

Determinants of *Clostridium difficile* Infection Incidence Across Diverse United States Geographic Locations

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Background. *Clostridium difficile* infection (CDI) is no longer restricted to hospital settings, and population-based incidence measures are needed. Understanding the determinants of CDI incidence will allow for more meaningful comparisons of rates and accurate national estimates.

Methods. Data from active population- and laboratory-based CDI surveillance in 7 US states were used to identify CDI cases (ie, residents with positive *C difficile* stool specimen without a positive test in the prior 8 weeks). Cases were classified as community-associated (CA) if stool was collected as outpatients or ≤ 3 days of admission and no overnight healthcare facility stay in the past 12 weeks; otherwise, cases were classified as healthcare-associated (HA). Two regression models, one for CA-CDI and another for HA-CDI, were built to evaluate predictors of high CDI incidence. Site-specific incidence was adjusted based on the regression models.

Results. Of 10 062 cases identified, 32% were CA. Crude incidence varied by geographic area; CA-CDI ranged from 28.2 to 79.1/100 000 and HA-CDI ranged from 45.7 to 155.9/100 000. Independent predictors of higher CA-CDI incidence were older age, white race, female gender, and nucleic acid amplification test (NAAT) use. For HA-CDI, older age and a greater number of inpatient-days were predictors. After adjusting for relevant predictors, the range of incidence narrowed greatly; CA-CDI rates ranged from 30.7 to 41.3/100 000 and HA-CDI rates ranged from 58.5 to 94.8/100 000.

Conclusions. Differences in CDI incidence across geographic areas can be partially explained by differences in NAAT use, age, race, sex, and inpatient-days. Variation in antimicrobial use may contribute to the remaining differences in incidence.

BACKGROUND

Clostridium difficile infection (CDI) is a global public health problem with increases in incidence and severity of disease being reported from several countries [1–4].

In the United States, an estimated 14 000 deaths associated with CDI occurred in 2007 based on death certificate data, with an estimated excess in medical costs related to CDI of up to \$4.8 billion in US acute care facilities [5, 6]. *Clostridium difficile* infection is now recognized to occur outside acute care hospitals, and reports of CDI among individuals in the community or in nursing homes have become increasingly common in the last few years [7–10]. Some of these patients do not require hospitalization for CDI treatment and are treated in outpatient or in nonacute care settings where the diagnosis of CDI was made [10, 11]. Therefore, population-level data are important for understanding the total burden of CDI at the national level.

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Accurate estimates of CDI nationally will require accounting for factors that influence CDI rates. Several factors such as age, sex, or type of *C difficile* diagnostic assay may influence incidence measures. Incidence of CDI is known to be higher among the elderly population, especially those over 65 years of age [1, 12, 13]. In addition, females seem to be more affected than males in some studies focusing on community-associated (CA) CDI [14, 15]. Finally, at least 8 nucleic acid amplification tests (NAATs) have been approved by the US Food and Drug Administration since 2009 [16]. These assays have a higher sensitivity than the traditional *C difficile* toxin assays, and some studies have shown that use of NAAT can increase the rate of diagnosed CDI at least 2-fold [17–19].

Understanding the population- or diagnostic-specific factors that influence CDI incidence measures is important for meaningful comparisons of CDI rates across facilities, states, and regions and for accurate national burden estimates.

METHODS

Surveillance Population and Definitions

The Emerging Infections Program (EIP) conducts active laboratory- and population-based surveillance for *C difficile*. The EIP CDI surveillance was approved by the institutional review boards at the Centers for Disease Control and Prevention and participating surveillance sites. The requirement to obtain informed consent to review medical records was waived.

In 2010, surveillance was conducted in selected counties across 7 US states for the full calendar year: California (San Francisco County: 805 235 persons), Colorado (Adams, Arapahoe, Denver, Douglas, and Jefferson Counties: 2 433 772 persons), Connecticut (18 towns in New Haven County: 594 811 persons), Georgia (Clayton, Cobb, DeKalb, Douglas, Fulton, Gwinnett, Newton, and Rockdale Counties: 3 682 873 persons), Minnesota (Benton, Morrison, Stearns, and Todd Counties: 247 186 persons), New York (Monroe County: 744 344 persons), and Oregon (Klamath County: 66 380 persons). The surveillance methods have been described elsewhere [20]. In brief, surveillance staff at each site identified all positive *C difficile* stool specimens by either toxin or molecular assay from inpatient and outpatient laboratories serving surveillance area residents. *Clostridium difficile* testing was based on provider discretion. A CDI case was defined as a positive *C difficile* toxin or molecular assay on a stool specimen from a resident of the surveillance catchment area ≥ 1 year of age who did not have a positive assay in the previous 8 weeks. *Clostridium difficile* infection cases were then classified as CA if a positive *C difficile* specimen was collected as an outpatient or within 3 days after hospital admission and the patient had no documented overnight stays in a healthcare facility in the prior 12 weeks; otherwise, they were classified as healthcare-associated (HA) and subdivided into 3 mutually exclusive categories: (1)

community-onset healthcare facility-associated (CO-HCFA) if the positive specimen was collected as an outpatient or within 3 days after hospital admission from a private residence and the patient had a documented overnight stay in a healthcare facility in the prior 12 weeks; (2) hospital-onset (HO) if the positive specimen was collected more than 3 calendar days after hospital admission or in a long-term acute care hospital; or (3) nursing HO (NHO) if the positive specimen was collected in a nursing home or within 3 days after hospital admission from a nursing home.

In 5 of the 7 EIP surveillance sites, medical record review was performed for all CDI cases identified to collect demographic and healthcare exposure data. Two EIP sites with the largest surveillance populations, Georgia and Colorado, performed full medical record review on a random sample of the CDI cases identified. Sampling was stratified by 4 age groups (ie, 1–17, 18–44, 45–64, ≥ 65 years) and gender category for a total of 8 strata (4 age groups \times 2 gender categories). All male and female pediatric CDI cases (ie, 1–17 years) were selected for full medical record review due to the low numbers of cases, whereas a 33% sampling was performed for the other 6 age group and gender strata. The sampled cases were then used to estimate the epidemiologic class and race of all CDI cases identified across these 2 sites.

Additional Data Sources

We used data from the 2009–2010 Area Resource File [21] to obtain county-level information on (1) healthcare utilization: average number of outpatient visits per hospital, average number of inpatient-days per hospital, and percentage of the population residing in nursing homes; and (2) population characteristics: percentage of population in urban centers and percentage of persons between 18 and 64 years of age without health insurance. County-level data were aggregated at the EIP surveillance site level.

Data on NAAT use for *C difficile* diagnosis were obtained through a survey of all laboratories ($N = 72$) serving the surveillance catchment population. The laboratory survey is conducted annually as part of the EIP CDI surveillance and assesses the type of diagnostic test used for *C difficile*, as well as any changes in testing algorithms during the calendar year and the date those changes occurred. Nucleic acid amplification test use was defined by the proportion of 2010 CDI cases identified by NAAT used as either a first- or second-line test. Finally, the 2010 population figures were obtained from the US Census for the incidence denominator. Persons < 1 year of age were excluded from the denominator because the surveillance case definition only included persons 1 year of age or older.

Statistical Analysis

Clostridium difficile infection cases with missing race (18%), including sampled cases from Georgia and Colorado, had race

Table 1. *Clostridium difficile* Infection (CDI) Cases by Surveillance Site and Epidemiologic Category, 2010

Surveillance Site	N of Cases	Healthcare-Associated			
		Community-Associated	Community-Onset Healthcare	Hospital-Onset	Nursing Home-Onset
			Facility-Associated		
		N (%)	N (%)	N (%)	N (%)
San Francisco County, CA	836	225 (27)	147 (18)	276 (33)	188 (22)
Adams, Arapahoe, Denver, Douglas, Jefferson Counties, CO ^a	3298	1033 (31) [95% CI, 931 (28)– 1136 (34)]	611 (19) [95% CI, 530 (16)– 691 (21)]	645 (19) [95% CI, 562 (17)– 728 (22)]	1009 (31) [95% CI, 904 (27)– 1114 (34)]
New Haven and Waterbury area, CT	862	174 (21)	147 (17)	239 (28)	302 (35)
Clayton, Cobb, Douglas, DeKalb, Fulton, Gwinnett, Newton, Rockdale Counties, GA ^a	3066	1133 (37) [95% CI, 1027 (34)– 1239 (40)]	573 (19) [95% CI, 494 (16)– 652 (21)]	739 (24) [95% CI, 650 (21)– 829 (27)]	621 (20) [95% CI, 538 (18)– 703 (23)]
Stearns, Benton, Morrison, Todd Counties, MN	377	193 (51)	87 (23)	51 (14)	46 (12)
Monroe county, NY	1566	419 (27)	316 (20)	390 (25)	441 (28)
Klamath County, OR	57	30 (53)	10 (18)	5 (9)	12 (21)
Total	10 062	3207 (32) [95% CI, 3063 (30)– 3351 (33)]	1891 (19) [95% CI, 1775 (18)– 2007 (20)]	2345 (23) [95% CI, 2220 (22)– 2470 (25)]	2619 (26) [95% CI, 2484 (25)– 2754 (27)]

Abbreviation: CI, confidence interval.

^a Site did stratified sampling of cases based on age and sex; point estimate and 95% CIs are presented for each specific epidemiologic category.

imputed based on the distribution of known race by age, sex, and surveillance site. A multiple imputation method was used to account for the uncertainty associated with imputing unknown values. After race imputation was performed, a domain (subpopulation) analysis was used to estimate CDI cases by epidemiological class and race in Georgia and Colorado.

Two regression models were built, one for CA-CDI and another for HA-CDI. A generalized linear mixed model with negative binomial distribution was used to evaluate the association of demographic, diagnostic, socioeconomic, and healthcare utilization factors with increased CA- or HA-CDI incidence. Because CDI incidence varied across surveillance sites, a random intercept was specified to account for surveillance site variations. For the CA-CDI model, the candidate variables for the model included age, sex, race, percentage of urban population, NAAT usage, percentage of population between 18 and 64 years of age without health insurance, and average of outpatient visits per hospital in each surveillance site; for the HA-CDI model, candidate variables included age, sex, race, NAAT usage, percentage of population in nursing homes, and average inpatient-days per hospital in each surveillance site. Final models were obtained using backward selection with a stay criterion of $P \leq .05$. The parameters in the final models from multiple imputed data were summarized and used to calculate standardized CA- and HA-CDI rates. Analyses were performed using SAS software version 9.3 (SAS Institute Inc., Cary, NC).

RESULTS

From January 1 through December 31, 2010, a total of 10 062 CDI cases among 9450 unique patients were identified; 8890 (94.1%) patients had a single incident episode, 512 (5.4%) patients had 2 incident episodes, 44 (0.5%) patients had 3 incident episodes, and 4 patients had 4 incident episodes during the calendar year. Of the 10 062 CDI cases identified, 2777 (27.6%) were estimated to be diagnosed by NAAT based on laboratory survey. Minnesota was the site with the highest percentage of cases (88.1%) detected by NAAT, followed by New York (41.9%), Colorado (29.5%), California (26.7%), Georgia (9.8%), and Connecticut (4.5%). Oregon was the only site with no cases identified by NAAT.

Of the 10 062 CDI cases, 32% were CA, 26% were NHO, 23% were HO, and 19% were CO-HCFA (Table 1). The proportion of CDI cases in each epidemiologic class varied greatly across sites. Minnesota and Oregon, the only 2 sites with rural counties, had the highest proportion of CA-CDI cases, 51% and 53%, respectively (Table 1).

Clostridium difficile Infection Incidence

Aggregated CDI incidence across the 7 surveillance sites was higher among persons 65 years of age or older, females, and persons of white race for both CA and HA infections (Table 2). Among pediatric patients (1–17 years) and young adult patients (18–44 years), incidence of CA-CDI was higher than HA-CDI,

Table 2. Age-, Gender-, Race-Specific *Clostridium difficile* Infection (CDI) incidence by Epidemiologic Category Aggregated Across 7 Emerging Infections Program Sites, 2010

Demographic	Community-Associated CDI		Healthcare-Associated CDI		Total	
	Rate per 100 000 Population	95% CI	Rate per 100 000 Population	95% CI	Rate per 100 000 Population	95% CI
Sex						
Male	29.8	27.5–32.2	69.2	65.9–72.4	99.0	93.4–104.6
Female	45.4	42.6–48.2	91.9	88.4–95.6	137.4	131.0–143.8
Age, years						
1–17	13.6	12.0–15.2	6.3	5.2–7.4	19.9	17.2–22.6
18–44	23.3	21.0–25.7	16.3	14.4–18.3	39.6	35.4–44.0
45–64	50.4	46.0–54.8	69.2	64.3–74.1	119.6	110.3–128.9
≥65	114.4	104.1–124.7	517.4	499.6–535.1	631.8	613.7–659.8
Race						
White	45.2	42.8–47.5	94.9	92.0–97.8	140.1	134.8–145.3
Black	28.2	24.7–31.8	64.2	58.8–69.5	92.4	83.5–101.3
Other	13.0	9.9–16.2	30.8	26.3–35.2	43.8	36.2–51.4

Abbreviations: CI, confidence interval.

13.6 vs 6.3 and 23.3 vs 16.3 per 100 000 population, respectively. With advancing age, the incidence of HA-CDI was higher than CA-CDI (Table 2).

Predictors of High *Clostridium difficile* Infection Incidence

In bivariate analysis for CA-CDI, older age ($P < .0001$), white race ($P = .007$), NAAT usage ($P = .009$), female sex ($P = .02$), and a lower percentage of urban population ($P = .05$) were associated with increased incidence. In the multivariable model, independent predictors of high CA-CDI were age, sex, race, and NAAT use. Table 3 provides the incidence rate ratio for each predictor, controlling for the other factors that remained in the final CA-CDI model. For each 10% increase in the number of cases detected by NAAT, CA-CDI rates were expected to increase 11% (95% confidence interval [CI], 6%–16%) after controlling for age, sex and race. Incidence of CA-CDI was 41% (95% CI, 23%–61%) higher among females compared with males, 45% (95% CI, 21%–75%) higher among whites compared with non-whites, and approximately 7-fold (95% CI, 5-fold to 9-fold) higher among those 65 and older compared with persons 1–17 years of age.

In bivariate analysis for HA-CDI, only age ($P < .0001$) and the average number of inpatient-days per hospital in the EIP surveillance site ($P = .04$) were significantly associated with increased incidence. These predictors remained associated with high HA-CDI incidence in the multivariable model (Table 3). Even though NAAT use was not significant in the final HA-CDI model, this factor was forced into the model due to reports from healthcare facilities of increased CDI rates after NAAT adoption [17, 18, 22]. Incidence of HA-CDI was approximately 68-fold (95% CI, 52-fold to 90-fold) higher among persons ≥65

years compared with persons aged 1–17 years after controlling for molecular diagnostic test use and healthcare utilization (ie, average number of inpatient-days per hospital in the region). In addition, a 10% (95% CI, 1%–20%) increase in HA-CDI incidence was found for every increase of 10 000 inpatient-days.

Variability of *Clostridium difficile* Infection Incidence Across Geographic Locations

Crude CA-CDI incidence was lowest in California (28.2/100 000 population) and highest in Minnesota (79.1/100 000 population). The differences in CA-CDI incidence across sites decreased substantially after rates were standardized by age, sex, race, and NAAT use; after adjustment, the lowest incidence was 30.7 (95% CI, 15.1–47.7)/100 000 population in California and the highest was 41.3 (95% CI, 23.6–60.9)/100 000 population in Georgia (Figure 1A).

The differences in HA-CDI incidence also decreased across sites after rates were adjusted based on the results of multivariable model. Crude incidence varied from as low as 45.7/100 000 population in Oregon to as high as 155.9/100 000 population in New York. After adjusting by age, inpatient-days, and NAAT use, the differences in HA-CDI incidence decreased, ranging from 58.5 (95% CI, 37.2–82.4)/100 000 population in California to 94.8 (95% CI, 66.5–126.9)/100 000 population in Colorado (Figure 1B).

DISCUSSION

This analysis including data from 7 US states, encompassing a population of ~10 million persons, showed that elderly patients, females, and those of white race seem to be at higher risk of

Table 3. Multivariable Modeling Analysis for Predictors of High Community- and Healthcare-Associated *Clostridium difficile* Infection (CDI) Incidence, 2010

Community-Associated CDI Multivariable Model ^a				
Predictor	Category	Incidence Rate Ratio ^b	95% CI	P
Age	1–17	1.00 (reference)		
	18–44	1.72	1.38–2.14	<.0001
	45–64	3.42	2.77–4.24	<.0001
	≥65	7.17	5.76–8.94	<.0001
Sex	Male	1.00 (reference)		
	Female	1.41	1.23–1.61	<.0001
Race	Non-white	1.00 (reference)		
	White	1.45	1.21–1.75	<.0001
Test	NAAT use by 10% increase	1.11	1.06–1.16	<.0001
Healthcare-Associated CDI Multivariable Model ^c				
Predictor	Category	Incidence Rate Ratio ^d	95% CI	P
Age	1–17	1.00 (reference)		
	18–44	2.67	2.01–3.54	<.0001
	45–64	11.23	8.54–14.76	<.0001
	≥65	68.79	52.56–90.03	<.0001
Inpatient-days	Increase in 10 000 inpatient-days per hospital	1.10	1.01–1.20	.02
Test	NAAT use by 10% increase	1.06	.99–1.14	.13

Abbreviations: CI, confidence interval; NAAT, nucleic acid amplification test.

^a Candidate variables included in the model: age, sex, race, NAAT usage, percentage of urban population, percentage of 18–64 years without health insurance, and average number of outpatient visits per hospital in each surveillance site.

^b Adjusted for the factors that remained in the final model (age, sex, race, test).

^c Candidate variables included in the model: age, sex, race, NAAT usage, average number of inpatient-days per hospital, and average number of nursing home patients in each surveillance site.

^d Adjusted for the factors that remained in the final model (age, inpatient-days, test).

CDI. Incidence of CDI has been reported to be higher among persons 65 years of age or older in several studies [1, 12, 13]. This result may be related to increased exposures to healthcare settings, increased antibiotic use, and impaired immune response to infectious pathogens [23–25]. Some studies have reported higher CDI incidence in females compared with males for CA infections; however, we observed that for both CA- and HA-CDI, females appear to be at higher risk [14, 15]. Although *C difficile* has been increasingly reported among peripartum women [26, 27], and females seem to be at increased risk of recurrent CDI [28], the reasons for the higher risk of CDI in females compared with males are still not clear. However, some possible explanations have been raised but not proven. Females may have greater exposure to infants who are known to have a high *C difficile* colonization rate, and infant exposure has been described as a risk factor for CA-CDI [8]. In addition, females are more likely to seek medical care, resulting in increased exposure to antibiotics [29]. A study in England and Wales showed that antibiotic prescribing rates in females were 40% higher compared with males [30]. Finally, host factors related

to immune system may explain some of the differences in CDI rates between females and males [31].

Another interesting finding in our study was the ~50% higher incidence among whites compared with blacks and 3-fold higher incidence of whites compared with other nonblack races. The relationship between white race and CDI has not been previously described. Many CDI published studies have either not collected race information or have not found a significant correlation between race and CDI. Although the reasons for white individuals to be at increased risk of CDI compared with other races are not known: one can hypothesize that greater access to healthcare and, therefore, the potential for more antibiotic exposure or increased diagnostic testing may play a role in the differences in race-specific CDI incidence we observed [32, 33].

According to our results, differences in CDI incidence across geographic locations can be partially explained by the type of diagnostic tests used for *C difficile*; demographic characteristics of the population such as age, sex, and race; and increased healthcare utilization. The remaining differences in adjusted

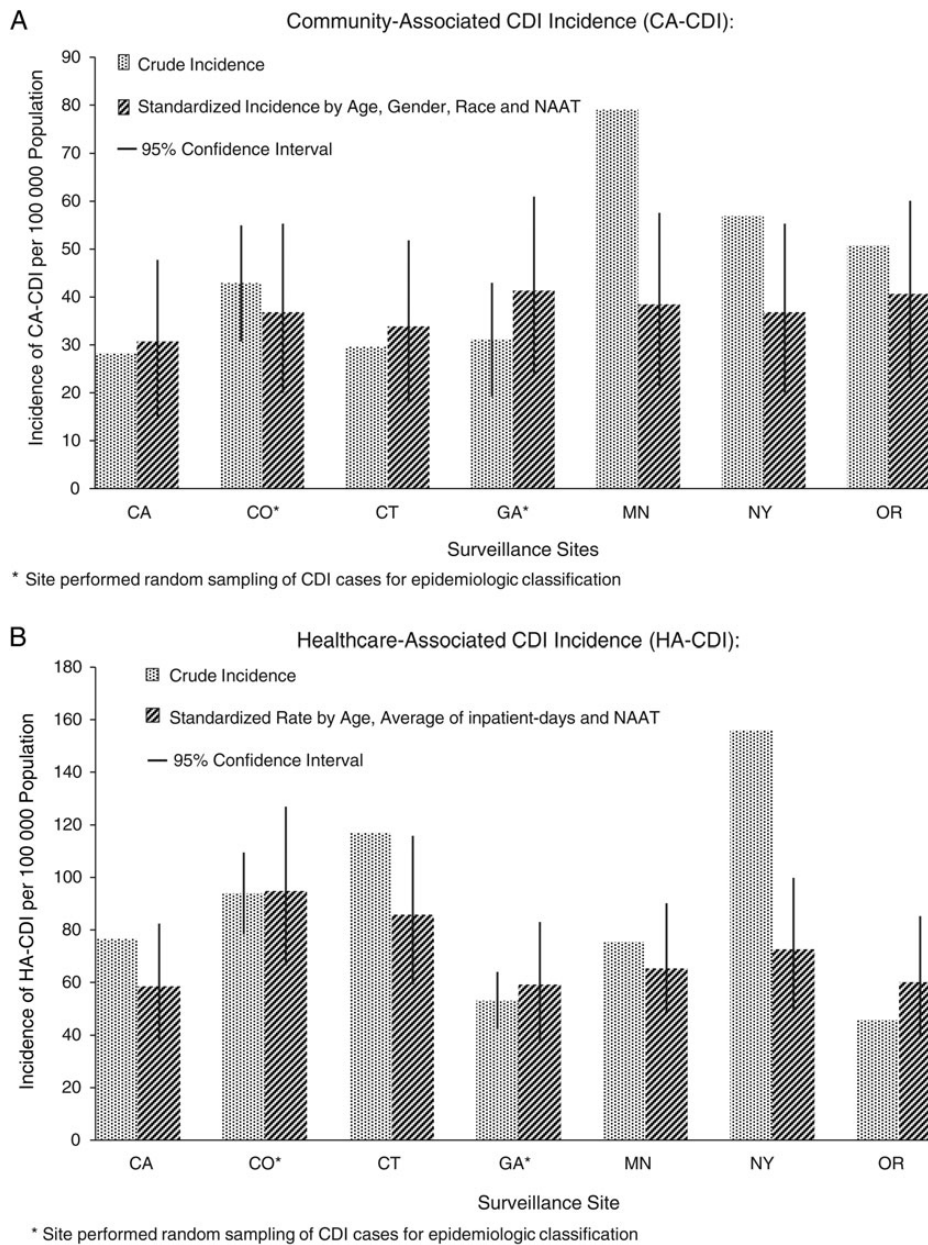


Figure 1. Crude and standardized community-associated (CA) and healthcare-associated (HA) *Clostridium difficile* infection (CDI) incidence per surveillance site, 2010.

CDI rates across states, especially for HA-CDI, suggest that other factors not accounted for in our analyses, such as differences in antibiotic prescribing practices, infection control practices, or the occurrence of *C. difficile* outbreaks during the surveillance period, may also play a role in the variability of CDI incidence across states. Although some studies have shown an association of NAAT with increased CDI incidence [17–19], we did not find NAAT use to be significantly associated with population level differences in HA-CDI incidence across states. It is possible that in contrast to CA-CDI rates, HA-CDI rates may be driven more by patient age and other

healthcare facility characteristics, such as volume of patients admitted and severity of illness of patients receiving care at the facilities, rather than the type of diagnostic test used. Nevertheless, our findings are critical to informing comparisons of CDI population-based rates across states and regions and to developing more robust national burden estimates of CDI that account for major determinants when projecting CDI rates to the national level. We plan to use these factors when we analyze EIP CDI surveillance data in the future to inform national rates.

Finally, the 32% of CA-CDI cases we found is higher than the rates of 20%–27% reported in Canada and in one region of the

United States using a similar definition [14, 34]. This higher proportion of CA-CDI cases may be explained by the inclusion of large commercial and outpatient laboratories in the surveillance. Similar to a study done in the United Kingdom [8], we also found that the 2 EIP sites, Minnesota and Oregon, with a more rural population under surveillance had a higher prevalence of CA-CDI cases compared with other sites with a more urban population, which may be related to either healthcare utilization factors or different sources of *C difficile* exposures. In addition, the crude incidence of CA-CDI we observed across sites of 28–79/100 000 population is higher than the crude incidence of 20–40/100 000 population that has been reported in other population-based studies before the introduction of molecular diagnostic tests for *C difficile* [8, 35]. Despite this large proportion of CA-CDI cases, the majority of CDI cases (68%) are still HA with disease onset either in nursing homes, hospitals, or within 12 weeks after discharge from a healthcare facility. Moreover, as previously reported, the majority of CA-CDI cases are related to the receipt of outpatient care [11].

This study has several limitations. First, we were not able to capture antibiotic prescribing data in our surveillance sites. Antibiotics are known to be a major risk factor for CDI [36, 37], and variability in prescribing practices across regions has been documented [24]. Second, the data on NAAT utilization were captured through a survey of participating laboratories, and it is possible that some CDI cases may have been misclassified as being identified by NAAT, especially in laboratories using NAAT as a second-line test. Third, classification of CA-CDI cases was based on medical record documentation and, therefore, some cases may have been misclassified if no documentation of prior hospitalization was available. However, a previous study using the same surveillance population [11] showed that misclassification only occurred in ~6% of CA-CDI cases. Finally, the incidence calculation relied on positive *C difficile* test, and it is possible that some patients may have been misclassified as cases if *C difficile* stool testing was not limited to patients with ≥ 3 unformed stools per 24 hour period as recommended by laboratory practice guidelines [38].

CONCLUSION

In conclusion, CA-CDI rates vary by age, sex, race, and type of diagnostic test, whereas HA-CDI rates vary by age and average number of inpatient-days per hospitals in a region. These factors must be taken into account for meaningful comparison of CDI incidence across different geographic locations and for more reliable projections of CDI burden in the United States.

Notes

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