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Antibiotic and antifungal use in paediatric departments at three academic hospitals in South Africa

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ABSTRACT

Objectives: South Africa implemented a National Strategic Framework to optimise antimicrobial stewardship in 2014; however, there is limited data on how this has affected prescribing, especially to children treated in academic centres.
Methods: We conducted a point prevalence survey using the World Health Organization (WHO) methodology to evaluate antibiotic and antifungal prescribing practices in paediatric departments at three academic hospitals in South Africa.
Results: We recorded 1946 antimicrobial prescriptions in 1191 children, with 55.2% and 39.2% of the antibiotics classified as WHO AWaRe Access and Watch drugs, respectively. There were significant differences in prescription of Reserve antibiotics and antifungals between institutions. Receipt of WHO Watch and Reserve antibiotics was independently associated with infancy (<12 months) and adolescents (13-17 years) (adjusted relative risk [aRR]: 2.09-9.95); prolonged hospitalisation (aRR: 3.29-30.08); rapidly or ultimately fatal illness (aRR: 1.94 to 5.52); and blood transfusion (aRR: 3.28-5.70). Antifungal prescribing was associated with treatment of hospital-associated infection (aRR: 2.90), medical prophylaxis (aRR: 3.30), and treatment in intensive care units (aRR: 2.15-2.27).
Conclusions: Guidance on optimisation of infection prevention and control practice and strengthening of antimicrobial stewardship would impact positively on the care of sick children in our setting.

Introduction

Overuse of antimicrobials leads to an accumulation of drug-resistance mutations in bacterial and fungal organisms, more difficult-to-treat infections, and increased mortality rates [1]. Drug-resistant infections will contribute to ~ 10 million deaths annually by the year 2050 [2]. Efforts have been made to increase clinician awareness of this threat through initiatives such as the World Health Organization (WHO) World Antimicrobial Resistance Awareness Week (WAAW), development of a tiered antibiotic classification by WHO (the AWaRe classification), and establishment of antimicrobial stewardship programmes (AMS) to guide rational prescribing.

In South Africa, a low-middle income country with a high burden of paediatric malnutrition, HIV type-1 exposure and infection, and tuberculosis, the Department of Health implemented a National Strategic Framework designed at rationalising antimicrobial prescribing nationwide, in 2014 [3]. From a 2018 South African antimicrobial point prevalence survey (PPS) of 18 public sector hospitals, provincial tertiary hospitals had the highest proportion of antimicrobials prescribed from the WHO Access category (66.4%). Antimicrobials from the Watch (32.3%) and Reserve (4.4%) groups were mainly prescribed at national central hospitals [4].

Although prior research has been done in South Africa to determine the prevalence of antimicrobial prescribing for paediatric patients in

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public sector hospitals [4,5], little has been conducted after widespread adoption of the National Strategic Framework. We undertook a prospective audit of antimicrobial prescribing in the paediatric departments of three academic hospitals in 2021 to 2022, and have previously reported a pooled antimicrobial prescribing prevalence of 22.9% (95% confidence interval: 15.5-32.5%) [6], which was lower than the antimicrobial point prevalence reported from a tertiary hospital in Cape Town (92%) [5] and in 18 public sector South African hospitals (49.7%) [4], from surveys conducted in 2015 and 2018, respectively. In this paper, we highlight the antimicrobials prescribed by treating clinicians at the three academic hospitals included in the survey, and the AWaRe classification of antibiotics recorded in the study.

Methods

The hospitals included in our survey, Chris Hani Baragwanath Academic Hospital (CHBAH), Steve Biko Academic Hospital (SBAH) (both in Gauteng Province) and Inkosi Albert Luthuli Central Hospital (IALCH; KwaZulu-Natal Province), were chosen in view of their multiple paediatric subspecialty services, including their capacity to treat paediatric patients referred for management of complex medical or surgical pathologies. IALCH and SBAH are quaternary referral hospitals, and CHBAH is a tertiary centre. Access to health services of CHBAH and SBAH functioned at all health care levels of service delivery while IALCH functioned only as a referral centre, the reasons for this being purely administrative and directed by the Provincial Departments of Health.

We used the WHO methodology for antimicrobial PPS on hospitalised patients [7] to evaluate antimicrobial prescriptions in children hospitalised at these three public sector teaching hospitals. Details on the inclusion and exclusion criteria for the study are reported elsewhere [6]. Briefly, children and adolescents aged from 0 days to 15 years were considered eligible for inclusion if they were hospitalised and prescribed systemic (oral or intravenous) antimicrobial therapy at 08h00 on each survey day. All sites enrolled participants weekly, on consecutive Wednesdays, until a sample size of 400 participants per site were enrolled. All children whose data are included in this analysis were sampled once, with no further collection of antimicrobial data if they were hospitalised over more than one week during the study period. Sites commenced the survey simultaneously on 22 September 2021, and the last participant was enrolled on 05 January 2022. In view of the large number of paediatric beds (>500 overall) at CHBAH, a sampling strategy was adopted at CHBAH as per WHO guidance [6,7].

Anonymised data on demographic characteristics, ward characteristics, microbiology results, and antimicrobial prescriptions were extracted from clinical notes and entered into REDCap electronic case report forms [8]. While data were captured on antiviral therapy, in addition to antibiotics and antifungals, the results presented here reflect the antimicrobial prevalence of antibiotic and antifungal prescriptions only.

We used the WHO AWaRe classification to categorize antibiotics into the Access, Watch and Reserve groups [9]. Antibiotics in the Access group are typically used to treat common infections, and should be accessible to prescribers working in outpatient clinics and all levels of hospital care in low-middle income countries. Examples of Access antibiotics are amoxicillin, co-amoxiclav, cloxacillin and co-trimoxazole. Antibiotics in the Watch group include those used to treat more severe infections, but are known to have a higher potential to promote resistance. Examples of Watch antibiotics include azithromycin, ceftriaxone, cefotaxime, ciprofloxacin and vancomycin. Antibiotics in the Reserve group are those that should be used under specialist guidance, and are prioritized as key targets for AMS programmes [9]. Colistin, linezolid and tigecycline are examples of Reserve antibiotics [9]. Certain antibiotics used to treat tuberculosis, e.g., ethambutol, ethionamide, isoniazid and pyrazinamide, are not included in the AWaRe classification system, and are termed Unclassified antibiotics. Rifampicin is a WHO Watch antibiotic [9].

Descriptive statistical analyses were undertaken to summarise the point prevalence, antimicrobial class, and AWaRe classification of the prescribed antimicrobials. For pairwise comparisons of antibiotic prescribing by AWaRe classification, P-values were adjusted for multiple comparison using the Benjamini-Hochberg method [10], and only results with adjusted two-sided *P*-values <0.001 were considered statistically significant. We conducted univariate and multivariable multinomial Poisson regression analyses to evaluate patient factors that were associated with receipt of WHO Watch and Reserve antibiotics, and antifungals. For Poisson regression analyses, two-sided *P*-values of <0.05 were considered statistically significant. Study sites are anonymised for the purposes of reporting.

Results

Antimicrobial prescriptions

We recorded 1946 antimicrobial prescriptions in 1191 children with a median age of 9 months (range, 0 to 180 months). The median length of hospitalisation at the time of survey was 5 days (interquartile range, 2 to 10 days). Characteristics of the participants, stratified by hospital, are presented in Table 1.

Most antimicrobials were administered parenterally (1610/1946; 82.7%), and prescribed for treatment of confirmed or presumed infection (1641/1946; 84.3%). A total of 251 antimicrobials (12.9%) were administered for prophylaxis. The most frequently prescribed antimicrobials were β-lactamase sensitive penicillins (15.5%), aminoglycosides (13.8%) and carbapenems (13.6%) (Table 2). Carbapenems were significantly more frequently prescribed in Hospital C (19.2%; 116/605 prescriptions) than in Hospital A (10.9%; 75/688 prescriptions) or Hospital B (11.2%; 73/653 prescriptions); *P*-value<0.001 for both comparisons.

AWaRe classification of antibiotics

Of the 1778 (91.4%) antibiotic prescriptions categorized using the WHO AWaRe classification, the Access group was most prevalent (55.2%), with 39.2% of prescriptions classified under the Watch group and 3.8% in the Reserve group (Figure 1a).

In pairwise comparisons, receipt of Reserve antibiotics was significantly more common in Hospital C compared to Hospital A; in the treatment of hospital-associated infections (HAIs) compared to community-acquired infections and surgical prophylaxis; in neonatal intensive care unit (NICU) and paediatric intensive care unit (PICU) compared to paediatric high-risk wards and paediatric medical wards; and in treatment of suspected or confirmed hospital-acquired infection/sepsis compared to treatment of community-onset presumed severe bacterial sepsis (Table 3).

Pairwise comparisons for Access, Watch and Unclassified antibiotics also revealed marked differences in the prevalence of prescribing by indication, ward type, speciality, and primary diagnosis (Figures 1c through 1f; data not shown). There were no significant differences in prescribing prevalence for Access, Watch and Unclassified antibiotics by hospital (Figure 1a). The only antibiotic class that was significantly associated with differences in prescribing prevalence in the age group stratified analysis, was the Unclassified group (i.e., anti-tuberculosis agents) which were prescribed in the 6-12 year age group (12/280, 4.3%) more frequently than in the neonatal age group (1/487, 0.2%) (data not shown).

The top eight primary indications for antimicrobial administration accounted for 90.0% of all diagnoses among the study participants. Hospital-acquired infection/sepsis (38.0%) and community-onset presumed bacterial sepsis (25.8%) were the most common primary diagnoses necessitating antimicrobial prescribing. Administration of Reserve antibiotics clustered exclusively among the children and adolescents with a primary diagnosis of hospital-acquired infection/sepsis (Figure 1e).

Table 1
Characteristics of study participants.

Parameter	Hospital A	Hospital B	Hospital C	Overall
n	390	395	406	1191
Median age (months, IQR)	12.00 [3.00, 60.00]	4.00 [0.00, 24.00]	11.00 [0.00, 48.00]	9.00 [1.00, 48.00]
Age category (%)				
0-28 days	47 (12.1)	118 (29.9)	123 (30.3)	288 (24.2)
29-364 days	137 (35.1)	124 (31.4)	86 (21.2)	347 (29.1)
1-5 years	115 (29.5)	97 (24.6)	112 (27.6)	324 (27.2)
6-12 years	90 (23.1)	49 (12.4)	76 (18.7)	215 (18.1)
13-17 years	1 (0.3)	7 (1.8)	9 (2.2)	17 (1.4)
Primary reason for antimicrobial use (%)				
GIT diseases	5 (1.3)	0 (0.0)	18 (4.4)	23 (1.9)
Lower respiratory tract infection	20 (5.1)	39 (9.9)	34 (8.4)	93 (7.8)
Medical prophylaxis	46 (11.8)	11 (2.8)	10 (2.5)	67 (5.6)
Meningitis	25 (6.4)	4 (1.0)	13 (3.2)	42 (3.5)
Nosocomial sepsis	117 (30.0)	143 (36.2)	122 (30.0)	382 (32.1)
Osteo-articular infections	2 (0.5)	27 (6.8)	10 (2.5)	39 (3.3)
Other	48 (12.3)	23 (5.8)	36 (8.9)	107 (9.0)
Sepsis	55 (14.1)	122 (30.9)	112 (27.6)	289 (24.3)
Surgical prophylaxis	67 (17.2)	22 (5.6)	34 (8.4)	123 (10.3)
Urinary tract infections	5 (1.3)	4 (1.0)	17 (4.2)	26 (2.2)
Secondary reason for antimicrobial use (%)				
Cancer	57 (14.6)	24 (6.1)	44 (10.8)	125 (10.5)
Cardiac pathology	46 (11.8)	7 (1.8)	19 (4.7)	72 (6.0)
Central nervous system pathology	62 (15.9)	27 (6.8)	25 (6.2)	114 (9.6)
GIT pathology	33 (8.5)	39 (9.9)	56 (13.8)	128 (10.7)
Injury/poisoning	10 (2.6)	23 (5.8)	14 (3.4)	47 (3.9)
Hospital-acquired infection/sepsis	3 (0.8)	46 (11.6)	2 (0.5)	51 (4.3)
Other	130 (33.3)	114 (28.9)	131 (32.3)	375 (31.5)
Prematurity	6 (1.5)	21 (5.3)	59 (14.5)	86 (7.2)
Respiratory pathology	29 (7.4)	35 (8.9)	11 (2.7)	75 (6.3)
Term neonate	14 (3.6)	59 (14.9)	45 (11.1)	118 (9.9)
Median length of stay (days, IQR)	6.00 [3.00, 13.00]	5.00 [2.00, 12.50]	4.00 [2.00, 7.00]	5.00 [2.00, 10.00]

Note: GIT = gastrointestinal tract; IQR = interquartile range.

Table 2
Antimicrobial use by Hospital and World Health Organization anatomical therapeutic chemical classification.

Anatomical therapeutic chemical drug classification	Hospital A	Hospital B	Hospital C	Total
n	688	653	605	1946
Beta-lactamase sensitive pencillin, Benzylpenicillin, Comb. of benzylpenicillin, procaine-benzylpenicillin	93 (13.5)	107 (16.4)	101 (16.7)	301 (15.5)
Aminoglycosides - Amikacin, Gentamicin, Tobramycin	90 (13.1)	90 (13.8)	88 (14.5)	268 (13.8)
Carbapenems - Ertapenem, Imipenem, Meropenem	75 (10.9)	73 (11.2)	116 (19.2)	264 (13.6)
Cephalosporins includes cefalexin, cefazolin sodium, cefotaxime, ceftazidime, ceftriaxone, cefepime	82 (11.9)	94 (14.4)	70 (11.6)	246 (12.6)
Antifungals includes Nystatin, Fluconazole, Voriconazole	93 (13.5)	76 (11.6)	29 (4.8)	198 (10.2)
Combinations of penicillins, including beta-lactamase inhibitors - Amoxicillin-clavulanate	11 (1.6)	70 (10.7)	87 (14.4)	168 (8.6)
Penicillins with extended spectrum, Tazobactam	65 (9.4)	50 (7.7)	18 (3.0)	133 (6.8)
Sulfonamides and trimethoprim	66 (9.6)	14 (2.1)	14 (2.3)	94 (4.8)
Glycopeptide antibacterial - Vancomycin	37 (5.4)	23 (3.5)	26 (4.3)	86 (4.4)
Beta-lactamase-resistant penicillins Cloxacillin, Flucloxacillin	17 (2.5)	15 (2.3)	5 (0.8)	37 (1.9)
Tuberculosis treatment - combination or prophylaxis	14 (2.0)	12 (1.8)	10 (1.7)	36 (1.8)
Linezolid	1 (0.1)	0 (0.0)	33 (5.5)	34 (1.7)
Polymyxins, Colistin	10 (1.5)	20 (3.1)	4 (0.7)	34 (1.7)
Other antibacterials includes Macrolide, Lincosamides, Tetracycline, Thiocarbarbamide derivative	13 (1.9)	7 (1.1)	4 (0.7)	24 (1.2)
Fluroquinolones - Ciprofloxacin, Moxifloxacin, Levofloxacin	21 (3.1)	2 (0.3)	0 (0.0)	23 (1.2)

Poisson regression models for prescribing of Watch and Reserve antibiotics

In multivariable multinomial Poisson regression analysis, receipt of Watch antibiotics was independently associated with age groups 0-28 days, 29-364 days, and 13-17 years (compared to the 6-12 year age group), length of hospitalisation at the time of the survey of 6 days or more, rapidly or ultimately fatal disease classification, and receipt of blood transfusion (Table 4). Similarly, receipt of Reserve antibiotics was associated with the 0-28 day, 29-364 day and 1-5 year old age groups (compared to the 6-12 year age group), longer period in hospital at the time of the survey, rapidly fatal or ultimately fatal diagnoses, and receipt of blood transfusion (Table 4). The magnitude of the adjusted risk ratios derived in the analysis for the covariates that were independently associated with receipt of Reserve antibiotics were generally greater than those for Watch antibiotics (Table 4).

Univariable analyses that did not contribute to variable selection in the multivariable model are tabulated in Supplemental Table 1.

Antifungal prescriptions

Antifungals were prescribed in 10.2% (198/1947) of all antimicrobial prescriptions, with 69.7% (n = 138) administered for treatment of HAI and 11.6% (n = 23) administered for medical prophylaxis. Receipt of antifungal agents was significantly more frequent in Hospital A (93/688, 13.5% prescriptions) and Hospital B (76/652, 11.7% prescriptions) compared to Hospital C (29/605, 4.8% prescriptions) (Supple-

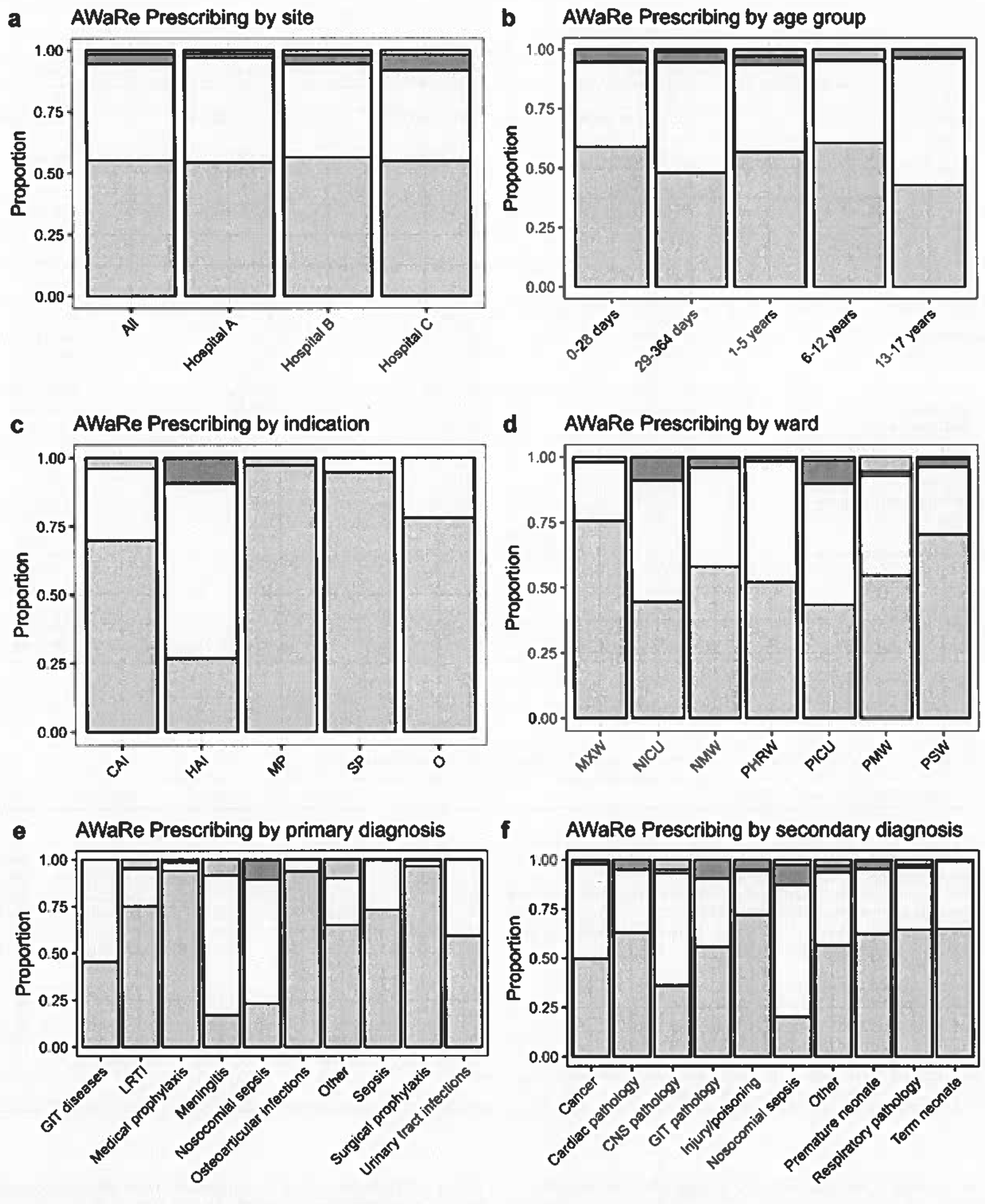

Figure 1. Prevalence of antibiotic prescribing stratified by different site and patient characteristics and World Health Organisation AWaRe classification.
CAI = community-acquired infection; HAI = hospital-associated infection; MP = medical prophylaxis; MXW = mixed ward; NICU = neonatal intensive care unit; NMW = neonatal medical ward; O = other indication; PHRW = pediatric high-risk ward; PICU = pediatric intensive care unit; PMW = pediatric medical ward; PSW = pediatric surgical ward; SP = surgical prophylaxis.

mental Figure 1a). Furthermore, prescription of antifungals was significantly associated with treatment of HAI, medical prophylaxis, treatment in NICU, PICU and paediatric high care wards, and for the management of hospital-acquired infection/sepsis events (Supplemental Figures 1c through 1f; data not shown).

Poisson regression models for prescribing of antifungals

In multivariable regression analysis, antifungal prescriptions were significantly more prevalent in Hospitals A and B compared to Hospital C (adjusted relative risk [aRR] 2.00 and aRR 2.48, respectively;

Table 3
Pairwise comparisons with adjusted *P*-values <0.001 to investigate for associations between key patient characteristics and reserve antibiotic prescriptions.

Group 1	Group 1 (%)	Group 2	Group 2 (%)	Adjusted *P*-value
Hospital				
Reserve in Hospital A	11/610 (1.8%)	Reserve in Hospital C	37/584 (6.3%)	<0.001
Indication	0/693 (0%)	Reserve in HAI	68/761 (8.9%)	<0.001
Reserve in community-acquired infection				
Reserve in HAI	68/761 (8.9%)	Reserve in surgical prophylaxis	0/154 (0%)	<0.001
Ward type	18/202 (8.9%)	Reserve in PHRW	6/360 (1.7%)	0.001
Reserve in NICU				
Reserve in PHRW	6/360 (1.7%)	Reserve in PICU	19/217 (8.8%)	0.001
Reserve in NICU	18/202 (8.9%)	Reserve in PMW	7/428 (1.6%)	<0.001
Reserve in PICU	19/217 (8.8%)	Reserve in PMW	7/428 (1.6%)	<0.001
Primary diagnosis	66/636 (10.4%)	Reserve in Sepsis	1/484 (0.2%)	<0.001
Reserve in hospital-acquired infection/sepsis				

Note: HAI = hospital-associated infection; NICU = neonatal intensive care unit; PHRW = paediatric high-risk ward; PICU = paediatric intensive care unit; PMW = paediatric medical ward.
P-values adjusted using the Benjamini-Hochberg method.

Table 4
Unadjusted and adjusted models of predictors of paediatric antimicrobial use according to the World Health Organization AWaRe classification in 957 patients at three academic hospitals in South Africa, 22 September 2021-05 January 2022.

	Characteristic	Relative risk (95% confidence interval)	*P*-value	Adjusted relative risk (95% confidence interval)	*P*-value
Age					
Receipt of watch antibiotics	6-12 years	Reference		Reference	
	0-28 days	1.62 (0.77-3.42)	0.204	2.09 (1.03-4.22)	0.041
	29-364 days	2.19 (1.16-4.15)	0.016	2.45 (1.42-4.23)	0.001
	1-5 years	1.06 (0.70-1.62)	0.775	1.36 (0.94-1.97)	0.107
	13-17 years	2.52 (1.11-5.72)	0.027	4.00 (1.67-9.59)	0.002
Receipt of reserve antibiotics	6-12 years	Reference		Reference	
	0-28 days	12.01 (2.75-53.25)	0.001	16.21 (2.86-91.83)	0.002
	29-364 days	10.79 (2.62-44.34)	0.001	9.95 (2.43-40.79)	0.001
	1-5 years	5.53 (1.09-27.96)	0.039	7.54 (1.44-39.51)	0.017
	13-17 years	10.08 (0.77-132.40)	0.079	No estimate	-
Duration of hospitalisation at time of survey					
Receipt of watch antibiotics	<3 days	Reference		Reference	
	3-5 days	1.48 (0.98-2.25)	0.061	1.32 (0.78-2.24)	0.299
	6-10 days	3.36 (1.88-6.03)	<0.001	3.27 (1.72-6.21)	<0.001
	11+ days	5.15 (2.43-10.88)	<0.001	4.10 (1.81-9.29)	0.001
Receipt of reserve antibiotics	<3 days	Reference		Reference	
	3-5 days	5.73 (1.91-17.22)	0.002	4.18 (1.38-12.63)	0.011
	6-10 days	11.31 (3.69-34.70)	<0.001	9.44 (3.44-25.87)	<0.001
	11+ days	45.60 (14.73-141.18)	<0.001	30.08 (10.03-90.19)	<0.001
McCabe Score of illness severity					
Receipt of watch antibiotics	All other	Reference		Reference	
	Rapidly or ultimately fatal	2.25 (1.29-3.93)	0.004	1.94 (1.07-3.52)	0.029
Receipt of reserve antibiotics	All other	Reference		Reference	
	Rapidly or ultimately fatal	6.65 (2.34-18.85)	<0.001	5.52 (1.95-15.58)	0.001
Receipt of blood transfusion					
Receipt of watch antibiotics	No	Reference		Reference	
	Yes	3.28 (1.86-5.78)	<0.001	2.48 (1.50-4.11)	<0.001
Receipt of reserve antibiotics	No	Reference		Reference	
	Yes	5.70 (2.00-17.85)	0.001	3.84 (1.41-10.48)	0.009

Supplemental Table 2). Furthermore, antifungal prescriptions were significantly associated with treatment of HAI (aRR 2.90), and for medical prophylaxis (aRR 3.30) (Supplemental Table 2). Receipt of care in NICU and PICU was also significantly associated with antifungal prescribing (aRR 2.27 and 2.15, respectively) (Supplemental Table 2).

Discussion

Our study highlights the spectrum of antimicrobial utilisation in paediatric departments at three academic hospitals in South Africa, as ascertained through a prospective audit of antimicrobial prescribing conducted using the WHO PPS methodology during the COVID-19 pandemic. WHO Access antibiotics comprised 55.2% of all antibiotic prescriptions, although there was considerable reliance on the use of Watch antibiotics overall (39.2%). Hospital C had the lowest prevalence of antimicrobial prescribing [6], yet had a significantly higher prevalence of Reserve antibiotic prescribing compared to Hospital A, and a higher rate of carbapenem prescribing than either Hospital A or B. On the other hand, Hospital C had a significantly lower prevalence of antifungal usage, compared to Hospitals A and B. Reasons for these differences in antimicrobial prescribing between facilities may have arisen due to differences in patient characteristics, treatment protocols or institutional and unit level antibiograms.

We have previously described the marked differences in antimicrobial prescribing by clinicians at the three academic hospitals included in this survey, with the point prevalence in antimicrobial prescribing ranging from 14.1% in Hospital C to 40.8% in Hospital B [6]. These differences likely reflect a mix of innate and potentially modifiable factors which impact on antimicrobial prescribing. Innate factors include functionality of the three institutions and type of patients managed at each facility. Hospital C has a particularly robust AMS programme, optimised by daily clinician reviews of prescription charts and rationalisation of antimicrobial prescriptions based on laboratory results. Optimisation of AMS services has been shown to have a favourable impact on antimicrobial prescribing to neonates and children [11,12], and may be further strengthened through the adoption of digital platforms to assist clinician prescribing [13].

This is one of the first antimicrobial point prevalence studies emanating from South Africa to describe antibiotic prescribing in terms of the WHO AWaRe classification system. Skosana et al. [4] described the antibiotic prescribing prevalence in paediatric inpatients at 18 public sector hospitals, in which Access antibiotics were administered in 55.9% of prescriptions overall, with considerable variability in the prevalence of Access antibiotic prescribing (ranging from 48.9% to 65.3%) depending on the type of hospital surveyed. A multinational study (NeoOBS), which included South African participants, presented the spectrum of antibiotic prescribing for neonatal patients in terms of the WHO AWaRe classification [14] and highlighted widely varying usage of Access, Watch and Reserve class antibiotics in the 19 participating Neonatal Units. In NeoOBS, Watch antibiotics were used empirically in 34.0% of hospitalised infants <60 days of age that were treated for suspected sepsis, and the use of Access antibiotics was observed in 39.7% [14].

Clinician decisions around antimicrobial prescribing in critically ill children vary by geographic and cultural context, with decisions around choice and duration of therapy being dictated based on patient characteristics, radiological findings and type of pathogen isolated [15]. In the Global Antimicrobial Resistance, Prescribing, and Efficacy in Neonates and Children (GARPEC) network PPS which reported on antimicrobial usage in over 23,000 children from 56 countries, Access antibiotics were frequently prescribed in Chile (59.0%), Slovenia (61.2%) and Spain (59.8%) and uncommonly used in China (7.8%) [16]. Use of Access antibiotics was estimated at approximately 60% in South Africa, and in up to 70% of South African children hospitalised with a lower respiratory tract infection, but were infrequently (33.3%) used in South African neonates [16].

A PPS of antimicrobial utilisation from five hospitals in Japan which included information on antimicrobials administered to paediatric patients, elucidated clinician dependence on Watch and Access antibiotics (in 54.4% and 43.1% of prescriptions, respectively) [17]. Similarly, in India 42.4% of intravenously administered antibiotics were of the WHO Access class, and 53.1% were WHO Watch antibiotics [18], while only 50.4% of outpatient antibiotic prescriptions were for drugs of the Access class [19]. Considering that the WHO target for Access antibiotic usage is 60% of all prescribed antibiotics [20,21], data observed through our current analysis (in which the prevalence of Access antibiotic usage was 55.2%), other studies from South African [4,14,16] and elsewhere which showed Access prescribing prevalence <60% is concerning.

Treatment with all classes of antibiotics drives accumulation of resistance in colonising microflora, and is associated with increased odds of colonisation or infection with multidrug-resistant organisms. Previous exposure to Access group antibiotics has been associated with a 1.6-fold increased odds of subsequent detection of extended-spectrum β-lactamase producing *Enterobacteriales* in a pooled meta-analysis of paediatric and adult studies, with restriction of the analysis to adult-only studies showing a lower odds (odds ratio 1.3, 95% confidence interval 1.1 to 1.5) of extended-spectrum β-lactamase *Enterobacteriales* detection [22]. Watch and Reserve antibiotic exposures have an even greater propensity to result in colonisation and/or infection with multidrug-resistant organisms [22].

In our analysis, risk factors independently associated with receipt of Watch and Reserve antibiotics included age (infants and adolescents compared to children aged 6 to 12 years), hospitalisation for >6 days at the time of the survey, underlying condition classified as rapidly or ultimately fatal, and receipt of blood transfusion. Point estimates of the adjusted risk associated with receipt of Reserve antibiotics according to age group and duration of hospitalisation had wide confidence bounds, indicating a high degree of imprecision because of the finite sample size of our study cohort. These factors imply prescription of antimicrobials to infants, children and adolescents with complicated disease processes. Optimisation of care, with careful adherence to infection prevention and control (IPC) measures, in the management of these vulnerable populations would be anticipated to limit the number of suspected or confirmed HAI episodes, and decrease clinician prescribing of Watch and Reserve antibiotics although not as yet demonstrated in studies comparing 'standard of care' to 'optimised IPC'.

Factors independently associated with receipt of antifungals in our analysis included institution in which care was delivered, treatment for HAI and in medical prophylaxis, and treatment in intensive care settings. A systematic review of antifungal prophylaxis in critically ill surgical patients found that receipt of antifungal prophylaxis prevented fungal infections, but had no impact on survival rates [23]. The authors cautioned that indiscriminate use of azoles may lead to increased rates of resistance to antifungals [23]. A Cochrane review of prophylactic antifungal use in critically ill, non-neutropenic patients (22 studies, 2761 participants) further indicated that all-cause mortality is not impacted by untargeted antifungal treatment, and made a recommendation that emergence of resistance to antifungals be incorporated as an outcome of interest in future trials evaluating the utility of antifungal prophylaxis [24]. There are conflicting reports on the emergence of resistant fungal strains in neonatal units following long-term utilisation of routine antifungal prophylaxis, with a site in Finland describing an increased prevalence of resistant fungi after 10 years of antifungal prophylaxis [25] and a site in Italy describing no impact on the emergence of resistance after 16 years of utilisation of this prophylactic approach [26]. A meta-analysis of antifungal prophylaxis administered to preterm infants indicated that, among five clinical trials that reported on the emergence of resistance subsequent to implementation of antifungal prophylaxis, only one observed an increase over time in the minimum inhibitory concentration to fluconazole [27].

Our study has limitations. We relied on collection of routine clinical data for our analyses, the quality of which may not have been optimised for robust analytic outputs, for example through numerous missing data points which impacted on the number of participants included in our multivariable Poisson regression models. Our survey was conducted in three academic paediatric departments, and therefore cannot be generalised to other facilities in South Africa's public health sector. A PPS of 18 South African health care facilities revealed substantial differences in prevalence of antimicrobial prescribing at different levels of care, and serves to illustrate the variability in prescribing across sites [4]. Serial point prevalence surveys of antimicrobial usage across a wide range of facilities, as is currently underway as part of the Global PPS [28], are crucial in terms of evaluating trends in antimicrobial prescribing over time and will assist in evaluating optimisation of AMS and IPC services across institutions at the national and global level [29].

Conclusion

We observed considerable differences in the prevalence of antibiotic and antifungal prescribing, and patterns of antimicrobials prescribed, between the three academic centres included in our survey. This variability in prescribing practice speaks to an urgent need to formalise guidance around judicious antibiotic and antifungal use, optimisation of AMS activities, and closer attention to detail in terms of preventing infection in hospitalised children. Our findings need to be considered in the light of treatment of infants, children, and adolescents with complicated disease processes, accessing care in referral facilities in a low-middle income setting.

Declarations of competing interest

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Ethical approval

This study was approved by the Ethics Review Committees of the University of the Witwatersrand and University of Pretoria Faculties of Health Sciences (clearance numbers: M201132 and EC023-5/2021). Reciprocal approval was obtained for the University of KwaZulu-Natal site (clearance number: 151/2020) from the University of the Witwatersrand approval. Participant informed consent and/or assent were waived as personal identifying information was not collected, with all data obtained through folder review of clinical notes.

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Author contributions

DPM contributed to data collection, data cleaning, analysis, interpretation of results, drafting of the manuscript and finalisation of the manuscript for submission for peer review and publication; TC contributed to study oversight, data cleaning and analysis, interpretation of results and approval of the manuscript; AvK, AP, FLN, JC, MA, MK, SM, RT and ZN contributed to data collection, data cleaning and interpretation of results, and approval of the manuscript; YS and TR contributed to data cleaning, analysis and interpretation of results, and approval of the manuscript; AG and PJ secured funding for the study, contributed to study oversight, data analysis, interpretation of results, refinement of the initial drafts of the manuscript, and approval of the final draft thereof.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijregi.2023.12.004.

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