

## A NOSOCOMIAL EPIDEMIC MODEL WITH INFECTION OF PATIENTS DUE TO CONTAMINATED ROOMS

CAMERON BROWNE AND GLENN F. WEBB

Mathematics Department  
Vanderbilt University  
Nashville, TN 37240, USA

**ABSTRACT.** A model of epidemic bacterial infections in hospitals is developed. The model incorporates the infection of patients and the contamination of healthcare workers due to environmental causes. The model is analyzed with respect to the asymptotic behavior of solutions. The model is interpreted to provide insight for controlling these nosocomial epidemics.

**1. Introduction.** We analyze a model of a nosocomial epidemic, that is, an epidemic of antibiotic resistant bacterial infections that occur in a hospital setting. The increasing magnitude of nosocomial epidemics has recently been documented in the WHO report *Antimicrobial resistance: Global report on surveillance* [8]. Although there has been extensive mathematical modeling of nosocomial epidemics, there has been little attention given to environmental contamination as a factor in their development and severity. In 2011 an outbreak of *Klebsiella pneumoniae carbapenemase* (KPC) infections arose in the Clinical Center at the National Institutes of Health in Bethesda, Maryland (CCNIH) [15]. The KPC outbreak at CCNIH, one of the most prestigious hospitals in the US, has caused great concern about the transmission and control of antibiotic resistant bacterial infections in hospitals. There is yet an incomplete understanding of the infection transmission routes for patient infections in this KPC outbreak.

The events in this KPC outbreak at CCNIH are as follows: A single patient with KPC was admitted to CCNIH, which had never had a previous case of KPC. This patient received high level infection control measures to prevent further patient infections, and was later discharged with no new infections having occurred. But several weeks later several patients, with no link to this first patient (no ICU time together, no common healthcare workers (HCW), no shared equipment) tested positive for the same strain of KPC. Over a period of months more patients contracted this resistant KPC strain and 11 died. With the implementation of extreme hygiene measures the epidemic seemed to have been contained. But one year later a new infection of the same KPC strain arose and this patient died.

Until recently, control of nosocomial epidemics was focused on HCW-patient hygiene measures, with less attention given to environmental infection routes. But the absence of symptomatic cases over extended time periods in this outbreak at CCNIH indicates transmission routes may not have been only through direct patient-HCW

---

2010 *Mathematics Subject Classification.* Primary: 92C60; Secondary: 34D20.

*Key words and phrases.* Bacterial infection, antibiotic resistance, local stability, Lyapunov functional, next generation matrix.

contacts. The timing, locales, and strict hygiene measures of the KPC cases at CCNIH raise the possibility that environmental transmissions played a significant role in this nosocomial epidemic. There has been recent interest in incorporating environmental transmission into epidemiological models, including mathematical models of nosocomial epidemics [4, 10, 17, 18, 19]. Our goal here is to further develop models of nosocomial epidemics that incorporate environmental infection transmission pathways, as well as standard HCW-patient contact infection transmission pathways.

A major difficulty in incorporating hospital environmental features into nosocomial epidemic models is the complexity of environmental factors involved [5]. Gram-negative bacteria such as KPC, *Clostridium difficile*, and *Acinetobacter baumannii* have the ability to persist for long time periods, even years, on bed rails, curtains, IV lines, faucets, switches, and many other inorganic surfaces. Inclusion of many such variables into a modeling framework poses great difficulties in organization and parameterization. On the other hand, a single abstract environmental compartment framework fails to characterize the important distinctions in the multiplicity of environmental contributions. Recently, several epidemiological studies in hospitals have collected and analyzed data on patient room contamination and cleaning, along with their effect on subsequent infection of patients and HCW contamination [6, 7, 14]. Thus, in order to include complexity, analytic tractability, and epidemiological relevance in modeling environment transmission of nosocomial infection, we choose an intermediate contamination framework: hospital environmental contamination in terms of patient rooms. We designate two levels of room contamination: level 0 rooms are uncontaminated or contaminated at low levels and level 1 rooms are contaminated at significantly higher levels. Our models can be extended to a hierachal sequence of room contamination levels, from low to high, but for simplicity we only consider two levels here. The advantage of this approach is that patient infection status can be tracked through room occupancy and room change. Additionally, environmental control measures can be applied to room cleaning efforts. The influence on the environment can thus be formulated, parameterized, and evaluated in terms of patient status, HCW status, and room status.

**2. The Patient-HCW-Rooms nosocomial model.** The model consists of the following six compartments: uninfected patients susceptible to acquiring the infection in level 0 contaminated rooms ( $S_0$ ), uninfected patients susceptible to acquiring the infection in level 1 contaminated rooms ( $S_1$ ), infected patients in level 0 contaminated rooms ( $I_0$ ), infected patients in level 1 contaminated rooms ( $I_1$ ), uncontaminated HCW ( $H_U$ ), and contaminated HCW ( $H_C$ ). The assumptions of the model are as follows:

- (1) All patients are uninfected at admission.
- (2) Infection of patients by HCW and contamination of HCW by patients occur during patient-HCW visits in patient rooms.
- (3) Infection of patients by the environment and contamination of HCW by the environment occur independently of patient-HCW direct contacts (but not necessarily independently of patient-HCW visits).
- (4) The ratio  $\rho$  of HCW to patients is constant.
- (5) There is an average length of time  $T_V$  between visits of HCW for patient-HCW visits. The probability that any patient is visited by any HCW during the time interval  $T_V$  is  $\rho$ . The time units of  $T_V$  are (fractions of) days.

(6) Uninfected patients in level 0 (level 1) rooms who exit their rooms are replaced by uninfected patients in level 0 (level 1) rooms.

(7) Infected patients in level 0 (level 1) contaminated rooms exit their rooms at rate  $1/T_0$  ( $1/T_1$ ), where  $T_0$  ( $T_1$ ) is their average length of stay in these rooms (RLOS). Room exit may result from transfer to another unit of the hospital, a change of room, hospital discharge, or other reasons. The RLOS may correlate to severity of infection, which in turn may correlate to level of room contamination.

(8) The fraction  $\alpha_0$  ( $\alpha_1$ ) of infected patients in level 0 (level 1) rooms who exit their room are replaced by uninfected patients in level 1 (level 0) rooms and the fraction  $1 - \alpha_0$  ( $1 - \alpha_1$ ) are replaced by uninfected patients in level 0 (level 1) rooms. Lower  $\alpha_0$  and  $\alpha_1$  values correspond to more effective room cleaning at each patient room exit. We allow  $\alpha_0 > 0$ , since cases with severe symptoms may result in higher level room contamination upon room exit.

(9) During each patient-HCW-visit in a level 0 (level 1) contaminated room by an uncontaminated HCW and an infected patient there is a probability  $\omega_0$  ( $\omega_1$ ) of contamination of the HCW. Note that the probability  $\omega_0$  should only describe contamination due to patient-HCW direct contact, whereas  $\omega_1$  describes both contamination due to direct contact and due to the environment. In addition, there is a probability  $\xi_1$  of an uncontaminated HCW becoming contaminated by the environment during a visit with an uninfected patient in a level 1 contaminated room. These probabilities of contamination take into account the hygiene of the HCW during the visit and at the conclusion of the visit.

(10) It is assumed that HCW remain contaminated an average time length  $T_V$  during one subsequent HCW-patient visit. This assumption on the average time of HCW contamination can be relaxed, but to reduce the number of parameters and emphasize the fast time scale of HCW de-contamination, we utilize this assumption.

(11) During each patient-HCW visit in a level 0 (level 1) contaminated room by a contaminated HCW and an uninfected patient, there is a probability  $\pi_0$  ( $\pi_1$ ) of infection of the patient. When an uninfected patient is infected in a level 0 (level 1) contaminated room, the patient remains in the same room, but is classified as an infected patient in a level 0 (level 1) room.

(12) Infected patients in level 0 (level 1) contaminated rooms transition (while remaining in the same room) to infected patients in level 1 (level 0) contaminated rooms at rate  $\delta_0$  ( $\delta_1$ ) per day. Higher  $\delta_0$  values correspond to less effective room cleaning each day and higher  $\delta_1$  values correspond to more effective room cleaning each day of rooms with infected patients. We assume  $\delta_1 > 0$  to incorporate the daily environmental degradation of bacteria, separate from decrease due to daily room cleaning.

(13) Uninfected patients in level 1 contaminated rooms transition to uninfected patients in level 0 contaminated rooms at rate  $\nu_1$  per day (while remaining in the same room). Higher  $\nu_1$  values correspond to more effective room cleaning each day of level 1 contaminated rooms occupied by uninfected patients. We assume  $\nu_1 > 0$  to incorporate the daily environmental degradation of bacteria, separate from decrease due to daily room cleaning.

(14) Uninfected patients in level 1 contaminated rooms become infected due to environmental contamination at rate  $\epsilon_1$  per day. We assume that level 0 rooms have sufficiently low contamination such that environmental infection of patients or environmental contamination of HCW is not possible.

Let  $S_0(t)$  ( $S_1(t)$ ) be the fraction of susceptible patients in level 0 (level 1) rooms, Let  $I_0(t)$  ( $I_1(t)$ ) be the fraction of infected patients in level 0 (level 1) rooms, let  $H_U(t)$  ( $H_C(t)$ ) be the fraction of uncontaminated (contaminated) HCW at time  $t$  (in days). It is assumed that the number of patients remains constant over time, as does the number of HCW. The equations of the model are as follows:

$$\frac{dS_0(t)}{dt} = \frac{1 - \alpha_0}{T_0} I_0(t) + \frac{1 - \alpha_1}{T_1} I_1(t) - \frac{\pi_0 \rho}{T_V} H_C(t) S_0(t) + \nu_1 S_1(t) \quad (1)$$

$$\frac{dS_1(t)}{dt} = \frac{\alpha_0}{T_0} I_0(t) + \frac{\alpha_1}{T_1} I_1(t) - \frac{\pi_1 \rho}{T_V} H_C(t) S_1(t) - \epsilon_1 S_1(t) - \nu_1 S_1(t) \quad (2)$$

$$\frac{dI_0(t)}{dt} = -\frac{1}{T_0} I_0(t) + \frac{\pi_0 \rho}{T_V} H_C(t) S_0(t) + \delta_1 I_1(t) - \delta_0 I_0(t) \quad (3)$$

$$\frac{dI_1(t)}{dt} = -\frac{1}{T_1} I_1(t) + \frac{\pi_1 \rho}{T_V} H_C(t) S_1(t) + \epsilon_1 S_1(t) - \delta_1 I_1(t) + \delta_0 I_0(t) \quad (4)$$

$$\frac{dH_U(t)}{dt} = \frac{1}{T_V} H_C(t) - \frac{1}{T_V} (\omega_0 I_0(t) + \omega_1 I_1(t) + \xi_1 S_1(t)) H_U(t) \quad (5)$$

$$\frac{dH_C(t)}{dt} = -\frac{1}{T_V} H_C(t) + \frac{1}{T_V} (\omega_0 I_0(t) + \omega_1 I_1(t) + \xi_1 S_1(t)) H_U(t) \quad (6)$$

The dynamics of the six differential equations compartments are illustrated in Fig. 2. Notice that  $S_0(t) + S_1(t) + I_0(t) + I_1(t) = 1$  for all time  $t$  (since  $\frac{d}{dt}(S_0(t) + S_1(t) + I_0(t) + I_1(t)) = 0$  for all  $t$  and it is assumed that  $S_0(0) + S_1(0) + I_0(0) + I_1(0) = 1$ ); thus one of the patient equations can be eliminated. Likewise,  $H_U(t) + H_C(t) = 1$  for all  $t$ , so one of the HCW equations can also be removed. Therefore, by substituting  $S_0(t) = 1 - S_1(t) - I_0(t) - I_1(t)$  and  $H_U(t) = 1 - H_C(t)$ , we arrive at the following system of four differential equations:

$$\frac{dS_1(t)}{dt} = \frac{\alpha_0}{T_0} I_0(t) + \frac{\alpha_1}{T_1} I_1(t) - \pi_1 \rho \frac{H_C(t)}{T_V} S_1(t) - \epsilon_1 S_1(t) - \nu_1 S_1(t) \quad (7)$$

$$\frac{dI_0(t)}{dt} = -\frac{1}{T_0} I_0(t) + \pi_0 \rho \frac{H_C(t)}{T_V} (1 - S_1(t) - I_0(t) - I_1(t)) + \delta_1 I_1(t) - \delta_0 I_0(t) \quad (8)$$

$$\frac{dI_1(t)}{dt} = -\frac{1}{T_1} I_1(t) + \pi_1 \rho \frac{H_C(t)}{T_V} S_1(t) + \epsilon_1 S_1(t) - \delta_1 I_1(t) + \delta_0 I_0(t) \quad (9)$$

$$\frac{dH_C(t)}{dt} = -\frac{1}{T_V} H_C(t) + \frac{1}{T_V} (\omega_0 I_0(t) + \omega_1 I_1(t) + \xi_1 S_1(t)) (1 - H_C(t)) \quad (10)$$

**3. Theoretical analysis.** The basic reproduction number  $\mathcal{R}_0$  can be defined utilizing the next-generation approach [16]. First define the feasible region for the system (7)-(10) as

$$\Gamma = \{(S_1, I_0, I_1, H_C) \in \mathbb{R}_+^4 : S_1 + I_0 + I_1 \leq 1, H_C \leq 1\},$$

where  $\mathbb{R}_+^4$  denotes the non-negative orthant of  $\mathbb{R}^4$ . We note that the original system (1)-(6) is quasi-positive, and thus its solutions remain non-negative when their initial values are nonnegative. Since the right-hand sides of (1)-(6) sum to 0, the solutions the system (7)-(10) remain in  $\Gamma$  when their initial values are in  $\Gamma$ . Notice that  $\mathcal{E}_0 := (0, 0, 0, 0)$  is the disease-free equilibrium of system (7)-(10), corresponding to no infected patients, no contaminated HCW, and no contaminated rooms.

We define a next-generation matrix by considering the linearized system at the disease-free equilibrium,  $\mathcal{E}_0$ . Write the linearized system as  $x' = (F - V)x$  where  $x =$

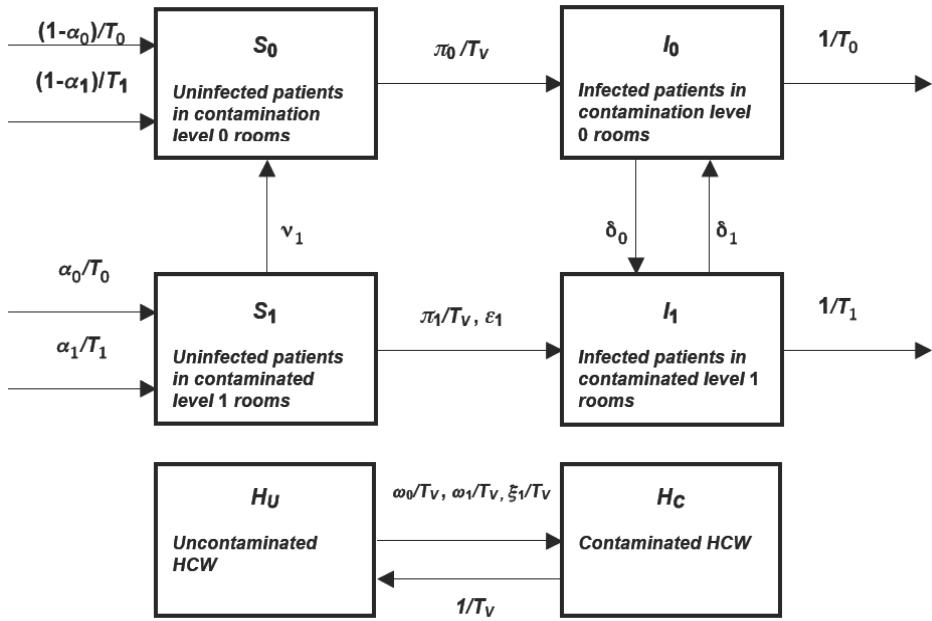


FIGURE 1. Schematic diagram of the model compartments and model parameters. The parameter corresponding to direct environmental infection of patients is  $\epsilon_1$  and direct environmental contamination of HCW is  $\xi_1$ . The parameters corresponding to patient infection by patient-HCW contacts are  $\pi_1, \pi_2$ . The parameters corresponding to HCW contamination by patient-HCW contacts are  $\omega_1, \omega_2$ . The parameters corresponding to room cleanings are  $\delta_0, \delta_1$ , and  $\nu_1$ .

$(S_1, I_0, I_1, H_C)^T$ , where  $F$  contains entries corresponding to new patient infections, and  $-V$  contains all other terms in the Jacobian matrix evaluated at  $\mathcal{E}_0$ . Thus, we consider the following matrices:

$$F = \begin{pmatrix} 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & \pi_0 \frac{\rho}{T_v} \\ \epsilon_1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix}, \quad V = \begin{pmatrix} \epsilon_1 + \nu_1 & -\frac{\alpha_0}{T_0} & -\frac{\alpha_1}{T_1} & 0 \\ 0 & \frac{1}{T_0} + \delta_0 & -\delta_1 & 0 \\ 0 & -\delta_0 & \frac{1}{T_1} + \delta_1 & 0 \\ -\xi_1 \frac{1}{T_v} & -\omega_0 \frac{1}{T_v} & -\omega_1 \frac{1}{T_v} & \frac{1}{T_v} \end{pmatrix}.$$

The next-generation matrix describing expected number of new patient infections caused by infected patients (through the routes of HCW or environmental transmission) is then defined as  $K := FV^{-1}$  [16]. Note that terms corresponding to HCW contamination events are not counted as new infections. Contaminated HCW are never actually infected, and therefore we are only interested in quantifying the reproduction number with respect to new patient infections. In other words, we treat HCW contamination (and environmental contamination) as an extended state of patient infectiousness [1]. This decomposition is not unique and other “epidemiological interpretable” splittings can be utilized where HCW or environmental contamination is counted as “new infections”. Each splitting yields a different formula

for basic reproduction number and these formulas all agree at the threshold value of 1, but yield different values away from unity.

It can be checked that this next-generation decomposition satisfies all the assumptions of the general approach in [16]. The basic reproduction number,  $\mathcal{R}_0$ , is the spectral radius of  $K$ ,  $\varrho(K)$ :

$$\mathcal{R}_0 = \varrho(K) = \varrho(FV^{-1}), \quad (11)$$

The formula for  $\mathcal{R}_0$  in terms of model parameters can be calculated utilizing *Mathematica* software and is found to be:

$$\mathcal{R}_0 = \frac{A + (A^2 - 4B)^{\frac{1}{2}}}{2T_V(1 + \delta_0T_0 + \delta_1T_1)(\epsilon_1 + \nu_1)} \quad (12)$$

where

$$A = T_V(\alpha_1 + T_0\alpha_1\delta_0 + T_1\alpha_0\delta_1)\epsilon_1 + \pi_0\rho\left(\alpha_0(\xi_1 + T_1\delta_1\epsilon_1) + T_0(\alpha_1\delta_0\xi_1 + (\epsilon_1 + \nu_1)(\omega_0 + T_1\delta_1\omega_0 + T_1\delta_0\omega_1))\right)$$

and

$$B = T_V(1 + T_0\delta_0 + T_1\delta_1)\epsilon_1\pi_0\rho(\epsilon_1 + \nu_1)(T_0\alpha_1\omega_0 - T_1\alpha_0\omega_1)$$

By utilizing Theorem 2 in [16], it can be shown that  $\mathcal{R}_0$  provides a local stability threshold for the disease-free equilibrium  $\mathcal{E}_0$ , which is stated in the following proposition.

**Proposition 1.** *If  $\mathcal{R}_0 < 1$ , then  $\mathcal{E}_0$  is locally asymptotically stable. On the other hand,  $\mathcal{E}_0$  is unstable if  $\mathcal{R}_0 > 1$ .*

We first consider (7)-(10) in the special case that room cleaning measures are highly effective. We require that all patient admissions are into level 0 contaminated rooms ( $\alpha_0 = 0$ ,  $\alpha_1 = 0$ ), which corresponds to highly effective cleaning of rooms occupied by infected patients upon their exit. In this case  $\mathcal{R}_0$  in (12) has the formula

$$\mathcal{R}_0 = \frac{T_0\pi_0\rho(\omega_0 + T_1\delta_1\omega_0 + T_1\delta_0\omega_1)}{T_V(1 + \delta_0T_0 + \delta_1T_1)}.$$

We also require highly effective daily room cleaning of level 0 contaminated rooms occupied by infected patients ( $\delta_0 = 0$ ). If we then add (7) and (9), we obtain

$$\frac{dS_1(t)}{dt} + \frac{dI_1(t)}{dt} = -\frac{1 + (\delta_1 + \nu_1)T_1}{T_1}S_1(t) \leq -\frac{1}{T_1}S_1(t),$$

which implies  $S_1(t) + I_1(t)$  is nonincreasing and

$$\frac{1}{T_1} \int_0^t S_1(s)ds \leq S_1(0) + I_1(0) - S_1(t) - I_1(t) \leq S_1(0) + I_1(0).$$

Then, (9) implies

$$\left(\frac{1}{T_1} + \delta_1\right) \int_0^t I_1(s)ds \leq \left(\frac{\pi_1\rho}{T_V} + \epsilon_1\right) \int_0^t S_1(s)ds + I_1(0) - I_1(t).$$

Thus,  $S_1(t) + I_1(t)$  is nonincreasing and integrable on  $[0, \infty)$  and  $\lim_{t \rightarrow \infty} S_1(t) = \lim_{t \rightarrow \infty} I_1(t) = 0$ . Thus, for  $\alpha_0 = 0$ ,  $\alpha_1 = 0$ ,  $\delta_0 = 0$ , we have

$$\mathcal{R}_0 = \frac{\omega_0\pi_0\rho T_0}{T_V}, \quad (13)$$

and the system (7)-(10) reduces to

$$\frac{dI_0(t)}{dt} = -\frac{1}{T_0}I_0(t) + \pi_0\rho \frac{H_C(t)}{T_V} (1 - I_0(t)) \quad (14)$$

$$\frac{dH_C(t)}{dt} = -\frac{1}{T_V}H_C(t) + \frac{\omega_0 I_0(t)}{T_V} (1 - H_C(t)). \quad (15)$$

The solutions of (14), (15) have the following asymptotic behavior:

**Proposition 2.** *If  $\mathcal{R}_0$  in (13) is  $< 1$ , then  $\mathcal{E}_0 = (0, 0)$  is the only steady state of (14), (15) in  $\Gamma_0 = \{(I_0, H_C) \in \mathbb{R}_+^2 : I_0 \leq 1, H_C \leq 1\}$  and  $\mathcal{E}_0$  is globally asymptotically stable in  $\Gamma_0$ . If  $\mathcal{R}_0$  in (13) is  $> 1$ , then*

$$\mathcal{E}_1 = \left( \frac{T_0\omega_0\pi_0\rho - T_V}{(T_V + T_0\pi_0\rho)\omega_0}, \frac{T_0\omega_0\pi_0\rho - T_V}{T_0\pi_0\rho(1 + \omega_0)} \right)$$

is also a steady state in  $\Gamma_0$  and  $\mathcal{E}_1$  is globally asymptotically stable in  $\Gamma_0$ .

*Proof.* See Appendix A. □

The formula for  $\mathcal{R}_0$  in (13) has the following interpretation for the threshold of endemicity for (14)-(15): on average, the total number of patient-HCW visits per patient over the average length of stay of a patient times the probability of patient infection per visit times the probability of HCW contamination per visit is greater than 1. We note that increasing  $T_V$  or decreasing  $\rho$  results in fewer HCW visits per patient, and thus reduces  $\mathcal{R}_0$ .

We next consider the opposite extreme to the case of highly efficient room cleaning, namely, that all rooms are contaminated without distinction of contamination level and no room contamination status changes due to room cleaning or bacteria degradation:  $S_0 = 0, I_0 = 0, T_0 = 0, \alpha_0 = 0, \alpha_1 = 1, \omega_0 = 0, \pi_0 = 0, \delta_0 = 0, \delta_1 = 0, \nu_1 = 0$ . From (8) we see that  $\lim_{t \rightarrow \infty} I_0(t) = 0$ , and (7)-(10) reduces to

$$\frac{dI_1(t)}{dt} = -\frac{1}{T_1}I_1(t) + \pi_1\rho \frac{H_C(t)}{T_V} (1 - I_1(t)) + \epsilon_1(1 - I_1(t)) \quad (16)$$

$$\frac{dH_C(t)}{dt} = -\frac{1}{T_V}H_C(t) + \frac{1}{T_V}(\omega_1 I_1(t) + \xi_1(1 - I_1(t)))(1 - H_C(t)) \quad (17)$$

In this case the epidemic can be extinguished only if  $\epsilon_1 = 0$  (no environmental infection of patients),  $\xi_1 = 0$  (no environmental contamination of HCW), and  $\pi_1\omega_1\rho T_1/T_V < 1$ . The solutions of (16)-(17) have the following asymptotic behavior:

**Proposition 3.** *Let  $\xi_1 = 0$ . If  $\epsilon_1 = 0$  and  $\pi_1\omega_1\rho T_1/T_V < 1$ , then the unique steady state of (16), (17) in  $\Gamma_1 = \{(I_1, H_C) \in \mathbb{R}_+^2 : I_1 \leq 1, H_C \leq 1\}$  is  $\mathcal{E}_0 = (0, 0)$ , and  $\mathcal{E}_0$  is globally asymptotically stable in  $\Gamma_1$ . If  $\epsilon_1 = 0$  and  $\pi_1\omega_1\rho T_1/T_V > 1$ , then*

$$\mathcal{E}_1 = \left( \frac{T_1\omega_1\pi_1\rho - T_V}{(T_V + T_1\pi_1\rho)\omega_1}, \frac{T_1\omega_1\pi_1\rho - T_V}{T_1\pi_1\rho(1 + \omega_1)} \right) \neq (0, 0)$$

is also a steady state in  $\Gamma_1$  and  $\mathcal{E}_1$  is globally asymptotically stable in  $\Gamma_1$ . Let  $\xi_1 \neq 0$ . Then  $\mathcal{E}_0$  is not a steady state of (16), (17), and there is a unique steady state (not  $\neq \mathcal{E}_0$ ) in  $\Gamma_1$ , which is globally asymptotically stable in  $\Gamma_1$ .

*Proof.* See Appendix A. □

For the model (7)-(10) with the distinction of level 0 and level 1 environmentally contaminated rooms, the parameter  $\pi_0$  is crucial for the behavior of solutions. If  $\pi_0 = 0$ , then  $\mathcal{R}_0$  in (12) is

$$\mathcal{R}_0 = \frac{(\alpha_1(1 + \delta_0)T_0 + \alpha_0\delta_1T_1)\epsilon_1}{(1 + \delta_0T_0 + \delta_1T_1)(\epsilon_1 + \nu_1)},$$

and the solutions have the following asymptotic behavior:

**Proposition 4.** *If  $\pi_0 = 0, \alpha_1 < 1$ , and either  $\nu_1 > 0$  or  $\epsilon_1 > 0$ , then  $\mathcal{R}_0 < 1$ ,  $\mathcal{E}_0 = (0, 0, 0, 0)$  is the only steady state of (7)-(10) in  $\Gamma$ , and  $\mathcal{E}_0$  is globally asymptotically stable in  $\Gamma$ .*

*Proof.* See Appendix A. □

Proposition (4) demonstrates the importance of maximally effective hand hygiene during patient-HCW visits in level 0 contaminated rooms ( $\pi_0 = 0$ ) and minimally effective cleaning of level 1 contaminated rooms occupied by infected patients upon their exit ( $\alpha_1 < 1$ ). If, additionally,  $\nu_1 > 0$  or  $\epsilon_1 > 0$ , the epidemic extinguishes. Intuitively,  $\epsilon_1 > 0$  worsens the epidemic, but in this case it acts indirectly to transfer uninfected patients from level 1 rooms to level 0 rooms by replacing those that become infected with new admissions in level 0 rooms, where the probability  $\pi_0$  of infection due to patient-HCW visits is 0. This transfer is accomplished directly if the daily cleaning of level 1 rooms occupied by uninfected patients is minimally effective ( $\nu_1 > 0$ ). We note that the time to extinction may require an extended period, dependent on initial conditions. We note also that if  $\nu_1 = 0, \alpha_0 = 1$ , and  $\alpha_1 = 1$ , then  $\mathcal{R}_0 = 1$  and there exist multiple nontrivial steady states of (7)-(10) in  $\Gamma$ , dependent on initial conditions.

Proposition (4) shows that for the model (7)-(10), environmental transmission cannot sustain an epidemic in the absence of direct transmission ( $\pi_0 = 0$ ) when there is environmental decay of bacteria ( $\nu_1 > 0$ ). However, if an additional contamination route is included in the system, then we find that a threshold quantity determines whether the bacteria persists in the case  $\pi_0 = 0, \nu_1 > 0$ . Indeed, consider the possibility that during patient visits, contaminated HCW can contaminate rooms which were previously uncontaminated. Thus, the mass-action term  $\beta_0 \frac{\rho}{T_V} H_C S_0$  can be a loss term in the  $S'_0$  equation and a positive term in the  $S'_1$  equation, representing contamination of rooms with uninfected patients by contaminated HCW. Also, an analogous term  $\beta_1 \frac{\rho}{T_V} H_C I_0$  can be incorporated into the  $I_0$  and  $I_1$  equations. In order to simplify the model, we consider this additional contamination route in the special case where there is only one infected patient compartment  $I_1$ , i.e. all infected patients are assumed to have level 1 contaminated rooms ( $\delta_0 \rightarrow \infty$ ). We also assume that  $\pi_1 = 0$  and  $\omega_1 = \xi_1$ , so that there is only environmental transmission. Then, with the additional parameter  $\beta_0$ , we obtain the following system:

$$\frac{dS_1(t)}{dt} = \beta_0 \rho \frac{H_C(t)}{T_V} (1 - S_1(t) - I_1(t)) + \frac{\alpha_1}{T_1} I_1(t) - (\epsilon_1 + \nu_1) S_1(t) \quad (18)$$

$$\frac{dI_1(t)}{dt} = -\frac{1}{T_1} I_1(t) + \epsilon_1 S_1(t) \quad (19)$$

$$\frac{dH_C(t)}{dt} = -\frac{1}{T_V} H_C(t) + \frac{\xi_1}{T_V} (I_1(t) + S_1(t)) (1 - H_C(t)) \quad (20)$$

The basic reproduction number,  $\mathcal{R}_0$ , for this model (defined similar to (11)) is as follows:

$$\mathcal{R}_0 = \frac{\epsilon_1(\beta_0\rho\xi_1T_1 + \alpha_1T_V)}{T_V(\epsilon_1 + \nu_1) - \beta_0\xi_1\rho}. \quad (21)$$

Notice that the denominator in  $\mathcal{R}_0$  contains a term which can go to zero and become negative. Thus, in order for  $\mathcal{R}_0$  to be positive and finite, the condition  $\epsilon_1 + \nu_1 > \xi_1\beta_0\frac{\rho}{T_V}$  is required. This condition compares the rate at which bacteria is spread solely through HCW contamination with the rate of transfer of uninfected patients in level 1 rooms. For this special case of the model, the following proposition can be obtained:

**Proposition 5.** *Consider the model (18)-(20). If  $\epsilon_1 + \nu_1 > \xi_1\beta_0\frac{\rho}{T_V}$  and  $\mathcal{R}_0 < 1$ , then the disease-free equilibrium  $\mathcal{E}_0$  is globally asymptotically stable. On the other hand, if  $\mathcal{R}_0 > 1$  or  $\epsilon_1 + \nu_1 \leq \xi_1\beta_0\frac{\rho}{T_V}$ , then  $\mathcal{E}_0$  is unstable, the disease is uniformly persistent and there is a unique endemic equilibrium  $\mathcal{E}_1 = (S_1^*, I_1^*, H_C^*)$ , given by*

$$S_1^* = \frac{(T_V(\epsilon_1 + \nu_1) - \beta_0\xi_1\rho)(\mathcal{R}_0 - 1)}{(1 + T_1\epsilon_1)\xi_1(\rho\beta_0(1 + T_1\epsilon_1) + \nu_1 + (1 - \alpha_1)\epsilon_1)}, \quad I_1^* = T_1\epsilon_1S_1^*,$$

$$H_C^* = \frac{\xi_1(S_1^* + I_1^*)}{1 + \xi_1(S_1^* + I_1^*)}.$$

*Proof.* See Appendix A. □

Thus the inclusion of contamination of rooms by contaminated HCW, described by the probability  $\beta_0$ , allows for persistence of the epidemic by environmental transmission only. Now we return to the original model (7)-(10). Note that the reproduction number  $\mathcal{R}_0$  (11) and the following two theorems can be extended to hold in the case that  $\beta_0$  and  $\beta_1$  are included in (7)-(10). However, for simplicity, we will neglect these factors. Instead, we give emphasis to the case that the epidemic would extinguish in the absence of environmental factors, that is,  $\omega_0\pi_0\rho T_0/T_V < 1$ , as in Proposition 2, but would not extinguish in the presence of constant environmental contamination in all rooms as in Proposition 3. We evaluate interventions that prevent endemicity in the model (7)-(10). These interventions, which are distinguished by room contamination levels 0 and 1, involve the parameters  $\alpha_0, \alpha_1$  (cleaning of rooms occupied by infected patients upon exit),  $\delta_0, \delta_1$  (daily cleaning of rooms occupied by infected patients),  $\nu_1$  (daily cleaning of level 1 contaminated rooms occupied by uninfected patients),  $\epsilon_1$  (environmental infection of uninfected patients in level 1 contaminated rooms), and  $\xi_1$  (environmental contamination of uncontaminated HCW in level 1 contaminated rooms occupied by uninfected patients).

Notice that the basic reproduction number  $\mathcal{R}_0$  (11) does not contain the parameter  $\pi_1$  corresponding to infection of susceptible patients in contaminated rooms through visits by contaminated HCW. Intuitively, one might expect this parameter to play a role in determining whether the disease persists. The absence of  $\pi_1$  in  $\mathcal{R}_0$  can be attributed to the local nature of the threshold  $\mathcal{R}_0$ . Since  $\mathcal{R}_0$  is only derived as a local threshold, it is of great interest to determine when local stability of  $\mathcal{E}_0$  implies global stability of  $\mathcal{E}_0$ . If certain conditions involving  $\pi_1$  are satisfied, then it can be proved that the disease-free equilibrium is globally asymptotically stable when  $\mathcal{R}_0 < 1$ . The result is contained in the following theorem:

**Theorem 3.1.** *Consider the model (7)-(10). Define the following quantities:*

$$\kappa = \frac{\pi_1}{\pi_0} \left( 1 + \frac{1}{T_0 \delta_0} \right), \quad K_i = \frac{1 + \alpha_i (\kappa - 1)}{T_i} \text{ for } i = 0, 1.$$

*Suppose that  $\mathcal{R}_0 < 1$  and consider the two following conditions:*

- (i)  $\kappa \leq 1$
- (ii)  $\max(K_0, K_1) \leq \epsilon_1 + \nu_1$ .

*If (i) holds, then  $\mathcal{E}_0$  is globally asymptotically stable in the entire state space  $\Gamma$ . If (ii) holds, then  $\mathcal{E}_0$  is globally asymptotically stable for initial conditions in  $\Gamma$  satisfying  $I_0(0) + I_1(0) + (1 - \kappa)S_1(0) \geq 0$ .*

*Proof.* See Appendix A. □

The condition (i) in Theorem 3.1 requires that  $\pi_0 \geq \pi_1 \left( 1 + \frac{1}{T_0 \delta_0} \right) > \pi_1$ . It is possible that  $\pi_0 > \pi_1$  if rooms at risk of contamination are identified (for example by tracking rooms previously occupied by infected patients), and extra hygiene measures are taken by HCW visiting these rooms. However, it may be more likely that  $\pi_0 \leq \pi_1$  since the contaminated rooms can have a higher probability of patient infection during a visit by a contaminated HCW worker. In this case condition (i) fails, but it may be true that condition (ii) holds, ensuring global extinction when  $\mathcal{R}_0 < 1$ . Condition (ii), in a sense, compares the exit rate of the  $S_1$  compartment with the exit rates of the  $I_0$  and  $I_1$  compartments, along with considering the magnitude of  $\kappa$  from the first condition and requiring the initial conditions to be contained in an invariant subset of the state space.

If the two conditions are not satisfied, it is possible that  $\mathcal{E}_0$  is only a local attractor and multiple positive equilibria are present when  $\mathcal{R}_0 < 1$  (sub-threshold positive equilibria). In this case, if we consider a bifurcation parameter for which  $\mathcal{R}_0$  increases to larger than 1 as the parameter is increased, there will be a *backward bifurcation* at  $\mathcal{R}_0 = 1$ . More precisely, consider a parameter of system (7)-(10), call it  $\mu$ , and write the system as  $\dot{x} = f(x, \mu)$ . Suppose that there exists  $\mu_Y$  such that  $\mathcal{R}_0 < 1$  for  $\mu < \mu_Y$  and  $\mathcal{R}_0 > 1$  for  $\mu > \mu_Y$ . Then the Jacobian  $D_x f(0, \mu_Y)$  has a zero eigenvalue and it can be shown that there is a transcritical bifurcation at  $x = 0, \mu = \mu_Y$ . In order to determine the nature of the transcritical bifurcation, we can apply Theorem 4 in [16], a result based on center manifold theory. Define  $v$  and  $w$  to be the left and right eigenvectors corresponding to the zero eigenvalue of  $D_x f(0, \mu_Y)$ . It can be shown that these eigenvectors can be chosen positive. Let

$$a := \frac{1}{2} \sum_{i,j,k}^4 v_i w_j w_k \frac{\partial^2 f_i}{\partial x_j \partial x_k}(0, \mu_Y).$$

If  $a < 0$ , then there is a forward bifurcation at  $(0, \mu_Y)$ , i.e. a locally asymptotically stable positive equilibrium branches out from  $(0, \mu_Y)$  for  $\mu > \mu_Y$ . If  $a > 0$ , then there is a backward bifurcation at  $(0, \mu_Y)$ , i.e. an unstable positive equilibrium branches out from  $(0, \mu_Y)$  for  $\mu < \mu_Y$ . The distinction between the two cases is important. A forward bifurcation usually signals that  $\mathcal{R}_0 < 1$  implies global extinction, whereas a backward bifurcation implies the disease may persist when  $\mathcal{R}_0 < 1$ . In the case  $a > 0$ ,  $\mathcal{R}_0 = 1$  does not provide a global threshold quantity, and there is some value  $0 < \mu_X < \mu_Y$  in which a saddle node bifurcation abruptly brings upon a change from global extinction to a regime of bistability for  $\mu_X < \mu < \mu_Y$ , where  $\mathcal{R}_0 < 1$ .

Considering the right-hand side of (7)-(10), it is found that  $a =$

$$w_4 \left[ \rho w_1 \left( \pi_1 v_3 - \pi_1 v_1 - \pi_0 v_2 - \frac{\xi_1 v_4}{\rho} \right) - w_2 (\rho \pi_0 v_2 + \omega_0 v_4) - w_3 (\rho \pi_0 v_2 + \omega_1 v_4) \right] \quad (22)$$

Notice that all terms of  $a$  are negative except for the positive term  $\pi_1(\rho w_4 w_1 v_3)$ . While the complexity of the system does not allow for the eigenvectors to be calculated and an explicit condition for backward bifurcation to be found, the formula does signal that the parameter  $\pi_1$  is crucial in determining the nature of the bifurcation. In Section 4, examples of the different types of bifurcations will be explored and the epidemiological implications will be discussed.

For the case of  $\mathcal{R}_0 > 1$ , the disease will uniformly persist. More precisely, the following result holds:

**Theorem 3.2.** *If  $\mathcal{R}_0 > 1$ , then the system is uniformly persistent, i.e. there exists  $\epsilon > 0$  such that if  $S_1(0) + I_0(0) + I_1(0) + H_C(0) > 0$ , then*

$$\liminf_{t \rightarrow \infty} S_1(t), I_0(t), I_1(t), H_C(t) > \epsilon.$$

Furthermore, there exists a positive endemic equilibrium when  $\mathcal{R}_0 > 1$ .

*Proof.* See Appendix A. □

**4. Examples of steady state behavior.** In Figures 2-7 we illustrate three different steady state behaviors of the model dependent on parameters.

In Figures 2 and 3,  $\alpha_1$  is a bifurcation parameter corresponding to the fraction of newly admitted uninfected patients replacing infected patients exiting level 1 rooms. All other parameters are held constant.  $\mathcal{R}_0 = \mathcal{R}_0(\alpha_1)$  is an increasing function for  $0.0 < \alpha_1 < 1.0$ . As  $\alpha_1$  increases through the critical value  $\alpha_{1X} \approx 0.672$ ,  $\mathcal{E}_0$  loses global stability, but is locally stable for  $\alpha_{1X} < \alpha_1 \leq 1.0$ . For  $\alpha_1 > \alpha_{1X}$ , two steady states branch from values significantly above 0 for each state variable (Figure 2, the branching for  $H_C$  is similar). The lower branch is unstable, and disappears as  $\alpha_1$  increases to  $\alpha_{1Y} \approx 0.804$ , which is the value such that  $\mathcal{R}_1(\alpha_{1Y}) = 1.0$ . Thus, there is a backward bifurcation at  $\alpha_{1Y}$ , as defined and discussed in the previous section. Indeed the quantity  $a$  expressed in (22) can be computed and is found to be  $a = 0.0197 > 0$ , which confirms the backward nature of the transcritical bifurcation in the figure. The upper branch is locally stable for  $\alpha_{1X} < \alpha_1 < 1.0$ . In this example  $\mathcal{R}_0$  does not distinguish epidemic extinction from endemicity. The epidemic extinguishes when  $\alpha_1 < \alpha_{1X}$ , but is endemic when  $\alpha_{1X} < \alpha_1 < \alpha_{1Y}$ , even though  $\mathcal{R}_1(\alpha_1) < 1.0$  for these values. In Figure 3A and 3B,  $\alpha_1 = 0.68$ , and a small increase in the number of uninfected patients initially in level 1 rooms separates epidemic extinction from endemicity. In Figure 3C  $\alpha_1 = 0.9$  and a small number of uninfected patients initially in level 1 rooms results in an epidemic outbreak after about one-half year.

In Figures 4 and 5,  $\pi_1$  is a bifurcation parameter corresponding to the probability of uninfected patients in level 1 rooms being infected by contaminated HCW. All other parameters are held constant.  $\mathcal{R}_0 \approx 0.975$  (independent of  $\pi_1$ ). As  $\pi_1$  increases through the critical value  $\pi_{1X} \approx 0.477$ ,  $\mathcal{E}_0$  loses global stability, but is locally stable for  $\pi_{1X} < \pi_1 \leq 1.0$ . For  $\pi_1 > \pi_{0X}$ , two steady states branch from values significantly above 0 for each state variable (Figure 4). The lower branch is unstable, and remains present as  $\pi_1$  increases to 1.0. The upper branch is locally stable for  $\pi_{1X} < \pi_1 \leq 1.0$ . In this example  $\mathcal{R}_0$  again does not distinguish epidemic

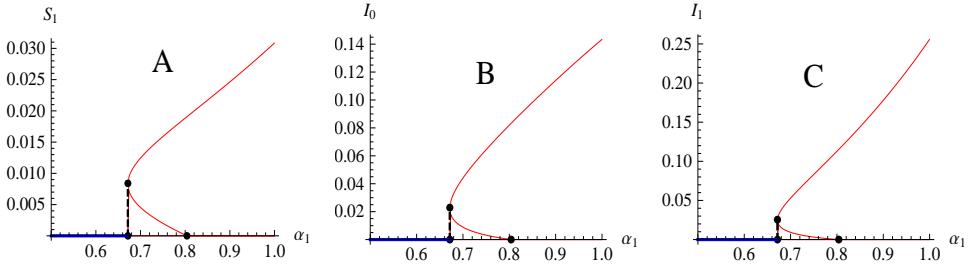


FIGURE 2. Saddle-node bifurcation of nontrivial steady states for A:  $S_1$ , B:  $I_0$ , C:  $I_1$  as the bifurcation parameter  $\alpha_1$  increases through the critical value  $\alpha_{1X} \approx 0.672$ . The upper branch is locally stable and the lower branch is unstable. The other parameter values are  $\alpha_0 = 0.0, \delta_0 = 0.2, \delta_1 = 0.1, \pi_0 = 0.02, \pi_1 = 0.5, \omega_0 = 0.3, \omega_1 = 0.4, T_0 = 7, T_1 = 7, T_V = 1/48, \epsilon_1 = 0.05, \xi_1 = 0.1, \nu_1 = 0.1, \rho = 1/3. \omega_0 \pi_0 \rho T_0 / T_V$  in (13) = 0.672 < 1.

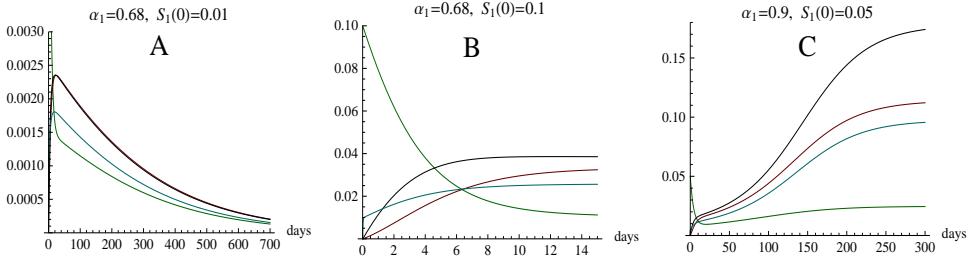


FIGURE 3. Trajectories of  $S_1(t)$  (green)  $I_0(t)$  (red),  $I_1(t)$  (black),  $H_C(t)$  (blue) for the bifurcation parameter  $\alpha_1$  as in Figure 2. A:  $\alpha_1 = 0.68, S_1(0) = 0.01, I_0(0) = 0.0, I_1(0) = 0.0, H_C(0) = 0.0$ ; B:  $\alpha_1 = 0.68, S_1(0) = 0.1, I_0(0) = 0.0, I_1(0) = 0.0$ ; C:  $\alpha_1 = 0.9, S_1(0) = 0.05, I_0(0) = 0.0, I_1(0) = 0.0, H_C(0) = 0.0$ .

extinction from endemicity. The epidemic extinguishes when  $\pi_1 < \pi_{1X}$ , but is endemic when  $\pi_{1X} \leq 1.0$  even though  $\mathcal{R}_0 < 1.0$  for these values. In Figure 5A the epidemic extinguishes for  $\pi_1 = .45$  with a small initial value for  $I_1(0)$ . In Figure 5B a larger initial value  $S_1(0)$  results in rapid endemicity with  $\pi_1 = 0.5$ . In Figure 5C the epidemic slowly extinguishes for a large value of  $\pi_1 = 0.9$ , but a small initial value for  $S_1(0)$ .

In Figures 6 and 7,  $\delta_0$  is a bifurcation parameter corresponding to the lack of cleaning efficiency of level 0 rooms occupied by infected patients. All other parameters are held constant.  $\mathcal{R}_0 = \mathcal{R}_0(\delta_0)$  is an increasing function for  $0.0 < \delta_0 < 1.0$ , and  $\mathcal{R}_0(\delta_{0Y}) = 1.0$  for  $\delta_{0Y} = 0.099$ . In this example, there is a forward bifurcation as the calculated value  $a = -0.0176$  (from equation (22)) confirms. As  $\delta_0$  increases through  $\delta_{0Y}$ ,  $\mathcal{E}_0$  loses global stability, and becomes unstable. For  $\delta_0 > \delta_{0Y}$ , one globally stable steady state rises from 0 for each state variable (Figure 4). In this example  $\mathcal{R}_0(\delta_0)$  distinguishes epidemic extinction from endemicity. In Figure 7A

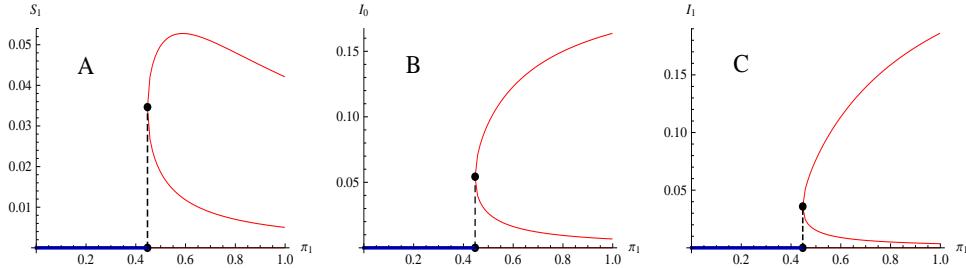


FIGURE 4. Saddle-node bifurcation of nontrivial steady states for A:  $S_1$ , B:  $I_0$ , C:  $I_1$  as the bifurcation parameter  $\pi_1$  increases through the critical value  $\pi_{1X} \approx 0.477$ . The upper branch is locally stable and the lower branch is unstable. The other parameter values are  $\epsilon_1 = 0.1$ ,  $\alpha_0 = 0.5$ ,  $\alpha_1 = 0.8$ ,  $\delta_0 = 0.033$ ,  $\delta_1 = 0.04$ ,  $\pi_0 = 0.05$ ,  $\omega_0 = 0.1$ ,  $\omega_1 = 0.2$ ,  $T_0 = 6$ ,  $T_1 = 5$ ,  $T_V = 1/48$ ,  $\xi_1 = 0.03$ ,  $\nu_1 = 0.1$ ,  $\rho = 1/3$ .  $\omega_0\pi_0\rho T_0/T_V$  in (13) = 0.48 < 1.

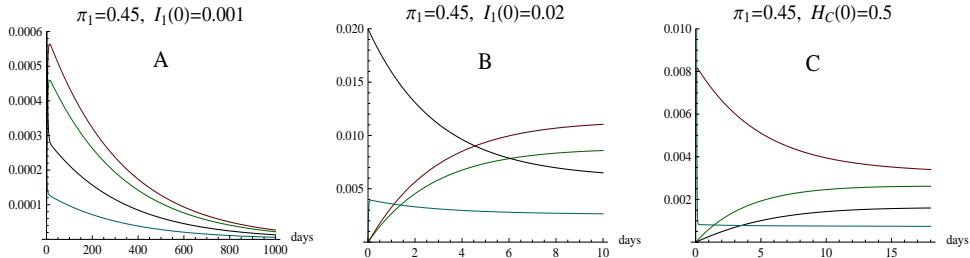


FIGURE 5. Trajectories of  $S_1(t)$  (green)  $I_0(t)$  (red),  $I_1(t)$  (black),  $H_C(t)$  (blue) for the bifurcation parameter  $\pi_1$  as in Figure 4. A:  $\pi_1 = 0.45$ ,  $S_1(0) = 0.0$ ,  $I_0(0) = 0.001$ ,  $I_1(0) = 0.0$ ,  $H_C(0) = 0.0$ ; B:  $\pi_1 = 0.5$ ,  $S_1(0) = 0.3$ ,  $I_0(0) = 0.0$ ,  $I_1(0) = 0.0$ ; C:  $\pi_1 = 0.9$ ,  $S_1(0) = 0.01$ ,  $I_0(0) = 0.0$ ,  $I_1(0) = 0.0$ ,  $H_C(0) = 0.0$ .

$\delta_0 = 0.01$  and the epidemic extinguishes slowly for a small initial value for  $S_1(0)$ . In Figure 7 B  $\delta_0 = 0.5$  and the epidemic rapidly becomes endemic for a larger initial value for  $S_1(0)$ . In Figure 7C  $\delta_0 = 0.9$ , and the epidemic slowly becomes endemic for a small initial value for  $I_0$ .

**5. Sensitivity analysis of  $\mathcal{R}_0$ .** We provide a sensitivity analysis of  $\mathcal{R}_0$  as a function of model parameters in Figures 8-12.

Figure 8 illustrates the dependence of  $\mathcal{R}_0$  on  $\alpha_0$  and  $\alpha_1$ . Lower values of  $\alpha_0$  ( $\alpha_1$ ) correspond to more efficient cleaning of level 0 (level 1) rooms occupied by infected patients when they exit their rooms. To maintain  $\mathcal{R}_0 < 1$ , a greater effort is required for level 1 room cleanings than level 0 room cleanings when infected patients exit their rooms..

Figure 9 illustrates the dependence of  $\mathcal{R}_0$  on  $\pi_0$  and  $\pi_1$ . Lower values of  $\pi_0$  and  $\pi_1$  correspond to greater hygiene efforts of HCW during visits to uninfected patients

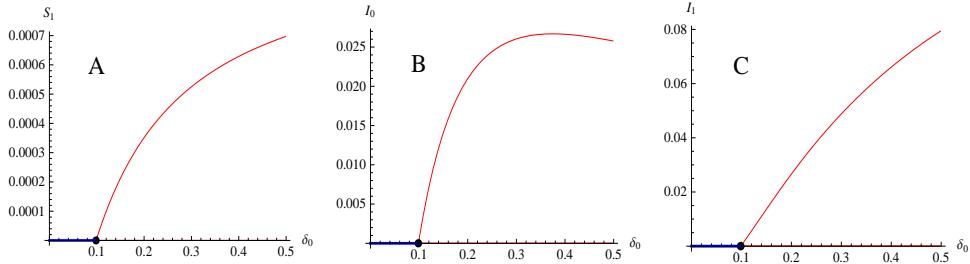


FIGURE 6. Appearance of nontrivial steady states as the bifurcation parameter  $\delta_0$  increases through the critical value  $\delta_{0Y} \approx 0.099$ .  $\mathcal{E}_0$  is globally stable for  $\delta_0 < \delta_{0Y}$  and unstable for  $\delta_{0Y} < 1.0$ . The nontrivial steady state is globally stable for  $\delta_{0Y} < 1.0$ . The other parameter values are  $\alpha_0 = 0.1, \alpha_1 = 0.1, \delta_1 = 0.1, \pi_0 = 0.05, \pi_1 = 0.5, \omega_0 = 0.1, \omega_1 = 0.1, T_0 = 10, T_1 = 14, T_V = 1/48, \epsilon_1 = 1.0, \xi_1 = 0.1, \nu_1 = 0.1, \rho = 1/3$ .  $\omega_0 \pi_0 \rho T_0 / T_V$  in (13) = 0.8 < 1.

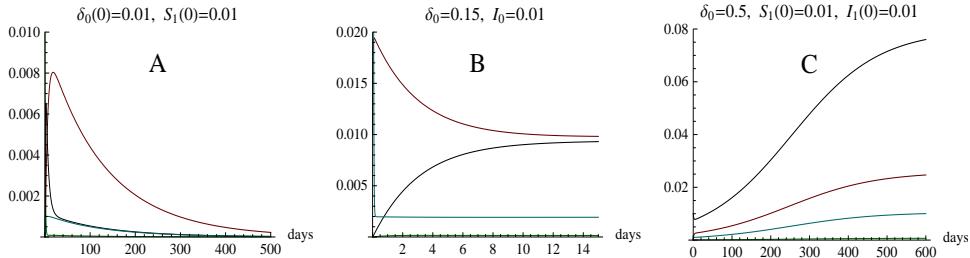


FIGURE 7. Trajectories of  $S_1(t)$  (green),  $I_0(t)$  (red),  $I_1(t)$  (black),  $H_C(t)$  (blue) for the bifurcation parameter  $\delta_0$  as in Figure 6. A:  $\delta_0 = 0.01, S_1(0) = 0.01, I_0(0) = 0.0, I_1(0) = 0.0, H_C(0) = 0.0$ ; B:  $\delta_0 = 0.5, S_1(0) = 0.1, I_0(0) = 0.0, I_1(0) = 0.0$ ; C:  $\delta_0 = 0.9, S_1(0) = 0.0, I_0(0) = 0.02, I_1(0) = 0.01, H_C(0) = 0.0$ . The other parameters are the same as in Figure 6.

in level 0 and level 1 rooms, respectively.  $\mathcal{R}_0$  is independent of  $\pi_1$ , and reduction of  $\mathcal{R}_0$  requires only reduction of  $\pi_0$ . The epidemic may persist, however, even though  $\mathcal{R}_0 < 1.0$ , if  $(\pi_0, \pi_1)$  is in the region of bistability. We remark that  $\pi_0 = 0.0$  (or  $\pi_0$  sufficiently small) implies the globally stability of  $\mathcal{E}_0$  for all  $\pi_1 \in [0, 1]$ , as in Proposition 4. Thus, reduction of patient infection during patient-HCW visits in level 0 contaminated rooms may be sufficient to control the epidemic, independently of patient infection during patient-HCW visits in level 1 contaminated rooms.

Figure 10 illustrates the dependence of  $\mathcal{R}_0$  on  $\delta_0$  and  $\delta_1$ . Lower values of  $\delta_0$  (higher values of  $\delta_1$ ) correspond to more efficient daily cleaning of level 0 (level 1) rooms occupied by infected patients. To maintain  $\mathcal{R}_0 < 1$ , a greater effort is required for level 1 room daily cleanings than for level 0 room daily cleanings occupied by infected patients.

Figure 11 illustrates the dependence of  $\mathcal{R}_0$  on  $\omega_0$  and  $\omega_1$ . Lower values of  $\omega_0$  and  $\omega_1$  correspond to greater hygiene efforts of HCW during visits to infected patients

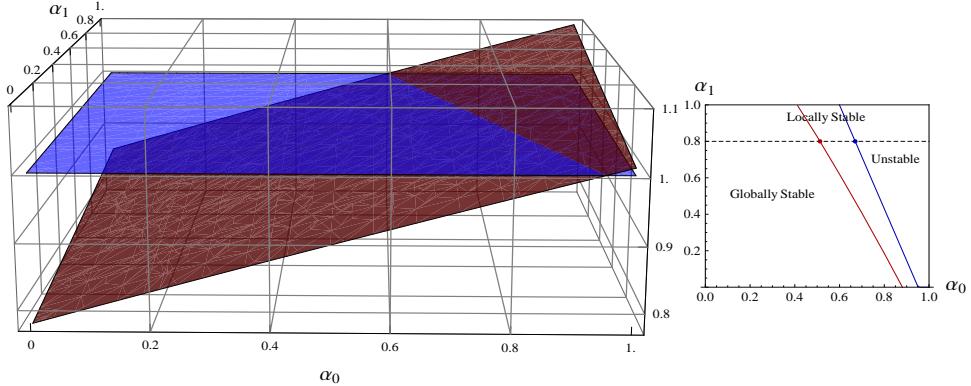


FIGURE 8. Dependence of  $\mathcal{R}_0$  on  $\alpha_0$  and  $\alpha_1$ . The stability of  $\mathcal{E}_0$  is illustrated in the right panel, where the blue graph corresponds to  $\mathcal{R}_0(\alpha_0, \alpha_1) = 1.0$ . The other parameters are  $\epsilon_1 = 0.05, \delta_0 = 0.08, \delta_1 = 0.08, \pi_0 = 0.025, \pi_1 = 0.5, \omega_0 = 0.3, \omega_1 = 0.3, T_0 = 6, T_1 = 8, T_V = 1/48, \xi_1 = 0.3, \nu_1 = 0.5, \rho = 1/3$ .  $\omega_0 \pi_0 \rho T_0 / T_V$  in (13) = 0.72 < 1.

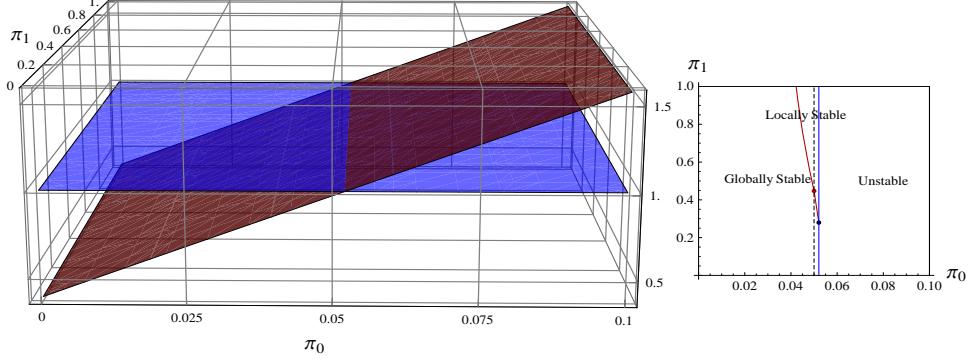


FIGURE 9. Dependence of  $\mathcal{R}_0$  on  $\pi_0$  and  $\pi_1$ . The dashed line corresponds to the value  $\pi_0 = 0.05$  in Figure 4. The stability of  $\mathcal{E}_0$  is illustrated in the right panel, where the blue graph corresponds to  $\mathcal{R}_0(\pi_0, \pi_1) = R_0(\pi_0) = 1.0$ . The other parameters are as in Figure 4.

in level 0 and level 1 rooms, respectively. To maintain  $\mathcal{R}_0 < 1$ , a greater effort is required for level 1 room visit hygiene than for level 0 room visit hygiene. We remark that  $\omega_0 = 0$  (or  $\omega_0$  sufficiently small) does not imply the globally stability of  $\mathcal{E}_0$  for all  $\omega_1 \in [0, 1]$ , in contrast to the values of  $\pi_0$  relative to  $\pi_1$ , as in Proposition 4. Thus, reduction of HCW contamination during patient-HCW visits in level 0 contaminated rooms may not be sufficient to control the epidemic, without concurrent reduction of HCW contamination during patient-HCW visits in level 1 contaminated rooms.

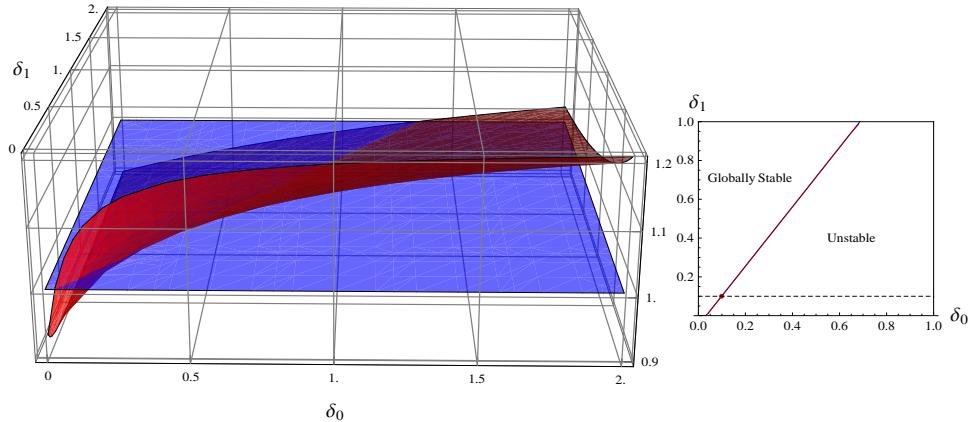


FIGURE 10. Dependence of  $\mathcal{R}_0$  on  $\delta_0$  and  $\delta_1$ . The dashed line corresponds to the value  $\delta_1 = 0.1$  in Figure 6. The stability of  $\mathcal{E}_0$  is illustrated in the right panel, where the blue graph corresponds to  $\mathcal{R}_0(\delta_0, \delta_1) = 1.0$ . The other parameters are as in Figure 6.

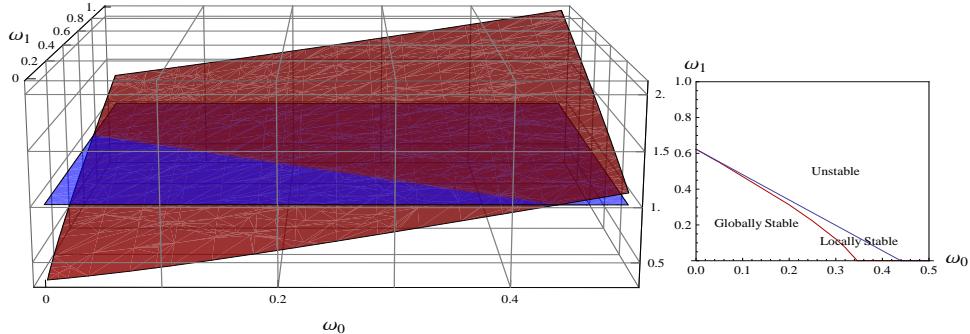


FIGURE 11. Dependence of  $\mathcal{R}_0$  on  $\omega_0$  and  $\omega_1$ . The stability of  $\mathcal{E}_0$  is illustrated in the right panel, where the blue graph corresponds to  $\mathcal{R}_0(\omega_0, \omega_1) = 1.0$ . The other parameters are  $\epsilon_1 = 0.5, \alpha_0 = 0.5, \alpha_1 = 0.5, \pi_0 = 0.025, \pi_1 = 0.5, \delta_0 = 0.083, \delta_1 = 0.83, T_0 = 6, T_1 = 8, T_V = 1/48, \xi_1 = 0.3, \nu_1 = 0.5, \rho = 1/3$ .  $\omega_0 \pi_0 \rho T_0 / T_V$  in (13) is  $< 1$  for  $\omega_0 < 0.41667$ .

Figures 12 and 13 show the sensitivity of  $\mathcal{R}_0$  with respect to  $\epsilon_1$  and  $\xi_1$ . Notice that for small values of  $\xi_1$ ,  $\mathcal{R}_0$  is a increasing function of  $\epsilon_1$ , but for sufficiently large values of  $\xi_1$ ,  $\mathcal{R}_0$  is a decreasing function of  $\epsilon_1$ . A consequence is, that for certain values of the probability  $\xi_1$  of HCW environmental contamination during patient-HCW visits in level 1 contaminated rooms, an increase in the environmental infection of uninfected patients in level 1 contaminated rooms results in epidemic extinction. This phenomenon illustrates the complexity of infection transmission pathways in the hospital. As previously mentioned in regard to Proposition 4,

intuitively increasing  $\epsilon_1$  worsens the epidemic, but it may actually reduce  $\mathcal{R}_0$  by infecting patients in contaminated rooms and, through cleaning upon discharge of the infected patient, this may reduce secondary infections compared to the case where the patient remains uninfected in a contaminated room.

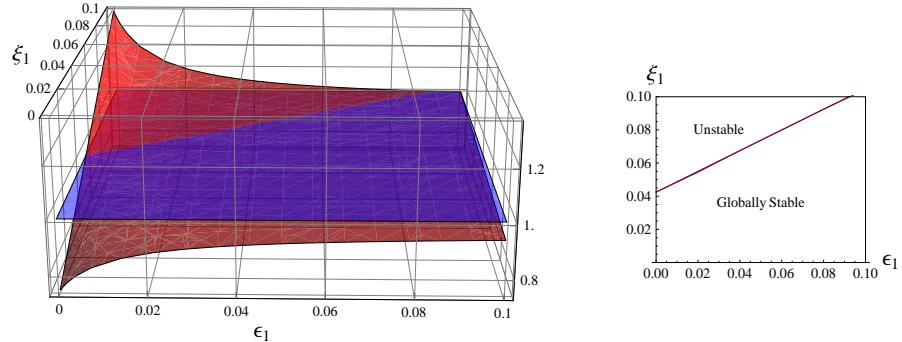


FIGURE 12. Dependence of  $\mathcal{R}_0$  on  $\epsilon_1$  and  $\xi_1$ . The stability of  $\mathcal{E}_0$  is illustrated in the right panel, where the blue graph corresponds to  $\mathcal{R}_0(\epsilon_1, \xi_1) = 1.0$ . The other parameters are  $\alpha_0 = 0.0, \alpha_1 = 0.5, \omega_0 = 0.2, \omega_1 = 0.3, \pi_0 = 0.025, \pi_1 = 0.025, \delta_0 = 0.1, \delta_1 = 0.1, T_0 = 8, T_1 = 8, T_V = 1/48, \nu_1 = 0.01, \rho = 1/3$ .  $\omega_0 \pi_0 \rho T_0 / T_V$  in (13)  $\approx 0.64 < 1$ .

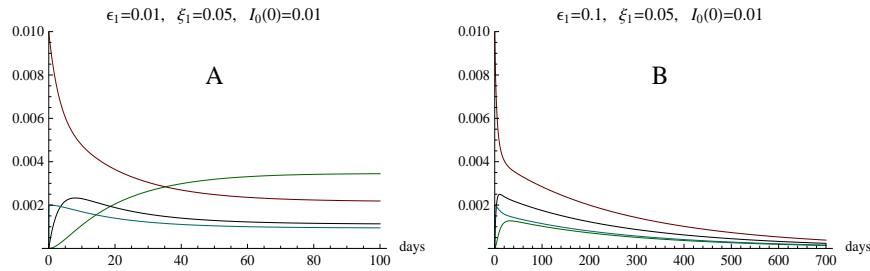


FIGURE 13. Trajectories of  $S_1(t)$  (green),  $I_0(t)$  (red),  $I_1(t)$  (black),  $H_C(t)$  (blue). The initial conditions are  $S_1(0) = 0.0$ ,  $I_0(0) = 0.01$ ,  $I_1(0) = 0.0$ , and  $H_C(0) = 0.0$ . The parameters are the same as in Figure 12 and  $\xi_1 = 0.05$ . A: the epidemic becomes endemic in about two months with  $\epsilon_1 = 0.01$ . B: the epidemic slowly extinguishes over two years with  $\epsilon_1 = 0.1$ .

Figure 14 illustrates the bistability of the locally stable steady state  $\mathcal{E}_0$  for various initial values with all parameters specified. The phase portrait in Figure 14A graphs trajectories for various initial values close to  $\mathcal{E}_0$ , all of which converge to  $\mathcal{E}_0$ . The phase portrait in Figure 14B graphs trajectories for various initial values slightly away from  $\mathcal{E}_0$ , all of which converge to the locally stable nontrivial steady state  $\mathcal{E}_1$ . The initial values  $H_C(0) = 0.0$  for all the trajectories (the trajectories of  $H_C(t)$  are not graphed). The black curves are the heteroclinic orbits connecting the steady

states. Slightly higher initial values ( $S_1(0)$ ,  $I_0(0)$ ,  $I_1(0)$ ,  $H_C(0)$ ) can precipitate an epidemic outbreak, which otherwise would extinguish.

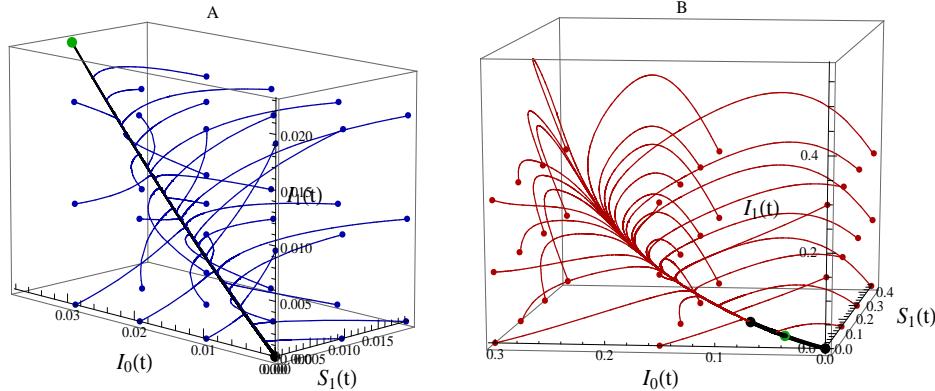


FIGURE 14. Phase portraits of  $(S_1(t), I_0(t), I_1(t))$  with varying initial values. The locally stable trivial steady state is  $\mathcal{E}_0 = (0, 0, 0, 0)$  (black dot). The locally stable nontrivial steady state is  $\mathcal{E}_1 \approx (0.0128, 0.0692, 0.0494, 0.0379)$  (black dot). The unstable nontrivial steady state is  $\mathcal{E}_2 \approx (0.0078, 0.0375, 0.0228, 0.0200)$  (green dot). The parameters are  $\epsilon_1 = 0.05$ ,  $\alpha_0 = 0.52$ ,  $\alpha_1 = 0.8$ ,  $\pi_0 = 0.025$ ,  $\pi_1 = 0.5$ ,  $\delta_0 = 0.083$ ,  $\delta_1 = 0.083$ ,  $\omega_0 = 0.3$ ,  $\omega_1 = 0.3$ ,  $T_0 = 6$ ,  $T_1 = 8$ ,  $T_V = 1/48$ ,  $\xi_1 = 0.3$ ,  $\nu_1 = 0.5$ ,  $\rho = 1/3$ .  $\omega_0 \pi_0 \rho T_0 / T_V$  in (13) =  $0.72 < 1$ .

**6. Stochastic simulations.** Because of the small population numbers in the hospital, stochastic effects may be important. Thus, we develop a stochastic counterpart to the ODE system (6). We consider a continuous time Markov chain model on the discrete set

$$\Omega = \{(S_0, S_1, I_0, I_1, H_U, H_C) \in \mathbb{Z}_+^6 : S_0 + S_1 + I_0 + I_1 = N_P, H_U + H_C = N_H\},$$

where  $\mathbb{Z}_+^6$  is the set of 6-tuples of non-negative integers,  $N_P$  is the number of patients and  $N_H$  is the number of HCW. The state transitions in the Markov chain correspond to the “reactions”, i.e. interactions, in system (1-6). For example, the state transition and the rate of occurrence corresponding to infection of an uninfected patient in a level 1 room can be written in the reaction format  $S_1 + H_C \xrightarrow{\pi_1} I_1 + H_C$ , meaning that the transition  $S_1 \rightarrow S_1 - 1, I_1 \rightarrow I_1 + 1$  occurs at the rate  $\pi_1 S_1 H_C$  (the time until next transition corresponding to this reaction is exponentially distributed with mean  $\frac{1}{\pi_1 S_1 H_C}$ ). All reactions are modeled in this way, and there are two Bernoulli random variables with parameters  $\alpha_i$ ,  $i = 0, 1$ , associated with the cleaning of discharged infected patients’ rooms. In this way, the number of patients remains constant as in the ODE model. The stochastic simulations are implemented by using Gillespie’s algorithm [3].

In Figure 15(a) and 15(b), one stochastic simulation of the model is presented for a set of parameters corresponding to poor cleaning of uninfected patient contaminated rooms ( $\nu_1 = 0.0001$ ). The simulation initiates with 1 contaminated room and no infected patients or contaminated HCW, i.e.  $S_1(0) = 1, I_0(0) = I_1(0) = H_C(0)$ .

The remainder of the parameters are specified in the caption of Figure 15. Observe that there is a long delay before an outbreak of infections occur. Of course, each simulation of the stochastic model can be different, but it illustrates how environmental contamination allows for a delayed outbreak, as was observed in the KPC outbreak at CCNIH. It is possible that the initial KPC infected patient at CCNIH caused a room to be contaminated, but did not cause any patient infections due to extreme caution by HCW. If the cleaning of rooms was not sufficient, the bacteria can persist for a long time in the contaminated room and cause an outbreak several months later. In Figure 15(c), the average paths of 200 simulations are plotted for the same parameters as Figure 15(a). Figure 15(d) displays the solution of the deterministic ODE for this set of parameters and initial conditions. Compared to the deterministic solutions, the averaged stochastic simulations result in lower number of infected due to the possibility of extinction and a longer delay to reach equilibrium distribution.

In Figure 16, the total infected patients as a function of time in the averaged stochastic simulations and deterministic solutions are displayed for three different values of the parameter  $\nu_1$ . Higher values of  $\nu_1$  correspond to more effective cleaning of uninfected patient contaminated rooms. Observe that increasing  $\nu_1$  has a dramatic effect on the total infected patients in the averaged stochastic simulations, but much less of an effect on the deterministic solutions. With the initial condition of one contaminated room, more effective cleaning of rooms can substantially increase the probability of bacterial extinction, which is not possible in the ODE.

**7. Discussion.** The contribution of the hospital environment to nosocomial epidemics involves complex interrelated dynamic factors. We have analyzed models that connect these factors to the environmental contamination status of patient rooms. The movement of patients through model compartments based on rooms is analogous to the flow of traffic through multiple lanes. Our rooms-based models separate environmental acquisition from patient-HCW contact acquisition. The advantage of our approach is that hospital rooms can be tracked with regard to patient occupancy, patient infection status, patient-HCW visits, and hygiene measures specific to rooms. We have emphasized the case that the epidemic would extinguish in the absence of environmental factors, but becomes endemic in their presence, particularly after extended time periods. We analyze the models with respect to intervention strategies that can mitigate these outbreaks.

Our models identify parameters that play key roles in transmission dynamics. These parameters, with the exception of  $\pi_1$  (HCW-patient transmission probability in contaminated rooms), are distilled into a single value  $\mathcal{R}_0$  that relates the roles of these parameters. Necessarily, there is a large number of such parameters, but their relative significance can be identified. The solutions of the model (7)-(10) possess a complex behavior that involves bifurcation of endemic steady states from the disease-free steady state  $\mathcal{E}_0$ . For most epidemic models,  $\mathcal{R}_0 < 1$  implies epidemic extinction and  $\mathcal{R}_0 > 1$  implies endemicity. But the model (7)-(10) allows endemicity even if  $\mathcal{R}_0 < 1$ , dependent on initial conditions. Figures 2-5 and Figure 12 illustrate this initial condition dependence. Even if  $\mathcal{R}_0 < 1$ , the epidemic rises very slowly when the initial populations  $S_1(0), I_0(0), I_1(0), H_C(0)$  are slightly above a very small threshold. A small increase in  $\alpha_1$  in Figures 2 and 3 (less effective cleaning of level 1 contaminated rooms occupied by infected patients upon their exit), or a small increase in  $\pi_1$  in Figures 4 and 5 (less effective HCW hand hygiene in level

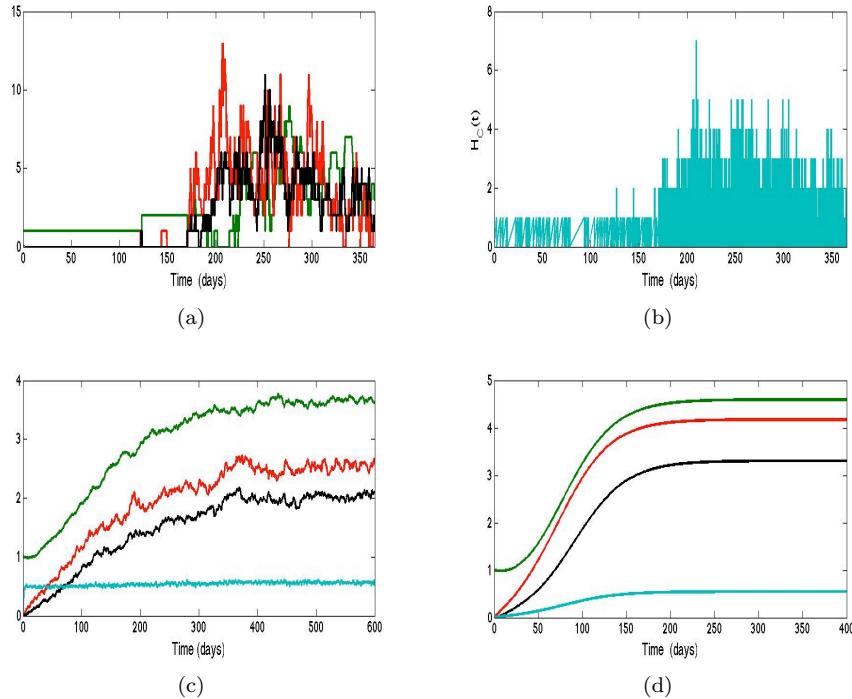


FIGURE 15. Simulations of  $S_1(t)$  (green),  $I_0(t)$  (red),  $I_1(t)$  (black) and  $H_C(t)$  (blue) for the stochastic model. The parameters are as follows:  $N_P = 30$ ,  $N_H = 10$ ,  $\alpha_0 = 0$ ,  $\alpha_1 = 0.8$ ,  $T_0 = 6$ ,  $T_1 = 8$ ,  $T_V = 1/48$ ,  $\pi_0 = 0.05$ ,  $\pi_1 = 0.08$ ,  $\epsilon_1 = 0.001$ ,  $\nu_1 = 0.001$ ,  $\delta_0 = 0.1$ ,  $\delta_1 = 0.1$ ,  $\xi_1 = 0.03$ ,  $\omega_0 = 0.2$ ,  $\omega_1 = 0.23$ ,  $\mathcal{R}_0 = 3.7116$ . The initial conditions are  $S_1(0) = 1$ ,  $I_0(0) = 0$ ,  $I_1(0) = 0$ ,  $H_C(0) = 0$ . (a)  $S_1(t)$ ,  $I_0(t)$ ,  $I_1(t)$  for one stochastic simulation illustrating the possibility of an outbreak after a long period of time. (b)  $H_C(t)$  for the simulation in (a). (c) Average of 500 stochastic simulations (d) Simulation of the deterministic model (10) for same parameters and initial conditions (fractions of patients/HCW are converted to number of individuals).

1 contaminated rooms), or a slightly increased re-set initial condition (in Figure 12) can explain an outbreak after an extended time when no infected patients are recognized.

The saddle-node bifurcation of steady states in the model means that outbreaks can arise suddenly. Figures 2 and 3 demonstrate this phenomenon in terms of  $\alpha_1$ . As  $\alpha_1$  increases through a critical value, both the  $I_0$  and  $I_1$  infected patient compartments may increase in a few days from 0% to  $\approx 3\%$  (assuming there is some environmental contamination), and the endemic level is much higher as  $\alpha_1$  increases. Thus, reduction of  $\alpha_1$  is effective in mitigating the epidemic. Figure 8 reveals, however, that it may be more effective to reduce  $\alpha_0$  (the fraction of uninfected patient admissions assigned to level 0 contaminated rooms exited by infected patients in those rooms). Figure 11 demonstrates similar claims for the probabilities

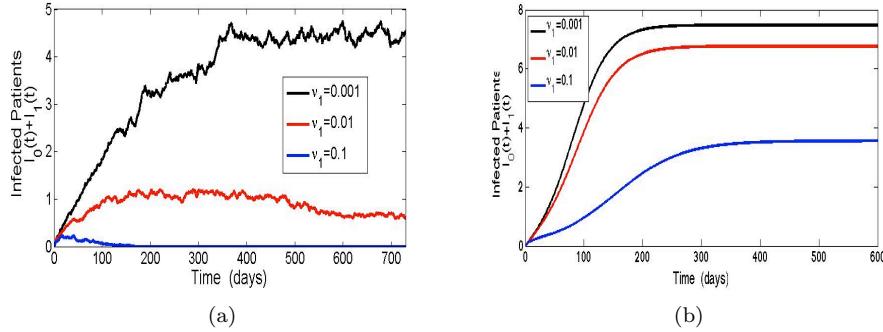


FIGURE 16. The effect of  $\nu_1$  on the total infected patients  $I_0(t) + I_1(t)$ . (a) Stochastic Simulations averaged over 500 runs. (b) Deterministic model.

$\omega_0$  and  $\omega_1$  of HCW contamination during patient-HCW visits. Again, reduction of HCW contamination in level 0 contaminated rooms may be more important than in level 1 rooms. Figures 4 and 5 demonstrate saddle-node bifurcation phenomenon in terms of  $\pi_1$  (the probability of uninfected patients becoming infected during patient-HCW visits in level 1 contaminated rooms). As  $\pi_1$  increases through a critical value, both  $I_0$  and  $I_1$  may increase in a few days from 0% to  $\approx 5\%$ , and the epidemic level is much higher as  $\pi_1$  increases. Although  $\pi_1$  does not appear in the formula for  $\mathcal{R}_0$  (11), it plays a significant role in the dynamic behavior of the epidemic. It is thus important to reduce patient-HCW visit infection of patients in level 1 contaminated rooms (Figures 4 and 5). But, as revealed in Figure 9, it may be more effective to reduce  $\pi_0$  (the probability of uninfected patient becoming infected during patient-HCW visits in level 0 contaminated rooms).

An important intervention relative to environmental contamination is daily room cleanings of rooms occupied by infected patients and contaminated rooms with uninfected patients. Distinction of level 0 and level 1 contaminated rooms may be difficult, but could be accomplished by tracking their occupancy history or by detection technology [9]. Figures 6,7, and 10 illustrate the roles of the parameters  $\delta_0$  (effectiveness of cleaning level 0 rooms occupied by infected patients) and  $\delta_1$  (effectiveness of cleaning level 1 rooms occupied by infected patients). Figure 6 reveals that as  $\delta_0$  increases past a critical value (less efficient cleaning), endemicity arises, with most of the infected patients in level 1 rooms. Figure 7 reveals that the outbreak may be delayed in time if the initial condition is mostly concentrated in the  $I_0$  compartment rather than the  $S_1$  compartment. Figure 10, which compares the roles of  $\delta_0$  and  $\delta_1$ , shows that to mitigate the epidemic it may be more effective to improve level 1 room daily cleanings than level 0 room daily cleanings. The stochastic simulations in Figures 15 and 16 show the importance the parameter  $\nu$  (effectiveness of cleaning level 1 rooms occupied by uninfected patients). In particular, if there are no infected patients, increasing  $\nu_1$  can substantially decrease the probability of an outbreak when there are contaminated rooms. In future work, we will further investigate intervention strategies by conducting parameter estimation and more thorough sensitivity analysis in both the deterministic and stochastic models.

### Appendix A. Proofs.

*Proof of Proposition 2.* By the Bendixson-Dulac Theorem, (14)-(15) cannot have periodic solutions in  $\Gamma_0$ , since

$$\begin{aligned} \frac{\partial}{\partial I_0} \left( -\frac{1}{T_0} I_0 + \pi_0 \rho \frac{H_C}{T_V} (1 - I_0) \right) + \frac{\partial}{\partial H_C} \left( -\frac{1}{T_V} H_C + \frac{\omega_0 I_0}{T_V} (1 - H_C) \right) \\ = -\frac{1}{T_0} - \frac{1}{T_V} - \frac{H_C \pi_0 \rho}{T_V} - \frac{I_0 \omega_0}{T_V} < 0. \end{aligned}$$

Let  $\mathcal{R}_0 = \omega_0 \pi_0 \rho T_0 / T_V < 1$ . Then  $\mathcal{E}_0$  is the only steady state in  $\Gamma_0$  and by the Poincare-Bendixson Theorem,  $\mathcal{E}_0$  is a global attractor  $\Gamma_0$ . Let  $\mathcal{R}_0 = \omega_0 \pi_0 \rho T_0 / T_V > 1$ . If  $\lim_{t \rightarrow \infty} H_C(t) = 0$ , then

$$\begin{aligned} I'_0(t) + H'_C(t) &= \left( -\frac{1}{T_0} + \frac{\omega_0}{T_V} - \left( \frac{\omega_0}{T_V} + \frac{\pi_0 \rho}{T_V} \right) H_C(t) \right) I_0(t) \\ &\quad + \left( \frac{\pi_0 \rho}{T_V} - \frac{1}{T_V} \right) H_C(t) > 0 \end{aligned}$$

for  $t$  sufficiently large, and  $I_0(t) + H_C(t)$  cannot converge to 0. By the Dulac-Bendixson Theorem, the only other steady state  $\mathcal{E}_1$  in  $\Gamma_0$  must be a global attractor in  $\Gamma_0$ .  $\square$

*Proof of Proposition 3.* By the Bendixson-Dulac Theorem, (16),(17) cannot have periodic solutions in  $\Gamma_1$ , since

$$\begin{aligned} \frac{\partial}{\partial I_1} \left( -\frac{1}{T_1} I_1 + \pi_1 \rho \frac{H_C}{T_V} (1 - I_1) + \epsilon_1 (1 - I_1) \right) \\ + \frac{\partial}{\partial H_C} \left( -\frac{1}{T_V} H_C + \frac{\omega_1 I_1 + \xi_1 (1 - I_1)}{T_V} (1 - H_C) \right) \\ = -\frac{1}{T_1} - \frac{1}{T_V} - \epsilon_1 - \frac{\xi_1}{T_V} (1 - I_1) - \frac{H_C \pi_1 \rho}{T_V} - \frac{I_1 \omega_1}{T_V} < 0. \end{aligned}$$

Let  $\xi_1 = 0$ ,  $\epsilon_1 = 0$ ,  $\pi_1 \omega_1 \rho T_1 / T_V < 1$ . Then  $\mathcal{E}_0 = (0, 0)$  is the unique steady state of (16),(17) in  $\Gamma_1$ , and  $\mathcal{E}_0$  is globally asymptotically stable in  $\Gamma_1$  by the Poincare-Bendixson Theorem. Let  $\xi_1 = 0$ ,  $\epsilon_1 = 0$ ,  $\pi_1 \omega_1 \rho T_1 / T_V > 1$ . If  $\lim_{t \rightarrow \infty} H_C(t) = 0$ , then

$$\begin{aligned} I'_1(t) + H'_C(t) &= \left( -\frac{1}{T_1} + \frac{\omega_1}{T_V} - \left( \frac{\omega_1}{T_V} + \frac{\pi_1 \rho}{T_V} \right) H_C(t) \right) I_1(t) \\ &\quad + \left( \frac{\pi_1 \rho}{T_V} - \frac{1}{T_V} \right) H_C(t) > 0 \end{aligned}$$

for  $t$  sufficiently large, and  $I_1(t) + H_C(t)$  cannot converge to 0. By the Dulac-Bendixson Theorem, the only other steady state  $\mathcal{E}_1$  in  $\Gamma_1$  must be a global attractor in  $\Gamma_1$ . Let  $\xi_1 \neq 0$ ,  $\omega_1 = \xi_1$ . Then the unique steady state of (16),(17) in  $\Gamma_1$  is

$$\mathcal{E}_2 = \left( \frac{T_1(\pi_1 \omega_1 \rho + T_V \epsilon_1 (1 + \omega_1))}{T_1 \pi_1 \omega_1 \rho + T_V (1 + T_1 \epsilon_1) (1 + \omega_1)}, \frac{\omega_1}{1 + \omega_1} \right) \neq (0, 0),$$

and  $\mathcal{E}_2$  is globally asymptotically stable in  $\Gamma_1$  by the Poincare-Bendixson Theorem. Let  $\xi_1 \neq 0$ ,  $\omega_1 \neq \xi_1$ . Then the unique steady state of (16),(17) in  $\Gamma_1$  is

$$\mathcal{E}_3 = \left( \frac{U - \sqrt{V}}{2(T_V(1 + T_1 T_V \epsilon_1 T_1 \pi_1 \rho)(\xi_1 - \omega_1)}, \frac{W + \sqrt{V}}{2T_1 \pi_1 \rho (1 + \omega_1)} \right) \neq (0, 0)$$

where

$$\begin{aligned} U &= T_V(1 + \xi_1 + T_1\epsilon_1(1 + 2\xi_1 - \omega_1)) - T_1\pi_1\rho(\omega_1 - 2\epsilon_1), \\ V &= T_V \left( T_V\xi_1(2 + \xi_1) + T_1^2\epsilon_1(1 + \omega_1)(2\pi_1\rho\omega_1 + T_V\epsilon_1(1 + \omega_1)) \right. \\ &\quad \left. + 2T_1(T_V\epsilon_1(1 + \xi_1)(1 + \omega_1) + \xi_1\pi_1\rho(2 + \omega_1)) \right) + (T_V - T_1\pi_1\omega_1\rho)^2, \\ W &= T_1\pi_1\rho\omega_1 - T_V(1 + \xi_1 + T_1\epsilon_1(1 + \omega_1)), \end{aligned}$$

and  $\mathcal{E}_3$  is globally asymptotically stable in  $\Gamma_1$  by the Poincare-Bendixson Theorem.  $\square$

*Proof of Proposition 4.* Define  $V = S_1(t) + I_0(t) + I_1(t)$ . Then

$$\dot{V} = S'_1(t) + I'_0(t) + I'_1(t) = \frac{I_0(t)T_1(\alpha_0 - 1) + I_1(t)T_0(\alpha_1 - 1) - S_1(t)T_0T_1\nu_1}{T_0T_1} \leq 0$$

and  $V$  is a Lyapunov functional for (7)-(10). Since  $\alpha_1 < 1$ ,  $\dot{V} = 0$  implies  $I_1 = 0$  in the omega limiting set of any trajectory. The LaSalle Invariance Principle and (8) then imply  $\lim_{t \rightarrow \infty} I_0(t) = 0$ . If  $\nu_1 > 0$  or  $\epsilon_1 > 0$ , (7) implies  $\lim_{t \rightarrow \infty} S_1(t) = 0$ , and then (10) implies  $\lim_{t \rightarrow \infty} H_C(t) = 0$ .  $\square$

*Proof of Proposition 5.* Define

$$F = \begin{pmatrix} 0 & 0 & 0 \\ \epsilon_1 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix}, \quad V = \begin{pmatrix} \epsilon_1 + \nu_1 & -\frac{\alpha_1}{T_1} & -\beta_0\frac{\rho}{T_V} \\ 0 & \frac{1}{T_1} + \delta_1 & 0 \\ -\xi_1\frac{1}{T_V} & -\xi_1\frac{1}{T_V} & \frac{1}{T_V} \end{pmatrix}.$$

Then, it can be shown that  $V^{-1} \geq 0$  if  $\epsilon_1 + \nu_1 > \xi_1\beta_0\frac{\rho}{T_V}$ . Thus, if this condition is satisfied, the next generation matrix  $K := FV^{-1} \geq 0$ . To track secondary infected patients caused by an infected patient, define the basic reproduction number  $\mathcal{R}_0 := \varrho(K)$  (as in 11). We obtain (21), i.e.  $\mathcal{R}_0 = \frac{\epsilon_1(\beta_0\rho\xi_1T_1 + \alpha_1T_V)}{T_V(\epsilon_1 + \nu_1) - \beta_0\xi_1\rho}$ .

For the rest of the proof, it is best to utilize a different next generation decomposition and the concept of the target reproduction number. Define

$$\hat{F} = \begin{pmatrix} 0 & \frac{\alpha_1}{T_1} & \beta_0\frac{\rho}{T_V} \\ \epsilon_1 & 0 & 0 \\ \xi_1\frac{1}{T_V} & \xi_1\frac{1}{T_V} & 0 \end{pmatrix}, \quad \hat{V} = \begin{pmatrix} \epsilon_1 + \nu_1 & 0 & 0 \\ 0 & \frac{1}{T_1} + \delta_1 & 0 \\ 0 & 0 & \frac{1}{T_V} \end{pmatrix}.$$

Define the next generation matrix  $\hat{K} := \hat{F}\hat{V}^{-1}$ . To track secondary infected patients caused by an infected patient, define the (target) basic reproduction number  $\mathcal{T}_0 := \varrho(P_1\hat{K}P_2(I - \hat{K} + P_1\hat{K}P_2)^{-1})$  (as in 11), where  $P_1 = \text{diag}(0, 1, 0)$ ,  $P_2 = \text{diag}(1, 0, 0)$ . From here, we obtain (21), i.e.  $\mathcal{T}_0 = \frac{\epsilon_1(\beta_0\rho\xi_1T_1 + \alpha_1T_V)}{T_V(\epsilon_1 + \nu_1) - \beta_0\xi_1\rho}$ . Thus  $\mathcal{T}_0 = \mathcal{R}_0$ .

It can be seen that  $\hat{K}$  is irreducible and  $\varrho(\hat{K} - P_1\hat{K}P_2) = \sqrt{\frac{\beta_0\rho\xi_1}{T_V(\epsilon_1 + \nu_1)}} < 1$  if  $\epsilon_1 + \nu_1 > \xi_1\beta_0\frac{\rho}{T_V}$ . Then, by Theorem 2 in [16] and Theorem 2.1 in [11],  $\mathcal{T}_0$  provides a local stability threshold for  $\mathcal{E}_0$  in system (18)-(20). Moreover, by Theorem 2.2 in [12],  $\mathcal{E}_0$  is globally asymptotically stable if  $\varrho(\hat{K}) < 1$  and, on the other hand, the system is uniformly persistent if  $\varrho(\hat{K}) > 1$ . Thus, by Theorem 2.1 in [11], the same dichotomy holds for  $\mathcal{T}_0$  when  $\epsilon_1 + \nu_1 > \xi_1\beta_0\frac{\rho}{T_V}$ . Also, the formula for  $\mathcal{E}_1$  can be calculated from the system of equations, and when  $\mathcal{R}_0 > 1$  or  $\epsilon_1 + \nu_1 \leq \xi_1\beta_0\frac{\rho}{T_V}$ ,  $\mathcal{E}_1$  is a positive equilibrium. . Thus, when  $\epsilon_1 + \nu_1 \leq \xi_1\beta_0\frac{\rho}{T_V}$ ,  $\mathcal{E}_0$  can not be globally stable, hence, the system must be uniformly persistent since the dichotomy holds

regardless of the sign of  $\epsilon_1 + \nu_1 - \xi_1 \beta_0 \frac{\rho}{T_V}$ . We note that although  $\mathcal{R}_0$  only can be thought of as a reproduction number for system (18)-(20) when  $\epsilon_1 + \nu_1 > \xi_1 \beta_0 \frac{\rho}{T_V}$ ,  $\varrho(\hat{K})$  can always be defined. However, the formula (in terms of parameters) for  $\varrho(\hat{K})$  is fairly complicated and it does not have the same interpretation of tracking secondary infected patients.  $\square$

In the following proof, we consider a different next-generation decomposition than the one utilized for computation of  $\mathcal{R}_0$  in (11), which turns out to be advantageous for constructing a Lyapunov function under the conditions prescribed in the hypothesis of Theorem 3.1. In particular, we consider the linearization of the system:  $x' = (\tilde{F} - \tilde{V})x$ , where

$$\tilde{F} = \begin{pmatrix} 0 & \frac{\alpha_0}{T_0} & \frac{\alpha_1}{T_1} & 0 \\ 0 & 0 & \delta_1 & \pi_0 \frac{\rho}{T_V} \\ \epsilon_1 & 0 & 0 & 0 \\ \xi_1 \frac{1}{T_V} & \omega_0 \frac{1}{T_V} & \omega_1 \frac{1}{T_V} & 0 \end{pmatrix}, \quad \tilde{V} = \begin{pmatrix} \epsilon_1 + \nu_1 & 0 & 0 & 0 \\ 0 & \frac{1}{T_0} + \delta_0 & 0 & 0 \\ 0 & -\delta_0 & \frac{1}{T_1} + \delta_1 & 0 \\ 0 & 0 & 0 & \frac{1}{T_V} \end{pmatrix}$$

We remark that this next-generation decomposition does not seem to have an epidemiological interpretation since the term corresponding to the room cleaning parameter  $\delta_1$  is counted as ‘‘new infection’’, i.e. in the  $\hat{F}$  matrix.

Note that assumptions (A1)-(A5) are satisfied in [16]. Thus, a quantity can be defined as the spectral radius of  $\tilde{F}\tilde{V}^{-1}$ , which provides a local stability threshold:

$$\mathcal{L}_0 = \varrho(\tilde{F}\tilde{V}^{-1}).$$

We use the notation  $\mathcal{L}_0$  in order to avoid confusion with the basic reproduction number  $\mathcal{R}_0$  defined earlier in (11).  $\mathcal{L}_0$  is not intended to measure the basic reproduction number of the system; it solely acts as a threshold quantity which is particularly useful in constructing the Lyapunov function in the proof below.

*Proof of Theorem 3.1.* Note that  $\mathcal{L}_0 < 1 \Leftrightarrow \mathcal{R}_0 < 1$  and  $\mathcal{L}_0 > 1 \Leftrightarrow \mathcal{R}_0 > 1$ . Also,  $\tilde{F} \geq 0$  and  $\tilde{V}^{-1} \geq 0$ . Indeed, the following can be calculated:

$$\tilde{V}^{-1} = \begin{pmatrix} \frac{1}{\epsilon_1 + \nu_1} & 0 & 0 & 0 \\ 0 & \frac{T_0}{T_0 \delta_0 + 1} & 0 & 0 \\ 0 & \frac{T_0 T_1 \delta_0}{(T_1 \delta_1 + 1)(T_0 \delta_0 + 1)} & \frac{T_1}{T_1 \delta_1 + 1} & 0 \\ 0 & 0 & 0 & T_V \end{pmatrix}.$$

By the Perron-Frobenius Theorem,  $\mathcal{L}_0 = \varrho(\tilde{F}\tilde{V}^{-1}) = \varrho(\tilde{V}^{-1}\tilde{F})$  is an eigenvalue of the non-negative matrix  $\tilde{V}^{-1}\tilde{F}$  with a non-negative left eigenvector, denoted by  $u^T = (u_1, u_2, u_3, u_4)$ . Utilizing a similar approach to [12], we claim that  $Q = u^T \tilde{V}^{-1} x$  is a Lyapunov function where  $x = (S_1, I_0, I_1, H_C)^T$ . Differentiating along the solutions of (7)-(10), we obtain:

$$\begin{aligned} Q' &= u^T \tilde{V}^{-1} x' \\ &= u^T \tilde{V}^{-1} (\tilde{F} - \tilde{V})x - u^T \tilde{V}^{-1} g(x) \\ &= (u^T \tilde{V}^{-1} \tilde{F} - u^T I)x - u^T \tilde{V}^{-1} g(x) \\ &= u^T (\mathcal{L}_0 - 1)x - u^T \tilde{V}^{-1} g(x) \end{aligned} \tag{A1}$$

where

$$g(x) = \begin{pmatrix} \pi_1 \frac{\rho}{T_V} H_C S_1 \\ \pi_0 \frac{\rho}{T_V} H_C (S_1 + I_0 + I_1) \\ -\pi_1 \frac{\rho}{T_V} H_C S_1 \\ (\xi_1 S_1 + \omega_0 I_0 + \omega_1 I_1) \frac{1}{T_V} H_C \end{pmatrix}.$$

Then

$$\begin{aligned} u^T \tilde{V}^{-1} g(x) &\geq u_1 \pi_1 \frac{\rho}{T_V} H_C S_1 \left( \frac{1}{\epsilon_1 + \nu_1} \right) + u_2 \pi_0 \frac{\rho}{T_V} H_C \frac{T_0}{T_0 \delta_0 + 1} (S_1 + I_0 + I_1) \\ &\quad + u_3 \pi_0 \frac{\rho}{T_V} H_C \frac{T_0 T_1 \delta_0}{(T_1 \delta_1 + 1)(T_0 \delta_0 + 1)} \left( S_1 + I_0 + I_1 - S_1 \frac{\pi_1}{\pi_0} \frac{T_0 \delta_0 + 1}{T_0 \delta_0} \right) \\ &= u_1 \pi_1 \frac{\rho}{T_V} H_C S_1 \frac{1}{(\epsilon_1 + \nu_1)} + u_2 \pi_0 \frac{\rho}{T_V} H_C \frac{T_0}{T_0 \delta_0 + 1} (S_1 + I_0 + I_1) \\ &\quad + u_3 \pi_0 \frac{\rho}{T_V} H_C \frac{T_0 T_1 \delta_0}{(T_1 \delta_1 + 1)(T_0 \delta_0 + 1)} \left( I_0 + I_1 + S_1 \left[ 1 - \frac{\pi_1}{\pi_0} \left( 1 + \frac{1}{T_0 \delta_0} \right) \right] \right) \end{aligned}$$

Notice that the first term in the sum is non-negative since  $\alpha_0, \alpha_1 \leq 1$ . Suppose that  $\kappa = \frac{\pi_1}{\pi_0} \left( 1 + \frac{1}{T_0 \delta_0} \right) \leq 1$  holds. Then, since  $\frac{\pi_1}{\pi_0} \frac{T_1 \delta_1}{T_1 \delta_1 + 1} \leq \kappa \leq 1$ , we obtain that  $u^T \tilde{V}^{-1} g(x) \geq 0$ . Then, (A1) implies that  $Q' \leq 0$  since  $\mathcal{L}_0 < 1$  and  $u^T \tilde{V}^{-1} g(x) \geq 0$ . Thus  $Q$  is a Lyapunov function. furthermore  $Q' = 0$  if and only if  $x = 0$  since  $g(0) = 0$  and  $\tilde{V}^{-1} \tilde{F}$  is irreducible which implies  $u^T > 0$ . By the Lasalle Invariance Principle, the omega limit set of any solution is contained in the largest invariant set where  $x = 0$ , which is  $\{\mathcal{E}_0\}$ . This proves the theorem for the case  $\kappa \leq 1$ . Now suppose that  $(\epsilon_1 + \nu_1) \geq \max(K_0, K_1)$ . Define the function  $h(x) = I_0 + I_1 + (1 - \kappa) S_1$ . We claim that the set  $\Gamma_1 := \{(x) \in \Gamma : h(x) \geq 0\}$  is positively invariant. Suppose that  $h(x) = 0$ , then we show that  $\frac{d}{dt} h(x) \geq 0$ .

$$\begin{aligned} \frac{d}{dt} h(x) &= I'_0 + I'_1 + (1 - \kappa) S'_1 \\ &= -\frac{1}{T_0} I_0 + \frac{\rho}{T_V} \pi_0 H_C (1 - S_1 - I_0 - I_1) + \delta_1 I_1 - \delta_0 I_0 \\ &\quad - \frac{1}{T_0} I_1 + \frac{\rho}{T_V} \pi_1 H_C S_1 + \epsilon_1 S_1 - \delta_1 I_1 + \delta_0 I_0 \\ &\quad + (1 - \kappa) \left( \frac{\alpha_0}{T_0} I_0 + \frac{\alpha_1}{T_1} I_1 - \frac{\rho}{T_V} \pi_1 H_C S_1 - (\epsilon_1 + \nu_1) S_1 \right) \\ &= H_C \frac{\rho}{T_V} (\pi_0 (1 - S_1 - I_0 - I_1) + \kappa \pi_1 S_1) + (\epsilon_1 + \nu_1) (1 - \kappa) S_1 - K_0 I_0 - K_1 I_1 \\ &= H_C \frac{\rho}{T_V} (\pi_0 (1 - S_1 - I_0 - I_1) + (\epsilon_1 + \nu_1) (I_0 + I_1) - K_0 I_0 - K_1 I_1 \\ &\quad (\text{since } h(x) = 0 \Rightarrow (1 - \kappa) S_1 = I_0 + I_1) \\ &\geq (\epsilon_1 + \nu_1 - K_0) I_0 + (\epsilon_1 + \nu_1 - K_1) I_1 \\ &\geq 0, \end{aligned}$$

by the assumption that  $(\epsilon_1 + \nu_1) \geq \max(K_0, K_1)$ . Thus,  $\Gamma_1$  is positively invariant. Then,  $Q$  is a Lyapunov function on the positively invariant set  $\Gamma_1$ . It is not hard to show that the system has a global attractor  $\mathcal{A}$  containing  $\mathcal{E}_0$  which must be contained in  $\Gamma_1$ . Since  $\mathcal{E}_0$  is the global minimum of the function  $Q$ , using a LaSalle Invariance type argument, we find that  $\mathcal{A} = \{\mathcal{E}_0\}$ . This proves the statement.  $\square$

*Proof of Theorem 3.2.* We apply Theorem 4.3 in [2]. Let  $X = \mathbb{R}^4$  and  $E = \Gamma$ . The requirement for the system to be dissipative is clearly satisfied. The maximal invariant set  $N$  on the boundary  $\partial E$  is the singleton  $\{\mathcal{E}_0\}$ . This set is acyclic in  $\partial E$  since there is no nontrivial solution on the boundary which links  $\mathcal{E}_0$  to itself. Let  $B_\epsilon$  denote the neighborhood of radius  $\epsilon$  around  $\mathcal{E}_0 = 0$  in  $\Gamma$ . Consider the Lyapunov function  $Q$  from the proof of Theorem 3.1. If  $\mathcal{R}_0 > 1$ , then there exists  $\epsilon > 0$  such that  $Q' = u^T(\mathcal{L}_0 - 1)x - u^T\tilde{V}^{-1}g(x) > 0$  on  $\Lambda_\epsilon := B_\epsilon \cap \{x \in \Gamma : x_i > 0 \text{ for some } i = 1, 2, 3, 4\}$  since  $\frac{\partial g}{\partial x_i}|_{(0)} = 0$  for all  $i$  and the eigenvector  $u$  is strictly positive. Also,  $Q(0) = 0$  and  $Q(x) > 0$  if  $x_i > 0$  for some  $i$ . It follows that solutions are “pushed out” of  $\Lambda_\epsilon$ . Thus,  $\{\mathcal{E}_0\}$  is isolated and  $W^s(\mathcal{E}_0) \cap E^\circ = \emptyset$  where  $W^s(\mathcal{E}_0)$  is the stable manifold of  $\mathcal{E}_0$  and  $E^\circ$  is the interior of the set  $E$ . By Theorem 4.3, the system is uniformly persistent. Uniform persistence and the positive invariance of the compact set  $\Gamma$  imply the existence of a positive endemic equilibrium of the system (7)-(10) by Theorem D.3 in [13].  $\square$

## REFERENCES

- [1] M. Bani-Yaghoub, R. Gautam, Z. Shuai, P. van den Driessche and R. Ivanek, Reproduction numbers for infections with free-living pathogens growing in the environment, *Journal of biological dynamics*, **6** (2012), 923–940.
- [2] H. Freedman, S. Ruan and M. Tang, Uniform persistence and flows near a closed positively invariant set, *Journal of Dynamics and Differential Equations*, **6** (1994), 583–600.
- [3] D. T. Gillespie, Exact stochastic simulation of coupled chemical reactions, *The journal of physical chemistry*, **81** (1977), 2340–2361.
- [4] E. S. McBryde and D. L. McElwain, A mathematical model investigating the impact of an environmental reservoir on the prevalence and control of vancomycin-resistant enterococci, *Journal of Infectious Diseases*, **193** (2006), 1473–1474.
- [5] M. McKenna, Clean sweep, *Scientific American*, **307** (2012), 30–31.
- [6] D. J. Morgan, E. Rogawski, K. A. Thom, J. K. Johnson, E. N. Perencevich, M. Shardell, S. Leekha and A. D. Harris, Transfer of multidrug-resistant bacteria to healthcare workers? gloves and gowns after patient contact increases with environmental contamination, *Critical care medicine*, **40** (2012), 1045–1051.
- [7] S. Nseir, C. Blazejewski, R. Lubret, F. Wallet, R. Courcol and A. Durocher, Risk of acquiring multidrug-resistant gram-negative bacilli from prior room occupants in the intensive care unit, *Clinical Microbiology and Infection*, **17** (2011), 1201–1208.
- [8] W. H. Organization et al., *Antimicrobial Resistance: Global Report on Surveillance 2014*. geneva, switzerland: Who, 2014, 2014.
- [9] S. Petti, G. A. Messano, A. Polimeni and S. J. Dancer, Effect of cleaning and disinfection on naturally contaminated clinical contact surfaces, *Acta stomatologica Naissi*, **29** (2013), 1265–1272.
- [10] N. Plipat, I. H. Spicknall, J. S. Koopman and J. N. Eisenberg, The dynamics of methicillin-resistant *staphylococcus aureus* exposure in a hospital model and the potential for environmental intervention, *BMC infectious diseases*, **13** (2013), p595.
- [11] Z. Shuai, J. Heesterbeek and P. van den Driessche, Extending the type reproduction number to infectious disease control targeting contacts between types, *Journal of mathematical biology*, **67** (2013), 1067–1082.
- [12] Z. Shuai and P. van den Driessche, Global stability of infectious disease models using lyapunov functions, *SIAM Journal on Applied Mathematics*, **73** (2013), 1513–1532.
- [13] H. L. Smith, *The Theory of the Chemostat: Dynamics of Microbial Competition*, vol. 13, Cambridge university press, 1995.
- [14] P. Strassle, K. A. Thom, J. K. Johnson, S. Leekha, M. Lissauer, J. Zhu and A. D. Harris, The effect of terminal cleaning on environmental contamination rates of multidrug-resistant *acinetobacter baumannii*, *American journal of infection control*, **40** (2012), 1005–1007.
- [15] PBS, PBS frontline: Hunting the nightmare bacteria, 2013, URL <http://www.pbs.org/wgbh/pages/frontline/health-science-technology/hunting-the-nightmare-bacteria/a-superbug-outbreak-at-nih/1>.

- [16] P. Van den Driessche and J. Watmough, **Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission**, *Mathematical biosciences*, **180** (2002), 29–48.
- [17] X. Wang, Y. Xiao, J. Wang and X. Lu, **A mathematical model of effects of environmental contamination and presence of volunteers on hospital infections in china**, *Journal of theoretical biology*, **293** (2012), 161–173.
- [18] X. Wang, Y. Xiao, J. Wang and X. Lu, **Stochastic disease dynamics of a hospital infection model**, *Mathematical biosciences*, **241** (2013), 115–124.
- [19] M. Wolkewitz, M. Dettenkofer, H. Bertz, M. Schumacher and J. Huebner, **Environmental contamination as an important route for the transmission of the hospital pathogen vre: modeling and prediction of classical interventions**, *Infectious Diseases: Research and Treatment*, **1** (2008), 3–11.

Received May 05, 2014; Accepted January 14, 2015.

*E-mail address:* [cameron.j.browne@vanderbilt.edu](mailto:cameron.j.browne@vanderbilt.edu)

*E-mail address:* [glenn.f.webb@vanderbilt.edu](mailto:glenn.f.webb@vanderbilt.edu)