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ARTICLE

The potential economic value of screening hospital admissions for *Clostridium difficile*

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Abstract Asymptomatic *Clostridium difficile* carriage has a prevalence reported as high as 51–85 %; with up to 84 % of incident hospital-acquired infections linked to carriers. Accurately identifying carriers may limit the spread of *Clostridium difficile*. Since new technology adoption depends heavily on its economic value, we developed an analytic simulation model to determine the cost-effectiveness screening hospital admissions for *Clostridium difficile* from the hospital and third party payer perspectives. Isolation precautions were applied to patients testing positive, preventing transmission. Sensitivity analyses varied *Clostridium difficile* colonization rate, infection probability among secondary cases, contact isolation compliance, and screening cost. Screening was cost-effective (i.e., incremental cost-effectiveness ratio [ICER] ≤$50,000/QALY) for every scenario tested; all ICER values were≤$256/QALY. Screening was economically dominant (i.e., saved costs and provided health benefits) with a ≥10.3 % colonization rate and ≥5.88 % infection probability when contact isolation compliance was ≥25 % (hospital perspective). Under some conditions screening led to cost savings per case averted (range, $53–272). *Clostridium difficile* screening, coupled with isolation precautions, may be a cost-effective intervention to hospitals and third party payers, based on prevalence. Limiting *Clostridium difficile* transmission can reduce the number of infections, thereby reducing its economic burden to the healthcare system.

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Introduction

Clostridium difficile (*C. difficile*) can cause a wide range of clinical disease in hospitalized patients [1, 2] and result in substantial healthcare costs [3]. It is the leading cause of infectious diarrhea in hospitalized patients and especially affects elderly and frail patients [4, 5]. Studies have found asymptomatic *C. difficile* carriage rates to be as high as 51–85 % in nursing facilities and in selected inpatient populations with a prolonged length of stay (LOS) [6–8]. Previous typing studies have suggested that as many as 84 % of incident hospital-acquired infections are linked to asymptomatic carriers [8]. Accurately identifying these carriers and taking appropriate precautions may limit the spread of *C. difficile* to other hospitalized patients.

Healthcare facilities do not routinely screen for this hospital-acquired pathogen. Detecting asymptomatic *C. difficile* carriers was previously limited to research laboratories equipped to perform anaerobic culture for *C. difficile*. Because non-toxigenic strains of *C. difficile* incapable of causing human infections exist, each isolate recovered by culture required confirmation of toxin production; the entire process of detecting asymptomatic carriers was thus impractical as a surveillance test, as the average turn-around time of 5–10 days

exceeded the median LOS for most hospitals. Existing *C. difficile* tests for toxin production could not be used as effective screening tools because of low sensitivity compared to the gold standard of culture, as even polymerase chain reaction (PCR)-based assays have been shown to have sensitivities of 77–86 % compared to toxigenic culture (i.e., the gold standard [9]), which is too low to serve as an effective screening test for carriage [10–12]. In addition, existing clinical tests for *C. difficile* toxin require use of a stool sample, which makes the sampling process inefficient for screening purposes. However, a novel screening method has recently been developed [13]. This method utilizes peri-rectal surveillance specimens that are pre-amplified in a *C. difficile* selective medium followed by toxin detection using a PCR assay, combining the sensitivity of anaerobic culture with the specificity and rapid turn-around of PCR-based testing without needing stool samples. The broth amplification process results in a 1.25- to 3.25-day turnaround time, which is comparable to other healthcare associated (HAI) surveillance tests [13].

Since adoption of this technology depends heavily on its economic value, we developed a computational analytic simulation model to determine the cost-effectiveness of this novel *C. difficile* screening method. Sensitivity analyses varied the key parameters of *C. difficile* colonization rate among admitted patients, the probability of infection, contact isolation compliance, and the cost of screening. Decision makers such as hospital administrators and third party payers can use the result of our study to make decisions about implementing *C. difficile* screening programs and reimbursement rates.

Methods

We further adapted our previously published *C. difficile* outcomes model [3] developed in TreeAge Pro 2009 (Williamstown, MA) to determine the cost-effectiveness of screening all hospital admissions for *C. difficile* from the hospital and third-party payer perspectives. Figure 1 outlines the general structure of our model and Table 1 provides the input parameters with values and sources. Upon admission, all patients (≥1 year old) were either screened (via peri-rectal swabbing) or not screened for *C. difficile*. Patients with a positive screening test were placed under contact isolation precautions (i.e., the use of gloves and gowns for each patient contact), regardless of true colonization status (i.e., true and false positive tests). Staff compliance with the contact isolation precautions reduced transmission of *C. difficile* to other patients (i.e., a reduction in reproductive rate based on compliance rates). Patient age and LOS for all admissions was based on statistics for all hospital stays from the Healthcare Utilization Project (HCUP) [14] (Table 1).

C. difficile screening consisted of peri-rectal swabbing, pre-amplification in a selective medium, and the use of real time PCR assay [13]. The test assumed a mean sensitivity of 99 % and specificity of 99.1 % (Table 1). Testing also had a 1.25–3.25 day turnaround time [13], during which colonized patients could freely transmit *C. difficile* to other patients, based on its reproductive rate (R), which is the average number of secondary colonizations generated by one colonized patient, regardless of the mode of transmission (e.g., person-to-person, environmental).

All secondary colonizations generated could develop a *C. difficile* infection (CDI) or remain colonized. Those developing CDI could have mild/moderate or severe CDI. We used standard treatments for CDI therapy [5, 9, 15]. Severe CDI patients could undergo surgery (i.e., a total colectomy), based on the results of a computed tomography (CT) scan. Patients undergoing surgery received enteral (PO) vancomycin and IV metronidazole (500 mg, every 8 hours for 10–14 days [5, 9, 15]), requiring the use of additional peripheral intravenous central catheter (PICC) line. Those patients not undergoing surgery were treated with oral vancomycin (125 mg, 4 times daily for 10–14 days [5, 9, 15]), which had a probability of being effective; if ineffective, a second course was given. Severe CDI episodes, regardless of surgery, were associated with a probability of mortality. Patients with mild/moderate CDI received oral metronidazole (500 mg, 3 times daily for 10–14 days [5, 15]). If treatment was ineffective, a second course was given, if this failed again, the patient was switched to vancomycin. Upon the second recurrence, all patients were given tapered vancomycin (4 times daily for 14 days, 2 times daily for 7 days, once daily for 7 days, once every 2 days for 8 days, once every 3 days for 15 days [5, 15]), regardless of disease severity. All secondary cases could experience up to two recurrences, for a total of ≤3 episodes of CDI. CDI's severity was independent of the previous episode's severity (i.e., a patient with mild CDI could have a recurrence with severe CDI and a severe CDI could recur as a mild CDI).

Each simulation sent 1,000 patient admissions (1st order trial or microsimulation) through the model 1,000 times (2nd order trial), for a total of one million trials with unique outcomes. The incremental cost-effectiveness ratio (ICER) was calculated for each simulation as:

$$= \left(\text{Cost}_{\text{screening}} - \text{Cost}_{\text{no screening}}\right) / \left(\text{Effectiveness}_{\text{screening}} - \text{Effectiveness}_{\text{no screening}}\right)$$

where effectiveness was measured in quality-adjusted life years (QALYs). CDI patients received a decrement to their age dependent healthy QALY value by the CDI's utility weight based on disease severity for the duration of each episode. QALY decrements for non-infectious diarrhea

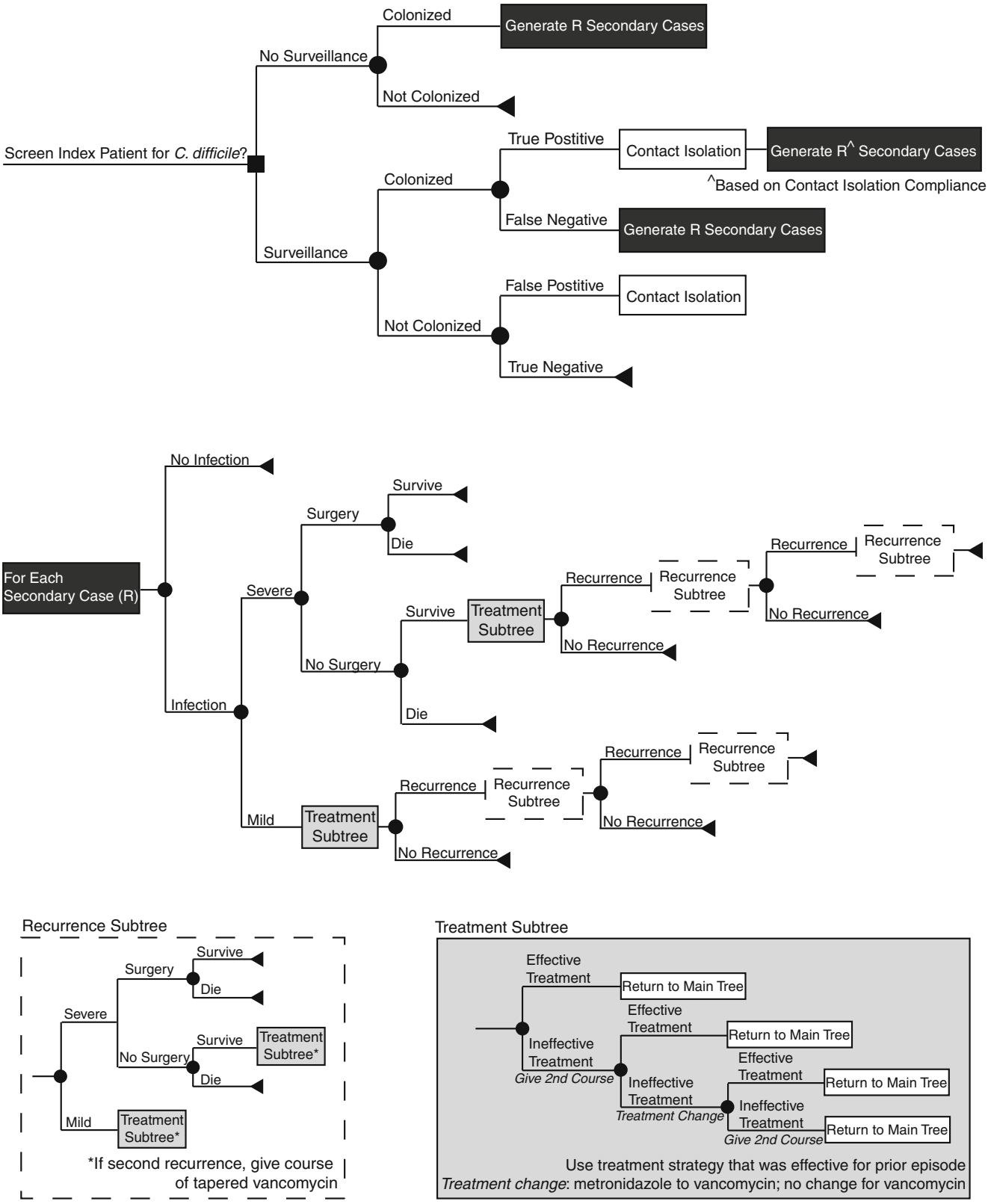

Fig. 1 Model structure

[16–18] were used as a proxy for *C. difficile* diarrhea, as more specific estimates are not yet published. Those who do not develop CDI received the full healthy QALY value for the duration of the simulation. For example, a 65-year-old

Table 1 Model input parameters and values

Parameters	Mean[a]	Standard deviation[b] or range	Source
Costs ($US 2011)			
Screening	7.66	3.32–15.88	[13]
Gloves (per pair)	0.0861		[45]
Gown	0.922		[45]
Technician wage (median hourly)	17.96	14.34–22.63	[46]
Nurse wage (median hourly)	31.10	21.24–45.74	[46]
Hospitalization			
1–17 years old	7,695.72	1157[b]	[14]
18–44 years old	8,557.51	318[b]	[14]
45–64 years old	10,833.81	250.5[b]	[14]
65–85 years	11,476.37	246.90[b]	[14]
85 years and older	10,324.00	215.6[b]	[14]
Hospital bed day	1,560	33.55[b]	[14]
Peripheral intravenous line insertion	97.63		[47]
CT scan	284.38	30.50	[47]
Colectomy			
1–17 years old	34,417.94	5731.92[b]	[14]
18–44 years old	32,982.51	3608.08[b]	[14]
45–64 years old	38,472.33	19626.24[b]	[14]
65–85 years	46,566.65	1,594.21[b]	[14]
85 years and older	45,913.49	3316.95[b]	[14]
Antibiotics (full course)			
Metronidazole (IV)	116.36	10.88	[48]
Metronidazole (oral)	57.41	38.59	[48]
Vancomycin (oral)	1,347.39	77.52	[48]
Vancomycin (tapered)	2,069.21	119.04	[48]
Utility weights			
Age 1–17 years	1.0		[49]
Age 18–64 years	0.96		[49]
Age 65 years and older	0.84		[49]
Mild *C. difficile* infection (CDI)	0.88		[16, 17]
Severe CDI	0.817		[16, 17]
Colectomy	0.536		[18]
Probabilities			
PCR sensitivity	99	94.9–100	[13]
PCR specificity	99.1	97.6–99.7	[13]
Given infection			
Severe disease	15.8	5.46	[6, 50–52]
Colectomy	0.27		[53]
Colectomy mortality	41.7	37.2–46.3	[54, 55]
Mortality if no colectomy	58.3		[56]
Recurrence	18.9	6.77	[52, 57, 58]
Treatment efficacies			
Metronidazole	87	85.4–88.2	[59]
Vancomycin	90.2	87.9–92.3	[59]
Vancomycin (tapered)	72.2	55–86	[60]
Durations			
Reproductive rate	1.04	0.52–1.99	[32]
Attributable CDI length of stay	3.6	1.5–6.2	[24]
Attributable CDI length of stay [c]	7.14	2.18	[25–29]
Turnaround time	2.25	1.25–3.25	[13]
Technician time (minutes)		10–12	[13]
Patient contacts per day		25–50	[61]
Time Don and Doff (minutes)	1		[45]
Patient characteristics			
Age			
1–17 years old	4.64		[14]
18–44 years old	28.56		[14]
45–64 years old	27.7		[14]
65–85 years	30.2		[14]
85 years and older	8.9		[14]
Length of stay for index patient			
1–17 years old	3.6	0.1	[14]
18–44 years old	3.6		[14]
45–64 years old	5.0		[14]
65–85 years	5.4		[14]
85 years and older	5.5	0.1	[14]

[a] Mean value unless otherwise noted

[b] Denotes value is a standard error

[c] Longer CDI attributable LOS used in additional analysis

patient who has one episode of severe CDI would receive 0.69 QALYs for 10 days (0.84*0.817; 65-year-old healthy QALY value*severe CDI's utility weight) and would receive 0.84 QALYs for the remaining time in the model. The age of secondary cases was also determined by the statistics for all stays from HCUP. ICER values≤$50,000/QALY were considered to be cost-effective [19] and screening was considered economically dominant when it saved both costs and QALYs. We also calculated the cost per case averted when screening is implemented (i.e., the difference in cost between screening and no screening divided by the number of cases that screening would prevent).

The hospital perspective measured illness costs in lost bed days (i.e., additional LOS attributable to CDI) by a method described by Graves [20]. The third party payer prospective included the direct costs of illness, such as hospitalization, diagnostic tests, and treatment. All costs, where applicable, were age-dependent. Other costs, such as screening (i.e., materials and technician time) and contact isolation of

those testing positive were incurred by each perspective being modeled. The cost of contact isolation included the cost of gloves and gowns for each patient contact per day for the duration of their hospitalization. Contact isolation was considered standard treatment for all secondary cases and its cost was included only from the hospital perspective.

Sensitivity analyses

Monte Carlo probabilistic sensitivity analyses simultaneously varied the parameters in Table 1 throughout the ranges listed. Sensitivity analysis varied the probability of colonization (0.5–20 % [8, 21, 22]) of the admitted patient, to represent differences in location and the risks associated with antibiotic exposure and hospitalization. The probability of infection given colonization for secondary cases was varied from 5.88 % [8] to 18.6 % [23]. Contact isolation compliance ranged from 25 % to 75 % (efficacy was assumed to be 100 % if implemented correctly). The sensitivity of the screening test varied from the baseline in Table 1 to 75 %. Initial scenarios assumed a CDI attributable LOS based on Kyne et al. (mean 3.6; 95 % confidence interval 1.5–6.2) [24]; additional runs explored the effects of an increased CDI attributable LOS (mean 7.14; standard deviation 2.18) [25–29].

Results

Table 2 shows the ICER values for *C. difficile* screening of hospital admissions from both the hospital and third party payer perspectives by varying rates of colonization, infection, and contact isolation compliance. Screening was cost-effective (i.e., ≤$50,000/QALY) for every scenario tested, with all ICER values≤$256/QALY from both perspectives. *C. difficile* screening was economically dominant (i.e., saved costs and QALYs) under several scenarios (Table 2). When the colonization rate was ≥10.3 % and probability of infection after *C. difficile* spore acquisition was ≥5.88 %, *C. difficile* screening dominated no screening when contact isolation compliance was a least 25 % from the hospital perspective. For a 5 % colonization rate, screening was economically dominant when the probability of *C. difficile* infection after spore acquisition rate was 18.6 % and contact isolation compliance was ≥25 % (hospital perspective). *C. difficile* screening remained cost-effective when costing $50 (ICERs≤$930/QALY) or $75 (ICERs≤$1,376/QALY) from both perspectives.

The cost of one secondary case having up to three CDI episodes was a median $7,178 (mean $7,177; range $6,817–7,562) from the hospital perspective and a median $12,979 (mean $12,979; range $12,403–13,629) from the third party payer perspective. Table 3 reports the cost per case averted from the hospital perspective. In some scenarios, the costs of *C. difficile* screening exceeded the cost savings in CDI cases averted, with $12 to $4,072 spent per case averted (Table 3). In some scenarios (when the population entering the model had a *C. difficile* prevalence ≥10.3 %), *C. difficile* screening led to cost savings to avert a case (i.e., negative values). Cost savings ranged from $53 to $272 per case averted in these scenarios. Screening always provided savings in scenarios where the population entering the model had a *C. difficile* prevalence ≥7.5 % when contact isolation compliance was ≥25 % (5.88 % probability of *C. difficile* infection after spore acquisition). The savings provided by screening were even higher with an 18.6 % infection rate and ranged from $250 (5 % admission colonization rate, contact

Table 2 Incremental cost-effectiveness ratio (ICER, $/QALY) for *C. difficile* screening compared to no screening

C. difficile colonization on admission (%)	Contact isolation compliance (%)		
	25	50	75
Hospital perspective			
Probability of infection after colonization=5.88 %			
0.5	256	241	208
1	122	105	94
5	5	3	1
10.3	Screen	Screen	Screen
15	Screen	Screen	Screen
20	Screen	Screen	Screen
Probability of Infection after colonization=18.6 %			
0.5	207	186	157
1	64	42	40
5	Screen	Screen	Screen
10.3	Screen	Screen	Screen
15	Screen	Screen	Screen
20	Screen	Screen	Screen
Third party payer perspective			
Probability of infection after colonization=5.88 %			
0.5	235	212	187
1	97	85	73
5	Screen	Screen	Screen
10.3	Screen	Screen	Screen
15	Screen	Screen	Screen
20	Screen	Screen	Screen
Probability of infection after colonization=18.6 %			
0.5	131	100	76
1	Screen	Screen	Screen
5	Screen	Screen	Screen
10.3	Screen	Screen	Screen
15	Screen	Screen	Screen
20	Screen	Screen	Screen

Screen=screening was dominant (less costly and more effective) than no screening

Table 3 Cost per case averted utilizing screening with a 5.88 % probability of *C. difficile* infection from the hospital perspective

C. difficile colonization on admission (%)	Contact isolation compliance (%)		
	25	50	75
0.5	4,072	3,787	3,238
1	1,936	1,655	1,482
5	77	47	12
7.5	−53	−89	−136
10.3	−146	−157	−189
12	−163	−195	−227
15	−190	−214	−241
20	−235	−242	−271

Negative values imply cost savings

isolation compliance 25 %) to $2,249 (20 % colonization rate on admission, contact isolation compliance 75 %).

Increasing the attributable LOS to an average 7.14 days decreased the ICER values from the hospital perspective (all ICERs≤$226/QALY) and screening became the dominant strategy at a 5 % admission colonization prevalence when contact isolation compliance was ≥25 % (5.88 % probability of infection after acquisition). For third party payers, the increased LOS did not have an effect on the cost effectiveness of screening (all ICERs≤$235/QALY). A test with 75 % sensitivity still yielded screening to be cost-effective with all ICER values≤$344/QALY from both perspectives.

Annual hospital savings

Assuming a 10.3 % colonization rate on admission [8], a hospital with 1,000 annual admissions would experience cost savings of $10,256, $12,278, and $16,071 when implementing universal screening plus contact isolation with 25 %, 50 %, and 75 % compliance, respectively. The costs or savings increased with increasing annual admissions. For 5,000 and 10,000 annual admissions, hospitals could save $51,280 to $80,356 and $102,560 to −$160,712, respectively, with contact isolation compliance rates ≥25 %. Extrapolating to the entire United States, with 34,705,583 annual discharges in 2009 [14], cost savings could range from $152 million (7.5 % admission prevalence, 25 % contact isolation compliance) to $1.6 billion (20 % admission prevalence, 75 % contact isolation compliance).

Discussion

C. difficile has become an increasing healthcare concern and can be a costly pathogen [3]. Reducing the number of HAI CDI cases can in turn reduce CDI's costs. The cost of one secondary case in our model (median values of $5,953 and $10,547 for one episode and a median $7,178 and $12,979 for up to three episodes, from the hospital and third party payer perspectives, respectively) is consistent with the previously published range of CDI costs ($2,000 to $72,000) [4, 30, 31]. While the number of secondary cases an index case will generate remains unclear, an extensive mathematical model has simulated a basic reproductive rate, suggesting that transmission within a ward is insufficient to account for sustained, endemic CDI within hospital facilities. This model, as well as other studies, has suggested that admission colonized patients play a key role in sustaining *C. difficile* transmission [8, 32]. Our results show that screening coupled with contact isolation precautions may be a cost-effective way to reduce the number of secondary CDI cases, leading to cost savings by averting cases. Economically dominant results strongly support the implementation of screening, as the intervention not only saves costs, but also provides health benefits.

Screening for other HAIs (i.e., *Staphylococcus aureus* and *Acinetobacter baumannii*) has shown cost-effectiveness in various populations [33–38]. Our goal was to inform various decision makers (e.g., infection control specialists, hospital administrators, insurance companies) about the potential cost-effectiveness of *C. difficile* screening, not to make the decision about implementation. Decision makers can use the results of our study to make decisions based on their own local circumstances. Our results suggest that *C. difficile* screening, even just at admission, is cost-effective over a range of colonization and contact isolation compliance rates. For community hospitals, where the population served might have prevalence of *C. difficile* colonization closer to that observed in healthy adults (0–15 %) based on prior studies [39–42], screening can be cost-effective and even cost saving if implemented with contact isolation compliance rates ≥25 %. For a community hospital with a 5 % prevalence of *C. difficile* carriers entering the facility, increasing contact isolation compliance can reduce the cost per case averted generated by screening (Table 3). It should be noted that the implementation of a new screening method may require additional start-up costs (e.g., new equipment) and ongoing microbiology laboratory personnel costs which were not included in the model.

Although we did not explicitly model other inpatient populations, our results could be particularly important for tertiary referral centers, long-term acute care hospitals, and some nursing facilities which have been associated with high prevalence of *C. difficile* carriage in previous studies [7]. However, they may not be applicable to those long-term acute care facilities and nursing homes, which have ongoing transmission from long-term residents with *C. difficile* colonization, in which repeated screening may be necessary. They also may not be applicable to hospitals that primarily

serve pediatric patients (patients <1 year old were not included in this study), as neonates are known to have very high rates of asymptomatic *C. difficile* carriage.

Our model attempted to be conservative about the benefits of *C. difficile* screening. We limited the number of unique CDI episodes to three per secondary case; some persons may experience more. The costs evaluated were only for the duration of hospitalization (with continuing treatment after discharge to complete the full course of antibiotics), additional costs may be associated with a longer time frame. Additionally, we used only the standard treatment regimens for CDI, other drug therapies may be used such as reconstituted IV vancomycin and fidaxomicin. We excluded rare CDI complications and comorbid conditions (e.g., irritable bowel syndrome or immunosuppressed patients), which may lead to additional costs. The health impact of CDI may be underestimated in our model; the QALY decrements used in our study are for non-infectious diarrhea, while diarrhea caused by *C. difficile* may be more severe, resulting in a larger decrement. Furthermore, our model only focused on identifying *C. difficile* carriers and how this can reduce its spread to other patients, but not how it may lead to the implementation of appropriate antibiotic treatment for those who may progress to infection or reduction in transmission of other epidemiologically significant organisms within hospitals. Although not explicitly modeled, screening may have additional benefits in increased environmental cleaning in rooms for those who test positive, further reducing transmission. However, it should be noted that a positive screening test should not prompt treatment in patients with minimal or no symptoms [5]; patients may acquire CDI as a result of the misguided treatment. Additional data on the colonization rate on admission in different inpatient and long-term care populations are needed to get a more accurate picture about the potential benefits *C. difficile* screening. The probability of infection given *C. difficile* colonization may vary as most studies do not report this since a patient's colonization status is not known.

By definition, all models are simplifications of real life [43] and therefore cannot account for every possible CDI event or outcome. Nor can the full spectrum of sociodemographic and clinical heterogeneity among admitted patients being screened or among secondary cases be represented. Our model inputs were derived from studies of varying quality. While adverse events attributable to contact isolation precautions have been reported [44], there are no published cost or utility estimates to quantify these effects and were therefore not included. In addition, contact precautions did not include the use of an isolation/private room, which may incur additional costs (e.g., patient transfer and cleaning). However, this arrangement is becoming more obsolete as new hospital construction in the United States now provides for 100 % single occupancy rooms. As constructed, our model does not account for potential transmission events from patients with negative admission screens who may go on to acquire *C. difficile* on a hospital ward.

Conclusion

Our model showed that *C. difficile* screening, coupled with contact isolation precautions, may be a cost-effective intervention (≤$256/QALY) to hospitals and third party payers. Reducing the transmission of *C. difficile* can reduce the number of CDI cases and episodes, therefore reducing its large economic burden to the healthcare system. Under some conditions, screening was economically dominant and could save costs if implemented.

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Conflict of interest The authors are not aware of any substantial conflict of interest.

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