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Clostridioides difficile–Associated Diarrhea: Infection Prevention Unknowns and Evolving Risk Reduction Strategies

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Abstract

Purpose of Review New controversies in the diagnosis and prevention of *Clostridiodes difficile* are challenging and at times changing infection control practice at many medical centers.

Recent Findings Molecular epidemiologic studies are changing our understanding of *C. difficile* and its spectrum of disease. *C. difficile* as a hospital-acquired infection is likely largely overdiagnosed given overly sensitive molecular testing and widespread colonization of ill or debilitated patients.

Summary *Clostridiodes difficile* infection continues to challenge infection prevention programs. Shifts in our understanding of the epidemiology of this organism and its spectrum of clinical presentations are changing the approach to prevention efforts. Nevertheless, cleanliness of the healthcare environment and antimicrobial stewardship remain core risk reduction strategies. Other strategies such as screening and isolation are inciting controversy. The optimal infection prevention strategies for *C. difficile* remain the subject of intense study and debate.

Keywords *Clostridiodes difficile* · *C. difficile* · Antibiotic stewardship · Diagnostic stewardship · Infection prevention

Background

Clostridioides difficile (*C. difficile*) impacts all areas of the healthcare delivery system and has extended into the community setting [1••]. As a rod-shaped, spore-forming, gram-positive organism, *C. difficile*, first identified and associated with antibiotic-resistant diarrhea in 1978, causes disease via the release of toxins [2]. The emergence of the B1/NAP1/027 strain coincides with the increase in morbidity and mortality of *C. difficile* infections (CDI) [1••, 3]. *C. difficile* is the most commonly recognized pathogen in infectious diarrhea and has now surpassed methicillin-resistant *Staphylococcus aureus* infections as the leading cause of healthcare-associated infections [2, 3]. Clinical presentation of *C. difficile* can range from asymptomatic colonization, mild to severe diarrhea, to pseudomembranous colitis, toxic megacolon, sepsis, and death [3].

The burden of *C. difficile* in the USA is estimated to be near 500,000 infections annually, causing 15,000–30,000 deaths per year, and with attributable acute care costs annually exceeding $4.8 billion [1••]. Community, convalescent, and long-term care reporting mechanisms are not as robust as acute care settings; thus, the actual incidence of CDI likely surpasses these estimates. Historically, CDI was associated with hospitalized patients that received antibiotics and were predominantly over age 65. It is now estimated that 40–50% of CDI cases are community acquired; these patients are younger, have fewer comorbidities, and may lack hospitalization and antibiotic exposures [2, 4].

Basic Infection Prevention Measures

Evidence-based guidelines exist with prioritized infection prevention measures for *C. difficile* risk reduction [5••]. These include preferential use of soap and water for hand hygiene with elevated rates of *C. difficile* infection, the use of

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sporicidal disinfectants for terminal and daily room cleaning, the use of contact isolation precautions for infected patients, and antibiotic restriction programs to limit the emergence of *C. difficile* in healthcare settings. The duration of contact precautions for *C. difficile*–infected patients and novel diagnostic test stewardship issues remain unresolved guideline items.

Non-touch Environmental Cleaning

Clostridioides difficile persists on surfaces for months, assisted by the ability to produce enduring spores [6]. Environmental cleaning is a core infection prevention strategy and needs to be performed consistently to maintain low levels of organism in environmental reservoirs within healthcare systems. Yet, quality environmental cleaning of hospital spaces is difficult to maintain with high fidelity, as it depends on the human behaviors of environmental services staff (EVS) [7]. Many interventions have been performed in an attempt to improve manual cleaning with success, albeit at a cost of high time investment and non-durable results without ongoing efforts [8, 9•, 10, 11]. Furthermore, spores are resistant to some disinfectants and may require extended contact time with sporicidal agents to ensure killing of spores [12].

Non-touch cleaning technologies claim to provide enhanced cleaning that is superior to manual cleaning alone in bioburden reduction. These devices include UV light–emitting robots and combinations of hydrogen peroxide droplet or aerosol-producing devices to disinfect whole rooms at terminal cleaning or at other times when patients and team members can evacuate the targeted clinical spaces [13]. They have grown in popularity in recent years, as they offer a standardized, automatized solution to cleaning which (apart from deployment) does not depend on human behaviors.

Non-touch devices are designed to kill microbes on environmental surfaces, and thus, not surprisingly, they are generally able to decrease bioburden of organisms on environmental surfaces including hospital rooms [12, 13] and devices [14, 15]. Furthermore, non-touch devices have been effective in aborting outbreaks of *C. difficile* [16, 17]. Outside of outbreak settings, however, evidence of non-touch device ability to decrease hospital-acquired infection is more limited. Most studies are limited by quasi-experimental design and inability to separate non-touch devices from other concurrent infection prevention initiatives [18]. The best study done to date evaluating the ability of UV-emitting devices to reduce acquisition of healthcare-acquired infections is the cluster randomized controlled trial done by Anderson and colleagues [19•] in which all patients admitted to rooms whose previous occupant had *C. difficile*, methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* (VRE), or *Acinetobacter* were followed for acquisition of these organisms after an initial terminal cleaning had been performed by 1 of 4 strategies: standard manual cleaning with a quaternary ammonium, standard + UV, bleach manual cleaning, and bleach + UV [20]. There was a significant difference in acquisition of all HAIs in the groups who had preceding terminal cleaning with UV device. However, this difference was largely driven by VRE, and in fact, there was no difference between the bleach versus bleach plus UV arms for *C. difficile* rooms [19•]. The authors recently completed a secondary analysis looking at hospital-wide infection rates (i.e., beyond their previously defined "at risk" population) [21]. They reported a significant decrease in *C. difficile* infection hospital-wide during the periods when high-risk rooms were cleaned with quaternary ammonium + UVC as opposed to the quaternary ammonium (standard clean) alone. However, there was again no difference between the bleach and bleach + UVC time periods for *C. difficile* acquisitions, in spite of the fact that over 300,000 admissions were included in this analysis [21]. Subsequent studies continue to show mixed results, with generally more favorable results from less robust study designs [18]. A recently published trial of UVC device in a high-risk bone marrow transplant unit was unable to show a difference in acquisitions as measured by serial active surveillance and clinical infection rates for *C. difficile* and VRE; the study used an interrupted time series design and included just over 700 admissions in this high-risk population [20].

Non-touch devices may add adjunctive benefit in decreasing bioburden provided attention to optimizing manual cleaning is not lost. It is important to note that these devices are generally unable to penetrate areas of heavy organic soiling [22, 23], such that the prerequisite manual part of the terminal cleaning is still critically important. In addition, because these devices require both a financial and human resources investment, it is important to ensure the infrastructure for consistent deployment exists in order to optimally capture the rooms which are targeted for enhanced cleaning.

Implementation of No-Touch Technology for Terminal Room Disinfection: from Theory to Practice

Prior to the implementation of no-touch technology for enhanced room disinfection, a comprehensive device utilization, implementation, and evaluation plan must be developed. Key stakeholders including an administration liaison, bed management, environmental services, nursing champions, and infection prevention should be included in this planning process to ensure established goals are realistic, clear, and measurable. Communication between these teams will be a key element in the success of the program.

Determining use of enhanced room disinfection is the first step in the process. The team must decide if enhanced room disinfection includes all rooms at terminal cleaning, only

contact isolation rooms, or rooms that housed targeted organisms like *Clostridioides difficile*. Next, the team to operate and deploy the devices must be established and receive vendor education on the use of the device. The deployment team responsible for conducting the enhanced room disinfection requires a notification process and compliance goal; the team must be rapidly and consistently informed of rooms requiring terminal disinfection with the non-touch device. Individuals or groups responsible for audit and feedback of the compliance data need to be established along with the route of dissemination of information back to the deployment team as well as to their leadership, nursing units, bed management, hospital infection prevention programs, and hospital leadership.

It is critically important that end users have comprehensive training to perform enhanced room disinfection since this can have significant impact on run cycles and patient throughput [24]. Equally important is permitting users of the device sufficient time for enhanced terminal disinfection [24]. It is critical that all involved teams have basic education about the selected device and the rationale for implementation of enhanced terminal room disinfection. The potential role of the environment in the transmission of multidrug-resistant organisms including *C. difficile* should also be a part of the education during the implementation process [25]. Ensuring that staff understand the program as an important patient safety initiative can help drive compliance.

The Role of Antimicrobial Stewardship

Antimicrobial use is a known risk factor for the development of *Clostridioides difficile* infection (CDI), and antimicrobial stewardship (AS) has been identified as a key strategy for reducing CDI. The Infectious Diseases Society of America (IDSA) recommends to "minimize the frequency and duration of high-risk antibiotic therapy and the number of antibiotic agents prescribed." Furthermore, recommendations include that "antibiotics to be targeted should be based on the local epidemiology and the *C. difficile* strains present. Restriction of fluoroquinolones, clindamycin and cephalosporins (except for surgical antibiotic prophylaxis) should be considered [1••]."

Antibiotic restriction is one of the core strategies used in the setting of CDI outbreaks [1]. Numerous quasi-experimental studies have been published on the use of AS strategies in preventing CDI, with targeted antimicrobials often focused on culprit agents in outbreak settings. Antimicrobials targeted in studies have included, but are not limited to, fluoroquinolones, cephalosporins, clindamycin, aminopenicillins, penicillin-β-lactamase inhibitor combination drugs, carbapenems, and aztreonam. AS strategies have been successful in reducing targeted antimicrobial use and have been associated with CDI incidence rate reductions of 33 to > 90%. Importantly, receiving multiple antimicrobials and longer durations of antimicrobial treatment have also been associated with CDI risk [1••].

Fluoroquinolones in particular have been associated with outbreaks with the NAP1/BI/027 strain of *C. difficile* [26, 27]. Epidemic spread of this hypervirulent strain has been associated with fluoroquinolone resistance [28]. A study from England identified fluoroquinolone use as a primary driver of CDI [28]. Utilizing whole gene sequencing from more than 4000 *C. difficile* isolates as well as CDI incidence and antimicrobial prescribing data from 1998 to 2014, these authors were able to conclude that CDI reduction was mainly due to fluoroquinolone restriction over the period studied (over infection prevention measures) [28].

Clindamycin has also been associated with CDI outbreaks with restriction leading to reductions in CDI incidence [29, 30]. Similarly, third- and fourth-generation cephalosporins have also been associated with CDI risk [31–33]. However, numerous other antimicrobials, including carbapenems, have been implicated in CDI risk, as well [1••, 34, 35].

Although the IDSA guidelines make special mention of fluoroquinolones, clindamycin, and cephalosporins, it is not clear what the potential collateral damage of restricting these agents (in isolation) might be on the development of gram-negative resistance for other antimicrobial classes. For example, if cefepime restriction leads to increased carbapenem use this might generate more carbapenem resistance locally. Antimicrobial stewardship programs should monitor local antibiotic use and resistance patterns closely, especially after initiating major new restriction campaigns.

Arguably, and in the context of recent FDA warnings regarding fluoroquinolone use [36], reducing suboptimal fluoroquinolone use should be a target of all AS programs. However, the most efficient and effective AS strategies to achieve this by healthcare setting need to be defined. Preauthorization and post-antibiotic order review with provider feedback can both be time consuming and take resources away from other AS activities. Lab-based strategies such as selective and cascade reporting may offer a creative solution for programs with limited resources. Selective reporting allows for the suppression of susceptibility reporting for targeted antimicrobials based on culture source. For instance, fluoroquinolone reporting might be restricted for all non-blood isolates in a given hospital setting. The use of selective reporting can lead to significant reductions in target antimicrobial use [37].

Since the majority of studies on the impact of AS on CDI have been performed in outbreak settings, more data are needed on optimal AS strategies for CDI risk reduction in non-outbreak settings, including in non-hospital settings. Additionally, more data are needed on the CDI risk reduction impact of real-world AS strategies that target a wide-range of suboptimal antibiotic use. Since the use of multiple antibiotics and increased antibiotic use duration have both been

associated with CDI development, AS strategies designed to curb all inappropriate antibiotic use likely will impact CDI risk, although the extent to which this is true is uncertain. Extrapolating from the infection prevention literature, "vertical" strategies that target a single antimicrobial class or organism will likely have less of an overall impact than "horizontal" strategies that focus on interventions that can affect a wide range of antimicrobial use or organisms. At this point, it is not clear what the most optimal outcome measures (including CDI rates) for AS programs are and to what degree AS resources should be committed towards any one outcome target. Opportunity costs related to targeting single organisms and potential collateral damage from focused antibiotic restriction efforts are real concerns as well. More research on optimal, real-world AS strategies for CDI reduction is needed.

Diagnostic Stewardship

Diagnosis of *C. difficile* infection is problematic as asymptomatic colonization is frequent, particularly among hospitalized patients. It is estimated that approximately 4–15% of patients are colonized with *C. difficile* upon admission [38•]. There has been a shift in recent decades away from immune-based testing and towards molecular or nucleic acid amplification testing (NAAT) in laboratories across the USA [39]. Many NAAT platforms are fully automated and designed for high throughput testing, making reversion back to non-molecular testing problematic for laboratories. Nevertheless, there is a growing awareness among healthcare centers that *C. difficile* rates may be directly proportional to the number of tests sent, given that a set proportion of inpatients will inevitably test positive from chronic colonization, whether they have true *C. difficile* infection or not. This "missing denominator" of testing volume is not currently captured in any quality metrics, and thus, many centers are now focusing on diagnostic stewardship, in order to limit inappropriate or unnecessary testing and reduce *C. difficile* reported rates.

Diagnostic test stewardship is defined as "coordinated systems or user-based interventions designed to promote evidence-based utilization of diagnostic tests, with the primary goals of improving value and care quality and safely reducing cost [40]." This strategy acknowledges that real harms may come to patients erroneously diagnosed with *C. difficile* when in fact they are only colonized. The potential harms come in the form of unnecessary contact isolation, exposure to unneeded antibiotics, and diversion of attention from true clinical disease. Contact isolation has been associated with less frequent provider visits, delays in patient access to testing and procedures, and patient psychological distress [41]. The very antibiotics we use to treat *C. difficile* are themselves disruptive to the gut microbiome and may increase patient risk for CDI in the future [42, 43]. Thus, it is important from a clinical perspective to distinguish patients with true CDI from those who are colonized.

Healthcare centers are developing algorithms for appropriate testing [44], providing staff education, and creating electronic medical record–based decision support in order to assist providers in sending only tests that are clinically indicated (Table 1) [45–49]. Other centers have reverted to non-molecular test methods or multistep testing algorithms in hopes of obtaining results that are more specific to *C. difficile* disease. For example, a two-step testing algorithm, in which toxin A/B immunoassay (EIA)/glutamate dehydrogenase antigen (GDH) combination testing is followed by PCR only for discrepant EIA/GDH results, is reported to have sensitivities rivaling NAAT [44]. Yet, sensitivity may be superior in that only those samples producing discordant results by the initial combination test will go on to molecular testing [50].

Table 1 Successful interventions to restrict provider ordering

Citation	Intervention	Outcome	Safety Assessment
Truong et al. [45]	Lab rejection of stools if patient on laxative or w/o documentation 3+	Decrease testing volume and in HO CDI incidence 13.0 to 9.7/10,000 patient days ($p < 0.0008$)	No difference in outcomes between those with canceled and negative tests
Yen et al. [46]	Lab rejection of stools if non-liquid or if > 24 h from order placement	Decrease in testing volume and in HO CDI incidence by 60%	No severe CDI outcomes in positive patients during the intervention period
White et al. [47]	EMR decision support alerting providers to recent laxative receipt	Decrease in testing, HO CDI incidence not reported	No difference in severe CDI outcomes in patients before and after the intervention
Nicholson et al. [48]	EMR decision support with criteria for *C. difficile* testing in infants and children as well as formal provider education	Decrease in testing, HO CDI incidence not reported	No serious CDI outcomes in patients testing positive
Madden et al. [49]	EMR decision support and financial incentive for providers	Decrease in testing, 31% decrease in HO CDI	Not addressed

Diagnostic stewardship is distinct from "gaming" efforts in that appropriate testing of patients with clinical signs and symptoms of CDI is encouraged. Nevertheless, the line between stewardship and "gaming" could become blurred, especially with financial incentives tied to hospitals who achieve low *C. difficile* rates. There have been concerns that adopting less sensitive testing or limiting testing could be causing patient harm. Some interventions to decrease testing not meeting specific clinical criteria have explored the issue of safety by comparing the patients with canceled tests to those with negative tests; outcomes including mortality, length of stay, ICU stay, and toxic megacolon/colectomy do not appear to differ between these two groups [51], suggesting that the canceled tests did not result in patient harm.

Similarly, existing data suggests that less sensitive testing methods may be safe in distinguishing clinically relevant *C. difficile* disease from other clinical scenarios that do not require treatment. Experiments have been performed in which multiple tests including a NAAT were performed for the same patient, but only the non-molecular testing results were reported to providers; patients with negative EIA or GDH but with positive molecular testing do not have poor outcomes despite not receiving *C. difficile*–directed therapy [50, 51]. This same observation may hold true even for those patients in this discordant result group who have some clinical evidence of infection [52], as Zou et al. [52] recently described outcomes of their cohort of "indeterminate" EIA negative/PCR positive patients. While 54% of these patients were deemed to have clinically relevant infection by chart review, outcomes between those groups did not differ at 8 weeks despite only 8 of the 110 patients receiving *C. difficile* treatment [52].

More work is needed to determine the clinical and diagnostic testing profiles of patients with clinically relevant CDI who would most benefit from antibiotic and other therapies. Yet, existing data support that the healthcare community is likely overdiagnosing this common healthcare-associated infection, to the determinant of both healthcare institutions and their patients.

Patient Screening and Isolation Strategies and Controversies

In a prospective study of *C. difficile* carriage performed at a tertiary care medical center, 3.1% of screened patients were colonized with toxigenic *C.difficile* on admission [53]. Both colonization with toxigenic strains and colonization during hospitalization significantly increased the relative risk of *C. difficile* infection [53]. Similarly, in a bone marrow transplant population, investigators reported decreases in *C. difficile* transmission by PCR screening and isolating patients with *C. difficile* colonization [54].

Recent reports suggest that screening for *C. difficile* colonization on hospital admission may impact transmission in healthcare settings. Longtin et al. [55] reported the impact of PCR rectal screening on admission for *C. difficile* colonization in a quasi-experimental study [55]. Patients colonized with *C. difficile* were placed on contact precautions. The authors estimated that the active detection and isolation strategy for *C. difficile* resulted in a 64% reduction in expected cases [55]. Utilizing a mathematical modeling analysis that incorporated screening and contact precautions for asymptomatic carriers in a general medical hospital ward, Lanzas and Dubberke [56] estimated that active detection and isolation of *C. difficile* carriers could reduce hospital-acquired colonization by 40–50% and incident cases by 10–25% [56].

Enthusiasm for active detection and isolation strategies for *C. difficile* infection prevention are counterbalanced by the findings of a prospective, observational study across 451 patients in a Swiss hospital [57]. Widmer and colleagues [57] observed the transmission of *C. difficile* over a 10-year period without the employment of contact precautions for patients not infected with hypervirulent, toxigenic strains. Patients having contact with index cases were screened for *C. difficile* carriage and toxigenic *C. difficile* status. Four hundred fifty-one contacts were paired with 279 index cases with a resultant low transmission of 1.3% [57]. In addition, recent data using whole genome sequencing challenges the paradigm of hospital transmission of *C. difficile*. Over a 3-year period, analysis of *C. difficile* strains by whole genome sequencing in the UK revealed that 45% of acute cases were genetically distinct and not cross transmitted within the hospital setting [58••]. Further, the authors concluded that diverse reservoirs, both community and hospital acquired, are the probable drivers of ongoing *C. difficile* transmission [58••].

Ongoing questions remain about the optimal use of contact precautions for the prevention of *C. difficile*. Further controversy exists regarding when to discontinue contact precautions for *C. difficile*–infected or colonized patients. A recent expert guidance statement was published by the Society for Healthcare Epidemiology of America on the duration of contact precautions for various pathogens [59]. *C. difficile*–infected (CDI) patients should remain in contact for at least 48 h after resolution of diarrhea. In addition, consideration should be given to extending contact precautions through the duration of hospitalization if elevated rates of *C. difficile* infection are present. Insufficient evidence remains for a formal recommendation on isolating patients readmitted with prior history of infection.

Towards a Horizontal Infection Prevention Strategy for *C. difficile* Control

Optimal *C. difficile* infection prevention strategies are yet to be defined (Table 2). Infection prevention strategies should be

Table 2 Summary of *C. difficile* infection prevention unknowns and evolving risk reduction strategies

Intervention	Known facts	Unknowns	Comments
Touchless technologies for terminal room disinfection	No-touch technologies decrease bioburden of epidemiologically important organisms including *C. difficile* from hospital surfaces	Does the decrease in bioburden correspond to meaningful reductions in hospital acquired infections	Requires structured implementation and continued audit and feedback to frontline users
C. difficile test stewardship	Decreases reported in *C. difficile* rates via decreases in testing volume	Potential for patient harm if diagnosis of true disease is delayed or blocked	
Antimicrobial stewardship (AS)	-Antibiotic use is linked to CDI -AS can reduce antibiotic use -Fluoroquinolones as a class are overutilized, have been linked to CDI, and are an attractive target for AS programs	-Which AS strategies will have the largest impact on CDI in any given setting	
Active detection and isolation for *C. difficile*	Reduces new *C. difficile* cases by 10–20% based on modeling data and reduces new colonization by even more	Relative benefit of isolating non-epidemic strains of *C. difficile*	Studies to date have conflicting conclusions; more data is needed in this area
Duration of contact precautions for C. *difficile*	Expert opinion supports that duration should be at least 48 h after resolution of diarrhea	Contact precautions through duration of hospital stay may also be reasonable given that ongoing shedding of the organism can occur, particularly in the setting of high local rates	The decision regarding duration of contact precautions will likely be informed by local resources pending stronger data to inform these decisions

based on local need, best possible evidence, available resources, and feasibility of execution. Recent molecular epidemiologic studies of *C. difficile* in Europe have shown repeatedly that much of the burden of this disease is not associated with the healthcare system contrary to traditional belief [58••, 60]. Adopting a horizontal infection prevention strategy, one in which infection prevention is prioritized on minimizing transmission by the most common means, contact, and emphasis should be on bioburden reduction. This includes ensuring appropriate levels of hand hygiene with soap and water, optimizing terminal and daily room disinfection with sporicidal agents, and isolating infected patients. A robust antimicrobial stewardship program should be in place to minimize antibiotic overuse. In the face of ongoing elevated rates of *C. difficile* infections, reasonable considerations include extending duration of contact precautions (for length of stay), deployment of no touch technologies for terminal room disinfection, implementing test stewardship diagnostic algorithms that limit over testing and minimize false-positive results and active detection, and isolation of colonized patients. Each incremental *C. difficile* prevention strategy should be critically assessed for both benefits and potential harms.

Conclusion

C. difficile remains a hospital-acquired pathogen of epidemiologic significance. Owing to the rising incidence and severity of *C. difficile* infections in modern healthcare settings, strategies are urgently needed to maximize infection risk reduction. Current guidelines support the use of hand hygiene with soap and water, contact isolation precautions, and terminal disinfection with sporicidal agents. Antimicrobial stewardship is employed to reduce antimicrobial use and minimize *C. difficile* infection. As most antimicrobial stewardship interventions in the face of rising *C. difficile* infections were implemented during times of outbreaks, the impact of antimicrobial stewardship measures for the control of endemic *C. difficile* infections remains uncertain. It is also unclear which specific AS interventions will have the greatest impact on CDI in any given healthcare setting. Heightened hospital surface disinfection with novel technologies such as UVC light–emitting robots appears promising but are supported by limited data. Further deployment of touchless UVC cleaning devices requires meticulous deployment and oversight. Overdiagnosis of *C. difficile* with sensitive PCR assays may impact reported *C. difficile* infection rates. Diagnostic test stewardship, through algorithm-based PCR ordering mechanisms, will likely decrease test overuse, yet the potential impact on patient harm remains unknown.

Although contact precautions for *C. difficile*–infected patients remain the standard of care, limited reports suggest that contact isolation minimally impacts transmission within the hospital, particularly for non-hyperendemic strains. Active detection and isolation strategies may decrease healthcare *C. difficile* transmission and, along with extended contact precautions for *C. difficile*–infected patients (duration of hospitalization), remain controversial. Healthcare infection prevention programs may consider all of the above interventions in

the face of rising *C. difficile* infection rates taking into account potential benefits, harms, and local resources.

Compliance with Ethical Standards

Conflict of Interest Kaila Cooper and Michael Stevens declare that they have no conflict of interest.

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