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Article

Diagnostic Accuracy of Meningitis/Encephalitis (ME) Panel for Central Nervous System Infections: An Updated Meta-Analysis

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Abstract

Background: Central nervous system infections (CNSI) are severe, life-threatening conditions that require rapid and accurate diagnosis for effective management. To address diagnostic challenges in CNSI, molecular diagnostic tools have been developed to improve the detection and identification of CNS pathogens. Objectives: This study aims to assess the diagnostic accuracy of the BioFire® FilmArray® Meningitis/Encephalitis (ME) Panel in detecting CNS pathogens and compare its performance with cerebrospinal fluid (CSF) culture and single-target polymerase chain reaction (PCR). Methods: A systematic literature search identified studies published between 2016 and 2024. Data were analyzed and evaluated the Cochrane RevMan Web. Results: Twenty-three studies were included with a total of 11,182 patients. The ME Panel exhibited high accuracy for viral pathogens, with an average sensitivity of 97% and specificity of 99.8%, particularly for Enterovirus, Herpes Simplex Virus (HSV), and Varicella Zoster Virus (VZV). Bacterial detection showed greater variability, with a pooled sensitivity of 89% and specificity of 99.6%, highlighting challenges in detecting S. pneumoniae and L. monocytogenes. Sensitivity for Cryptococcus was lower at 70%, although specificity remained high at 99%. Conclusion: The ME Panel provides rapid and accurate detection of CNSI, facilitating timely treatment decisions. However, its cost and limited pathogen coverage may hinder its use in resource-limited settings.

Keywords: CNS infections; meningitis; encephalitis; multiplex PCR; diagnostic accuracy; ME panel; FilmArray; meta-analysis

1. Introduction

Central nervous system infections (CNSI), including meningitis and encephalitis, represent significant causes of morbidity and mortality worldwide[1–3]. Often, the early clinical symptoms are nonspecific, which pose a diagnostic challenge for clinicians especially in resource-limited settings. To prevent severe complications and death from CNSI, timely and accurate detection and characterization of pathogens through laboratory testing are crucial.

In recent years, diagnostics in infectious diseases have transitioned from conventional methods to novel technologies that utilize molecular assays capable of identifying presence of pathogens within hours[4]. The first commercial multiplex polymerase chain reaction (PCR) tool for microbial detection—known as the BioFire® FilmArray® Meningitis/Encephalitis (ME) Panel (BioFire Diagnostics, Salt Lake City, Utah)—was introduced

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in 2015, which allowed for the simultaneous detection of 14 pathogens from CSF samples. These include 6 bacteria (Streptococcus pneumoniae, Neisseria meningitidis, Haemophilus influenzae, Listeria monocytogenes, Streptococcus agalactiae, Escherichia coli), 7 viruses (Herpes simplex virus 1 [HSV1], Herpes simplex virus 2 [HSV2], Varicella Zoster virus [VZV], Cytomegalovirus [CMV], Human herpesvirus 6 [HHV6], Human Parechovirus [HPeV], and Enterovirus), and 1 yeast (Cryptococcus neoformans/gattii). Studies have demonstrated the ME Panel's ability to reduce time to diagnosis (TTD) and comparable detection of CNS pathogens with traditional methods such as cultures that have slow turnaround times. Various studies have assessed the diagnostic accuracy of the ME panel against culture studies, showing an overall agreement rate ranging from 93% to 99% along with high sensitivity and specificity[5]. Moreover, the ME panel only requires approximately 200 microliter (uL) of CSF specimen[6], thereby potentially avoiding the challenges of multiple assays. Over the years, the ME panel has been increasingly used worldwide due to its clinical utility in diagnosing CNSI.

Previous meta-analyses on commercial ME panels were predominantly drawn from studies conducted in high-income or upper-middle-income countries[7,8]. While the adoption of this technology has expanded globally, data on the clinical utility of the ME panel in low-income and lower-middle-income countries remain scarce[9]. This is particularly concerning given that the burden of CNSI is significantly higher in these regions due to factors such as denser living conditions, lower vaccination coverage, and higher prevalence of co-existing health conditions. The lack of robust data from these healthcare settings presents a critical gap in understanding the full potential and challenges of implementing ME panels where they are most needed. This study aims to expand the evidence base by including studies from a broader range of geographic and economic settings, assessing the ME panel's diagnostic accuracy across diverse healthcare environments. As technological advancements and pathogen dynamics continue to evolve, an updated analysis could provide valuable insights into optimizing the use of ME panels for CNSI in a wider array of healthcare contexts.

Given the importance of accurate and timely diagnosis in the management of CNSI, it is essential to explore and assess the effectiveness of both traditional and modern diagnostic methods. Understanding how these methods perform in different clinical settings, especially where resources are limited, is crucial for improving the delivery of care.

2. Objectives

The primary objective of this study is to provide an updated and comprehensive analysis of the diagnostic accuracy of the commercial multiplex ME panel for each pathogen across diverse healthcare settings. Additionally, it seeks to fill gaps in existing research by incorporating data from low- and lower-middle-income countries, where the burden of CNS infections is greater, and where the implementation of ME panels may face distinct challenges. This expanded approach will offer a more complete understanding of the ME panel's performance in both resource-rich and resource-limited environments.

3. Materials and Methods

3.1. Protocol

A detailed presentation and description of selected articles used in this review were outlined in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.

3.2. Eligibility Criteria

The researcher applied specific inclusion criteria to ensure the relevance and quality of the selected studies. Articles were included if they met the following conditions: (1) they focused on the utilization of cerebrospinal fluid (CSF) in healthcare settings, such as hospitals, (2) employed molecular methods for the identification of micrMATERIALS AND METHODS Protocol A detailed presentation and description of selected articles used in this review were outlined in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.

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3.3. Information sources, Search Strategy, and Selection Process

In September 2024, a comprehensive electronic search in PubMed, Web of Science, and Embase was performed using keywords such as (CNS infection) (Meningitis/ Encephalitis Panel) (FilmArray) (BioFire) (PCR) OR (culture) AND (CSF) following the PRISMA protocol (Figure 1). The search was restricted to studies investigating CNSI using the BioFire® FilmArray® Meningitis/Encephalitis (ME) Panel. The inclusion criteria encompassed both in vivo and in vitro studies published in English. Non-English papers and studies that did not meet the predefined criteria were excluded. The database search identified 2022 articles potentially applicable for the analysis. After eliminating all duplications, 67 articles were screened. The researcher excluded 44 articles as the articles did not focus on the topic of this review. In total, 23 articles were then subjected to a full-text analysis.

3.4. Assessment of Methodological Quality

The qualities of each included study were assessed based on the Cochrane Handbook for Systematic Reviews of Interventions.

3.5. Data Collection and Data Items

The articles that met the inclusion criteria were extracted. The following data were used: first author, year of publication, study design, article title, methods used to examine in CSF, and their effectiveness and results. The extracted information was then entered into RevMan.

3.6. Statistical Analysis

Statistical analyses were performed using Cochrane RevMan Web. The researchers employed a bivariate random-effects model to calculate the pooled sensitivity and specificity, along with their corresponding 95% confidence intervals (95% CI). Study-specific sensitivities and specificities are displayed using forest plots.

3.7. Study Risk of Bias In Individual Studies

At the initial stage of study selection, the titles and abstracts were initially checked to minimize potential reviewer bias. Any disagreement about the inclusion or exclusion of an article was resolved by discussion between the reviewers.

3.8. Quality Assessment

The criteria for evaluating study design, implementation, and analysis included information such as method of CSF collection, type of molecular test performed, presence of a control group, sample size calculation, and the number of samples in a group. obial pathogens, (3) involved in vivo or in vitro studies, (4) were full-text publications, and (5) were written in English. Conversely, studies were excluded if they did not take place in healthcare environments, lacked molecular analysis, or were published in languages other than English. No restrictions were imposed on the year of publication, allowing for a comprehensive review of the literature across all time periods. This approach was designed to capture the most relevant and methodologically sound research on the topic.

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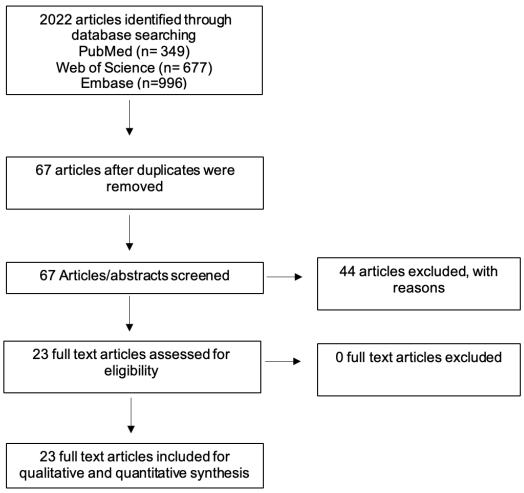

Figure 1. PRISMA Flow Diagram.

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The criteria for evaluating study design, implementation, and analysis included information such as method of CSF collection, type of molecular test performed, presence of a control group, sample size calculation, and the number of samples in a group.

4. Results

There were a total of 2,022 articles screened, of which 23 were included in the quantitative synthesis (Figure 1). The main characteristics of the included studies are summarized in Table 1. The diagnostic performance of the BioFire ME panel shows notable variability across different pathogens, reflecting both its strengths and limitations in clinical use. For Escherichia coli (Figure 2) (Figure 3), sensitivity ranges from 0.5 to 1.00, with several studies reporting "not estimable" values due to the absence of true positive (TP) or false negative (FN) cases. This variation raises concerns about the panel's reliability in detecting E. coli, especially in studies with smaller sample sizes. However, the specificity remains consistently high, indicating dependable exclusion of negative cases. Haemophilus influenzae generally exhibits perfect sensitivity (1.00), although some studies also report "not estimable" values due to a lack of TP cases. Despite the potential for false negatives, specificity remains consistently high, reinforcing the panel's reliability in ruling out negative results. For Listeria monocytogenes, sensitivity is often unmeasurable due to the absence of sufficient cases, but specificity remains robust across studies. Neisseria meningitidis demonstrates high specificity, although sensitivity varies depending on TP case availability, indicating context-dependent detection accuracy. Similarly, Streptococcus pneumoniae and Streptococcus agalactiae display near-perfect sensitivity and specificity, with occasional drops in sensitivity, underscoring the need for complementary diagnostic methods.

For viral pathogens, the ME panel consistently shows high accuracy. Cytomegalovirus sensitivity varies between 0.6 and 1.00, while specificity remains uniformly high. Enterovirus sensitivity ranges widely from 0.00 to 1.00, yet specificity remains consistently high, minimizing false positives. Both Human Herpesvirus 6 (HHV-6) and Human Parechovirus (HPeV) exhibit variable sensitivity but consistently high specificity. Herpes Simplex Virus (HSV) and Varicella Zoster Virus (VZV) display strong specificity, though HSV sensitivity ranges from 0.80 to 1.00, reflecting variability in detection across different populations.

For Cryptococcus neoformans and gattii, sensitivity ranges widely (0.00 to 1.00), but high specificity ensures reliable exclusion of false positives. Overall, the variability in sensitivity across pathogens suggests that while the ME panel demonstrates high specificity, additional diagnostic tests may be necessary to ensure comprehensive detection, particularly in resource-limited or low-prevalence settings.

Table 1. Summary of studies included in the meta-analysis (Part 1)

Study	Country//Type of study /Funding	Inclusion criteria	Number of patients/ Mean age	Number of patients for the meta-analysis	Microorganisms analyzed in the meta-analyses and reference tests used	Use of antimicrobials before LP
Leber 2016	United States of America (USA)/ Prospective/ Funding: BioFire Diagnostics	Samples that were obtained in a clinical situation that includes culture and that became available in the next seven days.	1560 patients Neonates, children and adults. 41% were children and 58% were older than 18 years.	1560 for virus and bacteria analyses	Bacteria: culture Viruses Enterovirus: PCR LDT assay target 5utr1/5utr2 HSV-1 y HSV-2: PCR LDT assay target UL30 UL42 VZV: PCR LDT assay target ORF 62 /ORF63	46 patients (34% of the positive results).
Hanson 2016	USA /Retrospective/ Funding: National Institute of allergy and infectious disease	Frozen samples of CSF that were studied with at least one conventional method and that there was remaining sample left	342 patients Children (145) & Adults (197)	145 patients for bacteria analyses	Bacteria: Culture Virus analysis was not performed because it was not clear which had specific PCR performed (there were 191 PCR LDT in total between all the viruses).	Uncertain
Messacar 2016	USA; Restropective Children's Hospital Colorado Research Scholars Award and NIH/NCATS Colorado	Frozen samples of CSF	138 patients	138 patients	Bacteria: CSF culture Virus: PCR	Uncertain
Arora 2016	USA/ Prospective (not clear) Funding: BioFire Diagnostics yThe Sarnaik Endowment Fund for Fellow Research at the Children's Research Center of Michigan	Neonates that had LP performed because of suspected sepsis and had bacteremia, abnormal CSF, leukocytosis, leucopenia or fever.	62 patients Children from 0 to 3 months.	62 patients for bacteria analyses.	Bacteria: CSF and blood cultures.	50 patients (80%).
Graf 2016	USA Retrospective Funding: None-no data	Samples of patients with suspected central nervous system infection.	133 patients	133 patients	Bacteria: CSF culture Virus: PCR	Uncertain

Table 2. Summary of studies included in the meta-analysis (Part 2)

Study	Country//Type of study /Funding	Inclusion criteria	Number of patients/ Mean age	Number of patients for the meta-analysis	Microorganisms analyzed in the meta-analyses and reference tests used	Use of antimicrobials before LP
Piccirilli 2018	Italy/ Prospective and retrospective/ Funding: BioFireDiagnostics	Samples of patients with suspected central nervous system infection. For meta-analysis: 14 patients of prospective group that had comparative tests performed.	77 patients: 63 retrospective (not included in the meta-analysis because they selected samples) and 14 prospective (for meta-analysis) Adults and children.	14 patients from the bacteria and virus prospective analyses	Bacteria: CSF culture, molecular test. Virus: Specific molecular assay.	Uncertain
Barnes 2018	Ethiopia/ Prospective/ Funding: Research Council of Norway	Patients with suspected meningitis with available CSF.	213 patients. Neonates, children and adults. Mean age for children and adults: 2.2 & 34.5 years, respectively	213 patients for bacteria analyses.	Bacteria: CSF and blood cultures.	Five which had some microorganism isolated in FA received antibiotics.
Bailu 2019	China/ Restrospective/ Funding: Love Charity Foundation Research Project in Shanghai Children's Medical Center. - Collaborative Innovation Center for Translational Medicine at Shanghai Jiao Tong University	Samples of patients with suspected CNS infection	68 patients Children. Mean age: 2.7 years.	68 patients for bacteria analyses.	Bacteria: Gram, CSF culture. Blood cultures, bacterial antigens.	50 (73.5%)
Leli 2019	Italy/ Retrospective/ Funding: None-no data	CSF samples processed as rutine clinical care and that cellularity and basic parameters studied.	109 patients Adults mean age: 60 years (41.5 to 71)	109 for bacteria analyses.	Bacteria: CSF culture	Uncertain
Radmard 2019	USA / Retrospective/ Funding: National Institute of Health (NIH)	Patients that had both LP and FA/ME performed.	705 patients/ Adults and children. Mean age: 20 years.	705 patients for bacteria analyses	Bacteria: CSF culture. Viruses: PCR LDR was used. This data was not included in the meta-analysis because PCR were only performed to FA/ME positive samples.	They report empiric antimicrobial therapy to 414 patients (59%). It is not clear in which patients it was given before LP.

Table 3. Summary of studies included in the meta-analysis (Part 3)

Study	Country//Type of study /Funding	Inclusion criteria	Number of patients/ Mean age	Number of patients for the meta-analysis	Microorganisms analyzed in the meta-analyses and reference tests used	Use of antimicrobials before LP
Eichinger 2019	Germany/ Retrospective/ Funding: None-no data	Patients that had an LP performed for infection without a clear source or suspected CNS infection.	187 patients Children (50% infants y 50% older children)	187 patients for bacteria analyses.	Bacteria: CSF and blood cultures.	Uncertain
Boudet 2019	France/ Retrospective/ Funding: Hospital Universitario de Nimes	CSF samples that had FA/ME ordered by a physician or microbiologist.	708 patients. Adults and children Mean age: 44 years (range 1-98 years)	708 patients for bacteria analyses.	Bacteria: CSF and blood cultures.	Two of those that had disagreement had FA positive and negative culture.
Domingues 2019	Brasil/ Prospective? / Funding: None?	CNS infection suspected with altered CSF (>10 leukocytes) in private hospitals of Sao Paulo.	436 patients Adults and children 32.7 ± 29.4 years	436 patients for bacteria analyses.	Bacteria: CSF and blood cultures.	Uncertain
Ellis 2019	Uganda/ Prospective?/ Funding: None	Patients with HIV with suspected meningitis	842 patients	45 samples for viral analysis 112 patients for cryptococcal test	Bacteria: CSF culture Virus: PCR Fungal: CSF CrAg LFA	Uncertain
Lee 2019	Taiwan/ Prospective Funding: none	CNS infection suspected	42 patients	42 patients for bacterial and viral analyses	Bacteria: CSF culture Virus: PCR	Uncertain

No: Number; FA/ME: Film Array/Meningitis encephalitis panel; PCR: Polymerase chain reacting; LP: lumbar puncture; CSF: Cerebrospinal fluid; LDT: Lab developed testing

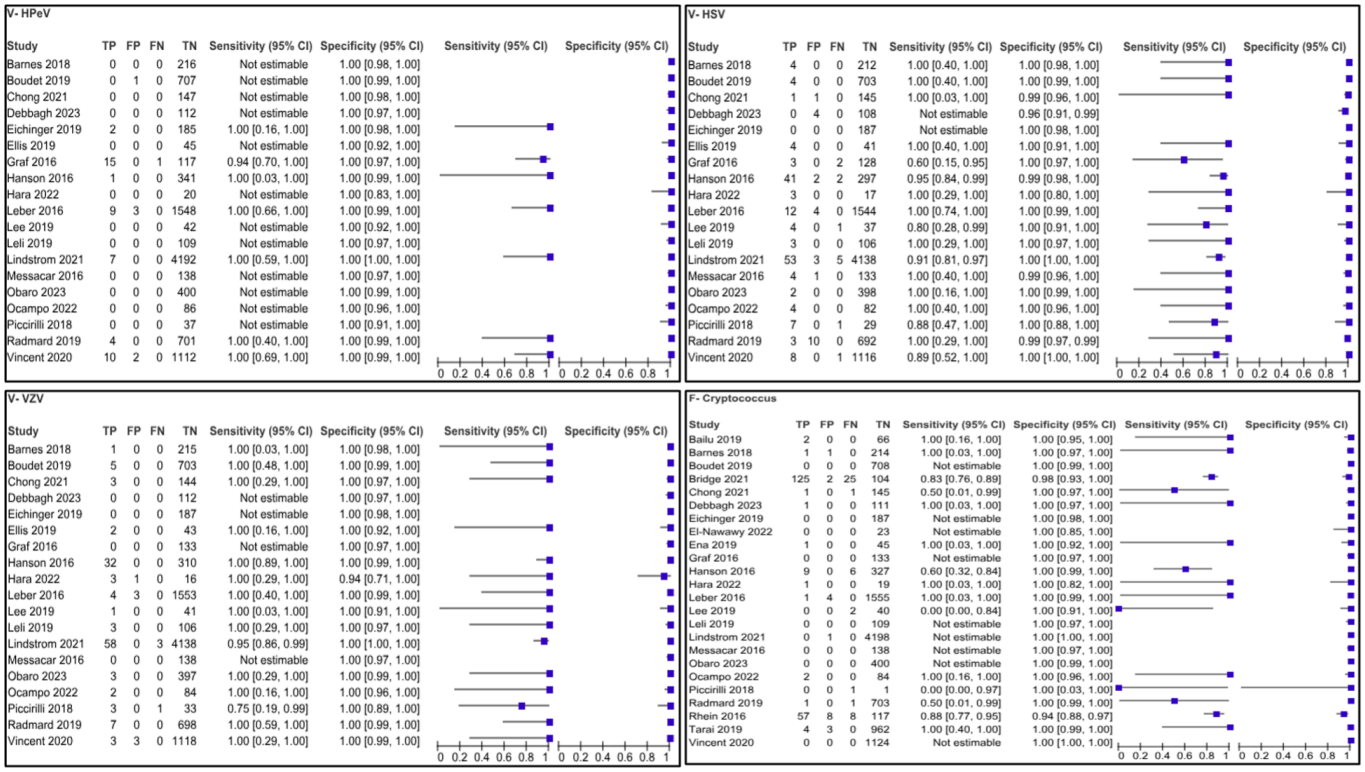

Figure 2. Forest plots for sensitivity and specificity of ME panel for Human Parechovirus (HPeV), Herpes Simplex Virus (HSV), Varicella Zoster Virus (VZV), and Cryptococcus.

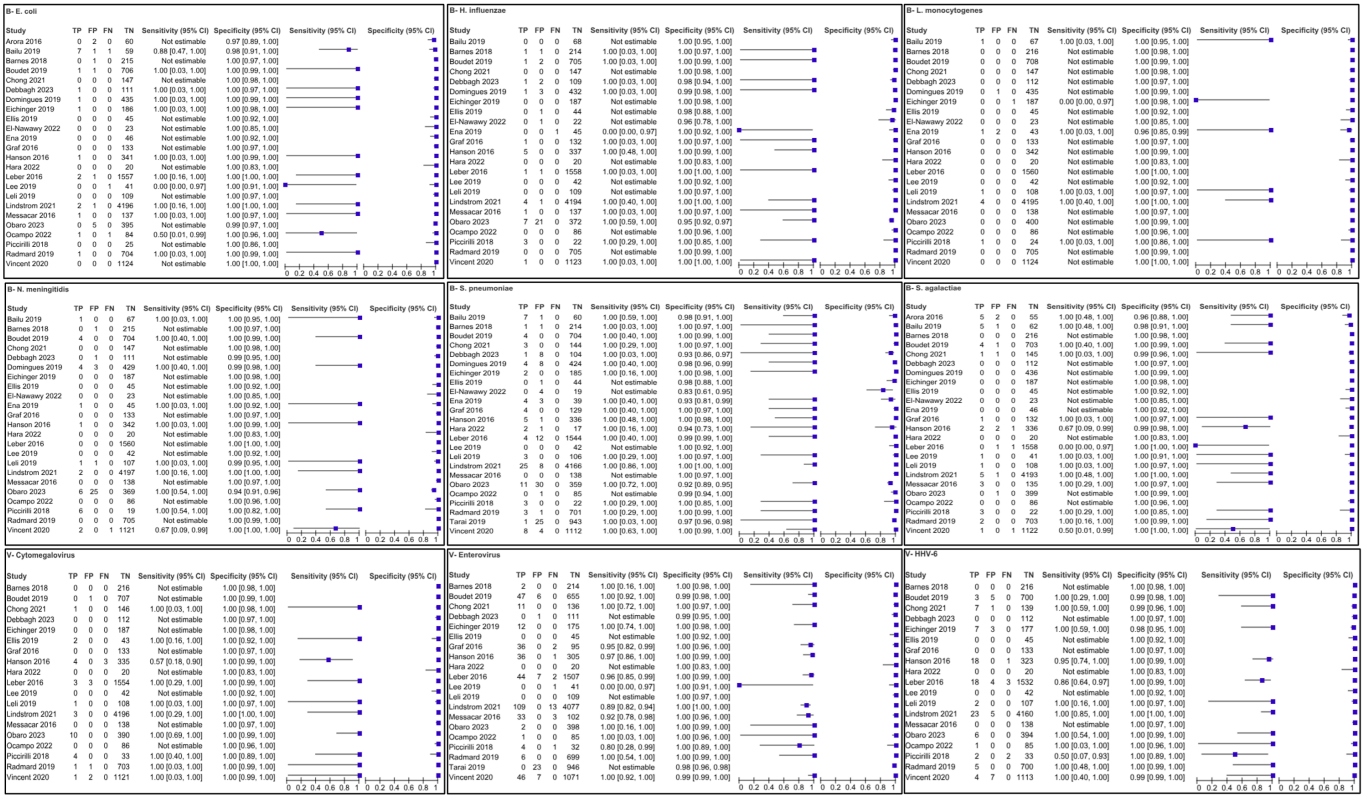

Figure 3. Forest plots of sensitivity and specificity of ME panel in CSF for E. coli, H. influenzae, L. monocytogenes, N. meningitidis, S. pneumoniae, S. agalactiae, Cytomegalovirus, Enterovirus, and Human Herpesvirus.

4.1. Risk of Bias

Shows the risk of bias and applicability concerns in all studies included. The four key domains of the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) was applied [10] (Figure 4) . It shows that there are mixed levels of biases in patient selection across the studies, showing both high and unclear risk indicators which may reflect variability in the methods of participant selection. Similar to patient selection, the Index Test, Reference Standard, and Flow and Timing also display considerable risks (high and unclear risk), reflecting potential inconsistencies in test application and how the diagnostic tests were timed respectively. Despite the presence of bias across different domains, the applicability concerns appear to be generally low across all categories, indicating that the results of these studies may still be broadly applicable in clinical practice. This underscores the importance of adopting and implementing advanced diagnostic techniques, provided that any identified biases are recognized and addressed wherever feasible. The contrast between high risk of bias in certain categories and low applicability concerns suggests that while internal validity issues may exist, the external validity or the generalizability of the findings remains strong.

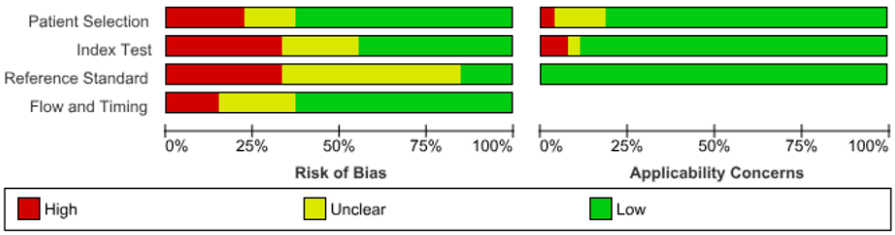

Figure 4. Risk of bias and applicability concerns.

5. Discussion

Overall, the ME Panel consistently demonstrated strong diagnostic capabilities, particularly for viral pathogens, with both sensitivity and specificity often exceeding 90%. Its strong performance in viral detection supports its clinical utility, especially in contexts where viral meningitis and encephalitis are the primary considerations. Its rapid turnaround time also contributes to timely, targeted management and better antimicrobial stewardship.

In contrast, the sensitivity of the panel shows a considerable variability, particularly for bacterial and fungal infections. For pathogens such as *E. coli*, *L. monocytogenes*, *S. pneumoniae*, and Cryptococci, the test results should be interpreted with caution, and additional supplementary/confirmatory tests such as culture and antigen studies may be considered. This variability in microbial detection underscores the need for context-dependent diagnostic strategies in actual clinical practice.

The consistently high specificity of the M/E panel across the board supports its use in ruling out CNS infections and in reducing false-positive results. This is especially important in avoiding unnecessary treatments, which can be resource-intensive. Clinicians can be reassured of the negative test results, particularly for viral pathogens where both sensitivity and specificity are high.

This study has certain limitations that should be acknowledged. First, the existing literature on the ME panel remains limited; the data utilized from different studies used different methodologies, patient populations, and diagnostic platforms. This heterogeneity may account for the variability in test sensitivity particularly for bacterial and fungal pathogens. Future meta-analyses would benefit from more standardized study designs to improve study comparability.

In some studies, test sensitivity for specific pathogens is not estimable due to either lack of positive cases or the small sample sizes. This is particularly problematic for the relatively rare pathogens (or those with low prevalence) as it limits the ability to draw firm conclusions about its diagnostic performance. Some studies also report wide confidence intervals, especially for sensitivity, thus reflecting uncertainty in the estimates. To fill in these data gaps, more studies with larger sample sizes are needed.

Despite its limitations, the panel's high specificity across different pathogens attests to its reliability in ruling out infections when test results are negative. While culture and single-target PCR assays remain as the gold standard for its accuracy in pathogen detection, the ME panel can serve as a valuable tool in emergency settings given its rapid turnaround time and high reliability. Laboratory advantages include small specimen volume (approximately 200mL of CSF), reduced hands-on time, and minimal technical expertise[7]. The main disadvantages of this multiplex PCR system, however, are its high costs, limited coverage, and its inability to test for antibiotic susceptibility.

The findings from this study underscore the need for healthcare systems, particularly in resource-limited settings, to implement diagnostic methods that not only provide high sensitivity and specificity, but are also practical and sustainable within their specific economic contexts. Therefore, the choice of the diagnostic method should take into account several factors such as availability of resources, patient population, and the urgency of the clinical situation.

5.1. Resource-limited healthcare environments

A subgroup analysis of studies[9,11–15] conducted in low- and lower-middle-income countries consistently demonstrated high specificity of the BioFire ME panel across diverse healthcare settings, ensuring reliable exclusion of false positives. However, the test sensitivity varied, particularly for bacterial and fungal pathogens such as *Listeria monocytogenes* and *Cryptococcus*. In contrast, studies from high-income to upper-middle-income countries[16–31] generally reported higher and more consistent sensitivity for these pathogens, which is likely attributable to better infrastructures, more standardized testing protocols, and larger sample sizes. The ME panel performed consistently well for viral pathogens in both settings, exhibiting high sensitivity and specificity. Nonetheless, studies from lower-resource settings highlight the need for complementary diagnostic methods for bacterial and fungal CNSI, emphasizing the importance of optimizing the ME panel for broader use in resource-constrained or high-burden environments. In addition, the economic strain of implementing new technologies in resource-limited settings remains a significant barrier to widespread adoption, largely due to high upfront costs and recurring operational expenses. Further research is needed to assess whether the clinical benefits of newer—and potentially more expensive—diagnostic tools can justify their costs in healthcare systems with already limited financial resources. Such studies could provide crucial insights into the cost-effectiveness and long-term value of advanced diagnostics in settings where healthcare expenditures are low.

5.2. Study Variability

The observed variability in sensitivity and specificity across different studies highlights the importance of considering context-specific factors when interpreting diagnostic test results. Factors such as study design, population demographics, sample quality, and laboratory conditions can all influence the performance of these diagnostic methods. The inclusion of a broad range of studies in this meta-analysis helps to provide a more comprehensive understanding of the strengths and limitations of both ME panel and conventional laboratory methods in different settings.

6. Conclusion

The BioFire® FilmArray® ME Panel demonstrates high diagnostic accuracy, particularly for viral pathogens. Its robust diagnostic yield enables earlier initiation of appropriate therapy. This study reaffirms the findings of previous meta-analyses, thereby validating its effectiveness in accurately identifying a broad spectrum of CNS pathogens. The panel holds a significant potential for improving clinical outcomes, particularly in settings where the burden of CNSI is higher. However, further research is essential to optimize the panel's application in more diverse clinical environments. The high cost of the panel still pose a challenge in low-resource settings. Expanding the panel's pathogen coverage and reducing its cost would significantly enhance its clinical utility, making it more accessible across a wider range of healthcare settings.

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9. Conclusions

This section is not mandatory, but can be added to the manuscript if the discussion is unusually long or complex.

Conflict of Interest

The authors declare no conflict of interest.

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