**Improving rifampicin resistant tuberculosis diagnosis with Xpert® MTB/RIF: modelling interventions and costs**

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**Conflicts of interest**

The authors declare that they have no financial or non-financial conflicts of interests.

**Setting**

Cape Town, South Africa

**Objective**

To model RMP-R diagnosis and laboratory costs in smear/culture and Xpert-based algorithms and the effect of varying adherence and HIV testing in the Xpert-based algorithm.

**Methods**

We used a validated operational model (100,000 population) and published laboratory cost data. We estimated the number and cost of RMP-R TB cases identified between a smear/culture and Xpert-based algorithm. We modelled varying adherence and different levels of known HIV-status to the Xpert-based algorithm.

**Results**

RMP-R TB cases identified increased from 603 with smear/culture to 1,178 with the Xpert-based algorithm (100% adherence - 60% knew their HIV status). The overall laboratory cost increased from U$1,073,858 to U$2,430,050 and the cost per RMP-TB case identified increased from U$1,781 to U$2,063 in respective algorithms.

When adherence to the Xpert-based algorithm was increased from 50% to 100% (60% knew their HIV-status), the number of RMP-R TB cases identified increased from 721 to 1,178.

**Conclusion**

The Xpert-based algorithm is efficient in identifying RMP-R TB as the increase in costs is offset by the increase in the number of cases identified. Adherence to the Xpert-based algorithm is important to ensure all presumptive TB cases receive the benefit of simultaneous TB and RMP-R testing.

**Introduction**

Globally the multidrug-resistant tuberculosis (MDR-TB) crisis is continuing. The burden of MDR-TB is decreasing more slowly than the overall burden of tuberculosis (TB) and in some countries the MDR-TB burden is on the increase.1 The World Health Organisation (WHO) collectively defines cases of MDR-TB (defined as resistance to rifampicin and isoniazid) and rifampicin-resistant (RMP-R) TB as MDR/RMP-R TB with the recommendation to start all these cases on a second-line MDR-TB regimen.1

The gaps between the estimated number of incident MDR/RMP-R TB cases, the number diagnosed and the number notified are still of major concern. Globally there were 3.4 million bacteriologically confirmed TB cases notified in 2015 of which only 30% were reported to have had a drug susceptibility test (DST) for rifampicin. In 2015, 132,120 cases of MDR/RMP-R TB were detected and notified globally which amounts to only 40% of the estimated 340,000 MDR/RMP-R TB cases that could have been detected had DST been provided to all pulmonary TB patients notified in 2015.1

In South Africa, there were a total of 294,603 TB cases notified in 2015 of whom 196,783 (66.8%) were tested for RMP resistance. Of the 19,613 MDR/RMP-R TB cases diagnosed only 12,527 were reported to have started treatment.1

The WHO endorsed the use of Xpert® MTB/RIF (Xpert) (Cepheid, Sunnyvale, CA, USA) in 20102 after which South Africa implemented Xpert in 2011 as a replacement test for smear microscopy for all presumptive TB cases. The introduction of the more sensitive Xpert test2,3 offered improved TB case detection with the added benefit of simultaneous screening for RMP-R. The Xpert test makes it possible for a RMP-R TB result to be available within a few hours for pre-treatment cases rather than in 2 to 6 weeks as would be the case with culture-based testing.4 However, studies have reported variable adherence to the Xpert-based algorithm. A nationwide retrospective cohort study in South Africa assessing second-line treatment initiation reported that in 2013, after full national rollout of Xpert, only 59% of RMP-R TB cases received an initial Xpert test and 63% of RMP-R TB cases diagnosed started treatment.5

The PROVE IT (Policy Relevant Outcomes from Validating Evidence on ImpacT) Study evaluating the impact of Xpert in Cape Town, South Africa, compared the proportion of RMP-R TB cases diagnosed pre-treatment in the smear/culture-based and Xpert-based algorithms.6 This study found that the proportion of TB cases with DST undertaken pre-treatment increased from 42.7% in the smear/culture-based algorithm to 78.9% in the Xpert-based algorithm. The proportion of TB cases with RMP-R diagnosed was 5.5% and 7.7% respectively - a 33.3% increase in RMP-R TB cases. A laboratory costing study in PROVE IT, reported a 42% increase in overall TB diagnostic costs and a 157% increase in the cost per TB case diagnosed with the transition from a smear/culture to the Xpert-based algorithm with a similar cost per MDR/RMP-R TB case diagnosed of US$190.14 and US$183.86 respectively.7 Underlying differences in the populations tested (prevalence of TB, HIV coinfection and drug resistance, TB cases with a previously history of TB treatment) and adherence to the algorithms may have contributed to these findings and was a limitation in both studies.

This study used an operational model to compare the number and proportion of RMP-R TB cases identified, and the cost per RMP-R TB case identified between a smear/culture and an Xpert-based algorithm. Since adherence to the Xpert-based algorithm in South Africa has been sub-optimal, we evaluated the effect of increased adherence to the algorithm and increased HIV testing amongst presumptive TB cases (which influences the ability to diagnose Xpert-negative TB cases) on the number and proportion of RMP-R TB cases identified.

**Methods**

**Definitions**

***Presumptive case:*** *We defined a presumptive TB case in the model as an individual who had pre-treatment sputum specimens collected for TB diagnostic purposes.*

***TB case:*** *We defined a TB case in the model as an individual with culture positive TB, irrespective of how the individual was ultimately identified (i.e. tested positive by either sputum smear microscopy or culture or Xpert). False positive cases (culture negative with a positive test result by either sputum smear microscopy or Xpert) identified in the model were excluded.*

***RMP-R TB case:*** *We defined a RMP-R TB case in the model as a TB case with rifampicin resistance. False positive RMP-R TB cases* (TB cases who are not RMP-R with an incorrect RMP-R result by either LPA or Xpert) *were excluded.*

***Adherence to algorithm:*** *We defined adherence to an algorithm as the**proportion of**presumptive TB cases that received the full sequence of test as stipulated by the diagnostic algorithm (Figure 1).*8

**Setting and timeframe**

The study is set in Cape Town, one of the large cities in South Africa, with a population of 3.7 million in 2011 (National Census 2011). MDR/RMP-R case notification among TB cases increased from 3.6% (1,020/28,644) in 2011 to 4.4% (1,134/25,846) in 2013 (Routine TB Programme Data, Cape Town Health Directorate, April 2016).

In Cape Town, free TB diagnostic services are provided at 142 primary health care (PHC) facilities in eight health sub-districts. All TB diagnostic tests are performed at a central laboratory, National Health Laboratory Services (NHLS), with all sputum specimens collected for TB testing at PHC facilities couriered to NHLS on a daily basis for testing and results returned to facilities via courier and fax.

Up until August 2011 a smear/culture-based algorithm was in place in Cape Town and from August 2011 an Xpert-based algorithm was introduced with Xpert replacing smear microscopy as a 1st-line test (Figure 1). The rollout of the Xpert-based algorithm was completed by February 2013 (16 Xpert GX XVI modules were introduced7).

**Model development**

We developed and validated an operational model using routine National Health Laboratory data collected for the period 2010 to 2013 in Cape Town, including the period when Xpert was rolled out.9 The Witness package10, a discrete event and continuous process simulator, was used to develop a comprehensive model to represent the diagnosis of pulmonary TB and RMP-R TB in Cape Town. The model incorporated the TB diagnostic algorithms (Figure 1) with specimen flow from specimen collection, through laboratory test procedures, to a test result returned to the PHC facilities where the specimen were collected. The model was developed for both the previous smear/culture-based and current Xpert-based algorithms as stipulated by the South African National TB programme.8

Further details regarding model development, validation as well as model sensitivity analysis was previously published.9

**Model inputs**

As part of the PROVE IT (Policy Relevant Outcomes from Validating Evidence on ImpacT) Study conducted in Cape Town, routine TB and MDR/RMP-R TB treatment data as well as NHLS data from presumptive TB cases had previously been collected and analysed to compare TB yield11 and RMP-R TB yield6 in the smear/culture and the Xpert-based algorithms. Input parameters for the model used probability distributions derived from these analyses (Table 2). We used identical input parameters to model the number and proportion of RMP-R TB cases identified amongst 100,000 presumptive TB cases screened in the smear/culture and Xpert-based algorithms.

Laboratory cost data per test in each algorithm were obtained from a costing evaluation undertaken at the high throughput central laboratory (NHLS) in Cape Town (Table 1).7 Costs were calculated for sputum smear microscopy, culture, line probe assay (LPA) and Xpert and used to estimate total TB diagnostic costs in each algorithm (all expressed in 2013 values).

In the Xpert-based algorithm, we modelled scenarios with varying levels of adherence to the algorithm (at increments of 10% from 50% to 100%) and varying the proportion of presumptive TB cases that knew their HIV status (at 60%, 80% and 100%) since routine NHLS data showed that 50% of presumptive TB cases knew their HIV status in 2013.9,11

**Model outputs and analysis**

We firstly modelled the RMP-R TB cases identified and missed in the smear/culture and Xpert-based algorithms. We report the RMP-R cases identified as a number and as a percentage of TB cases identified among the 100,000 presumptive TB cases evaluated.

The overall laboratory TB diagnostic costs per algorithm were calculated using model outputs on the number of tests undertaken and cost per test from the costing study (Table 1).7 We calculated the cost per RMP-R TB case identified in both algorithms by dividing the total TB diagnostic costs by the number of RMP-R TB cases identified. We calculated the cost per additional RMP-R TB case identified in the Xpert-based algorithm by dividing the difference in total diagnostic costs by the difference in the number of RMP-R TB cases identified between the algorithms.

In order to evaluate the effect of varying adherence levels to the Xpert-based algorithm and varying proportion of HIV testing in the Xpert-based algorithm we compared the number and proportion of RMP-R TB cases identified and missed in each scenario.

**Ethics statement**

The Health Research Ethics Committee at Stellenbosch University (IRB0005239) (N10/09/308) and Ethics Advisory Group at The International Union Against Tuberculosis and Lung Disease (59/10) approved the study. The City of Cape Town Health Directorate, Western Cape Health Department and National Health Laboratory Service granted permission to use routine health data.

**Results**

***Model outputs for the smear/culture and Xpert-based algorithms at 100% adherence to algorithms***

*RMP-R TB cases identified*

The model indicated that if 60% of presumptive cases knew their HIV status, 603 RMP-R cases (3.9% of 15,475 TB cases) were identified in the smear/culture compared to 1,178 RMP-R cases (7.2% of 16,332 TB cases) identified in the Xpert-based algorithm.

When 100% of presumptive cases knew their HIV status, 608 RMP-R cases (3.8% of 16,144 TB cases) were identified in the smear/culture compared to 1,232 RMP-R cases (7.3% of 16,968 TB cases) in the Xpert-based algorithm (Table 3).

*RMP-R TB cases missed*

In the scenario where 60% of presumptive cases knew their HIV status, a total of 795 (56.9%) RMP-R cases were missed in the smear/culture-based algorithm: 231 (16.5%) had a false negative TB test, 13 (0.9%) had a false negative RMP-R result and 551 (39.4%) had no DST done pre-treatment. In the Xpert-based algorithm a total of 220 (15.7%) RMP-R cases were missed: 144 (10.3%) had a false negative TB test, 76 (5.4%) had a false negative RMP-R result and all presumptive cases were screened for RMP resistance pre-treatment (Table 3).

When 100% of presumptive cases knew their HIV status, a total of 790 (56.5%) RMP-R cases were missed in the smear/culture-based algorithm: 226 (16.2%) had a false negative TB test, 13 (0.9%) had a false negative RMP-R result and 551 (39.4%) had no DST done pre-treatment. In the Xpert-based algorithm a total of 166 (11.9%) RMP-R cases were missed: 88 (6.3%) had a false negative TB test, 78 (5.6%) had a false negative RMP-R result and all presumptive cases were screened for RMP resistance pre-treatment (Table 3).

*Laboratory costs*

In the scenario where 60% of presumptive TB cases knew their HIV status the overall laboratory TB diagnostic cost was U$1,073,858 in the smear/culture and U$2,430,050 in the Xpert-based algorithm. The cost per RMP-R TB case identified was U$1,781 in the smear/culture compared to U$2,063 in the Xpert-based algorithm. If 100% of presumptive TB cases knew their HIV status the overall laboratory TB diagnostic costs were U$1,240,777 and U$2,700,384 respectively and the costs per RMP-R TB case identified were U$2,041 and U$2,192 respectively.

The cost per additional RMP-R TB cases identified in the Xpert compared to smear/culture-based algorithm was US$2,359 and US$2,339 in scenarios when 60% and 100% respectively knew their HIV status (Table 3).

***Model outputs for an Xpert-based algorithm with varying adherence to the algorithm***

*RMP-R TB cases identified*

In scenarios where 60% of presumptive cases knew their HIV status and with 50% adherence to the algorithm, 721 RMP-R cases (4.7% of 15,398 TB cases) were identified, increasing to 1,178 (7.2% of 16,332 TB cases) RMP-R cases identified with 100% adherence to the algorithm.

In scenarios where 100% of presumptive cases knew their HIV status and with 50% adherence to the algorithm, 742 RMP-R cases (4.7% of 15,892 TB cases) were identified, increasing to 1,232 (7.3% of 16,968 TB cases) RMP-R cases with 100% adherence to the algorithm (Table 4, Figure 2 and 3).

*RMP-R TB cases missed*

In a scenario when 60% of presumptive cases knew their HIV status and with 50% adherence in the Xpert-based algorithm, 677 (48.4%) RMP-R cases were missed: 240 (17.2%) had a false negative TB test, 40 (2.9%) had a false negative RMP-R result and 397 (28.4%) had no DST done pre-treatment. When adherence increased to 100%, 220 (15.7%) RMP-R cases were missed: 144 (10.3%) had a false negative TB test, 76 (5.4%) had a false negative RMP-R result and all cases had a DST done pre-treatment (Table 4, Figures 3).

***Model outputs for an Xpert-based algorithm with varying proportion of presumptive cases that knew their HIV status***

*RMP-R TB cases identified*

In scenarios where we set adherence to the algorithm at 50% and varied the proportion of presumptive cases who knew their HIV status, 721 RMP-R cases (4.7% of 15,398 TB cases) were identified when 60% of presumptive TB cases knew their HIV-status increasing to 742 RMP-R cases (4.7% of 15,892 TB cases) when 100% knew their HIV status.

When we set adherence at 100% 1,178 RMP-R cases (7.2% of 16,332 TB cases) were identified when 60% knew their HIV status increasing to 1,232 RMP-R cases (7.3% of 16,968 TB cases) when 100% knew their HIV status (Table 4, Figures 2 and 3).

*RMP-R TB cases missed*

In a scenario when 60% of presumptive cases knew their HIV status and with 50% adherence in the Xpert-based algorithm, 677 (48.4%) RMP-R cases were missed: 240 (17.2%) had a false negative TB test, 40 (2.9%) a false negative RMP-R result and 397 (28.4%) had no DST done pre-treatment. When 100% knew their HIV status 656 (46.9%) RMP-R cases were missed: 217 (15.5%) had a false negative TB test, 42 (3.0%) had a false negative RMP-R result and 397 (28.4%) were not screened for RMP-R pre-treatment (Table 4, Figures 3).

**Discussion**

In many countries, including South Africa, DST was historically limited to presumptive TB cases with a history of previous TB treatment as these cases have a higher risk than new cases of developing MDR-TB.12–14 Therefore, in the smear/culture-based algorithm DST was limited to those with a history of previous TB treatment, MDR-TB contacts or those in congregate settings. It was assumed that the small number of new TB case with MDR-TB missed pre-treatment would start 1st-line TB treatment and would eventually be diagnosed with MDR-TB when 1st-line treatment failed. In contrast, with the Xpert-based algorithm all presumptive TB cases receive an Xpert test and are simultaneously screened for RMP-R.

The PROVE IT Study which used a non-randomised stepped-wedge design to compare TB yield between the smear/culture and Xpert-based algorithms found no difference in TB yield between algorithms11. Possible factors contributing to this finding included the following: (1) a decline in TB prevalence over time; (2) higher than expected use of culture in the smear/culture-based algorithm; (3) limited use of culture for HIV-infected Xpert-negative cases; (4) and poor adherence to the Xpert-based algorithm. Despite this, the PROVE IT study found a 54% increase in the number of RMP-R TB cases diagnosed pre-treatment (from 269 to 415)6, which may be an underestimate of the benefit of the Xpert-based algorithm on RMP-R TB diagnosis. The model allowed us to address these issues and enabled comparison of the two algorithms with similar adherence and identical population characteristics.

The model showed small differences in the number of TB cases identified (Table 3) between the smear/culture and Xpert-based algorithms (a 5.5% and 5.1% increase in TB yield when 60% and 100% of presumptive cases respectively knew their HIV status). The real benefit of the Xpert-based algorithm was the 95.4% and 102.6% increase in the number of RMP-R TB cases identified when 60% and 100% of presumptive cases respectively knew their HIV status. The overall laboratory costs between algorithms increased by 126.3% and 117.6% when 60% and 100% of presumptive cases respectively knew their HIV status. These costs were off-set by the increase in the number of RMP-R TB cases identified, resulting only in a 15.8% and 7.4% increase respectively in the cost per RMP-R TB case identified in the Xpert-based algorithm.

In the Xpert-based algorithm, cases not tested by Xpert were tested by the previous smear/culture-based algorithm. When adherence to the Xpert-based algorithm was increased from 50% to 100%, the number of RMP-R TB cases identified increased by 63.4% if 60% of presumptive TB cases knew their HIV-status (Table 4). This illustrates the importance of simultaneous screening for TB and RMP-R, as occurs with adherence to the Xpert-based algorithm.

Increasing the proportion of presumptive TB cases who knew their HIV status had very little effect on the number of RMP-R TB cases identified in the Xpert-based algorithm. When the proportion was increased from 60% to 100%, the number of RMP-R TB identified increased by 2.9% and 4.6% at 50% and 100% adherence respectively. However, HIV-testing of presumptive TB cases does have other clinical importance, for example access to antiretroviral therapy.

**Strengths and limitations**

The strengths of the current study are that we used a validated model, based on real data on testing and diagnosis, to estimate the number and cost per RMP-R TB cases identified in the smear/culture and Xpert-based algorithms. Our study provides a better estimate of these as the PROVE IT laboratory costing and RMP-R TB yield studies included false-positive TB and RMP-R TB cases and were likely to have included populations with different characteristics.6,7,11

The model was validated against data from Cape Town, a well-resourced urban setting where there was extensive use of culture. This may limit the generalisability of our findings to other settings.

**Conclusion**

The model showed a substantial increase in the number of RMP-R TB cases identified with a transition from a smear/culture to an Xpert-based algorithm even though the increase in the number of TB cases identified was small. The Xpert-based algorithm was relatively efficient in diagnosing RMP-R TB cases as the overall increase in laboratory costs was offset by the increased number of RMP-R TB cases identified. Our model highlights the importance of adherence to the Xpert-based algorithm in order to ensure that all presumptive TB cases receive an Xpert test and are simultaneously tested for TB and RMP-R.

The value of this operational model is that future new diagnostic tests and their use in a TB diagnostic algorithm, within an operational setting, can be evaluated.

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Authors contributions: RD, PN, NB, and IL designed the study. RD conducted the modelling and data analysis and wrote the first draft of the Article. All authors reviewed.

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Table 1: Test costs for sputum smear microscopy, culture, line probe assay and Xpert in the smear/culture and Xpert-based algorithms\* (Reprinted with permission of the International Union Against Tuberculosis and Lung Disease. Copyright © The Union)7

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | Smear microscopy (Bleach treated)  US$ | Smear microscopy & culture  US$ | Culture confirmation  US$ | MTBDRplus  line-probe assay  US$ | Xpert  US$ |
| Smear/culture-based algorithm | | | | | |
| Building space | 0.02 | 0.14 | 0.05 | 0.15 | - |
| Equipment | 0.11 | 0.72 | 0.02 | 0.17 | - |
| Consumables | 0.36 | 3.87 | 0.84 | 12.67 | - |
| Staff | 0.55 | 2.21 | 0.57 | 1.34 | - |
| Overheads# | 1.80 | 1.80 | 0.00 | 1.80 | - |
| Cost per test | 2.85 | 8.75 | 1.49 | 16.12 | - |
| Xpert-based algorithm | | | | | |
| Building space | 0.02 | 0.14 | 0.05 | 0.15 | 0.06 |
| Equipment | 0.13 | 0.74 | 0.02 | 0.18 | 0.40 |
| Consumables | 0.36 | 3.87 | 0.84 | 12.67 | 14.62 |
| Staff | 0.55 | 2.21 | 0.57 | 1.34 | 1.32 |
| Overheads# | 2.64 | 2.64 | 0.00 | 2.64 | 2.64 |
| Cost per test | 3.70 | 9.62 | 1.49 | 16.98 | 19.03 |

*\*Test costs are for the central National Health Laboratory only. All costs are expressed in 2013 CPI-adjusted values. Overhead costs included costs for buildings, equipment, consumables and staff involved in specimen sorting and registration, results processing, procurement, stores, training, supervision and management. Specimen transport, electricity, water, sanitation, municipal and biohazardous waste disposal, cleaning and janitorial services, security services and telephone and Internet costs were also included. In each scenario tested, we determined the number of tests performed per algorithm, applied the above costs and calculated the cost per TB and RMP-R TB case identified.*

Table 2: Input parameters used for the smear/culture and Xpert-based algorithms

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | | | Input values (%) | |
|  | | | New presumptive cases | Previously treated presumptive cases |
|  | | | 75 | 25 |
| HIV status | | HIV-positive | 36 | 54 |
| HIV-negative | 64 | 46 |
| Best estimated TB prevalence amongst presumptive cases | | | 18 | 21 |
| Estimated proportion of RMP-R cases amongst TB cases | | | 6 | 12 |
| Accuracy of fluorescence light-emitting diode (LED) smear microscopy15,16 (1 specimen) | Sensitivity | HIV-positive | 55 | |
| HIV-negative | 60 | |
| Specificity | HIV-positive | 99 | |
| HIV-negative | 99 | |
| Accuracy of fluorescence light-emitting diode (LED) smear microscopy15,16 (2 specimens) | Sensitivity | HIV-positive | 65 | |
| HIV-negative | 75 | |
| Specificity | HIV-positive | 99 | |
| HIV-negative | 99 | |
| Accuracy of Xpert MTB/RIF for TB17 | Sensitivity | HIV-positive | 80 | |
| HIV-negative | 89 | |
| Specificity | HIV-positive | 98 | |
| HIV-negative | 98 | |
| Accuracy of GenoType® MTBDRplus LPA for RMP-R TB15,16 | Sensitivity | HIV-positive | 98 | |
| Specificity | HIV-positive | 98 | |
| Accuracy of Xpert MTB/RIF for RMP-R TB15,16 | Sensitivity | HIV-positive | 94 | |
| Specificity | HIV-positive | 98 | |

NHLS data from presumptive cases had been analysed previously as part of the PROVE IT (Policy Relevant Outcomes from Validating Evidence on ImpacT) study. Input parameters derived from these analyses were used as probability distributions for the model.6,9,11

Table 3: The number and percentage of TB and RMP-R TB cases identified in a smear/culture compared to an Xpert-based algorithm and laboratory diagnostic cost for both algorithms

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Smear/Culture-based algorithm  n (%) | | | Xpert-based algorithm  n (%) | | | Relative % difference in Xpert compared to smear/culture-based algorithm | | |
| % knew their HIV status\* | | | % knew their HIV status\* | | | % knew their HIV status\* | | |
| 60 | 80 | 100 | 60 | 80 | 100 | 60 | 80 | 100 |
| TB cases identified | 15,475  (15.5) | 15,810  (15.8) | 16,144  (16.1) | 16,332  (16.3) | 16,670  (16.7) | 16,968  (17.0) | 5.5 | 5.4 | 5.1 |
| RMP-R TB cases identified | 603  (3.9) | 607  (3.8) | 608  (3.8) | 1,178  (7.2) | 1,201  (7.2) | 1,232  (7.3) | 95.4 | 97.9 | 102.6 |
| RMP-R TB cases missed and the reasons why they were missed (% of total RMP-R TB cases) | | | | | | | | | |
| False negative TB test | 231  (16.5) | 227  (16.2) | 226  (16.2) | 144  (10.3) | 120  (8.6) | 88  (6.3) |  | | |
| False negative RMP-R result | 13  (0.9) | 13  (0.9) | 13  (0.9) | 76  (5.4) | 77  (5.5) | 78  (5.6) |
| No DST done | 551  (39.4) | 551  (39.4) | 551  (39.4) | 0 | 0 | 0 |
| Laboratory diagnostic cost | | | | | | | | | |
| Total TB diagnostic costs | 1,073,858 | 1,159,092 | 1,240,777 | 2,430,050 | 2,567,444 | 2,700,384 | 126.3 | 121.5 | 117.6 |
| Cost per RMP-R TB case identified | 1,781 | 1,910 | 2,041 | 2,063 | 2,138 | 2,192 | 15.8 | 12.0 | 7.4 |
| Cost per additional RMP-R TB case identified |  | | | 2,359 | 2,371 | 2,339 |  | | |

Amongst the population of 100,000 presumptive TB cases there were 18,155 true TB cases and 1,398 true RMP-R TB cases. Adherence to algorithms at 100%. All costs are expressed in 2013 CPI-adjusted values and in US$.  
\* Proportion of presumptive TB cases that knew their HIV status.

Table 4: The number and percentage of TB and RMP-R TB cases identified in an Xpert-based algorithm with varying adherence to the algorithm and proportion that knew their HIV status

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Adherence to the Xpert-based algorithm | | | | | | | | |
| 50% | | 60% | | 70% | | 80% | 90% | 100% |
| TB cases identified | | | | | | | | | |
| 60% knew their HIV status | 15,398  (15.4) | | 15,610  (15.6) | | 15,926  (15.9) | | 16,116  (16.1) | 16,243  (16.2) | 16,332  (16.3) |
| 80% knew their HIV status | 15,659  (15.7) | | 15,916  (15.9) | | 16,226  (16.2) | | 16,415  (16.4) | 16,568  (16.6) | 16,670  (16.7) |
| 100% knew their HIV status | 15,892  (15.9) | | 16,213  (16.2) | | 16,531  (16.5) | | 16,719  (16.7) | 16,869  (16.9) | 16,968  (17.0) |
| RMP-R TB cases identified | | | | | | | | | |
| 60% knew their HIV status | 721  (4.7) | | 855  (5.5) | | 963  (6.0) | | 1,034  (6.4) | 1,122  (6.9) | 1,178  (7.2) |
| 80% knew their HIV status | 730  (4.7) | | 869  (5.5) | | 979  (6.0) | | 1,051  (6.4) | 1,146  (6.9) | 1,201  (7.2) |
| 100% knew their HIV status | 742  (4.7) | | 884  (5.5) | | 996  (6.0) | | 1,074  (6.4) | 1,166  (6.9) | 1,232  (7.3) |
| RMP-R TB cases missed and the reasons why they were missed (% of total RMP-R TB cases) | | | | | | | | | |
| False negative TB test | | | | | | | | | |
| 60% knew their HIV status | 240  (17.2) | 184  (13.2) | | 174  (12.4) | | 165  (11.8) | | 138  (9.9) | 144  (10.3) |
| 80% knew their HIV status | 228  (16.3) | 172  (12.3) | | 159  (11.4) | | 146  (10.4) | | 116 (8.3) | 120  (8.6) |
| 100% knew their HIV status | 217  (15.5) | 156  (11.2) | | 141  (10.1) | | 122  (8.7) | | 97  (6.9) | 88  (6.3) |
| False negative RMP-R result | | | | | | | | | |
| 60% knew their HIV status | 40  (2.9) | 52  (3.7) | | 59  (4.2) | | 65  (4.6) | | 76  (5.4) | 76  (5.4) |
| 80% knew their HIV status | 43  (3.1) | 50  (3.6) | | 58  (4.1) | | 67  (4.8) | | 74  (5.3) | 77  (5.5) |
| 100% knew their HIV status | 42  (3.0) | 51  (3.6) | | 59  (4.2) | | 68  (4.9) | | 73  (5.2) | 78  (5.6) |
| No DST done | | | | | | | | | |
| 60% knew their HIV status | 397  (28.4) | 307  (22.0) | | 202  (14.4) | | 134  (9.6) | | 62  (4.4) | 0 |
| 80% knew their HIV status | 397  (28.4) | 307  (22.0) | | 202  (14.4) | | 134  (9.6) | | 62  (4.4) | 0 |
| 100% knew their HIV status | 397  (28.4) | 307  (22.0) | | 202  (14.4) | | 134  (9.6) | | 62  (4.4) | 0 |

Amongst the population of 100,000 presumptive TB cases there were 18,155 true TB cases and 1,398 true RMP-R TB cases.



Figure 1: TB diagnostic algorithms as stipulated by the South African National TB program.8 The simplified sequence of diagnostic tests in each algorithm and the action taken based on test results are shown.   
With the Xpert-based algorithm, two spot specimens were collected and the first was tested with Xpert. If TB was detected, the second specimen underwent smear and if RMP-R was detected, a culture and LPA test was undertaken. The second specimen underwent culture and LPA if the Xpert test was negative and the individual was HIV-infected.

With the smear/culture-based algorithm, all presumptive TB cases were required to submit two spot sputum specimens an hour apart to be tested with fluorescence smear microscopy. The second specimen underwent culture testing (BACTEC™ MGIT™ 960; BD, Spark, MD, USA) if the individual had a history of previous TB treatment, was from a congregate setting or had an MDR-TB contact. If culture-positive, a DST using GenoType® MTBDRplus LPA was undertaken. All new, smear-negative HIV-infected individuals required a culture test with no DST required. New smear-positive individuals do not receive DST at diagnosis.

In both algorithms, new and previously treated cases in which first line TB treatment regimens failed had specimens submitted for culture and LPA during the course of treatment.

Abbreviations: TB - tuberculosis; HIV – human immunodeficiency virus; MTB – mycobacterium tuberculosis; RIF – rifampicin; DST - drug susceptibility test; LPA - line-probe assay.

Figure 2: The number of TB cases identified in an Xpert-based algorithm with varying adherence to the algorithm and proportion that knew their HIV status. TB = tuberculosis; HIV = human immunodeficiency virus.

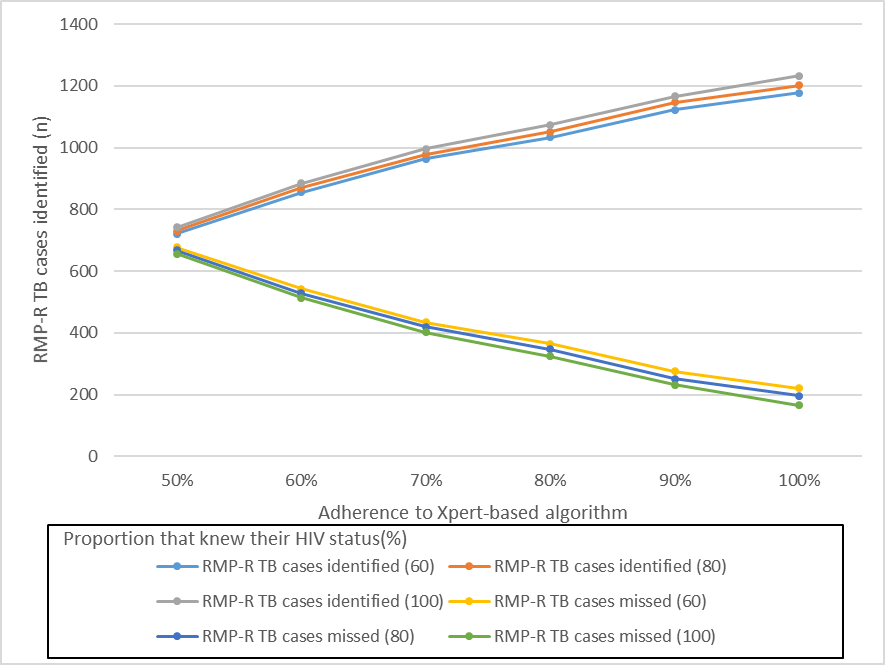


Figure 3: Number of RMP-R TB cases identified and missed in an Xpert-based algorithm with varying adherence to the algorithm and proportion that knew their HIV status. RMP-R TB = rifampicin resistant tuberculosis; HIV = human immunodeficiency virus