



Do high rates of empirical treatment undermine the potential effect of new diagnostic tests for tuberculosis in high-burden settings?

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In tuberculosis-endemic settings, patients are often treated empirically, meaning that they are placed on treatment based on clinical symptoms or tests that do not provide a microbiological diagnosis (eg, chest radiography). New tests for tuberculosis, such as the Xpert MTB/RIF assay (Cepheid, Sunnyvale, CA, USA), are being implemented at substantial cost. To inform policy and rationally drive implementation, data are needed for how these tests affect morbidity, mortality, transmission, and population-level tuberculosis burden. If people diagnosed by use of new diagnostics would have received empirical treatment a few days later anyway, then the incremental benefit might be small. Will new diagnostics substantially improve outcomes and disease burden, or simply displace empirical treatment? Will the extent and accuracy of empirical treatment change with the introduction of a new test? In this Personal View, we review emerging data for how empirical treatment is frequently same-day, and might still be the predominant form of treatment in high-burden settings, even after Xpert implementation; and how Xpert might displace so-called true-positive, rather than false-positive, empirical treatment. We suggest types of studies needed to accurately assess the effect of new tuberculosis tests and the role of empirical treatment in real-world settings. Until such questions can be addressed, and empirical treatment is appropriately characterised, we postulate that the estimated population-level effect of new tests such as Xpert might be substantially overestimated.

Introduction

Although several factors, including reduction of poverty and improved access to treatment, are crucial to reduce the global burden of tuberculosis, accurate and rapid diagnostic tests are a major unmet need. Xpert MTB/RIF—an automated real-time PCR platform for diagnosis of tuberculosis and detection of rifampicin resistance—is endorsed by WHO^{1,2} and the USA Food and Drug Administration and is undergoing implementation in several high-burden countries.³ Xpert is usable at the point-of-care^{4,5} and can detect about two-thirds of smear-negative tuberculosis cases in less than 2 h.⁶ The widespread implementation of Xpert will need substantial investment by international donors and governments of resource-poor countries.⁷

Modelling studies have indicated that accurate and potentially same-day tuberculosis diagnostics could reduce mortality by 20–35% by enabling earlier initiation of tuberculosis treatment.⁸ However, in HIV-endemic settings with a high tuberculosis-related mortality, clinicians compensate for the shortcomings of smear microscopy (frequently the only routinely available tuberculosis test) with the initiation of treatment on the basis of clinical symptoms, less specific tests (such as chest radiography), or absence of a response to broad-spectrum antibiotics.^{9,10} The initiation of treatment in the absence of a bacteriologically confirmed diagnosis is often referred to as empirical tuberculosis treatment.

In settings with high rates of empirical treatment, the effect of Xpert and other new tuberculosis tests such as the urine LAM (lipoarabinomannan) lateral flow assay¹¹ on individual-level outcomes and population-level epidemiology might be lower than predicted (table). Although the number of bacteriologically confirmed

diagnoses will increase with the roll-out of Xpert, how many of these newly detected patients would have been placed on treatment in the absence of Xpert, and when this would have occurred, is unknown. A proposed benefit of Xpert is improved outcomes (eg, lower mortality) in the sickest individuals; however, doctors are most likely to treat the same patients empirically (and treat them rapidly), such that the incremental benefit of Xpert might be diminished. Thus, certain key questions remain: will Xpert actually decrease the time to treatment initiation in high-burden settings with high rates of empirical treatment to an extent that affects outcomes for patients and ongoing transmission, or will it only replace empirical tuberculosis treatment that would otherwise occur near the same time? Will Xpert change empirical tuberculosis treatment practice, reduce the proportion of false-negative diagnoses, and reduce the proportion of patients with false-positive results who are placed on treatment inappropriately? Might some patients with tuberculosis but a negative Xpert result not receive treatment because of increased confidence in Xpert?

Empirical tuberculosis treatment initiation

Drivers of empirical treatment

The clinical basis for empirical tuberculosis treatment varies across settings in accordance with factors that contribute to a pretest probability of a patient having tuberculosis or a poor outcome or both, which is weighted against a variable and subjective threshold for treatment initiation (figure). Such factors include baseline tuberculosis prevalence (eg, among patients with HIV with advanced immunosuppression), a clinical presentation suggestive of tuberculosis, results (if any) of adjunctive but non-confirmatory diagnostic methods

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	Xpert MTB/RIF assay	Empirical treatment
Patient-level		
Time to diagnosis	Expected to be similar to smear microscopy (1–3 days); potentially offers same-day diagnosis but unlikely with centralised roll-out	Ranges from same-day to 1–2 weeks, depending on setting (highly setting and patient dependent); algorithms for smear-negative tuberculosis reduce the time to diagnosis, but not as much as do bacteriological tests
Time to treatment	Rapid (1–3 days)	Can be rapid in primary care for most patients, but will probably be 2–3 days behind Xpert (dependent on setting and patient); same-day empirical treatment can be common in primary care in Africa
Morbidity and mortality	Emerging data suggests that where high rates of rapid empirical treatment exist, the 1–3 day advantage in treatment initiation created by Xpert does not translate into improved patient-level morbidity; further research is needed	Rapid empirical treatment can reduce mortality, and clinicians empirically treat the sickest patients at the greatest risk; effect of Xpert on these endpoints might therefore be overestimated in such populations
Population-level		
Patients treated	90% sensitivity; susceptible to sampling error and paucibacillary disease	Sensitivity of 20–80%; can miss patients with tuberculosis who might not return after a negative test result at first visit
False-positive treatment without bacteriological confirmation of disease	Emerging data suggest a similar number of patients without microbiologically confirmed tuberculosis are placed on treatment when Xpert is available	Overtreatment for people without tuberculosis is a concern; the cost and health implications of inappropriate tuberculosis treatment needs further study
Transmission	Can reduce the infectious period, but perhaps by only a few days; whether this reduction is meaningful or cost effective is unclear; can detect rifampicin-resistant tuberculosis and thereby help to reduce its transmission, but this effect is dependent on availability of second-line drugs	Frequently started rapidly, but generally later than is treatment due to Xpert; when empirical treatment is initiated rapidly, the effect of Xpert on transmission might be overestimated because a few days difference in time to treatment is unlikely to make a meaningful difference; will not help to stop the spread of drug-resistant tuberculosis

Table: Expected effects of empirical tuberculosis treatment and Xpert MTB/RIF on key endpoints for the reduction of the tuberculosis epidemic in high-burden settings

(such as chest radiography), and concern that further delay might increase risk of severe morbidity or mortality. Inability to do microscopy or Xpert (as in sputum-scarce patients), substandard clinical training, and high likelihood of one-off encounters with patients might also drive the initiation of empirical treatment.^{11–13}

Accuracy

Because empirical tuberculosis treatment is not standardised, a global estimate of the accuracy of empirical treatment might not be measurable or useful. WHO developed an algorithm for smear-negative tuberculosis in high-burden HIV-endemic settings to standardise, and improve diagnosis and speed of initiation for, tuberculosis treatment.¹⁴ A meta-analysis¹⁵ of prospective assessments^{16–21} showed that empirical treatment has a pooled sensitivity of 61% (95% CI 55–67%) and specificity of 69% (66–72%) for smear-negative tuberculosis. In a post-mortem study²² in South Africa that was predominantly of individuals with HIV infection, the poor sensitivity of empirical treatment was shown by a tuberculosis prevalence of 50% for hospital inpatients not on treatment before death. In the TB-NEAT study,⁴ a randomised controlled trial of microscopy versus point-of-care Xpert as the initial test for 1500 patients from primary care clinics in South Africa, Tanzania, Zambia, and Zimbabwe, same-day microscopy combined with a WHO-compliant empirical treatment algorithm including chest radiography resulted in only 79% of culture-positive patients starting treatment. However, clinicians in real-world settings might do much better than standardised algorithms. For example, a review of Chinese programmatic data showed that only 3% of patients treated empirically for tuberculosis were confirmed to have an incorrect diagnosis.²³

Timing of empirical treatment initiation

Empirical treatment can be initiated at any stage in the diagnostic pathway: either before an available Xpert or microscopy result (eg, in very ill or immunosuppressed patients, or when a test is not available in peripheral facilities), a few days or weeks later (eg, after failure to respond to a short course of broad-spectrum antibiotics), or only once all available bacteriological tests, including culture if available, have failed to provide a positive result.²⁴ Data for timing of empirical treatment with Xpert availability are scarce; however, in the TB-NEAT study,⁴ 31% of patients with smear-negative tuberculosis who started treatment did so within 48 h of entering the health-care facility.

Advantages and disadvantages

Aside from averted diagnostic costs, several benefits—including reduced morbidity, mortality, and transmission—could result from empirical treatment if it leads to treatment initiation before a confirmed diagnosis is available. Other important advantages might be an effect on tuberculosis incidence (through the treatment of latent tuberculosis) and other bacterial infections.¹⁰ Empirical treatment without a definitive diagnosis can also cause important harms, including unnecessary cost, toxic effects, and inconvenience to people without tuberculosis, increased morbidity and mortality from other underlying diagnoses that are not considered, inability to collect information about drug resistance, stigmatisation of patients, and economic losses due to inappropriate tuberculosis diagnosis. This balance of harms and benefits depends on factors such as the specificity of empirical diagnosis (which can be low),²¹ relative cost of diagnosis versus treatment, and willingness of the clinician to

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