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Research Article

Uniform Case Definitions in Tuberculous Meningitis: A Systematic Review

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Abstract

Introduction: Tuberculous meningitis (TBM) poses a significant diagnostic challenge due to its non-specific clinical presentation and the lack of a universally accepted case definition. This variability often delays treatment, contributing to high mortality and morbidity rates, particularly in resource-limited settings. A standardized diagnostic framework is essential to improve early detection and outcomes. This systematic review aims to evaluate the development and application of uniform case definition criteria for TBM diagnosis, identifying gaps and proposing pathways for global consensus.

Methods: We conducted a systematic review following PRISMA guidelines, searching PubMed, Scopus, and Web of Science for studies published between 1990 and 2024. Keywords included "tuberculous meningitis," "diagnostic criteria," and "case definition." Inclusion criteria encompassed studies proposing or evaluating TBM diagnostic criteria, scoring systems, or consensus guidelines in English. Two reviewers independently screened and extracted data, assessing study quality using the QUADAS-2 tool.

Results: Thirty-two studies were included, highlighting heterogeneity in diagnostic approaches. The Marais criteria (2010) were most widely adopted (20 studies), followed by earlier frameworks like Ahuja's clinical criteria (1994). Sensitivity for Marais criteria ranged from 80-95%, but specificity varied, particularly in HIV-positive cohorts. Validation studies were limited for pediatric and immunocompromised populations.

Conclusion: This systematic review underscores the need for standardized criteria integrating clinical, laboratory, and imaging parameters to enhance diagnostic accuracy. Gaps in validation across diverse populations persist, necessitating a global consensus framework to improve early TBM detection and reduce associated mortality and morbidity.

Keywords: Uniform; Tuberculous Meningitis; Diagnosis

Introduction

Tuberculous meningitis (TBM), a devastating manifestation of extrapulmonary tuberculosis caused by *Mycobacterium tuberculosis*, represents approximately 1-5% of global tuberculosis cases. Despite its low prevalence, TBM carries a disproportionately high burden, with mortality rates exceeding 30% in high-risk settings and significant neurological sequelae among survivors. The disease predominantly affects vulnerable populations, including children, immunocompromised individuals, and those in resource-limited regions with high tuberculosis endemicity. Early diagnosis is paramount to initiating timely treatment and improving outcomes, yet TBM remains a diagnostic enigma due to its insidious onset and non-specific clinical presentation. Symptoms such as headache, fever, neck stiffness, and altered mental status mimic other central nervous system infections, including bacterial, viral, and fungal meningitis, confounding accurate identification [1-3,14,17,22,24].

The absence of a gold standard diagnostic test exacerbates these challenges. Conventional methods, such as cerebrospinal fluid (CSF) analysis, often reveal non-specific findings-lymphocytic pleocytosis, elevated protein, and low glucose-that overlap with other etiologies. Microbiological confirmation via acid-fast bacilli staining or culture is insensitive, with detection rates below 20% in many settings. Advanced diagnostics, such as nucleic acid amplification tests (e.g., Xpert MTB/RIF) and neuroimaging, improve sensitivity but are often inaccessible in low-resource settings where TBM is most prevalent. Compounding these issues is the lack of a universally accepted case definition, leading to variability in diagnostic approaches across clinical guidelines and research protocols. This inconsistency contributes to delayed or missed diagnoses, particularly in areas with limited access to specialized care, perpetuating poor outcomes and health disparities.

Efforts to standardize TBM diagnosis have gained traction in recent decades. Ahuja., *et al.* (1994) [1] provided an early framework, proposing clinical criteria based on symptoms and basic CSF findings to guide diagnosis in resource-constrained environments. While practical, these criteria suffered from low specificity, limiting their utility in differential diagnosis. Building on such foundational work, Marais., *et al.* (2010) [2] introduced a uniform case definition for TBM research, categorizing cases as definite, probable, or possible by integrating clinical, laboratory, and imaging parameters. This structured approach aimed to enhance diagnostic consistency and facilitate comparative studies. However, the Marais criteria's reliance on resource-intensive diagnostics raises questions about its applicability in low-income settings, and its validation across diverse populations-particularly pediatric and HIV-co-infected cohorts-remains incomplete [1-3,13,31].

This systematic review seeks to address these challenges by evaluating the evolution and performance of uniform case definition criteria for TBM diagnosis from 1990 to 2024. By synthesizing evidence on frameworks like those of Ahuja and Marais, alongside other scoring systems and consensus guidelines, this study aims to identify strengths, limitations, and gaps in current approaches. Ultimately, it strives to inform the development of a globally applicable diagnostic framework that balances accuracy, accessibility, and equity, addressing a critical need in tuberculosis control and public health.

Methodology

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to ensure a robust and transparent approach to evaluating uniform case definition criteria for diagnosing tuberculous meningitis (TBM). The objective was to synthesize evidence on the development, application, and performance of diagnostic frameworks, identifying gaps and informing future consensus efforts. To capture both foundational and contemporary studies, we searched three major databases-PubMed, Scopus, and Web of Science—for peer-reviewed articles published between January 1, 1990, and December 31, 2024. This extended timeframe was chosen to include seminal works, such as Ahuja., *et al*. (1994), which remain influential in TBM diagnostic research, alongside modern advancements.

The search strategy employed a combination of controlled vocabulary (e.g., MeSH terms) and free-text keywords, including "tuberculous meningitis," "TBM," "case definition," "diagnostic criteria," "uniform criteria," and "scoring system." Boolean operators (AND, OR) were used to refine queries, and filters were applied to limit results to human studies and English-language publications. To enhance comprehensiveness, reference lists of included studies and relevant reviews were manually screened for additional eligible articles. The final search was executed on December 15, 2024, to ensure inclusion of recent publications.

Inclusion criteria were defined to focus on studies that: (1) proposed or evaluated diagnostic criteria or scoring systems for TBM, (2) incorporated clinical, laboratory, or imaging parameters, and (3) were published in English-language, peer-reviewed journals. Exclusion criteria encompassed case reports, editorials, conference abstracts, and studies solely addressing TBM treatment outcomes or epidemiology without diagnostic focus. Studies lacking clear descriptions of diagnostic criteria or validation methods were also excluded to ensure methodological rigor.

The screening process involved two independent reviewers who evaluated titles and abstracts against the inclusion criteria using a standardized protocol. Discrepancies were resolved through discussion, with a third reviewer consulted if consensus could not be reached. Full-text articles of potentially eligible studies were retrieved and assessed for final inclusion. Data extraction was performed using a pre-designed template, capturing key variables: study design (e.g., prospective, retrospective), population characteristics (e.g., age, HIV status, geographic setting), diagnostic criteria (e.g., Marais, Thwaites, Ahuja), validation methods, and performance metrics (e.g., sensitivity, specificity, predictive values).

Quality assessment was conducted using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool, which evaluated risk of bias and applicability across four domains: patient selection, index test, reference standard, and flow/timing. Each study was independently scored by two reviewers, with disagreements resolved through consensus. Due to heterogeneity in study designs, populations, and outcome measures, a meta-analysis was deemed infeasible. Instead, findings were synthesized narratively, with thematic analysis used to summarize diagnostic frameworks, performance trends, and evidence gaps, addressing the research question comprehensively.

Results

This systematic review, encompassing 32 studies published between January 1, 1990, and December 31, 2024, evaluated the adoption and performance of various diagnostic criteria for tuberculous meningitis (TBM). The initial search identified 1,247 articles from PubMed, Scopus, and Web of Science. Following the removal of duplicates and a rigorous screening process, 32 studies met the predefined inclusion criteria (Table 1).

The included studies represented a global perspective, with a significant proportion conducted in Asia (18 studies), followed by Africa (8), Europe (4), and the Americas (2). The cohort sizes varied considerably (range: 50-1,200 patients), and the study designs included prospective (n = 12), retrospective (n = 20), and cross-sectional (n = 0) approaches.

Stage	Number of Articles
Identified through searches	1,247
Duplicates removed	342
Unique records screened	905
Full-text reviewed	112
Studies meeting criteria	32
Reasons for exclusion	
Non-English publication	(Not specified)
Lack of focus on diagnosis	(Not specified)
Ineligible study design	(Not specified)

Table 1: Study Selection Process.

Adoption and performance of established criteria

Marais., *et al.* (2010) Criteria: [2]

The Marais et al. (2010) uniform case definition criteria were the most frequently cited, appearing in 20 studies (62.5%). These criteria classify TBM as definite, probable, or possible. Twelve studies specifically validated the performance of these criteria across diverse populations (adults, children, HIV-positive individuals). The sensitivity for definite TBM ranged from 80% to 95%, indicating high accuracy when microbiological confirmation was available. However, specificity was more variable, ranging from 70% to 85%, with lower values (65-70%) observed in HIV-positive cohorts (Table 2). Studies from high-resource settings in Europe reported higher specificity, potentially due to the availability of advanced neuroimaging.

Outcome Measure	Range (%)	Observation
Sensitivity	80-95	Robust detection in cases with microbiological confirmation.
Specificity	70-85	More variable; lower in HIV-positive cohorts and resource-limited settings.

Table 2: Diagnostic Performance of Marais., *et al*. (2010) Criteria [2,5].

Thwaites Criteria [3]

Eight studies evaluated the Thwaites criteria, designed for resource-limited settings to differentiate TBM from bacterial meningitis using clinical and basic laboratory parameters. Predominantly assessed in Asia (n = 5) and Africa (n = 3), these criteria demonstrated high sensitivity (90-98%), making them effective for ruling out TBM in urgent situations. However, the specificity was lower (60-75%), particularly in regions with a high prevalence of other central nervous system infections (Table 3). The simplicity of relying on accessible tests was a key strength, but performance limitations were noted in pediatric and immunocompromised populations.

Outcome Measure	Range (%)	Observation
Sensitivity	90-98	Effective for ruling out TBM in resource-limited settings.
Specificity	60-75	Lower specificity, particularly in regions with high prevalence of other CNS infections.

Table 3: Diagnostic Performance of Thwaites Criteria [3,31].

Feature	Thwaites Criteria	Marais Criteria (Uniform Case Definition)	Ahuja Criteria
Year	**2002**	**2010**	**1994**
Purpose	To differentiate TBM from bacterial meningitis rapidly	To standardize TBM diagnosis for clinical research	To clinically diagnose TBM in resource-limited settings
Target Use	Clinical use, especially for differentiation from bacterial meningitis	Primarily for research and clinical trials	Clinical diagnosis in endemic settings
Components	5 clinical and laboratory parameters with score-based interpretation	Clinical, CSF, radiological, and evidence of TB elsewhere; scored system	Clinical, CSF, radiology, and extra-neural TB evidence
Scoring System	Yes (total score ≤ 4 suggests TBM)	Yes (Definite, Probable, Possible categories)	No scoring; diagnosis based on major and minor criteria
Major Criteria	None individually defined; combined score < 4 supports TBM	Definite: microbiological confirmation; Probable/Possible based on scores	CSF culture positive for MTB or suggestive imaging findings
Minor Criteria	Age >36 yrs, WBC <15,000/mm^3, CSF WBC <900/μL, CSF neutrophils <75%, duration of illness >6 days	Various clinical signs, CSF analysis, imaging findings, and systemic TB signs	Clinical symptoms >2 weeks, fever, vomiting, cranial nerve palsy, etc.
Use of Imaging	Not included	MRI/CT included in scoring	CT/MRI suggestive of TBM considered
Microbiological Evidence Required	No	Only for "Definite TBM"	Yes, if available; not mandatory
Diagnostic Categories	TBM vs. bacterial meningitis	Definite, Probable, Possible TBM	Clinical TBM diagnosis: definitive, probable, or possible
Advantages	Rapid, simple, useful in acute settings	Comprehensive, standardized, useful in research	Practical for endemic areas with limited resources
Limitations	May not differentiate all TBM cases	Complex, may not be feasible in low-resource settings	Not validated or standardized across all populations

Table 4: Comparative Analysis of Thwaites, Marais, and Ahuja Criteria for TBM [1-3].

Feature	Description
Key Clinical Features	Fever, headache, neck stiffness
	Headache, fever
Key CSF Findings	Lymphocytic pleocytosis, elevated protein, low glucose
	Lymphocytic pleocytosis, elevated protein, low glucose (supportive evidence)

Table 5: Ahuja., et al. (1994) Criteria for Tuberculous Meningitis [1].

Ahuja., et al. (1994) Criteria [1]

One study analyzed the performance of the foundational Ahuja., *et al*. (1994) clinical criteria. While demonstrating a sensitivity of 85%, the specificity was below 65%. This low specificity, attributed to the overlap of clinical and cerebrospinal fluid (CSF) findings with other meningitis, limited its utility for differential diagnosis, especially in settings lacking advanced diagnostics. Despite its historical significance, the lack of integration with modern microbiological and imaging techniques renders these criteria largely obsolete in contemporary practice.

Alternative scoring systems and biomarkers [4,7-9,11]

Five studies introduced alternative scoring systems, often incorporating factors like symptom duration (>7 days), cranial nerve palsies, and CSF adenosine deaminase (ADA) levels. Three of these focused on pediatric populations, where clinical presentations can be atypical. These systems showed promise for simplifying diagnosis in resource-constrained settings, but the absence of external validation limits their generalizability.

Four studies explored novel biomarkers, including CSF lipoarabinomannan (LAM) and host proteomic signatures. While LAM showed moderate sensitivity (40-60%), particularly in HIV-positive individuals, its integration into diagnostic criteria was lacking. Proteomic studies identified potential markers, but their diagnostic utility remains in the exploratory phase.

Evidence gaps and study limitations [10,16,21,24,28]

The reviewed literature revealed several key evidence gaps and methodological limitations. Notably, there was a paucity of data specific to pediatric TBM, with only five studies focusing on this vulnerable population despite the substantial disease burden. These studies underscored the difficulties in applying diagnostic criteria primarily developed for adults to children, who often exhibit distinct clinical presentations. Similarly, individuals co-infected with HIV were underrepresented, with only six studies addressing the unique diagnostic complexities in this group, known for atypical clinical and CSF profiles. The significant heterogeneity across studies in terms of patient demographics, diagnostic reference standards, and reported outcomes prevented a quantitative synthesis of the data through meta-analysis. Methodologically, the predominance of retrospective study designs (62.5%) raises concerns about potential selection bias. Furthermore, the high proportion of single-center studies (46.9%) limits the generalizability of their findings to broader populations. The limitations of the earlier Ahuja study were acknowledged in the context of the diagnostic capabilities available at the time of its inception. Finally, the QUADAS-2 assessment identified a moderate risk of bias related to reference standard applicability in a subset of studies (31.3%), where clinical diagnosis without microbiological confirmation was used as the primary diagnostic benchmark.

Literature Review

Despite advancements in tuberculosis diagnostics, tuberculous meningitis (TBM) remains a significant clinical challenge due to its protean manifestations that often mimic other central nervous system infections. Early diagnostic efforts focused on clinical and cerebrospinal fluid (CSF) parameters. The criteria proposed by Ahuja., *et al*. (1994) [1] emphasized a combination of clinical symptoms such as fever, headache, and neck stiffness, alongside CSF findings like lymphocytic pleocytosis, elevated protein, and low glucose. While offering a pragmatic approach for resource-limited settings with limited access to advanced diagnostics, the Ahuja criteria suf-

fered from low specificity due to the overlap of these features with viral, fungal, and other forms of meningitis, thereby hindering accurate differentiation of TBM from alternative etiologies [11-14].

The advent of molecular diagnostics, particularly nucleic acid amplification tests (NAATs) such as Xpert MTB/RIF, marked a significant step forward, improving the sensitivity for detecting Mycobacterium tuberculosis in CSF to approximately 50–60%. However, the widespread availability of NAATs in high-burden settings remains a challenge, and false-negative results can occur, especially in early or paucibacillary TBM. Traditional diagnostic methods, including acid-fast bacilli staining and culture, exhibit even lower sensitivity, detecting the pathogen in less than 20% of cases, underscoring the persistent need for robust diagnostic criteria [15-18].

A pivotal development in standardizing TBM diagnosis for research purposes was the introduction of the uniform case definition by Marais., *et al*. (2010). This framework classified TBM cases into definite, probable, or possible based on a composite assessment of clinical presentation, CSF analysis, and neuroimaging findings. The Marais criteria aimed to enhance the consistency of reporting across studies and improve diagnostic reliability. Validation studies have reported sensitivities of 85-90% for probable and definite TBM; however, specificity has shown greater variability (70-85%), particularly in HIV-positive individuals who often present with atypical features. The reliance of the Marais criteria on resource-intensive modalities like neuroimaging and advanced molecular tests limits its applicability in low-income settings, necessitating the exploration of alternative diagnostic strategies [2,26,27].

Recognizing the constraints of resource-limited environments, Thwaites and colleagues developed criteria that prioritize readily accessible clinical features (e.g., symptom duration, neurological signs) and basic laboratory parameters (e.g., CSF cell count, protein) to differentiate TBM from bacterial meningitis. While achieving high sensitivity (90-98%), these criteria exhibit lower specificity (60–75%), potentially leading to overdiagnosis in regions with a high prevalence of nontuberculous meningitis. Other scoring systems incorporating parameters such as CSF adenosine deaminase (ADA) or cranial nerve involvement have shown promise but lack widespread validation across diverse populations and settings. [2,3,7,11,12,31].

The existing literature reveals critical gaps. There is a paucity of prospective, multicenter studies validating current diagnostic criteria in key populations, including children, immunocompromised individuals, and those co-infected with HIV, where TBM often presents atypically. The historically significant Ahuja criteria lack integration with contemporary diagnostic tools like neuroimaging and NAATs, and their performance in modern cohorts remains underexplored. Furthermore, the potential of emerging biomarkers, such as interferon-gamma release assays, lipoarabinomannan (LAM), and proteomic profiles, in refining diagnostic algorithms remains largely untapped. These inconsistencies underscore the urgent need for a comprehensive synthesis of the strengths and limitations of existing criteria, the identification of critical evidence gaps, and the development of a globally applicable diagnostic consensus for TBM [12-15].

Discussion

This systematic review highlights the Marais., *et al*. (2010) uniform case definition criteria as a central framework in TBM diagnosis, being utilized by 62.5% of the included studies. Its structured classification system-definite (microbiologically confirmed), probable (strong clinical and CSF evidence), and possible (clinical suspicion)-provides a robust foundation for research consistency and clinical decision-making. By integrating clinical symptoms (e.g., headache, fever), laboratory findings (e.g., CSF lymphocytic pleocytosis, low glucose), and imaging features (e.g., basal meningeal enhancement), the Marais criteria demonstrate high sensitivity (80–95%) for definite TBM in settings with access to advanced diagnostics. However, the observed variability in specificity (70–85%) underscores its limitations in complex cases, particularly among HIV-positive patients who may exhibit atypical CSF profiles, such as neutrophilic predominance, complicating the differentiation from other causes of meningitis. The reliance on resource-intensive tools like magnetic resonance imaging (MRI), computed tomography (CT), and nucleic acid amplification tests (NAATs) such as Xpert MTB/RIF presents a significant barrier to its widespread

adoption in low-income settings where TBM prevalence is highest, highlighting a critical challenge in achieving universal diagnostic applicability. [2,7,8,9,13,18,19].

Conversely, the Thwaites criteria prioritize simplicity by utilizing readily available clinical features (e.g., symptom duration >5 days, cranial nerve palsies) and basic laboratory parameters (e.g., CSF cell count, protein) to distinguish TBM from bacterial meningitis. The high sensitivity (90-98%) reported in studies, predominantly from Asia and Africa, makes these criteria valuable for ruling out TBM in urgent clinical scenarios. However, the lower specificity (60-75%) poses a risk of overdiagnosis, especially in regions with a high prevalence of other central nervous system infections like viral or cryptococcal meningitis. While the accessibility of the Thwaites criteria is advantageous in resource-limited settings, their performance may be suboptimal in pediatric and immunocompromised populations where clinical and CSF findings can be less typical, indicating a need for improved applicability across diverse patient groups [2,3,31].

The Ahuja., *et al*. (1994) criteria represent a historical benchmark, offering an early clinical framework tailored for resource-constrained environments. By emphasizing easily ascertainable symptoms (e.g., fever, neck stiffness) and CSF abnormalities (e.g., elevated protein, low glucose), the Ahuja approach achieved a sensitivity of 85% but a specificity below 65%, limiting its utility for definitive differential diagnosis. The lack of integration with modern diagnostic modalities such as NAATs, MRI, or even basic microbiological confirmation reflects the technological limitations of the era in which they were developed. While foundational, the Ahuja criteria highlight the evolution towards more comprehensive diagnostic frameworks like the Marais criteria, which incorporate imaging and molecular evidence to enhance diagnostic accuracy [1-3,17,18,19].

Nevertheless, the simplicity of the Ahuja criteria serves as a reminder of the continued need for accessible diagnostic tools in settings where advanced technologies are unavailable, prompting consideration of how historical insights can inform contemporary adaptations [1].

The findings of this review underscore a critical need for a globally applicable case definition that effectively balances sensitivity, specificity, and accessibility across diverse clinical contexts. Current diagnostic frameworks exhibit suboptimal performance in key populations, particularly children and HIV-positive individuals. The limited number of studies focusing on pediatric TBM (only five), despite the significant morbidity and mortality in this age group, is a major concern. Children often present with non-specific symptoms (e.g., irritability, seizures) and less pronounced CSF abnormalities, potentially reducing the effectiveness of adult-centric criteria like Marais and Thwaites. Similarly, the underrepresentation of HIV-co-infected patients (addressed in only six studies), who frequently exhibit atypical presentations such as normal CSF profiles or a predominance of extra meningeal TB, poses a significant challenge to existing diagnostic algorithms. These evidence gaps highlight the urgent need for tailored diagnostic criteria that account for population-specific variations to ensure equitable diagnostic accuracy [1-5,7,8,10,16,17,21,24,29].

The integration of novel biomarkers offers a promising avenue for improving TBM diagnosis. While four studies explored CSF biomarkers such as LAM and host proteomic signatures, none have been incorporated into standardized case definitions. LAM, evaluated primarily in African cohorts, demonstrated sensitivities of 40–60%, with higher detection rates in HIV-positive patients, suggesting its potential as an adjunctive diagnostic tool. CSF adenosine deaminase (ADA), assessed in alternative scoring systems, showed diagnostic value (>10 IU/L) in both pediatric and adult cohorts, although its specificity varied across settings. Proteomic profiles, while representing an innovative area of research, remain in the exploratory phase and require large-scale validation to establish their clinical utility. The limited translation of these promising biomarkers into current diagnostic frameworks highlights a broader gap between research findings and clinical practice, necessitating collaborative efforts to validate and integrate such tools into diagnostic algorithms [9,12,15,20,21,23,25,29].

The generalizability of existing diagnostic criteria is further limited by the paucity of prospective, multicenter studies, with only 12 of the 32 included studies employing a prospective design. The

prevalence of retrospective studies (20 studies) introduces the potential for selection bias, while the high proportion of single-center studies (15 studies) restricts the applicability of their findings to diverse epidemiological settings. The QUADAS-2 assessment also revealed a moderate risk of bias in reference standard applicability in a subset of studies that relied on clinical diagnosis without microbiological confirmation, potentially leading to an overestimation of diagnostic performance. These methodological limitations underscore the critical need for robust, collaborative research to validate diagnostic criteria across both high- and low-burden settings, ensuring that findings are representative and directly translatable to clinical practice.

This review synthesizes the current state of TBM diagnostic criteria, bridging a critical knowledge gap and providing a foundation for the development of a consensus-driven diagnostic framework. A globally applicable case definition should integrate readily accessible clinical and laboratory parameters, supplemented by affordable and rapid diagnostics such as point-of-care NAATs or biomarker assays, to ensure utility in resource-limited settings. Such a framework would standardize TBM diagnosis, facilitating earlier treatment initiation and reducing disparities in patient outcomes between high- and low-resource regions. While the Marais criteria provide a strong foundation, adaptations such as simplified scoring systems for low-resource settings or pediatric-specific diagnostic modules could significantly enhance their reach. The simplicity of the Thwaites criteria could inform the development of point-of-care diagnostic tools, while the historical context of the Ahuja criteria highlights the enduring value of clinical acumen when advanced technology is scarce [5-8,10,11,13].

Emerging technologies hold transformative potential for TBM diagnosis. Point-of-care diagnostics, such as portable ultrasound for detecting hydrocephalus or rapid LAM assays, could democratize access to diagnostic tools, particularly in remote and rural areas. Machine learning models, integrating clinical, laboratory, and biomarker data, may further refine diagnostic accuracy, although their implementation requires rigorous validation in diverse patient cohorts. Collaborative international initiatives, such as global TBM research consortia, are essential to address the identified evidence gaps, prioritizing prospective, multicenter trials that specifically include pediatric and HIV-positive populations. Funding agencies and policymakers should prioritize support for such research efforts, recognizing the disproportionate impact of TBM on vulnerable communities [19,20,21].

The findings of this review have immediate implications for both clinical practice and future research. Clinicians in high-burden settings may need to adopt a pragmatic approach, combining elements of the Marais and Thwaites criteria while tailoring diagnostic strategies to the available resources. Researchers should prioritize the validation of promising biomarkers and the development of pediatric-specific diagnostic algorithms. Ultimately, the development and implementation of a universal TBM case definition have the potential to transform disease management, aligning with global health goals aimed at reducing tuberculosis-related mortality. By highlighting both the progress made and the significant challenges that remain, this review serves as a call to concerted action to advance TBM diagnosis, ensuring that no patient is left behind in the global fight against this devastating disease [22,25,32].

The findings of this review not only inform clinical practice and diagnostic standardization but also carry important implications for medical education and curriculum development. The variability in diagnostic criteria for tuberculous meningitis (TBM)-ranging from resource-intensive frameworks like the Marais criteria to simpler clinical tools such as the Thwaites and Ahuja criteria-offers a unique opportunity to improve clinical reasoning and decision-making skills among medical trainees [2,3,31].

Integrating diagnostic frameworks into training modules

The structured nature of the Marais criteria, which synthesizes clinical, laboratory, and imaging data, can serve as a valuable teaching tool in neurology and infectious disease curricula. Educators can incorporate case-based simulations that train students and residents to apply tiered diagnostic reasoning using "Definite," "Probable," and "Possible" classifications. This approach fosters analytical thinking, helps learners understand diagnostic uncertainty, and prepares them to manage cases in both high- and low-resource settings. [2]

Curriculum development and standardized instruction

Incorporating standardized diagnostic frameworks into undergraduate and postgraduate medical curricula can enhance consistency in clinical instruction across institutions. Uniform criteria

can serve as anchors in clinical protocols, checklists, and OSCE (Objective Structured Clinical Examination) stations, ensuring learners are assessed on globally validated parameters. For instance, incorporating the Thwaites scoring system into emergency medicine training can help future clinicians make timely decisions in resource-constrained environments.

Simulation and interdisciplinary learning

The differential diagnosis of meningitis provides fertile ground for interdisciplinary education. Training modules involving neurology, microbiology, radiology, and public health can be designed around TBM case definitions, allowing learners to appreciate the strengths and limitations of various diagnostic approaches. Simulation exercises could emphasize real-world constraints such as limited imaging availability or delays in laboratory results, preparing clinicians for pragmatic decision-making. [25].

Faculty development and consensus building

Standardized diagnostic frameworks can also assist faculty in maintaining consistency in bedside teaching and formative assessments. Educators across institutions can collaborate to develop consensus-driven educational resources, incorporating validated diagnostic models like the Marais criteria into clinical teaching rounds, ward-based assessments, and e-learning platforms. This harmonization is particularly important for global health training programs that prepare students to work across varied epidemiological and infrastructural contexts.

Future directions in educational research

Given the diagnostic complexity of TBM, future studies might explore how training in standardized case definitions influences diagnostic accuracy and confidence among medical trainees. Educational research could assess the impact of integrating these frameworks into teaching modules on learner outcomes, clinical judgment, and patient safety in neurology and infectious disease rotations.

Conclusion

This systematic review highlights the widespread adoption of the Marais criteria and the practical utility of the Thwaites criteria in resource-limited settings, despite their specificity limitations. The historical Ahuja criteria are largely superseded by modern diagnostic approaches. Emerging alternative scoring systems and biomarkers show potential but require further validation. Significant evidence gaps remain, particularly concerning pediatric and HIV-co-infected populations. The methodological limitations of the included studies underscore the need for more robust, prospective, multi-center research to improve the standardization and accuracy of TBM diagnosis globally.

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