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The pattern of antibiotic utilisation among intensive care unit patients hospitalised in a Gauteng (South African) provincial tertiary hospital: Comparing findings before and during COVID-19

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Background. Various mechanisms may contribute to and direct the progression of antibiotic resistance. A prominent driver associated with antibiotic resistance is inappropriate use or consumption. The sudden emergence of coronavirus disease 2019 (COVID-19) changed the conventional practices related to antibiotic utilisation through repurposing the use of antibiotics. Apart from the implementation of antibiotic stewardship programmes, the pressure COVID-19 placed on healthcare systems resulted in poor prescribing and medication review practices, potentially exacerbating antibiotic resistance. Furthermore, the public health system has issues that make it difficult to routinely monitor, quantify antibiotic consumption, and offer evaluation, feedback and intervention, particularly in low- and middle-income countries such as South Africa (SA). Therefore, this study aimed to determine antibiotic utilisation before and during the COVID-19 pandemic in a Gauteng provincial tertiary hospital (GPTH) in SA.

Objective. To determine, examine, and compare antibiotic consumption among intensive care unit (ICU) patients admitted to a GPTH during the pre-COVID-19 period and during the COVID-19 pandemic, in addition to determining the prevalence of the World Health Organisation (WHO) 'watch' category antibiotics before and following the emergence of COVID-19 .

Methods. A retrospective cross-sectional data analysis was undertaken of 335 medical files of ICU patients hospitalised in a GPTH between January 2017 and December 2021. Descriptive statistics were used to examine patient characteristics and antibiotic prescribing variables (antibiotic selection, dosage, route of administration, frequency, duration of course and indication for which antibiotic was prescribed).

Results. The study found that the most frequently prescribed antibiotics were amoxicillin in combination with clavulanate (pre-pandemic 31.99%; amid-COVID-19 38.43%), followed by ceftriaxone (pre-pandemic 15.44%; amid-COVID-19 14.55%), piperacillin in combination with tazobactam (pre-pandemic 11.40%; amid-COVID-19 8.58%) and azithromycin (pre-pandemic 7.725%; amid-COVID-19 19.78%).

Conclusion. The macrolide and penicillin (in combination with a beta-lactamase inhibitor) classes demonstrated an increase in consumption from the pre-pandemic period moving into the COVID-19 pandemic. This highlights the need for improved antibiotic stewardship programmes and policies to combat inappropriate and unnecessary antibiotic usage.

Keywords: Antibiotic use, antibiotic prescribing, AWaRe antibiotics, COVID-19, prescribed daily dose, defined daily dose, Gauteng, tertiary hospital

S Afr Med J 2024;114(7):e1812. https://doi.org/10.7196/SAMJ.2024.v114i7.1812

Antibiotic pharmacotherapy has stimulated significant progress in modern medicine.[1] For decades, it transformed and set the threshold for healthcare by lowering morbidity and mortality rates associated with bacterial infections.[2] As a result, these medications are critical in the treatment, management and prevention of infections.[3,4] However, inappropriate, and excessive use of antibiotics has fuelled the emergence of antibiotic resistance.[5,6]

Antibiotic resistance refers to bacteria's ability to change and become less susceptible to antibiotics over time.[7] Several mechanisms may facilitate and steer developing resistance against these agents.[5] A prominent driver associated with antibiotic resistance is inappropriate use or consumption.[8] Inappropriate use can be related to incorrect medical indication, antibiotic selection, dosing, route of administration and timeliness of antibiotic administration.[9] Studies have shown that these factors are incorrectly implemented in 30 - 50% of cases.[10] Moreover, in intensive care units (ICUs), 30 - 60% of antibiotics are unnecessary, inappropriate, or suboptimal.[11] This degree of error accelerates and exacerbates resistance, resulting in poor patient outcomes, which are coupled with the lack of antibiotic choices available.[13] Globally, antibiotic resistance has led to the death of ~700 000 people each year.[12] This mortality incidence estimate is predicted to surge to 10 million by the year 2050, paired with an increase in costs of up to USD100 trillion without any combative measures employed.[13]

To understand the prevalence of antibiotic use, and reduce antibiotic consumption and resistance, the World Health Organization (WHO) introduced the Access, Watch, and Reserve (AWaRe) classification of antibiotics. The 'Access' category includes empiric first- or second-choice antibiotics with a narrow spectrum of antibacterial activity and a low potential for resistance. Conversely, the 'watch' category includes antibiotics with a broader spectrum of antibacterial activity. However, antibiotics within this category are susceptible to a greater likelihood of resistance in comparison with antibiotics in the 'access' category. Furthermore, 'watch' category antibiotics are used in patients with severe clinical manifestations that are characterised by bacterial resistance and where antibiotics within the 'Access' category cannot be considered for the treatment and management of infectious diseases. Lastly,

the 'Reserve' category constitutes antibiotics with the highest potential of resistance, that are 'last choice or last resort'. This means that antibiotics within the 'Reserve' category are only to be prescribed and used in multidrug-resistant infections and in clinical instances where 'access' and 'watch' category agents are deemed unsuitable. The AWaRe classification of antibiotics objectifies the strengthening and monitoring of antimicrobial stewardship (AMS) programmes.[14,15] These AMS programmes are effective and useful in optimising antibiotic use, but have limited scope and do not consider the potentially broader impact of external drivers such as drug repurposing and the emergence of new infectious diseases.

The sudden emergence of coronavirus disease 2019 (COVID-19), a novel coronavirus caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), disrupted and changed the landscape of drug utilisation.[16,17] Global efforts were made in repurposing drugs and the navigation of pharmacotherapy approaches to manage and treat COVID-19.[17,18] In the scarcity of standard treatment guidelines, a prominent pharmacotherapy approach implemented was the use of antibiotics.[17-21] The use of antibiotics in the management and treatment of COVID-19 is delineated from the primary use of antibiotics that are indicated for bacterial infections.[18] Calderon-Parra *et al.*[22]] reported that despite a comparatively low bacterial co-infection rate, the prevalence of antibiotic usage in COVID-19 patients was still considerably high. Antibiotic usage in virulence is not advised in the absence of bacterial co-infections.[23] This addresses the poor AMS practices and selective pressure placed on antibiotics during the COVID-19 pandemic, intensifying an ongoing antibiotic resistance pandemic.[23-25] Inappropriate and irrational use of antibiotics is also a salient issue associated with antibiotic resistance in low- and middle-income countries (LMICs).[5]

In South Africa, a LMIC, antibiotic resistance is a pressing concern.[26] The SA National Department of Health's (NDoH) Antibiotic Resistance National Strategic Framework (2014 - 2024) and 'A pocket guide to antibiotic prescribing for adults in South Africa' by the SA Antibiotic Stewardship Programme (SAASP) were developed to optimise appropriate use of antibiotics and combat resistance.[27,28] Despite existing policies and procedures, the evolution of antibiotic resistance is a continuous phenomenon requiring more collaborative efforts in public health.[29] This may be due to the integration of the public healthcare system and AMS programmes.[5] The public healthcare system is often overburdened, and consequently, the intricacies regarding antibiotic utilisation and review are overlooked due to weak policy infrastructure and lack of resources.[30]

In SA, there is a paucity of information about antibiotic utilisation in the public healthcare sector, even following the emergence of the COVID-19 pandemic.[31] It is essential to determine the extent of antibiotic use to improve antibiotic utilisation and patient outcomes, and stimulate viable policies and initiatives to strengthen public healthcare antibiotic surveillance amid the challenges of increased infectious diseases, resistance and healthcare system inadequacies. This study therefore examined antibiotic prescribing patterns through a comparative analysis of antibiotic utilisation between the pre-COVID-19 period and amid the COVID-19 pandemic.

Methods

Study design

A retrospective, cross-sectional study design was implemented for ICU antibiotic utilisation by patient medical file review in a Gauteng provincial tertiary hospital (GPTH).

Study setting

The study was conducted in the ICU of a GPTH located in a township, situated on the East Rand in the city of Ekurhuleni, SA. The selected study site is a SA NDoH-designated COVID-19 hospital site. This designation was employed to facilitate and aid in the standardisation of care, optimisation of resource utilisation and protection of non-COVID-19 patients and healthcare workers. The designated study hospital had a single main ICU until the year 2021, in which a COVID-19 ICU was established to accommodate and quarantine COVID-19 -infected patients. In addition, it was essential to include the novel COVID-19 ICU to potentially determine whether antibiotics used in COVID-19 individuals differed from antibiotics used in the non-infected individuals. Therefore, both ICUs were considered. Furthermore, due to the high propagation of COVID-19, both ICUs upheld stricter infection prevention and control measures. Thus, the GPTH was an ideal study site to assess pre-to-COVID-19 antibiotic utilisation.

Study period

Medical files of patients admitted to the ICU between the period of January 2017 and December 2021 were reviewed. Periods before January 2020 were considered pre-pandemic, and the period during and following January 2020 was considered the COVID-19 pandemic period.

Study population

The study population comprised patients admitted in the ICU of the selected GPTH, specifically patients who received antibiotic treatment within the ICU.

Inclusion criteria

The eligible medical files for the study included patients in the ICU of various races, religions and sociodemographic statuses. The criteria also encompassed patients aged ≥18 years receiving ICU-initiated antibacterial pharmacotherapy. All medical files pertaining to antibiotics prescribed between January 2017 and December 2021 were considered. In SA, prescription-only medicines, including antibiotics, are exclusively prescribed by registered healthcare professionals such as medical doctors, clinicians and prescribing nurses. Therefore, all antibiotics administered to inpatients, including those in the ICU, are prescribed by these duly authorised healthcare providers.

Exclusion criteria

Patients on antibiotic regimens prior to hospital admission were excluded. Furthermore, incomplete and illegible patients' files were excluded.

Study size and sampling

The sample size was estimated using the web-based Raosoft sample size calculator by Raosoft Incorporated. The sample size formulated by the Raosoft sample size calculator was based on a margin of error of 5% and a confidence level of 95% in estimating the minimum sample size required. This resulted in an estimated sample size of 335 patients.

Sampling techniques

All 335 patient medical files that had antibiotics prescribed were retrieved and assessed for completeness of the information. All files that were used in the study were then selected using stratified random sampling (StRS). The StRS method stratified samples into strata defined by the year of patient admittance/study (2017 - 2021).

Therefore, the StRS method ensured that the sample size per stratum was proportionate to the number of patients admitted per year of study.

Measurements

Data collection

Patient data were manually inscribed into a drug utilisation review form designed and coded using the Research Electronic Data Capture (REDCap) tool hosted at the University of the Witwatersrand. The tool covered four sections throughout the patient medical file review process. These sections were demographics, hospital admission, patient concurrent pharmacotherapy and antibiotic therapy information (based on the essentials medicines list for tertiary-level hospitals). Patient files were retrieved and reviewed using the hospital file repository within the hospital archive department.

Variables

Data variables extracted from patient medical files included sociodemographic information such as age (≥18 years), gender and patient ICU category (ICU type –main (MICU) or COVID-19 ICU (C-19-ICU). Prescribing information such as antibiotic name, dosage, frequency, route of administration, duration of treatment and the disease condition for which the antibiotic was prescribed.

Dose utilisation review

A drug utilisation review/evaluation (DUR/DUE) is a robust tool used to evaluate patterns of antibiotic use and the appropriateness of prescriptions.[32,33] For each drug, including antibiotics, a defined daily dose (DDD) is assigned by the WHO for drug statistics and methodology as the assumed maintenance adult dose per day for its primary indication, while the prescribed daily dose (PDD; total dose divided by the number of days) is the actual average total dose prescribed to a patient. Utilisation indicators such as DDD and PDD are accompanied by the anatomical, therapeutic and chemical code (ATC) assigned to drugs according to the function and organ system in which it operates. Hence, antibiotics in the study were accompanied by the corresponding ATC code.[34] For this study, the DDD for each antibiotic was retrieved from the WHO AWaRe tool.[14,15,34] The PDD was calculated using the dosages, frequency and duration of therapy derived from the RedCap tool used to capture data.[16] The calculated PDD was then compared with the WHO precalculated/assigned DDD in a ratio (PDD/DDD). The study considered sub-use, optimal, or overuse as variables according to the difference from the unit: when the quotient of the PDD and DDD was <1.0, then it was considered sub-use, or overuse if a value is >1.0. Optimal use was considered at a prescribed dose equal to 1.0.

Change in antibiotic use

The relative change in antibiotic prescribing/use was calculated by the quotient of difference in antibiotic frequency of both periods of interest and pre-pandemic antibiotic frequency: (antibiotic frequency$_{\text{COVID-19}}$ – antibiotic frequency$_{\text{PRE-COVID-19}}$)/antibiotic frequency$_{\text{PRE-COVID-19}}$.

Data management and analysis

The data collected using RedCap were exported into Excel (Microsoft, USA) where they were cleaned before being imported into the statistical software. Statistical analysis was conducted using Statistical and Data Science Special Edition (STATA/SE; version 17.0) (StataCorp, USA). Descriptive statistics including proportions, frequency and counts were used to describe categorical variables such as demographics, patient diagnoses and antibiotic prescribing data. The PDD-DDD quotient was reported by medians (interquartile range).

Ethical considerations

The University of the Witwatersrand Health Research Ethics Committee (HREC) granted approval (ref. No. M220928) to conduct the study after protocol review. Permissions necessary to support and implement this study at the selected study site were obtained from the hospital chief executive officer (CEO) and the head of department (HOD) of internal medicine at the GPTH. Informed patient consent was not necessary as for retrospective record review, HOD and CEO permission from the study site is accepted as consent on behalf of the patient, since the CEO is considered the legal custodian of the institution. Furthermore, the integrity of the relevant patient data collected was upheld, with no alteration or manipulation of information during the duration of the study.

Results

Sociodemographic characteristics of patients based on the reviewed medical files

A total of 335 patient medical files were included in this study. During the pre-pandemic period, most files reviewed were those of male patients, amounting to 51.2% (*n*= 88) (Table 1). Most patients in the pre-pandemic period (35.5%; *n*=61) were between the ages of 41 and 61 years. Conversely, the COVID-19 period showed a female predominance of 63.19% (*n*=103), and most patients (44.79%; *n*=73) were between the ages of 26 and 40 years. Across both periods of the study, the MICU accounted for 80.6% (*n*=270) of the hospital ICU admissions and the C-19-ICU accounted for 19.4% of ICU admissions. During the COVID-19 study period, 53.4% (*n*=87) of patients included in the study tested negative and 46.6% (*n*=76) tested positive for COVID-19.

Common diagnosis categories

During the pre-pandemic period, the most common diagnoses for which antibiotics were prescribed included respiratory conditions (22.1%; *n*=38) and neurological conditions (20.9%; *n*=36) (Table 2). During COVID-19, the prevalence of most diagnosis categories decreased, apart from respiratory conditions, which increased to 33.7% (*n*=55). Furthermore, cardiovascular, dermatological, endocrinological and gynaecological conditions showed minor increases in observations.

Common diagnoses by COVID-19 status

Respiratory conditions made up the largest proportion of diagnoses, with COVID-19 -positive cases accounting for 54% (*n*=41) (Table 3). The majority of the diagnoses, not considering respiratory conditions, constituted the overall COVID-19-positive incidence (*n*=76).

Antibiotic prescriptions

Furthermore, prescriptions in the ICUs of the GPTH included 21 antibiotics derived from 10 pharmacological classes (Table 4). The most commonly prescribed antibiotic classes in the pre-pandemic period included penicillins and extended beta-lactamase inhibitors, cephalosporins and macrolides. The most commonly prescribed antibiotics within these classes were amoxicillin/clavulanate (pre-pandemic 31.99%; COVID-19 38.43%), followed by ceftriaxone (pre-pandemic 15.44%; COVID-19 14.55%), piperacillin/tazobactam (pre-pandemic 11.40%; COVID-19 8.58%) and azithromycin (pre-pandemic 7.72%; COVID-19 19.78%). The overall trend observed was a decline in antibiotic usage in the pre-pandemic period in comparison with the COVID-19 period. This was noted within antibiotic classes as well as in individual antibiotics, particularly amoxicillin/clavulanate (access category antibiotic, penicillins and extended beta-lactamase inhibitor class). Among the macrolides

Table 1. Demographic and clinical characteristics of patients at a Gauteng provincial tertiary-level hospital in South Africa from January 2017 to December 2021

	Study period		
Variable	**Pre-COVID-19, *n* (%)**	**COVID-19, *n* (%)**	**Total, *n* (%)**
Sex			
Female	84 (48.8)	103 (63.2)	187 (55.8)
Male	88 (51.2)	60 (36.8)	148 (44.2)
Total	172 (100)	163 (100)	335 (100)
Age group (years)			
18 - 25	27 (15.7)	17 (10.4)	44 (13.13)
26 - 40	54 (31.4)	73 (44.8)	127 (37.9)
41 - 60	61 (35.5)	52 (31.9)	113 (33.7)
61	30 (17.4)	21 (12.9)	511(5.22)
Total	172 (100)	163 (100)	335 (100)
ICU type			
MICU	172 (100)	98 (60.1)	270 (80.6)
C-19-ICU	0 (0)	65 (39.9)	65 (19.4)
Total	172 (100)	163 (100)	335 (100)
COVID-19 status			
Negative	172 (100)	87 (53.4)	259 (77.3)
Positive	0 (0)	76 (46.6)	76 (22.7)
Total	172 (100)	163 (100)	335 (100)

COVID-19 = coronavirus disease 2019; MICU = main intensive care unit; C-19-ICU = coronavirus disease 2019 intensive care unit.

Table 2. Primary diagnoses of patients at a Gauteng provincial tertiary-level hospital in South Africa from January 2017 to December 2021

	Study period		
Diagnosis	**Pre-COVID-19, *n* (%)**	**COVID-19, *n* (%)**	**Total, *n* (%)**
Cardiovascular	5 (2.91)	9 (5.52)	14 (4.18)
Dermatological	14 (8.14)	15 (9.20)	29 (8.66)
Endocrine	8 (4.65)	12 (7.36)	20 (5.97)
Gastrointestinal	14 (8.14)	10 (6.13)	24 (7.16)
Neurological	36 (20.9)	16 (9.82)	52 (15.5)
Gynaecology	8 (4.65)	10 (6.13)	18 (5.37)
Respiratory	38 (22.1)	55 (33.74)	93 (57.1)
Sepsis	16 (9.30)	9 (5.52)	25 (15.3)
Trauma and injuries	17 (9.88)	11 (6.75)	28 (17.2)
Other	16 (9.30)	16 (9.82)	32 (19.6)
Total	172 (100)	163 (100)	335 (100)

COVID-19 = coronavirus disease 2019.

Table 3. Primary diagnosis and COVID-19 statuses of patients at a Gauteng provincial tertiary-level hospital in South Africa from January 2017 to December 2021

	COVID-19 status		
Diagnosis	**Positive, *n* (%)**	**Negative, *n* (%)**	**Total, *n* (%)**
Cardiovascular	5 (6.58)	9 (3.47)	14 (4.18)
Dermatological	1 (1.32	28 (10.8)	29 (8.66)
Endocrine	4 (5.26)	16 (6.18)	20 (5.97)
Gastrointestinal	3 (3.95)	21 (8.11)	24 (7.16)
Neurological	6 (7.89)	46 (17.8)	18 (5.37)
Gynaecology	2 (2.63)	16 (6.18)	52 (15.5)
Respiratory	41 (54.0)	52 (20.1)	93 (26.76)
Sepsis	2 (2.63)	23 (8.88)	25 (7.46)
Trauma and injuries	2 (2.63)	26 (10.0)	28 (8.36)
Other	10 (13.2)	22 (8.49)	32 (9.6)
Total	76 (100)	259 (100)	335 (100)

COVID-19 = coronavirus disease 2019.

class observed, azithromycin prescribing increased across the pre-pandemic period to the COVID-19 pandemic period.

The 'access' group of antibiotics showed an increase in prescribing of approximately 7% following the commencement of COVID-19 (Table 5). 'Watch' antibiotics decreased in use by 8% from the pre-pandemic period to the COVID-19 period. 'Reserve' antibiotics were not prescribed among the study cohort in either pre-pandemic or COVID-19 periods. The 'watch' category (pre-pandemic 54.8%, *n*=149; COVID-19 51.1%, *n*=137) exceeded the 'access' category (pre-pandemic 45.2%, *n*=123; COVID-19 48.9%, *n*=131) across both periods.

Assessment of discrepancy of dose utilisation

The PDD and DDD quotient (PDD divided by the DDD) were calculated to determine the discrepancy in dose utilisation (Table 6). During the pre-pandemic period, overuse occurred in 17 out of the 21 antibiotics assessed, with 9 of these antibiotics prescribed more than once. The drug that showed the greatest extent of overuse in the pre-pandemic period was amoxicillin/clavulanate. The sub-use category reported 14 antibiotics out of the 21 antibiotics in the sample, which further indicated that 9 out of 21 antibiotics were prescribed more than once during the pre-pandemic period. Amoxicillin/clavulanate represented the higher proportion of sub-use. Optimal use was reported in 14 out of the 21 antibiotics assessed, and 8 out of 21 antibiotics were prescribed more than once during the pre-pandemic period. Antibiotics optimally used across both periods of the study included ceftriaxone, azithromycin and metronidazole. During the COVID-19 pandemic, overuse occurred in 11 out of the 21 antibiotics assessed, with 6 of 21 antibiotics being prescribed more than once. Amoxicillin/clavulanate, as in the pre-pandemic period, showed the greatest extent of use in the COVID-19 period. Azithromycin, ceftriaxone and metronidazole, similarly to the pre-pandemic period, constituted the higher proportions of optimal use. A relatively lower measure of sub-use was reported in 8 out of the 21 antibiotics assessed in comparison with the pre-pandemic period.

Table 4. Distribution by antibiotics prescribed to ICU patients admitted at a Gauteng provincial tertiary hospital in South Africa between January 2017 and December 2021

Antibiotic class	WHO AWaRe	ATC	Antibiotic	Pre-pandemic, *n* (%)	COVID-19, *n* (%)
Aminoglycosides	Access*	J01GB03	Gentamicin	2 (0.74)	1 (0.37)
		J01GB06	Amikacin	4 (1.47)	3 (1.12)
Carbapenems	Watch†	J01DH03	Ertapenem	11 (4.04)	0 (0)
		J01DH51	Imipenem	10 (3.68)	9 (3.36)
		J01DH02	Meropenem	15 (5.51)	7 (2.61)
Cephalosporins	Watch	J01DE01	Cefepime	5 (1.83)	2 (0.75)
	Access	J01DB04	Cefazolin	2 (0.74)	4 (1.49)
	Watch	J01DD01	Cefotaxime	2 (0.74)	0 (0)
	Watch	J01DD04	Ceftriaxone	42 (15.44)	39 (14.55)
Glycopeptides	Watch	J01XA01	Vancomycin	7 (2.57)	3 (1.12)
Lincosamides	Access	J01FF01	Clindamycin	8 (2.94)	7 (2.61)
Macrolides	Watch	J01FA10	Azithromycin	21 (7.72)	53 (19.78)
Nitroimidazoles	Access	J01XD01	Metronidazole	14 (5.15)	11 (4.10)
Penicillins and beta-lactamase inhibitors	Access	J01CA04	Amoxicillin	3 (1.10)	1 (0.37)
		J01CA01	Ampicillin	2 (0.74)	0 (0)
		J01CF02	Cloxacillin	1 (0.37)	0 (0)
		J01CR02	Amoxicillin/ clavulanate	87 (31.99)	103 (38.43)
	Watch	J01CR05	Piperacillin/ tazobactam	31 (11.40)	23 (8.58)
Tetracyclines	Access	J01AA02	Doxycycline	0 (0)	1 (0.37)
Fluoroquinolones	Watch	J01MA02	Ciprofloxacin	4 (1.47)	1 (0.37)
		J01MA14	Moxifloxacin	1 (0.37)	0 (0)

*'Access' category antibiotics: empiric first- or second-choice antibiotics with a narrow spectrum of antibacterial activity and a low potential for resistance.
†'Watch' category antibiotics: antibiotics with a broader spectrum of antibacterial activity. However, antibiotics within this category are susceptible to a greater likelihood of resistance in comparison to antibiotics in the 'access' category.
WHO = World Health Organization; WHO AWaRe = Access, Watch and Reserve; ATC = anatomical, therapeutical and chemical.

Table 5. Distribution of prescribed antibiotics according to the WHO AWaRe classification of ICU patients admitted at a Gauteng provincial tertiary hospital between January 2017 and December 2021

WHO AWaRe category	Pre-pandemic, *n* (%)	COVID-19, *n* (%)	Total, *n*	Relative change, %
Access antibiotics	123 (45.2)	131 (48.9)	254	6.5
Watch antibiotics	149 (54.8)	137 (51.1)	286	–8.1
Reserve antibiotics*	0 (0)	0 (0)	0	0.0
Total	272 (100)	268 (100)	540	–1.5

*'Reserve' category antibiotics: antibiotics with the highest potential of resistance, that are 'last choice or last resort', and are used in multidrug-resistant infections where 'access' and 'watch' category antibiotics are deemed unsuitable.
WHO = World Health Organization; AWaRe = access, watch, reserve.

Table 6. Association PDD/DDD, sub-use, optimal and overuse for antibiotics prescribed to ICU patients admitted at a Gauteng provincial tertiary hospital between January 2017 and December 2021. PDD/DDD ratio is described as median (25th percentile - 75th percentile)

				Pre-pandemic				COVID-19			
Antibiotic class	**Antibiotic**	***n***	**DDD (g)**	**PDD/DDD**	**Sub-use**	**Optimal**	**Overuse**	**PDD/DDD**	**Sub-use**	**Optimal**	**Overuse**
Aminoglycosides	Gentamicin	3	0.2	0.9 (0.8 - 1.0)	1 (1.33)	1 (1.05)	0	2.0 (2.0 - 2.0)	0	0	1 (0.87)
	Amikacin	7	0.6	1.7 (1.3 - 1.7)	1 (1.33)	0	3 (2.91)	1.7 (1.3 - 1.7)	0	0	3 (2.61)
Carbapenems	Ertapenem	11	1.0	1.0 (1.0 - 1.0)	1 (1.33)	8 (8.42)	2 (1.94)	1.0 (1.0 - 1.0)	0	0	0
	Imipenem	19	2.0	0.8 (0.5 - 1.5)	6 (8.00)	0	4 (3.88)	1.5 (1.1 - 1.5)	2 (3.45)	0	9 (7.83)
	Meropenem	22	3.0	1.0 (1.0 - 1.0)	3 (4.00)	9 (9.47)	3 (2.91)	0.7 (0.5 - 1)	4 (6.90)	2 (2.06)	1 (0.87)
Cephalosporins	Cefazolin	6	3.0	2.3 (2.0 - 2.7)	0	0	1 (0.97)	1.0 (1.0 - 1.0)	0	4 (4.12)	0
	Cefepime	7	4.0	0.8 (0.8 - 0.8)	4 (5.33)	0	1 (0.97)	0.1 (0.1 - 0.1)	0	2 (2.06)	0
	Cefotaxime	2	4.0	1.3 (1.0 - 1.5)	0	1 (1.05)	1 (0.97)	0	0	0	0
	Ceftriaxone	81	4.0	1.0 (0.5 - 1.0)	14 (18.67)	27 (28.42)	1 (0.97)	1.0 (0.5 - 1.0)	15 (25.86)	18 (18.56)	6 (5.22)
Glycopeptides	Vancomycin	10	2.0	1.0 (0.5 - 1.0)	2 (2.67)	4 (4.21)	1 (0.97)	0.5 (0.5 - 1.0)	2 (3.45)	1 (1.03)	0
Lincosamides	Clindamycin	15	1.8	1.0 (0.7 - 1.2)	3 (4.00)	3 (3.16)	2 (1.94)	1.0 (0.7 - 1.0)	2 (3.45)	4 (4.12)	1 (0.87)
Macrolides	Azithromycin	74	0.5	1.0 (1.0 - 1.0)	0	21 (22.11)	0	1.0 (1.0 - 1.0)	0	51 (52.58)	2 (1.74)
Nitroimidazoles	metronidazole	26	1.5	1.0 (1.0 - 1.0)	2 (2.67)	13 (13.68)	0	1.0 (1.0 - 1.0)	1 (1.72)	10 (10.30)	0
Penicillins and extended beta-lactamases	Amoxicillin	4	1.5	2.0 (1.0 - 2.4)	0	1 (1.05)	2 (1.94)	1.3 (1.3 - 1.3)	0	0	1 (0.87)
	Ampicillin	2	6.0	1.1 (0.7 - 1.5)	1 (1.33)	0	1 (0.97)	0	0	0	0
	Cloxacillin	1	2.0	4.0 (4.0 - 4.0)	0	0	1 (0.97)	0	0	0	0
	Amoxicillin/clavulanate	190	3.0	1.2 (1.2 - 1.2)	20 (26.67)	1 (1.05)	66 (64.08)	1.2 (1.0 - 1.2)	23 (39.66)	3 (3.09)	77 (66.96)
	Piperacillin/tazobactam	54	14	0.6 (0.4 - 1.3)	16 (21.33)	4 (4.21)	11 (10.68)	1.3 (0.5 - 1.3)	9 (15.52)	1 (1.03)	13 (11.30)
Tetracyclines	Doxycycline	2	0.1	10 (10 - 10)	0	0	1 (0.97)	2.0 (2.0 - 2.0)	0	0	1 (0.87)
Fluoroquinolones	Ciprofloxacin	5	0.8	1.1 (0.6 - 1.3)	1 (1.33)	1 (1.05)	2 (1.94)	1.0 (1.0 - 1.0)	0	1 (1.03)	0
	Moxifloxacin	1	0.4	1.0 (1.0 - 1.0)	0	1 (1.05)	0	0	0	0	0

PDD = prescribed daily dose; DDD = defined daily dose; ICU = intensive care unit; COVID-19 = coronavirus disease 2019.

Discussion

Several studies singularly evaluated and analysed antibiotic consumption data before the COVID-19 pandemic in SA and internationally. Johnston *et al.*[36] conducted a review in the ICU of a tertiary-level hospital in SA, reporting that the most frequently prescribed antibiotics in the ICU were amoxicillin/clavulanate, piperacillin/tazobactam and cefazolin. Similarly, the current study also observed high frequencies of amoxicillin/clavulanate and piperacillin/tazobactam in the pre-pandemic period. However, the present study was inconsistent with the prescribing frequency of cefazolin reported by Johnston *et al.*[36] Furthermore, the current study observed additional high prescribing frequencies in antibiotics such as ceftriaxone and azithromycin. Another study by Dlamini *et al.*[37] assessed antibiotic utilisation in 39 wards in a SA hospital, and the overall prevalence of antibiotics was higher in the ICU. Moreover, the study reported that beta-lactamase inhibitors were more prevalent within the ICU, corroborating the high usage of beta-lactamase inhibitors such as piperacillin/tazobactam and amoxicillin/clavulanate in the current study.[37] Balkhy *et al.*[38] investigated antibiotic usage across five adult ICUs, reporting that the most frequently prescribed antibiotics were meropenem, piperacillin/tazobactam, vancomycin and colistin across all ICUs.[39] The study partially supported the findings of the present study, but conversely, the present study found a relatively low frequency in meropenem and vancomycin. Furthermore, no patients in the current study were prescribed colistin. These pre-pandemic antibiotic utilisation studies provide baseline levels of antibiotic consumption, providing perspective on the extent of antibiotic engagement before the COVID-19 pandemic. This is crucial, as these studies indicate that antibiotic usage overall was already relatively high before the commencement of the COVID-19 pandemic.

The high transmissibility and critical severity associated with COVID-19 have since changed most attributes of healthcare globally related to diagnosis, clinical management, repurposing of antibiotics and administration of AMS programmes.[17,40] A few studies have since quantified, assessed and compared antibiotic utilisation between the pre-pandemic period and the COVID-19 pandemic, although studies related to the SA antibiotic consumption context comparing the pre-pandemic and COVID-19 pandemic use of these antibiotics could not be found at the time of review.[41-44] A study by Bednarčuk *et al.*[42] compared the period interval of interest (2018 - 2022), observing an increase in the use of amoxicillin/clavulanate and azithromycin.[42] These findings augmented the results of the present study that demonstrated

an increase in the consumption of amoxicillin/clavulanate and azithromycin across both periods of the study. Another study by Gonzalez-Zorn[43] investigated antibiotic use between the periods of January 2017 and February 2020. The use of azithromycin in March 2020 was 400% the use of the same antibiotic in February 2020, and >320% of the use of azithromycin in January 2019.[43] The present study observed an increase in azithromycin of ~152% between the periods of January 2017 and December 2021, which is comparatively lower than the cumulative increase in azithromycin reported by Gonzalez-Zorn *et al.*[43] Despite the inconsistencies in findings, both studies reported an increase in azithromycin use. Furthermore, Andrews *et al.*[41] compared antibiotic utilisation pre COVID-19 and during COVID-19 in communities and hospitals, concluding that there was an overall decrease in antibiotic consumption from pre to COVID-19 . Furthermore, the study also noted that more antibiotics were prescribed in a hospital setting over community prescriptions. Similarly, the present study observed an overall decrease in antibiotic use across most antibiotic classes, but on the contrary, amoxicillin/clavulanate and azithromycin sustained utilisation, and a further increase in prescribing and use was observed moving into the COVID-19 pandemic. Moreover, Andrews *et al.*[41] further reported a respiratory infection-related increase in the 'watch' category antibiotics, such as azithromycin, in April 2020, in alignment with the COVID-19 wave emergence period.[41] The present study correlated with the increase in respiratory illness observed by Andrews *et al.*,[41] having observed a 45% incline in respiratory diagnoses since the commencement of COVID-19 . Malcolm *et al.*[45] compared weekly antibiotic prescriptions between the years 2019 and 2020. A steep increase in the number of prescription antibiotics related to respiratory infections was observed in March 2020, 44% higher than the corresponding week in March 2019.[45] This study further emphasises the increased use of antibiotics attributed to respiratory infections reported by the present study. The increase in respiratory conditions alongside the overall increase in amoxicillin/clavulanate and azithromycin could be related to the broad-spectrum activity of these two antibiotics indicated for various conditions, including respiratory illness.[46]

The present study's secondary objective was the determination of the prevalence of the 'watch' category antibiotics as part of the WHO AwaRe classification system of antibiotics. The AwaRe classification is intended to promote the importance of optimal watch and reserve category antibiotics use in consideration of the potential for antibiotic resistance advancement and advocating the availability and use of access category antibiotics for global health coverage.[14] At the time of review, only one study had been conducted in SA according to the WHO AWaRe antibiotic classification methodology.[47] A study by Mthombeni *et al.*[47] described and tracked antibiotic consumption between 2014 and 2018, comparable with the pre-pandemic period, in the public sector of Limpopo Provinc, SA. Mthombeni *et al.*'s study[47] reported a consumption of 19.7% relative to the 'watch' category antibiotics. Contrary to this study, the present study observed a high frequency and proportion of 'watch' category antibiotics (52.10%) during the pre-pandemic period. Another study by Nguyen *et al.*[48] assessed antibiotic consumption from September 2017 to July 2018, reporting 792 (59%) 'access' category encounters, 527 (39.30%) 'watch' category antibiotics, and no reports of 'reserve' category antibiotics. Conversely, the present study observed high proportions of 'watch' category antibiotics to 'access' category antibiotics. This inconsistency may be due to the difference in antibiotics stipulated on the essential medicines list across different countries and facilities, as well as the variation in clinical severity and indications. Al-Azzam *et al.*[49] investigated antibiotic consumption from 2019 to 2020, synonymous with the pre to COVID-19 transition period. An increase in third-generation cephalosporins, carbapenems, macrolides and lincosamides was observed from 2019 to 2020. Furthermore, an increase in azithromycin and a decrease in amoxicillin/clavulanate was reported from 2019 to 2020. Al-Azzam *et al.*[49] further concluded an overall decrease in 'access' category antibiotics (18%) and an increase in 'watch' category antibiotics (24%).On the other hand, the current study indicated an increase in antibiotic consumption in penicillins (amoxicillin/clavulanate) and macrolides (azithromycin) classes of antibiotics, with an overall increase in access antibiotics and a decline in the consumption of 'watch' category antibiotics. Wang *et al.*[50] evaluated antibiotic use before and after the emergence of COVID-19 using an interrupted time series. Contrary to the present study, Wang *et al.*[50] reported a long-term slight increase in both 'access' and 'watch' categories between January 2019 and December 2021.[51]

In comparison with the present study, variability in results across all studies considering the AWaRe classification of antibiotics emphasises the diversity in antibiotic utilisation patterns across institutions and countries. Furthermore, there are not many studies that adopt the rationale of the WHO AWaRe methodology, especially in LIMCs such as SA.[48] A study by Abu-Ajaleh *et al.*[52] demonstrated that healthcare worker educational intervention on AWaRe classification of antibiotics and the related risk of antibiotic resistance is effective. The study concluded that hospital antibiotic use of 'access' antibiotics increased by 6.6% from pre to post intervention, while the use of 'watch' and 'reserve' group antibiotics decreased by 1.7%, and 43.1%, respectively.[52] Therefore, more efforts and public strategies need to be implemented in educating prescribers and dispensers about the WHO AWaRe classification of antibiotics, as well as system integration.

The present study also evaluated dosage utilisation through the comparison of the PDD and DDD (as determined by the WHO), reporting overuse in amoxicillin/clavulanate across the pre-pandemic and COVID-19 pandemic periods. This is consistent with prescribing patterns across both periods in the study. Azithromycin, however, demonstrated a great extent of optimal use across both periods of interest, despite the consumption increase from pre to COVID-19, demonstrating that there was a low discrepancy between the PDD and DDD of azithromycin. The study further indicated variability in usage categories for piperacillin/tazobactam and ceftriaxone, since dose utilisation is an estimation and does not always correspond to each dosage regimen, clinical indication and pharmacokinetic properties. Therefore, dosage utilisation will differ based on patient groups and age.[34,53] A study by Johnston *et al.*[36] in the ICU of a SA tertiary hospital reported that the PDD exceeded the DDD in most of the antibiotics prescribed. However, to our knowledge, there are no other recent studies in SA that have compared the PDD with the DDD to evaluate dosage utilisation before and during the COVID-19 pandemic. Moreover, very few international studies have compared PDD and DDD for patients. A study by Sánchez-Huesca *et al.*[54] estimated the PDD and compared it against DDD in outpatients in Mexico City. The study reported a high prevalence of either sub-use or overuse. A significant difference was reported in PDD from DDD in 14 antibiotic classes assessed, accounting for overuse that occurred in 15 out of the 27 antibiotics prescribed. The antibiotics that showed the greatest extent of overuse included amoxicillin, either alone or in combination with clavulanic acid, azithromycin, levofloxacin and clarithromycin.[54] Similarly, our study showed overuse in 17 and 11 of 21 antibiotics in the pre-pandemic and COVID-19 periods, respectively. The greatest extent of overuse was demonstrated by amoxicillin in combination with clavulanate. However, azithromycin was mostly optimally used, and

no patients were prescribed levofloxacin and clarithromycin in the current study. Furthermore, Sánchez-Huesca *et al.*[54] reported sub-use in 63% of antibiotics assessed, while the current study reported higher sub-use pre-pandemic (66.7%) and comparatively lower sub-use in the COVID-19 period (38.1%).[54] Despite the variation in results between the studies, the overuse of amoxicillin/clavulanate is consistent, due to the broad-spectrum activity and bacterial coverage of this antibiotic.

Compared with the scarcity of studies using PDD, several studies have quantified and evaluated antibiotic dosage utilisation using calculated DDDs (based on medication package quantity, size and strength), DDD per 1 000 inhabitants per day (DID) and days of therapy (DOTs).[47,55-58] The WHO recommends the use of the DDD utilisation indicator.[34] However, very few studies have quantified and evaluated the discrepancies and differences between PDD, calculated DDD and recommended daily dose (RDD).[53,59,60] Studies have considered and proposed that the DDD fails to address the discrepancies that exist between the actual prescribed daily dose (PDD) and the DDD.[59] Furthermore, overestimation in consumption is often reported using DDD measurements in antibiotic classes such as penicillins and macrolides.[59,60] Först *et al.*[59] recommended the use of a validated RDD as a supplementary measure to measure the DDD for a detailed analysis and to avoid misclassification in benchmark analysis.[59] Thus, using prescribed dosage measures enables more precision in estimating dose utilisation, and is an alternative to overcoming the paucity of variables (strength, quantity and pack size) required to calculate the DDD, which is often the case in the SA healthcare setting context.

Study limitations

This study was conducted across two ICUs (MICU and C-19-ICU) in a single GPTH. This restricted the number of potential patients and hospital departments, thus affecting the variability of observations. Patients were not followed up after being transferred out of the ICU to other departments. Furthermore, the inclusion of various designated COVID-19 institutions would have enabled the analysis for regional variability in antibiotic utilisation pre COVID-19 and during COVID-19 . Owing to the lack of pharmacy prescription data such as package size and quantity, the DDD could not be calculated.

Conclusion

This study measured antibiotic prescribing in the ICUs of a GPTH. The data revealed a rise in the prescribing of macrolides and penicillin classes of antibiotics transitioning from the pre-pandemic period into the COVID-19 pandemic. The most frequently used and prescribed antibiotics in these classes were azithromycin and amoxicillin in combination with clavulanate. Overall, the 'watch' category prescription volume exceeded that of the 'access' category, deviating from the prospects of the WHO AWaRe system that advocates the availability and use of access category antibiotics as first-line agents for global health coverage. Moreover, a decrease in 'watch' category antibiotics was seen transitioning into the COVID-19 period, with the adverse incline of azithromycin prescriptions within the category, indicating the need of for improved AMS practices and stricter prescribing practices across both 'access' and 'watch' categories. Moreover, the findings of this study can be used as an initiation point in the implementation, strengthening and adaptation of antibiotic stewardship programmes that should be built to include pandemic factors, such as drug repurposing. Furthermore, a sustainable reporting antibiotic surveillance framework built around the operational characteristics and resource parameters of a healthcare setting is necessary to achieve improved antibiotic review and feedback systems. This study was conducted in the ICUs of one GPTH, but even with this inherent limitation of the study, the methodology adopted is adequate to provide insight to potential antibiotic prescribing and usage trends between the pre-COVID-19 period and the COVID-19 pandemic in the SA public healthcare system. Future studies should focus on factors associated with inappropriate prescribing during the COVID-19 pandemic in the public healthcare system and the consumption of antibiotics in all hospital wards, across various hospital levels (district, regional, tertiary, and quaternary), and inter-provincially, which would be critical in establishing a national antibiotic consumption baseline.

Data availability. In compliance with the study protocol and conditions set by the study site, the raw and cleaned data sets will not be made available.

Declaration. This study was completed as part of LS's MPharm degree.

Acknowledgements. None.

Author contributions. SLdR and ZB conceived the study design. LS conducted the methods and performed analyses and first manuscript writing. LS, SLdR and ZB executed manuscript revision and editing. SLdR and ZB supervised the project.

Funding. None.

Conflicts of interest. None.

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Received 18 December 2023; accepted 16 May 2024.