HOSPITAL PRACTICE
2022, VOL. 50, NO. 4, 306–317
https://doi.org/10.1080/21548331.2022.2114251

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CLINICAL FEATURE
ORIGINAL RESEARCH

A national, multicentre web-based point prevalence survey of antimicrobial use in community healthcare centres across South Africa and the implications

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ABSTRACT

Objective: Up to 90% of antimicrobials globally are prescribed and dispensed in ambulatory care. However, there are considerable gaps regarding the extent and rationale for their use especially in low- and middle-income countries such as South Africa. Point prevalent surveys (PPS) are useful to determine current prescribing patterns, identify targets for quality improvement and evaluate the effectiveness of antimicrobial stewardship programmes (ASPs) within institutions. Consequently, the objective of this study was to undertake a PPS within community healthcare centers (CHCs) in South Africa given their importance to the public healthcare system. The findings will be used to provide guidance on future interventions to improve antimicrobial use in South Africa and wider.

Methods: A PPS of antimicrobial consumption was undertaken among patients attending 18 CHCs in South Africa. A web-based application was used to record the utilization data, with utilization assessed against World Health Organization (WHO) and South African guidelines.

Results: The overall prevalence of antimicrobial use amongst patients attending the CHCs was 21.5% (420 of 1958 patients). This included one or more antimicrobials per patient. The most frequently prescribed antimicrobials were amoxicillin (32.9%), isoniazide (11.3%) and a combination of rifampicin, isoniazid, pyrazinamide and ethambutol (Rifafour®) (10.5%), with the majority from the WHO Access list of antibiotics. There was high adherence to guidelines (93.4%). The most common indication for antibiotics were ear, nose and throat infections (22.8%), with no culture results recorded in patients' files.

Conclusions: It's encouraging to see high adherence to South African guidelines when antimicrobials were prescribed, with the majority taken from the WHO Access list. However, there were concerns with appreciable prescribing of antimicrobials for upper respiratory tract infections that are essentially viral in origin, and a lack of microbiological testing. The establishment of ASPs can help address identified concerns through designing and implementing appropriate interventions.

ARTICLE HISTORY
Received 21 December 2021
Accepted 15 August 2022

KEYWORDS
Antimicrobials; antimicrobial consumption; AWaRe list of antimicrobials; community healthcare centers; quality targets; point prevalence survey; South Africa

1. Introduction

In ambulatory care, especially among low- and middle-income countries (LMICs), oral antimicrobials are consistently in the top therapeutic classes of medicines by frequency of use [1,2]. Alongside this, there are concerns with high inappropriate prescribing among ambulatory care healthcare professionals (HCPs), enhanced by the time pressures on them combined with pressures from patients [1,3,4]. A considerable proportion of antimicrobials are prescribed and dispensed for acute respiratory tract infections which are essentially viral in origin [1,5,6]. Such activities have been exacerbated during the current COVID-19 pandemic with high use despite only limited bacterial or fungal co-infections [7].

Of concern is that antimicrobial utilization rates are increasing among LMICs [8]; however, this is often unnecessary due to a lack of regulations and their monitoring, concerns with training of HCPs and considerable informal use [8]. High and unnecessary use of antimicrobials enhances antimicrobial resistance (AMR) with its associated impact on morbidity, mortality and costs [9–11]. Growing rates of AMR across countries, and the consequences, led to the development of national action plans (NAPs) to reduce AMR, building on the World Health Organization's initiative [12,13]. South Africa is no exception [14]. However, there is currently limited data nationally on non-hospital (community/ ambulatory care) antimicrobial use across countries, which is exacerbated by the considerable purchasing of antibiotics without a prescription especially among LMICs [1,15].

A key element of NAPs is the documentation of current antimicrobial usage patterns across sectors including both hospital and ambulatory care [14,16].

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South Africa is a LMIC of 60.14 million people, with approximately two thirds living in urban areas [17,18]. In South Africa, ambulatory care in the public healthcare system is principally provided through a nurse-based, doctor-supported system consisting of over 3500 community healthcare centers (CHCs) and primary healthcare clinics (PHCs), which should be available within 5 km to over 90% of the population, and free at the point of use [19,20]. CHCs are the most visited healthcare facility among patients in South Africa. Their main function is to deliver most ambulatory care services to the South African population, especially those residing in rural areas. Services include advice on hygiene, vaccinations and health education as well as antenatal care and safe child birth delivery. CHCs also provide examinations for screening purposes, treatments and referrals [21].

We are aware of a number of studies conducted across South Africa investigating the utilization of antimicrobials in ambulatory care [22–25] combined with studies assessing total antimicrobial utilization in South Africa [26]. Alongside this, point prevalence surveys (PPS) have been undertaken among hospitals in South Africa to document their current utilization patterns [27–30]. However, we were unaware of any study undertaken to date to assess current antimicrobial prescribing within CHCs in South Africa. Consequently, we instigated this study to address this information gap considering previous concerns with inappropriate prescribing of antimicrobials within ambulatory care facilities in South Africa [20,24]. This is in line with the goals of the South African NAP on AMR including greater knowledge of current antimicrobial utilization rates coupled with programmes to reduce unnecessary antimicrobial prescribing exception [14,16].

2. Materials and methods

2.1 Study design

This was a PPS study to determine antimicrobial utilization patterns among 18 CHCs across South Africa using a web-based application (APP) [27]. We have used this approach before to assess current antimicrobial utilization patterns among the pediatric and adult populations in public sector hospitals in South Africa [29,31].

2.2 Study sites

We randomly selected 18 CHCs across South Africa from a total of 233 CHCs throughout the country. They comprised two CHCs from each of the nine provinces in South Africa, with prior selection before randomization. This was based on their proximity to an academic or tertiary hospital that was used for the referral of patients in the province as well as the availability of personnel to conduct the PPS study (convenient sampling).

2.3 Data collection tool and variables recorded

As before, we used an APP combined with a built-in paper-based data collection tool in order to reduce the time taken for data collection [27].The data collection tool was based on the Global PPS and European Center for Disease Prevention and Control study forms, which was subsequently adapted to include highly prevalent co-morbid conditions found in Sub-Saharan Africa, which includes the human immunodeficiency virus (HIV), malaria, malnutrition and tuberculosis (TB) [27,30,32–37]. In view of this, we included antimicrobials to treat patients with TB in this PPS study, and did not separate out antimicrobials prescribed for patients with TB versus those without TB, which included linezolid and quinolones. This is in line with our previous PPS studies in South Africa [29,30].

The data that was collected included the name of the CHC based on the South African National Department of Health (NDoH) classification [29,38]. The patient level data that was collected and recorded included the age of patients alongside their gender, the extent of any intubation, and the extent of any readmission as well as their antimicrobial history and any hospitalization during the last 90 days. Furthermore, the extent of any co-morbidities especially any HIV, TB and malaria were recorded.

Antimicrobial data with corresponding indications and route of administration were recorded for each patient. In addition, whether they were given for prophylaxis or for treatment. Antimicrobial utilization was analyzed according to different age groups of patients. This included neonates: 0 to 28 days; infants: 1 to 11 months; children: 1 to 11 years; adolescents: 12 to 17 years; younger adults: 18 to 35 years; middle age adults: 36 to 55 years; and older adults: 56 years and older, alongside the different ward categories. Antimicrobials were categorized on the basis of their WHO Anatomical Therapeutic Chemical (ATC) 3rd level classification system (2019) [39]. These included J01A, C, D, E, F, G, M and X; J02A; J04A; J05AB and P01A antimicrobials.

We also used the AWaRe classification as a quality indicator for antimicrobial prescribing especially in children [40–43]. Antibiotics from the Access list are considered as first-line or second-line treatments for key infections, and should be routinely available for appropriate prescribing and dispensing within countries especially LMICs [41]. There should be limited prescribing of antibiotics in the 'Watch' group as these are considered to have a higher resistance potential and toxicity, alongside limited prescribing of antibiotics in the 'Reserve' group, which are considered as a last resort. Antibiotics in both the 'Watch' and 'Reserve' group should be prioritized for antimicrobial stewardship programmes (ASPs) where their prescribing is a concern [42,44,45].

2.4 Patient selection and data collection

The files of all patients seen at each selected CHC on the day prior to the day of data collection were included in the study. All the relevant files were kept aside by clinic staff for the data collector to review the following day.

In order to calculate the point prevalence of antimicrobial use within each CHC, all the patients that were seen at the CHC on the day before the data collection day became the denominator, whether they were prescribed an antimicrobial or not. Data were collected over a period of five months between 1 March 2018 and 31 July 2018, with one full day spent at each of the CHCs. The CHC and the referring hospital data were collected collaboratively within the same week by the designated data collectors. The numerator included all patients who were subsequently prescribed an antimicrobial. The only exclusion criteria were patients who attended accident and emergency units, if such units were available with the CHC [29,30,36]. Data collection took place only on weekdays to optimize representation, with the data collectors spending one day at each CHC.

The utilization data were collected only by hospital and academic pharmacists that had received extensive training on how to conduct a PPS prior to data collection. This included a demonstration and a practice session on the use of the purposely developed APP, similar to the training provided in previous PPS studies conducted in South Africa and wider [29,30,36,37,46].

2.5 Quality indicators

We used a number of indicators to assess the quality of antimicrobial prescribing, which were based on previous studies [33,36,42,47–49]. The indicators used included current prevalence rates for the prescribing of antimicrobials as well as the number prescribed per patient. Alongside this, whether the indication for the antimicrobial being prescribing was recorded in the patient's notes. We also reviewed whether microbiological culture results were recorded in the patients' files.

We also assessed the ATC class of antimicrobial prescribed, the route of administration and whether the antimicrobials were being prescribed for prophylaxis or treatment [33,36,47,50]. Surgical prophylaxis is typically defined as the administration of antibiotics before, during, or after a surgical procedure to help prevent infectious complications, with medical prophylaxis defined as the prevention of infections in non-surgical situations [36,46,47]. In addition, we assessed the proportion of antimicrobials prescribed in each of the three AWaRe categories as the total number of antimicrobials prescribed in the respective Access, Watch, or Reserve groups as a percentage of the total number of antimicrobials prescribed among the participating CHCs [43,44,51].

Finally, we also assessed whether the antimicrobials prescribed followed the NDoH Essential Medicines List and Standard Treatment Guidelines (EML-STG) [33]. This is because there have been concerns with adherence rates to published guidelines in South Africa and among other African countries [20,52–54].

2.6 Data management and statistical analysis

The APP feeds directly into an Excel® database. The data are subsequently imported into SAS (version 9.4 for Windows) for analysis in consultation with a statistician. Before analysis, the data was cleaned and validated by ensuring that all the data required for subsequent analysis was present, that the correct units were used and entered, and that there were no errors or duplications among the submitted data. If errors were found, retracing was performed to try correct the anomaly or the data was removed if there was no accountability.

All patients aged below 18 years were regarded as pediatric patients, and broken down by specific age groups. Those aged 18 years and above were viewed as adults, and again broken down by specific age groups, as previously described. Situations where an antimicrobial was prescribed but the condition was not an infection were recorded as not applicable.

As mentioned, we assessed antimicrobial utilization as percentages (proportional use) by indication (prophylactic or therapeutic), age category and by AWaRe classification based on the 2017 WHO EML Access, Watch, Reserve grouping [43]. However, because some of the antimicrobials had not yet been classified, we included these as an unclassified group.

We used the Chi square ($\chi 2$) test with a p-value <0.05 for significance to assess the relationship between the categorical variables. Cramer's V or phi coefficient ≥0.50 was considered a strong association for interpretation, 0.30–0.49 as a moderate association, 0.10–0.29 as a weak association and <0.10 limited if any association.

2.7 Ethical approval

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 by applying unique study identification numbers for hospitals and patients. Alongside this, no personal identifiers were recorded for patients in order to maintain anonymity.

No patients, parents or guardians were approached for consent since this was a retrospective study based on data collected from patients' medical records, with no direct contact with patients, children, their parents, or guardians. This is similar to previous PPS studies performed by the coauthors [30,49,51,55–57].

3. Results

Overall, 1958 patients were reviewed across the 18 CHCs. The majority (84.8%;1661/1958) were adults while 15.2% were pediatric patients. The median (IQR) range for age was 41 (27–41) years and there were more females (64.0%; 1253/1958) than males. Of the 1661 adults, the majority were female (66.6%;1107/1661) whilst pediatric patients were almost equally distributed with 49.2% (146/297) females.

Antimicrobials were prescribed for 21.5% (420/1958) of patients among the 18 participating CHCs. Pediatric patients consumed more antimicrobials than adults at 25.3% (75/297) versus 20.8% (345/1661) for adults. However, due to majority of the population being adults in the study, most of the antimicrobials were prescribed for the adults. Overall, 19 antimicrobials were prescribed a total of 486 times, with a minority receiving more than one antimicrobial. Adults contributed 83.3% (405/486) of total antimicrobial prescribing, with the majority prescribed among adults aged 18–35 years (36.0%; 175/486) and those aged 36–55 years (31.9%; 155/486). Table 1 provides a further breakdown by the designated age groups.

Table 1. Overall antimicrobial consumption by patient demographics.

	Number of prescriptions with at least one antimicrobial (n = 486)	Percentage (%)
Age		
Neonate (0–28 days)	1	0.2
Infant (1–11 months)	10	2.1
Child (1–12 years)	55	11.3
Adolescent (13–17 years)	15	3.1
Adult (18–35 years)	175	36.0
Adult (36–55 years)	155	31.9
Adult (≥56 years)	75	15.4
Gender		
Female	274	56.4
Male	212	43.6

Antimicrobials were prescribed the most for indications of upper respiratory tract infections (URTIs), e.g., infections of the ear, nose, throat, larynx and mouth but excluding the bronchus (16.3%; 79/486), followed by TB (8.4%; 41/486) and subsequently soft tissue infections including cellulitis, wound and deep soft tissue, but excluding bone (5.1%; 25/486) (Table 2). On 50 occasions (10.3%) antimicrobials were prescribed but this was not an applicable indication for antimicrobial use. According to the South African CDC, this is when the indication is not an infection but antimicrobials are prescribed.

Out of the 420 patients on antimicrobials, 55 (13.1%) patients were prescribed more than one antimicrobial at the time of the survey whilst 365 (86.9%) received a single antimicrobial.

The beta-lactam antibacterials including the penicillins, were the most frequently prescribed class of antimicrobials (45.9%; 223/486), followed by antimicrobials for treating TB

Table 2. Indications along with the antimicrobials prescribed for treatment.

Indication	Antimicrobial prescribed	ATC class	Number of times antimicrobials prescribed	Percentage of the total within each indication
Asymptomatic bacteriuria (Presence of bacteria in urine without symptoms)			3	
	Amoxicillin	J01CA04	1	33.3%
	Azithromycin	J01FA10	1	33.3%
	Ciprofloxacin	J01MA02	1	33.3%
Bone and joint infections (e.g., septic arthritis, prosthetic joint infections, osteomyelitis)			11	
	Amoxicillin	J01CA04	9	82%
	Amoxicillin and beta-lactamase inhibitor	J01CR02	1	9%
	Flucloxacillin	J01CF05	1	9%
Acute bronchitis or exacerbations of chronic bronchitis			8	
	Amoxicillin	J01CA04	8	100%
Infections of the central nervous system			1	
	Amoxicillin	J01CA04	1	100%
Symptomatic lower urinary tract infection, e.g., cystitis			24	
	Amoxicillin	J01CA04	2	8%
	Amoxicillin and beta-lactamase inhibitor	J01CR02	1	4%
	Azithromycin	J01FA10	7	29%
	Ciprofloxacin	J01MA02	6	25%
	Cloxacillin	J01CF02	1	4%
	Doxycycline	J01AA02	1	4%
	Metronidazole (oral/rectal)	P01AB01	5	21%
	Metronidazole (parenteral)	J01XD01	1	4%
Upper respiratory tract Infections – ear, nose, throat, larynx, mouth excluding bronchus			79	
	Amoxicillin	J01CA04	54	68%
	Amoxicillin and beta-lactamase inhibitor	J01CR02	5	6%
	Azithromycin	J01FA10	8	10%
	Ceftriaxone	J01DD04	2	3%
	Metronidazole (oral/rectal)	P01AB01	4	5%
	Nystatin	A07AA02	1	1%
	Phenoxymethylpenicillin	J01CE02	5	6%
Extra pulmonary tuberculosis			14	
	Isoniazid	J04AC01	1	7%
	Pyrazinamide	J04AK01	1	7%
	(Rifampicin, isoniazid, pyrazinamide and ethambutol) Rifafour®	J04AM06	10	71%
	Rifampicin	J04AB02	2	14%
Eye infections e.g., endophthalmitis			5	
	Amoxicillin	J01CA04	4	80%
	Amoxicillin and beta-lactamase inhibitor	J01CR02	1	20%
Gastrointestinal infections, e.g., salmonellosis, bacterial-associated diarrhea			16	
	Amoxicillin	J01CA04	5	31%
	Amoxicillin and beta-lactamase inhibitor	J01CR02	1	6%
	Ceftriaxone	J01DD04	2	13%

(*Continued*)

Table 2. (Continued).

Indication	Antimicrobial prescribed	ATC class	Number of times antimicrobials prescribed	Percentage of the total within each indication
	Ciprofloxacin	J01MA02	1	6%
	Metronidazole (oral/rectal)	P01AB01	3	19%
	Phenoxymethylpenicillin	J01CE02	1	6%
	Sulfamethoxazole and trimethoprim	J01EE01	2	13%
	Sulfamethoxazole and trimethoprim	J01EE02	1	6%
Prostatitis, epididymo-orchitis, and sexually transmitted diseases in men			10	
	Amoxicillin	J01CA04	1	10%
	Azithromycin	J01FA10	3	30%
	Ciprofloxacin	J01MA02	5	50%
	Metronidazole (oral/rectal)	P01AB01	1	10%
Malnutrition			1	
	Amoxicillin and beta-lactamase inhibitor	J01CR02	1	100%
Not applicable for antimicrobial use other than treatment			50	
	Amoxicillin	J01CA04	28	56%
	Amoxicillin and beta-lactamase inhibitor	J01CR02	5	10%
	Ampicillin	J01CA01	1	2%
	Azithromycin	J01FA10	6	12%
	Ceftriaxone	J01DD04	1	2%
	Ciprofloxacin	J01MA02	3	6%
	Cloxacillin	J01CF02	2	4%
	Metronidazole (oral/rectal)	P01AB01	2	4%
	Phenoxymethylpenicillin	J01CE02	1	2%
	Sulfamethoxazole and trimethoprim	J01EE01	1	2%
Obstetric or gynecological infections, e.g., STDs in women, abortion related and post-partum sepsis			23	
	Amoxicillin	J01CA04	1	4%
	Azithromycin	J01FA10	4	17%
	Ceftriaxone	J01DD04	2	9%
	Ciprofloxacin	J01MA02	9	39%
	Metronidazole (oral/rectal)	P01AB01	6	26%
	Sulfamethoxazole and trimethoprim	J01EE01	1	4%
Pneumonia (other than TB)			16	
	Amoxicillin	J01CA04	9	56%
	Amoxicillin and beta-lactamase inhibitor	J01CR02	3	19%
	Ciprofloxacin	J01MA02	1	6%
	Sulfamethoxazole and trimethoprim	J01EE01	3	19%
Symptomatic upper urinary tract infection (ureter and kidney) e.g., pyelonephritis			3	
	Amoxicillin and beta-lactamase inhibitor	J01CR02	1	33%
	Azithromycin	J01FA10	1	33%
	Cefalexin	J01DB01	1	33%
Systemic inflammatory response syndrome with no clear anatomical site of infection.			1	
	Cloxacillin	J01CF02	1	100%
Soft tissue infections, e.g., cellulitis, wound and deep soft tissue – not involving bone			25	
	Amoxicillin	J01CA04	8	32%
	Amoxicillin and beta-lactamase inhibitor	J01CR02	4	16%
	Azithromycin	J01FA10	1	4%
	Cefalexin	J01DB01	1	4%
	Cloxacillin	J01CF02	1	4%
	Flucloxacillin	J01CF05	7	28%
	Metronidazole (oral/rectal)	P01AB01	3	12%
Pulmonary tuberculosis			41	
	(Rifampicin, isoniazid, pyrazinamide and ethambutol) Rifafour®	J04AM06	41	100%
Completely undefined; site with no systemic inflammation			15	
	Amoxicillin	J01CA04	12	80%
	Metronidazole (oral/rectal)	P01AB01	2	13%
	Sulfamethoxazole and trimethoprim	J01EE01	1	7%
Indication not in patient file			24	
Prophylaxis			116	
Total prescribed			486	

(22.4%; 109/486) and sulfonamides and trimethoprim (8.8%; 43/486) (Table 2 and Figure 1).

Considering specific antimicrobials, amoxicillin was the most frequently prescribed antimicrobial (32.9%; 160/486) followed by isoniazid (11.3%; 55/485) and a combination of rifampicin, isoniazid, pyrazinamide and ethambutol (Rifafour®) (10.5%; 51/486) (Table 3).

Figure 1 illustrates the different antimicrobial classes prescribed by age group.

Most of the antimicrobials prescribed were for oral administration (97.5%; 474/486) with the remainder administered parenteral (2.5%) (Table 4). None of the files reviewed contained any culture results in them. Consequently, all antimicrobials in this study were prescribed empirically.

Overall compliance with the current South African EML-STG for the antimicrobials prescribed was 93.4% (454/486), however, only 69.5% (338/486) were prescribed by their generic name (International nonproprietary name [INN]) (Table 4). More than half (62.1% 302/486) of the antimicrobials prescribed belonged to the Access category and 15% (73/486) were from the Watch category, with similar groupings across the age groups. Encouragingly, no Reserve antimicrobials were prescribed among the reviewed patients in the different age groups (Table 4). However, 22.8% of the antimicrobials prescribed could not be classified under the current AWaRe system (Table 4).

Antimicrobial prescriptions were mostly issued by medical officers (60.7% 295/486), followed by nurses (36.2% 176/486), with specialists only accounting for a minority 3.1% of the prescribed antimicrobials (Table 4).

4. Discussion

We believe this is the first study to fully assess antimicrobial prescribing among CHCs in South Africa as the first step to

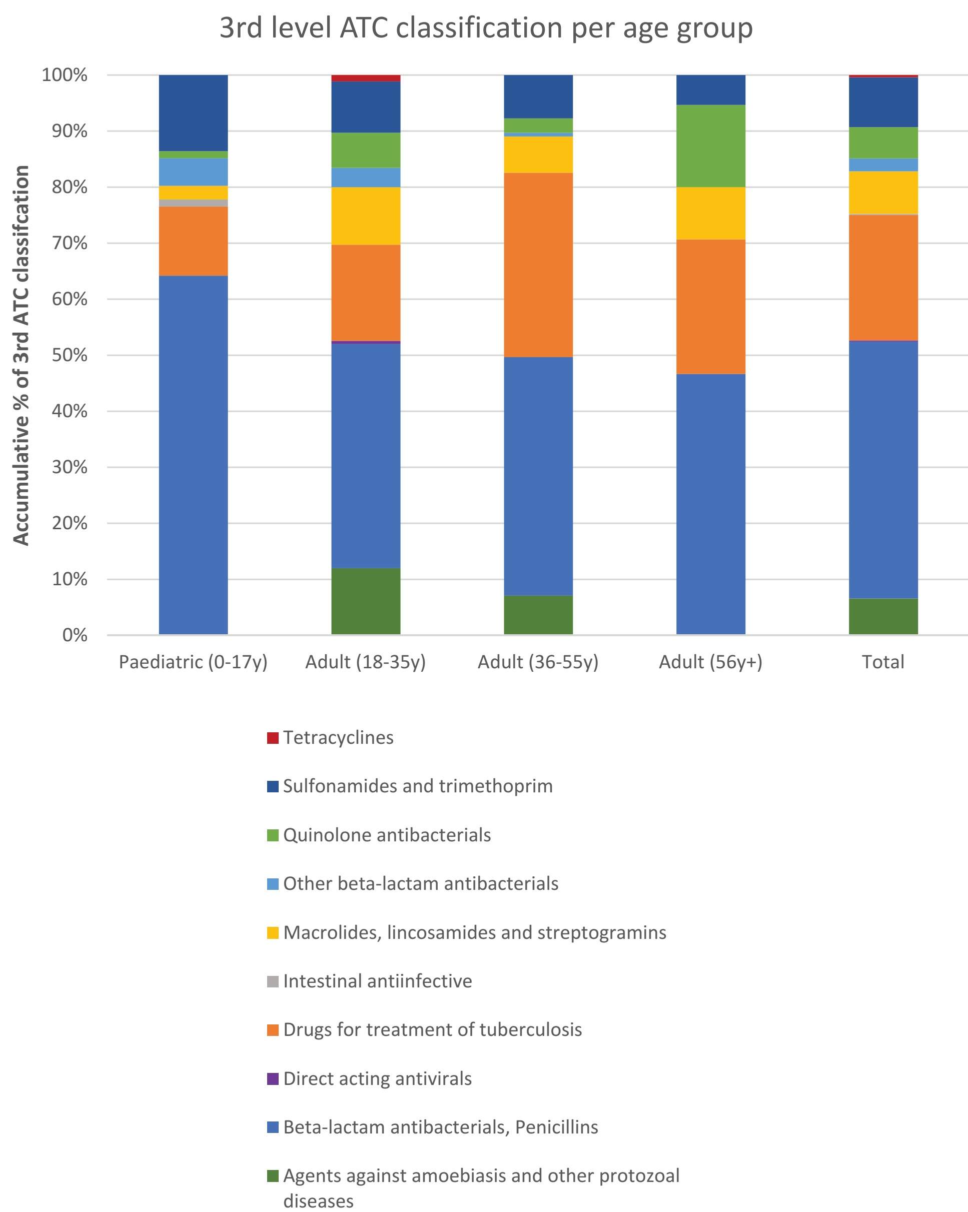

Figure 1. 3rd level ATC Classification of antimicrobials by age groups.

NB: Categorization of antimicrobial use among the pediatric population was combined, y = years

Table 3. Antimicrobials prescribed according to the top five antimicrobial classes.

ATC level 3	Antimicrobial	ATC code	Number of times antimicrobials are prescribed	Percentage of the total (486)
J01C: Beta-lactam antibacterials	Amoxicillin	J01CA04	160	32.9%
	Amoxicillin and beta lactamase inhibitor	J01CR02	32	6.6%
	Flucloxacillin	J01CF05	14	2.9%
	Cloxacillin	J01CF02	7	1.4%
	Ampicillin	J01CA01	1	0.2%
J01E: Sulfonamides and trimethoprim	Sulfamethoxazole and trimethoprim	J01EE01	43	8.9%
J01F: Macrolides, lincosamides and streptogramins	Azithromycin	J01FA10	37	7.6%
J04A: Drugs for treatment of tuberculosis	Isoniazid	J04AC01	55	11.3%
	Rifampicin, isoniazid, pyrazinamide and ethambutol	J04AM06	51	10.5%
	Rifampicin	J04AB02	2	0.4%
	Pyrazinamide	J04AK01	1	0.2%
P01A: Agents against amoebiasis and other protozoal diseases	Metronidazole (oral/rectal)	P01AB01	32	6.6%
Other classes			51	10.5%

Table 4. Quality indicator summary.

	Number of antimicrobials (n = 486)	Percentage of the total (%)
Route of administration		
Oral	474	97.5
Intravenous	9	1.9
Intramuscular	3	0.6
AWaRe classification		
Access	302	62.1
Watch	73	15.0
Reserve	0	0.0
Unclassified	111	22.8
Purpose for use		
Prophylaxis	116	23.9
Treatment	370	76.1
Item prescribed by		
Medical Officer	295	60.7
Nurse	176	36.2
Specialist	15	3.1
Item prescribed from South African EML-STG		
Yes	454	93.4
No	32	6.6
Item written by generic name (INN)		
Yes	338	69.5
No	148	30.5

NB: Unclassified means no classification currently in the WHO AWaRe list; EML-STG = Essential Medicines List and Standard Treatment Guidelines

improving their future prescribing. Overall, 21.5% of the admitted patients to CHCs in South Africa received at least one antimicrobial. The pediatric population had an antimicrobial consumption rate of 25.3% and this rate mirrors Fink *et al.* (2020), who ascertained a rate of 24.5% among young children attending healthcare facilities in LMICs [58]. Encouragingly, the overall rate of 21.5% in our study was appreciably lower than seen among public healthcare facilities (PHCs) in Ghana (59.9%), Pakistan (57.2%), India (49%), Thailand (46.9%), Nepal (44.7%), Botswana (42.7%) and Cameroon (36.7%) [2,59–64]. However, it was higher than that seen in the study of Ab Rahman *et al.* (2016) who found a rate of 6.8% among patients attending PHCs in Malaysia [65].

The prescribing rates among the CHCs in South Africa were also lower than a pooled prescribing prevalence rate of 51.5% to 52.0% among PHCs across Africa and other LMICs in the studies of Ofori-Asenso *et al.* (2015) and Sulis *et al.* (2020) [66,67]. The difference between the findings of Fink *et al.* (2020) and Sulis *et al.* (2020) may reflect differences in the nature of the PHCs and the ages of the populations studied. In addition, there is a potential mix of private and public healthcare facilities among the included publications. This is because we know that different incentives can influence antimicrobial prescribing habits in private versus public clinics [68,69]. In Malaysia, Ab Rahman *et al.* documented a prescribing rate of antibiotics at 30.8% of patients attending private clinics versus only 6.8% among those attending public clinics [65]. There was also high use of antimicrobials among private physicians in Botswana treating patients with upper respiratory tract infections (URTIs) enhanced by patient pressure, as well as a higher use of antibiotics and medicines administered by injection among the same physicians treating patients in private versus public clinics in Iran [69,70]. The lower rate of antimicrobial prescribing among the 18 CHCs in South Africa could be due to a number of factors. These include the establishment of ASPs within hospitals in South Africa coupled with the dissemination of the National Strategic Framework to reduce AMR [71–73]. However, further studies are needed to substantiate any perceptions.

Since URTIs were the most frequent diagnosis (22.8%), this may explain why the penicillins were the most prescribed antimicrobials (Table 2). Other studies have also shown that the penicillins (β-lactams) are among the most prescribed and dispensed class of antibiotics in ambulatory care given the high prevalence rates of URTIs [2,65,74–77]. β-lactams have continued to be the mainstay of antimicrobial therapy due to their wide spectrum of activity against both gram positive and negative organisms.

Isoniazide and a combination of rifampicin, isoniazid, pyrazinamide and ethambutol (Rifafour®) were also among the most prescribed antimicrobials in the surveyed CHCs across South Africa. This high rate may reflect the relatively high prevalence of TB in South Africa with eight countries currently accounting for two thirds of the global total prevalence of TB. South Africa currently contributes 3.6% of global cases, similar to other countries including Bangladesh (3.6%) and Nigeria

(4.4%) [78]. We have seen high rates of TB in other PPS studies in South Africa [30]; although lower in others [29]. These findings may reflect the different nature of patients treated in the different healthcare settings in South Africa. However, these findings make it mandatory to assess the profile of patients attending ambulatory healthcare centers in Africa and wider when seeking to compare antimicrobial utilization patterns including their rates across LMICs. This is because high rates of TB are typically not seen in a number of other LMICs, or high-income countries, making comparisons regarding antimicrobial prescribing difficult without such knowledge. This suggestion is further endorsed by a study conducted among PHCs in Botswana where high rates of prescribing of metronidazole were documented, which was due to a high burden of sexually transmitted and gynecological infections [2]. This is different to ambulatory care prescribing seen in many other countries where high rates of URTIs are seen [10,75].

It was also encouraging to see a high rate of prescribing of antibiotics in the Access group with no prescribing of Reserve antibiotics (Table 4). These rates are considerably higher compared with the findings of Hsia *et al*. (2018) where the utilization of antibiotics in the Access category only accounted for 33.3% of total utilization among the hospitals in South Africa taking part in the global PPS study [42]. However, this needs further evaluation especially given high prevalence rates for URTIs seen in our study, which are typically viral in origin.

It was also encouraging to see low use of injections in the surveyed CHCs (1.9%; Table 4). This compares to appreciably higher rates of injectable administration in hospitals in South Africa (64.3%) and wider across Africa (63.1% to over 80% of administered antimicrobials) [29,33,36,56]. Alongside this, it was encouraging to see high rates of adherence to the South African EML-STG when antimicrobials were prescribed (93.4%). This differs from recent studies where there have been concerns with guideline implementation in ambulatory care in South Africa [20,79] and among other African countries [52,54]. Compliance is important to enhance the quality of prescribing as well as improve stock control systems to limit the potential for shortages of antimicrobials and the concerns this cause if no suitable alternatives have been discussed beforehand [17,80–82].

There were reports regarding difficulties in obtaining microbiological results among the surveyed CHCs resulting in none of the files reviewed having culture results within them. This may be attributed to limited services currently at CHCs in South Africa, distance to such facilities and a delay in feedback of the results. Engler *et al*. (2021) in their study highlighted the challenges pertaining to the collection and reporting of culture and sensitivity across public healthcare facilities in South Africa [83]. These challenges are enhanced in CHCs, which have to wait for any results from the nearest referral hospital making it scarce to find such results in patient's files in CHCs. However, in the case of patients with TB, they contrast with the findings of McCarthy et al (2018) where empiric treatment accounted for only 15% of patients initially treated for TB in primary healthcare settings [25]. We are not sure of the reasons behind this appreciable difference. This urgently needs to be addressed including whether CHCs are dealing with follow-up TB patients or patients presenting to health care facilities for the first time. Generally though, limited diagnostic and surveillance data are currently the major shortcomings among public healthcare facilities in South Africa, which need addressing going forward to improve future antimicrobial prescribing and reduce AMR [83]. This also includes greater documentation generally in patients' notes of the rationale behind the antimicrobials prescribed including any diagnostic tests used.

In addition, ambulatory care facilities across South Africa do face many challenges especially among both PHC and CHC facilities where antimicrobial stewardship activities and ASPs are not fully implemented. This is important when initiating or reviewing potential treatment approaches for patients with infectious diseases attending CHCs to improve future prescribing. This especially given the concerns that can exist when inappropriately treating patients with infectious diseases in ambulatory care across Africa [20,53,54,70]. We will continue to monitor the situation to improve future antimicrobial prescribing.

Another identified concern was that not all prescriptions were written by their INN name (Table 4), which adds to costs given the low prices for multi-sourced medicines that have been obtained in countries versus originator prices [84–86]. The Medicines and Related Substances Control Amendment Act No. 90 of 1997 ensures that the South African government can undertake a variety of activities to provide a supply of affordable medicines. Further to this, multi-sourced medicines (generics) are the first choice in the public sector whilst those patients in medical aid schemes, as medical consumers, have the option whether or not to choose a generic medicine [87]. However, medicine prices became a critical issue from mid-2000 across South Africa. Consequently, generic medicines have been recommended for wider use, including the private sector. We are aware of concerns with the quality of generics in some African countries [88]; however, this should not apply to South Africa with its comprehensive procurement and regulatory practices coupled with patients obtaining their antibiotics directly from CHCs with no co-payment [17]. We will also be following this up in future studies.

Finally, of particular relevance to South Africa and other LMICs, is the potential contribution of nurses in the ambulatory care setting to improve future antibiotic utilization and reduce AMR [3,19,20,89]. In our study, 36.2% of the antimicrobials prescribed were by nurses. Consequently, there is a need to ensure their full knowledge regarding appropriate prescribing of antimicrobials against recognized guidance contained in the South African EML-STG and audit subsequent prescribing habits [20]. This is similar to the situation for other HCPs across Africa and to other LMICs to ensure appropriate knowledge regarding antibiotics, AMR and ASPs and to promote high adherence to national treatment guidelines [10,90,91]. As a result, enhancing appropriate prescribing of antimicrobials. These are projects for the future.

The results of this study will be disseminated among the CHCs taking part and others within the public healthcare system in South Africa. Hopefully, this will result in the implementation or progression of antimicrobial stewardship teams in line with Government guidance to maintain surveillance of current antimicrobial use by training all health care workers [71,83]. As a result, improving future antimicrobial prescribing, which includes greater collection of microbiological data to inform future empiric prescribing.

We are aware there are limitations with this study. These include the fact that we only included two CHCs from each province. In addition, the retrospective nature of the study precluded direct contact with prescribers to ascertain the rationale behind their prescribing of antimicrobials. This included the prescribing of antimicrobials for patients with URTIs, which are essentially viral in origin. No dosage data was collected, which could have added to other potential quality indicators for the study. In addition, the length of time taken for data collection, as well as the days when the surveys were undertaken in each hospital, may have influenced admission patterns. However, despite these limitations, we believe the findings are robust providing future guidance.

5. Conclusions

The prevalence of antimicrobial prescribing among CHCs in South Africa was 21.5% and URTIs were the most frequently diagnosed condition. This resulted in amoxicillin being the most prescribed antimicrobial. It was encouraging to see high adherence to the South African EML-STG when antimicrobials were prescribed, with the majority of antimicrobials in the WHO Access list. However, there were concerns with the extent of antimicrobial prescribing for patients with URTIs, which are essentially viral in origin, coupled with a lack of sensitivity testing. Alongside this, not all antimicrobials were prescribed by INN. The establishment of pertinent ASPs among CHCs should help improve antimicrobial prescribing in the future. This could include more routine testing of patients to identify resistant organisms to help improve future empiric prescribing.

Acknowledgments

The authors gratefully acknowledge Ms Petra Gaylard, a consultation statistician, for the statistical analysis of the data. We thank all the Departments of Health in the provinces, and the hospital management of the participating hospitals for allowing us to collect data from there. We also thank the MPharm interns and the support staff at SMU for their assistance with data collection.

Conflicts of interest and funding

The study was funded by the ENAABLERS grant and as part of a Newton Scholarship awarded to Natalie Schellack, when at SMU, jointly funded by the South African Medical Research Council and UK Medical Research Council.

Disclosure of any financial/other conflicts of interest

The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed. Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Author Contributions

Conceptualization, NS, BG, DK, MB and JCM; methodology, PS, NS, DK and JCM; data curation and analysis, PS, NS, DK, and AK; writing—original PS and BBG.; writing—review and editing, all authors. All authors have read and agreed to the published version of the manuscript.

Data Availability Statement

Additional data is available on reasonable request.

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