International Journal of Infectious Diseases 74 (2018) 16–23

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Paediatric antimicrobial use at a South African hospital

L.R. Koopmans[a,b], H. Finlayson[c], A. Whitelaw[d,e], E.H. Decloedt[f], A. Dramowski[c,*]

[a] Undergraduate Research Elective Programme, Department of Paediatrics and Child Health, Stellenbosch University, Cape Town, South Africa
[b] Radboud University, Radboud UMC, The Netherlands
[c] Department of Paediatrics and Child Health, Division of Paediatric Infectious Diseases, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa
[d] Department of Medical Microbiology, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa
[e] National Health Laboratory Services, Tygerberg Hospital, Cape Town, South Africa
[f] Department of Medicine, Division of Clinical Pharmacology, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa

ARTICLE INFO

Article history:
Received 16 March 2018
Received in revised form 24 May 2018
Accepted 29 May 2018
Corresponding Editor: Eskild Petersen, Aarhus, Denmark

Keywords:
Antibiotic
Antimicrobial
Paediatric
Antibiotic stewardship
Surveillance
Prescription
Pharmacy

ABSTRACT

Background: Data on antimicrobial use among hospitalized children in Africa are very limited due to the absence of electronic prescription tracking.
Methods: This study evaluated antimicrobial consumption rates, the antimicrobial spectrum used, and the indications for therapy on a paediatric ward and in the paediatric intensive care unit (PICU) at Tygerberg Hospital, Cape Town, South Africa. Antimicrobial prescription and patient demographic data were collected prospectively from May 10, 2015 to November 11, 2015. For the same period, data on antimicrobials dispensed and costs were extracted from the pharmacy electronic medicine management system. The volume of antimicrobials dispensed (dispensing data) was compared with observed antimicrobial use (prescription data).
Results: Of the 703 patients admitted, 415/451 (92%) paediatric ward admissions and 233/252 (92%) PICU admissions received ≥1 antimicrobials. On the ward, 89% of prescriptions were for community-acquired infections; 29% of PICU antimicrobials were prescribed for healthcare-associated infections. Ampicillin and third-generation cephalosporins were the most commonly prescribed agents. Antimicrobial costs were 67 541 South African Rand (ZAR) (5680 United States Dollars (USD)) on the ward and 210 484 ZAR (17 702 USD) in the PICU. Ertapenem and meropenem were the single largest contributors to antimicrobial costs on the ward (43%) and PICU (30%), respectively. The volume of antimicrobials dispensed by the pharmacy (dispensing data) differed considerably from observed antimicrobial use (prescription data).
Conclusions: High rates of antimicrobial consumption were documented. Community-acquired infections were the main indication for prescription. Although pharmacy dispensing data did not closely approximate observed use, this represents a promising method for antimicrobial usage tracking in the future.

Introduction

Antimicrobial overuse is an important contributor to the development of antimicrobial resistance worldwide. Antimicrobial consumption is particularly high among paediatric inpatients owing to a predominance of infectious pathologies (both community- and healthcare-associated infection) and non-specific disease presentations, with difficulty in excluding bacterial infections. Few studies have assessed the appropriateness of antimicrobial use in children, but in high-income settings, antimicrobial prescribing errors occur frequently, including incorrect dosing, inappropriate antimicrobial choice, no indication for therapy, inadequate treatment duration, and inappropriate route of administration (Blinova et al., 2013; Newland et al., 2012; Kreitmeyr et al., 2017).

A recent point prevalence study (Antibiotic Resistance and Prescribing in European Children – ARPEC) surveyed 17 693 paediatric inpatients in 41 countries, including six African hospitals (Versporten et al., 2013). Bacterial lower respiratory tract infections were the most common indication for antimicrobial prescription worldwide. At the six African hospitals studied, gentamicin and ceftriaxone were the most commonly prescribed

* Corresponding author.
E-mail address: dramowski@sun.ac.za (A. Dramowski).

https://doi.org/10.1016/j.ijid.2018.05.020
1201-9712/

antimicrobials, contributing 16% and 14%, respectively, of total antimicrobial usage. In an Ethiopian paediatric inpatient setting, gentamicin (26%) and ceftriaxone (44%) were also identified as the most commonly prescribed antimicrobials (Feleke et al., 2013). In the ARPEC study, 37% of all paediatric inpatients had one or more antimicrobials prescribed; the highest antimicrobial use rates (61%) were documented in paediatric intensive care units (PICU). Other international studies have confirmed high antimicrobial usage rates (ranging from 32% to 70%) (Grohskopf et al., 2005; Amadeo et al., 2010; Gandra et al., 2017; De Luca et al., 2016), with the highest paediatric inpatient antimicrobial consumption rates reported from African countries: Mozambique (98%), Botswana (72%), Ethiopia (98%), and Ghana (69%) (Monteiro et al., 2017; Labi et al., 2018; Fisher et al., 2009; Alemnew and Atnafie, 2015).

A specific challenge to monitoring and reporting paediatric antimicrobial consumption data is the lack of a standardized usage definition. Among adult patients, consumption patterns can be easily compared using the defined daily dose (DDD) for each antimicrobial agent (total grams of the drug divided by the number of grams in an average adult daily dose) (WHO, 2018). This method cannot be applied accurately to paediatric populations as antimicrobial dosage in children is based on body weight or body surface area.

Accurate and ongoing measurement of local antimicrobial consumption patterns helps stewardship teams set programmatic targets and assess the impact of interventions. Many high-income countries use electronic laboratory and pharmacy surveillance systems to measure usage trends and generate real-time/early warning systems for infectious disease outbreaks, supporting antimicrobial stewardship efforts. However, in resource-limited healthcare settings and particularly in Africa, surveillance of antimicrobial use through electronic prescribing is generally unavailable (Rattanaumpawan et al., 2017). Furthermore, the lack of electronic prescription tracking means that any antimicrobial consumption data must be collected manually, which is labour-intensive and more prone to error. The lack of tools for antimicrobial consumption monitoring hampers the publication of data on paediatric antimicrobial use from low- and middle-income countries (LMIC) (Dillon et al., 2014).

Although electronic prescribing is not available, electronic pharmacy stock management tools are widely used in public sector South African healthcare facilities. The potential use of electronic dispensing data for tracking antimicrobial usage trends is appealing, as it avoids the need for labour-intensive prescription audits. However, pharmacy dispensing data may not always accurately reflect usage data; for example, in low-resource neonatal/paediatric settings, the sharing of multi-dose antimicrobial vials between patients is a common practice. In such cases, dispensing data would only reflect the initial patient to whom the antimicrobial was dispensed and not the subsequent patients.

Given the paucity of data on antimicrobial use in Africa, this study was performed to evaluate antimicrobial consumption on two paediatric wards, comparing prescription chart audit data with pharmacy dispensing data at Tygerberg Hospital, Cape Town, South Africa.

Methods

Study setting

Tygerberg Hospital in Cape Town, South Africa is a large 1384-bed academic complex, including 300 neonatal/paediatric beds and 17 000 neonatal/paediatric (0–14 years) admissions annually. There are 13 children's wards: medical generalist wards, medical specialist wards, surgical wards, neonatal wards, and two intensive care units – neonatal and paediatric (PICU). Community-acquired infectious (CAI) diseases like human immunodeficiency virus (HIV), tuberculosis (TB), respiratory tract infections, and gastroenteritis are common indications for paediatric hospitalization. The treatment of paediatric healthcare-associated infections (HAI) is also a major contributor to antimicrobial use on the wards (Dramowski et al., 2016). The hospital implemented a formal antimicrobial stewardship programme in 2014 with annual antimicrobial use point prevalence surveys, weekly antimicrobial stewardship ward rounds, and a dedicated antimicrobial prescription chart. The hospital pharmacy has utilized an electronic medicine management system (JAC Medicines Management software) since the year 2000; however, comprehensive data on antimicrobial consumption rates by ward are not disseminated routinely. The JAC software system manages and streamlines procurement, stock keeping, dispensing, and distribution of pharmaceuticals within the pharmacy, but the hospital does not currently have access to the electronic prescribing JAC software module.

Study design

From May 10, 2015 to November 11, 2015, data from inpatient records and antimicrobial prescriptions were collected prospectively on two wards (the PICU and a general paediatric ward) for all children admitted for >48 h during a study to establish the incidence of paediatric HAI (Dramowski et al., 2016). This dataset (6-month antimicrobial prescription audit) included drug name, dose, duration, and indication type (CAI, HAI, or prophylaxis). Antiretrovirals, anti-TB drugs, and co-trimoxazole prophylaxis for *Pneumocystis jirovecii* were not included in the audit. For the same 6-month period and the same two wards, data were extracted from the pharmacy electronic medicine management system (JAC), including drug name, total units dispensed, total consumption (in milligrams, grams, or international units), and cost (in South African Rand). Observed antimicrobial use was described using the prospectively collected antimicrobial prescription audit data. Antimicrobial cost data were derived from the pharmacy dispensing data. The two datasets were compared to determine the variance between audit data (observed use) and dispensing data and the feasibility of using the pharmacy dispensing data for future surveillance of paediatric antimicrobial use.

Study definitions

CAI included all infectious diseases that were acquired prior to the current hospitalization episode. HAI included any infection that was neither present nor incubating at the time of hospital admission (National Healthcare Safety Network, 2013). Antimicrobial prophylaxis included the prescription of antimicrobials for the purpose of preventing inpatient surgical or medical infections (other than co-trimoxazole prophylaxis for *Pneumocystis jirovecii*, isoniazid prophylactic therapy, and antiretroviral prophylaxis for the prevention of mother-to-child transmission of HIV). 'Patient-days' was defined as the sum of all patient lengths of stay per ward per month. The antimicrobial consumption or utilization rate was defined as the total proportion of patients over the study period who received one or more antimicrobial drugs during their admission episode. Days of therapy (DOT) was calculated for each antimicrobial agent as the sum of all patient usage of that drug in the total number of days received (Tadesse et al., 2017). For calculation of antimicrobial costs, the currency conversion rate for South African Rand (ZAR) and United States Dollars (USD) that was applicable in May 2015 was used (1 USD = 11.89 ZAR).

Data handling and analysis, and ethical approval

The following indices were calculated for each ward using the prescription audit data only (as the necessary variables were not available from the dispensing data): (1) the antimicrobial prescription prevalence rate; (2) the mean number of antimicrobials per patient admission episode; (3) the indication/s for antimicrobial/s (CAI, HAI, prophylaxis); (4) the antimicrobial spectrum prescribed (antibacterial, antifungal, antiviral, and the proportional contribution of each drug to the overall antimicrobial usage); (5) the length of hospital stay versus number of antimicrobials prescribed. Antimicrobial costs were calculated from the dispensing data. Audit data were compared with dispensing data to calculate the variance in usage between datasets. In some instances, children had more than one admission episode to the selected wards during the study period; these admission episodes were included using the patient's current weight, age, and prescription indication.

Continuous and categorical data were analyzed using the Student *t*-test and Fisher's exact test/Chi-square test, as appropriate. Pearson's correlation coefficient was used to investigate the relationship between length of hospital stay and the number of antimicrobials prescribed. A *p*-value of <0.05 was considered statistically significant. Stata statistical software version 13.1 (StataCorp, USA) was used for the data analysis.

Ethical approval and a waiver of individual informed consent was obtained from the Human Health Research Ethics Committee of Stellenbosch University (Ref. No. S13/09/171).

Results

A total of 703 patients were admitted during the study period: 451 to the general paediatric ward and 252 to the PICU (Table 1). Of patients admitted to the ward, 415/451 (92%) were prescribed one or more antimicrobials during their hospital stay; an average of 2.2 antimicrobials were prescribed per admission episode (range 0–8 antimicrobials). Overall on the ward, 904 antimicrobials were prescribed, generating 4079 DOT and a usage rate of 1137 DOT/1000 patient-days. Among patients admitted to the PICU, 233/252 (92%) were prescribed one or more antimicrobial drugs with an average of 2.8 antimicrobials per patient (range 0–11). Overall, 662 antimicrobials were prescribed, generating 3810 DOT and a usage rate of 1323 DOT/1000 patient-days. Younger patients (neonates and infants) had significantly higher antimicrobial usage rates than older children, both on the ward and in the PICU. Patients in the PICU were significantly more likely to be prescribed an antimicrobial for HAI than patients on the ward ($p < 0.001$). As the number of antimicrobials prescribed per patient increased, the mean duration of stay increased significantly for the population (Pearson correlation coefficient 0.360 (moderate correlation), $p < 0.001$) (Figure 1a). For both ward and PICU combined ($n = 703$), patients who died ($n = 23$) received significantly more antimicrobials than those who survived (median of 5 vs. 2 antimicrobials, respectively) (Figure 1b).

Most antimicrobials were given parenterally (72% on the ward and 87% in the PICU). The third-generation cephalosporins (cefotaxime and ceftriaxone) were the most commonly prescribed intravenous (IV) antimicrobials on the paediatric ward (833 DOT) and in the PICU (436 DOT). On the ward, ampicillin (757 DOT) and gentamicin (442 DOT) were the second and third most frequently

Table 1
Demographics of the study population ($n = 703$).

	Paediatric ward ($n = 451$)			Paediatric ICU ($n = 252$)		
	≥1 antimicrobial prescription	No antimicrobial prescription	*p*-Value	≥1 antimicrobial prescription	No antimicrobial prescription	*p*-Value
Proportion of patients prescribed ≥1 antimicrobial drug	415 (92%)	36 (8%)	–	233 (92%)	19 (8%)	–
Total number of antimicrobials prescribed	904	NA	–	662	NA	–
Mean antimicrobials per patient, *n* (range)	2.2 (1–8)	NA	–	2.8 (1–11)	NA	–
Sex, male	233 (56.1%)	22 (61.1%)	0.564	130 (55.8%)	12 (63.1%)	0.534
Age in months, median (IQR)	5.5 (1.6–21.5)	27.4 (6.1–86.4)	<0.001	5.9 (2.2–21.5)	27.9 (10.0–47.5)	0.001
Age category			<0.001			0.015
Neonate (<28 days)	57 (13.7%)	0 (0%)		25 (10.7%)	0 (0%)	
Infant (29–364 days)	212 (51.1%)	13 (36.1%)		125 (53.7%)	6 (31.6%)	
Toddler (1–5 years)	104 (25.1%)	12 (33.3%)		59 (25.3%)	11 (57.9%)	
Child (>5 years)	42 (10.1%)	11 (30.6%)		24 (10.3%)	2 (10.5%)	
Weight in kilograms, median (IQR)	5.7 (3.7–9.4)	9.4 (5.8–15.7)	<0.001	6.5 (3.6–10.5)	9.8 (7.3–13.6)	0.036
HIV prevalence			0.815			0.05
HIV-infected	25 (6.0%)	2 (5.5%)		24 (10.3%)	0 (0%)	
HIV-exposed uninfected	77 (18.6%)	5 (13.9%)		31 (13.3%)	2 (10.5%)	
HIV-negative	293 (70.6%)	28 (77.8%)		164 (70.4%)	13 (68.4%)	
HIV unknown	20 (4.8%)	1 (2.8%)		14 (6.0%)	4 (21.1%)	
Length of stay in days, mean (SD)	6 (4–9)	6 (3–9)	0.437	9 (5–13)	3 (2–4)	<0.001
Indication for antimicrobial/s			–			–
Community-acquired infection	809/904 (89%)	NA		464/662 (70%)	NA	
Healthcare-associated infection	94/904 (10%)			191/662 (29%)		
Prophylaxis[a]	1/904 (0%)			7/662 (1%)		
Outcome			0.609			0.183
Discharged or transferred	412 (99.3%)	36 (100%)		213 (91.4%)	19 (100%)	
Died	3 (0.7%)	0 (0%)		20 (8.6%)	0 (0%)	

ICU, intensive care unit; NA, not applicable; IQR, interquartile range; SD, standard deviation; HIV, human immunodeficiency virus.
[a] Prophylaxis included medical and surgical prophylaxis other than co-trimoxazole prophylaxis for *Pneumocystis jirovecii*, isoniazid prophylactic therapy, and antiretroviral prophylaxis for prevention of mother-to-child transmission of HIV.

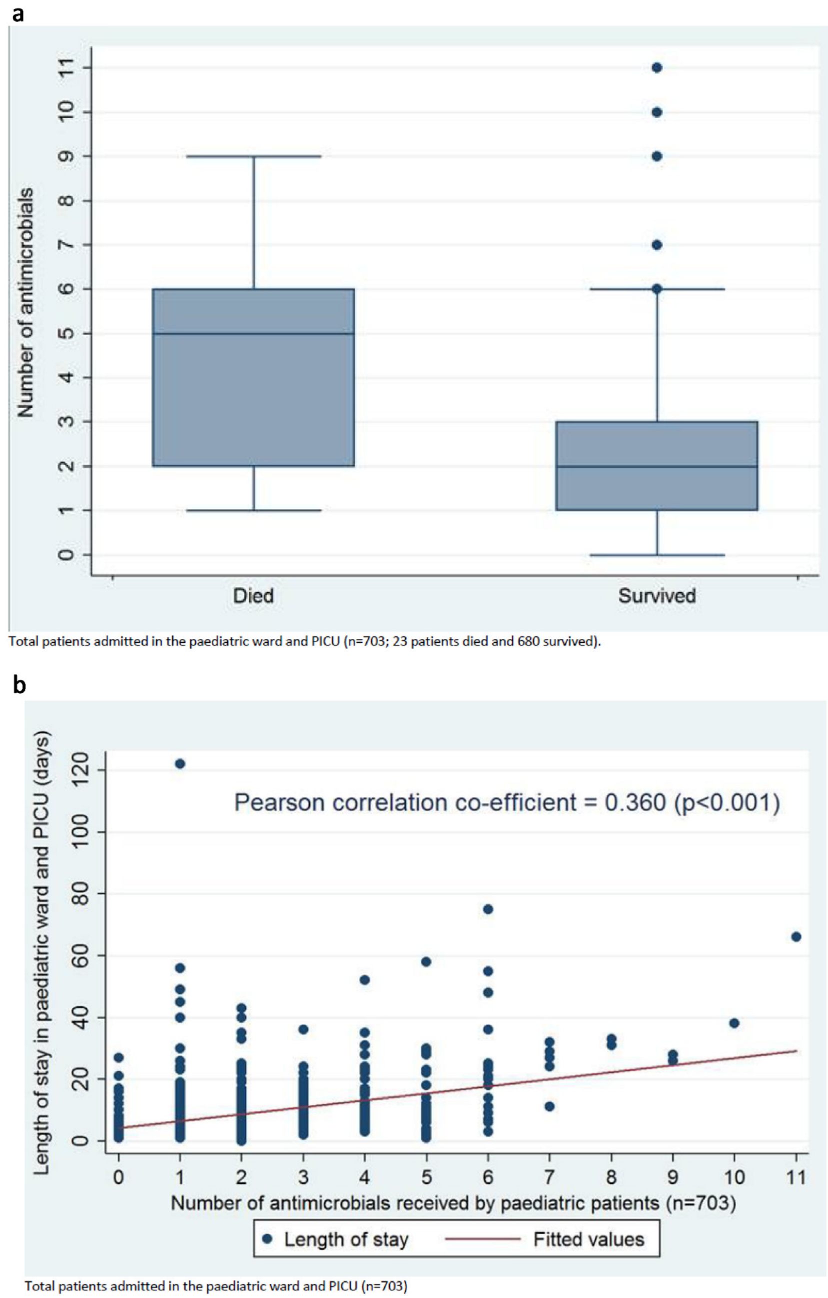

Figure 1. (a) Total number of antimicrobials prescribed versus outcome of hospitalization. (b) Total number of antimicrobials prescribed versus length of hospitalization.

prescribed IV antimicrobials. In the PICU, meropenem (422 DOT) and ganciclovir (383 DOT) were the second and third most frequently prescribed IV antimicrobials (Figure 2a, b). Commonly used oral antimicrobials on the ward were amoxicillin (489 DOT), amoxicillin–clavulanic acid (271 DOT), and penicillin VK (81 DOT). In the PICU, co-trimoxazole was the most commonly prescribed oral antimicrobial (141 DOT), followed by amoxicillin–clavulanic acid (129 DOT) and erythromycin (89 DOT) (Figure 2c, d).

CAI were the main indication for antimicrobial prescription (89% on the ward, 70% in the PICU; $p < 0.001$) with ampicillin and third-generation cephalosporins being the most common agents prescribed for CAI (Figure 3a, c). Ertapenem and meropenem were the most commonly prescribed antimicrobials for HAIs on the ward and in the PICU (Figure 3b, d). Prophylactic antimicrobials constituted a very small percentage of overall usage on the ward and in the PICU (0.1% and 1.1%, respectively).

Of the different antimicrobial classes, antibacterial agents were most commonly used (94% on the ward and 81% in the PICU), with antifungals and antivirals making up a small proportion of antimicrobials used. However, in terms of days of therapy, ganciclovir, aciclovir, and valganciclovir usage was substantial, being the 4th, 11th, and 14th overall largest contributors to DOT in the PICU. There was also a greater diversity of antimicrobials prescribed in the PICU than on the ward.

Antimicrobial costs calculated from the pharmacy dispensing data estimated a total antimicrobial spend on the general paediatric ward of 67 541 ZAR (USD 5680) in total, equating to 162 ZAR (USD 13.69) per infected patient. In the PICU, antimicrobial prescriptions totalled 210 484 ZAR (USD 17 702), and 903 ZAR (USD 75.98) per infected patient. Ertapenem and meropenem were the single largest contributor to antimicrobial costs on the ward (43% of total costs) and in the PICU (30% of

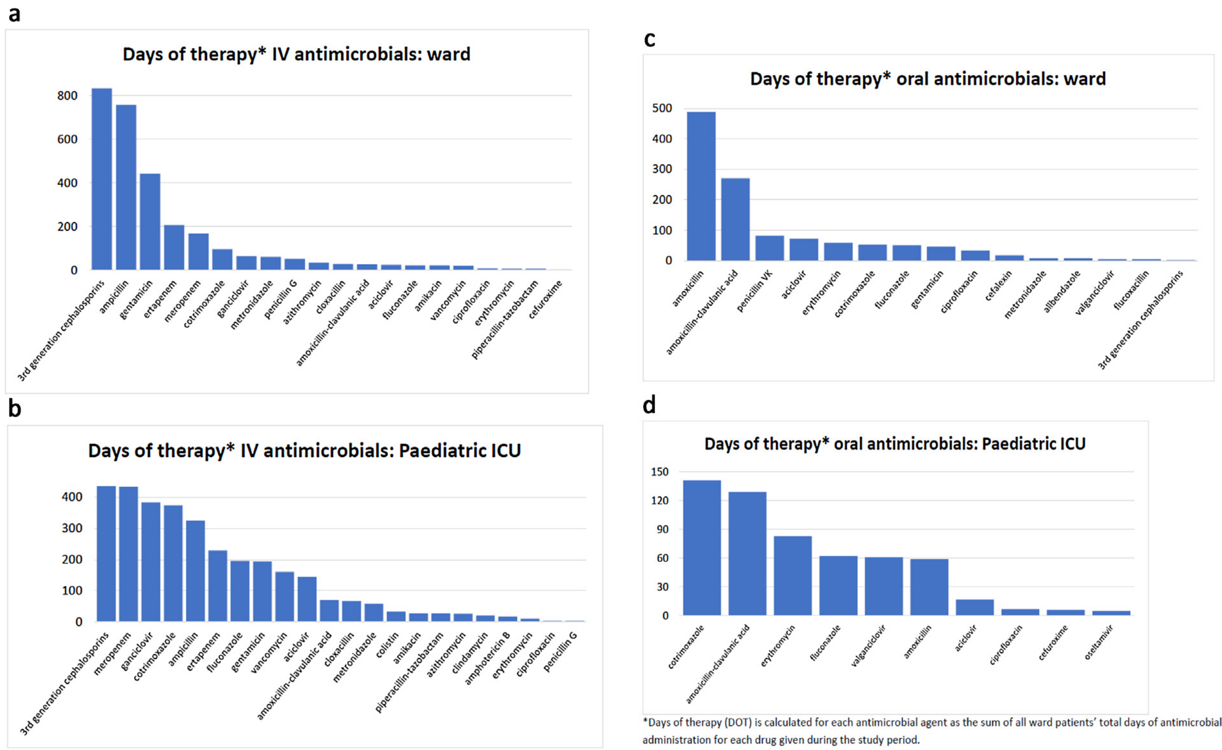

Figure 2. (a) Total days of intravenous (IV) antimicrobial therapy on the paediatric ward. (b) Total days of intravenous (IV) antimicrobial therapy in the paediatric ICU. (c) Total days of oral antimicrobial therapy on the paediatric ward. (d) Total days of oral antimicrobial therapy in the paediatric ICU.

total costs). The five antimicrobials with the highest cost are shown in Table 2.

The most commonly prescribed IV antimicrobials from the prescription audits were compared with the volume of the same antimicrobial agents dispensed according to the pharmacy data (Table 3). For the general paediatric ward, with the exception of amoxicillin–clavulanic acid and ertapenem, consumption exceeded volumes dispensed by up to 2.8-fold. Conversely in the PICU, a larger volume of antimicrobials was dispensed than was actually consumed.

Discussion

These data represent one of the first overviews of paediatric antimicrobial use at a South African hospital. Very high rates of antimicrobial use were documented both on the ward and in the PICU, exceeding rates reported from most other paediatric inpatient settings worldwide (Feleke et al., 2013; Grohskopf et al., 2005; Amadeo et al., 2010; Gandra et al., 2017; De Luca et al., 2016). In comparison to a German study of antimicrobial use on general paediatric wards (reporting DOT of 483/1000 patient-days) (Kreitmeyr et al., 2017), the general ward in the present study utilized 1137 DOT/1000 patient-days. This substantially higher usage may be ascribed to the inclusion of antivirals and antifungals in this study, and the greater burden of infectious diseases among the paediatric admissions. However, the antimicrobial usage data are not dissimilar to those reported in the few published studies from other African paediatric wards (Monteiro et al., 2017; Labi et al., 2018; Fisher et al., 2009; Alemnew and Atnafie, 2015). The present study data support existing evidence that antimicrobial use on the continent is substantial, highlighting the need for greater surveillance of antimicrobial use and the implementation of antimicrobial stewardship programmes in African hospitals.

In this Tygerberg Hospital cohort, it was possible to show a significant association between antimicrobial use and young age (every neonate had at least one antimicrobial prescribed), highlighting the difficulty in excluding infectious diseases in the neonate/young infant. Furthermore, an association between longer length of stay and greater number of antimicrobials prescribed was demonstrated, which probably reflects complicated clinical disease course and the greater likelihood of HAI as the length of hospital stay increases. Similarly, a significant association between antimicrobial use and outcome was shown, with PICU patients who received antimicrobials having a crude mortality rate of 8.6% versus no deaths among patients who did not receive antimicrobials.

In the global ARPEC point prevalence study, gentamicin and ceftriaxone were the most commonly prescribed antimicrobials among paediatric inpatients, whereas at the study institution, third-generation cephalosporins, ampicillin, and gentamicin were the most widely prescribed antimicrobials. For both the ward and PICU, CAI was the most common indication for receiving an antimicrobial/s: third-generation cephalosporins (23% on the general ward and 19% in the PICU) and ampicillin (25% on the general ward and 18% in the PICU) were most commonly used. In a Ghanaian teaching hospital, third-generation cephalosporins were commonly used for CAIs (28%) (Labi et al., 2018).

For HAI, the study institution predominantly used carbapenems, namely meropenem (31% on the general ward and 34% in the PICU) and ertapenem (39% on the general ward and 19% in the PICU). As part of ongoing antimicrobial stewardship efforts, broad-spectrum antimicrobial use for suspected HAI requires consultant approval and a named-patient prescription to pharmacy for authorization. This high carbapenem usage most likely reflects the hospital guidelines in 2015 at the time of data collection. Subsequently, the recommended empiric HAI treatment for ward patients has changed to piperacillin–tazobactam and amikacin (personal communication, Dr Heather Finlayson), which has led to an increase in consumption of these antibiotics. Clinicians are

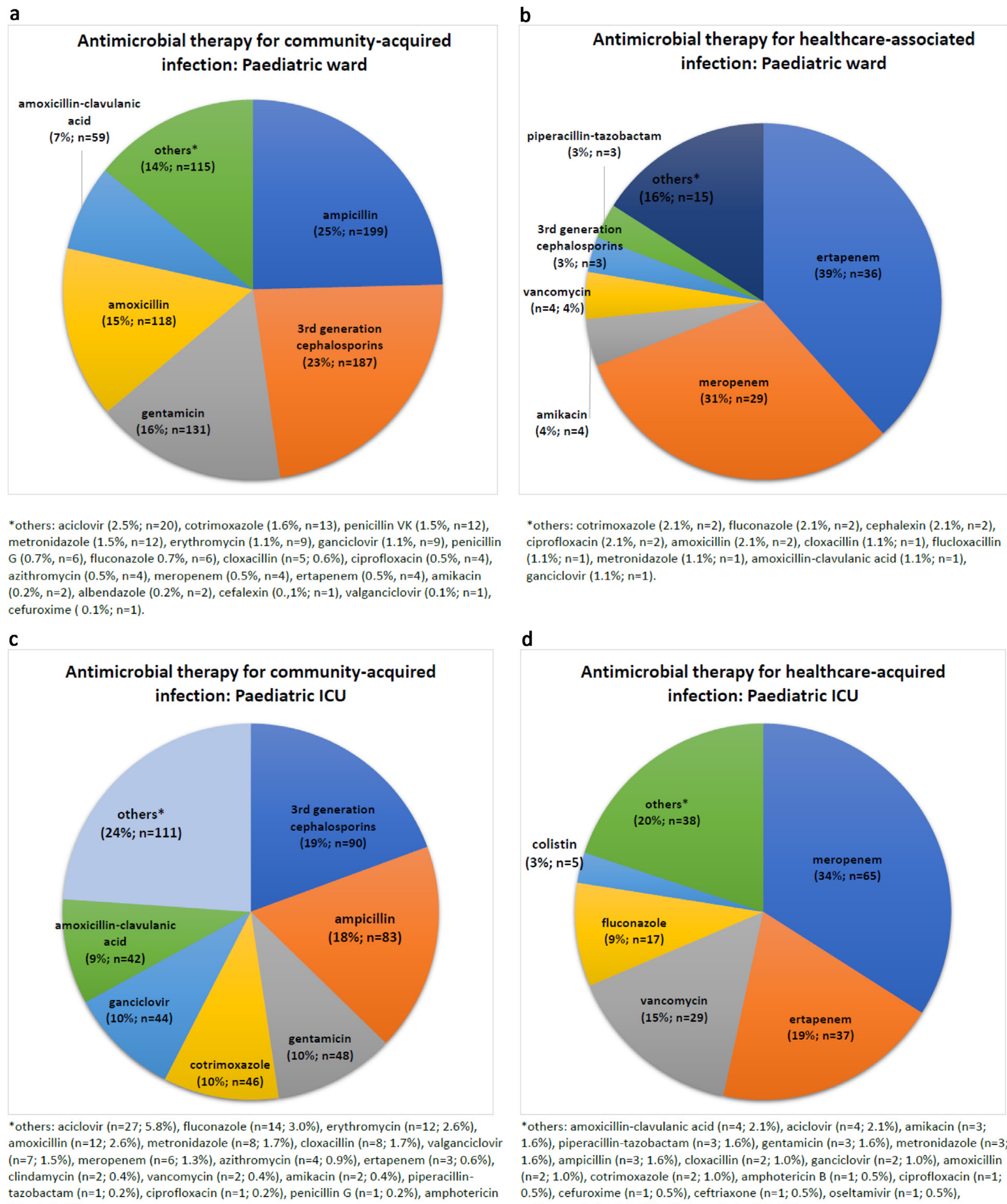

Figure 3. (a) Antimicrobials used for community-acquired infection on the paediatric ward ($n = 809$). (b) Antimicrobials used for healthcare-associated infection on the paediatric ward ($n = 94$). (c) Antimicrobials used for community-acquired infection in the paediatric ICU ($n = 464$). (d) Antimicrobials used for healthcare-associated infection in the paediatric ICU ($n = 191$).

encouraged (through the dedicated antimicrobial therapy prescription chart), to stop or de-escalate the empiric broad-spectrum antimicrobial therapy after 72 h if the initial laboratory investigations for sepsis are negative. HAI as an indication for antimicrobial prescription occurred more frequently in the PICU, although this finding was not surprising given the severity of illness, use of indwelling devices, and extended hospital stay of populations in an ICU setting.

Prophylaxis as an indication for antimicrobial use in the PICU and on the ward was rare, reflecting the small number of paediatric surgical patients included. A recent antimicrobial point prevalence survey in a teaching hospital in Ghana showed a different distribution of indications for antimicrobial therapy compared to the study institution: 40% were for CAI, 21% for HAI, 34% for surgical prophylaxis, and 5% for medical prophylaxis (this study included both adult and paediatric medical and surgical wards).

Table 2
Total costs of antimicrobials utilized in the paediatric ward and ICU.

General paediatric ward						Paediatric ICU					
Antimicrobial	Grams used	Cost in ZAR per gram	Cost in ZAR	Cost in USD	% of total cost	Antimicrobial	Grams used	Cost in ZAR per milligram	Cost in ZAR	Cost in USD	% of total cost
Ertapenem	79	368	29 095	2447	43%	Meropenem	470	132	62 114	5224	30%
Ampicillin	560	14	8056	678	12%	Ertapenem	141	368	51 930	4367	25%
Amoxicillin	3750	1.9	7125	599	11%	Ganciclovir	52	791	40 715	3424	19%
Aciclovir	25 (IV) 60 (PO)	235 (IV) 1.6 (PO)	5853	492	9%	Aciclovir	100 (IV) 15 (PO)	235 (IV) 1.6 (PO)	23 542	1978	11%
Meropenem	30	132	4008	337	6%	Ampicillin	506	14	7286	613	3%
Others	–	–	13 401	1127	20%	Others	–	–	24 913	2095	12%
Total	–	–	67 541	5680	100%	Total	–	–	210 484	17 702	100%

ICU, intensive care unit; ZAR, South African Rand; USD, United States Dollars; IV, intravenous; PO, oral.

Table 3
Variance between selected antimicrobials: pharmacy dispensed versus ward/PICU consumed.

Antimicrobial	Ward dispensed (grams)	Ward consumed (grams)	Variance[a]	PICU dispensed (grams)	PICU consumed (grams)	Variance[a]
Meropenem	30	67	0.4	470	289	1.6
Ertapenem	79	48	1.6	141	66	2.1
Vancomycin	3	10	0.3	170	77	2.2
Cefotaxime	262	284	0.9	180	152	1.2
Ceftriaxone	270	345	0.8	234	252	0.9
Ampicillin	560	739	0.8	506	575	0.9
Amoxicillin–clavulanic acid	24	22	1.1	174	62	2.8

PICU, paediatric intensive care unit.
[a] Variance was calculated as dispensed grams/consumed grams × 100.

The total cost of antimicrobials dispensed differed substantially by ward of origin: the antimicrobial cost per infected patient was five-fold higher for PICU patients (13.69 vs. 75.98 USD per infected patient). There are several potential explanations for the cost differential: PICU patients had higher rates of parenteral drug use, higher rates of HAI (with greater use of carbapenems), extended lengths of stay, and greater use of antivirals. However, an additional factor contributing to this cost calculation may have been overestimation of the volume of antimicrobials dispensed by the pharmacy. In high-income countries, ongoing analysis of drug utilization rates and prescribing trends has been used successfully by hospital antimicrobial stewardship programmes (Reddy et al., 2015; Araujo da Silva et al., 2017; Smith et al., 2015) to lower the cost of and reduce unnecessary antimicrobial use.

Lastly, it was aimed to determine whether pharmacy dispensing data accurately reflect antimicrobial consumption on paediatric wards, and whether dispensing data could be used as a ‘proxy’ for antimicrobial audits. Comparing the dispensed and the audit data, a substantial variation between the volumes of selected intravenous antimicrobials dispensed and the actual volumes given was observed. In general, the dispensing data recorded similar volumes of antimicrobials used for the treatment of CAI on the ward, e.g., ampicillin, amoxicillin–clavulanic acid, and third-generation cephalosporins. However, the pharmacy dispensing data underestimated antimicrobial use for restricted antimicrobials used for the treatment of HAI on the ward (i.e., more consumed than dispensed for meropenem, ertapenem, and vancomycin). The most likely explanation for this finding is that many wards keep commonly used antimicrobials as ward stock; therefore pharmacy orders do not necessarily reflect real-time use. In addition, interviews of nursing staff who administer antimicrobials on the wards confirmed that sharing of multi-dose vials between patients was common practice and that patients transferred between wards may be transferred with their dispensed antimicrobials, obviating the need to order stock from the pharmacy. In addition, some patients received their first doses of antimicrobials in the acute admission ward prior to transfer to the general paediatric ward or PICU, which may have also had a minor effect on estimating total antimicrobial volume consumed.

Conversely, the pharmacy dispensed greater volumes of antimicrobials to the PICU than were given according to the audit data, except for ampicillin and the third-generation cephalosporins, which correlated well with observed use. It was subsequently discovered that the pharmacy dispensing data combined orders from both the PICU and the adjacent neonatal intensive and high-care units (NICU), which is likely the main reason for the higher dispensed volumes.

Another finding when reviewing the pharmacy dispensing data was that broad-spectrum, restricted antimicrobials were commonly issued as ‘ward stock’, making it impossible to link antimicrobial use with a particular patient and indication. In view of these findings, it is clear that the pharmacy dispensing data capturing system would require refinements to improve its usefulness as a tool for tracking antimicrobial consumption and ward stock on the paediatric wards and PICU at the study institution. It should be noted that the pharmacy electronic medicine management system was originally implemented to manage the procurement and finances rather than to track antimicrobial consumption. In the interim, repeated point prevalence surveys and antimicrobial usage audits should be continued in order to track the impact of antimicrobial stewardship programmes on the wards. However, with some local system adaptations, pharmacy dispensing data could represent a viable method for antimicrobial consumption tracking in the future. Electronic prescribing, however, would be ideal to accurately assess antimicrobial usage.

The strengths of this study are the inclusion of a large inpatient population from two diverse wards at a large South African children’s hospital. Limitations of the study are the exclusion of patients who were admitted for less than 48 h, which may have led to either over- or underestimation of the antimicrobial use, and the lack of data on discharge prescriptions (which led to an underestimation of the total days of antimicrobial use, as children could take antimicrobials home or finish the course in another hospital). Although the study findings are not generalizable to all hospitals in Africa, the data can inform other paediatric centres that are developing antimicrobial consumption surveillance programmes.

In conclusion, antimicrobial usage rates at Tygerberg Hospital were very high compared to developed country estimates, but comparable to data from the African continent. Antimicrobial consumption as measured by the pharmacy dispensing data, differed from the antimicrobial use observed in prescription audits, but with some system adaptations, represents a feasible method for antimicrobial consumption tracking in the future.

Acknowledgements

The authors thank Melissa Erasmus (Tygerberg Hospital antimicrobial stewardship pharmacist), Theresa Blockman (Information Management, Department of Health, Western Cape Government), and the staff and patients of Tygerberg Hospital ward G7 and A9 PICU for their assistance.

Funding

Funding from the South African Medical Research Council's Clinician Researcher Programme and the Discovery Foundation's Academic Fellowship Award, supported the collection of the antimicrobial prescription data.

Conflict of interest

None.

Author contributions

AD and LK developed the study design, performed the data collection and analysis, and produced the first draft. HF, ED, and AW gave input on the data analysis and critically reviewed the manuscript. All authors read and approved the final manuscript.

References

Alemnew G, Atnafie SA. Assessment of the pattern of antibiotics use in pediatrics ward of Dessie referral hospital, North East Ethiopia. Int J Med Med Sci 2015;7 (1):1–7, doi:http://dx.doi.org/10.5897/ijmms2014.1101.

Amadeo B, Zarb P, Muller A, Drapier N, Vankerckhoven V, Rogues AM, et al. European Surveillance of Antibiotic Consumption (ESAC) point prevalence survey 2008: paediatric antimicrobial prescribing in 32 hospitals of 21 European countries. J Antimicrob Chemother 2010;65(10):2247–52, doi:http://dx.doi.org/10.1093/jac/dkq309.

Araujo da Silva AR, Albernaz de Almeida Dias DC, Marques AF, Biscaia di Biase C, Murni IK, Dramowski A, et al. Role of antimicrobial stewardship programmes in children: a systematic review. J Hosp Infect 2017;1:2, doi:http://dx.doi.org/10.1016/j.jhin.2017.08.003 pii: S0195-6701(17)30447-4.

Blinova E, Lau E, Bitnun A, Cox P, Schwartz S, Atenafu E, et al. Point prevalence survey of antimicrobial utilization in the cardiac and pediatric critical care unit. Pediatr Crit Care Med 2013;14(6):e280–288, doi:http://dx.doi.org/10.1097/PCC.0b013e31828a846d.

De Luca M, Dona D, Montagnani C, Lo Vecchio A, Romanengo M, Tagliabue C, et al. Antibiotic Prescriptions and Prophylaxsis in Italian Children. Is it time to change? Data from the ARPEC project. PLoS One 2016;11(5)e0154662, doi:http://dx.doi.org/10.1371/journal.pone.0154662.

Dillon DG, Pirie F, Rice S, Pomilla C, Sandhu MS, Motala AA, et al. African Partnership for Chronic Disease Research (APCDR). Open-source electronic data capture system offered increased accuracy and cost-effectiveness compared with paper methods in Africa. J Clin Epidemiol 2014;67(12):1358–63, doi:http://dx.doi.org/10.1016/j.jclinepi.2014.06.012.

Dramowski A, Whitelaw A, Cotton MF. Burden, spectrum, and impact of healthcare-associated infection at a South African children's hospital. J Hosp Infect 2016;94 (4):364–72, doi:http://dx.doi.org/10.1016/j.jhin.2016.08.022.

Feleke M, Yenet W, Lenjisa JL. Prescribing pattern of antibiotics in pediatric wards of Bishoftu Hospital, East Ethiopia. Int J Basic Clin Pharmacol 2013;2(6):718–22.

Fisher BT, Meaney PA, Shah SS, Irwin SA, Grady CA, Kurup S, et al. Short report: Antibiotic use in pediatric patients admitted to a referral hospital in Botswana. Am J Trop Med Hyg 2009;81(1):129–31.

Gandra S, Singh KS, Dasaratha JR, Ravishankar K, Ashok KC, Anita S, et al. Point prevalence surveys of antimicrobial use among hospitalized children in six hospitals in India in 2016. Antibiotics (Basel) 2017;6(3):19, doi:http://dx.doi.org/10.3390/antibiotics6030019.

Grohskopf LA, Huskins WC, Sinkowitz-Cochran RL, Levine GL, Goldmann DA, Jarvis WR, et al. Use of antimicrobial agents in United States neonatal and pediatric intensive care patients. Pediatr Infect Dis J 2005;24(9):766–73, doi:http://dx.doi.org/10.1097/01.inf.0000178064.55193.1c.

Kreitmeyr K, von Both U, Pecar A, Borde JP, Mikolajczyk R, Huebner J. Pediatric antibiotic stewardship: successful interventions to reduce broad-spectrum antibiotic use on general pediatric wards. Infection 2017;45(4):493–504, doi:http://dx.doi.org/10.1007/s15010-017-1009-0.

Labi AK, Obeng-Nkrumah N, Nartey ET, Bjerrum S, Adu-Aryee AN, i Ofori-Adjei YA, et al. Antibiotic use in a tertiary healthcare facility in Ghana: a point prevalence survey. Labi et al. Antimicrob Resist Infect Control 2018;7:15, doi:http://dx.doi.org/10.1186/s13756-018-0299-z.

Monteiro LGS, Chauque A, Barros MP, Ira TR. Determinants of antibiotic prescription in paediatric patients: the case of hospitals Maputo, Mozambique. S Afr J Child Health 2017;11(3):109–11, doi:http://dx.doi.org/10.7196/SAJCH.2017.v11i3.1224.

National Healthcare Safety Network. Surveillance definition of healthcare-associated infection and criteria for specific types of infections in the acute care setting. January 2013 (v.17-1). 2013 Available at: https://www.cdph.ca.gov/programs/hai/Documents/Slide-Set-20-Infection-Definitions-NHSN-2013.pdf. [Last accessed 27 February 2018].

Newland JG, Banerjee R, Gerber JS, Hersh AL, Steinke L, Weissman SJ. Antimicrobial stewardship in pediatric care: strategies and future directions. Pharmacotherapy 2012;32(8):735–43, doi:http://dx.doi.org/10.1002/j.1875-9114.2012.01155.x.

Rattanaumpawan P, Boonyasiri A, Vong S, Thamlikitkul V. Systematic review of electronic surveillance of infectious diseases with emphasis on antimicrobial resistance surveillance in resource-limited settings. Am J Infect Control 2017;10:, doi:http://dx.doi.org/10.1016/j.ajic.2017.08.006 pii: S0196-6553(17)30953-7.

Reddy SC, Jacob JT, Varkey JB, Gaynes RP. Antibiotic use in US hospitals: quantification, quality measures and stewardship. Expert Rev Anti Infect Ther 2015;13(7):843–54, doi:http://dx.doi.org/10.1586/14787210.2015.1040766.

Smith MJ, Gerber JS, Hersh AL. Inpatient antimicrobial stewardship in pediatrics: a systematic review. J Pediatric Infect Dis Soc 2015;4(4):e127–35, doi:http://dx.doi.org/10.1093/jpids/piu141.

Tadesse BT, Elizabeth A, Ongarello S, Havumaki J, Wijegoonewardena M, González IJ, et al. Antimicrobial resistance in Africa: a systematic review. Tadesse et al. BMC Infect Dis 2017;17:616, doi:http://dx.doi.org/10.1186/s12879-017-2713-1.

Versporten A, Sharland M, Bielicki J, Drapier N, Vankerckhoven V, Goossens H, et al. The antibiotic resistance and prescribing in European Children project: a neonatal and pediatric antimicrobial web-based point prevalence survey in 73 hospitals worldwide. Pediatr Infect Dis J 2013;32(6):e242–53, doi:http://dx.doi.org/10.1097/INF.0b013e318286c612.

World Health Organization. WHO. WHO Collaborating Centre for Drug Statistics: definitions and general considerations. Geneva: World Health Organization; 2018 Available from: https://www.whocc.no/ddd/definition_and_general_considera/. [Last accessed 8 March 2018].