# 2 Epidemiology of *Clostridioides difficile* Infection in Long-Term Care Facilities

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## Introduction

*Clostridioides difficile* (formerly known as *Clostridium difficile*) is a Gram-positive, spore-forming, anaerobic bacillus. It was first described in 1935 as part of the intestinal flora of newborn infants [1]. However, it was not recognized as a major cause of pseudomembranous colitis until 1978 [2]. Over the period of decades, *C. difficile* has reached an epidemic state with increasing incidence and severity in both healthcare and community settings [3]. *Clostridium difficile* is the leading cause of healthcare-associated gastrointestinal infections and the most commonly reported pathogen causing healthcare-associated infections in the USA accounting for 12.1% of all healthcare-associated infections [4].

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Because of the morbidity and mortality associated with CDI, CDC has called *C. difficile* as an urgent threat to public health [5]. Long-term care facilities (LTCF) should pay particular attention to this threat for several reasons. *C. difficile* colonization rates in LTCF have been shown to be higher than the surrounding community [6]. Similarly, transmission of *C. difficile* within LTCF has also been shown to be much higher than in the community [7]. In addition, the elderly residents of LTCF are at higher risk for getting *C. difficile* infections (CDI), and the mortality rates of CDI in this population are also higher than the mortality rates for community-associated and overall healthcare-associated CDI [8–11]. Therefore, it is important to review the epidemiology of CDI in long-term care setting.

## *C. difficile* Strain Diversity in Long-Term Care Facilities

In the past two decades, the epidemiology of CDI has changed significantly worldwide [12]. Reports of increased incidence and complications of CDI from severe forms of CDI started to emerge from different parts of the world. This shift, at least in part, was linked to the emergence and epidemic spread of a novel strain of *C. difficile* especially in North America and Europe [12]. This epidemic strain has reduced susceptibility to the fluoroquinolone as compared to the previously found isolates of *C. difficile*. Later on, this strain was identified as North American pulsed-field type 1 (NAP1), restriction endonuclease analysis (REA) group BI, and PCR ribotype 027 (also known as BI/NAP1/027) [12].

One report showed that the overall CDI hospitalization incidence in the USA rose from 6.4 cases per 10,000 in 2000 to 13.1 cases per 10,000 in 2005 [13]. In addition to that, the age-adjusted case-fatality rate for CDI hospitalizations nearly doubled during that time period (1.2% in 2000 to 2.2% in 2004) [13]. Even though CDI incidence rate increased in all age groups, the rate of increase was much steeper in adults over the age of 65 with the steepest trend noticed in adults over 85 years of age [13]. The slope for the linear trend was 11.3 (95% confidence interval [CI] 7.6–14.9, $p = 0.001$) in adults over 85 years of age as compared to 4.8 (95%

CI 3.2–6.0, $p < 0.001$) among the 65–84 age group and 0.2 (95% CI 0.1–0.3, $p < 0.001$) among the adults aged 18–44 years [13].

In a study conducted during 2010–2011 in the USA, ribotype O27 strain was found to be the most prevalent strain among inpatients admitted from LTCF [14]. Almost three quarters (71%) of the CDI patients admitted from the LTCF were infected with *C. difficile* ribotype 027 strains and 75% with strains with high-level fluoroquinolone resistance. This was much higher proportions as compared with 34% and 44%, respectively, for patients admitted from home. Patients infected with ribotype 027 strains had a higher all-cause mortality rate and more intestinal inflammation, as measured by quantitative fecal lactoferrin [14].

It has also been noticed that when *C. difficile* is present in LTCF residents, multiple strains of the organism are often found in the facility [15]. In a single nursing home outbreak in the USA, where all clinical specimens were found to have ribotype 027, 21% of the positive environmental cultures had *C. difficile* isolates other than ribotype 027 [16]. The prevalence of these strains in LTCF may also vary based on the geographic region. For example, a German study looking into the prevalence of *C. difficile* colonization among nursing home residents found ribotypes 014 and 001 as the most prevalent genotypes that accounted for 30% and 20% of toxigenic isolates in nursing homes, respectively [6]. A study conducted in eight nursing homes in Hong Kong demonstrated that the residents were most frequently colonized by *C. difficile* ribotypes 002 (40.8%), 014 (16.9%), 029 (9.9%), and 053 (8.5%) [17]. Another study conducted in 2013 in a Belgian nursing home found ribotype 027 as the predominant strain even though ribotypes 078 and 014/020 were the predominant strains in the hospitals around that time [18]. The proportion of hospitals with the ribotype 027 strain decreased from 34% in 2009 to 15% in 2013 in Belgium. The authors of this study hypothesized that they may see a change in the nursing home strains in a few years as changes in the nursing home strains usually come later than the hospitals.

It has also been shown that as compared to the hospital and outpatient setting, the clinically indicated specimens submitted for *C. difficile* from nursing homes have higher prevalence of

toxigenic strains (at least 2.5 times higher than either of the two settings) [19]. In the same study conducted in Southwest Virginia, it was found that the nursing homes have the lowest diversity of the ribotypes as compared to the inpatient and outpatient setting. Ribotype analysis of 190 toxigenic isolates was performed that included 56 inpatient, 69 outpatient, and 65 nursing home isolates. Only six different ribotypes were identified in nursing home patients as compared to 23 and 21 ribotypes for inpatients and outpatients, respectively. Ribotype 027 was the predominant strain and accounted for about half of the ribotypes identified in the nursing home patients [19].

## Incidence and Prevalence of *C. difficile* Infection

CDI in the past used to be considered a problem for acute care hospitals, but more recent data clearly shows that prevalence of CDI is not only a threat for the hospitalized patients but also for residents of long-term care settings and everyone in the community [8, 20–25]. The estimates of incidence and prevalence of CDI in LTCF vary from study to study. Incidence rates may be as high as 3.72 cases/1000 resident days in the US LTCF, and prevalence has been reported to be as high as 3.8% of LTCF admissions [26]. These numbers might even be higher in the setting of an outbreak. Subacute and rehabilitation units of LTCF (where majority of patients get admitted from hospital setting) have also been reported to have higher incidence and prevalence of CDI as compared to the traditional nursing home units (where patients typically get admitted from the community or after failing inpatient rehabilitation) [27].

Based on active population- and laboratory-based surveillance across 10 geographic areas, it was estimated that 453,000 (95% confidence interval [CI], 397,100–508,500) initial cases of CDI occurred in the USA during 2011 [8]. The incidence was estimated to be higher among females as compared to males (rate ratio, 1.26; 95% CI, 1.25–1.27), whites as compared to non-whites (rate ratio, 1.72; 95% CI, 1.56–2.0), and persons 65 years of age or older as compared to those younger than 65 years of age (rate

ratio, 8.65; 95% CI, 8.16–9.31) [8]. This particular study also investigated the origin of the CDI and classified community-associated infections as those CDI where the *C. difficile*–positive specimen was collected on an outpatient basis or within 3 days after hospital admission in those patients who had no documented overnight stay in a healthcare facility during the previous 12 weeks. The rest of the CDI were classified as healthcare-associated infections and further divided into three distinct groups: community onset associated with a healthcare facility, hospital onset, or nursing home onset. The national estimated incidence of community-associated and healthcare-associated CDI was 51.9 (95% confidence interval [CI], 43.2–60.5) and 95.3 (95% CI, 85.9–104.8) per 100,000 population, respectively. This accounted for an estimated 159,700 community-associated and 293,000 healthcare-associated CDI. Over a third (104,400, 95% CI, 94,100–115,800) of all healthcare-associated CDI cases were estimated to have a nursing home onset [8].

Another retrospective cohort study estimated prevalence of CDI in US LTCF by using the 2011 LTCF resident data from the Minimum Data Set 3.0 linked to Medicare claims. The nationwide CDI prevalence rate was 1.85 per 100 LTCF admissions (95% confidence interval [CI] 1.83–1.87) [11]. Older age, white race, presence of a feeding tube, unhealed pressure ulcers, end-stage renal disease, cirrhosis, bowel incontinence, prior tracheostomy, chemotherapy, and chronic obstructive pulmonary disease were independently related to "high risk" for CDI in this study.

The fact that some patients who developed CDI in LTCF may also have been exposed to hospital, ambulatory care, or community settings in the past few months before the diagnosis makes it harder to determine the setting of acquisition and presents a challenge in estimating true incidence of a nursing home–onset CDI. The reason for the uncertainty is that the studies have shown variable time interval for an individual to develop CDI after the exposure [28]. The range varies from less than a week to months (2–3 months). However, it has also been described that majority of the cases with a delayed-onset CDI have symptom onset within 4 weeks after the discharge from a hospital [28]. For the purposes of surveillance, the CDC defines the cases to be an LTCF onset if

the positive *C. difficile* sample was obtained more than 3 days after admission to the LTCF [29]. However, the CDC further subclassifies LTCF-onset CDI cases as acute-care transfer–LTCF onset if the stool specimen is collected ≤4 weeks following transfer from an acute-care facility [29]. Several studies have shown that majority (>50%) of LTCF onset CDI cases are diagnosed within a month after discharge from hospital [24, 30–33]. One VA study reported 85% of LTCF-onset CDI cases occurring within 1 month after transfer from the hospital [31]. However, a follow-up study in the same setting demonstrated that LTCF residents frequently acquired colonization with toxigenic *C. difficile* after transfer from the hospital [30]. Three quarters (75%) of initial CDI cases with onset within 1 month of transfer occurred in residents who acquired colonization in the LTCF. This result challenges the concept of classifying LTCF-onset CDI cases diagnosed within a month of hospital discharge as hospital associated. It is also important to note that antibiotic exposure in the hospital was identified as a potential risk factor for acquisition of colonization within LTCF in the same study which points toward the complexity of associating CDI cases with the hospital or the LTCF [30].

## Colonization of Long-Term Care Facility Residents with *C. difficile*

Asymptomatic *C. difficile* colonization generally starts with ingestion of the *C. difficile* spores [1]. The spores survive the gastric acid and germinate into vegetative cells in the intestine. Vegetative *C. difficile* cells penetrate the mucus layer in the large intestine to adhere and colonize the intestinal epithelium. Even though *C. difficile* has been isolated from small intestine, it primarily colonizes the large intestine [1]. However, colonization with vegetative *C. difficile* cells usually requires a disruption of the normal intestinal microbiota [1]. Up to 70% of residents in a LTCF receive one or more courses of systemic antibiotics over a year which may contribute toward the disruption of the normal intestinal microbiota and place the residents of LTCF at higher risk for *C. difficile* colonization [34].

Rates of asymptomatic colonization with *C. difficile* range from 0% to 51% among residents of LTCF [1, 6, 35]. The rate of colonization by toxigenic strain of *C. difficile* strains has been shown to be 10 times higher in nursing home residents than in the community [6]. In addition, LTCF with known actual or recent CDI cases have been found to have a higher likelihood of having colonized residents as opposed to those without known *C. difficile* infection cases [6]. Preceding outbreaks of *C. difficile* infections may also increase the rate of colonization in a LTCF and can explain some of the variability in the reported rates of colonization among various studies [36]. In order to explore the epidemiology of *C. difficile* colonization in LTCF, Ziakas et al. conducted a meta-analysis consisting of nine studies (six from the USA, one from Canada, and two from Europe). The pooled colonization with toxigenic *C. difficile* was 14.8% (95% CI 7.6–24.0) among 1371 residents included in the meta-analysis [37]. However, colonization estimates were significantly higher in facilities with preceding CDI outbreaks as opposed to those without preceding outbreaks (30.1% vs. 6.5%, $p = 0.01$) [37].

It is important to realize that various studies have used different definitions of *C. difficile* colonization which may also impact the reported colonization rates [1, 38]. One of the definition that describes colonization well is suggested by Furuya-Kanamori et al. [1] They defined asymptomatic *C. difficile* colonization as "the absence of diarrhea (or if present, attributable to a cause other than CDI) without colonoscopic or histopathologic findings consistent with pseudomembranous colitis, and either the detection of *C. difficile* or the presence of *C. difficile* toxins." This definition takes into account that individuals who have colonization with *C. difficile* may also have diarrhea that is unrelated to the presence of *C. difficile* colonization. Consideration should be given to the possibility of other infectious, non-infectious, or iatrogenic (e.g., laxative overdose) causes of the diarrhea when differentiating between *C. difficile* colonization and infection particularly when nucleic acid amplification testing is used to identify *C. difficile*.

In general, several factors have been found to be associated with increased risk of *C. difficile* colonization. These include antibiotic exposure, hospitalization within the last 12 months, abdominal surgery, presence of nasogastric tubes, exposure to corticosteroids, history of *C. difficile* infection, chronic dialysis, use of proton-pump inhibitors or histamine H2 antagonists, chemotherapy, and presence of antibody against toxin B [1, 37]. One meta-analysis that looked specifically for factors associated with colonization in long-term care facilities found previous CDI, antibiotic use in the last 3 months, and hospitalization within the past 3 months to a year to be associated with *C. difficile* colonization [37]. The odds ratio for these three risk factors were 6.07 (95% CI 2.06–17.88), 3.68 (95% CI 2.04–6.62), and 2.11 (OR 2.11; 95% CI 1.08–4.13), respectively. No association of *C. difficile* colonization was found with age, gender, proton-pump inhibitor use, and comorbidities (including diabetes and urinary/fecal incontinence) in this analysis. Median length of stay in LTCF was also found to be similar between the *C. difficile* colonized and non-colonized residents. Additionally, the study reported no significant difference in the median length of stay between colonized and non-colonized residents. However, this study had several limitations and the authors of the study themselves cautioned against completely ruling out some of these factors like proton-pump inhibitor use as possible risk factors for *C. difficile* colonization in nursing homes given the presence of evidence outside the long-term care setting [39, 40].

Colonization rates in residents of LTCF may also depend on facility level characteristics [1]. Higher colonization rates have been seen in rehabilitation facilities [1, 38, 41]. One study showed 50% of spinal cord rehabilitation patients to be asymptomatically colonized with *C. difficile* [41]. This study also demonstrated that in comparison with non-colonized individuals, colonized individuals had higher rates of skin and environmental contamination along with longer length of stay. These factors may contribute to transmission within the facilities which can also impact the colonization rates. LTCF with higher proportion of shared occupancy rooms may also have the potential for higher colonization rates

since living with roommates has been identified as a risk factor for CDI in long-term care setting [35, 42].

## Transmission of *C. difficile* in Residents of Long-Term Care Facilities

Overall CDI incidence in any kind of setting depends on several factors that include transmission of *C. difficile* within the setting, use of antimicrobial drug, and underlying population health [7]. One of the studies estimated that hospitals have the highest transmission risk for CDI followed by the long-term care facilities and community [7]. According to this study estimate, a patient with CDI in a LTCF transmits *C. difficile* at a rate of 27% that for a comparable patient in the hospital. This transmission risk is much higher than the risk estimated for a patient in the community. A patient with CDI in the community transmits *C. difficile* to others at a rate of 0.1% that of a comparable patient in the hospital [7]. It has also been demonstrated that the risk of healthcare facility–acquired CDI is greater for those individuals who were admitted to the hospitals or skilled nursing facilities with higher than median prevalence of CDI [21]. Colonization of residents in LTCF with *C. difficile* also contributes to the transmission [37, 43–46]. Evidence suggest that *C. difficile* intestinal colonization may persist up to 6 months in some individuals, although fecal spore shedding becomes less common 5–6 weeks after treatment of CDI [1, 47]. It is also known that *C. difficile* may continue to persist on the skin beyond 4 weeks after therapy and on inanimate surfaces for as long as 5 months that might also contribute to transmission [48–50].

Durham et al. evaluated the impact of low-risk or high-risk antimicrobial agents for CDI on the incidence of CDI by using a drug risk ratio of 1–20 [7]. It was estimated that per unit increase in antimicrobial drug risk increases the CDI incidence by a factor of 33% in LTCF which is lower than what is expected in the hospital (160%) but higher than what is expected in community (6.4%). This suggests that magnitude of impact of specific antimicrobial drug use on CDI incidence also depends on the transmission rates within a facility.

Even though it has been shown that CDI transmission risk is much higher in hospitals as compared to the LTCF and the community, it is important to note that infection prevention and control programs and environmental cleaning and disinfection practices have been found to be more suboptimal in LTCF [7, 51–53]. Transmission in this setting is likely occurring by direct spread from the hands of the personnel, fomites, and the other objects in the environment. It may also be facilitated by the facts that the residents share spaces with others in the facility for sleeping, eating, and toileting along with attending social events together [11, 51]. During a CDI outbreak investigation in a 146-bed LTCF in the USA, *C. difficile* was isolated in environmental cultures throughout the institution including bed handrails, television remote control, doorway entrances, shower seat surface, wheelchair arms, toilet handrails, bedside table, sink surfaces, physical therapy grip handrail, dining room table top, and communal shower chairs [16]. This particular risk factor for transmission may get further amplified by the fact that 25–75% of antibiotic use in LTCF has been shown to be inappropriate and these facilities also lack well-developed antibiotic stewardship programs [34, 54, 55]. Majority of the antibiotic stewardship programs in the US LTCF are not meeting all seven CDC recommended core elements [55]. These factors represent some unique challenges related to preventing transmission of CDI in LTCF.

## Risk Factors for *C. difficile* Infection and Colonization in Long-Term Care Facilities

Older adults, especially those residing in long-term care facilities, are at increased risk of acquiring *C. difficile* and developing severe disease associated with this infection [11]. Several factors have been identified that may contribute to this increased risk. Age-related changes in fecal flora and immunosenescence are among those contributing factors [15]. Lower gastric acidity, less *C. difficile* antibody production, and impaired *C. difficile* phagocytosis have been thought to play a role [56]. Environmental factors specific to long-term care setting, such as residents living in

close proximity, shared rooms and toilet, and limited ability of the facility to properly isolate residents with infection, may also contribute toward *C. difficile* transmission, colonization, and infection [56]. In addition, antibiotic use, the presence of various underlying diseases, and the use of certain medications in the residents of long-term care facilities have been shown to be associated with CDI. These factors are further described in Table 2.1.

**Table 2.1** Factors predisposing LTCF residents to higher risk for *C. difficile* colonization and infection

| Category | Risk factors |
|---|---|
| Demographic factors | Increased age [11] |
| | White race [11] |
| Antibiotic use | Previous antibiotic use (especially in previous 3 months) [37] |
| | Use of antibiotics that has been identified as high risk for CDI acquisition [7, 15] |
| Use of other medications | Proton-pump inhibitor [57] |
| | Chemotherapy [11] |
| | H2 blockers [15] |
| | Use of steroid [58] |
| Systemic factors | Hypoalbuminemia [57] |
| | Renal failure/ESRD [10, 11] |
| | Pressure ulcers [11] |
| | Cirrhosis [11] |
| | Chronic obstructive pulmonary disease [11] |
| | Functional disability and cognitive impairment [56] |
| | Congestive heart failure [10] |
| | Cerebrovascular disease [10] |
| | ≥3 comorbidities [9, 56] |
| Gastrointestinal factors | Fecal incontinence [11, 56] |
| | Prior *C difficile* infection [37] |
| Facility-related factors | Recent hospitalization (especially within previous 3 months to 1 year) [37] |
| | Frequent transition from LTCF to hospital [58] |
| | Residence in LTCF itself [7, 35] |
| Presence of devices | Presence of nasogastric tube [11, 15] |
| | Presence of gastrostomy tube [11, 15] |
| | Prior tracheostomy tube [11] |

## Mortality Associated with *C. difficile* Infection in Long-Term Care Facility Residents

In general, diarrhea is associated with a higher mortality in elderly as compared to the younger adults [9]. It has been shown that at least 30% of diarrheal deaths in elderly occur outside acute care setting, mainly in the nursing homes [9]. CDI is one of the predominant causes of infectious diarrhea in elderly residents living in nursing homes [9]. Based on active population- and laboratory-based surveillance across ten geographic areas in the USA, *C. difficile* was estimated to cause almost half a million infections and 29,000 deaths in 2011 [8]. The 30-day mortality rate was estimated to be 1.3% for community associated infections and 9.3% for healthcare-associated infections. However, studies that have looked specifically into mortality rates of CDI in nursing home residents have described higher mortality rates [10, 11].

A population-based retrospective cohort study focusing on US nursing homes by linking Medicare 5% random sample, Medicaid, and Minimum Data Set found the 30-day mortality after CDI episode to be 14.7% [10]. Mortality rates among CDI residents were consistently higher as compared to the non-CDI residents at 30-day (14.7% vs 4.3%, $p < 0.001$), 60-day (22.7% vs 7.5%, $p < 0.001$), 6-month (36.3% vs 18.3%, $p < 0.001$), and 1-year (48.2% vs 31.1%, $p < 0.001$) follow-up period. Total healthcare costs within 2 months following the first CDI episode were also significantly higher for those residents who had CDI as compared to those without CDI ($28,621 vs $13,644, $p < 0.001$). Overall, this study estimated 53,000 annual CDI cases in the residents of US long-term care facilities that were associated with 5500 deaths and $800 million in costs [10]. Another retrospective cohort study used US 2011 LTCF resident data from Minimum Data Set 3.0 linked to Medicare claims for examining the epidemiology of *C. difficile* in 2011 among LTCF residents >65 years old. Residents with CDI in this study also were found to have significantly higher mortality than those without CDI (24.7% vs 18.1%, $p = 0.001$). CDI was independently associated with mortality in multivariable analysis [11].

## Conclusions

It is very clear that the epidemiology of CDI has changed significantly worldwide over the past two decades with increase in incidence and prevalence in all healthcare settings. This change is in part has been linked to the emergence of BI/NAP1/027 strain. This strain has been described as the most prevalent strain among inpatients admitted from LTCF and predominant strain in nursing home residents with CDI. It has also been implicated in several nursing home *C. difficile* infection outbreaks. *C. difficile* colonization rates in the residents of LTCF may also be higher after an outbreak. In general, the residents of long-term care facilities are at higher risk for *C. difficile* colonization and infection due to several different individual and facility specific risk factors. Mortality rates secondary to CDI are usually higher for LTCF residents. High prevalence of antibiotic misuse and lack of well-developed antimicrobial stewardship and infection prevention and control programs along with suboptimal environmental cleaning and disinfection practices can contribute toward more *C. difficile* transmission, colonization, and infections in LTCF. Efforts will need to be focused on addressing all modifiable individual and facility specific risk factors in order to decrease *C. difficile* incidence and prevalence in long-term care setting.

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