

Diagnostic Challenges of CNS Tuberculosis in Resource-Limited Settings: Evidence from Developing Countries

Sahil Wilson¹, Dr. Shri Dhar Singh²

¹Department of Microbiology, School of Microbiology, NIILM University, Kaithal, Haryana, India

²Professor, Department of Zoology, NIILM University, Kaithal, Haryana, India

Abstract:

Central nervous system tuberculosis (CNS-TB) is one of the most serious and complicated forms of extrapulmonary tuberculosis (EP-TB) and has a high mortality rate, neurological disability and delayed diagnosis, especially in developing countries. In resource limited settings, the challenges in the diagnosis and treatment of CNS-TB are significant because of the lack of adequate healthcare infrastructure, lab capacity, access to advanced neuro-imaging techniques, and trained medical personnel. Common laboratory tests like smear microscopy and culture of the cerebrospinal fluid (CSF) have low sensitivity and are time-consuming, and molecular testing is not available in many rural and impoverished areas. In addition, vague symptoms, overlapping clinical features, co-infection with HIV, malnutrition and a late seeking of care make the diagnosis difficult in the early stages. The critical diagnostic problems of CNS tuberculosis in the developing world are critically discussed and the role of socioeconomic, infrastructural, and technological barriers on the outcome of the disease is explained. The review also includes discussion of some of the new diagnostic options that are emerging and the need for complex health strategies to enhance early detection and minimize the morbidity and mortality associated with CNS-TB.

Index Terms: Central nervous system tuberculosis, tuberculous meningitis, developing countries, diagnostic challenges, resource-limited settings, molecular diagnostics, neuroimaging

I. INTRODUCTION

Central nervous system tuberculosis (CNS-TB) is one of the most devastating forms of tuberculosis infection, and a major cause of neurological morbidity and mortality in the world [1]. It manifests mainly in the form of tuberculous meningitis (TBM), intracranial tuberculoma, spinal arachnoiditis, and tuberculous abscess, the most common being tuberculous meningitis [2]. Although there are improvements in the treatment of anti-tubercular drugs and molecular diagnostics, CNS-TB still presents significant diagnostic and therapeutic difficulties, especially for LMICs, where tuberculosis burden is highest [3]. According to the World Health Organization (WHO), tuberculosis is one of the leading public health challenges in developing countries where South Asia and Sub-Saharan Africa are responsible for 60% of the disease burden [4]. In these environments, poverty, overcrowding, malnutrition, HIV co-infection and poor health systems lead to a high risk of contracting TB and a poor outcome of the disease [5]. The mortality rate for CNS-TB is 20-50% and survivors are often left with

neurological sequelae such as hydrocephalus, seizures, cranial nerve palsies, cognitive dysfunction and stroke [6].

The diagnosis of CNS-TB is challenging due to the lack of specificity of the clinical features of the disease which may include fever, headache, vomiting, altered consciousness, and focal neurological deficits which overlap with other bacterial, viral, fungal and autoimmune neurological disorders [7]. The low sensitivity of the conventional microbiological diagnosis is due to the fact that the CSF is paucibacillary in most cases [8]. These difficulties are compounded in resource-poor environments, where there is a lack of sophisticated imaging systems and prompt referral systems, as well as inadequate laboratory infrastructure [9]. While newer technologies like GeneXpert MTB/RIF, Xpert Ultra and nucleic acid amplification tests have increased diagnostic sensitivity, they are not widely available to rural healthcare centres because of the complexity of infrastructure and cost [10]. Many clinicians therefore continue to use clinical judgment and empirical treatment strategies, and risk delayed diagnosis and inappropriate management [11].

II. BURDEN OF CNS TUBERCULOSIS IN DEVELOPING COUNTRIES

Central nervous system (CNS) tuberculosis (TB) is still a significant public health problem in developing countries and is responsible for a significant proportion of TB-associated morbidity and mortality in the world [1]. TB is more common in low and middle income countries with high TB transmission potential in these areas from poverty, overcrowding, malnutrition, poor sanitation, and substandard health care systems [2]. The majority of reports of CNS-TB have been reported in countries with a high burden of pulmonary TB and growing populations of immunocompromised people, including those in South Asia, Sub-Saharan Africa and Southeast Asia [3]. CNS-TB is regarded as one of the most serious clinical presentations of extrapulmonary tuberculosis as it has a high mortality rate and can result in irreversible neurological damage [4]. The most common form of CNS tuberculosis is tuberculous meningitis (TBM) with mortality rate between 20% to 50% despite anti-tubercular therapy (ATT) [5]. Common and long-term complications for survivors include hydrocephalus, seizures, cranial nerve palsies, stroke, hearing loss, cognitive deficits, and motor loss [6].

India is the largest contributor of TB cases in the world, and has a substantial number of CNS-TB cases reported each year [7]. The burden of TB on rural population in India is high due to late diagnosis, poor access to healthcare, lack of neurological diagnostic facilities, and lack of awareness among the population about neurological complications of TB [8]. These patterns also have been described in other nations, including Indonesia, South Africa, Nigeria, Bangladesh, and Pakistan, where socioeconomic factors and a lack of health care resources still hinder early diagnosis and treatment of disease [9]. Children are one of the most susceptible groups to be impacted by CNS TB in developing nations [10]. Maturity of the immune system, malnutrition and late clinical recognition are associated with severe tuberculous meningitis in children [11]. For most of the healthcare facilities in low resource areas, diagnosis is often made when the patients have reached more advanced neurological stages, leading to higher mortality and disability rates [12].

HIV co-infection also increases the disease burden of CNS TB in resource-limited areas [13]. Disseminated and extrapulmonary tuberculosis with involvement of the central nervous system occurs in

immunocompromised people at much higher frequencies [14]. HIV associated CNS-TB may have atypical clinical presentation, limited inflammatory response, and lack of effective treatment outcomes, which adds complexity to diagnosis and it is associated with higher mortality rates [15].

Socioeconomic factors also are important determinants of disease burden and treatment outcomes. Poor adherence to anti-tubercular therapy is significantly attributed to poverty [16], illiteracy, unemployment, malnutrition, and limited access to health care services [16] which delay the diagnosis of their illness. Access to neurologists, neuroimaging centers, advanced laboratory diagnostics is further limited in remote rural areas by geographic barriers [17]. Besides clinical problems, developing countries often have infrastructural problems like poor laboratory settings, dearth of qualified health care workers, weak surveillance system and irregular availability of ATDs [18]. Although smear microscopy and CSF sampling for culture are not sensitive and have a long turnaround time, they are still widely used in most peripheral healthcare centers [19]. The high operational cost of cost-sensitive equipment and technical requirements for advanced molecular diagnostic methods make their availability in tertiary care hospitals the norm [20].

Multidrug-resistant tuberculosis (MDR-TB) is now a significant problem in developing countries as well [21]. Treatment outcomes for drug-resistant CNS tuberculosis are much lower as delayed diagnosis and poor access to DST decreases treatment efficacy [22]. CNS TB remains a significant clinical, economic and public health problem in developing countries overall. Persistent high morbidity and mortality rates are attributed to delayed diagnosis, inadequate healthcare system and infrastructure, poverty, HIV co-infection, and limited diagnostic accessibility [23]. Increasing the effectiveness of TB control programs, increasing access to health care, and increasing rapid molecular diagnostic services are important to reduce the burden of CNS-TB in resource limited settings [24].

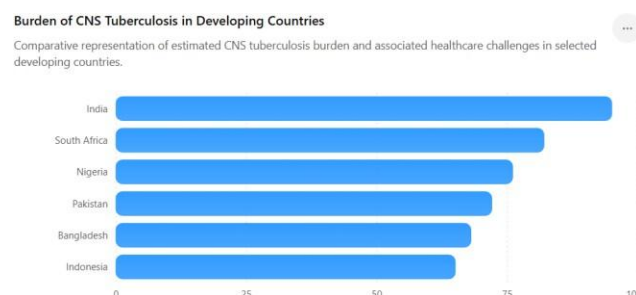


Figure 1 Comparative burden of central nervous system tuberculosis (CNS-TB) in selected developing countries. The graph highlights the disproportionately high disease burden in regions with limited healthcare infrastructure, delayed diagnostic accessibility, high tuberculosis prevalence, and increased socioeconomic vulnerability.

III. CLINICAL CHALLENGES IN EARLY DIAGNOSIS

A. Nonspecific Clinical Presentation

Culture The clinical presentation of CNS tuberculosis is extremely variable and non-specific, one of the major diagnostic problems [19]. Fever, headache, malaise, vomiting and lethargy are early signs of many infectious and inflammatory neurological diseases [20].

In a resource-limited setting, patients often do not appear at healthcare facilities until they are severely ill, because of poor health awareness, financial constraints and transportation limitations [21]. Thus severe neurological complications—seizures, hydrocephalus, and/or changes in consciousness—are often present when CNS-TB is diagnosed [22].

B. Overlapping Neurological Disorders

CNS-TB closely mimics numerous neurological diseases including bacterial meningitis, fungal meningitis, viral encephalitis, neurocysticercosis, brain tumors, and autoimmune encephalitis [23]. In rural healthcare settings where advanced neurodiagnostic facilities are unavailable, differentiation between these conditions becomes extremely difficult [24].

Misdiagnosis frequently leads to inappropriate treatment, delayed anti-tubercular therapy, and increased mortality [25].

TABLE 1: BURDEN OF CNS TUBERCULOSIS IN DEVELOPING COUNTRIES

Parameter	Description / Indicator	Evidence from Developing Countries	Impact / Significance	References
Global Contribution	Proportion of CNS-TB cases from developing countries	>85% of global CNS-TB cases occur in low- and middle-income countries.	Major contributor to global TB-associated neurological morbidity and mortality.	[1, 2]
High TB Prevalence	High burden of pulmonary TB fuels CNS-TB cases	South Asia and Sub-Saharan Africa have the highest TB incidence.	Increased risk of CNS involvement due to high transmission.	[3, 4]
Mortality Rate	Case fatality rate of tuberculous meningitis (TBM)	Mortality ranges between 20%–50% even with treatment.	High fatality despite availability of anti-tubercular therapy.	[5]
Neurological Sequelae	Long-term complications among survivors	Hydrocephalus, seizures, stroke, cranial nerve palsies and cognitive impairment are common.	Significant long-term disability and poor quality of life.	[6]
High Burden Countries	Countries reporting high CNS-TB burden	India, Nigeria, Pakistan, South Africa, Bangladesh and Indonesia report high cases.	Reflects poor access to early diagnosis and treatment.	[7, 8, 9]
Pediatric Population	CNS-TB burden in children	High incidence of TBM in children; delayed diagnosis leads to severe outcomes.	Higher risk of mortality and permanent neurological deficits.	[10, 11, 12]
HIV Co-infection	Association of HIV with CNS-TB	High HIV prevalence in Sub-Saharan Africa increases risk of disseminated TB.	Atypical presentation, poor treatment response and high mortality.	[13, 14, 15]
Socioeconomic Factors	Poverty, malnutrition, low literacy, unemployment	Common across rural and urban slums in developing countries.	Delayed healthcare seeking and poor treatment adherence.	[16, 17]
Healthcare System Limitations	Infrastructure and human resource constraints	Inadequate labs, shortage of specialists, limited neuroimaging and poor surveillance.	Delays in diagnosis and increased disease burden.	[18]
Diagnostic Constraints	Limited access to advanced diagnostic tools	Smeared microscopy and culture widely used despite low sensitivity and long turnaround.	Low diagnostic yield and late initiation of therapy.	[19, 20]
Drug Resistance	Rising multidrug-resistant TB (MDR-TB)	Increasing MDR-TB cases reported in many developing countries.	Poor prognosis due to limited DST facilities and treatment options.	[21, 22]
Overall Burden	Combined effect of above factors	High morbidity, mortality and economic burden in resource-limited settings.	Requires strengthened TB control programs and rapid diagnostics.	[23, 24]

Note: CNS-TB = Central Nervous System Tuberculosis; TBM = Tuberculous Meningitis; DST = Drug Susceptibility Testing.

IV. LABORATORY DIAGNOSTIC CHALLENGES

A. Limitations of Smear Microscopy

In developing countries, the Ziehl–Neelsen smear microscopy method continues to be used widely, due to its low cost and simplicity [26]. Its diagnostic sensitivity for CNS-TB is very low, however, because it is not a very concentrated specimen of CSF [27].

It has been demonstrated in several studies that smear microscopy is not able to detect a significant proportion of tuberculosis cases, especially in extrapulmonary and HIV-related disease [28]. In addition, peripheral healthcare centers suffer from the lack of trained laboratory staff, as well as from the poor staining quality affecting the accuracy [29].

B. Challenges Associated with CSF Culture

Culture methods like Lowenstein–Jensen media and MGIT systems are very specific and have a longer incubation time (days to weeks) [30]. Delayed diagnosis greatly limits the clinical usefulness because

CNS-TB requires immediate entry into treatment (EIT) [31].

Culture facilities are frequently lacking in places with limited resources, because of their high operating costs, lack of biosafety laboratories, and lack of technical skills.

C. Limited Access to Molecular Diagnostics

The use of advanced molecular diagnostics has recently become available for rapid diagnosis of CNS TB, with GeneXpert MTB/RIF and Xpert Ultra having made significant contributions [33]. These approaches have quicker results and greater sensitivity than standard microscopy [34].

The main challenges to adoption in developing countries are however equipment cost, limited electricity supplies, cartridge costs, maintenance demands and a shortage of trained operators [35]. As a result, most molecular testing occurs at tertiary care centres within urban areas [36].

TABLE 2. Laboratory Diagnostic Challenges in CNS Tuberculosis in Developing Countries

Diagnostic Method	Principle / Description	Advantages	Challenges / Limitations	Impact in Developing Countries	References
1. Smear Microscopy (Ziehl-Neelsen Stain)	Detection of acid-fast bacilli in CSF by Ziehl-Neelsen staining.	- Simple and inexpensive - Widely available - Rapid turnaround (same day)	- Very low sensitivity (10-30%) due to paucibacillary nature of CSF - Requires high bacillary load - Dependent on technician skill and quality of staining	- False negatives are common - Leads to delayed diagnosis - Over-reliance due to low cost and easy availability	[1, 2]
2. CSF Culture (Löwenstein-Jensen Solid Culture)	Growth of Mycobacterium tuberculosis on Löwenstein-Jensen medium.	- High specificity - Gold standard for diagnosis	- Low sensitivity (30-70%) - Prolonged turnaround time (4-8 weeks) - Requires viable bacilli and adequate sample volume	- Delays treatment initiation - Not feasible for urgent clinical decisions	[3, 4]
3. Liquid Culture (MGIT / BACTEC)	Growth detection of M. tuberculosis in liquid media using mycobacterial growth indicator tubes.	- Higher sensitivity (60-80%) - Faster than solid culture (7-14 days)	- Expensive equipment and reagents - Requires skilled personnel - High operational cost and maintenance - Risk of contamination	- Limited availability in peripheral laboratories - Restricted to referral centers	[5, 6]
4. Nucleic Acid Amplification Tests (NAATs) (GeneXpert MTB/RIF, Xpert Ultra)	Detection of M. tuberculosis DNA and rifampicin resistance using real-time PCR.	- High sensitivity (70-90% with Xpert Ultra) - Rapid results (2 hours) - Detects rifampicin resistance	- High cartridge and machine cost - Requires stable electricity and temperature control - Limited availability of cartridges - Need for trained operators	- Mostly available in tertiary centers - Inaccessible in rural/remote settings - High cost limits widespread use	[7, 8]
5. Loop-mediated isothermal amplification (LAMP)	Amplification of M. tuberculosis DNA under isothermal conditions.	- Rapid (1-2 hours) - Cost-effective - Simple equipment	- Lower sensitivity compared to PCR - Risk of false positives - Not widely standardized for CSF	- Promising but not widely implemented - Needs further validation	[9, 10]
6. Biomarkers (Adenosine Deaminase, Interferon-γ, IP-10)	Measurement of immune response markers in CSF to support diagnosis.	- Helpful adjunct tools - Results available within hours	- Low specificity - Cut-off values vary - Affected by co-infections (HIV, etc.)	- Useful where microbiological tools are limited - Cannot replace confirmatory tests	[11, 12]
7. Metagenomic Next-Generation Sequencing (mNGS)	Unbiased sequencing of all nucleic acids in CSF to identify pathogens.	- High sensitivity - Detects multiple pathogens	- Very high cost - Requires advanced laboratory infrastructure and bioinformatics - Long turnaround time	- Not available in most developing countries - Currently used only in research settings	[13, 14]

V. NEUROIMAGING CHALLENGES

A. Limited MRI Accessibility

Magnetic resonance imaging (MRI) is the most sensitive imaging modality for CNS-TB, which can detect basal meningeal enhancement, tuberculomas, infarctions and hydrocephalus [37].

But MRI services are still limited in rural and economically depressed areas [38]. Patients have to travel long distances to tertiary hospitals and this leads to delayed imaging and late diagnosis [39].

B. Limited MRI Accessibility

However, the cost of the investigations such as CT or MRI is high among the poor in developing countries [40]. Some patients do not have the financial means to repeat imaging exams and thus do not receive thorough diagnostic testing and treatment [41].

VI. IMPACT OF HIV CO-INFECTION AND MALNUTRITION

HIV co-infection significantly complicates diagnosis of CNS tuberculosis because immunosuppression alters typical inflammatory responses and clinical manifestations [42]. HIV-positive patients frequently demonstrate atypical CSF findings and increased risk of disseminated disease [43].

Malnutrition, which remains highly prevalent in developing countries, further weakens immune function and contributes to poor treatment outcomes [44].

VII. INFRASTRUCTURAL AND HEALTHCARE SYSTEM LIMITATIONS

Healthcare systems in resource-limited settings face multiple infrastructural challenges affecting CNS-TB diagnosis, including shortage of neurologists, inadequate laboratory capacity, delayed referral systems, poor specimen transportation, limited biosafety facilities, and inconsistent drug availability [45].

VIII. SOCIOECONOMIC AND GEOGRAPHIC BARRIERS

Socioeconomic and geographic barriers play a major role in delayed diagnosis, poor treatment accessibility, and increased mortality associated with central nervous system tuberculosis (CNS-TB) in developing countries [1]. The burden of CNS tuberculosis is disproportionately concentrated among economically disadvantaged populations living in rural, overcrowded, and resource-constrained environments where healthcare accessibility remains severely limited [2]. Poverty, illiteracy, malnutrition, unemployment, and inadequate healthcare infrastructure collectively contribute to delayed healthcare-seeking behavior and poor disease outcomes [3].

One of the most important socioeconomic determinants affecting CNS-TB diagnosis is poverty [4]. Individuals from low-income families often lack financial resources necessary for transportation, neuroimaging investigations, laboratory testing, hospitalization, and prolonged anti-tubercular therapy [5]. Since CNS tuberculosis frequently requires repeated diagnostic procedures such as lumbar puncture, CT scanning, MRI imaging, and molecular testing, treatment costs become unaffordable for many patients in low-resource settings [6]. Consequently, patients frequently delay medical consultation until severe neurological symptoms develop, including seizures, altered consciousness, cranial nerve palsies, or paralysis [7].

Illiteracy and low public awareness regarding tuberculosis-associated neurological manifestations further complicate early diagnosis [8]. In many developing countries, individuals remain unaware that tuberculosis can affect the brain and spinal cord in addition to the lungs [9]. Early symptoms such as headache, fever, vomiting, fatigue, and behavioral changes are often ignored or misinterpreted as minor illnesses, resulting in substantial diagnostic delays [10]. Misconceptions, social stigma, and reliance on traditional healers may additionally prevent timely access to qualified healthcare professionals [11].

Malnutrition represents another critical socioeconomic factor associated with increased CNS-TB burden [12]. Nutritional deficiency weakens host immune response, thereby increasing susceptibility to disseminated and extrapulmonary tuberculosis [13]. Malnourished children and immunocompromised adults are particularly vulnerable to severe forms of tuberculous meningitis and poor treatment outcomes [14]. In developing countries where food insecurity remains prevalent, malnutrition significantly contributes to disease progression and mortality [15].

Geographic barriers also substantially affect diagnosis and management of CNS tuberculosis [16]. Rural and remote regions frequently lack specialized healthcare facilities, neurologists, microbiology laboratories, and neuroimaging services [17]. Patients often need to travel long distances to tertiary care

hospitals for advanced investigations such as MRI, CSF culture, or molecular testing [18]. Delayed referral systems and poor transportation infrastructure further prolong diagnostic timelines and treatment initiation [19].

In many developing countries, primary healthcare centers are inadequately equipped to diagnose CNS-TB [20]. Peripheral hospitals may lack lumbar puncture facilities, trained laboratory personnel, molecular diagnostic platforms, and radiological services [21]. Consequently, patients are frequently managed empirically without microbiological confirmation, increasing the risk of misdiagnosis and inappropriate therapy [22].

Healthcare accessibility is further complicated by unequal distribution of medical resources between urban and rural regions [23]. Urban tertiary hospitals generally possess better diagnostic infrastructure and specialist availability, whereas rural communities remain dependent on under-resourced healthcare units [24]. This urban-rural healthcare disparity contributes significantly to late-stage presentation and poor neurological outcomes in CNS tuberculosis patients [25].

Social stigma associated with tuberculosis and HIV co-infection also acts as a barrier to healthcare-seeking behavior [26]. Fear of discrimination and social exclusion may discourage patients from seeking early medical attention or adhering to long-term anti-tubercular therapy [27]. Women and children in socioeconomically disadvantaged communities often face additional barriers related to dependency, gender inequality, and limited healthcare decision-making authority [28].

Financial limitations also affect continuity of treatment and follow-up care [29]. CNS tuberculosis requires prolonged multidrug therapy, repeated neurological assessments, and monitoring for complications such as hydrocephalus and drug toxicity [30]. Patients from economically unstable backgrounds frequently discontinue therapy because of medication costs, transportation expenses, and loss of daily wages during hospitalization [31]. Treatment interruption significantly increases the risk of relapse, drug resistance, and mortality [32].

Another major challenge involves poor public health infrastructure and weak surveillance systems in developing countries [33]. Many remote areas lack effective tuberculosis screening programs, community health education, and rapid referral mechanisms [34]. Delayed case detection contributes to continued disease transmission and increased burden of extrapulmonary tuberculosis including CNS involvement [35].

Natural disasters, political instability, armed conflict, and migration further worsen healthcare accessibility in several low-income regions [36]. Displacement and overcrowding increase tuberculosis transmission while simultaneously disrupting continuity of healthcare services and medication availability [37].

Overall, socioeconomic inequality and geographic inaccessibility remain major contributors to the persistent burden of CNS tuberculosis in developing countries [38]. Addressing these barriers requires strengthening rural healthcare infrastructure, expanding affordable diagnostic services, improving public awareness, reducing poverty-related healthcare disparities, and implementing community-based

tuberculosis control programs [39]. Integrated public health strategies focused on equitable healthcare delivery are essential for improving early diagnosis and reducing CNS-TB-associated morbidity and mortality in resource-limited settings [40].

IX. FUTURE PERSPECTIVES & CONCLUSION

Central nervous system tuberculosis (CNS-TB) is still considered one of the most serious and life-threatening forms of TB that occurs especially in developing countries where resources for health care and diagnostic facilities are limited [1]. Although global efforts to control TB have made great strides, CNS-TB still dramatically impacts clinical, neurological, socioeconomic, and public health outcomes by delaying diagnosis, restricting access to advanced diagnostics tools, and failing to provide access to health care systems and services [2]. The diagnosis of CNS tuberculosis is extremely difficult due to its clinical non-specificity, low bacillary load of CSF, overlapping clinical symptoms and underperforming sensitivity of classical diagnostic tools [3]. Although their usefulness is low and the turnaround time is long, methods like smear microscopy and CSF culture are still being used widely in resource poor areas [4]. While advanced molecular technologies such as GeneXpert MTB/RIF, Xpert Ultra, and nucleic acid amplification tests are associated with improved diagnostic sensitivity and speed, adoption is limited in many rural and economically disadvantaged areas due to a high operational cost, need for infrastructure and lack of trained personnel [5].

In some developing countries, socio-economic inequalities, malnutrition, poverty, overcrowding, illiteracy and HIV co-infection exacerbate the burden of CNS-TB [6]. Access to neuroimaging, laboratory diagnostics and specialized neurological care is significantly delayed by geographic barriers and disparities between urban and rural areas [7]. As a result, patients are often diagnosed at a later stage of the disease, when neurological complications are more severe and mortality rates are higher [8]. All of these findings point to the great need of increasing the capacity of the healthcare system, the capacity of the laboratory and the accessibility of rapid molecular diagnostic platforms in developing countries suffering from the relentless impact of CNS tuberculosis [9]. The use of affordable point-of-care diagnostic tools, better availability of neuroimaging, better clinician training, and efficient referral systems need to be integrated to enable timely diagnosis and initiation of treatment [10]. Awareness creation in the community, TB screening programs, nutritional interventions and socioeconomic development can also play a significant role in reducing disease burden and treatment success [11]. Some emerging technologies such as artificial intelligence-driven neuroimaging, biomarker-based diagnostics, loop-mediated isothermal amplification, and metagenomic next-generation sequencing could provide advantages in increasing the accuracy of diagnosis in resource-limited settings [12]. These technologies however, need to be implemented on a large scale, which demands international cooperation, governmental investment and formation of cost-effective healthcare policies appropriate to the low and middle income countries [13]. Finally, CNS tuberculosis remains an important clinical and therapeutic problem in developing countries due to various clinical, socioeconomic and infrastructural constraints [14]. Strengthening integrated healthcare, expanding rapid diagnostics and increasing equitable healthcare accessibility is vital to reducing the size of the burden of morbidity, neurological disability and mortality due to CNS-TB globally [15].

REFERENCES:

1. Wilkinson, R. J., Rohlwink, U., Misra, U. K., van Crevel, R., Mai, N. T. H., Dooley, K. E., & Caws, M. (2017). Tuberculous meningitis. *Nature Reviews Neurology*, 13(10), 581–598.
2. World Health Organization. (2024). *Global tuberculosis report 2024*. Geneva: World Health Organization.
3. Rock, R. B., Olin, M., Baker, C. A., Molitor, T. W., & Peterson, P. K. (2008). Central nervous system tuberculosis: Pathogenesis and clinical aspects. *Clinical Microbiology Reviews*, 21(2), 243–261.
4. Chin, J. H. (2014). Tuberculous meningitis: Diagnostic and therapeutic challenges. *Neurology Clinical Practice*, 4(3), 199–205.
5. Donovan, J., Thwaites, G. E., & Huynh, J. (2020). Tuberculous meningitis: Where to from here? *Current Opinion in Infectious Diseases*, 33(3), 259–266.
6. Torok, M. E. (2015). Tuberculous meningitis: Advances in diagnosis and treatment. *British Medical Bulletin*, 113(1), 117–131.
7. Central TB Division, Ministry of Health and Family Welfare, Government of India. (2023). *India TB report 2023*. New Delhi: Government of India.
8. Manyelo, C. M., Solomons, R. S., Snyders, C. I., Manngo, P. M., Mutavhatsindi, H., & Walzl, G. (2021). Diagnostic challenges in childhood tuberculous meningitis. *Journal of Tropical Pediatrics*, 67(3), fmab020.
9. Marais, S., Pepper, D. J., Schutz, C., Wilkinson, R. J., & Meintjes, G. (2011). Presentation and outcome of tuberculous meningitis in a high HIV prevalence setting. *PLoS ONE*, 6(5), e20077.
10. Bhosale, R., Kinikar, A., Gupte, N., Kadam, D., Suryavanshi, N., & Bharadwaj, R. (2015). Challenges in diagnosis of pediatric tuberculosis. *Indian Journal of Pediatrics*, 82(10), 915–921.
11. Rohlwink, U. K., Donald, K., Gavine, B., Padayachy, L., Wilmshurst, J. M., & Figaji, A. A. (2016). Clinical characteristics and neurodevelopmental outcomes of children with tuberculous meningitis and hydrocephalus. *Developmental Medicine & Child Neurology*, 58(5), 461–468.
12. Dunn, J. J., Starke, J. R., & Revell, P. A. (2016). Laboratory diagnosis of *Mycobacterium tuberculosis* infection and disease in children. *Journal of Clinical Microbiology*, 54(6), 1434–1441.
13. Vinnard, C., & Macgregor, R. R. (2009). Tuberculous meningitis in HIV-infected individuals. *Current HIV/AIDS Reports*, 6(3), 139–145.
14. Wilkinson, K. A., Seldon, R., Meintjes, G., Rangaka, M. X., Hanekom, W. A., Maartens, G., & Wilkinson, R. J. (2017). Discriminatory performance of inflammatory markers in HIV-associated tuberculous meningitis. *Clinical Infectious Diseases*, 64(9), 1217–1223.
15. Cresswell, F. V., Tugume, L., Bahr, N. C., Kwizera, R., Bangdiwala, A. S., Musubire, A. K., Meya, D. B., & Boulware, D. R. (2020). Xpert MTB/RIF Ultra for the diagnosis of HIV-associated tuberculous meningitis. *Lancet Infectious Diseases*, 20(3), 308–317.
16. Lawn, S. D., & Zumla, A. I. (2011). Tuberculosis. *Lancet*, 378(9785), 57–72.
17. Gupta, M., & Sharma, S. (2024). *CNS Tuberculosis*. StatPearls Publishing. Treasure Island, FL: StatPearls Publishing.
18. World Health Organization. (2021). *WHO consolidated guidelines on tuberculosis*. Geneva: World Health Organization.

20. Patel, V. B., Theron, G., Lenders, L., Matinyena, B., Connolly, C., Singh, N., Dheda, K., & Meldau, R. (2013). Diagnostic accuracy of quantitative PCR (Xpert MTB/RIF) for tuberculous meningitis in a high burden setting. *PLoS Medicine*, 10(10), e1001536.
21. Bahr, N. C., Marais, S., Caws, M., van Crevel, R., Wilkinson, R. J., Tyagi, J. S., & Thwaites, G. E. (2016). GeneXpert MTB/RIF to diagnose tuberculous meningitis: Perhaps the first test but not the last. *Clinical Infectious Diseases*, 62(9), 1133–1135.
22. Heemskerk, A. D., Bang, N. D., Mai, N. T. H., Chau, T. T. H., Phu, N. H., Loc, P. P., Chau, N. V. V., Hien, T. T., Farrar, J., & Thwaites, G. E. (2016). Intensified antituberculosis therapy in adults with tuberculous meningitis. *New England Journal of Medicine*, 374(2), 124–134.
23. Török, M. E., Yen, N. T. B., Chau, T. T. H., Mai, N. T. H., Phu, N. H., Mai, P. P., Dung, N. T., Chau, N. V. V., Bang, N. D., & Hien, T. T. (2011). Timing of initiation of antiretroviral therapy in human immunodeficiency virus-associated tuberculous meningitis. *Clinical Infectious Diseases*, 52(11), 1374–1383.
24. Palacios, C. F., Halliday, C., Welsh, J. A., Kiwanuka, J. P., Ssenkusu, J. M., Meya, D. B., & Boulware, D. R. (2020). Challenges in the diagnosis of tuberculous meningitis. *Journal of Clinical Tuberculosis and Other Mycobacterial Diseases*, 20, 100164.
25. Pai, M., Flores, L. L., Huddart, S., MacLean, E., & Pai,
26. N. P. (2019). New diagnostics for tuberculosis: Evolving landscape and future prospects. *Clinical Chest Medicine*, 40(4), 693–709.