



NATIONAL HEALTH
LABORATORY SERVICE

GeneXpert MTB/RIF

Progress Report

September 2011



GeneXpert Implementation Report Update

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1. Background to Project

This project was initiated at the request of the Honorable Minister of Health in early 2011. A pilot study was proposed by the National Department of Health (NDoH) (particularly the TB cluster) while due diligence was being done with respect to project feasibility. This was further prompted by the World Health Organization's strong recommendation 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 (i.e. all SA TB suspects).

The pilot phase was initiated in microscopy centres in high focus TB areas. The ministry requested that at least 1 instrument be placed in each province, preferably in a district that had a high burden of TB (Selections were made by TB cluster). Twenty-five microscopy centres were selected and a total of 30 instruments placed. The NDoH funded 9 GX16 and 14 GX4 instruments for the project. FIND donated 6 GX4 analysers and the Infinity or GX48 was supported by PEPFAR RTC. All instruments were placed by World TB day March 24th. 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.

2. Assays performed to date

In summary, a total of 104,098 specimens have been processed to date. The total % of MTB detected in this cohort amounted to 16.33% (17,001 new TB cases). The percentage positivity has remained on average between 16-17% monthly nationally. To date KZN has performed the largest number of tests which is probably as a result of the throughput of the GX48 analyser (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 per Province

Province	Conflicting Result	MTB Detected	MTB Not Detected	Test Unsuccessful	Total	% MTB Detected
Eastern Cape	1	1,536	7,475	280	9,292	16.53
Free State	1	1,258	6,738	31	8,028	15.67
Gauteng		1,230	8,028	224	9,482	12.97
Kwa-Zulu Natal	6	6,700	26,058	1,226	33,990	19.71
Limpopo	2	969	9,098	113	10,182	9.52
Mpumalanga		1,633	7,931	798	10,362	15.76
North West		1,328	6,693	190	8,211	16.17
Northern Cape	1	2,030	10,177	540	12,748	15.92
Western Cape		317	1,475	11	1,803	17.58
Total	11	17,001	83,673	3,413	104,098	16.33

Table 2: Provincial GeneXpert RIF Results in MTB detected cases

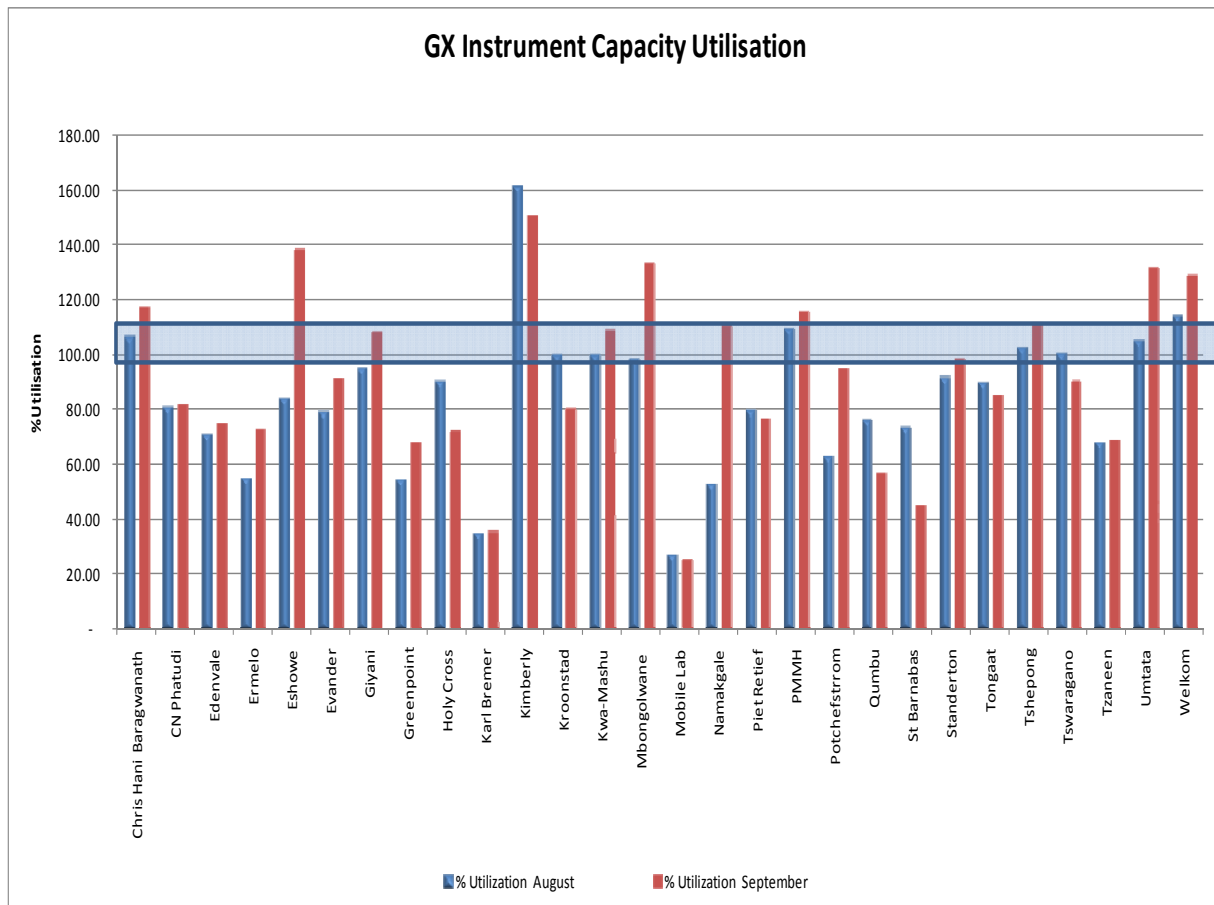
Province	No Result	Inconclusive	Resistant	Sensitive	Total	% RIF Resistance
Eastern Cape	59	6	111	1,360	1,536	7.23
Free State	1	15	70	1,172	1,258	5.56
Gauteng	1	11	92	1,126	1,230	7.48
Kwa-Zulu Natal	57	57	476	6,110	6,700	7.10
Limpopo	18	8	80	863	969	8.26
Mpumalanga	2	20	132	1,479	1,633	8.08
North West	4	15	113	1,196	1,328	8.51
Northern Cape	18	17	139	1,856	2,030	6.85
Western Cape	2	2	16	297	317	5.05
Total	162	151	1,229	15,459	17,001	7.23

In terms of test errors, these have ranged consistently below 3%, apart from May where a batch issue was identified with reagents. Details of invalid results, which likely represent sample issues is consistently below 1%. These are being monitored regularly and corrective action implemented where necessary.

Table 3: Number of Unsuccessful Tests and Reasons

MTB_Target	US_Target	March	April	May	June	July	August	September	Total
Conflicting Result				1		2	5	3	11
MTB Detected		652	2295	2637	2644	2883	3640	2250	17001
MTB Not Detected		2693	9828	12145	13427	14728	18765	12087	83673
Test Unsuccessful	Error	77	284	788	492	194	384	365	2584
Test Unsuccessful	Invalid	35	31	88	129	136	156	112	687
Test Unsuccessful	No Result	8	16	12	7	8	7	6	64
Test Unsuccessful	Pre-Analytical	1	10	25	8	8	15	11	78
Total		3466	12464	15696	16707	17959	22972	14834	104098
% Error		2.22	2.28	5.02	2.94	1.08	1.67	2.46	2.48
%Invalid		1.01	0.25	0.56	0.77	0.76	0.68	0.76	0.66
% No Result		0.23	0.13	0.08	0.04	0.04	0.03	0.04	0.06
% Pre-Analytical		0.03	0.08	0.16	0.05	0.04	0.07	0.07	0.07

3. Utilisation rates of instruments within the field



Kimberley, Prince Mshiyeni, Tshepong, Chris Hani Baragwanath, Welkom, Umtata, Tshwaragano, Mbongolwana, Kwa-Mashu and Kroonstad laboratories are utilizing their instruments above the set capacity per month with extended shifts. Instrument utilization has increased significantly from August to September.

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: Completion November/December

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. Specific GeneXpert Site Progress

Phase 2a

Instruments have all been placed at the end of phase 2a (see table 4).

Table 4: Sites for Phase 2a

Phase 2a							
Province	District	Lab	Instruments			Status	Date
			GX4	GX16	GX48		
EC	O.R. Tambo	HOLY CROSS		1		Completed	28-Sep-11
EC	O.R. Tambo	QUMBU	1			Completed	Pilot Phase
EC	O.R. Tambo	ST BARNABAS		1		Completed	29-Sep-11
EC	O.R. Tambo	UMTATA CLINICAL PATHOLOGY	1	1		In Progress	30-Sep-11
FS	Fezile Dabi	KROONSTAD		2		In Progress	30-Sep-11
FS	Lejweleputswa	GOLDFIELDS	1	1		In Progress	3-Oct-11
GP	City of Johannesburg	BARA ROUTINE		1		Completed	27-Sep-11
GP	City of Johannesburg	EDENVALE		1		Completed	27-Sep-11
KZN	eThekweni	Prince Mshiyeni			1	Completed	Pilot Phase
KZN	eThekweni	Kwa Mashu		1		Completed	28-Sep-11
KZN	eThekweni	Tongaat MC		1		Completed	29-Sep-11
LP	Mopani	CN PHATUDI	1			Completed	Pilot Phase
LP	Mopani	GIYANI		1		Completed	Pilot Phase
LP	Mopani	NAMAKGALE	1			Completed	Pilot Phase
LP	Mopani	TZANEEN		1		Completed	29-Sep-11
MP	Gert Sibande	ERMELO		1		Completed	Pilot Phase
MP	Gert Sibande	PIET RETIEF	1			Completed	Pilot Phase
MP	Gert Sibande	STANDERTON		1		Completed	30-Sep-11
MP	Gert Sibande	EVANDER	1			Completed	Pilot Phase
NC	Frances Baard	KIMBERLEY		1		Completed	29-Sep-11
NC	John Taolo Gaetsewe (Kgalagadi)	TSHWARAGANO		1		Completed	28-Sep-11
NW	Dr Kenneth Kaunda (Southern)	TSHEPONG TB		1		Completed	29-Sep-11
WC	City of Cape Town	GREENPOINT TB		5		Completed	28-Sep-11
WC	City of Cape Town	KARL BREMER	1			Completed	Pilot Phase

Training, interfacing to LIS and verification of analysers is underway. Further progress is dependent on release of further global, CDC and Gates funds.

Phases 2b, 3a and b are listed in tables below and remain dependent on further release of funding

Table 5: Phase 2b

Phase 2b							
Province	District	Lab	Instruments			Status	Date
			GX4	GX16	GX48		
EC	O.R. Tambo	ST ELIZABETH		1		Pending	1-Nov-11
EC	O.R. Tambo	ZITULELE		1		Pending	1-Nov-11
KZN	eThekweni	Addington		1		Pending	1-Nov-11
KZN	eThekweni	RK Khan		1		Pending	1-Nov-11
KZN	eThekweni	Wentworth		1		Pending	1-Nov-11
KZN	eThekweni	Mahatma Gandhi		1		Pending	1-Nov-11
GP	City of Johannesburg	NJH ROUTINE	1			Pending	1-Nov-11
KZN	eThekweni	Hlengisizwe MC	1			Pending	1-Nov-11
KZN	eThekweni	Clairwood	1		1	Pending	1-Nov-11
EC	O.R. Tambo	ST LUCY	1			Pending	1-Nov-11
KZN	eThekweni	Don Mackenzie MC	1			Pending	1-Nov-11
KZN	eThekweni	Osindisweni	1			Pending	1-Nov-11
KZN	eThekweni	FOSA MC	1			Pending	1-Nov-11
KZN	eThekweni	Verulam MC	1			Pending	1-Nov-11
LP	Mopani	SEKORORO	1			Pending	1-Nov-11
KZN	Zululand	Benedictine		1		Completed (GX4)	16-Sep-11
KZN	eThekweni	Dbn Chest Clinic MC		1		Pending	1-Nov-11
KZN	eThekweni	Inanda C MC		1		Pending	1-Nov-11
KZN	eThekweni	Charles James MC		1		Pending	1-Nov-11
KZN	eThekweni	KwaDabeka MC		1		Pending	1-Nov-11
KZN	eThekweni	PineTown MC		1		Pending	1-Nov-11
LP	Mopani	KGAPANE		1		Pending	1-Nov-11
LP	Mopani	PHALABORWA		1		Pending	1-Nov-11
MP	Gert Sibande	EMBHULENI		1		Pending	1-Nov-11
NC	Siyanda	UPINGTON		1		Pending	1-Nov-11
NW	Dr Kenneth Kaunda (Southern)	POTCHEFSTROOM		1		Pending	1-Nov-11
WC	City of Cape Town	GROOTE SCHUUR CLINICAL PATH		1		Pending	1-Nov-11
EC	Amathole	EAST LONDON TB			1	Pending	1-Nov-11
EC	Nelson Mandela Bay Metro	PORT ELIZABETH TB		3		Pending	1-Nov-11
GP	City of Johannesburg	CENTRAL TB	1	1		Pending	1-Nov-11
KZN	Uthungulu	Eshowe	2			One GX4 in place	1-Aug-11
KZN	Uthungulu	Mbongolwana	1			Pending	1-Nov-11
KZN	Sisonke	RIETVLEI		1		Pending	1-Nov-11
KZN	Sisonke	St. Appolinaris	1			Pending	1-Nov-11
KZN	Sisonke	Pholela HCC	1			Completed	27-Sep-11
KZN	Sisonke	Kokstad	2			Pending	1-Nov-11

Table 6: Phase 3a

Phase 3a							
Province	District	Lab	Instruments			Status	Date
			GX4	GX16	GX48		
EC	Alfred Nzo	MARY THERESA		1		Pending	1-Nov-11
EC	Alfred Nzo	MT AYLIFF		1		Pending	1-Nov-11
EC	Chris Hani	ALL SAINTS		1		Pending	1-Nov-11
FS	Thabo Mofutsanyane	BETHLEHEM		1		Pending	1-Nov-11
GP	City of Tshwane	PRETORIA WEST		1		Pending	1-Nov-11
GP	Ekurhuleni	BOKSBURG BENONI	1	1		Pending	1-Nov-11
GP	Ekurhuleni	TEMBISA		1		Pending	1-Nov-11
EC	O.R. Tambo	ST PATRICK		1		Pending	1-Nov-11
GP	City of Johannesburg	HELEN JOSEPH		1		Pending	1-Nov-11
MP	Nkangala	WITBANK		1		Pending	1-Nov-11

6. Training: Laboratory and Clinical

A total of 55 staff members have been trained since July 2011 (Summarized in table 5). This is over and above staff trained prior to launch. This will be an ongoing process to support NDoH training on clinical algorithm. Laboratory staff will receive both clinical and technical training.

Table 7: Training summary since July

Venue	Date	# Participants	Trainer	Training Outcomes
Greenpoint	14-15 July	8	Tessa	GeneXpert Operation, Maintenance, Troubleshooting and Data Entry
Eshowe	4-Aug-11	10	Floyd	GeneXpert Operation, Maintenance, Troubleshooting and Data Entry
Mbongolwana	4-Aug-11	5	Floyd	GeneXpert Operation, Maintenance, Troubleshooting and Data Entry
Chris Hani Baragwanath	26 & 30 August	10	Fimmie	GeneXpert Operation, Maintenance, Troubleshooting and Data Entry
Benedictine	6-Sep	8	Veeresh	GeneXpert Operation, Maintenance, Troubleshooting and Data Entry
Benedictine	14-Sep	5	Nico	GeneXpert Operation, Maintenance, Troubleshooting and Data Entry
Benedictine	14-Sep	8	Nico	GeneXpert Overview and Algorithm
Siloah	15-Sep	11	Nico	GeneXpert Overview and Algorithm

The training indicated above, excludes training of X laboratory personnel before rollout of the pilot study and clinical training conducted in collaboration with the DOH in the different provinces.

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

- **Alignment of enthusiastic donors to support one plan**
- **Finalisation of the algorithm and the request forms:** As expected, this took a significant amount of time and consultation with the final algorithm presented in figure 1 below:
- **The development of a National TB costing model**
- **Clinical Algorithm:** Understanding of the algorithm still poses a major challenge, however this is being addressed during the clinical training held in the different provinces.
- **Error rates** which have largely been resolved

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 6 below:

Table 8: Recent publications: GeneXpert for pulmonary TB

Manuscript	Sample population (n=...)	Sensitivity	Specificity
Boehme,C et al, NEJM, 2010	1730	98.2% (smear positive), 72.5% (smear negative) sputum 94.6% overall 83.7% overall	99.2% overall
Boehme et al, Lancet 2011	1033	90.3% culture + 76.9% smear -/culture +	99% specific
Hilleman, D et al 2011	521 tissue specimens	77.3% (100% urine and stool)	98.2%
Theron,G et al, Am J Respir Crit Care Med	480	78.7% overall group 55% smear negative culture positive	94.4
Armand,S et al, J Clin Micro, 2011	97 (n=60 respiratory, n=37 nonrespiratory)	79% compared to IS6110 realtime PCR in respiratory 53% nonrespiratory	100% in smear positive/culture positive
Marlowe,EM et al, CM 2011	217 respiratory	Overall of 89% (98% smear +, 72% smear -)	
Moure,R, J clin Micro, 2011	N= 78 respiratory N= 7 non respiratory	75.3% overall	100% overall
Rachow et al PloSone 2011	92 respiratory	88.4%	99%
Bowles et al Int J Tuberc lung dis, 2011	89 (n=86 sputum, n=1 pleural fluid, n=1 gastric fluid, n=1 bronchial washing)	Overall 93.8%	92%
Fiedrich, J Clin Micro, 2011	140	92.9% compared to Genotype MTBDR (90.5%)	
Vadwai, J Clin Micro 2011	547 extrapulmonary	81% overall	99.6%
Scott,L et al 2011 PloS Medicine	311 respiratory	86% total group, 84% HIV positive group, 61% smear negative culture	>97%

positive

In addition, several studies have been conducted demonstrating the use of the assay for extra-pulmonary TB

Author and Journal	Sample types	Processing performed
Vadwai et al. (2011) J Clin Micro	<ul style="list-style-type: none"> N=284 biopsies (147 tissues , 82 lymph nodes, 55 FNA) N=147 pus N=93 body fluids (11 synovial, 3 pericardial, 66 pleural fluid, 13 peritoneal, 23 CSF) 	<p>Biopsies: chopped into small pieces with sterile blade in sterile petri dish, added 2:1 SR to specimen.</p> <p>Fluid: direct addition of SR to specimen in 2.</p>
Archontakis et al. (2011). Myco Dis Diag	<ul style="list-style-type: none"> Concentrated urine Gastric samples Pleural fluids 	<p>Concentrated urine and gastric samples centrifuged, resuspended in 500ul dH2O and NALC/NaOH decontaminated before SR addition.</p> <p>Pleural fluids centrifuged, 500ul dH2O added before addition of SR.</p>
Moure et al. (2011). J Clin Micr	<ul style="list-style-type: none"> Pleural fluid, Gastric aspirate; Urine; Stool; CSF; Ascetic fluid; Lymph node aspirate; Skin biopsy; Mammary abscess 	NALC/NaOH pellets frozen and 1ml tested on Xpert.
Armand et al. (2011) J Clin Micro	<ul style="list-style-type: none"> Lymph nodes; Pleural fluids; Bones; Abscesses; Urine <p>+60 respiratory (sputa, bronchial aspirates, gastric aspirates, BAL)</p>	NALC/NaOH pellets frozen and 0.5ml tested on Xpert.
Ciftci et al. (2011) Mikrobiyol Bul Abstract only	<ul style="list-style-type: none"> BAL Thorasynthesis fluid Urine 	Direct testing on Xpert.
Bowles et al.(2011) Int J Tuber Lung Dis	<ul style="list-style-type: none"> Pleural fluid; Gastric fluid; Bronchial wash 	Not stated

Hilleman et al. (2011) J Clin Micro	<ul style="list-style-type: none"> N = 91 urine, N = 30 gastric aspirates; N=245 tissue; N=113 pleural fluid; N=19 CSF; N=23 stool 	NALC/NaOH pellets and 0.5ml tested on the Xpert.
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9. Grants submitted

UNITAID proposal was submitted on 20 September 2011 to source funding to fully capacitate the NHLS with the Xpert MTB/RIF test to provide full coverage of such TB diagnostic service for the national TB program in South Africa. The developed implementation protocol and cost model will then be expanded to neighbouring countries. This is quite a long shot due to the fact that we are a middle income country and this is a single country application

10. Funding issues

- Urgency remains to conclude Global fund negotiations and release funds
- Recurrent assay cost price needs to be agreed upon before new financial year

CDC Funded Instruments as of 30 September 2011

Province	Site	Phase	GX16
Eastern Cape	Holy Cross	Za	1
Eastern Cape	St. Barnabas	Za	1
Free State	Kroonstad	Za	1
Free State	Kroonstad	Za	1
Gauteng	Baragwanath	Za	1
Gauteng	Edenrale	Za	1
Kwazulu Natal	KwaMashu	Za	1
Kwazulu Natal	Tongaat	Za	1
Limpopo	Tzaneen	Za	1
Mpumalanga	Standerton	Za	1
North West	Tshepong	Za	1
Northern Cape	Kimberley	Za	1
Northern Cape	Tshwaragano	Za	1
Western Cape	Greenpoint TB	Za	1
TOTAL			14