Risk factors for community-associated Clostridioides difficile infection in young children

M. K. Weng1, S. H. Adkins1, W. Bamberg2, M. M. Farley3,4,5, C. C. Espinosa4,5, L. Wilson6, R. Perlmutter6, S. Holzbauer7,8, T. Whitten7, E. C. Phipps9, E. B. Hancock9, G. Dumyati10, D. S. Nelson10, Z. G. Beldavs11, V. Ocampo11, C. M. Davis12, B. Rue12, L. Korhonen1, L. C. McDonald1 and A. Y. Guh1

1Division of Healthcare Quality Promotion, Centers for Disease Control and Prevention, Atlanta, GA, USA; 2Colorado Department of Public Health and Environment, Denver, CO, USA; 3Department of Medicine, Emory University, Atlanta, GA, USA; 4Georgia Emerging Infections Program, Decatur, GA, USA; 5Atlanta Veterans Affairs Medical Center, Atlanta, GA, USA; 6Maryland Department of Health, Baltimore, MD, USA; 7Minnesota Department of Health, St Paul, MN, USA; 8Career Epidemiology Field Officer Program, Centers for Disease Control and Prevention, Atlanta, GA, USA; 9New Mexico Emerging Infections Program, University of New Mexico, Albuquerque, NM, USA; 10New York Emerging Infections Program and University of Rochester Medical Center, Rochester, NY, USA; 11Oregon Health Authority, Portland, OR, USA and 12Tennessee Department of Health, Nashville, TN, USA

Abstract

The majority of paediatric Clostridioides difficile infections (CDI) are community-associated (CA), but few data exist regarding associated risk factors. We conducted a case–control study to evaluate CA-CDI risk factors in young children. Participants were enrolled from eight US sites during October 2014–February 2016. Case-patients were defined as children aged 1–5 years with a positive C. difficile specimen collected as an outpatient or ≤3 days of hospital admission, who had no healthcare facility admission in the prior 12 weeks and no history of CDI. Each case-patient was matched to one control. Caregivers were interviewed regarding relevant exposures. Multivariable conditional logistic regression was performed. Of 68 pairs, 44.1% were female. More case-patients than controls had a comorbidity (33.3% vs. 12.1%; P = 0.01); recent higher-risk outpatient exposures (34.9% vs. 17.7%; P = 0.03); recent antibiotic use (54.4% vs. 19.4%; P < 0.0001); or recent exposure to a household member with diarrhoea (41.3% vs. 21.5%; P = 0.04). In multivariable analysis, antibiotic exposure in the preceding 12 weeks was significantly associated with CA-CDI (adjusted matched odds ratio, 6.25; 95% CI 2.18–17.96). Improved antibiotic prescribing might reduce CA-CDI in this population. Further evaluation of the potential role of outpatient healthcare and household exposures in C. difficile transmission is needed.

Background

Clostridioides difficile (formerly Clostridium difficile), a Gram-positive, spore-forming anaerobic bacillus, is the most common cause of healthcare-associated diarrhoea in the USA [1]. Acquisition of C. difficile, most frequently through faecal–oral transmission, can lead to asymptomatic colonisation or a range of clinical manifestations from mild diarrhoea to pseudomembranous colitis, bowel perforation or death [2, 3]. Children have not been thought to be a particularly high-risk population for C. difficile infection (CDI). However, the severity and incidence of CDI-related hospitalisations have increased in both paediatric and adult populations [4–6] and CDI-related hospitalisations are associated with higher costs and longer length of stay [7–10]. Asymptomatic colonisation with C. difficile occurs at much higher rates in infants aged <1 year than in adults [11] but decreases rapidly after the first year of life [12]. In one paediatric study, CDI incidence was found to be highest in those aged 1–3 years, with similar clinical presentation, disease severity and outcomes as older children; coinfection with other enteric pathogens was rare, supporting C. difficile as the causative aetiology in this young age group [13].

Although traditionally a healthcare-associated infection, CDI is increasingly spread through community acquisition [14–16]. Among paediatric CDI cases identified through population-based surveillance, 71–75% were determined to be community-associated (CA) [13, 17]. While several studies have assessed CA-CDI risk factors in adults, limited data exist for children. The few studies to examine CA-CDI risk factors in children have primarily focused on traditional risk factors, such as outpatient healthcare and medication exposures [18, 19], although one study also assessed exposures to household members younger than 1 year of age or who had a diagnosis of CDI [18]. The objective of this study was to evaluate various potential

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healthcare- and community-related risk factors for CA-CDI in children, including different types of outpatient healthcare and household exposures as well as dietary and daycare exposures. Because of the higher incidence of CDI observed in younger children [13], we limited our study to children aged 1–5 years.

**Methods**

Active, population-based CDI surveillance is conducted by the US Centers for Disease Control and Prevention (CDC)’s Emerging Infections Program (EIP) in 10 geographically-diverse US sites. During October 2014–February 2016, children residing in the surveillance catchment areas of eight of the 10 EIP sites were enrolled for this study (Colorado, Georgia, Maryland, Minnesota, New Mexico, New York, Oregon and Tennessee), which comprised a surveillance population of >10 million persons. The study protocol was approved by institutional review boards at the CDC and participating EIP sites. Verbal consent from participants’ caregivers was obtained prior to enrolment.

**Case definition and enrolment**

All laboratories serving the residents of the EIP surveillance catchment areas reported all positive *C. difficile* test results obtained during routine clinical care to the EIP site staff. For EIP surveillance, a CDI case was defined as a positive *C. difficile* toxin or molecular assay in a person aged 12 months or older who had no positive test in the prior 8 weeks. Based on review of medical records, all cases reported to EIP were classified as either healthcare-associated CDI or community-associated CDI, which was defined as a *C. difficile*-positive stool collected as an outpatient or within 3 days of hospitalisation in a person who had no admission to a healthcare facility in the prior 12 weeks. The definition of healthcare-associated CDI has been described elsewhere [16]. We used the EIP CDI surveillance system to identify community-associated case-patients aged 12–60 months for potential enrolment in the study. Because the EIP CDI case definition was based on a laboratory diagnosis, to increase the likelihood that enrolled case-patients had a true infection and were not colonised with *C. difficile*, only case-patients with a diarrhoeal illness (≥3 watery stools in a 24 h period) associated with their positive stool specimen were included in the study. Case-patients were interviewed to determine their eligibility for the study. Case-patients who did not report an associated diarrhoeal illness, who did not reside in the EIP surveillance catchment area, who reported an inpatient admission in the prior 12 weeks, or who reported any prior history of CDI or if they had a prior positive *C. difficile* test reported to EIP were considered ineligible for the study. In addition, case-patients were excluded from the study if their caregiver could not be interviewed about their exposures or if they could not be matched to a control within 90 days of the specimen collection date.

**Control enrolment**

Each case-patient was matched to one control by site and age group (12–23, 24–47, 48–60 months). Controls were chosen randomly from a commercial database of residential telephone numbers or from birth registries if the subjects were aged 12–23 months. Controls had to reside in the same surveillance catchment area as the matched case-patient at the time of the case-patient’s specimen collection. Controls were excluded if they had a diarrhoeal illness or an overnight stay in a healthcare facility within 12 weeks prior to the matched case-patient’s onset of illness, or if they ever had a CDI diagnosis.

**Data collection**

Trained interviewers used a standardised questionnaire to collect information by telephone. Demographics and underlying comorbidities were recorded. Caregivers were interviewed about participants’ relevant healthcare, household and dietary exposures, as well as water sources within the 12 weeks prior to the case-patient’s illness onset date. Medication use was assessed in the 2, 2–4 and 4–12 weeks prior to the case-patient’s illness onset date. Additional information about case-patients’ clinical course was collected as part of routine surveillance.

**Statistical analysis**

Descriptive analyses were performed to summarise demographic and clinical characteristics. Because there was a low frequency of exposure to several of the outpatient settings, a new variable was created that combined the outpatient exposures into either a higher- or lower-risk exposure category based on criteria used in prior studies [20, 21]. The following outpatient settings were classified as higher-risk exposures: emergency room, outpatient procedure centre, haemodialysis facility, hospital-based outpatient setting, urgent care and ambulatory surgical centre. Lower-risk exposures included the following: dental office, doctor’s office, outpatient laboratory and physical therapy centre. Univariate exact conditional logistic regression was performed. Variables with *P*-value <0.20 on the univariate test were entered into a multivariable conditional logistic regression model using stepwise selection to identify CA-CDI predictors. If specific types of outpatient exposures as well as the combined variable of higher- or lower-risk outpatient exposure all had a *P*-value <0.20 on the univariate test, only the combined higher- or lower-risk exposure variable was included in the multivariable model to avoid collinearity. In multivariable analysis, *P*-values <0.05 were considered significant. SAS statistical software version 9.3 (SAS Institute Inc, Cary, NC, USA) was used for the analysis.

**Results**

Of the 136 children (68 matched pairs) enrolled in the study, 44.1% were female and 69.1% were 12–23 months old (Table 1). The median number of participants (case-patients and controls) per EIP site was 14 (range: 2–60), with 44.1% of all participants from one of the eight sites, Georgia. The distribution of Georgia and non-Georgia participants did not differ by sex (46.7% vs. 42.1% females; *P* = 0.59) and age group (70.0% vs. 68.4% were aged 12–23 months; *P* = 0.84).

Of the 68 case-patients, 64 (94.1%) caregivers interviewed recalled the onset date of diarrhoeal illness. Other commonly reported symptoms included vomiting (58.8%), fever (54.4%) and abdominal pain (50.0%). *C. difficile* diagnostic testing information was available for all 68 case-patients: 22 (32.4%) were positive by a toxin enzyme immunoassay, 10 (14.7%) were positive by a molecular assay only (toxin-negative) and 36 (52.9%) were diagnosed by a laboratory that only utilised a molecular assay (no information available on toxin positivity for these 36 patients). Of the 68 case-patients, only 10 (14.7%) had another enteric pathogen detected at the time of their CDI diagnosis.
Higher-risk outpatient exposures were more common among case-patients compared with controls (34.9% vs. 19.4%). This difference was most pronounced for exposures to β-lactam and/or β-lactamase inhibitor combinations, with cephalosporins being more frequently reported among case-patients than controls (20.6% vs. 1.5%, \( P = 0.001 \)). The most commonly reported indication for antibiotic treatment was ear, sinus or respiratory infection among both case-patients (67.6%) and controls (76.9%) (Table 3). Of the 14 case-patients with prior cephalosporin use, eight (57.1%) reported that treatment of an ear, sinus or respiratory infection was the only indication for receiving antibiotics. Exposures to gastric-acid suppressants and antidepressants were also assessed, but no significant differences were found (Table 2).

Nine (13.6%) of the 66 case-patients with data available, compared with 17 (25.0%) of 68 controls, did not have any outpatient healthcare or relevant medication exposures in the preceding 12 weeks (\( P = 0.12 \)). However, all except one of these nine case-patients had >1 community-based exposures: six (66.7%) had attended daycare, three (33.3%) had a household member who volunteered or worked in a healthcare facility, two (22.2%) had a household member who wore diapers and two (22.2%) had a household member with recent diarrheal illness.

Overall, a greater percentage of case-patients reported daycare attendance compared with controls, although the difference was not statistically significant (55.2% vs. 37.3%; \( P = 0.06 \)) (Table 4). Case-patients were more likely to have a household member who had a recent diarrheal illness (41.3% vs. 21.5%, \( P = 0.04 \)); notably, 24% of these case-patients compared with none of the controls had a household member with CDI. No significant difference was detected in the proportion of case-patients and controls who had a recently hospitalised household member or a household member who volunteered or worked in a healthcare facility.

Case-patients were not more likely than controls to be exposed to a diverse diet or to specific food types or water source (Table 4). Furthermore, no difference was detected in the frequency of formula feeding within the first 6 months of life. However, there was less frequent dairy intake in case-patients compared with controls, although this difference was not statistically significant (74.6% vs. 88.1%, \( P = 0.06 \)).

In multivariable analysis, only antibiotic exposure in the preceding 12 weeks was significantly associated with CA-CDI (adjusted matched odds ratio 6.25; 95% CI 2.18–17.96). We performed three separate sensitivity analyses: excluding case-patients (and corresponding controls) in the 12–23 month age group, excluding case-patients (and their corresponding controls) who tested positive for another enteric pathogen or who were not tested at all for other enteric pathogens, and excluding case-patients (and their corresponding controls) who were not treated for CDI or had missing treatment information. In all three sensitivity analyses, recent antibiotic exposure remained the only significant finding in multivariable analysis.

**Discussion**

This is one of the few multi-site studies to date to explore a wide range of healthcare- and community-related risk factors for CA-CDI in young US children. We found that the majority of case-patients had prior outpatient healthcare exposures (81.8%) and antibiotic use (54.4%), whereas 13.6% did not have any traditional risk factors. Recent antibiotic use was the only independent risk factor for CA-CDI in this study. Although not significant in multivariable analysis, both underlying chronic medical conditions and exposures to high-risk outpatient healthcare settings were more common among case-patients than controls. No

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**Table 1. Age, sex and state of residence of study participants**

| Variable          | Number of study participants, n (%) |
|-------------------|-------------------------------------|
| Age group         |                                     |
| 12–23 months      | 94 (69.1)                           |
| 24–47 months      | 22 (16.2)                           |
| 48–60 months      | 20 (14.7)                           |
| Sex               |                                     |
| Female            | 60 (44.1)                           |
| State of residence|                                     |
| Georgia           | 60 (44.1)                           |
| Maryland          | 6 (4.4)                             |
| Minnesota         | 14 (10.3)                           |
| New Mexico        | 14 (10.3)                           |
| New York          | 14 (10.3)                           |
| Oregon            | 2 (1.5)                             |
| Tennessee         | 10 (7.4)                            |
Table 2. Univariate analysis: select demographic and clinical characteristics and healthcare and medication exposures among study participants

| Variable                                | Cases No. (%) | Controls No. (%) | Unadjusted matched odds ratio (95% CI) | P-value |
|------------------------------------------|---------------|-----------------|----------------------------------------|---------|
| **Demographic information**              |               |                 |                                        |         |
| White race                               | 54/68 (79.4)  | 46/68 (67.6)    | 1.73 (0.78–4.01)                       | 0.20    |
| Hispanic/Latino                          | 19/68 (27.9)  | 18/68 (26.5)    | 1.08 (0.46–2.59)                       | 1.00    |
| Have health insurance                    | 67/68 (98.5)  | 67/68 (100.0)   | 1.00 (0.00–19.00)                      | 1.00    |
| Household income >$50k                   | 37/62 (59.7)  | 40/64 (62.5)    | 1.17 (0.50–2.76)                       | 0.85    |
| **Select medical conditions**            |               |                 |                                        |         |
| Any medical condition                    | 22/66 (33.3)  | 8/66 (12.1)     | 3.17 (1.22–9.69)                       | 0.01    |
| Congenital heart disease                 | 3/67 (4.5)    | 1/67 (1.5)      | 3.00 (0.24–157.49)                     | 0.63    |
| Cystic fibrosis                          | 1/67 (1.5)    | 0/67 (0.0)      | 1.00 (0.05–undenf)                     | 1.00    |
| Gastrointestinal condition               | 5/67 (7.5)    | 1/67 (1.5)      | 5.00 (0.56–236.49)                     | 0.22    |
| Short-gut disease                        | 3/67 (4.5)    | 0/67 (0.0)      | 3.85 (0.58–undenf)                     | 0.25    |
| Asthma                                   | 3/67 (4.5)    | 1/66 (1.5)      | 3.00 (0.24–157.49)                     | 0.63    |
| Bronchopulmonary dysplasia               | 2/66 (3.0)    | 0/67 (0.0)      | 2.41 (0.29–157.49)                     | 0.50    |
| Organ transplant                         | 1/67 (1.5)    | 0/67 (0.0)      | 1.00 (0.05–undenf)                     | 1.00    |
| Neurologic illness                       | 7/67 (10.4)   | 3/67 (4.5)      | 2.33 (0.53–13.98)                      | 0.34    |
| **Healthcare exposures**                 |               |                 |                                        |         |
| Any higher-risk outpatient exposureb     | 23/66 (34.9)  | 12/68 (17.7)    | 4.20 (1.09–19.36)                      | 0.03    |
| Any lower-risk outpatient exposureb      | 31/66 (47.0)  | 38/68 (55.9)    | 1.34 (0.50–3.83)                       | 0.68    |
| Exposure to any outpatient setting       | 54/66 (81.8)  | 50/68 (73.5)    | 1.63 (0.62–4.52)                       | 0.38    |
| Dentist’s office                         | 8/65 (12.3)   | 10/68 (14.7)    | 0.75 (0.21–2.46)                       | 0.79    |
| Doctor’s office                          | 47/62 (75.8)  | 42/68 (61.8)    | 1.90 (0.84–4.57)                       | 0.14    |
| Emergency department                     | 12/65 (18.5)  | 5/68 (7.4)      | 5.00 (1.07–46.93)                      | 0.04    |
| Haemodialysis                            | 0/66 (0.0)    | 0/68 (0.0)      | –                                      | –       |
| Hospital-based outpatient setting        | 6/66 (9.1)    | 1/68 (1.5)      | 6.73 (1.22–undenf)                     | 0.06    |
| Outpatient laboratory                    | 1/65 (1.5)    | 5/68 (7.4)      | 0.20 (0.004–1.79)                      | 0.22    |
| Outpatient procedure centre              | 4/65 (6.2)    | 4/68 (5.9)      | 1.00 (0.13–7.47)                       | 1.00    |
| Outpatient surgery centre                | 5/65 (7.7)    | 0/68 (0.0)      | 6.73 (1.22–undenf)                     | 0.06    |
| Physical therapy centre                  | 4/65 (6.2)    | 1/66 (1.5)      | 4.00 (0.39–196.99)                     | 0.38    |
| Urgent care                              | 3/65 (4.6)    | 3/68 (4.4)      | 1.00 (0.13–7.47)                       | 1.00    |
| Received any outpatient procedure        | 12/65 (18.5)  | 13/68 (19.1)    | 0.89 (0.29–2.59)                       | 1.00    |
| Dental cleaning                          | 6/65 (9.2)    | 10/68 (14.7)    | 0.50 (0.11–1.87)                       | 0.39    |
| Endoscopy                                | 1/65 (1.5)    | 1/68 (1.5)      | 1.00 (0.01–78.49)                      | 1.00    |
| X-ray that required bowel preparation    | 0/65 (0.0)    | 1/68 (1.5)      | 1.00 (0.00–19.00)                      | 1.00    |
| Surgical procedure                       | 6/65 (9.2)    | 3/68 (4.4)      | 2.00 (0.43–12.36)                      | 0.51    |
| Visited or accompanied a person to a healthcare facility | 18/66 (27.3)  | 12/67 (17.9)    | 1.50 (0.63–3.73)                       | 0.42    |
| Had a feeding tube                       | 2/68 (2.9)    | 0/68 (0.0)      | 2.41 (0.29–undenf)                     | 0.50    |
| **Birth**                                |               |                 |                                        |         |
| Delivered via C-section                  | 19/67 (28.4)  | 22/67 (32.8)    | 0.84 (0.41–1.73)                       | 0.74    |
| Stayed in NICU                           | 18/67 (26.9)  | 8/67 (11.9)     | 3.00 (1.04–10.55)                      | 0.04    |
| **Medication exposures**                 |               |                 |                                        |         |
| Any antibiotic use in prior 12 weeks     | 37/68 (54.4)  | 13/67 (19.4)    | 5.80 (2.22–19.19)                      | <0.0001 |
| Any antibiotic use in prior 4 weeks*     | 25/66 (37.9)  | 6/66 (9.1)      | 6.87 (2.20–29.21)                      | 0.0001  |

(Continued)
community-related risk factors were found to be independently associated with CA-CDI.

Our finding of recent antibiotic use as a risk factor for CA-CDI in children is consistent with previous studies and underscores the importance of outpatient antibiotic stewardship [18, 19, 22]. Not surprisingly, the most frequently reported indication for antibiotic use in this study of young children was ear, sinus or respiratory infection. Inappropriate antibiotic prescribing for acute respiratory tract infections is well-documented, including the overuse of antibiotics not generally recommended for first-line therapy, such as cephalosporins and fluoroquinolones [23–25]. Both of these antibiotic classes have been linked to CA-CDI in children and adults [18, 19, 21, 26]. We observed a significantly higher frequency of cephalosporin use among case-patients, more than half of whom received the antibiotic exclusively for treatment of an ear, sinus or respiratory infection, according to their caregiver. Continued efforts to identify effective interventions to improve outpatient prescribing, particularly for acute respiratory tract infections, are greatly needed.

Although antibiotic use can have long-term impacts on the intestinal microbiota, some studies have found the risk for CDI is highest during and within the first month following antibiotic use [19, 26, 27], including one paediatric study that found a significant association between CA-CDI and antibiotic use only in the prior 30 days [19]. Similarly, when we assessed whether certain time intervals during the 12-week exposure period were associated with higher CA-CDI risk, we found a stronger association with antibiotic use in the prior 4 weeks than in the prior 4–12 weeks.

In univariate analysis, we found case-patients (33.3%) were more likely to have an underlying medical condition, which could lead to more frequent and prolonged outpatient healthcare exposures and potentially more antibiotic exposures, increasing the risk for CDI. Both neurologic and gastrointestinal conditions were the most commonly reported comorbidities in our study, whereas malignancy was the most prevalent condition found in hospitalised children with CDI who were aged 1–5 years [4]. Other studies that included older children with CA-CDI have found as high as 62–73% had underlying comorbidities [19, 28]. We did not identify any specific medical condition or use of a gastrointestinal feeding tube to be associated with CA-CDI, but a history of solid organ transplantation has been associated with CDI in hospitalised children [22], and the presence of a gastrointestinal feeding tube has previously been identified to be associated with CA-CDI, whereas malignancy was the most prevalent condition found in hospitalised children with CDI who were aged 1–5 years [4]. Other studies that included older children with CA-CDI have found as high as 62–73% had underlying comorbidities [19, 28]. We did not identify any specific medical condition or use of a gastrointestinal feeding tube to be associated with CA-CDI, but a history of solid organ transplantation has been associated with CDI in hospitalised children [22], and the presence of a gastrointestinal feeding tube has previously been identified to be a risk factor for CDI among both hospitalised children and those with community-associated disease [19, 22].

We found case-patients were also more likely to have been admitted to the NICU in early infancy. Prior NICU stay could conceivably have affected the course of intestinal maturation and composition as a result of early exposures to hospital

### Table 2. (Continued.)

| Variable | Cases (N = 37) | Controls (N = 13) | Unadjusted matched odds ratio (95% CI) | P-value |
|----------|----------------|------------------|---------------------------------------|---------|
| Any antibiotic use in prior 4–12 weeks<sup>a</sup> | 10/66 (15.2) | 6/66 (9.1) | 3.32 (0.85–15.85) | 0.09 |
| Azithromycin | 2/68 (2.9) | 1/67 (1.5) | 2.00 (0.01–117.99) | 1.00 |
| β-lactam and/or β-lactamase inhibitor combination | 14/68 (20.6) | 9/67 (13.4) | 1.71 (0.62–5.14) | 0.36 |
| Cephalosporin | 14/68 (20.6) | 1/67 (1.5) | 14.00 (2.13–591.97) | 0.001 |
| Clindamycin | 1/68 (1.5) | 0/67 (0.0) | 1.00 (0.05–undef) | 1.00 |
| Erythromycin/sulfamethoxazole | 1/68 (1.5) | 0/67 (0.0) | 1.00 (0.05–undef) | 1.00 |
| Fluoroquinolone | 1/68 (1.5) | 2/67 (3.0) | 0.50 (0.01–9.60) | 1.00 |
| Metronidazole | 2/68 (2.9) | 0/67 (0.0) | 2.41 (0.29–undef) | 0.50 |
| Trimethoprim/sulfamethoxazole | 1/68 (1.5) | 0/67 (0.0) | 1.00 (0.05–undef) | 1.00 |
| Vancomycin (intravenous) | 1/68 (1.5) | 0/67 (0.0) | 1.00 (0.05–undef) | 1.00 |
| Any acid reducing medication | 4/66 (6.1) | 2/67 (3.0) | 3.00 (0.24–157.49) | 0.63 |
| Any antidepressant | 1/67 (1.5) | 0/66 (0.0) | 1.00 (0.05–undef) | 1.00 |

<sup>a</sup>Participants could report more than one indication for antibiotic use.

<sup>b</sup>The reference group for the higher- and lower-risk exposure categories were participants with no outpatient exposure. A higher-risk outpatient exposure was defined as exposure to an emergency room, outpatient procedure centre, haemodialysis facility, hospital-based outpatient setting, urgent care or ambulatory surgical centre. A lower-risk outpatient exposure was defined as exposure to a dental office, doctor’s office, outpatient laboratory or physical therapy centre.

<sup>c</sup>Two case-patients and one control subject could not recall the exact time-frame of antibiotic exposure during the preceding 12 weeks.

### Table 3. Reported indications for antibiotic use among study participants

| Indications for antibiotic use<sup>a</sup> | Cases (N = 37) | Controls (N = 13) | P-value |
|-----------------|----------------|------------------|---------|
| Ear, sinus or upper respiratory tract infection | 25 (67.6) | 10 (76.9) | 0.71 |
| Eye infection | 3 (8.1) | 1 (7.7) | 0.50 |
| Skin or soft tissue infection (abscess or cellulitis) | 2 (5.4) | 1 (7.7) | 0.50 |
| Surgery | 4 (10.8) | 0 (0.0) | 0.21 |
| Urinary tract infection | 2 (5.4) | 0 (0.0) | 0.21 |
| Urinary tract infection prophylaxis | 2 (5.4) | 0 (0.0) | 0.21 |
| Gastrointestinal infection | 1 (2.7) | 0 (0.0) | 0.21 |
| Other | 4 (10.8) | 1 (7.7) | 0.21 |
| Unknown reason | 1 (2.7) | 0 (0.0) | 0.21 |

<sup>a</sup>Participants could report more than one indication for antibiotic use.

CI, confidence interval; NICU, neonatal intensive care unit.

Continued

Continued efforts to identify effective interventions to improve outpatient prescribing, particularly for acute respiratory tract infections, are greatly needed.

Although antibiotic use can have long-term impacts on the intestinal microbiota, some studies have found the risk for CDI is highest during and within the first month following antibiotic use [19, 26, 27], including one paediatric study that found a significant association between CA-CDI and antibiotic use only in the prior 30 days [19]. Similarly, when we assessed whether certain time intervals during the 12-week exposure period were associated with higher CA-CDI risk, we found a stronger association with antibiotic use in the prior 4 weeks than in the prior 4–12 weeks.

In univariate analysis, we found case-patients (33.3%) were more likely to have an underlying medical condition, which could lead to more frequent and prolonged outpatient healthcare exposures and potentially more antibiotic exposures, increasing the risk for CDI. Both neurologic and gastrointestinal conditions were the most commonly reported comorbidities in our study, whereas malignancy was the most prevalent condition found in hospitalised children with CDI who were aged 1–5 years [4]. Other studies that included older children with CA-CDI have found as high as 62–73% had underlying comorbidities [19, 28]. We did not identify any specific medical condition or use of a gastrointestinal feeding tube to be associated with CA-CDI, but a history of solid organ transplantation has been associated with CDI in hospitalised children [22], and the presence of a gastrointestinal feeding tube has previously been identified to be a risk factor for CDI among both hospitalised children and those with community-associated disease [19, 22].

We found case-patients were also more likely to have been admitted to the NICU in early infancy. Prior NICU stay could conceivably have affected the course of intestinal maturation and composition as a result of early exposures to hospital
organisms or antibiotics [29]. In fact, increased *C. difficile* colonisation has been observed in both preterm infants and infants hospitalised after birth [30]. Interestingly, 61% of our case-patients who had a NICU stay during infancy were diagnosed with CDI during their second year of life. Whether a portion of these case-patients initially acquired their *C. difficile* during their NICU stay and subsequently developed disease is unknown.

Consistent with previous adult and paediatric studies [18, 19, 21], we found in univariate analysis that a higher proportion of case-patients had prior outpatient healthcare exposures. When stratified by types of outpatient exposures, case-patients were more likely to have been exposed to higher-risk settings, such as emergency departments, outpatient procedure centres and hospital-based outpatient clinics. These are settings where there is potentially higher frequency of patient contact with healthcare providers and the environment, which could facilitate the spread of *C. difficile*. In an adult *C. difficile* study, recent care at one or more of these outpatient settings was more common in case-patients than in controls, with recent exposure to an emergency department being an independent risk factor for CA-CDI [21].

Of note, 13.6% of case-patients did not report any recent outpatient healthcare or antibiotic exposures. The majority of these case-patients, however, had recent daycare or relevant household exposures, such as having a household member with recent diarrhoeal illness (including CDI). In another paediatric study, recent exposure to a household member with CDI was a significant risk factor for CA-CDI [18]. Studies that have examined *C. difficile* carriage in households of CDI cases have recovered *C. difficile* from as high as 11–13% of household contacts and 27–33% of domestic pets [31, 32]. *C. difficile* has also been isolated from household environments of persons with CDI [31, 33]. To minimise potential *C. difficile* spread in households, continued education about the importance of hand hygiene is needed, particularly in young children where hand hygiene adherence might be suboptimal, and for caregivers who change diapers. Additional measures, including using separate bathrooms and improving household environmental cleaning and disinfection, especially of the bathroom and diaper changing areas, should be emphasised [34].

The major strengths of this study included enrolment of participants from diverse geographical locations and the use of in-depth interviews to identify exposures that would be missed if relying only on medical records or claims data. The primary limitation of the study was that we could not exclude the possibility that some case-patients were actually colonised with *C. difficile* and had diarrhoea due to another aetiology. This includes patients who tested positive only by a molecular assay as well as patients who tested positive for another enteric pathogen. Information regarding the presence of other enteric pathogens was not available for 10 case-patients. However, among the 58 case-patients who were tested for other enteric pathogens, the

### Table 4. Univariate analysis: select non-healthcare, household and dietary exposures among study participants

| Variable                                                              | Cases No. (%) | Controls No. (%) | Unadjusted matched odds ratio (95% CI) | P-value |
|----------------------------------------------------------------------|---------------|------------------|---------------------------------------|---------|
| Attended daycare                                                     | 37/67 (55.2)  | 25/67 (37.3)     | 2.09 (0.98–4.75)                      | 0.06    |
| **Household exposures**                                             |               |                  |                                       |         |
| Household member wore diapers                                       | 19/68 (27.9)  | 25/68 (36.8)     | 0.67 (0.29–1.46)                      | 0.36    |
| Household member attended child or adult daycare                     | 21/68 (30.9)  | 20/67 (29.9)     | 1.07 (0.49–2.32)                      | 1.00    |
| Household member had diarrhoea                                       | 26/63 (41.3)  | 14/65 (21.5)     | 2.50 (1.05–6.56)                      | 0.04    |
| Household member had *C. difficile* infection                       | 6/25 (24.0)   | 0/14 (0.0)       | 1.00 (0.05–undef)                     | 1.00    |
| Household member with overnight stay in a hospital                  | 6/68 (8.8)    | 3/67 (4.5)       | 2.00 (0.43–12.36)                     | 0.51    |
| Household member volunteered or worked in a healthcare facility      | 9/68 (13.2)   | 16/68 (23.5)     | 0.50 (0.17–1.32)                      | 0.19    |
| **Dietary exposures**                                               |               |                  |                                       |         |
| Eggs                                                                  | 11/67 (16.4)  | 8/67 (11.9)      | 1.5 (0.48–5.12)                       | 0.61    |
| Dairy                                                                  | 50/67 (74.6)  | 59/68 (88.1)     | 0.36 (0.10–1.05)                      | 0.06    |
| Fresh raw vegetables                                                 | 19/67 (28.4)  | 19/67 (28.4)     | 1.00 (0.44–2.26)                      | 1.00    |
| Plant-based protein                                                  | 12/67 (17.9)  | 5/67 (7.5)       | 2.75 (0.81–11.84)                     | 0.12    |
| Red meat                                                             | 3/67 (4.5)    | 6/67 (9.0)       | 0.50 (0.08–2.34)                      | 0.51    |
| Poultry                                                              | 14/67 (20.9)  | 13/67 (19.4)     | 1.10 (0.42–2.89)                      | 1.00    |
| Seafood                                                              | 1/67 (1.5)    | 2/67 (3.0)       | 0.50 (0.01–9.60)                      | 1.00    |
| Diverse diet                                                         | 18/68 (26.5)  | 23/68 (33.8)     | 0.69 (0.29–1.58)                      | 0.44    |
| Well or spring water                                                 | 59/62 (95.2)  | 66/66 (90.9)     | 2.50 (0.41–26.25)                     | 0.45    |
| Formula-fed at least 75% of the time in first 6 months of life       | 23/68 (33.8)  | 23/67 (34.3)     | 0.94 (0.43–2.03)                      | 1.00    |
| Formula-fed almost 100% of the time in first 6 months of life        | 19/68 (27.9)  | 15/67 (22.4)     | 1.30 (0.53–3.31)                      | 0.68    |

CI, confidence interval.
Participants could have declined to answer a question; any missing response to a variable was excluded from the denominator.
Exposure period was during the 12 weeks preceding illness onset.
Unless otherwise specified, dietary exposure is defined as the consumption of a food product with a frequency of more than five times during a typical week.
Defined as the consumption of any of the food product listed in the table (except for plant-based protein) during a typical week, regardless of the frequency of consumption.
Source of drinking water around the time of illness onset.
majority (82.8%) did not have a positive test for another pathogen, suggesting that a positive test result for another pathogen was not included in the medical record for review, since access to outpatient records was sometimes limited. We believe this may have happened in four instances where the case-patient reported having tested positive for another enteric pathogen, but there was no documentation of the positive test result in the medical records that were available for review. In addition, the majority of case-patients were in the 12–23 month age group, which might include more colonisation than true infection compared with other age groups. However, among case-patients with treatment information available, 80.6% were treated specifically for CDI, suggesting that providers thought most of the case-patients had a true infection. To address the concern that some case-patients might have been colonised, we performed three separate sensitivity analyses (excluding the youngest age group, excluding patients who tested positive for another enteric pathogen or who were not tested at all for other enteric pathogens, and excluding patients who did not receive CDI treatment or had missing treatment information) and still found the same result in multivariable analysis.

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