

# CDC Antimicrobial Resistance Threats Report

## *Clostridioides difficile* Data Methods

National estimates of the total number of cases of *Clostridioides difficile* (*C. diff*) infections (CDI) were calculated from data submitted to CDC's Emerging Infections Program (EIP) CDI surveillance program.

### Definitions

- **CDI case:** A case of CDI was defined as a positive stool test (toxin or molecular assay) in a person aged  $\geq 1$  year who did not have a positive test during the previous eight weeks [1].
- **Healthcare-associated CDI:** the stool specimen that tested positive for *C. diff* was collected more than three days after admission to a hospital or was collected from a resident of a long-term care facility; or it was collected in an outpatient setting or in the first three days of hospital admission from a person with an overnight stay in a healthcare facility in the 12 weeks before stool specimen collection [1].
- **Community-associated CDI:** the stool specimen that tested positive for *C. diff* was collected in an outpatient setting or in the first three days of hospital admission from a person with no overnight stay in a healthcare facility in the 12 weeks before stool specimen collection [1].

### National case estimates

Data from EIP CDI surveillance were used to estimate the total number of CDI cases in the United States from 2018 to 2023. As previously described, EIP CDI surveillance is active, laboratory- and population-based [1]. From 2018 to 2023, 35 counties in 10 states participated in EIP CDI surveillance.

The EIP CDI surveillance program performs medical record reviews on all CDI cases in eight of 10 EIP sites to collect demographic and clinical data. In the remaining two EIP sites, medical records are reviewed for all pediatric CDI cases ( $<18$  years of age) and a stratified random sample comprising 33% of adult CDI cases from each age range (18-44 years, 45-64 years,  $>64$  years) and sex stratum.

Multiple imputation analysis was performed for CDI cases with missing race and epidemiologic class (community-associated versus healthcare-associated) based on the distribution of known race and epidemiologic class by age, sex, and EIP site. For the two EIP sites that performed sampling of adult cases, weighted domain analysis was used to estimate the total number of CDI cases in each specific domain (or sub-population) defined by the combination of race, age, sex, epidemiologic class, and hospitalization status.

The population estimates from the U.S. Census Bureau, stratified by age, sex, and race distribution of the U.S. and EIP population, were used to calculate the sampled weights to estimate the 2018-2023 national burden of all CDI. Data were also stratified by age group ( $<65$  and  $\geq 65$  years). While they are weighted, single year calculations do not account for changes in testing practices by reporting facilities or other factors potentially related to CDI incidence. Therefore, annual changes in EIP CDI burden estimates should be interpreted carefully.

### Attributable mortality estimates

The estimated number of CDI deaths in 2018–2023 was calculated by multiplying the national estimate of the number of CDI cases requiring hospitalization by an estimate of CDI attributable mortality (expressed as a percentage) obtained from the literature. Although estimates of CDI-attributable mortality published since 2000 range from 4.5% to 16.7%, the attributable mortality of CDI appears higher during epidemic periods; estimates of attributable mortality range from 4.5% to 5.7% during endemic periods [2]. Because it was derived from a patient population most similar to patients with CDI requiring hospitalization, an estimate of attributable mortality of 5.7% at 180 days was used [3].

### Attributable healthcare cost estimates

Total costs attributable to CDI were estimated by multiplying the national estimate of CDI cases stratified by both age group (<65 and ≥65 years) and setting (hospitalized and non-hospitalized) by CDI attributable cost estimates derived from the literature [4–6]. Estimates of the medical cost associated with CDI among patients aged <65 and ≥65 years stratified by hospitalization status are provided in the table below. These costs represent one-year attributable costs after CDI infection. Due to variability of studies in the literature and variation in insurance options in the United States, costs are stratified by age (i.e., <65 and ≥65 years), representing eligibility for Medicare coverage. Further, to account for significant variability in treatment costs, CDI costs are also stratified by patient hospitalization status.

For patients aged <65 years, median payments were derived from a retrospective cohort analysis of commercially insured individuals and further processed to estimate mean and standard deviation for hospitalized and non-hospitalized CDI cases [4]. Payment for various epidemiologic classifications were adjusted to 2023 U.S. dollar amounts using the Producers Price Indices [7] and combined into a single estimate for hospitalized and non-hospitalized CDI cases separately.

For patients aged ≥65 years, payments were obtained from two sources representing Medicare Advantage and Fee-for-Service populations [5,6]. For Medicare Advantage beneficiaries, healthcare- and community-associated payments were adjusted to 2023 U.S. dollar amounts using Producers Price Indices [7] and combined into a single estimate for hospitalized and non-hospitalized CDI cases separately. Similarly, for Fee-for-Service, hospitalized payments were calculated by combining hospital-onset and non-hospital-onset payments adjusted to 2023 U.S. dollar amounts.

The Medicare Advantage and Fee-for-Service estimates were then combined to obtain estimates for hospitalized and non-hospitalized CDI cases by combining across studies using random effects. For both age groups, payments were adjusted to costs using the hospital payment-to-cost ratios published by the American Hospital Association [8].

**Table: Final attributable cost and standard errors for CDI cases**

| Age       | Hospitalization Status | Attributable Cost | Standard Error |
|-----------|------------------------|-------------------|----------------|
| <65 years | Hospitalized           | \$27,938          | \$87           |
|           | Not Hospitalized       | \$2,917           | \$29           |
| ≥65 years | Hospitalized           | \$28,578          | \$9,415        |
|           | Not Hospitalized       | \$4,349           | \$2,794        |

## Uncertainty and confidence intervals

Confidence intervals (CI), or the range of values likely to include the true value, for burden estimates were calculated using survey-based variance estimation that accounted for sampling weights, stratification by sex, clustering by state, and uncertainty from multiple imputation. The confidence intervals overlap across all years, except between 2018 and 2020 for all cases and healthcare-associated cases, suggesting that assessment of changes from year to year should be made cautiously.

CIs for both attributable mortality and costs were calculated by combining uncertainty from the estimated number of CDI cases, the estimated attributable mortality or costs, and the uncertainty inherent in a Poisson process [9].

## Threat level change from “urgent” to “serious”

*C. diff* is included in the current Antimicrobial Resistance Threats Report (AR Threats Report) as a Serious Threat, which is a change from previous reports where it was an Urgent Threat [10,11]. The rationale for lowering the threat level from Urgent to Serious is based largely upon significant decreases in CDI cases observed over the past 15 years [10-16]. Other factors that were considered included the availability of well-established, evidence-based methods for infection prevention and control and antimicrobial stewardship practices, as well as effective treatments [17-18].

The 2013 AR Threats Report indicated 250,000 hospitalized infections occurred per year with 14,000 deaths based on data reported to the EIP in 2011 [10]. In the 2019 AR Threats Report there were an estimated 223,900 cases in hospitalized patients with 12,800 deaths in 2017 [11]. In the current report, there were an estimated 200,100 hospitalized cases in 2023 (95% CI: 183,500 to 216,800), and the number of deaths was 11,300 (95% CI: -2,600 to 25,300).

Other analyses and data sources also show significant decreases in CDI. For example, previously published analyses using data from EIP CDI surveillance reported significant decreases in the national burden of CDI between 2011 and 2017, driven largely by decreases in healthcare-associated cases [12]. In the EIP hospital point prevalence survey of healthcare-associated infections, healthcare-associated CDI prevalence was significantly lower in the 2023 survey compared with the 2015 survey [16]. In addition, data from the National Healthcare Safety Network for the past 10 years have shown year-to-year decreases in the national hospital-onset CDI Standardized Infection Ratio [13,14].

For the first time, the 2026 update to the AR Threats Report includes the unadjusted total burden of CDI in the United States, including hospitalized and non-hospitalized cases, showing that the estimated total number of cases was lower in 2023 (412,500; 95% CI: 358,643 to 466,365) compared with 2018 (455,600; 95% CI: 407,700 to 503,500), although the confidence intervals overlap.

The change in threat level does not diminish the importance of *C. diff* prevention and control measures for patient safety. *C. diff* remains one of the most common causes of healthcare-associated infections in hospitals [16], and there is an even greater burden of community-associated cases. Ongoing vigilance is essential. CDC will continue to monitor trends in CDI burden as well as the potential for developing resistance to recommended treatments.

## Data methods references

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## Additional references

The following additional references were used for the development of the AR Threats Report content for *C. diff* not already included in the data methods.

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