NATIONAL HEALTH LABORATORY SERVICE

GeneXpert MTB/RIF

Progress Report

October 2012

NATIONAL HEALTH LABORATORY SERVICE

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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 728,880 specimens have been processed to date (31 October 2012). The total % of *Mycobacterium tuberculosis* complex (MTBC) detected in this cohort was 14.99% (109,287). 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	Total
Eastern Cape	14,854	77,555	2,948	**95,357**
Free State	12,471	78,125	240	**90,836**
Gauteng	11,087	74,390	2,172	**87,649**
Kwa-Zulu Natal	33,703	163,082	6,476	**203,261**
Limpopo	4,782	38,522	578	**43,882**
Mpumalanga	5,980	31,189	2,082	**39,251**
North West	7,399	36,796	2,174	**46,369**
Northern Cape	6,365	35,345	1,761	**43,471**
Western Cape	12,646	65,775	383	**78,804**
Total	**109,287**	**600,779**	**18,814**	**728,880**

Table 2: Provincial GeneXpert RIF Results in MTB detected cases

Province	Inconclusive	Resistant	Sensitive	No Rif Result	Total
Eastern Cape	185	1,027	13,521	121	**14,854**
Free State	156	723	11,565	27	**12,471**
Gauteng	120	723	10,240	4	**11,087**
Kwa-Zulu Natal	509	2,777	30,008	409	**33,703**
Limpopo	68	378	4,299	37	**4,782**
Mpumalanga	81	527	5,292	80	**5,980**
North West	94	619	6,675	11	**7,399**
Northern Cape	85	403	5,873	4	**6,365**
Western Cape	138	622	11,884	2	**12,646**
Total	**1,436**	**7,799**	**99,357**	**695**	**109,287**

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.

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	MTB Result	Total
Eastern Cape	2,645	220	83	92,409	**95,357**
Free State	188	18	34	90,596	**90,836**
Gauteng	1,908	215	49	85,477	**87,649**
Kwa-Zulu Natal	5,083	1,138	255	196,785	**203,261**
Limpopo	475	90	13	43,304	**43,882**
Mpumalanga	1,925	134	23	37,169	**39,251**
North West	1,964	158	52	44,195	**46,369**
Northern Cape	606	236	919	41,710	**43,471**
Western Cape	327	39	17	78,421	**78,804**
Total	**15,121**	**2,248**	**1,445**	**710,066**	**728,880**

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

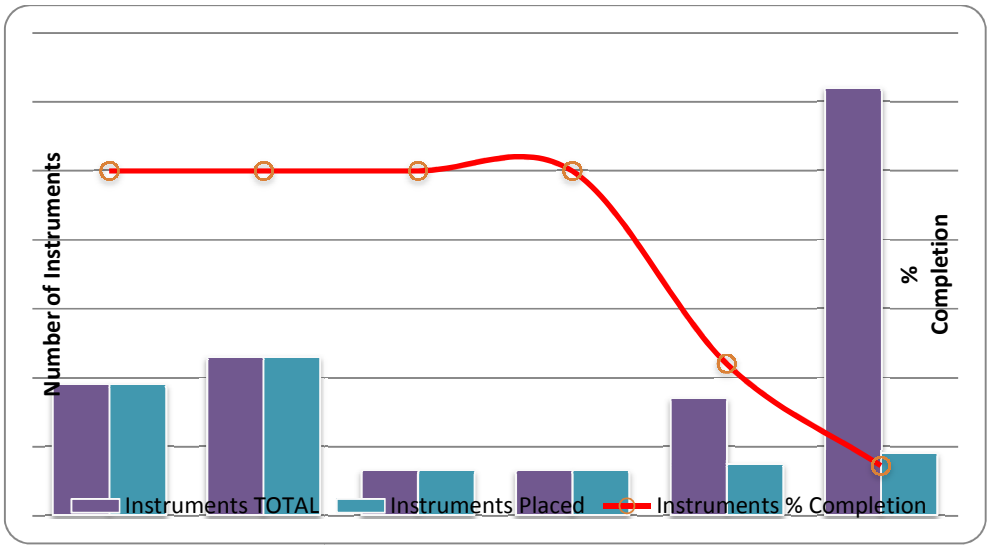
Phase IIb: Full capacitation of high burden districts. Completed

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

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.

Table 5: Phase 3b

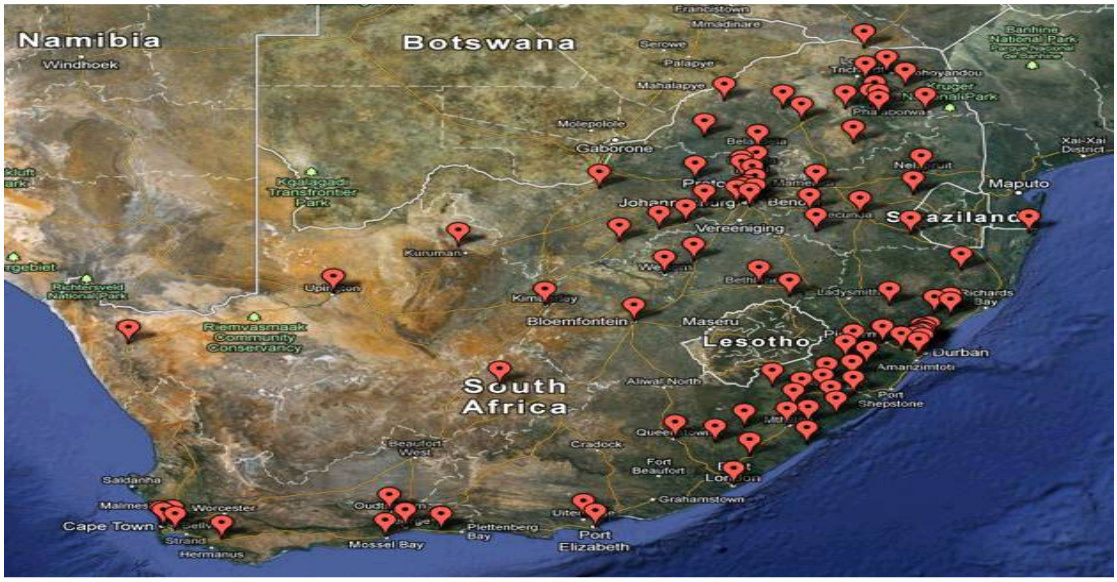
Province	District	Lab	GX4	GX16	Funding By
EC	Chris Hani	COFIMVABA		1	Gates Control
EC	Chris Hani	QUEENSTOWN	1	1	Gates Control & CDC DOH
EC	Nelson Mandela Bay Metro	UITENHAGE		1	Gates Control
FS	Thabo Mofutsanyane	MANAPO		1	Gates Control
GP	City of Tshwane	JUBILEE		1	Gates Control
GP	Ekurhuleni	NATALSPRUIT		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

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 227 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
Yoon et al, 2012, PloSOne	N= 477 patients in Uganda. Sputum specimens	Sensitivity: 79% in culture positive TB 42% in smear negative cases	Specificity: = 96% in culture positive TB
Bates et al, 2012 Lancet Infec Dis	Of 930 children: n=142 produced sputum	Sensitivity = 68·8% (95% CI 53·6-80·9)	Specificity = 99·3% (98·3-99·8)

	n= 788 gave Gastric Lavage Aspirate from non-sputum producers	for GLA versus 90·0% (54·1-99·5; p=0·1649) for sputum samples	for GLA and 98·5% (94·1-99·7; p=0·2871) for sputum samples.
Al-Ateah et al 2012 Saud Med J	**239 (172 respiratory, and 67 non respiratory)**	The sensitivity = 95.4% (95% CI: 89-100%) for respiratory samples, Sensitivity for non-respiratory specimens was 94.4% (95% CI: 90.2-98.5), and the	Specificity =100% (95% CI: 93.6-100%) for respiratory samples. Specificity for non-respiratory specimens was 100% (95% CI: 95.8-100%).
Clouse et al, 2012, SA Med J	Experiences of launching Xpert as the POC, initial diagnostic for all TB suspects at a primary healthcare clinic in Johannesburg	• Actual turn-around time was longer for most patients because of sample preparation time and clinic congestion. • GX4 instrument did not result in a 16-test capacity during an 8-hour working day • Some patients did not receive same-day results. • Loss to follow-up was an unforeseen challenge • Staff with high school education successfully performed the assay after minimal training. • A minimum of 2 staff needed	
Kim et al, 2012, Int J Tuberc Lung Dis	N=71 sputum sediments	Xpert detected M. tuberculosis in 71 (100%) specimens. The median time saved was 18.5 days (range 9-30) for the diagnosis of M. tuberculosis and 81.5 days (65-136) for RMP susceptibility in smear-negative, culture-positive patients	

Barnard et al, 2012, JCM	N=282 consecutive specimens were subjected to Xpert and Hain LPA v.2	Sensitivities of the GenoType MTBDRplus (v2.0) = 73.1% Xpert MTB/RIF =71.2%, for detection of culture positive	Both 100%

9. Update on GeneXpert Research projects:

- Dried Culture Spot (DCS) Verification (n=200 panels) for Phase IIIb of instrument implementation have been manufactured and are ready for transportation to sites with new Gx instruments
- 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-
- DCS EQA & verification program development - ACTG (4 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 have received both EQA and Verification Material to aid in their initial setup.
- 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) scope has been finalized and development will be completed by 30 November, 2012. Phase 3 includes EQA qualitative and quantitative evaluation and reporting of sites. 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 unprocessed specimens. The culture confirmation is awaiting for about ¾ of the results.

iii. Protocol under development to test residual SR buffered Xpert specimens on the line probe assay for DST resulting – of n=30 residual SR buffered Xpert positive specimens tested directly on the Hain MTBDrplus assay. Only one sample gave a discordant result between Xpert and Hain. This protocol shows the feasibility of DST LPA testing directly on residual Xpert specimens to decrease turnaround time.

- Connectivity: Collaboration with Cepheid ongoing
  i. Remote connectivity – System deployed on 96 sites by Cepheid and the NHLS (. More than 160,000 results reported to date. Cepheid pre-install the system on the instruments before delivery to sites. NHLS have been responsible for installing (remotely) on existing sites. This pilot system will remain active under the full product is launched. A 2-day workshop was conducted with Cepheid and Axeda (platform developers) to review the pilot system and investigate additional features which are to be included in the full product version.
  ii. Remote Calibration – Product launch date has been confirmed as December, 2012.

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 selection of first site (Grace Mokgomo, North West Province) for randomized controlled trial (RCT) has been finalized and staff trained.
- Currently three sites are operational, Grace Mokgomo, Botshabelo and Tigane clinics
- four new staff members have been employed: 1x nurse and 3x counselors
- RCT: ~n=230 patients recruited into the study.
- 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. An abstract has been submitted to ASLM, Cape Town 2012.

- 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 has been configured and tested and will be installed at the second site as soon as the necessary hardware has been delivered (expected , week 1 December, 2012).

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 Tswane 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.