NATIONAL HEALTH LABORATORY SERVICE

GeneXpert MTB/RIF

Progress Report

November 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 805,571 specimens have been processed to date (30 November 2012). The total % of *Mycobacterium tuberculosis* complex (MTBC) detected in this cohort was 14.92% (120,167). The percentage positivity has remained on average between 15-16% for the past seven months 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).

Table 1: GeneXpert MTB Results by province

Province	MTB Detected	MTB Not Detected	Test Unsuccessful	Total	% MTB Detected
Eastern Cape	17,239	90,898	3,221	**111,358**	**15.48**
Free State	13,475	85,525	287	**99,287**	**13.57**
Gauteng	12,650	83,822	2,476	**98,948**	**12.78**
Kwa-Zulu Natal	36,227	177,408	7,137	**220,772**	**16.41**
Limpopo	5,333	42,899	690	**48,922**	**10.90**
Mpumalanga	6,280	32,873	2,154	**41,307**	**15.20**
North West	7,928	39,831	2,373	**50,132**	**15.81**
Northern Cape	6,845	37,694	1,882	**46,421**	**14.75**
Western Cape	14,190	73,715	519	**88,424**	**16.05**
Total	**120,167**	**664,665**	**20,739**	**805,571**	**14.92**

Table 2: Provincial GeneXpert RIF Results in MTB detected cases

Province	Inconclusive	Resistant	Sensitive	No RIF Result	Total	% RIF Resistant
Eastern Cape	221	1,179	15,694	145	**17,239**	**6.84**
Free State	183	821	12,444	27	**13,475**	**6.09**
Gauteng	140	829	11,676	5	**12,650**	**6.55**
Kwa-Zulu Natal	545	3,032	32,217	433	**36,227**	**8.37**
Limpopo	74	402	4,818	39	**5,333**	**7.54**
Mpumalanga	86	566	5,547	81	**6,280**	**9.01**
North West	103	649	7,164	12	**7,928**	**8.19**
Northern Cape	90	438	6,309	8	**6,845**	**6.40**
Western Cape	154	706	13,328	2	**14,190**	**4.98**
Grand Total	**1,596**	**8,622**	**109,197**	**752**	**120,167**	**7.18**

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 as this leads to significant confusion in all aspects of the testing cycle, as well as in some cases being more onerous to TB suspects.

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Table 3: Rif Concordance by LPA or DST

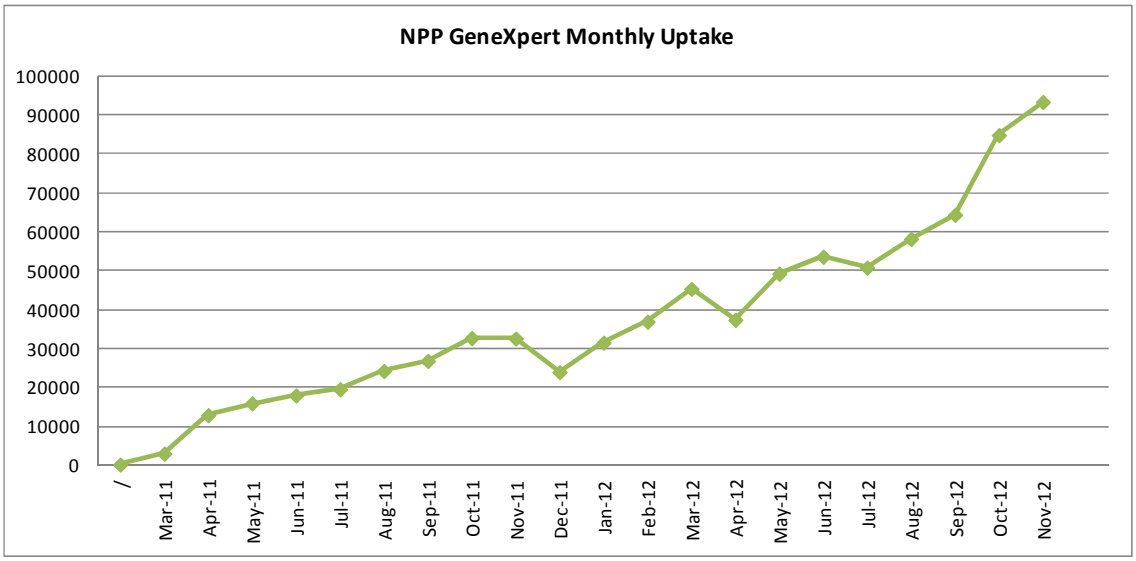
Province	DST	LPA
Eastern Cape	19.0%	94.9%
Free State	58.3%	81.4%
Gauteng	80.0%	94.7%
Kwazulu-Natal	93.8%	87.1%
Limpopo	96.4%	95.7%
Mpumalanga	98.5%	87.5%
North West	80.0%	97.4%
Northern Cape	76.2%	82.4%
Western Cape	0.0%	96.7%
National	**88.1%**	**89.9%**

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	No Raw Result	MTB Result	Total	% Error Total
Eastern Cape	2,870	235	98	18	108,137	**111,358**	**2.58**
Free State	231	20	26	10	99,000	**99,287**	**0.23**
Gauteng	2,192	227	57		96,472	**98,948**	**2.22**
Kwa-Zulu Natal	5,630	1,166	339	2	213,635	**220,772**	**2.55**
Limpopo	571	102	16	1	48,232	**48,922**	**1.17**
Mpumalanga	1,994	136	23	1	39,153	**41,307**	**4.83**
North West	2,132	168	73		47,759	**50,132**	**4.25**
Northern Cape	633	252	23	974	44,539	**46,421**	**1.36**
Western Cape	461	40	18		87,905	**88,424**	**0.52**
Total	**16,714**	**2,346**	**673**	**1,006**	**784,832**	**805,571**	**2.07**

3. Utilization rates of instruments within the field



Instrument utilization remains variable over the months, but has increased significantly across all testing facilities, with the exception of few sites which were affected by the global shortage of cartridges. 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

Phase IIb: Full capacitation of high burden districts. Completed

Phase IIIa and b: Gates funded study (Gauteng, EC and Free State). Phase 3a Completed

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

Phase IIId: Completion of all current microscopy and clinic sites

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5. Phased Implementation Progress

Phase	GX4	GX16	GX48	TOTAL	Placed	% Completion
Phase 1/2a	7	30	1	38	38	100
Phase 2b	22	23	1	46	46	100
Phase 3a	3	10	0	13	13	100
Phase 3b	2	11	0	13	13	100
Phase 3c	6	28	0	34	15	44
Phase 3d	41	83	0	124	18	15
TOTAL	**81**	**185**	**2**	**268**	**143**	**53**

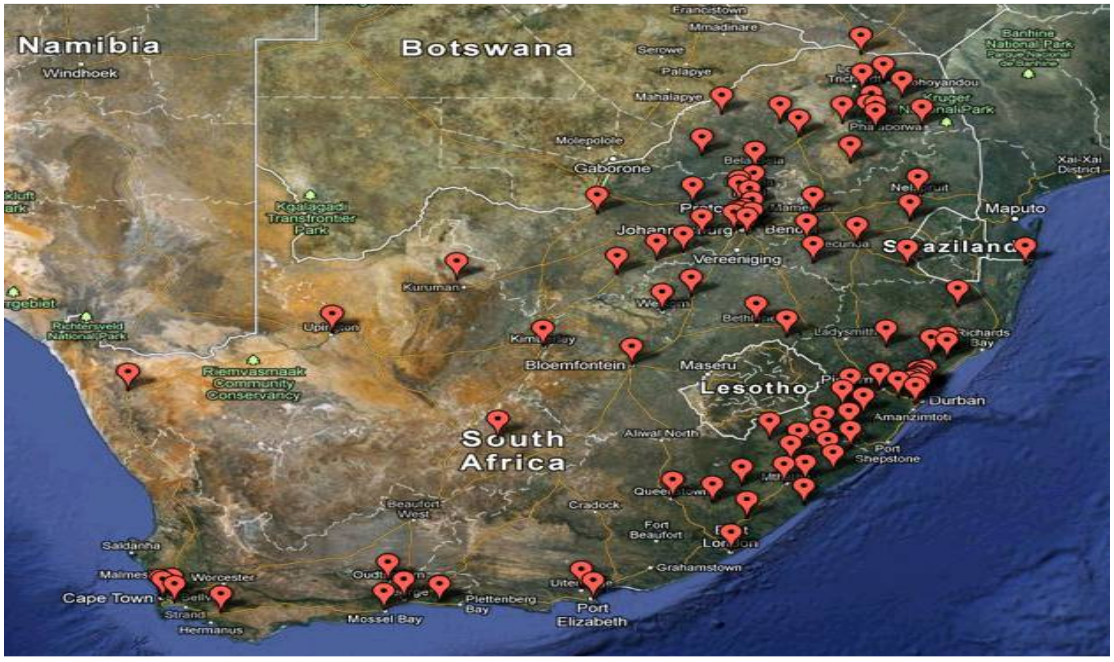
To date implementation is 53% complete. Installations, instrument verification, training and interfacing of phase 3b instruments are currently underway.

Phase 3c and 3d

Funding approved by Global Fund to complete the rollout (59, 985, 000 ZAR)

- 125 additional instruments will be placed over 9 months starting in January 2013

Figure 1: Current GeneXpert Placement (100 testing centers, 143 analysers, Gx4: 51; Gx16: 90; GX48:2) ***20 clinic placements**



6. Training: Laboratory and Clinical

A total of 243 laboratory staff and 1421 health care workers have been trained since December 2011. This will be an ongoing process to support NDoH training on clinical algorithm. Laboratory staff will receive both clinical and technical training.

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

- Delay in training health care workers, especially doctors whose availability is limited, on clinical algorithm: is being addressed
- Site readiness assessment for the 125 instruments to be placed- will require help from the regional CCMT coordinators
- Plan for additional interface licenses
- Global shortage of GXP cartridges: resolved
- Rollout of EGK to avoid duplications
- Laboratories using GXP for monitoring treatment (and not just diagnosis): is being addressed through training
- Under expenditure on the GeneXpert
    - Reduction in the price of the cartridge.
    - Delay in release of funds by Global Fund
    - Global shortage of cartridges
    - Delay in implementation of the automated billing system by the NHLS which will only be operation from the 1st of September 2012.
    - Delay in setting up billing accounts: KZN, Northern Cape and Free State

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
Kurbatova et al, Eur J Clin Microbiol Infect Dis. 2012	N= 238 sputums for Xpert comparison Subset of n=104 specimens, for TB-Biochip (microarray based) comparison	Sensitivity: Xpert = 95.3 % TB-Biochip = 97.3 %	Specificity: Xpert = 86.0 % TB-Biochip = 78.1 %
		Compared with MGIT DST, Xpert correctly identified 98.2 % of RIF-R and 95.5 % of RIF-susceptible (RIF-S) specimens. TB-Biochip correctly identified 100 % of RIF-R, 94.7 % of RIF-S, 98.2 % of INH-R, and 78.6 % of	

		INH-S specimens compared to MGIT DST.
Pantoja et al, Eur Resp J, 2012	Assessed the cost, globally and in 36 high-burden countries (HBCs), of two strategies for diagnosing TB and multidrug-resistant TB (MDR-TB): Xpert with follow-on diagnostics, and conventional diagnostics.	Using Xpert to diagnose MDR-TB would cost US$ 0.09 billion/year globally -lower cost than conventional diagnostics globally. Diagnosing TB in HIV-positive people using Xpert would also cost about US$ 0.10 billion/year - lower cost than conventional diagnostics globally. Testing everyone with TB signs and symptoms would cost almost US$ 0.47 billion/year globally - more than conventional diagnostics.
Winetsky et al, PloSMed 2012	Developed a dynamic transmission model of TB and drug resistance matched to the epidemiology and costs in Former Soviet Union prisons.	Using Xpert as an annual primary screening tool among the general prison population in Russion most effectively reduced overall TB prevalence (from 2.78% to 2.31%) and MDR-TB prevalence (from 0.74% to 0.63%), and cost US$543/QALY
Walters et al, Pead Infec Dis J, 2012	N= 11 Gastric Aspirate and n=8 stool	Xpert on stool and GA detected 3 of 4 (75%) children with intrathoracic TB and positive GA cultures, and 3 of 6 (50%) children with *M. tuberculosis* cultured from any site.
Menzies et al, PlosMed, 2012	Evaluated potential health and economic consequences of implementing Xpert in five southern African countries-Botswana, Lesotho, Namibia, South Africa, and Swaziland using a calibrated, dynamic mathematical model	Compared to status quo, implementation of Xpert would avert 132,000 (95% CI: 55,000-284,000) TB cases and 182,000 (97,000-302,000) TB deaths in southern Africa over the 10 y following introduction, and would reduce prevalence by 28% (14%-40%) by 2022. Health system costs are projected to increase substantially with Xpert, by US$460 million (294-699 million) over 10 y. Antiretroviral therapy for HIV represents a substantial fraction of these additional costs

9. Update on GeneXpert Research projects:

- Dried Culture Spot (DCS) for verification of GeneXperts to be rolled out for quarter 1 of 2013 will be manufactured.
- The following potential EQA materials are being investigated through a pilot, feasibility study (n=11 sites):
    - **i.** DCS EQA panel
    - **ii.** Liquid EQA panel (Vircell)
    - **iii.** Lyophilised EQA panel from the CDC
    - **iv.** Liquid EQA panel from WHO-

  The feasibility pilot is complete. At present the data is being analysed and results written up for publication as well as, more importantly presentation to QAD in order to choose the most suitable panel.
- DCS EQA & verification program development - ACTG (6 sites) and MSF included in program: first batch of verification and pilot EQA material have been shipped to ACTG sites. n=2 site results have been returned. Rwanda has received both EQA and Verification Material to aid in their initial setup. The Feedback received, was thet the DCS performed well according to both users and the providers at that side.
- 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. The next major upgrade Phase 3 has been completed (31 November 2012) and is currently undergoing validation testing. Expected to be switched live 28 Feb, 2013. Phase 4 scope of work has been generated. Awaiting finalization of specification.
- Alternative specimen preparation protocols:
    i. Protocols being developed for Extra-pulmonary TB diagnosis
    ii. 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 R&D GeneXpert has been placed for study commencement. The study commenced in the last week of August, investigating 0.5ml of un-centrifuged or concentrated residual EPTB specimens. The activity is ongoing. Thus far about a 20% positivity has been

observed on just over 700 unprocessed specimens. The culture confirmation is awaiting for about ¾ of the results.

- Connectivity: Collaboration with Cepheid ongoing
    i. Remote connectivity – System deployed on more than 100 sites by Cepheid and the NHLS. More than 310,000 results reported to date. The pilot has reached maximum capacity and no further routine sites will be added until the full product launch. The current pilot system cannot handle the additional testing capacity which will be added in the full product version.
    ii. The first point of care site (Botshabelo Clinic, North West Province) has gone live on the Cepheid Dashboard with an additional 2 sites to be connected. These sites are using Metacom-sponsored routers (3G) connection for reporting.

10. HIV/TB Integration

- Grand Challenges Canada project: Multiple POC HIV/TB integration feasibility 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 three sites are operational (Grace Mokgomo, North West Province), staff trained for randomized controlled trial (RCT)
    - Four new staff members have been employed: 1x nurse and 3x counselors
    - RCT: ~n=297 patients (POC arm =148; SOC =149) recruited into the study. Prelim results show that of study patients, 64% on the POC arm and 47% on the SOC arm where eligible for ART initiation, of which 80% on POC and 61% on SOC where initiated. Median time to initiation for POC was 1day versus 20 days on SOC.
    - 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). Interim results show that multiple POCT can feasibly be performed on multiple or a single finger stick for all tests, CD4, hemoglobin, ALT and creatinine measurements.

Patients prefer to receive multiple finger sticks over a venepuncture. Results presented at ASLM, Cape Town 2012. Results are being written up for publication.

- A 2nd sub study protocol to investigate various blood specimen storage and transport options is being developed. This study will compare Viral load testing on Dried Blood Spots (DBS) to new technologies/alternatives such as Hemaform plates, Primestore tubes and a thicker DBS card.

- Connectivity:
  - Conworx (POCcelerator) and LDS (AegisPOC) to be trialed in 2 sites during RCT. AegisPOC was installed at the first connectivity on 15 September, 2012. The Conworx solution was installed on the 14th of December, 2012. The system is currently running without remote access due to the lack of GPRS signal. Antennae being installed to assist in signal gain for full system functionality.

11. Grants Submitted

None

12. Funding

Table 12: Total and Percentage Contribution to date by Donor

Donor	% Contribution
NDoH	34.68
Bill & Melinda Gates Foundation	10.38
TB Reach	2.05
MSF	1.30
FIND	0.64
USAID	3.53
CDC NHLS 2010/11	21.32
CDC NDoH	1.03
CDC NHLS 2011/12	2.00
Dr. Niebauer	0.29
Gobal Fund NDOH	14.76
Global Fund RTC	4.02
CDC NDoH	4.00
Subtotal	**100**

CDC has contributed 28, 35% towards the program to date.

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.

Another campaign was held in Brits on the 4th of July 2012. The National Priority Programme CD4 team, with the generous assistance of Beckman Coulter, managed to secure a local mobile unit into which one XL flow cytometers and three GX16 instruments were housed. The instruments were successfully installed, validated and verified for accuracy on the day preceding events, with confirmatory quality control measures passed on the day of testing. In total, 61 patients were tested for an absolute CD4 count and 18 for TB using the GeneXpert. Test results were released to local coordinators for follow up of patients.

At the Union buildings in Tshwane an HCT day campaign was held during the week in October. Few patients were tested as the campaign was aimed at working civil servants. Nevertheless the infrastructure set-up went well, and patients got their results from the local clinics.