \\ \frac{(1-\eta)}{N}\beta_{PH}H_U & 0 & 0 \\ \frac{(1-\xi)}{N}\beta_{PV}V_U & 0 & 0 \end{pmatrix}\Bigg|_{E_0} \\ &= \begin{pmatrix} 0 & \frac{(1-\eta)}{N}\beta_{PH}\frac{\lambda}{\delta_U} & \frac{(1-\xi)}{N}\beta_{PV}\frac{\lambda}{\delta_U} \\ \frac{(1-\eta)}{N}\beta_{PH} & 0 & 0 \\ \frac{(1-\xi)}{N}\beta_{PV} & 0 & 0 \end{pmatrix}, \end{aligned}$$

and

$$V = \left[\frac{\partial \mathscr{V}_i}{\partial x_j}(x_0)\right] = \begin{pmatrix} \delta_C & 0 & 0 \\ 0 & \gamma_H & 0 \\ 0 & 0 & \gamma_V \end{pmatrix},$$

then

$$V^{-1} = \begin{pmatrix} \frac{1}{\delta_C} & 0 & 0 \\ 0 & \frac{1}{\gamma_H} & 0 \\ 0 & 0 & \frac{1}{\gamma_V} \end{pmatrix}.$$

Thus,

$$\begin{aligned} FV^{-1} &= \begin{pmatrix} 0 & \frac{(1-\eta)}{N}\beta_{PH}\frac{\lambda}{\delta_U} & \frac{(1-\xi)}{N}\beta_{PV}\frac{\lambda}{\delta_U} \\ \frac{(1-\eta)}{N}\beta_{PH} & 0 & 0 \\ \frac{(1-\xi)}{N}\beta_{PV} & 0 & 0 \end{pmatrix} \cdot \begin{pmatrix} \frac{1}{\delta_C} & 0 & 0 \\ 0 & \frac{1}{\gamma_H} & 0 \\ 0 & 0 & \frac{1}{\gamma_V} \end{pmatrix} \\ &= \begin{pmatrix} 0 & \frac{(1-\eta)\beta_{PH}\lambda}{\delta_U\gamma_H N} & \frac{(1-\xi)\beta_{PV}\lambda}{\delta_U\gamma_C N} \\ \frac{(1-\eta)\beta_{PH}}{\delta_C N} & 0 & 0 \\ \frac{(1-\xi)\beta_{PV}}{\delta_C N} & 0 & 0 \end{pmatrix}. \end{aligned}$$

Then

$$R_0 = \sqrt{\frac{(1-\eta)^2\beta_{PH}^2\lambda}{\delta_U\delta_C\gamma_H N^2} + \frac{(1-\xi)^2\beta_{PV}^2\lambda}{\delta_U\delta_C\gamma_V N^2}},$$

which is the dominant eigenvalue of FV^{-1}. Furthermore, we have the following theorem from van den Driessche and Watmough:[28]

Theorem. *If $P_U^0, P_C^0 \geqslant 0$, the solutions are non-negative and remain bounded in the positive cone of $\mathbb{R}^6$. If $R_0 < 1$, the disease-free steady state E_0 is locally asymptotically stable. If $R_0 > 1$, E_0 is unstable.*

Model simulations

Model simulations using the parameter values given in Table 1 were performed for comparison with the reported data on the numbers of colonized patients in the EW and RICU in Beijing Tongren Hospital from 3 March 2009 to 28 February 2010. The results are compared in Figure 2.2. Since the populations in the EW and RICU were small, the numerical simulations were performed according to the stochastic model, and compared with the simulations using the deterministic model for both the EW and RICU in Figure 2.3. Simulations using the stochastic model appeared to provide a better explanation of the transmission dynamics for small populations.

Since β_{PV} represents the transmission rate between patients and volunteers, it is possible to analyze the effect of using volunteers on MRSA transmission. The transmission rate is the proportion of contacts between colonized and uncolonized individuals that result in infection. Thus, in numerical terms, it is the transmission probability per contact $\times$ contact rate. As volunteers interact with patients on a one-to-one basis, the transmission rate from volunteers to patients is less than that from HCWs to patients. If there were no volunteers, an equal or smaller number of

HCWs would have to replace these volunteers. We consider the case that all of the volunteers were replaced by the same number of HCWs under assumptions that equal transmission rates were used for both HCWs and volunteers and other parameters were kept the same as we have used in numerical simulations. Figure 2.4 shows that if volunteers were replaced by HCWs (i.e. $\beta_{PV} = \beta_{PH}$), the number of colonized patients would increase; this was confirmed by analysis of R_0.

2.5 Summary

Traditional strategies include reducing transmission rates between patient and nurses. In this study, the introduction of volunteers provides more options in designing control intervention strategies. Meanwhile, decreasing the transmission rates between patients and HCWs and between patients and volunteers, while increasing hand hygiene compliance of HCWs and volunteers, are all important in controlling infection based on the sensitivity analysis of R_0 for these parameters. However, among these parameters, an increase in handwashing compliance for HCWs and volunteers would decrease R_0 most dramatically, as the dependence is almost linear. If volunteers were replaced by HCWs and handwashing compliance was not 100%, MRSA transmission would increase. We get this conclusion under assumptions that equal transmission rates were used for both HCWs and volunteers and other parameters were kept the same as we have used in numerical simulations. However, if we replaced volunteers with HCWs, there would be only four compartments in the model: colonized and uncolonized patients, and contaminated and uncontaminated HCWs. Meanwhile, we should reestimate values of parameters. More accurate description and analysis of this case are required in future research. The simulation results can be explained

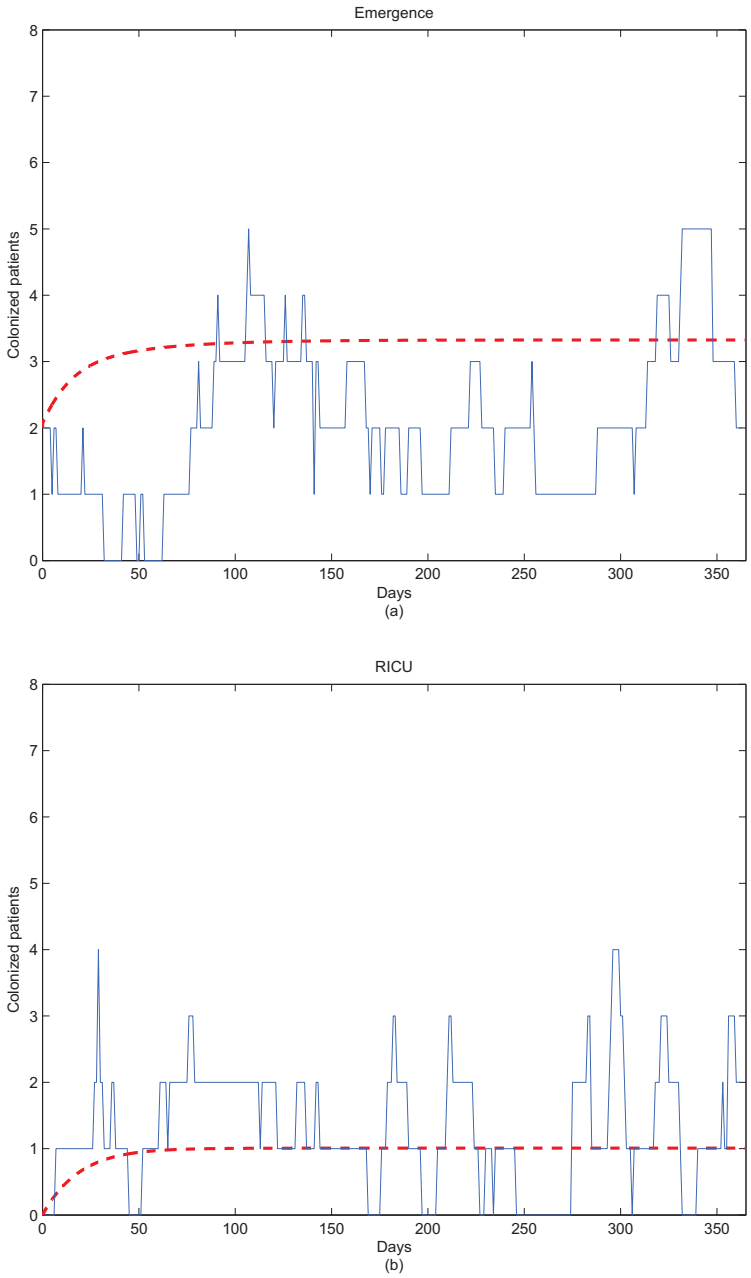

Figure 2.2: *Model simulations using baseline parameters from Table 1 for the numbers of patients colonized with methicillin-resistant* Staphylococcus aureus *(dotted line) compared with the actual data (solid line) for (a) the emergency ward and (b) the respiratory intensive care unit at Beijing Tongren Hospital. Euler's method was used to plot the data.*

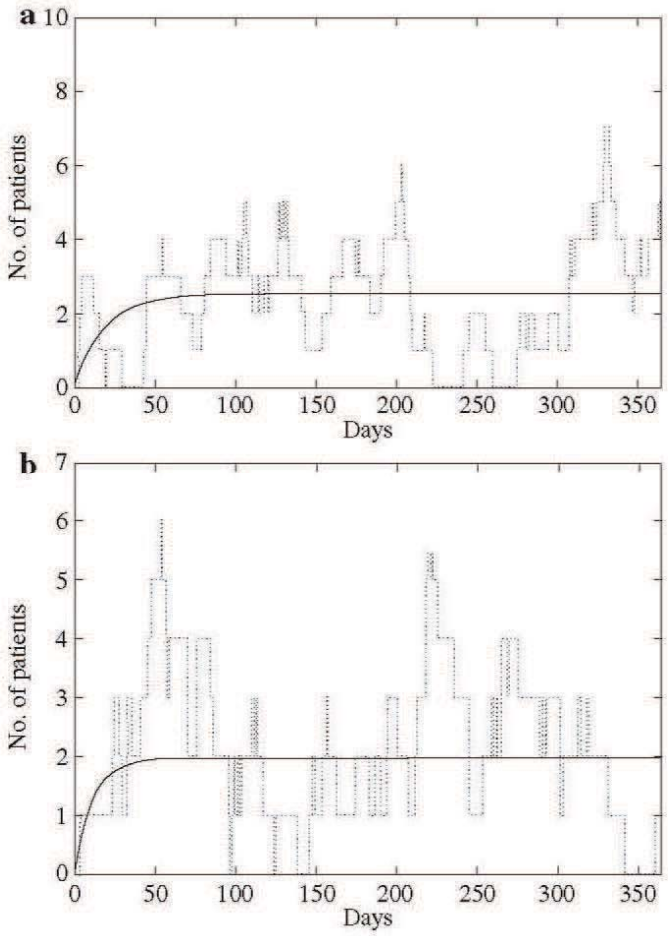

Figure 2.3: *Numerical simulations for both the deterministic stochastic models over one year corresponding to (a) the emergency ward and (b) the respiratory intensive care unit, using the parameters in Table 1. Solid lines correspond to the deterministic model and dotted lines correspond to the stochastic model.*

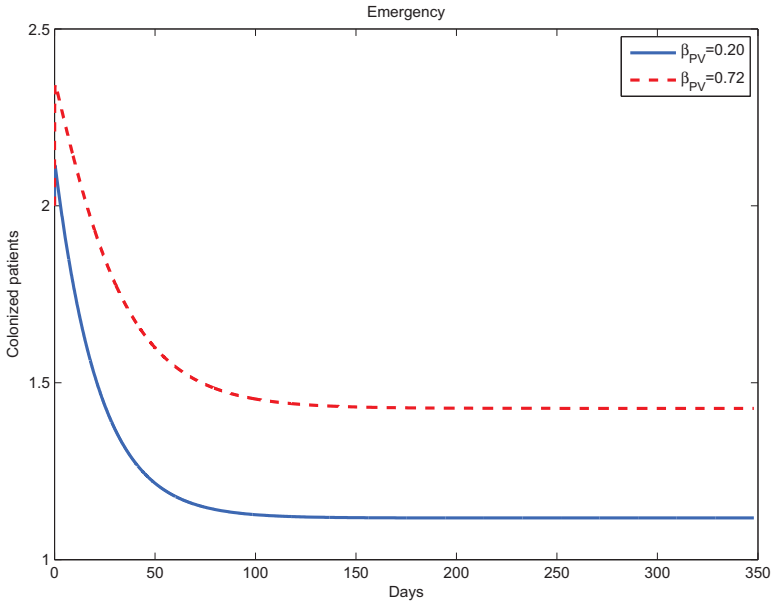

Figure 2.4: *Numbers of methicillin-resistant Staphylococcus aureus positive patients in the emergency ward with volunteers and healthcare workers (HCWs) (β_{PV}=0.2, solid line) and HCWs alone ($\beta_{PV} = 0.72$, dotted line). This indicates that the number of colonized patients would increase if the volunteers were replaced by HCWs.*

by previous studies, which showed that increasing the workload of HCWs was closely associated with higher nosocomial infection rates.[13] Employment of volunteers would decrease the workload of HCWs dramatically. Cohort nursing is known to be one of the most effective ways to prevent cross-transmission.[3, 19] The ward is divided so that each nurse cares for a certain cohort of patients (i.e. cohort nursing). Provided no contact routes are duplicated, then the increase in staff numbers will lead to a reduction in the number of hazardous contacts, and through a reduction in work pressure will likely result in better hand hygiene compliance and improved housekeeping practices. The volunteer system in the study hospital is similar to cohort nursing, and volunteers can conduct many nursing tasks, thus reducing multi-patient contact by HCWs. Cohort nursing by fully trained HCWs would be even more effective. This study also investigated the behaviors of volunteers during the study period. Compared with HCWs, more frequent contacts were observed between volunteers and environmental surfaces, and this may increase the probability of transmission of MRSA from the surrounding environment of MRSA patients to other environmental surfaces and vice versa. Volunteers' behaviors may be partly influenced by their long-term assignment to a ward. However, a recent study revealed that proper education for volunteers in infection control can decrease the nosocomial infection rate, which suggests that employment of volunteers undergoing nursing training is an alternative approach to nursing care. In conclusion, improving the handwashing compliance of volunteers, who cohort nurse patients, will decrease MRSA transmission dramatically.

Chapter 3

Nosocomial infection model with environment contamination

3.1 Model description and assumptions

In this chapter, we introduce a nosocomial infection model with environment contamination in hospital based on the previous model we discussed in Chapter 2. Patients in the hospital unit are classified by compartment as either uncolonized $P_u(t)$, or colonized $P_c(t)$; health-care workers are classified by compartment as either uncontaminated $H_u(t)$, or contaminated $H_c(t)$. The bacterial load in the environment is the compartment $B_e(t)$. We do not consider the compartment of volunteers in this model. The relation between different compartments inside hospital unit is depicted in the compartmental scheme of Figure 3.1. Patients are admitted at a total rate of Λ per day with the fraction of colonized patients θ. Since the total number of beds in hospital unit is a fixed number, we assume that the inflow of patients is $\Lambda = \gamma_u P_u + \gamma_c P_c$, based on the assumption of full occupation of the unit, where γ_u and γ_c are discharge rates of uncolonized patients and colonized patients per day from hospital, respectively. Hence, the total number of patients in the unit remains constant at N_p. Note that the total number of HCWs is also assumed to be a constant, N_h. It is

assumed that there is no cross-infection between patients, so that patients can only be colonized with antibiotic-resistant bacteria by contacting contaminated health-care workers $\alpha_p\beta_p(1-\eta)P_u(t)H_c(t)$ or the contaminated environment $k_pP_u(t)B_e(t)$, where α_p is the contact rate, β_p is the probability of colonization per contact, η is the compliance rate with the hand hygiene, and k_p is the colonization rate from the environment. Health-care workers can be contaminated with antibiotic-resistant bacteria by contacting colonized patients $\rho\alpha_p\beta_hP_c(t)H_c(t)$ and the contaminated environment $k_hH_u(t)B_e(t)$, where β_h is the probability of contamination per contact, ρ is the ratio of HCWs to patients, and k_h is the contamination rate from the environment. μ_c is the decontamination rate for the HCWs, ν_p and ν_h are the rate that colonized patients and contaminated HCWs contaminate the environment, respectively, and γ_b is the cleaning/disinfection rate of the environment. Details for parameters in this model can be found in Table 2.

The equations of the basic model are

$$\begin{cases} \dfrac{dP_u(t)}{dt} = (1-\theta)\left[\gamma_uP_u(t)+\gamma_cP_c(t)\right] - \alpha_p\beta_p(1-\eta)P_u(t)H_c(t) - k_pP_u(t)B_e(t) - \gamma_uP_u(t) \\ \dfrac{dP_c(t)}{dt} = \theta\left[\gamma_uP_u(t)+\gamma_cP_c(t)\right] + \alpha_p\beta_p(1-\eta)P_u(t)H_c(t) + k_pP_u(t)B_e(t) - \gamma_cP_c(t) \\ \dfrac{dH_u(t)}{dt} = -\rho\alpha_p\beta_hP_c(t)H_u(t) + \mu_cH_c(t) - k_hH_u(t)B_e(t) \\ \dfrac{dH_c(t)}{dt} = \rho\alpha_p\beta_hP_c(t)H_u(t) - \mu_cH_c(t) + k_hH_u(t)B_e(t) \\ \dfrac{dB_e(t)}{dt} = \nu_pP_c(t) + \nu_hH_c(t) - \gamma_bB_e(t) \end{cases}, \tag{3.1}$$

with initial conditions $P_u(0)=P_u^0, P_c(0)=P_c^0, H_u(0)=H_u^0, H_c(0)=H_c^0, B_e(0)=B_e^0$ specified at time 0.

Since system (3.1) is developed from system (2.1), here are some remarks on the connection between two systems.

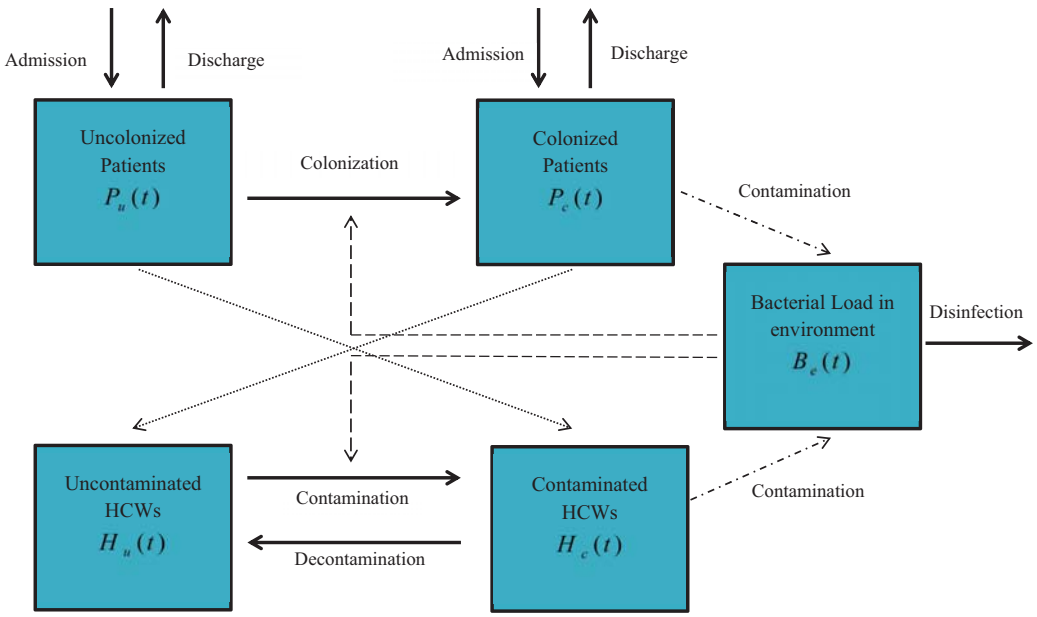

Figure 3.1: *A compartmental model of transmission dynamics of meticillin-resistant Staphylococcus aureus among patients and healthcare workers (HCWs) with environmental contamination.*

(R1) They both have admission of patients into hospital with fraction of colonized patients. In (2.1), the fraction is ϕ; in (3.1), the fraction is θ.

(R2) The admission of patients is given in different ways. In (2.1), we consider it to be a constant λ; however, in (3.1), the inflow of patients is $\Lambda = \gamma_u P_u + \gamma_c P_c$ by the assumption of full occupation of the unit.

(R3) In (2.1), $\frac{(1-\eta)}{N}\beta_{PH}$ is used to represent the proportion of newly colonized patients by contacting contaminated HCWs; in (3.1) we use $\alpha_p\beta_p(1-\eta)$ to describe this proportion.

(R4) In (2.1), $\frac{(1-\eta)}{N}\beta_{PH}$ is also used to represent the proportion of newly contaminated HCWs by contacting colonized patients; however, in (3.1), we consider it to be a different probability; that is, $\rho\alpha_p\beta_h$.

(R5) Bacteria in the environment are now considered.

3.2 Basic reproduction number

We obtain R_0 by using the method from van den Driessche and Watmough.[28]. When $\theta = 0$, that is no colonized patients are admitted into hospital, DFE is defined to be

$$E_0 = (P_u, P_c, H_u, H_c, B_e) = (N_p, 0, N_h, 0, 0),$$

where N_p, N_h are total number of patients and HCWs, respectively. The infected compartments are colonized patients P_c, contaminated HCWs H_c and bacterial load B_e; the uninfected compartments are uncolonized patients P_u and uncontaminaed HCWs H_u. Thus, for our model, $n = 5, m = 3$. After rearrangement, we denote

$$x = (P_c, H_c, B_e, P_u, H_u)^t, \quad x_0 = (0, 0, 0, N_p, N_h),$$

and

$$\dot{x_i} = f_i(x) = \mathscr{F}_i(x) - \left(\mathscr{V}_i^-(x) - \mathscr{V}_i^+(x)\right),$$

with

$$\mathscr{F}(x) = \begin{pmatrix} \mathscr{F}_1(x) \\ \mathscr{F}_2(x) \\ \mathscr{F}_3(x) \\ \mathscr{F}_4(x) \\ \mathscr{F}_5(x) \end{pmatrix} = \begin{pmatrix} \alpha_p\beta_p(1-\eta)P_uH_c + k_pP_uB_e \\ \rho\alpha_p\beta_hP_cH_u + k_hH_uB_e \\ 0 \\ 0 \\ 0 \end{pmatrix}, \tag{3.2}$$

and

$$\mathscr{V}^-(x) = \begin{pmatrix} \gamma_cP_c \\ \mu_cH_c \\ \gamma_bB_e \\ \alpha_p\beta_p(1-\eta)P_uH_c + k_pP_uB_e + \gamma_uP_u \\ \rho\alpha_p\beta_hP_cH_u + k_hH_uB_e \end{pmatrix}, \mathscr{V}^+(x) = \begin{pmatrix} 0 \\ 0 \\ \nu_pP_c + \nu_hH_c \\ \gamma_uP_u + \gamma_cP_c \\ \mu_cH_c \end{pmatrix}. \tag{3.3}$$

It is easy to check that (A1)-(A5) are satisfied.

Thus,

$$\begin{aligned} F &= \left[\frac{\partial \mathscr{F}_i}{\partial x_j}(x_0)\right] \\ &= \begin{pmatrix} -\alpha_p\beta_p(1-\eta)H_c - k_pB_e & \alpha_p\beta_p(1-\eta)(N_p-P_c) & k_p(N_p-P_c) \\ \rho\alpha_p\beta_h(N_h-H_c) & -\rho\alpha_p\beta_hP_c - k_hB_e & k_h(N_h-H_c) \\ 0 & 0 & 0 \end{pmatrix}\Bigg|_{E_0} \\ &= \begin{pmatrix} 0 & \alpha_p\beta_p(1-\eta)N_p & k_pN_p \\ \rho\alpha_p\beta_hN_h & 0 & k_hN_h \\ 0 & 0 & 0 \end{pmatrix}, \end{aligned} \tag{3.4}$$

and

$$V = \left[\frac{\partial \mathscr{V}_i}{\partial x_j}(x_0)\right] = \begin{pmatrix} \theta\gamma_u + (1-\theta)\gamma_c & 0 & 0 \\ 0 & \mu_c & 0 \\ -\nu_p & -\nu_h & \gamma_b \end{pmatrix}, \tag{3.5}$$

then

$$V^{-1} = \frac{1}{\gamma\mu_c\gamma_b} \begin{pmatrix} \mu_c\gamma_b & 0 & 0 \\ 0 & \gamma\gamma_b & 0 \\ \nu_p\mu_c & \gamma\nu_h & \mu_c\gamma \end{pmatrix}, \tag{3.6}$$

with $\gamma = (\theta\gamma_u + (1-\theta)\gamma_c)$.

Thus,

$$\begin{aligned} FV^{-1} &= \frac{1}{\gamma\mu_c\gamma_b} \begin{pmatrix} 0 & \alpha_p\beta_p(1-\eta)N_p & k_pN_p \\ \rho\alpha_p\beta_hN_h & 0 & k_hN_h \\ 0 & 0 & 0 \end{pmatrix} \cdot \begin{pmatrix} \mu_c\gamma_b & 0 & 0 \\ 0 & \gamma\gamma_b & 0 \\ \nu_p\mu_c & \gamma\nu_h & \gamma\mu_c \end{pmatrix} \\ &= \frac{1}{\gamma\mu_c\gamma_b} \begin{pmatrix} k_p\nu_p\mu_cN_p & [\alpha_p\beta_p(1-\eta)\gamma_b + k_p\nu_h]\,\gamma N_p & k_p\gamma\mu_cN_p \\ (\rho\alpha_p\beta_h\gamma_b + k_h\nu_p)\mu_cN_h & k_h\gamma\nu_hN_h & k_h\gamma\mu_cN_h \\ 0 & 0 & 0 \end{pmatrix}. \end{aligned} \tag{3.7}$$

The basic reproduction number is defined by the largest eigenvalue of FV^{-1}:

$$\begin{aligned} R_0 = {} & \frac{k_p\nu_pN_p}{2\gamma\gamma_b} + \frac{k_h\nu_hN_h}{2\mu_c\gamma_b} \\ & + \frac{\sqrt{(k_p\nu_p\mu_cN_p - k_h\nu_h\gamma N_h)^2 + 4[(\alpha_p\beta_p(1-\eta)\gamma_b + k_p\nu_h)\,(\rho\alpha_p\beta_h\gamma_b + k_h\nu_p)\mu_c\gamma N_hN_p]}}{2\gamma\mu_c\gamma_b}, \end{aligned} \tag{3.8}$$

where $\gamma = \theta\gamma_u + (1-\theta)\gamma_c$.

There is a general limitation on using R_0. If there is an external source that introduces infection into the system, then it is usually impossible to use R_0 to get information about how the system will behave.

Chapter 4

Mathematical and numerical analysis

In this chapter, we will perform the mathematical and numerical analysis relevant to the model of Chapter 3. In epidemiology, there are two types of states of an infection: the disease-free state when there is no infection in the dynamic system, and the endemic state when infection is maintained in the dynamical system, corresponding with disease-free and endemic equilibrium in the model, respectively. In general, for an ordinary differential equation system:

$$\frac{dN}{dt} = f(N) \quad or \quad \frac{dN_i}{dt} = f_i(N_1, ..., N_n), \quad i = 1, ..., n,$$

where $N(t)$ is an n-dimensional vector, and $f(N)$ is a n-dimensional vector of nonlinear function of N, an equilibrium solution N^* is solution of $f(N) = 0$.[21, chap. 1,3] Usually, there is only one disease-free equilibrium (DFE) N_0 when we consider there is no infection in terms of $f(N)$. However, there may be several other equilibria N^*, which depend on the function $f(N)$. In this chapter, we focus on the analysis of the disease-free state, because it may provide a basis for better control measures to help eliminate MRSA transmission in hospital.

4.1 Steady-state analysis

Theorem 4.1. *If $P_u^0, P_c^0, H_u^0, H_c^0, B_e^0 \geqslant 0$, then solutions are non-negative and remain bounded in the positive cone of $\mathbb{R}^5$*

$$G := \{(P_u, P_c, H_u, H_c, B_e) \in R_+^5 : P_u + P_c + H_u + H_c + B_e \leqslant N\},$$

where N is a fixed integer.

Proof. It is easy to see that the solutions remain in the positive cone if the initial conditions are in the positive cone.[26, app. B] Let $T(t) = P_u(t) + P_c(t) + H_u(t) + H_c(t) + B_e(t)$. From (3.1) we have

$$\begin{aligned}\frac{dT(t)}{dt} = \frac{dB_e(t)}{dt} &= \nu_p P_c(t) + \nu_h H_c(t) - \gamma_b B_e(t) \\ &\leqslant \nu_p N_p + \nu_h N_h - \gamma_b B_e(t),\end{aligned}$$

which implies that

$$B_e(t) \leqslant \frac{(\nu_p N_p + \nu_h N_h)}{\gamma_b}(1 - e^{-\gamma_b t}) + B_e^0 e^{-\gamma_b t}.$$

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

$$M = \frac{(\nu_p N_p + \nu_h N_h)}{\gamma_b} + B_e^0.$$

Let $N = N_p + N_h + M$, then

$$P_u(t) + P_c(t) + H_u(t) + H_c(t) + B_e(t) \leqslant N.$$

Thus, the solutions remain bounded in a positive cone of $\mathbb{R}^5$, and the system induces a global semiflow in the positive cone of $\mathbb{R}^5$. □

The stability of disease-free equilibrium is a result of van den Driessche and Watmough.[28]

Theorem 4.2. *If $R_0 < 1$, the disease-free state $(N_p, 0, N_h, 0, 0)$ is locally asymptotically stable. If $R_0 > 1$, the disease-free state is unstable.*

4.2 Estimation of parameters

The best way to estimate parameters is from data collected from the hospital directly. We are not able to obtain such data; however, there are good resources from two references [30, 31] about Beijing Tongren Hospital to use as our estimates. Parameters are grouped into two categories: direct reference, for those we could use immediately from two references; indirect estimation, for those we have to do our own estimation.

(1) Direct reference.

Based on the assumption that the total number of HCWs remains fixed and bed occupancy is 100%, we have $N_p = 23$ and $N_h = 23$. The proportion of colonized patients admitted to hospital is $\theta = 0.067$. The daily discharge rates of uncolonized patients and colonized patients are $\gamma_u = 0.067$ and $\gamma_c = 0.046$, respectively. The hand hygiene compliance of HCWs is $\eta = 0.4$. The decontamination rate of HCWs is $\mu_c = 24$. The probability of colonization from colonized patients to uncontaminated HCWs is $\beta_p = 0.72$.

(2) Indirect estimation.

It is assumed that each patient has one contact from one HCW per day, so that the contact rate between patients and HCWs is $\alpha_p = \frac{1}{N_h}$. In Wang et al.[30], it is assumed that a contaminated HCW has the same ability of transmission as a contaminated volunteer, so the probability of colonization from contaminated HCW to uncolonized patient is $\beta_h = 0.20$. We assume that Beijing Tongren Hospital maintains the same standard for the clearance of the environment, so that the cleaning / disinfection rate

of the environment is $\gamma_b = 0.7$ in the EW unit. In a similar way, the colonization rate from the environment to uncolonized patients and uncontaminated HCWs are $k_p = 0.000004$ and $k_h = 0.00001$, respectively, in the EW unit. Note that the units of k_p and k_h is CFUs/day. In microbiology, colony-forming unit (CFU) is a measure of viable bacterial or fungal numbers. Unlike direct microscopic counts where all cells, dead and living, are counted, CFU measures viable cells. It is assumed that a colonized patient and a contaminated HCW have the same effect of contamination of the environment; then the contamination rate to the environment of colonized patients ν_p is equal to the contamination rate to environment of contaminated HCWs ν_h, and it is half the value of the shedding rate of patients[31], which is 235. The units of nu_p and ni_h is also CFUs/day. From remark (R4), we estimate the value of ρ to be $1 - \eta$, which is 0.6.

We notice that γ_b, k_p and k_h are small, ν_p and ν_h are large. This is because B_e is in units that make it come out to be a large number. And this is what is happening in the simulation with initial value in (4.1).

4.3 Numerical simulations

In this section, we perform numerical simulations for solutions of the deterministic epidemic system. Once we obtain the estimates of parameters, it is the most efficient and direct way to check the result and its properties. We will use Euler's method by using Matlab.[20] The stepsize is defined based on practical need. In general, smaller stepsizes will provide better simulations. However, it will increase the amount of calculation time of computer program. Thus, we have to choose an appropriate step

Table 2: Baseline parameters values and estimates for the transmission MRSA in the Emergency Ward (EW) in Beijing Tongren Hospital. The unit of time is one day.

Parameter	Symbol	Parameter Estimate	Source
Proportion of colonized patients admitted in hospital (1/day)	θ	0.067	[30]
Number of patients	N_p	23	[30]
Number of HCWs	N_h	23	[30]
Contact rate (1/day)	α_p	0.0435	[30]
Probability of colonization (1/day)			
By colonized patients	β_p	0.72	[30]
By contaminated HCWs	β_h	0.20	estimated
Discharge rate (1/day)			
Uncolonized patients	γ_u	0.067	[30]
Colonized patients	γ_c	0.046	[30]
Cleaning / disinfection (1/day) rate of environment	γ_b	0.7	[31]
Colonization rate from environment (CFUs/day)			
Of uncolonized patients	k_p	0.000004	[31]
Of uncontaminated HCWs	k_h	0.00001	[31]
Ratio of HCWs to patients	ρ	0.6	[30]
Hand hygiene compliance of HCWs	η	0.4	[30]
Decontamination rate of HCWs (1/day)	μ_c	24	[30]
Contamination rate to environment (CFUs/day)			
By colonized patients	ν_p	235	estimated
By contaminated HCWs	ν_h	235	estimated

size. Here, we define h to be 0.01, and we have $R_0 = 0.7579 < 1$. The initial value that we choose is

$$(P_u^0, P_c^0, H_u^0, H_c^0, B_e^0) = (10, 13, 17, 6, 1000). \tag{4.1}$$

The numerical simulation of solutions of the deterministic epidemic model is given in Figure 4.1.

4.4 Sensitivity analysis and discussion

In general, there are two types of analysis for determining how influential parameter variation is on the final model output: uncertainty analysis and sensitivity analysis. The uncertainty analysis is to determine the uncertainty in the model output, given the uncertainties in the parameter values. And sensitivity analysis means to quantitatively decide which parameters are most influential in the model output. In this paper, we focus on the sensitivity analysis, because two references[30, 31] have provided good resources for quantitative analysis. In this section, we will perform sensitivity analysis of R_0 in terms of model parameters. We consider inputs by pairs. First, we consider the hand hygiene compliance and the disinfection rate of the environment. That is because hand hygiene and disinfection of the hospital are both significantly important interventions. Figure 4.2 shows that if we increase the hand hygiene compliance of HCWs, R_0 would be reduced substantially. Similarly, if we only consider to increase the disinfection rate of the environment, R_0 would also be greatly decreased. Thus, it is necessary to check the output of combining these two control methods. The result has been shown in Figure 4.3. when we increase both

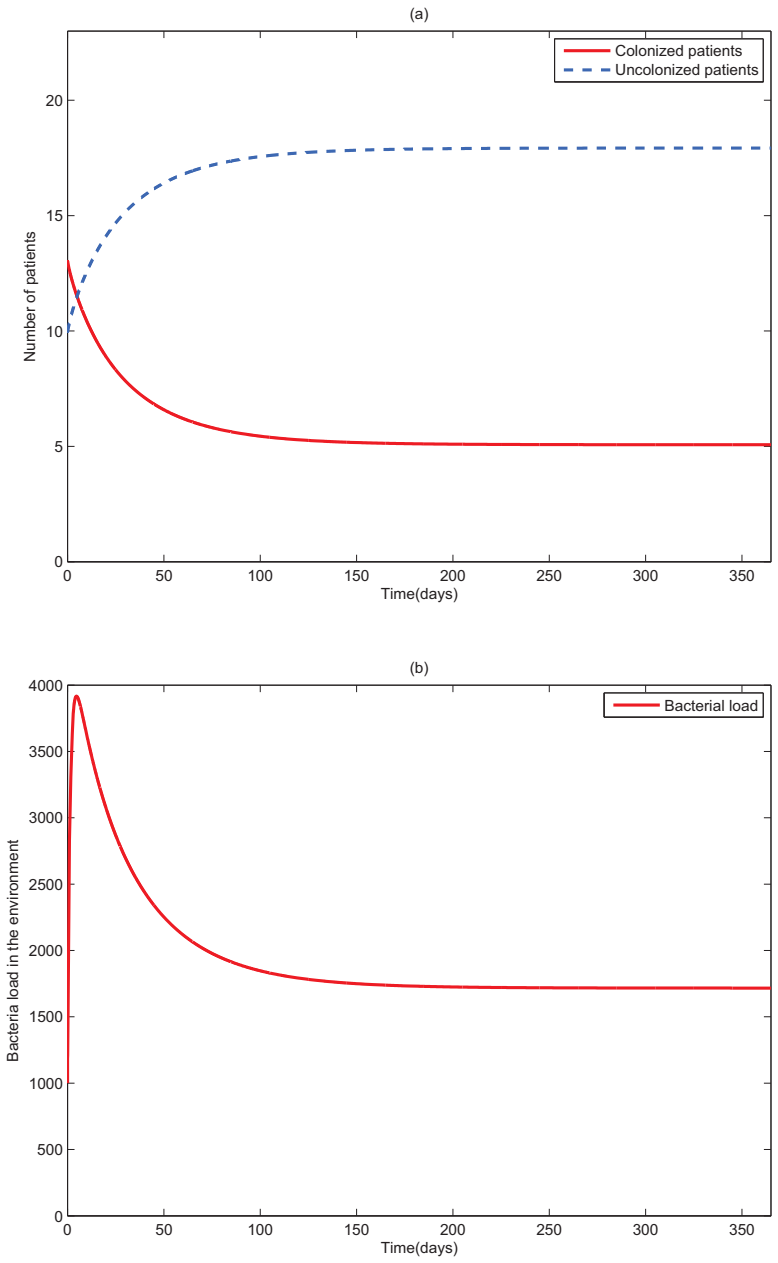

Figure 4.1: *(a) Solution of colonized and uncolonized patients of deterministic epidemic model (3.1) with initial value* $(P_u^0, P_c^0, H_u^0, H_c^0, B_e^0) = (10, 13, 17, 6, 1000)$. *(b) Solution of bacteria load in environment in deterministic epidemic model (3.1) with initial value* $(P_u^0, P_c^0, H_u^0, H_c^0, B_e^0) = (10, 13, 17, 6, 1000)$.

the hand hygiene compliance and disinfection rate, the basic reproduction number would drop dramatically. In numerical simulations, we assume that the contamination rate to environment of colonized patients ν_p is equal to the contamination rate to environment of contaminated HCWs ν_h. However, in the sensitivity analysis, we will change them to observe their influences separately. Figure 4.4 gives a natural explanation of increasing contamination to the environment by colonized patients or contaminated HCWs. The basic reproduction number would increase in both cases. However, we notice that in Figure 4.4(a), the increment of R_0 is greater than that in Figure 4.4(b), implying that it would be more effective to control the contamination rate to the environment by colonized patients than that of contaminated HCWs. Figure 4.5 presents the consequence of controlling both of them at the same time. Similarly, we consider the colonization rate from environment of uncolonized patients and uncontaminated HCWs under the same scalar in Figure 4.6. It is easy to see that R_0 would increase much more significantly when the contamination rate from environment to uncolonized patients increases, than that to uncontaminated HCWs. Combining with Figure 4.4, it can be seen that it would be more important to control the contamination rate related to patients than to HCWs. Figure 4.7 shows the trend of R_0 if we adjust both of them.

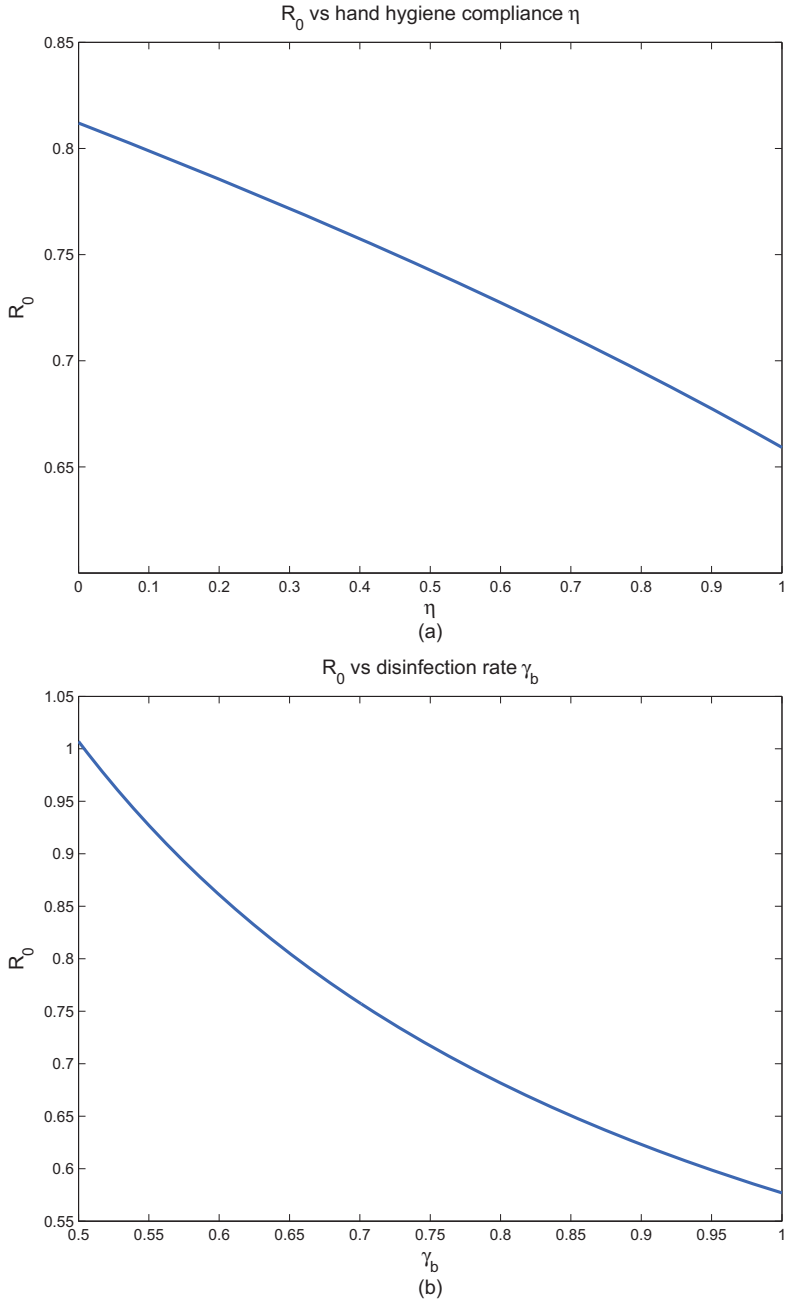

Figure 4.2: *R_0 vs hand hygiene compliance η, and R_0 vs disinfection rate γ_b.*

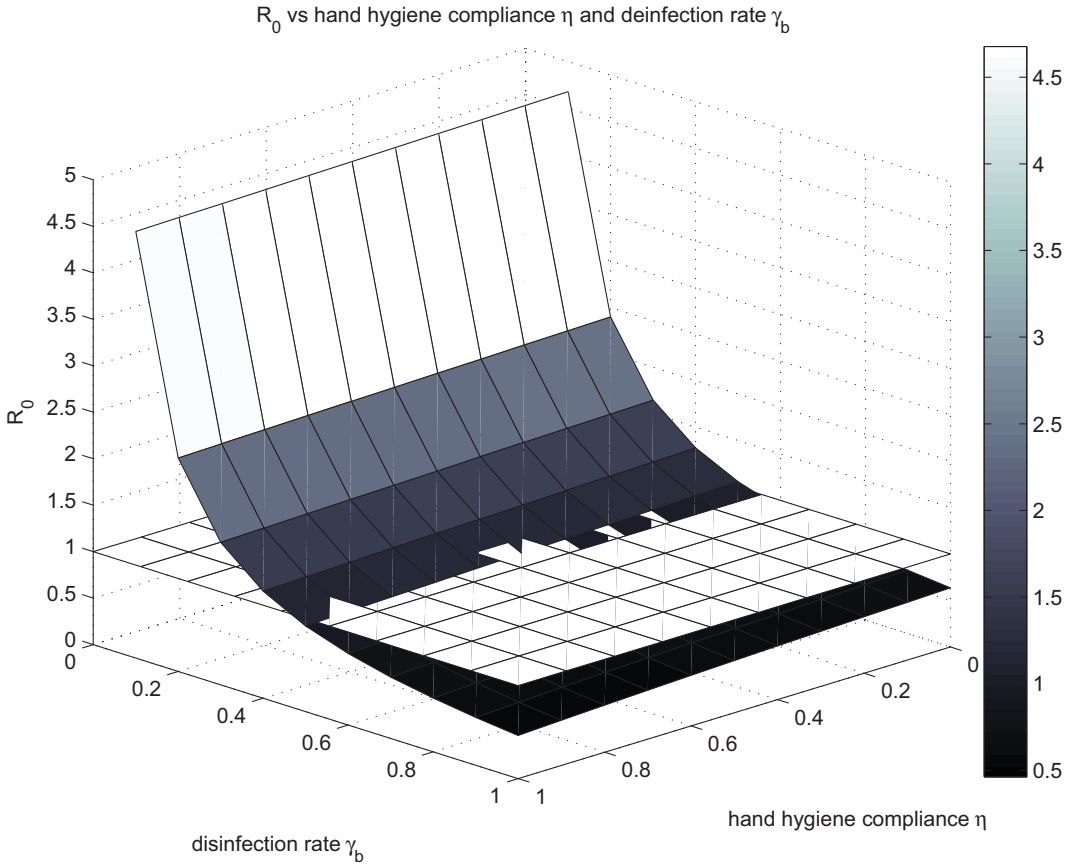

Figure 4.3: *R_0 vs hand hygiene compliance η and disinfection rate γ_b, compared with the baseline plane of $R_0 = 1$*

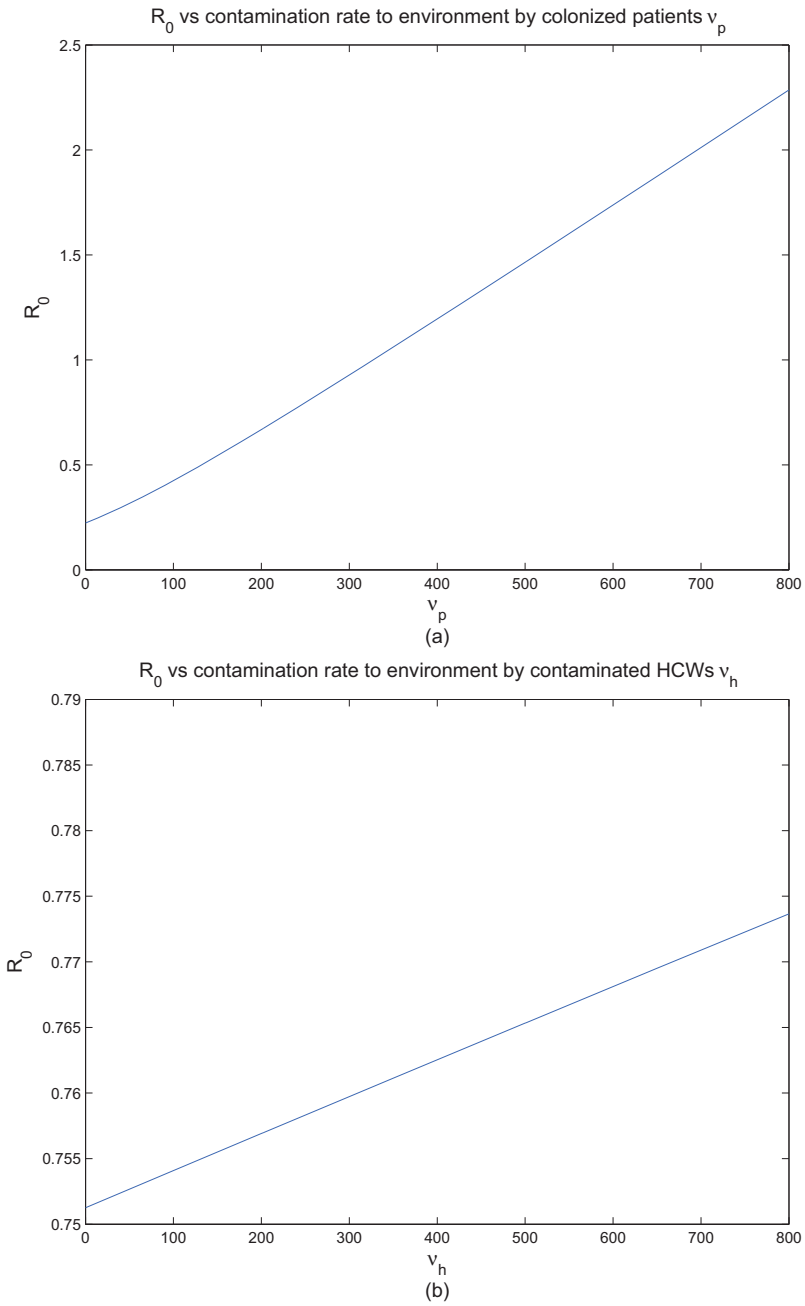

Figure 4.4: *R_0 vs contamination rate of the environment by colonized patients ν_p, and R_0 vs contamination rate of the environment by contaminated HCWs ν_h.*

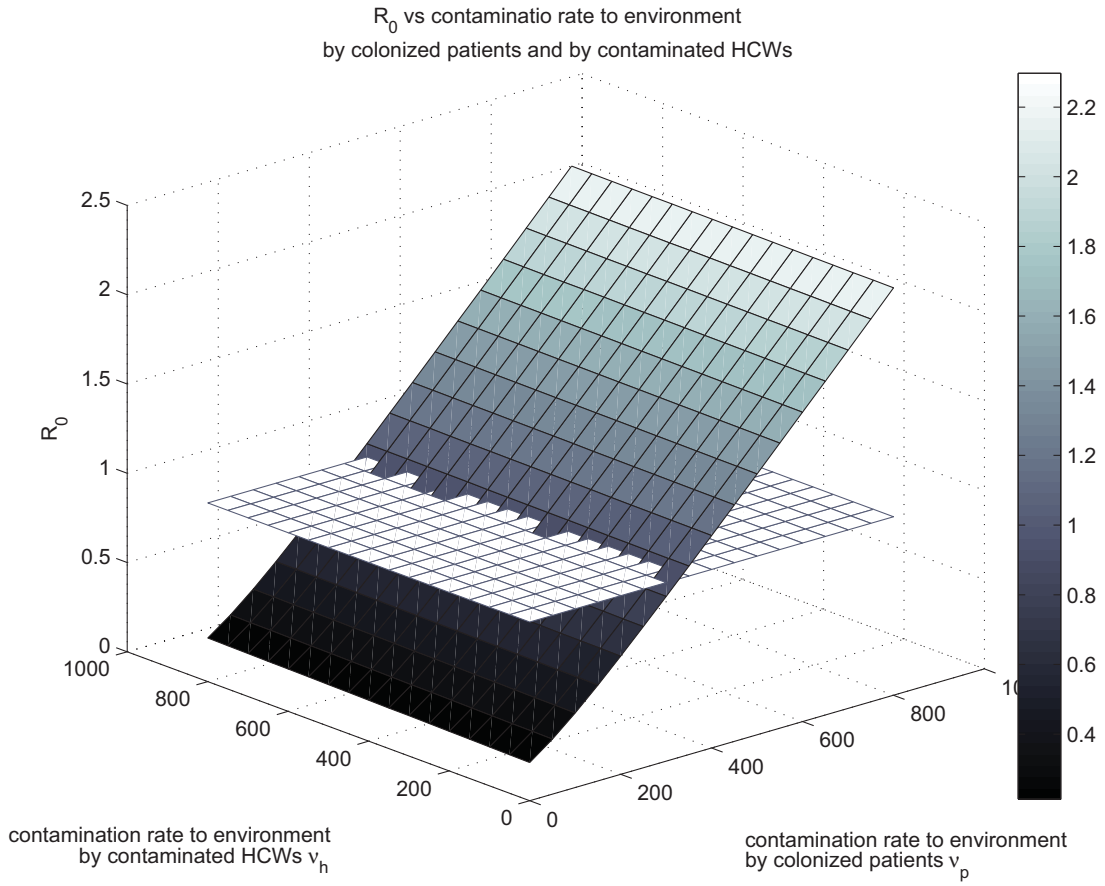

Figure 4.5: *R_0 vs contamination rate of the environment by colonized patients ν_p and contamination rate of the environment by contaminated HCWs ν_h, compared with the baseline plane of $R_0 = 1$*

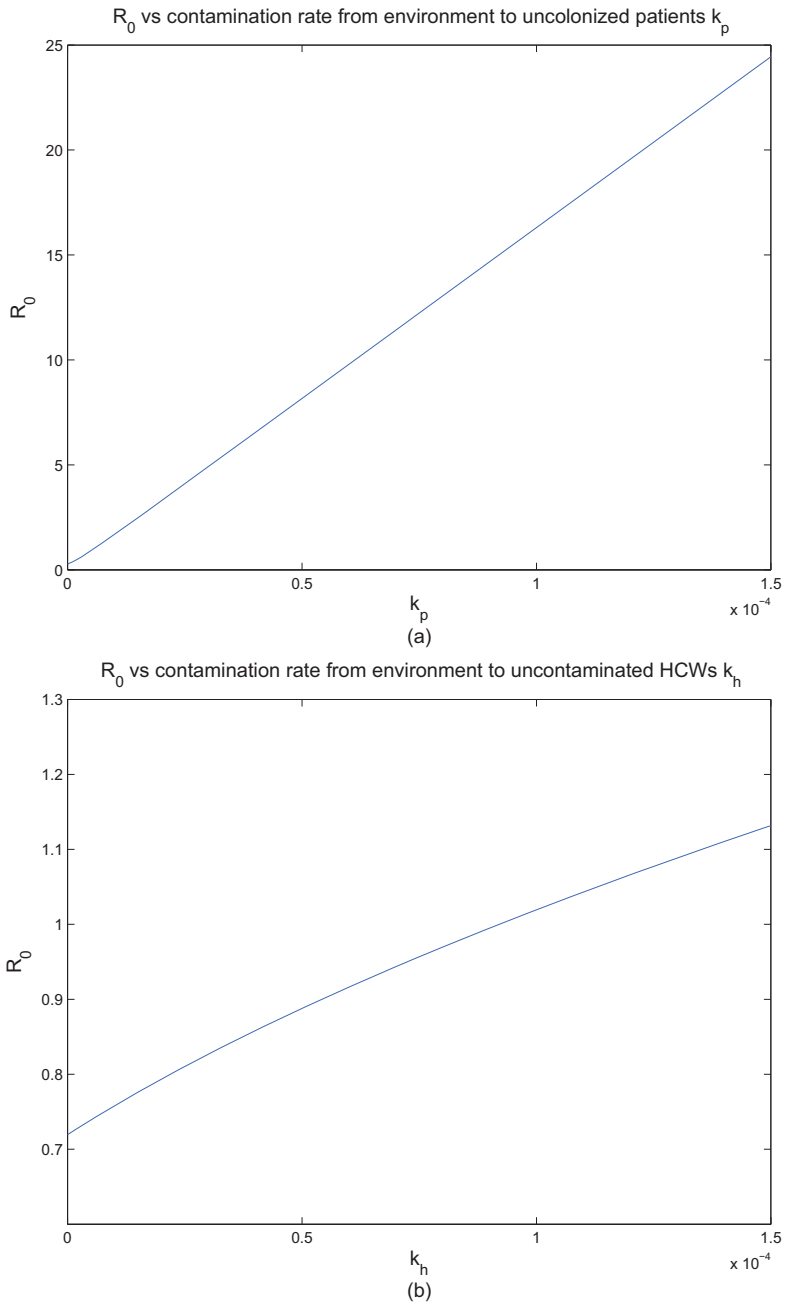

Figure 4.6: *R_0 vs contamination rate from the environment to uncolonized patients k_p, and R_0 vs contamination rate from the environment to uncontaminated HCWs k_h.*

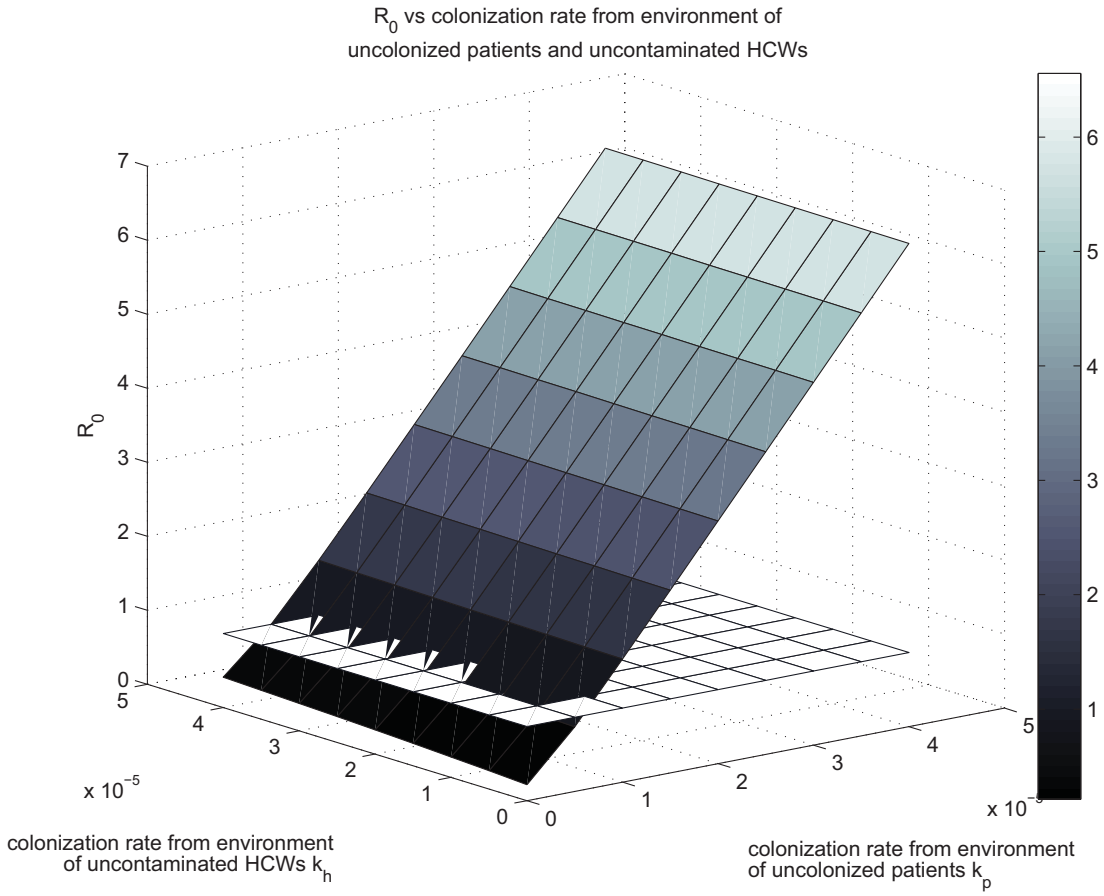

Figure 4.7: *R_0 vs colonization rate from the environment to uncolonized patients k_p and colonization rate from the environment to uncontaminated HCWs k_h, compared with the baseline plane of $R_0 = 1$*

Chapter 5

Stochastic epidemic models

In this chapter, we consider the stochastic version of the nosocomial infection model with environmental contamination. The inspiration for introducing the stochastic model comes from Figure 2.2. It seems that the number of colonized and uncolonized patients fluctuates randomly due to the small number of patients. Meanwhile, from Figure 2.3, simulations using the stochastic model appeared to provide a better explanation of the transmission dynamics for small populations.

The history of stochastic epidemic models and their application is much shorter than deterministic epidemic models. There are a lot differences between stochastic epidemic models and deterministic ones. For instance, the basic reproduction number, whose importance has been introduced in Chapter 2 can be expressed analytically only in deterministic models. On the other hand, when the sample size is very small, the stochastic simulations can describe the variability of the actual data, which numerical simulations from deterministic models do not do. The traditional way of obtaining a stochastic epidemic model of a well-known disease is based on its deterministic epidemic model.[1, chp. 3] Basically, there are three types of stochastic

model formulations: discrete time Markov chain (DTMC), continuous time Markov chain (CTMC) and stochastic differential equations (SDE). These models differ in the underlying assumptions regarding the time and the state variables. We will consider a continuous time Markov chain (CTMC) model for our system, that is to say, the time is continuous, but the state is discrete and embedded in R^5. In order to construct a stochastic epidemic model, we need to consider the probability of changes in variables, the infinitesimal mean and variance, and the drift and diffusion terms of stochastic equation. This construction will be performed in detail in the second section of this chapter.

5.1 Model description and assumptions

It is assumed that $P_u(t) + P_c(t) = N_p, H_u(t) + H_c(t) = N_h, \forall t \geqslant 0$, so the process is trivariate $\{P_c(t), H_c(t), B_e(t)\}$ in $\mathbb{R}^3$, with $P_u(t) = N_p - P_c(t)$ and $H_u(t) = N_n - H_c(t)$. These three variables have a joint probability given by

$$p_{(s,j,k)}(t) = \text{Prob}\left\{P_c(t) = s, H_c(t) = j, B_e(t) = k\right\}, \tag{5.1}$$

with $s = 0, ..., N_p, j = 0, ..., N_h$ and $k \geqslant 0$. The process has Markov property and is time-homogeneous.

The transition probabilities are determined as follows. Assume that Δt can be chosen sufficiently small such that at most one change in state occurs during the time interval Δt. In particular, there can only be either a new colonization or decolonization on patients or HCWs, or a new contamination or decontamination of environment. The transition probabilities are written as follows:

$$
\begin{aligned}
&p_{(s+i_1,j+i_2,k+j_3);(s,j,k)}(\Delta t) \\
&\quad = \text{Prob}\left\{(\Delta P_c, \Delta H_c, \Delta B_e) = (i_1, i_2, i_3) \middle| \, (P_c(t), H_c(t), B_e(t)) = (s, j, k)\right\},
\end{aligned}
\tag{5.2}
$$

where $\Delta P_c = P_c(t + \Delta t) - P_c(t)$, and $i_1, i_2, i_3 \in \{-1, 0, 1\}$. Hence,

$$
p_{(s+i_1,j+i_2,k+j_3);(s,j,k)}(\Delta t) = \begin{cases}
\Big\{\theta\big[\gamma_u(N_p - s) + \gamma_c s\big] + \alpha_p\beta_p(1-\eta)(N_p - s)j & \\
\quad + k_p(N_h - s)k\big]\Big\}\Delta t, & (i_1, i_2, i_3) = (1, 0, 0) \\
\gamma_c s\Delta t, & (i_1, i_2, i_3) = (-1, 0, 0) \\
\left[\rho\alpha_p\beta_h s(N_h - j) + k_h(N_h - j)k\right]\Delta t, & (i_1, i_2, i_3) = (0, 1, 0) \\
\mu_c j\Delta t, & (i_1, i_2, i_3) = (0, -1, 0) \\
\left(\nu_p s + \nu_h j\right)\Delta t, & (i_1, i_2, i_3) = (0, 0, 1) \\
\gamma_b k\Delta t, & (i_1, i_2, i_3) = (0, 0, -1) \\
1 - \theta\left[\gamma_u(N_p - s) + \gamma_c s\right]\Delta t - \alpha_p\beta_p(1-\eta)(N_p - s)j\Delta t & \\
\quad - k_p(N_h - s)k\Delta t - \gamma_c s\Delta t & \\
\quad - \left[\rho\alpha_p\beta_h s(N_h - j) + k_h(N_j - j)k\right]\Delta t & \\
\quad - \mu_c j\Delta t - \left(\nu_p s + \nu_h j\right)\Delta t - \gamma_b k\Delta t, & (i_1, i_2, i_3) = (0, 0, 0) \\
0, & \text{otherwise.}
\end{cases}
\tag{5.3}
$$

We notice that the time step Δt must be chosen to be sufficiently small such that all of these probabilities could stay in the interval $[0, 1]$. The transition matrix is too complicated to express, however, we could still write out the probabilities $p_{(s,j,k)}(t +$

Δt) by using the Markov property:

$$\begin{aligned}
p_{(s,j,k)}(t+\Delta t) &= p_{(s-1,j,k)}(t)\Big\{\theta\left[\gamma_u(N_p-s+1)+\gamma_c(s-1)\right]+\alpha_p\beta_p(1-\eta)(N_p-s+1)j \\
&+ k_p(N_p-s+1)k\Big\}\Delta t + p_{(s+1,j,k)}(t)\gamma_c(s+1)\Delta t \\
&+ p_{(s,j-1,k)}(t)\left[\rho\alpha_p\beta_h s(N_h-j+1)+k_h(N_h-j+1)k\right]\Delta t + p_{(s,j+1,k)}(t)\mu_c(j+1)\Delta t \\
&+ p_{(s,j,k-1)}(t)\left(\nu_p s+\nu_h j\right)\Delta t + p_{(s,j,k+1)}(t)\gamma_b(k+1)\Delta t \\
&+ p_{(s,j,k)}(t)\Big\{1-\big\{\theta\left[\gamma_u(N_p-s+1)+\gamma_c(s-1)\right]+\alpha_p\beta_p(1-\eta)(N_p-s)j+\gamma_c s \\
&+ k_p(N_p-s)k+\rho\alpha_p\beta_h s(N_h-j)+k_h(N_h-j)k+\mu_c j+\nu_p s+\nu_h j+\gamma_b k\big\}\Delta t\Big\}.
\end{aligned} \tag{5.4}$$

Meanwhile, a system of forward Kolmogorov differential equations could be derived:

$$\begin{aligned}
\frac{dp_{(s,j,k)}}{dt} &= p_{(s-1,j,k)}\Big\{\theta\left[\gamma_u(N_p-s+1)+\gamma_c(s-1)\right]+\alpha_p\beta_p(1-\eta)(N_p-s+1)j \\
&+ k_p(N_p-s+1)k\Big\} + p_{(s+1,j,k)}\gamma_c(s+1) \\
&+ p_{(s,j-1,k)}\left[\rho\alpha_p\beta_h s(N_h-j+1)+k_h(N_h-j+1)k\right] + p_{(s,j+1,k)}\mu_c(j+1) \\
&+ p_{(s,j,k-1)}\left(\nu_p s+\nu_h j\right) + p_{(s,j,k+1)}(t)\gamma_b(k+1) \\
&+ p_{(s,j,k)}\Big\{1-\big\{\theta\left[\gamma_u(N_p-s+1)+\gamma_c(s-1)\right]+\alpha_p\beta_p(1-\eta)(N_p-s)j \\
&+ k_p(N_p-s)k+\gamma_c s+\rho\alpha_p\beta_h s(N_h-j)+k_h(N_h-j)k+\mu_c j+\nu_p s+\nu_h j+\gamma_b k\big\}\Big\}.
\end{aligned} \tag{5.5}$$

5.2 Stochastic simulations

In this section, we will first construct a stochastic epidemic model from the deterministic epidemic model (3.1), then use data in Table 2 to run stochastic simulations of our model.

The system has three variables with a joint probability

$$p_{(s,j,k)}(t) = \text{Prob}\left\{P_c(t)=s, H_c(t)=j, B_e(t)=k\right\},$$

with $s = 0, ..., N_p, j = 0, ..., N_h$ and $k \geqslant 0$, whose transition probabilities have been given in (5.3). Let $X(t) = (P_c(t), H_c(t), B_e(t))^T$, with infinitesimal $\Delta X(t) = (\Delta P_c(t), \Delta H_c(t), \Delta B_e(t))^T$. It is possible for us to write out the infinitesimal mean matrix $f(X(t), t)$ as following:

$$E\left(\Delta X(t)|X(t)\right) = \begin{pmatrix} e_p \\ e_h \\ e_b \end{pmatrix} \cdot \Delta t = f(X(t), t) \cdot \Delta t, \tag{5.6}$$

where

$$\begin{aligned} e_p &= \theta\left[\gamma_u(N_h - P_c) + \gamma_c P_c\right] + \alpha_p\beta_p(1-\eta)(N_p - P_c)H_c + k_p(N_h - P_c)B_e - \gamma_c P_c, \\ e_h &= \left[\rho\alpha_p\beta_h P_c(N_h - H_c) + k_h(N_h - H_c)B_e\right] - \mu_c H_c, \\ e_b &= \nu_p P_c + \nu_h H_c - \gamma_b B_e, \end{aligned}$$

and the infinitesimal variance matrix $\Sigma(X(t), t)$ given by:

$$E\left(\Delta X(t)\left(\Delta X(t)\right)^T|X(t)\right) = \begin{pmatrix} \delta_p & 0 & 0 \\ 0 & \delta_h & 0 \\ 0 & 0 & \delta_b \end{pmatrix} \cdot \Delta t = \Sigma(X(t), t) \cdot \Delta t, \tag{5.7}$$

where

$$\begin{aligned} \delta_p &= \theta\left[\gamma_u(N_h - P_c) + \gamma_c P_c\right] + \alpha_p\beta_p(1-\eta)(N_p - P_c)H_c + k_p(N_h - P_c)B_e + \gamma_c P_c, \\ \delta_h &= \left[\rho\alpha_p\beta_h P_c(N_h - H_c) + k_h(N_h - H_c)B_e\right] + \mu_c H_c, \\ \delta_b &= \nu_p P_c + \nu_h H_c + \gamma_b B_e. \end{aligned}$$

It is easy to see that $\delta_p, \delta_h, \delta_b$ are all nonnegative. Diffusion matrix G is the solution of $GG^T = \Sigma$. There may be several solutions of this equation depending on the expression of Σ, however, we could always pick the most visible one as

$$G = \begin{pmatrix} \sqrt{\delta_p} & 0 & 0 \\ 0 & \sqrt{\delta_h} & 0 \\ 0 & 0 & \sqrt{\delta_b} \end{pmatrix}. \tag{5.8}$$

Then the Itô SDE takes the following form:

$$dX(t) = f(X(t), t)dt + G(X(t), t)dW(t). \tag{5.9}$$

More precisely,

$$\begin{cases} \dfrac{dP_c(t)}{dt} = e_p dt + \sqrt{\delta_p} dW_1(t) \\ \dfrac{dH_c(t)}{dt} = e_h dt + \sqrt{\delta_h} dW_2(t) \\ \dfrac{dB_e(t)}{dt} = e_b dt + \sqrt{\delta_b} dW_3(t), \end{cases} \tag{5.10}$$

where W_1, W_2, W_3 are three independent Wiener processes. If the terms associated with the Wiener processes are dropped, then we have the same ODE model as in (3.1).

Once we obtain the stochastic epidemic model, we are able to run stochastic simulations by using data in Table 2. Simulations are done by Matlab.[1, chp. 3] Consider variable P_c for a more specific explanation of this process. For k from 1 to n, where n is the path number of simulation; let j be the state from 1, then

$$P_c(j+1, k) = P_c(j, k) + e_p \cdot dt + \sqrt{\delta_p} \cdot \sqrt{dt} \cdot r_p, \tag{5.11}$$

where $dt = 0.01$ is the time step, r_p is a standard normal random variable, and

$$\begin{aligned}
e_p = \theta\,[&\gamma_u \cdot \max\left((N_h - P_c(j,k)), 0\right) + \gamma_c P_c(j,k)] \\
&+ \alpha_p \beta_p (1-\eta) \cdot \max\left((N_h - P_c(j,k)), 0\right) \cdot H_c(j,k) \\
&+ k_p \cdot \max\left((N_h - P_c(j,k)), 0\right) \cdot B_e(j,k) - \gamma_c P_c(j,k), \\
\delta_p = \theta\,[&\gamma_u \cdot \max\left((N_h - P_c(j,k)), 0\right) + \gamma_c P_c(j,k)] \\
&+ \alpha_p \beta_p (1-\eta) \cdot \max\left((N_h - P_c(j,k)), 0\right) \cdot H_c(j,k) \\
&+ k_p \cdot \max\left((N_h - P_c(j,k)), 0\right) \cdot B_e(j,k) - \gamma_c P_c(j,k).
\end{aligned}$$

For each variable, we will present ten sample paths and compare them with the corresponding solution curves from the deterministic model. Usually, to verify whether a stochastic simulation is good or not, the mean and the variance of the difference between simulation and target value will be calculated. In this chapter, we will not check these means and variances due to the complexity of calculation. However, it is practicable to verify by observation: whether these sample paths are close to each other, and whether they have small noise according to the deterministic solution.

We provide three figures as results of stochastic simulations of numbers of colonized patients $P_c(t)$, number of contaminated HCWs $H_c(t)$ and bacterial load in the environment $B_e(t)$, compared with deterministic solution curves, respectively. As shown, in each run, ten sample paths are close to each other, and oscillate around the black solid curve, which is the solution curve of the deterministic system. Noticed that in the last figure, the deterministic solution curve is almost close to zero. This is because the size of populations of patients and HCWs are both very small. However, the noise of this run was controlled to under four. Thus, we have provided a good explanation of the transmission dynamics for small populations with environment

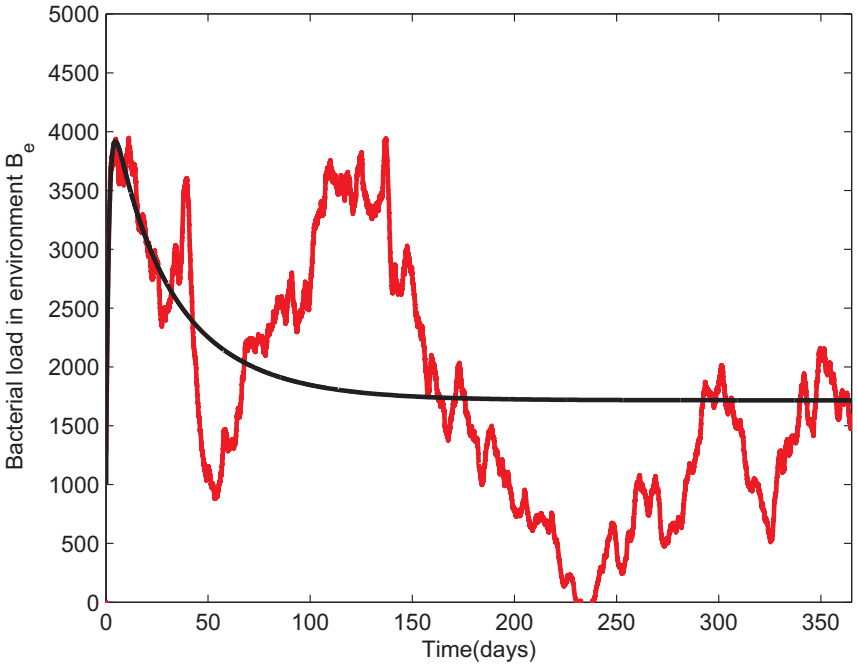

Figure 5.1: *Ten sample paths of bacterial load in environment in nosocomial infection model with environment infection are graphed with the deterministic solution (black curve). The parameter values are* $\Delta t = 0.01, N_p = 23, N_h = 23, \theta = 0.067, \alpha_p = 0.0435, \beta_p = 0.72, \beta_h = 0.20, \eta = 0.4, \gamma_u = 0.067, \gamma_c = 0.046, \gamma_b = 0.7, k_p = 0.000004, k_h = 0.00001, \rho = 0.6, \mu_c = 24, \nu_p = 235, \nu_h = 235, time = 365, P_c^0 = 13, H_c^0 = 6, B_e^0 = 1000.$

infection.

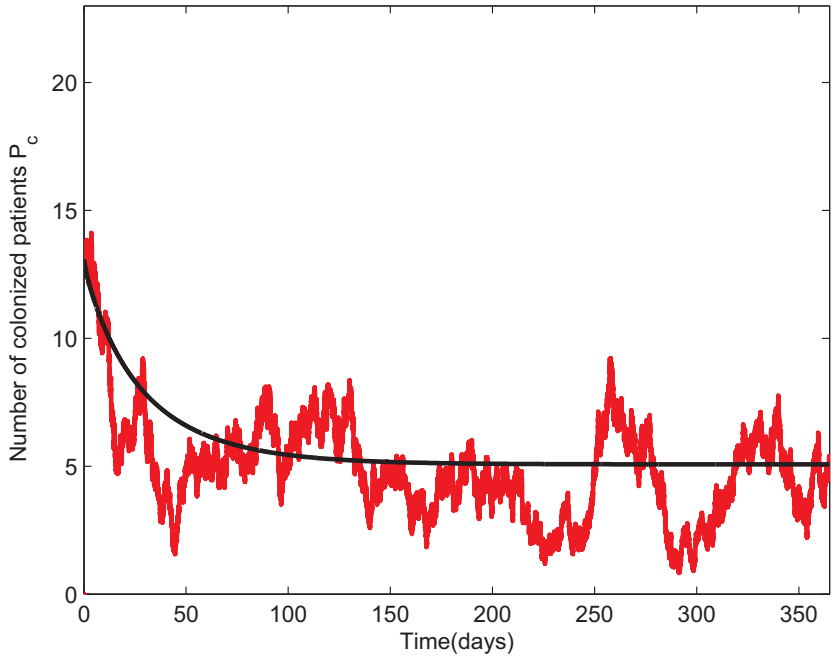

Figure 5.2: *Ten sample paths of number of colonized patients in nosocomial infection model with environment infection are graphed with the deterministic solution (black curve). The parameter values are* $\Delta t = 0.01, N_p = 23, N_h = 23, \theta = 0.067, \alpha_p = 0.0435, \beta_p = 0.72, \beta_h = 0.20, \eta = 0.4, \gamma_u = 0.067, \gamma_c = 0.046, \gamma_b = 0.7, k_p = 0.000004, k_h = 0.00001, \rho = 0.6, \mu_c = 24, \nu_p = 235, \nu_h = 235,$ *time* $= 365, P_c^0 = 13, H_c^0 = 6, B_e^0 = 1000.$

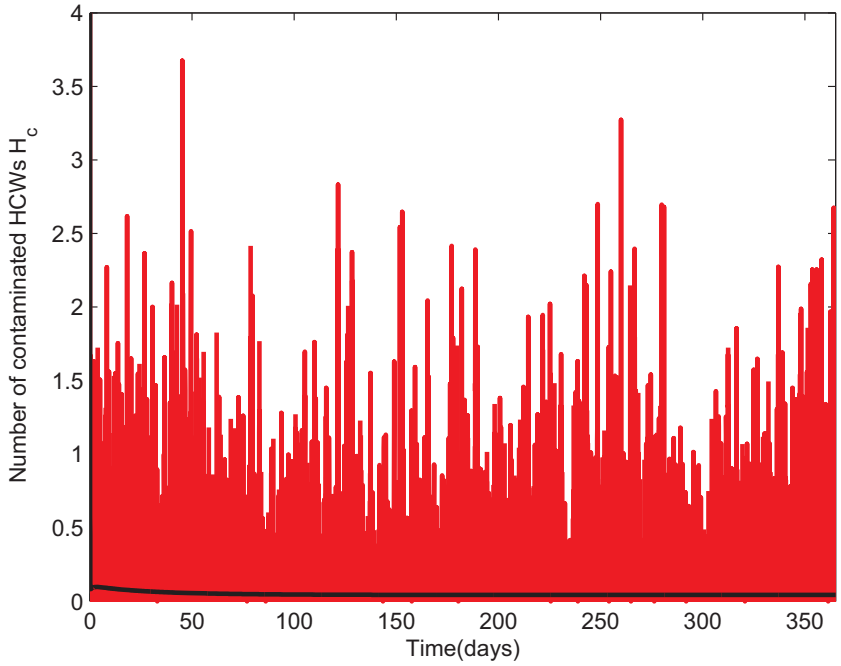

Figure 5.3: *Ten sample paths of number of contaminated HCWs in nosocomial infection model with environment infection are graphed with the deterministic solution (black curve). The parameter values are* $\Delta t = 0.01, N_p = 23, N_h = 23, \theta = 0.067, \alpha_p = 0.0435, \beta_p = 0.72, \beta_h = 0.20, \eta = 0.4, \gamma_u = 0.067, \gamma_c = 0.046, \gamma_b = 0.7, k_p = 0.000004, k_h = 0.00001, \rho = 0.6, \mu_c = 24, \nu_p = 235, \nu_h = 235, time = 365, P_c^0 = 13, H_c^0 = 6, B_e^0 = 1000.$

Chapter 6

Discussion

Traditional strategies of controlling nosocomial infection have been provided in many references.[30, 35] These measures include reducing the transmission rate between HCWs and patients, and the transmission rate between volunteers and patients; as well as raising the hand hygiene compliance of HCWs and volunteers. In this study, we introduce the environmental infection in a nosocomial infection model. The importance of understanding the role of environmental infection in a hospital has been discussed in Chapter 1. Our research is devoted to suggesting more possibilities for determining the control intervention strategies, which are based on the sensitivity analysis of the basic reproduction number R_0.

The first conclusion is that increasing the disinfection rate of environment will help to control the transmission dynamics of MRSA in the hospital. This includes 1) appropriate use of cleaners and disinfectants; 2) appropriate maintenance of medical equipment (e.g., automated endoscope reprocessors or hydrotherapy equipment); 3) adherence to water-quality standards for hemodialysis, and to ventilation standards for specialized care environments (e.g., airborne infection isolation rooms, protective

environments, or operating rooms); and 4) prompt management of water intrusion into the facility.[25] Meanwhile, it is essential to control the contamination rates between the environment and patients and HCWs. To be more specific, decreasing the contamination rate to the environment by colonized patients and contaminated HCWs, or decreasing the contamination rate from the environment to uncolonized patients and uncontaminated HCWs, will be helpful for controlling the infection in hospital. Two basic recommendations are limiting the scope of activities of patients, especially, for those high-risk patients, to avoid non-essential contacts with the environment, and increasing hand hygiene compliance of HCWs, in particular, before contacting any patient. It would be ideal if we could reduce both contamination rates to the environment from colonized patients and contaminated HCWs, and both contamination rates from the environment to uncolonized patients and uncontaminated HCWs. However, from the practical point of view, for instance, because of the financial budget and the lack of supervision, it is possible that not all of these transmission rates could be controlled at the same time. Our research indicates that under such situations, we should give priority to controlling the contamination rates related between the environment and patients. The sensitivity analysis of ν_p (i.e., contamination rate to environment from colonized patients) has explained that an increase of ν_p would increase the value of R_0 dramatically, compared with the influence of the same increment of ν_h (i.e., contamination rate to environment from contaminated HCWs). Similarly, the sensitivity analysis of k_p (i.e., contamination rate from environment to uncolonized patients) has shown that under the same scale, the increase of k_p would result in huge jump of R_0, compared with k_h (i.e., contamination rate from environment to uncontaminated HCWs). Thus, to reduce unnecessary contacts between patients and environment would decrease the transmission of MRSA significantly.

During the process of numerical simulations and sensitivity analysis, we apply data from the unit of EW (Emergency Ward) of Beijing Tongren Hospital from 3 March 2009 to 28 February 2010. There are both HCWs and volunteers working in the EW during the process of data collection. Since we do not consider the compartment of volunteers, it is not accurate to compare the patient data with solution of deterministic epidemic model or stochastic simulations. However, we still would able to estimate parameters from the original data.

In conclusion, decreasing the contamination rates between patients and environment, and HCWs and environment, increasing the disinfection rate of environment, and increasing the hand hygiene compliance of HCWs would decrease MRSA transmission remarkably.

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