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Stochastic disease dynamics of a hospital infection model

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Abstract

A stochastic model for hospital infection incorporating both direct transmission and indirect transmission via free-living bacteria in the environment is investigated. We examine the long term behavior of the model by calculating a stationary distribution and normal approximation of the distribution. The quasi-stationary distribution of the model is studied to investigate the models' behavior before extinction and the time to extinction. Numerical results show agreement between the calculated distributions and results of event-driven simulations. Hand hygiene of volunteers is more effective in terms of reducing the mean (or standard deviation) of the stationary distribution of colonized patients and the expected time to extinction compared to hand hygiene of health care workers (HCWs), on the basis of our parameter values. However, the indirect (or direct) transmission rate can lead to either increase or decrease in the standard deviation of the stationary distribution, but the impact of the indirect transmission is much greater than that of the direct transmission. The findings suggest that isolation of new admitted colonized patients is most effective in reducing both the mean and standard deviation of the stationary distribution and measures related to indirect transmission are secondary in their effects compared to other interventions.

Highlights

▸ Isolation of new admitted colonized patients is the most effective measure. ▸ Hand hygiene of volunteers is more effective compared to hand hygiene of health care workers. ▸ Transmission rates can lead to increase or decrease in the standard deviation of colonized patients. ▸ Departure rate of patients contribute substantially to the expected time to extinction. ▸ The expected time to extinction may be different even if the basic reproduction number is the same.

Keywords

Stationary distribution; Time to extinction; Normal approximation; Stochastic simulation; Modeling

1. Introduction

Hospital infections have been studied by many medical scientists and mathematicians. Almost all researches on hospital infections in mathematics use a models of transmission dynamics in hospital wards [1], [2], [3], [7], [11]. Because of the small population in a ward, most of papers studied ward models using both deterministic and stochastic versions. Most of them first establish a proper deterministic mathematical model and then simulate the model by stochastic simulation methods, such as the event-driven method. An exception was Austin [2] who also considered the distribution in the equilibrium. The classical ward model [1] has recently been extended to consider the effects of a contaminated environment and volunteers on the transmission of MRSA in a hospital ward [19] and also analyzed the equilibrium and stability of the deterministic model. In addition the authors ran semi-stochastic simulations to consider the behavior of the model under the influence of random factors and assessed the effectiveness of some control measures. However, a single simulation alone cannot show clearly whether the simulated results are the average dynamical behavior or merely a random exception value as a result of a rare combination of events. Therefore, large numbers of replicate simulations are required to establish confidence in results. Thus, the results of event-driven models must be subject to the same statistical treatments as would be employed for any experimental observation.

These ensemble equation methods can be easily used to generate the exact equilibrium distribution and provide a richer understanding of the dynamics of stochastic event-driven simulations [10]. In addition, a number of approximation methods exist (such as diffusion approximations and moment closure techniques), which overcome the requirement of a large number of simulations by providing analytical approximations for expected behavior of the population and often approximations for variability in this behavior [4], [5]. In the case that the state space includes an absorbing state and some transient states, the quasi-stationary distribution is also a focus of concern [9], [12], [13], [14], [15], [16], [17], [18]. The aim of the current work is to look in more detail at the stochastic version of the hospital infection model considering environmental contamination and the role of volunteers and, in particular, to concentrate on those stochastic features which are not well described by the deterministic model.

In section one, we introduce a hospital infection model and give the model description and assumptions. In section two we first use the ensemble equation method to generate the exact stationary distribution of variables of the stochastic process and then use the diffusion approximation method to approximate the distribution by a bivariate normal distribution. In section three, we consider the quasi-stationary distribution of the stochastic version of the model when there are no colonized patients admitted into the ward and further study the expected time to extinction. Finally, we describe simulations by these methods

and consider the effects of direct and indirect transmission on the mean and standard deviation of the marginal distribution of colonized patients and the expected time to extinction.

2. Model

Our model is derived from the paper considering the effects of contaminated environment and volunteers on the transmission of methicillin-resistant Staphylococcus aureus (MRSA) in an intensive care unit (ICU) of a hospital in China [19]. Let H^S (H^C) be the number of susceptible (contaminated) health care workers; P^S (P^C) represents the number of susceptible (colonized) patients; W is the density of bacteria in the ward (ICU) including on floors, door handles, bed tables etc. N_H (N_P) is the total number of health care workers (HCWs) (patients); N_V is the number of volunteers which is the same as that of patients ($N_V = N_P$) because of the one to one relationship between the two. Note that here, volunteers are a special group of less-qualified carers, who takes care of patients daily lives, helps them to transfer from home to hospital and report irregular results of patients to doctors, but does not undertake any medical care. Their existence is due to lack of professional nurses in China's health care system. Usually, one volunteer can only care one patient so that they are in a one to one ratio. Precisely because of this we assume that the states of volunteers are the same as their corresponding patients. That is to say a volunteer who cares a colonized patient is always contaminated because of their frequent contacts, and vice versa. Therefore, the dynamics of volunteers is not explicitly included in the main equations. The diagram is shown in Fig. 1 and the model is as follows:

$$\begin{cases} \frac{dH^S}{dt} = -(\beta_1 P^C + \nu_1 W)H^S + \gamma H^C \\ \frac{dH^C}{dt} = (\beta_1 P^C + \nu_1 W)H^S - \gamma H^C \\ \frac{dP^S}{dt} = (1-\phi)\Lambda - (\beta_2 H^C + \nu_2 W)P^S - d_1 P^S \\ \frac{dP^C}{dt} = \phi\Lambda + (\beta_2 H^C + \nu_2 W)P^S - d_2 P^C \\ \frac{dW}{dt} = \lambda P^C - (\mu + \xi N_V + \nu_1 N_H)W \end{cases} \quad (1)$$

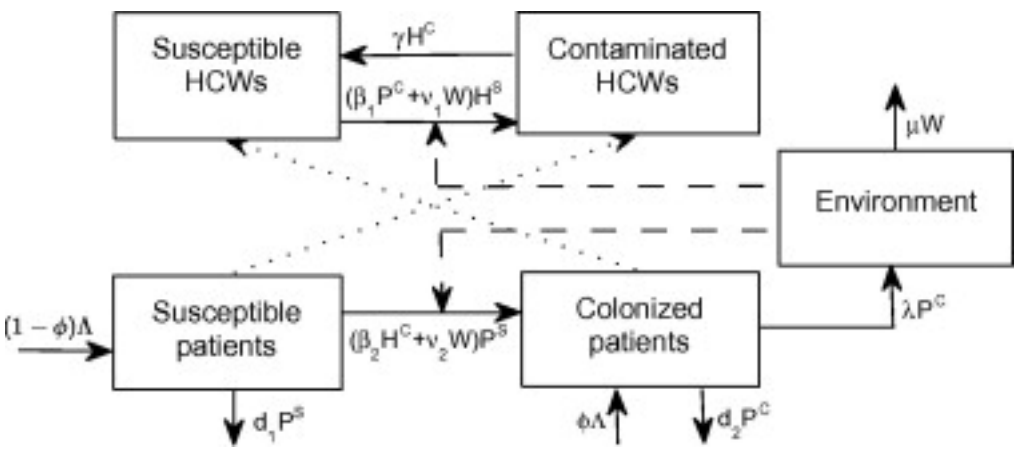

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Fig. 1. A flow diagram for HCW-Patient-Volunteer MRSA transmission in an ICU showing the possible effect of hospital infection control measures.

Colonized patients are patients on the body of which the bacteria can breed itself. But contaminated HCWs only carry bacteria on their hand and they can be decontaminated soon after washing their hands. So, only

colonized patients can shed bacteria to the environment although both of them are infectious. Therefore, the environment in the ward can only be contaminated by colonized patients at a rate of λ. These free-living bacteria in the environment can be cleaned at a rate of μ due to sterilization of the hospital and also are collected by HCWs and volunteers. The susceptible HCWs can be contaminated by contacts with colonized patients ($\beta_1 H^S P^C$) or by the contaminated environment ($\nu_1 H^S W$) while susceptible patients can be colonized by contacts with contaminated HCWs ($\beta_2 H^C P^S$) or volunteers ($\nu_2 P^S W$). Here, $\nu_2 P^S W$ can be written in more detail to be $\beta_3 \xi V^S W$, where V^S represents the number of susceptible volunteers, ξ represents the transmission rate between volunteers and free-living bacteria in the environment and β_3 represents the transmission rate from contaminated volunteers to patients. In particular, $V^S = P^S$ due to the assumption that states of volunteers are the same as those of patients under their care. Because the decolonization of patients needs a long time we assume that once patients become colonized they remain colonized for the duration of their stay in the ward.

Because the total number of HCWs remains constant model (1) can be simplified to four dimensions. In addition, optimal use of available resources frequently requires that available beds be always occupied (i.e. $N_P \to \frac{\Lambda}{d}$, $d_1 = d_2 = d$). So, in common with many other authors [1], [3], we assume that the discharge rates of susceptible patients and colonized patients are the same. Under this assumption the model can be determined by the following three differential equations:

$$\begin{cases} \frac{\mathrm{dH}^C}{\mathrm{dt}} = (\beta_1 P^C + \nu_1 W)(N_H - H^C) - \gamma H^C \\ \frac{\mathrm{dP}^C}{\mathrm{dt}} = \phi\Lambda + (\beta_2 H^C + \nu_2 W)(N_P - P^C) - \mathrm{dP}^C \\ \frac{\mathrm{dW}}{\mathrm{dt}} = \lambda P^C - (\mu + \xi N_V + \nu_1 N_H)W \end{cases} \tag{2}$$

While there is a significant separation of time-scales of H^C, P^C and W, the quasi-steady state (QSS) approximation ($\mathrm{dW/dt} = 0$), would provide an accurate approximation to the dynamics of the equation. Let the last equation of model 2 be zero. Then,

$$W = \frac{\lambda P^C}{\mu + \xi N_V + \nu_1 N_H}$$

Substituting this equality into the equation of H^C and P^C, then the model becomes:

$$\begin{cases} \frac{\mathrm{dH}^C}{\mathrm{dt}} = \left(\beta_1 P^C + \nu_1 \frac{\lambda P^C}{\mu + \xi N_V + \nu_1 N_H}\right)(N_H - H^C) - \gamma H^C \\ \frac{\mathrm{dP}^C}{\mathrm{dt}} = \phi\Lambda + \left(\beta_2 H^C + \nu_2 \frac{\lambda P^C}{\mu + \xi N_V + \nu_1 N_H}\right)(N_P - P^C) - \mathrm{dP}^C \end{cases} \tag{3}$$

It is easy to analyze the dynamic behavior of system (3). To get the equilibrium point of system (3), we let the right hand of the equation be zero, then we get the following equation

$$-\nu_2 \tfrac{\lambda}{m}(P^C)^3 + (\nu_2 N_P \tfrac{\lambda}{m} - \beta_2 N_H - d)(P^C)^2 + \left(\phi\Lambda + \beta_2 N_P N_H + \frac{\nu_2 N_P \frac{\lambda}{m} - d}{\beta_1 + \nu_1 \frac{\lambda}{m}}\gamma\right)P^C + \frac{\phi\Lambda\gamma}{\beta_1 + \nu_1 \frac{\lambda}{m}} = 0$$

where $m = \mu + \xi N_V + \nu_1 N_H$. We can prove that the equation has only one positive solution. So, the deterministic system (3) has only one positive equilibrium point (H^{C*}, P^{C*}).

The Jacobian matrix of model (3) at the endemic equilibrium is

$$J^*(H^{C*}, P^{C*}) = \begin{pmatrix} -\beta_1 P^{C*} - \nu_1 \frac{\lambda}{m} P^{C*} - \gamma & \beta_1 N(N_H - H^{C*}) + \nu_1 \frac{\lambda}{m}(N_H - H^{C*}) \\ \beta_2 (N_P - P^{C*}) & -\beta_2 H^{C*} + \nu_2 \frac{\lambda}{m}(N_P - P^{C*}) - \nu_2 \frac{\lambda}{m} P^{C*} - d \end{pmatrix}$$

Doing some simple elementary transformation, we get that the eigenvalue of the Jacobian matrix is

$$l_1 = -\beta_1 P^{C*} - \nu_1 \frac{\lambda}{m} P^{C*} - \gamma,$$

$$l_2 = -\beta_2 H^{C*} + \nu_2 \frac{\lambda}{m}(N_P - P^{C*}) - \nu_2 \frac{\lambda}{m} P^{C*} - d + \frac{\beta_2 (N_P/N - P^{C*})}{\beta_1 P^{C*} + \nu_1 \frac{\lambda}{m} P^{C*} + \gamma}$$

Obviously, $l_1 < 0$ when the parameters are positive. Also, through some complicated algebraic calculation we can prove that $l_2 < 0$. So, the equilibrium (H^{C*}, P^{C*}) is locally asymptotically stable.

When $\phi = 0$ the equation is simplified to

$$-\nu_2 \frac{\lambda}{m}(P^C)^3 + (\nu_2 N_P \frac{\lambda}{m} - \beta_2 N_H - d)(P^C)^2 + \left(\beta_2 N_P N_H + \frac{\nu_2 N_P \frac{\lambda}{m} - d}{\beta_1 + \nu_1 \frac{\lambda}{m}} \gamma\right) P^C = 0$$

Let

$$a = -\nu_2 \frac{\lambda}{m}, \quad b = \nu_2 N_P \frac{\lambda}{m} - \beta_2 N_H - d, \quad c = \beta_2 N_P N_H + \frac{\nu_2 N_P \frac{\lambda}{m} - d}{\beta_1 + \nu_1 \frac{\lambda}{m}} \gamma$$

We can prove that the system has one disease free equilibrium (0,0), while there is also a positive equilibrium (H_0^{C*}, P_0^{C*}) for $R_0 > 1$, where

$$R_0 = \frac{1}{2md^2\gamma}(\gamma\nu_2 \Lambda\lambda + \sqrt{\gamma^2 \nu_2^2 \Lambda^2 \lambda^2 + 4md^2 \gamma N_H \Lambda\nu_1 \lambda\beta_2 + 4m^2 d^2 \gamma N_H \Lambda\beta_1 \beta_2})$$

$$P_0^{C*} = \frac{-b + \sqrt{b^2 - 4ac}}{2a}, \quad H_0^{C*} = N_H - \frac{\gamma N_H}{(\beta_1 P^C + \nu_1 \frac{\lambda P_0^{C*}}{m}) + \gamma}$$

When $R_0 < 1$ the Jacobian matrix of the model (3) at the disease-free equilibrium is

$$J_0(0,0) = \begin{pmatrix} -\gamma & \beta_1 N_H + \nu_1 \frac{\lambda}{m} N_H \\ \beta_2 N_P & \nu_2 \frac{\lambda}{m} N_P - d \end{pmatrix}$$

Doing some simple elementary transformation, we get that the trace of the Jacobian matrix is smaller than zero and the determinant of it is bigger than zero if and only if $R_0 < 1$. Therefore, the disease-free equilibrium is locally asymptotic stable when $R_0 < 1$ and otherwise it is unstable.

When $R_0 > 1$, by the same method, we can prove that the endemic equilibrium is locally asymptotic stable.

3. Stationary distribution when $\phi \neq 0$

3.1. Exact equilibrium distribution

Due to the small number of patients and HCWs in the ward, a stochastic version of the model usually cannot be neglected. A full stochastic version of model (3) is described by the transition rates in Table 2

treating H^C and P^C as discrete variables, and the timing of events as a stochastic process. Let $p_{H^C,P^C}(t)$ be the probability that there are H^C colonized HCWs and P^C colonized patients at time t. Then, the so-called Kolmogorov forward equation, which construct a set of differential equations for these state probabilities, is as follows:

$$\frac{\mathrm{dp}_{H^C,P^C}}{\mathrm{dt}} = p_{H^C-1,P^C}\left(\left(\beta_1 P^C + \nu_1 \frac{\lambda P^C}{m}\right)(N_H - H^C + 1)\right) + p_{H^C+1,P^C}(\gamma(H^C+1)) + p_{H^C,P^C-1}(\phi\Lambda + \left(\beta_2 H^C + \nu_2 \frac{\lambda P^C}{m}\right)$$

where $H^C = -1$, $H^C = N_H + 1$, $P^C = -1$ and $P^C = N_P + 1$ are not feasible states and therefore $p_{-1,\cdot}, p_{H+1,\cdot}, p_{\cdot,-1}$ and $p_{\cdot,P+1}$ are set to zero. For this model, there are $M = (N_H+1)(N_P+1)$ possible disease states $(0 <= H^C <= N_H, 0 <= P^C <= N_P)$, and so M different p_{H^C,P^C} variables. To formulate a matrix expression, we need to find a method of mapping the two-dimensional p_{H^C,P^C}, into a one-dimensional vector p. An efficient means of achieving this is to set the probability p_{H^C,P^C} as the $((N_P+1)H^C + P^C + 1)$th element of the vector. In this vector notation, the Kolmogorov forward equation becomes

$$\frac{\mathrm{dp}}{\mathrm{dt}} = \mathrm{pQ}$$

where the matrix Q consists of the transition rates.

Provided that all of the parameters of our model are strictly positive, then, when $\phi \neq 0$, our disease process is a Markov process on a finite, irreducible state space C. So, it is standard that the transition rate matrix Q has a unique left eigenvector $\pi = (\pi_1, \pi_2, \ldots, \pi_{(N_H+1)(N_P+1)})$ with eigenvalue zero such that $\Sigma_{i=1}^{(N_H+1)(N_P+1)} \pi_i = 1$, and the other eigenvalues are negative [10]. So, this eigenvector gives the unique limiting distribution of the process. That is to say, whatever the initial state of the process,

$$\lim_{t\to\infty} P(H^C(t), P^C(t)) = \pi$$

3.2. Normal approximation

Although we have got the method of analyzing the exact equilibrium, to calculate the eigenvector is not trivial when the number of patients or HCWs is large. Also, the exact method cannot give an analytical expression of the probability at the stationary distribution and an intuitive idea of the shape of the distribution. So, to simplify the calculation and investigate statistical properties of the stationary distribution we try to approximate the distribution by the method developing by Kurtz [8]. Let $N = N_P + N_H$. Define a family of scaled process indexed by N by

$$V_N(t) = \frac{1}{N}(H_N^C(t), P_N^C(t))$$

The approximating deterministic process $(u(t), v(t))$ satisfies

$$\begin{cases} \frac{\mathrm{du}}{\mathrm{dt}} = \beta_1 \mathrm{Nv}(N_H/N - u) + \nu_1 N \frac{\lambda v}{\mu + \xi N_V + \nu_1 N_H}(N_H/N - u) - \gamma u \\ \frac{\mathrm{dv}}{\mathrm{dt}} = \phi\Lambda/N + \beta_2 \mathrm{Nu}(N_P/N - v) + \nu_2 N \frac{\lambda v}{\mu + \xi N_V + \nu_1 N_H}(N_P/N - v) - \mathrm{dv} \end{cases} \tag{4}$$

By the analysis in section one we know that the system has only one equilibrium (u^*, v^*) and it is locally asymptotically stable.

Now, consider the process $Z_N(t) = \sqrt{N}(V_N(t) - (u(t), v(t)))$. By the results of Kurtz [8], the process $Z_N(t)$

may be approximated by a two dimensional Ornstein–Uhlenbeck process, whose local drift matrix is $A(u^*, v^*)$ and local covariance matrix is G_w, close to the equilibrium, where

$$A_w(u^*, v^*) = \begin{pmatrix} -\beta_1 \mathrm{N}v^* - \nu_1 \frac{\lambda}{m} v^* - \gamma & \beta_1 N(N_H/N - u^*) + \nu_1 \frac{\lambda}{m}(N_H/N - u^*) \\ \beta_2 N(N_P/N - v^*) & -\beta_2 \mathrm{N}u^* + \nu_2 N\frac{\lambda}{m}(N_P/N - v^*) - \nu_2 N\frac{\lambda}{m} v^* - d \end{pmatrix}$$

$$G_w = \begin{pmatrix} g_{11} & 0 \\ 0 & g_{22} \end{pmatrix}$$

where

$$g_{11} = \beta_1 \mathrm{N}v^* (N_H/N - u^*) + \nu \frac{\lambda}{m} v^* (N_H/N - u^*) + \gamma u^*$$

$$g_{22} = \phi\Lambda/N + \beta_2 \mathrm{N}u^* (N_P/N - v^*) + \nu_2 N\frac{\lambda}{m} v^* (N_P/N - v^*) + \mathrm{d}v^*$$

The state of this Ornstein–Uhlenbeck process at time t is distributed according to a bivariate normal distribution with mean vector $M(t)$ and variance matrix $S(t)$ satisfying

$$\begin{cases} \frac{\mathrm{dM}}{\mathrm{dt}} = A(u^*, v^*)M \\ \frac{\mathrm{dS}}{\mathrm{dt}} = A(u^*, v^*)S + \mathrm{SA}(u^*, v^*) + G \end{cases} \tag{5}$$

The eigenvalues of $A(u^*, v^*)$ are negative, so that $\det(A(u^*, v^*)) > 0$. Therefore, the mean vector in equilibrium is the zero vector and the variance matrix in equilibrium is given by the solution of the following equation

$$A(u^*, v^*)\Sigma + \Sigma A(u^*, v^*)^T = -G.$$

Thus, we can approximate the equilibrium distribution of the disease process $(H^C(t), P^C(t))$ by a bivariate normal distribution with mean $(\mathrm{N}u^*, \mathrm{N}v^*)$, variance matrix $N\Sigma$. Hence, the normal density function at the point (H^C, P^C) is

$$p(H^C(t), P^C(t)) = \frac{1}{2\pi\sqrt{\det(N\Sigma)}} e^{-(H^C - \mathrm{N}u^*, P^C - \mathrm{N}v^*)(2N\Sigma)^{-1}(H^C - \mathrm{N}u^*, P^C - \mathrm{N}v^*)^T}$$

4. Quasi-stationary distribution and time to extinction when $\phi = 0$

When $\phi = 0$, for the deterministic version of the model, there are two equilibria: one is the disease free equilibrium and the other is an endemic equilibrium. When $R_0 < 1$ the disease free equilibrium is stable and otherwise the endemic equilibrium is stable. However, for the stochastic version of the model, our disease process is a Markov process on a finite, reducible state space. The state (0, 0) is the only recurrent state and the rest of the states are transient states. So, the rest of the transient states combine an irreducible state space C' and that eventual departure from C' occurs with probability 1. That is when t goes to infinity the disease process will stabilize at (0, 0) for whatever initial values with probability 1. In this case, what we are interested is the distribution of contaminated patients and colonized patients conditional on non-extinction and the time to extinction. So, instead of studying the stationary distribution we consider the quasi-stationary distribution which is supported on the transient states.

Now we study the process conditional on non-extinction. Let Q_0 be a matrix without the first row and column of Q. p_{mn} is the probability that $H^C = m$ $P^C = n$ at time t. From the Kolmogorov forward equations

we have

$$p_{00}^{'} = \gamma p_{10} + \mathrm{dp}_{01}$$

Let $q_{\mathrm{mn}}(t)$ be the corresponding state probability conditional on non-extinction and $q(t)$ be the row vector of the values of $q_{\mathrm{mn}}(t), m = 1,2,\ldots N_H$, $n = 1,2,\ldots,N_P$. Then,

By differentiating the equation above we get

$$q_{\mathrm{mn}}^{'}(t) = \frac{p_{\mathrm{mn}}^{'}(t)}{1 - p_{00}(t)} + \frac{p_{\mathrm{mn}}(t)}{(1 - p_{00}(t))^2}(\gamma p_{10} + \mathrm{dp}_{01}) = \frac{p_{\mathrm{mn}}^{'}(t)}{1 - p_{00}(t)} + \frac{p_{\mathrm{mn}}(t)}{1 - p_{00}(t)}(\gamma q_{10} + \mathrm{dq}_{01})$$

So,

$$q^{'}(t) = q(t)Q_0 + (\gamma q_{10} + \mathrm{dq}_{01})q(t)$$

The quasi-stationary distribution is the stationary solution of this system of differential equation. Therefore, the quasi-stationary distribution satisfies the following equations

$$\mathrm{qQ}_0 = -(\gamma q_{10} + \mathrm{dq}_{01})q$$

By the result of Nasell [13], the quasi-stationary distribution is a left eigenvector of Q_0 corresponding to the eigenvalue $\gamma q_{10} + \mathrm{dq}_{01}$.

Let τ be the time to extinction for the process without the original condition. Obviously, we have

$$P\{\tau \leqslant t\} = P\{H^C(t) = 0, P^C(t) = 0\} = p_{00}(t)$$

So,

$$p_{\mathrm{mn}}^{'}(0) = q_{\mathrm{mn}}^{'}(t)(1 - p_{00}(t)) - (\gamma q_{10} + \mathrm{dq}_{01})p_{\mathrm{mn}}(t) = -(\gamma q_{10} + \mathrm{dq}_{01})p_{\mathrm{mn}}(t)$$

Here, we put $q_{\mathrm{mn}}^{'}(t) = 0$ which indicates that it has been stabilized.

Integrating the differential equation with the initial condition

$$p_{\mathrm{mn}}(0) = q_{\mathrm{mn}}$$

we have

$$p_{\mathrm{mn}}(t) = q_{\mathrm{mn}} \exp[(\gamma q_{10} + \mathrm{dq}_{01})t]$$

Then,

$$p_{00}(t) = q_{00} \exp[(\gamma q_{10} + \mathrm{dq}_{01})t] = \frac{p_{00}(t)}{1 - p_{00}(t)} \exp[(\gamma q_{10} + \mathrm{dq}_{01})t]$$

Therefore,

$$p_{00}(t) = 1 - \exp[(\gamma q_{10} + \mathrm{dq}_{01})t]$$

Thus, if the initial distribution equals the quasi-stationary distribution, the distribution of τ is exponential with the parameter ($\gamma q_{10} + dq_{01}$). So,

$$E[\tau] = \frac{1}{\gamma q_{10} + dq_{01}}$$

5. Numerical simulation and comparison

Our data are on cases of MRSA patients and non-MRSA patients from Beijing Tongren hospital which is a university-affiliated teaching hospital with 1600 beds. The data included 522 patients admitted to an emergency ward for which the capacity is 23, from 2nd March 2009 to 30th October 2010. Most of the parameters in the paper come from Wang et al. [19] except the departure rate of patients. To keep the total number of patients constant the departure rate of both susceptible and colonized patients are assumed to be the same value 1/16.2046 which is the average departure rate of all patients of our data. Parameter values are shown in Table 1 [19]. The total number of patients which will go towards $\frac{\Lambda}{d}$ must be an integer in the numerical simulation of the stationary distribution. So, we assumed that the value of N_P is $\frac{\Lambda}{d}$ rounded up to an integer.

Table 1. Definitions of the parameters used in the model.

Parameter	Definition (units)	Value	References
N_H	Numbers of health care workers	8	Data
β_1	Transmission rate from patients to HCWs (/person/day)	0.22	–
β_2	Transmission rate from HCWs to patients (/person/day)	0.0105	–
ν_1	Indirect transmission rate between HCWs and the environment (/CFU[a]/day)	0.00001	Semi-stochastic simulation
ν_2	Indirect transmission rate between patients and the environment via volunteers (/CFU/day)	0.000004	Semi-stochastic simulation
Λ	Inflow rate of patients to hospital (/day)	0.86	Data
ϕ	Proportion of admissions already colonized When being hospitalized	0.067	Data
λ	Shedding rate of patients (CFUs/day)	470	Semi-stochastic simulation
d	Outflow rate of patients (/day)	1/16.2046	Data
γ	Recovery rate of infectious for HCWs (/HCW/day)	24	Austin et al., 1999
μ	Clearance rate of bacteria from the environment (/day)	0.7	Semi-stochastic simulation
ξ	Indirect transmission rate between volunteers and the	0.00008	Semi-stochastic simulation

environment via free-living bacteria (/CFU/day)

[a] Colony-forming unit.

Table 2. Events and their rates for fully stochastic model.

Event	State transition	Rates
Patient-carer transmission	$(H^C, P^C) \to (H^C + 1, P^C)$	$\beta_1 P^C (N_H - H^C)$
Environment-carer transmission	$(H^C, P^C) \to (H^C + 1, P^C)$	$\nu_1 \frac{\lambda P^C}{\mu + \xi N_V + \nu_1 N_H} (N_H - H^C)$
HCW hand washing	$(H^C, P^C) \to (H^C - 1, P^C)$	γH^C
Carer-patient transmission	$(H^C, P^C) \to (H^C, P^C + 1)$	$\beta_2 H^C (N_P - P^C)$
Environment-patient transmission	$(H^C, P^C) \to (H^C, P^C + 1)$	$\nu_2 \frac{\lambda P^C}{\mu + \xi N_V + \nu_1 N_H} (N_P - P^C)$
Admission of colonized patients	$(H^C, P^C) \to (H^C, P^C + 1)$	$\phi\Lambda$
Colonized patient removal	$(H^C, P^C) \to (H^C, P^C - 1)$	dP^C

In this section, we first compare simulation results of the event-driven stochastic simulation method, the exact equilibrium method and the normal approximation method. Then, we investigate effects of some interventions (increasing hand hygiene rate of HCWs or volunteers, isolation rate of colonized patients and clearance rate of the ward) on the marginal distribution of colonized patients and the time to extinction.

5.1. Numerical study

To compare the distribution of HCWs and patients generated by both the exact equilibrium method and the normal approximation method, we calculate the left eigenvector of Q corresponding to the zero eigenvalue and the density function of the normal distribution introduced above, numerically, with parameter values shown in Table 1. Fig. 2(a) and (b) show the distribution of H^C and P^C generated by the two methods respectively while Fig. 2(c) and (d) show the contour plot of the two distributions. From Fig. 2(a) and (b) we can see that both the approximation and exact methods give similar shapes of distributions. Fig. 2(c) shows that the smaller the number of H^C and P^C the bigger the probability of them. However, this is not exactly the same as the distribution of the bivariate normal distribution approximation. It follows from Fig. 2(d) that the probability of P^C increases initially and then decreases as P^C increases. These two figures indicate that the domain of the approximated distribution is a bit bigger than that of the exact distribution. Just because of this, the biggest probability value of the exact distribution is larger than that of the approximated distribution.

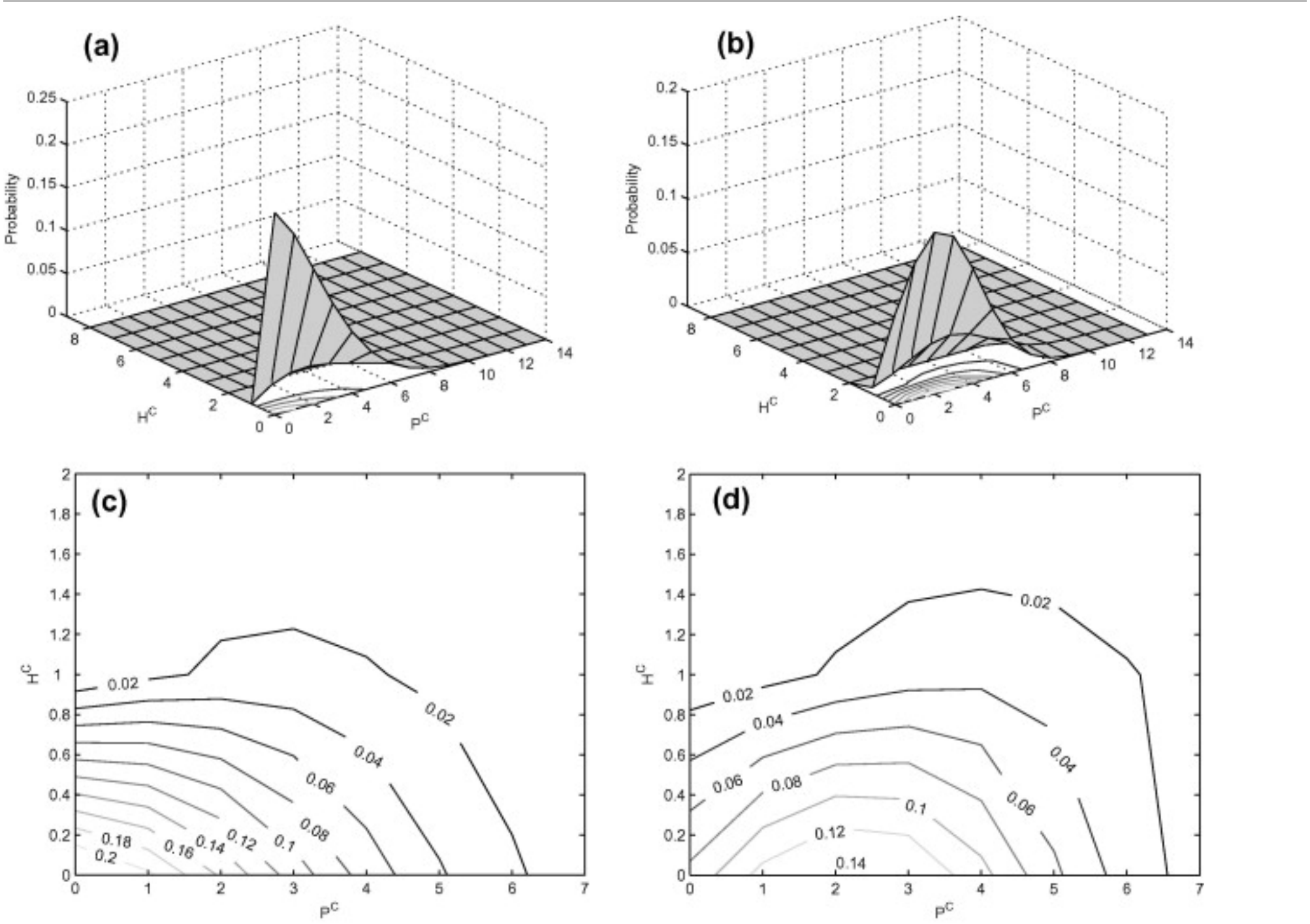

Fig. 2. (a) The distribution of H^C and P^C generated by the exact method. (b) The distribution of H^C and P^C generated by the bivariate normal distribution approximation. (c) Contour plot of the exact stationary distribution. (d) Contour plot of the approximated distribution. All parameters are shown in Table 1.

For nosocomial infections, what we are most concerned about is the number of colonized patients. So, the marginal distribution of P^C is very important. Fig. 3 shows the distribution of P^C generated by stochastic simulation of models (2) and (3). The grey one is obtained by 10,000 semi-stochastic simulations of model (2) and the black one is got by 10,000 fully stochastic simulations of model (3). Both of them are the distribution on the 500th day when these values have stabilized. It follows from this figure that the two distributions are in good agreement. This indicates that the quasi-steady state (QSS) approximation of our model almost does not affect the simulation result and further implies the rationality of our approximation.

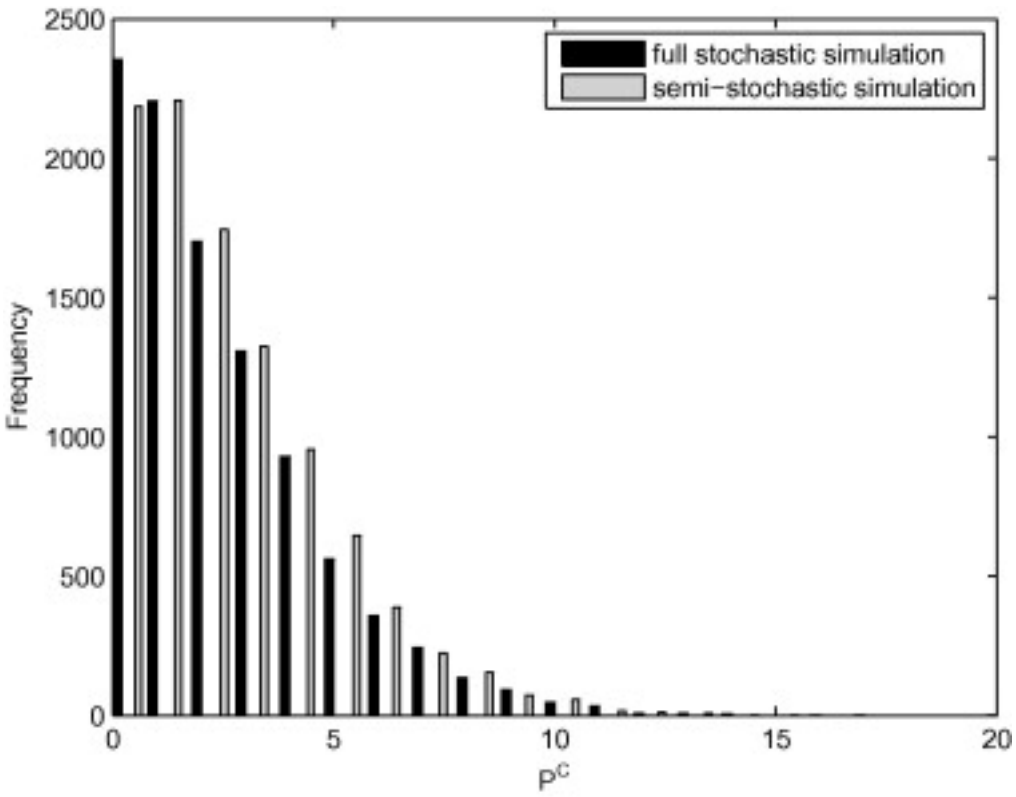

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Fig. 3. The grey bar shows distribution of colonized patients generated by 10,000 semi-stochastic simulations of model (2). The black bar shows distribution of colonized patients generated by 10,000 full stochastic simulations of model (3). All parameters are shown in Table 1.

Fig. 4(a) shows the comparison of the frequency of colonized patients generated by full stochastic simulation of model (3) (grey bars), the exact stationary distribution (stars) and the normal approximation (squares). From this figure we can clearly see that the exact equilibrium distribution and the stochastic simulation results are in good agreement. The normal approximation fits very well when $P^C > 6$ but it has a few deviations when $P^C \leqslant 6$. This may be because on the basis of our parameters the transmission of the disease in the ward was not serious enough to reach the normal distribution. To generate the stationary distribution one needs at least thousands of series of data but we only have one series. In fact, the distribution of colonized patients over an interval when the number of colonized patients has stabilized may be similar to the stationary distribution. So, we show the frequency of our data over 608 days in Fig. 4(b) to confirm the results calculated above. The grey bar in Fig. 4(b) shows the frequency of our data for P^C. Stars and squares represent the frequency obtained by the exact equilibrium distribution and the bivariate normal approximation distribution. Fig. 4(b) shows that the frequency of the two distributions is not coinciding with the data very well but their patterns are similar.

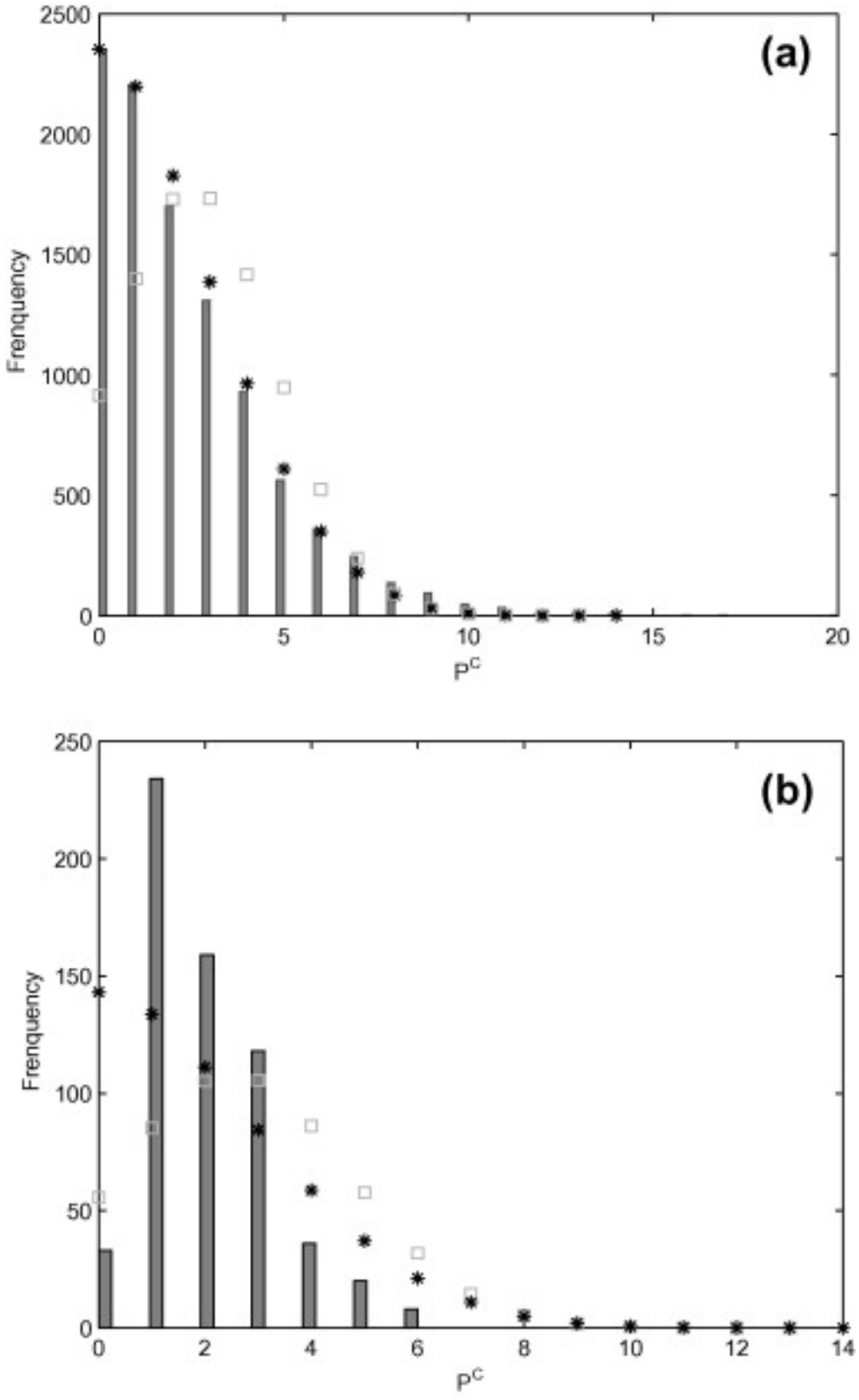

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Fig. 4. (a) The frequency of colonized patients generated by 10,000 stochastic simulation results (grey bars) comparison to the exact stationary distribution (stars) and the normal approximation (squares). (b) The frequency of colonized patients generated by the data (608 days) (grey bars) comparison to the exact stationary distribution (stars) and the normal approximation (squares). All parameters are shown in Table 1.

This may be caused by the limitation of the amount of our data or the parameter values chosen. In real life, random extinction may be reduced due to environmental contamination. Mean and standard deviation for our data, simulation results, exact stationary distribution and the normal approximation are shown in Table 3. It follows from this table that the mean and standard deviation of the semi-stochastic simulation of model (2) and full stochastic simulation of model (3) are almost the same and also the means of the exact equilibrium distribution and the normal approximation distribution are similar. To assess the results obtained here, we also calculated the mean and the standard deviation of the real data which are 1.9704 and 1.2414, respectively. The mean of the real data is very close to that of the exact equilibrium distribution and

a little smaller than that of the normal approximation distribution and the event-driven simulations. However, the standard deviation of the real data is almost half those of the others.

Table 3. Mean and variance of P^C derived from distributions gained by different methods.

	Data	Simulation model (2)	Simulation model (3)	Stationary distribution	Normal approximation
Mean	1.9704	2.3546	2.3035	2.1379	2.569
SD[a]	1.2414	2.2179	2.2656	1.9454	2.2432

[a] Standard deviation.

To assess the quasi-stationary distribution obtained calculating the left eigenvector of the matrix Q_0 corresponding to the eigenvalue $\gamma q_{10} + \mathrm{dq}_{01}$, we investigate event-driven stochastic simulations of model (3) when $\phi = 0$. Fig. 5(a) shows the quasi-stationary distribution of model (3) when $\phi = 0$. It indicates that before extinction the most frequent states are (0,1) and (0,2). Fig. 5(b) shows the marginal distribution of P^C conditional on non-extinction. The line in this figure represents the results of 10,000 stochastic simulations on the 45th day. Dots represent the results obtained by the quasi-stationary distribution. Obviously, marginal distributions obtained by these two methods coincide with each other very well. The expected time to extinction initiated from the quasi-stationary distribution is calculated to be 41.0341. This result is lower than that in the paper of Wang et al. [19] which is 74.9. To analyze the reason, we investigate the expected time to extinction of the model (2) with parameter values in Table 1 by using semi-stochastic simulations with the same initiation as that in the paper of Wang et al. [19] and obtained that the average extinction time is 44.7972 which is in agreement with the expected time of model (3) that we calculate by the eigenvector method. Therefore, the reduction of the extinction time is caused by the assumption of $d_1 = d_2$ and the value of d. This also indicates that the value of the departure rate of patients have a significant impact on the time to extinction.

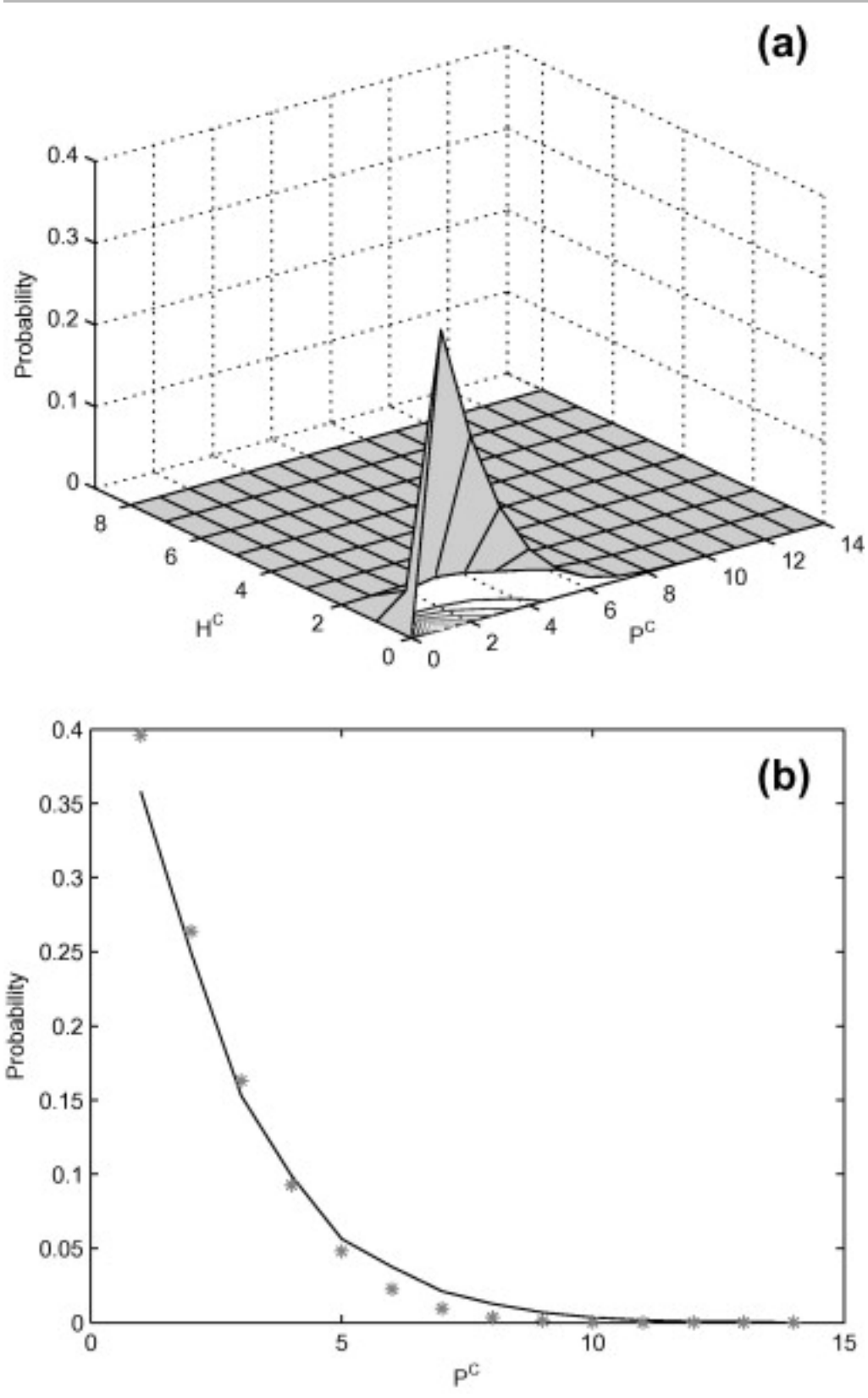

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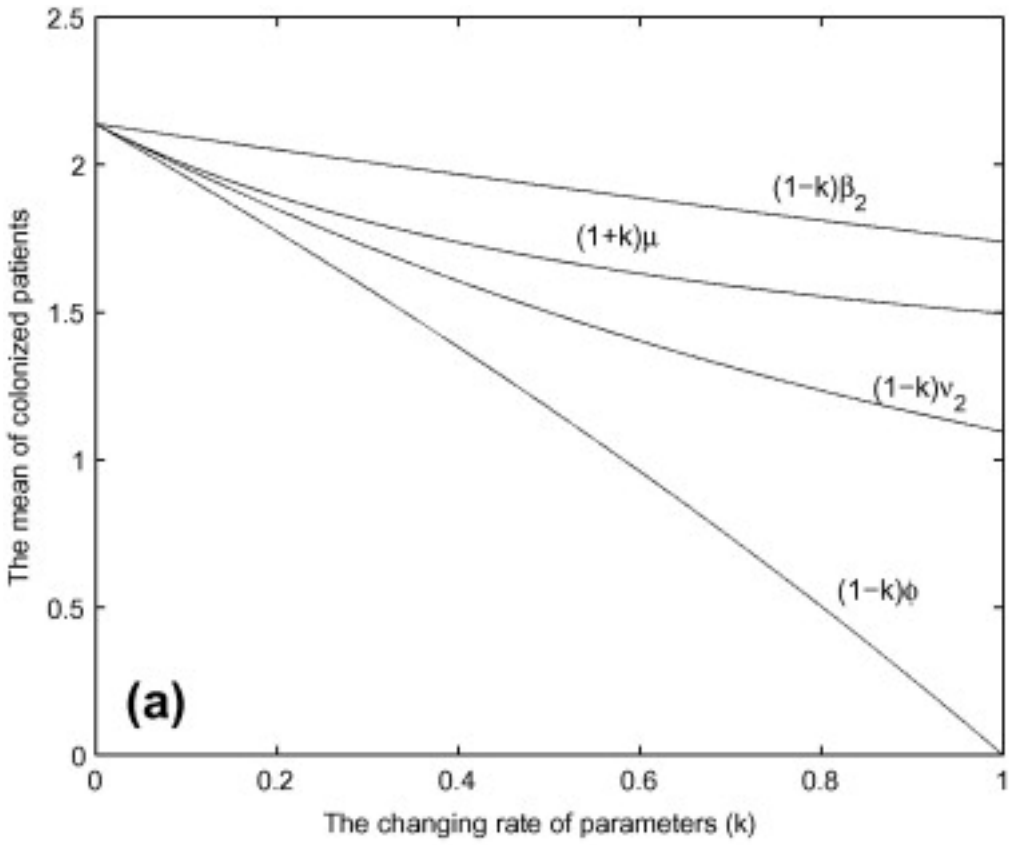
Fig. 5. (a) Quasi-stationary distribution of P^C and H^C when the admission prevalence is zero ($\phi = 0$). (b) Marginal distribution of P^C derived from the quasi-stationary distribution conditional on non-extinction when $\phi = 0$. The curve shows the stochastic simulation result while dots show the marginal distribution generated by the quasi-stationary distribution. All parameters are as shown in Table 1.

5.2. Effects of intervention

According to the sensitivity analysis in the paper of Wang et.al, 2012 [19], the clearance rate μ, the indirect transmission rate of volunteers ν_2 , the direct transmission rate of HCWs β_2 and the isolation rate of newly admitted colonized patients ϕ are four critical parameters which greatly affect the basic reproduction number and the number of colonized patients daily. So, we vary these four important parameters while keeping other parameters fixed to study effects of interventions on the stationary distribution. We calculate the mean and the standard deviation in the stationary distribution of colonized patients with these parameter values changing. To keep the changes of parameter values at the same scale, we let k be the

changing rate of parameters. Fig. 6(a) shows the variation of the mean of the marginal distribution of colonized patients by varying those parameters (μ,ν_2 ,β_2 and ϕ) while Fig. 6(b) shows the changes of the standard deviation, where μ,ν_2 ,β_2 and ϕ are changing with respect to k. It follows from Fig. 6 that isolation of newly admitted positive patients is the most effective intervention and hand hygiene of volunteers is more effective than cleaning and hand hygiene of HCWs in terms of reducing the mean of the marginal distribution of colonized patients. Also, from Fig. 6 we find that tendencies of variations of the mean and the standard deviation along with the changes of μ,ν_2 and β_2 are similar. With the reducing of ϕ, the standard deviation first reduces slowly and then sharply but the mean reduces smoothly. Fig. 6(a), which shows the effects of some parameters to the mean of the marginal distribution, is in agreement with that shown in Fig. 9(a) developed by Wang et al. (2012) for the deterministic model [19]. This implies that some control measures have almost the same effects on either the mean of the stationary distribution or the prevalence of P^C of the steady state of the deterministic model. The deterministic model can only tell us about the mean behavior but the stationary distribution gives more details such as the standard deviation, which can be used to evaluate the robustness of our results. Fig. 6(b) implies that under either of these control measures the standard deviation of the marginal distribution of colonized patients will become smaller, which indicates that our conclusions of impacts of varying these parameters are relatively stable.



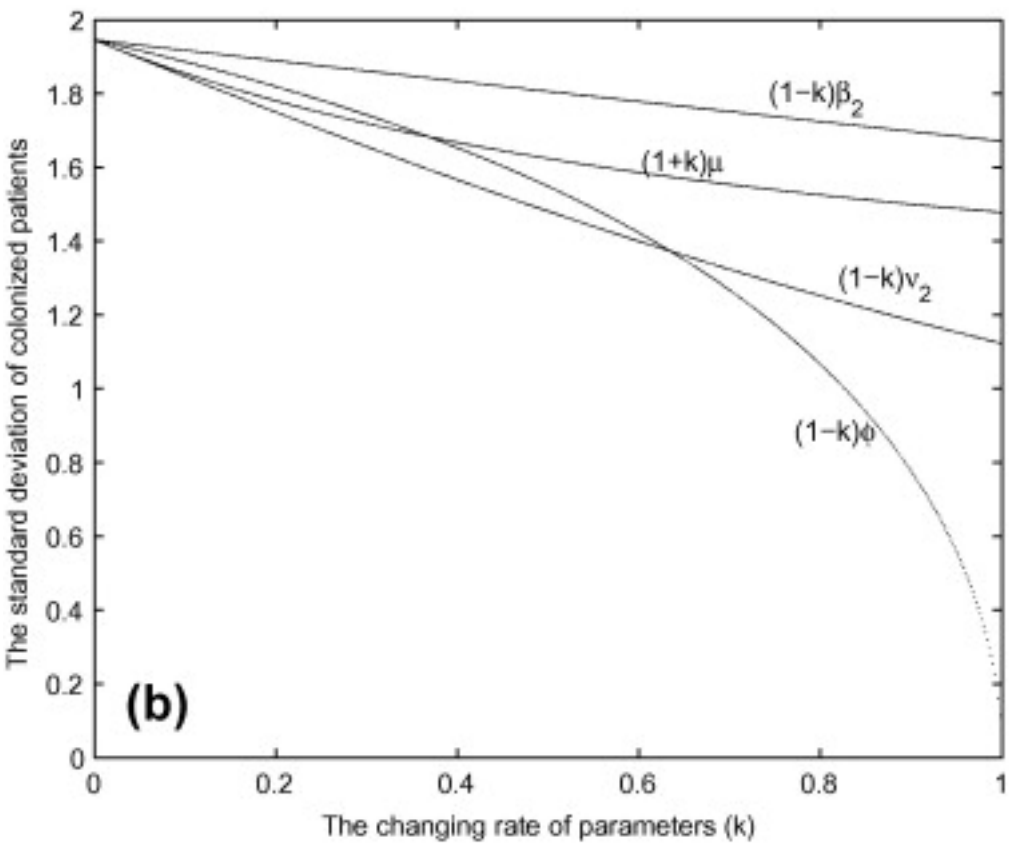


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Fig. 6. (a) The variation of the mean of the marginal distribution of P^C by varying k (the rate of changing μ,ν_2 ,β_2 and ϕ). (b) The variation of the standard deviation of the marginal distribution of P^C with respect to k. All other parameters are as shown in Table 1.

Fig. 6(b) has shown the effects of some interventions on the standard deviation of the stationary distribution. But these interventions are considered based on the default parameter values. To know whether the standard deviation increases with the direct and indirect transmission parameters increasing, we investigate effects of varying direct and indirect transmission parameters (β_2 and ν_2) on the standard deviation of the marginal distribution of colonized patients in a larger parameter region. It follows from Fig. 7(a) that the standard deviation first increases and then decreases as either the indirect transmission parameter ν_2 or the direct transmission parameter β_2 increases. But it also shows that the impact of varying ν_2 is greater than that of varying β_2 which makes the standard deviation increase or decrease more

dramatically. So, it implies that indirect transmission may lead to a larger or smaller standard deviation compared to the direct transmission and whether the standard deviation will decrease or increase when we reduce the value of β_2 and ν_2 depends on their default values. Fig. 7(b) shows the variation in the mean of colonized patients with the direct and indirect transmission parameters. It shows that the mean of colonized patients increases with increasing these two parameters. Comparing Fig. 7(a) and (b) implies that the peaks of the standard deviation correspond to the fastest increasing in the mean of colonized patients. It further indicates that the mean of the data alone cannot determine parameter values. The standard deviation is also an important point which may not be neglected.

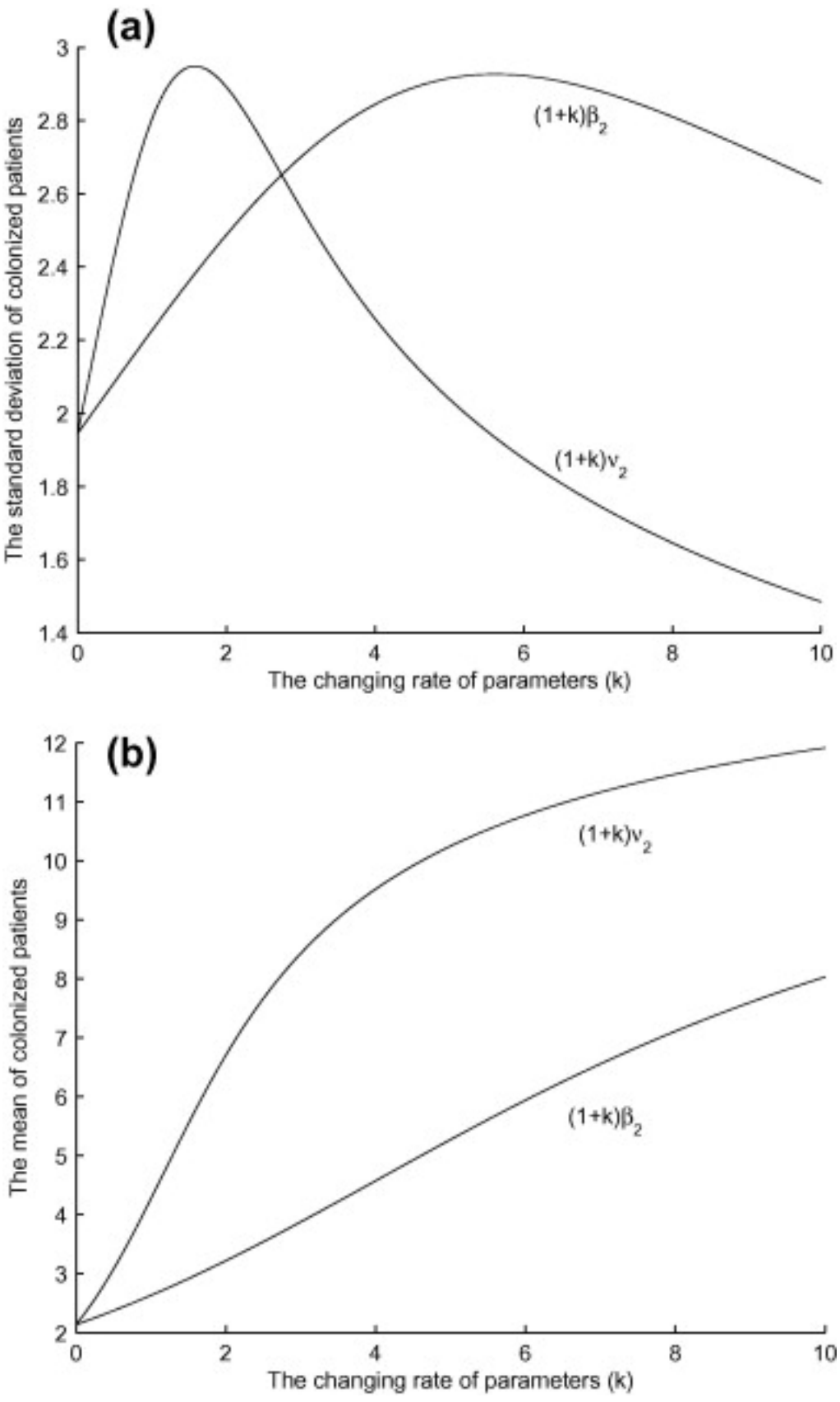

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Fig. 7. Variation in the standard deviation (a) and mean (b) of the marginal distribution of P^C with ν_2 (indirect transmission rate between patients and the environment via volunteers) and β_2 (transmission rate from HCWs to patients) from their default values to ten times. All parameters are shown in Table 1.

The basic reproduction number is a threshold which determines the persistence and extinction of the deterministic model. But for the stochastic model the disease will go to extinction when $\phi = 0$, whether the basic reproduction number is smaller than one or not. However, is there any relationship between the two? Will the extinction time increase with the basic reproduction increasing? To see the relationship of the extinction time and the basic reproduction number and how they are affected by the direct and indirect transmissions, we investigate the change of basic reproduction number and the expected time to extinction initiated at the quasi-stationary distribution when $\phi = 0$ with respect to ν_2 and β_2 which varies from zero to twice of their default values. Fig. 8(a) shows the change of R_0 ; while Fig. 8(b) shows that of the expected time to extinction. As shown in Fig. 8(a), the basic reproduction number increases as ν_2 or β_2 increases, but the rate of change of R_0 caused by ν_2 is much bigger than that caused by β_2 . This indicates that ν_2 is more sensitive than β_2 to the basic reproduction number. It follows from Fig. 8(b) that the greater the indirect transmission (the direct transmission) the longer the expected time to extinction and the rate of change of the expected time to extinction is increasing with the value of the indirect transmission (the direct transmission) increasing. Therefore, the effectiveness of control measures corresponding to one of the two parameters depends on the value of the other one. However, generally speaking, measures related to ν_2 can shorten the time to extinction more effectively. Moreover, from these two figures we find that increasing tendencies of the basic reproduction number and the expected time to extinction with the increasing of these two parameters are very different. So, contour lines of these two figure must have points of intersection. Therefore, the expected time to extinction may have very different values even if the value of the basic reproduction number is the same because of different parameter values. Also, the extinction time may decrease when the basic reproduction number increases. Thus, the basic reproduction number which is a threshold of the deterministic model could not be used to determine the length of the extinction time.

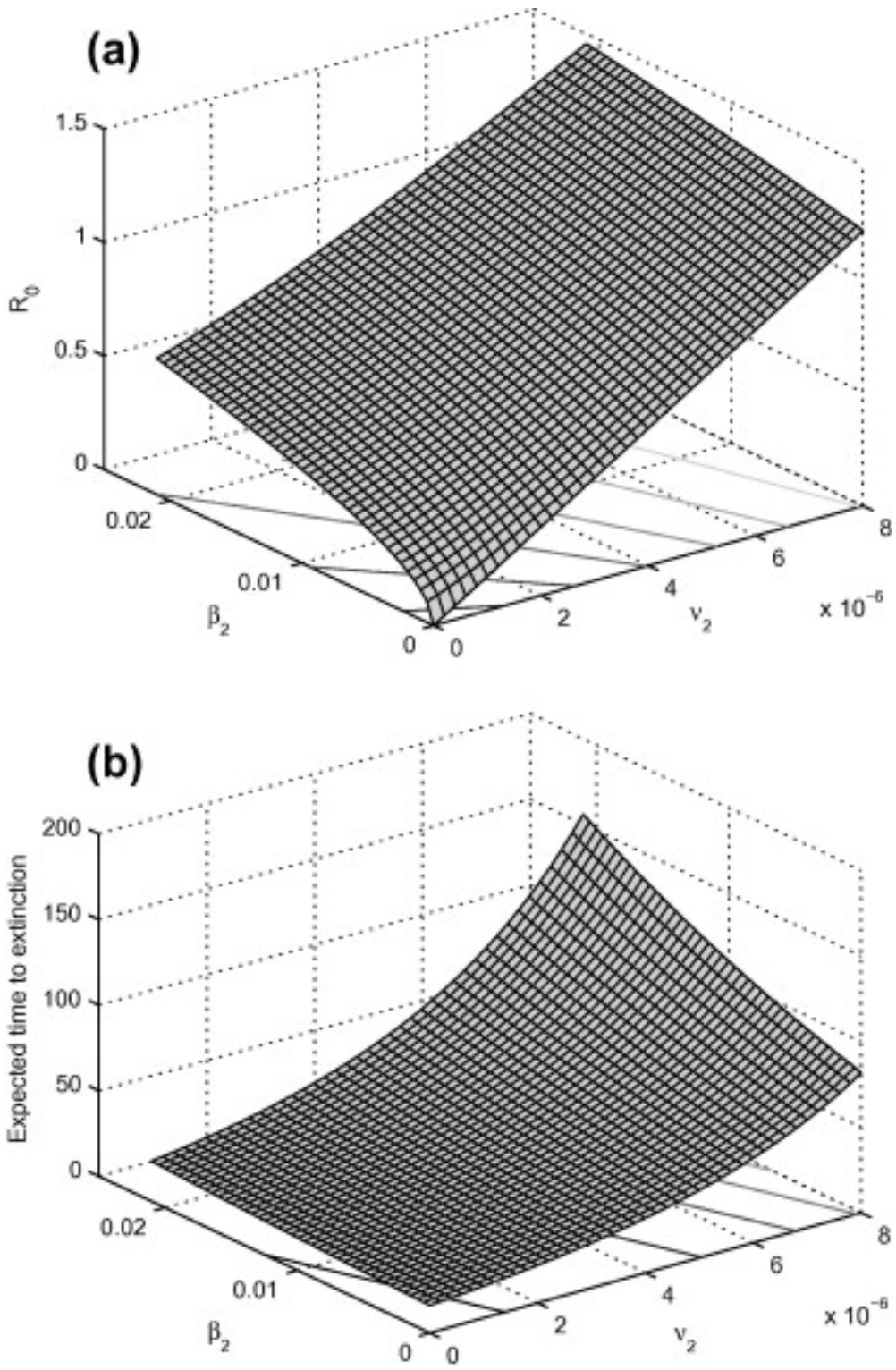

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Fig. 8. (a) The change of R_0 with respect to ν_2 (indirect transmission rate between patients and the environment via volunteers) and β_2 (transmission rate from HCWs to patients). (b) The change of the expected time to extinction initiated at the quasi-stationary distribution when $\phi = 0$ with respect to ν_2 and β_2 . ν_2 and β_2 are changing from zero to twice of their default values. All other parameters are as shown in Table 1.

6. Discussion

In this paper, we initially simplified the model developed by Wang et al. [19] from a five dimension system to a two dimension one by the quasi-steady state approximation and an assumption of keeping the number of patients in the ward constant, which is often used in papers about hospital infection [1], [3]. Then, we study the equilibrium and basic reproduction number for the simplified deterministic model and further explore the stochastic properties of the stochastic version of the simplified model. One of the main focuses of this paper is on the stationary distribution of the stochastic model. Here we not only consider the stationary distribution when $\phi \neq 0$ by two methods: the exact method and the normal approximation, but

also investigate the quasi-stationary distribution and the expected time to extinction when $\phi = 0$.

Results of semi-stochastic simulation of model (2) and full stochastic simulation of model (3), which are shown in Fig. 3, indicate that the quasi-steady state approximation almost does not affect the simulation results and further supports the rationale of our approximation. Stationary distributions of H^C and P^C have been obtained by the exact equilibrium method, normal approximation method and their simulation results, showing that these two variable distributions have similar shapes. HCWs in the ward cannot be colonized but contaminated so that the marginal distribution of P^C is a focus of concern. Table 3 shows that the standard deviations of our simulation results is much larger than that of the real data. Also, Fig. 7(a) shows that the indirect (or direct) transmission rate ν_2 (or β_2) can lead to increase or decrease in the standard deviation of the stationary distribution, depending on the values of indirect (or direct) transmission. Therefore, the larger standard deviation of our simulation results may be caused by inaccurate parameter values which are estimated by fitting the mean prevalence of colonized patients to the data [19]. This indicates that the standard deviation of the data is also an important item of information for us to determine some of these parameters.

According to theoretical results of the deterministic model in the paper of wang et al. [19], if $\phi = 0$ the disease in the ward will go to extinction when the basic reproduction number is less unity, otherwise it will persist. However, The deterministic version of the model is only an approximation of the stochastic model as the population size approaches infinity. So, there are no similar results for the stochastic counterpart of the model. When $\phi = 0$, the state space is a finite space with one absorbing state and some transient states. So, whatever the value of the basic reproduction number, the disease will be extinct with probability one, although it may take a considerable time before extinction when R_0 is very large. Therefore, when $\phi = 0$ what we are concerned about is not the stationary distribution but the quasi-stationary distribution, namely, the distribution conditional on non-extinction. At the same time, the expected time to extinction is also an important problem. We have given the method of calculating the quasi-stationary distribution and the expected time to extinction initiated at the quasi-stationary distribution (section 4) and verified the coincidence of the marginal distribution of colonized patients generated by the quasi-stationary distribution and stochastic simulations (Fig. 5(b)). Moreover, we find that assuming $d_1 = d_2$ has a great influence on the estimation of the time to extinction. Therefore, under this assumption the determination of the departure rate of patients is an important problem and reducing the length of stay of patients in the ward is a very effective intervention in terms of shortening the time to extinction.

Effects of some control measures on the equilibrium of the deterministic model have been studied by Wang et al. [19]. In this paper we consider the problem in more detail including not only effects on the mean of colonized patients but also their standard deviation. On the basis of our parameters, isolation of new colonized patients is the most effective measure to reduce the mean and the standard deviation of the stationary distribution. Hand hygiene of volunteers is more effective than that of HCWs in terms of reducing the mean of colonized patients. However, for our model, Fig. 7(a) implies that both direct and indirect transmission can not only lead to reduction of the standard deviation but also to increase it and the influence of the indirect transmission ν_2 is greater than that of the direct transmission β_2. This is a little different from that in the paper of Clancy [6] which concludes that indirect transmission leads to reduction of the standard deviation. It follows from Fig. 7(a) and (b) that the peaks of the standard deviation correspond to the fastest increasing in the mean of colonized patients. Note that the peaks of the standard deviation are not associated with the threshold of $R_0 = 1$. That is because the standard deviations are

derived when the admission prevalence is non zero, whilst the basic reproduction number is only feasible for zero admission prevalence.

When $\phi = 0$, according to the results of Section 4, the disease will go to extinction with probability one. Therefore, under such circumstances, what we are most concerned about is how to reduce the time to extinction. Our earlier paper [19] was concerned with the time to extinction by the method of stochastic simulation but did not consider effects of parameters on the expected time to extinction because it needs repeated simulations. However, by the method of the eigenvector we can easily get the result which is shown in Fig. 8. It follows from this figure that under the influence of random factors the size of the basic reproductive number cannot determine the length of the expected extinction time, although it is a threshold which determines the persistence and the extinction in the deterministic model. It implies that effects of interventions (hand hygiene of volunteers or HCWs) to control indirect transmission or direct transmission depends on the value of the other one, but under the default parameter values interventions to control indirect transmission will be more effective than that to control direct transmission in terms of shorter time to extinction. This result is in agreement with that of Clancy [6].

In general, under the assumption of $d_1 = d_2$ and the quasi-steady state approximation we have studied the stochastic features in detail. The quasi-steady state approximation almost has no effect on the simulation results, but the assumption of $d_1 = d_2$ greatly affects the time to extinction and it may limit the ability of the model to reproduce the MRSA data. So we shall concentrate on formulating a comprehensive model to reproduce all characteristics of MRSA data - in particular, the variance of the number of colonized patients in the future. Moreover, parameter values used in this paper are not very accurate because the standard deviation cannot fit the data well. So, how to reproduce all characteristics of the data, to analyze the stochastic feature without the assumption ($d_1 = d_2$) and to estimate parameter values based on the mean and the standard deviation of the data is planned for future research.

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