



REVIEW

Decision-making in the diagnosis of tuberculous meningitis

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Tom H. Boyles ^{1,2}, Lutgarde Lynen ³, James A. Seddon ^{4,5},
Tuberculous Meningitis International Research Consortium

¹ANOVA Health Institute, Johannesburg, South Africa

²Infectious and Tropical Diseases, London School of Hygiene & Tropical Medicine, London, UK

³Department of Clinical Sciences, Institute of Tropical Medicine, Antwerp, Belgium

⁴Department of Infectious Diseases, Imperial College London, London, UK

⁵Desmond Tutu TB Centre Department of Paediatrics and Child Health, Stellenbosch University, Stellenbosch, South Africa

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Abstract

Tuberculous meningitis (TBM) is the most devastating form of tuberculosis (TB) but diagnosis is difficult and delays in initiating therapy increase mortality. All currently available tests are imperfect; culture of *Mycobacterium tuberculosis* from the cerebrospinal fluid (CSF) is considered the most accurate test but is often negative, even when disease is present, and takes too long to be useful for immediate decision making. Rapid tests that are frequently used are conventional Ziehl-Neelsen staining and nucleic acid amplification tests such as Xpert MTB/RIF and Xpert MTB/RIF Ultra. While positive results will often confirm the diagnosis, negative tests frequently provide insufficient evidence to withhold therapy. The conventional diagnostic approach is to determine the probability of TBM using experience and intuition, based on prevalence of TB, history, examination, analysis of basic blood and CSF parameters, imaging, and rapid test results. Treatment decisions may therefore be both variable and inaccurate, depend on the experience of the clinician, and requests for tests may be inappropriate. In this article we discuss the use of Bayes' theorem and the threshold model of decision making as ways to improve testing and treatment decisions in TBM. Bayes' theorem describes the process of converting the pre-test probability of disease to the post-test probability based on test results and the threshold model guides clinicians to make rational test and treatment decisions. We discuss the advantages and limitations of using these methods and suggest that new diagnostic strategies should ultimately be tested in randomised trials.

Keywords

Tuberculosis Meningitis Diagnosis Threshold Decision

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1. **David W. Dowdy** , Johns Hopkins
Bloomberg School of Public Health,
Baltimore, USA
2. **James J.C. Nuttall** , University of Cape
Town, Cape Town, South Africa
3. **Zongde Zhang**, Beijing Chest Hospital,
Capital Medical University, Beijing, China

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



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Corresponding author: Tom H. Boyles (tomboyles@yahoo.com)

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Introduction

Tuberculous meningitis (TBM) is the most devastating form of tuberculosis (TB) with more than 100,000 new cases occurring each year¹. Most cases of TBM are not diagnosed and mortality without treatment approaches 100%. Outcomes are poor, even with treatment, particularly in children and patients who are co-infected with HIV. Of children who receive treatment, 20% die and over half of survivors have long-term neurodisability². For individuals living with HIV, TBM mortality is around 60%, even when treatment is initiated^{3–5}. Delayed diagnosis and treatment are important risk factors for poor outcome and yet diagnosis can be difficult. Clinical and laboratory results commonly overlap with other diagnoses and cerebrospinal fluid (CSF) cell counts, glucose levels and protein levels are not diagnostic for TBM; but rather provide suggestive characteristics that indicate the diagnosis. These parameters can also be normal in up to 5% of culture-confirmed cases⁶. Culture of *Mycobacterium tuberculosis* from the CSF occurs in around a half of adults, but is less common in children⁷. While culture confirmation is an important part of the case definition of TBM⁸, it is too slow to be of value in making immediate treatment decisions.

The most widely available rapid tests are smear microscopy on CSF following conventional Ziehl–Neelsen staining (CZN) and recently introduced nucleic acid amplification tests (NAATs) such as Xpert MTB/RIF and Xpert MTB/RIF Ultra (Ultra; Cepheid, Sunnyvale, CA, USA). The specificity of these tests is very high, and treatment should be started in almost all cases if positive. Sensitivity, however, is lower. The sensitivity of CZN is highly operator dependent, ranging from 12% to 47% at different sites in a recent study⁹. The pooled sensitivity of Xpert MTB/RIF and Xpert MTB/RIF Ultra were 71% and 90% respectively, but were lower for patients with HIV (58% to 81%)¹⁰. As a result, in many scenarios a negative test result is insufficient evidence to withhold therapy. There are no studies of Ultra in children with suspected TBM.

A new framework is required around decision-making in the diagnosis of TBM. Given that all existing tests are imperfect, it is important that we understand when we should be undertaking these tests, what these tests are able to tell us, and how they might influence our decision-making around starting treatment. We also need to use this framework to understand the place of new tests as they are developed and evaluated. In this article we discuss the use of Bayes' Theorem, test parameters, such as likelihood ratios, and the concept of the *therapeutic threshold* to make better decisions in the field of TBM.

Conventional approach to diagnosing TBM

The conventional diagnostic approach begins with a clinical evaluation of the patient, involving history, examination and analysis of basic blood and CSF parameters. In large clinical cohorts comparing features of patients with TBM to those without, several clinical factors are more common in those with TBM (Table 1). These include young age, male sex, extrapyramidal movements, neck stiffness, longer duration of symptoms, focal neurological deficit (including cranial nerve palsy), higher temperature, and lower Glasgow Coma Scale score. HIV positivity, lower CD4 count, and lower serum sodium are also

more common in patients with TBM than controls. Important CSF parameters that might help discriminate those with TBM from those without are CSF appearance, total leukocytes, total neutrophils, total lymphocytes, protein, glucose, Gram stain, adenosine deaminase activity, lactate dehydrogenase, India ink stain and cryptococcal antigen. Other potentially helpful tests are brain imaging and the search for extra-neural TB¹¹.

Typically, clinicians estimate a probability of TBM based on the evidence that is available to them using experience and intuition. In addition to the clinical factors mentioned above, this also includes factors such as the prevalence of TB in the geographical region that the patient may have been infected, and evidence of exposure through a close contact with TB. Inevitably therefore, there is significant variability in these estimates depending on the experience of clinicians. To standardise decision making, there have been multiple attempts to develop and validate multivariable prediction models to calculate the probability of TBM in a reproducible way. At least 12 models have been published with area under receiver operator characteristic curve ranging from 0.90 to 0.99, but a major limitation is that the performance of these models is variable when they are validated in new populations and settings (Table 1). A major reason for this is case mix variation, meaning that the distribution of predictor variables such as HIV status, age, and the prevalence of TBM are variable. This can lead to differences in model performance, even when the value of predictors is consistent¹².

Conventionally, when new information in the form of test results or response to treatment becomes available, a clinician will update their estimate of the probability of TBM using experience and intuition. Ultimately, the clinician decides about the need to start, withhold, or stop TB therapy. Bayes' theorem is a mathematical approach for the process of updating probabilities based on new information, which gives insight into the intuitive decision making of clinicians¹³.

Bayes' theorem

Bayes' theorem describes the process of converting the pre-test probability of disease to the post-test probability based on new information becoming available, usually in the form of a test result. The information from the test is defined by the positive and negative likelihood ratios. The positive likelihood ratio is the probability of a person who has the disease testing positive, divided by the probability of a person who does not have the disease testing positive and ranges from 1 (no diagnostic value) to infinity (confirms the diagnosis when positive). The positive likelihood ratio can be calculated from a diagnostic accuracy study as sensitivity/ (1- specificity). The negative likelihood ratio is the probability of a person who has the disease testing negative divided by the probability of a person who does not have the disease testing negative and ranges from 0 (excludes the diagnosis when negative) to 1 (no diagnostic value). The negative likelihood ratio can be calculated from a diagnostic accuracy study as (1-sensitivity)/ specificity. Combining pre-test probability with the likelihood ratio gives the post-test probability, which is represented visually with a Fagan nomogram (Figure 1)^{14,15}.

Table 1. Published clinical diagnostic rules for the diagnosis of tuberculous meningitis (TBM). CSF=cerebrospinal fluid (adapted from Wilkinson *et al.*)¹.

| Publication | Population from which rule derived | Case comparison | Predictors of TBM | Area under receiver operator characteristic curve |
|--------------------------------------|--|------------------------------------|--|---|
| Kumar <i>et al.</i> ¹⁶ | Children from India | TBM versus other meningitis | Symptoms ≥ 7 days Optic atrophy Focal neurological deficit Extrapyramidal movements CSF leukocytes $< 50\%$ neutrophils | Not reported |
| Thwaites <i>et al.</i> ¹⁷ | Adults from Vietnam | TBM versus bacterial meningitis | Age < 36 years Blood leukocytes $< 15 \times 10^9/l$ Symptoms ≥ 6 days CSF leukocytes $< 750/mm^3$ CSF neutrophils $< 90\%$ | 0.99 |
| Youssef <i>et al.</i> ¹⁸ | Children and adults from Egypt | TBM versus bacterial meningitis | Symptoms > 5 days CSF leukocytes $< 1000/mm^3$ Clear CSF CSF lymphocytes $> 30\%$ CSF protein > 100 mg/l | Not reported |
| Cohen <i>et al.</i> ¹⁹ | Adults from Malawi (77% HIV-infected) | TBM versus cryptococcal meningitis | Low CSF opening pressure Neck stiffness Raised CSF leukocytes Low Glasgow Coma Scale score High fever | 0.87 |
| Patel <i>et al.</i> ²⁰ | Adults from South Africa (84% HIV-infected) | TBM versus other meningitis | CSF:blood glucose ratio ≤ 0.2 CSF lymphocytes $> 200/mm^3$ CD4+ cell count $< 200 \times 10^6/l$ Negative cryptococcal antigen test | Not reported |
| Hristea <i>et al.</i> ²¹ | Adults from Turkey | TBM versus viral meningitis | Symptoms ≥ 5 days MRC grade II or III CSF:blood glucose ratio < 0.5 CSF protein > 100 mg/dl | 0.977 |
| Vibha <i>et al.</i> ²² | Adults from India | TBM versus bacterial meningitis | Living in a rural area Symptoms ≥ 6 days Cranial nerve palsy Hemiplegia Clear CSF CSF neutrophils $< 75\%$ | 0.996 |
| Dendane <i>et al.</i> ²³ | Adults from Morocco | TBM versus bacterial meningitis | Female sex Symptoms ≥ 10 days Focal neurological deficits Blood leukocytes $< 15 \times 10^9/l$ Plasma sodium < 130 mmol/l CSF leukocytes $< 400/mm^3$ | 0.906 |
| Zhang <i>et al.</i> ²⁴ | Adults from China (all HIV-uninfected) | TBM versus cryptococcal meningitis | Female sex Reduced consciousness No visual or hearing loss Evidence of extraneural tuberculosis CSF leukocytes $\geq 68/mm^3$ CSF protein > 0.91 mg/dl | 0.931 |
| Qamar <i>et al.</i> ²⁵ | Children from Pakistan | TBM versus bacterial meningitis | Hydrocephalus on brain CT CSF leukocytes $< 800/mm^3$ CSF protein:glucose ratio ≥ 2 | 0.90 |
| Chusri <i>et al.</i> ²⁶ | Adults from Thailand with non-suppurative meningitis | TBM versus other meningitis | HIV infection Diabetes mellitus Symptoms < 14 days Hydrocephalus CSF ADA level > 10 IU | 0.95 |
| Lee S <i>et al.</i> ¹¹ | Adults from Korea | TBM versus viral meningitis | Serum sodium < 135 mmol/L CSF lactate dehydrogenase > 70 (U/L) CSF protein > 160 (mg/dL) Voiding difficulty Cranial nerve palsies | 0.90 |

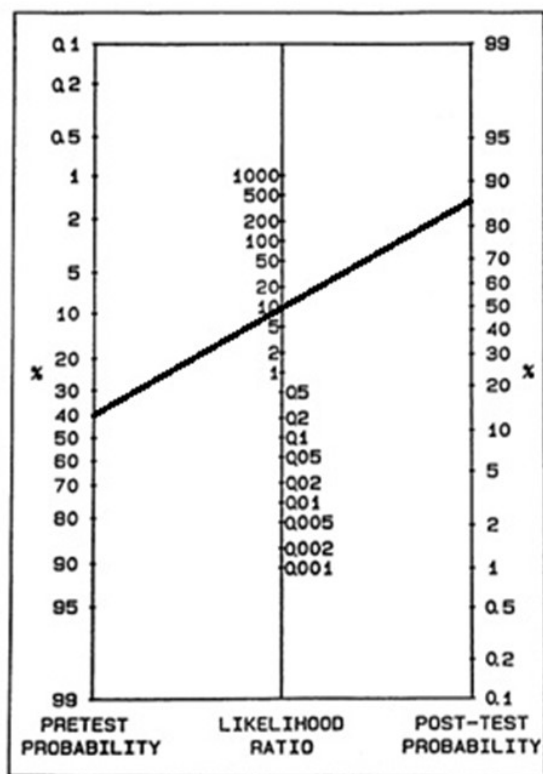


Figure 1. Fagan nomogram, the black line begins at pre-test probability (40%), travels through the positive likelihood ratio (10) to arrive at the post-test probability (85%). Values chosen for illustration only.

The threshold model of decision-making

Tests are only useful if the result is likely to influence patient management. The potential of a test to influence treatment decisions can be understood with the threshold model of decision making, which was first described in 1975²⁷. Pauker and Kassirer first described the *therapeutic threshold*, which is the probability of disease at which the clinician feels indifference between treating or not treating a patient when no further diagnostic tests are available. It can also be defined as the probability at which the risks and benefits of treatment, such as drug toxicity, clinical cure, and the ability to stop other empiric therapies, balance the risks and benefits of no treatment, such as progression of untreated disease and the avoidance of drug toxicities. The *therapeutic threshold* can vary considerably from one condition to another and depends on the clinical condition of the patient, as the costs of withholding treatment from a severely ill patient are greater than in a less severely ill patient. It also varies depending on the subjective weight given to risks and benefits by individual clinicians and informed patients. It also changes over time if the patient's condition improves or deteriorates.

There is no consensus on the optimal method of determining the *therapeutic threshold*, despite multiple attempts by investigators to quantify this parameter^{28–32}. Only one attempt has been made to determine the therapeutic threshold for TBM. In this study, only adults with HIV co-infection were included and it

was found that the *therapeutic threshold* values ranged from 51.4% for a very stable patient to 0% for a very unstable patient³³. This means that clinicians felt that if the patient was clinically stable and the probability of TBM was <51.4% when no further tests were available, they would prefer a watch and wait approach to initiating empiric TBM therapy. For a very unstable patient the probability would have to be close to zero before they would use this approach, preferring to offer empiric therapy in most cases.

In 1980, Pauker and Kassirer introduced two further thresholds based on the availability of a single diagnostic test with imperfect accuracy, a situation that is common in TBM, namely a *test-treatment threshold* and a *test threshold*³². Most relevant to TBM is the *test-treatment threshold*, which is the point of equipoise regarding the decision to gather additional data by doing the test or to rule in the disease and initiate treatment without the need for a test. When the pre-test probability lies above *test-treatment threshold*, the post-test probability will lie above the *therapeutic threshold* even if the test is negative and so the test will not influence the decision to initiate therapy.

This is illustrated in Figure 2. In this example, the *therapeutic threshold* and negative likelihood ratio have been determined empirically to be 2% and 0.1 respectively. The line from 2%

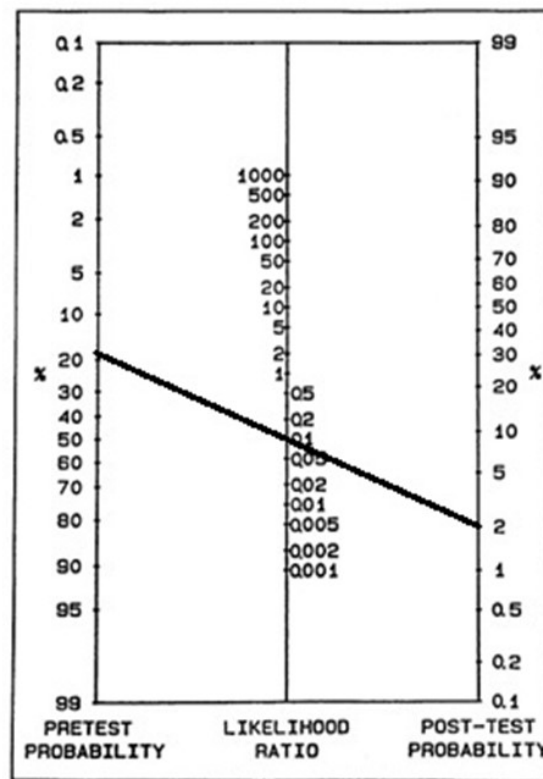


Figure 2. Fagan nomogram illustrating a realistic tuberculous meningitis scenario. The therapeutic threshold (post-test probability) is 2% and negative likelihood ratio 0.01. The pre-test probability is 20% which defines the test-treatment threshold as any pre-test probability greater than 20% will give a post-test probability above 2% and will not influence the decision to initiate therapy.

post-test probability (equated to the *therapeutic threshold* in our example), passes through the likelihood ratio of 0.1 and intersects the pre-test probability at 20%. This defines the *test-treatment threshold*, as at any pre-test probability greater than 20%, a negative test will give a post-test probability above 2%, and treatment should be started regardless of the result. It follows that for any given *therapeutic threshold* and negative likelihood ratio, the *test-treatment threshold* can be recalculated using Bayes' theorem. The *test-treatment threshold* is an important concept in decision-making for TBM and other diseases. Testing will sometimes be appropriate even when the pre-test probability is above the *test-treatment threshold*, for example to determine whether other diagnoses should be pursued or to detect drug resistance, but it is important that treatment is initiated even if the test is negative. (Figure 3).

Pauker and Kassirer defined the *test threshold* as the point of equipoise regarding the decision to rule out the disease or gather additional data by performing a test³². For TBM, the *test threshold* is of less relevance when CZN or Ultra are available as any positive test will mean that treatment should be initiated. In practice, the *test threshold* for TBM is influenced largely by the availability of resources. Use of the threshold model of decision-making has the potential to improve treatment decisions and reduce the costs associated with unnecessary tests, which can be financial or clinical. It also reduces the likelihood of clinical errors occurring, such as a clinician being unduly influenced by a negative Xpert Ultra and withholding TB treatment, when the probability of disease remains above *therapeutic threshold*. However, the model is based on several assumptions that are not always met and has important limitations.

One limitation is that it relates to a single cause for the patient's symptoms, with a single definitive treatment. The original example given by Pauker and Kassirer was a patient with right iliac fossa pain who may or may not require an operation for

appendicitis, with an implicit assumption that a cause of the symptoms other than appendicitis was of limited clinical significance²⁷. However, patients with clinical features in keeping with TBM often have several important competing diagnoses, such as cryptococcal, viral, or bacterial meningitis, which complicate decision-making. So, while a positive or negative test result may not influence the decision to initiate treatment for TBM, it may influence the probability of competing diagnoses. For example, a positive CZN or Ultra may allow treatments for alternative conditions, such as antibiotics to be confidently withheld. Similarly, a negative test for TBM may not mean that TB treatment is withheld, but it may increase the probability of alternative diagnoses and therefore prompt further testing or empiric treatments (Figure 4). It is also possible that a positive test may result in the initiation of treatment at an earlier stage than if the diagnosis is not confirmed. For TBM, any delay in treatment initiation can have severe consequences.

Complexity also arises with the use of NAATs that answer more than one question. For example, Xpert Ultra sometimes provide additional useful information about the presence of rifampicin resistance, which has important implications for the choice of drug regimen. It could be argued that Ultra should be performed regardless of the pre-test probability of TBM, as a finding of rifampicin resistance will always influence patient management. In practice, the decision to use Ultra purely as a test for rifampicin resistance should be based on local prevalence, patient factors such as previous TB treatment, and availability of resources.

A final aspect of clinical care, not addressed by the threshold model of clinical decision-making, is the inherent value to patients, clinicians and researchers in confirming a diagnosis. For patients, a confirmed test result may increase confidence in the diagnosis, and consequently their willingness to complete long and sometimes unpleasant treatment. For clinicians, a confirmed diagnosis reduces the time, effort, risk and cost

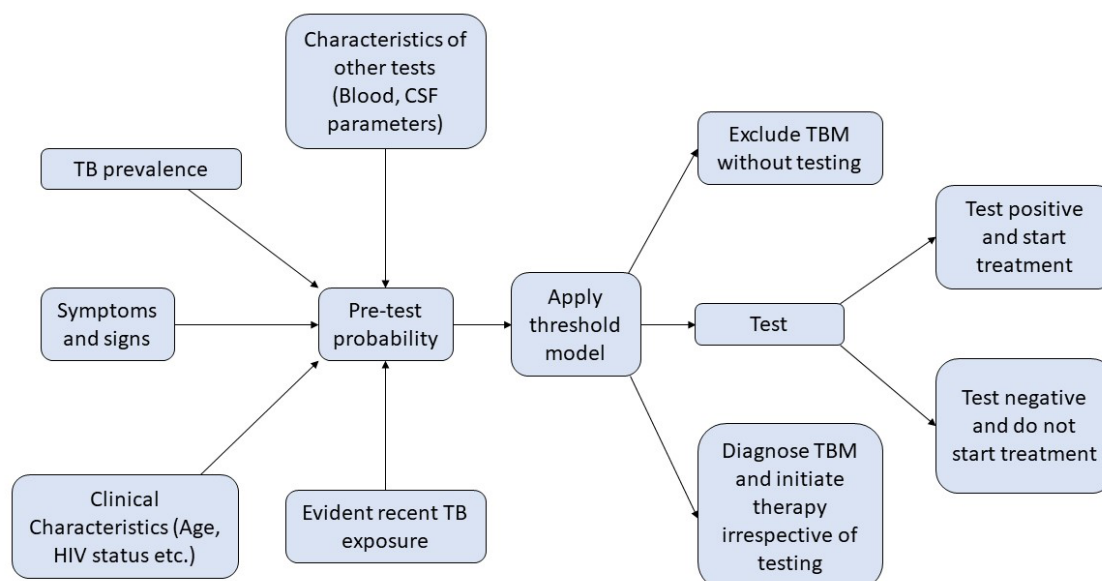


Figure 3. Using a threshold model to make decisions on whether to use a diagnostic test. TBM -Tuberculous meningitis, CSF – Cerebral spinal fluid.

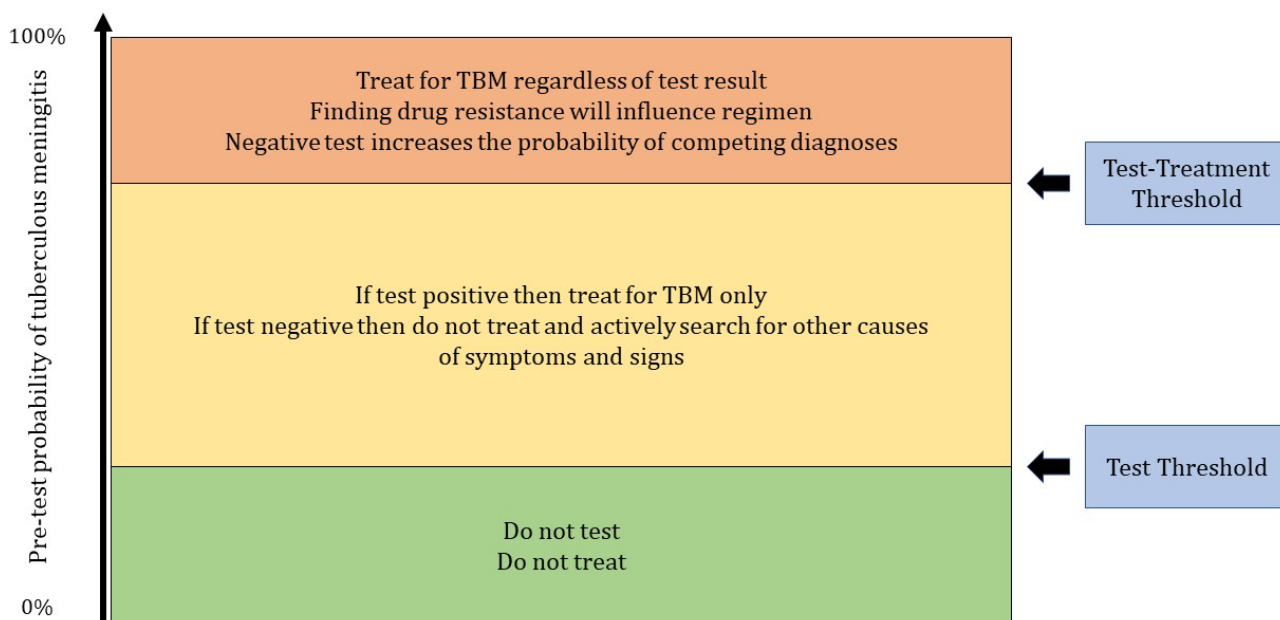


Figure 4. A visual depiction of how pre-test probability and both the test threshold and test-treatment threshold influence clinical decision making. TBM -Tuberculous meningitis.

associated with investigating for other causes of the symptoms and increases the confidence that the patient has in the ability of the clinician, likely improving the doctor-patient relationship. Finally, for epidemiological surveillance and both diagnostic and therapeutic research, a confirmed diagnosis increases the rigour of the scientific question being evaluated.

Everyday use of Bayes' theorem and the threshold model of decision-making

To apply Bayes' theorem and the threshold model of decision-making to TBM it is first necessary to develop validated clinical prediction models so that pre-test probability can be accurately determined from readily available data. A systematic review and individual patient data meta-analysis is currently underway to develop a prediction model that is generalizable to multiple geographical locations and different case mixes³⁴.

Next, it is necessary to determine the *therapeutic threshold* over the full range of patient disease severities, in children as well as adults, and in different geographical regions. Several methods have been used, prescriptive (based on calculations) or descriptive (derived from observing clinical practice). Prescriptive methods can be based purely on values of costs and benefits from the literature (e.g. expected utility theory)^{27,32} or include subjective values and socio-economic factors (e.g. regret based models and dual processing threshold models)³⁰. Descriptive methods rely on decision-making by clinicians when faced with clinical scenarios (e.g. derived thresholds and discrete choice experiments)^{28,29}. All methods have strengths and weaknesses and there is no consensus on the best approach. It may be that the optimal strategy is to combine multiple different methods.

Once the threshold has been established, diagnostic accuracy, in particular the likelihood ratios of available tests, needs to be determined using robust methods and be reported according to the STARD (Standards for the Reporting of Diagnostic Accuracy Studies) guideline³⁵. By combining the *therapeutic threshold*, negative likelihood ratios and pre-test probability it is possible to determine whether testing is necessary or whether empiric therapy should be offered.

An advantage of using Bayes' theorem and decision thresholds is that once the *therapeutic threshold* has been determined empirically, it is possible to recalculate *test threshold* and *test-treatment threshold* whenever a novel test has been developed, based on the likelihood ratios. In this way, it is possible to determine the likely impact of a novel test in terms of the proportion of patients in which it would be likely to influence treatment decisions.

Testing diagnostic strategies

While the use of the methods described above can theoretically improve treatment decisions and allow for the evaluation of novel tests based on diagnostic accuracy studies, it is important that diagnostic strategies are tested in real world randomised controlled trials³⁶. As an example, for a diagnostic strategy based on a clinical prediction model, the accuracy of a test and decision thresholds could be integrated into a smartphone application which gives advice to clinicians regarding the need to initiate empiric therapy, proceed to testing or hold off any testing or treatment. Such a strategy should be tested against the current standard of care in a randomised trial, possibly using a stepped wedge design, to determine if it can reduce mortality, morbidity, and costs.

Conclusion

The consequences of withholding therapy from a patient with TBM is almost certain death and so treatment decisions can be highly emotive for both clinicians and patients. Currently, we have only a basic understanding of the best predictors of TBM from history, examination, and CSF interpretation, particularly in children and HIV-positive patients who are the most vulnerable. While the introduction and widespread use of Ultra would be welcomed, the imperfect sensitivity means that treatment should be started in patients with a moderate pre-test probability, regardless of the test result. Even carrying out the test should be queried if treatment will be started irrespective of test result. While the use of Bayes' theorem and clinical decision thresholds has limitations, a clear understanding is key to evaluating existing and novel diagnostic strategies for TBM.

Data availability

Underlying data

No data are associated with this article

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Zongde Zhang

Laboratory for Drug Resistant Tuberculosis Research, Beijing Chest Hospital, Capital Medical University, Beijing, China

Tuberculous meningitis (TBM) is the most devastating form of tuberculosis and is difficult to diagnosis. Conventional tests such as Ziehl-Neelsen staining and Culture of Mycobacterium tuberculosis from the cerebrospinal fluid (CSF) is considered the most accurate test but is often negative. The positive rate of newly developed nucleic acid amplification tests such as Xpert MTB/RIF and Xpert MTB/RIF Ultra is still low.

The conventional diagnostic approach is to determine the probability of TBM using experience and intuition, based on prevalence of TB, history, examination, analysis of basic blood and CSF parameters, imaging, and rapid test results. Treatment decisions may therefore be both variable and inaccurate.

This article discusses the use of Bayes' theorem and the threshold model of decision making as ways to improve testing and treatment decisions in TBM. It will guide clinicians to make rational test and treatment decisions.

One minor suggestion: Could the authors please use Bayes' theorem to give an example by parameters of a TBM patient for a decision making?

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: Tuberculosis

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 14 September 2020

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James J.C. Nuttall 

Paediatric Infectious Diseases Unit, Red Cross War Memorial Children's Hospital and Department of Paediatrics and Child Health, University of Cape Town, Cape Town, South Africa

This article describes clinicians' decision-making processes about the diagnosis and initiation of treatment in patients with suspected tuberculous meningitis (TBM). The authors outline a mathematical framework based on understanding pre-and post-test probability and the threshold model of decision-making with the aim of making decision-making less subjective and more standardized. This is of particular relevance to TBM as microbiological confirmation of the diagnosis is constrained by the relatively low sensitivity of currently available tests, the delay to obtaining a culture result or lack of access to testing.

The therapeutic threshold for initiating TBM treatment in certain populations, such as children and HIV-infected patients in TB endemic regions, is appropriately low and the diagnostic utility of novel tests need to be critically evaluated in this context. An important contribution of the article is in highlighting how the pre-test probability of a diagnosis based on epidemiology and basic clinical and laboratory assessment impacts the interpretation of test results and the post-test probability of the diagnosis. The interpretation of negative tests results with low sensitivity should lead us to question whether or not the additional tests (for example nucleic acid amplification tests (NAAT)) are routinely justified as they may not alter clinical management and negative results have the potential to delay or miss a diagnosis of TBM resulting in treatment delays or inappropriate discontinuation of treatment. An acknowledged exception to a rigid test-treatment threshold approach includes the utility of positive NAAT tests not just in confirming a diagnosis of TBM but in rapid identification of drug-resistant TB in regions with high prevalence of rifampicin resistance and taking into account individual patient factors.

The variability in the performance of clinical prediction scoring systems in settings with different

case mixes is also highlighted. Lack of well-validated pre-test probability estimates based on clinical information is currently a limitation of using the test threshold and test-treatment threshold approaches. Although the authors reasonably assert that validated clinical prediction models and therapeutic thresholds must be developed before Bayes' theorem and threshold model of decision-making may be applied, this may be challenging in practice. Variability of TBM clinical presentations across geographical regions, age of patients, co-morbidities, clinical stage of disease at presentation, and the complexities of clinician experience and conscious or sub-conscious decision-making question whether or not a mathematically derived algorithmic approach will perform more reliably than conventional clinician-centred approaches.

The article is well-written and clearly expressed with useful figures and tables. I have no additional specific comments.

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: Paediatric HIV and TB

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.

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David W. Dowdy 

Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

This manuscript describes the application of Bayes' theorem and likelihood ratios to decision-

making in the context of tuberculous meningitis (TBM). In my opinion, the manuscript is well written and makes its primary points clearly. I have a number of minor suggestions, as detailed below, but nothing that would require major revision on the part of the authors. Congratulations to the authors on putting together such a clear description of decision-making in the diagnosis of TBM.

1. It could be useful for the authors to actually write out Bayes' theorem. This manuscript is written for a level of readership that could likely understand the theorem and its application.
2. In the first paragraph under "Bayes' theorem" subheading, some of the language is a little imprecise. The likelihood ratio, for example, is a ratio of likelihoods, not probabilities - and these likelihoods are not "of a person who has the disease testing positive", for example. Likelihoods could be described in terms of probabilities, but it's probably useful not to conflate the two.
3. I don't feel strongly about this, but the authors might want to describe Bayes' theorem in terms of pre-test and post-test odds, so that readers without access to the Fagan nomogram could still make the relevant calculations. (Again, I don't feel strongly, and recognize that this could over-complicate the manuscript.)
4. Figure 3 could probably be clarified further, illustrating the test threshold, the test-treatment threshold, and the test result itself. Many of the boxes to the left (feeding into "pre-test probability") could likely be combined into a single box with multiple bullets. Then, for example, after "apply threshold model", indications could be given as to which box corresponds to a pre-test probability below the test threshold, between the test threshold and test-treatment threshold, and above the test-treatment threshold. Similarly, after "test", indications could be more clear about the result of the test, separating the test result from the treatment decision. This could be done by placing labels on the corresponding lines or using boxes of a different shape, for example.
5. The authors argue that the test threshold is less relevant for TBM - but there are still a large number of patients for whom the pre-test probability of TBM is sufficiently low that testing for TBM is never even considered by the clinician. This might be clarified in the manuscript - it's not that the test threshold is irrelevant, but rather that virtually all patients in whom TBM might ever be considered are likely to have a pre-test probability that falls above that threshold.
6. On p.6, line 10 of column 2, perhaps use an example other than "such as antibiotics" - since antibiotics would be used for TBM as well. ("Antifungal agents", perhaps?)
7. The authors implicitly assume that all Xpert testing is via Xpert Ultra cartridges (for example, "Xpert Ultra sometimes provide*s* additional useful information about the presence of rifampicin resistance"). Many of these statements are true of the earlier Xpert MTB/RIF cartridge as well - it may be worthwhile simply using "Xpert" rather than "Xpert Ultra" for these statements.
8. In Figure 4, consider changing the y-axis to more appropriately reflect the actual values of the thresholds under consideration. For example, the authors argue that the test-treatment

threshold might reasonably be at a pre-test probability of 0.2 - but in this figure, it looks more like it is at 0.8.

9. In the section on "everyday use of Bayes' theorem...", the authors occasionally write as if a single threshold value can be established. Their nuanced description of different methods for setting thresholds is welcome, but they then proceed to suggest that a threshold can be established. At a minimum, they should acknowledge that this threshold may be different in different settings. But in reality, this threshold may vary at an individual patient or clinician level - and it may be worthwhile (briefly) discussing the pros and cons of this situation, relative to one in which a single agreed-upon threshold could be established.

Again, I would like to congratulate the authors on this important and well-written contribution, which reflects a tremendous amount of work. It has been a pleasure to review this piece, and I hope these comments are helpful.

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: epidemiology of tuberculosis

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.
