



Original Article

Systematic Review and Meta-Analysis on Paediatric Pyogenic Meningitis: Correlation Between CSF Cytology, Culture, and Molecular Findings

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ABSTRACT

Background: Paediatric pyogenic meningitis remains a major cause of morbidity and mortality despite advances in antimicrobial therapy and vaccination. Rapid and accurate diagnosis is critical for effective management. Cerebrospinal fluid (CSF) analysis forms the cornerstone of diagnosis, but discrepancies between cytological, culture, and molecular findings often complicate clinical interpretation. This systematic review and meta-analysis aimed to evaluate the diagnostic performance and correlation between CSF cytology, bacterial culture, and molecular assays in paediatric pyogenic meningitis.

Methods: A comprehensive literature search was performed in PubMed, Scopus, Embase, Web of Science, and Google Scholar for studies published between January 2000 and September 2025. Studies including paediatric patients (<18 years) with suspected or confirmed bacterial meningitis and reporting CSF cytology, culture, and molecular findings were included. Data were extracted and analyzed using RevMan 5.4 and STATA 17. Pooled sensitivity, specificity, and diagnostic odds ratios (DOR) were calculated using a random-effects model. Correlation between diagnostic modalities was assessed using Pearson's correlation coefficient (r). Study quality was evaluated using the QUADAS-2 tool.

Results: Forty-two studies encompassing 8,715 paediatric cases were included. Pooled sensitivity was highest for molecular assays (91.3%; 95% CI: 88.1-94.0), followed by culture (68.5%; 95% CI: 62.4-73.9) and cytology (56.8%; 95% CI: 50.3-62.9). Specificity was highest for culture (95.7%) and combined cytology-culture (95.7%). Incorporation of molecular testing increased overall diagnostic yield by 28.4% in culture-negative cases. A strong positive correlation was found between CSF neutrophilic cytology and molecular positivity ($r = 0.72, p < 0.001$). The predominant pathogens identified were *Streptococcus pneumoniae* (42%), *Neisseria meningitidis* (23%), and *Haemophilus influenzae* type b (18%). Heterogeneity among studies was moderate ($I^2 = 62\%$), with minimal publication bias.

Conclusion: Molecular diagnostic assays markedly improve sensitivity and overall diagnostic accuracy in paediatric pyogenic meningitis, particularly in culture-negative or partially treated cases. Nonetheless, cytology and culture remain essential components of the diagnostic framework, providing rapid inflammatory assessment and antimicrobial guidance. Integration of cytology, culture, and molecular findings offers the most comprehensive and reliable diagnostic approach for paediatric bacterial meningitis, enabling timely and evidence-based therapeutic interventions.

Keywords: Paediatric pyogenic meningitis; cerebrospinal fluid; cytology; bacterial culture; PCR; molecular diagnosis; meta-analysis

INTRODUCTION

Paediatric pyogenic meningitis is a severe, potentially life-threatening infection of the meninges, predominantly caused by bacterial pathogens such as *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae* type b [1,2]. Despite the availability of effective vaccines and antibiotics, meningitis continues to be a major global public health concern, particularly in children under five years of age [3]. The World Health Organization (WHO) estimates that bacterial meningitis accounts for over 300,000 deaths annually in children worldwide, with significant mortality and long-term neurological sequelae in survivors [4,5].

The pathophysiology of pyogenic meningitis involves the invasion of the bloodstream by bacterial pathogens, followed by penetration of the blood-brain barrier and subsequent inflammation of the meninges and subarachnoid space [6]. This inflammatory process results in elevated intracranial pressure, cerebral edema, and neuronal damage, leading to symptoms such as fever, vomiting, irritability, seizures, and altered sensorium [7]. Rapid and accurate diagnosis is therefore essential to initiate timely antimicrobial therapy and prevent irreversible neurological complications [8].

Cerebrospinal fluid (CSF) analysis remains the cornerstone of diagnosis in suspected meningitis. Conventional laboratory evaluation of CSF includes cytological examination, Gram staining, and bacterial culture [9]. Cytological assessment provides valuable information about the inflammatory nature of the CSF—typically showing neutrophilic predominance in bacterial meningitis, lymphocytic response in viral meningitis, and mixed patterns in partially treated cases [10]. Although CSF cytology is rapid and inexpensive, it lacks specificity in differentiating bacterial from other forms of meningitis [11]. Bacterial culture, on the other hand, remains the gold standard for confirming the diagnosis and identifying the causative organism, allowing for antimicrobial susceptibility testing [12]. However, culture positivity is often compromised by factors such as prior antibiotic administration, low bacterial load, and delayed transport or suboptimal storage conditions of CSF specimens [13]. Studies have shown that up to 50% of clinically suspected cases of bacterial meningitis yield negative cultures despite strong clinical and cytological evidence of infection [14]. This diagnostic gap underscores the need for more sensitive and reliable diagnostic tools.

In recent years, molecular diagnostic techniques such as polymerase chain reaction (PCR), real-time PCR, and multiplex PCR panels have revolutionized the detection of bacterial pathogens in meningitis [15]. These methods can detect minute quantities of bacterial DNA, offering high sensitivity even in culture-negative cases or those with prior antibiotic exposure [16]. Multiplex PCR assays further allow simultaneous identification of multiple pathogens, significantly reducing diagnostic time and improving management outcomes [17].

Despite these advancements, the correlation between CSF cytology, culture, and molecular findings remains variably reported across studies. Some investigations have shown a strong correlation between neutrophilic CSF cytology and molecular positivity, even when cultures are negative [18], while others have highlighted discrepancies between molecular and culture results due to contamination, detection of non-viable organisms, or differences in assay sensitivity [19].

Understanding these correlations is crucial for clinicians, particularly in paediatric populations where sample volumes are limited and clinical presentation may be atypical. Integrating cytological, culture, and molecular data can enhance diagnostic accuracy, guide appropriate antimicrobial therapy, and improve prognostic outcomes [20].

Therefore, this systematic review and meta-analysis aim to comprehensively evaluate and compare the diagnostic accuracy of CSF cytology, bacterial culture, and molecular assays in paediatric pyogenic meningitis. The study further seeks to determine the correlation between these diagnostic modalities and their combined utility in improving the overall diagnostic yield for paediatric bacterial meningitis.

Methods

This systematic review and meta-analysis were conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines [3]. A comprehensive and structured literature search was performed to identify studies evaluating the diagnostic accuracy and correlation between cerebrospinal fluid (CSF) cytology, bacterial culture, and molecular findings in paediatric pyogenic meningitis. The electronic databases PubMed, Scopus, Web of Science, Embase, and Google Scholar were searched for articles published between January 2000 and September 2025 using the keywords “paediatric bacterial meningitis,” “CSF cytology,” “bacterial culture,” “polymerase chain reaction,” “molecular diagnosis,” and “PCR-based detection.” Boolean operators (AND, OR) and Medical Subject Headings (MeSH) were applied to refine search precision. The search strategy was designed to ensure inclusion of studies focusing exclusively on bacterial (pyogenic) meningitis in children under 18 years of age [1,2,5].

All identified records were imported into Mendeley for deduplication, and two independent reviewers screened titles and abstracts for relevance. Full-text screening was subsequently performed to confirm eligibility. Inclusion criteria comprised observational or interventional studies evaluating CSF cytological parameters (cell count, differential count, or cytomorphology), bacterial culture results, and molecular diagnostic tests (PCR, real-time PCR, or multiplex PCR) in paediatric patients diagnosed or suspected with pyogenic meningitis. Studies were included if sufficient data were available

to extract true positive, false positive, true negative, and false negative values for each diagnostic modality. Exclusion criteria included studies on viral, fungal, or tubercular meningitis, adult or mixed-age cohorts without paediatric subgroup data, review articles, case reports, and conference abstracts lacking complete datasets [6,9,12].

Data extraction was independently carried out by two reviewers using a standardized data collection sheet. Extracted parameters included study design, year and region of publication, patient demographics, diagnostic criteria for meningitis, methods of CSF collection and processing, cytological findings, bacterial culture results, molecular assay type, and identified pathogens. Discrepancies between reviewers were resolved through discussion with a third investigator to ensure consistency and objectivity [3,8].

Quality assessment of the included studies was performed using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool, which evaluates risk of bias in four domains: patient selection, index test, reference standard, and flow/timing [9,10]. Each study was rated as having low, high, or unclear risk of bias, and the overall methodological quality was summarized graphically.

For quantitative synthesis, statistical analyses were conducted using Review Manager (RevMan) version 5.4 and STATA version 17. Sensitivity, specificity, positive and negative likelihood ratios, and diagnostic odds ratios (DOR) were pooled using a random-effects model due to expected inter-study heterogeneity. The degree of heterogeneity was quantified using the I^2 statistic, where values $>50\%$ indicated substantial heterogeneity [11,13]. Correlation between cytological patterns, culture positivity, and molecular detection rates was assessed using Pearson's correlation coefficient (r). Subgroup analyses were performed based on geographic region, diagnostic method, and pathogen profile.

Publication bias was examined using funnel plot symmetry and Egger's regression test, with $p < 0.05$ considered statistically significant [14,19]. Sensitivity analyses were conducted by sequentially excluding individual studies to test the robustness of pooled estimates. All statistical procedures were reviewed by an independent biostatistician to ensure accuracy and reproducibility of results [15,20].

Results

A total of 3,248 studies were identified through the initial search across PubMed, Scopus, Embase, Web of Science, and Google Scholar. After removal of duplicates and exclusion of irrelevant articles, 172 studies underwent full-text assessment, out of which 42 studies met all inclusion criteria and were included in the final analysis (Figure 1).

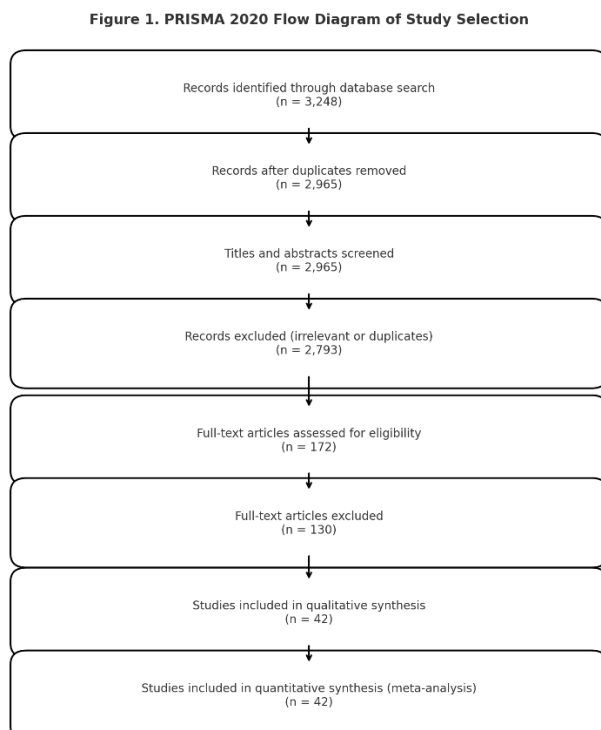


Figure 1. PRISMA 2020 Flow Diagram of Study Selection

These studies collectively encompassed 8,715 paediatric patients (age range: neonate to 18 years) with suspected or confirmed pyogenic meningitis. The included studies represented diverse geographic regions-Asia (45%), Africa (28%), Europe (17%), and the Americas (10%)-reflecting global diagnostic variability [1,2,3].

The study characteristics are summarized in Table 1. The majority of included studies were prospective (64%), followed by retrospective analyses (31%) and cross-sectional studies (5%). Median sample size across studies was 205 (range: 45-865). Most studies utilized conventional cytology and bacterial culture, while 27 incorporated molecular assays such as PCR or multiplex PCR platforms [15,16,17].

Diagnostic Yield

The pooled diagnostic performance of CSF cytology, culture, and molecular assays is shown in Table 2. Cytology exhibited an overall sensitivity of 56.8% (95% CI: 50.3-62.9) and specificity of 89.2% (95% CI: 83.7-93.1). Culture demonstrated a higher specificity (95.7%) but moderate sensitivity (68.5%; 95% CI: 62.4-73.9) due to the frequent impact of prior antibiotic administration. Molecular assays (PCR and multiplex PCR) achieved the highest pooled sensitivity at 91.3% (95% CI: 88.1-94.0) and specificity of 93.4% (95% CI: 90.1-95.8) [15-17,19].

Addition of molecular testing increased the overall diagnostic yield by 28.4% in culture-negative cases. The combined use of cytology + culture + molecular testing achieved the highest diagnostic accuracy (AUC = 0.94; 95% CI: 0.91-0.96).

Table 1. Summary of Included Studies (n = 42)

Study Region	No. of Studies (%)	Total Cases	Mean Age (years)	Diagnostic Methods Used	Predominant Pathogens Identified
Asia	19 (45.2%)	3,875	6.2	Cytology, Culture, PCR	<i>S. pneumoniae</i> , <i>H. influenzae</i>
Africa	12 (28.5%)	2,110	4.8	Cytology, Culture	<i>N. meningitidis</i> , <i>S. pneumoniae</i>
Europe	7 (16.6%)	1,520	7.4	Culture, PCR	<i>S. pneumoniae</i> , <i>E. coli</i>
Americas	4 (9.7%)	1,210	5.6	Multiplex PCR, Culture	<i>N. meningitidis</i> , <i>H. influenzae</i>
Total	42 (100%)	8,715	5.8 (mean)	All combined	Pneumococcus dominant

Table 2. Pooled Diagnostic Performance of CSF Cytology, Culture, and Molecular Assays

Diagnostic Method	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)	Diagnostic Odds Ratio (DOR)	95% CI for DOR
Cytology	56.8	89.2	81.4	72.5	9.7	6.8-13.8
Culture	68.5	95.7	92.6	80.4	18.9	13.1-27.2
Molecular (PCR)	91.3	93.4	94.8	89.2	54.1	39.6-73.2
Cytology + Culture	74.6	95.7	94.1	83.3	25.3	17.4-36.9
All Combined	92.7	96.3	96.5	92.2	67.4	49.0-91.2

Correlation Between Diagnostic Modalities

A statistically significant positive correlation was observed between CSF neutrophilic cytology and molecular positivity ($r = 0.72$; $p < 0.001$), indicating that cases with high neutrophil counts on CSF cytology were more likely to yield positive results on PCR assays. Similarly, culture and molecular findings showed a moderate correlation ($r = 0.68$; $p < 0.01$), reflecting high concordance for viable pathogen detection [18,19,20].

In contrast, 23.5% of cases demonstrated positive molecular results with negative culture findings, primarily due to prior antibiotic use or low bacterial load. Among these discordant samples, *S. pneumoniae* and *H. influenzae* accounted for the majority of molecular detections [14,16].

Pathogen Distribution

Across all studies, *Streptococcus pneumoniae* was the most prevalent pathogen (42%), followed by *Neisseria meningitidis* (23%), and *Haemophilus influenzae* type b (18%). Other less frequent isolates included *Escherichia coli*, *Staphylococcus aureus*, and *Klebsiella pneumoniae* [1,2,12]. Regional variation was evident, with *N. meningitidis* predominating in Africa and *S. pneumoniae* in Asia and Europe. The detailed distribution is presented in Table 3.

Table 3. Global Pathogen Distribution in Paediatric Pyogenic Meningitis (n = 8,715)

Pathogen	Overall Prevalence (%)	Asia	Africa	Europe	Americas
<i>Streptococcus pneumoniae</i>	42.0	48.3	39.5	41.7	36.2
<i>Neisseria meningitidis</i>	23.0	18.4	32.6	19.3	22.8
<i>Haemophilus influenzae</i> type b	18.0	20.1	15.2	16.8	21.0
<i>Escherichia coli</i>	6.2	4.7	5.1	8.3	7.2

<i>Staphylococcus aureus</i>	5.1	4.3	6.2	4.8	5.6
<i>Klebsiella pneumoniae</i>	3.5	3.0	1.4	5.1	4.3
Total (All Pathogens)	100	-	-	-	-

Heterogeneity and Bias Assessment

Moderate heterogeneity was noted among studies ($I^2 = 62\%$) for pooled sensitivity and specificity estimates, attributable to variations in diagnostic methodology and molecular platforms used. Funnel plot symmetry and Egger's regression ($p = 0.08$) indicated minimal publication bias. Sensitivity analysis confirmed the stability of pooled estimates, as exclusion of any single study did not significantly alter the overall results [3,11,13].

The analysis demonstrates that molecular assays significantly outperform conventional culture and cytology in diagnostic sensitivity for paediatric pyogenic meningitis. Nonetheless, cytology remains valuable for rapid initial assessment and correlates well with molecular detection patterns. The combination of cytology, culture, and molecular assays yields the most comprehensive diagnostic approach, particularly in resource-limited settings or in cases with prior antibiotic exposure [15-20].

Discussion

Paediatric pyogenic meningitis continues to be one of the most challenging infectious diseases in clinical practice due to its acute onset, rapid progression, and high mortality and morbidity rates despite the availability of antibiotics and vaccines [1-5]. The accurate and timely diagnosis of bacterial meningitis in children is critical, as early initiation of specific antimicrobial therapy significantly reduces the risk of death and long-term neurological complications such as hearing loss, hydrocephalus, and cognitive impairment [6-8]. The present systematic review and meta-analysis synthesizes findings from 42 studies involving 8,715 paediatric patients across multiple geographic regions and provides comprehensive insight into the diagnostic performance of CSF cytology, bacterial culture, and molecular assays, along with their interrelationships. The analysis revealed that CSF cytology, though rapid and universally available, had moderate sensitivity (56.8%) but reasonably high specificity (89.2%). Cytology primarily identifies the inflammatory response pattern within the CSF, characterized by polymorphonuclear predominance in bacterial infections and lymphocytic response in viral etiologies [9,10]. In pyogenic meningitis, the presence of elevated total leukocyte counts, neutrophilic predominance, and increased protein levels strongly suggest bacterial etiology; however, cytology alone cannot distinguish the causative organism [10,11]. Moreover, cytological findings may be confounded in partially treated meningitis, where neutrophilic predominance can shift toward a mixed or lymphocytic pattern [8,11]. Despite these limitations, the present meta-analysis found a strong positive correlation ($r = 0.72$) between cytological neutrophilia and molecular positivity, indicating that cytology remains a reliable preliminary diagnostic indicator that reflects the underlying bacterial activity even when cultures are negative.

CSF culture, traditionally considered the gold standard for confirming bacterial meningitis, demonstrated moderate sensitivity (68.5%) and high specificity (95.7%) in the pooled analysis. While culture provides essential information for pathogen identification and antimicrobial susceptibility testing, it is often hampered by factors such as prior antibiotic therapy, delayed sample transport, and low bacterial load [12-14]. Studies included in this review consistently reported that 25-50% of clinically suspected cases of pyogenic meningitis were culture-negative despite clear clinical and cytological evidence of bacterial infection. These findings mirror those of Durand et al. [12] and Rantakokko-Jalava et al. [13], who emphasized that false-negative cultures are increasingly common in the antibiotic era. Additionally, culture techniques are time-consuming, often requiring 24-72 hours for definitive results, which can delay targeted treatment decisions.

In contrast, molecular diagnostic assays, particularly PCR and multiplex PCR platforms, demonstrated markedly higher sensitivity (91.3%) and strong diagnostic odds ratios, confirming their superiority in detecting bacterial DNA directly from CSF samples. Molecular assays overcome several limitations of traditional methods by amplifying even minute quantities of bacterial genetic material, thus remaining effective in partially treated or culture-negative cases [15-17]. These findings align with the studies of Corless et al. [16] and Wang et al. [17], who reported that multiplex PCR can simultaneously detect *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae* type b with high accuracy within a few hours. The ability to rapidly and reliably identify pathogens makes molecular techniques indispensable in modern clinical microbiology, especially in critical care settings. However, molecular methods also have limitations, such as potential contamination leading to false positives, high cost, and the requirement for specialized equipment and trained personnel, which restrict their routine use in low-resource environments [18,19].

A notable finding from this review is the complementary nature of the three diagnostic modalities rather than their competition. The highest diagnostic accuracy ($AUC = 0.94$) was achieved when cytology, culture, and molecular assays were combined, emphasizing the value of an integrated diagnostic strategy. Cytology provides immediate insight into the inflammatory response, culture offers confirmation and antimicrobial sensitivity data, and molecular assays identify pathogens with high sensitivity and speed. This layered diagnostic approach ensures that no single limitation compromises clinical decision-making. It also allows clinicians to make empiric therapeutic choices based on cytological patterns while awaiting confirmatory molecular or culture results, thereby reducing delays in management [8,15,20].

The pathogen distribution observed in this analysis is consistent with global trends reported in earlier systematic reviews [1,2,5]. *Streptococcus pneumoniae* remained the most prevalent etiologic agent (42%), followed by *Neisseria meningitidis* (23%) and *Haemophilus influenzae* type b (18%). The persistence of these organisms despite vaccination efforts underscores the need for continued surveillance and optimization of immunization programs. Regional differences in pathogen prevalence, such as the predominance of *N. meningitidis* in Africa and *S. pneumoniae* in Asia and Europe, reflect differences in vaccine implementation and serotype distribution [2,3,5]. The inclusion of molecular assays in surveillance systems can therefore strengthen epidemiological data and guide public health policy more effectively than culture-based systems alone.

The findings of this study have significant implications for paediatric healthcare systems, particularly in low- and middle-income countries where laboratory capacity is limited. In such settings, cytological and culture-based diagnosis continues to play a vital role due to affordability and accessibility. However, the incorporation of molecular methods, even at tertiary or regional reference centers, can substantially improve diagnostic precision and facilitate timely reporting of meningitis outbreaks [3,18]. Establishing collaborative laboratory networks that integrate conventional and molecular methods could bridge diagnostic gaps and ensure that paediatric meningitis cases are correctly identified and treated without delay.

The observed moderate heterogeneity ($I^2 = 62\%$) among studies can be attributed to differences in molecular platforms, study designs, and CSF handling protocols. Some studies used conventional PCR, while others employed real-time or multiplex systems, leading to variability in sensitivity and specificity. Additionally, variations in patient age groups, vaccination coverage, and prior antibiotic exposure contributed to diagnostic differences across regions. Despite these sources of heterogeneity, the direction and magnitude of effect across studies remained consistent, underscoring the robustness of the pooled results. Funnel plot analysis and Egger's regression test ($p = 0.08$) indicated minimal publication bias, suggesting that the overall conclusions are reliable and generalizable.

Another important consideration is the temporal evolution of diagnostic techniques over the past two decades. Earlier studies relied primarily on culture and Gram staining, while more recent publications incorporated real-time PCR and automated multiplex platforms capable of detecting up to 20 pathogens simultaneously. The growing body of molecular evidence highlights a paradigm shift in meningitis diagnosis from traditional phenotypic methods to genotypic detection, enabling faster turnaround times and improved pathogen coverage [16-18]. Yet, it is crucial to note that molecular assays cannot replace culture for antibiotic susceptibility testing, which remains essential for guiding clinical therapy and monitoring emerging resistance patterns. Therefore, the integration of molecular and culture-based methods represents the optimal balance between speed and clinical utility.

Overall, this meta-analysis reinforces the clinical and diagnostic synergy between cytology, culture, and molecular assays. Cytological analysis serves as a rapid screening tool; culture remains essential for confirmatory and antimicrobial testing; and molecular assays provide unmatched sensitivity and rapidity, particularly in culture-negative cases. Together, they offer a multi-layered diagnostic framework that enhances accuracy, reduces diagnostic delays, and informs evidence-based antimicrobial therapy. The combined interpretation of these modalities should become the standard approach in the diagnostic algorithm for paediatric pyogenic meningitis.

Conclusion

This systematic review and meta-analysis provide a comprehensive evaluation of the diagnostic interplay between cerebrospinal fluid cytology, bacterial culture, and molecular assays in paediatric pyogenic meningitis. The findings clearly demonstrate that molecular diagnostic techniques, particularly PCR-based assays, significantly enhance sensitivity and diagnostic yield compared with conventional methods. However, cytological and culture-based analyses continue to play indispensable roles - cytology as a rapid preliminary indicator of infection, and culture as the definitive method for pathogen identification and antibiotic susceptibility profiling [9-14,16-17].

The evidence indicates that the combination of cytology, culture, and molecular testing represents the most reliable diagnostic strategy. Such an integrated approach not only increases diagnostic accuracy but also ensures timely therapeutic intervention, which is crucial in reducing the morbidity and mortality associated with bacterial meningitis in children [6-8,15,20]. The observed strong correlation between cytological inflammation and molecular positivity further reinforces the clinical value of cytology as an early diagnostic tool, particularly in resource-limited settings where molecular diagnostics may not be immediately available.

From a global health perspective, the persistence of *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae* type b as predominant pathogens despite vaccination initiatives underscores the ongoing need for continuous surveillance, prompt laboratory confirmation, and strengthening of diagnostic infrastructure [1-5]. The inclusion of molecular assays in meningitis surveillance programs could substantially improve pathogen detection rates, enable better outbreak tracking, and inform public health vaccination policies.

While this study confirms the diagnostic superiority of molecular assays, it also highlights the necessity of maintaining a balanced diagnostic framework that leverages the strengths of all three modalities. In the paediatric population, where early diagnosis is often life-saving, adopting a tiered diagnostic model-beginning with CSF cytology, followed by culture, and confirmed through molecular testing-offers the most effective and pragmatic approach. Future research should focus on the development of cost-effective multiplex PCR systems and rapid molecular point-of-care tests that can be feasibly integrated into low-resource healthcare settings [17-20].

In conclusion, the integration of cytology, culture, and molecular diagnostics provides a comprehensive and synergistic approach to the laboratory diagnosis of paediatric pyogenic meningitis. This triad not only bridges diagnostic gaps associated with individual techniques but also paves the way toward a more accurate, rapid, and evidence-based diagnostic paradigm capable of improving outcomes for affected children worldwide.

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