ORIGINAL ARTICLE

Burden of *Clostridium difficile* Infection in the United States

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ABSTRACT

BACKGROUND

The magnitude and scope of *Clostridium difficile* infection in the United States continue to evolve.

METHODS

In 2011, we performed active population- and laboratory-based surveillance across 10 geographic areas in the United States to identify cases of *C. difficile* infection (stool specimens positive for *C. difficile* on either toxin or molecular assay in residents ≥1 year of age). Cases were classified as community-associated or health care–associated. In a sample of cases of *C. difficile* infection, specimens were cultured and isolates underwent molecular typing. We used regression models to calculate estimates of national incidence and total number of infections, first recurrences, and deaths within 30 days after the diagnosis of *C. difficile* infection.

RESULTS

A total of 15,461 cases of *C. difficile* infection were identified in the 10 geographic areas; 65.8% were health care–associated, but only 24.2% had onset during hospitalization. After adjustment for predictors of disease incidence, the estimated number of incident *C. difficile* infections in the United States was 453,000 (95% confidence interval [CI], 397,100 to 508,500). The incidence was estimated to be higher among females (rate ratio, 1.26; 95% CI, 1.25 to 1.27), whites (rate ratio, 1.72; 95% CI, 1.56 to 2.0), and persons 65 years of age or older (rate ratio, 8.65; 95% CI, 8.16 to 9.31). The estimated number of first recurrences of *C. difficile* infection was 83,000 (95% CI, 57,000 to 108,900), and the estimated number of deaths was 29,300 (95% CI, 16,500 to 42,100). The North American pulsed-field gel electrophoresis type 1 (NAP1) strain was more prevalent among health care–associated infections than among community-associated infections (30.7% vs. 18.8%, P<0.001)

CONCLUSIONS

C. difficile was responsible for almost half a million infections and was associated with approximately 29,000 deaths in 2011. (Funded by the Centers for Disease Control and Prevention.)

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Changes in the epidemiology of *Clostridium difficile* infections have occurred since the emergence of the North American pulsed-field gel electrophoresis type 1 (NAP1) strain, which has been responsible for geographically dispersed hospital-associated outbreaks.[1-3] In the United States, hospitalizations for *C. difficile* infection among nonpregnant adults doubled from 2000 through 2010 and were projected to continue to increase in 2011 and 2012, especially as laboratories transition to more sensitive *C. difficile* assays, such as the nucleic acid amplification test (NAAT).[4-6] On the basis of data from U.S. death certificates, *C. difficile* infection is the leading cause of gastroenteritis-associated death and was estimated to cause 14,000 deaths in 2007.[7] *C. difficile* has become the most common cause of health care–associated infections in U.S. hospitals, and the excess health care costs related to *C. difficile* infection are estimated to be as much as $4.8 billion for acute care facilities alone.[8-10] In addition, *C. difficile* infection has been increasingly reported outside of acute care facilities, including in community and nursing homes settings, where infection may be diagnosed and treated without hospitalization.[11-13] As the epidemiology of *C. difficile* changes, both in health care and community settings, it is important to understand the magnitude and scope of this infection in the United States to help guide priorities for prevention.

In 2009, the Centers for Disease Control and Prevention (CDC) started active population- and laboratory-based surveillance for *C. difficile* infection at 7 U.S. sites. This surveillance was expanded to 10 sites in 2011 to provide better national estimates of disease burden, incidence, recurrence, and mortality by capturing data across the spectrum of health care delivery and community settings.

Methods

Surveillance Population and Case Definition

C. difficile surveillance is a component of the CDC's Emerging Infections Program (EIP). In 2011, *C. difficile* surveillance was conducted at 10 EIP sites across 34 counties (total population, approximately 11.2 million) for the entire calendar year. Surveillance catchment areas included California (1 urban county; population, 812,826), Colorado (5 urban counties; population, 2,488,410), Connecticut (1 urban county; population, 861,113), Georgia (8 urban counties; population, 3,753,452), Maryland (3 rural and 8 urban counties; population, 835,893), Minnesota (2 rural and 2 urban counties; population, 248,079), New Mexico (1 urban county; population, 670,968), New York (1 urban county; population, 745,625), Oregon (1 rural county; population, 66,299), and Tennessee (1 urban county; population, 635,475).

The surveillance methods have been described previously.[14,15] Briefly, surveillance staff at each EIP site identified all positive *C. difficile* test results from 88 inpatient and 33 outpatient laboratories serving residents in surveillance areas in 2011. A case of *C. difficile* infection was defined as a positive result on a *C. difficile* toxin or molecular assay of a stool specimen obtained from a surveillance-area resident at least 1 year of age who had not had a positive assay in the previous 8 weeks (i.e., incident infection). This surveillance was approved by the institutional review boards at the CDC and at the participating EIP sites.

Data Collection

We performed an initial medical-record review to collect data on demographic characteristics, the location of stool collections, and health care exposures on all cases of *C. difficile* infection in 8 of the 10 EIP sites. In 2 EIP sites with the largest surveillance populations (Georgia and Colorado), we performed an initial medical-record review on a random sample of cases, as described previously.[15]

On the basis of the initial medical review, a case was classified as community-associated if the *C. difficile*–positive specimen was collected on an outpatient basis or within 3 days after hospital admission and the patient had no documented overnight stay in a health care facility during the previous 12 weeks. All other cases were classified as health care–associated and further categorized into three mutually exclusive groups: community onset associated with a health care facility, hospital onset, or nursing home onset (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). All cases that were classified as either community-associated or community-onset health care–associated underwent full medical-record review to collect information on coexisting medical conditions, medication exposures, first laboratory-confirmed recurrences (i.e., positive specimen

within 2 to 8 weeks after the last positive test), and death within 30 days after diagnosis of *C. difficile* infection. In addition, we reviewed a sample consisting of 10% of cases with an onset in a nursing home or hospital.

A convenience sample of clinical laboratories across the EIP sites (37 laboratories) submitted all *C. difficile*–positive stool specimens from cases with full medical-record review for culture.[16] Recovered isolates underwent pulsed-field gel electrophoresis (PFGE). PFGE patterns were analyzed with the use of BioNumerics software, version 5.10 (Applied Maths) and grouped into pulsed-field types with the use of Dice coefficient analysis and UPGMA (unweighted pair group method with arithmetic mean) clustering. An 80% similarity threshold was used to assign North American PFGE (NAP) types.[17] Isolates also underwent polymerase-chain-reaction (PCR) assay to detect the presence of *tcdA*, *tcdB*, and binary toxin (*cdtA* and *ctdB*) genes and a subset of the most common NAP types underwent PCR ribotyping.[18]

Between November 2011 and January 2012, all laboratories serving the surveillance population were surveyed to assess the type of *C. difficile* diagnostic tests that were used during 2011.[19] Laboratory surveys were used to estimate the proportion of cases in the surveillance areas that were identified by means of NAAT.

STATISTICAL ANALYSIS

Data were analyzed with the use of SAS software, version 9.3 (SAS Institute). In cases of *C. difficile* infection in which the patient's race was unknown (18.7%), including sampled cases from Georgia and Colorado, we imputed race on the basis of the distribution of known races according to age, sex, and surveillance site.[20] After race imputation was performed, a domain (subpopulation) analysis was used to estimate the number of cases according to epidemiologic class and race in the two EIP sites where sampling was performed (Georgia and Colorado).[21]

To generate an estimate of the national burden of *C. difficile* infection, we built two generalized linear mixed models with negative binomial distribution, one for health care–associated cases and another for community-associated cases, using predictors that had been shown to be associated with infection incidence in each epidemiologic category.[15] We estimated the national number of health care–associated infections using model coefficients that accounted for the age of the population, the volume of inpatient days, and the proportion of cases identified by means of NAAT across EIP sites, since the rate of NAAT use in the United States is unknown. We estimated the national number of community-associated cases in a similar way, accounting for age, sex, and race of the U.S. population, as well as NAAT use across the EIP sites. We constructed 95% confidence intervals for the national estimates according to each epidemiologic category using imputation error, sampling error for Georgia and Colorado, and modeling error.[20,21] We then calculated the total national burden of *C. difficile* infection by adding estimated numbers of community-associated and health care–associated cases and 95% confidence intervals.

We estimated the numbers of recurrences and deaths within 30 days and corresponding 95% confidence intervals by performing domain analysis[21] to account for sampling design across EIP sites and using site-specific and national sampling weights for the national projections. We calculated the population-based incidence of *C. difficile* infection (site-specific and national) using 2011 U.S. Census data.[22] In this calculation, we excluded infants under the age of 1 year from the denominator, since they were not included in the numerator. We also performed a sensitivity analysis to estimate the national burden of *C. difficile* infection according to different levels of NAAT use.

RESULTS

INCIDENCE AND BURDEN OF *C. DIFFICILE* INFECTION

From January 1, 2011, to December 31, 2011, we identified 15,461 cases of *C. difficile* infection in 14,453 patients across the 10 EIP sites. Of these cases, 65.8% were health care–associated, and 24.2% were hospital-onset. The crude incidence per 100,000 population ranged from 30 to 120 cases of community-associated infection and from 50 to 160 cases of health care–associated infection across the EIP sites. The incidence of health care–associated infection was higher than the incidence of community-associated infection for all sites except Minnesota, where the surveillance population was primarily rural (Table 1).

The pooled mean crude incidence of community-associated infection was 48.2 per 100,000 population. After accounting for age, sex, and race of the U.S. population and NAAT use across EIP sites, the national estimated incidence of community-associated *C. difficile* infection was 51.9 (95% confidence interval [CI], 43.2 to 60.5) per 100,000 population, for a national burden estimate of 159,700 cases (95% CI, 132,900 to 186,000). For health care–associated infection, the pooled mean crude incidence was 92.8 cases per 100,000 population. After accounting for the age of the U.S. population, the volume of inpatient days, and a presumed NAAT use of 52% on the basis of the EIP sites, the national estimated incidence of health care–associated *C. difficile* infection was 95.3 (95% CI, 85.9 to 104.8) per 100,000 population, for a national burden estimate of 293,300 cases (95% CI, 264,200 to 322,500). Overall, we estimated that 453,000 cases of *C. difficile* infection (95% CI, 397,100 to 508,500) occurred in 2011 (Table 2). Incidence estimates were higher among females than among males (rate ratio, 1.26; 95% CI, 1.25 to 1.27), among whites than among nonwhites (rate ratio, 1.72; 95% CI, 1.56 to 2.00), and among persons 65 years of age or older than among those under the age of 65 years (rate ratio, 8.65; 95% CI, 8.16 to 9.31).

Of the 293,300 health care–associated cases, we estimated that 107,600 (95% CI, 97,200 to 118,000) had a hospital onset, 104,400 (95% CI, 94,100 to 115,800) had a nursing home onset, and 81,300 (95% CI, 72,900 to 89,000) had a community onset associated with a health care facility (Fig. 1).

As determined on sensitivity analysis, the national estimates of health care–associated, community-associated, and overall infection burden could change substantially, depending on NAAT use, ranging from a total of 325,300 cases (95% CI, 286,300 to 364,000) if no U.S. laboratories were using NAAT to 622,600 cases (95% CI, 543,400 to 701,100) if all U.S. laboratories adopted NAAT (Fig. S1 in the Supplementary Appendix).

C. DIFFICILE RECURRENCE AND MORTALITY

Among the cases of community-associated infection, the estimated rate was 13.5% for first

Table 1. Incidence of *Clostridium difficile* Infection (CDI), According to Geographic Location and Epidemiologic Category, 2011.*

Site	Counties under Surveillance	Population ≥1 Yr of Age	Community-Associated CDI		Health Care–Associated CDI	
			Total No. of Cases	Incidence per 100,000 Persons	Total No. of Cases	Incidence per 100,000 Persons
		no.				
All sites		10,971,319	5284	48.2	10,177	92.8
California	San Francisco	804,110	297	37.0	733	91.1
Colorado†	Adams, Arapahoe, Denver, Douglas, Jefferson	2,454,142	1229	50.1	2,200	89.7
Connecticut	New Haven	851,962	393	46.1	1,355	159.1
Georgia†	Clayton, Cobb, Douglas, DeKalb, Fulton, Gwinnett, Newton, Rockdale	3,699,307	1395	37.7	2,381	64.7
Maryland	Caroline, Cecil, Dorchester, Frederick, Kent, Somerset, Talbot, Queen Anne's, Washington, Wicomico, Worcester	826,430	485	58.7	1,056	127.7
Minnesota	Stearns, Benton, Morrison, Todd	244,884	303	123.7	177	72.3
New Mexico	Bernalillo	661,779	354	53.4	727	109.9
New York	Monroe	737,270	634	86.0	1,145	155.3
Oregon	Klamath	65,545	27	41.2	31	47.3
Tennessee	Davidson	625,890	167	26.7	372	59.4

* The 2011 population is based on estimates from the U.S. Census Bureau.[22] The epidemiologic category was statistically imputed for cases with unknown epidemiologic data as follows: 3 cases in California, 39 cases in Maryland, and 43 cases in New Mexico.
† The weighted frequency of cases was based on 33% random sampling.

Table 2. Adjusted U.S. National Estimates of Burden and Incidence of CDI, 2011.

Demographic Characteristic	Community-Associated CDI*		Health Care–Associated CDI†		All CDI	
	Estimated No. of Cases	Incidence per 100,000 Persons	Estimated No. of Cases	Incidence per 100,000 Persons	Estimated No. of Cases	Incidence per 100,000 Persons
All cases	159,700 (132,900–186,000)	51.9 (43.2–60.5)	293,300 (264,200–322,500)	95.3 (85.9–104.8)	453,000 (397,100–508,500)	147.2 (129.1–165.3)
Sex						
Male	64,300 (52,800–75,300)	42.5 (34.8–49.8)	132,700 (118,700–146,700)	87.7 (78.5–97.0)	197,000 (171,500–222,000)	130.2 (113.3–146.8)
Female	95,400 (80,100–110,700)	61.0 (51.2–70.8)	160,600 (145,500–175,800)	102.7 (93.1–112.5)	256,000 (225,600–286,500)	163.8 (144.3–183.3)
Age group						
1–17 yr	12,500 (10,000–15,000)	17.9 (14.1–21.4)	4400 (3200–5800)	6.3 (4.6–8.3)	16,900 (13,200–20,800)	24.2 (18.7–29.7)
18–44 yr	35,600 (26,000–39,200)	28.7 (22.9–34.5)	20,800 (16,700–24,800)	18.3 (14.7–21.9)	53,400 (42,700–64,000)	47.0 (37.6–56.4)
45–64 yr	54,100 (45,600–62,600)	65.4 (55.1–75.6)	68,800 (61,000–76,600)	83.1 (73.7–92.5)	122,900 (106,600–139,200)	148.5 (128.8–168.1)
≥65 yr	60,500 (51,300–69,200)	146.2 (124.0–167.2)	193,300 (183,300–215,300)	481.5 (442.8–520.1)	259,800 (234,600–284,500)	627.7 (566.8–687.3)
Race‡						
White	138,100 (118,500–157,700)	57.4 (49.2–65.5)	259,900 (230,100–273,800)	104.7 (95.6–113.8)	390,000 (348,600–431,500)	162.1 (144.8–179.3)
Nonwhite	21,600 (14,400–28,300)	32.2 (21.5–42.2)	41,400 (34,100–48,700)	61.8 (50.9–72.7)	63,000 (48,500–77,000)	94.0 (72.4–114.9)

* Data for community-associated *Clostridium difficile* infection (CDI) were adjusted for age, sex, race, and a rate of use of nucleic acid amplification test (NAAT) of 52%. Ranges in parentheses are 95% confidence intervals.
† Data for health care–associated CDI were adjusted for age, inpatient days, and a rate of use of NAAT of 52%.
‡ Race was imputed for 18.7% of the observed cases of *C. difficile* infection.

recurrence and 1.3% for death within 30 days after diagnosis of *C. difficile* infection, for national estimates of 21,600 first recurrences (95% CI, 16,900 to 26,300) and 2000 deaths (95% CI, 1200 to 2800). Recurrence and death were more commonly observed among the health care–associated infections than among community-associated infections. Of the patients with health care–associated infection, the rate of first recurrence was estimated at 20.9%, and the rate of death within 30 days was 9.3%, resulting in an estimated 61,400 recurrences (95% CI, 40,200 to 82,600) and 27,300 deaths (95% CI, 15,300 to 39,300) nationally (Table 3).

ISOLATE CHARACTERIZATION

C. difficile was isolated in samples obtained from 1364 of 1625 patients (83.9%) in whom stool culture was performed. The three most common strains in both community- and health care–associated cases were NAP1, NAP4, and NAP11, which represented mostly PCR ribotypes 027, 020, and 106, respectively (Table 4). The NAP1 strain was more common among health care–associated cases than among community-associated cases (30.7% vs. 18.8%, P<0.001). Among the 138 community-associated cases and 193 health care–associated cases with NAP1 strains, 12 isolates (8.7%) and 3 isolates (1.6%), respectively, were negative for binary toxin. The NAP7 strain (PCR ribotype 078) represented less than 4% of the isolates in the two groups, and all NAP7 isolates were positive for binary toxin.

DISCUSSION

We estimated that *C. difficile* caused approximately 453,000 incident infections and was associated with approximately 29,000 deaths in the United States in 2011 on the basis of data from active population- and laboratory-based surveillance across diverse geographic locations in the United

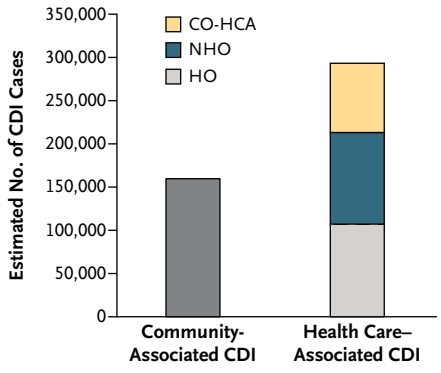

Figure 1. Estimated U.S. Burden of *Clostridium difficile* Infection (CDI), According to the Location of Stool Collection and Inpatient Health Care Exposure, 2011.

Of the estimated cases of community-associated CDI, 82% were estimated to be associated with outpatient health care exposure.[11] CO-HCA denotes community-onset health care–associated infection, HO hospital onset, and NHO nursing home onset.

States. Persons 65 years of age or older, whites, and females had higher incidences than their comparators. This national estimate of *C. difficile* infection is higher than previous U.S. estimates (240,000 to 333,000) that relied on passive surveillance, data from health care facilities in a single state, administrative data, or data from managed-care populations in a specific region.[23-25] However, comparisons with previous estimates are limited by differences in definitions of *C. difficile* infection and in analytical methods, especially the emergence of NAAT testing.

Only an estimated 24% of cases occurred in hospital settings, leading to an estimate of approximately 107,600 hospital-onset infections nationally. This number is higher than the 80,400 cases of hospital-onset infections that were recently reported from a point-prevalence survey conducted from May 2011 through September 2011 in the 10 EIP sites with the use of similar definitions.[9] A possible explanation for this difference is the uptake of molecular testing for *C. difficile* diagnosis by hospital laboratories during 2011.[5,19]

According to our estimates, nearly 345,400 cases occurred outside of hospitals, indicating that the prevention of *C. difficile* infection should go beyond hospital settings. Although 46.2% of those cases were community-associated and by definition had no documented inpatient health care exposure, in a recent study that used the same surveillance program and sites but included earlier years of data, 82% of patients with community-associated *C. difficile* infection reported during telephone interviews that they had visited outpatient health care settings, such as a doctor's or dentist's office, in the 12 weeks before the collection of a *C. difficile*–positive stool sample.[11] Therefore, most patients with *C. difficile* infection had either inpatient or outpatient health care exposures before disease onset. Finally, our adjusted national rate of community-associated infection of 51.9 per 100,000 population is higher than the rate of 20 to 40 per 100,000 population that was reported from population-based studies outside the United States that were conducted before the introduction of NAAT.[26,27] However, it is possible that some of the cases detected by NAAT represent colonization rather than true infection, given that NAAT detects the presence of the organism but not necessarily if it is disease-causing and has high sensitivity.[28,29] The rate of asymptomatic colonization in nonhospitalized adults is estimated to be 2%, with a higher rate, up to 26%, in those with health care exposures.[30-32]

Recurrence rates for health care–associated *C. difficile* infection have been reported to vary from 5% to 50%, with an average of 20%.[33-35] In our study, at least one recurrence of *C. difficile* infection occurred in approximately 21% of cases of health care–associated infection and 14% of cases of community-associated infection on the basis of repeated stool testing between 14 and 56 days after the initial *C. difficile* episode, leading to an estimated burden of 83,000 first recurrent infections. These numbers are worrisome, given challenges in treating recurrent infections and the ongoing risk of transmission when symptoms recur.[32,36,37]

C. difficile is known to cause severe disease and death.[2,3] The estimated total number of deaths within 30 days after the diagnosis of *C. difficile* infection nationally was 29,300, and the majority of these deaths were among patients with health care–associated infection. This number equated to an observed 30-day crude case fatality rate of 9.3% for patients with health care–associated infection, a rate that is similar to that reported in studies of hospitalized patients with *C. difficile* infection.[38-40] Since the mortality that is attributable to *C. difficile* infection is estimated

Table 3. Adjusted U.S. National Estimates of Recurrences and Deaths Associated with CDI, According to Epidemiologic Category, 2011.*

Characteristic	Estimated Recurrences		Recurrence Rate		Estimated Deaths		Death Rate	
	CA CDI	HCA CDI	CA CDI	HCA CDI	CA CDI	HCA CDI	CA CDI	HCA CDI
	no. (95% CI)		*no. per 100,000 persons (95% CI)*		*no. (95% CI)*		*no. per 100,000 persons (95% CI)*	
All cases	21,600 (16,900–26,300)	61,400 (40,200–82,600)	7.0 (5.5–8.6)	19.9 (13.0–26.9)	2000 (1200–2800)	27,300 (15,300–39,300)	0.7 (0.4–0.9)	8.9 (5.0–12.8)
Sex								
Male	7800 (5100–10,500)	27,300 (12,800–41,800)	5.2 (3.4–6.9)	18.0 (8.5–27.6)	900 (450–1350)	12,300 (3800–20,700)	0.6 (0.3–0.9)	8.1 (2.5–13.7)
Female	13,800 (9900–17,600)	34,000 (18,700–49,400)	8.8 (6.3–11.3)	21.7 (12.0–31.6)	1100 (400–1700)	15,000 (6600–23,500)	0.7 (0.3–1.1)	9.6 (4.2–15.0)
Age group								
1–17 yr	1400 (900–1900)	300 (100–500)	2.0 (1.3–2.7)	0.4 (0.1–0.7)	NA	NA	NA	NA
18–44 yr	2600 (1300–3900)	3400 (1000–5700)	2.3 (1.1–3.4)	3.0 (0.9–5.0)	50 (0–120)	NA	<0.1 (0–0.1)	NA
45–64 yr	6200 (4000–8300)	9000 (4400–13,700)	7.5 (4.8–10.0)	10.9 (5.3–16.6)	420 (120–720)	4500 (1020–8000)	0.5 (0.1–0.9)	5.4 (1.2–9.7)
≥65 yr	11,400 (7400–15,400)	48,700 (28,100–69,200)	27.5 (17.9–37.2)	117.6 (67.9–167.2)	1500 (750–2200)	22,800 (11,300–34,200)	3.6 (1.8–5.3)	55.1 (27.3–82.6)
Race								
White	19,600 (14,900–24,200)	54,900 (34,000–75,700)	8.1 (6.2–10.1)	22.8 (14.1–31.5)	1800 (980–2600)	25,700 (13,900–37,600)	0.8 (0.4–1.1)	10.7 (5.8–15.6)
Nonwhite	2000 (900–3200)	6500 (400–12,600)	3.0 (1.3–4.8)	9.7 (0.6–18.8)	200 (0–390)	1600 (0–3500)	0.3 (0.0–0.6)	2.4 (0.0–5.2)

* A recurrence was defined as a positive result on testing for *C. difficile* in a stool specimen during the period from 14 days through 56 days after the initial episode of *C. difficile* infection (CDI). Death from CDI was defined as any death occurring within 30 days after positive results on testing for *C. difficile* in a stool specimen. CA denotes community-associated, HCA health care–associated, and NA not applicable because no deaths within 30 days were observed.

to be approximately 50% of the crude mortality,[38] the total number of deaths in our study that would be attributable to *C. difficile* infection is about 15,000. The three most common strains we observed in both community-associated and health care–associated infection (NAP1, NAP4, and NAP11) are similar to the strains that have been reported in other countries.[41,42] The NAP7 strain has been isolated from food and food animals and represented around 4% of the isolates in our collection; this finding is consistent with the prevalence observed in England (4%), but lower than the 8% prevalence reported from a hospital survey involving 34 European countries.[43-46]

Our analyses have several limitations. First, the case definition relied solely on positive results on *C. difficile* toxin or molecular assay because diarrhea is usually poorly documented in charts and existing guidelines for laboratory practice recommend *C. difficile* testing only on unformed stools.[47,48] It has been documented that laboratories are adopting stricter policies to reject formed stools when transitioning to NAAT.[19] Second, the type of *C. difficile* diagnostic test that is used has implications for measured disease incidence. Several studies have shown that laboratories transitioning to NAAT are expected to observe an increase in *C. difficile* incidence, which may partially represent overdiagnosis of *C. difficile* infection owing to a highly sensitive assay that does not distinguish between colonization and disease.[5,6,19,28,29] Our estimates of incidence and disease burden were based on a rate of NAAT use of 52%, which was observed across the EIP sites. Although this rate may not be representative of the rate of NAAT use in the United States, a sensitivity analysis showed how the

Table 4. Distribution of *C. difficile* Strains, According to Epidemiologic Category.*

Strain	Community-Associated CDI (N=735)	Health Care–Associated CDI (N=629)
	no. of cases (%)	
NAP1	138 (18.8)	193 (30.7)
NAP1-related†	13 (1.8)	20 (3.2)
NAP2	13 (1.8)	10 (1.6)
NAP3	3 (0.4)	12 (1.9)
NAP4	84 (11.4)	65 (10.3)
NAP5	3 (0.4)	6 (1.0)
NAP6	56 (7.6)	27 (4.3)
NAP7	25 (3.4)	13 (2.1)
NAP7-related‡	2 (0.3)	2 (0.3)
NAP8	5 (0.7)	1 (0.2)
NAP9	22 (3.0)	9 (1.4)
NAP10	21 (2.9)	15 (2.4)
NAP11	79 (10.7)	63 (10.0)
NAP12	9 (1.2)	16 (2.5)
Unnamed§	245 (33.3)	163 (25.9)
Could not be typed¶	17 (2.3)	14 (2.2)

* Molecular typing was performed with the use of pulsed-field gel electrophoresis (PFGE). PFGE types represented the following ribotypes on polymerase-chain-reaction assay, according to an analysis that was performed on a random sample of 35 of the most prevalent NAP (North American PFGE) types: NAP1, 027; NAP4, 020; NAP6, 002; NAP7, 078; and NAP11, 106.

† This strain has characteristics of NAP1 (i.e., positive for toxins A and B and *C. difficile* binary toxin with a 18-bp deletion in *tcdC*) but does not meet the 80% cutoff for relatedness on PFGE.

‡ This strain has characteristics of NAP7 (i.e., positive for toxins A and B and *C. difficile* binary toxin with a 39-bp deletion in *tcdC*) but does not meet the 80% cutoff for relatedness.

§ The strains in the unnamed category include 80 PFGE types that do not fall within NAP1 through NAP12.

¶ DNA from these samples produced no bands on PFGE after three attempts.

burden estimate varies on the basis of NAAT use (Fig. S1 in the Supplementary Appendix). Third, since we collected data on rates of recurrence and death in a random sample of cases, these rates may not be representative. In addition, our study underestimates both recurrence and mortality, given that we assessed only first recurrences and deaths that were documented in the medical record. It is likely that a subset of patients had multiple recurrences or died after discharge from the hospital or nursing home. Additional limitations are discussed in the Supplementary Appendix.

Despite these limitations, our national estimates are based on a large, longitudinal, U.S. population–based surveillance for *C. difficile* infection and on active laboratory case finding by trained personnel. Our results also support the growing evidence that *C. difficile* is no longer restricted to acute care settings. Thus, in the absence of a vaccine, future efforts to prevent *C. difficile* will cross health care settings and focus more on appropriate antibiotic use, which has been shown to be successful in decreasing rates of *C. difficile* infection in England, where a multifaceted program including antimicrobial stewardship was implemented.[49] The prevention of *C. difficile* infection is a U.S. priority, with 2020 national reduction targets being established and all hospitals participating in the Hospital Inpatient Quality Reporting Program of the Centers for Medicare and Medicaid Services, which has reported data regarding *C. difficile* infection to the National Healthcare Safety Network since 2013.[50,51]

In conclusion, on the basis of active population- and laboratory-based surveillance across 10 U.S. geographic areas, we estimated that *C. difficile* caused almost half a million infections in the United States in 2011. An estimated 83,000 of the patients with such infections had at least one recurrence, and approximately 29,000 died within 30 days after the initial diagnosis. Continued surveillance for *C. difficile* infection will be needed to monitor progress toward prevention.

The views expressed in this article are those of the authors and do not necessarily represent the official position of the CDC.

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APPENDIX

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