

Interventions to Reduce the Incidence of Hospital-Onset *Clostridium difficile* Infection: An Agent-Based Modeling Approach to Evaluate Clinical Effectiveness in Adult Acute Care Hospitals

Anna K. Barker,¹ Oguzhan Alagoz,^{1,2} and Nasia Safdar^{3,4}

¹Department of Population Health Sciences, School of Medicine and Public Health, ²Department of Industrial and Systems Engineering, College of Engineering, and ³Division of Infectious Diseases, Department of Medicine, School of Medicine and Public Health, University of Wisconsin–Madison, and ⁴William S. Middleton Memorial Veterans Hospital, Madison, Wisconsin

Background. Despite intensified efforts to reduce hospital-onset *Clostridium difficile* infection (HO-CDI), its clinical and economic impacts continue to worsen. Many institutions have adopted bundled interventions that vary considerably in composition, strength of evidence, and effectiveness. Considerable gaps remain in our knowledge of intervention effectiveness and disease transmission, which hinders HO-CDI prevention.

Methods. We developed an agent-based model of *C. difficile* transmission in a 200-bed adult hospital using studies from the literature, supplemented with primary data collection. The model includes an environmental component and 4 distinct agent types: patients, visitors, nurses, and physicians. We used the model to evaluate the comparative clinical effectiveness of 9 single interventions and 8 multiple-intervention bundles at reducing HO-CDI and asymptomatic *C. difficile* colonization.

Results. Daily cleaning with sporicidal disinfectant and *C. difficile* screening at admission were the most effective single-intervention strategies, reducing HO-CDI by 68.9% and 35.7%, respectively (both $P < .001$). Combining these interventions into a 2-intervention bundle reduced HO-CDI by 82.3% and asymptomatic hospital-onset colonization by 90.6% (both, $P < .001$). Adding patient hand hygiene to healthcare worker hand hygiene reduced HO-CDI rates an additional 7.9%. Visitor hand hygiene and contact precaution interventions did not reduce HO-CDI, compared with baseline. Excluding those strategies, healthcare worker contact precautions were the least effective intervention at reducing hospital-onset colonization and infection.

Conclusions. Identifying and managing the vast hospital reservoir of asymptomatic *C. difficile* by screening and daily cleaning with sporicidal disinfectant are high-yield strategies. These findings provide much-needed data regarding which interventions to prioritize for optimal *C. difficile* control.

Keywords. *C. difficile*; infection control; agent-based modeling; intervention bundles; healthcare epidemiology.

Despite intensified efforts to reduce *Clostridium difficile* infection (CDI) by hospitals nationwide, its clinical and economic impacts have continued to worsen [1–3]. The rate of community-acquired [2, 4–6] and antibiotic-resistant CDI are increasing [1, 7, 8], and *C. difficile* has surpassed methicillin-resistant *Staphylococcus aureus* (MRSA) as the most common cause of healthcare-associated infections in the United States [9]. As of January 2017, hospitals with the highest CDI rates incur a financial penalty imposed by the Medicare Hospital-Acquired Condition Reduction Program [10].

In an effort to rapidly decrease CDI rates, hospitals typically implement multiple *C. difficile* interventions at the same time

in a CDI bundle [11–15]. These bundles vary considerably in composition, strength of evidence, and effectiveness [15]. When several interventions are introduced simultaneously, it is difficult to isolate the effects of individual CDI strategies [11, 16]. The optimal bundle for CDI prevention is unknown, which hinders CDI prevention.

Unlike traditional epidemiologic studies, computer simulation modeling allows examination of counterfactual scenarios that can identify the isolated effects of individual interventions to reduce CDI. Agent-based models can account for the indirect effects and underlying complexity of hospital infection control dynamics [16, 17]. All other covariates, transmission dynamics, and assumptions are kept constant across simulation runs, so that the resulting difference between CDI rates is due to the implemented intervention or chance.

Being able to evaluate the clinical effectiveness of CDI interventions is essential to making evidence-based implementation decisions in the context of constrained hospital resources. Agent-based modeling is uniquely poised to evaluate

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Correspondence: A. K. Barker, Warf Office Bldg, 610 Walnut St #707, Madison, WI 53726 (akbarker@wisc.edu).

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intervention comparative effectiveness, yet this methodology has been underutilized in the field [16].

Our group published an initial agent-based model of *C. difficile* transmission in 2014, investigating the clinical effectiveness of vancomycin treatment, contact isolation and cohorting, healthcare worker (HCW) hand hygiene, and environmental cleaning [18]. Subsequent changes in CDI epidemiology, diagnostic testing modalities, and the rapid implementation of novel interventions aimed at CDI prevention prompted us to design a new version of that original model. Here, we developed an agent-based model of *C. difficile* transmission in a midsized adult hospital that reflects current CDI epidemiology and hospital practices, and evaluate the clinical effectiveness of 9 infection control interventions.

METHODS

Approach

We developed an agent-based simulation model of *C. difficile* transmission in a 200-bed adult hospital. Agent-based modeling is an extension of discrete-event simulation in which individuals have unique attributes, are tracked individually, and interact with each other and the environment [17, 19, 20]. The hospital is divided into 10 identical wards, each containing 20 single-bed patient rooms, a visitor common area, nursing station, and physician workroom. Each model run simulates a 1-year period. The model time-step is 5 minutes.

Agents

The model includes 4 agent types: patients, visitors, nurses, and physicians. Patients are assigned a room upon arrival, although intra- or interward patient transfers can occur. Each patient is categorized into 1 of 9 clinical states representing CDI status (Table 1). These states are updated every 6 hours based on probabilities in the model's underlying discrete-time Markov chain (Figure 1), adapted from our previous agent-based *C. difficile* model [18]. Patients are assessed for high-risk antibiotic usage at the beginning of their second hospital day. At that time, all nonsusceptible patients using these antibiotics are moved

to the susceptible state. Discussion of modifications made to our previous model and recalibration details are shown in Supplementary Materials 1 and 2, respectively.

Visitors are assigned to 1 patient, whom they stay with until they leave the hospital, exiting through the ward's common room. As in the existing *C. difficile* transmission model by Rubin et al, 2 types of HCWs are included: nurses working on a designated ward and physicians working hospital-wide [21]. HCWs and visitors can become transiently exposed to *C. difficile*, and therefore contagious, transmitting *C. difficile* via spores on their hands, clothing, or medical equipment [22]. We assume that sick visitors and HCWs do not visit the hospital and that individuals without conventional risk factors such as hospitalization and recent antibiotic usage have a low risk of colonization [23]. Therefore, HCWs and visitors in the model cannot become colonized or infected. A discussion of the overall order of events in the model and flow diagrams of patient, visitor, and HCW logic are included in Supplementary Material 3.

Transmission

There are 10 agent and environmental interactions that can result in a new *C. difficile* exposure (Figure 1C). The probability of *C. difficile* transmission during an interaction is proportional to the duration of the interaction. Each possible transmission event is coded in the model as a Bernoulli trial (Supplementary Figures 1–3). We tracked all transmissions to quantify the contributions of each agent type and the environment to *C. difficile* exposure.

Parameters

To maximize model generalizability, we derived input parameter estimates from relevant results in >50 peer-reviewed studies, including literature published through April 2017 (Table 2). Each parameter estimate was reviewed by content experts. The model was run using the mean parameter estimates. The distributions were used for sensitivity analyses, as described below.

Interventions

Nine infection control interventions were modeled, including 4 hospital centered and 5 patient centered (Table 3).

Table 1. Patient Clinical States

State	Patient's Condition
Susceptible	No symptoms or disease; at risk for <i>C. difficile</i> colonization
Nonsusceptible	Not at risk for colonization or CDI during the hospital stay
Exposed	Exposed to <i>C. difficile</i> through interactions with contagious agents or contaminated environment
Cleared	Prior infection or colonization has subsided
Death	Death due to CDI
<i>Colonized</i>	No symptoms, but gastrointestinal colonization of <i>C. difficile</i>
<i>Infected</i>	Symptomatic, clinically diagnosed CDI
<i>Recolonized</i>	Recovered from symptoms, but gastrointestinal colonization remains
<i>Infection recurrence</i>	Symptoms return to a previously infected patient

Patients in the states marked with italic text are contagious and can expose others and the environment to *Clostridium difficile*, whereas patients in the other states cannot. Abbreviation: CDI, *Clostridium difficile* infection.

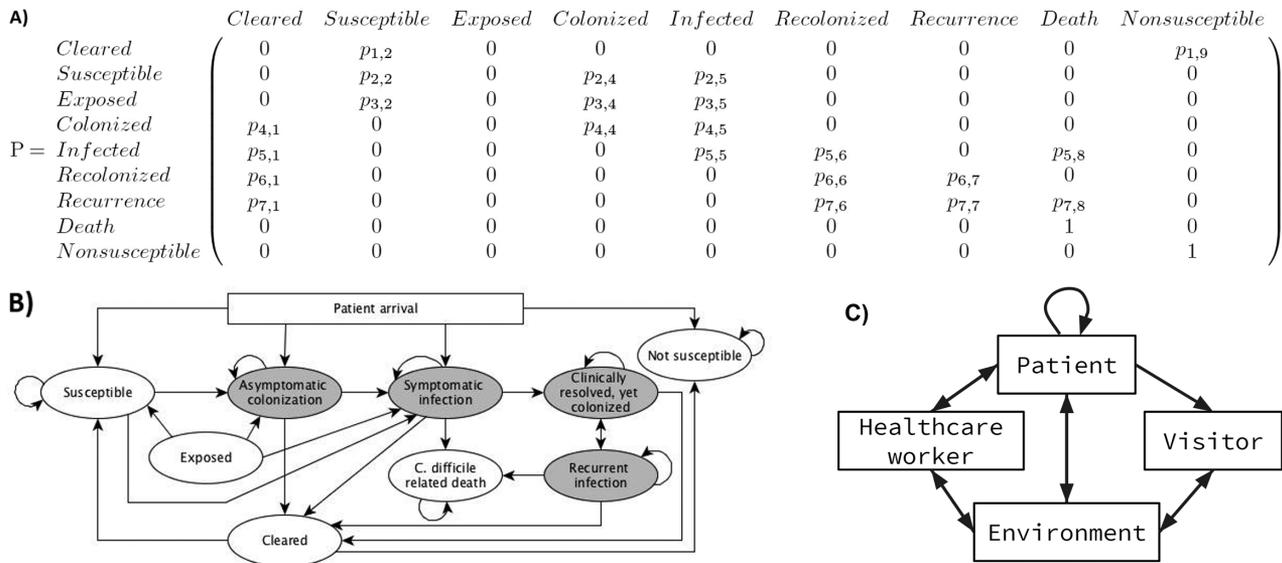


Figure 1. Matrix (A) and transition state (B) diagram representations of the discrete-time Markov chain underlying transitions between clinical states. The gray ovals represent clinical states from which *C. difficile* can be transmitted, while the white ovals are the noninfective states. Patient clinical states are updated every 6 hours. C, There are 10 agent:agent or agent:environmental interactions that can lead to a *C. difficile* transmission event. Abbreviation: *C. difficile*, *Clostridium difficile*

Each was modeled at 3 levels, enhanced, ideal, and a baseline, nonintervention state. The baseline state served as the control and reflected standard hospital practices expected to occur without the implementation of any active intervention.

As with the model input parameters (Table 2), intervention effectiveness and compliance parameters were derived from an extensive literature review. The derivation of these parameters utilized an additional 50 peer-reviewed studies (Table 4). The distinction between enhanced and ideal interventions was based on intervention implementation details provided in the primary studies. The enhanced level reflected effects of typical intervention implementation. The ideal level reflected maximum possible effects of an intervention implemented under optimal conditions, such as additional financial resources, strong stakeholder support, leadership buy-in, and an expanded infection control workforce. Patient transfer data were lacking in the literature, so we derived these estimates from primary administrative data collected at the University of Wisconsin Hospital in Madison (Supplementary Material 4).

Interventions were evaluated both individually and in CDI bundles that introduced several interventions simultaneously. Intervention bundle composition was determined via 2 mechanisms. We took a stepwise approach first, adding interventions sequentially to bundles based on their level of clinical effectiveness when introduced in isolation. We also evaluated CDI bundles composed of interventions that content experts deemed most likely to be implemented together, for example, HCW and patient hand hygiene.

Outcomes

The 2 primary outcomes were the hospital-onset CDI (HO-CDI) rate per 10000 patient-days and the asymptomatic *C. difficile* colonization rate per 1000 admissions. HO-CDI was defined as having both symptomatic diarrhea and a positive laboratory result on a specimen collected >3 days after admission to the hospital [24].

Simulation

The model was developed and simulated in NetLogo software version 5.3.1 [25]. We employed a model with synchronized common random numbers to reduce stochastic noise leading to variance in the results and allow for direct comparison of counterfactual scenarios [26]. Details of synchronization are included in Supplementary Material 5. Details of model verification and validation, including sensitivity analyses and a limited cross-validation, are included in Supplementary Material 6.

Ultimately, we conducted 5000 runs for 19 single-intervention scenarios: 1 at baseline, 9 with 1 enhanced-level intervention, and 9 with 1 ideal-level intervention and 8 multiple-intervention bundles (Table 5).

Statistical Analysis

Pairwise comparisons between baseline, enhanced single-interventions, ideal single-interventions, and enhanced level intervention bundles were conducted using the χ^2 test at a significance level of $\alpha = .05$, using R software (3.3.3).

RESULTS

There were significant reductions in HO-CDI and asymptomatic colonization upon implementation of enhanced and ideal

Table 2. Input Parameter Estimates for the Agent-Based Model

Parameter	Mean	Distribution (Range)	Source ^a	
Agent parameters				
Patient	Length of stay, d	4.8	Lognormal (SD = 4.8)	[51–54]
	CDI attributable length of stay increase, d	2.3	Exponential (mean = 2.1–2.4)	[55]
	Arrival rate per day	26	...	[51, 56]
	Nursing visits per 6 h	5	...	[21, 57–59]
	Doctor visits per 6 h	1	...	[21, 57–59]
	Proportion on high CDI risk antibiotics	20%	Triangular (15–25)	[60–62]
	Vancomycin treatment time, d	14	...	[39]
	Vancomycin success rate	81%	Triangular (78–83)	[63–66]
Nurse	Number per ward	4	...	[58, 67–69]
	Service time, min	4.7	Exponential (mean = 3–7)	[58, 59, 70, 71]
Doctor	Number per ward	2	...	[51, 58]
	Service time, min	10.8	Exponential (mean = 4–14)	[58, 59, 70, 71]
Visitor	Daily probability of receiving visitors	0.5	Triangular (0.3–0.7)	[72, 73]
	No. of visitors per visit	2	Triangular (1–3)	[73, 74]
	Service time, min	15	Exponential (mean = 10–30)	[58, 73–75]
Admission parameters				
	Proportion of susceptible patients	39.7%	Triangular (30%–50%)	[52, 76–79]
	Proportion asymptomatic colonized patients	6.1%	Triangular (4%–10%)	[40, 80–89]
	Proportion of patients with CDI	0.29%	Triangular (0.25%–1%)	[80, 86, 90, 91]
	Proportion of nonsusceptible patients	53.9%
Transmission parameters				
	Probability patient:patient contact	5% per 30 min	Triangular (1%–15%)	EO
	Probability patient:nurse contact	36% per 4.7 min	Triangular (26%–46%)	[58]
	Probability patient:doctor contact	69% per 10.8 min	Triangular (59%–79%)	[58]
	Probability patient:visitor contact	65% per 15 min	Triangular (55%–75%)	[58]
	Probability environment:nurse contact	70% per 4.7 min	Triangular (60%–80%)	[58]
	Probability environment:doctor contact	90% per 10.8 min	Triangular (80%–100%)	[58]
	Probability environment:visitor contact	93% per 15 min	Triangular (83%–100%)	[58]
	Probability environment:patient contact	100%, constant
	<i>C. difficile</i> transfer efficiency person:person	30%	Triangular (15%–45%)	[92]
	<i>C. difficile</i> transfer efficiency environment:person	44%	Triangular (29%–59%)	[93]
Contamination parameters				
	Colonized patient contaminated	38%	Triangular (15%–60%)	[94–96]
	Active CDI patient contaminated	70%	Triangular (60%–80%)	[96]
	Colonized patient room contaminated	19%	Triangular (14%–35%)	[96–98]
	Active CDI patient room contaminated	47%	Triangular (36%–60%)	[96–101]
	Non- <i>C. difficile</i> patient room contaminated	7%	Triangular (5%–15%)	[97, 100, 101]

Abbreviations: CDI, *Clostridium difficile* infection; EO, expert opinion; SD, standard deviation.

^aReferences for input parameter sources are included in the Supplementary Materials.

levels of 6 interventions: daily and terminal cleaning, HCW hand hygiene, patient hand hygiene, screening at admission, and patient transfer reduction (Figure 2 and Supplementary Table 7).

Daily cleaning with a sporicidal disinfectant and screening at admission were the 2 most effective enhanced single interventions, reducing HO-CDI to 2.48 (95% confidence interval [CI], 2.46–2.50) and 5.13 (95% CI, 5.10–5.16) cases per 10 000 patient-days, respectively. These correspond to 68.9% and 35.7% reductions in HO-CDI, compared to the baseline rate of 7.98 (95% CI, 7.95–8.02) HO-CDIs per 10 000 patient days (both $P < .001$). They also reduced asymptomatic colonization 77.5% and 39.2%, respectively. Visitor hand hygiene and visitor

contact precaution interventions did not reduce HO-CDI or asymptomatic colonization, compared to baseline. Excluding these 2 visitor strategies, HCW contact precautions was the least effective intervention at reducing hospital-onset colonization and infection.

The difference in intervention effectiveness between enhanced and ideal intervention implementation strategies varied across interventions, ranging between 0 and 18.8% additional reduction in HO-CDI rates for the ideal implementation strategy (Figure 2). Ideal strategies provided the greatest improvement for HCW hand hygiene and patient hand hygiene, the 2 interventions with the largest absolute increases in compliance between the enhanced and ideal intervention levels.

Table 3. Hospital- and Patient-Centered Interventions Considered in This Study

	Intervention	Intended Effect	Timing for Potential Intervention Events	Transmission Events Directly Affected
Hospital Centered	HCW hand hygiene	Improve overall HCW HH compliance; increase utilization of soap and water vs ABHR for CDI or known colonized patients	HCW entry and exit of patient room	HCW: to and from environment or patient
	HCW contact precautions	Improve HCW contact precautions usage; provide education to reduce contact precaution contamination on donning and doffing; maintain until discharge for CDI or known colonized patients	HCW entry of patient room	HCW: to and from environment or patient
	Daily cleaning	Increase proportion of room cleaned daily by staff; utilize sporicidal product in all patient rooms, visitor common areas, and staff workrooms	Once every 24 h	Environment: to and from patient, HCW, and visitor
	Terminal cleaning	Increase proportion of room cleaned by staff at discharge or room transfer; utilize sporicidal product in all patient rooms	Patient discharge or room transfer	Environment: to and from patient, HCW, and visitor
Patient Centered	Patient hand hygiene	Improve overall patient HH compliance; increases utilization of soap and water vs ABHR for CDI or known colonized patients	Once every 6 h; upon visitor and HCW exit of patient room, patient entry and exit of common room, inter- and intraward transfer, and discharge	Patient: to visitor, to and from HCW, to and from environment, and between patients
	Patient transfer	Decrease hospital-wide patient transfer rate; restrict room transfers of CDI or known colonized patients	Between 0 and 4 times per patient per stay (maximum 2 intra- and 2 interward)	None; indirect effects via increased terminal cleaning
	Screening	Screen asymptomatic patients within 24 h of hospital admission via stool sample or, if necessary, rectal swab; if colonized, enact all polices as if CDI patient, except do not treat	Once, at time of admission	None; indirect effects via all 8 other interventions
	Visitor hand hygiene	Improve overall visitor HH compliance; increases utilization of soap and water vs ABHR for CDI or known colonized patients	Visitor exit of patient room	Visitor: from environment and patient; indirectly to environment
	Visitor contact precautions	Improve visitor contact precautions usage; provide education to reduce contact precaution contamination on donning and doffing; maintain until discharge for CDI or known colonized patients	Visitor exit of patient room	Visitor: from environment and patient; indirectly to environment

Abbreviations: ABHR, alcohol-based hand rub; CDI, *Clostridium difficile* infection; HCW, healthcare worker; HH hand hygiene.

We assessed 8 CDI bundles, simulated for 5000 runs each (Table 6). All significantly reduced both HO-CDI and asymptomatic colonization rates. The most effective 2-intervention bundle was composed of daily cleaning and screening, reducing HO-CDI by 82.3% and asymptomatic colonization by 90.6%. Adding HCW and patient hand hygiene interventions resulted in a small, significant, additional decrease to HO-CDI and asymptomatic colonization rates. Visitor hand hygiene and contact precautions were not included in bundles, due to their negligible effect on reducing CDI or asymptomatic colonization and sustained instability at 5000 runs.

The patient-centered bundle comprised of screening at admission, patient hand hygiene, and reducing intra- and interward room transfers was more effective than the 2-pronged patient and HCW hand hygiene bundle. However, adding patient hand hygiene to the single HCW hand hygiene intervention significantly reduced HO-CDI rates by an additional 7.9%.

Nursing staff and the environment were the main sources of *C. difficile* transmission, each responsible for >40% of exposures at baseline conditions (Table 7). Transmission via direct

patient-to-patient contact was minimal under all scenarios, resulting in a maximum of 0.24% of exposures.

Full sensitivity analysis results are shown in Supplementary Material 7. Trends in relative clinical effectiveness of the 7 evaluated interventions changed slightly under parameter estimate variation. Cross-validation results are included in Supplementary Material 8.

DISCUSSION

Because prevalence of asymptomatic *C. difficile* carriage is much higher than active CDI, previous studies have postulated that asymptomatic colonization may be responsible for a considerable proportion of new CDI cases [21, 27]. Consistent with this, our 2 most effective single-intervention strategies were daily cleaning with a sporicidal disinfectant and screening at admission. These largely act by reducing transmission of *C. difficile* from asymptotically colonized patients.

The daily cleaning intervention utilized a sporicidal agent in all patient rooms and common areas. The substitution of

Table 4. Intervention Parameter Estimates

Parameter		Baseline Mean (Range)	Enhanced Mean (Range)	Ideal Mean	Source ^a
Hand hygiene					
Soap and water effectiveness		96 (90–100)			[102–104]
ABHR effectiveness		29 (13–36)			[92, 103]
Standard Room Compliance	Nurse	60 (46–68)	79 (74–84)	96	[105–115]
	Doctor	50 (40–55)	71 (57–80)	91	[105–117]
	Visitor	35 (20–50)	55 (50–67)	84	[106, 118–124]
	Patient	33 (30–40)	59 (55–65)	84	[120, 125–129]
	Fraction soap and water (vs ABHR)	10 (5–25)			[110, 130]
Known <i>C. difficile</i> Room Compliance	Nurse	69 ^b	84 ^b	97	[59, 131–133]
	Doctor	61 ^b	77 ^b	93	[59, 131–133]
	Visitor	50 ^b	65 ^b	88	[59, 131–133]
	Patient	48 ^b	68 ^b	88	[59, 131–133]
	Fraction soap and water (vs ABHR)	80 (70–90)	90 (80–95)	95	[134]
Contact precautions					
Gown and glove effectiveness		70 (60–80)	86 (80–90)	97	[135–137]
Healthcare worker compliance		67 (62–72)	77 (71–85)	87	[59, 118, 138–142]
Visitor compliance		50 (42–52)	74 (70–80)	94	[118, 138, 139]
Environmental cleaning					
Daily cleaning compliance		46 (40–50)	80 (70–85)	94	[29–33]
Terminal cleaning compliance		47 (40–50)	77 (70–82)	98	[29, 143–146]
Nonsporicidal effectiveness		45 (35–50)			[147, 148]
Sporicidal effectiveness		99.6			[148–151]
Asymptomatic screening at admission					
Compliance		0	96 (92–99)	98	[38, 152]
PCR test sensitivity; specificity		93 (90–94); 97 (95–99)			[153–155]
Patient transfer					
Intraward transfer rate		5.7 (4–7.4)	2.8 (2.2–3.5)	1.4	Internal data
Interward transfer rate		13.7 (10–17.4)	6.8 (5–8.7)	3.4	Internal data
Proportionate time between transfers		24% (time between transfer/length of stay; 20–30)			Internal data

Abbreviations: ABHR, alcohol-based hand rub; *C. difficile*, *Clostridium difficile*; PCR, polymerase chain reaction.

^aReferences for input parameter sources are included in the Supplementary Materials.

^bKnown *Clostridium difficile* room compliance range based on the range in standard room and standard *C. difficile* infection hand hygiene noncompliance ratio (1.34).

sporicidal for nonsporocidal agents in the rooms of patients without a known CDI requires little additional time for cleaning services staff [28] and, once implemented, necessitates few workflow changes. Previous studies of daily cleaning interventions have reported drastically increased compliance, resulting in >75% average daily cleaning rates for high-touch surfaces [29–33]. Sustaining this level of compliance can be challenging

and requires continued administrative support, yet the potential benefits are substantial. In addition to *C. difficile* reduction, hospital-wide use of sporicidal products may reduce vancomycin-resistant *Enterococcus* colonization rates by nearly 25% [34].

In the context of implementation, screening patients at admission requires fewer stakeholders and behavioral changes than more complex interventions such as HCW hand hygiene

Table 5. List of the Multiple-Intervention Bundle Components Considered in This Study

Bundle Type	Intervention Components
Hand hygiene	HCW hand hygiene, patient hand hygiene
Cleaning	Daily cleaning, terminal cleaning
Patient-centered	Surveillance, patient transfer, patient hand hygiene
Additive maximum effectiveness bundle	Daily cleaning, surveillance
	Daily cleaning, surveillance, HCW hand hygiene
	Daily cleaning, surveillance, HCW hand hygiene, patient hand hygiene
	Daily cleaning, surveillance, HCW hand hygiene, patient hand hygiene, terminal cleaning
	Daily cleaning, surveillance, HCW hand hygiene, patient hand hygiene, terminal cleaning, patient transfer

Abbreviation: HCW, healthcare worker.

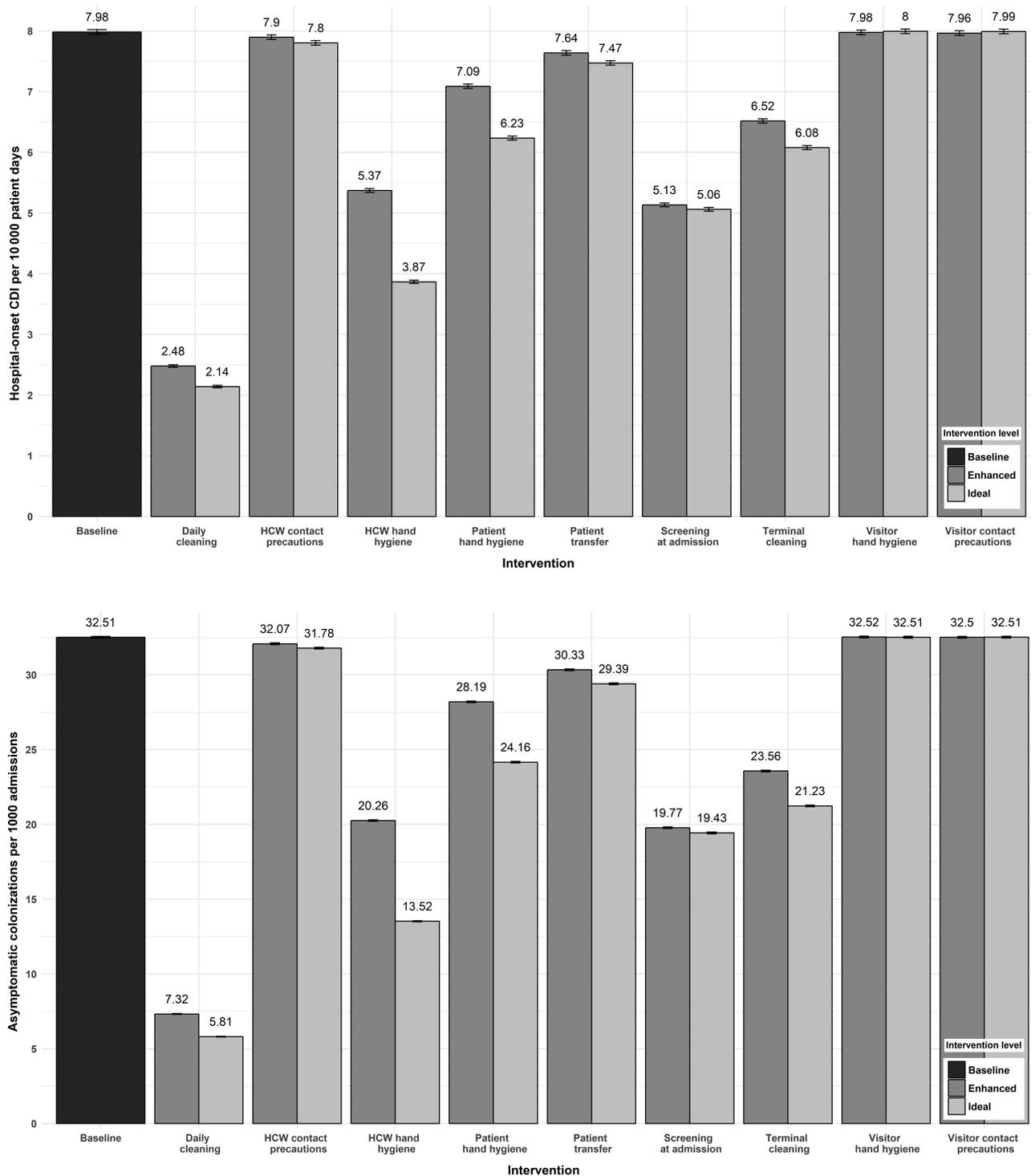


Figure 2. Comparative effectiveness of 9 interventions at reducing hospital-onset *Clostridium difficile* infection (A) and asymptomatic colonization (B). Abbreviations: CDI, *Clostridium difficile* infection; HCW, healthcare worker.

or contact precautions [35–37]. The intervention can be targeted to a subset of hospital employees, namely, front-line nursing staff and laboratory services. A work systems study of a pilot *C. difficile* screening intervention currently in place on 1 unit at our facility found the intervention to be well received by

stakeholders, including patients (unpublished data). Screening for MRSA, a similarly transmitted nosocomial pathogen, has been successfully implemented at Veterans Affairs hospitals nationwide [38]. This screening intervention had a 96% participation rate and reduced MRSA by 45% among non-intensive

Table 6. Comparative Clinical Effectiveness of 8 Multiple-Intervention Bundles

Bundle Components	HO-CDI per 10000 Patient-days (95% CI)	Asymptomatic Colonization per 1000 Admissions (95% CI)
Baseline	7.98 (7.95–8.02)	32.51 (32.44–32.57)
Patient and HCW HH	4.74 (4.71–4.77)	17.33 (17.29–17.38)
Terminal and daily cleaning	2.44 (2.41–2.46)	6.96 (6.93–6.99)
Screening, patient HH, patient transfer	3.75 (3.73–3.78)	13.14 (13.09–13.19)
Daily cleaning, surveillance	1.41 (1.39–1.43)	3.05 (3.03–3.07)
Daily cleaning, surveillance, HCW HH	1.18 (1.17–1.20)	2.00 (1.99–2.01)
Daily cleaning, surveillance, HCW HH, patient HH	1.13 (1.11–1.14)	1.67 (1.66–1.68)
Daily cleaning, surveillance, HCW HH, patient HH, terminal cleaning	1.12 (1.10–1.13)	1.61 (1.60–1.62)
Daily cleaning, surveillance, HCW HH, patient HH, terminal cleaning, patient transfer	1.11 (1.10–1.12)	1.59 (1.57–1.60)

Comparative effectiveness of 8 multiple-intervention combination bundles.

Abbreviations: CI, confidence interval; HCW, healthcare worker; HH hand hygiene; HO-CID, hospital-onset *Clostridium difficile* infection.

care unit patients. This reduction is similar to the 35.7% reduction in HO-CDI we simulated due to *C. difficile* screening.

While asymptomatic *C. difficile* screening is not routinely recommended [39], the single large existing study in which screening was implemented as a single intervention found a 56% reduction in HO-CDIs [40]. This reduction is likely higher than our model because of a concomitant, unintended increase in HCW hand hygiene during the study period. In the study, HCWs caring for asymptomatic carriers were required to use gloves and to wash their hands with soap and water. Daily disinfection of patient rooms was conducted using a chlorine-based, sporicidal product.

Patient hand hygiene was another highly effective patient-centered intervention. Adding patient hand hygiene to HCW hand hygiene reduced HO-CDI rates an additional 7.9%. Typical patient hand hygiene interventions focus on patient empowerment as a strategy for increasing HCW hand hygiene, but improving compliance among patients themselves has rarely been a goal [41]. However, patients' hand hygiene rates typically decline in the hospital, and key opportunities are missed for washing hands before eating and after toileting [42].

Patients are central to the *C. difficile* transmission pathway as they experience direct physical contact with HCWs, visitors, and the environment, and should be a focus for hand hygiene interventions.

Visitor hand hygiene and contact precaution interventions had no effect on HO-CDI rates. This is likely due in part to the short duration of time that visitors spent with patients. The impact of visitor interventions may vary in settings with extensive visitor contact, such as pediatric hospitals and long-term care facilities. Future modeling studies are needed to evaluate CDI interventions in these contexts.

Another reason for the null effect of visitor contact precautions may be related to limited effectiveness of contact precaution interventions in general. HCW contact precautions showed only a small effect, even though precautions were continued for the duration of a known *C. difficile* patient's stay. Contact precaution use is not without costs and may be associated with increased adverse effects [43]. These include higher rates of anxiety and depression [44] and increases in preventable adverse events, such as falls and pressure ulcers [45]. Current infection control guidelines state that in areas where MRSA and

Table 7. Comparative Contribution of Agents and the Environment to Patients' *Clostridium difficile* Exposures

Intervention	Environment, % of Exposures (95% CI)	Nursing, % of Exposures (95% CI)	Physicians, % of Exposures (95% CI)	Patient, % of Exposures (95% CI)
Baseline	40.77 (40.74–40.81)	42.79 (42.76–42.82)	16.37 (16.35–16.40)	0.062 (.061–.064)
Daily cleaning	20.21 (20.16–20.27)	56.13 (56.05–56.20)	23.42 (23.36–23.49)	0.236 (.230–.243)
HCW contact precautions	40.94 (40.91–40.97)	42.73 (42.70–42.76)	16.27 (16.24–16.29)	0.062 (.061–.064)
HCW hand hygiene	46.39 (46.35–46.43)	39.32 (39.28–39.36)	14.20 (14.17–14.23)	0.090 (.088–.093)
Patient hand hygiene	41.27 (41.23–41.30)	42.66 (42.62–42.69)	16.02 (15.99–16.05)	0.056 (.054–.057)
Patient transfer	39.74 (39.70–39.77)	43.57 (43.54–43.61)	16.63 (16.60–16.65)	0.065 (.064–.067)
Screening	43.58 (43.53–43.62)	41.66 (41.61–41.70)	14.73 (14.70–14.77)	0.033 (.032–.035)
Terminal cleaning	34.97 (34.94–35.01)	46.92 (46.88–46.96)	18.03 (18.00–18.06)	0.079 (.077–.081)
Visitor hand hygiene	40.77 (40.74–40.81)	42.78 (42.74–42.81)	16.39 (16.36–16.41)	0.062 (.060–.064)
Visitor contact precautions	40.77 (40.74–40.81)	42.80 (42.77–42.83)	16.37 (16.34–16.39)	0.062 (.060–.063)

Abbreviations: CI, confidence interval; HCW, healthcare worker.

vancomycin-resistant enterococci are endemic, visitors may not be required to use contact precautions for these pathogens [46]. While hospitals are still recommended to consider contact precautions for visitors of CDI patients, the evidence for this recommendation is weak.

Three other agent-based models of *C. difficile* transmission have previously evaluated intervention effectiveness, including an admissions screening model [47], 6-intervention model [21], and our group's initial 4-intervention model [18]. Lanzas and Dubberke reported that screening reduced HO-CDI by 25% and new colonizations by 52%, under the conditions that most closely replicate our model [47]. In comparison, the screening intervention rates of HO-CDI reduction (35.7%) and asymptomatic colonization reduction (39.2%) were highly correlated in our model. The smaller reduction in HO-CDI in the Lanzas and Dubberke model compared to the asymptomatic colonization rate may be due to modeling decisions and underlying assumptions regarding transitions between different patient clinical states.

The 6-intervention model by Rubin et al found that HCW hand hygiene had the greatest single-intervention impact on CDI rate [21]. Environmental cleaning was not effective, although it did not include sporicidal agents for terminal cleaning of non-*C. difficile* rooms or daily cleaning of any room and thus is not comparable to our study interventions. Similar to our findings, Rubin et al found HCW contact precautions to be ineffective at reducing HO-CDI. Our group's original model simulated treatment, HCW hand hygiene, environmental cleaning, and contact isolation [18]. While considerable changes have been introduced to the current model, it is notable that the environmental cleaning strategy was the most effective in both models.

Predictive validity, or a model's ability to predict future outcomes in real-life scenarios, has not been assessed for any *C. difficile* agent-based model in the literature. Our model is easily customizable to an individual hospital's infection control context. By inputting its own intervention compliance data, a facility could determine customized results on intervention comparative effectiveness at its institution. Future evaluations of predictive validity are needed to provide additional evidence for the applicability of outcomes to real-world settings.

Despite its complexity, this model relies on many simplifications and assumptions that allow the model to be computationally tractable and reflect the availability of parameter estimate data in the literature. For example, the model does not incorporate patient heterogeneity beyond age and antibiotic usage. Yet, known risk factors such as immunocompromised status, history of hospitalization, and prior *C. difficile* infection result in underlying variability in *C. difficile* susceptibility to colonization and infection.

Infection and colonization are also simulated by a generic *C. difficile* strain. Thus, the model does not account for inherent differences in transmission and health outcomes across

strains such as BI/NAP1/027. Furthermore, the hospital layout is defined as a series of identical patient rooms and wards. This does not allow for investigation of potentially unique transmission dynamics in an intensive care unit or bone marrow transplant ward, or for evaluation of the impact of these high-risk units on hospital-wide *C. difficile* transmission.

Finally, we did not evaluate an antibiotic stewardship intervention. While recent evidence has shown that fluoroquinolone restrictions may be particularly effective at reducing CDI rates [48], proper modeling of this intervention requires more robust consideration of patient heterogeneity than is possible using currently available data in the literature. Thus, the effectiveness of an antibiotic stewardship intervention has not been evaluated by any existing agent-based *C. difficile* models to date [18, 21, 47].

CONCLUSIONS

This *C. difficile* agent-based model is the first to compare patient-centered interventions with hospital-centered strategies. Our results provide much-needed direction to HCWs and infection control leadership regarding which interventions to prioritize to optimally control disease transmission. The findings also highlight the importance of patients' own hand hygiene, which has historically been overlooked. Many interventions we found to be highly effective are horizontal approaches to infection control that are not pathogen-specific [22, 39, 49, 50]. These strategies are key to the prevention of countless infectious diseases and our results have implications well beyond prevention of *C. difficile*.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the author to benefit the reader, the posted materials are not copyrighted and are the sole responsibility of the author, so questions or comments should be addressed to the author.

Notes

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