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1 **Comparing laboratory costs of smear/culture and Xpert® MTB/RIF-based tuberculosis diagnostic**
2 **algorithms**

3
4
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25

26 **ABSTRACT**

27

28 **Setting:** Cape Town, South Africa, where Xpert® MTB/RIF was introduced as a screening test for all
29 presumptive tuberculosis (TB) cases in primary health services.

30

31 **Study Aim:** To compare laboratory costs of smear/culture- and Xpert MTB/RIF-based TB diagnostic
32 algorithms in routine operational conditions.

33

34 **Methods:** Economic costing was undertaken from a laboratory perspective. We used an ingredients-based
35 costing approach with test costs based on the cost per unit and quantities utilised for buildings, equipment,
36 consumables, staff and overheads. Cost allocation was based on reviews of standard operating procedures
37 and laboratory records, observation and timing of test procedures, measurement of laboratory areas and
38 manager interviews. We analysed electronic laboratory test data to compare overall costs and cost per
39 pulmonary TB and MDR-TB case diagnosed. All costs were expressed as 2013 CPI-adjusted values.

40

41 **Results:** Total TB diagnostic costs increased by 43% from \$440,967 in the smear-culture-based algorithm
42 (April-June 2011) to \$632,262 in the Xpert-based algorithm (April-June 2013). The cost per TB case
43 diagnosed increased by 157% from \$48.77 to \$125.32 with 1601 and 1281 cases diagnosed respectively.
44 The total cost per MDR-TB case diagnosed was similar at \$190.14 and \$183.86 in respective algorithms and
45 the number of cases diagnosed increased by 13%, from 95 to 107.

46

47 **Conclusion:** The introduction of the Xpert-based algorithm resulted in substantial cost increases. This was
48 not matched by the expected increase in TB diagnostic efficacy, calling into question the sustainability of this
49 expensive new technology.

50

51 **INTRODUCTION**

52

53 New molecular diagnostic tests for tuberculosis (TB) such as GenoType® MTBDRplus line probe assay
54 (Hain LifeScience GmbH, Nehren, Germany) (LPA) and Xpert® MTB/RIF (Cepheid, Sunnyvale, CA, USA)
55 (Xpert) hold the promise of improving TB and multidrug-resistant (MDR)-TB diagnosis as both are sensitive
56 and faster than culture and conventional drug susceptibility tests (DST). The accuracy of these tests is well
57 established from laboratory and demonstration studies^{1,2}. A meta-analysis of ten LPA studies showed high
58 sensitivity (98.1% (95% CI 95.9 to 99.1)) and specificity (98.7% (95% CI 97.3 to 99.4)) for rifampicin
59 resistance and lower, more variable sensitivity of 84.3% (95% CI 76.6 to 89.8) and specificity of 99.5% (95%
60 CI 97.5 to 99.9) for isoniazid resistance³. A Cochrane Review of fifteen studies where Xpert was used as the
61 initial test replacing smear microscopy, showed a pooled sensitivity of 88% (95%CrI 83% to 92%) and
62 specificity of 98% (95% CrI 97% to 99%) for detecting *Mycobacterium tuberculosis* (MTB). In eleven of these
63 studies, pooled sensitivity was 94% (95% CrI 87% to 97%) and specificity 98% (95% CrI 97% to 99%) for
64 rifampicin resistance⁴.

65

66 Policy recommendations^{5,6} have been based mainly on accuracy data from laboratory and demonstration
67 studies⁷⁻⁹. However demonstration studies tend not to reflect the realities of a test being used within an
68 operational context^{8,9}. There is a tendency to over-estimate effectiveness partly due to greater resource
69 availability than would be found in routine settings⁸. Insufficient emphasis is placed on costs and an over-
70 estimate of effectiveness may provide a more optimistic view of cost-effectiveness than would be found in
71 routine settings.

72

73 Cost estimates are essential to making decisions on the most effective use of limited resources. One of the
74 challenges to evaluating costs and cost-effectiveness is the lack of standard accepted evaluation
75 methods^{10,11}. Current guidelines are too broad and generalised and poor adherence to guidelines contributes
76 to the failure to provide consistent and comparable cost data to policy makers¹². For example, two studies in
77 South Africa reported Xpert costs of \$25.90 (in 2010 \$US)¹³ and \$14.93 (in 2012 US\$)¹⁴ respectively.
78 Differences in costs were partly attributable to the exclusion of cartridge shipping costs and specimen
79 transport costs in the latter.

80

81 A guideline on laboratory costs¹⁵ emphasises the importance of an ingredients-based approach to costing
82 that includes all resource elements, including quality assurance and control. It emphasises the need to
83 accurately allocate overhead costs and deal with capital assets in a way that takes “time preference” into
84 account i.e. that \$1 in 2 years is worth less than \$1 today, reflecting a societal and individual preference to
85 have money and resources today rather than in the future. Capital costs need to be discounted to reflect this
86 preference¹⁶.

87

88 Xpert is an expensive test and making the case for additional expenditure requires empirical data to
89 supplement the estimates used in decision-making. Operational data can help improve the reliability of
90 estimates used in cost and cost-effectiveness analyses and is particularly important in high-burden settings
91 with resource constraints.

92

93 The aim of this study was to compare laboratory costs for the diagnosis of pulmonary TB and MDR-TB in a
94 new Xpert-based algorithm to that in the previous smear/culture-based algorithm within a routine operational
95 context. The study was part of a PROVE IT (Policy Relevant Outcomes from Validating Evidence on Impact)
96 evaluation (<http://www.treattb.org/>) to assess the impact of new molecular diagnostic tests.

97

98 **METHODS**

99

100 **Setting**

101 The study was undertaken in Cape Town, South Africa, a city with a high TB and MDR-TB burden with
102 28,644 TB cases (752/100,000 population) and 1,020 MDR-TB cases notified in 2011. In comparison,
103 25,846 TB cases (663/100,000 population) and 1,134 MDR-TB cases were notified in 2013. Human
104 immunodeficiency virus (HIV) co-infection rates amongst TB cases were 47% (97% tested) and 44% (98%
105 tested) in respective years (Source: J. Caldwell, Routine TB Programme Data, Cape Town Health
106 Directorate, April 2016).

107

108 Free TB diagnostic services were provided at 142 primary health care facilities in eight sub-districts. All
109 sputum specimens collected at primary health care facilities were sent by courier to the National Health
110 Laboratory Services (NHLS). Test results were entered into a networked, electronic laboratory database.

111

112 **TB diagnostic algorithms**

113 A smear/culture-based algorithm (Figure 1) was used in the “comparator” period (April to June 2011=T1). All
114 presumptive TB cases were evaluated by smear microscopy from two spot sputum specimens, taken 1-hour
115 apart. In high MDR-TB risk cases (>four weeks previous TB treatment, from congregate settings or with an
116 MDR-TB contact), the second specimen underwent liquid culture (BACTEC™ MGIT™ 960) and drug
117 susceptibility testing (DST) using the GenoType® MTBDRplus line probe assay (LPA) and second line
118 testing as required. Smear-negative, HIV-infected, low MDR-TB risk cases were required to submit a third
119 specimen for culture.

120

121 An Xpert-based algorithm was used in the “intervention” period (April to June 2013=T2) with Xpert replacing
122 smear microscopy for all presumptive TB cases (Figure 1). Two sputum specimens were evaluated: the first
123 was tested with Xpert; if MTB was detected the second underwent smear microscopy. In HIV-infected cases
124 with negative Xpert tests, the second specimen underwent culture. Confirmatory LPA and second line DST
125 were undertaken for cases with rifampicin resistance.

126

127 **Costing methods**

128 Economic costing was undertaken from a laboratory perspective for the high throughput central laboratory in
129 Cape Town. Only costs related to the dedicated TB laboratory were assessed. Costs were calculated from
130 the time the courier collected specimens from health facilities to the time results were returned. Costs were
131 assessed only for pulmonary TB (PTB) tests for smear, culture, LPA and Xpert.

132

133 An excel-based costing tool was developed, based on that used in the Foundation for Innovation and
134 Development (FIND) GenoType® MTBDRplus demonstration study. We used an ingredients-based costing

135 approach with test costs based on the cost per unit and quantities utilised for buildings, equipment,
136 consumables, staff and overheads. Cost allocation was determined by reviews of standard operating
137 procedures and laboratory records, direct observation and timing of the test procedures outlined in Figure 2,
138 measurement of laboratory areas used for test processes and interviews with managers. Quality assurance
139 samples were included in batch costs and outputs adjusted accordingly.

140

141 Building costs per square metre, including air-conditioning and consoles, were provided by the Council for
142 Scientific and Industrial Research for a Level 2 laboratory for 2013. Equipment and consumables costs were
143 sourced from laboratory financial records and quotes from suppliers for 2013. These costs were corrected by
144 the consumer price index (CPI) to derive 2011 costs¹⁷. Staff and overheads costs were provided from
145 laboratory financial records for both years. Overhead costs included costs for buildings, equipment,
146 consumables and staff involved in specimen sorting and registration, results processing, procurement,
147 stores, training, supervision and management. Specimen transport, electricity, water, sanitation, municipal
148 and biohazardous waste disposal, cleaning and janitorial services, security services and telephone and
149 internet costs were also included. Further information on costs is provided in online appendices 1, 2 and 3.

150

151 Building and equipment costs were spread over their expected lifespan and discounted to present values at
152 a “risk-free” rate of 3%^{11,18} with maintenance based on expenditure or estimated at 10% of annual costs.
153 Laboratory utilisation was based on a 10-hour weekday for 21 days per month and a 4-hour Saturday shift.
154 The cost of staff time was based on a 40-hour week for 46 weeks of the year with efficiency estimated at
155 80%.

156

157 All costs were calculated in local currency (ZAR). For comparative purposes, 2011 costs were expressed as
158 2013 CPI-adjusted values and converted to US\$ based on average United Nations treasury operational rates
159 in 2013 (ZAR9.75 = US\$1.00)¹⁹.

160

161 **Study population and analysis**

162 All sputum specimens processed in the laboratory in T1 (smear/culture-based algorithm) and T2 (Xpert-
163 based algorithm) and resources related to the processing of these specimens were included in the
164 assessment of laboratory and test costs. Overall laboratory costs were based on the cost per test and test
165 volumes for microscopy (bleach-treated specimens), microscopy and culture, LPA and Xpert.

166

167 We used laboratory data for presumptive PTB cases from five of the eight sub-districts to estimate the cost
168 per TB and MDR-TB case diagnosed. These sub-districts were included in a prior analysis of TB yield and
169 their selection criteria have been described elsewhere²⁰. The analysis required the full sequence of tests
170 undertaken for presumptive TB cases. We therefore identified cases with specimens submitted in May 2011
171 and May 2013 and linked all diagnostic tests from the preceding and following months to identify the full
172 sequence of tests undertaken for each case. Linkage was undertaken with MS-SQL using a combination of
173 facility name, patient folder number, name, surname and age or birth-date.

174

175 We defined a *TB case* as an individual with one or more smears positive and / or culture positive for MTB
176 and / or MTB detected on Xpert. An *MDR-TB case* was defined as an individual with rifampicin resistance on

177 LPA or Xpert. We compared the mean cost per patient diagnosed with TB and MDR-TB in each algorithm.
178 MDR-TB costs were reported as additional to a TB diagnosis.

179

180 **Ethics statement**

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

186

187 **RESULTS**

188

189 **Comparison of total laboratory costs and activities**

190 In T1, 79,544 specimens were tested at the central laboratory compared to 59,238 in T2. The majority (96%
191 and 94% respectively) were for PTB tests.

192

193 Total laboratory costs for PTB tests increased from \$440,967 in T1 to \$632,262 in T2 (Table 1). Costs for
194 bleach treated smears decreased by 49% from \$128,916 to \$65,799; smear and culture costs decreased by
195 35% from \$247,771 to \$161,707 and LPA by 50% from \$64,279 to \$32,339, all driven by decreased test
196 volumes. The increase in total cost was attributable to Xpert test which accounted for 59% of total laboratory
197 costs in the Xpert-based algorithm.

198

199 Annual overhead costs increased by 12% from \$137,101 in T1 to \$153,628 in T2. The largest contributors to
200 the increase were specimen transport costs, utilities, biohazardous waste and janitorial services (Online
201 Appendix 3). Overhead costs were allocated based on test volume as this was identified as the key driver for
202 these costs. Overhead costs per test were increased by 47% from \$1.80 in the smear/culture-based
203 algorithm to \$2.63 in the Xpert-based algorithm, due to both increases in overhead costs and reductions in
204 test volumes.

205

206 **Comparison of test costs (Table 1)**

207 **Smear microscopy** costs (per bleach-treated specimen) increased from \$2.85 in the smear/culture-based
208 algorithm to \$3.70 in the Xpert-based algorithm. Overhead costs were the main driver, accounting for 63% of
209 costs in the smear/culture-based algorithm and 71% in the Xpert-based algorithm.

210

211 **Microscopy and culture** costs (per sodium hydroxide/sodium citrate-treated specimen) increased from
212 \$8.75 in the smear/culture-based algorithm to \$9.62 per test in the Xpert-based algorithm. Consumables
213 (44% and 40% in respective algorithms), staff costs (25% and 23% respectively) and overheads (21% and
214 27% respectively) were the key cost drivers. The highest cost component for consumables was for BACTEC
215 MGIT tubes and supplement.

216

217 **MTBDRPlus Line Probe Assay** costs per test were similar at \$16.12 in the smear/culture-based algorithm
218 and \$16.98 per test in the Xpert-based algorithm. Most tests were done on culture isolates and culture costs

219 have not been included in these totals. Consumables were the greatest cost-driver (79% and 75% in
220 respective algorithms) due mostly to the cost of the GenoType® MTBDRplus kit.

221

222 **Xpert MTB/RIF** cost per test was \$19.03. The largest cost driver was consumables (77%), due mostly to the
223 cost of the XpertMTB/RIF cartridges.

224

225 **Cost per TB case diagnosed**

226 In May 2011 7,842 presumptive TB cases were tested through the smear/culture-based algorithm. The full
227 sequence of tests for these individuals included 10,472 bleach-treated microscopy tests, 5,347 sodium
228 hydroxide/sodium citrate-treated microscopy and culture tests and 980 tests for MTB culture confirmation at
229 a total cost of \$78,080. The mean cost per TB case diagnosed (n = 1601) was \$48.77 (Table 2).

230

231 In May 2013 7,714 presumptive TB cases were tested through the Xpert-based algorithm. The full sequence
232 of tests for these individuals included 2,711 bleach-treated microscopy tests, 3,689 sodium
233 hydroxide/sodium citrate-treated microscopy and culture tests, 431 tests for MTB culture confirmation and
234 6,009 Xpert tests at a total cost of \$160,536. The mean cost per TB case diagnosed (n = 1281) was \$125.32.

235

236 The cost per TB case is influenced by the proportion of TB cases identified, which decreased in the Xpert-
237 based algorithm (probably due to a decline in prevalence – see discussion for further details). We assessed
238 a scenario where TB diagnostic yield in the Xpert-based algorithm was similar to that in the smear/culture-
239 based algorithm which reduced the cost per TB case diagnosed to \$101.94.

240

241 **Cost per MDR-TB case diagnosed**

242 There were 833 LPA tests done for TB cases in the smear/culture-based algorithm at a cost of \$13,430 and
243 mean additional cost per MDR-TB case (n = 95) of \$141.37 (Table 2). In comparison 369 LPA tests were
244 done amongst TB cases in the Xpert-based algorithm at a cost of \$6,264 and mean additional cost per MDR-
245 TB case (n=107) of \$58.54. When these costs were added to the “base” cost of the TB diagnosis, the total
246 cost per MDR-TB case diagnosed was \$190.14 in the smear-culture-based algorithm compared to \$183.86
247 in the Xpert-based algorithm.

248

249 As our prior analysis showed no difference in TB yield between the algorithms²⁰, we apportioned all
250 additional costs to the additional MDR-TB cases diagnosed. This produced an incremental cost-
251 effectiveness ratio (ICER) of \$6,274 per additional MDR-TB case diagnosed.

252

253 **DISCUSSION**

254

255 The use of the more sensitive Xpert test^{4,21,22} as a replacement for smear microscopy was expected to
256 increase the number of TB cases diagnosed and simultaneous drug-susceptibility screening for all
257 presumptive TB cases (not only those at high MDR-TB risk) expected to increase the number of MDR-TB
258 cases diagnosed. A modelling study in South Africa, estimated that at full coverage Xpert would increase
259 annual TB diagnostic costs by 53-57% to \$48-70 million per year but that this would be partially off-set by a
260 30% to 37% increase in TB and 69 to 71% increase in MDR-TB cases diagnosed annually²³.

261

262 Our study found a 43% increase in PTB laboratory costs, from \$440,967 in the smear-culture-based
263 algorithm to \$632,262 in the Xpert-based algorithm for 3-month periods. However, the increase in laboratory
264 costs was not matched by an increase in TB diagnostic efficacy. Although the number of presumptive TB
265 cases evaluated was similar in the smear/culture (n=7842) and Xpert-based algorithms (n=7714), the
266 proportion of TB cases diagnosed (yield) decreased from 20.4% (n=1601) to 16.6% (n=1281). A prior
267 stepped-wedge analysis undertaken **as part of** PROVE IT for 2010-2013 showed a temporal decline in TB
268 diagnostic yield in both algorithms²⁰. This may have been partly attributable to a declining TB prevalence,
269 due perhaps to the rapid scale-up of anti-retroviral treatment in South Africa. When estimates were adjusted
270 for the temporal trend, the study showed no significant difference in TB yield between the algorithms.

271

272 The increase in total costs and decrease in number of cases identified **in the current study** increased the cost
273 per TB case diagnosed by 157% from \$48.77 in the smear/culture-based algorithm to \$125.32 in the Xpert-
274 based algorithm. On the other hand, even a scenario with a similar proportion of TB cases identified in the
275 Xpert-based algorithm to that in the smear/culture-based algorithm would increase the cost per TB case
276 diagnosed by 109% (to \$101.94).

277

278 The cost per MDR-TB case diagnosed was similar at \$190.14 in the smear/culture based algorithm and
279 \$183.86 in the Xpert-based algorithm. In the smear and culture-based algorithm, drug susceptibility testing
280 was only undertaken in high MDR-TB risk presumptive TB cases. One of the advantages of Xpert is that it
281 provides simultaneous screening for TB and rifampicin resistance. The use of Xpert for all presumptive TB
282 cases contributed to the 13% increase in the number of MDR-TB cases identified. Whilst these additional
283 cases may have been diagnosed later in the smear/culture-based algorithm (i.e. after 1st line treatment
284 failed), early diagnosis potentially reduces transmission, avoids the amplification of drug resistance and
285 reduces patient morbidity and mortality. This modest benefit has to be weighed against the heavy overall
286 expenditure, as shown by the MDR-TB ICER of \$6,274. This figure needs to be viewed with some caution as
287 possible changes in TB and thus MDR-TB prevalence has not been taken into consideration. Additional
288 studies are required to assess whether Xpert or other drug susceptibility tests can be targeted more cost-
289 effectively.

290

291 The cost-effectiveness of newly introduced laboratory tests is influenced by how services are re-organised
292 and whether under-utilised assets can be redeployed. In the short-term it may be difficult to reduce costs
293 until new systems and workloads are well established; however in the future efforts could be made to reduce
294 overhead costs. Overhead costs per test could be reduced by increasing test volumes (through additional
295 case-finding efforts for example). However, consumable costs were by far the greatest cost-drivers –
296 accounting for 40% and 60% of total costs in respective algorithms. It remains to be seen whether global
297 increases in test volumes or the availability of generic tests can reduce **these** costs substantially.

298

299 **Strengths and limitations**

300 The major strength of the analysis was that we collected detailed information to accurately estimate the cost
301 per TB and MDR-TB case diagnosed. By including the full sequence of tests undertaken for individuals we

302 reflected the real-life variation found in diagnostic practices, including for example additional culture testing
303 for smear and Xpert-negative cases in respective algorithms.

304

305 The extent to which our results can be generalised is limited by the setting as Cape Town has a relatively
306 good laboratory and health infrastructure. Additional evidence is required from **poorly-resourced settings**
307 **including where culture is not available (as the benefit of Xpert may be greater in areas previously using only**
308 **smear microscopy) and from** rural settings (where specimen transport costs may be higher, economies of
309 scale cannot be readily achieved and expertise may differ). The possible difference in TB prevalence
310 **between** the two time-periods is a limitation, and has been taken into consideration in the analysis. The
311 analysis was undertaken from a laboratory perspective only; the impact of new molecular diagnostic tests on
312 patient costs is important and has been reported elsewhere²⁴.

313

314 **Implications for policy and practice**

315 The increase in total laboratory costs is in a similar range to that projected by two South African studies^{13,23}.
316 However we did not find the expected increases in TB-yield. Our findings are in keeping with a national study
317 showing an 8% decrease in the number of laboratory confirmed PTB cases from 2011 to 2012, despite the
318 introduction of Xpert²⁵. Even when temporal trends of a possible declining prevalence were taken into
319 account in our study, increased costs were not matched with increased TB diagnostic efficacy. It is difficult to
320 justify the increased laboratory costs incurred through the introduction of Xpert and cost implications should
321 not be underestimated. If the \$160,411 spent on TB diagnosis in the Xpert-based algorithm was used for
322 testing as per the smear/culture-based algorithm, the number of presumptive TB cases screened could have
323 been increased by over 100% (from 7,714 to 16,158).

324

325 There is strong impetus to increase the use of Xpert. To mid-2014, 7.5 million Xpert cartridges were procured
326 internationally with more than half being procured by South Africa²⁶. However, the broader impact of Xpert
327 remains questionable. Although studies have reported early TB^{21,27,28} and MDR-TB^{29,30} treatment initiation,
328 Xpert had no impact on TB morbidity and mortality^{27,31,32}. This together with the increased costs warrants a
329 review of the role of Xpert in TB diagnosis.

330

331 Having invested heavily in this new technology, a reversion to a smear/culture-based algorithm is unlikely.
332 Thus either technical adjustments need to be sought to improve Xpert sensitivity and / or the price of Xpert
333 has to be substantially reduced to improve cost-effectiveness in our setting. Urgent efforts need to be made
334 to optimise costs through improved efficiency of the Xpert-based algorithm, including exploring alternative
335 options. Theron et al, for example, showed that pre-screening with smear reduced the cost of a TB diagnosis
336 in their model by more than 20%³³. **A discrete event simulation model has been developed and validated as**
337 **part of PROVE IT and will be used to evaluate more cost-effective diagnostic options.**

338

339 This study highlights the need for thorough costing during early implementation to inform scale-up. As new
340 diagnostic technologies become available, consideration should also be given to the wider costs of serial
341 implementation of different technologies, overlapping of different technologies and redundancies that are
342 created when existing technologies are also retained⁹.

343

344 **CONCLUSION**

345

346 Economic costing is a key component in the decision to implement new TB diagnostic tests and careful
347 consideration should be given to cost implications, particularly in resource-constrained, high-burden settings.

348 The introduction of the Xpert-based algorithm has resulted in substantial increases in cost which are in line
349 with modelling exercises undertaken in South Africa. However these were not matched by an increase in TB
350 diagnostic efficacy; massive cost increases persist even when temporal trends of a possible declining TB
351 prevalence were taken into consideration. One of the benefits of the Xpert-based algorithm was the modest
352 increase in the number of MDR-TB cases diagnosed, which comes at high cost.

353

354 In view of the limited benefits, we have serious concerns about the sustainability of this expensive, new
355 technology. More sensitive tests that are comparable to culture and that are substantially cheaper than Xpert
356 (at current prices) are required, particularly if TB screening is to be substantially scaled up as suggested by
357 the draft Global Plan to Stop TB 2016-2020³⁴.

358

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364 **sharing the costing tool which was adapted for this study.**

365

366 **Author contributions:**

367 All authors were involved in the study design. PN, RD and MVN collected the data. PN, RD and JM analysed
368 the data. PN wrote the manuscript. All authors provided input to the manuscript and approved the final draft
369 for submission.

370

371 **Conflicts of interest:**

372 The authors declare that they have no conflicts of interest.

373

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487 **Table 1: Comparison of test costs in the smear/culture and Xpert-based algorithms**

| | | Smear microscopy (Bleach treated) | Smear microscopy & culture | Culture confirmation | MTBDRPlus Line Probe Assay | Xpert MTBRif |
|---|-----------------|--|---|---------------------------------|---|-------------------------|
| Smear/culture- based algorithm (April – June 2011)(T1) | 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 | - |
| | Number of tests | 45 252 | 27 508 | 4 747 | 3 987 | - |
| | Total costs | \$128 916 | \$240 706 | \$7 065 | \$64 279 | - |
| Xpert-based algorithm (April – June 2013)(T2) | 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 |
| | Number of tests | 17 770 | 16 503 | 2 020 | 1 905 | 19 565 |
| | Total costs | \$65 799 | \$158 700 | \$3 007 | \$32 339 | \$372 418 |

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489 *Test costs and volumes are for the central National Health Laboratory only. Total laboratory costs were \$440,967 in the*
 490 *smear-culture-based algorithm compared to \$632,262 in the Xpert-based algorithm for respective 3-month periods. All*
 491 *costs are expressed in 2013 CPI-adjusted values.*

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Table 2: Costs per pulmonary TB and MDR-TB case diagnosed in the smear/culture and Xpert-based algorithms

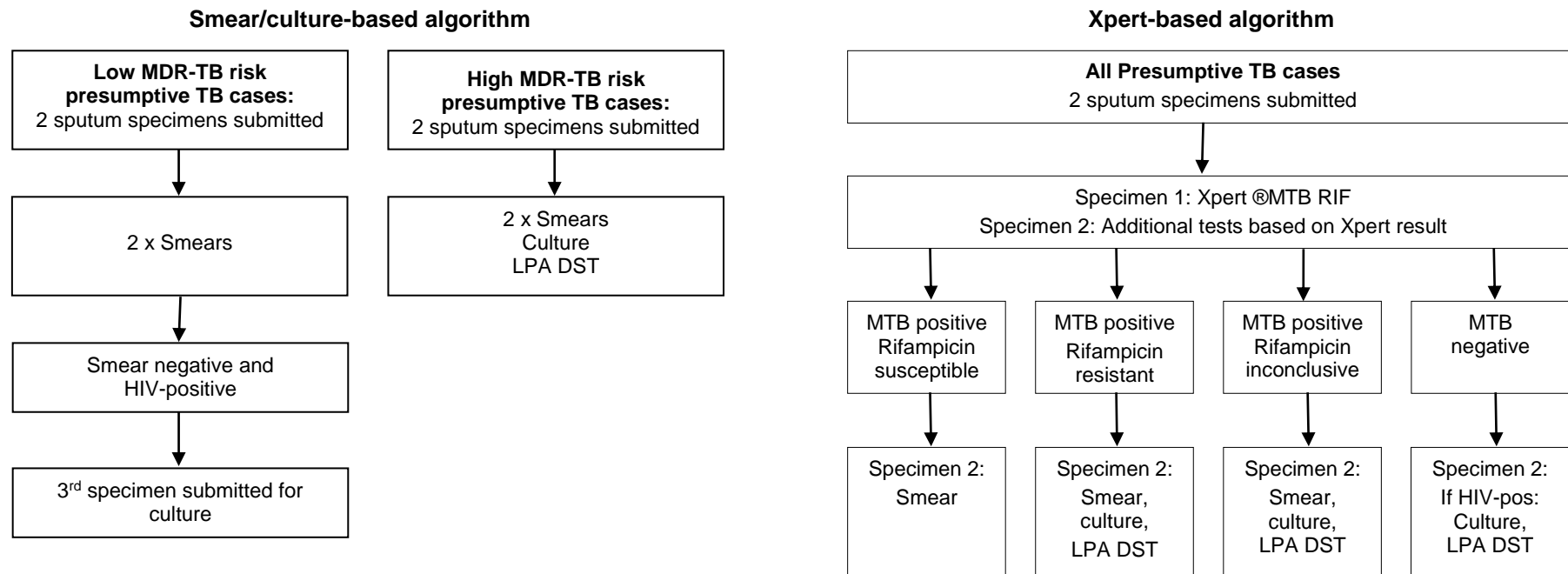
495

| | Costs in the smear/culture-based algorithm | Costs in the Xpert-based algorithm | Changes with the Xpert-based algorithm |
|--|--|------------------------------------|--|
| Smear microscopy (Bleach treated) | \$29 833.23 (n=10,472) | \$10 038.29 (n=2,711) | -\$19 794.94 |
| Smear microscopy & culture (Sodium hydroxide/sodium citrate-treated) | \$46 788.44 (n=5,347) | \$35 475.12 (n=3,689) | -\$11 313.32 |
| Culture confirmation | \$1 458.51 (n=980) | \$641.53 (n=431) | -\$816.98 |
| Xpert MTB Rif | – | \$114 380.73 (n=6,009) | \$114 380.73 |
| Total TB diagnostic costs | \$78 080.18 | \$160 535.67 | \$82 455.50 |
| Number of presumptive TB cases evaluated | 7 842 | 7 714 | -128 |
| Number TB cases identified | 1 601 | 1 281 | -320 |
| Mean cost per TB case identified | \$48.77 | \$125.32 | \$76.55 |
| Total costs for MTBDRPlus Line Probe Assay | \$13 429.75 (n = 833) | \$6 264.02 (n = 369) | -\$7 165.73 |
| Number of MDR-TB cases diagnosed | 95 | 107 | 12 |
| Mean additional cost per MDR-TB case diagnosed | \$141.37 | \$58.54 | -82.82 |
| Mean total cost per MDR-TB case diagnosed | \$190.14 | \$183.86 | -\$6.27 |

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Figure 1: Testing protocols in TB diagnostic algorithms



The simplified sequence of diagnostic tests in each algorithm and the action taken based on test results is shown. Abbreviations: TB - tuberculosis; LPA – Genotype MTBDRPlus line probe assay; DST - drug susceptibility testing; HIV – human immunodeficiency virus; MTB – mycobacterium tuberculosis. Reprinted from: Naidoo P, Dunbar R, Lombard C, du Toit E, Caldwell J et al. Comparing tuberculosis diagnostic yield in smear/culture and Xpert® MTB/RIF-based algorithms using a non-randomised stepped-wedge design. PLoS One. 2016;11(3):e0150487.

Figure 2: Laboratory workflow and test processes

