Feasibility of using point prevalence surveys to assess antimicrobial utilisation in public hospitals in South Africa; a pilot study and implications

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ABSTRACT

Objectives: There is currently a lack of data regarding antimicrobial use among public hospitals in South Africa (SA). This is a concern given their growing use and increasing antimicrobial resistance rates in SA. Consequently, the objectives of this study were to firstly determine the appropriateness of point prevalence survey (PPS) data collection instruments for performing antimicrobial utilisation studies among public sector hospitals in SA; secondly, to determine current antimicrobial utilisation in a public sector hospital, and thirdly evaluate the prescribing of antimicrobials with those contained within the national Essential Medicines List and Standard Treatment Guidelines (EML/ STGs). The findings will be used to guide future activities in SA. **Methods**: A PPS was conducted in Dr George Mukhari Academic Hospital. For each in-patient ward, all patients' files were completely surveyed on a single day. The number of patients who were on antimicrobials served as the numerator and the denominator comprised the total number of patients in the ward. **Results**: 39 wards and 512 patient files were surveyed. The overall prevalence of antimicrobial use was 38.5%, highest in the ICUs. Beta lactamase inhibitors and antimicrobials for tuberculosis were the most prevalent antimicrobials. More than two thirds (83%) of antimicrobial treatment was modified following culture sensitivity test results when requested, and 98% of antimicrobials prescribed were contained within the current EML/ STGs. In 10.8% of occasions, antimicrobials appear to have been prescribed other than for treatment, i.e. no systemic infection. There were concerns though with the lack of IV to oral switching. **Conclusion**: The PPS method offers a standardized tool that can be used to identify targets for quality improvement. However, there were concerns with the time taken to conduct PPS studies, which is an issue in resource limited situations. This is being addressed alongside concerns with the lack of IV to oral switching.

1. INTRODUCTION

Antimicrobials play a vital role in reducing morbidity and mortality through the management of infection [1-3]. They reduce mortality by 10% to 75% depending on the disease area, with estimates suggesting life expectancy is increased by 20 years with their use [4]. However, their excessive utilisation has appreciably increased antimicrobial resistance rates (AMR), which is now a global concern [5-8]. With the diminishing effectiveness of antimicrobials, the world is facing a major predicament of how infections will be treated in the future. This is leading to calls to develop global and national action plans to reduce morbidity, mortality and costs associated with AMR, including increased governance [3-4, 8-12].

The World Health Organization (WHO) and others have for many years promoted the monitoring of antimicrobial use across sectors and raised awareness of the consequences of AMR, which includes the WHO Africa region [8,13-21]. These activities include the instigation of point prevalence surveys

(PPS) in hospitals to provide data on current utilisation and resistance patterns using a standardised methodology to plan future interventions [20-29]. This is particularly important in sub-Sahara Africa, including South Africa, with high rates of infectious diseases including HIV, malaria and tuberculosis (TB) [26,30-35]. In addition, in South Africa there are growing resistance to penicillins as well as non-β-lactam antibiotics, including the macrolides, tetracycline, chloramphenicol, the fluoroquinolones and co-trimoxazole [36]. It has been estimated that over 50% of isolates in hospitals in South Africa are methicillin resistant *Staphylococcus aureus* (MRSA), with up to 75% of *Klebsiella pneumoniae* isolates having extended spectrum beta-lactamase (ESBL) activity, and with *K. pneumoniae* showing a higher rate of resistance than *E. coli* bacteraemia. There have also been outbreaks of vancomycin-resistant Enterococci (VRE), as well as *K. pneumoniae* resistance against carbapenems [3,17,37,38]. These concerns have resulted in the development of plans in South Africa to improve antibiotic utilisation and reduce resistance rates across all sectors in the coming years. This includes regular updates on treatment guidance via mobile technologies as there have been concerns with inappropriate antimicrobial use against current guidelines, and the recognized need for improved surveillance tools [3,4,34,39-43].

In addition, a PPS conducted between April and August 2015 in a large tertiary hospital in Cape Town, South Africa, indicated that 31% (359/1156) of patients were receiving antibiotics and the majority (83%) of antibiotic prescriptions were empirical [44]. The implication of these results is that antibiotics were administered in public hospitals without the availability of cultures. In addition, only a few doctors (11%) documented the stop/review date on the prescription.
Data on antibiotic utilisation were also collected in a number of hospitals in the Gauteng Province during World Antibiotic Awareness Week in 2015. However, these data were not sufficiently robust to make reliable and valid interpretations and recommendations, highlighting the need for assessing antimicrobial utilisation using valid and reliable surveillance tools such as a PPS study design to provide a reliable baseline for future surveys and interventions, ultimately aiming at increasing rational antimicrobial use. This is particularly important as a recent study in SA using antimicrobial procurement as data source (one of the approaches in obtaining antimicrobial utilization data), showed a substantial increase in their utilisation in the public sector in recent years, which needs to be addressed to reduce AMR rates [11].

Overall, there is a paucity of reliable data on the use of antimicrobials among public hospitals in South Africa. This is a concern as the vast majority of patients in South Africa are currently treated in the public sector in South Africa [34]. This prompted undertaking this study to determine antimicrobial consumption at Dr George Mukhari Academic Hospital (DGMAH) using a PPS method, building on the earlier study in Cape Town [44]. Information was obtained with PPS data collection instruments that were initially developed in Botswana with input from the WHO, building on the European Centre for Disease Prevention and Control (ECDC) and Global studies [21, 22,]. The forms were subsequently refined following a pilot study in Botswana before being used throughout Botswana and subsequently in South Africa [26,45-47]. The findings will assist with the instigation of pertinent programs in this hospital to improve future antimicrobial use. We also believe the study results will help with assessing the feasibility of using a PPS design within public hospitals in South Africa to identify additional targets for quality improvement programs regarding antimicrobial utilisation. This is particularly important given, as mentioned, the high rate of infectious diseases in South Africa as well as growing antimicrobial use in the public sector.

2. METHODS

2.1 Study design, setting and study period

The study design was a PPS. Within a PPS design, all beds in a single ward are completely surveyed on one day to be able to correctly calculate the denominator and the numerator [. The study forms were based on those subsequently used for the PPS in Botswana following the pilot. As mentioned, they were adapted for the African setting based on input from the WHO and personnel involved in both the ECDC and Global PPS studies [2-22,26]. This included greater recognition of the higher prevalence of HIV, TB and malaria in sub-Sahara Africa than currently seen in Western countries, which is important for comparison purposes [20,26,30-34].

Data was collected over a period of two months, from February to March 2017 at DGMAH. DGMAH was chosen as it is a public sector hospital and one of four teaching hospitals in the Province and situated in Ga-Rankuwa, Pretoria, Gauteng Province. DGMAH is a 1,650-bed hospital with 28 clinical departments, 20 approved ICU beds, 60 high care beds and 17 surgical theatres, providing services

to an estimated 1.7 million people from the surrounding area. Consequently, providing an appropriate site for this initial study.

Data was collected on weekdays only in order not to bias the results. The principal researcher (NND) collected the data together with a team of trained data collectors who were pharmacist interns. Data collectors reviewed medical records on the survey date to determine whether patients may have been receiving an antimicrobial on the day of survey. If so, the information was collected on antimicrobial use. There was no contact with any of the ward staff including physicians or nurses, or patients, during the PPS to ascertain further details as necessary as one of the outputs of the survey was to ascertain the extent of information contained within patients' records.

For each antimicrobial, data collectors recorded the rationale for its use, i.e., the treatment of the infection, whether surgical or medical prophylaxis, or a non-infection-related reason. Empirical use of antimicrobial drugs for suspected infections was considered treatment. For antimicrobial drugs given to treat infections, data collectors identified the anatomical site of the infection from the patient's records only if this was recorded. The data collectors also documented any antimicrobial use in the previous 90 days based on data contained within the patients' records. Antimicrobials included antibiotics, anti-tuberculosis medicines and antifungals in line with previous PPS studies and in view of the high rate of TB and use of antifungals, potentially playing a role in resistance development [20,27,28,34,35].

2.2 Study population and sample

As this was a PPS, no sampling was undertaken. Data was collected only once, from all the in-patient wards in the hospital except for day admissions such as renal dialysis patients as well as emergency and accidents wards. Each ward within the hospital was surveyed only once. The wards in the hospital were not all necessarily surveyed on the same day, but all beds in a given ward were completely surveyed in one day. This ensured that the denominator (number of admitted patients) was calculated correctly.

2.3 Data entry and analysis

The data was taken from patients' bed charts, which are paper-based and organized in a file, containing all the patients' records. The data was subsequently captured onto Microsoft Excel™ spread sheets and analysed using SPSS Version 8.0 for Windows. The entered data was subsequently checked for accuracy and cleaned prior to analysis. This was a descriptive, explanatory analysis of information including epidemiologic parameters, as well as the prevalence and degree of consumption of antimicrobials. This includes the number of prescriptions and drug prescription profiles considering different ages and genders. Descriptive statistics were performed on the retrieved data. Categorical variables were calculated as percentages and measures of central tendency for continuous variables, which included the mean with standard deviation (SD), the median with inter quartile range (IQR) and 95% confidence intervals (CI).

Antimicrobials prescribed were analysed according to the WHO's Anatomical Therapeutic Chemical (ATC) classification of medicines (ATC level 5) [48] , the dose, frequency and route of administration.

2.4 Quality of prescribing

The appropriateness of the prescribed antimicrobials was evaluated based on whether they were included in the national EML/STGs [49]. We did not ascertain whether the doses of antimicrobials prescribed, or their indication, were in line with the national EML/ STG as undertaken in other PPS studies [25,50,51] as the main emphasis of this study was ascertaining whether the PPS study design was suitable and sustainable for collecting antimicrobial data among public hospitals in a resource limited setting such as South Africa.

However, further analysis included whether antimicrobial sensitivity analyses were requested and subsequently acted upon, and whether treatment was empiric or not. The later given concerns with the high rate of empiric prescribing in a tertiary South African hospital in 2015 [44]. In addition, comparing our findings with the recently published findings of the Global PPS study as well as the 5 African countries taking part in the Global PPS [21]. Along side this, the extent of IV to oral switching as the earlier study in South Africa had stated only 11% of physicians had documented the stop/review date on the prescription [44], which should have included an assessment for changing IV to oral antibiotics.

2.5 Ethical considerations
Data collection commenced after receiving ethical approval from the Sefako Makgatho University Research Ethics Committee (SMUREC/H/210/2016:PG). Permission was thereafter obtained from the Chief Executive Officers of DGMAH. Patient confidentiality was maintained at all times and unique identification numbers were used for all patients in order to keep them anonymous.

3. RESULTS

A total of 512 patient files were surveyed. This included 400 adults of which 175 (43.8%) were males and 225 (56.3%) females. The mean age (SD) for males was 42.25 (17.29) years and the median age (IQR) was 43 (28.5) years. For females, the mean age (SD) was 46.10 (18.8) years and the median age 43 (28) years (Table 1). Most (85%) of the admitted adults were younger than 65 years, with the occupation of nearly two thirds (61%) of patients unknown (Table 1). In the paediatric wards, there were more infants and children than neonates, with a mean (SD) age of 3 years (± 3.65) and a median (IQR) age of 1 (4.17).

Table 1: Demographics of adult patients

Parameter	Male	Female	Total
Number of adults; n (%)	175 (43.8)	225 (56.3)	400 (100)
Age (years) < 65; n (%) ≥ 65; n (%) Mean (± SD) Median (IQR)	 153 (38) 22 (6) 42.25 (17.3) 43 (28.5)	 185 (46) 40 (10) 46.10 (18.8) 44 (28.0)	 338 (84.5) 62 (15.5) 45.1(17.9) 43 (28.3)
Occupation; n (%) Employed Unemployed unknown	 13 (3.3) 45 (11.3) 117 (29.3)	 9 (2.3) 89 (22.3) 127 (31.8)	 22 (5.5) 134 (33.5) 244 (61.0)
Transferred in; n (%) Yes No Unknown	 45 (11.3) 118 (29.5) 12 (3.0)	 25 (6.3) 190 (47.5) 10 (2.5)	 70 (17.5) 308 (77) 22 (5.5)

3.1 Antimicrobial use prevalence
Of the total number of 512 patients surveyed, 193 patients received at least one antimicrobial. The total prevalence of antimicrobial use was 38.5%. The prevalence of antimicrobial use was the highest in the various ICUs (Table 2).

Table 2: Antimicrobial use prevalence in the wards

Ward speciality	Total number of patients	Patients receiving antimicrobials (n)	Prevalence % [95% CI]
Neonatal ICU	24	17	70.8 [52.6 - 89.0]
Paediatric ICU	9	6	66.7 [35.9 - 97.5]
Adult ICU	28	15	53.6 [35.1 - 72.1]
Adult medical ward	128	60	46.9 [38.3 - 55.5]
Haematology - Oncology Paediatric Medical Ward	12	5	41.7 [13.8 - 69.6]
Adult surgical ward	194	56	28.9 [17.0 - 40.8]
Paediatric Medical Ward	58	19	32.8 [20.7 - 44.9]
Obstetric and Gynaecology	50	15	3.3 [-1.7 - 8.3]
Paediatric Surgical Ward	9	0	0.0, 0.0
Total	**512**	**193**	

3.2 Antimicrobial drugs administered to treat infections

Of all the antimicrobials used to treat infections in the 193 patients, 46 (15% [95% CI: 10.92-18.88]) antimicrobials were used to treat clinical sepsis in 28 patients, 37 (12.0 [95% CI: 8.37 -15.63]) for pulmonary tuberculosis (TB) in 19 patients, 32 (10.4% [95% CI: 6.99 -13.81]) for pneumonia, and 21 (6.8% [95% CI: 3.99 - 9.61]) for bone and joint infection as well as obstetrics and gynaecological infections in 17 and 14 patients respectively (Table 3). Antimicrobials were also used for prophylaxis, with 17 antimicrobials (5.6%) having no defined infection site for their use documented in the patient records with no evidence of infection and in 5.2% of occasions antibiotics were prescribed other than for treatment (Table 3).

Table 3: Infection sites for which patients received antimicrobials

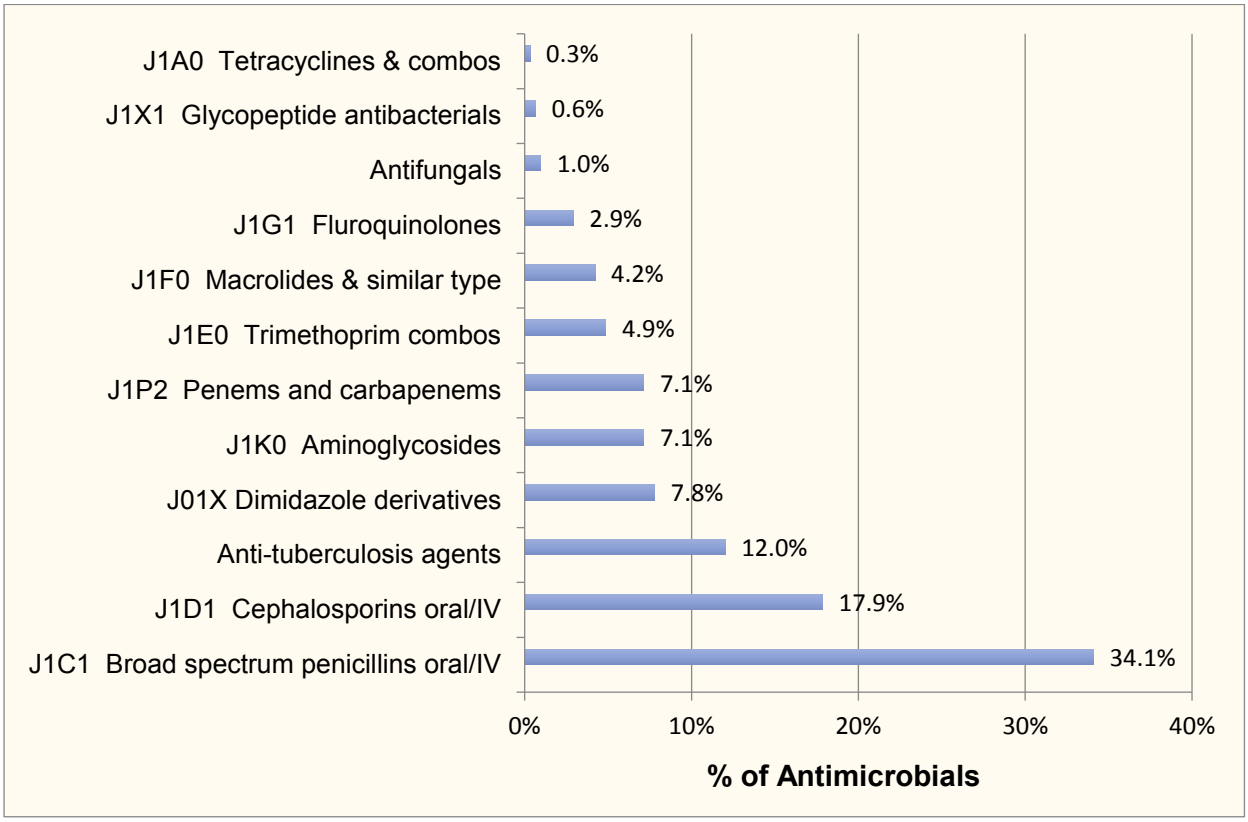
Infection site[a]	**Number of antimicrobials (%) [95% CI] (n = 308)**	**Number of patients (%) [95% CI] (n = 193)**
Clinical sepsis (bloodstream)	46 (14.9%) [10.92-18.88]	28 (14.5%) [9.53 -19.47]
Pulmonary tuberculosis	37 (12.0%) [8.37 -15.63]	19 (9.8%) [5.61 -13.99]
Pneumonia	32 (10.4%) [6.99 -13.81]	24 (12.4%) [7.75 -17.05]
Bone and joint infections	21 (6.8%) [3.99 -9.61]	17 (8.8%) [4.80 -12.79]
Obstetrics and gynaecology	21 (6.8%) [3.99- 9.61]	14 (2.1%) [15.25 -26.75]
Soft tissue infections	19 (6.2%) [3.51 -8.89]	14 (2.1%) [0.08 - 4.12]
Central nervous system	17 (5.5%) [2.95 -8.05]	15 (7.8%) [4.02 -11.58]
No defined site for infection with no systemic inflammation	17 (5.6 %) [3.03 -8.17]	15 (7.8) [4.02 - 11.58
Gastrointestinal	17 (5.5%) [2.95 -8.05]	13 (6.7%) [3.17-10.23]
Ear, nose, and throat	12 (3.9%) [1.74 - 6.06]	10 (5.2) [2.07- 8.33]
Urinary tract	11 (3.6%) [1.52 -5.68]	10 (5.2%) [2.07 -8.33]
Cardiovascular	11 (3.6%) [1.52 -5.68]	9 (4.7%) [1.71 -7.69]
Febrile neutropenia	7(2.3%) [0.63 -3.97]	6 (3.1 %) [0.65 -5.55]
Intraabdominal	7 (2.3%) [0.63-3.97]	4 (2.1%) [0.07-4.13]
Extra pulmonary TB	4 (1.3%) [0.034 -2.57]	3 (1.6%) [-0.17 - 3.37]
Eye infections	3 (0.9%) [-0.15- 1.95]	3 (1.6%) [-0.17-3.37]
Bronchitis	3 (0.97%) [-0.12 -2.06]	3 (1.6%) [-0.17 -3.37]
Asymptomatic bacteuria	2 (0.7%) [-0.25 - 1.55]	2 (1.0%) [-0.40- 2.40]
Genitourinary for males	2 (0.6%) [0.26 – 1.46]	2 (1.0%) [-0.40 -2.40]
Laboratory confirmed bacteremia	1 (0.32 %) [-0.31 -0.95]	1 (0.5%) [-0.50 -1.50]
Antimicrobial use other than treatment	16 (5.2%) [2.72 -7.68]	16 (8.3%) [4.41 -12.19]

[a] Antimicrobials could be used for more than one anatomical site of infection.

3.3 Antimicrobial use by ATC

Broad spectrum penicillins were the most commonly prescribed antimicrobials (34.1%), followed by the cephalosporins (17.9%) and anti-tuberculosis agents (12.0%). The least used antimicrobials were the tetracyclines (0.3%) (Figure1).

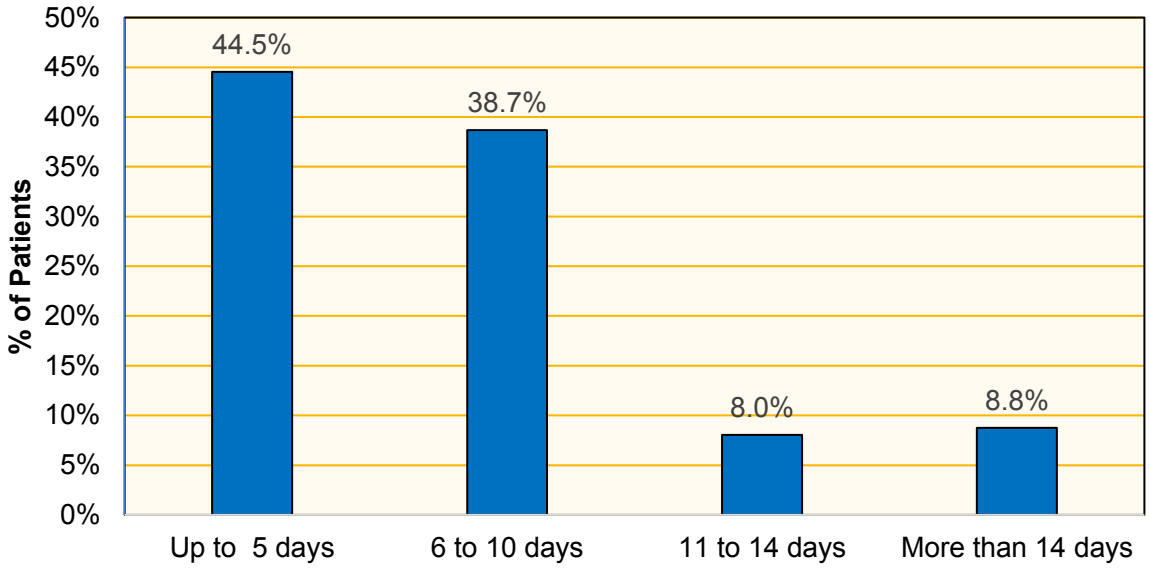
Figure 1: Antimicrobial use by ATC



3.4 Antimicrobial use in the past 90 days prior to admission

Less than half (44.5%) of the patients (137) who were on antimicrobials in the last 90 days prior to admission had been prescribed antimicrobials for up to five days, while 8.8% were taking antimicrobials for more than 14 days (Figure 2). The remaining patients had taken antimicrobials for between 6 and 14 days.

Figure 2: Antimicrobial use in the past 90 days (n=137)



3.5 Culture and sensitivity testing (CST) (n=193), compliance to national guidelines (EML/STGs), and IV to oral switching

In 37% of patients' files, culture and sensitivity tests (CST) results were recorded. Where these were recorded, the majority (83%) of antimicrobial treatment was modified following CST results when CST was requested and in 12 situation (8.8%) antimicrobial treatment was not modified as per CST results.

Most of the antimicrobial agents prescribed (98%) were from the national EML/STG. Nearly half (46%) of the patients were on IV medication. However, no patient when assessed had been switched from IV to oral even though some patients appeared to be suitable candidates based on their notes, e.g. they had a stable GI tract and other antibiotics had a good oral bioavailability, which could have been a better choice over IV medication. However, this was not investigated further as this was not the principal aim of this PPS study.

4. Discussion

The findings show that it is feasible to collect data on current antimicrobial use within public hospitals in South Africa using a PPS design, building on the previous study in South Africa, the Global PPS as well as studies conducted in Botswana, Kenya and Zimbabwe [20, 21, 25,26,52,53]. A concern though was the length of time taken to complete the forms. This included the need to search for information in the files, which was not always there. This is a particular issue in resource limited situations in terms of both the costs to undertake the survey if multiple researchers are needed as well as available time for pharmacists and others to undertake the surveys in addition to their normal workloads. We have subsequently developed an APP to address these concerns, with a pilot study suggesting that using the APP considerably shortens survey time [54]. We are currently testing this APP across 44 centers in South Africa, and will be reporting the findings in due course.

Antimicrobial utilization was seen among 38.5% of the patients surveyed (Table 2). This is similar to the previous PPS study in South Africa (31%) [44] and the consolidated findings from the Global PPS (34.4%) [21]. However, appreciably lower that seen recently in Botswana (70.6% of admissions were for infectious diseases), Kenya (54.7% to 67.7%) and 50% among the African countries taking part in the Global PPS study [20,21,25,26,53]. The reason for this lower rate in our study is unknown, and envisaged to be higher given the high prevalence of infectious diseases in South Africa [30,33-35,55]. In addition, prior antimicrobial exposure promotes colonization and subsequent infection with antimicrobial-resistant pathogens. This is known to enhance AMR rates [14]. Overall, 44.5% of patients in our study who had been prescribed at least one antibiotic in hospital had used antimicrobials in the past 90 days. These concerns will also be the subject of future projects to fully assess the appropriateness of antimicrobial prescribing among public hospitals in South Africa. This builds on recent studies in both the hospital and ambulatory care sectors in South Africa as well as other countries [39,43,50,56].

Having said this, it was unfortunate to see a low level of CSTs requested; however, encouraging to see a high level of modification of antimicrobial treatment following CST results when requested. This is not always the case as seen in other studies performed among African countries where there has been a low rate of antimicrobial modification [20,25,26]. However, there were concerns that antimicrobial treatment was not modified in a minority (17%) following the results, and there may well have been situations when CST could have been ordered but not recorded or available in the files at the time of data collection. These are also considerations for the future. In 5.6% of occasions, an antimicrobial was prescribed, while there was no clear indication for its use with no signs of systemic infection, and on 5.2% of occasions, antimicrobials were prescribed other than for treatment (Table 3). This is a concern that needs to be addressed to reduce inappropriate prescribing and the potential for increasing AMR rates. However, we are aware that among African countries in the Global PPS, on 29.6% of occasions no reason for antimicrobial prescribing was documented in the patients' notes [21].

Most antimicrobials were used to treat infection rather than prophylaxis, similar to other studies [13, 22, 23, 26,44] as well as the Global PPS study [21], although different to a recent PPS study in Kenya [25]. The high burden of TB in South Africa [6, 33,34] is a possible reason for the relatively high use of anti-TB agents in DGMAH (Figure 1). In line with other studies performed in SA [11, 44] and across

Africa [21], there was a high utilization rate of penicillins versus other antimicrobials (Figure 1). This may be due to restrictions on second line antibiotics such as cephalosporins and fluroquinolones. Antibiotic policies to optimize the use of penicillins also help preserve newer antimicrobials [23]. However, care is needed as the high use of penicillins poses a risk to the development of resistance including methicillin resistant *Staphylococcus aureus* (MRSA) [12,23]. The use of penicillins along with the appropriateness of the use of antibiotics will now be monitored closely in DGMAH.

Encouragingly as well, the majority of antimicrobials prescribed (98%) were medicines that were available as part of the EML. This is higher than a study conducted in South Africa in 2003 (90%) [57], reflecting that STGs and the EML have been promoted for a number of years alongside support measures to promote prescribing according to these guidelines [34, 57]. The procurement of medicines in public sector hospitals is highly influenced by national standard guidelines such as the EML/ STGs [57] resulting in the high compliance rates seen. However, as mentioned, we will be looking more closely at the use of antimicrobials against STGs in this and other public sector hospitals in SA in the future to help enhance their use as part of quality improvement programmes. This will also include looking more closely at the use of antibiotics to prevent surgical site infections, including the length of prescribing, given concerns in SA and in a number of sub-Saharan African countries [43,58,59].

Of concern was that no antimicrobial was switched from IV to oral in our study even if the patient had a stable GIT. This may be due to lack of confidence with oral antibiotics, and this will also be explored in future studies in view of the cost implications and potential ways to address this [60-63].

Limitations

We are aware of a number of limitations with this study. Firstly, the accuracy of the findings depends on the accuracy of the documentation in the patient's files as this was not an interventional survey with no patient, nurse of physician contact for clarification or additional information. The use of data collectors had a positive impact in accelerating the process of data collection; however, they had to be continuously monitored and the data collected was greatly influenced by their accuracy and level of commitment. Variables such as hospital or community acquired infections were also not clear cut.

In addition, we are aware that the results presented on this study were obtained from one public hospital in the country and any generalization to all public sector hospitals in SA based on these results is not possible. However, this was not the primary aim of this study. Having said this, DGMAH is a leading public sector hospital in South Africa and the findings could potentially be used to suggest improvement programmes in this and other hospitals in SA.

5. Conclusion

The PPS design is appropriate for collecting data on current antimicrobial use within public sector hospitals in SA. Encouragingly, there was high use of antimicrobials contained with national EMLs/ STGs. In addition, the results showed a high use of broad spectrum penicillins and low use of restricted or newer antimicrobials (e. g carbapenems), which is encouraging. CST results were also acted on in the majority of situations. However, there is a concern with the lack of IV to oral switching, and that not all suitable patients have CST and not all results are acted upon. These are suggested quality improvement programmes for the future.

There was also a concern about the length of time to survey each patient and enter the findings onto standardized forms for analysis. Further work is now ongoing developing a standardised data collection tool for such surveys using a web-based application to address this concern. These findings will be reported in the future.

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