Clostridium difficile infection in a French university hospital
Eight years of prospective surveillance study
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Abstract

The epidemiology of Clostridium difficile infection (CDI) has changed with an increase in incidence and severity. Prospective surveillance was therefore implemented in a French university hospital to monitor the characteristics of patients at risk and to recognize local trends. Between 2007 and 2014, all hospitalized patients (≥18 years) with CDI were included. During the survey, the mean incidence rate of CDI was 2.9 per 10,000 hospital-days. In all, 590 patients were included. Most of the episodes were healthcare-associated (76.1%). The remaining cases were community-acquired (18.1%) and unknown (5.9%). The comparison with healthcare-associated cases showed that the community-acquired group had a lower rate of antimicrobial exposure (P < 0.001), proton pump inhibitor (P < 0.001), and immunosuppressive drugs (P = 0.02). Over the study period, death occurred in 61 patients (10.3%), with 18 (29.5%) being related to CDI according to the physician in charge of the patient. Active surveillance of CDI is required to obtain an accurate picture of the real dimensions of CDI.

Abbreviations: Alg = algorithm, ATB = antibiotics, CA = community-acquired, CDI = Clostridium difficile infection, EIA = enzyme immunoassay, ER = emergency room, GDH = glutamate dehydrogenase, HCA = healthcare-associated, HD = hospital-days, ICU = intensive care unit, IQR = interquartile range, PCR = polymerase chain reaction, PMC = pseudomembranous colitis, PPI = proton pump inhibitor.

Keywords: Clostridium difficile, Clostridium difficile infection, community, France, surveillance

1. Introduction

Clostridium difficile is the most frequent infectious cause of nosocomial diarrhea and a major financial burden for healthcare systems.1,2 It is responsible for up to 25% of reported antibiotic-associated diarrhea cases and virtually all cases of pseudomembranous colitis (PMC).3 The clinical spectrum of C difficile infection (CDI) varies in severity from asymptomatic carriage to self-limited, mild, watery diarrhea, to PMC, intestinal perforation, toxic megacolon, sepsis, fulminant colitis, and death.4 The epidemiology of CDI has changed since the emergence of the 027/NAP1/BI strain, which has been implicated in large outbreaks, with a notable increase in the incidence and severity of the disease.4,5 In Europe, the reported incidence of CDI increased from CDI per 10,000 patient bed-days to 7.0 cases.6 In France, after the emergence of the 027 strain, the French Institute for Public Health Surveillance published recommendations for the surveillance and prevention of CDI, with mandatory notifications of severe CDI and/or outbreaks.7

Upon comparing data, many factors must be considered. Diagnostic procedures, methodology of surveillance, and typing availability can all vary widely across hospitals and/or countries. The epidemiology of CDI is not well-known in France except some papers on local and global data.8 In this context, we undertook a prospective surveillance study of CDI in a large university hospital in Lyon, France. The aim of this study was to estimate the incidence of infection and to compare CDI cases according to their origin of acquisition.

2. Methods

2.1. Study location and patients

From January 2007 to December 2014, a prospective surveillance study was conducted in an 860-bed public teaching hospital in Lyon, France. All hospitalized patients over 18 years of age with CDI were included in this study. According to French law, such a
study does not require ethics committee approval because it is observational surveillance approved under national regulations (Comité National Informatique et Liberté). The protocol design was approved by the Hospital Institutional Review Board. The study was reported according to Strobe guidelines.

2.2. Microbiological data

During the study period, *C. difficile* testing was performed only on unformed stool samples on specific request by physicians. Before November 2011, the presence of *C. difficile* was assessed by enzyme immunoassay (EIA; ImmunoCard Toxins A&B, Meridian Biosciences) of fresh stool samples coupled with culture (algorithm, Alg1). For culture, stool samples were plated on CLO medium (Biomérieux) and incubated in anaerobic conditions at 37°C for 48 hours. If the assay yielded negative toxin results and the culture was positive for *C. difficile*, isolate toxicity was assessed in vitro (toxigenic culture). Between November 2011 and January 2013, an algorithm protocol was used involving glutamate dehydrogenase (GDH) (ImmunoCard *C. difficile* GDH assay; Meridian Biosciences) antigen screening test, and if it was positive, stools were subsequently tested for *C. difficile* toxins A and B by EIA and culture as previously described (Alg2). Beginning in February 2013, the laboratory replaced the last algorithm with a combined immunochromatographic test of GDH and toxins (C. DIFF QUIK CHEK COMPLETE; Alere) coupled with polymerase chain reaction (PCR) (GeneXpert Systems, Cepheid). If the screening test was positive and the toxins were negative, PCR was then performed as a confirmatory test (Alg3).

2.3. Definitions

Diarrhea was defined as 3 or more unformed stools per 24-hour period. A CDI case was considered as a patient with diarrhea and a positive stool result (EIA for toxins A and/or B, or positive toxigenic culture or immunochromatographic test or PCR) and/or endoscopically or histologically proven colitis presumably due to *C. difficile*.

A case of CDI was defined as recurrent if it occurred with resurgence of symptoms after at least 10 days, but no more than 2 months, after the onset of the first episode, accompanied by a *C. difficile*-positive test result. According to the recommended guidelines, CDI was assumed to be nosocomial if diarrhea started more than 2 days after hospital admission or if symptoms occurred within 4 weeks of hospital discharge. Cases were defined as community-acquired (CA) if CDI signs presented in the absence of previous hospitalization within the past 12 weeks in outpatients or in inpatients within the first 48 hours of admission. Cases that did not fit any of these criteria were classified as unknown.

A case of severe CDI was defined when at least one of the following criteria was met: leukocytosis (>20,000 cells/μL), endoscopically or histologically proven colitis, megacolon, intestinal perforation, colectomy, septic shock or CDI requiring intensive care unit (ICU) admission, or related death in 30 days. Incidence was calculated as the number of CDI diagnosed at the hospital per 10,000 hospital-days (HD) and per 1000 hospitalized-patients.

2.4. Data collection

The full medical files of our cohort were reviewed. For each patient, we completed a standardized questionnaire that included the following variables: demographic characteristics, length of hospital stay, date and patient location at the onset of symptoms related to CDI, ward in which CDI was diagnosed, CDI symptoms, origin of acquisition of the infection, results of microbiological and endoscopic tests, specific CDI therapy, and infection outcome. Attributable mortality was defined as recorded by physician in charge of the patient. Exposure to factors associated with CDI in the past 30 days before the onset of diarrhea was recorded, including previous antibiotics (ATB), antiserotonergic drugs (anti-H2, proton pump inhibitors [PPIs]), immunosuppressors, and gastrointestinal surgery. Administrative data (total number of patients admitted and total number of HD) were obtained for each year.

2.5. Statistical analysis

For bivariate analyses in which we compared patient characteristics, 2-sided *P* values were assessed with Pearson chi-square test or Fisher exact test for categorical variables, and with the Wilcoxon rank-sum test or Mann–Whitney *U* test for continuous variables. *Clostridium difficile* rates were computed by year and hospital ward to evaluate temporal trends, overall and by ward. The numerator was the number of *C. difficile* cases in each stratum and the denominator was the hospitalized population in each stratum (10,000 HD). A Poisson regression model was used to assess longitudinal trend (unadjusted and adjusted on algorithm of testing). Model fit was assessed through Akaike information criterion, deviance, and Pearson chi-square statistics. Statistical analyses were performed with the statistical package for the social sciences (SPSS, version 17.0 for Windows, SPSS Inc., Chicago, IL) and R statistical software (v.3.0.2) (R Foundation for Statistical Computing, Vienna, Austria; URL: http://www.R-project.org/).

3. Results

3.1. Diagnosis and incidence

The data on patients tested for CDI were only available from 2008. Between 2008 and 2014, CDI was tested in 8753 patients, representing 3.4% of the hospitalized patients. The number of patients tested was stable over the study period with a mean incidence of testing of 49.5 per 10,000 hospitalized patients (Fig. 1). The percentage of positive tests increased from 6.6% in 2008 to 7.5% in 2014, with an overall incidence of 3.1 per 10,000 HD.

From January 1, 2007 to December 31, 2014, we identified 631 cases of CDI in 590 patients. Our patients totaled 599 hospital stays. Thirty-six patients had more than 1 episode (6.1%), 15 patients had 2 episodes, and 1 had 3 episodes during their first hospital stay; 19 experienced a second episode after a second admission, 1 patient developed CDI during his third admission, and 1 patient cumulated 4 episodes during 4 hospital stays.

Among our patients, 627 episodes (99.4%) had positive microbiological results and 4 episodes (0.6%) had confirmed PMC. In terms of the diagnostic test used, 492 episodes (78.5%) were diagnosed by positive toxins assays, and 80 (12.8%) and 55 episodes (8.8%) were confirmed by PCR and toxigenic culture, respectively.

Over the study period, there were a total of 697,468 hospital admissions and 2,108,095 HD. During this time, the rate of CDI

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diagnosed at our hospital varied between 2.37 in 2007 and 3.41 episodes per 10,000 HD in 2014 (unadjusted odds of diagnosis; \( P = 0.004 \)), with a mean of 2.9 per 10,000 HD (Fig. 2). The incidence increased by 37.5% in 2013 after the introduction of PCR. The test of tendency by a Poisson regression model showed that the increasing of positivity was only explained by this latest algorithm (\( P < 0.001 \)).

Clostridium difficile infection was more frequently diagnosed in geriatrics, the emergency room (ER), ICU, and nephrology (7.11, 7.04, 6.31, and 4.46 episodes per 10,000 HD, respectively). Approximately 60% of the CDI episodes were diagnosed during the fall-winter seasons, but there was not a temporal correlation with influenza.

The incidence of CDI acquired in our hospital varied from 0.84 in 2007 to 1.57 per 1000 hospitalized patients in 2014, with a mean of 1.18 per 1000 hospitalized patients or 1.71 per 10,000 HD. The highest incidences of CDI acquired in specific wards were observed in hematology, geriatrics, ICU, and nephrology (4.69, 3.33, 2.74, and 2.39 episodes per 1000 hospitalized patients, respectively). Figure 3 shows the annual distribution of CDI cases acquired in these wards. The characterization and typing are not routinely performed in our hospital. However, any strain 027 was not observed in cases diagnosed by PCR (Alg3).

### 3.2. Patient characteristics

The mean age of our patients was 64.4 years (range 19–104 years) and just over half (\( n = 309, 52.4\% \)) were male. Our patients had a total of 18,012 HD with 19 days (interquartile range [IQR] 7–40) as a median of length of stay.

Diagnosed CDI was classified as acquired in our hospital in 398 episodes (63.1%) and just over half (\( n = 309, 52.4\% \)) were of unknown origin. Patients with healthcare-associated (HCA)-CDI (acquired in our hospital and imported from other hospitals) are compared with CA cases in Table 1. For patients with confirmed HCA-CDI, the median interval between admission and microbiological diagnosis was 5 days (IQR 0–16 days).

Of the 590 patients, 394 (66.8%) had received antibiotics within the month preceding the onset of diarrhea. The mean...
number of antibiotics received per patient was 1.7, and 51% of them were exposed to third-generation cephalosporins, fluoroquinolones, and/or aminopenicillins. Of the 196 patients (113 had HCA-CDI and 73 had CA-CDI) who did not receive antimicrobial treatment, 35 (18%) were under 45 years of age, and 112 (57.1%) and 178 (90.8%) had not previously been treated either with PPI or immunosuppressive medication. Previous exposure to factors associated with CDI, clinical signs, and biological data are described in Table 2.

3.3. Clinical management and treatment

A total of 481 patients (81.5%) were specifically treated for CDI. Treatment included metronidazole therapy alone (n = 392, 66.4%) or vancomycin alone (n = 28, 4.7%), or both in combination or sequentially (n = 58, 9.8%). The mean duration of treatment was 10 days for metronidazole and 13 days for vancomycin. Probiotics were only administered in 2 patients and 66 received antidiarrheal drugs (11.4%). The management of CDI according to the origin of acquisition is detailed in Table 3.

3.4. Patient outcome

Among included patients, 43 (7.3%) had PMC and 51 (8.6%) had colitis. Thirty-six patients (6.1%) relapsed within 60 days. Recurrence was not different between the CA and HCA-CDI cases (Table 3). Overall, 14 (2.4%) of the patients (4.4% in the CA group and 1.8% in the HCA-CDI group) required intensive care. Death occurred in 61 patients (10.3%) and CDI was considered the primary cause or a contributing cause of death in

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Table 1

|                      | All included patients (N = 590) | Healthcare-associated CDI (n = 448, 75.9%) | Community-acquired CDI (n = 113, 19.1%) | p value |
|----------------------|---------------------------------|------------------------------------------|----------------------------------------|---------|
| Age, median (IQR)   | 67 (52–79)                      | 67 (54–79)                               | 61 (42.5–79)                           | 0.03    |
| Age, yrs (categorical) |                                  |                                          |                                        |         |
| <45                  | 92 (15.6)                       | 56 (12.5)                                | 32 (28.3)                              | <10−3   |
| 45–65                | 194 (32.9)                      | 153 (34.2)                               | 31 (27.4)                              |         |
| >65                  | 304 (51.5)                      | 239 (53.3)                               | 50 (44.6)                              |         |
| Sex (female)         | 281 (47.6)                      | 204 (45.5)                               | 65 (57.5)                              | 0.02    |
| Origin               |                                  |                                          |                                        |         |
| Home                 | 452 (76.6)                      | 325 (72.5)                               | 103 (91.2)                             | <10−3   |
| Other hospital       | 138 (23.4)                      | 123 (27.5)                               | 10 (8.8)                               | <10−3   |
| Ward where diagnosis was made |                        |                                          |                                        |         |
| Geriatrics           | 57 (9.7)                        | 47 (10.5)                                | 7 (6.2)                                |         |
| Hepato-gastroenterology and GI surgery | 71 (12)                             | 53 (11.8)                               | 15 (13.3)                              |         |
| Hematology           | 20 (3.4)                        | 17 (3.8)                                 | 1 (0.9)                                |         |
| ICU                  | 106 (18)                        | 94 (21.0)                                | 10 (8.8)                               |         |
| Medical ER           | 142 (24.1)                      | 89 (19.9)                                | 44 (38.9)                              |         |
| Medicine             | 54 (9.2)                        | 41 (9.2)                                 | 9 (8.0)                                |         |
| Nephrology           | 84 (14.2)                       | 66 (14.7)                                | 12 (10.6)                              |         |
| Surgery              | 30 (5.1)                        | 27 (6.0)                                 | 3 (2.7)                                |         |
| Surgical ER          | 26 (4.4)                        | 14 (3.1)                                 | 12 (10.6)                              |         |

CDI, Clostridium difficile infection; ER, emergency room; GI, gastrointestinal; ICU, intensive care unit; IQR, interquartile range.

* p value of the comparison between health care and community-associated cases.
18 patients (3.1% overall or 29.5% in the deceased patients). The mortality rate was higher in the HCA group, but the contribution of CDI was higher in the CA group (37.5% vs 30.6% in the HCA-CDI cases).

### Table 2
Comparison of previous exposure to factors associated with CDI, clinical signs, and laboratory results in healthcare-associated and community-associated episodes of CDI diagnosed at Edouard Herriot Hospital, Lyon, between January 2007 and December 2014.

| Exposure in the past 30 d to factors associated with CDI | All included patients (N=590) | Healthcare-associated CDI (n=448, 75.9%) | Community-acquired CDI (n=113, 19.1%) | P^∗ |
|----------------------------------------------------------|-------------------------------|------------------------------------------|---------------------------------------|------|
| ATB                                                      | 394 (66.8)                    | 335 (74.8)                               | 40 (35.4)                             | <10^−3 |
| Aminoglycosides                                          | 67 (11.4)                     | 66 (14.7)                                | 0 (0)                                 | <10^−3 |
| Amoxiclav                                                | 114 (19.3)                    | 95 (21.2)                                | 17 (15.0)                             | 0.14 |
| Clindamycin                                              | 9 (1.5)                       | 8 (1.8)                                  | 1 (0.9)                               | 0.50 |
| Imipenem                                                 | 37 (6.3)                      | 36 (8.0)                                 | 0 (0)                                 | 0.002 |
| Meronidazole                                             | 37 (6.3)                      | 33 (7.4)                                 | 4 (3.5)                               | 0.14 |
| Quinolones                                               | 139 (23.6)                    | 126 (28.1)                               | 6 (5.3)                               | <10^−3 |
| Third-generation cephalosporins                         | 174 (29.5)                    | 159 (35.5)                               | 8 (7.1)                               | <10^−3 |
| Tazocillin                                               | 78 (13.2)                     | 77 (17.2)                                | 0 (0)                                 | <10^−3 |
| Vancomycin                                               | 45 (7.6)                      | 43 (9.6)                                 | 0 (0)                                 | <10^−3 |
| Other ATB                                                | 249 (42.2)                    | 225 (50.2)                               | 15 (13.3)                             | <10^−3 |
| Other drugs                                              |                              |                                          |                                       |      |
| Antibiotics                                              | 18 (3.1)                      | 17 (3.8)                                 | 0 (0)                                 | 0.04 |
| GI surgery                                               | 28 (4.7)                      | 26 (5.8)                                 | 2 (1.8)                               | 0.08 |
| Immunosuppressors                                        | 89 (15.1)                     | 77 (17.2)                                | 9 (8.0)                               | 0.02 |
| H2-blockers                                              | 4 (0.7)                       | 4 (0.9)                                  | 0 (0)                                 | 0.30 |
| PPI                                                      | 327 (55.4)                    | 271 (60.5)                               | 37 (32.7)                             | <10^−3 |
| Peristaltic agents                                       | 166 (28.1)                    | 135 (28.1)                               | 22 (16.2)                             | 0.04 |
| Biological features and clinical signs                   |                              |                                          |                                       |      |
| Mean time between admission and diarrhea, d              | 7.30                          | 12.5                                     | -11.0                                 | <10^−3 |
| Abdominal pain                                           | 190 (32.2)                    | 124 (27.7)                               | 54 (47.6)                             | <10^−3 |
| Fever (T >38°C)                                          | 177 (30.0)                    | 126 (28.1)                               | 41 (36.3)                             | <10^−3 |
| Leukocytosis (>20,000/mL)                                | 61 (10.3)                     | 46 (10.3)                                | 12 (10.6)                             | 0.91 |
| Microbiological results                                  | 460 (78)                      | 343 (76.6)                               | 89 (78.8)                             | 0.62 |

ATB, antibiotics; CDI, Clostridium difficile infection; PCR, polymerase chain reaction; PPI, proton pump inhibitor.

^∗P value of the comparison between healthcare and community-associated cases.

### Table 3
Treatment and prognosis of healthcare-associated and community-associated episodes of CDI diagnosed at Edouard Herriot Hospital, Lyon, between January 2007 and December 2014.

| Treatment of CDI episodes | All included patients (N=590) | Healthcare-associated CDI (n=448, 75.9%) | Community-acquired CDI (n=113, 19.1%) | P^∗ |
|---------------------------|-------------------------------|------------------------------------------|---------------------------------------|------|
| ATB for CDI               | 481 (81.5)                    | 369 (82.4)                               | 93 (82.3)                             | 0.99 |
| Fidaxomicin               | 3 (0.5)                       | 2 (0.4)                                  | 0 (0)                                 | 0.48 |
| Metronidazole             | 451 (76.4)                    | 345 (77.0)                               | 91 (80.5)                             | 0.42 |
| Vancomycin                | 88 (14.9)                     | 69 (15.4)                                | 11 (9.7)                              | 0.12 |
| Antidiarrheal             | 67 (11.4)                     | 53 (11.8)                                | 12 (10.6)                             | 0.72 |
| Probiotics                | 2 (0.3)                       | 2 (0.4)                                  | 0 (0)                                 | 0.48 |
| Prognosis                 |                              |                                          |                                       |      |
| Length of stay, median (IQR), d | 19 (7–40)                 | 22.5 (11–44)                             | 8 (3–20)                              | <10^−3 |
| Admission to ICU for CDI  | 14 (2.4)                      | 8 (1.8)                                  | 5 (4.4)                               | 0.09 |
| Colsis                    | 51 (8.6)                      | 36 (8.1)                                 | 14 (12.4)                             | 0.15 |
| PMC                       | 43 (7.3)                      | 30 (6.7)                                 | 13 (11.5)                             | 0.09 |
| Relapse                   | 36 (6.1)                      | 30 (6.7)                                 | 6 (5.3)                               | 0.59 |
| Severe CDI                | 116 (19.7)                    | 86 (19.2)                                | 27 (23.9)                             | 0.27 |

ATB, antibiotics; CDI, Clostridium difficile infection; ICU, intensive care unit; IQR, interquartile range; PMC, pseudomembranous colitis.

^∗P value of the comparison between healthcare and community-associated cases.

### 4. Discussion
The incidence of CDI is not well-known in France. Previous reports based on analyses of mortality and hospital data have reported that the incidence varies between 0.5 and 3 per 10,000...
HD. Similar estimations were observed in a laboratory-based retrospective and a multicenter European study.\cite{11,12} The overall incidence in French hospitals observed in the Infections à \textit{Clostridium difficile}-Réseau d’alerte, d’investigation et de surveillance des infections nosocomiales [ICD-RAISIN] national study was of 2.28 and 1.14 per 10,000 HD in acute and long-term care facilities, respectively.\cite{91} After the emergence of the 027 epidemic strain in 2006 and the publication of national guidelines regarding this infection, we implemented prospective surveillance of CDI in our hospital.

Our study provides a reliable estimate of the burden of the disease in a large university hospital (83,000 admissions per year) which was submitted to \textit{C difficile} testing over an 8-year period. Data from our study showed that the rate of CDI among patients undergoing \textit{C difficile} toxin testing was on average 2.9 per 10,000 HD and that this frequency significantly increased during the years of the study with the peak (3.74 per 10,000 HD) in 2013. The incidence of CDI acquired in our hospital was lower than the average incidence reported in North America and in the European studies.\cite{12-14}\ Of note, a significant geographic variation was reported with the highest rate in Finland (19.1 per 10,000 HD) and the lowest in Turkey and Bulgaria (0.6 per 10,000 HD). Our incidence was almost stable until 2012 and then increased significantly by 37.5% after the introduction of PCR as a consequence of increased sensitivity.\cite{13}\ This study demonstrates that laboratory methods can have a significant impact on CDI rates. Indeed, performing PCR to confirm CDI diagnosis led to an increase in incidence rates as observed elsewhere.\cite{16}\ However, molecular techniques do not distinguish asymptomatic colonization from CDI; therefore, in our hospital, testing was limited to symptomatic patients.

Active surveillance with rapid action for new cases was ongoing during the study period, and no outbreaks were detected.

The rate of testing is similar to national data. At our hospital, it is only based on physician prescriptions which can impact the number of diagnosed cases, as proven by the clearly established correlation between such strategy and the incidence of CDI.\cite{6}\ This diagnostic strategy based on prescriptions and/or our active surveillance could account for this low incidence.

Our study showed that 19% of the CDI cases were CA, a finding that is similar to other studies.\cite{17,18}\ Females were more frequent in the CA cases (57%), which is similar to a large American study conducted in 2010.\cite{19}\ Advanced age is known to be associated with CDI.\cite{20}\ Our work demonstrates that 15% of cases were younger than 45 years. CDI in young people has been described in the literature, work demonstrates that 15% of cases were younger than 45 years. CDI in young people has been described in the literature, and was associated with longer hospital stays and adverse outcomes. Antibiotic therapy and PPI treatment were more frequent in HCA-CDI cases. The rates of CA-CDI around the world are increasing, and this was proven in our study with 19% of the cases classified as CA. Two-thirds of CA-CDI cases were not exposed to antimicrobial drugs or PPI. This number of cases without reported or recorded known factors suggests that there could be other unrecognized risk factors contributing to the increased incidence of CA-CDI. Possible sources for CA-CDI including food and animals have been suggested but more epidemiological evidence is needed to support or refute this hypothesis. This study demonstrates that laboratory methods can have a significant impact on CDI rates. The use of an adequate diagnostic strategy, and also the implementation of continuous monitoring of CDI through surveillance programs with standardized definitions are required to improve our understanding of the epidemiological changes of this disease.

5. Conclusions

In conclusion, the incidence of CDI was similar to national data and was associated with longer hospital stays and adverse outcomes. Antibiotic therapy and PPI treatment were more frequent in HCA-CDI cases. The rates of CA-CDI around the world are increasing, and this was proven in our study with 19% of the cases classified as CA. Two-thirds of CA-CDI cases were not exposed to antimicrobial drugs or PPI. This number of cases without reported or recorded known factors suggests that there could be other unrecognized risk factors contributing to the increased incidence of CA-CDI. Possible sources for CA-CDI including food and animals have been suggested but more epidemiological evidence is needed to support or refute this hypothesis. This study demonstrates that laboratory methods can have a significant impact on CDI rates. The use of an adequate diagnostic strategy, and also the implementation of continuous monitoring of CDI through surveillance programs with standardized definitions are required to improve our understanding of the epidemiological changes of this disease.

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