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Original Article

Reducing *C. difficile* in children: An agent-based modeling approach to evaluate intervention effectiveness

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Abstract

Objective: *Clostridioides difficile* infection (CDI) is rapidly increasing in children's hospitals nationwide. Thus, we aimed to compare the effectiveness of 9 infection prevention interventions and 6 multiple-intervention bundles at reducing hospital-onset CDI and asymptomatic *C. difficile* colonization.

Design: Agent-based simulation model of *C. difficile* transmission.

Setting: Computer-simulated, 80-bed freestanding, tertiary-care pediatric hospital, including 8 identical wards with 10 single-bed patient rooms each.

Participants: The model includes 5 distinct agent types: patients, visitors, caregivers, nurses, and physicians.

Interventions: Daily and terminal environmental disinfection, screening at admission, reduced intrahospital patient transfers, healthcare worker (HCW), visitor, and patient hand hygiene, and HCW and visitor contact precautions.

Results: The model predicted that daily environmental disinfection with sporicidal product, combined with screening for asymptomatic *C. difficile* at admission, was the most effective 2-pronged infection prevention bundle, reducing hospital-onset CDI by 62.0% and asymptomatic colonization by 88.4%. Single-intervention strategies, including daily disinfection, terminal disinfection, asymptomatic screening at admission, HCW hand hygiene, and patient hand hygiene, as well as decreasing intrahospital patient transfers, all also reduced both hospital-onset CDI and asymptomatic colonization in the model. Visitor hand hygiene and visitor and HCW contact precautions were not effective at reducing either measure.

Conclusions: Hospitals can achieve substantial reduction in hospital-onset CDIs by implementing a small number of highly effective interventions.

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Clostridioides difficile infection (CDI) affects nearly 8,000 hospitalized children in the United States annually.[1] The rate is rapidly increasing in pediatric hospitals nationwide, and it rose from 20.0 to 31.5 CDIs per 10,000 patients between 2003 and 2009.[1,2] This trend will likely continue as community-acquired CDI becomes more prevalent.

Far less is known about the pathology of CDI in children than adults, and its control is complicated by considerable variability in the natural history of the infection across the pediatric age spectrum. Rates of asymptomatic intestinal colonization in children younger than 2 years old are consistently >10%, even among healthy individuals in the community.[3,4] Unlike in adults and older children, *C. difficile* colonization at this young age rarely progresses to symptomatic diarrheal infection.[5,6] However, because of their high prevalence of colonization, infants and young children are a potential reservoir for *C. difficile* transmission.[3,7–9] Above age 3, a child's gastrointestinal microbiome composition approximates that of an adult, and *C. difficile* colonization occurs at a rate similar to young and middle-aged adults.[5,6,10]

Pediatric hospitals face several unique challenges to preventing *C. difficile* transmission, including extended patient-to-patient interactions in hospital common areas and extensive family visits. Traditionally, CDI has been considered a problem of adult facilities, and children's hospitals are not required to track rates of hospital-onset CDI (HO-CDI). Therefore, institution-specific

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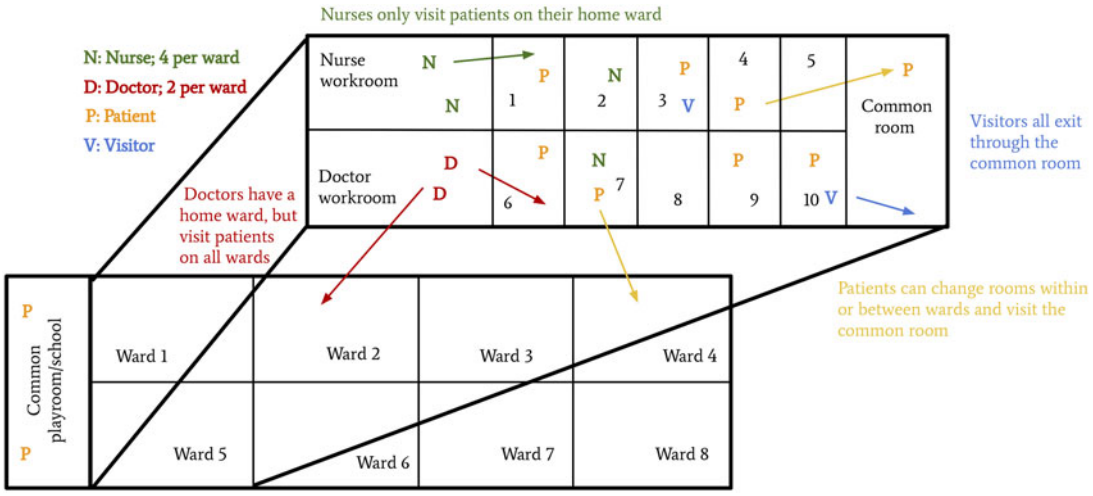


Fig. 1. The model hospital is an 80-bed facility divided into 8 wards with 10 beds each and a hospital-wide playroom/school.

pediatric surveillance data are lacking, and few pediatric studies have evaluated the effectiveness of *C. difficile* interventions.[11]

Current Society for Healthcare Epidemiology of America recommendations focus primarily on *C. difficile* prevention in the adult, acute-care setting, and there is little guidance for pediatric infection prevention staff and hospital administrators to follow when deciding which interventions to implement.[12] As CDI becomes a more pressing pediatric issue, prioritizing interventions that are highly effective in this specific context has become critical.

Computer-simulation modeling can assess the effectiveness of countless permutations of single and multiple-intervention strategies.[13,14] Evaluating interventions by traditional epidemiologic methods would rapidly become time-consuming and cost-prohibitive. Furthermore, infection prevention interventions are typically implemented simultaneously in multiple-intervention bundles.[12,15] Observational studies and randomized controlled trials cannot differentiate the individual effects of a single intervention in such a bundle. By modeling counterfactual scenarios, simulation modeling can evaluate the isolated effects of single-intervention strategies.

Agent-based modeling is a type of stochastic simulation in which members of a system are tracked individually and can interact with each other and the environment. By evaluating transmission at the individual level, these models can account for the indirect and downstream effects of seemingly minor changes. Several agent-based and other mathematical models of *C. difficile* have been used in the adult setting.[13,16–18] However, to our knowledge, no *C. difficile* transmission simulation model exists in the pediatric context. Thus, we developed an agent-based model of *C. difficile* transmission in a children's hospital and employed it to evaluate the effectiveness of 9 infection prevention interventions and 6 multi-intervention bundles.

Methods

Approach

We constructed an agent-based simulation model of healthcare-associated *C. difficile* transmission in an 80-bed, generic, free-standing children's hospital. The size and characteristics of the generic hospital are based on American Hospital Association data regarding mid-sized facilities[19]; it does not approximate any specific real-world facility. The hospital is divided into 8 general pediatric wards, each containing 10 single-bed patient rooms, a nursing station, physician workroom, and a multipurpose patient and visitor common area (Fig. 1). All wards are identical, with high-risk specialty populations, such as oncologic, transplant, or gastrointestinal patients, included on the same wards as lower-risk patients. The hospital also contains a central room where all non-isolated patients can visit and older students can attend school.

Agents

The model uses 5 types of agents: patients, visitors, caregivers, nurses, and physicians. All patients are assigned to a specific room and 1 of 3 initial *C. difficile* states at admission: susceptible to infection, asymptomatically colonized, or actively infected. Every 6 hours each patient has the potential to be recategorized into 1 of 8 *C. difficile* clinical states, as determined by probabilities in the model's discrete-time Markov chain (Fig. 2). The Markov chain, representing the progression of CDI in a patient, is recalibrated for the pediatric setting from Markov chains used in prior agent-based *C. difficile* models for adults (Supplement S2 online).[16,18]

Visitors are assigned 1 patient with whom they spend an average of 15 minutes before leaving the hospital. Caregivers represent parents or guardians, who typically stay with the patient overnight or for several daytime hours, and they are involved in activities such as patient feeding, bathing, and attending school. Among healthcare-worker agent types, nurses work on 1 ward and physicians work hospital-wide. The overall order of model events and flow diagrams of agent logic are included in Supplement S4 (online).

Clostridioides difficile transmission can occur via 14 interactions between agents and the environment (Supplementary Fig. S1 online). The probability of transmission is proportional to the duration of time that contaminated agents interact with each other or the environment. A Bernoulli trial determines the success of transmission at the time each interaction occurs (Supplementary Fig. S2 online). Visitors, caregivers, nurses, and physicians can be exposed to *C. difficile* and act as a contagious vector to propagate infection. However, these agents cannot become colonized or infected, as the prevalence of *C. difficile* colonization among healthy healthcare personnel is less than 1%.[20]

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(A)

$$P = \begin{array}{c} \\ Cleared \\ Susceptible \\ Exposed \\ Colonized \\ Infected \\ Recolonized \\ Recurrence \\ Nonsusceptible \end{array} \begin{array}{c} \begin{array}{cccccccc} Cleared & Susceptible & Exposed & Colonized & Infected & Recolonized & Recurrence & Nonsusceptible \end{array} \\ \begin{pmatrix} 0 & p_{1,2} & 0 & 0 & 0 & 0 & 0 & p_{1,8} \\ 0 & p_{2,2} & 0 & p_{2,4} & p_{2,5} & 0 & 0 & 0 \\ 0 & p_{3,2} & 0 & p_{3,4} & p_{3,5} & 0 & 0 & 0 \\ p_{4,1} & 0 & 0 & p_{4,4} & p_{4,5} & 0 & 0 & 0 \\ p_{5,1} & 0 & 0 & 0 & p_{5,5} & p_{5,6} & 0 & 0 \\ p_{6,1} & 0 & 0 & 0 & 0 & p_{6,6} & p_{6,7} & 0 \\ p_{7,1} & 0 & 0 & 0 & 0 & p_{7,6} & p_{7,7} & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 \end{pmatrix} \end{array}$$

(B)

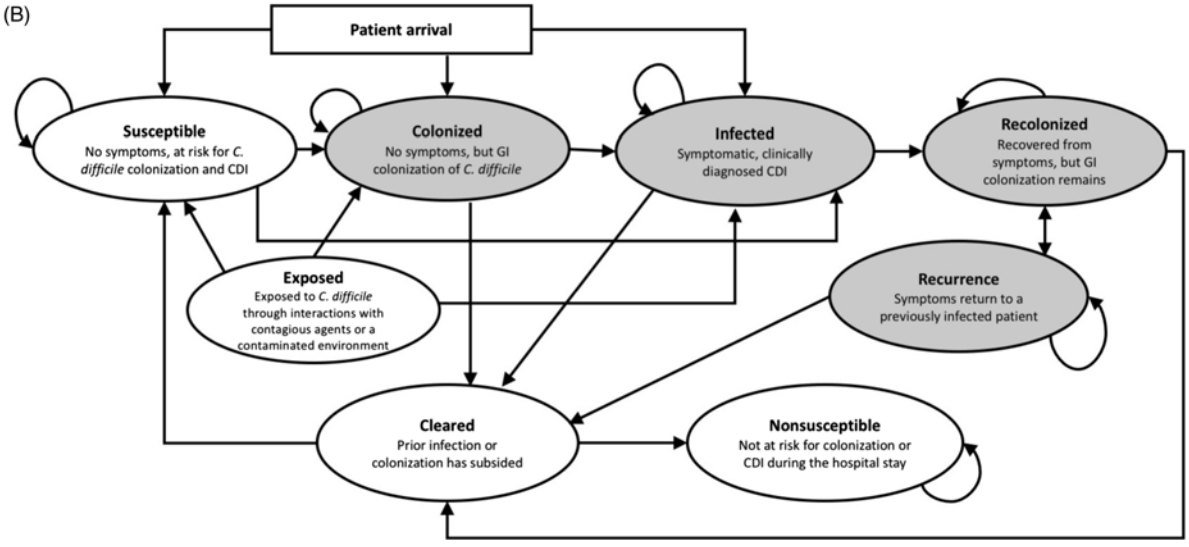


Fig. 2. Representations of the discrete-time Markov chain in (A) matrix and (B) transition state diagram form. Patients in the gray states are contagious and can expose others and the environment to *C. difficile* (thereby, sending affected patients to the exposed state), but patients in the white states cannot. Note. GI, gastrointestinal.

Interventions

We evaluated the comparative clinical effectiveness of 9 interventions and 6 multi-intervention bundles (Table 1). These bundles included a hand hygiene bundle, a sporicidal disinfection bundle, and 4 additive maximum effectiveness bundles that ranged in size from 2 to 5 interventions. All strategies were implemented at the initiation of the model run and continued throughout the entire simulation period. They were applied equally across all patients in the model, regardless of age. Each single intervention was modeled at a typical and ideal implementation level. "Typical" reflects a standard intervention rollout, whereas "ideal" corresponds to optimal implementation conditions, such as strong stakeholder support and leadership buy-in. We also modeled a third implementation level for the visitor contact precautions intervention, consistent with an opt-in–only policy, which corresponded to a 5% compliance rate. All interventions were compared to a baseline control state that reflected standard hospital infection prevention practices prior to active intervention implementation.

The multi-intervention bundles were developed in a stepwise process, with typical level interventions added in the order of their single-intervention effectiveness. Two additional bundles, focused on hand hygiene and environmental disinfection, were constructed on the basis of expert opinion as likely implementable intervention combinations.

Parameters

To maximize model generalizability across US children's hospitals, parameter estimates were derived from the results of >100 peer-reviewed studies (Tables 2 and 3). Primary administrative data from the American Family Children's Hospital in Madison, Wisconsin, were only used to determine the distribution for patient length of stay and patient transfer intervention estimates because these data were not available from the literature (Supplements S3 and S5 online). Several parameter estimates were based on studies conducted in adult patients because pediatric studies are lacking. However, many such estimates are unlikely to vary appreciably between contexts, such as *C. difficile* transfer efficiencies. All parameter estimates were reviewed for their applicability in a pediatric setting by the hospital epidemiologist at our children's hospital before inclusion in the model.

Outcomes

Intervention effectiveness was evaluated by 2 primary outcomes: HO-CDIs per 10,000 patient days and asymptomatic *C. difficile* colonizations per 1,000 admissions. HO-CDI was defined by symptomatic diarrhea and a positive polymerase chain reaction result on a specimen collected >3 days after hospital admission.[21] Asymptomatic colonization was defined as carriage of *C. difficile* bacteria in the gastrointestinal tract without clinical symptoms of diarrhea.

Simulation

The model was coded and simulated in NetLogo software version 5.3.1,[22] which employs a 5-minute time step. Each run simulates 1 calendar year. We implemented synchronized common random numbers to reduce variance in the results caused by stochastic

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Table 1. Modeled Intervention Strategies

Strategy	Components
Single interventions	
HCW hand hygiene	At the time of HCW entry and exit of patients' rooms, increase (1) HCW hand hygiene compliance and (2) proportionate usage of soap and water (compared to nonsporicidal ABHR) when interacting with known *Clostridioides difficile* patients.[a]
HCW contact precautions	Increase (1) in-room HCW compliance with gowning and gloving and (2) the effectiveness of their use through education and (3) require contact precautions until *C. difficile* patient discharge.
Daily disinfection	(1) Increase the proportion of patient rooms cleaned each day and (2) implement hospital-wide use of sporicidal products.
Terminal disinfection	At the time of patient discharge or room transfer, (1) increase the proportion of patient rooms cleaned and (2) implement the use of sporicidal products. Terminal disinfections take longer and require more product usage than daily disinfections.
Patient hand hygiene	During the routine, 4 times daily hand washing, or when patients, visitors, or HCWs exit a patient's room, increase (1) the rate of patients' hand hygiene compliance and (2) proportionate usage of soap and water (compared to nonsporicidal ABHR) for patients diagnosed with *C. difficile* colonization or CDI.[a]
Patient transfer	(1) Decrease the overall rate of patient intra- and interward transfers and (2) prohibit patients with known *C. difficile* from transferring.
Screening	(1) One-time screen for *C. difficile* colonization during each patient's first 24 hours of admission; conduct PCR testing on stool samples, using rectal swabs if the patient does not produce stool and (2) enact CDI protocols (except treatment) for all colonized patients.
Visitor hand hygiene	At the time visitors exit the hospital, increase (1) their hand hygiene compliance and (2) proportionate usage of soap and water (compared to nonsporicidal ABHR) when interacting with known *C. difficile* patients.[a]
Visitor contact precautions	Increase (1) in-room visitor compliance with gowning and gloving and (2) the effectiveness of their use through education and (3) require contact precautions until *C. difficile* patient discharge.
Multi-intervention bundles	
Hand hygiene bundle	HCW and patient hand hygiene interventions
Disinfection bundle	Daily and terminal disinfection interventions
Additive maximum effectiveness bundles	Screening and daily disinfection interventions
	Screening, daily disinfection, and HCW hand hygiene interventions
	Screening, daily disinfection, HCW hand hygiene, and terminal disinfection interventions
	Screening, daily disinfection, HCW hand hygiene, terminal disinfection, and patient hand hygiene interventions

Note. ABHR, alcohol based hand rub; HCW, healthcare worker.
[a]Soap and water hand hygiene is currently recommended by the Infectious Disease Society of America's *C. difficile* prevention guidelines only in outbreak and hyperendemic settings.[12]

noise and to allow for direct comparison of the results across counterfactual scenarios (Supplement S6 online).[23] Model verification and validation, including sensitivity analyses and cross-validation, are described in Supplement S7 (online).

We simulated 5,000 runs for 6 multi-intervention bundles and 20 single-intervention scenarios: 1 at baseline, 9 with 1 typical-level intervention, 9 with 1 ideal-level intervention, and 1 opt-in–only visitor contact-precautions intervention.

Results

The model predicted that daily disinfection of all hospital rooms with a sporicidal product was the most effective single-intervention typical level strategy for decreasing both HO-CDI (48.5% reduction) and asymptomatic *C. difficile* colonization (73.6% reduction) (Fig. 3). Screening for asymptomatic intestinal colonization at admission was the second most effective modeled strategy (HO-CDI reduction, 28.5%; colonization reduction, 38.6%). Terminal environmental disinfection, healthcare worker (HCW) and patient hand hygiene, and reducing room transfers also considerably decreased both outcomes.

Modeling HCW hand hygiene at the ideal level resulted in an additional 15.3% overall reduction in HO-CDI. It was 1 of 4 interventions for which the model showed meaningful improvement in HO-CDI prevention when increasing implementation from the typical to ideal level strategies. The other 3 interventions were patient hand hygiene (additional 7.9% reduction), daily disinfection (5.4%), and terminal disinfection (3.8%).

The model predicted that visitor hand hygiene and visitor and HCW contact precautions were not effective at reducing either HO-CDI or asymptomatic colonization. The modeled strategy in which visitor contact precautions were removed from the hospital and used by only 5% of visitors who opted-into the program showed no change in the HO-CDI (95% CI: −0.07 to 0.07) or asymptomatic colonization rate (95% CI, −0.16 to 0.12), compared to the baseline.

We assessed 6 CDI bundles, simulated for 5,000 runs each (Table 4). Adding terminal sporicidal disinfection to daily sporicidal disinfection resulted in no additional reduction in HO-CDI in the model, but it improved the asymptomatic colonization rate over the daily disinfection intervention alone. All bundles reduced HO-CDI and asymptomatic colonization compared to the baseline. The model predicted the most effective 2-intervention bundle included daily disinfection and screening, which reduced HO-CDI by 62.0% and asymptomatic colonization by 88.4%. Adding HCW hand hygiene to the 2-intervention bundle reduced HO-CDI another 1.8%. Increasing this 3-strategy bundle to

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

Parameter	Mean; Distribution[a]	Source[b]
Agent parameters		
Patient		
Length of stay (days)	4.4; lognormal (SD, 7.1)	1–3, internal data
Arrival rate per day	10.1; exponential	4, 5
Nursing visits per 6 h	8	6–9, 36–38
Doctor visits per 6 h	1	6–9
Vancomycin treatment time, d	14	10
Vancomycin success rate, %	81	11–14
Daily probability of visiting ward common room, %	10	EO
Daily probability of visiting hospital common area, %	50	EO
Nurse		
No. per ward	4	8, 15–17
Service time, min	4.7; exponential	8, 9, 18, 19
Doctor		
No. per ward	2	4, 8
Service time, min	10.8; exponential	8, 9, 18, 19
Visitor		
Daily probability of receiving visitors	0.5	20, 21
No. of visitors per visit	2	21, 22
Service time, min	15; exponential	8, 21–23
Caretaker		
Daily probability overnight caretaker, %[c,d]	53.9	1, 24, 25, EO
Service time overnight caretaker, h	12; exponential	EO
Daily probability daytime caregiver, %[c,e]	69.3	1, 24, 25, EO
Service time daytime caretaker, h	5; exponential	EO
Admission parameters, %		
Proportion of susceptible patients	91.01	
Proportion asymptomatic colonized patients	8.7	26–32
Proportion of patients with CDI	0.29	33
Transmission parameters, %		
Probability patient–patient contact	15 per 30 min	EO
Probability patient–nurse contact	36 per 4.7 min	8, 9, 18, 19
Probability patient–doctor contact	69 per 10.8 min	8, 9, 18, 19
Probability patient–visitor/caregiver contact	100	. . .
Probability environment–nurse contact	70 per 4.7 min	8, 9, 18, 19
Probability environment–doctor contact	90 per 10.8 min	8, 9, 18, 19
Probability environment–visitor contact	93 per 15 min	8
Probability environment–patient contact	100, constant	. . .
C. difficile transfer efficiency person–person	30 per contact	34
C. difficile transfer efficiency environment–person	44 per contact	35
Contamination parameters, %		
Colonized patient contaminated	38	36–38
Active CDI patient contaminated	70	38
Colonized patient room contaminated	19	38–40
Active CDI patient room contaminated	47	38–43
Non–*C. difficile* patient room contaminated	7	39, 42, 43

Note. EO, expert opinion; SD, standard deviation.
[a]Unless otherwise specified.
[b]References in Supplement 1 (online).
[c]Based on age distribution of nonneonatal hospitalized patients.
[d]Assumption that 70% of children <15 years old will have an overnight caregiver.[29]
[e]Assumption 90% of children <15 years old will have a daytime caregiver.[29]

include 4 and 5 interventions did not further reduce HO-CDI, although it did result in an additional reduction in asymptomatic colonization.

The results of the sensitivity analyses are shown in a series of tornado diagrams, which evaluated the impact of changing 6 key input parameters on model conclusions (Supplementary Fig. S2 online). Among these 6 input parameters, person-to-environment and person-to-person transfer efficiency were the most influential parameters affecting model results. Trends among the 3 most effective interventions were stable across variations in parameter estimates, with the exception of the person-to-environment parameter. Using the lowest estimate for person-to-environment transfer efficiency, 29%, screening at admission resulted in a slightly lower HO-CDI rate than daily disinfection. The model underwent limited cross-validation using the 2 existing relevant pediatric infection prevention intervention studies in the literature (Supplement S8 online).

Discussion

An agent-based model predicted that daily sporicidal disinfection and screening at admission was by far the most effective 2-pronged strategy for reducing *C. difficile*. Combining these interventions potentially enables hospitals to reduce HO-CDI by >60% and asymptomatic colonization by nearly 90%. In terms of implementation, replacing nonsporicidal cleaner with well-tolerated sporicidal products in a daily disinfection intervention would likely encounter fewer barriers than most modeled strategies. The system workflow changes and additional time requirements that this product substitution entails are negligible.[24] Environmental disinfection interventions have been successful at improving disinfection rates of high touch surfaces in the adult setting, such as bed rails, door handles, and call buttons.[21,22,25–27] Daily sporicidal disinfection was also the most effective intervention in our adult hospital agent-based *C. difficile* model.[16] However, unique aspects of

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Table 3. Intervention Parameter Estimates for the Agent-Based Model

Parameter	Baseline Mean	Enhanced Mean	Ideal Mean	Source[a]
Hand hygiene				
Soap and water effectiveness[b]		96 (90–100)		44–46
ABHR effectiveness[b]		29 (13–36)		34, 45
Standard room compliance				
Nurse	60 (46–68)	79 (74–84)	96	47–58
Doctor	50 (40–55)	71 (57–80)	91	47–60
Visitor and caregiver	35 (20–50)	55 (50–67)	84	48, 61–67
Patient	33 (30–40)	59 (55–65)	84	63, 68–72
Fraction soap and water vs ABHR		10 (5–15)		52
***C. difficile* room compliance**				
Nurse	69[c]	84[c]	97	9, 73–75
Doctor	61[c]	77[c]	93	9, 73–75
Visitor and caregiver	50[c]	65[c]	88	9, 73–75
Patient	48[c]	68[c]	88	9, 73–75
Fraction soap and water vs ABHR	80 (70–90)	90 (80–95)	95	76
Contact precautions				
Gown and glove effectiveness[d]	70 (60–80)	86 (80–90)	97	77–79
Healthcare worker compliance	67 (62–72)	77 (71–85)	87	9, 61, 80–84
Visitor compliance	50 (42–52)	74 (70–80)	94	61, 80, 81
Caregiver compliance	30 (15–45)	50 (42–52)	74	61, 80, 81, EO
Environmental disinfection				
Daily compliance	40 (35–50)	80 (70–85)	94	85–89, EO
Terminal compliance	47 (40–50)	77 (70–82)	98	85, 90–93
Nonsporicidal effectiveness[b]		45 (35–50)		94, 95
Sporicidal effectiveness[b]		99.6		95–98
Asymptomatic screening at admission				
Compliance	0	96 (92–99)	98	99, 100
PCR test sensitivity; specificity, %		93 (90–94); 97 (95–99)		101–103
Patient transfer				
Intraward transfer rate	8.0 (6.1–10.1)	50% reduction	75% reduction	Internal data
Interward transfer rate	22.9 (19.9–25.9)	50% reduction	75% reduction	Internal data
Proportionate time between transfers, %	28% (time between transfer/length of stay; 25–35)			Internal data

Note. ABHR, alcohol-based hand rub; PCR, polymerase chain reaction.
[a]References in Supplement 1 (online).
[b]Effectiveness at removal of spores.
[c]Known *C. difficile* room compliance range based on the range in standard rooms and a standard: CDI hand hygiene noncompliance ratio, 1.34.
[d]Effectiveness at preventing contamination with spores.

environmental disinfection in the pediatrics context must be accounted for in any proposed interventions. Toys are a common source of bacterial pathogens that require disinfection between patients.[28] Future studies should be conducted to determine the movement and sharing of toys between patients and throughout the hospital because this potentially mobile reservoir of disease is not accounted for in traditional conceptualizations of the physical environment.

Implementation of hospital-wide screening would likely receive more initial pushback from front-line providers than daily disinfection. Testing children for *C. difficile* before age 3 remains controversial, due to their high rate of asymptomatic colonization and the predominance of viral infections as a major cause of diarrhea, and the American Academy of Pediatrics is concerned with overtreatment.[5] However, in settings in which *C. difficile* containment has proven challenging, this strategy may be deployed judiciously. Notably, the primary goal of screening is not to reduce colonization in infants and young children themselves, but to reduce hospital-wide morbidity and mortality by interrupting the spread of infectious spores to other hospitalized children.

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Table 4. Comparative Effectiveness of Intervention Bundles

Bundle components	HO-CDI per 10,000 Patient Days		Asymptomatic Colonizations per 1,000 Admissions	
	Mean	95% CI	Mean	95% CI
Baseline	5.50	5.45–5.56	32.73	32.63–32.83
Patient and HCW HH	4.07	4.02–4.11	19.73	19.66–19.81
Terminal and daily disinfection	2.80	2.77–2.84	8.22	8.17–8.27
Daily disinfection, surveillance	2.09	2.06–2.12	3.81	3.78–3.84
Daily disinfection, surveillance, HCW HH	1.99	1.96–2.03	2.83	2.80–2.86
Daily disinfection, surveillance, HCW HH, terminal disinfection	2.01	1.98–2.04	2.72	2.70–2.75
Daily disinfection, surveillance, HCW HH, terminal disinfection, patient HH	1.96	1.93–1.99	2.40	2.38–2.43

Note. CI, confidence interval; HCW, healthcare worker; HH, hand hygiene.

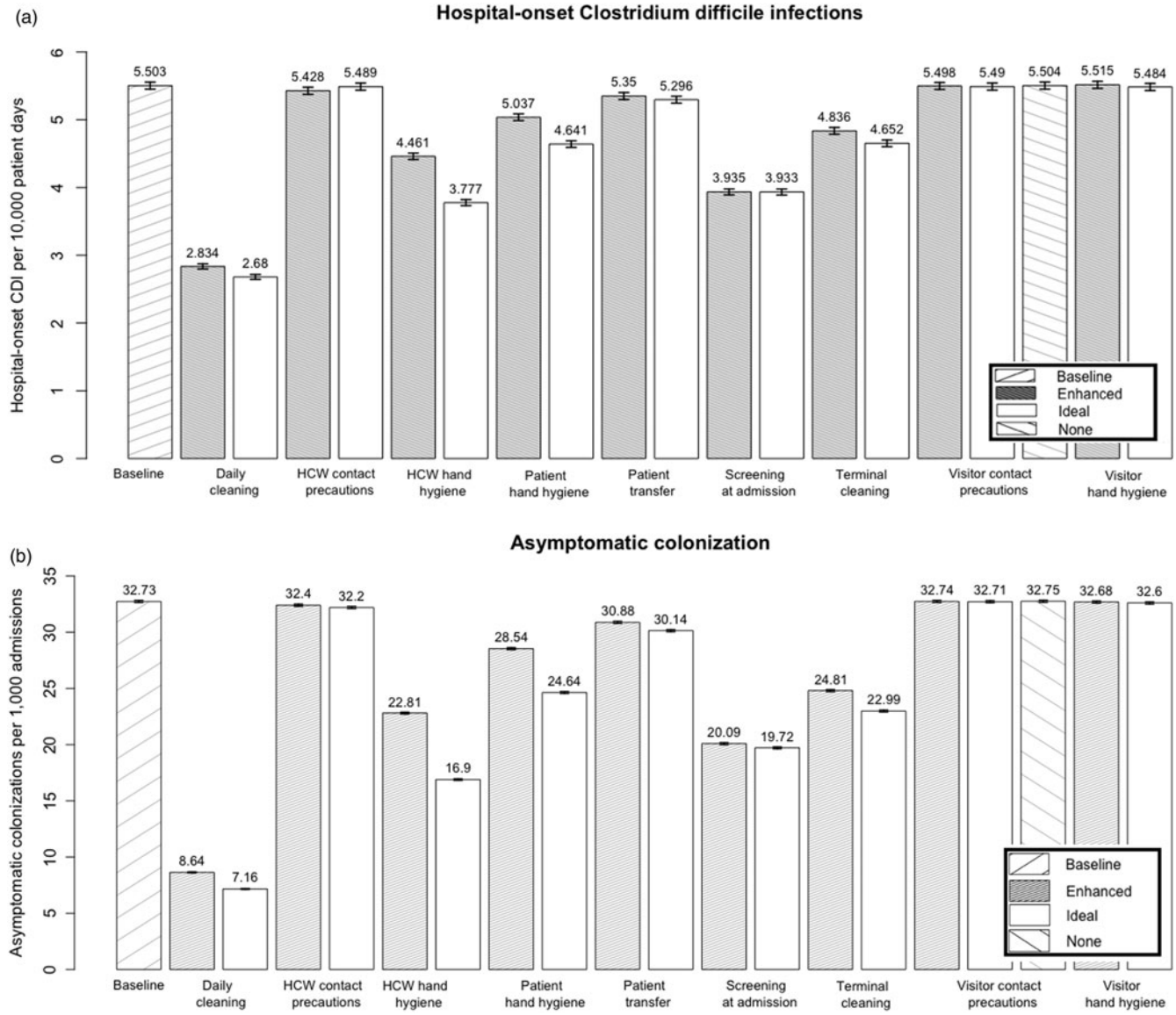


Fig. 3. Comparative effectiveness of infection prevention interventions at reducing (a) hospital-onset CDIs and (b) asymptomatic colonization.

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The CDI pathology in children more than 3 years old is similar to that in adults. It has severe and costly consequences, including a longer average hospital length of stay, treatment failure, recurrent infection, and rarely, death.[29,30] Recent genetic and modeling studies have shown that asymptomatically colonized people are key reservoirs and transmitters of the disease.[17,31] These findings are consistent with observational studies that show high levels of skin and environmental contamination among hospitalized, asymptomatic colonized patients.[32]

Screening at admission could help break the chain of contamination that occurs when healthcare personnel transition from an unknown, contagious, asymptomatically colonized patient to a susceptible patient. This intervention implements soap and water hand hygiene, sporicidal cleansers, and contact precautions for patients who screen positive, but it does not initiate treatment. The single existing hospital-wide study of a nonbundled *C. difficile* screening intervention reported a 56% reduction in HO-CDI in the adult setting.[33] Screening interventions in pediatric hospitals have not yet been reported, and additional work is needed to determine optimal target populations.

In light of the unique epidemiology of *C. difficile* in infants, it is essential that any screening intervention also be implemented simultaneously with an education component focused on appropriateness of treatment. As with adults, asymptomatic patients who test positive for *C. difficile* on screening should not receive treatment.[33] Thus, inpatient antibiotic prescribing patterns should be carefully tracked and evaluated before and after initiation of a screening intervention. Guidelines from the American Academy of Pediatrics should be followed if young patients become symptomatic; other causes of diarrhea should be ruled out before CDI is diagnosed and treated.[5]

Neither the visitor contact isolation nor visitor hand hygiene intervention was effective at reducing *C. difficile*. This finding is consistent with our group's prior study of visitor interventions in the adult hospital setting,[16] even with the addition of caregiver agents in the pediatric model who remain in the hospital 12 hours at a time. Similar HO-CDI rates for the modeled opt-in and baseline visitor contact isolation policies bring into question the benefit from contact precautions among visitors of pediatric *C. difficile* patients. Contact isolation is associated with increased rates of anxiety and depression in the adult setting.[34] Yet, physical barriers are likely even more distressing for pediatric patients, who are additionally restricted from playrooms, school, and social interactions that may have significant impact on healing. Careful consideration of these risks and benefits is essential to maintaining visitor contact-isolation practices.

The negligible impact of visitor interventions is likely because a series of low-probability events must occur in the model for a visitor to transmit infection. These events include an initial exposure in which the visitor is contaminated by the patient they are visiting or the environment. It must be followed by a second event, in which the visitor transmits infectious spores from their hands either directly to a patient, or to a patient's room or common room environment, such as a door knob, water fountain, or elevator button. If the later happens, a third event must occur, in which a susceptible patient is subsequently exposed to the contaminated environment. Unlike healthcare personnel, who come into physical contact with several patients a day, visitors spend most of their time with 1 patient. The risk of direct transmission of *C. difficile* from visitors to this single patient is minimal, as are the clinical effects of the visitor targeted interventions.

All modeling studies are limited by the data quality and conceptual framework that underpin the model's logic and parameter estimates. This is the first simulation model of *C. difficile* transmission in the pediatric setting. We relied heavily on studies conducted in adult hospitals when developing many of our parameter estimates. Behaviors such as intervention compliance may occur at different rates in child and adult contexts. However, in many cases, relevant pediatric-specific studies do not currently exist in the literature. Intervention studies available to cross-validate the model with real-life results are scarce.[11,15] Future model development would benefit from additional pediatric-focused work, including general workflow systems analyses and targeted evaluations of ongoing infection prevention interventions.

Several additional simplifications and assumptions should be considered in light of the currently available data in the pediatric setting. *Clostridioides difficile* susceptibility did not vary based on antibiotic usage, comorbidities, previous hospitalization, nor prior CDI. In part because of this lack of patient heterogeneity, we did not evaluate interventions involving antibiotic stewardship or probiotic use. However, both appear promising in recent pediatric studies.[35,36] We also did not address differences in transmission and virulence between *C. difficile* strains, instead modeling a generic colonization and infection. All spore transmission was based on physical contact, and air dispersal was not considered. Finally, the physical hospital layout was simplified. All rooms and wards were modeled identically, and potentially unique aspects of *C. difficile* transmission dynamics and risk profiles in units such as oncology, transplant, and intensive care were ignored. Units with >10 beds or that include non–single rooms may have more shared surfaces, with increased risk of transmission from the environment. The results of this model may not be generalizable to these contexts, and additional spatial considerations should be considered in future pediatric simulation models.

Ultimately, this is the first mathematical model to evaluate *C. difficile* transmission in the pediatric setting. Our finding of 60% reduction in HO-CDI rates using a 2-pronged daily disinfection and asymptomatic screening bundle is promising, especially given the suspected relative ease of substituting sporicidal for nonsporicidal disinfection products. Because the goal of these interventions is infection prevention, we recommend utilizing them continually, rather than only for outbreak control. These results provide much-needed direction to an infection prevention field lacking the literature and *C. difficile*–targeted guidelines available in the adult setting. Furthermore, many of the most effective interventions modeled are horizontal approaches to infection prevention that impact transmission of other hospital-associated infections, beyond *C. difficile*. Thus, these findings ultimately have implications for the control of numerous pediatric infectious diseases.

Supplementary material. To view supplementary material for this article, please visit https://doi.org/10.1017/ice.2020.14

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Conflicts of interest. O.A. has served as consultant to Biovector, a startup company active in the area of infection prevention. None of his consulting work is related to this manuscript and the company has not seen this manuscript. All other authors report no conflicts related to this article.

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