Infection and Drug Resistance Dovepress

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Antimicrobial Use Among Hospitalized Neonates and Children; Findings and Implications from a Comprehensive Point Prevalence Survey Among General Tertiary Hospitals in Pakistan

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Purpose: Antimicrobial resistance is a global health crisis exacerbated by excessive and inappropriate use of antibiotics, especially among low- and middle-income countries including Pakistan. The paediatric population is a key area in view of their vulnerability and excessive prescribing of antibiotics in Pakistan. Consequently, there is an urgent need to robustly assess antimicrobial use among hospitalized neonates and children in tertiary hospitals in Pakistan as they are generally the training centres for new physicians subsequently treating children.

Patients and Methods: A point prevalence survey (PPS) was conducted in the children's wards of 14 tertiary care hospitals in Punjab Province, covering over 50% of the population of Pakistan. This builds on a previous PPS among tertiary care hospitals treating exclusively neonates and children.

Results: A total of 1811 neonates and children were surveyed with 1744 patients prescribed antibiotics, a prevalence of 96.3%. A total of 2747 antibiotics were prescribed to these 1744 neonates and children, averaging 1.57 antibiotics per patient. Overall, 57.7% of the patients were prescribed one antibiotic and 27.2% two antibiotics, with 85.6% of antibiotics administered parenterally. Over a third (34.4%) of the antibiotics were prescribed prophylactically, with 44.7% of them for surgical procedures. Among those prescribed antibiotics for surgical procedures, 75.2% were prescribed for more than one day. Overall, 92.2% of antibiotics were prescribed empirically, with 86.2% prescribed without mentioning the rationale for their choice in the notes, with 77.6% having no stop date. Respiratory tract infections were the most common indication (43.4%). *Staphylococcus* species (36.0%) were the most common pathogen with limited Culture and Sensitivity Testing performed. Three quarters (75.2%) of antibiotics were from the Watch list, and 24.4% were Access antibiotics.

Conclusion: A very high prevalence of antibiotic use among neonates and children in tertiary hospitals in Pakistan, including Watch antibiotics, mirroring previous studies. Consequently, initiatives including antimicrobial stewardship programmes are urgently needed to address current inappropriate prescribing.

Keywords: point prevalence survey, tertiary hospitals, children, neonates, antibiotics, AWaRe classification, Pakistan

Introduction

Childhood morbidity and mortality are a continuing concern globally, with infectious diseases a principal cause of death among children, particularly among low- and middle-income countries (LMICs).[1–4] Whilst mortality rates among children below the age of five years were reduced by up to 60% between 1990 and 2020, there is still considerable

Received: 14 August 2024
Accepted: 31 October 2024
Published: 6 December 2024

mortality in sub-Saharan African and South-Asian countries, currently accounting for 80% of the global mortality burden.[5] This needs to be addressed going forward.

Pakistan is a LMICs located in South-Asia, with the third highest mortality rate in children below the age of five years at 61.0/1000 live births in 2022, however, declining appreciably in recent decades.[5,6] There is still though room for improvement, with 20–30% of childhood deaths currently due to respiratory tract infections.[1,7]

Antibiotics are currently one of the most frequently prescribed classes of medicines among neonates and children worldwide,[8,9] with antibiotics often inappropriately prescribed to neonates and children across LMICs in recent years.[9–14] This has resulted in an appreciable increase in their use among sick children in LMICs between 2005 and 2017.[15,16] The overuse and misuse of antibiotics, including the overprescribing of broad-spectrum antibiotics, are the principal drivers of antimicrobial resistance (AMR) alongside poor infection prevention and control (IPC) measures, poor sanitation and low vaccination rates in LMICs.[17–20]

AMR is now seen as one of the biggest threats to global health, growth and human development due to its considerable impact on morbidity, mortality and costs.[21–24] This is reflected by the United Nations General Assembly (UN GA) in September 2024 urgently requesting countries to instigate additional policies to reduce AMR.[25]

AMR is currently an appreciable threat in Pakistan.[26,27] Both multidrug resistance (MDR) and extensive drug resistance (XDR) cases have been reported in various parts of the country in recent years.[28–32] We are also aware that AMR in neonates and children is currently a considerable challenge in Pakistan, exacerbated by appreciable irrational prescribing of antibiotics.[33–35] Hospitalized settings, particularly in LMICs, are especially vulnerable to AMR due to extensive irrational antibiotic use.[9,36]

Many initiatives have been undertaken globally to address rising AMR rates and their consequences.[37–40] Initiatives include the development of the "Global Action Plan (GAP)" against AMR endorsed by the World Health Assembly in 2015.[39] The primary objectives of the GAP were raising awareness, understanding, knowledge strengthening, surveillance and research against AMR.[39,40] In line with the recommendations of WHO, the Government of Pakistan put forward its own National Action Plan (NAP) against AMR, with similar objectives as the GAP.[41,42] However, there are currently many challenges in the country with implementing the NAP.[27]

Alongside these global initiatives, the WHO also developed its own methodology to document the current utilization of antimicrobial agents among hospitalized patients, especially among LMICs.[43] Their methodology is similar to other PPS methodologies, which include the global PPS methodology.[9,44–46] PPS studies are seen as a robust, effective and an easy to perform methodology to acquire baseline information concerning antibiotic prescribing habits within a specific time frame to formulate and implement future quality improvement programs, including antimicrobial stewardship programmes (ASPs).[44,46–50] Coupled with the GAP initiative, the WHO also developed the AWaRe (Access, Watch, Reserve) classification with the Access group including antibiotics with a lower potential of developing AMR.[51–53] The Watch group includes antibiotics with a greater potential to develop resistance.[53,54] The Reserve group are last-resort antibiotics and should be reserved for life-threatening conditions, including MDR cases.[53–55]

Irrational antibiotic prescribing, which includes high rates of empiric prescribing including those from the Watch list, coupled with a lack of monitoring and culture and sensitivity testing (CST) due to costs, results in appreciable inappropriate antibiotic use across all sectors in Pakistan, including among neonates and children.[11,56–62] This also includes high rates of inappropriate antibiotic prescribing in neonates and children during the recent COVID-19 pandemic.[35,63] A Global PPS comparative study has also shown high rates of prescribing of Watch antibiotics among neonates and children in Pakistan compared with a number of other LMICs as well as high-income countries, with low use of Reserve antibiotics.[9] In view of this, there is an urgent need to update knowledge regarding antibiotic utilisation patterns among hospitalized neonates and children in Pakistan starting with tertiary care hospitals. Tertiary hospitals are important as they are the principal training centres for new physicians in Pakistan, and there are currently considerable concerns with antibiotic prescribing practices in hospitals in Pakistan as well as ambulatory care, including among neonates and children.[11,35,57,60–62,64,65] Consequently, there is a need to build on these findings, including our initial study among selected tertiary hospitals dealing exclusively with neonates and children,[65] with the updated information helping to provide an additional basis for establishing pertinent quality improvement initiatives, including ASPs, in Pakistan. This necessarily starts with general and specific tertiary hospitals treating neonates and children in Pakistan in view of their importance. As a result, help the health authorities in Pakistan design appropriate interventions to improve future antibiotic prescribing in line with the NAP targets, as well as the new UN GA target of 70% for Access antibiotics.[25,41] These were the aims and objectives for this study.

Materials and Methods

Study Design and Setting

A PPS was undertaken among the paediatric wards and sub-wards of 14 tertiary care hospitals in the Punjab Province using the WHO standardized methodology, building on our previous studies among neonates and children.[9,43,60,64] Punjab Province was chosen for this current study because it is the most populous province of the country, currently containing more than half of the country's population.[60,62] As a result, it has the majority of public tertiary hospitals in the country at 60 hospitals (Supplementary Table S1) compared with 8 Public Sector Tertiary Hospitals in Sindh Province, 9 in Khyber Pakhtunkhwa Province and none in Balochistan Province.[11,60,66,67] Punjab is currently divided into 10 metropolitan divisions, with each division divided into district and tehsil levels.[60,62]

In Pakistan, healthcare provision is provided via both the public sector, which is owned by the state government of Pakistan, and the private sector, which is owned by entrepreneurs, health managers and healthcare providers. The public sector health department in Punjab is divided into tertiary care/teaching hospitals named as "Specialized Healthcare and Medical Education Department (SHCME)" and "Primary & Secondary Healthcare Department (P&SHD)".[60,68] From the 60 tertiary care hospitals currently in Punjab Province (Supplementary Table S1), only 3 tertiary care hospitals are specified for neonates and children.[64] Since all three of these hospitals were included in our initial study with neonates and children,[64] they were excluded from this current study. In this phase, 32 tertiary care hospitals of general category (having all specialties) were approached, and the key healthcare professionals (HCPs) of these health facilities were invited for the participation of their hospital in this current study. In order to ensure participation from across the province, at least one tertiary care hospital was included from each metropolitan division in the final list of surveyed hospitals. As a result, it enhances the robustness of the findings.

Fourteen tertiary hospitals were finally included in this PPS study and were designated anonymously as H1, H2, and up to H14 in line with other PPS studies involving multiple hospitals.[43,64] All these hospitals are equipped with the necessary facilities to provide tertiary-level care. This includes neonatal medical wards, neonatal intensive care units (NICU), paediatric medical wards, paediatric surgical wards and paediatric intensive care wards.

Data Collection Procedure

The PPS methodology was used to collect baseline information about antibiotic use among neonates and children admitted to these 14 health facilities over a six-month period (July–December, 2023). The principal investigator (ZUM) briefed participating HCPs concerning the purpose of the study and its methodology, as well as inclusion and exclusion criteria before initiation of data collection.

The data collection team subsequently visited different wards of the participating hospital at 8:00 AM on the day of the survey, in line with the Global and WHO methodologies.[43–46] They first obtained the number of inpatients present in the ward at 08:00 AM from the clinical staff for the purpose of having the denominator to calculate point prevalence antibiotic prescribing. Following this, the medical records of only patients present at 08:00 AM were thoroughly reviewed by the team to obtain the necessary data to be recorded in the data collection forms. Clinical staff were only contacted during data collection, in case of any clarification needed, based on the information contained in the medical records.

The data collection form was divided into three sections in line with the initial PPS study in the selected tertiary hospitals dealing exclusively with neonates and children, similar to other PPS studies:[9,60,64]

i) The first two sections collected information relating to the hospital, which included the total number of beds in the hospital and in the children's wards. In addition, the functionality and the total number of beds in each of the children's wards in each of the tertiary hospitals.

ii) In the third section, patient-related information was gathered. This included the age, sex, reason for hospitalization and diagnosis. The different age groups included in the study population were neonates (1–28 days), infants (29 days-1 year), young children (>1–5 years) and children (>5–12 years) in line with previous PPS studies.[60] For surgical prophylaxis, the duration of prescribed antibiotics was also recorded since ideally only short courses should be given and not be extended post-operatively to reduce costs and adverse reactions as well as AMR.[69] This section also collected detailed information about the Anatomical Therapeutic Chemical (ATC) classification code for prescribed antibiotics,[70] their route of administration, the rationale for the antibiotics being prescribed (if recorded), and the stop date/time (if recorded). The antibiotics prescribed were further classified according to the WHO's AWaRe classification to help assess the quality of prescribing with an initial target of Access antibiotics accounting for 60% of total utilization although extended to 70% by the UN GA in September 2024.[25,53,54] Where possible, CST data was collected from patients' medical records acknowledging this is a challenge in Pakistan with high patient copayments for these tests and many hospitals, including secondary care hospitals, typically not having CST facilities.[60,64]

Inclusion and Exclusion Criteria

All inpatient children and neonates who had stayed overnight and who were present in the ward at 8:00 AM on the day of survey were included in the study. All children who had visited these hospitals for short-stays, including those who visited hospital's emergency departments or day care centers, or attended the hospital for short procedures such as day-case surgery, were excluded.

Details of any antibiotics that were prescribed after 8:00 AM on the day of the survey were excluded alongside the details of any antibiotics prescribed via the topical route, in line with the PPS methodology.[9,44,60,64]

Data Management and Statistical Analysis

All the data were entered into SPPS version 22 for descriptive analysis. Continuous data were summarized as means, while categorical data were expressed as frequencies and percentages. For calculating the prevalence of antibiotic prescribing, the denominator comprised the total number of patients present in the respective wards at 08:00 AM on the morning of the survey, while the number of patients, who had an antibiotic prescribed in their medical records at that point in time, served as the numerator. The total number of antibiotics prescribed served as the denominator when discussing the number and nature of antibiotics prescribed.

Ethical Approval

The study complied with the Declaration of Helsinki. Ethical approval of the PPS studies was obtained from the Human Research Ethics Committee, Department of Pharmacy Practice, The University of Lahore (REC/DPP/FOP/69) as well as the Ethics Committee of Universiti Sains Malaysia (USM/JEPeM/PP/23090693). Approval and permission to conduct the study were also obtained from the participating hospitals prior to initiation of the study. Data were obtained from medical records, and consequently, the need for written informed consent was waived by the Ethics Committee in line with other PPS studies.[59,60,71–74] Furthermore, the data obtained from participants' medical records were deidentified through coding and stored in a password-protected file, accessible to the researchers only. As a result, it complies with the Declaration of Helsinki.

Results

Records of 1811 neonates and children were surveyed among 2047 beds in the children's wards and sub-wards of the 14 public sector tertiary care hospitals, participating on the day of the survey. Overall, the beds in neonatal and children's wards in these 14 tertiary hospitals represented 12.1% of the total number of beds in the participating hospital, with the beds split between neonatal and paediatric ICUs as well as neonatal and paediatric medical and surgical wards. This compares with 100% among tertiary hospitals exclusively treating neonates and children.

Overall, 1744 neonates and children were prescribed antibiotics, giving a 96.3% prevalence rate (Table 1).

The majority of the neonates and children receiving antibiotics were male (62.6%) and neonates (46.4%), with 57.7% of the surveyed patients prescribed one antibiotic and 27.2% prescribed two antibiotics. The average was 1.57 antibiotics

Table 1 Hospital Wards, Beds, Patient-Related Information and Prescribed Antibiotics Distributed by Hospital

Variables	Number per hospital														Total; n (%)
	H1	H2	H3	H4	H5	H6	H7	H8	H9	H10	H11	H12	H13	H14	
Total beds in hospital	630	400	1450	550	780	1160	600	1500	1670	2300	1800	920	900	2150	16,810
Beds in children's ward	65	53	196	80	82	119	70	254	111	277	236	80	94	330	2047 (12.1%)
Beds in children's sub-wards															
Neonatal medical ward	12	20	70	22	18	40	14	58	13	48	57	30	36	92	530 (25.9)
Neonatal ICU	10	8	14	12	10	28	8	52	18	78	62	16	10	66	392 (19.1)
Pediatric medical ward	24	13	60	20	24	26	24	64	23	63	62	18	26	50	497 (24.3)
Pediatric surgical ward	6	4	26	12	14	7	6	46	40	48	25	8	8	74	324 (15.8)
Pediatric ICU	13	8	26	14	16	18	18	34	17	40	30	8	14	48	304 (14.9)
Patients in children's sub-wards															
Neonatal medical ward	10	14	61	18	14	39	12	51	11	44	55	26	30	89	474 (26.2)
Neonatal ICU	8	8	13	9	10	26	8	50	17	72	60	14	10	60	365 (20.1)
Pediatric medical ward	20	10	51	18	20	26	18	60	23	57	60	14	20	45	442 (24.4)
Pediatric surgical ward	4	4	8	7	12	7	4	34	39	40	22	3	5	71	260 (14.4)
Pediatric ICU	12	8	24	12	14	16	14	30	17	38	27	6	12	40	270 (14.9)
Total number of patients in children's ward at 8:00 AM on the day of the survey	54	44	157	64	70	114	56	225	107	251	224	63	77	305	1811
Patients prescribed an antibiotic in children's sub-wards															
Neonatal medical ward	8	13	49	16	14	39	12	46	11	44	55	26	28	83	444 (25.6)
Neonatal ICU	8	8	13	9	10	26	8	50	17	72	60	14	10	60	365 (20.9)
Pediatric medical ward	17	10	41	14	18	26	16	58	23	57	60	12	16	45	413 (23.7)
Pediatric surgical ward	4	4	8	7	10	7	4	30	39	40	20	3	5	71	252 (14.4)
Pediatric ICU	12	8	24	12	14	16	14	30	17	38	27	6	12	40	270 (15.5)
Total number of neonates and children in each hospital prescribed an antibiotic	49	43	135	58	66	114	54	214	107	251	222	61	71	299	1744 (96.3)
Total number of prescribed antibiotics	81	87	212	112	128	191	105	317	207	337	330	88	132	420	2747
Patients per age group															
Neonates	16	21	62	25	24	65	20	96	28	116	115	40	38	143	809 (46.4)
Infants	6	7	23	8	13	8	7	26	14	48	28	5	10	43	246 (14.1)
Young child	14	10	21	4	16	13	14	37	18	30	21	9	17	77	301 (17.3)
Child	13	5	29	21	13	28	13	55	47	57	58	7	6	36	388 (22.2)

(*Continued*)

Table 1 (Continued).

Variables	Number per hospital														Total; n (%)
	H1	**H2**	**H3**	**H4**	**H5**	**H6**	**H7**	**H8**	**H9**	**H10**	**H11**	**H12**	**H13**	**H14**	
Antibiotics prescribed per patient															
One antibiotic	26	12	88	26	23	55	21	141	29	182	134	40	32	204	1005 (57.7)
Two antibiotics	14	18	33	10	24	41	15	43	56	52	68	15	17	69	475 (27.2)
Three antibiotics	9	13	22	22	19	18	18	30	22	17	20	6	22	26	264 (15.1)
Sex of those prescribed antibiotics															
Male	23	16	101	36	42	69	23	132	76	159	121	41	42	211	1092 (62.6)
Female	26	27	34	22	24	45	31	82	31	92	101	20	29	88	652 (37.4)
Route of administration															
Oral	12	9	36	18	13	41	8	41	24	54	36	14	23	67	396 (14.4)
Parenteral	69	78	176	94	115	150	97	276	183	283	294	74	109	353	2351 (85.6)
Sub-specialty															
Medical	42	36	94	45	42	82	55	126	106	156	183	34	42	146	1189 (43.3)
Surgical	13	9	21	14	17	22	16	48	18	61	34	14	16	38	341 (12.4)
ICU	26	42	97	53	69	87	34	143	83	120	113	40	74	236	1217 (44.3)
Indications															
Therapeutic use	61	63	112	65	89	125	70	179	91	181	236	45	82	205	1611 (58.7)
Prophylaxis use	16	13	81	42	34	48	27	124	109	131	78	31	47	164	945 (34.4)
Unknown	4	11	12	5	5	18	8	14	14	25	16	12	3	51	191 (7.9)
Indications for prophylaxis															
Surgical	6	6	38	17	18	13	10	56	52	52	39	13	17	86	423 (44.7)
Medical	10	7	43	25	16	35	17	68	57	79	39	18	30	78	522 (55.3)
Duration of surgical prophylaxis															
Single dose	1	0	5	0	1	2	0	5	2	3	0	1	3	13	36 (8.5)
One day	2	2	4	3	5	1	0	8	9	13	2	0	2	18	69 (16.3)
More one day	3	4	29	14	12	10	10	43	41	36	37	12	12	55	318 (75.2)

Indication of infection for prescribed antibiotics															
Non-hospital acquired, eg prophylaxis or admitted with an infection	67	82	176	103	117	150	91	291	184	319	322	88	124	364	2478 (90.2)
Hospital acquired	14	5	36	9	11	41	14	26	23	18	8	-	8	56	269 (9.8)
Reasons noted for the antibiotic prescribed															
No	65	71	181	106	104	145	102	253	189	256	274	84	118	338	2286 (86.2)
Yes	16	16	31	6	24	46	3	64	18	81	56	4	14	82	461 (16.8)
Antibiotic stop date noted															
Yes	49	64	118	66	77	139	105	236	198	266	311	80	115	307	2131 (77.6)
No	32	23	94	46	51	52	-	81	9	71	19	8	17	113	616 (22.4)
Types of therapy															
Empirical therapy	75	87	196	103	122	178	91	289	199	303	314	81	119	376	2533 (92.2)
Targeted therapy	6	-	16	9	6	13	14	28	8	34	16	7	13	44	214 (7.8)

per patient. ICU patients (paediatric and neonatal) accounted for 44.3% of the prescribed antibiotics, followed by medical (43.3%) and surgical wards (12.4%).

Overall, 58.7% of antibiotics were prescribed therapeutically and 34.4% prophylactically principally via the parenteral route of administration (85.6%). Within prophylaxis, 44.7% were prescribed for a surgical procedure, with 75.2% prescribed antibiotics for more than one day following surgery. Most antibiotics (90.2%) were prescribed for either community-acquired infections or for prophylaxis, with the remainder (9.8%) prescribed for hospital acquired infections.

Alongside this, 86.2% of antibiotics were prescribed without mentioning the reasons for the choice of antibiotics in the medical records. Three quarters (77.6%) of neonates and children also had no stop date for the prescribed antibiotics recorded in their medical notes.

Respiratory tract infections were the most common indication (43.4%) for antibiotics. Other common indications included prophylaxis for medical problems (14.1%) and prophylaxis for surgical procedures (12.8%) (Table 2).

The vast majority (92.2%) of antibiotics were prescribed empirically, with CST data only recorded in 7.8% of neonates and children. As a result, only 7.8% received targeted antibiotics (Table 1). Among the pathogens identified following limited CST testing, the *Staphylococcus* species were the most common (36.0%) followed by the *Klebsiella* species (16.3%) and *Escherichia* coli (16.3%). The common resistant antibiotics for the *Staphylococcus* species were penicillins, erythromycin, ciprofloxacin and levofloxacin, while the common sensitive antibiotics were vancomycin, linezolid and imipenem. Other pathogens reported among the neonates and children were the *Pseudomonas* species (13.1%), *Shigella* species (9.4%) and the *Proteus* species (9.4%) (Table 3).

Details of prescribed antibiotic classes and individual agents are presented in Table 4. Ceftriaxone was one of the most commonly prescribed antibiotics (28.8%), followed by cefotaxime (13.2%). Antibiotic prescriptions, categorised according to the WHO AWaRe classification, are shown in Figure 1 with their respective percentages for each category. Overall, 75.2% of antibiotics were prescribed from the Watch category with only 24.4% from the Access category. However, there was appreciable variation between the participating hospitals (Figure 1).

Discussion

We believe this is the first study to comprehensively document antibiotic prescribing patterns among neonates and children in public tertiary care referral hospitals in Pakistan that treat all patients since the launch of the NAP as well as the new prescribing targets for Access antibiotics set by the UN GA in September 2024. These findings build on our previous study among three selected tertiary care hospitals dealing exclusively with neonates and children, the studies of

Table 2 Indications for Prescribed Antibiotics Among the Study Participants Distributed by Hospital

Infection Type	Number per hospital														Total; n (%)
	H1	H2	H3	H4	H5	H6	H7	H8	H9	H10	H11	H12	H13	H14	
Respiratory tract infections	16	21	43	14	25	60	24	78	78	117	123	28	34	126	757 (43.4)
Prophylaxis for medical problems	8	4	11	06	4	11	11	22	13	47	24	7	12	67	247 (14.1)
Prophylaxis for surgical diseases	6	4	24	9	9	7	5	37	24	20	18	4	5	51	223 (12.8)
Blood stream infection	5	7	21	14	10	7	5	22	9	16	17	8	4	15	160 (9.2)
Gastrointestinal infections	7	2	13	3	8	11	5	21	6	14	14	8	5	23	140 (8.0)
Sepsis	1	2	11	10	2	14	3	11	4	19	13	4	4	4	102 (5.9)
Urinary tract infections	3	2	05	0	3	2	1	12	0	11	7	0	5	7	58 (3.3)
Skin and soft tissue infections	3	1	07	02	5	2	0	11	3	7	6	2	2	6	57 (3.3)

Table 3 Antibiotic Resistance and Antibiotic Sensitivity Profiles of Commonly Identified Bacterial Species Distributed by Hospital

Commonly Identified Bacterial Species	Common Resistance Antibiotics	Common Sensitive Antibiotics	Number per Hospital														Total; n (%)
			H1	H2	H3	H4	H5	H6	H7	H8	H9	H10	H11	H12	H13	H14	
Staphylococcus species	Ampicillin Amoxicillin, Erythromycin, Ciprofloxacin, Levofloxacin,	Vancomycin, Linezolid, Imipenem	3	–	6	3	–	7	6	8	1	13	6	2	6	16	77 (36.0)
Klebsiella species	3rd generation cephalosporins eg Cefotaxime, Ceftriaxone	Cefoperazone +beta-lactamase inhibitor, Meropenem, Imipenem, Fosfomycin	1	-	3	3	1	1	3	7	3	2	2	2	-	7	35 (16.3)
Escherichia coli	Ampicillin, Amoxicillin, Third-generation cephalosporins	Carbapenems egMeropenem, Imipenem, Fosfomycin, Amikacin	1	-	3	1	3		2	6		4	3	1	3	8	35 (16.3)
Pseudomonas species	Ceftazidime, Piperacillin/ Tazobactam, Penicillins, Amikacin, Gentamicin	Colistin, Cefepime	-	-	2	1	2	4	-	4	-	6	2	1	2	4	28 (13.1)
Shigella species	Ampicillin, Amoxicillin	Ciprofloxacin, Third-generation cephalosporins	-	-	2				3	2	2	6	-	1	1	3	20 (9.4)
Proteus species	Tigecycline, Piperacillin/ Tazobactam	Amikacin, Cefoperazone, Ciprofloxacin, Imipenem, Meropenem	1	-		1		1		1	2	3	3	-	1	6	19 (8.9)

Table 4 Details of Prescribed Antibiotics According to ATC Classification Distributed by Hospital

ATC Class	Name of Antibiotic (ATC code)	Number Per Hospital														Total; n (%)
		H1	H2	H3	H4	H5	H6	H7	H8	H9	H10	H11	H12	H13	H14	
Third-generation cephalosporins	Ceftriaxone (J01DD04)	26	37	59	33	37	42	27	66	93	81	101	16	31	142	791 (28.8)
	Cefotaxime (J01DD01)	7	7	19	8	13	43	7	56	24	64	38	14	13	51	364 (13.2)
	Ceftazidime (J01DD02)	8	4	7	12	8	16	13	22	4	6	19	22	8	24	173 (6.3)
	Cefixime (J01DD08)	4	0	6	0	0	0	0	0	0	0	0	0	4	16	30 (1.1)
	Cefoperazone + beta-lactamase inhibitor (J01DD12)	4	2	4	3	7	6	4	14	0	0	8	0	0	8	60 (2.2)
Aminoglycoside	Amikacin (D06AX12)	13	10	36	12	23	6	13	16	12	27	24	12	25	33	262 (9.5)
Glycopeptide antibacterials	Vancomycin (J01XA01)	3	6	8	2	8	8	7	17	14	22	23	0	4	17	139 (5.1)
Macrolides	Azithromycin (J01FA10)	0	1	5	5	0	0	0	0	3	6	12	2	9	14	57 (2.1)
	Clarithromycin (J01FA09)	0	3	4	4	0	22	0	10	13	34	24	6	6	6	132 (4.8)
Piperacillin and enzyme inhibitor	Piperacillin + enzyme inhibitor (J01CR05)	0	0	5	0	0	0	6	7	0	2	0	0	4	8	32 (1.2)
Aminopenicillins	Ampicillin (J01CA01)	0	0	14	5	13	14	7	35	8	35	22	6	9	21	189 (6.9)
Amoxicillin + beta-lactamase inhibitors	Amoxicillin + beta-lactamase inhibitors (J01CR02)	3	3	10	6	0	0	0	12	0	0	0	0	2	12	48 (1.7)
Carbapenems	Meropenem (J01DH02)	2	8	9	11	6	15	13	28	28	41	31	0	7	22	221 (8.0)
	Imipenem and cilastatin (J01DH51)		0	0	0	0	0	0	3	0	0	5	0	0	4	12 (0.4)
Fluoroquinolones	Ciprofloxacin (J01MA02)	3	2	05	3	5	8	3	3	2	5	7	0	3	4	53 (2.0)
Imidazole derivatives	Metronidazole (J01XD01)	5	2	13	3	8	11	5	21	6	14	14	8	5	23	138 (5.0)
Fourth-generation cephalosporins	Cefepime (J01DE01)	0	0	0	2	0	0	0	7	0	0	2	0	2	0	13 (0.5)
Penicillins with extended spectrum	Amoxicillin (J01CA04)	3	2	8	3	0	0	0	0	0	0	0	2	0	15	33 (1.2)

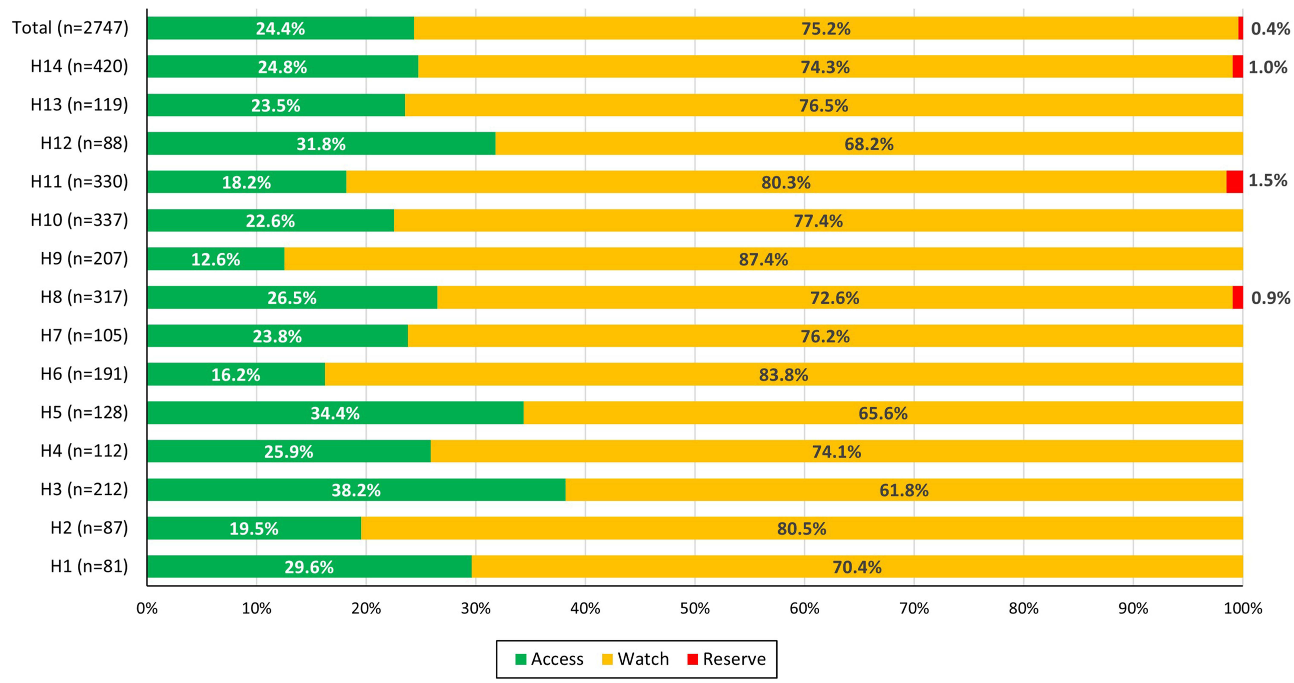

Figure 1 Number (%) of antibiotics prescribed according to the WHO AWaRe classification distributed by hospital.

Arif et al, involving two public tertiary care hospitals, and Ambreen et al, which included paediatric wards among both public and private tertiary hospitals, reporting antibiotic point prevalence rates ranging from 84% to 99%.[61,64,65] This is similar to our findings of a prevalence rate of 96.3%, suggesting continuing concerns in trying to improve antibiotic prescribing among neonates and children in Pakistan to attain NAP and UN GA targets for AMR. We also saw high rates of prescribing of antibiotics at 97% in our PPS study conducted among neonates and children in 16 public secondary care hospitals in Pakistan, confirming concerns among all types of public hospitals in Pakistan.[60] Similar prevalence rates of antibiotics prescribed to neonates and children were also seen in studies conducted in India (up to 89%), Nigeria (89.7% pre ASP), South Africa (92%), China (up to 93%), and Mozambique (97.5%).[75–79] However, lower rates of antibiotic prescribing have been seen among hospitalized neonates and children in other LMICs, including also South Africa (49.7%),[73] India (51.6% to 61.5%),[12,80] China (66.1% to 67.76%),[13,81] Nigeria (49.5%),[82] and Myanmar (63.4%).[83] We are not sure of the reasons behind these differences among countries. However, this may reflect different populations, the availability and use of appropriate diagnostic facilities including CST findings, as well as the availability and use of treatment guidelines as part of ASPs.[84–86] Lower rates of antibiotic prescribing among hospitalized neonates and children in other LMICs can be used as exemplars to key stakeholder groups in Pakistan to instigate appropriate measures to improve future prescribing among this vulnerable population, including ASPs. As a result, it helps towards attaining NAP and UN GA AMR mortality goals.[25,27]

Our study also revealed that the average number of antibiotics prescribed per patient was 1.57 among participating hospitals, similar to our previous studies undertaken among secondary (2.06) and selected tertiary care hospitals (1.9).[60,64] In contrast to these findings, a multi-country study showed lower rates of antibiotics prescribed per neonate in neonatal intensive care units (≥1),[87] providing a goal for key stakeholders treating neonates and children in hospitals in Pakistan. Most of the neonates and children (57.7%) in our current study were prescribed one antibiotic on the day of the survey, which compares with Italy, where the authors documented in their PPS that 40% of children were prescribed one antibiotic.[88] However, higher than only 19.6% of neonates and children in the three selected tertiary hospitals in Pakistan dealing exclusively with this population, with 59.9% receiving two antibiotics and 20.4% three or more.[64] These differences may reflect differences and concerns, including the extent of IPC initiatives and attitudes towards antibiotic prescribing, which we will be following up.

Our study also showed that the majority of the antibiotics were prescribed via the parenteral route of administration (85.6%), similar to our previous PPS studies in secondary (95.8%) and selected tertiary care hospitals (92.3%) as well as other studies from Pakistan and those from China, Mozambique and South Africa.[60,61,64,79,81,89] This is a concern as the parenteral route of administration can cause problems. These include pain at the injection site, poor patient compliance, phlebitis, local and systemic infections, as well as potentially increasing the length of hospital stay and associated costs.[90–93] A European study involving paediatric patients showed an appreciably lower percentage of participants prescribed antibiotics via the parenteral route, again providing future guidance to hospitals in Pakistan.[94]

Our current study further demonstrated considerable antibiotic use among children admitted to medical wards of the tertiary care hospitals compared to ICUs, comparable to previous studies from India and Turkey as well as our initial study among selected tertiary care hospitals in Pakistan dealing exclusively with neonates and children.[12,64,95] This must also be addressed going forward to help reduce AMR.

Of equal concern is that nearly one-third of the total number of antibiotics prescribed prophylactically, especially for surgical prophylaxis, were prescribed for more than one day. Whilst these findings were comparable to those in our earlier studies among secondary care hospitals and selected tertiary care hospitals, as well as other LMICs,[44,60,64,69,96–98] this also needs to be addressed moving forward in Pakistan to reduce adverse drug reactions, costs and AMR. Overall, the duration of prophylactic antibiotic use should be less than one day.[69,99,100]

Alongside this, most of the neonates and children in our study were prescribed antibiotics empirically and without documenting the rationale behind the chosen antibiotic, mirroring our earlier studies among secondary care and selected tertiary care hospitals.[60,64] This is important as CST can guide appropriate antibiotic use. Notwithstanding this, empiric prescribing of antibiotics also happens in other LMICs due to a number of challenges. These include insufficient resources, high patient co-payments and lack of awareness among HCPs regarding diagnostic facilities.[69,72,76,101–103] We also see similar situations in higher-income countries, with three-quarters of infants who received antibiotics for >48 hours in neonatal units in the US not having their infections proven using the results of cultures.[104] However, this is not always the case.[105] Consequently, going forward, hospitals particularly those across LMICs, including those in Pakistan, need to have appropriate diagnostic facilities routinely in place, alongside trained personnel, to help with the selection of appropriate antibacterial therapy. We will continue to monitor this to improve the appropriateness of antibiotic prescribing in neonates and children throughout Pakistan given current concerns.

Another area of concern in our findings is that the majority of antibiotics were prescribed without mentioning the reason for their selection in patients' medical records or the stop date and time, similar to our previous studies among secondary care and selected tertiary care hospitals, as well as in other LMICs.[48,60,64,72,76] However, these findings were different from those from a European study.[94] This again needs to be addressed going forward and linked to concerns about a lack of CST findings, as well as guidelines, to improve future prescribing.

Respiratory tract infections were a common indication of antibiotic prescriptions in our study, followed by antibiotics prescribed for prophylaxis, blood stream and gastrointestinal tract infections, similar to our previous study involving secondary care as well as selected care tertiary hospitals as well as the Global PPS study of Hsia et al.[9,60,64] This contrasts with the findings from a study in Myanmar where more than a quarter of children were prescribed antibiotics for surgical prophylaxis.[83] This though may reflect the different age groups of the children included in the various studies, with differences in the rationale for antibiotic prescribing.

Another key concern was the appreciable prescribing of antibiotics from the Watch list in our study (75.2% of all antibiotics prescribed), although there was very limited prescribing of Reserve antibiotics at just 0.4% (Figure 1). Whilst these rates are similar to our previous study in Pakistan involving tertiary hospitals exclusively treating neonates and children (76.6% Watch and 21.6% Access), they are higher than seen among hospitals in Pakistan in the Global PPS study of Hsia et al.[9,64] This increase may reflect the growing prescribing generally of antibiotics from the Watch and Reserve groups in recent years among LMICs.[106] Having said this, our recent study among neonates and children treated in secondary care hospitals showed a higher utilisation of antibiotics from the Access group at 49.5% of all antibiotics, with lower use of Watch antibiotics at 45.5%, with again limited prescribing of Reserv antibiotics.[60] This was similar to the findings from South Africa, where between 55.2% and 55.9% of antimicrobials prescribed in hospitalized paediatric patients were from the Access group.[73,89] The high rate of prescribing of third-generation cephalosporins, especially ceftriaxone, in our study, as well as other Watch antibiotics may reflect high rates of empiric prescribing with currently limited use of CST to guide targeted treatment. This needs to be urgently addressed if Pakistan is to reach the suggested UN GA goal of 70% of antibiotic use across sectors being from the Access group. The recent publication of the AWaRe book, providing prescribing guidance across a range of infectious diseases, should help with improving future antibiotic prescribing,[51,107] and we will continue to monitor this situation along with advocating greater use of CST. The limited extent of CST testing in this study identified *Staphylococcus* species, *pseudomonas* species, *Escherichi*a *coli* and *Klebsiella* species as common bacterial isolates and were mostly susceptible to vancomycin, levofloxacin and carbapenems, respectively, similar to a previous study from South Africa as well as among selected tertiary care hospitals in Pakistan,[60,64,73] and in addition, similar to the findings of Williams et al which concern antibiotic prescribing in serious bacterial infections in neonates and children among Southeast Asian and Pacific countries.[102]

Principal ways forward to address the current appreciable prescribing of Watch antibiotics in this vulnerable population include the introduction of appropriate ASPs among tertiary hospitals in Pakistan, building on our PPS findings.[84,85,108,109] We are aware that the introduction of ASPs can be challenging across LMICs due to resource and personnel constraints.[110,111] However, this is changing given their potential impact, and provides direction to all key stakeholders in Pakistan going forward.[46,49,50,84,85,112–116] This is important given concerns with current knowledge and ASP activities among hospitals in Pakistan.[111,117,118] Proposed activities start with training regarding the rationale and activities involved with instigating ASPs in hospitals. These activities can be undertaken by those involved with the training of future physicians, pharmacists and other relevant personnel in tertiary hospitals. Subsequently, we are instigating pertinent ASPs, including those surrounding prophylaxis, based on the AWaRe book and other recognised international guidance.[49,51,55,69,86,109] Such measures could also include the introduction of agreed quality indicators, with the long-term aim of reducing the prescribing of Watch antibiotics to at least 30% of all antibiotics prescribed among hospitals treating children.[25,97,119,120] This will take time in Pakistan given current high rates of the prescribing of Watch antibiotics in all hospitals including among children. However, it is important to start with neonates and children in tertiary hospitals given our current findings, building on previous publications.

We are aware of a number of limitations with our study. First, we only conducted this study in the Punjab Province for the reasons stated. Second, as explained, we collected data only from public sector hospitals and did not include hospitals from the private sector again for the reasons stated. Third, we did not assess IPC practices and available diagnostic facilities at the participating hospitals as this is typically not part of PPS studies, which just rely on patient records. However, we believe the findings of our study are novel and robust to comprehensively ascertain the prevalence of antibiotic use among neonates and children hospitalised in tertiary hospitals across the province, building on our previous studies among secondary care as well as selected tertiary care hospitals. Consequently, the combined study findings should be helpful for all key stakeholder groups across Pakistan to urgently formulate comprehensive and pertinent ASPs to address excessive and inappropriate antibiotic prescribing among neonates and children in the country.

Conclusion

Overall, there was a very high prevalence of antimicrobial prescribing among hospitalized neonates and children in tertiary hospitals in Pakistan, including high rates of prescribing via the parenteral route, empirically, and from the Watch category. Extended prophylactic use was also common, alongside a lack of documentation of the rationale behind the selection of prescribed antibiotics and stop date/times. These concerns urgently need to be addressed with the training and instigation of pertinent ASPs to reach the UN GA goals of 70% antibiotic prescribing being from the Access group. The recent introduction of the AWaRe book and associated quality indicators should help in this regard. Alongside this, instigating measures especially in tertiary hospitals to enhance CST. We will continue to monitor the situation.

Acknowledgments

We are grateful to the administration and the healthcare providers of the surveyed hospitals for access to the records and their support during data collection, which contributed to the successful completion of this project.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This research received no external funding, and the authors declare no relevant conflicts of interest.

Disclosure

The authors report no conflicts of interest in this work.

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