Quantifying Transmission of Clostridium difficile within and outside Healthcare Settings

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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.

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fection 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 ≥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, nontoxigenic 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
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 asymptptomatically colonized with *C. difficile* because of transmission from asymptomatic patients, transmission from patients with CDI, or through acquisition from background sources in the community. Asymptomatically 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 (16–18). We assumed that all patients with CDI were first asymptptomatically 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 patients 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).
Transmission

We specified 5 *C. difficile* transmission rates: 1) the base CDI rate at which patients without a diagnosis and asymptomatic CDI transmit in the hospital, 2) the base asymptomatic rate at which asymptatically 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 asymptotically 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 asymptatically 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, asymptatically colonized patients transmit at the base asymptomatic rate multiplied by the LTCF transmission rate modifier.
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

| Parameter description | Posterior rate (95% CI) |
|-----------------------|------------------------|
| Hospital force of colonization† | 0.023 (0.017–0.032) |
| Base CDI transmission rate within hospital† | 1.2 × 10⁻³ (0.65–2.1 × 10⁻³) |
| Base CDI transmission rate within hospital accounting for isolation/control measures† | 6.0 × 10⁻² (3.6–9.7 × 10⁻²) |
| Base asymptomatic transmission rate within hospital† | 4.0 × 10⁻⁴ (2.4–5.5 × 10⁻⁴) |
| Relative transmission from patients with CDI compared with asymptomatically colonized patients, accounting for isolation/control measures‡ | 0.023 (0.017–0.032) |
| LTCF force of colonization† | 3.7 × 10⁻³ (0.96–7.7 × 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 × 10⁻³) |
| Community transmission rate, relative to hospital‡§ | 5.2 × 10⁻³ (3.3–8.9 × 10⁻⁴) |
| Community transmission rate, relative to hospital, accounting for hospital CDI isolation/control measures‡§ | 1.0 × 10⁻³ (0.62–2.0 × 10⁻³) |
| Rate of community acquisition from nonhuman reservoirs§ | 1.2 × 10⁻³ (0.50–2.3 × 10⁻³) |
| Base rate of CDI developing in hospital¶ | 2.1 × 10⁻⁴ (1.0–4.7 × 10⁻⁴) |
| Base rate of CDI developing in LTCF¶ | 8.6 × 10⁻⁵ (1.1–22 × 10⁻⁵) |
| Base rate of CDI developing in community¶ | 6.3 × 10⁻⁶ (2.9–12 × 10⁻⁶) |
| Base rate of CDI developing given concurrent conditions¶ | 2.6 (0.78–6.6) |

*CDI, Clostridium difficile; 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

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**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.
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); nontoxicigenic 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 asymptomatically colonized persons, residents of LT CFs, 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 LT CFs 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.

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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 \( \lambda_H \), where \( g \) indicates the overall hospital hygiene control parameter, \( \text{CDI}_H \) indicates the number of hospitalized patients with symptomatic *C. difficile* infection (\( \text{CDI}_1 + \text{CDI}_2 + \text{CDI}_3 \)), and \( \text{C}_H \) indicates the number of asymptotically colonized patients in the hospital (\( \text{NC} + \text{AC} + \text{OC} + \text{RC} \); \( \text{N} \), patients not receiving antimicrobial drugs; \( \text{C} \), asymptotically colonized patients; \( \text{A} \), patients receiving antimicrobial drugs; \( \text{O} \), patients with a recent history of receiving antimicrobial drugs; \( \text{RC} \), symptomatically infected patients or colonized patients and subject to recurrence). The LTCF force-of-colonization was \( \lambda_L \) with \( \text{CDI}_L \) and \( \text{C}_L \) representing the number of symptomatic CDI and asymptomatic colonized patients, respectively, in the LTCF. The community force-of-colonization was \( \lambda_C \) with \( \text{CDI}_C \) and \( \text{C}_C \) representing the number of symptomatic CDI and asymptomatic colonized patients, respectively, in the community.

Equation 1

\[
\begin{align*}
\lambda_H & = g[(1 - \pi)\beta_S\text{CDI}_H + \beta_A\text{C}_H] + \pi(1 - \epsilon)\beta_S\text{CDI}_H \\
\lambda_L & = \beta_L(\beta_S\text{CDI}_L + \beta_A\text{C}_L) \\
\lambda_C & = \beta_C(\beta_S\text{CDI}_C + \beta_A\text{C}_C) + \chi
\end{align*}
\]
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 asymptotically 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 $2.0 \times 10^{-6}$ and $1.7 \times 10^{-5}$, 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 $5.1 \times 10^{-5}$. We estimated a daily LTCF mortality rate among persons >65 years of age of 0.0020.

Parameter Assumptions and Derivation

Rate ($\mu$) at Which Symptomatic CDI Develops in Asymptomatically Colonized Patients

We partitioned $\mu$ into components by age, concurrent condition, antimicrobial drug history, and hospitalization status. First, we specified that asymptptomatically 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 $\mu_C$, $\mu_H$, or $\mu_L$, 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 $\mu_{50}$ times as likely to show development of CDI as those <50 years of age. Colonized patients >65 years of age were parameterized to be $\mu_{65}$ 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 $\mu_A$ times as likely to show development of CDI as those without such exposure (26–30). Finally, persons with concurrent conditions were parameterized to be $\mu_n$ 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 $\mu_{H}l_{50}M_{N14}$.

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).

$$\frac{dNC(t)}{dt} = -\left(\phi + \mu + m_{H} + \delta + d_{H}\right)NC(t)$$

$$\frac{dAC(t)}{dt} = \phi NC(t) - \left(\rho + \mu_{A} + m_{H} + \delta + d_{H}\right)AC(t)$$

$$\frac{dOC(t)}{dt} = \rho AC(t) - \left(\mu_{A} + m_{H} + \delta + d_{H}\right)OC(t)$$

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

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

$$CDI(t) =$$

$$\frac{-\left(\mu e^{-\left(\sigma + \mu + \phi\right)}(-1 + \mu_{A})(\sigma + \mu_{A})(\mu + \phi) - e^{-\left(\sigma + \mu_{A}\right)}\mu_{A}\Phi(\sigma + \mu + \phi) - (\mu(-1 + \mu_{A}) - \phi)(\sigma + \mu_{A}(\mu + \phi))\right)}{\left((\sigma + \mu_{A})(\mu(-1 + \mu_{A}) - \phi)(\sigma + \mu + \phi)\right)}$$

We define the outflow parameter $\sigma = m_{H} + \delta + d_{H}$ 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(∞) – CDI(2) gives the probability of development of CDI ≥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.

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

$
e^{-2(\theta + \mu + \phi)(1 - \mu_d)(\alpha + \mu_d)(\mu + \phi) + e^{-2(\theta + \mu + \phi)}\mu_d\phi(\alpha + \mu + \phi)}

(\mu(1 - \mu_d + \phi)(\alpha + \mu_d(\mu + \phi)))$

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

| Parameter description | Symbol |
|-----------------------|--------|
| **Epidemiology**      |        |
| All-cause CDI mortality | $\alpha$ |
| Rate at which patients complete antimicrobial drug course | $\rho$ |
| 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 | $\theta$ |
| Rate of recovery from CDI | $\gamma$ |
| 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 | $r_2$ |
| Relative risk for development of CDI while receiving antimicrobial drugs | $\mu_A$ |
| Relative risk for CDI among persons 50–65 years of age vs. those <50 years of age | $\mu_{50}$ |
| Relative risk for CDI among persons >65 years of age vs. those <50 years of age | $\mu_{65}$ |
| Spontaneous clearance of asymptomatic *C. difficile* colonization | $\delta$ |
| **Hospital protocols** |        |
| All-cause fraction of community-onset CDI that are hospitalized | $\tau$ |
| All-cause fraction of LTCF-onset CDI that are hospitalized | $\tau_L$ |
| Increased attributable length of stay for hospitalized patients with CDI | $\lambda_{CDI}$ |
| Effectiveness of enhanced infection control measures in reducing transmission | $e$ |
| Probability that a patient with CDI is identified and given enhanced infection control measures | $\pi$ |
| **Antimicrobial drug rates** |        |
| Prescription rate among persons in the community | $\phi_C$ |
| Prescription rate among patients in the hospital | $\phi_H$ |
| Prescription rate among patients in the LTCF | $\phi_L$ |
| **Transmission** |        |
| Hospital force of colonization | $\lambda_H$ |
| Community force of colonization | $\lambda_C$ |
| LTCF force of colonization | $\lambda_L$ |
| Base CDI transmission rate within the hospital | $\beta_S$ |
| Base asymptomatic transmission rate within the hospital | $\beta_A$ |
| LTCF transmission rate relative to hospital | $\beta_L$ |
| Community transmission rate relative to hospital | $\beta_C$ |
| Rate of community acquisition from nonhuman reservoirs | $\chi$ |
| 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† | 37.7 (18.6–56.8)‡ | Normal (37.7, 9.72) | (?1) |
| Overall | 37.7 (18.6–56.8)‡ | Normal (37.7, 9.72) | (?1) |
| 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                    | $1.2 \times 10^{-3}$ | 0.66      | 0                       |
| 50–65 without concurrent conditions | $2.7 \times 10^{-4}$ | 0.16      | $6.5 \times 10^{-5}$    |
| 50–65 with concurrent conditions | $3.4 \times 10^{-4}$ | 0.049     | $5.9 \times 10^{-4}$    |
| >65 without concurrent conditions | $2.8 \times 10^{-4}$ | 0.056     | $3.7 \times 10^{-4}$    |
| >65 with concurrent conditions | $1.1 \times 10^{-3}$ | 0.069     | $3.4 \times 10^{-3}$    |

### 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: 0.16; >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 $\times 10^{-6}$; 50–65 with concurrent conditions: 2.8 $\times 10^{-5}$; >65 without concurrent conditions: 4.2 $\times 10^{-5}$; >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: $2.0 \times 10^{-6}$; 50–64: $1.7 \times 10^{-6}$; >65: $5.1 \times 10^{-6}$ |

*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, asymptomatically 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.