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Clostridioides difficile (including epidemiology)

Clostridioides difficile infection and testing rates in South Africa: A multicentre study, 2017–2020

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ABSTRACT

Objectives: To describe *Clostridioides difficile* infection (CDI) rates and testing practices, at three tertiary/quaternary hospitals in South Africa (SA) for the period 2017 to 2020.
Methods: A retrospective laboratory record review of all *C. difficile* testing at the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH), Tygerberg Hospital (TBH) and Inkosi Albert Luthuli Central Academic Hospital (IALCH) was performed. Clinical records of patients with rCDI were reviewed to determine recurrent CDI (rCDI) rates.
Results: The median primary CDI rates per 10 000 patient-days (PD) were 5.3 at CMJAH, 1.8 at TBH, and 0.3 at IALCH. In 2020, all hospitals reported an increase in primary CDI rates compared to 2019. The median testing rates per 10 000 PD were 39 at CMJAH, 14 at TBH, and 4 at IALCH. The median age of patients with primary CDI was 33 years (IQR: 22–45 years). The rCDI rates ranged from 2 to 5 per 100 incident episodes.
Conclusion: Significant variations in CDI and testing rates were observed across the three hospitals. An increase in CDI rates was noted at all centres during the 2020 SARS-CoV-2 outbreak. Advanced age was not prevalent in the cohort, and rCDI rates were relatively low. These findings highlight the need for systematic surveillance of healthcare-onset CDI across SA hospitals.

1. Introduction

Clostridioides difficile infections (CDI) are among the leading healthcare-associated infections worldwide and are associated with significant morbidity and mortality [1,2]. Certain risk factors predisposing patients to the development of CDI are well-established [1]. In South Africa (SA), risk factors associated with CDI include documented tuberculosis (TB) infection (including multidrug-resistant TB), hospitalisation prior to current admission [2], and antimicrobial exposure [2,3]. The relationship between TB and CDI is further emphasised by the high incidence of CDI in specialised TB hospitals [4]. Antimicrobial consumption in SA is also substantial and the use of broad-spectrum agents is common [5]. Although an association between CDI and low CD4 counts in HIV-infected individuals has been suggested [2], there is currently a lack of data particularly from the SA context, which houses the largest antiretroviral programme in the world, to support this [2,6].

CDI is a notifiable medical condition in SA, but co-ordinated surveillance of CDI is not practiced and the burden of disease is likely underestimated due to a lack of awareness and limited access to laboratory diagnostics in some settings [7–9]. A national assessment of the burden of CDI over a one-year period in 2016/2017 revealed a test positivity rate of 18.5 %. The national incidence rate was 53.89/100 000 admissions and was highest in the Gauteng province followed by the Western Cape. Testing rate, positivity rate and incidence varied widely

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between provinces and levels of care, with specialised TB hospitals bearing the highest burden, followed by quaternary level facilities [4].

Recurrent CDI (rCDI), a complication occurring in up to 40 % of patients, is associated with even higher morbidity [10], is challenging to manage and is resource-intensive for the healthcare system [10,11]. Treatment options recommended for rCDI, like fidaxomicin and faecal microbiota transplant, are costly and often not accessible in resource-constrained settings [12]. The entity of rCDI in Africa is poorly described [6]. In SA, low rates of rCDI have been recorded (2.14 %) [4], but data are limited.

CDI is not well-understood in SA, despite the high associated morbidity and mortality [11], its emerging association with TB [2], its propensity to cause outbreaks [13,14] and the challenges associated with its treatment [1,13]. This study aimed to describe *C. difficile* testing practices and the epidemiology of CDI over a 4-year period at three academic hospitals based in the most populous provinces of South Africa: Gauteng, Western Cape and KwaZulu Natal.

2. Methods

2.1. Study design and setting

This retrospective record review was performed at three hospitals: Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) (1080 beds, Gauteng, quaternary), Tygerberg Hospital (TBH) (1384 beds, Western Cape, tertiary) and Inkosi Albert Luthuli Central Academic Hospital (IALCH) (890 beds, KwaZulu Natal, quaternary). The study was conducted on patients admitted between January 1, 2017 and December 31, 2020. Diagnostic stewardship provided at the three hospitals is to consider CDI in patients 2 years and older with the following clinical presentation: (1) inpatients with new-onset diarrhoea, (2) inpatients with diarrhoea on admission and that continues for more than 3 days and for which an alternate aetiology is not found and (3) patients presenting with diarrhoea and having known risk factors for CDI. However, submission of samples for CDI testing is at the discretion of attending clinician. The laboratories reject formed stool samples submitted for CDI testing. Laboratory and demographic data were obtained from the National Health Laboratory Services (NHLS) Corporate Data Warehouse. Patient-days (PD) data were obtained from the hospital administrative departments. Clinical records were reviewed to assess for recurrence in the rCDI cases identified by laboratory testing. Positive tests within two weeks of a previous positive test were regarded as the same CDI episode.

2.2. Laboratory testing

A two-step algorithm has been used for *C. difficile* testing since 2017 at each of the three clinical microbiology laboratories based at the hospitals. Stool samples initially underwent testing with a combination lateral flow glutamate dehydrogenase (GDH)-toxin immunoassay (C. diff Quik Chek, Techlab, Virginia, USA). Samples that tested GDH negative and toxin negative were reported as negative, and samples that tested GDH positive and toxin positive were reported as positive. Samples that were GDH positive and toxin negative were subsequently tested with the Xpert *C. difficile* assay (Cepheid, California, USA). The Xpert result (positive or negative) was reported as the final result.

An exception to the above testing algorithm occurred at TBH from 1 January to June 30, 2017. During this period, all samples were tested only with the Xpert *C. difficile* assay.

2.3. Data analysis

Demographic data, namely patient age, sex and ward of admission, were collected and analysed. Patients under 2 years of age were excluded from the analysis.

Test positivity rates refer to the proportion of tests performed that were positive. Recurrent CDI rates were expressed as the number of patients with at least one rCDI episode as a proportion of the total number of initial CDI cases for that period. Testing and infection rates were reported per 10 000 PD.

Recurrent CDI was defined as positive *C. difficile* results on laboratory testing WITH new onset of symptoms including diarrhoea (documented in clinical records) between 2 and 8 weeks after the onset of symptoms from the previous CDI episode. In cases where diarrhoea was not documented or medical records were not available to confirm the presence of diarrhoea, these episodes were excluded.

2.4. Statistical analysis

Descriptive statistical analysis was performed using Microsoft Excel. Continuous numerical variables were summarised using medians and interquartile ranges for data not normally distributed. Categorical variables were summarised using proportions and 95 % confidence intervals (CI) were generated. The two-sample Z-test was used to compare categorical variables (Epitools). A two-tailed p-value of <0.05 was considered statistically significant.

2.5. Ethical considerations

A waiver of informed consent was granted for this retrospective study involving results already generated and applied in routine patient care (CMJAH: University of the Witwatersrand M210529; May 31, 2021, TBH: Stellenbosch University N21/06/051; July 15, 2021 and IALCH BREC/00003845/2022); March 3, 2022. Approval was granted from hospital management at each hospital.

3. Results

3.1. Total CDI

Primary CDI rates fluctuated during the period of study, as summarised in Fig. 1. Primary CDI rates at CMJAH were 3.0- and 15.9-fold higher than those at TBH and IALCH, respectively. All three centres had an increase in primary CDI rates in 2020 compared to 2019. This did not surpass the 2017 estimate at TBH.

Demographic data for patients with CDI are outlined by facility in Table 1. Overall, patients with primary CDI had a median age of 39 years (IQR 22–45). This varied by centre: 38 years (IQR 26–52 years), 42 years (IQR 29–56 years) and 31 years (IQR 18–44 years) for CMJAH, TBH and IALCH, respectively. Most patients were from the adult medical wards, with the intensive care units well represented despite their limited bed capacity.

Laboratory testing.

A total of 4712, 2449 and 275 tests were performed at CMJAH, TBH and IALCH respectively, over the four-year study period, equating to median testing rates of 39, 14 and 4 per 10 000 PD respectively. The yearly testing rates are shown in Fig. 2. *C. difficile* testing rates at CMJAH were 2.7- and 10.4-fold higher than those at TBH and IALCH, respectively.

The test positivity rates over the four years were 15 % (95 % CI 14–16), 12 % (95 % CI 11–14) and 8 % (95 % CI 2–11) for CMJAH, TBH and IALCH, respectively, and were significantly higher at CMJAH ($p < 0.001$). The yearly positivity proportions are shown in Fig. 2. This was significantly higher in 2020 compared with the base year of 2017 at CMJAH ($p = 0.013$), but did not differ significantly at the other two facilities.

3.2. Recurrent CDI

In this cohort, 25 patients were identified with rCDI. Table 2 summarizes the rCDI episodes and rates. Three of the 25 patients had two rCDI episodes. The overall rCDI rate per centre ranged from 2 to 5 per 100 incident episodes. The combined rCDI rate for all three centres was

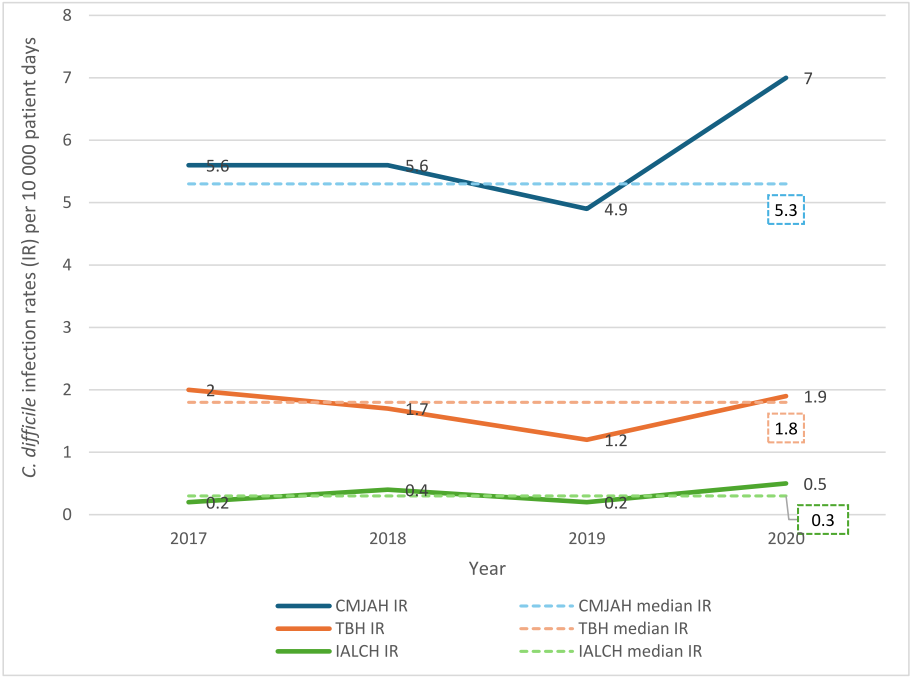

Fig. 1. Primary *C. difficile* infection rates (IR) and median per 10 000 patient days by hospital, 2017–2020. CMJAH: Charlotte Maxeke Johannesburg Academic Hospital; TBH: Tygerberg Hospital; IALCH: Inkosi Albert Luthuli Central Hospital.

Table 1
Pooled 2017–2020 demographics for patients with *C. difficile* infection per hospital.

	CMJAH N = 696 (%)	TBH N = 301 (%)	IALCH N = 23 (%)	Overall N = 1020 (%)
Sex				
Male	350 (50) (95 % CI 47–54)	157 (52) (95 % CI 47–58)	16 (70) (95 % CI 49–84)	523 (51) (95 % CI 48–54)
Age in years				
2–18	80 (11)	26 (9.64)	1 (4)	107 (11)
≥18-<45	352 (51)	155 (51)	15 (65)	522 (51)
≥45-<65	185 (27)	85 (28)	5 (22)	275 (27)
≥65	79 (11)	35 (12)	2 (9)	116 (11)
[a]Ward type				
Adult Surgical	153 (22)	78 (26)	4 (17)	235 (23)
Adult Medical	412 (59)	133 (45)	8 (35)	553 (54)
Adult ICU	114 (16)	60 (20)	10 (44)	184 (18)
Obstetrics and Gynaecology	4 (1)	7 (3)	1 (4)	12 (1)
Paediatric Surgical	13 (2)	2 (1)	0 (0)	15 (2)
Paediatric Emergency Centre		15 (5)		15 (2)

CMJAH: Charlotte Maxeke Johannesburg Academic Hospital; TBH: Tygerberg Hospital; IALCH: Inkosi Albert Luthuli Central Hospital.
[a] Ward type was not stated for 6 adult patients at TBH.

3 per 100 incident episodes.

4. Discussion

This multicentre study of CDI found large differences in infection and testing rates at tertiary/quaternary hospitals located in three different provinces in South Africa. *C. difficile* testing rates and positivity proportions in Gauteng were higher than those in the Western Cape and KwaZulu Natal. This mirrors previously published national data, although the use of different denominators impairs direct comparison [4]. The CDI rate at IALCH was unexpectedly low for a quaternary facility. Possible reasons for the inter-hospital variation include differences in the types of specialist services being offered, differences in antimicrobial prescribing practices, at least somewhat influenced by differences in resistance epidemiology [15], and variable infection prevention and control (IPC) practices. Differences in the prevalent *C. difficile* strains may also have played a role [6].

The median primary CDI rates in this study were lower than the incidence of 8.5 per 10 000 PD reported for developing countries (Africa-Middle East, Latin America, China and developing Asia) from 2000 to 2017 [7]. A recently published systematic review of the burden of CDI in the USA, Canada, Europe and Asia-Pacific regions showed an incidence of 4.00 per 10 000 PD [1], but rates varied widely in the individual countries from the regions. Hospital-acquired CDI rates in the USA and Scotland were 8.00 and 1.99/10 000 PD, respectively. We could not differentiate between hospital-acquired and community-acquired disease for patients with primary CDI in this study.

The higher primary CDI rate seen at TBH in 2017 compared to may have been influenced by undetected outbreaks. The primary CDI rate at IALCH increased substantially in 2018, although the absolute number of cases were small.

Intra-hospital variation in testing rates occurred over time, and the positivity proportion of primary CDI increased at CMJAH in 2020, coinciding with the SARS-CoV-2 pandemic [16]. Additionally, in 2020, the three centres had an increase in primary CDI rates compared to the 2019 rates. The three centres are based in the provinces that had the highest numbers of Covid-19- related admissions in South Africa in 2020 [16]. The increased CDI rates may be due to the increase in antimicrobial use during the pandemic [17,18], or a prioritisation of IPC resources on patients known to be SARS-CoV2-infected at the expense of other pathogens [19]. The usual antimicrobial stewardship (AMS) activities at the three hospitals were negatively impacted by the pandemic [17]. Interestingly, our study was not consistent with findings suggesting reduced CDI rates during the pandemic due to heightened IPC protocols [19].

In this cohort, patients with primary CDI were relatively young, in keeping with SA's population structure [20]. This also aligns with advanced age not being commonly identified as a risk factor for CDI in other African studies [6]. However, data on the overall demographics of

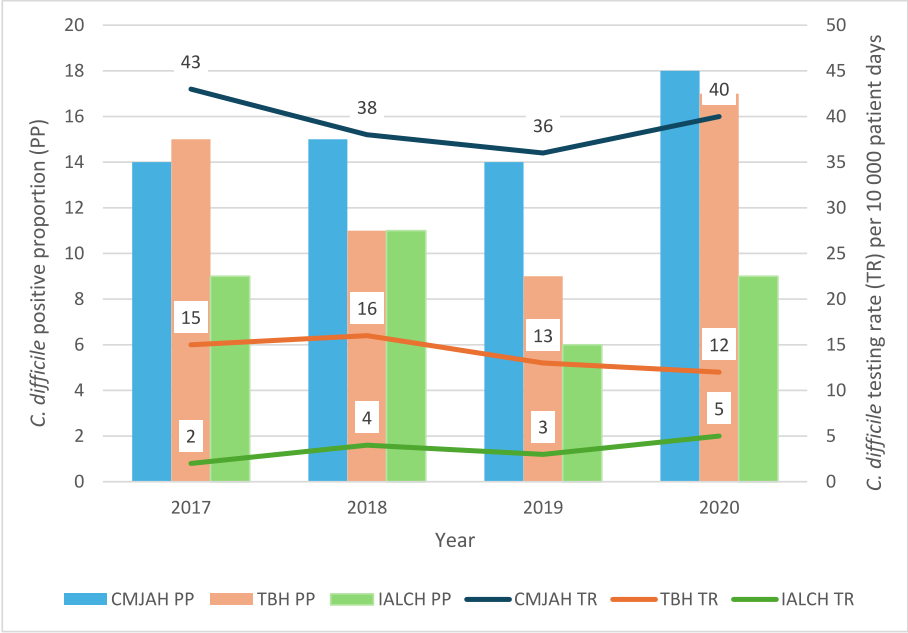

Fig. 2. *C. difficile* positivity proportion (PP) and testing rates (TR) per 10 000 patient days by hospital, 2017–2020. CMJAH: Charlotte Maxeke Johannesburg Academic Hospital; TBH: Tygerberg Hospital; IALCH: Inkosi Albert Luthuli Central Hospital.

Table 2
Recurrent *C. difficile* infection number of episodes and rates.

	Year	No. Of patients with rCDI	No. with 1 rCDI episode	No. with 2 rCDI episodes	rCDI rate (%)
CMJAH	2017	5	5	0	3
	2018	2	1	1	1
	2019	4	3	1	3
	2020	2	2	0	1
	Total	13	11	2	2
TBH	2017	5	5	0	6
	2018	2	1	1	3
	2019	1	1	0	2
	2020	3	3	0	4
	Total	11	10	1	4
IALCH	2017	1	1	0	33
	2018	0	0	0	0
	2019	0	0	0	0
	2020	0	0	0	0
	Total	1	1	0	5

rCDI: Recurrent *C. difficile* infection; CMJAH: Charlotte Maxeke Johannesburg Academic Hospital; TBH: Tygerberg Hospital; IALCH: Inkosi Albert Luthuli Central Hospital.

patients at the three centres was not accessible to allow for comparisons. Whilst advanced age is well established independent risk factor for CDI in other settings, CDI can affect younger populations with specific comorbidities such as chronic kidney disease and inflammatory bowel disease [10]. TB and HIV are other potential comorbidities that may have contributed to the CDI incidence in younger patients. The burden of TB and HIV in SA is significant, particularly among young and middle-aged adults [21,22]. Legenza et al. identified TB as a risk factor for CDI in their retrospective review of CDI epidemiology at district hospitals in Cape Town (in the Western Cape) [2]. As expected, adults comprised the majority of CDI cases in our study, with patients in ICU settings contributing notably [23]. Our retrospective review is limited by not having access to TB and HIV results in the cohort with primary CDI. This should be specifically explored in future research.

This study identified rCDI by combining laboratory testing results with clinical record review for symptoms. Rates of rCDI were low overall, ranging from 2 to 5 per 100 incident cases, in keeping with previous data from SA [4]. The global rCDI rate has been estimated at 10–20 % (median 17 %) with marked differences between regions [1], although there is a striking lack of data from Africa. Rates of rCDI vary from 9.1 % (Asia Pacific region) [24] to 20.8 % (southern Brazil) [25] and 23.7 % (Canada) [1,24,25]. In the United States, it is suggested that up to 35 % of index cases will recur [11] and that this number is on the increase, necessitating continued monitoring to detect trends. Possible explanations for the low rate of rCDI in our setting include inadequate awareness and testing, recurrent infections occurring more than 8 weeks after the initial episode, recurrent symptoms for which patients sought medical care at another institution, and a lack of mortality data for all primary CDI cases. The presence of different strain types in the local setting may also have played a role.

Only three of the 25 patients with rCDI had a second episode of recurrence in our study (12 %), in contrast with a previous estimate of up to 60 % [11]. The rates for multiply recurrent CDI and reasons for potentially lower rates require further investigation in the South African population.

The strengths of this study include the inclusion of hospitals from three provinces in the country and the use of standardized testing algorithms for most of the study period. Longitudinal data allowed for tracking of changes in CDI rates and rCDI was specifically assessed. Limitations of the study include the inability to distinguish between healthcare-associated and community-associated CDI and incomplete data due to missing medical records, The absence of hospital-specific antibiotic consumption and *C. difficile* strain type data limited investigation of possible associations with CDI rates. Differences in the types of specialist services and patient populations, and IPC and AMS practices across the three hospitals, could not be controlled for.

This study found vast differences in *C. difficile* testing and CDI rates. From a diagnostic stewardship perspective, increasing clinician awareness of the risk factors for CDI and indications for CDI testing is important. In addition, promoting awareness of the current CDI treatment guidelines is required. The study findings also support the recommendation that all hospitals should perform surveillance for healthcare facility-onset CDI [26], and it is crucial to continue this practice post SARS-CoV-2-pandemic to understand trends and intervene where appropriate. Baseline data for hospitals is much needed and will

allow benchmarking with other hospitals providing similar care. Prevention of CDI requires attention to IPC measures aiming to prevent exposure to spores and AMS to reduce the risk of *C. difficile*-associated disease in patients colonized with *C. difficile*. CDI rates can be incorporated into hospital AMS quality indicators. There is a need for tracking of rCDI rates, investigation of risk factors, and generation of isolates to facilitate strain typing, in SA and the rest of Africa.

CRediT authorship contribution statement

Trusha Nana: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Conceptualization. **Praksha Ramjathan:** Writing – review & editing, Investigation, Formal analysis. **Khine Swe-Swe Han:** Writing – review & editing, Methodology. **Kessendri Reddy:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will me made available upon request

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