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A point prevalence survey of antimicrobial utilisation patterns and quality indices amongst hospitals in South Africa; findings and implications

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Abstract
Objectives: Antimicrobial use is growing, driven mainly by rising demands in developing countries. Knowing how antimicrobials are prescribed is important. Consequently, we undertook a point prevalence survey (PPS) quantifying antimicrobial consumption among 18 public sector hospitals across South Africa. **Method**: A purpose-built web-based application was used to collect PPS data. **Results:** Out of 4407 patients surveyed, 33.6% were treated with an antimicrobial. The most frequently prescribed groups were a combination of penicillins including β-lactamase inhibitors. Amoxicillin combined with an enzyme inhibitor accounted for 21.4% total DDDs. In the medical and surgical wards, Access antimicrobials (54.1%) were mostly used, while in the ICU, Watch antimicrobials (51.5%) were mostly used. Compliance with the South African Standard Treatment Guidelines and Essential Medicines List was 90.2%; however, concerns with extended use of antimicrobials for surgical prophylaxis (73.2% of patients). **Conclusion**: The web-based PPS tool was easy to use and successful in capturing PPS data since the results were comparable to other PPS studies across Africa. High use of amoxicillin combined with an enzyme inhibitor possibly because it was among the broad-spectrum antimicrobials in the Access group. The findings will assist with future targets to improve antimicrobial prescribing among public sector hospitals in South Africa.

Key words: antimicrobial consumption, point prevalent surveys, AWaRe list of antimicrobials, South Africa, public hospitals, quality indicators; rational medicine use; Standard Treatment Guidelines; surgical prophylaxis

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1. Introduction

Antimicrobial resistance (AMR) is a global public health concern in view of its impact on morbidity, mortality and costs [1-6], with inappropriate prescribing and dispensing of antimicrobials the primary driver of AMR [4]. Antimicrobial use is growing across countries, driven mainly by rising demand in low- and middle-income countries (LMICs) including South Africa [7,8]. Between 2000 and 2015, global antibiotic consumption, expressed in defined daily doses (DDD), increased by 65% (21.1–34.8 billion DDDs), which reduced to 39% when population sizes were factored in, i.e. from 11.3 to 15.7 DDDs per 1,000 inhabitants per day from 2000 to 2015 [7]. Antimicrobial use in South Africa was 21,149 standard units per 1000/population in 2015, which was appreciably higher than most other countries in the world, although similar to other BRIC (Brazil, Russia, India, China and South Africa) countries [9]. This is a concern given the high rates of infectious diseases in South Africa including human immunodeficiency virus (HIV) and tuberculosis (TB) [10-13], which has dominated healthcare in South Africa in recent years along with high rates of AMR [9,14]. These concerns with the over use of antimicrobials and increase rates of AMR have resulted in initiatives internationally, regionally, and nationally to improve future antimicrobial prescribing [15-22], with South Africa no exception [14,23]. Strategies promoting the rational use of antimicrobials help slow down the emergence of AMR and extend the useful lifetime of effective antimicrobials [24-26].

Antimicrobial utilisation data is essential to fully assess current consumption patterns across different healthcare sectors to inform the development of future initiatives to promote the rational use of antimicrobials and reduce AMR [24,27-33]. This includes South Africa with its ongoing strategy to reduce AMR rates [23]. Typically though, there is a paucity of antimicrobial utilisation data across Africa, including South Africa, which urgently needs to be addressed [30,34-36] as the first stage to reduce inappropriate antimicrobial use.

Approaches in hospitals to collect antimicrobial utilisation data include point prevalence surveys (PPS), which assess overall utilisation patterns as well as the nature and extent of antimicrobial use for specific events, which include preventing surgical site infections (SSIs) and treating healthcare associated infections (HAIs) [30,37-44]. This typically involves the manual collection of hospital data in LMICs given the current paucity of electronic data collection systems [8,30,40,42]. Assessing antimicrobial utilisation patterns in ambulatory care again includes a variety of approaches, which include interrogating prescribing databases, undertaking surveys and manual assessments including import data [27,45-48].

A number of quality indicators have been developed to improve antibiotic prescribing across the sectors [27,30,49,50]. The indicators can be general including the extent of prescribing according to the World Health Organization's (WHO) recent AWaRe list (Access, Watch and Reserve) [51-53]; alternatively, specific including the extent of prescribing according to a specific Standard Treatment Guideline (STG) for a specific infectious disease [54,55]. The Access group of antibiotics are considered as first- or second-line choices for empiric treatment for up to 26 common or severe clinical syndromes, with recommended first-line choices typically having a narrow spectrum and low toxicity risk. The Watch group of antibiotics are considered to have a higher toxicity or resistance potential, and the Reserve group should be considered as a last resort and prioritised as key targets for antimicrobial stewardship programmes (ASPs) for national and local monitoring [52,56].

In hospitals, potential indicators include the extent of antimicrobial use per patient or bed day, recording of the rationale for the initial antimicrobial prescription and any subsequent changes, recording start and stop dates, the extent of empiric versus targeted antimicrobial treatment, the extent of switching from IV to oral antibiotics, the availability of local guidelines (STGs) and adherence to these including those for surgical prophylaxis, and the extent of prolonged prophylaxis (> 1 day), to prevent surgical site infections (SSIs) [30,36,42,57-60]. The latter are particularly important in LMICs given considerable concerns with the timing of the first dose and the current high rates of prolonged prophylaxis [61]. In outpatients, potential indicators include adherence to current guidelines, withholding antibiotics for suspected viral upper respiratory tract infections as well as routine stocking of antibiotics within essential medicines lists [55,62].

In South African communities and primary healthcare, these indicators can include the extent of broad versus narrow spectrum antibiotics prescribed, the extent of third and fourth generation cephalosporins and fluoroquinolones versus total antibiotics prescribed, and the extent of prescribing in compliance to current guidelines [27,50,54,63,64]. In addition, indicators based on the AWaRe list [51,65,66].

We and others have previously reported on PPS studies in South Africa across selected hospitals including the use of a web-based application (APP) for data recording [67-69]. However, we believe our current study is the first national PPS study using a web-based application to record antimicrobial consumption to enhance the speed and efficiency of data collection and analysis. We are aware that a number of PPS studies have been undertaken in other African countries including Botswana, Ghana, Kenya and Nigeria, as well as among the African countries taking part in the Global-PPS study [30,40,57.70-75]. We wanted to expand on this and include the collection of antimicrobial utilisation data within public sector hospitals across South Africa. This builds on current initiatives within hospitals across South Africa to reduce AMR rates, with public hospitals particularly important with approximately 80% of patients in South Africa currently treated in the public sector [10]. We also wanted to explore the use of a web-based application for collection of antimicrobial data nationally to assess its feasibility especially given its documented speed and efficiency in an initial PPS study in South Africa [68]. We believe this is important in countries with limited resources including available manpower to undertake PPS on a regular basis and to report the findings in a timely fashion as part of quality improvement programmes.

Consequently, the objectives of this study are to collect data on antimicrobial utilisation patterns with a new web-based application among a range of public sector hospitals in South Africa at a given point in time and to compare the findings with other African countries and wider to provide future guidance. This is important given the high prevalence of HIV, TB, and malaria among sub-Saharan African countries versus Western countries [40]. The findings will also contribute to ongoing debates about possible quality initiatives to introduce within the healthcare systems in South Africa and wider to improve future antibiotic utilisation and reduce AMR rates using web-based applications.

2. Methods

2.1 Study design

This was a quantitative observational PPS of antimicrobial consumption with descriptive data collected from 18 public sector hospitals in South Africa, using a purpose-built web-based application (APP).

2.2 Study sites

For the purpose of this PPS, 18 hospitals were selected including all the nine academic national central and tertiary hospitals across South Africa as well as nine conveniently selected district hospitals (one per province), considering their proximity to the academic or tertiary hospital used for referrals.

Public sector hospitals in South Africa differ according to the level of service provided. They are managed in accordance with the national policy as determined by the South African Government and categorised in the Gazette [76]:

- District hospital: A bed capacity of 50 – 600 beds and support primary healthcare sectors
- Regional hospital: 200 -800 beds and receive outreach and support from tertiary hospitals. They must provide health services in at least one of the following specialties - (i) orthopaedic surgery; (ii) psychiatry; (iii) anaesthetics; (iv) diagnostic radiology
- Tertiary hospital: Provide specialist level services through regional hospitals and provide intensive care services under the supervision of a specialist or specialist intensivist
- Central hospital: Must provide tertiary hospital services and central referral services whilst providing national referral services. They must conduct research and must be attached to a medical school as the main teaching platform. Patients referred to it are from more than one Province and must have a maximum of 1200 beds.
- Specialised hospital: Provides specialised health services including psychiatric services, tuberculosis services, infectious, diseases and rehabilitation services. They have a maximum of 600 beds.

Overall, the 18 public sector hospitals chosen represent the different geographical locations within the 9 provinces of South Africa and the different levels of care, with the hospitals randomly selected using the different categories set out by Government [76].

2.3 Data collection tool and variables recorded

A structured data collection tool was used. This was based on the study designs of the European Centre for Disease Prevention and Control (ECDC) and Global-PPS and subsequently adapted for sub-Saharan Africa, initially in Botswana and then for South Africa [30,35,40,67,77]. The data collection sheets were subsequently converted into a web-based APP to reduce the time taken to prepare for the study and to appreciably speed-up data collection and analysis, which has been validated in a previous study [68].

The data collection tool made provision for the collection of hospital level data, which included the name and classification of the hospital according to the National Department of Health (NDoH) [68], the wards surveyed, specifying the speciality rendered in the particular ward with the number of patients surveyed in that ward. Demographical data for patients included their age, gender, employment status, catheter use, extent of intubations, readmissions, antimicrobial history and hospitalisation in the last 90 days. Compared to the ECDC study and Global-PPS, key factors also included in the data collection tool were the extent of co-morbidities, especially HIV, TB and malaria, availability of laboratory services, route of administration and duration of antimicrobial use.

For the antimicrobial data, the antimicrobial prescribed was documented according to WHO ATC index and using Defined Daily Dose (DDDs) (2019 version) [78]. The route of administration and dose were also recorded. It was noted whether the antimicrobial was prescribed for treatment or prophylaxis, and if for prophylaxis, whether it was for medical or surgical prophylaxis. Surgical prophylaxis included the administration of antimicrobials prophylactically to prevent SSIs, with medical prophylaxis defined as the use of antimicrobials to prevent infections in patients with medical conditions [30,42]. For surgical prophylaxis, the antimicrobial administered was recorded along with the date of administration, duration, and number of doses given as there have been concerns with extended prophylaxis among African countries [30,38,40,61,79,80]. The indications for the antimicrobials prescribed were also recorded where documented and whether cultures were taken or not, and whether the findings changed the antimicrobial prescribed or not.

2.3 Patient selection and data collection

Data were collected by pharmacists and other research assistants on weekdays only and over a period of five months, from April to August 2018. A detailed training session was conducted for all the data collectors prior to data collection, similar to other PPS studies [40,67].

Within a PPS, all patients in a single ward are completely surveyed within one day to be able to accurately calculate the denominator and the numerator in order to determine antimicrobial consumption at a specific point in time, i.e. the % of patients receiving antimicrobials [81]. It is also important to aim at collecting the data for all facilities within one season since the consumption of antimicrobials might be higher in one season, e.g., winter compared to summer, which could complicate comparisons across facilities. Furthermore, PPS studies are very resource-demanding and with limited manpower, it may be impossible to conduct the survey on all patients. We therefore adopted the patient selection approach as recommended by WHO [81]. All patients admitted in the hospital and present in the ward at 08:00 on the day of the survey were included if the hospital had a bed capacity of <700. For hospitals with a capacity of 700-1500 beds, one in every two patients were surveyed and one in every three patients if the bed capacity was >1500. Depending on the bed capacity of the hospital, upon entering a ward at 08:00, the first, second or third patients were randomly selected. From this random starting point, the data collector either surveyed all patients or selected every second or third patient until the survey in the ward was complete [81].

For the purpose of calculating the point prevalence of antimicrobial use, the number of patients present in the ward at 08:00 on the day of data collection was used as the denominator, which means these patients had been admitted at least the previous day and are still in the ward at 08:00. For the numerator, all patients who were prescribed antimicrobials were recorded. Patients attending accident and emergency departments, admitted for day case surgery or minor procedures, chemotherapy, and dialysis outpatients, as well as those in labour wards, were excluded in line with other PPS studies [40].

2.4 Quality indicators

For the purpose of this survey, the quality indicators chosen included the extent of antimicrobial consumption compared with other PPS studies in South Africa and across Africa [30,40,57,69-75] using the WHO ATC index with Defined Daily Dose (DDDs) of 2019 [78], and against current WHO AWaRe classification guidance [52,56]. In addition, whether the indication for antimicrobial use was documented, the duration of antimicrobial prophylaxis to prevent SSIs, the extent of IV administration of antimicrobials and prescribing against the current South African Standard Treatment Guidelines and Essential Medicines List (STG/EML) in hospitals [30,82]. The prescribing of antimicrobials against agreed guidelines is a well recognised indicator of the quality of prescribing across sectors [30,54,58.60,63].

2.5 Data management and statistical analysis

Data captured by the data collectors using the web-based APP were exported to Microsoft Excel® in order to consolidate the data from all participating sites prior to analysis. The data were subsequently validated and cleaned before analysis by three of the authors (PS, NS and DK) in consultation with a statistician

(PG). This included exploring errors such as extremely high or low values, typographical errors and incomplete or missing data.

For the purpose of this paper, wards offering the same speciality were grouped together per discipline, namely surgical wards (male and female wards), medical wards (male and female wards) and all adult ICUs. The prevalence of antimicrobials prescribed was calculated as a percentage (%) using the number of patients receiving an antimicrobial (numerator) divided by the total number of inpatients surveyed (denominator). Data on antimicrobial use was examined descriptively and aggregated at the active substance level according, as mentioned, to the ATC classification [78]. In addition, we captured antimicrobial utilisation based on a DDD basis, which is a technical unit of measure for comparison of consumption on an international level, as well as per 100 bed days to provide greater data on utilisation patterns in line with recommendations (DDD/100 bed days) [59,83-86]. The DDDs per 100 bed days is applied when drug consumption among inpatients is being considered. It is calculated using the following formula:

For the DDD = DDD = dose (g) * number of doses per day / WHO DDD

$$\text{DDD/100 bed days} = \frac{\text{Utilisation in DDD}}{\text{Number of occupied bed days}} * 100$$

The mean DDDs with 95% confidence interval (CI) for each antimicrobial was calculated and compared to the WHO ATC index with DDDs using the single-sample t-test. The mean DDD was subsequently calculated by adding the doses of all the administrations of a given antimicrobial, divided by the number of administrations for that antimicrobial and by the WHO standard DDD for that antimicrobial. To compare how great or less the mean DDD administered was from the WHO DDD, we made the DDD = 1, i.e. the DDD was equal to the recorded DDD (100%), so the null hypothesis for the test (H0) is that the mean DDD=1. We recognise that the DDD does not refer to the recommended dose, and is primarily used to help compare utilisation rates across centres and countries. However, we believe it provides a starting point for potential future quality initiatives.

Whilst we looked to ascertain overall antimicrobial use across the various hospital types, our primary focus was on key quality indicators to improve future use. In addition, we prophesised that the patient characteristics would be different in terms of key considerations including the extent of intubation and catheterisation making direct comparisons between hospital types difficult.

The Chi-square (X^2) test or the Fisher's exact test was used to examine associations between categorical variables, such as ward types, as appropriate using a 5% significance level. The strength of associations was measured by Cramer's V and the phi coefficient respectively. For interpretation Cramer's V or phi coefficient ≥0.50 was considered a strong association, 0.30 - 0.49 moderate, 0.10 - 0.29 weak- and <0.10 little if any association. Data analysis was conducted using SAS (version 9.4 for Windows).

2.6 Ethical considerations

Data collection commenced after receiving ethical approval from the Sefako Makgatho University Research Ethics Committee (SMUREC/P/36/2018: PG) and permissions from the various study sites. Patient and hospital confidentiality was maintained at all times. Unique study identification numbers were used for hospitals and patients, and no personal identifiers for patients were recorded.

3. Results

3.1 Overview

A total of 4407 adult patient files were reviewed, of whom 1479 (33.6%) were on antimicrobials. A total of 2204 antimicrobials were prescribed, of which the medical wards overall, had the highest proportion (n=1409; 63.9%) of antimicrobials prescribed. Antimicrobial use was investigated based on the facility type. There was a significant, weak, association between facility type and whether patients were on antimicrobials at the time of the audit (p<;0.0001; Cramer's V=0.12): Compared to other facility types, the hospitals categorised as national central had a lower proportion of patients on antimicrobials. The demographics according to the hospital type is documented in Table 1.

Table 1. Overview of patient files surveyed according to hospital type

Parameter description	All hospitals (n=18)	National central (n=10)	Provincial tertiary (n=3)	Regional (n=2)	District (n=5)
Patient files reviewed; n	4407	2854	541	265	747
Medical wards; n (%)	2697 (61.2%)	1589 (55.68%)	413 (76.3%)	232 (87.5%)	463 (62.0%)
Surgical wards; n (%)	1402 (31.8%)	982 (34.4%)	113 (20.9%)	31 (11.7%)	276 (36.9%)
ICU wards; n (%)	308 (7.0%)	283 (9.9%)	15 (2.8%)	2 (0.8%)	8 (1.1%)
Patients on antimicrobials; n (%)	1479 (33.6%)	846 (29.6%)	202 (37.3%)	413 (76.3%)	322 (43.1%)
Antimicrobials prescribed; n	2204	1185	297	160	562

Overall, there was a significant, weak, association between hospital type and whether patients were on antimicrobials at the time of the audit (p<;0.0001; Cramer's V=0.12). Compared with other hospital types, national central hospitals had a lower proportion of patients on antimicrobials (Table 1). However, there was no significant difference (p=0.33) between the ward types considering the proportion of patients on antimicrobials in the medical wards (33.8%), surgical wards (32.5%) and ICU wards (36.7%).

The results showed that, there was no significant association between hospital type and overall catheterisation. However, urinary and central line catheterisation was more prevalent in national central and regional hospitals, and haemodialysis was carried out exclusively in national central hospitals (Table 2). This impacted on antimicrobial use with a significant, weak, association between antimicrobial use and catheterisation overall (p<0.0001; Cramer's V=0.22), with antimicrobial use higher in catheterised (47.2%) compared with non-catheterised (25.9%) patients. Significantly higher antimicrobial use was associated with central line (p<0.0001; Cramer's V=0.11) and peritoneal (p<0.0072; Cramer's V=0.04) catherization, while significantly lower antimicrobial use was associated with peripheral (p<0.0001; Cramer's V=0.20) and urinary (p<0.0001; Cramer's V=0.09). Although statistically significant, all these associations were weak.

Table 2. Extent and nature of catherization and intubation according to hospital type

		Total (n=4407)	Central (n=2854)	Provincial (n=541)	Regional (n=265)	District (n=747)	p
Catherisation	**No**	2821 (64.0%)	1807 (63.3%)	350 (64.7%)	184 (64.4%)	480 (64.3%)	
	Yes	1586 (36.0%)	1047 (36.7%)	191 (35.3%)	81 (30.6%)	267 (35.7%)	0.25
Catheter Type	**Peripheral**	1256 (28.5%)	841 (29.5%)	131 (24.2%)	69 (26.0%)	215 (28.8%)	0.072
	Urinary	597 (13.6%)	453 (15.9%)	71 (13.1%)	11 (4.2%)	62 (8.3%)	<0.0001
	Central Line	197 (4.5%)	141 (4.9%)	29 (5.4%)	7 (2.6%)	20 (2.7%)	0.017
	Peritoneal	30 (0.7%)	16 (0.6%)	7 (1.3%)	0 (0%)	7 (0.9%)	0.10
	Haemodialysis	17 (0.4%)	17 (0.6%)	0 (0%)	0 (0%)	0 (0%)	0.023
Intubation	**No**	4122 (93.5%)	2655 (93.0%)	505 (93.3%)	250 (94.3%)	712 (95.3%)	
	Yes	285 (6.5%)	199 (7.0%)	36 (5.7%)	0 (0%)	35 (4.7%)	0.14

3.2 Antimicrobial use by ATC and DDD

At ATC level 3, penicillins were the antimicrobial class mostly used (J01C: 34.8%; n=766), followed by the other beta lactams (J01D: 20.8%; n=458) and agents against amoebiasis and other protozoal diseases (P01A: 9.4%; n=206) (Table 3).

The most utilized antimicrobial was amoxicillin combined with an enzyme inhibitor (J01CR02: 23.1%; n=509) followed by ceftriaxone (J01DD04: 10.7%; n=236). In the ICU, the top four antimicrobials used were of the beta-lactam family, which accounted for 40.5% of the antimicrobials used. All the ward types prescribed amoxicillin and an enzyme inhibitor (J01CR02) as their first choice antimicrobial, followed by piperacillin and an enzyme inhibitor (J01CR05). Overall, piperacillin and an enzyme inhibitor (J01CR05) was administered to 10.1% of patients in ICUs. Ceftriaxone (J01DD04) was the most prescribed antimicrobial in medical wards (11.8%) and cefazolin (J01DB04) the most prescribed in surgical wards (11.1% of patients). Overall, there was a significant, weak, association between antimicrobial class and ward type (n=2175; p<0.0001; Cramer's V=0.17) with beta-lactam antibiotics & penicillins (J01C) more prevalent in surgical wards with other beta-lactam antibiotics more prevalent in surgical and ICU wards.

Table 3. Top 16 antimicrobials prescribed with their route of administration and frequency

ATC level 3 classes	Antimicrobial	ATC code	Route	Number of times AM prescribed	Percentage (based on total DDDs) %
JO1C: Beta-lactam antibacterials, penicillins	Cloxacillin	J01CF02	IV	32	1.6
	Amoxicillin and enzyme inhibitor	J01CR02	PO	90	4.1
	Amoxicillin and enzyme inhibitor	J01CR02	IV	420	19.1
	Amoxicillin	J01CA04	PO	33	1.5
	Piperacillin and enzyme inhibitor	J01CR05	IV	89	4.0
	Ampicillin	J01CA01	IV	69	3.1
JO1D: Other beta-lactam antibacterials	Ceftriaxone	J01DD04	IV	236	10.7
	Cefazolin	J01DB04	IV	112	5.1
	Meropenem	J01DH02	IV	32	1.5
JO1E: Sulfonamides and trimethoprim	Sulfamethoxazole and trimethoprim	J01EE01	PO	90	4.1
	Sulfamethoxazole and trimethoprim	J01EE01	IV	12	0.5
JO1F: Macrolides, lincosamides and streptogramins	Azithromycin	J01FA10	PO	75	3.4
	Azithromycin	J01FA10	IV	14	0.6
JO1G: Aminoglycoside antibacterials	Gentamicin	J01GB03	IV	35	1.6
JO1M: Quinolone antibacterials	Ciprofloxacin	J01MA02	PO	63	2.9
	Ciprofloxacin	J01MA02	IV	19	0.9
JO1X: Other antibacterials	Vancomycin (parenteral)	J01XA01	IV	40	1.8
	Metronidazole (oral/rectal)	J01XD01	IV	119	5.4
JO2A: Antimycotics for systemic use	Fluconazole	J02AC01	PO	50	2.3
	Fluconazole		IV	26	1.2
JO4A: Drugs for treatment of tuberculosis	Rifafour	J04AM06	PO	103	4.7

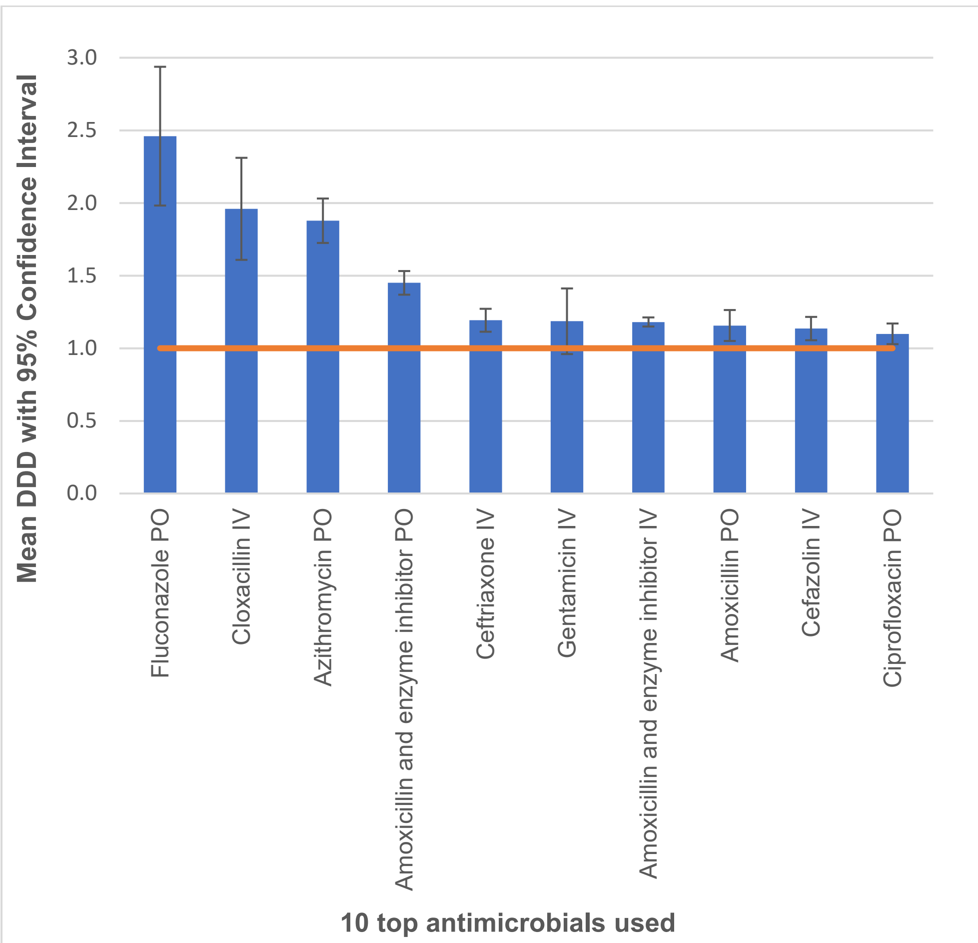
P01A: Agents against amoebiasis and other protozoal diseases	Metronidazole (oral/rectal)	P01AB01	PO	87	3.9

IV: intravenous; PO: oral

Figure 1 shows if the actual mean DDD was significantly greater (>1) or smaller (<1) than the calculated DDD=1.

In terms of DDD/100 bed days, the total consumption rate was 35 DDDs/100 bed days. The national central hospitals were the largest consumers for all the beta-lactam antibiotics accounting for a total of 27.4% of total DDDs (Total DDD= 13172.7). Amoxicillin and an enzyme inhibitor was the most commonly prescribed antibiotic class accounting for 21.4% of total DDDs. The consumption rate of the next three most consumed classes were other beta-lactam antibacterials (18.2% of total DDDs), antimicrobials for the treatment of TB (10.1% of total DDDs) and antimycotics for systemic use (9.4 % of total DDDs).

Figure 1. Mean DDD for the 10 most-used antimicrobials compared to the standard DDD=1 from ATC index 2019



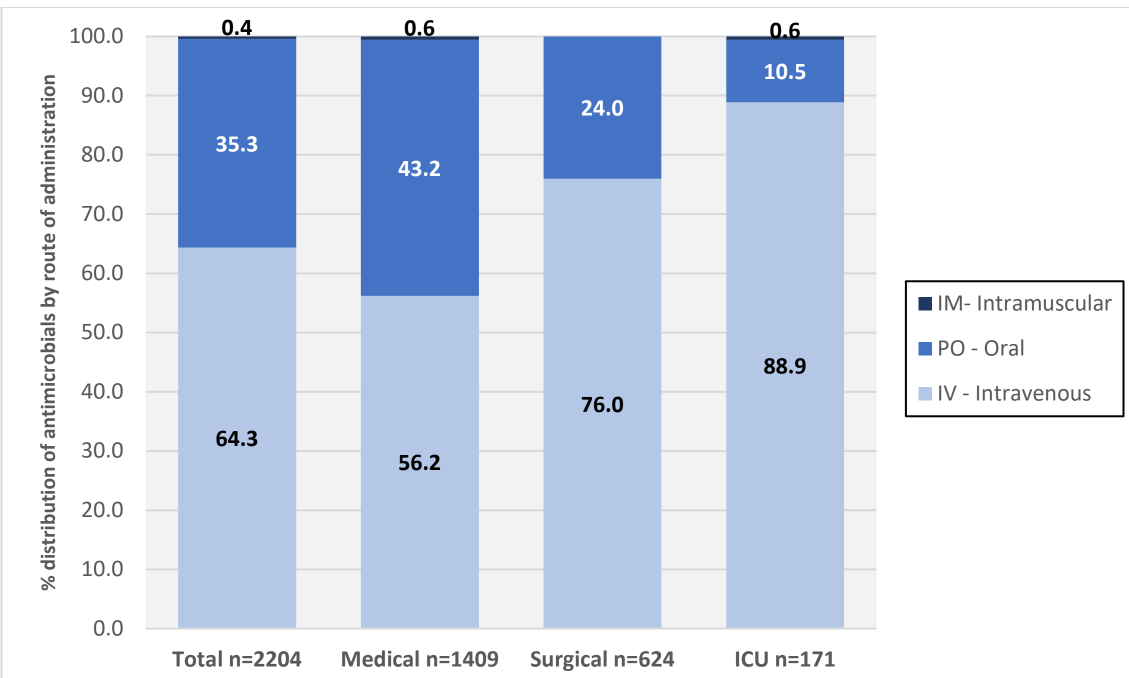
Nearly all the other groups of antimicrobials followed with statistically significant deviations in the calculated DDD = 1. Fluconazole was 2.3 times higher in DDDs followed by cloxacillin (Figure 1).

Using the WHO ATC/ DDD as a reference, doses prescribed for most of the beta-lactam antibiotics were approximately equal to the WHO DDD (Figure 1), although, as mentioned, we acknowledge that DDDs should not be taken as the recommended dose or taken to measure appropriate or irrational prescribing

[78]. Fluconazole doses were significantly higher ($p<0.00001$) due to the latest WHO cryptococcal meningitis guidelines [87].

3.3 Route of administration
The proportion of parenteral antimicrobial use differed considerably between the types of hospital wards (Figure 2). There was a significant association between the route of administration and the ward type (n=2195, 2204 when the intramuscular route is included; $p<0.0001$; Cramer's V=0.23). More than half (64.3%; n=1418) of all antimicrobials were administered intravenously, with the IV route most prevalent in ICU and on the surgical wards. For surgical prophylaxis, parenteral administration was used in 87% of the cases. The most common antibiotic administered IV was amoxicillin and an enzyme inhibitor, used parenterally in 76.8% (n=509) of cases where administered.

Figure 2. Overall distribution of antimicrobials by route of administration within the hospital (all wards) and within the different types of wards



3.4 Antimicrobial use by indication
The top three indications accounted for >34% of total antimicrobial utilisation. Skin and soft tissue infections were the most common site (12.97%), followed by pneumonia (10.84%) and pulmonary TB (10.51%). Amoxicillin and an enzyme inhibitor was the most prevalent prescribed antimicrobial in most of the indications. It was the most common antimicrobial for medical prophylaxis (22.4% of case), skin and soft tissue infections (39.6% of cases), pneumonia (30.9% of cases) and clinical sepsis (16.8% of cases).

3.5 Antimicrobial use for surgical prophylaxis
For surgical prophylaxis, cefazolin (J01DB04) was the most commonly used antimicrobial (45.5% of cases) followed by amoxicillin combined with an enzyme inhibitor (22.3% of cases), ceftriaxone (9.8% of cases), metronidazole (oral/rectal) (5.4% of cases) and ampicillin (4.5% of cases).

The duration for antimicrobial prophylaxis was evaluated based on whether it was prescribed for one dose, one day or more than one day. In the majority (73.2%; n=108) of cases, prophylaxis was prescribed for more than one day. Cefazolin was the most prescribed antimicrobial for the duration of less than one day (66.7%), whereas metronidazole, ciprofloxacin, amoxicillin and piperacillin combined with enzyme inhibitors were always (100%) used for more than one day for surgical prophylaxis (Figure 3). Table 1 in the Appendix gives further details.

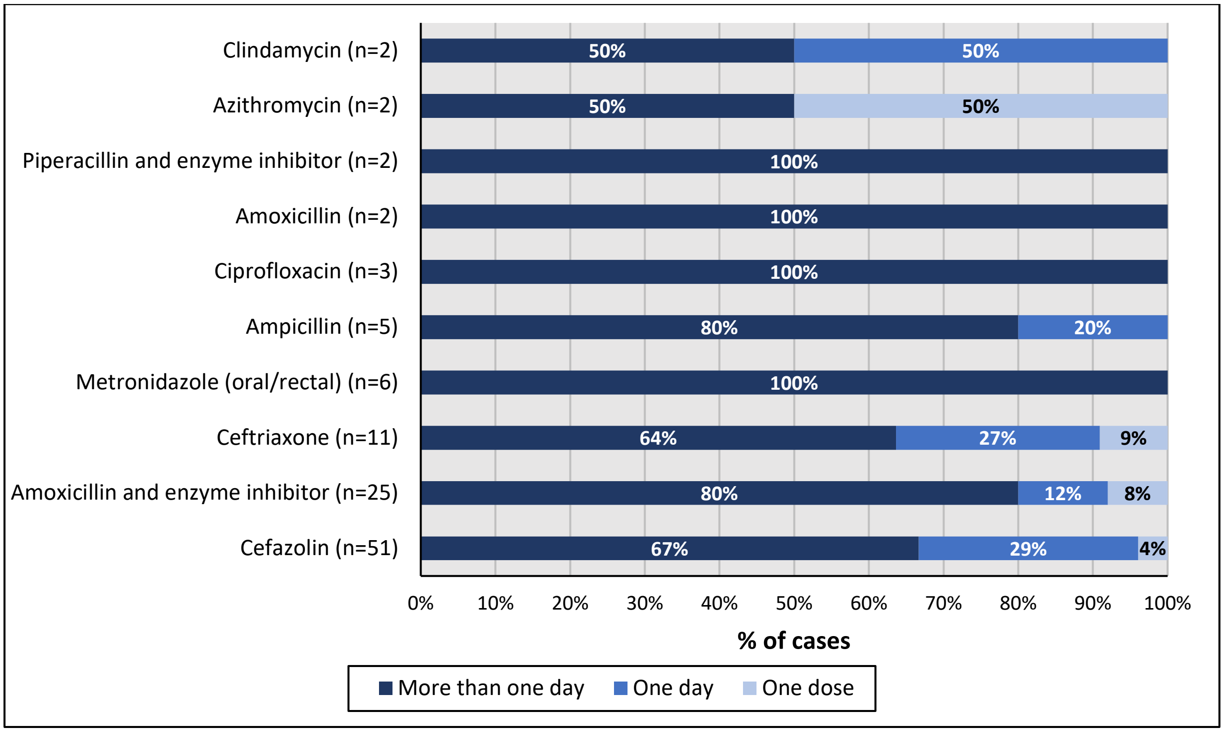


Figure 3. Duration of treatment for the top 10 antimicrobials utilised for surgical prophylaxis
NB: n=number of cases

3.6 Additional quality indicators – antimicrobial use based on availability in EML and AWaRe classification

The overall compliance with the current South African STGs/EML was 90.2% for all the antimicrobials prescribed. The difference between ward types showed that the prescribing of antimicrobials outside of the STGs/EML was more prevalent among the surgical wards (11.5%; n=72/624) of antimicrobials prescribed) followed by the medical wards (9.9%; n=139/1409 antimicrobials prescribed). The ICU had the highest compliance rate at 94.2% (n=161/171) of occasions (Table 4 shows these indicators and their compliance by ward type).

There were only 5.1% (n=111) missed doses which was slightly higher in the surgical wards with the medical wards being the highest contributors to this percentage (55.9%). Overall, there was a significant, weak, association between missed doses and ward type (n=2190; p=0.0073; Cramer's V=0.07) with missed doses more prevalent in surgical wards by 7.3% (45/624). Culture and sensitivity results were only available in 159 files (8.8%) with ICUs contributing 24.5% to this percentage recorded in the patient files. However, there was a significant, weak, association between CST result available and ward type (n=1801; p<0.0001; Cramer's V=0.18).

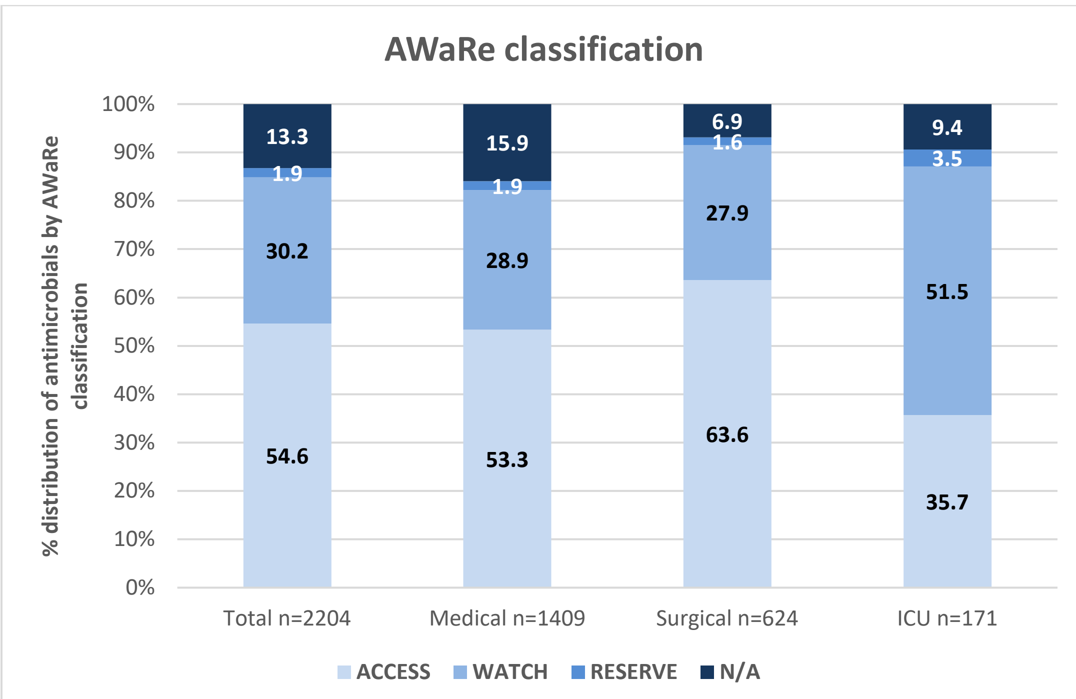
Table 4. Quality indicators for antimicrobial prescribing by ward type

Quality indicators	Total n= 2204 (%)	Medical (%)	Surgical (%)	ICU (%)
Compliance to STGs/EML guidelines	1975 (90.2)	1266 (89.9)	548 (87.8)	161 (94.2)
Number of missed doses (1 or more)	111 (5.0)	62 (4.4)	45 (7.2)	4 (2.3)
CST results available in file (n=1804)	159 (8.8)	70 (6.1)	53 (10.5)	36 (24.5)

NB: Figures in brackets are percentages in relation to the wards

The Access antibiotics were used on 54.6% of occasions. They were the leading class in the medical (53.3%) and surgical (63.6%) wards. There was a significant difference (p<0.0001) in the ICU where the Watch drugs were the most prevalent at 51.5% of all antimicrobials prescribed. The reserve antimicrobials were used mostly in the ICU as expected since most critical cases are seen there (Figure 4).

Figure 4: AWaRe classification by ward type



4 Discussion

We believe this is the most comprehensive study to date assessing national antimicrobial prescribing among a range of hospitals in the public sector in South Africa, building on earlier published studies [67-69,88]. Overall, 33.5% of patients were on antimicrobials, which is similar to previous studies conducted in South Africa [67,69]. There was a higher rate of antimicrobial utilisation among district and regional hospitals (Table 1), with the nature of catherization influencing this (Table 2). However. antimicrobial consumption rates were appreciably lower among these public hospitals in South Africa compared with those in Botswana (70.6% of patients), Ghana (51.4% to 82% of patients), Kenya (54.7% - 67.7% of patients), and Nigeria (55.9% - 69.7% of patients) as well as 50.0% of patients among the African hospitals taking part in the Global-PPS. In addition, an average of 62.7% of patients among eighteen African hospitals included in a recent systematic review of PPS studies; however, this did include hospitals from Botswana, Kenya, Nigeria and South Africa [30,32,40,57,70,72-75]. We are not sure of the reasons why antimicrobial use was lower in South Africa given the high rates of infectious diseases in South Africa including HIV, and will be investigating this further in future studies [13,14]. However this could be explained, at least partially, by South Africa's Antimicrobial Resistance National Strategy Framework to which an average compliance of 59.5% was recorded among 26 public sector facilities with the national central hospitals having the highest compliance (73.5%) followed by referral hospitals at 66.9% [89]. This framework was launched towards the end of 2014, and implementation guidelines and subsequent guidelines for the prevention and containment of AMR in South African hospitals followed in 2017 and 2018 [23]. Current antimicrobial utilisation rates may also reflect more prudent antimicrobial prescribing among hospital physicians in South Africa versus others across Africa. Alternatively, less concerns regarding the cleanliness of wards and operating theatres among healthcare facilities in South Africa, which has been an explanation for extended prophylaxis for surgical site infections across countries including Africa [61]. However, it is difficult to say anything with certainty without further studies.

Amoxicillin coupled with an enzyme inhibitor was the most frequently prescribed antibiotic class in this PPS study (23.1%), similar to some of the hospitals in Ghana but different to the 12 African hospitals taking part in the Global PPS where carbapenems were the most prescribed antimicrobial, as well as different to hospitals in Botswana, Kenya, and Nigeria [30,40,57,72-75]. This could be due to the fact that amoxicillin coupled with an enzyme inhibitor as a broad spectrum antibiotic is in the Access group [52,56]; however, it is difficult to confirm this without further studies. Ceftriaxone was the next most commonly prescribed antimicrobial in this study (10.7%) with metronidazole the third most prescribed antimicrobial. This is similar to some hospitals in Nigeria where ceftriaxone was the most prescribed antibiotic followed by metronidazole [74]. This also compares with one hospital in Kenya where ceftriaxone was the most prescribed antibiotic followed by benzyl penicillin and then metronidazole [73], with high use of third generation cephalosporins in another [72]. In addition, in one hospital in Ghana where there was high use of amoxicillin coupled with an enzyme inhibitor along with ceftriaxone and metronidazole [70], with high use of ceftriaxone versus other cephalosporins seen in another hospital in Ghana [57]. There was also high use of metronidazole among public hospitals in Botswana with high use of ceftriaxone among the private hospitals [40].

As mentioned, the doses of fluconazole administered were significantly higher than the DDD ($p<0.00001$), which we believe could be accounted to the new guideline changes by WHO that state that for cryptococcal meningitis the initiation dose should be 1.2 grams given with amphotericin B [90]. We will be exploring this further given concerns.

The most common indication for antimicrobial use in our study was skin and soft tissue infections followed by pneumonia. This is similar to the African countries taking part in the Global PPS [30] and Ghana [57]. However, different to the PPS study in Botswana where obstetrics and gynaecology was the most common indication followed by pneumonia and skin and soft tissue infections [40], and in Kenya where medical prophylaxis was the most common indication [72]. There was also a high proportion of prescribing of antimicrobials for medical prophylaxis (73%, n=292) in our study, which warrants further research to identify the reasons for this pattern.

More than half of the antimicrobials were given via the parenteral route (64.8%). This is similar to the African hospitals taking part in the Global PPS (62.7%) [30], Botswana where 53.0% of patients had a peripheral IV cannula [40] and Kenya where 63.1% of patients were administered antimicrobials IV [72]. However, lower than Ghana where antibiotics were commonly administered IV [57] and Nigeria where IV administration ranged from 57.4% to 92.5% depending on the ward [74]. Further research is needed to evaluate the appropriateness of the IV route as part of any Antimicrobial Stewardship Programme (ASP), and we will be following this up.

Encouragingly, overall compliance to the South African STGs/EML was 90.2%, with ICU having 97.6% compliance. This is higher than the African countries taking part in the Global PPS (67.9%) [30] and appreciably higher than hospitals in Kenya (45.8%) [73] and Nigeria (0.3% - 7.1% depending on the ward) [74]. It is also an improvement on previous studies undertaken among primary healthcare centres in South Africa where there was low compliance to treatment guidelines [54]. As mentioned, adherence to agreed guidelines is seen as important to improve the general quality of prescribing and to encourage comparisons between different countries and studies [30,55,63,91]. However, antimicrobials from the Access group accounted for only 54.6% of all antimicrobials prescribed in our study with antimicrobials in the Watch list typically prescribed in the ICU. This may reflect greater resistance to Access antibiotics among patients in ICU, alternatively empiric use covering likely causative organisms before the results of sensitivity tests are available [92-94]. In any event, this shows that there is room for improvement moving forward [92], and we will be monitoring this in the future.

Cefazolin was the drug of choice for surgical prophylaxis as stated in the South African STGs [82]. This is encouraging as there have been concerns with compliance to STGs for the prevention of SSIs among hospitals in South Africa in the past [60]. However, a major concern was the prolonged duration of more than 1 day (73.2%), which high rates also seen among other African countries including those taking part in the Global PPS [30,38,40,57,61,73,74]. In most instances, a single antibiotic dose prior to the procedure is sufficient for prophylaxis [95-98]. Postoperative antimicrobial administration is not recommended for most surgeries when there are no preoperative infection or severe complications as this increases AMR rates [95,96,99]. This will be a focus on quality improvement programmes going forward building on concerns across countries, as seen in recent reviews and a meta-analysis regarding the extent of prophylaxis for SSIs among LMICs and potential ways to address this [61,100].

Finally, we believe we have shown it is feasible to carry out PPS studies using mHealth techniques. This approach can quickly facilitate the identification of targets for quality improvement programmes, as well as monitor progress with quality improvement programmes, given concerns with available personnel and costs among LMICs to conduct PPS studies alongside rising AMR rates. We will continue to monitor the situation.

Limitations

We acknowledge there are a number of limitations with our study. Firstly, since PPS studies do take a lot of resources and time, not all patients could be surveyed for hospitals with more than 700 beds. However, the sampling method used is recommended by the WHO, and provides a representative sample size per hospital. Secondly, these results do not evaluate the appropriateness of antimicrobial treatment but focus more on utilisation. This can be used as a starting point in pursuing further studies investigating prescribing patterns according to national guidelines and therefore appropriateness. Thirdly, we concentrated mor on hospital types rather than combining facilities to compare overall utilisation rates due to the inherent nature of the sampling and the objectives of the study. However, the results of the study have shown to be in line with other similar studies conducted; consequently, we believe our findings are representative of the antimicrobial utilisation patterns among public hospitals in South Africa providing future direction.

5. Conclusion

The web-based PPS tool was easy to use and successful in capturing PPS data representative of antimicrobial utilisation among public healthcare facilities across South Africa. This study contributes to continued national awareness regarding antimicrobial use in the public sector in South Africa, illustrating that only a third of all patients surveyed received antimicrobials, with just over a half of these from the Access category. This is important to establish quality targets to improve future antibiotic prescribing within public hospitals in South Africa and wider, building on current ASPs within hospitals across South Africa. A number of targets were identified for future research and quality improvement programmes. These include the high use of Watch antibiotics and extended prophylaxis, and we will be following this up in the future.

Conflict of interest
We declare that the authors have no conflicts of interest.

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Author contributions

NS, BBG, JCM and MB designed the concept of the study. PS, NS and BBG orchestrated the literature review. NS, PS and DK undertook the training sessions and co-ordinated the data collectors with the help of JCM. PS, DK and NS undertook the analysis of the findings and all authors contributed to the write-up of the study. All authors approved the initial and revised paper.

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