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Impact of visitors and hospital staff on nosocomial transmission and spread to community

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HIGHLIGHTS

- Metapopulation model to qualify disease transmission in a community and its healthcare facility.
- Focus on the roles of healthcare workers at and visitors to the healthcare facility.
- Quantify disease transmission within the facility and to the community during a disease outbreak.
- Infections by infective residents and visitors in healthcare facility are most important factors.
- Preventing infections of healthcare staff is of the highest priority in disease prevention.

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ABSTRACT

We develop a deterministic meta-population model to qualitatively capture some key features of disease transmission between a community and its healthcare facility. We consider the disease transmission dynamics within a healthcare facility and between the healthcare facility and its community. The focus of this study is to quantify the roles of the healthcare workers at and visitors to this healthcare facility in shaping the transmission dynamics during a disease outbreak. We stratify the total population into the general population in the community and the healthcare workers and visitors in the healthcare facility, to account for nosocomial transmission in the case when an individual in the community may be exposed to an infection due to a visit to the healthcare facility. Equilibrium stability analysis is carried out to inform long-term outcomes of disease dynamics in the coupled community-health care facility system. The basic reproduction number is calculated and its dependence on the waiting time and various disease transmission rates is analyzed. Numerical simulations are performed with pertussis as the disease in question. The results show that waiting time only affects the peak number of infections in the waiting reception area. The results also indicate that transmission rate of infective residents in the community and the transmission rate of the infective visitors at the healthcare facility have decisive impact on disease eradication/persistence of the coupled system; while other modes of transmissions are less important, affecting the peak number of infections at best.

1. Introduction

In recent years, impact of travel on the spread of diseases has become an important topic of interest for public health policy formation and implementation, qualification of which has imposed a formidable challenge to modelers. Rvachev and Longini (1985) considered the airline network and used discrete time difference equations to study the global spread of influenza. Sattenspiel and Dietz (1995) proposed a model with travel between populations to describe the transmission dynamics of measles in the Caribbean island of Dominica. More recently, Arino and van den Driessche (2003a) formulated an SIS model with patches for residents of multiple cities (or discrete geographical regions) who may travel between them, and gave an explicit expression for the basic reproduction number for the model, which is a threshold between extinction and invasion of the disease, with simulations to illustrate that travel can both stabilize and destabilize the disease-free equilibrium. An SEIRS model was later

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considered by Arino and van den Driessche (2003b), with analytical results similar to those of Arino and van den Driessche (2003a). In these studies, travel was assumed to be independent of disease states. Relevant studies also include Wang and Mulone (2003) and Wang and Zhao (2004, 2005). Salmani and van den Driessche (2006) considered an SEIRS epidemic model for a population with travel between multiple patches, and established the global asymptotical stability of the disease-free equilibrium when the basic reproduction number is less than unity. They also presented a detailed study of the disease transmission dynamics for a disease with very short exposed and immune periods in an environment with two patches. Hsieh et al. (2007a) formulated an SEIRP model including partially immune individuals, and established relations, expressed by inequalities, between the basic reproduction number of the full model and the basic reproduction number of each patch in isolation. Their numerical simulations indicated that banning the border does not necessarily always have a positive impact on the overall spread of disease. Similar results were also obtained in Gojovic et al. (2009) using the USA and Canada as two separated patches connected primarily by border crossing. All these studies demonstrate that travel between patches can influence disease spread in a very complicated way.

The concepts of patch and travel can be considered in a very general setting, depending on how a heterogeneous population is partitioned into non-overlapping sub-populations with flows among them. In this study, by considering one of the patches as a major health care facility such as a hospital, we use a patch model to address nonsocomial infections and infections spread between the facility and its community. Nosocomial infections of many communicable diseases are widespread, they result in substantial morbidity, prolong hospital stay and lead to increase in direct patient care costs and mortality. Nosocomial transmission can occur between patients, hospital personnel or, less often, visitors, from people who may be infectious, in the incubation period (with mild or no symptoms), or even from chronic carriers. The US Centers for Disease Control and Prevention (USCDC) reports that nearly two million patients each year were infected while in a US hospital, with about 90,000 of them died from the infection. Deaths due to nosocomial infections is the fourth leading cause of death in US after heart disease, cancer, and strokes. The USCDC also estimated an additional cost of 5 billion dollars to US healthcare in 2000 due to nosocomial infections.

Although our understanding of the epidemiology of nosocomial transmission has increased dramatically over the last two decades, the incidence of nosocomial transmission continues to affect the hospitalized patients. This is particularly so for the 2003 SARS outbreak when nosocomial transmission occurred in all the affected regions. This first major infectious disease outbreak in the 21st century has been modeled and investigated intensively (e.g., Lipsitch et al., 2003; Riley et al., 2003; Chowell et al., 2003, 2004; Wang and Ruan, 2004; Gumel et al., 2004; Hsieh et al., 2004a, 2005, 2007b; Webb et al., 2004; Zeng et al., 2007), where model-based analysis clearly revealed the profound impact of nosocomial transmissions. In Taiwan, 301 (77.3%) of the 390 cases with a confirmed source of infection had been infected within a hospital, of which 67 (22.3%) had died. In particular, of 232 SARS patients who had been admitted to the National Taiwan University Hospital (NTUH) from March 14 to June 19, 31 (13.4%) did not have a history of travel, exposure to SARS patients, or a hospital visit within 10 days before illness. Hence the only contact history for these patients was at the NTUH Emergency Room (ER) (Chen et al., 2004). These 31 cases were almost evenly divided among 3 groups: ER patients, people who accompanied or visited the patients, and hospital staff. This ER outbreak finally led to a temporary shutdown of emergency service at NTUH on May 12 (Hsieh et al., 2004b). A major reason for this outbreak at NTUH was the closing of two nearby hospitals on April 24 and 26 due to nosocomial SARS outbreaks, which forced many individuals living in the neighborhood community who had been visiting these two hospitals regularly prior to shutdowns (including some individuals who had already been infected) to seek medical care at NTUH instead. This directly contributed to a more congested ER at NTUH, longer waiting time, and increased likelihood of contacting SARS infectives during this period before its shutdown. Since some of those infected in NTUH during this period later infected others in the community, their clinical visit and waiting time had a direct impact on their likelihood of being infected nosocomially and on the subsequent spread of SARS in the community.

Another more current example is the nosocomial transmission of *Bordetella pertussis*, also commonly called whooping cough, classically recognized as a disease of infants and children. Reported incidence in adolescents and adults has increased globally at a significant rate over the past decade or so (Edwards and Talbot, 2006). The incubation period for pertussis is typically seven to ten days with range of four to 21 days, after which there are usually some cold-like symptoms such as mild coughing, sneezing, or runny nose. After one to two weeks, the coughing classically develops into uncontrollable fits of severe coughing, mostly in children that could continue for weeks. One of the reasons for this increase is nosocomial infection of healthcare workers (HCWs) (Wright et al., 1999; De et al., 2000) by unsuspected (asymptomatic/subclinical) pertussis patients. Infected HCWs then serve as vectors of infection to other susceptible contacts, including their patients, other employees, and even their own children at home, resulting in substantial costs to the healthcare system. Prevention by vaccination is of primary importance given the seriousness of the disease in children. Although treatment is of little direct benefit to the person infected, antibiotics are recommended because they shorten the duration of infectiousness (Heininger, 2010).

In this work, we propose a deterministic compartmental model that focuses on waiting and clinical visit and their roles in disease transmission within a healthcare facility and in a community. We assume that individuals waiting at a hospital (or an emergency room) reception and waiting area can get infected during the waiting process due to the nosocomial transmission from others waiting there. We also assume that individuals can get infected during clinical visits due to the nosocomial transmission from other visiting individuals as well as infected hospital personnel. Those infected within the healthcare facility then serve as vectors of infection for community spread. Incorporating these assumptions into a patch model involving two patches, i.e., the community and the healthcare facility, leads naturally to a system of differential equations.

The paper is organized as follows. We formulate the model in Section 2. In Section 3, we obtain the basic reproduction number of the model explicitly in terms of model parameters and we describe the stability of the disease-free equilibrium when the basic reproduction number is below unity, and persistence of the disease and the existence of the positive equilibrium when the basic reproduction number is larger than unity. Numerical simulations, with pertussis as the disease being modeled, are given in Section 4, to demonstrate the impact of various model parameters, such as within-patch and between patch disease transmission, waiting/visiting, and others, that might affect the disease spread. Finally, we give our conclusions in Section 5.

2. Model formulation

We consider an SIR type of disease transmission, where the population is divided into three classes: susceptible individuals, infectious individuals, and recovered individuals. Susceptible

individuals become infected after contact with infectious individuals, and remain infective until they recover with immunity.

We consider an idealized situation where populations are stratified into two patches, patch 1 for those in the community and patch 2 for healthcare facilities, hence index i reflects this stratification. Individuals in patch 2 account for all HCWs, inpatients, and other people who regularly work in a healthcare facility. Namely we let $S_i(t)$, $I_i(t)$ and $R_i(t)$ be respectively the numbers of susceptible, infective, and recovered individuals of patch i who are currently (at time t) in the patch i. Note that residents of patch j who are currently visiting patch i ($i \neq j$) are not included in the above classes. We also let

$$N_i(t) = S_i(t) + I_i(t) + R_i(t).$$

Let $S_{12}^W(t)$, $I_{12}^W(t)$, and $R_{12}^W(t)$ be the numbers of the waiting susceptibles, infectives, and recovered at time t at the waiting/reception area, respectively. This category is designed specifically to examine the impact of outpatients on nosocomial infections. Also let $S_{12}^V(t)$, $I_{12}^V(t)$ and $R_{12}^V(t)$ be the numbers of visiting susceptibles, infectives and recovered at time t, who visit the residents in patch 2, or left the reception/waiting area after completing the waiting process, respectively.

In what follows, we describe the disease transmission dynamics during two different phases in the hospital: waiting and visit. For visiting individuals, we include outpatients (including ER patients) on clinical visits, their companions, visitors to inpatients in the wards, and visitors (friends/relatives, delivery persons, etc.) of the hospital staff. We assume that during the two phases of visits, the visitors first mingle (or mix) among themselves in a reception/waiting area, before proceeding to their respective visits to have contacts with physicians, nurses, inpatients, other hospital staff members, in addition to other visitors whom they might come in contact with during the visiting phase. We also assume homogeneous mixing and standard (frequency-dependent) incidence. We refer to Fig. 1 for a schematic illustration of the model. Descriptions of waiting and visiting phases are provided assuming that the patch 2 is a hospital. Similar explanations are possible when patch 2 is of other types of healthcare facilities.

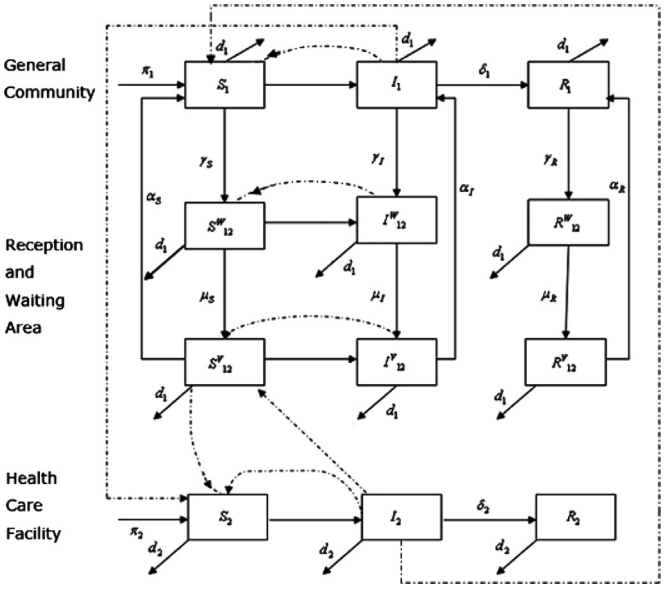

Fig. 1. Schematic diagram of disease progression (horizontal) and transmission (vertical).

2.1. Waiting

We consider the situation where some individuals from patch 1 leave patch 1 to enter patch 2: spending some waiting time in the reception/waiting area before visiting some residents of patch 2.

Let γ_S, γ_I and γ_R be the transfer rate of susceptible, infective, and recovered individuals going from patch 1 to patch 2, respectively. Therefore, while waiting in reception/waiting area we have

$$\begin{cases} \dot{S}_{12}^W = \gamma_S S_1 - \dfrac{\sigma S_{12}^W I_{12}^W}{N_{12}^W} - (\mu_S + d_1) S_{12}^W, \\ \dot{I}_{12}^W = \gamma_I I_1 + \dfrac{\sigma S_{12}^W I_{12}^W}{N_{12}^W} - (\mu_I + d_1) I_{12}^W, \\ \dot{R}_{12}^W = \gamma_R R_1 - (\mu_R + d_1) R_{12}^W, \\ N_{12}^W = S_{12}^W + I_{12}^W + R_{12}^W, \end{cases} \tag{2.1}$$

where σ is the disease transmission rate of one infective to a susceptible individual during the waiting process. μ_S, μ_I and μ_R are the progression rates to the visiting phase. d_1 is the natural death rate, which is very small.

2.2. Visiting

Next we consider the visiting phase. We have

$$\begin{cases} \dot{S}_{12}^V = \mu_S S_{12}^W - \dfrac{\beta_{12}^V S_{12}^V I_{12}^V}{N_{12}^V} - \dfrac{\beta_{21}^V S_{12}^V I_2}{N_2} - (\alpha_S + d_1) S_{12}^V, \\ \dot{I}_{12}^V = \mu_I I_{12}^W + \dfrac{\beta_{12}^V S_{12}^V I_{12}^V}{N_{12}^V} + \dfrac{\beta_{21}^V S_{12}^V I_2}{N_2} - (\alpha_I + d_1) I_{12}^V, \\ \dot{R}_{12}^V = \mu_R R_{12}^W - (\alpha_R + d_1) R_{12}^V, \\ N_{12}^V = S_{12}^V + I_{12}^V + R_{12}^V. \end{cases} \tag{2.2}$$

β_{12}^V is the disease transmission rate between infective and susceptible visitors from patch 1 during their visit in patch 2, β_{21}^V is the transmission rate of infective residents in patch 2 to susceptible visitors from patch 1. α_S, α_I and α_R are the respective transfer rate of susceptible, infective, and recovered individuals from patch 2 to patch 1 after their visit.

2.3. Community and healthcare facility

We assume that residents in the community (patch 1) can be infected by infected individuals present in the community, including those who had been in a healthcare facility and those who work in the healthcare facility (thus claiming residency in patch 2). In addition to general mixing in the community, residents in patch 2 get infected from other infectives in the healthcare facility which includes coworkers (I_2) and visitors (I_{12}^V). The transmission dynamics within each patch is given as follows. For patch 1,

$$\begin{cases} \dot{S}_1 = \pi_1 - \dfrac{(\beta_{11} I_1 + \beta_{21} I_2)}{N_1 + N_2} S_1 - (d_1 + \gamma_S) S_1 + \alpha_S S_{12}^V, \\ \dot{I}_1 = \dfrac{(\beta_{11} I_1 + \beta_{21} I_2)}{N_1 + N_2} S_1 - (d_1 + \delta_1 + \gamma_I) I_1 + \alpha_I I_{12}^V, \\ \dot{R}_1 = \delta_1 I_1 - (d_1 + \gamma_R) R_1 + \alpha_R R_{12}^V. \end{cases} \tag{2.3}$$

For patch 2,

$$\begin{cases} \dot{S}_2 = \pi_2 - d_2 S_2 - \dfrac{\beta_2 S_2 I_2}{N_2} - \dfrac{(\beta_{12} I_1 + \beta_{22} I_2)}{N_1 + N_2} S_2 - \dfrac{\overline{\beta}_{12} S_2 I_{12}^V}{N_{12}^V}, \\ \dot{I}_2 = \dfrac{\beta_2 S_2 I_2}{N_2} + \dfrac{(\beta_{12} I_1 + \beta_{22} I_2)}{N_1 + N_2} S_2 + \dfrac{\overline{\beta}_{12} S_2 I_{12}^V}{N_{12}^V} - (d_2 + \delta_2) I_2, \\ \dot{R}_2 = \delta_2 I_2 - d_2 R_2. \end{cases} \tag{2.4}$$

Here π_1 is the daily number of newborns (into the susceptible class) of patch 1; π_2 is the constant recruitment (into the susceptible class) of patch 2; d_2 is the natural death rate of residents in patch 2, β_{11} and β_2 are the respective disease transmission rates between residents in patch 1 and patch 2; δ_i is the recovery rate of the infectives in patch i; β_{21} is the transmission rate of the infective residents in patch 2 to the susceptibles in patch 1 in the community; β_{12} is the transmission rate of the infectious residents in patch 1 to the susceptible residents in patch 2 in the community; β_{22} is the transmission rate of the infectives in patch 2 to the susceptible residents in patch 2 in the community; and $\overline{\beta}_{12}$ is the disease transmission rate of infective visitors from patch 1 to susceptible residents in patch 2 in the healthcare facility. For pertussis, most infected adult healthcare workers have only mild cold-like symptoms and therefore are asymptomatically infectious while remaining at work. Moreover, in our model for pertussis, the recovery compartment as we defined in the model includes the removed individuals.

We further set the initial conditions for System (2.1)–(2.4) as follows:

$$S_{12}^l(0)\geq 0,\quad I_{12}^l(0)\geq 0,\quad R_{12}^l(0)\geq 0,\quad l=W,V,$$
$$S_i(0)\geq 0,\quad I_i(0)\geq 0,\quad R_i(0)\geq 0,\quad i=1,2. \tag{2.5}$$

It is very easy to verify that the solution of System (2.1)–(2.4) with nonnegative initial values is biologically realistic. That is, the solution is nonnegative and bounded for finite time T.

Lemma 2.1. *The solution of System (2.1)–(2.4) with an initial condition (2.5) is nonnegative for all $t\geq 0$.*

Lemma 2.2. *There exists a positive number $M>0$ such that for any solution of System (2.1)–(2.4) with initial condition (2.5), there must be a $T>0$ such that $S_{12}^l(t)\leq M$, $I_{12}^l(t)\leq M$, $R_{12}^l(t)\leq M$, $S_i(t)\leq M$, $I_i(t)\leq M$, and $R_i(t)\leq M$, for $l=W,V$, $i=1,2$, and $t\geq T$.*

Proof. For $V(t)=N_{12}^W(t)+N_{12}^V(t)+N_1(t)+N_2(t)$ and $m=\min\{d_1,d_2\}$, we have

$$\dot{V}(t)=\pi_1+\pi_2-d_1(N_{12}^W(t)+N_{12}^V(t)+N_1(t))-d_2N_2(t)\leq \pi_1+\pi_2-mV(t). \tag{2.6}$$

Hence, a straightforward argument of the standard comparison argument of differential equations yields that, for any $\varepsilon>0$, there exists $T>0$ such that $V(t)\leq M\triangleq(\pi_1+\pi_2)/m+\varepsilon$, for $t\geq T$. The proof is complete. □

3. Reproduction number and disease eradication

For System (2.1)–(2.4), we have the disease-free equilibrium $E_0=(S_{12}^W,I_{12}^W,R_{12}^W,S_{12}^V,I_{12}^V,R_{12}^V,S_1,I_1,R_1,S_2,I_2,R_2)=(S_{12}^{W^*},0,0,S_{12}^{V^*},0,0,S_1^*,0,0,S_2^*,0,0)$, where $S_{12}^{W^*}=\pi_1\gamma_S(d_1+\alpha_S)/a$, $S_{12}^{V^*}=\pi_1\mu_S\gamma_S/a$, $S_1^*=\pi_1(d_1+\alpha_S)(d_1+\mu_S)/a$, $S_2^*=\pi_2/d_2$, and $a=d_1(d_1+\mu_S)(d_1+\alpha_S)+d_1\gamma_S(\mu_S+d_1+\alpha_S)$.

In order to calculate the basic reproduction number $\mathcal{R}_0$, which is the mean number of secondary infections caused by an infected individual in a population of susceptibles, based on the next generation matrix (Diekmann et al., 1990; van den Driessche and Watmough, 2002), we define

$$\mathcal{F}=\begin{pmatrix} \frac{\sigma S_{12}^W I_{12}^W}{N_{12}^W} \\ \frac{\beta_{12}^V S_{12}^V I_{12}^V}{N_{12}^V}+\frac{\beta_{21}^V S_{12}^V I_2}{N_2} \\ \frac{(\beta_{11}I_1+\beta_{21}I_2)}{N_1+N_2}S_1 \\ \frac{\beta_2 S_2 I_2}{N_2}+\frac{(\beta_{12}I_1+\beta_{22}I_2)}{N_1+N_2}S_2+\frac{\overline{\beta}_{12}S_2I_{12}^V}{N_{12}^V} \end{pmatrix}$$

and

$$\mathcal{V}=\begin{pmatrix} (\mu_I+d_1)I_{12}^W-\gamma_I I_1 \\ (\alpha_I+d_1)I_{12}^V-\mu_I I_{12}^W \\ (d_1+\delta_1+\gamma_I)I_1-\alpha_I I_{12}^V \\ (d_2+\delta_2)I_2 \end{pmatrix}.$$

Then,

$$F=\begin{pmatrix} \sigma & 0 & 0 & 0 \\ 0 & \beta_{12}^V & 0 & \frac{\beta_{21}^V S_{12}^{V^*}}{S_2^*} \\ 0 & 0 & \frac{\beta_{11}S_1^*}{S_1^*+S_2^*} & \frac{\beta_{21}S_1^*}{S_1^*+S_2^*} \\ 0 & \frac{\overline{\beta}_{12}S_2^*}{S_{12}^{V^*}} & \frac{\beta_{12}S_2^*}{S_1^*+S_2^*} & \beta_2+\frac{\beta_{22}S_2^*}{S_1^*+S_2^*} \end{pmatrix},$$

$$V=\begin{pmatrix} \mu_I+d_1 & 0 & -\gamma_I & 0 \\ -\mu_I & \alpha_I+d_1 & 0 & 0 \\ 0 & -\alpha_I & d_1+\delta_1+\gamma_I & 0 \\ 0 & 0 & 0 & d_2+\delta_2 \end{pmatrix}.$$

Then $\mathcal{R}_0=\rho(FV^{-1})$, where $\rho(A)$ denotes the spectral radius of a matrix A, is the basic reproduction number for System (2.1)–(2.4).

Define

$$M_1=\begin{pmatrix} \sigma-(\mu_I+d_1) & 0 & \gamma_I & 0 \\ \mu_I & \beta_{12}^V-(\alpha_I+d_1) & 0 & \frac{\beta_{21}^V S_{12}^{V^*}}{S_2^*} \\ 0 & \alpha_I & \frac{\beta_{11}S_1^*}{S_1^*+S_2^*}-(d_1+\delta_1+\gamma_I) & \frac{\beta_{21}S_1^*}{S_1^*+S_2^*} \\ 0 & \frac{\overline{\beta}_{12}S_2^*}{S_{12}^{V^*}} & \frac{\beta_{12}S_2^*}{S_1^*+S_2^*} & \beta_2+\frac{\beta_{22}S_2^*}{S_1^*+S_2^*}-(d_2+\delta_2) \end{pmatrix}.$$

The stability modulus of an $n\times n$ matrix A, denoted by $s(A)$, is defined by

$$s(A)\triangleq\max\{\mathbb{R}ez : z \text{ is an eigenvalue of } A\}.$$

Clearly, M_1 is irreducible and has nonnegative off-diagonal elements. Then $s(M_1)$ is a simple eigenvalue of M_1 with a positive eigenvector (see Smith and Waltman, 1995, Theorem A.5). And note that if $M_1=F-V$, then the following is implied by the proof of van den Driessche and Watmough (2002, Theorem 2) with $J_1=M_1$.

Lemma 3.1. *The following equivalences hold:*

$$\mathcal{R}_0>1\Leftrightarrow s(M_1)>0,\quad \mathcal{R}_0<1\Leftrightarrow s(M_1)<0.$$

The linearization of (2.1)–(2.4) at E_0 is as follows:

$$\begin{cases} \dot{S}_{12}^W=\gamma_S S_1-\sigma I_{12}^W-(\mu_S+d_1)S_{12}^W, \\ \dot{I}_{12}^W=\gamma_I I_1+\sigma I_{12}^W-(\mu_I+d_1)I_{12}^W, \\ \dot{R}_{12}^W=\gamma_R R_1-(\mu_R+d_1)R_{12}^W. \end{cases} \tag{3.1}$$

$$\begin{cases} \dot{S}_{12}^V=\mu_S S_{12}^W-\beta_{12}^V I_{12}^V-\dfrac{\beta_{21}^V S_{12}^{V^*}}{S_2^*}I_2-(\alpha_S+d_1)S_{12}^V, \\ \dot{I}_{12}^V=\mu_I I_{12}^W+\beta_{12}^V I_{12}^V+\dfrac{\beta_{21}^V S_{12}^{V^*}}{S_2^*}I_2-(\alpha_I+d_1)I_{12}^V, \\ \dot{R}_{12}^V=\mu_R R_{12}^W-(\alpha_R+d_1)R_{12}^V. \end{cases} \tag{3.2}$$

$$\begin{cases} \dot{S}_1=-\dfrac{\beta_{11}S_1^*}{S_1^*+S_2^*}I_1-\dfrac{\beta_{21}S_1^*}{S_1^*+S_2^*}I_2-(d_1+\gamma_S)S_1+\alpha_S S_{12}^V, \\ \dot{I}_1=\dfrac{\beta_{11}S_1^*}{S_1^*+S_2^*}I_1+\dfrac{\beta_{21}S_1^*}{S_1^*+S_2^*}I_2-(d_1+\delta_1+\gamma_I)I_1+\alpha_I I_{12}^V, \\ \dot{R}_1=\delta_1 I_1-(d_1+\gamma_R)R_1+\alpha_R R_{12}^V. \end{cases} \tag{3.3}$$

$$\begin{cases} \dot{S}_2 = -d_2 S_2 - \dfrac{\beta_{12} S_2^*}{S_1^*+S_2^*} I_1 - \left(\beta_2 + \dfrac{\beta_{22} S_2^*}{S_1^*+S_2^*}\right) I_2 - \dfrac{\overline{\beta}_{12} S_2^*}{S_{12}^{V^*}} I_{12}^V, \\ \dot{I}_2 = \dfrac{\beta_{12} S_2^*}{S_1^*+S_2^*} I_1 + \dfrac{\overline{\beta}_{12} S_2^*}{S_{12}^{V^*}} I_{12}^V + \left(\beta_2 + \dfrac{\beta_{22} S_2^*}{S_1^*+S_2^*} - d_2 - \delta_2\right) I_2, \\ \dot{R}_2 = \delta_2 I_2 - d_2 R_2. \end{cases} \tag{3.4}$$

Then we have the characteristic equation

$$(\lambda+d_2)^2 g_1(\lambda) g_2(\lambda) g_3(\lambda) = 0,$$

where

$$g_1(\lambda) = (\lambda+\mu_S+d_1)(\lambda+d_1+\gamma_S)(\lambda+\alpha_S+d_1) - \mu_S\gamma_S\alpha_S,$$
$$g_2(\lambda) = (\lambda+\mu_R+d_1)(\lambda+d_1+\gamma_R)(\lambda+\alpha_R+d_1) - \mu_R\gamma_R\alpha_R,$$

and

$$\begin{aligned} g_3(\lambda) = (\lambda+\mu_I+d_1-\sigma)\Bigg\{ & (\lambda-\beta_{12}^V+\alpha_I+d_1)\left[\left(\lambda - \frac{\beta_{11} S_1^*}{S_1^*+S_2^*} + d_1+\delta_1+\gamma_I\right)\right. \\ & \times \left(\lambda - \beta_2 - \frac{\beta_{22} S_2^*}{S_1^*+S_2^*} + d_2+\delta_2\right) - \frac{\beta_{12}\beta_{21} S_1^* S_2^*}{(S_1^*+S_2^*)^2} - \frac{\beta_{21}^V S_{12}^{V^*}}{S_2^*} \\ & \left.\times \left[\frac{\alpha_I \beta_{12} S_2^*}{S_1^*+S_2^*} + \frac{\overline{\beta}_{12} S_2^*}{S_{12}^{V^*}}\left(\lambda - \frac{\beta_{11} S_1^*}{S_1^*+S_2^*} + d_1+\delta_1+\gamma_I\right)\right]\right\} \\ & - \mu_I\gamma_I\left[\alpha_I\left(\lambda - \beta_2 - \frac{\beta_{22} S_2^*}{S_1^*+S_2^*} + d_2+\delta_2\right) + \frac{\beta_{21} S_1^*}{S_1^*+S_2^*}\frac{\overline{\beta}_{12} S_2^*}{S_{12}^{V^*}}\right]. \end{aligned} \tag{3.5}$$

So, $g_1(\lambda) = \lambda^3 + a_1\lambda^2 + a_2\lambda + a_3$, where $a_1 = 3d_1 + \mu_S + \alpha_S + \gamma_S$, $a_2 = (d_1+\mu_S)(2d_1+\alpha_S+\gamma_S) + (d_1+\gamma_S)(d_1+\alpha_S)$,
$a_3 = (d_1+\mu_S)(d_1+\gamma_S)d_1 + (d_1+\mu_S+\gamma_S)d_1\alpha_S$. Then $a_i > 0$, $i = 1, 2, 3$, and
$a_1a_2 - a_3 = [a_1(d_1+\alpha_S) + (d_1+\mu_S)(d_1+\gamma_S)](2d_1+\mu_S+\gamma_S) + \mu_S\alpha_S\gamma_S > 0$.
Thus by Routh–Hurwitz criterion, $g_1(\lambda) = 0$ has roots with negative real parts. Similarly, we can also show that $g_2(\lambda) = 0$ has roots with negative real parts. So, stability of the disease-free equilibrium is totally determined by the distribution of solutions of $g_3(\lambda) = 0$. Note that $g_3(\lambda) = 0$ is the characteristic equation of the following

$$\begin{cases} \dot{I}_{12}^W = \gamma_I I_1 + \sigma I_{12}^W - (\mu_I + d_1) I_{12}^W, \\ \dot{I}_{12}^V = \mu_I I_{12}^W + \beta_{12}^V I_{12}^V + \dfrac{\beta_{21}^V S_{12}^{V^*}}{S_2^*} I_2 - (\alpha_I + d_1) I_{12}^V, \\ \dot{I}_1 = \dfrac{\beta_{11} S_1^*}{S_1^*+S_2^*} I_1 + \dfrac{\beta_{21} S_1^*}{S_1^*+S_2^*} I_2 - (d_1+\delta_1+\gamma_I) I_1 + \alpha_I I_{12}^V, \\ \dot{I}_2 = \dfrac{\beta_{12} S_2^*}{S_1^*+S_2^*} I_1 + \dfrac{\overline{\beta}_{12} S_2^*}{S_{12}^{V^*}} I_{12}^V + \left(\beta_2 + \dfrac{\beta_{22} S_2^*}{S_1^*+S_2^*} - d_2 - \delta_2\right) I_2. \end{cases} \tag{3.6}$$

Since

$$\begin{pmatrix} \dot{I}_{12}^W \\ \dot{I}_{12}^V \\ \dot{I}_1 \\ \dot{I}_2 \end{pmatrix} = M_1 \begin{pmatrix} I_{12}^W \\ I_{12}^V \\ I_1 \\ I_2 \end{pmatrix},$$

the solutions of $g_3(\lambda) = 0$ are the eigenvalues of M_1. Hence, by Lemma 3.1, if $\mathcal{R}_0 < 1$, all roots of $g_3(\lambda) = 0$ have negative real parts. If $\mathcal{R}_0 > 1$, $g_3(\lambda) = 0$ has at least one root with positive real part.

Theorem 3.1. *If $\mathcal{R}_0 < 1$, the disease-free equilibrium E_0 is asymptotically stable, but unstable if $\mathcal{R}_0 > 1$.*

From Lemma 3.1, we have $\mathcal{R}_0 = 1 \Leftrightarrow s(M_1) = 0$; i.e., $\lambda = 0$ is an eigenvalue of M_1. That is to say, $\mathcal{R}_0 = 1 \Leftrightarrow g_3(0) = 0$. Note that $g_3(+\infty) \to +\infty$. Then $g_3(0) < 0$ if and only if $g_3(\lambda) = 0$ has one positive root. Hence, $\mathcal{R}_0 < (>) 1 \Leftrightarrow g_3(0) > (<) 0$.

It is therefore important to calculate $g_3(0)$, which is given by

$$\begin{aligned} g_3(0) = (\mu_I + d_1 - \sigma)\Bigg\{ & (-\beta_{12}^V + \alpha_I + d_1)\left[\left(-\frac{\beta_{11} S_1^*}{S_1^*+S_2^*} + d_1+\delta_1+\gamma_I\right)\right. \\ & \times \left(-\beta_2 - \frac{\beta_{22} S_2^*}{S_1^*+S_2^*} + d_2+\delta_2\right) - \frac{\beta_{12}\beta_{21} S_1^* S_2^*}{(S_1^*+S_2^*)^2} - \frac{\beta_{21}^V S_{12}^{V^*}}{S_2^*} \\ & \left.\times \left[\frac{\alpha_I \beta_{12} S_2^*}{S_1^*+S_2^*} + \frac{\overline{\beta}_{12} S_2^*}{S_{12}^{V^*}}\left(-\frac{\beta_{11} S_1^*}{S_1^*+S_2^*} + d_1+\delta_1+\gamma_I\right)\right]\right\} \\ & - \mu_I\gamma_I\left[\alpha_I\left(-\beta_2 - \frac{\beta_{22} S_2^*}{S_1^*+S_2^*} + d_2+\delta_2\right) + \frac{\beta_{21} S_1^*}{S_1^*+S_2^*}\frac{\overline{\beta}_{12} S_2^*}{S_{12}^{V^*}}\right]. \end{aligned} \tag{3.7}$$

Although we are unable to derive an explicit expression for $\mathcal{R}_0$, the matrices F and V that do shed some lights on is dependent on the model parameters. In addition to the disease transmission rates being important parameters, the transfer rates between patches and the progression rate from waiting to visiting phase (i.e., waiting time) both appear in F or V, and hence play a role in the disease dynamics. We now present a theorem which assures the existence of a disease endemic equilibrium and disease persistence, when the basic reproduction number is larger than unity. The proof is given in the Appendix.

Theorem 3.2. *Let $R_0 > 1$. Then System (2.1)–(2.4) has one positive equilibrium, and there is an $\epsilon > 0$ such that every solution $(S_{12}^W(t), I_{12}^W(t), R_{12}^W(t), S_{12}^V(t), I_{12}^V(t), R_{12}^V(t), S_1(t), I_1(t)), R_1(t), S_2(t), I_2(t), R_2(t))$ of (2.1)–(2.4) with initial condition (2.5) and $I_{12}^W(0) + I_{12}^V(0) + I_1(0) + I_2(0) > 0$ satisfies*

$$\liminf_{t\to\infty} S_{12}^l(t) \geq \epsilon, \quad \liminf_{t\to\infty} I_{12}^l(t) \geq \epsilon, \quad \liminf_{t\to\infty} R_{12}^l(t) \geq \epsilon, \quad l = W, V,$$
$$\liminf_{t\to\infty} S_i(t) \geq \epsilon, \quad \liminf_{t\to\infty} I_i(t) \geq \epsilon, \quad \liminf_{t\to\infty} R_i(t) \geq \epsilon, \quad i = 1, 2.$$

In the next section, we will attempt to investigate the actual impact of the waiting time and disease transmission rates on the dynamic behavior of the system based on the results of our analysis, and to illustrate the biological significance of these results with the help of numerical simulations.

4. Numerical simulations

In this section, we perform numerical simulations with pertussis as the illness in question to illustrate our results. The time unit for the model parameters is in days. For the pertussis, the average infectious period is about three weeks, so $\delta_1 = \delta_2 = 1/21$ (Hethcote, 1997, 2000). Assuming that the average lifetime of a person is around 60 years, then the natural death rate is $d_1 = d_2 = 1/(60 \times 365) \approx 4.57 \times 10^{-5}$ (Hsieh et al., 2007a). Suppose that the waiting time is 3 h and the visiting time is 1 h, then $\mu_s = \mu_I = \mu_R = 8$, $\alpha_S = \alpha_I = \alpha_R = 24$. We also assume $\gamma_S = \gamma_R = 0.01$ and $\gamma_I = 0.3$, i.e., on the average 1% population in the community will move from patch 1 to patch 2 every day while an infected (symptomatic) person goes to patch 2 (hospital) within 3.3 days. We let $\beta_{11} = 0.2$, and all the other transmission rates are 0.1. We also assume that the daily births in the community are $\pi_1 = 5$ (assuming that the yearly birth rate is approximately 1.8% in the community of 100 000) and the recruitment in the health facility is $\pi_2 = 0.1$ (assuming that the yearly recruitment rate in the healthcare facility is also 1.8%). The model parameters and their values are listed in Table 1.

In all simulations, we use initial values of (200, 100, 50, 100, 50, 30, 100 000, 1000, 500, 2000, 100, 100). That is, we consider a hypothetical scenario of a community with a population of around 100 000, hospital(or a healthcare system) with around 2000 staff members (including non-medical workers) (World Health Organization, 2012; Bigbee, 2007), and initially a low pertussis prevalence (around 1%). The first simulation result is given in Fig. 2, where for the blue trajectory we have $\mu_S = \mu_I = \mu_R = 8$, i.e., mean waiting time of 3 h, and subsequently $R_0 = 5.73$. Note that

Table 1
Summary table for model parameters and their values used in simulations.

Parameter	Definition	Value
γ_S	Transfer rate of susceptible individual leaving patch 1 to patch 2	0.01
γ_I	Transfer rate of infective individual leaving patch 1 to patch 2	0.3
γ_R	Transfer rate of recovered individual leaving patch 1 to patch 2	0.01
μ_S	Progression rate of susceptible individual to visiting phase	8
μ_I	Progression rate of infective individual to visiting phase	8
μ_R	Progression rate of recovered individuals to visiting phase	8
α_S	Transfer rate susceptible individual leaving patch 2 to patch 1 after the visiting	24
α_I	Transfer rate infective individual leaving patch 2 to patch 1 after the visiting	24
α_R	Transfer rate recovered individual leaving patch 2 to patch 1 after the visiting	24
σ	Disease transmission rate during the waiting process	0.1
d_1, d_2	Natural death rates of patch 1 and patch 2, respectively	4.57×10^{-5} (Hsieh et al., 2007a)
π_1	Daily number of newborns in patch 1	5.0
π_2	Recruitment rate of patch 2	0.1
β_{11}	Disease transmission rate between residents in patch 1	0.2
β_2	Disease transmission rate between residents in patch 2	0.1
β_{12}^V	Disease transmission rate between visitors from patch 1 during their visit stay in patch 2	0.1
β_{21}^V	Disease transmission rate of infective residents in patch 2 to susceptible visitors from patch 1	0.1
β_{21}	Disease transmission rate of infectious residents in patch 2 to susceptibles in patch 1 in the community	0.2
β_{12}	Disease transmission rate of infectious residents in patch 1 to susceptible residents in patch 2 in the community	0.1
β_{22}	Disease transmission rate of infectives in patch 2 to susceptible residents in patch 2 while in the community	0.1
$\overline{\beta}_{12}$	Disease transmission rate of infective visitors from patch 1 to susceptible residents in patch 2 in the healthcare facility	Variable
δ_1, δ_2	Recovery rate of infectives in patch 1 and patch 2, respectively	$\frac{1}{21}$ (De et al., 2000; Hethcote, 1997)

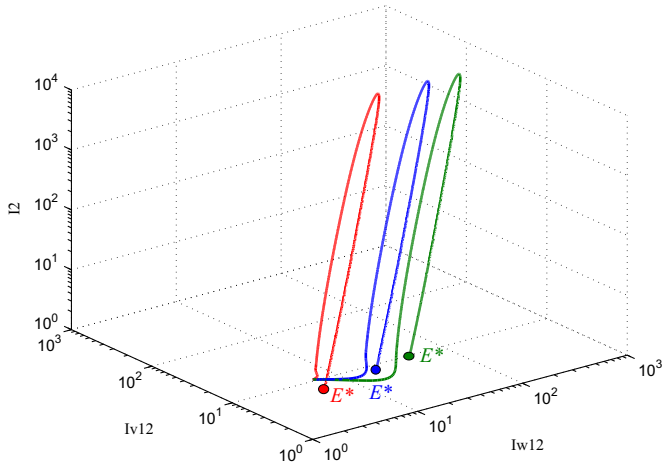

Fig. 2. $\overline{\beta}_{12} = 0.1$ and all other parameter values are as shown in Table 1. System (2.1)–(2.4) has a global stable endemic equilibrium E*. Blue line: $\mu_S = \mu_I = \mu_R = 8$, $R_0 = 5.73$. Green line: $\mu_S = \mu_I = \mu_R = 4$, $R_0 = 5.79$. Red line: $\mu_S = \mu_I = \mu_R = 24$, $R_0 = 5.69$. All axes are in log base 10 scale. (For interpretation of the references to color in this figure caption, the reader is referred to the web version of this paper.)

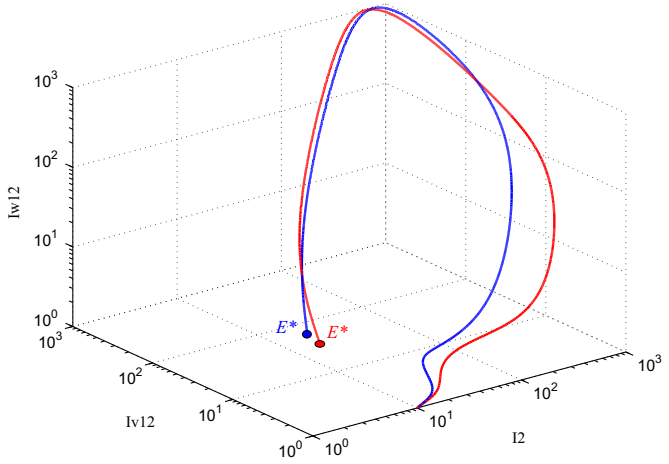

Fig. 3. Blue line: $\overline{\beta}_{12} = 0.3$. $R_0 = 7.30$. All other parameters are shown in Table 1 and initial values are as in Fig. 2. System (2.1)–(2.4) has a global stable endemic equilibrium E*. Red line: $\overline{\beta}_{12} = 2$. $R_0 = 13.49$. All axes are in log base 10 scale. (For interpretation of the references to color in this figure caption, the reader is referred to the web version of this paper.)

the basic reproduction numbers for the pertussis models in Hethcote (2000) are found to be 3.7 and 5.4. Also note that in Fig. 2 as well as in the next figure, all axes are given in log base 10 scale, to better highlight some scenarios where the outbreak initially peaks at a large number of infections, but eventually goes to the DFE or approaches an endemic equilibrium with low prevalence.

The outbreak increases initially, peaking for all infective classes at approximately $t = 37$, then decreases to 0 as the system tends to the globally asymptotically stable endemic equilibrium E^*. If we further increase the waiting time from 3 h to 6 h ($\mu_S = \mu_I = \mu_R = 4$ for green trajectory) while keeping all other parameter values the same, $R_0 = 5.79$ is only slightly increased and the peak is almost the same as the blue trajectory.

However, the peak number of the infectives in the waiting/reception area (I_{12}^W) increases (comparing the green trajectory with the blue trajectory) as the waiting time increases while the other three infective classes are not noticeably affected. Therefore, a longer waiting time at clinics leads to a more significant increase in peak number of infections in the waiting/reception area.

On the other hand, if we decrease the waiting time to 30 min by letting $\mu_S = \mu_I = \mu_R = 24$ as in the red trajectory, $R_0 = 5.69$ decreases only slightly and the system still approaches an endemic equilibrium. Hence decrease in waiting time does not drastically alter the dynamic behavior of the system.

In Fig. 3, we now increase the transmission rate of infective visitors in the community to susceptible residents in the healthcare facility $\overline{\beta}_{12}$ from 0.1 to 0.3 while keeping all other parameters the same as in Fig. 2, then we have $R_0 = 7.30$ and the system still approaches an endemic equilibrium (blue trajectory), as the analytical result predicts. Interestingly, an increase in $\overline{\beta}_{12}$ causes the peak number of infectives in the healthcare facility (I_2) to increase, while having no noticeable effect on the numbers of any other infec'tive class. The red trajectory, with an even higher transmission rate $\overline{\beta}_{12} = 2$, further confirms our observation.

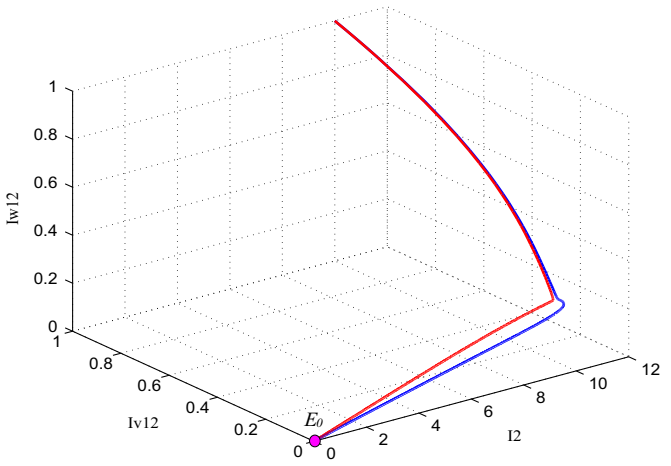

Fig. 4. $\beta_{11}=0.02$, $\beta_2=0.01$, $\gamma_I=0.02$. All other parameters are shown in Table 1 and initial values are as in Fig. 2. Blue line: $\overline{\beta}_{12}=0.05$ and R_0=0.93. System (2.1)–(2.4) has a globally stable disease-free equilibrium E_0=(136.5, 0, 0, 45.5, 0, 0, 109 227.1, 0, 0, 2188.2, 0, 0). Red line: $\overline{\beta}_{12}=0.01$ and System (2.1)–(2.4) also approaches E_0. (For interpretation of the references to color in this figure caption, the reader is referred to the web version of this paper.)

However, if we decrease the transmission rates between residents in the community $\beta_{11}=0.02$ and in the healthcare facility $\beta_2=0.01$, and the transmission rate of infective visitors to $\gamma_I=0.02$, with all other parameters and initial values the same as in Fig. 2, then $R_0=0.93<1$. Subsequently, System (2.1)–(2.4) has a globally stable disease-free equilibrium E_0=(136.5, 0, 0, 45.5, 0, 0, 109 227.1, 0, 0, 2188.2, 0, 0) given blue trajectory in Fig. 4. If we also decrease the transmission rate of infective visitors in the community to susceptible residents in the healthcare facility $\overline{\beta}_{12}=0.01$, we get an even smaller R_0=0.776 and System (2.1)–(2.4) also approaches E_0, as in the red trajectory in Fig. 4.

Extensive numerical simulations with different transmission rates indicate that only decreasing β_{11}, β_2, $\overline{\beta}_{12}$ can decrease R_0 down to less than 1, while decrease in other transmission rates results only in minor decrease in R_0. Therefore, the transmission rates of the infectives in the community and in the healthcare facility are most impactful in determining the dynamic behavior of the epidemic.

5. Conclusions/discussion

Although the waiting time of visitors at healthcare clinics does not affect the asymptotic (long-term) behaviors of the system, an increase in waiting time can lead to an increase in peak number of infections among the susceptibles waiting in the waiting/reception area while not affecting the number of infections among any other groups of susceptibles (Fig. 2). During the outbreak of SARS cases that were linked to the NTUH Emergency Room between April 29 and May 16, 2003, 11 of 31 (35%) infections that were determined to have occurred in the NTUH ER had onset within 2 short days during May 11–12, leading to a complete shutdown of the ER on May 12 (Chen et al., 2004). Hence, a long waiting time in a crowded ER might very well contribute to a drastic upsurge in cases in a short time, resulting in a stern challenge to hospital emergency healthcare response and perhaps even in the need for extreme intervention measures. Note further that the waiting times of both the susceptibles and the infectives (respectively μ_S and μ_I) appear in the formula for R_0, indicating that how long these individuals are kept waiting in the waiting-reception area does impact the likelihood of an outbreak, although not the qualitative dynamic behaviors of the system.

An increase in transmission rate of infective visitors in the community to susceptible residents in the healthcare facility $\overline{\beta}_{12}$ causes only the peak number of infectives in the healthcare facility (I_2 or the healthcare facility staff) to increase, while having no noticeable effect on the numbers of any other infective class (Fig. 3). Thus our simulations highlight the important role that infective visitors may play in a nosocomial outbreak.

Furthermore, only the disease transmission rates between residents in the community β_{11} and in the healthcare facility β_2, along with the transmission rate of the infective visitors from the community to the susceptible residents in the healthcare facility $\overline{\beta}_{12}$, are important in affecting the dynamic behavior of the epidemic model (Fig. 4). That is, sufficient decrease in these three rates can effectively lower R_0 down to below 1 and thus alter the asymptotic behavior of the system from globally stable endemicity to a disease-free state. All other transmission rates have little effect in decreasing R_0. Therefore, in order to eradicate the epidemic, it is critical to prevent infections by the infective residents in the community and in the healthcare facility, and by the infective visitors from community to residents in healthcare facility. Preventing infections among infective visitors in the healthcare facility β_{12}^V and through infective residents of healthcare facility to susceptible visitors β_{21}^V are, on the other hand, comparatively not as crucial as the aforementioned control measures. Similarly for the transmission rates in the community involving the residents of healthcare facility namely, β_{12}, β_{21}, and β_{22}, which do not lead to a noticeable change in R_0.

We have isolated three modes of transmission that are candidates for effective infection prevention: transmissions between residents in the community and between residents in the healthcare facility, and transmission from infective visitors to susceptible residents in the healthcare facility. Noting that the residents in healthcare facility are in fact the healthcare workers and other staff in the facility, increased infections among the healthcare facility staff is a certain sign of a nosocomial outbreak. Subsequently, preventing infections among healthcare staff is of the highest priority as a public health measure in prevention of nosocomial outbreaks.

Finally, although we use pertussis as the illness modeled in our numerical simulation study, there are many diseases that are transmitted by healthcare workers. An example is the outbreak of antibiotic resistant bacteria, where the healthcare workers might be contaminated for a short duration until they properly wash their hands, but never become infected. However, they could conceivably cause infections among patients through contacts with the patients while being contaminated (e.g., D'Agataa et al., 2007). It would be interesting to see how our model structure can be modified to address this type of contamination–infection interaction. Moreover, studies have shown that there are many ways to reduce infections among residents, e.g., frequent hand washing and vaccination of unsuspected pertussis patients, including asymptomatically infected healthcare workers. These are not the focus of the present study. How to incorporate a wide range of interventions at the community level and the equally wide range of contamination reduction measures in the healthcare facility in a comprehensive model to understand the infection dynamics of the coupled facility-community remains an interesting and challenging task for future studies.

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Appendix A. Proof of Theorem 3.2

Proof. From (2.3) and (2.4), we have

$$\begin{cases} \dot{S}_1 \geq \pi_1 - (\beta_1^* + d_1 + \gamma_S)S_1, \\ \dot{S}_2 \geq \pi_2 - (\beta_2 + \beta_2^* + \overline{\beta}_{12} + d_2)S_2, \end{cases}$$

where $\beta_1^* = \max\{\beta_{11}, \beta_{21}\}$, $\beta_2^* = \max\{\beta_{12}, \beta_{22}\}$. Then, $S_1(t)$ and $S_2(t)$ are ultimately bounded below by some positive constant, for example, $m_{S_1} = \pi_1/(2(\beta_1^* + d_1 + \gamma_S))$ and $m_{S_2} = \pi_2/(2(\beta_2 + \beta_2^* + \overline{\beta}_{12} + d_2))$, which are independent of the initial conditions. Then there is a $t_1 > 0$ such that $S_1(t) \geq m_{S_1}$, $S_2(t) \geq m_{S_2}$ for $t \geq t_1$. By (2.1), we have

$$\dot{S}_{12}^W = \gamma_S S_1 - \frac{\sigma S_{12}^W I_{12}^W}{N_{12}^W} - (\mu_S + d_1)S_{12}^W \geq \gamma_S m_{S_1} - (\sigma + \mu_S + d_1)S_{12}^W.$$

for $t \geq t_1$. By a standard comparison argument, there exists $t_2 > t_1 > 0$, such that $S_{12}^W \geq m_{S_{12}^W} \triangleq \gamma_S m_{S_1}/(2(\sigma + \mu_S + d_1))$ for $t \geq t_2$, which implies that S_{12}^W is ultimately bounded below by some positive constant. Similarly, we can show that S_{12}^V is ultimately bounded below by some positive constant. And so is R_{12}^W, R_{12}^V, R_i, $i = 1, 2$, if I_{12}^W, I_{12}^V, I_i, $i = 1, 2$, are ultimately bounded below by some positive constant independent of initial values. Therefore, it suffices to prove that

$$\liminf_{t\to\infty} I_{12}^l(t) \geq \epsilon, \ \ l = W, V, \liminf_{t\to\infty} I_i(t) \geq \epsilon, \ \ i = 1, 2.$$

Define

$$X = \{(S_{12}^W, I_{12}^W, R_{12}^W, S_{12}^V, I_{12}^V, R_{12}^V, S_1, I_1, R_1, S_2, I_2, R_2) \in \mathbb{R}_+^{12} : i = 1, 2\},$$

$$X_0 = \{(S_{12}^W, I_{12}^W, R_{12}^W, S_{12}^V, I_{12}^V, R_{12}^V, S_1, I_1, R_1, S_2, I_2, R_2) \in X : I_{12}^W + I_{12}^V + I_1 + I_2 > 0\},$$

$$\partial X_0 = X \backslash X_0.$$

Next we will show that System (2.1)–(2.4) is uniformly persistent with respect to $(X_0, \partial X_0)$. It is easy to verify that X and X_0 are positively invariant with respect to System (2.1)–(2.4). Furthermore, by Lemma 2.2, there exists a compact set B in which all solutions of (2.1)–(2.4) initiated in X will enter and remain forever after. The compactness condition $(C_{4.2})$ in Thieme (1993) is easily verified for this set B. Let $\Phi(t) = (S_{12}^W(t), I_{12}^W(t), R_{12}^W(t), S_{12}^V(t), I_{12}^V(t), R_{12}^V(t), S_1(t), I_1(t), R_1(t), S_2(t), I_2(t), R_2(t))$. Denote

$$M_\partial = \{\Phi(0) : \Phi(t) \in \partial X_0, t \geq 0\}.$$

We now show that

$$M_\partial = \{(S_{12}^W, 0, R_{12}^W, S_{12}^V, 0, R_{12}^V, S_1, 0, R_1, S_2, 0, R_2) : S_{12}^W \geq 0, \ R_{12}^W \geq 0, \ S_{12}^V \geq 0, R_{12}^V \geq 0, S_i \geq 0, R_i \geq 0, \ i = 1, 2\}. \tag{A.1}$$

Suppose that $\Phi(0) \in M_\partial$. It suffices to show that $I_{12}^W = 0$, $I_{12}^V = 0$, $I_i(t) = 0$ for any $t \geq 0$ and i=1,2. If it is not true, then there exists $t_0 \geq 0$ such that $I_{12}^W(t_0) + I_{12}^V(t_0) + I_1(t_0) + I_2(t_0) > 0$. Then $\Phi(t_0) \in X_0$ contradicts to $\Phi(0) \in M_\partial$. This proves (A.1).

Denote the ω-limit set of the solution of System (2.1)–(2.4) starting in $\Phi(0) \in X$ by $\omega(\Phi(0))$. Let

$$\Omega = \cup \{\omega(\Phi(0)) : \Phi(0) \in M_\partial\}.$$

Restricting System (2.1)–(2.4) on M_∂ gives

$$\begin{cases} \dot{S}_{12}^W = \gamma_S S_1 - (\mu_S + d_1)S_{12}^W, \\ \dot{R}_{12}^W = \gamma_R R_1 - (\mu_R + d_1)R_{12}^W, \\ \dot{S}_{12}^V = \mu_S S_{12}^W - (\alpha_S + d_1)S_{12}^V, \\ \dot{R}_{12}^V = \mu_R R_{12}^W - (\alpha_R + d_1)R_{12}^V, \\ \dot{S}_1 = \pi_1 - (d_1 + \gamma_S)S_1 + \alpha_S S_{12}^V, \\ \dot{R}_1 = \alpha_R R_{12}^V - (d_1 + \gamma_R)R_1, \\ \dot{S}_2 = \pi_2 - d_2 S_2, \\ \dot{R}_2 = -d_2 R_2. \end{cases} \tag{A.2}$$

It is easy to verify that System (A.2) has an unique equilibrium $E_1 = (S_{12}^{W^*}, 0, S_{12}^{V^*}, 0, S_1^*, 0, S_2^*, 0)$. Thus $(S_{12}^{W^*}, 0, 0, S_{12}^{V^*}, 0, 0, S_1^*, 0, 0, S_2^*, 0, 0)$ is the unique equilibrium of System (2.1)–(2.4) in M_∂. It is easy to check that E_1 is locally asymptotically stable. This implies that E_1 is globally asymptotically stable since (A.2) is a linear system. Therefore $\Omega = \{E_0\}$. And E_0 is a covering of Ω, which is isolated and is acyclic(since there exists no solution in M_∂ which links E_0 to itself). Finally, the proof of the persistence will be done if we show E_0 is a weak repeller for X_0, i.e.

$$\limsup_{t\to\infty} dist(\Phi(t), E_0) > 0,$$

where $\Phi(t)$ is an arbitrarily solution with initial value in X_0. By Leenheer and Smith (2003, Proof of Lemma 3.5), we need only prove

$$W^s(E_0) \cap X_0 = \varnothing, \tag{A.3}$$

where $W^s(E_0)$ is the stable manifold of E_0. Suppose that it is not true, then there exists a solution $\Phi(t)$ in X_0, such that

$$\begin{aligned} &\lim_{t\to\infty} S_{12}^W(t) = S_{12}^{W^*}, \quad \lim_{t\to\infty} S_{12}^V(t) = S_{12}^{V^*}, \\ &\lim_{t\to\infty} S_1 = S_1^*, \\ &\lim_{t\to\infty} S_2(t) = S_2^*, \quad \lim_{t\to\infty} I_i(t) = 0, \\ &\lim_{t\to\infty} I_{12}^W(t) = \lim_{t\to\infty} R_{12}^W(t) = 0, \\ &\lim_{t\to\infty} I_{12}^V(t) = \lim_{t\to\infty} R_{12}^V(t) = 0, \\ &\lim_{t\to\infty} R_i(t) = 0, \ \ i = 1, 2. \end{aligned}$$

Then, for $\delta > 0$, there exists $T > 0$ such that

$$\begin{aligned} &S_{12}^{W^*} - \delta < S_{12}^W(t) < S_{12}^{W^*} + \delta, \quad S_{12}^{V^*} - \delta < S_{12}^V(t) < S_{12}^{V^*} + \delta, \\ &S_1^* - \delta < S_1 < S_1^* + \delta, \quad S_2^* - \delta < S_2 < S_2^* + \delta, \quad 0 \leq I_{12}^W(t) < \frac{\delta}{2}, \\ &0 \leq R_{12}^W(t) < \frac{\delta}{2}, \quad 0 \leq I_{12}^V(t) < \frac{\delta}{2}, \quad 0 \leq R_{12}^V(t) < \frac{\delta}{2}, \\ &0 \leq I_i(t) < \frac{\delta}{2}, \quad 0 \leq R_i(t) < \frac{\delta}{2}, \end{aligned} \tag{A.4}$$

for all $t \geq T$ and i=1,2. Then for $t \geq T$, we have

$$\begin{aligned} \frac{\beta_{21}^V S_{12}^V I_2}{N_2} &\geq \frac{\beta_{21}^V (S_{12}^{V^*} - \delta)}{S_2^* + 2\delta} I_2 = \frac{\beta_{21}^V S_{12}^{V^*}}{S_2^*} I_2 - \frac{\beta_{21}^V (2S_{12}^{V^*} + S_2^*)\delta}{(S_2^* + 2\delta)S_2^*} I_2 \\ &\geq \frac{\beta_{21}^V S_{12}^{V^*}}{S_2^*} I_2 - \frac{\beta_{21}^V (2S_{12}^{V^*} + S_2^*)\delta}{(S_2^*)^2} I_2, \end{aligned}$$

$$\begin{aligned} \frac{S_1}{N_1 + N_2} &\geq \frac{S_1^* - \delta}{S_1^* + S_2^* + 2\delta} = \frac{S_1^*}{S_1^* + S_2^*} \\ &\quad - \frac{(3S_1^* + S_2^*)\delta}{(S_1^* + S_2^*)(S_1^* + S_2^* + 2\delta)} \end{aligned}$$

$$\geq \frac{S_1^*}{S_1^*+S_2^*}-\frac{(3S_1^*+S_2^*)\delta}{(S_1^*+S_2^*)^2},$$

$$\frac{S_2}{N_1+N_2}\geq \frac{S_2^*-\delta}{S_1^*+S_2^*+2\delta}=\frac{S_2^*}{S_1^*+S_2^*}-\frac{(S_1^*+3S_2^*)\delta}{(S_1^*+S_2^*)(S_1^*+S_2^*+2\delta)}$$
$$\geq \frac{S_2^*}{S_1^*+S_2^*}-\frac{(S_1^*+3S_2^*)\delta}{(S_1^*+S_2^*)^2},$$

$$\frac{\overline{\beta}_{12}S_2I_{12}^V}{N_{12}^V}\geq \frac{\overline{\beta}_{12}(S_2^*-\delta)}{S_{12}^{V^*}+2\delta}I_{12}^V=\frac{\overline{\beta}_{12}S_2^*}{S_{12}^{V^*}}I_{12}^V-\frac{\overline{\beta}_{12}(S_{12}^{V^*}+2S_2^*)\delta}{(S_{12}^{V^*}+2\delta)S_{12}^{V^*}}I_{12}^V$$
$$\geq \frac{\overline{\beta}_{12}S_2^*}{S_{12}^{V^*}}I_{12}^V-\frac{\overline{\beta}_{12}(S_{12}^{V^*}+2S_2^*)\delta}{(S_{12}^{V^*})^2}I_{12}^V.$$

Then from (2.1)–(2.4), we have

$$\begin{cases}
\dot{I}_{12}^W \geq \gamma_I I_1+\dfrac{\sigma(S_{12}^{W^*}-\delta)}{S_{12}^{W^*}}I_{12}^W-(\mu_I+d_1)I_{12}^W,\\
\dot{I}_{12}^V \geq \mu_I I_{12}^W+\dfrac{\beta_{12}^V(S_{12}^{V^*}-\delta)}{S_{12}^{V^*}}I_{12}^V+\dfrac{\beta_{21}^V S_{12}^{V^*}}{S_2^*}I_2-\dfrac{\beta_{21}^V(2S_{12}^{V^*}+S_2^*)\delta}{(S_2^*)^2}I_2-(\alpha_I+d_1)I_{12}^V,\\
\dot{I}_1 \geq \left[\dfrac{S_1^*}{S_1^*+S_2^*}-\dfrac{(3S_1^*+S_2^*)\delta}{(S_1^*+S_2^*)^2}\right](\beta_{11}I_1+\beta_{21}I_2)-(d_1+\delta_1+\gamma_I)I_1+\alpha_I I_{12}^V,\\
\dot{I}_2 \geq \dfrac{\beta_2(S_2^*-\delta)}{S_2^*}I_2+\left[\dfrac{S_2^*}{S_1^*+S_2^*}-\dfrac{(S_1^*+3S_2^*)\delta}{(S_1^*+S_2^*)^2}\right](\beta_{12}I_1+\beta_{22}I_2)+\dfrac{\overline{\beta}_{12}S_2^*}{S_{12}^{V^*}}I_{12}^V\\
\quad -\dfrac{\overline{\beta}_{12}(S_{12}^{V^*}+2S_2^*)\delta}{(S_{12}^{V^*})^2}I_{12}^V-(d_2+\delta_2)I_2,
\end{cases} \tag{A.5}$$

for all $t\geq T$. Define

$$M_2=\begin{pmatrix}
\frac{\sigma}{S_{12}^{W^*}} & 0 & 0 & 0\\
0 & \frac{\beta_{12}^V}{S_{12}^{V^*}} & 0 & \frac{\beta_{21}^V(2S_{12}^{V^*}+S_2^*)}{(S_2^*)^2}\\
0 & 0 & \frac{\beta_{11}(3S_1^*+S_2^*)}{(S_1^*+S_2^*)^2} & \frac{\beta_{21}(3S_1^*+S_2^*)}{(S_1^*+S_2^*)^2}\\
0 & \frac{\overline{\beta}_{12}(S_{12}^{V^*}+2S_2^*)}{(S_{12}^{V^*})^2} & \frac{\beta_{12}(S_1^*+3S_2^*)}{(S_1^*+S_2^*)^2} & \frac{\beta_2}{S_2^*}+\frac{\beta_{22}(S_1^*+3S_2^*)}{(S_1^*+S_2^*)^2}
\end{pmatrix},$$

then, (A.4) implies that

$$\begin{pmatrix}\dot{I}_{12}^W\\ \dot{I}_{12}^V\\ \dot{I}_1\\ \dot{I}_2\end{pmatrix}\geq (M_1-\delta M_2)\begin{pmatrix}I_{12}^W\\ I_{12}^V\\ I_1\\ I_2\end{pmatrix}$$

for $t\geq T$.

Since $\mathcal{R}_0>1$ implies $s(M_1)>0$, we can choose $\delta>0$ small enough such that $s(M_1-\delta M_2)>0$. Since matrix $M_1-\delta M_2$ has a positive eigenvalue $s(M_1-\delta M_2)$ with a positive eigenvector, it is easy to see that $I_{12}^W\to\infty$, $I_{12}^V\to\infty$, $I_1\to\infty$, $I_2\to\infty$ as $t\to\infty$, a contradiction to (A.4). Thus (A.3) holds. By Zhao (1995, Theorem 2.4), System (2.1)–(2.4) has an equilibrium $E^*=(\overline{S}_{12}^W,\overline{I}_{12}^W,\overline{R}_{12}^W,\overline{S}_{12}^V,\overline{I}_{12}^V,\overline{R}_{12}^V,\overline{S}_1,\overline{I}_1,\overline{R}_1,\overline{S}_2,\overline{I}_2,\overline{R}_2)\in X_0$. Then, $\overline{I}_{12}^W+\overline{I}_{12}^V+\overline{I}_1(t)+\overline{I}_2>0$, without loss of generality, we suppose $\overline{I}_{12}^W>0$. Let $\overline{N}_1=\overline{S}_1+\overline{I}_1+\overline{R}_1$, $\overline{N}_2=\overline{S}_2+\overline{I}_2+\overline{R}_2$, $\overline{N}_{12}^V=\overline{S}_{12}^V+\overline{I}_{12}^V+\overline{R}_{12}^V$. From the first equations of (2.3) and (2.4), it follows that $\overline{S}_1>0$ and $\overline{S}_2>0$. Otherwise, we have $\pi_1+\alpha_S\overline{S}_{12}^V=0$ and $\pi_2=0$, which is a contradiction. By the second equation of (2.2), $\overline{I}_{12}^V>0$. Otherwise, we have $\mu_I\overline{I}_{12}^W+\beta_{21}^V\overline{S}_{12}^V\overline{I}_2/\overline{N}_2=0$, again a contradiction. If $\overline{I}_1=0$, then by the second equation of (2.3), we have $\beta_{21}\overline{S}_1\overline{I}_2/(\overline{N}_1+\overline{N}_2)+\alpha_I\overline{I}_{12}^V=0$, a contradiction, thus $\overline{I}_1>0$. Hence, $\overline{R}_1=(\delta_1\overline{I}_1+\alpha_R\overline{R}_{12}^V)/(\gamma_R+d_1)>0$, $\overline{R}_{12}^W=\gamma_R\overline{R}_1/(\mu_R+d_1)>0$, $\overline{R}_{12}^V=\mu_R\overline{R}_{12}^W/(\alpha_R+d_1)>0$. If $\overline{I}_2=0$, then by the second equation of (2.4), we have $\beta_{12}\overline{S}_2\overline{I}_1/(\overline{N}_1+\overline{N}_2)+\overline{\beta}_{12}\overline{S}_2\overline{I}_{12}^V/\overline{N}_{12}^V=0$, a contradiction, thus $\overline{I}_2>0$. Hence, $\overline{R}_2=\delta_2\overline{I}_2/d_2>0$. If $\overline{S}_{12}^W=0$, then by the first equation of (2.1), we have $\gamma_S\overline{S}_1=0$ which is a contradiction, then $\overline{S}_{12}^W>0$ and $\overline{S}_{12}^V=0$. Otherwise, by the first equation of (2.2), we have $\mu_S\overline{S}_{12}^W=0$, a contradiction again. Thus we have $E^*=(\overline{S}_{12}^W,\overline{I}_{12}^W,\overline{R}_{12}^W,\overline{S}_{12}^V,\overline{I}_{12}^V,\overline{R}_{12}^V,\overline{S}_1,\overline{I}_1,\overline{R}_1,\overline{S}_2,\overline{I}_2,\overline{R}_2)>0$ which is a component-wise positive equilibrium of (2.1)–(2.4). This completes the proof. □

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