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Effectiveness of screening hospital admissions to detect asymptomatic carriers of Clostridium difficile: A modeling evaluation

Cristina Lanzas
University of Tennessee - Knoxville
Erik R. Dubberke
Washington University School of Medicine in St. Louis

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Author(s): Cristina Lanzas, PhD; Erik R. Dubberke, MD

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ORIGINAL ARTICLE

Effectiveness of Screening Hospital Admissions to Detect Asymptomatic Carriers of *Clostridium difficile*: A Modeling Evaluation

Cristina Lanzas, PhD;[1] Erik R. Dubberke, MD[2]

OBJECTIVE. Both asymptomatic and symptomatic *Clostridium difficile* carriers contribute to new colonizations and infections within a hospital, but current control strategies focus only on preventing transmission from symptomatic carriers. Our objective was to evaluate the potential effectiveness of methods targeting asymptomatic carriers to control *C. difficile* colonization and infection (CDI) rates in a hospital ward: screening patients at admission to detect asymptomatic *C. difficile* carriers and placing positive patients into contact precautions.

METHODS. We developed an agent-based transmission model for *C. difficile* that incorporates screening and contact precautions for asymptomatic carriers in a hospital ward. We simulated scenarios that vary according to screening test characteristics, colonization prevalence, and type of strain present at admission.

RESULTS. In our baseline scenario, on average, 42% of CDI cases were community-onset cases. Within the hospital-onset (HO) cases, approximately half were patients admitted as asymptomatic carriers who became symptomatic in the ward. On average, testing for asymptomatic carriers reduced the number of new colonizations and HO-CDI cases by 40%–50% and 10%–25%, respectively, compared with the baseline scenario. Test sensitivity, turnaround time, colonization prevalence at admission, and strain type had significant effects on testing efficacy.

CONCLUSIONS. Testing for asymptomatic carriers at admission may reduce both the number of new colonizations and HO-CDI cases. Additional reductions could be achieved by preventing disease in patients who are admitted as asymptomatic carriers and developed CDI during the hospital stay.

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Clostridium difficile is an important nosocomial pathogen that causes diarrhea, pseudomembranous colitis, and possibly death. The incidence, mortality, and medical care cost of *C. difficile* infection (CDI) have reached historic highs. In the United States, the number of discharges in which the patient was diagnosed with CDI doubled from 2000 to 2009; *C. difficile* is estimated to cause as many as 250,000 new infections and 14,000 deaths per year, and in US acute care facilities alone, the cost is as much as $3.2 billion per year.[1-5] In the latest report on antibiotic resistance threats in the United States released by the Centers for Disease Control and Prevention in 2013, *C. difficile* was classified within the highest threat level of urgent.[5] The increase in *C. difficile* infection rates is attributed partially to the emergence of the epidemic NAP1/B1/027 strain, which has high levels of toxin A and B production and carries the binary toxin.[6-8] Despite the burden and threat posed by *C. difficile*, CDI prevention has changed little in recent decades. Current control strategies rely on limiting the spread of *C. difficile* from symptomatic patients. Therefore, patients with diarrheal stool are tested for *C. difficile*, and if the patient tests positive, isolation and contact precaution measures are applied.[9] To more effectively contain *C. difficile*, there is a critical need to identify additional control strategies.

Using highly discriminatory typing methods, recent epidemiological studies have challenged the notion that symptomatic patients are the main contributors to *C. difficile* transmission.[10-12] Similarly, Curry et al[12] found that CDI cases were as frequently linked to transmission from asymptomatic as to symptomatic patients. Therefore, the contribution of symptomatic cases to transmission and new infection is likely to be lower than previously thought. In addition, the likelihood of transmission and infection appears to also be strain specific. In a recent hospital ward–based transmission study, only 19% of cases were traced to other known CDI cases; however, for the epidemic strain NAP1/B1/027, up to 63% of cases were traced to other CDI cases.[11] Consequently, CDI

Affiliations: 1. Department of Biomedical and Diagnostic Sciences, University of Tennessee, Knoxville, Tennessee; 2. Department of Medicine, Washington University School of Medicine, St. Louis, Missouri.

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TABLE 1. List of Simulated Scenarios with the Parameter Values That Were Modified

	Test sensitivity	Turnover time	Colonized patients at admission, %	Patients colonized with 027 at admission, %
Baseline	NA	NA	10	20
Diagnostic tests scenarios	0.75, 0.90, 0.99	0.5, 1, 2.5	10	20
Colonization at admission scenarios	0.90	1	5, 10, 20, 30	20
Strain carriage at admission	0.90	1	10	0, 10, 20, 30, 40

NOTE. NA, not applicable.

might be more effectively controlled by targeting additional sources of *C. difficile* transmission beyond clinical cases.

Asymptomatic colonization prevalence for *C. difficile* among admitted patients has been reported to be up to 20%,[6,13,14] and admitted colonized patients may play an important role in sustaining *C. difficile* transmission in acute healthcare facilities. Therefore, preventing secondary infection transmission from asymptomatic colonized patients can be an additional control point to decrease CDI burden in hospitals.[15] For other nosocomial pathogens, such as methicillin-resistant *Staphylococcus aureus*, universal screening at admission has resulted in reduced rates of hospital-acquired infections.[16] Recent advances in diagnostic testing for *C. difficile* have encouraged the evaluation of the feasibility of screening patients at admission for *C. difficile* and subsequent application of isolation precautions.[17-19] An outcome model identified *C. difficile* screening, coupled with isolation precautions, as a cost-effective intervention when the proportion of admitted patients with *C. difficile* colonization was greater than approximately 10%.[20]

For healthcare-associated infections, computational models of pathogen transmission have become valuable tools to evaluate healthcare interventions, especially in the absence of controlled intervention studies.[21] In this study, we evaluated the effect of screening patients for *C. difficile* colonization at admission—followed by contact precautions for patients who tested positive—on preventing colonization and disease in an endemic setting. We used an agent-based model of *C. difficile* transmission to specifically address how diagnostic test characteristics (ie, sensitivity and turnaround time) used for screening, colonization prevalence, and type of strain carried by colonized patients at admission affected the effectiveness

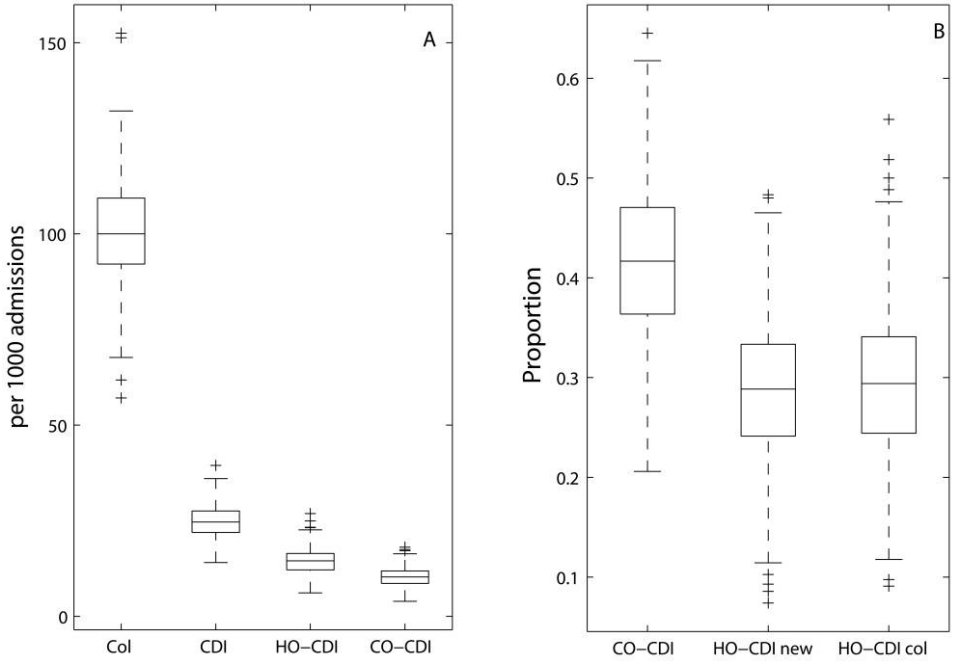

FIGURE 1. Model outcomes for the baseline scenario (no testing for asymptomatic carrier detection). *A*, Number of new colonizations (Col), total *Clostridium difficile* infection (CDI) cases, hospital-onset CDI cases (HO-CDI), and community-onset CDI cases (CO-CDI) per 1,000 admissions. *B*, Proportion of CO-CDI cases, HO-CDI cases who were not already colonized at the ward (HO-CDI new), and HO-CDI cases who were admitted as colonized and developed CDI within the ward (HO-CDI col). The middle line in the box represents the median, and upper and lower areas of the box indicate the seventy-fifth and twenty-fifth percentiles.

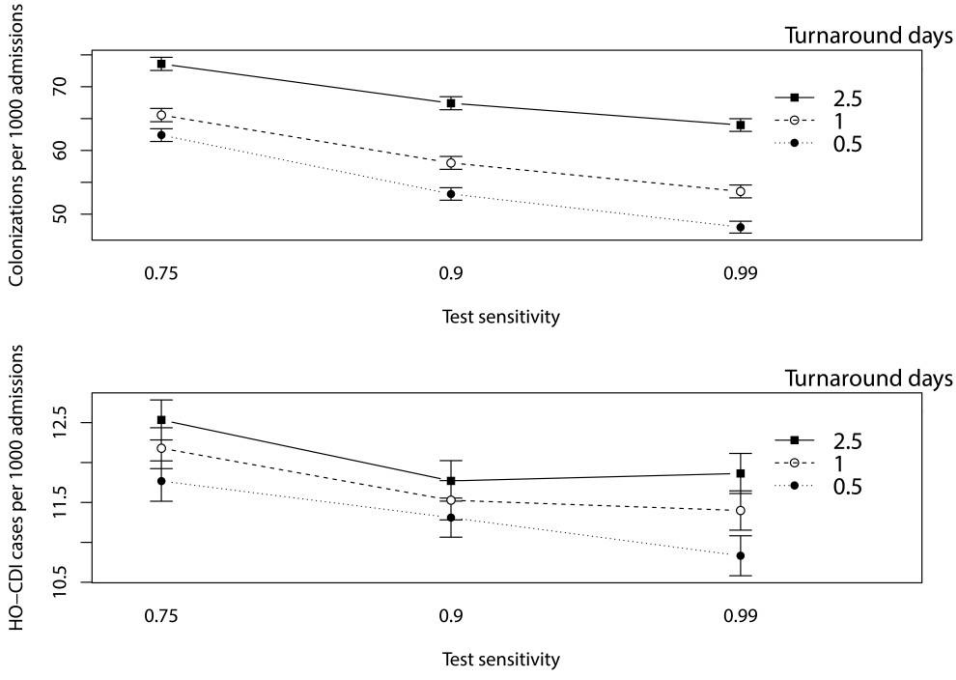

FIGURE 2. Effects of test sensitivity and turnaround time on the mean number (±95% confidence interval) of new colonizations (*A*) and hospital-onset *Clostridium difficile* infection (HO-CDI) cases per 1,000 admissions (*B*) when screening for asymptomatic carriers and isolation precautions are applied, with colonization prevalence on admission of 10%.

of screening for asymptomatic carriers in reducing transmission and hospital-onset CDIs (HO-CDIs) in a hospital ward.

METHODS

Model Overview

We developed an agent-based model for the transmission of *C. difficile* in a hospital ward. Electronic data were collected retrospectively from 6 medicine wards at Barnes-Jewish Hospital in St. Louis, Missouri, from January 1 through December 31, 2008, using the hospital's medical informatics databases. The data set included 11,046 admissions. The mean age of patients was 57 years, and 54% of patients were female, with a mean Charlson comorbidity score of 1.8. The model follows the conceptual modeling framework presented by Lanzas et al[15] and incorporates a more detailed description of antibiotic exposure, type of *C. difficile* strain, screening, and contact precautions.

Because a higher proportion of patients who acquire the epidemic strain NAP1/B1/027 develop CDI compared with other strains,[6,11] the model was expanded to include 2 strain groups: epidemic strain NAP1/B1/027 (027 group) and other strains (non-027 group). We expanded the model to consider screening at admission in the following way: patients identified as asymptomatic carriers at admission would be placed in contact precautions. Patients in isolation were assumed to remain in the same ward they were in. Additional information is available directly from the authors regarding the overview, design concepts, and details protocol, a suggested standardized protocol to describe agent-based models.[22] We implemented the model in NetLogo (ver. 5.0), an open-source, agent-based modeling tool.

Scenarios

Table 1 summarizes evaluated intervention scenarios. The baseline scenario represents current control strategies (ie, only patients with diarrheal stools are tested for the presence of *C. difficile* toxin). We evaluated scenarios that varied by the sensitivity and turnaround time of the diagnostic tests available to identify asymptomatic colonized patients. Test specificity was assumed to be 100%. Polymerase chain reaction–based tests have reasonable sensitivity and reduced turnover time compared with other methods, such as the cytotoxicity cell assay, and therefore have the potential to be used for screening at admission. On the basis of published validation studies for diagnostic polymerase chain reaction tests for *C. difficile*, the scenarios differed in test sensitivity to detect asymptomatic carriers (0.75, 0.90, and 0.99) and in turnaround time (0.5, 1, and 2.5 days).[17,18,23] Test sensitivity and turnaround time were evaluated in a factorial-like design. The baseline value for the efficacy of contact precautions was conservatively set to 75% to account for the fact that imple-

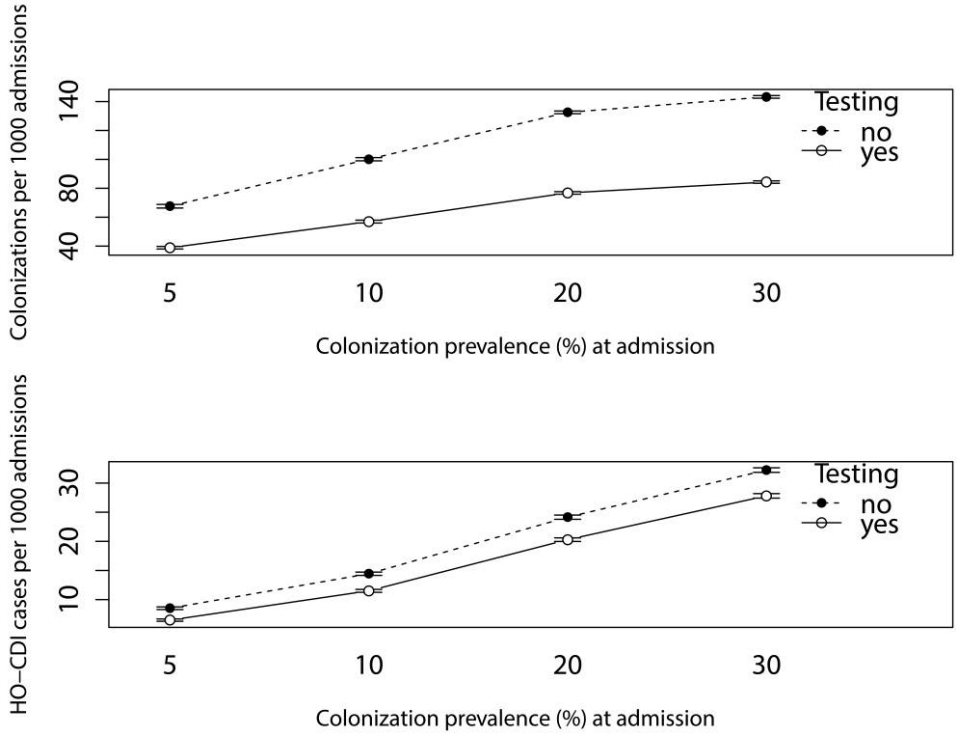

FIGURE 3. Effects of colonization prevalence at admission on the mean number (±95% confidence interval) of new colonizations (*A*) and hospital-onset *Clostridium difficile* infection (HO-CDI) cases for 1,000 admissions (*B*). Assumed screening sensitivity, 0.90; turnaround time, 1 day.

mentation of and adherence to control measures may not necessarily be perfect.[24]

Additional factors that may influence the efficacy of the interventions are the colonization prevalence at admission and the type of strain the colonized patients carried at admission (Table 1). Model outcomes include the number of *C. difficile* colonizations and total CDI cases per 1,000 admissions. The use of an agent-based model allows us to track individual timelines for infection and disease of each simulated patient. We divided the CDI cases into the number of community-onset (CO) cases and the number of HO cases. For the HO cases, we tracked whether the patient was colonized and developed CDI within the ward or was admitted as colonized and subsequently developed CDI at the hospital. When 2 variables were varied simultaneously in the simulations, their effects on the model outcomes were evaluated using a 2-way ANOVA analysis. Analysis of the model output was carried out in R 2.15 (R Development Core Team).

RESULTS

The model outcomes for the listed scenarios in Table 1 are presented in Figures 1–4. At the baseline scenario (ie, no testing to detect asymptomatic carriers), the total number of CDI cases per 1,000 admissions was highly variable, with a mean of 24.7 and a standard deviation of 4.18 (Figure 1*A*). The number of new colonizations was 100 per 1,000 admissions, with a standard deviation of 13.19. On average, 58% of CDI cases were HO cases, for a mean of 14.5 per 1,000 admissions. Approximately half of the HO-CDI cases were patients admitted colonized who became diseased in the ward (Figure 1*B*).

Applying admission testing with reasonable test sensitivity (greater than 0.75) and turnaround time (less than 2.5 days) decreased new colonizations by a mean of 40% to 60.15 per 1,000 admissions (interquartile range [IQR], 18.82 per 1,000 admissions). HO-CDI cases were reduced by 19% to 11.70 per 1,000 admissions (IQR, 3.95 per 1,000 admissions) compared with the baseline scenario (Figure 2). For the best-case scenario (sensitivity, 0.99; turnaround time, 0.5 days), the mean numbers of new colonizations and HO-CDIs were reduced by approximately 52% (48 cases per 1,000 admissions) and 25% (10.8 cases per 1,000 admissions), respectively (Figure 2). Both test sensitivity and turnaround time had an overall significant effect on both new colonizations and HO-CDI cases (Figure 2). The scenario with a sensitivity of 0.99 and a turnover of 2.5 days had a slightly high number of HO-CDI cases compared with the scenario with a sensitivity of 0.90 and a turnover of 2.5 days (mean, 11.77 vs 11.86 cases per 1,000 admissions); the difference was not found to be statistically significant.

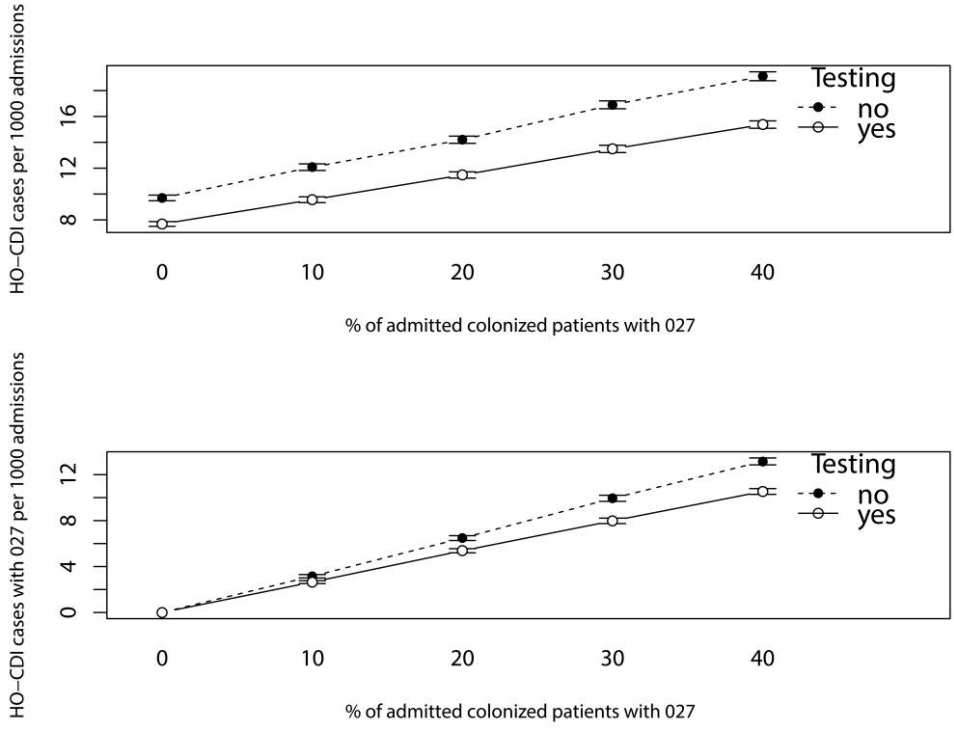

FIGURE 4. Effects of 027 strain prevalence at admission on the mean number (±95% confidence interval) of hospital-onset *Clostridium difficile* infection (HO-CDI) cases per 1,000 admissions (*A*) and HO-CDI cases caused by 027 per 1,000 admissions (*B*). Assumed screening sensitivity, 0.90; turnaround time, 1 day.

We further evaluated the effect of testing at different colonization prevalences (Figure 3) and whether the relative proportion of admitted colonized patients with 027 versus other strains affected testing efficacy (Figure 4). Assuming a screening sensitivity of 0.90 and a turnaround time of 1 day, applying testing coupled with contact precautions reduced new colonizations by approximately 42% and HO-CDI cases by 14%–24%, depending on colonization prevalence at admission. There was a significant interaction between the colonization prevalence at admission and the testing efficacy in reducing both new colonizations and HO-CDI cases. The number of patients needed to screen at admission to prevent 1 colonization event or 1 clinical case within a year are presented in Table 2.

As the percentage of admitted patients colonized with 027 increased, the model predicted an increase in the number of HO-CDI cases (Figure 4). The efficacy of testing remained fairly constant at a 20% reduction of HO-CDI cases, despite the increase in admitted patients colonized with 027 for a given prevalence. The proportion of HO-CDI cases caused by 027 was greater than the proportion of admitted colonized patients with 027. When 027 was responsible for 20% of the admitted colonized patients, the resultant simulation predicted that the number of HO-CDI cases caused by 027 would be approximately 50%.

DISCUSSION

Evidence-supported strategies to prevent *C. difficile* infection are limited to the use of gloves when caring for patients with CDI and antimicrobial stewardship.[9,25] The application of these strategies and other suggested measures, such as environmental decontamination, have resulted in modest reductions in CDI incidence in endemic settings.[26] Thus, further research to identify additional sources of CDI and novel control strategies are necessary. We previously used the same modeling framework to evaluate the contribution of asymptomatic carriers and CDI patients to new colonizations at the ward level.[15] Our results indicated that admission of asymptomatic carriers highly influenced *C. difficile* outcomes and underscored the need to further evaluate the role of asymptomatic colonized patients. Recent epidemiological studies have also shown that in addition to CDI patients, asymptomatic carriers and unknown sources of *C. difficile* are important contributors to new CDI cases.[10-12,27]

Patients can develop CDI through 3 different infection histories: they can be admitted with CDI (CO-CDI), be admitted as colonized patients and become diseased during the hospital stay, or become both colonized and diseased patients during the hospital stay. Preventing CDI for these different timelines likely requires different prevention strategies (eg,

TABLE 2. Decrease in the Colonization Rate and Hospital-Onset *Clostridium difficile* Infection (HO-CDI) Cases per 1,000 Admissions

Scenario	Colonization prevalence at admission, %	Patients colonized with 027, %	Colonization rate reduction	NNT for colonization	HO-CDI rate reduction	NNT for HO-CDI
S1	5	20	28.71 (26.55–30.87)	35 (32–38)	2.04 (1.37–2.71)	490 (369–730)
S2	10	20	43.14 (40.98–45.3)	23 (22–24)	2.93 (2.26–3.61)	341 (277–442)
S3	20	20	55.74 (53.58–57.90)	18 (17–19)	3.86 (3.18–4.54)	259 (220–314)
S4	30	20	58.94 (56.78–61.10)	17 (16–18)	4.43 (3.75–5.10)	225 (196–267)
S5	10	0	42.52 (40.10–44.93)	24 (22–25)	2.01 (1.41–2.62)	498 (382–709)
S6	10	10	42.8 (40.39–45.22)	23 (22–25)	2.52 (1.91–3.12)	397 (321–524)
S7	10	20	40.63 (38.21–43.05)	25 (23–26)	2.73 (2.12–3.33)	366 (300–472)
S8	10	30	42.81 (40.40–45.23)	23 (22–25)	3.41 (2.80–4.02)	293 (249–357)
S9	10	40	41.6 (39.18–44.02)	24 (23–26)	3.73 (3.13–4.34)	268 (230–319)

NOTE. Data are means (95% confidence intervals), unless otherwise indicated, of decrease achieved with testing at admission and their associated number needed to treat (NNT) for the scenarios in which the colonization prevalence was varied (S1–S4) and the prevalence of the 027 strain at admission was varied (S5–S9). The NNT indicates the number of admitted patients who would need to be tested at admission in order to prevent 1 colonization or HO-CDI event.

preventing colonization vs preventing CDI in those patients already colonized); the different pathways may help explain why current strategies appear to have a floor effect, since they focus mostly on reducing secondary cases from symptomatic patients.[25,28,29] In our baseline scenario, patients who became colonized and diseased within the hospital ward represented, on average, 50% of the possible HO-CDI cases. Those colonized on admission have been considered to be at lower risk for subsequent onset of disease than those not colonized.[30] However, emerging data suggest that this may no longer be the case.[6,31] Of note, if asymptomatic carriage of *C. difficile* does maintain a protective effect against CDI and fewer than 50% of HO-CDI cases are from patients colonized on admission, the efficacy of testing should be even greater than found in this study. Given the prevalence of patient colonization at admission, these patients represent an important source of HO-CDI, and approaches to prevent disease in patients who are already colonized at admission are necessary.

In the different simulated scenarios, testing was highly effective in reducing colonization events. However, the scope of the model—the hospital ward—does not allow us to fully assess the implications of reducing colonization rates within the ward. A reduced colonization rate could result in an overall reduction in the disease burden in healthcare networks beyond the ward. Patients who become colonized at the ward level could develop CDI at the community level or at other healthcare settings, such as nursing homes, or be readmitted and develop HO-CDI in future hospital visits. Elderly patients and residents of long-term care facilities are disproportionally affected by CDI because of their inherent susceptibility, frequent hospitalization, and exposure to antimicrobials; therefore, they could particularly benefit from a reduced probability of colonization during their multiple readmissions in hospitals. Models that represent a full healthcare network are necessary to evaluate the implications of reducing hospital *C. difficile* transmission beyond the hospital level. Testing for asymptomatic carriers at admission can reduce both the number of new colonizations and CDI cases. Additional reductions could be achieved by preventing disease in patients who are admitted as asymptomatic carriers and might develop CDI during the hospital stay. In our current model, we assumed that it was feasible to establish contact precautions for all patients identified as *C. difficile* carriers in the ward. However, for hospital wards with shared rooms, complete compliance may not be feasible.

Screening patients at admission to detect and isolate asymptomatic carriers could decrease the number of new colonizations and HO-CDI cases at the ward level. In our various scenarios, screening patients, coupled with isolation precautions, reduced the number of new colonizations up to 50% and the number of HO-CDI cases up to 25%, approximately. These values agree with the predicted transmission events associated with asymptomatic carriers in our previous modeling study.[15] We specifically evaluated the efficacy of this strategy when test characteristics and proportion of colonized patients at admission were varied. Our simulations indicated that tests with a sensitivity greater than 90% and turnaround times less than 2.5 days could reduce the number of secondary new colonizations (and subsequent CDIs) caused by asymptomatic carriers. Although screening for asymptomatic *C. difficile* colonization appears promising on the basis of these simulations, additional research is needed to determine the costs, feasibility, and impact of screening on patient outcomes. In addition, the use of the model to support policy recommendations will require the assessment of the model performance in other populations, since the parameters and assumptions are specific to the setting in which the data that informed the model were collected (ie, adults on medical wards). For example, parameters such as discharge rates or ability to mount immune response after colonization are population specific.

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Address correspondence to Cristina Lanzas, PhD, Department of Biomedical and Diagnostic Sciences, University of Tennessee, 2407 River Drive, Room A205, Knoxville, TN 37996-4543 (clanzas@utk.edu).

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