ERJ Express. Published on December 20, 2012 as doi: 10.1183/09031936.00147912

Xpert MTB/RIF for the rapid diagnosis of TB and drug-resistant TB: a cost and affordability analysis

90 characters title:

Xpert MTB/RIF for diagnosis of TB and drug-resistant TB: a cost and affordability analysis

Running head: Cost and affordability analysis of Xpert MTB/RIF

Andrea Pantoja[1], Christopher Fitzpatrick[1], Anna Vassall[2,3], Karin Weyer[1] and Katherine Floyd[1].

1 Stop TB Department, World Health Organization, Geneva, Switzerland, **2** Department of Global Health, and Amsterdam Institute of Global Health and Development, Academic Medical Center, Amsterdam, The Netherlands, **3** Department of Global Health and Development, London School of Hygiene & Tropical Medicine, London, United Kingdom.

Corresponding author: Andrea Pantoja

ABSTRACT

Xpert MTB/RIF is a rapid test to diagnose tuberculosis (TB) and rifampicin-resistant TB. Cost and affordability will influence its uptake.

We assessed the cost, globally and in 36 high-burden countries (HBCs), of two strategies for diagnosing TB and multidrug-resistant TB (MDR-TB): Xpert with follow-on diagnostics, and conventional diagnostics. Costs were compared with funding available for TB care and control, and donor investments in HIV prevention and care.

Using Xpert to diagnose MDR-TB would cost US$ 0.09 billion/year globally and be lower cost than conventional diagnostics globally and in all HBCs. Diagnosing TB in HIV-positive people using Xpert would also cost about US$ 0.10 billion/year and be lower cost than conventional diagnostics globally and in 33/36 HBCs. Testing everyone with TB signs and symptoms would cost almost US$ 0.47 billion/year globally, much more than conventional diagnostics. However, in European countries, Brazil and South Africa the cost would represent <10% of TB funding.

Introducing Xpert to diagnose MDR-TB and to diagnose TB in HIV-positive people is warranted in many countries. Using it to test everyone with TB signs and symptoms is affordable in several middle-income countries, but financial viability in low-income countries requires large increases in TB funding and/or further price reductions.

Word count abstract: 200
Word count manuscript: 4290 (773 + 1303 + 1014 + 1200)

Introduction *(word count =773)*

Conventional diagnostic tests for tuberculosis (TB), including those for the detection of drug-resistant forms of TB and the diagnosis of TB in people living with the human immunodeficiency virus (HIV) infection, have limitations that are major constraints to progress in global TB care and control (1-5). Sputum smear microscopy, the most widely used test, has relatively low sensitivity in field conditions (typically in the range 50%–70%), and cannot be used to identify paucibacillary TB, extrapulmonary TB or drug resistance (6). Diagnosis using culture methods - the current reference standard - requires laboratory infrastructure that is not widely available in most countries with a high burden of TB, and test results take up to 3 months to obtain.

In December 2010, WHO endorsed a new rapid molecular test, called Xpert MTB/RIF® (Cepheid, Sunnyvale, USA). The test can simultaneously diagnose pulmonary TB and identify resistance to the most powerful first-line anti-TB drug, rifampicin. In five demonstration sites, the sensitivity of the test (compared with culture) for TB was 91% and specificity 99%; for rifampicin resistance, sensitivity was 95% and specificity 98%(7). The test takes less than 2 hours with minimal hands-on time (8-10). In May 2011, WHO published policy guidance with a strong recommendation that Xpert MTB/RIF should be used as the initial diagnostic test in two groups of people: individuals suspected of multidrug-resistant tuberculosis (MDR-TB), and those living with HIV who are suspected of having TB (11). MDR-TB is defined as resistance to at least rifampicin and isoniazid, the two most effective anti-TB drugs (12).

By the end of March 2012, around 61 countries had started to introduce Xpert MTB/RIF(13); others are actively considering its introduction. Widespread implementation could help to achieve the diagnosis and treatment targets set out in the Global Plan to Stop TB 2011–2015(13, 14). In 2015, the target is to diagnose and treat almost 7 million people with drug-susceptible TB (up from 5.7 million in 2010) and 0.3 million people with MDR-TB (up from around 50,000 in 2010). The funding required for treatment has been estimated at US$ 1 to 2 billion per year for MDR-TB, and US$ 4 to 5 billion per year for TB(14). The plan was prepared before the endorsement of Xpert MTB/RIF by WHO, and hence did not consider the cost of using Xpert MTB/RIF to diagnosis TB and MDR-TB, or how these costs compare with those for conventional diagnostics.

Evidence and commentary on Xpert MTB/RIF are growing (9, 15, 16). However, data on cost and cost-effectiveness are currently limited to three countries. Use of Xpert MTB/RIF for the diagnosis of smear-negative pulmonary TB has been found to be cost-effective when compared with the alternative of sputum microscopy and X-rays in India, South Africa and Uganda (17). The authors observed that it would be necessary to build on their study by evaluating the cost and affordability of Xpert MTB/RIF. A separate study in South Africa reported that Xpert MTB/RIF would increase the cost per case diagnosed (18) and a third study has suggested that the combination of smear microscopy followed by Xpert MTB/RIF (performed if smear-negative) has the highest accuracy and lowest cost compared with the use of each test in isolation (19).

In this paper, we assess the cost and affordability of using Xpert MTB/RIF to diagnose TB and multidrug-resistant TB globally and in 36 high TB and MDR-TB burden countries, compared with use of only conventional diagnostics.

Methods *(word count 1303)*

It should be stressed at the outset that our analysis focuses on comparing the costs of alternative approaches to diagnosis from the perspective of the health system and does not consider treatment costs of TB, MDR-TB and HIV, or costs from the perspective of patients. The reasons for not considering treatment costs are that treatments for TB and MDR-TB are the same following diagnosis by both Xpert MTB/RIF and conventional diagnostics, and that the costs of scaling up the treatment of TB and MDR-TB to reach global targets have already been assessed(14). We acknowledge at the outset that because Xpert MTB/RIF makes diagnosis of drug-resistant TB much easier (when someone tests positive for TB, a result on rifampicin-resistance is available at the same time), it is likely to lead to a more rapid increase in people diagnosed with MDR-TB and associated treatment costs, compared with continued reliance on conventional diagnostics alone. The reason for not considering patient costs was that evidence on how these costs change when Xpert MTB/RIF is introduced is not yet available, although they could conceivably be lower given fewer patient visits.

Countries and target populations considered

We considered the world as a whole, and 36 individual countries. The 36 countries appear in one or both of the lists of 22 high TB burden countries (22 HBCs) that account for about 80% of TB cases globally (1), and 27 high MDR-TB burden countries that account for about 85% of the world's cases of MDR-TB (20).

In line with WHO policy guidance, we defined three target populations in which Xpert MTB/RIF could be considered (21). The first group was all people presenting at health facilities with signs and symptoms consistent with TB. The size of this group was estimated using the numbers of TB cases reported by countries to WHO in 2011 (1) and the assumption (and widely used “rule of thumb”) that for every reported case of smear-positive pulmonary TB, there are approximately 10 people who would be tested for TB based on signs and symptoms. The second group was all people living with HIV (or whose HIV status is unknown in high HIV settings) presenting at health facilities with TB signs and symptoms. The size of this group was estimated according to the number of TB patients and the proportions of TB patients co-infected with HIV reported by countries to WHO in 2011(1), and the same 10:1 ratio between people suspected of having TB and the number of people diagnosed with TB. The third group was all individuals considered at risk of having MDR-TB. The size of this group was estimated as 20% of new TB cases (those with defined risk factors for MDR-TB) and all previously treated TB cases, in accordance with targets set out in the Global Plan (12, 14). Further details are provided in Table 1.

Alternative strategies

For each population group, two alternative strategies for the diagnosis of TB and MDR-TB were considered. The first strategy was use of Xpert MTB/RIF, supplemented by follow-on tests using conventional diagnostics where appropriate. Follow-on tests for resistance to isoniazid (and to confirm rifampicin resistance in

settings where such resistance is rare) using conventional methods are needed to confirm or rule-out MDR-TB for cases found to be rifampicin-resistant using Xpert MTB/RIF (21). To estimate the number of TB patients who would need follow-on tests we used the latest country data on levels of rifampicin resistance in new and previously treated cases(22). The second strategy was the use of conventional diagnostic algorithms according to WHO guidelines, which involve smear microscopy, culture examinations, drug susceptibility tests on solid or liquid media, and X-rays (4, 12, 23). The types and quantities of tests required in each diagnostic strategy, and associated sources of evidence, are defined in detail in Table 1.

We assumed that all population groups would receive the appropriate test(s) as recommended in the algorithm.

Costs

To estimate the annual resource requirements for the alternative strategies, the unit costs of all tests were estimated in US dollars (US$) in year 2011 prices. All unit costs and respective sources of evidence are defined in detail in Table 2(17, 21, 24-30). Seven points are worth highlighting. First, the unit costs of culture and drug susceptibility testing (DST) were based on available literature (17, 25-28). Second, the unit cost of a single Xpert MTB/RIF assay used in the baseline analysis (US$ 9.98) was based on the outcome of price negotiations concluded in August 2012 (29). Third, we assumed that one Xpert MTB/RIF cartridge per person tested is needed (a second test for TB using Xpert MTB/RIF for the same person is not recommended) (21). Fourth, costs for TB diagnosis using Xpert MTB/RIF include the annual costs of staff for performing the tests in the laboratory, annual calibration by the manufacturer and training (21). Fifth, the additional laboratory equipment that would be needed for conventional testing was identified based on the targets set out in the Global Plan and the current capacity reported by countries (Table 1b). Sixth, capital costs (e.g. equipment) were annualized using a standard discount rate of 3% (31) and an expected years of useful life of 5 years. Seventh, costs were calculated for both solid and liquid media for culture and DST; the lower end of the range shown in the results represents costs when solid media are used and the upper end of the range represents costs when liquid media are used. Finally, staff costs were included in all of the different diagnostic strategies.

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.

We selected 8 countries that illustrate results for countries in different geographic regions, countries that are both low and middle-income, and countries with varying burdens of HIV prevalence and MDR-TB. We then identified the countries that they represented, in terms of comparable relative patterns of costs when the alternative strategies were compared (for example, diagnostic costs for HIV-positive people with TB signs and symptoms were lower than costs associated with conventional diagnostics in the selected and represented countries). Results for all 36 countries are available in the supplementary material. The 8 countries, and the associated list of countries that they were considered to represent, are defined in Table 3.

Affordability at country level

We assessed affordability by comparing the costs of Xpert MTB/RIF relative to the funds that countries are already spending on health, in particular on TB care and control and on HIV prevention, treatment and care (the latter is of particular relevance to the costs of using Xpert MTB/RIF to diagnose TB among people living with HIV). We first compared costs with available funding for TB control in 2011 (1, 32). Second, we compared costs with budgets reported to WHO by national TB control programmes. Third, for African countries with a high burden of TB and HIV, we compared costs with 2011 country budgets allocated through the US President's Emergency Plan for AIDS Relief (PEPFAR) (33). Since the results for the second analysis were very similar to comparisons with available funding for TB care and control, only the results for the first and third analyses are reported in this paper.

Sensitivity analysis

Sensitivity analyses were undertaken for a) the expected years of life of capital items (buildings and equipment) of 10 years instead of 5 years; and b) the plausible range in the unit cost of culture, with a lower limit of US$12.1 and an upper limit of US$ 22.8 (Table 2). There is also uncertainty about the size of the population requiring testing for TB and MDR-TB in both strategies, but any changes affect both strategies in the same way and therefore do not affect relative comparisons.

All analyses were performed using Stata SE 11.

Results *(word count = 1014)*

Global number of tests and costs

Globally, around 1.8 million Xpert MTB/RIF assays per year would be needed to test patients at high risk of MDR-TB. For people living with HIV with TB signs and symptoms, approximately 3.8 million Xpert MTB/RIF tests per year would be needed to test for TB. If all individuals presenting at health facilities with signs and symptoms of TB were tested for TB using Xpert MTB/RIF, a best estimate of 26 million tests per year would be needed (Table 4).

Worldwide, the total cost per year of using Xpert MTB/RIF (including the conventional diagnostics needed to confirm or rule out a diagnosis of MDR-TB) ranged from US$ 70–89 million to test only those at high-risk of having MDR-TB, to US$ 90–101 million for testing all people living with HIV with TB signs and symptoms, to US$ 434–468 million for testing all people with TB signs and symptoms (Figure 1, Figure 2). The total costs of using conventional diagnostics according to WHO-recommended algorithms in these same population groups were US$ 123–191 million (the lower and upper ends of the range are costs using solid and liquid media for culture and DST, respectively), US$ 166 million and US$ 179 million respectively. There are no ranges for the latter two groups because in the first case only liquid media are recommended and in the second case neither culture nor DST are part of the diagnostic algorithm.

In a strategy using Xpert MTB/RIF, the Xpert MTB/RIF cartridge is the biggest item in the total cost of testing those with TB signs and symptoms, including those living with HIV (Figure 2). For testing among people at risk of MDR-TB, the cost of conventional culture and DST represent about 50% of the total cost.

36 high TB burden and high MDR-TB burden countries

The 8 countries shown in Figure 3 represent the relative cost patterns found in the other 28 high TB burden or high MDR-TB burden countries.

For every country, using Xpert MTB/RIF was a lower cost approach to diagnosis of MDR-TB than using conventional diagnostics (culture and DST) alone, sometimes by a large amount (Figure 3).

In low-income countries with a high prevalence of HIV (as illustrated by Kenya, which represents the pattern in DR Congo, Ethiopia, Mozambique, Tanzania, Uganda and Zimbabwe), the cost of using Xpert MTB/RIF to diagnose TB in people living with HIV was less than the cost of using conventional diagnostics. In countries with a low prevalence of HIV, using Xpert MTB/RIF to test for TB in people living with HIV with TB signs and symptoms was either less expensive or of similar cost compared with the use of conventional diagnostics according to the WHO-recommended algorithm (as illustrated by India and Myanmar, which represent the pattern seen in, among others, Brazil, Thailand, Indonesia and Bangladesh). In almost all countries (33/36), the cost of using Xpert MTB/RIF to test for TB in people living with HIV was similar or lower cost than the conventional culture-based diagnostic algorithm recommended by WHO.

For almost all countries, using Xpert MTB/RIF to test all people with TB signs and symptoms would increase costs approximately five-fold compared with the conventional practice of smear microscopy and follow-on chest X-ray for those with smear-negative results. The major exceptions were South Africa and the Russian Federation. In South Africa, the cost of using Xpert MTB/RIF for all people with TB signs and symptoms appears less costly compared with the costs of using conventional diagnostics. For the Russian Federation, annual costs increased by about 20%. The reason for the different results for these two countries is that tests for TB and MDR-TB using conventional culture is already a routine part of TB diagnosis. In Russia, the cost of using Xpert MTB/RIF was higher than conventional diagnostics (as opposed to South Africa) because the proportion of new cases that are likely to have MDR-TB in Russia is ten times higher than in South Africa (18% compared with 1.8%)(1), and therefore there is a greater need for follow-up tests to confirm or rule-out resistance to isoniazid and rifampicin.

Affordability at country level

The affordability of Xpert MTB/RIF in the 36 high TB and/or high MDR-TB burden countries relative to national funding for TB care and control in 2011 is illustrated in Figure 4.

For people suspected of having MDR-TB, the cost of Xpert MTB/RIF represents less than 4% of annual funding for TB in 24/36 countries including all of the European countries where the prevalence of MDR-TB among TB cases is highest. In several high TB burden countries in Asia as well as Nigeria and DR Congo, the cost ranged from 5% (both African countries) to 17% in Pakistan.

For HIV-positive people with TB signs and symptoms, the cost of using Xpert MTB/RIF represents less than 4% of annual funding for TB care and control in 18/36 countries including all of the European countries, with a range from 0.02% of national TB funding in Kazakhstan to 20% in Zimbabwe. In 27/36 countries, the cost of using Xpert MTB/RIF for HIV-positive people with TB signs and symptoms was less than 10% of the available funding for TB care and control in 2011. In 8 out of the 9 African countries the cost of using Xpert MTB/RIF was only 1-3% of the approved funding in the PEPFAR operational plans of 2011; in DR Congo it represents 6%.

For all people with TB signs and symptoms, the cost of using Xpert MTB/RIF represents less than 10% of annual funding for TB care and control in high burden countries in Europe as well as Brazil and South Africa, with costs negligible as a proportion of total spending on TB care and control in some European countries including the Russian Federation. In most of the high TB burden countries in Africa and Asia, costs represented at least 20% of TB spending in 2011, with much higher figures of above 80% in India, Bangladesh, Indonesia and Pakistan.

Sensitivity analysis

The results of sensitivity analyses are shown in Table 4. If the useful life of equipment is 10 instead of 5 years and using the baseline price per cartridge (US$ 9.98), the total cost of using Xpert MTB/RIF would be lowered by 7–28%, depending on the population group. Changes in the unit cost of culture, within the plausible range reported in the literature, had very small effects on total costs of strategies using

Xpert MTB/RIF (< 1%) and on testing for MDR-TB using conventional diagnostics only (<5%). The effect on total costs of testing using conventional diagnostics for people living with HIV was bigger, at ±10–11%. If purchased GeneXpert instruments are used at only 50% capacity, the unit cost per person tested would increase by US$ 3 (up from about US$ 16-18 in the baseline analysis), and if used at 25% capacity the unit cost per person tested would increase by US$ 9.

Discussion *(Word count=1200)*

This is the first study to assess the global costs of rolling-out Xpert MTB/RIF for the rapid diagnosis of TB and drug-resistant TB as well as the likely cost in all of the 36 high TB and high MDR-TB burden countries. Our results suggest that Xpert MTB/RIF reduces the costs of diagnosing MDR-TB globally and in all 36 countries, and that in 33/36 countries, as well as globally, it reduces the cost of diagnosing TB among people living with HIV, compared with use of only conventional diagnostics according to WHO guidelines. As a consequence, for these population groups, Xpert MTB/RIF is more affordable than conventional diagnostics. In high MDR-TB countries, the cost of using Xpert MTB/RIF to diagnose MDR-TB represents less than 4% of available TB funding. In most high TB burden African countries, the cost of using Xpert MTB/RIF to diagnose TB in HIV-positive people with TB signs and symptoms represents only 1-3% of the funding approved for PEPFAR operational plans. In contrast, the cost of using Xpert MTB/RIF to diagnose TB in all people presenting with signs and symptoms of TB disease is about five times higher than conventional diagnostics in most countries, although in several high MDR-TB burden countries in Europe as well as other middle-income countries the cost represents a small share of total national spending on TB care and control each year. Six limitations of our analysis should be noted. First, we may have underestimated the annual fixed costs of using Xpert MTB/RIF each year, which include staff, training, technical assistance and calibration. We used the best information currently available, which suggests a cost per year and per machine of US$ 11,800 (21). By 2013 there will be much more evidence from data that are being collected by early implementers and our analyses can be updated. Second, for strategies using Xpert MTB/RIF, we included the cost of follow-on DST for 2 drugs (rifampicin and isoniazid). In settings with high levels of MDR, such confirmation of rifampicin resistance is not essential; if only DST for isoniazid is performed, costs will be lower than our estimates suggest. Third, we were not able to assess the cost implications of the alternative strategies for patients. It will be important to consider how these are affected by the introduction of Xpert MTB/RIF; in theory, Xpert MTB/RIF should reduce costs to patients by reducing the number of visits to a health facility for diagnostic tests. Studies are now underway in several countries(34). Fourth, we used a single unit cost for culture and DST for all countries. While these unit costs were based on amounts reported in the published literature and we incorporated uncertainty in our analyses, in particular to explore the impact of different unit costs of culture tests on total costs, more evidence on the cost of culture and DST in varied country settings would be useful. The methods used in our study could also be replicated or adapted at country level, based on the conventional diagnostic algorithms in use (e.g. with or without X-rays) and available country-specific data on the unit costs of culture, DST and X-rays. Fifth, the costs of transporting culture and DST specimens were not included; it is thus possible that the cost of conventional diagnostics has been underestimated, since Xpert MTB/RIF is a more decentralized technology that does not require such frequent transportation of specimens. Sixth, we did not attempt to account for the additional costs associated with Xpert MTB/RIF cartridges that are lost as a consequence of

factors such as high temperatures, failure to use cartridges before their expiry date or power outages; this will become possible once more evidence on the frequency of these problems becomes available, likely in 2013 from early implementers of the technology.

Our analyses suggest that high MDR-TB burden countries implementing Xpert MTB/RIF should first focus on using the test to diagnose drug-resistant TB, while countries with a high prevalence of HIV but low levels of MDR should focus on using it to diagnose TB in people living with HIV. This is fully in line with WHO policy guidance issued in 2011. From a cost and affordability perspective, countries that already use culture as a routine part of TB diagnosis could also start to shift to the use of Xpert MTB/RIF for all people with TB signs and symptoms. Its introduction to test all people with TB signs and symptoms is also affordable in middle-income countries, but to be financially viable in low-income countries a big increase in funding for TB control and/or further reductions in the price of the Xpert MTB/RIF assay are required. As stated at the beginning of the methods, our analysis focuses on the cost of alternative ways of diagnosing TB and drug-resistant TB. If Xpert MTB/RIF is used to test for TB among people living with HIV or all people with TB signs and symptoms, the simultaneous testing for TB and rifampicin-resistant TB will identify larger numbers of patients with drug-resistant TB compared with the conventional algorithm that will identify only TB. When introducing Xpert MTB/RIF among these population groups, it is therefore essential that countries assess, plan and mobilize funds for the likely number of people that will be identified as having MDR-TB, for whom a longer and most costly second-line drug regimen is the appropriate course of treatment. Most of the funding required for treatment of MDR-TB is needed in upper and lower middle-income countries (14), notably China, India, South Africa and 13/15 of the high MDR-TB burden European countries (the exceptions are Tajikistan and Kyrgyzstan, which are low-income), where domestic capacity to fund such treatment is relatively good(1). In these countries, the lower costs of Xpert MTB/RIF combined with rapid results and much reduced need for sophisticated laboratory capacity to identify resistance to isoniazid and rifampicin (conventional DST is required only for those with a rifampicin-resistant result rather than all those suspected of having MDR-TB) also mean that using Xpert MTB/RIF could make a big contribution to facilitating the scale-up of diagnosis and treatment of MDR-TB in line with Global Plan targets.

Monitoring treatment of TB and MDR-TB requires that the laboratory capacity for microscopy and culture is retained or extended where needed. Published evidence on the cost-effectiveness of MDR-TB treatment shows that the monitoring costs are only between 3% and 6% of the total cost of treatment per MDR-TB patient; these costs typically include expansion of laboratory capacity, culture tests and tests for drug susceptibility (25, 27, 28, 35). Therefore, the cost implications of an increase in the volume of people diagnosed with MDR-TB when Xpert MTB/RIF is implemented will be relatively minor from the laboratory monitoring perspective.

Conclusions

Scaling-up capacity to diagnose TB and MDR-TB will greatly facilitate TB prevention, care and control. From a cost and affordability perspective, wide-scale introduction of Xpert MTB/RIF to diagnose MDR-TB and to diagnose TB in people living with HIV is warranted, in line with WHO policy guidance. Its introduction to

test all people with TB signs and symptoms is affordable in middle-income countries, but to be financially viable in low-income countries a big increase in funding for TB control and/or further reductions in the price of the Xpert MTB/RIF assay are required.

The authors declared that no competing interests exist.
An ethics statement was not required for this work.
No funding was received for this work, and no funding bodies played any role in the design, writing or decision to publish this manuscript.

References

1. WHO. Global tuberculosis control: WHO report 2011. Geneva: World Health Organization. 2011. Report No.: WHO/HTM/TB/2011.16.

2. Getahun H, Harrington M, O'Brien R, Nunn P. Diagnosis of smear-negative pulmonary tuberculosis in people with HIV infection or AIDS in resource-constrained settings: informing urgent policy changes. Lancet. 2007 Jun 16;369(9578):2042-9.

3. Small PM, Pai M. Tuberculosis diagnosis--time for a game change. N Engl J Med. 2010 Sep 9;363(11):1070-1.

4. WHO. Improving the diagnosis and treatment of smear-negative pulmonary and extrapulmonary tuberculosis among adults and adolescents. Recommendations for HIV-prevalent and resource-constrained settings. Geneva: World Health Organization (WHO/HTM/TB/2007.379); 2007.

5. WHO. Multidrug and extensively drug-resistant TB (M/XDR-TB): 2010 global report on surveillance and response. Geneva: World Health Organization (WHO/HTM/TB/2010.3); 2010.

6. Steingart KR, Henry M, Ng V, Hopewell PC, Ramsay A, Cunningham J, et al. Fluorescence versus conventional sputum smear microscopy for tuberculosis: a systematic review. The Lancet Infectious Diseases. 2006;6(9):570-81.

7. Boehme CC, Nicol MP, Nabeta P, Michael JS, Gotuzzo E, Tahirli R, et al. Feasibility, diagnostic accuracy, and effectiveness of decentralised use of the Xpert MTB/RIF test for diagnosis of tuberculosis and multidrug resistance: a multicentre implementation study. The lancet. 2011;377(9776):1495-505.

8. Helb D, Jones M, Story E, Boehme C, Wallace E, Ho K, et al. Rapid detection of Mycobacterium tuberculosis and rifampin resistance by use of on-demand, near-patient technology. Journal of clinical microbiology. 2010 Jan;48(1):229-37.

9. Rie AV, Page-Shipp L, Scott L, Sanne I, Stevens W. Xpert® MTB/RIF for point-of-care diagnosis of TB in high-HIV burden, resource-limited countries: hype or hope? Expert review of molecular diagnostics. 2010 2010/10/01;10(7):937-46.

10. Boehme CC, Nabeta P, Hillemann D, Nicol MP, Shenai S, Krapp F, et al. Rapid molecular detection of tuberculosis and rifampin resistance. N Engl J Med. 2010 Sep 9;363(11):1005-15.

11. WHO. Policy statement: automated real-time nucleic acid amplification technology for rapid and simultaneous detection of tuberculosis and rifampicin resistance: Xpert MTB/RIF system. Geneva: World Health Organization (WHO/HTM/TB/2011.4); 2011. Available from: http://who.int/tb/laboratory/mtbrifrollout/en/index.html.

12. WHO. Guidelines for the programmatic management of drug-resistant tuberculosis – 2011 update. Geneva: World Health Organization (WHO/HTM/TB/2011.6); 2011.

13. WHO. Implementation and roll-out of Xpert MTB/RIF - Update May 2012. Geneva: World Health Organization. ; 2012 [Date last accessed: 20 May 2012]; Available from: http://www.stoptb.org/wg/gli.

14. WHO and Stop TB Partnership. The global plan to stop TB 2011-2015: transforming the fight towards elimination of tuberculosis. Geneva: World Health Organization (WHO/HTM/STB/2010.2); 2010.

15. Trébucq A, Enarson DA, Chiang CY, Van Deun A, Harries AD, Boillot F, et al. Xpert MTB/RIF for national tuberculosis programmes in low-income countries: when, where and how? The International Journal of Tuberculosis and Lung Disease. 2011;15(12):1567-72.

16. Singh JA, Bhan A. The ethics of national tuberculosis programmes in low-income countries not rolling out Xpert MTB/RIF. The International Journal of Tuberculosis and Lung Disease. 2011;15(12):1563-.

17. Vassall A, van Kampen S, Sohn H, Michael JS, John KR, den Boon S, et al. Rapid Diagnosis of Tuberculosis with the Xpert MTB/RIF Assay in High Burden Countries: A Cost-Effectiveness Analysis. PLoS medicine. 2011;8(11):e1001120.

18. Meyer-Rath G, Bistline K, Long L, MacLeod W, Sanne I, Stevens W, et al. The incremental cost of introducing Xpert® MTB/RIF into the South African national tuberculosis programme: Results of the National TB Cost Model 2011/12 - 2016/17. HE²RO Policy Brief Number 1, Health Economics and Epidemiology Research Office. 2011.

19. Theron G, Pooran A, Peter J, van Zyl-Smit R, Mishra HK, Meldau R, et al. Do adjunct TB tests, when combined with Xpert MTB/RIF, improve accuracy and the cost of diagnosis in a resource-poor setting? European Respiratory Journal. 2011 November 10, 2011.

20. WHO. Towards universal access to diagnosis and treatment of mulridrug-resistant ans extensively drug-resistant tuberculosis by 2015: WHO Progress Report 2011. Geneva: World Health Organization. 2011. Report No.: WHO/HTM/TB/2011.3.

21. WHO. Rapid implementation of the Xpert MTB/RIF diagnostic test: technical and operational 'How-to'; practical considerations. Geneva: World Health Organization (WHO/HTM/TB/2011.2); 2011. Available from: http://who.int/tb/laboratory/mtbrifrollout/en/index.html.

22. Matteo Zignol, Wayne van Gemert, Dennis Falzon, Charalambos Sismanidis, Philippe Glaziou, and KF, et al. Surveillance of anti-tuberculosis drug resistance in the world: an updated analysis, 2007–2010. Bulletin of the World Health Organization. 2012 February 2012;90(2):111-9d.

23. WHO. Treatment of Tuberculosis: guidelines for national programmes - 4th edition. Geneva: World Health Organization (WHO/HTM/TB/2009.420); 2010. Available from: http://whqlibdoc.who.int/publications/2010/9789241547833_eng.pdf.

24. WHO. TB planning and budgeting tool. [Date last accessed: 15 February 2012]; Available from: http://www.who.int/tb/dots/planning_budgeting_tool/en/index.html.

25. Tupasi TE, Gupta R, Quelapio MI, Orillaza RB, Mira NR, Mangubat NV, et al. Feasibility and Cost-Effectiveness of Treating Multidrug-Resistant Tuberculosis: A Cohort Study in the Philippines. PLoS medicine. 2006 Sep 12;3.

26. Mueller DH, Mwenge L, Muyoyeta M, Muvwimi MW, Tembwe R, McNerney R, et al. Costs and cost-effectiveness of tuberculosis cultures using solid and liquid media in a developing country. The International Journal of Tuberculosis and Lung Disease. 2008;12(10):1196-202.

27. Pedro G Suárez, Katherine Floyd, Jaime Portocarrero, Edith Alarcón, Elisabetta Rapiti, Gilbert Ramos, et al. Feasibility and cost-effectiveness of standardised second-line drug treatment for chronic tuberculosis patients: a national cohort study in Peru. The Lancet. 2002;359.

28. Floyd K, Hutubessy R, Kliiman K, Centis R, Khurieva N, Jakobowiak W, et al. Cost and cost-effectiveness of MDR-TB treatment in Estonia and the Russian Federation. European Respiratory Journal. 2012;erj01694-2011.

29. UNITAID. UNITAID approves US$ 30 million for innovative project to roll out ground-breaking tuberculosis test at reduced cost. [Date last accessed: 30 June 2012]; Available from: http://www.unitaid.eu/resources/news/releases.

30. Foundation for Innovative New Diagnostics. FIND-negotiated prices for BACTEC and MGIT and country list. [Date last accessed: 20 February 2012]; Available from: http://www.finddiagnostics.org/about/what_we_do/successes/find-negotiated-prices/bactec-mgit.html.

31. Drummond MF, et. al, . Methods for the Economic Evaluation of Health Care Programs (Oxford Medical Publications) (Paperback) Oxford University Press 2005.

32. WHO. Tuberculosis database. [Date last accessed: 27 February 2012]; Available from: http://www.who.int/tb/country/data/profiles/en/index.html.

33. PEPFAR - The U.S. president'semergency plan for AIDS relief. Fiscal Year 2011: PEPFAR Operational Plan. [Date last accessed: 14 May 2012]; Available from: http://www.pepfar.gov/documents/organization/183974.pdf, .

34. TREAT TB. Xpert® MTB/RIF Research Projects. 2012 [Date last accessed: 1 September 2012]; Available from: http://xrmt.treattb.org/projects-listing2.

35. Fitzpatrick C, Floyd K. A systematic review of the cost and cost effectiveness of treatment for multidrug-resistant tuberculosis. Pharmacoeconomics. 2012;30(1):81.

Order of figures and tables as appeared in text:

Table 1a, 1b
Table 2
Table 3
Figure 1
Figure 2
Table 4
Figure 3
Figure 4

Figures and Legends

Figure 1

Global estimates of the annual cost of TB and MDR-TB diagnosis using Xpert MTB/RIF, compared with the costs of conventional diagnostics following WHO-recommended algorithms, US$ millions (2011 prices). [Estimates include costs for solid or and liquid media for culture and DST. The grey section of the bar depicts the additional cost for liquid media of culture and/or DST]

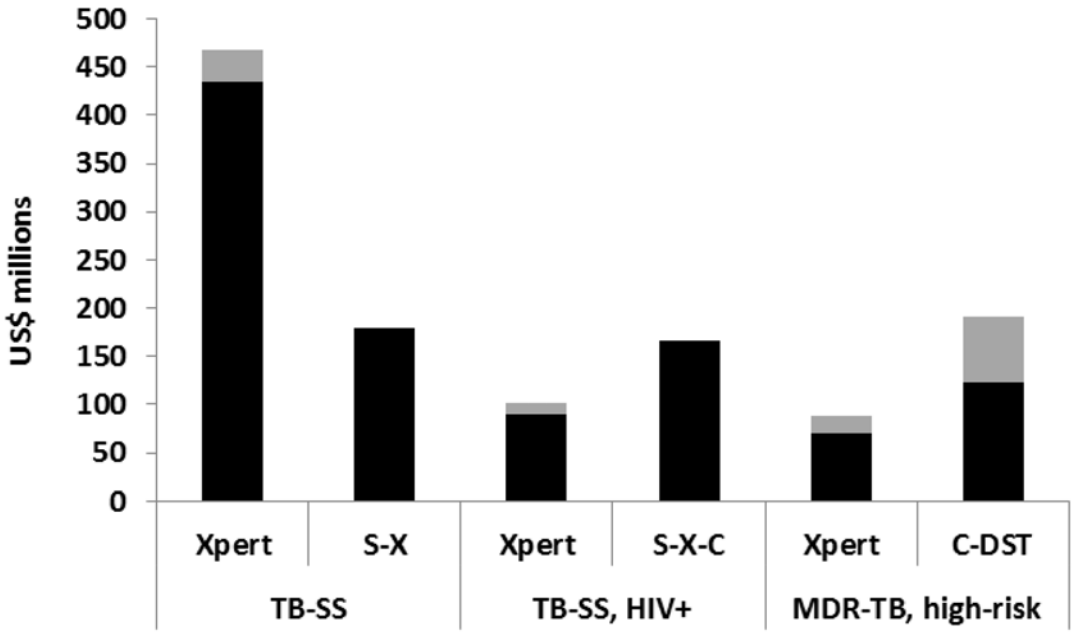

Figure 2

Global estimates of the annual cost of TB and MDR-TB diagnosis using Xpert MTB/RIF, breakdown of costs, US$ millions (2011 prices)

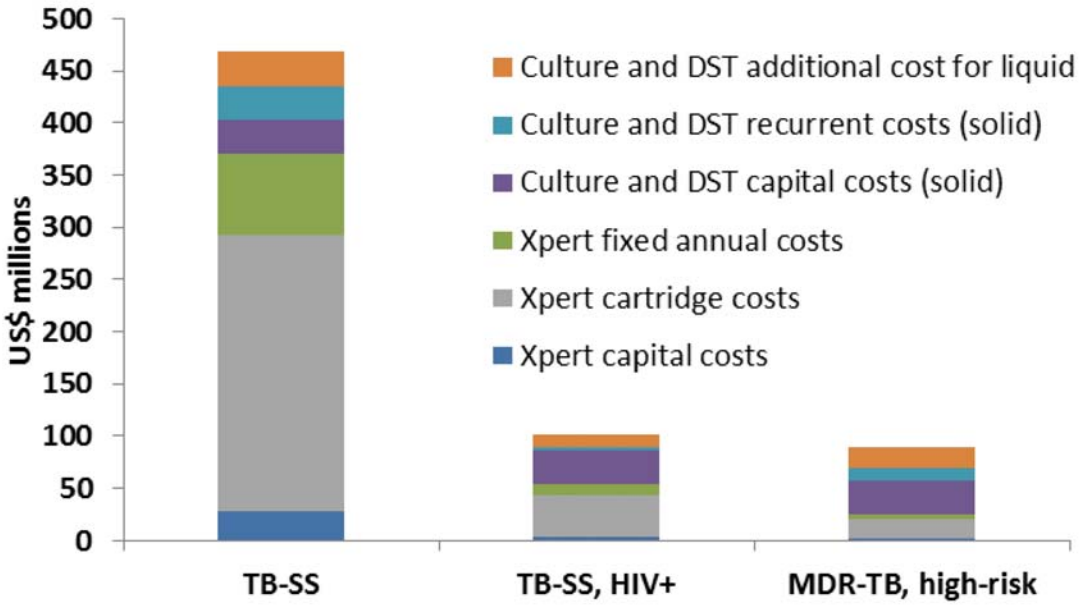
500
450
400
350
300
250
200
150
100
50
0
US$ millions
Culture and DST additional cost for liquid
Culture and DST recurrent costs (solid)
Culture and DST capital costs (solid)
Xpert fixed annual costs
Xpert cartridge costs
Xpert capital costs
TB-SS
TB-SS, HIV+
MDR-TB, high-risk

Figure 3

Estimated annual cost of TB and MDR-TB diagnosis using Xpert MTB/RIF, compared with the costs of conventional diagnostics following WHO-recommended algorithms, 8 representative high-burden countries, US$ millions (2011 prices). [Estimates include costs for solid or and liquid media for culture and DST. The grey section of the bar depicts the additional cost for liquid media of culture and/or DST]

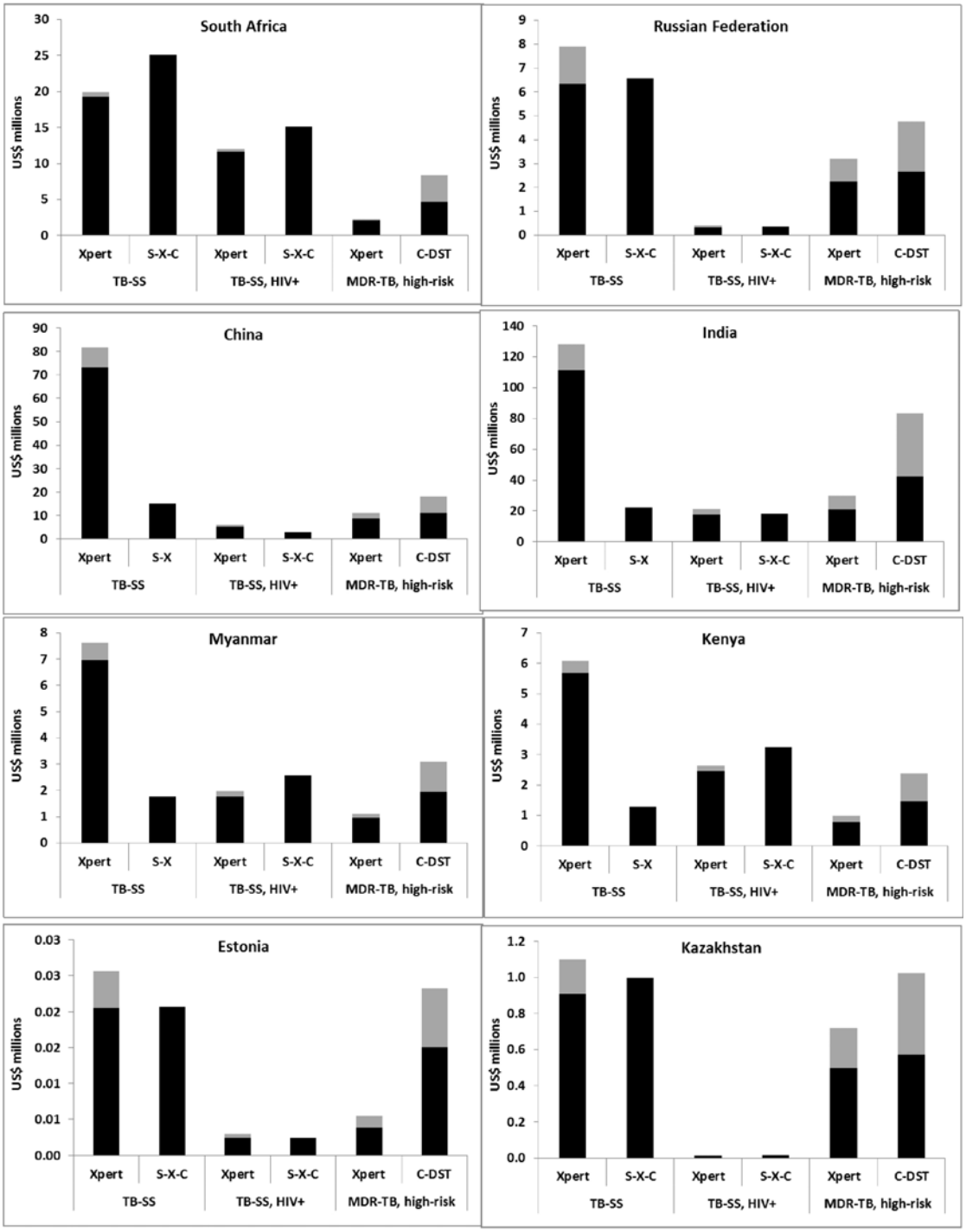

Figure 4

Total annual cost of TB and MDR-TB diagnosis using Xpert MTB/RIF as a proportion of available national funding for TB in 2011, 33 high TB-burden and high MDR-TB burden countries

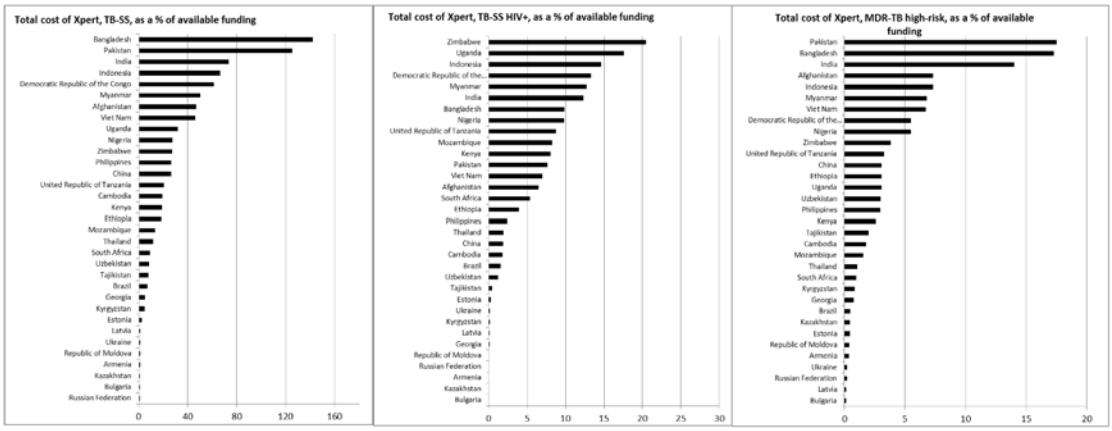

Table 1a: Methods – Assumptions for the target populations considered

Three target populations:	Description	Reference [Reference number]
1. All people with TB(a) signs and symptoms		
Shortened title used in figures:	TB-SS	
number:	Assume 10 suspects per 1 smear-positive TB case notified in 2011.	2011 Global TB Report [1].
Conventional practice for diagnosis:	2 smears and 1 x-ray for those smear-negative [S-X](b)	WHO guidelines [23].
additional tests for South Africa, Russia, Estonia and Kazakhstan:	1 culture test [S-X-C](c)	
Xpert MTB/RIF:	1 test per person	Xpert MTB/RIF rapid implementation [21].
DST(d) (and culture) follow-on test when using Xpert MTB/RIF (confirmatory test):	1 culture test followed by 1 DST for 2 first-line drugs (rifampicin and isoniazid; solid or liquid) per patient with rifampicin- resistant result with Xpert MTB/RIF	Xpert MTB/RIF rapid implementation [21].
Proportion of Xpert tested patients with rifampicin-resistant positive result:	Proportion of rifampicin resistance (where data are available); and estimated proportion of new TB cases that have MDR-TB (e)	Zignol M. [22]; and 2011 Global TB Report [1].
2. HIV-positive individuals (f) (or HIV unknown in high HIV settings) with TB signs and symptoms		
Shortened title used in figures:	TB-SS, HIV+	
number:	Proportion of tested TB patients HIV positive multiplied by all TB suspects	2011 Global TB Report [1].
Conventional practice for diagnosis	2 smears, 1 X-ray and 1 culture [S-X-C]	WHO guidelines for TB/HIV [4].
Xpert MTB/RIF:	1 test per suspect	Xpert MTB/RIF rapid implementation [21].
DST (and culture) follow-on test when using Xpert MTB/RIF (confirmatory test):	1 culture test followed by 1 DST for 2 first-line drugs (rifampicin and isoniazid; solid or liquid) per patient with rifampicin- resistant result with Xpert MTB/RIF	Xpert MTB/RIF rapid implementation [21].
Proportion of Xpert tested patients with Rifampicin-resistant positive result:	Proportion of rifampicin resistance (where data are available); and estimated proportion of new TB cases that have MDR-TB	Zignol M. [22]; and 2011 Global TB Report [1].
3. Individuals at risk of having MDR-TB, diagnosed with TB or with TB signs and symptoms		
Shortened title used in figures:	MDR-TB, high-risk	
number:	20% of all new TB cases, + 100% of relapse TB cases, + 100% TB retreatment cases	2011 Global TB Report [1].
Conventional practice for diagnosis:	1 culture test plus 1 DST for 2 drugs (rifampicin and isoniazid; solid or liquid media)	WHO guidelines for MDR-TB [12].
Xpert MTB/RIF:	1 test per person	Xpert MTB/RIF rapid implementation [21].
DST (and culture) follow-on test when using Xpert MTB/RIF (confirmatory test):	1 culture test followed by 1 DST for 2 first-line drugs (rifampicin and isoniazid; solid or liquid) per patient with rifampicin- resistant result with Xpert MTB/RIF	Xpert MTB/RIF rapid implementation [21].
Proportion of Xpert tested patients with Rifampicin resistance result:	Proportion of rifampicin resistance (where data are available); and estimated proportion of new TB cases that have MDR-TB	Zignol M. [22]; and 2011 Global TB Report [1].

(a)TB=Tuberculosis; (b) S=smear-microscopy and X=X-ray; (c) C=culture; (d) DST= drug susceptibility testing; (e) MDR-TB== multidrug-resistant tuberculosis;
(f) HIV-positive individuals **=** people living with the human immunodeficiency virus (HIV) infection

Table 1b: Methods – Assumptions for number of laboratories, as per targets and indicators in The global plan to Stop TB 2006-2011

Assumptions	1 AFB (a) microscopy laboratory per 100,000 population; 1 culture laboratory per 5,000,000 population; 1 DST laboratory per 5,000,000 population
Description	Baseline number of laboratories per country was obtained from the WHO's global TB database. This number was compared with the target number set out in the Global Plan. The difference is the number of new laboratories that require laboratory equipment for any of the three diagnostic methods; hence, capital investment for laboratories refers only to equipment, infrastructure is not included in the analysis.

(a) AFB= acid-fast bacilli

Table 2: Methods - Unit costs, US$, 2011 prices

Item	US$	Quantities	Source
Diagnostic tests and other annual costs			
Smears	1	2	TB Planning and budgeting Tool (24) .
Culture	17.4 (12.1 – 22.8)	1	References [17, 25-28].
DST for first-line drugs on solid media, per drug	9.1 (8.8 – 9.4)	2	References [17, 25-28].
DST for first-line drugs on liquid media, per drug	23.15 (19.6 – 26.7)	2	References [17, 25-28].
Digital X-ray	1.5	1	Recent experience in TB prevalence surveys.
Xpert test, agreed price for second half of 2012	9.98	1	UNITAID [29].
Annual calibration, annual technician salary, annual training/technical assistance, annual cost per machine	11,800	1	Xpert MTB/RIF rapid implementation [21].
Laboratory equipment (a)			
AFB microscopy equipment, per new laboratory	19,624	1	TB Planning and budgeting Tool [24].
Culture in solid media, per new laboratory	177,698	1	TB Planning and budgeting Tool [24].
(Culture and) DST lab in solid media, per new laboratory	185,681	1	TB Planning and budgeting Tool [24].
MGIT for liquid culture and DST, per new laboratory	79,655	1	TB Planning and budgeting Tool [24].
MGIT for liquid culture and DST for countries for which FIND has negotiated prices, per new laboratory	38,950	1	FIND (30).
GeneXpert machine, 4 modules	17,500	1	Xpert MTB/RIF rapid implementation [21].
Shipment, Printer, UPS	1,700	1	Xpert MTB/RIF rapid implementation [21].

(a) Costs for infrastructure, annual maintenance, and quality assurance are not included.

Table 3: Eight countries selected to illustrate results and the countries for which they are representative of cost patterns when diagnostic strategies are compared

8 representative countries	associated 36 countries
South Africa	South Africa
The Russian Federation	The Russian Federation
China	China
India	Brazil, Thailand, Indonesia, the Philippines, Viet Nam, Nigeria, Pakistan and India
Myanmar	Afghanistan, Bangladesh, Cambodia and Myanmar
Kenya	Democratic Republic of the Congo, Ethiopia, Mozambique, Uganda, United Republic of Tanzania, Zimbabwe, and Kenya
Estonia	Lithuania, Latvia and Estonia
Kazakhstan	Armenia, Azerbaijan, Bulgaria, Belarus, Georgia, Kyrgyzstan, Republic of Moldova, Tajikistan, Ukraine, Uzbekistan and Kazakhstan

Table 4: Global estimates of total annual costs, US$ millions (2011 prices): sensitivity analysis for life expectancy for equipment, for unit cost of cultures and resulting unit cost per person tested*

Variable considered in sensitivity analysis	Total cost of diagnostic strategy		Unit cost per person tested		Best estimate of numbers to be tested, globally§
	Xpert MTB/RIF	Conventional diagnostics	Xpert MTB/RIF	Conventional diagnostics	
Life expectancy of GeneXpert machine 5 years (unit cost of culture US$17.4)					
TB-SS	434-468	179	16-18	6.7	26,600,000
TB-SS, HIV+	90-101	166	23-26	43	3,897,376
MDR-TB, high-risk	70-89	123-191	38-49	67-104	1,828,259
Life expectancy of GeneXpert machine 10 years					
TB-SS	407-436	152	15-16	5.7	26,600,000
TB-SS, HIV+	73-81	126	19-21	32	3,897,376
MDR-TB, high-risk	54-69	96-156	30-38	53-85	1,828,259
Unit cost of culture US$12.1					
TB-SS	430-463	177	16-17	6.7	26,600,000
TB-SS, HIV+	89-101	150	23-26	38	3,897,376
MDR-TB, high-risk	68-87	114-182	37-48	62-100	1,828,259
Unit cost of culture US$22.8					
TB-SS	439-473	181	17-18	6.8	26,600,000
TB-SS, HIV+	90-102	183	23-26	47	3,897,376
MDR-TB, high-risk	72-90	132-200	39-49	72-109	1,828,259
GeneXpert machines underused at 50%					
TB-SS	505-559	179	19-21	6.7	26,600,000
TB-SS, HIV+	101-113	166	26-29	43	3,897,376
MDR-TB, high-risk	75-95	123-191	41-52	67-104	1,828,259
GeneXpert machines underused at 25%					
TB-SS	585-638	179	22-24	6.7	26,600,000
TB-SS, HIV+	113-125	166	29-32	43	3,897,376
MDR-TB, high-risk	80-101	123-191	44-55	67-104	1,828,259

*Lower range refers to cost estimate with culture and DST on solid media; upper range refers to cost estimate with culture and DST on liquid media.
§There is some overlap in the number of tests between the group of HIV-positive individuals with TB signs and symptoms and the group of individuals at risk of having MDR-TB. However, it should be noted that this overlap is limited since most countries with a high prevalence of HIV are in Africa, where the burden of MDR-TB is relatively low.