Feasibility, accuracy, and clinical effect of point-of-care Xpert MTB/RIF testing for tuberculosis in primary-care settings in Africa: a multicentre, randomised controlled trial

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Outline

• Gaps in our knowledge about Xpert
• Study design, aims, and clinic setting
• Feasibility of nurse-performed Xpert at the clinic
• Impact on time-to-result, and time-to-treatment
• Role of empirical anti-TB treatment, and the impact of Xpert on patient morbidity
• Drug resistance, loss-to-follow-up, and mortality
• Limitations and conclusions
Accurate TB diagnostics are needed, and their benefit may be maximised by point-of-care placement.

Projected impact on incidence:

- 28% (4-38%) of patients who test positive in Africa do not start treatment
  
  Macpherson et al., WHO Bull., 2013

- Xpert will never substitute for an accurate bedside test, but does its far-patient placement undermine the potential of the most accurate and rapid test we currently have?

- Can a case be made for the rational placement of Xpert at the POC in well-resourced clinics within TB hotspots?

**6. Implementation considerations**

As with any new technology, a range of implementation issues was identified, without which Xpert MTB/RIF use would not be optimal. These include:

- **Positioning:** Xpert MTB/RIF is suitable for use at district and sub-district level. Although testing with Xpert MTB/RIF does not require additional laboratory equipment, the sophisticated nature of the device requires care of handling, i.e. stable and uninterrupted electrical supply to avoid interruption of the procedure and subsequent loss of results, security against theft, adequate storage space for the cartridges, dedicated staff to perform testing, and biosafety procedures similar to microscopy.

WHO, 2010
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Hypothesis, design, and endpoints

**Hypothesis:** One Xpert performed by a nurse at the point-of-care is feasible, and will improve time-to-result, time-to-treatment and TB morbidity amongst patients in primary care, compared to same-day microscopy.

Study staff did not initiate treatment. Patients were referred to routine clinical staff after diagnostic testing.

**Endpoints**
- **Feasibility** of Xpert by a nurse in the clinic vs. that by technician in a research or reference lab
- **Time-to-diagnosis**
- **Rates of treatment initiation**
- **Differences in TB morbidity score** (TBscore) and Karnofsky Performance Score between TB patients at 2 and 6 months
Clinic and nurse information

• Teams of two nurses each were placed at:
  • Gugulethu TB Clinic (Cape Town, South Africa), Mabvuku Polyclinic (Harare, Zimbabwe), Kanyama TB Clinic (Lusaka, Zambia), St. Mary’s Day Clinic (Durban, South Africa), and Ifisi Day Clinic (Mbeya, Tanzania).
• Each had an attached microscopy lab (with the exception of Cape Town), DOTS treatment facility, and a dedicated space for Xpert.
• Aside from security features and an IRB-required biosafety cabinet in Harare, no other infrastructure (e.g., power upgrades) were installed.
• Nurses received one day of technical training.
• Unannounced inspections by technicians were conducted ≥1 per month, and user appraisals were regularly performed.
Kanyama TB clinic, Lusaka.
St. Mary's Clinic, Durban.
Gugulethu Clinic, Cape Town.
Figure 1: Study profile
### Site characteristics

<table>
<thead>
<tr>
<th>Clinic Location</th>
<th>Number of patients</th>
<th>Age (IQR)</th>
<th>Women (%)</th>
<th>Previous TB (%)</th>
<th>HIV Infected</th>
<th>On ART at recruitment (%)</th>
<th>Number of TB culture-positive patients (%)</th>
<th>Overall</th>
<th>P-value for comparisons across sites</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gugulethu TB Clinic (Cape Town, South Africa)</td>
<td>419</td>
<td>39 (31-49)</td>
<td>160 (38)</td>
<td>178 (43)</td>
<td>133 (32)</td>
<td>51/133 (38)</td>
<td>74 (18)</td>
<td>1502</td>
<td>-</td>
</tr>
<tr>
<td>Mabvuku Polyclinic (Harare, Zimbabwe)</td>
<td>400</td>
<td>38 (32-45)</td>
<td>215 (54)</td>
<td>67 (17)</td>
<td>324 (81)</td>
<td>96/324 (30)</td>
<td>77 (19)</td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Kanyama TB Clinic (Lusaka, Zambia)</td>
<td>400</td>
<td>35 (30-41)</td>
<td>131 (33)</td>
<td>85 (21)</td>
<td>268 (67)</td>
<td>54/268 (20)</td>
<td>152 (38)</td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>St. Mary’s Day Clinic (Durban, South Africa)</td>
<td>200</td>
<td>37 (30-50)</td>
<td>96 (48)</td>
<td>52 (26)</td>
<td>121 (61)</td>
<td>29/121 (24)</td>
<td>35 (18)</td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Ifisi Day Clinic (Mbeya, Tanzania)</td>
<td>83</td>
<td>37 (31-54)</td>
<td>41 (49)</td>
<td>2 (1)</td>
<td>49 (59)</td>
<td>2/49 (4)</td>
<td>29 (35)</td>
<td>367 (24)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Overall</td>
<td>1502</td>
<td>37 (30-46)</td>
<td>643 (43)</td>
<td>384 (26)</td>
<td>895 (60)</td>
<td>232/895 (26)</td>
<td></td>
<td></td>
<td>0.0010</td>
</tr>
</tbody>
</table>

- **Number of patients**: 1502 patients across all sites.
- **Age (IQR)**: Range from 31-49 years.
- **Women (%)**: Majority of patients are female, ranging from 33% to 54%.
- **Previous TB (%)**: A significant percentage of patients have a history of TB.
- **HIV Infected**: More than half of the patients are HIV-infected.
- **On ART at recruitment (%)**: A notable percentage of patients are on ART.
- **Number of TB culture-positive patients (%)**: A proportion of patients test positive for TB cultures.
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Feasibility of nurse-performed Xpert at the point-of-care

<table>
<thead>
<tr>
<th></th>
<th>At recruitment</th>
<th>At study close</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Smear microscopy</td>
<td>Point-of-care Xpert</td>
</tr>
<tr>
<td></td>
<td>Sensitivity</td>
<td>Specificity</td>
</tr>
<tr>
<td>Overall</td>
<td>50% (42.9, 57.2)</td>
<td>96.5% (94.6, 97.7)</td>
</tr>
<tr>
<td></td>
<td>91/182</td>
<td>540/560</td>
</tr>
</tbody>
</table>

Kappa = 0.69 (“substantial agreement”)

<table>
<thead>
<tr>
<th>Operating temperature, °C (95% CI)</th>
<th>Overall</th>
<th>Guquletho TB Clinic (Cape Town, South Africa)</th>
<th>Mabvuku Polyclinic (Harare, Zimbabwe)</th>
<th>Kanyama TB Clinic (Lusaka, Zambia)</th>
<th>St Mary’s Day Clinic (Durban, South Africa)</th>
<th>Ifisi Day Clinic (Mbeya, Tanzania)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Operating temperature, °C (95% CI)</td>
<td>23.2°C (21.3-25.3)</td>
<td>21.0°C (18.0-23.0)</td>
<td>26.4°C (24.9-27.7)</td>
<td>23.2°C (19.2-24.3)</td>
<td>27-4°C (24-9-28-0)</td>
<td>23.4°C (21.1-25.2)</td>
</tr>
<tr>
<td>Humidity, % (95% CI)</td>
<td>55% (48-25-61)</td>
<td>66% (66-66)</td>
<td>42% (26-61.5)</td>
<td>58.5% (44-25-67)</td>
<td>55% (52-63)</td>
<td>56% (50-63)</td>
</tr>
</tbody>
</table>
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Does Xpert improve time-to-diagnosis?

- **366/1502** patients culture-positive by day 56
- **154/185** TB cases detected by Xpert by day 56
- **91/182** TB-cases detected by microscopy by day 56

<table>
<thead>
<tr>
<th>Days to result</th>
<th>Smear microscopy (N=758)</th>
<th>Xpert MTB/RIF (N=744)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>By day 1</td>
<td>79/182 (43%)</td>
<td>150/185 (81%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>By day 2</td>
<td>186/182 (47%)</td>
<td>153/185 (83%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>By day 3</td>
<td>187/182 (48%)</td>
<td>153/185 (83%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>By day 14</td>
<td>142/182 (75%)</td>
<td>166/185 (90%)</td>
<td>0.0023</td>
</tr>
<tr>
<td>By day 28</td>
<td>176/182 (97%)</td>
<td>182/185 (98%)</td>
<td>0.30</td>
</tr>
<tr>
<td>By day 56</td>
<td>181/182 (99%)</td>
<td>182/185 (100%)</td>
<td>0.31</td>
</tr>
<tr>
<td>Days to first positive result</td>
<td>0 (0-6)</td>
<td>0 (0-9)</td>
<td>0.0055</td>
</tr>
<tr>
<td>Days to culture result</td>
<td>10 (6-14)</td>
<td>9 (6-15)</td>
<td>0.86</td>
</tr>
</tbody>
</table>

Data are n/N (%) or median (IQR). *Positive results could be from smear microscopy or culture in the smear microscopy group, or by Xpert MTB/RIF or culture in the Xpert MTB/RIF group.

Table 4: Patients with a positive smear microscopy, Xpert MTB/RIF, or culture result, and days to result, per allocation group.
Does Xpert improve time-to-treatment in culture-positive patients?

- Xpert reduced culture-positive drop-out from 16% to 9%
- Median time-to-treatment was 2 days in the microscopy arm versus 1 day in the Xpert arm (p=0.0004)
- Culture had little utility:
  - 6% of culture-positive patients where initiated based on their culture-result (10/182 in smear arm, and 9/185 in Xpert arm)
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What is the role of empirical treatment?

- Proportion of patients treated empirically was less with Xpert (17% vs. 26%; p<0.0001)
- Empirical treatment was rapid (median time of 3 days in either arm)
- 70% of smear-negative TB cases were detected by Xpert at the study end, yet 93% of these were treated rapidly on empirical grounds anyway
The “appropriateness” of empirical treatment did not change

- Although there is **overall less empirical treatment** with Xpert (due to more patients receiving a rapid bacteriological diagnosis):
  - A similar number of “false-negative” empirical treatment decisions occurred in either arm: 26% of culture-negatives in smear arm vs. 22% in Xpert arm

<table>
<thead>
<tr>
<th>versus a single culture</th>
<th>Specificity (%) (95 CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empirical treatment in the microscopy arm</td>
<td>74.15 (70.05, 77.78) 416/561</td>
</tr>
<tr>
<td>Empirical treatment in the Xpert arm</td>
<td>78.35 (74.89, 81.80) 427/545</td>
</tr>
</tbody>
</table>

$p=0.1013$
## Did Xpert improve TB-related morbidity?

<table>
<thead>
<tr>
<th></th>
<th>TBscore</th>
<th></th>
<th></th>
<th>Karnofsky performance score</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Microscopy</td>
<td>Xpert</td>
<td>P-value</td>
<td>Microscopy</td>
<td>Xpert</td>
<td>P-value</td>
</tr>
<tr>
<td><strong>Baseline</strong> (n=153 and n=168 in each arm)</td>
<td>5 (4-7)</td>
<td>5 (4-7)</td>
<td>0.56</td>
<td>70 (60-80)</td>
<td>70 (57.5-90)</td>
<td>0.89</td>
</tr>
<tr>
<td><strong>Two month follow-up</strong> (87/153 and 108/168 in each arm; p=0.17)</td>
<td>2 (0-3)</td>
<td>2 (0.25-3)</td>
<td>0.85</td>
<td>80 (70-90)</td>
<td>90 (80-90)</td>
<td>0.23</td>
</tr>
<tr>
<td><strong>Six month follow-up</strong> (81/153 and 97/168 in each arm; p=0.39)</td>
<td>1 (0-3)</td>
<td>1 (0-3)</td>
<td>0.35</td>
<td>100 (90-100)</td>
<td>100 (90-100)</td>
<td>0.85</td>
</tr>
</tbody>
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Drug-resistant TB in TB-NEAT

- In South Africa (and China), 80% of DR-TB is be caused by person-to-person transmission  
  Streicher et al., Infect. Gen. Evol., 2011; Zhao et al., NEJM, 2012

<table>
<thead>
<tr>
<th></th>
<th>Gugulethu TB Clinic (Cape Town, South Africa)</th>
<th>Mabvuku Poly clinic (Harare, Zimbabwe)</th>
<th>Kanyama TB Clinic (Lusaka, Zambia)</th>
<th>St. Mary's Day Clinic (Durban, South Africa)</th>
<th>Ifisi Day Clinic (Mbeya, Tanzania)</th>
<th>Overall</th>
<th>P-value for comparisons between sites</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifampicin monoresistant (%)</td>
<td>1/67 (1)</td>
<td>7/73 (10)</td>
<td>8/152 (5)</td>
<td>0/32 (0)</td>
<td>0/26 (0)</td>
<td>16/350 (5)</td>
<td>0.1550</td>
</tr>
<tr>
<td>Isoniazid monoresistant (%)</td>
<td>5/67 (7)</td>
<td>1/73 (1)</td>
<td>3/152 (2)</td>
<td>1/32 (3)</td>
<td>3/26 (12)</td>
<td>13/350 (4)</td>
<td>0.0580</td>
</tr>
<tr>
<td>Multi-drug resistant (%)</td>
<td>5/67 (7)</td>
<td>1/73 (1)</td>
<td>0/152 (0)</td>
<td>0/27 (0)</td>
<td>0/25 (0)</td>
<td>6/345 (2)</td>
<td>0.0090</td>
</tr>
</tbody>
</table>

- Accuracy of lab-based Xpert for Rif^R TB in patients with complete data was sub-optimal:

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MTBDRplus as a reference standard</td>
<td>23.6% (9.6, 47.3)</td>
<td>98.9% (96.8, 99.7)</td>
<td>57.2% (25.1, 84.2)</td>
<td>95.4% (92.2, 97.3)</td>
</tr>
<tr>
<td></td>
<td>4/17</td>
<td>264/267</td>
<td>4/7</td>
<td>264/277</td>
</tr>
</tbody>
</table>
Loss-to-follow-up and mortality

<table>
<thead>
<tr>
<th></th>
<th>Microscopy arm</th>
<th>Xpert arm</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Loss-to-follow-up in patients placed on treatment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Two months</td>
<td>70/324 (21)</td>
<td>69/321 (21)</td>
<td>0.9730</td>
</tr>
<tr>
<td>TB cases</td>
<td>33/154 (21)</td>
<td>36/170 (21)</td>
<td>0.9559</td>
</tr>
<tr>
<td>Non-TB cases</td>
<td>37/170 (22)</td>
<td>33/151 (22)</td>
<td>0.9845</td>
</tr>
<tr>
<td>Six months</td>
<td>71/324 (22)</td>
<td>74/321 (23)</td>
<td>0.7289</td>
</tr>
<tr>
<td>TB cases</td>
<td>36/154 (23)</td>
<td>36/170 (21)</td>
<td>0.6343</td>
</tr>
<tr>
<td>Non-TB cases</td>
<td>35/170 (21)</td>
<td>38/151 (25)</td>
<td>0.3288</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Microscopy arm</th>
<th>Xpert arm</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mortality</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Two months</td>
<td>26/324 (8)</td>
<td>14/321 (4)</td>
<td>0.0538</td>
</tr>
<tr>
<td>TB cases</td>
<td>5/67 (7)</td>
<td>11/154 (7)</td>
<td>0.1452</td>
</tr>
<tr>
<td>Non-TB cases</td>
<td>15/170 (9)</td>
<td>8/151 (6)</td>
<td>0.2216</td>
</tr>
<tr>
<td>Six months</td>
<td>35/324 (11)</td>
<td>28/321 (9)</td>
<td>0.3737</td>
</tr>
<tr>
<td>TB cases</td>
<td>14/154 (9)</td>
<td>14/170 (8)</td>
<td>0.7843</td>
</tr>
<tr>
<td>Non-TB cases</td>
<td>21/170 (12)</td>
<td>14/151 (9)</td>
<td>0.3766</td>
</tr>
</tbody>
</table>
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Limitations

• This was a short-term study in Southern Africa amongst TB suspects that needs to be viewed in the context of high burden settings with high rates of empirical treatment. Xpert in different populations will have a different effect.

• Programmatic monitoring, machine maintenance, and the task shifting implications of POC Xpert placement are important, but were outside the scope of this trial. Most sites in Africa have POC microscopy available, however.

• CXRs were available to clinicians, even though radiography is not standard-of-care everywhere. XTEND has, however, also reported high rates of empirical treatment (35% of patients starting treatment prior to Xpert were smear-negative).

• Xpert appeared to perform poorly for drug-resistance detection, however, this is not definitive due to the small number of cases.

• The selective placement of Xpert at the POC will be very expensive, but will it be worth it? This work will inform a cost-effectiveness study.
The way forward: taking new molecular tests into the community?
Concluding thoughts

• In our RCT, although Xpert did not impact morbidity, it
  • is feasible in primary care and does not require technical personnel
  • increased rates of same day treatment
  • resulted in less patients with TB “dropping-out”

• If POC placement has little clinical effect, how likely is it that centralised testing will? Will the key benefit arise from preventing TB patient drop-out? Other studies not using POC Xpert have been unable to demonstrate a reduction in pre-treatment drop-out.

• While Xpert reduces the volume of empirical treatment, it does not improve its accuracy or “appropriateness”

• Empirical TB treatment has many disadvantages, but have we underestimated it’s role when projecting the impact of new diagnostics?

• How will the clinical handling of test-negative patients change with the long-term implementation of Xpert?

• Does improving clinical decision making and training need to be given an as big a priority as merely rolling out a new test?
Thanks and acknowledgements

Patients

**Field team**
Cape Town: M Pretorius, M Pascoe, B Soetwater, M Wyngard, L Pool
Harare: MM Chipiti and P Kaguru
Lusaka: C Viny, M Kasonde, L Manjeta
Durban: T Mthiyane, N Ntshuba, S Gumede, T Mvuyane, P Mbmamo.
Mbeya: C Mangu, F Kayombo, A Temihanga, M Kimaro, B Mnyanyi, I Mgogo, B Ambukege, T Sanga

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Lusaka: J Mzyece
Durban: F Madaar
Mbeya: F Kayombo, H Mbilinyi, G. Rojas-Ponce, D Mapamba, C Lueer, A Bauer, L Njovu

**Data team**
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Harare: T Pswarayi
Lusaka: V Kapotwe

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