4. *Clostridioides difficile*[a] Infection

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Introduction

Preventing *Clostridioides difficile* infection (CDI) in healthcare settings is an important U.S. public health priority and has led to new research, guidelines, and reporting requirements that have emerged since the last version of this report, *Making Health Care Safer II* (MCHS II). While many of the patient safety practices (PSPs) that help prevent a range of healthcare-associated infections (HAIs) also help to prevent the transmission of CDI (e.g., contact precautions), several CDI-specific practices address the unique risk factors, pathology, and transmission of CDI.

After discussions with the Agency for Healthcare Research and Quality (AHRQ) and the Technical Expert Panel, as well as an indepth review of published guidelines and PSP research, the following CDI-specific PSPs were selected for review in the CDI chapter of this report:

- Antimicrobial Stewardship
- Hand Hygiene
- Environmental Cleaning
- Surveillance
- Testing

We retrieved and screened studies that evaluated these PSPs and were published in English from 2008 onward. Many studies were quasi-experimental with a pre-post design, and most were in hospital settings (although some research was in long-term care facilities [LTCFs]).

The search revealed multiple studies that evaluated outcomes following combined implementation of more than one enhanced prevention strategy. After reviewing the results of our search for the five above PSPs, we decided to include a section on:

- Multicomponent CDI prevention Interventions.

Multicomponent studies show outcomes associated with different combinations of CDI PSPs. They also offer insight into implementation methods, as well as challenges and facilitators of CDI prevention interventions.

Other CDI PSPs such as contact precautions and patient isolation continue to be recommended by experts[1] and were addressed briefly in the last MHCS report. Communication and staff education were also identified in the CDI PSP guidelines and are often important components of the reviewed PSPs (e.g., clinician *education* about revised antimicrobial prescribing guidelines and *communication* of CDI status

[a]During the writing of this report, the Clinical and Laboratory Standards Institute (CLSI) and the CDC transitioned from use of the name *Clostridium difficile* to *Clostridioides difficile*. For the purposes of this report, the names are synonymous.

after testing). Since these are cross-cutting practices and little research focused on these practices and this harm area specifically, they are discussed separately in the cross-cutting chapter of the report.

Background

C. difficile is a contagious bacterium that can cause diarrhea, fever, colitis (an inflammation of the colon), toxic megacolon (a dilated colon that may be accompanied by septic shock), and, in some cases, death. The *C. difficile* bacterium colonizes in the large intestine. In infected patients, toxins produced by the organism cause CDI symptoms, primarily diarrhea and colitis. The most common risk factors for CDI are antimicrobial use, advanced age, hospitalization, and a weakened immune system. *C. difficile* is transmitted through the fecal-oral route and acquisition is most frequently attributed to the healthcare setting.[2,3]

Complications are common in patients age 65 and older and an estimated 1 in 11 patients 65 and older with healthcare-associated CDI dies within 30 days of CDI diagnosis.[4] Patients with a healthy immune response to the organism can be carriers of *C. difficile* (and contagious) but asymptomatic. These patients are considered "colonized" and are at higher risk of developing CDI.[5]

Research on CDI prevention practices has evolved and expanded over the last decade. Therefore, to address *C. difficile* prevention, this report dedicates an entire chapter to CDI PSPs; in the last report, much of the information on HAI PSPs was grouped together, in a more "horizontal" approach to prevention. In addition, the previous report noted the emergence of hypervirulent *C. difficile* strains and briefly discussed research on CDI risk prediction tools. That report noted that CDI PSPs with good supporting evidence were wearing gloves and antimicrobial stewardship. Alternatively, the current review found strong evidence that supports not just contact precautions and antimicrobial stewardship, but also environmental cleaning practices, surveillance, and testing as effective PSPs for preventing CDI.

The research reviewed in this report reflects not only new knowledge, but also new technologies and policies now in widespread use. For example, electronic health records (EHRs) are now commonly used and are valuable for antimicrobial stewardship efforts and CDI surveillance. Research on no-touch decontamination technology has grown in the last 10 years, as has understanding of CDI transmission pathways. Testing methods have also evolved, with Food and Drug Administration (FDA) approval of nucleic acid amplification tests (NAATs) in 2009. There are increased mandates for surveillance of CDI and the standard interim CDI case definitions that the CDC published in 2007 have been revised in recent years.[1,6] Facilities have implemented new automated surveillance systems, and CDI data collection at the national level is now standardized, with the advent of the National Healthcare Safety Network's (NHSN's) LabID Event reporting in 2013.

Importance of Harm Area

CDI is among the most common HAIs, representing roughly 12 percent of all HAIs.[7] According to a recent estimate, approximately half a million incident clinical infections occur (with more than 100,000 in U.S. nursing homes) per year in the United States, with around 30,000 deaths per year as a result of the pathogen.[3,4] The financial cost of CDI is also high; in recent years, CDI has resulted in about $5 billion a year in healthcare costs.[8,9] Costs attributable to primary and recurrent CDI are $24,205 and $10,580 per case, respectively.[10] CDI colonization is also a concern, and two U.S. studies found that around 10 percent of admitted hospital patients were colonized with *C. difficile*.[11,12]

CDI incidence nearly tripled in the first decade of the 21st century,[13] and data from 2010 to 2016 showed CDI rates plateauing. However, after falling short of 2013 reduction goals, the Department of Health and Human Services set a target reduction of 30 percent in hospital-onset CDI from 2015 to 2020.[14] Healthcare-associated CDI has been decreasing slightly, while community-associated (CA) CDI is stable or increasing slightly; according to CDC estimates, in 2015, almost half of CDI cases were CA.[15]

The clinical severity of the infection has also evolved since the last report. Increasingly virulent strains were a concern roughly 10 years ago.[1] However, a 10-year study of a sample of inpatient data found CDI-related mortality rates declined from 2005 to 2014.[16] Other CDI incidence outcomes, including rates of recurrent CDI, have increased.[17] It is notable that healthcare-associated CDI incidence trends differ based on setting, with a greater decline seen in nursing homes versus hospitals and other healthcare facilities.[18]

Reimbursement policies have increasingly mandated and reinforced the reduction of CDI. CDI LabID Event reporting began in January 2013 for all acute care hospitals facilitywide using the NHSN. The Centers for Medicare & Medicaid Services (CMS) Inpatient Quality Reporting program's CDI reporting requirements became mandatory as of January 1, 2013. Since 2017, CDI rates are among the hospital-acquired complications CMS uses to penalize the lowest performing hospitals. Many States also now mandate CDI data submission by hospitals to NHSN as part of State HAI public reporting programs.[19] In the future, participation in surveillance reporting will increase and include a broader spectrum of settings. For example, data from a larger group of LTCFs will be used to establish national benchmarks and track achievement of prevention goals.[20]

PSP Selection

To identify the PSPs for inclusion in this report, we started by reviewing the consensus guidelines for CDI prevention published by government agencies and reputable organizations. From this review, we developed an initial list that was reviewed by AHRQ and the Technical Expert Panel. The focus of this review was to identify practices that combat a prevalent harm in the U.S. healthcare system or a harm that has a high impact (e.g., high mortality). After this review and a narrowing of practices, we conducted a literature search in two databases (CINAHL and MEDLINE) and reviewed resulting abstracts for relevance. As noted, some CDI PSPs (e.g., staff training) spanned multiple harm areas, so they were moved to cross-cutting chapters (and some CDI PSP searches yielded too few articles to warrant a review [e.g., communication, contact precautions]).

Five PSPs had sufficient research in the last 10 years to conduct a review. While screening articles, we found several studies of interventions that included more than one CDI PSP (i.e., multicomponent prevention interventions). Due to the number of studies on multicomponent interventions that included patient outcomes, we decided to include an addendum on this topic.

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4.1 PSP 1: Antimicrobial Stewardship

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This review includes a summary of evidence published from 2008 to 2018 for antimicrobial stewardship[b] as a practice to prevent CDI. After a brief overview of the foundational elements of antimicrobial stewardship programs (ASPs) as recommended by the CDC, this review explains how antimicrobial stewardship is believed to work as a safety practice for preventing CDI and discusses implications of recent policy changes. We examine the evidence for the estimated effect of ASPs on CDI incidence rates, starting with meta-analyses and followed by individual studies in hospitals and LTCFs. We then provide a summary of common ASP components and explores additional implementation and contextual factors, including settings, resources, and provider buy-in. Finally, we discuss research gaps and future directions for ASPs and CDI prevention.

Key Findings

- Most studies showed statistically significant or statistically nonsignificant decreases in facility or ward-level CDI after a period of antimicrobial stewardship.
- The most common ASP interventions are formulary restrictions, audit and feedback, and education.
- In the reviewed studies, significant reductions in CDI were associated with higher baseline CDI rates/outbreaks, ASPs developed specifically to reduce CDI (as opposed to ASPs focused on other clinical and microbiological outcomes), and ASPs that included restrictions of high-risk antimicrobials and/or a preauthorization component.
- Research is needed on the impact of different ASP components, financial costs/savings of ASPs, and ASPs in a variety of healthcare settings.
- ASPs require staffing, technological resources, and provider buy-in.
- In the future, ASPs and ASP research will benefit from improved study design and a regional perspective on CDI prevention.

4.1.1 Practice Description

ASPs are intended to limit and optimize antimicrobial prescribing, reduce the evolution of antibiotic-resistant bacteria, and improve patient outcomes. To meet these goals, the CDC provides the "Summary of Core Elements of Hospital Antibiotic Stewardship Programs." The elements outlined below provide a basic framework of recommendations for hospital settings. (The CDC also provides core elements for nursing homes, outpatient settings, and small and critical access hospitals, and resource-limited settings).[1]

- Leadership Commitment: Dedicating necessary human, financial, and information technology resources.
- Accountability: Appointing a single leader responsible for program outcomes. Experience with successful programs shows that a physician leader is effective.
- Drug Expertise: Appointing a single pharmacist leader responsible for working to improve antibiotic use.
- Action: Implementing at least one recommended action, such as systemic evaluation of ongoing treatment needs after a set period of initial treatment (e.g., "antibiotic time out" after 48 hours).
- Tracking: Monitoring antibiotic prescribing and resistance patterns.
- Reporting: Regularly reporting information on antibiotic use and resistance to doctors, nurses, and relevant staff.
- Education: Educating clinicians about resistance and optimal prescribing.

[b]The term "antibiotic stewardship" is also used in the research; however, increasingly, "antimicrobial stewardship" is the preferred term, as it includes medicines used to treat a broader scope of organisms. In this review, we use the terms synonymously.

These elements are foundational and meant to complement additional ASP guidelines. The CDC notes that no template exists for an ASP, and ASPs can be effective in a variety of settings and under a diverse set of conditions. While the ASPs studied in the papers selected for this report included these foundational elements to varying degrees, they take many different forms based primarily on a particular facility's resources and needs. Frequently, the ASPs were developed and executed by a multidisciplinary team with medical, pharmaceutical, and/or microbiological expertise.

The studied ASPs required tracking and reporting of data (at minimum quantifying antimicrobial use and CDI rates), as well as staff education and outreach. The "Action" element was operationalized through different strategies, the most common of which were patient case reviews, audits of antimicrobial use, restrictions on high-risk antimicrobials, and provider education. The Infectious Diseases Society of America and Society for Healthcare Epidemiology of America (IDSA/SHEA) guidelines[2] recommend minimizing the frequency and duration of high-risk antimicrobials and using local epidemiology to determine which antimicrobials to address in an ASP. The guidelines further state that ASPs should consider reducing/restricting the use of drugs including fluoroquinolones, clindamycin, and cephalosporins.

4.1.2 Antimicrobial Stewardship as a PSP

Antimicrobial exposure is widely considered one of the most significant and modifiable risk factors for CDI. In the last two decades, at the population level, increasing rates of CDI have been linked to increases in antimicrobial prescribing, particularly in older patients.[3] Patients receiving, or having recently received, antimicrobial therapy are more susceptible to colonization or infection with pathogenic bacteria such as *C. difficile* because antimicrobials alter gastrointestinal tract flora, destroying the bacteria that help to protect against *C. difficile.*

The length and type of regimen also impacts CDI risk. Several broad-spectrum antimicrobials have been most strongly linked to CDI,[4] and certain outbreaks appear to be associated with heavy prescribing of particular antimicrobials.[5] Therefore, many CDI ASPs are designed to reduce the use of particular "high-risk" antimicrobials. The CDC found that people receiving high-risk antimicrobials had a three times higher risk of CDI than did people with low-risk or no antibiotic use.[6]

There is increasing urgency about reducing overreliance on antimicrobials).[7] The CDC estimates that between 30 and 50 percent of antimicrobial prescriptions are clinically inappropriate.[8] In 2015, the White House released a National Action Plan that included goals to implement antimicrobial stewardship in healthcare facilities. In 2016, CMS implemented a rule requiring nursing homes and LTCFs to have ASPs to monitor the use of antimicrobial drugs; and in 2017, The Joint Commission began assessing ASPs as part of their accreditation standards. Other countries have similar efforts,[9] and a number of resources are designed to help facilities implement ASPs. We highlight some of these resources later in this section.

4.1.3 Methods

This section describes literature search and review methods specific to the CDI PSPs; general methods will be described in a Methods chapter for the whole report.

The question of interest for this review is: Do ASPs reduce the risk of CDI?

To answer this question, we searched two English language databases (CINAHL, MEDLINE) for papers published from 2008 through 2019 for "*Clostridium difficile*" and other related Medical Subject Heading (MeSH) terms and synonyms, as well as "Antimicrobial Stewardship" or "Antibiotic Stewardship" or "Antibiotic Prescribing Practices." The search string also included all healthcare settings, including "hospitals," "inpatient," "ambulatory care," "long-term care," "nursing homes," "transitional care," and "home health." The search included both "prevention" and "treatment."

The initial search of databases yielded 134 results and 16 papers from other sources. After duplicates were removed, 126 papers were screened for inclusion. From these papers, 43 full-text articles were retrieved. Of those, 17 studies, 3 meta-analyses, and 2 systematic reviews were selected for this review. Reference lists of included articles were also screened to ensure thoroughness. Articles were excluded at each stage if they were not primary studies, systematic reviews, or meta-analyses; treatment variables or outcomes were not relevant; or study design was insufficient. Studies in which antimicrobial stewardship implementation was accompanied by other significant infection control practices (e.g., changes in environmental cleaning) were ruled out for this section and are considered in Section 4.6, Multicomponent CDI Prevention Interventions.

General methods for this report are described in the Methods section of the full report.

For this patient safety practice, a PRISMA flow diagram and evidence table, along with literature-search strategy and search-term details, are included in the report appendixes A through C.

4.1.4 Review of the Evidence

We reviewed the evidence from 3 meta-analyses and 17 individual studies that examined ASPs and CDI. Three meta-analyses found significant decreases in CDI following implementation of ASPs. Six individual studies on CDI outcomes showed statistically significant decreases in CDI following ASP implementation[5, 10-14], 1 showed borderline significance, and 9 showed statistically nonsignificant decreases in CDI following ASP implementation. One additional study reviewed local strategies for determining high-risk antimicrobials.[15] Study designs were generally quasi-experimental (pre-post analyses).

4.1.4.1 Meta-Analyses

Three meta-analyses of ASP studies in hospital settings found that studies collectively show that antimicrobial stewardship is effective in reducing CDI rates.[16-18] Feazel et al. (2014) analyzed studies published between 1997 and 2012 on ASPs in hospitals during non-outbreak situations. When the results of all studies were pooled in a random effects model, ASPs conferred a significant 52 percent risk reduction (pooled risk ratio 0.48; 95% confidence interval [CI], 0.38 to 0.62; $p<0.00001$) on CDI incidence. Of note, geriatric patients had the largest risk reduction for CDI following implementation of an ASP.[16]

Similarly, in their meta-analysis of hospital ASPs in 11 articles going back several decades, Baur et al. (2017) determined that following ASP implementation periods, the incidence of CDI decreased 32 percent (incidence rate 0.68, 95% CI, 0.53 to 0.88; $p=0.0029$).[17] Davey et al. (2017) reviewed seven studies published up to January 2015 on hospital antimicrobial stewardship and CDI. They found a range of CDI rate reductions related to antimicrobial stewardship (median 48.6%, interquartile range 19.2% to 80.7%). They note that across all antimicrobial stewardship studies (including those that measured

impact on other infections), antimicrobial stewardship generally reduced hospital stay and did not appear to impact patient mortality.[18]

4.1.4.2 Studies: Overview

Studies reviewed for this report show that ASPs are usually effective in reducing the use of targeted antibiotics and are often, but not always, associated with decreased CDI rates. In addition, studies that measured clinical outcomes, such as mortality or length of hospital stay, following the implementation of an ASP found that ASPs did not appear to influence the efficacy of a patient's treatment.[5,19] Factors found to be most associated with significant CDI decreases were:

- ASPs in smaller facilities,
- Higher pre-ASP baseline CDI rates (more room to improve),
- ASPs developed specifically to reduce CDI (as opposed to ASPs focused on other clinical and microbiological outcomes), and
- ASPs that included a formulary restriction component.

The majority of the studies on CDI outcomes (13/16) examined ASPs in hospitals or hospital units. The duration of the ASP period ranged from 6 months to a little over 6 years (mean 19.3 months; standard deviation [SD] 16.7). Most studies were quasi-experimental (interrupted time series or before and after design) and lacked a control or comparison group. All included studies measured the amount of prescribed antimicrobials (e.g., defined daily dose, or DDD, as defined by the World Health Organization [WHO], per 1,000 patient days) and CDI rates pre- and post-ASP implementation.

While many of the studies controlled for other contemporaneous prevention initiatives, the study designs may not account for potential covariates and confounders such as previous infection prevention efforts (e.g., hand hygiene, environmental cleaning), patient risk factors, changes in testing method, or seasonal, regional CDI fluctuations. This finding is consistent with the findings of two systematic reviews by Louh and colleagues (2017) and Pitiriga et al. (2017), which both indicated that the diversity in ASPs and weaknesses in study design undermine the strength of the evidence.[20,21]

4.1.4.3 Studies: ASPs With Significant CDI Reductions

Six of the 16 studies on CDI outcomes and ASPs found statistically significant reductions in CDI, using $p<0.05$ as the basis for statistical significance.[5, 10-14] For example, Libertin et al. (2017) studied a new ASP in a rural community hospital with fewer than 100 beds. This ASP included an educational lecture series and the dissemination of clinical guidelines and algorithms on advised antibiotic use for specific infectious disease syndromes. When a provider ordered antimicrobial therapy that used one of 12 targeted antimicrobials, they were allowed to order an initial 72-hour course. Ordering of one of the targeted antimicrobials triggered review by a clinical pharmacist and infectious disease physician, and microbiologic data were given to the provider to aid in antimicrobial selection and de-escalation. The rate of CDIs went from 3.35 cases per 1,000 occupied bed days in 2013 (the year prior to the ASP) to 1.35 cases per 1,000 1 year later ($p<0.001$). Overall antimicrobial use (in DDDs per 1,000 occupied bed days) decreased 10 percent from before the ASP initiative to 1 year after, and annualized antimicrobial savings was $280,000.[10]

Another example of significant reductions in CDI after a period of ASP was at an acute general hospital with over 500 beds in the United Kingdom.[5] This ASP consisted of removal of "high-risk" antibiotics such as fluoroquinolones, cephalosporins, clindamycin, and broad-spectrum penicillins such as amoxicillin/clavulanate, from ward stocks in order to reduce their availability. These antimicrobials were targeted because they were associated with antimicrobial resistance and CDI. New prescribing guidelines with low-risk alternatives were featured in educational sessions and hospital posters and distributed to clinicians as laminated pocket-sized guides. In addition, an antibiotic management team performed regular ward rounds five times a week (compared with irregular rounds 3x/week) to optimize adherence to revised antibiotic guidelines and control the use of high-risk antibiotics. These changes corresponded to a 58.5 percent drop in fluoroquinolone use and a 45.8 percent drop in cephalosporin use. A negative binomial regression showed a significant decrease in CDI associated with the ASP (incidence rate ratio [IRR] 0.34; 95% CI, 0.20 to 0.58, $p<0.0001$). The researchers found no significant differences in clinical outcomes (as measured by length of stay and readmission rate for elderly patients treated for urinary tract and lower respiratory tract infections) associated with the change in prescribing practices.[5]

4.1.4.4 Studies: ASPs With Borderline Significant CDI Reductions

One study at a 48-bed orthopedic ward in Mexico showed borderline significant reductions in CDI[22] after restricting clindamycin (i.e., only patients with a previous infectious disease consult could receive clindamycin). After a 7-month baseline period, there was a 16-month ASP period in which clindamycin use, measured in mean DDDs per 1,000 patient days, decreased by 92.61 percent ($p=0.0002$). CDI rates went from 1.07 per 1,000 patient days during the baseline period to 0.12 per 1,000 patient days during the ASP period, constituting a decrease of 88.78 percent ($p=0.056$).[22]

The reductions in CDI were generally greater in studies with higher pre-ASP (i.e., baseline) CDI rates. This finding could be because those hospitals had more room to improve than hospitals where rates were already low. Another possibility is that studies that report ASPs in the context of an outbreak could find reductions that reflect a natural regression to the mean as the outbreak wanes, rather than a result of the intervention.[23]

4.1.4.5 Studies: ASPs With Nonsignificant Decreases in CDI Rates

Nine studies in hospital settings showed statistically nonsignificant changes or no decrease in CDI associated with ASP implementation.[19,24-31] In one example, antimicrobial stewardship practices were enhanced at a 525-bed public safety-net hospital, where CDI and antimicrobial prescribing rates were declining and already low, relative to other hospitals in the region.[24] New ASP practices included a preauthorization requirement for select broad-spectrum, toxic, or costly antibiotics, retrospective audit and feedback, and revised prescribing guidelines. After the changes, Jenkins et al. (2015) found total antimicrobial and high-risk antimicrobial use declined, and antimicrobial expenditures decreased, but CDI rates did not change.[24] While there are confounding factors, such as a switch to more sensitive testing methods, the authors point out that in the context of relatively low CDI rates and low antimicrobial prescribing, there may have been little room for additional decreases, since a minimal level of antimicrobial use is necessary to maintain optimal clinical outcomes.

Hospital ASPs in which CDI was not the primary clinical/microbiological target also showed nonsignificant changes or no decrease in CDI rates.[25-29] For example, Taggart et al. (2015) examined an ASP in two intensive care units (ICUs) in a 465-bed teaching hospital in Toronto, Canada. The ICUs

included a trauma and neurosurgery ICU and a medical/surgical ICU. In both units, following a 12-month audit and feedback ASP, there were no significant changes in the CDI rate. Mean total monthly antimicrobial use declined in the trauma/neuro ICU but increased in the medical/surgical ICU. The authors speculate that the baseline prescribing practices in the medical/surgical unit were more appropriate (with more room to improve in the trauma/neuro ICU).[25]

4.1.4.6 Studies: ASPs in LTCFs

While most of the studies included in this review examined ASPs in hospitals, three studies evaluated ASPs in LTCFs.[11,14,31] LTCFs are important sites for antimicrobial stewardship due to the number of patient infections, frequent overuse of antimicrobials, and numerous transfers to and from the hospital.[31] ASPs that centered on outside infectious disease consultation showed promising results in LTCFs.[11,14] For example, Jump et al. (2012) measured antimicrobial use and CDIs 36 months before and 18 months after bringing in a Long-Term Care Infectious Disease consult team to a 160-bed Veterans Affairs (VA) LTCF. The team was composed of an infectious disease physician and a nurse practitioner who examined residents at the facility once each week and provided case review, feedback, and antimicrobial prescribing recommendations. In contrast to the pre-ASP period, total systemic antibiotic administration decreased by 30 percent ($p<0.001$), with steeper decreases in use of certain broad-spectrum antimicrobials.

The rate of change of positive *C. difficile* tests in the pre-ASP period showed a trend toward increasing ($p=0.09$), whereas in the post-ASP period the trend was reversed ($p=0.21$). The difference between the slopes in pre- versus post-ASP period is significant ($p=0.04$). While the rate of change in positive *C. difficile* tests did not change significantly over time for the two individual time periods, the difference in the rates of change between the two time periods was significantly different.[14]

4.1.4.6.1 Interventions

Several common ASP interventions were studied in this review. To implement changes in prescribing practices, the ASPs use various strategies or interventions, which, as shown in Table 1, are typically grouped into the following categories: formulary restrictions, audit and feedback, and provider education. There is some research about outcomes associated with each individual strategy, but usually ASPs use more than one of the above interventions, making it difficult to assess each approach individually. Feazel et al. (2014) state that approaches that are “restrictive,” (i.e., restrict high-risk antimicrobials) are more effective than the “persuasive” strategies (i.e., audit and feedback, education, guidelines).[16] Pitiriga et al. (2017) made no such overarching distinction about the efficacy of different strategies.[21] There is no consensus on which interventions are most effective, and it is likely that the most effective approach may differ in different settings; effective programs are dynamic and can be adapted to facility needs.[32]

Table 1: Studies on Antimicrobial Stewardship and *Clostridioides difficile* Infection Outcomes Published 2008 to 2018

Article	ASP Intervention: Formulary Restrictions	ASP Intervention: Audit and Feedback	ASP Intervention: Education	*Clostridioides dfficile* Infection (CDI) Outcomes
Carbo et al., 2016[26]		✓	✓	The incidence of CDI did not differ between pre-antimicrobial stewardship program (ASP) and ASP groups (p=0.81).
Chung et al., 2015[15]	✓			Although the relationship between piperacillin and tazobactam and CDI remained, third- and fourth-generation cephalosporins and fluoroquinolones were no longer significantly associated with CDI.
Cruz-Rodriguez et al., 2014[22]	✓			Borderline statistically nonsignificant reduction of 88% in CDI (1.07 to 0.12 per 1,000 patient days, p=0.056)
Dancer et al., 2013[29]			✓	Adjusting for a decreasing trend, the ASP policy was associated with a 45.22% reduction (95% confidence interval [CI], -4.79% to 72.05%; p=0.09) in the rate of CDIs.
Jenkins et al., 2015[24]	✓	✓	✓	Few apparent changes in CDI and other patient-centered outcomes (p-values not provided).
Jump et al., 2012[14]		✓	✓	The rate of change of positive *C. difficile* tests in the pre-ASP period showed a trend toward increasing (p=0.09), whereas in the post-ASP period, the trend reversed (p=0.21). The difference between the slopes in pre- versus post-intervention period was significant (p=0.04).
Libertin et al., 2017[10]		✓	✓	Decrease from 3.35 cases per 1,000 occupied bed days in 2013 to 1.35 cases per 1,000 occupied bed days in 2015 (p<0.001).
Lowe et al., 2017[27]		✓		No statistically significant difference in CDIs pre-/post-ASP (p=0.24).
Ostrowsky et al., 2014[28]	✓	✓	✓	On average, intervention hospitals reported slightly fewer hospital-onset CDI cases (2.8 fewer CDI cases per 10,000 patient days), as well as slightly fewer hospital-onset CDI combined with community-onset (CO)-healthcare facility-associated (HCFA) CDI cases (3.9 fewer CDI cases per 10,000 patient days). Both of these rate differences were not statistically significant.
Patton et al., 2018[19]			✓	Statistically nonsignificant reduction in CDI of 7.0 cases/1,000 admissions (relative change -24% [95% CI, -55 to 6]) in Medicine, but no change in Surgery (estimated 0.1 fewer cases/1,000 admissions [-2% {95% CI, -116 to 112}]).
Rahme, et al, 2016[31]			✓	CDI rate per 1,000 resident days pre- and post-intervention showed statistically nonsignificant decrease of 19.47% from 0.094 to 0.076 (p=0.58).
Shea et al., 2017[12]	✓		✓	CDI rates decreased significantly (p=0.044) from pre-intervention using education (3.43 cases/10,000 patient days) and restriction (2.2 cases/ 10,000 patient days). In addition, mean and SD monthly CDI cases/10,000 patient days decreased by roughly 50% from 4.0 (SD=2.1) pre-intervention to 2.2 (SD=1.35) post-restriction.
Taggart et al., 2015[25]		✓		Nonsignificant decreases in CDI in two intensive care units (ICUs) (e.g., the rate of CDI in the trauma/neuro ICU decreased from 0.66 cases per 1,000 patient days pre-intervention to 0.48 cases per 1,000 patient days post-intervention; p=0.69).
Talpaert et al., 2011[5]		✓	✓	Significant decrease in CDI following the intervention (IRR 0.34 [0.20 to 0.58], p<0.0001).
Tedeschi et al., 2017[11]		✓	✓	The incidence of CDI decreased from 3.6 to 1.2 cases per 10,000 patient days (p=0.001).

Article	ASP Intervention: Formulary Restrictions	ASP Intervention: Audit and Feedback	ASP Intervention: Education	*Clostridioides dfficile* Infection (CDI) Outcomes
Wenisch et al., 2014[13]	✓	✓	✓	The mean (+/- standard error of the mean) numbers of CDI cases in the baseline period were 59 +/-3 per month and in period 2 were 32 +/-3 per month (46% reduction; p=0.0044)
Yam et al., 2012[30]		✓	✓	Nosocomial CDI decreased from an average of 5.5 cases per 10,000 patient days to an average of 1.6 cases per 10,000 patient days (no p-value provided).

4.1.4.7 Target Antimicrobials, Antimicrobial Formulary Restrictions, and Preauthorization Requirements

An important first step in formulary restriction is determining which antimicrobials to target for restriction. In addition to reducing the high-risk antimicrobials outlined in current guidelines, facilities may use data on regional and facility associations between CDI and antimicrobials. In one example, an ASP team examined temporal associations between antimicrobial use and CDI cases in their facility to determine which antimicrobials to target for restriction.[19]

Several studies examined the role of different CDI ribotypes (more common in certain regions) and certain antimicrobials.[5,13] Using case-control studies to identify antibiotics that should be restricted is one way to assess local associations between antimicrobial classes and CDI. In a multicenter study in New York, each hospital performed its own case-control study to determine CDI-associated antimicrobials.[28] The hospitals used odds ratios to compare case (CDIs) and control groups. Chung et al. (2014) describe this process in more detail and found that, while more complex matching strategies are preferable, using criteria such as admission date (to correct for variation in hospital CDI prevalence) and length of stay (as a surrogate for cumulative risk of developing CDI) may be sufficient to identify high-risk antibiotics associated with CDI. For more accurate associations between antimicrobials and CDI, the researchers included additional matching variables, such as age and comorbidities.[15]

Once target antimicrobials have been identified, ASPs may use strategies such as preauthorization requirements and removing access to the target antimicrobials. In their review, Feazel et al. (2014) reported that interventions that included restricting high-risk antimicrobials (e.g., preauthorization requirements, restrictions on certain antibiotics except in unusual circumstances) were associated with the greatest reductions in CDI rates.[16]

To assess the CDI associations with a formulary restriction, Dancer and colleagues (2013) measured the associations of an ASP education program and restriction policy separately. They attributed decreases in CDI (a decline of 6.59% per month [95% CI,-2.52% to 15.02%; p=0.169) to the educational component of the ASP, while the restriction policy was associated with a 45.22 percent reduction (95% CI, -4.79% to 72.05%; p=0.09) in the rate of CDIs (although neither intervention had a statistically significant effect at the 0.05 level.) This study was one of the few to measure the unique contributions of individual ASP interventions.[29]

4.1.4.8 Audit and Feedback

Audit and feedback include case reviews of patients receiving antimicrobial therapy, often involving a multidisciplinary team (e.g., prescribers, pharmacists, infectious disease experts, administrators) and feedback to providers, as well as audits of targeted antibiotics and other clinical measures both before and/or after treating the patient. Feedback to prescribers may include advice about switching to alternative antimicrobial agents (e.g., broad to narrow spectrum), discontinuation of antimicrobial treatment, shortened duration of microbial dose, higher or lower dose, and switch from intravenous to oral antibiotics. The latter recommendation is based on the idea that an earlier switch to oral therapy allows faster discharge from the hospital, thereby reducing exposure to CDI and drug-resistant organisms.[23]

ASPs with an audit and feedback component were common in the studies we reviewed, and these are widely recommended antimicrobial stewardship practices;[17,21] however, ASPs based solely on an audit and feedback program showed no statistically significant reductions in CDI.[25,27] One benefit of audit and feedback is that the practice itself educates prescribers and other healthcare staff.[11,14] In most studies, audit and feedback are accompanied by a staff education component, making it difficult to find associations between audit and feedback alone and CDI rates.

4.1.4.9 Staff Education

Researchers suggest that education is important to provide context and convince physicians and other staff to participate in antimicrobial stewardship activities.[11,29] Jump et al. (2012) note that some rehabilitation physicians may be aware of the problem of antimicrobial resistance but unaware of local resistance patterns. The education programs described in the reviewed studies included information about antimicrobial resistance, local and facility antibiogram data, treatment guidelines, and/or CDI-specific education. Educational methods included the use of emails, pocket cards, presentations, and trainings.[14]

In an attempt to isolate the CDI associations of an educational program (as part of a multicomponent strategy), Shea et al. (2017) assessed results associated with a 3-month education campaign, then, separately, the results following a subsequent 12 months of a fluoroquinolone restriction policy. The shorter education component appeared to have a significant impact, which was enhanced by the restriction policy. Compared with pre-ASP, the four hospitals experienced 48 percent and 88 percent average reductions in fluoroquinolone utilization (days of therapy per 1,000 patient days) after education and restriction, respectively. CDI rates decreased significantly ($p=0.044$) from 4.0 cases/10,000 patient days pre-ASP to 3.43 cases/10,000 patient days following staff education, and to 2.2 cases/10,000 patient days following restriction.[12]

4.1.5 Unanticipated Outcomes of ASPs

One potential consideration with ASPs is that they may encourage the use of (untargeted) broad-spectrum agents and/or alternative “lower-risk” antimicrobials, which, in turn, may lead to increased resistance to the unrestricted drugs. Pitiriga and colleagues (2017) promoted the restriction of quinolones but also warn against the so-called “squeezing the balloon” phenomenon, wherein restriction policies for use of one set of drugs leads to increased use of unrestricted alternatives, which leads to resistance. This practice runs counter to the goal of decreasing antimicrobial selection pressure.[21]

While many of the reviewed studies found overall reductions in antibiotic use up to 30 percent ($p<0.001$),[14] or no significant change in overall antimicrobial use,[13,22] some researchers reported increases in nontargeted antimicrobials.[5] For example, Dancer and colleagues (2013) found that while targeted antimicrobials decreased during the ASP period, use of empiric amoxicillin and gentamicin increased, and resistance to these antimicrobials increased.[29]

One of the positive outcomes of a CDI-targeted ASP can be lower rates of MRSA (methicillin-resistant *Staphylococcus aureus*), ESBL (extended-spectrum beta-lactamases)-producing coliform infections, and other MDROs (multidrug-resistant organisms). For example, while the primary reason for the antimicrobial restrictions and revised prescribing guidelines in the ASP studied by Dancer et al. (2013) was to decrease CDI rates at the hospital, the researchers also found decreases in ESBL-producing coliforms following the ASP an 8.21 percent reduction [95% CI, -0.39% to 16.15%]). During the following 3 years, both ESBL-producing coliform infections and MRSA declined.[29]

Similarly, from the baseline to the end of the intervention period, Tedeschi et al. (2017) reported the prevalence of extensively drug-resistant strains decreased from 55 percent to 12 percent for *P. aeruginosa* ($p<0.001$) and from 96 percent to 73 percent for *A. baumannii* ($p=0.03$). In addition, the prevalence of ESBL-producing strains decreased from 42 percent to 17 percent for *K. pneumoniae*; the prevalence of carbapenem-resistant strains decreased significantly from 42 percent to 17 percent ($p=0.005$); and MRSA strains decreased significantly from 77 percent to 40 percent ($p<0.0008$).[11]

One additional benefit (or perhaps less identified outcome of an ASP) was an increase in the accuracy of patient diagnoses following audit and feedback interventions. Talpaert et al. (2011) found that, out of 386 interventions by the ASP team, on 75 occasions the clinicians changed the patient's diagnosis.[5] Similarly, Lowe et al. (2017) describe how virology results tied to ASP consults helped facilitate appropriate antimicrobial treatment. Many patients in that study (17/19) who were on empiric oseltamivir were found not to have proven influenza, and following proper diagnosis, oseltamivir was promptly discontinued.[27]

4.1.6 Implementation Barriers and Facilitators

ASPs require resources, and sometimes creative mechanisms to address resource gaps. Researchers noted challenges with staffing limitations (when additional staff were not hired for the ASP) and a need for technical resources to track antimicrobial use.[28] In addition, the lack of EHRs in many LTCFs can make it hard to track the exact indication for antimicrobial use.[30,31] However, even with limited means, antimicrobial stewardship can produce meaningful benefits.[26] For example, Yam et al. (2012) described the challenges of resource constraints in a small rural hospital. The ASP team decided to use scheduled and as-needed consultations with a remote infectious disease specialist physician. After the ASP worked with the remote specialist for 13 months, the researchers found nosocomial CDI decreased from an average of 5.5 cases per 10,000 patient days to an average of 1.6 cases per 10,000 patient days, and antibiotic purchase costs decreased nearly 50 percent.[30]

The CDC provides recommendations for resource-limited settings,[33] which include:

- Using nontraditional staff types to lead the ASP (e.g., infection control nurses, clinical microbiologists, or pharmacists without infectious disease training);
- Using telehealth for advising on prescribing decisions;

- Identifying a single priority hospital unit (e.g., ICU) in which to implement an ASP; or
- Choosing and implementing a single prescribing practice (e.g., reviewing the need for antibiotics after 48 hours, or improving adherence to guidelines for empiric treatment for CA pneumonia or sepsis).

There are several examples of ASP collaborations that overcame resource and expertise gaps. Lowe et al. (2017) described an efficient collaboration between the ASP physician or pharmacist and the virology laboratory for polymerase chain reaction (PCR) testing on respiratory tract infection, in order to optimize antiviral and antimicrobial use.[27] LTCFs often lack appropriate personnel, funding, and electronic resources, and face a paucity of well-validated strategies for their sector.[14]

To implement an ASP in an LTCF, Rahme et al. (2016) document a hospital that collaborated with an LTCF for antimicrobial stewardship in part because the facilities shared patients and there was concern about interfacility HAI transmission.[31] The hospital ASP team provided microbiology data, provider education and treatment guidelines, and a 24-hour hotline for LTCF prescribers. Some LTCFs collaborated with outside consultants to implement audit and feedback ASPs.[11,14,30]

Resistance on the part of providers is a major barrier to ASP implementation that is described in the literature; conversely, a facilitator to implementation is a good relationship between the ASP team and prescribers.[17] Educating physicians and providing proof of ASP safety and efficacy are essential to garnering support.[19] Dancer et al. (2013) found that gaining support for their ASP was challenging at the outset, especially when ASP recommendations for prescribing conflicted with previously published guidelines for a specific infection. For example, gastroenterologists initially refused to curtail ciprofloxacin prescribing for spontaneous bacterial peritonitis.[29] After being educated about the microbiological etiology of the infection, the gastroenterologists were persuaded to change prescribing practices. This observation aligns with the findings of Libertin and colleagues (2017), who noted that development of a "collegial environment for a health care provider's growth in ASP knowledge was important in achieving acceptance of the program" (p. 981).[10]

4.1.6.1 Resources To Assist With Implementation

The following are resources for implementing an ASP, starting with a CDI-specific resource and followed by ASP resources in general:

AHRQ: Toolkit for Reduction of Clostridium difficile Infections Through Antimicrobial Stewardship: https://www.ahrq.gov/professionals/quality-patient-safety/patient-safety-resources/resources/cdifftoolkit/index.html

CDC Antibiotic Stewardship Implementation Resources: https://www.cdc.gov/antibiotic-use/healthcare/implementation.html

IDSA/SHEA Guidelines on implementing antimicrobial stewardship: https://www.idsociety.org/globalassets/idsa/practice-guidelines/implementing-an-antibiotic-stewardship-program-guidelines-by-the-infectious-diseases-society-of-america-and-the-society-for-healthcare-epidemiology-of-america.pdf

National Quality Forum stewardship in acute care: a practical playbook: https://www.qualityforum.org/Publications/2016/05/National_Quality_Partners_Playbook__Antibiotic_Stewardship_in_Acute_Care.aspx

SHEA Antimicrobial Stewardship: Implementation Tools & Resources: https://www.shea-online.org/index.php/practice-resources/priority-topics/antimicrobial-stewardship/implementation-tools-resources

4.1.7 Gaps

There is a notable absence of research on the implementation of ASPs in settings other than hospitals. Of the 16 studies included in this review, we only found 3 ASP studies in LTCFs.[11,14,31] In these three studies, facilities worked with outside consultants to provide expertise and feedback. Researchers commented on the challenges of ASP implementation in LTCF settings due to high rates of infection[25] and a "treat-first" culture.[34] At the same time, ASPs in these settings could potentially have a large impact as they serve high-risk patients and share patients with other facilities. In addition, ASPs in outpatient settings warrant attention, since according to 2016 data reported to the NHSN, CA CDI is on the rise.[8] Our search found no studies on CDI and ASPs in outpatient settings. This is an important gap in the literature and an area for further exploration, especially given the links between antimicrobial prescribing in the outpatient setting and CA CDI.[35]

The reviewed articles had little information on financial outcomes and antimicrobial stewardship. While Jenkins et al. (2015), Libertin et al., (2017) and Taggart et al. (2015) show total reductions in the cost of antibiotics, particularly from reductions in use of costly broad-spectrum antibiotics,[10,24,25] other financial outcomes are not examined in these or other ASP studies. It has been speculated that the financial savings of ASPs measured in cost of antimicrobials and expenses associated with CDI management outweigh the costs of investing in infectious disease expertise to support an ASP.[11]

On a national level, it is believed that antimicrobial stewardship is extremely cost effective in terms of prevention of healthcare costs.[36] However, there is a need for more economic information for healthcare systems and facilities to determine costs and savings.[37] More robust and nuanced cost-effectiveness analyses would help staff in various settings, particularly those with resource limitations, to consider how to best invest in support for an ASP.

Despite the methodological, technological, and resource challenges of research on ASPs, many researchers noted a need for more rigorous study design, including randomized controlled trials (in addition to pre-post) study design.[16] There is also a need for studies that consider the costs and benefits of antimicrobial stewardship over the course of multiple years, to measure longer term associations that may not be evident in shorter study periods.[17]

Researchers have pointed out that reducing antimicrobial use is not always equivalent to improved prescribing and antibiotic appropriateness is as important as counts of prescriptions.[38] One of the issues that comes up in systematic reviews and studies of ASPs is the heterogeneity in process measures, which, in addition to study design, makes comparison and generalization difficult.[38] As noted by Ostrowsky et al. (2014), the prescribed daily doses relative to WHO DDDs may vary between hospitals.[28] DDDs are based on standard dosing and therefore may not accurately capture administered doses that are lower than the routine dose. Point prevalence (accurate surveys taken at particular points in time that can compared) has been suggested as a low-cost way to understand antimicrobial consumption.[39]

Finally, there are different measures of clinical and microbiological outcomes,[38] as evidenced in the studies in this review.

4.1.8 Future Directions

Some future directions for ASPs to reduce CDI include patient and family education on antimicrobial stewardship. The ASP described by Rahme et al. (2016) included an education component to address the pressure on prescribers from patients' families in an LTCF. It was theorized that including a focus on family education would lessen the pressure on prescribers to treat symptoms unnecessarily with antibiotics.[31] Findings of qualitative provider surveys confirm that family pressure can be a challenge. For example, Cole (2014) found that 55 percent of doctors felt under pressure—mainly from patients—to prescribe antibiotics.[40] Similarly, Sanchez et al. (2014) reported a major reason for nonadherence to prescribing guidelines is a concern for patient or family satisfaction.[41]

In LTCFs, doctors report being influenced by family pressure to prescribe antimicrobials, especially in situations when they are undecided about whether to prescribe an antimicrobial.[42] Greater public awareness could help patients and families to better understand why judicious use of antimicrobials is important, thereby lessening pressure on prescribers and promoting better prescribing practices.

The use of technology for more accurate and rapid diagnosis of viral versus bacterial infections is another area for future ASP improvement. Lowe et al. (2017) point out how rapid diagnostics can help decrease antimicrobial use, as in the case of PCR testing to help determine if antibiotic treatment is required.[27] Pitiriga et al. (2017) also endorse "diagnostic stewardship programs" incorporating rapid molecular diagnostics, genomic pathogen profiling, and estimation of patient–pathogen–treatment interactions to help individualize prescribing practices.[21] A more detailed review of the use of improved diagnostics can be found in the Section 4.5, Testing.

Finally, regionally and ecologically informed antimicrobial stewardship is another direction for the future. CDI is transferred across settings in a region, and regional resistance patterns and CDI strains are important prescribing considerations.[14] Regional, multifacility, and collective ASP efforts could be especially effective strategies. As ASPs become more common due to increasing regulations, more LTCFs will be involved, intervening with a population at high risk of CDI and providing an opportunity for an increased understanding of ASPs.

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4.2 PSP 2: Hand Hygiene

Reviewers: Arjun Srinivasan, M.D., and Andrea Hassol, M.S.P.H.

This review includes a summary of evidence published from 2008 to 2018 on hand hygiene as a prevention practice for CDI. After a brief practice description of hand hygiene, as recommended by IDSA, the review explains how hand hygiene is believed to work as a safety practice for preventing the transmission of *C. difficile*. Next, we examine evidence for the estimated effect of healthcare worker (HCW) and patient hand hygiene interventions on CDI incidence rates, and we provide a brief look at research on specific hand hygiene methods for *C. difficile*. The review then explores hand hygiene intervention implementation and contextual factors, including compliance strategies, sink location, and tailoring to staff needs. Finally, we explore research gaps and future directions for hand hygiene and CDI prevention. The review's key findings are located in the box on the right.

Key Findings

- Gloves and handwashing with soap and water are the recommended hand hygiene practices for *C. difficile* prevention.
- Multiple experimental studies show ABHRs are not effective in eliminating *C. difficile* spores.
- Studies were quasi-experimental and showed large and mostly statistically nonsignificant decreases in CDI following implementation of hand hygiene programs that targeted multiple HAIs (statistical significance was impacted by small sample sizes).
- Studies are needed that measure *C. difficile*-targeted hand hygiene initiatives, as well as financial outcomes, and hand hygiene programs in nonhospital settings.
- Important contextual factors for CDI/hand hygiene include sink location, visibility, and accessibility.
- Future directions for hand hygiene programs include patient hand hygiene, studies on glove compliance, electronic monitoring, and sustainable interventions.

4.2.1 Practice Description

In the 2017 clinical practice guidelines for preventing *C. difficile*, IDSA states that HCWs "must" use gloves while caring for CDI patients, including when entering a room with a CDI patient. In CDI outbreaks or hyperendemic settings (periods of persistently high levels of CDI), the guidelines include performing hand hygiene with soap and water before and after caring for a patient with CDI and after removing gloves. When working with CDI patients in routine or endemic situations, the guidelines recommend washing hands with soap and water or using alcohol-based hand rubs (ABHRs) for hand hygiene after removing gloves.[1] While ABHRs are the preferred means of disinfecting hands for most pathogens, alcohol is not active against *C. difficile* spores, and it is b ·ved that the most efficacious way to eliminate *C. difficile* is via the mechanical action of handwashing.[2,3] Washing hands with soap and water is recommended after any contact with feces.[1]

The 2002 CDC and 2009 WHO recommendations for HCW hand hygiene are the most commonly cited guidelines in the literature reviewed for this report. The 2002 CDC guidelines do not include a recommendation to wash hands for CDI prevention, but it is promoted on other CDC sites online and the agency's current "Clean Hands Count" campaign.[4] Both sets of recommendations have been incorporated into campaigns to promote HCW hand hygiene. The WHO campaign, "My Five Moments for Hand Hygiene," promotes hand hygiene at the following times:

- Before touching a patient
- Before clean/aseptic procedures
- After body fluid exposure/risk
- After touching a patient

- After touching patient surroundings

Use of proper handwashing technique is important for *C. difficile* spore removal.[5] When handwashing is indicated, both the CDC and WHO recommend vigorous and thorough washing of all surfaces for at least 15 seconds.[6] The entire process from start to finish should take between 40 and 60 seconds.[7] This technique has been tested against unstructured and alternative techniques and found to be most effective at removing *C. difficile* spores.[5]

Concerning the type of soap to use during handwashing, the general CDC recommendations (for all HAIs) call for antibacterial soap over plain soap. However, in experimental studies, some researchers have found that plain soap is more effective for removing *C. difficile* spores.[2,8] This is one of several unresolved issues in hand hygiene for *C. difficile* that is explored in the research included in this review.

The CDC defines hand hygiene as "a general term that applies to either handwashing, antiseptic hand wash, antiseptic hand rub, or surgical hand antisepsis" (pp. 12-40).[c] As such, glove use was not included in most of the reviewed studies. However, *C. difficile* hand hygiene recommendations strongly recommend the use of gloves.[1,9] One study found that universal glove use (with emollients for skin care) at 78 percent compliance was more effective than standard contact precautions (use of gowns and gloves; 67% compliance) to avoid *C. difficile* transmission.[10]

According to the WHO (2009), HCWs should conduct hand hygiene before and after wearing gloves. Appropriate technique helps prevent potential hand contamination when removing gloves.[11,12] Gloves should not be reused on more than one patient.[7] The 2009 WHO guidelines also provide guidance on proper skin and nail care.[7]

4.2.2 Hand Hygiene as a PSP

Multiple studies have found *C. difficile* contamination on HCWs' hands and several studies have linked cases of CDI and CDI outbreaks to HCW transmission.[11] Similarly, inadequate hand hygiene has been linked to higher incidence of CDI.[13] A study that looked specifically at HCW hand contamination after contact with CDI patients found that 24 percent of HCW hands ($p<0.001$) were contaminated with CDI (even when gloves were used in 356/386 of patient contacts). In addition, contact without the use of gloves was independently associated with hand contamination (adjusted OR, 6.26; 95% CI, 1.27 to 30.78; $p=0.02$).[14]

Tomas et al. (2016) found that HCWs may spread *C. difficile* directly from one patient to another or by touching contaminated surfaces in the environment.[15] Each hand-to-surface exposure can result in the hand transmission of microorganisms.[16] Cross-contamination of *C. difficile* originates in the feces of people who are infected, including in the form of spores (a resilient form of the bacterium), which, if not properly cleaned, can survive in the patient's surroundings on any surface (e.g., toilet areas, clothing, sheets, furniture[7]) for over 4 days.[17] *C. difficile* is transmitted when the spores found in feces are ingested via the fecal-oral route or into the colon directly through shared equipment.[18]

Recent studies provide additional evidence supporting handwashing with soap and water over ABHRs for *C. difficile* prevention.[3,8,19,20] For example, Kundrapu et al. (2014) tested hands contaminated with *C.*

[c]See National Healthcare Safety Network (NHSN) Patient Safety Component Manual, Chapter 12, Multidrug-Resistant Organism & *Clostridioides difficile* Infection (MDRO/CDI) Module for more information on hand hygiene.

difficile after several methods of hand hygiene. Before conducting hand hygiene, roughly half of the subjects were found to have *C. difficile* spores on their hands. Handwashing significantly reduced the percentage of positive cultures (from ~48% to 10%, n=62; p=0.0005), as well as the number of spores recovered from contaminated hands; conversely, ABHR did not significantly reduce positive cultures or spores (from ~51% to ~49% positive cultures, n=59; p=0.85).[19] While the in vitro evidence for handwashing is consistent across multiple studies, evidence is limited on the impact of handwashing on CDI rates in healthcare settings.

Due to concern about HAI rates and poor HCW hand hygiene compliance, hand hygiene (including use of ABHRs) has been heavily promoted over the last two decades. One systematic review found median hand hygiene compliance across 96 studies in a variety of healthcare settings was 40 percent,[21] and hand hygiene rates are potentially even lower at LTCFs.[22] Single-facility studies on compliance with CDI-specific guidelines also show the need for improved practice. Deyneko et al. (2016) found that, at a 637-bed tertiary care hospital in Canada, glove use compliance was 85.4 percent (211/247), but handwashing compliance after care of CDI patients was only 14.2 percent (35/247) and hand rubbing with ABHR was performed instead of handwashing in 33.2 percent of opportunities (82/247).[23] Similarly, in a study in a single surgical transplant unit, Zellmer et al. (2015) found that the baseline percentage of visitors and staff seeing CDI patients that did not practice hand hygiene was 72.5 percent (58/80) before entering the room and 54.6 percent (42/77) after exiting the room (11.7% of which was ABHR hygiene only).[24]

Regulatory agencies have implemented hand hygiene and reporting requirements in an effort to improve compliance. In 2004, The Joint Commission required healthcare facilities to implement hand hygiene programs, and starting in 2018, observation by surveyors of *individual* staff failure to perform hand hygiene in the process of direct patient care began to be cited as a deficiency. CMS also identifies deficiencies in LTCFs that do not meet hand hygiene standards, and requirements for Medicare and Medicaid participation were revised in 2016 to reflect advances in the theory and practice of patient safety.

4.2.3 Methods

The question of interest for this review is: Is hand hygiene effective at preventing CDI?

To answer this question, we searched the databases CINAHL and MEDLINE from 2008 to 2018 for "*Clostridium difficile*" and related MeSH terms and synonyms, as well as "Hand Hygiene," "Hand Disinfection," or "anti-infective agents." The initial search yielded 168 results, and, after duplicates were removed, 165 were screened for inclusion and 20 full-text articles were retrieved. Of those, 11 studies and one systematic review were selected for inclusion in this review. Reference lists of included articles were also screened to ensure thoroughness and four additional studies were retrieved via this method. Articles were excluded if the outcomes were not relevant or precisely reported or study design was insufficient. Studies in which hand hygiene was accompanied by other significant infection control practices (e.g., changes in environmental cleaning) were ruled out for this section and are considered in Section 4.6, Multicomponent CDI Prevention Interventions.

General methods for this report are described in the Methods section of the full report.

For this patient safety practice, a PRISMA flow diagram and evidence table, along with literature-search strategy and search-term details, are included in the report A through C appendixes.

4.2.4 Review of the Evidence

We reviewed five quasi-experimental studies on HCW hand hygiene initiatives and CDI rates in real-world clinical settings. Most of the studies (4/5) showed statistically nonsignificant improvements in CDI rates after implementation of a hand hygiene intervention. In all the studies, the hand hygiene initiatives targeted multiple HAIs and not CDI specifically. In this review of the evidence, we first present important methodological considerations, followed by more detailed study outcomes. We then highlight one study on patient hand hygiene. Then we discuss an additional five in vitro studies that focus on methods for hand hygiene (e.g., type of cleaning agent, handwashing technique, glove removal) to reduce *C. difficile* hand contamination.

4.2.4.1 Evidence Limitations

Consistent with the findings of others (e.g., Louh et al., 2017), the studies on hand hygiene and CDI were generally of low quality and did not address multiple confounding factors.[25] In some studies, the researchers failed to control for important variables, such as antimicrobial prescribing.[26] In addition, there were issues with internal validity when measuring hand hygiene compliance, such as observer reliability and the potential of workers to temporarily alter their behavior while being observed (i.e., Hawthorne effect). The studied hand hygiene interventions were intended to reduce transfer of multiple infectious agents; while the researchers state that the interventions followed established guidelines, it was not always clear how "compliance" was defined and measured and whether CDI-specific hand hygiene guidelines were included.

More specifically, the studied hand hygiene initiatives aimed to reduce multiple HAIs, and study authors reported that the interventions included the promotion of ABHRs (either through additional dispensers or by encouraging ABHR use). It is therefore important to consider the potential impact of ABHRs as a strategy on the incidence of CDI. While ABHRs work to eliminate many other pathogens that cause infection, ABHRs are shown to have limited effectiveness for CDI eradication.[2,3] However, several hospital studies that measured CDI rates after ABHR hand hygiene campaigns found that CDI rates decreased or remained stable.

For example, Knight et al. (2010) conducted a retrospective chart analysis following 5 years of a hospital ABHR policy (which included education and installation of ABHR dispensers) and found a significant decrease in CDI (3.98 per 10,000 patient days after implementation of the ABHR policy, compared with 4.96 per 10,000 patient days before implementation ($p=0.0036$).[27] Conversely, Silva et al. (2013) found that hospital CDI rates remained stable despite several years of increased use of ABHRs.[28] Researchers speculate that these findings may be attributable to improved compliance with CDI prevention strategies, increased awareness of the importance of hand hygiene in reducing infection, and the effect of hand rubbing in reducing the bacterial load on hands. It is because promotion of ABHRs has not been linked to increases in CDI that the CDC guidance promotes handwashing (not ABHRs) in cases of high endemic CDI or CDI outbreaks.[9]

4.2.4.2 HCW Hand Hygiene Interventions and CDI Outcomes

As noted, the studied hand hygiene initiatives were intended to reduce several HAIs and included some or all of the following components: staff education, compliance monitoring and feedback, incentives, promotion of guidelines, and, in some studies, new ABHR dispensers. Using $p<0.05$ as the standard, four studies found decreases in CDI that were not statistically significant.[29-31] One study did not provide a p-

value.[26] The duration of the studied hand hygiene interventions ranged from 1 to 4 years. Measures were based on pre-/post-hand hygiene compliance data and CDI incidence data. Results are presented in Table 2.

Table 2: Studies on HCW Hand Hygiene Initiatives and CDI Rates (Published 2008-2018)

Article	Setting	Intervention	CDI Outcome
Al-Tawfiq et al., 2017[30]	Oncology unit at 350-bed hospital	Root cause evaluation tool, targeted staff education, monitoring	Decrease in CDIs from 7.95 (CI, 0.8937 to 28.72) to 1.84 (CI, 0.02411 to 10.26) per 10,000 patient days (p=0.23)
Kirkland et al., 2012[29]	383-bed hospital	Staff education, promotions, measurement and feedback	Decline in CDIs from 0.9 to 0.6 per 1,000 patient days (p=0.1).
Schweon et al., 2013[31]	174-bed skilled nursing facility	Increased ABHR dispensers, staff education, monitoring, monthly staff hand hygiene champion, patient education	Decrease in CDI rate per 1,000 resident days from 0.08 to 0.04 (p=0.36)
Sickbert-Bennett et al., 2016[28]	853-bed hospital	Staff education, promotion/communications, data collection and feedback	14% reduction in healthcare-acquired CDI (p=0.070)
Stone et al., 2012[26]	187 acute hospitals	Regional program, increased ABHR dispensers, staff education, communications/ promotion, hand hygiene audits	Decrease in CDI from 16.75 to 9.49 cases per 10,000 bed days (no p-value given).

Sickbert-Bennett et al. (2016) evaluated HCW hand hygiene compliance and HAIs following the implementation of "Clean In, Clean Out" in an 853-bed hospital in North Carolina. The hospital hand hygiene program included focus on cleaning hands before and after working with patients, covert observation of compliance, staff data collection, and feedback. After 17 months, the researchers found a 10 percent improvement in appropriate hand hygiene compliance and a 14 percent reduction in healthcare-acquired CDI (p=0.070), as well as decreases in other HAIs. The published article did not clarify what constituted hand hygiene compliance, and whether ABHR use or handwashing was considered compliant, making it difficult to determine which practice may have contributed to the CDI reduction.[32]

Following a 3-year hand hygiene initiative in a 383-bed teaching hospital in rural New Hampshire, Kirkland et al. (2012) evaluated hand hygiene compliance and HAI rates. This study described promotion of published hand hygiene guidelines but did not specify whether handwashing for CDI was emphasized. The initiative included leadership endorsement, measurement and feedback on hand hygiene compliance, and education. Over the study period, observed hand hygiene compliance increased significantly from 41 percent to 87 percent (p<0.01), and the overall HAI rate declined significantly (from 4.8 to 3.3 per 1,000 inpatient days; p<0.01). The decline in CDI was not statistically significant (0.9 to 0.6 per 1,000 patient days, p=0.1); like other smaller studies, statistical significance was potentially due to small sample size.[29] This was one of three studies that found statistically nonsignificant decreases in CDI following staff hand hygiene initiatives.[29-31]

Several studies explored initiatives in which ABHR protocols were described as a key component. For example, in the only study in a nonhospital setting, Schweon et al. (2013) studied a hand hygiene program in a 174-bed skilled nursing facility. The program included installation of a number of new ABHR dispensers, staff education on handwashing guidelines, staff monitoring, and patient education on *when* to conduct hand hygiene. A monthly hand hygiene champion was recognized, and hand hygiene posters were placed around the facility. Following the year-long program, most HAIs decreased but only lower respiratory tract infections showed statistically significant decreases. CDI rate per 1,000 resident

days decreased but was not significant (from 0.08 to 0.04; p=0.36). Again, it is not clear the degree to which the use of ABHRs was deemed an appropriate practice for hand hygiene.[31]

Like the hand hygiene program studied by Schweon and colleagues (2013),[31] the regional initiative described by Stone et al. (2012) measured HAI rates following a hygiene initiative at acute care hospitals in England and Wales, which included ABHR promotion in addition to other strategies (although in year 4 of the study, the 2009 WHO protocols for hand hygiene were adopted). The initiative titled "Cleanyourhands" was informed by Habit-Forming Theory[33,34] and included installation of ABHR dispensers, materials promoting hand hygiene, and regular hand hygiene audits. After 4 years, the CDI rate decreased from 16.75 to 9.49 cases per 10,000 bed days, but the report did not mention statistical significance. Researchers found that increases in the amount of soap purchased by facilities was independently associated with reduced CDI throughout the study. The researchers also noted potential confounders that they did not study (e.g., antimicrobial prescribing rates).[26]

4.2.4.3 Patient Hand Hygiene

In the past decade, patient hand hygiene has received increasing attention as a potential major source of *C. difficile* transmission in healthcare settings. Patients colonized with *C. difficile* often go undetected and may transmit *C. difficile* to HCWs' hands directly, or indirectly through contaminated surfaces in the healthcare environment. Patient mobility, dexterity, and cognitive limitations can be barriers to patient hand hygiene.[20,35] One study found patient hand hygiene compliance rates as low as 10 percent.[36]

Pokrywka et al. (2017) conducted a study in a 495-bed university-affiliated medical center on a patient handwashing program focused specifically on CDI reduction. In this intervention, hospital staff were educated about specific times when they should encourage and assist patients with handwashing and hand hygiene (i.e., practicing hand hygiene prior to meals, after using the toilet or bedpan, prior to touching dressings and incisions, after returning from testing or a procedure, before and after having visitors). After a trial conducted on four units in the hospital, the initiative was implemented hospitalwide.

Post-implementation patient survey results showed some improvement in staff assistance with patient hand hygiene, and the CDI standardized infection ratio (SIR) decreased in the first two quarters after implementation, from 0.834 to 0.572 and 0.497 ($p \leq 0.05$). (The NHSN uses SIRs to track HAIs over time; the SIR compares the actual number of HAIs at each hospital with the predicted number). Infection rates increased in the third and final quarters of the measurement period, which potentially shows the need for sustained staff education and reminders to consistently educate new patients.[35]

4.2.4.4 Studies on Hand Hygiene Methods for *C. difficile* Decontamination

It is believed that the mechanical action and friction from handwashing helps to remove *C. difficile* spores from hands. To explore this theory, Isaacson et al. (2015) experimented with the use of sand to remove *C. difficile* spores from hands and compared these results with washing with soap and water. In this study, 14 subjects each used five different hand hygiene methods following contamination with *C. difficile* (4×10^5 colony forming units). The hand hygiene methods were water rinse, water rub and rinse, water and antibacterial soap, oil/baking soda/dish detergent/water, and sand rub and water rinse. The use of sand and water resulted in the greatest reduction in spores, but results were not significant. Compared with antibacterial soap and water, which resulted in an average 1.84 log reduction (SD 0.46)

or 98.5 percent, sand and water resulted in an average 2.34 log reduction (SD 0.33) or 99.5 percent. Compared with soap and water, the sand and water method removed a statistically significant greater average amount of *C. difficile* spores (-0.50; p=0.003).[37]

Other studies examined the efficacy of handwashing with soap and water. To compare five practical strategies for hand hygiene, Oughton et al. (2009) conducted an experiment with 10 volunteers to measure the efficacy for *C. difficile* spore removal from the whole hand or just the surface of the palm. The researchers found that, using both whole hand and palmar surface protocols, washing with warm water with plain soap left the lowest amount of *C. difficile* spores, followed by cold water with plain soap, warm water with antibacterial soap, antiseptic hand wipe, ABHR, and no hand hygiene.

Perhaps the most interesting finding from this study was that plain soap performed better than antimicrobial soap in the whole-hand protocol.[2] Washing with non-antimicrobial soap and water was more effective for removing *C. difficile* than 4% chlorhexidine gluconate hand wash. The researchers speculate that this finding may be because a higher amount of organic matter is present on the whole hand than on the palm, and high levels of organic matter interfere with the activity of chlorhexidine. Edmonds et al. (2013) found similar results and noted that the most effective antibacterial products were too harsh to be used on human skin (e.g., peracetic acid surfactant prototype [Triton-X], commercial ink and stain remover, sodium tetraborate decahydrate powder [Borax]).[8]

Tomas et al. (2015) explored preventing HCW hand contamination from the removal of gloves and other personal protective equipment. The study found that, after CDI patient care, 16 percent of HCWs had CDI spores on their hands after removing gloves and personal protective equipment (n=25). The frequency of contamination was reduced to 7 percent after an educational intervention on proper glove/gown removal (p=0.4) and further reduced to 0 percent after disinfection of gloves with bleach wipes (p=0.04).[12]

Due to complaints of irritation from the bleach wipes, Tomas et al. (2016) conducted a second study in which HCWs used a sporicidal formula (of acidic ethanol) instead of bleach for glove decontamination (to use before glove removal). The findings suggest that the sporicidal properties of certain solutions could be useful for glove disinfection before removal, when caring for CDI patients. The reduction achieved by the sporicidal ethanol solution (70% ethanol pH 1.3) was equivalent to the 1:100 dilution of bleach on artificially contaminated gloves. Researchers tested glove contamination of HCWs following 159 CDI patient care episodes and found that the sporicidal ethanol resulted in significantly reduced glove contamination, whereas 70% ethanol did not. Despite the promise of glove decontamination as a prevention strategy, the authors stipulate that decontaminating gloves would not replace HCWs washing their hands after glove removal.[15]

4.2.4.5 Economic Outcomes

In general, the literature regarding hand hygiene indicates that the costs associated with preventing HAIs far outweigh the costs to improve hand hygiene compliance.[29,32] Sickbert-Bennett et al. (2016) reported that the cumulative prevention of HAIs saved approximately $5 million at their institution.[32] Although some cost-effectiveness analyses are available for hand hygiene programs in general, we could not find financial outcomes related to hand hygiene and CDI specifically. To better understand and encourage the implementation of hand hygiene initiatives, it would be beneficial to take into account the cost of a hand hygiene initiative (staffing, staff time, supplies, installation of sinks, etc.), as well as

the costs of sustaining a program, and compare these totals with estimated savings in terms of medical costs from CDI prevention.

4.2.5 Implementation

A systematic review by Neo et al. (2016) of 73 studies published from 2002 to 2015 on interventions to increase hand hygiene compliance in healthcare settings found five general intervention types:

- Education
- Facility design (installation of sinks and ABHRs)
- Unit-level protocols and procedures
- Hospitalwide programs
- Multimodal interventions

Among the review's conclusions were recommendations that hand hygiene education be interactive and engaging and that interventions be tailored to the institution's unique needs.[38] Researchers have assessed barriers to hand hygiene and report that hand hygiene interventions should be tailored to the particular classification/role of staff and that context and staff needs should be taken into account when designing hand hygiene interventions. For example, Kirkland et al. (2012) noted that regular review of data linking hand hygiene performance to HAIs was persuasive for physicians, but they were less likely to engage in educational programs geared toward staff with less medical knowledge.[29]

In an example of addressing a facility's unique needs, Al-Tawfiq et al. (2018) described positive experience using The Joint Commission Center for Transforming Healthcare's web-based Targeted Solutions Tool® (TST®) to improve hand hygiene and reduce HAIs in a 30-bed oncology/hematology inpatient unit in Saudi Arabia. The tool is designed to identify root causes of nonadherence to hand hygiene and improve process outcomes. Researchers found that housekeepers needed more help than other staff help with improving hand hygiene, but these workers were not fluent in either English or Arabic (the dominant languages) and their educational levels varied substantially. To address this issue, an extensive training program was developed for housekeeping staff using in-action learning tools and translators. After 1 year, the hand hygiene compliance rate increased from 75.4 percent at baseline to 88.6 percent ($p<0.0001$). Researchers found a decrease in CDIs from 7.95 (CI, 0.8937 to 28.72) to 1.84 (CI, 0.02411 to 10.26) infections per 10,000 patient days that was not significant ($p=0.23$) and cited sample size as a barrier to statistical significance.[30]

An interactive strategy to assist HCWs in improving glove and gown removal technique includes the use of fluorescent lotion. In the training described by Tomas et al. (2015), fluorescent lotions were used to help HCWs learn proper glove and gown removal to minimize hand contamination. The fluorescent lotion provides immediate visual feedback on contaminated sites.[12] A similar strategy includes the use of nonpathogenic RNA beads that fluoresce under ultraviolet (UV) light to help track contamination during removal of personal protective equipment. This practice can help HCWs see that glove use does not preclude the need for hand hygiene.[39]

4.2.6 Additional Contextual Factors

The design of the healthcare environment can affect hand hygiene compliance. Some researchers suggest a human factors engineering approach that calls for abundant, convenient, and available sinks, handwashing products, and ABHRs to improve compliance.[40] Several researchers found that longer distances to sinks, and sink visibility, were related to HCW handwashing compliance. For example, Zellmer et al. (2015) reviewed the practices of HCWs and visitors for CDI-positive patients on a transplant medical-surgical unit at a large academic medical center. While there were sinks in the patients' rooms, these were not used due to the placement of furniture, patients' personal items blocking access, and lack of foot pedals. Before the study began, the only two easily accessible sinks were at the end of a hallway. After the installment of two highly visible sinks in the unit, completion of proper hand hygiene on exiting the CDI patient room improved by 18 percent ($p=0.03$).[24]

In another example, Deyneko et al. (2016) investigated the relationship between sink location and HCW compliance with handwashing; their multivariate analysis found that increased distance between the patient zone and the nearest sink was inversely associated with handwashing compliance. The median distance to the nearest sink was 7.6 meters when hand hygiene was correctly performed, but 14.9 meters when it was omitted ($p<0.001$). There was also a strong association between the number of 90° turns required to reach the sink and handwashing compliance.[23]

4.2.7 Resources To Assist with Implementation

AHRQ Safety Program for Long-Term Care: HAIs/CAUTI – The How-To's of Hand Hygiene:
https://www.ahrq.gov/professionals/quality-patient-safety/quality-resources/tools/cauti-ltc/modules/implementaion/education-bundles/infection-prevention/hand-hygiene/hand-hygiene-slides.html

CDC Clean Hands Count Campaign:
https://www.cdc.gov/handhygiene/campaign/index.html

Sequence for putting on and removing personal protective equipment:
https://www.cdc.gov/hai/pdfs/ppe/PPE-Sequence.pdf

The Joint Commission Center for Transforming Healthcare Hand Hygiene Targeted Solutions Tool:
https://www.centerfortransforminghealthcare.org/what-we-offer/targeted-solutions-tool/hand-hygiene-tst

Veterans Health Administration: Infection: Don't Pass It On education and communication materials:
https://www.publichealth.va.gov/infectiondontpassiton/index.asp

WHO Hand Hygiene Tools and Resources:
https://www.who.int/infection-prevention/tools/hand-hygiene/en/

4.2.8 Gaps and Future Directions

As already noted, there is a need for more real-world randomized and crossover hand hygiene studies in which CDI prevention is a primary focus. One of the most important omissions of the reviewed clinical/quasi-experimental studies was that compliance with hand hygiene practices specific to CDI was not distinctly measured and reported. In several of the reviewed studies, hand hygiene processes (end points) were clinician hand hygiene at the appropriate moments, not whether a CDI-appropriate

method (e.g., use of gloves and washing hands in outbreak/hyperendemic settings) was used.[30,32] CDI-specific research would help improve understanding about the impact of using ABHRs versus handwashing when working with CDI patients. In addition, the strength of the research on hand hygiene in clinical settings and hand hygiene methods was limited by small sample sizes.

Research on hand hygiene interventions in a wide variety of setting types (and in multiple settings) is needed given that hand hygiene behaviors and challenges differ across settings. Neo et al. (2016) found in their review that most studies of hand hygiene interventions were in hospitals or ICUs.[38] As CDI disproportionately impacts elderly and immunocompromised patients, more research is needed on CDI and hand hygiene in LTCFs that serve these specific patient populations. In addition, LTCFs have unique staffing and environmental factors and require different types of patient contacts than hospitals do. Many nursing home facilities are designed to encourage social contact between patients, and patients move throughout the facility coming into contact with spaces outside their rooms (e.g., dining room, physical therapy room). In such settings, hand hygiene programs aimed at patients could be particularly impactful. Additional studies in the outpatient setting would also be useful.

Patient hand hygiene is a promising area of prevention and research. As the role of colonized patients is increasingly understood, patient hand hygiene analyses will likely account for patients with asymptomatic colonization in addition to those with CDI. As found by Kundrapu et al. (2014), the numbers of CDI colonies recovered from patients' hands were similar for those diagnosed with CDI and asymptomatic carriers.[19] Due to some of the barriers for patient hand hygiene, including mobility, some have suggested more research into the potential of using skin-safe cleaning wipes with *C. difficile* eliminating agents (e.g., sporicidal electrochemically generated hypochlorous acid solution) for patients who cannot ambulate or be brought to sinks for routine handwashing.[19,41] Patient education about *C. difficile* is potentially important. Kundrapu et al. (2014) found that 73 percent of colonized and infected patients in their study were not aware that ABHR does not kill *C. difficile* spores.[19]

Some research has been conducted to identify new ways to decontaminate HCWs' hands. Researchers may continue to explore potential noncorrosive hand rubs that provide the convenience of a hand rub and are more effective at killing all pathogens, including *C. difficile* spores.[35] For example, an experimental study by Nerandzic et al. (2013) found that sporicidal electrochemically generated hypochlorous acid solution (Vashe), used to soak or as a wipe, is effective in reducing spores. Wiping with Vashe-soaked cloths significantly enhanced reduction of *C. difficile* spores by approximately 68 percent (0.5 $\log_{10}$ CFU [colony-forming unit]; $p<0.01$).[41] Vashe is FDA approved for use on wounds, and more research is needed to determine safety for other uses. In addition, more real-world research is needed to determine efficacy for HCW exposure to *C. difficile.*

Direct and persistent observation is both a study technique and an intervention to encourage hand hygiene. There are some limits to in-person monitoring, including cost, feasibility of achieving sufficient sample size, sustainability, potential for HCWs to temporarily alter behavior while being observed, and lack of consistency (within and across studies) for measuring compliance. Monitoring by video is another observation strategy that eliminates the physical presence of the observer but has some of the same drawbacks as in-person monitoring.[41]

Staats et al. (2017) studied the use of electronic monitoring, using radio frequency identification, in 71 hospital units. HCWs were given badges that communicated with a network of sensors throughout the hospital and at hand hygiene stations. Monitoring measured whether the HCWs used hand hygiene

stations at the appropriate place and time. The researchers found that electronically monitoring individual compliance resulted in a large, positive increase in compliance that was not sustained.[43]

One drawback of electronic monitoring and censors is cost, and more research is needed. Other strategies include use of electronic counters on ABHRs and measuring handwashing product use. The drawbacks of these strategies is they do not account for appropriate hand hygiene technique, hand hygiene moments, and person using the product (patients and visitors may also use these products).[42]

The use of gloves for preventing transmission of CDI is strongly recommended in the guidelines yet not well studied in the healthcare setting. More research could be done on promoting HCW compliance with glove use, barriers and facilitators, and best practices for glove use when working with CDI patients.

Finally, interventions for hand hygiene will need to address issues of sustainability, as multiple studies reported declines in compliance after the hand hygiene intervention period.[35,43] For example, Pokrywka et al. (2017) report that sustainability requires ongoing leadership, continued staff reminders, education for new staff, and ongoing resources, without which hand hygiene compliance rates will fall.[35] Kirkland et al. (2012) report that understanding the hospital context, based on responses to the initiative across units and HCW types, helped sustain improved hand hygiene compliance rates for a year following a 3-year hand hygiene initiative.[29] Additional research concerning the sustainability of hand hygiene programs would be helpful to improve understanding.

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4.3 CDI PSP 3: Environmental Cleaning and Decontamination

Reviewers: Arjun Srinivasan, M.D., and Katharine Witgert, M.P.H.

This review includes a summary of evidence published from 2008 to 2018 on environmental cleaning and decontamination as a prevention practice for CDI. We start with a definition of terms by the CDC and a brief practice description for environmental cleaning and decontamination for C. difficile from the 2017 guidelines by the IDSA and SHEA. The review then provides an overview of how environmental cleaning and decontamination work as a safety practice for preventing the transmission of C. difficile.

Next, we summarize the evidence for the impact of environmental cleaning and decontamination interventions on CDI rates and highlight some experimental research on cleaning agents for *C. difficile*. We then explore implementation factors, including monitoring and improving the performance of environmental service workers and challenges with the use of decontamination equipment. Finally, we explore gaps and future directions for environmental cleaning and decontamination for *C. difficile*. The review's key findings are located in the box on the right.

Key Findings

- The most recommended cleaning and decontamination agents for manual use are chlorine-based solutions.
- In many of the reviewed studies, the addition of hydrogen peroxide decontamination (HPD) or ultraviolet light decontamination (UVD) to standard cleaning was associated with significant reductions in facility-level CDI rates.
- HPD and UVD have drawbacks, including expense and the time it takes to decontaminate a room. However, the process for UVD is shorter than for HPD.
- The performance of environmental cleaning services staff is important and can be improved through the use of training, checklists, and audit and feedback.
- There is a need for higher quality studies, multifacility studies, and studies that compare cleaning and decontamination methods.
- Future directions include research and development of nontoxic decontamination agents, new technologies, and research on patient outcomes and environmental cleaning in diverse healthcare settings.

4.3.1 Practice Description

The CDC (2008) in their guideline for sterilization and disinfection of healthcare facilities define the practice of cleaning in the healthcare environment as "the removal of visible soil (e.g., organic and inorganic material) from objects and surfaces" (page 9).[1] The CDC defines disinfection as the elimination of many or all pathogenic microorganisms from the environment, while sterilization refers to the elimination of all forms of microbial life.

Decontamination is the process to remove pathogenic microorganisms from objects for the purposes of safe handling and use. The CDC states that cleaning (i.e., removing visible material from surfaces) is a first step in the decontamination process so that organic or inorganic material does not interfere with decontamination. As outlined in this report, the use of sporicidal agents to manually clean healthcare environments is a form of both cleaning and decontamination. Use of touchless automated methods are solely for the purpose of environmental decontamination.

Recommended environmental cleaning and decontamination practices are outlined in the IDSA/SHEA 2017 revised guidelines for *C. difficile*.[2] These recommendations include IDSA/SHEA statements about the strength of the recommendation and quality of evidence. Recommendations applicable to environmental cleaning and decontamination include:

- Terminal room cleaning (cleaning after a patient is discharged or transferred from a room) with a sporicidal agent should be considered in conjunction with other measures to prevent CDI during endemic high rates or outbreaks, or if there is evidence of repeated cases of CDI in the same room *(weak recommendation, low quality of evidence)*.
- Daily cleaning with a sporicidal agent should be considered in conjunction with other measures to prevent CDI during outbreaks or in hyperendemic (sustained high rates) settings, or if there is evidence of repeated cases of CDI in the same room *(weak recommendation, low quality of evidence)*.
- Measures of cleaning effectiveness should be incorporated to ensure quality of environmental cleaning (*good practice recommendation*).
- Disposable patient equipment should be used when possible and reusable equipment should be thoroughly cleaned and disinfected, preferably with a sporicidal disinfectant that is equipment compatible *(strong recommendation, moderate quality of evidence).*

The IDSA/SHEA state in the guidelines that they have no recommendation for the use of automated touchless terminal (i.e., upon discharge) disinfection CDI prevention due to data limitations. The CDC guidelines for environmental cleaning and decontamination for *C. difficile* include the creation of daily and terminal cleaning protocols and checklists for patient-care areas and equipment.[3] Other guidelines from an earlier SHEA/IDSA report for acute care facilities recommend frequent education for environmental service personnel in the primary language of the cleaning team and the use of various techniques to help improve cleaning and decontamination practice as outlined by the CDC[4] (e.g., observation, fluorescent markers, and bioluminescence).[4,5]

Safety practices for laundry, bedding, and other environmental services are included in the CDC's "Guidelines for Environmental Infection Control in Health Care Facilities."[6] Guidelines for specific facility types, including hospitals, nursing homes, long-term acute care facilities, and outpatient facilities, are available from the CDC and other healthcare agencies. We include some of these resources later in this chapter.

4.3.2 Environmental Cleaning as a Safety Practice

The healthcare environment is recognized as a primary source of *C. difficile* transmission.[7] *C. difficile* is spread through the feces of infected and colonized patients. Patients with contaminated hands may spread *C. difficile* by touching surfaces in the healthcare environment. Some evidence suggests *C. difficile* may be dispersed to surfaces near the patient through droplets in the air.[8,9] Transmission can occur when other patients, healthcare staff, or visitors touch contaminated surfaces and orally ingest *C. difficile* (e.g., while eating).[7] Those who take antimicrobials, are advanced in age, or have compromised immune systems are at high risk of getting CDI from exposure to the pathogen. Others may become asymptomatic carriers of *C. difficile*.[2]

Both symptomatic and asymptomatic carriers have the potential to contaminate the environment. In one hospital, *C. difficile* was recovered from 59 percent of samples in rooms of asymptomatic carriers[10] and 75 percent of samples of rooms with patients with CDI.[11] Patients may continue to contaminate the environment after treatment.[12] The most contaminated areas, or "high-touch surfaces," include the bed rails, bed surface, supply cart, over-bed table, and intravenous pumps.[13]

In one study, CHWs' hands were just as likely to be contaminated with *C. difficile* after touching high-touch surfaces as they were by touching a CDI patient.[14] *C. difficile* produces spores that are especially robust and may remain viable in the environment for over 4 days.[15] Shaughnessy et al. (2011) examined the potential role of environmental transmission of *C. difficile* through a prior room occupant and found that the prior occupant's CDI status was a significant risk factor for acquiring CDI (p=0.01; hazard ratio, 2.35), after controlling for other risk factors (e.g., antimicrobial use, age, proton pump inhibitors).[16]

Eliminating *C. difficile* in the healthcare environment requires specialized practices. Evidence shows that *C. difficile* spores are resistant to alcohol and many hospital disinfectants.[17] In one study, exposure of the bacteria to low levels of certain cleaning agents resulted in higher CDI sporulation capacity (the ability for vegetative cells to forms spores during unfavorable environmental conditions).[18]

Among cleaning and decontamination agents for washing surfaces by hand, chlorine-releasing solutions (e.g., bleach), at sufficient concentration and with appropriate exposure time (at least 10 minutes), demonstrate the best evidence for killing *C. difficile*.[17] The CDC-recommended cleaning/decontamination agents for *C. difficile* can be found on EPA List K: Registered Antimicrobial Products Effective Against *Clostridium difficile* Spores.[19]

Decontamination by hand is challenging and not always effective in reaching all contaminated surfaces in the healthcare environment.[12,20] Automated touchless methods have been developed and implemented to supplement cleaning by hand and prevent the spread of CDI and other HAIs. The two most commonly studied touchless methods for *C. difficile* decontamination are hydrogen peroxide decontamination (HPD)—including vaporized, aerosolized, atomized, and dry mist systems—and ultraviolet disinfection (UVD), which includes UV radiation and pulsed xenon UV light systems. In laboratory studies, both methods have shown effectiveness in almost entirely eliminating *C. difficile* contamination from targeted surfaces.[21,22]

Although subject to some debate, it is generally recommended that surfaces be precleaned by hand prior to use of UVD or HPD, as organic matter is thought to reduce the efficacy of the UVD and HPD methods.[23] In their review, Doll et al. (2015) found that studies were mixed as to which no-touch method (UVD or HPD) was most effective at killing *C. difficile.* The UVD methods generally take less time than HPD to decontaminate a room.[23]

There is increasing incentive for facilities to implement an effective environmental cleaning and decontamination program as facility rankings and CMS reimbursement rates are tied to reported rates of healthcare facility-acquired onset (HO CDI). The 2016 revised requirements for participation in Medicare and Medicaid outlined the specific components of an effective infection control program, including environmental cleaning and decontamination procedures. One review found that, among several PSPs, environmental cleaning and decontamination practices were the most cost effective for reducing facility-level CDI rates.[24]

4.3.3 Methods

The question of interest for this review is: What are the most effective and feasible environmental cleaning and decontamination practices to prevent CDI?

To answer this question, we searched the databases CINAHL and MEDLINE from 2008 to 2018 for "*Clostridium difficile*" and related MeSH terms and synonyms, in combination with terms such as

"Disinfection," "Decontamination," and "No-touch decontamination." The search string also included a variety of healthcare settings, including "hospitals," "inpatient," "ambulatory care," "long-term care," and "transitional care." After duplicates were removed, the initial search yielded 121 results that were screened for inclusion. Of these, 45 full-text articles were retrieved. Of those, 18 studies and 3 systematic reviews were selected for this review.

Reference lists of retrieved articles were also screened to ensure thoroughness, and five studies were retrieved that way. Articles from the searches were excluded if the outcomes were not relevant or precisely reported or study design was insufficient (e.g., opinion pieces, nonsystematic reviews). Due to the number of experimental studies on this topic, a select group are included in the evidence tables and cited in the review. Studies in which environmental cleaning and decontamination were accompanied by other significant infection control practices (e.g., changes in hand hygiene practices) were ruled out for this section and are considered in Section 4.6, Multicomponent CDI Prevention Interventions.

General methods for this report are described in the Methods section of the full report.

For this patient safety practice, a PRISMA flow diagram and evidence table, along with literature-search strategy and search-term details, are included in the report appendixes A through C.

4.3.4 Review of the Evidence

In this evidence summary, we review 12 articles and 2 reviews on environmental cleaning and CDI patient outcomes. These studies were primarily (10/12) based in hospitals and examined CDI rates after a period of enhanced cleaning and decontamination. In our search of the literature, we also found numerous experimental studies published from 2008 to 2018 on environmental cleaning and disinfection methods and CDI. Among these were three studies that compared UVD or HPD with bleach cleaning. We also found two studies on alternatives to chlorine-based solutions for the manual elimination of *C. difficile* from healthcare surfaces. We include a review of these experimental studies and information from one qualitative study on concerns about the effects of bleach on HCWs. Two systematic reviews included studies on environmental cleaning and CDI rates, and a third examined research on cleaning agents used to eliminate the *C. difficile* organism.

4.3.4.1 Environmental Cleaning and Patient Outcomes: Studies and Reviews

As shown in Table 3, the evidence for environmental cleaning and decontamination and CDI patient outcomes includes 12 studies published from 2008 to 2018. Most studies showed statistically significant reductions in CDI rates after a period of an environmental cleaning intervention; however, study quality was low. These findings align with the review conducted by Louh et al. (2017) in their examination of studies on CDI prevention practices in acute care hospitals from 2009 to 2015.[24] We review five of the same studies here.[25-29]

Louh et al. (2017) reported that environmental cleaning was the most cost effective of the multiple strategies they studied.[24] Khanafer et al. (2015) found nine studies on environmental cleaning and CDI published from 1982 to December 2013.[30] They concluded that environmental cleaning with a 10:1 bleach solution was both practical and effective. Of the nine studies, four are included here;[26,27,29,31] we excluded the remaining studies because they were published before 2008 or measured the combined effect of several PSPs.

The environmental decontamination strategies in this review fall into one of four categories: use of a chlorine-based agent, use of a chlorine-based agent plus the use of HPD, a chlorine-based agent plus the use of UVD, and one study about washable bed covers. Within these categories, certain variables differed, such as the frequency of cleaning (e.g., daily or at discharge) and the area of cleaning (e.g., CDI patient rooms, all patient rooms, communal spaces).

The studies reviewed here were primarily quasi-experimental with a before-after approach. The study by Anderson et al. (2017) was the only randomized trial in the group of studies.[32] The cleaning intervention period ranged roughly from 8 months[31] to 2 years.[26] Two of the studies on HPD no-touch decontamination methods received some financial support from the makers of the products, in the form of free use of equipment[33] and reduced cost to use the products.[31] Two UVD studies had more than one author who was an employees of Xenex, the company that sells the machines that were studied in the intervention.[34,35]

Table 3: Studies From 2008 to 2018 on Environmental Cleaning/Decontamination and CDI Patients

Article	Setting	Intervention	CDI Outcome
Anderson et al., 2017[32]	9 hospitals	Rooms from which a patient with infection or colonization with *C. difficile* was discharged were terminally disinfected with one of two strategies: (1) bleach, and (2) UVD and bleach.	CDI incidence among exposed patients was not changed after adding UV to cleaning with bleach (n=38 vs. 36; 30,4 cases vs. 31,6 cases per 10,000 exposure days (relative risk [RR] 1.0, 95% CI, 0.57 to 1.75; p=0.997).
Best et al., 2014[33]	30-bed stroke rehabilitation unit	The unit performed one-time deep cleaning (1,000 parts per million [ppm] chlorine-based disinfectant) and atomized HPD, following a high incidence of CDI in the unit.	There were 20 CDI cases in the 10 months before the intervention and 7 CDI cases in the following 10 months.
Boyce et al., 2008[31]	500-bed university hospital	Highest incidence wards received wardwide HPD cleaning. The hospital also added terminal disinfection of rooms occupied by CDI patients using HPD (in addition to cleaning with 5,000 ppm dilution of household bleach).	On five high-incidence wards, the incidence of nosocomial *Clostridium difficile*-associated disease (CDAD) was significantly lower during the intervention period than during the pre-intervention period (1.28 vs 2.28 cases per 1,000 patient days, p=0.047).
Hacek et al., 2010[26]	3 hospitals with total ~850 beds	Quaternary ammonium compound was replaced as a room cleaning agent with diluted bleach (5,000 ppm sodium hypochlorite) for terminal cleaning of rooms occupied by patients with CDI. Cleaning walls was added to checklist.	There was a 48% reduction in the prevalence density of CDI after the bleaching intervention [95% CI, 36% to 58%, p<0.0001].
Haas et al., 2014[25]	643-bed tertiary care academic medical center	UVD followed discharge cleaning of contact precautions rooms (with 5,550 ppm bleach solution) and other high-risk areas.	Significant decrease in all measured HAIs. Healthcare associated CDI decreased from 0.79 per 1,000 patient days to 0.65 per 1,000 patient days (p=0.02).
Hooker et al., 2015[37]	Two long-term acute care hospitals, one with 74 beds and the other with 30 beds	A washable cover was used for the mattress and bed deck. The cover was removed at discharge and laundered with hot water, chlorine, and detergent.	At Hospital A, the use of bedcovers reduced the rate of HO CDI by 47.8% (95% CI, 47.1 to 48.6), controlling for the rate of handwashing compliance and length of stay in days. At Hospital B, the use of bedcovers reduced the rate of HO CDI by 50% (95% CI, 47.5 to 52.7), controlling for the rate of handwashing compliance and length of stay in days (no p-value provided).

Article	Setting	Intervention	CDI Outcome
Levin et al., 2013[28]	140-bed acute care community hospital	UVD followed terminal cleaning with chlorine-based wipes (5,250 ppm) in CDI rooms. UVD was used in CDI and contact precautions rooms.	In 2010, the hospital-associated CDI rate was 9.46 per 10,000 patient days; in 2011, (1 year post-intervention), the CDI rate was 4.45 per 10,000 patient days (53% reduction, p=0.01).
Manian et al., 2013[29]	900-bed community hospital	Terminal "enhanced cleaning" consisted of use of bleach (5,000 ppm) followed by HPD using a priority scale based on the pathogen and room location.	The nosocomial CDAD rate dropped significantly from 0.88 cases/1,000 patient days to 0.55 cases/1,000 patient days (rate ratio, 0.63; 95% CI, 0.50 to 0.79, p<0.0001).
Miller et al., 2015[35]	Long-term acute care facility (bed count not provided)	UVD disinfection system was used for patient rooms (at discharge) and common areas (weekly).	Healthcare-associated CDI rates decreased over a 15-month period from 19.3 per 1,000 patient days to 8.3 per 1,000 patient days, a 56.9% reduction (p=0.02).
Nagaraja et al., 2015[36]	180-bed ICU	Terminal cleaning with UVD was used in addition to standard cleaning for all contact precautions rooms.	Compared with pre-UVD, during UVD, CDI was 22% less (p=0.06) (borderline statistical significance).
Orenstein et al., 2011[27]	2 medical units at 1,249-bed hospital	Daily and terminal cleaning with germicidal bleach wipes (0.55% bleach, i.e., 5,500 ppm) took place in all patient rooms. (Replaced quaternary ammonium compound.)	Hospital-acquired CDI incidence decreased by 85%, from 24.2 to 3.6 cases per 10,000 patient days (p<0.001).
Vianna et al., 2016[34]	206-bed community hospital	In the ICU, the goal was for all room discharges and transfers to be treated with UVD disinfection after standard cleaning and prior to the next patient occupying the room. For all non-ICU discharges and transfers, the UVD was only used for *C. difficile* discharges.	CDIs decreased by 41% (p=0.01). Greater reductions were seen in ICU versus hospital (61% vs. 29%).

4.3.4.2 Studies: Cleaning With Bleach

Two of the reviewed studies examined patient outcomes after a period in which patient rooms were cleaned with bleach either daily or at patient discharge. Hacek et al. (2010) evaluated a cleaning intervention at three hospitals with a total of approximately 850 beds in which terminal cleaning of the rooms occupied by CDI patients was conducted with a bleach solution (5,000 ppm) as a replacement for quaternary ammonium compound. In addition to the switch to bleach, walls were added to a checklist of surfaces to clean after patient discharge. The change in cleaning practices was a response to increases in CDI at the hospitals. The cleaning initiative included periodic unannounced cleaning assessments by supervisory staff.

Following 2 years of the new cleaning procedures, the average number of CDI patients per 1,000 patient days decreased from 0.85 before the use of bleach to 0.45 during bleach cleaning. There was a 48 percent reduction in the prevalence density of CDI (95% CI, 36% to 58%, p<0.0001) compared with the 10 prior months. The researchers report that there were no other significant infection prevention practice changes during the cleaning intervention implementation period.[26]

Orenstein et al. (2011) measured CDI outcomes following a cleaning intervention on two hospital wards with high baseline incidences of CDI. The cleaning program included switching from the use of quaternary ammonium compound to that of germicidal bleach wipes (5,500 ppm active chlorine) for daily and terminal cleaning of patient rooms. To evaluate progress and cleaning performance, certain

rooms were randomly assessed for cleanliness with the use of adenosine triphosphate bioluminescence, which detects organic matter on surfaces.

Following a year of the new cleaning procedures, the researchers found a reduction in hospital-acquired CDI incidence of 85 percent, from 24.2 to 3.6 cases per 10,000 patient days ($p<0.001$). The researchers cite evidence about the role of asymptomatic carriers in contaminating the environment with *C. difficile* and conclude that *daily* bleach cleaning of *all* rooms on the wards with high incidence of CDI may be more effective than only terminal cleaning of the CDI rooms. They theorize that cleaning with bleach helps to reduce the chance of transmission of *C. difficile* via the environment and onto the hands of HCWs. Orenstein et al. (2011) examined the potential influence of confounding factors and report that they controlled for other infection prevention practices prior to the intervention.[27]

4.3.4.3 Studies: Hydrogen Peroxide Decontamination

Three reviewed studies examined the use of HPD for patient room decontamination and found reductions in CDI rates.[29,31,33] The three cleaning and decontamination interventions all added the use of HPD to cleaning with bleach and were using bleach for terminal cleaning of CDI rooms prior to the intervention. The frequency of HPD varied across the studies, ranging from a one-time HPD deep clean of a ward,[33] to priority-based HPD terminal cleaning of rooms,[29] to a one-time deep HPD cleaning of five high-incidence wards followed by terminal HPD cleaning of CDI patient rooms.[31]

Boyce et al. (2008) found that, following a deep cleaning of five wards with HPD, then 8 months of terminal cleaning of CDI-occupied rooms with bleach and HPD, the incidence of nosocomial CDI decreased from 2.28 to 1.28 cases per 1,000 patient days ($p=0.047$).[31] Manian et al. (2013) evaluated an intervention at a 900-bed community hospital, in which HPD was added to terminal cleaning of all rooms. When HPD decontamination was not possible, CDI rooms were cleaned with four rounds of bleach cleaning. After approximately 7 months, the rate of nosocomial CDAD dropped significantly, from 0.88 cases/1,000 patient days to 0.55 cases/1,000 patient days (rate ratio, 0.63; 95% CI, 0.50 to 0.79, $p<0.0001$). These results are somewhat difficult to interpret as approximately half of the CDI rooms were cleaned with HPD and half were cleaned with four rounds of bleach cleaning.[29]

4.3.4.4 Studies: Ultraviolet Environmental Disinfection

Six studies selected for this review examined the use of UVD and CDI patient outcomes. Of these, four studies showed statistically significant decreases in CDI following a period of UVD added to standard terminal cleaning with bleach of CDI patient rooms[25,28,34,35] and one found borderline significant reductions in CDI.[36] In one example, Vianna et al. (2016) report on the addition of UVD to terminal cleaning with bleach in a 206-bed hospital. The terminal UVD procedure was implemented for all room discharges in the ICU and for rooms occupied by patients with *C. difficile* in the rest of the hospital.

Following 21 months of the UVD intervention, the researchers reported a 41 percent decrease in CDI ($p=0.01$). CDI reductions were greater in the ICU than in the rest of the hospital (61% vs. 29%). The results indicate that UVD is effective when deployed to higher risk/higher acuity settings (e.g., the ICU) and/or when used in all room discharges (not just for patients with *C. difficile*). One potential confounder was an ASP, implemented 11 months prior to adoption of UVD. However, this change was not statistically linked to the reduction in CDI rates during the UVD period.[34]

Long-term acute care facilities have different environmental cleaning/decontamination needs than hospitals. For example, patient stays are longer than in the hospital, so patient rooms turn over less

frequently. In a study of CDI patient outcomes and environmental cleaning in a long-term acute care facility, Miller et al. (2015) looked at the addition of UVD to standard procedures for cleaning patient rooms at discharge and for cleaning common areas on an approximately weekly basis. For rooms occupied by *C. difficile* patients, standard procedures also included cleaning with a bleach solution.

During a 15-month period of added UVD, CDI rates decreased from 19.3 per 1,000 patient days to 8.3 per 1,000 patient days, a 56.9 percent reduction (p=0.02). It is important to note that in the prior year, the facility had implemented additional infection prevention measures consisting of education for staff around hand hygiene for CDI, disposable equipment, additional handwashing sinks, reminders about equipment decontamination, and a checklist for terminal cleaning. It is possible that the reductions in CDI rates reflect the longer term impact of these measures.[35]

In the most robust study, less favorable results were found in a broad cluster-randomized study of nine hospitals, in which terminal cleaning with bleach of all rooms occupied by CDI patients was compared with terminal cleaning with bleach plus UVD. In this crossover trial, Anderson et al. (2017) found that, comparing the strategies for 7 months each, the incidence of CDI infection among patients exposed to rooms previously occupied by patients with CDI was unchanged (n=38 vs 36; 30.4 cases vs 31.6 cases per 10,000 exposure days; relative risk 1.0, 95% CI 0.57 to 1.75, p=0.997).[32]

4.3.4.5 Study: Launderable Bed Covers

Hooker et al. (2015) examined CDI rates associated with the introduction of launderable bed covers at two long-term acute care hospitals. The researchers note that prior studies had shown that HAIs could be spread through contaminated mattresses (which are difficult to clean without damaging) and bedframes (i.e., bed decks). To prevent this source of transmission, the cleaning intervention consisted of the use of washable bed covers that covered both the mattress and bed deck. (The covers consisted of the same material used in high-end mattresses and allow moisture transmission.) The washable covers were used on all patient beds, removed after every patient discharge, and replaced with a clean cover.

After 14 months of use of the bed covers, the rate of CDIs at one hospital decreased 47.8 percent (95% CI, 47.1 to 48.6), controlling for the rate of handwashing compliance and length of stay in days. At the second hospital, the rate of CDIs decreased by 50 percent (95% CI, 47.5 to 52.7), controlling for the rate of handwashing compliance and length of stay in days. Data were not available on antimicrobial use, so this variable was not factored into the analyses. Hooker and colleagues (2015) theorized that, in addition to reducing the spread of *C. difficile*, the use of bed covers could help to reduce room turnover time between patients as the bed surfaces did not require thorough cleaning.[37]

4.3.4.6 Laboratory and Quasi-Experimental Studies

A number of studies and one review compare the performance of different cleaning agents and methods in removal/eradication of the *C. difficile* organism. We provide a sample of studies in the next two segments.

4.3.4.6.1 Experimental Studies: HPD and UVD Versus Bleach

Several experimental studies compared the touchless methods with bleach cleaning with mixed results. Ghantoji et al. (2015) examined whether, after cleaning with standard detergents, terminal cleaning with bleach solution or UVD was more effective at removing *C. difficile*. High-touch surfaces in rooms

previously occupied by CDI patients were sampled after discharge and before and after the use of both methods. The researchers found that the difference in final contamination levels between the two cleaning protocols was not significant (p=0.98).[38] Similarly, Mosci et al. (2017) looked at hydrogen peroxide and silver ion solution compared with cleaning with bleach following standard cleaning for removing *C. difficile* on different surfaces in a hospital. After disinfection, 0 percent (p<0.001) of samples were contaminated with *C. difficile* after HPD, and 3 percent (p<0.001) of samples were contaminated after bleach cleaning. The differences between groups was not statistically significant and the time for each cleaning intervention was roughly the same.[39]

Barbut et al. (2009) found that an *in situ* hydrogen peroxide dry mist system was more effective than 0.5% sodium hypochlorite solution at eradicating *C. difficile* spores; samples taken from hydrogen peroxide-treated rooms showed a 91 percent decrease in *C. difficile,* whereas samples taken after hypochlorite decontamination showed a 50 percent decrease in *C. difficile* (p<0.005).[40]

4.3.4.6.2 Experimental Studies: Alternatives to Bleach

While cleaning with bleach and chlorine-based solutions has been shown to be highly effective in eliminating *C. difficile* from surfaces, these agents can be corrosive to metals and irritating to skin and mucus membranes.[17] Housekeepers have reported respiratory irritation when using bleach and other chlorine-based disinfectants.[41] One reason for terminal cleaning rather than daily cleaning of CDI patient rooms is for environmental services staff to avoid excessive exposure to bleach.[26] Concerns for patients and employees include the appearance of bleach residue left on surfaces, odors, and respiratory tract irritation.[41] Due to the toxicity of bleach, the Occupational Safety and Health Administration recommends using gloves and eye protection, ventilating the room properly, preparing the bleach solution daily, and allowing the solution to stand at least 30 minutes after preparation before use.

Several studies have examined potential alternatives to bleach. For example, Alfa et al. (2008) looked at different formulations of hydrogen peroxide for cleaning toilets contaminated with *C. difficile.* The researchers found that one of the tested hydrogen peroxide alternatives was equivalent to bleach 1,000 ppm after 1 minute but was not as efficient as that achieved for bleach at 5,000 ppm (1:10 bleach to water).[42]

Peracetic acid has performed similarly to bleach.[43] Kundrapu et al. (2012) studied the potential use of a peracetic acid-based disinfectant because preliminary studies indicated that it was as effective as bleach solution but less corrosive and irritating. The peracetic acid was associated with a significant reduction in the frequency of acquisition of pathogens on investigators' hands after contact with the surfaces and in the mean number of colony-forming units acquired. Patients in the rooms reported no adverse effects during use of the product, and there were no complaints from the nursing staff.[44]

4.3.4.7 Economic Outcomes

In the reviewed studies, there was limited financial information on the studied cleaning and disinfection interventions. The article by Orenstein et al. (2011) was an exception, reporting that the cost of the bleach wipes used for the daily and terminal cleaning of two medical units was $12,684 per year. They estimated that 27 cases of healthcare-associated CDI were prevented in this study, resulting in healthcare savings of between $135,000 and $216,000. While additional staffing time for daily and terminal bleach cleaning was not factored into the analyses, the researchers say that "it added little

extra time to the housekeepers' daily routine" (page 1138), indicating that there were minor increases in room turnover time.[27]

Other reviewed studies provided some information about the costs of UVD and HPD. These findings are summarized in Table 4. Specifically, Miller et al. (2015) and Vianna et al. (2016) reported that UVD was cost effective in terms of CDIs avoided.[34,35] Levin et al. (2013) reported that the cost to lease two UVD machines was less than $5,000 per month[28] and Doan et al. (2012) estimated the cost of HPD equipment was $1,154.98 per month.[43]

Ghantoji et al. (2015) reported that UVD was more cost effective than HPD, primarily because of the time needed to use each device—HPD takes longer than UVD per room. Both methods require that rooms be vacant and items be placed in a manner that allows adequate contact with the hydrogen peroxide mist or UV light. Before the HPD process starts, all heating, ventilation, and air-conditioning ducts in the area need to be sealed.[38]

Boyce et al. (2008) reported that the HPD process took approximately 3 to 4 hours per patient room and approximately 12 hours for an entire ward. Doll et al. (2015) stated the time per room for UVD depended on the type of UVD; pulsed xenon UV takes 15 to 20 minutes and UVC radiation takes 20 to 40 minutes.[31] Haas et al. (2014) reported that the time for UVD light exposure in their study was around 6 minutes, but it took close to a half hour for setup (including setting up blackout curtains), depending on the room. Haas et al. (2014) also reported that cleaning can be more efficient by using UVD first in the bathroom, while finishing cleaning the larger room by hand.[25]

While UVD may be more time efficient than HPD, it has some limitations; the process has decreased effectiveness at higher distances (over 1.22 m) and cannot decontaminate items in shadow.[36] Finally, in their review of multiple cleaning methods, Doan et al. (2012) report that decontamination with bleach was cheaper than and as effective as touchless methods.[43]

Table 4: Cost, Decontamination Time, and Setup for HPD and UVD

	Equipment Costs	Time for Cleaning	Room Setup for Cleaning
HPD	$1,155/mo. for 1 unit (Doan et al., 2012)	3–4 hours per patient room 12 hours per ward	Must be vacant Must have HVAC ducts sealed
UVD	<$5,000/mo. for 2 units (Levin et al., 2013)	15–40 minutes per patient room	Must be vacant Requires blackout curtains (for windows and to cordon off areas of rooms) Requires items be moved out of shadows

4.3.5 Implementation: Challenges and Facilitators

One of the challenges reported across several of the studies on HPD and UVD was being able to use the touchless machines in all intended cases.[28,29] For example, Levin et al. (2013) reported that the goal was to conduct terminal UVD on all contact precautions rooms but only 56 percent of discharged contact precautions rooms received the UVD treatment. This discrepancy was due to limited device availability or the presence of a second room occupant.[28]

Similarly, Haas et al. (2014) reported 76 percent of contact precautions rooms received the UVD treatment, rather than the intended 100 percent. Reasons for not conducting the UVD included a second room occupant who could not be moved, an urgent need for the room, and labor constraints.[25] Manian et al. (2013) report that using a system that prioritized use of the HPD machine based on the

HAI of the discharging patient (with CDI as the top priority) allowed the machine to be used for rooms not inhabited by CDI patients when possible. When the HPD machine was not available for a CDI room, the room was cleaned multiple times with bleach.[29]

Compliance with cleaning procedures is essential for eliminating active *C. difficile* from the environment. Research shows that touchless methods require appropriate operation. For example, the UVD machine may require repositioning in order to be most effective.[23,36] Ways to assist with manual cleaning compliance include cleaning checklists and audit and monitoring. Khanafer et al. (2015) recommend the use of checklists to guide housekeepers on the cleaning sequence and provision of education and direct and immediate feedback to environmental services staff.[30]

Denton et al. (2016) discussed survey results from cleaning staff and others following a period of use of an audit and monitoring tool. They reported positive responses about the tool, saying that education of—and investment by—the housekeeping staff, in addition to positive, approachable, and supportive leaders, helped make the tool effective.[45] The use of adenosine triphosphate bioluminescence[27] or fluorescent markers can be effective in auditing/monitoring the thoroughness of cleaning and a basis from which to provide feedback.[46]

4.3.6 Resources To Assist With Implementation

C. difficile Collaborative Non-ICU Environmental Cleaning Checklist**:**
http://www.rochesterpatientsafety.com/Images_Content/Site1/Files/Pages/Hospitals/Non-ICU%20Cleaning%20Checklist.pdf

CDC Guide to Infection Prevention for Outpatient Settings:
https://www.cdc.gov/infectioncontrol/pdf/outpatient/guide.pdf

CDC Options for Evaluating Environmental Cleaning:
https://www.cdc.gov/HAI/toolkits/Evaluating-Environmental-Cleaning.html

List K: EPA's Registered Antimicrobial Products Effective Against *Clostridium difficile* Spores:
https://www.epa.gov/pesticide-registration/list-k-epas-registered-antimicrobial-products-effective-against-clostridium

Not Just a Maid Service:
https://www.youtube.com/watch?v=nfZftqBELsA

SHEA/IDSA Clinical Practice Guidelines for *C. difficile*: 2017 Update:
https://www.idsociety.org/globalassets/idsa/practice-guidelines/clinical-practice-guidelines-for-clostridium-difficile.pdf

SHEA/APIC Guideline: Infection Prevention and Control in the Long-Term Care Facility:
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3319407/

4.3.7 Gaps

There are several gaps in the studies on environmental cleaning for CDI prevention. While much of the evidence is promising for the environmental cleaning interventions included in this review, there is a need for more high-quality (e.g., randomized, robust) studies in diverse healthcare environments and larger multifacility studies to better understand this PSP. The only randomized/crossover study, by

Anderson et al. (2017), found no significant change in CDI incidence following the addition of UVD to bleach cleaning for room discharges at nine hospitals.[32] More randomized studies are needed to compare the evidence. In addition, more robust financial evaluations that investigate the various methods and combinations of methods and incorporate staff time, room turnover time, and cost of no-touch devices and other cleaning machines and supplies would be beneficial.

There is also a gap in the literature with regard to cleaning and CDI patient outcomes outside of the patient rooms in the larger facility environment. Only Miller et al. (2015) describe decontamination of common areas,[35] while Best et al. (2014) and Boyce et al. (2008) describe one-time "deep" cleaning of entire wards using HPD.[31,33] While patient rooms are the primary focus of most of the reviewed studies, *C. difficile* contamination has been found in nonisolation rooms, in physician and nurse work areas, and on portable equipment.[47]

Finally, there is a shortage of studies on environmental cleaning/decontamination in long-term facilities, outpatient, and other nonhospital settings. We identified only two studies of sufficient sample size on environmental cleaning and CDI outcomes in long-term acute care settings.[35,37] Nursing home residents are at high risk for CDI due to frequent antimicrobial exposure and the relatively high number of colonized patients in LTCFs. A systematic review found that 14.8 percent (95% CI, 7.6% to 24.0%) of LTCF residents are asymptomatic carriers of toxigenic *C. difficile*.[48]

CDI recurrence is also high in LTCFs due to new infection or recurrence of the original infection. Given longer patient stays and the presence of more patient belongings (creating additional possible transmission pathways), and that LTCFs are intended to promote social interaction, LTCFs have unique environmental decontamination needs that require further study.[49]

4.3.8 Future Directions

Future directions for environmental cleaning practices to prevent *C. difficile* transmission include advances in hospital equipment and standard hospital items.[50] For example, research has explored the use of copper for hospital surfaces (e.g., cabinets, tables). Copper has been shown to provide a significant (>70 percent) reduction in survival of *C. difficile* vegetative cells and spores on copper alloys compared with stainless steel.[15] Sporicidal properties in common hospital items such as curtains has also been explored.[51] Installation of items such as toilet lids can help prevent the spread of CDI droplets when a contaminated toilet is flushed.[8] Some studies show that microfiber cloths (made of a combination of polyamide and polyester) perform better than standard cotton materials at removing *C. difficile*.[52]

Future research could build on and enhance existing cleaning and decontamination technologies. One example is hand-held wands that can be used on items such as keyboards and portable medical devices to kill pathogens with UV radiation.[53] Another example involves rendering *C. difficile* spores more susceptible to UVD and increasing the efficacy of UVD by initiation of *C. difficile* germination. (The initiation of germination has been shown to make spores more susceptible to heat and radiation.) Application of germination solution to a contaminated surface prior to UVD was shown to increase the number of spores killed by UVD compared with UVD alone.[54] Finally, continued research on environmental services systems and efficacy of methods, as well as improved support and training of environmental services workers, will help to advance cleaning and decontamination practices in the future.

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4.4 PSP 4: Surveillance

Reviewers: Arjun Srinivasan, M.D., and Luba Katz, Ph.D.

This review includes a summary of evidence published from 2008 to 2018 on surveillance practices for CDI. After a brief practice description from CDC, IDSA/SHEA, and others, the review explains how regional and facility-level surveillance work as safety practices for preventing the transmission of C. difficile. Next, we provide a review of studies on CDI surveillance methods and explore surveillance contextual factors, such as setting and CDI testing method. Finally, we discuss research gaps and future directions for CDI surveillance. The review's key findings are listed in the box below.

4.4.1 Practice Description

The CDC defines public health surveillance as "the ongoing, systematic collection, analysis, and interpretation of health data, essential to the planning, implementation and evaluation of public health practice, closely integrated with the dissemination of these data to those who need to know and linked to prevention and control."[1,2] Experts emphasize the importance of using standard surveillance criteria to make accurate comparisons over time, report data to the public, and compare data across facilities.[3,4] According to the IDSA/SHEA *C. difficile* clinical practice guidelines,[4] facilities should implement the following surveillance activities for adult patients (the strength of recommendation is from the IDSA/SHEA guidelines):

Key Findings

- Research has shown that automated surveillance systems are generally accurate and save time and resources, compared with manual case review.
- Automated laboratory alerts have been shown to help expedite contact precautions for CDI patients.
- Classifying CDI cases using standard case definitions is important although some researchers have found that the current definitions over represent the number of nosocomial cases.
- There is a need for research that evaluates and compares different facility-level CDI surveillance strategies and implementation barriers and facilitators.
- Genotyping provides detail about differences in *C. difficile* virulence and has helped to identify transmission pathways and outbreaks.
- Promising technologies include rapid molecular typing, integrated systems that can track CDIs across health systems and facilities, and facility-access to regional real-time surveillance data.

- Use available standardized case definitions for surveillance of (1) healthcare facility-onset (HO) CDI; (2) community-onset, healthcare facility–associated (CO-HCFA) CDI; and (3) community-associated (CA) CDI (*good practice recommendation*).
- At a minimum, conduct surveillance for HO CDI in all inpatient healthcare facilities to detect elevated rates or outbreaks (*weak recommendation, low quality of evidence*).
- Express the rate of HO CDI as the number of cases per 10,000 patient days. Express the CO-HCFA prevalence rate as the number of cases per 1,000 patient admissions *(good practice recommendation*).
- In settings of high endemic rates or outbreaks, stratify data by patient location to target control measures when CDI incidence is above national or facility reduction goals, or if an outbreak is noted (*weak recommendation, low quality of evidence*).

Facility *C. difficile* surveillance practices include conducting internal surveillance data collection and analyses and reporting to State and Federal agencies via CDC's NHSN. The NHSN assists facilities in collecting data to help determine local, regional, and national infection prevention priorities. The NHSN also helps facilities meet quality benchmarks, identify areas for improvement, and comply with CMS

infection reporting requirements. To track national CDI incidence and establish reduction targets, the NHSN calculates standardized infection ratios. The standardized infection ratio is a risk-adjusted summary measure used to track HAIs at a national, statewide, or local level over time and by facility type. The NHSN also collects information on certain infection safety practices and antimicrobial resistance.[5]

Another national surveillance program is the CDC Emerging Infections Program, a network of 10 State health departments, academic institutions, Federal agencies, and other public health stakeholders that collect data and support research and training to inform policy and public health practice. The national Healthcare Cost and Utilization Project is a database resource sponsored by AHRQ that has been used to track and report *C. difficile* hospitalizations.[6] *C. difficile* is also among the conditions tracked in the AHRQ National Scorecard on Hospital-Acquired Conditions.[7]

At the State level, CDI reporting requirements vary; some States require facilities to report on *C. difficile* (via the NHSN) either by adopting CMS's quality reporting requirements as State law, or through State mandates.[8] Many States implemented reporting requirements in 2013, the year in which hospitals were first required to report HAIs via NHSN for the CMS Hospital Inpatient Quality Reporting program.[9]

Internal facility surveillance practices vary depending on facility resources and local requirements. Facilities may use the NHSN system to conduct internal CDI surveillance using the MDRO/CDI Module.[10] The LabID option, introduced in 2013, uses admission date, laboratory test results, and patient care location to automatically estimate measures of CDIs. An incident case is defined as any CDI LabID event from a specimen obtained more than 56 days after the most recent CDI LabID Event. A recurrent case is any CDI LabID event from a specimen obtained >14 days and ≤56 days after the most recent CDI LabID event for that patient. The day of the first specimen collection is considered day 1. HO-CDI cases are those LabID events collected more than 3 days after admission to an inpatient facility (i.e., on or after day 4). The Infection Surveillance Reporting option for CDI is based on clinical case reviews to identify and report CDIs. Facilities may report at the facility level or by different units within the facility.

Facilities may also report on adherence to hand hygiene and contact precautions for *C. difficile* patients. The NHSN system allows facilities to use their data to:

- Calculate CDI measures (e.g., prevalence at admission, CO prevalence, facility or unit incidence),
- Create charts,
- Filter data,
- Track incidence in different facility locations,
- Identify trends,
- Recognize deviations from the norm, and
- Compare rates with other facilities.

The NHSN also collects data on antimicrobial use and resistance in a separate module. CDC's Targeted Assessment for Prevention (TAP) provides infection prevention resources and guidance on how to interpret surveillance data and report feedback to stakeholders such as facility leaders and administrators.[11] Links to this and other resources are available later in this section of the CDI chapter.

Facility surveillance practices include using alerts for positive CDI cultures and tracking the movement of CDI patients within a facility or health system.[12,13] It is recommended that facilities have procedures for investigating outbreaks, protocols to guide referrals for strain typing, and processes to communicate with associated healthcare facilities and relevant jurisdictional bodies, as required.[14]

4.4.2 Surveillance as a PSP

The epidemiology of CDI has been evolving, with particular increases in CO CDI and hypervirulent strains.[15] Regional and national surveillance provide information on CDI epidemiology and help to identify clusters, outbreaks, and emerging ribotypes. Analyses of these data inform policy and public health programs.[16]

At the facility level, CDI surveillance is used to identify transmission pathways and CDI clusters, evaluate safety improvement initiatives, and signal when facilities must enhance measures to prevent further transmission.[13,16] Monitoring HO-CDI incidence is a first step in identifying and controlling outbreaks at facilities. In one example, an outbreak on a vascular surgery unit was identified by an increase in the number of cases within 30 days and a change in the pattern of new cases. Samples were sent to a regional lab for PCR testing and results revealed that outbreak cases were caused by *C. difficile* ribotype 106, a clindamycin-resistant strain. Based on these findings, the facility implemented restrictions on the prescribing of clindamycin. Controlling the outbreak was attributed to this measure.[17] Root cause analysis of HO-CDI cases, another surveillance practice, helps facilities understand the reasons for hospital transmission and make workflow improvements, such as reducing testing delays.[18]

In 2007, the CDC adopted standardized case definitions to track disease trends, detect outbreaks, facilitate comparison of CDI rates among similar institutions, and incorporate previous healthcare facility exposure information.[19] These definitions have been updated. For example, the 2007 case definition for healthcare facility onset was defined as a patient with CDAD symptom onset more than 48 hours after admission to a healthcare facility. Now, the definition for healthcare facility onset is defined as LabID events collected >3 days after admission to an inpatient facility.[4]

CDI case identification and classification were traditionally conducted by individual case review; however, manual data abstraction is labor intensive, burdensome, and costly.[20] As technology evolves and reporting mandates increase, more facilities are using commercial infection control systems that process electronic health data to identify and classify cases.[12,20] Swift and automated identification of patients with *C. difficile* helps expedite contact precautions and reduce the potential for additional healthcare transmissions.[12] Research using genotyping technology (described below) supports rapid identification of CDI isolates and helps track transmission and identify virulent strains both within a facility and regionally.[21] Ribotyping (described below) during periods of increased CDI incidence can help identify CDI clusters and outbreaks.[22]

Currently, there are a lack of studies that compare or evaluate facility-level CDI surveillance strategies.

4.4.3 Methods

The question of interest for this review is: What are the most recommended and promising institutional surveillance practices for *C. difficile*?

To answer this question, we searched the databases CINAHL and MEDLINE from 2008 to 2018 for "*Clostridium difficile*" and related MeSH terms and synonyms, as well as "Surveillance" OR "monitoring

and surveillance" OR "epidemiologic surveillance" OR "infectious diseases surveillance" and synonyms. The search string also included a variety of healthcare settings, such as "hospitals," "inpatient," "long-term care," "transitional care," and "home health." After duplicates were removed, the initial search yielded 503 results, all of which were screened for inclusion, and 42 full-text articles were retrieved.

Reference lists of included articles were also screened to ensure thoroughness and 14 additional studies were identified and retrieved. Articles were excluded if the intervention or outcomes were not relevant or precisely reported or if the study design was insufficient (e.g., opinion pieces, nonsystematic reviews). Studies in which surveillance was followed by other significant infection control practices (e.g., changes in environmental cleaning) were ruled out for this section and are considered in Section 4.6, Multicomponent CDI Prevention Interventions. Of the total retrieved articles, 16 studies and 2 systematic reviews were selected for inclusion in this review.

General methods for this report are described in the Methods section of the full report.

For this patient safety practice, a PRISMA flow diagram and evidence table, along with literature-search strategy and search-term details, are included in the report A through C appendixes.

4.4.4 Review of the Evidence

We found 16 studies and 2 systematic reviews that examined facility *C. difficil*e surveillance practices. These practices include the use of different statistical analyses, automated surveillance alerts, CDI case identification and classification, genotyping practices, and use of biomarkers to track CDI virulence. Most of these studies are descriptive case studies with no comparison group. Several studies examined the utility and accuracy of International Classification of Diseases (ICD) code data alone or in combination with medication data to conduct HO-CDI surveillance. Overall, there is a gap in the literature with regard to facility practices for implementing surveillance to reduce CDI.

4.4.4.1 Surveillance To Identify CDI Outbreaks and Clusters

One study from the United Kingdom demonstrates how surveillance can be used to identify CDI clusters and trigger implementation of enhanced infection prevention practices. In this study, Hardy et al. (2010) described the use of an HO-CDI case threshold to identify CDI clusters at a 1,800-bed teaching hospital. The case threshold was two or more HO-CDI cases within a 28-day period. Two or more HO-CDI cases was considered a period of increased incidence. The studied intervention was implemented upon identification of a period of increased CDI incidence. It included a standardized set of interventions, including notifying staff of the increased incidence and auditing compliance with hand hygiene, using environmental decontamination practices, isolating patients, and providing clinical management of patients with confirmed or suspected CDI.

If the audit identified any shortcomings in these prevention practices, steps were taken to make improvements. Additional enhanced cleaning was also implemented upon identification of the period of increased incidence (PII). If there were postaudit incident HO-CDI cases, a more detailed environmental audit was conducted by one of the head nurses. In the first 9 months of the study, isolates were ribotyped on PIIs with more than 10 cases; for the last 8 months of the study, isolates were ribotyped for all PIIs. In this case, an outbreak was defined as two or more cases of the same PCR ribotype within a 28-day period.

While less common in the United States outside of research contexts, ribotyping of *C. difficile* isolates helps determine transmission pathways and confirm presence of an outbreak. During roughly 1.5 years of the intervention, the number of PIIs investigated per month decreased from a peak of 14 per month in February 2008 to 1 in June 2009. For the first 9 months, five of seven periods with more than 10 cases were confirmed as outbreaks. In the final 8 months, ribotyping of the isolates confirmed nine (32%) of these periods to be outbreaks, with three being due to ribotype 027, two ribotype 078, and all the others distinct ribotypes.[22]

Two of the included studies examined different statistical methods for CDI surveillance.[23,24] Lavan et al. (2012) compared the value and efficiency associated with manual tracking and calculating the incidence and prevalence of CDI in two wards in an acute 751-bed hospital in Ireland that were experiencing an increase in the number of severe CDI cases. For 6 weeks, the researchers measured the prevalence of CDI, antibiotic use, and associated comorbidity, and then for 13 weeks identified all new CDI cases, all using manual data collection. CDI cases were assessed for CDI risk factors, disease severity, response to treatment, and outcomes at 6 months.

The researchers found that manual data collection and analysis took less time in their prevalence study than the incidence study. The prevalence study provided useful information about differences between the two wards in CDI prevalence and CDIs with MRSA colonization, the extent of multiple antibiotic prescriptions in CDIs, and areas that required more indepth surveillance. The incidence study permitted a more detailed evaluation of CDI risk factors, origin and severity of disease, and patient outcomes. Overall, researchers found that incidence analysis was more useful for their institution for planning preventive initiatives and focusing antibiotic stewardship efforts.[23]

Screening for outbreaks is often based on a relative increase in incidence or when incidence reaches an absolute threshold.[16] A temporal scan statistic approach examines new cases within a particular window of time and can be used prospectively or retrospectively. Faires et al. (2014) applied a retrospective scan statistic to identify several CDI clusters and potential outbreaks in a hospital based on 5 years of laboratory results and bacteriology reports. PCR was used to identify *C. difficile* isolates for the most recent year of data. CDI clusters were identified using the temporal scan statistic, and statistically significant clusters were compared with CDI outbreaks that had been identified using standard hospital surveillance. A negative binomial regression model identified associations between year, season, and month rate of CDI cases.

Results of the statistical analyses indicated that the incidence rate for CDI was significantly higher in the spring than in the fall and winter seasons. Overall, 86 CDI cases were identified, 18 specimens were analyzed, and 9 ribotypes were classified. The temporal scan statistic identified three significant clusters ($p \leq 0.05$), including potential outbreaks, not previously identified by hospital personnel using standard surveillance analyses. One outbreak was identified as starting a month before it had been recognized by the hospital. The researchers note that temporal analyses, applied prospectively and in tandem with other methods, could be useful in identifying clusters and outbreaks in a timely manner.[24]

4.4.4.2 Integrating Automation Into Surveillance

Over the last 10 years, CDI surveillance has become increasingly automated.[25] Automated and consistent measurement of CDI is preferable to disparate systems for surveillance of CDI.[21] Several studies in this review examined the feasibility and efficacy of electronic surveillance systems. Studies have found that

the use of automated systems and EHR data assist in the rapid detection of cases and outbreaks,[12,13,26] and electronic strategies can provide timely alerts and help expedite contact precautions. Zilberberg et al. (2011) demonstrate that electronic patient data can be used to calculate risk-stratified HO-CDI rates to help inform practice.[27] Dubberke at al. (2012) and Benoit et al. (2011) found that automated surveillance using electronically available data (e.g., admission date) was accurate and more efficient than manual case review.[28,29]

4.4.4.2.1 Automated CDI Surveillance

Dubberke et al. (2012) developed and validated an automated CDI surveillance algorithm using 1 year of available electronic data from four U.S. hospitals located in different regions. Each hospital customized the algorithm to accommodate variability in datasets. Electronic surveillance was highly sensitive and specific and showed good agreement with manual review for HO; CO, study facility-associated; indeterminate; and recurrent CDI. The overall sensitivities, specificities, and kappa values of the algorithm compared with the manual case review were:

- HO: 92 percent sensitivity, 99 percent specificity, and 0.90 kappa;
- CO, study facility-associated: 91 percent, 98 percent, and 0.84;
- CO, CA: 96 percent, 94 percent, and 0.69;
- Indeterminate cases: 80 percent, 98 percent, and 0.76; and
- Recurrent cases: 94 percent, 99 percent, and 0.94.

The results for CO, other HCFA were less sensitive (57%), were highly specific (99%), and had a kappa value of 0.65. In discussing the lower sensitivity for CO, other HCFA infections, they note the challenges of accurately capturing previous healthcare episodes using the available data. Several hundred discordant cases (out of 1,767 patients with a positive CDI test) required review and correction due to misclassifications in the data. Overall, the researchers reported that automated surveillance reduces staff time and may help facilities better track CO CDI.[28]

While Dubberke et al. (2012) found that sensitivity and specificity for automated surveillance using EHR data was adequate, other researchers have found that, in practice, automated surveillance may overestimate the rate of HO CDI.[30,31] For example, Durkin et al. (2015) compared LabID reporting (for the NHSN) with traditional surveillance in 29 community hospitals in the southeastern United States. LabID is designed to use electronically captured laboratory data and hospital admission dates to determine HO versus CO surveillance CDI categories.

LabID surveillance resulted in a higher HO-CDI incidence rate than did traditional surveillance. The overall HO-CDI rate was 6.0 versus 4.4 per 10,000 patient days for LabID and traditional surveillance, respectively ($p<0.001$). After 6 months, 286 (23%) mismatched CDI events were detected. The most frequent causes of mismatched cases by LabID were:

- Diagnostic testing delay >3 days despite the presence of symptoms of CDI in the first 2 days of admission triggering an HO-CDI LabID categorization,
- Misclassification of recurrent or continuation episodes as incident events by LabID, and
- Lack of an indeterminate category in LabID definitions.

The differences based on surveillance method may affect hospital quality rankings.[31] Several hospitals in the study showed significantly lower rankings based on LabID surveillance (versus traditional surveillance). Once the coding was corrected, hospital rankings based on LabID HO rates were similar to rankings based on traditional surveillance.

In a recent study, Albert et al. (2018) examined the misclassification of HO CDIs reported to the NHSN by a large urban medical center. Using retrospective chart review of 212 HO-CDI cases, they found that only 62.2 percent of the cases reported to NHSN actually met the clinical definition of probable or possible HO CDI. The researchers estimate that the remaining cases may have been misclassified due to delays in testing, inappropriate testing, or use of stool softeners and laxatives. The researchers cite prior evidence that PCR testing is less able to distinguish between infection and colonization cases and that testing patients for CDI either too late or without clinically significant diarrhea contributes to overdiagnosis of HO CDI.[32] Truong et al. (2017) suggest real-time electronic tracking of diarrheal episodes and laxative therapy, to verify *C. difficile* testing criteria.[33]

4.4.4.2.2 Automated Alerts

Quan et al. (2015) explored the accuracy and efficiency of a system for five MDROs and *C. difficile* tracking in a 410-bed tertiary care center that automated the following: monitoring microbiology results and initiating chart-based flags, ordering contact precautions on admission, and ensuring appropriate removal of precautions. The system was initiated as an alternative to manual case review, which required the assessment of laboratory results and tracking prior history of MDRO carriage and *C. difficile* infection. The system automatically reviewed daily positive laboratory results for 110,212 patient days and identified 1,543 results representing either new incident CDI cases or cases not previously known to the system, which triggered organism-specific flags. The automated ordering of precautions for inpatients occurred immediately after laboratory results were finalized, without a delay for manual order submission.

To test the accuracy of the system, the researchers conducted a point-prevalence assessment and found that all precautions were appropriate. The advantages of the automated system included preventing missed precautions and timelier weekend and after-hours isolation precautions. The researchers estimated that the automated alerts could save 850 annual hours of staff time.[12] Automated alerts have also been shown to expedite contact precautions and significantly increase the rate of appropriately isolated patients for other HAIs.[26]

4.4.4.3 Using ICD Code Data for HO-CDI Surveillance

Automated surveillance of CDI can be conducted using clinical data (e.g., the LabID system) or administrative code data.[34] We found three studies and a systematic review that examined the accuracy of using ICD code data for the identification of CDI.[20,35-37] There are advantages to using ICD data since these codes are used by all facilities for insurance billing purposes and are stored in electronic formats.[20,35] One disadvantage is that the ICD coding rules may not match the standard surveillance definitions or account for testing sensitivity[35] or clinical context.[38] While useful for tracking overall CDI burden, some research shows that ICD-9 codes are not adequately accurate in identifying the place of onset (i.e., HO CDI vs. CO-HCFA infection).

Use of present-on-admission (POA) criteria, which CMS required to better distinguish CO versus HO-CDI cases began on October 1, 2008. In a review of overall cases of CDI, ICD coding may be useful, as

evidenced in a recent national report using Healthcare Cost and Utilization Project data that focused on the burden of CDI for hospitals (using ICD-9 codes) and provided quarterly and annual estimates of CDI hospitalization rates from 2011 through 2015.[6] The POA indicator in ICD codes can be used to help distinguish which cases originated in the facility. This report shows how the POA-CDI rate is associated with the HO-CDI rate. However, the numbers do not account for CDI infections that resolved without an inpatient stay and cases that originated in a different health facility. Another challenge when working with these data is that coding practices may differ across hospitals and States.[6]

To improve the accuracy of ICD data, Schmiedeskamp et al. (2009) examined the use of ICD-9 Clinical Modification code CDI data combined with medication treatment data, in an automated HO-CDI case identification system. The researchers examined a year of discharge data (23,920 adult patients) for over 300 hospitals. They identified adults discharged with an ICD-9-CM code for CDI and documentation of CDI therapy with oral vancomycin or metronidazole compared with ICD-9 code only. Case review was used to determine true cases. The sensitivity of the ICD-9-CM code alone for identifying nosocomial CDI was 96.8 percent, the specificity was 99.6 percent, the positive predictive value was 40.8 percent, and the negative predictive value was 100 percent. When CDI drug therapy was included with the ICD-9-CM code, the sensitivity ranged from 58.1 percent to 85.5 percent, specificity was virtually unchanged, and the range in positive predictive value was 37.9 percent to 80.0 percent, depending on the parameters of number of days of therapy and when therapy started.[36]

4.4.4.4 *C. difficile* Genotyping

Although primarily used in research, genotyping technologies can enhance investigations into *C. difficile* transmission, identify virulent strains, and assist in understanding antimicrobial resistance.[16] Methods for genotyping (also called molecular typing) include:

- PCR ribotyping,
- Pulsed field gel electrophoresis variable-number tandem-repeat analysis,
- Whole-genome sequencing,
- Next-generation sequencing, and
- Multilocus sequence typing.

One U.K. study explored how PCR ribotyping can be used to help identify local/facility outbreaks and virulent strains and inform infection prevention initiatives.[39] Wilcox et al. (2012) evaluated England's Clostridium difficile Ribotyping Network and changes in CDI rates in the country. From 2007 to 2010, the network received samples from facilities for 10.8 percent of all CDI patients in the country (12,603 fecal specimens), along with demographic information, the name of the requesting hospital, and antibiotic history in the 30 days before the onset of CDI symptoms.

Hospitals were notified of the ribotyping results with a targeted turnaround time of less than 2 weeks. Ribotype 027, a ribotype associated with increased complications and mortality, was the most frequently detected in all 3 years but decreased over the 3 years. After 3 years, there was a 61 percent reduction in reported *C. difficile* in England. The researchers believe that the Clostridium difficile Ribotyping Network helped facilities get control of ribotype 027 by providing timely data on ribotypes, enabling targeted interventions for ribotype 027.[39]

4.4.4.5 Innovations

Compared with PCR ribotyping, whole genome sequencing offers greater detail about diversity within genotypes. Next-generation sequencing is a rapid form of whole genome sequencing. These technologies identify differences between isolates usually using single nucleotide variants.[16,40] With PCR ribotyping only, there is a greater likelihood of cases being flagged as sharing the same genotype, simply by chance.[16]

Moloney et al. (2016) used next-generation sequencing to enhance epidemiological information and identify and resolve a *C. difficile* outbreak at an Irish hospital. Seven patients with CDI were all found to have ribotype 020 and *C. difficile* with a particular classification of bacterial isolates (sequence type 295). Using this information, the researchers were able to link the patients and track transmission back to a community hostel for homeless adults. Infection prevention and control measures were taken in the hostel under the guidance of public health personnel, and the outbreak was resolved. Of note, the standard surveillance definitions inaccurately classified three of the cases as HO CDI when in fact they were exposed in the hostel. For most patients in the study, the researchers suspected several weeks between ST-295 exposure and symptoms.[40]

Monitoring patient biomarkers is a potential research strategy for early detection of increasing *C. difficile* strain virulence. Schlackow et al. (2012) used an automated monitoring system to examine routinely collected laboratory hospital data at a group of U.K. hospitals. In particular, they used iterative sequential regression and monitored biomarkers of inflammation and neutrophil counts upon CDI diagnosis, because these measures are taken frequently prior to therapy and are associated with mortality in *C. difficile* colitis.

Examining over 10 years of data from 7,272 CDI-positive adults, the researchers found a strong association ($p<0.0001$) between a severe strain of *C. difficile*, ST1, and higher neutrophil counts at diagnosis. Mean neutrophil count among cases with the highly virulent ST1 strain was 13.5×10^9/L, while in the non-ST1 *C. difficile* isolates it was 10.7×10^9/L (difference in means 2.8; 95% CI, 1.5 to 4.5, $p=0.0001$). Molecular typing confirmed that an increase in CDI mortality was likely due to the ingress of ST1. The researchers found similar trends in difference between severe strain biomarkers using secondary data analyses of two multicenter studies. Because of the timely availability of the laboratory data, researchers found that monitoring biomarkers was a more rapid way to identify severe strains of CDI than using mortality data.[41]

4.4.5 Contextual Factors

Contextual factors include the type of setting in which *C. difficile* surveillance is conducted as participation in the NHSN expands beyond acute care facilities. In addition, the sensitivity and specificity of different testing methods impact surveillance rates. There is debate about the role of asymptomatic colonized *C. difficile* carriers—how they impact surveillance data and whether they should be actively surveilled.

4.4.5.1 Surveillance Settings

In addition to acute care hospitals, current participants in NHSN *C. difficile* reporting include skilled nursing facilities, LTCFs, long-term acute care hospitals, inpatient rehabilitation facilities, and inpatient psychiatric units (NHSN, n.d.). Some argue that surveillance case definitions may overestimate LTCF-associated CDI. For example, current surveillance case classifications may overestimate the incidence of

nursing home-associated CDI. Mylotte et al. (2012) found that of 75 incident CDI cases, 52 (69%) developed within 30 days of admission to an LTCF and 23 (31%) developed more than 30 days after admission.

Of the 52 cases that developed within 30 days, 68 percent were in residents admitted for subacute care. The mean number of days ± SD to develop CDI was 10.5 ± 2.5 in those who developed infection within 30 days, and 75 percent of these cases developed within 15 days of admission.[42] Jump and Donskey (2015) proposed surveillance definitions for LTCFs in which a case would not be considered as originating in the LTCF if a patient had been discharged from a hospital in the last 30 days; such a case would be considered LTCF onset, hospital acquired.[43]

4.4.5.2 Testing Methods and *C. difficile* Colonization

CDI testing methods have different sensitivities and specificities, which impact CDI rates. Therefore, the CDC adjusts for the different tests in NHSN reporting. A number of recent studies have shown that more sensitive molecular testing methods result in higher CDI surveillance rates. For example, Moehring et al. (2013) studied a change in testing from nonmolecular to molecular testing using PCR at 10 hospitals. The mean incidence rate of CO-HCFA CDI (using the 2007 case definitions) before the switch was 6.0 CDIs per 10,000 patient days compared with 9.6 CDIs per 10,000 patient days 18 months after the switch. The researchers stated that the improved sensitivity of molecular tests allows infected and colonized patients to be rapidly and reliably identified but can be "too good" at identifying patients who are colonized but not truly infected with *C. difficile*.[44] We explore the impact of testing type on CDI rates in more detail in Section 4.5, Testing (Indepth).

4.4.6 Resources To Assist With Implementation

CDC Targeted Assessment for Prevention (TAP) Strategy:
https://www.cdc.gov/hai/prevent/tap.html

CDC Updated Guidelines for Evaluating Public Health Surveillance Systems:
https://www.cdc.gov/mmwr/preview/mmwrhtml/rr5013a1.htm

CDC Healthcare Associated Infections – Community Interface: *Clostridioides difficile* Infection Tracking:
https://www.cdc.gov/hai/eip/cdiff-tracking.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fhai%2Feip%2Fclostridium-difficile.html

Clinical Practice Guidelines for *Clostridium difficile* Infection in Adults and Children: 2017 Update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA):
https://www.idsociety.org/globalassets/idsa/practice-guidelines/clinical-practice-guidelines-for-clostridium-difficile.pdf

Greater New York Hospital Association: Reducing *C. difficile* Infections Toolkit:
https://apic.org/Resource_/TinyMceFileManager/Practice_Guidance/cdiff/C.Diff_Digital_Toolkit_GNYHA.pdf

How to: Surveillance of Clostridium difficile infections:
https://www.ncbi.nlm.nih.gov/pubmed/29274463

NHSN Surveillance for *C. difficile* (CDI) and Multidrug Resistant Organisms (MRDO): https://www.cdc.gov/nhsn/ltc/cdiff-mrsa/index.html

4.4.7 Gaps

While there are numerous case studies on CDI surveillance and how surveillance practices may overestimate HO CDI, there is limited research on CDI surveillance implementation, best practices, and challenges. In addition, while several studies pointed to the cost-effectiveness of automated surveillance systems [12,29] a more robust economic analysis of CDI surveillance programs could be beneficial. As with other PSPs, most of the CDI surveillance studies are in the context of hospitals, and other settings are poorly represented. The IDSA/SHEA 2017 *C. difficile* guidelines[4] identified additional gaps in understanding the epidemiology of *C. difficile,* including the need to better understand sources for *C. difficile* transmission in the community and the incubation period for *C. difficile*. Finally, some researchers have called for a standardized surveillance classification to define an "outbreak" of CDI.[16]

4.4.8 Future Directions

The implementation and capabilities of automated surveillance will continue to grow[25] and global strategies may be implemented. In the future, integrated healthcare databases to track CDI patients across health systems could help track transmission outside a particular facility, ward, or healthcare system.[17] Increased research and tracking of CO CDI and CO-HCFA CDI will help to better understand CDI epidemiology outside of the healthcare setting. Although tracking CO-HCFA CDI is not mandated and requires the collection/evaluation of patients' prior healthcare facility admissions, it is useful in order to better understand the epidemiology of CDI.[45]

Strains of *C. difficile* have shown resistance to certain antimicrobials, and resistance plays a role in occurrence and recurrence of CDI.[46] According to Peng et al. (2017), with technological advances in the future, clinical microbiology laboratories could rapidly perform antimicrobial susceptibility testing to determine antimicrobial resistance and report the information to clinicians in real time.[46] Similarly, more rapid and affordable genotyping and molecular typing has the potential to identify cases that are part of an outbreak and improve response times.[4,16]

Efforts in Europe have shown the potential for more standardized *C. difficile* PCR ribotyping.[47] After examining *C. difficile* ribotypes from six locations across the United States, Waslawski et al. (2013) called for greater *C. difficile* ribotype data in order to better understand the impact of ribotype on sensitivity and specificity of testing and clinical treatment for CDI. They also recommend the establishment of an internationally recognized *C. difficile* ribotype reference collection.[48]

Participation in surveillance reporting will increase and include a broader spectrum of settings. For example, data from a larger group of LTCFs will be used to establish national benchmarks and track achievement of prevention goals.[49] A number of studies found discrepancies between surveillance definitions and clinical incidence.[40,50,51] Review and refining of surveillance definitions may be warranted as we continue to better understand CDI incubation periods. Finally, in the future, there is likely to be continued debate about "active surveillance" for *C. difficile*, i.e., the identification and isolation of asymptomatic carriers at hospital admission.[52,53] We explore this issue in more detail in Section 4.5, Testing (In-Depth).

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4.5 PSP 5: Testing

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This section includes a summary of evidence published from 2008 to 2018 on diagnostic testing as a safety practice for CDI. After providing a brief practice description and testing recommendations by the IDSA/SHEA and others, we review how testing works as a safety practice for preventing CDI. In the evidence summary, we discuss testing criteria and whether to test asymptomatic patients, a summary of systematic reviews and meta-analyses on the accuracy of different testing methods, and studies on tools to predict CDI and CDI severity. Finally, we discuss gaps and future directions for CDI testing. Key findings are located in the box on the right.

Key Findings

- Some research supports universal *C. difficile* testing for hospitalized patients with diarrhea.
- Screening and isolating asymptomatic carriers can prevent CDI transmission but is resource intensive.
- NAATs of unformed stool have relatively accurate sensitivity and specificity.
- Concerns with NAATs include that they detect toxigenic *C. difficile* genes, not the actual damaging toxins and may capture colonized patients in addition to those infected with *C. difficile*.
- Certain multistep test algorithms (that include a test for *C. difficile* and for CDI toxins) perform as well as or better than NAATs but take longer.
- Tools that identify patient risk for CDI could be useful in preventing CDI.
- Tools that identify a high risk of severe CDI or mortality show promise for prevention of severe CDI outcomes.
- Future directions include improved diagnostic technology for increased efficiency and accuracy of diagnosis.

4.5.1 Practice Description

The IDSA and SHEA recommend the following testing practices for suspected *C. difficile* in adults (the recommendation and quality of evidence come from IDSA/SHEA):

- Use patients with unexplained and new-onset ≥3 unformed stools in 24 hours as the preferred target population for testing for CDI *(weak recommendation, very low quality of evidence)*.
- Use a stool toxin test as part of a multistep algorithm (i.e., glutamate dehydrogenase [GDH] plus toxin; GDH plus toxin, arbitrated by NAAT; or NAAT plus toxin) rather than NAAT alone for all specimens received in the clinical laboratory when there are no preagreed institutional criteria for patient stool submission (*weak recommendation, low quality of evidence)*.
- Use NAAT alone or a multistep algorithm for testing (i.e., GDH plus toxin; GDH plus toxin, arbitrated by NAAT; or NAAT plus toxin) rather than a toxin test alone when there are preagreed institutional criteria for patient stool submission *(weak recommendation, low quality of evidence)*.
- Do not perform repeat testing (within 7 days) during the same episode of diarrhea and do not test stool from asymptomatic patients, except for epidemiological studies (strong recommendation, moderate quality of evidence).

Recent published guidelines and systematic reviews recommend only testing symptomatic patients for *C. difficile*, except for the purpose of epidemiological studies.[1,2] The recommendations are somewhat flexible with regard to the number of episodes of diarrhea that justify the need for CDI testing, noting that providers should take into account whether the patient has risk factors for CDI, most notable of which is antimicrobial use.[3] Before testing, physicians should attempt to rule out other causes of diarrhea.[4] Considerations with regard to *repeat* testing include the background prevalence of CDI at the facility.[1,4] SHEA/IDSA provide no recommendations for the use of biologic markers as an adjunct to diagnosis and do not recommend testing to determine if CDI has been cured.[1]

The guidelines also recommended that, while laboratory diagnosis is pending, treatment should be initiated empirically for patients who present with fulminant CDI or if obtaining the test results takes more than 48 hours. If test results cannot be obtained on the same day, patients with suspected CDI should be placed on preemptive contact precautions pending the *C. difficile* test results. As treatment recommendations differ, it is important to know the severity of the infection and whether it is an initial or recurrent episode.[1]

An abdominal CT scan may be used to differentiate between CDI and other causes of colitis and to determine the extent of the disease. However, to diagnose regular CDI (e.g., while test results are pending), when an abdominal CT has poor sensitivity, endoscopy can be used in certain urgent situations. The American College of Gastroenterology guidelines recommend endoscopy when a rapid diagnosis is needed or an initial negative toxin assay when CDI is strongly suspected, when there is an ileus and stool is not available, or when other colonic diseases are in the differential diagnosis.[5]

4.5.2 Testing as a PSP

Patients with *C. difficile* shed *C. difficile* spores, which contaminate the environment and may infect other patients.[6,7] Rapid identification of patients with CDI helps expedite contact precautions and isolation of these patients and prevent transmission to other patients.[8] The symptoms of CDI often match those of other causes of diarrhea[9,10]; therefore, early and rapid diagnosis is important to start the appropriate treatment and improve patient outcomes.[11] Starting treatment and infection protocols sooner may ultimately reduce hospital length of stay, thereby reducing healthcare costs.[12] Rapid diagnosis also ensures that providers modify any existing therapies, such as discontinuing antimicrobial agents, which could worsen a patient's condition.[13]

While testing accuracy and speed have improved in the last 10 years, there is currently no consensus on the best testing method.[1,14] It is helpful for clinicians to understand the strengths and limitations of the testing methods when interpreting test results. The testing methods have varying sensitivities and specificities, due to each test's detection ability and the tests' different detection targets.

Each class of test targets one of the following: *C. difficile* toxin, genes that produce toxin, or identification of toxigenic *C. difficile* in the stool. Detection of genes that produce toxins and toxigenic *C. difficile* indicates a patient may be colonized or infected with *C. difficile*. Detection of *C. difficile* toxin indicates infection. Each of the targets can indicate different stages in the progression of the disease.[9] Some patients may remain colonized and acquire protection from disease while others progress to the disease. Some with symptoms may be treated and become asymptomatic carriers.[15]

While the guidelines support accounting for *C. difficile* risk factors, Marra and Ng (2015) point out that the common risk factors for HA CDI are not as prevalent in CA CDI.[16] The criteria for whom to test for CDI such as the number and frequency of diarrheal stools that should trigger testing have decreased in the last few decades.[1] Whole genome sequencing and molecular typing indicate that most CDI is acquired from sources other than symptomatic cases.[17,18]

Asymptomatic colonized patients do not shed as many *C. difficile* spores as CDI patients; however, they still contaminate the environment.[7] Evidence supports identifying asymptomatic colonized *C. difficile* patients for the purpose of isolation and contact precautions.[19-21] One study found that 29 percent of CDI cases were linked to transmission from colonized patients.[22]

In the last decade, the most commonly used standalone test method has shifted from enzyme immunoassays to tests that detect DNA. Known as nucleic acid amplification testing, or NAAT, these tests generally have better detection abilities than enzyme immunoassays.[3] A shift to more rapid and accurate testing results in less use of unnecessary CDI-targeted antimicrobials[23] and a decrease in laboratory testing volume.[24]

NAAT detects toxigenic *C. difficile* genes, not the damaging toxins, and may identify asymptomatic carriers as well as those with *C. difficile* disease; also, there is debate about whether the presence of toxigenic *C. difficile* alone is sufficient to diagnosis CDI. Guidelines therefore suggest that only *symptomatic* (i.e., those with diarrhea) patients should be tested.[25]

To improve accuracy, combinations of tests are being used. Particularly if laboratories lack clinical input on specimen criteria and accept any unformed stool for testing, it may be most appropriate to use a combination of tests such as a test for organism combined with a relatively sensitive test for toxin in the stool.[3] These combinations test for the toxigenic organism and test for the actual toxin. Some guidelines do not promote the use of NAATs as a singular method even when patients are symptomatic.[4,9]

We discuss the testing methods in more detail in the evidence summary. Some evidence from European studies shows that CDIs are being underdiagnosed due to lack of clinical suspicion or inaccurate testing.[26,27] It is likely that continued research will lead to improved testing methods and protocols.

4.5.3 Methods

The question of interest for this review is: What are the best testing methods and protocols for identifying and preventing CDI?

To answer this question, we searched the databases CINAHL and MEDLINE from 2008 to 2018 for ""*Clostridioides difficile*" and related MeSH terms and synonyms, as well as terms such as "diagnostic test," "testing algorithms," "rapid identification," "stool sampling," and "screening." The search string also included a variety of healthcare settings, including "hospitals," "inpatient," "long-term care," "transitional care," and "home health." The search yielded 732 results. After duplicates were removed, there were 710 papers, all of which were screened for inclusion. Articles were excluded if they were out of scope or were not primary studies, meta-analyses, or systematic reviews, leaving 78 full-text articles that were retrieved.

Reference lists of included articles were also screened to ensure thoroughness and seven additional studies were retrieved via this method. An additional systematic review was identified and retrieved when we researched background information on *C. difficile* testing.[28] Of the retrieved articles, 26 studies, 3 systematic reviews, and 4 meta-analyses were selected for inclusion in this review. Articles were excluded at each step if the outcomes were not relevant or precisely reported or if the study design was insufficient.

Due to the large number of search results for certain topics, we include a sample of studies rather than all results. Similarly, for the performance of individual test types, we chose to include a summary of published meta-analyses instead of reviewing individual studies.

General methods for this report are described in the Methods section of the full report.

For this patient safety practice, a PRISMA flow diagram and evidence table, along with literature-search strategy and search-term details, are included in the report appendixes A through C.

4.5.4 Review of the Evidence

This review includes 26 studies, 3 systematic reviews, and 4 meta-analyses that address key issues in diagnostic testing for *C. difficile*. Four studies examined CDI testing criteria, including whether to systematically test hospitalized patients with diarrhea and whether to conduct repeat testing for CDI. Four studies and one review examined the question of whether to screen for and isolate asymptomatic *C. difficile* carriers.

We summarize the CDI testing methods and implications outlined by several reviews and studies. The performance of the tests is summarized by five recent meta-analyses. We also review five studies that evaluated tools for measuring patient risk of CDI and five studies that evaluated tools for measuring risk of CDI severity, including mortality.

4.5.4.1 Testing Criteria

While the guidelines promote testing of patients with three unformed stools in a 24-hour period, some researchers advocate for a more systematic process for *C. difficile* identification. Reigadas et al. (2015) tested all diarrheal stool for 6 months at a 1,550-bed hospital in Spain, regardless of clinician request. They found that 45 (18.1%) positive CDIs would have been excluded from testing because they did not meet the testing criterion (three unformed stools in 24 hours). Community-acquired cases and young age were risk factors for underdiagnoses.

Reigadas et al. (2015) recommend that all patients hospitalized with diarrhea be tested for CDI.[27] The European Society of Clinical Microbiology and Infectious Diseases suggests that all submitted unformed stool samples (whether they are submitted for testing for other conditions or for CDI) from patients 3 years or older should be tested for CDI.[4]

Several studies evaluated the use of repeat testing. To better understand the factors that might contribute to a negative test followed by a positive test, Mostafa et al. (2018) examined 2 years of hospital laboratory test orders for *C. difficile* PCR, for which the test result, clinic-pathologic patient features, and previous test results were recorded. In a retrospective chart review, they found that 1,637 of 20,866 lab orders were repeat tests within the first 7 days of initial diagnosis. Out of 554 patients who first tested positive, 2.3 percent (13) of patients were retested as negative within 7 days. Of the patients who first tested negative (970), 4.5 percent (44) were positive on the repeat test. Prior *C. difficile* infection was the only factor significantly correlated with change from negative to positive *C. difficile* test result within 7 days.[29]

The likelihood of a change in test result after a repeat test within 7 days appears to be somewhat linked to the test type and whether the initial test was positive or negative. Aichinger et al. (2008) conducted an observational study and examined the results of patients who had been retested within 7 days of the initial test result. There were 792 patients tested twice by enzyme immunoassay samples and 351 patients tested twice by PCR samples. The patients were all retested within 7 days of the initial diagnosis.

The authors found that retesting patients who were initially negative by enzyme immunoassay and PCR tests resulted in positive tests in 1.9 percent and 1.7 percent of cases, respectively. Patients with

positive enzyme immunoassays and PCR results retested as negative in 4.8 percent and 2.9 percent of cases, respectively.[30] The findings about retesting negative results are consistent with the findings of others; it is generally noted that that negative CDI tests are very unlikely to change within 7 days.[1] Repeat testing on negative tests may be helpful in an endemic or outbreak setting.[4]

4.5.4.2 Screening and Isolation of Asymptomatic Carriers

Preemptively identifying hospital patients at risk for CDI, and for severe courses of CDI, has been proposed as a patient safety strategy. At the patient level, it is recommended to screen symptomatic patients primarily so that providers can identify those in need of CDI treatment. The arguments in support of *only screening symptomatic patients* include:

- Screening asymptomatic patients requires significant laboratory resources,
- Studies on MRSA found that active surveillance was not more effective than enhanced infection control policies,
- Isolating asymptomatic CDI carriers requires additional hospital resources (e.g., single rooms), and
- Other interventions, such as hand hygiene, are effective at reducing multiple HAIs and are a better use of resources.[31]

In addition, cohorting symptomatic patients with colonized but asymptomatic patients increases risk of infection of the latter.[32]

Several published studies found public health benefits from screening asymptomatic carriers. One quasi-experimental study and three simulations found that detecting and isolating asymptomatic carriers was associated with prevention of future cases.[19-21,33] In the quasi-experimental study, Longtin et al. (2016) examined the impact of testing all patients admitted through the emergency room at a 354-bed Canadian acute care facility. Patients with a positive test were put into isolation (excluding patients who stayed less than 24 hours). Roughly 92.5 percent of eligible patients were screened over 17 months and 368 (4.8%) were identified as asymptomatic *C. difficile* carriers. During the intervention, 38 patients (3.0 per 10,000 patient days) developed an HA CDI compared with 416 patients (6.9 per 10,000 patient days) during the pre-intervention baseline period ($p<0.001$).[19]

In their simulation, Lanzas and Dubberke (2014) also found that testing asymptomatic carriers reduced the number of new colonizations and HO-CDI cases by 40 percent to 50 percent and 10 percent to 25 percent, respectively, compared with the baseline scenario.[20] In the simulations, factors that impacted the percentage of reduced cases include test sensitivity, test turnaround time (as it relates to delaying isolation), colonization prevalence at admission, strain, and effectiveness of patient isolation.[20,21]

Screening and treating high-risk populations (regardless of CDI symptomology) is also explored in the literature. Saab et al. (2015), for example, conducted a simulation model with cirrhosis patients to compare costs and outcomes of two strategies for screening CDI. The first strategy consisted of screening all cirrhosis patients (regardless of symptoms) for CDI and treating if *C. difficile* was detected. In the second strategy, only patients with symptomatic CDI were treated.

The results showed that screening all cirrhosis patients for CDI was consistently associated with improved healthcare outcomes and decreased healthcare utilization across all variables in the one- and two-way sensitivity analyses. Using baseline assumptions, the authors found the costs associated with

only screening symptomatic patients for CDI were 3.54 times greater than the costs to screen all cirrhosis patients.[33]

Another approach, outlined by Furuya-Kanamori et al. (2015) in their review, suggests that patients at high likelihood of being asymptomatic carriers are not tested but medical staff should use enhanced infection control practices such as the use of gloves. In addition, units or facilities with high likelihood of asymptomatic carriers should carry out CDI cleaning protocols.[15]

4.5.4.3 Diagnostic Testing Strategies

In this segment, we start by providing an overview of the distinctions between "reference standard" tests and tests most commonly used in clinical practices. We then summarize recent meta-analyses on commercial diagnostic testing methods. These meta-analyses are highlighted in Table 5.

4.5.4.3.1 Reference Standards

The two most common reference standards for identifying *C. difficile* are toxigenic culture (TC) and cell cytotoxicity assay (CCTA). These are the "gold standards" against which commercial tests are compared.[3,9,10] Neither test is useful in a clinical setting as they take several days to complete and require specific expertise and equipment.[2,25]

TC is intended to detect whether *C. difficile* is present and whether it can produce toxins. This test takes between 4 and 7 days.[16] Typically, toxigenic strains of *C. difficile* cause symptoms and the disease of *C. difficile*; however, the presence of toxigenic strains may not always result in active infection.[9] Therefore, a positive test result is not entirely indicative of a CDI.

The other common reference standard, the CCTA, measures the presence of free toxin in feces. The detection of free toxin with CCTA indicates that the patient has diarrhea caused by *C. difficile.* This test takes about 2 to 4 days for results and has a higher specificity than TC.[16] Planche et al. (2013) sought to validate the reference methods according to clinical outcomes using test results, length of hospital stay, and 30-day mortality. In a study of 12,420 fecal samples from four U.K. laboratories, the researchers found no increase in mortality when toxigenic *C. difficile* was present (as indicated by a positive TC test). CCTA was positivity correlated with clinical outcomes, making this a better reference method to define CDI and *C. difficile*-associated disease.[14]

TC is useful for identifying patients who may be asymptomatic and capable of transmitting the organism to others. Culture for the organism of *C. difficile* (regardless of the potential for toxin production) was rarely mentioned in the reviewed studies and meta-analyses, except by Crobach et al. (2016) as a reference test for GDH immunoassays.[4]

4.5.4.3.2 Commercial *C. difficile* Tests Overview

Many studies compare and measure the performance of individual tests. We report here on systematic reviews and meta-analyses to summarize the accuracy of different diagnostic testing methods.[4,16,28,34] We focus on the testing methods and not distinctions between the brands of tests available for each method. However, performance of tests does vary across manufacturers.[2,10] Table 5 outlines the detection targets and drawbacks of common reference and commercial *C. difficile* testing methods.

Table 5: *C. difficile* Testing Methods

Test	Detects	Drawback
TC	Toxigenic *C. difficile*	Toxigenic *C. difficile* does not always produce toxins; may detect colonized carriers; takes several days
CCTA	CDI toxins	Takes several days and requires specialized equipment
Toxin immunoassay	CDI toxins	Inconsistent sensitivity (depending on particular brand and study)
GDH immunoassay	*C. difficile* enzyme common in toxigenic and nontoxigenic organism	Unable to tell if the *C. difficile* organism produces toxins
NAATs (PCR and loop-mediated isothermal amplification [LAMP])	Genes for toxigenic *C. difficile*	Toxigenic *C. difficile* does not always produce toxins; may detect colonized asymptomatic carriers

TC and CCTA were standard diagnostic practice when *C. difficile* was first discovered, but now faster and less expensive tests are widespread.[16,35] The first alternatives to TC and CCTA to be used widely were toxin enzyme immunoassays.[9] Studies and meta-analyses group the immunoassays generally into those that test for toxins A and B and those that test for GDH. Crobach et al. (2016) further characterized the immunoassays into well-type and membrane-type; well-type tests are used for testing samples in batches, and membrane-type tests are used for testing solitary samples.[4]

The enzyme immunoassays for *C. difficile* toxins A and B cost $5 to $15 per test[10] and take a few hours to complete.[16] It is most appropriate to compare toxins A and B tests against CCTA since these tests detect *C. difficile* toxins.[9] The immunoassays for toxins A and B were widely used as standalone tests until about 10 years ago. Because of very poor sensitivity, and moderately poor specificity, they are now primarily recommended as part of a two-step or three-step testing algorithm.[9,16,25,36]

GDH is a common *C. difficile* enzyme antigen produced in large amounts by all strains of *C. difficile*, independent of toxigenicity.[2] Like TC, the GDH test indicates the presence of the organism in feces and does not indicate toxin production. Although the GDH immunoassay is sensitive, it is not as specific for CDI since both toxigenic and nontoxigenic organisms produce GDH.[16] The cost per test is $5 to $15[10] and test time is 15 to 45 minutes.[16] Because the GDH immunoassay does not detect toxin-producing *C. difficile*, it is not recommended as a standalone test and should be paired with a test that detects toxin.[25]

After FDA approval in 2009, NAATs became available .[2] NAATs include rapid testing PCR and LAMP. NAATs test for the genes of *C. difficile* that produce toxins and identify the presence of toxigenic *C. difficile*.[25] NAATs are more expensive than the enzyme immunoassays for toxins A and B and GDH at about $30 to $50 a test.[10] NAAT testing is estimated to take about 1 to 2 hours.[9]

Due to the limitations of these individual tests, combinations of tests can be used to improve specificity and positive predictive value of diagnosis.[16] While the SHEA/IDSA guidelines support the use of NAATs as a single step, Crobach et al. (2016) found that none of the individual commercial methods was satisfactory as a single test to diagnose CDI.

Several strategies can be used for multi-step testing.[4] One is to do two simultaneous rapid tests and then retest concordant results. Another strategy involves testing for GDH and toxins A and B, then further testing concordant positive results with PCR.[25] In their prospective study of 12,420 fecal samples, Planche et al. (2013) found that the optimal algorithm when TC was the reference was a combination of

GDH and NAAT. For CCTA as the reference, the best algorithms were toxins A and B/NAAT and GDH/toxins A and B.[14]

4.5.4.4 Diagnostic Studies Meta-Analyses Overview

Table 6 presents a summary of sensitivities and specificities from six studies. Butler et al. (2016) reviewed and pooled results from 37 studies from 2011 to 2014.[28] For studies that used multiple reference standards, such as culture, TC, and cell cytotoxicity neutralization assay (CCNA), Crobach et al. (2016) conducted a meta-analysis of immunoassay tests, including those for toxins A and B and GDH, as well as NAATs. They found 56 studies that included sensitivity and specificity for toxins A and B, 31 studies with sensitivities and specificities for GDH tests, and 14 studies on NAATs.[4]

O'Horo et al. (2012) reviewed 11 databases and found 25 PCR studies going back to the mid-1990s and 6 LAMP studies going back to 2005. Heterogeneity in the LAMP studies did not allow meta-analysis.[34] Wei et al. (2015) conducted a meta-analysis of nine LAMP studies published before February 2014 and concluded that LAMPs were suitable as standalone tests for CDI.[37]

Bagdasarian et al. (2015) reviewed 13 studies on testing algorithms. In general, multistep algorithms using NAAT had good sensitivity (0.68–1.0) and specificity (0.92–1.0), but algorithms using only GDH or toxin enzyme immunoassay testing performed worse and had greater variability.[25] Four of the studies analyzed by Butler et al. (2016) involved multistep algorithms.

Table 6: Meta-Analyses of CDI Diagnostic Tests

Types of Tests	Study	Sensitivity (95% CI)	Specificity (95% CI)	Notes
Immunoassays for *Clostridium difficile* toxins A and B	**Butler et al., 2016[28]**	0.70 (0.66 to 0.74)	0.98 (0.97 to 0.99)	Summary reference; moderate strength of evidence; mixed reference, primarily TC
	Crobach et al., 2016[4]	0.83 (0.76 to 0.88)	0.99 (0.98 to 0.99)	Reference: CCNA
		0.57 (0.51 to 0.63)	0.99 (0.98 to 0.99)	Reference: TC
Immunoassays for GDH	**Butler et al., 2016[28]**	0.90, (0.78 to 0.96)	0.94 (0.89 to 0.97)	Moderate strength of evidence; mixed references
	Crobach et al., 2016[4]	0.94 (0.89 to 0.97)	0.90 (0.88 to 0.92)	Reference: CCNA
		0.96 (0.86 to 0.99)	0.96 (0.91 to 0.98)	Reference: TC
		0.94 (0.86 to 0.97)	0.96 (0.92 to 0.98)	Reference: Culture *C. difficile*
NAATS that include PCR and LAMP	**Butler et al., 2016[28]**	LAMP: 0.95 (0.90 to 0.97)	LAMP 0.98 (0.96 to 0.99)	High strength of evidence; mixed references
		PCR: 0.95 (0.93 to 0.96)	PCR 0.97 (0.96 to 0.98)	
	Crobach et al., 2009[4]	0.96 (0.93 to 0.98)	0.94 (0.93 to 0.95)	Reference: CCNA
		0.95 (0.92 to 0.97)	0.98 (0.97 to 0.99)	Reference: TC
	O'Horo et al., 2012[34]	PCR 0.92 (0.91 to 0.94)	PCR 0.94 (0.94 to 0.95)	Reference: TC
		PCR 0.87 (0.84 to 0.90)	PCR 0.97 (0.97 to 0.98)	Reference: CCNA
	Wei et al., 2015[37]	LAMP 0.93 (0.91 to 0.95)	LAMP 0.98 (0.98 to 0.99)	Mixed references
Two- or three-step algorithms	**Bagdasarian et al., 2015[25]**	(0.68 to 1.0)	(0.92 to 1.0)	13 studies; only CI is provided. Both TC and CCNA used as reference; mixed algorithms.
	Butler, et al., 2016[28]	0.73 (0.62 to 0.82)	1.00 (0.99 to 1.0)	Low strength of evidence; mixed references; mixed algorithms

4.5.4.5 Implications of More Sensitive Testing Tools

Because PCRs are highly sensitive, they may detect asymptomatic colonized patients as well as symptomatic infected patients.[38,39] Koo et al., for example, found that universal PCR testing of all 101 adult hospitalized patients resulted in 18 positive tests, and of these, 72 percent were for patients with

asymptomatic *C. difficile* colonization, which, from a treatment perspective is a false positive.[38] Therefore, many experts recommend only testing symptomatic patients with PCR.[1,25]

Some researchers have pointed out that more sensitive testing methods result in an increase in reported HO CDI. Moehring et al. (2013) studied 10 hospitals (and 22 controls) that switched to PCR from immunoassays. The mean incidence rate of HCFA CDI before the switch was 6.0 CDIs per 10,000 patient days compared with 9.6 CDIs per 10,000 patient days a year and a half after the switch. After adjustment in the mixed-effects model, the overall IRR comparing CDI incidence after the switch to before the switch was 1.56 (95% CI, 1.28 to 1.90).[40] There is concern about lack of standardization in testing and higher HO-CDI reporting rates for those facilities using more sensitive methods.[41]

Other researchers found decreased or stable CDI rates after switching from enzyme immunoassays to NAATs and a decrease in laboratory testing volume. Casari et al. (2018) found that more sensitive testing methods had beneficial results in terms of reductions in the number of samples tested and minor reductions in positive CDI tests at a 750-bed hospital. In 2011, the hospital tested 2,746 samples and the following year, after switching from toxin A and B immunoassay to NAAT with sampling criteria, 677 samples. The rate of healthcare-acquired CDI infections decreased from 3.74 per 1,000 admissions to 2.92 per 1,000 admissions a year after the switch in testing method. Other hospitals in the region saw steady CDI rates.[42]

Napierala et al. (2013) found that 20 months after a switch from toxin A and B immunoassay to PCR for diagnosis of CDI at three hospitals, there was a significant decrease in laboratory testing volume (and decreased associated workload). Site-specific *C. difficile* testing volume decreased by 32.5 to 53.9 percent following implementation of PCR. *C. difficile* toxin detection rates were largely unchanged across the three hospitals.[24]

4.5.4.6 Testing Methods Financial Analyses

Schroeder et al. (2014) conducted an economic evaluation comparing eight algorithms for CDI testing in a hypothetical cohort of 10,000 adult inpatients suspected of having CDI. The testing methods included:

- Standalone PCR;
- GDH testing with positive results confirmed by PCR; and
- Both GDH and *C. difficile* toxin A and B with concordant positives treated, concordant negatives not treated, and discordant results confirmed by PCR.

For the model, the researchers assessed cost and effectiveness from the hospital/healthcare perspective (e.g., laboratory testing, isolation protocol, treatment, prolonged hospitalization, and transmission of disease). For traditional algorithms, in which the test results were available after 4 hours, the assumption was that patients would be placed in isolation and initiated on CDI treatment while awaiting CDI test results. For the rapid testing algorithms, the assumption was no presumptive isolation or treatment.

A cost analysis (including estimated costs of missed cases) favored standalone PCR in most contexts but favored immunoassays then PCR if:

- A missed CDI case resulted in less than $5,000 of extended hospital stay costs and <2 transmissions,

- GDH diagnostic sensitivity was >93 percent, or
- The symptomatic carrier proportion among the TC-positive cases was >80 percent.

The number of missed CDI cases was minimized by standalone PCR, whereas the number of false-positive diagnoses was minimized by GDH/PCR.[43]

4.5.4.7 Risk Prediction Tools

It is theorized that identifying patients at risk of CDI could help guide preemptive testing, infection prevention measures, and treatment.[44,45] As shown in Table 7, five studies developed or validated tools for predicting patients' risk of developing CDI.[44-48] In one study, researchers measured patient outcomes associated with a screening tool that identified high-risk patients and implemented enhanced infection control policies for these patients.[45] The screening tool was informed by literature on CDI risk factors and a retrospective examination of 1 year of data on healthcare-acquired CDI at a 20-bed vascular-thoracic ICU.

Patients who met certain criteria (e.g., over 55 years old, prescribed a fluoroquinolone agent for any duration or prescribed any other antimicrobial agents for ≥5 days, history of immunosuppression) were identified as high risk for CDI. Measures were taken to reduce risk, such as a review of medication, hand hygiene audits and enhanced environmental cleaning measures for the patients' rooms, and education for patients and families. During the first year, 1,066 patients were screened, and 157 patients were placed in the preventive model. During the pre-intervention phase, 10 cases of healthcare-acquired CDI occurred (overall incidence rate, 14.7) and during the 12-month study period, two cases of healthcare-acquired CDI were identified (incidence rate, 3.12) (p=0.025).

Other tools for predicting risk of CDI were validated retrospectively but were not implemented as a preventive measure. For example, Cooper et al. (2013) developed a tool that weighted certain EHR variables, such as admission from another facility, to provide a patient risk score. The variables were selected based on review of hospital data and previously published data on CDI risk factors. When a patient's score met the tool criteria, the risk factors and score, along with the patient's basic demographic data, appeared on a daily review report. The tool was validated over the course of a year and the final model resulted in an area under the curve (AUC) of 0.929 (95% CI, 0.926 to 0.932).

AUC is a measure of how well a tool can distinguish between two diagnostic groups. The AUC is calculated from a graph of the true positive rate (sensitivity) with the false positive rate for different cutoff points of the parameter. A perfect tool would result in an AUC of 1.0. The optimal cutoff score was 0.636, where both sensitivity and specificity were at 91.61 and 86.96, respectively. Of 4,927 patients identified as at risk for CDI, 254 (92.7% of total CDI cases in the study period) developed the disease.[44]

Table 7: Predictive Tools for CDI Incidence

Author	Setting/Population	Tool	Outcome
Cooper et al., 2013[44]	A 255-bed community hospital; 4,927 records identified as at risk for CDI.	An electronic screening tool to help identify patients at risk of CDI.	The final model resulted in an area under the curve of 0.929 (95% CI, 0.926 to 0.932).

Author	Setting/Population	Tool	Outcome
Cruz-Betancourt et al., 2016[45]	A 20-bed vascular-thoracic ICU; 1,066 screened patients.	Predictive model for prevention of *C. difficile* infection in patients in ICUs. Evidence-based interventions (bundle) were implemented for patients identified as being at high risk for HA CDI.	During the pre-intervention phase, 10 cases of healthcare-acquired CDI occurred (overall incidence rate, 14.7) and during the 12-month study period, two cases of HA CDI were identified (incidence rate, 3.12) (p=0.025).
Kuntz et al., 2014[48]	Records of outpatient visits in a large healthcare system. Tool was validated with cohort of 296,550 patients.	Predicting CDI after an outpatient visit using electronic medical record.	The area under the receiver operating curve curve was 0.790.
Stites et al., 2016[46]	A large safety net hospital; prospective analyses for 10,990 admissions.	A predictive model that identifies patients at high risk for CDI at the time of hospitalization. Model to help inform antimicrobial stewardship.	The model identified 55% of patients who later tested positive as being at high risk for CDI at the time of admission (c-statistic 0.77, 95% CI, 0.69 to 0.84).
Tabak et al., 2015[47]	Six acute care hospitals; 78,080 adult admissions, 323 HO-CDI cases.	An HO-CDI predictive model using EHR clinical data present at time of admission.	The model had a c-statistic of 0.78 (95% CI, 0.76 to 0.81).

We found several other studies that validated tools to predict CDI severity or mortality; five of these studies are highlighted in Table 8. Van der Wilden et al. (2014), for example, studied and validated a risk scoring system to identify patients at risk for developing fulminant *C. difficile* colitis, which carries a high risk of mortality. Patients with *fulminant colitis* may have frequent bloody stools, abdominal pain, distension, and acute, severe toxic symptoms, including fever. It is possible that early surgical intervention may help improve outcomes for patients at risk of developing severe *C. difficile* colitis.[49]

The researchers sought to develop a simplified scoring system based on four weighted factors: age >70, white blood cell count ≥20.000 or ≤2.000/µL, cardiorespiratory failure (the need for mechanical ventilation or vasopressor support), and diffuse abdominal tenderness. Over the course of 2 years, all patients with fulminant *C. difficile* colitis (746) were prospectively enrolled in the study; 48 (6.4%) of them progressed to fulminant *C. difficile* colitis. The risk scoring system (RSS) successfully distinguished patients with CDI from those who went on to have fulminant *C. difficile* colitis (AUC, 0.98). The researchers found that the system performed as well as a more complex system based on 12 variables and suggested that it could be useful as a bedside tool for clinicians to identify patients at risk of fulminant *C. difficile* colitis.[49]

Table 8: Predictive Tools for CDI Severity and Mortality

Article	Setting/Population	Tool	Results
Archbald-Pannone et al., 2015[60]	A U.S. academic hospital; enrolled the 362 hospitalized adult subjects who did not have chronic diarrhea and followed them for 30 days after CDI diagnosis or until death.	A parsimonious predictive model for CDI mortality.	The area under the ROC curve was 0.804.

Article	Setting/Population	Tool	Results
Figh et al., 2017[63]	A hospital; the study group consisted of all cases that resulted in death (n = 79). The control group consisted of all surviving patients who were identified as having CDI based on ICD-9 documentation (n =192).	Two published clinical prediction tools, the Velazquez-Gomez Severity Score Index (VGSSI) and ATLAS (age, temperature, leukocytosis, albumin, and systemic concomitant antibiotic use) scores, were evaluated, and variables showing the greatest correlation with mortality in patients with CDI. were identified to further develop an objective, mortality-based clinical prediction tools.	Mortality indices in patients with CDI were strongly associated with VGSSI and ATLAS scores: Pearson's correlation coefficients r =0.9536 (p=0.002) and 0.9103 (p=0.0001), respectively. Did not hold for intermediate ranges.
Kassam et al., 2016[61]	Used data from the United States 2011 Nationwide Inpatient Sample (NIS) database to develop. Then a sample tool was validated in an independent sample of all CDI hospitalizations from the 2010 NIS dataset. All CDI-associated hospitalizations were identified using discharge codes (ICD-9-CM); 77,776 CDI hospitalizations were identified.	To develop a novel CDI risk score to predict mortality titled Clostridium difficile associated risk of death score (CARDS).	The severity scoring system had a c-statistic of 0.77.
Van Beurden et al., 2017[62]	A 750-bed tertiary care center; the validation cohort comprised 148 patients diagnosed with CDI between May 2013 and March 2014.	External validation of three tools to predict a complicated course of CDI.	The performance of all three prediction models was poor when applied to the total validation cohort with an estimated AUC of 0.68 for the Hensgens model, 0.54 for the Na model, and 0.61 for the Welfare model.
Van der Wilden et al., 2014[49]	Massachusetts General Hospital; all patients (746) with *C. difficile* colitis admitted to the hospital were prospectively enrolled in a specific database.	An RSS for patients at risk of developing fulminant *C. difficile*.	The RSS successfully discriminates patients with *C. difficile* infection from those who have fulminant *C. difficile* (AUC, 0.98).

4.5.5 Resources To Assist With Implementation

APIC Implementation Guide: Guide to Preventing *Clostridium difficile* Infections: Includes section on *C. difficile* diagnosis:
https://apic.org/wp-content/uploads/2019/07/2013CDiffFinal.pdf

CDC: FAQs for clinicians about *C. difficile*: Which laboratory tests are commonly used for diagnosis?
https://www.cdc.gov/cdiff/clinicians/faq.html#anchor_1529601768432

SHEA/IDSA Clinical Practice Guidelines for C. difficile: 2017 Update: These guidelines provide updated recommendations regarding *C. difficile* epidemiology, diagnosis, treatment, infection prevention, and environmental management. Each recommendation includes a brief summary of the literature on the practice:
https://www.idsociety.org/globalassets/idsa/practice-guidelines/clinical-practice-guidelines-for-clostridium-difficile.pdf

4.5.6 Gaps and Future Directions

It may be beneficial for further exploration into the range of factors that impact the speed and accuracy of testing. For example, Kundrapu et al. (2013) found that delays included not providing stool collection supplies to patients in a timely fashion, rejecting specimens due to incorrect labeling or leaking from the container, and holding samples in the laboratory for batch processing. A corrective intervention consisted of easier-to-use containers, prioritization of CDI testing at the laboratory, on-demand specimen pickup and delivery (rather than at scheduled pickup times), and clinician education. The intervention was associated with reduced average time from CDI test order to result from 1.8 to 0.8 days. Additional studies that help inform systems processes would help expedite CDI testing.[50]

Obtaining stool specimens may delay testing since it is not always possible to obtain specimens on demand, if a patient is not able to produce stool. Another study examined the use of rectal swabs (rectal swabs with liquid transport medium and nylon flocked dry swabs) for diagnosing CDI, with mixed results. The authors concluded that rectal swabs could not replace stool samples in the two-step laboratory diagnosis of CDI, as the sensitivities were too low, probably due to diluting effects of the fecal sample in the liquid medium. For simple PCR-based detection of *C. difficile*, however, dry swabs were a suitable alternative to stool samples.[51]

Factors that lead to case misclassification will continue to be studied, especially given financial penalties for HO CDI. One study addressed concern about overreporting of HO-CDI rates and examined the role of laxatives. As diarrhea in the hospital can have many causes, including the use of laxatives, Truong et al. (2017) evaluated a system in which lab testing criteria combined the presence of diarrhea (≥3 unformed stools in 24 hours) and absence of laxative intake in the prior 48 hours. The researchers found that 7.1 percent (164) and 9.1 percent (211) of 2,321 *C. difficile* test orders were canceled due to absence of diarrhea and receipt of laxative therapy, respectively. HO-CDI incidence rate decreased from an average of 13.0 cases to 9.7 cases per 10,000 patient days (p=0.008). Oral vancomycin days of therapy decreased from an average of 13.8 days to 9.4 days per 1,000 patient days (p=0.009).[52]

In the future, it is likely that the speed, accuracy, and convenience of CDI testing will continue to improve. One weakness of NAAT testing is that it does not detect *C. difficile* toxin. Some have proposed tests for toxin that are as accurate as CCTAs but fast and more practical for the clinical setting.[53] Other researchers examined lightweight, rapid, and portable CDI testing systems that could expedite and simplify the diagnostic process.[54,55]

Yet another rapid CDI identification strategy explored in the literature is the use of dogs to scent-detect patients with *C. difficile*. Bomers et al. (2014) conducted a study in which a trained 5-year-old dog was presented with patients and asked to identify those with CDI. During a total of nine hospital visits, the dog performed 651 screenings involving 371 patients and correctly identified 12 of 14 CDI cases (sensitivity 86 percent [95% CI, 56% to 97%]) and 346 of 357 CDI-negative participants (specificity of 97% [95% CI, 94% to 98%]). Of the 11 CDI-negative participants that were "falsely" indicated by the dog as positive, 2 (18%) developed CDI during the 3 months of followup after the detection period, compared with only 12 of the 346 participants (3.5%) that the dog identified as *C. difficile* negative (p=0.06).[56] More research on this technique with larger samples would be useful.

Currently, genotyping is used for CDI surveillance and understanding transmission pathways, but the technology also has potential diagnostic value. Identifying a patient's particular strain of CDI could help

inform antimicrobial treatment decisions.[57] Whole genome sequencing has shown promise in identifying whether recurrent infection is due to relapse or reinfection with CDI.[58] Durovic et al. (2017) used genotyping to determine whether CDIs were due to recurrent infection or reinfection. Among 750 patients with CDI, 130 (17.3%) were diagnosed with recurrence or reinfection and strains were available from 106 patients. The period that showed the best indication of when an infection might actually be a reinfection was 20 weeks. None of the independent clinical characteristics was statistically sufficient to indicate whether infection was due to relapse or recurrence.[59]

If *C. difficile* continues to be a common cause of infection and mortality, risk identification tools could be implemented for clinical use. In addition, understanding of differences in the symptomology of CA CDI may help improve diagnostic accuracy. Finally, the role of asymptomatic carriers as a source of CDI transmission will continue to be discussed and potentially addressed by actively screening for colonized carriers. More real-world research is needed to explore the potential of this practice.

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4.6 Multicomponent CDI Prevention Interventions

Reviewer: Katharine Witgert, M.P.H.

Our search for articles on individual CDI PSPs published from 2008 to 2018 uncovered studies that looked at patient outcomes associated with the combination of two or more CDI PSPs. To accurately reflect the number of articles on multicomponent CDI prevention interventions, we decided to include a review of these studies.

In this addendum to the CDI patient safety chapter, we provide a practice description and evidence summary of the research published from 2008 to 2018 on multicomponent CDI prevention interventions. We then discuss qualitative research on implementation barriers and facilitators, as well as gaps and future directions.

Most of the included articles were identified in the searches for the five other PSPs (hand hygiene, antimicrobial stewardship, environmental cleaning and decontamination, surveillance, and testing) or from reference lists of articles identified in these searches. To ensure thoroughness, we conducted a brief additional search for multicomponent interventions and identified three additional sources.[1-3]

Key Findings

- Multicomponent interventions to prevent CDI were associated with decreases in CDI rates.
- The most common component was environmental cleaning, followed by hand hygiene and patient isolation practices; antimicrobial stewardship and contact precautions; and CDI testing and surveillance.
- No single CDI prevention resource was used across studies.
- Information was limited on staff compliance and financial costs of interventions.
- Collaborations and teamwork were reported to be facilitators of implementation of multicomponent interventions.
- Additional facilitators of staff compliance included adequate supplies (e.g., gowns, soap), communication, signage, and institutional support. Barriers included time it takes to perform prevention practices (e.g., wash hands, put on gowns), inadequate staff education, inconsistency in testing criteria and unclear roles for ordering CDI tests, visitors not practicing contact precautions, and lack of isolation rooms.
- Real-world studies on the implications of different practice combinations, as well as studies on regional prevention efforts and nonhospital settings, will help improve understanding.

For all searches, we excluded articles without clearly stated methodology or a methods section. We also excluded studies that did not quantify or clearly report CDI outcomes, did not clearly explain the interventions, did not describe baseline prevention practices, or did not measure statistical associations with more than one of the interventions. The remaining eight studies and three reviews addressed multicomponent prevention interventions and CDI patient outcomes. Key findings are located in the box above.

4.6.1 Practice Description

Barker et al. (2017) describe a CDI bundle as any set of multiple (>1) interventions focused on reducing CDI in the inpatient setting. To guide their decision about which set of practices to implement, the researchers whose studies we reviewed cited different influences. Several cited prior research and recent IDSA/SHEA recommendations as guiding the decision.[4,5] In one study, a team of experts (assembled by the facility) reviewed facility epidemiological data and determined which practices to implement.[6] Two articles stated that the practices in their respective facilities were guided by government mandates or recommendations.[7,8]

Some studies and resources recommend that facilities assess their current practices to identify gaps and targets for improvement. Facilities should use multidisciplinary teams to oversee cross-cutting efforts

and set achievable goals.[9,10] There are different contextual recommendations within the 2017 IDSA/SHEA guidelines.[11] Several of the guidelines are framed as minimum recommendations and some are tailored for outbreak or endemic situations.[11] Resources are available to assist facilities in identifying targets for a multicomponent intervention, for example, CDC's CDI Targeted Assessment for Prevention (TAP) tool, which helps facilities use surveillance data to inform prevention efforts.[12]

4.6.2 Review of the Evidence

Three reviews and eight studies found reductions in CDI rates following implementation of multicomponent CDI prevention interventions. In this evidence summary, we first provide an overview of the reviews and then examine the studies in depth and present the primary outcomes, different intervention components, cross-cutting factors, process measures, and economic outcomes. We then present two simulation studies that attempt to measure the impact of different combinations of prevention components.

4.6.2.1 Reviews

Three systematic reviews address multicomponent interventions and had sufficient methodologic quality for inclusion in this report.[1,2,13] The reviews found that studies on multicomponent interventions showed reductions in CDI, although Barker et al. (2017)[14] noted that p-values were not provided in 11 of the studies they reviewed. Barker et al. (2017)[14] reviewed 26 studies on multicomponent interventions published from database inception up to April 30, 2016. Seven of the studies they found are included in this review (many of the studies they included were published prior to 2008 and thus were not within the parameters of our searches). We include one study by Koll et al. (2014)[9] that was not included in the review by Barker et al. (2017).[14]

In another review, Louh et al. (2017) examined studies published from January 1, 2009, to August 1, 2015, on CDI prevention practices in acute care hospitals. They identified 14 studies on "bundled" interventions,[13] 5 of which we include in this review. Yakob et al. (2014)[2] conducted a meta-analysis of studies published up until March 2014 that measured CDI rates before and after implementation of multicomponent prevention interventions. Six studies were included, four of which are included in this review.[4,7,9,15] The six studies showed reductions in CDI from 33 to 61 percent. In addition to the review, they conducted simulations to assess the impact of different combinations of multicomponent interventions. These findings are described later in this section.

4.6.2.2 Studies

We found eight studies that measured CDI rates before and after implementation of a multicomponent CDI prevention intervention [3-9,15] and two simulation studies that explored different combinations of prevention components.[2,14] The eight real-world studies were observational or quasi-experimental with an interrupted time series or pre/post design. These studies are presented in Table 9.

Using $p<0.05$ as the cutoff, we found that the eight real-world studies showed significant declines in CDI rates following implementation of a multicomponent prevention intervention.[3-9,15] The studies are primarily in single hospital settings, except the studies by Koll et al. (2014), which evaluated a regional program implemented by 35 hospitals,[9] and Cheng et al. (2015), which assessed efforts in 4 hospitals.[3] Two studies examined long-term hospital care, one in a long-term acute care hospital[5] and another in three extended-care hospitals (in addition to one acute care hospital).[3]

Across studies there was a range in the number of implemented components; the multicomponent intervention studied by Price et al. (2009) included two components (a dedicated CDI isolation ward and antimicrobial stewardship),[8] while the remaining studies we reviewed all included more than three components. Studies outside of the United States are noted as such in the "Setting" column of Table 9.

Table 9: Studies on Multicomponent CDI Prevention Interventions 2008–2018

Article	Setting	Interventions	CDI Outcomes
Abbett et al., 2009[4]	A 750-bed tertiary care university-affiliated hospital	• All-staff education campaign • Promotion of awareness of CDI testing • Discontinuation of nonessential antimicrobials • Contact precautions • Promotion of hand hygiene • Sign on CDI patient doors • Dedicated stethoscopes • Lab communication protocols • Enhanced patient isolation • Terminal bleach cleaning for CDI rooms • CDI treatment checklist	The incidence rate of healthcare-associated CDI decreased from an average of 1.10 cases per 1,000 patient days (95% CI, 1.00 to 1.21) during the pre-intervention period (~2 years) to 0.66 cases per 1,000 patient days (95% CI 0.60 to 0.72) during the post-intervention period (~2.5 years).
Brakovich et al., 2013[5]	A 50-bed long-term acute care hospital	• Environmental services education • HPD • Microfiber mops • New diagnostic assay • Removal of ABHRs from patient rooms • Promotion of hand hygiene • Private CDI rooms • Dedicated equipment • Antimicrobial stewardship • CDI care coordination liaisons • Data collection and feedback • Surveillance education	The pre-implementation cumulative CDI rate was 46.86 per 10,000 patient days. The post-implementation cumulative infection rate after 12 months was 26.26 per 10,000 patient days ($p<0.001$).
Cheng et al., 2015[3]	A university-affiliated acute hospital and three extended-care hospitals with a total of 3,200 beds, Hong Kong	• Environmental services education • Patient cohorting • Dedicated equipment • Promotion of handwashing with soap and water • Twice daily cleaning and cleaning at patient discharge (with bleach solution) of CDI patient rooms • Terminal curtain change • Outbreak investigation	Before the implementation of infection control interventions, the incidence rates of healthcare-associated CDI per 10,000 admissions and per 10,000 patient days increased significantly by 15.3% and 17.0%, respectively, per quarter ($p<0.001$) from 2008 1Q to 2010 1Q. Both healthcare-associated CDI rates per 10,000 admissions and per 10,000 patient days declined significantly by 47% ($p<0.001$) after the implementation of interventions in the second quarter of 2010.
Koll et al., 2014[9]	35 acute care hospitals	• Regional multifacility collaborative (regional dissemination of CDI prevention bundle, baseline surveys, site visits, intrafacility strategizing, knowledge sharing, collaborative learning, data collection/feedback on CDI case definitions and bundle compliance) • Contact precautions for patients with diarrhea • Signs on CDI patient doors • Dedicated rectal thermometer • Patient isolation and/or cohorting • Standardized cleaning protocol and checklists	A regression analysis demonstrated that the predicted HO-CDI reduction over time was significant over the course of the project ($p<0.001$). Based on the regression estimation, participating hospitals had 1,084 fewer cases of hospital-onset CDI than were expected (exact rates not provided) over the 22-month project.

Article	Setting	Interventions	CDI Outcomes
Power et al., 2010[6]	5 wards - 850-bed university teaching hospital, UK	On five wards with high baseline CDI: • Formation of teams • Learning sessions on theory and practice of improvement • Selection of key drivers and development of test of change • Visits from executive team Hospitalwide: • Rapid response cleaning team • Promotion of handwashing (staff and patients) • Staff hand hygiene audits • Antimicrobial stewardship • CDI education • Disposable washbowls	In the five wards, there were 2.60 (95% CI, 2.11 to 3.17) cases per 1,000 occupied bed days at baseline. After 3 months of the intervention, a shift occurred representing a reduction of 73% (0.69, 95% CI, 0.50 to 0.91). In the rest of the hospital at baseline, there were 1.15 (95% CI, 1.03 to 1.29) cases per 1,000 occupied bed days. The cases decreased 56% from baseline (0.51, 0.44 to 0.60) after 6 months.
Price et al., 2009[8]	A 820-bed teaching hospital, UK	• Patient cohorting • New antibiotic policy restricting the use of cephalosporins and quinolones	The number of CDI cases each month was falling before the intervention; there was a significant increase in the rate of reduction after the intervention from 3% to 8% per month (trend: 0.92, 95% CI, 0.86 to 0.99, p=0.03).
Salgado et al., 2009[15]	A 610-bed, tertiary care, academic institution	• Placing patients with diarrhea into empiric contact precautions until CDI was ruled out as the cause of diarrhea • Cleaning equipment and the environment with a bleach solution in areas occupied by CDI patients • Requiring soap and water for hand hygiene for staff working with patients with CDI	The overall mean outbreak CDI rate was 3.90 per 1,000 patient days, and the peak outbreak CDI rate (November 2004) was 5.52 per 1,000 patient days. Immediate postoutbreak CDI rate was 1.84 per 1,000 patient days, and mean postoutbreak rate, maintained for 36 months beyond the outbreak, was 1.24 per 1,000 patient days (p <0.0001).
Weiss et al., 2009[7]	A 554-bed, acute care tertiary hospital, Canada	• Rapid *C. difficile* testing for all hospitalized patients who had at least one occurrence of liquid stool • Rapid isolation of CDI patients • Dedicated/trained housekeeping for CDI rooms • Increase in housekeeping hours • Patient cohorting • Handwashing in/out of CDI rooms • Limit of one visitor at a time • Promotion of gloves • Promotion of patient handwashing • Revised prescribing guidelines • Hiring of four infection prevention experts • Installation of 85 new sinks • CDI surveillance	Most interventions were implemented in late 2005. During the 2003–2004 period, there were 762 cases of CDI (mean annual rate, 37.28 cases per 1,000 admissions), compared with 292 cases of CDI (14.48 cases per 1,000 admissions) during the 2006–2007 period (odds ratio, 0.379 [95% CI, 0.331 to 0.435]; p <0.001), a 61% reduction.

4.6.2.2.1 Infection Prevention Practices

As shown in Table 10 below, in the reviewed studies, the most common component of the multicomponent interventions was environmental cleaning and decontamination, which was included in seven of the eight studies. Isolation of CDI patients and hand hygiene practices were the next most common components—each was included in five studies. Antimicrobial stewardship practices and contact precautions were each included in four studies. Testing and surveillance practices were included in three studies. In their review, Barker et al. (2017) found that in 26 studies, hand hygiene and environmental cleaning were the most common components (each in 23/26 studies) followed by patient

isolation/cohorting (20/26) and contact precautions (19/26) and antimicrobial stewardship (19/26).[1] Louh et al. (2017) did not quantify the individual components across studies.[13]

Table 10: Components in Multicomponent CDI Prevention Interventions

Intervention Component	Number of Studies	Specific Practices Mentioned
Environmental cleaning and decontamination	7	Increase in environmental services hours and training, dedicated CDI cleaning teams, cleaning equipment, dedicated equipment, disposable washbowls, daily and terminal cleaning with bleach solution, terminal hydrogen peroxide decontamination, terminal curtain change, protocols and checklists
CDI patient isolation	5	CDI patient cohorts, private rooms for CDI patients, wards for CDI patients, rapid isolation
Hand hygiene	5	Removal of ABHRs, promotion of handwashing with soap and water when working with CDI patients, patient hand hygiene, hand hygiene observations/audits, installation of sinks
Antimicrobial stewardship	4	Discontinuation of nonessential antimicrobials, restriction of the use of clindamycin, cephalosporins, and quinolones, revised guidelines and formularies
Contact precautions	4	Use of gowns and gloves when working with CDI patients, limits on patient visitors, empiric contact precautions
Testing	3	Testing at first sign of diarrhea, promotion of testing, new diagnostic assay
Surveillance	3	Tracking and classification of CDI cases, education, outbreak investigation

The individual practices deemed crucial to the multicomponent interventions varied across studies in this review. Some researchers felt that inclusion of antimicrobial stewardship as part of a multicomponent intervention was the primary factor in reducing CDI.[6,8] Conversely, Salgado et al. (2009),[15] Weiss et al. (2009),[7] Koll et al. (2014),[9] and Cheng et al. (2015)[3] all emphasized that they saw CDI reductions by focusing on *C. difficile* transmission prevention, without the inclusion of antimicrobial stewardship or reductions in antimicrobial use. Across the studies, the most common transmission prevention practices were use of gloves/handwashing with soap and water,[3,5,7,15] new training and protocols for environmental cleaning staff training,[3,5,7,9] and CDI patient isolation/cohorting.[3,8,9]

Notably, Louh et al. (2017) found that multicomponent interventions that included environmental cleaning and decontamination were more effective than multicomponent interventions that did not include a focus on environmental cleaning.[13] However, Brakovich et al. (2013) called out the importance of surveillance as part of a multicomponent intervention in a long-term acute care hospital.[5]

4.6.2.2.2 Cross-Cutting Practices

When discussing which cross-cutting practices facilitated the success of a multicomponent intervention, researchers highlighted several practices. The use of checklists and assigned roles was noted [4,5,9](as well as staff education).[3,5,6,9,15] Barker et al. (2017) and Abbett et al. (2009) stated the importance of improved workflow systems and Barker et al. (2017) also pointed out that staff compliance with bundle practices is highly important and rarely adequately measured.[4,14] Communicating laboratory results[4] and communicating CDI patient status through door signs[4,9] were also highlighted. Two studies spoke to the benefits of teams, inter- and intrafacility collaborations, data collection and feedback, and collaborative learning.[6,9]

In the study by Power et al. (2010),[6] an 850-bed hospital implemented a multicomponent intervention that included antimicrobial stewardship, hand hygiene, environmental cleaning and decontamination, and education about CDI. In five wards with higher baseline CDI rates, there was an implementation of an “improvement collaborative,” in which staff were broken into teams who planned, implemented, and

measured the impact of selected PSPs as outlined by a systems improvement toolkit.[16] The five selected collaborative wards saw a 73 percent reduction in HA-CDI cases per 1,000 patient bed days after 3 months, and the rest of the hospital saw a 56 percent reduction in CDI cases per 1,000 patient bed days after 6 months (see Table 10).[6]

4.6.2.2.3 Process Measures

Process measures included antimicrobial use, CDI tests ordered, and staff compliance with intervention components. Although not all interventions included antimicrobial stewardship, antimicrobial use was a common process measure.[3,7,8,15] For example, following a multicomponent intervention that included antimicrobial stewardship (in addition to a new isolation ward), Price et al. (2010) found decreases in antimicrobial use. The multicomponent intervention took place in an 820-bed hospital in the United Kingdom. After 15 months, the level of cephalosporin and quinolone use declined (22.0% and 38.7%, respectively, $p<0.001$), and antipseudomonal penicillin use increased by 20.7 DDD per month ($p=0.011$).[8]

Abbett et al. (2009) measured number of CDI tests as a process measure. The multicomponent intervention was in a 750-bed hospital and included the promotion of testing of suspected CDI patients (in addition to several other practices). After 2 years, Abbett et al. (2009) found a 15 percent increase in the rate (tests per 1,000 patient days) of *C. difficile* testing (testing rate ratio, 1.15 [95% CI, 1.12 to 1.17]; $p<0.001$). Koll et al. (2014) collected data on compliance from 35 acute care hospitals participating in a regional CDI prevention effort. For the submitted data (based on staff observations), the mean reported compliance with a prevention bundle was 95 percent and the mean reported compliance reported for an environmental cleaning protocol was 96 percent.[4]

4.6.2.2.4 Economic Outcomes

Brakovich et al. (2013) and Weiss et al. (2009) provided financial information on the cost to implement the respective prevention interventions. Brackovich et al. (2013) reported that the cost of HPD equipment and contracted services was $1,800 per month. The cost of new microfiber mops and environmental services staff training was approximately $650.[5] While exact figures were not provided, Weiss et al. (2009) reported that costs of the intervention they studied included paying salary for four new infection preventionists and a 26.2 percent increase in staffing costs for environmental services personnel. They also reported an increase of 89.6 percent in cost of cleaning supplies, although this amount represented less than 0.03 percent of the total hospital budget.[7]

In addition, Koll et al. (2014) reported savings in healthcare costs associated with a regional multicomponent intervention. They noted that 35 hospitals prevented approximately 1,084 cases of HO CDI, resulting in cost savings of $2.7 million to $6.8 million on healthcare costs.[9]

4.6.2.3 Multicomponent Intervention Simulation Studies

To determine what combination of CDI prevention practices are most effective as a multicomponent intervention, Barker et al. (2017) conducted a simulation using a model of *C. difficile* transmission. The model was based on prior data to construct potential *C. difficile* transmissions by patients, visitors, nurses, and physicians and includes parameters such as patient antimicrobial use and length of stay. The interventions were “implemented” in a theoretical 200-bed hospital for 1 year.

After analyzing nine multicomponent intervention strategies, the researchers found that daily cleaning with sporicidal disinfectant and screening and isolating asymptomatic *C. difficile* carriers reduced CDI by

68.9 percent and 35.7 percent, respectively (both p<0.001). Combining these interventions into a two-intervention bundle reduced hospital-onset CDI by 82.3 percent and asymptomatic HO colonization by 90.6 percent (both, p<0.001). Adding patient hand hygiene to HCW hand hygiene reduced hospital-onset CDI rates an additional 7.9 percent (p<0.001).[14]

Yakob et al. (2014) conducted a series of simulations of different combinations of prevention methods based on their model of *C. difficile* transmission. The prevention methods included antimicrobial stewardship; administration of probiotics/intestinal microbiota transplantation; and improved hygiene and sanitation. They also examined the impact of reduced length of stay for inpatients. The researchers examined the impact of the prevention interventions on both colonization and CDI rates and found that, for infection control, the combined benefit of reducing length of stay and improving sanitation and hand hygiene significantly exceeds that achieved with either method alone. Antimicrobial stewardship showed greater efficacy in colonization control than it did in disease control. In terms of symptomatic disease incidence reduction, antimicrobials, probiotics, and intestinal microbiota transplantation proved substantially less effective than reducing length of stay and improving hygiene.[2]

4.6.3 Implementation

Two studies used a systems engineering framework to examine barriers and facilitators to prevention practices.[17,18] A systems engineering framework is one that examines workflow systems in relation to tasks, tools, and technologies, the physical environment, and the organization.[18] Yanke et al. (2018) conducted a qualitative analysis on barriers and facilitators of implementation of the VA *C. difficile* prevention bundle. The study consisted of four focus groups of healthcare staff in a variety of roles (e.g., physicians, nurses, and health technicians) at an 87-bed VA hospital. Bundle components included rapid PCR testing and diagnosis, hand hygiene promotion, and contact isolation precautions; facilitators and barriers were identified for each component.

For testing, facilitators included positive aspects of PCR testing (expedient, efficient, highly sensitive) and almost universal testing of newly admitted patients with diarrhea. Testing barriers included certain laboratory policies (e.g., only testing stool once per week, rejection of nonliquid stool), ambiguity between nurse practitioners and resident and attending physicians on who should order testing, inconsistent threshold for testing, and delays in obtaining specimens. For hand hygiene, facilitators were adequate soap supplies, extra sinks, and signage reminders. Multiple barriers were identified, such as:

- Uncertainty about where to wash hands (e.g., inside or outside of patient rooms),
- Sink water that was too hot,
- Lack of access to sinks in patient rooms due to clutter in and around sinks,
- Need to touch curtains with potentially contaminated hands,
- Time it takes to wash hands in a busy environment,
- Lack of education, and
- Broken soap dispensers.

Finally, facilitators of contact isolation precautions included proactive isolation of patients by nurses when testing was ordered, supply of clean gowns, institutional support for compliance, and clear signs on contact isolation rooms. Barriers to implementation of contact precautions included:

- Problems with location of equipment,
- Inconsistent compliance by patients' visitors, food service workers, and healthcare staff,
- Lack of clarity around responsibility for enforcing family member compliance,
- Time it takes to don or implement contact precautions,
- Electronic record functionality for identifying contact precaution patients,
- Lack of isolation rooms,
- Inappropriate removal of isolation stethoscopes, and
- Overloaded linen bags.

Certain overarching factors were identified in the focus groups, such as a desire by some staff for more information on the bundle and data on compliance. Perspectives varied depending on staff roles (i.e., nurses, residents, and attending doctors); the researchers highlight the importance of collecting interprofessional perspectives.[17]

Ngam et al. (2017) examined the perspectives of 10 nurses at a large academic teaching hospital. In a focus group, the nurses were asked questions about barriers and facilitators to the facility's CDI prevention bundle. Testing facilitators included the staff's commitment to testing and the ease of placing orders in the EHR, while barriers included challenges in collecting stool samples (e.g., patient discomfort) and lack of consistency/communication challenges around who orders the test. Contact precautions barriers included inadequate supplies, time it takes to practice contact precautions, and challenges with family/visitor compliance. Inadequate sink access was identified as a barrier to hand hygiene, while signage and sink foot pedals were facilitators. Barriers to disinfection of the environment included moving tools in and out of rooms and confusion around roles and policies and procedures for disinfection.[18]

4.6.4 Resources To Assist With Implementation

2017 IDSA/SHEA *C. difficile* Clinical Practice Guidelines:
https://www.idsociety.org/practice-guideline/clostridium-difficile/

CDC HAI Prevention Toolkits:
https://www.cdc.gov/HAI/prevent/prevention_tools.html

CDC Targeted Assessment for Prevention (TAP) Strategy:
https://www.cdc.gov/hai/prevent/tap.html

Greater New York Hospital Association United Hospital Fund: Reducing *C. difficile* Infections Toolkit:
https://apic.org/Resource_/TinyMceFileManager/Practice_Guidance/cdiff/C.Diff_Digital_Toolkit_GNYHA.pdf

Health Research and Educational Trust *Clostridium difficile* Change Package: http://www.hret-hiin.org/Resources/cdi/16/HRETHEN_ChangePackage_CDI.pdf

4.6.5 Gaps and Future Directions

Additional research into overcoming barriers to compliance with recommended CDI prevention practices as part of multicomponent prevention interventions would be useful as staff compliance is a major factor in intervention success.[1,19] More robust financial analysis that includes costs for staffing, trainings, supplies, delays in room turnover, testing, antimicrobials, patient treatment, and other items would also help facilities considering implementing a multicomponent intervention.

As with other CDI PSP studies in this report, higher quality, case-control/cohort/randomized, and longer term studies would also help improve knowledge and understanding.[1,13] In the future, studies of regional initiatives and multicomponent interventions in a variety of settings (e.g., outpatient, nursing home) will help improve CDI prevention.

Future efforts will benefit from improved resources to assist facilities in developing customized multicomponent interventions and determining which strategies to implement. This review found that intervention components, while informed by recent recommendations, varied across studies. Hospital resources and facility limitations are important considerations in implementing a tailored multicomponent strategy.[7]

As demonstrated by Barker et al. (2017), outcomes associated with multicomponent interventions are more complex than just the sum of their parts,[15] and different *combinations* of practices may be more effective than others.[2] To determine the most effective components in different contexts, McFarland (2017) recommended stepwise evaluation, with standardized outcomes, and measuring the efficacy attributable to each component, while accounting for compliance, over time.[19]

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Conclusion

The PSPs reviewed in this chapter aim to prevent CDI by:

- Reducing risk,
- Stopping the transmission of the *C. difficile* organism,
- Identifying and isolating patients with CDI as early as possible, and
- Tracking cases and identifying outbreaks, transmission pathways, and virulent strains.

The evidence in support of these practices, when implemented in real-world healthcare settings, ranges in depth, quality, and consistency:

- Environmental cleaning and multicomponent interventions had the most consistently positive outcomes across the reviewed studies.
- Antimicrobial stewardship shows promising results for reducing CDI, especially under certain conditions.
- Reducing CDI rates through hand hygiene (washing hands with soap and water) is well supported by in vitro studies but not well tested in real-world studies.
- Research on surveillance explores the accuracy of case definitions, automation, and innovations.
- Studies that address CDI testing explore sensitivity and specificity of testing methods and considerations of who and when to test.

Additional key findings from each of the PSPs in this chapter follow.

Antimicrobial Stewardship: The reviewed meta-analyses found ASPs were associated with decreases in CDI. Individual study outcomes were mixed, showing statistically significant decreases (6/15 studies) and statistically nonsignificant decreases/no change (9/15 studies) in facility- or ward-level CDI. Interventions included formulary restrictions, prescriber education, and audit and feedback/case review practices.

Significant reductions in CDI were associated with higher baseline CDI rates/outbreaks, ASPs developed specifically to reduce CDI (as opposed to ASPs focused on other clinical and microbiological outcomes), and ASPs that included restrictions to high-risk antimicrobials or a preauthorization component. Prescriber buy-in and staffing and technical resources were factors that impacted implementation.

Hand Hygiene: In laboratory testing, washing with soap and water outperforms ABHRs for removal of *C. difficile* spores from hands; ABHRs are not effective in killing *C. difficile* spores.[1,2] It is the mechanical action of washing that removes the organism; therefore, proper handwashing technique is important.[3] In the studies reviewed for this report, interventions targeted multiple HAIs or included the use of ABHRs, which made it difficult to draw concise conclusions about the impact of practices targeting *C. difficile*. The studies found statistically nonsignificant reductions in CDI following hand hygiene interventions.

Most studies took place in hospitals and interventions included: hand hygiene education, data collection/observation, and additional hand hygiene supplies/sinks. Hand hygiene is frequently

framed as an HCW compliance issue, with studies measuring the impact of sink location and education on hand hygiene compliance. Patient hand hygiene initiatives show promise for helping prevent the spread of CDI.[4]

Environmental cleaning and decontamination for *C. difficile* was associated with significant decreases in facility-level CDI rates in most studies. Practices with positive outcomes include daily and terminal cleaning of CDI patients' rooms with bleach solutions (typically 5,000 ppm), and terminal bleach cleaning plus the use of no-touch decontamination methods such as hydrogen peroxide or UVD. The UVD process takes less time than the hydrogen peroxide method. Both methods require the room or area be vacant, which is an implementation challenge.[5,6] Studies suggest that standardized cleaning protocols and training and observation of environmental cleaning services staff help improve cleaning and decontamination for *C. difficile*.[7]

For CDI **surveillance**, using standardized and accurate case definitions is an important practice.[8] Much research in the last 10 years has examined the accuracy of healthcare facility-onset/associated case definitions using different data and data collection methods. Studies also examined automated surveillance, laboratory alerts, risk stratification, statistical methods, and impact of the different testing methods on incidence. Research using new technologies for *C. difficile* genotyping and ribotyping has helped identify outbreaks.[9,10] Despite the role CDI surveillance plays in understanding epidemiology and informing prevention practices, CDI surveillance implementation is not well studied.

Testing for CDI was a frequent topic of research. Rapid and accurate identification of CDI is important in order to initiate treatment and discontinue antimicrobials (if appropriate) for CDI patients.[11] Our search yielded a relatively large number of studies on the performance of different test types and brands. Research also explored the best practices for when to test a patient based on symptoms, how to interpret results, and which methods have the most accurate, rapid, and useful outcomes. If test results cannot be obtained on the same day, patients with suspected CDI should be placed on preemptive contact precautions pending test results.[8]

The evidence indicates that NAATs and multistep test combinations show best results.[8] CDI risk-prediction tools show promise for preemptive intervention. There are different perspectives on whether to test for (and subsequently isolate) asymptomatic carriers; However, some studies show this practice is resource intensive.[12-15]

Multicomponent CDI prevention interventions included environmental cleaning, hand hygiene, patient isolation, antimicrobial stewardship, testing, and surveillance, as well as other PSPs and cross-cutting strategies. Studies consistently showed associations between multicomponent interventions and statistically significant reductions in CDI. Factors that facilitated implementation of multicomponent interventions included the use of checklists and assigned roles,[16-18] staff education,[17-21] and collaboration and teamwork.[17,20]

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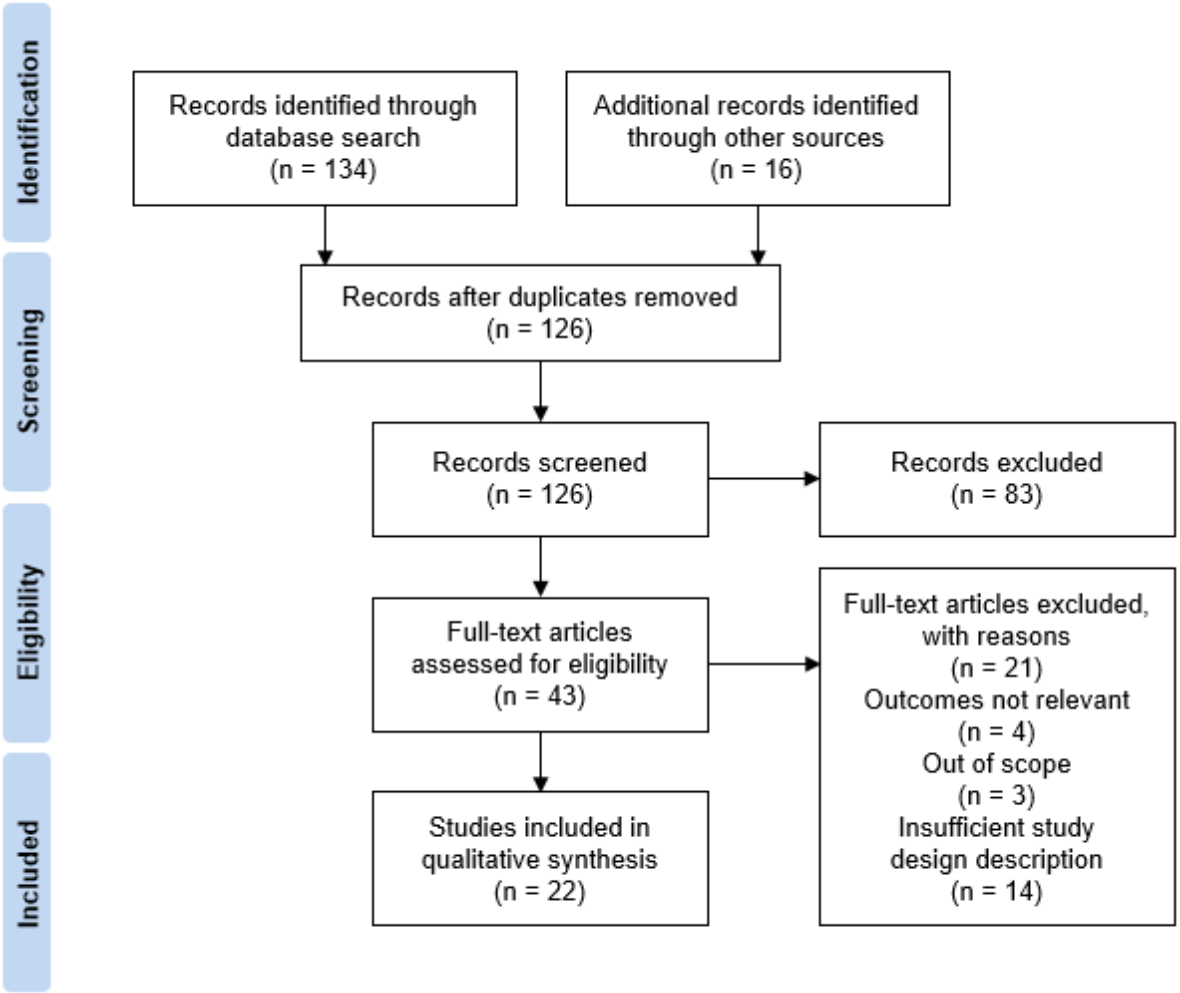
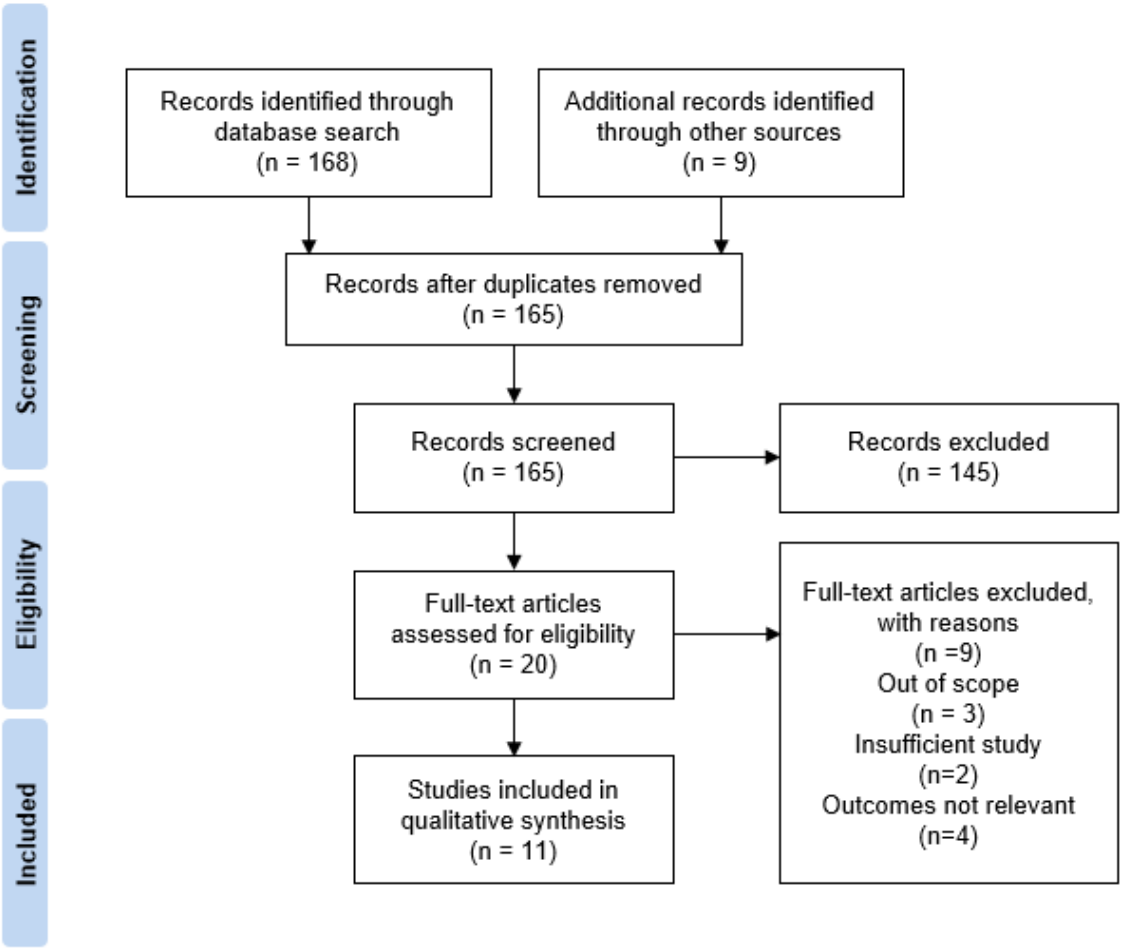
Appendix A. *Clostridioides difficile* Infection PRISMA Diagrams

Figure A.1: Antimicrobial Stewardship Programs for *Clostridioides difficile*–Study Selection for Review



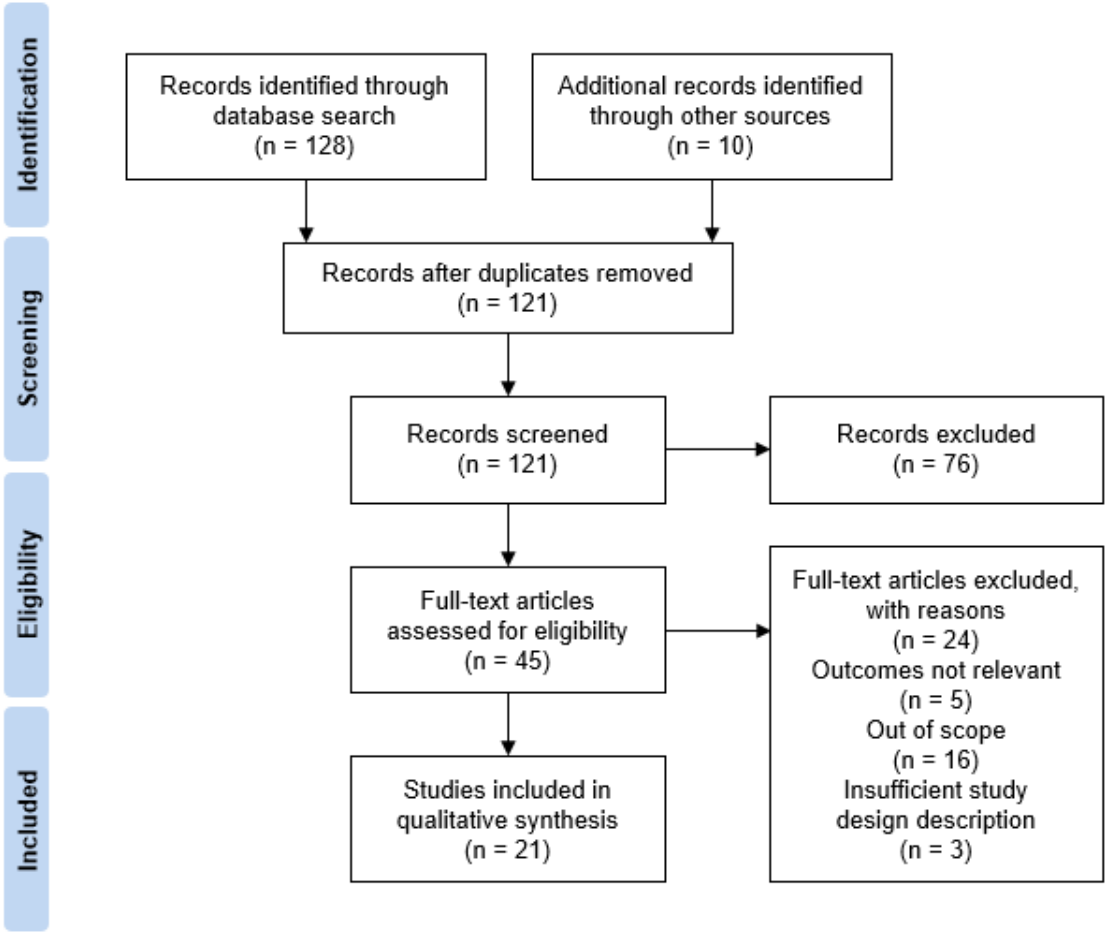
PRISMA criteria described in Moher D, Liberati A, Tetzlaff J, et al. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med. 2009 Jul 21;6(7): e1000097. doi:10.1371/journal.pmed1000097.

Figure A.2: Hand Hygiene for Clostridioides d*ifficile*–Study Selection for Review



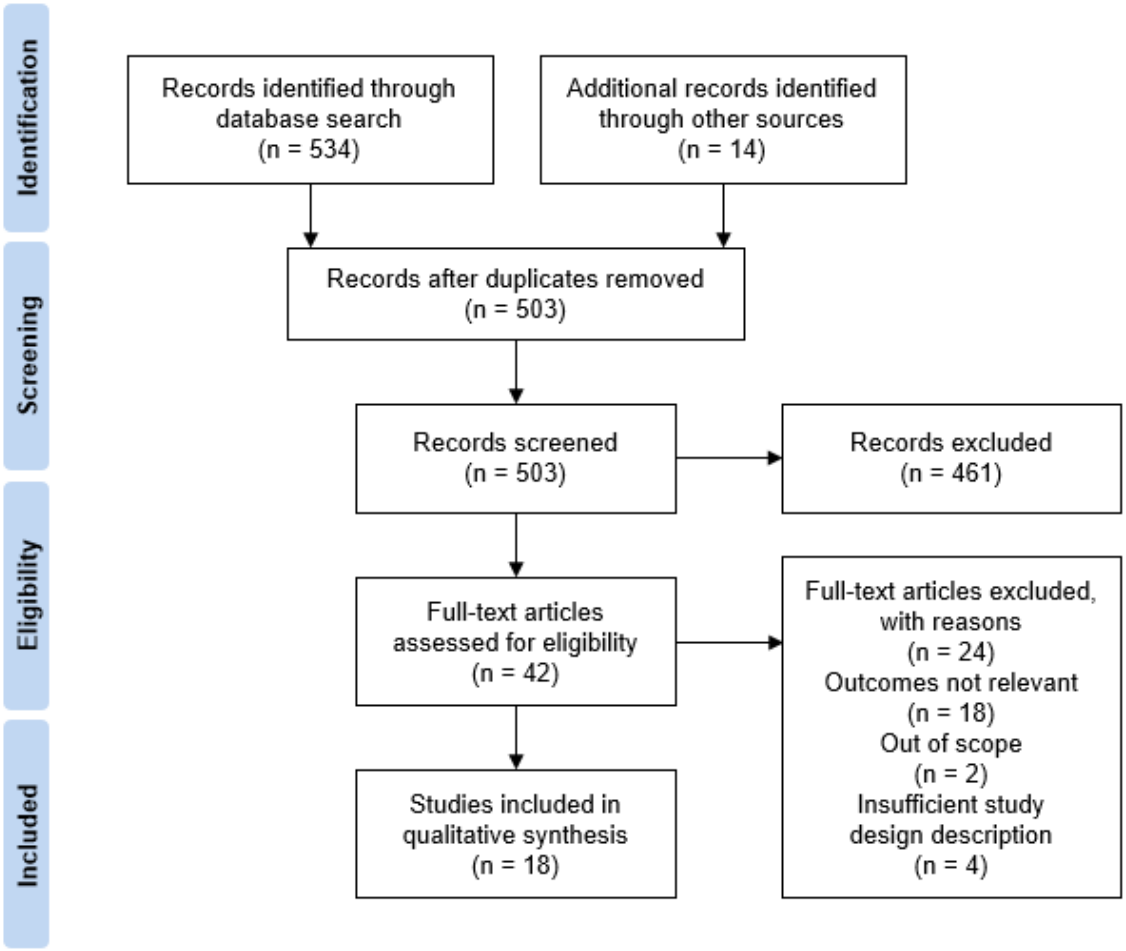
PRISMA criteria described in Moher D, Liberati A, Tetzlaff J, et al. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med. 2009 Jul 21;6(7): e1000097. doi:10.1371/journal.pmed1000097.

Figure A.3: Environmental Cleaning and Decontamination for *Clostridioides difficile*–Study Selection for Review



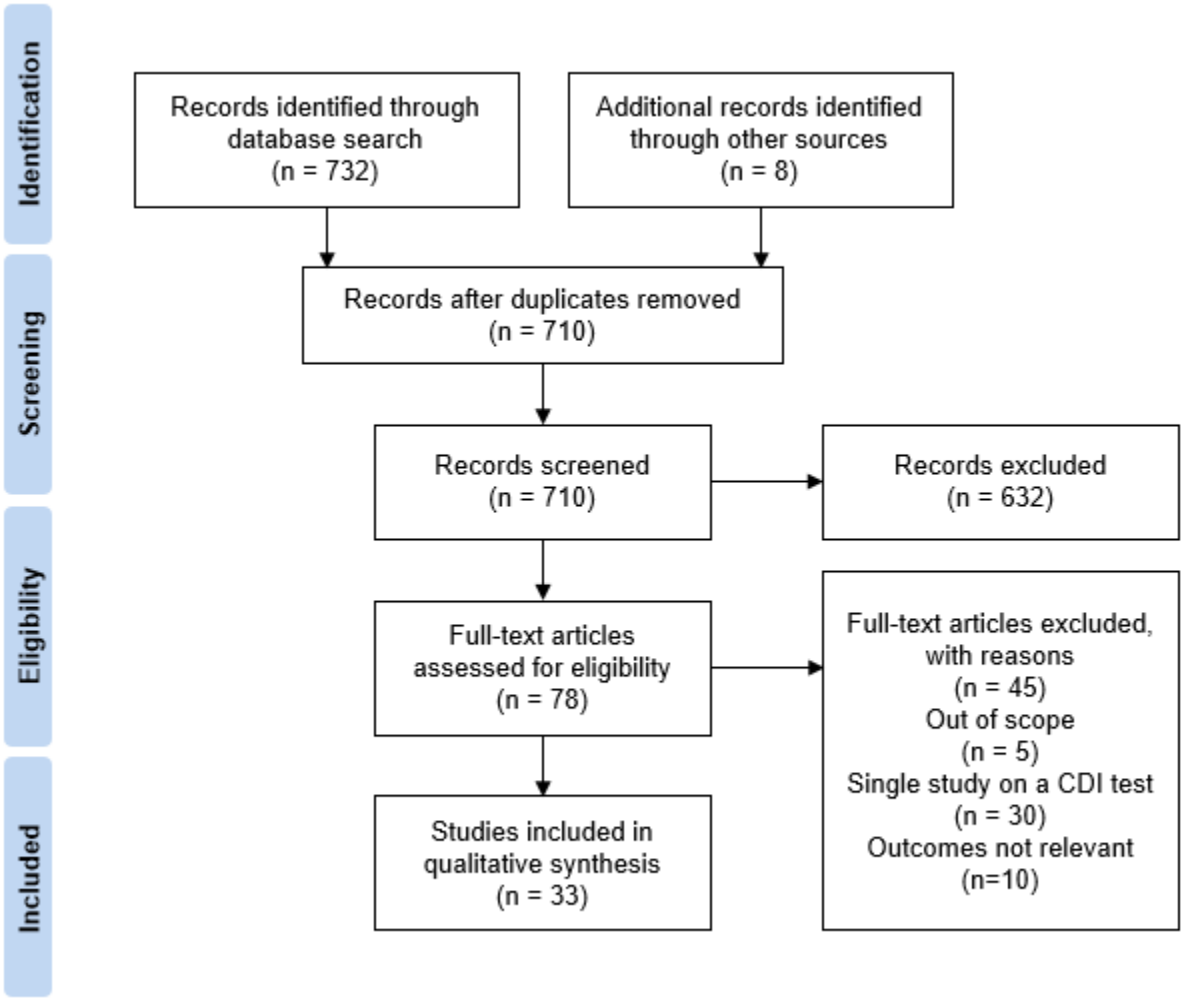
PRISMA criteria described in Moher D, Liberati A, Tetzlaff J, et al. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med. 2009 Jul 21;6(7): e1000097. doi:10.1371/journal.pmed1000097.

Figure A.4: Surveillance for Clostridioides *difficile*–Study Selection for Review



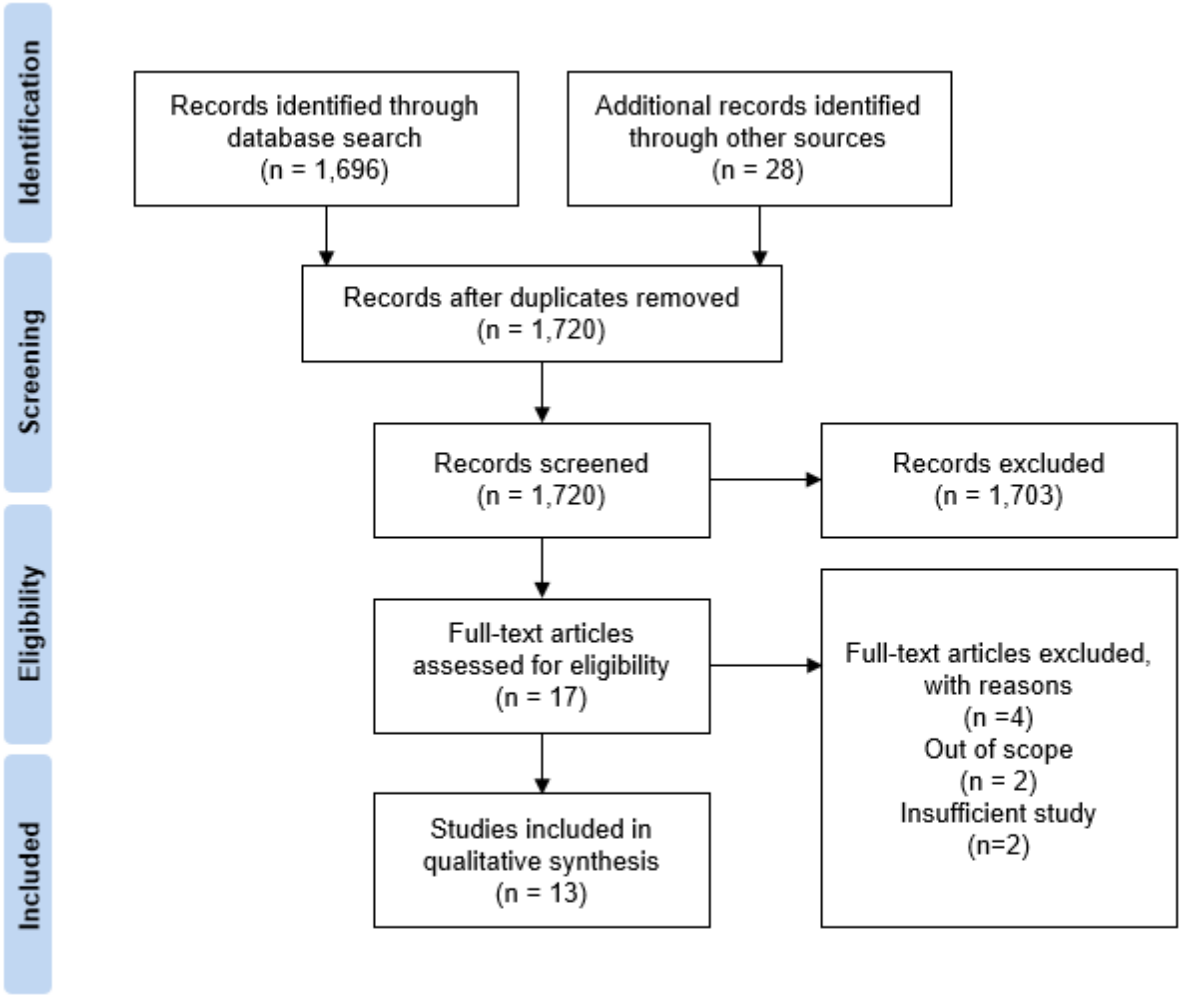
PRISMA criteria described in Moher D, Liberati A, Tetzlaff J, et al. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med. 2009 Jul 21;6(7): e1000097. doi:10.1371/journal.pmed1000097.

Figure A.5: Testing for *Clostridioides difficile*–Study Selection for Review



PRISMA criteria described in Moher D, Liberati A, Tetzlaff J, et al. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med. 2009 Jul 21;6(7): e1000097. doi:10.1371/journal.pmed1000097.

Figure A.6: Multicomponent Prevention Interventions for Clostridioides *difficile*–Study Selection for Review



PRISMA criteria described in Moher D, Liberati A, Tetzlaff J, et al. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med. 2009 Jul 21;6(7): e1000097. doi:10.1371/journal.pmed1000097.

Appendix B. *Clostridioides difficile* Infection Evidence Tables

Table B.1: Clostridioides *difficile*, Antimicrobial Stewardship–Single Studies

Note: Full references are available in the Section 4.1 reference list.

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/ Findings	Risk of Bias (High, Moderate, Low)	Comments
Carbo et al., 2016[26]	Antimicrobial stewardship in which automated protocols were not used, and the infectious diseases pharmacist reviewed each patient's chart daily. Complex cases were reviewed with the infectious diseases physician.	A retrospective cohort study encompassing the study period January 1, 2005–October 31, 2014. Population: Male veterans admitted for treatment of complicated urinary tract infection; (n=118 and n=123 in the pre-ASP and ASP group, respectively).	A 150-bed Veterans Affairs Healthcare System facility in Buffalo, NY	The incidence of CDI did not differ between stewardship groups (p=0.81). However, duration of antibiotic therapy was significantly shorter in the antimicrobial stewardship program (ASP) group (10.32 days vs. 11.96 days; p<0.0001), as was length of hospitalization (5.76 days vs. 6.76 days; p=0.015). Accepted interventions (n=153) occurred as follows: intravenous [IV] to oral conversion (n=48), de-escalation (n=39), duration of antibiotics (n=38), antibiotic selection (n=9), dose adjustment (n=9), escalation (n=7), and drug interaction (n=3). Interventions that were not accepted (n=17) included duration of antibiotics (n=10), de-escalation (n=2), escalation (n=2), IV to oral conversion (n=2), and antibiotic selection (n=1).	Not provided	The ASP included brief monthly educational conferences on antimicrobial stewardship and local antimicrobial resistance, to underline the importance of microbial cultures and to promote appropriate use of antimicrobial agents. The stewardship team consisted of a board-certified pharmacist and infectious diseases physician support.	Moderate	Article was not specifically targeted to CDI.

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/ Findings	Risk of Bias (High, Moderate, Low)	Comments
Chung et al., 2014[15]	A resource-efficient method for identifying antibiotic targets for antimicrobial stewardship interventions. Study was a prelude to a more extensive Agency for Healthcare Research and Quality (AHRQ)-funded project (Evaluation & Research on Antimicrobial Stewardship's Effect on Clostriodiodes *difficile*).	Exploratory evaluation about using different matching criteria with select control groups to determine target antimicrobials. A total of 126 cases were matched to six groups of 252 controls, using different matching strategies.	A 700-bed urban academic tertiary care center	Cases were more likely than five control groups to have been exposed to piperacillin and tazobactam, fluoroquinolones, and third- and fourth- generation cephalosporins; however, the magnitudes of the association varied. Five groups of controls were matched to cases (2:1 ratio) using group-specific matching criteria, including admission date, age, type of admission, length of stay (LOS) to discharge, and/or LOS to CDI diagnosis. The final control group was selected from patients who received antibiotics during hospitalization. Data, including demographics and antibiotic use, were compared between case and control groups. Researchers performed a sixth case-control study using only CDI-negative patients who received antibiotics and were rigorously matched to specific criteria as controls. Although the relationship between piperacillin and tazobactam and CDI remained, third- and fourth-generation cephalosporins and fluoroquinolones were no longer significantly associated with CDI.	Not provided	Because of differences in antimicrobial prescribing practices and formularies between institutions, it is important to use local data to select targets. It is also important to use thorough but feasible matching strategies. Using matching criteria may make it possible to identify high-risk antibiotics associated with CDI.	Low to moderate	Study is about how to determine antibiotic targets for ASPs.

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/ Findings	Risk of Bias (High, Moderate, Low)	Comments
Cruz-Rodríguez et al., 2014[22]	Pharmacy restriction of clindamycin (in an orthopedics ward with high rates of CDI)	Pre-/post-interventional study that consisted of two periods: a 7-month baseline period (December 2011 through June 2012) and a 16-month intervention period (July 2012 through October 2013); 684 patients were included during the baseline and 1,720 during the intervention period.	An orthopedics ward with high rates of CDI in a university teaching hospital in Mexico. 48-bed area with a mean of 1,200 admissions per year.	A reduction of 88% in CDI (1.07 to 0.12 per 1,000 patient days, p=0.056) and 84% for all-cause diarrhea (2.40 to 0.38 per 1,000 patient days, p=0.021) was achieved. Clindamycin was reduced 92.61% without an increase in other antibiotics.	Not provided	The intervention period consisted of a pharmacy restriction of clindamycin for the entire orthopedics ward. Only patients with a previous infectious disease consult could receive clindamycin in their antibiotic scheme.	Low to moderate	Several other studies are noted in which clindamycin reduction resulted in significant CDI reduction.

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/ Findings	Risk of Bias (High, Moderate, Low)	Comments
Dancer et al., 2013[29]	Restrictive policy banning the routine use of third-generation cephalosporins, specifically ceftriaxone, and quinolones throughout the hospital, following an educational campaign	Daily antibiotic doses, hospital-acquired CDI, MRSA, and extended spectrum beta lactamase (ESBL) cases measured 9 months before until 16 months after policy introduction. Population: the hospital admits adult patients only, specializing in care of older adults, as well as in respiratory medicine, endocrinology, and cardiology.	A 450-bed district general hospital in a rural area just outside Glasgow, UK	Between the first and final 6 months of the study, average monthly consumption of ceftriaxone decreased by 95% (from 46.213 to 2.129 DDDs/1,000 pt-bds) and that for ciprofloxacin by 72.5% (109.804 to 30.205 DDDs/1,000 pt-bds). Over the same periods, hospital-acquisition rates for *C. difficile* decreased by 77% (2.398 to 0.549 cases/1,000 pt-bds), for MRSA by 25% (1.187 to 0.894 cases/1,000 pt-bds) and for ESBL-producing coliforms by 17% (1.480 to 1.224 cases/1,000 pt-bds). Time-lag modelling confirmed significant associations between ceftriaxone and *C. difficile* cases at 1 month (correlation 0.83; $p<0.005$). An audit performed 3 years after the policy showed sustained reduction in *C. difficile* rates (0.259 cases/1,000 pt-bds), with additional decreases for MRSA (0.409 cases/1,000 pt-bds) and ESBL-producing coliforms (0.809 cases/1,000 pt-bds).	Consumption of empirical amoxicillin and gentamicin escalated throughout the study and could have confounded the overall effect. It is possible that the restrictive policy has had some impact on extreme drug resistance in this hospital.	It was decided to initiate an educational program encouraging prescribers to reduce consumption of cephalosporins and quinolones on a voluntary basis. This education included providing a series of lectures to all medical staff starting in January 2008 and weekly teaching for small groups of junior doctors. Feedback on HAI rates was sent to clinicians and managers. Gaining support was difficult. By far, the best method of restricting use of a particular drug was physical removal from ward stores by the pharmacists.	Low to moderate Strength: researchers state there were no additional infection control interventions over the study period.	None

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/ Findings	Risk of Bias (High, Moderate, Low)	Comments
Jenkins et al., 2015[24]	An antimicrobial stewardship program (ASP) in a hospital with low baseline antibiotic use	A time-series analysis to evaluate the impact of the ASP over a 6.25-year period (July 1, 2008–September 30, 2014) while controlling for trends during a 3-year pre-intervention period (July 1, 2005 to June 30, 2008).	A 525-bed public safety net hospital in Denver, CO	During the pre-intervention period, total antibacterial and antipseudomonal use were declining (−9.2 and −5.5 days of therapy [DOT]/1,000 patient days [PD] per quarter, respectively). Both continued to decline after the intervention, although at lower rates (−3.7 and −2.2 DOT/1,000 PD, respectively), resulting in a slope change of 5.5 DOT/1,000 PD per quarter for total antibacterial use (p=0.10) and 3.3 DOT/100 PD per quarter for antipseudomonal use (p=0.01). During the stewardship period, significant reductions were seen in high-risk antibiotics (imipenem-cilastatin, β-lactam/β-lactamase inhibitor combinations, fluoroquinolones, and aminoglycosides). Antibiotic expenditures declined markedly during the stewardship period (−$295.42/1,000 PD per quarter, p=0.002), largely as a result of declining antipseudomonal expenditures.	Not provided	A formal ASP was implemented by an infectious diseases physician and an infectious diseases pharmacist, with support from hospital leadership, infectious diseases physicians, data management and information technology specialists, and an infection prevention program. Focus in three areas: (1) preauthorization requirement for select broad-spectrum, toxic, or costly antibiotics; (2) postprescription review with real-time feedback to prescribers; and (3) development and implementation of local guidelines for common infections.	Low to moderate	None

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/ Findings	Risk of Bias (High, Moderate, Low)	Comments
Jump et al., 2012[14]	Infectious Disease Consultation Service (audit and feedback, education)	Pre-/post-systemic antimicrobial use and the rate of positive *C. difficile* tests at the LTCF were compared for 36 months before and 18 months after the initiation of the infectious diseases consultation service using segmented regression analysis of an interrupted time-series.	A 160-bed Veterans Affairs (VA) urban LTCF	In contrast to the pre-intervention period, total systemic antibiotic administration decreased by 30% (p<.001), with a significant reduction in both oral (32%, p<.001) and IV (25%, p=.008) administration. Greatest reductions in tetracylines, clindamycin, sulfamethoxazole/ trimethoprim, fluoroquinolones. Rates of change for positive *C. difficile* tests at the LTCF declined in the post- versus pre-intervention periods (p=.04). (While the rate of change in positive *C. difficile* tests did not change significantly over time for the two individual periods, the difference in the rates of change between the two periods was significantly different.)	Not provided	The facility instituted an onsite LTCF Infectious Disease Consultation Service as a multifaceted intervention to improve the use of antimicrobials at the LTCF. The consult team consisted of an infectious diseases physician and nurse practitioner. They examined residents at the LTCF once each week and were available for remote consultation the remainder of the week.	Low to moderate	None

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/ Findings	Risk of Bias (High, Moderate, Low)	Comments
Libertin et al., 2017[10]	Prospective audit with healthcare provider feedback and targeting 12 antimicrobial agents. An educational grand rounds lecture series was provided before implementation of the ASP to all prescribers. To improve this selection, prescribers were given algorithms to aid the selection of empirical antibiotics for specific infectious disease syndromes based on local antibiograms.	Pre-/post intervention comparison of CDI rates, antimicrobial costs. Data on use of 12 targeted antimicrobial agents were used for comparison with the post-ASP initiation.	A rural community hospital (with low patient census) in GA	CDIs decreased from 3.35 cases per 1,000 occupied bed days (OBDs) in 2013 to 1.35 cases per 1,000 OBDs in 2015 ($p<0.001$). Total targeted antimicrobial costs decreased 50% from $16.93 per patient day in 2013 to $8.44 per patient day in 2015. Annualized savings were $280,000 in 1 year, based on drug savings only.	Not provided	Authors note that development of a collegial environment for a healthcare provider's growth in ASP knowledge was important in achieving acceptance of the program. The approach on how to implement an ASP depends on many factors, including need for an infectious diseases consultant, an infectious disease-trained pharmacist, a person with a doctor of pharmacy degree, or a combination of these; institution size; composition of the providers; and resources provided by the institutional leadership.	Moderate; no sample size given. No control group. Small rural hospital—results may not be generalizable.	No formulary restriction and pre-authorization were used for the targeted antimicrobial agents. The intervention did not include strategies to limit antibiotic therapy to the shortest effective duration.

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/ Findings	Risk of Bias (High, Moderate, Low)	Comments
Lowe et al., 2017[27]	Targeted antimicrobial stewardship (audit and feedback) for patients with a viral respiratory tract infection. Prospective audit and feedback was implemented based on two criteria: microbiology (no positive bacterial cultures) and chest imaging (absence of pneumonia or consolidation on radiology dictation).	A quasi-experimental before-and-after study. Intervention was conducted for 1 year starting December 1, 2015; 92 patients were included in the prospective cohort and 118 in the retrospective cohort.	Two Canadian health centers	Antimicrobial stewardship recommendations for hospitalized patients with viral respiratory tract infections were accepted for 77% of cases. This targeted approach translated into a 1.3-day (95% confidence interval, 0.3 to 2.3; p<0.01) decrease in mean days of antibiotics post-viral diagnosis compared with the previous year without systematic interventions. There was a 32% reduction in antibiotic days per patient.	Not provided	Facility initiated a collaboration between the virology laboratory and the ASP team to integrate reporting of respiratory virus PCR with an ASP audit and feedback intervention. Algorithm used a combination of microbiology, radiologic imaging, and clinical context after discussion with the ASP team to de-escalate antibiotics.	Moderate	CDI was not the prime focus of the study. A review of patient outcomes did not reveal statistically significant differences for length of stay, ICU admission within 14 days, mechanical ventilation within 14 days, antibiotics prescribed within 14 days, CDI diagnosed within 30 days, or readmission within 30 days.

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/ Findings	Risk of Bias (High, Moderate, Low)	Comments
Ostrowsky et al., 2014[28]	Controlled use of target antibiotics. Facilities identified target antibiotics using case-control studies. All hospitals selected at least one back-end audit and feedback strategy as one of their intervention strategies, with up to three other interventions implemented per hospital.	A multicenter before-and-after 20-month intervention comparative study in 10 medical centers (six intervention, four controls). The six intervention hospitals reported 108,268 distinct episodes of antibiotic use for 68 antibiotics; 3,491 CDI cases were reported.	Ten medical facilities in greater New York City region. The mean bed size for intervention hospitals was 573 (range, 396 to 871). All were nonprofit facilities and combined had more than 240,000 inpatient admissions annually.	Intervention facilities identified piperacillin/ tazobactam, fluoroquinolones, or cefepime (odds ratio, 2.0 to 9.8 in CDI case patients compared with those without CDI) as intervention targets. Intervention hospitals reduced the use of targeted antibiotics to varying degrees, depending on the measures used and the intervention. Total target antibiotic use significantly decreased ($p<0.05$) when measured by days of therapy and number of courses but not by defined daily dose. Number of courses with all forms of these antibiotics was reduced ($p<.005$). Intervention hospitals reported fewer hospital-onset CDI cases (2.8 rate point difference) compared with nonintervention hospitals; however, there were no statistically significant decreases in aggregate hospital-onset CDI either between intervention and nonintervention groups or within the intervention group over time.	Not provided	Each intervention hospital did its own case control study to identify target antimicrobials. For piperacillin/ tazobactam and cefepime, hospitals did audits and feedback. For quinolone, hospitals used restrictions or algorithms asking the prescriber to reevaluate the choice. The implementation of ASP interventions was typically more complex than expected. Each site developed ASP activities to meet its needs and respond to local resource constraints.	Low to moderate	None

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/ Findings	Risk of Bias (High, Moderate, Low)	Comments
Patton et al., 2018[19]	Following national guidance on restriction of antimicrobials associated with a high risk of CDI [high-risk antimicrobials in October 2008, the hospital policy for empirical treatment of infection changed to remove cefuroxime for any indication, include ceftriaxone only for meningitis, limit fluoro-quinolones to a few specific indications, and reduce use of clarithromycin, clindamycin, and co-amoxiclav. Cefuroxime was also removed from the policy for antibiotic prophylaxis in general surgery.	The study period was October 2006 to September 2010. The study was an observational pre-/post evaluation of intervention effects in medical and surgical wards. It included all patients age 18 years and older admitted through the acute medical unit or one of six general surgical wards.	An 855-bed university hospital, UK; medicine and surgery wards	Six months post-intervention, there were relative reductions in high-risk antimicrobial use of 33% (95% CI, 11 to 56) in the medicine ward and 32% (95% CI, 19 to 46) in the surgery ward. At 12 months, there was an estimated reduction in CDI of 7.0 cases/1,000 admissions (relative change -24% [95% CI, 55 to 6]) in Medicine, but no change in Surgery (estimated 0.1 fewer cases/1,000 admissions [-2% {95% CI, 116 to 112}]). Mortality was reduced throughout the study period, unaffected by the intervention. Pre-intervention CDI rates and trends influenced the intervention effects.	Not provided	Evaluation of the effect of real-world stewardship interventions on outcomes other than prescribing remains methodologically challenging and worthy of further effort. Pre-intervention outcome data should be examined before resource-intense interventions and evaluations are undertaken, and all evaluations should include balancing measures. There are limitations in using mortality as a stewardship outcome, due to confounding, but it does have value as a balancing measure, and most studies do not report any clinical outcome data.	Low to moderate	This article also includes a systematic review to compare findings with those of other studies. Authors measured mortality owing to concerns raised by clinicians about the change in antimicrobial policy.

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/ Findings	Risk of Bias (High, Moderate, Low)	Comments
Rahme et al., 2016[31]	H-AST =hospital-based antimicrobial stewardship teams working with an LTCF. Campaign that included (1) creation of LTCF urinary guidelines; (2) an in-service for providers on appropriate treatment of urinary tract infection (UTI), skin and soft tissue infection (SSTI), and respiratory tract infection (RTI); (3) an educational event for family members, discussing the risks of overusing antimicrobial agents; and (4) a telephone hotline for the LTCF to contact the H-AST for questions.	Pre- and post-intervention measures of target antimicrobials (12-month mean DDD per 1,000 resident days [RD]) and CDI rates in the LTCF. No sample size given.	A 520-bed, long-term skilled nursing facility (working with an infection prevention team from a community teaching hospital)	Significant 38.7% decrease in ciprofloxacin use. A decrease in overall antibiotic use: 11.68%, from 82.33 to 72.71 DDD per 1,000 RD (p=0.06). A comparison of infection rates per 1,000 RD pre- and post-intervention showed a 5.51% decrease in UTI diagnosis/treatment, from 1.71 to 1.61 (p=0.28), and a 5.73% decrease in RTI from 1.35 to 1.27 (p=0.67). There was an 11.10% increase in the rate of SSTI during the post-intervention period, from 0.92 to 1.04 (p=0.27). The rate of CDI in the LTCF decreased by 19.47%, from 0.094 to 0.076 (p=0.58) in the post-intervention period.	Not provided	The LTCF medical director, nursing manager, and infection prevention nurse collaborated with the H-AST. The education campaign focused on creating treatment guidelines for UTI, SSTI, and RTI. A pocket card outlining the recommendations was developed for each disease state. LTCF providers and nursing staff commonly stated that a large obstacle to appropriate antimicrobial prescribing is family pressure. Providing family member education was a unique element to this stewardship initiative.	Low to moderate; the LTCF performed environmental changes during the pre-intervention period that could have affected the CDI rates during the post-intervention period. Single site; no sample size given.	Levofloxacin and moxifloxacin use did not show a statistically significant change, going from 6.16 to 6.72 and 0.34 to 0.32 DDD per 1,000 RD, respectively (p = 0.65 and 0.93). Total FQ consumption (Cipro-floxacin, levofloxacin, and moxifloxacin) also did not change significantly.

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/ Findings	Risk of Bias (High, Moderate, Low)	Comments
Shea et al., 2017[12]	Healthcare system antimicrobial stewardship-initiated respiratory fluoroquinolone restriction and education program on its use, appropriate-ness of quinolone-based therapy based on institutional guidelines, and CDI rates.	A multicenter, quasi-experimental study	Four of 12 adult hospitals within Seton Healthcare Family, a large, urban, not-for-profit healthcare system located throughout Central Texas. The four hospitals ranged from 124 to 534 licensed beds.	Compared with pre-intervention, the four hospitals experienced 48% and 88% average reductions in use (DOT/1,000 PD) after education and restriction, respectively. Using segmented regression analysis, both education (14.5 DOT/1,000 PD per month decrease; p=0.023) and restriction (24.5 DOT/1,000 PD per month decrease; p<0.0001) were associated with decreased use. A significant reduction in the annual acquisition cost of moxifloxacin, the formulary respiratory fluoroquinolone, was observed postrestriction compared with pre-intervention within the healthcare system ($123,882 vs. $12,273; p=0.002). CDI rates decreased significantly (p=0.044) from pre-intervention using education (3.43 cases/10,000 PD) and restriction (2.2 cases/10,000 PD).	Not provided	Prior to this study, an extensive literature review was performed to guide the initial development of institutional treatment guidelines, including community-acquired pneumonia and antibiotic therapy in chronic obstructive pulmonary disease exacerbations. These literature findings and expert opinion were used to develop educational material, respiratory fluoroquinolone restriction criteria, and institutional treatment guidelines.	Low to moderate	None

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/ Findings	Risk of Bias (High, Moderate, Low)	Comments
Taggart et al., 2015[25]	Antimicrobial stewardship audit and feedback program. ICU patients were reviewed Monday to Friday by a physician and pharmacist with infectious diseases training. Recommenda-tions related to appropriate antimicrobial use were presented to ICU teams during a dedicated daily meeting. Initiative was part of an Ontario-wide quality improvement project to introduce audit and feedback programs into ICUs.	A controlled interrupted time series analysis was used to compare outcomes in the 12 months before and after the intervention in 2012–2014; 2,635 ICU patients (from two ICUs). Cardiovascular and coronary care ICUs served as control units.	Four adult ICUs at St. Michael's Hospital, a 465-bed academic teaching hospital in Toronto, Ontario, Canada.	Mean total monthly antimicrobial use in defined daily doses (DDD) per 1,000 patient days was reduced 28% in the trauma and neurosurgery (TN) ICU (1,433 vs. 1,037), but increased 14 % in the medical surgical (MS) ICU (1,705 vs. 1,936). There was a significant reduction in antibacterials by 29% (p=0.0001), antibiotics with activity against *Pseudomonas* species by 44% (p<0.0001), and fluoroquinolones by 80% (p<0.0001). The rate of *C. difficile* infection in the TNICU decreased from 0.66 cases per 1,000 patient days pre-intervention to 0.48 cases per 1,000 patient days post-intervention. However, the result was not statistically significant (p=0.69). There were no significant changes in the use of the specific agents or classes of antimicrobials in the MSICU. There was a non-significant decrease in the rate of *C. difficile* infection in the MSICU. Rates in the control ICUs were also reduced.	One of the intervention groups showed a decrease in use of anti-microbials, but the other (MSICU) showed an increase.	Little change in overall antibiotic prescribing, but reduction in high-risk antibiotics. Before intervention, antibiotic selection was performed by ICU teams. During the post-intervention period, an infectious diseases trained pharmacist and physician reviewed all patients admitted to the intervention ICUs daily (weekdays only). Patients who remained in the ICU were reassessed every weekday until ICU discharge. The ICU team maintained prescribing autonomy.	Low to moderate	CDI reductions were not statistically significant, and the rates in the control ICUs were also reduced. The mean total cost of anti-microbials in the TNICU decreased from $18.40 per patient day before the intervention to $14.53 per patient day after the intervention (p=0.017).

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/ Findings	Risk of Bias (High, Moderate, Low)	Comments
Talpaert et al., 2011[5]	Revised antibiotic guidelines for empirical treatment of common infections and enhanced stewardship on reducing broad-spectrum antibiotic use	A retrospective, quasi-experimental study using interrupted time series (ITS) over 12 months before and after the intervention (2005–2007). Population: all adult inpatients. Number of ASP patients: 386.	Adult medical and surgical wards, in a ~500-bed acute general hospital in London.	The intervention was associated with a significant reduction in the use of fluoroquinolones by 105.33 defined daily doses (DDDs)/1,000 occupied bed-days (OBDs) per month (95% CI, 34.18 to 176.48, p<0.001) and cephalosporins by 45.93 DDDs/1,000 OBDs/month (95% CI 24.11 to 67.74, p<0.0001). These changes in levels correspond to a 58.5% and 45.8% drop in fluoroquinolone and cephalosporin use, respectively. There was no significant change in total antibiotic, clindamycin, amoxicillin, or co-amoxiclav use. There was a significant increase in use of “low-risk antibiotics.” There was a significant decrease in CDI following the intervention (IRR 0.34 [0.20 to 0.58], p<0.0001). No differences in clinical outcomes were associated with the intervention.	Not provided	The intervention included audit and feedback, education, and revised guidelines saying to avoid broad-spectrum antibiotics, for example, fluoroquinolones, cephalosporins, clindamycin, amoxicillin, and co-amoxiclav. Instead, “low-risk” antibiotics were recommended. Formation of an antibiotic management team (AMT) comprising a consultant microbiologist and an antibiotic pharmacist. Any high-risk antibiotic prescribed by clinicians or supplied by the Pharmacy Department was brought to the attention of the AMT.	Low to moderate	CDI was endemic at the facility: between April 2005 and March 2006, 349 cases of CDI were recorded. The limited information available indicates the emergence of the 027 ribotype during 2007.

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/ Findings	Risk of Bias (High, Moderate, Low)	Comments
Tedeschi et al., 2017[11]	An ASP was implemented based on systematic bedside infectious disease consultation and structural interventions (i.e., revision of protocols for antibiotic prophylaxis and education focused on the appropriate-ness of antibiotic prescriptions).	Quasi-experimental study of the periods before (from January 2011 to June 2012) and after (from July 2012 to December 2014) ASP implement-tation.	A 150-bed rehabilitation hospital dedicated to patients with spinal cord injuries.	Antibiotic consumption decreased from 42 to 22 defined daily dose (DDD) per 100 patient days (p<0.001). The main reductions involved carbapenems (from 13 to 0.4 DDD per 100 patient days; p=0.01) and fluoroquinolones (from 11.8 to 0.99 DDD per 100 patient days; p=0.006), with no increases in mortality or length of stay. The incidence of CDI decreased from 3.6 to 1.2 cases per 10,000 patient days (p=0.001). Between 2011 and 2014, the prevalence of extensively drug-resistant (XDR) strains decreased from 55% to 12% in *P. aeruginosa* (p<0.001) and from 96% to 73% in *A. baumannii* (p=.03). The prevalence of ESBL-producing strains decreased from 42% to 17% in *E. coli* (p=0.0007) and from 62% to 15% in *P. mirabilis* (p=0.0001). A trend toward lower mortality and a significant shortening of length of stay were observed.	Not provided	An ASP based on infectious diseases consultation was effective without affecting patient outcomes. The ASP intervention had two steps: First, a systematic bedside infectious diseases consultation activity. A dedicated infectious diseases consultant was present onsite three times a week and was available for remote consultations. Second, regular 6-monthly revisions of the internal protocol for antibiotic prophylaxis were performed and educational activities were conducted.	Low to moderate	The population at this setting is highly exposed to anti-microbials. Patients cared for in these facilities are prone to Infections. Rehabil-itation physicians are worried about antibiotic resistance but may remain unaware of the local epidemiology and the most common mechanisms of antibiotic resistance.

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/ Findings	Risk of Bias (High, Moderate, Low)	Comments
Wenisch et al., 2014[13]	An information campaign on CDI, formal restriction of moxifloxacin, and direct feedback	Pre-/post study. The pre-intervention period (period 1) was January through May 2013, and the intervention period (period 2) was June through December 2013. The study recorded the defined daily doses (DDD) of moxifloxacin and the number of CDI patients/ month.	A 1,000-bed tertiary care community teaching hospital with 1,081 beds (Vienna, Austria)	Moxifloxacin use was reduced from a mean (+/- standard error of the mean [SEM]) of 1,038 +/- 109 DDD per month (period 1) to 42 +/- 10 DDD per month (period 2) (p=0.0045). In total, quinolone use decreased by about 37% in period 2 compared with period 1. Total antibiotic use was stable. The mean (+/-SEM) numbers of CDI cases in period 1 were 59 +/-3 per month and in period 2 were 32 +/-3 per month (46% reduction; p=0.0044).	Not provided	The development of evidence-based practice guidelines incorporating local microbiology and resistance patterns is strongly recommended in antimicrobial stewardship programs. The numbers of CDI cases and ribotype 027 isolates seemed to be related to moxifloxacin (a high-risk broad-spectrum antibiotic) use. The antibiotic stewardship team was appointed by the hospital management and consisted of a clinical pharmacist, a pathologist, and infection control professionals.	Low to moderate	While the CDI numbers were stable at 200 patients per year from 2009 to 2011 (0.56, 0.51, and 0.50 per 1,000 patient days, respectively), an increase to 313 patients was observed in 2012 (0.88/1,000 patient days).

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/ Findings	Risk of Bias (High, Moderate, Low)	Comments
Yam et al., 2012[30]	A multi-disciplinary team was formed to implement a stewardship program targeting six antimicrobials with a high potential for misuse. A key part of the program was the participation of a remotely located infectious diseases physician specialist in weekly case review tele-conferences.	Pre-/post-program evaluation. Measurements taken at 13 months after implement-tation.	A 141-bed rural hospital	The rate of nosocomial CDI decreased from an average of 5.5 cases per 10,000 patient-days to an average of 1.6 cases per 10,000 patient-days. An evaluation of the first 13 months of the initiative (May 2010–June 2011) indicated that pharmacist-initiated antimicrobial stewardship interventions increased dramatically after program implementation, from a baseline average of 2.1 interventions per week to an average of 6.8 per week. An analysis of 2010 purchasing data demonstrated a decrease in annual antibiotic costs of about 28% from 2009 levels (and a further decrease of about 51% in the first two quarters of 2011).	Not provided	After a review of baseline data, a novel process was developed. The strategy was to follow recommended IDSA–SHEA guidelines while addressing major gaps in hospital resources. Included use of a remotely located physician specialist in infectious diseases, improvement of existing information technology, and education and training of pharmacists to provide daily antimicrobial reviews were the major strategies used to provide an ASP for use in a rural setting.	Moderate: inability to quantify and evaluate the progress of the program due to the lack of consistent pharmacist reporting methods	None

Table B.2: Clostridioides *difficile*, Antimicrobial Stewardship–Systematic Review

Note: Full references are available in the Section 4.1 reference list.

Author, Year (Reference)	Description of Patient Safety Practice	Setting/s, Populations	Summary of Systematic Review Findings	Implementation Themes/Findings	Notes
Baur et al., 2017[17]	Antibiotic stewardship programs	Hospitals	Search for studies published from January 1, 1960, to May 31, 2016. Excluded LTCF. Included 32 studies. The main outcomes were incidence ratios (IRs) of target infections and colonization per 1,000 patient-days before and after implementation of antibiotic stewardship. Meta-analyses were done with random-effect models, and heterogeneity was calculated with the I^2 method. Antibiotic stewardship programs reduced the incidence of infections and colonization with multidrug-resistant Gram-negative bacteria (51% reduction; IR 0·49, 95% CI 0.35 to 0.68; p<0·0001), extended-spectrum β-lactamase-producing Gram-negative bacteria (48%; 0.52, 0.27 to 0.98; p=0.0428), and methicillin-resistant *Staphylococcus aureus* (37%; 0.63, 0.45 to 0.88; p=0.0065), as well as the incidence of CDIs (32%; 0.68, 0.53 to 0.88; p=0.0029). Most effective when implemented with other measures. Significant heterogeneity between studies was detected. Among the different types of antibiotic stewardship interventions, antibiotic cycling was found to be the most effective, followed by audits and feedback and antibiotic restriction. The interventions became more effective over time, ranging from 10% reduction of antibiotic resistance for 1980 to 2000 to 32% reduction for 2006 to 2013. Studies of guideline implementation and single antibiotic classes did not show any effect for these interventions on resistance rates, perhaps because of short followup. ASPs were more effective in the hematology-oncology settings.	When planning future studies of ASPs, it would be advisable to use controlled interventional study designs and data-reporting consistencies. Implementation facilitators: high compliance among physicians, the additional educational effect of feedback, a closer working relationship between physicians and the antibiotic stewardship team because of audits, audits in conjunction with antibiotic stewardship programs, educational effects, and the Hawthorne effect due to putting electronic monitoring systems in place. Auditing is effective in all settings.	None

Author, Year (Reference)	Description of Patient Safety Practice	Setting/s, Populations	Summary of Systematic Review Findings	Implementation Themes/Findings	Notes
Davey et al., 2017[18]	Antimicrobial stewardship	Hospital inpatient	Review of articles published up to January 2015 to estimate the effectiveness and safety of interventions to improve antibiotic prescribing to hospital inpatients and to investigate the effect of two intervention functions: restriction and enablement. There was very low-certainty evidence about the effect of the interventions on reducing *Clostridium difficile* infections (median, -48.6%; interquartile range, -80.7% to -19.2%; seven studies). The duration of antibiotic treatment decreased by 1.95 days (95% CI, 2.22 to 1.67; 14 randomized controlled trials [RCTs]; 3,318 participants; high-certainty evidence) from 11.0 days. Information from nonrandomized studies showed interventions to be associated with improvement in prescribing according to antibiotic policy in routine clinical practice, with 70% of interventions being hospitalwide compared with 31% for RCTs. The risk of death was similar between intervention and control groups (11% in both arms), indicating that antibiotic use can likely be reduced without adversely affecting mortality (RD 0%, 95% CI, 1 to 0; 28 RCTs; 15,827 participants; moderate-certainty evidence). Antibiotic stewardship interventions probably reduce length of stay by 1.12 days (95% CI, 0.7 to 1.54 days; 15 RCTs; 3,834 participants; moderate-certainty evidence).	Both enablement and restriction were independently associated with increased compliance with antibiotic policies, and enablement enhanced the effect of restrictive interventions (high-certainty evidence). Enabling interventions that included feedback were probably more effective than those that did not (moderate-certainty evidence). One RCT and six nonrandomized studies raised concerns that restrictive interventions may lead to delay in treatment and negative professional culture because of breakdown in communication and trust between infection specialists and clinical teams (low-certainty evidence).	None

Author, Year (Reference)	Description of Patient Safety Practice	Setting/s, Populations	Summary of Systematic Review Findings	Implementation Themes/Findings	Notes
Feazel et al., 2014[16]	Antibiotic stewardship programs (ASPs) to prevent CDI in hospitals (non-outbreak situations)	Hospitals (non-outbreak situations)	Objective was to perform a meta-analysis of published studies to assess the effect of ASPs on the risk of CDI in hospitalized adult patients; 16 studies met inclusion criteria. The average quality of the studies was low, as measured by the modified Downs and Black tool. Most studies suffered from poor internal validity, particularly with respect to bias. Heterogeneity in studies' settings. When the results of all studies were pooled in a random effects model, a significant protective effect (pooled risk ratio 0.48; 95% CI, 0.38 to 0.62) was observed between ASPs and *C. difficile* incidence. When pooled results were stratified by intervention type, a significant effect was found for restrictive ASPs (complete removal of drug or prior approval requirement). Furthermore, ASPs were particularly effective in geriatric settings. The duration of each ASP also affected the magnitude of the effect, with longer studies resulting in a greater protective effect than shorter studies. Majority of studies are from UK, limiting generalizability.	ASPs effectively decrease the incidence of CDI. Restrictive policies that modified physician prescription practices were more effective than persuasive policies. ASPs are most effective with geriatric populations. Studies were subject to many biases. Future studies should use designs with higher internal validity, either through a cluster-randomized design or by the addition of non-equivalent control groups. Thus, given the apparent benefit of ASPs in reducing CDI, further research and implementation of active ASPs are needed in North America, as well as multiple measurement.	Articles went back as far as 1997 and up to 2013.

Author, Year (Reference)	Description of Patient Safety Practice	Setting/s, Populations	Summary of Systematic Review Findings	Implementation Themes/Findings	Notes
Louh et al., 2017[20]	Review of several interventions to reduce CDI, including hand hygiene, chlorohexidine bathing, probiotics, environmental cleaning, bundles, and ASPs	Acute care hospitals	Systematic search for ASP interventions to reduce the rate of CDI in acute care hospitals. Review of articles published between January 1, 2009, and August 1, 2015. Review identified 13 studies that implemented ASPs. Common approaches were prospective audit and feedback when targeted antimicrobials were prescribed, or preauthorization requirements for antimicrobials. Both methods appeared to be effective in reducing CDI in acute care hospitals. One study saw a decrease in CDI rates from 8.2 of 10,000 to 3.1 of 10,000 patient-days with an audit and feedback system for six high-risk antimicrobials, although this result may be confounded by a change in environmental cleaning practice made immediately preceding this evaluation. Similarly, another study implemented stewardship educational lectures and restricted use of ceftriaxone and ciprofloxacin, resulting in CDI reduction from 24 of 10,000 to 5.5 of 10,000 patient-days. Hospitals with relatively low baseline rates of CDI did not see a substantial change after deployment of an ASP.	ASPs were generally effective in reducing CDI. Audit and feedback and restrictions were primary methods. Better results for institutions with higher CDI rates. Institutions with few resources should strive to improve environmental practices, with implementation of bleach-based cleaning. Institutions with more resources should consider bundled interventions that incorporate environmental cleaning, *restrictive* ASPs, and checklists.	Authors found that, in prevention studies performed in acute care hospitals, bleach-based environmental disinfection appeared to have the most effect in preventing CDI. Bundled interventions and antimicrobial stewardship showed promise for reducing CDI rates.
Pitiriga et al., 2017[21]	Antimicrobial stewardship targeting quinolone prescribing	Hospital and community sites	Article synthesizes the impact of antibiotic stewardship practices, including interventions on (1) quinolone resistance rates and (2) healthcare-associated infections (MRSA, ESBLs bacteria, and CDI). Most of the existing stewardship studies document possible improvements in susceptibility rates among both nosocomial and community Gram-negative isolates and decrease in CDI (three CDI-focused studies). However, there are possible pitfalls in the existing study designs; more clinical data are needed. Article includes recommendations for quinolone-targeted practices such as: restriction policies, audit and feedback, prior authorization, IV switch to oral program, educational programs, and local antibiotic guidelines, as well as monitoring of Gram-negative susceptibility patterns. Novel approaches for identifying bacterial resistance include: use of molecular diagnostics, mass spectrometry, microarrays, and whole-genome sequencing, as well as prompt investigation of the clonality of quinolone-resistant strains.	Recommendations for quinolone-targeted practices include: restriction policies and prospective audits with feedback. However, clinicians should be aware of the ‘‘squeezing the balloon’’ effect—i.e., the association of restriction policies with progressive resistance to unrestricted antimicrobials. Quinolone bundling on the basis of antimicrobial spectrum; syndrome-specific interventions; multifaceted approaches.	Background: studies have linked use of quinolones with increase in antibiotic resistance and infections involving MRSA and *C. difficile*. (This article is not specific to *C. difficile*.)

Table B.3: Clostridioides *difficile*, Hand Hygiene–Single Studies

Note: Full references are available in the Section 4.2 reference list.

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting:	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/Findings	Risk of Bias (High, Moderate, Low)	Comments
Al-Tawfiq et al., 2018[30]	The Joint Commission Centre for Transforming Healthcare's web-based Targeted Solutions Tool (TST) for improving hand hygiene; hand hygiene compliance	Trained unknown and known observers monitored compliance, and rates of hospital-acquired infections were tracked and correlated against the changes in hand hygiene compliance. In total, the secret observers recorded 5,669 hand hygiene observations; 4-month baseline; 1 year intervention period.	A 30-bed oncology/hematology inpatient unit and a 350-bed community hospital located in eastern Saudi Arabia	The compliance rate increased from 75.4% at baseline (May to August 2014) to 88.6% during the intervention (13 months) and the control periods ($p<0.0001$; not statistically significant). Reductions in healthcare-associated infection rates were recorded for *Clostridium difficile* infections from 7.95 (95% CI 0.8937 to 28.72) to 1.84 (95% CI 0.0241 to 10.26) infections per 10,000 patient-days ($p=0.23$).		The top contributing factors for noncompliance were improper use of gloves, hands full of supplies or medications, and frequent entry or exit in isolation areas. Researchers concluded that the application of TST allowed healthcare organizations to improve hand hygiene compliance and to identify the factors contributing to noncompliance. An action plan was developed to decrease improper glove use through education and focusing particularly on the primary noncompliant groups.	Low/ moderate—potential for Hawthorne effect; part of an overall quality improvement project. Single site, small.	The researchers identified obstacles to hand hygiene such as inappropriate use of gloves, particularly within the house-keeping department.

Edmonds et al., 2013[8]	Washing with plain soap and water	Pre/post-experimental study. This two-phase study was conducted to determine whether surrogate organisms were predictive of *C. difficile* spore removal and to compare the efficacy of various hand washing preparations at removing *C. difficile*. Nine subjects completed evaluations for a nonantimicrobial body wash or tap water for removal of spores of *B. atrophaeus*, *C. sporogenes*, and *C. difficile*. In phase 2, three to nine subjects completed evaluations for 10 test products and a tap water control for removal of *C. difficile* spores using a modification of a standard hand wash test method.	Controlled experiment	A peracetic acid and surfactant formulation was the most effective test preparation and achieved significantly greater reductions of *C. difficile* spores than did the tap water control, the 4% chlorhexidine gluconate (CHG) hand wash, 0.5% bleach, 8% hydrogen peroxide, 0.3% triclosan hand wash, nonantimicrobial hand wash, and nonantimicrobial body wash ($p<.05$). An ink and stain remover (applied with and without a brush) was significantly more effective than the tap water control, nonantimicrobial body wash, and 4% CHG hand wash ($p<.05$). The sodium tetraborate decahydrate powder was also significantly more effective than tap water ($p<.05$). The remaining preparations were statistically equivalent and not more effective than tap water alone.		Findings demonstrated that existing hand hygiene interventions have limited efficacy against *C. difficile* spores. Therefore, HCWs should continue to follow the recommendations for hand washing with soap and water and emphasize contact precautions (especially gloves) for care of patients with CDI. The lack of readily available *C. difficile* spore suspensions makes it difficult to evaluate the efficacy of hand wash products against *C. difficile*. Surrogate organisms should not be used to predict efficacy of hand hygiene agents against *C. difficile* spores. The only other products to achieve significantly higher $\log_{10}$ reductions than the tap water were sodium tetraborate decahydrate powder and the ink and stain remover. However, these products also contain harsh ingredients that are unacceptable for routine use in healthcare environments.		The peracetic acid and surfactant formulation likely achieved the highest log reduction through a combination of spore removal and inactivation. However, the active concentration or contact time would negatively impact skin tolerability.

Isaacson et al., 2015[37]	Hand washing using friction, that is, sand and water	Experimental comparison between different hand washing methods. Fourteen HCW subjects completed six study arms in randomized order: (1) no hand washing; (2) negative hand washing control: 30 seconds of rubbing with 5 mL of water and 30 seconds of tap water rinsing; (3) 30 seconds of rubbing with 5 mL of 0.3% triclosan soap and 30 seconds of rinsing; (4) 30 seconds of rubbing with a paste consisting of 15 mL of sand mixed with 15 mL of tap water and 30 seconds of rinsing; (5) 15 seconds of rubbing with 5 mL of a 50% baking soda and 50% vegetable oil mix, and 15 seconds of rubbing with 5 mL of liquid dish detergent, followed by 30 seconds of rinsing; and (6) 60 seconds of rinsing. Contamination was measured after each method.	Controlled experiment	Hand washing with sand resulted in an additional 0.5 log reduction in spore recovery compared with the current standard of soap and water. Sand was the only intervention statistically superior to water, removing an additional 0.36 log of spores (p=.019). Compared with triclosan soap/water, sand removed 0.5 log more spores (p=.003), and oil/baking soda followed by dish detergent removed 0.37 log more spores (p<.001).		Although the sand used in this study was well tolerated by participants and resulted in no irritation after a single use, abrasives might not be suitable for routine hand washing. This study did not find a significant difference in residual spore counts after washing with triclosan soap versus tap water, consistent with findings from previous studies. This finding may occur because triclosan soap is not sporicidal and confers no additional friction.	Moderate—small sample—potential variation in technique across participants. Spores left over from the prior intervention. Did not use a “wash out” period, although they found that they did not necessarily need that.	Study was based on the idea that augmenting the friction of hand washing would result in a reduction in contamina-tion.
Kirkland et al., 2012[29]	Hand hygiene compliance using (1)	Three-year interrupted time series with multiple	383-bed teaching hospital, rural	HH compliance increased significantly from 41% to 87%	Not provided	Monthly data show that the single biggest improvement in HH	Low/ moderate—cannot	When this initiative began, the

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting:	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/Findings	Risk of Bias (High, Moderate, Low)	Comments
	leadership/ accountability; (2) measurement/ feedback; (3) hand sanitizer availability; (4) education/ training; and (5) marketing/ communication.	sequential interventions and 1-year post-intervention followup. Tracked two primary outcomes monthly: (1) HH compliance rates and (2) healthcare-associated infection rates. Between 2006 and 2008, HH observations increased from 244 to 498 average monthly observations.	New Hampshire	(p<0.01) during the initiative and improved further to 91% (p<0.01) the following year. Nurses achieved higher HH compliance (93%) than physicians (78%). There was a significant, sustained decline in the healthcare-associated infection rate, from 4.8 to 3.3 (p<0.01) per 1,000 patient-days. Refills for wall-mounted dispensers increased 37%. In the final year, overall HAIs declined; and the CDI rate stayed the same (0.9 to 0.6 per 1,000 patient-days, p=0.1). The rates of *S. aureus* infection (2.5 to 1.6 per 1,000 patient-days, p<0.001) and bloodstream infection (2.1 to 1.4 per 1,000 patient-days, p=0.004) fell significantly.		overall, and in physician HH specifically, occurred after a year of measurement and monthly feedback citing poor performance. Physicians reported that, for them, regularly seeing data linking HH performance to healthcare- associated infections was important. Intervention built on the work of Goldmann, which framed the need for both system and personal accountability for HH. Routine HH audits on all units, with monthly unit-specific data, were published on an intranet site available to all staff, as were strategies to optimize availability of hand sanitizer (Purell, 62% ethyl alcohol formulation).	precisely measure each intervention; single site, small; potential participant bias. Strength: covert observation; use of tracer condition—in comparison with OR (where intervention would not have made an impact), HAI rates decreased overall.	culture was one in which autonomy was valued and enthusiasm for quality improvement activities varied; such efforts typically attracted small groups of committed nurses. Infection rate reduction lags behind HH improvement.

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting:	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/Findings	Risk of Bias (High, Moderate, Low)	Comments
Knight et al., 2010[27]	Hospital-wide alcohol-based hand rub (AHBR) policy	A retrospective chart review analysis to compare incidence rates of CDAD before and after implementation of the ABHR policy. Population: inpatient status between January 1, 2001, and June 30, 2008. Full implementation of the ABHR policy was completed by May 1, 2003. A total of 766 patients with healthcare facility-onset, healthcare facility-associated CDAD were identified.	A 795-bed community teaching hospital	The incidence rate of CDAD was 3.98 per 10,000 patient- days after implementation of the ABHR policy, compared with 4.96 per 10,000 patient days before implementation (p=.0036). The crude mortality rate in patients diagnosed with CDAD was 10.7% after implementation, compared with 13.3% before implementation (p=.275). After implementation of the ABHR policy, compliance with hand hygiene, including both ABHR and soap and water, rose dramatically.	The rate of sepsis in patients diagnosed with CDAD was 19.6% after implemen-tation, compared with 5.2% before implement-tation (p<.0001).	Before implementation, only a 2% chlorhexidine-based soap product was available in the hospital. At the time of implementation, all existing antimicrobial products were removed and replaced with the alcohol-based hand foam. The only soap product available was a lotion soap with no antimicrobial activity. During a cluster, outbreak, or evidence of nosocomial transmission of *C. difficile*, the authors recommend switching to soap and water only for hand hygiene.	Low/ moderate; single site. Possible other IPC improve-ments during period. Strengths: relatively long study period; controlled for doses of antibiotics as a potential confounder.	None

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting:	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/Findings	Risk of Bias (High, Moderate, Low)	Comments
Oughton et al., 2009[2]	Hand washing with soap and water (vs. alcohol-based hand rubs)	Randomized crossover comparison among 10 volunteers with hands experimentally contaminated by nontoxigenic *C. difficile* (no hand washing training was conducted). A crossover format was used so that all volunteers would be exposed to all interventions once for each contamination protocol during the observation period of June–July 2007. Minimum of 24 hours between interventions; 318 observations; included use of control group.	Controlled experiment	Under the whole-hand protocol, the greatest adjusted mean reductions were achieved by warm water with plain soap (2.14 log10 CFU/mL [95% credible interval (CrI), 1.74 to 2.54 log10 CFU/mL]); cold water with plain soap (1.88 log10 CFU/mL [95% CrI, 1.48 to 2.28 log10 CFU/mL]); and warm water with antibacterial soap (1.51 log10 CFU/mL [95% CrI, 1.12 to 1.91 log10 CFU/mL]), followed by antiseptic hand wipes (0.57 log10 CFU/mL [95% CrI, 0.17 to 0.96 log10 CFU/mL]). Alcohol-based hand rub (0.06 log10 CFU/mL [95% CrI, 0.34 to 0.45 log10 CFU/mL]) was equivalent to no intervention. Hypothenar (odds ratio, 10.98 [95% CrI, 1.96 to 37.65]) and the fingertips (odds ratio, 6.99 [95% CrI, 1.25 to 23.41]) were less likely to remain heavily contaminated after hand washing.	Not provided	Alcohol-based hand rub produced a significant reduction in contamination, although of a lesser magnitude than was seen with the other hand hygiene interventions. The reason that antibacterial soap seems slightly inferior to plain soap according to the whole-hand protocol but not according to the palmar surface protocol is uncertain. It may be due to a higher concentration of organic matter present in the whole-hand protocol, which interferes with the activity of chlorhexidine.	Low/ moderate—in vitro study, no gloving, small sample, single site.	Study included surface (i.e., palms) and whole-hand contami-nation. With 10 paired assessments for each product, a power of more than 99% to detect a 1.0 log10 difference was calculated. All of the hand washing interventions studied were performed for less time than recommended by the manufacturers of the products.

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting:	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/Findings	Risk of Bias (High, Moderate, Low)	Comments
Pokrywka et al., 2017[35]	Patient hand hygiene (PHH)	A biphasic, quasi-experimental study was performed to increase PHH through education for staff and to provide education, assistance, and opportunities to the patient for hand cleaning. PHH practice was assessed by patient surveys and analyzed by Chi squared test. Phase 1: four medical-surgical nursing units: pre/post-intervention patient surveys; Phase 2: whole hospital pre/post-intervention patient surveys.	A 495-bed university-affiliated medical center in a large healthcare system	Patient-reported HH opportunities and frequency improved for patients in Phase 1 and 2, although the improvement was greater for Phase 1. CD SIRs for the study period showed a decrease in the number of observed hospital-onset (HO) LabID events in the first two quarters (Qs) after the implementation of PHH in March 2015, and a corresponding decrease in the HO SIRs from 0.834 to 0.572 and 0.497, respectively. SIR p-values for Q2 and Q3 (0.0157 and 0.0103, respectively) were significantly lower than expected ($p \leq 0.05$). The Q4 SIR, however, showed an increase to 0.3844 over the two preceding quarters.	The average frequency of PHH the patients reported did not change (average 2.4 before the initiative vs. 2.6 times after).	PHH may be a potentially underused preventive measure for CDI. Hospitalized patients are often not provided the opportunity to clean their hands. Limited patient mobility and acuity along with a lack of education present obstacles. Surveys of patients at the institution showed a need for increased PHH opportunities. Staff provided encouragement for PHH. Laminated signs were posted in each patient room with reminders for staff to assist patients in washing their hands throughout the day. This practice was augmented with screensavers and signage in staff areas. The increase in CDI in Q4 may show need for continued support and education.	Low/ moderate: surveys collected data from patients and were therefore susceptible to social desirability bias. CDI rates—small sample/ single site. Increased staff HH could have impact. Strength: no IPC changes were made during Phase 2.	None

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting:	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/Findings	Risk of Bias (High, Moderate, Low)	Comments
Schweon et al., 2013[31]	Multimodal hand hygiene program	Quasi-experimental pre/post. Data were collected for 22 months (May 2009 through February 2011). In March 2010, a comprehensive hand hygiene program was implemented, including increased product availability, education for healthcare personnel (HCP) and residents, and an observation tool to monitor compliance.	A 174-bed skilled nursing facility, in Stroudsburg, PA	CDI rate decrease 0.08 to 0.04, p=.36 (insignificant). Infection rates for LRTIs were reduced from 0.97 to 0.53 infections per 1,000 resident-days (p=.01) following the intervention, a statistically significant decline. Infection rates for SSTIs were reduced from 0.30 to 0.25 infections per 1,000 resident-days (p=.65). A 54% compliance rate was observed among HCP.	Not provided	Not provided	Low/ moderate—resident compliance not monitored; single site.	None

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting:	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/Findings	Risk of Bias (High, Moderate, Low)	Comments
Sickbert-Bennett et al., 2016[32]	Clean In, Clean Out, cleaning hands before/after working with patient, covert observation, audit and feedback	Quasi-experimental: compared hand hygiene compliance data from the last quarter of the covert observations by infection preventionists and designated nursing staff with compliance data from the first month of the new program. Study used a Chi squared to compare the average historical HAI rate from January 2013 until the implementation of the new program in October 2013 with the average HAI rate during the study period of October 2013 to February 2015, after implementation of the new program. More than 4,000 unique observers made more than 140,000 observations.	853-bed hospital, North Carolina	The researchers found that a 10% improvement in hand hygiene was associated with a 14% reduction in HA-CDI (p=0.070). They found a significant increase in the overall hand hygiene compliance rate (p<0.001) and a significantly decreased overall HAI rate (p=0.0066), supported by 197 fewer infections and an estimated 22 fewer deaths. These reductions resulted in an overall savings of approximately U.S. $5 million.	Not provided	Engaging all hospital staff in measuring hand hygiene compliance created a Hawthorne effect. A key feature of the intervention was that the focus for observation was simply on cleaning hands upon entering and leaving patient rooms.	Low—single site. Strength: no other formal IPC efforts were being implemented at the same time.	None

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting:	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/Findings	Risk of Bias (High, Moderate, Low)	Comments
Stone et al., 2012[26]	National "Cleanyour-hands" campaign in England and Wales, which included installation of bedside alcohol hand rub, materials promoting hand hygiene and institutional engagement, and regular hand hygiene audit.	Prospective, ecological, interrupted time series study of 187 trusts from July 1, 2004, to June 30, 2008 (4 years). Assessed associations between procurement and infection rates by a mixed effect Poisson regression model (accounting for bed occupancy, length of stay, hospital type, and timing of other national interventions targeting these infections).	Regional: 187 acute hospital trusts in England and Wales	Combined procurement of soap and alcohol hand rub tripled from 21.8 to 59.8 mL per patient bed-day; procurement rose in association with each phase of the campaign. Rates fell for MRSA bacteremia (1.88 to 0.91 cases per 10,000 bed-days) and CDI (16.75 to 9.49 cases). MSSA bacteremia rates did not fall. Increased procurement of soap was independently associated with reduced CDI throughout the study. The adjusted incidence rate ratio for 1mL increase per patient bed-day was 0.993 (95% CI 0.990 to 0.996; p<0.0001). Publication of the Health Act 2006 and visits by DPH improvement teams reduced CDI for at least two quarters after the visit.	Not provided	The campaign took place in the context of a high-profile political drive and other national interventions to reduce MRSA bacteremia and CDI. It received central sustained funding and coordination. The World Health Organization currently offers a very similar intervention as part of its Save Lives initiative. Although caution should be exercised when extrapolating from these results, the campaign could offer a model for other countries to adopt or adapt.	Low/ moderate—large scope, controlled for confounders (although these are not listed), except antibiotics—which potentially would be a big confounder.	None

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting:	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/Findings	Risk of Bias (High, Moderate, Low)	Comments
Tomas et al., 2016[15]	A sporicidal formulation of ethanol for glove decontami-nation (to use before glove removal) to prevent CDI	Experiment and quasi-experiment: (1) Blind comparison of intervention versus bleach, 70% ethanol, and no cleaning. Gloves were contaminated with spores and then cleaned (the three ways listed); then samples were taken. (2) Study was repeated on gloved hands of personnel after caring for CDI patients. Sample size not given for artificially contaminated gloves. For personnel caring for *C. difficile* patients: 159 patient care episodes (67 by nurses, 52 by physicians, and 40 by allied health providers) involving 24 CDI patients.	Experiment at the Cleveland Veterans Affairs Medical Center	The reduction achieved by the sporicidal ethanol solution was equivalent to the 1:100 dilution of bleach (1.87 vs 1.69 logs; p=.97). A further reduction occurred when the solution was applied as a wipe. No personnel noted that the sporicidal ethanol solution had an adverse odor or caused respiratory irritation or staining of clothing (compared with bleach, which caused discoloration).	Use of a specific formulation of ethanol only for glove disinfection after care of CDI patients may be impractical to implement and might add to the cost of care. Although the sporicidal ethanol solution was not associated with adverse effects, the formulation tested has an acidic pH.	In the study, bleach wipes were effective in reducing spore contamination on gloves, but discoloration of clothing due to inadvertent spills, and aversion to the odor of bleach, were common complaints by personnel. Findings suggest that the sporicidal ethanol solution could be useful for glove disinfection before removal when caring for CDI patients. Glove disinfection might be useful but it would not replace the need for hand washing after glove removal when caring for CDI patients.	High	Study measures **glove contami-nation**, not impact on CDI rates.

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting:	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/Findings	Risk of Bias (High, Moderate, Low)	Comments
Tomas et al., 2015[12]	Education on glove and PPE removal and use of bleach wipes for glove decontami-nation	Quasi-experimental study. Pre/post; 28 healthcare workers. Comparison of *C. difficile* hand contamination before and after education intervention and glove contamination intervention.	Cleveland VA Medical Center	After phase 1 (education and practice on PPE removal), acquisition of *C. difficile* on hands occurred in 2 of 27 (7%) episodes of care. After phase 2 (disinfection of gloves with bleach wipes), contamination was significantly reduced compared with the pre-intervention period (0% vs. 16%; p=.04).	Although there were no reported adverse effects attributed to the use of bleach wipes, several personnel complained about the strong odor of bleach. In addition, some participants expressed a concern that staining of clothing or respiratory irritation would be a problem if bleach wipes were used routinely.	In this study, researchers found that despite PPE use, healthcare personnel frequently acquired *C. difficile* spores on their hands while caring for patients with CDI. In a quasi-experimental intervention, improving PPE technique with education led to a nonsignificant reduction in contamination. Adding glove disinfection significantly reduced contamination, with no acquisition of spores detected during 30 episodes of patient care. The researchers postulate that the findings suggest that simple interventions may be effective in decreasing the risk for hand contamination while providing care to patients with CDI. Results are consistent with previous studies demonstrating that simulations using fluorescent lotions can be useful in improving infection control techniques, including PPE removal.	Low—small sample is reflected by p-values	None

Table B.4: *Clostridioides difficile*, Hand Hygiene–Single Systematic Reviews

Note: Full references are available in the Section 4.2 reference list.

Author, Year	Description of Patient Safety Practice	Setting/s, Population/s	Summary of Systematic Review Findings	Implementation Themes/Findings	Notes
Louh et al., 2017[25]	Hand hygiene	Acute care hospitals	Systematic search for controlled trials of interventions to reduce the rate of CDI in acute care hospitals. Search for articles published between January 1, 2009, and August 1, 2015. Review of four studies that evaluated the effect of hand hygiene campaigns. These used multifaceted campaigns that included access to alcohol-based hand rub, education, auditing, and feedback on hand hygiene compliance, in addition to advertising the use of hand hygiene. Mixed results. A nationwide hand hygiene campaign in hospitals in England and Wales showed significant reduction in CDI rates, but studies that investigated single-hospital campaigns showed no change in CDI acquisition. Hand hygiene was included in some but not all bundled interventions—bundled interventions all reduced CDI rates. Although older studies (before 2009) have shown a significant reduction in nosocomial infections from observing good hand hygiene, further benefit from promoting hand hygiene is unlikely, as the margin for improvement diminishes.	If an institution has adequate hand hygiene processes, incremental efforts to improve hand hygiene may not be as beneficial as other interventions. Institutions with few resources should strive to improve environmental practices, with implementation of bleach-based cleaning. Institutions with more resources should consider bundled interventions that incorporate environmental cleaning, restrictive ASPs, and checklists.	Review covers multiple PSPs. Environmental cleaning (daily/terminal with bleach) is found as most effective PSP of the five PSPs reviewed.

Table B.5: Clostridioides *difficile*, Environmental Cleaning–Single Studies

Note: Full references are available in the Section 4.3 reference list.

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting:	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/ Findings	Risk of Bias (High, Moderate, Low)	Comments
Alfa et al., 2008[42]	Accelerated hydrogen peroxide (AHP) cleaner (0.5% AHP) for cleaning toilets in non-outbreak situations	A prospective clinical comparison during non-outbreak conditions. A total of 243 patients and 714 samples were analyzed.	450-bed acute care facility	The efficacy of spore killing is formulation specific and cannot be generalized. The Oxivir$_{TB}$® AHP formulation resulted in statistically significantly (p=0.0023) lower levels of toxigenic *C. difficile* spores in toilets of patients with *C. difficile*-associated disease (CDAD) compared with the stabilized hydrogen peroxide cleaner formulation that was routinely being used (28% vs. 45% culture positive).	Not provided	The AHP formulation evaluated that has some sporicidal activity was significantly better than the currently used hydrogen peroxide cleaner formulation. It is a one-step process that significantly lowered the *C. difficile* spore level in toilets during non-outbreak conditions. The researchers report the formulation is less toxic than 5,000 ppm bleach. Interestingly, the background level of toxigenic *C. difficile* spores was 10% in toilets of patients with diarrhea not due to CDAD.	Low to moderate	Funds for this study were provided by Manitoba Medical Services Foundation as well as an unrestricted research grant from Virox Technologies Inc. and JohnsonDiversey Inc. All AHP used for this study was provided by Virox Inc.

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting:	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/ Findings	Risk of Bias (High, Moderate, Low)	Comments
Anderson et al., 2017[32]	Enhanced terminal room disinfection: rooms from which a patient with infection or colonization with *C. difficile* was discharged were terminally disinfected with one of two strategies, bleach or ultraviolet (UV) light and bleach	Cluster-randomized, crossover trial. Every strategy was used at each hospital in four consecutive 7-month periods. 31,226 patients were exposed. Convenience sample of multiple types of hospitals.	Nine hospitals in southeastern United States	The incidence of CDI among exposed patients was not changed after adding UV to cleaning with bleach (n=38 vs. 36; 30.4 cases vs. 31.6 cases per 10,000 exposure days; rate ratio 1.0, 95% CI 0.57 to 1.75; p=0.997).	4 minutes longer cleaning time, 10–20 minutes longer admit times	Adding UV to bleach cleaning had no impact on CDI rates although the researchers thought that in actuality, based on prior research, UV disinfection helped prevent CDI. This study was the most robust of the studies reviewed for this section. reviewed.	Low to moderate	Study covered interventions and harms in addition to *C. difficile*: MRSA (methicillin-resistant *Staphylococcus aureus*), VRE (Vancomycin-resistant enterococci), and multidrug-resistant *Acinetobacter*. Adding UV light to standard cleaning reduced incidence of these organisms (but not for *C. difficile*).

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting:	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/ Findings	Risk of Bias (High, Moderate, Low)	Comments
Aronhalt et al., 2013[41]	The intervention used bleach wipes for daily and terminal patient room cleaning; a 1:10 (~6,000 ppm) dilution of hypochlorite solution	Post-intervention survey. 94 patients and 6 staff.	Patient care units at a single hospital with a relatively high incidence of CDI	Patients (n=94) (91%) continued to be very satisfied with how well their rooms were cleaned everyday. Bleach wipes were well tolerated by patients (n=44) (100%) surveyed on the medical units and less tolerated by patients (n=50) (22%) on the hematology-oncology units.	Environmental services housekeeping staff reported less satisfaction and more respiratory irritation during the initial month of the project.	Potential concerns for patients and employees include the appearance of residue left on surfaces, odors, and respiratory tract irritation. Patient and employee satisfaction with these processes is critical for sustainability of process improvement initiatives because the change process influences both populations.	Low	Qualitative study, measured patient/staff satisfaction with cleaning with bleach. However, does get into implementation challenges.

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting:	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/ Findings	Risk of Bias (High, Moderate, Low)	Comments
Barbut et al., 2009[40]	Hydrogen peroxide dry-mist system versus 0.5% hypochlorite solution for disinfecting surfaces contaminated with *C. difficile*	Prospective, randomized, before-and-after trial. 748 surface samples were collected (360 from rooms treated with hydrogen peroxide and 388 from rooms treated with hypochlorite).	Two hospitals, France	After disinfection, 23 (12%) of 194 samples from hypochlorite-treated rooms and 4 (2%) of 180 samples from hydrogen peroxide-treated rooms showed environmental contamination, a decrease in contamination of 50% after hypochlorite decontamination and 91% after hydrogen peroxide decontamination (HPD) ($p<0.005$).	Not provided	In this experiment, the hydrogen peroxide dry-mist disinfection system was significantly more effective than 0.5% sodium hypochlorite solution at eradicating *C. difficile* spores. Researchers note a need to find less corrosive and user-dependent alternatives to hypochlorite-based products. Hydrogen peroxide dry-mist disinfection process rooms do not have to be sealed.	Low to moderate	During the in vitro experiments, time-dependent sporicidal activity was observed for hypochlorite.

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting:	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/ Findings	Risk of Bias (High, Moderate, Low)	Comments
Best et al., 2014[33]	Deep cleaning and HPD, following a high incidence of CDI	Pre/post. Extensive environmental sampling (342 sites on each occasion) for *C. difficile* using sponge wipes was performed before and after deep cleaning with detergent/ chlorine agent immediately following HPD, and at two later occasions, 19 days and 20 weeks following HPD. *C. difficile* isolates underwent polymerase chain reaction ribotyping and multi-locus variable repeat analysis.	A single stroke rehabilitation unit (SRU)	*C. difficile* was recovered from 10.8%, 6.1%, 0.9%, 0%, and 3.5% of sites at baseline, following deep cleaning, immediately after HPD, and 19 days and 20 weeks after HPD, respectively. CDI incidence (number of cases on SRU per 10 months [January to October 2011]) declined from 20 before to 7 after the intervention.	Closed ward for 10 days. The whole ward had to be moved to alternative accommodation, which is a major undertaking and depends on the availability of decant space, an increasingly rare resource in some hospitals.	Emerging evidence shows that a minority of CDI cases is linked to other cases when endemic as opposed to epidemic infection rates prevail. There may therefore be an optimum level of CDI at which HPD is most likely to be cost effective. Results may demonstrate that HPD may be a useful method for decontaminating a hospital ward with a high CDI incidence.	Low to moderate	Determining a role for HPD should include long-term cost-effectiveness evaluations.

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting:	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/ Findings	Risk of Bias (High, Moderate, Low)	Comments
Boyce et al., 2008[31]	One-time decontamination followed by terminal disinfection using hydrogen peroxide vapor (HPV) decontamination of rooms occupied by patients with *C. difficile*-associated disease (CDAD)	A prospective before-and-after intervention study. Intensive HPV decontamination of five high-incidence wards followed by hospitalwide decontamination of rooms vacated by patients with CDAD. The pre-intervention period was June 2004 through March 2005, and the intervention period was June 2005 through March 2006 (8 months).	Five high-incidence wards at a 500-bed university hospital	On five high-incidence wards, the incidence of nosocomial CDAD was significantly lower during the intervention period than during the pre-intervention period (1.28 vs 2.28 cases per 1,000 p=0.047). Eleven (25.6%) of 43 cultures of samples collected by sponge from surfaces before HPV decontamination yielded *C. difficile*, compared with 0 of 37 cultures of samples obtained after HPV decontamination (p<0.001).	Not provided	The time required for the entire process was 3 to 4 hours for a patient room and approximately 12 hours for an entire ward. The HPV decontamination process used in this study was reported to be safe for use in healthcare facilities, as long as the area to be decontaminated is appropriately sealed and hydrogen peroxide levels outside the area being decontaminated are closely monitored. During the intervention period, hospital staff did not report any adverse effects attributable to the HPV decontamination process, among patients or personnel.	Low to moderate	None

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting:	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/ Findings	Risk of Bias (High, Moderate, Low)	Comments
Ghantoji et al., 2015[38]	Pulsed xenon UV (PX-UV) light versus bleach (after standard cleaning)	Before-and-after quasi-experimental. High-touch surfaces in rooms previously occupied by *C. difficile*-infected patients were sampled after discharge but before and after cleaning using either bleach or nonbleach cleaning followed by 15 minutes of PX-UV treatment. A total of 298 samples were collected using a moistened wipe specifically designed for the removal of spores.	A single major comprehensive cancer center in the United States. The environmental surfaces in 30 *C. difficile* infection isolation rooms were sampled immediately after patients with a CDI were discharged.	Prior to disinfection, the mean contamination level was 2.39 colony-forming units (cfu) for bleach rooms and 22.97 for UV rooms. After disinfection, the mean level of contamination for bleach was 0.71 cfu (p=0.1380), and 1.19 cfu (p=0.0017) for PX-UV disinfected rooms. The difference in final contamination levels between the two cleaning protocols was not significantly different.	Not provided	The current study shows that PX-UV disinfection was equivalent to bleach in decreasing environmental contamination with *C. difficile* spores. PX-UV technology can be easily incorporated into routine environmental decontamination and has a potentially faster turnaround time than either HPV or bleach. Approximately 45 minutes to clean a room with bleach and 15 minutes with PX-UV, resulting in staff savings.	Low to moderate	None

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting:	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/ Findings	Risk of Bias (High, Moderate, Low)	Comments
Haas et al., 2014[25]	Ultraviolet environmental disinfection (UVD) following discharge cleaning of contact precautions rooms and other high-risk areas	A retrospective study of the implementation of UVD following discharge cleaning of contact precautions rooms and other high-risk areas. Incidence rates of hospital-acquired multidrug-resistant organisms (MDROs) plus CDI before and during the UVD use were evaluated using rate ratios and piecewise regression. The period before UVD was 30 months (January 2009 to June 2011), and the UVD period was 22 months (July 2011 to April 2013).	A single 643-bed tertiary care academic medical center	The average time per UVD was 51 minutes, and machines were in use 30% of available time. UVD was used 11,389 times; 3,833 (34%) of uses were for contact precautions discharges. UVD was completed for 76% of contact precautions discharges. There was a significant 20% decrease in hospital-acquired MDRO plus CD rates during the 22-month UVD period compared with the 30-month pre-UVD period (2.14 cases/1,000 patient-days vs. 2.67 cases per 1,000 patient days; rate ratio, 0.80; 95% CI, 0.73 to 0.88, p<0.001). CDI before UVD: number, 390, rate, 0.79; CDI after UVD: number, 228, rate, 0.65; rate ratio, 0.83 (0.70 to 0.97) p=0.02.	UVD added an average of 51 minutes per discharge. This time included approximately 31 minutes for arrival, including setup of machine and blackout curtains in areas that had open bays or glass windows and walls. UVD machines were in use for approximately 30% of the total time available.	Facility used bleach-based (sodium hypochlorite 0.55%) disinfectants daily and at discharge for all rooms occupied by adults. In preparation for UVD use. An assessment of the number and timing of contact precautions discharges found the mean rate of contact precautions discharges was 0.87 per hour during peak discharge times of 2 p.m. to 6 p.m. Labor cost and availability should be considered in the budget and implementation plan for UVD. The machines were in use only 30% of the total available time in large part because of labor constraints.	Moderate	None

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting:	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/ Findings	Risk of Bias (High, Moderate, Low)	Comments
Hacek et al., 2010[26]	Replacing quaternary ammonium compound as a room cleaning agent with diluted bleach (approximate concentration of 5,000 ppm sodium hypochlorite) to disinfect rooms of patients with CDI upon discharge	To determine the effectiveness of this program, rates of nosocomial CDI for all three hospitals were determined using the MedMined Virtual Surveillance Interface for 10 months prior to and 2 years after the cleaning intervention. Statistical significance was determined using Poisson regression analysis.	Three hospitals in a San Diego health system with approximately 850 beds and 40,000 annual admissions	There was a 48% reduction in the prevalence density of *C. difficile* after the bleaching intervention (95% CI, 36% to 58%, p<0.0001).	Not provided	Daily room cleaning routine remained unchanged during the study. The surfaces cleaned in each room remained the same; however, washing the walls was added to the list. Periodic, unannounced cleaning observations also were carried out by the infection control preventionists to assess compliance.	Low	Initiative was response to increase in CDI at three facilities.

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting:	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/ Findings	Risk of Bias (High, Moderate, Low)	Comments
Hooker et al., 2015[37]	A washable cover for the mattress and bed deck. The cover is removed and laundered with hot water, chlorine, and detergent. The covers are manufactured using material similar to that found in high-end bed mattresses. They are constructed to allow vapor-moisture transmission.	Two long-term acute-care hospitals (LTACHs) began using a launderable mattress and bed deck cover on beds starting in May 2013. One facility had 74 beds and the other had 30 beds. Covers were changed after every patient. The covers were laundered using hot water, detergent, and chlorine. Rates for CDIs were compared using Poisson regression between the 16 months before use of the washable cover and the 14 months after the cover started being used.	Two LTACHs in Indiana with single-patient rooms	At Hospital A, the use of bedcovers reduced the rate of CDIs by 47.8% (95% CI, 47.1 to 48.6), controlling for the rate of hand washing compliance and length of stay in days. At Hospital B, the use of bedcovers reduced the rate of CDIs by 50% (95% CI, 47.5 to 52.7), controlling for the rate of hand washing compliance and length of stay in days.	Not provided	Article states that after training, all environmental services employees could install the covers in approximately 2 minutes. A new cover was placed after terminal cleaning and patient admission. Although no formal time and motion studies were done, the researchers state that use of the washable covers should improve room turnover times because bed surface is no longer grossly contaminated and time is not needed to remove blood and organic material from the mattress. Could help reduce other healthcare-acquired infections as well.	Low to Moderate Study did not control for anti-microbial use. Strength: Controlled for hand washing.	National Institutes of Health funded

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting:	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/ Findings	Risk of Bias (High, Moderate, Low)	Comments
Kundrapu et al., 2012[44]	Daily disinfection of high-touch surfaces in CDI and MRSA isolation rooms. A peracetic acid-based disinfectant (surface sporicide and disinfectant, branded by STERIS) versus terminal cleaning with bleach.	Quasi-experimental, randomized nonblinded trial. Compared percentage of positive cultures on gloved hands that touched the high-touch surfaces between the standard and enhanced cleaning rooms.	A single site: Cleveland Veterans Affairs Medical Center, a 215-bed hospital with an affiliated long-term care facility	Intervention was associated with a significant reduction in the frequency of acquisition of both pathogens on investigators' hands after contact with the surfaces and in the mean number of colony-forming units acquired. Daily disinfection samples: 0/20 (0%) positive; standard cleaning: 3/28 (11%) samples positive.	Disinfection of high-touch surfaces required about 20 minutes per room.	A peracetic acid-based disinfectant was chosen because preliminary studies indicated that it was as effective as sodium hypochlorite solution but less corrosive and irritating. High-touch surfaces included bed rails, bedside table, call button, telephone, chair, and wall-mounted items.	Low to moderate. Study nonblinded —could impact results. Small sample size. Strength: Similar comparison groups.	Prior to interventions, less than 10% of high-touch surfaces in CDI or MRSA rooms were cleaned daily by housekeepers during the study period. STERIS provided some financial support to the study (in addition to Department of Veterans affairs and AHRQ)

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting:	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/ Findings	Risk of Bias (High, Moderate, Low)	Comments
Levin et al., 2013[28]	Portable pulsed xenon ultraviolet (PPX-UV) light after terminal cleaning (with chlorine-based agents)	During January 2011, the use of two PPX-UV devices to disinfect patient rooms was added to routine hospital discharge cleaning in a community hospital.	Single site: a 140-bed acute care community hospital	In 2010, the hospital-associated (HA) CDI rate was 9.46 per 10,000 patient days; in 2011, the HA CDI rate was 4.45 per 10,000 patient days (53% reduction, p<0.01). Previously rates were stable at an average of 9.22 for the years 2008 to 2010 (compared with 2011, 52% reduction; p=0.002). The number of deaths and colectomies attributable to HA CDI also declined dramatically.	It should be noted that, of the 15 patients who were diagnosed with HA CDI in 2011, 11 (73%) were placed in rooms that had not been treated with the PPX-UV device prior to occupation. Overall, 56% of discharged rooms received the UV light treatment.	Study used a chlorine-based product (Clorox Clean-up and Clorox Germ Wipes (The Clorox Company, Oakland, CA) in *C. difficile* rooms. This process was followed by the use of PPX-UV, for three 7-minute exposures (once in the bathroom and then in two locations in the main patient room). The overall room turnover time was extended by approximately 15 minutes over a standard terminal cleaning because cleaning could continue in the main room during PPX-UV treatment of the bathroom.	Low	Prior to implementation of PPX-UV, environmental services workers were trained in the use of the device as well as the important role the workers play in preventing illness and death. Although adding PPX-UV to their routine did increase their workload, as a group they felt great pride in being a part of the infection prevention team.

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting:	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/ Findings	Risk of Bias (High, Moderate, Low)	Comments
Manian et al., 2013[29]	"Enhanced cleaning" of patient room consisting of use of bleach followed by HPV decontamination. Since not all room could be targeted the intervention included use of a priority scale based on the pathogen and room location. Rooms vacated by patients with CDAD but for which HPV decontamination was not possible the same day underwent four rounds of cleaning with bleach instead.	A retrospective quasi-experimental before-and-after study. The intervention period was January 2009–December 2009, 196,313 patient days. During the pre-intervention period (January 2007 to November 2008), rooms vacated by patients with CDAD or on contact precautions for other targeted pathogens underwent one or more rounds of cleaning with bleach. During the intervention period (January–December 2009), targeted newly evacuated rooms underwent "enhanced cleaning" consisting of use of bleach followed by HPV decontamination using a priority scale based on the pathogen and room location.	A 900-bed community hospital	Of 334 rooms vacated by patients with CDAD (May–December 2009), 180 (54%) underwent HPV decontamination. The nosocomial CDAD rate dropped significantly from 0.88 cases/1,000 patient-days to 0.55 cases/1,000 patient-days (rate ratio, 0.63; 95% CI, 0.50 to 0.79, p<0.0001), a 37% reduction in the CDAD rate following institution of the described intervention.	Not provided	Use of HPV decontamination was found to be safe with no instances of any leakage of HPV outside of sealed patient rooms. The priority scale was developed primarily to help expedite assignment of rooms to HPV.	Low to moderate	Study design did not allow for assessment of the relative contribution of HPV versus four rounds of cleaning.

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting:	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/ Findings	Risk of Bias (High, Moderate, Low)	Comments
Miller et al., 2015[35]	PX-UV disinfection system for patient rooms and common areas	Quasi experimental, before and after; two intervention periods. Period one: reinforcement of infection prevention control procedures; Period two: use of UVD.	A single LTACF (bed count not provided)	In period two, CDI rates decreased from period one from 19.3 per 1,000 patient-days to 8.3 per 1,000 patient-days, a 56.9% reduction, p=0.02. Based on these outcomes, it is predicted that the facility was able to prevent 29 HA CDIs and generate over 210 additional patient bed days within the 15-month intervention. Each case results in $13,500 in hospital care costs; therefore, the intervention could have potentially resulted in net savings of approximately $300,000.	Not provided	Prior to UVD, a multidisciplinary *C. difficile* prevention team was formed and there was re-education around hand hygiene for CDI, disposable equipment implemented as well as additional sinks and reminders about equipment decontamination, reinforcement of contact isolation, and a checklist for terminal cleaning. The usage goal across the LTACF included all patient rooms after discharge and communal living areas on a weekly basis, such as dining rooms, rehabilitation areas, and lounges.	Moderate: Unclear if reductions in period two were, at least in part, the carryover result of the practices implement-ed in period one.	After discharge, rooms and bathrooms were terminally cleaned with a sodium hypochlorite solution.

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting:	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/ Findings	Risk of Bias (High, Moderate, Low)	Comments
Mosci et al., 2017[39]	Automated disinfection system with hydrogen peroxide <0.8 solution and silver ions versus bleach	A randomized multicenter trial. When patients with *C. difficile* were discharged, their rooms were randomized to one of two decontamination arms. The surfaces were sampled using swabs, before and after disinfection. Swab samples were cultured for quantitative detection of microbial mesophilic contamination and qualitative detection of *C. difficile*. 448 samples taken.	Hospital wards that had been occupied previously by patients with CDI; 28 hospital rooms across several hospitals	Hydrogen peroxide versus bleach. The difference in the overall reduction of contaminated rooms due to hydrogen peroxide and silver ions and sodium hypochlorite was not statistically significant (p=0.497), but a significant reduction after disinfection was noted in both groups. However, the disinfection with hydrogen peroxide and silver ions is preferable due to less dependence on operators.	Not provided	The complexity of environmental surfaces in healthcare facilities has increased and cleaning is highly operator dependent. A new technology is the use of hydrogen peroxide atomized by specific equipment, with associated silver compounds; however, this can only be used in vacated rooms, and total time for disinfection is roughly the same. Hydrogen peroxide and silver ion disinfection greatly reduces the environmental impact.	Low to moderate	No clinical outcomes—swabs taken from the environment. The most contaminated sites were the light and nursing call devices and the horizontal surface of the bedside table.

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting:	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/ Findings	Risk of Bias (High, Moderate, Low)	Comments
Nagaraja et al., 2015[36]	Terminal cleaning with PX-UVD in addition to standard cleaning	Pre/post intervention. This study compares a pre-UVD period (May 1, 2010, to April 30, 2011) with the UVD period (July 1, 2011, to June 30, 2012) for total CDI rates, hospital-acquired CDI rates, length of stay, and room occupancy. Pre-UVD was 139,677 patient-days and intervention was 132,574 patient-days.	ICU with 180 beds (The intensive care unit is a referral center for highly immune-compromised patients).	Compared with pre-UVD, during UVD, hospital-acquired CDI was 22% less (p=0.06). There was a 70% decrease for the adult ICUs (p<0.001), where the percentage of room discharges with UVD was greater (p<0.001). No significant difference was found in days to hospital-acquired CDI in rooms with a prior CDI occupant.	Oncology and pediatric rooms CDI rates increased.	Due to environmental contamination with *C. difficile* and cleaning performance variability, disinfection procedures that do not depend solely on individual practice are being used. Logistical barrier: the UV light is not effective at killing bacteria at greater distances (over 1.22 m).	Moderate. In some cases, during the intervention period, UVD was not applied due to logistical and other issues. Single site. Confounder: change to new environ-mental services company.	UVD machines cannot be used in occupied rooms. Evaluation of UVD should include data for hospitalized community-acquired CDI cases because these cases may impact the HA-CDI rate.

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting:	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/ Findings	Risk of Bias (High, Moderate, Low)	Comments
Orenstein et al., 2011[27]	Daily and terminal cleaning with germicidal bleach wipes (0.55% bleach) on wards with a high incidence of HA CDI	Quasi-experimental, pre/post-intervention measures. From August 1, 2008, through August 1, 2009, all rooms were cleaned daily and at hospital discharge with a quaternary ammonium compound. Intervention: From August 2, 2009, through July 31, 2010, housekeepers replaced this product with Clorox brand germicidal bleach wipes with 0.55% active chlorine.	Two medical units at a 1,249-bed hospital in Rochester, Minnesota. These units were selected because they were contiguous and had high endemic CDI incidence.	The intervention reduced HA-CDI incidence by 85%, from 24.2 to 3.6 cases per 10,000 patient-days ($p<0.001$) and increased the median time between HA-CDI cases from 8 to 80 days. Twenty-seven cases of HA CDI were prevented in this study. The incremental cost of an HA CDI is estimated to be between $5,000 and $8,000. Thus, between $135,000 and $216,000 of excess costs may have been averted by these simple measures.	All rooms were cleaned daily with bleach, regardless of whether the occupant had CDI. The process added little extra time to the housekeepers' daily routine.	Even though terminal cleaning with bleach has shown to be effective, because a substantial reservoir of colonized patients or asymptomatic carriers may not be in isolation, the researchers believe that *daily* cleaning may be more effective than discharge-only cleaning.	Low to moderate. Weak-nesses: Single site, unblinded Strength: Control for confounders	During the study, 444 buckets of bleach wipes were used at an annualized cost of $12,684. The bleach was allowed to dry to achieve the recommended 10-minute contact time to inactivate *C. difficile* spores.

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting:	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/ Findings	Risk of Bias (High, Moderate, Low)	Comments
Vianna et al., 2016[34]	PX-UV system for disinfecting all discharges and transfers after standard cleaning and prior to occupation of the room by the next patient. For all non-ICU discharges and transfers, the PX-UV system was only used for *Clostridium difficile* rooms	The intervention period was compared with baseline using a two-sample Wilcoxon rank-sum test. Beginning in November 2012, a PX-UV disinfection system was implemented as an adjunct to traditional cleaning methods on discharge of select rooms. PX-UV disinfection was implemented in >200 patient rooms per month from November 2012 to August 2014 (>4,400 rooms total) and compared with January 2011 to October 2012.	A single community hospital with 126 medical-surgical beds. The facility also houses an 80-bed psychiatric care unit.	A significant 29% facilitywide decrease in all three MDROs (*C. difficile*, MRSA, and VRE) was determined (p=0.01), statistically driven by a 41% decrease in *C. difficile* infection (p=0.01). In the ICU alone, all three infection types similarly experienced significant reductions (p=0.01) together. However, changes in VRE incidence was only statistically significant alone (p=0.01). Nonetheless, *C. difficile*, MRSA, and VRE rates decreased by 45%, 56%, and 87%, respectively. On all other non-ICU floors combined, only a 40% change in *C. difficile* infections alone was significant (p=0.04).	Not provided	According to the study, the difference in infection rates for the ICU compared with the non-ICU areas demonstrated the increased risk of infection in the ICU and the leverage that ICU-based interventions can have on facilitywide rates. Recommended PX-UV in an area of higher acuity and patient flow. A novel aspect of this study is that it examines two different deployment strategies for UVD: using UVD for every terminal discharge on a unit and for *C. difficile* isolation rooms only.	Low to moderate. Single site. An anti-microbial stewardship program was initiated in January 2012 (11 months before the ultraviolet device was introduced); and other confounders could have also influenced results.	None

Table B.6: Clostridioides *difficile*, Environmental Cleaning–Systematic Reviews

Note: Full references are available in the Section 4.3 reference list.

Author, Year	Description of Patient Safety Practice	Setting/s, Population/s	Summary of SR Findings	Implementation Themes/Findings	Notes
Khanefer et al., 2015[30]	Environmental cleaning/ disinfection	Hospitals	Studies published between 1982 and December 2013 were reviewed. Nine studies on environmental cleaning/disinfection; most were part of bundles. The frequency of room disinfection varied depending on the study, being performed daily or on discharge. A significant decrease in CDI rate was observed after replacement of quaternary ammonium compound with bleach in highly endemic wards. The effect was more significant when bleach was used daily (85% vs. 47%). Compliance with recommended procedures should be monitored routinely. Checklists to instruct housekeepers on the cleaning sequence should be promoted. Moreover, education, implementation of standardized processes, and direct interaction with or immediate feedback to domestic staff are all interventions that have been reported to improve the efficiency of disinfection of contaminated surfaces. No-touch methods have good outcomes but high cost and turnaround times.	Disinfection with 1:10 hypochlorite solution is practical and inexpensive. It is challenging to develop a sporicidal and practical disinfectant for a wide variety of surfaces that is sufficiently nontoxic for routine application. A comparison of clinical and cost-effectiveness of eight *C. difficile* environmental disinfection methods has shown that the cheaper tradition of disinfection with a chlorine-releasing agent is as effective as modern techniques.	None

Author, Year	Description of Patient Safety Practice	Setting/s, Population/s	Summary of SR Findings	Implementation Themes/Findings	Notes
Louh et al., 2017[24]	Environmental cleaning. Recommend: Daily to twice daily cleaning of high-touch surfaces and terminal cleaning of patient rooms using chlorine-based products	Acute care hospitals	Systematic search for controlled trials of interventions to reduce the rate of CDI in acute care hospitals. Searched for articles published between January 1, 2009, and August 1, 2015. The five studies on environmental disinfection used a variety of interventions: daily bleach disinfection with auditing, terminal room disinfection with hydrogen peroxide vapor, terminal room UV treatment, and complete surface terminal bleach disinfection. Daily and terminal disinfection of the patient room with bleach-containing products in conjunction with auditing led to significant reduction in CDI. Terminal cleaning with UV light in addition to bleach cleaning had uncertain efficacy. Study quality weak. In the review of the recent CDI prevention studies performed in acute care hospitals, bleach-based environmental disinfection and bundled interventions appeared to have the most effect in preventing CDI. Bundled interventions with environmental efforts appeared to be more effective than those without them.	Institutions with few resources should strive to improve environmental practices, with implementation of bleach-based cleaning. Institutions with more resources should consider bundled interventions that incorporate environmental cleaning, restrictive ASPs, and checklists.	Review covers multiple PSPs. Environmental cleaning findings are summarized in this table. Environmental cleaning (daily/terminal with bleach) is found as most effective PSP of the five PSPs reviewed.
McLeod-Glover and Sadowski, 2010[17]	Cleaning products for *C. difficile*	Hospitals and inpatient rehabilitation care	Review of articles pertinent to the efficacy of cleaning products against *C. difficile* or studies with outcomes related to rates of CDAD. Evidence was level II. Evidence to support decision making about the use of environmental cleaners is weak. Search yielded nine studies and one research letter describing research into the efficacy of cleaning products against *C. difficile* spores. Chlorine-releasing agents are more effective than detergents for killing spores produced by *C. difficile*. No level I evidence is available to determine if the use of chlorine-releasing agents has an effect on rates of CDAD. Of interest is the effect of subinhibitory levels of cleaning agents on the sporulation capacity of *C. difficile*. One study showed that exposure to low levels of cleaning agents resulted in higher sporulation capacity compared with no exposure to cleaning agents, suggesting that sporulation capacity might increase in response to environmental stresses such as cleaning.	Hydrogen peroxide and peracetic acid had mixed results. Detergent alone or 70% isopropyl alcohol showed no benefit. Although chlorine-releasing agents are more effective for killing spores than detergents are in the laboratory setting, efficacy related to reducing levels of spores in the environment or rates of CDAD in the hospital has not been consistently shown.	None

Table B.7: Clostridioides *difficile,* Surveillance–Single Studies

Note: Full references are available in the Section 4.4 reference list.

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/Findings	Risk of Bias (High, Moderate, Low)	Comments
Albert et al., 2018[32]	Reporting cases of healthcare facility-onset CDI (HO CDI) using the National Healthcare Safety Network (NHSN) CDI laboratory-identified (LabID) event definition.	Assessment of accuracy of facility reporting of HO CDI to NHSN. Retrospective chart review was performed on 212 NHSN LabID HO-CDI cases. The electronic medical record for each case was reviewed for various clinical events that contributed to *C. difficile* testing. The presence of fever, abdominal pain, and diarrhea was recorded from each case along with the timing and duration of symptoms.	A large urban medical center	Not provided	Study found only 62% of reported HO-CDI cases met clinical surveillance criteria. Of the reported HO-CDI cases, review of charts found that 13.6% were CA-CDI, 2.8% were recurrent, 1.9% were asymptomatic colonization, 18.4% were symptomatic colonization, 38.7% were possible HO CDI, and 24.5% were probable HO CDI. Within 24 hours of testing, 34.1% had received a stool softener and/or laxative.	Laxative use and failure to identify community-onset infection may contribute to misclassification of HO CDI. Many reported HO-CDI cases involved patients with underlying medical conditions that may mimic symptoms of CDI, highlighting challenges in distinguishing colonization from active disease. Of the reported HO-CDI cases, 103 had documentation of inflammatory bowel disease, chemotherapy, tube feedings, or gastrointestinal bleeding.	Moderate—small sample; chart review is imperfect.	Study about errors in classification/ reporting of CDI to NHSN. An intervention was not tested.

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/Findings	Risk of Bias (High, Moderate, Low)	Comments
Benoit et al., 2011[29]	Electronic laboratory and admission-discharge-transfer data from BioSense, a national automated surveillance system. A total of 4,585 patients from 34 hospitals in 12 States had *C. difficile*–positive assay results.	Retrospective, multi-center cohort study; validation of surveillance system by comparison with other widely accepted surveillance results.	Thirty-four hospitals sending inpatient emergency department and/or outpatient data to BioSense.	Electronic laboratory data sent to the BioSense surveillance system were successfully used to produce disease rates of CDI comparable to those of other studies, which shows the feasibility of using electronic laboratory data to track a disease of public health importance. More than half (53.0%) of the cases were CO CDI, and 30.8% of these occurred in patients who were recently hospitalized. The overall rate of HO CDI was 7.8 cases per 10,000 patient-days, with a range among facilities of 1.52 to 7.8 cases per 10,000 patient-days.	Not provided	Laboratory codes and text-parsing methods were used to extract *C. difficile*–positive toxin assay results from laboratory data sent to BioSense from January 1, 2007, through June 30, 2008; these were merged with administrative records to determine whether cases were community-associated or healthcare onset. Although hospitals incur initial costs in capturing electronic data, the data are useful for tracking many diseases other than CDI. Few hospitals had LOINC- or SNOMED-coded laboratory test and result data, which emphasizes the need for widespread adoption of standard vocabularies to facilitate public health use of electronic data.	Low. Did not include CO CDI, because data were limited to certain health systems. Variability across hospitals in CDI onset type. The electronic data that were analyzed were not validated by comparison with hospital records.	BioSense is a national automated surveillance system operated by the Centers for Disease Control and Prevention (CDC) that receives, analyzes, and visualizes electronic health data for public health use.

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/Findings	Risk of Bias (High, Moderate, Low)	Comments
Dubberke et al., 2012[28]	Automated surveillance algorithm using electronically available data based on recommended surveillance definitions (Surveillance Definitions from CDC 2007)	Validation of an automated CDI surveillance algorithm, comparing the algorithm with chart review. A second chart review was performed for discordant results and determined to be the gold standard (the correct categorization). The study population included all adult patients ≥ 18 years of age admitted to four U.S. hospitals from July 1, 2005 to June 30, 2006. 1,767 patients with stool positive for *C. difficile* toxins were identified.	Four CDC Prevention Epicenter hospitals	A total of 1,767 patients had a positive *C. difficile* toxin test. Of these, 440 were CDI cases that the automated and chart review surveillance classified differently. The discordant cases were re-reviewed. The overall sensitivities, specificities, and kappa values of the algorithm by CDI onset compared with the gold standard: hospital onset: 92%, 99%, and 0.90; community onset, study facility–associated: 91%, 98%, and 0.84; community onset, other healthcare facility–associated: 57%, 99%, and 0.65; community onset, community associated: 96%, 94%, and 0.69; indeterminate cases: 80%, 98%, and 0.76; and recurrent cases: 94%, 99%, and 0.94.	The algorithm did not have good agreement with chart review for hospital-onset CDI for hospital B. Community-onset and other healthcare facility–associated CDI showed a wide range of sensitivities (16% to 96%) and kappa values (0.25 to 0.93). Similar trends were seen for community-onset, community-associated, and indeterminate CDI.	Previous research indicates electronic surveillance is more accurate and reliable than manual surveillance. Automated surveillance also requires less time, as it eliminates the need to do chart review, potentially allowing infection preventionists to devote more time to infection prevention efforts. Each hospital had to individualize the algorithm to their facility. Electronic surveillance requires access to an electronic health record (EHR) system.	Low to moderate. Each hospital had different data available. For example, Hospitals A, B, and C did not have discrete data on where a patient was admitted from (e.g., admitted from home, long-term care facility), whereas hospital D did.	Study found that electronic surveillance performed better than chart review in identifying the types of onset of CDI.

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/Findings	Risk of Bias (High, Moderate, Low)	Comments
Dubberke, 2010[35]	ICD-9 code-based hospital-onset *Clostridium difficile* infection surveillance	Validation of ICD-9 codes for CDI surveillance (by comparison with toxic assay results). HO-CDI cases were identified at five U.S. hospitals between July 2000 and June 2006 using two surveillance definitions: positive toxin assay results (gold standard) and secondary ICD-9 diagnosis codes for CDI. Chi-square tests were used to compare incidence rates, linear regression models were used to analyze trends, and the test of equality was used to compare slopes. A total of 930,692 hospital discharges during the 6-year study period.	Five U.S. academic medical centers—MO, MA, OH, UT, IL. All study hospitals participated in the CDC Epicenter Program.	Of 8,670 hospital-onset CDI cases, 38% were identified by both toxin assay and ICD-9 code, 16% by toxin assay alone, and 45% by ICD-9 code alone. Nearly half (47%) of CDI cases identified by ICD-9 code alone were community-onset cases by toxin assay. The hospital-onset CDI rate was significantly higher by ICD-9 codes compared with toxin assays overall ($p < 0.001$), as well as individually at three of the five hospitals ($p < 0.001$ for all). The agreement between toxin assays and ICD-9 codes was moderate, with an overall kappa value of 0.509 and hospital-specific kappa values that ranged from 0.489 to 0.570. Overall, the annual increase in CDI incidence was significantly greater for rates determined by ICD-9 codes than by toxin assays ($p=0.006$).	Although ICD-9 codes appear to be adequate for measuring the overall CDI burden, use of the *C. difficile* ICD-9 code without present-on-admission classification is not an acceptable surrogate for hospital-onset CDI surveillance.	While ICD-9 codes may be an adequate surrogate for tracking the overall CDI burden, they may be less useful for tracking HO-CDI incidence compared with toxin assay results. In the future, present-on-admission codes—which became mandatory for Medicare patients discharged on or after October 1, 2007 (i.e., after the study period)—may add precision to ICD-9 code-based CDI surveillance. These codes might provide a mechanism to distinguish pre-existing conditions, and ultimately reduce misclassification of community-onset CDI cases. Discharge diagnosis codes reflect conditions diagnosed or treated during the entire admission, but do not give information regarding the location or date of CDI onset.	Low	ICD-9 codes significantly overreported the incidence of hospital-onset CDI compared with toxin assay results, and the degree to which this happened varied by year and by hospital.

Durkin et al., 2015[31]	National Healthcare Safety Network (NHSN) reporting of laboratory identified (LabID) *Clostridium difficile* infection (CDI) versus traditional surveillance methods. LabID: designed to use electronically captured laboratory data and hospital admission dates to determine hospital-onset (HO) versus community-onset (CO) surveillance categories.	Validation of LabID surveillance using a cohort study. A period of 6 months (January 1, 2013, to June 30, 2013) of prospectively collected data using both LabID and traditional surveillance definitions. A total of 1,252 incident LabID CDI events were identified during 708,551 patient-days. CDI events with mismatched surveillance categories between LabID and traditional definitions were identified and characterized further. Hospital-onset CDI (HO-CDI) rates for the entire cohort of hospitals were calculated using each method, then hospital-specific HO-CDI rates and standardized infection ratios (SIRs) were calculated. Hospital rankings based on each CDI surveillance measure were compared.	A cohort of 29 community hospitals in the south-eastern United States	A total of 1,252 incident LabID CDI events were identified during 708,551 patient-days; 286 (23%) mismatched CDI events were detected. The overall HO-CDI rate was 6.0 versus 4.4 per 10,000 patient-days for LabID and traditional surveillance, respectively ($p < 0.001$); of 29 hospitals, 25 (86%) detected a higher CDI rate using LabID compared with the traditional method.	Hospital rank in the cohort differed greatly between surveillance measures. A rank change of at least five places occurred in 9 of 28 hospitals (32%) between LabID and traditional CDI surveillance methods.	LabID surveillance resulted in a higher hospital-onset CDI incidence rate than did traditional surveillance. Hospital-specific rankings varied based on the HO-CDI surveillance measure used. A clear understanding of differences in CDI surveillance measures is important when interpreting national and local CDI data. Hospitals that adopt the LabID surveillance method should expect to observe higher HO-CDI incidence rates than with traditional surveillance. Mismatched cases between LabID and traditional surveillance that are due to delays in diagnostic testing may potentially penalize hospitals on publicly reported SIR measures.	Low	None

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/Findings	Risk of Bias (High, Moderate, Low)	Comments
Faires et al., 2014[24]	Outbreak investigation using the temporal scan statistic in a hospital	Case study. For patients detected with CDI from March 2010 to February 2011, stool specimens were obtained. *Clostridium difficile* isolates were characterized by ribotyping and investigated for the presence of toxin genes by PCR. CDI clusters were investigated using a retrospective temporal scan test statistic. Statistically significant clusters were compared with known CDI outbreaks within the hospital. A negative binomial regression model was used to identify associations between year, season, month, and rate of CDI cases.	A Canadian hospital	Overall, 86 CDI cases were identified. Eighteen specimens were analyzed and nine ribotypes were classified, with ribotype 027 (n=6) the most prevalent. The temporal scan statistic identified significant CDI clusters at the hospital (n=5), service (n=6), and ward (n=4) levels ($p \leq 0.05$). Three clusters were concordant with the one *C. difficile* outbreak identified by hospital personnel. Two clusters were identified as potential outbreaks.	Not provided	Application of the temporal scan statistic identified several clusters, including potential outbreaks not detected by hospital personnel. The identification of time periods with decreased or increased CDI rates may have been a result of specific hospital events. Understanding the clustering of infectious diseases, spatially or temporally, can help identify risk factors, facilitate detailed investigations to determine the association between exposures and disease interventions, and detect outbreaks. A commonly used statistical technique to detect disease clusters, the scan statistic has been used to investigate a wide array of infectious diseases or pathogens.	Low to moderate	None

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/Findings	Risk of Bias (High, Moderate, Low)	Comments
Gase et al., 2013[30]	NHSN surveillance versus clinical infection surveillance	30 facilities collected 6 months of data using a clinical infection surveillance definition, while also submitting the NHSN LabID event for CDI. The datasets were matched and compared to determine whether the assigned clinical case status matched the LabID case status. A subset of mismatches was evaluated further, and reasons for the mismatches were quantified.	30 New York State acute care hospitals	A total of 3,301 CDI cases were reported. Analysis of the original data yielded a 67.3% (2,223/3,301) overall case status match. After review and validation, there was 81.3% (2,683/3,301) agreement. The most common reason for disagreement (54.9%) occurred because the symptom onset was less than 48 hours after admission but the positive specimen was collected on hospital day 4 or later. The NHSN LabID hospital-onset rate was 29% higher than the corresponding clinical rate.	Not provided	Use of the NHSN LabID event minimizes the burden of surveillance and standardizes the process. With a greater than 80% match between the NHSN LabID event data and the clinical infection surveillance data, the New York State Department of Health decided to use the NHSN LabID event CDI data for public reporting purposes.	Low	None

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/Findings	Risk of Bias (High, Moderate, Low)	Comments
Hardy et al., 2010[22]	Use of measure of period of increased incidence (PII) to identify clusters and trigger interventions	Case study. Observational 18-month study of 102 PIIs involving 439 patients. For January 2008 to September 2008, multiple interventions were implemented, with PCR ribotyping of isolates being carried out on those PIIs with more than 10 cases. From October 2008 to July 2009, isolates from all PIIs were ribotyped 9. A PII was classified as an outbreak of CDI if there were two or more cases of the same PCR ribotype within a 28-day period.	A large teaching hospital with a total of 1,800 beds at three different sites	During roughly 1.5 years of the intervention, the number of PIIs investigated per month decreased, from a peak of 14 per month in February 2008 to 1 in June 2009. In the first 9 months of the study, isolates were ribotyped on those PIIs with more than 10 cases; for the last 8 months of the study, isolates were ribotyped for all PIIs. In this case, an outbreak was defined as two or more cases of the same PCR ribotype within a 28-day period. In the final 8 months, ribotyping of the isolates confirmed nine (32%) of these PIIs to be outbreaks, with three being due to ribotype 027, two to ribotype 078, and all the others being distinct ribotypes.	Not provided	The current study aimed to preempt and prevent outbreaks of CDI from becoming established, as opposed to being reactive and trying to control CDI once an outbreak was evident. The early identification and notification of PIIs enabled actions to be prompt and targeted. The authors postulate that concentrating on selected PII wards reduced the potential environmental sources of CDI transmission to the rest of the hospital.	Low to moderate	None

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/Findings	Risk of Bias (High, Moderate, Low)	Comments
Jones et al., 2012[37]	ICD 10 data for CDI surveillance	Evaluation of ICD-10 codes for CDI surveillance. Retrospective data analysis; during 2000–2010, 317,040 hospitalizations. Laboratory results and/or the ICD-10 code for *C. difficile* infection were positive for 698 cases.	A 750-bed university-affiliated public hospital in Paris	Sensitivity of the ICD-10 code, with laboratory results as the standard, was 35.6% (95% CI, 31.9 to 39.5), and specificity was 99.9% (95% CI, 99.9 to 100.0). The positive and negative predictive values were 79.2% (95% CI, 73.9 to 83.7) and 99.9% (95% CI, 99.8 to 99.9).	The sensitivity of ICD-10 codes in this study is inferior to that of values previously reported in the United States (71%–78%) and in Singapore (49.6%).	Compared with use of laboratory results, use of ICD-10 codes to estimate incidence of *C. difficile* infection resulted in underestimates. The relationship between methods for yearly incidence during the 11-year period was strong. Low sensitivity could be due to poor coding.	Low	None

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/Findings	Risk of Bias (High, Moderate, Low)	Comments
Lavan et al., 2012[23]	Monitoring CDI in an acute hospital with limited resources/ technology: prevalence or incidence studies?	Comparison of two CDI surveillance methods (incidence and prevalence). Prevalence of CDI, antibiotic use, and associated co-morbidity was assessed weekly on two wards over 6 weeks. In addition, CDI incidence surveillance was performed on all new CDI cases over a 13-week period. Cases were assessed for CDI risk factors, disease severity, response to treatment, and outcome at 6 months. A prospective Microsoft Excel database was created. Fisher's test was used for comparisons between count data, and continuous variables were assessed with two-sample t-test or Mann–Whitney test for nonparametric data.	Two wards in an acute hospital, Ireland	*Clostridium difficile* infection prevalence was 3.5% (range 2.9% to 6.1%) on the medical ward and 1.1% (range 0 to 3.5%) on the surgical ward. In the context of the study, it took, on average, 25 minutes per ward per week to measure prevalence. The workload to calculate incidence amounted to an average of 2.15 hours per day in the current study and depended on the number of ongoing cases. In contrast to the prevalence study, the incidence study was able to provide data on risk factors, symptoms, treatment, and patient outcomes.	Not provided	The studies were done without sophisticated technology—case counting and Excel spreadsheets were used. CDI prevalence surveillance gives a broad overview of CDI, and pointed to areas that required more-detailed surveillance and required little time. However, patient-based CDI incidence surveillance provided a more useful analysis of CDI risk factors, disease, and outcomes for planning preventive programs and focusing antibiotic stewardship efforts.	Low to moderate	None

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/Findings	Risk of Bias (High, Moderate, Low)	Comments
Quan et al., 2015[12]	A system for MDROs and *C. difficile* tracking that automated the following three main surveillance and tracking activities: monitoring microbiology results and initiation of chart-based flags, ordering contact precautions on admission, and ensuring appropriate removal of precautions.	Quasi-experimental before-and-after study. In 2012, the system automatically reviewed daily positive laboratory results for 110,212 patient-days and cross-checked these results with historical MDRO and *C. difficile* flags, to determine whether 2,375 positive results represented incident cases.	A 410-bed tertiary care academic medical center	Automation saved 43 infection preventionist hours per 1,000 admissions (850 hours of infection preventionist time annually). It also saved previously unquantified hours spent reviewing MDRO history for every admission. Automatic retiring of certain MDRO flags ensured removal of contact precautions after a specified time. A point-prevalence assessment of eligibility for discontinuation found that all precautions were appropriate, with none of them eligible for removal.	Not provided	Automated tracking useful for determining when to start/ discontinue contact precautions/ put patients in single person rooms. When the EHR system detected a finalized positive laboratory test result, it automatically checked whether an organism-specific flag was already present and added the flag if needed. For *C. difficile* specifically, because precautions are based on diarrheal symptoms, any readmission within 60 days of an initial flag resulted in an automated order for precautions. Discontinuation criteria were displayed for review when physicians attempted to discontinue a precaution order.	Low to moderate	Automated ordering prevented missed precautions, which might be caused by errors, such as admitting providers not noticing a flag, or healthcare workers missing history of infection on manual review.

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/Findings	Risk of Bias (High, Moderate, Low)	Comments
Saeed et al., 2018[18]	*Clostridium difficile* multidisciplinary team root cause analysis (MDT-RCA) (vs. on-the-spot investigation) of a breached case	Investigation of the financial impact of MDT-RCAs to the Trust. Methodology: over 2 years, the MDT-RCA forum reviewed 84 hospital-onset CDI cases. HFT serves a population of approximately 600,000.	Three hospitals in UK totaling over 850 beds	In total, 543 staff attended the MDT-RCAs at a potential cost to the Trust of £23,795.74 to £51,670.10. Over 24 months, the Trust had appealed against financial penalties for 27 cases, and 14 appeals were successful. This suggests that £140,000 would have been avoided had 14 cases not breached hospital CDI case targets. (Hospital groups, i.e., trusts, are required to demonstrate year-on-year reductions in CDI cases. Breaches of *C. difficile* targets—in this case, 37 cases for the first year— incur financial penalties to the Trust to the value of £10,000 per case.) After the appeal, only two cases breached the threshold.	In the end, targets were breached by only two cases, meaning £20,000 in fines was avoided. Deducting this from the total costs of the MDT-RCA meant the Trust lost £3,795.74 to £31,670.	Over the 2 years reviewed, the MDT-RCA proved to be costly to the Trust, with "no additional learning or quality improvement measures identified." Key learning themes from the 84 cases: the delay in isolating symptomatic patients and the delay in sending stool samples to the laboratory. Concerns were also raised with lack of documentation, such as the clinical and nursing teams not completing the *C. difficile* care pathway and diarrhea and vomiting risk assessment. One possible benefit of the MDT-RCA meetings may have been heightening the awareness of CDI among staff that attended.	Low to moderate	Touches on issues of financial penalties for "preventable" CDI cases. Article is about financial implications of RCA specific to the commission-ing groups in the UK.

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/Findings	Risk of Bias (High, Moderate, Low)	Comments
Schlackow et al., 2012[41]	Biomarker- based surveillance: automated electronic systems providing early warning of the changing severity of infectious conditions. Iterative sequential regression (ISR)-based severity monitoring.	Assessed the generalizability of ISR-based severity monitoring. Study of 5,551 toxin-positive and 20,098 persistently toxin-negative patients tested for CDI between February 1998 and July 2009, in a group of hospitals. Investigated 28-day mortality and biomarkers of inflammation collected at diagnosis using ISR, a novel join point-based regression technique. Assessed the generalizability of ISR-based severity.	A group of UK hospitals	ISR-based severity monitoring allowed the detection of the severity change years earlier than mortality monitoring. Among *C. difficile* toxin-positive patients in the Oxford hospitals, mean neutrophil counts on diagnosis increased from 2003, peaked in 2006–2007, and then declined; 28-day mortality increased from early 2006, peaked in late 2006–2007, and then declined. Molecular typing confirmed these changes were likely due to the ingress of the globally distributed severe *C. difficile* strain, ST1. Strong associations found between isolation of the ST1 severe strain and higher neutrophil counts at diagnosis in two unrelated large multi-center studies. Similar trends were	One concern is feasibility. The samples used to predict severity were routinely collected and came from inpatients. Although in many hospitals in high-income countries, such samples are taken in most admissions, this may not be the case in lower resourced settings.	General methods of detecting changing virulence that would permit early recognition and control, and optimal management of such threats, would be highly desirable. The studied method requires that there be at least one routinely collected biomarker associated with disease-related mortality for each target condition. Researchers envisage that initially a number of potential severity markers could be investigated for each infection—retrospectively, using historical data if available, or prospectively, based on routine electronic databases. Comparing historical data with mortality retrospectively, and/or investigating any ‘‘signals’’ prospectively, would identify which biomarkers were most useful for passive severity monitoring.	Low to moderate	None

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/Findings	Risk of Bias (High, Moderate, Low)	Comments
Schmiedeskamp et al., 2009[36]	Use of ICD-9 codes and use data to identify nosocomial CDI (vs. ICD-9 code alone)	Validation sample cross-sectional study. Laboratory and medical records were queried to identify symptomatic CDI toxin–positive adult patients with nosocomial CDI and were compared with records of patients whose cases were predicted to be nosocomial by means of ICD-9-CM code and CDI therapy data. Administrative claims data from July 1, 2004, to June 30, 2005, were queried. Population/sample size: 23,920 adult patients discharged from the hospital.	An academic health center in Virginia	The sensitivity of the ICD-9-CM code alone for identifying nosocomial CDI was 96.8%. The specificity was 99.6%, the positive predictive value was 40.8%, and the negative predictive value was 100%. When CDI drug therapy was included with the ICD-9-CM code, the sensitivity ranged from 58.1% to 85.5%, specificity was virtually unchanged, and the range in positive predictive value was 37.9% to 80.0%.	Combining the ICD-9-CM code for CDI with drug therapy information increased the positive predictive value for nosocomial CDI, but decreased the sensitivity.	Beginning October 1, 2008, the Centers for Medicare & Medicaid Services required hospitals to indicate which diagnoses were present on admission. The method proposed in this investigation should be useful to help determine the post-admission day that nosocomial CDI became evident. A limitation in using ICD-9-CM codes to identify CDI is the inability to determine which cases are nosocomial, because ICD-9-CM codes are assigned to all patients with CDI at any time during hospitalization.	Low to moderate	The purpose of this study was to determine whether combining the ICD-9-CM code with medication treatment data for CDI in hospitalized patients could be used to distinguish between patients with nosocomial CDI and patients who were admitted with CDI.

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/Findings	Risk of Bias (High, Moderate, Low)	Comments
Truong et al., 2017[33]	Real-time electronic tracking of diarrheal episodes and laxative therapy for verification of *Clostridium difficile* clinical testing criteria	A quasi-experimental study from June 22, 2015, to June 30, 2016, on consecutive inpatients with *C. difficile* test orders; 2,321 cancelled *C. difficile* test orders	An academic hospital	Use of *C. difficile* testing decreased upon implementation from an average of 208.8 tests to 143.0 tests per 10,000 patient-days (p<0.001). HO-CDI incidence rate decreased from an average of 13.0 cases to 9.7 cases per 10,000 patient-days (p=0.008).	Not provided	Real-time electronic clinical data tracking is an effective tool for verification of *C. difficile* clinical testing criteria and safe reduction of inflated HO-CDI rates. Oral vancomycin days of therapy decreased from an average of 13.8 days to 9.4 days per 1,000 patient-days (p=0.009). Clinical complication rates were not significantly different in patients, with 375 canceled orders, compared with 869 episodes with diarrhea but negative *C. difficile* results.	Low	None

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/Findings	Risk of Bias (High, Moderate, Low)	Comments
Wilcox, et al., 2012[39]	Enhanced surveillance in England using the *Clostridium difficile* Ribotyping Network	Case study/system evaluation. Criteria used to assess the service include investigation of increases in the frequency of CDI cases (or high baseline rates) and increased severity, recurrence, complications, or mortality associated with CDI. A standardized request form for clinical and epidemiological data is used and is available via a web-based electronic requesting (and reporting) portal.	Regional, UK	Overall in England, mortality decreased, as did CDI incidence. In the first 3 years (2007 to 2010), the CDRN service processed 12,603 fecal specimens for culture and ribotyping. The average proportion of patients in England with reported CDI from whom samples were sent for ribotyping over the whole analysis period (2007 to 2010) was 10.8%. The reasons cited by requestors for referral to CDRN did not change over this time: case clusters (46% to 55%); unexplained increase in CDI rate (12% to 13%); and increased severity of symptoms (10% to 13%).	Not provided	Access to CDRN ribotyping is limited to several regional microbiology laboratories in England, which aim to provide timely access to *C. difficile* culture and ribotyping according to standardized criteria for submission of fecal samples. The target turnaround time for delivery of ribotyping results, is <2 weeks. There was a 61% reduction in reports of *C. difficile* in England (36,095, 25,604, and 21,698 in 2008 to 2009, 2009 to 2010, and 2010 to 2011, respectively). The reduction was coincident with the control of the epidemic *C. difficile* ribotype 027, which accounted for 55%, 36%, and 21% of samples submitted to CDRN in 2007 to 2008, 2008 to 2009, and 2009 to 2010, respectively.	Low to moderate	Responding to a national public health need, the Health Protection Agency created the CDRN for England, as part of an enhanced surveillance program for *C. difficile* in 2007.

Table B.8: Clostridioides *difficile*, Surveillance–Systematic Reviews

Note: Full references are available in the Section 4.4 reference list.

Author, Year	Description of Patient Safety Practice	Setting/s, Population/s	Summary of Systematic Review Findings	Implementation Themes/Findings	Notes
Goto et al., 2014[20]	Administrative Code Data (ACD) for surveillance ACD include International Classifications of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes.	General healthcare	This systematic review summarizes evidence for the accuracy of ACD for the detection of selected HAIs and includes a meta-analysis for surgical site infections (SSIs) and CDIs, where acceptable numbers of primary studies were available. For these two conditions, ACD have moderate sensitivity and high specificity, but evidence for detection of other HAIs is limited. With current low prevalence of HAIs, the positive predictive value of ACD algorithms would be low. ACD may be inaccurate for detection of many HAIs and should be used cautiously for surveillance and reporting purposes. The systematic literature review included 19 studies. Of those included studies, seven (five in the U.S.) reported results for CDI. When these parameters were applied to currently reported incidence of CDI (8.75 per 1,000 discharges) in U.S. acute care hospitals, estimated positive predictive value (PPV) was 87.0% (95% CI, 66.2 to 100), and estimated negative predictive value (NPV) was 99.7% (95% CI, 99.6 to 99.9). This systematic review found that ACD detect CDI and SSI with moderate sensitivity and high specificity compared with traditional surveillance.	These findings suggest that ACD may be useful as part of algorithmic automated HAI surveillance but should not be the sole primary case finding method in hospital performance measurement or epidemiologic research. The moderate sensitivity for CDI and SSI means that ACD may miss important cases of HAI. In addition, the relatively low prevalence of HAIs will limit the positive predictive value of ACD, despite their moderate sensitivity and high specificity. Thus, as increasing attention is paid to HAI prevention, lower infection incidence in the future with the accompanying lower PPVs will further compromise the utility of ACD.	According to article, the major limitations of ACD are that they were developed for the entirely different purpose of billing, and their coding criteria may differ from public health surveillance definitions. Also, coding for billing generally focuses on physician documentation and provided care, rather than clinical information of the patient's status.

Author, Year	Description of Patient Safety Practice	Setting/s, Population/s	Summary of Systematic Review Findings	Implementation Themes/Findings	Notes
Krutova et al., 2018[21]	Key components of surveillance for CDI	Acute care hospitals in Europe	The review provides a summary of components of CDI surveillance and includes suggestions. According to the review, the key components for CDI surveillance are appropriate case definitions of CDI, standardized CDI diagnostics, agreement on CDI case origin definition, and presentation of CDI rates with well-defined numerators and denominators. Incorporation of microbiological data is required to provide information on prevailing PCR ribotypes and antimicrobial susceptibility to first-line CDI treatment drugs. Implications: incidence rates of CDI, obtained from a standardized CDI surveillance system, can be used as an important quality indicator. In the future, surveillance data will be linked to antimicrobial use and real time CDI surveillance data. Linkage of hospital administrative information systems to microbiological information systems will eventually permit automated reporting of CDI data, enabling rapid identification of outbreaks. Such centers could also provide molecular typing support for CDI outbreaks in healthcare facilities and early intervention.	Use recommended testing practices: when to test and which test (e.g., two-step algorithm); appropriate case origin (CA, HA, recurrent, or unknown); calculate incidence rate or incidence density rate; use PCR ribotyping for CDI surveillance. In the future, technology will help improve speed and accuracy of surveillance.	Article also includes surveillance protocol for Europe.

Table B.9: Clostridioides *difficile*, Testing–Single Studies

Note: Full references are available in the Section 4.5 reference list.

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting:	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/Findings	Risk of Bias (High, Moderate, Low)	Comments
Aichinger et al., 2008[30]	Not repeating negative CDI tests within 7 days of initial result	Retrospective review of stool testing for *C. difficile* from June 2006 through December 2007. 5,788 patients tested by enzyme immunoassay (EIA) and 2,827 patients tested by polymerase chain reaction (PCR).	An unspecified healthcare facility	The group of EIA patients tested only twice consisted of 792 subjects (13.7% of patients tested with EIA). Twenty (2.5%) patients had a negative result on the first test with subsequent positive results on the following tests. Thirty-eight (4.8%) went from positive to negative. For PCR, 351 were tested twice; 2% (7) went negative to positive and 2.9% (10) went positive to negative.	Not provided	The researchers concluded that the diagnostic gains of repeat testing are equally low for PCR and EIA and that repeat testing for *C. difficile* should not be routine. Several authors have suggested that it may be useful to test more than one stool specimen for *C. difficile* toxin by use of an immunoassay. Nevertheless, there are limited data supporting this practice.	Not provided	None

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting:	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/Findings	Risk of Bias (High, Moderate, Low)	Comments
Archbald-Pannone et al., 2015[60]	Clinical factors to predict mortality following *C. difficile* infection (CDI)	A parsimonious predictive model was chosen using Akaike information criterion (AIC) and a best subsets model selection algorithm. Area under the receiver operating characteristic (ROC) curve was used to assess the model's comparative, with AIC as selection criterion for all subsets to measure fit and control for over-fitting. 362 inpatients diagnosed with CDI who did not have chronic diarrhea. Followed them for 30 days after CDI diagnosis or until death.	U.S. academic hospital/ University of Virginia clinical laboratory	The area under the ROC curve was 0.804. The bootstrap estimate of optimism was -0.034; suggesting that this model applied to a novel cohort is expected to have an area under the curve (AUC) of 0.770. With this model, 1 point corresponds to approximately an 11% increase in the odds of death within 30 days. The selected model included Charlson comorbidity index (CCI), white blood cell count (WBC), blood urea nitrogen (BUN), intensive care unit, and delirium. The logistic regression coefficients were converted to a point scale and calibrated so that each unit on the CCI contributed 2 points, ICU contributed 5, unit of WBC (natural log scale) contributed 3, unit of BUN contributed 5, and delirium contributed 11.	Not provided	Clinicians could use this tool to enhance the early recognition of high-risk patients with CDI, implement a more intensive treatment regimen, and aid in the decision for earlier surgical consultation. The predictive model was directly calculated from the five retained variables: Charlson score, ICU at diagnosis, WBC, BUN, and delirium. Patients who were admitted from a long-term care facility, who were diagnosed in the ICU, and who developed delirium were at highest risk of dying within 30 days of CDI diagnosis.	Moderate	Background: According to article, current models to define severe CDI lack either sensitivity or specificity.

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting:	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/Findings	Risk of Bias (High, Moderate, Low)	Comments
Bogaty et al., 2017[41]	Different CDI testing strategies (and their association with CDI incidence rates): EIA, glutamate dehydrogenase (GDH), GDH plus toxigenic cultures, nucleic acid amplification tests (NAATs)	Cross-sectional study of 95 hospitals by surveys conducted in 2010 and in 2013 to 2014. The association between testing strategies and institutional CDI incidence rates was analyzed via multivariate Poisson regressions.	95 hospitals in Quebec, Canada	Between 2010 and 2014, 35 institutions (37%) modified their algorithm. Institutions detecting toxigenic *C. difficile* instead of *C. difficile* toxin increased from 14 to 37 ($p<0.001$). Institutions detecting toxigenic *C. difficile* had higher CDI rates (7.9 vs 6.6 per 10,000 patient-days; $p=0.01$). Institutions using single-step NAATs, GDH plus toxigenic cultures, and GDH plus cytotoxicity assays had higher CDI rates than those using an EIA-based algorithm ($p<0.05$).	Not provided	Infection control professionals should be aware that local CDI incidence rates may be influenced by the local choice of diagnostic test. The research found that laboratory detection of CDI has changed since 2010 and there is an association between diagnostic algorithms and CDI incidence. The heterogeneity of available tests can pose a significant threat to the validity of surveillance systems regarding interinstitutional comparisons.	Low to moderate	Background: Many surveillance programs, including Quebec's, provide no recommendations regarding the choice of laboratory tests to use, and CDI incidence rates are not adjusted to take this variable into consideration.

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting:	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/Findings	Risk of Bias (High, Moderate, Low)	Comments
Casari et al., 2018[42]	Use of NAAT plus clear sampling criteria (unformed stool)	Prospective, pre/post study. Analyses of sample numbers, numbers of positive results, and proportion of cases assessed as healthcare acquired over a 6-year period during which the testing method was changed from a toxin A/B immunoassay to a standalone commercial nucleic acid test after the first 2 years (2012)	A 750-bed tertiary care university hospital in Milan	Sample numbers and numbers of cases assessed as healthcare-acquired CDI fell after the introduction of the NAAT and sampling guidance, while infection rates in other hospitals in the same region remained relatively stable. A total of 8,680 samples were tested for CDI over the study period: 2,841, 2,746, 677, 768, 805, and 843 tests in 2010, 2011, 2012, 2013, 2014, and 2015, respectively. For the corresponding years, the total number of positive samples and those categorized as healthcare acquired was 106/105 for 2010, 108/104 for 2011, 92/79 for 2012, 95/75 for 2013, 93/76 for 2014, and 91/78 for 2015, respectively.	Not provided	This study showed that moving from a toxin EIA to a standalone NAAT resulted in fewer samples tested and lower positivity rates, largely due to a reduction in the number of healthcare-associated cases. According to the authors, the reasons for these findings are likely to be multifactorial. Lack of confidence in the sensitivity of the toxin tests meant that clinicians often repeated the test up to three or more times before declaring the patients free from *C. difficile* infection and releasing them from isolation, resulting in a poor use of isolation facilities.	Low	None

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting:	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/Findings	Risk of Bias (High, Moderate, Low)	Comments
Cooper et al., 2013[44]	An electronic screening tool to help identify patients at risk of CDI	Logistic regression was used to weigh six variables, and then a predictive model was devised to help identify which patients may be at risk for developing CDI. A retrospective review of 29,453 records of hospitalizations was conducted, including 274 cases of *C. difficile* toxin-positive patients, to retrieve data for the model.	A 255-bed, community hospital located in Virginia's Shenandoah Valley	The final model resulted in an area under the curve of 0.929, which suggests that the electronic screening tool will be an accurate predictor of predisposition to the disease. Model testing suggests a positive relationship between the total weight or score and the probability of developing the disease.	The impact of the tool to the prevalence and control of the disease itself may be difficult to ascertain in isolation from other infection control measures. Further studies are warranted on the economic benefits of the electronic screening tool and how it affects physician decision making.	This study suggests that an electronic screening tool for CDI can be devised locally and result in reasonably accurate screening of patients at risk of developing the disease. This model could be applied to the electronic medical record to automatically generate updated lists of patients who may need monitoring for prompt testing, isolation, or treatment. Being alerted that a patient is at high risk for CDI may help the clinician to consider prompt isolation and empiric treatment in cases when the laboratory test (especially EIA) is negative or is still pending.	Low to moderate	None

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting:	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/Findings	Risk of Bias (High, Moderate, Low)	Comments
Cruz-Betancourt et al., 2016[45]	A predictive preventive model for prevention of *Clostridium difficile* infection in patients in ICUs	A predictive screening tool was developed based on risk factors identified in the literature and validated by retrospective analysis of all HA-CDI cases occurring in critically ill patients during 2013. The tool was used to screen all patients admitted to an intensive care unit. Evidence-based interventions (bundle) were implemented for patients identified as being at high risk for HA CDI. Effectiveness of the model was measured by reduction of the HA-CDI rate during the intervention period compared with the pre-intervention period.	A vascular-thoracic ICU, a 20-bed unit providing care to patients following vascular surgery as well as to patients with chronic ventilator dependency	During the study period, 1,066 patients were screened using the predictive screening tool; 217 high-risk patients were identified as infected with *Clostridium difficile*. Sixty-two of these met exclusion criteria, resulting in a study population of 157 patients. During the pre-intervention phase, 10 cases of HA CDI occurred (overall incidence rate, 14.7). During the 12-month study period, two cases of HA CDI were identified (incidence rate, 3.12). The reduction was statistically significant.	Not provided	The combination of a predictive screening tool with preventive interventions in the vascular-thoracic ICU appeared effective in reducing HA-CDI rates. The two patients who developed CDI during the implementation period did not have the preventive bundle measures instituted due to procedural deviation. The major pharmacologic interventions related to adjustment or discontinuation of acid suppression therapy. Improved environment cleaning to reduce transmission in addition to improved hand hygiene rates also likely played a role in reducing HA-CDI rates, according to the authors.	Low to moderate	This study describes both the use of a predictive model and its integration into daily practice of interdisciplinary efforts at CDI reduction to demonstrate a method of clinical use of a predictive model.

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting:	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/Findings	Risk of Bias (High, Moderate, Low)	Comments
Figh et al., 2017[63]	Two published clinical prediction tools (CPTs): the Velazquez-Gomez Severity Score Index (VGSSI) and ATLAS scores	A retrospective review of the charts of 271 hospitalized patients with CDI. VGSSI and ATLAS scores were assigned. Means and correlations of these scores with mortality were evaluated. Multivariate logistic regression analysis was performed on 32 known potential mortality predictor variables. The review included 271 patient charts.	A hospital	Mortality was overall strongly associated with VGSSI and ATLAS scores with poor correlation within the intermediate ranges. Mean scores for nonsurvivors indicated poor calibration.	Although both CPTs revealed the ability to discriminate patients at greater risk for mortality, precision and overall calibration were lacking.	An external validation of VGSSI and ATLAS scoring systems showed that these two CPTs are inaccurate in stratifying patients into the appropriate severity index score for severe CDI. In the application of the VGSSI and the ATLAS score, it is clear that there is an overall correlation of these models with mortality.	Low to moderate	These tools are used to predict the *severity* of CDI. There is a wide range of CDI severity. Approximately 25% will progress to pseudo-membranous colitis, and in this high-risk group, another 1–8% will become fulminant CDI.
Islam et al., 2013[32]	Cohorting patients—recognize risk of reinfection	Data describing patient demographics, comorbidity, CDI severity, and treatment were collected for 248 CDI patients between October 2008 and June 2011. The primary outcome was symptomatic recurrence within 30 days of diagnosis.	A single hospital ward	A total of 158 (55.6%) CDI patients was admitted to the cohort ward. On multivariate analysis, cohorting (3.94; 95% CI 1.23 to 12.65; p=0.021) and urinary infection (4.27; 1.62 to 11.24; p=0.003) were significant predictors of recurrence.	Not provided	Patients admitted to a *C. difficile* cohort ward may be at increased risk of recurrence because they are at increased risk of reinfection. Study suggests that hospitals using cohort wards to control *C. difficile* should manage patient flow through the cohort to minimize this risk.	Low to moderate	None

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Kassam et al., 2016[61]	CDI-related mortality prediction tool to prevent CDI mortality: *C. difficile* Associated Risk of Death Score (CARDS)	Retrospective analysis of United States 2011 Nationwide Inpatient Sample (NIS) database. All CDI-associated hospitalizations were identified using discharge codes (ICD-9-CM, 008.45). Predictive properties of model discrimination were assessed using the c-statistic and validated in an independent sample using the 2010 NIS database.	A large U.S. database, 374,747 cases with an associated diagnosis of CDI	The overall risk score in the cohort ranged from 0 to 18. Mortality increased significantly as CARDS increased. CDI-associated mortality was 1.2% with a CARDS of 0 compared with 100% with a CARDS of 18. The model performed similarly in the validation cohort. The severity scoring system had a comparable performance with a c-statistic of 0.77.	Not provided	The CARDS model displayed good discriminative ability, which was validated in an independent CDI cohort. Age has been identified as a risk factor of initial CDI development and CDI-associated mortality. ICU admission was also a strong independent predictor of CDI-associated mortality (odds ratio 5.23, 95% CI, 4.79 to 5.72). A number of chronic comorbidities are important predictors of CDI-associated mortality. Inflammatory bowel disease, malignancy, and liver disease were all independently identified to increase the odds of CDI-associated death in the model.	Low	None

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Koo et al., 2014[38]	Taking into account false positives for real-time PCR for *Clostridium difficile*-associated disease (CDAD) detection	CDAD rates were compared before and after real-time PCR implementation. After real-time PCR introduction, all hospitalized adult patients were screened for *C. difficile* by testing a fecal specimen by real-time PCR, toxin enzyme-linked immunosorbent assay, and toxigenic culture. The study included 199 enrolled hospital subjects.	A 600-bed university hospital in Houston, TX	CDAD hospital rates significantly increased after changing from cell culture cytotoxicity assay to a real-time PCR assay; 199 hospitalized subjects were enrolled, and 101 fecal specimens were collected. *C. difficile* was detected in 18 subjects (18%), including 5 subjects (28%) with either definite or probable CDAD and 13 patients (72%) with asymptomatic *C. difficile* colonization.	The difficulty in interpreting the clinical significance of *C. difficile* detected by NAATs is emphasized by recent studies describing the importance of confirmation of *C. difficile* toxin production. In spite of the high sensitivity of NAATs for *C. difficile* detection, PCR assays cannot distinguish asymptomatic colonization from symptomatic disease; i.e., there are false positives	Study reports that most healthcare-associated diarrhea is not attributable to CDAD, and the prevalence of asymptomatic *C. difficile* colonization exceeds CDAD rates in healthcare facilities. PCR detection of asymptomatic *C. difficile* colonization among patients with non-CDAD diarrhea may be contributing to rising CDAD rates and a significant number of CDAD false positives. PCR may be useful for CDAD screening, but further study is needed to guide interpretation of PCR detection of *C. difficile* and the value of confirmatory tests. A gold standard CDAD diagnostic assay is needed.	Moderate	Most subjects identified with *C. difficile* were asymptomatic, irrespective of the detection method, including 8 of 12 (67%) *C. difficile*-positive subjects by PCR. The only significant difference between subjects with CDAD and *C. difficile*-colonized patients was the mean number of stools passed in the previous 24 hours. Limitations of this study include enrollment of 51% of eligible patients and fecal specimen collection from only half of enrolled subjects.

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Kuntz et al., 2014[48]	Tool to predict risk of CDI after an outpatient visit	Developed and validated a prognostic risk score to predict CDI risk for individual patients following an outpatient healthcare visit. A cohort of Kaiser Permanente Northwest (KPNW) patients with an index outpatient visit between 2005 and 2008, and identified CDI in the year following that visit. Researchers applied Cox regression and synthesized a priori predictors into a CDI risk score, which was validated among a Kaiser Permanente Colorado (KPCO) cohort. They calculated and plotted the observed 1-year CDI risk for each decile of predicted risk for both cohorts.	Cohort of 356,920 patients from a health system	Among 356,920 KPNW patients, 608 experienced CDI, giving a 1-year incidence of 2.2 CDIs per 1,000 patients. The Cox model differentiated between patients who do and do not develop CDI: there was a c-statistic of 0.83 for KPNW. The simpler points-based risk score, derived from the Cox model, was validated successfully among 296,550 KPCO patients, with no decline in the area under the receiver operating characteristic curve: 0.785 (KPNW) vs. 0.790 (KPCO).	Not provided	The predicted risk for CDI agreed closely with the observed risk. The CDI risk score used data collected during usual care to successfully identify patients who developed CDI, discriminating them from patients at the lowest risk for CDI. The prognostic CDI risk score provides a decision-making tool for clinicians in the outpatient setting. The patient characteristics that contributed >30 points to the risk score, indicating an approximate doubling of risk, were: age 55 years and older (38 to 100 points, depending on age category); hospitalization of 7 days (37 points); liver disease (47 points); inflammatory bowel disease (43 points); and cephalosporin use (38 points) or clindamycin use (58 points).	Low	None

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Lanzas and Dubberke, 2014[20]	Screening patients at admission to detect asymptomatic *C. difficile* carriers and placing positive patients into contact precautions	An agent-based transmission model for *C. difficile* that incorporates screening and contact precautions for asymptomatic carriers in a hospital ward. Simulation of scenarios that vary according to screening test characteristics, colonization prevalence, and type of strain present at admission.	Electronic data were collected retrospectively from six medicine wards at Barnes-Jewish Hospital in St. Louis, Missouri	On average, testing for asymptomatic carriers reduced the number of new colonizations and hospital-onset (HO)-CDI cases by 40% to 50% and 10% to 25%, respectively, compared with the baseline scenario. Test sensitivity, turnaround time, colonization prevalence at admission, and strain type had significant effects on testing efficacy.	Not provided	Screening patients at admission to detect and isolate asymptomatic carriers could decrease the number of new colonizations and HO-CDI cases at the ward level. Simulations indicated that tests with a sensitivity greater than 90% and turnaround times less than 2.5 days could reduce the number of secondary new colonizations (and subsequent CDIs) caused by asymptomatic carriers. Additional research is needed to determine the costs, feasibility, and impact of screening on patient outcomes.	Low to moderate	Simulation: "The contribution of symptomatic cases to transmission and new infection is likely to be lower than previously thought, and the likelihood of transmission and infection appears to also be *strain specific*."

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Longtin et al., 2016[19]	Detecting and isolating *C. difficile* asymptomatic carriers at hospital admission	Controlled quasi-experimental study between November 19, 2013, and March 7, 2015; 7,599 patients screened at admission.	A 354-bed Canadian acute care facility	During the intervention, 38 patients (3.0 per 10,000 patient-days) developed an HA CDI compared with 416 patients (6.9 per 10,000 patient-days) during the pre-intervention control period ($p<0.001$). The researchers estimated that the intervention had prevented 63 of the 101 (62.4%) expected cases. By contrast, no significant decrease in HA-CDI rates occurred in the control groups.	Not provided	The cost-benefit of this strategy is unknown, but preliminary estimates suggest that the intervention may be cost effective. The intervention cost U.S. $130,000 over 17 periods and prevented approximately 63 cases. Because each case costs U.S. $3,427 to $9,960, the savings in averted CDI (U.S. $216,000 to $627,000) are greater than the costs of the intervention.	Low	Context: "Present guidelines do not recommend screening and isolating asymptomatic carriers."

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Maghdoori and Moghadas, 2017[21]	Screening at the time of hospital admission, and screening in-hospital patients with potential exposure to *C. difficile*, to detect colonized/ asymptomatic patients (in the context of imperfect patient isolation)	Stochastic modeling for the transmission dynamics of CDI in a hospital ward. Simulation of various scenarios for detection and isolation of colonized patients. Model incorporated several parameters representing the level of patient screening, effectiveness of isolation, treatment failure, and level of susceptibility to infection.	A hospital ward with 50 beds (simulation)	When the effectiveness of patient isolation was 100%, the daily incidence of *C. difficile* was reduced by over 79% (95% CI, 78% to 79.6%) as a result of 92.5% *rapid* screening *at the time of hospital admission*. For isolation with less than 100% effectiveness, the benefits of screening and detection of colonized patients were reduced as a result of within-ward transmission. Compared with the results for rapid testing, results that take 2 days (without patient isolation) significantly lowered the effect of admission screening on reducing the prevalence of CDI. When screening 90% of *in-hospital patients starting on day 100*, there was an increasing trend in the percentage reduction of *C. difficile* incidence over time, reaching levels over 76%.	Findings indicate that if infection control measures are implemented inefficiently, within-ward transmission can potentially offset the benefits of patient screening.	The analysis found that if rapid screening of patients at the time of hospital admission and screening of in-hospital patients are implemented individually, then the former would always outperform the latter in terms of reducing the prevalence and incidence of CDI irrespective of the reproduction number, time delay in the release of laboratory tests, or effectiveness of patient isolation. Model shows that impact of screening at admission or day 100 is dramatically reduced when test results take 2 days.	Moderate	Study is based on several simulations. Addresses the issue of asymptomatic carriers in CDI transmission and suggests screening for asymptomatic carriers may be effective under certain conditions.

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Moehring, et al., 2013[40]	Change from nonmolecular to molecular testing techniques—impact on surveillance	Comparison of the relative change in incidence rate (IRR) of healthcare facility-associated (HCFA) CDI among hospitals in the Duke Infection Control Outreach Network before and after the date of switch from nonmolecular tests to polymerase chain reaction (PCR) using prospectively collected surveillance data from July 2009 to December 2011. Data from 10 hospitals that switched and 22 control hospitals were included. Individual hospital estimates were determined using Poisson regression. 1,805 cases of CDI over 4,038,447 patient days.	32 hospitals in the Duke Infection Control Outreach Network	For those hospitals that switched to PCR, mean incidence rate of HCFA CDI before the switch was 6.0 CDIs per 10,000 patient-days compared with 9.6 CDIs per 10,000 patient-days after the switch. After adjustment in the mixed-effects model, the overall IRR comparing CDI incidence after the switch to before the switch was 1.56 (95% CI, 1.28 to 1.90). Time-trend variables did not reach statistical significance. Hospitals that switched from nonmolecular to molecular tests experienced an approximate 56% increase in the rate of HCFA CDI after testing change.	Improved test sensitivity because of the change to molecular diagnostic testing can produce both positive and negative effects. A molecular test is more expensive to implement, may cause confusion among ordering providers, and may be overused because of its novelty. Also, the more sensitive test may be "too good" at identifying patients who are colonized but not truly infected with *C. difficile*.	Study shows that increase in CDI rates in the United States up to 2009 were due at least in part to "surveillance bias" (e.g., changing definitions and new testing methods). The purpose of this study was to adjust for time-dependent factor and isolate the impact of the change in testing method. All 10 hospitals that switched to PCR testing used the Cepheid Xpert *C. difficile* assay (Xpert CD assay; Cepheid). In the context of testing for potentially transmittable diseases within the hospital setting, the improved sensitivity of molecular tests allows infected and colonized patients to be rapidly and reliably identified.,.	Low to moderate	Centers for Disease Control and Prevention (CDC) National Healthcare Safety Network surveillance definitions were used to identify incident cases of community-onset HCFA and HO HCFA CDI. The study period corresponds with introduction of the 2008 change in CDC surveillance definitions for CDI, which included source type interpretations. should be noted. In fact, two hospitals in the study saw a numerical decrease in their incidence rates after the switch.

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Mostafa et al., 2018[29]	Factors for conversion from negative to positive PCR CDI test	A retrospective chart review of 20,866 laboratory test orders (2 years) for *C. difficile* PCR was conducted. The test result, clinico-pathologic patient features, and previous test results were recorded. Univariate and multivariate analysis were conducted to compare patients with initial and repeat negative results (n=248) with a group of patients with conversion from negative to positive results within 7 days.	Medical college and diagnostic laboratory	Among these charts, 1,637 (8.0%) were tests repeated within 7 days of previously valid test result. Based on only single repeat test orders, 970 (59.3%) followed an initial negative and 554 (33.8%) followed an initial positive test result. An additional 113 (6.9%) tests were repeated more than once within 7 days of the original test. Patients with a history of *C. difficile* confirmed by PCR within the 60 days prior to initial test were 19 times more likely to have a repeat positive result within 7 days of a negative result (95%, CI, 6.64 to 54.17, p<0.001). Conversely, patients with history of any antibiotic therapy within 14 days prior to initial test were 3.9 times more likely to have a repeat negative result (95% CI, 1.6 to 10.0, p=0.003).	Not provided	Identification of prior *C. difficile* infection as the only factor significantly correlated with conversion from negative to positive *C. difficile* test result within 7 days aids in selective test use and reduces the costs associated with unnecessary laboratory testing. The study demonstrates a potential for cost savings. Over a 2-year period, they found that 8% of tests were repeated within 7 days of a valid result, with an estimated cost of $61,537.50. Limiting repeat testing within 7 days to only those patients with a history of CDI within the previous 60 days would reduce this cost by ~90%.	Low to moderate	None

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Napierela et al., 2013[24]	PCR testing	Pre/post. The 20-month interval of *C. difficile* toxin A/B EIA testing that directly preceded commencement of *C. difficile* tcdB PCR was reviewed, as well as the first 20 months of PCR testing.	Three hospitals with 166, 538, and 260 beds	All three hospitals experienced significant reductions in healthcare-associated CDI upon introduction of molecular diagnostics ($p \leq 0.05$). Site-specific *C. difficile* testing volume decreased by 32.5–53.9% following implementation of tcdB PCR.	Not provided	These data suggest a strong influence of *C. difficile* toxin testing modality on healthcare-associated CDI. Conversion from *Clostridium difficile* toxin A/B EIA to tcdB PCR for diagnosis of CDI resulted in significant decreases in laboratory testing volume, reducing the workload. There were generally unchanged *C. difficile* toxin detection rates.	Low	None

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Planche et al., 2013[14]	Toxin (cytotoxin assay) testing as a CDI reference method	Prospective, observational multicenter study, cytotoxigenic culture and cytotoxin assays on 12,420 fecal samples in four U.K. laboratories. Also performed tests that represent the three main targets for CDI detection: bacterium (glutamate dehydrogenase), toxins, or toxin genes. Use of routine blood test results, length of hospital stay, and 30-day mortality to clinically validate the reference methods. Data were categorized by reference method result.	Four U.K. laboratories	A multivariate analysis accounting for potential confounders confirmed the mortality differences between groups 1 and 3 (odds ratio 1.61, 95% CI, 1.12 to 2.31). Multistage algorithms performed better than did standalone assays. In more than 6,000 patients with diarrhea, no increase in mortality occurred when a toxigenic *C. difficile* strain alone was present (cytotoxigenic culture positive, cell cytotoxin assay negative). By contrast, toxin (cell cytotoxin assay) positivity was associated with clinical outcome. Other clinical indicators were worse for cell cytotoxin assay-positive cases, but no difference was noted between cytotoxigenic culture-positive, cell cytotoxin assay-negative cases, and negative controls.	Not provided	Researchers found that toxin (cell cytotoxin assay) positivity was associated with clinical outcome and state that this reference method (of the three groups) best defines true cases of *C. difficile* infection. A positive cell cytotoxin assay indicates that the diarrhea was probably caused by CDI infection, whereas a positive cytotoxigenic culture indicates that a patient could be infectious even though the diarrhea might have resulted from another cause. A new diagnostic category of potential *C. difficile* excretor (cytotoxigenic culture positive but cytotoxin assay negative) could be used to characterize patients with diarrhea that is probably not due to *C. difficile* infection.	Low	Highly technical. Article looks at predictor of disease severity. Background: Cytotoxigenic culture detects toxigenic CDI and gives a positive result more frequently (because of colonization, which means that individuals can have the bacterium but no free toxin) than does the cytotoxin assay, which detects preformed toxin in feces.

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Reigadas et al., 2015[27]	Systematic testing of diarrheal stool for CDI regardless of clinician request	Prospective study in which systematic testing for toxigenic *C. difficile* on all diarrheic stool samples was performed regardless of the clinician's request. A total of 3,673 unformed stool samples from patients age >2 years was processed for detection of toxigenic *C. difficile*.	A 1,550-bed hospital	Testing found 249 episodes of CDI. Of these, 45 episodes (18.1%) were excluded because they did not fulfill the criteria for diarrhea (3 unformed stools/24 h). Therefore, 204 CDI episodes met the inclusion criteria (CDI episodes in patients age >2 years); of these, 178 had raised clinical suspicion and 26 (12.7%) had no clinical request for toxigenic *C. difficile* testing. Community-acquired cases and young age were risk factors for clinical underdiagnosis.	Not provided	The introduction of a systematic search for toxigenic *C. difficile* in all diarrheic stools arriving at a microbiology laboratory reveals a significant proportion of unsuspected cases and provides a more complete picture of the situation of CDI in a nonselected population. The main risk factors for lack of clinical suspicion were community-associated CDI and young age. In this study, 31.4% of CDI patients had not previously received antibiotics.	Low to moderate	None

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Saab et al., 2015[33]	CDI screening of hospitalized patients with cirrhosis	A Markov model was used to compare costs and outcomes of two strategies for the screening of CDI. The first strategy consisted of screening all patients for CDI and treating if detected (screening). In the second strategy, only patients found to have symptomatic CDI were treated (no screening).	Hospital simulation	The results of the model showed that screening for CDI was consistently associated with improved healthcare outcomes and decreased healthcare use across all variables in the one- and two-way sensitivity analyses. Using baseline assumptions, the costs associated with the no-screening strategy were 3.54 times those of the screening strategy. Moreover, the mortality for symptomatic CDI was lower in the screening strategy than the no-screening strategy.	Not provided	Evidence demonstrated that cirrhotic patients may be particularly affected by CDI. The results of the study showed that screening and treating *C. difficile* in asymptomatic patients are not cost effective but cost saving.	Moderate	None

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Schroeder et al., 2014[43]	PCR or GDH plus on-demand PCR as most cost-effective diagnostic strategies	Decision analysis from the hospital perspective to compare multiple CDI testing algorithms for adult inpatients with suspected CDI, assuming patient management according to laboratory results; 10,000 symptomatic adults	Hospital simulation	A cost-benefit analysis (including estimated costs of missed cases) favored standalone on-demand PCR (vs. batch PCR) in most settings but favored on-demand PCR preceded by lateral-flow testing if a missed CDI case resulted in less than $5,000 of extended hospital stay costs and <2 transmissions, if lateral-flow GDH diagnostic sensitivity was >93% or if the symptomatic carrier proportion among the toxigenic culture-positive cases was >80%. These results can aid guideline developers and laboratory directors who are considering rapid testing algorithms for diagnosing CDI.	Not provided	This economic evaluation found that rapid testing is likely to be cost saving and more effective relative to the other technologies. Under most reasonable scenarios, standalone on-demand PCR as a one-step test is the strategy that minimizes false-negative results and costs to the healthcare system. However, where costs of a missed CDI diagnosis are minimal, where lateral-flow GDH/on-demand PCR or lateral-flow GDH-Tox/on-demand PCR can be performed with high diagnostic sensitivity, or where the symptomatic carrier proportion is high, testing with lateral-flow GDH or lateral-flow GDH-Tox before on-demand PCR is a justifiable option.	Moderate	None

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Silva et al., 2017[28]	PCR testing *plus* clinical assessment to diagnose CDI	A matched case-control study was conducted on inpatients in a tertiary care center. The first 50 patients with diarrhea and a positive PCR were identified as cases. Control patients were hospitalized patients receiving antibiotics, but with no diarrhea, housed in a room as close as possible to each case during the same admission time. A convenience sample of healthcare workers who cared for *C. difficile*-infected patients was also tested.	A tertiary care center. a 670-bed facility in the city of Sao Paulo, Brazil	There were two positive PCR results for *C. difficile* in controls (4.1%). None of the healthcare workers were positive for *C. difficile* by PCR. There was no difference between groups with respect to overall antibiotic use before the requested PCR for *C. difficile* (p=0.359). Most cases had a high proportion of gastrointestinal disorders (71.4%) compared with control (8.2%), p<0.001.	Not provided	The only non-antimicrobial predictor for CDI was gastrointestinal symptoms (p<0.001). Recommend assessing patients for diarrhea and interpreting laboratory results considering the clinical setting and the likelihood of other etiologies. The significance of a positive PCR result creates difficulties for clinical interpretation, due to the large number of positive tests from individuals without disease. According to the study, the use of molecular tests alone to diagnose CDI, without the toxin or host response tests, will likely lead to an excessive number of positively diagnosed cases, excessive treatment, and increased healthcare costs.	Low to moderate	Background: The diagnosis of CDI increases concern that asymptomatic carriers of toxigenic *C. difficile* may be diagnosed with CDI.

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Stites et al., 2016[46]	A predictive model that identifies patients at high risk for CDI at the time of hospitalization. This approach to early identification was evaluated to determine if it could improve upon a pre-existing antimicrobial stewardship (AMS) program. The hospital's AMS program was administered as part of routine care, consistent with the guidelines of the Infectious Diseases Society of America.	Logistic regression and ROC curve analyses were used to develop an analytic model to predict risk for CDI at the time of hospitalization in a retrospective cohort of inpatients. The model was validated in a prospective cohort. Concurrence between the model's risk predictions and a pre-existing AMS program was assessed. This cohort study analyzed electronic medical record (EMR) data from 42,120 patient admissions retrospectively in 2014, and prospectively for 10,990 admissions between July and September 2015.	A large safety-net hospital in Philadelphia, PA (inner city)	The model identified 55% of patients who later tested positive as being at high risk for CDI at the time of admission. One in every 32 high-risk patients with potentially modifiable antimicrobial risk factors tested positive for CDI. Half (53%) tested positive before meeting the risk criteria for the hospital's AMS program (c-statistic 0.77, 95% CI, 0.69 to 0.84). The model was faster than the AMS program. One in four patients in the highest risk category at the time of admission later experienced one or more of the AMS program antimicrobial risk factors during hospitalization. Approximately half (53%) tested positive after being identified by the PIPAR model but before meeting the criteria for the AMS program. All results were similar in the prospective cohort.	Over half of the patients who tested positive (55%) were identified at the time of admission by the PIPAR model as "very high risk" (highest of six categories). Approximately 2 in every 100 of these patients tested positive for CDI while hospitalized. (Thus, almost half were not identified as the highest risk, although still more accurate and timely than the existing system.)	Identification of patients predisposed to CDI at the time of admission would allow the AMS program to target high-risk patients earlier than current standard practice, which relies on retrospective chart reviews, and to use multiple strategies. By using the risk data to identify patients proactively, the AMS program could implement a prospective control system to ensure that antimicrobial therapy is appropriate at the time of initiation, including choice of agent, dose, and duration.	Low	Testing criteria: The laboratory only tested samples from patients with more than three liquid stools within a 24-hour period.

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Tabak et al, 2015[47]	An HO-CDI predictive model using electronic health records clinical data present at time of admission	Retrospective data analysis of 78,080 adults discharged from six acute care hospitals between January 1, 2007, and June 30, 2008; 323 HO-CDI cases (including 310 nonrecurrent and 13 recurrent CDIs) were identified. A logistic regression model to predict the risk of HO CDI and validation of the model using 1,000 bootstrap simulations.	Six U.S. acute care hospitals	About 21% patients within the higher risk strata accounted for 65% of all HO-CDI cases. The logistic regression model yielded 14 independent predictors, including hospital community-onset CDI pressure, patient age ≥65, previous healthcare exposures, CDI in previous admission, admission to the ICU, albumin ≤3 g/dL, creatinine >2.0 mg/dL, bands >32%, platelets ≤150 or >420 10^9/L, and WBC >11,000 mm3. The model had a c-statistic of 0.78 (95% CI, 0.76 to 0.81) with good calibration. For 79% of patients with risk score of 0–7, there were 19 HO CDIs per 10,000 admissions; for patients with risk score of 20+, there were 623 HO CDIs per 10, 000 admissions (p<0.0001)	Not provided	Using clinical parameters available at the time of admission, this HO-CDI model displayed good predictive ability. It may have utility as an early risk identification tool for HO-CDI preventive interventions and outcome comparisons. Application of the risk score needs to be tested prospectively, preferably in hospitals with advanced electronic health records. The number needed to treat with an intervention to prevent one case of HO CDI will be required to determine the overall cost-effectiveness of the tool.	Low	There are risk factors due to the care process (e.g., hospital antimicrobial exposure) but also those present on admission. The researcher asserted that on-admission risk stratification may help with prevention.

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting:	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/Findings	Risk of Bias (High, Moderate, Low)	Comments
Van Beurden et al., 2017[62]	Three published prediction tools for patients at risk of a complicated course of CDI. The three models were from: Hensgens (2014), Na (2015), and Welfare (2011). A course of CDI was considered complicated if any of the following criteria were met within 30 days after the diagnosis of CDI: (1) death as a direct or indirect consequence of CDI, (2) admission to the ICU for treatment of CDI or its complications, (3) surgery (colectomy) for toxic megacolon, perforation or refractory colitis.	The validation cohort comprised 148 patients diagnosed with CDI between May 2013 and March 2014. During this period, 70 endemic cases of CDI occurred as well as 78 cases of CDI related to an outbreak of *C. difficile* ribotype 027. Model calibration and discrimination were assessed for the three prediction rules. To quantify how close predictions are to the actual outcome (calibration), the authors plotted the observed number of complicated cases against the predicted number of complicated CDI courses in the simplified risk categories provided by the original studies.	A 750-bed tertiary care center in Amsterdam	For those patients diagnosed with CDI due to nonoutbreak strains, the prediction model developed by Hensgens performed the best, with an AUC of 0.78. For entire cohort, AUC was 0.68. This prediction model can therefore be used in an endemic setting to identify patients at risk for CDI complications, aiding clinicians in deciding which patients to monitor closely for CDI-related complications. In conclusion, the study shows that a prediction rule can only be used in a cohort comparable with the derivation cohort.	The performance of all three prediction models was poor when applied to the total validation cohort with an estimated AUC of 0.68 for the Hensgens model, 0.54 for the Na model, and 0.61 for the Welfare model.	Early identification of patients at risk of a complicated course or death could help clinicians inform patients and might help doctors guide antibiotic treatment. All three prediction models performed poorly when validated using the total cohort, which included CDI cases from an outbreak as well as endemic cases. The prediction model of Hensgens performed relatively well for patients diagnosed with CDI due to nonoutbreak strains, and this model may be useful in endemic settings.	Low to moderate	Search of PubMed and Embase for studies on prediction tools for a severe or complicated course of CDI up to February 2016 (Appendix A). Selected studies that (1) predicted at least one relevant outcome (i.e., severity, complications, mortality) and (2) developed a prediction model or risk score.

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting:	Outcomes: Benefits	Outcomes: Harms	Implementation Themes/Findings	Risk of Bias (High, Moderate, Low)	Comments
Van der Wilden, 2014[49]	A risk scoring system (RSS) for patients at risk of developing fCDC (fulminant *C. difficile* colitis)	All patients (746) with *C. difficile* colitis admitted to Massachusetts General Hospital were prospectively enrolled in a specific database aiming to collect data on *C. difficile* infections. Various criteria/weighted risk factors were collected. Univariate analysis was performed to compare patients with and without fCDC.	Massachusetts General Hospital	The RSS successfully discriminates patients with *C. difficile* infection from those who have fCDC (AUC, 0.98). Calibration was low (Brier score of 0.019), indicating that the possibility of developing fCDC could be estimated accurately. A cutoff of 6 points was used to divide patients at high risk of developing fCDC, which classified 97.9% of patients correctly. In combination with a high specificity (88.4%) and excellent negative predictive value (99.8%), this scoring system proved it has the potential to be used at the bedside in order to safely rule out the possibility of fCDC.	The positive predictive value of 36.7% is low and should be considered against the background of its estimation in a low-prevalence setting (6.4% of total cohort was diagnosed with fCDC).	The researchers believe that the next step would be to externally validate the RSS to allow widespread implementation.	Moderate	The RSS included four variables: Age >70 years, WBC ≥20.000/µL or ≤2,000/µL, cardiorespiratory failure (defined as CDC-related vasopressor and/or mechanical ventilation requirement), and diffuse abdominal tenderness on physical exam.

Table B.10: Clostridioides *difficile*, Testing–Systematic Reviews

Note: Full references are available in the Section 4.5 reference list.

Author, Year	Description of Patient Safety Practice	Setting/s, Population/s	Summary of Systematic Review Findings	Implementation Themes/Findings	Notes
Bagdasarian et al., 2015[25]	Test only symptomatic patients. Multistep algorithms using polymerase chain reaction (PCR) for the toxin genes or single-step PCR on liquid stool samples have the best test performance characteristics.	Healthcare general; adults	Review of articles published between January 1978 and October 31, 2014. Recommendations include that CDI diagnosis requires presence of diarrhea (3 unformed stools in 24 hours) or radiographic evidence of ileus or toxic megacolon; and a positive stool test result for toxigenic *C. difficile* or its toxins, or colonoscopic or histopathologic evidence of pseudomembranous colitis. Diagnostic testing for CDI should be performed only in symptomatic patients. Laboratory testing cannot distinguish between asymptomatic colonization and symptomatic infection with *C. difficile*. The gold standard for detecting toxigenic *C. difficile* in stool is toxigenic culture; however, this method is time intensive and requires specialized equipment and personnel. Diagnostic approaches are complex due to the availability of multiple testing strategies. Multistep algorithms using PCR for the toxin genes or single-step PCR on liquid stool samples have the best test performance characteristics (for multistep, sensitivity was 0.68–1.00 and specificity was 0.92–1.00; for single step, sensitivity was 0.86–0.92 and specificity was 0.94–0.97). In one study, 56% of patients who responded to treatment asymptomatically shed *C. difficile* spores for as many as 6 weeks. Thus, a test of cure is not recommended.	Test only symptomatic patients. Laboratory testing cannot distinguish between colonization and infection. Diagnostic testing strategies for CDI vary. Multistep approaches using PCR for the toxin genes or single-step PCR on liquid stool samples have the highest sensitivity and specificity. Test of cure is not recommended after CDI treatment.	Article is also a review of treatment practices.

Author, Year	Description of Patient Safety Practice	Setting/s, Population/s	Summary of Systematic Review Findings	Implementation Themes/Findings	Notes
Butler et al., 2017[28]	Early diagnosis of CDI; diagnostic testing methods	Adult patients	Review of four databases from 2010 through April 2015 plus reference lists of included studies and recent systematic reviews. Included 37 studies on diagnostic tests. Research on diagnostic testing for and interventions to treat CDI expanded considerably in 4 years. High-strength evidence showed that nucleic amplification tests were sensitive and specific for CDI when using culture as the reference standard. Clinicians are not always well informed on the best diagnostic test to use, the operating characteristics of the tests used in their practice setting, or the relatively low likelihood of a false-negative result (e.g., evidence suggests retesting with the same test is common practice, yet not recommended).	NAATs are sensitive and specific; tests for toxin A/B are insensitive and specific; tests for GDH are sensitive but less specific; multistep steps are insensitive but specific.	Review provides pooled sensitivities, specificities, positive likelihood ratios and negative likelihood ratios, and 95% CIs for each class of tests. Also a review of prevention and treatment.

Author, Year	Description of Patient Safety Practice	Setting/s, Population/s	Summary of Systematic Review Findings	Implementation Themes/Findings	Notes
Crobach et al., 2016[4]	Diagnostic testing methods and criteria	Adult patients	Review/meta-analysis by the European Society of Microbiology and Infectious Diseases. Searched four databases for articles published between 2009 and June 2014. A total of 56 studies (15 from the previous meta-analysis and 41 published since 2009) were included in the meta-analysis. Toxin A/B EIAs tended to be the most specific assays, while GDH EIAs and NAATs were more sensitive tests. Although many toxin A/B EIAs belong to the least sensitive tests, the sensitivity of this category of assays is not as low as reported earlier. Different reference tests provide different results since each test has different targets. A rapid CDI diagnosis is associated with more prompt CDI treatment and fewer unnecessarily treated patients. However, two problems arise: First, the positive predictive values (PPVs) of even the most specific tests are inadequate at low disease prevalence. Second, as the targets identified by the index tests are (just like the targets of the reference test) different from each other, a positive index test does not necessarily indicate a real CDI case. Recommend a two-step algorithm—tests can be combined in such a way that the percentage of false-positive results can be decreased. After application of a first sensitive test (GDH EIA or NAAT), the toxin A/B EIA can then be performed as a second step on all samples that tested positive by NAAT or GDH EIA. Samples with a positive second test result can be classified as CDI likely to be present. However, samples with a first positive test result but a negative toxin A/B EIA need to be clinically evaluated.	According to the review, no single commercial test can be used as a standalone test for diagnosing CDI as a result of inadequate PPVs at low CDI prevalence. Therefore, the use of a two-step algorithm is recommended. Samples without free toxin detected by toxins A and B EIA but with positive GDH EIA, NAAT, or toxigenic culture (TC) results need clinical evaluation to discern CDI from asymptomatic carriage.	Review provides pooled sensitivities, specificities, PPV and negative predictive value, and 95% CIs for each class of tests.

Author, Year	Description of Patient Safety Practice	Setting/s, Population/s	Summary of Systematic Review Findings	Implementation Themes/Findings	Notes
Furuya-Kanamori et al., 2015[15]	Enhanced IPC for those at high risk for asymptomatic CDI; no active screening for asymptomatic *C. difficile* patients	Asymptomatic *C. difficile* colonized patients; healthcare settings	A narrative review was performed in PubMed for articles published from January 1980 to February 2015 using search terms "*Clostridium difficile*" and "colonization" or "colonisation" or "carriage." The review explores information about the definition, epidemiology, and biology of asymptomatic CDI colonization. The authors found there is no consistent definition for asymptomatic *C. difficile* colonization. Due to the findings, they agree with the guidelines not to perform active screening for asymptomatic *C. difficile* colonization for infection control purposes. Given the transmission potential of asymptomatic *C. difficile*-colonized patients, the increased prevalence among certain clinical groups, limited management options, and the limited utility of screening, instead, intensive infection control practices, normally reserved for diseased patients, should be targeted at individuals or clinical areas with higher risk of asymptomatic *C. difficile* colonization. Empirical research should be conducted into the impact of targeted, risk-based, intensive infection control programs before changes to the current SHEA guidelines for asymptomatic *C. difficile* colonized patients are considered.	Recommends: Intensive infection control practices (e.g., gloves and environmental cleaning), normally reserved for diseased patients, should be targeted at individuals or clinical areas with higher risk of asymptomatic *C. difficile* colonization. A standard definition for asymptomatic *C. difficile* colonization is needed. Suggest that patients with diarrheal symptoms with nontoxigenic strains of *C. difficile* should be considered colonized unless there is definitive evidence of disease. Estimates of asymptomatic colonization may be too low as stool culture is not practical in a clinical setting; however, this constitutes important future epidemiological study.	Review is mostly about the epidemiology, risk factors, transmission, toxin production, and duration of asymptomatic CDI. Article does address whether to test for asymptomatic colonization.

Author, Year	Description of Patient Safety Practice	Setting/s, Population/s	Summary of Systematic Review Findings	Implementation Themes/Findings	Notes
Marra and Ng, 2015[16]	Diagnostic testing for *C. difficile*: PCR or a two-step algorithm to improve sensitivity and specificity.	Not specified	A search for systematic reviews, clinical practice guidelines, and randomized control trials (RCTs) was conducted on articles going back to 1966. Article discusses findings for different testing methods, when to test, risk factors, epidemiology, and treatment of *C. difficile*. Each testing method has pros and cons in terms of time to conduct test, availability, and sensitivity and specificity. The stool culture test, also known as the cell culture cytotoxicity neutralization assay (CCCNA), has high sensitivity but is labor intensive and time consuming, taking 48–96 hours for results, and is not very specific. Using a procedure known as TC can overcome this problem by placing stool in a culture medium and then testing isolates with an immunoassay designed to detect toxin production. Compared with CCCNA, TC has a sensitivity of 67% to 79% but is too slow to be clinically useful (taking 4–7 days to obtain results). Enzyme immunoassays are fast and inexpensive but insensitive and not very specific. It is unclear where exactly PCR should be used; some laboratories are using it as a standalone test, while American College of Gastroenterology guidelines suggest it should be used as a confirmatory test. CDI testing algorithms suggest using GDH as the initial screening test, followed either by NAAT such as PCR or by EIA testing for GDH-positive specimens only. Only GDH-positive specimens undergo additional testing. The use of PCR has rapid turnaround to detect the gene for toxin production (tcdB gene) is promising as a standalone test for CDI but and has a rapid turnaround but costs 510 times more than EIA.	Diagnostic testing for CDI is in a state of flux. Review found that recent evidence and guidelines are suggesting a two- or three-step algorithmic approach to improve specificity and PPV. A few days may be necessary before confirmatory tests become available. Therefore, it is paramount that when CDI is suspected, appropriate antimicrobial therapy is initiated without delay and is reassessed once the laboratory testing is complete.	The objectives of this review are: to review the incidence of *C. difficile* infections around the world.

Author, Year	Description of Patient Safety Practice	Setting/s, Population/s	Summary of Systematic Review Findings	Implementation Themes/Findings	Notes
O'Horo et al., 2012[34]	Two rapid molecular diagnostic techniques, PCR and loop-mediated isothermal amplification (LAMP)	Healthcare general	Systematic review and meta-analysis. Search yielded 25 PCR studies, including 11,801 samples that met inclusion criteria and 6 heterogeneous studies that evaluated LAMP. For PCR, with TC as a standard, pooled sensitivity was 0.92 (95% CI, 0.91 to 0.94); specificity, 0.94 (95% CI, 0.94 to 0.95); and diagnostic odds ratio, 378 (95% CI, 260 to 547). With cytotoxicity as a standard, pooled sensitivity was 0.87 (95% CI, 0.84 to 0.90); specificity, 0.97 (95% CI, 0.97 to 0.98); and diagnostic odds ratio, 370 (95% CI, 226 to 606). The six studies about LAMP used heterogeneous reference methods.	Review found that PCR is a highly accurate test for identifying CDI. Likelihood ratios, in particular when compared with a TC reference standard, indicate that the test is useful in determining post-test probability of CDI. Heterogeneity in LAMP studies did not allow meta-analysis; however, further research into this promising method is warranted.	None
Wei et al., 2015[37]	LAMP for the diagnosis of CDI	Healthcare general	Meta-analysis of studies on accuracy of LAMP for diagnosing CDI. Search of four databases up to February 2014. Nine studies met inclusion criteria for the present meta-analysis. The pooled sensitivities and specificities for diagnosing CDI were 0.93 (95% CI, 0.91 to 0.95) and 0.98 (95% CI, 0.98 to 0.99), respectively. The positive likelihood ratio was 47.72 (95% CI, 15.10 to 150.82), negative likelihood ratio was 0.07 (95% CI, 0.04 to 0.14), and diagnostic odds ratio was 745.19 (95% CI, 229.30 to 2421.72). The area under the ROC was 0.98. Meta-regression indicated that the total number of samples was a source of heterogeneity for LAMP in detection of CDI. The funnel plots suggested no publication bias. Compared with other non-culture-based methods, LAMP is a sensitive and specific method, although more expensive than traditional assay. LAMP can be performed in any laboratory without special requirements such as separate pre- and post-PCR rooms, which are necessary for real-time PCR or other PCR-based techniques, and LAMP cost-efficiency ($26) compared with the Xpert *C. difficile* assay ($46).	The LAMP test meets the minimum desirable characteristics of a diagnostic test of sensitivities and specificities, as well as other measures of accuracy in the diagnosis of CDI, and it is suitable as a rapid, effective, and reliable standalone diagnostic test, potentially decreasing morbidity and nosocomial spread of CDI.	None

Table B.11: Clostridioides difficile, Multicomponent Interventions–Single Studies

Note: Full references are available in the Section 4.6 reference list.

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcome: Harms	Implementation Themes/Findings	Risk of Bias (High, moderate, Low)	Comments
Abbett et al., 2009[4]	The intervention included three components: an educational campaign, a prevention bundle, and a treatment bundle. The prevention checklist included: testing on suspected CDI, discontinuation of nonessential antimicrobials, contact precautions, hand hygiene reminders, dedicated stethoscope, flagging/ communication (sign on patients' doors, communication to team), isolation, terminal bleach cleaning for CDI rooms, and confirmation with supervisor that bleach cleaning was used. Guidelines were from Infectious Diseases Society of America and Society for Healthcare Epidemiology of America (IDSA/SHEA).	Observational before-and-after study of adult patients admitted to a tertiary care, university-affiliated hospital from January 2004 through December 2008. Followed patients for a total of 1,047,849 patient-days.	A 750-bed tertiary care, university-affiliated hospital, United States	Four years of data. Healthcare-associated CDI incidence rates fell from an average of 1.10 cases per 1,000 patient-days (95% confidence interval [CI], 1.00 to 1.21) before intervention to 0.66 cases per 1,000 patient days (95% CI, 0.60 to 0.72) after intervention. This statistically significant decrease amounts to a 40% reduction in incidence after the intervention. The decreasing rates of CDI noted after the implementation are even more striking because of the more complete ascertainment of cases of CDI that would be expected with an increased frequency of *C. difficile* toxin testing. No changes in chance of mortality.	Number of *C. difficile* toxin tests sent to the microbiology laboratory increased significantly from the pre-intervention period (rate, 28.0 tests per 1,000 patient-days [95% CI, 27.5 to 28.5]) to the post-intervention period (rate, 32.1 tests per 1,000 patient-days [95% CI,31.7–32.6]).	The intervention did not include antimicrobial stewardship, citing resource intensiveness of this PSP. Bundle delineated individual responsibilities for physicians, physician assistants, nurse practitioners, floor nurses, microbiology staff, infection control practitioners, and environmental services personnel. The bundle begins with "provider suspicion," which is defined as the ordering of a stool *C. difficile* toxin test. Intervention relied on increasing provider suspicion for CDI. Authors report that providers may be under pressure from payers who may no longer reimburse for cases of CDI and other healthcare-associated infections, and may be pushed to limit toxin testing and other documentation of CDI. Researchers suggest use of checklists to increase/measure compliance.	Low to moderate	Cost-effectiveness not measured

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcome: Harms	Implementation Themes/Findings	Risk of Bias (High, moderate, Low)	Comments
Barker et al., 2017[1]	Eight multiple-intervention bundles at reducing hospital-onset (HO) CDI and asymptomatic *C. difficile* colonization	An agent-based model of *C. difficile* transmission in a 200-bed adult hospital using studies from the literature, supplemented with primary data collection. The model includes an environmental component and four distinct agent types: patients, visitors, nurses, and physicians. Each model run simulates a 1-year period.	Simulated 200-bed adult hospital	Daily cleaning with sporicidal disinfectant and *C. difficile* screening at admission were the most effective single-intervention strategies, reducing HO CDI by 68.9% and 35.7%, respectively (both p <0.001). Combining these interventions into a two-intervention bundle reduced HO CDI by 82.3% and asymptomatic hospital-onset colonization by 90.6% (both, p <0.001). Adding patient hand hygiene to healthcare worker hand hygiene reduced HO CDI rates an additional 7.9%.	Visitor hand hygiene and contact precaution interventions did not reduce HO CDI compared with baseline. Excluding those strategies, healthcare worker contact precautions were the least effective intervention at reducing hospital-onset colonization and infection.	Article concludes that identifying and managing the vast hospital reservoir of asymptomatic *C. difficile* by screening and daily cleaning with sporicidal disinfectant are high-yield strategies. These findings provide data regarding which interventions to prioritize for optimal *C. difficile* control. The optimal bundle for CDI prevention is unknown, which hinders CDI prevention. Computer simulation modeling can allow examination of counterfactual scenarios that can identify the isolated effects of individual interventions to reduce CDI. Agent-based models can account for the indirect effects and underlying complexity of hospital infection control dynamics.	Moderate	Study also examined nine single interventions.
Brakovich et al., 2013[5]	A tiered approach that included environmental cleaning and disinfection, diagnostics and surveillance, contact isolation, contact precautions, hand hygiene (soap and water) for CDI	Pre/post-intervention measurements. Patients are admitted from surrounding hospitals, have an expected stay of at least 25 days, and are acutely ill. Most of the	A 50-bed long-term acute-care hospital (LTACH) in the southeastern United States	Based on year-end results, the facility achieved a 27.61% decrease in the CDI rate. Over the course of 2 years, the CDI rate decreased 44.25%. The program was cost efficient barring the contract for the decontamination service.	Not provided	Researchers believed that training for environmental services was crucial. They also noted the development of a cleaning checklist and use of HPV for disinfection of rooms occupied by patients with CDI. Isolation signs for patient doors were redesigned to include guidelines for staff	Low to moderate	Ventilated patients, patients requiring extended intravenous antibiotic therapy, and medically complex patients make up the

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcome: Harms	Implementation Themes/Findings	Risk of Bias (High, moderate, Low)	Comments
	patients, and antibiotic stewardship. Approach was based on the IDSA/SHEA guidelines.	patient population is ventilator dependent, immune compromised, and treated with antimicrobials.		The hydrogen peroxide vapor (HPV) equipment and services contracted by the facility incurred the cost of $1,800 per month. This cost included decontamination of all rooms previously occupied by patients with CDI. The cost of microfiber mops and environmental services staff education was approximately $650.		and families on appropriate isolation attire. Strict adherence to hand hygiene, which included washing with soap and water while applying friction, was strongly enforced and hand sanitizers were removed from patient rooms. Use of Interdisciplinary team. Researchers emphasized importance of surveillance, ongoing education, and reinforcement of intervention during daily meetings.		population of an LTACH.
Cheng et al., 2015[3]	Education, monitoring hand hygiene, antimicrobial stewardship, dedicated medical equipment, and items such as bedpans and commodes. Hand washing with soap and water was the preferred method of hand hygiene after caring for patients with CDI. The patient's room was cleaned at least twice daily with sodium hypochlorite 1,000 ppm. Cleaning staff were trained on high-touch surfaces. Terminal cleaning of the patient's room for	Pre/post-observational study of 329 patients with healthcare-associated CDI	A university-affiliated acute hospital and three extended-care hospitals with a total of 3,200 beds, Hong Kong	The incidence rates of HA CDI per 10,000 admissions and 10,000 patient-days increased significantly by 15.3% and 17.0%, respectively, per quarter ($p<0.001$) from 2008 1Q to 2010 1Q by segmented Poisson regression. Coincident with the promotion of hand hygiene using alcohol-based hand rubs (ABHRs), the overall compliance of hand hygiene increased from 57.8% (2008) to 78.6% (2012), while the proportion of hand washing using soap and water gradually decreased from 19.0% (2008) to 13.3% (2012).	Not provided	More about the intervention: Cleaning staff were trained for 20 minutes with specific emphasis on the meticulous disinfection of high-touch areas, such as bedrail, bedside table, and locker. Education health talks were given to infection control-linked persons and ward staff four times a year. The compliance of hand hygiene of healthcare workers was monitored. Three or more CDI patients epidemiologically linked to the same ward were identified. An antibiotic stewardship program was maintained throughout the study	Low to moderate	None

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcome: Harms	Implementation Themes/Findings	Risk of Bias (High, moderate, Low)	Comments
	30 minutes and change of curtains.			The consumption of broad-spectrum antibiotics presented as divided daily dose per 1,000 acute bed-day occupancy was 140.9 and 152.3 per quarter before and after infection control interventions, respectively.		period. The consumption of broad-spectrum antibiotics was monitored.		
Koll et al., 2014[9]	Collaborative intervention, interdisciplinary teams, environmental cleaning, data reports, checklists, contact precaution for all patients with diarrhea, personal protective equipment readily available and used, adherence to hand hygiene protocol, dedicated rectal thermometers, private room for CDI (confirmed or suspected), patient cohorting, if private room unavailable, as a last option, dedicated bathroom for CDI patients in a shared room with non-CDI patient	Quasi-experimental pre-post. Data were collected monthly from March 2008 to December 2009. Hospitals collected and reported total patient days and discharges, as well as 14 patient-level data elements for each CDI case. Data were received for 14,591 cases of CDI.	35 acute care hospitals in the New York metropolitan region. Mostly teaching hospitals.	Before data collection, 52% of hospitals measured and monitored prevention practices. The mean reported compliance with the prevention bundle was 95%; the mean compliance reported for the environmental cleaning protocol was 96%. There was a pronounced downward trend in the hospital-onset (HO)-CDI rate from ~13.5 per 10,000 patient-days to ~8.2 per 10,000-patient days (no exact figure given) based on the chart. A regression analysis demonstrated that the predicted HO reduction over time was significant over the course of the project ($p<0.001$). Hospitals reporting the highest CDI rates at the project's beginning	Not provided	Study reports that implementing interventions to interrupt and prevent *C. difficile* transmission may be more successful regionally than at individual hospitals because existing evidence suggests community and regional factors, including transferring patients between healthcare facilities, contributes to the epidemiology of *C. difficile*. In the intervention, hospitals were asked to establish an internal interdisciplinary team to drive CDI reduction efforts that comprised, at a minimum, infection preventionists, physician and nurse champions, support staff from environmental and transport services, and quality improvement personnel. Hospitals received monthly data reports to monitor	Low	Weakness: no control group, inconsistencies in implementation across hospitals. Strength: large sample.

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcome: Harms	Implementation Themes/Findings	Risk of Bias (High, moderate, Low)	Comments
				generally demonstrated the greatest reductions.		performance changes over time.		
Power et al., 2010[6]	Enhanced cleaning, hand hygiene audits, education, antimicrobial stewardship	Interrupted time series in five collaborative wards (intervention group) and 35 non-collaborative wards (control group)	An 850-bed university teaching hospital, United Kingdom	At baseline, the non-collaborative wards had 1.15 (95% CI, 1.03 to 1.29) cases per 1,000 occupied bed days. In August 2007, cases decreased 56% from baseline (0.51, 95% CI, 0.44 to 0.60), which has been maintained since that time. In the collaborative wards, there were 2.60 (95% CI 2.11 to 3.17) cases per 1,000 occupied bed days at baseline. A shift occurred in April 2007, representing a reduction of 73% (0.69, 95% CI, 0.50 to 0.91) from baseline, which has been maintained.	Not provided	Study found that a collaborative learning model can enable teams to test and implement changes that can accelerate, amplify, and sustain control of *C. difficile*. Teams worked together over a 9-month period (mid-March to mid-December 2007). They attended learning sessions, which provided instruction in the theory and practice of improvement, participated in action periods in which they tested changes. During the 6 months that predated the collaborative, changes were made to infection control throughout the hospital. These included the introduction of a rapid response cleaning team, a deep clean program, and a focus on hand hygiene and uniform protocols.	Low	Context: 2006, Salford Royal had 350 cases of CDI in patients over 65, the fourth highest rate of infection in northwestern England. In spite of systemwide changes in infection control, infections rose, peaking at 115 cases during the first quarter of 2007.
Price et al., 2010[8]	The initiative introduced had two main components: (1 the opening of an 11-bed cohort ward for patients with CDI and (2) a new antibiotic policy restricting the	A retrospective interrupted time series analysis looking at antibiotic use and number of CDI cases was conducted, with	An 820-bed teaching hospital, United Kingdom	Although the number of CDI cases each month was falling before the intervention, there was a significant increase in the rate of reduction after the intervention from 3% to	Not provided	A demonstration of a statistically robust change in CDI rates after the intervention supports the efficacy of enhanced isolation and antibiotic restriction in reducing CDI. The cohorting ward was	Low to moderate	None

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcome: Harms	Implementation Themes/Findings	Risk of Bias (High, moderate, Low)	Comments
	use of cephalosporins and quinolones	the pre-intervention phase being January to December 2007 and the post-intervention phase being January 2008 to March 2009.		8% per month (0.92, 95% CI, 0.86 to 0.99, p=0.03).		specifically for patients with CDI. Patients testing positive for CDI who still had ongoing diarrhea were transferred to the cohort ward on the same day. The ward had its own nursing staff and all patients admitted to the ward were transferred to the care of the infectious diseases team. All staff working on the ward wore scrubs and put on a new apron and gloves between each patient contact. The new antibiotic policy replaced cephalosporin and quinolone antibiotics with aminopenicillin or antipseudomonal penicillins.		
Salgado et al., 2009[15]	Multicomponent intervention "enhanced infection control measures" (EICM), including placing patients with diarrhea into empiric contact precautions, cleaning with a bleach product in areas with CDI patients, and requiring soap and water hand hygiene. Memos describing EICM were sent to all patient care areas of the hospital and detailed in-services	Pre/post-intervention measurements of CDI rates, amount of antibiotics prescribed, cleaning in areas with CDI patients, and trends in hand hygiene, i.e., washing with soap and water. Time series methodology was used to	A 610-bed, tertiary care, academic institution, South Carolina	During the outbreak (October 2004 to May 2005), the authors observed 144 excess cases of CDI. The CDI rate decreased after EICM were implemented (p<0.0001) and maintained for 36 months beyond the outbreak. The CDI rate decreased significantly over the subsequent 6 months after EICM were implemented (p <.0001). The greatest absolute as well as relative decrease in CDI rates occurred	Not provided	Without instituting a targeted antibiotic control program or any formulary changes, in this case an outbreak of nosocomial CDI was controlled with the use of EICM as recommended by the CDC. This finding may indicate that interruption of patient-to-patient spread can be an effective control measure for CDI. EICM were implemented early in the outbreak. Environmental services employees used a daily checklist to ensure proper	Low to moderate	Only nosocomial CDI rates were measured. Environmental hand hygiene compliance ranges from 62% to 80%. The results of this study would suggest a positive association between hospitalwide CDI rates and

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcome: Harms	Implementation Themes/Findings	Risk of Bias (High, moderate, Low)	Comments
	were conducted in areas with high CDI rates just prior to full implementation. (Historically, patients with diarrhea were routinely placed into contact precautions once they were diagnosed with CDI; hand hygiene and environmental cleaning not discussed or monitored.)	examine the association between CDI and antibiotic use.		over the first 3 months after implementing EICM (a 2.50 per 1,000 patient-days rate decrease and 45.3% decrease, respectively). Measured antibiotic use increased. Multivariate analysis revealed positive associations between CDI rates and cefazolin use (p=0.008) and levofloxacin/gatifloxacin use (p=0.015).		cleaning techniques and use of proper products for patients with epidemiologically important organisms (such as *C. difficile*). To encourage the use of soap and water, signs were posted over the alcohol gel dispensers.		use of some antimicrobials.
Weiss et al., 2009[7]	Dedicated housekeeping for CDI rooms; increase in housekeeping hours, 1:50 mixture of bleach to water, dedicated ward for CDI patients, contact isolation, hand washing out of rooms, limit of one visitor at a time, gloves, patient hand hygiene, prescribing guidelines, rapid enzyme immunoassay for each patient at first liquid stool, hiring of four infection prevention and control experts, staff education, 85 new sinks, no ABHRs when working with CDI patients, surveillance	Five-year (2002 to 2006) prospective observational study; most interventions occurred between years 3 and 4.	A 554-bed acute-care tertiary teaching hospital, Canada	From 2003 to 2004, there were 762 cases of CDI (mean annual rate, 37.28 cases per 1,000 admissions) recorded in the study, compared with the 292 cases of CDI (14.48 cases per 1,000 admissions) from 2006 to 2007 (odds ratio, 0.379, 95% CI, 0.331 to 0.435; p<0.001), a 61% reduction. This finding was comparable to the decreasing rates observed in other Quebec institutions once the provincial government started investing in infection control measures and forced institutions to implement them. Since the implementation of all the measures, there was	Not provided	Outbreak situation. It is difficult to pinpoint a single intervention as the most effective. Simple, low-technology measures such as hand washing with soap and water, environmental cleaning with bleach, and rapid contact isolation of infected patients in a dedicated ward seemed to have an impact on number of CDI cases. With a decreasing number of CDI cases, physicians who were following published evidence-based guidelines started prescribing fluoroquinolones again. The authors report that antibiotic use seems to act more as a triggering factor.	Low	Massive CDI outbreak that affected the province of Quebec mainly from 2002 to 2005.

Author, Year	Description of Patient Safety Practice	Study Design; Sample Size; Patient Population	Setting	Outcomes: Benefits	Outcome: Harms	Implementation Themes/Findings	Risk of Bias (High, moderate, Low)	Comments
				a plateau, with monthly rates usually oscillating between 9 and 14 cases per 1,000 admissions. From 2002-2003 to 2006-2007, there was also a 26.2% increase in the number of hours dedicated to housekeeping, compared with 2003-2004.				
Yakob et al., 2014[2]	Four control methods were explored in this analysis: (1) improved hand hygiene and sanitation; (2) stricter antimicrobial stewardship; (3) reduced length of stay for inpatients; and (4) expedited gut microbiota recovery, which can be achieved either through administering probiotics or through intestinal microbiota transplantation.	Simulation: A biological model of *C. difficile* used to simulate the modern epidemiology of the pathogen; and analysis of control combination. Number of patients in the model is not provided.	Simulated acute healthcare facility	The only combination of methods that provided significant gains in ameliorating CDI incidence was the simultaneous reduction in length of stay and the transmission coefficient. All control methods generated marked improvements in reducing the colonized ratio. Reducing the transmission coefficient through improvements to hygiene and sanitation had a comparatively large effect in decreasing the incidence of disease. Antimicrobial stewardship yielded meager benefits in terms of reducing the incidence of CDI, regardless of combination with other methods.	Not provided	The simulation output agrees in that it also demonstrates an inability to eliminate *C. difficile* from the hospital simply through cessation of within-hospital transmission. However, simulations indicate that under this highly idealized scenario of no within-hospital transmission, closer to 60% of infections can be controlled. More research is needed on different combinations of interventions. The next phase of development for this research is the conversion of the general, strategic framework presented here into a more tactical (idiosyncratic) tool for exploring control options for CDI in a specified healthcare setting.	Moderate	None

Table B.12: Clostridioides *difficile,* Multicomponent Interventions–Systematic Review

Note: Full references are available in the Section 4.6 reference list.

Author, Year	Description of Patient Safety Practice	Setting/s, Population/s	Summary of Systematic Review Findings	Implementation Themes/Findings	Notes
Barker et al., 2017[1]	*C. difficile* prevention bundles	Inpatient/ hospitals in a variety of contexts	Systematic review to examine the components of CDI bundles, their implementation processes, and their impact on CDI rates. Twenty-six studies met inclusion criteria. Despite different settings and the variety of bundle components used, all studies reported an improvement in CDI rates. Implementation and adherence factors to interventions were variably and incompletely reported, making study reproducibility and replicability challenging. Authors noted a lack of randomized controlled trials in the literature, making it unclear if CDI reduction can be attributed to a similar mechanism across all studies. The most common bundle components were: hand hygiene and environmental cleaning—both were included in 88.5% (23/26) of the studies. These were followed by isolation and/or cohorting (77%, 20/26). Contact precautions, antibiotic stewardship, and staff education were each included in 73% (19/26) of studies. System and workflow changes were in 54% (14/26), dedicated equipment, 27% (7/26), patient education, 19% (5/26), and proton pump inhibitor stewardship, 12% (3/26). (Within each category, the interventions were multifaceted.) The improvement was significant at the 0.05 level for the 15 studies reporting p-values (60%, 15/25). Authors concluded that, given the lack of randomized controlled trials in the literature, assessing a causal relationship between bundled interventions and CDI rates is currently impossible. Almost all articles reported measuring adherence for at least one component in the bundle (96.2%, 25/26) and 46.2% measured adherence for each component (12/26). However, most studies only stated that they had evaluated adherence to a bundle component, without reporting compliance results.	In all studies reviewed, bundle implementation was associated with a decline in CDI rates. There was considerable variation among the choice of bundle elements, making it hard to determine which components to implement. Despite the effectiveness of bundles, the authors conclude that there are three potential reasons for a lack of decline in CDI rates in certain hospitals: First, compliance with interventions may be below the threshold necessary to be effective. If adherence to bundle elements was low in the reviewed studies, the potential impact of *C. difficile* bundles may be underestimated. Second is the lack of infection control strategies focusing on asymptomatic carriers. Finally, since ABHRs do not kill CDI spores, hand hygiene compliance data that include the use of pure ABHRs may provide hospitals with an inaccurate assessment of CDI prevention efforts.	Article explores bundles' effectiveness in reducing CDI, issues with studies about bundles, and a discussion of the problem of healthcare workers' implementation of and compliance with bundles. Re: setting: This review draws from a wide range of hospital types, locations, and infection control contexts. Authors state that, since CDI rates improved across all studies despite contextual differences and the variety of bundle components, a tailored bundle approach may be effective.

Author, Year	Description of Patient Safety Practice	Setting/s, Population/s	Summary of Systematic Review Findings	Implementation Themes/Findings	Notes
Louh et al., 2017[13]	Review of interventions to reduce CDI, including bundles	Acute care hospitals	Systematic search for controlled trials of interventions to reduce the rate of CDI in acute care. Review of articles published between January 1, 2009, and August 1, 2015. Overall, 14 studies described the implementation of multiple interventions either simultaneously or sequentially. All found significant reductions in CDI from baseline. However, there was substantial heterogeneity among the studies, with some using concurrent environmental cleaning, which may have affected the results. Most common bundles incorporate two or more of the following: cleaning, isolation, checklists, education, antimicrobial stewardship programs (ASPs), contact precautions and hand hygiene. Bundled interventions with environmental efforts appeared to be more effective than those without them. Several interventions, including disposable thermometers, hand hygiene, universal gloving, and chlorhexidine gluconate bathing, do not need further evaluation and have sufficient evidence to make firm recommendations regarding managing CDI in acute care hospitals. In contrast, there is still much to learn about ASPs given the heterogeneity of study results.	Institutions with few resources should strive to improve environmental practices, with implementation of bleach-based cleaning. Institutions with more resources should consider bundled interventions that incorporate environmental cleaning, restrictive ASPs, and checklists.	Authors found that, in prevention studies performed in acute care hospitals, bleach-based environmental disinfection and bundled interventions appeared to have the most effect in preventing CDI.
Yakob et al., 2014[2]	*C. difficile* control bundles	Healthcare facilities	Search for articles published up to March 2014. Studies eligible for inclusion were those describing patient levels of symptomatic *C. difficile* infection before and after the implementation of multiple, overlapping infection transmission interventions. The relatively few studies detailing a bundle approach to *C. difficile* control indicate substantial reductions in disease incidence in healthcare settings from 33% to 61%. Assessments of these multicomponent interventions cannot partition the level of infection reduction to the individual control methods. Disentangling the efficacies of the different controls when they are used in conjunction is impossible, as is the precise estimation of any synergistic effect between control methods.	Multicomponent interventions appear to be effective. Research into strategic infection control combinations for healthcare-acquired pathogens is underdeveloped and needed to better understand the impact of different combinations of interventions.	None

Appendix C. *Clostridioides difficile* Search Terms

Method	Search	Search String for: CINAHL	Search String for: MEDLINE
Search 2008-Present, English Only MedLine Publication Types: • Clinical Trial • Clinical Trial, Phase I • Clinical Trial, Phase II • Clinical Trial, Phase III • Clinical Trial, Phase IV • Comparative Study • Controlled Clinical Trial • Corrected and Republished Article • Evaluation Studies • Guideline • Journal Article • Meta-Analysis • Multicenter Study • Practice Guideline • Published Erratum • Randomized Controlled Trial • Review • Scientific Integrity Review • Technical Report	Antimicrobial Stewardship	(((MH "Clostridium Difficile" OR "Clostridium Infections" OR "Enterocolitis, Pseudomembranous" OR "Clostridium Infections/PC") OR AB ("Clostridium Difficile Infection" OR "Infections, Clostridium" OR "Antibiotic-Associated Colitis" OR "Clostridium Enterocolitis" OR "Colitis, Pseudomembranous" OR "Pseudomembranous Colitis" OR "Pseudomembranous Enteritis" OR "Pseudomembranous Enterocolitis" OR ("Clostridium Difficile" AND Colonization)) AND ((MH "Antimicrobial Stewardship" OR MH "Antibiotic Stewardship") OR (AB "Antibiotic Prescribing Practices")) AND ((MH Hospitals OR Inpatients OR Outpatients OR "Ambulatory Care Facilities OR "Practitioner's Office" OR "Long Term Care" OR "Palliative Care" OR "Subacute Care" OR "Rehabilitation Centers" OR "Residential Facilities" OR "Transitional Care" OR "Primary Health Care" OR "Home Health Care" OR "Nursing Homes" OR "Surgicenters") OR AB ("Hospital" OR "Inpatient" OR "Ambulatory Care" OR "Ambulatory Care Facilities" OR "Physicians' Offices" OR "Long-Term Care" OR "Long-Term Care Facilities" OR "Palliative Care" OR "Subacute Care" OR "Rehabilitation Centers" OR "Residential Facilities" OR "Transitional Care" OR "Ambulatory Surgery Center" OR "Primary Care" OR "Specialty Care" OR "Home Health")))	(((MH "Clostridium Difficile" OR "Clostridium Infections" OR "Enterocolitis, Pseudomembranous" OR "Clostridium Infections/PC") OR (AB "Clostridium Difficile Infection" OR "Infections, Clostridium" OR "Antibiotic-Associated Colitis" OR "Clostridium Enterocolitis" OR "Colitis, Pseudomembranous" OR "Pseudomembranous Colitis" OR "Pseudomembranous Enteritis" OR "Pseudomembranous Enterocolitis" OR ("Clostridium Difficile" AND Colonization)) AND ((MH "Antimicrobial Stewardship" OR MH "Antibiotic Stewardship") OR (AB "Antibiotic Prescribing Practices")) AND ((MH Hospitals OR Inpatients OR Outpatients OR "Ambulatory Care Facilities OR "Practitioner's Office" OR "Long Term Care" OR "Palliative Care" OR "Subacute Care" OR "Rehabilitation Centers" OR "Residential Facilities" OR "Transitional Care" OR "Primary Health Care" OR "Home Health Care" OR "Nursing Homes" OR "Surgicenters") OR AB ("Hospital" OR "Inpatient" OR "Ambulatory Care" OR "Ambulatory Care Facilities" OR "Physicians' Offices" OR "Long-Term Care" OR "Long-Term Care Facilities" OR "Palliative Care" OR "Subacute Care" OR "Rehabilitation Centers" OR "Residential Facilities" OR "Transitional Care" OR "Ambulatory Surgery Center" OR "Primary Care" OR "Specialty Care" OR "Home Health")))

Method	Search	Search String for: CINAHL	Search String for: MEDLINE
• Twin Study • Validation Studies CINAHL Publication Types: • Clinical Trial • Corrected Article • Journal Article • Meta-Analysis • Meta Synthesis • Practice Guidelines • Randomized Controlled Trial • Research Review • Systematic Review			
Search 2008-Present, English Only MedLine Publication Types: • Clinical Trial • Clinical Trial, Phase I • Clinical Trial, Phase II • Clinical Trial, Phase III • Clinical Trial, Phase IV • Comparative Study	Testing	(((MH "Clostridium Difficile" OR "Clostridium Infections" OR "Enterocolitis, Pseudomembranous") OR (AB "Clostridium Difficile Infection" OR "Infections, Clostridium" OR "Antibiotic-Associated Colitis" OR "Clostridium Enterocolitis" OR "Colitis, Pseudomembranous" OR "Pseudomembranous Colitis" OR "Pseudomembranous Enteritis" OR "Pseudomembranous Enterocolitis" OR ("Clostridium Difficile" AND Colonization)) AND (AB "Diagnostic Test" OR "Testing Algorithms" OR Diagnosis OR "Stool Sampling" OR Technique OR Detection OR "Clinical Laboratory Tests" OR "Laboratory Diagnosis" OR "Clinical Laboratory Techniques" OR "Screening" OR "Diagnostic Testing" OR	(((MH "Clostridium Difficile" OR "Clostridium Infections" OR "Enterocolitis, Pseudomembranous") OR (AB "Clostridium Difficile Infection" OR "Infections, Clostridium" OR "Antibiotic-Associated Colitis" OR "Clostridium Enterocolitis" OR "Colitis, Pseudomembranous" OR "Pseudomembranous Colitis" OR "Pseudomembranous Enteritis" OR "Pseudomembranous Enterocolitis" OR ("Clostridium Difficile" AND Colonization)) AND (AB "Diagnostic Test" OR "Testing Algorithms" OR Diagnosis OR "Stool Sampling" OR Technique OR Detection OR "Clinical Laboratory Tests" OR "Laboratory Diagnosis" OR "Clinical Laboratory Techniques" OR "Screening" OR "Diagnostic Testing" OR "Identification" OR "Recognition"

Method	Search	Search String for: CINAHL	Search String for: MEDLINE
• Controlled Clinical Trial • Corrected and Republished Article • Evaluation Studies • Guideline • Journal Article • Meta-Analysis • Multicenter Study • Practice Guideline • Published Erratum • Randomized Controlled Trial • Review • Scientific Integrity Review • Technical Report • Twin Study • Validation Studies CINAHL Publication Types: • Clinical Trial • Corrected Article • Journal Article • Meta-Analysis • Meta Synthesis • Practice Guidelines • Randomized Controlled Trial		"Identification" OR "Recognition" OR "Rapid Identification" OR "Rapid Diagnostics"))	OR "Rapid Identification" OR "Rapid Diagnostics"))

Method	Search	Search String for: CINAHL	Search String for: MEDLINE
• Research Review • Systematic Review			
Search 2008-Present, English Only MedLine Publication Types: • Clinical Trial • Clinical Trial, Phase I • Clinical Trial, Phase II • Clinical Trial, Phase III • Clinical Trial, Phase IV • Comparative Study • Controlled Clinical Trial • Corrected and Republished Article • Evaluation Studies • Guideline • Journal Article • Meta-Analysis • Multicenter Study • Practice Guideline • Published Erratum • Randomized Controlled Trial • Review	Surveillance	(((MH "Clostridium Difficile" OR "Clostridium Infections" OR "Enterocolitis, Pseudomembranous") OR (AB "Clostridium Difficile Infection" OR "Infections, Clostridium" OR "Antibiotic-Associated Colitis" OR "Clostridium Enterocolitis" OR "Colitis, Pseudomembranous" OR "Pseudomembranous Colitis" OR "Pseudomembranous Enteritis" OR "Pseudomembranous Enterocolitis" OR ("Clostridium Difficile" AND Colonization)) AND ((MH "Mass Screening") OR (AB Surveillance OR "Monitoring and Surveillance" OR "Epidemiologic Surveillance" OR "Infectious Diseases Surveillance" OR Screening OR "Diagnostic Tests, Routine")))	(((MH "Clostridium Difficile" OR "Clostridium Infections" OR "Enterocolitis, Pseudomembranous") OR (AB "Clostridium Difficile Infection" OR "Infections, Clostridium" OR "Antibiotic-Associated Colitis" OR "Clostridium Enterocolitis" OR "Colitis, Pseudomembranous" OR "Pseudomembranous Colitis" OR "Pseudomembranous Enteritis" OR "Pseudomembranous Enterocolitis" OR ("Clostridium Difficile" AND Colonization)) AND ((MH "Mass Screening") OR (AB Surveillance OR "Monitoring and Surveillance" OR "Epidemiologic Surveillance" OR "Infectious Diseases Surveillance" OR Screening OR "Diagnostic Tests, Routine")))

Method	Search	Search String for: CINAHL	Search String for: MEDLINE
• Scientific Integrity Review • Technical Report • Twin Study • Validation Studies CINAHL Publication Types: • Clinical Trial • Corrected Article • Journal Article • Meta-Analysis • Meta Synthesis • Practice Guidelines • Randomized Controlled Trial • Research Review • Systematic Review			
Search 2008-Present, English Only MedLine Publication Types: • Clinical Trial • Clinical Trial, Phase I • Clinical Trial, Phase II • Clinical Trial, Phase III	Hand Hygiene	(((MH "Clostridium Difficile" OR "Clostridium Infections" OR "Enterocolitis, Pseudomembranous") AND (AB "Clostridium Difficile Infection" OR "Infections, Clostridium" OR "Antibiotic-Associated Colitis" OR "Clostridium Enterocolitis" OR "Colitis, Pseudomembranous" OR "Pseudomembranous Colitis" OR "Pseudomembranous Enteritis" OR "Pseudomembranous Enterocolitis" OR ("Clostridium Difficile" AND Colonization)) AND ((MH “Hand Hygiene” OR MH “Hand Disinfection”) OR (AB Handwashing OR “Hand Washing” OR “Hand Sanitization”	(((MH "Clostridium Difficile" OR "Clostridium Infections" OR "Enterocolitis, Pseudomembranous") OR (AB "Clostridium Difficile Infection" OR "Infections, Clostridium" OR "Antibiotic-Associated Colitis" OR "Clostridium Enterocolitis" OR "Colitis, Pseudomembranous" OR "Pseudomembranous Colitis" OR "Pseudomembranous Enteritis" OR "Pseudomembranous Enterocolitis" OR ("Clostridium Difficile" AND Colonization)) AND ((MH “Hand Hygiene” OR MH “Hand Disinfection”) OR (AB Handwashing OR “Hand Washing” OR “Hand

Method	Search	Search String for: CINAHL	Search String for: MEDLINE
• Clinical Trial, Phase IV • Comparative Study • Controlled Clinical Trial • Corrected and Republished Article • Evaluation Studies • Guideline • Journal Article • Meta-Analysis • Multicenter Study • Practice Guideline • Published Erratum • Randomized Controlled Trial • Review • Scientific Integrity Review • Technical Report • Twin Study • Validation Studies CINAHL Publication Types: • Clinical Trial • Corrected Article • Journal Article • Meta-Analysis • Meta Synthesis • Practice Guidelines		OR “Hand Hygiene” OR “Hand Disinfection”)))	Sanitization” OR “Hand Hygiene” OR “Hand Disinfection”)))

Method	Search	Search String for: CINAHL	Search String for: MEDLINE
• Randomized Controlled Trial • Research Review • Systematic Review			
Search 2008-Present, English Only MedLine Publication Types: • Clinical Trial • Clinical Trial, Phase I • Clinical Trial, Phase II • Clinical Trial, Phase III • Clinical Trial, Phase IV • Comparative Study • Controlled Clinical Trial • Corrected and Republished Article • Evaluation Studies • Guideline • Journal Article • Meta-Analysis • Multicenter Study • Practice Guideline • Published Erratum • Randomized	Ennvironme-ntal Cleaning and Decontamination	(((MH "Clostridium Difficile" OR "Clostridium Infections" OR "Enterocolitis, Pseudomembranous" OR "Clostridium Infections/PC") OR (AB "Clostridium Difficile Infection" OR "Infections, Clostridium" OR "Antibiotic-Associated Colitis" OR "Clostridium Enterocolitis" OR "Colitis, Pseudomembranous" OR "Pseudomembranous Colitis" OR "Pseudomembranous Enteritis" OR "Pseudomembranous Enterocolitis" OR ("Clostridium Difficile" AND Colonization)) AND ((MH "Disinfection/I/M/OA/S/U" OR "Decontamination/I/M/S") OR (AB "ATP Bioluminescence" OR "Pulsed UV Treatment" OR "Ultraviolet light" OR "UV Light" OR "No-Touch Decontamination")))	(((MH "Clostridium Difficile" OR "Clostridium Infections" OR "Enterocolitis, Pseudomembranous" OR "Clostridium Infections/PC") OR (AB "Clostridium Difficile Infection" OR "Infections, Clostridium" OR "Antibiotic-Associated Colitis" OR "Clostridium Enterocolitis" OR "Colitis, Pseudomembranous" OR "Pseudomembranous Colitis" OR "Pseudomembranous Enteritis" OR "Pseudomembranous Enterocolitis" OR ("Clostridium Difficile" AND Colonization)) AND ((MH "Disinfection/I/M/OA/S/U" OR "Decontamination/I/M/S") OR (AB "ATP Bioluminescence" OR "Pulsed UV Treatment" OR "Ultraviolet Light" OR "UV Light" OR "No-Touch Decontamination")))

Method	Search	Search String for: CINAHL	Search String for: MEDLINE
Controlled Trial • Review • Scientific Integrity Review • Technical Report • Twin Study • Validation Studies CINAHL Publication Types: • Clinical Trial • Corrected Article • Journal Article • Meta-Analysis • Meta Synthesis • Practice Guidelines • Randomized Controlled Trial • Research Review • Systematic Review			

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