NATIONAL HEALTH LABORATORY SERVICE

# GeneXpert MTB/RIF

## Progress Report

April 2012

## GeneXpert Implementation Report Update

## Table of Contents

## 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 355,578 specimens have been processed to date (30 April 2012). The total % of *Mycobacterium tuberculosis* complex (MTBC) detected in this cohort was 16.39% (58,285). 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 | 6,878 | 33,182 | 1,271 | 41,331 | 16.64 |
| Free State | 5,801 | 32,756 | 79 | 38,636 | 15.01 |
| Gauteng | 5,024 | 32,708 | 728 | 38,460 | 13.06 |
| Kwa-Zulu Natal | 19,935 | 79,020 | 2,796 | 101,751 | 19.59 |
| Limpopo | 3,006 | 25,122 | 341 | 28,469 | 10.56 |
| Mpumalanga | 3,683 | 18,181 | 1,425 | 23,289 | 15.81 |
| North West | 3,603 | 18,279 | 914 | 22,796 | 15.81 |
| Northern Cape | 4,359 | 21,941 | 791 | 27,091 | 16.09 |
| Western Cape | 5,996 | 27,659 | 100 | 33,755 | 17.76 |
| **Grand Total** | **58,285** | **288,848** | **8,445** | **355,578** | **16.39** |

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

| Province | Inconclusive | Resistant | Sensitive | No Results | Grand Total | % RIF Resistant |
|---|---|---|---|---|---|---|
| Eastern Cape | 87 | 516 | 6,169 | 106 | 6,878 | 7.50 |
| Free State | 76 | 333 | 5,384 | 8 | 5,801 | 5.74 |
| Gauteng | 50 | 328 | 4,639 | 7 | 5,024 | 6.53 |
| Kwa-Zulu Natal | 258 | 1,534 | 17,842 | 301 | 19,935 | 7.70 |
| Limpopo | 46 | 224 | 2,709 | 27 | 3,006 | 7.45 |
| Mpumalanga | 52 | 296 | 3,280 | 55 | 3,683 | 8.04 |
| North West | 41 | 284 | 3,270 | 8 | 3,603 | 7.88 |
| Northern Cape | 46 | 264 | 4,046 | 3 | 4,359 | 6.06 |
| Western Cape | 60 | 289 | 5,643 | 4 | 5,996 | 4.82 |
| **Grand Total** | **716** | **4,068** | **52,982** | **519** | **58,285** | **6.98** |

Rifampicin concordance is good for both Line Probe Assay (Hain LifeSciences, Germany) and culture. There is significant Rifampicin mono-resistance geographical variation. The national average for Rifampicin mono-resistance detection is 12% by Drug Susceptibity Testing and 18% by 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. This requires standardisation.

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

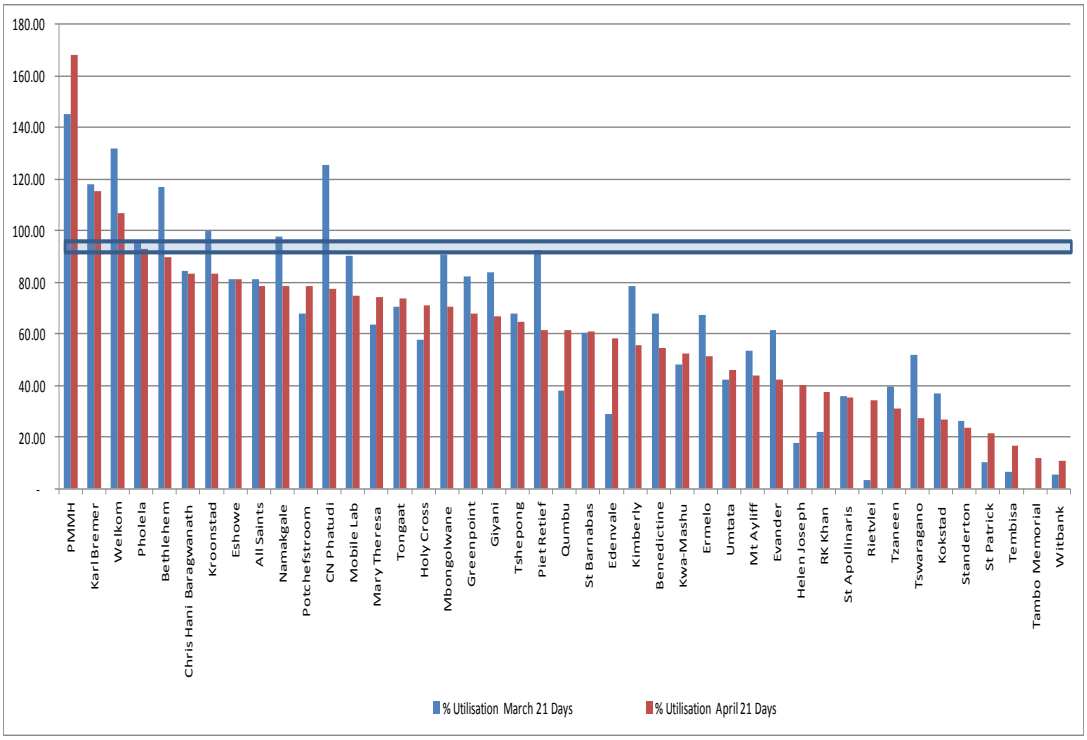
| Province | LPA | DST |
|---|---|---|
| Eastern Cape | 93.3% | 12.5% |
| Free State | 83.3% | 75.0% |
| Gauteng | 92.3% | 88.2% |
| Kwazulu-Natal | 82.2% | 93.3% |
| Limpopo | 80.0% | 94.4% |
| Mpumalanga | 81.0% | 97.2% |
| North West | 100.0% | 50.0% |
| Northern Cape | 76.2% | 66.7% |
| Western Cape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

Errors are reported consistently below 3%. Details of invalid results, which likely represent sample issues, remain 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 | 1,150 | 105 | 16 | 40,060 | 41,331 | 2.78 |
| Free State | 67 | 9 | 3 | 38,557 | 38,636 | 0.17 |
| Gauteng | 629 | 81 | 18 | 37,732 | 38,460 | 1.64 |
| Kwa-Zulu Natal | 1,986 | 746 | 64 | 98,955 | 101,751 | 1.95 |
| Limpopo | 276 | 55 | 10 | 28,128 | 28,469 | 0.97 |
| Mpumalanga | 1,313 | 102 | 10 | 21,864 | 23,289 | 5.64 |
| North West | 858 | 48 | 8 | 21,882 | 22,796 | 3.76 |
| Northern Cape | 579 | 194 | 18 | 26,300 | 27,091 | 2.14 |
| Western Cape | 81 | 14 | 5 | 33,655 | 33,755 | 0.24 |
| **Grand Total** | **6,939** | **1,354** | **152** | **347,133** | **355,578** | **1.95** |

## 3. Utilization rates of instruments within the field




Instrument utilization remains variable over the months and 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 decentralisation 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.

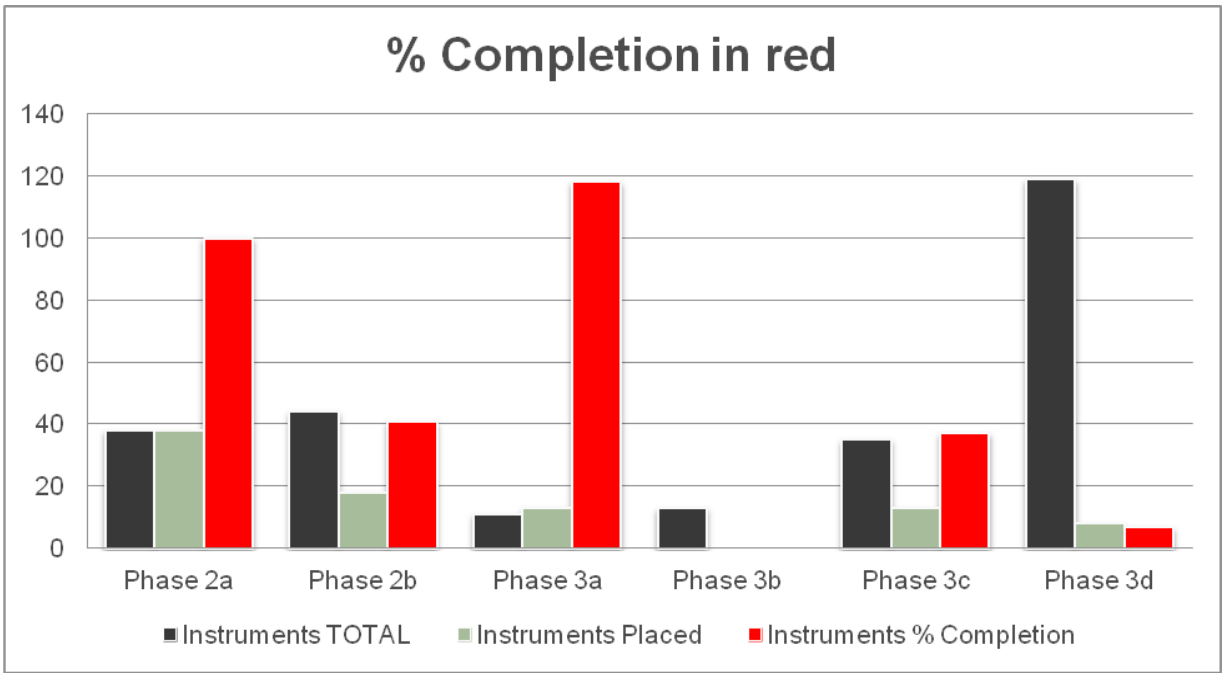
**Phase IIb:** Full capacitation of high burden districts.

**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 2a | 11 | 26 | 1 | 38 | 38 | 100 |
| Phase 2b | 21 | 22 | 1 | 44 | 18 | 41 |
| 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. The Global Fund funding for phase 2b has been approved. Singing of contracts between the primary recipients and sub-recipients was completed in May 2012. Phase 2b is projected to roll-out in June 2012. Nineteen instruments have been installed at 12 sites. Training, verification and LIS interfacing of the instruments are completed.

**Table 5: Phase 2b**

| Province | District | Lab | GX4 | GX16 | Capacity Per Day | Comment |
|---|---|---|---|---|---|---|
| GP | City of Johannesburg | NJH ROUTINE | 1 | | 16 | From Edenvale |
| KZN | eThekwini | Hlengisizwe MC | 1 | | 16 | Installation Completed |
| KZN | eThekwini | Clairwood | 1 | | 16 | Installation Completed |
| EC | O.R. Tambo | ST LUCY | 1 | | 16 | Instrument Delivered. Installation Pending |
| KZN | eThekwini | Catherine Booth | 2 | | 16 | Instrument Delivered. Installation Pending |
| KZN | eThekwini | Osindisweni | 1 | | 16 | Installation Completed |
| KZN | eThekwini | Manguzi | 2 | | 32 | Installation Completed |
| KZN | eThekwini | Verulam MC | 1 | | 16 | Installation Completed |
| LP | Mopani | SEKORORO | 1 | | 16 | Installation Completed |
| EC | O.R. Tambo | ST ELIZABETH | | 1 | 64 | Global Fund DOH |
| EC | O.R. Tambo | ZITULELE | | 1 | 32 | Global Fund DOH |
| KZN | eThekwini | Addington | | 1 | 32 | Global Fund DOH |
| KZN | eThekwini | RK Khan | | 1 | 64 | Global Fund DOH |
| KZN | eThekwini | Wentworth | | 1 | 32 | Global Fund DOH |
| KZN | eThekwini | Mahatma Ghandi | | 1 | 48 | Global Fund DOH |
| KZN | Zululand | Benedictine | | 1 | 48 | Global Fund DOH |
| KZN | eThekwini | Dbn Chest Clinic MC | | 1 | 64 | Global Fund DOH |
| KZN | eThekwini | Inanda C MC | | 1 | 32 | Global Fund DOH |
| KZN | eThekwini | Charles James MC | | 1 | 32 | Global Fund DOH |
| KZN | eThekwini | KwaDabeka MC | | 1 | 32 | Global Fund DOH |
| KZN | eThekwini | PineTown MC | | 1 | 48 | Global Fund DOH |
| KZN | Sisonke | RIETVLEI | 2 | | 48 | Installation Completed |
| LP | Mopani | KGAPANE | | 1 | 32 | Global Fund DOH |
| LP | Mopani | PHALABORWA | | 1 | 32 | Global Fund DOH |
| MP | Gert Sibande | EMBHULENI | | 1 | 32 | Global Fund DOH |
| NC | Siyanda | UPINGTON | | 1 | 64 | Global Fund DOH |
| WC | City of Cape Town | GROOTE SCHUUR | | 1 | 48 | Global Fund DOH |
| KZN | Sisonke | Kokstad | 1 | 1 | 16 | Installation Completed. GX16 Pending Global Fund |
| GP | City of Johannesburg | CENTRAL TB | 1 | 1 | 80 | GX4 from Baragwanath + Global Fund DOH |
| | | | **14** | **19** | **1040** | |

**Phase 3a Progress**

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

**Table 6: Phase 3b**

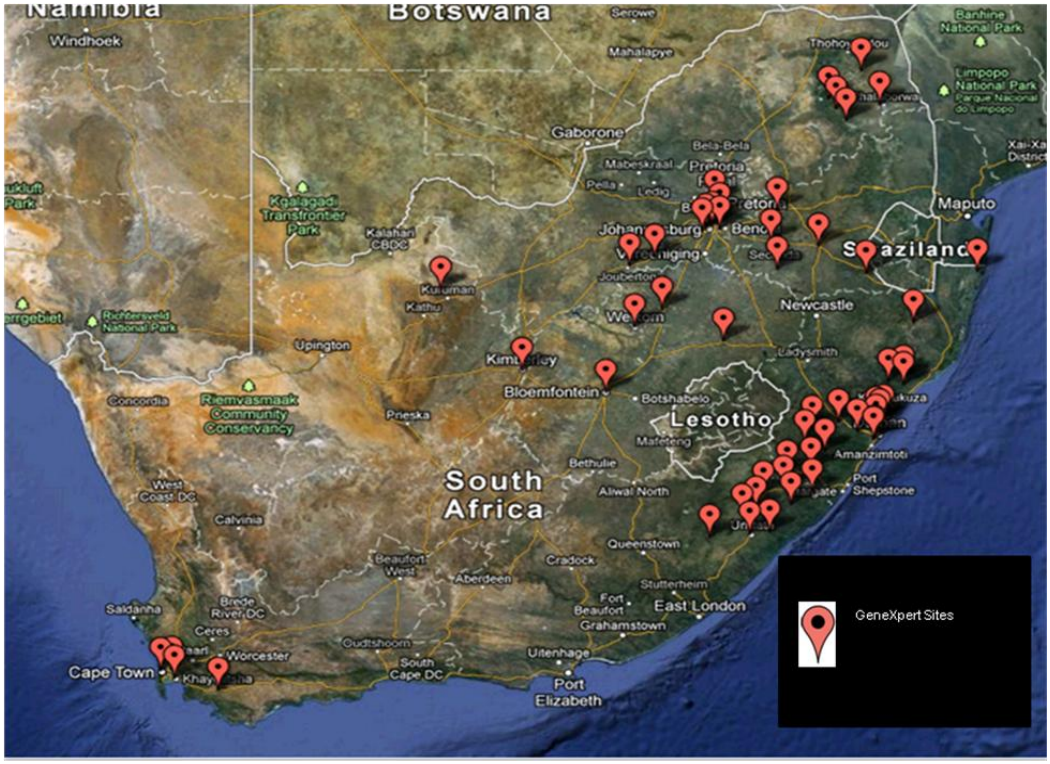
The remaining 10 machines will be placed in September 2012 in the following laboratories:

| Serial | Province | District | Lab | GX4 | GX16 | GX48 | Capacity Per Day | Status | Donor |
|---|---|---|---|---|---|---|---|---|---|
| 25 | EC | Chris Hani | COFIMVABA | | 1 | | 64 | Pending | Gates Foundation |
| 29 | EC | Chris Hani | QUEENSTOWN | 1 | 1 | | 80 | Pending | Gates Foundation |
| 33 | EC | Nelson Mandela Bay Metro | UITENHAGE | | 1 | | 64 | Pending | Gates Foundation |
| 57 | FS | Thabo Mofutsanyane | MANAPO | | 1 | | 48 | Pending | Gates Foundation |
| 68 | GP | City of Tshwane | JUBILEE | | 1 | | 48 | Pending | Gates Foundation |
| 69 | GP | City of Tshwane | MAMELODI | | 1 | | 64 | Pending | Gates Foundation |
| 77 | GP | Ekurhuleni | NATALSPRUIT | | 1 | | 64 | Pending | Gates Foundation |
| 85 | GP | West Rand | CARLETONVILLE | | 1 | | 64 | Pending | Gates Foundation |
| 46 | EC | Ukhahlamba | TAYLOR BEQUEST | 1 | 1 | | 80 | Pending | Gates Foundation |
| 133 | MP | Ehlanzeni | NELSPRUIT | | 2 | | 128 | Pending | Gates Foundation |

**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** (55 testing centers, 79 analysers, Gx4: 39; Gx16: 40; GX48:1)
***20 clinic placements**



## 6. Training: Laboratory and Clinical

A total of 94 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 7: 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 | GeneXpert Operation, Maintenance, Troubleshooting and Data Entry |
| St. Apollinaris | 13 December 11 | Veeresh | 3 | GeneXpert Operation, Maintenance, Troubleshooting and Data Entry |
| Thembisa | 15 December 11 | Sebaka/Sheila | 7 | GeneXpert Operation, Maintenance, Troubleshooting and Data Entry |
| Pretoria West | 10 January 12 | Sebaka/Sheila | 4 | GeneXpert Operation, Maintenance, Troubleshooting and Data Entry |
| Mary Theresa | 11-12 January 12 | Maxine | 4 | GeneXpert Operation, Maintenance, Troubleshooting and Data Entry |
| Mt Ayliff | 10 January 12 | Trevor | 4 | GeneXpert Operation, Maintenance, Troubleshooting and Data Entry |
| All Saints | 11 January 12 | Trevor | 4 | GeneXpert Operation, Maintenance, Troubleshooting and Data Entry |
| St Patrick | 13 January 12 | Maxine | 3 | GeneXpert Operation, Maintenance, Troubleshooting and Data Entry |
| Bethlehem | 23 January 12 | Trevor | 3 | GeneXpert Operation, Maintenance, Troubleshooting and Data Entry |
| Helen Joseph | 23 January 12 | Sheila | 11 | GeneXpert Operation, Maintenance, Troubleshooting and Data Entry |
| Witbank | 16 January 12 | Sheila | 10 | GeneXpert Operation, Maintenance, Troubleshooting and Data Entry |
| Tembisa | 20 January 12 | Sheila | 5 | GeneXpert Operation, Maintenance, Troubleshooting and Data Entry |
| Tambo Memorial | 12 January 12 | Sheila & Sebaka | 11 | GeneXpert Operation, Maintenance, Troubleshooting and Data Entry |
| Verulam | 03 April 12 | Trevor | 1 | GeneXpert Operation, Maintenance, Troubleshooting and Data Entry |
| Osindisweni | 11 April 12 | Trevor | 2 | GeneXpert Operation, Maintenance, Troubleshooting and Data Entry |
| Rietvlei | 11 April 12 | Veeresh | 3 | GeneXpert Operation, Maintenance, Troubleshooting and Data Entry |
| Manguzi | 19-20 April 12 | Veeresh | 4 | GeneXpert Operation, Maintenance, Troubleshooting and Data Entry |

**Laboratory Training Cont:**

| Venue | DATE | Trainer | TOTAL # OF | Outcomes |
|---|---|---|---|---|
| Letaba | 17-18 April 12 | Donovan | 2 | GeneXpert Operation, Maintenance, Troubleshooting and Data Entry |
| Pelonomi | 17-18 April 12 | Trevor | 8 | GeneXpert Operation, Maintenance, Troubleshooting and Data Entry |

**Table 8: 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
- Lengthy time between training and going live with testing,
    - Pretoria West and Helen Joseph due to shortage of staff
- LIS downtime impacting on TAT(Witbank)

## 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 9 below:

**Table 9: Recent publications (GeneXpert for pulmonary TB and extrapulmonary TB)**

| Manuscript | Sample population and specimen type (n=…) | Results | |
|---|---|---|---|
| | | Sensitivity | Specificity |
| Lawn, AIDS 2012 | Adults enrolling in a South African township ART clinic were systematically screened for pulmonary TB by testing paired sputum samples using microscopy, liquid culture and Xpert MTB/RIF in a centralised laboratory.<br><br>Stored urine samples were retrospectively tested for LAM using the Determine TB-LAM assay | Of patients with CD4 counts < 200 cells/µL and complete results (n = 325), 59 (18.2%) had culture-positive TB. Of these, 23 (39%) patients tested urine LAM-positive and 36 (61%) urine LAM-negative. TB-LAM positive patients also had evidence of higher mycobacterial load, more frequently testing sputum smear-positive, Xpert-positive (sputum and urine) and having a shorter time to sputum culture positivity. | Xpert = 100% |

| | | | |
|---|---|---|---|
| Lawn et al J Acquir Immune Defic Syndr. 2012 | Determined the diagnostic yield of the Xpert MTB/RIF assay for TB when testing small volumes of urine from ambulatory HIV-infected patients prior to starting antiretroviral therapy (ART).<br><br>Compared to a gold standard of sputum culture | The sensitivities of Xpert were (P=0.001):<br>CD4<50: 44.4%<br>CD4 50-100: 25.0%<br>CD4>100: 2.7% | None stated |
| Miotto et al, Eur Resp J, 2012 | 10 patient samples processed and tested on Xpert with and without prior PMA treatment (chemical compound that can intercalates the DNA of non-viable (or membrane-damaged) organisms) | PMA pre-treatment demonstrated the possibility of distinguishing between live and dead mycobacteria. Data indicates that quantitative molecular techniques combined with the PMA method could be an alternative to direct microscopy and culture for monitoring early treatment response and for preliminary evaluation of personalized regimens. | |
| Taylor et al, JCM, 2012 | 9 CSF, 13 gastric aspirates, 8 tissue and 17 stool – spiked with M.tb. Flotation studies with sucrose and NaCL done prior to Xpert testing (to concentrate bacilli). Ct values compared between treated and untreated specimens | Flotation studies with sucrose or NaCl did not consistently result in lowered cycle thresholds in stool or gastric aspirates but >10 cycle reduction was achieved in two of the three pooled CSF samples. | |

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

- DCS Verification – all phase 2a instruments verified.
- Cepheid Liquid EQA pilot to 17 sites: low conformance from sites in returning results (65% return); 100% correct result reporting. Questionnaires demonstrated a preference of sites for liquid format (vs DCS).
- DCS EQA panel and a liquid EQA panel (Vircell®) to be piloted at 10 selected NHLS labs
- DCS EQA pilot: n= 4 panels (NTM, Neg, MTB+, MTB+ Rif resistant) sent to Baragwanath Hospital. One error (5007), and one no result were detected but on re-testing 100% were correct.
- 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

- Alternative specimen preparation protocols:
    i. Protocols developed for Pediatric TB diagnosis and Extra pulmonary TB diagnosis
    ii. Paediatric study at Rahima Moosa Mother and Child Hospital: 394 TB suspects have been recruited to the study for comparison of Xpert® MTB/RIF assay to smear and culture on paediatric specimens. The study is ongoing.
    iii. Protocols are under development for solid tissue, gastric aspirates etc. at the Braamfontein TB referral lab. A laboratory technician has been recruited and a GX4 will be placed for the study to begin by July.
    iv. Sputum heat inactivation study: to determine whether heat inactivation can be used prior to Xpert®MTB/RIF testing to render it safe for further manipulation (n=121) – ongoing.
    v. Protocol under development to test residual SR buffered Xpert® MTB/RIF specimens on the LPA for DST resulting.
- 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 – Remote connectivity pilot protocol approved. System currently piloted within the NHLS at one site (Chris Hani Baragwanath) with 3 Gx16 instruments. Pilot to be expanded to further sites.
    ii. Remote Calibration – Pilot evaluation to be conducted between the 3rd and 10th June at a number of NHLS sites. Remote calibration cartridge expected to be released Sept 2012.

**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) has been completed and analysis of results are underway.
- 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=10 patients recruited into the study; n=5 randomized to standard of care and n=5 randomized to POC arm.
- The second study site is due to be initiated by end of June. Staff are being interviewed.

- 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.