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Impact of the COVID-19 pandemic on *Clostridioides difficile* infection in a tertiary healthcare institution in Belgium

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ABSTRACT

Objectives: *Clostridioides difficile* infection (CDI) causes the greatest number of healthcare-associated infectious diarrhoea. CDIs are transmitted by direct and indirect patient-to-patient contact and risk increases with the use of antibiotics. Since early 2020, the COVID-19 pandemic has affected healthcare systems in many ways including substantial changes in hygiene behaviour. The aim of this study was to assess whether CDI incidence differed during the COVID-19 pandemic compared to a year before.

Methods: All tests for suspected CDI cases were recorded for a hospital in Brussels, Belgium. The percentage of CDI-positive results and incidences (total and healthcare-associated (HA-CDI)) for years 2019, 2020, 2021, and 2022 were calculated. Antibiotic consumption was analysed for years 2019 and 2020.

Results: Since the COVID-19 pandemic struck, a significant reduction of up to 39% was observed in the number of *Clostridioides difficile* stool tests in our hospital. A significant decrease in the percentage of positive tests and a 50% decrease in the incidence of CDI (total and HA-CDI) was found for 2020 compared with 2019 and confirmed for years 2021 and 2022. The decrease in CDI incidence was mostly marked in haematology, nephrology, and gastroenterology units. No significant change in the use of antibiotics was found.

Conclusion: The global decrease in CDI incidence observed in our hospital was not associated with a change in the use of antibiotics. The control measures implemented to prevent COVID-19 transmission may explain a reduction in CDI incidence. An underdiagnosis of CDI cannot be excluded.

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Introduction

Clostridioides difficile (*C. difficile*) has been recognised as the main cause of healthcare-associated infectious diarrhoea and is rapidly becoming an urgent global public health threat [1]. The symptoms of *C. difficile* infection (CDI) range from mild diarrhoea to life-threatening toxic megacolon and therefore the clinical and economic burdens of these infections are highly significant [2]. CDI is responsible for 15 to 25% of antibiotic-associated diarrhoeas and more than 95% of pseudomembranous colitis cases [3]. Recurrences after an initial episode of CDI are common, with an estimated rate of 15 to 35% of all cases [4]. The principal risk factors for infection are advanced age, prolonged hospitalisation, and exposure to antimicrobials [5–7]. Recent studies have described epidemiological changes including the bacterium spreading further into the community as well as an increase in the incidence, recurrence, and severity of CDI in North America and Europe [8,9]. These shifts

have mainly been attributed to the emergence of highly virulent *C. difficile* clones including PCR ribotype (RT) 027 and RT078 [10].

The route of infection for *C. difficile* is faecal-oral [11], with transmission by direct patient-to-patient contact but also by indirect contact via the hands of caregivers, the environment, and contaminated equipment [12]. The high contamination of *C. difficile* by various routes is partly due to *C. difficile* sporulation. The spores produced by this bacterium are resistant to heat, conventional detergents, alcohol, and acidic environments which facilitates its persistence in the environment for long periods of time [13]. Antimicrobial stewardship and compliance with hand hygiene and personal protective equipment (PPE) protocols are required to reduce horizontal CDI transmission [14].

In January 2020 the COVID-19 outbreak struck the world hard with a range of consequences on both healthcare and community levels. The pandemic created a focus on hygiene. The aim of this

study was to evaluate whether CDI incidence differed during the COVID-19 pandemic compared to previous years in a tertiary-care teaching hospital.

Materials and methods

Study design

difficile infections from 2019 to 2022 in a 973-inpatient bed tertiary-care teaching hospital (Cliniques universitaires Saint-Luc Hospital, Brussels, Belgium) were retrospectively analysed. The diagnosis of CDI was based on clinical symptoms (presence of diarrhoea) and confirmed by microbiological evidence of toxin-producing *C. difficile* in stools [15]. The infection was considered community-acquired (CA) if symptoms were present within two days of admission and was considered healthcare-associated (HA) if symptoms appeared more than two days after admission. We performed two types of analyses: comparison of the percentage of positive toxigenic *C. difficile* tests (per month and per unit) and comparison of CDI incidence (total CDI incidence per 100 admissions and HA-CDI per 100 hospitalisation days) for the entire hospital and within the most prevalent *C. difficile* hospital units (at least 2 cases of CDI in 2019).

C. difficile testing methods and ribotyping

Determination of toxin-producing *C. difficile* is routinely performed on all diarrheic fresh stool samples from patients older than two years with CDI suspicion (>3 episodes of non-forming stools in 24 hours) using the two-step algorithm recommended by the European Society of Clinical Microbiology and Infectious Diseases [15]. The diagnostic algorithm test consists of a combined enzyme immunoassay that detects glutamate dehydrogenase and toxins A and B (Immunocard STAT!®; Meridian Bioscience, Cincinnati, OH, USA) as an initial step with a real-time PCR assay (Xpert® *C. difficile* BT Assay; Cepheid, Sunnyvale, CA, USA) for confirmation of glutamate dehydrogenase assay-positive and toxin enzyme immunoassay-negative samples. In addition, all samples were cultured on a selective medium (CHROMID® *C. difficile* agar; bioMérieux, Marcy-l'Étoile, France). Finally, suspected *C. difficile* colonies were confirmed using MALDI-TOF MS (Bruker Daltonik GmbH, Bremen, Germany). All *C. difficile* isolates were characterised by PCR ribotyping using capillary gel electrophoresis (3500xL Genetic Analyzer; Applied Biosystems, Thermo Fisher Scientific, Waltham, MA, USA).

Antibiotic consumption

Total antibiotic consumption as well as the antibacterials which most often lead to CDI (i.e. 2nd and 3rd generation cephalosporins, fluoroquinolones,

clindamycin, and carbapenems) were examined within the most prevalent *C. difficile* hospital units for the years 2019 and 2020. Included units were haematology, oncology, gastroenterology, geriatrics, nephrology, internal medicine, digestive surgery, and non-digestive surgery. Defined daily dose per 100 days of hospitalisation (DDD/100 hospital days) was used to evaluate antibiotic use.

Statistical analysis

One-way analysis of variance (ANOVA) with Tukey's multiple comparison post hoc test and two-way analysis of variance with Dunnett's multiple comparison post hoc test were utilised. Results were considered statistically significant if $p < 0.05$. Statistical analyses were performed with GraphPad Prism (ver. 7; San Diego, CA, USA).

Results

Compared to the pre-pandemic period of 2019, the results showed a decrease of 14% in the number of admissions in 2020 (70,169 vs 60,162, respectively). When looking at hospitalisation days, they followed a similar pattern with a decrease of 12% in 2020 (241,618 in 2019 vs 212,463 in 2020). The number of admissions and hospitalisation days remained constant during the period from 2020 to 2022 with a mean of 62,635 admissions and 219,977 hospitalisation days. Likewise, a significant reduction of up to 39% was observed in the number of *C. difficile* stool tests: from 3,230 in 2019 to 2,516 in 2020, 1,963 in 2021, and 2,119 in 2022 ($p < 0.01$) (Table 1 and Figure 1).

In 2019, the percentage of positive toxigenic *C. difficile* tests was 5.23% and the total CDI incidence was 0.241/100 admissions with 63.31% HA-CDI and 38.69% CA-CDI. The percentage of positive toxigenic *C. difficile* tests and the CDI incidence (total and HA-CDI) decreased significantly in 2020 and 2021 compared to 2019 ($p < 0.05$) (Table 1 and Figure 1).

The two months with the lowest percentage of positive tests recorded in the study period (0.60% in May 2020 and 0.50% in September 2020) fell within the COVID-19 epidemic waves. The total CDI incidence was mostly below 0.15/100 admissions during the first COVID-19 outbreak. No significant differences were observed for percentage of positive toxigenic *C. difficile* tests between 2020 and 2021 nor for the CDI incidence (total and HA-CDI) between 2020, 2021, and 2022. Notably, in 2022 the percentage of positive toxigenic *C. difficile* tests escalated during the last quarter to reach 5.78% in December 2022. The proportion of HA-CDI and CA-CDI remained stable over the study period with a slight increasing trend for HA-CDI (72.46%) in 2021.

Table 1. Patient data pertaining to *Clostridioides difficile* testing, hospitalisations, admissions, and incidences for the entire hospital.

	2019	2020	2021	2022
Number of tests	3,230	2,516	1,963	2,119
Percentage of positive toxigenic <i>C. difficile</i> tests (%)	5.23	3.06	3.52	4.01
Number of admissions	70,129	60,162	64,351	63,391
Number of hospitalisation days	241,618	212,463	222,491	224,977
Total CDI incidence/100 admissions	0.241	0.128	0.107	0.134
HA-CDI incidence/100 hospitalisation days	0.044	0.022	0.022	0.024
HA-CDI/CA-CDI ratio	1.72	1.56	2.63	1.74

CA: community-acquired; CDI: *Clostridioides difficile* infection; HA: healthcare-associated.

For the eight most prevalent hospital units, a reduction in number of admissions and hospitalisation days were observed in 2020, mainly in digestive surgery, and internal medicine (Table S1 in supplementary material). Over the time of our survey, the number of stool tests decreased up to 33% in total for these 8 units, following the general hospital pattern decrease. However, when looking at specific units, this did not hold true for the haematology and oncology units, where number of tests increased (Table S1 and S2 in supplementary material). The total CDI incidence per 100 admissions of these eight units significantly decreased from 0.365 in 2019 to 0.191 in 2020, 0.184 in 2021, and 0.190 in 2022. A marked decrease in CDI incidence (total and HA-CDI) and percentage of positive toxigenic *C. difficile* tests were observed in the last three years compared to 2019 in the haematology and nephrology departments (Figure 2). In gastroenterology and digestive surgery units, the percentage of positive toxigenic *C. difficile* tests decreased in 2020–2021 but rose in 2022. Except for these last two units, the percentage of positive toxigenic *C. difficile* tests remained constant between 2021 and 2022.

Considering antibiotic consumption, DDD/100 hospitalisation days for the most prevalent units was calculated for 2019 (pre-COVID-19) and 2020 (Figure 3). No significant differences were observed in total antibiotic consumption (495.82 DDD/100 hospitalisation days in 2019 vs 480.59 in 2020) nor in the use of antibiotics which are known to promote CDIs [16] (197.51 DDD/100 hospitalisation days in 2019 vs 187.08 in 2020).

A total of four hundred *C. difficile* isolates corresponding to toxigenic *C. difficile* isolates collected from 2019 to 2022 were characterised by PCR ribotyping (Figure 4). When considering the five most common RTs (representing 45% of all isolates in 2019, 46% in 2020 and 2021, and 42% in 2022), the most frequently isolated clone in 2019 was RT014 (16.3% of the samples). A decrease in prevalence of this RT was observed in 2021 (8.24% of the samples) along with an increase in RT106 which became the most frequent RT isolated during 2020 and 2021 (4.81% of samples in 2019, 14.56% in 2020, and 12.94% in 2021). In 2022, the percentages of the five most common RTs among all ribotyped isolates

were similar to 2019. The emergence of RT011 isolates was observed over different time periods in 2021 (5.88% of all isolates) from three patients of different units. RT011 was found in 2019 and 2020, but not in 2022.

Discussion

The results showed a significant change in CDI incidence (total and HA-CDI) during the first outbreak of the COVID-19 pandemic. The CDI incidence and the percentage of positive toxigenic *C. difficile* tests in our hospital decreased in 2020 including for the eight most prevalent units. A general CDI decrease trend has also been reported for other hospitals in 2020 [17,18]. Several factors could contribute to this result. We hypothesised that the decline in CDI incidence could be caused by three main reasons: a decrease in testing, a decrease in antibiotic consumption, and/or an increase in hygiene measures related to COVID-19 prevention.

Our data shows that fewer tests were performed in 2020 and 2021 compared to pre-pandemic 2019. An unintended but inappropriate diminution of testing could have occurred that resulted in underdiagnosing of CDI. Other studies showing similar results hypothesised the following reasons to explain testing and CDI numbers: because diarrhoea is a symptom of COVID-19, testing was not always systematically performed [17–19]; a possible decrease in healthcare quality in general and delayed diagnosis due to restricted hospital referral for CA-CDI led to a decrease in CDI incidence [20]; and/or over- or inappropriate testing may have occurred before the pandemic [18,21]. In our hospital, the number of *C. difficile* tests decreased along with admissions and hospitalisation days but the role of the number of tests performed to explain CDI incidence remains uncertain since the percentage of positive tests also decreased. Furthermore, the greatest decrease in CDI incidence did not take place in units experiencing the greatest reduction in testing. Indeed, in the haematology unit where CDI incidence (total and HA-CDI) significantly dropped, a decrease in testing was not observed.

Regarding the impact of antibiotics, the use of broad-spectrum antibiotics is known to be associated

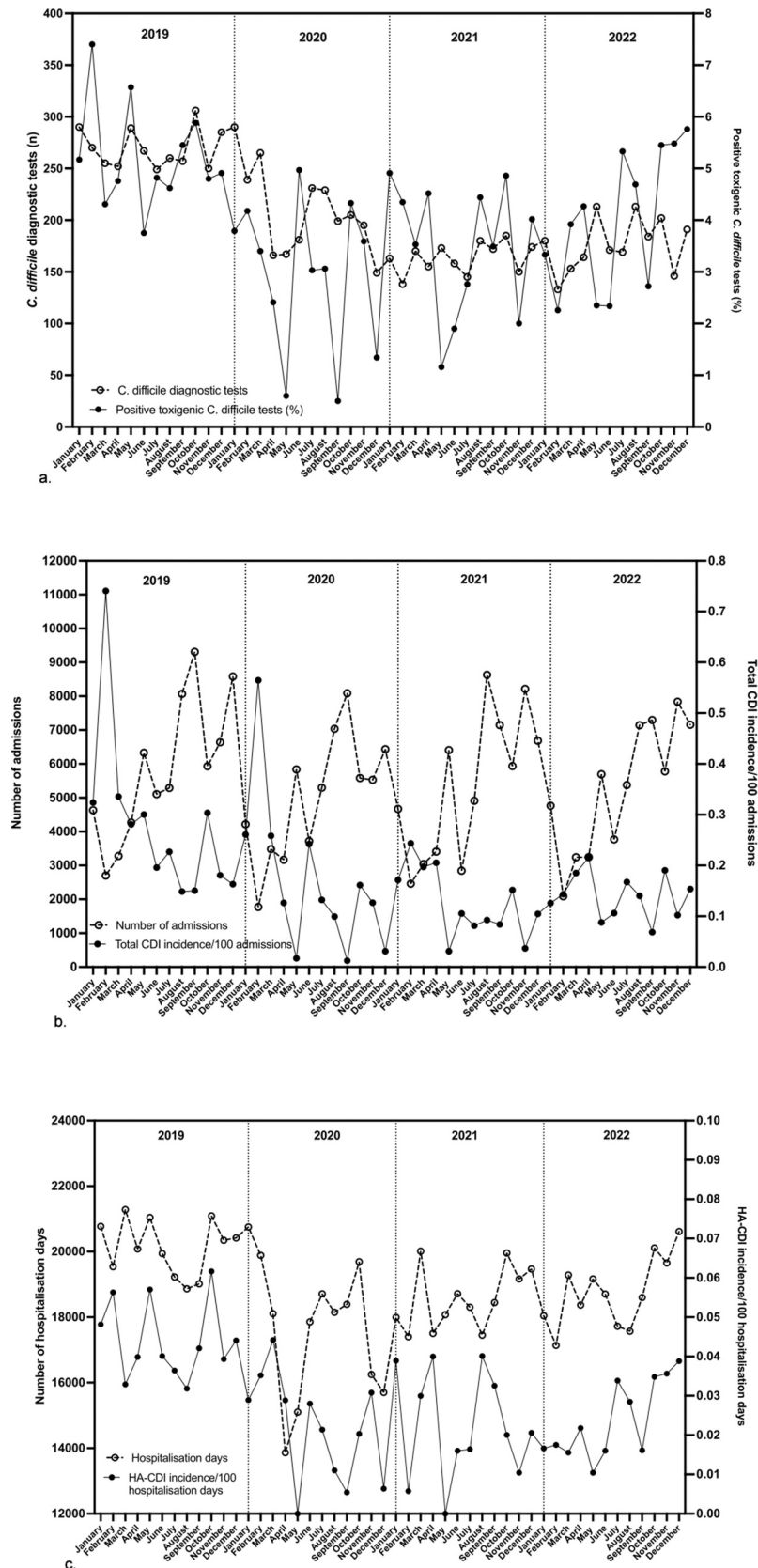


Figure 1. Total *C. difficile* diagnostic tests performed (white circles) and percentage of positive tests (black circles) per month from 2019 to 2022 (A), total admissions (white circles) and total CDI incidence per 100 admissions (black circles) per month from 2019 to 2022 (B), and total hospitalisation days (white circles) and HA-CDI incidence per 100 hospitalisations days (black circles) per month from 2019 to 2022 (C). *C. difficile*: *Clostridioides difficile*.

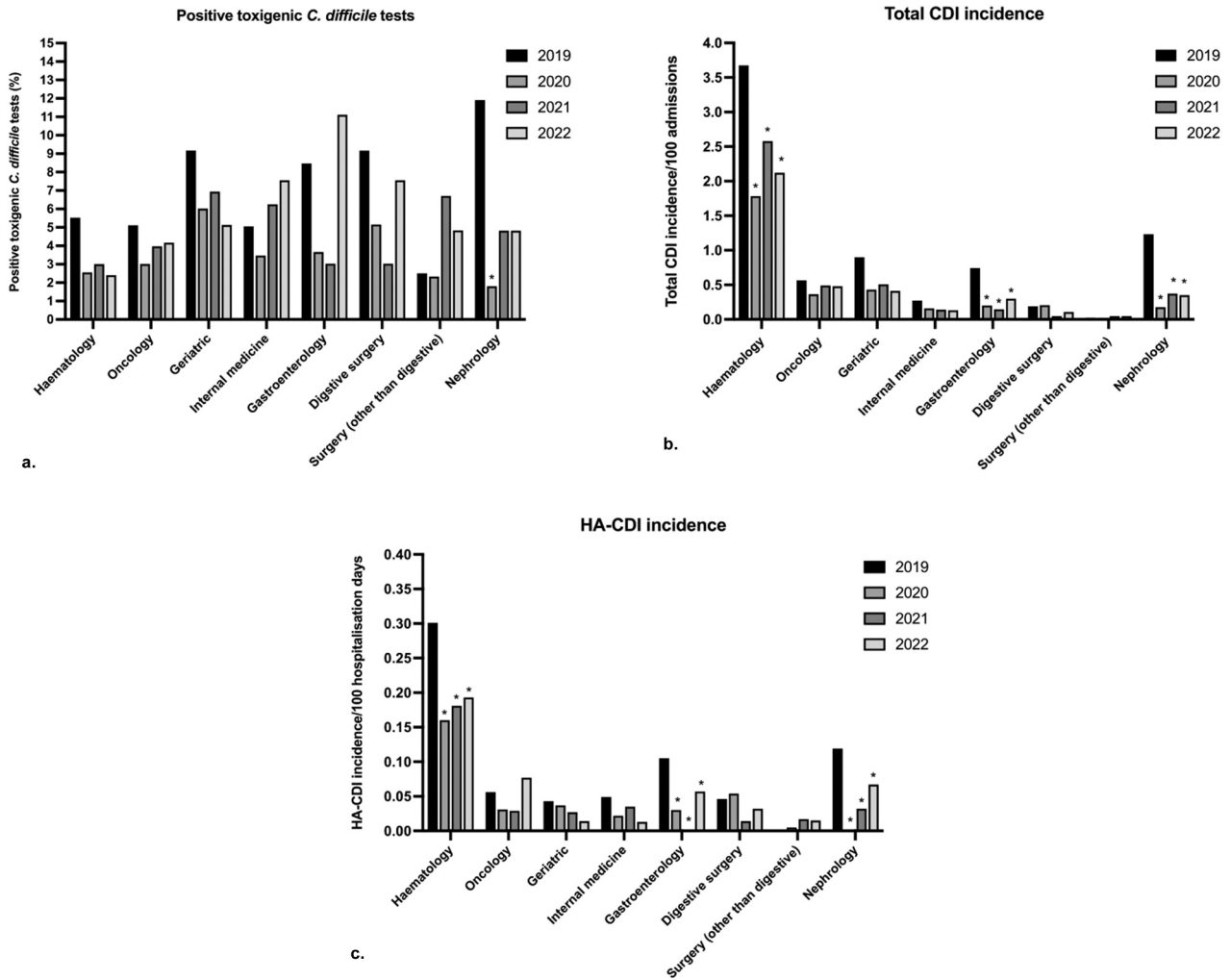


Figure 2. Percentage of positive toxigenic *C. difficile* tests (A), total CDI incidence (B), and HA-CDI incidence (C) in the eight most *C. difficile* prevalent units from 2019 to 2022. Statistical analysis: * $p < 0.05$ by two-way analysis of variance with Dunnett’s multiple comparison post hoc test for comparison between 2019 (closed bar) and the other years. *C. difficile*: *Clostridioides difficile*; CDI: *Clostridioides difficile* infection.

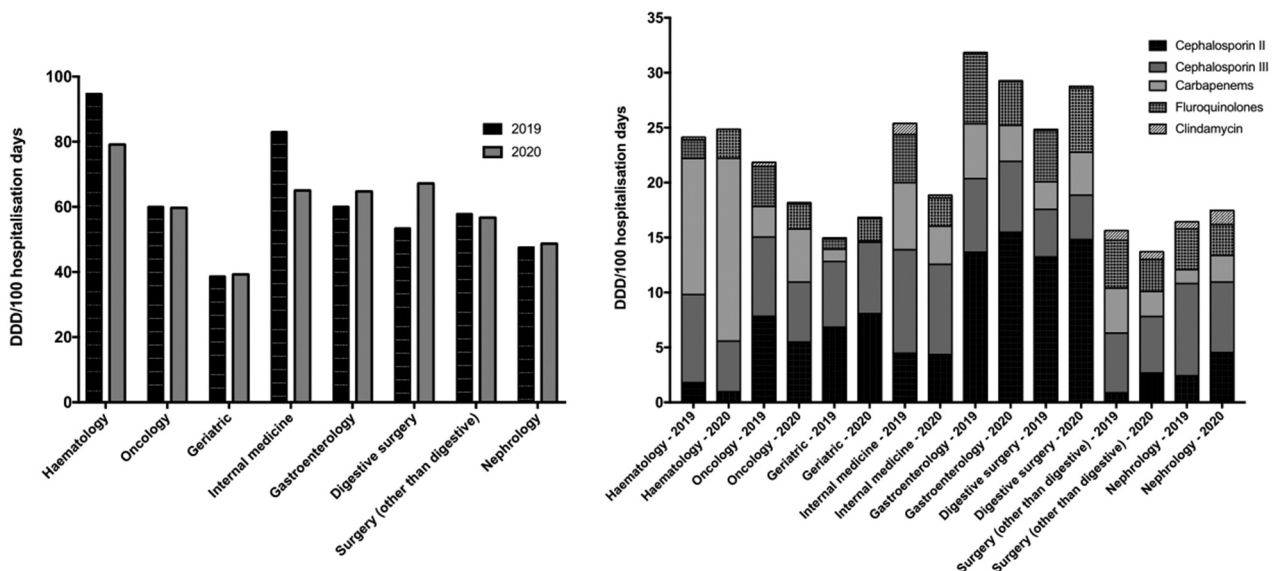


Figure 3. Total consumption of antibiotics for systemic use (left) or consumption of antibiotics which promote *C. difficile* infection (2nd and 3rd generation cephalosporins, fluoroquinolones, clindamycin, and carbapenems; right) expressed in defined daily dose DDD/100 hospitalisation days in the eight most prevalent units during 2019 and 2020. DDD: defined daily dose.

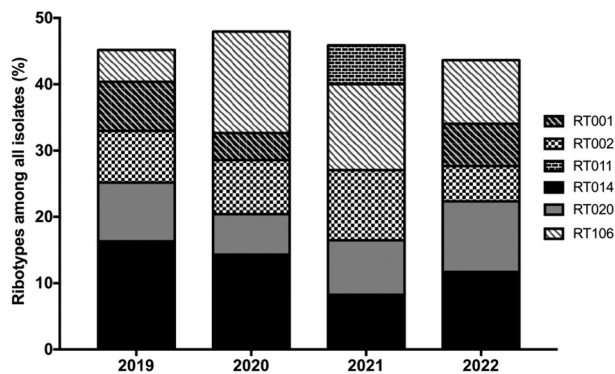


Figure 4. Relative percentages of the five most common RT from 2019 to 2022. RT: ribotypes.

with a higher incidence of HAI [22]. Most studies have shown an increase in antibiotic use in hospitals (including high-risk antibiotics) [17,23] in 2020, although many local differences were observed [24–27]. Within our hospital, a slight non-significant decrease in antibiotics use (including high-risk) was shown in the units with highest *C. difficile* prevalence. In units experiencing the greatest decrease in CDI incidence (total and HA-CDI) (haematology and nephrology), use of high-risk antibiotics slightly increased. Based on these findings, a conclusion on whether a change in antibiotics consumption was associated with CDI incidence cannot be made, confirming other studies suggesting that hospital antibiotics consumption has a low impact on HA-CDI [28,29].

In this study and others, 2020 and 2021 were marked by a series of reinforced hygiene measures including a hospital-wide transmission-based precautions educational program, increased focus on hand hygiene compliance and audits, use of PPE, social distancing, and reduced ward occupancy [18,19,30]. Although hand hygiene measures (which have been shown to significantly reduce CDI [31,32]) were already in place, compliance generally increased during the COVID-19 pandemic [33,34]. Other studies that attempted to explain the decrease in CDI incidence speculated that the preventive measures put in place during the pandemic also significantly reduced HA-CDI [18,19,30]. Similarly, we also hypothesised that infection prevention and control measures implemented in our institution to prevent COVID-19 transmission would influence CDI. The haematology unit is a good case in point: testing did not change from 2019 to 2020 and increased in 2021 and 2022. However, CDI incidence (total and HA-CDI) decreased in 2020 and has remained very low since. As patients in haematology tend to present immunocompromised conditions, it is likely that the medical staff was more compliant to COVID-19 prevention measures. An audit of the different hygiene measures in this unit could help verify this hypothesis and be a catalyst for taking appropriate actions in other hospital units.

However, while hygiene is part of the bundle-care strategy to prevent HAIs in general [35], incidences of HA bloodstream infections were found to increase in 2020–2022 compared to 2019 in our hospital (data not shown). Other studies have also reported an increase in non-CDI HAI but decrease in CDI during the pandemic [36]. Indeed, many HAIs are device-associated infections, which were more influenced by length of stay and additional comorbidities than by hygiene [37–40].

Ribotyping analyses showed an increase of RT106 and decrease of RT014 during 2020–2021 compared to 2019. No epidemic-related surges in CDI were identified in this study. Indeed, none of the most frequent RTs were ever detected at the same place and at the same time. The underlying reasons for the increase of RT106 clone and the decrease of RT014 during the pandemic remains unknown. Ribotyping analyses in the next years will help to determine if these shifts were related or not to COVID-19.

Over time the pandemic has waned, yet testing has not returned to pre-COVID-19 levels. During the first trimester of 2022, the number of tests was still low along with CDI incidence (total and HA-CDI) and the percentage of positive tests. Then, a slight trend to an increase in the percentage of positive tests and HA-CDI incidence occurred, but not in testing. Finally, over the last trimester of 2022, the number of hospitalisation days increased which suggested that hospital activity was heading back to pre-pandemic levels. The number of tests, percentage of positive tests, and CDI incidence (total and HA-CDI) should be profiled again in the future to evaluate whether the multifactorial process responsible for our observations are stable or if a return to pre-COVID-19 numbers is ongoing.

There were limitations to this study. The proportion of hospital patients who were positive for COVID-19 during the evaluated time periods was not measured. In some instances, the hospital units that were evaluated became COVID-19 units to various extents. Patient-level data and clinical spectrum of CDI were not analysed over the study period. Indeed, other *C. difficile* risk factors such as recent hospitalisation, age above 65 years, severe comorbidities, intake of immunosuppressors, intake of long-term proton pump inhibitors, recent gastrointestinal surgery, and enteral feeding were not evaluated. A possible change in the general patient profile and in clinical presentations and complications rates could have occurred during the pandemic as suggested by other studies [20,41]. In addition, lengths of stay during the time of our survey were not included in the analysis. Finally, antibiotic use was only considered for 2019 and 2020 because only these data were available at the time of the study. A CDI incidence decrease despite

stable use of antibiotics cannot be demonstrated for 2021 and 2022.

Although the full impact of the COVID-19 pandemic on CDI remains to be determined, our study suggests that the CDI incidence (total and HA-CDI) diminution that was observed in our hospital during the pandemic is likely a product of the control measures implemented to prevent COVID-19 transmission. Further studies are needed to evaluate whether other factors such as the hospital patient profile, the clinical spectrum of CDI and the CA-CDI incidence have been modified in the past few years. Understanding the decrease of CDI incidence is crucial for taking appropriate measures in long-term CDI management.

Disclosure statement

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