



REVIEW

REVIEWED Establishing the cascade of care for patients with tuberculous meningitis [version 2; peer review: 2 approved]

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Abstract

Meningitis is a relatively rare form of tuberculosis, but it carries a high mortality rate, reaching 50% in some settings, with higher rates among patients with HIV co-infection and those with drug-resistant disease. Most studies of tuberculosis meningitis (TBM) tend to focus on better diagnosis, drug treatment and supportive care for patients in hospital. However, there is significant variability in mortality between settings, which may be due to specific variation in the availability and quality of health care services, both prior to, during, and after hospitalization. Such variations have not been studied thoroughly, and we therefore present a theoretical framework that may help to identify where efforts should be focused in providing optimal services for TBM patients. As a first step, we propose an adjusted cascade of care for TBM and patient pathway studies that might help identify factors that account for losses and delays across the cascade. Many of the possible gaps in the TBM cascade are related to health systems factors; we have selected nine domains and provide relevant examples of systems factors for TBM for each of these domains that could be the basis for a health needs assessment to address such gaps. Finally, we suggest some immediate action that could be taken to help make improvements in services. Our theoretical framework will hopefully lead to more health system research and improved care for patients suffering from this most dangerous form of tuberculosis.

Keywords

tuberculosis, meningitis, cascade of care, patient pathway analysis, health systems

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



This article is included in the [Tuberculous Meningitis International Research Consortium](#) collection.

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REVISED Amendments from Version 1

Under 'cascade of care analysis' (page 3, right column, 1st paragraph):

- We have added a comment on the difficulty of establishing the number of people with TBM in the community.
- Replaced *highly specialized qualified team* with *experienced professionals*.

Under the 'first loss in the cascade (2nd paragraph):

- We have added a comment on the importance of awareness of possible TBM among professionals, and lack of a test that can rule out TBM.

In the 3rd paragraph (on the 3rd cascade - treatment), we have added that severity of disease may affect decisions to start treatment.

In Table 1 we have replaced 'neurologists' with 'doctors or other health staff' (given the shortage of neurologists in many high burden settings).

Any further responses from the reviewers can be found at the end of the article

Introduction

Tuberculosis (TB) is a global health emergency, leading to more than 10 million new cases and an estimated 1.6 million deaths in 2017¹. Tuberculous meningitis (TBM) only makes up a small proportion of TB cases (1–2%, probably more in human immunodeficiency [HIV]-endemic settings) but disproportionately contributes to TB-associated mortality². Up to 50% of TBM patients in published studies die, and mortality is substantially higher among those with drug-resistant TB or HIV co-infection². An unknown proportion of TBM patients even die before diagnosis is made or treatment is started. Moreover, studies with longer follow-up show that TBM patients remain at increased risk of dying after completion of TB treatment^{3,4}. Finally, among those patients who survive, some will have permanent disability.

Mortality of TBM shows high variability between settings. This may be due to differences in disease severity, prevalence of HIV co-infection and drug resistance, but could also be explained by specific variation in availability and quality of health care services (health system factors). The Lancet Global Health Commission on high quality health systems, published in 2018, estimated that 50% of TB deaths result from poor-quality care⁵. This figure might even be higher for TBM, as its diagnosis and treatment are complex and technically demanding, requiring advanced diagnostics and specialized care which are often either absent or suboptimal in low-resource settings.

Research aimed at improving outcome on TBM mainly focuses on better diagnosis^{6–8}, drug treatment^{2,9,10} and supportive care for patients in hospital¹¹, rather than on the patient's journey from the moment he or she develops symptoms until no further care is needed. In the absence of empirical data, we aim to provide a theoretical framework that may help identify barriers and challenges in providing optimal care for TBM patients,

by combining cascade of care, patient pathway and health needs analyses. This framework will hopefully lead to more health system research to assess and improve the quality of care for patients with this most dramatic manifestation of TB.

Cascade of care analysis

The outcome of TBM patients depends on the care they receive, which is a complex process, comprising a cascade of essential steps, with each step unable individually to guarantee a good outcome. The TB care cascade represents a normative model, based on the International Standards for Tuberculosis Care, which defines the proper stages of high-quality TB treatment¹². In its most simple form, it starts with the number of TB patients (the first step in the cascade); followed by the number of patients that accesses TB services or testing; then the number diagnosed with TB; started on treatment; and then finally, the number who successfully complete treatment¹³. Secondary cascades can be drawn for subgroups of patients, for instance when drug-resistance is diagnosed¹⁴. TB programs can use cascade of care analysis to further assess their performance in key processes and, after identifying the underlying reasons for the losses found, to prioritize areas for focused improvement¹².

To our knowledge, no assessment of the cascade of care have been conducted for TBM. We propose that a theoretical cascade might comprise of the numbers in sequence: TBM patients in a particular community (something that will be very hard to establish); those accessing a health facility able to diagnose TBM; those diagnosed as TBM; those started on treatment; those discharged alive; those retained to care after discharge; and those completing treatment without significant disability (Figure 1). It should be noted that this cascade is not based on universal international guidelines but rather represents an 'ideal scenario' that in high-burden settings may only exist in some centers, with qualified or experienced professionals and appropriate services. It should also be noted that secondary cascades can be drafted for patients with drug-resistant TBM, with HIV co-infection, or with complications requiring critical care, neurosurgical interventions, rehabilitation or appropriate support because of neurological disability etcetera.

The first loss in the cascade is related to access of patients to health services that are appropriately equipped for TBM diagnosis. The second loss across the cascade is related to diagnosis of TBM. Even when patients reach appropriate services, doctors may fail to consider or diagnose TBM. Awareness among health care workers to think about brain infections and tuberculosis is needed, and an appropriate diagnostic workup has to be done, including brain imaging and analysis of cerebrospinal fluid (CSF) obtained through a lumbar puncture (LP). Unfortunately, no single diagnostic CSF can rule out TBM. Also, there may be contraindications for doing LP, or patients or their family may refuse LP¹⁵.

The third loss is related to treatment. After a presumptive or confirmed diagnosis of TBM is made, treatment should be started immediately, especially for critically ill patients. Besides timely antimycobacterial treatment, critically ill TBM patients

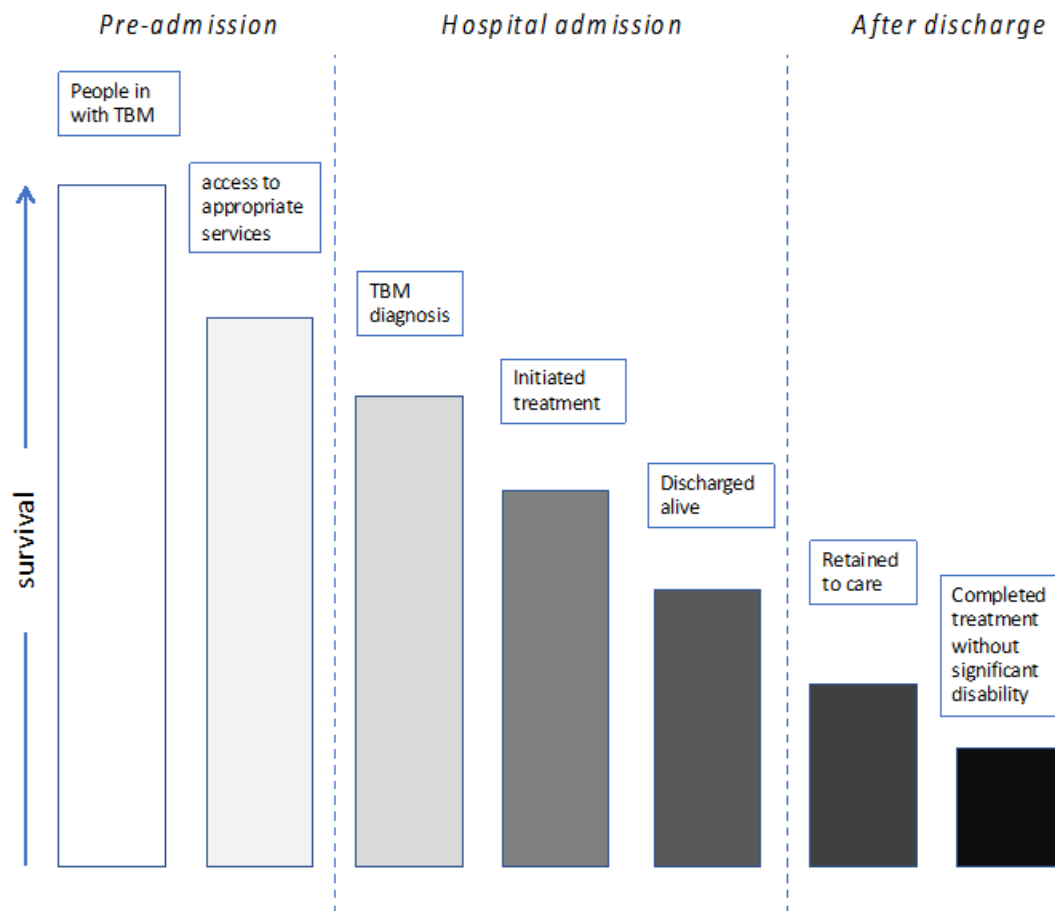


Figure 1. Hypothetical cascade of care for tuberculosis meningitis (TBM). Hypothetical cascade for TBM, that is not based on universal guidelines or empiric data. This simplified cascade does not take time between steps into consideration. Additional cascades of care can be drafted for patients with HIV co-infection, drug-resistant TBM, or other needs such as critical care or rehabilitation.

require corticosteroids¹⁶, optimal supportive or neurocritical care¹¹, and sometimes neurosurgical management treatment¹⁷. Patients also need to be monitored closely. Treatment is made up of different components, which creates opportunities for multiple possible gaps between these different elements.

The fourth loss is related to the period after hospitalization. Patients that survive the initial phase and recover will be discharged, mostly after weeks of hospitalization. At this point, patients still need to continue antimicrobial treatment for months, but patients may skip dosages, stop taking medication all together, or be lost to follow-up during ambulatory treatment. Patients with disabilities may need some form of rehabilitation or support, and this may not be available or may not be offered. Furthermore, incomplete drug intake, or lack of follow-up or rehabilitation may contribute to the fact that mortality remains elevated until years after diagnosis of TBM^{3,4}.

HIV co-infection, which doubles mortality of TBM and adds to the complexity of care for TBM patients¹⁸, has its own cascade of care. Patients with an untreated HIV infection have to start antiretroviral treatment (ART) several weeks after initiation of

TB drugs but this may not happen, or compliance or treatment monitoring may be suboptimal, or patients may stop taking drugs or be lost to follow-up from HIV care. Similar to HIV co-infection, drug-resistance among TBM patients worsens outcome¹⁹ and has its own parallel cascade of diagnosis and treatment.

Importantly, traditional cascades only measure loss over a cascade, but some studies have also measured the time between steps¹⁴. This is very important for TBM, which can be rapidly progressive if no diagnosis is made or treatment started. Time between onset of symptoms and access to appropriate services, presentation and LP, and diagnosis and antibiotic treatment could be prioritized for measurement.

Patient pathway analysis

Patient pathway studies are used to identify factors that account for losses across a cascade of care. Patient-pathway analyses assess the alignment of health systems' infrastructure (e.g. diagnostic, referral and treatment capacity) with patients' care-seeking behavior²⁰. Patient pathways of TBM patients are probably highly variable. Even in relatively well-organized health systems, with good access to healthcare, the trajectory

of TBM patients can be short and tragic. As TBM usually has a subacute or non-specific clinical presentation, similar to pulmonary TB¹², many patients may pay multiple visits to different health practitioners, and in some patients eventually a diagnosis is made, while in others it is not. Similarly, some patients may be started on appropriate treatment and be retained to care but others not. Importantly, for some patients a successful pathway to diagnosis and treatment may be short, while in others there may be significant delays leading to unnecessary morbidity and mortality.

Patient pathway studies might help identify factors that account for losses and delays across the cascade of care for TBM, the first being access to appropriate health services. The initial presentation of TBM is non-specific, and its diagnostic work-up (different from other forms of TB) can only be done at secondary or tertiary hospitals. Therefore, the first challenge for a patient developing TBM is to reach such specialized health services in time. Patients (and their family members) may not consider the possibility of life-threatening brain infection, or may not have access to specialized services. For pulmonary TB, it is estimated that the majority of patients begin seeking care in informal (e.g. traditional or homeopathic doctors, and pharmacists) and private doctors⁵. This leads to considerable and unnecessary delays and costs to patients. For TBM and other forms of extrapulmonary TB, the situation may be even more difficult; in a recent study in India, only 12% of patients with extrapulmonary TB first sought medical advice, most patients visited three or more clinics, and the average delay to reaching

appropriate services was two months²¹. Even when appropriate services are reached, some patients may need repeated visits to such services, and the time it takes until a diagnosis is reached and treatment is started may vary considerably. Similarly, pathways may vary after hospital discharge.

Health systems factors

Many of the possible gaps in diagnosis and treatment of TBM are related to health systems factors. Health systems factors, such as the availability of the right facilities or workforce, health information, guidelines, drugs, financing, and organization of the health system can explain the wide variability in patient pathways, losses across the 'cascade of care' and delays across different settings and countries, and thereby the variable mortality of TBM.

Even though health systems are highly context-specific, they share certain characteristics that are essential for delivering good care. The World Health Organization (WHO) has proposed a framework with six 'building blocks' of health systems²². This WHO framework was adjusted to evaluate health systems factors for management of multi-drug resistant (MDR) TB²³. We used the nine domains of that study and our experience in Indonesia to illustrate health systems factors that may be relevant for TBM (Table 1).

The situation may be different in different settings, and as a first step, similar as was done for management of MDR-TB, the conceptual framework could be tailored further for TBM, and

Table 1. Theoretical framework of health systems factors that are likely to be relevant for tuberculosis meningitis (TBM).

Domain/parameter *	Factors possibly relevant for TBM in Indonesia **
Facilities and specialists	There is often a lack of trained doctors or other health staff with knowledge of neuro-infections. Many facilities lack high-level care, necessary laboratory tests and neuroimaging.
Incidence and outcome data	No programmatic data are collected for TBM incidence and outcome to help adjust policy or service delivery.
Available guidance and protocols	There is a national guideline for TBM, but translation of specific care components to patient management protocols is lacking.
Health systems financing	Universal health insurance does not cover cost needed for neuroimaging, critical care and rehabilitation. TBM likely inflicts catastrophic costs to patients and their families.
Health and social system organization	Efficiency of referral from primary/secondary care level is often difficult and slow. Follow-up of 'no shows' (e.g. by social workers) after discharge is not routine. Rehabilitation for neurological sequelae is hardly available in Indonesia.
Health systems regulation	Regulation related to health insurance often prohibits patient referral to specific (tertiary) care facilities.
Uninterrupted drug supply	Intravenous antimycobacterial drugs that may be helpful in unconscious patients are unavailable.
Public health information	Information related to TBM targeted to professionals or the general public is frequently lacking.
Behavior and attitude of health care workers (HCW)	HCW can feel 'hopeless' in light of the severity of TBM, or may stigmatize patients, especially when HIV co-infected.

* Adjusted from 23.

** Based on the authors' personal impression or experience²⁴, and not on systematic studies. The situation may be similar for many high-burden countries, but systematic studies are lacking.

questionnaires could be circulated to physicians involved in TBM management to help identify and possibly amend health systems issues. Single studies have evaluated some of the factors in Table 1. For instance, with respect to facilities necessary for TBM diagnosis, in a survey among Indonesian neurologists, only 74% mentioned that they had access to routine CSF analysis (cells, protein, glucose), and only 26% and 34% had access to CSF molecular testing and culture, respectively, to confirm TBM²⁴.

A health needs assessment to quantify gaps in care

A health needs assessment framework takes the measurement of indicators of performance across system parameters and quantifies the gaps in care, which vary between settings, against an 'ideal' system. It then considers, using pre-determined criteria, different options to fill each gap. We have previously used a public health framework to identify gaps between current and ideal practice for management of child-case TB contacts²⁵. Based on such an assessment, interventions that will help most in a particular setting can be selected; this concept is now examined for management of latent TB in a multi-country cluster-randomized clinical trial²⁶. Based on Table 1, performance indicators can be identified for TBM, such as: the availability of a neurologist trained in neuro-infections at a facility; the availability of appropriate diagnostics; and management protocols. Sometimes, assessment of policy-practice gaps results in simple action, like advocacy to hospital management for making certain laboratory tests available, like Xpert MTB/RIF or cryptococcal antigen testing on CSF (Darma Imran, personal experience). Or, if gaps are identified in ambulatory care after hospital discharge, development of a simple discharge protocol might help to ensure that medication is continued correctly, that ambulatory follow-up is ensured, and that patients and family are adequately counselled about compliance and possible disease complications that may occur later, such as toxicity or paradoxical worsening.

Possible next actions

Establishing the cascade of care for TBM, conducting a patient pathway analysis, and further study of health systems factors could help identify priority areas for further action to improve care and outcomes for TBM patients. The health needs assessment as described in the previous paragraph is likely to reveal a lack of knowledge and awareness about TBM and other brain infections among the general public, contributing to late presentation. Immediate action might therefore include some kind of community engagement to stimulate earlier presentation. Such engagement should probably also involve community clinics and doctors; in a cohort study in Jakarta, two thirds of patients presenting at a tertiary hospital with a possible central nervous system infection were self-referrals who had visited other health providers²⁷.

Based on our experience, further study is also likely to identify significant gaps in diagnosis and treatment once patients reach tertiary facilities. Different interventions might be needed to address these gaps, but even without a systematic assessment, development and socialization of management protocols seems a rational thing to do. This might for instance include simple

guidance and socialization of indications, contraindications and optimal yield from LPs in high-endemic settings.

Two things may complicate efforts to improve the outcome of TBM using our proposed approach focusing on the cascade of care and quality of services. First, brain infections including TBM are relatively rare, and as such – although they have a huge and often devastating impact on individual patients and their families – have less priority for policy makers. For instance, for national programs, TBM has no priority as it does not pose a public health risk in terms of transmission.

Second, care for TBM is very complex. It has previously been shown that it is not individual factors that make or break a technology implementation effort but the interaction between these individual factors. For interventions (like standard care for TBM) or innovations (new tools for TBM management), the more complex a setting in which it is introduced (like a busy emergency room in a high-burden setting), the less likely it is to be successfully adopted, scaled up, spread, and sustained^{28,29}. Implementing new or complex medical care beyond individual facilities can be very difficult, especially in low-resource settings. In an effort to address this challenge, a recent publication describes the use of the 'nonadaptation, abandonment, scale-up, spread and sustainability' (NASSS) framework for complex interventions³⁰. This framework, based on an extensive literature review of previous technology implementation frameworks and empirical study, helps raise challenges, classified as 'simple', 'complicated' or 'complex'. Care for TBM is definitely not simple, but this framework might help address some of the interacting challenges related to the adoption scale-up, distant spread, and long-term sustainability of care for TBM patients.

Conclusion

Mortality of TBM is highly variable 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. To address this knowledge gap, we have proposed a cascade of care and patient pathway analysis to address factors underlying gaps and delays in this cascade, and nine health systems domains that we think are relevant for TBM and that could help design a structured health needs assessment to address gaps in care. This theoretical framework will hopefully lead to more health system research and improved care for patients suffering from TBM as the most dramatic manifestation of TB.

Data availability

No data are associated with this article.

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References

- World Health Organization: **Global tuberculosis report 2018**. Geneva, Switzerland: World Health Organization; 2018. 2018.
[Reference Source](#)
- Cresswell FV, Te Brake L, Atherton R, *et al.*: **Intensified antibiotic treatment of tuberculosis meningitis**. *Expert Rev Clin Pharmacol*. 2019; **12**(3): 267–288.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Török ME, Nguyen DB, Tran TH, *et al.*: **Dexamethasone and long-term outcome of tuberculous meningitis in Vietnamese adults and adolescents**. *PLoS One*. 2011; **6**(12): e27821.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- van Laarhoven A, Dian S, Ruesen C, *et al.*: **Clinical Parameters, Routine Inflammatory Markers, and LTA4H Genotype as Predictors of Mortality Among 608 Patients With Tuberculous Meningitis in Indonesia**. *J Infect Dis*. 2017; **215**(7): 1029–1039.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Reid MJA, Arinaminpathy N, Bloom A, *et al.*: **Building a tuberculosis-free world: The Lancet Commission on tuberculosis**. *Lancet*. 2019; **393**(10178): 1331–1384.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Heemskerk AD, Donovan J, Thu DDA, *et al.*: **Improving the microbiological diagnosis of tuberculous meningitis: A prospective, international, multicentre comparison of conventional and modified Ziehl-Neelsen stain, GeneXpert, and culture of cerebrospinal fluid**. *J Infect*. 2018; **77**(6): 509–515.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Chaidir L, Annisa J, Dian S, *et al.*: **Microbiological diagnosis of adult tuberculous meningitis in a ten-year cohort in Indonesia**. *Diagn Microbiol Infect Dis*. 2018; **91**(1).
[PubMed Abstract](#) | [Publisher Full Text](#)
- Bahr NC, Nuwagira E, Evans EE, *et al.*: **Diagnostic accuracy of Xpert MTB/RIF Ultra for tuberculous meningitis in HIV-infected adults: a prospective cohort study**. *Lancet Infect Dis*. 2018; **18**(1): 68–75.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Ruslami R, Ganien AR, Dian S, *et al.*: **Intensified regimen containing rifampicin and moxifloxacin for tuberculous meningitis: an open-label, randomised controlled phase 2 trial**. *Lancet Infect Dis*. 2013; **13**(1): 27–35.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Heemskerk AD, Bang ND, Mai NT, *et al.*: **Intensified Antituberculosis Therapy in Adults with Tuberculous Meningitis**. *N Engl J Med*. 2016; **374**(2): 124–134.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Donovan J, Figaji A, Imran D, *et al.*: **The neurocritical care of tuberculous meningitis**. *Lancet Neurol*. 2019; **18**(8): 771–783.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Agins BD, Ikeda DJ, Reid MJA, *et al.*: **Improving the cascade of global tuberculosis care: moving from the “what” to the “how” of quality improvement**. *Lancet Infect Dis*. 2019; pii: S1473-3099(19)30420-7.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Naidoo P, Theron G, Rangaka MX, *et al.*: **The South African Tuberculosis Care Cascade: Estimated Losses and Methodological Challenges**. *J Infect Dis*. 2017; **216**(suppl_7): S702–S713.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Soeroto AY, Lestari BW, Santoso P, *et al.*: **Evaluation of Xpert MTB-RIF guided diagnosis and treatment of rifampicin-resistant tuberculosis in Indonesia: A retrospective cohort study**. *PLoS One*. 2019; **14**(2): e0213017.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Thakur KT, Mateyo K, Hachaambwa L, *et al.*: **Lumbar puncture refusal in sub-Saharan Africa: A call for further understanding and intervention**. *Neurology*. 2015; **84**(19): 1988–1990.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Prasad K, Singh MB, Ryan H: **Corticosteroids for managing tuberculous meningitis**. *Cochrane Database Syst Rev*. 2016; **4**: CD002244.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Figaji AA, Fieggen AG: **The neurosurgical and acute care management of tuberculous meningitis: evidence and current practice**. *Tuberculosis (Edinb)*. 2010; **90**(6): 393–400.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Wilkinson RJ, Rohlwick U, Misra UK, *et al.*: **Tuberculous meningitis**. *Nat Rev Neurol*. 2017; **13**(10): 581–598.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Heemskerk AD, Nguyen MTH, Dang HTM, *et al.*: **Clinical Outcomes of Patients With Drug-Resistant Tuberculous Meningitis Treated With an Intensified Antituberculosis Regimen**. *Clin Infect Dis*. 2017; **65**(1): 20–28.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Hanson CL, Osberg M, Brown J, *et al.*: **Conducting Patient-Pathway Analysis to Inform Programming of Tuberculosis Services: Methods**. *J Infect Dis*. 2017; **216**(suppl_7): S679–S685.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Purohit MR, Purohit R, Mustafa T: **Patient Health Seeking and Diagnostic Delay in Extrapulmonary Tuberculosis: A Hospital Based Study from Central India**. *Tuberc Res Treat*. 2019; **2019**: 4840561.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- World Health Organization: **Monitoring the building blocks of health systems: a handbook of indicators and their measurement strategies**. 2010.
[Reference Source](#)
- de Vries G, Tsovala S, Anderson LF, *et al.*: **Health system factors influencing management of multidrug-resistant tuberculosis in four European Union countries - learning from country experiences**. *BMC Public Health*. 2017; **17**(1): 334.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Imran D, Satiti S, Sugianto P, *et al.*: **Barriers to diagnosis and management of CNS infections in Indonesia**. *Neurology*. 2019; **92**(2): 104–106.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Rutherford ME, Ruslami R, Anselmo M, *et al.*: **Management of children exposed to *Mycobacterium tuberculosis*: a public health evaluation in West Java, Indonesia**. *Bull World Health Organ*. 2013; **91**(12): 932–941A.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Oxlade O, Trajman A, Benedetti A, *et al.*: **Enhancing the public health impact of latent tuberculosis infection diagnosis and treatment (ACT4): protocol for a cluster randomised trial**. *BMJ Open*. 2019; **9**(3): e025831.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Imran D, Estiasari R, Maharani K, *et al.*: **Presentation, etiology, and outcome of brain infections in an Indonesian hospital: A cohort study**. *Neurol Clin Pract*. 2018; **8**(5): 379–388.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Atun R, de Jongh T, Secci F, *et al.*: **Integration of targeted health interventions into health systems: a conceptual framework for analysis**. *Health Policy Plan*. 2010; **25**(2): 104–111.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Cresswell K, Sheikh A: **Organizational issues in the implementation and adoption of health information technology innovations: an interpretative review**. *Int J Med Inform*. 2013; **82**(5): e73–86.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Greenhalgh T, Wherton J, Papoutis C, *et al.*: **Beyond Adoption: A New Framework for Theorizing and Evaluating Nonadoption, Abandonment, and Challenges to the Scale-Up, Spread, and Sustainability of Health and Care Technologies**. *J Med Internet Res*. 2017; **19**(11): e367.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)

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Lutgarde Lynen 

Department of Clinical Sciences, Institute of Tropical Medicine, Antwerp, Belgium

I agree with the revisions. Thanks, It can be indexed in its revised form.

Competing Interests: I have submitted a paper with Tom Boyles "Decision-Making in the Diagnosis of Tuberculous Meningitis" to Wellcome Open Research. Some of my comments are related to that paper.

Reviewer Expertise: HIV, TB, clinical decision making

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.

Version 1

Reviewer Report 27 January 2020

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Lutgarde Lynen 

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Page 3 second column:

1. The cascade of care for TB meningitis, a hypothetical framework. The main problem here is

how to determine the number of patients with TB meningitis in the community, your denominator? We know how many are diagnosed, but we have no idea on how many are unnoticed. How would you estimate the denominator?

2. You mention that a problem of the cascade is that it only applies to an ideal scenario, and that it may not be available in all settings. I do not entirely agree, you may also discuss the appropriate level of care adapted to the available resources.
3. In the second loss of the cascade I would also add the **awareness** among health care workers to think about tuberculosis, as the initial step in the diagnostic process. Many patients with grade 1 BMRC severity of TBM (GCS normal and no focal signs) may never get a diagnostic work-up started.
4. And at the end (part of the second loss), failure to make a diagnosis of **presumptive TB meningitis**, because all tests are negative. No test is sensitive enough to rule out TB meningitis, and clear guidance should be given to health care workers when to go for a presumptive TB diagnosis and treatment. In HIV-TB co-infected patients, the guidelines to improve the diagnosis of smear-negative TB in HIV prevalent settings (WHO 2006) led to a reduction in diagnostic delay and treatment delay^{1,2}.

The required probability of TBM to start TB treatment ranges from 0-50% depending on the severity of the presentation³. Uniform case definitions of probable and possible TBM exist for research purposes, why not starting to use them in clinical care^{4,5}? Prediction rules including these case definitions allow for the calculation of the post-test probability and may help in taking the decision to treat presumptive TBM⁶. They can be used in settings where an LP can be done.

Theoretical framework of health systems

I fear that some bias may have crept in, because the author is a neurologist. As you mention yourself, TBM may not be seen as a public health priority by policy makers. Therefore we have to be careful to propose a theoretical framework and performance indicators that are realistic. I have personally never had access to a neurologist when working in Asia or Africa, and I still was able (I think) to treat patients with TB meningitis. In many settings referral of a patient to a tertiary care hospital will not be feasible or acceptable. General doctors, infectious diseases specialists, TB specialists, clinical officers and nurses can be trained to do an LP, and use the information in a diagnostic rule to reach a certain probability of TB meningitis leading to empiric or confirmed diagnosis.

Therefore, instead of the neurologist trained in neuro-infections I would propose availability of appropriate diagnostics (whatever level) and staff trained to use adapted guidelines for diagnosis and treatment at each level.

In general, before proposing improvements of management of TBM, using a theoretical health systems framework, it would be good to reach consensus on the indicators to measure, taking into account a broader perspective than the tertiary care level. Which intervention across the cascade will have the highest impact?

References

1. Koole O, Thai S, Khun K, Pe R, et al.: Evaluation of the 2007 WHO Guideline to Improve the

Diagnosis of Tuberculosis in Ambulatory HIV-Positive Adults. *PLoS ONE*. 2011; **6** (4). [Publisher Full Text](#)

2. Abebe G, Deribew A, Apers L, Abdissa A, et al.: Evaluation of the 2007 WHO guideline to diagnose smear negative tuberculosis in an urban hospital in Ethiopia. *BMC Infectious Diseases*. 2013; **13** (1). [Publisher Full Text](#)

3. Boyles T, Locatelli I, Senn N, Ebell M: Determining clinical decision thresholds for HIV-positive patients suspected of having tuberculosis. *Evidence Based Medicine*. 2017; **22** (4): 132-138 [Publisher Full Text](#)

4. Marais B, Heemskerk A, Marais S, van Crevel R, et al.: Standardized methods for enhanced quality and comparability of tuberculous meningitis studies. *Clinical Infectious Diseases*. 2016. [Publisher Full Text](#)

5. Solomons R, Wessels M, Visser D, Donald P, et al.: Uniform Research Case Definition Criteria Differentiate Tuberculous and Bacterial Meningitis in Children. *Clinical Infectious Diseases*. 2014; **59** (11): 1574-1578 [Publisher Full Text](#)

6. Boyles T: Xpert Ultra's place in the diagnosis of tuberculous meningitis. *The Lancet Infectious Diseases*. 2018; **18** (3): 248-249 [Publisher Full Text](#)

Is the topic of the review discussed comprehensively in the context of the current literature?

Yes

Are all factual statements correct and adequately supported by citations?

Yes

Is the review written in accessible language?

Yes

Are the conclusions drawn appropriate in the context of the current research literature?

Partly

Competing Interests: I have submitted a paper with Tom Boyles "Decision-Making in the Diagnosis of Tuberculous Meningitis" to Wellcome Open Research. Some of my comments are related to that paper.

Reviewer Expertise: HIV, TB, clinical decision making

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, however I have significant reservations, as outlined above.

Author Response 28 Jan 2020

reinout van crevel, Nuffield Department of Medicine, University of Oxford, Oxford, UK

Dear editor

Please below find our point by point to the reviewer's comments:

1. The cascade of care for TB meningitis, a hypothetical framework. main problem here is how to determine the number of patients with TB meningitis in the community, your denominator? We know how many are diagnosed, but we have no idea on how many are unnoticed. How would you estimate the denominator?

Answer: *We think this will be impossible. It is a relatively rare disease, that is hard to diagnose and may start with non-specific symptoms. Barriers to health access and diagnosis may result in patient dying in the community, or with a false diagnosis; it is even hard to establish the number of patients **diagnosed** with TB meningitis.*

1. You mention that a problem of the cascade is that it only applies to an ideal scenario, and that it may not be available in all settings. I do not entirely agree, you may also discuss the appropriate level of care adapted to the available resources.

Answer: This is a valid point. We now write: It should be noted that this cascade is not based on universal international guidelines but rather represents an 'ideal scenario' that in high-burden settings may only exist in some centers, with a qualified or experienced team of professionals and appropriate services.

1. In the second loss of the cascade I would also add the **awareness** among health care workers to think about tuberculosis, as the initial step in the diagnostic process. Many patients with grade 1 BMRC severity of TBM (GCS normal and no focal signs) may never get a diagnostic work-up started.

Answer: This is a valid point we now write: Awareness among health care workers to think about brain infections and tuberculosis is needed, and an appropriate diagnostic workup has to be done

1. And at the end (part of the second loss), failure to make a diagnosis of **presumptive TB meningitis**, because all tests are negative. No test is sensitive enough to rule out TB meningitis, and clear guidance should be given to health care workers when to go for a presumptive TB diagnosis and treatment. In HIV-TB co-infected patients, the guidelines to improve the diagnosis of smear-negative TB in HIV prevalent settings (WHO 2006) led to a reduction in diagnostic delay and treatment delay^{1,2}.

Answer: we now write Unfortunately, no single diagnostic CSF can rule out TBM. The required probability of TBM to start TB treatment ranges from 0-50% depending on the severity of the presentation³. Uniform case definitions of probable and possible TBM exist for research purposes, why not starting to use them in clinical care^{4,5}? Prediction rules including these case definitions allow for the calculation of the post-test probability and may help in taking the decision to treat presumptive TBM⁶. They can be used in settings where an LP can be done.

Answer: We agree with the reviewer that a presumptive diagnosis should lead to treatment (we write: After a presumptive or confirmed diagnosis of TBM is made, treatment should be started ..), **and severity will dictate the level of uncertainty we are ready to accept (we have added : , "...especially for critically ill patients"** **the international case definitions are not based on empiric data and have not been cross-validated between settings. This is a complex matter in the absence of a gold standard, and we feel this is a bit beyond the scope of this article.**

Theoretical framework of health systems

I fear that some bias may have crept in, because the author is a neurologist. As you mention yourself, TBM may not be seen as a public health priority by policy makers. Therefore we have to be careful to propose a theoretical framework and performance indicators that are realistic. I have personally never had access to a neurologist when working in Asia or Africa, and I still was able (I think) to treat patients with TB meningitis. In many settings referral of a patient to a tertiary care hospital will not be feasible or acceptable. General doctors, infectious diseases specialists, TB specialists, clinical officers and nurses can be trained to do an LP, and use the information in a diagnostic rule to reach a certain probability of TB meningitis leading to empiric or confirmed diagnosis.

Therefore, instead of the neurologist trained in neuro-infections I would propose availability of appropriate diagnostics (whatever level) and staff trained to use adapted guidelines for diagnosis and treatment at each level.

Answer: we have and replaced “neurologists” with “doctors or other health staff”

In general, before proposing improvements of management of TBM, using a theoretical health systems framework, it would be good to reach consensus on the indicators to measure, taking into account a broader perspective than the tertiary care level. Which intervention across the cascade will have the highest impact?

Answer: we totally agree and already wrote: “.. Based on such an assessment, interventions that will help most in a particular setting can be selected”

We thank this reviewer for her helpful comments which we hope we have addressed appropriately.

On behalf of our co-authors

Reinout van Crevel

Competing Interests: no conflict

Reviewer Report 24 January 2020

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The authors are reporting on a very important topic-tuberculous meningitis, a disease with high fatality. However, the review elaborates mainly on the factors affecting the cascade of care for TBM rather than proposing an actual cascade of care to guide clinicians.

It was also not clear how much patient factors such as stigma influenced the pre-admission and post discharge flow since TB related stigma is still one of the greatest barriers to TB control in the developing world.

With regards to the proposed cascade in figure 1, what informed the decline rate across the 7 care points? Is the loss at a steady, equal rate? Also, why is y-axis labelled as survival and not frequency or number of patients?

Is the topic of the review discussed comprehensively in the context of the current literature?

Yes

Are all factual statements correct and adequately supported by citations?

Yes

Is the review written in accessible language?

Yes

Are the conclusions drawn appropriate in the context of the current research literature?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Clinical and epi-immunology of tuberculosis and its co-infections or co-morbidities

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.
