

Antimicrobial Resistance Pattern Among Paediatric Inpatients; A Retrospective Cross Sectional Study Of A Tertiary Hospital In Markudi, Benue State Of Nigeria.

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Abstract

Introduction: Antimicrobial resistance (AMR) is considered one of the biggest threats to global health, food security and development. Presently, it is considered one of the most critical public health threats worldwide and should be considered a high priority by all healthcare workers and institutions.

Objectives: This study aimed to assess antimicrobial resistance patterns among the paediatric population in a Nigerian tertiary hospital.

Method: It was a retrospective cross-sectional study that extracted data from the medical records of 180 paediatric patients (Children < 14 years of age) who were admitted to the paediatric wards of the hospital from January 2019 to December 2019. The selection of samples was by systematic random sampling. Only records of paediatric patients with at least three consecutive days of hospitalisation with not more than three missing data were included. A well-designed proforma was used to collect data, which was entered into a spreadsheet using Microsoft Excel 2021. Analysis for Frequency tables and charts was done using the International Business Machine (IBM).

Result: The result documented 180 participants, 102 of whom were males and 91 below the age of 1 month. Over all resistance was highest with ciprofloxacin (n=50(21.8)), followed by cloxacillin (n=32(14.0)) and ampicillin (n=27(11.8)). Resistance to ciprofloxacin was observed to be highest with *S.typhi* (29.4%), followed by *E. coli* (27.9%), then *S. aureus* (23.9%) and lastly by *Pseudomonas spp* (10.2%). Multidrug resistance was highest with *S. aureus* (40.2%) and list with *S. typhi* (7.4%).

Conclusion: Ciprofloxacin was the antibiotic with the highest resistance level. Resistance to cotrimoxazole was observed to be nil. The primary isolates were *Staphy. aureus*, *E. coli*, *Pseudomonas* species and *Salmonella typhi*. The isolates were multidrug-resistant, the preponderance of which was exhibited by *S. aureus*.

Keywords: Antimicrobial resistance, pattern, paediatrics, inpatients, tertiary hospital.

Introduction

The problem of Antimicrobial Resistance (AMR) among children was typically neglected until it was discovered that they are significant antibiotic users and carriers of antimicrobial-resistant microbes. AMR resistance is a public health threat of utmost importance, especially for children ^[1]. To understand the relevance of the threat posed by AMR, WHO estimated that every year in the world, infections caused by multidrug-resistant (MDR) bacteria result in 700,000 deaths across all ages, of which around 200,000 are newborns ^[2]. In Europe, infections in paediatric patients may represent up to 30% of the total cases of MDR ^[3]. In regions of the Middle East, 90% of newborns with sepsis, hospitalised in an intensive care unit (ICU), had resistant bacteria; in some areas of South East Asia, 83% of children had *E. coli* resistant to first-line antibiotics ^[4]; in Sub-Saharan Africa, 66% of neonatal sepsis and meningitis were found to be caused by bacteria resistant to antibiotics ^[5]; in a United States of America (USA) study, 20% of paediatric patients receiving colistin to treat already MDR Gram-negative bacteria developed resistance ^[6]. A study in Sokoto state, Northwest, Nigeria, reported 88.9% of multidrug-resistant isolates ^[7]. This study was, however, done using the general patient population.

Another study in Nigeria, specifically Southwest Nigeria, reported that one-third of the isolates were multidrug resistant^[8]. This is a serious cause for concern.

Antimicrobial resistance (AMR) happens when microbes like bacteria, viruses and fungi develop a defence against the drugs designed to kill or retard their growth. As a result of drug resistance, antibiotics and other antimicrobial medicines become ineffective, and infections become increasingly difficult or impossible to treat^[9]. According to the Food and Agriculture Organisation of the United States (FAO), drug-resistant microorganisms can spread between and within animal, human and plant populations and migrate through the environment^[10].

In 1945, Alexander Fleming warned against the danger of AMR emergence due to the abuse of antibiotics. However, there has been abuse of these agents. This abuse was the leading driver of the evolution of resistance in bacteria^[11]. Furthermore, medical malpractice contributed to selected MDR strains of bacteria through unnecessary, inappropriate or suboptimal prescribing, observed in 30% to 60% of the antibiotic therapies given to outpatients and inpatients in some studies^[1,12]. This abuse happens not only in human medical practice but also in veterinary medical practice agricultural and livestock practices.

Antimicrobial resistance (AMR) is one of the most critical public health threats worldwide. It should be considered a high priority by all healthcare workers and institutions. The institution of antimicrobial stewardship and the development of antimicrobial use policy documents will help curtail this public health menace. We were conducting a study to determine antimicrobial utilisation patterns among paediatric patients in the hospital to provide baseline data to help develop antimicrobial prescribing policy documents. We felt that data on antimicrobial resistance among the same patients would provide more insight into the choice of antimicrobials in the policy document. Therefore, the study's broad objective was to assess antimicrobial resistance patterns among the paediatric population in a Nigerian tertiary hospital.

Specifically, this study evaluated the major microorganisms responsible for childhood illnesses, which microorganism demonstrated the highest level of resistance and which antimicrobial agents these organisms were more resistant to.

Methods

Study Setting

The study was conducted at Federal Medical Centre Makurdi (FMCM), Benue State, North Central, Nigeria. FMCM is a 400-bed hospital that offers primary, secondary and tertiary health care to the people of the state and environs. The hospital has several specialised clinical departments (Paediatric, Pharmacy, Nursing, Obstetrics and Gynaecology, Internal Medicine, Family Medicine, Laboratory Sciences, Optometry, Physiotherapy, Radiology, Dietetics, Clinical Psychology, Ophthalmology and so on. The Paediatric Department operates the Special Care Baby Unit (SCBU), Emergency Paediatric Unit (EPU), Paediatric ward and Surgical Paediatric ward.

Study Design

This study was a retrospective cross-sectional study. Medical records of paediatric patients (Children < 14 years of age) who were admitted to the paediatric wards of the hospital were used to assess antimicrobial resistance patterns. Data for the study was extracted from case files of patients who accessed care at the hospital's paediatric department from January 2019 to December 2019.

Sampling

From a population of 3336, as obtained from the records department, a sample size of 357 was derived using Taro Yamane's formula for sample size calculation, as shown by Raphael, 2014^[1]. Systematic random sampling (where one out of every 9 case files was selected) was used to select records using a sampling frame from paediatric records from January 2019 to December 2019. However, due to

misfiling and missing data, only 180 case files met the inclusion criteria and were used for data extraction.

Only records of paediatric patients with at least three consecutive days of hospitalisation with not more than three missing data were included. Find below the determination of sample size and sampling interval:

Sample size determination, $n = N/1+N(e)^2$

where n = sample size, N = Study population and e = level of significance (0.05), therefore,
 $n = 3336/1+3336(0.05)^2 = 3336/1+3336(0.0025) = 3336/1+8.34 = 3336/9.34 = 357$ approximately

The sampling interval was calculated by dividing the study population by the sample size = $3336/357 = 9$ approximately.

Data Collection and Analysis

The data for this study was collected using a well-designed proforma. Information retrieved from patients' records includes Demographic Data, Diagnosis, Culture and Sensitivity results. The data obtained was entered into a spreadsheet using Microsoft Excel 2021, and the analysis for Frequency tables and charts was done using the International Business Machine (IBM) SPSS 22.

Ethical Consideration

Ethical clearance was obtained from the Hospital Ethical Research Committee (HREC). Confidentiality of patient medical information was held at high importance.

Results

Table 1: Socio-demographic Characteristics (n=180)

Variable	Frequency	Percent
Age(in months)		
<1 month	91	50.6
1-12 months	34	18.9
13-24months	11	6.1
>24 months	44	24.4
Gender		
Male	102	56.7
Female	78	43.3
Weight		
<2.5	55	30.6
2.5-5.9	49	27.2
6-10.9	36	20.0
11-15	32	17.8
>15	8	4.4
Source of prescription orders		
EPU	103	57.2
SCBU	77	42.8

EPU=Emergency Paediatric Unit, SCBU= Special Care Baby Unit

An overall of 180 participants were enrolled in this research from the Emergency Paediatrics Unit (EPU), which contained 103(57.2%) patient folders and the Special Baby Care Unit (SCBU), which contained 77(42.8%) patient folders. 102(56.7%) were males, 91(50.6%) were below one month, and 44(24.4%) were above 24 months, 55(30.6%) were below 2.5kg, while 8(4.4%) were above 15kg. See Table 1.

Table 2: Resistance pattern of isolates to antibiotics

n= number of resistant antimicrobial agents

Antibiotic	Organism Isolated				
	Staphylococcus Aureus n(%) n=92	Escherichia Coli n(%) n=61	Pseudomonas Spp n(%) n=59	Salmonella Typhi n(%) n=17	Overall n(%) n=229
Ciprofloxacin	22(23.9)	17(27.9)	6(10.2)	5(29.4)	50(21.8)
Cloxacillin	13(14.1)	4(6.6)	14(23.7)	1(5.9)	32(14.0)
Ampicillin	16(17.4)	9(14.8)	1(1.7)	1(5.9)	27(11.8)
Amoxicillin	11(12.0)	5(8.2)	0(0.0)	2(11.8)	18(7.9)
Norbactin	5(5.4)	5(8.2)	2(3.4)	2(11.8)	14(6.1)
Erythromycin	2(2.2)	0(0.0)	8(13.6)	0(0.0)	10(4.4)
Ofloxacin	5(5.4)	1(1.6)	4(6.8)	0(0.0)	10(4.4)
Streptomycin	2(2.2)	5(8.2)	0(0.0)	1(5.9)	8(3.5)
Rifampicin	1(1.1)	0(0.0)	4(6.8)	2(11.8)	7(3.1)
Norfloxacin	0(0.0)	0(0.0)	4(6.8)	2(11.8)	6(2.6)
Ceftazidime	2(2.2)	1(1.6)	3(5.1)	0(0.0)	6(2.6)
Metronidazole	0(0.0)	6(9.8)	0(0.0)	0(0.0)	6(2.6)
Gentamycin	3(3.3)	0(0.0)	2(3.4)	0(0.0)	5(2.2)
Levofloxacin	0(0.0)	4(6.6)	0(0.0)	1(5.9)	5(2.2)
Nalidixic Acid	3(3.3)	1(1.6)	2(3.4)	0(0.0)	6(2.6)
Cefuroxime	2(2.2)	0(0.0)	3(5.1)	0(0.0)	5(2.2)
Ceftriaxone	2(2.2)	0(0.0)	2(3.4)	0(0.0)	4(1.7)
Chloramphenicol	0(0.0)	1(1.6)	2(3.4)	0(0.0)	3(1.3)
Amoxicillin/Clavulanic Acid	1(1.1)	0(0.0)	2(3.4)	0(0.0)	3(1.3)
Pefloxacin	2(2.2)	0(0.0)	0(0.0)	0(0.0)	2(0.9)
Ampicillin/cloxacillin	0(0.0)	2(3.3)	0(0.0)	0(0.0)	2(0.9)
Cotrimoxazole	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)

According to Table 2 above, among 180 patients, only 72 had culture and sensitivity reports. *S. typhi* expressed the highest resistance against ciprofloxacin [n=17, 5(29.4%)]. The overall resistance rate to ciprofloxacin was 50(21.8%).

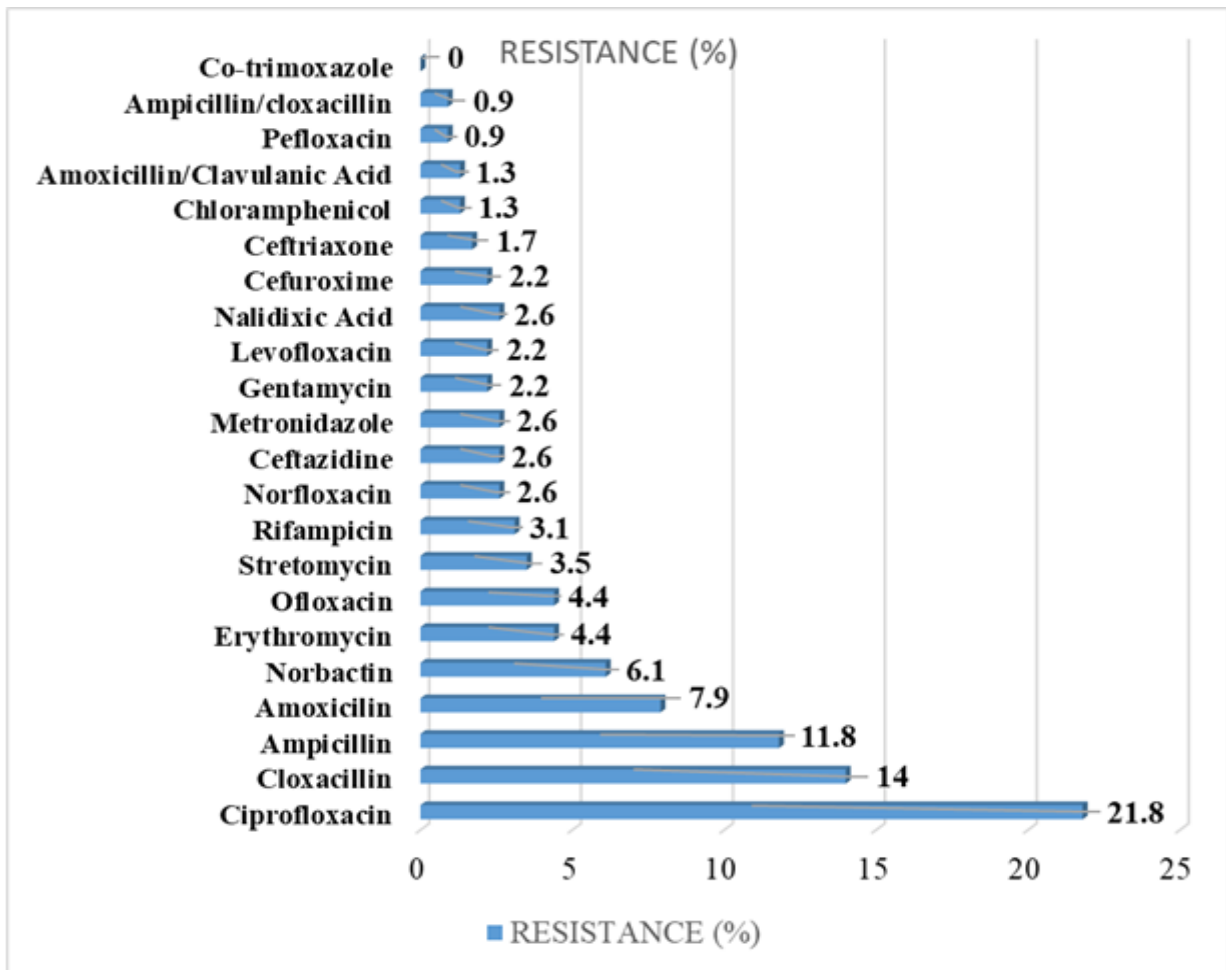
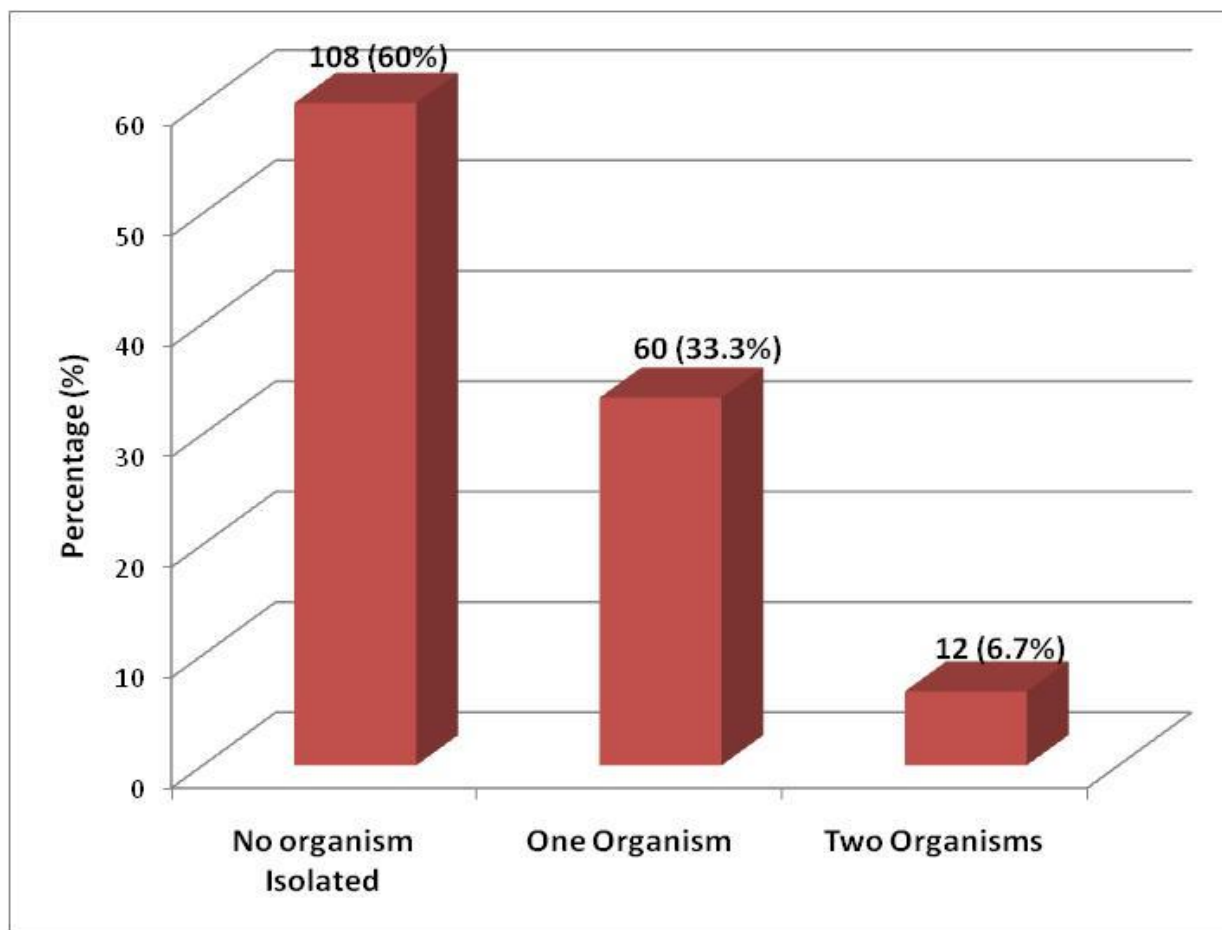


figure 1: Antibiotic Resistance Pattern

According to Figure 1 above, the antibiotics with the highest resistance pattern are Ciprofloxacin (21.8%), Cloxacillin (14.0%), Ampicillin (11.8%) and Amoxicillin (7.9%). Resistance was found to be lowest with Ampicillin/Cloxacillin and Pefloxacin and nil with Cotrimoxazole (Trimethoprim/Sulfamethoxazole).

Microorganism resistance pattern



*No organism isolated = no culture and sensitivity done

Figure 2: Number of isolates per patient

Figure 2 above reports that out of 180 patients, 108(60%) had no culture and sensitivity report, 60(33.3%) had one isolate, and 12(6.7%) had two isolates.

Table 3: Distribution of isolates (n=84)

Organism Isolated	Frequency	Percent
Staphylococcus aureus	26	31.1
Pseudomonas spp	25	29.7
Escherichia coli	25	29.7
Salmonella typhi	8	9.5

Table 3 above reports that 72 patients had culture and sensitivity testing. The microorganism isolated from these cultures include; Staphylococcus aureus 26(31.1%), Pseudomonas specie 25(29.7%), Escherichia coli 25(29.7%) and Salmonella typhi 8(9.5%). Note 12 of the results showed two isolates each, making the number of isolates Eighty-Four (n=84). See table figure 2.

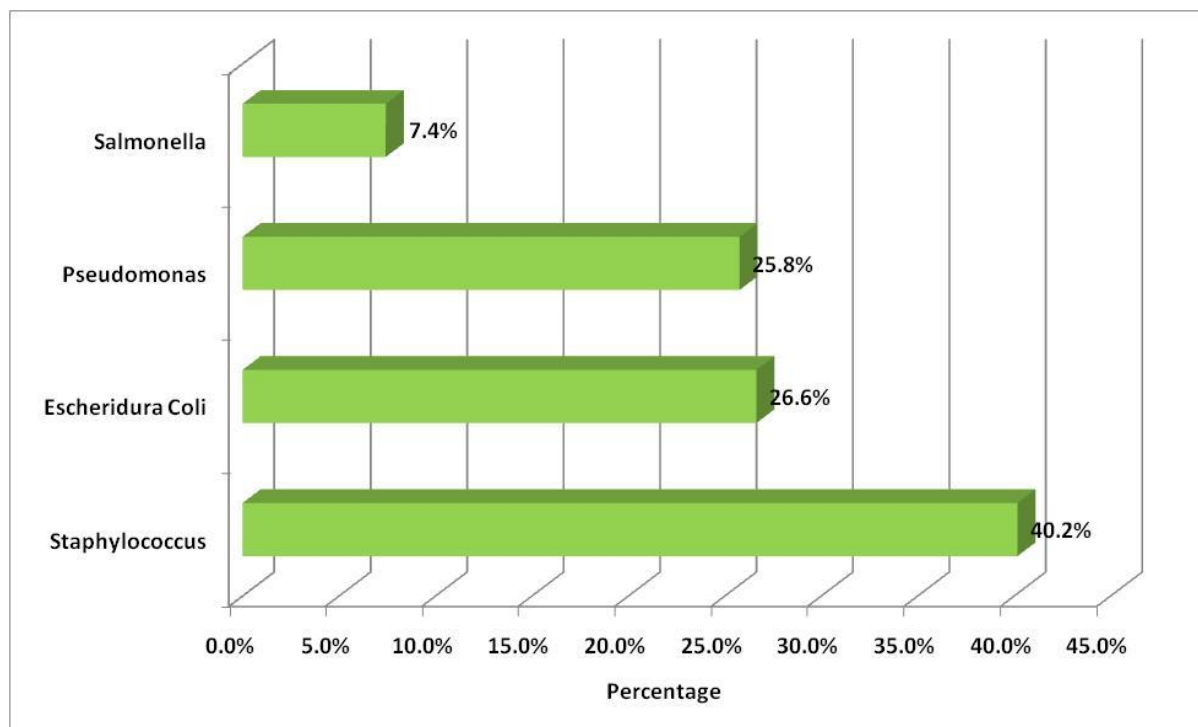


Figure 3: Pattern of microorganism developing multidrug resistance

According to Figure 3 above, the isolates exhibited resistance to multiple antibiotics. *Staphylococcus aureus* demonstrated the highest multidrug resistance (40.2%).

Discussion

Antibiotic resistance is escalating far more than the introduction of new antimicrobials into clinical practice, leading the world to a global health burden. Due to the widespread production and reckless use of antibiotics, many microbes have developed resistance against these antibiotics, rendering them useless.

In this study, *Staph. aureus* was seen to be the predominant isolate. This finding is not uncommon, as a previous study among children with community-acquired febrile illness in a tertiary hospital in Nigeria revealed *Staph. aureus* as the most prevalent Gram-positive isolate^[8]. However, Esther et al.; 2021^[14] found *Klebsiella pneumonia* as the major isolate (88.8%), followed by *Pseudomonas* spp (45.0%) and *E.coli* (40.6%). Our study found the second most predominant isolate to be *E.coli*, followed by *Pseudomonas* spp and *Salmonella typhi*. It was strange to discover that Esther et al., whose study was done at Nsukka, Enugu state of Southeast Nigeria and Otukpo, Gboko and Katsinala in Benue state of North Central Nigeria, same state where this recent study was conducted, had *Klebsiella* as the most prevalent isolate. *Pseudomonas* spp and *E.coli* were, however, common to both studies. The implication is that antibiograms should be produced at the individual hospital level rather than state-wise. The preponderance of *Staph aureus* infection may be attributed to its ease of transmissibility. *Staph* is commonly found on the skin and can easily be transmitted from person to person via contaminated hands. Also, certain situations such as HIV infection, diabetes, the effect of immune suppressants and poor hygiene may have some implications.

The major antibiotics that suffered the highest level of microbial resistance were ciprofloxacin, cloxacillin, ampicillin and amoxicillin, with overall resistance being highest to ciprofloxacin and least to ampicillin/cloxacillin and perfloxacin. It would have been strange if the result was otherwise, as there has been practical high abuse of these classes of drugs in the surrounding communities. None of the isolates were resistant to cotrimoxazole (trimethoprim+sulphamethoxazole). Disagreeably, resistance to cotrimoxazole was 83.3% by *Staph. aureus* and 100% by *S. pneumonia*, according to Shittu et al.; 2021 in Southwest Nigeria^[8]. Therefore, a countrywide antimicrobial use policy may not satisfy the needs of the individual clinical settings in Nigeria. Also, while there was generally high resistance to

cloxacillin and ampicillin as single agents, resistance to the combination of the two agents (ampiclox) was low, further strengthening the rationale for the combination drug.

Staphylococcus aureus is a troublesome human pathogen that can cause various infections [15,16]. Development of resistance by *Staph. aureus* can pose a serious threat to the health of the public. Our study reported that *Staph. aureus* was more resistant to ciprofloxacin, followed by ampicillin, cloxacillin, and amoxicillin. This extent of resistance is slightly similar to different studies conducted in different parts of the world [17]. The exhibition of resistance to several antibiotics by *Staph. aureus* in this study further attests to the fact that *Staphylococcus aureus* is a Multidrug Resistant Organism (MDRO). Approaches to managing multidrug resistance should be considered while managing patients with *Staph aureus* infection. There has been an increase in resistance to fluoroquinolones among isolates of *Staph. aureus* in recent years. While *Staph. aureus* showed the highest resistance to ciprofloxacin; it was mildly resistant to ofloxacin, perfloxacin and nalidixic acid. Again, this may be attributed to self-medication, which is more common with ciprofloxacin than other fluoroquinolones.

It is worth noting that some antibiotics have precise contraindications in paediatric age, affecting the range of antimicrobial options to treat infections. For example, due to safety concerns, fluoroquinolones remain largely unused in children. These antibiotics have shown irreversible adverse events on cartilage development in young animals through the inflammation and disruption of weight-bearing joints [18]. The potential occurrence of these severe arthropathies has limited the use of fluoroquinolones in children, as these events have been reported in various pediatric studies [19,20]. Despite these safety concerns, fluoroquinolones were used on these patients. The reason for this action may be considered a topic for further research. However, it is vital that prescribers trade with caution the use of these drugs in the paediatric population.

Typhoid fever is a growing concern worldwide. World Health Organization (WHO) estimates that there are about 22 million cases of typhoid fever worldwide every year. *Salmonella typhi* is a major cause of typhoid fever. In the present study, *S. typhi* showed a high resistance profile. However, its resistance was minimal when compared to the other three pathogens. Its resistant activity was highest to ciprofloxacin, followed by amoxicillin, norbactin, rifampicin and norfloxacin and least to cloxacillin, ampicillin, streptomycin and levofloxacin. It was clear from this study that, except for Nalidixic acid and perfloxacin, *S.typhi* was resistant to all fluoroquinolones tested and penicillins.

Interestingly, these drugs are commonly used to treat typhoid fever in the local communities. The prevalence of resistance to these agents might be attributed to over-prescribing and self-medication due to uncontrolled access. Regulatory activities must be strengthened to ensure rational prescribing and access to antimicrobials and other prescription-only medicines (POM).

Our study also focused on antibiotic resistance by *Pseudomonas* spp. We found that *Pseudomonas* spp. isolates had the second lowest levels of resistance (n=59). Resistance was highest to cloxacillin, followed by erythromycin, then ciprofloxacin. *Pseudomonas* spp exhibited nil resistance to 8 (ampicillin, streptomycin, metronidazole, levofloxacin, perfloxacin, ampiclox and cotrimoxazole) out of the 22 antibiotics under evaluation. In a study conducted in Nepal, there was no resistance against ampicillin, gentamicin, norfloxacin and ofloxacin; however, the prevalence of resistance against ceftriaxone, cephalexin,, ciprofloxacin and cotrimoxazole were 50%, 100%, 50% and 100%, respectively [21]. An Indian investigation revealed that the *Pseudomonas* spp. isolates of wound swab samples harboured the highest levels of resistance against ciprofloxacin (87.93%), ceftazidime (73.27%), gentamycin (78.44%) and ofloxacin (87.93%), which was very different from our findings, maybe due to the difference in methodology, materials and setting.

Escherichia coli - a Gram-negative bacteria, is considered a major source of urinary tract infections; it is a good indicator of resistance in gram-negative bacteria. In our study, *E. coli* ranked second to *Staph. aureus* with respect to resistance profile (n=61) even though it was not resistant to 8 of the 22 antimicrobial agents under study. *E. coli* exhibited second to the highest resistance level against ciprofloxacin, followed by ampicillin and metronidazole. It was resistant to all penicillins except the amoxicillin/clavulanic acid combination. The only isolate resistant to ampicillin/cloxacillin (ampiclox) combination and metronidazole. This resistance to ampiclox and metronidazole may be attributed to the high-level abuse of these agents for self-medication. A study in Southeast Nigeria documented that almost half of the children (46.7%) used unprescribed antibiotics during an episode of diarrhoea [22]. Caregivers need to be appropriately enlightened about the consequences of self-

medication, especially in children. Such can be incorporated into their routine pre and post-natal services.

The Gram-positive pathogen, *Staph. aureus* was found to be the single most predominant etiologic agent across all age groups, accounting for (31.1%) of total isolates. This aligns with reports from previous studies ^[23,24,25]. However, Obaro et al., in a recent multicenter study, revealed that *Salmonella* species were the most common cause of childhood bacteremia in the North Central (Abuja) and North Eastern (Kano) parts of Nigeria ^[26]. The study, however, did not report the prevalence of associated risk factors (e.g. malnutrition, malaria, HIV infections, and level of hygiene), which could have been responsible for the preponderance of *Salmonella* species. Similarly, the current did not capture risk factors (HIV infection, malnutrition, level of hygiene and immune-suppressing medications), which may have been responsible for the preponderance of *Staph aureus*.

The resistance of *Staph. aureus* to antibiotics, especially ciprofloxacin (21.8%) in this study, is low compared to a study done in Osun State (34.38%) ^[27], United States (51%), Italy (58.6%) and France (40.5%) but comparable to that reported in Canada (24.1%), Germany (26.1%) and India (21.95%) ^[17]. The gram-negative bacteria (*E. coli* and *Salmonella typhi*) reported low resistance rates of 26.6% and 7.4% compared to *Staph. aureus* (40.2%). This, however, does not undermine the high-level need for antimicrobial stewardship programmes.

Limitations

Misfiling and incomplete/missing data limited the sample size for the study. Data on sensitivity to antimicrobial agents were not captured; therefore, resistance pattern *visa viz* sensitivity pattern cannot be categorically related.

Conclusion

The major isolates were *Staph. aureus*, *E. coli*, *Pseudomonas* species and *S. typhi* with *Staph. aureus* being the most resistant isolate. Resistance was seen to be predominant with fluoroquinolones, most especially ciprofloxacin and penicillins. Multidrug resistance was documented amongst the isolates. A periodic summary of antimicrobial susceptibilities of local bacterial isolates should be done. This will help the clinicians assess local susceptibility rates, guiding the selection of antibiotics for empiric use. It will also help to track resistance trends within the health facility over time. The result of this study will help management develop policy documents for antimicrobial prescriptions for paediatric patients. It will also help choose the right antibiotics to treat infectious diseases in the hospital, not only in the paediatric population but also in the adult population. The scope of antimicrobial testing was limited to antibiotics.

Recommendation

Strengthening Antimicrobial Stewardship (AMS) is essential to combat AMR in paediatrics.

Accidental Findings.

Out of the 72 patients on whom culture and sensitivity tests were carried out, only 38 were prescribed antimicrobial agents based on culture reports.

Authors' contributions

All authors contributed substantially to the conduct of the study, gave approval for publishing and agreed to take responsibility for all aspects of the work.

Conflict of interest

The Authors reported no conflict of interest.

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