International Journal of Infectious Diseases 164 (2026) 108315

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Global trends in *Clostridioides difficile* infection–related mortality, 2001-2023: An observational study

Hideharu Hagiya[1], Yoshito Nishimura[2], Ko Harada[3], Maki Yamamoto[4], Tatsuaki Takeda[5], Quynh Thi Vu[4,6], Keith Pardillada Belangoy[4], Hanane Ouddoud[4], Yoshito Zamami[7], Toshihiro Koyama[4,*]

[1] *Department of Infectious Diseases, Okayama University Hospital, Okayama, Japan*
[2] *Division of Hematology/Oncology, Mayo Clinic, Rochester, Minnesota, USA*
[3] *Brookdale Department of Geriatrics and Palliative Medicine, Icahn School of Medicine at Mount Sinai, New York, New York, USA*
[4] *Department of Health Data Science, Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama University, Okayama, Japan*
[5] *Department of Education and Research Centre for Clinical Pharmacy, Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama University, Okayama, Japan*
[6] *Department of Pharmaceutics and Pharmaceutical Technology, Faculty of Pharmacy, Haiphong University of Medicine and Pharmacy, Haiphong, Vietnam*
[7] *Department of Pharmacy, Okayama University Hospital, Okayama, Japan*

ARTICLE INFO

Article history:
Received 16 October 2025
Revised 4 December 2025
Accepted 4 December 2025

Keywords:
Aging
Locally weighted regression model
Infection
Clostridioides difficile
Disparity

ABSTRACT

Objectives: *Clostridioides difficile* infection (CDI) is a major public health concern, particularly in aging populations. The aim of this study was to evaluate global trends in CDI-related mortality to inform sustainable and cost-effective management strategies.

Methods: We conducted an observational study using mortality data from the World Health Organization (WHO) database spanning 2001 to 2023. Sixty-three countries with satisfactory data quality and at least 12 years of data between 2001 and 2023 were included. Crude and age-standardized CDI-related mortality rates per 1,000,000 individuals were calculated after stratification by age, sex, WHO region, and sociodemographic index (SDI). Global trends were analyzed using locally weighted regression.

Results: The global age-standardized CDI-related mortality rate was 0.76 per 1,000,000 individuals in 2001, peaked at 4.08 in 2010, and declined to 2.44 in 2023. The most notable downward trends were observed in the Americas and high-SDI countries. These improvements may reflect the impact of multidisciplinary efforts in CDI prevention and management.

Conclusions: Although CDI-related mortality has declined globally over the past decade, the disease remains a significant threat, especially in older populations. Ongoing global efforts are essential to further reduce CDI-related deaths.

Introduction

Clostridioides difficile, formerly known as *Clostridium difficile*, is a spore-forming, toxin-producing, ubiquitous enteropathogen typically isolated from hospitalized patients with diarrhea and pseudomembranous colitis [1]. With its robust and pathogenic characteristics, *C. difficile* infection (CDI) constitutes a public healthcare burden, mostly in industrialized Western countries [2,3]. CDI, a representative hospital-acquired infection, is possibly involved in 10-25% of all antibiotic-associated diarrhea cases [4], imposes a substantial financial burden for management [5], is associated with high rates of recurrence and mortality [6,7], and can cause large hospital outbreaks [8], with a case-fatality rate of ≥10% [9]. Multidisciplinary expert panels have established comprehensive clinical guidelines to improve the management of patients with CDI [10,11].

The global CDI incidence has increased over the last two decades. In the United Kingdom and Finland, antimicrobial stewardship campaigns have successfully reduced the CDI incidence [9,12]. However, CDI remains a major healthcare issue in many countries, particularly in North America and Europe [13–15]. The CDI incidence doubled from 2001 to 2010 in the United States [16] and in Australia, with an annual incidence exceeding 24%: from 3.25 to 4.03 per 10,000 patient-days in 2011 and 2012, respectively

* Corresponding author: Tel.: +81-86-235-6585; fax: +81-86-235-6585.
E-mail address: koyam-t@cc.okayama-u.ac.jp (T. Koyama).

https://doi.org/10.1016/j.ijid.2025.108315

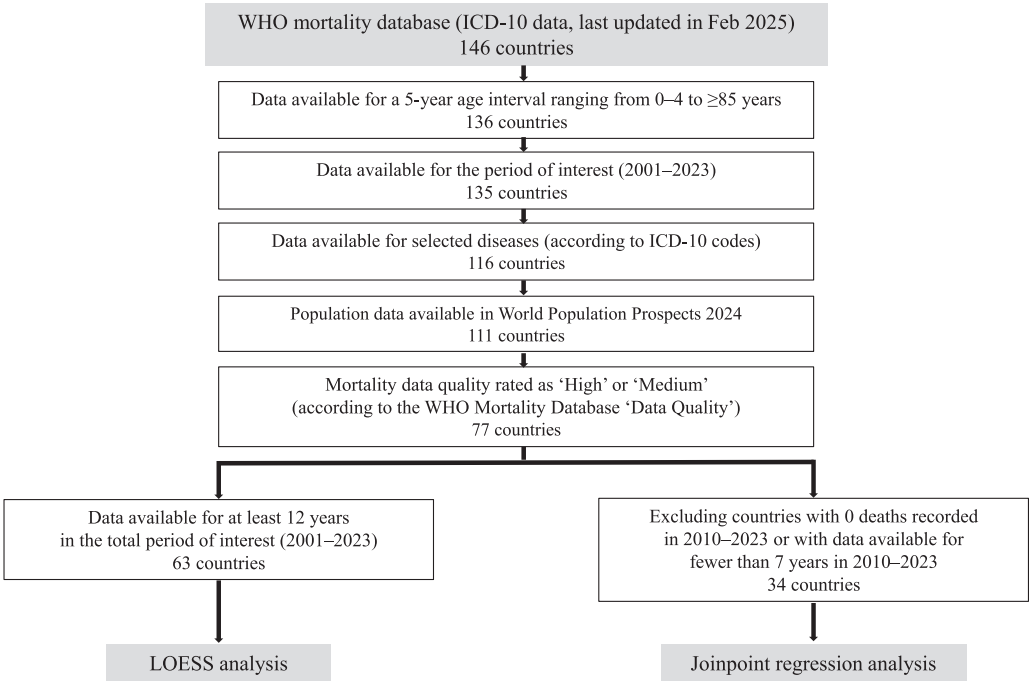

Figure 1. Flow of the country-selection process.

[17]. A newly emerged epidemic strain, *C. difficile* polymerase chain reaction (PCR) ribotype 027, has been strongly associated with increased morbidity and mortality in these regions [18,19]. In Asian countries, the incidence has been lower; however, a nationwide study in South Korea indicated an increasing trend, with an annual increase of 39% between 2004 and 2008 [20]. Furthermore, a population-based observational study in Hong Kong uncovered an increasing incidence: from 15.4 to 36.3 cases per 100,000 persons from 2006 to 2014, respectively, with an annual increase of 26% [21]. In Japan, no nationwide study has been conducted on CDI prevalence, although a recent systematic review estimated its incidence and prevalence to be 0.8-4.71 per 10,000 patient-days and 0.3-5.5 per 1000 patients, respectively [22].

The current global burden of developing sustainable and cost-effective management methods for patients with CDI remains unclear. Thus, we aimed to determine the recent trends in CDI-related mortality on a global scale.

Methods

Data sources

For this observational study, we accessed the World Health Organization (WHO) Mortality Database (last update, February 1, 2025) [23], which contains the number of deaths of interest by country, year, sex, and age group, recorded in national vital registration systems since 1950. The underlying cause of death is reported according to the International Statistical Classification of Diseases and Related Health Problems (ICD) criteria (Versions 7-10). From this extensive database, which is annually reported by the public registration systems of each WHO member country, mortality data attributed to CDI were extracted. CDI is defined with ICD-10 code A04.7 as enterocolitis due to *C. difficile* according to the ICD-10 criteria [24].

Statistical analysis and data processing

Figure 1 depicts the flow of statistical analysis. Countries were included if they had data available for a 5-year age interval ranging from 0-4 to ≥85 years for the period 2001-2023, and vital CDI registration data were extracted. Vital registration data quality was categorized as high, medium, or low according to the latest usability estimates from 2008 to 2019, which were ≥80%, 60 to <80%, or <60%, respectively [25]. The WHO uses a metric termed "usability" to evaluate the overall quality of national vital registration data: "Usability is defined as the percentage of all deaths which are registered with meaningful cause-of-death information" [25]. It was calculated by multiplying completeness (the proportion of registered deaths in a country or geographic area with a medically certified cause of death) by the proportion of registered deaths that have been coded with a meaningful cause of death. Usability scores were obtained from the WHO website [25]. To enhance the robustness of our analysis, countries with mortality data quality rated as "high" or "medium" were deemed eligible for inclusion in the study. Data available for at least 12 years during the period of interest were included in the trend analysis.

The crude CDI mortality rate was calculated by dividing the number of CDI-related deaths by the corresponding population size. Mid-year population data for each nation were obtained from the United Nations World Population Prospects 2024 [26]. If countries reported no deaths due to CDI, these deaths were considered true zeros, as previously described [27]. To improve comparability among countries and exclude the effect of different age distributions during the study period, the new WHO World Standard Population distribution was used to calculate age-standardized mortality rates [28]. The mortality rate in this study is presented as the number of deaths per 1,000,000 people.

A smoothed curve of long-term global mortality rates was created using a locally weighted regression (LOESS) model [29], weighted using the population of each selected country on the basis of the available data [27,30]. LOESS-smoothed mortality rates, along with 95% confidence intervals (CIs), were calculated, and mortality rate trends were stratified using the WHO country group [31] and the sociodemographic index (SDI) for the year of 2021 [32]. After excluding countries where the number of deaths was recorded as zero in any of the study years and those that did not have data for at least 7 years between 2010 and 2023, joinpoint regression analysis was applied to estimate the average an-

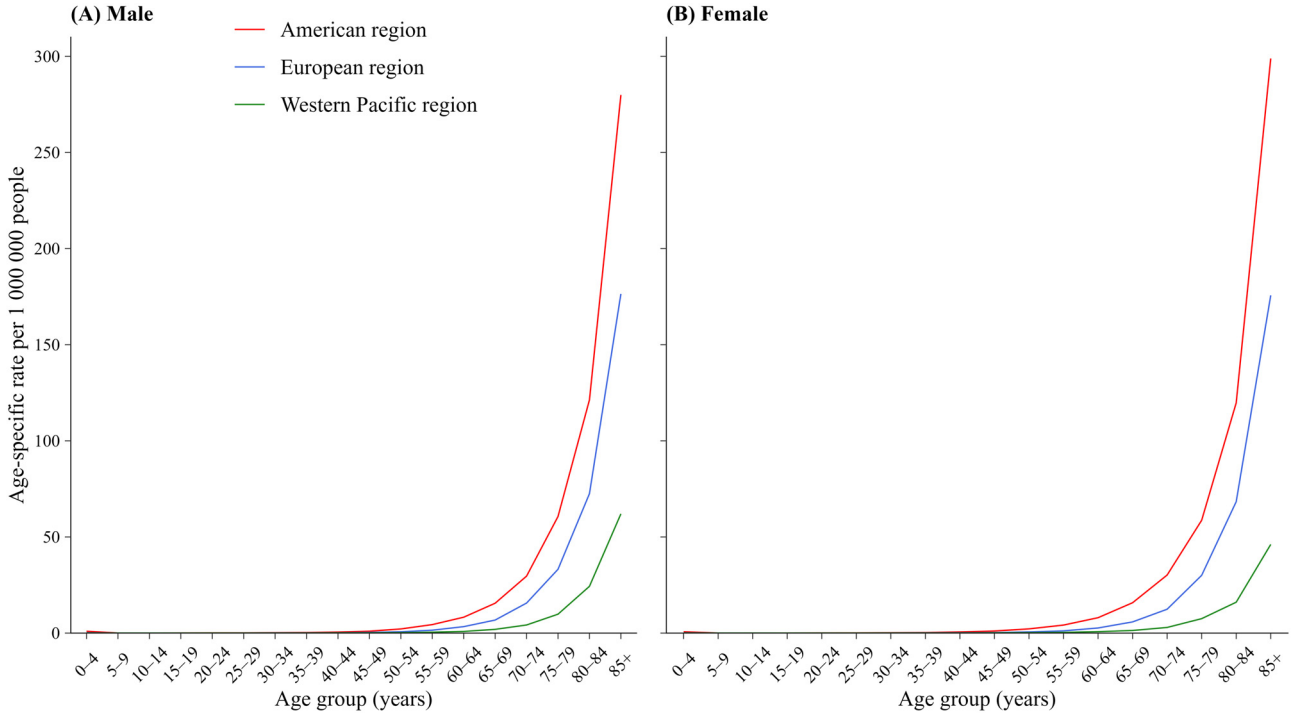

Figure 2. Age distribution for crude *Clostridioides difficile* infection–related mortality per 1,000,000 individuals from 2001 to 2023 by sex and WHO region classification. WHO, World Health Organization.

nual percent change (AAPC) in the age-standardized mortality rates using the Joinpoint Regression Program, version 5.4.0.0, April 2025 (Statistical Research and Applications Branch, Surveillance Research Program, National Cancer Institute) [33]. This model has the advantage of being able to identify the year in which marked changes in trends occur and can estimate the magnitude of the increase or decrease in each linear slope by calculating the annual percentage change.

Data processing and aggregation were performed using Microsoft Access® 2013 (Microsoft Corporation, Redmond, WA, USA). R software (R version 4.5.0, R Foundation for Statistical Computing, Vienna, Austria) was used for statistical analyses in this study. In all analyses, statistical significance was set at a *P*-value of <0.05.

Ethics approval

Ethics approval was obtained from the Institutional Review Board of the Okayama University Hospital (Approval number 2007-011). The requirement for informed consent was waived because this was a retrospective analysis of publicly accessible anonymized data.

Results

Data from 63 eligible countries were analyzed. Of these, 30 were from the European region, 27 from the Americas, four from the Western Pacific region, and two from other WHO regions. For the joinpoint analysis, 34 countries were included on the basis of our inclusion criteria. Supplementary Table S1 shows the lists of eligible countries based on the WHO regional classification and SDI.

During the last two decades (2001-2023), the total number of CDI-related deaths in these countries was 246,377. Male patients accounted for 39.5% (male:female = 97,585:148,792) of all cases, although their proportion decreased with age (Supplementary Table S2). Deaths among people aged ≥60 years accounted for >95% (233,672/246,377) of all CDI-related deaths. The crude CDI-related mortality rates for both sexes increased for those in their 50s in the Americas (Figure 2). In European countries, crude CDI-related mortality rates showed an upward trend beginning in the 60-year-old age group. In Western Pacific countries, the clinical burden of CDI appeared to have a limited impact, affecting the older population, including those in their 70s and 80s.

Figure 3 shows the trends in crude and age-standardized CDI-related mortality rates for all 63 countries over time. Supplementary Tables S3 and S4 show the estimated data for the LOESS model. From the early 2000s, the number of CDI-related deaths increased globally, with a peak crude mortality rate of 8.88 per 1,000,000 individuals (95% CI: 7.90-9.87) in 2013. This rate subsequently declined, reaching 5.61 per 1,000,000 individuals (95% CI: 3.30-7.92) in 2023. The age-standardized mortality rate showed a similar trend, with a peak of 4.08 per 1,000,000 individuals (95% CI: 3.63-4.52) in 2010. Supplementary Figure S1 shows the trends in age-standardized mortality rates by sex. The LOESS estimates of the male and female mortality rates peaked in 2012 (4.18; 95% CI: 3.73-4.62) and 2010 (4.02; 95% CI: 3.57-4.47) per 1,000,000 individuals, respectively, and both showed similar declining trends until the end of the study period (Supplementary Tables S5 and S6).

Figure 4 shows the regional differences in trend changes and AAPC of age-standardized CDI-related mortality rates. Supplementary Table S7 presents the detailed data. The LOESS estimate of the CDI-related mortality rate in 2001 in the European region was 0.63 (95% CI: −0.54 to 1.80) per 1,000,000 individuals, which was lower than that in the Americas (1.09; 95% CI: −0.32 to 2.50). The CDI-related mortality rate in the European region plateaued at approximately 3.0 per 1,000,000 individuals in the late 2000s, retaining this trend until 2023. In contrast, the CDI-related mortality rate in the Americas showed a remarkable increase in the initial 10 years, peaking at approximately 5.50 per 1,000,000 people in 2011. Thereafter, the LOESS estimate decreased markedly to 3.01 per 1,000,000 people by the end of the study period. The Western Pacific region showed lower rates than these regions, with a peak of 1.36 (95% CI: 1.15-1.57) per 1,000,000 individuals in 2013. Among European

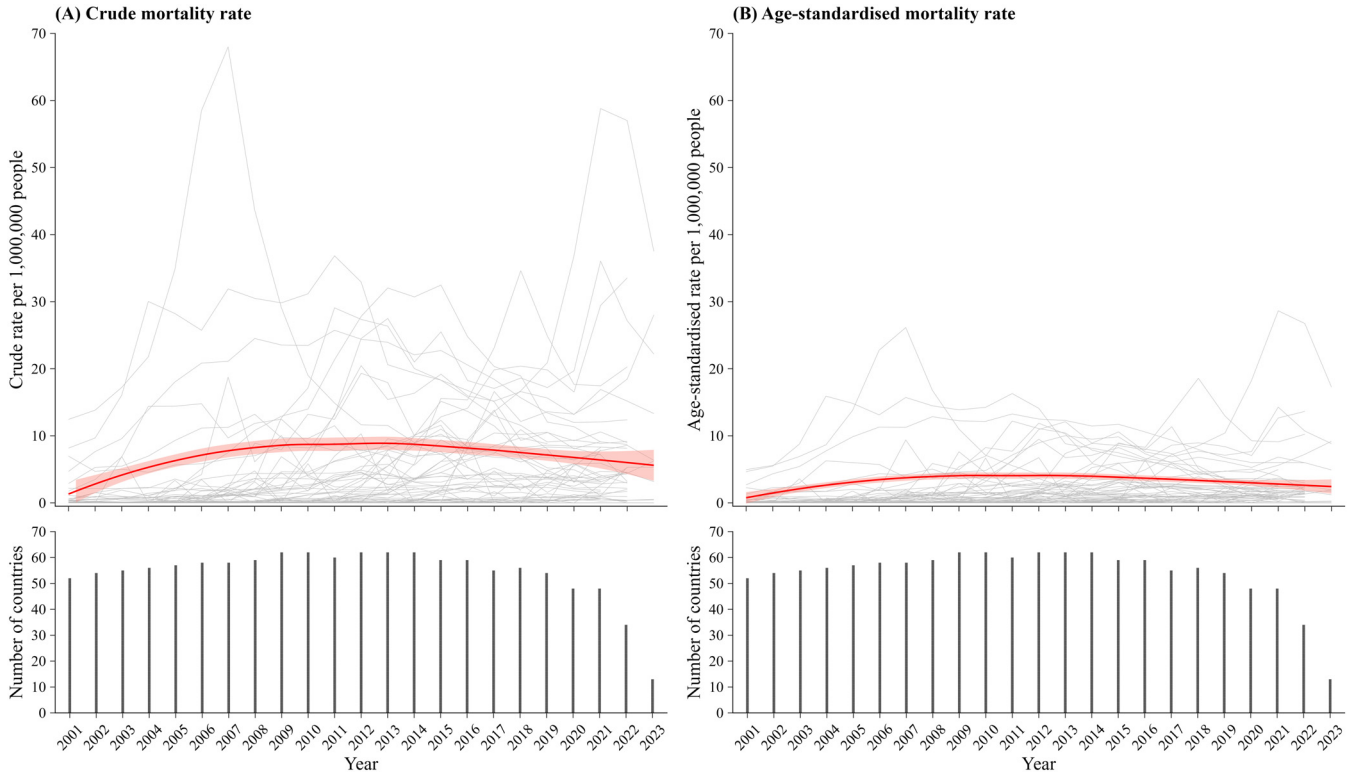

Figure 3. Trends in crude and age-standardized *Clostridioides difficile* infection–related mortality per 1,000,000 individuals for all 63 countries from 2001 to 2023. (a) Crude mortality rate, (b) age-standardized mortality rate. Locally weighted regression rates (red line) with 95% confidence intervals (light red shadows) are shown.

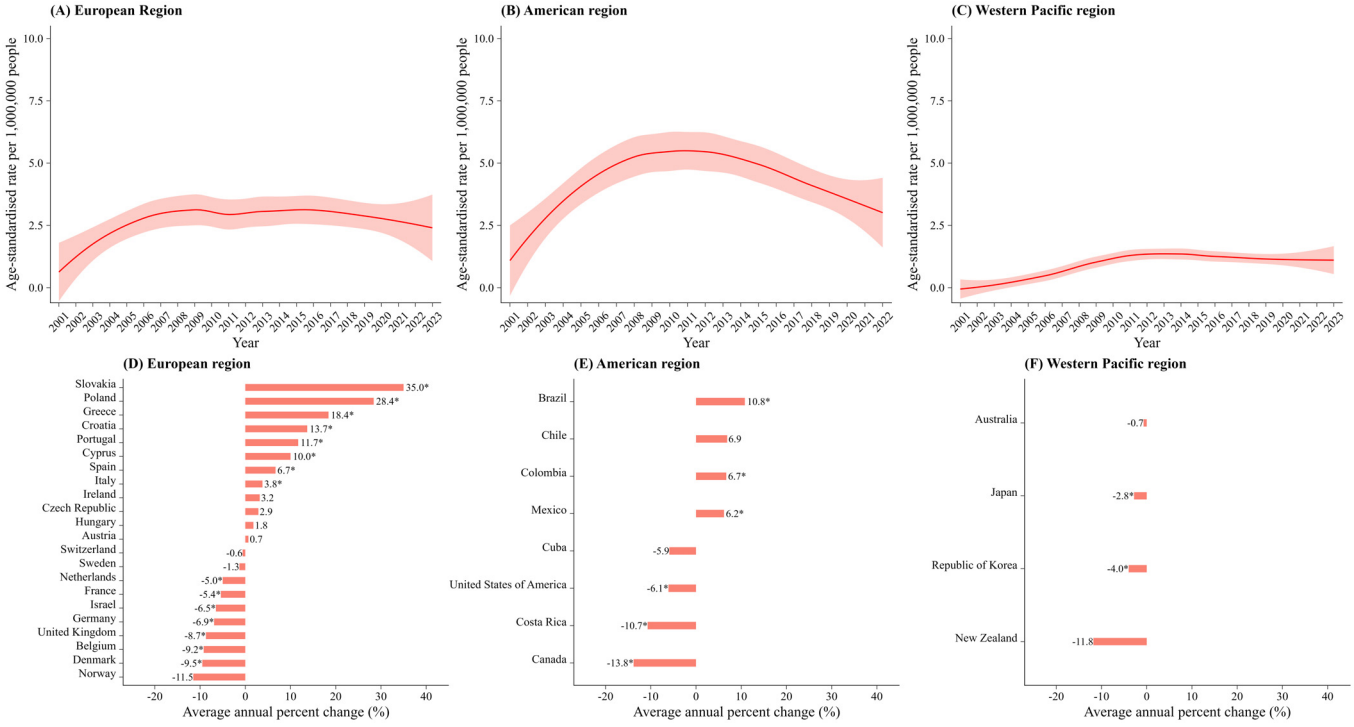

Figure 4. Trends in age-standardized *Clostridioides difficile* infection–related mortality rate by WHO regional classification. Locally weighted regression rates (red line) with 95% confidence intervals (light red shadow) during 2001-2023 are shown for (a) Europe, (b) Americas, and (c) Western Pacific. The average annual percentage change in age-standardized rates during 2010-2023 for each country is shown for (d) Europe, (e) Americas, and (f) Western Pacific. *Significantly different from zero (P <0.05).
WHO, World Health Organization.

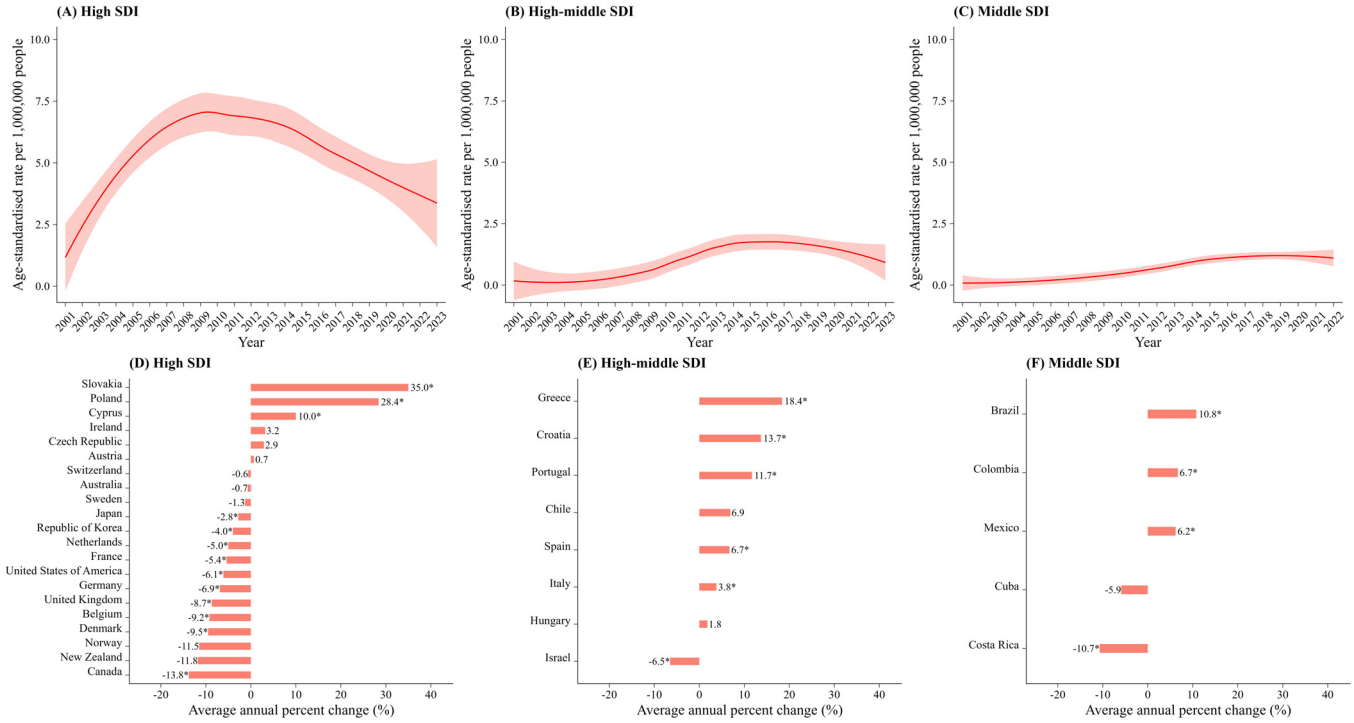

Figure 5. Trends in age-standardized *Clostridioides difficile* infection–related mortality rate by SDI group. Locally weighted regression rates (red line) with 95% confidence intervals (light red shadow) during 2001-2023 are shown for groups of countries with (a) high SDI, (b) high-middle SDI, and (c) middle SDI. The average annual percentage change in age-standardized rates during 2010-2023 for each country with (d) high SDI, (e) high-middle SDI, and (f) middle SDI. *Significantly different from zero (P <0.05). SDI, sociodemographic index.

countries, Slovakia (35.0%), Poland (28.4%), Greece (18.4%), Croatia (13.7%), and Portugal (11.7%) had high AAPC values, suggesting an increasing trend in CDI-related deaths, whereas marked decreases in AAPC were observed in Norway (−11.5%), Denmark (−9.5%), Belgium (−9.2%), and the United Kingdom (−8.7%). Among countries in the Americas, the AAPC of Brazil (10.8%) was the highest, whereas Canada (−13.8%), Costa Rica (−10.7%), the United States (−6.1%) and Cuba (−5.9%) showed downward trends in AAPC. In the Western Pacific, New Zealand indicated a notable decline in AAPC (−11.8%).

Figure 5 shows the age-standardized CDI-related mortality rate data stratified using the SDI, and Supplementary Table S8 shows the detailed data. The LOESS estimate of the CDI-related mortality rate in the high-SDI group showed a sharp increase during the 2000s, peaking at 7.03 (95% CI: 6.24-7.83) per 1,000,000 individuals in 2009. This unfavorable condition subsequently exhibited a clear downward trend. The high-middle SDI group increased moderately, reaching a peak of 1.76 (95% CI: 1.44-2.08) in 2016, and then decreased to 0.92 (95% CI: 0.18-1.66) in 2023. The middle SDI group showed a modest but steady upward trend. The joinpoint regression model indicated that AAPC was highest in Slovakia and lowest in Canada among the high-SDI countries. Among the high-middle SDI countries, many countries (Greece, Croatia, Portugal, Chile, Spain, Italy, and Hungary) showed an increased AAPC, except Israel (−6.5%). AAPC varied across nations in the middle SDI countries.

Discussion

This study demonstrated global trends and differences in the clinical burden of CDI over the last two decades. Higher numbers of deaths among people aged ≥60 years suggest a greater disease burden in aging societies. The data indicate that CDI needs to be considered a fatal geriatric disease, requiring the exploration of multifaceted solutions.

The data demonstrated high CDI-related mortality among older populations, particularly those in the Americas and European regions [34]. According to a multicenter study in Canada, the risk of CDI increased by 2% with each additional year of age, suggesting that aging is a consistent risk factor for CDI [35]. In Hong Kong, the number of CDI cases in the older population increased threefold between 2006 and 2014 [21]. A previous review reported that higher mortality was associated with aging, with 9.4% and 13.5% mortality rates among those aged 71-80 and >80 years, respectively [36]. Developed countries have already become, or are about to become, aging societies [37]; thus, this age distribution of the disease is likely to have a marked public health impact worldwide.

The increasing incidence of community-associated CDI, which can affect anyone without any underlying disease, is of great concern [38,39]. After the acute phase, a CDI episode subsequently continues as a debilitating and devastating condition, adversely affecting patients' physical, psychological, social, and professional quality of life [40]. Approximately one-third of CDI cases in North America [41], Europe [42], and Australia [17] were developed as community-onset cases more than a decade ago. The circulation of *C. difficile* strains within a "One Health" framework might explain disease progression [43]. Multidisciplinary efforts have demonstrated its broadened ecological prevalence beyond health care systems, including the presence of this organism in food, wastewater, soil, compost, manure, livestock, and air [44,45]. This results in spore contamination of foods consumed daily [46] and subsequently contributes to a persistent community source of *C. difficile*. Certain genetic lineages, including *C. difficile* sequence type 11 and PCR ribotypes 078 and 014, are known to transfer between humans, animals, and the environment [47]. CDI is increasingly found in older people living in nursing homes [48] and those living in the community [49]. This observation indicates the increasing burden of and need for management of CDI outside hospitals in an aging global population. As the first step, further promotion of proper

antimicrobial prescription is indispensable to reduce the risk of CDI in the community [50].

This study had limitations that warrant consideration. Firstly, underreporting of the disease is a concern. The data were derived from the WHO Mortality Database, which comprises data obtained from death certificates of each country. Previous studies have suggested that the final diagnosis of CDI indicated on death certificates is underestimated [51,52]. Secondly, detection bias could have affected the results. The accuracy of diagnostic testing methods has improved over the last two decades, but misdiagnosis was possible, especially during the first part of the study period. However, this could not be reviewed or adjusted for because of the absence of clinical data. Thirdly, the underdiagnosis of the disease is a factor to be considered, even in recent years [53]. According to a multicenter point-prevalence study, one-fourth of true CDI cases were undiagnosed in European countries in the early 2010s [54]. Underdiagnosis is common, particularly in outpatient settings, owing to the absence of clinical suspicion. Another point-prevalence study in 2018 reported that over three times as many undetected CDI cases occurred in the community compared with nosocomial settings [55]. The clinical impact of community-onset CDI has increased; however, our data lacked information on disease onset. A multimodal training program might be effective in facilitating appropriate diagnosis and decreasing the underdiagnosis of CDI [56]. Fourth, we observed that certain countries experienced temporary increases and decreases in their mortality rates over the past two decades. Such fluctuations may result from short-term outbreaks or shifts in diagnostic or therapeutic practices within specific countries, although our inquiry did not identify any specific events or concrete causes underlying these spikes. Finally, data accessibility varied across WHO regions, with countries in the Americas and Europe accounting for most of the available data. Because of the poor quality of the data, only a few countries from the Western Pacific and other regions were included, which could have resulted in an underestimation of mortality in these regions. Nevertheless, we recognize that data quality varies both across countries and within countries over time.

In conclusion, continuous monitoring of the prevalence and mortality of CDI should be conducted using a global epidemiological approach. Improvements in health care policy for CDI management strategies should be highlighted and implemented.

Declaration of competing interest

The authors have no competing interests to declare.

Funding

This work was supported by the Pfizer Health Research Foundation; Ohyama Health Foundation, Inc.; and the Japan Society for the Promotion of Science (KAKENHI, grant number 22K10415).

Ethical approval statement

Ethics approval was obtained from the Institutional Review Board of the Okayama University Hospital (Approval number 2007-011). The requirement for informed consent was waived because this was a retrospective analysis of publicly accessible anonymized data.

Acknowledgment

We would like to express our heartfelt gratitude to the WHO for providing the data source. We take full responsibility for the analysis, interpretation, and conclusions of this study

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2025.108315.

References

[1] Vitiello A, Sabbatucci M, Zovi A, Salzano A, Ponzo A, Boccellino M. Advances in therapeutic strategies for the management of Clostridioides difficile infection. *J Clin Med* 2024;**13**:1331. doi:10.3390/jcm13051331.

[2] Clements ACA, Magalhães RJS, Tatem AJ, Paterson DL, Riley TV. Clostridium difficile PCR ribotype 027: assessing the risks of further worldwide spread. *Lancet Infect Dis* 2010;**10**:395–404. doi:10.1016/S1473-3099(10)70080-3.

[3] Finn E, Andersson FL, Madin-Warburton M. Burden of Clostridioides difficile infection (CDI) – a systematic review of the epidemiology of primary and recurrent CDI. *BMC Infect Dis* 2021;**21**:456. doi:10.1186/s12879-021-06147-y.

[4] Badger VO, Ledeboer NA, Graham MB, Edmiston CE. Clostridium difficile: epidemiology, pathogenesis, management, and prevention of a recalcitrant healthcare-associated pathogen. *JPEN J Parenter Enteral Nutr* 2012;**36**:645–62. doi:10.1177/0148607112446703.

[5] Wingen-Heimann SM, Davies K, Viprey VF, Davis G, Wilcox MH, Vehreschild MJGT, et al. Clostridioides difficile infection (CDI): a pan-European multi-center cost and resource utilization study, results from the combatting bacterial resistance in Europe CDI (COMBACTE-CDI). *Clin Microbiol Infect* 2023;**29**:651 e1–8. doi:10.1016/j.cmi.2022.12.019.

[6] Lessa FC, Mu Y, Bamberg WM, Beldavs ZG, Dumyati GK, Dunn JR, et al. Burden of Clostridium difficile infection in the United States. *N Engl J Med* 2015;**372**:825–34. doi:10.1056/NEJMoa1408913.

[7] Granata G, Petrosillo N, Adamoli L, Bartoletti M, Bartoloni A, Basile G, et al. Prospective study on incidence, risk factors and outcome of recurrent Clostridioides difficile infections. *J Clin Med* 2021;**10**:1127. doi:10.3390/jcm10051127.

[8] Magnusson C, Mernelius S, Bengnér M, Norén T, Serrander L, Forshell S, et al. Characterization of a Clostridioides difficile outbreak caused by PCR ribotype 046, associated with increased mortality. *Emerg Microbes Infect* 2022;**11**:850–9. doi:10.1080/22221751.2022.2049981.

[9] Kuijper EJ, Coignard B, Tüll P. EUROPEAN SOCIETY OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES Study Group for Clostridium Difficile, EU Member States, European Centre for Disease Prevention and Control. Emergence of Clostridium difficile-associated disease in North America and Europe. *Clin Microbiol Infect* 2006;**12**:2–18. doi:10.1111/j.1469-0691.2006.01580.x.

[10] Van Prehn J, Reigadas E, Vogelzang EH, Bouza E, Hristea A, Guery B, et al. European Society of Clinical Microbiology and Infectious Diseases: 2021 Update on the treatment guidance document for Clostridioides difficile infection in adults. *Clin Microbiol Infect* 2021;**27**:S1–21. doi:10.1016/j.cmi.2021.09.038.

[11] Johnson S, Lavergne V, Skinner AM, Gonzales-Luna AJ, Garey KW, Kelly CP, et al. Clinical practice guideline by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA): 2021 focused update guidelines on management of Clostridioides difficile infection in adults. *Clin Infect Dis* 2021;**73**:755–7. doi:10.1093/cid/ciab718.

[12] Dingle KE, Didelot X, Quan TP, Eyre DW, Stoesser N, Golubchik T, et al. Effects of control interventions on Clostridium difficile infection in England: an observational study. *Lancet Infect Dis* 2017;**17**:411–21. doi:10.1016/S1473-3099(16)30514-X.

[13] Kuijper EJ, Barbut F, Brazier JS, Kleinkauf N, Eckmanns T, Lambert ML, et al. Update of Clostridium difficile infection due to PCR ribotype 027 in Europe, 2008. *Euro Surveill* 2008;**13**:18942.

[14] Jones AM, Kuijper EJ, Wilcox MH. Clostridium difficile: a European perspective. *J Infect* 2013;**66**:115–28. doi:10.1016/j.jinf.2012.10.019.

[15] Warny M, Pepin J, Fang A, Killgore G, Thompson A, Brazier J, et al. Toxin production by an emerging strain of Clostridium difficile associated with outbreaks of severe disease in North America and Europe. *Lancet* 2005;**366**:1079–84. doi:10.1016/S0140-6736(05)67420-X.

[16] Reveles KR, Lee GC, Boyd NK, Frei CR. The rise in Clostridium difficile infection incidence among hospitalized adults in the United States: 2001–2010. *Am J Infect Control* 2014;**42**:1028–32. doi:10.1016/j.ajic.2014.06.011.

[17] Slimings C, Armstrong P, Beckingham WD, Bull AL, Hall L, Kennedy KJ, et al. Increasing incidence of Clostridium difficile infection, Australia, 2011–2012. *Med J Aust* 2014;**200**:272–6. doi:10.5694/mja13.11153.

[18] Loo VG, Poirier L, Miller MA, Oughton M, Libman MD, Michaud S, et al. A predominantly clonal multi-institutional outbreak of Clostridium difficile–associated diarrhea with high morbidity and mortality. *N Engl J Med* 2005;**353**:2442–9. doi:10.1056/NEJMoa051639.

[19] Kuijper EJ, van den Berg RJ, Debast S, Visser CE, Veenendaal D, Troelstra A, et al. Clostridium difficile ribotype 027, toxinotype III, the Netherlands. *Emerg Infect Dis* 2006;**12**:827–30. doi:10.3201/eid1205.051350.

[20] Kim YS, Han DS, Kim YH, Kim WH, Kim JS, Kim HS, et al. Incidence and clinical features of Clostridium difficile infection in Korea: a nationwide study. *Epidemiol Infect* 2013;**141**:189–94. doi:10.1017/S0950268812000581.

[21] Ho J, Dai RZW, Kwong TNY, Wang X, Zhang L, Ip M, et al. Disease burden of Clostridium difficile infections in adults, Hong Kong, China, 2006–2014. *Emerg Infect Dis* 2017;**23**:1671–9. doi:10.3201/eid2310.170797.

[22] Riley TV, Kimura T. The epidemiology of Clostridium difficile infection in Japan: a systematic review. *Infect Dis Ther* 2018;**7**:39–70. doi:10.1007/s40121-018-0186-1.
[23] World Health Organization. WHO Mortality Database (the Last Update 1 February 2025), https://www.who.int/data/data-collection-tools/who-mortality-database#:~:text=The%20WHO%20Mortality%20Database%20is,death%20as%20reported%20by%20countries; 2025 [accessed 01 April 2025].
[24] World Health Organization. International Statistical Classification of Diseases and Related Health Problems. 10th revision, https://icd.who.int/browse10/2019/en; 2019 [accessed 01 March 2024].
[25] World Health Organization. Data quality, https://platform.who.int/mortality/about/data-quality; n.d [accessed 01 March 2024].
[26] United Nations, Department of Economic and Social Affairs, Population Division. World Population Prospects 2024, https://www.un.org/development/desa/pd/world-population-prospects; 2024 [accessed 01 March 2025].
[27] Ebmeier S, Thayabaran D, Braithwaite I, Bénamara C, Weatherall M, Beasley R. Trends in international asthma mortality: analysis of data from the WHO mortality database from 46 countries (1993–2012). *Lancet* 2017;**390**:935–45. doi:10.1016/S0140-6736(17)31448-4.
[28] Ahmad OB, Boschi-Pinto C, Lopez AD, Murray CJ, Lozano R, Inoue M. Age standardization of rates: a new WHO standard, https://cdn.who.int/media/docs/default-source/gho-documents/global-health-estimates/gpe_discussion_paper_series_paper31_2001_age_standardization_rates.pdf; 2001;9:1–14 [accessed 01 March 2024].
[29] Cleveland WS, Devlin SJ. Locally weighted regression: an approach to regression analysis by local fitting. *J Am Stat Assoc* 1988;**83**:596–610. doi:10.1080/01621459.1988.10478639.
[30] Barco S, Mahmoudpour SH, Valerio L, Klok FA, Münzel T, Middeldorp S, et al. Trends in mortality related to pulmonary embolism in the European region, 2000–15: analysis of vital registration data from the WHO mortality database. *Lancet Respir Med* 2020;**8**:277–87. doi:10.1016/S2213-2600(19)30354-6.
[31] World Health Organization *World health statistics 2022: monitoring health for the sustainable development goals*. Geneva: World Health Organization; 2022.
[32] Global Burden of Disease Collaborative Network *Global burden of disease study 2021 (GBD 2021) Socio-Demographic Index (SDI) 1950–2021*. Seattle: Institute for Health Metrics and Evaluation (IHME); 2024. doi:10.6069/dwqg-3z75.
[33] Liu B, Kim HJ, Feuer EJ, Graubard BI. Joinpoint regression methods of aggregate outcomes for complex survey data. *J Surv Stat Methodol* 2023;**11**:967–89. doi:10.1093/jssam/smac014.
[34] Donskey CJ. Update on Clostridioides difficile infection in older adults. *Infect Dis Clin North Am* 2023;**37**:87–102. doi:10.1016/j.idc.2022.10.001.
[35] Loo VG, Bourgault A-M, Poirier L, Lamothe F, Michaud S, Turgeon N, et al. Host and pathogen factors for Clostridium difficile infection and colonization. *N Engl J Med* 2011;**365**:1693–703. doi:10.1056/NEJMoa1012413.
[36] Karas JA, Enoch DA, Aliyu SH. A review of mortality due to Clostridium difficile infection. *J Infect* 2010;**61**:1–8. doi:10.1016/j.jinf.2010.03.025.
[37] United Nations, Department of Economic and Social Affairs, Population Division. World Population Prospects 2024, https://population.un.org/wpp/; 2024 [accessed 28 August 2024].
[38] Chitnis AS, Holzbauer SM, Belflower RM, Winston LG, Bamberg WM, Lyons C, et al. Epidemiology of community-associated Clostridium difficile infection, 2009 through 2011. *JAMA Intern Med* 2013;**173**:1359–67. doi:10.1001/jamainternmed.2013.7056.
[39] Ofori E, Ramai D, Dhawan M, Mustafa F, Gasperino J, Reddy M. Community-acquired Clostridium difficile: epidemiology, ribotype, risk factors, hospital and Intensive Care Unit outcomes, and current and emerging therapies. *J Hosp Infect* 2018;**99**:436–42. doi:10.1016/j.jhin.2018.01.015.
[40] Armstrong EP, Malone DC, Franic DM, Pham SV, Gratie D, Amin A. Patient experiences with Clostridioides difficile infection and its treatment: a systematic literature review. *Infect Dis Ther* 2023;**12**:1775–95. doi:10.1007/s40121-023-00833-x.
[41] Khanna S, Pardi DS, Aronson SL, Kammer PP, Orenstein R, St Sauver JL, et al. The epidemiology of community-acquired Clostridium difficile infection: a population-based study. *Am J Gastroenterol* 2012;**107**:89–95. doi:10.1038/ajg.2011.398.
[42] Viseur N, Lambert M, Delmee M, Van Broeck J, Catry B. Nosocomial and non-nosocomial Clostridium difficile infections in hospitalised patients in Belgium: compulsory surveillance data from 2008 to 2010. *Euro Surveill* 2011;**16**:20000. doi:10.2807/ese.16.43.20000-en.
[43] Lim SC, Knight DR, Riley TV. Clostridium difficile and one health. *Clin Microbiol Infect* 2020;**26**:857–63. doi:10.1016/j.cmi.2019.10.023.
[44] Frentrup M, Thiel N, Junker V, Behrens W, Münch S, Siller P, et al. Agricultural fertilization with poultry manure results in persistent environmental contamination with the pathogen Clostridioides difficile. *Environ Microbiol* 2021;**23**:7591–602. doi:10.1111/1462-2920.15601.
[45] Kabelitz T, Biniasch O, Ammon C, Nübel U, Thiel N, Janke D, et al. Particulate matter emissions during field application of poultry manure – the influence of moisture content and treatment. *Sci Total Environ* 2021;**780**:146652. doi:10.1016/j.scitotenv.2021.146652.
[46] Tkalec V, Janezic S, Skok B, Simonic T, Mesaric S, Vrabic T, et al. High Clostridium difficile contamination rates of domestic and imported potatoes compared to some other vegetables in Slovenia. *Food Microbiol* 2019;**78**:194–200. doi:10.1016/j.fm.2018.10.017.
[47] Knight DR, Riley TV. Genomic delineation of zoonotic origins of Clostridium difficile. *Front Public Health* 2019;**7**:164. doi:10.3389/fpubh.2019.00164.
[48] Arvand M, Moser V, Schwehn C, Bettge-Weller G, Hensgens MP, Kuijper EJ. High prevalence of Clostridium difficile colonization among nursing home residents in Hesse, Germany. *PLoS One* 2012;**7**:e30183. doi:10.1371/journal.pone.0030183.
[49] Kotila SM, Mentula S, Ollgren J, Virolainen-Julkunen A, Lyytikäinen O. Community- and healthcare-associated Clostridium difficile infections, Finland, 2008–2013. *Emerg Infect Dis* 2016;**22**:1747–53. doi:10.3201/eid2210.151492.
[50] Srinivasan A. Antibiotic stewardship: why we must, how we Can. *Cleve Clin J Med* 2017;**84**:673–9. doi:10.3949/ccjm.84gr.17003.
[51] Hota SS, Achonu C, Crowcroft NS, Harvey BJ, Lauwers A, Gardam MA. Determining mortality rates attributable to Clostridium difficile infection. *Emerg Infect Dis* 2012;**18**:305–7. doi:10.3201/eid1802.101611.
[52] Redelings MD, Sorvillo F, Mascola L. Increase in Clostridium difficile-related mortality rates, United States, 1999–2004. *Emerg Infect Dis* 2007;**13**:1417–19. doi:10.3201/eid1309.061116.
[53] Viprey VF, Granata G, Vendrik KEW, Davis GL, Petrosillo N, Kuijper EJ, et al. European survey on the current surveillance practices, management guidelines, treatment pathways and heterogeneity of testing of Clostridioides difficile, 2018–2019: results from the combatting bacterial resistance in Europe CDI (COMBACTE-CDI). *J Hosp Infect* 2023;**131**:213–20. doi:10.1016/j.jhin.2022.11.011.
[54] Davies KA, Longshaw CM, Davis GL, Bouza E, Barbut F, Barna Z, et al. Underdiagnosis of Clostridium difficile across Europe: the European, multicentre, prospective, biannual, point-prevalence study of Clostridium difficile infection in hospitalised patients with diarrhoea (Euclid). *Lancet Infect Dis* 2014;**14**:1208–19. doi:10.1016/S1473-3099(14)70991-0.
[55] Viprey VF, Davis GL, Benson AD, Ewin D, Spittal W, Vernon JJ, et al. A point-prevalence study on community and inpatient Clostridioides difficile infections (CDI): results from combatting bacterial resistance in Europe CDI (COMBACTE-CDI), July to November 2018. *Euro Surveill* 2022;**27**:2100704. doi:10.2807/1560-7917.ES.2022.27.26.2100704.
[56] Sopena N, Freixas N, Bella F, Pérez J, Hornero A, Limon E, et al. Impact of a training program on the surveillance of Clostridioides difficile infection. *Epidemiol Infect* 2019;**147**:e231. doi:10.1017/S0950268819001080.