A decade of Clostridioides difficile infection: a constant challenge to maintain the status quo

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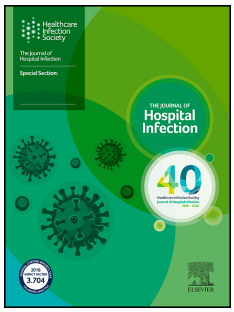

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Abstract

Clostridioides difficile infection (CDI) is a leading cause of healthcare-associated (HA) diarrhoea. We retrospectively investigated data from a comprehensive, multidisciplinary *C. difficile* surveillance programme focusing on hospitalised patients in a tertiary Irish hospital over ten years.

Data from 2012 to 2021 were extracted from a centralised database, including patient demographics, admission, case and outbreak details, ribotypes (RT), and (since 2016) antimicrobial exposures and CDI treatments. Counts of CDI by origin of infection were explored using $\chi 2$ analyses, Poisson regression used to investigate trends in rates of CDI and possible risk factors. Time to recurrent CDI was examined by a Cox proportional hazards regression.

Over 10 years, 954 CDI patients had a 9% recurrent CDI rate. CDI testing requests occurred in only 22% of patients. Most CDIs were HA (82.2%) and affected females (OR 2.3 $p<0.01$). Fidaxomicin significantly reduced the hazard ratio of time to recurrent CDI. No trends in HA-CDI incidence were observed despite key time-point events and increasing hospital activity. In 2021 community-associated (CA)-CDI increased. RTs did not differ for HA versus CA for the commonest RTs (014, 078, 005 and 015). Average length- of-stay differed significantly between HA (67.1 days) and CA (14.6 days) CDI.

HA-CDI rates remained unchanged despite key events and increased hospital activity, whereas by 2021, CA-CDI was at its highest in a decade. The convergence of CA and HA RTs, and the proportion of CA-CDI, question the relevance of current case definitions when increasingly patients receive hospital care without an overnight hospital stay.

Introduction

Clostridioides difficile infection (CDI) is a leading cause of healthcare-associated (HA) diarrhoea ranging from 1.1 to 631.8 per 100,000 population globally [1]. CDI has been classified as an urgent public health threat by the Centres for Disease Control and Prevention and is associated with $1 billion attributable healthcare costs [2]. In Europe, HA-CDI infects one-in-twenty patients with HA infection, and is responsible for 48% of all HA gastrointestinal infections [3].

In Ireland, CDI has been a notifiable infectious disease since 2008 and HA-CDI rates per 10,000 bed days used (BDU) a national key performance indicator since 2014. In 2020, the reported national HA-CDI rate was 2.4 /10,000 BDU [4]. Recent reports indicate reductions in HA-CDI, with concurrent increases in community-associated (CA) CDI. Until 2022, Ireland lacked a national *C. difficile* reference laboratory; hence information on circulating *C. difficile* ribotypes (RT) is limited. Only 22% of CDI cases reported in Ireland in 2020 had associated RT data, with 078, 014, 002 and 020 most common [4].

Reported nosocomial CDI epidemiology tend to focus on shorter periods (e.g. three to eight years) with mixed approaches to surveillance i.e. laboratory data only or combined laboratory and clinical data. We aimed to retrospectively examine data trends from our comprehensive multidisciplinary (MDT) CDI surveillance established in 2012 in our institution, a tertiary hospital in Dublin, Ireland. Here our prospective data over a decade is explored and predictor variables for first episode and recurrence investigated.

Methods

We conducted an observational cohort study investigating CDI data from hospitalised inpatients prospectively captured and followed up between 2012 and 2021. The study was approved by the Beaumont Hospital Ethics Committee (REC reference 19/33) and followed STROBE guidelines [5].

Beaumont Hospital, Dublin is an adult tertiary referral centre with over 800 beds; 136 single rooms, 77% with *en suite* facilities and 12 airborne isolation rooms. Most accommodation is multi-occupancy, with one shared bathroom for up to six patients. Over the study period, there was a mean of 24,494 inpatient admissions annually; 76% acute (emergency) admissions. In 2021, the proportion of acute admissions increased to 80%. The annual average inpatient length-of-stay (LOS) over the study period ranged from 9.1 to 9.9 days (mean 9.47 days). Annually, the average patient age ranged from 55.2 to 60.6 years (mean 57.8 years).

All stool samples which take the shape of the container, irrespective of clinician request, are tested daily on-site for *C. difficile*. In 2011, the laboratory introduced a two-step testing protocol of glutamate dehydrogenase (GDH) enzyme linked immunoassay, which if positive was followed by *C. difficile tcdB* PCR testing. In 2015, the protocol changed to *C. difficile tcdB* PCR and if positive, enzyme immunoassay (EIA) for *C. difficile* toxin.

All PCR positive results, irrespective of EIA result, are phoned daily by the clinical microbiologist and significance determined with clinical teams. A treatment plan is advised stratified by CDI severity and based on hospital prescribing guidelines. The infection prevention and control (IPC) nurse visits the ward to advise on patient placement and IPC precautions. The first positive faeces sample per patient is prospectively sent for RT (*C. difficile* Ribotyping Network reference laboratory in Leeds, UK) and results reviewed to determine any possible intra-hospital cross transmission. Multi-locus variable-number tandem repeat analysis is used for outbreak investigations where common RTs are identified or where an unusual RT appears, without obvious epidemiological links. Outbreaks are declared when three of more CDI patients are identified in the same clinical area and notified to public health. Outbreaks can be retrospectively identified or confirmed on review of RT results. Outbreak summary data and the associated line list of cases are stored in the centralised database.

The following data on *C. difficile* PCR positive samples are prospectively captured in a secure centralised MDT CDI database: Patient demographics (age, sex, length of hospitalisation), admission details (emergency/elective, admitting specialty), details of *C. difficile* testing results and patient outcome at discharge. Assignments of CDI case type, origin (HA or CA), onset and disease severity, as per national case definitions are discussed weekly by clinical microbiology, IPC nursing and surveillance scientists, and agreed outcomes recorded in the database (Appendix 1) [6]. Since 2016 during liaison with clinical teams regarding positive *C. difficile* results, the clinical microbiologist records if patients had antimicrobial exposure (but not the specific antimicrobial agents) in the three months before CDI onset and details of

recommended CDI treatment. The CDI database is quality-assured monthly by a consultant microbiologist and surveillance scientist. Data on concurrent enteric infections are not captured in the CDI database hence were not examined.

Data were extracted from the CDI database with, the following exclusion criteria:

- Repeat samples: a patient's CDI case classification remained unchanged from preceding positive sample
- Patients who did not meet the CDI case definition
- Patients who were not admitted to hospital
- Patient less than 18 years of age

Other data reviewed included BDU (used as denominator), average age and LOS by specialty. Annual hospital activity data was calculated using the total number of admissions, outpatient attendances, emergency department attendances and day cases.

The first RT recorded per patient was included in RT analysis. The number of patients with a RT per year were counted. The five dominant RTs were identified each year and resulting data investigated for incidence patterns and trends over the 10 years.

Patient age and sex as well as CDI onset, origin, admission type, *C. difficile* positive samples in previous 12 weeks, antibiotics exposure in previous 12 weeks and patient specialty were investigated for differences between the HA and CA-CDI cohorts using $\chi 2$ for categorical and Wilcoxon rank sum test for continuous variables. Predictors of new CDI were investigated

using Poisson regression analysis and results presented as adjusted incidence rate ratios (IRRs) with 95% confidence intervals (CI). To examine time to recurrence of CDI a Cox proportional hazards regression was used. For those without recurrent CDI, data was censored at date of data extraction (March 2022). Adjusted hazard ratios (HR) and 95% CI were calculated for each predictor. All analysis were performed using Stata version 16.1. Significance at $p < 0.05$ was assumed.

Results

There were 954 patients with a new CDI and 87 (9%) with a recurrent CDI. The majority were HA-CDI (n=781, 82.2%) (Table I). *C. difficile* testing was requested in only 214 (22.4%) cases, active screening of all diarrhoeal samples for CDI identified the remainder. Forty-six (4.8%) patients had a positive *C. difficile* laboratory result that did not meet the case definition in the preceding 12 weeks. After clinical liaison, anti-CDI treatment was recommended in 10 patients (fidaxomicin n=1, vancomycin n=1 and metronidazole=8). These patients would have been isolated/cohorted as per IPC policy if ongoing diarrhoea. CA-CDI was more likely in females (odds ratio (OR) 2.27 $p<0.01$).

The mean LOS of CDI patients was 57.9 days (interquartile range (IQR) 11 to 60 days) which differed significantly between HA and CA cohorts ($p<0.01$). Patients over 70 years accounted for greater than 60% of all CDI cases. The average age of CA-CDI patients was nearly 10 years younger than HA-CDI (62 years versus 71 years, $p<0.01$). Acute admissions (87.2%) and healthcare-onset (78.5%) were observed in the majority of cases. In 7.9% of HA-CDI

community onset was observed indicating patients recently discharged (in the previous four weeks) from a healthcare facility presented with CDI. Approximately 2% of cases developed severe CDI which was similar in both CA (1.8%) and HA-CDI (2.3%). The all-cause inpatient mortality rate of CDI was 16.5%. This varied by origin (6.5% CA-CDI, 18.6% HA-CDI).

From 2016 to 2021, CDI treatment data was available for 551 patients (57.7% of all patients reviewed) with 300 of 451 HA-CDI (66.5%) and 57 of 100 CA-CDI (57.0%), respectively, prescribed fidaxomicin. Metronidazole was prescribed for 79 (17.5%) HA-CDI and 18 (18.0%) CA-CDI, vancomycin for 70 (15.5%) HA-CDI and 25 (25.0%) CA-CDI and combination therapy of vancomycin and metronidazole for two (0.4%) HA-CDI. No combination therapy was prescribed for CA-CDI. Patients who had received recent antibiotics were five times more likely to develop CDI than those who did not. Of patients with recurrent CDI, 38.7% received metronidazole, 35.4% received fidaxomicin and 22.6% received vancomycin as first line treatment. First line treatment was not known in 3.2% of cases.

General medicine (27.04%) and general surgery (21.70%) specialties had the greatest burden of CDI patients, followed by medicine for the elderly (MFTE) (13.42%). When compared to CA-CDI, HA-CDI dominated across all specialties, accounting for 100% of cases in neurosurgical patients, 92.19% of MFTE and 85.95% of renal patients. Gastroenterology patients (36.21%) had the highest proportion of CA-CDI.

Poisson regression analysis and adjusted IRRs investigating risk factors for new CDI cases are presented in Table II. HA-CDI and acute admission significantly increased the IRR for new

CDI. Surgical and general medical patients had CDI rates comparable with MFTE, with significantly less CDI in neurosurgical patients. Wilcoxon rank-sum tests indicated that age and LOS were significantly associated with new CDI ($p<0.01$).

RT was performed for 95% of patients with 126 different RTs identified. Figure 1 presents the five dominant RTs identified each year. RT014 and RT002 predominated. Other common RTs year on year included; 078, 005, 015 and 020 with no evident patterns according to case type and origin.

CDI recurrence occurred in 9.1% (n=87, one severe CDI), with a 1.5|1.0 female-to-male ratio and an average age of 74.4 years (IQR 68 – 85) years. Most patients had one recurrence (n= 68, 78.16 %) and 19 (21.84%) had two or more recurrences. Cox regression analysis showed use of fidaxomicin as first-line treatment significantly reduced the HR in recurrent CDI patients to 0.54 (C.I. 0.3 -0.9). No other significant factor was identified.

Numbers of new CDI patients ranged from 100 (2017) to 236 (2019) annually. Figure 2 displays rates of HA and CA-CDI and hospital activity data over the decade. No overall significant trend in either HA or CA-CDI was found despite key time-point events including introduction of HPV decontamination and changes to a more sensitive laboratory testing protocol. The rate of CA-CDI was at its highest in 2021. Hospital activity data increased by 21% between 2012 and 2021. No significant trends in seasonality were found however monthly averages of HA-CDI were highest in January, March and July. CA-CDI was highest in July to September. Regression analysis indicated no significant trends in either cohort.

Twenty-seven CDI outbreaks were managed over the decade with no year without a CDI outbreak (Table III). The mean number of patients and wards per outbreak was 18 and three. Annually the number of outbreaks ranged from one to six. The greatest burden was observed in 2012 (six outbreaks in six wards with 36 patients), 2015 (six outbreaks over eight wards and 21 patients) and in 2019 there were two outbreaks of which one was hospital-wide with 62 patients affected. A single RT was identified in the majority of outbreaks (66%) with mixed RTs in the remaining third.

Discussion

CDI remains a significant patient safety and IPC issue. In our hospital, HA-CDI rates have remained broadly unchanged despite key time-point events, changeover to a more sensitive laboratory testing algorithm and increasing hospital activity. CDI continues to impact our more vulnerable and older patients with longer LOS. One in ten patients experienced recurrent CDI, with one in twenty having two or more recurrences. Fidaxomicin treatment reduced the likelihood of recurrent CDI. The recent increase in CA-CDI requires further investigation, although it might reflect the impact of the COVID-19 pandemic on healthcare access and antimicrobial utilisation outside the hospital setting. The majority of CA-CDI and over one-in-twenty HA-CDI have symptom onset in the community, highlighting the need for ongoing CDI awareness efforts outside the hospital setting. The cause of observed sex differences in CA-CDI is unclear and requires further investigation.

The factors that contribute to CDI rates in a hospital are complex and include laboratory protocols for *C. difficile* detection. International guidelines recommend testing all diarrhoeal samples for *C. difficile* irrespective of clinician request [7]. Indeed, most CDI cases would have been missed if we had not adopted a universal testing approach. CDI under-diagnosis presents a significant transmission risk, especially in hospitals with multi-bedded wards and shared bathrooms. Patients with *C. difficile* detected but not meeting the case definition in the previous 12 weeks appeared to be protected against subsequent CDI. This may reflect colonisation with non-toxigenic *C. difficile* which can prevent subsequent CDI. Alternatively increased CDI awareness in these particular patients may results in more focused antimicrobial stewardship efforts [8]. One-in-five patients had community-onset CDI (the majority CA-CDI) and were diagnosed first when admitted to hospital. CDI under diagnosis presents unique challenges in the community. Absence of clinical suspicion accounted for three times more undiagnosed CDI in the community compared with hospitals in a recent study in 12 European countries [9]. It is therefore important that in the post-pandemic era, CDI awareness remains a focus in all healthcare settings. During the decade our laboratory switched from GDH to PCR as the first test in the two –step testing algorithm. PCR as a more sensitive first test could have impacted CDI rates [10]. Indeed, previous studies have reported significant increases in HA-CDI rates when laboratory testing moves to molecular methods [11, 12]. However, our remaining post-analytical processes remained unchanged including daily clinical liaison to determine significance of positive results and weekly IPCT sign-off of CDI cases. This along with intensive IPC efforts likely contributed to the broadly unchanged HA-CDI rates in this study.

Increasing age is a widely-reported CDI risk factor [13]. In our study, patients with CA-CDI and neurosurgical patients with CDI were younger. Sex differences in CDI hospitalisation rates and in colonisation with non-toxigenic *C. difficile*/CDI risk have been described previously [14, 15]. In the Netherlands, hospitalised patients with CO-CDI tended to be younger and female [16]. Likewise, in a US population-based study, CA-CDI patients tended to be younger and female (76%) [17]. Female gender was one of the commonest risk factors for new CDI in a recent systematic review [1]. However, the reasons behind this remain unclear. In our study, significant sex differences in CA-CDI, but not HA-CDI were found. Sex differences in health seeking behaviour and healthcare utilization may be one reason for this discrepancy, although further investigation is required [18, 19].

Medical and surgical patients had CDI rates similar to MFTE, which likely reflects the age groups in the hospital catchment area. In contrast, CDI was significantly less common in neurosurgical patients, who were the youngest cohort, with age differences between neurosurgical patients with and without CDI patients less pronounced. Gastroenterology patients had the highest proportion of CA-CDI. Additional information on concurrent gastrointestinal conditions such as inflammatory bowel disease is not captured in the CDI database. CDI status (if gastrointestinal symptoms are determined due to *C. difficile*) and patient management are agreed during liaison with the gastroenterology clinical team.

CDI displayed seasonality, peaking in spring with a reduction in summer/autumn [20]. This could be attributed to antibiotic prescribing during the winter influenza season. HA-CDI

seasonality observed in our study may also reflect trainee doctor changeover periods (typically January and July), where new staff may take time to become familiar with local antimicrobial stewardship policies. Without further investigation, the seasonal pattern of CA-CDI peaking in summer/autumn is difficult to explain.

The most common RTs in our study were similar to those previously reported and except for the 2019 RT002 outbreak, the most common circulating RTs remained generally stable [4, 21]. An increase in RT002 was also noted at a national level between 2018 and 2019 however returned to baseline prevalence in 2020 [4]. RT078 was common year-on-year, but notably RT027 was absent over the decade. The CA-CDI cohort is not a true representation of CA-CDI, as our study was confined to hospitalised patients. However, the similarity of dominant RTs between HA-CDI and CA-CDI raises questions as to the exposure and interaction of CA-CDI patients with healthcare facilities and the reliability of CDI origin case definitions which required an overnight hospital stay for HA-CDI case classification [6]. With increases in day-case hospital care, this may require reconsideration.

Recurrent CDI is associated with higher healthcare costs and prolonged hospital stay [22]. CDI recurrence rates vary with ribotype, although are generally 15-30% [23]. Risk factors for recurrence in hospitalised patients include; prior/current antimicrobials, older age and LOS [24]. Ten percent of our patients developed recurrent CDI which was generally HA, with a fifth having two or more recurrences. Fidaxomicin treatment was the only significant factor that reduced the likelihood of recurrence. This has been reported in other studies and was one factor favouring fidaxomicin as first line therapy in recent guidelines [25].

CDI IPC is challenging especially in a hospital with predominant multi-bedded bays such as ours. Despite rigorous local CDI IPC and surveillance programmes, several key time-point events and increased hospital activity, the overall HA-CDI rate has not changed, whereas CA-CDI more recently reached the highest rate in a decade. The COVID-19 pandemic brought significant changes to the healthcare services worldwide, including our hospital. Despite initial reported CDI decreases [26], HA-CDI has rebounded to pre-pandemic levels, along with hospital activity, similar to that reported in Canada [27]. In the UK, over the pandemic, significant increases in CA-CDI and HA-CDI were reported with a marked increase in CDI case fatality if recent COVID-19 [28, 29]. Our recent increase in CA-CDI may be accounted for by a number of potential factors including, delays in diagnosis (difficulty accessing primary healthcare; inadequate access to *C. difficile* testing because of the focus on SARS-CoV-2 testing), the increased incidence of respiratory illness leading to more antimicrobial prescribing after the relaxation of lockdown measures, increased CDI risk and/or factors such as frailty and comorbidity as a consequence of lockdowns. Education among primary care teams is important to ensure that CDI is part of the differential when investigating diarrhoeal symptoms, particularly when the patient has been recently discharged from a healthcare facility or has accessed healthcare in the community such as attending a day centre.

Limitations to this study include; its single site limiting the generalisability, inclusion of only hospitalised patients, lack of follow-up post-discharge, which may have impacted recurrent CDI rates, lack of detail regarding patient comorbidity and prior antimicrobials, follow-up

outcome data and antimicrobial susceptibility of *C. difficile* isolates. However, the strength of this study is the robustness of analysed data. All patients with a positive *C. difficile* result were prospectively assessed by the same MDT resulting in real-time allocation to standardised case type designation, which were subsequently validated weekly by the IPCT, RT was performed on all positive samples by the same laboratory and the CDI database was prospectively quality-assured monthly.

CDI control remains a constant challenge. We maintained the status quo despite significant increases in hospital activity with ongoing IPC interventions underpinned by prospective surveillance. Our findings reinforce the importance of testing all diarrhoeal specimens for *C. difficile* irrespective of request and of prospective surveillance to provide local information in real-time for MDT action. The recent increase in CA-CDI highlights a need to raise awareness of CDI among community based healthcare workers. The convergence of CA and HA RTs, and the proportion of CO and CA-CDI, question the relevance of current CDI case definitions which require hospital admission for HA-CDI, when increasingly patients receive hospital care without an overnight hospital stay

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Conflicts of Interest

HH has received research grants from Pfizer and Astellas and has been a recipient of a consultancy fee from Pfizer

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References

[1] 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 infectious diseases 2021;21(1):456. https://doi.org/10.1186/s12879-021-06147-y.

[2] Centres for Disease Control Strategy Unit. Antibiotic resistance threats in the United States, https://stacks.cdc.gov/view/cdc/82532; 2019 [accessed 15th October 2022] .

[3] European Centre for Disease Control. Point prevalence survey of healthcare-associated infections and antimicrobial use in European acute care hospitals 2011-2012. https://doi.org/0.2900/86011; 2013 [accessed 17th Septmber 2022].

[4] Health Protection Suveillance Centre. *Clostridioides difficile* infection in Ireland 2020, https://www.hpsc.ie/a-z/microbiologyantimicrobialresistance/clostridioidesdifficile/cdifficiledataandreports/annualreports/AER_CDI_2019_2020_Reviewed.pdf; 2022 [accessed 01st October 2022].

[5] von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. The Lancet 2007;370(9596):1453-7. https://doi.org/10.1016/S0140-6736(07)61602-X.

[6] Health Protection Suveillance Centre. Case Definitions for *C. difficile* Enhanced Surveillance, https://www.hpsc.ie/a-z/microbiologyantimicrobialresistance/clostridioidesdifficile/enhancedsurveillance/File,14699,en.pdf; 2014 [accessed 01st October 2022].

[7] Crobach MJ, Planche T, Eckert C, Barbut F, Terveer EM, Dekkers OM, et al. European Society of Clinical Microbiology and Infectious Diseases: update of the diagnostic guidance document for *Clostridium difficile* infection. Clin Microbiol Infect 2016;22 Suppl 4:S63-81. https://doi.org/10.1016/j.cmi.2016.03.010.

[8] Gerding DN, Meyer T, Lee C, Cohen SH, Murthy UK, Poirier A, et al. Administration of spores of nontoxigenic *Clostridium difficile* strain M3 for prevention of recurrent *C. difficile* infection: a randomized clinical trial. JAMA 2015;313(17):1719-27. https://doi.org/10.1001/jama.2015.3725.

[9] 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 surveillance : bulletin Europeen sur les maladies transmissibles = European communicable disease bulletin 2022;27(26). https://doi.org/10.2807/1560-7917.Es.2022.27.26.2100704.

[10] Longtin Y, Trottier S, Brochu G, Paquet-Bolduc B, Garenc C, Loungnarath V, et al. Impact of the type of diagnostic assay on *Clostridium difficile* infection and complication rates in a mandatory reporting program. Clin Infect Dis 2013;56(1):67-73. https://doi.org/10.1093/cid/cis840.

[11] Moehring RW, Lofgren ET, Anderson DJ. Impact of change to molecular testing for *Clostridium difficile* infection on healthcare facility-associated incidence rates. Infection control and hospital epidemiology 2013;34(10):1055-61. https://doi.org/10.1086/673144.

[12] Murad YM, Perez J, Nokhbeh R, Ybazeta G, Dewar B, Lefebvre S, et al. Impact of polymerase chain reaction testing on *Clostridium difficile* infection rates in an acute health

care facility. American journal of infection control 2015;43(4):383-6. https://doi.org/10.1016/j.ajic.2014.12.021.

[13] 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 Internal Medicine 2013;173(14):1359-67. https://doi.org/10.1001/jamainternmed.2013.7056.

[14] Esteban-Vasallo MD, Naval Pellicer S, Domínguez-Berjón MF, Cantero Caballero M, Asensio Á, Saravia G, et al. Age and gender differences in *Clostridium difficile*-related hospitalization trends in Madrid (Spain) over a 12-year period. European journal of clinical microbiology & infectious diseases : official publication of the European Society of Clinical Microbiology 2016;35(6):1037-44. https://doi.org/10.1007/s10096-016-2635-7.

[15] Natarajan M, Rogers MA, Bundy J, Micic D, Walk ST, Santhosh K, et al. Gender Differences in Non-Toxigenic *Clostridium difficile* Colonization and Risk of Subsequent *C. difficile* Infection. Clinical research in infectious diseases 2015;2(2).

[16] Crobach MJT, Notermans DW, Harmanus C, Sanders I, De Greeff SC, Kuijper EJ. Community-Onset *Clostridioides difficile* Infection in Hospitalized Patients in The Netherlands. Open Forum Infect Dis 2019;6(12):ofz501. https://doi.org/10.1093/ofid/ofz501.

[17] 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(1):89-95. https://doi.org/10.1038/ajg.2011.398.

[18] Roy K, Chaudhuri A. Gender Differences in Healthcare Utilization in Later Life. In: Kuhlmann E, Annandale E, editors. The Palgrave Handbook of Gender and Healthcare,

London: Palgrave Macmillan UK; 2012, p. 256-72. https://doi.org/10.1057/9781137295408_16.

[19] Thompson AE, Anisimowicz Y, Miedema B, Hogg W, Wodchis WP, Aubrey-Bassler K. The influence of gender and other patient characteristics on health care-seeking behaviour: a QUALICOPC study. BMC Family Practice 2016;17(1):38. https://doi.org/10.1186/s12875-016-0440-0.

[20] Furuya-Kanamori L, McKenzie SJ, Yakob L, Clark J, Paterson DL, Riley TV, et al. *Clostridium difficile* infection seasonality: patterns across hemispheres and continents - a systematic review. PloS one 2015;10(3):e0120730. https://doi.org/10.1371/journal.pone.0120730.

[21] Freeman J, Vernon J, Pilling S, Morris K, Nicolson S, Shearman S, et al. Five-year Pan-European, longitudinal surveillance of *Clostridium difficile* ribotype prevalence and antimicrobial resistance: the extended ClosER study. European journal of clinical microbiology & infectious diseases : official publication of the European Society of Clinical Microbiology 2020;39(1):169-77. https://doi.org/10.1007/s10096-019-03708-7.

[22] Tresman R, Goldenberg SD. Healthcare resource use and attributable cost of *Clostridium difficile* infection: a micro-costing analysis comparing first and recurrent episodes. J Antimicrob Chemother 2018;73(10):2851-5. https://doi.org/10.1093/jac/dky250.

[23] Song JH, Kim YS. Recurrent *Clostridium difficile* Infection: Risk Factors, Treatment, and Prevention. Gut Liver 2019;13(1):16-24. https://doi.org/10.5009/gnl18071.

[24] Alrahmany D, Ereshefsky BJ, El Nekidy WS, Harb G, Pontiggia L, Ghazi IM. Risk Factors for Recurrence of *Clostridioides difficile* in Hospitalized Patients. J Infect Public Health 2021;14(11):1642-9. https://doi.org/10.1016/j.jiph.2021.09.016.

[25] 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. Clinical Microbiology and Infection 2021;27:S1-S21. https://doi.org/10.1016/j.cmi.2021.09.038.

[26] Hazel K, Skally M, Glynn E, Foley M, Burns K, O'Toole A, et al. The other 'C': Hospital-acquired *Clostridioides difficile* infection during the coronavirus disease 2019 (COVID-19) pandemic. Infection control and hospital epidemiology 2022;43(4):540-1. https://doi.org/10.1017/ice.2021.3.

[27] Xia Y, Tunis MC, Frenette C, Katz K, Amaratunga K, Rose SR, et al. Epidemiology of *Clostridioides difficile* infection in Canada: A six-year review to support vaccine decision-making. Can Commun Dis Rep 2019;45(7-8):191-211. https://doi.org/10.14745/ccdr.v45i78a04.

[28] UK Health Security Agency (UKHSA) Healthcare Associated Infections (HCAI) and Antimicrobial Resistance (AMR). Quarterly epidemiology commentary: mandatory MRSA, MSSA and Gram-negative bacteraemia and *C. difficile* infection in England (up to January to March 2022), https://www.gov.uk/government/statistics/mrsa-mssa-gram-negative-bacteraemia-and-cdi-quarterly-report/quarterly-epidemiological-commentary-mandatory-mrsa-mssa-and-gram-negative-bacteraemia-and-c-difficile-infection-data-up-to-january-to-march-2022#fig6a; 2022 [accessed 01st October 2022].

[29] UK Health Security Agency (UKHSA) Healthcare Associated Infections (HCAI) and Antimicrobial Resistance (AMR). Thirty-day all-cause mortality following MRSA, MSSA and Gram-negative bacteraemia and *C. difficile* infections, 2020 to 2021. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment

data/file/1039272/hcai-all-cause-fatality-report-2021.pdf; 2021 [accessed 01st October

https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_

data/file/1039272/hcai-all-cause-fatality-report-2021.pdf; 2021 [accessed 01st October

2022].

Table I: Healthcare versus community acquisition of 954 patients with first episode of *Clostridioides difficile* infection (new CDI), from 1st January 2012 to 31st December 2021, Beaumont Hospital, Dublin.

	Total Patients N (%)	Community acquired (CA) – CDI N (%)	Healthcare acquired (HA) -CDI N (%)	HA vs CA -CDI Odds Ratio (95% Confidence Interval)
New CDI	954	169 (17.79)	781 (82.21)	
Recurrent CDI	87 (9.12)	7 (8.05)	80 (91.95)	
Clinician CDI test request	214 (22.43)	25 (14.79)	189 (24.08)	1.83 (1.16 - 2.88)
Faecal specimens tested (no CDI request) [#]	740 (77.57)	144 (85.21)	596 (75.91)	
Previous positive result that did not meet the case definition* [#]	46 (4.82)	2 (1.18)	44 (5.61)	4.96 (1.18 - 20.76)
Female[#]	541 (56.71)	122 (72.19)	419 (53.38)	2.27 (1.57 - 3.27)
Male	413 (43.29)	47 (27.81)	366 (46.62)	
Admission type				
Emergency [#]	833 (87.32)	156 (92.31)	677 (86.24)	0.52[#] (0.29 -0.95)
Elective	121 (12.68)	13 (7.69)	108 (13.79)	
Healthcare onset CDI[#]	749 (78.51)	26 (15.38)	723 (92.10)	64.14 (32.79 - 129.40)
Community onset CDI	205 (21.49)	143 (84.62)	62 (7.90)	
Admission Specialty[#]				
Gastroenterology	116 (12.16)	42 (36.21)	74 (63.79)	
Medicine for the elderly (MFTE)	128 (13.42)	10 (7.81)	118 (92.19)	

	Total Patients N (%)	Community acquired (CA) – CDI N (%)	Healthcare acquired (HA) -CDI N (%)	HA vs CA -CDI Odds Ratio (95% Confidence Interval)
General medicine	258 (27.04)	53 (20.54)	205 (79.46)	
Renal	121 (12.68)	17 (14.05)	104 (85.95)	
Neurosurgery	49 (5.14)	0	49 (100)	
Oncology	75 (7.86)	9 (12.00)	66 (88.00)	
General surgery	207 (21.70)	38 (18.36)	169 (81.64)	

CI: Confidence Interval

IQR: interquartile range

*Positive *C. difficile* laboratory results that did not meet CDI case definition (DNMCD) in the preceding 12 weeks

#Indicates significance, $p<0.05$

Table II: Poisson regression analysis (adjusted incidence rate ratio and 95% confidence interval) investigating risk factors of 954 patients for the first episode of *Clostridioides difficile* infection, from 1st January 2012 to 31st December 2021, Beaumont Hospital, Dublin

		Adjusted incidence rate ratio (IRR)	95% Confidence Interval
Clinician request for *C. difficile* test[#] (no CDI request – reference group)		0.73	(0.63 – 0.85)
Previous positive result*[#]		0.45	(0.33 – 0.60)
Sex	**Female**	0.92	(0.81 – 1.05)
	Male		
Admission type[#]	**Emergency**	1.56	(1.28 – 1.89)
	Elective		
Healthcare onset CDI[#]		1.37	(1.12 – 1.67)
Admission Specialty	Gastroenterology	0.79	(0.61 – 1.02)
	Medicine for the elderly	-	-
	General medicine	1.19	(0.96 – 1.49)
	Renal	0.79	(0.62 – 1.02)
	Neurosurgery[#]	0.64	(0.45 – 0.90)
	Oncology	0.76	(0.56 – 1.01)
	General surgery	0.94	(0.75 – 1.18)

*Positive *C. difficile* results in the 12 weeks prior to onset of first CDI

- Reference group

[#]Indicates significance, p<0.05

Table III: Summary of *Clostridioides difficile* infection (CDI) outbreaks in Beaumont Hospital by year, 2012 to 2021

Year	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021
CDI outbreaks	6	1	2	6	3	1	4	2	1	1
CDI cases associated with outbreaks	36	5	8	21	16	3	15	62	6	7
Number of wards affected	6	1	3	8	3	1	4	HW*	1	1
Minimum number of patients	2	n/a	2	2	3	n/a	3	4	n/a	n/a
Maximum number of patients	11	n/a	6	7	9	n/a	8	62	n/a	n/a

*HW – Hospital wide ribotype 002

n/a – Not applicable

Figure 1: Frequency of the top five *Clostridioides difficile* ribotypes (RT) annually, from 1st January 2012 to 31st December 2021, Beaumont Hospital, Dublin.

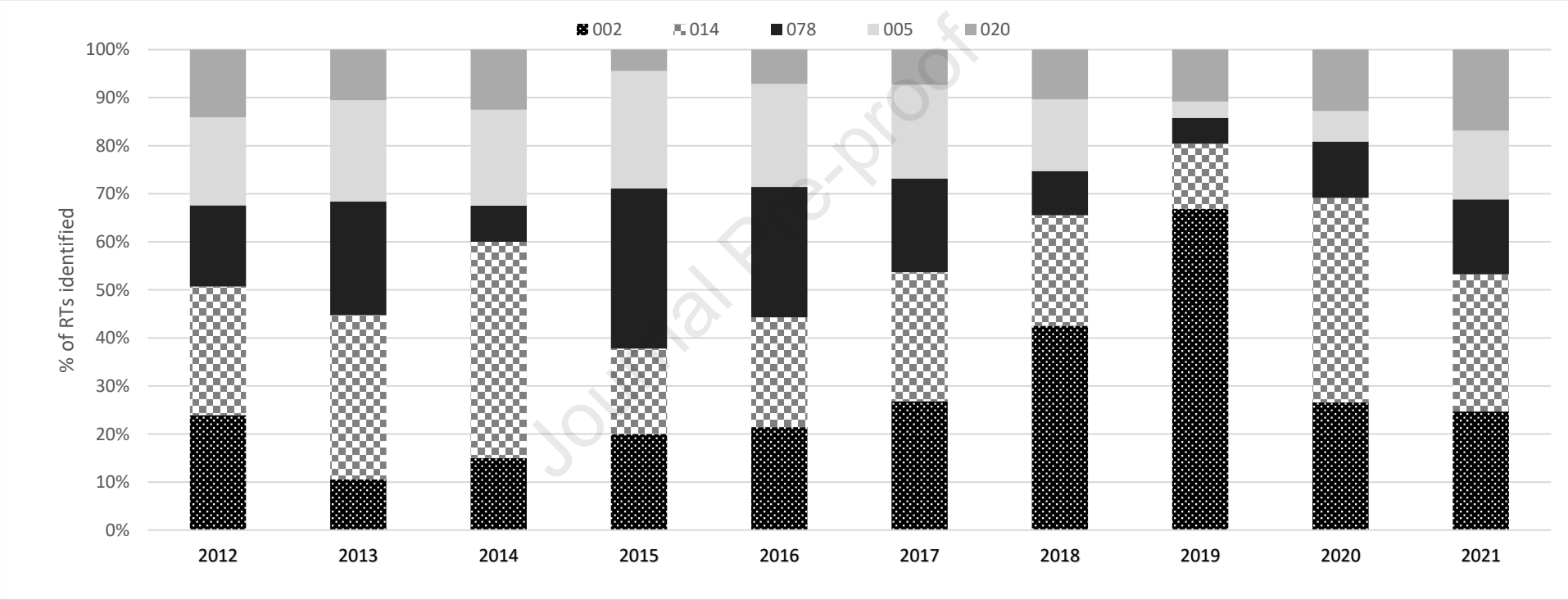
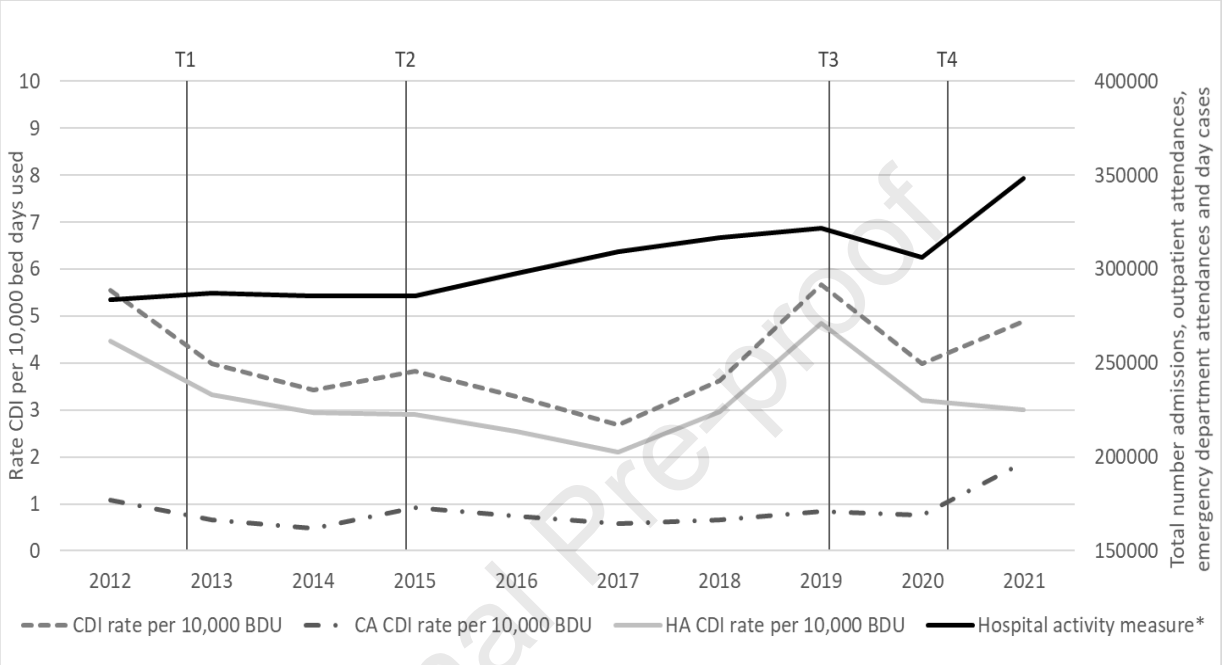


Figure 2: *Clostridioides difficile* infection (CDI) by quarter and case type (healthcare, HA and community acquired, CA CDI) per 10,000 bed days used (BDU) in relation to key time-point events (T1-T4)and hospital activity data from 1st January 2012 to 31st December 2021, Beaumont Hospital, Dublin.



T1 - Q1 2013: Hydrogen peroxide vapour (HPV) decontamination of single rooms once vacated by CDI patients

T2 - Q1 2015: CDI patient ward review by clinical microbiologist. Introduction of PCR/EIA testing algorithm. Fidaxomicin as first line anti-CDI treatment. Rolling ward programmes for commode, mattress and bedpan replacement.

T3 - Q1 2019: Hospital wide outbreak of RT002

T4 - Q2 2020: COVID-19 pandemic

*Hospital activity is the annual total number of admissions, outpatient attendances, emergency department attendances and day cases