Annual Surveillance Summary: *Clostridium difficile* Infections in the Military Health System (MHS), 2015

NMCPHC-EDC-TR-189-2017

By Charlotte Neumann and Uzo Chukwuma
EpiData Center Department
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Charlotte Neumann, Uzo Chukwuma

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
EpiData Center
Navy and Marine Corps Public Health Center
620 John Paul Jones Circle, Suite 1100
Portsmouth, VA 23708-2103

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Abstract

This report summarizes trends for *Clostridium difficile* infection (CDI) among Military Health System (MHS) beneficiaries in calendar year (CY) 2015. The overall CDI incidence rate increased 29.5% from the weighted historic average incidence rate; however, the CDI rate showed normal variation when compared to historical rates in the overall MHS beneficiary population. Incidence rates were higher in health care regions with larger inpatient CDI reservoirs, which were estimated by the healthcare-associated infection (HAI) metrics of overall and admission prevalence. Overall prevalence rates were only slightly higher (<1.0%) than admission prevalence rates, which suggests that CDI importation is the driving force for inpatient exposure compared to other hospital exposures that lead to hospital-onset infection.

The traditional risk factors for CDI (antibiotic use, ages 65 years and older, and hospitalization) continue to be important in the diagnostic evaluation of CDI. However, the majority of MHS CDI episodes were acquired in the community in beneficiaries aged 45 years and older. In addition, although most cases had an antibiotic prescribed in the 90 days before symptom onset, approximately 32% of beneficiaries did not have a history of antibiotic use. Therefore, providers should suspect CDI in any patient with acute inflammatory diarrhea, including patients with no antibiotic use or prior healthcare facility exposures.

Contents

Background

Clostridium difficile (CD) is a spore-forming, gram-positive, anaerobic bacillus with toxigenic and non-toxigenic strains. Toxin-negative strains are generally considered non-pathogenic, whereas toxigenic strains produce two major virulence determinants: toxin A and toxin B. Changes in the balance of normal colon flora that allow for massive colonization of toxigenic strains cause *Clostridium difficile* infection (CDI), which manifests as diarrhea and pseudomembranous colitis.[1] Broad-spectrum antibiotic use is the most common cause of CD overgrowth in the colon and subsequent development of diarrhea.

Historically, CDI has been known as a hospital-acquired, antibiotic-associated diarrheal infection presenting in the immunocompromised and the elderly with comorbid conditions. Incidence has been relatively stable since 1978 when *C. difficile* was first identified as a causative agent in the majority of antibiotic-associated diarrhea cases.[2] However, in 2000, reports of increased incidence and severity renewed interest in the epidemiology of CDI.[3-4]Among patients admitted to United States (US) hospitals, the CDI incidence rate nearly doubled from 2001 to 2010 from 4.5 to 8.2 per 1,000 hospital discharges, respectively.[5] However, the investigators noted that incidence peaked in 2008 and declined slightly through 2010, suggesting that incidence among hospitalized patients was beginning to stabilize. More recently, CDI was recognized in the community among patient populations previously described as low risk, including patients without prior exposure to antibiotics, peripartum women, patients with inflammatory bowel disease (IBD), and younger age groups (mean age, 26 years).[6-8] As community-acquired CDI surveillance has evolved, approximately 20-40% of CDI is reported to be community-acquired with an estimated incidence of 20-30 infections per 100,000 population.[9,10,37] The increase in incidence in both community- and hospital-acquired CDI over the last 20 years is attributed to a combination of three main factors: the emergence of a previously rare and more virulent strain, NAP1/BI/027; inappropriate use of antibiotics; and an increase in the elderly population at risk.[11-14]

Traditionally, the most common risk factors for CDI are antibiotic use, advanced age (i.e., 65 years of age or older), comorbidity, use of gastric acid suppressants, and prolonged hospitalization. Although antibiotic use is the primary CDI risk factor, several studies have reported CDI among antibiotic-naïve patients.[15,16] This finding has led to the investigation of other medications that have mechanisms of action able to influence CDI development. In February 2012, the US Food and Drug Administration (FDA) informed the public that proton pump inhibitors (PPIs) may be associated with an increased risk of *C. difficile*-associated diarrhea.[17] PPIs decrease gastric acidity (pH), which provides pathogens the opportunity to colonize the normally sterile upper gastrointestinal (GI) tract, increasing the risk of enteric infections such as CDI. The FDA is reviewing the risk of CDI in users of histamine-2 (H2) receptor blockers. H2 receptor blockers may increase CDI risk due to suppression of gastric acid in the GI tract. However, the role of gastric acid suppressant use as an independent risk factor for CDI is controversial because of the association with certain comorbidities and concomitant use with antibiotics.[18,19]

Chronic disease is a risk factor for CDI patients not only due to the underlying disease, but also because of greater health care utilization and use of antibiotics to treat infectious complications related to the chronic condition.[20] Specific chronic illnesses associated with CDI include chronic obstructive pulmonary disease (COPD), cancer, renal disease, and diabetes.[20,21] Khanna et al. found that CDI patients with comorbidities experienced severe CDI and a greater need for hospitalization.[22] Therefore, comorbidity may predict which CDI patients are especially vulnerable to worse outcomes.

Diagnosis of CDI is based on recognizing clinical symptoms of diarrhea (greater than three non-formed stools in a 24 hour period) and confirming the diagnosis with laboratory testing for toxigenic strains of CD.[23] Enzyme immunoassay (EIA) testing of CD toxins A and B has been the most widely used test due to its rapid turnaround time and low cost. However, EIA has a sensitivity and specificity of approximately 75% and is no longer recommended as a standalone test.[24] In September 2010, the American Society for Microbiology (ASM) recommended the use of either a nucleic acid amplification test (NAAT) as a standalone diagnostic test to detect *C. difficile* toxin genes or the use of a two- or three-step testing algorithm that includes an initial screening glutamate dehydrogenase (GDH) assay and confirmation with either a toxin A/B EIA, cytotoxin neutralization test, or a NAAT.[24] These testing methods have greater sensitivity than the EIA alone and, therefore, are expected to improve the ability to detect and manage CDI.

Antibiotic treatment is generally required for initial CDI episodes. The selection of an antibiotic is dependent on the severity of disease, whether the episode is new or recurrent, and the patient's potential risk for recurrence.[25-26] Metronidazole and oral vancomycin have been the first-line antibiotics for an initial CDI treatment episode for over 25 years. However, neither metronidazole nor vancomycin is effective in preventing recurrent infection, which occurs in 10%-60% of patients.[27] In 2011, the FDA approved fidaxomicin as either an alternative treatment for an initial recurrence of CDI or as an initial therapy for patients at high risk for recurrence. Fidaxomicin was found to reduce recurrence by 45% as compared to vancomycin.[28] Fecal microbiota transplantation (FMT) with donor feces has become an effective treatment for recurrent CDI.[29] This treatment is based on the concept that the protective microbiome of natural colonic flora can be replaced to its former balanced state. FMT is not currently part of routine management for initial CDI episodes.

Clearly, CDI has emerged as a major public health concern. The changing epidemiology, combined with a highly virulent epidemic strain, has created a growing challenge for diagnosis, treatment, and infection control. Standardized surveillance methods can ensure timely tracking of CDI incidence and early identification of at-risk groups within the Military Health System (MHS) beneficiary population. This report presents an annual update of previously reported retrospective data for calendar year (CY) 2015 that describes the demographics, clinical characteristics, and prescription practices for *C. difficile* infections among MHS beneficiaries.

Methods

The EpiData Center (EDC) at the Navy and Marine Corps Public Health Center (NMCPHC) conducted retrospective laboratory-based *C. difficile* infection surveillance in the MHS in CY 2015 (1 January – 31 December 2015).

Epidemiologic Infection Classification

CDI was identified from positive CD test results in Health Level 7 (HL7) formatted microbiology and chemistry records. Figure 1 shows the lab-based surveillance algorithm used to categorize CD-positive test results; the algorithm is based on published surveillance definitions.[30] An incident CDI episode was defined as a positive CD test result with no positive CD test result in the previous eight weeks. An episode was considered recurrent if there was a positive CD test result between two and eight weeks after the most recent CD-positive test result. CD-positive test results dated within two weeks of a prior positive CD test were considered duplicate infections and excluded from analysis.

Incident CDI episodes were further classified into four categories to approximate CDI acquisition using the positive CD test collection date as a proxy for symptom onset and the presence of an inpatient encounter in the Standard Inpatient Data Record (SIDR) to identify potential hospital exposure.[26] SIDR is the electronic database of inpatient healthcare services provided to Department of Defense (DOD) beneficiaries at fixed military treatment facilities (MTFs). In brief, each acquisition category provides information regarding the specific environment (community or hospital) that may have influenced CDI development. The categories are as follows:

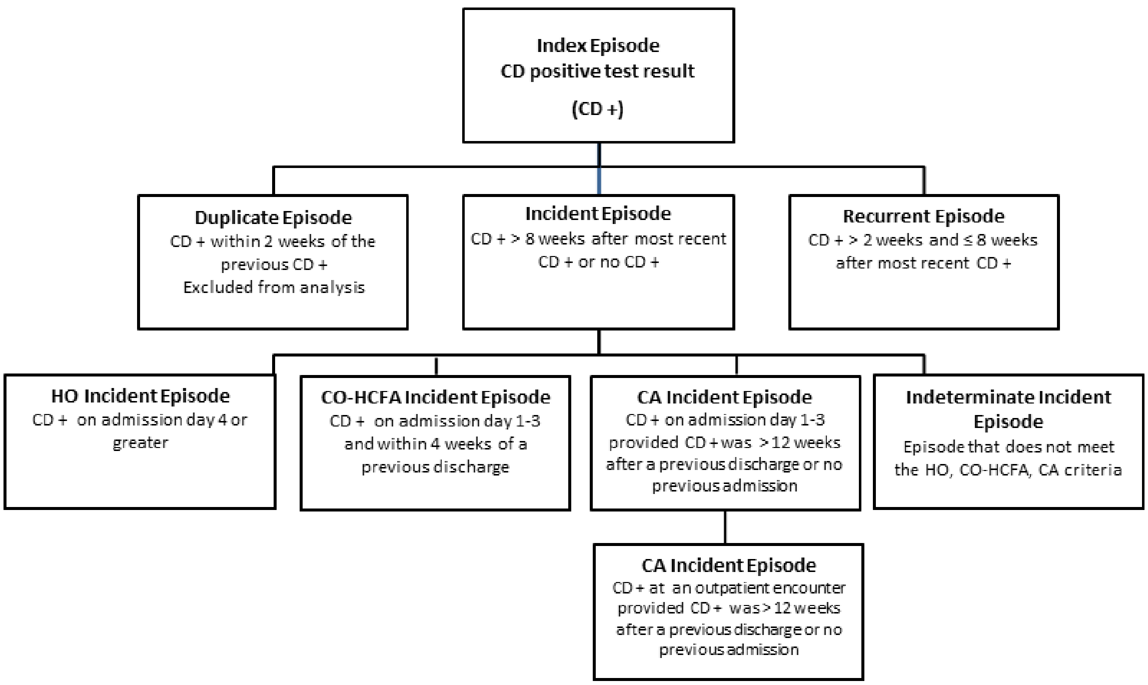
- Hospital-onset (HO): HO CDI incident episodes were acquired in the hospital based on the CD collection date. CD-positive test results with collection dates on day four or greater of inpatient admission establish that the patient developed CDI in the hospital.

- Community-onset, healthcare facility associated (CO-HCFA): CO-HCFA CDI episodes were related to CD symptom onset in the community based on the positive CD test collection date, but the history of hospital admission may have influenced the development of CDI. CD-positive test results with a collection date on days one, two, or three of the inpatient admission were used to establish that the CDI symptom onset was in the community and a previous hospital discharge within four weeks of the current CD collection date established that the exposures in the hospital environment influenced CDI development.

- Community-acquired (CA): CA CDI incident episodes were acquired in the community based on the timing of the CD-positive test result. Consequently, hospital admission was not considered a factor in CDI development. The CA incident episode category includes positive CD test results that were collected during an ambulatory encounter with no previous hospital discharge or no hospital discharge within 12 weeks of the current CD specimen collection date. The category may also include positive CD test results with collection dates within three days of the inpatient admission and no previous hospital discharge within 12 weeks of the most recent collection date.

- Indeterminate: The indeterminate incident episode category includes positive CD test results that did not meet the HO, CO-HCFA, or CA case definitions.

Figure 1. *C. difficile* Lab-Based Surveillance Algorithm



Prepared by the EpiData Center Department, Navy and Marine Corps Public Health Center, on 28 February 2017.

The analysis examined the clinical characteristics of the total number of incident CDI episodes and the index episode because a patient could have more than one incident episode during the surveillance period. For example, all incident episode values were included for analysis of antibiotic treatment; in contrast, only the index episode value was retained for analysis of demographics such as age.

Demographic and Clinical Characteristics Classification

Demographic data were derived from the HL7-formatted Composite Health Care System (CHCS) microbiology and chemistry records. The index CDI episode was classified according to the patient's gender, age, sponsor service (Air Force, Army, Marine Corps, or Navy), duty status

(Active Duty, Retired, Family Member, or Other), and region of the facility where the specimen was collected. The Active Duty (AD) category included both active duty and recruit personnel, defined by the beneficiary type codes of 11 and 13, respectively.

C. difficile incidence rates were aggregated into six spatial regions and visualized as maps created in ESRI ArcGIS software (version 10.2.2). *C. difficile* identified in each region may act as a reservoir within that region and contribute to the burden of exposure. Geographic regions were assessed within the continental United States (CONUS) and outside the CONUS (OCONUS), with the spatial regions identified as follows:

- **Northeast**: Maine, New Hampshire, Vermont, Massachusetts, Rhode Island, Connecticut, New York, Pennsylvania, New Jersey.
- **Midwest**: Michigan, Wisconsin, Minnesota, Ohio, Indiana, Illinois, Iowa, Missouri, Kansas, Nebraska, North Dakota, South Dakota.
- **West**: California, Oregon, Washington, Idaho, Montana, Wyoming, Colorado, New Mexico, Arizona, Utah, Nevada, Alaska, Hawaii.
- **South**: Texas, Oklahoma, Arkansas, Louisiana, Mississippi, Alabama, Tennessee, Kentucky.
- **South Atlantic**: Delaware, Maryland, District of Columbia, Virginia, West Virginia, North Carolina, South Carolina, Georgia, Florida.
- **OCONUS**: All US territories and non-US countries

The Elixhauser comorbidity index of categorizing chronic medical conditions, based on International Classification of Diseases (ICD) diagnosis codes, was used to determine the number of coexisting medical diagnoses among CDI patients in the year preceding CDI symptom onset.[31] Thirty-one different diagnosis categories are used in the Elixhauser measure. Since the measure's introduction in 1998, the method has been modified and updated by Deyo and Quan for use with administrative databases containing Clinical Modification codes from the Ninth and Tenth editions of ICD (ICD-9-CM and ICD-10-CM).[32-33] SIDR and the ambulatory databases were used to create the Elixhauser measure. The number and type of comorbidities among MHS beneficiaries, as determined in this analysis by the Elixhauser index, was used to describe which CDI patients may have poor health outcomes.[31-33]

Pharmacy Transactions

CDI treatment, previous antibiotic use, gastric suppressant use, and CDI treatment were determined from HL7 pharmacy records. The HL7 pharmacy data source contains three pharmacy data types: outpatient (OP), unit-dose (UD), and intravenous (IV). Cancelled prescriptions or those with zero or null filled prescriptions were removed prior to analysis. Antimicrobials recommended for *C. difficile* infection treatment according to the Johns Hopkins Antibiotic Guide were retained for analysis.[34]

Prescription transactions for metronidazole, vancomycin, or fidaxomicin seven days before or after each incident CDI episode laboratory certification date were used to examine *C. difficile* antibiotic treatment. All incident episodes were retained for the treatment analysis. Prescriptions ordered in the seven-day period before the laboratory certification dates were applied to account for presumptive treatment. Previous antibiotic use, a risk factor for CDI, was determined from pharmacy prescriptions transacted within the preceding 90 days for each incident episode collection date. Metronidazole, vancomycin, and fidaxomicin were excluded from the previous antibiotic use analysis if the laboratory certification date was within the described antibiotic treatment timeframe. Any antibiotic prescribed from the selected antibiotic classes in Table 1 was included in the previous antibiotic use analysis. Use of PPIs (dexlansprazole, esomeprazole magnesium, lansoprazole, omeprazole, rabeprazole) and H2 antagonists (cimetidine, famotidine, nizatidine, ranitidine) was also evaluated in the 90 days preceding the incident CDI episode collection date. Only provider-prescribed gastric acid suppressants were included in the analysis.

Table 1. Selected Antibiotic Classes for Previous Antibiotic Use Analysis
Aminoglycosides
Carbapenems
Cephalosporins (generations 1-4)
Clindamycin
Fluoroquinolones
Glycopeptides
Macrolides
Metronidazole
Penicillins/penicillin beta-lactam inhibitors Sulfonamides and/or trimethoprim
Nitrofurantoin
Tetracycline
Other[a]

[a]Colistin, fosfomycin, isoniazid, ethambutol, rifampin, fosfomycin.
Prepared by the EpiData Center Department, Navy and Marine Corps Public Health Center, on 28 February 2017.

Exposure Burden Metrics

C. difficile is shed in feces and transmission occurs as a result of the fecal-oral route. Infected or colonized patients are the primary reservoir that strengthens the link between exposure and CDI transmission. To evaluate the potential exposure burden in the MHS, both admission and overall prevalence were estimated from the first unique *C. difficile*-positive test result per patient per admission.

The admission prevalence metric, which approximates CDI importation into the MHS hospitals, was derived from CD samples collected up to and including the third day of admission, as well as samples from current inpatients who tested positive for CDI in the prior calendar year. The overall prevalence metric included all inpatients with CDI identified from a sample collected at any point during the admission, or samples from current inpatients who tested positive for CD in the prior calendar year. The prior and current calendar year data were included to reflect the potential patient reservoir from both CDI infection and colonization during the current hospital admission. Regional rates of exposure burden were calculated as the rate of exposure (admission or overall prevalence) per 1,000 inpatient admissions per region per year.

Statistical Analysis

Population-based incidence rates are presented to provide a measure of the annual frequency of new CD incident episodes in the MHS population. Population estimates for calendar year 2015 were derived from the MHS Mart (M2) database using the mid-year (July) eligible beneficiary population estimates for MHS beneficiaries. Annual incidence rates were expressed as the number of incident episodes per 100,000 persons per year.

Due to the transient nature of the military beneficiary population and an inability to account for the proportion of the beneficiary population that receives medical care outside of the MHS, estimated rates are used for comparison of rates from year to year. Overall trends in infection rates are described using a weighted average of incidence rates for the three years prior to the analysis year, as well as the percent change between the weighted average and the 2015 incidence rate. A baseline was created using the weighted average of the immediately preceding three years. Historical baseline of the incidence rate serves as a clinical reference for the 2015 incidence rate. Two standard deviations on either side of the baseline were calculated to assess variation in infection incidence rate in the most recent years leading up to current evaluation period. Two standard deviations provides the upper and lower warning limits (approximately 95%) for assessing when observed occurrence was less likely due to chance, and for consideration of clinically significant change in trends.

Results

Section A – Descriptive Epidemiology

C. difficile Infection Incidence

In 2015, a total of 1,962 CDI incident episodes occurred among 1,868 MHS beneficiaries. The overall annual CDI incidence rate was 20.8 per 100,000 persons per year; a 29.4% relative difference from the weighted historic average (Table 2). However, the 2015 rate was within ± 2 standard deviations (SDs) of the weighted average incidence rate, suggesting that CDI in 2015 showed normal variation within the expected baseline range. The Air Force, Army, and Navy rates reflected the same pattern of change from the weighted historic incidence rate in addition to following normal variation within two standard deviations of the weighted historic IR. However, the 2015 IR for the Marine Corps was 51.7% above the weighted historic IR and greater than two standard deviations above the historic observations.

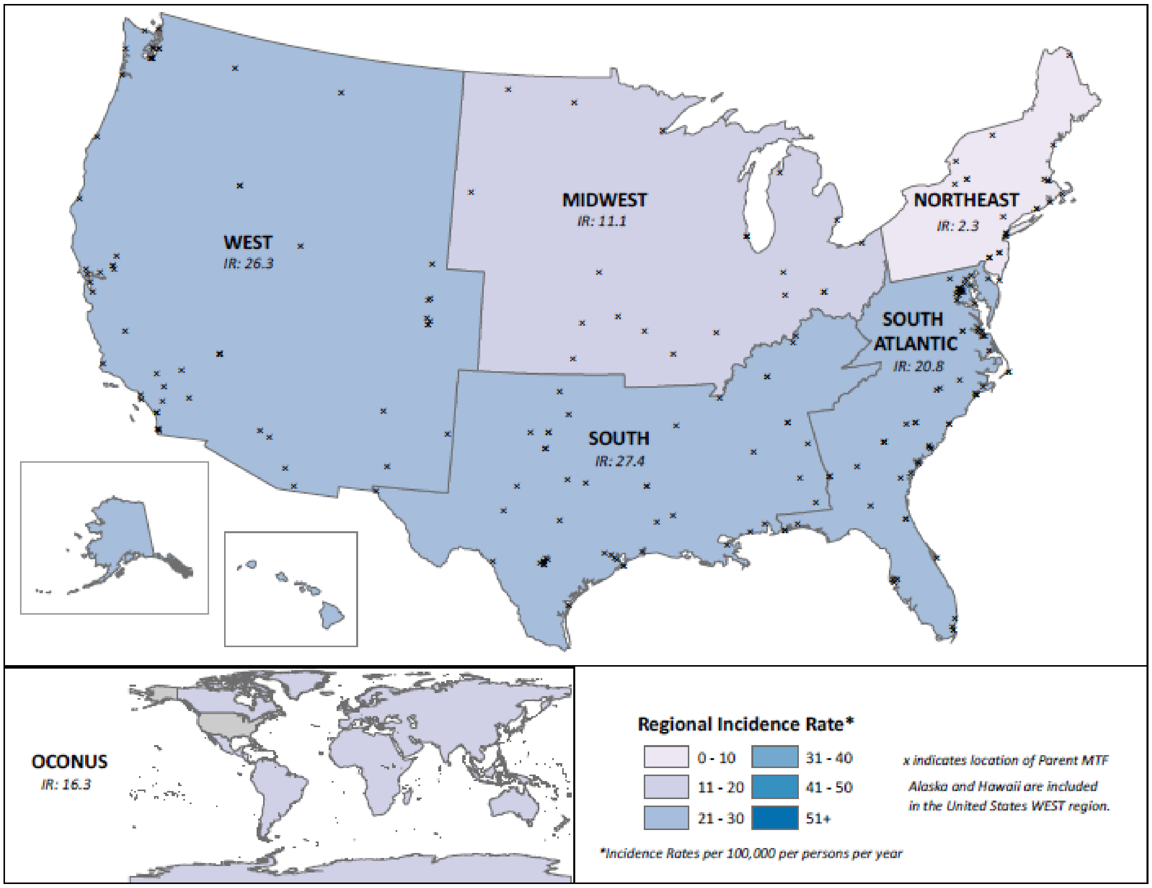
Table 2. Incidence Rate (IR) for *C. difficile* Infections in the MHS, CY 2015

Population	2015 IR	Weighted Historic[a] IR 2012 - 2014	Two Standard Deviations: Weighted Historic[a] IR	2015	
				Direction	Percent Change[b]
MHS Beneficiaries	20.8	16.1	5.9	↑	29.4%
Air Force	21.1	16.0	6.5	↑	32.0%
Army	19.3	15.0	7.2	↑	29.2%
Marine Corps	16.0	10.5	0.7	↑	51.7%
Navy	18.3	14.4	4.5	↑	27.3%

Incidence rates are presented as the rate per 100,000 persons per year.
A green arrow indicates an increasing percent change and a blue arrow indicates a decreasing percent change.
[a] Historic IR reflects the weighted average of the three years prior to the analysis year.
[b] This reflects the percent change from the weighted historic IR to the IR of the current analysis year.
Data Source: NMCPHC HL7-formatted CHCS microbiology, chemistry, and MHS M2 databases.
Prepared by the EpiData Center Department, Navy and Marine Corps Public Health Center, on 28 February 2017.

Regionally, the South Atlantic, South, and West incidence rates were equal to or higher than the overall annual CDI incidence rate, whereas the incidence rates in the Midwest, Northeast, and OCONUS locations were lower than the annual rate (Figure 2).

Figure 2. Annual Incidence Rate (IR) for *C. difficile* Infections in the MHS by Region, CY 2015



Rates are presented as the rate per 100,000 persons per year.
Data Source: NMCPHC HL7-formatted CHCS microbiology, chemistry, SIDR, and MHS M2 databases.
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C. difficile Demographic Distribution

CDI was more likely to occur among family members (49.4%) and individuals aged 45 years and older (55.2%), whereas CDI occurred equally by gender (Table 3). Approximately 10.3% (n = 192) of patients experiencing an incident CDI episode also experienced a recurrent CDI episode. The demographic distribution of patients with recurrent CDI was similar to patients who experienced an incident episode (data not shown).

Table 3. Demographic Characteristics of *C. difficile* Infections in the MHS, CY 2015

	N = 1,868	
	Count	**Percent**
Gender		
Female	931	49.8
Male	937	50.2
Age Group (in Years)		
0-17	219	11.7
18-24	170	9.1
25-34	250	13.4
35-44	198	10.6
45-64	458	24.5
65+	573	30.7
Beneficiary Type		
Active Duty	317	17.0
Family Members	923	49.4
Retired	413	22.1
Other	215	11.5

The frequency is based on the demographic value of the index incident episode.
Data Source: NMCPHC HL7-formatted CHCS microbiology and chemistry databases.
Prepared by the EpiData Center Department, Navy and Marine Corps Public Health Center, on 28 February 2017.

C. difficile Clinical Characteristics

In 2015, approximately 21.7% of MHS beneficiaries had a diagnosis of at least one of the comorbid medical conditions included in the Elixhauser comorbidity index within the same year as the incident CDI episode (Table 4). The five most frequent medical conditions among CDI patients included diabetes, hypertension, renal disease, deficiency anemias, and fluid/electrolyte disorders. Patients with the selected comorbidities represent a segment of the MHS population that may be especially vulnerable to CDI.

Table 4. Selected Comorbid Medical Conditions among MHS Beneficiaries with CDI, 2015

	Count	Percent
Any Selected Comorbidity[a*]	406	21.7
Comorbidities per Person[b]		
0	1398	74.8
1-2	213	11.4
3-4	108	5.8
5+	85	4.6
Selected Comorbid Medical Condition[c]		
Hypertension	205	11.0
Fluid and electrolyte disorders	129	6.9
Deficiency anemias	94	5.0
Renal failure	78	4.2
Chronic pulmonary disease	65	3.5
Alcohol abuse	61	3.3
Diabetes without chronic complications	60	3.2
Hypothyroidism	57	3.1
Depression	56	3.0
Other neurological disorders	47	2.5
Diabetes with chronic complications	45	2.4
Congestive heart failure	43	2.3
Obesity	41	2.2
Solid tumor w/out metastasis	23	1.2
Coagulopathy	22	1.2
Liver disease	21	1.1
Peripheral vascular disease	19	1.0
Rheumatoid arthritis/collagen vas	19	1.0
Valvular disease	17	0.9
Metastatic cancer	15	0.8
Paralysis	14	0.7
Weight loss	14	0.7
Lymphoma	8	0.4
Drug abuse	8	0.4
Pulmonary circulation disease	7	0.4
Psychoses	7	0.4
Peptic ulcer disease x bleeding	6	0.3
Chronic blood loss anemia	6	0.3

[a] The percentage of CDI patients that experienced at least one comorbidity during the calendar year of the CDI incident episode.
[b] The percentage of comorbidities per CDI patient.
[c] The percentage of each comorbidity among CDI patients.
*3.4% of CDI patients had no MHS encounter data to evaluate comorbidity.
Data Source: NMCPHC HL7-formatted CHCS microbiology, chemistry, and SIDR databases.
Prepared by the EpiData Center Department, Navy and Marine Corps Public Health Center, on 28 February 2017.

Exposure Burden Metrics

Table 5 presents two different metrics defining CDI rates for healthcare-associated exposures. The admission prevalence metric measures the magnitude of infection at the time of admission (importation of CDI into the healthcare system) or one year prior, while the overall prevalence metric measures the exposure of infection at any point during the admission or one year prior. Among CDI patients admitted to MHS hospitals, the overall prevalence was slightly higher than the admission prevalence in the MHS beneficiary population and in all regions where region-specific rate calculation was applicable (Table 5). This finding suggests that the majority of CDI was imported into the hospital setting from the community, adding to the burden of CDI.

Table 5. *C. difficile* HAI Exposure Burden Metrics in the MHS, CY 2015

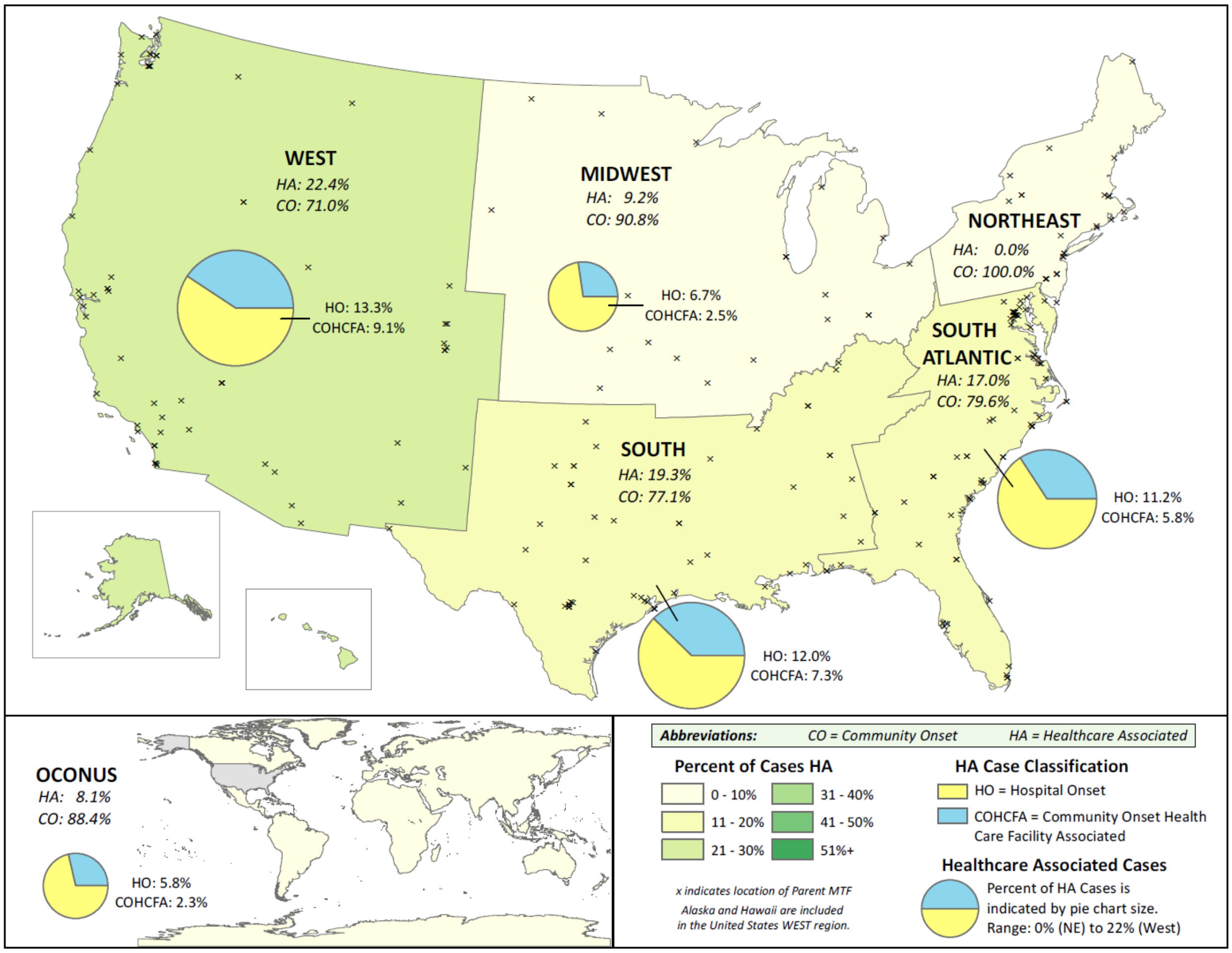
	Overall CDI Prevalence[a]		Admission CDI Prevalence[b]	
	Count	Rate[c]	Count	Rate[c]
Region				
OCONUS	30	1.7	25	1.4
US Midwest	26	2.5	21	2.1
US Northeast	1	––	1	––
US South	306	5.2	255	4.3
US South Atlantic	301	3.6	242	2.9
US West	404	5.0	344	4.2
Total	1,068	4.2	888	3.5

[a] Overall CDI prevalence included all individuals with CDI identified from a sample collected at any point during the admission, as well as samples that tested positive for infection in the prior calendar year.
[b] Admission prevalence included all individuals with CDI identified from samples collected up to and including the third day of admission, as well as samples that tested positive for infection in the prior calendar year.
[c] Rates are presented as the rate per 1,000 inpatient admissions per year. Rates are not calculated for counts less than or equal to five.
Data Source: NMCPHC HL7-formatted CHCS microbiology database.
Prepared by the EpiData Center Department, Navy and Marine Corps Public Health Center, on 28 February 2017.

Regional Epidemiologic Infection Classifications

Overall, the majority of the 1,962 CDI incident episodes identified among MHS beneficiaries in CY 2015 were acquired in the community setting (CO) (77.5%) compared to the healthcare-associated (HA) setting, (HO and CO-HCFA) (18.3%). Most CDI in the healthcare associated setting was among HO CDI (11.5%) cases versus CO-HCFA CDI (6.8%) cases. The described trends were observed in both CONUS and OCONUS regions (Figure 3). The indeterminate classification was not included in Figure 3.

Figure 3. Proportion of Healthcare and Community-Associated *C. difficile* Infections in the MHS by Region, CY 2015



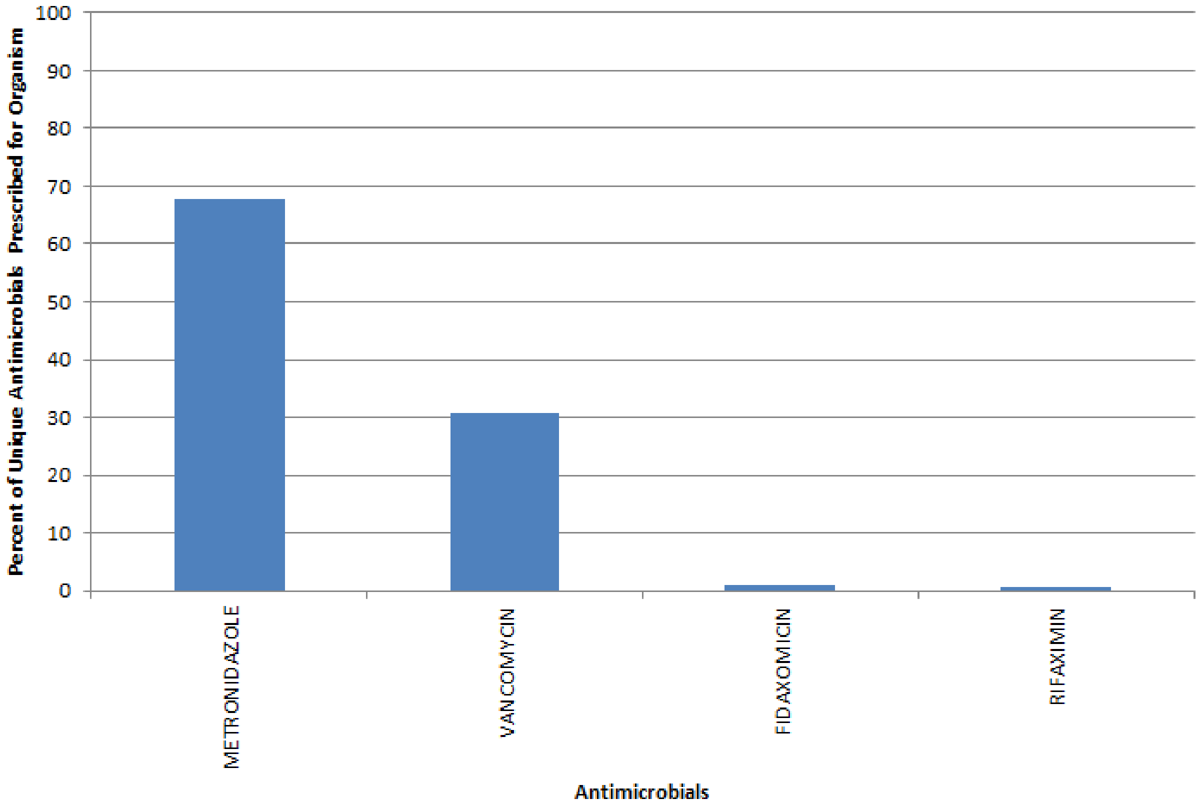
4.2% of incidence cases were indeterminate epidemiologic infection classification.
Data Source: NMCPHC HL7-formatted CHCS microbiology, chemistry, SIDR, and MHS M2 databases.
Prepared by the EpiData Center Department, Navy and Marine Corps Public Health Center, on 28 February 2017.

Section B – Antimicrobial Use

Antimicrobial Consumption/Prescription Practices

Metronidazole was the most frequently prescribed medication for an initial CDI episode, representing 67.6% of CDI antibiotic treatment.

Table 6. *C. difficile* Infection Prescription Practices in the MHS, CY 2015



The first occurrence of a unique antibiotic was counted per person per infection, regardless of administration route.
Data Source: NMCPHC HL7-formatted CHCS microbiology, chemistry, and pharmacy databases.
Prepared by the EpiData Center Department, Navy and Marine Corps Public Health Center, on 28 February 2017.

Use of antibiotics and gastric acid inhibitors is regarded as a risk factor for CDI. Table 7 shows that 68.0% of patients were prescribed an antibiotic within the 90 days prior to a CDI incident episode. The top three antibiotics prescribed were cephalosporins (generations 1-4), fluoroquinolones, and penicillin/penicillin beta-lactam inhibitors. Approximately 45.8% of CDI incident episodes had a gastric acid inhibitor prescribed 90 days prior to the incident event (PPIs [35.6%] and H_2-receptor blockers [10.2%]).

Table 7. Selected Medication Use 90 Days Prior to CDI, MHS Beneficiaries, CY 2015

Any Antibiotic Class Prescribed[a]		
	Count	**Percent**
	1329	68.0
Selected Antibiotic Classes Prescribed [b]		
Aminoglycosides	41	3.1
Carbapenems	133	10.0
Cephalosporins (generations 1-4)	608	45.7
first generation	190	14.3
second generation	44	3.3
third generation	230	17.3
fourth generation	144	10.8
Clindamycin	263	19.8
Fluoroquinolones	609	45.8
Glycopeptides	236	17.8
Macrolides	114	8.6
Metronidazole	264	19.9
Penicillins/penicillin beta-lactam inhibitors	592	44.5
Sulfonamides and/or trimethoprim	123	9.3
Nitrofurantoin	58	4.4
Tetracycline	52	3.9
Other	28	2.1
Range	1-7	
Mean ± SD	2.3 ± 1.5	
Selected Gastric Acid Suppressant Classes Prescribed[c]		
Proton Pump Inhibitor	700	35.6
H2 Receptor Blocker	201	10.2

[a] The percent of antibiotics prescribed per class per CD incident episode (n = 1964) in the previous 90 days.
[b] The percent of each antibiotic class prescribed among CDI patients prescribed an antibiotic (n = 1329) in the previous 90 days.
[c] The percent of each gastric acid suppressant class prescribed per CD incident episode (n = 1964) in the previous 90 days.
Data Source: NMCPHC HL7-formatted CHCS microbiology, chemistry, and pharmacy databases.
Prepared by the EpiData Center Department, Navy and Marine Corps Public Health Center, on 28 February 2017.

Discussion

This report summarizes trends for *C. difficile* infection among MHS beneficiaries for calendar year 2015. The overall CDI incidence rate was 29.4% above the weighted historic average. The 2015 incidence rate was within the normal variation of what is expected in the overall MHS beneficiary population compared to the historic average. Even so, the 2015 incidence rate does represent an increase in CDI from historic rates; the clinical importance relative to the local population should be considered at the MTF level. A possible explanation for the increase in overall incidence is the MHS transition to more sensitive CD testing methods.[21] An analysis of population-based surveillance data from three states found that switching from toxin EIA to NAAT as a first-line CDI testing method could increase CDI incidence rates by as much as 67% due to greater sensitivity.[30,35,36] The finding supports that the testing change has the potential to influence CDI incidence rates. Additionally, in 2014 the NMCPHC EDC HL7-formatted microbiology and chemistry databases had enhanced data capture, meaning there were a greater number of records available for CDI case analysis which may have influenced the magnitude of the increase in CDI incidence.

CDI incidence rates were higher in health care regions with larger inpatient CDI reservoirs, which were estimated by the HAI metrics of overall and admission prevalence. Overall prevalence rates were only slightly higher (<1.0%) than admission prevalence rates, which suggests that CDI importation from community-onset (CA, CO-HCFA) cases were the driving force for inpatient exposure compared to other hospital exposures that lead to hospital-onset infection. Because the majority of incidence was community-onset, the question remains: what is causing community-onset acquisition? Several studies have suggested outpatient healthcare visits as a potential source for CDI transmission and predisposing antibiotics.[15, 37, 38] Other studies cited potential reservoirs such as residents of long term care facilities (LTCs), asymptomatic CD carriage in infants, farm animals, and environmental sources such as water and soil.[39-42] Although these reservoirs have been identified as sources of potential exposure, the relative importance in the role of CDI transmission has not been conclusively established.

Among the demographic characteristics evaluated, the burden of CDI is greater for individuals aged 45 years and older and nearly equal for males and females. These results are consistent with studies that report a median age of 51 years for patients with CDI, although CDI occurs in all age groups.[23,43] The relatively low percentage of comorbidities among MHS beneficiaries suggests that CDI occurs in a mostly healthy population with a subset of beneficiaries with coexisting health problems that put them at high risk for CDI and poor health outcomes.

Selected medication use shows that 32.0% of beneficiaries were not prescribed an antibiotic in the 90 days before an incident CDI episode, which contrasts with classical observations that indicated antibiotic exposure was a prerequisite for CDI occurrence.[37,38] Recent literature recognizes that a significant proportion of patients have not used antibiotics prior to the onset of CDI, especially among CA CDI cases.[5,7] This contradiction caused researchers to question the current understanding of CDI, as well as study biases, including ascertainment and detection biases, that could have contributed to studies finding 100% previous antibiotic exposure prevalence among CDI patients.[7] Almost half of CDI patients were prescribed a gastric acid suppressant in the 90 days preceding CDI onset. Over-the-counter gastric acid suppressant use was not evaluated in this report; consequently, the true proportion could be higher if these medications were routinely used among CDI patients.

Antibiotic use, advanced age, and hospitalization continue to be important risk factors for CDI. However, most CDI episodes among MHS beneficiaries were acquired in the community in individuals aged 45 years and older. Therefore, providers should suspect CDI even among patients with no antibiotic use or healthcare facility exposures that have had moderate to severe diarrhea for three days or longer with fever or abdominal pain.[26] In addition, interventions that reduce antibiotic exposure are the primary measures recommended to reduce CDI incidence and recurrence. These measures include limiting the use of unnecessary antibiotics, prescribing antibiotics that are lower risk for CDI, and using antibiotics for the shortest reasonable duration.[44] The MHS population can benefit from these interventions to decrease both CDI incidence and antibiotic selective pressure that may influence the development of multidrug-resistant organisms.

Limitations

The focus of this report was to evaluate CDI among MHS beneficiaries who received care at an MTF in CY 2015. Because the priority for access to medical care at MTFs is provided to active duty personnel members with space-available limitations imposed on family members and retirees, the overall incidence and demographic and clinical characteristics of CDI may be influenced by these restrictions; therefore, comparisons to the overall US population are not necessarily generalizable. However, an analysis of the CDI epidemiology that occurs at the MTFs is important for practitioners whose primary responsibility is providing healthcare in the MTF domain.

HL7-formatted data are generated within the CHCS at fixed MTFs; therefore, this analysis does not include microbiology records from purchased care providers, shipboard facilities, battalion aid stations, or in-theater facilities.

Microbiology data are useful for identifying laboratory-confirmed infections. However, infections that were treated presumptively without laboratory confirmation do not exist in the microbiology and chemistry data. Clinical practice with regards to testing varies between providers and facilities. Examples of situations where cultures may not be performed include confirmatory tests for patients with influenza-like illness (ILI) symptoms, or patients with superficial infections who are treated presumptively. Therefore, infections identified here may be an underestimate of the actual burden of *C. difficile* in the MHS.

The EDC data feed does not include records on medical encounters conducted outside the MHS (e.g., purchased care in the community) and it cannot be determined if an individual truly had no healthcare contact or other risk factors for *C. difficile* infection, or if the individual had a risk factor that was not visible in the available data. Data on other factors commonly used to define HO infections were not available (e.g., presence of an invasive device, history of dialysis or surgery, a long-term care facility stay in the 12 months preceding the culture). Therefore, there may be HO infections currently miscategorized as CO infections. Without the ability to identify these HO infections, a more accurate estimate of CO infections could not be determined. Given the relatively healthy military population, however, any misclassification bias is likely minimal.

The pharmacy databases consist of outpatient non-intravenous prescriptions (outpatient), inpatient non-intravenous prescriptions (unit dose), and intravenous prescriptions (intravenous). Though treatment compliance in the inpatient setting can be assumed, outpatient pharmacy records indicate that a patient received a prescription and subsequent compliance is unknown. Due to near real-time data feeds, analysts are able to determine if a prescription was edited or canceled; however, the time difference between these events may allow for a short period of treatment not considered in this analysis. During ongoing surveillance efforts, patient treatment status may change as edited or canceled prescription records are received.

It is possible that not all antibiotic prescriptions were dispensed in response to a *C. difficile* infection. Antibiotics that were prescribed within the appropriate timeframe to be associated with a *C. difficile* specimen collection date may have actually been provided for reasons other than the documented infection, such as a different infection occurring after *C. difficile* was isolated. However, most antibiotics identified as being associated with a *C. difficile* infection were antibiotics that are typically used to treat *C. difficile*, so it is likely that the majority of prescriptions in this analysis were truly in response to the *C. difficile* infection.

A prescription filled at a retail pharmacy rather than an MTF pharmacy would likely underestimate previous antibiotic use in the DOD beneficiary population. Efforts are underway at the EDC to enhance this analysis by including retail pharmacy data. In addition, because gastric acid suppressants are available over-the-counter, the present report could not measure use among beneficiaries who did not acquire these medications through prescription, thus gastric acid suppressant use is likely underestimated.

Infections may not be uniformly distributed within a spatial region; no distinctions were made with regard to the heterogeneity of incidence rates or prevalence among subunits (e.g., states, non-US countries). The choropleth maps represent an annual snapshot of infections and do not reflect the geographic movement of service members within the course of a year. Infections were georeferenced according to the locations of the MTFs where they were encountered, not according to the deployment locations or home locations of the service members. Map area does not equate to population size; parent MTF locations are displayed within US regions to convey the density of military medical facilities within each region.

An inpatient admission record (SIDR) is created at discharge or transfer from an inpatient MTF for all TRICARE beneficiaries. For active duty personnel, this occurs for non-military medical treatment facility discharges as well. For all other beneficiaries, a SIDR is created upon discharge from an MTF. Patient encounter records depend on correct ICD-9-CM and ICD-10-CM coding practices. Data for medical surveillance are considered provisional and medical infection counts may change if the discharge record is edited after the patient is discharged from the medical treatment facility. As this is a retrospective report, it can be presumed with relative certainty that the records identified are the final and complete records for an inpatient encounter; however, the possibility does exist that records still may be modified, thereby altering the infection counts and other clinical characteristics.

This report contains ambulatory data from health encounters at fixed MTFs in the MHS only. Records of ambulatory medical encounters depend on correct ICD-9-CM and ICD-10-CM coding practices. Data for ambulatory medical surveillance are considered provisional and medical infection counts may change between the time the report is created and distributed. Additionally, because records are submitted into the system at different times, there may be patients who have had an inpatient or outpatient encounter, but were not captured in the current data.

POINT OF CONTACT

Navy and Marine Corps Public Health Center
Hospital Associated Infections and Patient Safety Division
EpiData Center Department 757.953.0970
WWW.NMCPHC.MED.NAVY.MIL/
usn.hampton-roads.navmcpubhlthcenpors.list.nmcphc-epi-datactr@mail.mil

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Appendix A: Acronym and Abbreviation List

Acronym/Abbreviation	Definition
AD	active duty
ASM	American Society for Microbiology
CA	community-associated
CD	*Clostridium difficile*
CDC	Centers for Disease Control and Prevention
CDI	*Clostridium difficile* infection
IBD	inflammatory bowel disease
CHCS	Composite Health Care System
CA	community-associated
CO-HCFA	community-onset, healthcare facility associated
COPD	chronic obstructive pulmonary disease
CY	calendar year
DMIS	Defense Medical Information System
DOD	Department of Defense
EIA	enzyme immunoassay
EDC	EpiData Center Department
FMT	fecal microbiota transplantation
FDA	Food and Drug Administration
GI	gastrointestinal
GDH	glutamate dehydrogenase
HL7	Health Level 7
H2	histamine-2
HO	hospital-onset
ICD	International Classification of Diseases
IDSA	Infectious Disease Society of America
IV	intravenous
MEPRS	Medical Expense and Performance Reporting System
M2	MHS Data Mart
MHS	Military Health System
MTF	military treatment facility
NAP1	North American pulsed-field type 1
NMCPHC	Navy and Marine Corps Public Health Center
NAAT	nucleic acid amplification test
OCONUS	outside of the continental United States
OP	outpatient
PATCAT	patient category
PPIs	proton pump inhibitors
PCR	polymerase chain reaction
SHEA	Society for Healthcare Epidemiology of America
SIDR	Standard Inpatient Data Record
UD	unit dose
US	United States