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Cristina Lanzas
Cornell University

Erik R. Dubberke
Washington University School of Medicine in St. Louis

Z Lu
Cornell University

Kimberly Ann Reske
Washington University School of Medicine in St. Louis

Y T. Grohn
Cornell University

ORIGINAL ARTICLE

Epidemiological Model for *Clostridium difficile* Transmission in Healthcare Settings

C. Lanzas, DVM, PhD;[1,2] E. R. Dubberke, MD, MPH;[3] Z. Lu, PhD;[1] K. A. Reske, MPH;[3] Y. T. Gröhn, DVM, PhD[1]

OBJECTIVE. Recent outbreaks of *Clostridium difficile* infection (CDI) have been difficult to control, and data indicate that the importance of different sources of transmission may have changed. Our objectives were to evaluate the contributions of asymptomatic and symptomatic *C. difficile* carriers to new colonizations and to determine the most important epidemiological factors influencing *C. difficile* transmission.

DESIGN, SETTING, AND PATIENTS. Retrospective cohort study of all patients admitted to medical wards at a large tertiary care hospital in the United States in the calendar year 2008.

METHODS. Data from six medical wards and published literature were used to develop a compartmental model of *C. difficile* transmission. Patients could be in one of five transition states in the model: resistant to colonization (R), susceptible to colonization (S), asymptomatically colonized without protection against CDI (C^-), asymptomatically colonized with protection against CDI (C^+), and diseased (ie, with CDI; D).

RESULTS. The contributions of C^-, C^+, and D patients to new colonizations were similar. The simulated basic reproduction number ranged from 0.55 to 1.99, with a median of 1.04. These values suggest that transmission within the ward alone from patients with CDI cannot sustain new *C. difficile* colonizations and therefore that the admission of colonized patients plays an important role in sustaining transmission in the ward. The epidemiological parameters that ranked as the most influential were the proportion of admitted C^- patients and the transmission coefficient for asymptomatic carriers.

CONCLUSION. Our study underscores the need to further evaluate the role of asymptomatically colonized patients in *C. difficile* transmission in healthcare settings.

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Clostridium difficile is the leading cause of infectious diarrhea in hospitals and has become, along with methicillin-resistant *Staphylococcus aureus*, one of the most common causes of health care–associated infections.[1,2] The incidence and severity of *C. difficile* infection (CDI) have increased dramatically since 2000, and CDI is estimated to cause as many as 20,000 deaths and to cost as much as $3.2 billion per year in US acute care facilities alone.[3-5] CDI outbreaks have become more common, and infection control–based CDI prevention efforts appear to be less effective than in the past.[2,6]

Studies on *C. difficile* nosocomial transmission were undertaken in the late 1980s.[7-9] Clabots et al.[9] provided evidence that asymptomatically colonized patients newly admitted to a ward were an important source of transmission. Patients with symptomatic CDI, as compared to asymptomatic *C. difficile* carriers, were more likely to contaminate their surroundings and the hands of healthcare workers with *C. difficile*.[7,8] Therefore, it was concluded that symptomatic CDI patients were the main source of *C. difficile* transmission. As a result, current CDI prevention efforts, such as isolation and contact precautions, target only symptomatic CDI patients.[10] Changes in the epidemiology of *C. difficile* and health care delivery since the original transmission studies were conducted may have shifted the relative contribution of symptomatic CDI patients and asymptomatic carriers.[11] For example, since 2002 alcohol-based hand hygiene products have been recommended as the primary form of hand hygiene in healthcare settings.[12] *C. difficile* spores are resistant to the bactericidal effects of alcohol.[13] Use of alcohol-based hand hygiene products by healthcare workers after they have cared for asymptomatic *C. difficile* carriers may increase those carriers' contribution to *C. difficile* transmission.[13] Conversely, rapid identification of patients with CDI and placing these patients in contact precautions may have reduced the contribution to *C. difficile* transmission from patients with CDI.[10,14]

Mathematical models of disease transmission provide a conceptual framework for understanding and quantifying

Affiliations: 1. Department of Population Medicine and Diagnostic Sciences, College of Veterinary Medicine, Cornell University, Ithaca, New York; 2. Department of Comparative Medicine, College of Veterinary Medicine, University of Tennessee, Knoxville, Tennessee; 3. Department of Medicine, Washington University School of Medicine, St. Louis, Missouri.

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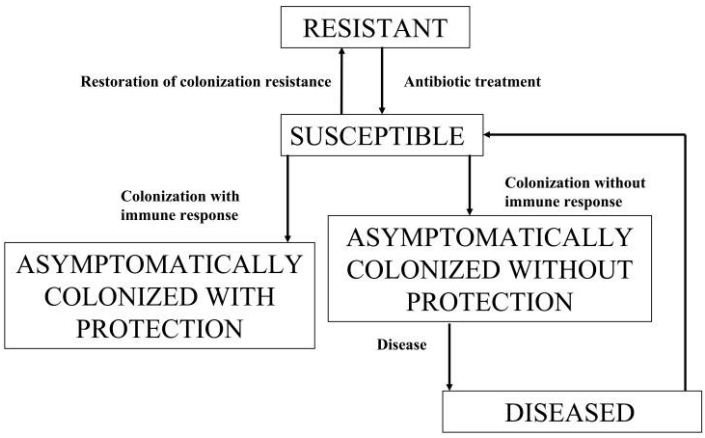

FIGURE 1. Flow diagram of the epidemiological model for *Clostridium difficile* transmission in a hospital ward. Five transition states are included: resistant (R), susceptible (S), asymptomatically colonized without protection against *C. difficile* infection (C^-), asymptomatically colonized with protection against *C. difficile* infection (C^+), and diseased (D).

transmission and intervention strategies. Mathematical models have helped researchers to understand the epidemiology of other nosocomial pathogens, such as vancomycin-resistant enterococcus[15,16] and methicillin-resistant *S. aureus*.[17] To date, efforts to model *C. difficile* transmission have been limited; Starr et al.[18] modeled *C. difficile* transmission in a geriatric ward. They quantified *C. difficile* transmission within and between rooms but did not address the relative contributions of asymptomatic and clinical patients as sources of new infections.[18] In addition, the data were collected prior to the changes in CDI epidemiology.[19]

Our objectives were to provide a framework for evaluating the relative contributions of asymptomatically and symptomatically colonized patients to new colonizations and to determine the most important epidemiological factors influencing *C. difficile* transmission at the ward level. For that purpose, we developed an epidemiological model of *C. difficile* and evaluated the impact of different epidemiological parameters on *C. difficile* transmission. We used recent data from a large tertiary care hospital and published literature to estimate model parameters.

METHODS

Data

Data were collected retrospectively from six medicine wards at Barnes-Jewish Hospital in St. Louis, Missouri, during the calendar year 2008. The data were collected electronically from the hospital's medical informatics databases and included patient demographics, dates of hospital and ward admission, discharge, and transfers, laboratory tests, and medication exposures. Two of the wards had 26 beds each, 1 had 29 beds, and 3 had 30 beds each. On average, 153 patients were admitted per ward per month, including 109 per month whose length of stay was greater than 48 hours. The microbiology laboratory at Barnes Jewish Hospital tests only diarrheal stool for the presence of *C. difficile* toxin (Remel ProSpecT *C. difficile* Toxin A/B). Testing stool for the presence of *C. difficile* toxin requires a physician order. During the study period, patients with a diagnosis of CDI were placed into isolation, and contact precautions were initiated. Isolation and precautions were typically initiated only after the patient had received a diagnosis of CDI. The data set included 11,046 patients. The mean age of patients was 57 years old. They had a mean Charlson Comorbidity Score of 1.8, and 54% were female. On average, there were 2.2 incident cases of clinical CDI (patients who acquired CDI after admission) per month in each ward (157 in total for all six wards) and 2.2 prevalent cases of clinical CDI (patients with CDI on admission) per month on each ward.

Epidemiological Model

We developed an epidemiological model for *C. difficile* transmission in a ward (Figure 1). In an epidemiological model, the patient population is divided into transition states according infection status. The *C. difficile* epidemiological model included the following transition states: resistant to colonization (R), susceptible to colonization (S), asymptomatically colonized without protection against CDI (C^-), asymptomatically colonized with protection against CDI (C^+), and diseased (ie, with CDI, D; Table 1). Resistant individuals were defined as patients who had not received antimicrobial treatment and had a normal intestinal microbiota that provided "colonization resistance" against *C. difficile*.[20] Although patients with normal flora can be colonized with *C. difficile*, such colonizations appear to be transient, and a normal flora is associated with a much lower risk of development of CDI than is an altered flora.[8,9,21] Hence, we assumed that individuals with a normal intestinal microbiota were resistant to *C. difficile* colonization. Susceptible patients received antimicrobial treatment and could be colonized by

TABLE 1. Summary of the Transition States Included in the Epidemiological Model for *Clostridium difficile* Transmission Based on Four Criteria: Antimicrobial Treatment, Presence of Toxigenic *C. difficile*, Immune Response, and Clinical Symptoms

	Antimicrobial treatment	Presence of toxigenic *C. difficile*	Immune response against *C. difficile*	*C. difficile* symptoms
Resistant	−	−	−	−
Susceptible	+	−	−	−
Colonized without protection	+	+	−	−
Colonized with protection	+	+	+	−
Diseased	+	+	+/−	+

C. difficile. Antibiotic treatment disrupts the normal microbiota, making patients significantly more susceptible to *C. difficile* colonization and development of CDI after colonization.[22] Three types of colonized patients were included in the model: C^-, C^+, and D. We considered two types of asymptomatically colonized patients, according to the risk of developing CDI. Colonized patients either could or could not mount a protective response. Asymptomatically colonized patients who did not mount an immune response could develop disease. Diseased patients were treated with antibiotics. Depending on treatment success, diseased patients could either continue to be diseased or become susceptible again at the end of therapy. Patients could be admitted and discharged in any of the five states, and C^+ patients were assumed to be colonized during the entire duration of their hospitalization.[7-9] The mathematical model is presented in the appendix.

Parameterization

Model parameters are described in Table 2. The proportions of admitted patients defined as resistant (R) and diseased (D) were obtained from the hospital data. Patients who did not receive antibiotics during their admission were considered resistant. Patients with a positive stool sample within 48 hours after admission were considered to have been diseased when admitted.[10] The antibiotic prescription rate was obtained from the hospital data set and was based on the admission rate and the percentage of individuals who received antibiotics during their stay. Patients were considered susceptible after being exposed to antibiotics. The microflora returns to normal 1–49 days after the end of the treatment, depending on the antimicrobial group.[22] We set the restoration rate to 0.033/day, which means that the microflora of each patient recovers by 3.3% each day and therefore returns to normal after 30 days, on average. Vancomycin and metronidazole are considered the standard treatments for CDI. For 80% of patients with CDI, diarrhea symptoms resolve within a typical 10-day treatment, regardless of antibiotic type.[24] Therefore, the treatment rate was set to 0.10/day, the inverse of the treatment duration, and the probability of successful treatment was set to 0.80. The clinical disease rate is the inverse of the incubation period.[9,25] The mean fraction of colonized patients that mounted an immune response was set at 0.60; 60% of the patients that became colonized had detectable antibody responses.[23] Discharge rates, the inverse of length of stay, were obtained from the hospital data set. Patients without antimicrobial treatment (R) during the hospitalization had the shortest length of stay (3 days). Susceptible and colonized patients had an average length of stay of 6.7 days. For clinical CDI (ie, D patients), the length of stay was 14.7 days (Table 2). Default values for transmission coefficients and the proportion of patients admitted in states S, C^-, and C^+ were set to match observed attack rates.

Simulations

The model predicted the following outcomes: the basic reproduction number (R_0), the average number of secondary colonizations generated by each type of admitted colonized patient (C^-, C^+, D), and the number of CDI cases per 1,000 admitted patients. The basic reproduction number is the average number of secondary colonizations generated by a primary *C. difficile* colonization in a *C. difficile*–free ward. It conveys information regarding the transmissibility of the pathogen in a specific setting. The higher the R_0, the greater the pathogen transmissibility. To quantify R_0 and the contribution of the three types of admitted colonized patients to new colonizations, we constructed the so-called next-generation matrix for the model.[26] The next-generation matrix allowed us to express outcomes as a function of the epidemiological model parameters.[26] Then we performed a sensitivity analysis to assess which epidemiological parameters were the most influential. The sensitivity analysis used the Sobol' sensitivity indices.[27] Sobol' indices are an ANOVA-like decomposition, and they partition the variability of the model output (ie, expected secondary colonizations and R_0) into main effects of the parameters and total effects (including interactions between parameters). In addition, simulations of the stochastic model (see "Stochastic Model" in the appendix for details) were performed to evaluate the effect of varying the proportions of admitted colonized and diseased patients and other parameters on the number of CDI cases per 1,000 admitted patients.

RESULTS

Model simulations are presented in Figures 2–5. The R_0 ranged from 0.55 to 1.99 (Figure 2). For almost 50% of the

TABLE 2. Parameters for the *Clostridium difficile* Model

Symbol	Description, units	Baseline value	Range used in sensitivity analysis	Source
a_r	Proportion of admitted patients that are resistant, dimensionless	0.75	...	Hospital data[a]
a_s	Proportion of admitted patients that are susceptible, dimensionless	0.22	0.15–0.29	Estimated[b]
a_{cn}, a_{cp}	Proportion of admitted patients that are colonized (C^- and C^+, respectively), dimensionless	0.01	...	Estimated[b]
a_d	Proportion of admitted patients with *C. difficile* infection (diseased), dimensionless	0.01	...	Hospital data[a]
α	Antibiotic prescription rate, per day	0.5	0.35–0.65	Hospital data[a]
θ	Restoration rate of colonization resistance, per day	0.033	0.023–0.043	Rafii et al[22]
β_c, β_d	Transmission coefficients for asymptomatic carriers and diseased patients, respectively, per individual-day	0.007	0.004–0.01	Estimated[b]
f	Fraction of colonized patients that mount immune response, dimensionless	0.60	0.45–0.75	Kyne et al[23]
ε	Treatment rate, per day	0.10	0.07–0.13	McFarland[24]
p	Probability of successful treatment, dimensionless	0.80	0.56–1	McFarland[24]
ϕ	Clinical disease rate, per day	0.2	0.14–0.26	Clabots et al;[9] Chang et al[25]
k_r	Discharge rate for resistant patients, per day	0.33	0.23–0.43	Hospital data[a]
k	Discharge rate for susceptible and colonized patients, per day	0.15	0.105–0.195	Hospital data[a]
k_d	Discharge rate for diseased patients, per day	0.068	0.048–0.088	Hospital data[a]

[a] Parameters obtained directly from the hospital data.
[b] Values set to match observed attack rate.

simulations, R_0 was less than 1. This is a threshold value because if R_0 is greater than 1, on average 1 colonization leads to more than 1 secondary colonization and therefore, the number of colonizations will grow in the population. The parameters that explained most of the variation in R_0 were the variation in transmission parameters (β_c and β_d) and the duration of stay of the colonized patients (k and k_d; Figure 2). Specifically, the two most influential parameters were the transmission coefficient for asymptomatic patients (β_c) and the discharge rate for susceptible and colonized patients (k). The proportion of the R_0 variation that was not explained directly by the parameters was very small (1%) and was due to interactions among parameters (Figure 2).

Figure 3 displays the average number of new colonizations that each type of colonized patient can produce once admitted to a *C. difficile*–free ward. These values may not be attainable because the wards are not completely occupied by susceptible individuals and have a continuous inflow of newly admitted patients and outflow of discharged patients. Nevertheless, they provide a way to rank the contributions of different types of admitted colonized individuals to new colonizations. The three types of colonized patients contributed similarly to new colonizations, each resulting in an average of 0.40 new C^- colonizations and 0.60 new C^+ colonizations (Figure 3). Admitted C^- patients contribute to new colonizations as C^- and D (if they move into the D state). The parameters that explained most of the variation in the contribution of the three types of colonized patients were the fraction of newly colonized patients that mount an immune response (f), the transmission coefficient for diseased patients (β_d), the transmission coefficient for asymptomatic carriers (β_c), and the discharge rate of colonized and susceptible patients (k).

Figures 4 and 5 display the results of the stochastic simulations. The proportion of patients admitted as C^- was the epidemiological parameter with the strongest influence on the number of new CDI cases per 1,000 admitted patients. For the scenario with the baseline parameters, the median for the number of CDI cases was 17.85 per 1,000 patients (Figure 4). Increasing the proportion of admitted C^- by 0.01 increases the median attack rate to 27.54 new cases per 1,000 patients. Changing the proportions of C^+ and D patients had similar effects, but their influence on the number of CDI cases was lower than that of the proportion of C^- patients (Figure 4). Among the other parameters evaluated, transmission coefficients, clinical disease rate, and the fraction of newly colonized patients that mount an immune response were the most influential (Figure 5).

DISCUSSION

We present a mathematical model of the transmission of *C. difficile* in healthcare settings. We considered three types of colonization during hospitalization (Table 1). We omitted other states and transitions that may be relevant at the community level. Proposed models for community-associated *C. difficile* included states such as "clinically resolved–colonized"

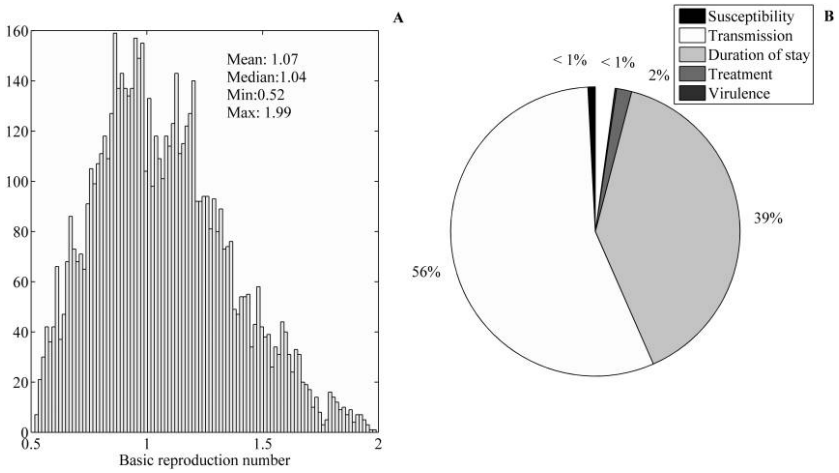

FIGURE 2. Distribution of the basic reproduction number when parameters are varied (*A*) and contribution of the grouped parameters to the variation observed in the basic reproduction number (*B*). We grouped the parameters according to whether they determine (1) patient susceptibility (a_s, α, θ, k_r), (2) transmission (β_c, β_d), (3) duration of stay of colonized individuals (k, k_d), (4) treatment (ε, p), or (5) virulence (f, ϕ). Parameters are defined in Table 2.

(CDI successfully treated but patient remains colonized) and transitions such as decolonization.[28] At the hospital level, the likelihood of observing some of these states and transitions is low because of the short duration of patient stay. For example, we assumed that the colonization lasted for the complete duration of the hospitalization because follow-up studies have indicated that patients remained colonized 30 days after discharge.[23]

The increases in CDI incidence and severity and difficulties in controlling CDI have led to the conclusion that the epidemiology of *C. difficile* has changed in recent years.[11,29] Potential explanations include alterations in healthcare practices over the past 20 years, increased asymptomatic carriage, increased patient susceptibility, and organism-specific factors that have increased virulence or transmission.[30] All these changes may have increased transmission coefficients (eg, the use of alcohol-based hand hygiene products over hand washing may have increased β_c), increased the proportions of admitted asymptomatic carriers (a_{cn} and a_{cp} for C^- and C^+ patients, respectively) and diseased patients (a_d), or decreased the fraction of colonized patients capable of mounting an immune response (f), among other effects. We evaluated the effect of modifying these epidemiological parameters in *C. difficile* epidemiology. The admission of colonized patients, especially C^- patients, highly influenced *C. difficile* outcomes. The number of CDI cases increased as the percentage of admitted colonized patients increased (Figure 3). In addition, the basic reproduction number (R_0) ranged from 0.55 to 1.99. These values suggest that for a wide range of parameter values, transmission within the ward alone cannot sustain *C. difficile* colonization. Therefore, the admission of colonized patients plays an important role in sustaining transmission in the ward. An increase in the proportion of admitted patients who are already colonized is possible, as data indicate that *C. difficile* contamination of foodstuffs is more common than previously recognized and that community-associated CDI is increasing.[31,32]

The number of CDI cases was also sensitive to variations in the incubation period. As the incubation period increased, the number of cases due to transmission decreased because the chances that an asymptomatic colonized patient left before becoming diseased increased. Therefore, increased incubation periods may increase the number of patients with community-onset, healthcare facility–associated CDI. These patients may be readmitted later as diseased patients. Previous research indicates that patients with health care–onset CDI were more likely to receive a fourth-generation cephalosporin or intravenous vancomycin than were patients with community-onset healthcare facility–associated CDI.[33] These

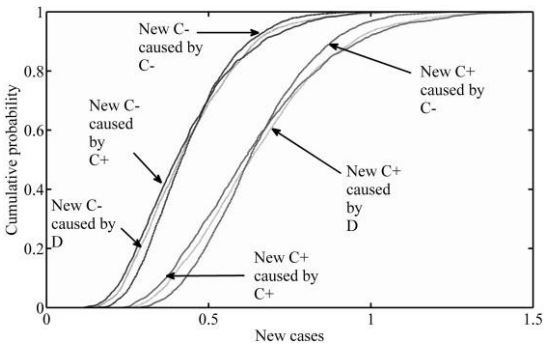

FIGURE 3. Number of new secondary colonizations (state C^- or C^+) generated by each type of admitted colonized patient (C^-, C^+, or D). See Figure 1 for definition of states C^-, C^+, and D.

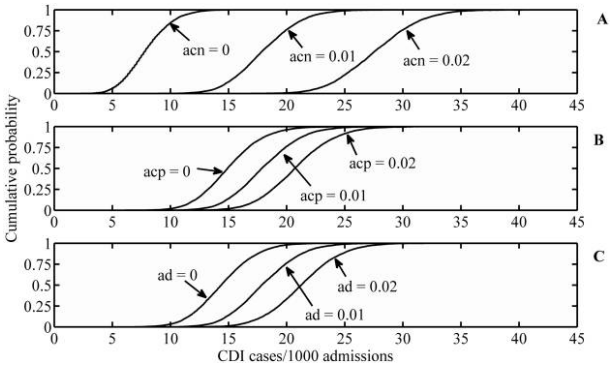

FIGURE 4. Effect of varying the proportions of admitted patients colonized without immunity (a_{cn}; *A*), colonized with immunity (a_{cp}; *B*), and with disease (a_d; *C*) on the average number of *Clostridium difficile* infection (CDI) cases per 1,000 admissions.

antibiotics may shorten the incubation period because of their broad impact on the normal microflora, or they may be markers for sicker patients more susceptible to *C. difficile*.[22,34] Other influential parameters were the transmission coefficients and the fraction of patients that mounted an immune response against *C. difficile*. These results are supported by studies demonstrating that efforts to reduce transmission of *C. difficile* from hands of healthcare workers are highly effective[35] and by data demonstrating the importance of the immune response and the risk of developing CDI.[10]

Interestingly, epidemiological parameters linked to patient susceptibility, such as antimicrobial treatment rate, had little impact on *C. difficile* transmission (Figure 2). This appears to be contrary to CDI prevention recommendations and data indicating that antimicrobial stewardship is effective at preventing CDI.[23,36] There are several potential explanations for this. In this study, we did not differentiate between classes of antibiotics in terms of risk of CDI. This may have limited our ability to detect a reduction in CDI incidence caused by limiting antibiotic exposures. A large percentage of patients were considered susceptible because of antimicrobial treatment; therefore, the rate at which the resistant patients become susceptible patients was not a limiting factor in *C. difficile* transmission. Conversely, most data supporting antimicrobial stewardship to prevent CDI occur in outbreak settings in conjunction with other prevention efforts. It is possible that antimicrobial stewardship by itself is less effective in nonoutbreak situations or in the absence of efforts to reduce *C. difficile* transmission.

There are some limitations to this study. Actual *C. difficile* colonization prevalence on admission and at discharge from the study wards was not available. However colonization prevalence reported in the literature was used for the parameter estimates, and assessment of colonization status conducted after the study period indicates that the levels of prevalence of *C. difficile* colonization on admission and discharge at the study hospital are consistent with those in the literature (5% and 15%, respectively; E. R. Dubberke, unpublished data). The diagnosis of CDI was based on the result of a toxin enzyme immunoassay in patients with diarrhea. Toxin enzyme immunoassays suffer from variable sensitivities, possibility missing true occurrences of CDI.[36] This often results in repeat testing and consequently increases the risk of having a false positive result as well.[37] Transmission coefficients were identified as important parameters. Therefore, the different routes of transmission through contaminated healthcare workers and environment must be considered explicitly in the model to design future interventions to prevent *C. difficile* transmission.

The epidemiology of *C. difficile* has changed dramatically in the past decade, with notable increases in CDI incidence and severity. Current prevention recommendations appear to be effective in combating CDI outbreaks; however, they may be less effective at preventing endemic CDI.[38] Our study underscores the need to further evaluate the role of asymptomatically colonized patients in *C. difficile* transmission and to identify methods to best prevent *C. difficile* transmission from these patients. The integration of *C. difficile*–based transmission modeling with culture-based data available after changes in CDI epidemiology and the development of methods to rapidly and reliably identify asymptomatic *C. difficile* carriers are necessary for a complete understanding of the most cost-effective methods of preventing CDI, the most common health care–associated infection.

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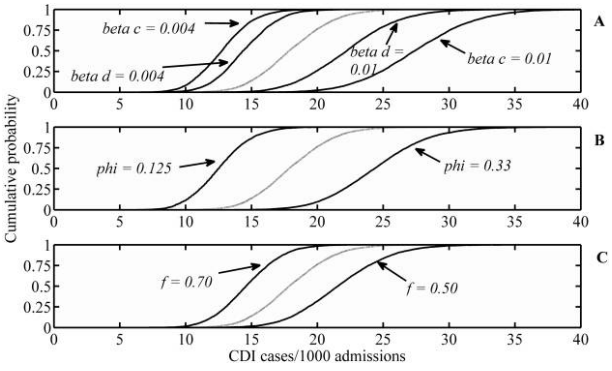

FIGURE 5. Effect of varying the transmission coefficients (β_c and β_d; *A*), the clinical disease rate (ϕ; *B*), and the proportion of colonized patients who mount an immune response (f; *C*) on the number of *Clostridium difficile* infection (CDI) cases per 1,000 admissions. The dashed line represents the simulation with the baseline parameter values.

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Potential conflicts of interest. E.R.D. reports that he has been a consultant for Optimer, Pfizer, Merck, Steris, Becton-Dickinson, and Meridian and that he has performed research for Optimer and Merck. All other authors report no conflicts of interest relevant to this article.

Address correspondence to Cristina Lanzas, DVM, PhD, Department of Comparative Medicine, College of Veterinary Medicine, University of Tennessee, 2407 River Drive A205, Knoxville, TN 37996-4543 (clanzas@utk.edu).

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APPENDIX

The deterministic differential equations for the model are as follows (parameters are defined in Table 2):

$$\frac{dR}{dt} = a_r\delta N + \theta S - k_r R - \alpha R, \tag{A1}$$

$$\frac{dS}{dt} = a_s\delta N + \alpha R + p\varepsilon D - \theta S - kS - \lambda S, \tag{A2}$$

$$\frac{dC^-}{dt} = a_{cn}\delta N + (1-f)\lambda S - \phi C^- - kC^-, \tag{A3}$$

$$\frac{dC^+}{dt} = a_{cp}\delta N + f\lambda S - kC^+, \tag{A4}$$

$$\frac{dD}{dt} = a_d\delta N + \phi C^- - p\varepsilon D - k_d D, \tag{A5}$$

$$\lambda = \beta_c(C^- + C^+) + \beta_d D, \tag{A6}$$

$$N = R + S + C^- + C^+ + D. \tag{A7}$$

At the disease-free equilibrium, the number of susceptible patients (S_0) can be described as a function of antibiotic prescription (α), colonization resistance restoration (θ), discharge rates (k, k_r), and number of ward beds (N) as

$$S_0 = \frac{(a_s k_r + \alpha)N}{[\alpha + a_s k_r + (1-a_s)k + \theta]}. \tag{A8}$$

For the next-generation matrix, we define the matrices **F** and **V** as

$$\mathbf{F} = \left[\frac{\partial F_i(x)}{\partial x_j}\right]_{x=x_0},$$

$$\mathbf{V} = \left[\frac{\partial V_i(x)}{\partial x_j}\right]_{x=x_0},$$

where $F_i(x)$ is the number of new infections in the ith compartment from x_j infectious individuals and $V_i(x)$ is the net change of individuals in the ith compartment by any other means. The rates are evaluated at the disease-free equilibrium $x = x_0$. For the model, **F** and **V** are given as

$$\mathbf{F} = \begin{bmatrix} (1-f)\beta_c S_0 & (1-f)\beta_c S_0 & (1-f)\beta_d S_0 \\ f\beta_c S_0 & f\beta_c S_0 & f\beta_d S_0 \\ 0 & 0 & 0 \end{bmatrix},$$

$$\mathbf{V} = \begin{bmatrix} k+\phi & 0 & 0 \\ 0 & k & 0 \\ -\phi & 0 & p\varepsilon + k_d \end{bmatrix},$$

$$\mathbf{V}^{-1} = \begin{bmatrix} \frac{1}{k+\phi} & 0 & 0 \\ 0 & \frac{1}{k} & 0 \\ \frac{\phi}{(p\varepsilon + k_d)(\phi + k)} & 0 & \frac{1}{p\varepsilon + k_d} \end{bmatrix}.$$

The next-generation matrix, **K**, is $\mathbf{FV}^{-1}$. The entry (i, j) of **K** is the expected number of secondary infections in compartment i produced by individuals initially in compartment j,

$$\mathbf{K} = \mathbf{FV}^{-1} = \begin{bmatrix} K_{c^-c^-} & K_{c^-c^+} & K_{c^-d} \\ K_{c^+c^-} & K_{c^+c^+} & K_{c^+d} \\ 0 & 0 & 0 \end{bmatrix},$$

where

$$K_{c^-c^-} = \frac{(1-f)\beta_c S_0}{\phi + k} + \frac{(1-f)\phi\beta_d S_0}{(p\varepsilon + k_d)(\phi + k)}, \tag{A9}$$

$$K_{c^-c^+} = \frac{(1-f)\beta_c S_0}{k}, \tag{A10}$$

$$K_{c^-d} = \frac{(1-f)\beta_d S_0}{p\varepsilon + k_d}, \tag{A11}$$

$$K_{c^+c^-} = \frac{f\beta_c S_0}{\phi + k} + \frac{f\phi\beta_d S_0}{(p\varepsilon + k_d)(\phi + k)}, \tag{A12}$$

$$K_{c^+c^+} = \frac{f\beta_c S_0}{k}, \tag{A13}$$

$$K_{c^+d} = \frac{f\beta_d S_0}{p\varepsilon + k_d}. \tag{A14}$$

Each entry (i, j) in the **K** matrix represents the expected number of secondary colonizations in compartment i produced by individuals initially in compartment j. The basic reproduction number is the spectral radius of the matrix **K**,

$$R_0 = \rho(\mathbf{K}) = \frac{(1-f)\beta_c S_0}{\phi + k} + \frac{(1-f)\phi\beta_d S_0}{(p\varepsilon + k_d)(\phi + k)} + \frac{f\beta_c S_0}{k}. \tag{A15}$$

Stochastic Model

We developed an individual-based stochastic model based on Figure 1. A combined algorithm based on the Gillespie direct

TABLE A1. Transition Probabilities and Discharge Events

Events	Transition probability	Duration	Changes
Restoration colonization resistance	$\theta S\Delta t + o(\Delta t)$		$R = 1, S = -1$
Antibiotic treatment	$\alpha R\Delta t + o(\Delta t)$		$R = -1, S = 1$
Treatment success	$p\varepsilon D\Delta t + o(\Delta t)$		$S = 1, D = -1$
Colonization without immune response	$(1 - f)\lambda S\Delta t + o(\Delta t)$		$S = -1, C^- = 1$
Colonization with immune response	$f\lambda S\Delta t + o(\Delta t)$		$S = -1, C^+ = 1$
Disease	$\phi C^-\Delta t + o(\Delta t)$		$C^- = -1, D = 1$
State of patient upon discharge			
R		$1/k_r$	$R = -1$
S		$1/k$	$S = -1$
C^-		$1/k$	$C^- = -1$
C^+		$1/k$	$C^+ = -1$
D		$1/k_d$	$D = -1$

and first-reaction methods was used to simulate our individual-based stochastic model.[39] In our simulations, when patients were admitted to hospital or moved to a different state, they were supposed to stay in a constant duration (depending which state they were in) prior to discharge unless they moved to another state. To utilize full beds in a ward, the admission was assumed to be immediate once a patient was discharged. Our model is a modified continuous-time Markov chain model, where time is continuous, $t \in [0, \infty)$, and the state space is discrete. The state space for the model is

$$\mathbf{X}(t) = (R(t), S(t), C^-(t), C^+(t), D(t)),$$

and $\Delta\mathbf{X}(t) = \mathbf{X}(t + \Delta t) - \mathbf{X}(t)$. The probability of a transition is

$$P[\Delta\mathbf{X}(t) = (r, s, c^-, c^+, d)\mathbf{X}(t)].$$

We assume that Δt is sufficiently small that the values of r, s, c^-, c^+, and d are nonzero. There are 11 possible changes in state where at least one of (r, s, c^-, c^+, d) is nonzero. The transition probabilities for the possible changes between states and the five types of discharge events are defined in Table A1.

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