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Xpert MTB/RIF assay for the diagnosis of TB

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Abbreviations

AFB	acid-fast bacilli
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
CrI	credible interval
DOI	Declaration of Interests
DST	drug-susceptibility testing
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GDG	Guideline development group
HIV	human immunodeficiency virus
MDR-TB	multidrug-resistant tuberculosis
MTBC	*Mycobacterium tuberculosis* complex
PCR	polymerase chain reaction
PICO	Population, Intervention, Comparator, Outcome
TB	tuberculosis
USAID	United States Agency for International Development
WHO	World Health Organization

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Declaration and management of conflict of interest

All the contributors completed a WHO Declaration of Interest form. All stated declarations of interest were evaluated by members of the Steering Group for the existence of any possible financial conflict of interest which might warrant exclusion from membership of the Guidelines Development

Group or from the discussions as part of the guidelines development process. Intellectual conflict of interest was not considered for exclusion from membership of the Guidelines Development Group, as broader expertise on cost, cost-effectiveness and affordability of the Xpert MTB/RIF assay was considered as criteria for the selection. In addition, the diversity and representation in the Groups was large enough to balance and overcome any potential intellectual conflict of interest. During the guidelines development process and the meeting, any emergence of intellectual conflict of interest was monitored by the Chair and there was no perceived intellectual conflict of interest identified during the meeting.

The following interests were declared:
None declared

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Daniela Cirillo declared that she had received funding to conduct research on new TB diagnostic tools including for the Xpert MTB/RIF. A total of approximately USD 19,000 was paid to her constituency, the San Raffaele Scientific Institute, Milan, Italy to perform this work.

Richard Lumb declared that he had undertaken laboratory strengthening assessments as part of his WHO TB Supranational Reference Laboratory responsibilities in Indonesia, Viet Nam and the, Solomon Islands. A total of USD 490,000 was paid to his constituency, South Australia Pathology, Adelaide, Australia to perform this work.

Hojoon Sohn declared that he conducted a cost and cost-effectiveness analysis in Viet Nam and Malawi for a WHO Guideline Development Group meeting assessing the use of TB-LAMP in 2016. He also declared that he was co-author of the 2011 cost-effectiveness analysis of Xpert MTB/RIF by Vassell *et al. PLoS Medicine*, 2011, 8:e1001120 and the systematic review by Steingart *et al*. Cochrane Database Syst Rev. 2013 ,31;(1):CD009593.

Bertie Squire declared that he had obtained research grants from different agencies (USAID, LHL, MRC, Welcome Trust) for the amount of approximately USD 1.3 million which was paid to his constituency, the Liverpool School of Tropical Medicine. He had also declared that he was involved in a project assessing the cost-effectiveness of Xpert MTB/RIF and was co-author of the cost-effectiveness analysis by Langley *et al*. Lancet Glob Health, 2014, 2; 10, e581-591.

Thomas Shinnick declared that he was a former employee of the United States Centres for Disease Control and Prevention (CDC) until January 2016. As an employee, he had often represented CDC's positions on laboratory services needed for tuberculosis diagnosis, treatment and control

Karen Steingart declared that she had conducted systematic reviews on different TB diagnostic tools including Xpert MTB/RIF, LF-LAM and second-line line probe assays and had received funds of approximately USD 25,000 to perform this work.

Anna Vassall declared that she had conducted a costing study on Xpert MTB/RIF in India for FIND and approximately USD 4500 was paid to her constituency, the London School of Hygiene and Tropical Medicine, London, England to perform this work. She also declared that she was the lead author for two published Xpert MTB/RIF economic evaluations conducted in 2011 and 2016.

Wendy Stevens declared that she had received funding for a number of TB assay validations in the form of reagents from different diagnostic companies (Cepheid, Abbott, Roche, Hain Lifesciences, DNA Genotek and Alere)

Executive summary

The Global TB Programme of WHO convened a Guideline Development Group (GDG) via webinar on 23 August 2016 to assess available economic and feasibility data to update the 2013 policy recommendations for the use of Xpert MTB/RIF as the initial diagnostic test in all persons with signs and symptoms of tuberculosis. An updated review of the cost and cost-effectiveness of Xpert MTB/RIF was commissioned as well as an analysis of the financial needs, affordability and feasibility if Xpert MTB/RIF is used as the initial diagnostic test for all persons with signs and symptoms of TB globally and in the 30 high TB burden countries.

Fifteen cost-effectiveness studies were included in the review, ten were set in sub-Saharan Africa. with one of those studies also including results from India (in addition to Uganda and South Africa). Two studies were set in the United States of America, three in India (including the study with three settings), and one in the former Soviet Union countries. Twelve of the fifteen economic evaluations found Xpert MTB/RIF to be cost effective in their setting. Xpert MTB/RIF was considered to be not cost effective or cost neutral in three studies conducted in India, Malawi and South Africa.

Of the 5.2 million incident pulmonary TB patients notified globally in 2014, only 3.0 million (58%) were bacteriologically confirmed, i.e., were smear- or culture-positive or positive according to a WHO-recommended rapid diagnostic such as Xpert MTB/RIF. Globally, around 30 million tests per year would be needed if all individuals presenting at health facilities with signs and symptoms of TB were tested for TB using Xpert MTB/RIF, assuming one Xpert test per person with signs and symptoms of TB. The estimated number of tests needed would be much higher if the 42% of clinically diagnosed cases of TB also received a bacteriological confirmation. In 2014, 4.7 million Xpert MTB/RIF catridges were delivered to countries.

The costing evaluation considered for the analysis the 30 high TB burden countries, which together account for about 85% of TB cases globally. The target population for this assessment of costs was all persons presenting to existing health facilities with signs and symptoms consistent with TB. Two alternative strategies were considered for the diagnosis of TB and MDR-TB. Strategy 1 considered the costs of using Xpert MTB/RIF as the initial test for all persons with signs and symptoms of TB (subsequently referred to as “Xpert for all”). Strategy 2 considered the use of conventional diagnostic algorithms according to WHO guidelines, which involve smear microscopy, culture examinations, drug susceptibility tests on liquid media, X-rays and Xpert MTB/RIF where already available.

The difference in costs between both diagnostic strategies was moderate in the 30 TB high burden countries. For 26 of these countries using “Xpert for all” would mean an increase in costs of less than five million dollars in absolute terms. In average, adopting the strategy “Xpert for all” would mean for the 30 high TB burden countries an annual increase in costs of 38%. The difference in costs between both strategies is less or equal in all countries compared with the results of a similar analysis published in 2012. However, The GDG felt there were important concerns that the global cost estimates and affordability projections for the “Xpert for all” strategy may be underestimated.

The “Xpert for all” strategy presumed a complete replacement of the conventional diagnostic strategy with the Xpert MTB/RIF over a one year period. The GDG felt that it is unlikely that a transition to “Xpert for all” could occur in a single year; hence affordability at country level should consider the costs for transitioning over a longer period and for a minimum of three years. This would also be necessary to allow for the simultaneous scale-up of additional services for the programmatic management of drug-resistant TB that would be needed to treat the large number of rifampicin-resistant TB patients that would be detected.

Although no systemic review was performed, two trials were discussed assessing the benefits and adverse effects of Xpert MTB/RIF on patient outcomes that failed to demonstrate improved outcomes for patients in terms of reduced mortality.

The GDG noted that TB diagnosis is a priority for global TB control and that a reliable and accurate test for TB diagnosis is available. However, there was low certainty of the effects of the test results being linked to patient management decisions given prevalent use of empiric treatment for TB in the settings evaluated. Three general considerations encompassed the discussion around the quality of economic evidence around costs, cost-effectiveness and affordability, presented to the GDG. Firstly, it was recognised that there was a lack of internationally recognized thresholds for cost-effectiveness and affordability which hinders the interpretation of whether results are cost-effective or affordable at the country level, without direct country engagement. Secondly, and related to this first issue, the GDG acknowledged the difficulty with drawing global recommendations when the emerging evidence varies by setting, and lacks some standardisation. Thirdly, comprehensive uncertainty analysis in all affordability and economic evaluations is imperative to address these concerns, and was a limitation in the affordability analysis commissioned.

The resource requirements needed for test implementation was judged to be large, with moderate certainty of the evidence of resource requirements. Cost-effectiveness was judged probably to be in favour of the intervention, and health equity probably increased. The intervention was judged to be probably acceptable to key stakeholders and probably feasible to implement. The GDG determined that there was insufficient evidence to elevate the strength of the recommendation for the use of Xpert MTB/RIF as the initial diagnostic test for all persons with signs and symptoms of TB from conditional to strong.

WHO Recommendations

Xpert MTB/RIF may be used rather than conventional microscopy and culture as the initial diagnostic test in all **adults** with signs and symptoms of tuberculosis (**conditional recommendation** acknowledging resource implications, high-quality evidence).

Xpert MTB/RIF may be used rather than conventional microscopy and culture as the initial diagnostic test in all **children** suspected of having TB (**conditional recommendation** acknowledging resource implications, very low-quality evidence).

1.0 Background

Tuberculosis (TB) causes 9 million cases and 1.5 million deaths annually and it is estimated that 3 million cases go undiagnosed each year[1]. Multidrug (MDR) and extensively drug-resistant (XDR) TB are major threats to global TB control. Ending the global TB epidemic will be achievable over the next 20 years only if there is intensive action by all countries which have endorsed the End TB Strategy and its ambitious targets[2]. It requires a paradigm shift from focused actions that gradually reduce the incidence of TB to enhanced, multisectoral actions that have been shown to drive down the epidemic at a rapid pace. Early diagnosis and prompt treatment of all persons of all ages with any form of drug-susceptible or drug-resistant TB is fundamental. WHO-endorsed rapid TB diagnostics and drug susceptibility testing (DST) should be available to all persons with signs and symptoms of TB to meet the targets of the End TB Strategy.

The Xpert™ MTB/RIF assay (Cepheid, Sunnyvale Ca., USA) is an automated, cartridge-based nucleic acid amplification test that uses the multi-disease GeneXpert™ (Cepheid, Sunnyvale Ca., USA) platform. The Xpert MTB/RIF assay is performed directly on sputum, processed sputum sediment and selected extrapulmonary specimens from adults and children.

The technology was first recommended by WHO in 2010, and a policy update was issued in 2013 to assess its use for detecting pulmonary and extrapulmonary TB and rifampicin resistance in both adults and children. As of 31 December 2015, a total of 4,672 GeneXpert instruments (comprising 21,549 modules) and 16,241,390 Xpert MTB/RIF cartridges had been procured in the public sector in 122 of the 145 countries eligible for concessional pricing[3]. In 2015, 6.2 million cartridges were procured in the public sector under concessional pricing, up from 4.8 million in 2014. The current price per cartridge is USD 9.98, following a novel financing agreement reached in August 2012 between the manufacturer and the United States Agency for International Development (USAID), the United States President's Emergency Plan for AIDS Relief (PEPFAR), UNITAID and the Bill & Melinda Gates Foundation.

2.0 Objectives for the Guideline Development Group Meeting

The purpose of this guideline development group meeting was to evaluate the evidence base for possible updated policy recommendations on the use of Xpert MTB/RIF as the initial diagnostic tool for all persons with signs and symptoms of TB, based on the most recent cost, cost-effectiveness and affordability data. Earlier cost-effectiveness analyses did not consider the lower cost of the Xpert MTB/RIF cartridges following the financing agreement which lowered the cost of each cartridge to USD 9.98. Furthermore, since 2013 there have been large global implementation projects such as "TB Xpert" [4] and "TB REACH"[5] which have been used to assess the feasibility of large-scale implementation of the Xpert MTB/RIF assay in low- and middle-income countries.

2.1 Objectives for the Guideline Development Group Meeting

1. To review updated evidence on the cost and cost-effectiveness of Xpert MTB/RIF use, based on the data published in peer-reviewed literature up to 2016;
2. To estimate the financial needs and affordability if Xpert MTB/RIF is used at the initial

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[1] World Health Organisation 2015. Global Tuberculosis Report 2015 WHO/HTM/TB/2015.22
[2] World Health Organization 2015. Implementing the end TB strategy: the essentials. WHO/HTM/TB/2015.31
[3] World Health Organization monitoring of Xpert MTB/RIF roll-out: Procurements of GeneXperts and Xpert MTB/RIF cartridges. Available at: http://apps.who.int/tb/laboratory/xpertmap/
[4] TB Xpert project: Factsheet http://www.who.int/tb/publications/TBXpert_briefing_note.pdf
[5] TB REACH project: http://www.stoptb.org/global/awards/tbreach/xpertmtbrif.asp

diagnostic test for all persons with signs and symptoms of TB in the 30 high TB burden countries;

3. To review findings from large Xpert MTB/RIF implementation projects to assess the feasibility of using Xpert MTB/RIF as the initial diagnostic tool for TB for all persons with signs and symptoms of TB.

2.2 Current WHO recommendations:

Xpert MTB/RIF should be used rather than conventional microscopy, culture and DST as the initial diagnostic test in **adults** presumed to have MDR-TB or HIV-associated TB (**strong recommendation**, high-quality evidence).

Xpert MTB/RIF should be used rather than conventional microscopy, culture and DST as the initial diagnostic test in **children** presumed to have MDR-TB or HIV-associated TB (**strong recommendation**, very low-quality evidence).

Xpert MTB/RIF may be used rather than conventional microscopy and culture as the initial diagnostic test in all **adults** with signs and symptoms of tuberculosis (**conditional recommendation** acknowledging resource implications, high-quality evidence).

Xpert MTB/RIF may be used rather than conventional microscopy and culture as the initial diagnostic test in all **children** suspected of having TB (**conditional recommendation** acknowledging resource implications, very low-quality evidence).

2.3 Guideline Development Group Meeting

The WHO Steering Group was responsible for scoping the guideline, drafting the key questions and overseeing the evidence retrieval and analyses. The Steering Group was also responsible for selecting members for the GDG and External Review Group, for managing declarations of interest, and for organising the GDG meeting via webinar. A brief biography of each of the GDG members was made available for public scrutiny on the WHO Global TB Programme website (http://www.who.int/tb/laboratory/policy_statements/en/) two weeks prior to the GDG meeting.

Questions were drafted by the WHO Steering Group and were presented to the GDG for discussion and modification. The Steering Group also prepared an initial list of relevant outcomes including desirable effects and undesirable effects, and requested the GDG to identify any other important outcomes.

On 23 August 2016, a webinar was conducted with the GDG to refine and finalize the proposed patient outcomes and to rate their relative importance and review the findings from the economic analyses. The following outcomes for each PICO question were determined, and the ratings of their importance were presented and agreed:

- Critical outcomes – diagnostic accuracy as reflected by true-positive, true-negative, false-positive and false-negative results, incremental yield above sputum smear microscopy
- Important outcomes – cost, cost effectiveness, equity, acceptability and feasibility

The format for the Evidence to Recommendations tables was discussed and agreed upon by the GDG members during the webinar. The format included the following categories: description of the problem; diagnostic test accuracy; patient values and preferences; certainty of the evidence of the effect on management's effects; benefits and harms of the test's use; resources required; equity;

acceptability; feasibility to guide the formulation of the strength and direction of the recommendations.

A draft Evidence to Recommendations table was developed by the Steering Group in order to facilitate the recommendation development process during the GDG meeting. Judgments were made and recorded during the meeting.

The meeting was chaired by a guideline methodologist with expertise in guideline development processes and methods. The methodologist participated in the initial planning, scoping and development of the key questions for the GDG meeting. During the meeting, GDG members made judgments. Decisions were based on consensus, which was defined as unanimous agreement among all GDG members. Consensus was achieved for all categories in the evidence to recommendations table. Voting was used to determine the strength of the recommendation.

3.0 Evidence base

The accuracy of Xpert MTB/RIF for the diagnosis of pulmonary TB and rifampicin resistance in adults was assessed in 2013[6]. The accuracy of Xpert MTB/RIF in detecting TB assessed data from 22 studies involving 9008 participants. When used as the initial diagnostic test replacing sputum smear microscopy, Xpert MTB/RIF achieved pooled sensitivity of 88% (95% credible interval [CrI], 84-92%) and a pooled specificity of 99% (95% CrI, 98-99%). Twenty four studies involving 2969 participants assessed the accuracy of Xpert MTB/RIF to detect rifampicin resistance. When used to detect rifampicin resistance, Xpert MTB/RIF achieved a pooled sensitivity of 95% (95% CrI, 90-97%) and a pooled specificity of 98% (95% CrI, 97-99%). The evidence base for these studies was evaluated as high quality. Given the certainty of evidence of the accuracy of Xpert MTB/RIF, data on accuracy of the assay was not further evaluated by the GDG.

3.1 Cost effectiveness of Xpert MTB/RIF

A comprehensive search was done of the following databases: PubMed, CINAHL, The York Centre for Reviews and Dissemination and the TUFTS CEA Registry. The search was restricted to the time period January 2010 up to 30 July 2016. In addition, health economists with expertise in economic analyses of TB diagnostics were contacted for additional published studies. Reference lists from included studies were also searched.

Publications were selected for inclusion when full-text was available for review and if studies were published in English. Studies that performed an economic evaluation which either resulted in a cost-effectiveness ratio (or cost-utility ratio) or incremental net benefit when comparing Xpert MTB/RIF for the diagnosis of TB with standard practice used in each study setting were included. Studies that performed a cost analysis only were excluded. Published correspondence, reviews or commentaries were also not included.

A total of 107 unique records were identified for possible inclusion, with 15 selected for full text review. Since the 2013 WHO policy update on the use of Xpert MTB/RIF (which identified five cost-effectiveness analyses) (Vassall 2011, Abimbola 2012, Andrews 2012, Menzies 2012, Winetsky 2012), a further 10 have been published. These reported on the cost-effectiveness, cost-utility or net incremental benefit of the use of Xpert MTB/RIF and met the inclusion criteria for this review. These studies are referred to in this report as follows: (Choi 2013, Millman 2013, Shah 2013, Langley 2014, Little 2014, Drobniewski 2015, Suen 2015, You 2015, Zwerling 2015, Vassall 2016 unpublished). The list of papers selected for full text review is given in Section 5.0 of this report. Annex 1 provides a list of excluded studies and the reasons for exclusion.

3.1.1 Characteristics of included studies

Of the 15 studies that were included in the review, eight originated from sub-Saharan Africa (Tanzania, South Africa, Botswana, Lesotho, Namibia, Swaziland, Uganda and Malawi), with one of those studies also including results from India. Two additional studies provided results from India. A further five studies reported on cost-effectiveness analyses of Xpert MTB/RIF in high-income settings.

Of the five studies performed in high-income settings, two studies were performed in the United States of America (Choi et al. 2013, Millman et al. 2013), one study in the United Kingdom (Drobniewski et al. 2015), one study in Hong Kong (You et al. 2015), and one study conducted in the former Soviet Union countries (Winetsky et al. 2012) (classification performed using the World Bank income classification based on Gross National Income per capita).

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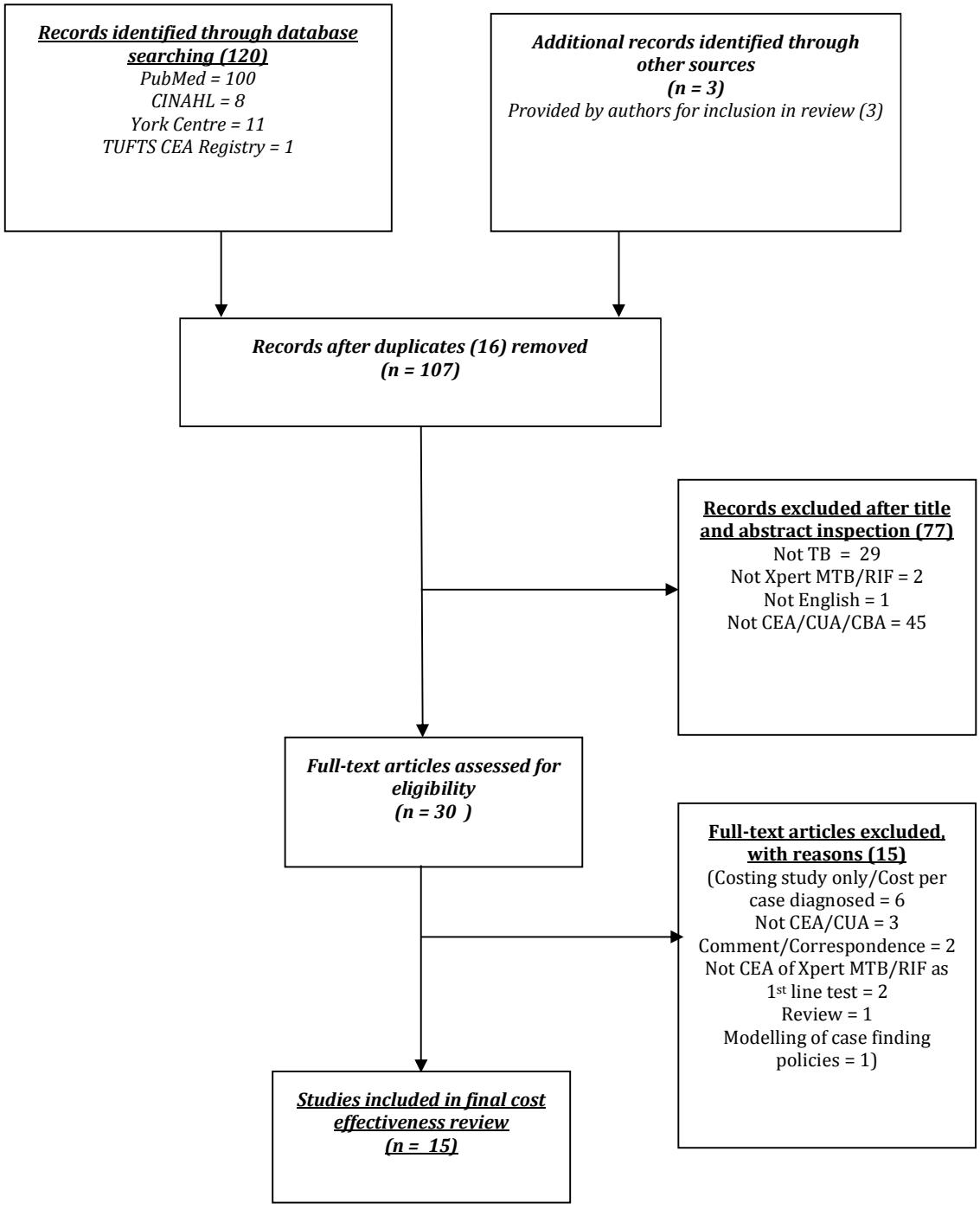
[6] World Health Organization 2013. Policy update. Xpert MTB/RIF assay for the diagnosis of pulmonary and extrapulmonary TB in adults and children. WHO/HTM/TB/2013.16

Four studies reported on the cost-effectiveness of Xpert MTB/RIF in upper-middle income settings. These four studies were conducted in South Africa (Vassall 2011, Andrews 2012, Menzies 2012, Vassall 2016, unpublished). The study by Menzies 2012 was a multicountry cost-effectiveness analysis performed in South Africa, Namibia and Botswana. Three studies were performed in India (Vassall 2011, Little 2014, Suen 2015), and one study in Swaziland and Lesotho (Menzies 2012).

There were four studies that performed cost-effectiveness analyses on Xpert MTB/RIF in low-income countries. These countries were Uganda (Vassall 2011 and Shah 2013), Malawi (Zwerling 2015), and Tanzania (Langley 2014).

Of the 15 studies, 12 studies were performed from a health system perspective, two studies from a societal perspective (Suen 2015, and Vassall 2016, unpublished) and one study included both public and private sector health care costs (Little 2014). Two of the 15 included studies focused on persons with HIV infection who were screened for TB (Abimbola 2012 and Andrews 2012). The remaining studies assessed all persons with signs and symptoms of TB, irrespective of HIV status. In all 15 studies smear microscopy was listed as at least one of the comparators when compared with Xpert MTB/RIF. Combinations of clinical symptom screening, conventional smear microscopy, chest X-ray, and/or culture made up the majority of the comparator diagnostic strategies. Seven studies included the costs of anti-retroviral treatment (ART) in the estimation of costs and 12 of the studies included treatment of MDR-TB in the estimation of costs.

Figure 1. The flow diagram showing study inclusion and exclusion for the cost effectiveness analysis review



Legend: CEA Cost effectiveness analysis; CUA cost utility analysis; CBA cost benefit analysis

3.1.2 Studies where Xpert MTB/RIF was found to be cost-effective

Twelve of the 15 included studies found that the use of Xpert MTB/RIF for the diagnosis of TB was cost-effective when compared to current practice in the settings where each study was performed. In all reported studies, the comparator included at least sputum smear microscopy in combination with one or more of clinical examination, chest X-ray, or mycobacterial culture.

One study (Abimbola 2012) performed in a sub-Saharan African setting found that an algorithm in which Xpert MTB/RIF (only) was used as a replacement test for sputum smear microscopy in people with HIV (with chest X-ray for sputum smear-negative individuals) costed less per patient and averted one death per 100 prevalent TB cases. Probability sensitivity analyses showed that Xpert MTB/RIF was 90% likely to be cost-effective in a sub-Saharan African setting, assuming the willingness to pay was equivalent to the South African GDP per capita (equivalent to USD 5,678 in 2010).

Another study (Andrews 2012), conducted in South Africa found that Xpert MTB/RIF screening of all persons living with HIV and commencing anti-retroviral therapy (regardless of symptomatology) was cost-effective. Menzies 2012 performed a multi-country analysis conducted in five countries in southern Africa where drug resistance and TB-HIV coinfection are prevalent (Botswana, Lesotho, Namibia, Swaziland and South Africa). This study showed that the use of Xpert MTB/RIF as replacement of smear microscopy and culture (with culture testing reserved for sputum smear-negative persons suspected to have TB or for persons with a history of previous TB treatment) was cost-effective. Modelling was used to estimate the incremental cost-effectiveness ratio which was less than three times the modelled countries' per capita GDP.

One study in Uganda, (Shah 2013) found that Xpert MTB/RIF testing alone was cost-effective when replacing sputum smear microscopy in all persons with signs and symptoms of TB. Vassall (2011) found that Xpert MTB/RIF was a cost-effective diagnostic strategy compared to sputum smear microscopy plus a clinical diagnosis. This was found for three settings (South Africa, Uganda, and India). Langley (2014) found that full rollout of Xpert MTB/RIF as the initial diagnostic test for all persons with signs and symptoms of TB was cost-effective in Tanzania, but that it would represent a large increase in the total health expenditure for Tanzania.

Two studies that performed analyses in the Indian health care setting (Little 2014, and Suen 2015) found that Xpert MTB/RIF was cost-effective when used as a replacement for sputum smear microscopy as Xpert MTB/RIF identified fewer false positives and saved unnecessary TB treatment costs.

The five studies performed in high-income settings also found that Xpert/MTB-RIF was cost–effective despite not having access to the preferential price for the Xpert MTB/RIF cartridges.

3.1.3 Studies where Xpert MTB/RIF was found not to be cost-effective

Three recent studies found that Xpert MTB/RIF may not be cost-effective in all settings. One study (Zwerling 2015) performed a cost-effectiveness analysis based on observed conditions in Malawi comparing LED microscopy and Xpert MTB/RIF with standard routine screening (using clinical judgment and sputum smear microscopy). Cost per DALY averted was greater than three times the per capita GDP of Malawi. This was despite apparently reporting costs of Xpert cartridges that reflect

preferential pricing arrangements[7]. This study used Xpert MTB/RIF as a screening tool for TB among newly diagnosed HIV-positive persons. The low prevalence of TB in the population screened was reported to be likely reason that Xpert MTB/RIF was found not to be cost-effective, as many patients would need to be tested to identify the active TB cases in the population.

In another study in India (Suen 2015) found that it was the scenario in which Xpert MTB/RIF was implemented that affected its cost-effectiveness. This study modeled different scenarios of Xpert implementation using a combination of public and/or privately provided diagnostic testing models. Xpert MTB/RIF was not considered to be cost effective if implemented on its own for either drug susceptibility testing only ("Xpert for DST"), or for all diagnosis of tuberculosis ("Xpert for all diagnosis") in the public sector. A "PPM-only" (PPM = public-private mix) strategy, and a "PPM strategy in conjunction with Xpert MTB/RIF for drug susceptibility testing", and "PPM in conjunction with Xpert MTB/RIF for all tuberculosis diagnosis" were found to be more cost-effective than the implementation of Xpert MTB/RIF alone as a replacement of current diagnostic practice (microscopy and culture).

An unpublished study from South Africa (Vassall 2016) found that the mean incremental costs and mean incremental impact of Xpert MTB/RIF averted fewer DALYs compared with microscopy. The authors suggested that this might be due the finding that few people who tested negative with Xpert MTB/RIF were followed up and started on treatment (with resultant TB-related mortality being accrued to the Xpert MTB/RIF "arm"). Furthermore the authors caution against interpreting this finding as meaning that Xpert MTB/RIF was not a value-for-money investment in South Africa – they did find that Xpert MTB/RIF did not cost as much as was originally anticipated. However, they emphasized that their study highlights the importance of ensuring that "real-world" economic analyses of technologies need to occur to understand standard clinical practice and ensure that this is accurately reflected in models of cost-effectiveness.

3.1.4 Quality of reporting and risk of bias of included studies

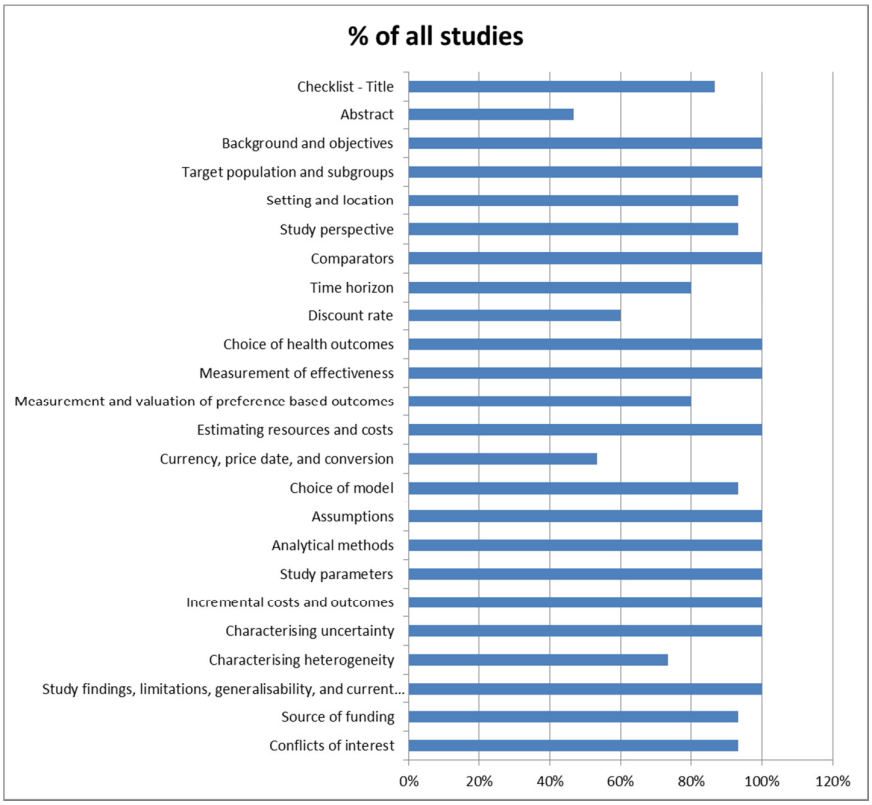
The quality of reporting and risk of bias the cost-effectiveness studies included in this review was assessed using the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) Statement (Husereau 2013). The CHEERS checklist consists of 24 items required for quality reporting of health economic evaluations.

Figure 2 shows that the majority of included studies met most or all of the reporting requirements and were considered to be of reasonable to good quality.

The reporting quality of the studies identified for this review are generally quite satisfactory, and there can be a reasonable level of confidence that these studies can allow decision makers to assess the value of Xpert MTB/RIF in their particular settings, where contextual factors are similar to those of the identified studies in this review. Decision makers need to ensure that appropriate comparators for each setting are considered, together with elements of credible decision analytic modeling (such as appropriate measuring and valuing of resource use, appropriate measuring and valuing of health outcomes, and the uncertainty around those parameters).

[7] Table 2 of Zwerling et al (2015) stated that Xpert MTB/RIF cartridge was 58% of the Xpert MTB/RIF consumables costs, listed at a total of $16.44 (USD2010). This price is lower than the USD 2012 $9.98 preferential price - possibly reflecting the deflation of prices to 2010 levels in this study.

Figure 2 Proportion of studies meeting the CHEERS reporting requirements



3.1.5 Conclusion

The majority of economic evaluations found Xpert MTB/RIF to be cost-effective in their particular settings. Most studies used decision analytic models that did not capture the probable reduction in transmission risk caused by faster diagnosis and commencement of appropriate TB treatment (as opposed to mathematical models or discrete event simulations or microsimulation models, which can incorporate the dynamics of appropriate, faster diagnosis and treatment on transmission risk). As such, most of the decision analytic models in this review can be considered to be conservative in their estimation of cost-effectiveness.

Cost-effectiveness is highly affected by context, influenced by factors such as current capacity to deploy, the performance of current (standard) diagnostic algorithms, cost of treatment regimens for TB and MDR-TB, the mode of implementation (including site/volume and infrastructure considerations), and the modeling approach used to assess cost-effectiveness. The many contextual factors from different settings make any prediction or conclusion regarding the cost-effectiveness of Xpert MTB/RIF in all settings globally challenging.

3.2 Cost of diagnosis of TB using Xpert MTB/RIF

The target population for the assessment of costs was all persons presenting to public health facilities with signs and symptoms consistent with TB. Two alternative strategies were considered for the diagnosis of TB and MDR-TB. Strategy 1 considered the costs of using Xpert MTB/RIF as the initial test for all persons with signs and symptoms of TB. Strategy 2 considered the use of conventional diagnostic algorithms according to WHO guidelines, which involve smear microscopy, culture examinations, drug susceptibility tests on liquid media, X-rays and Xpert MTB/RIF where already available.

Both strategies assume that 10 suspects needed to be tested to identify each new TB case bacteriologically confirmed. The calculations performed a one-year cost analysis without considering transmission, based on TB cases notified in 2014 and reported in the 2015 WHO Global TB Report. Of the 5.2 million incident pulmonary TB patients notified globally in 2014, only 3.0 million (58%) were bacteriologically confirmed, i.e., were smear- or culture-positive or positive according to a WHO-recommended rapid diagnostic such as Xpert MTB/RIF.

Globally, around 30 million tests per year would be needed if all individuals presenting at health facilities with signs and symptoms of TB were tested for TB using Xpert MTB/RIF, assuming one Xpert test per person with signs and symptoms of TB. The estimated number of tests needed would be much higher if the 42% of clinically diagnosed cases of TB also received a bacteriological confirmation. In 2014, 4.7 million Xpert MTB/RIF cartridges were delivered to countries. The economic evaluation was done with two considerations – global cost for all countries and cost for the 30 high TB burden countries as per the WHO list[8]. These 30 countries together account for about 85% of TB cases globally[9].

3.2.1 Comparison of costs for the alternative strategies

The first strategy used Xpert MTB/RIF as the first diagnostic test for all people presenting to health facilities with signs and symptoms consistent with TB. This strategy, subsequently referred to as "Xpert for all" included the follow-on tests required to confirm diagnosis of TB in HIV-positive individuals or to diagnose MDR-TB.

- One additional Xpert MTB/RIF test was included for HIV-positive individuals in whom the first Xpert was negative[10].
- The assumed positivity rate of Xpert MTB/RIF among HIV-positive individuals was 79%[11].
- One additional Xpert MTB/RIF test was included in individuals in whom the first Xpert MTB/RIF test was rifampicin-resistant for persons at low risk for MDR-TB[12].
- The cost of a second-line line probe assay for all rifampicin-resistant TB cases and culture and DST to fluoroquinolones and SLIDs for 25% of RR-TB cases[13] were also included.

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[8] World Health Organization. Use of high burden country lists for TB by WHO in the post-2015 era: Summary [Internet]. [cited 2016 Jul 4]. Available from: http://www.who.int/tb/publications/global_report/high_tb_burdencountrylists2016-2020summary.pdf?ua=1

[9] World Health Organization. Global tuberculosis report 2015. Geneva; 2015. Report No.: WHO/HTM/TB/2015.22

[10] World Health Organization. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Recommendation for a public health approach. Geneva; 2016.

[11] Steingart KR, Schiller I, Horne DJ, Pai M, Boehme CC, Dendukuri N. Xpert® MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults (Review). The Cochrane Collaboration; 2014.

[12] World Health Organization. Xpert MTB/RIF implementation manual: technical and operational "how-to"; practical considerations. [Internet]. 2014. Report No.: WHO/HTM/TB/2014.1. Available from: http://apps.who.int/iris/bitstream/10665/112469/1/9789241506700_eng.pdf?ua=1

The second strategy used conventional diagnostic algorithms while acknowledging the level of implementation of Xpert MTB/RIF in the 30 high burden countries as reported by countries in 2014.

- The level of implementation of Xpert MTB/RIF was based on the number of cartridges procured in 2014 assuming that one cartridge was used to test one individual.
- The number of persons tested with conventional diagnostics was the total number of all persons with signs and symptoms of TB less the number of Xpert MTB/RIF cartridges delivered.
- Costs for two sputum smears, one chest x-ray and one liquid culture were estimated for all persons.
- One liquid culture was added for the diagnosis of TB in persons living with HIV where there were insufficient cartridges available.
- This strategy estimated the costs for performing DST for rifampicin and isoniazid for only 20% of new bacteriologically confirmed cases.

The types and quantities of tests required in each diagnostic strategy and the associated sources of evidence are defined in detail in Annex 2.

To estimate the annual resource requirements for the two strategies, the unit costs of all tests were estimated in US dollars (USD) in year 2014 prices. Capital costs (e.g. equipment for microscopy, culture and DST, and Xpert) were annualized using a standard discount rate of 3% and an expected five years of useful life[14]. It was assumed that liquid media was used for culture and DST. All unit costs and respective sources of evidence are defined in detail in Annex 2. The total annual costs of each diagnostic strategy were calculated by multiplying unit costs by the quantities of tests required per year, for each country and target population.

Both alternatives included the diagnosis of drug-resistant TB in new TB cases. Diagnosis of rifampicin resistance is offered to 100% of people with signs and symptoms of TB in strategy "Xpert for all". In the strategy of conventional diagnostics the diagnosis of drug-resistant TB is offered to **only 20%** of the new TB cases bacteriologically confirmed, in line with the 2015 targets in the Global Plan to Stop TB. Acknowledging that the populations covered for diagnosis of drug resistance is different in the strategies, and that the WHO End TB Strategy calls for universal access to DST, a simulation of the costs of testing 100% of the new bacteriologically confirmed TB cases for drug resistance in the strategy of conventional diagnostics was performed.

The estimated annual total costs, worldwide, of using "Xpert for all" was USD 351 million. The estimated total cost of using conventional diagnostics, according to WHO-recommended algorithms, was USD 255 million (Figure 3). The difference in costs between the strategies is mainly explained by the higher number of cartridges of Xpert MTB/RIF used for all people with signs and symptoms of TB (in Strategy 1).

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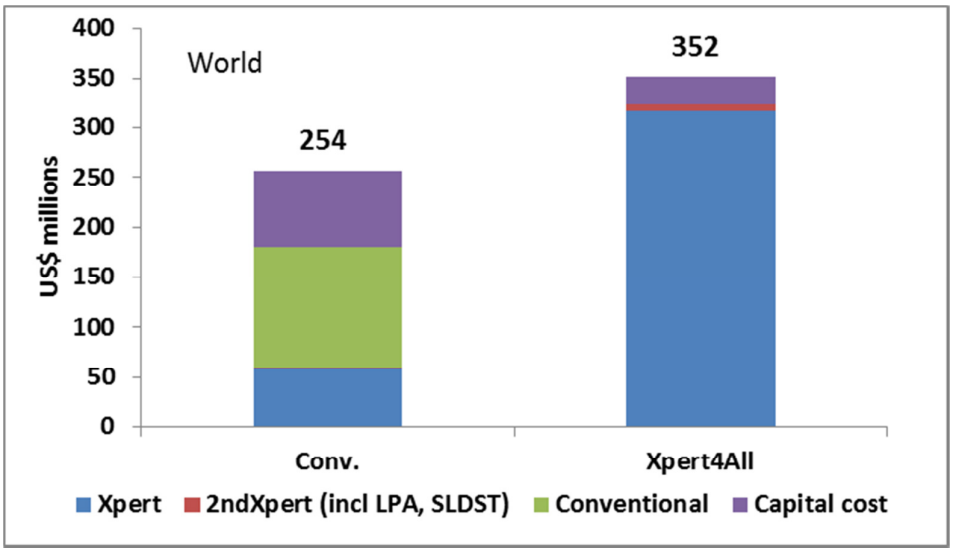
[13] World Health Organization. The use of molecular line probe assays for the detection of resistance to second-line anti-tuberculosis drugs. Policy guidance. [Internet]. 2016. Report No.: WHO/HTM/TB/2016.07. Available from: http://www.who.int/tb/areas-of-work/laboratory/WHOPolicyStatementSLLPA.pdf?ua=1

[14] Drummond MF, Sculpher MJ, Torrance GW, O'Brien BJ, Stoddart GL. Methods for the economic evaluation of health care programmes. Third edition. New York, USA: Oxford University Press; 2005.

Figure 3. Estimated annual costs to diagnose TB and MDR-TB of alternative strategies: 1. Use of conventional WHO-recommended algorithms – 20% DST coverage (Conv.) and 2. Use of Xpert MTB/RIF as initial diagnosis for all people presenting to health facilities with signs and symptoms of TB (Xpert for all).



For all high TB burden countries, using Xpert MTB/RIF as the initial diagnostic test for all people with signs and symptoms of TB would increase costs by an average of 38% compared with the use of conventional diagnostics. Fifteen countries show a difference in annual costs of the two strategies of less than USD 1 million (Table 1); most of these countries are already using Xpert MTB/RIF as the initial diagnostic test for the majority of individuals with TB signs and symptoms. A major exception is the Russian Federation, where using Xpert MTB/RIF for all people appeared to be less costly compared with the costs of using conventional diagnostics. The main reason for this different result is that routine diagnosis for TB and MDR-TB uses culture for all persons. In relative terms, nine countries seemed to have an increase of less than 40% in their annual costs for diagnosis when using Xpert MTB/RIF for all persons with TB signs and symptoms. In addition, 17 of these high TB burden countries seemed to have an increase between 41% and 60%. Thailand is the country showing the largest difference in costs between the two strategies in relative terms (i.e. costs of the strategy "Xpert for all" seemed to be 61% higher compared with the costs of conventional strategy). In absolute terms, the highest difference in costs between both strategies seemed to be in India, where the costs of strategy "Xpert for all" seemed to be USD 33 million higher than the costs of conventional strategy.

When an equivalent between the two strategies was made i.e. 100% DST coverage for all new TB cases being offered culture and DST for diagnosis of drug-resistant TB up-front, the costs of the strategy of conventional diagnostics would increase to USD 387 million (Figure 4). Costs of conventional strategy probably would be higher compared with the strategy Xpert for all.

Figure 4. Estimated annual costs to diagnose TB and MDR-TB of alternative strategies with 100% coverage of DST: 1. Use of conventional WHO-recommended algorithms – 100% DST coverage (Conv.) and 2. Use of Xpert MTB/RIF as initial diagnosis for all people presenting to health facilities with signs and symptoms of TB (Xpert for all).

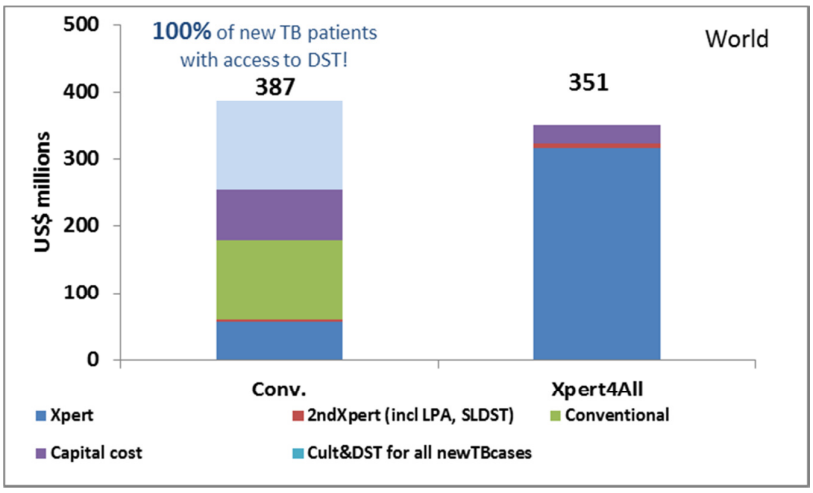


Table 1. 30 TB high-burden countries according to the difference in annual costs between both diagnostic strategies: annual cost of strategy "Xpert for all" minus annual cost of strategy using conventional diagnostics

Range of difference	Country
Below US$ 1 Million	Angola, Brazil, Central African Republic, Congo, Cambodia, Liberia, Lesotho, Namibia, Papua New-Guinea, Russian Federation, Sierra Leone, Tanzania, South Africa, Zambia and Zimbabwe
Between US$ 1 and $ 5 Million	Bangladesh, Democratic Republic of the Congo, Ethiopia, Kenya, Myanmar, Mozambique, Nigeria, Philippines, DPR Korea, Thailand and Viet Nam
Above US$ 5 Million	China, India, Indonesia, Pakistan

3.2.2 Conclusions

This analysis estimated the costs of diagnosing TB in people presenting to health facilities with signs and symptoms of TB. Two diagnostic strategies were considered and evaluated. The first one used Xpert MTB/RIF as initial diagnosis for all people, with a follow-on test (second Xpert, SL-LPA and SL-DST). The second one used conventional diagnostics, as per WHO guidelines, which involves smears, X-rays, Xpert MTB/RIF, liquid culture, and DST. This analysis used the lowest price for Xpert MTB/RIF cartridges (USD 9.98 per cartridge) and excluded additional costs related to distribution, customs

clearance, equipment maintenance which can vary markedly in different settings. The latter factors create a lot of uncertainty regarding the magnitude of costs of the Xpert for all strategy.

Results of the analysis suggest that the difference in costs between the two diagnostic strategies was moderate in the 30 TB high-burden countries. For 26 of these countries using "Xpert for all" would mean an increase in annual costs of less than USD five million in absolute terms. In relative terms, adopting the strategy "Xpert for all" would mean in average for the 30 high TB burden countries an increase of 38% in annual costs. The difference in costs between the two strategies was less or equal in all countries compared with the results of a similar analysis published in 2012[15].

The cost analysis of the strategy using conventional diagnostics only included costs for performing DST for 20% of new cases of bacteriologically confirmed TB cases compared with the "Xpert for all" strategy which included DST for rifampicin in all cases. However, the costs for performing DST for all confirmed TB cases (universal access of DST) would make the costs for the conventional strategy much higher.

Several limitations can be acknowledged and we highlight here the three most important. First, the cost analysis used empirical and guideline unit costs; for those tests where the guideline unit cost is used it is probable that costs are an underestimate. Second, cost analysis used global assumptions for calculating number of tests needed (e.g. 10 tests to identify one TB case) as opposed to setting specific assumptions. Costs of both strategies will be affected in the same direction when using setting specific data, however, the affordability at country level will be different. Third, the lack of a comprehensive uncertainty analysis makes it difficult to know how robust results could be.

3.3 Affordability of Xpert MTB/RIF

The affordability of Xpert MTB/RIF as initial diagnostic test for all persons with signs and symptoms of TB was explored in three ways. First, costs for performing Xpert MTB/RIF were compared with available funding for TB control using an average of available funds between 2014 and 2015[8]. Second, costs for performing Xpert MTB/RIF were compared with total government expenditures on health in 2014[16]. Finally, for African countries with a high burden of TB and HIV, the Xpert MTB/RIF resource requirements were compared with the 2014 country expenditures from the US President's Emergency Plan for AIDS Relief (PEPFAR)[17]. The affordability of Xpert MTB/RIF in the 30 high TB burden countries relative to national funding for TB control in 2014 is illustrated in Figure 4.

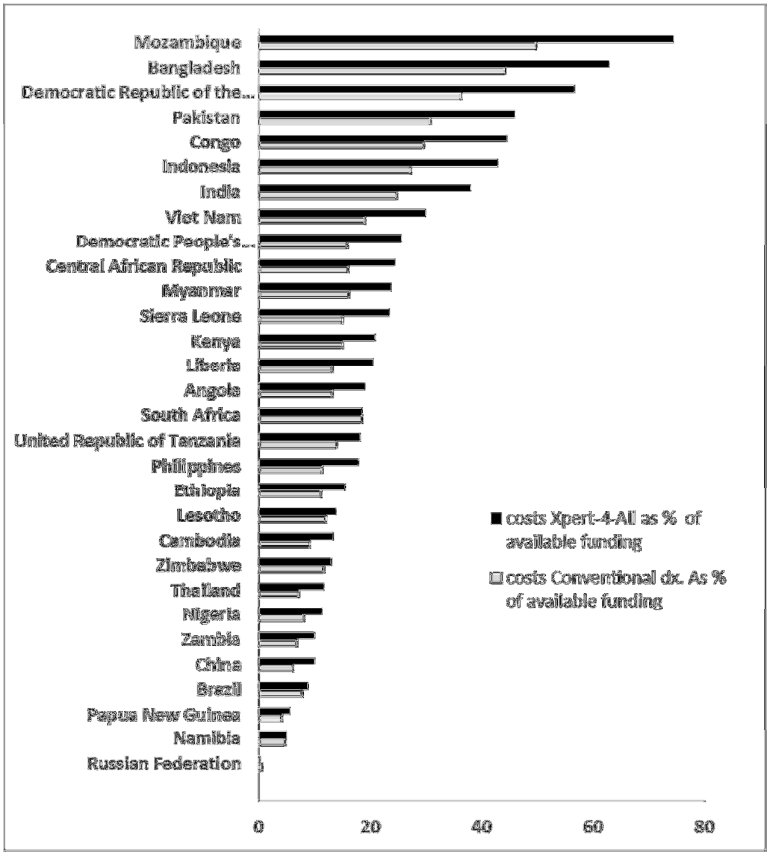
[15] Pantoja A, Fitzpatrick C, Vassall A, Weyer K, Floyd K. Xpert MTB/RIF for diagnosis of tuberculosis and drug-resistant tuberculosis: a cost and affordability analysis. Eur Respir J. 2013; 42(3):708–720.

[16] World Health Organization. Global Health Expenditure Database [Internet]. [cited 2016 Jun 28]. Available from: http://apps.who.int/nha/database/Select/Indicators/en

[17] PEPFAR. PEPFAR Dasboard [Internet]. [cited 2016 Jul 4]. Available from: https://data.pepfar.net/global

Figure 5. Estimated annual costs as a proportion of available national funding for TB in 2014 in 30 TB high-burden countries

The black bar indicates the costs of Strategy Xpert-for-All as a proportion of available funding for TB. The grey bar indicates the costs of Strategy of conventional diagnosis as a proportion of available funding for TB.

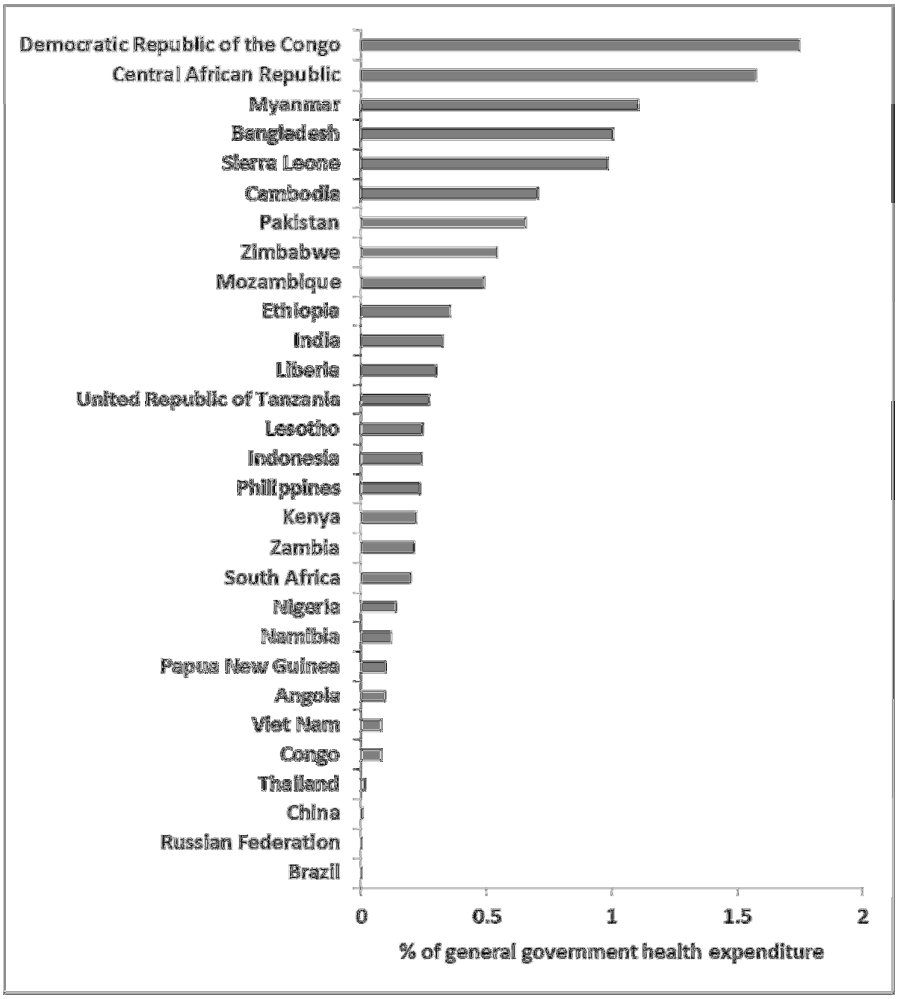


Estimated cost of using Xpert MTB/RIF as initial diagnostic for all people with signs and symptoms of TB represents on average 24% of the annual available funding for TB in the group of 30 TB high burden countries. For the Russian Federation these costs were negligible as a proportion of available TB funding. For Brazil, China, Namibia, Papua New Guinea and Zambia these costs seemed to be less than 10% of total available funding for TB. For 18 countries the financial burden seemed to be between 11% and 38%. DR Congo, Bangladesh and Mozambique would be the three countries with the largest financial burden: costs seemed to be 57%, 63% and 74% of TB available funding in 2014.

As a proportion of general government health expenditure, the estimated annual cost of using Xpert MTB/RIF for all people with signs and symptoms of TB ranged from 0.01% (Brazil, China, Russian

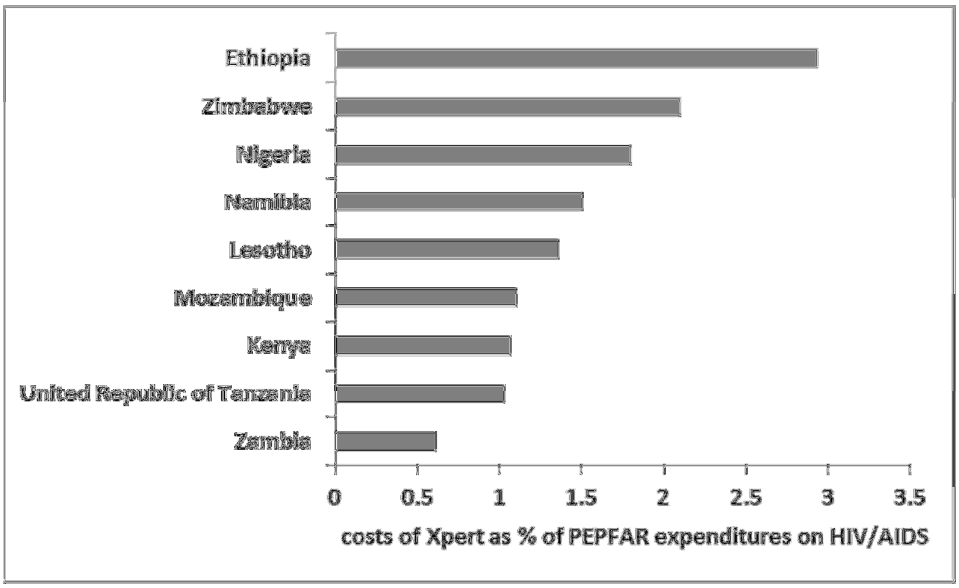
Federation and Thailand) to 1.6% (DR Congo) (Figure 5). The difference in costs between the use of Xpert-for-all and the use of conventional diagnostics was less than 0.1% of the general government health expenditure for 22 of these countries.

Figure 6. Estimated annual costs of using Xpert-for-All as a proportion of general government health expenditure (GGHE) in 2014, 29 TB high-burden countries. (No data of GGHE available for DPR Korea)



For nine African countries with high burdens of TB and HIV the cost of using Xpert MTB/RIF as initial diagnostic for all people with signs and symptoms of TB represented less than 3% of the PEPFAR expenditures on HIV (Figure 6). The estimated cost of using Xpert MTB/RIF as initial diagnostic seemed to be 0.61% of PEPFAR expenditures in Zambia, and a maximum of 2.9% in Ethiopia.

Figure 7. Estimated annual costs of using Xpert-for-All as a proportion of PEPFAR expenditures in 2014, 9 African countries.



3.3.1 Conclusions

The incremental costs of using Xpert MTB/RIF for all people with signs and symptoms of TB were less than 0.1% of the general government health expenditure for 22 of the 30 high TB burden countries. For seven other countries the incremental costs represented only between 0.21%-0.62% of the general government health expenditure. Costs of using Xpert MTB/RIF were less than 2% of the PEPFAR expenditures in HIV/AIDS for most African countries on the list of the 30 TB high burden countries.

Other studies have already confirmed the cost-effectiveness of using Xpert MTB/RIF (see section 3.1) as initial diagnostic method for TB. From a cost and affordability perspective, scaling-up the use of Xpert MTB/RIF to diagnose TB in all adults implies an increase in funds available to TB programmes. The increase in costs as a result of adopting the strategy Xpert for all seemed affordable compared to the general government health expenditures and the PEPFAR expenditure on HIV/AIDS. However, the lack of a global-recognised threshold for affordability hinders an answer on whether the increase in costs could be affordable or not.

4.0 Summary of evidence to recommendations

An assessment of the evidence following a structured assessment of the following categories: description of the problem; diagnostic test accuracy; patient values and preferences; certainty of the evidence for test accuracy; benefits and harms of the test's use; resources required; equity; acceptability; feasibility to formulate the strength and direction on recommendations for the use of Xpert MTB/RIF as the initial diagnostic test for all persons with signs and symptoms of TB[18] [19]. (Annex 3)

Accuracy of the assay was not re-evaluated but the judgment of the GDG convened in 2013 was used where the test was evaluated as being very accurate with high quality of evidence. The GDG also did not reconsider the harms and benefits for using Xpert MTB/RIF at different pre-test probabilities for TB, having considered the 2013 policy update accuracy data and the associated surrogate markers for patient outcomes as still applicable.

4.1 Desirable and undesirable consequences for the use of the test

The GDG agreed that using Xpert MTB/RIF as the initial diagnostic test for all individuals with signs and symptoms of TB would result in the majority of patients receiving a correct diagnosis, with large health benefits. The GDG also felt that very few patients with TB would be missed and agreed that any undesirable health-related effects would be small.

4.2 Certainty of the evidence of the impact of Xpert MTB/RIF

Although no systemic review was performed, the results from two trials assessing the impact of Xpert MTB/RIF on patient outcomes were presented and discussed. The first study was a multi-country study, TB-NEAT[20], conducted in South Africa, Zambia, Zimbabwe and Tanzania. The other was a cluster-randomised controlled trial embedded in the Xpert MTB/RIF roll-out in South Africa (XTEND)[21].

The TB-NEAT trial compared the use of sputum smear microscopy and Xpert MTB/RIF to test persons with signs and symptoms of TB, most of whom were HIV positive. The use of Xpert MTB/RIF did not translate into lower TB-related morbidity, partly due to broad use of chest X-ray for diagnosis of TB and a high level of empirical treatment for TB in sputum smear-negative patients.

Similarly, the XTEND randomised control trial, testing predominately HIV-positive individuals using either sputum smear microscopy or Xpert MTB/RIF found no reduction in mortality or time to treatment initiation at 6 months. This study was conducted early on in the implementation of the

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[18] GRADE evidence to decision frameworks for tests in clinical practice and public health. Schünemann HJ, Mustafa R, Brozek J, Santesso N, Alonso-Coello P, Guyatt G, Scholten R, Langendam M, Leeflang MM, Akl EA, Singh JA, Meerpohl J, Hultcrantz M, Bossuyt P, Oxman AD; GRADE Working Group. J Clin Epidemiol. 2016 Feb 27. pii: S0895-4356(16)00136-0. doi: 10.1016/j.jclinepi.2016.01.032.

[19] GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 1: Introduction. Alonso-Coello P, Schünemann HJ, Moberg J, Brignardello-Petersen R, Akl EA, Davoli M, Treweek S, Mustafa RA, Rada G, Rosenbaum S, Morelli A, Guyatt GH, Oxman AD; GRADE Working Group. BMJ. 2016 Jun 28;353:i2016. doi: 10.1136/bmj.i2016

[20] Theron G, Zijenah L, Chanda D, Clowes P, Rachow A, Lesosky M, Bara W, Mungofa S, Pai M, Hoelscher M, Dowdy D, Pym A, Mwaba P, Mason P, Peter J, Dheda K; TB-NEAT team. Feasibility, accuracy, and clinical effect of point-of-care Xpert MTB/RIF testing for tuberculosis in primary-care settings in Africa: a multicentre, randomised, controlled trial. Lancet. 2014 Feb 1;383(9915):424-35.

[21] Churchyard, G. J., W. S. Stevens, L. D. Mametja, K. M. McCarthy, V. Chihota, M. P. Nicol, L. K. Erasmus, N. O. Ndjeka, L. Mvusi, A. Vassall, E. Sinanovic, H. S. Cox, C. Dye, A. D. Grant and K. L. Fielding, 2015, Xpert MTB/RIF versus sputum microscopy as the initial diagnostic test for tuberculosis: a cluster-randomised trial embedded in South African roll-out of Xpert MTB/RIF, Lancet Glob Health, 3, 8, e450-457

Xpert MTB/RIF at the initial diagnostic test for all persons in South Africa. The authors concluded that the introduction of a new test into a health system where linkages between diagnostic and treatment services were not fully optimised may partly explain the results. The authors also concluded that the lack of impact on patient mortality could also be ascribed to widespread use of empiric TB treatment in South Africa.

Considering the limited evidence on impact of the Xpert MTB/RIF on patient management, the GDG felt that there was low certainty that Xpert MTB/RIF use would positively change patient management in settings where health systems are weak or where significant empiric treatment is applied.

4.3 Certainty of resource requirements

The GDG felt that there were important concerns that the estimates of cost and affordability projections for the "Xpert for all" strategy may have been underestimated. The unit cost used in the affordability analysis for the conventional diagnostic tests and for Xpert MTB/RIF were based on a mix of guideline and empirical estimates; as a result, total cost of those tests could be an underestimate. It was noted that the total cost of an Xpert MTB/RIF test varies markedly across countries and even within the same country. As a result the GDG felt that the model used to calculate Xpert MTB/RIF costs was probably biased. It was suggested that sensitivity analyses were needed to assess the variability of Xpert MTB/RIF costs with different overall unit cost and at different prevalences of TB, based on emerging empirical work.

The GDG was also concerned that there was a further underestimation of cost of the "Xpert for all" strategy as the model assumed that sputum smear microscopy would be completely replaced, whereas in reality that would not be the case. The slight increase in costs with the "Xpert for all" strategy presented was considered not to be realistic as smear laboratories will have to be maintained to monitor treatment. Experience from South Africa showed a significant decline in the need for microscopy and culture (reserved for treatment monitoring) after several years of Xpert MTB/RIF scale-up, but a minimal scale-back in conventional phenotypic DST capacity (required for management of drug-resistant TB patients).

The"Xpert for all" strategy presumed a complete replacement of the conventional diagnostic strategy by Xpert MTB/RIF over a one-year period. The GDG felt that it was highly unlikely that a transition to "Xpert for all" could occur in a single year. Hence, affordability at country level should consider the costs for transitioning over a longer period (probably a minimum of three years). This would also be necessary to allow for the simultaneous scale-up of additional services for the programmatic management of drug-resistant TB that would be needed to treat the increased number of drug-resistant TB patients that would be detected.

The GDG therefore concluded that the resource requirements needed for test implementation was judged to be large, with moderate certainty of the evidence of resource requirement-.

4.4 Cost-effectiveness

The GDG noted that the cost-effectiveness of Xpert MTB/RIF was highly affected by context such as deployment capacity, the performance of current (standard) diagnostic algorithms, cost of treatment regimens for TB and MDR-TB, the mode of implementation (including site/volume and infrastructure considerations), and the modeling approach used to assess cost-effectiveness. The many contextual factors (including those from high-income settings) make predictions or conclusions regarding the cost-effectiveness of Xpert MTB/RIF in all settings globally very challenging. Nevertheless, the GDG felt that the overall balance of evidence probably favoured the

implementation of Xpert MTB/RIF as the initial diagnostic test for all persons with signs and symptoms of TB.

4.5 Other considerations

Health equity: The GDG felt that the impact of Xpert MTB/RIF on health equity would largely depend on how Xpert MTB/RIF was deployed, and considered that it would be more pronounced if Xpert MTB/RIF was deployed in more peripheral or difficult-to-access settings. Overall, the GDG felt that health equity would probably be substantially increased, especially in poor and/or disadvantaged populations.

Acceptability: The GDG felt that Xpert MTB/RIF as initial diagnostic for all persons with signs and symptoms of TB would be acceptable by patients, clinicians and laboratory workers. However, given the uncertainty around the actual costs for performing Xpert MTB/RIF and the need for additional analyses on cost and affordability it was unclear whether Xpert MTB/RIF for all would be acceptable from a purely financial perspective, including by Ministries of Health/Finance and external donors. The GDG expressed concerns about the long-term sustainability of implementing Xpert MTB/RIF as a replacement test for sputum smear microscopy, concerns regarding the manufacturer's monopoly, and the significant resource implications for management of drug-resistant TB in a scenario of Xpert MTB/RIF for all persons with signs and symptoms of TB. Nevertheless, the GDG considered that the WHO End TB Strategy (endorsed by the World Health Assembly consisting of 193 member states) calls for universal DST and rapid expansion of diagnostic services in order to reach millions of missed TB and MDR-TB cases. The GDG therefore concluded that Xpert MTB/RIF for all persons with signs and symptoms of TB would probably be acceptable to key stakeholders.

Feasibility: The GDG expressed concerns that the evidence presented on the large implementation projects was largely qualitative and that there was no in-depth analysis of sustainability. Nevertheless, given the qualitative findings of the implementation projects and the rapid increased in procurement of GeneXpert instruments and Xpert MTB/RIF cartridges as of December 2015 (4,672 GeneXpert instruments (comprising 21,549 modules) and 16.2 million Xpert MTB/RIF cartridges procured in the public sector in 122 of the 145 countries eligible for concessional pricing) the GDG concluded that the intervention is probably feasible to implement.

4.6 Summary of judgments

The GDG noted that TB and MDR-TB diagnosis was a priority in global control of these epidemics and that the Xpert MTB/RIF assay was a highly accurate test, with large desirable and small undesirable health effects anticipated from its widespread use. However, the overall certainty of the evidence of the impact of the test on patient outcomes and the link between management decisions and test results was low. Resource requirements needed for implementation at scale were judged to be large, with moderate certainty of the evidence for resource requirements. Cost-effectiveness was judged to be probably in favour of the intervention, with health equity also probably increased. The intervention was judged to be probably acceptable to key stakeholders and probably feasible to implement.

When considering all desirable and undesirable consequences, all GDG members unanimously supported the direction of the recommendation, i.e. for (rather than against) the test as an intervention. There were differences of opinion regarding the strength of the recommendation, which resulted in a vote among the 16 GDG members. Thirteen voted for a conditional recommendation and three members voted for a strong recommendation.

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6.0 Annexes

Annex 1. References to studies excluded from the cost-effectiveness review (with reasons for exclusion)

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Annex 2. Assumptions for cost estimations

Table 2.1 Assumptions for the strategies used

Conventional diagnosis for TB	Description	Reference
Total number of people to be tested (all suspects)	Assume 10 suspects per 1 new TB case bacteriologically confirmed notified in 2014	2015 Global TB Report (1)
People to be tested via Xpert	Assume 1 suspect per Xpert cartridge sold in 2014 - data per country (assume 5% waste)	WHO/GLI website (2)
People to be tested via microscopy/culture	Difference between all suspects and suspects to be tested via Xpert	
HIV-positive people to be tested	Number of HIV-positive tuberculosis patients	2015 Global TB Report (1)
TB patients to be tested for MDR-TB	20% of new TB cases	The Global Plan (3)
Tuberculosis diagnosis		
All people presumed to have tuberculosis	2 smears, 1 x-ray or, 1 Xpert according to the cartridges left after testing tuberculosis in HIV+ people or, 1 culture (liquid) for Russia	WHO guidelines for treatment of TB (4), Country experience
People living with HIV presumed to have TB	1 Xpert, assume Xpert cartridges first for diagnosing tuberculosis in HIV+ people or, 1 liquid culture if bulk of cartridges not enough	Xpert MTB/RIF implementation manual (5), WHO guidelines for treatment of TB (4)
	1 additional Xpert test for HIV-positive people in whom first Xpert was negative. Assume positivity rate of Xpert among HIV-positive as 79%	WHO policy guidance for preventing HIV infection (7), Steingart (8)
People tested with Xpert with rifampicin-result positive	1 additional Xpert test in whom the first Xpert test was rifampicin-resistant.	Xpert MTB/RIF implementation manual (5)
	1 second-line Line Probe Assay (assay) in whom the second Xpert test was rifampicin-resistant; assume 95% of positivy rate of rifampicin-resistant among the second Xpert test. 1 culture and DST for second-line drugs for 25% of TB cases in whom the first Xpert was rifampicin resistant.	WHO Policy guidance on SL-LPA (9), Expert Opinion (10)
	Assume rifampicin-resistant among Xpert tested people as the estimated proportion of new TB cases that have MDR-TB. Assume 10% of TB among people tested.	2015 Global TB Report (1)
Diagnosis of MDR-TB	1 culture test followed by one DST for two first-line drugs (Rifampicin and Isoniazid; liquid)	WHO guidelines for treatment of TB (4)
Number of additional laboratories needed	Assume 1 microscopy laboratory per 100,000 population (ideal)	The Global Plan (3)
	Assume 1 culture and DST laboratory per 5 million population (ideal)	The Global Plan (3)
	Existing number of microscopy and culture laboratories	2015 Global TB Report (1)
	Additional laboratories needed are the difference between ideal number and existing number	

	Each additional laboratory equipped for microscopy or culture and DST	
Number of G-4 Xpert machines to buy	Number of Xpert cartridges sold in 2014 divided by 3000	WHO/GLI website (2)
	Assume each machine does 3000 tests per year	WHO – expert opinion (10)
Xpert MTB/RIF for all suspects		
Total number of people to be tested (all suspects)	Assume 10 suspects per 1 new TB case bacteriologically confirmed notified in 2014.	2015 Global TB Report (1)
Diagnosis of TB	1 test (Xpert) per TB suspects	
	1 additional Xpert test for HIV-positive people in whom Xpert was negative. Assume positivity rate of Xpert among HIV-positive as 79%	WHO policy guidance for preventing HIV infection (7), Steingart (8)
Diagnosis of MDR-TB	1 additional Xpert test in whom the first Xpert test was rifampicin-resistant.	Xpert MTB/RIF implementation manual (1)
	1 second-line Line Probe Assay in whom the second Xpert test was rifampicin-resistant; assume 95% of positivy rate of rifampicin-resistant among the second Xpert test. 1 culture and DST for second-line drugs for 25% of TB cases in whom the first Xpert was rifampicin resistant.	WHO Policy guidance on SL-LPA (9), Expert Opinion (10)
	Assume rifampicin-resistant among all Xpert tested people as the estimated proportion of new TB cases that have MDR-TB. Assume 10% of TB among all population.	2015 Global TB Report (1)
Number of G-4 Xpert machines to buy	Number of Xpert cartridges sold in 2014 divided by 3000	WHO/GLI website (2)
	Assume each machine does 3000 tests per year	WHO – expert opinion (10)
Number of additional laboratories needed	Assume 1 culture and DST laboratory per 5 million population (ideal)	The Global Plan (3)

Table 2.2. Unit cost assumptions

	US$	Quantities	Source
Diagnostic tests and other annual costs			
Smears	1	2	TB Planning and Budgeting Tool (11)
Digital X-ray	1.5	1	Prevalence surveys exprience
Culture (liquid media)	18.6	1	References (12-16)
DST for first-line drugs on liquid media, per drug	26.1	2	References (12-16)
DST for second-line drugs on liquid media (fluoroquinolones and injectables)	132	1	TB Planning and Budgeting Tool (11)
Second-line Line Probe Assay (LPA)	20	1	WHO Fact-Sheet SL-LPA (17)
Xpert, per cartridge (incl. shipment cost $1.2 per cartridge)	11.1	1	Xpert MTB/RIF implementation manual (5)
Annual calibration, annual technician salary, annual training/technical assistance	12,250	1	Xpert MTB/RIF implementation manual (5)

Laboratory equipment			
AFB laboratory, per new laboratory (incl. maintenance)	3,486	1	TB Planning and Budgeting Tool (11)
Culture in solid media, per new laboratory (incl. maintenance)	168,303	1	TB Planning and Budgeting Tool (11)
(Culture and) DST lab in solid media, per new laboratory (incl. maintenance)	172,431	1	TB Planning and Budgeting Tool (11)
MGIT for liquid culture and DST, per new laboratory (incl. maintenance)	91,603	1	TB Planning and Budgeting Tool (11)
MGIT for liquid culture and DST for countries for which FIND has negotiated prices*, per new laboratory (incl. maintenance)	50,898	1	TB Planning and Budgeting Tool (11)
GeneXpert machine, 4 modules	17,500	1	Xpert MTB/RIF implementation manual (5)
Shipment, Printer, UPS	2,400	1	Xpert MTB/RIF implementation manual (5)
DST for first-line drugs on solid media, per drug	9.1 (8.8 – 9.4)	2	References [18-22].

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Annex 3. Evidence to recommendations table

Question: Should **Xpert MTB/RIF** be used to diagnose **tuberculosis** in **all persons with signs and symptoms of TB**?

POPULATION:	all persons with signs and symptoms of TB	BACKGROUND:	The WHO End TB Strategy calls for the early diagnosis of TB and universal drug susceptibility testing (DST), highlighting the critical role of laboratories for rapidly and accurately detecting TB and drug resistance.
INTERVENTION:	Xpert MTB/RIF		
PURPOSE OF THE TEST:	To diagnose TB and RR-TB		
ROLE OF THE TEST:	Using the test as a replacement test (instead of bacteriological Dx strategies - sputum smear microscopy, culture)		
LINKED TREATMENTS:	According to WHO guidelines		
ANTICIPATED OUTCOMES:			
SETTING:	High burden countries (HBC)		
PERSPECTIVE:	Global perspective/Health system perspective		
SUBGROUPS:	Children to be included,		

Assessment

	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
PROBLEM	**Is the problem a priority?** ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	In 2014, TB killed 1.5 million people (1.1 million HIV-negative and 0.4 million HIV-positive). The toll comprised 890 000 men, 480 000 women and 140 000 children. TB now ranks alongside HIV as a leading cause of death worldwide. Worldwide, 9.6 million people are estimated to have fallen ill with TB in 2014: 5.4 million men, 3.2 million women and 1.0 million children. Drug-resistant tuberculosis continues to threaten global TB control and remains a major public health concern in many countries. Globally an estimated 3.3% of new cases and 20% of previously treated cases of TB have developed multidrug-resistant forms of disease (MDR-TB). In 2014 there were estimated 480,000 new cases and approximately 190,000 deaths from MDR-TB.	Reference: Global TB Report. WHO 2015. WHO/HTM/TB/2015.22
TEST ACCURACY	**How accurate is the test?** ○ Very inaccurate ○ Inaccurate	**Accuracy for the detection of TB** 21 studies (8880 participants) provided data that compared the sensitivity of Xpert MTB/RIF with smear microscopy. For smear microscopy, the pooled sensitivity was	Reference: Xpert MTB/RIF Policy update. WHO 2013.

	○ Accurate ● Very accurate ○ Varies ○ Don't know	65% (95% CrI 57-72%). For Xpert MTB/RIF, the pooled sensitivity was 88% (95% CrI 84-92%). The pooled specificity for Xpert MTB/RIF was 99% (95% CrI 98-99%). **Accuracy for the detection of rifampicin resistance** 34 studies (33 study centres, 2969 participants) provided data on detecting rifampicin resistance, and included 555 rifampicin-resistant specimens. The pooled sensitivity by univariate analysis was 95% (95% CrI, 90–97%); the pooled specificity was 98% (95% CrI, 97–99%). The pooled sensitivity and specificity were the same when bivariate analysis was used for the subset of studies that provided data on both sensitivity and specificity (17 studies, 2624 participants).	WHO/HTM/TB/2013.6
DESIRABLE EFFECTS	**How substantial are the desirable anticipated effects?** ○ Trivial ○ Small ○ Moderate ● Large ○ Varies ○ Don't know	Xpert MTB/RIF can be performed in a single day to allow the initiation of an appropriate treatment regimen. Accuracy data were used as a surrogate for the anticipated health benefits for patients. The anticipated desirable effect is the correct diagnosis of TB (TP) and correct exclusion of TB in persons without TB. Xpert would correctly identify 44 cases out of 50 per 1000 individuals tested if the pre-test probability of TB is 5%. For 10-30% there would be 88 and 264 patients respectively. Correct identification of TB cases should lead to higher cure rates, less sequelae to the individual patient, and less transmission in the community. Similarly Xpert MTB/RIF would correctly identify 941 patients without TB (TN) out of 950 per 1000 individuals tested if the prevalence of TB was 5%. For 10-30% prevalence's there would be 891 and 693 patients respectively (see table below). Correct identification of persons without TB cases should lead to avoiding unnecessary treatment and greater costs. In addition to accurate results, Xpert MTB/RIF can be performed in a single day to allow the initiation of an appropriate treatment egimen.	Reference: Xpert MTB/RIF Policy update. WHO 2013. WHO/HTM/TB/2013.6 Judgement is based on accuracy data, acknowledging the limitations of their use as proxy for patient important outcomes
UNDESIRABLE EFFECTS	**How substantial are the undesirable anticipated effects?** ○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know	The anticipated undesirable effect is the incorrect identification of an individual with or without TB (FN or FP). Xpert would misclassify 6 cases as FN per 1000 individuals tested if the pre-test probability of TB is 5%, and 12 to 36 cases under pre-test probabilities of 10-30%. Incorrect identification of an individual with TB may have a potential increased risk of patient morbidity and mortality, continued risk of community transmission of TB. Xpert MTB/RIF would misclassify 10 cases as FP per 1000 individuals tested if the pre-test probability of TB is 5%, and 9 to 7 cases under pre-test probabilities of 10-30%. Incorrect classification of an individual without TB may lead to patient anxiety, stigma, possible delays in further diagnostic evaluation, prolonged and unnecessary treatment with drugs.	Judgement is based on accuracy data, acknowledging the limitations of their use as proxy for patient important outcomes
OF THE EVIDENCE OF TEST	**What is the overall certainty of the evidence of test accuracy?** ○ Very low ○ Low ○ Moderate	In this review the **risk of bias** was undetected **Indirectness -** none	**Quality of evidence for test accuracy** is: HIGH Reference: Xpert MTB/RIF Policy

	● High ○ No included studies	**Inconsistency** - none **Imprecision** - none **Publication bias** – none for all studies.	update. WHO 2013. WHO/HTM/TB/2013.6
CERTAINTY OF THE EVIDENCE OF TEST'S EFFECTS	**What is the overall certainty of the evidence for any critical or important direct benefits, adverse effects or burden of the test?** ○ Very low ● Low ○ Moderate ○ High ○ No included studies	Results from two trials are available, one multinational (TB-NEAT: South Africa, Zambia, Zimbabwe, Tanzania); another from South Africa (XTEND). TB-NEAT trial: in people tested for TB, most of whom were HIV positive, compared with sputum microscopy, implementation of Xpert resulted in - more patients starting same day treatment; - more culture-positive patients starting treatment; - shorter time to treatment However benefits have not translated into lower tuberculosis-related morbidity, partly due to broad use of X-ray and high level of empirical treatment in smear negative patients. XTEND trial: in people tested for TB, many of whom were HIV positive, compared with sputum microscopy, implementation of Xpert - - did not reduce mortality at 6 months; - caused 49% increase in the proportion a positive index test result among tested; - did not increase number of people receiving TB treatment by 6 months. Not massive empiric treatment, less HIV prevalence as compared with the previous study. Of note: XTEND study was conducted very early in the course of implementation of the Xpert technology, with some sites only having Xpert implemented for two weeks. As such study may reflect health system limitations, in particular linkage of patient's diagnosis and care.	Empiric treatment widely used High proportion of HIV-positive patients
CERTAINTY OF THE EVIDENCE OF MANAGEMENT'S EFFECTS	**What is the overall certainty if the evidence of effects of the management that is guided by the test results?** ○ Very low ● Low ○ Moderate ○ High ○ No included studies	Ideally test results should guide management decisions, provided use of test is adopted by national policy. Both positive and negative results of the test should be sufficient for a patient to start treatment.	
EVIDENCE OF TEST	**How certain is the link between test results and management decisions?** ○ Very low	The link between test results and management decisions may be uncertain in various settings. In some occasions clinicians use empirical treatment for TB. In others capacity of health system may be insufficient to provide the patient with necessary	

	● Low ○ Moderate ○ High ○ No included studies	treatment.	
CERTAINTY OF EFFECTS	**What is the overall certainty of the evidence of effects of the test?** ○ Very low ● Low ○ Moderate ○ High ○ No included studies	This question is intended to summarize previous four questions on the certainty of the evidence.	
VALUES	**Is there important uncertainty about or variability in how much people value the main outcomes?** ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability	Assuming diagnostic accuracy /Test results as a predictor for the patient treatment outcomes there is no uncertainty about or variability in how much people value the main outcomes.	
BALANCE OF EFFECTS	**Does the balance between desirable and undesirable effects favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	The judgement is restricted to health effects and favours the intervention. The effect of the intervention is probably more pronounced in regard to the rifampicin resistance detection as compares to TB detection.	
RESOURCES REQUIRED	**How large are the resource requirements (costs)?** ● Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	In preparation for the GDG meeting, the calculations were made of using Xpert MTB/RIF as initial diagnosis for all people with signs and symptoms of TB for all (30) high TB burden countries. The conclusion was made that such an approach would increase costs by an average of 38% compared with the use of conventional diagnostics. Fifteen countries show a difference in annual costs of both strategies of less than US$ 1 million - most of these countries are already using Xpert MTB/RIF as initial diagnosis for the majority of suspects.	Ref: Naidoo S. 2016 Report to WHO: Review of the costs and cost-effectiveness of Xpert MTB/RIF. Ref: Pantoja A. 2016 Report to WHO: Estimated costs and affordability of

		During the GDG deliberations, however, there were important concerns, that global cost and affordability projections may be underestimated, due to the following reasons: Unit cost of diagnostic tests is based on mix of guideline and empirical estimates. Cost of Xpert excludes HR, transportation, annual calibration, paraphernalia (UPS etc). Culture and DST costs would include HR, transportation, maintenance, calibration and other costs. Unit cost for Xpert estimated to be much higher that 10 USD, which seriously biases results of the model, whereas empiric costs are used for other tests estimations. Even within the same country the cost for Xpert test, may vary substantially (between USD 13 to 18). To correct for this sensitivity analyses needs to be made, in order to assess how much these results are changing with different unit costs and different prevalence's. Related expenditures necessary for the new assay implementation, i.e. cost of training, monitoring, policy revision, etc. were not included into the model. In addition, consequent diagnostic and patient management costs (HIV, ART, MDR-TB related) were not included as well. Underestimation of Xpert arm as projections are made that microscopy and culture would be excluded completely, whereas in reality it is not the case. Savings for partial replacing of microscopy by Xpert are possible, but these are relatively marginal. Slight increase with the Xpert strategy adoption is not realistic. Smear and culture laboratories cannot be dismantled until the treatment follow up is done by smear and culture. The model for change in the strategy is theoretical and presents complete replacement of conventional strategy with the Xpert one in a year or so, whereas in reality phased scale back of microscopy and the culture services would need to take place. A lot of variability may depend on a setting. Affordability needs to be looked at within the context for particular country and for achieving all of the global targets, i.e. scaling up MDR-TB treatment, etc. Suggestion was made to model for particular countries, considering specific context in more details, for longer time period (3 years). There is possibility that newly adopted strategy, which is more expensive, may not be sustained due to limited funding (Example of Brazil). In this case microscopy may have to be rolled back, for this case, the skills need to be retained. In response to the abovementioned concerns, it was highlighted, that objective of the modelling is a complete replacement of a microscopy with Xpert for diagnostic purposes. Some of the microscopy facilities are not suitable for the Xpert testing.	diagnosis of TB and MDR-TB using Xpert MTB/RIF.

		They may be maintained, but their role may change. Instead of performing microscopy tests these centres may collect and transfer samples to more centralized Xpert testing centres. In the same time some of these centres, which currently already perform HIV, malaria or other laboratory tests, may continue doing so while stop doing smear microscopy. Still other TB testing centres, especially with poor infrastructure, and/or understaffed may be closed and their workload re-distributed. Experience from South Africa's implementation shows that number of cultures and microscopies are going down when Xpert is scaled up. This is proven by data from trials conducted in South Africa as well.	
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	**What is the certainty of the evidence of resource requirements (costs)?** ○ Very low ○ Low ● Moderate ○ High ○ No included studies	While in response to the previous question it was judged that resource requirements for the new assay implementation will be large across different settings, the imprecision and inconsistency of these data were considered not dramatic enough to affect the judgement of the expenditures being large. In the same time there is some indirectness which downgrades the judgement from high to moderate certainty.	For more details please refer to: Pantoja A. 2016 Report to WHO: Estimated costs and affordability of diagnosis of TB and MDR-TB using Xpert MTB/RIF, Annex 2: Assumptions, Methods, Unit prices used in the assessment; Table 4 Unit costs
COST EFFECTIVENESS	**Does the cost-effectiveness of the intervention favor the intervention or the comparison?** ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	Since the last review performed for the 2013 WHO policy update for the use of the Xpert assay, a further 10 studies have been identified that analysed cost-effectiveness, cost-utility, or net incremental benefit of Xpert for the diagnosis of TB giving a total of 15 economic evaluations. These have been performed in a variety of countries, mostly low/middle income settings (sub-Saharan African countries, India), but also Hong Kong, the USA, the UK, Russia. There has also been a mix of studies across TB/HIV prevalence settings. Most new studies have been performed from a health system perspective, however two of the recent studies were performed from a societal perspective. Key characteristics of the included studies have included Populations: - 10 studies: Persons with signs and symptoms of tuberculosis. (2 specified that they included HIV+ patients in the population analyzed (Langley 2014,	

		Menzies 2012)); - 4 studies: focus on people living with HIV and who may have tuberculosis: Symptomatic (Abimbola 2012, Shah 2013, Zwerling 2015); Screening of HIV patients initiating ART for TB (Andrews 2012); - 1 Study : detecting TB in prison populations in the former Soviet Union (including non-symptomatic annual screening, symptomatic screening, and self-referral. (Winetsky, 2012)). Comparator: Smear microscopy comparator (sometimes in combination with X-Ray, Culture, Clinical Examination) in all analyses; Xpert was generally used as first-line test in most studies (Some modeled use of Xpert as follow-on test in addition to Xpert as first-line test); MDR treatment costs – generally included; HIV treatment costs – included in studies that included people living with HIV. The majority of studies (12 out of 15) reported that the use of Xpert for the diagnosis of TB was cost effective when compared to current practice in the particular settings where each study was performed. Xpert was not considered to be cost effective in three studies conducted in India, Malawi, South Africa. During the GDG deliberations concerns were expressed : - on different design (and consecutively value) of different studies, i.e. early (descriptive) vs late (modeling) studies; - irrelevance of the studies from high-income settings (USA, UK, Hong Kong); - irrelevance of the design of the particular studies (screening of inmates).	
EQUITY	**What would be the impact on health equity?** ○ Reduced ○ Probably reduced ○ Probably no impact ● Probably increased ○ Increased ○ Varies ○ Don't know	Health equity was defined as increased access to health services for poor / disadvantaged populations. Impact of assay on health equity would largely depend on how Xpert is deployed, and is more pronounced in case Xpert is deployed in more peripheral settings. In the same time it was noted that in certain disadvantaged populations the increase in health equity may be substantial. In the same time it was noted that in certain disadvantaged populations the increase in health equity may be substantial.	

ACCEPTABILITY	**Is the intervention acceptable to key stakeholders?** ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	The judgement would depend on the perspective: from clinician, laboratory technician and patients perspective - probably yes. Uncertainty remains for funders' perspective (donors, MoH), which may be eased by the additional data/analysis on affordability and cost-effectiveness. There were expressed concerns about sustainability of the new assay as well as manufacturer's monopoly.	
FEASIBILITY	**Is the intervention feasible to implement?** ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	There were concerns expressed, that the presented evidence is only qualitative (statements from TB-REACH on possibility of assay's implementation). In addition to that it was noted, that in-depth analysis on sustainability, cost-implications of the problem-solving with a new assay were missing.	Evidence is qualitative. No robust quantitative evidence available.

Summary of judgements

	JUDGEMENT						IMPLICATIONS
PROBLEM	No	Probably no	Probably yes	**Yes**	Varies	Don't know	Favors Xpert MTB/RIF
TEST ACCURACY	Very inaccurate	Inaccurate	Accurate	**Very accurate**	Varies	Don't know	Favors Xpert MTB/RIF
DESIRABLE EFFECTS	Trivial	Small	Moderate	**Large**	Varies	Don't know	Probably favors Xpert MTB/RIF
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial	Varies	Don't know	Probably favors Xpert MTB/RIF
CERTAINTY OF THE EVIDENCE OF TEST ACCURACY	Very low	Low	Moderate	**High**	No included studies		Favors Xpert MTB/RIF

	JUDGEMENT							IMPLICATIONS
CERTAINTY OF THE EVIDENCE OF TEST'S EFFECTS	Very low	**Low**	Moderate	High		No included studies		Probably favors [comparator test]
CERTAINTY OF THE EVIDENCE OF MANAGEMENT'S EFFECTS	Very low	**Low**	Moderate	High		No included studies		Probably favors [comparator test]
CERTAINTY OF THE EVIDENCE OF TEST RESULT/MANAGEMENT	Very low	**Low**	Moderate	High		No included studies		Probably favors [comparator test]
CERTAINTY OF EFFECTS	Very low	**Low**	Moderate	High		No included studies		Probably favors [comparator test]
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	**No important uncertainty or variability**			Probably favors Xpert MTB/RIF	
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know	Probably favors Xpert MTB/RIF
RESOURCES REQUIRED	**Large costs**	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know	Favors [comparator test]
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	**Moderate**	High			No included studies	Probably favors Xpert MTB/RIF
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	No included studies	Probably favors Xpert MTB/RIF
EQUITY	Reduced	Probably reduced	Probably no impact	**Probably increased**	Increased	Varies	Don't know	Probably favors Xpert MTB/RIF

	JUDGEMENT						IMPLICATIONS
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes	Varies	Don't know	Probably favors Xpert MTB/RIF
FEASIBILITY	No	Probably no	**Probably yes**	Yes	Varies	Don't know	Probably favors Xpert MTB/RIF

Should Xpert MTB/RIF be used to diagnose tuberculosis in all persons with signs and symptoms of TB?

TYPE OF RECOMMENDATION	Strong recommendation against the intervention ○	Conditional recommendation against the intervention ○	Conditional recommendation for either the intervention or the comparison ○	Conditional recommendation for the intervention ●	Strong recommendation for the intervention ○
RECOMMENDATION	Xpert MTB/RIF may be used rather than conventional microscopy and culture as the initial diagnostic test in all adults with signs and symptoms of tuberculosis (conditional recommendation acknowledging resource implications, high-quality evidence).				
JUSTIFICATION					
SUBGROUP CONSIDERATIONS					
IMPLEMENTATION CONSIDERATIONS					
MONITORING AND EVALUATION					
RESEARCH PRIORITIES					

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