Lessons learnt from Xpert implementation and holistic solutions required for the successful scale-up of Omni

Professor Wendy Stevens
University of the Witwatersrand & National Priority Program of the NHLS
HIV & TB in South Africa: Laboratory Context

- Total Population ~54 Million at last census, middle income country
- TB Prevalence: 380/100 000 (210-590) (WHO, 2015); Incidence 450/100 000 (400-510) (WHO, 2015)
- over 7.4 million GeneXpert tests since project inception; MTB positivity 16 to 9%
- Rif Resistance: 6% stable
- South Africa still purchases 50% of global Xpert supply

- Estimated 6.3 million HIV infected individuals of which 3 million are receiving ARV therapy
- Currently Conduct approximately ~3.9 million CD4 tests annually, 3 million million viral loads and currently 360 000 EID assays (2014);
- Acceleration of VL requirements exceeds expectations: >30%; 3.6 million (fiscal year: 4.2 million (April 2015-March 2016))
- 30-40% of all public health sector laboratory expenditure for HIV&TB: (15% of total budget)
- Adoption of 90’s for HIV and TB

Xpert distribution in public sector by district (March 2011 - October 2015)

314 GeneXpert instruments: 4188 modules
GX4: 115; GX16: 190; GX48: 1; GX80: 8 in 211 sites – both urban and rural settings - across 9 provinces

Legend
- Xpert Testing Labs
- DOH Facilities

Average test/module: 3/day
Backbone facilitated expansion to vulnerable populations

242 facilities in 48 clusters

GIS mapped to NHLS lab

150,000 offenders (50,000 in remand)

7 mini labs on-site at Max Security

181,569 assays conducted

Average MTB positivity of 4.6% and a RIF resistant rate of 4.3% (n=360)

SMS printers implemented

120 webview results

Linked to local laboratory

Infection Control: major issue

National Task Team established by NPP with all stakeholders: NDoH, DCS, Clinicians, NHLS, human rights and advocacy groups, facility security, M&E group, research group, donors; infection control
Nationwide and regional incidence of microbiologically confirmed pulmonary tuberculosis in South Africa, 2004–12: a time series analysis

Ananta Nanoo, Alane Izu, Nazir A Ismail, Chikwe Ihekweazu, Ibrahim Abubakar, David Mametja, Shabir A Madhi

Summary
Background South Africa has the highest incidence of tuberculosis in the world, largely resulting from a high population prevalence of HIV infection. We investigated the incidence of microbiologically confirmed pulmonary tuberculosis, and new cases of pulmonary tuberculosis registered for treatment, nationally and provincially in South Africa from 2004 to 2012, during which time there were changes in antiretroviral therapy (ART) coverage among individuals with HIV infection.

Methods We identified cases of microbiologically confirmed pulmonary tuberculosis from 2004 to 2012 from the National Health Laboratory Service Corporate Data Warehouse. New cases registered for treatment were identified from National Department of Health electronic registries. A time series analysis, using autoregressive models, was undertaken on incidence of microbiologically confirmed pulmonary disease nationally and provincially; this trend was also examined relative to ART coverage of adults with HIV infection.

Findings During the 9-year period, 3523371 cases of microbiologically confirmed pulmonary tuberculosis were recorded nationally. Annual incidence (per 100 000 population) increased from 650 (95% CI 648–652) in 2004 to 848 (845–850) in 2008, declining to 774 (771–776) by 2012 (9% decrease from 2008 to 2012). Incidence varied by age-group, sex, and province. There was an inverse association between incidence of microbiologically confirmed disease and ART coverage among HIV-infected individuals nationally and provincially. Trends in incidence of tuberculosis cases registered for treatment mirrored those of microbiologically confirmed cases nationally and provincially; however, incidence of microbiologically confirmed cases was consistently higher than cases registered for treatment nationally and in seven of nine provinces.

Interpretation Since its peak in 2008, the incidence of microbiologically confirmed pulmonary tuberculosis in South Africa had declined by 2012; this decline is associated with an increase in ART coverage. Future integration of registries for microbiologically confirmed cases and new cases registered for treatment would improve the assessment of the burden of pulmonary tuberculosis in South Africa.
Reason for optimism
Change in Xpert positivity, by month, by province

- Eastern Cape
- Free State
- Gauteng
- Kwazulu-Natal
- Limpopo
- Mpumalanga
- Northern Cape
- North West
- Western Cape
1. High level political commitment needed
2. Multi-disciplinary team required
3. Trends in molecular testing approach synergistic with HIV programs
4. All components of a quality system needed (high volume to POC)
5. Complexity of validations slows progress
6. Measurement of diagnostic impact needs review
7. Huge gaps in assay performance and supporting assays (current & future)
8. Diagnostic intervention needs to result in HCW behaviour change/management of patient
9. Continuous connectivity: results, analyzer performance, real-time surveillance, hot spot identification
10. Managing changes in technology; G3/G4; software
11. Needs Driven Innovation
12. Linkage to care
13. Models for implementation, including OMNI
1. Success: High level political commitment

- Bold, courageous, continues with Adoption of the 90’s for TB and HIV
- Engagement of public, private and civil society sectors, NGO’s, donors, treasury, all tiers of government
- Establishment of focused Priority Program team focus
- Multi-disciplinary Teams required
- One national plan; initial vertical implementation worked best
- National footprint facilitated access in vulnerable populations such as correctional services & mines
- Costing and modelling /forecasting models matured
- Shared NDoH and Donor funded
- Sustainability through treasury
2. For national program implementation: Who do you need on your team at a minimum?

- **Relevant stakeholders** to the problem/intervention
- **NDoH**: always; without their support it is likely to fail
- **Clinicians**: represented by strong bodies providing easy access to opinions e.g. in HIV, HIV clinician’s Society which are needed for expertise and acceptance for HIV assays
- **NHLS**: Pathologists and their expert teams
  - R&D (scientists)
  - Operational research
  - Quality management
- **Supplier partnerships**
- **Health economists**: most valuable addition
- **Bioinformatics, epidemiology and statisticians**
- **Project managers, engineers** (software development; process management)
- **Strong IT support**
- **M&E team with clear goals/indicators**
- **Ad hoc experts**: people affected, humanities representation, section 27 (legal), ethics, specific experts
HIV Diagnostics Timeline: Lessons Learnt

Molecular paradigm

1992
1st HIV DNA PCR

1995
Manual HIV Viral Load

1999
Semi-automated HIV Viral Load

2004
South Africa VL program start

2005
Fully automated HIV Viral Load

2010
WHO endorses TB

2011
Rapid adoption Molecular TB

2011
WHO guideline endorses VL

2013
Molecular TB Testing “replacement”

2014
Dual Target Viral Load

2015
Dual target TB test

2015

90:90:90
3. Lessons learned: Same as for HIV

- Molecular testing implementation needs mirrored HIV: EID and VL change lags HIV thinking currently
- Less understanding in TB arena: dynamic process, evolution of guidelines & technology
- Diagnostic impact not demonstrable in 1 year (XTEND).
- Complexity of evaluations hold back progress; move away from culture in routine? (phenotypic vs. genotypic)
- Performance of 2nd line molecular resistance tests poor
- Less understanding of pathogenesis yet themes the same for HIV; (disease progression, persistence, latency, reproductive fitness of resistant strains?)
- Clinical algorithm too complex and hence not followed
- Paediatric diagnosis remains problematic
- Role in different compartments not understood and while EPTB testing results improved; implementation very difficult
- Polyvalency possible when synergies/forecasting are identified
- Connectivity: ? Alternative surveillance/ continuous quality monitoring
7. Gaps in Assays?

• Module failure: improved but remains a concern
• Improved sensitivity in HIV + GXP-ve
• Rif discordance; solved by algorithms?
• LPA & culture difficult to standardize assay & interpretation
• Poor second line drug resistance assays
• What is missing?
  • earlier screen, improved resistance assays, diagnose latent TB & predict progress
8. Change in HCW practice difficult to achieve?

• **Examples**
  
  - **National data** shows algorithm not followed: although improvement demonstrated 20%~50%
  - **EXIT RIF study**: earlier treatment initiation & reduced mortality, but failure to follow algorithm
  - **GCC POC study**: assay selection not based on symptom screening

• **Contributing factors**
  
  - Basic collection practices
  - Complex clinical algorithm
  
  - No difference in scenarios for use of VL 14 years post implementation
  - Training simplified and continuous
9. Continuous Connectivity?

• Continuous quality monitoring (IQC essential)
• Alternative real-time surveillance
• Program monitoring
• mhealth Hub

• Can be expanded to all tiers of healthcare/laboratory system?
GeneXpert Dashboard

Remote Xpert

A Web portal that is a device relationship management platform

Device GeoLocation

[Map showing geographic location with data]

Module Data

[Chart showing data]

Courtesy Prof Wendy Stevens, NHLS NPP and Cepheid
Monitoring and Evaluation of Effectiveness of CCMT Programme

NDoH Health Information System (TIER.net)
National Health Laboratory Service

Summary indicators for CCMT M&E in SA
Period: from Q1 2013 to Q3 2014

# People on treatment (DHIS)

% People with CD4 tests done, with a CD4 count <= 350 cells/mm³

% People with CD4 tests done, with a CD4 count <= 200 cells/mm³

% People with CD4 tests done, with a CD4 count <= 100 cells/mm³

# People with a VL test done in the last 12 months

% People in care and on ART with a VL <= 1000 copies/ml

% Children < 5 years infected by vertical transmission

% HIV+ people in care and on ART, who have a VL done at least annually

Courtesy Dr Sergio Carmona
Interrogating molecular features to identify “hot spots” of TB transmission

What do we know about the Gx molecular’s characteristics

- Majority RR cases are due to drop out probes not delayed *(Blakemore.R et al 2010).*

Explore:

- Frequency of 5 rpoB probes (81bp) = mutation profile?
- Can cycle threshold (Ct) (mean, SD) = population disease burden?

Scott.L.E et al CROI, 2012, Van Rie, A et al, in press
Real time molecular surveillance

POSITIVITY RATE by DISTRICTS
South Africa, 2014

RIF RESISTANCE RATE by DISTRICTS
South Africa, 2014

Space-time analysis identifies increases in MTB positivity rates

Acknowledgement:
Scott, van Rie, 2015
10. Any technology changes challenge all aspects of the program significantly

- Increased sensitivity: HIV positive GXP negative: planning for culture labs
- Increased specificity: melting temperatures; software changes, surveillance, monitoring of performance?
- Transition to be managed very carefully

**Xpert Ultra: Increased sensitivity for TB detection**

- **Xpert MTB/RIF:** Detects TB with a single copy target (rpoB gene)
- **Ultra:** Detects two different multi-copy targets (IS6110 & IS1081)

11. Needs Based Innovation

- Model of implementation triggered profile of Implementation Science
- Development of a quality assurance program and project used globally
  - (African Innovation award for social impact)
- mHealth app (MILINC): nomination for health app
- SMS printer design & improvements
MDR-TB | Pilot Location

12. Linkage to Care & adherence

THE MDR-TB Partnership

MDR-TB | Solution

1. Suspect tests for TB at PHC clinic and enroll in emocha
2. Lab results appear on tablet in real time; Linkage status visualized
3. Linkage officer contacts suspects who are MDR-TB positive
4. Patient checks-in to MDR-TB clinic

Digital Health Captains of Industry
Linkage to care

South African mHealth-HUB

Optional app training service (monthly fee TBC)

Field Device Management (Connectivity, maintenance of phones/tablets): Monthly fee TBC

External vendors

Data sharing agreements & SDK’s

TherapyEdge
momCONNECT
eKAPA
Mobenzi
miLINC
TREAT-TB

Data Integration (INFORMATICNA)

Central Data Warehouse

NETEZZA (Server)

Microstrategy (Advanced Business Intelligence)

Common Dashboard (e.g. HIV/TB)

Standardised reporting to stakeholders (e.g. NDoH)

Project-specific dashboards and alerts

Data Integration (INFORMATICA)

Laboratory Information System (LIS)

Private Sector: Lancet, Pathcare, etc.

DISA

TrakCare

With compliments: Lynsey Isherwood
13. Models for implementation

Model depends on the clinical use, clinically relevant TAT?

1. National Coverage (Access)

- Classic Tiered model (variations): 265 NHLS facilities; limited tiering to district (CD4)
- Total centralization: VL, EID (17 centres)
- Total de-centralization: HIV rapid test, sms printers (potentially 4400 HIV/TB alone)
  - POC clinic/hospital, POC community

2. Specific niched placement

- TB contact tracing, VL, EID at labour wards

3. Considerations

- **Dependent on:** volumes, distances, capability of technology; skill set
- Integrated service delivery model (previously described)
- Can a single national plan change POC procurement models
- Platform polyvalency
AS IS: Largely centralized PCR (HIV), CD4, TB (GeneXpert) laboratory footprint (total: 265)

**CD4 labs**
The NHLS enumerates CD4 for the public sector at 62 labs – current footprint for >3.8m test. Beckman Coulter, PLG CD4

**HIV viral load labs**
17 laboratories
8 sites with Abbott m2000 system
9 sites with Roche CAP/CTM
Current instrument capacity (8 hour shift)
50: 50 supplier test split

**GeneXpert TB testing labs**
National policy
Roll out March 2011, testing at smear microscopy labs
>6.5million tests to date.
Gx at POC:NTCM=too costly
Testing centres: 221
Analysers: 309
Clinic placements: 20
Gx4: 110
Gx16: 190
GX80:48: 1
GX8:7

Limited tier to district level

Highly centralized: doubling in capacity

Significant tiered de-centralization
Device De-centralization: A different scale completely?

- SMS printers to **improve turn-around-time** of results back to facilities from the labs
- **Beneficial in remote**, far-reaching areas where no internet access is available
- **SMS is automatically generated** from the lab’s LIS
- **Roll-out in 2009: new model (GF)**
  - Currently >2500 SMS printers in the field: CD4 Count, HIV VL, EID, GeneXpert TB and TB Microscopy.
  - Monitored by a dashboard

- Over 7636 health facilities
- Over **4400** ARV clinics

256 NHLS labs
1. What have we learnt from highly centralized VL & EID programs?

- **Total centralization**: VL, EID,
  - Feasible with collection material (PPT & DBS) & logistics, generally only used in 7 days time/clinic schedule: current TAT; 24-48 hours
  - Previously tiering not possible: no mid-volume or POCT
  - As volumes head for 4 million VL & double EID volumes: some centralized backbone will be necessary

<table>
<thead>
<tr>
<th>Advantages</th>
<th>disadvantages</th>
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<tbody>
<tr>
<td>Cost-efficient backbone</td>
<td>When 1000/8hrs/high end analyzer; risk mitigation needed</td>
</tr>
<tr>
<td>Quality control: continuous</td>
<td>• More than one supplier</td>
</tr>
<tr>
<td>Expertise for outliers</td>
<td>• Engineering support significant</td>
</tr>
<tr>
<td>Data collection easy: LIS and CDW</td>
<td>• Data entry rate limiting</td>
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<tr>
<td></td>
<td>• Resulting strategies have to be improved with redundancies</td>
</tr>
<tr>
<td>Polyvalency for TB, HBV, HCV, HPV</td>
<td>• Testing capacity redundancy &amp; disaster recovery</td>
</tr>
<tr>
<td>Supplier partnership: procurement model</td>
<td>• Logistics critical, ideal staff volumes, procurement</td>
</tr>
<tr>
<td>Ability to switch logistics via central co-ordination</td>
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Developed the Integrated Tiered Service Delivery Model (ITSDM): (Red=additional tiers vs. black=existing tiers):

- **Tier 0**: patient centred/community HCW
- **Tier 1**: True POC: Delivers CD4 testing at single health-clinics providing ART in hard-to-reach, remote areas (<5 samples/day)
- **Tier 2**: POC Hub: Laboratory-based testing or CHC sites processing 30–40 CD4 samples/day), consolidating POCT across 8–10 health-clinics with other HIV-related testing.
- **Tier 3**: Community Laboratory: serving +40 health-clinics, processing <150 samples/day
- **Tier 4**: District Laboratory: Serving +100 facilities and process <350 samples/day
- **Tier 5**: Metro/Centralised Laboratory: High volume laboratories (>350 <=1500 tests/day, serving +200 health-clinics)
- **Tier-6**: Coordinated national support for standardisation, harmonization and quality across services (NPP).

Acknowledgements: Cassim, Glencross, 2014
## Is total decentralization possible?

### Viral Load performance between: April 1, 2014 to March 31, 2015

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Data</th>
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<tbody>
<tr>
<td>Total VL tests per annum (pa)</td>
<td>2,834,462</td>
</tr>
<tr>
<td>NDoH VL Facilities</td>
<td>4,420</td>
</tr>
<tr>
<td>Median number of tests per facility (pa)</td>
<td>286 IQR (98-737.5)</td>
</tr>
<tr>
<td>Daily demand</td>
<td>1,14 VL / Facility / Day*</td>
</tr>
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</table>

*Median VL per day (assuming 22 working days per month)

# Facilities that requested a viral load in 2014/15 and provide ART

Data source: NHLS Data corporate warehouse

Credit: Prof. W. MacLeod

**Acknowledgements**

Carmona, Macleod, 2015
Is the OMNI feasible?

Criteria

- simple: ✔✔
- Robust: ✔
- speed: ❓
- Power: ✔✔
- Battery: 4 hours: ✔✔
- Connectivity: ✔✔

Ticks the right boxes!

GeneXpert® Omni®
The True Point of Care Molecular Diagnostic System

* Statements and products depicted are forward-looking. Not available for diagnostic use. Projected release in 2010.
### Cost of POC services

<table>
<thead>
<tr>
<th>RCT Cost effectiveness</th>
<th>SOC</th>
<th>POC</th>
<th>Difference (POC-SOC)</th>
</tr>
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<tbody>
<tr>
<td>Eligible patients (n)</td>
<td>188</td>
<td>226</td>
<td>38</td>
</tr>
<tr>
<td>Cost per patient initiated</td>
<td>R1,158</td>
<td>R2,147</td>
<td>R989</td>
</tr>
<tr>
<td>Cost to produce a patient in care and responding</td>
<td>R6,936</td>
<td>R10,882</td>
<td>R3,946</td>
</tr>
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</table>
Considerations: What did we learn and how to scale?

• Developed the CCPLP (combined clinical POC lab Platform)
  – Multi-POC evaluation protocols, SOP’s, starter kit, training material, EQA, connectivity solutions.
• Determined:
  – Nurse-operated POC as good as Lab (within allowable differences). Nurses also perform EQA within limits.
  – Training: <½ day for POCT, except GeneXpert (computer illiteracy).
  – Multiple POCT:
    • 69% patients need >3 tests (CD4, ALT, Cr, Hb) plus HCT.
    • 22 extra duties added to nurses and POC testing times up to 1hr47mins incl. CD4.
  – Finger stick POC:
    • Patients prefer finger stick over venepuncture.
    • 150ul max volume and can perform multiple POC off single FS.
    • Increased tests variability in colder weather, 98% finger-sticks generate a result, 8% may require >1 finger-stick.
• Multiple POCT will require new cadre of staff and dedicated secure space.

• Gous.N, et g for HIV Anti-Retroviral Treatment Initiation and Monitoring from Multiple or Single Fingersticks. PlosOne 2013 | e85265
Considerations: What did we learn and how to scale?

Connectivity is a critical component to POC

- National data ("real-time"), M&E, billing, QA
- Connectivity requires permanent IT support:
  - Loss, availability and stability of internet connections (web-based vs local installation)
  - IT "policing" required: viruses, excessive downloads.
  - 62% results captured correctly – requires a lot of support and on-going training.
- Operational dashboards and/or middleware

GeneXpert on the move!!: Peri-mining communities

**SPECIFICATIONS**

**VW Crafter 50 80KW LWB**

**GX-IV Processing Unit:**

11.00” w x 12.00” h x 11.70” d

GeneXpert Instrument uses 200W per Instrument

**Additional Items installed:**

- 2 x Computer (FIXED)
- 1 x Desktop Printer (FIXED)
- Unit with sink and Fridge
- Cupboard storage space (bottom and top)
- Invertor - Continuous power to Instrument UPS
- Air-Con unit
- Waste (general and biohazard)