South Africa’s “Reality Check”

>1 million Xpert tests

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University of the Witwatersrand and
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On behalf of the GeneXpert Team
South Africa’s burden of TB

Xpert program
- National plan,
- Results, positivity, Rif concordance to DST/LPA
- Impact studies
- EPTB, paediatrics

Challenges
- Verification and EQA
- Module Failures and calibration
- Training
- Ct values – surveillance? Monitoring?
• ~500,000 new cases and 25,000 deaths due to TB.
• TB incidence continues to rise (~incidence 993 per 100,000)
• Fuelled by HIV epidemic (largest burden of HIV-infected individuals worldwide (5.6 million in 2011)).
• >65% of new TB cases coinfected with HIV
• TB leading cause of death among HIV infected
• High risk populations
  – Mining populations 4000/100,000
  – Correctional Services 4500/100,000
• Increasingly smear negative (8-10% positivity prior Xpert), diagnosis made to late to avoid mortality late to avert mortality (Lawn, JID 2011; Corbett, 2003, Holmes, JAIDS 2006)

Urgent interventions are needed, one of which has been the need for rapid diagnosis of MTB technology.
Where are now?

Cumulative number of GeneXpert instrument modules and Xpert MTB/RIF cartridges procured under concessional pricing:

- SA Public sector: >1.1 million assays since Q2 2011
- Remains >50% of total cartridge HBDC purchase
- Excludes private sector

As of 31 December 2012, a total of 966 GeneXpert instruments (comprising 1,072 modules and 1,891,970 Xpert MTB/RIF cartridges) had been procured in the public sector of 145 countries eligible for concessional pricing.

Monthly uptake since Initiation of Implementation

NPP GeneXpert Monthly Uptake

1. Expected seasonal variation
2. Stock issues
3. New Round of implementation


Courtesy NPP, NHLS
Interfacing any new molecular technology e.g. GeneXpert: **DISRUPTIVE TECHNOLOGY**

1. Interface with other molecular tests and conventional microbiology
2. Interface with Clinical Diagnostic and Treatment Guidelines for TB and HIV
3. Interface with Laboratory Information Systems/Instrument performance monitoring
4. Interface with Quality Management Systems: EQA, verification
5. Interface with Training programs and health systems strengthening activities
6. Interface with actionable result reporting: requisition/order entry, reflex testing/not, LIS rules, instrument performance management rules, result distribution for more rapid action,
7. Interfacing data collection at lab with clinical data systems: provincial and national levels
8. Interfacing with financial modelling, costing and forecasting, procurement strategy
9. Interfacing with donors and managing expectations
10. Interface with specimens other than sputum and pulmonary TB (Extrapulmonary, pediatric)

**SA Experience**

Health systems strengthening needed at all levels to support the roll-out
Address these issues upfront now that we know what they are

Positive Aspect: You will find the weaknesses in your Current TB Programs at both a laboratory and clinical level

W. Stevens, 2012, IUTLD, Malaysia
WHO’s Strong Recommendation in December 2010

“The new automated DNA test for TB should be used as the initial diagnostic test in individuals suspected of MDR-TB or HIV/TB” *(i.e. Most TB suspects in SA)*

• In March 2011, South Africa developed and initiated a National Plan for phased implementation of the technology, as a replacement for microscopy as the initial diagnostic screen for TB suspects

• Using existing microscopy centres facilitated rapid implementation *(244 centres)*

• Significant support from CDC, Global fund, BMGF, UNITAID, amongst others

• Performed over **1,180 669 tests** to date (March 2013), across all 9 provinces

• **Significant increase in case detection** in suspects (8 to 16%) in first year, second year: 14%

• **Significant increase in detection of drug resistance (7%)**

• Expanded access to correctional services inmates and miners

• Several SA research studies emerging confirm the increase in laboratory detection, reduced time to diagnosis and treatment initiation and a possible reduction in empiric treatment
**WHO Dec 2010**

- Coordinate efforts, define priorities
- Develop implementation plan, documents
- Prepare sites
- Build capacity for training (lab + clinic), support resources
- Support data collection and impact evaluation

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**South Africa’s implementation process:** January 2011: one National Plan

1. **NDoH/NHLS engage**
   - Funders
   - Supplier
   - Laboratory
   - Clinical
   - Economists

2. **Discuss with partners**
   - Pilot I (March 2011)
   - Phased plan developed
   - Algorithm
   - NTCM model

3. **Formed advisory team (NPP)**
   - Phase II Instruments
   - Kit orders
   - Forecasting
   - Supplier negotiation
   - Clinical algorithm
   - Impact study planned

4. **Funders engage**
   - Training material
   - SOP
   - Verification program
   - Instrument interface
   - Paediatrics
   - EPTB
   - POC
   - Smear negative

5. **Require R&D**
   - LIS installation
   - Instrument installation
   - Verify instruments
   - On-site training/test witness
   - Parallel clinic training

6. **Initiate sites: 95 to date 125 planned**
   - Manage assay version change (Dec 2011)
   - Manage stock-out in August
   - Remote calibration
   - Remote connectivity

7. **Commence testing at sites**

8. **Meetings**
   - Bi-weekly meetings with team and supplier
   - Monthly NHLS EXCo
   - Quarterly NDoH
   - Model review

9. **Monthly monitoring**
   - Data analysis
   - Utilization
   - Errors

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USG technical approach for Xpert roll-out only published 28 August 2012
Phased implementation of GeneXpert in SA
One National Plan

• Three phases of implementation in microscopy centres

• Phase I: Pilot in high burden districts in 9 provinces

• Phase II: Completion of high burden districts
  a. Full capacitation of Phase I labs
  b. Full capacitation of high burden districts

• Phase III: XTEND Study (Aurum: BMGF funded, RCT)
  a. Intervention arm
  b. Control arm.
  c/d. Completion of all sites

• Full financial commitment attained for the National Program originally described, treasury support for test till 2016

• Now Program to be expanded for mines and correctional services with aspects of both surveillance, screening and case finding and Xpert to be used as front-line
Phased implementation Progress
Where are we now?

- Phases 1-3b completed; Phases 3c 85%; Phase 3d 53%
- 142 testing centres established (~76% coverage)
  - 203 instruments: GX4: 65; GX16-8: 1; GX16: 135; GX48: 1; GX80-48: 1
- Additional 39 instruments (37 facilities) to be placed in Q2
  - Will increase coverage to 90%
  - Placement of 7 infinities (Steve Biko, CHB, Leratong, Tshepong, Pelonomi, Greenpoint, PE): 6 month production time
- Train-the-Trainer courses conducted
- 100 centres actively reporting on the Remote Connectivity website
- Remote calibration active from November 2012
Current GeneXpert Placements

- 142 testing centres
- 203 analysers
- *20 clinic placements
- Gx4: 65
- Gx16: 135
- Gx48: 1
- GX80-48: 1
Planned Total Rollout for the GeneXpert, with NDOH Health facilities

GeneXpert sites: green
NDoH clinic sites: red
Test Volume Comparisons

GeneXpert Testing Volumes 2011-2013

- **2011**
  - JAN: 3495
  - FEB: 12641
  - MAR: 16412
  - APR: 17901
  - MAY: 19303
  - JUN: 25112
  - JUL: 27176
  - AUG: 32448
  - SEP: 32482
  - OCT: 23489

- **2012**
  - JAN: 32243
  - FEB: 38043
  - MAR: 44609
  - APR: 17901
  - MAY: 17901
  - JUN: 19303
  - JUL: 25112
  - AUG: 27176
  - SEP: 63771
  - OCT: 93732
  - NOV: 60490

- **2013**
  - JAN: 91915
  - FEB: 10559

**Total No. of Tests**
GeneXpert Summary 01 March 2011 - 31 March 2013

- 1,180,669 assays to date nationally
- 14.6% MTB positive cumulative
- Results demonstrating a downward trend

<table>
<thead>
<tr>
<th>Province</th>
<th>MTB Detected</th>
<th>MTB Not Detected</th>
<th>Test Unsuccessful</th>
<th>Total</th>
<th>% MTB Detected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eastern Cape</td>
<td>27881</td>
<td>147474</td>
<td>4765</td>
<td>180,120</td>
<td>15.48</td>
</tr>
<tr>
<td>Free State</td>
<td>17835</td>
<td>117802</td>
<td>524</td>
<td>136,161</td>
<td>13.10</td>
</tr>
<tr>
<td>Gauteng</td>
<td>18963</td>
<td>124431</td>
<td>4002</td>
<td>147,396</td>
<td>12.87</td>
</tr>
<tr>
<td>Kwa-Zulu Natal</td>
<td>48148</td>
<td>247615</td>
<td>11332</td>
<td>307,095</td>
<td>15.68</td>
</tr>
<tr>
<td>Limpopo</td>
<td>9137</td>
<td>76899</td>
<td>2125</td>
<td>88,161</td>
<td>10.36</td>
</tr>
<tr>
<td>Mpumalanga</td>
<td>8084</td>
<td>42664</td>
<td>2636</td>
<td>53,384</td>
<td>15.14</td>
</tr>
<tr>
<td>North West</td>
<td>11132</td>
<td>60475</td>
<td>3431</td>
<td>75,038</td>
<td>14.84</td>
</tr>
<tr>
<td>Northern Cape</td>
<td>9272</td>
<td>50960</td>
<td>2516</td>
<td>62,748</td>
<td>14.78</td>
</tr>
<tr>
<td>Western Cape</td>
<td>21340</td>
<td>107996</td>
<td>1230</td>
<td>130,566</td>
<td>16.34</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>171,792</strong></td>
<td><strong>976,316</strong></td>
<td><strong>32,561</strong></td>
<td><strong>1,180,669</strong></td>
<td><strong>14.55</strong></td>
</tr>
<tr>
<td>% Total</td>
<td>14.55</td>
<td>82.69</td>
<td>2.76</td>
<td>100</td>
<td></td>
</tr>
</tbody>
</table>

- 1,180,669 assays to date nationally
- 14.6% MTB positive cumulative
- Results demonstrating a downward trend
## Rif Resistance in MTB positive samples

### Stable RIF resistance rates, geographical variation

#### Provincial GeneXpert RIF Results (MTB Detected)

<table>
<thead>
<tr>
<th>Province</th>
<th>Inconclusive</th>
<th>Resistant</th>
<th>Sensitive</th>
<th>No Rif Result</th>
<th>Total</th>
<th>% RIF Resistant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eastern Cape</td>
<td>409</td>
<td>1967</td>
<td>25234</td>
<td>271</td>
<td>27,881</td>
<td>7.05</td>
</tr>
<tr>
<td>Free State</td>
<td>262</td>
<td>1064</td>
<td>16476</td>
<td>33</td>
<td>17,835</td>
<td>5.97</td>
</tr>
<tr>
<td>Gauteng</td>
<td>241</td>
<td>1254</td>
<td>17389</td>
<td>79</td>
<td>18,963</td>
<td>6.61</td>
</tr>
<tr>
<td>Kwa-Zulu Natal</td>
<td>747</td>
<td>4037</td>
<td>42894</td>
<td>470</td>
<td>48,148</td>
<td>8.38</td>
</tr>
<tr>
<td>Limpopo</td>
<td>134</td>
<td>640</td>
<td>8245</td>
<td>118</td>
<td>9,137</td>
<td>7.00</td>
</tr>
<tr>
<td>Mpumalanga</td>
<td>116</td>
<td>795</td>
<td>7084</td>
<td>89</td>
<td>8,084</td>
<td>9.83</td>
</tr>
<tr>
<td>North West</td>
<td>150</td>
<td>860</td>
<td>10075</td>
<td>47</td>
<td>11,132</td>
<td>7.73</td>
</tr>
<tr>
<td>Northern Cape</td>
<td>130</td>
<td>566</td>
<td>8414</td>
<td>162</td>
<td>9,272</td>
<td>6.10</td>
</tr>
<tr>
<td>Western Cape</td>
<td>254</td>
<td>1083</td>
<td>20000</td>
<td>3</td>
<td>21,340</td>
<td>5.07</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>2,443</strong></td>
<td><strong>12,266</strong></td>
<td><strong>155,811</strong></td>
<td><strong>1,272</strong></td>
<td><strong>171,792</strong></td>
<td><strong>7.14</strong></td>
</tr>
<tr>
<td><strong>% Total</strong></td>
<td><strong>1.42%</strong></td>
<td><strong>7.14%</strong></td>
<td><strong>90.70%</strong></td>
<td><strong>0.74%</strong></td>
<td><strong>100%</strong></td>
<td></td>
</tr>
</tbody>
</table>
**% RIF Concordance by LPA or DST n=9549 (March 2011-March 2013)**

<table>
<thead>
<tr>
<th>Province</th>
<th>Rif Resistant Cases</th>
<th>Rif Resistant Cases</th>
<th>Rif Concordance</th>
<th>Pre-analytical/No result</th>
<th>Rif Concordance</th>
<th>Rif Concordance</th>
<th>LPA</th>
<th>Rif Concordance</th>
<th>Indeterminate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>#</td>
<td>%</td>
<td>#</td>
<td>%</td>
<td>#</td>
<td>%</td>
<td>#</td>
</tr>
<tr>
<td>Eastern Cape</td>
<td>1459</td>
<td>22</td>
<td>4</td>
<td>18.2%</td>
<td>0</td>
<td>86</td>
<td>5.9%</td>
<td>81</td>
<td>94.2%</td>
</tr>
<tr>
<td>Free State</td>
<td>838</td>
<td>22</td>
<td>8</td>
<td>36.4%</td>
<td>0</td>
<td>149</td>
<td>17.8%</td>
<td>111</td>
<td>74.5%</td>
</tr>
<tr>
<td>Gauteng</td>
<td>1108</td>
<td>27</td>
<td>20</td>
<td>74.1%</td>
<td>0</td>
<td>136</td>
<td>12.3%</td>
<td>129</td>
<td>94.9%</td>
</tr>
<tr>
<td>KwaZulu-Natal</td>
<td>3181</td>
<td>377</td>
<td>368</td>
<td>97.6%</td>
<td>0</td>
<td>380</td>
<td>11.9%</td>
<td>325</td>
<td>85.5%</td>
</tr>
<tr>
<td>Limpopo</td>
<td>478</td>
<td>15</td>
<td>13</td>
<td>86.7%</td>
<td>0</td>
<td>36</td>
<td>7.5%</td>
<td>25</td>
<td>69.4%</td>
</tr>
<tr>
<td>Mpumalanga</td>
<td>649</td>
<td>87</td>
<td>86</td>
<td>98.9%</td>
<td>0</td>
<td>154</td>
<td>23.7%</td>
<td>134</td>
<td>87.0%</td>
</tr>
<tr>
<td>North West</td>
<td>523</td>
<td>16</td>
<td>15</td>
<td>93.8%</td>
<td>0</td>
<td>54</td>
<td>10.3%</td>
<td>47</td>
<td>87.0%</td>
</tr>
<tr>
<td>Northern Cape</td>
<td>447</td>
<td>19</td>
<td>12</td>
<td>0.0%</td>
<td>0</td>
<td>50</td>
<td>11.2%</td>
<td>44</td>
<td>0.0%</td>
</tr>
<tr>
<td>Western Cape</td>
<td>866</td>
<td>4</td>
<td>1</td>
<td>0.0%</td>
<td>0</td>
<td>757</td>
<td>87.4%</td>
<td>730</td>
<td>96.4%</td>
</tr>
<tr>
<td>National</td>
<td>9 549</td>
<td>589</td>
<td>527</td>
<td>89.5%</td>
<td>0</td>
<td>1 802</td>
<td>18.9%</td>
<td>1 626</td>
<td>90.2%</td>
</tr>
</tbody>
</table>

**Concordance for Rif Resistance now reaching 90%: Beyond questioning accuracy**
- Algorithm adherence concerns: ~ 20-30%
- Although small numbers E. Cape now deferring to LPA.
- Western Cape is our role model: 87% adherence to algorithm, Rif Concordance 96-100%
- (only difference: two sputums collected upfront: 1 Xpert, reflex testing done by lab)
- KZN and W Cape: greatest number of confirmations: INH positivity: KZN (87.4% INH resistance); W.Cape: (82%)
Summary of country activities: ongoing and new

- Publications
- Early impact studies:  
  - Time to diagnosis  
  - Time to treatment
- New impact studies
- Cost model
- Algorithm
- Paediatrics and EPTB
Summary of country activities: ongoing and new

- Publications
- Early impact studies:
  - Time to diagnosis
  - Time to treatment
- New impact studies
- Cost model
- Algorithm
- Paediatrics and EPTB

<table>
<thead>
<tr>
<th>Published articles from South Africa on the Xpert MTB/RIF assay</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of publication</strong></td>
</tr>
<tr>
<td>Commentary</td>
</tr>
<tr>
<td>Review</td>
</tr>
<tr>
<td>Case report</td>
</tr>
<tr>
<td>Laboratory research</td>
</tr>
<tr>
<td>Clinical research</td>
</tr>
<tr>
<td>EPTB</td>
</tr>
</tbody>
</table>

*From Oct 2010 to April 2013 (some publications may be missing due to inaccessibility of articles)*
Summary of country activities: ongoing and new

- Publications
- Early impact studies:
  - Time to diagnosis
  - Time to treatment
- New impact studies
- Cost model
- Algorithm
- Paediatrics and EPTB
New impact studies

**XTEND**: Aurum/BMGF funded/NHLS: cluster randomized trial Xpert testing sites with/out Xpert to review cost-effectiveness and impact.

**X-Phactor**: Xpert MTB/RIF for people attending HIV care: interventional cohort study to guide rational implementation.

**EXIT-RIF**: UNC, NC/RTC/WITS/NIH funded/NHLS: Observation study: Rif resistant patients identified arm 1 by culture, arm 2 by Xpert

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**MSF: Implementing Xpert MTB/RIF in Zimbabwe (S. Van Den Broucke, IAS 2012):**

- **Xpert doubled detection rate**;
- **Increased the no. of lab confirmed TB cases - less empiric diagnosis of TB**;
- **Triples/quadruples the number of MDR – TB diagnosed**

RTC in central Karoo region *(T,van den Handel: personal communication):*

- Xpert increased case detection
- Pre-Xpert: **22%** cases treated were smear negative, culture negative vs **1%** post Xpert.
- Pre-Xpert **21%** patients initiated in 5 days, post expert **95%** initiated in 5 days.
Summary of country activities: ongoing and new

• Publications
• Early impact studies:
  – Time to diagnosis
  – Time to treatment
• Cost model

National TB Cost Models in SA in 2011

• To estimate implementation
• To inform budget requirements (2011-2017)
• To estimate the incremental national health service cost
• XTEND study (BMGF funded): cluster randomised trial design (phase 3a and b) to verify modelling and evaluate cost-effectiveness in routine conditions
• Early implementation decisions were based on NTCM model.

Model predictions

• Scale-up lead to national test capacity of 11,428 tests/day.
• Total capital cost require 20 million USD
• Additional annual budget requirement (53-57%) or USD 46-70 million per year
• Clinic (decentralized placement) is 46% more expensive.
Summary of country activities: ongoing and new

- Publications
- Early impact studies:
  - Time to diagnosis
  - Time to treatment
- Cost model
- New impact studies
- Algorithm
- Paediatrics and EPTB

A model is just that………Flexibility needed and constant re-evaluation
Indirect Laboratory Savings and Unexpected costs

**Anticipated Savings**
- Staff time: fewer and less skilled: realize as program matures?
- Remote calibration project
- EQA product and management system
- Remote connectivity for instrument performance = audit indicators

**Unanticipated and under-estimated costs**
- Underestimated training requirements at clinical level on algorithm
- Under-estimated awareness campaign costs
- Change in requisition forms, reporting structures
- R&D costs for paediatric and extra-pulmonary samples, monitoring studies
- Data collection changes: NHLS CDW; clinical Etr.net
- **Cost of phased implementation: 2 parallel systems**
- Module failure: 150 modules replaced in the field.
- Stock shortage, Assay version change management
Costs of current algorithm for HIV+ Xpert - TB suspects

- In 2014, with full implementation of current Xpert algorithm
  - 436,025 TB cases will be notified
  - 20,714 will be Xpert- HIV+, culture+ PTB (<5%)
  - To diagnose these 20,714 PTB cases, we will do **1,668,607** cultures
  - R3,674 per TB diagnosis (overall), R6,885 per TB case diagnosed by culture
- What if we restrict culture testing for those still symptomatic after antibiotics?
  - assume 62% still symptomatic at 2\textsuperscript{nd} visit
  - 434,928 TB cases notified (**missed TB in <1% of cases**)
  - R2,942 per TB diagnosis (**20% reduction**)
  - annual saving of R322 million

Complicated algorithm one of the problems for Linkage to Care

Investigation of HIV+ Xpert –ve TB suspects

- 100 HIV+ TB suspects
- 80 TB -
- 80 GXP - and TB -
- 4 GXP - and TB + (sans. 80%)
- Investigate 84 suspects with culture, for 4 TB+ (5%)
- Is this cost-effective?
- Will culture results change management?
Significant algorithm simplification required

**TB SUSPECTS**
TB and DR-TB contacts, non-contact symptomatic individuals, re-treatment after relapse, failure and default
Collect one sputum specimen at the health facility under supervision

- **GXP positive**
  - **Rifampicin sensitive**
    - Treat as TB
    - Start on Regimen 1
    - Send one specimen for microscopy
    - **Follow up with microscopy**

- **GXP positive**
  - **Rifampicin resistant**
    - Treat as MDR-TB
    - Refer to MDR-TB Unit

- **GXP positive**
  - **Rifampicin unsuccessful**
    - Treat as TB
    - Start on Regimen 1
    - Collect one specimen for microscopy and LPA

- **GXP negative**
  - **HIV positive**
    - Collect one specimen for culture and LPA or culture and DST (for R and H)
    - Treat with antibiotics and review after 5 days
    - Do chest X-ray

- **HIV negative**
  - **Treat with antibiotics**

- **GXP unsuccessful**
  - Collect one sputum specimen for a repeat GXP

- **Poor response to antibiotics**
  - Clinically TB
  - TB on chest X-ray
  - **Treat as TB**
  - Start on Regimen 1
  - Review culture results

- **LPA/DST results**
  - Resistant to R and H/R only
  - **Treat as MDR-TB**
  - Refer to MDR-TB Unit

- **Good response**
  - No further follow up
  - Advise to return when symptoms recur

- **Poor response**
  - Consider other diagnosis
  - Refer for further investigation

Follow up with microscopy and culture
Xpert performance in paediatric TB: Better than smear but not good enough using sputum!

Johannesburg study: Gous N, Scott LE; Khan S; Reubenson G; Coovadia A; Cunningham B; Stevens W. CROI 2012,

Reality of Xpert MTB/RIF at POC for Diagnosing Childhood TB using Raw Sputum

- 67% specimens below required volume for Xpert testing.
- Sensitivity vs culture = 40%, versus MTB confirmed =66.7%
Added EPTB specimens other than FNA: Xpert Validation, preliminary results (Aug – Jan 2013):
(Elizabeth Prentice, Lesley Scott, Gloria Nkuna, Natalie Beylis, Wendy Stevens)

- Contamination: NALC-NaOH decontaminate
  - No contamination: Inoculate MGIT (~0.5 ml)
  - Residual Xpert tested: >0.5 ml

Exclusions:
- Numbers received in total <10 (0.6%)
- Not enough residual for Xpert – needs to exceed 0.5 ml after routine processing (30%)
  - Most common specimens excluded:
    - CSF (37%)
    - Pleural fluid (14%)
    - Other aspirates (9%)
  - Blood (1%)
EPTB specimen types received in a high throughput central laboratory, n=6112 received in 6 months (April 2012-Jan 2013)

**Study on additional EPTB specimens tested by Xpert n=865**

- Pleural fluid n=405 (47%)
- Aspirate not FNA n=91 (11%)
- Tissue n=12 (1%)
- Cerebrospinal fluid n=27 (3%)
- Pus n=70 (8%)
- Ascitic fluid n=63 (7%)
- Unspecified fluid n=151 (18%)
- Miscellaneous specimens n=19 (2%)
Findings

- Overall sensitivity of Xpert compared to MGIT = 55.9% (CI 48.8; 62.8)
- Absolute number: 159 new cases (18% of total referrals)
- Cost-effective?
Ensuring on-going quality testing

- **Verification**
  - Once off or upon instrument placement, maintenance / module swap-out
  - Prove the instrument is “fit-for-purpose”
  - Every module tested

- **EQA**
  - Proficiency testing of the laboratory staff
  - Assurance of instrument performance
  - 3 x per annum/per instrument, cost?

- **Continuous monitoring through remote connectivity**

Verification already performed for NHLS implemented instruments 2011-2012

<table>
<thead>
<tr>
<th></th>
<th>GX4s</th>
<th>GX16s</th>
<th>GX48</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>#Modules</td>
<td>54</td>
<td>96</td>
<td>2</td>
<td>152</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>128</td>
<td></td>
<td>1880</td>
</tr>
</tbody>
</table>

soon to be upgraded to Gx80

How do you do verification and EQA with this modular format?
No available EQA at time of initiation?
Novel approach using Dried Culture Spots

Manufacture of bulk culture: single cell suspension
Inactivation in Xpert SR buffer (2 hrs), confirmation by MGIT
Quantify using flow cytometry: small particle counting (1um)
Calculate bacterial events/ul
Spot onto Whatman paper cards
Send to sites for Gx testing

Expanded to: Kenya, Malawi, Mozambique, Zimbabwe and with AIDS Clinical Trials Group (ACTG) to Brazil, Peru and USA.

Global interest in DCS product

- # modules verified using DCS to date = 1261
- Average SD for probe A Ct = 2.7
- Total number errors = 24 (1.9%)
A multi-centre feasibility study to assess five EQA panels for Xpert in South Africa

**4 EQA trial programs**

<table>
<thead>
<tr>
<th>Matrix</th>
<th>Vircell</th>
<th>CDC</th>
<th>MQCI</th>
<th>GLI</th>
<th>DCS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lyophilised</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Dried Tube pellet</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Liquid (E.coli)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Dried Culture Spot</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Number of sites: 11 smear microscopy sites, now performing Xpert MTB/RIF, 1 Reference site

Collaborative project, NHLS, GLI, FIND, CDC, 2012/2013
### Results under review by collaborators

#### Qualitative analysis (n=11)

<table>
<thead>
<tr>
<th>Panel</th>
<th>Vircell</th>
<th>CDC</th>
<th>MMQCI</th>
<th>GLI</th>
<th>DCS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Correct result</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Instrument error related to volume</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cold chain and special packaging required</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Extra consumables required</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

#### Questionnaire (n=10)

<table>
<thead>
<tr>
<th>Question</th>
<th>Vircell</th>
<th>CDC</th>
<th>MMQCI</th>
<th>GLI</th>
<th>DCS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Received in good condition</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>SOP clarity</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Easy to open</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Easy to handle</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Easy to rehydrate and dissolves fully</td>
<td>1</td>
<td>1</td>
<td>1*</td>
<td>1*</td>
<td>1</td>
</tr>
<tr>
<td>Easy to transfer to Xpert cartridge</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

#### Quantitative analysis

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Vircell</th>
<th>CDC</th>
<th>MMQCI</th>
<th>GLI</th>
<th>DCS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased probe Ct SD above pool</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>PCR inhibition</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

| Subtotal                                  | 9       | 9   | 6     | 9   | 9   |

Scoring System: up for modifications and suggestions

Interest in Ct variability for ensuring Rif call rates
Summary

• MMQCI panel, which was the only panel that required cold storage which contributed to a lower score.

• All panels where received in good condition and therefore good for shipping across distances, and all showed compatibility with the Xpert testing process.

• No panel caused any PCR inhibition.

• Matrix requirement (liquid or dry) did not appear to be a distinguishing criterion as had reduced scores on: insufficient volumes; need for extra consumables; ability to transfer to the Xpert cartridge.

• Minimal variation in probe Ct may be more attractive for monitoring RIF call rates using differences in probe drop out or probe delayed hybridisation.

• Factors such as SOP clarity, label bar-code scanning, and use of the web based program highlight the need for any EQA program to be accompanied by training and ongoing improvements.
Automated Platform for Xpert MTB/RIF Verification and EQA data management: www.tbgxmonitor.com

- TBGxMonitor™ was developed to assist in the automated report generation for GeneXpert (MTB/RIF) Verification and EQA programmes.
- EQA Provider Neutral – samples barcoded by expected result for cross compatibility and standardized reporting.
- Inclusion of GMP documentation and traceability for accreditation (next development phase).
- Currently supports
  - 95 sites (laboratories and clinics)
  - 134 instruments
  - 8 countries

New feature: barcode labels for scanning contains result and panel details.

Upload results from laboratory

Central review and release of reports Can be automated fully

Cunningham B, Scott L, Molapo S, Gous N, Erasmus L, Stevens W, 3rd SA TB Conference, June 2012, South Africa
Potential for expanding DCS for other EQA programs like LPA testing

Objective: to determine the value of DCS as a potential EQA format for the Hain Line probe assay

- N=48 DCS tested
- Resuspended in 2ml PBS for 15 minutes
- Panel composition: x24 MTB Rif resistant and x24 NTM strains
  - x8 M. intracellulare
  - x8 M. kansasii
  - x8 M. fortuitum
- 1ml used for DNA extraction: Genolyse kit (Hain Lifesciences)
- Hain MTBDr plus v2.0 testing
- All n=24 correctly identified as M.tb positive, Rifampicin resistant
- All N=24 M.tb negative by Hain v2.0
- 1ml residual for repeat testing if required
- x6 M. intracellulare correctly identified
- x6 M. kansasii correctly identified
- x6 M. fortuitum correctly identified

Further Hain CM testing
Cepheid/NHLS Remote Connectivity project

- Operational dashboard for real-time monitoring of results, errors, resistance and positivity rates
- Pre-configured on all newly installed GeneXperts

User Workshop held 5-9\textsuperscript{th} November to improve usability and facilitate design changes, Johannesburg
How can the dashboard tool be used for improved program management

- Common features between NHLS LIS and Cepheid monitoring tool.
- Validation against NHLS LIS showed 1% bias due to duplicate removal and repeat on error testing not extracted by LIS.

<table>
<thead>
<tr>
<th>Variables</th>
<th>CDW/LIS/data extraction</th>
<th>Cepheid RM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient names and hospital ID*</td>
<td>yes</td>
<td>No (customer server)*</td>
</tr>
<tr>
<td>Date and time of assay run</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Laboratory number</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Cartridge number</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Duration of run</td>
<td>no</td>
<td>yes</td>
</tr>
<tr>
<td>Test type (test code)</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Lot number</td>
<td>no</td>
<td>yes</td>
</tr>
<tr>
<td>Result</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Error</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Error code</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Test user name</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Module ID (serial number)</td>
<td>no</td>
<td>yes*</td>
</tr>
<tr>
<td>Pressure and temperature curves</td>
<td>no</td>
<td>Yes*</td>
</tr>
<tr>
<td>Error log per module</td>
<td>no</td>
<td>Yes*</td>
</tr>
<tr>
<td>Instrument status</td>
<td>no</td>
<td>Yes*</td>
</tr>
<tr>
<td>Module status</td>
<td>no</td>
<td>Yes*</td>
</tr>
<tr>
<td>Monitoring and trending</td>
<td>?</td>
<td>Yes*</td>
</tr>
<tr>
<td>Module usage</td>
<td>Manual analysis per laboratory</td>
<td>Directly</td>
</tr>
<tr>
<td>Central data control</td>
<td>Requires data extraction (analyst)</td>
<td>Directly</td>
</tr>
<tr>
<td>Historical data</td>
<td>Yes (requires extraction)</td>
<td>yes</td>
</tr>
<tr>
<td>Real-time</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Technical status</td>
<td>no</td>
<td>yes</td>
</tr>
<tr>
<td>Share with external applications</td>
<td>No</td>
<td>Yes (login user specific)</td>
</tr>
<tr>
<td>Ct value and SPC</td>
<td>Yes (data extraction, manual analysis)</td>
<td>Yes*</td>
</tr>
<tr>
<td>Probe frequency</td>
<td>Yes for result upload</td>
<td>Requires extraction*</td>
</tr>
<tr>
<td>TAT</td>
<td>yes for time cartridge placed in instrument</td>
<td>yes for time cartridge placed in instrument</td>
</tr>
<tr>
<td>Usage</td>
<td>Manual for monthly</td>
<td>Yes (day, month etc) and time of day schedule testing</td>
</tr>
<tr>
<td>Calibration</td>
<td>yes*</td>
<td>no</td>
</tr>
<tr>
<td>EOA/QC</td>
<td>Only if identified</td>
<td>Only if identified</td>
</tr>
<tr>
<td>Duplication and serial testing</td>
<td>yes</td>
<td>no</td>
</tr>
</tbody>
</table>

*may be date of birth, hospital number or national ID.
Reduction in TB detection over time: visualize semi-quantitative values.

National GeneXpert MTB positivity

“Community bacterial load?” Can Xpert be used for surveillance (probe frequency, Ct) Scott LE, et al. CROI 2012, Seattle.
NPP data analysis to date: What can we learn from n=33 858 MTBC positive Xpert Ct values?

<table>
<thead>
<tr>
<th>Variable</th>
<th>Obs</th>
<th>Mean</th>
<th>Std. Dev.</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROBE_A_CT-E</td>
<td>33858</td>
<td>21.93891</td>
<td>6.12613</td>
<td>0</td>
<td>40.2</td>
</tr>
<tr>
<td>PROBE_B_CT-E</td>
<td>33858</td>
<td>23.14183</td>
<td>6.108638</td>
<td>0</td>
<td>40.9</td>
</tr>
<tr>
<td>PROBE_C_CT-E</td>
<td>33858</td>
<td>22.32343</td>
<td>5.933259</td>
<td>0</td>
<td>39.8</td>
</tr>
<tr>
<td>PROBE_D_CT-E</td>
<td>33858</td>
<td>23.25527</td>
<td>6.270021</td>
<td>0</td>
<td>40.9</td>
</tr>
<tr>
<td>PROBE_E_CT-E</td>
<td>33858</td>
<td>22.69467</td>
<td>7.507461</td>
<td>0</td>
<td>39.8</td>
</tr>
</tbody>
</table>

SPC = the internal control

- SPC internal control shows n=144 results where probes bound but SPC= 0 (sample overload!).
- n=668 (1.97%) have internal control values >34Ct (important for use of the assay for monitoring – i.e. these samples show inhibition and therefore not reliable for follow up monitoring without being aware of “first sample” visit).

Courtesy Scott, Stevens 2012
Audit indicators

Module trends:
- identify module outliers from same instrument, same lab over time.

User trends and training needs:
- Users with increased rates of positivity
- Users with increased error rates
Workflow analysis and throughput vs capacity

- Testing times/day/week
  - Identifies 8h, 12h, 24hr workflow
  - Actual testing vs capacity

G3 to G4 change over
Training needs and managing staff turnover

Higher error rates at first testing

High staff turnover and staff task shifting
Cepheid remote monitoring tool.

- # tests analysed = 348,645
- # modules = 1,335
  - Max number results/module = 1,424
  - Median number results/module = 197
  - Max number errors/module = 137
  - Number of errors/day/module = 7
  - Problem modules = 101 (>7% error rate)

### NHLS LIS

<table>
<thead>
<tr>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total No. of Modules</td>
<td>1,888</td>
</tr>
<tr>
<td>No of Modules Replaced</td>
<td>150</td>
</tr>
<tr>
<td>% Replaced within 2 Yrs. (n=150)</td>
<td>7.94</td>
</tr>
<tr>
<td>% Replaced within 1 Yr. (n=125)</td>
<td>6.62</td>
</tr>
<tr>
<td>X Time to Failure</td>
<td>278</td>
</tr>
<tr>
<td>Median Time to Failure</td>
<td>219</td>
</tr>
<tr>
<td>Max</td>
<td>699</td>
</tr>
<tr>
<td>Min</td>
<td>2</td>
</tr>
</tbody>
</table>

### Time and number of module failure

- 0-100: 21; 14%
- 100-200: 41; 27%
- 200-300: 51; 34%
- 300-400: 12; 8%
- 400-500: 11; 7%
- 500-700: 14; 10%
- 700-800: 10; 6%

### Additional Information

- Total No. of Modules: 1,888
- No of Modules Replaced: 150
- % Replaced within 2 Yrs. (n=150): 7.94%
- % Replaced within 1 Yr. (n=125): 6.62%
- X Time to Failure: 278
- Median Time to Failure: 219
- Max: 699
- Min: 2
Overcoming hurdles to rollout Calibration: Too expensive and impractical? NHLS collaboration with Cepheid

- Calibration cartridges as opposed to swap-out module.
- Run cartridge as a normal Xpert assay (21 minutes)
- Software calibration is performed once the calibration file has been verified by Cepheid.
- Calibration key = barcode to be scanned in the calibration software to activate the calibration.

- Phase 1 (June 2012) and 2 (August 2012) study completed
- Expected product launch December 2012
- Original annual costs: R7,148,940 ($831,272) (quoted costs + travel costs for current instrument load)
- 80% reduction in costs anticipated?

User runs calibration software & loads the calibration cartridges
Cepheid analyzes data
Activation code is provided to user to update calibration
Certificate issued
Customer Service notified for follow-up

Data sent by internet or by CD
Remote calibration of GX modules

- Two Gx 16 modules were tested using DCS verification material before and after remote calibration.
  - n=6 modules failed (4 x Valve drive failures, 1 x Ambient Temperature failure) before 6 months.
Pre-post calibration Ct value analysis

- Probe A evaluated:
  - Ct decrease after calibration
  - Less variability in Ct after calibration
  - Not statistically significant (p=0.175)

- 2000 tests or 1 year may not be the optimal indicator for calibration but rather change in SD of Ct value/module

Concern: the use of Ct for patient monitoring?

<table>
<thead>
<tr>
<th></th>
<th>Pre calibration</th>
<th>post calibration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Instrument 1</strong> (n=13)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average Ct</td>
<td>18.5</td>
<td>17.9</td>
</tr>
<tr>
<td>SD</td>
<td>4.4</td>
<td>1.6</td>
</tr>
<tr>
<td><strong>Instrument 2</strong> (n=11)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average Ct</td>
<td>19.3</td>
<td>17.4</td>
</tr>
<tr>
<td>SD</td>
<td>2.2</td>
<td>1.5</td>
</tr>
</tbody>
</table>
Cost-effectiveness doesn’t equal affordability or uptake: linkage to care!

- Feasibility and impact of Xpert at POC (~2hr test result).
  - Concerns: Expanding Xpert to POC could result in important patient benefits but requires substantial strengthening of primary care facilities and investment in human resources (a minimum of two full-time staff required to supervise sputum collection, process sputum, perform assays, document and communicate results for an average of 15 TB suspects daily). Some patients did not receive same day treatment due to specimen preparation times.

(Clouse, K et al, SAMJ 2012)
Current Challenges

• **Global shortages of cartridges**
  - Situation resolving with deliveries of backorders currently underway
  - Remains a concern as other countries come on-line

• **Phased implementation: Incomplete access to testing: two algorithms in place (smear & GXP)**
  - Equity issues: rollout of instrumentation brought forward
  - Confusion at lab and clinical level

• **Non-adherence to algorithm / confusion regarding test requests**
  - No confirmatory testing for Rif resistant (from 20-40%)
  - Multiple tests requested on one form
  - Simplification required

• **Paediatric Testing, Extra-pulmonary samples**

• **Level of placement (sub-district labs v clinics)**
  - **GXP in clinic:** required 2.5 staff members to get 15 patients from test to treatment same day. Clouse K, Page-Shipp L, Dansey H, Moatlhodi B, Scott L, Bassett J, Stevens WS, Sanne I, van Rie A. Implementation of Xpert MTB/RIF for routine point-of-care diagnosis of tuberculosis at the primary care level. Accepted to PLOS Medicine, March 2012
Solutions and Action needed…

• Confidence in technology capabilities and limitations
• Development of a clinical algorithm: requires urgent review
• Training of both laboratory and clinical staff massive ramping up required
• Slowed down by a temporary global shortage of cartridges: stable stock supply
• Appropriate instrument placement: flexibility needed
• All instruments interfaced in real-time to central data monitoring system (LIS for results,
• Rolling out of remote connect system for instrument performance and continuous quality monitoring
• Finalization of EQA plan
• Remote calibration performance reviewed
• Need for electricity, sensitive to huge temperature fluctuations

• HEALTH SYSTEM STRENGTHENING NEEDED: FIRST STEP IN CONTINUUM OF CARE
Xpert MTB/RIF field testing for NDoH campaign and using DCS to verify mobile Gx units.
World TB day: 10 X GX16 in mobile vehicles
Acknowledgements

- Honorable Minister of Health: Dr Motsoaledi
- NHLS National Priority Program staff: Dr Leigh Berrie, Mr Sebaka Molapo
- NDoH: Drs Mametje, Pillay, Mvusi, Barron, Mabope, Nshuti
- Centre for Tuberculosis: Drs N. Ismail, L. Erasmus
- CDC for funding and support
- HERO team, G. Meyer – Rath, K. Bistline, Prof S. Rosen, Dr Billl Macleod
- Right to care: Prof Ian Sanne
- MM&H: Prof Scott, N. Gous, B. Cunningham, Dr E. Prentice
- Centre for TB excellence: Dr Bavesh Khana
- NHLS TB Expert working group: Dr A Whitelaw, Prof M. Nichol
- USAID, South Africa
- FIND: new work on EQA, R&D projects: Heidi Albert, Dr Boehme
- Aurum Institute: Prof G Churchyard, XTEND study and staff
- Bill and Melinda Gates foundation
- Cepheid for new collaboration: regarding remote calibrations and connectivity
- Arnoud and Alex de Nooy: supported my projects over a 15 year period