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Current Epidemiology of *Clostridioides difficile* Infection in Adults in the United States

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Vaccines and Related Biological Products Advisory Committee
September 22, 2022

No Financial Disclosures

The findings and conclusions in this presentation are those of the author and do not necessarily represent the official position of the Centers for Disease Control and Prevention

Outline

- **Describe landscape of *Clostridioides difficile* infection (CDI) in the United States in the past decade**
  - Background and epidemiology of CDI in earlier years
  - Changes in CDI incidence since 2011
  - Emergence of community-associated CDI
  - CDI recurrence and mortality

Background

Clostridioides difficile background

- **Anaerobic, gram-positive, spore-forming gastrointestinal pathogen**
- **Transmission via oral-fecal route**
- **Clinical spectrum ranges from asymptomatic colonization to mild or severe disease with fulminant colitis and death**
- **Risk of *C. difficile* infection (CDI) increases with gut microbiome disruption and immunosuppression**
  - Antibiotic use, proton pump inhibitor use, advanced age, chemotherapy

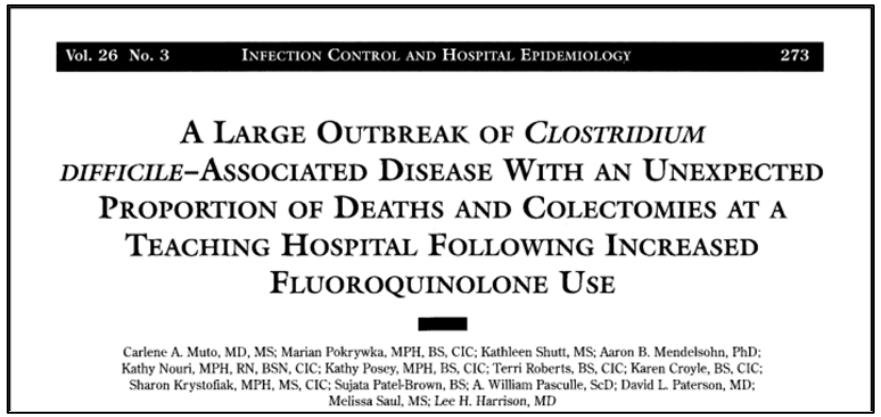
Epidemiology of CDI in the United States in earlier years

- **Outbreaks of clindamycin-resistant strains in 1980s and 1990s**
- **Emergence of ribotype 027 strain in early 2000s coincided with increased CDI incidence, severity, and mortality**
  - Hospital stays with CDI increased from 85,700 in 1993 to 336,600 in 2009, with a sharp rise starting in 2000
  - *C. difficile* mortality increased from 2675 deaths (10/1 million person-years) in 2000 to 14,368 deaths (48/1 million person-years) in 2007
- **CDI increasingly detected in non-hospital settings and community**
  - Ohio 2006: >50% of healthcare-associated CDI with onset likely in nursing homes
  - Mid-2000s: severe cases of CDI reported in otherwise healthy persons living in the community and peripartum women

AHRQ. https://www.hcup-us.ahrq.gov/reports/statbriefs/sb124.pdf
Campbell RJ et al. Infect ControlHosp Epidemiol 2009; 30:526–33.
Hall AJ et al. Clin Infect Dis. 2012;55:216-23.
Lessa F et al. Open Forum Infect Dis. 2014 Jul 28;1(2):ofu048

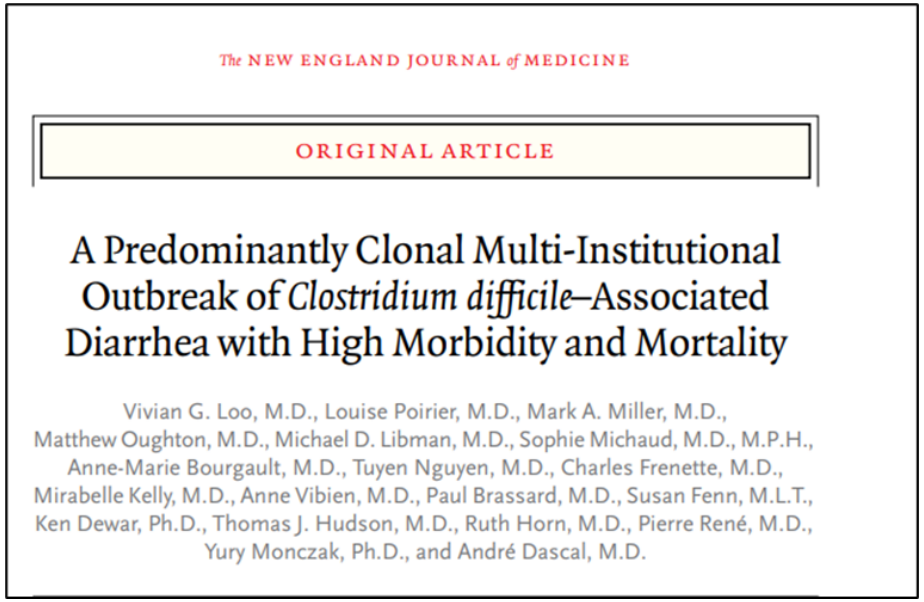
Ribotype 027 strain

- Several hospital outbreaks of severe CDI in North America, spreading worldwide
- Has high-level resistance to fluoroquinolones
- Produces substantially more toxin than most other *C. difficile* strains
- More likely to be associated with severe outcomes and death than other strains
- Although predominantly a healthcare-associated strain, has been detected among community-associated cases


Vol. 26 No. 3 INFECTION CONTROL AND HOSPITAL EPIDEMIOLOGY 273

A LARGE OUTBREAK OF *CLOSTRIDIUM DIFFICILE*–ASSOCIATED DISEASE WITH AN UNEXPECTED PROPORTION OF DEATHS AND COLECTOMIES AT A TEACHING HOSPITAL FOLLOWING INCREASED FLUOROQUINOLONE USE

Carlene A. Muto, MD, MS; Marian Pokrywka, MPH, BS, CIC; Kathleen Shutt, MS; Aaron B. Mendelsohn, PhD; Kathy Nouri, MPH, RN, BSN, CIC; Kathy Posey, MPH, BS, CIC; Terri Roberts, BS, CIC; Karen Croyle, BS, CIC; Sharon Krystofiak, MPH, MS, CIC; Sujata Patel-Brown, BS; A. William Pasculle, ScD; David L. Paterson, MD; Melissa Saul, MS; Lee H. Harrison, MD


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Predominantly Clonal Multi-Institutional Outbreak of *Clostridium difficile*–Associated Diarrhea with High Morbidity and Mortality

Vivian G. Loo, M.D., Louise Poirier, M.D., Mark A. Miller, M.D., Matthew Oughton, M.D., Michael D. Libman, M.D., Sophie Michaud, M.D., M.P.H., Anne-Marie Bourgault, M.D., Tuyen Nguyen, M.D., Charles Frenette, M.D., Mirabelle Kelly, M.D., Anne Vibien, M.D., Paul Brassard, M.D., Susan Fenn, M.L.T., Ken Dewar, Ph.D., Thomas J. Hudson, M.D., Ruth Horn, M.D., Pierre René, M.D., Yury Monczak, Ph.D., and André Dascal, M.D.

Warny M et al. Lancet. 2005;366:1079-84.
See I et al. Clin Infect Dis. 2014;58:1394-1400.

U.S. surveillance systems for CDI

- **CMS mandated hospital reporting of CDI in 50 states, DC, and PR in 2013**
  - Provides national data on risk-adjusted measure of hospital-onset CDI (standardized infection ratio)

- **Active laboratory- and population-based surveillance for CDI in 10 states since 2011**
  - Captures all healthcare- and community-associated cases, including subset of isolates, in 35 U.S. counties
  - Use data to estimate national CDI burden and monitor changes in strain prevalence

https://arpsp.cdc.gov/
https://www.cdc.gov/hai/eip/haicviz.html

Current Epidemiology

U.S. burden of CDI near its highest level in the early 2010s

- **Estimated 476,400 incident CDI cases (155 per 100,000 persons) in the United States in 2011**
  - 306,500 healthcare-associated CDI cases* (100 per 100,000 persons)
  - 170,000 community-associated CDI cases* (55 per 100,000 persons)
  - 239,100 hospitalizations with CDI
- ***C. difficile* was the most common healthcare-associated pathogen**
  - Accounting for 12% of healthcare-associated infections in U.S. hospitals in 2011

*Estimates do not add up to total burden of CDI due to rounding

Guh AY et al. N Engl J Med 2020;382:1320–30.
Magill SS et al. N Engl J Med 2014; 370(13):1198-1208

Increased diagnostic use of nucleic acid amplification tests (NAAT) in the United States in past decade

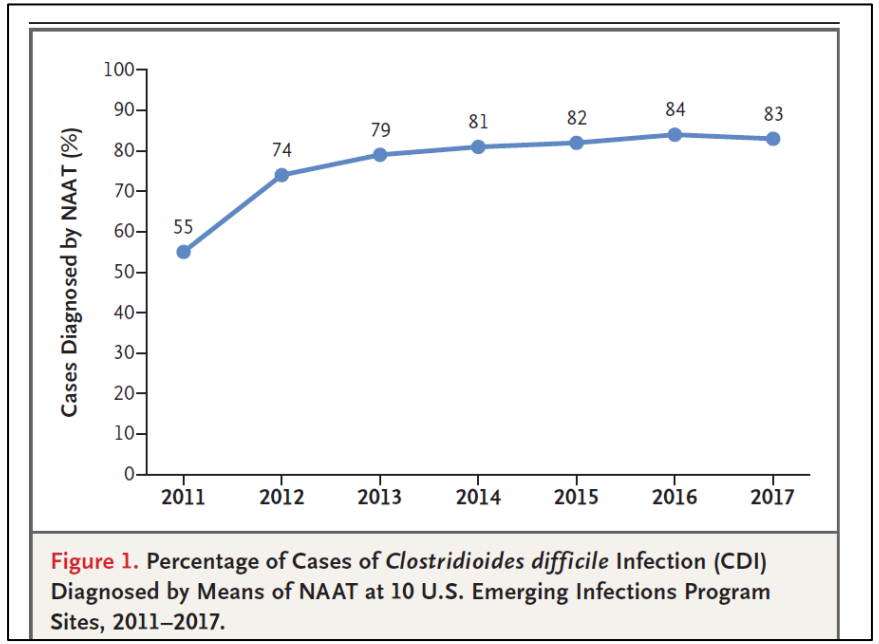


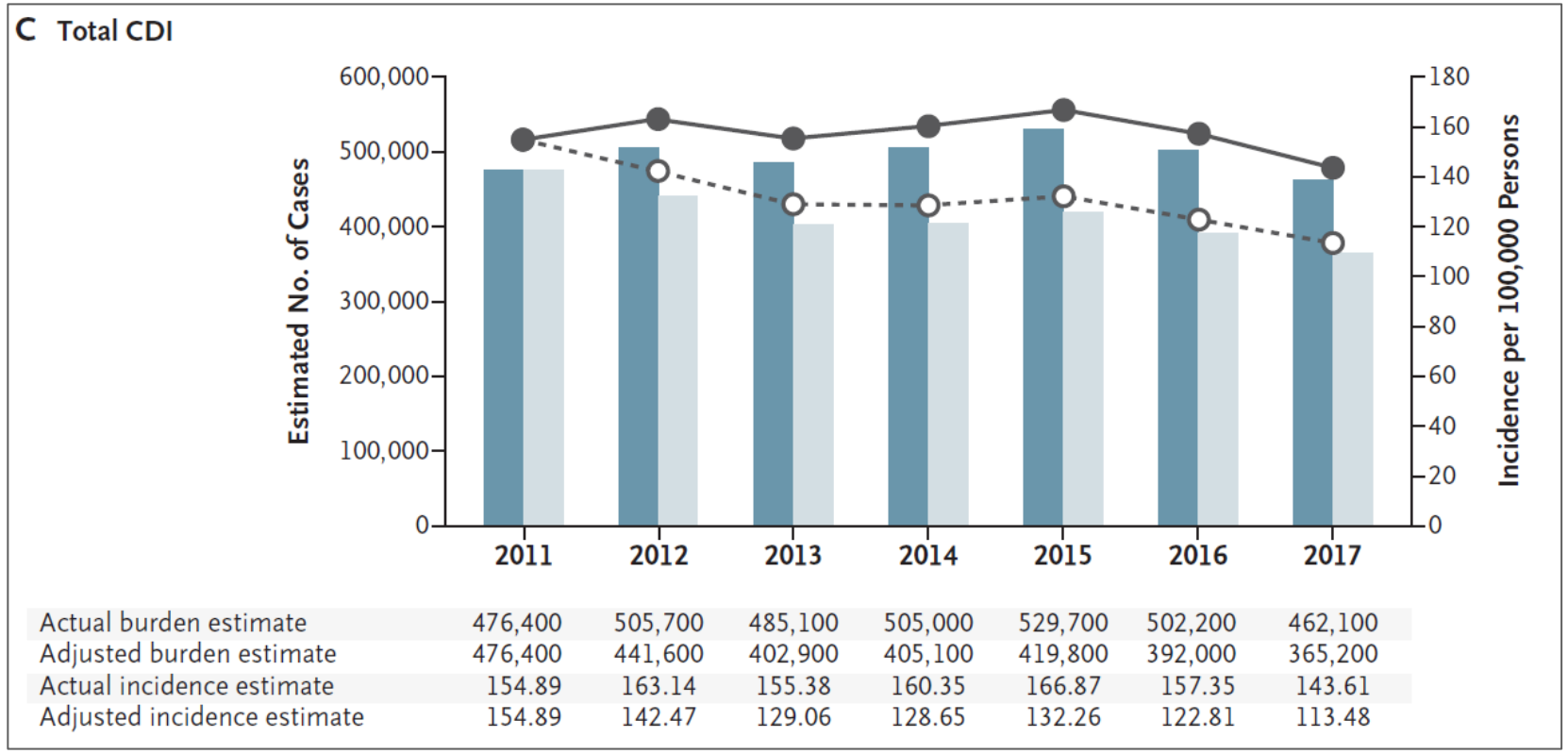
Figure 1. Percentage of Cases of *Clostridioides difficile* Infection (CDI) Diagnosed by Means of NAAT at 10 U.S. Emerging Infections Program Sites, 2011–2017.

NOTE. NAAT use includes NAAT alone or as part of a multistep testing algorithm in which NAAT was the last test performed

- **Several commercially available NAATs in late 2000s**
- **Lower sensitivity of toxin enzyme immunoassays (EIA) led to increased NAAT use**
  - CDI cases diagnosed by NAAT increased from 55% in 2011 to 84% in 2016, leveling off in 2017
- **NAAT is highly sensitive for toxigenic *C. difficile* strains (detects toxin gene) and can impact CDI incidence rates**
  - Switching from toxin EIA to NAAT increased CDI incidence rates by 43% to 67%
- **Need to account for higher sensitivity of NAAT when comparing CDI burden estimates and incidence rates over time**

Guh AY et al. N Engl J Med. 2020;382:1320–30.
Gould C et al. Clin Infect Dis. 2013 Nov;57(9):1304-7

Decrease in overall CDI burden in the United States, 2011 to 2017



	2011	2012	2013	2014	2015	2016	2017
Actual burden estimate	476,400	505,700	485,100	505,000	529,700	502,200	462,100
Adjusted burden estimate	476,400	441,600	402,900	405,100	419,800	392,000	365,200
Actual incidence estimate	154.89	163.14	155.38	160.35	166.87	157.35	143.61
Adjusted incidence estimate	154.89	142.47	129.06	128.65	132.26	122.81	113.48

- To remove the effect of increased NAAT use over time, held NAAT usage rate constant at 55% to adjust burden estimates
- From 2011 to 2017, adjusted CDI burden estimate decreased by 24% (95% CI, 6% to 36%)

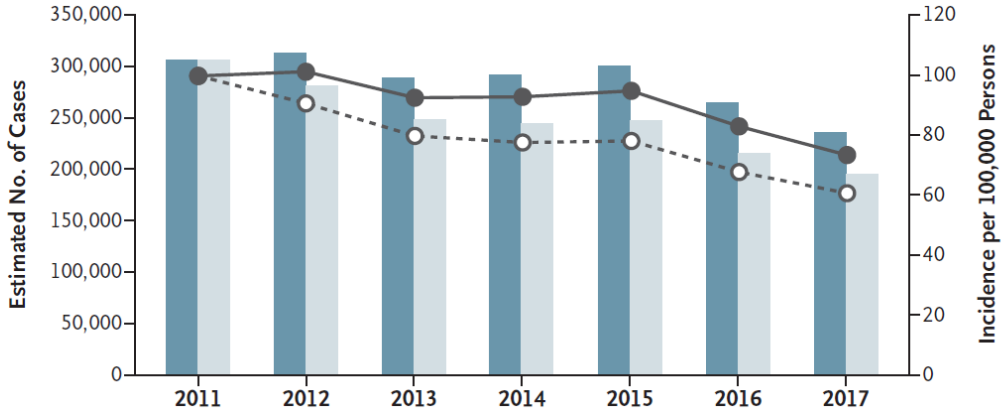
- Actual burden estimates based on actual NAAT usage rate in that year, adjusting for age, sex, and race of U.S. population
- Adjusted burden estimates based on 2011 NAAT usage rate of 55%, adjusting for age, sex, and race of U.S. population.

Guh AY et al. N Engl J Med. 2020;382:1320–30.

Healthcare-associated CDI decreased, whereas community-associated CDI remain unchanged

National Burden Estimates of Healthcare-associated CDI

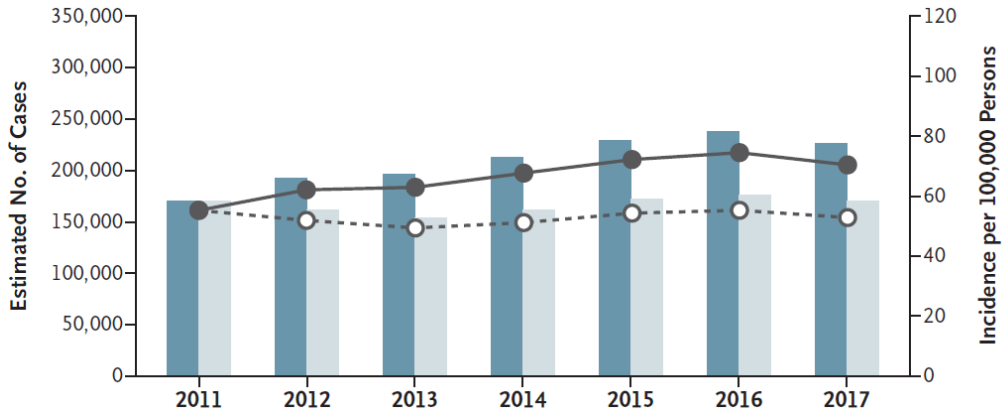
Adjusted national burden estimate decreased by 36% (95% CI, 24% to 54%)



	2011	2012	2013	2014	2015	2016	2017
Actual burden estimate	306,500	313,100	288,400	291,900	300,400	264,400	235,700
Adjusted burden estimate	306,500	280,600	248,600	244,000	247,500	215,700	194,900
Actual incidence estimate	99.63	101.02	92.39	92.68	94.63	82.86	73.25
Adjusted incidence estimate	99.63	90.51	79.64	77.47	77.97	67.59	60.57

National Burden Estimates of Community-associated CDI

No change in adjusted national burden estimate (0%; 95% CI, -2 to 3)

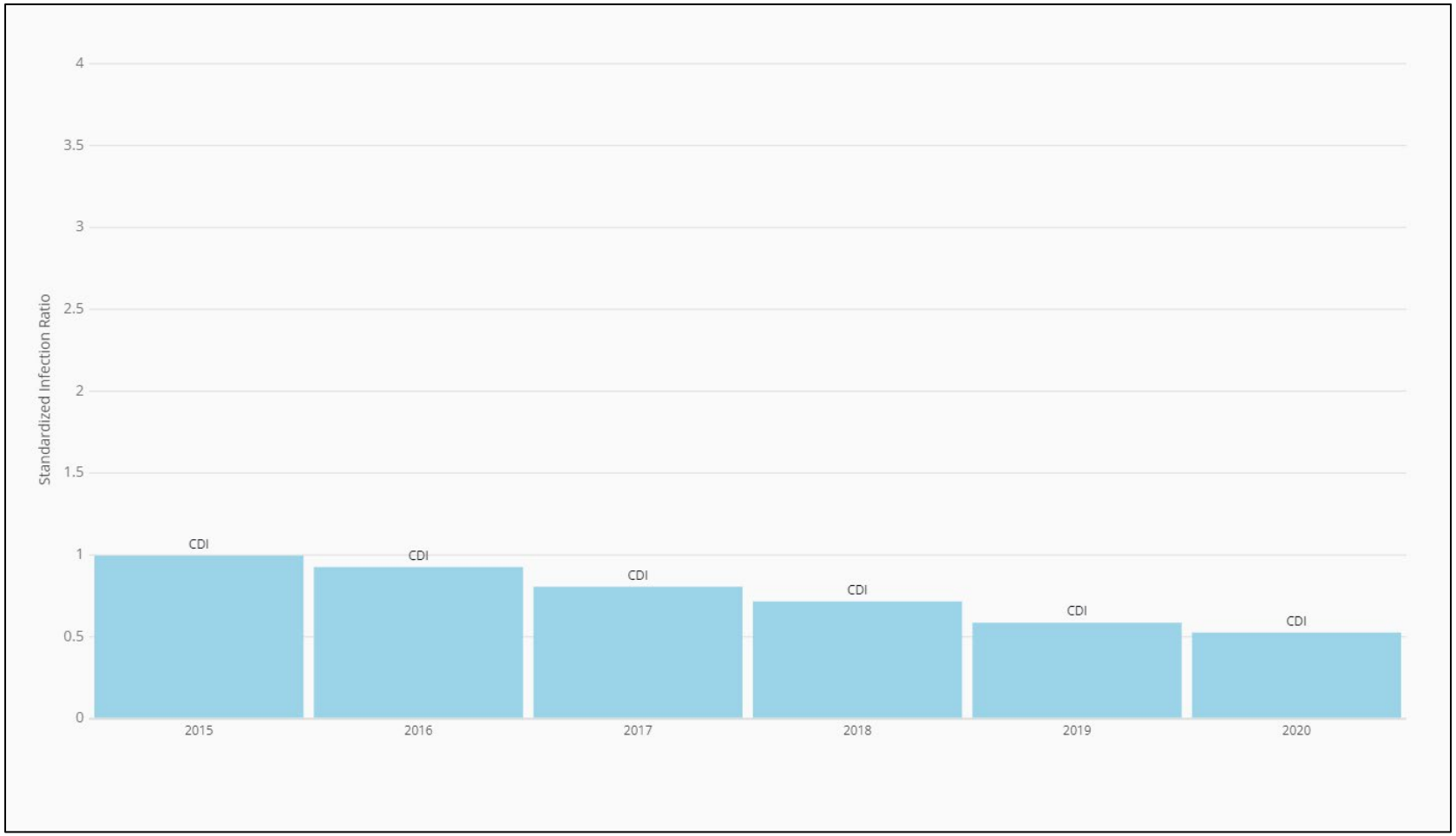


	2011	2012	2013	2014	2015	2016	2017
Actual burden estimate	170,000	192,500	196,700	213,100	229,300	237,800	226,400
Adjusted burden estimate	170,000	161,100	154,300	161,200	172,300	176,300	170,300
Actual incidence estimate	55.26	62.12	62.99	67.67	72.24	74.49	70.36
Adjusted incidence estimate	55.26	51.96	49.42	51.18	54.29	55.23	52.91

- Actual burden estimates based on actual NAAT usage rate in that year, adjusting for age, sex, and race of U.S. population
- Adjusted burden estimates based on 2011 NAAT usage rate of 55%, adjusting for age, sex, and race of U.S. population.

Guh AY et al. N Engl J Med. 2020;382:1320–30.

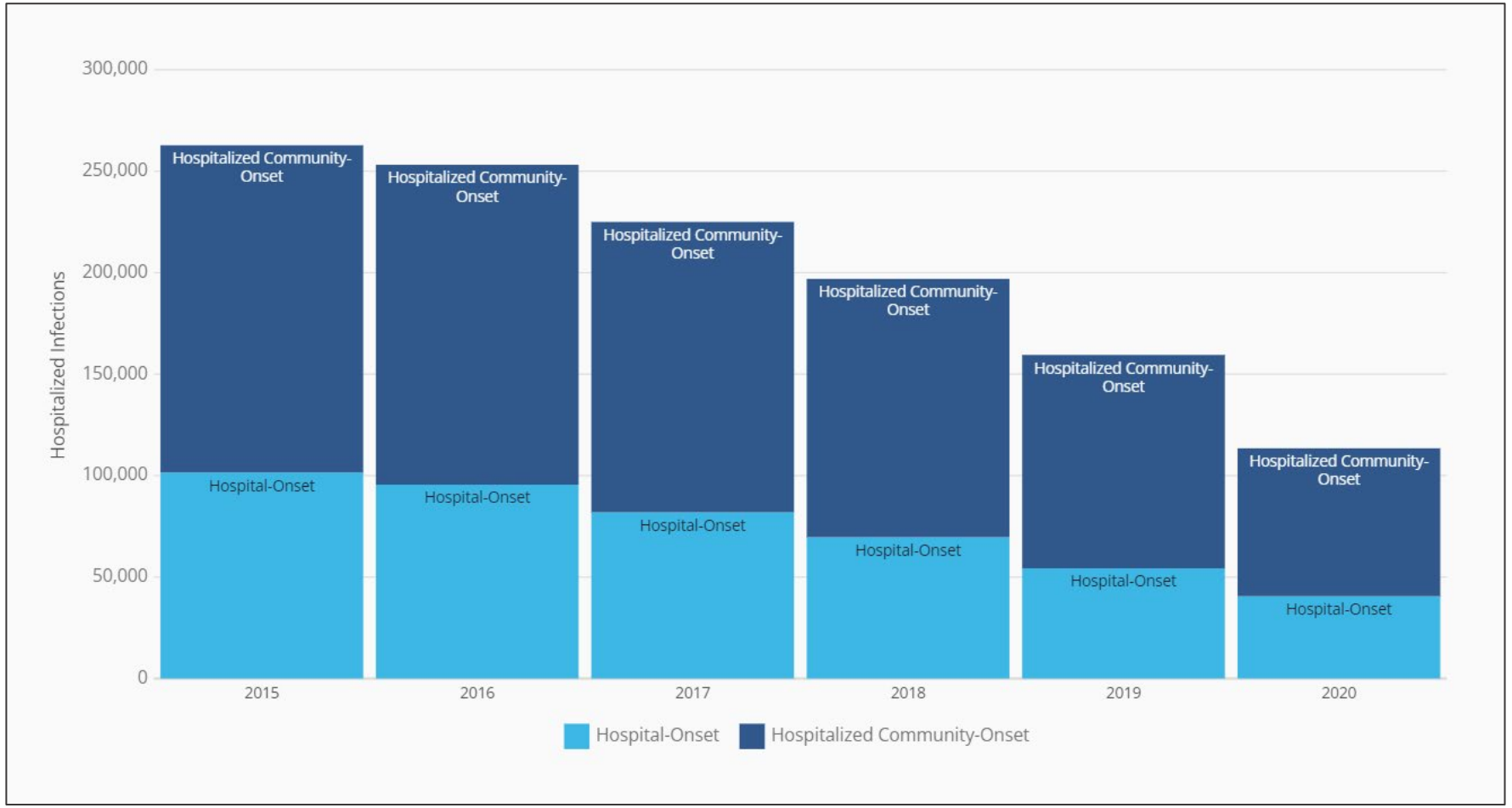
Decrease in risk-adjusted measure of hospital-onset CDI in the United States, 2015 to 2020



- 48% decline in the national CDI standardized infection ratio (SIR) from 2015 to 2020

Data from CDC's National Healthcare Safety Network; available at: https://arpsp.cdc.gov/profile/nhsn/cdi

Decrease in hospitalized laboratory-identified CDI events in the United States, 2015 to 2020



Crude data reported to NHSN:

- 55% decline in hospitalized community-onset CDI
- 60% decline in hospital-onset CDI

Data from CDC's National Healthcare Safety Network; available at: https://arpsp.cdc.gov/profile/nhsn/cdi

Further look at impact of COVID-19 on CDI incidence in the United States

- **Most US studies reported no change or a decrease in healthcare-associated or hospital-onset CDI rates**
  - Study of 148 HCA healthcare-affiliated hospitals: CDI was not significantly associated with COVID-19 burden
  - Study of 128 acute-care and 132 long-term care Veteran Affairs facilities: CDI rates significantly decreased during COVID-19 pandemic compared to pre-pandemic
  - NHSN data: national CDI SIR significantly decreased in all quarters of 2020 compared to 2019, with overall decrease of 11% between 2019 and 2020
- **Limited data on community-associated CDI rates**
  - EIP data: 2017-2019 community-associated CDI rates were relatively stable (crude annual rate of 63 /100,000 persons); 2020 data pending

Baker MA et al. Clin Infect Dis. 2022;74:1748-54.
Evans ME et al. Infect Control Hosp Epidemiol. 2022 Apr 5:1-24.
Weiner-Lastinger LM et al. Infect Control Hosp Epidemiol. 2022;43:12-25.
Clostridioides difficile Infection (CDI) Tracking | HAIC Activities | HAI | CDC

Decrease in healthcare-associated CDI is multifactorial

- **Improvement in infection prevention practices in healthcare facilities**
- **Significant decline in ribotype 027 strain although still remains most common ribotype among healthcare-associated CDI**
  - 21% in 2012 were ribotype 027 compared with 15% in 2017
- **Reduction in inappropriate antibiotic prescribing, including reduced inpatient fluoroquinolone use**
  - Restriction of fluoroquinolone prescribing in England led to drastic reduction in CDI
- **Changes in *C. difficile* diagnostic testing practices**
  - Increased emphasis on diagnostic stewardship to reduce inappropriate testing
  - Continued decreases partly due to recent shift back to toxin EIA over NAAT (due to concerns for potential overdiagnosis) for reporting CDI
    - Starting in 2019, rise in EIP labs using toxin EIA instead of NAAT as confirmatory test

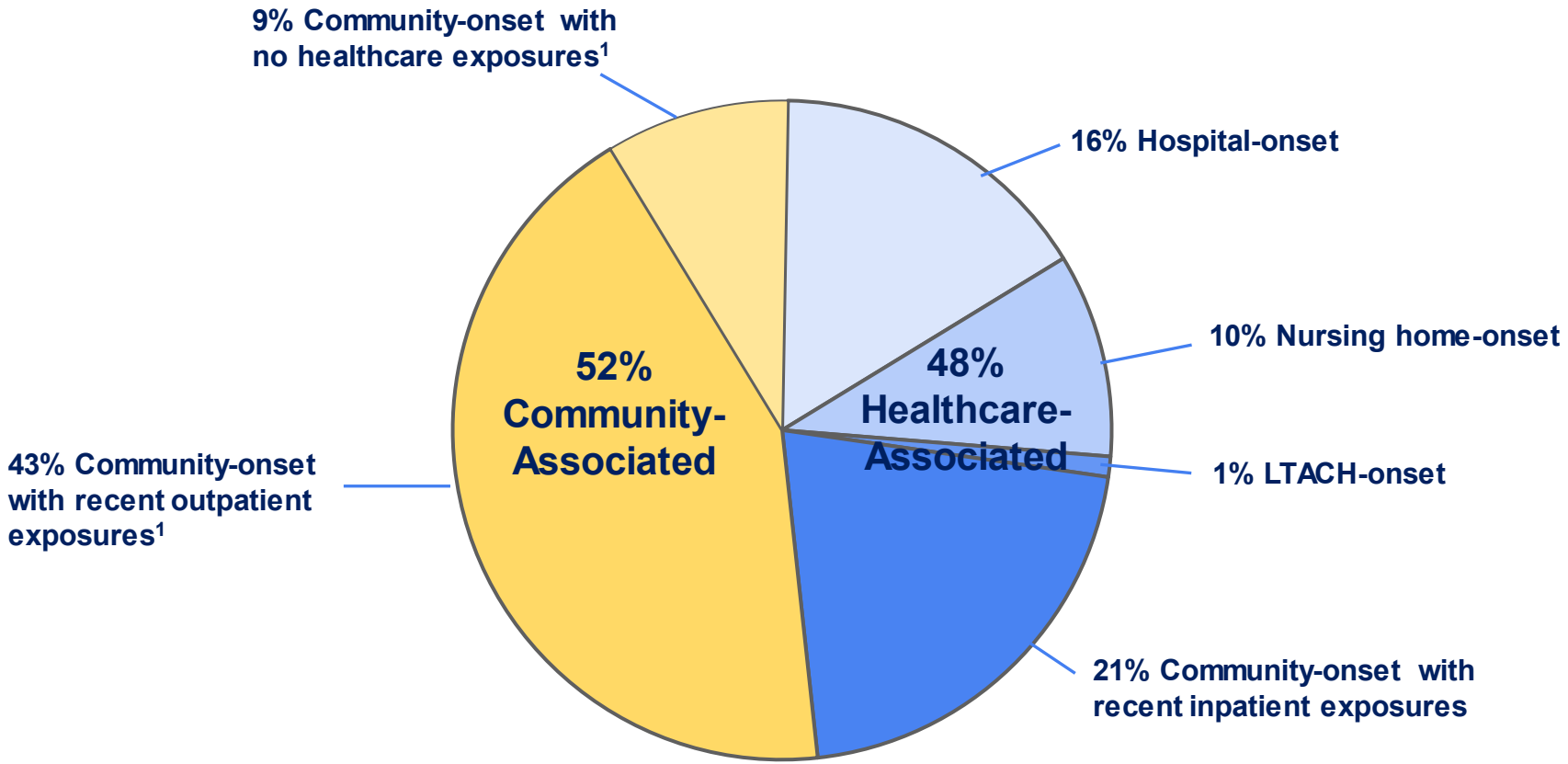
Baggs J et al. JAMA Intern Med 2016;176:1639-1648.
Guh AY et al. N Engl J Med. 2020;382:1320–30.
Dingle K et al. Lancet Infect Dis 2017;17:411-421.

What is known about community-associated CDI?

- **Higher incidence among younger population (<45 years of age)**
- **31% require hospitalization and 11%-14% develop recurrent CDI**
- **Healthcare-related risk factors:**
  - Recent antibiotic use remains a primary risk factor (2/3 of cases)
  - >80% have had recent outpatient healthcare exposures
  - Remote hospitalizations among older patients was a risk factor
- **Several non-healthcare sources of *C. difficile:***
  - Toxigenic strains isolated from various types of food, water, animals
  - Distinct pattern of genetic relatedness among some *C. difficile* isolates in Europe suggest transmission other than via person-to-person, such as food chain route or environment

Guh AY et al. Open Forum Infect Dis. 2017;4:ofx171.
Bauer MJ et al. Infect Dis Clin North Am. 2015;29:29-35.
Eyre DW et al. Clin Infect Dis 2018;67: 1035-1044.

Epidemiology of CDI in the United States



Source: 2019 EIP data
[1]Guh AY et al. Open Forum Infect Dis. 2017;4(4):ofx171

Overview of CDI recurrence

- **Majority of first recurrent episodes occur within 8 weeks of initial CDI**
- **Risk of recurrence increases with each episode:**
  - Up to 20% to 25% after first episode
  - Up to 40% to 45% after second episode
  - More than 60% to 65% after three or more episodes
- **2018 EIP data on multiple recurrence within 180 days of initial CDI diagnosis:**
  - 5% with ≥2 recurrences, 1% with ≥3 recurrences, 0.2% with ≥4 recurrences
- **Risk factors for recurrent CDI generally include:**
  - Advanced age, immunosuppression, prior CDI, infection with ribotype 027
  - Treatment of primary CDI (i.e., lower risk in those treated with fidaxomicin)
- **Recurrent CDI associated with 2.5-fold higher hospital readmission rate, 4-fold longer hospital stay, and 33% higher mortality rate than primary CDI**
- **Estimated attributable healthcare costs: $10,850 per recurrent case**

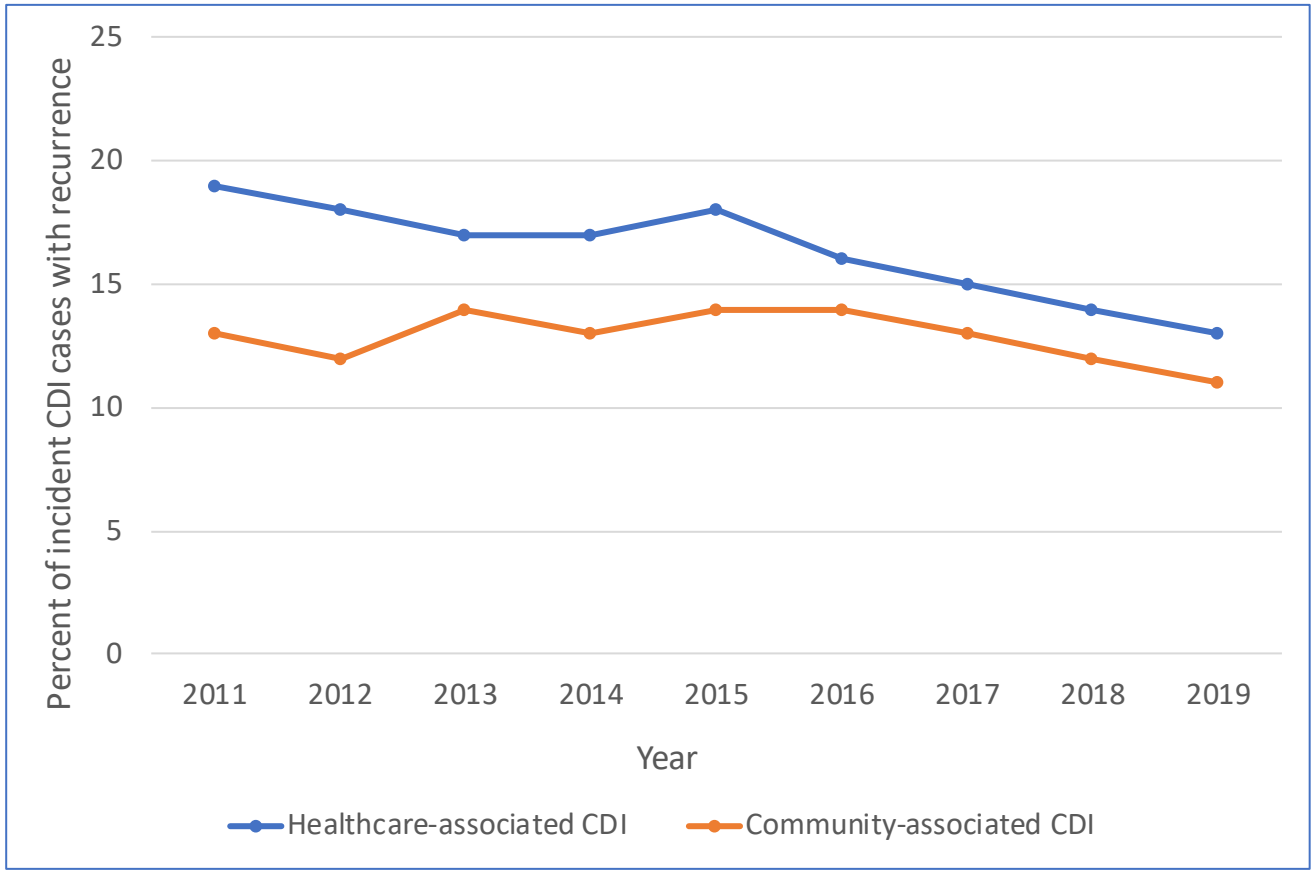
Tsigrelis C. Cleve Clin J Med. 2020;87:347-359.
Olson MA et al. Clin Microbiol Infect. 2015;21:164–170.
Olson MA et al. Am J Infect Control. 2015;43:318–322.
Zhang D et al. Clin Infect Dis. 2018;66:1326–1332.

Recurrent CDI trends in the United States

- **Most studies define recurrence as CDI occurrence within 2-8 weeks of prior episode**
- **2001 to 2012: annual incidence of multiply recurrent CDI increased 189% (from 0.0107 to 0.0309 case per 1000 person-years)**
- **Estimated national burden of first CDI recurrences was 84,600 in 2011 and 69,800 in 2017**
  - No change in adjusted recurrent CDI burden estimates after accounting for NAAT use
- **16% reduction in the adjusted risk of 180-day recurrent CDI in 2018 compared with 2013**
  - Used longer follow-up period to assess recurrence than previous studies
  - Accounted for patient mortality but not for NAAT use
  - Several potential factors for decrease, with a key driver being the increased use of NAAT for initial CDI diagnosis, which might have detected milder infections
    - No change in adjusted 2018 and 2013 rCDI rates among toxin-positive only patients
  - Less likely due to changes in treatment for initial CDI
    - Only 1.3% of initial CDI were treated with fidaxomicin in 2018

Ma GK et al. Ann Intern Med 2017; 167: 152–158.
Guh AY et al. N Engl J Med. 2020;382:1320–30.
Guh AY et al. Open Forum Infect Dis 2022; ofac422.

Crude CDI recurrence rates by epidemiologic class, 10 EIP sites, 2011-2019

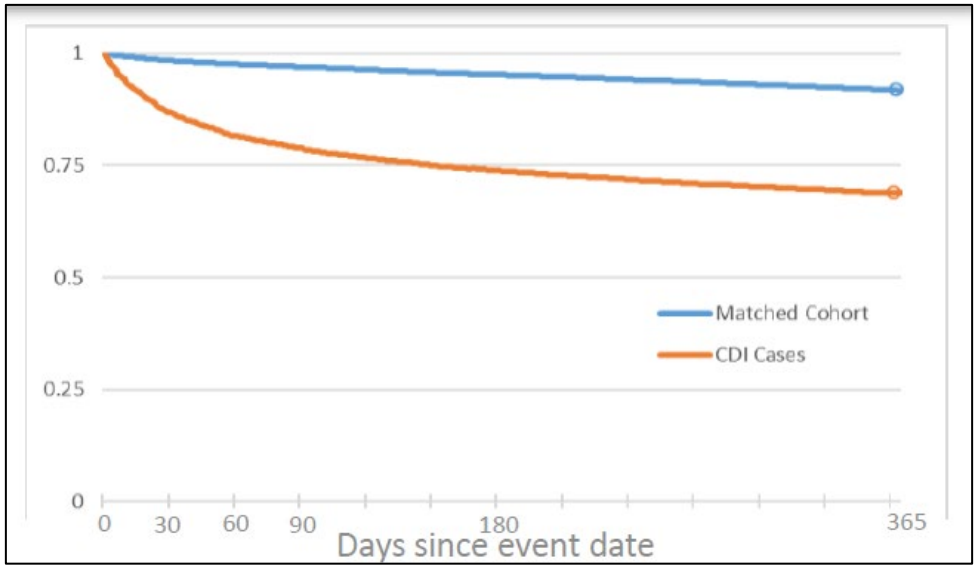


- Both healthcare-associated and community-associated CDI cases showed similar decreases in the percentage with recurrence after 2016

Clostridioides difficile Infection (CDI) Tracking | HAIC Activities | HAI | CDC
Guh AY et al. N Engl J Med. 2020;382:1320–30.

Overview of CDI mortality

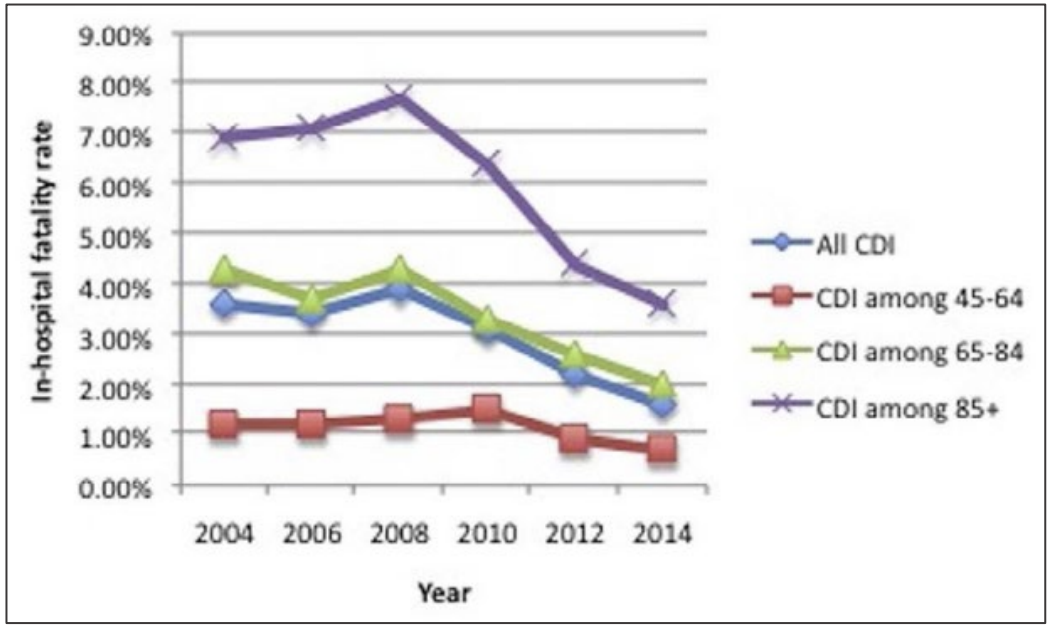
- **All-cause mortality has ranged from 11.8% to 38%**
- **Since 2000, attributable mortality has ranged from 4.5% to 5.7% during endemic periods and 6.9% to 16.7% during epidemic periods**
  - Estimated 11,500 deaths among hospitalized patients with CDI in the United States in 2019
- **Several studies have shown increased adjusted mortality in older patients with CDI**
  - Persons aged ≥65 years have 3 times higher odds of mortality in the year following CDI compared to a matched cohort
    - Using linked laboratory-confirmed population-based surveillance and administrative data
    - Adjusting for severity of illness, chronic conditions, skilled nursing facility residence and matching on length of hospitalization



Kwon JH et al. Infect Dis Clin North Am. 2015;29:123-134.
2022 SPECIAL REPORT: COVID-19 U.S. Impact on Antimicrobial Resistance (cdc.gov)
Hatfield KM et al. 2018 IDWeek abstract.

Decrease in mortality in U.S. hospitalized CDI patients

- **Several studies have utilized data from Healthcare Cost and Utilization Project (HCUP) Nationwide Inpatient Sample to assess mortality**
- **Most found decrease in in-hospital mortality among CDI patients late 2000s through 2014**
  - CDI-associated mortality decreased from 3.6% in 2004 to 1.6% in 2014 (P<0.001)
  - Greater decrease in mortality in older patients than in younger patients
- **Decrease possibly due to several factors**
  - Decreased prevalence of ribotype 027
  - Potentially greater proportion with milder infections
    - Increasing proportion of CDI are community-associated than healthcare-associated
    - Increased diagnostic use of NAAT
  - Unclear role of CDI treatment



Shrestha MP et al. Am J Med. 2018;131:90-96.

Summary

- **CDI incidence and mortality have declined in the United States over the past decade**
  - Largely due to the decrease in healthcare-associated CDI
  - Several contributing factors, including decreased prevalence of ribotype 027 and increased emphasis on diagnostic and antibiotic stewardship
- **CDI recurrence rates appear to have declined in more recent years**
  - Several contributing factors, including increased diagnostic use of NAAT for initial CDI
- **Overall burden of incident and recurrent CDI still substantial and associated with high morbidity and costs**
- **Increasing proportion of CDI are community-associated**
  - Large portion of cases require hospitalization
  - Majority have had recent antibiotic and outpatient healthcare exposures

Thank You

For more information, contact CDC
1-800-CDC-INFO (232-4636)
TTY: 1-888-232-6348 www.cdc.gov