Tuberculous meningitis

A neglected tropical disease?

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Abstract

Tuberculosis (TB) surpassed HIV as the world's leading infectious cause of death in 2014. Although billions of dollars have been invested to reduce the global burden of pulmonary TB, tuberculous meningitis (TBM), the most lethal manifestation of the disease, has remained largely neglected with a paucity of evidence-based guidelines. Research is urgently needed to obtain reliable estimates of the global incidence of TBM, develop high performance technologies to detect TBM in CSF, and evaluate drug regimens with greater penetration of the CNS.

According to the U.S. National Institute of Allergy and Infectious Diseases, “Neglected tropical diseases (NTDs), such as dengue, lymphatic filariasis, trachoma, and leishmaniasis, are called “neglected,” because they generally afflict the world’s poor and historically have not received as much attention as other diseases. NTDs tend to thrive in developing regions of the world, where water quality, sanitation, and access to health care are substandard. However, some of these diseases also are found in areas of the United States with high rates of poverty.”¹

The World Health Organization (WHO) applies the following criteria for NTDs²: “(1) disproportionately affect populations living in poverty; and cause important morbidity and mortality—including stigma and discrimination—in such populations, justifying a global response, (2) primarily affect populations living in tropical and sub-tropical areas, (3) are immediately amenable to broad control, elimination or eradication by applying one or more of the 5 public health strategies adopted by the Department for Control of NTDs, and/or, (4) are relatively neglected by research—i.e., resource allocation is not commensurate with the magnitude of the problem—when it comes to developing new diagnostics, medicines and other control tools. Disease conditions that fulfill all 4 criteria may be considered for inclusion in category A, while those that do not fulfill criteria 3 may be considered for inclusion in category B. While diseases included in category A will be included for large scale action in the portfolio of the NTD Department for control, elimination or eradication, those in category B will be supported by activities leading to advocacy by stakeholders and the development of new diagnostics, medicines or other control tools and strategies.” Herein I propose and provide evidence that TBM fulfills the WHO criteria for inclusion in category B as an NTD.

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Urbanization, crowding, poverty, incarceration, HIV, diabetes, and alcoholism will continue to fuel the TB epidemic for years to come.

What is the epidemiologic trajectory of tuberculosis?

Tuberculosis (TB) is the leading infectious disease killer in the world with 10 million incident cases estimated in 2017.³ Twenty-two of the 30 highest-burden countries are low-income or lower-middle-income countries. India, China, Indonesia, the Philippines, Pakistan, Nigeria, Bangladesh, and South Africa accounted for two-thirds of all TB cases in 2017. Although global incidence rates per capita have declined steadily since 2000, the absolute number of annual new TB cases continues to rise in many countries as a result of population growth, which is most pronounced in the high-burden WHO South-East Asia and African regions. Urbanization, crowding, poverty, incarceration, HIV, diabetes, and alcoholism will continue to fuel the TB epidemic for years to come. Rising prevalence of HIV infection and inadequate support for HIV treatment and care in certain countries in Eastern Europe are contributing to a high incidence rate of TB in this region. Equally concerning is the global threat of multidrug resistant TB and the lack of resources for diagnosis, reporting, and treatment of cases in many countries.⁴

What are the incidence and mortality rates of TBM?

The global incidence of TBM is unknown. There are no published national or subnational population-based incidence studies from regions with a high burden of TB. Globally, only 64% of all new TB cases were reported in 2017 due to weak surveillance and vital registration systems in many less-developed countries.³ In resource-limited countries, the etiology of many cases of meningitis are never determined and it is probable that many patients with both TBM and non-mycobacterial bacterial meningitis die outside of the health-care system. Delayed presentation for medical treatment, reliance on traditional healers, inability to perform or refusal of lumbar puncture to obtain CSF, lack of laboratory facilities for rapid diagnostic tests and cultures, and unavailability or unaffordability of antibiotics are contributors to the gaps in diagnosis and treatment. India's national guidelines for the treatment of extrapulmonary TB estimate that 1% of all TB cases in India may be TBM.⁵ At a global level, the number of TBM cases would be over 100,000 annually if 1% of all TB cases were TBM, rivaling the burden of many NTDs. Published

case series and clinical trials report high mortality rates from TBM. A Cochrane review of 9 clinical trials of adjunctive corticosteroids for TBM reported median mortality rates of 41% and 31% without and with corticosteroids, respectively.⁶

What advances have been made in the diagnosis and treatment of TBM?

TBM has been a diagnosis of exclusion and high clinical suspicion for many years. The diagnosis is strongly suspected based on a subacute clinical presentation, lymphocytic pleocytosis and reduced glucose levels in CSF, focal neurologic deficits including hemiparesis and cranial nerve palsies, brain imaging (CT or MRI) showing infarcts, diffuse or basal meningeal enhancement, and/or hydrocephalus, and negative microbiological studies for nonmycobacterial bacteria and fungi.⁷ For experienced clinicians, the diagnosis of TBM can be made with reasonable confidence without microbiological confirmation of the presence of *Mycobacterium tuberculosis* (MTB) in CSF. However, for less experienced clinicians, a reliance on microbiological confirmation often results in misdiagnosis or a delay in diagnosis and initiation of antituberculous therapy.⁸ The development and WHO approval of the Xpert MTB/resistance to rifampicin (RIF) assay in 2010, a rapid point-of-care test for the detection of MTB DNA in clinical samples, provided a novel diagnostic tool to assist in the diagnosis of TBM. The recent WHO approval and roll-out of the highly sensitive next-generation Xpert MTB/RIF Ultra assay in 2017 to replace Xpert MTB/RIF may be a game changer for the diagnosis of TBM.⁹ Additional studies are needed to confirm the encouraging results of the single published study of Xpert MTB/RIF Ultra for the detection of TBM in HIV-infected individuals.¹⁰

Current WHO and national guidelines for the treatment of TBM recommend extended-duration treatment for TBM using the standard four-drug oral regimen (isoniazid, rifampicin, pyrazinamide, and ethambutol) used to treat pulmonary TB.⁵ However, the minimum recommended duration of treatment varies widely from 6 to 24 months. Controlled clinical trials comparing different treatment durations are lacking. Corticosteroids are considered standard of care as adjunctive treatment for TBM based on a Cochrane review that reported a reduction in mortality.⁶ A large clinical trial (N = 817) conducted in 2011–2014 in Vietnam compared a 9-month regimen using standard-dose oral rifampicin with a 9-month regimen using higher-dose oral rifampicin plus levofloxacin for the first 8 weeks and found no difference in survival rates at 9 months.¹¹ A smaller trial (N = 60) conducted in Indonesia reported a lower mortality at 6 months with higher-dose intravenous rifampicin compared to standard-dose oral rifampicin.¹² Guy Thwaites and colleagues of the Tuberculosis Meningitis International Research Consortium recently proposed standardized methods for tuberculosis meningitis research.¹³

Population-based incidence studies should be performed in high-burden countries employing multiple case ascertainment sources including death registries, hospital medical records, and community-based verbal autopsies.

The majority of TBM patients, particularly in resource-limited settings, are treated empirically without the knowledge of MTB drug susceptibility determined by either polymerase chain reaction-based diagnostic assays, for example, Xpert MTB/RIF and Xpert MTB/RIF Ultra, or by phenotypic drug susceptibility testing of MTB culture isolates. Recent studies have demonstrated the potential applications of pyrosequencing and next-generation sequencing for the detection of MTB and identification of drug resistance mutations.^{14–16}

What are the urgent priorities going forward?

Research is needed to address the critical knowledge gaps in the epidemiology, diagnosis, treatment, and management of TBM. Specifically, population-based incidence studies should be performed in high-burden countries employing multiple case ascertainment sources including death registries, hospital medical records, and community-based verbal autopsies. The performance of Xpert MTB/RIF Ultra for the detection of TBM needs to be confirmed in HIV-infected individuals and studied in HIV-negative individuals. Randomized controlled clinical trials should be conducted to compare different treatment durations of standard oral antituberculous therapy with well-defined protocols for monitoring and evaluation to assess treatment response and cure, for example, CSF analyses and brain imaging. Finally, public education campaigns are needed to increase awareness of the early symptoms of meningitis and the importance of seeking urgent medical attention. NTD status for TBM would generate the much-needed advocacy required to raise the levels of domestic and international funding for research, clinical training, and patient care and support. The time has come to shine a spotlight on TBM and include this deadly disease on the list of NTDs.

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Appendix Author contributions

Name	Location	Role	Contribution
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