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# Trends in incidence of long-term-care facility onset *Clostridium difficile* infections in 10 US geographic locations during 2011-2015

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Conflicts of interest: DNG holds patents and technology for the treatment and prevention of *Clostridium difficile* infections, and is a consultant or advisory board member for Merck, MGB, Actelion, Sanofi Pasteur, Rebiotix, DaVolterra, Pfizer, and Summit. GD serves on the Drug Safety Monitoring Board for a *C difficile* treatment study by Seres. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

## Abstract

During 2011-2015, the adjusted long-term-care facility onset *Clostridium difficile* infection incidence rate in persons aged ≥65 years decreased annually by 17.45% (95% confidence interval, 14.53%-20.43%) across 10 US sites. A concomitant decline in inpatient fluoroquinolone use and the *C difficile* epidemic strain NAP1/027 among persons aged ≥65 years may have contributed to the decrease in long-term-care facility-onset *C difficile* infection incidence rate.

### Keywords

NAP1/027; Fluoroquinolone

The Centers for Disease Control and Prevention Emerging Infections Program (EIP) conducts *Clostridium difficile* infection (CDI) surveillance in 10 US sites. A decline in long-term care facility (LTCF)-onset CDI incidence from 2011-2014 was observed in Monroe County, NY, 1 of the EIP sites.[1] To assess whether this was an isolated finding, we assessed the trend in LTCF-onset CDI incidence rates across all 10 sites from 2011-2015. In addition, we explored potential causes for the decline, including changes in CDI testing practices and the prevalence of NAP1/027, which is a *C difficile* strain with high-level fluoroquinolone resistance and associated with increased CDI incidence. The incidence of CDI is disproportionately higher among older persons. Given that more than half of LTCF-onset CDI occur in recently hospitalized residents,[2] we also assessed for changes in the inpatient use of 2 antibiotic classes associated with the highest CDI risk, specifically fluoroquinolones and extended-spectrum cephalosporins

## METHODS

Laboratories serving the 10 EIP sites (California, Colorado, Connecticut, Georgia, Maryland, Minnesota, New Mexico, New York, Oregon, and Tennessee) reported all positive *C difficile* tests. A case was defined as a positive stool test (toxin or molecular assay) in a person aged ≥1 without a positive test during the prior 8 weeks. Cases were assigned epidemiologic classes, including LTCF-onset, which was defined as having stool collected in an LTCF or from a LTCF resident within 3 days of hospital admission. Definitions of the other epidemiologic classes (hospital onset, community onset, health care associated, and community associated) have been described elsewhere.[3] Multiple imputation was performed for missing race and epidemiologic class. For 2 EIP sites where only a sample of cases underwent medical record review, domain analysis was used to estimate race and epidemiologic class using a weighted frequency based on 33% random sampling.

Because 85% of LTCF-onset CDI cases from the surveillance catchment areas occurred in persons aged ≥65 years, we limited the trend analysis to this age group. We used US census data to calculate LTCF-onset CDI incidence rates and built a generalized linear mixed model with negative binomial distribution, adjusting for sex, race, and the percent of cases diagnosed by nucleic acid amplification test. To exclude possible surveillance artifact, EIP site staff queried LTCFs in 2014 to assess for changes since 2011 in the frequency of empiric CDI treatments (ie, treating without ordering diagnostic stool test).

A convenience sample of specimens from CDI cases across the 10 EIP sites was cultured for *C difficile*. Recovered isolates under-went strain typing by pulsed-field gel electrophoresis, and starting in 2012, by capillary-based polymerase chain reaction-ribotyping. Results were analyzed against a library of standard profiles using BioNumerics software (Applied Math, Austin, TX). An 80% similarity threshold was used to assign North American pulsed-field gel electrophoresis (NAP) types.[4] The proportion of isolates that were NAP1/027 between 2011 and 2015 was compared using $\chi^2$ test.

We assessed changes in inpatient fluoroquinolone and extended-spectrum cephalosporin (ie, third- and fourth-generation cephalosporin) use by utilizing the Truven Health MarketScan Hospital Drug Database. The database contains data of antibiotics dispensed for hospitals in 5 of the 7 US census divisions where EIP sites are located. For those hospitals with data available from 20102014, we developed a multivariable linear regression model to examine trends in antibiotics dispensed among patients aged ≥65 years, measured as days of therapy (DOT) per 1,000 patient-days, adjusting for select facility characteristics, including case mix index, bed size category, teaching status, facility urban or rural location, proportion of surgical discharges, average comorbidity score for the facility, and the proportion of inpatient days in which the primary ICD-9-CM diagnosis code for that admission was related to an infection.[5]

## RESULTS

Of 12,821 LTCF-onset CDI cases in persons aged ≥65 years during 2011-2015, 3,151 occurred in 2011 compared with 1,909 in 2015, corresponding to a 49% decrease in overall crude incidence rate across the 10 EIP sites (253.82 to 129.08 per 100,000 persons) (Fig 1). By EIP site, the decrease in crude LTCF-onset CDI incidence rates ranged from 6%-65% among 8 of the 10 EIP sites that had a decline during the 5-year period.

The overall adjusted LTCF-onset CDI incidence rate across all EIP sites decreased by 55% from an estimated 311.19 (95% confidence interval [CI], 249.81-372.57) per 100,000 persons in 2011 to an estimated 138.88 (95% CI, 107.91-169.85) per 100,000 persons in 2015. The adjusted annual decrease was 17.45% (95% CI, 14.53%-20.43%) ($P < .0001$).

Of 364 LTCFs surveyed in 9 of 10 EIP sites, 196 (54%) had knowledge about their *C difficile* testing practices. Of these 196, 162 (83%) reported no changes since 2011 in the frequency of CDI treatments without ordering a stool test; 22 (11%) reported a decrease and 12 (6%) reported an increase.

*C difficile* isolates were available from 286 (2%) LTCF-onset CDI cases in persons aged ≥65 years; of these, 25 of 54 isolates in 2011 (46%) were NAP1/027 compared with 23 of 58 in 2015 (40%) ($P = .57$). Because so few isolates were available from LTCF-onset cases, we also assessed changes in NAP1/027 prevalence across all epidemiologic classes in persons aged ≥65 years. Among 2,778 (6%) of 47,744 persons aged ≥65 years with isolates available, 177 of 617 in 2011 (29%) were NAP1/027 compared with 88 of 498 in 2015 (18%) ($P < .0001$).

From 2010-2014, inpatient fluoroquinolone use (ie, dispensed) significantly decreased among patients aged ≥65 years ($P < .0001$); the absolute change in DOT per 1,000 patient-days was –25 (95% Cl, –15 to –36). Inpatient extended-spectrum cephalosporin use did not significantly decrease ($P = .34$); the absolute change in DOT per 1,000 patient-days was –0.2 (95% CI, –7 to 7).

## DISCUSSION

LTCF-onset CDI incidence rate among persons aged ≥65 years decreased annually by an adjusted 17% from 2011–2015 across 10 geographic areas. Overall, NAP1/027 prevalence significantly decreased among all persons with CDI who were aged ≥65 years. Although not statistically significant, there was also a decrease in the prevalence of NAP1/027 among persons with LTCF-onset CDI. The decrease coincided with a significant decline in inpatient fluoroquinolone use in hospitals in regions where 8 of the 10 EIP sites are located, suggesting that a deselection of NAP1/027 through reduced fluoroquinolone use could be among the factors contributing to the decline in LTCF-onset CDI in this age group.

Marked reduction in CDI rates coinciding with the control of NAP1/027 has been observed in England, and has been attributed more to the decreased use of fluoroquinolones than cephalosporins.[6,7] In Scotland, a reduction in high-risk antibiotic use was associated with concomitant decreases in NAP1/027 and CDI incidence.[8] In contrast, a decrease of NAP1/027 was observed in the Netherlands, but there was no change in nationwide fluoroquinolone use.[9] Similarly, decreases in LTCF-onset CDI incidence and NAP1/027 in Monroe County, NY, preceded local efforts to reduce fluoroquinolone use,[10] suggesting that other factors might also be contributing, such as changes in infection prevention practices, LTCF antibiotic use, or natural changes in *C difficile* strain distribution.

Most LTCFs reported no change or a decrease in the frequency of empiric CDI treatments, indicating the observed LTCF-onset CDI decline is unlikely to be a surveillance artifact; however, we only assessed practices through 2014 and did not have access to the number of stool tests ordered and pharmacy data to verify the responses. We had few isolate data to fully assess the change in NAP1/027 prevalence among LTCF-onset CDI cases, which could have limited our ability to detect a statistically significant decrease. In addition, the percentage of EIP laboratories that used nucleic acid amplification test for CDI diagnosis increased from 44% in 2011 to 78% in 2015. The increased detection of less toxigenic strains (ie, non-NAP1/027 strains) due to the high sensitivity of nucleic acid amplification test could have contributed to the observed decline in NAP1/027. However, there were no changes to the diagnostic tests used in Monroe Country during this period, suggesting the decline in NAP1/027 at this site is likely real. Lastly, inpatient antibiotic data were only available through 2014, but we expect that the use of fluoroquinolones continued to decrease in 2015.

To inform prevention strategies in LTCFs and possibly other settings, further efforts are needed to determine the factors driving the decline in LTCF-onset CDI incidence, including a better understanding of the changing molecular epidemiology of *C difficile* and its influence on CDI incidence.

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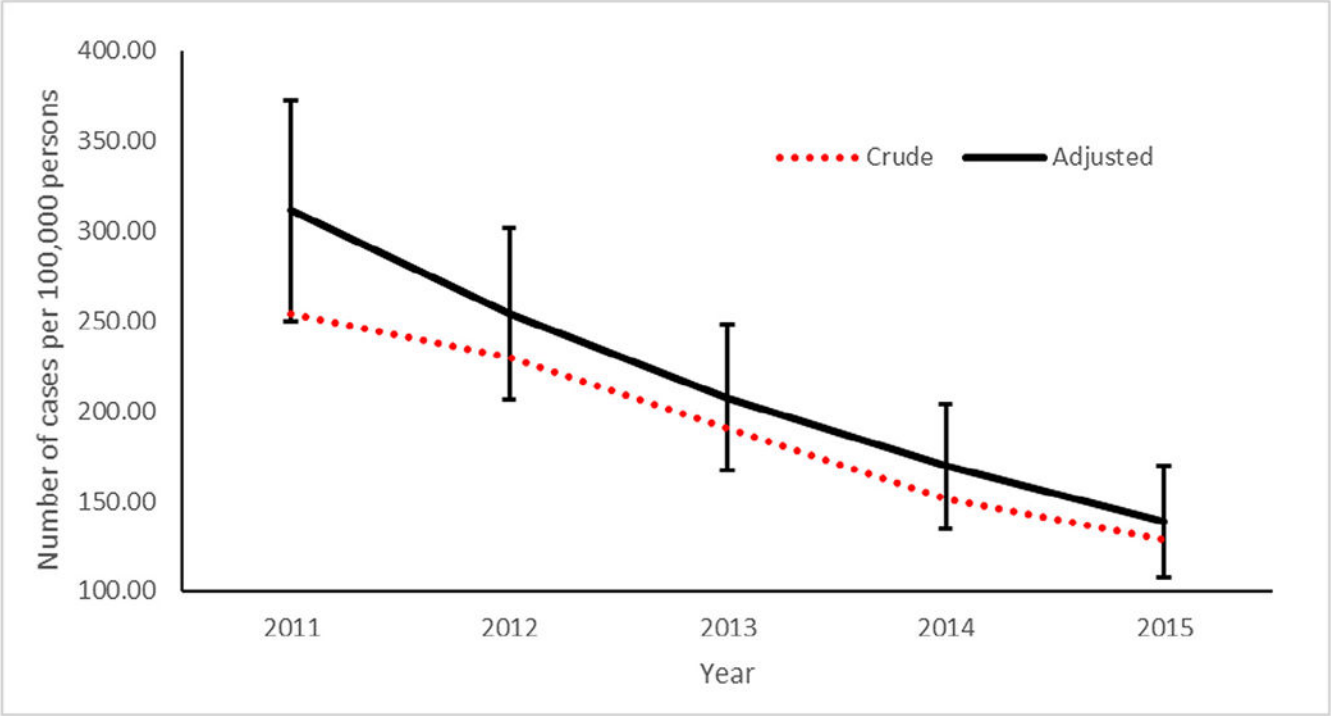


**Fig 1.**

Crude and adjusted annual long-term care facility onset *Clostridium difficile* infection incidence rates across 10 US sites, 2011-2015. The crude incidence rates are shown by the dotted line, and the adjusted incidence rates (adjusting for sex, race, and percent of cases diagnosed by nucleic acid amplification test) are shown by the solid line. Error bars reflect the 95% confidence intervals around the adjusted incidence rates.