

Quantifying Transmission of *Clostridium difficile* within and outside Healthcare Settings

David P. Durham, Margaret A. Olsen, Erik R. Dubberke, Alison P. Galvani, Jeffrey P. Townsend

To quantify the effect of hospital and community-based transmission and control measures on *Clostridium difficile* infection (CDI), we constructed a transmission model within and between hospital, community, and long-term care-facility settings. By parameterizing the model from national databases and calibrating it to *C. difficile* prevalence and CDI incidence, we found that hospitalized patients with CDI transmit *C. difficile* at a rate 15 (95% CI 7.2–32) times that of asymptomatic patients. Long-term care facility residents transmit at a rate of 27% (95% CI 13%–51%) that of hospitalized patients, and persons in the community at a rate of 0.1% (95% CI 0.062%–0.2%) that of hospitalized patients. Despite lower transmission rates for asymptomatic carriers and community sources, these transmission routes have a substantial effect on hospital-onset CDI because of the larger reservoir of hospitalized carriers and persons in the community. Asymptomatic carriers and community sources should be accounted for when designing and evaluating control interventions.

Infection with the nosocomial pathogen *Clostridium difficile* is a major risk in healthcare settings and long-term care facilities (LTCFs) and has an increasing prevalence in the broader community. Infection is diagnosed in $\geq 250,000$ hospitalized persons annually in the United States (1). Colonization of the gut microbiota with *C. difficile* can be innocuous and asymptomatic. However, antimicrobial drugs disrupt the normal intestinal microbial architecture and can enable proliferation of *C. difficile* (2). An insufficient host antibody response to *C. difficile* toxins A and B can then lead to *C. difficile* infection (CDI). CDI is a severe diarrheal disease that is concentrated among elderly persons and those with extended hospital stays or residing in LTCFs. The relative risk for CDI, given recent antimicrobial drug exposure, differs greatly among antimicrobial drug classes and ranges from no relative risk when receiving tetracyclines to a 20-fold relative risk when receiving clindamycin

(2). Despite an increasing interest in *C. difficile* biology and the epidemiology of CDI, fundamental questions about reservoirs and routes of transmission remain unanswered.

Molecular typing and contact tracing studies have estimated that 10%–38% of CDI cases that occur ≥ 48 hours after hospital admission (termed hospital-onset CDI) can be attributed to transmission from known symptomatic contacts within the hospital (3–6). These estimates suggest that a substantial proportion of CDI arises from other sources, such as transmission from patients with asymptomatic colonization or community acquisition (3,5,7,8). The relative role of these routes of transmission to the epidemiology of *C. difficile* is crucial for determining effectiveness of hospital-based measures to control infection. In addition, toxin-targeting treatments, such as vaccines, nontoxicogenic *C. difficile*, and monoclonal antibodies, might protect against CDI but are unlikely to prevent asymptomatic colonization with *C. difficile* (9). To predict the effectiveness of these emerging therapies, it is critical to understand the role of asymptomatic carriers in CDI epidemiology.

Mathematical models of *C. difficile* colonization have generated insights regarding the epidemiologic role of antimicrobial drugs on CDI outbreaks (10). Such models have also quantified the effect of hospital-based control interventions (11–14) and demonstrated the crucial roles of asymptomatic colonization and patients with exposure before hospital admission in sustaining hospital transmission (7,13). Most studies have focused on the hospital setting. To fully understand the epidemiology of the pathogen and to inform decisions regarding control strategies, it is crucial to quantify the relative transmission of *C. difficile* in the hospital and in the broader community (8).

To evaluate the relative role of asymptomatic hospital transmission, symptomatic hospital transmission, LTCF transmission, and community transmission, we integrated diverse clinical and epidemiologic data into a dynamic model of *C. difficile* transmission within and among hospitals, LTCFs, and community settings in the United States. We parameterized our model by using Medicare and Healthcare Cost and Utilization Project databases and data from published epidemiologic and clinical research. To estimate infectivity of symptomatic and asymptomatic

Author affiliations: Yale School of Public Health, New Haven, Connecticut, USA (D.P. Durham, A.P. Galvani, J.P. Townsend); Washington University School of Medicine, St. Louis, Missouri, USA (M.A. Olsen, E.R. Dubberke)

DOI: <http://dx.doi.org/10.3201/eid2204.150455>

patients in the hospital; corresponding infectivity of persons in LTCFs and in the community; and average risks for acquiring *C. difficile* in the hospital, LTCF, and the community, we fit our model to estimated toxigenic *C. difficile* colonization and CDI incidence in each of these settings. Furthermore, we calculated the effect on CDI incidence of targeting key aspects of CDI epidemiology with control interventions in each of the 3 settings.

Methods

Definitions

We refer to acquisition of *C. difficile* from human sources as *C. difficile* transmission and acquisition of *C. difficile* from nonhuman sources as nonhuman acquisition. Asymptomatic persons carrying *C. difficile* are referred to as colonized. Persons carrying *C. difficile* and symptomatic for diarrheal disease associated with *C. difficile* are referred to as persons with CDI.

Model Structure

Previous models have focused almost exclusively on the hospital setting (7,8,10,12). We constructed a new model that encompasses *C. difficile* transmission and symptomatic CDI within a hospital, an LTCF, and an associated mid-sized community and quantifies patient movement between these settings. We parameterized our model with data from a combination of sources, including published literature, the US Census, national hospital and LTCF surveys, and the Healthcare Cost and Utilization Project and Medicare databases (online Technical Appendix, <http://wwwnc.cdc.gov/EID/article/22/4/15-0455-Techapp1.pdf>).

We structured our model in compartments (Figure 1) composed of patients who are currently receiving antimicrobial drugs, those who have a history of antimicrobial drug use and an increased risk for CDI, or those who do not have a recent history of receiving antimicrobial drugs. Consistent with clinical observations (15), we assumed that the increased risk for CDI after antimicrobial drug use reverted to normal in an average of 45 days. Uncolonized patients could become asymptotically colonized with *C. difficile* because of transmission from asymptomatic patients, transmission from patients with CDI, or through acquisition from background sources in the community. Asymptotically colonized patients could remain asymptomatic, spontaneously clear their colonization, or develop symptomatic CDI. Patients with CDI could recover and be at temporarily increased risk for recolonization, could recover and remain colonized and at risk for recurrence, or could die from the disease. We included 3 CDI and recurrence classes, each with a successively higher likelihood of recurrence, to reflect clinical observations of the increasing likelihood of recurrence after multiple CDI episodes

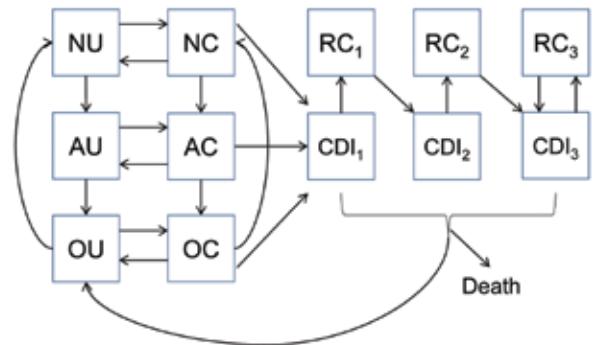


Figure 1. Compartmental model structure for *Clostridium difficile* infection (CDI) within each setting (hospital, long-term care facility, and community). Patients are classified as not receiving antimicrobial drugs (N), are receiving antimicrobial drugs (A), having a recent history of receiving antimicrobial drugs (O), uncolonized (U), asymptotically colonized (C), symptomatically infected (CDI), or colonized and subject to recurrence (RC) of CDI. Arrows indicate changes in individual epidemiologic status. Subscripts indicate primary, secondary, or tertiary CDI.

(16–18). We assumed that all patients with CDI were first asymptotically colonized before symptoms developed.

We embedded this epidemiologic model within a model of patient flow between the hospital, LTCF, and community (Figure 2), parameterized from national hospital and long-term-care-facility survey data. Patients with CDI remained hospitalized for an additional 3.1 days (95% CI 2.3–4.0 days) (19–21). Patients with CDI had a 96% (95% CI 93%–99%) probability of being given a diagnosis and subjected to isolation protocols that reduced transmission by 53% (95% CI 37%–72%) (22–25). We further assumed that persons in the community and in an LTCF in whom CDI developed were hospitalized with probabilities of 26% (95% CI 23%–28%) and 27% (95% CI 23%–32%), respectively (Table 1) (26,27).

Demographics

To represent demographically stratified CDI risk between the 3 settings, we modeled 5 demographic groups: persons <50 years of age, those 50–65 years of age without concurrent conditions, those 50–65 years of age with concurrent conditions, those >65 years of age without concurrent conditions, and those >65 years of age with concurrent conditions. Therefore, our full model consisted of base epidemiology (Figure 1) applied to each of the 5 demographic groups, and each group populated and moved between the hospital, LTCF, and the community (Figure 2) at rates calibrated from published *C. difficile* literature, US hospital discharge and census data, and Medicare and Healthcare Cost and Utilization Project databases (online Technical Appendix Table 4). We assumed that colonized patients with concurrent conditions are at greater risk for development of CDI (online Technical Appendix).

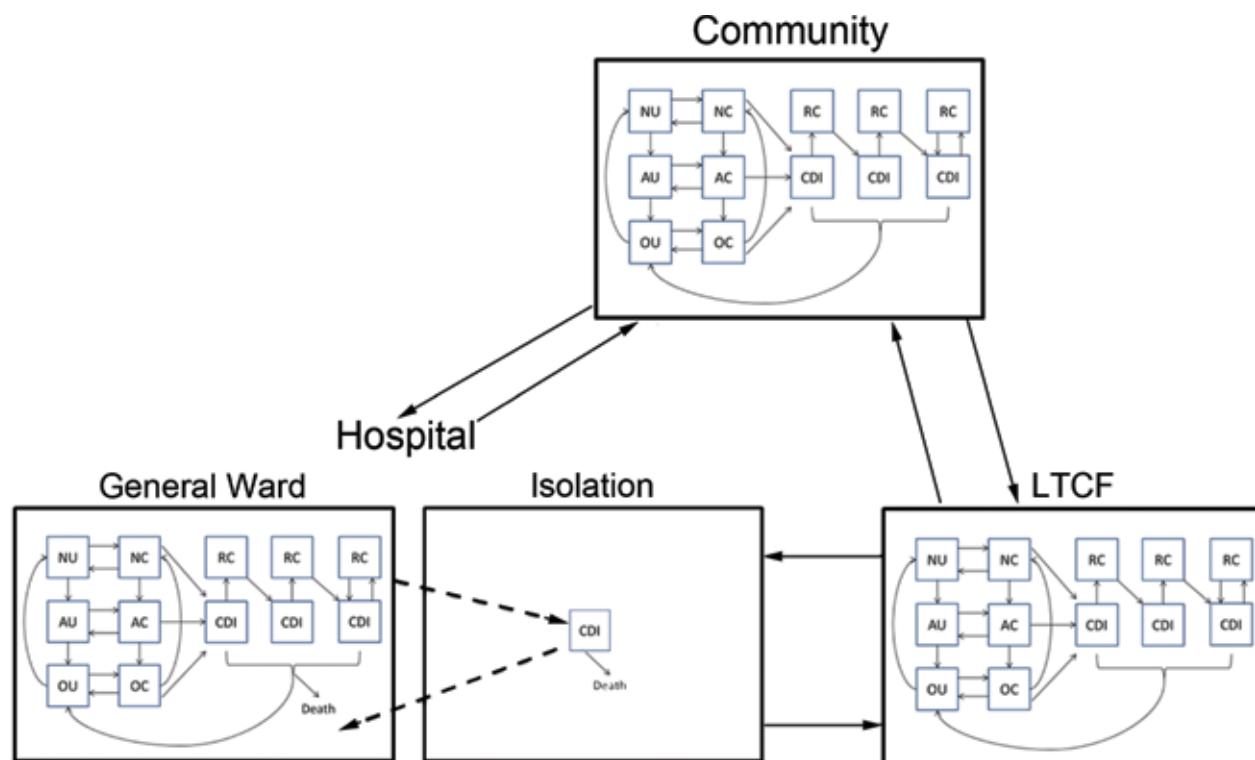


Figure 2. Transitions between settings (hospital, LTCF, and the non-healthcare community) for model structure of *Clostridium difficile* infection (CDI). Transitions were parameterized at demographically calibrated, age-specific rates. Hospitalized patients with CDI who were given a diagnosis are subject to enhanced isolation protocols that reduce transmission. All hospitalized CDI patients are discharged at a slower rate than non-CDI patients, which reflects longer hospitalization attributable to CDI. N, patients not receiving antimicrobial drugs; A, patients receiving antimicrobial drugs; O, patients with a recent history of receiving antimicrobial drugs; U, uncolonized patients; C, asymptomatically colonized patients; RC, symptomatically infected patients or colonized patients and subject to recurrence; LTCF, long-term care facility. Solid arrows indicate changes in individual epidemiologic status and patient movement between the hospital, community, and LTCF. Dashed arrows indicate isolation of CDI patients.

Transmission

We specified 5 *C. difficile* transmission rates: 1) the base CDI rate at which patients without a diagnosis and symptomatic CDI transmit in the hospital, 2) the base asymptomatic rate at which asymptomatically colonized patients transmit in the hospital, 3) the LTCF transmission rate representing the relative infectivity of persons in LTCFs compared with patients in the hospital, 4) the community transmission rate representing the relative infectivity of persons in the community compared with patients in the hospital, and 5) the rate of *C. difficile* acquisition from nonhuman reservoirs. We further defined the force of colonization as the rate at which uncolonized patients become asymptomatically colonized with *C. difficile* and specified 3 separate force-of-colonization rates: 1) the hospital, 2) LTCF, and 3) the community.

For the force of colonization in the hospital, we specified that nonisolated symptomatic patients with CDI transmit at the base CDI rate, that isolated patients with CDI transmit at the base CDI rate multiplied by the probability that isolation measures are insufficient, and that

asymptomatically colonized patients transmit at the base asymptomatic rate. We assumed direct contact mixing and density-dependent transmission, which is consistent with the observation that larger hospitals have greater CDI incidence than smaller hospitals (36). Environmental contamination and transmission mediated by healthcare workers were implicitly included by our calibration of the base CDI rate and the base asymptomatic rate. Hospital hygiene was separated into 2 components: overall hospital hygiene, which influenced transmission from asymptomatically colonized patients and from undiagnosed patients with CDI; and the probability of, and effectiveness of, enhanced isolation protocols for patients given a diagnosis of CDI.

For the force of colonization in the LTCF, we made 3 assumptions. First, enhanced isolation protocols were not available. Second, patients with CDI transmit at the base CDI rate multiplied by the LTCF transmission rate modifier. Third, asymptomatically colonized patients transmit at the base asymptomatic rate multiplied by the LTCF transmission rate modifier.

Table 1. Epidemiologic and clinical model parameters for infection with *Clostridium difficile**

Parameter description	Prior rate (95% CI)†	Posterior rate (95% CI)†	Reference
Epidemiology			
All-cause CDI mortality rate, %			(28)
Age, y			
<50	4.7 (2.6–7.6)	4.5 (2.6–7.5)	
50–64	12 (8.7–16)	12 (8.5–16)	
≥65	16.6 (14–19)	17 (14–19)	
Rate at which patients complete antimicrobial drug course	0.22 (0.17–2.29)	0.22 (0.17–2.29)	(29)
Rate at which recurrence develops in recovered patients	0.13 (0.24–1)	0.2 (0.32–1.05)	(30)
Rate at which patients not receiving antimicrobial drugs at increased risk for CDI revert to normal risk	0.038 (0.012–0.062)	0.033 (0.014–0.056)	(15)
Rate of recovery from CDI	0.099 (0.090–0.11)	0.099 (0.092–0.11)	(22)
Probability that a patient recovering from primary CDI will have ≥1 recurrence	22 (13–34)	24 (15–36)	(16,17)
Probability that a patient recovering from a first recurrence will have a second recurrence	33 (19–48)	34 (20–48)	(16,17)
Probability that a patient recovering from multiple recurrences will have an additional recurrence	56 (42–70)	56 (41–68)	(17,18)
Relative risk for CDI developing while a patient receives antimicrobial drugs	8.9 (4.9–13.)	8.3 (4.2–12)	(2,15)
Relative risk for CDI among persons 50–65 y of age vs. those <50 y of age	2.2 (1.4–3.4)	2.2 (1.5–3.0)	(31)
Relative risk for CDI among persons >65 y of age compared with those <50 y of age	2.9 (1.9–4.4)	3.2 (2.1–4.3)	(31)
Spontaneous clearance of asymptomatic <i>C. difficile</i> colonization	0.020 (0.015–0.025)	0.021 (0.016–0.026)	(32)
Hospital protocols			
All-cause fraction of community-onset CDI in patients who are hospitalized	0.26 (0.23–0.28)	0.26 (0.23–0.28)	(26)
All-cause fraction of LTCF-onset CDI in patients who are hospitalized	0.27 (0.23–0.32)	0.27 (0.23–0.32)	(27)
Increased attributable length of stay for hospitalized patients with CDI	3.1 (2.3–4.0)	3.1 (2.3–4.1)	(19–21)
Effectiveness of enhanced infection control measures in reducing transmission	53 (37–72)	52 (37–68)	(22,23)
Probability that a patient with CDI is properly identified and given enhanced infection control measures	0.96 (0.93–0.99)‡	0.96 (0.94–0.99)	(24,25)
Antimicrobial drug use rates			
Prescription rate among persons in community			(33,34)
Age, y			
<50	0.0013 (0.00095–0.0017)	0.0014 (0.00095–0.0018)	
50–64	0.0014 (0.00097–0.0018)	0.0014 (0.00097–0.0017)	
≥65	0.0017 (0.0013–0.0021)	0.0017 (0.0013–0.0022)	
Prescription rate among patients in hospital	0.37 (0.22–0.66)	0.37 (0.21–0.68)	(29)
Prescription rate among patients in LTCF	0.0054 (0.0027–0.009)	0.0052 (0.0026–0.0087)	(35)

*CDI, *C. difficile* infection; LTCF, long-term care facility.

†Parameter rates are per day unless otherwise indicated.

‡A total of 73% of sites initiated protocols before laboratory confirmation and 27% initiated protocols after confirmation. Sensitivity was 86% for laboratory tests, which yielded an effective diagnosis rate of $0.73 + 0.27 \times 0.86 = 0.96$.

For the force of colonization in the community, we assumed that *C. difficile* could be acquired from nonhuman reservoirs (37), that patients with CDI transmit at the base CDI rate multiplied by the community transmission rate modifier, and that asymptotically colonized patients transmit at the base asymptomatic rate multiplied by the community transmission rate modifier. Because there are insufficient published data with which to statistically differentiate between human transmission in the community and nonhuman acquisition, we estimated the force of colonization directly during our model calibration and then calculated the upper bounds for the

community transmission rate modifier and for the rate of nonhuman acquisition.

Although age, history of antimicrobial drug use, and concurrent conditions are predictors of diarrheal CDI, they are not predictors of asymptomatic *C. difficile* colonization (38,39). Therefore, we assumed that the rate at which symptomatic CDI developed in colonized patients was dependent on age, antimicrobial drug use, concurrent conditions, and hospitalization status. Transmission parameters and force of colonization were independent of age, antimicrobial drug use or concurrent conditions (online Technical Appendix).

Calibration

We used the Markov Chain Monte Carlo Metropolis algorithm (40) to calibrate our stochastic model and combined prior parameter densities (Table 1) with epidemiologic data, including asymptomatic prevalence and CDI incidence in the hospital, LTCF, and community (online Technical Appendix Table 2). This analysis yielded an ensemble of 1,000 parameter sets that estimated the joint posterior distribution for parameters with prior literature estimates (Table 1) for the 5 transmission parameters and for the base rate at which CDI developed in asymptotically colonized persons (Table 2). Details of coding, the stochastic model, and calibration are provided in the online Technical Appendix.

Epidemiologic Analysis

To estimate relative infectivity of a hospitalized patient with CDI compared with a hospitalized asymptotically colonized patient, accounting for isolation protocols, we computed the ratio of 1) the base CDI transmission rate from a hospitalized patient with CDI multiplied by the probability that the patient is either not given a diagnosis or that isolation protocols are improperly implemented to 2) the base asymptomatic transmission rate from a hospitalized, asymptotically colonized patient. To generate a posterior distribution for this ratio, we repeated this calculation for each of the 1,000 runs in our posterior sample. To estimate the average risk for a person to become exposed to and colonized with *C. difficile*, for each of the runs, we computed the average force of colonization within the hospital, community, and LTCF.

To estimate an upper bound for the community transmission rate and for nonhuman acquisition, we first

computed the daily average community force of colonization, which represents the sum of *C. difficile* transmission from other persons in the community plus acquisition from nonhuman reservoirs. By setting the nonhuman acquisition rate to 0, we calculated an upper bound for the community transmission rate. Likewise, by setting the community transmission rate to 0, we calculated an upper bound for nonhuman acquisition. We repeated this step for each of the 1,000 runs and generated posterior distributions for the upper bounds of the community transmission rate and the nonhuman acquisition rate.

Control Strategy Analysis

To quantify the effect of transmission control interventions on CDI incidence, we varied each of the following factors: CDI diagnosis rate of a hospitalized patient with CDI, effectiveness of isolation protocols for a patient given a diagnosis, overall hospital hygiene, improvements in community transmission, and improvements in LTCF transmission across a range from 0 to double the model-fitted maximum likelihood estimate and while sampling all other model parameters from their posterior distributions. We used linear regression to determine the reduction for hospital-onset CDI, community-onset CDI, and LTCF-onset CDI incidence per 1% improvement in each transmission control intervention.

To compute the effect of different classes of antimicrobial drugs on CDI incidence, we varied the antimicrobial drug risk ratio in the hospital from 1, which is representative of low-risk antimicrobial drugs (e.g., tetracyclines), to 20, which is representative of high-risk antimicrobial drugs (e.g., clindamycin) (2). While varying the antimicrobial drug risk ratio, we sampled all other parameters, including

Table 2. Calibrated posterior estimates of previously unknown epidemiologic parameters for infection with *Clostridium difficile**

Parameter description	Posterior rate (95% CI)
Hospital force of colonization†	0.023 (0.017–0.032)
Base CDI transmission rate within hospital†	1.2×10^{-2} (0.65–2.1 $\times 10^{-2}$)
Base CDI transmission rate within hospital accounting for isolation/control measures†	6.0×10^{-3} (3.6–9.7 $\times 10^{-3}$)
Base asymptomatic transmission rate within hospital†	4.0×10^{-4} (2.4–5.5 $\times 10^{-4}$)
Relative transmission from patients with CDI compared with asymptotically colonized patients, accounting for isolation/control measures‡	15 (7.2–32)
LTCF force of colonization†	3.7×10^{-3} (0.96–7.7 $\times 10^{-3}$)
LTCF transmission rate, relative to hospital‡	0.13 (0.068–0.22)
LTCF transmission rate, relative to hospital, accounting for hospital CDI isolation/control measures‡	0.27 (0.13–0.51)
Community force of colonization†	1.2×10^{-3} (0.50–2.3 $\times 10^{-3}$)
Community transmission rate, relative to hospital‡§	5.2×10^{-4} (3.3–8.9 $\times 10^{-4}$)
Community transmission rate, relative to hospital, accounting for hospital CDI isolation/control measures‡§	1.0×10^{-3} (0.62–2.0 $\times 10^{-3}$)
Rate of community acquisition from nonhuman reservoirs§	1.2×10^{-3} (0.50–2.3 $\times 10^{-3}$)
Base rate of CDI developing in hospital†¶	2.1×10^{-4} (1.0–4.7 $\times 10^{-4}$)
Base rate of CDI developing in LTCF†¶	8.6×10^{-5} (1.1–2.2 $\times 10^{-5}$)
Base rate of CDI developing in community†¶	6.3×10^{-6} (2.9–12 $\times 10^{-6}$)
Base rate of CDI developing given concurrent conditions†¶	2.6 (0.78–6.8)

*CDI, *C. difficile* infection; LTCF, long-term care facility.

†Parameter rates are per day.

‡Parameter rate expresses relative risk.

§Parameter rate represents an upper bound on the risk for transmission or acquisition within the community.

¶For a detailed decomposition of the rate of development of CDI, see the online Technical Appendix (<http://wwwnc.cdc.gov/EID/article/22/4/15-0455-Techapp1.pdf>).

community and LTCF antimicrobial drug risk, from their posterior distributions, thereby obtaining 95% CIs for our estimates of the effect of antimicrobial drug class on CDI incidence. We repeated this analysis for antimicrobial drug risk in the community and the LTCF. We then calculated changes in hospital-onset CDI, community-onset CDI, and LTCF CDI incidence as hospital, community, and LTCF risk for antimicrobial drug use were varied.

Results

Epidemiology

For within the hospital, we computed that the ratio of transmission from an isolated symptomatic patient with CDI with transmission from an asymptomatic patient was 15 (95% CI 7.2–32) (Table 2). This high ratio indicates that a symptomatic patient with CDI contributes more to transmission than does an asymptotically colonized patient, even after accounting for *C. difficile* protocols. Within the LTCF, the transmission rate from a person with CDI to an uncolonized person is 27% (95% CI 13%–51%) that of the hospital, and the transmission rate from an asymptotically colonized person to an uncolonized person is 13% (95% CI 6.8%–22%) that of the hospital. Within the community, the transmission rate from a person with CDI to an uncolonized person is 0.1% (95% CI 0.062%–0.2%) that of the hospital, and the transmission rate from an asymptotically colonized person to an uncolonized person is 0.052% (95% CI 0.033%–0.089%) that of the hospital (Table 2).

To estimate the average risk for a person to become exposed to and be colonized with *C. difficile*, we computed the force of colonization. We calculated that an uncolonized person in the hospital has a probability of 2.3% (95% CI 1.7%–3.2%) per day of acquiring *C. difficile* and becoming a carrier (with or without symptoms); an uncolonized person in the community has a probability of 0.12% (95% CI 0.050%–0.23%) per day, and a person in an LTCF has a probability of 0.37% (95% CI 0.096%–0.77%) per day (Table 2). These

results provide a quantitative estimate of the average risk for *C. difficile* exposure to persons in each setting.

Control Strategy

To estimate the effect of transmission control interventions on CDI incidence, we computed the percentage reduction in hospital-onset CDI, community-onset CDI, and LTCF CDI per percentage improvement in hospital CDI diagnosis rate, effectiveness of isolation protocols, overall hospital hygiene, transmission in the community, and transmission in an LTCF (Figure 3). We found that CDI diagnosis rate, effectiveness of isolation, overall hospital hygiene, and transmission in the community, but not transmission in an LTCF, affected hospital-onset CDI. In addition, community-onset CDI and LTCF CDI were not affected by hospital-based transmission interventions.

As the relative risk for antimicrobial drug class prescribed within each of the settings was increased, the CDI incidence likewise increased within that setting (Figure 4). However, there was no relationship between the antimicrobial drug class prescribed within a location and CDI incidence in another location. Specifically, we estimated that for every unit increase in antimicrobial drug risk ratio, the CDI incidence increased by 160% (95% CI 98%–320%) in the hospital, 33% (95% CI 13%–83%) in the LTCF, and 6.4% (95% CI 3.9%–13%) in the community. These results indicate that the effect of antimicrobial drug risk on CDI incidence is intertwined with *C. difficile* transmission dynamics, which differ between the hospital, LTCF, and community.

Discussion

Through stochastic simulation and Bayesian model calibration, we estimated *C. difficile* transmission rates within and outside the healthcare setting. We also quantified the effect on CDI incidence of control interventions that reduce these transmission rates. We found that a person with CDI in an LTCF transmits at a rate 27% that for a comparable patient in the hospital, and a colonized person or a person

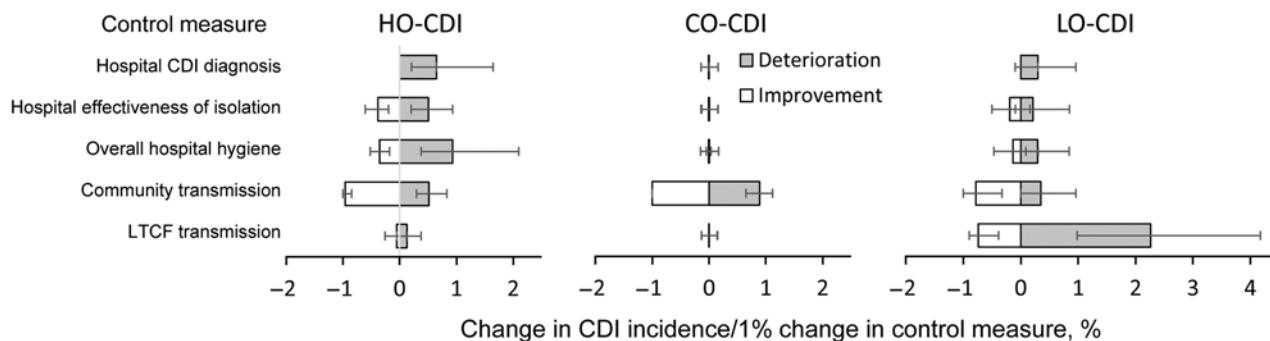


Figure 3. Effectiveness of *Clostridium difficile* infection (CDI) control parameters on incidence of infection quantified as percentage change in hospital-onset CDI (HO-CDI), community-onset CDI (CO-CDI), and long-term care facility (LTCF)–onset CDI (LO-CDI), quantified as percentage change in incidence per 1% change in each of 5 transmission parameters. Error bars indicate 95% CIs. LTCF, long-term care facility.

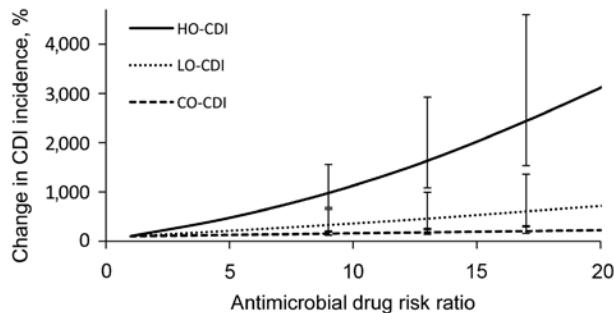


Figure 4. Increase in *Clostridium difficile* infection (CDI) incidence from use of antimicrobial drugs for in hospital-onset (HO-CDI), community-onset (CO-CDI), and long-term care facility-onset (LO-CDI) illnesses classified by drug risk ratio for CDI. *Clostridium difficile* infection (CDI) incidence from use of antimicrobial drugs for low through high CDI risk. Change in CDI incidence is measured as a multiple of the CDI incidence for an antimicrobial drug risk ratio = 1.0. Error bars indicate 95% CIs.

with CDI in the community transmits *C. difficile* to others at a rate $<0.1\%$ that of a comparable patient in the hospital. Despite the lower community transmission rate, we found that because of the much larger pool of colonized persons in the community, interventions that reduce community transmission hold substantial potential to reduce hospital-onset CDI by reducing the number of patients entering the hospital with asymptomatic colonization. Moreover, our results show that in the hospital, symptomatic CDI patients under isolation and infection control measures nonetheless transmit CDI to uncolonized patients at a rate that is 15 times greater than that of asymptomatic carriers. This higher rate of transmission indicates that toxin-targeting treatments (such as vaccines); nontoxicogenic *C. difficile*; and monoclonal antibodies, which might protect against symptomatic CDI but not against asymptomatic colonization, could be effective tools for reducing not only primary CDI cases but also for further transmission (9).

Our epidemiologic results underscore the need for incorporating and understanding transmission dynamics within and outside healthcare settings when evaluating *C. difficile* control strategies. Although *C. difficile* transmission rates are lower among asymptotically colonized persons, residents of LTCFs, and persons in the community than in hospitalized patients with symptomatic CDI, overall CDI incidence is driven by several factors: transmission, antimicrobial drug use, and underlying population health. We found that, per unit increase in relative antimicrobial drug risk, CDI incidence increases by a factor of 160% in the hospital and 33% in the LTCF but only by a factor of 6.4% in the community. This finding is a consequence of amplification by concentration.

When we compared patients in the hospital and LTCF with persons in the community, we found that patients are

closer to each other, are more frequently receiving antimicrobial drugs, and tend to have poorer overall health or may be immunocompromised. These attributes combine to yield a greater risk for infection and transmission. This finding of amplification-by-concentration has major implications for antimicrobial drug risk management: those antimicrobial drugs strongly associated with CDI, such as clindamycin, cephalosporins, and fluoroquinolones (2), will have a more detrimental effect on overall CDI incidence in a high-transmission setting, such as a hospital, than they will in a moderate-transmission setting, such as an LTCF, or in a low-transmission setting, such as the community.

We found no major effect of hospital-based transmission interventions on LTCF-onset CDI or of LTCF-based transmission interventions on hospital-onset CDI. This finding suggests that although *C. difficile* can be introduced by a patient who acquired the bacteria in the hospital, CDI outbreaks in LTCFs are driven primarily from within and are best mitigated by targeted transmission interventions within the facility. Likewise, any interventions to reduce transmission within an LTCF will have limited effect on hospital-onset CDI because LTCF transmission interventions will not influence continued introduction of *C. difficile* to the hospital from the community.

The control strategies we evaluated (Figure 3) are representative of a broad range of interventions. For example, an improvement in hospital isolation effectiveness could be achieved through enhanced hospital staff adherence to precautions, or alternatively through an increased capacity to keep a patient with CDI in isolation for the duration of the disease. An improvement in the LTCF transmission rate could be achieved through an improvement to LTCF staff hygiene and cleanliness, through an increased availability of private facilities for residents, or through the isolation of LTCF residents with CDI.

Although there are few data with which to differentiate the sources of community-associated *C. difficile*, we were able to use a community *C. difficile* colonization study (37) to calibrate our model. From our calibrated model, we estimated the overall community force of colonization and calculated an upper bound for the community transmission rate. Future studies of similar design but with greater statistical power than the study used for our calibration (37), which survey healthy, nonhospitalized adults for asymptomatic *C. difficile* carriage while differentiating community risk factors, would provide the necessary data with which our model could directly quantify transmission from human sources and acquisition from nonhuman reservoirs.

Our analyses demonstrated that *C. difficile* transmission among healthcare settings and the community is interconnected, and there are comparable effects of community-based transmission and hospital-based transmission on hospital-onset CDI. We found that the effect of antimicrobial

drug use on CDI incidence is modulated by transmission dynamics, with specific antimicrobial drugs exacerbating incidence, and doing so to a greater degree in high-transmission settings than in low-transmission settings. These results underscore the need for empirical quantification of community-associated transmission and the need of understanding transmission dynamics in all settings when evaluating *C. difficile* interventions and control strategies.

Acknowledgments

We thank Clifford McDonald for helpful comments and suggestions and Dustin Stwalley for assistance with data acquisition.

This study was supported by Sanofi-Pasteur and the Notsaw Orm Sands Foundation. Sanofi Pasteur assisted with study design and data acquisition and provided feedback on the completed manuscript. Simulations were run on the Yale University Biomedical High Performance Computing Center, which is supported by National Institutes of Health grants RR19895 and RR029676-01.

A.P.G., J.P.T., and D.P.D. have received research support from Sanofi-Pasteur and have consulted for Sanofi-Pasteur and Merck. M.A.O. has received research support from Sanofi-Pasteur and Pfizer and has been a consultant for Sanofi-Pasteur, Pfizer, and Merck. E.R.D. has received research support from Rebiotix, Microdermis, Merck, and Sanofi-Pasteur and has been a consultant for Sanofi-Pasteur, Rebiotix, Pfizer, Valneva, Merck, Summitt, and Daiichi.

Dr. Durham is an associate research scientist in the Center for Infectious Disease Modeling and Analysis at the Yale School of Public Health, New Haven, Connecticut. His research focuses on using mathematical and computational models to quantify the impact of control interventions upon *Clostridium difficile*, hepatitis C virus, and human papillomavirus.

References

- Zilberberg MD. Increase in adult *Clostridium difficile*-related hospitalizations and case-fatality rate, United States, 2000–2005. *Emerg Infect Dis*. 2008;14:929–31. <http://dx.doi.org/10.3201/eid1406.071447>
- Deshpande A, Pasupuleti V, Thota P, Pant C, Rolston DD, Sferra TJ, et al. Community-associated *Clostridium difficile* infection and antibiotics: a meta-analysis. *J Antimicrob Chemother*. 2013;68:1951–61. <http://dx.doi.org/10.1093/jac/dkt129>
- Svenungsson B, Burman LG, Jalakas-Pornull K, Lagergren A, Struwe J, Akerlund T. Epidemiology and molecular characterization of *Clostridium difficile* strains from patients with diarrhea: low disease incidence and evidence of limited cross-infection in a Swedish teaching hospital. *J Clin Microbiol*. 2003;41:4031–7. <http://dx.doi.org/10.1128/JCM.41.9.4031-4037.2003>
- Walker AS, Eyre DW, Wyllie DH, Dingle KE, Harding RM, O'Connor L, et al. Characterisation of *Clostridium difficile* hospital ward-based transmission using extensive epidemiological data and molecular typing. *PLoS Med*. 2012;9:e1001172. <http://dx.doi.org/10.1371/journal.pmed.1001172>
- Norén T, Akerlund T, Bäck E, Sjöberg L, Persson I, Alriksson I, et al. Molecular epidemiology of hospital-associated and community-acquired *Clostridium difficile* infection in a Swedish county. *J Clin Microbiol*. 2004;42:3635–43. <http://dx.doi.org/10.1128/JCM.42.8.3635-3643.2004>
- Curry SR, Muto CA, Schlackman JL, Pasculle AW, Shutt KA, Marsh JW, et al. Use of multilocus variable number of tandem repeats analysis genotyping to determine the role of asymptomatic carriers in *Clostridium difficile* transmission. *Clin Infect Dis*. 2013;57:1094–102. <http://dx.doi.org/10.1093/cid/cit475>
- Lanzas C, Dubberke ER, Lu Z, Reske KA, Gröhn YT. Epidemiological model for *Clostridium difficile* transmission in healthcare settings. *Infect Control Hosp Epidemiol*. 2011;32:553–61. <http://dx.doi.org/10.1086/660013>
- Otten AM, Reid-Smith RJ, Fazil A, Weese JS. Disease transmission model for community-associated *Clostridium difficile* infection. *Epidemiol Infect*. 2010;138:907–14. <http://dx.doi.org/10.1017/S0950268809991646>
- Gerding DN, Johnson S. Management of *Clostridium difficile* infection: thinking inside and outside the box. *Clin Infect Dis*. 2010;51:1306–13. <http://dx.doi.org/10.1086/657116>
- Starr JM, Rogers TR, Impallomeni M. Hospital-acquired *Clostridium difficile* diarrhoea and herd immunity. *Lancet*. 1997;349:426–8. [http://dx.doi.org/10.1016/S0140-6736\(97\)80053-0](http://dx.doi.org/10.1016/S0140-6736(97)80053-0)
- Lofgren ET, Moehring RW, Anderson DJ, Weber DJ, Fefferman NH. A mathematical model to evaluate the routine use of fecal microbiota transplantation to prevent incident and recurrent *Clostridium difficile* infection. *Infect Control Hosp Epidemiol*. 2014;35:18–27. <http://dx.doi.org/10.1086/674394>
- Starr JM, Campbell A, Renshaw E, Poxton IR, Gibson GJ. Spatio-temporal stochastic modelling of *Clostridium difficile*. *J Hosp Infect*. 2009;71:49–56. <http://dx.doi.org/10.1016/j.jhin.2008.09.013>
- Yakob L, Riley TV, Paterson DL, Clements AC. *Clostridium difficile* exposure as an insidious source of infection in healthcare settings: an epidemiological model. *BMC Infect Dis*. 2013;13:376. <http://dx.doi.org/10.1186/1471-2334-13-376>
- Rubin MA, Jones M, Leecaster M, Khader K, Ray W, Huttner A, et al. A simulation-based assessment of strategies to control *Clostridium difficile* transmission and infection. *PLoS ONE*. 2013;8:e80671. <http://dx.doi.org/10.1371/journal.pone.0080671>
- Dial S, Kezouh A, Dascal A, Barkun A, Suissa S. Patterns of antibiotic use and risk of hospital admission because of *Clostridium difficile* infection. *CMAJ*. 2008;179:767–72. <http://dx.doi.org/10.1503/cmaj.071812>
- Lowy I, Molrine DC, Leav BA, Blair BM, Baxter R, Gerding DN, et al. Treatment with monoclonal antibodies against *Clostridium difficile* toxins. *N Engl J Med*. 2010;362:197–205. <http://dx.doi.org/10.1056/NEJMoa0907635>
- Figuerola I, Johnson S, Sambol SP, Goldstein EJC, Citron DM, Gerding DN. Relapse versus reinfection: recurrent *Clostridium difficile* infection following treatment with fidaxomicin or vancomycin. *Clin Infect Dis*. 2012;55(Suppl 2):S104–9. <http://dx.doi.org/10.1093/cid/cis357>
- McFarland LV. A randomized placebo-controlled trial of *Saccharomyces boulardii* in combination with standard antibiotics for *Clostridium difficile* disease. *JAMA*. 1994;271:1913–8. <http://dx.doi.org/10.1001/jama.1994.03510480037031>
- Kyne L, Hamel MB, Polavaram R, Kelly CP. Health care costs and mortality associated with nosocomial diarrhea due to *Clostridium difficile*. *Clin Infect Dis*. 2002;34:346–53. <http://dx.doi.org/10.1086/338260>
- Dubberke ER, Butler AM, Reske KA, Agniel D, Olsen MA, D'Angelo G, et al. Attributable outcomes of endemic *Clostridium difficile*-associated disease in nonsurgical patients. *Emerg Infect Dis*. 2008;14:1031–8. <http://dx.doi.org/10.3201/eid1407.070867>
- O'Brien JA, Lahue BJ, Caro JJ, Davidson DM. The emerging infectious challenge of *Clostridium difficile*-associated disease

- in Massachusetts hospitals: clinical and economic consequences. *Infect Control Hosp Epidemiol*. 2007;28:1219–27. <http://dx.doi.org/10.1086/522676>
22. Jarvis WR, Schlosser J, Jarvis AA, Chinn RY. National point prevalence of *Clostridium difficile* in US health care facility inpatients, 2008. *Am J Infect Control*. 2009;37:263–70. <http://dx.doi.org/10.1016/j.ajic.2009.01.001>
 23. Harris AD, Pineles L, Belton B, Johnson JK, Shardell M, Loeb M, et al. Universal glove and gown use and acquisition of antibiotic-resistant bacteria in the ICU: a randomized trial. *JAMA*. 2013;310:1571–80.
 24. Wilkinson K, Gravel D, Taylor G, McGeer A, Simor A, Suh K, et al. Infection prevention and control practices related to *Clostridium difficile* infection in Canadian acute and long-term care institutions. *Am J Infect Control*. 2011;39:177–82. <http://dx.doi.org/10.1016/j.ajic.2011.01.007>
 25. Sloan LM, Duresko BJ, Gustafson DR, Rosenblatt JE. Comparison of real-time PCR for detection of the *tcdC* gene with four toxin immunoassays and culture in diagnosis of *Clostridium difficile* infection. *J Clin Microbiol*. 2008;46:1996–2001. <http://dx.doi.org/10.1128/JCM.00032-08>
 26. Chitnis AS, Holzbauer SM, Belflower RM, Winston LG, Bamberg WM, Lyons C, et al. Epidemiology of community-associated *Clostridium difficile* infection, 2009 through 2011. *JAMA Intern Med*. 2013;173:1359–67. <http://dx.doi.org/10.1001/jamainternmed.2013.7056>
 27. Pawar D, Tsay R, Nelson DS, Elumalai MK, Lessa FC, Clifford McDonald L, et al. Burden of *Clostridium difficile* infection in long-term care facilities in Monroe County, New York. *Infect Control Hosp Epidemiol*. 2012;33:1107–12. <http://dx.doi.org/10.1086/668031>
 28. Hensgens MP, Goorhuis A, Dekkers OM, van Benthem BH, Kuijper EJ. All-cause and disease-specific mortality in hospitalized patients with *Clostridium difficile* infection: a multicenter cohort study. *Clin Infect Dis*. 2013;56:1108–16. <http://dx.doi.org/10.1093/cid/cis1209>
 29. Polk RE, Hohmann SF, Medvedev S, Ibrahim O. Benchmarking risk-adjusted adult antibacterial drug use in 70 US academic medical center hospitals. *Clin Infect Dis*. 2011;53:1100–10. <http://dx.doi.org/10.1093/cid/cir672>
 30. McFarland LV, Elmer GW, Surawicz CM. Breaking the cycle: treatment strategies for 163 cases of recurrent *Clostridium difficile* disease. *Am J Gastroenterol*. 2002;97:1769–75. <http://dx.doi.org/10.1111/j.1572-0241.2002.05839.x>
 31. Dubberke ER, Reske KA, Olsen MA, McMullen KM, Mayfield JL, McDonald LC, et al. Evaluation of *Clostridium difficile*-associated disease pressure as a risk factor for *C. difficile*-associated disease. *Arch Intern Med*. 2007;167:1092–7. <http://dx.doi.org/10.1001/archinte.167.10.1092>
 32. Simor AE, Yake SL, Tsimidis K. Infection due to *Clostridium difficile* among elderly residents of a long-term-care facility. *Clin Infect Dis*. 1993;17:672–8. <http://dx.doi.org/10.1093/clinids/17.4.672>
 33. Zhang Y, Steinman MA, Kaplan CM. Geographic variation in outpatient antibiotic prescribing among older adults. *Arch Intern Med*. 2012;172:1465–71. <http://dx.doi.org/10.1001/archinternmed.2012.3717>
 34. Hicks LA, Taylor TH, Hunkler RJ. Outpatient antibiotic prescribing, 2010. *N Engl J Med*. 2013;368:1461–2. <http://dx.doi.org/10.1056/NEJMc1212055>
 35. Mylotte JM. Antimicrobial prescribing in long-term care facilities: prospective evaluation of potential antimicrobial use and cost indicators. *Am J Infect Control*. 1999;27:10–9. [http://dx.doi.org/10.1016/S0196-6553\(99\)70069-6](http://dx.doi.org/10.1016/S0196-6553(99)70069-6)
 36. McDonald LC, Owings M, Jernigan D. *Clostridium difficile* infection in patients discharged from US short-stay hospitals, 1996–2003. *Emerg Infect Dis*. 2006;12:409–15. <http://dx.doi.org/10.3201/eid1205.051064>
 37. Galdys AL, Nelson JS, Shutt KA, Schlackman JL, Pakstis DL, Pasculle AW, et al. Prevalence and duration of asymptomatic *Clostridium difficile* carriage among healthy subjects in Pittsburgh, Pennsylvania. *J Clin Microbiol*. 2014;52:2406–9. <http://dx.doi.org/10.1128/JCM.00222-14>
 38. Alasmari F, Seiler SM, Hink T, Burnham C-AD, Dubberke ER. Prevalence and risk factors for asymptomatic *Clostridium difficile* carriage. *Clin Infect Dis*. 2014;59:216–22. <http://dx.doi.org/10.1093/cid/ciu258>
 39. Loo VG, Bourgault A-M, Poirier L, Lamothe F, Michaud S, Turgeon N, et al. Host and pathogen factors for *Clostridium difficile* infection and colonization. *N Engl J Med*. 2011;365:1693–703. <http://dx.doi.org/10.1056/NEJMoa1012413>
 40. Metropolis N, Rosenbluth AW, Rosenbluth MN, Teller AH, Teller E. Equation of state calculations by fast computing machines. *J Chem Phys*. 1953;21:1087. <http://dx.doi.org/10.1063/1.1699114>

Address for correspondence: David P. Durham, Center for Infectious Disease Modeling and Analysis, Department of Epidemiology of Microbial Diseases, Yale School of Public Health, 135 College St, Ste 200, New Haven, CT 06520, USA; email: david.durham@yale.edu



Manage your email alerts so you only receive content of interest to you.

Sign up for an online subscription: wwwnc.cdc.gov/eid/subscribe.htm

Quantifying Transmission of *Clostridium difficile* within and outside Healthcare Settings

Technical Appendix

Supplemental Methods

Model Parameterization

Our model (Technical Appendix Figure 1) is parameterized according to the specified rates (Technical Appendix Table 1). Parameter values and CIs are provided in the main text (Table 1). *Clostridium difficile* transmission is separately modeled as the force of colonization within the hospital, within the long-term care facility (LTCF), and within the community (Equation 1). The hospital force-of-colonization was λ_H , where g indicates the overall hospital hygiene control parameter, CDI_H indicates the number of hospitalized patients with symptomatic *C. difficile* infection ($CDI_1 + CDI_2 + CDI_3$), and C_H indicates the number of asymptotically colonized patients in the hospital ($NC + AC + OC + RC$; N, patients not receiving antimicrobial drugs; C, asymptotically colonized patients; A, patients receiving antimicrobial drugs; O, patients with a recent history of receiving antimicrobial drugs; RC, symptomatically infected patients or colonized patients and subject to recurrence). The LTCF force-of-colonization was λ_L with CDI_L and C_L representing the number of symptomatic CDI and asymptomatic colonized patients, respectively, in the LTCF. The community force-of-colonization was λ_C with CDI_C and C_C representing the number of symptomatic CDI and asymptomatic colonized patients, respectively, in the community.

Equation 1

$$\lambda_H = g\{(\mathbf{1} - \pi)\beta_S CDI_H + \beta_A C_H\} + \pi(\mathbf{1} - \epsilon)\beta_S CDI_H$$

$$\lambda_L = \beta_L(\beta_S CDI_L + \beta_A C_L)$$

$$\lambda_C = \beta_C(\beta_S CDI_C + \beta_A C_C) + \chi$$

Model Implementation

We used the Gibson-Bruck (*I*) adaptation of the Gillespie algorithm to run simulations coded in C++ over 2-year time horizons. To ensure a well-mixed model, we discarded the first year of results and stored results from the second year. We averaged these results for every analysis and parameter set over 10 independent runs of the model. We found 2-year time horizons with a 1-year burn-in and ten-run averages sufficient to average out the stochastic variance of the Gillespie algorithm, generating summary statistics without undue computational burden.

Model Outcome Tracking

In our stochastic model, we distinguished between *C. difficile* that was acquired in the hospital, in the community, or in the LTCF, as well as whether that acquisition was caused by transmission from a person with a CDI, from an asymptomatic carrier, or from nonhuman acquisition. By storing this information, we identified for every new CDI case where that case originated. We then computed the proportion of hospital-onset CDI that was caused by transmission from other patients with CDI (Technical Appendix Table 2).

Model Initial Conditions

We initialized our model with an endemic *C. difficile* colonization prevalence in the hospital, LTCF, and community (Technical Appendix Table 2). We specified a total population of 100,000 persons distributed according to age, concurrent condition, and location (Technical Appendix Table 3).

Model Calibration

To estimate unknown parameters, we fit our model to a range of epidemiologic and demographic data. We divided model parameters and epidemiologic outcomes into 3 categories: 1) those for which extensive data are available, which we used to fit the model; 2) those for which extensive data are available, which we used to validate the fitted model; and 3) those for which little data are available, which we estimated from the fitted model.

We specified data-driven prior values and 95% CIs for each parameter for which data are available (Table 1 in main text), as well as for epidemiologic outcomes, such as CDI incidence and asymptomatic colonization (Technical Appendix Table 2). We fit our model by using a Markov Chain Monte Carlo (MCMC) simulation. The MCMC simulation proceeded by

generating a candidate estimate for each unknown parameter (Table 2 in main text), simultaneously sampled from prior distributions of the known parameters (Table 1 in main text), and then ran the model under the candidate parameter set. The candidate parameter set, which included samples from known and unknown parameters, was accepted or rejected according to the Metropolis algorithm (12). We based the Metropolis objective function upon the log-likelihood of the epidemiologic outcomes, which was defined as the sum of the logs of the target distributions for the epidemiologic outcomes (Technical Appendix Table 2), and evaluated at the candidate parameter set. Using a computing cluster, we generated 100 independent MCMC chains of 10,000 runs each. We discarded the first 2,000 runs of each chain, visually confirmed convergence of the likelihood and of each model parameter, and thinned each chain at equally spaced intervals to obtain a final ensemble of 1,000 runs.

Model Validation

Our model predicted that 0.16% (95% CI 0.10%–0.23%) of hospital admissions had symptomatic CDI, which was consistent with current estimates for the United States (13,14). We calculated the source of acquisition for hospital-onset CDI cases, and separated these cases into 3 groups. Our calibrated model predicted that 29% (95% CI 19%–41%) of cases were acquired from another symptomatic CDI patient in the hospital, 49% (95% CI 32%–62%) were acquired from an asymptomatically colonized patient in the hospital, and 22% (95% CI 12%–35%) were among patients who entered the hospital with endogenous *C. difficile* colonization and in whom diarrheal CDI subsequently developed during their hospital stay. These results are consistent with findings from molecular typing and contact tracing, which estimate 30%–35% of hospital-onset from symptomatic patients and at least 45% of hospital-onset CDI from asymptomatic contacts or from nonhospital-transmission sources (11,15).

Model Demographics

We parameterized population distribution, non-CDI deaths, and patient movement from published *C. difficile* literature, the Healthcare Cost and Utilization Project Nationwide Inpatient Sample, the Centers for Medicare and Medicaid 5% random sample Chronic Conditions Warehouse database (Medicare), the Truven Health Analytics MarketScan (MarketScan), the Healthcare Cost and Utilization Project State Inpatient Databases, US hospital discharge and long-term-care survey reports, and US Census data. We specified a total population size of

100,000 persons. We used the Elixhauser definition for concurrent conditions (16,17) and excluded hypertension because of its high prevalence among elderly persons (18).

Population Distribution

To quantify the percentage of the population that is hospitalized and in each of the age stratifications (Technical Appendix Table 3), we estimated from the National Hospital Discharge Survey that 37.4%, 19.5%, and 43.0% of hospital patient-days are occupied by those <50, 50–65, and >65 years of age, respectively (19). We anchored this age breakdown to our estimate that, at any given time, 1.06% of the US population >65 years of age is hospitalized (Medicare). We combined these estimates with our estimates that, in the hospital, 55% of patients 50–65 years of age and 79% of patients >65 years of age have concurrent conditions (Medicare, MarketScan).

To quantify the percentage of the US population that is in an LTCF, we estimated that 1.38 million persons in the United States reside in LTCFs at any point in time, of whom 85.1% are >65 years of age (20). We assumed that the remaining 14.9% are 50–65 years of age. We estimated that 90.14% of LTCF residents have concurrent conditions (Medicare).

To estimate the population breakdown of the United States that lives in the community (e.g., not hospitalized or in an LTCF), we calculated the population remaining according to our hospital and LTCF calculations and stratified this community population according to US Census age profiles and our estimate that 54.97% of persons >65 years of age and 23.74% of persons 50–65 years of age the general community have concurrent conditions (Medicare, MarketScan, 67).

Patient Movement

To estimate rates of movement between the hospital, LTCF, and community (Technical Appendix Table 4), we calculated the hospital discharge rate, LTCF discharge rate, and LTCF discharge destination from published sources (19,21). We estimated the fraction of hospital discharges that are sent to an LTCF vs. those sent to home (Medicare, Healthcare Cost and Utilization Project State Inpatient Databases). We assumed that 40.5% of LTCF residents were admitted from a hospital, and we used this value to calculate the rate of admission from the community (22). Finally, we calculated the hospitalization and LTCF admission rates from the community that would produce an equilibrium population distribution. Because of limited data, we parameterized LTCF discharge rates independently of age or concurrent conditions.

Non-CDI Death Rate

From the National Hospital Discharge Survey, we estimated a death rate of 0.0016 deaths/day among inpatients <50 years of age, 0.0034 deaths/day among inpatients 50–65 years of age, and 0.0073 deaths/day among inpatients >65 years of age. From the US Census and the National Hospital Discharge Survey, we estimated that among the 210 million persons <50 years of age, there are 252,000 annual deaths, of which 97,000 occur within a hospital (19,23) (Technical Appendix Table 5). For the 65 million persons 50–65 years of age, there are 506,000 annual deaths, of which 109,000 occur within a hospital. For the 40 million persons >65 years of age, there are 1.8 million annual deaths, of which 525,000 occur within a hospital. We assumed that for persons <50 and 50–65 years of age, all nonhospital deaths occur in the community, which yields a daily mortality rate of 2.0×10^{-6} and 1.7×10^{-5} , respectively. For persons >65 years of age, we estimated that 39% of all deaths occur in home or hospice care (24), which yields a daily mortality rate in the community of 5.1×10^{-5} . We estimated a daily LTCF mortality rate among persons >65 years of age of 0.0020.

Parameter Assumptions and Derivation

Rate (μ) at Which Symptomatic CDI Develops in Asymptomatically Colonized Patients

We partitioned μ into components by age, concurrent condition, antimicrobial drug history, and hospitalization status. First, we specified that asymptomatically colonized persons <50 years of age without concurrent conditions and with no recent antimicrobial drug use showed development of CDI at a base rate of μ_C , μ_H , or μ_L , which reflected current residence and underlying health in the community, in the hospital, or in the LTCF, respectively. When we controlled for all other factors, we found that colonized patients 50–65 years of age were parameterized to be μ_{50} times as likely to show development of CDI as those <50 years of age. Colonized patients >65 years of age were parameterized to be μ_{65} times as likely to show development of CDI as those <50 years of age (25). Second, we parameterized colonized persons with current or recent antimicrobial drug use history (AC or OC) to be μ_A times as likely to show development of CDI as those without such exposure (26–30). Finally, persons with concurrent conditions were parameterized to be μ_m times as likely to show development of CDI as those without concurrent conditions. Thus, for a colonized patient 50–65 years of age with concurrent

conditions, currently in the hospital and taking antimicrobial drugs, the daily risk for CDI developing would be $\mu_H \mu_{50} \mu_m \mu_A$.

Hospital-Onset CDI Calculation

We calculated the number of patients with hospital-onset CDI as the sum of the number of patients with *C. difficile* acquired in the hospital with symptom onset in the hospital, plus the number of patients with *C. difficile* acquired outside the hospital with symptom onset in the hospital >48 hours after admission. To estimate the probability that a patient colonized at hospital admission shows development of symptoms while in the hospital, and does so ≥ 48 hours after hospital admission, we solved the subset of model equations given below, with boundary conditions $NC(0) = 1$, $AC(0) = OC(0) = CDI(0) = 0$. Thus, $CDI(t)$ gives the probability that a patient entering the hospital, with *C. difficile* colonization acquired outside the hospital and without recent antimicrobial drug use (NC), will show development of CDI while in the hospital (Technical Appendix Figure 2).

$$\frac{dNC(t)}{dt} = -(\phi + \mu + m_H + \delta + d_H)NC(t)$$

$$\frac{dAC(t)}{dt} = \phi NC(t) - (\rho + \mu \mu_A + m_H + \delta + d_H)AC(t)$$

$$\frac{dOC(t)}{dt} = \rho AC(t) - (\mu \mu_A + m_H + \delta + d_H)OC(t)$$

$$\frac{dCDI(t)}{dt} = \mu \mu_A AC(t) + \mu \mu_A OC(t) + \mu NC(t)$$

The closed form solution of $CDI(t)$, the probability that an NC (colonized at admission, but not taking antimicrobial drugs) patient will show development of CDI in the hospital by day t , is given by

$$CDI(t) = \frac{-\left(\mu(e^{-t(\phi+\mu+\phi)}(-1+\mu_A)(\phi+\mu\mu_A)(\mu+\phi) - e^{-t(\phi+\mu\mu_A)}\mu_A\phi(\phi+\mu+\phi) - (\mu(-1+\mu_A)-\phi)(\phi+\mu_A(\mu+\phi)))\right)}{((\phi+\mu\mu_A)(\mu(-1+\mu_A)-\phi)(\phi+\mu+\phi))}$$

We define the outflow parameter $\phi = m_H + \delta + d_H$ to simplify the notation. $CDI(\infty)$ provides the probability that an NC patient will show development of CDI during the hospital stay, and $1 - CDI(\infty)$ provides the probability that an NC patient will spontaneously clear colonization, die, or be discharged before development of CDI. Because $CDI(2)$ gives the

probability that an NC patient will show development of CDI during the first 2 days of hospitalization, it follows that $CDI(\infty) - CDI(2)$ gives the probability of development of $CDI \geq 2$ days after admission. We compute the probability P_2 that a patient, colonized at hospital admission and with CDI onset in the hospital, will show development of symptoms ≥ 2 days after hospital admission. We then use P_2 to compute the total rate of hospital-onset.

$$P_2 = P(CDI \text{ onset} \geq \text{two days after admission} \mid CDI \text{ onset during hospital stay}) = \frac{CDI(\infty) - CDI(2)}{CDI(\infty)} = 1 - \frac{CDI(2)}{CDI(\infty)}$$

$$= \frac{(e^{-2(\sigma+\mu+\phi)}(1-\mu_A)(\sigma+\mu\mu_A)(\mu+\phi) + e^{-2(\sigma+\mu\mu_A)}\mu_A\phi(\sigma+\mu+\phi))}{(\mu(1-\mu_A)+\phi)(\sigma+\mu_A(\mu+\phi))}$$

References

1. Gibson MA, Bruck J. Efficient exact stochastic simulation of chemical systems with many species and many channels. *J Phys Chem A*. 2000;104:1876–89. <http://dx.doi.org/10.1021/jp993732q>
2. Loo VG, Bourgault A-M, Poirier L, Lamothe F, Michaud S, Turgeon N, et al. Host and pathogen factors for *Clostridium difficile* infection and colonization. *N Engl J Med*. 2011;365:1693–703. [PubMed http://dx.doi.org/10.1056/NEJMoa1012413](http://dx.doi.org/10.1056/NEJMoa1012413)
3. Guerrero DM, Becker JC, Eckstein EC, Kundrapu S, Deshpande A, Sethi AK, et al. Asymptomatic carriage of toxigenic *Clostridium difficile* by hospitalized patients. *J Hosp Infect*. 2013;85:155–8. [PubMed http://dx.doi.org/10.1016/j.jhin.2013.07.002](http://dx.doi.org/10.1016/j.jhin.2013.07.002)
4. Kyne L, Warny M, Qamar A, Kelly CP. Asymptomatic carriage of *Clostridium difficile* and serum levels of IgG antibody against toxin A. *N Engl J Med*. 2000;342:390–7. [PubMed http://dx.doi.org/10.1056/NEJM200002103420604](http://dx.doi.org/10.1056/NEJM200002103420604)
5. Ziakas PD, Zacharioudakis IM, Zervou FN, Grigoras C, Pliakos EE, Mylonakis E. Asymptomatic carriers of toxigenic *C. difficile* in long-term care facilities: a meta-analysis of prevalence and risk factors. *PLoS ONE*. 2015;10:e0117195. [PubMed http://dx.doi.org/10.1371/journal.pone.0117195](http://dx.doi.org/10.1371/journal.pone.0117195)
6. Galdys AL, Nelson JS, Shutt KA, Schlackman JL, Pakstis DL, Pasculle AW, et al. Prevalence and duration of asymptomatic *Clostridium difficile* carriage among healthy subjects in Pittsburgh, Pennsylvania. *J Clin Microbiol*. 2014;52:2406–9. [PubMed http://dx.doi.org/10.1128/JCM.00222-14](http://dx.doi.org/10.1128/JCM.00222-14)
7. Lessa FC, Mu Y, Winston L, Dumyati G, Farley MM, Beldavs Z, et al. Determinants of *Clostridium difficile* infection across diverse U.S. geographic locations. *Open Forum Infect Dis*. 2014;1:ofu048.

8. Dubberke ER, Butler AM, Yokoe DS, Mayer J, Hota B, Mangino JE, et al. Multicenter study of *Clostridium difficile* infection rates from 2000 to 2006. *Infect Control Hosp Epidemiol*. 2010;31:1030–7. [PubMed http://dx.doi.org/10.1086/656245](http://dx.doi.org/10.1086/656245)
9. Campbell RJ, Giljahn L, Machesky K, Cibulskas-White K, Lane LM, Porter K, et al. *Clostridium difficile* infection in Ohio hospitals and nursing homes during 2006. *Infect Control Hosp Epidemiol*. 2009;30:526–33. [PubMed http://dx.doi.org/10.1086/597507](http://dx.doi.org/10.1086/597507)
10. Pawar D, Tsay R, Nelson DS, Elumalai MK, Lessa FC, Clifford McDonald L, et al. Burden of *Clostridium difficile* infection in long-term care facilities in Monroe County, New York. *Infect Control Hosp Epidemiol*. 2012;33:1107–12. [PubMed http://dx.doi.org/10.1086/668031](http://dx.doi.org/10.1086/668031)
11. Curry SR, Muto CA, Schlackman JL, Pasculle AW, Shutt KA, Marsh JW, et al. Use of multilocus variable number of tandem repeats analysis genotyping to determine the role of asymptomatic carriers in *Clostridium difficile* transmission. *Clin Infect Dis*. 2013;57:1094–102. [PubMed http://dx.doi.org/10.1093/cid/cit475](http://dx.doi.org/10.1093/cid/cit475)
12. Metropolis N, Rosenbluth AW, Rosenbluth MN, Teller AH, Teller E. Equation of state calculations by fast computing machines. *J Chem Phys*. 1953;21:1087. <http://dx.doi.org/10.1063/1.1699114>
13. Zilberberg MD. Increase in adult *Clostridium difficile*-related hospitalizations and case-fatality rate, United States, 2000–2005. *Emerg Infect Dis*. 2008;14:929–31. [PubMed http://dx.doi.org/10.1093/cid/cin100](http://dx.doi.org/10.1093/cid/cin100)
14. McDonald LC, Owings M, Jernigan D. *Clostridium difficile* infection in patients discharged from US short-stay hospitals, 1996–2003. *Emerg Infect Dis*. 2006;12:409–15. [PubMed http://dx.doi.org/10.1093/cid/cil100](http://dx.doi.org/10.1093/cid/cil100)
15. Eyre DW, Cule ML, Wilson DJ, Griffiths D, Vaughan A, O'Connor L, et al. Diverse sources of *C. difficile* infection identified on whole-genome sequencing. *N Engl J Med*. 2013;369:1195–205. [PubMed http://dx.doi.org/10.1056/NEJMoa1216064](http://dx.doi.org/10.1056/NEJMoa1216064)
16. Elixhauser A, Steiner C, Harris DR, Coffey RM. Comorbidity measures for use with administrative data. *Med Care*. 1998;36:8–27. [PubMed http://dx.doi.org/10.1097/00005650-199801000-00004](http://dx.doi.org/10.1097/00005650-199801000-00004)
17. Comorbidity software. Healthcare cost and utilization project, 2014 [cited 2015 Dec 29]. <http://www.hcup-us.ahrq.gov/toolssoftware/comorbidity/comorbidity.jsp>
18. Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK, He J. Global burden of hypertension: analysis of worldwide data. *Lancet*. 2005;365:217–23. [PubMed http://dx.doi.org/10.1016/S0140-6736\(05\)70151-3](http://dx.doi.org/10.1016/S0140-6736(05)70151-3)

19. CDC/NCHS. National Hospital Discharge Survey, 2010 [cited 2015 Dec 29].
<http://www.cdc.gov/nchs/nhds.htm>
20. Harris-Kojetin L, Sengupta M, Park-Lee E, Valverde R. Long-term care services in the United States: 2013 overview. *Vital Health Stat 3*. 2013; (37):1–107. [PubMed](#)
21. Arling G, Kane RL, Cooke V, Lewis T. Targeting residents for transitions from nursing home to community. *Health Serv Res*. 2010;45:691–711. [PubMed](#) <http://dx.doi.org/10.1111/j.1475-6773.2010.01105.x>
22. Jones AL, Dwyer LL, Bercovitz AR, Strahan GW. The National Nursing Home Survey: 2004 overview. *Vital Health Stat 13*. 2009;(167):1–155. [PubMed](#)
23. US Census Bureau. National Population Projections, 2014 [cited 2015 Dec 29].
<https://www.census.gov/population/projections/data/national/2014.html>
24. Teno JM, Gozalo PL, Bynum JPW, Leland NE, Miller SC, Morden NE, et al. Change in end-of-life care for Medicare beneficiaries: site of death, place of care, and health care transitions in 2000, 2005, and 2009. *JAMA*. 2013;309:470–7. [PubMed](#) <http://dx.doi.org/10.1001/jama.2012.207624>
25. Dubberke ER, Reske KA, Olsen MA, McMullen KM, Mayfield JL, McDonald LC, et al. Evaluation of *Clostridium difficile*-associated disease pressure as a risk factor for *C difficile*-associated disease. *Arch Intern Med*. 2007;167:1092–7. [PubMed](#)
<http://dx.doi.org/10.1001/archinte.167.10.1092>
26. Dial S, Kezouh A, Dascal A, Barkun A, Suissa S. Patterns of antibiotic use and risk of hospital admission because of *Clostridium difficile* infection. *CMAJ*. 2008;179:767–72. [PubMed](#)
<http://dx.doi.org/10.1503/cmaj.071812>
27. Hensgens MP, Goorhuis A, Dekkers OM, Kuijper EJ. Time interval of increased risk for *Clostridium difficile* infection after exposure to antibiotics. *J Antimicrob Chemother*. 2012;67:742–8. [PubMed](#)
<http://dx.doi.org/10.1093/jac/dkr508>
28. Marwick CA, Yu N, Lockhart MC, McGuigan CC, Wiuff C, Davey PG, et al. Community-associated *Clostridium difficile* infection among older people in Tayside, Scotland, is associated with antibiotic exposure and care home residence: cohort study with nested case-control. *J Antimicrob Chemother*. 2013;68:2927–33. [PubMed](#) <http://dx.doi.org/10.1093/jac/dkt257>
29. Kuntz JL, Chrischilles EA, Pendergast JF, Herwaldt LA, Polgreen PM. Incidence of and risk factors for community-associated *Clostridium difficile* infection: a nested case-control study. *BMC Infect Dis*. 2011;11:194. [PubMed](#) <http://dx.doi.org/10.1186/1471-2334-11-194>

30. Deshpande A, Pasupuleti V, Thota P, Pant C, Rolston DD, Sferra TJ, et al. Community-associated *Clostridium difficile* infection and antibiotics: a meta-analysis. J Antimicrob Chemother. 2013;68:1951–61. PubMed <http://dx.doi.org/10.1093/jac/dkt129>

Technical Appendix Table 1. Parameter names and symbols used for the model of *Clostridium difficile* infection*

Parameter description	Symbol
Epidemiology	
All-cause CDI mortality	α
Rate at which patients complete antimicrobial drug course	ρ
Rate at which recovered patients show recurrence	q
Rate at which patients not receiving antimicrobial drugs and at increased CDI risk revert to normal risk	θ
Rate of recovery from CDI	γ
Probability that a patient recovering from primary CDI will have at least 1 recurrence	r
Probability that a patient recovering from a first recurrence will have a second recurrence	r_2
Probability that a patient recovering from multiple recurrences will have additional recurrence	r_3
Relative risk for development of CDI while receiving antimicrobial drugs	μ_A
Relative risk for CDI among persons 50–65 years of age vs. those <50 years of age	μ_{50}
Relative risk for CDI among persons >65 years of age vs. those <50 years of age	μ_{65}
Spontaneous clearance of asymptomatic <i>C. difficile</i> colonization	δ
Hospital protocols	
All-cause fraction of community-onset CDI that are hospitalized	τ
All-cause fraction of LTCF-onset CDI that are hospitalized	τ_L
Increased attributable length of stay for hospitalized patients with CDI	d_{CDI}
Effectiveness of enhanced infection control measures in reducing transmission	ε
Probability that a patient with CDI is identified and given enhanced infection control measures	π
Antimicrobial drug rates	
Prescription rate among persons in the community	ϕ_C
Prescription rate among patients in the hospital	ϕ_H
Prescription rate among patients in the LTCF	ϕ_L
Transmission	
Hospital force of colonization	λ_H
Community force of colonization	λ_C
LTCF force of colonization	λ_L
Base CDI transmission rate within the hospital	β_S
Base asymptomatic transmission rate within the hospital	β_A
LTCF transmission rate relative to hospital	β_L
Community transmission rate relative to hospital	β_C
Rate of community acquisition from nonhuman reservoirs	χ
Overall hospital hygiene	g

*Parameter values and CIs are provided in the main text. CDI, *C. difficile* infection; LTCF, long-term care facility.

Technical Appendix Table 2. Epidemiologic data used to compose the likelihood function for the MCMC simulation of *Clostridium difficile* infection*

Clinical and epidemiologic data	Estimate (95% CI)	Likelihood distribution	Reference
Asymptomatic hospital colonization prevalence	11% (5.6%–18%)	Gamma (11.7, 106)	(2–4)
Asymptomatic colonization in LTCF	14.8% (7.6%–24%)	Normal (0.148, 0.0418)	(5)
Asymptomatic colonization among healthy adults in community	6.6% (2.8%–12%)	Beta (7, 99)	(6)
Community-onset CDI†			(7)
Overall	37.7 (18.6–56.8)‡	Normal (37.7, 9.72)	
Age 50–64 years	50.4 (46–55)	Normal (50.4, 2.24)	
Age ≥65 years	114.4 (104–124)	Normal (114, 5.2)	
Hospital-onset rate CDI†	7.6 (5.7–9.8)§	Gamma (52.9, 6.98)	(8,9)
Hospital recurrence	1.6 (0.24–2.9)§	Normal (1.55, 0.67)	(8)
LTCF-onset incidence†	2.3 (0–5.3)§	Normal (2.25, 1.56)	(9,10)
LTCF recurrence	0.85 (0–2.4)§	Normal (0.85, 0.815)	(9,10)
Proportion of hospital-onset cases attributable to other CDI patients	30% (19%–43%)	Beta (17, 39)	(11)

*MCMC, Markov Chain Monte Carlo; LTCF, long-term care facility; CDI, *C. difficile* infection.

†Excludes recurrent cases.

‡Units of cases/100,000 person-years.

§Units of cases/10,000 patient-days.

Technical Appendix Table 3. Normalized demographic population breakdown in the United States for *Clostridium difficile* infection

Age, y	Hospital	Community	Long-term care facility
<50	1.2×10^{-3}	0.66	0
50–65 without concurrent conditions	2.7×10^{-4}	0.16	6.5×10^{-5}
50–65 with concurrent conditions	3.4×10^{-4}	0.049	5.9×10^{-4}
>65 without concurrent conditions	2.8×10^{-4}	0.056	3.7×10^{-4}
>65 with concurrent conditions	1.1×10^{-3}	0.069	3.4×10^{-3}

Technical Appendix Table 4. Rate of patient movement between hospital, LTCF, and community, United States*

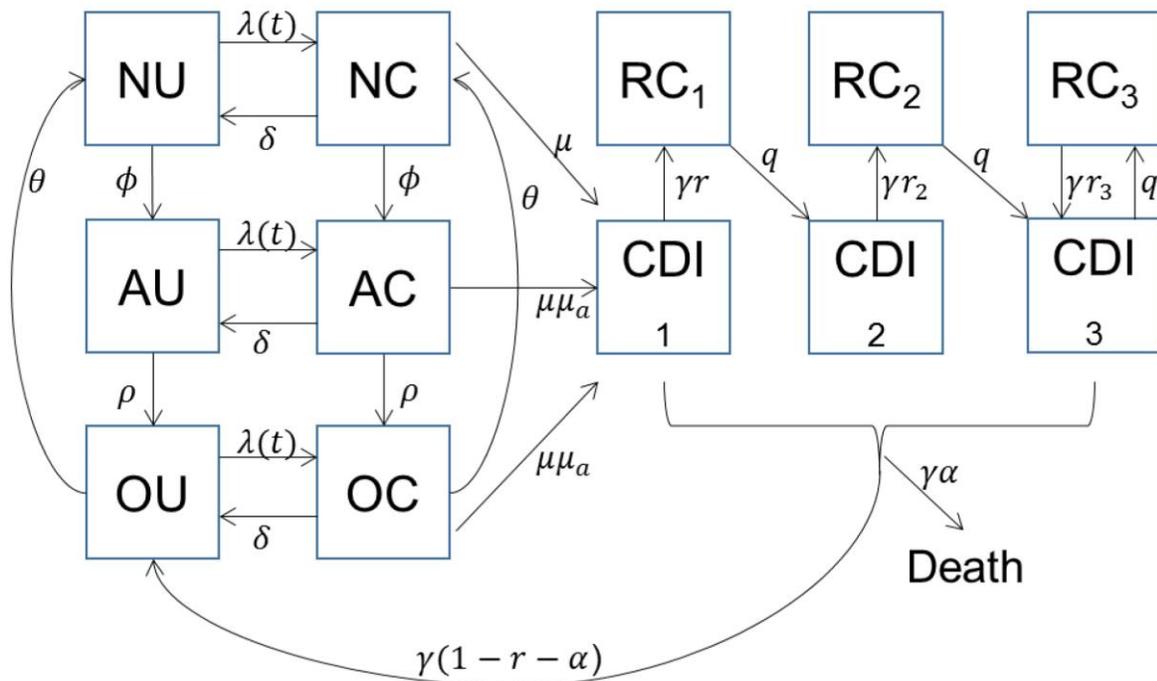
Parameter description	Symbol	Age, y, rate/day
Hospital discharge to community	d_{HC}	<50: 0.22; 50–65 without concurrent conditions: 0.18; 50–65 with concurrent conditions: 0.18; >65 without concurrent conditions: 0.16; >65 with concurrent conditions: 0.15
Hospital discharge to LTCF	d_{HL}	<50: 0; 50–65 without concurrent conditions: 0.00086; 50–65 with concurrent conditions: 0.0028; >65 without concurrent conditions: 0.0056; >65 with concurrent conditions: 0.0095
LTCF admission from community	d_{CL}	<50: 0; 50–65 without concurrent conditions: 2.2×10^{-6} ; 50–65 with concurrent conditions: 2.8×10^{-5} ; >65 without concurrent conditions: 4.2×10^{-5} ; >65 with concurrent conditions: 0.00021
Hospital admission from community	d_{CH}	<50: 0.00038; 50–65 without concurrent conditions: 0.00031; 50–65 with concurrent conditions: 0.0013; >65 without concurrent conditions: 0.00078; >65 with concurrent conditions: 0.0024
Discharge from LTCF to community	d_{LC}	0.0056
Discharge from LTCF to hospital	d_{LH}	0.00032

*LTCF, long-term care facility.

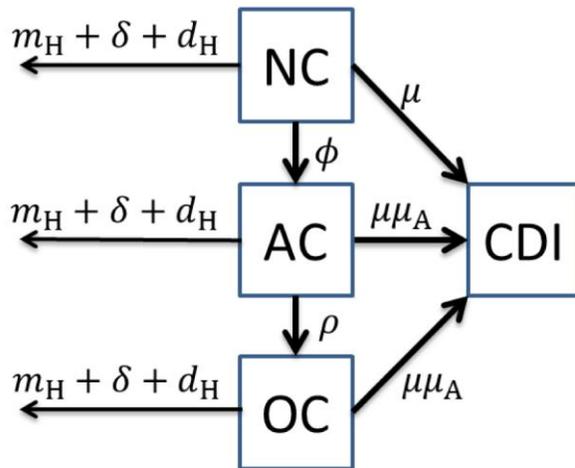
Technical Appendix Table 5. Age-specific mortality rates for non-*Clostridium difficile* infections for hospital, LTCF, and community, United States*

Parameter description	Symbol	Age, y, rate/day
Non-CDI mortality rate in hospital	m_H	<50: 0.0016; 50–64: 0.0033; >65: 0.0073
Non-CDI mortality rate in LTCF	m_L	<50: 0; 50–64: 0; >65: 0.0020
Non-CDI mortality rate in community	m_C	<50: 2.0×10^{-6} ; 50–64: 1.7×10^{-5} ; >65: 5.1×10^{-5}

*CDI, *C. difficile* infection; LTCF, long-term care facility.



Technical Appendix Figure 1. *Clostridium difficile* infection model flowchart, including parameters. N, patients not receiving antimicrobial drugs; U, uncolonized patients; C, asymptotically colonized patients; RC, symptomatically infected patients or colonized patients and subject to recurrence; A, patients receiving antimicrobial drugs; CDI, *C. difficile* infection; O, patients with a recent history of receiving antimicrobial drugs. Arrows indicate changes in individual epidemiologic status. Subscripts indicate primary, secondary, or tertiary CDI.



Technical Appendix Figure 2. Submodel of a larger model of *Clostridium difficile* infection (CDI), which was used separately to mathematically estimate the proportion of cases with colonization outside of the hospital but with diarrheal CDI arising in the hospital that are classified as hospital onset (occurring ≥ 48 hours after hospital admission). N, patients not receiving antimicrobial drugs; C, asymptotically colonized patients; A, patients receiving antimicrobial drugs; O, patients with a recent history of receiving antimicrobial drugs. Arrows indicate changes in individual epidemiologic status.