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Evidence Summaries

The accuracy of the Xpert[®] MTB/RIF assay for detecting pulmonary tuberculosis and rifampicin resistance in adults: Summary of the evidence and implications for public health programmes

Thambu David Sudarsanam^{a,*}, Prathap Tharyan^b

^a Professor of Medicine, Christian Medical College, Vellore 632002, Tamil Nadu, India

^b Professor of Psychiatry, Director, South Asian Cochrane Centre, Prof BV Moses & ICMR Centre for Research and Training in Evidence-Informed Healthcare and Health Policy, Christian Medical College, Vellore 632002, Tamil Nadu, India

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ABSTRACT

This review demonstrates that Xpert[®] is accurate in diagnosing pulmonary TB as well as detecting rifampicin resistance. None of the studies were done in the primary health care setting where the public health benefits are likely to be maximum. The studies used the older generations of Xpert[®]. It is that the performance of current Xpert G4, will be different. Caution has to be exercised in interpreting the results of rifampicin resistance, as this is influenced by baseline risk of MDR TB in that community & patient's individual risk. Cost will have a bearing on adoption of this test into control programmes.

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* Corresponding author.

E-mail addresses: thambu@cmcvellore.ac.in, thamsup@yahoo.com (T.D. Sudarsanam).

1. The evidence

A Cochrane diagnostic test accuracy systematic review and meta-analysis identified 18 studies where the Xpert MTB/RIF[®] (hereafter referred to as Xpert[®]), an automated, rapid, polymerase chain reaction (PCR) assay, was used as an initial test replacing smear microscopy (15 studies with 7517 participants) or as an add-on test following negative smear microscopy (14 studies with 5719 participants). The reference standard for pulmonary TB detection was culture; the reference standard for rifampicin resistance detection was phenotypic culture-based drug susceptibility testing. The majority of studies (56%) were performed in low- and middle-income countries, and trained technicians performed the test in reference laboratories in 17 studies.

When Xpert[®] was used as an initial test replacing smear microscopy, the pooled sensitivity was 88% (95% credible interval (CrI) 83%–92%), and pooled specificity was 98% (95% CrI 97%–99%). As an add-on test following a negative smear microscopy result, Xpert[®] had a pooled sensitivity of 67% (95% CrI 58%–74%) and pooled specificity of 98% (95% CrI 97%–99%).

In subgroup analyses, the pooled sensitivity was higher in 15 studies for adults with smear-positive, culture-positive TB (98%; 95% CrI 97%–99%) than for smear-negative, culture-positive TB (68%; 95% CrI 59%–75%). Among patients living with HIV infection in four studies, the pooled sensitivity was 80% (95% CrI 67%–88%), while sensitivity was 89% (95% CrI 81%–94%) in those without HIV infection. For rifampicin resistance detection (11 studies, 2340 participants), Xpert[®] achieved a pooled sensitivity of 94% (95% CrI 87%–97%), and specificity of 98% (97%–99%). Xpert[®] accurately differentiated TB from non-tuberculous mycobacteria (only 1/139 specimens misidentified). The number of people wrongly diagnosed by Xpert[®] to have rifampicin resistance would depend on the prevalence of rifampicin resistance and would be lower when this prevalence is high. At levels of accuracy in the studies reviewed, the wrong diagnosis of rifampicin resistance would increase by >40% if the prevalence of rifampicin resistance in the population tested decreased from 30% to 2%.

This review concluded that, “Xpert used as an initial diagnostic test for TB detection and rifampicin resistance detection in patients suspected of having TB, MDR-TB, or HIV-associated TB is sensitive and specific. Xpert may also be valuable as an add-on test following microscopy for patients who have previously been found to be smear-negative. An Xpert result that is positive for rifampicin resistance should be carefully interpreted and take into consideration the risk of MDR-TB in a given patient and the expected prevalence of MDR-TB in a given setting”. The review suggested that the increased use of the Xpert[®] test in routine programmatic and peripheral health care settings, and at the point of care in high TB burden countries, could provide evidence on the actual clinical impact of the test in detecting TB and rifampicin resistance.

2. Why is this question important?

- Tuberculosis (TB) is among the commonest infectious diseases in the world and contributes to a large amount of morbidity and mortality. Pulmonary TB is its common form of presentation. Early and accurate diagnosis is vital for both the patient’s well-being, and for the community as undiagnosed patients spread the disease. Early diagnosis of resistance is also vital to choose the correct treatment regimen. Sputum smears are known to have poor sensitivity and culture based resistance testing is cumbersome and time consuming. Rapid diagnostic tests that can both diagnose TB as well as confirm resistance are a potential answer to this problem.
- The Xpert[®] MTB/RIF assay uses an automated molecular technique (nucleic acid amplification using polymerase chain reaction (PCR)) to detect both *Mycobacterium tuberculosis* complex and rifampicin resistance in a single test generally within 2 h; the assay’s reagent, used to liquefy sputum, has the ability to kill TB bacteria, and therefore permits the test to be taken out of a reference laboratory and used nearer to the patient without bio-safety concerns.
- Xpert[®], if accurate, would help in earlier diagnosis and the opportunity to begin earlier, appropriate treatment; and provide opportunities to interrupt TB transmission, especially in developing countries.

Review on which this evidence summary is based:

Steingart KR, Sohn H, Schiller I, Kloda LA, Boehme CC, Pai M, Dendukuri N. Xpert[®] MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults. Cochrane Database of Systematic Reviews 2013, Issue 1. Art No 1: CD 009593. <http://dx.doi.org/10.1002/14651858.CD009593.pub2>. This summary presents an overview of the findings and the implications for low and middle income countries. For further details, please read the full review that can be downloaded, free of charge (through various funded provisions) in most parts of the world, from The Cochrane Library (www.thecochranelibrary.com).

What did the systematic review seek and what did they find?

Review objectives:

To determine summary estimates of the diagnostic accuracy of Xpert for the diagnosis of pulmonary TB and for detecting rifampicin resistance in adults.

	What did the review authors search for?	What did the review find?
Types of studies	Randomized controlled trials, cross-sectional, and cohort studies that used respiratory specimens to compare Xpert® with culture for detecting TB; and Xpert® with conventional phenotypic drug susceptibility testing for detecting rifampicin resistance. Excluded were case control studies, because these types of studies are prone to bias, in particular, studies enrolling patients with severe disease and healthy participants without disease.	The review included 18 studies conducted in 27 study centres. All studies used a cross-sectional study design. Of the 18 studies, 15 were included for meta-analysis for TB detection and 11 for rifampicin resistance detection.
Setting	Peripheral (typically district or sub-district laboratories or more decentralized peripheral microscopy centres); intermediate (typically regional laboratories); and central level (typically national or reference) laboratories. The authors were interested in studying the usefulness of the Xpert® test in peripheral health care settings that could satisfy the technical requirements for the test, such as an uninterrupted and stable electrical power supply (note: Xpert® is currently not intended for use at peripheral microscopy centres).	No studies were found that used Xpert® in peripheral health centres providing direct patient care (such as primary care clinics) and one study used the test in laboratories associated with district and subdistrict health centres and provincial hospitals. All the rest (17 studies) used reference laboratories. Two of the studies were international multicentre studies. Nineteen study centres (70%) in 10 studies (56%) were located in low-income or middle-income countries.
Participants	Adults aged 15 years and older.	The authors assumed that specimens obtained by gastric aspiration would be used for children and did not include studies using these specimens. They performed a sensitivity analysis for studies that did and did not report age.
Index test	A nucleic acid amplification test using PCR called Xpert®, done on sputum samples. The reference standard for TB detection was sputum culture for mycobacteria. The reference standard for rifampicin resistance detection was phenotypic drug susceptibility testing using conventional culture methods.	In 15 studies with 7517 participants, Xpert® was used as an initial test replacing smear microscopy. In 14 studies with 5719 participants, Xpert® was used as an add-on test following a negative smear microscopy. In 11 studies with 2340 participants, rifampicin resistance detection was evaluated. All the studies used earlier generation Xpert® assays (G1-3) as opposed to the currently available G4 assay.
Outcomes	The review's primary outcomes were the diagnostic accuracy (sensitivity and specificity) of the Xpert® test for TB detection and rifampicin resistance detection where Xpert® was used for the following purposes: 1. When used as a replacement for sputum microscopy (TB detection); 2. When used as an add-on test in patients previously tested with smear microscopy and found to be negative (TB detection); 3. When used as an initial test for rifampicin resistance replacing conventional phenotypic drug susceptibility testing as the initial test (rifampicin resistance detection).	The review included 18 studies in 7816 participants that evaluated Xpert® for TB detection. The prevalence of TB in the 18 studies ranged from 18.3% to 100%. Of the 18 studies, 11 studies including 2340 participants provided data for rifampicin resistance detection. Of the remaining studies, four studies reported that all specimens were found to be drug sensitive (no rifampicin resistant specimens); two studies provided data jointly for pulmonary and extra-pulmonary specimens and one study did not report information on rifampicin resistance. The prevalence of rifampicin resistance in the 11 studies ranged from 0.8% to 29.4%. Most studies used expectorated (coughed-up) sputum. TB incidence rates per 100,000 population ranged from 4.1 (USA) to 981 (South Africa). The percent MDR-TB among new TB cases ranged from 0.9% (Greece and South Africa, Cape Town) to 22.3% (Azerbaijan) and among retreatment cases, ranged from 0% (Tanzania) to 55.8% (Azerbaijan).
Date of the last search: 15 December 2011.		
Funding sources: Liverpool School of Tropical Medicine, UK and the McGill University, Canada.		

What was the diagnostic accuracy of Xpert® in this review?

Table 1 summarizes the evidence from the review regarding the accuracy of Xpert®. When Xpert® was used as an initial test replacing smear microscopy, it had a pooled sensitivity of 88% and pooled specificity of 98%, with narrow credible intervals (CrI). As an add-on test following a negative smear microscopy, the pooled sensitivity with Xpert® was lower 67% (95% CrI 58%–74%), but specificity was high (98%; 95% CrI 97%–99%). In subgroup analyses, Xpert® was more accurate in 15 studies with smear-positive, culture-positive TB (98%; 95% CrI 97%–99%), than for smear-negative, culture-positive TB (68%; 95% CrI 59%–75%). Among patients living with HIV infection the pooled sensitivity was 80%, compared to 89% in those without HIV infection. The condition of the specimen, specimen preparation, prevalence of TB, and country income level had no impact on the diagnostic accuracy of the test. Xpert® could distinguish between TB and non-tuberculous mycobacteria (NTM) in clinical samples with high accuracy.

How did Xpert® compare with conventional culture methods for rifampicin resistance detection?

For rifampicin resistance detection, Xpert® achieved a pooled sensitivity of 94% and pooled specificity of 98%, with narrow credible intervals. **Table 1** also presents hypothetical scenarios in a cohort of 1000 individuals suspected of having rifampicin resistance, where if the prevalence of rifampicin resistance is 30%, on average Xpert® would wrongly identify 14 patients as being rifampicin resistant. If the prevalence of rifampicin resistance was 2%, the number of individuals wrongly identified as rifampicin resistant would increase to 20, an increase of 43%.

What were the conclusions of the review?

The review authors recommended the use of Xpert® as an initial diagnostic test for TB detection and rifampicin resistance detection in patients suspected of having TB, multidrug-resistant TB (MDR-TB), or HIV-associated TB as it is sensitive and specific. Xpert® may also be valuable as an add-on test following microscopy for patients who have previously been found to be smear-negative. The authors cautioned that an Xpert® result that is positive for rifampicin resistance should be carefully interpreted, taking into consideration the risk of MDR-TB in the patient and the expected prevalence of MDR-TB in the setting.

What were the assessments of the overall quality of the evidence?

The review authors assessed the overall quality of the evidence of included studies with the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool.¹ QUADAS-2 consists of four domains: patient selection, index test, reference standard, and flow and timing of testing. The review authors also assessed studies for risk of bias in applicability. In the patient selection domain, they considered data from 20 study centers (74%) to be at low risk of bias because participants were enrolled consecutively. The majority of the remaining study centers were considered to be at high risk of bias, mainly because of the convenience sampling method used. With regard to applicability (patient characteristics and setting), of the 27 study centers the authors judged six study centers (in one study) to be of low concern because they evaluated Xpert® in decentralized laboratories associated with health clinics and provincial hospitals. In the index test domain, all study centers were considered to be at low concern for both risk of bias and applicability. In the reference standard domain, they judged 23 study centers (85%) to be at low risk of bias for TB detection, and 24 study centers (89%) to be at low risk of bias for rifampicin resistance detection. In the flow and timing domain, 23 study centers (85%) were considered to be of low concern for risk of bias because all patients were accounted for in the analysis and information about indeterminate results were provided.

Limitations

While the methods used were sound, the included studies did not evaluate the current G4 Xpert® test and so applicability with regard to the G4 test is unclear. This review only included studies in adults with pulmonary TB and the results do not apply to children with TB or to people with extra-pulmonary TB. In addition, at least three studies are on-going and other studies have been published after the search date for this review, though personal communication with the first author reveals that an update of the review is currently underway. The results of this review will need to be supplemented by data from elsewhere on costs, and on incremental cost-effectiveness ratios if the test was to be used as a replacement for, or in addition to, smear microscopy, in high TB burden, low- and middle-income countries.

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Did the results and conclusions of the review differ from other reviews on this topic?

The Cochrane review cited one published systematic review and meta-analysis on the diagnostic accuracy of Xpert[®].² This review used other statistical methods for meta-analysis than the currently recommended bivariate random-effects models. This meta-analysis included 18 studies (10,224 suspected specimens). The summary estimate for TB diagnosis was 90.4% (95% confidence interval (CI) 89.2%–91.4%) for sensitivity, 98.4% (95% CI 98.0%–98.7%) for specificity. The sensitivity and specificity of detecting rifampicin resistance was 94.1% and 97.0%, respectively. In subgroup analyses, the accuracy of Xpert[®] MTB/RIF assay was higher in smear-positive than in smear-negative specimens and the sensitivity of diagnosing TB in adults was higher than that in children (90.8% versus 74.3%). These findings are similar to those in the Cochrane review.

What further research is required?

The review authors recommended that future studies should assess the diagnostic accuracy of Xpert[®] in settings other than reference laboratories such as primary health facilities, TB screening centers, and antiretroviral clinics, especially settings where the test is performed at the point of care. Systematic reviews of studies on Xpert in children, and in extra-pulmonary TB are expected to be available shortly and will complement the evidence in this review. Systematic reviews that address patient outcomes (clinical impact), cost, and cost effectiveness are also needed.

What are the implications of the review for public health?

1. This review demonstrates that Xpert[®] is accurate in diagnosing pulmonary TB as well as detecting rifampicin resistance (as a marker for MDR-TB). However the review highlights that none of the studies were done in the primary health care setting where the public health benefits are likely to be maximum, but where ensuring similar accuracy may be challenging.
2. The studies used the older generations of Xpert[®]. It is therefore possible that the performance of Xpert G4, the current generation of Xpert, will be different.
3. Caution has to be exercised in interpreting the results of Xpert[®] for detection of rifampicin resistance based on the baseline risk of MDR TB in that community and the patient's individual risk for MDR TB. Apart from false positive results for rifampicin resistance with Xpert[®], even confirmed rifampicin resistance does not necessarily indicate resistance to all anti-TB drugs.
4. Xpert[®] does not eliminate the need for subsequent culture and phenotypic drug susceptibility testing, which are required to monitor treatment progress and to detect resistance to drugs other than rifampicin.
5. Since the majority of studies included in the review were from low- and middle-income countries where advanced, smear-positive TB is common, the results may not directly apply to high-income countries where most TB cases are smear-negative, have minimal disease, and induced sputum samples are often necessary for diagnosis.
6. Costs of introducing the new test, including the equipment, ensuring an uninterrupted and stable electrical power supply, temperature control, and maintenance of the cartridge modules; as well as manpower, training, and quality control, will have a bearing on the wider adoption of this test into TB control programmes and in peripheral laboratories, in low and middle-income countries. A previous cost-effectiveness analysis of Xpert[®]³ had concluded that the implementation of Xpert[®] in addition to, or instead of, sputum smear microscopy will be cost-effective in low- and middle-income countries. The calculated incremental cost-effectiveness ratios (ICERs), or the incremental cost of each disability adjusted life year (DALY) averted by introduction of Xpert[®], was estimated to be below the gross domestic product per capita for high TB burden countries such as India, South Africa, and Uganda. However, the authors of this cost-effectiveness analysis cautioned that this did not necessarily mean that these countries would have the resources to implement the test; and additional unknown costs associated with the scale-up of Xpert[®] and other parameters, such as patient costs, not included in their model, could also affect CERs. Although the model strongly suggests that Xpert[®] will be cost-effective, the authors suggested careful monitoring and evaluation of Xpert[®] in an initial roll-out, before a full scale-up was considered.

Table 1 – Summary of findings of the diagnostic accuracy of Xpert MTB/RIF assay for detection of pulmonary TB and rifampicin resistance: all patients and subgroups (modified from the review).

Analysis: number of participants (number of studies)	Effect: median-pooled (95% credible interval) ^a	Likely effects with differing TB prevalence		
		TB prevalence: 5% (if 1000 people are tested, 50 will have TB, 950 will not)	TB prevalence: 15% (if 1000 people are tested, 150 will have TB, 850 will not)	TB prevalence: 30% (if 1000 people are tested, 300 will have TB, 700 will not)
TB detection				
Xpert used as an initial test replacing microscopy 7517 (15)	Sensitivity: 88% (83, 92)	Correctly identified (TP): 44 Wrongly missed (FN): 6	Correctly identified (TP): 132 Wrongly missed (FN): 18	Correctly identified (TP): 264 Wrongly missed (FN): 36
	Specificity: 98% (97, 98)	Correctly untreated (TN): 931 Unnecessarily treated (FP): 19	Correctly untreated (TN): 833 Unnecessarily treated (FP): 17	Correctly untreated (TN): 686 Unnecessarily treated (FP): 14
Xpert used as an add-on test following a negative smear microscopy result 5719 (14)	Sensitivity: 67% (58, 74)	Correctly identified (TP): 34 Wrongly missed (FN): 16	Correctly identified (TP): 101 Wrongly missed (FN): 49	Correctly identified (TP): 201 Wrongly missed (FN): 99
	Specificity: 98% (97, 98)	Correctly untreated (TN): 931 Unnecessarily treated (FP): 19	Correctly untreated (TN): 833 Unnecessarily treated (FP): 17	Correctly untreated (TN): 686 Unnecessarily treated (FP): 14
Smear-positive, culture-positive subgroup (within- study comparison) 1735 (15)	Sensitivity: 98% (97, 99)	Correctly identified (TP): 49 Wrongly missed (FN): 1	Correctly identified (TP): 147 Wrongly missed (FN): 3	Correctly identified (TP): 294 Wrongly missed (FN): 6
	Specificity: Could not be estimated	Correctly untreated (TN): Not estimable Unnecessarily treated (FP): Not estimable	Correctly untreated (TN): Not estimable Unnecessarily treated (FP): Not estimable	Correctly untreated (TN): Not estimable Unnecessarily treated (FP): Not estimable
Smear-negative, culture-positive subgroup 5771 (15)	Sensitivity: 68% (59, 75)	Correctly identified (TP): 34 Wrongly missed (FN): 16	Correctly identified (TP): 102 Wrongly missed (FN): 48	Correctly identified (TP): 204 Wrongly missed (FN): 96
	Specificity: 98% (97, 99)	Correctly not treated (TN): 931 Unnecessarily treated (FP): 19	Correctly not treated (TN): 833 Unnecessarily treated (FP): 17	Correctly not treated (TN): 686 Unnecessarily treated (FP): 14
HIV-positive subgroup 1163 (4)	Sensitivity: 80% (67, 88)	Correctly identified (TP): 40 Wrongly missed (FN): 10	Correctly identified (TP): 120 Wrongly missed (FN): 30	Correctly identified (TP): 240 Wrongly missed (FN): 60
	Specificity: 97% (93, 99)	Correctly not treated (TN): 922 Unnecessarily treated (FP): 28	Correctly not treated (TN): 825 Unnecessarily treated (FP): 25	Correctly not treated (TN): 729 Unnecessarily treated (FP): 21
HIV-negative subgroup 1981(4)	Sensitivity: 89% (81, 94)	Correctly identified (TP): 45 Wrongly missed (FN): 5	Correctly identified (TP): 134 Wrongly missed (FN): 16	Correctly identified (TP): 267 Wrongly missed (FN): 33
	Specificity: 99% (96, 99)	Correctly not treated (TN): 941 Unnecessarily treated (FP): 9	Correctly not treated (TN): 842 Unnecessarily treated (FP): 8	Correctly not treated (TN): 693 Unnecessarily treated (FP): 7

(continued on next page)

Table 1 – (continued)

Analysis: number of participants (number of studies)	Effect: median-pooled (95% credible interval) ^a	Likely effects with differing prevalence of rifampicin resistance among individuals with TB		
		TB prevalence: 2% (if 1000 people are tested, 20 will be rifampicin resistant; 980 will not)	TB prevalence: 15% (if 1000 people are tested, 150 will be rifampicin resistant; 850 will not)	TB prevalence: 30% (if 1000 people are tested, 300 will be rifampicin resistant; 700 will not)
Rifampicin resistance detection Xpert used as an initial test replacing conventional drug susceptibility testing 2340 (11)	Sensitivity: 94% (87, 97) Specificity: 98% (97, 99)	Correctly identified (TP): 19 Wrongly missed (FN): 1 Correctly untreated (TN): 960 Unnecessarily treated (FP): 20	Correctly identified (TP): 141 Wrongly missed (FN): 9 Correctly untreated (TN): 833 Unnecessarily treated (FP): 17	Correctly identified (TP): 282 Wrongly missed (FN): 18 Correctly untreated (TN): 686 Unnecessarily treated (FP): 14

TP, true positive; FN, false negative; TN, true negative; FP, false positive.

^a The 95% credible interval is the Bayesian equivalent of the classical 95% confidence interval (CI) and represents the interval that has a 95% probability of capturing the true value of the sensitivity or specificity, given the observed data and the prior information.

If not accurate, the Xpert® test may over-diagnose or under-diagnose cases of TB. It could also lead to wrong conclusions of rifampicin resistance. The test is more costly than smear microscopy which could negatively impact TB control in resource limited settings. The test requires an uninterrupted and stable electrical power supply, temperature control, and yearly calibration of the cartridge modules.

Declaration of interest

TDS and PT are contributors to The Cochrane Collaboration. TDS is an editor with the Cochrane Infectious Diseases Group. PT is a programme partner of the Effective Healthcare Research Consortium.

Conflicts of interest

All authors have none to declare.

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