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Case Series

Microbiology Section

# Invasive Pneumococcal Disease in Children: A Case Series on Clinical Profile, Serotypes and Antibiotic Resistance from Southern India

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## ABSTRACT

Invasive Pneumococcal Disease (IPD) is defined as the isolation of pneumococci from normally sterile sites, including blood, cerebrospinal fluid, pleural fluid, ascitic fluid and synovial fluid. Despite widespread vaccination, IPD continues to be a major public health concern worldwide. Studying antibiotic resistance in the context of emerging serotypes and vaccines for IPD is crucial for optimising clinical management, guiding vaccine strategies and forming public health policies. By understanding the interplay between serotype dynamics, antibiotic resistance and vaccination, researchers and healthcare professionals can better mitigate the impact of pneumococcal disease on global health. In this case series, the authors describe the clinical profile, serotypes and antibiotic resistance of five cases of IPD in the paediatric age group. All five children exhibited severe signs of IPD, such as meningitis or septicaemia. The serotypes identified were 15C (2 cases), 6B, 19F and 23F. All five cases were sensitive to chloramphenicol, vancomycin, linezolid and levofloxacin. All cases were resistant to penicillin, and only one case was sensitive to erythromycin; all others were resistant. Cefotaxime was sensitive in three cases and intermediate in two cases. Cotrimoxazole was resistant in three cases, sensitive in one and intermediate in another case. The currently available Pneumococcal Conjugate Vaccine (PCV) offer substantial protection against IPD, but the occurrence of severe IPD cases, such as meningitis and septicaemia, necessitates the introduction of newer vaccines with broader coverage, such as PCV 15 and PCV 20.

**Keywords:** Antimicrobial susceptibility, Serotyping, *Streptococcus pneumoniae*, Vaccine

## INTRODUCTION

Despite widespread vaccination, IPD continues to be a major public health concern worldwide. Mortality in children under-five years remains high in Southeast Asian countries, with around 25% of deaths due to IPD occurring in India [1]. IPD is defined as the isolation of pneumococci from normally sterile sites, including blood, cerebrospinal fluid, pleural fluid, ascitic fluid and synovial fluid [2]. It affects all age groups, but it is particularly severe in individuals under two years of age and those over 65 years of age [3]. The incidence, severity and mortality of the disease depend on age, associated co-morbidities, socio-economic factors and serotype.

Among the various serotypes, few are more prone to cause invasive infections. These serotypes have been included in pneumococcal vaccines. The first PCV was the seven-valent PCV 7, which targeted serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F and was licensed in 2000. It has since been replaced by the ten-valent PCV10, which additionally targets serotypes 1, 5, and 7F, and the 13-valent PCV13, which also targets serotypes 3, 6A, and 19A. In some countries, primarily high-income countries, the 23-valent Pneumococcal Polysaccharide Vaccine (PPV23) was introduced for adults who received PCV7, 10, or 13 in childhood. PCV7 was effective, leading to approximately an 80% reduction in IPD caused by vaccine types (VT-IPD) among children under two years of age during the first year, and the introduction of PCV13 resulted in a further reduction of 94% in IPD cases among children. An overall reduction in the rate of IPD of approximately 20% across all age groups was also observed, which is related to the indirect effects of the vaccine. However, due to serotype replacement, there has been an increase in IPD caused by non vaccine serotypes [4,5].

For the proper effectiveness of PCV vaccination, region-specific data are important for the appropriate selection of vaccine serotypes. Due to the scarcity of region-specific data, local serotype prevalence remains unknown. This case series analyses the clinical profile, major serotypes and emerging penicillin and erythromycin resistance in children admitted to IPD of the hospital from May 1, 2022, to October 31, 2023. Serotyping was conducted at Christian Medical College, Vellore,Tamil Nadu, India using the Quellung reaction.

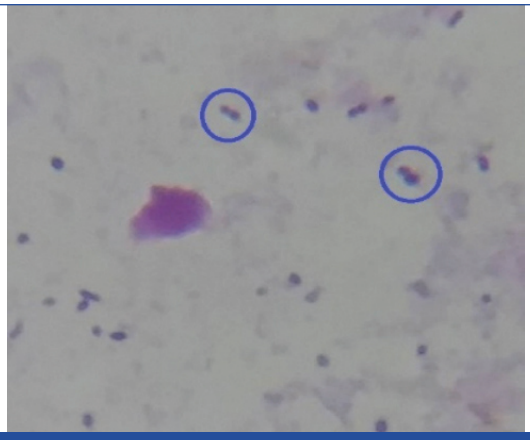
## CASE SERIES

### Case 1

A four-and-a-half-year-old child with no known co-morbidities presented with fever and throat pain for five days. The child was referred from a local hospital due to a single episode of projectile vomiting and a seizure. The fever was high-grade and intermittent, not associated with chills or rigors. The child had not been vaccinated for pneumococci. On examination, the child appeared sick and irritable. The Central Nervous System (CNS) examination revealed nystagmus, neck stiffness and a positive Kernig sign. Investigations showed an elevated total White Blood Cell (WBC) count, an Erythrocyte Sedimentation Rate (ESR) of 70 mm/hr, and a C-Reactive Protein (CRP) level of 90.9 mg/dL. The Cerebrospinal Fluid (CSF) study showed a total cell count of 220, with 59% polymorphs and 41% lymphocytes, protein at 171 mg/dL, and sugar at 2 mg/dL. The CSF gram stain revealed numerous pus cells along with Gram-positive cocci in pairs [Table/Fig-1]. *Streptococcus pneumoniae* was isolated from the culture, and the child was started on intravenous (i.v.) ceftriaxone and vancomycin. The serotype identified was 15C. After 14 days of antibiotic treatment, the child became asymptomatic and was discharged with advice to receive two doses of PCV 13, eight weeks apart.

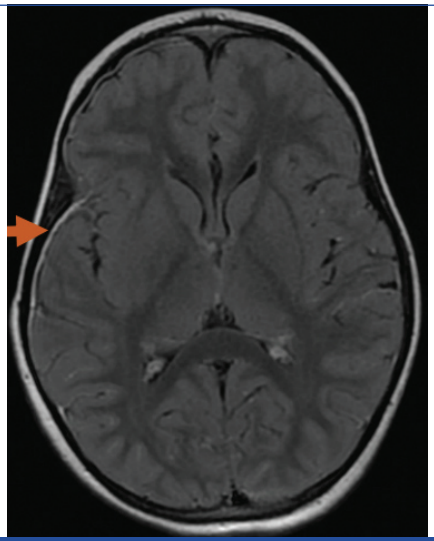
### Case 2

A five-year-old child, who was not immunised with PCV, experienced a high-grade intermittent fever for four days. After being managed



**[Table/Fig-1]:** CSF gram stain showing gram positive diplococci at 100x magnification.

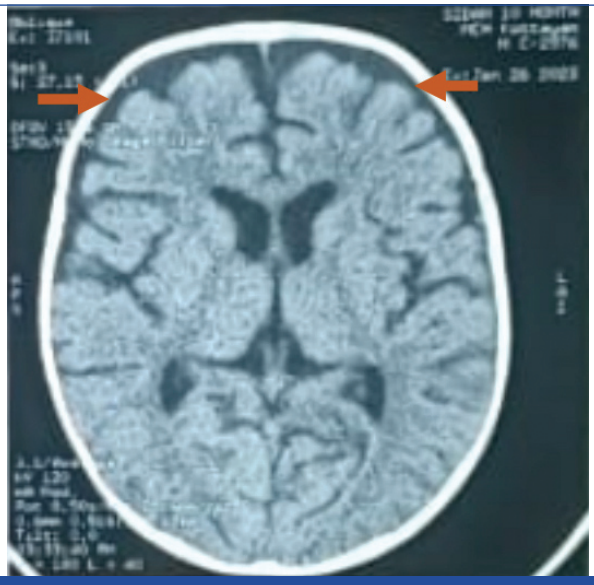
symptomatically and treated with oral antibiotics from a local hospital, the child developed bilateral headaches, altered sensorium, fatigue and vomiting. Upon examination, the child appeared sick and irritable. The CNS examination revealed that the child was irritable, with a Glasgow Coma Scale (GCS) score of 15/15, neck stiffness and a positive Kernig sign. Magnetic Resonance Imaging (MRI) showed leptomeningeal thickening and enhancement in the bilateral cerebral convexities and posterior fossa, suggestive of meningitis [Table/Fig-2]. Blood reports indicated a CRP of 8.9 mg/dL and a Total Count (TC) of 10,640/mm$^3$. The CSF study suggested pyogenic meningitis, with a total cell count of 40, polymorphs at 10%, lymphocytes at 90%, protein level at 172 mg/dL, and sugar level at 17.1 mg/dL. CSF culture yielded *Streptococcus pneumoniae*, with the identified serotype being 15C. The child was treated with i.v. ceftriaxone and vancomycin for 14 days. He responded well to treatment and was discharged after 17 days. The child was active and showed no fever after two weeks, and he was advised to receive the PCV vaccine two weeks later.



**[Table/Fig-2]:** MRI Brain T2 flair showing leptomeningeal thickening and enhancement marked by red arrow.

## Case 3

A 10-month-old infant, vaccinated with three doses of PCV10, presented with high-grade intermittent fever for four days and was admitted to a local hospital where he was managed with paracetamol. During his stay, he developed tonic posturing of the limbs, deviation of the angle of the mouth, and upward rolling of the eyes, followed by loss of consciousness for 20-30 minutes on the second day. As his symptoms worsened, he was subsequently referred to a higher centre. Upon examination, the child was irritable and distressed. Computed Tomography (CT) and MRI of the brain showed prominent subarachnoid space in the frontotemporal parenchyma [Table/Fig-3]. The CSF study was consistent with pyogenic meningitis (total count: 102 cells, polymorph: 19%, lymphocyte: 81%, protein: 214 mg/dL, and sugar: 2 mg/dL). Both CSF and blood cultures yielded *Streptococcus pneumoniae*, with the serotype identified as 6B. He responded well to treatment with i.v. ceftriaxone and vancomycin and was discharged after 20 days of treatment. When the child was reviewed two weeks later, he had no further episodes of fever or seizures.



**[Table/Fig-3]:** CT brain showing prominent subarachnoid space marked by red arrows.

## Case 4

A 10-year-old male child, who had not received PCV, developed a high-grade intermittent fever for three days, associated with headache and giddiness, for which he was symptomatically treated at a local hospital. After three days, the child developed 3-4 episodes of vomiting and was referred. On examination, the child was alert and active, with normal sensorium. CNS examination revealed a GCS of 15/15, with pupils that were equal and reactive to light bilaterally. Neck stiffness and a positive Kernig sign were present, while Brudzinski neck and leg signs were negative. CT of the brain showed no significant abnormalities. CRP was elevated at 135 mg/dL. The CSF study showed a total cell count of 10 cells, with polymorphs at 2% and lymphocytes at 98%, protein at 381 mg/dL, and sugar at 5 mg/dL. CSF culture yielded *Streptococcus pneumoniae*, with the serotype identified as 19F. The child was started on i.v. ceftriaxone and vancomycin, which continued for 14 days. His condition improved, but he developed hearing loss. Audiological examination showed right-sided sensorineural hearing loss and left-sided low-frequency hearing loss. He was given a short course of corticosteroids under the guidance of the Ear, Nose and Throat (ENT) department and was referred for further evaluation and rehabilitation at higher centres. The child showed symptomatic improvement with the therapy, completed his PCV vaccination, and is currently under follow-up.

## Case 5

A two-year-old male child, who had not been immunised with PCV, presented with symptoms of high-grade intermittent fever and decreased feeding for three days. The child also developed 5-6 episodes of vomiting. On examination, the child was irritable with mild dehydration. Systemic examination revealed no abnormalities. Blood reports showed a total WBC count of 25,040/mm$^3$ and a CRP of 86.3 mg/dL. Blood culture grew *Streptococcus pneumoniae*, with the serotype identified as 23F. He was treated with i.v. ceftriaxone and vancomycin for 14 days. His condition improved, he started taking feeds, and was discharged home. At the time of follow-up two weeks later, the child had no fever, was feeding well, and was advised to receive the PCV vaccine after two weeks.

The summary of all the cases is included in [Table/Fig-4-6].

| Case no. | Age | Sex | Clinical presentation | Antibiotic treatment received | PCV vaccination status | Outcome |
|---|---|---|---|---|---|---|
| 1 | 4 ½ years | M | Meningitis | Ceftriaxone, Vancomycin | No | Recovered |
| 2 | 5 years | F | Meningitis | Ceftriaxone, Vancomycin | No | Recovered |
| 3 | 10 months | M | Meningitis, septicaemia | Ceftriaxone, Vancomycin | Yes | Recovered |
| 4 | 10 years | M | Meningitis | Ceftriaxone, Vancomycin | No | Recovered Sequela+ |
| 5 | 2 years | M | Septicaemia | Ceftriaxone, Vancomycin | No | Recovered |

**[Table/Fig-4]:** Clinical profile of all cases.

| Case no. | CRP (mg/dL) | Total count (/mm$^3$) | CT/MRI brain | Culture reports | Serotype |
|---|---|---|---|---|---|
| 1 | 90.9 | 19900 | Normal | *S. pneumoniae* isolated from CSF | 15C |
| 2 | 8.9 | 10640 | Leptomeningeal thickening and enhancement | *S. pneumoniae* isolated from CSF | 15C |
| 3 | 118 | 26200 | Prominent subarachnoid spaces | *S. pneumoniae* isolated from CSF and blood | 6B |
| 4 | 135 | 21,800 | Normal | *S. pneumoniae* isolated from CSF | 19F |
| 5 | 86.3 | 25,040 | - | *S. pneumoniae* isolated from blood | 23F |

**[Table/Fig-5]:** Investigation reports of all cases.

| Case no. | Penicillin | Cefotaxime | Erythromycin | Levofloxacin | Linezolid | Vancomycin | Chloramphenicol | Cotrimoxazole |
|---|---|---|---|---|---|---|---|---|
| 1 | 1 R | 0.5 S | 8 R | 0.50 S | 1 S | 0.19 S | 2 S | 4 R |
| 2 | 0.75 R | 0.75 I | 0.064 S | 0.50 S | 0.75 S | 0.19 S | 2 S | >32 R |
| 3 | 1 R | 0.75 I | 8 R | 0.38 S | 0.38 S | 0.25 S | 1.5 S | 4 R |
| 4 | 0.75 R | 0.5 S | 8 R | 0.50 S | 1 S | 0.19 S | 1.5 S | 0.5 S |
| 5 | 0.75 R | 0.5 S | >256 R | 0.50 S | 0.38 S | 0.25 S | 2 S | 0.75 I |

**[Table/Fig-6]:** Antibiotic Sensitivity Test (AST) and Minimum Inhibitory Concentration (MIC) reports of all cases.
S: Susceptible, I: Intermediate, R: Resistant

## DISCUSSION

Pneumococci are classified into different serotypes based on the nature of their capsule. Around 100 serotypes have been identified so far [6]. The different serotypes have varying abilities to cause diseases. Approximately 10 serotypes are responsible for 62% of IPD worldwide [4]. The serotypes found in this case series were 15C, 6B, 19F, and 23F. Interestingly, serotype 15C, which was rarely seen in previous studies, appeared in two cases in this series. This suggests that 15C might be the main serotype causing IPD in Central Kerala. Additionally, one case each of serotype 15C was reported in two studies from Vellore. Multiple cases of other serotypes seen in this series were also found in studies from Vellore [7,8]. However, serotypes 1 and 5, which are commonly found in national hospital-based surveillance studies and Vellore studies, were not identified in this series [9]. A systematic review of Indian studies shows that the most frequent serotypes obtained from children five years and younger with IPD were 14, 1, 19F, 6B, 5, 6A, 9V, and 23F [10]. A review study from Southeast Asia identified common serotypes causing IPD as 19F, 23F, 14, 6B, 1, and 3 [11]. In contrast, data from Sweden, a developed country, showed common serotypes as 1, 7F, 9V, 14, 4, and 12F [12]. Comparing these findings with the serotypes found in this case series, it appears that there is a trend towards changing serotype distribution. This emphasises the significance of monitoring the distribution of serotypes to identify new types and mixed strains as they emerge. Such information is essential for developing suitable vaccination strategies tailored to each region.

In this study, all serotypes identified, except for 15C, are covered by the currently used pneumococcal vaccines in the country for immunisation in children, PCV 10 and PCV 13. Among the five children in the study, only one received the PCV vaccine. The vaccinated child, infected with the 6B serotype, had received the PCV 10 vaccine. The vaccine coverage appears to be lower in this cohort compared to global data. According to the 2022 WHO/UNICEF Estimates of National Immunisation Coverage, PCV coverage was 65% in low-income countries and 64% in lower-middle-income countries, but only 37% in upper-middle-income countries, while it was 87% in high-income countries [13]. It is important to consider region-specific invasive serotypes when planning vaccination strategies against IPD. The herd immunity provided by the current vaccine may not fully protect against the common serotype found in this region. Additionally, the potential for serotype conversion after vaccination is an important factor to consider when developing vaccination strategies for IPD.

In this case series, all five children showed severe signs of IPD, such as meningitis or septicaemia. All of them improved with antibiotic treatment and recovered from IPD. However, one child infected with the 19F serotype experienced hearing loss as a sequela of the illness. Sensorineural hearing loss is very common following pneumococcal meningitis. It can be due to direct damage to the eighth cranial nerve, cochlear cells, or the labyrinth by the pneumococcus, or it may occur following an inflammatory response with evident MRI abnormalities. In some cases, it can be transient, and the deficit can improve following steroid administration, but usually, it is permanent, and the child may need cochlear implants [14].

Antimicrobial resistance is a growing concern for pneumococcus, just as it is for other pathogens. In this study, all five cases were sensitive to chloramphenicol, vancomycin, linezolid, and levofloxacin. All cases were resistant to penicillin. Only one case was sensitive to erythromycin; all others were resistant. Cefotaxime was sensitive in three cases and intermediate in two cases. Cotrimoxazole was resistant in three cases, sensitive in one, and intermediate in another case. In a systematic literature review of hospital-based observational studies, pneumococcal resistance rates were found to be 81% for trimethoprim/sulfamethoxazole, 37% for erythromycin, 10% for penicillin, 8% for chloramphenicol, 6% for levofloxacin, and 4% for cefotaxime, while no resistance to vancomycin was reported [10]. According to the Asian Network for Surveillance of Resistant Pathogens (ANSORP) data, the prevalence rate of penicillin-non-susceptible pneumococci (MIC >4 mcg/mL) was 4.6%, and penicillin resistance (MIC >8 mcg/mL) was very rare (0.7%). Resistance to erythromycin was 72.7%, and Multidrug Resistance (MDR) was observed in 59.3% of isolates from Asian countries [15]. In present series, there appears to be an increase in penicillin resistance, while erythromycin resistance remains stable compared to previous data. This differs from data from developed countries like the USA, where there has been a 72.3% decline in penicillin non susceptibility, although erythromycin non susceptibility remains stable at 37-45% over the years [16].

## CONCLUSION(S)

The persistence of serotypes 6B, 19F, and 23F, which are included in the current pneumococcal vaccines, alongside the emergence of serotype 15C as a significant cause of IPD in Central Kerala, underscores an evolving epidemiological challenge. Additionally, the rising prevalence of penicillin-resistant pneumococcal strains in this region raises concerns about the efficacy of standard treatment protocols. To effectively manage IPD and address the growing issue of antimicrobial resistance, it is crucial to implement continuous surveillance systems and develop tailored vaccination strategies.

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