NATIONAL HEALTH LABORATORY SERVICE

# GeneXpert MTB/RIF

## Progress Report

May/June 2012

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## 1. Background to Project

This project was initiated at the request of the Honorable Minister of Health, Dr Aaron Motsoaledi, in early 2011, following the World Health Organization's strong recommendation published in December 2010 that "the new automated DNA test for TB be used as the initial diagnostic test in individuals suspected of MDR-TB or HIV/TB". In essence this comprises the majority of TB suspects in South Africa. A pilot study was proposed by the TB Cluster within the National Department of Health (NDoH) while a project feasibility study was being performed with due diligence.

The pilot study was initiated in microscopy centres in high focus TB areas. The NDoH requested that at least 1 instrument be placed in each province, preferably in high burden districts. Selections were made by the TB cluster, with twenty-five microscopy centres being selected and a total of 30 instruments placed.

The NDoH funded 9 GX16 and 14 GX4 instruments for the project. FIND (The Foundation for Innovative New Diagnostics) donated 6 GX4 analysers and the Infinity or GX48 was supported by PEPFAR Right to Care funds. All instruments were placed by World TB day March 24th 2011. This placement represented about 10% of national coverage. The basis for the calculations was an assumption that 2 smears at diagnosis would be replaced by 1 Xpert® MTB/RIF assay. All instruments were interfaced to the NHLS Laboratory Information System (LIS) allowing for troubleshooting and data collection.

The remainder of the roll-out is being performed in a phased manner by the National Priority Programmes of the NHLS and the NDoH, the progress of which is described in point 4 below.

## 2. Assays performed to date

In summary, a total of 423,172 specimens have been processed to date (11 June 2012). The total % of *Mycobacterium tuberculosis* complex (MTBC) detected in this cohort was 15.98% (67,630). The percentage positivity has remained on average between 16-17% monthly country-wide. To date Kwa-Zulu Natal (KZN) has performed the greatest number of tests which is probably as a result of the throughput of the GX48 analyzer (Refer to table 1). Average Rifampicin resistance detection rates have remained around 7% since project inception (Refer to table 2).

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**Table 1: GeneXpert MTB Results by province**

| Province | MTB Detected | MTB Not Detected | Test Unsuccessful | Grand Total | % MTB Detected |
|---|---|---|---|---|---|
| Eastern Cape | 8,446 | 42,060 | 1,710 | 52,216 | 16.18 |
| Free State | 7,031 | 41,207 | 125 | 48,363 | 14.54 |
| Gauteng | 6,087 | 40,524 | 873 | 47,484 | 12.82 |
| Kwa-Zulu Natal | 22,748 | 93,573 | 3,501 | 119,822 | 18.98 |
| Limpopo | 3,230 | 27,138 | 376 | 30,744 | 10.51 |
| Mpumalanga | 4,021 | 20,245 | 1,558 | 25,824 | 15.57 |
| North West | 4,020 | 20,975 | 1,225 | 26,220 | 15.33 |
| Northern Cape | 4,779 | 24,463 | 833 | 30,075 | 15.89 |
| Western Cape | 7,268 | 35,023 | 133 | 42,424 | 17.13 |
| **Grand Total** | **67,630** | **345,208** | **10,334** | **423,172** | **15.98** |

**Table 2: Provincial GeneXpert RIF Results in MTB detected cases**

| Province | Inconclusive | Resistant | Sensitive | No Results | Grand Total | % RIF Resistant |
|---|---|---|---|---|---|---|
| Eastern Cape | 113 | 627 | 7,574 | 132 | 8,446 | 7.42 |
| Free State | 92 | 406 | 6,504 | 29 | 7,031 | 5.77 |
| Gauteng | 61 | 411 | 5,608 | 7 | 6,087 | 6.75 |
| Kwa-Zulu Natal | 314 | 1,772 | 20,276 | 386 | 22,748 | 7.79 |
| Limpopo | 49 | 242 | 2,912 | 27 | 3,230 | 7.49 |
| Mpumalanga | 61 | 325 | 3,564 | 71 | 4,021 | 8.08 |
| North West | 50 | 325 | 3,637 | 8 | 4,020 | 8.08 |
| Northern Cape | 61 | 294 | 4,396 | 28 | 4,779 | 6.15 |
| Western Cape | 77 | 347 | 6,840 | 4 | 7,268 | 4.77 |
| **Grand Total** | **878** | **4,749** | **61,311** | **692** | **67,630** | **7.02** |

Rifampicin concordance is good for both LPA and culture. There is Rifampicin mono-resistance significant geographical variation. The national average is 12% for DST and 18% for LPA. This could be attributed to a number of factors such as geographical variation, laboratory variation, and interpretation of LPA, reliability of gold standard or even strain variation.

Testing and clinical algorithms show variation across provinces, requiring standardisation.

**Table 3: Rif Concordance by LPA or DST**

| Province | LPA | DST |
|---|---|---|
| Eastern Cape | 93.3% | 12.5% |
| Free State | 83.3% | 75.0% |
| Gauteng | 92.3% | 88.2% |
| Kwazulu-Natal | 82.2% | 93.3% |
| Limpopo | 80.0% | 94.4% |
| Mpumalanga | 81.0% | 97.2% |
| North West | 100.0% | 50.0% |
| Northern Cape | 76.2% | 66.7% |
| Western Cape | 95.9% | 100.0% |
| **National** | **87.2%** | **89.7%** |

Errors have ranged consistently below 3%. Details of invalid results, which likely represent sample issues remains below 1%. These are being monitored regularly and corrective action implemented where necessary.

**Table 4: Number of Unsuccessful Tests and Reasons**

| Province | Error | Invalid | No Result | GXP Result | Grand Total | % Error Total |
|---|---|---|---|---|---|---|
| Eastern Cape | 1,546 | 139 | 25 | 50,506 | 52,216 | 2.96 |
| Free State | 109 | 13 | 3 | 48,238 | 48,363 | 0.23 |
| Gauteng | 766 | 86 | 21 | 46,611 | 47,484 | 1.61 |
| Kwa-Zulu Natal | 2,566 | 809 | 126 | 116,321 | 119,822 | 2.14 |
| Limpopo | 308 | 57 | 11 | 30,368 | 30,744 | 1.00 |
| Mpumalanga | 1,434 | 113 | 11 | 24,266 | 25,824 | 5.55 |
| North West | 1,146 | 69 | 10 | 24,995 | 26,220 | 4.37 |
| Northern Cape | 586 | 226 | 21 | 29,242 | 30,075 | 1.95 |
| Western Cape | 111 | 17 | 5 | 42,291 | 42,424 | 0.26 |
| **Grand Total** | **8,572** | **1,529** | **233** | **412,838** | **423,172** | **2.03** |

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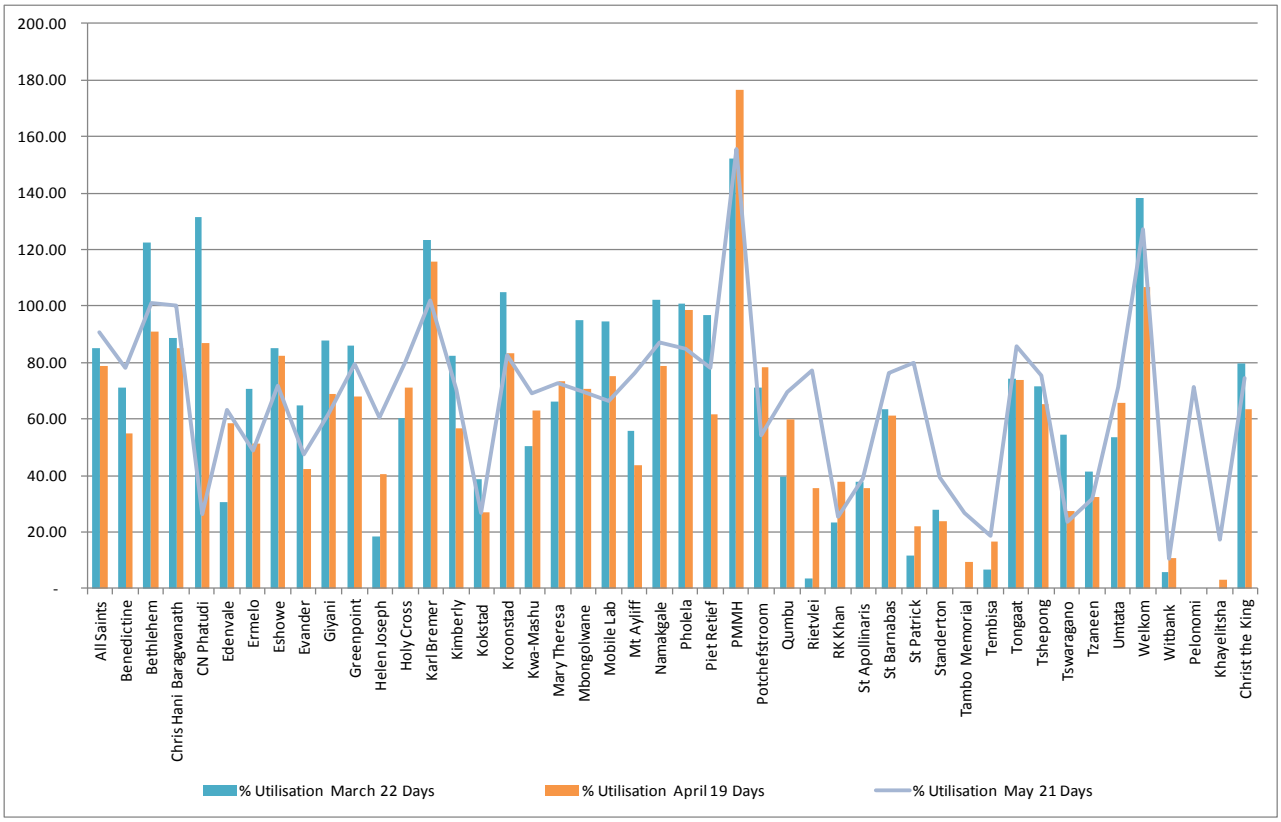
## 3. Utilization rates of instruments within the field




Instrument utilization remains variable over the months, but has picked up in the month of May in most of the laboratories. Utilization is dependent on requests from various health care facilities that refer samples to the laboratories. Other factors affecting utilization could be attributed to clinical training, staff turnover, implementation of fee for service, number of public holidays, as well as decentralization of stock ordering.

## 4. Further project phases as defined in the NTCM model

**Phase I** has been completed and has been reported on in the section above.

**Phase IIa** involves full capacitation of existing labs: Completed October.

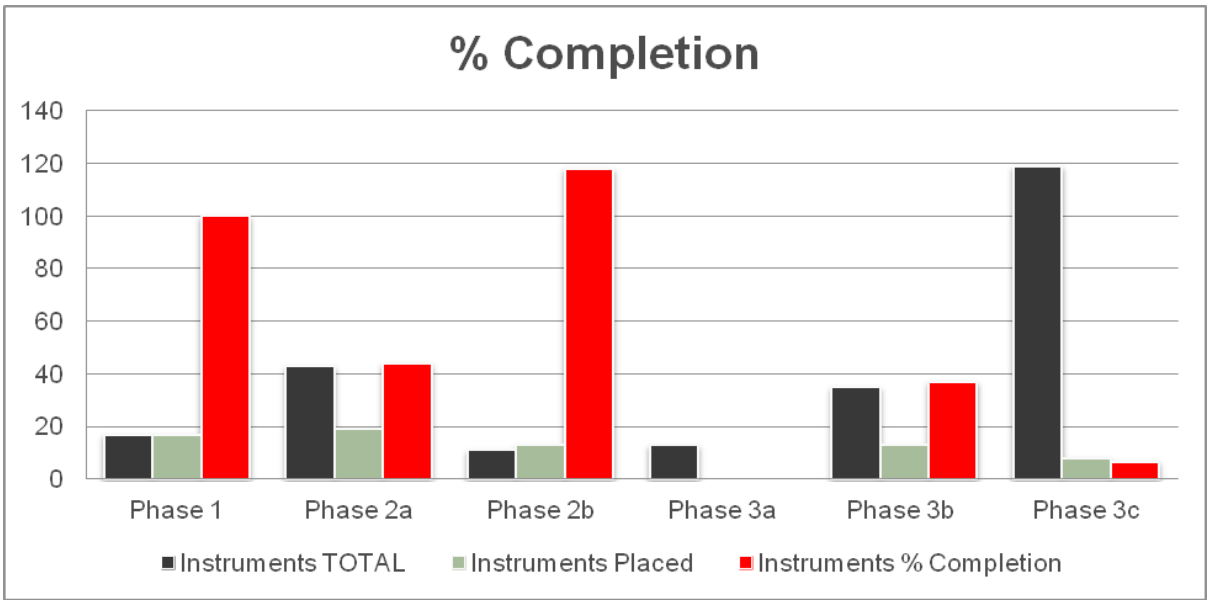
**Phase IIb:** Full capacitation of high burden districts.

**Phase IIIa and b:** Gates funded study (Gauteng, EC and Free State)

**Phase IIIc:** ensuring all districts have a minimum of 1 instrument per district

**Phase IIId:** Completion of all current microscopy and clinic sites

## 5. Phased Implementation Progress




| Phase | GX4 | GX16 | GX48 | TOTAL | Placed | % Completion |
|---|---|---|---|---|---|---|
| **Phase 1** | 20 | 9 | 1 | 30 | 30 | 100 |
| **Phase 2a** | - | 17 | - | 17 | 17 | 100 |
| **Phase 2b** | 20 | 22 | 1 | 43 | 19 | 44 |
| **Phase 3a** | 1 | 10 | 0 | 11 | 13 | 118 |
| **Phase 3b** | 2 | 11 | 0 | 13 | 0 | 0 |
| **Phase 3c** | 9 | 26 | 0 | 35 | 13 | 37 |
| **Phase 3d** | 38 | 81 | 0 | 119 | 8 | 7 |

To date implementation is 35% complete. An order has been placed to completed phase 2b and part of phase 3c and 3d through Global Fund and CDC NDOH respectively. On-site deliveries, Installations, instrument verification, training and interfacing will commence in the second week of July. Eleven instruments of varying sizes funded through the URC-USAID were placed at nine sites (refer to table 5). With this placement the Waterberg district will have wide coverage of the GeneXpert such that every TB suspect in the district has GeneXpert as the first diagnostic test for TB and for rifampicin resistance. Training, verification and LIS interfacing of the instruments are underway.

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**Table 5: URC/USAID Sites**

| Province | District | Lab | Required Instrument | |
|---|---|---|---|---|
| | | | GX4 | GX16 |
| EC | Amathole | BUTTERWORTH | | 1 |
| LP | Greater Sekhukhune | JANE FURSE | | 1 |
| LP | Waterberg | ELLISRAS | 1 | 1 |
| LP | Waterberg | GEORGE MASEBE | 1 | |
| LP | Waterberg | THABAZIMBI | 1 | |
| LP | Waterberg | WARMBATHS | 2 | |
| LP | Waterberg | POTGIETERSUS | | 1 |
| NW | Bojanala Platinum | RUSTENBURG | | 1 |
| NW | Ngaka Modiri Molema (Central) | MAFIKENG | | 1 |

**Table 6: Phase 2b Placements (Global Fund NDOH)**

| Province | District | Lab | GX4 | GX16 |
|---|---|---|---|---|
| EC | O.R. Tambo | ST ELIZABETH | | 1 |
| EC | O.R. Tambo | ZITULELE | | 1 |
| GP | City of Johannesburg | CENTRAL TB | 1 | 1 |
| KZN | eThekwini | Dbn Chest Clinic MC | | 1 |
| KZN | eThekwini | Hlengisizwe MC | 1 | |
| KZN | eThekwini | Inanda CMC | | 1 |
| KZN | eThekwini | KwaDabeka MC | | 1 |
| KZN | eThekwini | Kwa-Mashu | | 1 |
| KZN | eThekwini | Mahatma Ghandi | | 2 |
| KZN | eThekwini | PineTown MC | | 1 |
| KZN | Sisonke | Kokstad | 1 | |
| KZN | uMgungundlovu | Edendale | | 1 |
| KZN | uMgungundlovu | Imbalenhle Clinic MC | | 1 |
| KZN | Umzinyathi | Church of Scotland Hospital | | 1 |
| KZN | Zululand | Benedictine | | 1 |
| LP | Mopani | KGAPANE | | 1 |
| LP | Mopani | Namakgale | | 1 |
| MP | Gert Sibande | EMBHULENI | | 1 |
| NC | Siyanda | UPINGTON | | 1 |
| NW | Dr Kenneth Kaunda (Southern) | Potchefstroom | | 1 |
| WC | City of Cape Town | GROOTE SCHUUR CLINICAL PATH | | 1 |
| WC | Eden | OUDTSHOORN | | 1 |
| **TOTAL** | | | **1** | **21** |

**Table 7: Phase 2b Placements (Global Fund Right to Care)**

| Province | District | Lab | Instrument | | |
|---|---|---|---|---|---|
| | | | GX4 | GX16 | GX48 |
| EC | Nelson Mandela Bay Metro | PORT ELIZABETH TB | 1 | 3 | |
| EC | Amathole | EAST LONDON TB | | | 1 |

**Phase 3a Progress**

Installations, training an instrument verifications using dried culture spots completed.

**Table 8: Phase 3b**

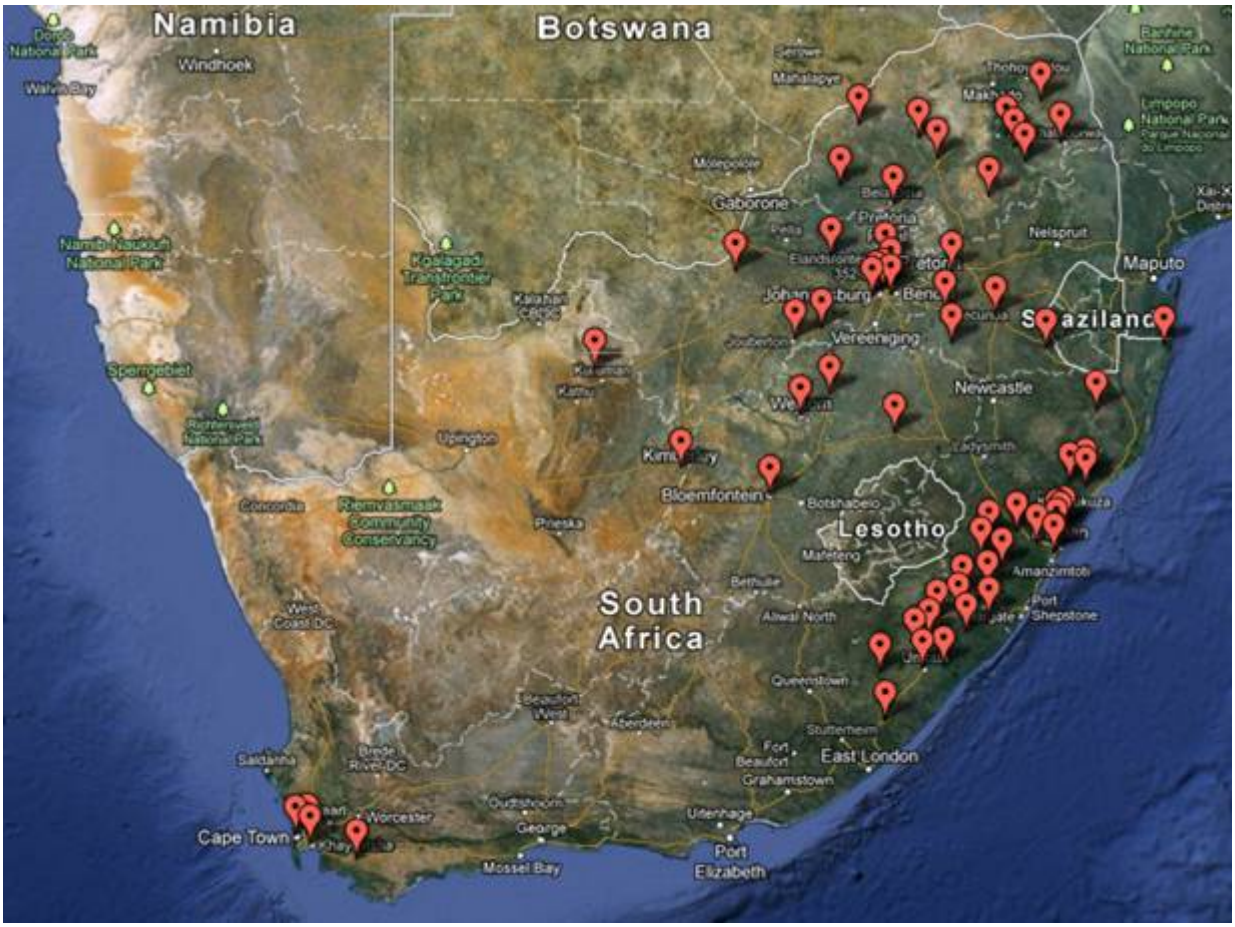
The remaining 10 machines will be placed in September 2012 in the following laboratories:

| Province | District | Lab | GX4 | GX16 | Funding By |
|---|---|---|---|---|---|
| EC | Chris Hani | COFIMVABA | | 1 | Gates Control |
| EC | Chris Hani | QUEENSTOWN | 1 | 1 | Gates Control & CDC DOH |
| EC | Nelson Mandela Bay Metro | UITENHAGE | | 1 | Gates Control |
| FS | Thabo Mofutsanyane | MANAPO | | 1 | Gates Control |
| GP | City of Tshwane | JUBILEE | | 1 | Gates Control |
| GP | City of Tshwane | MAMELODI | | 1 | Gates Control |
| GP | Ekurhuleni | NATALSPRUIT | | 1 | Gates Control |
| GP | West Rand | CARLETONVILLE | | 1 | Gates Control |
| EC | Ukhahlamba | TAYLOR BEQUEST | 1 | 1 | Gates Control & CDC DOH |
| MP | Ehlanzeni | NELSPRUIT | | 2 | Gates Control & CDC DOH |

**Phase 3c and 3d remain on further release of funding**

Pelonomi, Edendale, Christ the King and St. Appolinaris laboratories were fast tracked. This was made possible through a partnership between TB/HIV Care Association who donated two GX4s and PEPFAR CDC (4 GX16 machines).

**Figure 1: Current GeneXpert Placement** (64 testing centers, 90 analysers, Gx4: 44; Gx16: 46; GX48:1)
***20 clinic placements**




## 6. Training: Laboratory and Clinical

A total of 119 laboratory staff and 721 health care workers have been trained since December 2011 as summarized in table 7 and 8. This will be an ongoing process to support NDoH training on clinical algorithm. Laboratory staff will receive both clinical and technical training.

**Table 9: Laboratory Training**

| Venue | DATE | Trainer | TOTAL # OF DELEGATES | Outcomes |
|---|---|---|---|---|
| Christ The King | 12 December 11 | Veeresh | 2 | GeneXpert Operation, Maintenance, Troubleshooting and Data Entry |
| Kokstad | 15 December 11 | Trevor | 2 | |
| St. Apollinaris | 13 December 11 | Veeresh | 3 | |
| Thembisa | 15 December 11 | Sebaka/Sheila | 7 | |
| Pretoria West | 10 January 12 | Sebaka/Sheila | 4 | |
| Mary Theresa | 11-12 January 12 | Maxine | 4 | |
| Mt Ayliff | 10 January 12 | Trevor | 4 | |
| All Saints | 11 January 12 | Trevor | 4 | |
| St Patrick | 13 January 12 | Maxine | 3 | |
| Bethlehem | 23 January 12 | Trevor | 3 | |
| Helen Joseph | 23 January 12 | Sheila | 11 | |
| Witbank | 16 January 12 | Sheila | 10 | |
| Tembisa | 20 January 12 | Sheila | 5 | |
| Tambo Memorial | 12 January 12 | Sheila/Sebaka | 11 | |
| Verulam | 03 April 12 | Trevor | 1 | |
| Osindisweni | 11 April 12 | Trevor | 2 | |
| Rietvlei | 11 April 12 | Veeresh | 3 | |
| Manguzi | 19-20 April 12 | Veeresh | 4 | |
| Letaba | 17-18 April 12 | Donovan | 2 | |
| Pelonomi | 17-18 April 12 | Trevor | 8 | |
| Warmbaths | 26 June 12 | Fimmie | 4 | |
| Mafikeng | 20-21 June 12 | Donovan | 5 | |
| Rustenburg | 20 & 25 June 12 | Anne | 8 | |
| Butterworth | 27-28 June | Veeresh | 5 | |
| Ellisras | 26-27 June | Donovan | 3 | |

**Table 10: Clinical Training**

| Venue | Date | Trainer | Total # of Delegates | Outcomes |
|---|---|---|---|---|
| Manapo Dept. of Social Services | 08 & 09 Feb | Sebaka | 28 | Background to GeneXpert, TB Testing Algorithm, Recording and Reporting |
| Siphosensimbi CHC | 17 Feb 12 | Linda | 18 | |
| Phola CHC | 20 Feb 12 | Linda | 8 | |
| eThafeni CHC | 23 March 12 | Linda | 4 | |

| | | | | |
|---|---|---|---|---|
| Tembisa Main Clinic | 23 March 12 | Linda | 5 | |
| Vosloorus Poly Clinic | 30 March 12 | Linda | 12 | |
| Dawn Park Clinic | 02 April 12 | Linda | 11 | |
| Mpumalanga District | 25 March 12 | Elizabeth | 40 | |
| Emalahleni Sub-District | 12 April 12 | Elizabeth | 13 | |
| City of Tshwane | 19 April 12 | Elizabeth | 56 | |
| Germiston Clinic | 08 May 12 | Sylvia | 14 | |
| Phola Park CHC | 09 May 12 | Sylvia | 16 | |
| Vosloorus Poly Clinic | 10 May 12 | Sylvia | 16 | |
| Volsloorus Clinic | 18 May 12 | Sylvia | 30 | |

## 7. Challenges identified during the course of the project to date

- Finalization of request forms: Incorporate TB testing in the CCMT form if we are to bill using existing channels
- Delay in training health care workers on clinical algorithm

## 8. Literature Update For GeneXpert

There has been an expansion of the literature with respect to the assay performance. The highlights are summarized in table 11 below:

**Table 11: Recent publications (GeneXpert for pulmonary TB and extrapulmonary TB)**

| Manuscript | Sample population and specimen type (n=…) | Results | |
|---|---|---|---|
| | | Sensitivity | Specificity |
| Meyer-Rath et al, PLoS One, 2012 | Estimated the incremental cost and impact on diagnosis and treatment uptake of national rollout of Xpert above the cost of current guidelines from 2011-2016 | Xpert will increase the number of TB cases diagnosed per year by 30%-37% and the number of MDR-TB cases diagnosed by 69%-71%.<br>It will diagnose 81% of patients after the first visit, compared to 46% currently.<br>The cost of TB diagnosis per suspect will increase by 55% to USD 60-61 and the | |

| | | |
|---|---|---|
| | | cost of diagnosis and treatment per TB case treated by 8% to USD 797-873. The incremental capital cost of the Xpert scale-up will be USD 22 million and the incremental recurrent cost USD 287-316 million over six years. |
| Schnippel et al, Trop Med Int Health, 2012 | Compared the cost of placing Xpert at points of TB treatment (all primary clinics and hospitals) with the cost of placement at sub-district laboratories by estimating:<br>▪ Xpert's cost/test in a primary clinic pilot and in the pilot phase of the national Xpert roll-out to smear microscopy laboratories;<br>▪ The expected future volumes for each of 223 laboratories or 3799 points of treatment;<br>▪ The number and cost of Xpert instruments required;<br>▪ The national cost of using Xpert for PTB diagnosis for each placement scenario in 2014. | In 2014,<br>▪ South Africa will test 2.6 million TB suspects.<br>▪ Laboratory placement requires 274 Xpert instruments, while point-of-treatment placement requires 4020 instruments. With an Xpert cartridge price of $14.00, the cost/test is $26.54 for laboratory placement and $38.91 for point-of-treatment placement.<br>▪ National placement of Xpert at laboratories would cost $71 million/year; point-of-treatment placement would cost $107 million/year, 51% more |

**9. Update on GeneXpert Research projects:**

- DCS Verification – DCS (n=~500) for Phase IIb of instrument implementation have been manufactured and will transported with instruments.
- The following potential EQA materials are being investigated through small pilots:
  - **i.** DCS EQA panel and additional liquid EQA panel (Vircell) to be piloted at 10 selected NHLS labs
  - **ii.** A liquid EQA format from the CDC - to 10 sites
  - **iii.** GLI liquid - to 10 sites
- DCS EQA & verification program development - ACTG (3 sites) and MSF included in program: first batch of verification and pilot EQA material ready for shipment to ACTG sites.
- Flow cytometry on raw/processed sputum still under development
- A clinical validation of the new Abbott NM assay (NearMedic) is underway for comparison to smear, culture and Xpert – possible high volume TB screening
- Alternative specimen preparation protocols:

i. Protocols developed for Pediatric TB diagnosis and Extra-pulmonary TB diagnosis
ii. Paediatric study at Rahimma Moosa Mother and Child Hospital: n=400 TB suspects have been recruited to the study for comparison of Xpert MTB/RIF assay to smear and culture on paed specimens. Awaiting culture results for comparison.
iii. Protocols under development for EPTB: A GeneXpert room has been refurbished at the Braamfontein TB referral lab for the study. A laboratory technician has been recruited and trained. The GeneXpert will be placed shortly for study commencement.
iv. Sputum heat inactivation: to determine whether heat inactivation can be used prior to Xpert testing to render it safe for further manipulation (n=121) – study will continue.
v. Protocol under development to test residual SR buffered Xpert specimens on the line probe assay for DST resulting – study ongoing.

- TBGxMonitor™ (www.tbgxmonitor.com) automated GeneXpert Verification and EQA reporting platform has been upgraded to include full EQA report processing. Both Verification and EQA components have been completed. Next development phase to include EQA qualitative and quantitative evaluation and reporting of sites.
- Connectivity: Collaboration with Cepheid ongoing
    i. Remote connectivity - System currently piloted within the NHLS at two sites (Chris Hani Baragwanath and Wits Medical School – Research lab) with 3 Gx16 instruments and 2 Gx4's. To date more than 7000 tests (prospective) have been uploaded to the system. Pilot to be expanded to existing sites with the NHLS IT group, Cepheid (South Africa) will be installing the software at all new installations of GeneXperts.
    ii. Remote Calibration – Pilot evaluation completed. Cepheid received positive feedback as well as a number of useful modifications to the user interface to ensure the system is robust and intuitive. User interaction and feedback conducted at 5 sites with a variety of user types ranging from GeneXpert trainers to Laboratory Managers as well as nurse-trained operators.

**10. HIV/TB Integration**

- Grand Challenges Canada: Multiple POC HIV/TB integration project
  - Phase I complete
  - Phase II: Evaluation of nurse operated POC versus routine lab completed at HJH Themba Lethu clinic (n=326) complete.
  - Site visits completed (n=12) and selection of first site (Grace Mokgomo, North West Province) for randomized controlled trial (RCT) has been finalized and staff trained.
  - RCT: The study site has been initiated and ~n=20 patients recruited into the study; n=10 randomized to standard of care and n=10 randomized to POC arm.
  - A second POC nurse has been recruited for the next study site to initiate end of July.
  - A sub-study to investigate feasibility and patient acceptance of multiple finger sticks for POC testing has been completed at Tshwane District Hospital (n=300). Awaiting routine laboratory results for comparison.
- Connectivity:
  - Conworx (POCcelerator) and LDS (AegisPOC) to be trialed in 2 sites during RCT
  - HemoCue project at CMJAH – network installation for the Hemocue's has been completed. Awaiting installation of offline version of TrakCare by NHLS.

**11. Grants Submitted**

None

**12. Funding Issues**

None

**13. Recent Campaigns**

NHLS together with the National Department of Health (HIV and AIDS and STIs Chief Directorate), as well as other key Government Departments and Partners participated in the HCT campaigns in support of the deputy minister in Qwa-Qwa stadium on 10th of May and Pimville, Soweto on 13th of May 2012. The NPP GeneXpert team, with the generous assistance of Cepheid SA, managed to install two GeneXpert 16 instruments at each site for rapid detection of MTBC and Rifampicin. Forty patients were tested for MTBC in Qwa-Qwa and 33 in Pimville. Results were released to patients on the day.