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The Epidemiology of *Clostridium difficile* Infection Inside and Outside Health Care Institutions

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INTRODUCTION

Clostridium difficile is an unusual gastrointestinal bacterial infection highly associated with health care exposure and generally occurring only in subjects whose normal protective gut bacterial microbiota have been disrupted in some manner, usually by prior antimicrobial use. *C difficile* is ubiquitous in nature and able to survive for long periods in the environment through sporulation. Widespread presence of *C difficile* in animals (dogs, cats, pigs, calves, horses, sheep), particularly during their early development, and in common environmental sites such as surface water, drinking water, swimming pools, and soil has been shown.[1] In addition, low-level contamination of foods with *C difficile* spores has been found in beef, pork, turkey, shellfish, and a variety of ready-to-eat vegetables.[2–4] As a result of the widespread presence of *C difficile* spores and its long survival in the environment, it is highly likely that humans ingest *C difficile* frequently. However, because of limited antimicrobial exposure, most humans who ingest *C difficile* remain asymptomatic and uncolonized as a result of the colonization resistance of an intact gut microbiota.

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HEALTH CARE–ASSOCIATED *CLOSTRIDIUM DIFFICILE* INFECTION

Although *C difficile* spores have widespread distribution in community sites, the initial clinical report of severe diarrhea and pseudomembranous colitis associated with clindamycin use came from a hospital setting in St Louis, Missouri, and precipitated the search for a causal agent eventually identified as *C difficile*.[5,6] Key factors in the occurrence of *C difficile* infection (CDI) in this hospital were the use of a new antibiotic, clindamycin, with an extensive antianaerobic bacterial spectrum coupled with the likely presence of *C difficile* in the hospital environment leading to exposure of highly susceptible patients to the organism. As early as 1979, it was shown that hospital environments are contaminated with *C difficile* spores.[7] Perhaps more importantly, *C difficile* contamination of the hands of hospital personnel and the environmental persistence of *C difficile* spores for up to 20 weeks was shown in 1981.[8] High rates of environmental spore contamination in hospitals are presumed to be the result of frequent CDI diarrheal episodes in hospitalized patients coupled with the resistance of spores to killing by environmental cleaners and disinfectants other than bleach.

Understanding of the epidemiology of CDI in health care settings was slow to emerge. It was not until 1986 that the first prospective case-control study of CDI was published, in which 87% of 149 CDI cases were found to be hospital associated.[9] *C difficile* was found in the stool of 21% of hospitalized case-matched control patients who did not have diarrhea, suggesting asymptomatic acquisition of *C difficile* in the hospital. CDI risk factors included receipt of clindamycin and receipt of multiple antibiotics for the treatment of infection within 14 days before CDI onset.[9] In a landmark article in 1989, McFarland and colleagues[10] used weekly rectal swab specimens to identify *C difficile* hospital acquisition in 21% of patients, most of whom (63%) were asymptomatic. The additional sophistication of molecular health care epidemiology was added by Johnson and colleagues,[11] who also used weekly rectal swab cultures plus restriction endonuclease analysis (REA) organism typing to document hospital acquisition of *C difficile* by 21% of patients, 82% of whom were asymptomatic. The use of REA typing identified 18 unique REA types of *C difficile* in these patients, but symptomatic CDI was caused only by 2 closely related REA types, B1 and B2, which were identified as causing a hospital outbreak of CDI at the time and suggesting the possibility of strain-related virulence variation in *C difficile*.[12]

Molecular strain typing was also used to show that admission to a hospital ward of asymptomatic patients carrying *C difficile* in their stool preceded acquisition of that specific strain of *C difficile* by other patients on that ward in 85% of acquisitions, indicating a possible role for asymptomatic colonized patients in transmission of *C difficile*.[13] Contrary to intuitive thinking based on methicillin-resistant Staphylococcus aureus and vancomycin-resistant enterococci epidemiology, asymptomatic patients colonized with *C difficile* have a significantly lower risk of developing CDI compared with uncolonized patients on the same hospital wards at the same time,[14] even though they may be a source of *C difficile* transmission to other patients. It is presumed that these asymptomatic colonized patients are protected from CDI either because they have developed antibodies against the *C difficile* toxins or they are colonized by harmless nontoxigenic strains of *C difficile* that lack toxin genes.[14,15]

The lack of a universally sensitive and reproducible typing system has slowed progress in the molecular epidemiology of CDI, but polymerase chain reaction (PCR) ribotyping, pulsed field gel electrophoresis (PFGE), multilocus variable-number tandem-repeat analysis, and REA have been the most frequent typing systems in use. Using REA typing, Belmares and colleagues[12] identified a total of 174 unique REA types over a 10-year period, two-thirds of which were sporadic and identified only in a single year. This finding compares with a tertiary referral hospital in which 55 unique REA types of *C difficile* were identified in a 1-year endemic period.[16] Belmares and colleagues[12] also identified large clusters of CDI cases (≥10 cases in consecutive months) caused by the same REA types, whereas smaller clusters (4–9 cases in consecutive months) were associated with a variety of other REA types. Taken together, these studies suggest that new *C difficile* strains are frequently introduced to hospitals from a large pool of strains, some of which result in hospital transmission to multiple patients, whereas most are sporadic and result in few or no transmissions. The source for these new strains is not well defined, but it is probably related to admissions and transfers of patients with active or recently resolved CDI and asymptomatically colonized patients.

Whole-genome sequencing (WGS) is the most sensitive and specific new method for molecular typing of *C difficile* isolates. In an early study using REA, 50% of second episodes of CDI (many of them multiple months after the previous episode) were caused by a new *C difficile* strain different from the original isolate (ie, reinfection)[17]; however, a more recent larger study of recurrence of CDI within 30 days after the end of treatment identified the same strain as the cause of recurrence in more than 80% of instances (ie, relapse).[18] The more sensitive WGS typing of these isolates confirmed the REA results indicating that relapses with the original strain are more common for recurrences within 30 days.[19] In a much larger epidemiologic study in the United Kingdom, WGS was used to type 1223 *C difficile* isolates using less than or equal to 2 single nucleotide variants to define identical strains and showed that only 38% of patients harboring identical strains had close contact with another symptomatic patient with CDI with the same strain. The investigators concluded that there must be diverse sources of *C difficile* other than symptomatic patients with CDI. The study was done during a nonoutbreak period of stable to declining endemic CDI rates in the United Kingdom and in the study hospital, did not include testing for asymptomatic colonized patients, and identified CDI cases using an insensitive enzyme immunoassay test for fecal toxin that could have resulted in failure to identify some CDI cases. Nonetheless, WGS elegantly documented the high number of different *C difficile* strains causing CDI and the lack of transmission that occurs with most of these strains as suggested in previous less sensitive typing studies.

Although large numbers of different *C difficile* strains have been found to cause CDI in hospitals endemically, when a health care–associated outbreak or epidemic occurs it is likely to be caused by a single or closely related strains that are being transmitted within the hospital.[12] Some of these epidemic strains have been reported in multiple hospitals that are often geographically distant from each other. For example, the REA J group caused outbreaks of CDI in multiple US hospitals in the 1990s and was also a leading outbreak strain in the United Kingdom, where it was shown by PCR ribotyping to be ribotype 001.[20,21] These J/001 strains were highly clindamycin resistant and increased CDI

incidence was associated with prior clindamycin exposure in the patients infected with J/001 strains.[20] These epidemic strains result in outbreaks, but then diminish in frequency and are supplanted by new molecular types. Perhaps the most severe of these epidemic strains are the *C difficile* toxinotype III strains that first appeared in the United States and Canada at the turn of the twenty-first century. These strains produce a third or binary toxin, have a deletion and stop codon in the *tcdC* toxin regulator gene, and are characterized by PFGE as type NAP1, by REA as group BI, and by PCR as ribotype 027.[22,23] They are highly resistant to fluoroquinolone antibiotics and prior fluoroquinolone use has been identified as a risk factor.[23]

The health care epidemiology of CDI has changed markedly since the identification of BI/NAP1/027 *C difficile* outbreaks first in the United States and Canada, then rapidly spreading to the Europe. CDI caused by these strains is of particularly high severity, causing increased mortality and requiring increased use of colectomy to treat patients who are refractory to medical management.[22–25] In Montreal, health care–associated CDI (HA-CDI) incidence increased to as high as 22.5 CDI cases per 1000 discharges with a 30-day attributable mortality of 6.9%.[23] Subsequent elegant molecular studies have shown there were 2 distinct lineages of NAP1/BI/027 designated FQR1 and FQR2 that acquired both fluoroquinolone resistance mutations and a highly related conjugative transposon.[26] The strains subsequently spread throughout the world with the FQR1 lineage, which originated in and was widely disseminated in the United States, eventually spreading to Asia and Switzerland. The FQR2 lineage was found in multiple US sites and in Montreal in Canada and spread more widely than FQR1 to Europe. Rates of CDI overall, and specifically CDI caused by BI/NAP1/027, have decreased significantly in the United Kingdom but remain high in the United States, where 28.4% of 2057 recent *C difficile* isolates were NAP1.[25,27,28]

Recent reports suggest that the epidemiology of HA-CDI is changing. Rates of CDI in US hospitals have increased steadily since 1993 to more than 336,000 CDI hospitalizations in 2009, of which nearly one-third had CDI listed as the primary diagnosis.[29] In a 2011 prevalence survey across 183 US hospitals, *C difficile* was the most commonly reported pathogen (causing 12.1% of the health care–associated infections identified).[30] CDI continues to be a health care–associated infection, with 94% of all CDI being related to various precedent and concurrent health care exposures. However, some of these exposures are occurring in the outpatient setting, perhaps reflecting the increase in health care being delivered in the outpatient setting (Fig. 1).[31] In addition, 75% of CDIs now occur in nursing homes or in the community based on laboratory test identification, in contrast with the 87% of CDIs that were reported to be hospital onset in 1986.[9] Therefore, many patients are already admitted with CDI. Recent data from the US National Healthcare Safety Network showed that 52% of CDI patients already have CDI present at the time of hospital admission.[31] The overall rate of hospital-onset CDI in the 711 US acute-care hospitals in 2010 was 7.4 per 10,000 patient-days, with a median hospital rate of 5.4 per 10,000. Some patients were exposed to multiple health care settings; 20% of hospital-onset CDIs occurred in patients who were residents of a nursing home in the prior 12 weeks, and 67% of nursing home–onset CDI cases occurred in patients recently discharged from an acute-care hospital.[31]

Nursing home or long-term-care residents seem to be at the highest risk of CDI within the first month of admission to the nursing home, when 52% to 69% of CDI cases in nursing homes are diagnosed, but overall rates of CDI per 10,000 patient-days are about 25% of those in acute-care hospitals in the same geographic area.[32,33] Among patients who developed CDI within the first month of admission to a nursing home, 68% were residents admitted for subacute care.[32] In a large study conducted across 33 nursing homes in New York, CDI resulted in hospitalization in 16% of the residents, 70% of whom had severe CDI.[33]

COMMUNITY-ASSOCIATED *CLOSTRIDIUM DIFFICILE* INFECTION

C difficile was thought to cause disease only in hospitalized and elderly patients until the beginning of the twenty-first century when reports of CDI in the community among young and previously healthy individuals in North America and Europe were published.[34–36] Since these initial reports, *C difficile* has been increasingly recognized outside health care settings.

The definition for community-associated CDI (CA-CDI) has differed among studies, especially before the publication of the interim surveillance definitions in 2007 by the Society for Healthcare Epidemiology of America, which defined CDI cases as community associated if patients had diarrhea onset in the community or within 48 hours after hospitalization and had not been discharged from a health care facility in the prior 12 weeks; otherwise CDI cases were defined as health care associated.[37] In addition to differences in surveillance definitions, some studies have also used different surveillance methods to identify CA-CDI. The proportion of total CDI cases that are reported to be CA-CDI ranges from 10% to 30% when using hospital-based surveillance and the recommended surveillance case definition,[38,39] but ranges from 30% to 50% when using population-based surveillance.[40–42] The lower proportion of CA-CDI in hospital-based studies can be explained by the report of Chitnis and colleagues,[43] which showed that approximately 25% of patients with CA-CDI are hospitalized; thus, most are treated as outpatients. Therefore, hospital-based surveillance likely underestimates the burden of CA-CDI.

Before the introduction of more sensitive assays for *C difficile* diagnosis, the population-based CA-CDI incidence was reported to be 20 to 40 per 100,000 persons[39,44]; however, a study done in 2010 after the introduction of molecular assays showed that CA-CDI yearly incidence can be up to 80 per 100,000 persons in some US regions, but could also represent some overdiagnosis from the use of highly sensitive molecular testing.[42] Patients with CA-CDI are usually younger than those with HA-CDI,[45,46] and also less likely to recur. The CDI recurrence rate has been reported to be 10% among CA-CID cases[47] but approximately 20% among HA-CDI cases.[48,49] The lower recurrence rate among CA-CDI cases may be related to several factors, such as (1) fewer exposures after the initial CDI diagnosis to *C difficile*-provocative antimicrobials and to inpatient health care settings, which are known to be associated with increased risk of recurrence; and (2) younger age (median age of patients with CA-CDI is 53 years, compared with 78 years for patients with HA-CDI).[45]

The data on strain types causing disease in persons in the community are sparse. However, the few studies reporting strain data on CA-CDI cases suggest that the prevalence of strain

types causing CA-CDI may differ slightly between countries. In the United States, the most common strain types in CA-CDI are PCR ribotype 027/NAP1, which is the epidemic strain, ribotype 014/020 (primarily represents NAP4), and ribotype 016 (primarily represents NAP11).[43,45] In Europe, where decreases in the prevalence of ribotype 027/NAP1 are being observed,[28,29] the most prevalent strains causing CA-CDI are ribotypes 014/020, 106, and 015.[50,51] Ribotype 078 (or NAP 7/NAP8) is usually isolated from food and food animals, represents 2% to 7% of CA-CDI isolates in humans in both Europe and North America, and has the potential to cause severe disease.[43,45,52,53] Because the *C difficile* molecular epidemiology is both diverse and dynamic, as shown by Belmares and colleagues,[12] it is possible that other strains will emerge as important causes of CDI in the community. Recent reports from Australia and New Zealand[54,55] described the emergence of ribotype 244, toxinotype IX, causing severe CDI in the community and health care settings. Ribotype 244 produces binary toxin in addition to toxin A and toxin B but, unlike ribotype 027, it did not show high-level resistance to fluoroquinolones.

C difficile is a ubiquitous pathogen that may be found in the environment, food, and animals; therefore, the source of *C difficile* in CA-CDI is difficult to establish. A study by Chitnis and colleagues[43] involving telephone interviews of almost 1000 patients with CA-CDI showed that 82% of them had outpatient health care exposures such as doctor or dentist office visits, outpatient surgeries, or emergency department visits in the 12 weeks before the positive *C difficile* stool specimen. Outpatient settings can either be the place where antimicrobials, which disrupt the gut microbiota, are prescribed or a potential source of *C difficile* acquisition. In a study by Jury and colleagues,[56] toxigenic *C difficile* was isolated from several environmental surfaces in outpatient clinics and emergency departments with the providers' work areas and the patients' examination tables being the most frequently contaminated environmental sites. *C difficile* spores can survive for prolonged periods of time in the environment[57] and environmental disinfection in outpatient settings may be suboptimal because of high patient turnover.

In addition to outpatient settings, other potential sources of *C difficile* in the community have been described. Exposure to infants, who are known to have a high rate of *C difficile* colonization, and household members with active CDI have been reported to be associated with increased risk of CA-CDI.[44,58] *C difficile* has also been isolated from food and animals in several countries; however, its association with CDI in humans has not been shown. The prevalence of *C difficile* in retail meats has ranged substantially across studies; however, in most studies the prevalence is less than 7%.[59–61] The prevalence of *C difficile* in vegetables, including lettuce, potatoes, onions, carrot, radish, mushroom, and cucumber, is less understood. A study from France[2] reported that 2.9% of samples of ready-to-eat salad contained toxigenic *C difficile* strains, whereas a prevalence of 4.5% was reported in a similar study from Canada.[62] A recent study from Janezic and colleagues,[63] involving 112 *C difficile* isolates from 13 animal species in 12 different countries, showed a large variability of strains. Although ribotype 078 (or NAP 7) was the most prevalent, other ribotypes often found in humans, such as ribotype 014/020 and 002, were also common in animals across several countries. Some of the most prevalent strains among humans in the United States and part of Europe, including ribotype 027 (epidemic strain), ribotype 016, and ribotype 106,[27,43,53] were infrequently isolated from animals. Nevertheless, the partial

overlap of strains between humans and animals increases the concern for potential zoonotic transmission, which needs to be further studied.

CLOSTRIDIUM DIFFICILE INFECTION IN CHILDREN

Reports of CDI in hospitalized children have increased substantially since 1997.[64,65] In the United States, rates of pediatric CDI-related hospitalizations went from 0.72 to 1.28 per 1000 hospitalizations from 1997 to 2006. Data from both hospital-based and population-based surveillance have shown that the highest CDI incidence is among children 1 to 4 years of age, with children 1 year old (ie, 12–23 months old) being the most affected; this is an age at which some asymptomatic *C difficile* colonization may still be present and may confound diagnostic testing, especially with the use of highly sensitive molecular methods such as PCR (Fig. 2).[65,66] According to population-based data, most (~70%) CDI in children is community associated and the hospitalization rate ranges from 11% to 25% depending on the age group.[67] CDI-related complications, including death, are rare in children. A prospective study among 82 hospitalized children with CDI found that toxic megacolon, gastrointestinal perforation, pneumatosis intestinalis, and surgical intervention occurred in less than 2% of cases.[67] Although dedicated pediatric studies evaluating risk factors are limited in number, recent studies have suggested that children 1 year of age or older with comorbid conditions such as cancer, solid organ transplant, gastrostomy, or jejunostomy are at increased risk for CDI.[68,69]

Infants less than 1 year of age have a high rate (~70%) of *C difficile* colonization by toxigenic and nontoxigenic strains[70,71] and are usually excluded from pediatric studies because it is difficult to differentiate colonization from infection in this age group. Asymptomatic colonization decreases rapidly during the second and third years and, by the time children reach 3 years of age, the rate of *C difficile* asymptomatic carriage is 0% to 3%, which is similar to that of adults.[72] Some experts have speculated that infants do not develop clinical illness even when colonized with toxigenic strains because of the absence of mature intestinal receptors for *C difficile* toxins as shown in rabbits, but this hypothesis has yet to be proved in humans.[71,73] The current recommendations advise against testing of *C difficile* in infants less than 1 year of age in the United States and less than 2 years of age in the United Kingdom. However, further studies are needed to determine how often *C difficile* causes disease in non-newborn children less than 2 years of age.

CLOSTRIDIUM DIFFICILE INFECTION RISK FACTORS

Risk factors for CDI, for recurrent CDI, for CDI severity, and for CDI caused by the epidemic NAP1/BI/027 strain are summarized in Box 1. The risk for developing CDI is dominated by prior antimicrobial exposure and increases with the duration and number of antimicrobials received.[74] Risk is highest during therapy and for the first month after antimicrobial therapy, and decreases between 1 and 3 months after antibiotic use.[75] Highest risk for CDI occurs with clindamycin, fluoroquinolones, and second-generation and higher cephalosporins.[76] Other important CDI risk factors are advanced patient age, immunosuppression, prior hospitalization, and increased severity of underlying illness.[77] The use of acid-suppressive agents, particularly proton pump inhibitors (PPIs), has been

associated with increased risk for CDI, especially in the community, where up to 40% of the patients with CDI have reported no recent antibiotic exposure.[36,78,79] However, some studies have shown no such association, and the mechanism by which PPIs may increase the risk of CDI is still not well described. Other factors that have recently been suggested to be associated with CDI in hospital settings include antidepressants[80] and obesity[81,82]; however, these associations need to be confirmed by larger, multicenter studies.

Risks for recurrent CDI are similar to those for an initial episode but increase with each antecedent episode of CDI. Antimicrobial treatment either during or after the initial CDI episode further increases risk of recurrence, and the most elderly patients and those with the most severe underlying disease are at highest risk of recurrent CDI.[83,84] Severe CDI is usually defined as involving death, intensive care unit admission, megacolon, perforation, or colectomy for treatment. Patient predictors such as a white blood cell (WBC) count greater than 15,000/μL or 20,000/μL, an increase in creatinine level of greater than 1.5 times baseline (or a serum creatinine level ≥1.5 mg/dL) have correlated with more severe outcomes.[85] Low serum albumin and increased WBC levels have been found to predict CDI severity independently of infecting strain type, but higher 14-day mortality has been observed with infection caused by 2 strains of *C difficile*, NAP7-8-9/BK/078 and NAP1/BI/027, as well as with the presence of increased WBC and C-reactive protein levels, and low serum albumin level.[52] Several studies have shown the association between infection with NAP1/BI/027 strains and increased disease severity,[25,52] but this has not been a universal finding.[86] A meta-analysis and strain risk comparisons have identified fluoroquinolone exposure and age more than 65 years as risks for CDI caused by NAP1/BI/027.[87]

SUMMARY

The epidemiology of *C difficile* inside and outside health care settings has changed markedly over the last decade since the emergence of the BI/NAP1/07 strain. *C difficile* is now the most common health care–associated pathogen and is no longer restricted to health care settings. It has emerged as an important cause of diarrhea in the community, with an annual incidence of CA-CDI as high as 80 per 100,000 persons in some regions. Although *C difficile* is a ubiquitous pathogen that has been isolated from the environment, food, and animals, the mechanisms of *C difficile* acquisition in the community are still poorly understood. However, the high proportion of CA-CDI cases with exposure to outpatient health care settings suggests that *C difficile* largely remains a health care–associated pathogen. Patients exposed to antimicrobials are at high risk of developing disease both in the community and in health care settings. However, other drugs, such as acid-suppressive agents, have been associated with increased risk of CDI, especially in the community. Because the molecular epidemiology of *C difficile* is both diverse (with numerous molecular types causing CDI) and dynamic (with changing dominance of strains), it is likely that new strains will emerge as epidemic strains and that understanding of the epidemiology of this microorganism will continue to evolve.

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Box 1:

Risks for development of primary CDI, recurrent CDI, severe CDI, and CDI caused by the epidemic BI/NAP1/027 strain of *C difficile*

Risk factors for development of primary CDI

- Antibiotic exposure
- Increased patient age
- Prior hospitalization
- Severity of underlying illness
- Proton pump inhibitors and H2 blockers
- Abdominal surgery
- Nasogastric tube
- Long duration of hospitalization
- Long-term care residency

Risk factors for development of recurrent CDI

- Any prior episodes of CDI
- Additional antibiotic use
- Advanced age
- Prolonged or recent stay in health care facility
- High severity of Horn Index for underlying illness
- Proton pump inhibitor use
- Infection with NAP1/BI/027 strain type
- Absence of an antitoxin A antibody response

Risk factors for development of severe CDI

- White blood cell count greater than 15,000/μL
- Serum creatinine level greater than 1.5 × baseline
- Low serum albumin level
- Increased C-reactive protein level
- Infection with NAP7-8-9/BK/078 and NAP1/BI/027 *C difficile* strains

Risk factors for development of CDI caused by BI/NAP1/027 C difficile

- Age greater than 65 years
- Fluoroquinolone antibiotic exposure

KEY POINTS

- *Clostridium difficile* has increased in incidence and severity, becoming the most common pathogen of health care–associated infections.
- The epidemiology of *C difficile* is shifting, with most patients having disease onset outside hospital settings.
- Most patients with onset of infection (CDI) in the community either had a recent inpatient or outpatient health care exposure, suggesting that *C difficile* *C difficile* continues to be largely a health care–associated pathogen.
- The molecular epidemiology of CDI is dynamic and other epidemic strains are likely to emerge.

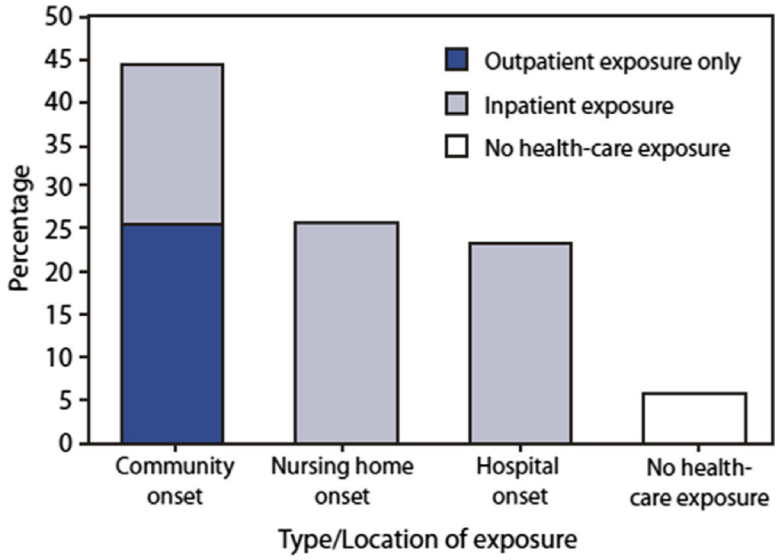

Fig. 1.

Percentage of CDI cases (N = 10,342), by inpatient or outpatient status at time of stool collection and type/location of exposures (United States, Emerging Infections Program, 2010). (*From* Centers for Disease Control and Prevention. Vital signs: preventing *Clostridium difficile* infections. MMWR Morb Mortal Wkly Rep 2012;61:157–62.)

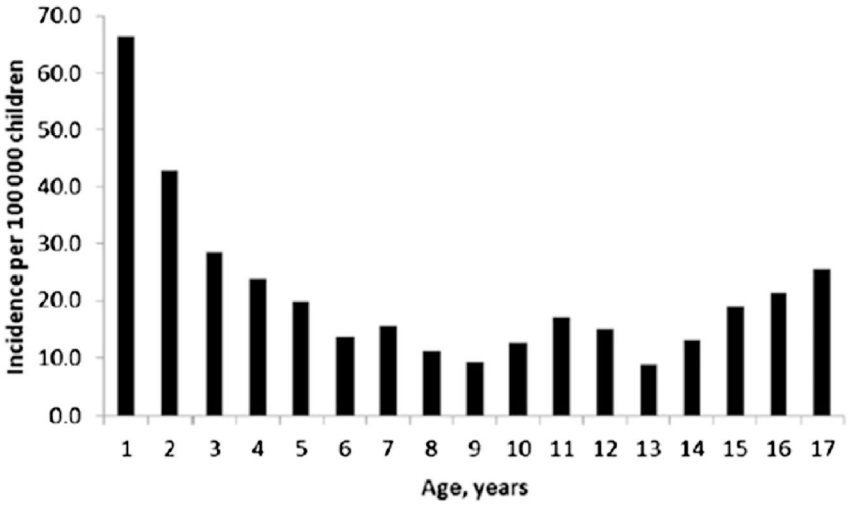

Fig. 2.

Pediatric CDI crude incidence per 100,000 children by age, 2010 to 2011 (N = 944). (*From* Wendt JM, Cohen JA, Mu Y, et al. *Clostridium difficile* infection among children across diverse US geographic locations. Pediatrics 2014;133:653, with permission.)