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REVIEW

Screening for Asymptomatic *Clostridioides difficile* Carriage Among Hospitalized Patients: A Narrative Review

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ABSTRACT

Clostridioides difficile infection (CDI) has become the most common healthcare-associated infection in the United States, with considerable morbidity, mortality, and healthcare costs. Assessing new preventive strategies is vital. We present a literature review of studies evaluating a strategy of screening and isolation of asymptomatic carriers in hospital settings. Asymptomatic detection of *C. difficile* is reported in ~ 10–20% of admitted patients. Risk factors for carriage include recent hospitalization, previous antibiotics, older age, lower functional capacity, immunosuppression, and others. Asymptomatic *C. difficile* carriers of toxigenic strains are at higher risk for progression to CDI. They are also shedders of *C. difficile* spores and may contribute to the persistence and transmission of this bacterium. Screening for asymptomatic carriers at hospital admission can theoretically reduce CDI by isolating carriers to reduce transmission, and implementing antibiotic stewardship measures targeting carriers to prevent progression to clinical illness. Several observational studies, summarized in this review, have reported implementing screening and isolation strategies, and found a reduction in CDI rates. Nevertheless, the data are still limited to a few observational studies, and this strategy is not commonly practiced. Studies supporting screening were performed in North America, coinciding with the period of dominance of the 027/BI/NAP1 strain. Additional studies evaluating screening, followed by infection control and antibiotic stewardship measures, are needed.

Keywords: *Clostridioides difficile*; Screening; Infection control; Contact isolation; Antibiotic stewardship

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Key Summary Points

Clostridioides difficile was recently designated by the Centers for Disease Control and Prevention (CDC) selected as one of five urgent threats to public health.

Toxigenic *Clostridioides difficile* asymptomatic carriage is common among hospitalized patients and carries a risk for progression to *C. difficile* infection (CDI) along with spread to other patients.

Screening for asymptomatic carriage may reduce CDI rates by contact isolation of carriers and limiting antibiotic use among them.

Further studies are needed to evaluate the effectiveness of this preventive strategy.

INTRODUCTION

C. difficile Burden of the Disease

Clostridioides difficile (*C. difficile*), causing *C. difficile* infection (CDI), has become the most common healthcare-associated infection in the United States [1]. The prevalence of this infection is significant, with over 400,000 cases and almost 30,000 deaths annually from *C. difficile*-associated diarrhea in the US [2, 3]. The economic burden of *C. difficile* infection is also substantial, with direct healthcare costs exceeding US$5 billion annually [3]. Moreover, infection with *C. difficile* can cause a broad spectrum of illnesses, ranging from mild diarrhea to severe complications, including pseudomembranous colitis, toxic megacolon, bowel perforation, sepsis, and death [3]. The Centers for Disease Control and Prevention (CDC) designated CDI as one of five urgent threats to public health in its 2019 Antimicrobial Resistance Threat Report [4]. Given the high burden of *C. difficile* infection, its clinical impact, and economic consequences, assessing new strategies for CDI prevention, such as screening for asymptomatic carriers in hospital settings, is vital.

This review discusses the definitions, prevalence, and significance of asymptomatic *C. difficile* state among hospitalized patients. We provide an overview of currently available data on screening admitted patients for *C. difficile* and isolation of positive patients as a strategy for preventing CDI among hospitalized patients.

We performed a comprehensive PubMed search up until April 2023, utilizing the MeSH term "*Clostridium difficile*" in conjunction with the terms "carrier," "carriage," "colonization," "asymptomatic," and "screening." Our investigation focused on examining clinical studies that explored the screening of asymptomatic carriage or colonization with *C. difficile*.

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Definition of Carriage

Clostridioides difficile carrier status is defined as any positive diagnostic test for the presence of *C. difficile* in the absence of diarrhea [5]. The optimal diagnostic tests for carriage include PCR (for toxin B (*tcdB*), binary toxin (*cdtA*), or *tcdC* deletion associated with the ribotype 027 strain) or toxigenic culture [5, 6]. It is essential to differentiate between carriage, which is a single detection of *C. difficile* that can represent only "pass-through" of spores, from colonization which is the persistent carriage that can be detected by the same restriction endonuclease analysis (REA) type of toxigenic *C. difficile* on two or more occasions [7, 8]. Nevertheless, these terms are used interchangeably in the literature [9]. We use the term 'carriage' in this review to address the presence of *C. difficile* in the absence of diarrhea unless stated 'colonization' in the original study addressed.

C. DIFFICILE CARRIAGE PATHOGENESIS AND GUT MICROBIOME

C. difficile is a spore-forming, Gram-positive anaerobic bacillus that spreads through fecal–oral transmission of spores, which remain viable for long periods ex-vivo [10, 11].

Although initially considered strictly a nosocomial infection and not typically part of the gut microbiome, it is now well established that *C. difficile* strains can also circulate in the community, resulting both in community-acquired CDI and in asymptomatic carriage. The sources of these strains are multiple, and the epidemiology is complex. Human reservoirs in the community may include infants below the age of 2 years who are frequently colonized [12]. However, numerous environmental sources, including agricultural sources, contaminated food products, and household pets, probably all contribute to *C. difficile* circulation [13].

The first step in establishing *C. difficile* colonization is the germination of spores into toxin-producing vegetative cells, which is stimulated by primary bile acids. Secondary bile acids inhibit *C. difficile* growth, and members of the phylum Firmicutes can metabolize primary bile acids into secondary bile acids (see Fig. 1). A disruption in the intestinal microbiota and depletion of Firmicutes may cause an increase in primary bile acids and a decrease in secondary bile acids. This change in bile acid composition could lead to an increased risk of *C. difficile* colonization and infection [14].

Our current comprehension of the progression from carriage to symptomatic CDI remains constrained. Earlier investigations have indicated that both carriers and symptomatic patients generate comparable levels of toxin [15], yet the underlying cause of why the latter group develops diarrhea remains obscure. Alterations in gut microbial composition in *C. difficile* carriers are less well described than in CDI patients. Still, some studies show a decreased species richness and microbial diversity in *C. difficile* carriers [16]. A study with antibiotic-exposed mice challenged with *C. difficile* spores demonstrated a shift toward Proteobacteria in animals that developed severe CDI symptoms. In contrast, the group that was only colonized by *C. difficile* had a microbiota dominated by Firmicutes, resembling that of mice without antibiotics [17]. Therefore, further studies are needed to understand the mechanisms of *C. difficile* carriage and its pathophysiology.

RISK FACTORS FOR ASYMPTOMATIC CARRIAGE

Several epidemiological and clinical risk factors for *C. difficile* carriage at hospital admission have been identified. These include recent hospitalization, older age, lower functional capacity, chronic dialysis, corticosteroid or immunosuppressant use, gastric acid suppressant medication, and antibodies against toxin B [20, 27–32].

A recent study has also demonstrated a significantly increased risk for *C. difficile* carriage among patients with residential proximity to livestock farms [33].

In the context of *C. difficile* infection, the use of antibiotics is not only a well-known risk factor but is in fact an inseparable component of the pathogenesis [34]. Antibiotic treatment is also associated with the carriage of *C. difficile* [29, 30]. Furthermore, there is a dose–response relationship, where an increase in antibiotic use leads to a more remarkable persistence of *C. difficile* on the skin and in the environment [35]. A mouse model demonstrated that prolonged antibiotic treatment could also induce a "supershedder" state, which results in the overgrowth of *C. difficile* and the excretion of large amounts of spores [36]. Specifically, Dubberke et al. reported cephalosporin use as a risk factor for *C. difficile* acquisition. This could be explained by either gut selective pressure favoring *C. difficile* growth, or undetected preexisting carriage, exposed following antibiotic use [29].

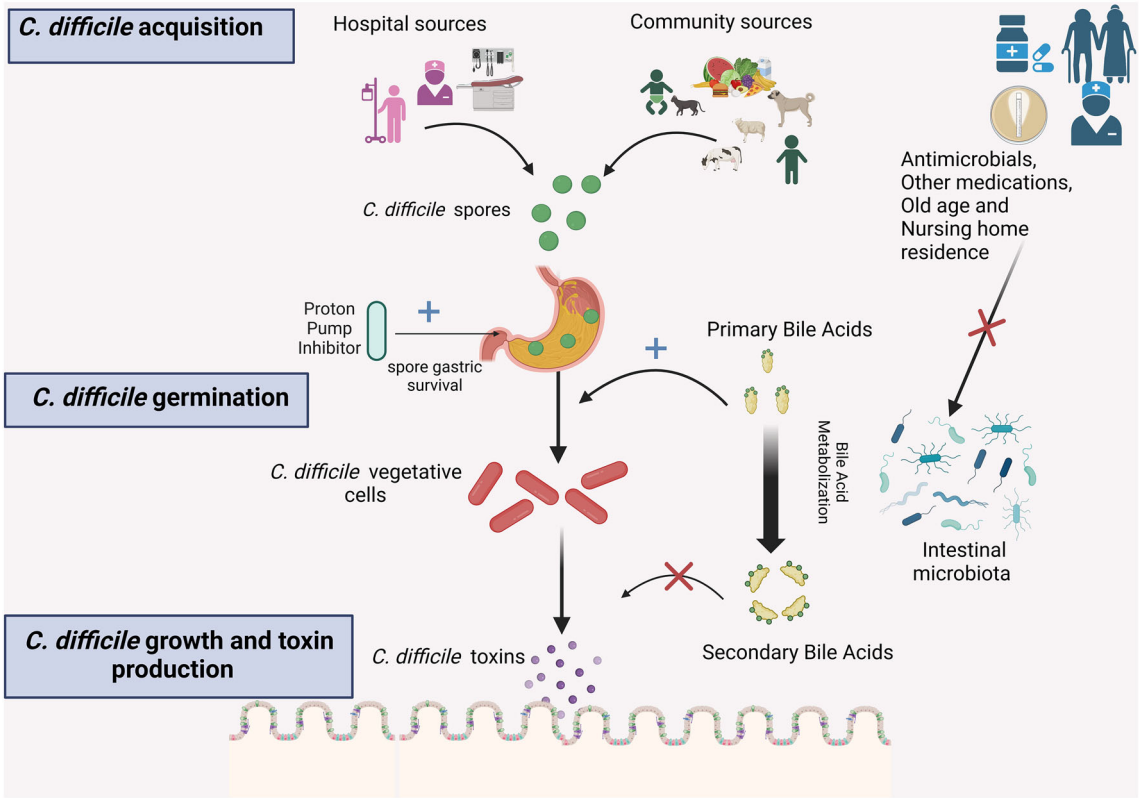

Fig. 1 Pathogenesis of *Clostridioides difficile* carriage and infection: *C. difficile* spores are acquired from various sources in both hospital and community settings. Hospital sources include the hospital environment, other individuals infected or colonized with *C. difficile*, and hospital staff. Community sources may include food products, animals, and asymptomatic carriers, particularly infants. Following the acquisition, spores may germinate into *C. difficile* vegetative cells, a process facilitated by primary bile acids. These vegetative cells replicate and produce toxins; the production of toxins and replication is inhibited by secondary bile acids. The composition of the intestinal microbiota, specifically the presence of certain microbes within the *Phylum Firmicutes*, promotes the conversion of primary bile acids into secondary bile acids. Various factors, such as antimicrobials, medications, advanced age, and residing in nursing homes, can impact the intestinal microbiota, decreasing these beneficial bacteria. Created with BioRender.com

PREVALENCE OF ASYMPTOMATIC *C. DIFFICILE* CARRIAGE

Asymptomatic carriage rates of *C. difficile* among patients admitted to hospitals range from 3 to 21% [6, 18–24]. This rate can vary based on region and demographic factors. In long-term care facilities, carriage state has been reported to be as high as 50% of screened residents [25]. A recent meta-analysis reported pooled prevalence of toxigenic *C. difficile* carriage of 8.1% among almost 9000 hospital-admitted patients [26]. Prevalence in North American studies was 10% in this meta-analysis.

PROGRESSION FROM CARRIAGE TO ACTIVE INFECTION

While, initially, *C. difficile* carriage was considered protective against the future development of symptomatic CDI, and progression was considered rare [37], it is now suggested that patients asymptomatically colonized by toxigenic strains are at higher risk for progression to

CDI during admission, whereas those colonized by nontoxigenic strains have no increased risk of progressing to CDI and may even be protected from developing CDI [6, 22, 26, 38–40],. The evidence of the former is limited mostly to non-adjusted data (Table 1).

A large study that screened 3,605 hospital admissions found that patients carrying toxigenic strains on admission were at a significantly higher risk of developing CDI (CDI rate of 9.4% vs. 2.3% for non-toxigenic *C. difficile* carriers). The relative risk for developing CDI from asymptomatic carriage in this study was 9.32, while carriage of a non-toxin-encoding strain did not increase risks for CDI [38].

We have recently reported that, among 2368 patients admitted to internal medicine wards, there were 81 *C. difficile* carriers with an incidence of hospital onset CDI of 76.7 cases per 10,000 patient days, while among the remaining 2287 non-carriers, the incidence was 4.6 cases per 10,000 patient days [relative risk (RR) 16.6 95% CI 4.0–69.1] [32].

A meta-analysis evaluating the association between the carriage of toxigenic strains and

Table 1 Studies evaluating the prevalence of CDI among carriers and non-carriers

Study ID; country	Design	Number of screened patients	Patients screened; frequency	Number of carriers	Number of CDI cases in non-carriers	Number of CDI cases in carriers	Study years
Meltzer 2018; Israel	Prospective	2368	Admitted; single screen	81	4.6/10,000 patient days	76.7 cases/ 10,000 patient days	2017
Baron 2019; USA	Prospective	220	Sample of admitted patients	21	4/199 (2%)	8/21 (38.1%)	2017–2018
Worley 2021;USA	Prospective	1897	Intensive care unit patients upon admission and weekly thereafter	140	20/1757 (1.1%)	5/140 (3.6%)[a]	Not described
Blixt 2017; Denmark	Prospective	3565	All patients admitted to medical wards	213	80/3340 (2.4%)	23/225 (10.2%) Adjusted OR[b] (95% CI) 3.92 (2.36–6.51)	2012–2013
Curry 2023; USA	Prospective	4498	A convenience sample of hospital and long-term care facility residents on admission	319	58/4179 (1.4%)	39/219 (12.2%)	2016–2018

CDI Clostridioides difficile infection, *OR* odd ratio, *CI* confidence interval

[a]In this study, 32% were carriers of non-toxigenic strains

[b]Adjusted to the number of admittances during the study period, age, hospitalization in the last year, sex, length of stay, and comorbidities

CDI has demonstrated an almost six times higher risk for carriers [26].

THE ROLE OF SCREENING OF ASYMPTOMATIC CARRIERS IN THE PREDICTING CDI

Otles et al. evaluated *C. difficile* screening as a predictor of hospital-onset CDI. Screening 1859 patients admitted to intensive care unit (ICU) and oncology wards, the negative predictive value (NPV) of a negative screen was high (98.5%); however, the positive predictive value (PPV) was low (9%). Nine patients out of 39 who developed CDI were detected by screening. The authors compared this prediction ability to a daily risk estimate produced by a machine-learning model. The latter had a similar NPV with a lower PPV. The model identified different patients from those identified by screening who later developed CDI. This suggests a potential advantage of a machine-learning model because screening cannot identify at-risk patients who are not already colonized [41].

TARGETED ANTIBIOTIC STEWARDSHIP FOR *C. DIFFICILE* CARRIERS

Antimicrobial stewardship programs (ASPs) have successfully reduced CDI rates by decreasing inappropriate antimicrobial use [42–44]. Some antibiotics have been known to increase the risk of CDI [45], yet information regarding the association between specific antibiotic usage and loss or acquisition of *C. difficile* carriage is sparse—one study found that cephalosporin use was associated with the acquisition of *C. difficile* colonization while β-lactam-β-lactamase inhibitor combinations and metronidazole were associated with loss of colonization [30]. An additional study has found that piperacillin–tazobactam usage was associated with decreased rates of *C. difficile* carriage [46]. Nevertheless, these data are sparse, and the common knowledge is to avoid any antibiotics among carriers as much as possible.

Poirier et al. evaluated predictors of hospital-onset CDI among 513 asymptomatic carriers identified by active screening. Of these, 39 developed CDI, with exposure to multiple antibiotics and other factors, such as increased length of stay, cirrhosis, and opioids identified as predictors [47].

Since asymptomatic patients are not widely screened for CD carriage, ASPs targeted at this population have not been studied [43]. Patients with prior CDI, an easily identifiable subset of asymptomatic carriers, may represent suitable targets for focused stewardship efforts, as they are at the highest risk of developing infection [48]. One study showed a threefold increase in CDI recurrence in patients exposed to non-CDI antimicrobials after resolved CDI compared to those not exposed, regardless of the duration of treatment. However, any treatment with other antibiotics while receiving anti-CDI antibiotics was not associated with recurrent CDI [48]. After implementing an intervention to detect and isolate *C. difficile* carriers at hospital admission, anti-*C. difficile* antibiotic use was significantly decreased, although there was a small but significant increase in the global use of other antimicrobials [21].

Targeting antibiotic stewardship efforts towards CD carriers, especially those with a history of CDI, could help reduce CDI and the inappropriate use of antimicrobials.

C. DIFFICILE SHEDDING FROM CARRIERS

Carrier shedding of *C. difficile* spores is an essential factor contributing to the persistence and transmission of this bacterium. Both index patient skin and the patient's environment have been reported to be contaminated by spores, posing a risk for healthcare-associated transmission [7, 49]. The frequency of environmental contamination with *C. difficile* depends on the patient's *C. difficile* status (i.e., carriage or clinical CDI). A study by McFarland et al. found that fewer than 8% of rooms of culture-negative patients, 8–30% of rooms of patients with asymptomatic colonization, and 9–50% of

rooms of patients with CDI were contaminated with *C. difficile* [50]. Moreover, we have reported in a prospective observational study that environmental shedding of toxigenic *C. difficile* by asymptomatic carriers is relatively frequent. The study found that 41% of rooms inhabited by *C. difficile* carriers had more than residual contamination, and 24% were heavily contaminated. In contrast, only one room (6%) in the control group of non-CD carriers had more than residual contamination, and none were heavily contaminated [51].

THE ROLE OF ASYMPTOMATIC CARRIERS IN THE TRANSMISSION OF *C. DIFFICILE* AND CDI DEVELOPMENT

According to several studies, asymptomatic carriers of *C. difficile* play a significant role in the transmission of the bacteria. Studies using multilocus sequence typing demonstrated that only 25–55% of patients with symptomatic CDI could be linked to a previously identified CDI patient, suggesting additional pathways for transmission besides active CDI patients, such as *C. difficile* carriers [52–54].

Blixt et al. found that 2.6% of patients who were not exposed to *C. difficile*-colonized patients developed CDI, while this percentage increased to 4.6% for patients who were exposed [38]. Integrated genomic and epidemiologic analyses have identified multiple potential transmission events from asymptomatic carriers to other patients [22]. Moreover, a model of *C. difficile* transmission in healthcare settings confirmed that patients colonized on admission likely play a significant role in sustaining ward-based transmission [55]. Donskey et al., using genomic and epidemiological data, showed that carriers linked to a transmission had a high burden of carriage and high skin and environment shedding [7]. In a large multicenter Canadian study using whole genome sequencing, 81 (40%) of 201 CDI cases could be linked to another case in the ward, 65 (32%) of them could be linked either to a carrier or an active CDI patient, 28 (14%) could be exclusively linked to an active CDI patient, and only 12 (6%) could be solely linked to a carrier [56]. Crobach et al. [57] conducted a multicenter study, screening 2211 patients for *C. difficile* carriage and finding 49 patients to be colonized. The team used whole genome sequencing to analyze *C. difficile* from 183 CDI episodes that took place in the participating hospitals throughout the study period. Their analysis revealed that only one CDI case could potentially have resulted from transmission from a colonized patient. This study was conducted in the Netherlands, which has the lowest antibiotic consumption rate in Europe.

While it remains unknown what proportion of symptomatic infection results from transmission from asymptomatic carriers, research indicates that this does occur. And though transmission events from asymptomatic carriers might be rare, the high prevalence of asymptomatic carriage suggests that they might significantly transmit *C. difficile* in the hospital setting and long-term care facilities [7, 27].

THE ROLE OF SCREENING OF ASYMPTOMATIC CARRIERS IN PREVENTING HOSPITAL-ACQUIRED (HA) CDI

Screening policies have been suggested as an effective way to prevent *C. difficile* outbreaks in healthcare facilities [58, 59]. Theoretically, the identification of asymptomatic carriers can reduce the spread of *C. difficile* through two mechanisms: first, isolation of carriers can reduce transmission to uninfected patients, and second, antibiotic stewardship interventions targeting carriers can potentially prevent progression to symptomatic *C. difficile* [6].

Mathematical modeling of *C. difficile* transmission and simulation of screening and isolation of carriers have shown the intervention required to effectively reduce CDI rates [60–63]. This intervention was also highly cost-effective, with estimates ranging between 128 and 310$ per quality-adjusted life year, or even less if screening was targeted to high-risk populations;

Table 2 Studies evaluating *C. difficile* screening

Study ID; country	Design	Number of screened patients	Patients screened; frequency	Number of carriers	Action taken for carriers	Primary outcome	Summary of primary outcome results	Study years
Before-after studies evaluating screening effect on CDI rate								
Longtin 2016; Canada	Controlled quasi-experimental; time series analysis	7599	All admitted; admission only	368	Isolation[a]	Incidence of HA-CDI	Decrease of 7% of HA-CDI per 4-week period (rate ratio, 0.93; 95% CI, 0.87–0.99 per period; $p = 0.02$)	2013–2015
Xiao 2018; Canada (substudy of Longtin 2016)	Retrospective time series analysis	806,357 patient-days	All admitted; admission only	Isolation of CDI until symptom resolution: 3636 isolation-days Isolation of CDI until discharge: 6704 isolation-days Isolation of CDI + CD carriers until discharge: 10,115 isolation-days	Isolation[a]	Total isolation-days	12.9 / 26.2 / 37.8 isolation-days/1000 patient-days; 66% increase Isolation-days for CDI 11% lower (0.723–1.09)	2008–2016

Table 2 continued

Study ID; country	Design	Number of screened patients	Patients screened; frequency	Number of carriers	Action taken for carriers	Primary outcome	Summary of primary outcome results	Study years
Paquet-Bolduc 2018; Canada	Prospective – compared historical control periods	114	All in outbreak wards; single round screening on outbreak detection	15 (13%)	Isolation[a]	Incidence of HA-CDI Outbreak duration	2 CDI (13%) of carriers; no difference in total CDI compared historical controls (median 7.0 vs 7.5 cases, $p = 0.99$) No difference in outbreak duration (median, 26.5 vs 34 days, $p = 0.72$)	2011–2016
Linsenmeyer 2018; USA	Prospective before-after	1250 screened, 773 evaluated	Surgical wards and surgical ICU during outbreak; single screen on admission	24 (3.1%)	Contact isolation as for CDI	Incidence of HA-CDI	Before–after intervention decrease in HA-CDI incidence per 10,000 bed days from 10.9 to 3.0	2016–2017
Peterson 2020; USA	Prospective before–after	63,057 admissions before, 62,760 after	Targeted screen: hospitalized within two months, past positive CD test, long-term care facility in the prior six months	NS	Contact isolation as for CDI	Incidence of HO-CDI	5.96–4.23 cases/10,000 patient days; 2.9 in final 9 months	2017–2018

Table 2 continued

Study ID; country	Design	Number of screened patients	Patients screened; frequency	Number of carriers	Action taken for carriers	Primary outcome	Summary of primary outcome results	Study years
Collison 2020; USA	Prospective compared historical control periods	47,048	All admitted to adult inpatient units	2010	Contact isolation as for CDI	Incidence of lab identified *C. difficile* events	13.3 cases/10,000 patient days before intervention decreases to 5.0 cases/10,000 patient days after intervention	2015–2018
Cho 2018; USA	Prospective before–after	470	HSCT unit admitted; single screen of stool sample	70	Contact isolation	Incidence of HO-CDI	35 (50%) developed diarrhea and treated as CDI without testing HO-CDI rate in the HSCT unit decreased 72.5 cases/10,000 patient days to 14.4 in periods before and after screening	2009–2013

Table 2 continued

Study ID; country	Design	Number of screened patients	Patients screened; frequency	Number of carriers	Action taken for carriers	Primary outcome	Summary of primary outcome results	Study years
Non clinical studies								
Reagan 2023; USA	Non-clinical study mathematical model	Non-clinical	Bone-marrow unit; model for active detection and isolation (ADI)	NA	NA	Predicted CDI rates using ADI compared to testing symptomatic patients	24.5% decrease in total cases with ADI (6.2 cases per year) 84% decrease in HA-CDI with ADI	2014–2019

CDI Clostridioides difficile infection, *HA-CDI* health care–associated *Clostridioides difficile* infection, *HO-CDI* hospital-onset *Clostridioides difficile* infection, *HSCT* hematopoietic stem cell transplant, *ICU* intensive care unit

[a]Isolation was modified not to include the use of gowns, no private room, and no contact isolation needed on transportation

under some conditions, screening might lead to cost savings per case averted [64–66].

Real-life data assessing the effectiveness of carrier screening in reducing hospital-acquired CDI are sparse. Relevant studies are summarized in Table 2. Longtin et al. implemented a *C. difficile* carriage screening policy, along with contact isolation precautions for carriers during hospitalization, and found a significant decrease in CDI cases following the intervention. The authors estimated that the intervention could prevent ~ 60% of expected cases of healthcare-associated CDI [21]. A follow-up study from the same group showed that isolating CD carriers led to an initial increase in isolation days that was later compensated by a decrease in isolation days for CDI [67]. Cho et al. implemented universal *C. dificile* screening for all patients hospitalized in a hematopoietic stem cell transplantation unit; this intervention decreased the rate of hospital-acquired *C. dificile* from 72.5/10,000 patients days before the intervention to 14.4/10,000 patient days during the intervention period [68]. Collison et al. implemented universal inpatient *C. dificile* screening at an 800-bed hospital in Chicago, and the number of confirmed CDI events decreased from 13.3 events per 10,000 patient days, the year before the intervention, to 5.0 per 10,000 patient days for the 1 year after the study period [24].

The effectiveness of screening in an outbreak setting is not conclusive, and, while a study conducted during an outbreak in a surgical ward in Boston showed that ward-based screening of all newly admitted patients and isolation of carriers averted 5 out of 10 expected hospital-acquired CDI [69], a different study that implemented a one-time unit-wide screening during CDI outbreaks and modified contact precautions for the carriers was ineffective in decreasing the number of CDI cases or the outbreak duration. In this study, unscreened patients admitted after the unit-wide screening event were probably the outbreak's source [39].

Peterson et al. performed a non-randomized stepped-wedge initiative, during which patients previously identified as at high risk for *C. difficile* carriage (had a recent previous

hospitalization, previous positive C. difficile test, or patients arriving from long-term care facilities) were screened for *C. difficile*. Those testing positive were placed into contact isolation. In this study, among 63,057 patients in the pre-intervention period, hospital-onset CDI incidence was 6 cases per 100,000 patient-days (PD), compared with 4/100,000 PD among 62,760 patients admitted during the screening period ($p = 0.02$). No other changes in practice or antibiotic use were reported [70].

Differences in intervention protocols may account for the variations in screening intervention results. Studies differ by the population screened (targeted high-risk population [68, 70] or universal screening [21, 24, 69]), timing of screening (single whole-ward screening [39] or screening of every new patient admitted [21, 24]), analysis of recurrent admissions (repeated admissions for the same patient included or excluded [69]), screening methods (rectal swab [21, 67] or stool sample [57, 68]); and setting (outbreak [39, 69] or endemic [21, 67, 68, 70]), as well as the contact isolation precautions implemented (modified contact isolation precautions including gloves, handwashing with soap and water and dedicated equipment [21, 39, 67] or traditional contact isolation precautions as used for active CDI patients, including gowns and single room or cohorting [24, 69, 70]).

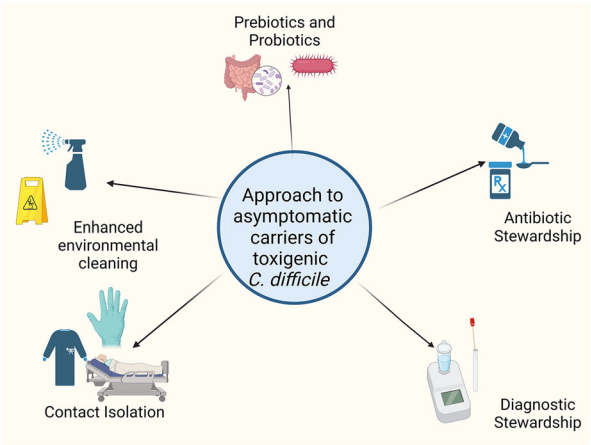

Fig. 2 Adopting a multimodal strategy for asymptomatic carriers of *C. difficile*: when strategizing a screening intervention for asymptomatic toxigenic *C. difficile* carriers, a comprehensive multimodal approach should be deployed. Each element—including contact isolation procedures, enhanced environmental cleaning, antibiotic stewardship, diagnostic stewardship, as well as prebiotic and probiotic treatments—represents a potential intervention point or an aspect that necessitates staff education

These studies cited above [21, 39, 67, 69, 70] were conducted in North America from 2008 to 2019, coinciding with the period of dominance of the 027/BI/NAP1 *C. difficile* strain in hospital outbreaks, particularly in North America [71]. Only one study [21] addressed this issue, in which the rate of the 027/BI/NAP1 strain varied throughout the different periods of follow-up, ranging between 59.2% at the beginning of follow-up to 20% near the end of the follow-up period. A sensitivity analysis that excluded the epidemic period showed similar results as the original analysis. In a study originating from the Netherlands [57], the focus was not on screening's utility for CDI prevention but rather on the onward transmission from carriers. Despite identifying 49 carriers, only a single potential case of onward transmission was reported in a European context where the 027/BI/NAP1 strain was absent. This suggests that the effectiveness of such interventions may be limited to regions with a high prevalence of endemic strains. Another possible explanation for this low onward transmission could be the specific antibiotic prescribing practices, that vary between different countries, and that are more constrictive in the Netherlands compared to North America [72].

Carrier screening remains an uncommonly used strategy; a survey among infection prevention specialists in different medical centers across the US found that only 4% of respondents indicated testing patients for asymptomatic carriage of *C. difficile*. Of those who reported testing patients to detect asymptomatic carriers, most reserved this policy for patients admitted to select units such as intensive care and oncology/hematopoietic cell transplant units. After detecting asymptomatic carriage of *C. difficile*, healthcare facilities most commonly implemented contact precautions, followed by enhanced environmental cleaning [73].

SUMMARY AND DISCUSSION

CDI significantly burdens the healthcare system, resulting in considerable morbidity and mortality. Carriers of *C. difficile* probably play a role in spreading the disease through environmental shedding. Carriers of a toxigenic strain are also at higher risk of evolving into active CDI, particularly after antibiotic treatment. Screening for asymptomatic carriers could potentially reduce the incidence of CDI through improved isolation, contact precautions, and antibiotic stewardship. Most studies evaluating this strategy reported reductions in CDI rates. Nevertheless, the number of studies evaluating screening are limited, all relevant studies are observational, and the intervention applied following positive screen test differs in different studies. Moreover, practically, this strategy is not commonly practiced.

It is worth noting a limitation highlighted by Collison et al., but overlooked in other studies: providers might opt for empirical CDI treatment in carriers presenting with diarrhea. These instances might not have been correctly categorized as CDI events, possibly accounting for some of the observed decrease in CDI events following the introduction of universal screening [24].

When assessing the effectiveness of screening strategies, one must also consider their drawbacks. While the cost of screening can be substantial, a comparison with the reduced expenses from preventing CDI cases could render it cost-effective [55, 64, 66]. However, aside from financial costs, there may be additional consequences. For instance, a study revealed that 15% of carriers (9/58) among solid organ transplant recipients received unnecessary oral vancomycin treatment due to misinterpreting carriage results as active infection, leading to unwarranted antibiotic therapy [74]. Additionally, the enforcement of isolation precautions has been linked to an increased risk of adverse events, including prolonged hospital stays, elevated readmission rates, medication errors, and injuries [75, 76] It can also negatively affect patients' perception of care and satisfaction [77].

The optimal approach following positive screening for *C. difficile* is yet to be determined. Consideration should include type of isolation and contact precautions, duration of these measures, strategy for environmental cleaning, use of pre and/or probiotics, strategy of antibiotic stewardship, and definitions for CDI diagnosis in the presence of a positive screening (Fig. 2) In addition, screening strategies should also be more accurately defined, emphasizing the importance of screening specifically for toxigenic strains, as these are the ones posing risk for CDI.

Innovative methods for preventing CDI are emerging. Prior studies have shown that probiotics and prebiotics can be effective in preventing CDI, particularly in high-risk groups [78, 79]. Specifically, certain bacteria like *Bacillus clausii* and *Lactobacillus reuteri* are of interest because they produce substances that directly inhibit *C. difficile* [80, 81]. Other beneficial bacteria, such as *Clostridium scindens*, create secondary bile acids that increase resistance to *C. difficile* [82]. Moreover, non-toxigenic *C. difficile* can also help by competing for resources, reducing the opportunity for harmful strains to proliferate. A previous randomized controlled trial has shown that administration of non-toxigenic *C. difficle* spores can prevent recurrent CDI episodes [83]. Carriers of toxigenic *C. difficile* pose ideal candidates for such interventions due their high risk of contracting active infection.

Additional research is necessary to thoroughly evaluate the effectiveness of *C. difficile* screening in decreasing the burden of CDI. It is clear that any such screening intervention should constitute a multimodal effort. This includes not only enhanced contact precautions and cleaning procedures in these cases but also comprehensive staff education on screening implications for antibiotic selection and diagnostic stewardship for *C. difficile* testing. Moreover, healthcare-associated CDI definitions should be adjusted to encompass carriers who develop diarrhea as a distinct identity, recognizing the intricacies of this condition. Further research should assess the cost–benefit of these interventions..

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