Healthcare-Associated Infections Drive Antimicrobial Prescribing in Pediatric Departments at Three Academic Hospitals in South Africa

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Background: The prevalence of antimicrobial prescriptions for healthcare-associated infections (HAI) in South Africa is largely unknown. This study aimed to estimate the point prevalence of pediatric antibiotic and antifungal usage in 3 South African academic hospitals.

Methods: This cross-sectional study included hospitalized neonates and children (0–15 years). We used the World Health Organization methodology for antimicrobial point prevalence studies, with weekly surveys to achieve a sample size of ~400 at each site.

Results: Overall, 1,946 antimicrobials were prescribed to 1,191 patients. At least 1 antimicrobial was prescribed for 22.9% [95% confidence interval (CI): 15.5–32.5%] of patients. The prevalence of antimicrobial prescribing for HAI was 45.6%. In the multivariable analysis, relative to children 6–12 years, neonates [adjusted relative risk (aRR): 1.64; 95% CI: 1.06–2.53], infants (aRR: 1.57; 95% CI: 1.12–2.21) and adolescents (aRR: 2.18; 95% CI: 1.45–3.29) had significantly increased risk of prescriptions for HAI. Being preterm (aRR: 1.33; 95% CI: 1.04–1.70) and underweight (aRR: 1.25; 95% CI: 1.01–1.54) was predictive of antimicrobial usage for HAI. Having an indwelling device, surgery since admission, blood transfusions and classification as rapidly fatal on McCabe score also increased the risk of prescriptions for HAI.

Conclusions: The high prevalence of antimicrobial prescribing for HAI to treat children with recognized risk factors in academic hospitals in South Africa is concerning. Concerted efforts need to be made to strengthen hospital-level infection prevention and control measures, with a critical review of antimicrobial usage through functional antibiotic stewardship programs to preserve the available antimicrobial armamentarium at the hospital level.

Key Words: antimicrobial consumption, pediatric, neonatal, healthcare-associated infections

(*Pediatr Infect Dis J* 2023;42:e283–e289)

Antimicrobial overuse is an important contributor to the development of antimicrobial resistance worldwide. High consumption is seen among pediatric inpatients due to infectious pathologies, nonspecific disease presentations, including sepsis,[1] and difficulty excluding various infections. Antimicrobial usage for pediatric inpatients ranges from 33% to 93%.[2,3] Challenges exist in balancing appropriate antimicrobial access with avoiding excessive use, particularly in low-to-middle-income (LMIC) settings.[4]

In South Africa with its multiple burdens of HIV, tuberculosis, malnutrition, novel coronavirus disease (COVID-19) and prematurity, antimicrobial usage for neonatal and pediatric healthcare-associated infections (HAI) is under-researched.

HAIs are associated with increased antibiotic usage, which may drive antimicrobial resistance.[5] Antimicrobial use for HAIs ranged from 14.4% in 2012 in African countries to 29% in a South African hospitals in 2018.[3,5] From sparse South African literature in hospitalized neonates and children, HAI is due to bloodstream infections, urinary tract infections and hospital-acquired pneumonia.[6–8] In a 2016 cross-sectional Kenyan study of pediatric HAI, the point prevalence of culture-positive bacterial HAI was 2.6% [95% confidence interval (CI): 2.8–6.7].[9] *Klebsiella pneumoniae* (36.4%), *Enterococcus cloacae* (18.2%) and *Pseudomonas aeruginosa* (9.1%) were the commonest organisms isolated.[9] Risk factors

Accepted for publication April 4, 2023
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This study was funded by UNICEF (grant number ZAR/PCA2021212/PD2021219-1). D.P.M. is, in part, supported by a grant awarded by the Carnegie Corporation of New York.

The authors have no conflicts of interest to disclose.
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Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (www.pidj.com).

ISSN: 0891-3668/23/428-e283-e289
DOI: 10.1097/INF.0000000000003954

for HAI included prematurity, malnutrition, intensive care admission and having indwelling devices.[7,10–12] HIV exposure and infection are also HAI risk factors in South African children.[7,13]

Neonatal infections and sepsis justify prompt treatment with antimicrobial agents, especially antibiotics.[14,15] In a cross-sectional survey in neonatal intensive care units, antimicrobial use varied from 17% to 48% in LMIC.[12] Therapy was mainly empiric (55%, 293/531), with 38% for specific infections.

Sparse data exist on whether HAI drives antimicrobial use in LMIC settings. This study aimed to evaluate pediatric antimicrobial usage for HAI in 3 academic public sector hospitals in South Africa.

MATERIALS AND METHODS

Study Design and Participation

We conducted a cross-sectional point prevalence survey (PPS) of all neonates and children admitted to neonatal and pediatric wards at the Chris Hani Baragwanath Academic Hospital (CHBAH) and Steve Biko Academic Hospital (SBAH) in Gauteng and Inkosi Albert Luthuli Hospital (IALCH) in KwaZulu-Natal, every Wednesday between September 22, 2021 and January 05, 2022 until study sample sizes were reached. Institutions were randomly assigned as hospital A, B and C. World Health Organization (WHO) methodology for estimating antibiotic use was implemented.[16]

The admission age at each hospital is 0–16 years. As per study protocol, we surveyed all hospitalized patients (0–15 years) with an antimicrobial prescription at 08:00 h on each survey day from pediatric medical, pediatric surgical, neonatal medical, neonatal surgical, pediatric high risk, pediatric intensive care and neonatal intensive care wards (see Table, Supplemental Digital Content 2, http://links.lww.com/INF/F37). These included short-stay and urgent care wards. The following patients were not considered: patients previously recruited into the survey during the same admission; patients undergoing treatment or surgery and discharged on the same day; patients in outpatient departments; discharged patients awaiting transportation; patients receiving outpatient parenteral antibiotic therapy; patients with only antiviral prescriptions and patients receiving topical or ophthalmologic antibiotics.

Patient Sampling

The antimicrobial prevalence among hospitalized patients was estimated at 40% with ± 4% precision nationally.[16] A minimum sample size of 384 children per hospital was required to estimate prevalence rates ranging from 30% to 40% within a 6% error margin, considering a design effect of 1.5 per site. Each hospital aimed to recruit 400 patients to account for poor data quality. As CHBAH has more than 500 neonatal and pediatric inpatient beds, alphabetized ward patient lists were compiled on survey days, and every second patient was sampled and included if eligibility was met. SBAH and IALCH surveyed all hospitalized pediatric patients on survey days.

Variables

Data were collected from inpatient records and antimicrobial prescriptions for all eligible children. Hospital data included hospital type, size, beds and patients. Ward data included ward type and number of eligible patients surveyed. Individual patient data included demographics, risk factors, and detailed antimicrobial prescription data (type, dose, duration, administration route, indication, and diagnoses). Patients were categorized as neonates (0–28 days), infants (29–364 days), children (1–5 years and 6–12 years) and adolescents (13–15 years). Microbiology data included specimen type, culture result, microorganism, antibiotic susceptibility test results and resistant phenotype. Where cultures of possible contaminants or pathogens were identified, relevant clinical records were reviewed, and organisms were assigned accordingly. We used the anatomical therapeutic chemical groups to classify antimicrobial agents for systemic use: J01 (antibacterial for systemic use), J04A (antimycobacterial for tuberculosis) and D01B (antifungals for systemic use). Data on co-trimoxazole prophylaxis for *Pneumocystis jirovecii,* and antivirals (including antiretrovirals) were also included. We extracted organism and antimicrobial sensitivity data from the National Health Laboratory Service database. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) positive status was assigned in patients who tested positive for SARS-CoV-2 on real-time reverse transcriptase polymerase chain reaction testing.

Study Definitions

Antimicrobials were defined as antibiotic and antifungal prescriptions. HAI included any infection that was neither present nor incubating at admission or in children readmitted to the hospital within 2 weeks of a previous hospitalization episode.[11] Children with infections before the current hospital admission were classified as having a community-acquired infection (CAI).[10] We defined antimicrobial prophylaxis as antimicrobial prescriptions to prevent inpatient medical or surgical infections. High-risk wards were pediatric or adult high/intensive care, burn unit, hematology-oncology and COVID-19 wards. Clinically significant coagulase staphylococcal infections were assigned in high-risk participants (eg, premature neonates or hematology-oncology patients) with cultures positive for clinically significant coagulase staphylococcal that were treated with antimicrobial agents (ie, vancomycin or linezolid) targeted at treating this infection.

Z scores were used to assign normal and underweight children. As premature infants were inappropriately assigned as underweight using WHO growth standards, ages of children born premature were first corrected, and weight for age Z scores was assigned using PediTools.[17] Birth and current weights (up to 50 weeks) were categorized using the 2013 Fenton methodology.[18] A hybrid model utilizing prematurity status, clinical assessment and gestational age at birth was applied for a composite nutritional assessment. WHO growth standards were used for premature children over 50 weeks and term children.[17]

Data Analysis

Data were captured at participating hospitals in the web-based REDCap application (https://projectredcap.org/resources/citations/) with anonymized data entry and validation.

Descriptive statistical methods assessed frequency distributions and cross-tabulations. Overall and categorized ward and site indices included: antimicrobial prescription prevalence rate; mean antimicrobial number per patient; prescription indication (empiric or directed) (CAI, HAI or prophylaxis); antimicrobial spectrum prescribed (antibacterial, antimycobacterial, or antifungal) and proportional contribution to overall antimicrobial usage.

We calculated antimicrobial prescribing for HAI prevalence, stratified by ward, discipline, and hospital, with 95% CI. CAI and HAI were treated independently with a small overlap in each group. We converted risk factor data from continuous to binary categorical variables where needed.

Separate univariable and multivariable Poisson regression analyses were conducted to test variables for association with HAI (risk factors with P values <0.1 were included in multivariable

models). As HAI prevalence was high, we reported relative risk instead of odds ratios (which would overestimate the effects).[22] We compared differences in antimicrobial use and indications between hospitals using χ^2 tests or Fisher exact test where appropriate. Data were analyzed overall and across sites using STATA version 16 (Stata Corp., College Station, TX).

Ethics

The South African Medical Council, University of Witwatersrand, University of Pretoria, and University of KwaZulu-Natal Research Ethics Committee (EC023-5/2021, M201132; 151/2020, respectively) approved the study. We obtained site-specific institutional and provincial approvals. As personal identifying data other than birth dates were not collected, informed consent was waivered, and staff privacy was ensured. The study took a no-blame approach to antimicrobial prescribing and usage. Hospital data were anonymized when reporting study results.

TABLE 1. Prevalence of Antimicrobial (antibiotic and antifungal) Consumption Across 3 Academic Hospitals in South Africa, September 22, 2021–January 5, 2022

Hospital Type	Total Patients	Number of Patients Prescribed an Antibiotic or Antifungal	Prevalence (%) of Antibiotic or Antifungal use (95% CI)	Number of Antibiotic or Antifungal Prescriptions	Average Number of Antibiotic or Antifungal Prescriptions per Patient, Mean (SD)
Hospital A	1342	390	29.1 (16.3–46.3)	688	1.8 (0.9)
Hospital B	969	395	40.8 (22.0–62.6)	653	1.7 (0.8)
Hospital C	2889	406	14.1 (8.2–23.0)	605	1.5 (0.6)
Total	5200	1191	22.9 (15.5–32.5)	1946	1.6 (0.8)

RESULTS

There were 1,191 patients with 1,946 antimicrobial prescriptions (Table 1), of which 1,167 patients had antibiotic prescriptions and 125 patients had antifungal prescriptions. Patient distribution were as follows: 390 from Hospital A (32.7%), 395 (33.2%) from Hospital B and 406 (34.1%) from Hospital C. Hospital A surveyed 1,342 patients over 10 days (~134.2 patients per survey day), Hospital B surveyed 969 patients over 6 days (~161.5 patients per survey day), and Hospital C surveyed 2,889 patients over 16 days (~180.6 patients per survey day).

Antimicrobial Prevalence

The antimicrobial prevalence was 22.9% (1,191/5,200; 95% CI: 15.5–32.5%) at the 3 hospitals (Table 1). The antimicrobial point prevalence was 29.1% at Hospital A (95% CI: 16.3–46.3%), 40.8% at Hospital B (95% CI: 22.0–62.6%) and 14.1% at Hospital C (8.2–23.0%). The mean prescription per patient was 1.6 (SD: 0.8]). The commonest prescribed antibiotics in neonates and infants were β-lactamase sensitive penicillins, aminoglycosides and carbapenems. Children and adolescents were frequently prescribed a combination of penicillins and carbapenems, respectively (Fig. 1).

Patient Characteristics

Overall, 1,076 prescriptions were administered to males (55.3%) (Table 2). The median age was 9 months [interquartile range (IQR): 1–48 months]. The study population mainly comprised infants (29.1%), children aged 1–5 years (27.2%) and neonates (24.2%).

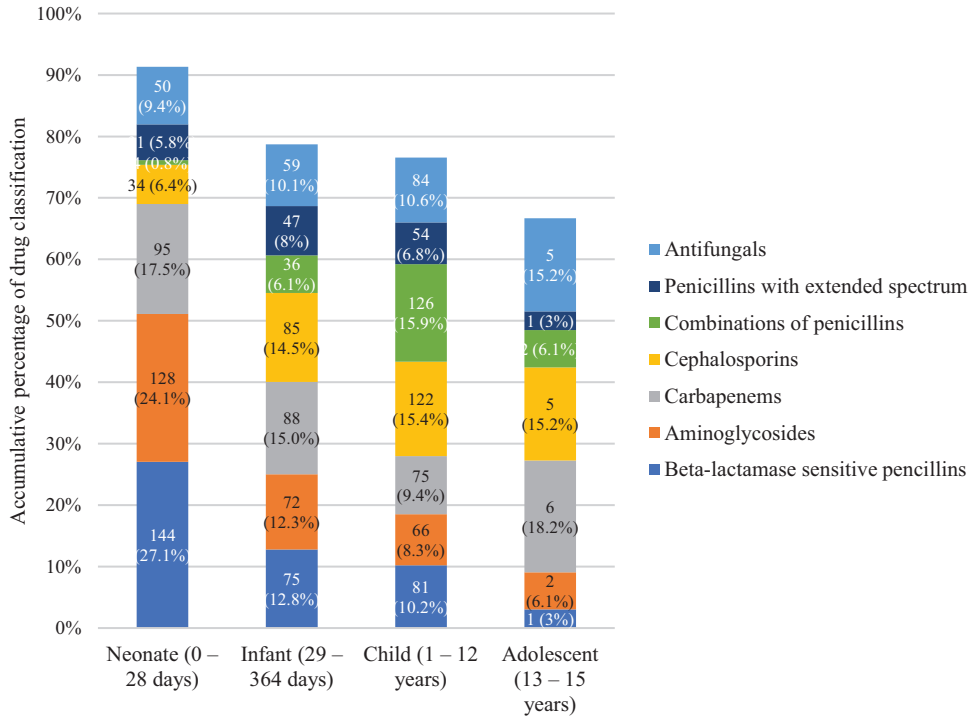

FIGURE 1. Classification of pediatric antimicrobial use by age group and WHO anatomical therapeutic chemical (ATC) classification at 3 academic hospitals in South Africa, September 22, 2021–January 05, 2022 – Most prescribed.

TABLE 2. Demographics of the Pediatric Study Population at 3 Academic Hospitals in South Africa, September 22, 2021–January 5, 2022

Characteristic	Number of Children (%), n = 1191	Number of Prescriptions (%), n = 1946
Sex*		
Male	665 (55.8)	1076 (55.3)
Female	525 (44.1)	869 (44.7)
Age in months, median (IQR)	9 (1–48)	n/a
Age category		
Neonate (0–28 days)	288 (24.2)	532 (27.3)
Infant (29–364 days)	347 (29.1)	587 (30.2)
Child (1–5 years)	324 (27.2)	487 (25.0)
Child (6–12 years)	215 (18.1)	307 (15.8)
Adolescent (13–15 years)	17 (1.4)	33 (1.7)
HIV status		
HIV-infected	33 (2.8)	70 (3.6)
HIV uninfected, exposed	189 (15.9)	328 (16.9)
HIV uninfected, unexposed	529 (44.4)	891 (45.8)
HIV uninfected, unknown exposure	168 (14.1)	274 (14.1)
HIV unknown	272 (22.8)	383 (19.7)
COVID-19 status		
COVID-19 positive	54 (4.5)	83 (4.3)
COVID-19 negative	1085 (91.1)	1791 (92.0)
COVID-19 unknown	52 (4.4)	72 (3.7)
Length of stay at the point of study enrolment [in days, median (IQR)]	5 (2–10)	n/a
Ward		
Pediatric medical	293 (24.6)	451 (23.2)
Pediatric surgical	242 (20.3)	313 (16.1)
Neonatal medical	140 (11.8)	232 (11.9)
Pediatric ICU	114 (9.6)	252 (12.9)
Neonatal ICU	123 (10.3)	243 (12.5)
Pediatric high risk	240 (20.2)	406 (20.9)
Mixed	39 (3.3)	49 (2.5)
Indication for antimicrobial/s		
HAI		887 (45.6)
Non-HAI		1059 (54.4)
CAI		708 (36.4)
Prophylaxis (medical)		96 (4.9)
Prophylaxis (surgical)		155 (8.0)
Other†		100 (5.1)

*Missing for n = 1.

†Congenital infection, disease-modifying agent, prophylaxis for malignancies, neonatal sepsis.

CAI indicates community-acquired infection; HAI, healthcare-associated infection;

Six of 17 adolescent patients prescribed antimicrobials (35.3%) had malignancies with the remainder having infective diagnoses. Most patients were distributed across pediatric medical (24.6%), surgical (20.3%) and high-risk wards (20.2%) (Table 2).

Of the 33 HIV-infected children (2.8%), 28 were on antiretroviral therapy (84.8%), and 2 were newly diagnosed with HIV infection and still on nevirapine prophylaxis (6.1%) on survey days (see Text, Supplemental Digital Content 1, http://links.lww.com/INF/F36, for additional data on HIV-infected children). There were 70 antimicrobial prescriptions in HIV-infected children (excluding co-administered antiretroviral therapy).

In 54 SARS-CoV-2 positive patients (4.5%), there were 83 antimicrobial prescriptions (Table 2). Overall, the antimicrobial prevalence in children with COVID-19 was 48.2% (54/112).

Antimicrobials were mainly indicated for HAI (45.6%, n = 887 prescriptions). Non-HAI prescriptions (54.4%) included CAI (36.4%), medical prophylaxis (4.9%), surgical prophylaxis (8.0%) and other prescriptions (Table 2). The median hospitalization length at enrolment was 5 days (IQR: 2–10 days).

Primary Reasons for Antimicrobial Use (All Indications and All Populations)

Antimicrobials were most frequently prescribed for nosocomial sepsis (32.1%), clinical sepsis (24.1%), surgical prophylaxis (10.3%), lower respiratory tract infections (7.7%) and medical prophylaxis (5.5%) with secondary reasons being term infants (9.9%), prematurity (7.2%), cancer (6.2%) and anomalies of the gastrointestinal tract (6.5%), central nervous system (6.1%) and cardiac system (6.0%) (see Table 3 and Table, Supplementary Digital Content 2, http://links.lww.com/INF/F37 for reasons for antimicrobial use by ward).

Organisms Identified by Culture

There were 323 organisms cultured from various specimens; 78 were clinically nonsignificant (24.1% culture contamination rate). There were 11 clinically significant cultures; 4 were blood and cerebrospinal fluid, 6 were blood cultures and 1 was neither blood nor cerebrospinal fluid. Of the 224 clinically significant organisms, the most frequently cultured organisms were *Acinetobacter baumannii* (16.1%), *Klebsiella pneumoniae* and *Staphylococcus aureus* (9.4% each) (Figure, Supplemental Digital Content 3, http://links.lww.com/INF/F38).

Characteristics of HAI

The median hospitalization length on the survey day was 9 days for HAI (IQR: 5–19 days) (n = 458). Over 55.0% of patients with HAI were referred to study hospitals from other healthcare settings. Patients with HAI were distributed across pediatric high-risk

TABLE 3. Top 10 Primary and Secondary Reasons for Pediatric Antimicrobial Use (n = 1191 patients) at Three Academic Hospitals in South Africa, September 22, 2021–January 05, 2022

Primary Reason For Antimicrobial Use (Relating To Main Diagnosis and Reason for Hospitalisation)	n (%)	Number of Prescriptions Per Child; Mean (SD)
Nosocomial sepsis	382 (32.1)	1.9 (0.9)
Sepsis	287 (24.1)	1.7 (0.7)
Surgical prophylaxis	123 (10.3)	1.1 (0.3)
Lower respiratory tract infection	92 (7.7)	1.6 (1.0)
Medical prophylaxis	66 (5.5)	1.2 (0.5)
Central nervous system infection	42 (3.5)	1.5 (0.8)
Bone and soft tissue infection	32 (2.7)	1.2 (0.5)
Infections of the genito-urinary tract	25 (2.1)	1.1 (0.3)
Upper respiratory tract infection	23 (1.8)	1.3 (0.9)
Gastroenteritis or colitis of infectious origin	15 (1.3)	1.5 (0.8)

Secondary (underlying) reason for antimicrobial use*	n (%)	Number of prescriptions per child; mean (SD)
Term neonate	118 (9.9)	1.9 (0.6)
Prematurity	86 (7.2)	1.6 (0.6)
Anomalies of the gastrointestinal tract	77 (6.5)	1.8 (0.8)
Hematological malignancies	74 (6.2)	1.7 (0.9)
Congenital abnormalities of the central nervous system	73 (6.1)	1.6 (0.8)
Anomalies of the cardiac system	72 (6.0)	1.5 (0.8)
Diseases of the respiratory system	66 (5.5)	1.8 (1.0)
Non-hematological malignancies	51 (4.3)	1.9 (0.7)
Injury, poisoning or certain other consequences of external causes	47 (3.9)	1.3 (0.5)
Anomalies of the face, mouth, or teeth	44 (3.7)	1.1 (0.3)
Diseases of the central nervous system	41 (3.4)	1.3 (0.6)

*No secondary reason for antimicrobial use in 102 patients (8.6%).

wards (19.2%), neonatal intensive care units (18.3%), intensive care units (17.9%), neonatal medical (16.8%), pediatric surgical (13.1%) and pediatric medical wards (10.6%). The commonest reason for HAI antimicrobials was nosocomial sepsis (91.9%). Antifungals, penicillins with the extended spectrum, and aminoglycosides were most prescribed for HAI (n = 887) (Supplementary Digital Content 4, http://links.lww.com/INF/F39 and Supplementary Digital Content 5, http://links.lww.com/INF/F40).

Predictors of Antimicrobials for HAI

Among 870 patients with HAI included in the regression analysis, age predicted HAI antimicrobial use. In univariable analyses, neonates, older infants, and adolescents were more likely to have HAI antimicrobial prescriptions versus children 6–12 years old (Table 4). This effect remained significant in the adjusted model (Table 4). Adolescents had the highest risk of HAI prescriptions [adjusted relative risk (aRR): 2.18; 95% CI: 1.45–3.29].

Preterm birth was a significant risk factor for HAI in multivariable analyses (aRR: 1.33; 95% CI: 1.04–1.70). Being underweight was also significantly associated with HAI prescriptions versus normal weight in multivariable analyses.

In multivariable analysis, indwelling devices, blood transfusions, and having surgery since admission, increased the risk of antimicrobial use for HAI by 3.78-fold, 1.29-fold, and 1.67-fold, respectively (Table 4). Disease classified as rapidly fatal (McCabe score) also predicted antimicrobial use for HAI. HIV infection and COVID-19 did not significantly affect HAI risk.

DISCUSSION

This study explored the prevalence and determinants of antimicrobial HAI utilization in pediatric departments at 3 public sector academic hospitals in South Africa. Overall, 22.9% of pediatric patients received at least 1 antimicrobial prescription. In this study, 45.6% of prescriptions were for HAIs. HAI was independently associated with age, with neonates having a 1.6-fold greater risk of using antimicrobials for HAI versus children aged 6–12 years. Age, prematurity, underweight, rapidly fatal diseases, and invasive devices/procedures were predictive of antimicrobial use for HAI with neonates having a 1.6-fold greater risk than children aged 6–12 years.

This study's pooled pediatric antimicrobial point prevalence is lower than reported in global (2012) (36.7%)[3] and South African studies.[5,20] In 2018, Skosana et al.[20] reported 49.7% of pediatric patients in a South African hospital received at least 1 antimicrobial agent (n = 1,013 prescriptions). The pooled point prevalence reported in this study is also lower than other African countries (34.4%–40.9%),[21,22] and India (61.5%–79.8%).[2,23] This may be due to antimicrobial stewardship programs implemented across South Africa following the National Strategic Framework introduced in

TABLE 4. Unadjusted and Adjusted Models of Predictors of Pediatric Antimicrobial Use for HAI in 870 Patients at Three Academic Hospitals in South Africa, September 22, 2021–January 05, 2022

	Unadjusted		Adjusted	
Characteristic	Relative Risk (95% CI)	*P* Value	Relative Risk (95% CI)	*P* Value
Gender				
Male	Reference			
Female	0.93 (0.85–1.03)	0.173	0.89 (0.76–1.05)	0.175
Age				
6–12 years	Reference			
0–28 days	2.13 (1.23–3.70)	0.007	1.64 (1.06–2.53)	0.027
29–364 days	2.20 (1.40–3.45)	0.001	1.57 (1.12–2.21)	0.009
1–5 years	1.41 (0.92–2.16)	0.118	1.43 (0.95–2.13)	0.084
13–15 years	2.32 (1.46–3.70)	<0.001	2.18 (1.45–3.29)	<0.001
Preterm birth				
No	Reference		Reference	
Yes	1.70 (1.34–2.16)	<0.001	1.33 (1.04–1.70)	0.024
Weight category*				
Normal weight	Reference		Reference	
Underweight	1.60 (1.30–1.97)	<0.001	1.25 (1.01–1.54)	0.024
Overweight	0.94 (0.63–1.39)	0.748	0.86 (0.65–1.13)	0.280
HIV status				
HIV negative	Reference		–	–
HIV unexposed	1.39 (1.00–1.92)	0.050		
HIV exposed	1.17 (0.80–1.72)	0.413	–	–
HIV positive	0.82 (0.37–1.84)	0.626		
COVID-19				
Negative			–	–
Positive	0.72 (0.35–1.48)	0.380	–	–
McCabe score				
Not fatal	Reference		Reference	
Rapidly fatal or ultimately fatal	1.50 (0.98–2.29)	0.060	1.44 (1.02–2.02)	0.037
Surgery since admission				
No	Reference		Reference	
Yes	1.24 (0.82–1.88)	0.320	1.29 (1.02–2.02)	0.037
Any indwelling device				
No	Reference		Reference	
Yes	8.81 (3.43–22.65)	<0.001	3.78 (1.27–11.28)	0.017
Blood transfusion				
No	Reference		Reference	
Yes	2.25 (1.75–2.91)	<0.001	1.67 (1.65–2.19)	<0.001

2017.[24,25] Study design, antimicrobial definitions and hospital setting may also explain discrepancies; few studies included hospitals with specialized services.[20,21] Our study included children 0–15 years, whereas most studies included patients under 18 years. Further, we excluded patients with only antiviral prescriptions.

Notably, the antimicrobial point prevalence ranged from 14.1% in Hospital C to 40.8% in Hospital B. The varied PPS hospital estimates may be related to the services provided. Hospital A is a quaternary-level facility which treats only referred patients. Hospitals B and C offer regional/tertiary/quaternary-level care with walk-in patients and referrals accepted. The lower antimicrobial point prevalence at Hospital C is likely due to the routine practice, implemented before this study began, of daily consultant review of antibiotic scripts with linkage to culture results and early stopping or de-escalation of empiric antimicrobial therapy if initial laboratory cultures are negative. Moreover, prescribed antimicrobials are aligned with organisms cultured in the unit, and blood cultures are repeated when antimicrobials are changed. There is also minimal use of prophylactic antibiotics. Using a digital platform can further improve the efficacy of time-consuming manual antibiotic tracking.

The highest antimicrobial consumption was in children aged 1–12 years, similar to the South African study mentioned earlier.[20] We found that more antimicrobials were prescribed in neonates than children 6–12 years old, contradictory to prior studies.[3,5,20] Notably there were only 17 participants over 12 years of age, with 33 antimicrobial prescriptions. The commonest secondary reason for antibiotic use was being a term infant, and the second commonest was prematurity. This finding may be related to the study design, as preterm infants stay longer in the hospital, and the study excluded preterm infants from weekly enrolment if previously enrolled. Notwithstanding this, as seen in Table 4, being preterm increased the risk of antimicrobial use in HAI by 33%.

In our study, antimicrobial prescribing was driven by HAIs (45.6%) which is higher than the 2018 South African study, and the 2012 PPS reported earlier.[3,5] Versporten et al.[3] reported that antibiotics for HAIs in neonates were 34.9% (14.2% in Africa to 68.0% in Latin America) versus children (28.3%; from 14.5% in Africa to 48.9% in Latin America). In a study from a South African tertiary hospital, 29% of antimicrobials in pediatric intensive care units were for HAIs,[5] similar to our findings. This finding is consistent with patients treated with more severe, complex diseases requiring invasive devices, blood transfusions and procedures. Antimicrobial stewardship programs should therefore target wards or specific units and sub-specialties with high antimicrobial point prevalence. Critical care teams should establish strong collaborations with comprehensive infection prevention and control (IPC) services allied with organizational quality and patient safety programs to minimize HAIs.

Age, particularly adolescents, and underweight children were associated with a higher risk of HAI, similar to prior studies.[10,11,26,27] Preterm infants have functionally less mature innate and adaptive immune systems than older children[28] predisposing these infants to infections.[7,27] Similarly, children with oncologic or hematologic diseases are predisposed to severe bacterial and antifungal diseases,[29] and antimicrobials prescribed for these patients in our study may have been to treat confirmed or suspected infections, or for medical prophylaxis. While critical risk factors of HAI in neonates, gestational age and birth weight, cannot be modified, stringent IPC measures and antimicrobial policies in vulnerable children are warranted.

Antimicrobial usage in this study had multiple drivers, with 54.4% of prescriptions for non-HAI causes, including CAI. High co-amoxiclav utilization may have been due to pediatric community-acquired pneumonia guidelines.[30] Surgical prophylaxis required 3 doses, with the second and third given in the wards and the first occasionally ordered by the premedical anesthetist. Notably, HIV and COVID-19 were not associated with HAI prescriptions in our study, consistent with a prior South African study.[27] Few HIV-infected patients were included, almost all of whom were on antiretroviral therapy. Few COVID-19 patients were included before South Africa's fourth COVID-19 (from 15 November 2020). Antimicrobial prevalence in COVID-19 patients was 48.2% similar to studies from Latin America and the United Kingdom (24.5%–64.3%, respectively).[31,32]

A key study strength was the large sample size of pediatric inpatients across 3 tertiary hospitals in South Africa during COVID-19. The study methodology was informed by WHO PPS guidance and data collectors were trained and supervised by pediatric infectious disease specialists. To limit information bias, specialist pediatricians rigorously checked data to identify incomplete, missing or discrepant variables. There were several limitations. Only hospital records were used for data collection; thus, study findings are dependent on documentation quality. Further, the data is potentially generalizable to pediatric inpatients at specialized hospitals. While sites commenced data collection simultaneously, the varied data collection period may have introduced bias, particularly as 2 sites collected data during a COVID-19 wave, leading to a more heterogeneous population.

In this study, the high antimicrobial prescribing prevalence in academic hospitals in South Africa was driven by HAIs. Improving HAI requires targeting known risk factors by optimizing IPC and establishing functional antibiotic stewardship programs. Further, limiting antimicrobial resistance requires a multipronged approach including adherence to isolation procedures, appropriate antibiotic use, educational interventions and prescribing guidelines with restricted use of some antibiotics.

ACKNOWLEDGMENTS

The authors acknowledge the contributions of the following clinical staff members who assisted in facilitating the set-up of this study at the Chris Hani Baragwanath Academic Hospital site: Professor S Velaphi, Department of Pediatrics and Child Health; Professor G Naidu, Department of Pediatric Hematology-Oncology; Professor J Loveland, Department of Pediatric Surgery; Professor M T Ramokgopa, Department of Orthopedic Surgery; Professor R Ouma and Dr. D Poati. Department of Neurosurgery; Dr. M R Ahmed, Department of Otorhinolaryngology; Professor R Mathivha and Dr. K Naidoo, Pediatric Critical Care; Dr. J Wadula, Clinical Microbiology, National Health Laboratory Service; Matron M Ntikana, Pediatric Nursing. We further acknowledge the following staff members who assisted with data capture at the Chris Hani Baragwanath Academic Hospital site: Mr. J Serumula and Mr. T Mentoor.

The team at IALCH would like to acknowledge Dr. SA Thula, Pediatric Critical Care; Dr. L Naidoo, Neonatal Intensive Care; Dr. L Mubaiwa, Department of Pediatric Neurology; Professor R Bhimma, Department of Pediatric Nephrology; Dr. E Hoosen, Department of Pediatric Cardiology; Dr. S H Sheik-Gafoor, Department of Pediatric Surgery; Dr. W Kuhn, Department of Otorhinolaryngology; Dr. B Enicker, Department of Neurosurgery; Prof M Madaree, Department of Plastic & Reconstructive Surgery; Dr. B Neethling, Department of Pediatric Hematology/Oncology; Prof T Hardcastle, Department of Trauma & Burns; Dr. R Madansein, Department of Cardiothoracic and Dr. Y Mahabeer, Clinical Microbiology, National Health Laboratory Services.

The team at SBAH would like to acknowledge the following clinical staff members who assisted in facilitating the set-up of this study: Professor R Green, Department of Pediatrics and Child Health;

Dr. E Müller, Department of Pediatric Surgery; Professor R Goller, Department of Pediatric Orthopedic Surgery; Professor M Tshifularo, Department of Otorhinolaryngology; Dr. N Lourens, Department of Pediatric Urology. We further acknowledge the following staff members who assisted with data capture at the Steve Biko Academic Hospital: Dr. T Gokar, Dr. S Ndlovu and Ms. C Shabalala.

We would like to acknowledge and thank the data management team: Ms. Natasha Titus, Mr. Skhumbuzo Mzimela and Ms. Khanya Mohlabi for the development of the database and data cleaning and curation.

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