

Epidemiology of *Clostridioides difficile* in South Africa

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Declaration

I, Pieter de Jager, declare that this research report is my own, unaided work. It is being submitted for the degree of Master of Medicine in the branch of Anaesthesiology at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other university.



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To my wife and daughter, thank you for your support and understanding.

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Abstract

Background:

Clostridioides difficile (CD) is the most common healthcare associated enteric infection. Based on evidence from high income countries, the burden of CD Infection (CDI) is growing and associated with significant morbidity and mortality. However, there is currently very limited epidemiological evidence on CDI incidence in South Africa.

Aim: To describe the epidemiology of CDI in the South African public sector for the period 1 July 2016 to 30 June 2017.

Methods: A secondary data analysis utilizing two primary data sources was conducted to describe the epidemiology of CDI in South Africa. Patient level data (age, sex, province, district, facility name, date of specimen taken, CD testing method and result) were obtained from the National Health Laboratory Service (NHLS) for all patients referred for a stool CD test between 1 July 2016 and 30 June 2017. Facility level admission data were obtained from the District Health Barometer (DHB). We assessed the patient-level association between variables of interest, CDI and CDI recurrence, by undertaking both univariate and multivariate analysis. Adjusted odds ratios (aOR) were calculated utilizing multivariate logistic regression. The incidence of CDI, CDI recurrence and CD testing was estimated by Poisson regression for various levels of care and provinces.

Results: A total of 14 023 samples were tested for CD during the study period. After applying exclusion criteria (<18 years of age, missing data, private sector patients), we were left with a sample of 9 282 of which 1 730 (18.64%) had CDI. A positive and significant association between CDI and level of care is found, with patients treated in a specialised tuberculosis (TB) hospital having a more than 11 fold increased risk for CDI (aOR 11.17, CI95% 8.50 – 14.69) compared to those managed in primary care. Patients receiving care at a secondary, tertiary or central hospital had 40%, 83% and 44% increased risk of CDI compared to those managed in primary care, respectively. National incidence of CDI is estimated at 53.89 cases per 100 000 hospitalisations (CI95% 51.58 – 56.29), the incidence of recurrence at 21.39 (CI95% 15.06 – 29.48) cases per 1 000 cases and a recurrence rate of 2.14% (CI95% 1.51 – 2.94). There is significant variability in the incidence of CD testing and CDI across provinces and levels of care.

Conclusion: This is the first study in South Africa to estimate the national burden of CDI. Compared to European countries, we found a comparable incidence of CDI. However, our estimates are lower than those for the United States. This study found a significantly lower CDI recurrence in the South African public sector, compared to high income countries.

Introduction

Clostridioides difficile (CD) is a spore-forming Gram-positive obligate anaerobic bacillus, first identified as part of the commensal gut-flora in healthy infants.(1) CD spores are resistant to various environmental factors, including most antimicrobial agents and disinfectants, and can survive on external surfaces for months.(2) Spores are transmitted via the faecal-oral route and are activated in the duodenum by bile salts and L-glycine, acting as a co-germinant CspC receptor on the spore.(3) Germinants induce enzyme-mediated degradation of the spore cortex, releasing the chromosome-containing core and allowing proliferation of vegetative cells.(4) Once vegetative CD bacilli have proliferated, the mucolytic enzyme Cwp84 degrades mucosal protective barriers in the gut, allowing access to the intestinal epithelium and subsequent colonisation of the large intestine.(5) CD expresses a number of pathogen-associated molecular patterns (PAMPS), including Toxin A (TcdA), Toxin B (TcdB), flagellin, surface layer protein A (SlpA) and peptidoglycan fragments which each stimulate the host innate immune response via pattern recognition receptors, leading to both a local and systemic inflammatory response.

Virulence of CD is primarily mediated by the production of toxins encoded for in the pathogenicity locus (PaLoc).(6) PaLoc codes for three protein toxins: toxin A (TcdA), toxin B (TcdB) and CD transferase toxin (CDT).(7) Of these TcdA and TcdB are more pathogenic, causing receptor-mediated inactivation of Rho with subsequent disruption of the cellular cytoskeleton, breakdown of tight junctions and enterocyte apoptosis.(7,8) Depending on the virulence of the strain and host immunity, symptoms vary from asymptomatic colonisation to fulminant colitis which is

associated with high levels of morbidity and mortality.(9) Patients typically present with three or more episodes of watery diarrhoea within a 24 hour period, with or without systemic signs such as fever and dehydration.(10) If the disease progresses to a haemorrhagic colitis patients develop bloody diarrhoea and severe abdominal pain. Clinical and laboratory markers of severity include: body temperature greater than 38.5°C; severe abdominal pain; an elevated lactate level; elevated serum creatinine level; and a white cell count of greater than $15 \times 10^9/L$.(11)

Clostridioides difficile infection (CDI) is defined by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA) as ‘the presence of symptoms (usually diarrhoea) and either a stool test positive for CD toxins or detection of toxigenic *CD*, or colonoscopy or histopathologic findings revealing pseudomembranous colitis’.(12)

Notwithstanding the increasing incidence of community acquired CDI, recent hospitalization and administration of antibiotics remain the main risk factors for acquiring CDI.(13) Additional risk factors include outpatient antibiotic exposure, co-morbidities such as renal failure, malignancies and immunosuppression and age over 65 years.(14) Despite large variability in the reported incidence of CDI, it is clear that the burden of CDI has grown substantially since the late 1990’s, particularly in high income countries.(1) CDI is associated with significant morbidity and mortality and places an economic burden on healthcare systems.(15) However, our current understanding of the epidemiology of CDI is primarily informed by studies from high-income countries, with very few from South Africa estimating the burden of CDI.(16–18)

Methods

Secondary data sources for the period 1 July 2016 to 30 June 2017 were utilised to identify risk factors for CDI and CDI recurrence, and to describe the epidemiology in the South African public sector. Findings are reported in line with Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement.

Ethics

The protocol for this study was reviewed by the Human Research Ethics Committee (Medical) at the University of the Witwatersrand, Johannesburg and clearance was obtained (Ref: M200114) prior to commencing the study.

Study Setting

South Africa is an upper-middle income country with a 2016 mid-year estimated population of 55.91 million.(19) The health sector has three tiers – a national level, provincial level (9 provinces) and district level (52 districts). Healthcare facilities are divided into community health centres providing primary and community-based care, district hospitals, regional hospitals, tertiary and central hospitals as well as specialized service hospitals (e.g. tuberculosis and psychiatric).(20) Approximately 84% of South Africans rely on the public healthcare sector to access hospital care with laboratory diagnostic services provided by the National Health Laboratory Services (NHLS).(21,22)

The NHLS has a national database of all processed laboratory results in the South African public sector. Routine healthcare utilization and private health insurance coverage rates are collected and annually reported by the District Health Barometer.(23)

Data management and analysis

Data from all patients who had a stool sample submitted to the NHLS between 1 July 2016 and 31 June 2017 for CD testing were considered for inclusion in the study. The NHLS only test specimens for CD that conform to the shape of the container. Testing is conducted utilizing enzyme immunoassay, polymerase chain reaction (PCR), GeneXpert or other PCR-based assays and standard diagnostic protocols. Data on healthcare facility level utilization rates for the period 1 July 2016 to 31 June 2017 were obtained from the District Health Barometer database. To estimate crude national incidence, mid-year population estimates from Statistics South Africa for 2016 were utilized and adjusted for medical insurance coverage.

Figure 1 summarises the data management process utilised in assessing the risk factors associated with CDI. A total of 14 023 CD tests were conducted by the NHLS nationally between 1 July 2016 and 30 July 2017. Of these a total of 2 540 were removed due to duplication, namely a repeat test performed for the same patient within the 14 days, the period that distinguishes therapeutic failure from recurrence. A further 2 146 patients were removed because of missing data, sex (n=74); age < 18 years (n=1 912) and tests conducted for private sector patients (n=160). This resulted in a final sample of 9 282 of which 1 730 (18.64%) and 7 552 (81.36%) were CD positive and negative respectively.

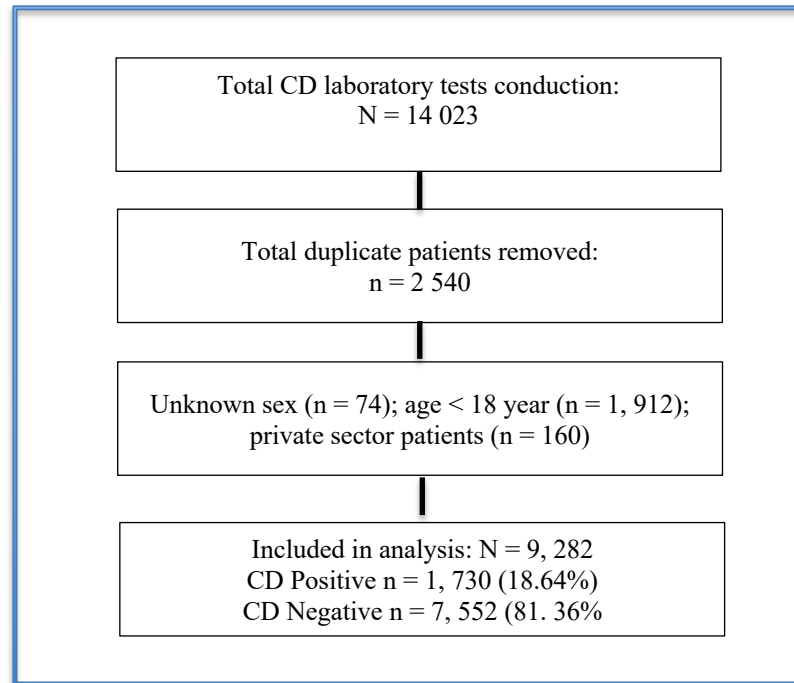


Figure 1: Summary of data management for CDI risk factors

Data from the NHLS was merged with that from the District Health Barometer to calculate incidence rates. No facility level public sector utilisation data stratified by age and sex, and no utilization data for the private sector were available. To estimate the incidence of CDI in the public sector we excluded tests from the private sector and those from patients under the age of 1 year (given that CD is a known commensal in infants). Subsequently a slightly higher sample size for the incidence analysis was obtained (N = 10 977; CD positive n = 2, 038; CD negative n = 8, 939).

For analysis, data were imported into Stata version 16. Patient ages were recoded into a categorical variable (18 – 30; 31 – 40; 41 – 60; 61 or older). Level of care was defined at primary [district, community health centre or non-infectious disease specialist facility (psychiatric and rehabilitation hospitals)]; secondary (regional hospital, typically providing general medical or surgical specialist-level care); tertiary

(providing sub-speciality care), central hospital care (providing quaternary level care) and specialised tuberculosis (TB) hospitals . Finally, binary variable were coded to compare high dependency care unit (ICU/HC) patients with those receiving care in a general ward (non-ICU/HC).

Categorical variables are reported in terms of frequencies, proportions and percentages, and continuous data in terms of measures of spread and central tendency. Univariate analysis was conducted to assess the relationship between CDI or CDI recurrence and variables of interest using χ^2 or Fishers' Exact test. Level of significance is defined at a two-tailed α of 0.05 for both the univariate and multivariate analysis. In the multivariate analysis a logistic regression model was developed to estimate crude and adjusted odds ratios and 95% confidence intervals for factors associated with CDI.

Seasonality of CDI over the study period of interest was assessed by constructing an epidemiological curve and the proportion of CDI cases diagnosed for each month (July 2016 – June 2017). All incidence estimates were calculated in Stata version 16 by Poisson regression and a time period of one year. National crude incidence was estimated utilizing adjusted 2016 mid-year population estimates and expressed as cases per million population. Provincial and level of care incidence was calculated with healthcare facility utilization data and expressed as cases per 100 000 admission. The incidence of recurrence is estimated in terms of the CD positive population and expressed recurrence incidence as cases per 1000 CDI cases.

Finally a geographic information system (GIS) analysis was undertaken to map the incidence and positivity rates across provinces. GIS analysis was conducted in GeoDa (<https://geodacenter.github.io/>) and the provincial shape file was obtained from GDAM (<https://gadm.org/index.html>). Calculated incidence and positivity rate point estimates were manually entered into GeoDa prior to dividing these estimates into four quartiles to represent the data graphically.

Results

The majority of individuals that were tested for CD were between 41 and 60 years of age (34.06%) female (57.41%) and received care at a central hospital (44.59%) in a non-ICU/HC environment (89.31%). Of those with CDI, females (18.28%) and patients in the age group 31 – 40 years (20.35%) had a slightly higher representation compared to males and other age groups respectively (Table 1). The proportion of patients with CDI was significantly higher among those receiving care in a specialised TB hospital (62.01%) compared to tertiary, central, secondary and primary care facilities respectively at 20.80%, 17.13%, 16.19% and 12.66%. On univariate analysis only level of patient care was statistically significantly associated with CDI ($p < 0.001$) (Table 1).

Table 1: Univariate analysis of factors associated with CDI

	n (%)	CDI n (%)	Non-CDI n (%)	p-value
Age (years)				
18 - 30	1, 889 (20.35)	347 (18.37)	1, 542 (81.63)	
31 – 40	2, 427 (26.15)	494 (20.35)	1, 933 (79.64)	
41 – 60	3, 162 (34.06)	578 (18.28)	2, 583 (81.69)	
61 or older	1, 805 (19.45)	311 (17.23)	1, 494 (82.77)	0.060
Gender				
Female	5, 329 (57.41)	974 (18.28)	4, 335 (81.35)	
Male	3, 953 (42.59)	756 (15.92)	3, 197 (67.32)	0.300
Level of Care				
Primary	1, 627 (17.53)	206 (12.66)	1, 421 (87.34)	
Specialised TB	308 (3.32)	191 (62.01)	117 (37.99)	
Secondary	1, 112 (11.98)	188 (16.91)	924 (83.09)	
Tertiary	2, 096 (22.58)	436 (20.80)	1, 660 (79.20)	
Central	4, 139 (44.59)	709 (17.13)	3, 430 (82.87)	<0.001
ICU/HC				
Non-ICU/HC	8, 290 (89.31)	1, 559 (18.81)	6, 731 (81.91)	
ICU/HC	992 (10.69)	171 (17.24)	821 (82.76)	0.231

Results from the multivariate analysis are summarized in Table 2. No statistically significant differences were found between age groups, males and females (OR 1.06 CI95% 0.95 – 1.17, $p = 0.300$) or non-ICU/HC and ICU/HC patients (OR 0.90 CI95% 0.76 – 1.07, $p = 0.231$). However, compared to primary care, patients receiving secondary level care were 40% (OR 1.40 CI95% 1.13 – 1.74, $p = 0.002$) more likely to test positive. Similarly, patients receiving care at a tertiary or central hospital were 81% (OR 1.81 CI95% 1.51 – 2.17, $p = 0.000$) and 43% (OR 1.43 CI95% 1.21 – 1.69, $p < 0.001$) more likely to have CDI. Receiving care in a specialized TB hospital resulted in a more than 11-fold increase in the risk of CDI (OR 11.26 CI95% 8.57 – 14.48, $p < 0.001$).

After adjusting for age, sex and ICU/HC, the level of care remained statistically significant in its association with CDI with a 40% (aOR 1.40 CI95% 1.13 – 1.74), 83% (aOR 1.83 CI95% 1.52 – 2.18) and 44% (aOR 1.44 CI95% 1.22 – 1.71) increased risk compared to primary care for secondary, tertiary and central hospital care respectively. The strong association with receiving care in a specialized TB hospital also remained statistically significant after adjusting for sex, age and ICU/HC (aOR 11.17 CI95% 8.50 – 14.69).

Table 2: Unadjusted and adjusted risk factors associated with CDI

	Unadjusted OR (CI95%)	p-value	Adjusted OR (CI95%)	p-value
Age				
18 - 30	Reference		Reference	
31 – 40	1.13 (0.97 – 1.32)	0.103	1.11 (0.95 – 1.30)	0.189
41 – 60	0.99 (0.86 – 1.15)	0.940	1.01 (0.87 – 1.18)	0.900
61 or older	0.93 (0.78 – 1.10)	0.366	1.02 (0.86 – 1.122)	0.781
Gender				
Female	Reference		Reference	
Male	1.06 (0.95 – 1.17)	0.300	1.01 (0.90 – 1.12)	0.888
Level of Care				
Primary	Reference		Reference	
Specialised TB	11.26 (8.57 – 14.48)	<0.001	11.17 (8.50 – 14.69)	<0.001
Secondary	1.40 (1.13 – 1.74)	0.002	1.40 (1.13 – 1.74)	0.002
Tertiary	1.81 (1.51 – 2.17)	<0.001	1.83 (1.52 – 2.18)	<0.001
Central	1.43 (1.21 – 1.69)	<0.001	1.44 (1.22 – 1.71)	<0.001
ICU/HC				
Non-ICU/HC	Reference		Reference	
ICU/HC	0.90 (0.76 – 1.07)	0.231	0.95 (0.80 – 1.14)	0.599

After applying the exclusion criteria, 37 cases of CDI recurrence were identified between 1 July 2016 and 30 June 2017. The mean time to recurrence was 43.30 days (CI95% 28.97 – 57.65) and the probability of a subsequent episode of recurrence 12.12% (CI95% 3.4 – 28.2). We estimated the incidence of recurrence to be 21.39 (CI95% 15.06 – 29.48) cases per 1, 000 cases of CDI. This translates to a recurrence

rate of 2.14% (CI95% 1.51 – 2.94). On univariate analysis, none of the variables under investigation (age, gender, level of care or ICU/HC) were found to be significantly associated with recurrence (Table 3). However, there was a higher incidence of recurrence at specialised TB hospitals (3.14%) and Central hospitals (2.68%) compared to other levels of care (range 1.38% - 1.60%)

Table 3: Univariate analysis of factors associated with CDI recurrence

	n (%)	Recurrence n (%)	No recurrence n (%)	p-value
Age (years)				
18 - 30	347 (20.06)	8 (2.31)	339 (97.69)	
31 – 40	494 (28.55)	13 (2.63)	481 (97.37)	
41 – 60	578 (33.41)	12 (2.08)	566 (97.92)	
61 or older	311 (17.98)	4 (1.29)	307 (98.71)	0.638
Gender				
Female	974 (56.30)	19 (2.00)	955 (98.00)	
Male	756 (43.70)	18 (2.38)	738 (97.62)	0.326
Level of Care				
Primary	206 (11.91)	3 (1.46)	203 (98.54)	
Specialised TB	191 (11.04)	6 (3.14)	185 (96.86)	
Secondary	188 (10.87)	3 (1.60)	185 (98.40)	
Tertiary	436 (25.20)	6 (1.38)	430 (98.62)	
Central	709 (40.98)	19 (2.68)	687 (97.32)	0.458
ICU/HC				
Non-ICU/HC	1, 559 (90.12)	33 (2.12)	1, 524 (97.88)	
ICU/HC	171 (9.88)	4 (2.34)	166 (97.66)	0.505

Figure 2 illustrates the epidemiological curve for CDI cases between July 2016 and June 2017. CDI cases varied during the year with the most number of cases diagnosed during the month of December (n=195) and the lowest during May and July (n=155). From the epidemiological curve, it would appear that there were slightly more cases during the summer months compared to winter months.

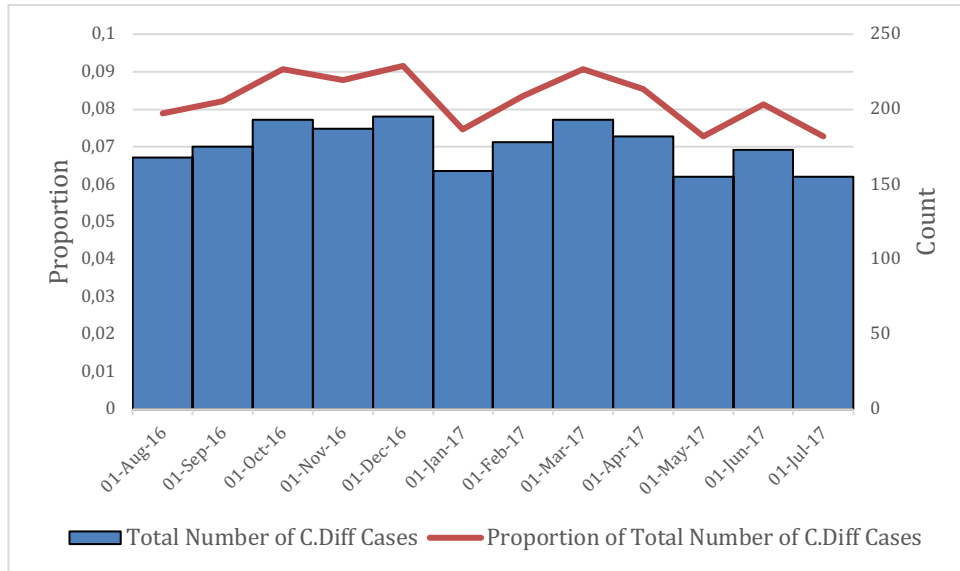


Figure 2: Seasonal variation in number of CDI cases diagnosed in the South African public healthcare sector 2016/2017.

This analysis found a crude national CDI incidence of 0.101 (CI95% 0.097 – 0.105) per 1000 000 population and a crude national CD testing incidence of 0.544 (CI95% 0.533 – 0.554) per 1000 000 population for the South African public sector.

Nationally, the estimate of CDI incidence per 100 000 public sector admissions were 53.89 (CI95% 51.58 – 56.29). Figure 3 summarises results from the GIS analysis of CD testing, CDI incidence and positivity rates by quintile for various provinces.

Incidence varied widely across provinces with Gauteng’s incidence of CDI estimated at 158.45 (CI95% 149.69 – 167.59) per 100 000 admissions followed by the Western Cape at 107.52 (CI95% 98.96 – 116.62). In contrast the Northern Cape recorded no CDI cases and for Limpopo province, we estimated an incidence of 0.81 (CI95% 0.26 – 1.90) cases per 100 000 admissions (Table 4). There was less variation in the positivity rate across provinces. The national average positivity rate was estimated at 18.57% (CI95% 17.85 – 19.31). The highest positivity rate was recorded in the North

West (28.57%) followed by the Eastern Cape (27.84%). Lowest positivity rates were in the Free State (6.65%) and KwaZulu Natal (6.98%).

Table 4: Incidence of CDI, CD testing and positivity rate by province

	CDI Incidence (CI95%)	Testing Incidence (CI95%)	Positivity rate (CI95%)
National	53.89 (51.58 – 56.29)	290.29 (284.89 – 295.78)	18.57 (17.84 – 19.31)
Eastern Cape	30.31 (25.41 – 35.87)	108.88 (99.41 – 119.02)	27.84 (23.89 – 32.05)
Free State	10.60 (6.64 – 16.05)	159.51 (142.79 – 177.65)	6.65 (4.21 – 9.89)
Gauteng	158.45 (149.69 – 167.59)	801.09 (781.23 – 821.33)	19.78 (18.79 – 20.80)
KwaZulu-Natal	3.55 (2.30 – 5.24)	50.86 (45.72 – 56.41)	6.98 (4.57 – 10.14)
Limpopo	0.81 (0.26 – 1.90)	3.90 (2.50 – 5.80)	20.83 (7.13 – 42.15)
North West	26.27 (19.23 – 35.04)	91.94 (78.29 – 107.29)	28.57 (21.74 – 36.21)
Northern Cape	0 (-)	94.55 (73.85 – 119.26)	-
Western Cape	107.52 (98.96 - 116.62)	620.91 (600.09 – 642.26)	17.32 (16.05 – 18.64)
Mpumalanga	0.81 (0.10 – 2.92)	5.26 (2.80 – 9.00)	15.38 (1.92 – 45.45)

A higher level of care was associated with higher incidence of CDI. Central hospitals had a pooled CDI incidence of 230.92 (CI95% 216.43 – 246.14) per 100 000 admissions, more than double that of tertiary facilities with an estimated incidence of 100.06 (CI95% 91.35 – 109.37) per 100 000 admissions. A further reduction in the incidence of CDI was found in secondary (20.97 CI95% 18.30 – 23.92 cases per 100 000 admissions) and primary care (11.85 CI95% 10.23 – 101.63) facilities.

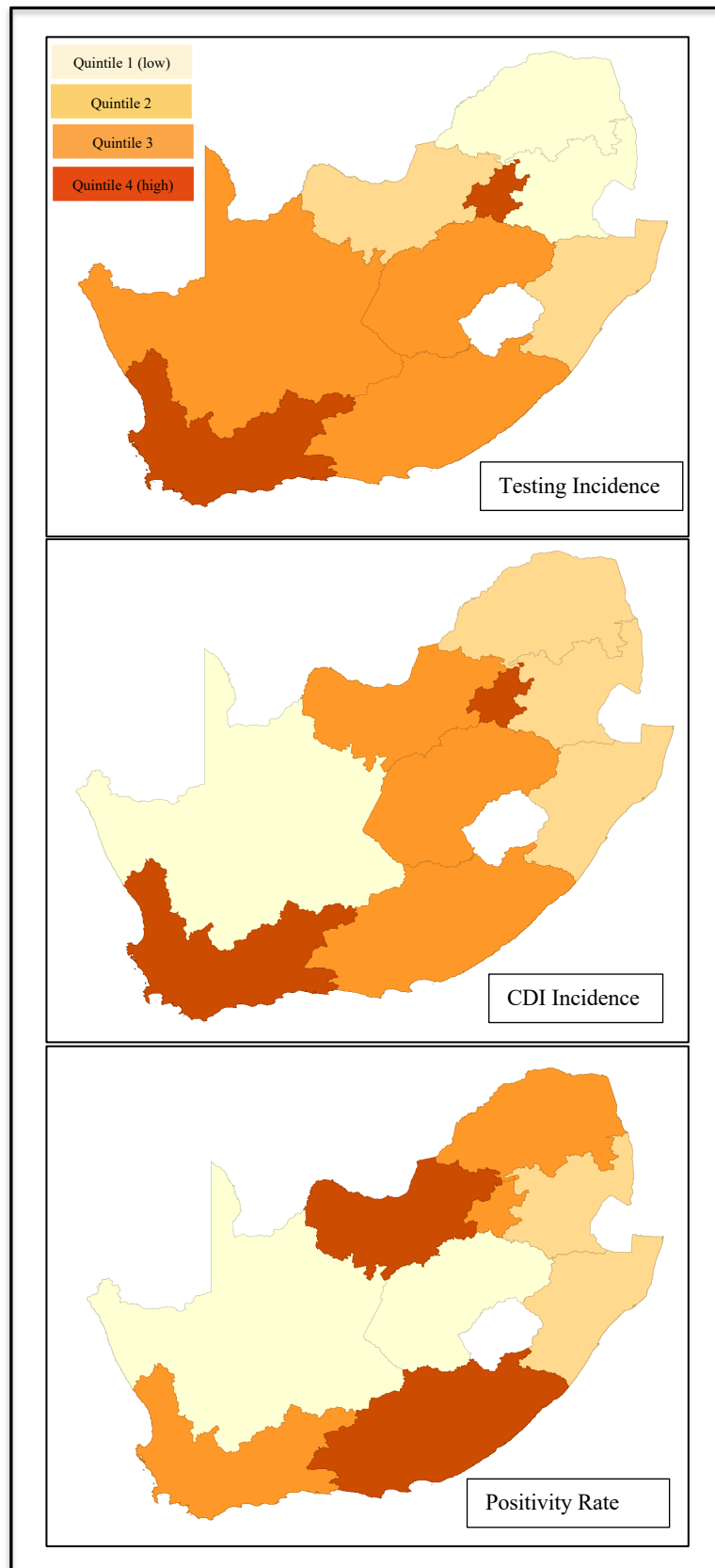


Figure 3: Provincial Clostridioides Difficile Testing, CDI incidence and positivity rates by quintile

Central hospitals were also much more likely to test for CD (1 298.46 tests per 100 000 admissions) than tertiary (539.30 tests per 100 000 admissions), secondary (133.45 tests per 100 000 admissions) and primary care facilities (10.87 tests per 100 000 admissions) (Table 5). Therefore there is less variability in the positivity rate (12.29% – 19.82%) across levels of care than the incidence of CDI. As a group, specialised TB hospitals are a clear outlier with a CDI incidence of 683.98 (CI95%; 589.46 – 7789.35) cases per 100 000 admissions, a higher testing incidence of 1 115.58 (CI95%; 993.88 – 1, 248.07) per 100 000 admissions and positivity rates three time greater than the national average (61.31%; CI95% 55.59 – 66.81).

Table 5: Incidence of CDI, *Clostridioides Diff* testing and positivity rate by level of care

	CDI Incidence (CI95%)	Testing Incidence (CI95%)	Positivity rate (CI95%)
Central	230.92 (216.43 – 246.14)	1, 298.46 (1, 263.76 – 1, 333.88)	17.78 (16.76 – 18.84)
Tertiary	100.06 (91.35 – 109.37)	504.82 (485.01 – 525.22)	19.82 (18.26 – 21.46)
Secondary	20.97 (18.30 – 23.92)	126.14 (119.47 – 133.10)	16.63 (14.67 – 18.74)
Primary	10.87 (9.39 – 12.52)	88.48 (84.15 – 92.96)	12.29 (10.70 – 14.01)
Specialised TB	683.98 (589.46 – 789.35)	1, 115.58 (993.88 – 1, 248.07)	61.31 (55.59 – 66.81)

Discussion

This is the first study to determine the incidence of CDI in the South African public sector. CDI incidence is estimated at 53.89 CDI cases per 100 000 hospitalizations, lower than estimates for the US (115.1), but higher than those for England (19.3).(24) In Europe the reported incidence of CDI at healthcare facility level varies between 42 to 1 318 per 100 000 admissions,(25) placing estimates for South Africa at the lower end of the European spectrum.

Previous studies to estimate the incidence of CDI in South Africa are limited. Compared to the central hospitals incidence in our study of 230.92 per 100 000 admissions, a single centre prospective study in a Cape Town central hospital estimated the incidence of hospital acquired CDI at 87 per 100 000 admissions in 2013.(17) A second study from two tuberculosis hospitals in Cape Town found the incidence to be 7007.0 per 100 000 admissions from 2014 to 2015.(18) This is much higher than the pooled estimate for specialised TB hospitals nationally (683.98 per 100 000 admissions). A possible reason for these difference are that this study's estimates included all public care facilities in South Africa, some of which had no cases of CDI. A facility-level analysis of our data also revealed significant variability in CDI incidence among central hospitals (range 5.35 to 529.36 cases per 100 000 admissions) and specialised TB hospitals (range 0 to 10 661.76 cases per 100 000 admissions). A second possible explanation is that we were unable to differentiate between community and hospital acquired cases, therefore our estimates of CDI may include cases of community acquired CDI which may overestimate the incidence. However, a study in 2019 found the prevalence of CD colonization among those living in residential care facilities in Cape Town to be 1.6%.(26) In contrast an earlier study from a central hospital in Cape Town found that of those patients diagnosed with CDI (N=59), 32% (n=19) had community acquired CDI.(17)

There is very limited data on recurrence rates of CDI in South Africa. From this analysis recurrence is estimated at 2.14% which is lower than that reported in one South African prospective study where three (5.08%) of 59 patients had a recurrence.(17) A large British single-centre prospective study of 2 043 CDI patients with a median follow-up of 11 months found a recurrence rate of 22%, in a quarter of

whom the recurrence was with a different CD strain.(27) In addition to advanced age, co-morbidities, healthcare and antibiotic exposure; initial infection with epidemic BI/NAP1/027 CD strain has been found to be a risk factor for relapse (as opposed to re-infection).(28) The prevalence of BI/NAP1/027 was estimated to be 22% between 2013 and 2016 in US, and 41.3% in the UK between 2007 and 2008.(29,30) There is very sparse data on the epidemiology of BI/NAP1/027 in South Africa. One study found the prevalence to be 3.4% (3/59).(17) The possible reasons for our apparent low recurrence rates are multiple. Firstly, we only had data for one year which may have excluded possible cases of recurrence at the beginning and the end of the study period. Secondly, some may have been lost to follow-up or died prior to being diagnosed with a recurrence. Thirdly, it is possible that South Africa's demographic and population disease profile, antibiotic prescription practices and a lower prevalence of BI/NAP1/027 have resulted in a true lower incidence of recurrence. Finally, CDI management protocols in South Africa differ from those in countries with higher recurrence rates. Recommended first-line treatment for CDI in South Africa in 2016/17 was oral metronidazole(31) and this was the most common first-line treatment prescribed.(32) Current IDSA recommendations for first-line treatment of is either oral vancomycin or fidaxomicin and only where vancomycin or fidaxomicin are not available should metronidazole be considered as treatment for mild CDI.(12) For recurrences vancomycin or fidaxomicin administered for longer tapered periods or as pulsed regimens are recommended, and faecal microbiota transplantation can also be considered.(12)

An assessment of CDI seasonality suggested a slight increase in cases during the summer months, however any conclusions regarding this are limited by the fact that

we only reviewed data over one year. We are not aware of any other studies from South Africa which have attempted to assess the seasonality of CDI. In contrast to our findings, a systematic review of twenty studies, of which two were conducted in the southern hemisphere, found consistent evidence of seasonality in the incidence of CDI with cases peaking in spring and reducing during summer.(33)

Assessment of risk factors associated with CDI is limited by a lack of potential explanatory variables in this study: age, sex, level of care and high dependency care unit versus ward care. Notwithstanding these limitations, a strong positive association was found between CDI and treatment in a specialised TB hospital, a finding which is supported by a previous facility level analysis in the Western Cape.(18) This association, as well as the association found between CDI and tertiary or quaternary care, can be explained by the fact that patients in these facilities typically suffer from multiple comorbidities and tend to have longer hospital stays and healthcare exposures than primary care patients. Particularly in the case of specialised TB hospitals, patients are more likely to be on prolonged courses of antimicrobial therapy resulting in a disruption of the gut microbiome and subsequent CD proliferation.

Conclusion

This is the first study in South Africa to estimate the national burden of CDI. Compared to European countries, this analysis found a comparable incidence of CDI. However, estimates are lower than those for the United States. A significantly lower CDI recurrence was found in the South African public sector, compared to high income countries. Further work is necessary to obtain a clearer picture of the burden of CDI in South Africa. Firstly, analysis should be extended to include other years

and if possible the private sector. This will allow for assessment of CDI trends, allow for a more robust analysis of CDI seasonality and a comparison between the public and private healthcare sectors. Secondly, analysis should be extended to include patients under the age of 18 years and incidence data determined on a district level. Thirdly, the prevalence and trends in the incidence of BI/NAP1/027 should be determined. Of the 14 023 CD tests conducted by the NHLS between 1 July 2016 and 30 June 2017 8, 442 (60.20%) utilised GeneXpert technology which routinely reported the presence or absence of BI/NAP1/027 strain. Finally, an economic analysis utilizing existing epidemiological and cost data should be undertaken to estimate the economic burden of CDI on the public healthcare system.

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