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Short Communication

Impact of COVID-19 pandemic on prevalence of *Clostridioides difficile* infection in a UK tertiary centre

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ABSTRACT

Serious concerns have been raised about a possible increase in cases of *Clostridioides difficile* infection (CDI) during the COVID-19 pandemic. We conducted a retrospective observational single centre study which revealed that total combined community and hospital-based quarterly rates of CDI decreased during the pandemic compared to the pre-pandemic period.

1. Introduction

Coronavirus disease (COVID-19), caused by the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), emerged in Wuhan (China) in early December 2019 and has spread rapidly worldwide, causing a global pandemic. The elderly population is disproportionately affected by COVID-19, with initial reports showing that ~80% of the deaths due to COVID-19 occur in those over the age of 65 [1]. Due to the enhanced usage of broad-spectrum antibiotics during the current pandemic, overcrowding in hospitals, and the fact that *Clostridioides difficile* infection (CDI) largely affects the elderly, serious concerns have been raised about a consequent possible increase in transmission of hospital-acquired infections such as CDI, particularly in frail, elderly patients [2]. There are very few clinical surveillance studies reporting CDI with COVID-19. Sandhu et al. described 9 patients at a medical centre in Detroit, Michigan, with SARS-CoV-2 and CDI during March 11 - April 22, 2020, the majority of whom were elderly females with high ATLAS scores (https://www.mdcalc.com/atlas-score-clostridium-difficile-infection) and multiple co-morbidities [3]. The onset of diarrhoea was found to occur after COVID-19 diagnosis in 7 of these cases, with a median of 6 days from CDI diagnosis to COVID-19 diagnosis. In another high-volume US tertiary-care centre, Mount Sinai, New York, Luo et al. did not find a difference in hospital onset CDI (HO-CDI) rate during the pandemic despite a trend toward increased high-risk antibiotic exposures [4] and is further corroborated by similar findings of a retrospective study by Allegretti et al. across 9 hospitals in Massachusetts [5]. More recently, Sehgal et al. identified 21 patients (20 hospitalized) with median age 70.9 years who had CDI and COVID-19 within 4 weeks of each other [6].

From a European perspective, Granata et al. identified 32 COVID-19 patients who developed HO-CDI across 8 participant hospitals in Italy during the study period from February through July 2020, corresponding to a HO-CDI prevalence of 0.38%. The presence of

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previous hospitalization, steroid administration, and consumption of antibiotics during hospitalization were the main risk factors associated with CDI [7]. Bentivegna et al. assessed differences in hospital-acquired CDI (HA-CDI) in the medical wards of a hospital in Rome before and during the COVID-19 pandemic, finding that HA-CDI was significantly lower during the pandemic with respect to previous years. However, COVID-19 departments showed higher HA-CDI incidence respect to COVID-19 free wards during 2020, suggesting that SARS-CoV-2 infection may be a possible risk factor for CDI [8]. In a Spanish tertiary centre study, Ponce-Alonso et al. observed a 70% reduction in the incidence density of nosocomial CDI during the period with the maximal incidence of COVID-19 compared with the same period in the preceding year, which they attributed to the reinforcement of infection control measures [9]. In contrast, Lewandowski et al. found a significant increase in the incidence of CDI during the COVID-19 pandemic compared with the pre-pandemic period in their single centre study in Warsaw, Poland (10.9% vs 2.6%; $P < 0.001$) [10].

The main aim of this study was to assess the impact of the COVID-19 pandemic on total hospital and community-associated quarterly rates of CDI and in-hospital antimicrobial consumption patterns before and during the pandemic. We hypothesized that the reinforcement of infection control measures implemented to prevent COVID-19 transmission would lead to a decrease in total CDI case burden in our tertiary care centre.

2. Methods

We conducted a single centre retrospective analysis in Nottingham University Hospitals NHS Trust (NUHT), UK, from Jan 2019 through to June 2021. NUHT is a large acute teaching hospital in England with 1700 beds, 90 wards and approximately 16,000 staff, providing specialist medical and surgical services to 2.5 million residents of Nottingham and its surrounding communities, and tertiary services to a total of 3–4 million people from neighbouring counties. During the pandemic, NUHT continued to admit both COVID-19 and non-COVID-19 patients and was therefore not complicitly dedicated to coronavirus disease. Throughout the pandemic infection control measures (including PPE, mask wearing, heightened cleaning, adherence to social distancing and the limiting of visitors) were implemented and adapted in line with national guidance. Prudent antibiotic prescribing practices remained in place throughout the pandemic and the Pharmacy department launched an antibiotic prescribing guideline for COVID-19 to help reinforce appropriate use of antibiotics during the pandemic. All antibiotic audits remained in place throughout the pandemic.

Using the database of the participant Trust, we identified total CDI case burden (community and hospital-combined in all subjects $\geq$2 years of age) and hospitalized adult ($\geq$18 years old) COVID-19 patients with CDI reported from January 2019 (one year before the first UK lockdown in March 2020), through to end of June 2021. We compared total quarterly CDI cases per 10,000 occupied bed days (OBD) during the pandemic with the preceding control years 2019/2020. We also documented OBD (%), total COVID-19 admissions, and consumption of antimicrobials by quarter. A diagnosis of CDI was made in patients with new onset diarrhoea and confirmed by means of toxin immunoassays. Some PCR positive, toxin negative cases were treated. However, this was based on clinical suspicion or susceptibility of the patient and thus not definitive clinical cases, thus these were not included in the analysis. Basic demographic and laboratory data were collected using Excel Office and analysed by means of descriptive statistics. Rates of CDI per 10,000 OBD were compared between quarters by means of binomial test of proportions. A corrected P-value of $\leq$0.008 was considered significant to account for multiple comparisons. The research was reviewed by the clinical governance team at the Nottingham University Hospitals NHS Trust and informed consent was not required since this was a service evaluation and minimal risk retrospective study.

3. Results

A total of 491 cases of CDI were observed over the study period in over 1.4 million bed days. The CDI infection rates per 10,000 OBD for each yearly quarter for 2019, 2020 and 2021 are shown in Fig. 1. The CDI rate per 10,000 OBD was significantly lower in the first and second quarters of 2021 compared to that seen during the same period in 2020 ($p < 0.0001$). The quarterly defined daily doses (DDD) of antimicrobials per 10,000 OBD were also lower in the first quarter of 2021 compared to the preceding 2 years (Supplementary Fig. 1). However, the total CDI rates in 2020 were significantly higher for the quarterly period from July–Sept compared to the same time in 2019, $p = 0.005$. Data pertaining to the number of CDI cases, number of OBD and DDD of antimicrobials per 10,000 OBD in the time periods before, during and after the emergence of the pandemic are detailed in Supplementary Table 1. Details of OBD (%) and total COVID-19 admissions per quarter are presented in Fig. 2.

We identified 8 cases (median age 74.5 years, range 65–84 years with male:female ratio 5:3) with SARS-CoV-2 and CDI. The mean duration from SARS-CoV-2 diagnosis to CDI diagnosis was 21 days, and in all cases, CDI was diagnosed after SARS-CoV-2 diagnosis.

4. Discussion

In this study, we observed a significant reduction in the total CDI infection rate per 10,000 OBD during the current pandemic compared with the pre-pandemic period. There are several potential reasons for this observation. Firstly, it is likely that a reduction in patient mobility, including a general reluctance to present to primary or secondary practice, as well as a reduction in overall testing, may have under-estimated the true burden of CDI in the community. Despite the widespread use of antibiotics, the total CDI burden may have been suppressed due to aggressive reinforcement of infection control measures such as frequent handwashing, augmented environmental cleaning regimes, universal PPE, social distancing, in addition to limited patient visits and movement, all of which may have indirectly limited the nosocomial spread of *C. difficile*. Furthermore, a forced reduction in hospital consultations and surgical procedures may have contributed to fewer opportunities of introducing *C. difficile* into the hospital from the community.

The higher CDI case burden seen in July–Sept in 2020 may be partially explained by Annual Epidemiological Commentary data on seasonal trends from Public Health England which showed that the greatest proportion of CDI cases was reported in the July–September quarter of financial year from 2016/17 onwards (between 26% and 29% of cases each year) [11]. An explanation for this shift in seasonality is currently lacking. Interestingly, studies have demonstrated seasonal variability in rates of CDI [12,13]. Rodriquez-Palacios et al. [12] observed that *C. difficile* was more commonly isolated from retail meat in Canada in winter, suggesting a seasonal component may exist. Clements et al. [13] analysed 20 studies in their systematic review, which reported a peak in CDI cases in the spring and contrastingly lower frequencies of CDI in summer/autumn across Northern and Southern hemispheres and continents. It remains possible that environmental or food contamination with *C. difficile* spores may explain variation in seasonal patterns of CDI. Indeed, strains of *C. difficile* have been detected in various environmental sources, including farms, livestock animals, water (sewage and

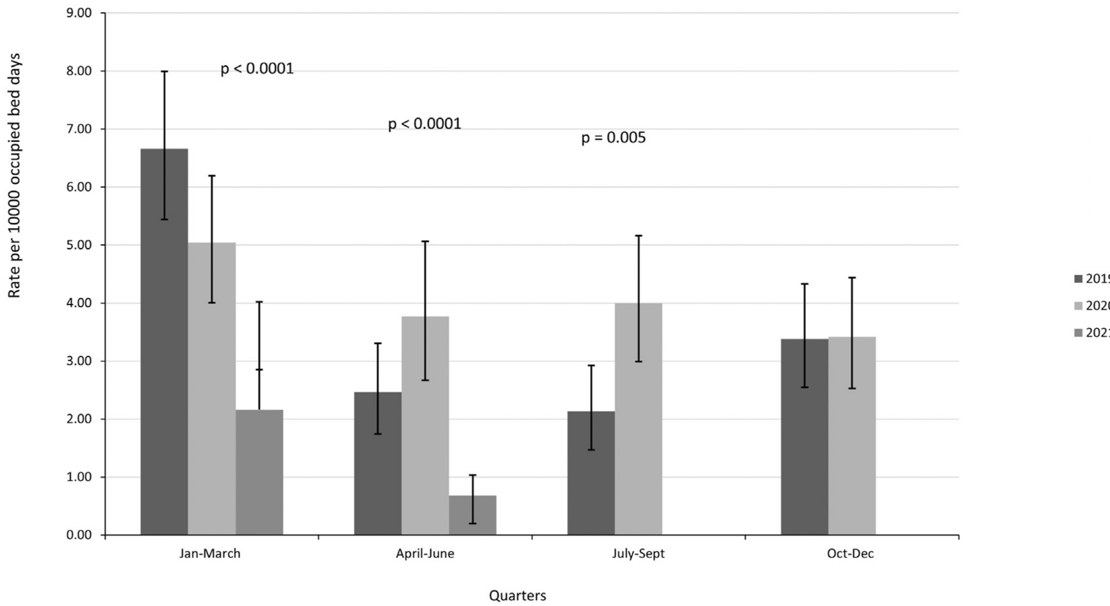

Fig. 1. Total community and hospital-acquired *C. difficile* infection (CDI) rate per 10,000 occupied bed days between January 1st, 2019 to June 30th, 2021.

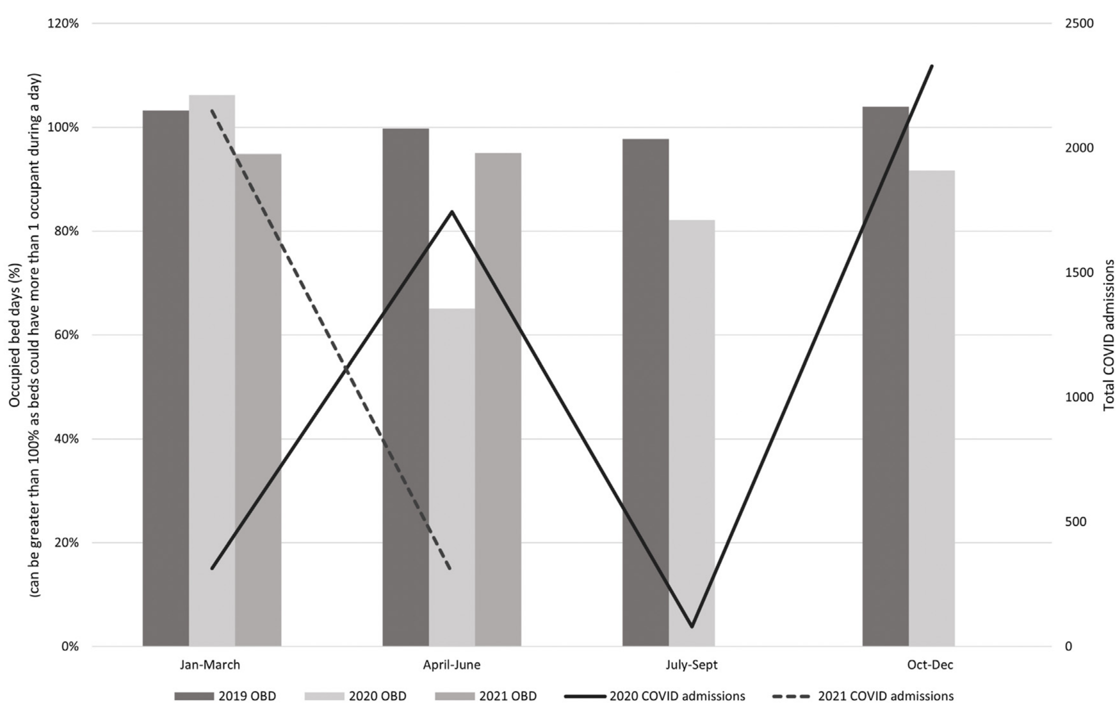

Fig. 2. Occupied bed days (%) and total COVID-19 admissions by quarter. Data between January 1st, 2019 and June 30th, 2021.

rivers) and agricultural produce [14–16] as well as public lawn spaces [17]. However, there have been no reported cases of food-borne transmission of CDI reported to date.

Our study is limited by its retrospective design and single centre analysis. We did not distinguish between community-acquired and hospital-acquired CDI. Nevertheless, our findings support the importance of maintaining a heightened level of attention regarding infection control measures during the pandemic, which may help significantly decrease overall *C. difficile* transmission and related health economic costs.

Author contributions

T.M and C.C planned and drafted the study. S.V. collated the data with the assistance of R.M. A.C. H.T, S.B. T.H. and H.A. S.V., T.M., and C.C. analysed and evaluated the results. All authors contributed to writing the manuscript and approved of the final submitted version of the manuscript.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: T.M. is a consultant advisor for Takeda. All other authors declare that they have no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.anaerobe.2021.102479.

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