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Knowledge gaps and research priorities in tuberculous meningitis [version 1; peer review: 3 approved]

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Abstract

Tuberculous meningitis (TBM) is the most severe and disabling form of tuberculosis (TB), accounting for around 1-5% of the global TB caseload, with mortality of approximately 20% in children and up to 60% in persons co-infected with human immunodeficiency virus even in those treated. Relatively few centres of excellence in TBM research exist and the field would therefore benefit from greater co-ordination, advocacy, collaboration and early data sharing. To this end, in 2009, 2015 and 2019 we convened the TBM International Research Consortium, bringing together approximately 50 researchers from five continents. The most recent meeting took place on 1st and 2nd March 2019 in Lucknow, India. During the meeting, researchers and clinicians presented updates in their areas of expertise, and additionally presented on the knowledge gaps and research priorities in that field. Discussion during the meeting was followed by the development, by a core writing group, of a synthesis of knowledge gaps and research priorities within seven domains, namely epidemiology, pathogenesis, diagnosis, antimicrobial therapy, host-directed therapy, critical care and implementation science. These were circulated to the whole consortium for written input and feedback. Further cycles of discussion between the writing group took place to arrive at a consensus series of priorities. This article summarises the consensus reached by the consortium concerning the unmet needs and priorities for future research for this neglected and often fatal disease.

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Any reports and responses or comments on the article can be found at the end of the article.

Keywords

Tuberculosis, Tuberculous Meningitis, Research Priorities, Epidemiology, Diagnosis, Treatment, Critical Care, Care Cascade

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Introduction

Tuberculous meningitis (TBM) is caused when *Mycobacterium tuberculosis* enters the cerebrospinal fluid (CSF), leading to inflammation of the meninges, and subsequent clinical features of meningitis[1]. Cerebral ischaemia, hydrocephalus, raised intracranial pressure, and cranial nerve dysfunction commonly occur. TBM is the most severe form of tuberculosis (TB) and is universally fatal if untreated. Even with treatment, mortality is high, and some degree of morbidity is near universal. Our current understanding of the epidemiology, natural history and pathophysiology of TBM is limited and it will only be through an improved appreciation of these areas that appropriate clinical and public health interventions will be possible. Current diagnostic tools have inadequate test performance, meaning that most individuals with TBM are either not diagnosed or diagnosed late, once significant cerebral damage has occurred. Current antimicrobial treatment is based mainly on the treatment of pulmonary TB with little consideration to mode of drug action or CSF penetration. Given that most damage caused by TBM is due to host inflammation, it is anticipated that host-directed therapies should play an important role in modulating the damaging immune-medicated effects. However, other than corticosteroids, no agent has been demonstrated to be effective in reducing mortality and corticosteroids have not been shown to improve long-term morbidity[2]. The critical care management of TBM is also poorly understood, with highly divergent practice in the management of raised intracranial pressure, hydrocephalus, blood pressure, oxygenation and hyponatraemia[3]. Understanding the optimal management of these areas would almost certainly improve the long-term outcome of diagnosed patients. Finally, the management of TBM within health systems is sub-optimal with services and tools rarely provided at the locations where patients present. Public sensitisation is infrequently undertaken, and clinical training is often limited.

Globally, there are relatively few researchers of TBM and only a small number of centres of excellence. The field, therefore, would benefit from greater co-ordination, collaboration and data sharing. In 2009, the TBM International Research Consortium was formed and met for the first time in Cape Town, South Africa. Subsequent meetings took place in 2015 in Dalat, Vietnam, and in 2019 in Lucknow, India. The Consortium brings together approximately 50 experts from five continents. At the Lucknow meeting, the Consortium felt that it would be useful to develop a document detailing research priorities in TBM. The practice of establishing knowledge gaps and priorities for research helps researchers to focus efforts on areas that are perceived to be most likely to lead to clinical benefit. It also allows funders to target their funding. This practice can also be beneficial for advocacy through a clearer message and co-ordinated agenda. In this article we describe the process of developing a TBM research agenda and outline the priorities that were developed.

Identifying knowledge gaps and research priorities for TBM

The 3rd TBM International Research Consortium took place in Lucknow on the 1st and 2nd March 2019. During the meeting,

research updates were presented by leading researchers and clinicians in each respective field. Each had been requested to additionally present their thoughts and suggestions for knowledge gaps and research priorities in that field. Following each presentation, debate around these gaps and priorities took place. After the meeting, these priorities were assimilated into tables of research gaps by a core writing group, with gaps grouped into the themes of epidemiology, pathogenesis, diagnosis, antimicrobial therapy, host-directed therapy, critical care and care cascades. For each knowledge gap, study designs were proposed that might address them. These tables were circulated to the whole consortium who were asked to provide input and make suggestions as to which areas were the highest priority. Through further cycles of discussion within the writing group, the tables of knowledge gaps were updated (Table 1–Table 7) and a consolidated list of top priorities for TBM research was developed, which are presented in Table 8. This article describes the knowledge gaps and research priorities for TBM.

Epidemiology

Accurate estimates of the incidence of TBM are lacking, in part as many cases die prior to diagnosis. Adult autopsy studies demonstrate that a high proportion of those with human immunodeficiency virus (HIV), in a high TB-burden setting, die from undiagnosed disseminated TB[4]. Given that *M. tuberculosis* is now the most common cause of bacterial meningitis in some high TB burden settings[5], following wide implementation of routine vaccinations to meningococcus, pneumococcus and haemophilus, it is likely that this situation is replicated in children.

The World Health Organization (WHO) estimates that 10 million individuals developed TB in 2017[6]. Of the 6.4 million cases that were notified to WHO that year, 14% were classified as extrapulmonary[6]. Given that a patient with any pulmonary involvement is classified by WHO as a pulmonary case (such as an individual with both pulmonary TB and TBM)[7], the proportion of patients who have extrapulmonary involvement is higher than this. To be notified, an individual must have been diagnosed and so it is likely that TBM is under-represented in cases notified to WHO.

Data on the proportion of all TB cases that have extrapulmonary involvement is limited and likely varies with multiple factors including the age and gender characteristics of the population, the HIV prevalence, where the cohort is recruited from (hospital vs. community), and the force of TB infection. The proportion of all TB patients that have TBM is even less clear. A population-based estimate in a low TB-prevalence setting suggested that around 1% of TB cases were TBM[8], while a paediatric hospital-based cohort of confirmed TB in a high TB-burden setting suggested that over 10% of TB cases were TBM[9]. If 1% of the overall TB burden is TBM then 100,000 individuals develop TBM each year. This figure could be significantly higher. TBM is universally fatal if untreated[10] but estimates of mortality in treated TBM are poor. A fifth of children die, with half of survivors experiencing neurodisability[11]. In some cohorts of HIV-infected adults, mortality is as high as 60%[12,13]. To improve estimates, it would be informative to review the extensive pre-chemotherapy literature to both quantify the proportion of meningitis deaths that are

Table 1. Knowledge gaps in the epidemiology of tuberculous meningitis.

	Question	Potential study designs
Understanding burden	How many children/adults in each country develop TBM each year?	• Systematic review of the pre-chemotherapy literature to identify proportion of TB cohorts that are TBM/which patients get TBM • Cross-sectional studies/analysis of TB registers to identify what proportion of TB cohorts are TBM/which patients get TBM • Modelling studies to quantify burden
	How many children/adults die from TBM in each country each year?	• Autopsy studies of deaths from clinical meningitis • Systematic reviews of published studies that report on outcome of cohorts of TBM • Analysis of register data at district, national and international level to evaluate proportion of outcomes for TBM that are registered as death • Modelling studies to evaluate the number of deaths from TBM, given number of cases, the proportion diagnosed and expected mortality treated and untreated
	What is the morbidity from TBM?	• Systematic reviews of published studies that have evaluated the neurological disability in survivors of TBM • Modelling studies to quantify the burden of morbidity in different countries and regions given the burden of treated TBM • Cohorts of children and adults with long-term neurocognitive outcomes and quality of life documented
	What is the cost of TBM?	• Collection of costing data in different settings to determine the cost of diagnosis and treatment of TBM, as well as the cost of caring for an individual who is disabled by TBM from a health system and societal perspective • Health economic evaluations to determine the health system and family costs of TBM diagnosis, treatment, mortality and disability in terms of life years, DALYs and QALYs lost due to TBM
Individual risk factors for developing TBM	Which adults and children are most likely to develop TBM following TB exposure and infection?	• Systematic reviews of household contact studies to identify risk factors in household contacts of developing both TB and TBM • Cohort studies of individuals who have been exposed to TB and followed to determine who progresses to TBM and evaluates risk factors for progression • Case control studies of people who had been exposed to TB who developed TBM, compared to TB-exposed individuals who developed pulmonary TB or no TB. • Cross-sectional study comparing TBM cases with pulmonary TB cases, to evaluate which patients with TB are at increased risk of TBM
	Which adults and children are at high risk of developing drug-resistant TBM?	• Evaluation of treatment resisters to compare cases of drug-resistant TBM with drug-susceptible TBM • Cross-sectional studies of TBM cases, comparing those with drug-resistant TBM with those with drug-susceptible TBM
Understanding risk factors for outcome in TBM	Which adults and children are at risk of dying once diagnosed with TBM?	• Evaluation of treatment registers to identify risk factors for mortality among TBM cases • Cohort studies of TBM patients with evaluation of risk factors for mortality • Biomarker research to determine if any samples taken at baseline or during treatment predict mortality
	Which clinical and biological characteristics are associated with poor outcome?	• Cohort studies of TBM patients with evaluation of baseline and follow up risk factors for mortality and morbidity
	Which adults and children are at risk of developing severe neurological disability if the survive TBM?	• Cohort studies of TBM patients to identify risk factors for morbidity in survivors • Biomarker research to determine if any samples taken at baseline or during treatment predict morbidity in survivors

TBM, tuberculous meningitis; DALY, disability adjusted life year; QALY, quality adjusted life year; TB, tuberculosis.

Table 2. Knowledge gaps in our understanding of the pathogenesis of tuberculous meningitis.

	Question	Potential study designs (see legend)
CNS penetration	How do bacilli cross the intact blood brain barrier?	A, B
	How does Bacille Calmette Guérin confer protection against TBM?	B, C
CNS inflammation	What are the soluble and cellular determinants of brain inflammation?	A, B, D
	What are the modifying effects of age, host genotype and HIV co-infection on these responses?	D
Metabolic derangement	What patterns of metabolic derangement does CNS inflammation establish?	A, B, D
	How does metabolic derangement contribute to cerebral dysfunction and brain injury?	A, D
Mycobacterial characteristics	How do different strain types of M tuberculosis impact on disease pathogenesis?	A, D
Ongoing brain injury	What patterns of brain injury contribute to poor outcome in TBM?	A, B, D
	By what mechanisms is brain injury perpetuated in TBM?	A, B, D
Advanced and dynamic cerebral imaging studies	Which areas of the brain are most affected by TBM?	B, imaging
	Which areas and patterns of brain damage correlate with poor outcome or good resolution of TBM	B, D

TBM, tuberculous meningitis; CNS, central nervous system; HIV, human immunodeficiency virus.

A. *In vitro* models including isolated cell populations, blood brain barrier models and cerebral organoids.

B. *In vivo* models including zebrafish, mice, rabbits and non-human primates.

C. Correlates of protection studies in humans.

D. Observational, diagnostic and randomised intervention studies in humans.

Table 3. Knowledge gaps in the diagnosis of tuberculous meningitis.

	Question	Potential study designs
Pathogen-based	Do novel nucleic amplification tests improve sensitivity, management and outcome of TBM?	• Adequately designed and powered STARD compliant multicentre diagnostic evaluations that encompass important subgroups including children, HIV co-infected persons and those with drug resistant disease. • Biobanking of well-characterised samples to aid discovery and evaluation of novel diagnostic modalities
	Do novel tests that rely on M. tuberculosis derived molecules or metabolites have useful rule-in value?	
	Is metagenomic sequencing a feasible and accurate means to detect M. tuberculosis in CSF?	
Host-response based	Can single or multiplexed combinations of host-derived molecules adequately rule out TBM when applied to CSF, serum of peripheral blood?	• Capitalise on interest in the development of point of care tests for all forms of tuberculosis and specifically apply to TBM • Adequately designed and powered STARD compliant multicentre diagnostic evaluations that encompass important subgroups including children, HIV co-infected persons and those with drug resistant disease. • Biobanking of well-characterised samples to aid discovery and evaluation of novel diagnostic modalities
Clinical algorithms	Do clinical algorithms have useful diagnostic accuracy when evaluated against microbiological and composite endpoints?	• Adequately designed and powered STARD compliant multicentre diagnostic evaluations that encompass important subgroups including children, HIV co-infected persons and those with drug-resistant disease.
	Do clinical algorithms positively or negatively influence patient outcome?	
Diagnostic Strategies	How can clinical, pathogen and host-response diagnostic approaches be combined into a diagnostic strategy?	• Integrated Phase 1, 2 and 3 studies to evaluate how different individual tests might be combined to diagnose TBM

CSF, cerebrospinal fluid; TBM, tuberculous meningitis; STARD, Standards for Reporting Diagnostic Accuracy; HIV, human immunodeficiency virus.

Table 4. Knowledge gaps in the development of anti-microbial drugs for tuberculous meningitis and our understanding drug distribution.

	Question	Potential study designs (see legend)
Higher dose antibiotics	Does high-dose rifampicin improve outcome?	D
	Should higher-dose isoniazid be prescribed to rapid acetylators or to all TBM patients?	D
Alternative drugs	Can linezolid or other 2nd line drugs improve outcome?	B, D
Better drug delivery	Can modification of drug delivery (e.g. by liposome or nanoparticle-mediated permeation) improve outcome?	A, B, D
	Does inhibition of efflux mechanisms improve outcome?	A, B, D
Optimal treatment in specific patient categories	How can we improve outcomes in HIV-infected patients, children, and individuals with drug-resistant TBM?	C, D
	What is the optimal duration and regimen for tuberculomas and spinal TB?	D
Study design	What is the best way to find optimal treatment regimens for TBM?	B, D

TBM, tuberculous meningitis; HIV, human immunodeficiency virus; TB, tuberculosis.

A. *In vitro* models including isolated cell populations, blood brain barrier models and cerebral organoids.

B. *In vivo* models including zebrafish, mice, rabbits and non-human primates.

C. Correlates of protection studies in humans.

D. Observational, diagnostic and randomised intervention studies in humans.

caused by *M. tuberculosis* as well as to define what proportion of all TB cases are TBM and how this varies by age. It would also be useful to carry out contemporary studies to document the proportion of TB cases that are TBM in large cohorts of routine data or research cohorts, and document outcomes in those treated. Mathematical modelling could be used to estimate the incidence of TBM, as well as mortality.

Improved estimates of incidence and mortality would be vital for appropriate advocacy and resource planning. It would also be important to quantify morbidity in TBM survivors and the cost impact of TBM to society. TBM commonly causes profound neurodisability in survivors, requiring ongoing medical care and extensive community/family support. The degree of long-term disability in survivors has been poorly quantified, especially the impact on education, employment and quality of life. Better estimates of morbidity and cost to society could be developed through collection of appropriate qualitative, neurodevelopmental and costing data, combined with modelling studies.

Beyond burden estimates, it would be useful to better understand why some individuals develop TBM and characteristics that influence clinical outcome. These could be elucidated through systematic review of published studies, as well as larger, prospective clinical cohorts. Knowledge gaps for TBM epidemiology are shown in Table 1.

Pathogenesis

The pathogenesis of TBM has recently been reviewed in depth[14]. The classic paradigm is that meningitis arises as a consequence of bloodborne dissemination, with a single breach of the blood brain barrier being sufficient to form a central nervous system (CNS) focus[15], although this has been challenged[16]. Whether bacilli predominantly transit the endothelium directly or within infected cells is incompletely understood, with a recent study suggesting both are possible[17]. This work was performed using *Mycobacterium marinum* in zebrafish, an ostensibly attractive system due to genetic tractability, high-throughput and the transparency of larvae, which allows *in vivo* imaging. Determinants of Zika virus host tropism by deep mutational scanning in cerebral organoids have recently been described[18]; this may also be a tractable system to study TBM. Attempts to develop murine models of TBM to study pathogenesis *in vivo* have been described[19], but have not been widely adopted, as mice incompletely replicate pathological features of TB, in particular caseous necrosis. The most commonly used animal model therefore has been the rabbit, which does recapitulate some of the pathological features of TBM[20]. However, high dose intracisternal infection to rapidly produce neurological features also results in dissemination to other organs, which is the reverse of what is envisaged to occur in humans. Dose de-escalation studies may have a role in reproducing the early indolent phase of infection. The original description of the *Cynomolgus* model of TB, now increasingly adapted as most representative animal model of human TB, described the occurrence of meningitis[21], but this finding does not appear to have been exploited and may be worth revisiting.

Bacille Calmette Guérin (BCG) vaccine has shown consistently high efficacy against childhood TBM[22]. Negative association between positivity in immune tests of *M. tuberculosis* sensitisation and prior history of vaccination[23,24] encouraged the recent re-evaluation of BCG revaccination in adolescents with similar results[25]. The inference is that BCG may have partial efficacy to prevent infection but it is unclear whether this is sufficient to explain protection against TBM. Further, it has also been shown that BCG-exposed haematopoietic stem cells generate

Table 5. Knowledge gaps in the understanding and use of host directed therapies for tuberculous meningitis.

	Question	Potential study designs
Corticosteroids	What is the best drug, dose, route of administration and duration?	• Comparative randomised trials against the current standard of dexamethasone in adults, and prednisolone in children
	What determines corticosteroid treatment effect and how do they improve outcomes?	• Unbiased characterisation of the cerebral pathophysiology of TBM, using serial brain imaging and CSF analysis of inflammatory and metabolic pathways, in those treated with or without corticosteroids (ideally linked to a randomised comparison)
	Do corticosteroids prevent or reduce the severity of cerebral immune reconstitution inflammatory syndrome in patients co-infected with HIV and starting anti-retroviral therapy	• Randomised placebo-controlled trial of corticosteroids given at the initiation of antiretroviral therapy
Thalidomide	What is the role of thalidomide in the management of TBM?	• Randomised trial of thalidomide for corticosteroid-refractory complications of TBM (e.g. tuberculomas, vasculitis with multiple infarcts)
Anti-TNF biological agents (e.g. infliximab)	Do they have a role in the management of the inflammatory complications of TBM?	• *In vivo* models, including rabbits and mice • Randomised trial of anti-TNF biologic, possibly versus thalidomide, for the treatment of corticosteroid refractory tuberculomas and vasculitis with multiple infarcts
Aspirin	Does aspirin reduce death and disability from TBM?	• Phase 3 randomised controlled trials of aspirin in adults and children
	How does aspirin influence pathophysiology and improve outcomes	• *In vivo* models, including rabbits and mice • Systematic characterisation of brain imaging and CSF inflammatory (including lipid-mediated) and metabolic pathways in those recruited to aspirin trials
Customised host directed therapies, targeting molecules and/or pathways known to influence pathophysiology and clinical outcome of TBM	How can new targets for host directed therapy be identified?	• *In vivo* models, including rabbits and mice • Unbiased 'omics' approach to investigate genes, proteins, inflammatory mediators and metabolites that associate with clinical endpoints, including inflammatory complications occurring after the start of treatment and longer-term survival and disability
	Are there drugs widely and safely used in the treatment of other diseases that can be re-purposed for host directed therapy for TBM? For example, verapamil, doxycycline and metformin	• *In vivo* models, including rabbits and mice • Phase 2 clinical trials exploring dose, safety, and potential efficacy. Require details linked laboratory and imaging studies to support potential clinical efficacy with mechanistic understanding
Personalized use of host-directed therapy	Can use of simple biomarkers or genetic traits help personalize choice of adjuvant treatment?	• Randomised controlled trial stratifying steroid-use by LTA4H-genotype • Mendelian randomization or stratification of results of randomised controlled trials examining host-directed therapy by blood or CSF biomarker profiles
Optimal treatment in specific patient categories	HIV-infected patients, children, MDR- and XDR-TB disease	• Sub-group analysis in randomised controlled trials • Specific randomised controlled trials

TBM, tuberculous meningitis; TNF, tumour necrosis; CSF, cerebrospinal fluid; LTA4H, Leukotriene-A4 hydrolase, MDR, multidrug-resistant; XDR, extensively drug-resistant; TB, tuberculosis; HIV, human immunodeficiency virus.

epigenetically modified macrophages, providing protection against virulent *M. tuberculosis* infection when compared with naive macrophages[26]. Careful correlate of protection studies of infants entering trials of novel live tuberculosis vaccines thus may have the potential to illuminate protection against TBM.

A relatively large number of studies in humans have explored the hypothesis that the inflammatory consequences of TBM are mediated by cytokine or matrix metalloproteinase (MMP) dysregulation, with consistent associations documented for tumour necrosis factor (TNF), vascular endothelial growth factor (VEGF), and MMP-9[1]. Similarly, a substantial number of associations between TBM and genetic polymorphism in immune response genes are also reported[1]. Recent studies, however, have opened three further lines of enquiry. First, increased survival in microbiologically-confirmed TBM patients randomised to high

Table 6. Knowledge gaps in our understanding and use of critical care in tuberculous meningitis.

	Question	Potential study designs
Acute management of hydrocephalus	How should raised intracranial pressure be managed in the acute setting?	• Trials of medical therapy, continuous lumbar drainage, external ventricular drainage, early ventriculoperitoneal shunting/ETV
Subacute/Long term management of hydrocephalus	Should hydrocephalus be managed based on communicating versus non-communicating level of CSF block?	• Trial of surgical (based on agreed criteria) versus medical therapy first in patients with communicating hydrocephalus
	For surgically treated patients, is ventriculoperitoneal shunting or endoscopic third ventriculostomy preferable?	• Where surgery is indicated, trial of shunting versus endoscopy
Treatment thresholds for raised intracranial pressure	Should treatment thresholds for raised intracranial pressure be based on standard norms or should it be more aggressive?	• Compare standard versus more aggressive threshold for ICP treatment
Monitoring of intracranial pressure	Is intracranial pressure monitoring valuable?	• Compare standard of care (where ICP is not monitored) with treatment directed by monitored ICP
	What technique is optimal, considering availability, safety, effectiveness, and economics?	• Compare current options for monitoring intracranial pressure clinically
	What non-invasive techniques are valuable in screening for and/or monitoring raised intracranial pressure?	• Compare current (and novel) methods of non-invasive ICP measurement with measured ICP in a real-world setting
Blood pressure management	Is there benefit from blood pressure optimisation/blood pressure augmentation?	• Compare standard of care with targeted blood pressure management
	If cerebral perfusion pressure monitoring is possible, what should the target be, normal or supra-normal?	• Compare minimum thresholds of CPP (based on current recommendations) with CPP augmentation
	What methods of blood pressure management are preferable?	• After basic resuscitation, compare intravascular fluids with inotropes, particularly with vasopressors
Systemic oxygenation	Does supplemental oxygen improve brain oxygenation?	• Compare standard of care, supplemental oxygen, and normobaric hyperoxia
Hyponatraemia	Does the treatment of hyponatremia depend on the correct diagnosis?	• Compare standard therapy for all patients (saline/hypertonic saline) versus (attempted) diagnosis-based directed therapy
	What is the safest and most effective protocol for treating hyponatremia?	• Compare saline therapy, hypertonic saline, fludrocortisone
Early prognostic indicators to direct acute therapy	What are the early clinical and radiological early warning signs for patients at high risk of deterioration and outcome?	• Develop a multivariable predictive score
	Are there criteria for futility of care?	• Determine a predictive threshold of the score for futility of care

CSF, cerebrospinal fluid; ETV, endoscopic third ventriculostomy; ICP, intracranial pressure; CPP, cerebral perfusion pressure.

dose (1000 mg) adjunctive aspirin therapy was associated with a distinct shift in the pattern of arachidonic acid metabolites[27], corroborating prior work by the same group that a polymorphism in the gene encoding leukotriene A4 hydrolase (LTA4H) influences both intracerebral inflammation and survival from TBM[28], and also associates with corticosteroid responsiveness[29]. Second, metabolomic profiling and quantitative trait analysis demonstrated increased survival associated with decreased CSF tryptophan levels, partially under genetic influence[30]. Third, a recent RNA sequence-based study of ventricular and lumbar CSF in children also indicated significant enrichment associated with glutamate- and GABA-mediated neuronal excitotoxicity and cerebral damage[31]. The finding that metabolic

derangement may contribute to ongoing brain damage was also suggested by a study of markers of brain injury (non-specific enolase, glial fibrillary acidic protein and S100B), which remained elevated despite a reduction of cytokine mediators in children whose outcome was poor[32]. Taken together, these studies illuminate the power of unbiased 'omics' approaches using materials from the site of disease, which have great potential to better understand pathogenesis and thus illuminate new adjunctive treatments in humans.

The 2019 TBM International Research Consortium meeting in Lucknow also collated information on a significant expansion of ongoing and intended clinical trials activity in TBM

Table 7. Knowledge gaps related to the cascade of care for tuberculous meningitis[33].

	Question	Potential study designs
Cascade of Care	What are barriers to accessing appropriate services for TBM?	• Patient pathway analyses • Interview and focus groups of TBM patients, families and community health professionals
	What are barriers to adequate and timely clinical TBM diagnosis, including performing lumbar puncture?	• Interview and focus groups of TBM patients, families and community health professionals • Establishment and measurement of quality indicators for diagnosis
	What are barriers to improve quality of care for TBM in hospital and increase the proportion of patients discharged alive?	• Recording of in-hospital mortality • Interview and focus groups of doctors and nurses involved in TBM care • Establishment and measurement of quality indicators for in-hospital care
	What are barriers to retain patients to care after hospital discharge?	• Recording of loss to follow-up after hospital discharge • Interview and focus groups of patients, families and health providers in ambulatory care • Establishment and measurement of quality indicators for post-discharge care
	What are barriers to provide necessary care (e.g. rehabilitation) after hospital discharge?	• Establishment of indications for additional care and measurement of care provided • Interview and focus groups of patients, families and health providers in ambulatory care
Health systems factors	What is the availability of facilities with necessary high-level care for TBM and neurologists trained in TBM?	• Health systems research; assessment of available health statistics, facilities, interviews with health providers etc
	How can incidence and outcome data be collected and reported?	• Collection of TBM cohort data • Interviews with health providers, national programs etc
	What national protocols and patient management protocols are available?	• Interviews with health providers, national programs etc
	How does the health system organisation and regulation affect TBM care (e.g. in terms of referral systems)?	• Health systems research; assessment of available health statistics, facilities, interviews with policy makers, health providers etc
	What are financial barriers to TBM care? how is TBM care covered in public/private health insurance?	• Health-economic studies including patient / family interviews
	What health information should be given to patients and health professionals?	• Knowledge assessment; establishment of minimum requirement of knowledge for patients and health professionals

TBM, tuberculous meningitis.

which is long overdue. These trials provide an unrivalled opportunity to collect materials for *ex vivo* analysis as above and to understand interventions. They also present opportunity, where facilities exist, to non-invasively track metabolic disturbance and drug interventions by dynamic imaging (e.g. combined positron emission and computed tomographic [PET/CT], advanced magnetic resonance image [MRI] sequences, or magnetic resonance spectroscopy [MRS]). An interesting example of such an approach in the context of drug intervention was recently provided by the use of ^{11}C-rifampicin PET/CT in rabbits and humans to investigate rifampicin biodistribution in TBM[34]. Cancer imaging is more advanced in this respect, for example with the availability of a Caspase 3 tracer to detect apoptosis during treatment for cerebral malignancy[35]. Caspase 1 and 5 mediated inflammation via inflammasome activation are implicated in TBM[31,36] and the prospect to determine the anatomical distribution and potential treatment-mediated reduction of such inflammation is of interest. Knowledge gaps for TBM pathogenesis are shown in Table 2.

Diagnosis

Lack of diagnostic suspicion and thus delay is a major contributor to poor outcome in TBM[37]. Modalities in use include pathogen-based or host-response-based tests; and clinical algorithms, which may be supported by radiographic means where available.

Microbiological tests (microscopy, culture and nucleic amplification tests) mostly have good specificity but suboptimal sensitivity and, in the case of culture, render results too late to influence immediate management. The GeneXpert Ultra appears to provide an advance in sensitivity over the first generation of this test and, importantly, where positive, gives early indication of rifampicin resistance[38,39], which presents an especially difficult management challenge. Poor sensitivity of around 22–24%, but high potentially useful 'rule-in' specificity, has recently been reported for lipoarabinomannan (LAM) detection in CSF or urine by means of a lateral flow assay[40]. A second generation

Table 8. Research priorities in tuberculous meningitis.

Theme	Research priorities
Epidemiology	• To identify individual characteristics associated with poor outcome in TBM • To quantify the burden and outcome of TBM across different sites and in different risk groups
Pathogenesis	• To identify the causes brain injury using pathway analysis in order to determine which pathways should be targeted • To determine the pattern of brain injury using advanced and dynamic cerebral imaging
Diagnosis	• To evaluate strategies that use currently-available tools (such as Xpert Ultra) in rigorous multicentre studies to determine sensitivity and specificity across relevant sub-groups and in different contexts • To evaluate host-based biomarkers of CSF that do not rely on mycobacterial identification for the diagnosis of TBM • To evaluate non-CSF tests for the diagnosis of TBM
Anti-Microbial Drug Therapy	• To determine if higher doses of rifampicin improve outcome in adults and children with TBM • To evaluate if the inclusion of newer drugs, such as linezolid, improve outcome • To evaluate novel mechanisms of drug delivery to the sites of disease
Host directed therapy	• To identify which patients will benefit most from corticosteroids and which will not • To determine how to manage steroid-resistant paradoxical reactions • To determine if aspirin improves outcome
Critical Care	• To evaluate the optimal method for managing raised intracranial pressure • To quantify the target systemic blood pressure for minimal brain injury evolution in TBM • To identify the optimal method of treating hyponatraemia • To determine the minimum package of supportive care that can improve outcome in TBM that can be delivered in a low-resource setting
Cascade of Care	• To establish the cascade of care for TBM patients in different settings • To identify factors associated with loss or delay across the cascade in different settings • To develop and test interventions aimed at improving the cascade of care for TBM in different settings

TBM, tuberculous meningitis; CSF, cerebrospinal fluid.

of this test with greater sensitivity has also recently reported and would appear to warrant prospective evaluation[41].

Host-response-based tests include the CSF determination of free, or antigen-specific release of, interferon-γ, adenosine deaminase, and anti-TB antibodies[1,42]. Diagnostic accuracy tends towards suboptimal, especially in specificity. However, multiplexed point-of-care assays to be performed either on CSF or perhaps serum with cut-offs set at useful triage levels of sensitivity may be of utility and could be evaluated further[43]. Lumbar puncture is invasive and may fail or be impracticable in primary care and thus, blood or other body fluid-based tests applicable at the point of care may have utility. There is, for example, great interest in the application of blood-based transcriptomic assays to the diagnosis of TB and expansion of such evaluations to TBM studies may be of interest[44].

A substantial number of clinical algorithms have been proposed for TBM: one widely cited and in use was originally intended not for clinical diagnostic use but to help standardise research case definitions to aid comparability of studies[45]. Prospective evaluations of such definitions against microbiological and composite clinical endpoints could be incorporated into prospective diagnostic evaluations.

A general deficiency in TBM research is that high-quality adequately-powered STARD compliant diagnostic evaluations are few[46]. Multi-centre designs would be efficient and also potentially increase generalisability by the inclusion of important groups such as children and HIV co-infected participants, in whom diagnostic accuracy may differ. Coupled to the standardised biobanking of samples for future discovery and evaluation of novel diagnostic, this would seem an obvious priority. An interesting issue is whether such studies should be randomised to one test or another to best-reflect the likely clinical application that only one test would be performed. Concentration techniques applied to CSF consistently improve microbiological yield: in clinical practice large volumes of CSF tend not to be drawn for TB tests. However, the efficient alternative is to divide the same CSF sample for different diagnostic tests. In the context of a prospective well-designed research evaluation, a greater volume than may be considered routine (15–20 ml in adults) is regarded as safe and feasible. Knowledge gaps for the diagnosis of TBM are shown in Table 3.

Antimicrobial therapy

One intuitive way to improve outcome of TBM is by intensifying antimicrobial treatment[47]. Transporters, like P-glycoprotein (P-gp), actively pump substances out of the brain and into the blood or CSF, to protect the CNS from the free entry of potentially neurotoxic substances[48]. These pumps also lower penetration of some first-line TB drugs, especially rifampicin and ethambutol. Also, it is largely unknown how the anatomical distribution, quantity and metabolic status of *M. tuberculosis* bacilli in TBM

affect the killing effect of specific anti-tuberculous drugs, and if antimicrobial killing may induce (damaging) host inflammatory responses in TBM.

There are different strategies to optimize TBM treatment. Prolonging treatment is unlikely to help; in a meta-analysis, the risk of relapse was extremely low (~0.8%), and virtually identical in patients who received <6 months versus >6 months of therapy[49]. A more promising strategy is to increase drug exposures in the CNS by increasing doses of poorly penetrating drugs. In a phase II clinical trial in Indonesia, rifampicin administered intravenously (600 mg, or 13 mg/kg iv) for two weeks resulted in a three-fold higher exposure to rifampicin in plasma and CSF than 450mg (~10 mg/kg) given orally, and a 50% lower mortality[50]. In contrast, a large trial involving 817 TBM patients in Vietnam did not show a survival benefit of an intensified regimen with 15 (rather than 10) mg/kg of oral rifampicin plus levofloxacin versus standard of care for eight weeks[51], except for patients with isoniazid-mono-resistant TBM[52]. The lack of an effect in that study might be explained by the relatively modest dose increase of rifampicin, as modelling of >1100 pharmacokinetic measurements and survival data from 133 TBM patients in Indonesia suggest that rifampicin exposure strongly predicts survival and that the optimal oral dose is likely to be 35 mg/kg or higher[53]. These findings were corroborated in a study that examined rifampicin cerebral distribution in a rabbit model of TBM[34]. This dose is used in a phase 3 randomised controlled trial (RCT) to be conducted in Uganda, South Africa and Indonesia (ISRCTN: 15668391), and other RCTs that are planned.

Although isoniazid has excellent CSF penetration[54], its dose may also be important. Isoniazid is metabolized by the genetically polymorphic N-acetyltransferase 2 (NAT2), and rapid acetylators have lower isoniazid exposure in plasma and CSF[55], and might benefit from higher doses.

Fluoroquinolones have also been examined, but no effect was seen, both in Indonesia[50] and Vietnam[51]. Other second-line or new drugs that may provide meaningful benefit include cycloserine or ethionamide (though these drugs carry high risk of toxicity)[56], linezolid, and possibly the nitroimidazoles (e.g. delamanid or pretomanid)[57]. It is hoped that new compounds in the pipeline will have characteristics associated with high probability of achieving effective concentrations in the brain and CSF.

Besides higher drug doses or new drugs, modification of drug delivery (e.g. by liposome or nanoparticle-mediated permeation), or inhibition of efflux pumps might also increase drug exposure and effect[48,58,59]. Knowledge gaps for antimicrobial drug therapy in TBM are shown in Table 4.

Host directed therapies

The importance of intra-cerebral inflammation to the complications and outcome of TBM has been appreciated ever since it became a treatable disease in the late 1940s. Streptomycin, the first anti-tuberculosis drug to be trialled in humans, converted TBM from a universally fatal disease to one in which around 30–40% survived[60]. Contemporaneous with this breakthrough was the notion that outcomes might be further improved if inflammation was controlled whilst antibiotics killed the bacteria.

Corticosteroids were the first host directed therapy to be employed in TBM treatment, with trials published in the early 1950s suggesting they caused faster resolution of symptoms and CSF inflammatory indices[61]. However, it took 50 more years to acquire the definitive data from randomised controlled trials that showed adjunctive corticosteroids reduced deaths from TBM[2].

Corticosteroids for TBM remain the only host directed therapy for any form of tuberculosis with high-quality randomised controlled trial evidence of benefit. There are, however, many reasons to be dissatisfied with them as therapeutic agents. First, they reduce deaths, but do not reduce disability. Second, their benefit appears heterogenous; some patients respond rapidly, with marked improvements in clinical and radiological parameters, whilst others do not respond at all. Third, the mechanism by which they reduce deaths is unknown; it does not, for example, appear to associate with a measurable anti-inflammatory effect[61]. Finally, corticosteroids have a panoply of well-recognised side effects, that can limit their use.

The limitations of corticosteroids as host directed therapy have stimulated various avenues of investigation, all of which represent current research priorities. There is much interest in trying to understand the underlying mechanisms of their therapeutic heterogeneity and how they reduce the risk of death in some people with TBM but not others. The objective of these investigations is to identify the relevant molecules or pathways, which may be targeted by more effective and less toxic drugs.

Clinical necessity in those with corticosteroid-refractory disease has driven the use and study of other available anti-inflammatory drugs. Their selection has mostly been predicated on the hypothesis that tumour necrosis factor (TNF) is a critical cytokine in TBM pathogenesis and its inhibition may improve clinical outcomes. To this end, thalidomide and the anti-TNF biological drugs have all been studied, but only in individual reports or small case series[1]. Adequately powered clinical trials have yet to be instigated with these agents.

There is growing interest in the use of aspirin as a host directed therapy for TBM. Brain infarcts are an important cause of disability following TBM and are not reduced by corticosteroids. Thus, the hypothesis that aspirin might prevent infarcts is attractive, but to date has only been subject to three relatively small phase 2 clinical trials[27,63,64]. The most recent trial compared low dose (81mg/day) with higher dose (1000mg/day) aspirin for the first 60 days treatment of 120 adults, complementing clinical response assessments with serial brain imaging and the measurement of lipid inflammatory mediators in the CSF[27]. The results suggested higher dose aspirin may reduce infarcts and deaths, possibly through the up-regulation of lipid mediators that stimulate inflammation resolution. Large phase 3 trials of adjunctive aspirin are now a priority.

Aside from research driven by the benefit and limitations of corticosteroids, and the exploration of other already available anti-inflammatory agents, the priority is to better understand the pathophysiology of TBM. This approach may expose novel pathways and molecules amenable to drugs and could lead to innovative new host directed therapies. It will likely require

coordinated investigations that link cellular and animal disease models with careful clinical studies characterising molecular determinants of outcome. The application of 'omics' technologies and analyses may assist in the search for new drug targets. Knowledge gaps for host directed therapy in TBM are shown in Table 5.

Critical care

Critical care, or acute supportive care, is important because neurological disability and mortality commonly occurs early after presentation. TBM pathology initiates secondary mechanisms such as cerebral ischemia, increased intracranial pressure (ICP), excitotoxicity, and other metabolic derangements[30,31], all of which may interact in a negative downward spiral. Several factors limit our current ability to detect and respond to such derangements, including lack of laboratory and bedside tools to study the disease processes, limited capacity for advanced brain imaging, and few neuromonitoring strategies, compounded by the general lack of resources at sites where TBM is most common. Lack of clinicians trained in critical care and surgical care at these sites further limits options for clinical intervention and research. Late diagnosis may lead to consequences of cerebral pathology too advanced for therapeutic intervention to make a significant difference. Key aspects of initial clinical treatment of TBM are not standardised and practice at different centres is widely divergent. For example, even though hydrocephalus is common in TBM and is the leading cause of increased ICP, there is no consensus on optimal care, including the evaluation of increased ICP, the role of the level of CSF block (communicating versus non-communicating hydrocephalus), indications for medical therapy, criteria for surgical intervention, or the choice of surgical technique[65].

Although there are small single centre randomised trials of surgical technique, selection criteria vary, and the studies have major limitations. Similarly, hyponatremia is common and associates with poor outcome. Hyponatraemia may be caused by cerebral salt wasting, or the syndrome of inappropriate ADH secretion, or both, and distinguishing between them is difficult. This is important because optimal treatment depends on the diagnosis, and inappropriate care may lead to harm. Protocols for safe and effective amelioration of hyponatremia are needed[3]. Supportive systemic care, including haemodynamic and respiratory support, are important in a general sense, but whether more aggressive interventions, such as blood pressure augmentation and optimization of systemic and cerebral oxygenation, can limit cerebral ischemia remains unknown.

Advanced monitoring of the brain to detect derangements in perfusion and metabolism has been increasingly employed for other acute neurological conditions, but there is little experience of these in TBM and the costs are substantial[66,67]. Non-invasive means to detect increased ICP or impaired brain perfusion have been used in several conditions with variable success and remain under investigation[68–71]. Finally, early identification of patients at high risk of neurological deterioration, based on clinical criteria, radiological features, and/or biomarkers, could help direct more aggressive care before permanent infarction

occurs. Knowledge gaps for the critical care of individuals with TBM are shown in Table 6.

The cascade of care for tuberculous meningitis

Mortality of TBM varies between settings and this may be due to specific variation in the availability and quality of health care services, both prior to, during and after hospitalization. It was recently estimated that 50% of TB deaths result from poor-quality care[72]. For TBM it might be even worse, as it requires advanced diagnostics and specialized care, which are often either absent or suboptimal in low-resource settings.

Care for TB patients comprises a cascade of essential steps, with each step unable individually to guarantee a good outcome. It starts with the number of TB patients, followed by the number of patients that accesses TB services for testing, the number diagnosed, the number started on treatment, and finally the number successfully completing treatment[73]. For TBM, the cascade should probably be adjusted to include additional steps such as 'discharged alive' or 'retained to care after discharge' and 'those completing treatment without significant disability'[33]. Some studies have also measured the time between steps[74]. This will be important for TBM, which can be rapidly progressive if no diagnosis is made or treatment started.

Patient pathway studies, which asses the alignment of health systems' infrastructure (e.g. diagnostic, referral and treatment capacity) with patients' care-seeking behavior, could help identify factors that account for losses or delays across a cascade of care for TBM[75]. Many of the possible gaps in diagnosis and treatment of TBM are related to health systems factors, such as the availability of the right facilities or workforce, health information, guidelines, drugs, financing, and organization of the healthy system. A health needs assessment framework measures indicators of performance across system parameters and quantifies the gaps in care against an 'ideal' system, and then considers, using pre-determined criteria, different options to fill each gap. Such public health frameworks have previously been used to identify gaps between current and ideal practice for management of child-case TB contacts[76], and interventions based on this framework are now tested in a multi-country cluster-randomized clinical trial[77]. Establishing the cascade of care for TBM, conducting a patient pathway analysis, and further study of health systems factors could thus help identify priority areas for further action to improve care and outcomes for TBM patients. Some of the knowledge gaps are presented in Table 7, and the theoretical framework is presented in more detail elsewhere in this supplement[33].

Conclusions

TBM is the most severe form of TB and contributes disproportionately to TB mortality and morbidity. In order to improve the care of patients with this devastating condition we need to have a better understanding of the disease epidemiology and pathogenesis, as well as improved diagnostic tests and treatment strategies. These then need to be incorporated into the health systems in which care is delivered. Many questions remain unanswered and much research is required. However, the process of defining

these questions and deciding on areas of priority allows researchers to focus and coordinate their efforts and allows funders a clearer idea of how and where to spend their money.

Data availability
No data are associated with this article.

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Open Peer Review

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Version 1

Reviewer Report 09 March 2020

https://doi.org/10.21956/wellcomeopenres.17054.r37820

✔ **Hardeep Singh Malhotra** (iD)
Department of Neurology, King George's Medical University, Lucknow, India

Seddon *et al.* have put in an excellent effort to shortlist the knowledge gaps and research priorities in tuberculous meningitis (TBM) based on the 3rd TBM International Research Consortium meeting in Lucknow, India, in March 2019.

Regarding "Knowledge gaps in the epidemiology of tuberculous meningitis", it has been proposed that the local and national registers be looked into. In this regard it would be worthwhile suggesting that notification regarding TBM, as well as its verification, be made mandatory. Practically, patients belonging to the 'non-definite' group are lost either because of laxity or because of delay in assessing a measurable response to treatment. Thus, even if patients are suspected of TBM or have been listed as 'possible or probable' TBM, they should be trackable and be tracked.

The co-morbid ailments associated with TBM, that may or may not have a bearing on the outcome of TBM, have not been studied systematically. A considerable subset of patients with immunological (rheumatoid arthritis, systemic lupus erythematosus, etc.) disorders (especially secondary to disease modifying therapies) and endocrinological (diabetes mellitus, cortisol disturbances, etc.) disorders at some stage are either diagnosed with tuberculosis or are referred to the neurological services to rule out CNS involvement. This aspect may, therefore, be included for epidemiological data references.

Regarding "better drug delivery", besides what has been mentioned in the manuscript, parenteral drug delivery systems have always been at the back seat. The gastrointestinal irritation and resultant vomiting (with or without hepatic dysfunction) associated with the current primary drugs possibly impair the drug absorption in toto. Thus, exploring parenteral routes of drug delivery would be worthwhile.

The question "Do corticosteroids prevent or reduce the severity of cerebral immune reconstitution inflammatory syndrome in patients coinfected with HIV and starting anti-retroviral therapy" may either be broadened to include "paradoxical reactions" or a separate question framed to address the issues encountered in patients with possibly intact immunocompetence or evolving immunocompetence.

In the section on "Optimal treatment in specific patient categories" pregnancy needs to be mentioned.

The research question "How should raised intracranial pressure be managed in the acute setting?" appears discordant with "Acute Management of Hydrocephalus". It may be rephrased to "How should hydrocephalus be managed in the acute setting?". My contention relates to the fact that one-on-one relationship does not exist between lumbar CSF pressure and hydrocephalus; at the same time intracranial probe monitoring to look for raised ICP is not universally used and cannot be generalized. Secondary, raised ICP in patients with TBM may be present secondary to venous thrombosis, stroke, or mass lesion.

Instead of addressing hyponatremia singularly, I would suggest looking into endocrinological disorders collectively in patients with TBM. At least a couple of original articles have addressed this aspect.

In Table 8, the authors introduce the term "paradoxical reactions" that are steroid-resistant. I think this should first become a part of the main body clarifying if they are alluding to "inflammatory complications associated with treatment of TBM".

I second the opinion of Christopher Vinnard in going ahead with a multicenter design that would meet most research-related and management issues. For example, the Indian subcontinent accounts for a substantial number of patients with TBM and also provides an insight into epidemiological variability, but because of lack of a common platform heterogeneity contaminates the research output. Using a multicenter design would very importantly address the question "How do different strain types of M tuberculosis impact on disease pathogenesis?"

Is the rationale for the Open Letter provided in sufficient detail?
Yes

Does the article adequately reference differing views and opinions?
Partly

Are all factual statements correct, and are statements and arguments made adequately supported by citations?
Yes

Is the Open Letter written in accessible language?
Yes

Where applicable, are recommendations and next steps explained clearly for others to follow?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: My area of research is Tropical Medicine, especially tuberculosis of the central nervous system, neurocysticercosis, and subacute sclerosing panencephalitis.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 11 February 2020

https://doi.org/10.21956/wellcomeopenres.17054.r37818

✔ **Jamie Rylance** 🆔

Liverpool School of Tropical Medicine, Liverpool, UK

The letter describes a consortium meeting comprising experts from wide geographic scope and areas of research. It is an accessible summary of the symposium.

It would be helpful to give more detail about the processes taken to define knowledge gaps and prioritise the research foci, although perhaps not required in a letter. Specifically:

1. How were the research updates produced? Incomplete or partial summaries would have the potential to skew subsequent discussion - which methods were employed to mitigate against this?

2. Are the knowledge gaps presented in the latter an exhaustive list of those identified during discussions? If not, what selection processes took place?

3. Table 8 priorities were derived from the themed discussions on knowledge gaps - was the prioritisation formalised, and if so, what methods were used?

Minor points:

1. Some tables refer to "correlate of protection" studies (notated 'C'). Is this intended to convey a case-control approach? If not, how does this category differ from those described as "observational studies" (notated 'D').

2. "and organisation of the healthy system" needs correction.

Is the rationale for the Open Letter provided in sufficient detail?
Yes

Does the article adequately reference differing views and opinions?
Yes

Are all factual statements correct, and are statements and arguments made adequately supported by citations?
Yes

Is the Open Letter written in accessible language?
Yes

Where applicable, are recommendations and next steps explained clearly for others to follow?
Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Clinical research in low and middle income countries, including acute medicine, infection and respiratory illness.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 24 January 2020

https://doi.org/10.21956/wellcomeopenres.17054.r37190

Christopher Vinnard
Public Health Research Institute, Rutgers, The State University of New Jersey, Newark, NJ, USA

Dr. Seddon *et al.* provide a comprehensive summary of tuberculous meningitis research priorities, arising from discussions during the 3rd TBM International Research Consortium that met in March 2019. The authors have summarized knowledge gaps and research priorities related to tuberculous meningitis epidemiology, pathogenesis, diagnostics, antimicrobial therapies, host-directed therapies, critical care support, and cascade of care. Under each area, specific questions are presented alongside potential study designs (both pre-clinical and clinical). Overall, the manuscript is clearly written, concise, and provides a valuable roadmap towards synergizing diverse research efforts towards the common purpose of improving patient outcomes for tuberculous meningitis. I have only a few minor comments to consider.

The value of biomarkers of treatment response is included in several areas (epidemiology, therapeutics, critical care). I would add the tremendous potential value of an early treatment response biomarker in supporting greater efficiency in the design of clinical trials of novel therapies, whether pathogen- or host-directed, including the potential for adapative clinical trial designs.

Second, the role of clinical algorithms in the diagnosis of tuberculous meningitis is highlighted as a knowledge gap, stressing the importance of including key sub-groups to support generalizability. It might be worthwhile to stress that a multicenter design, which includes both derivation and validation cohorts, is essential given the role of patient genetic factors in pathogenesis and treatment response. The geographic variability in the local epidemiology of central nervous system diseases, which compete with tuberculous meningitis on the differential diagnosis, can also be addressed by appropriate multicenter designs.

Finally, although perhaps less pressing than the acute issues surrounding timely diagnosis and initiation of effective antimicrobial therapy, there continues to be uncertainty regarding the appropriate duration of therapy for tuberculous meningitis, with regards to the risk of relapse. This is a particular challenge with rifampin-resistant disease. For example, what is the role of serial imaging (where available) to guide clinical decision-making for cessation of treatment. Although these questions appear to be the focus of a separate review stemming from the Consortium, it could be worthwhile to highlight this question as well in the broader overview.

In summary, Dr. Seddon *et al.* have developed an essential framework for the tuberculous meningitis

research community, which should be of great value to investigators, public health authorities, and funding agencies.

Is the rationale for the Open Letter provided in sufficient detail?
Yes

Does the article adequately reference differing views and opinions?
Yes

Are all factual statements correct, and are statements and arguments made adequately supported by citations?
Yes

Is the Open Letter written in accessible language?
Yes

Where applicable, are recommendations and next steps explained clearly for others to follow?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Clinical epidemiology and population pharmacokinetics.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.