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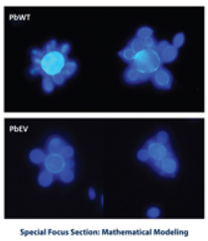

Virulence

ISSN: 2150-5594 (Print) 2150-5608 (Online) Journal homepage: http://www.tandfonline.com/loi/kvir20

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To cite this article: Tan N Doan, David CM Kong, Caroline Marshall, Carl MJ Kirkpatrick & Emma S McBryde (2016) Modeling the impact of interventions against Acinetobacter baumannii transmission in intensive care units, Virulence, 7:2, 141-152, DOI: 10.1080/21505594.2015.1076615

To link to this article: http://dx.doi.org/10.1080/21505594.2015.1076615

RESEARCH PAPER

Virulence 7:2, 141–152; February/March 2016; Published with license by Taylor & Francis Group, LLC

Modeling the impact of interventions against *Acinetobacter baumannii* transmission in intensive care units

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Keywords: *Acinetobacter baumannii*, infection control, intensive care units, mathematical modeling, transmission dynamics

Abbreviations: CFU, colony-forming unit; ICU, intensive care unit; LoS, length of stay

The efficacy of infection control interventions against *Acinetobacter baumannii* remains unclear, despite such information being critical for effective prevention of the transmission of this pathogen. Mathematical modeling offers an alternative to clinical trials, which may be prohibitively expensive, unfeasible or unethical, in predicting the impact of interventions. Furthermore, it allows the ability to ask key "what if" questions to evaluate which interventions have the most impact. We constructed a transmission dynamic model to quantify the effects of interventions on reducing *A. baumannii* prevalence and the basic reproduction ratio (R_0) in intensive care units (ICUs). We distinguished between colonization and infection, and incorporated antibiotic exposure and transmission from free-living bacteria in the environment. Under the assumptions and parameterization in our model, 25% and 18% of patients are colonized and infected with *A. baumannii*, respectively; and R_0 is 1.4. Improved compliance with hand hygiene ($\geq$87%), enhanced environmental cleaning, reduced length of ICU stay of colonized patients ($\leq$ 10 days), shorter durations of antibiotic treatment of *A. baumannii* ($\leq$6 days), and isolation of infected patients combined with cleaning of isolation rooms are effective, reducing R_0 to below unity. In contrast, expediting the recovery of the intestinal microbiota (e.g. use of probiotics) is not effective. This study represents a biologically realistic model of the transmission dynamics of *A. baumannii*, and the most comprehensive analysis of the effectiveness of interventions against this pathogen. Our study provides important data for designing effective infection control interventions.

Introduction

Acinetobacter baumannii is a leading cause of severe infections, such as ventilator-associated pneumonia, bacteremia, urinary tract infections and meningitis, in patients in intensive care units (ICUs).[1] Infections caused by *A. baumannii* are difficult to treat because it is resistant to many antibiotics.[2] As such, limiting the emergence and spread of this pathogen is of paramount importance.

The acquisition and spread of *A. baumannii* is a complex and dynamic process determined by various inter-related factors. Exposure to antibiotics and the resultant disruption of the intestinal microbiota are known to predispose to *A. baumannii* acquisition.[3] Other major contributing factors for the acquisition of *A. baumannii* in ICUs include patient-related factors such as use of invasive procedures, and ICU-related factors such as transmission between patients within the ward (cross-transmission).[4,5] Furthermore, *A. baumannii* can remain viable in the hospital environment for a prolonged period of time, serving as an important reservoir and contributing to acquisition by susceptible patients (environment-patient transmission).[6,7] As such, a multifaceted approach which encompasses reducing cross-transmission, environment-patient transmission and antibiotic exposure could be required to limit the acquisition and spread of this pathogen. However, the relative contribution of each component remains unclear. Historically, such data can be obtained by conducting clinical and epidemiological studies. However, these studies are time-consuming and may be prohibitively expensive in the hospital setting. Operational and/or ethical constraints may further limit whether interventions can be evaluated in clinical studies. Additionally, these studies are inherently unable to capture the interdependence between individuals. As such, these studies only provide individual patient-level data and fail to fully characterize the transmission dynamics of the pathogen.

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Submitted: 06/05/2015; Revised: 07/17/2015; Accepted: 07/21/2015
http://dx.doi.org/10.1080/21505594.2015.1076615

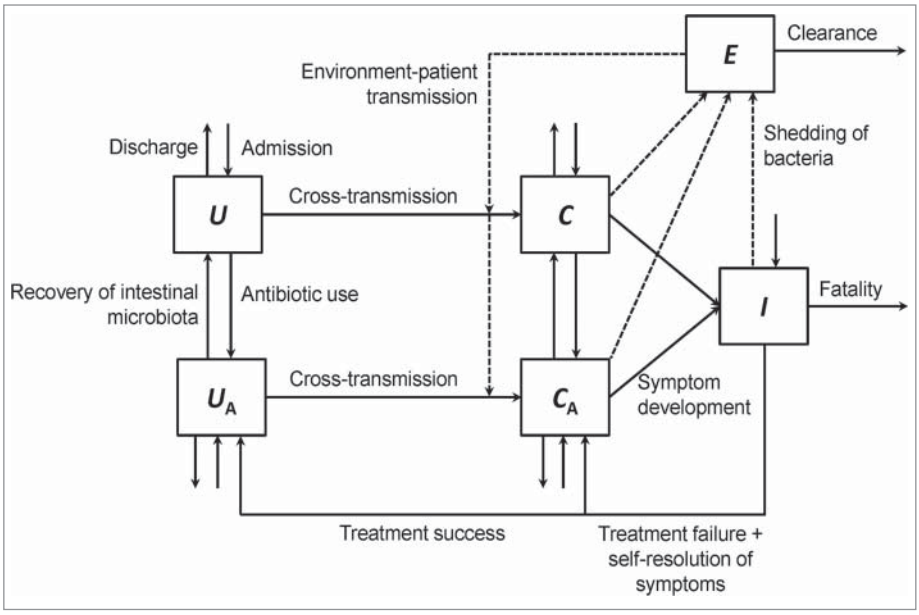

Figure 1. A compartmental model describing the transmission dynamics of *A. baumannii* in an intensive care unit. The solid arrows represent entry to and exit from the 5 compartments: *C*, colonized without antibiotic exposure; C_A, colonized with antibiotic exposure; *I*, infected; *U*, uncolonized without antibiotic exposure; U_A, uncolonized with antibiotic exposure. The broken arrows represent the shed of bacteria into the environment (*E*) from colonized and infected patients, and the transmission from free-living bacteria in the environment to susceptible (uncolonized) patients.

Population-level mathematical models, by providing a theoretical framework to conceptualize the dynamic interactions between interdependent variables, can overcome the aforementioned challenges.[8] They provide important insights into the underlying dynamics of an infection; and enable us to quantify the potential impact of various interventions without conducting those interventions.[8] Mathematical models also allow us to test "what-if" scenarios for the design of optimal intervention strategies.[8] While various models have investigated the effects of interventions against Gram-positive pathogens;[9-12] data on the population-level impact of interventions against *A. baumannii* (and other Gram-negative organisms alike) are scant. To date, there are only 2 modeling studies that investigate the transmission dynamics of *A. baumannii*.[4,7] Although both studies provide important insight into the spread of this pathogen, they have limitations. In our previous model, environment and interventions were not considered;[4] whereas the model by Wang et al.[7] did not distinguish between colonization and infection, nor did it take into account the effects of antibiotic exposure. Furthermore, nurse cohorting and nurse-patient ratio were the only interventions investigated in Wang et al.[7]

Consequently, we have developed a comprehensive mechanistic model to describe the transmission dynamics of *A. baumannii* in ICUs, and to quantify the effects of various interventions on reducing *A. baumannii* transmission. Unlike most previous models,[9-11,13,14] we have differentiated between patients colonized and infected with *A. baumannii*, and incorporated the important role of antibiotic exposure and free-living bacteria in the environment.

Materials and Methods

Mechanistic transmission dynamic model

A mechanistic model was developed to describe the transmission dynamics of *A. baumannii* in a hypothetical 100-bed ICU (**Fig. 1**). In this model, patients were in 5 mutually exclusive states according to their infection status: uncolonized without or with antibiotic exposure (U and U_A, respectively), colonized without or with antibiotic exposure (C and C_A, respectively), or clinically infected (I). Antibiotic exposure was defined as currently receiving any systemic antibiotic or having received antibiotics within the last 30 d.[15] Colonized and infected patients harbor the pathogen; however only infected patients manifest clinical symptoms. Patients could be admitted to the ICU in any of these 5 states. Of new admissions, 57.6% and 36.8% were uncolonized without and with antibiotic exposure, respectively;[16] and 0.3% and 5.3% were colonized without and with antibiotic exposure, respectively.[16] New admissions that were already clinically infected with *A. baumannii* were 0%.[17] Patients could be discharged from any compartment, except for the infected compartment where they were manifesting symptoms.[18] Discharge occurred at a rate of γ per day, calculated as the inverse of the length of ICU stay (hereinafter referred to as length of stay, LoS) specific for each compartment. Uncolonized and colonized patients, irrespective of their antibiotic exposure status, stayed in the ICU for an average of 5.5 and 16.5 d, respectively.[19-22] We assumed that the ICU was fully occupied, and that new admissions balanced discharges, resulting in a constant population size of $N = U + U_A + C + C_A + I = 100$.[4,12]

The movement from uncolonized or colonized without antibiotic exposure (U, C, respectively) to the corresponding compartments with antibiotic exposure (U_A, C_A, respectively) occurred at a rate of $\varepsilon = 0.12$ per day (antibiotic prescribing rate), which calibrated to 59.5% of ICU patients being prescribed antibiotics (for reasons other than treatment of *A. baumannii* infection) at any time during their stay.[23,24] The reverse process (moving from U_A to U, and from C_A to C) occurred when a patient's intestinal microbiota recovered after discontinuation of antibiotics, which was assumed to take 35 d.[25] The recovery rate of the intestinal microbiota, λ, was calculated as the inverse of this recovery time ($\lambda = 0.03$ per day). The use of probiotics was assumed to act by expediting this recovery process.[26]

Uncolonized patients could become colonized via cross-transmission between patients within the ICU. This acquisition process was determined by the cross-transmission coefficient,

Table 1. Baseline input values of model variables

Variable	Definition (unit)	Baseline value	Reference
ε	Antibiotic prescribing rate (/day)[a]	0.12	23,24
λ	Recovery rate of intestinal microbiota (/day)	0.03	25
β	Cross-transmission coefficient (/colonized/susceptible/day)	50×10^{-4}	4
ζ	Environment-patient transmission coefficient (/CFU/susceptible/day)	4×10^{-6}	30
Ω_1	Infectivity of C_A relative to C	1.67	29
Ω_2	Infectivity of I relative to C	2	29
θ_A	Rate of C_A becoming infected (symptom development rate) (/day)	0.11	5
θ	Rate of C becoming infected (symptom development rate) (/day)	$\theta_A/5$	32
τ	Treatment of *A. baumannii* infection (/day) (1/antibiotic treatment duration of infected patients)	0.08	33,34
σ	Treatment success rate of *A. baumannii* infection (/treated patient)	0.76	34
η	Rate of self-resolution of symptoms (/day)[b]	0.018	35
f	Fatality rate of infected patients (/day)[c]	0.016	36
r	Environmental cleaning rate (/day)	0.70	30
α	Efficacy of environmental cleaning (/CFU)	0.55	31
h	Compliance with hand hygiene	0.82	27
γ_U, γ_{UA}	Discharge rate of U and U_A (/day)	0.18	19,20
γ_C, γ_{CA}	Discharge rate of C and C_A (/day)	0.06	21,22
Λ	Admission rate (/day)	Rate of leaving the ICU[d]	
μ_U, μ_{UA}	Proportion of U and U_A on admission	57.6%; 36.8%	16
μ_C, μ_{CA}, μ_I	Proportion of C, C_A and I on admission	0.3%; 5.3%; 0%	16,17
Φ_1, Φ_2, Φ_3	Bacterial density shed into the environment by C, C_A and I (CFU/patient/day)	281; 470; 563	30

[a]Calibrates to 59.5% of patients receiving antibiotics any time during their ICU stay.
[b]Calibrates to 15% of infected patients having symptoms that self-resolve.
[c]Calibrates to 14% attributable mortality rate.
[d]Admission rate, $\Lambda = \gamma_U U + \gamma_A U_A + \gamma_C C + \gamma_{CA} C_A + fI$
C, colonized without antibiotic exposure; C_A, colonized with antibiotic exposure; CFU, colony-forming unit; *I*, infected; ICU, intensive care unit; *U*, uncolonized without antibiotic exposure; U_A, uncolonized with antibiotic exposure.

$\beta = 50 \times 10^{-4}$ per colonized per susceptible per day, which was estimated in our previous model.[4] This cross-transmission coefficient incorporates both direct transmission between patients and transmission between patients via transiently contaminated hands of healthcare workers.[4] Of note, the latter is responsible for most cross-transmission because ICU patients are not moving in the ward.[4] Cross-transmission could be reduced by improving the rate of compliance with hand hygiene, *h*, which was 82% at baseline.[27] Hand hygiene was assumed to be 100% effective.[28] Uncolonized patients with antibiotic exposure (U_A) were assumed to be 1.67 times more susceptible than uncolonized patients without antibiotic exposure (*U*); whereas colonized patients with antibiotic exposure (C_A) and infected patients (*I*) were assumed, respectively, to be 1.67 and 2 times more infectious than colonized patients without antibiotic exposure (i.e. infectivity of C_A relative to *C*, $\Omega_1 = 1.67$; infectivity of *I* relative to *C*, $\Omega_2 = 2$).[29]

Colonized and infected patients shed bacteria into the environment (i.e., ICU), which could survive for a prolonged period of time, serving as another important source of transmission (environment-patient transmission). This transmission process was determined by the environment-patient transmission coefficient, $\zeta = 4 \times 10^{-6}$ (per colony-forming unit [CFU] per susceptible per day).[30] Hand hygiene among healthcare workers or cleaning of the ICU (environmental cleaning), which occurred at a rate of $r = 0.7$ per day, would reduce this transmission source.[30] Environmental cleaning was assumed to eradicate 55% of the bacteria (environmental cleaning efficacy, α).[31] Free-living bacteria were assumed to be uniformly distributed in the environment and modeled in our study as another compartment (*E*).[30]

Colonized patients with antibiotic exposure became infected (movement from C_A to *I*) at a rate of $\theta_A = 0.11$ per day.[5] Colonized patients without antibiotic exposure were assumed to be 5-times less likely to become infected than those with antibiotic exposure.[32] Antibiotic treatment of patients infected with *A. baumannii* was assumed to take 13 d ($\tau^{-1} = 13$) with a successful clearance rate of $\sigma = 0.76$ per treated patient.[33,34] Infected patients who were successfully treated and cleared of the pathogen returned to the uncolonized with antibiotic exposure compartment; whereas the remaining treated patients returned to the colonized with antibiotic exposure compartment. Fifteen percent

Table 2. Variation range for variables evaluated in sensitivity analysis

Variable	Symbol	Range	Reference
Treatment success rate of *A. baumannii* infection	σ	0.6–0.9	34
Rate of self-resolution of symptoms	η	0.018–0.022	±10%
Cross-transmission coefficient	β	$39–71 \times 10^{-4}$	4
Environment-patient transmission coefficient	ζ	$3.4–4.6 \times 10^{-6}$	30
Fatality rate of infected patients[a]	*f*	0.006– 0.020	36,55
LoS of colonized patients	γ_C^{-1}	7–25	4,43

[a]Calibrates to 6% and 17% attributable mortality rate, respectively.
LoS, length of stay.

of infected patients had self-resolving symptoms and returned to the colonized with antibiotic exposure compartment;[35] and 14% of infected patients died as a result of the disease.[36] **Table 1** summarizes the input values of the model variables with their definitions and references. The system of ordinary differential equations that describe the transition between compartments is as follows:

$$\frac{dU}{dt} = \Lambda\mu_{\mathrm{U}} + \lambda U_{\mathrm{A}} - \frac{U\beta(1-h)(C+\Omega_1 C_{\mathrm{A}}+\Omega_2 I)}{N} - \gamma_{\mathrm{U}}U - \varepsilon U - \zeta(1-h)EU;$$

$$\frac{dU_{\mathrm{A}}}{dt} = \Lambda\mu_{\mathrm{UA}} + \varepsilon U + \sigma\tau I - \frac{U_{\mathrm{A}}\beta\times 1.67\times(1-h)(C+\Omega_1 C_{\mathrm{A}}+\Omega_2 I)}{N} - \lambda U_{\mathrm{A}} - \gamma_{\mathrm{UA}}U_{\mathrm{A}} - \zeta(1-h)EU_{\mathrm{A}};$$

$$\frac{dC}{dt} = \Lambda\mu_{\mathrm{C}} + \lambda C_{\mathrm{A}} + \frac{U\beta(1-h)(C+\Omega_1 C_{\mathrm{A}}+\Omega_2 I)}{N} - \varepsilon C - \gamma_{\mathrm{C}}C - \theta C + \zeta(1-h)EU;$$

$$\frac{dC_A}{dt} = \Lambda\mu_{\mathrm{CA}} + \varepsilon C + \frac{U_{\mathrm{A}}\beta\times 1.67\times(1-h)(C+\Omega_1 C_{\mathrm{A}}+\Omega_2 I)}{N} + (1-\sigma)\tau I + \eta I - \gamma_{\mathrm{CA}}C_{\mathrm{A}} - \lambda C_{\mathrm{A}} - \theta_{\mathrm{A}}C_{\mathrm{A}} + \zeta(1-h)EU_{\mathrm{A}};$$

$$\frac{dI}{dt} = \Lambda\mu_{\mathrm{I}} + \theta C + \theta_{\mathrm{A}}C_{\mathrm{A}} - fI - \eta I - \sigma\tau I - (1-\sigma)\tau I;$$

$$\frac{dE}{dt} = \Phi_1 C + \Phi_2 C_{\mathrm{A}} + \Phi_3 I - r\alpha E.$$

The model was simulated for one year (365 days). The following outcome measures were estimated: prevalence of colonized and infected patients, and the basic reproduction ratio, R_0. Briefly, R_0 is the average number of secondary colonized cases resulting from one single infectious individual in a totally susceptible population.[37] It is an important predictor of whether and how quickly an infection will spread. The aim of any intervention is to reduce R_0 to below unity. The next generation matrix method (described in **Appendix 1**) was used to estimate R_0 in our study.[38]

Interventions

Simulations were performed to evaluate the efficacy of various interventions in reducing the prevalence of colonized and infected patients, and R_0. The following interventions were investigated: (1) improved compliance with hand hygiene (h); (2) reduced antibiotic prescribing rate (ε); (3) reduced antibiotic treatment duration in patients infected with *A. baumannii* (τ^{-1}); (4) improved recovery rate of the intestinal microbiota (λ, via use of probiotics); (5) reduced LoS of colonized patients (γ_{C}^{-1}) following evidence that LoS is a major risk factor for *A. baumannii*;[39] (6) increased environmental cleaning rate (r, more frequent cleaning); (7) improved environmental cleaning efficacy (α, e.g., more effective cleaning products, training for cleaning teams); and (8) isolation of infected patients combined with cleaning of isolation rooms.

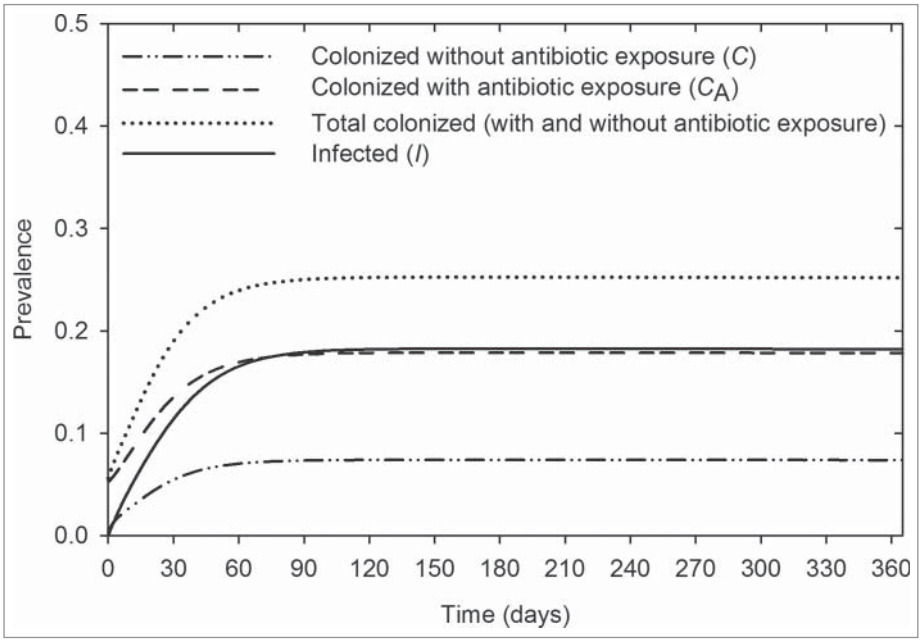

Figure 2. Prevalence of patients colonized and infected with *A. baumannii* at baseline.

Sensitivity analysis

Multivariate sensitivity analysis was carried out to investigate the key drivers of the outcome measures and the sensitivity of model outputs to changes in model inputs. The following variables were assessed: success rate of *A. baumannii* treatment (σ), rate of self-resolution of symptoms (η); cross-transmission coefficient (β); environment-patient transmission coefficient (ζ); fatality rate of infected patients (f); and LoS of colonized patients (γ_{C}^{-1}). The range of each variable is shown in **Table 2**. The Latin hypercube sampling method was performed. Partial rank correlation coefficients were calculated to evaluate the

strength of the correlation between each outcome measure and each variable.[40] All analysis was performed using MATLAB (version R2015a, MathWorks, Natick, MA, USA). The differential equations were solved using the *ode45* solver.

Results

Baseline scenario

Using the baseline parameters (**Table 1**), we estimate that 25% of patients are colonized, and 18% are infected with *A. baumannii* (**Fig. 2**). Acquisition is predominantly caused by within-ward transmission (98%), rather than colonization already present on admission. R_0 is estimated to be 1.4.

The impact of interventions

Figure 3 shows the predicted effects of individual interventions on reducing the prevalence of *A. baumannii* and R_0. The relative effects among the interventions investigated are shown in **Figure 4**. Compliance with hand hygiene (h) is the most effective intervention whereby a modest improvement in compliance rate, from 82% (baseline) to 87%, reduces R_0 from 1.4 to unity, and reduces the prevalence of colonized and infected patients by 6% (from 25% to 19%) and 4% (from 18% to 14%), respectively (**Fig. 3A**). In an idealized scenario where compliance rate is 100%, R_0 is reduced to zero; however, *A. baumannii* always persists at a low level (**Fig. 5A**). This is because of the constant admission of colonized patients into the ICU, with 5.6% of admitted patients already colonized at baseline. **Figure 5A** shows that when colonized patients are not admitted, *A. baumannii* will become extinct when R_0 is below unity. When R_0 is above unity, *A. baumannii* is always endemic irrespective of whether colonized patients are admitted (**Fig. 5B**).

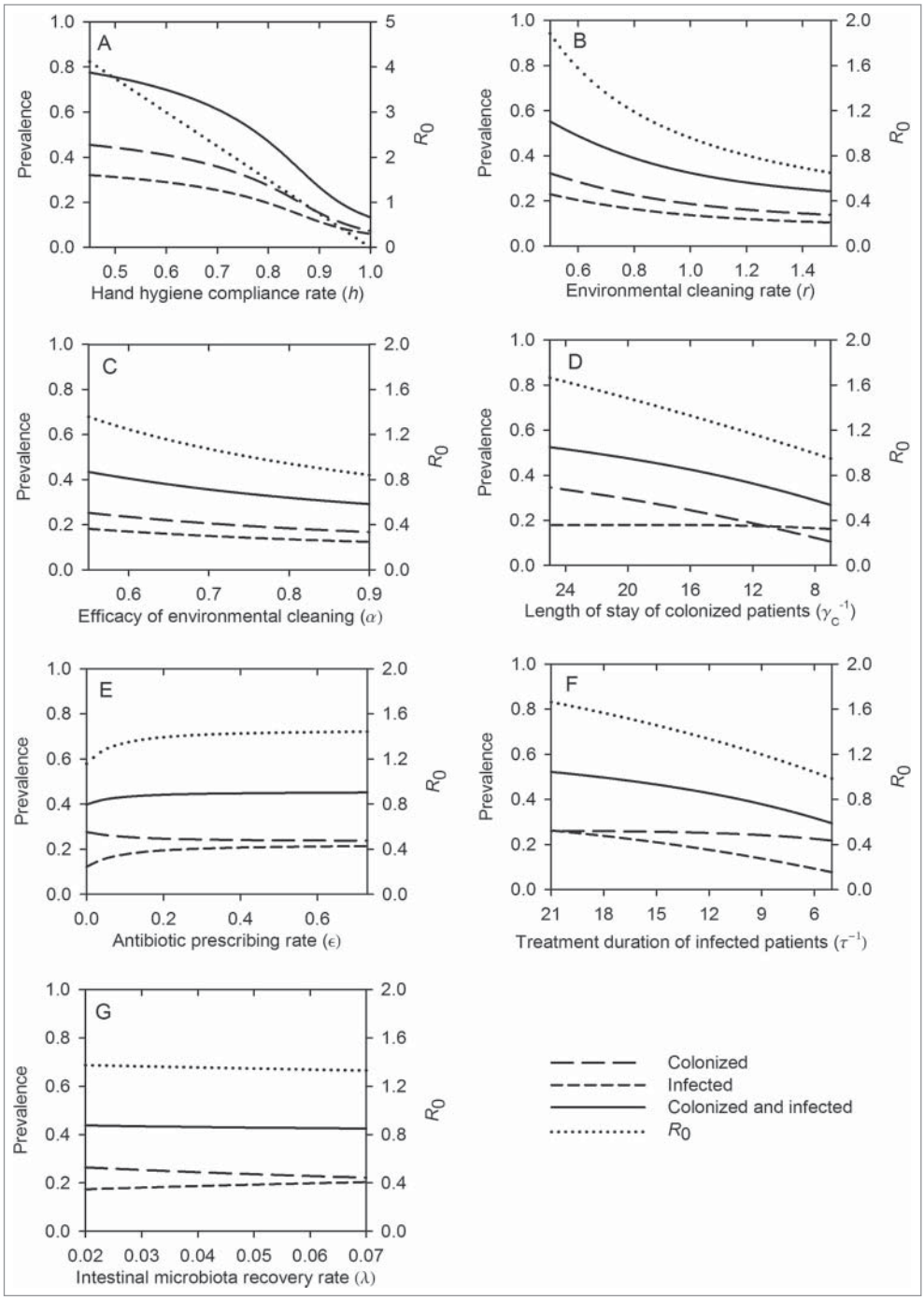

Figure 3. Effects of individual interventions on the prevalence of colonization (long-dashed lines), infection (short-dashed lines), total colonization and infection (solid lines), and the basic reproduction ratio, R_0 (dotted lines). The following interventions were investigated: compliance with hand hygiene (**A**), environmental cleaning rate (**B**), environmental cleaning efficacy (**C**), length of stay of colonized patients (**D**), antibiotic prescribing rate (**E**), treatment duration of infected patients (**F**), and recovery of intestinal microbiota (**G**).

Frequent ward cleaning (r) is also an effective intervention (**Fig. 3B**). Increasing environmental cleaning rate from 0.7 (baseline) to 1 (daily cleaning) reduces the prevalence of colonized and infected patients from 25% to 19% and from 18% to 14%, respectively. Daily ward cleaning also reduces R_0 to unity. Similar

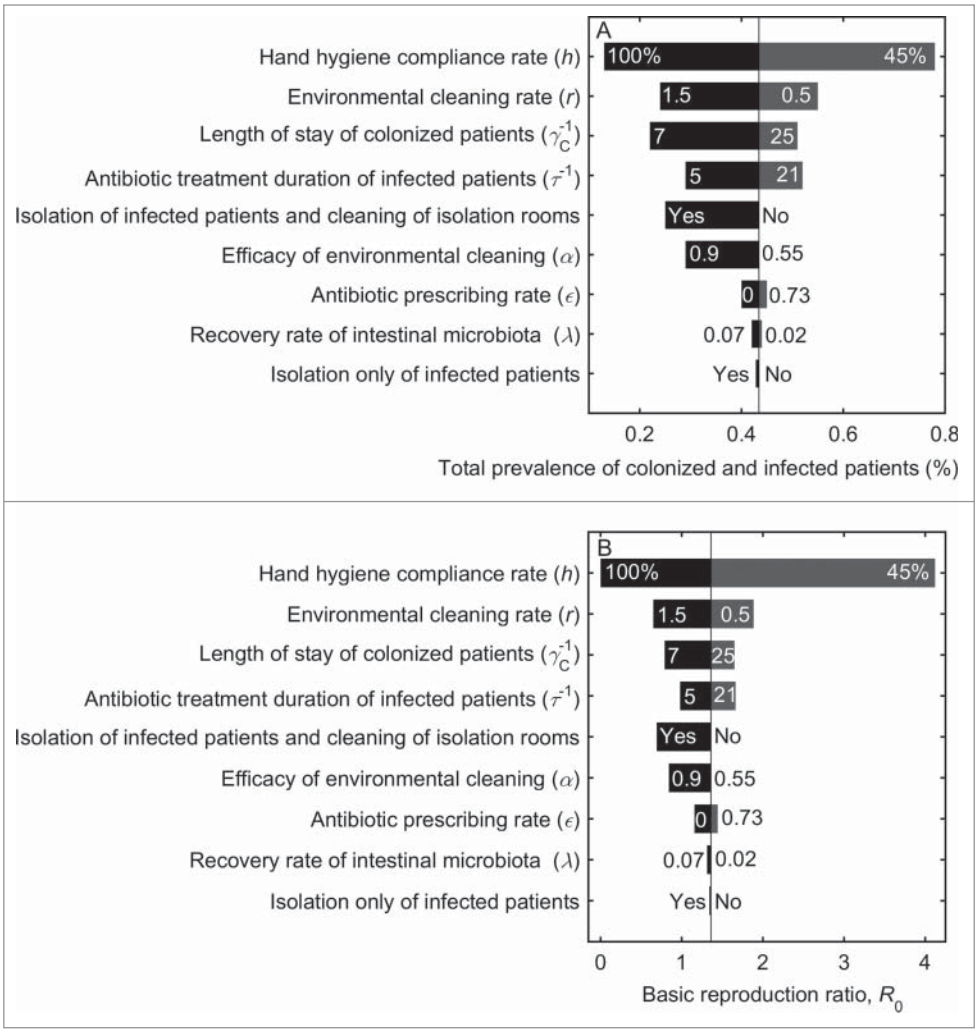

Figure 4. Relative effects of different interventions on the total prevalence of colonized and infected patients (**A**), and the basic reproduction ratio, R_0 (**B**).

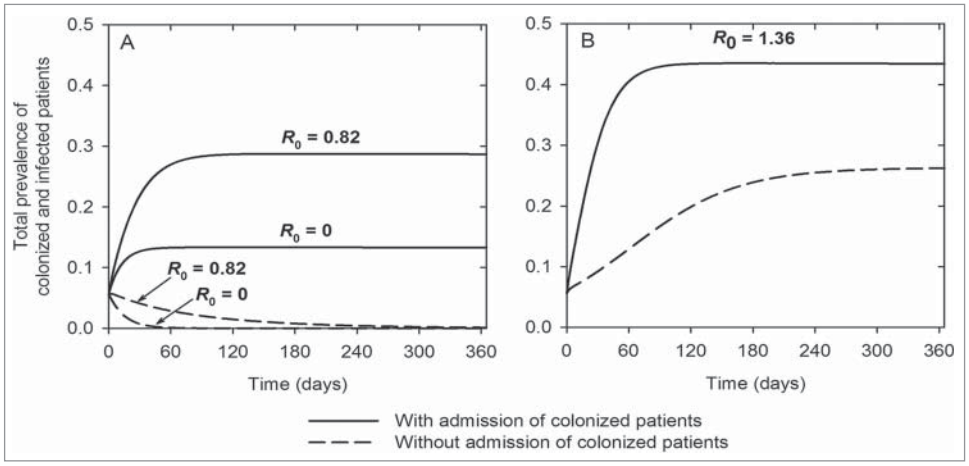

Figure 5. Prevalence of *A. baumannii* when the basic reproduction ratio, $R_0 < 1$ (**A**) and $R_0 > 1$ (**B**). When $R_0 < 1$, *A. baumannii* persists when colonized and infected patients are admitted (solid lines), and will die out if there is no admission of colonized and infected patients (broken lines). When $R_0 > 1$, *A. baumannii* always persists, once it has been introduced into the ward, irrespective of whether colonized and infected patients are admitted.

reductions can be achieved when the efficacy of environmental cleaning (α) is improved from 55% (baseline) to 75% (**Fig. 3C**). **Figures 6A and B** show the combined effects of enhanced cleaning rate and cleaning efficacy. Combining the 2 interventions yields improved benefits compared to each intervention alone. For example, daily ward cleaning combined with improved cleaning efficacy (from 55% to 75%) reduces the total prevalence of colonization and infection by 18%, compared to 10–11% reduction achievable with each intervention alone. Isolation of infected patients has modest effects (**Fig. 4**). However, isolation combined with cleaning of isolation rooms is effective, significantly reducing the prevalence of colonized patients from 25% (baseline) to 14%, and the prevalence of infected patients from 18% (baseline) to 11%. With this strategy, R_0 is 0.7 (**Fig. 4**).

Figure 3D shows the effects of reducing the LoS of colonized patients (γ_C^{-1}). The prevalence of *A. baumannii* decreases with shorter LoS (increased discharge rate). Specifically, when the LoS is reduced from the baseline of 16.5 d to 10 days, R_0 reduces to below unity, and the prevalence of colonization and infection reduces by 7% (from 25% to 18%) and 5% (from 18% to 13%), respectively.

When antibiotic prescribing rate (ε) among ICU patients (for reasons other than treatment of *A. baumannii* infection) and antibiotic treatment duration of infected patients (τ^{-1}) are investigated separately, only the latter is effective. Reducing antibiotic prescribing rate from 0.12 (baseline) to 0 (no antibiotic use) only results in a 4% reduction in the total prevalence of colonized and infected patients (**Fig. 3E**). In contrast, similar reductions in antibiotic treatment duration of infected patients (τ^{-1}, from 13 d to 5 days) decrease the total prevalence of colonized and infected patients by 14% (from

43% to 29%) and R_0 to unity (**Fig. 3F**). This intervention has greater effects on the prevalence of infected patients than on colonized patients because it specifically targets the former (**Fig. 3F**). Combining the 2 interventions fails to yield any improvements in reducing *A. baumannii* prevalence compared to each intervention alone (**Figs. 6C and D**). For example, simultaneously reducing antibiotic prescribing rate from 0.12 to 0 and antibiotic treatment duration of infected patients from 13 d to 5 d only results in a 14% reduction in the total prevalence of colonized and infected patients. Comparable reduction would be achievable with reduced antibiotic treatment duration of infected patients alone.

The use of probiotics to expedite the recovery of the intestinal microbiota (λ, 1/recovery time) is not effective. Reducing the recovery time from 35 d to 14 d only reduces the total prevalence of colonization and infection by 1% (**Fig. 3G**). No enhanced effects are achieved when probiotics are used in conjunction with reduced antibiotic prescribing rate (**Figs. 6E and F**).

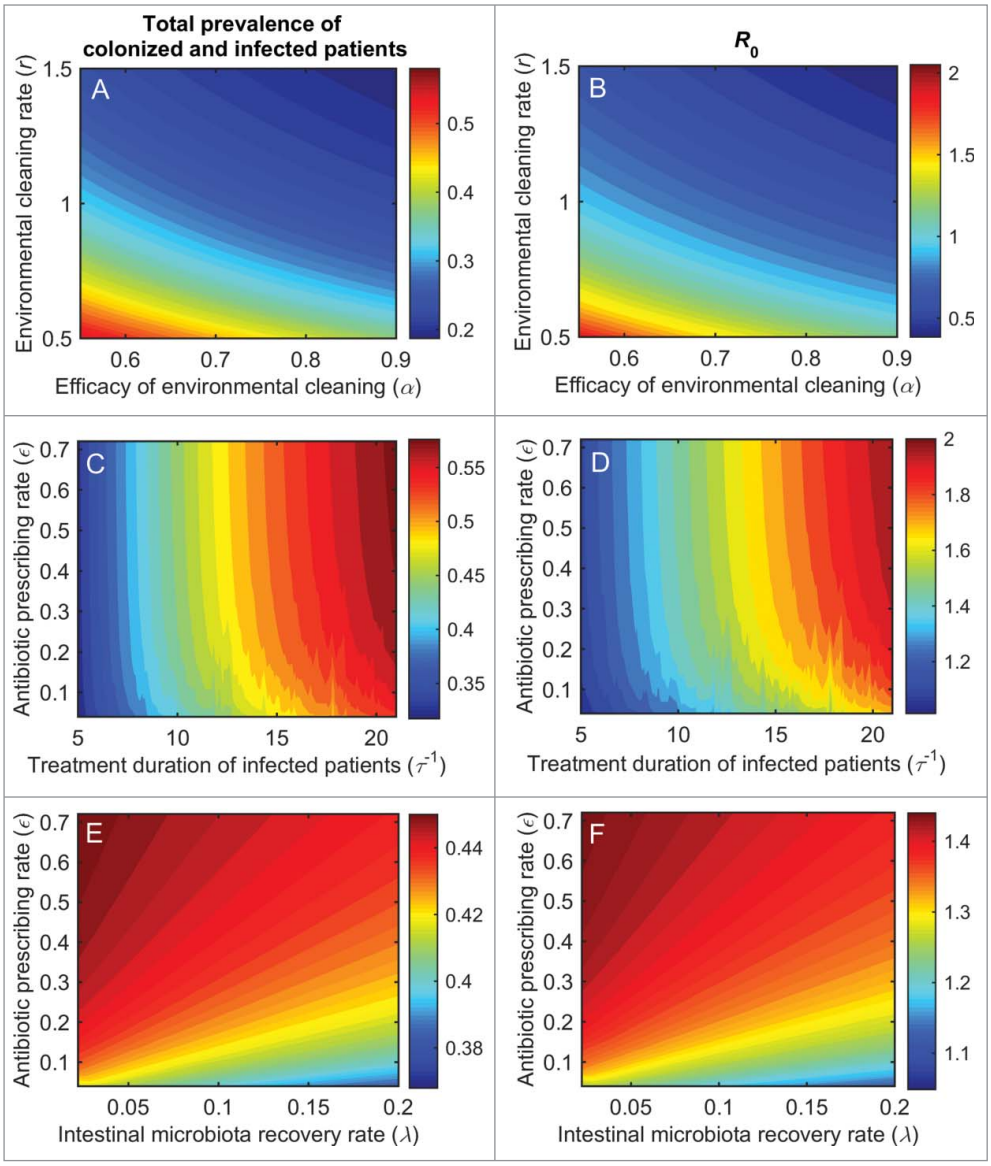

Figure 6. Effects of different combinations of interventions on the total prevalence of colonization and infection (**A, C, E**), and the basic reproduction ratio, R_0 (**B, D, F**).

Varying transmission coefficients

Figure 7 shows the effects of varying the cross-transmission coefficient (β) or environment-patient transmission coefficient (ζ) on the prevalence of *A. baumannii* and R_0. Contaminated environment is the predominant acquisition source compared to cross-transmission. Complete elimination of environment-patient transmission ($\zeta = 0$) generates substantial benefits, reducing the prevalence of colonization from 25% to 7% and infection from 18% to 6%. Eliminating this transmission source reduces R_0 to zero. In contrast, only modest impact occurs when cross-transmission is limited.

Sensitivity analysis

Figure 8 shows the sensitivity of the outcome measures to changes in model inputs. The outcome measures are most sensitive to LoS of colonized patients (γ_C^{-1}), *A. baumannii* treatment success rate (σ), environment-patient transmission coefficient (ζ) and fatality rate of infected patients (f). The correlation coefficients are shown in **Table 3**.

Discussion

Our study represents the most comprehensive transmission dynamic model for *A. baumannii*. Unlike previous studies,[7,9-11,13,14,41] we differentiated between colonized and infected patients because of their differences in clinical characteristics, particularly in pathogenesis, infectivity and infection control management. Under the baseline values found from review of the literature, we predict that *A. baumannii* is likely to be endemic in ICUs. The estimated prevalence of colonization and infection is 25% and 18%, respectively. Although we did not calibrate our model to any outcome

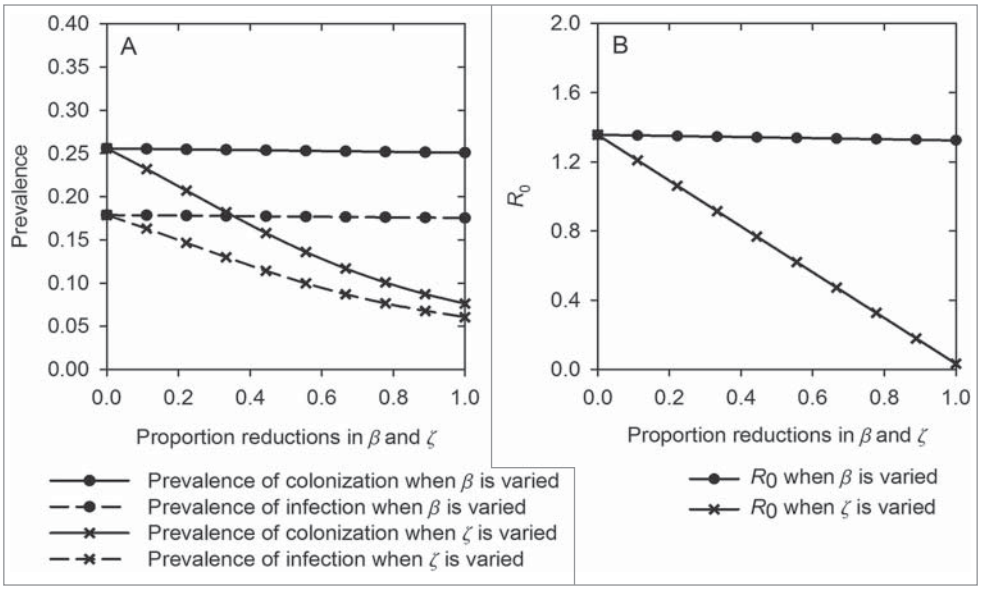

Figure 7. Effects of varying cross-transmission coefficient (β) and environment-transmission coefficient (ζ) on the prevalence of colonization and infection (**A**), and the basic reproduction ratio, R_0 (**B**). β and ζ were set at 50×10^{-4} and 4×10^{-6} at baseline, respectively.

values, our estimates are comparable with the mean values of the prevalence of *A. baumannii* colonization (21%)[4,16,42,43] and infection (16%)[5,42,44] reported in the literature. We found that *A. baumannii* transmission continues even when R_0 is below unity owing to admission of already colonized patients to the ICU. Our finding suggests that active screening on admission and subsequent isolation of positive cases is an essential component of any infection control policy to eliminate the transmission of this pathogen. Although this strategy may be effective in controlling *A. baumannii*, active screening is currently not in place in most hospitals worldwide. This may be due in part to concerns about the high costs of implementing such programs.[8] Nevertheless, a comprehensive cost-effectiveness analysis of active screening programs is needed.

Hand hygiene is the most effective intervention in our study because it limits both the transmission between patients and, between patients and the environment. The rate of compliance with hand hygiene was set at 82% at baseline in line with Australian data.[27] Although it is effective, inexpensive and simple, compliance with hand hygiene remains obstinately low in some settings, with estimated compliance rates as low as 50%.[45] When this compliance rate was considered, the prevalence of colonization, infection, and R_0 were estimated to be 44%, 31%, and 3.7, respectively. Using **Figure 3A**, predictions of *A. baumannii* prevalence and R_0 could be obtained for any level of hand hygiene compliance. Our model predicts that a modest improvement in compliance rate, from 82% to 87%, will reduce R_0 to below unity. Previous studies have shown that such improvements would be achievable with increased education and training, increased availability of alcohol-based hand rubs, workplace reminders, and performance feedback.[45]

Our model also shows that shorter durations of antibiotic treatment in patients infected with *A. baumannii* are associated with lower prevalence of *A. baumannii*. This suggests that treating patients as quickly and effectively as possible may be an effective strategy. Indeed, previous clinical studies have shown that the durations of antibiotic therapy could be safely reduced to ≤7 d based on clinical, laboratory and radiologic measures without any adverse effects on patient's outcomes while reducing the prevalence of infection and resistance.[46-48] These findings emphasize the importance of effective antimicrobial stewardship programs in reducing the duration of antibiotic therapy. However, it should be noted that the translation of the findings of these studies into clinical practice is currently unknown; and that the optimal durations of antibiotic treatment for many common infections remain to be established. Effective antimicrobial stewardship programs can also lead to reductions in antibiotic usage.[49] However, we found that reducing antibiotic prescribing rate among patients who are not infected with *A. baumannii* has a modest impact on *A. baumannii* prevalence, consistent with previous studies.[12,18] This is because this strategy only targets the small subset of patients who are uncolonized or colonized without prior antibiotic exposure in our model.

Clinical evidence on the efficacy of probiotics in reducing infections is inconclusive. It has been shown to be beneficial in some studies;[50] while others have shown minimal effects.[51] Our model suggests that using probiotics has a modest impact on the population-level transmission dynamics of *A. baumannii*, consistent with previous clinical studies.[51] Nevertheless, our finding does not necessarily negate the health benefits of these products on an individual-patient level.[26]

We found that reducing LoS is effective in attenuating *A. baumannii*, in support of evidence from clinical studies and previous models.[10,18,52] This is because this strategy reduces patient's risk factors for acquiring *A. baumannii* in the ICU.[16] Our finding is in contrast with Cooper et al.[28] who demonstrated in their model that shorter LoS resulted in higher within-ward colonization.[28] This may be explained by the increased number of susceptible patients admitted to the ward as a result of reduced LoS (increased discharge rate). Nevertheless, it should be noted that LoS of patients should be based on their clinical characteristics and response to treatment. As such, reducing LoS is likely to be impractical in reality.

The current model incorporates transmission from free-living bacteria in the environment, which has been ignored in the majority of previous models.[4,9-12,18,53] We found that

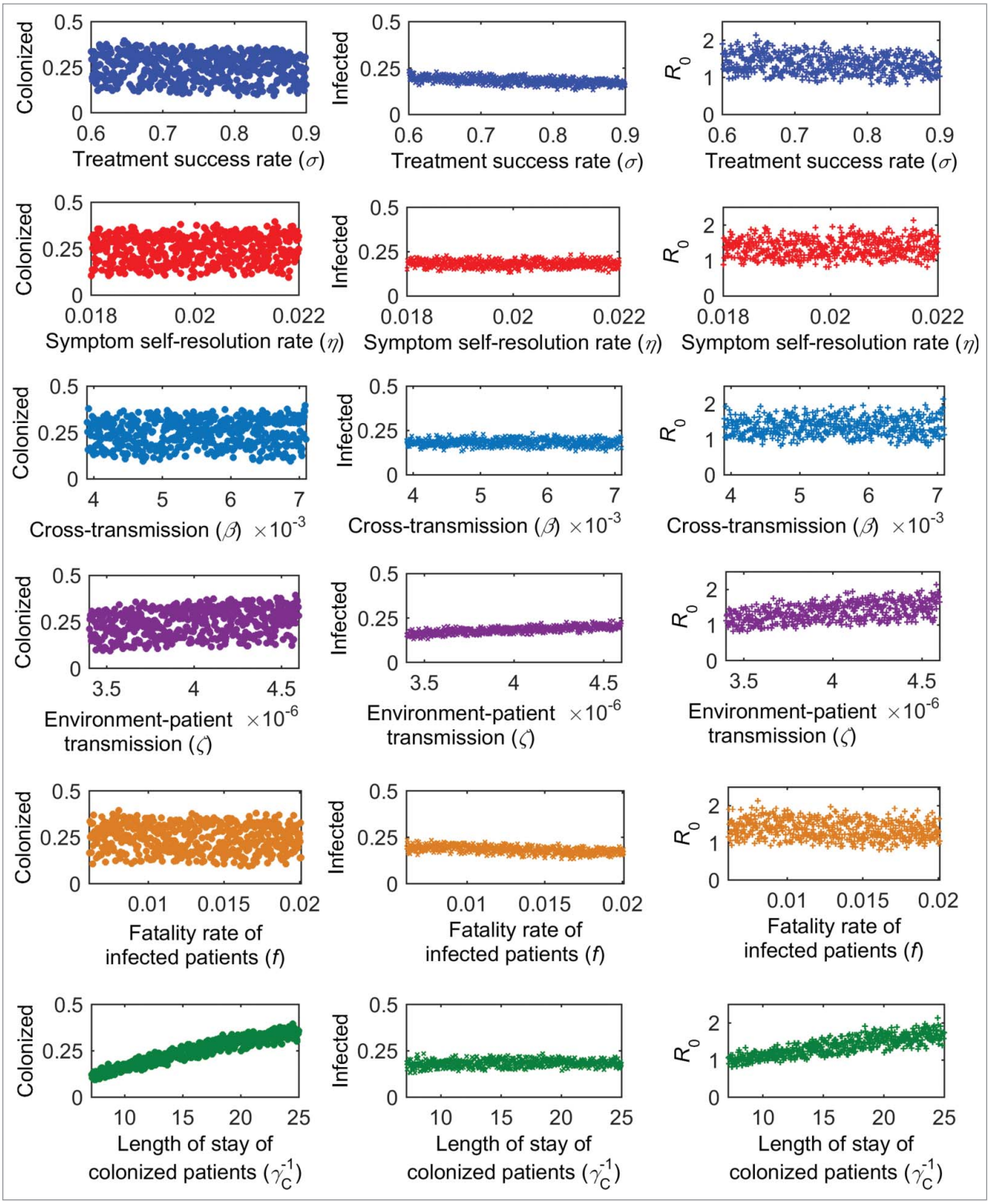

Figure 8. Sensitivity analysis.

contaminated environment is the major source of acquisition. Our finding reinforces the importance of environmental cleaning in controlling health-care associated infections as previously shown in clinical studies.[31,54] We found that improving the effectiveness of environmental cleaning would substantially reduce *A. baumannii*. This could be achieved by using more effective cleaning products, training and monitoring the efficacy of decontamination with feedback to cleaning teams. In our

Table 3. Correlation coefficients

Variable	Correlation coefficients		
	Prevalence of colonized patients	Prevalence of infected patients	R_0
Treatment success rate of *A. baumannii* infection (σ)	−0.85	−0.93	−0.94
Rate of self-resolution of symptoms (η)	0.15	−0.29	0.00
Cross-transmission coefficient (β)	0.13	0.16	0.26
Environment-patient transmission coefficient (ζ)	0.93	0.96	0.98
Fatality rate of infected patients (*f*)	−0.37	−0.93	−0.86
LoS of colonized patients (γ_C^{-1})	1	0.60	0.99

LoS, length of stay; R_0, basic reproduction ratio.

model, free-living bacteria in the ICU were assumed to be uniformly distributed. In fact, bacterial density may be different between places in the ICU (e.g., environment around infectious patients versus computer keyboards or door knobs). Future models that take into account such heterogeneity in contamination status are needed. Direct transmission between patients and free-living bacteria in the environment should also be considered in future studies.

Our study represents a biologically realistic model for the transmission dynamics of *A. baumannii* in ICUs. It provides a comprehensive analysis of the impact of interventions against this pathogen. We have incorporated crucial factors to the epidemiology of this pathogen such as antibiotic exposure, transmission from contaminated environment and, distinguishing colonization and infection. Like most biologically realistic simulation models, we were unable to simulate a specific setting because there is no single clinical study that provides complete parameterization for our model. Importantly, our model provides a framework that can be easily adjusted when such studies become available. Given that the epidemiology of *A. baumannii* varies considerably over time and between different settings, the intention of our model is not to provide numerical estimates that apply to every setting. However, our model can be adjusted to incorporate institution-specific data to guide infection control. Our model can be modified to integrate greater complexity such as co-morbidities, immune status, antibiotic resistance, co-infection with other pathogens, and the effects of stochasticity.

Disclosure of Potential Conflicts of Interest

DCM.K. has sat on advisory boards of Pfizer, Merck Sharp & Dohme, and receives financial/travel support (unrelated to the current work) from Pfizer, Roche, Merck Sharp & Dohme, Novartis and Gilead Sciences. C.M.J.K has undertaken collaborative research projects unrelated to the current work with Roche, Pfizer, CSL and d3 Medicine. All other authors have no potential conflicts of interest to disclose.

Funding

T.N.D. is a recipient of the Monash Graduate Scholarship and Monash International Postgraduate Research Scholarship. E. S.M. has received financial support from the Australian National Health and Medical Research Council (NHMRC) Career Development Fellowship. All other authors: none to declare.

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Appendix 1 The next generation matrix for estimating the basic reproduction number, R_0

The next generation matrix method involves linearizing the original nonlinear ordinary differential equations at disease-free equilibrium.[38] At the disease-free equilibrium, X^*, the numbers of individuals in each compartment are given by:

$$X^* = \left\{ U^* = \frac{-\lambda N - \gamma_{UA} N \mu_U}{\gamma_U \mu_U - \gamma_{UA} \mu_U - \lambda - \gamma_U - \varepsilon},\ U_A^* = N - U^*,\ C^* = 0,\ C_A^* = 0,\ I^* = 0 \right\}.$$

Let F be the transmission matrix, describing the production of new infections; and V be the transition matrix, describing changes in state (including removal by discharge or death). F and V are defined as follows:

$$F = \left[\frac{\partial F_i(X)}{\partial X_j} \right]_{X = X^*} \text{ and } V = \left[\frac{\partial V_i(X)}{\partial X_j} \right]_{X = X^*}$$

where $F_i(X)$ is the number of new infections in the i^{th} compartment from X_j infectious individuals; and $V_i(X)$ is the net change of individuals in the i^{th} compartment by any other means. The rates are evaluated at the disease-free equilibrium, X^*. The next generation matrix, K, is then given by $K = -FV^{-1}$. The (i,j) element of the K matrix represents the number of secondary infected cases in compartment i produced by individuals in compartment j. The basic reproduction number, R_0, is given by the spectral radius of the K matrix.

For our model, the transmission and transition matrices in the case with only cross-transmission between patients (F_P and V_P, respectively) are given by:

$$F_P = \begin{bmatrix} \frac{U^* \beta (1-h)}{N} & \frac{U^* \beta (1-h) \Omega_1}{N} & \frac{U^* \beta (1-h) \Omega_2}{N} \\ \frac{U_A^* \beta \times 1.67 \times (1-h)}{N} & \frac{U_A^* \beta \times 1.67 \times (1-h) \Omega_1}{N} & \frac{U_A^* \beta \times 1.67 \times (1-h) \Omega_2}{N} \\ 0 & 0 & 0 \end{bmatrix};$$

$$V_P = \begin{bmatrix} -(\gamma_C + \theta + \varepsilon) & \lambda & 0 \\ \varepsilon & -(\gamma_{CA} + \theta_A + \lambda) & (1-\sigma)\tau + \eta \\ \theta & \theta_A & -(f + \tau + \eta) \end{bmatrix}.$$

The next generation matrix with only cross-transmission is then given by $K_P = -F_P V_P^{-1}$.

The transmission and transition matrices in the case with only environment-patient transmission (F_E and V_E, respectively) are given by:

$$F_E = \begin{bmatrix} \zeta U^* (1-h) \\ \zeta U_A^* (1-h) \\ 0 \end{bmatrix};\ V_E = [-r\alpha].$$

The next generation matrix with only environment-patient transmission, K_E, is then given by

$$K_E = F_E V_E^{-1} [\Phi_1 \quad \Phi_2 \quad \Phi_3]\ V_P^{-1}.$$

The next generation matrix of the model is then given by $K = K_P + K_E$; and R_0 is given by the spectral radius of the K matrix. The high-dimension of the K matrix makes analytical solution for R_0 intractable. R_0 therefore was derived numerically in our model. Detailed discussion of the next generation matrix method for compartmental epidemic models can be found in Diekmann et al.[38]