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Original Investigation

Epidemiology of Community-Associated *Clostridium difficile* Infection, 2009 Through 2011

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IMPORTANCE *Clostridium difficile* infection (CDI) has been increasingly reported among healthy individuals in the community. Recent data suggest that community-associated CDI represents one-third of all *C difficile* cases. The epidemiology and potential sources of *C difficile* in the community are not fully understood.

OBJECTIVES To determine epidemiological and clinical characteristics of community-associated CDI and to explore potential sources of *C difficile* acquisition in the community.

DESIGN AND SETTING Active population-based and laboratory-based CDI surveillance in 8 US states.

PARTICIPANTS Medical records were reviewed and interviews performed to assess outpatient, household, and food exposures among patients with community-associated CDI (ie, toxin or molecular assay positive for *C difficile* and no overnight stay in a health care facility within 12 weeks). Molecular characterization of *C difficile* isolates was performed. Outpatient health care exposure in the prior 12 weeks among patients with community-associated CDI was a priori categorized into the following 3 levels: no exposure, low-level exposure (ie, outpatient visit with physician or dentist), or high-level exposure (ie, surgery, dialysis, emergency or urgent care visit, inpatient care with no overnight stay, or health care personnel with direct patient care).

MAIN OUTCOMES AND MEASURES Prevalence of outpatient health care exposure among patients with community-associated CDI and identification of potential sources of *C difficile* by level of outpatient health care exposure.

RESULTS Of 984 patients with community-associated CDI, 353 (35.9%) did not receive antibiotics, 177 (18.0%) had no outpatient health care exposure, and 400 (40.7%) had low-level outpatient health care exposure. Thirty-one percent of patients without antibiotic exposure received proton pump inhibitors. Patients having CDI with no or low-level outpatient health care exposure were more likely to be exposed to infants younger than 1 year (P = .04) and to household members with active CDI (P = .05) compared with those having high-level outpatient health care exposure. No association between food exposure or animal exposure and level of outpatient health care exposure was observed. North American pulsed-field gel electrophoresis (NAP) 1 was the most common (21.7%) strain isolated; NAP7 and NAP8 were uncommon (6.7%).

CONCLUSIONS AND RELEVANCE Most patients with community-associated CDI had recent outpatient health care exposure, and up to 36% would not be prevented by reduction of antibiotic use only. Our data support evaluation of additional strategies, including further examination of *C difficile* transmission in outpatient and household settings and reduction of proton pump inhibitor use.

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Clostridium difficile is the most common cause of health care–associated infectious diarrhea.[1] Traditional risk factors for *C difficile* infection (CDI) include antibiotic use, advanced age, and prior hospitalization.[2] Since 2005, CDI has been increasingly reported among young, healthy individuals residing in the community.[3-6] An estimated 20% to 28% of CDI is community associated,[5,7] with an incidence of 20 to 50 cases per 100 000 population in the United States,[5] Sweden,[7] and England.[8] Previous studies[3-6] have shown that approximately 40% of patients acquiring community-associated CDI were not exposed to antibiotics, suggesting that additional factors may contribute to infection. Although *C difficile* has been isolated from soil, food, water, animals, asymptomatic infants, and health care environments, the role of these sources in community *C difficile* acquisition is not well understood.[9] Understanding the importance of novel sources will help guide strategies to prevent community-associated CDI.

We interviewed patients with community-associated CDI identified through a longitudinal, population-based, surveillance program across 32 counties in 8 US states. We describe demographics, clinical characteristics, and outpatient exposures and outcomes and evaluate potential sources of acquisition of CDI in the community.

Methods

CDI Surveillance

This project was approved by the institutional review boards at the Centers for Disease Control and Prevention and participating sites. Verbal consent was obtained from all patients interviewed.

In 2009, the Emerging Infections Program began active laboratory-based and population-based surveillance for CDI in select counties across 10 US states. The surveillance methods have been described elsewhere.[10] In brief, surveillance staff at each site identify all positive *C difficile* toxin or molecular assays in stool specimens from all inpatient and outpatient laboratories serving surveillance catchment area residents. *C difficile* infection is defined as a positive *C difficile* toxin or molecular assay on a stool specimen from a surveillance area resident 1 year or older who did not have a positive assay in the previous 8 weeks. For each patient identified with CDI, medical records are initially reviewed to determine if the infection had a hospital onset (ie, positive stool specimen collected >3 days after admission) or a community onset (ie, positive stool specimen collected as an outpatient or ≤3 days after admission). For all patients with community-onset CDI, an in-depth medical record review is performed, and patients are classified as having putative community-associated CDI if no recent (ie, within 12 weeks before the stool specimen collection date) overnight stay in a hospital or long-term care facility was recorded. Information on disease severity, clinical outcomes, medication exposures, and underlying conditions pertaining to the Charlson comorbidity index,[11] as well as those conditions relevant to CDI such as inflammatory bowel disease and diverticular disease, is obtained from the medical records for all patients with putative community-associated CDI.

Study Population and Data Collection

From January 1, 2009, through May 31, 2011, a sequential sample of patients with putative community-associated CDI was contacted by telephone for an interview in 8 of 10 US surveillance sites (California, Colorado, Connecticut, Georgia, Maryland, Minnesota, New York, and Tennessee). All patients who agreed to be interviewed were initially asked if they had a history of recent overnight stay in a health care facility (ie, nursing homes, acute care hospitals, or long-term acute care hospitals). Those patients reporting an overnight stay in a health care facility were reclassified as having community-onset health care–associated CDI and did not proceed with the interview; patients not reporting an overnight stay were classified as confirmed patients with community-associated CDI and were asked additional questions regarding medical history, clinical symptoms, health care occupation requiring direct patient care, and recent (ie, within 12 weeks before the *C difficile*–positive specimen) exposures to day care settings, children in diapers, infants younger than 1 year, outpatient health care settings, household members with CDI, and antibiotic and other medication use, as well as food and animal exposures. All 8 participating sites completed at least 50 interviews.

Only confirmed patients having community-associated CDI with diarrhea documented in the medical record or reported in the interview as 3 or more loose stools in a 24-hour period at the time of the *C difficile*–positive specimen were included in the analyses. Because *C difficile* is often transmitted in hospital settings,[2] where invasive procedures are performed and where the duration and frequency of patient contact with health care providers and the environment are long and high, we a priori categorized outpatient health care exposure in the 12 weeks before the *C difficile*–positive stool specimen into the following 3 levels: (1) high-level health care exposure, defined as dialysis, a job requiring direct contact with patients, outpatient surgery or an invasive procedure, emergency department or urgent care visit, or inpatient care at a health care facility without an overnight stay; (2) low-level health care exposure, defined as a visit to a dentist, physician, or other outpatient clinic (eg, psychology, warfarin sodium, or pharmacy clinic visit); and (3) no health care exposure, defined as no recent outpatient health care exposure. Patients with community-associated CDI were classified into 1 of the 3 exposure levels based on the highest level of exposure reported during the telephone interview. For example, a patient who reported both low-level and high-level exposures was included in the high-level exposure group; levels of exposure were mutually exclusive.

A convenience sample of *C difficile*–positive stool specimens (approximately 40%) from interviewed patients was cultured,[12] and molecular characterization of recovered *C difficile* isolates was performed. Pulsed-field gel electrophoresis patterns were analyzed using available software (BioNumerics version 5.10; Applied Maths) and were grouped into pulsed-field types using Dice coefficient and unweighted pair group method with arithmetic mean algorithm clustering, and an 80% similarity threshold was used to assign North American pulsed-field gel electrophoresis (NAP) types.[13]

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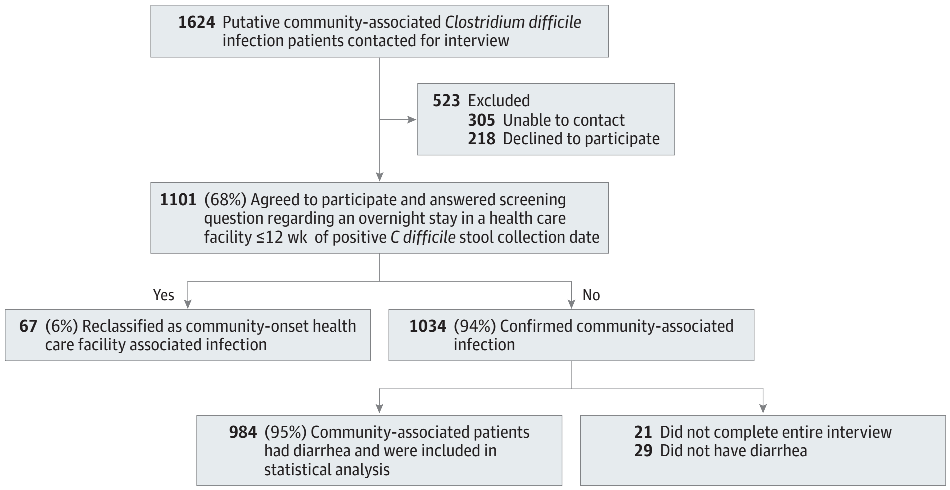
Figure. Ascertainment and Classification



Ascertainment and classification of patients with community-associated *Clostridium difficile* infection, 2009 through 2011.

Statistical Analysis

Univariate analyses of demographics, clinical characteristics, and potential sources of *C difficile* acquisition were conducted among patients with community-associated CDI stratified by level of health care exposure. The χ^2 test or Fisher exact test was used to compare categorical variables, and the Wilcoxon rank sum test was used to compare continuous variables.

Multinomial logistic regression analysis was used to identify predictors of no and low-level health care exposure using high-level exposure as the reference group. Predictors of interest included potential sources of *C difficile* acquisition. Variables eligible for inclusion in models had $P < .20$ in univariate analysis and were biologically plausible sources of *C difficile* acquisition. Prior exposure to antibiotics was included as an interaction term with potential sources of *C difficile* acquisition. A backward logistic regression modeling strategy was used with a stay criterion of $P \leq .10$ for all variables. Sensitivity analyses for the final model were conducted by restricting data to patients who received antibiotics. All analyses were conducted using statistical software (SAS version 9.2; SAS Institute, Inc), and 2-sided $P \leq .05$ was considered statistically significant.

Results

Detection and Classification of CDI

From January 1, 2009, through May 31, 2011, a total of 1624 patients with putative community-associated CDI were contacted for an interview; 1101 (67.8%) agreed to be interviewed, and 523 (32.2%) could not be contacted or declined participation. Of 1101 patients with putative community-associated CDI for whom interview data were available, 67 (6.1%) were reclassified as having community-onset health care facility–associated CDI because they reported having an overnight stay in a health care facility in the 12 weeks before the positive *C difficile* stool specimen collection. Of 1034 confirmed patients with community-associated CDI, 1013 (98.0%) completed the entire interview; 984 (97.1%) of these reported diarrhea at the time of collection of the *C difficile*–positive stool specimen and were included in all analyses (**Figure**).

Compared with 573 patients (523 putative and 50 confirmed) excluded from analyses, the 984 confirmed patients with community-associated CDI were more likely to be female (66.6% vs 58.4%) and of white race (86.3% vs 59.1%) ($P < .01$ for both). No difference in the proportion of patients 18 years or younger was detected (13.3% vs 10.8%, $P = .15$).

Demographics and Clinical Characteristics

Among 984 confirmed patients with community-associated CDI, the median age of patients was 51 years, and the median Charlson comorbidity index was 0; 66.6% were female, and 86.3% were of white race (**Table 1**). Antibiotics were used within 12 weeks of *C difficile*–positive stool specimen collection among 631 of 984 patients (64.1%); cephalosporins, β-lactam or β-lactamase inhibitor, penicillins, fluoroquinolones, and clindamycin were most commonly used. Among 631 patients with CDI who used antibiotics, the most commonly reported reasons for receiving antibiotics were ear, sinus, or upper respiratory tract infection (34.7%), followed by dental cleaning or oral surgery (15.1%), urinary tract infection (9.3%), skin infection (7.5%), and bronchitis or pneumonia (7.5%).

Of 984 patients with CDI, 273 (27.7%) reported recent proton pump inhibitor (PPI) use, 91 (9.2%) had used immune-suppressing agents, and 90 (9.1%) had exposure to an H_2-receptor antagonist. A higher proportion of patients without prior antibiotic exposure reported PPI use (31.2% vs 25.8%, $P = .07$) or the use of an immune-suppressing agent such as chemotherapy, oral corticosteroids, and interleukin receptor antagonists (12.2% vs 7.6%, $P = .01$) compared with patients with prior antibiotic exposure, while the proportion of patients receiving an H_2-receptor antagonist (9.6% vs 8.9%, $P = .68$) did not differ by antibiotic exposure status. Of 91 patients who received immune-suppressing agents, only 17 (18.7%) did not

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Table 1. Demographics, Clinical Characteristics, and Outcomes Among Patients With Community-Associated *Clostridium difficile* Infection, 2009 Through 2011

Variable	Value (n = 984)
Age, median (range), y	51 (1-97)
Female sex, No. (%)	655 (66.6)
Race, No. (%)	
White	849 (86.3)
Black	79 (8.0)
Asian, Hawaiian, or Pacific Islander	20 (2.0)
Native American	13 (1.3)
Unknown	23 (2.3)
Charlson comorbidity index, median (range)	0 (0-14)
Select medical conditions, No. (%)[a]	
Pulmonary disease	136 (13.8)
Solid tumor, nonmetastatic	110 (11.2)
Inflammatory bowel disease	105 (10.7)
Chronic renal insufficiency	67 (6.8)
Diverticular disease	62 (6.3)
None	391 (39.7)
Medication use within 12 wk before *C difficile* infection, No./total No. (%)[a]	
Antibiotics[b]	631 (64.1)
Cephalosporins	149/631 (23.6)
β-Lactam or β-lactamase inhibitors	145/631 (23.0)
Penicillins	143/631 (22.7)
Fluoroquinolones	139/631 (22.0)
Clindamycin	119/631 (18.9)
Macrolides	60/631 (9.5)
Folic acid inhibitors	38/631 (6.0)
Tetracyclines	15/631 (2.4)
Proton pump inhibitors	273 (27.7)
H_2-receptor antagonists	90 (9.1)
Immune-suppressing agents[c]	91 (9.2)
Hospitalization, No./total No. (%)[d]	251 (25.5)
C difficile infection primary reason	125/251 (49.8)
Admitted to an intensive care unit within 30 d of *C difficile* infection	12/251 (4.8)
White blood cell count ≤1000/μL or ≥15 000/μL	67/251 (26.7)
Toxic megacolon or ileus on radiography	8/251 (3.2)
Colectomy within 30 d of *C difficile* infection	2/251 (0.8)
Death within 30 d of *C difficile* infection	4/251 (1.6)
Severe *C difficile* infection outcome[e]	15/251 (6.0)
Patients having *C difficile* infection with NAP strain type result available, No. (%)	313 (31.8)
NAP, No./total No. (%)	
1	68/313 (21.7)
2	10/313 (3.2)
3	4/313 (1.3)
4	36/313 (11.5)
5	3/313 (1.0)
6	23/313 (7.3)
7	19/313 (6.1)
8	2/313 (0.6)
9	7/313 (2.2)
10	9/313 (2.9)
11	34/313 (10.9)
12	6/313 (1.9)
Unnamed NAP type	92/313 (29.4)

Abbreviation: NAP, North American pulsed-field gel electrophoresis type.

SI conversion factor: To convert white blood cell count to $\times 10^9$/L, multiply by 0.001.

[a] Medical conditions and medications used are not mutually exclusive.

[b] The median (range) number of antibiotic classes is 1 (1-5).

[c] Chemotherapy, corticosteroid use, or interleukin receptor antagonists. Inhaled corticosteroids are not included.

[d] Hospitalization at the time of or within 7 days after the *C difficile* specimen collection date.

[e] Death, colectomy, or admission to an intensive care unit within 30 days of the *C difficile* specimen collection date.

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report other medication exposure (ie, PPI, antibiotic, or H_2-receptor antagonist).

Community-Associated CDI Outcomes

As given in Table 1, hospitalization within 7 days of a positive *C difficile* stool specimen collection occurred in 251 patients with CDI (25.5%); for 125 (49.8%) of these, *C difficile* was listed as the reason for admission. Admission to an intensive care unit (4.8%), toxic megacolon (3.2%), death (1.6%), and colectomy (0.8%) were uncommon among hospitalized patients with CDI.

Stool specimens from 388 patients with CDI (39.4%) were collected and submitted for toxigenic *C difficile* culture. *Clostridium difficile* was recovered from 313 of 388 toxin-positive specimens (80.7%); NAP1 (21.7%) was the most common strain type detected, followed by NAP4 (11.5%) and NAP11 (10.9%); NAP7 and NAP 8 were uncommon (6.7%).

Table 2. Frequency and Type of Outpatient Health Care Exposure in the 12 Weeks Before Community-Associated *Clostridium difficile* Infection, 2009 Through 2011

Outpatient Health Care Exposure	No./Total No. (%) (n = 984)
No exposure	177 (18.0)
Low-level exposure[a]	400 (40.7)
Physician office visit	359/400 (89.8)
Dentist office visit	119/400 (29.8)
Other outpatient visit	11/400 (2.8)
High-level exposure[a]	407 (41.4)
Surgery or procedure	229/407 (56.3)
Inpatient care but not an overnight admission	116/407 (28.5)
Emergency department or urgent care visit	98/407 (24.1)
Job required direct contact with patients	69/407 (17.0)
Dialysis	12/407 (2.9)

[a] Variables are not mutually exclusive.

Sources of *C difficile* Acquisition

Of 984 patients with community-associated CDI, 177 (18.0%) had no recent outpatient health care exposure, 400 (40.7%) had a low-level health care exposure, and 407 (41.4%) had a high-level health care exposure (**Table 2**). Patients having CDI with no, low-level, and high-level outpatient health care exposure differed in age, PPI use, medical conditions, antibiotic exposure in the 12 weeks before CDI, and exposure to household members who had active CDI, who were infants younger than 1 year, or who were diapered children younger than 4 years (**Table 3**). Patients having CDI with no outpatient health care exposure were less likely to have received antibiotics in the prior 12 weeks compared with patients having low-level or high-level health care exposure ($P < .001$). Exposure to PPIs, H_2-receptor antagonists, animals and different types of food, and

Table 3. Comparison of Clinical Characteristics and Potential Sources of *Clostridium difficile* Acquisition Among Patients With Community-Associated *C difficile* Infection by Level of Outpatient Health Care Exposure, 2009 Through 2011[a]

	Outpatient Health Care Exposure			
Variable	None (n = 177)	Low Level (n = 400)	High Level (n = 407)	*P* Value[b]
Age, median (range), y	53 (1-93)	48 (1-97)	53 (1-94)	.01
Female sex, No. (%)	110 (62.1)	267 (66.8)	278 (68.3)	.34
No medical conditions, No. (%)	65 (36.7)	190 (47.5)	136 (33.4)	<.01
Antibiotic use within 12 wk before infection, No. (%)	77 (43.5)	272 (68.0)	282 (69.3)	<.01
Proton pump inhibitor use, No. (%)	43 (24.3)	98 (24.5)	132 (32.4)	.01
H_2-receptor antagonist use, No. (%)	22 (12.4)	30 (7.5)	38 (9.3)	.16
Household members, No. (%)[c]				
Infant younger than 1 y	8 (4.5)	24 (6.0)	10 (2.5)	.04
Children younger than 4 y in diapers	27 (15.3)	64 (16.0)	42 (10.3)	.04
Children younger than 4 y who attended child care settings	12 (6.8)	43 (10.8)	26 (6.4)	.05
Who had recent stay in a health care facility	5 (2.8)	27 (6.8)	20 (4.9)	.13
Whose job required direct contact with patients	9 (5.1)	29 (7.3)	23 (5.7)	.50
With active *C difficile* infection	3 (1.7)	7 (1.8)	1 (0.2)	.05
Food exposure, No. (%)[c]				
Chicken or poultry	152 (85.9)	356 (89.0)	360 (88.5)	.55
Beef	125 (70.6)	287 (71.8)	295 (72.5)	.89
Pork	74 (41.8)	181 (45.3)	192 (47.2)	.48
Lamb	5 (2.8)	14 (3.5)	17 (4.2)	.70
Animal exposure, No. (%)[c]				
Pet in the house	76 (42.9)	205 (51.3)	193 (47.4)	.16
Visited place where animals present	15 (8.5)	47 (11.8)	50 (12.3)	.39
Occupational exposure to animals	5 (2.8)	12 (3.0)	7 (1.7)	.46

[a] Antibiotic use, household members, and animal exposure were defined as an exposure within 12 weeks of the positive *C difficile* stool specimen. Food exposure was defined as food consumed during a typical week.

[b] *P* values were determined for categorical variables by means of the Pearson χ^2 or Fisher exact statistic and indicate significant differences in the proportion of patients exposed to household members, food, and animals by level of outpatient health care exposure. *P* values were determined for continuous variables by means of the Mood median test.

[c] Exposures to household members, food, or animals are not mutually exclusive.

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Table 4. Multivariable Analysis for Sources of *Clostridium difficile* Acquisition in Patients Having Community-Associated *C difficile* Infection With No or Low-Level Outpatient Health Care Exposure, 2009 Through 2011[a]

	Odds Ratio (95% CI)	
Variable	No Exposure	Low-Level Exposure
No medical conditions	1.1 (0.8-1.6)	1.7 (1.3-2.3)
Household members		
Infant younger than 1 y	1.8 (0.7-4.6)	2.1 (1.1-4.5)
With active *C difficile* infection	6.8 (0.7-65.9)	6.9 (0.9-56.7)

[a] Odds ratios were calculated using multinomial logistic regression using high-level outpatient health care exposure as the reference group. Candidate variables included clinical characteristics (age, sex, and no medical conditions), potential sources of *C difficile* infection (infant younger than 1 year, household member with active *C difficile* infection, and children younger than 4 years who attended child care settings), and antibiotic use as an interaction term with potential sources of *C difficile* infection. The final model was selected using a backward logistic regression strategy with a stay criterion of $P \leq .10$ for variables.

household members who had active CDI or who were infants younger than 1 year was similar between patients having CDI with no and low-level health care exposure ($P > .05$). Of 177 patients having CDI with no outpatient health care exposure, 108 (61.0%) reported prior medication exposure; 42 (38.9%) of those were exposed only to antibiotics, 16 (14.8%) only to PPIs, 8 (7.4%) only to H_2-receptor antagonists, and 6 (5.6%) only to immune-suppressing agents.

In multivariable analysis, patients having CDI with low-level health care exposure were more likely to have no medical conditions (odds ratio, 1.7; $P < .01$) and have household members who were infants younger than 1 year (odds ratio, 2.1; $P = .05$) compared with patients with high-level health care exposure (**Table 4**). Although the association between having household members with CDI and low-level outpatient health care exposure was strong, it was not statistically significant (odds ratio, 6.9; $P = .07$). For patients having CDI without outpatient health care exposure, no statistically significant association was found with having household members younger than 1 year or household members with active CDI; however, the point estimates were high and were similar to point estimates found for patients having CDI with low-level health care exposure, suggesting that an association may exist. No differences in the final model were detected when analyses were restricted to 631 patients who used antibiotics.

Discussion

Although community-associated CDI is defined based on the interim surveillance recommendations[14] as the absence of inpatient overnight stay in a health care facility, we found that 82.0% of patients acquiring *C difficile* in the community had either a recent outpatient health care exposure or an inpatient health care exposure without an overnight stay. Outpatient settings such as physicians' offices, emergency departments, and dialysis facilities can be the source of *C difficile* acquisition by exposure to contaminated environmental surfaces, as well as the prescription of antibiotics that disrupt the lower intestinal microbiota. In our study, 64.1% of patients with CDI received outpatient antibiotics within 12 weeks before infection, and the most common indications for antibiotic therapy were ear, sinus, or upper respiratory tract infection or a dental procedure. Multiple studies[15-20] have noted that ear, sinus, or upper respiratory tract infections are common reasons for inappropriate antibiotic use in outpatient settings. The many patients receiving antibiotics for dental procedures was notable because the current American Heart Association guideline for prevention of infective endocarditis restricts prophylactic antibiotic use for dental procedures to patients with underlying cardiac conditions associated with the highest risk of adverse outcome from infective endocarditis.[21] Therefore, it is likely that a substantial proportion of patients in our study received antibiotics inappropriately, emphasizing that antibiotics should be prescribed more judiciously by outpatient health care providers and that the overuse of outpatient antibiotics may have an adverse effect on community-associated CDI rates. Antimicrobial stewardship programs in acute care facilities have been associated with decreases in CDI rates up to 60%[22,23]; aspects of these strategies may need to be considered for use in outpatient health care settings as well.

Thirty-six percent of patients in our study did not report antibiotic exposure in the 12 weeks before infection. Since discovery of the causal role for *C difficile* in pseudomembranous colitis was made in the late 1970s,[24] there have been occasional reports of CDI occurring without precedent antibiotic exposure.[25-27] However, the overall importance of community-associated CDI and its frequent occurrence in the absence of antibiotic exposure were not appreciated until approximately 8 years ago.[3] Our study is the largest assessment of antibiotic exposures among patients with community-associated CDI in the United States to date, and the proportion we identified without such exposure is consistent with other recent estimates.[3-6] Although it is unknown from these or other data whether CDI in the absence of antibiotic exposure is increasing, other emerging factors may have a role similar to that of antibiotics in weakening the important host defense afforded by intact lower intestinal microbiota.

We found that patients having community-associated CDI without antibiotic exposure had a trend toward having received PPIs more frequently than patients with antibiotic exposure. In some studies,[28,29] PPIs have been shown to increase the risk of community-associated CDI, and the US Food and Drug Administration[30] issued a recent warning advising physicians of the increased CDI risk in patients receiving PPIs. However, no data indicating the effect of restricting PPI use on CDI incidence are available to date. In addition, the mechanism by which PPIs may increase the risk of CDI is not fully understood, and it has been suggested that PPIs may have a more important role in patients with minimal antibiotic exposure.[31] Based on our data, if the effect of reducing unnecessary PPI use on community-associated CDI is limited to those patients who have not received recent antibiotics, such an in-

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tervention would prevent only 11.2% of community-associated CDI.

Clostridium difficile spores can survive for prolonged periods in the environment,[2] and the health care environment where patients with *C difficile* are treated can serve as a source of transmission.[32] To identify sources of *C difficile* in the community other than the outpatient health care environment and the transiently contaminated hands of health care personnel, we compared *C difficile* patients by level of health care exposure. In these exploratory analyses adjusted for antibiotic use, a plausible association existed between low-level health care exposure and exposure to household members younger than 1 year. Infants younger than 1 year are known to be frequent asymptomatic carriers of *C difficile*, with the results of some studies[33,34] suggesting up to a 70% colonization rate. Our findings are consistent with a study by Wilcox et al,[8] which found that contact with children younger than 2 years was associated with an increased risk of community-associated CDI. Although *C difficile*–colonized infants and children can shed the organism into the environment[35] and a study[36] has reported a *C difficile* outbreak in a day care center, additional studies in day care, home day care, and household settings are needed before setting-specific environmental recommendations can be made. We also found higher odds of having a household member with CDI among the no and low-level health care exposure groups. However, due to the low prevalence of household members with CDI, this association was not statistically significant. This finding is consistent with a recent Canadian study,[37] which demonstrated that household contacts with patients having active CDI are at increased risk of infection. Our data provided no evidence to support a role for food or animal exposure as a source of *C difficile* acquisition beyond health care exposure. Only 6.7% of culture-positive isolates were NAP7 or NAP8, strains primarily detected in food and animals.[38] In recent studies[39-42] in North America, *C difficile* detection in retail meat samples has ranged from 0% to 10%. This low prevalence of *C difficile* among retail meat in conjunction with our findings suggests that food and animal exposures could account for only a small proportion of community-associated CDI. Furthermore, antibiotics may be present in consumed foods,[43] and it is unclear at this point whether food can be a source of *C difficile* or another potential factor that can disturb the gut microbiota and predispose patients to CDI.

Despite that a large sample of patients across multiple geographic locations was included in our analyses, the study is subject to several limitations. First, only a sample of patients having community-associated CDI was interviewed, and these patients were more likely to be female and white compared with patients having CDI who refused to be interviewed. In addition, only a convenience sample of the patients interviewed had stool specimens sent for further testing. Therefore, patients and *C difficile* isolates included in this analysis may not be representative of all US patients with community-associated CDI, and the data should be interpreted cautiously because women of perimenopausal age, for example, may be submitted to more medical maneuvers or may be receiving other medications to counteract menopause symptoms. Second, because interviews were conducted up to 12 weeks after detection of *C difficile* and because exposures to medications and sources of *C difficile* acquisition were self-reported, it is possible that these exposures were misclassified. Nevertheless, this study assesses exposures for *C difficile* using medical records and health interviews and may provide a more accurate description of exposures compared with studies that solely relied on data collected from medical records. Third, the lack of a comparison group without CDI precluded us from confirming risk factors for community-associated CDI that we observed in this study. Fourth, because few patients had CDI without outpatient health care exposure, we were likely limited in our ability to detect any statistically significant association among this group. Nonetheless, our findings raise important hypotheses to be tested in future studies.

Most patients identified with community-associated CDI had received antibiotics and had outpatient health care exposure. Prevention of community-associated CDI should primarily focus on reducing inappropriate antibiotic use and better infection control practices in outpatient settings. Our data support evaluation of additional strategies, including further examination of *C difficile* transmission in outpatient and household settings and reduction of PPI use.

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Invited Commentary

Clostridium difficile Leaves the Hospital—What's Next?

Kent A. Sepkowitz, MD

Since their introduction after World War II, antibiotics have been known to cause gastrointestinal problems, including nausea and diarrhea. By the late 1970s, *Clostridium difficile* was put forward as the cause of a large proportion of cases of diarrhea,[1] and the hunt began for an optimal control strategy. At first, control of the situation seemed easy: clindamycin, an agent with potent anaerobic activity, was implicated, a connection that made biologic sense and was supported by the newly developed hamster model.[2] Better yet, less clindamycin use resulted in less *C difficile,* at least early on, and the problem briefly came under control.[3]

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However, things were not as simple as they first seemed. Soon, additional antibiotics were incriminated, including ampicillin and third-generation cephalosporins and then fluoroquinolones, until eventually the list of associated antibiotics became almost synonymous with the hospital antibiotic formulary. The classic study by McFarland et al,[4] using larger data sets, found that advanced age and comorbid illness, along with bowel perturbation, were associated with *C difficile* disease in hospitalized patients. Further progress in understanding was made with the recognition that cases were occurring in the community, far from the harsh corridors of the modern medical center.[5]

In the past few years, a new and disturbing smoking gun has been identified. In 2010, this journal ran a pair of articles,[6,7] along with a pointed editorial,[8] about the health consequences of the overuse of a different class of medications: not antibiotics, but America's third favorite drugs, proton pump inhibitors (PPIs), a multibillion-dollar product. One of the unexpected adverse effects was an increase in *C difficile*, with a corresponding dose response connecting the degree of acid suppression to the risk of *C difficile*–associated diarrhea.

The link has proved to be of sufficient scope and significance that in February 2012 the Food and Drug Administration issued a safety announcement to inform the public that the "use of stomach acid drugs known as proton pump inhibitors (PPIs) may be associated with an increased risk of *Clostridium difficile*–associated diarrhea."[9] Their evidence base was 28 observational studies in 26 reports, as well as their own passive Adverse Event Reporting System. In general, the risk of *C difficile*–associated diarrhea was 1.4 to 2.8 times higher among patients who had PPI exposure compared with those who did not have PPI exposure.

The important article by Chitnis et al[10] in this issue of *JAMA Internal Medicine* adds substantially more evidence. In a remarkably thorough epidemiological study across 8 states, the authors determined risks for about 1000 cases of community-acquired *C difficile*–associated diarrhea. The patients were divided into those with high-level health care exposure (including recent hospitalization and dialysis or other invasive procedures), low-level exposure (such as a visit to a physician's or dentist's office), or no health care exposure at all. Overall, more than one-third (36%) of the patients had no antibiotic exposure in the 12 weeks before diagnosis, while 31% had received PPIs, a disturbingly high proportion. The investigators then zeroed in on the 177 patients with no health care exposure in the 12 weeks before diagnosis. Of these, more than one-third were taking acid-reducing medications, including PPIs (24%) and H_2-receptor antagonists (12%).

This observation raises several important questions. The first is why America has such an upset stomach. Most of the use of PPIs is for symptoms well outside of the label indica-

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