



Published in final edited form as:

Infect Dis Clin North Am. 2025 December ; 39(4): 567–580. doi:10.1016/j.idc.2025.07.002.

Changes in the Epidemiology of *Clostridioides difficile* Infection

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Keywords

Clostridioides difficile infection; Epidemiology; Surveillance; Risk factors

INTRODUCTION

Clostridioides difficile was first associated with human disease in the 1970s, followed by outbreaks of clindamycin-resistant *C difficile* strains in the late 1980s and early 1990s.¹ However, it was not until the emergence of the epidemic *C difficile* strain, ribotype (RT) 027/sequence type (ST) 1, in North America in the early 2000s that a dramatic shift in the epidemiology of *C difficile* infection (CDI) was observed for the first time. RT027/ST1 spread from North America to Europe and other countries, garnering worldwide attention and bringing CDI to the forefront, including the initiation of surveillance in several global regions. However, RT027/ST1 has still not been commonly reported in some parts of the world. In the subsequent decades, as the molecular epidemiology of CDI continued to evolve, with a decline in the prevalence of RT027/ST1 and the emergence of other strains, the incidence of CDI in some regions and countries also changed. This article summarizes common aspects of surveillance, as well as global trends in the incidence or prevalence of CDI over the last decade, with a focus on available data from recent years. Additionally, this review describes selected risk factors for CDI according to their role in the acquisition and development of disease, highlighting recent advancements in identifying sources of CDI.

COMMON CHARACTERISTICS OF SURVEILLANCE DEFINITIONS AND RISK ADJUSTMENT

While it is impossible to outline the specific characteristics of surveillance definitions used across every global region, several general characteristics are common among these definitions. Clinically, the diagnosis of CDI is based on ≥ 3 diarrhea stools over a 24-h period, without other recognized cause, with a positive test suggesting that toxigenic *C*

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DISCLOSURES

The authors have nothing to disclose.

difficile is etiologic. Most commonly, CDI is defined for surveillance purposes by the presence of a positive test for *C difficile* and/or a clinical diagnosis of CDI recorded in a medical record.² Time criteria are used to discount duplicate tests and define episodes (usually 10–14 days), and delineate incident from recurrent (ie, within 8 weeks) episodes. Sometimes, the requirement of verified, specific clinical symptoms is added, although this is usually more difficult to implement. In some settings, administrative billing data using the International Classification of Diseases, Tenth Revision (ICD-10) codes for CDI are used for surveillance purposes.

Along with common aspects across specific case definitions, most surveillance involves stratifying cases into healthcare-associated versus community-associated (CA) cases.^{2,3} Often, a health care determination is based on a recent (eg, within 8–12 weeks) hospital discharge or long-term care facility stay, or a current inpatient status (eg, >3 days after hospital admission) at the time of meeting criteria for a CDI case. CA cases are those without such health care exposures. Health care-associated cases may be further stratified into hospital-onset or community-onset, health care facility-associated (Fig. 1).

Like case definitions, it would be impossible to describe all the various ways CDI surveillance data may be risk adjusted, but age-adjustment, or at least stratification of surveillance data by age, is common, given the importance of older age as a risk factor and the general availability of age data for CDI cases. Sex and race/ethnicity are also common stratifications if not adjustments to the data. Finally, although more difficult to implement and therefore less common, adjusting surveillance data by diagnostic test type is important, given the major differences in sensitivity between the 2 major modalities (ie, less sensitive enzyme immunoassay toxin detection versus more sensitive nucleic acid amplification tests [NAAT] to detect toxin genes).³

In our opinion, it is worth the extra effort to capture at least positive test results in preference to using only administrative codes. The accuracy of a positive laboratory test as a surrogate for clinical case reporting (ie, including verification of symptoms) depends upon whether diagnostic stewardship is employed. In addition, capturing results from a toxin assay used for diagnosis, with or without results from a more sensitive NAAT (results of which, when used alone, are more likely to misclassify colonization as CDI), may increase the accuracy of laboratory-based reporting as a surrogate for clinical case reporting. Assessing exposure to inpatient health care settings is important to inform prevention practices that may need to be implemented across care settings. Adjusting for diagnostic test type is most important when there is variation in testing practices between hospitals and other care settings, to prioritize prevention practices across settings, or when there are changes in testing practice over time, to assess trends in the effectiveness of prevention efforts.

INCIDENCE OR PREVALENCE OF *CLOSTRIDIoidES DIFFICILE* INFECTION

North America

The emergence of RT027/ST1 contributed to an initial drastic increase in the incidence and severity of CDI in North America. In 2011, the annual national burden of CDI in the United States reached an estimated 476,400 cases, based on data extrapolated from the US

Centers for Disease Control and Prevention's Emerging Infections Program (EIP).⁴ Since then, however, the US incidence of CDI has declined from an estimated 154.9 cases/100,000 population in 2011 to 143.6 cases/100,000 population in 2017. After accounting for changes in diagnostic testing, the adjusted incidence of CDI in 2017 was estimated to be 113.5 cases/100,000 population, which corresponded to an adjusted decrease of 24% in the incidence of CDI since 2011.⁴ The decrease in CDI incidence has been attributed to a steady decline in healthcare-associated CDI. The onset of the coronavirus disease 2019 (COVID-19) pandemic in 2020 appeared to have had minimal impact on the decreasing incidence of healthcare-associated CDI in the United States, with most multicenter studies reporting no change or a decrease in healthcare-associated or hospital-onset CDI rates compared to the pre-pandemic period.^{5,6} In addition, between 2015 and 2020, there was a 56.8% decrease in the number of hospitalized CDI events, including hospital-onset CDI, that was reported to the US National Healthcare Safety Network (Fig. 2); this decrease corresponded to a 47.5% decline in the national CDI standardized infection ratio, which is a risk-adjusted measure of hospital-onset CDI.⁷ Since 2020, the annual number of reported hospitalized CDI events has remained stable.⁷ Several factors may have contributed to the decline in healthcare-associated CDI over the last decade, including improved infection control and prevention practices, antibiotic stewardship, a decrease in the prevalence of RT027/ST1, and changes in CDI diagnostic testing practices.⁴

In contrast, the estimates of the US burden of CA CDI, adjusted for factors such as testing practices, have not decreased over the last decade.⁴ In fact, since the initial reports of severe CDI cases in the community in the mid-2000s,⁸ the crude incidence of CA CDI has steadily increased over time, with the exception of 2020, when the crude incidence rate dropped, likely due to a decrease in outpatient health care utilization during the onset of the COVID-19 pandemic.⁹ Since then, the crude incidence rate of CA CDI has risen back to the pre-pandemic level. As of 2022, over half of the CDI cases reported through CDC's EIP surveillance are CA, with the majority having had recent outpatient health care exposures. Meanwhile, hospital-onset and postdischarge CDI cases each account for only 19% to 20% of all reported cases (Fig. 3).

Similarly, the epidemiology of CDI in Canada has evolved since the initial outbreaks of RT027/ST1 in the early 2000s. From 2009 to 2015, the national rate of healthcare-associated CDI in Canada decreased from 5.9 to 4.3 cases/10,000 patient-days and was associated with a reduction in the prevalence of RT027/ST1.¹⁰ Subsequent surveillance during 2015 to 2019 showed an additional decrease of 23.8% in healthcare-associated CDI from 4.7 to 3.6 cases/10,000 patient-days.¹¹ Early on, between 2011 and 2014, there appeared to be an increasing trend in the national rate of hospitalized CA CDI.¹² However, between 2015 and 2019, the national rate of hospitalized CA CDI decreased by 18.8%.¹¹

Data from Mexico are included in a later section describing Latin America.

Europe

Since its initial spread from North America, RT027/ST1 has become less frequently detected in Europe in recent years, coinciding with a decline in CDI rates in some European countries. The concomitant decrease in CDI rates has been most striking in the United

Kingdom, where rates in England declined by 77.0% from 107.6 cases/100,000 population in 2007–08 to 24.8 cases/100,000 population in 2013–14.¹³ Rigorous epidemiologic assessment of declining fluoroquinolone prescribing in England during this period, and its association with declines in the fluoroquinolone-resistant RT027/ST1, point to the important role of restrictions on fluoroquinolone prescribing over and above infection control in these declines.¹⁴ However, starting in 2021–22, rates have increased annually by 9.2%–11.3%, including increases in both healthcare-associated and CA CDI rates.¹³

Since 2016, 26 countries have reported hospital-based surveillance data to the European Center for Disease Prevention and Control. Data from 17 countries were available for 2018 to 2020, revealing the mean hospital incidence density of healthcare-associated CDI to be 2.8, 2.0, and 2.6 cases/10,000 patient-days in 2018, 2019, and 2020, respectively.¹⁵ The reported mean hospital incidence of CA CDI (which also included cases with unknown epidemiologic association) was 0.7 cases/10,000 patient discharges in 2018 and 2019 and 1.4 cases/1000 patient discharges in 2020, although the majority of the data in 2020 were contributed by Germany, which had a comparatively higher incidence of CA CDI than the other countries.¹⁵

Australia

In Australia, patient administrative data are used to monitor the national incidence of CDI. The overall rates of CDI diagnoses among hospitalized patients remained relatively stable from 2012 to 2019, with the average annual rate varying between 3.8 and 4.3 cases per 10,000 patient-bed days.¹⁶ However, during 2020 to 2021, large variations in quarterly rates of CDI were observed. Starting in the second quarter of 2021, CDI rates steadily increased, resulting in an average annual rate of 4.8 cases/10,000 patient-bed days, which was the highest reported since 2016.¹⁶ During 2020 to 2021, community-onset CDI accounted for over 80% of the hospitalizations with a CDI diagnosis.¹⁶ While reasons for these recent increases and prominence of the community in the epidemiology of *C. difficile* in Australia are not clear, a close examination of infection control and antibiotic prescribing in ambulatory settings appear warranted. However, an in-depth look at the phylogenetics and resistome of major strains of circulating *C. difficile* suggest the need to consider the role of emerging environmental and One Health sources of *C. difficile* in Australia.¹⁷

Asia

Compared to the West, CDI incidence is less well characterized in Asia, where there is currently no national surveillance system for CDI. The few studies that have provided national or regional CDI data thus far are from East Asia. These include a multicenter study in Korea, where active surveillance for CDI was conducted over a 3-month period in 18 hospitals across the country during 2020 to 2021, resulting in an overall incidence of 7.04 cases/10,000 patient days.¹⁸ Using national health insurance claims data, the same investigators found the incidence of CDI in Korea had increased annually between 2008 and 2020, from 0.3 to 1.8 cases/10,000 patient days and from 6.9 to 56.9 cases/100,000 population.¹⁸ Similarly, in Hong Kong, a territory-wide study found that the crude incidence of CDI had increased substantially from 16.2 cases/100,000 population in 2006 to 49.4 cases/100,000 population in 2014.¹⁹ A subsequent study indicated the crude incidence of

CDI in Hong Kong peaked at 56.9 cases/100,000 in 2017, followed by slight decreases during 2018 to 2019.²⁰ In a meta-analysis of 33 studies from 14 provinces in China published during 2017 to 2022, the pooled prevalence of CDI among symptomatic patients was 11.4%, with a higher prevalence in northern (13.6%) than southern China (11.0%).²¹ The pooled prevalence rates of healthcare-associated and CA CDI were 13.3% and 9.5%, respectively. In Japan, a study of patients aged ≥ 50 years in 9 hospitals in Tokyo during 2018 to 2020 revealed an incidence rate of 2.0 cases/10,000 patient-days and 97 cases/100,000 population per year.²² Extrapolation of this data to the national level indicated that greater than 57,000 hospitalized CDI cases occur annually in Japan in persons aged ≥ 50 years.²²

Other Regions of the World

Little is known about the epidemiology of CDI in other parts of the world, where there may be less awareness of the organism and no formal surveillance in many low-income and middle-income countries. In Latin America, most of the studies on CDI have come from Brazil, where the prevalence of CDI among hospitalized patients varied between 0% and 41.7% during 2017 to 2019.^{23,24} In a multicenter study in Mexico that included 16 hospitals from different regions, the incidence of CDI during 2016 to 2022 was 4.8 cases/10,000 patient days.²⁵ Although there are limited data on CA CDI in Latin America, one single-center study in Argentina reported that 34.4% among all CDI cases identified during 2014 to 2019 were CA.²⁶

Among studies conducted in Africa during 2015 to 2018, the prevalence of toxigenic *C. difficile* in pediatric or adult patients with diarrhea generally ranged from 3.0% to 33.8%.²⁷ One outlier study in Kenya reported a high CDI prevalence of 92.4% among patients presenting with diarrhea over a 3-month period,²⁸ raising the possibility that the data might represent an outbreak.²⁷ A study in South Africa that used data from the national laboratory database reported an estimated crude national incidence of 53.9 cases/100,000 admissions in 2016 to 2017.²⁹ More recently, a multicenter study of hospitals from 3 different provinces in South Africa reported median CDI rates ranging from 0.3 to 5.8 cases/10,000 patient-days during 2017 to 2020, with an increase in rates in 2020 compared to 2019.³⁰

CLOSTRIDIODES DIFFICILE INFECTION RISK FACTORS

Risk factors for CDI generally contribute to disease pathogenesis through one or more of the following mechanisms: deficient or waning immunity, microbiome disruption, and transmission leading to new acquisition.

Impairment of the Immune System

Extensive studies of the innate immunity to CDI have uncovered pivotal roles played by various immune cells and cytokines.³¹ In addition, early studies of antibody responses to CDI, as well as later studies evaluating the use of monoclonal antibodies, suggest that an adequate humoral response to *C. difficile* toxins A and B can protect against initial and recurrent disease.³² Thus, impairment of the immune system, as seen in older age and in immunocompromised individuals, whether due to a primary or secondary immunodeficiency, can increase the risk of CDI. Among immunocompromised patients,

prevalence or rates of CDI have ranged from 6% to 33% in the hematology-oncology population, 0.6% to 23% in solid organ transplant recipients, and 7.1 to 8.3 cases/1000 patient-years in patients with human immunodeficiency virus.³³

Microbiome Disruption

Disruption of the homeostasis of the gastrointestinal microbiome can lead to changes in the composition of commensal organisms as well as the metabolome (especially bile acids), pH, and epithelial mucus, all of which can allow *C difficile*, if present, to proliferate and cause symptomatic infection.³⁴ Antibiotic use is a well-recognized CDI risk factor due to its profound and long-lasting impact on the microbiome. Almost every antibiotic has been implicated, but those with broad-spectrum activity or those to which some *C difficile* strains are highly resistant appear to have the highest risk for CDI.¹ These include clindamycin, cephalosporins, fluoroquinolones, and penicillins, whereas risk of CDI is lower with macrolides and sulfonamides and lowest with tetracyclines.^{35,36} Risk of CDI also varies within classes of antibiotics. For example, amoxicillin-clavulanate has the highest level of risk within its class, supporting the notion that penicillin-beta-lactamase combinations should be regarded differently from other penicillins.^{35,36} Risk of CDI also differs by duration of antibiotic exposure, with a 14-day course on average having 27% more risk compared to a 7-day course, while a 5-day course has 9% less risk.³⁶ However, risk is greater with longer durations of high-risk antibiotics than low-risk antibiotics. Moreover, exposure to multiple antibiotics and cumulative exposures over 2 to 3 months increase the risk of CDI more than a short course of a single antibiotic.³⁷ While direct antibiotic exposure is associated with an increased risk of CDI, studies have found that even antibiotic use among other patients in the same ward or a prior occupant of the same hospital room can independently increase an individual's risk for CDI.^{38,39} Although the specific mechanisms underlying the herd effects of antibiotics have not been thoroughly studied, it is likely that antibiotics may promote *C difficile* shedding, resulting in a higher environmental burden of the organism and an increased risk of acquisition in surrounding and subsequent patients.

While antibiotics are well-studied, there is increasing recognition that other medications can also disrupt the intestinal microbiome. Still, thus far, only a few of these have been linked to an increased risk of CDI. These include acid-suppressing medications, with more evidence supporting an association with proton pump inhibitors (PPIs) than histamine-2 receptor blockers.⁴⁰ Although conflicting data exist, a review of meta-analyses and systematic reviews conducted between 2000 and 2020 found a significant association between PPIs and CDI, with the majority of studies reporting 50% to 100% higher odds of CDI among PPI-users compared to nonusers.⁴⁰ In addition, the hypochlorhydria effect of PPIs has been demonstrated to promote *C difficile* sporulation,⁴¹ as well as alter the taxa involved in colonization resistance to *C difficile*.⁴² On a population level, it is possible that the effect of PPIs on CDI risk might be greater than that of antibiotics since PPIs are more commonly used and often given on a chronic basis for maintenance therapy compared to antibiotics that are usually given for a shorter duration.⁴³ Less data are available regarding other medications, with a few studies suggesting an increased risk of CDI from antidepressant use,⁴⁴ although the mechanisms for this are not clear and could include not only alteration of the microbiota but also dysregulation of the immune system.⁴⁵

Certain patient characteristics or underlying conditions can also disrupt the microbiome. For example, while older age can increase the risk of CDI through waning immunity, there are data indicating that older age is also associated with changes in the intestinal microbiome, including a reduced diversity of species that can result in less inhibitory effect on *C difficile* growth.⁴⁶ Other conditions include inflammatory bowel disease, where affected patients have a higher incidence of developing CDI compared with the general population.⁴⁷ In addition to the increased risk from frequent immunosuppressant use, patients with inflammatory bowel disease have an altered microbiome due to the underlying pathogenesis of the disease, which can potentially facilitate *C difficile* growth. This is supported by the finding that patients with ulcerative colitis have a significantly higher risk of CDI than those with Crohn's disease, who generally have less extensive colonic disease.⁴⁷

Transmission and Acquisition of *Clostridioides difficile*

The risk of a patient acquiring *C difficile* depends on the duration of exposure and the burden of the organism in the surrounding area, which includes not only the extent of the environmental contamination with *C difficile*, but also the number of patients in each unit who are actively infected or colonized with *C difficile*. In addition, risk of *C difficile* transmission is influenced by individual behavior or practices. These consist of lapses in infection control and prevention practices by facility staff that could facilitate *C difficile* transmission between patients, including suboptimal hand hygiene and/or glove or gown use, as well as nonadherence to recommended cleaning and disinfection procedures for patient rooms and shared medical equipment or devices. Additional practices that could increase transmission risk include the sharing of toilets or bathrooms or the use of lidless toilets.⁴⁸ While these practices can be independently associated with *C difficile* transmission, their level of risk may vary according to the environmental burden of the organism and the level of colonization pressure (ie, proportion of patients in the unit colonized with *C difficile*).

Colonization pressure is a known risk factor for several healthcare-associated infections⁴⁹; however, it has been less studied in the context of CDI, as screening for asymptomatic *C difficile* carriers is not routinely performed. However, 1 early study of intensive-care unit patients indicated that *C difficile* colonization pressure was an independent risk factor for CDI,⁵⁰ and in recent years, several studies have demonstrated that asymptomatic carriers can serve as a reservoir for CDI. For instance, 1 study found that incident CDI cases in a hospital were as frequently linked to transmission from asymptomatic carriers (29%) as symptomatic patients (30%).⁵¹ Another study found that among healthcare-associated CDI cases identified in a hospital and its affiliated long-term care facility, 19% were linked to long-term care facility residents with CDI or asymptomatic carriage of toxigenic *C difficile*.⁵² All of the asymptomatic carriers linked to transmission in the study had a relatively high burden of *C difficile* based on the colony count from their perirectal swab and evidence of shedding from positive groin, skin, and/or environmental cultures.

While *C difficile* contamination of the hospital environment has been well-described and linked to hospital-onset CDI,⁵³ limited data indicate that outpatient settings can also be contaminated with *C difficile* and potentially serve as a reservoir for CA CDI. In 1 study, point-prevalence cultures of high-touch surfaces revealed that 14% of outpatient clinic and

emergency department rooms were contaminated with *C difficile*.⁵⁴ A more recent study found a lower rate of *C difficile* environmental contamination in outpatient clinics, ranging from 0% to 5% of high-touch surfaces.⁵⁵ Prevalence of *C difficile* contamination likely varies by outpatient setting type and is influenced by patient volume, frequency of patient turnovers, and the ability of facility staff to perform adequate environmental cleaning and disinfection between patient encounters. Studies have reported that as high as 82% of CA CDI cases have had an outpatient health care encounter in the preceding 12 weeks.⁵⁶ Thus, it is conceivable that some cases could have acquired *C difficile* from their recent outpatient encounter, particularly if there was prolonged exposure and contact with providers and the health care environment. In a large, multisite study, an emergency department visit in the preceding 12 weeks, independent of receiving antibiotics, was significantly associated with CA CDI, suggesting that emergency departments could be an environmental source of CDI.⁵⁶

Increasing evidence suggests that a large portion of hospital-onset CDI are caused by strains that originated from the community, either acquired before hospital admission or from another patient who is asymptomatically colonized.⁵⁷ In addition, the increasing incidence of CA CDI in some countries has prompted greater attention to community sources of CDI. Studies have shown that infants and infected household members, as well as farm animals, could be a source of CA CDI.^{58–60} The use of whole-genome sequencing has revealed potential transmission of *C difficile* strains RT078 and RT046 between humans and pigs in Europe^{61,62} and RT014 and RT001 between humans and livestock in Nigeria.⁶³ Toxigenic *C difficile* has also been isolated from soil,⁶⁴ water,⁶⁵ and various types of food,^{66,67} including retail meats and root vegetables. Although no direct foodborne link has been established for CDI, a European study identified 2 distinct patterns of *C difficile* spread: one reflecting healthcare-associated transmission, and the other suggesting transmission via other routes or sources, such as the food chain.⁶⁸

SUMMARY

The incidence and prevalence of CDI over the last decade have varied greatly across countries and regions, with some reporting a decrease, while others reported an increase. Among countries that were impacted by the emergence and initial spread of RT027/ST1, most experienced a decline in the overall incidence of CDI in the ensuing years during which there was a concomitant decline in RT027/ST1. For some of these countries, the incidence of CDI has since plateaued or has started to increase again. Although data on CA CDI are not available in most parts of the world, an increase in the incidence of CA CDI has been observed in selected countries. The lack of formal CDI surveillance in many low-income and middle-income countries limits the ability to characterize the evolving global epidemiology of CDI and to identify factors contributing to the geographic differences in incidence of disease. Furthermore, although there are many common elements to CDI case definitions, specifics do vary between jurisdictions, as does any risk adjustment or important stratifications—this limits comparability between jurisdictions and countries.

Recent research into CDI risk factors has led to a greater understanding of the intricate roles that the immune system and the intestinal microbiome play in the pathogenesis of disease.

While certain CDI risk factors, such as antibiotics, advanced age, and immunosuppression, continue to remain important, future research on the microbiome is needed to determine if additional drugs or underlying conditions can increase CDI risk. The discovery of any novel risk factors will be critical to informing our ability to manage and prevent CDI.

Recent evidence has also reinforced the role of asymptomatic carriers as a transmission source of *C difficile*. Future efforts to prevent transmission of *C difficile* should include the development of effective decolonization strategies for asymptomatic carriers. This might include exploring microbiome-based interventions to eradicate or significantly reduce the burden of *C difficile* in asymptomatic carriers.

Given the increasing incidence of CA CDI in some parts of the world, further efforts are needed to elucidate associated risk factors and prevention strategies. This includes determining the attributable risk of various outpatient health care exposures and remote hospitalizations. In addition, as more studies are conducted that extend beyond the health care setting, further insights might be gained into the potential role of food, animals (ie, a One Health approach), and environmental sources in the transmission of *C difficile*.

DISCLAIMER

The findings and conclusions in this article are those of the authors and do not necessarily represent the official position of the US Centers for Disease Control and Prevention.

Abbreviations

CA	community-associated
CDI	<i>Clostridioides difficile</i> infection
EIP	emerging infections program
NAAT	nucleic acid amplification tests
RT	ribotype
ST	sequence type

REFERENCES

1. Guh AY, McDonald LC. Infectious gastroenteritis. In: Jarvis WR, editor. Bennett & Brachman's hospital infections. 7th Edition. Philadelphia (PA): Wolters Kluwer; 2023. p. 511–29.
2. McDonald LC, Coignard B, Dubberke E, et al. Recommendations for surveillance of *Clostridium difficile*-associated disease. *Infect Control Hosp Epidemiol* 2007;28(2):140–5. [PubMed: 17265394]
3. McDonald LC, Gerding DN, Johnson S, et al. 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). *Clin Infect Dis* 2018;66(7):e1–48. [PubMed: 29462280]
4. Guh AY, Mu Y, Winston LG, et al. Trends in U.S. Burden of *Clostridioides difficile* infection and outcomes. *N Engl J Med* 2020;382:1320–30. [PubMed: 32242357]
5. Baker MA, Sands KE, Huang SS, et al. The impact of coronavirus disease 2019 (COVID-19) on healthcare-associated infections. *Clin Infect Dis* 2022;74:1748–54. [PubMed: 34370014]

6. Evans ME, Simbartl LA, Kralovic SM, et al. Healthcare-associated infections in Veterans Affairs acute-care and long-term healthcare facilities during the coronavirus disease 2019 (COVID-19) pandemic. *Infect Control Hosp Epidemiol* 2023; 44:420–6. [PubMed: 35379366]
7. Centers for Disease Control and Prevention. Antimicrobial resistance & patient safety portal, *C. difficile* infections. Available at: <https://arpsp.cdc.gov/profile/nhsn/cdi>. Accessed February 10, 2025.
8. Centers for Disease Control and Prevention. Severe *Clostridium difficile*-associated disease in populations previously at low risk—four states, 2005. *MMWR Morb Mortal Wkly Rep* 2005;54:1201–5. [PubMed: 16319813]
9. Centers for Disease Control and Prevention. Healthcare-associated infections (HAIs), *Clostridioides difficile* infection (CDI) surveillance, annual reports. Available at: <https://www.cdc.gov/healthcare-associated-infections/php/haic-eip/cdiff.html>. Accessed February 10, 2025.
10. Katz KC, Golding GR, Choi KB, et al. The evolving epidemiology of *Clostridium difficile* infection in Canadian hospitals during a postepidemic period (2009–2015). *CMAJ (Can Med Assoc J)* 2018;190:E758–65. [PubMed: 29941432]
11. Du T, Choi KB, Silva A, et al. Characterization of healthcare-associated and community-associated *Clostridioides difficile* infections among adults, Canada, 2015–2019. *Emerg Infect Dis* 2022;28:1128–36. [PubMed: 35470794]
12. Xia Y, Tunis MC, Frenette C, et al. Epidemiology of *Clostridioides difficile* infection in Canada: a six-year review to support vaccine decision-making. *Can Commun Dis Rep* 2019;45:191–211. [PubMed: 31355824]
13. UK Health Security Agency. Annual epidemiological commentary: gram-negative, MRSA, MSSA bacteraemia and *C. difficile* infections, up to and including financial year 2022 to 2023. Available at: <https://www.gov.uk/government/statistics/mrsa-mssa-and-e-coli-bacteraemia-and-c-difficile-infection-annual-epidemiological-commentary/annual-epidemiological-commentary-gram-negative-mrsa-mssa-bacteraemia-and-c-difficile-infections-up-to-and-including-financial-year-2022-to-2023>. Accessed February 10, 2025.
14. Dingle KE, Didelot X, Quan TP, et al. Effects of control interventions on *Clostridium difficile* infection in England: an observational study. *Lancet Infect Dis* 2017;17(4):411–21. [PubMed: 28130063]
15. European Centre for Disease Prevention and Control. *Clostridioides difficile* infections - annual epidemiological report for 2018–2020. Available at: <https://www.ecdc.europa.eu/en/publications-data/clostridioides-difficile-infections-annual-epidemiological-report-2018-2020>. Accessed February 10, 2025.
16. Australian Commission on Safety and Quality in Health Care. *Clostridioides difficile* infection – 2017, 2019, and 2020 and 2021 data snapshot. Available at: <https://www.safetyandquality.gov.au/publications-and-resources>. Accessed February 10, 2025.
17. O’Grady K, Hong S, Putsathit P, et al. Defining the phylogenetics and resistome of the major *Clostridioides difficile* ribotypes circulating in Australia. *Microb Genom* 2024;10(5):001232. [PubMed: 38717815]
18. Kim J, Myung R, Kim B, et al. Incidence of *Clostridioides difficile* infections in Republic of Korea: a prospective study with active surveillance vs. National data from health insurance review & assessment service. *J Korean Med Sci* 2024;39:e118. [PubMed: 38565175]
19. Ho J, Dai RZW, Kwong TNY, et al. Disease burden of *Clostridium difficile* infections in adults, Hong Kong, China, 2006–2014. *Emerg Infect Dis* 2017;23:1671–9. [PubMed: 28930010]
20. Guo CLT, Kwong TNY, Mak JWY, et al. Trends in incidence and clinical outcomes of *Clostridioides difficile* infection, Hong Kong. *Emerg Infect Dis* 2021;27:3036–44. [PubMed: 34812719]
21. Wen B, Dong N, Ouyang Z, et al. Prevalence and molecular characterization of *Clostridioides difficile* infection in China over the past 5 years: a systematic review and meta-analysis. *Int J Infect Dis* 2023;130:86–93. [PubMed: 36906122]
22. Tateda K, Ishida J, Ito S, et al. Population-based incidence of hospitalized *Clostridioides difficile* infection among older adults in Ota-ku, Japan: a prospective surveillance study. *Anaerobe* 2022;76:102607. [PubMed: 35787452]

23. Maestri AC, Raboni SM, Morales HMP, et al. Multicenter study of the epidemiology of *Clostridioides difficile* infection and recurrence in southern Brazil. *Anaerobe* 2020;64:102238. [PubMed: 32717474]
24. Girão ES, de Melo Tavares B, Alves Dos Santos S, et al. Prevalence of *Clostridioides difficile* associated diarrhea in hospitalized patients in five Brazilian centers: a multicenter, prospective study. *Anaerobe* 2020;66:102267. [PubMed: 33080372]
25. De-la-Rosa-Martinez D, Vilar-Compte D, Martínez-Rivera N, et al. Multicenter study on *Clostridioides difficile* infections in Mexico: exploring the landscape. *Infect Control Hosp Epidemiol* 2024;1–8.
26. Fox B, Ricci V, Bergese S, et al. Community-associated *Clostridioides difficile* infection in a general hospital from Argentina. *Anaerobe* 2023;82:102744. [PubMed: 37302567]
27. Kullin B, Abratt VR, Reid SJ, et al. *Clostridioides difficile* infection in Africa: a narrative review. *Anaerobe* 2022;74:102549. [PubMed: 35337974]
28. Oyaro MO, Plants-Paris K, Bishoff D, et al. High rate of *Clostridium difficile* among young adults presenting with diarrhea at two hospitals in Kenya. *Int J Infect Dis* 2018;74:24–8. [PubMed: 29960098]
29. de Jager P, Smith O, Bolon S, et al. Epidemiology of *Clostridioides difficile* in South Africa. *PLoS One* 2021;16:e0259771. [PubMed: 34813626]
30. Nana T, Ramjathan P, Swe-Swe Han K, et al. *Clostridioides difficile* infection and testing rates in South Africa: a multicentre study, 2017–2020. *Anaerobe* 2024;91:102937. [PubMed: 39710297]
31. Wang L, Villafuerte Gálvez JA, Lee C, et al. Understanding host immune responses in *Clostridioides difficile* infection: implications for pathogenesis and immunotherapy. *Imeta* 2024;3(3):e200. [PubMed: 38898983]
32. Rees WD, Steiner TS. Adaptive immune response to *Clostridium difficile* infection: a perspective for prevention and therapy. *Eur J Immunol* 2018;48(3):398–406. [PubMed: 29272036]
33. Revolinski SL, Munoz-Price LS. *Clostridium difficile* in immunocompromised hosts: a review of epidemiology, risk factors, treatment, and prevention. *Clin Infect Dis* 2019;68(12):2144–53. [PubMed: 30281082]
34. Zhang Y, Saint Fleur A, Feng H. The development of live biotherapeutics against *Clostridioides difficile* infection towards reconstituting gut microbiota. *Gut Microbes* 2022;14(1):2052698. [PubMed: 35319337]
35. Miller AC, Arakkal AT, Sewell DK, et al. Comparison of different antibiotics and the risk for community-associated *Clostridioides difficile* infection: a case–control study. *Open Forum Infect Dis* 2023;10(8):ofad413. [PubMed: 37622034]
36. Brown KA, Langford B, Schwartz KL, et al. Antibiotic prescribing choices and their comparative *C. Difficile* infection risks: a longitudinal case-cohort study. *Clin Infect Dis* 2021;72(5):836–44. [PubMed: 32069358]
37. Stevens V, Dumyati G, Fine LS, et al. Cumulative antibiotic exposures over time and the risk of *Clostridium difficile* infection. *Clin Infect Dis* 2011;53(1):42–8. [PubMed: 21653301]
38. Brown K, Valenta K, Fisman D, et al. Hospital ward antibiotic prescribing and the risks of *Clostridium difficile* infection. *JAMA Intern Med* 2015;175(4):626–33. [PubMed: 25705994]
39. Freedberg DE, Salmasian H, Cohen B, et al. Receipt of antibiotics in hospitalized patients and risk for *Clostridium difficile* infection in subsequent patients who occupy the same bed. *JAMA Intern Med* 2016;176(12):1801–8. [PubMed: 27723860]
40. Tawam D, Baladi M, Jungsuwadee P, et al. The positive association between proton pump inhibitors and *Clostridium difficile* infection. *Innov Pharm* 2021;12(1). 10.24926/iip.v12i1.3439.
41. Wetzel D, McBride SM. The impact of pH on *Clostridioides difficile* sporulation and physiology. *Appl Environ Microbiol* 2020;86(4):e02706–19. [PubMed: 31811041]
42. Freedberg DE, Toussaint NC, Chen SP, et al. Proton pump inhibitors alter specific taxa in the human gastrointestinal microbiome: a crossover trial. *Gastroenterology* 2015;149(4):883–5.e9.
43. Moreels N, Boven A, Gressani O, et al. The combined effect of systemic antibiotics and proton pump inhibitors on *Clostridioides difficile* infection and recurrence. *J Antimicrob Chemother* 2024;79(3):608–16. [PubMed: 38267263]

44. Rogers MA, Greene MT, Young VB, et al. Depression, antidepressant medications, and risk of *Clostridium difficile* infection. *BMC Med* 2013;11:121. [PubMed: 23647647]
45. Boustany A, Feuerstadt P, Tillotson G. The 3 Ds: depression, dysbiosis, and *Clostridioides difficile*. *Adv Ther* 2024;41(11):3982–95. [PubMed: 39276186]
46. Shin JH, High KP, Warren CA. Older is not wiser, immunologically speaking: effect of aging on host response to *Clostridium difficile* infections. *J Gerontol A Biol Sci Med Sci* 2016;71:916–22. [PubMed: 26809495]
47. Rodemann JF, Dubberke ER, Reske KA, et al. Incidence of *Clostridium difficile* infection in inflammatory bowel disease. *Clin Gastroenterol Hepatol* 2007;5(3):339–44. [PubMed: 17368233]
48. Wilson GM, Jackson VB, Boyken LD, et al. Bioaerosols generated from toilet flushing in rooms of patients with *Clostridioides difficile* infection. *Infect Control Hosp Epidemiol* 2020;41(5):517–21. [PubMed: 32000872]
49. Ajao AO, Harris AD, Roghmann MC, et al. Systematic review of measurement and adjustment of colonization pressure in studies of methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant enterococci, and *Clostridium difficile* acquisition. *Infect Control Hosp Epidemiol* 2011;32(5):481–9. [PubMed: 21515979]
50. Lawrence SJ, Puzniak LA, Shadel BN, et al. *Clostridium difficile* in the intensive care unit: epidemiology, costs, and colonization pressure. *Infect Control Hosp Epidemiol* 2007;28(2):123–30. [PubMed: 17265392]
51. Curry SR, Muto CA, Schlackman JL, et al. Use of multilocus variable number of tandem repeats analysis genotyping to determine the role of asymptomatic carriers in *Clostridium difficile* transmission. *Clin Infect Dis* 2013;57(8):1094–102. [PubMed: 23881150]
52. Donskey CJ, Sunkesula VCK, Stone ND, et al. Transmission of *Clostridium difficile* from asymptomatically colonized or infected long-term care facility residents. *Infect Control Hosp Epidemiol* 2018;39(8):909–16. [PubMed: 29848392]
53. Weber DJ, Rutala WA. The role of the environment in transmission of *Clostridium difficile* infection in healthcare facilities. *Infect Control Hosp Epidemiol* 2011;32(3):207–9. [PubMed: 21460504]
54. Jury LA, Sitzlar B, Kundrapu S, et al. Outpatient healthcare settings and transmission of *Clostridium difficile*. *PLoS One* 2013;8(7):e70175. [PubMed: 23894609]
55. Cadnum JL, Pearlmutter BS, Jencson AL, et al. Microbial bioburden of inpatient and outpatient areas beyond patient hospital rooms. *Infect Control Hosp Epidemiol* 2022;43(8):1017–21. [PubMed: 34294185]
56. Guh AY, Adkins SH, Li Q, et al. Risk factors for community-associated *Clostridium difficile* infection in adults: a case-control study. *Open Forum Infect Dis* 2017;4(4):ofx171. [PubMed: 29732377]
57. Eyre DW, Cule ML, Wilson DJ, et al. Diverse sources of *C. difficile* infection identified on whole-genome sequencing. *N Engl J Med* 2013;369(13):1195–205. [PubMed: 24066741]
58. Wilcox MH, Mooney L, Bendall R, et al. A case-control study of community-associated *Clostridium difficile* infection. *J Antimicrob Chemother* 2008;62(2):388–96. [PubMed: 18434341]
59. Miller AC, Segre AM, Pemmaraju SV, et al. Association of household exposure to primary *Clostridioides difficile* infection with secondary infection in family members. *JAMA Netw Open* 2020;3(6):e208925. [PubMed: 32589232]
60. Muñoz-Price LS, Hanson R, Singh S, et al. Association between environmental factors and toxigenic *Clostridioides difficile* carriage at hospital admission. *JAMA Netw Open* 2020;3(1):e1919132. [PubMed: 31922563]
61. Werner A, Mölling P, Fagerström A, et al. Whole genome sequencing of *Clostridioides difficile* PCR ribotype 046 suggests transmission between pigs and humans. *PLoS One* 2020;15(12):e0244227. [PubMed: 33347506]
62. Knetsch CW, Connor TR, Mutreja A, et al. Whole genome sequencing reveals potential spread of *Clostridium difficile* between humans and farm animals in The Netherlands, 2002 to 2011. *Euro Surveill* 2014;19(45):20954. [PubMed: 25411691]
63. Ngbede EO, Junker V, Kolte B, et al. *Clostridioides difficile* recovered from hospital patients, livestock and dogs in Nigeria share near-identical genome sequences. *Microb Genom* 2025;11(1).

64. Moono P, Lim SC, Riley TV. High prevalence of toxigenic *Clostridium difficile* in public space lawns in Western Australia. *Sci Rep* 2017;7:41196. [PubMed: 28145453]
65. Romano V, Pasquale V, Krovacek K, et al. Toxigenic *Clostridium difficile* PCR ribotypes from wastewater treatment plants in southern Switzerland. *Appl Environ Microbiol* 2012;78(18):6643–6. [PubMed: 22798376]
66. Limbago B, Thompson AD, Greene SA, et al. Development of a consensus method for culture of *Clostridium difficile* from meat and its use in a survey of U.S. retail meats. *Food Microbiol* 2012;32(2):448–51. [PubMed: 22986214]
67. Lim SC, Foster NF, Elliott B, et al. High prevalence of *Clostridium difficile* on retail root vegetables, Western Australia. *J Appl Microbiol* 2018;124(2):585–90. [PubMed: 29193458]
68. Eyre DW, Davies KA, Davis G, et al. Two distinct patterns of *Clostridium difficile* diversity across Europe indicating contrasting routes of spread. *Clin Infect Dis* 2018;67(7):1035–44. [PubMed: 29659747]

KEY POINTS

- CDI surveillance commonly uses a case definition based on a positive laboratory test and/or clinical diagnosis and involves stratification and risk adjustment of data.
- In the last decade, some countries reported an increase in CDI incidence, while others reported a decrease, along with a decline in ribotype 027/sequence 1.
- Factors that impair the immune system, disrupt the gastrointestinal microbiome, or facilitate transmission and acquisition of *C. difficile* can increase an individual's risk of developing CDI.

CLINICS CARE POINTS

- The use of a toxin assay, with or without the more sensitive NAAT, may increase the accuracy of laboratory-based CDI surveillance as a surrogate for clinical case reporting.
- Almost every antibiotic is associated with CDI, but those with broad-spectrum activity or those to which some *C difficile* strains are highly resistant have the highest risk for CDI.

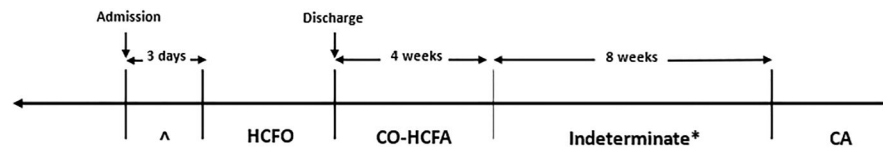


Fig. 1.

Example of a surveillance definition for CDI. CA, community-associated; CO-HCFA, community-onset, healthcare facility-associated; HCFO, healthcare facility-onset (eg., hospital-care or long-term care facility-onset). Cases with onset during this period are either CO-HCFA, indeterminate, or CA, depending upon time since last overnight stay in any health care facility; ^asome surveillance definitions may classify indeterminate cases with onset during this period as CO-HCFA. (McDonald LC, Coignard B, Dubberke E, Song X, Horan T, Kuty PK. Recommendations for Surveillance of Clostridium difficile–Associated Disease. *Infection Control & Hospital Epidemiology*. 2007;28(2):140–145. doi:10.1086/511798.)

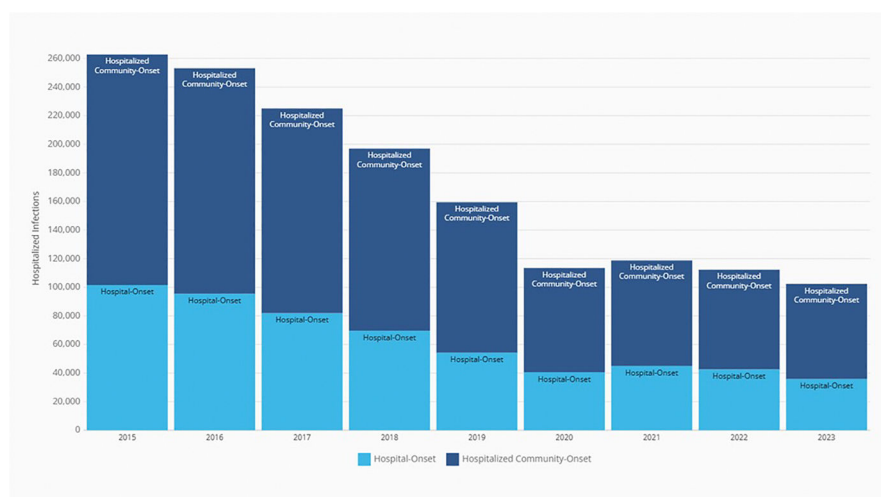


Fig. 2. Annual number of hospitalized community-onset and hospital-onset CDI events reported to the National Healthcare Safety Network, 2015 to 2023. (*From CDC's Antibiotic Resistance & Patient Safety Portal (Available at <https://arpsp.cdc.gov/profile/nhsn/cdi>).*)

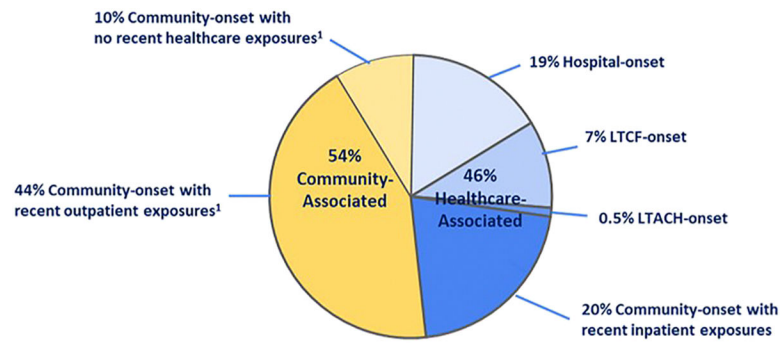


Fig. 3. Percentage of CDI cases by inpatient or outpatient status at time of stool collection and type/location of exposures in the 12 weeks preceding CDI diagnosis, EPI, 2022. LTACH, long-term acute care hospitals; LTCF, long-term care facility onset. (*Adapted from Unpublished CDC data.*)