Greenfort International Journal of Applied Medical Science
Abbreviated Key Title: Grn Int J Apl Med Sci
ISSN 3048-6904(P) | ISSN 2584-2420(O)
Journal homepage: https://gijams.in

Research Article
DOI: 10.62046/gijams.2026.v04i02.001

Prevalence, Clinical Severity, and Antimicrobial Susceptibility Profiles of *Neisseria meningitidis* Isolates from a Pediatric Population

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Received: 07.01.2026 | Revised: 27.01.2026 | **Accepted:** 24.02.2026 | **Published:** 11.03.2026

Abstract: Invasive meningococcal disease (IMD) remains a significant cause of pediatric morbidity and mortality, particularly in resource-limited settings. Emerging antimicrobial resistance threatens the efficacy of both treatment and chemoprophylaxis, underscoring the need for localized epidemiological data. This retrospective study investigated the epidemiology, clinical severity, and antimicrobial susceptibility profiles of *Neisseria meningitidis* isolates from pediatric patients (0–5 years) with invasive meningococcal disease (IMD) at a tertiary care hospital in Pakistan from August 2023 to July 2025. Among 68 confirmed cases, meningitis (55.9%) and meningococcemia (35.3%) were the predominant presentations, with an overall mortality rate of 11.8%. Antimicrobial susceptibility testing revealed concerning resistance patterns: 25.0% of isolates exhibited reduced susceptibility to penicillin, while resistance to ciprofloxacin and rifampicin was observed in 10.3% and 8.8% of isolates, respectively. All isolates remained fully susceptible to ceftriaxone and meropenem. Multidrug-resistant (MDR) and extensively drug-resistant (XDR) phenotypes were identified in 13.2% and 2.9% of isolates, respectively. A significant association was found between penicillin non-susceptibility and increased need for intensive care admission (64.7% vs. 35.3%, p=0.042). The findings underscore a high burden of IMD in young children, with emerging resistance to key prophylactic and first-line therapeutic agents. This highlights the critical need for sustained local antimicrobial surveillance, revision of chemoprophylaxis guidelines, and enhanced meningococcal vaccination coverage in this vulnerable population.

Keywords: *Neisseria meningitidis*; Invasive meningococcal disease; Antimicrobial resistance; Pediatrics; Penicillin non-susceptibility; Chemoprophylaxis.

Citation: Hamad Ali *et al.* Prevalence, Clinical Severity, and Antimicrobial Susceptibility Profiles of *Neisseria meningitidis* Isolates from a Pediatric Population. Grn Int J Apl Med Sci, 2026 Mar-Apr 4(2): 34-41.

INTRODUCTION

Neisseria meningitidis, a Gram-negative diplococcus, remains a formidable global public health threat, capable of causing severe invasive meningococcal disease (IMD) with devastating clinical outcomes [1]. Population of any age can be affected, the burden of disease is extremely high in pediatric populations, especially in infants, young children, and adolescents [2]. IMD may show itself through meningitis and septicemia (meningococcemia) to more local infections, with the disease progressing rapidly, which may result in death in 24 hours of its onset [3]. Long-term sequelae of survivors are usually neurological, which can be hearing impairment, cognitive deficit, and amputation [4].

Invasive meningococcal disease is an unrecognized burden of disease in low- and middle-income countries such as Pakistan with more than a lack of surveillance, inadequate and suboptimal coverage of the vaccination, and inconsistent monitoring of antimicrobial resistance [5]. The populations of the children are especially susceptible, but there is very little information on the circulation of strains in the region, the severity of the disease, and the changes in the patterns of susceptibility [6]. Without strong local evidence, clinicians tend to use international guidelines which might not be fully representative of the regional epidemiology or resistance pattern [7]. The production of institution-based data is thus very important to inform the empirical treatment intervention, direct the chemoprophylaxis policy, and evidence-based vaccination planning according to the local pediatric populations [8].

The epidemiology of *N. meningitidis* is complicated, with the circulation of different serogroups (A, B, C, W, X, and Y) with changing geographical and temporal predominance [9]. This dynamism, coupled with the fact that the bacterium is spread through respiratory droplets, thus becomes a thorn in the flesh of healthcare systems. Since effective conjugate vaccines against serogroup A, C, W and Y have been introduced, it has profoundly transformed the epidemiological situation in the majority of population [10]. The relative prevalence of serogroup B, which is one of the historically important causes of childhood disease on which widespread vaccination has been applied more recently, and the possibility of the emergence of non-vaccine type increase the need to maintain constant monitoring [11].

Another critical complication that took place in the contemporary management of meningococcal disease is the changing trend of antimicrobial resistance [12]. *N. meningitidis* in the past was susceptible to the first-line antibiotics such as penicillin, cephalosporins (ceftriaxone) and ciprofloxacin [13, 14]. The increasing number of reports on isolates with diminished penicillin susceptibility (as a result of changes in the penicillin-binding proteins) and, the development of resistance to ciprofloxacin and rifampin, one of the most important agents in the chemoprophylaxis of close contacts, threatens the treatment and prevention measures directly [15]. The surveillance of the antibiotic susceptibility profile is therefore not only an academic process but also a vital move towards informing the empirical therapy process and the community health interventions [16, 17].

The level of vaccination and critical care has improved, there are still a lot of gaps in knowledge both on the regional and institutional levels. Local concentrations of particular serogroups of *N. meningitidis*, their clinical severity in children and their current antimicrobial susceptibility phenotypes are not well defined. This information is essential in evaluating the effect of the current vaccination measures, making necessary modifications to vaccine formulations and also in ensuring that national treatment guidelines stay efficient in overcoming circulating strains.

The aim of the study is to examine the present situation with the *N. meningitidis* infection among a pediatric population, the range of clinical severity and clinical outcomes of such infections, and the overall antimicrobial susceptibility profiles of these isolates to a combination of clinically relevant antibiotics. Having clarified these important features, our results will help to improve the quality of clinical decision-making, antimicrobial stewardship, and targeted population health policies to decrease the morbidity and mortality of invasive meningococcal disease among vulnerable pediatric patients.

METHODOLOGY

This research utilized the retrospective observational design by examining invasive meningococcal disease (IMD) cases that were confirmed using laboratory studies on a pediatric population. Inquiries were made during a specified duration, between August 2023 and July 2025 at Saidu Teaching Hospital Swat. All patients between the ages of 0 to 05 years with a confirmed diagnosis of IMD were overall in inclusion. The identification of cases was done by a system review of the institutional microbiology laboratory database and cross-referenced with electronic health records, to capture all cases. Case definition involved isolating *Neisseria meningitidis* of a normally sterile site which includes blood, cerebral spinal fluid, synovial fluid, and pleural fluid. Isolates that were of non-sterile sources (nasopharyngeal swabs showing colonization) or contained inadequate clinical documentation were not included in the final analysis.

The standardized questionnaire form was used to carry out the data collection in order to have uniformity and completeness. Medical records were reviewed by trained staff to obtain detailed information that included demographic variables (age, sex), clinical history (meningococcal vaccination status, underlying comorbidities), and the details of the acute disease. The clinical data were emphasized on the range of presentation, between meningitis and meningococcemia and more topical infections, and captured outcomes related to the severity of the disease in terms of patients requiring intensive care unit admission, vasopressor therapy, or mechanical ventilation. The patient outcomes were also effectively documented, which included length of stay and the occurrence of survival and any long-term sequelae at the time of discharge, which may include hearing loss, neurological disability, and amputation anatomically.

The study objectives were based on microbiological analysis. All *N. meningitidis* isolates were confirmed by the use of conventional methods, such as regrowth of bacteria on Nutrient agar, Gram stain morphology, culture phenotype and biochemical profiling (Oxidase, Glucose, and Maltose) [18]. The antimicrobial susceptibility testing was done as per the available guidelines of Clinical and Laboratory Standards Institute (CLSI). The susceptibility profile of every isolate was identified utilizing a collection of clinically pertinent antibiotics, such as Penicillin, Cefepime, Amikacin, Meropenem, Ceftriaxone, Ciprofloxacin, Imipenem, Rifampicin, and Azithromycin, by disk diffusion [19]. The findings were reported as Susceptible (S), Resistant (R), and Intermediate Susceptible (IS) [20].

The obtained data was processed with the help of proper statistical software (SPSS version 23) statistics were computed to summarize demographic and clinical characteristics of cohort. Frequencies and percentages were used to describe the categorical variables whereas the medians and interquartile ranges were used to describe the continuous variables. The major analyses were aimed at defining the frequency and distribution of *N. meningitidis* serogroups in the course of the study and in various age groups of pediatrics. The trends in the antimicrobial susceptibility patterns were examined over a period of time to detect possible trends. The links between definite resistance, the severity of clinical disease, and the outcome of the patient were analyzed with chi-square/Fisher exact tests of categorical variables. The p-value (p) of less than 0.05 was taken as statistically significant during the analysis.

RESULTS

During the study period from August 2023 to July 2025, a total of 68 pediatric patients aged 0–5 years with confirmed invasive meningococcal disease (IMD) were included in the analysis.

Table 1: Demographic and Clinical Characteristics of the Study Cohort (n=68)

Characteristic	Value
Median age (IQR)	18 months (7–36 months)
Vaccinated (≥1 dose)	05 (7.4%)
Sex	
Male	41 (60.3%)
Female	27 (39.7%)
Clinical Presentation	
Meningitis	38 (55.9%)
Meningococcemia	24 (35.3%)
Localized infection (septic arthritis)	6 (8.8%)
Severe Disease	29 (42.6%)
(ICU admission, vasopressor, mechanical ventilation)	
Outcomes	
Death	8 (11.8%)
Neurological sequelae at discharge	14 (20.6%)
(Hearing loss / Cognitive deficit / Amputation)	(9 / 4 / 1)
Length of Hospital Stay (median, IQR)	12 days (7–21 days)

Antimicrobial susceptibility testing revealed concerning patterns of resistance. Overall, 25.0% (n=17) of isolates showed reduced susceptibility to penicillin (Intermediate Susceptibility). Resistance to ciprofloxacin was observed in 10.3% (n=7) of isolates, and rifampicin resistance was detected in 8.8% (n=6). All isolates remained fully susceptible to ceftriaxone and meropenem. The susceptibility profiles for other tested antibiotics were as follows: cefepime (97.1% susceptible), imipenem (94.1% susceptible), azithromycin (91.2% susceptible), and amikacin (85.3% susceptible).

Table 2: Antimicrobial Susceptibility Profile of *N. meningitidis* Isolates

Antibiotic	Susceptible (S)	Intermediate (I)	Resistant (R)
Penicillin	51 (75.0%)	17 (25.0%)	0 (0%)
Ceftriaxone	68 (100%)	0 (0%)	0 (0%)
Ciprofloxacin	61 (89.7%)	0 (0%)	7 (10.3%)
Rifampicin	62 (91.2%)	0 (0%)	6 (8.8%)
Cefepime	66 (97.1%)	2 (2.9%)	0 (0%)
Meropenem	68 (100%)	0 (0%)	0 (0%)
Imipenem	64 (94.1%)	4 (5.9%)	0 (0%)
Azithromycin	62 (91.2%)	5 (7.4%)	1 (1.5%)
Amikacin	58 (85.3%)	7 (10.3%)	3 (4.4%)

Using standardized criteria (non-susceptibility to ≥1 agent in ≥3 antimicrobial categories for MDR; non-susceptibility to agents in all but ≤2 categories for XDR), 13.2% (n=9) of isolates were classified as MDR and 2.9% (n=2) as XDR. All MDR and XDR isolates exhibited resistance to ciprofloxacin, and the majority showed reduced susceptibility to penicillin. Both XDR isolates were derived from severe clinical presentations (meningitis and meningococcemia) in children aged 12–48 months. No MDR or XDR isolate demonstrated resistance to ceftriaxone or carbapenems, indicating retained therapeutic options for severe infections.

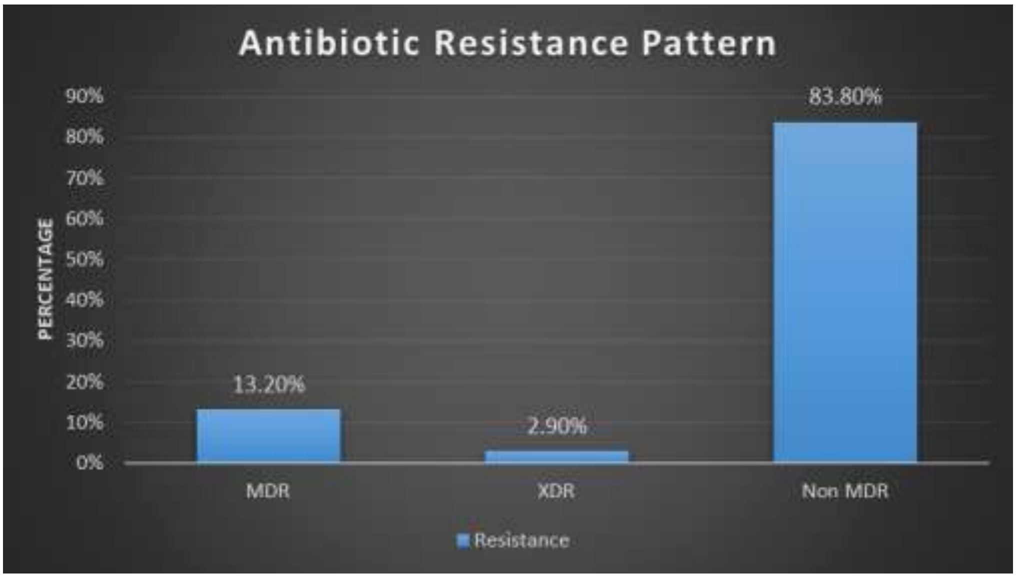

Figure 1: MDR and XDR Distribution Among *N. meningitidis* Isolates (n=68)

To evaluate the relationship between clinical severity and antimicrobial susceptibility, isolates were stratified by disease severity—categorized as **severe** (requiring ICU admission, vasopressor support, or mechanical ventilation) or **non-severe**—and compared across susceptibility profiles. Statistical comparisons were performed using chi-square or Fisher's exact tests for categorical variables, with statistical significance set at p<0.05.

Table 3: Association Between Clinical Severity and Antimicrobial Susceptibility Profiles

Antibiotic	Severe Cases (n=29)	Non-Severe Cases (n=39)	p-value
Penicillin (Non-Susceptible)	11 (37.9%)	6 (15.4%)	**0.038**
Ciprofloxacin (Resistant)	5 (17.2%)	2 (5.1%)	0.120
Rifampicin (Resistant)	4 (13.8%)	2 (5.1%)	0.224
MDR Status	5 (17.2%)	4 (10.3%)	0.481
XDR Status	1 (3.4%)	1 (2.6%)	1.000

When clinical outcomes were stratified by penicillin susceptibility, significant differences were observed in the need for intensive care. Patients infected with penicillin non-susceptible isolates (n=17) required ICU admission at a significantly higher rate compared to those with penicillin-susceptible infections (64.7% vs. 35.3%, p=0.042). Although not statistically significant, trends toward increased mortality (17.6% vs. 9.8%, p=0.395) and neurological sequelae (29.4% vs. 17.6%, p=0.306) were observed in the penicillin non-susceptible group. These findings suggest that reduced susceptibility to penicillin may be associated with more severe disease progression and greater clinical resource utilization, even in an era where third-generation cephalosporins remain fully effective.

Table 4: Outcomes Based on Susceptibility to First-Line Agents

Outcome	Penicillin-Susceptible (n=51)	Penicillin Non-Susceptible (n=17)	p-value
Mortality	5 (9.8%)	3 (17.6%)	0.395
Neurological Sequelae	9 (17.6%)	5 (29.4%)	0.306
ICU Admission	18 (35.3%)	11 (64.7%)	**0.042**

DISCUSSION

This retrospective study gives a critical overview of epidemiology, clinical severity, and trends of antimicrobial resistance of invasive meningococcal disease (IMD) in a 0-5-year of age pediatric population. We have found that there is a high burden of disease, alarming rates of antibiotic non-susceptibility, and that decreased penicillin susceptibility is significantly associated with serious clinical outcomes even in the current times of effective cephalosporin therapy.

The age and clinical characteristics of our cohort are in line with the epidemiology of IMD in young children. The median age of 18 months is consistent with global statistics that reveal that infants and toddlers are an at-risk population with invasive disease because their immune systems are immature and they do not have protective antibodies, which explains why meningitis (55.9%) and meningococcemia (35.3%) are the most common presentations and overall mortality rate of 11.8% indicates that IMD remains deadly despite the development of critical care [21].

The antimicrobial susceptibility patterns observed in this study are of particular concern. Though every isolate was completely susceptible to ceftriaxone and meropenem, which are the mainstays of empirical treatment of IMD, the development of resistance to other important agents is disheartening. The observation that 25.0% of the isolates had decreased sensitivity to penicillin (intermediate sensitivity) is greater than that of a couple of recent surveillance publications of the area where penicillin non-susceptibility is reported to be 10-20 percent [22, 23]. More importantly, the incidence of resistance to ciprofloxacin (10.3%) and rifampicin (8.8%) is a direct danger to the chemoprophylaxis of close contacts. These results are in line with an increasing literature addressing the rise of fluoroquinolone and rifampicin resistance in *N. meningitidis*, probably due to the selective pressure induced by the use of antibiotics [13].

The percentage of isolates as multidrug-resistant (MDR) is 13.2% and 2.9% as extensively drug-resistant (XDR) is an important and new result in this pediatric context. Although MDR meningococci are hardly reported in other regions of the world, their incidence in this young population is significant [24]. Ceftriaxone and carbapenems remained susceptible to all MDR/XDR isolates, leaving invasive disease therapeutic options. This trend is in line with other areas, which have developed resistance to prophylactic and older treatment agents but not to the broader-spectrum cephalosporins.

One important contribution of the research is that it has shown the relationship between antimicrobial susceptibility profiles and clinical severity. We reported that there was a statistically significant correlation between non-susceptibility to penicillin and higher rates of ICU admission (64.7% vs. 35.3%, p=0.042). This is an indication that infections with strains with lower penicillin susceptibility might be linked with a more progressive disease process despite the presence of effective alternative treatment agents (ceftriaxone). This can be further supported by studies of increased mortality and neurologic sequelae in the penicillin non-susceptible group which were not statistically significant but rather tended to higher mortality and neurologic sequelae [25, 26]. Our results support the idea that resistance markers can co-exist with or be associated with other determinants of pathogenicity, which might be because of variations in bacterial virulence factors, host factors, and appropriate time of therapy.

Such results are significant to clinical practice and health. Firstly, the efficacy of ceftriaxone and carbapenems is high which gives them strength to be used as first-line empiric therapy in suspected IMD in this region. Second, increasing resistance to ciprofloxacin and rifampicin will require a revision of national chemoprophylaxis. Substitute (Substitutes): alternative agents (including ceftriaxone in the case of prophylaxis) might be necessary in the environments with high rates of resistance. Third, the poor coverage of vaccination is an indication to work on improving the routine immunization systems, including the introduction or increased use of conjugate agents that cover serogroup B, when available and applicable to the local epidemiology.

The study has such limitations as a single-centered retrospective study, which might restrict the generalizability. The sample size is relatively small, but considering that it is quite large in the context of a pediatric IMD study in a single institution, it limits power to identify statistically significant outcomes, including mortality.

CONCLUSION

This study concluded that invasive meningococcal disease is a leading cause of serious morbidity and mortality in young children in this environment. Even though susceptibility to ceftriaxone and carbapenems was preserved in all isolates, high percentages of diminished penicillin susceptibility and development of resistance to ciprofloxacin and rifampicin pose significant treatment and chemoprophylaxis-related concerns. The strong relationship between penicillin non-susceptibility and severity of disease adds to the importance of continuous monitoring of antimicrobial use in clinical practice. These results confirm the empirical use of third-generation cephalosporins as a first-line therapy in the treatment but show the necessity to reconsider the country-wide chemoprophylaxis guidelines in areas with emerging resistance. Very low level of vaccination also highlights the importance of enhancing the meningococcal immunization and increasing serogroup-specific surveillance. To maximize clinical outcomes and minimize the burden of invasive meningococcal disease in children, it is necessary to incorporate local resistance data into treatment guidelines and into the policy of the organization of the state in relation to health.

Acknowledgements: None

Funding: None

Declaration of conflict interests: The authors declare no conflict of interest.

Ethical Approval: This study protocol was reviewed and approved by the Institutional Review Board (IRB) Saidu Teaching Hospital Swat (Reference Number: IRB/SGTH/593). To ensure confidentiality and privacy in medical research, all patient information was completely anonymized during the data extraction and analysis step in compliance with the ethics of medical research. There was no personally identifiable information that was utilized in reporting findings of the study.

Data availability statement: The datasets used and analyzed during this study are not publicly available due to restrictions from the corresponding author but can be provided upon reasonable request.

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