

Assessing bacterial prevalence and resistance in paediatric meningitis: safeguarding the central nervous system

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Introduction: Paediatric bacterial meningitis (PBM) represents a major contributor to childhood morbidity and mortality globally, with heightened susceptibility in low- and middle-income nations where antimicrobial resistance (AMR) is highly prevalent. Pakistan exemplifies this setting, with widespread antibiotic overuse driving AMR expansion. Thus, expediting PBM diagnosis and targeted antibiotic therapy is imperative yet challenged by the dynamic local epidemiology. This study aimed to delineate the recent bacterial etiologies and AMR profiles of PBM from a major Pakistani diagnostics laboratory to inform empirical treatment.

Materials and methods: This prospective observational investigation evaluated PBM epidemiology in patients under 18 years old admitted to the study hospital. Standard cerebrospinal fluid analysis identified bacterial pathogens and antibiotic susceptibility patterns.

Results: Among 171 PBM cases, 152 (88.9%) had bacterial isolates confirmed via culture. The cohort was 42.7% male with a mean age of 3 months. The most prevalent pathogens among infants younger than 3 months were *Escherichia coli, Enterococcus faecium,* and *Staphylococcus epidermidis*, contrasting with *S. epidermidis, Streptococcus pneumoniae,* and *Staphylococcus hominis* predominating in older children. Staphylococcal isolates exhibited considerable penicillin and erythromycin resistance but maintained vancomycin and linezolid susceptibility. Other resistance patterns varied.

Conclusion: These findings highlight the pressing threat of paediatric AMR in Pakistan, underscoring the need for vigilant AMR surveillance and judicious antimicrobial use. This study provides a reference to current PBM epidemiology to guide context-specific empirical therapy.

Keywords: antimicrobial resistance, bacterial, LMIC, meningitis, paediatric, Pakistan

Introduction

Paediatric bacterial meningitis (PBM) represents a major contributor to childhood morbidity and mortality globally^[1]. The indiscriminate use of antimicrobial agents has propagated extensive

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article

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Received 11 January 2024; Accepted 29 February 2024

Published online 12 March 2024

http://dx.doi.org/10.1097/MS9.000000000001953

HIGHLIGHTS

- Paediatric bacterial meningitis (PBM) represents a major contributor to childhood morbidity and mortality globally, with heightened susceptibility in low-income and middleincome nations where antimicrobial resistance (AMR) is highly prevalent.
- This study aimed to delineate the recent bacterial etiologies and AMR profiles of PBM from a major Pakistani diagnostics laboratory to inform empirical treatment.
- These findings highlight the pressing threat of paediatric AMR in Pakistan, underscoring the need for vigilant AMR surveillance and judicious antimicrobial use. This study provides a reference of current PBM epidemiology to guide context-specific empirical therapy.

antimicrobial resistance (AMR) in developing nations, including Pakistan, exerting selective pressure on bacterial populations^[2]. Conservative estimates indicate over 5 million annual deaths globally result from AMR infections, disproportionately affecting low-income and middle-income regions such as Pakistan^[3].

Given the extreme virulence of PBM and its propensity to elicit devastating neurological consequences, expeditious diagnosis and prompt initiation of evidence-based antimicrobial therapy is imperative to mitigate the substantial morbidity and mortality conferred by this condition and alleviate its burden on afflicted

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Annals of Medicine & Surgery (2024) 86:2671–2676

communities^[4]. The selection of appropriate empirical antibiotics relies heavily on contemporaneous insights into the causal pathogens underlying PBM and their corresponding antimicrobial resistance profiles in a given region^[4]. However, the aetiologic agents implicated in PBM have been shown to demonstrate extensive variability across different geographies, time periods, and patient age groups^[5-8]. For example, surveillance data accumulated in England and Wales from 2004 to 2011 indicated that the predominant pathogens responsible for PBM were Neisseria meningitidis, Streptococcus pneumoniae, and Staphylococcus aureus^[5]. In contrast, meningitis surveillance performed in African nations between 2011 and 2016 found S. pneumoniae and Hemophilus influenzae to be the leading aetiologic agents underlying paediatric cases^[6,7]. Moreover, an investigation of PBM epidemiology conducted in the southwestern Chinese province between 2012 and 2015 reported that ~46.0% of cases were attributable to Escherichia coli and S. pneumoniae^[8]. This heterogeneity underscores the importance of continually re-evaluating region-specific PBM epidemiology to formulate appropriate empirical antibiotic recommendations. The aetiologic agents underlying PBM have been documented to vary substantially based on geographic region, temporality, and patient age, underscoring the importance of periodic reevaluation of local epidemiology^[5,9,10]. Additionally, the antimicrobial resistance profiles of PBM pathogens demonstrate significant variability and rapid evolution, further emphasizing the need for frequent surveillance^[11]. Therefore, timely analysis and dissemination of data regarding contemporary causative organisms and antimicrobial resistance patterns is imperative to promote evidence-based selection of empirical therapeutic agents by clinicians. Despite a paucity of existing surveillance data, preliminary evidence suggests that a sizable proportion of bacterial isolates in Pakistan exhibit resistance to commonly utilized antimicrobial drugs, highlighting the escalating public health threat posed by antimicrobial resistance in this nation and the urgency of comprehensive assessment^[11]. To contribute data to this crucial endeavour, the present study aims to elucidate the antimicrobial resistance trends among prominent pathogenic isolates from a major diagnostic laboratory in Pakistan. These findings will provide clinically valuable insights into the evolving landscape of PBM aetiology and antimicrobial resistance in Pakistan to promote informed decision-making. However, larger multicenter studies are warranted to confirm generalizability due to the sample size limitations of a single-centre analysis. This study aims to underscore the pressing need for coordinated surveillance, stewardship, and public health efforts to mitigate the threat of escalating antimicrobial resistance in Pakistan and globally.

Primary objective

To delineate the most prevalent organisms isolated from cerebrospinal fluid cultures.

Secondary objective

To characterize the antimicrobial resistance profiles of these major pathogens and to elucidate patterns of resistance among isolates.

Material and methods

This prospective observational study aimed to characterize the demographic attributes, bacterial etiologies, and antimicrobial resistance patterns among paediatric cases of bacterial meningitis presenting to the study hospital between August 2022 and January 2023. Of the 171 children screened with suspected meningitis, 152 satisfied the inclusion criteria and were confirmed to have bacterial meningitis via cerebrospinal fluid analysis and culture. The study methodology entailed collecting demographic, clinical, and microbiological data at admission and throughout hospitalization using standardized diagnostic approaches, including bacterial culture of cerebrospinal fluid specimens and antibiotic susceptibility testing. The aim was to delineate the distribution of bacterial pathogens underlying paediatric meningitis in this setting and evaluate their antimicrobial resistance profiles to guide context-specific empirical therapy selection. Detailed descriptive statistical analyses were performed to characterize demographics, including age, sex, and clinical department. The distribution of bacterial isolates was analyzed by age group. Antimicrobial resistance patterns of Gram-positive and Gram-negative organisms were assessed by determining antibiotic-specific susceptibility and resistance rates. Appropriate statistical tests such as chi-squared tests were applied to determine significant differences, with P less than 0.05 denoting statistical significance. While the single-centre design limits generalizability, this study provides valuable insights into current local epidemiology to inform clinical decision-making. Further multicenter studies are warranted to corroborate these findings and continue AMR surveillance as microbial distributions and resistance profiles evolve. Overall, the study highlights the need for evidence-based measures to combat paediatric AMR and preserve antimicrobial efficacy.

Results

Demographic characteristics

This prospective study screened 171 children under 18 years of age with suspected meningitis presenting to the study hospital between August 2022 and January 2023. Following application of exclusion criteria, 152 were confirmed to have bacterial meningitis via cerebrospinal fluid analysis. Of the analyzed cohort, 65 patients (42.7%) were male and a majority of 87 (57.2%) were female. The mean age was 3 months, with 70 patients (45.9%) under 3 months old and 99 patients (64.9%) within the first year of life, after which the proportion declined steeply with age.

Microbiological testing identified 193 bacterial isolates from the 152 confirmed paediatric meningitis cases. Gram-positive organisms constituted ~66.3% (n=128) of total isolates. The most prevalent Gram-positive pathogen was *Staphylococcus epidermidis* at 16.6% (n=32), followed by *Streptococcus pneumoniae*, *Enterococcus faecium*, *Staphylococcus hominis*, Group B streptococcus, and *Staphylococcus aureus*. Gram-negative isolates comprised 33.6% (n=65) of total isolates, with *Escherichia coli* representing the most common at 12.4% (n=24), followed by *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and other Gram-negative species. These findings provide key insights into the distribution of bacterial etiologies underlying paediatric meningitis in this

 Table 1

 Distribution of pathogens causing bacterial meningitis

Pathogen	N (%)
Gram-positive organisms	
Staphylococcus epidermidis	32 (16.6)
Streptococcus pneumoniae	21 (10.9)
Enterococcus faecium	18 (9.3)
Staphylococcus hominis	14 (7.2)
Group B streptococcus	10 (5.2)
Staphylococcus aureus	5 (2.6)
Other Gram-positive organisms	28 (14.5)
Gram-negative organisms	
Escherichia coli	24 (12.4)
Klebsiella pneumoniae	6 (3.1)
Acinetobacter baumannii	5 (2.6)
Pseudomonas aeruginosa	4 (2.1)
Other Gram-negative organisms	26 (13.5)
Total	193 (100)

setting during the study period. Ongoing surveillance is warranted to track epidemiological trends as meningitis epidemiology continues to evolve (Table 1).

Distribution of pathogens causing bacterial meningitis (Fig. 1)

This study analyzed 193 bacterial pathogens isolated from paediatric meningitis cases, categorizing isolates as Gram-positive or Gram-negative.

Among infants under 3 months of age, the most prevalent pathogens were *Escherichia coli* (22.2%), *Enterococcus faecium* (14.5%), and *Staphylococcus epidermidis* (10.9%). However, for

patients over 3 months of age, the primary isolates were *S. epidermidis* (20.7%), *Streptococcus pneumoniae* (17.6%), and *Staphylococcus hominis* (8.2%). Overall, the leading causes of bacterial meningitis across all ages were *S. epidermidis* (20.9%), *S. pneumoniae* (17.5%), and *S. hominis* (8.5%). Infants harboured the greatest number of isolates, with *E. coli* the most common (17.3%), followed by *S. epidermidis* (13.5%) and *E. faecium* (11.3%).

The incidence of *S. epidermidis* was significantly higher in surgical wards (30.1%) compared to paediatric intensive care (11.8%) and other wards (13.7%) (P < 0.01). In contrast, *S. pneumoniae*, *E. coli*, and *E. faecium* were more prevalent in paediatric ICUs and non-surgical wards versus surgical departments (P < 0.05). These findings provide insights into age-specific and location-specific distributions of bacterial meningitis etiologies. Continued surveillance is critical as epidemiological trends evolve over time and space.

AMR patterns of Gram-positive pathogens

Staphylococcus epidermidis, Staphylococcus hominis and Staphylococcus haemolyticus were the 3 major coagulase-negative staphylococcus pathogens identified from CSF cultures. In this study, a staggering 71% of the isolated bacterial species exhibited resistance to both penicillin and erythromycin. This alarming finding underscores the urgent need for targeted interventions and vigilant antimicrobial stewardship. The efficacy of these once-potent antibiotics is waning, posing a significant threat to patient outcomes. These pathogens showed 100% sensitivity to linezolid and vancomycin. Except for Staphylococcus haemolyticus, ~65% of the pathogens were sensitive to fluoroquinolones, aminoglycoside, rifampicin, cotrimoxazole and tetracycline. The isolates also showed susceptibility of 74.8%, 59% and 50% toward amoxicillin, cefotaxime and ceftriaxone,

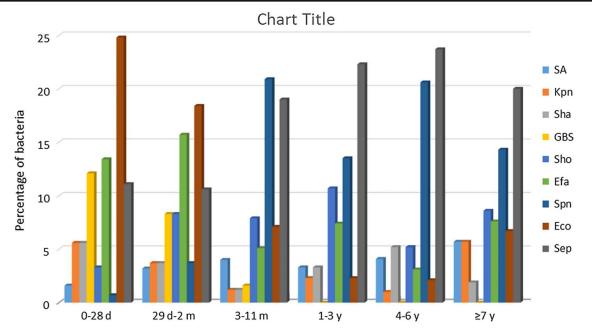


Figure 1. Percentage of organisms causing PBM. *Percentage Organisms causing bacterial meningitis in children. Eco, *E-coli;* Efa, *Enterococcus faecium;* GBS, Group B Streptococcus; Kpn, *Klebsiella pneumonia;* PBM, paediatric bacterial meningitis; SA, *Staphylococcus aureus;* Sha-, *Staphylococcus haemolyticus;* Sho, *Staphylococcus hominis;* Spn, Streptococcus.

respectively. Around 95% of *E. faecium* species demonstrated sensitivity towards vancomycin, linezolid and tigecycline with resistance of ~63% to other antibiotics. However, ~84% of Streptococcus pneumoniae species showed resistance towards erythromycin, clindamycin, trimethoprim sulfamethoxazole and tetracycline. Table 2 showing AMR patterns of Gram-negative pathogens.

Around 93% of E. coli species showed susceptibility towards cefoxitin, cefoperazone/sulbactam, piperacillin/tazobactam, carbapenems and amikacin with more than 82% resistance for piperacillin and ampicillin. E. coli demonstrated sensitivity of 65.3%, 47.6-73.6% and 44.3-46.4% to aztreonam, third-generation cephalosporin and fluoroquinolones, respectively, and resistance of 5% towards carbapenem. The sensitivity rate of Klebsiella pneumoniae for fluoroquinolones, aminoglycosides, cotrimoxazole, imipenem and ertapenem was greater than 51%, but showed resistance of ~50% towards other antibiotics. Acinetobacter baumannii had a sensitivity rate of over 55% for fluoroquinolones and aminoglycosides. For cephalosporin and carbapenems the rates varied from 37.5-66.7% and 45.5-68.4%, respectively. Pseudomonas aeruginosa showed resistance of ~92% for antimicrobial peptides and ampicillin/ sulbactam and over 60% susceptibility rate towards third-generation cephalosporin, PIP, fluoroquinolones and carbapenems. Table 3 showing AMR patterns of Gram-positive pathogens.

Discussion

Despite significant advancements in the diagnosis and management, paediatric bacterial meningitis still remains a grave menace worldwide. In our study, *Staphylococcus epidermidis* was the main causative bacteria at 16.6%, followed by *Escherichia coli*

Table 2	
AMR patterns of Gram-negative pathogens	

Antimicrobial agent	SA A/ B% ^a	GBS A/ B% ^a	Efa A/ B% ^a	Spn A/ B% ^a	Sha A/ B% ^a	Sho A/ B% ^a	Sep A/ B% ^a
Oxacillin	29.0	b	b	b	86.1	76.1	80.0
Penicillin G	96.6	1.7	97.8	82.8	84.8	87.9	89.9
Amoxicillin	b	b	b	25.2	b	b	b
Ampicillin	_	3.7	95.5	_	_	_	_
Cefotaxime	_	—	—	41.0	—	—	_
Ceftriaxone	_	_	_	50.0	_	_	_
Erythromycin	71.0	90.3	98.2	96.6	97.2	71.4	83.8
Clindamycin	36.0	91.8	_	92.3	_	_	_
Gentamicin	6.5	_	_	_	63.9	20.3	27.0
Ciprofloxacin	3.2	—	92.7		83.3	21.7	27.9
Moxifloxacin	0	—	—	0	58.8	23.6	30.9
Levofloxacin	6.5	47.5	89.2	0	52.6	13.8	30.6
Rifampin	3.2	—	—		34.4	12.1	16.6
Nitrofurantoin	0	—	62.9	—	—	—	—
Cotrimoxazole	25.8	—	—	84.9	83.3	25.4	34.8
Tetracycline	21.9	68.8	74.8	91.5	37.8	27.9	27.3
Vancomycin	0	0	0.9	0	0	0	0
Linezolid	0	0	4.4	0	0	0	0
Tigecycline	—	—	0	—	—	—	—

AMR, antimicrobial resistance; Efa, Enterococcus faecium; GBS, group B Streptococcus; SA, Staphylococcus aureus; Sep, Staphylococcus epidermidis; Sha, Staphylococcus haemolyticus; Sho, Staphylococcus hominis; Spn, Streptococcus pneumoniae.

aA/B%, number resistant/number tested (percentage resistant).

^bA dash (----) shows that antibiotics were not tested against the isolated pathogens.

Table 3	
AMR patter	ns of Gram-positive pathogens

Antimicrobial agent	Eco A/B% ^a	Aba A/B%	Kpn A/B%	Pae A/B%
Ampicillin	84.0	77.8	96.2	92.3
Piperacillin	82.4	60.0 ^b	78.6	38.5
Cefazolin	50.0	—	78.3	_
Cefuroxime	52.4	—	50.0	—
Cefoxitin	0	—	62.5	
Ceftriaxone	49.4	53.3	66.7	—
Cefotaxime	49.2	62.5	70.0	—
Ceftazidime	26.4	38.1	62.5	31.2
Cefepime	32.1	33.3	53.1	17.6
Amoxicillin/clavulanic acid	—	61.5	—	—
Ampicillin/sulbactam	56.9	33.3	76.9	100
Piperacillin/tazobactam	2.5	41.7	66.7	40.0
Cefoperazone/sulbactam	5.9	_		—
Tobramycin	41.1	10.0	0	25.0
Gentamicin	38.6	41.7	43.3	15.4
Amikacin	0	12.5	35.5	6.2
Ciprofloxacin	55.7	25.0	41.4	7.7
Levofloxacin	53.6	23.8	37.5	18.8
Aztreonam	34.7	—	65.4	50.0
Tetracycline	78.9	55.6	30.0	_
Cotrimoxazole	68.8	59.1	14.7	
Meropenem	6.8	54.5	64.0	15.4
Ertapenem	0	—	8.3	—
Imipenem	2.9	31.6	22.7	37.5

Aba, Acinetobacter baumannii, AMR, antimicrobial resistance; Eco, Escherichia coli; Kpn, Klebsiella pneumoniae; Pae, Pseudomonas aeruginosa.

aA/B%, number resistant/number tested (percentage resistant)

^bA dash (-) shows that antibiotics were not tested against the isolated pathogens.

(12.4%) and Streptococcus pneumoniae (10.9%). These results were similar to those of the study by Jiang et al.^[8] from China. On the contrary, Neisseria meningitidis, Streptococcus pneumoniae and Hemophilus influenzae were the leading causative agents of paediatric BM in various studies from Britain^[5], Africa^[6,7] and USA^[12]. The variation between the results of these studies is most probably due to environmental conditions and socioeconomic differences among these regions. Hence, it is urgent that prompt reporting and summary of the characteristics of the aetiological agents causing PBM be done. There is a great variability in the distribution of bacterial meningitis-causing pathogens among children of different age groups^[8–10]. Escherichia coli, Enterococcus faecium and Staphylococcus epidermidis were the top three pathogens in infants under 3 months in our study, at 22.2%, 14.5% and 10.9%, respectively. This was consistent with the studies done by Chinese in Yunnan^[8] and Shanghai^[13]. However, studies from the USA^[14], UK and Ireland^[15] were not comparable to our study and showed that the main pathogens causing PBM in infants aged less than 3 months were Group B Streptococcus, Escherichia coli and Staphylococcus aureus. Our study demonstrated that Staphylococcus epidermidis (20.7%), Streptococcus pneumoniae (17.5%) and Staphylococcus hominis (8.2%) were the chief bacteria causing PBM in children more than 3 months of age. These findings were different from literature data from Wales and England^[5] but consistent with the study conducted by Jiang et al.^[8]. Furthermore, we observed that the greatest number of pathogenic organisms in children less than 1 year of age was Escherichia coli, followed by Staphylococcus epidermidis and Enterococcus faecium. Therefore, age should be kept in mind while choosing empiric antimicrobial agents for

patients with paediatric BM. In our study, coagulase-negative Staphylococcus isolates showed more than 71% resistance rates towards penicillin and erythromycin. This was comparable to previous studies done by Pedroso *et al.*^[16] (100% and 86.2%, respectively) and Cui *et al.*^[17] (94.9% and 92.4%, respectively). Similar to previous literature^[16–19], in our study, no isolates were found resistant towards linezolid and vancomycin. Even though no vancomycin-resistant isolates were detected in the surveillance data, it exists in the clinics and the emergence of vancomycinresistant CoNS (VRCoNS) can be a momentous concern in paediatric bacterial meningitis. The massive antibiotic resistance of Klebsiella pneumoniae and Escherichia coli is of significant concern^[20-24]. The resistance rates of *Escherichia coli* towards ceftriaxone and cefotaxime (49.4% and 49.2%, respectively) in our study were comparable to those found in previous literature^[8,10]. The proportion of carbapenem-resistant Escherichia coli was 5%. CHINET surveillance demonstrated resistance rates of Escherichia coli towards imipenem and meropenem to be 1.0% and 2.2%, respectively^[23] and survey reports in the USA showed increased rates of carbapenem resistance from 2001 till 2010^[24]. However, in our study, the incidence of ESBL production and the resistance of Klebsiella pneumoniae toward cephalosporins, carbapenems and aminoglycosides were more than those found in Escherichia coli isolates. A study in Greece^[25] showed 60% resistance rate of Klebsiella pneumoniae towards carbapenems, which is similar to our results. Literature shows a mortality rate of ~26.0-44.0%^[26], higher economic burden^[27] and prolonged hospital stay caused by carbapenem-resistant Enterobacteriaceae. Moreover, resistance towards carbapenems has emerged as an utmost challenge in the management of carbapenem-resistant Klebsiella pneumoniae. More focused research is needed on the mechanism behind CRKP production in the future.

Our study showed that the resistance rate of Streptococcus pneumoniae to penicillin was ~82.8%, which was higher than the studies done by Jiang et al.^[8] and Houri et al.^[28]. The resistance rates of 41.0% and 50.0% were demonstrated by Streptococcus pneumoniae towards cefotaxime and ceftriaxone, respectively. A study done in Yunnan^[8] showed that 16.7% of Streptococcus pneumoniae were resistant to ceftriaxone, and another study by Li et al.^[10] resistance rates of 14.0% to cefotaxime and 11.3% to ceftriaxone. Assegu et al.^[29] showed resistance of S. pneumoniae towards cefotaxime and ceftriaxone to be 60.0% and 60.0%, respectively. Although different levels of resistance were demonstrated in previous literature, higher exposure to antibiotic treatment can be ascribed as the cause of the greater incidence of resistance in our study. Hence, serious thoughts on antibiotic use should be given to control antibiotic resistance. Predictably, in similarity with previous studies^[8–10,28–30], no isolate of Streptococcus pneumoniae showed resistance towards linezolid or vancomycin.

This study provides valuable insights into contemporary aetiologic and resistance trends underlying paediatric bacterial meningitis. Medical professionals can tailor evidence-based diagnostic and therapeutic strategies to the local landscape of prevalent meningitis pathogens and their susceptibility profiles. The urgency of addressing AMR is emphasized, urging swift efforts in stewardship and infection control. There were several limitations to our study. First, community and hospital-acquired paediatric bacterial meningitis, their epidemiological differences, and the relationship between the distribution of pathogens and hospital-acquired paediatric bacterial meningitis could not be distinguished due to the unavailability of detailed patients' clinical data. Second, even though the antibiotic resistances were checked according to CLSI guidelines, differences were found in technical skills, observation platforms and automated systems, and these discrepancies might have influenced our antimicrobial sensitivity reports to some extent. Thirdly, the limited sample size constraints and potential lack of representativeness were a key limitations. Further multicenter studies are needed for broader validation. Additionally, the study lacks context on socioeconomic factors and healthcare infrastructure which impact AMR.

The threat of AMR is far more than a mere buzzword in Pakistan—it constitutes an escalating public health crisis that necessitates urgent action. The findings from this study provide valuable insights into contemporary aetiologic and resistance trends underlying paediatric bacterial meningitis in this setting. This data can help guide medical professionals in devising evidence-based diagnostic and therapeutic strategies tailored to the local landscape of prevalent meningitis pathogens and their susceptibility profiles. However, some limitations exist regarding sample size and representativeness that necessitate further multicenter studies to corroborate generalizability. Nevertheless, these findings highlight AMR patterns that cannot be ignored in the hopes that resistance will resolve on its own. Without swift and coordinated efforts in stewardship, infection control, and research, we risk losing the precious antimicrobial tools that made once deadly infections treatable. The time for united action against AMR is now before resistance renders our current antibiotics obsolete and reshapes the practice of modern medicine. Ongoing surveillance paired with public health mitigation strategies provides our best hope of preserving antimicrobial efficacy, saving lives, and confronting the very real threat posed by rampant AMR. However, progress will require commitment from every level, from policymakers to health systems to individual physicians and patients.

Conclusion

The authors found that a significant proportion of bacterial pathogens in Pakistan exhibit resistance to commonly used antibiotics, highlighting the growing public health challenge posed by AMR in Pakistan. The study provides valuable insight into the epidemiology of bacterial meningitis in children in Pakistan and the need for a comprehensive assessment of the country's AMR situation.

Ethical approval

Ethical approval for this study was approved by Rawalpindi medical university –IRB NO-21/RMU/DRB-NSD/2022.

Consent

Written informed consent was obtained from the patient's parents/legal guardian for publication and any accompanying image.

Source of funding

Not applicable.

Author contribution

All authors have contributed equally in formation of all form of manuscript.

Conflicts of interest disclosure

Not applicable ..

Research registration unique identifying number (UIN)

Not applicable.

Guarantor

Bipin Chaurasia.

Data availability statement

Not applicable.

Provenance and peer review

Exempted.

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