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**Original Article**

# Multicenter study on *Clostridioides difficile* infections in Mexico: exploring the landscape

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## Abstract

Objective: This study aims to outline *Clostridioides difficile* infection (CDI) trends and outcomes in Mexican healthcare facilities during the COVID-19 pandemic.

Design: Observational study of case series.

Setting: Sixteen public hospitals and private academic healthcare institutions across eight states in Mexico from January 2016 to December 2022.

Patients: CDI patients.

Methods: Demographic, clinical, and laboratory data of CDI patients were obtained from clinical records. Cases were classified as community or healthcare-associated infections, with incidence rates calculated as cases per 10,000 patient days. Risk factors for 30-day all-cause mortality were analyzed by multivariate logistic regression.

Results: We identified 2,356 CDI cases: 2,118 (90%) were healthcare-associated, and 232 (10%) were community-associated. Common comorbidities included hypertension, diabetes, and cancer. Previous high use of proton-pump inhibitors, steroids, and antibiotics was observed. Recurrent infection occurred in 112 (5%) patients, and 30-day mortality in 371 (16%). Risk factors associated with death were a high Charlson score, prior use of steroids, concomitant use of antibiotics, leukopenia, leukocytosis, elevated serum creatine, hypoalbuminemia, septic shock or abdominal sepsis, and SARS-CoV-2 coinfection. The healthcare-associated CDI incidence remained stable at 4.78 cases per 10,000 patient days during the pre-and pandemic periods. However, the incidence was higher in public hospitals.

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Conclusions: Our study underscores the need for routine epidemiology surveillance and standardized CDI classification protocols in Mexican institutions. Though CDI rates in our country align with those in some European countries, disparities between public and private healthcare sectors emphasize the importance of targeted interventions.

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## Introduction

*Clostridioides difficile* infection (CDI) is a global healthcare challenge. However, its impact in Latin America is poorly understood.[1] Despite extensive studies in other regions, the epidemiology and clinical characteristics of CDI in Mexico require further study, particularly in light of the potential changes caused by the SARS-CoV-2 pandemic.[2]

CDI's well-documented consequences, which span from increased morbidity and mortality to prolonged hospital stays and heightened healthcare costs, paint a compelling backdrop for research. Nevertheless, the complex interaction between CDI and Mexico's demographics, healthcare infrastructure, and clinical practices underscores the importance of adopting a localized perspective. Previous research extensively documented epidemiological trends in individual hospitals, offering valuable insights. However, these findings do not reflect the broader national context.[3–5] During the early part of the last decade, one study reported that the average rate of CDI per 1000 hospital days was 0.28.[6] Additionally, CDI is not consistently reported in the national surveillance system, leading to unreliable recording and monitoring of this infection.[7]

The impact of the COVID-19 pandemic on healthcare utilization, antimicrobial stewardship, and infection control practices may have had profound repercussions on the epidemiology of CDI. Therefore, we conducted a multicenter study to understand how CDI evolved before and during the COVID-19 pandemic in Mexico.

## Methods

This observational study of CDI patients included 16 Mexican hospitals (11 [69%] public and 5 [31%] private academic healthcare institutions across eight states in the country). Participating centers were Instituto Nacional De Ciencias Médicas y Nutrición Salvador Zubirán (INCMNSZ) (Mexico City), Hospital Regional De Alta Especialidad Del Bajío (Leon), Hospital Civil De Guadalajara Fray Antonio Alcalde (Guadalajara), Christus Muguerza Hospital Alta Especialidad (Monterrey), Hospital Regional De Alta Especialidad De Oaxaca (HRAEO) (Oaxaca), Hospital Ángeles del Carmen (HAC) (Guadalajara), Christus Muguerza Hospital Del Parque (Chihuahua), Hospital Español De Veracruz (Veracruz), Hospital Nacional de Rehabilitación (Mexico City), Hospital Regional De Alta Especialidad De la Península de Yucatan (Merida), Hospital General "Dr Agustin O'Horan" (Merida), Instituto Nacional de Cancerología (INCan) (Mexico City), Hospital Universitario "Dr José Eleuterio González" (Monterrey), Instituto Nacional de Enfermedades Respiratorias (INER) (Mexico City), Hospital General "Dr Manuel Gea González" (Mexico City), and Hospital Ángeles Chihuahua (Chihuahua).

Each institution collected available data on adults with CDI from January 2016 to December 2022. Data from electronic records and medical charts were integrated into a standardized dataset that included variables related to demographic and clinical characteristics, laboratory results, treatments, individual outcomes, and pertinent institution information for estimations of disease incidence. The study underwent review and approval by the ethics committees of each participating hospital. Informed consent was waived and data confidentiality was assured.

### Definitions

A case of CDI was defined as a patient presenting diarrheal syndrome and evidence of toxigenic *C. difficile* strains confirmed by a positive polymerase chain reaction (PCR) or an enzyme immunoassay (EIA). Depending on the institution, some cases followed a sequential testing algorithm where a glutamate dehydrogenase (GDH) test was performed as the initial diagnostic step.

CDI cases were categorized based on the likely place of acquisition, distinguishing between healthcare-associated CDI (HA-CDI) and community-associated CDI (CA-CDI) cases. We considered the date of symptom onset and the individual's hospitalization history to classify cases according to international guidelines.[8] HA-CDI cases included patients with symptoms beginning ≥4 days after admission to a healthcare facility and those with symptoms starting in the community or within 4 days from admission but with a history of hospital admission within the previous 12 weeks. Conversely, a CA-CDI case was identified when symptoms started in the community or within 4 days of hospital admission, provided the onset of the symptoms occurred >12 weeks after the last discharge from a healthcare facility.

Steroid use was defined when consumption of at least 20 mg/day of prednisone or its equivalent occurred for a minimum of 14 days before the diagnosis of CDI. The use of systemic antibiotics, proton-pump inhibitors, and cytotoxic chemotherapy use was defined as any used within 30 days before the diagnosis, with antibiotics further subclassified by number and type. Monoclonal antibodies, including anti-TNF agents or rituximab, were assessed for six months before the diagnosis. Chronic use of immunosuppressive agents, such as methotrexate, azathioprine, sirolimus, 6-mercaptopurine, cyclosporine, mycophenolate, everolimus, or tacrolimus, was also evaluated. Solid organ transplantation and hematopoietic stem cell transplantation (HSCT) were also considered risk factors if they occurred within two months and six months before the diagnosis, respectively.

Treatment response to CDI was defined as the absence of diarrhea, fever, and abdominal pain by day 7. Recurrence was defined as the re-initiation of diarrheal symptoms within 2 to 8 weeks after the resolution of the initial episode, confirmed by a positive laboratory *C. difficile* test. Disease severity was evaluated according to international guidelines,[9] and mortality was reported as 30-day in-hospital all-cause mortality.

### Statistical analysis

A descriptive analysis of demographic and clinical variables was performed using frequencies and proportions for categorical

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variables, while medians and interquartile ranges (Q1-Q3) were used to summarize continuous variables. Univariate logistic regressions were used to compare variables. A multivariate analysis was conducted with statistically significant ($P < 0.05$) variables obtained from the bivariate analysis to establish risk factors for 30-day all-cause mortality; afterward, odds ratios (OR) and their corresponding 95% confidence intervals (95% CI) were calculated. Analyses were carried out using RStudio software version 2023.12.1 + 402.

We calculated the individual and pooled incidence for the included institutions based on the total number of CDI cases and patient days during the study period. Periods during which some institutions reported zero CDI cases were excluded from the pooled estimates because including them might have led to underestimating the observed CDI incidence. We attributed these zero-case reports to the absence of surveillance during those specific periods. Additionally, we stratified the incidence rates by the type of center (public vs private) and compared the pre-pandemic and pandemic periods.

## Results

Of the 16 participating centers, 11 (69%) were public hospitals, and 5 (31%) were private institutions. The centers were distributed across the country, with 4 (25%) located in the northern, 8 (50%) in the central region, and 4 (25%) in the southern region. Twelve centers (75%) were tertiary-care institutions serving populations that require specialized medical care. The hospitalization capacities of these institutions ranged from 40 to 800 beds, with an average capacity of 230 beds.

During the study period, we identified 2,356 cases of CDI. Of these, 2,118 (90%) and 232 (10%) were classified as HA-CDI and CA-CDI cases, respectively. The acquisition source could not be determined in 6 cases (0.3%) due to unavailable information. Diagnostic methods varied: 821 cases (34.8%) were diagnosed using PCR alone, 779 (33.1%) with a sequential algorithm of GDH followed by PCR, 493 (20.9%) by GDH followed by EIA, and 263 (11.2%) by EIA toxin assay only. Xpert® *C. difficile* tests (Xpert CD assay; Cepheid, Sunnyvale, CA, USA) were conducted in 1,159 patients (49.2%), of which 486 (41.9%) tested positive for the epidemic BI/NAP1/027 strain. This strain was associated with higher mortality in bivariate analysis (OR 1.59; 95% CI: 1.13-2.22; $P = 0.001$).

### *Demographic characteristics and previous medical treatments*

Among the included cases, 1,256 (53.3%) were male with an overall mean age of 53 years (Q1-Q3: 37-65). Regarding comorbidities, 855 patients (36.3%) had hypertension and 733 (31.1%) type 2 diabetes, with a median Charlson score of 3.00 (Q1-Q3: 2–5). Additionally, 698 (29.6%) patients were diagnosed with cancer, including 347 (49.7%) with solid tumors and 351 (50.2%) with hematological malignancies (Table 1). Regarding prior antibiotic exposure, 1,813 cases (77.0%) had used antibiotics before the CDI diagnosis. Carbapenems were the most prevalent (826 cases; 46%), followed by third-generation cephalosporins (591 cases; 33%), other beta-lactams (amoxicillin and piperacillin) (362 cases; 20%), fluoroquinolones (317 cases; 17%), and clindamycin (126 cases; 7%). The number of antibiotics used varied: 890 (37.8%), 580 (24.6%), and 330 (14.0%) patients had one, two, or three different antibiotics prescribed, respectively. Proton-pump inhibitors were used in nearly half of the patients (1,139 cases; 48.3%), and prior use of steroids or chemotherapy was noted in 16% (364 cases) and 15% (354 cases) of the population, respectively.

### *CDI clinical characteristics and outcomes*

The median number of diarrheal episodes during the study was 5 per day (Q1-Q3: 4–7), and 1,163 (49.4%) patients reported abdominal pain. Fever was observed in 950 (40.3%) patients; of these, 777 (81.8%) had temperatures ranging from 37.5°C to 38.3°C, and 173 (18.2%) had fevers that exceeded 38.3°C.

Leukocytosis (≥15,000 cells/mm$^3$) was documented in 608 (25.8%) patients, while leukopenia (<2000 cells/mm$^3$) was observed in 240 (10.2%). Mild neutropenia (<1500 cells/mm$^3$) was found in 294 (12.5%) patients, and severe neutropenia (<500 cells/mm$^3$) in 192 (8.1%). Hypoalbuminemia (<3.5 mg/dL) was noted in 1,844 (78.3%) and elevated serum creatinine (>1.5 mg/dL) in 631 (26.8%) patients.

Regarding disease severity, 1,172 (49.7%) patients presented non-severe disease, 826 (35.1%) severe infection, and 346 (14.7%) fulminant disease. Recurrence was documented in 112 (5%) cases. Septic shock or abdominal sepsis developed in 307 (13.0%) cases, ileus in 72 (3.1%), and toxic megacolon in 59 (2.5%). During the pandemic period, concurrent CDI and SARS-CoV-2 infections were diagnosed in 149 (14%) cases.

In our cohort, among the 2,271 (96.4%) patients with documented treatment, the most common therapeutic agent was oral vancomycin in 1141 (50%), followed by a combination of vancomycin and metronidazole in 832 cases (37%), and metronidazole alone in 272 (12%) instances. Fidaxomicin, either alone or in combination, was used in 14 (0.6%) patients, while fecal transplantation and colectomy were completed in 21 (0.9%) and 31 (1.3%) patients as part of the CDI treatment scheme, respectively. Admission to the intensive care unit occurred in 332 cases (14%), and 371 (16%) died within 30 days of CDI diagnosis.

In multivariate analysis, factors associated with 30-day mortality were septic shock or abdominal sepsis (OR 5.87; 95% CI: 4.31–7.99; $P < 0.001$), leukopenia (OR 2.88; 95% CI: 1.19–6.97; $P = 0.019$), SARS-CoV-2 coinfection (OR 2.32; 95% CI: 1.48–3.62; $P < 0.001$), leukocytosis (OR 1.85; 95% CI: 1.38–2.47; $P < 0.001$), prior steroid use (OR 1.76; 95% CI: 1.26–2.46; $P < 0.001$), hypoalbuminemia (OR 1.68; 95% CI: 1.08–2.64; $P = 0.021$), elevated serum creatinine (OR 1.60; 95% CI: 1.19–2.17; $P = 0.002$), concomitant antibiotic use during clinical disease (OR 1.35; 95% CI: 1.003–1.82; $P = 0.048$), and a higher Charlson score (OR 1.07; 95% CI: 1.01–1.14; $P = 0.022$) (Table 2).

### *Trends in the CDI incidence*

The overall incidence of CDI during the study period was 4.78 cases per 10,000 patient days, ranging from 3.81 to 5.98 (Table 3). The incidence of 4.80 cases/10,000 patient days (pre-pandemic period, 2016–2019) was similar to the 4.74 cases/10,000 patient days observed during the SARS-CoV-2 pandemic (2020–2022). Notably, the lowest incidence occurred in 2020 (3.81 cases/10,000 patient days), while the highest occurred in 2022 (5.98 cases/10,000 patient days). Incidence across specific hospitals varied significantly, ranging from 0.92 to 14.51 cases per 10,000 patient days (Figure 1).

Compared to private institutions, public hospitals had a higher disease incidence (2.27 versus 5.13 cases per 10,000 patient days, respectively). In specific, INCMNSZ and INCan, which primarily focus on treating immunocompromised and cancer patients, reported incidence rates of 14.51 and 7.89 cases per 10,000 patient

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**Table 1.** Characteristics and outcomes of patients with *Clostridioides difficile* infection

| Variables | Female (N = 1100) | Male (N = 1256) | Overall (N = 2356) |
|---|---|---|---|
| Age – years | 54 (40–66) | 52 (35–65) | 53 (37–65) |
| Comorbidities | | | |
| Hypertension | 441 (40.1%) | 414 (33.0%) | 855 (36.3%) |
| Diabetes mellitus | 340 (30.9%) | 393 (31.3%) | 733 (31.1%) |
| Cancer | 329 (29.9%) | 369 (29.4%) | 698 (29.6%) |
| Chronic kidney disease | 219 (19.9%) | 263 (20.9%) | 482 (20.5%) |
| Dialysis | 135 (12.3%) | 173 (13.8%) | 308 (13.1%) |
| HIV infection | 16 (1.5%) | 84 (6.7%) | 100 (4.2%) |
| Charlson score - median [min, max] (missing = 1) | 3.00 (2, 5) | 3.00 (1, 5) | 3.00 (2, 5) |
| Previous medical treatment | | | |
| Proton-pump inhibitors (missing = 15) | 550 (50.0%) | 589 (46.9%) | 1139 (48.3%) |
| Steroids (missing = 5) | 182 (16.5%) | 182 (14.5%) | 364 (15.5%) |
| Chemotherapy (missing = 2) | 166 (15.1%) | 188 (15.0%) | 354 (15.0%) |
| Monoclonal antibodies (missing = 2) | 41 (3.7%) | 43 (3.4%) | 84 (3.6%) |
| Other immunosuppressive agents | 102 (9.3%) | 82 (6.5%) | 184 (7.8%) |
| HSCT (missing = 22) | 14 (1.3%) | 8 (0.6%) | 22 (0.9%) |
| Solid organ transplantation | 7 (0.6%) | 18 (1.4%) | 25 (1.1%) |
| Use of antibiotic within the previous 30 days (missing = 6) | 830 (75.5%) | 983 (78.3%) | 1813 (77.0%) |
| Type of antibiotic (missing = 11): | | | |
| No antibiotic[a] | 269 (32.4%) | 268 (27.3%) | 537 (29.6%) |
| Carbapenems[a] | 370 (44.6%) | 456 (46.4%) | 826 (45.6%) |
| Third-generation cephalosporin[a] | 266 (32.0%) | 325 (33.1%) | 591 (32.6%) |
| Beta-lactam Antibiotics[a] | 155 (18.7%) | 207 (21.1%) | 362 (20.0%) |
| Fluoroquinolone[a] | 159 (19.2%) | 158 (16.1%) | 317 (17.5%) |
| Clindamycin[a] | 44 (5.3%) | 82 (8.3%) | 126 (6.9%) |
| Other[a] | 334 (40.2%) | 410 (41.7%) | 744 (41.0%) |
| Use of antibiotics during infection (missing = 11) | 571 (51.9%) | 734 (58.4%) | 1305 (55.4%) |
| Laboratory findings | | | |
| Leukocyte count - cells/mm$^3$ (missing = 20) | 9400 (5300–15125) | 9950 (5800–15300) | 9700 (5600–15300) |
| Neutrophil count - cells/mm$^3$ (missing = 23) | 7180 (3632–12437) | 7680 (3927–12747) | 7480 (3800–12620) |
| Serum albumin - g/dL (missing = 129) | 2.7 (2.1–3.2) | 2.6 (2.1–3.1) | 2.6 (2.1–3.2) |
| Serum creatinine - mg/dL (missing = 29) | 0.72 (0.50–1.64) | 0.90 (0.60–1.90) | 0.83 (0.53–1.79) |
| Serum sodium - mEq/L (missing = 644) | 136 (133–139) | 137 (134–140) | 137 (133–140) |
| Serum chloride - mEq/L (SD) (missing = 646) | 104 (99–107) | 104 (100–107) | 104 (100–107) |
| Serum potassium - mEq/L (SD) (missing = 644) | 3.80 (3.4–4.2) | 3.80 (3.4–4.3) | 3.80 (3.4–4.2) |
| Treatment and prognosis | | | |
| Received CDI treatment (missing = 12) | 1067 (97.0%) | 1204 (95.9%) | 2271 (96.4%) |
| Type of treatment (missing = 12) | | | |
| Not treated | 28 (2.6%) | 45 (3.7%) | 73 (3.2%) |
| Vancomycin[b] | 549 (51.4%) | 592 (49.1%) | 1141 (50.2%) |
| Vancomycin + metronidazole[b] | 373 (34.9%) | 459 (38.1%) | 832 (36.6%) |
| Metronidazole[b] | 128 (11.9%) | 144 (11.9%) | 272 (11.9%) |
| Fidaxomicin[b,c] | 11 (1.03%) | 3 (0.25%) | 14 (0.61%) |

(*Continued*)

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**Table 1.** (*Continued*)

| Variables | Female (N = 1100) | Male (N = 1256) | Overall (N = 2356) |
|---|---|---|---|
| No reported antibiotic use for treatment[b] | 6 (0.56%) | 6 (0.50%) | 12 (0.53%) |
| Colectomy[b] (missing = 10) | 12 (1.1%) | 19 (1.5%) | 31 (1.3%) |
| Treatment failure (missing = 51)[b] | 103 (9.7%) | 110 (9.1%) | 213 (9.4%) |
| ICU stay (missing = 11) | 123 (11.2%) | 207 (16.5%) | 330 (14.0%) |
| 30-day all-cause mortality (missing = 88) | 158 (14.4%) | 213 (17.0%) | 371 (15.7%) |
| SARS-CoV-2 coinfection (missing = 1) | 52 (4.7%) | 97 (7.7%) | 149 (6.3%) |

Note. [a]The proportion relative to patients that received antibiotics (n = 1813). [b]The proportion relative to patients that received treatment for CDI (n = 2271). [c]Fidaxomicin as monotherapy or a combination of vancomycin and metronidazole algorithms. The median and quartiles 1 and 3 (Q1-Q3) are reported for continuous variables. HIV, human immunodeficiency virus, HSCT, hematopoietic stem cell transplantation, CDI, *Clostridioides difficile* infection, ICU, intensive care unit.

**Table 2.** Risk factors for a fatal outcome among patients with *Clostridioides difficile* infection

| | Alive | Dead | Bivariate | Multivariate | | |
|---|---|---|---|---|---|---|
| | (N = 1897) | (N = 371) | P value | OR | 95% CI | *P*-value |
| Age – years | 52.0 (36–64) | 56.0 (40–68) | 0.001 | 1.005 | (0.996–1.014) | 0.278 |
| Gender – male | 1006 (53.0%) | 213 (57.4%) | 0.122 | – | – | – |
| Diabetes mellitus | 581 (30.6%) | 124 (33.4%) | 0.287 | – | – | – |
| Hypertension | 666 (35.1%) | 142 (38.3%) | 0.244 | – | – | – |
| Chronic kidney disease | 391 (20.6%) | 79 (21.3%) | 0.767 | – | – | – |
| Dialysis | 241 (12.7%) | 57 (15.4%) | 0.166 | – | – | – |
| Cancer | 552 (29.1%) | 133 (35.8%) | 0.010 | 1.253 | (0.837–1.875) | 0.274 |
| HIV infection | 80 (4.2%) | 20 (5.4%) | 0.315 | – | – | – |
| Charlson score (missing = 1) | 3.00 (1–5) | 4.00 (2–6) | <0.001 | 1.077 | (1.011–1.146) | 0.022 |
| Proton-pump inhibitors (missing = 12) | 891 (47.0%) | 198 (53.4%) | 0.028 | 1.217 | (0.935–1.584) | 0.145 |
| Steroids (missing = 5) | 256 (13.5%) | 87 (23.5%) | <0.001 | 1.766 | (1.265–2.467) | 0.001 |
| Chemotherapy (missing = 2) | 276 (14.5%) | 76 (20.5%) | 0.004 | 0.796 | (0.494–1.284) | 0.350 |
| Monoclonal antibodies (missing = 2) | 70 (3.7%) | 10 (2.7%) | 0.343 | – | – | – |
| Immunotherapy | 154 (8.1%) | 25 (6.7%) | 0.368 | – | – | – |
| HSCT (missing = 22) | 16 (0.8%) | 5 (1.3%) | 0.358 | – | – | – |
| Solid organ transplantation | 22 (1.2%) | 2 (0.5%) | 0.297 | – | – | – |
| Prior use of antibiotic (30 d) (missing = 4) | 1434 (75.6%) | 312 (84.1%) | <0.001 | 1.169 | (0.812–1.681) | 0.401 |
| Use of antibiotics during infection (missing = 8) | 1002 (52.8%) | 259 (69.8%) | <0.001 | 1.351 | (1.003–1.82) | 0.048 |
| Leukopenia [<2000 cells/mm$^3$] (missing = 17) | 170 (9.0%) | 68 (18.3%) | <0.001 | 2.883 | (1.192–6.972) | 0.019 |
| Leukocytosis [>15000 cells/mm$^3$] (missing = 17) | 442 (23.3%) | 147 (39.6%) | <0.001 | 1.851 | (1.383–2.477) | <0.001 |
| Neutropenia [<1500 cells/mm$^3$] (missing = 20) | 218 (11.5%) | 73 (19.7%) | <0.001 | 1.006 | (0.432–2.34) | 0.989 |
| Hypoalbuminemia [<3.5 mg /dL] (missing = 118) | 1456 (76.8%) | 334 (90.0%) | <0.001 | 1.691 | (1.081–2.647) | 0.021 |
| Serum creatinine [>1.5 mg /dL] (missing = 24) | 475 (25.0%) | 138 (37.2%) | <0.001 | 1.609 | (1.191–2.172) | 0.002 |
| Recurrent CDI | 92 (4.8%) | 16 (4.3%) | 0.657 | – | – | – |
| Ileus (missing = 7) | 42 (2.2%) | 25 (6.7%) | <0.001 | 0.914 | (0.466–1.79) | 0.793 |
| Septic shock or abdominal sepsis (missing = 9) | 150 (7.9%) | 154 (41.5%) | <0.001 | 5.873 | (4.313–7.996) | <0.001 |
| Toxic megacolon (missing = 10) | 28 (1.5%) | 30 (8.1%) | <0.001 | 1.773 | (0.906–3.467) | 0.094 |
| SARS-CoV-2 coinfection | 90 (4.7%) | 52 (14.0%) | <0.001 | 2.323 | (1.488–3.627) | <0.001 |

Notes. Median and quartiles 1 and 3 (Q1-Q3) are reported for continuous variables. HIV, human immunodeficiency virus, HSCT, hematopoietic stem cell transplantation, CDI, *Clostridioides difficile* infection.

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**Table 3.** Incidence of *C. difficile* infection from 2016 to 2022 among 16 Mexican hospitals

| | Community-associated CDI | Healthcare-acquired CDI | | | |
|---|---|---|---|---|---|
| | | | Incidence: cases per 10,000 patient days | | |
| Year | Total cases | Total cases | Overall | Private institution | Public institution |
| 2016 | 39 | 271 | 5.51 | – | 5.51 |
| 2017 | 21 | 287 | 5.28 | 0.40 | 5.51 |
| 2018 | 28 | 304 | 4.65 | 1.58 | 5.17 |
| 2019 | 37 | 312 | 4.15 | 1.72 | 4.47 |
| 2020 | 31 | 217 | 3.81 | 2.43 | 4.07 |
| 2021 | 23 | 291 | 4.18 | 2.02 | 4.62 |
| 2022 | 53 | 451 | 5.98 | 3.63 | 6.45 |
| Total | 232 | 2133 | 4.78 | 2.27 | 5.13 |

CDI, *C. difficile* infection.

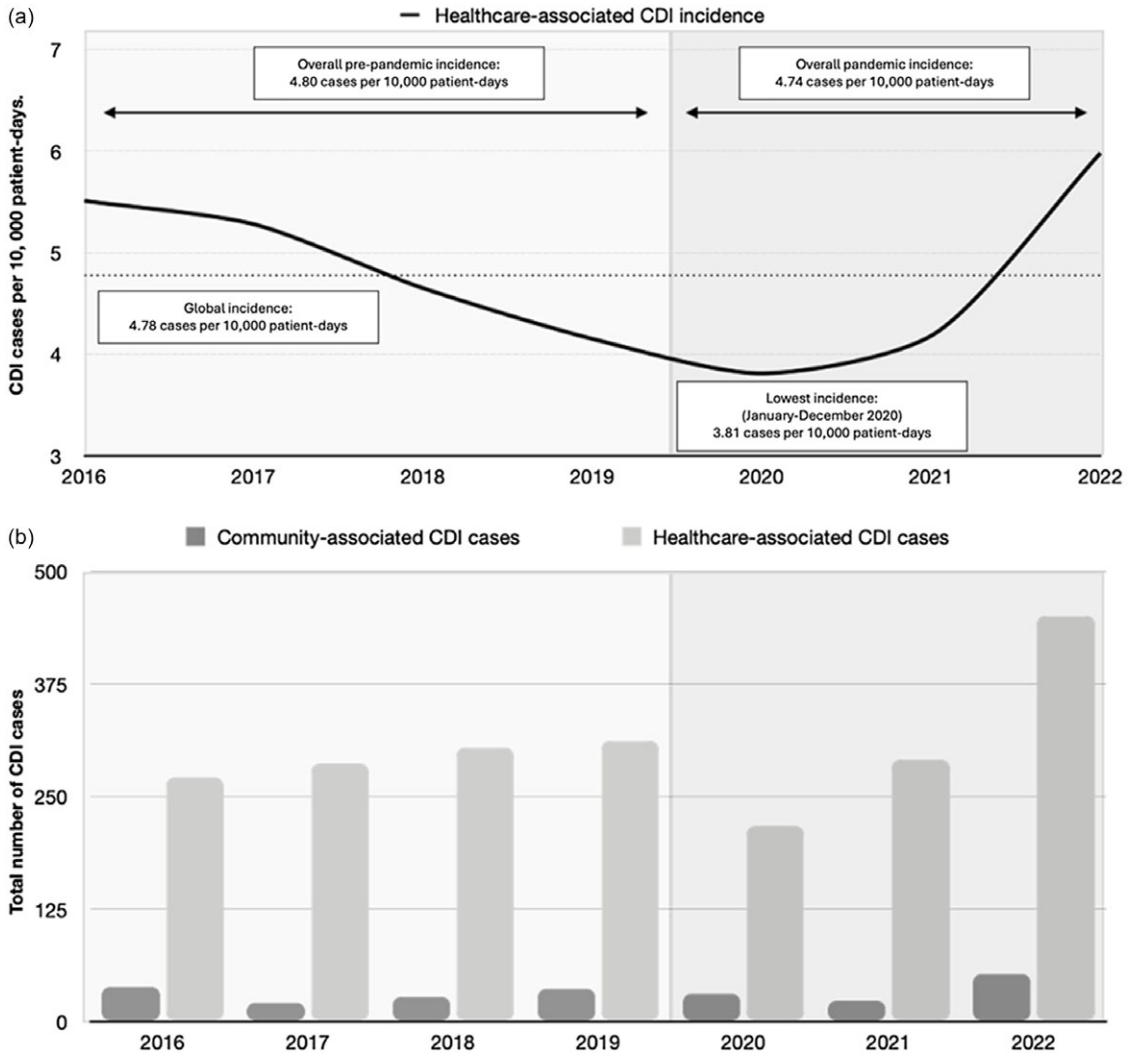


**Figure 1.** Trends of CDI incidence in 16 Mexican institutions during the study period (2016 to 2022). a) Healthcare-associated CDI incidence during the pre-pandemic and pandemic periods; b) total number of healthcare- and community-associated CDI cases during the study period. CDI, *Clostridioides difficile* infection.

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days, respectively, which are higher than the mean CDI rate observed in the study period. High incidence rates were also found at INER (5.19 cases per 10,000 patient days), HRAEO (5.15 cases per 10,000 patient days), and HAC (4.97 cases per 10,000 patient days). Among these institutions, four offer public services, while HAC provides private services.

## Discussion

This study provides an exploratory view of the evolving landscape of CDI in Mexican healthcare institutions. In Latin America, where clinical data on such infections are scarce, this represents the largest compilation of clinical characteristics and outcomes of patients with CDI in our country.

The overall incidence of CDI in our study was 4.78 cases per 10,000 patient days, similar to other reports. For instance, the 2016–2017 European Centers for Disease Control *Clostridioides (Clostridium) difficile* Infections Annual Epidemiological Report recorded a crude incidence of 3.48 cases per 10,000 patient days.[10] Notably, the incidence in tertiary-care hospitals from that European study was 3.87 cases per 10,000 patient days, close to that observed in our study.

Interestingly, we observed a marked difference in CDI rates between public and private institutions. There are several hypotheses associated with this discrepancy, including the type of patients attended to in each center. In our study, institutions with the highest incidence rates were public hospitals focused on treating immunocompromised and cancer populations, who have been previously recognized as high-risk groups for CDI acquisition. Furthermore, public institutions handle a higher volume of patients, which could contribute to the elevated CDI rates observed during the study period. Additionally, differences in surveillance practices between centers may contributed to exacerbate these differences.

In line with the findings of Jorge et al. in Argentina,[11] our study found an HA-CDI rate ranging from 2.8 to 5.2 cases per 10,000 patient days, similar to the rate they reported between 2017 and 2019. Although their patients had a higher overall mortality (19.8% versus 16.3%), their study included a 90-day follow-up period.[11] Compared to other countries, our prevalence appears similar to that reported in studies from Germany, Canada, Spain, and the United Kingdom.[12] Notably, even at its highest peak, our reported incidence was lower than that of countries such as the Republic of Korea, where the CDI reached 7.04 per 10,000 patient days.[13]

An overall decline in the incidence of CDI was observed before the SARS-CoV-2 pandemic, with a progressive decrease in North America noted in U.S. Medicare Advantage enrollees[14] and elderly Medicaid patients.[15] Similarly, our study observed a declining pattern in healthcare-associated CDI incidence before 2020, which quickly returned to pre-pandemic levels by 2022.

In this series, most of our cases were classified as possibly acquired in the healthcare setting, with a small proportion considered community acquired. Although the real setting is difficult to corroborate due to the heterogeneity in incubation periods, we hypothesize that the CDI community burden is underrepresented in our country since private practitioners can treat diarrheic diseases empirically without testing or confirmation of the disease. Furthermore, most of the included institutions in our study are referral centers, which decreases the probability of capturing community cases, except for those individuals with follow-up for existing chronic or acute diseases that require special medical attention.

Recurrent *C. difficile* infection poses a significant clinical challenge, with recurrence rates varying across studies. Our study found a recurrence rate of 5%, lower than rates reported elsewhere. CDI typically recurs in approximately 25% of patients after initial treatment, which can rise to 40%–65% among patients with a previous history of recurrent disease.[16,17] However, Latin American studies have shown recurrence rates significantly lower than those reported elsewhere, such as 8.5%, comparable to our study.[11] This trend aligns with findings from other regions, where recurrence rates range from 3% to 6.8%,[18,19] with specific studies reporting rates of 3.4% in Singapore[20] and 8.9% in Taiwan.[21]

Certain strains, such as BI/NAP1/027, have been associated with a high risk of recurrence. Although we observed a high prevalence of BI/NAP1/027 in our cohort, this finding was based on a small number of patients who underwent GeneXpert testing. The use of this assay may have been biased by the severity of the disease, increasing the likelihood of detecting a positive BI/NAP1/027 strain and potentially overestimating its prevalence. Similarly, the possible inclusion of PCR-positive individuals as part of the CDI case definition could have partially contributed to the low recurrence rate found in our analysis due to the detection of colonized patients.

In our study context, it is important to highlight that although some patients had close primary follow-up at included institutes, the majority could have returned to their primary care providers in case of re-initiation of diarrheal symptoms. This could have made it difficult to access testing and reporting, leading to an underrepresentation of the actual CDI recurrence burden.

Mortality in our study was assessed using all-cause mortality, which was recorded at 16%. This figure falls within the reported range of 3%–30%, varying significantly due to the clinical characteristics of the patients and the fact that CDI often occurs as part of a complex clinical scenario.[22–24] We identified several variables associated with a fatal outcome, including specific cytopenias and several comorbidities, along with other previously reported severity markers, such as leukocytosis, albumin and creatinine levels, and septic shock.[25–27] Of note, patients in our cohort with concurrent SARS-CoV-2 infection were more likely to have a fatal outcome, consistent with findings from other studies where COVID-19 has been shown to increase mortality in patients with CDI.[28]

We acknowledge certain limitations in our study. For instance, the lack of a clear CDI case definition may have led to an overestimation of its incidence. In this context, patients with positive PCR results could include both true CDI cases and those colonized. Although several algorithms have attempted to address this issue by employing sequential diagnostic tests, this approach has not been universally accepted. Despite this, we believe that understanding the prevalence of PCR-positive patients, regardless of their symptomatic status, remains crucial to assessing transmission dynamics and disease nosocomial burden.

Similarly, classification inaccuracies regarding the acquisition settings (community vs healthcare-associated cases) could have occurred due to potential information bias inherent to the retrospective nature of this study and the high heterogeneity in the incubation and colonization periods of the disease. Additionally, CDI incidence could have been affected by differences in diagnosis rates among the included centers, as not all had active surveillance during the evaluated period.

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On the other hand, we could not assess epidemiological ribotypes across participating hospitals, as no standardized evaluation was used, and assessments were conducted solely for research purposes, as documented in previous studies[29–31]. Finally, although we included incidence over a 7-year period, we were only able to recover data for 79% of the time frame, as information from some centers was unavailable.

In conclusion, the incidence of CDI was similar throughout the study period, with the lowest and highest incidence in 2020 and 2022, respectively. Most cases were healthcare-associated, and public hospitals bore the greatest disease burden. CDI risk factors were similar to those previously described, with a high use of antibiotics. The 30-day death rate was 16% with a CDI recurrence rate of 5%; SARS-CoV-2 infection was associated with an increased risk of death.

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