Clostridium difficile Infection Among Children Across Diverse US Geographic Locations

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KEY WORDS

Clostridium difficile, pediatric, community-associated, antimicrobial stewardship

ABBREVIATIONS

CDI—*Clostridium difficile* infection
CA—community-associated
CO-HCFA—community-onset, health care facility–associated
EIP—Emerging Infections Program
HCFO—health care facility–onset
NAAT—nucleic acid amplification test
NAP—North American pulsed-field gel electrophoresis
WBC—white blood cell

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WHAT'S KNOWN ON THIS SUBJECT: Little is known about the epidemiology and pathogenicity of *Clostridium difficile* infection among children, particularly those aged ≤3 years in whom colonization is common and pathogenicity uncertain.

WHAT THIS STUDY ADDS: Young children, 1 to 3 years of age, had the highest *Clostridium difficile* infection incidence. Considering that clinical presentation, outcomes, and disease severity were similar across age groups, *C difficile* infection in the youngest age group likely represents true disease and not asymptomatic colonization.

abstract

OBJECTIVE: Little is known about the epidemiology of *Clostridium difficile* infection (CDI) among children, particularly children ≤3 years of age in whom colonization is common but pathogenicity uncertain. We sought to describe pediatric CDI incidence, clinical presentation, and outcomes across age groups.

METHODS: Data from an active population- and laboratory-based CDI surveillance in 10 US geographic areas during 2010–2011 were used to identify cases (ie, residents with *C difficile*–positive stool without a positive test in the previous 8 weeks). Community-associated (CA) cases had stool collected as outpatients or ≤3 days after hospital admission and no overnight health care facility stay in the previous 12 weeks. A convenience sample of CA cases were interviewed. Demographic, exposure, and clinical data for cases aged 1 to 17 years were compared across 4 age groups: 1 year, 2 to 3 years, 4 to 9 years, and 10 to 17 years.

RESULTS: Of 944 pediatric CDI cases identified, 71% were CA. CDI incidence per 100 000 children was highest among 1-year-old (66.3) and white (23.9) cases. The proportion of cases with documented diarrhea (72%) or severe disease (8%) was similar across age groups; no cases died. Among the 84 cases interviewed who reported diarrhea on the day of stool collection, 73% received antibiotics during the previous 12 weeks.

CONCLUSIONS: Similar disease severity across age groups suggests an etiologic role for *C difficile* in the high rates of CDI observed in younger children. Prevention efforts to reduce unnecessary antimicrobial use among young children in outpatient settings should be prioritized. *Pediatrics* 2014;133:651–658

Clostridium difficile causes a wide spectrum of clinical illness, from asymptomatic colonization and mild diarrhea to pseudomembranous colitis and toxic megacolon. Among adults, *C difficile* infection (CDI) incidence and severity increased markedly in the past decade, attributed partly to the emergence of the North American pulsed-field gel electrophoresis (NAP) type 1 (NAP1).[1] CDI incidence in hospitalized children has also increased since 1997,[2,3] but little is known about the epidemiology of CDI in the general pediatric population.

Infants acquire *C difficile* in the first months of life, with reported prevalence of asymptomatic colonization as high as 73% by 6 months of age[4]; colonization can occur by both toxigenic and nontoxigenic *C difficile* strains.[5] Asymptomatic colonization decreases rapidly during the second and third years; and by the time children reach 3 years of age, *C difficile* asymptomatic carriage is 0% to 3%, similar to that in adults.[6] Why infants do not develop clinical illness even when colonized with toxigenic strains is not known; a possible explanation that has been raised but not yet demonstrated is the absence of mature intestinal receptors for *C difficile* toxins.[5,7] On the basis of this apparent lack of association between carriage and disease, published guidelines from the American Academy of Pediatrics recommend against testing children <12 months of age unless the infant has a severe motility disorder or if in an outbreak situation.[8]

In children 1 to 3 years of age, the clinical significance of detecting *C difficile* is not well understood. *C difficile* laboratory diagnostic methods such as enzyme immunoassay or nucleic acid amplification test (NAAT) do not differentiate between colonization and disease. In the context of rapidly changing epidemiology and severity of CDI among populations previously at low risk of CDI, a better understanding of the association between *C difficile*–positive stool and clinical disease among young children to help guide clinical management and prevention efforts has become important.[9]

METHODS

Pediatric CDI Surveillance

In 2010, the Emerging Infections Program (EIP) conducted active population-based CDI surveillance in select counties in 8 US states: California, Colorado, Connecticut, Georgia, Minnesota, New York, Oregon, and Tennessee. In 2011, the surveillance expanded to Maryland and New Mexico. The population of children aged 1 to 17 years across the EIP sites in 2010 and 2011 was 1 940 194 and 2 462 433, respectively.[10] The surveillance methods have been described elsewhere.[11] Briefly, surveillance staff at each EIP site identified all positive *C difficile* test results either by toxin or molecular assay from all laboratories serving surveillance area residents. A pediatric CDI case was defined as a *C difficile*–positive stool specimen in a surveillance area resident aged 1 to 17 years who did not have a positive assay in the previous 8 weeks. Infants <12 months of age were excluded from surveillance. For each CDI case, medical records were reviewed to determine if the infection was health care facility–onset (HCFO; ie, positive stool collected >3 calendar days after admission) or community-onset (all others).[12] Community-onset CDI cases were further classified into 2 mutually exclusive groups: (1) community-onset, health care facility–associated (CO-HCFA) if there was a recent (ie, within 12 weeks before stool collection date) overnight stay in a health care facility or (2) community-associated (CA) if no recent overnight stay in a health care facility was documented. Data on clinical presentation, disease severity, clinical outcomes, medication exposures in the 2 weeks before stool collection, and underlying medical conditions were obtained from the medical records for all CDI cases. A 2-week instead of a 12-week period was used for medication exposure during the medical record review for operational purposes. However, the highest risk period for CDI is reported to be within 2 weeks of antibiotic cessation.[13] Information on other enteric pathogens tested on the same day as the positive *C difficile* specimen was collected. Stool collection and testing for *C difficile* or other enteric pathogens was based on provider discretion.

A convenience sample of CA CDI cases with stool collected from January 1, 2010, to December 31, 2011, were contacted for a telephone interview within 3 to 6 months after stool collection. Persons aged 13 to 17 years were interviewed directly, whereas a parent or legal guardian was interviewed for children 1 to 12 years of age. Interviewees were asked additional questions regarding the CDI case's clinical symptoms, medical history, exposures to outpatient health care settings, medications in the 12 weeks before stool collection, indication for taking antibiotics, and household exposures.

A separate convenience sample of *C difficile*–positive stool specimens was cultured, and recovered isolates underwent pulsed-field gel electrophoresis. Pulsed-field gel electrophoresis patterns were analyzed by using BioNumerics version 5.10 (Applied Maths, Austin, TX) and grouped into pulsed-field types by using Dice/UPGMA clustering, and an 80% similarity threshold was used to assign NAP types.[14]

This project was approved by the institutional review boards at the Centers for Disease Control and Prevention and participating sites. Verbal consent or assent, when appropriate, was obtained from all persons interviewed.

Statistical Analysis

The total 2010 and 2011 US population census of children aged 1 to 17 years from surveillance areas was used to calculate

incidence rates per 100 000 children across the 2 calendar years. Cases were stratified into ages 1 year, 2 to 3 years, 4 to 9 years, and 10 to 17 years. Missing race data (37%) were statistically imputed on the basis of the distribution of known race by age, gender, and surveillance site.

The proportion of cases diagnosed by NAAT was estimated by using data from annual laboratory practices surveys conducted among clinical, reference, and commercial laboratories serving the surveillance areas.

Demographic, exposure, and clinical characteristics and type of *C difficile*–positive diagnostic assay were compared by using χ^2 or Fisher's exact tests to detect any difference across the 4 age groups. The Wilcoxon rank sum test was used to compare continuous variables. All analyses were conducted by using SAS version 9.2 (SAS Institute, Cary, NC).

RESULTS

Incidence and Epidemiologic Classification of CDIs

During January 1, 2010, to December 31, 2011, 944 cases of pediatric CDI were identified among 885 children. There was no difference in the incidence of CDI between boys and girls, but the incidence was highest among white children and those aged 1 year old (ie, 12–23 months old) (Table 1). The incidence decreased between ages 1 to 6 years from 66.3 to 13.8 per 100 000 children and increased between ages 13 to 17 years from 8.8 to 25.6 per 100 000 children (Fig 1). Of the 944 cases identified, 667 (71%) were CA, 163 (17%) were CO-HCFA, and 114 (12%) were HCFO. In every age group, >50% of cases were CA (Fig 2).

Laboratory Diagnosis and Clinical Characteristics

The estimated proportion of cases detected by NAAT was not different across the age groups (Table 2). Presenting signs and symptoms were mild and similar across the age groups. Within 1 day of stool collection, diarrhea and a white blood cell (WBC) count of ≥15 000 cells per mm^3 was documented in 680 (72%) and 68 (7%) of cases, respectively; 3 cases had radiographic evidence of ileus and 5 cases developed pseudomembranous colitis within 5 days of stool collection. Recurrence, defined as *C difficile*–positive stool within 2 to 8 weeks after previously positive stool, was documented in 100 (11%) cases overall, but it was less frequent among cases aged 10 to 17 years (P = .04) than in cases in other age groups.

TABLE 1 Incidence of Pediatric CDI by Select Demographic Characteristics: EIP, 2010–2011

Characteristic	*n* (%)	Population[a], *n*	Total Incidence	*P*
Gender				.26
Male	499 (53)	2 247 607	22.2	
Female	445 (47)	2 155 020	20.6	
Race[b]				<.0001
White	656 (69)	2 745 611	23.9	
Nonwhite	288 (31)	1 657 016	17.4	
Age group				<.0001
1 year	171 (18)	257 797	66.3	
2–3 years	188 (20)	526 231	35.7	
4–9 years	245 (26)	1 567 904	15.6	
10–17 years	340 (36)	2 050 695	16.6	

N = 944.
[a] Population of children aged 1–17 years in surveillance catchment areas during 2010–2011 based on 2010 and 2011 US census data.
[b] Statistically imputed for 353 (37%) cases with missing or unknown race.

Severe Disease, Underlying Medical Conditions, and Hospitalizations

The proportion of cases with severe disease, defined by abnormal radiographic finding (ileus or toxic megacolon), WBC count of ≥15 000 cells per mm^3, pseudomembranous colitis, or ICU admission, was low (76; 8%) and similar across the age groups (P = .08) (Table 2). Underlying medical conditions were more frequently documented for cases aged 10 to 17 years (P < .001), particularly inflammatory bowel disease (P = .004). In most cases (830; 88%), *C difficile*–positive stool was collected as an outpatient, but the proportion of *C difficile*–positive stool collected as outpatient was significantly lower among cases aged 10 to 17 years compared with cases in other age groups (P = .005); cases aged 10 to 17 years were also more likely to be hospitalized within 7 days of stool collection (P = .004). Six cases overall required ICU admission, 1 case required colectomy, and there were no deaths.

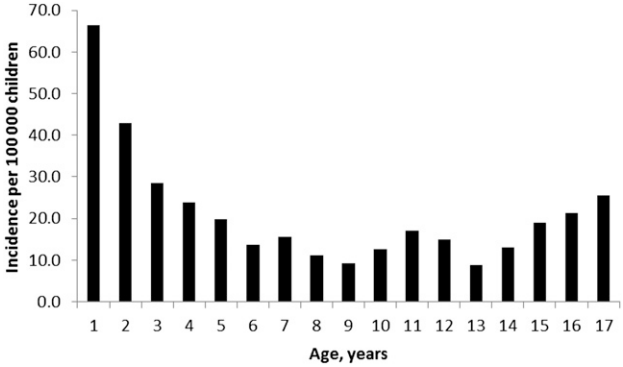

FIGURE 1
Pediatric CDI crude incidence per 100 000 children by age, 2010–2011 (N = 944).

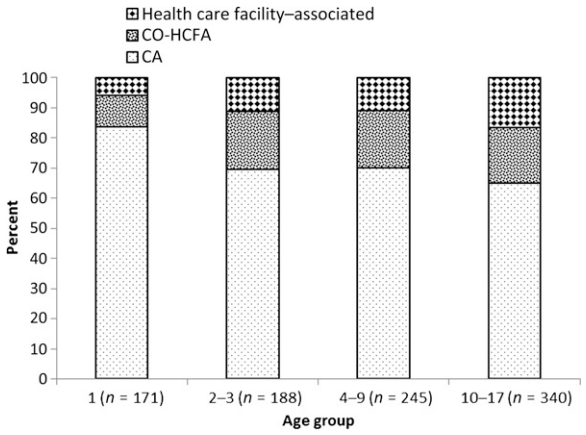

FIGURE 2
Proportion of pediatric CDI cases in each epidemiologic class by age group.

Medication Exposure

Antibiotic use during the 14 days before *C difficile*–positive stool collection was documented in 33% of cases and did not differ across the age groups (P = .23). Among cases that used antibiotics, cephalosporins (131; 41%) and β-lactam agents with increased activity (98; 31%) were most commonly documented; a combination of amoxicillin and clavulanate (92; 94%) was the most common β-lactam with increased activity. The use of gastric acid suppressors, systemic steroids, chemotherapy, or other immunosuppressive therapies was not common and did not differ across the age groups.

Coinfected Cases

Coinfection with another enteric pathogen was identified in 17 (3%) of 535 cases. The identified copathogens were bacterial (n = 12), protozoal (n = 4), and viral (n = 1) (Table 2). Evidence of coinfection was more common among children aged 2 to 9 years than among children in other age groups (P = .03). Compared with 518 cases who did not have coinfection identified, the coinfected cases were similar with respect to hospitalization (19% vs 29%; P = .34) and disease severity (9% vs 18%; P = .19).

C difficile Molecular Characterization

C difficile was recovered from 132 (78%) of 169 positive specimens cultured; age distribution did not differ between culture-positive and culture-negative cases (P = .4). The 2 HCFO cases with *C difficile* isolates available were combined with the 29 CO-HCFA cases to assess differences in strain distribution between health care–associated and CA cases. NAP1 was the most common strain (30; 23%) followed by NAP11 (17; 13%) and NAP4 (15; 11%) (Table 3). There was no difference in the proportion of CA and health care–associated cases that were NAP1 (22% vs 26%; P = .63). Four cases were NAP7 or NAP8, and all were CA.

Health Interviews

Of 667 CA CDI cases, 123 (18%) were contacted for health interviews; 95 (77%) completed interviews, 15 (12%) could not be contacted, and 13 (11%) declined participation. Among 95 patients interviewed, 84 (88%) reported diarrhea on the day of stool collection and were included in the analyses. The 84 included cases were similar to the CA CDI cases not interviewed with regard to age and gender, but interviewed cases were more likely to be white (93% vs 64%; $P < .0001$).

Of the 84 cases included, 61 (73%) reported antibiotic use during the 12 weeks before diarrhea onset, and the most commonly reported reason for antimicrobial therapy was for ear, sinus, or upper respiratory tract infection (51; 84%) (Table 4). Penicillins (27; 44%) were the most commonly reported antibiotics used, followed by cephalosporins (24; 39%) and β-lactams with increased activity (16; 26%). The use of gastric acid suppressors (proton pump inhibitors or histamine$_2$-receptor blockers) was not common (8; 9%). Among 73 (87%) cases who reported any outpatient health care exposures during the 12 weeks before diarrhea onset, a doctor's office visit was the most common (71; 97%), followed by a dental office visit (23; 32%). Only 7 (8%) cases had neither outpatient health care nor antibiotic exposure.

Among 19 (23%) cases exposed to household members with diarrhea, 3 reported exposure to a household member with confirmed CDI. Fourteen (17%) and 12 (14%) cases reported exposure to household members who worked in health care facilities and to infants, respectively.

DISCUSSION

Most of the CDI cases among children from diverse US locations were CA and clinically mild. Although children aged 1 to 3 years, particularly the 1-year-old children, had the highest incidence of CDI, the clinical presentation, disease severity, and outcomes were similar across the 4 age groups studied, suggesting that the presence of positive *C difficile* specimens in patients 1 to 3 years of age likely represents infection as it does in older children.

Infants, who were excluded from our study, are well known to be colonized with *C difficile*, but at what age and to what degree *C difficile* becomes pathogenic among young children are not clear. If the high incidence among children 1 year of age represented only persistent colonization beyond infancy, we would have expected to observe milder clinical disease among the youngest cases compared with cases in older age groups. In fact, similar clinical characteristics were

TABLE 2 Comparison of Clinical Characteristics, Disease Severity, and Outcomes Among Pediatric CDI Cases by Age Group, 2010–2011

Variable	Total (N = 944), n %	Age Group, n (%)				P
		Year 1 (n = 171)	2–3 Years (n = 188)	4–9 Years (n = 245)	10–17 Years (n = 340)	
Cases diagnosed by NAAT[a]	367 (39)	67 (39)	73 (39)	99 (40)	128 (38)	.93
Diarrhea within 1 day of stool collection	680 (72)	133 (78)	140 (74)	173 (71)	234 (69)	.15
WBC count ≥15 000 cells per mm^3 within 1 day of stool collection	68 (7)	8 (5)	9 (5)	18 (7)	33 (10)	.09
Radiographic ileus within 5 days of stool collection	3 (0.3)	0	0	2 (1)	1 (0.5)	.53
Pseudomembranous colitis documented on surgical pathology or endoscopy performed within 5 days of stool collection	5 (0.5)	1 (1)	1 (1)	0	3 (1)	.56
Recurrence	100 (11)	23 (13)	20 (11)	33 (13)	24 (7)	.04
Severe disease[b]	76 (8)	9 (5)	10 (5)	21 (9)	36 (11)	.08
Stool collected as outpatient	830 (88)	161 (94)	167 (89)	218 (89)	284 (84)	.005
Hospitalized within 7 days of outpatient stool collection	154 (19)	18 (11)	30 (18)	36 (17)	70 (25)	.004
Admitted to ICU	6 (4)	0	1	4 (11)	1 (1)	.07
Underlying medical conditions, any[c]	395 (42)	49 (29)	73 (39)	96 (39)	177 (52)	<.001
Pulmonary disease	64 (16)	7 (14)	12 (16)	15 (16)	30 (17)	.11
Hematologic or solid malignancy	52 (13)	5 (10)	9 (12)	14 (15)	24 (14)	.97
Inflammatory bowel disease	28 (7)	0	1 (1)	7 (7)	20 (11)	.004
Medications						
Antibiotics, any[c]	316 (33)	56 (33)	68 (36)	91 (37)	101 (30)	.23
Cephalosporins	131 (41)	20 (36)	27 (40)	39 (43)	45 (45)	.72
β-Lactams with increased activity[d]	98 (31)	21 (38)	33 (49)	20 (22)	24 (24)	.0008
Folic acid inhibitors	53 (17)	6 (11)	14 (21)	15 (16)	18 (18)	.52
Clindamycin	27 (9)	0	1 (1)	7 (8)	19 (19)	<.0001
Macrolide	27 (9)	6 (11)	6 (9)	7 (8)	8 (8)	.92
Fluoroquinolones	22 (7)	2 (4)	3 (4)	4 (4)	13 (13)	.07
Penicillins[e]	15 (5)	3 (5)	0	9 (10)	3 (3)	.02
Proton pump inhibitors	91 (10)	11 (6)	18 (10)	24 (10)	38 (11)	.40
$Histamine_2$-receptor blockers	48 (5)	8 (5)	11 (6)	12 (5)	17 (5)	.96
Systemic steroids	81 (9)	6 (4)	17 (9)	23 (9)	35 (10)	.07
Chemotherapy or other immune suppressing agents	24 (3)	2 (1)	4 (2)	7 (3)	11 (3)	.53
Stool concurrently tested for coinfection	535 (57)	107 (63)	111 (59)	136 (56)	181 (53)	.20
Coinfected[f]	17 (3)	0	6 (5)	7 (5)	4 (2)	.03

[a] Estimated by using data from annual laboratory practices surveys across laboratories serving the surveillance areas.
[b] Abnormal radiographic finding: WBC ≥15 000 cells per mm^3, pseudomembranous colitis, or ICU admission.
[c] Not mutually exclusive
[d] Includes amoxicillin and clavulanate; ampicillin and sulbactam; piperacillin and tazobactam.
[e] Includes penicillin and amoxicillin.
[f] Identified copathogens include the following: *Campylobacter jejuni* (5), *Salmonella* spp (4), *Shigella* (2), shiga toxin–producing *Escherichia coli* (1), *Cryptosporidium parvum* (2), *Entamoeba histolytica* (1), *Giardia lamblia* (1), and rotavirus (1).

observed despite a higher proportion of older cases having underlying comorbid conditions, in particular, inflammatory bowel disease. Among hospitalized children, inflammatory bowel disease has been shown to be associated with CDI recurrence, treatment failure, and increased length of hospitalization.[15] Comorbid conditions may affect clinical presentation less significantly among nonhospitalized CA CDI cases. Finally, the high CDI incidence we observed among the youngest age group may be related to the finding that children 0 to 2 years of age have the highest outpatient antibiotic prescribing rate, even when compared with patients ≥65 years.[16]

Women have been reported to have a higher incidence of CDI than men in studies involving adult populations, but no difference in incidence was seen between girls and boys in our study.[17] Environmental exposures that confer risk for *C difficile* acquisition may differ by gender among adults but not among children. CDI incidence is higher among white than nonwhite populations in our data, which may be explained by higher outpatient health care utilization reported among whites than nonwhites, likely reflecting, in part, differences in health care access.[18]

The CDI burden among pediatric patients appears to be much higher in community compared with hospital settings. Our finding that 71% of CDI pediatric cases are CA supports the reported increase in CA CDI among children in other studies.[19,20] These CA cases did not have an overnight stay in a health care facility, but 87% of them reported exposure to outpatient health care facilities before CDI, which may represent either the source of *C difficile* acquisition or where antibiotics were prescribed. Other sources of *C difficile* in the community have been speculated. A review of CDI cases in Canada reported a substantial increase in short-term relative risk of CDI among spouses and children of index CDI cases.[21] Day care centers

TABLE 3 Distribution of Pediatric *C difficile* NAP Types by Epidemiologic Class

Strain Type	CA (*n* = 101)	Health Care–Associated[a] (*n* = 31)
NAP1	22 (22)	8 (26)
NAP4	11 (11)	4 (13)
NAP 7 or NAP8	4 (4)	0 (0)
NAP9	8 (8)	1 (3)
NAP11	11 (11)	6 (19)
Other[b]	45 (44)	12 (39)

Data are presented as *n* (%). *N* = 132.

[a] CO-HCFA (*n* = 29) and HCFO (*n* = 2) cases were combined.

[b] Other NAP types include NAP2, NAP3, NAP6, NAP10, NAP12, and unnamed.

have also been raised as a potential source of *C difficile* in the community. Matsuki et al[22] found *C difficile* environmental contamination in a day nursery and a kindergarten, and even though the strains isolated in the environment were identical to the strains isolated from the children, they were not linked to clinical illness. In our study, day care attendance was not assessed. Finally, *C difficile* has been isolated from retail meats in some studies, and some have speculated food as a source of *C difficile* in the community.[23–25] In our study, NAP7 and NAP8, the strains that have been most frequently isolated from meat samples, were uncommon.

Of the CA CDI cases who were interviewed, a large proportion (73%) reported recent antibiotic exposure, which was slightly higher than the 64% reported by Chitnis et al[26] among both adult and pediatric CA CDI cases. The most commonly reported reason for antimicrobial therapy was ear, sinus, or upper respiratory tract infection. Our data are consistent with other findings that otitis media and upper respiratory tract infections are the most common reasons for antibiotic use, a large proportion of which is thought to be inappropriate.[27,28]

Exposure to antibiotics is the most important modifiable risk factor for CDI.[13,29] The findings from our study underscore the opportunity for effective antibiotic stewardship programs in pediatric outpatient settings to affect CDI incidence. Although the use of gastric acid–suppressing medications has been described as a risk factor for CDI among both hospitalized and nonhospitalized patients, the use of proton pump inhibitors and histamine$_2$-receptor blockers was relatively uncommon among children in our study.[30–32]

The identification of coinfection was rare in our study, and there was no association between coinfection and severity of illness. Although a single-center study reported a 11% rate of *C difficile* coinfection among pediatric cases, most of the coinfected cases were <1 year of age.[33]

The distribution of NAP types in our study was consistent with recent US findings among adults with CA CDI, in whom NAP1 was the most common strain type.[26] The predominance of the NAP1 strain among CA pediatric cases is notable, because 1 factor postulated to have contributed to its emergence is high-level resistance to fluoroquinolones. This class of antibiotics is commonly used in adults but not in children.[34] These findings provide further evidence of the ability of NAP1 to spread across a range of hospital and nonhospital settings, causing disease in a population traditionally thought to be at low risk of infection.

Our study is subject to limitations. First, health interviews were completed in

TABLE 4 Characteristics and Exposures Among Interviewed Pediatric CA CDI cases With Diarrhea at Time of *C difficile*–Positive Stool Collection

Variable	*n* (%)
Antibiotics during 12 weeks before *C difficile*–positive stool collection	61 (73)
Reasons for antimicrobial therapy	
Ear, sinus, upper respiratory infections	51 (84)
Bronchitis/pneumonia	11 (18)
Urinary tract infections	4 (7)
Skin infections	3 (5)
Dental cleaning/surgery	1 (2)
Class of antibiotics used	
Penicillins	27 (44)
Cephalosporins	24 (39)
β-Lactams with increased activity	16 (26)
Macrolides	5 (8)
Clindamycin	2 (3)
Fluoroquinolones	1 (2)
Proton pump inhibitor	7 (8)
Histamine$_2$-receptor blocker	1 (1)
Outpatient health care exposure during 12 weeks before *C difficile*–positive stool collection	73 (87)
Doctor's office	71 (97)
Dentist's office	23 (32)
Outpatient clinic at a hospital	9 (12)
Emergency department	4 (5)
Household member had diarrhea during 12 weeks before case's *C difficile*–positive stool collection	19 (23)
Household member's diarrhea diagnosed as *C difficile*	3 (16)
Household member works in health care facility	14 (17)
Have household members aged 0–11 months	12 (14)

N = 84.

a convenience sample of CA cases, and a higher proportion of white cases completed the interviews than nonwhite cases. Health care–associated cases were not interviewed. Similarly, only a sample of cases had stool submitted for culture and strain typing. Therefore, cases who completed health interviews and cases who had *C difficile* isolates strain-typed may not be representative of all pediatric cases identified in the surveillance. Second, although published guidelines for CDI diagnosis recommend *C difficile* testing only on unformed stool,[12] on chart reviews 28% of our cases did not have documentation of diarrhea. However, relying solely on diarrhea documented in medical records likely underestimates the number of cases with diarrhea, because the proportion of cases who did not report diarrhea decreased to 12% after patients were interviewed. Third, the proportion of coinfected cases identified in our study may be an underestimate given that we only captured other enteric pathogens tested on the same day as the *C difficile*–positive stool. In addition, some enteric viruses are not routinely tested for by clinical laboratories. Finally, antibiotic exposure may have been overestimated because some physicians may only consider a *C difficile* diagnosis in children with recent antibiotic exposure, even though current US guidelines do not recommend this practice given increasing reports of CDI in the absence of antibiotic exposure.[8,12]

CONCLUSIONS

To our knowledge, this study is the largest active population-based surveillance of CDI in US children. We found that the highest burden of pediatric CDI is in the community. Children from 12 to 23 months of age are at the highest risk of infection; and clinical presentation, disease severity, and outcomes are similar across ages, supporting a pathogenic role of *C difficile* among symptomatic young children. Exposure to antibiotics was very common, indicating the need for prevention efforts that focus on antibiotic stewardship in pediatric outpatient health care settings. Future studies will be important to identify potential sources of *C difficile* acquisition among children in the community.

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