XDR-TB diagnosis: a systematic review of economic aspects in different scenarios

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Abstract

Background: An analysis of cost and relative merits of strategies for the diagnosis of extensively drug-resistant tuberculosis (XDR-TB) in different settings would be useful for decision-making. Aims of the study were 1) to systematically review the published evidence on cost/cost-effectiveness of XDR-TB rapid testing; and 2) to discuss implications for countries with varied resources and TB incidence.

Methods: A systematic strategy for terms related to XDR-TB diagnosis and cost was used to search Pubmed and Embase up to September 2022. PRISMA guidelines were followed.

Collected data were analysed using STATA 17 (StataCorp, 2021) software. Cost data were reported in USD ($) and summarised by mean, standard deviation (±SD), and range. Country income level was defined according to the World Bank country classification. Three simplified scenarios were also used to explore testing implications, based on TB incidence (low, intermediate, and high).

Results: Of 157 records, 25 studies were included with 24 reporting the cost of Xpert/Rif and two studies evaluating the implementation of the MTBDRplus test. The total rapid test cost ranged from $12.41 to $218, including $1.13 - $74.60 for reagents and consumables and $0.40 - $14.34 for equipment.

Conclusion: The cost of XDR-TB diagnostics is lower in low resource settings. However, cost-effective implementation of XDR-TB diagnostic algorithms requires judicious consideration of local resources and prevalence to avoid missed identification and prescription of inappropriate regimens.

Introduction

Resistance to anti-tuberculosis (TB) drugs is a public health priority, causing substantial morbidity and mortality[1]. A pre-requisite for effective treatment includes the capacity to detect drug-resistance patterns in a routine, timely and accessible way[2,3]. Although *Mycobacterium tuberculosis* strains resistant to isoniazid and rifampicin, the two core anti-TB drugs defining multidrug-resistant (MDR)-TB are often diagnosed, more complicated drug resistant forms of TB exist including extensively drug-resistant tuberculosis[4-9] (XDR-TB), e.g. MDR-TB strains plus additional resistance to any fluoroquinolone and at least one WHO Group A drug (i.e., bedaquiline, linezolid) and its preliminary 'step' recently defined as pre-XDR (MDR-TB plus resistance to fluoroquinolones)[10,11]. The clinical management of MDR/XDR-TB is complex, taking advantage of a few active drugs which are expensive and often toxic, requiring mostly long treatment duration (although six-month regimens are now available) and achieving often sub-optimal outcomes[2,12].

According to the 2021 WHO estimates, out of 5.3 million existing pulmonary TB cases 63% are bacteriologically confirmed and 71% tested for rifampicin resistance, 38% using the WHO-recommended rapid diagnostics[9]. In 2021, 161,746 people with MDR/RR -TB were enrolled on treatment representing only about one in three of the people who develop MDR/RR -TB each year[9].

Recently, Cochrane Reviews[13,14] and a systematic review[2] investigated the role of the available rapid methods to diagnose pre-XDR/XDR-TB (including Line Probe Assays-LPAs, and the Xpert MTB/XDR assay) clearly showing that setting-specific algorithms are necessary to use the available rapid tools and integrate them with the other microbiological diagnostics as culture and drug susceptibility testing (DST).

A comprehensive cost-analysis of the approaches adopted to diagnose MDR- and XDR-TB, accompanied by a description of relative merits of the available algorithms in different scenarios does not exist, but it would be useful to inform clinical and public health decisions.

Based on recent evidence[2,13,14], we therefore aimed:

1) to perform a systematic review of the published evidence on the cost and cost-effectiveness of rapid tests to diagnose XDR-TB in different settings (High, Low, Lower-middle and Upper-middle income countries), and

2) to discuss the relative merits of algorithms used in countries with varied resources and TB incidence, to support future comprehensive assessment and research.

METHODS

Systematic review of the published evidence on the cost and cost-effectiveness of rapid tests to diagnose TB in different settings

Search strategy

A systematic search was conducted to collect the published evidence on the cost and cost-effectiveness of rapid tests to diagnose TB in different settings. The following string was adopted to search on Pubmed and Embase databases: "xpert mtb/rif" OR "xpert mtb/rif ultra" OR "xpert mtb/XDR" OR "mtbdrsl" AND "costs" AND "diagnosis" NOT "screening". Inclusions were limited to English language manuscripts and original peer-reviewed articles published until September 2022, with reports published in the grey literature or in the social and non-conventional media were excluded given the risk of unreliable and sub-optimal scientific information on the methodology adopted.

Study selection and data extraction

The inclusion and the exclusion criteria of the current systematic review were pre-registered. Both interventional and observational studies aiming at assessing the economic burden of TB rapid diagnostic tests were included.

Eligible types of economics evaluations included Cost-Effectiveness, Cost-Benefit, Cost-Minimization, and Cost-Utility analyses. Each study was required to have a reported diagnostic process of rapid TB testing. The review process was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA)[15] by two independent investigators, in order to check the eligibility of titles and abstracts, followed by full-text review. Any discordance was resolved with the intervention of a third investigator. The following variables were extracted from the selected manuscripts and collected in an *ad hoc* database: authors, year of publication, test type, country, country income, number of evaluated tests, total cost/test, direct and indirect costs. Incremental cost effectiveness ratio (ICER) was collected as an outcome measure.

Statistical analysis

Collected data were analysed using STATA 17 (StataCorp, 2021) software. Cost data were reported in USD ($) and summarised by mean, standard deviation (±SD), and range, with exchange rate as of September 2022 where conversion was required. Country income level was defined according to the World Bank country classification as of 2022[16].

Scenarios and evaluation

Three simplified scenarios were identified: a) low TB incidence countries with adequate availability of resources and diagnostics, b) countries with intermediate incidence of TB and moderate availability of resources and diagnostics, and c) high TB incidence countries with limited economic resources and diagnostics, which were mainly located in and around the capital and the main urban centres. Although we do not refer to specific countries, a classification of countries based on TB incidence is available[17].

The unit cost (including direct and indirect cost) of the tests reported in the 3 scenarios were derived from the systematic review[18-42], or, where not available, by other literature sources[43-58].

Illustrative scenario outcomes were considered according to first principles based on discussion with clinical and programmatic TB experts, and decided by consensus.

Scenario A: Countries with low TB incidence and adequate economic resources

This scenario identifies countries approaching the pre-elimination phase[59-62]. In these countries, spread across Europe, the Americas, the Eastern Mediterranean Region, Asia, and Oceania[9], the national/local guidelines are more stringent on the need to perform rapid tests and DST[63] than the global WHO ones[8].

In Scenario A the majority of patients are estimated to perform the proposed diagnostic examinations. Although not yet widely implemented so far in all low TB incidence countries, we assume comprehensive integration of Xpert XDR into diagnostic algorithms.

Scenario B: Countries with intermediate incidence and intermediate resources.

These countries are distributed in all continents, covering settings where MDR-TB can be highly prevalent or less important.

In these countries the main focus is usually represented by testing retreatment cases with Xpert, with a small proportion undergoing Xpert XDR and a consistent proportion of them undergoing DST and/or second-line LPA[9]. In the majority of new cases Xpert is the initial test, and a substantial proportion of those diagnosed as RR have access to phenotypic DST, which does not currently test for all drugs included in MDR/XDR TB regimens (in particular bedaquiline and linezolid).

Scenario C: Countries with high TB incidence and limited resources.

These countries are located in Africa, Asia, Latin America, and Oceania, and may show high prevalence of MDR-TB. The majority of retreatment patients and a fraction of the newly diagnosed subjects undergo Xpert (or Ultra), but Xpert XDR is usually not implemented, and only a fraction of

the RR undergo DST, which does not currently test for all drugs included in MDR/XDR TB regimens (in particular bedaquiline and linezolid)[9].

RESULTS

Systematic review of the published evidence on the cost and cost-effectiveness of rapid tests to diagnose TB in different settings

A total of 157 records were identified through the literature search in Pubmed and Embase databases and, of these, 58 duplicates were excluded. No additional references were added from other sources. After screening for title and abstract pertinence, 25 studies met the inclusion criteria (Figure 1). However, since some of the studies had a multicentric design or evaluated more than one rapid diagnostic test, results reported data for 30 settings/diagnostic techniques.

Publication years ranged from 2011[38] to 2022[18,19]. All the studies reported the cost of Xpert/Rif with the exception of two studies which evaluated the implementation of the MTBDRplus test[26,35]. Following the World Bank country classification for years 2021-2022[16], data were collected for 2 High Income[33,34,42], 2 Low Income[18,21,28,29,32,38,39], 5 Lower-middle Income[19,20,23,27,38], and 3 Upper-middle Income countries[22,24-26,30,31,35-38,40,41] (Table 1). Total Cost per rapid TB test ranged from $12.41[28] to $218[33], reagents and consumable from $1.13[20] to $74.60[34] and equipment ranged from $0.40[25] to $14.34[34]. Additional information on the number of estimated tests, staff and building and utilities costs are summarized in Table 1.

The costs of performing a rapid test (GeneXpert MTB/RIF or MTBDRplus) or of performing the GeneXpert MTB/RIF stratified by income ranged from $18.1 in Low Income to $149.7 in High Income countries, or between $16.6 in Low Income and $149.7 in High Income countries (Tables 2-3). Costs were reported as total cost per test, equipment, staff, reagents and consumables, building and utilities. The highest amount of testing expenditure in the considered scenarios was dedicated to reagents and consumables.

The outcome of most of the identified economic studies was measured as incremental cost-effectiveness ratio (ICER), defined as the change in costs over the change in the effectiveness of moving to the usage of a rapid diagnostic technique (GeneXpert MTB/RIF or MTBDRplus) from the gold standard (*i.e.* sputum smear microscopy)[18,21,23,28,30]. Other ICERs included: cost-effectiveness estimates per additional MDR-TB case diagnosed[26]; per treatment initiation, per treatment initiation on the same days as diagnosis, per treatment completed, or per improved morbidity[23]; per DALY averted[32]; per treatment day gained or per *status quo* per individual[42]; per QALY gained[34]. The outcome was reported as incremental savings in total cost only in the study of Millman and colleagues[33] (Table 4).

Scenarios and discussion of the algorithms

The illustrative impact and relative merits of approaches to diagnosing XDR-TB in the 3 scenarios is presented in Table 5.

DISCUSSION

Aims of our study were: 1) to perform a systematic review of the published evidence on the cost and cost-effectiveness of rapid tests to diagnose XDR-TB in different settings (High, Low, Lower-middle and Upper-middle income countries) and 2) to discuss the relative merits of algorithms used in countries with varied resources and TB incidence, to support future comprehensive assessment and research.

The results of our study identified the published cost for Xpert and Xpert Ultra and LPA (Table 2,3). As anticipated, they are progressively cheaper in countries with weaker economies, as a combined result of subsidized prices of tests and reagents, higher routine use and lower cost of equipment, staff, building and utilities. Although the sample of countries with relevant publications on costs is far from complete, the cost of the XDR-TB test in High Income countries was about 8 times higher than those of Low Income countries.

Important variability of the ICER indicator was found; although inter-country comparisons cannot be carried out following the adoption of different methodological approaches and different economic conditions (e.g., taxes, different prices in low- and high-income countries, etc.), the ICER of rapid testing per TB patient in comparison with a gold standard is less than $5,000 across most settings. An integration of economic studies is needed when implementation of a new diagnostic or therapeutic approach is planned. Defining an agreed standard for acceptable ICER threshold would be helpful for future evaluations. The methodology of the health technology assessment can allow a comprehensive evaluation of the added value of an intervention (i.e., scientific, economic, financial, ethical, and social), which should be tailored to the local needs.

Specific assumptions were made for the costs in the 3 scenarios identified, although it was impossible to assign a definite proportion of patients undergoing rapid testing and DST in different settings, as the literature is insufficiently detailed and large differences exist among countries belonging to the same scenario in terms of DST availability and use. As examples, in 2021 the percentage of MDR/RR-TB cases tested for resistance to any fluoroquinolone over the laboratory-confirmed cases of MDR/RR-TB was higher in the WHO African Region than the South-East Asia Region (60% and 36%, respectively), nevertheless the latter accounting for 10 times higher laboratory-confirmed cases of pre-XDR-TB or XDR-TB[9]. Thus, the diagnostic situation is heterogeneous within the high TB

234 incidence countries and even within the same WHO regions, preventing to make average assumptions
235 on the proportion of patients undergoing DST specifically of second-line drugs. Reassuringly,
236 laboratory coverage of MDR/RR-TB testing for pre-XDR-TB or XDR-TB diagnosis was well
237 established in the WHO European Region (83%) displaying high rate of resistance.
238 Clearly, approaches which seek to minimise cost with limited testing may cause delays in
239 implementing an effective regimen and potentially additional transmission of MDR/XDR-TB strains
240 in the community (Table 5).
241 *Scenario A* has the highest costs because of the larger comprehensive approach to XDR-TB diagnosis
242 (the Universal DST approach recommended by WHO) and no access to subsidized prices[64]. This
243 approach allows for rapid design of a regimen based on evidence to susceptibility to most first- and
244 second-line drugs in most patients. However, we found limited data regarding costs and cost-
245 effectiveness for such strategies.
246 In this scenario no case (or very few) undergoes inappropriate treatment and no or limited treatment
247 delays are likely to occur. This strategy also allows for the detection of isoniazid-monoresistant cases,
248 therefore avoiding inappropriate initiation of the standard regimen for new cases with presumed
249 susceptibility to first-line agents, which may facilitate the development of MDR-TB in isoniazid-
250 monoresistant patients. Nevertheless, beyond fluoroquinolones and isoniazid, availability of DST for
251 new/repurposed drugs (particularly bedaquiline, clofazimine, linezolid, and delamanid) remains
252 limited in some settings at lower TB incidence because of costs and lack of specialized infrastructure
253 and staff[65].
254 *Scenario B* countries' focus is to test retreatment cases with Xpert and Xpert XDR, with a proportion
255 of them undergoing DST. In the majority of new cases Xpert is the initial test, and not all those
256 diagnosed as rifampicin resistant (RR) have access to DST, which does not currently test for all drugs
257 included in MDR/XDR TB regimens (in particular bedaquiline and linezolid). A certain proportion
258 of XDR-TB cases (but also of isoniazid-mono resistant) will therefore not be detected, leading to
259 potential treatment delays, further transmission and development of super-resistance. A proportion of
260 isoniazid-monoresistant cases will undergo treatment for drug-susceptible cases (2HRZE/4RH) thus
261 facilitating treatment failure and the development of further resistance towards MDR-TB. Barriers to
262 accessing DST in this scenario are represented by the higher costs for laboratory testing, as most of
263 the countries under this situation have limited resources and speciality laboratory workers, but do not
264 have access to subsidized prices[65].
265 In *Scenario C* countries, the majority of retreatment patients and a fraction of the newly diagnosed
266 undergo Xpert (or Xpert Ultra), and a certain fraction of the RR undergoes further DST, with
267 extremely heterogeneous distribution at global level, which does not cover all drugs (mainly first-line

drugs and fluoroquinolones only). Serious gaps in access to DST of new/repurposed drugs exist in this scenario[65]. The delays in prescribing an effective regimen, the additional MDR-TB transmission occurring after diagnosis and before adequate treatment starts (leading to proportion of inappropriate treatment regimens prescribed) will be more important than in Scenario B.

The WHO shorter regimen for MDR-TB is less important in Scenario A than in Scenarios B and C, since a potential weakness is represented by the sub-optimal testing practices in some countries, which may lead to the development of additional resistances if resistance to its components is not excluded[66].

Our study has some limitations. Despite our systematic search strategy, a publication bias on the countries with relevant and available studies on costs is likely to exist. Furthermore, the description of the 3 scenarios is purely illustrative and aimed to offer a basis for future comprehensive analyses and research, supported by health economic modelling. Despite the effort done to estimate cost and proportion of patients accessing a given test, the reader should consider the large intra-country and intra-setting differences existing in the real world and that research studies running cost analyses are performed using different costing methods. Finally, not all countries at low incidence are high income (for example Cuba)[59].

In conclusion, different settings for XDR-TB diagnosis led to differences in costs with the lower cost being observed in settings with financial constraints, reflective of the less comprehensive approach to early identification of existing resistance and potential prescription of ineffective regimens. As no comprehensive real-world evidence exists on cost and effectiveness of different approaches to diagnosis of XDR-TB, the results of this study may guide future research in this direction.

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453 **Table 1. Reported costs from the studies included in the systematic review.**

First author	Publication year	Test type	Country	Income	No. of estimated tests/time (when appropriate)	Total cost/test (USD)	Cost for equipment (USD)	Cost for staff (USD)	Cost for reagents and consumable (USD)	Cost for buildings and utilities (USD)
Ejalu DL[18]	2022	Xpert MTB/RIF	Eastern Uganda	Low	20,800/ 5 years	15.32	1.22	0.15	10.38	1.34
Nadjib M[19]	2022	Xpert MTB/RIF	Indonesia	Low-middle	2,880–3,000/ 1 year	70.16	NA	NA	NA	NA
Muniyandi M[20]	2021	Xpert MTB/RIF	India	Low-middle	29/ month	16.48	9.36	3.05	1.13	4.14
Kaso AW[21]	2021	Xpert MTB/RIF	Ethiopia	Low	1,332 patients tested/1 year time frame	12.90	1.30	0.70	10.70	0.20
Wang SQ[22]	2019	Xpert MTB/RIF	China	Up-middle	2,922 test performed/ 2 year	13.20	3.24	0.11	10.05	0.02
Pooran A[23]	2019	Xpert MTB/RIF	Tanzania	Low-middle	2,029 performed/1 year	23.40	10.24	0.58	11.10	0.31
			Zambia	Low-middle	3,356 performed/1 year	23.18	10.18	0.57	11.03	0.16
			Zimbabwe	Low-middle	958 performed/1 year	30.59	10.12	0.51	10.31	3.52
Castro AZ[24]	2018	Xpert MTB/RIF	Brazil	Up-middle	87 performed/ 1 year	25.01	7.21	2.06	15.34	0.39
Dunbar R[25]	2018	Xpert MTB/RIF	South Africa	Up-middle	100,000	19.03	0.40	1.32	15.02	0.06
Naidoo P[26]	2016	MTBDRplus	South Africa	Up-middle	1,905	17.38	0.18	1.34	13.07	0.15

Rupert S[27]	2017	Xpert MTB/RIF	India	Low-middle	10,000	13.03	1.26	0.05	11.09	0.29
Walusimbi S[28]	2016	Xpert MTB/RIF	Uganda	Low	NA	12.41	1.37	0.15	10.37	0.29
Hsiang E[29]	2016	Xpert MTB/RIF	Uganda	Low	248	17.02	4.33	0.37	12.14	0.18
Jha S[30]	2016	Xpert MTB/RIF	South Africa	Up-middle	100	14.45	2.32	1.32	11.48	0.14
Pinto M [31]	2015	Xpert MTB/RIF	Brazil	Up-middle	34/day	40.14	2.42	13.27	22.01	2.04
Shah M [32]	2013	Xpert MTB/RIF	Uganda	Low	NA	17.42	4.38	0.41	12.20	1.23
Millman AJ[33]	2013	Xpert MTB/RIF	USA	High	234	218.00	59.00	35.00	60.00	NA
Choi HW[34]	2013	Xpert MTB/RIF	USA	High	3,000	98.10	14.34	5.18	74.60	5.18
Shah M[35]	2013	Xpert MTB/RIF	South Africa	Up-middle	NA	15.33	1.33	1.13	12.37	0.90
		MTBDRplus	South Africa	Up-middle	NA	23.46	1.60	3.46	14.13	4.28
Van Rie A[36]	2013	Xpert MTB/RIF	South Africa	Up-middle	199	21.19	3.42	1.30	10.28	1.17
Schnippel K[37]	2012	Xpert MTB/RIF	South Africa	Up-middle	NA	26.54	NA	2.90	14.36	3.08

Vassall A[38]	2011	Xpert MTB/RIF	India	Low-middle	10000	23.03	3.24	0.11	19.47	0.20
			South Africa	Up-middle		25.90	3.50	2.22	20.02	1.36
			Uganda	Low		27.55	7.00	0.24	20.18	0.52
Tucker A[39]	2021	Xpert MTB/RIF	Uganda	Low	NA	25.04	8.90	2.11	13.38	1.45
Meyer-Rath G[40]	2012	Xpert MTB/RIF	South Africa	Up-middle	NA	32.00	NA	3.00	23.00	3.00
Figueredo LJA[41]	2020	Xpert MTB/RIF	Brazil	Up-middle	NA	17.37	0.26	2.22	15.29	NA
Oxlade O[42]	2016	Xpert MTB/RIF	Canada	High	NA	133.03	4.03	67.03	62.50	NA

The number of estimated tests is herein reported as evaluated in the original manuscripts. Total cost per test is not the exact sum of the herein reported costs, since includes other expenditures that were not objects of the current study. Cost for equipment, staff, reagents and consumables, and buildings and utilities was extracted where available. NA = not available.

458 **Table 2. Costs of GeneXpert MTB/RIF and MTBDR plus stratified by income levels according to World Bank country classification by**
459 **income: 2021-2022.**

Variables	Income			
	High* **(n= 3)**	**Upper-Middle** **(n= 13)**	**Lower-middle** **(n= 7)**	**Low** **(n= 7)**
	Mean (SD; range) USD			
Total cost per test	149.7 (61.7; 98.1-218)	22.3 (7.6; 13.2-39.7)	28.4 (19.3; 12.6-70.2)	18.1 (5.9; 12.4-27.6)
Equipment	25.5 (29.5; 3.6-59)	2.2 (2.0; 0.2-6.8)	7.2 (4.0; 1.3-10.1)	4.0 (3.1; 0.8-8.9)
Staff	35.5 (30.9; 4.8-66.6)	2.7 (3.3; 0.1-13.3)	0.8 (1.0; 0.1-2.7)	0.5 (0.6; 0.2-1.7)
Reagents and consumable	65.7 (7.8; 60-74.6)	15.0 (4.2; 10.1-23.0)	10.6 (5.9; 0.7-19.5)	12.6 (3.3; 10.4-19.8)
Building and utilities	4.8 (-) 1/3	1.3 (1.4; 0.0-4.3)	1.4 (1.8; 0.2-3.7)	0.6 (0.5; 0.2-1.5)

460 Total cost per test is not the sum of the different cost items. *No studies reported MTBDR plus data for high income countries. SD: standard
461 deviation

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463 **Table 3. Costs of GeneXpert MTB/RIF stratified by income levels according to World Bank country classification by income, 2021-2022.**

Variables	Income			
	High **(n= 3)**	**Upper-Middle** **(n= 13)**	**Lower-middle** **(n= 7)**	**Low** **(n= 7)**
	Mean (SD; range) USD			
Total cost per test	149.7 (61.7; 98.1-218)	22.3 (8.5; 13.2-39.7)	29.1 (23.4; 12.6-70.2)	16.6 (4.6; 12.4-25.0)
Equipment	25.5 (29.5; 3.6-59)	2.4 (2.1; 0.3-6.8)	5.8 (4.4; 1.3-9.8)	3.5 (3.1; 0.8-8.9)
Staff	35.5 (30.9; 4.8-66.6)	2.8 (3.8; 0.1-13.3)	0.9 (1.2; 0.1-2.7)	0.6 (0.6; 0.2-1.7)
Reagents and consumable	65.7 (7.8; 60-74.6)	14.8 (4.5; 10.1-23.0)	10.5 (7.7; 0.7-19.5)	11.4 (1.1; 10.4-13.0)
Building and utilities	4.8 (-) 1/3	1.2 (1.2; 0.02-3.0)	1.1 (1.7; 0.2-3.7)	0.7 (0.5; 0.2-1.5)

Total cost per test is not the sum of the different cost items. SD: standard deviation

465 **Table 4. Study outcomes.**

First author	Publication Year	Test type	Country	ICER (USD)	Other estimated parameter (USD)	NOTE
Ejalu DL[18]	2022	Xpert MTB/Rif	Eastern Uganda	31.73		ICER of rapid testing per TB patient in comparison with the gold standard
Kaso AW[21]	2021	Xpert MTB/RIF	Ethiopia	20		ICER of rapid testing per TB patient in comparison with the gold standard
Pooran A[23]	2019	Xpert MTB/RIF	Tz, Zm, Zw	4186		ICER of rapid testing per TB patient in comparison with the gold standard
			Tz, Zm, Zw	1464		ICER per starting treatment
			Tz, Zm, Zw	561		ICER per starting treatment on the same days as diagnosis
			Tz, Zm, Zw	1211		ICER per completing the treatment
			Tz, Zm, Zw	1918		ICER per improved morbidity
Naidoo P[26]	2016	MTBDRplus	South Africa	6274		ICER of rapid testing per TB patient in comparison with the gold standard
Walusimbi S[28]	2016	Xpert MTB/RIF	Uganda	71		ICER of rapid testing per TB patient in comparison with the gold standard
Jha S[30]	2016	Xpert MTB/RIF	South Africa	1200-1720		ICER of rapid testing per TB patient in comparison with the gold standard
Shah M[32]	2013	Xpert MTB/RIF	Uganda	58		ICER per DALY averted
Millman AJ[33]	2013	Xpert MTB/RIF	U.S.		2278	Incremental savings in total cost
Choi HW[34]	2013	Xpert MTB/RIF	U.S.	39,992 per 1000 suspect TB		ICER per QALY gained
Shah M[35]	2013	Xpert MTB/RIF	South Africa	57		ICER per DALY averted
Vassall A[38]	2011	Xpert MTB/RIF	India	68.0		ICER per DALY averted
			South Africa	138.0		
			Uganda	52.0		

Oxlade O[42]	2016	Xpert MTB/RIF	Canada	164		ICER per incremental cost Gene Xpert per treatment day gained
				100		ICER per incremental cost Gene Xpert Vs *status quo* per individual

466 ICER: Incremental cost effectiveness ratio; TB: tuberculosis; QALY: Quality-adjusted life years; DALY: disability-adjusted life year

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469 **Table 5 Costs of diagnostic tests to detect XDR-TB in 3 scenarios (Low, Intermediate and High incidence countries)**

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	Low TB incidence countries		**Intermediate TB incidence countries**		**High TB incidence countries**	
Test	**Country**	**Unit cost (USD)**	**Country**	**Unit cost (USD)**	**Country**	**Unit cost (USD)**
Sputum smear	United States[43]	13.59	Brazil[41]	13.31	Botswana[46]	6.13
			Hong Kong[44]	7.5	Lesotho[46]	3.31
			Rep. Moldova[45]	8.15	Namibia[46]	5.31
			Georgia[58]	8.18	Swaziland[46]	4.24
					Ethiopia[21]	3.1
					India[20]	4.72
					Indonesia[19]	5.81
					Malawi[19]	4.06
					Mozambique[48]	3.13
					Myanmar[49]	5.4
					South Africa[50]	8.67
					Nigeria[67]	6.33
					Uganda[32]	1.99
					Zambia[23]	1.90
					Zimbawe[23]	2.55

	-	-	mean (range)	9.3 (7.5 -13.3)	mean (range)	4.4 (1.9-8.7)
Xpert MTB/RIF or Xpert MTB/RIF Ultra	mean (range)	149.7 (98.1-218)	mean (range)	25.7 (12.6-70.2)	mean (range)	16.6 (12.4-25.0)
Xpert XDR		NA		NA		NA
First- and second-line LPAs [#]	NA	NA	Rep. Moldova[45]	44.78	India[53]	59.21
			Russian Federation[54]	52.5	South Africa[35]	46.92
			Georgia[58]	154.98	Uganda[38]	43.68
			mean (range)	84.1 (44.8-155)	mean (range)	49.9 (43.7-59.2)
Liquid culture + First- and second-line DST	UK[52]	383.4	Brazil[51]	292.5	Namibia[46]	84.75
			Rep. Moldova[45]	89.85	South Africa[46]	94.7
			Georgia[58]	115.99	Botswana[46]	97.8
					Swatziland[46]	67.59
					Lesotho[46]	52.88
					India[46]	102.0
	-	-	mean (range)	166.1 (292.5-89.9)	mean (range)	83.3 (52.9 -102.0)
Solid culture + First- and second-line DST	NA	NA	NA	NA	India[46]	70.29
					Nigeria[46]	107.66
					mean (range)	89.0 (70.3-107.7)
What is likely to happen by scenario						
Rapid diagnosis	++++		++		++	

Interruption of infection transmission	++++	++	+
Effective diagnosis	++++	+	+/-
Adequate regimen selection	++++	+	+/-
Selection of resistant mutants	----	--	+/-

Papers published from 2012 to 2021 reporting direct and indirect costs of sputum smear, solid and/or liquid culture, first- and second-line line probe assays and drug susceptibility test for first and second-line drugs (the number of first- and second-line drugs tested not always specified) assessed from a health system perspective. # For countries reporting only first-line LPA cost, we assumed that the cost of second-line LPA was the same. NA: not available: LPA: line probe assay; DST: drug susceptibility testing

476 **Figure 1: PRISMA 2020 flow diagram for the present systematic review.**

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