NATIONAL HEALTH LABORATORY SERVICE

GeneXpert MTB/RIF

Progress Report

December 2011

NATIONAL HEALTH LABORATORY SERVICE

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 209,099 specimens have been processed to date (05 Jan 2012). The total % of MTB detected in this cohort amounted to 17.09% (35,737 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 analyzer (Refer to table 1). Average Rifampicin resistance detection rates have remained around 7% since project inception (Refer to table 2). We have highlighted to CDW that some Health Districts are incorrect.

Table 1: GeneXpert MTB Results by province

Province	MTB Detected	MTB Not Detected	Test Unsuccessful	Total	% MTB Detected
Eastern Cape	3,385	15,622	578	19,585	17.28
Free State	2,928	15,157	26	18,111	16.17
Gauteng	3,116	19,030	435	22,581	13.80
Kwa-Zulu Natal	12,271	43,992	1,567	57,830	21.22
LIMPOPO	2,139	18,011	176	20,326	10.52
MPUMALANGA	3,595	16,306	1,261	21,162	16.99
North West	2,701	13,312	551	16,564	16.31
Northern Cape	3,238	16,043	689	19,970	16.21
Western Cape	2,364	10,562	44	12,970	18.23
Grand Total	**35,737**	**168,035**	**5,327**	**209,099**	**17.09**

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Table 2: Provincial GeneXpert RIF Results in MTB detected cases

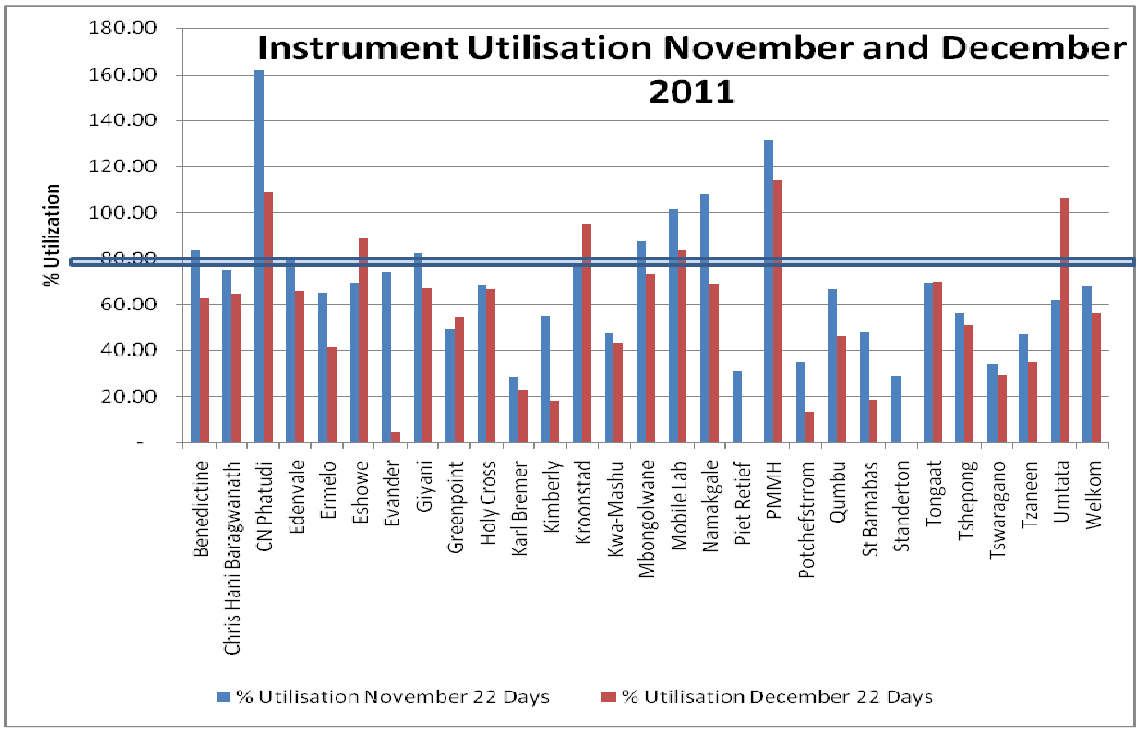
Province	Health District	Inconclusive	No RIF Result	Resistant	Sensitive	Grand Total	% RIF Resistant
Eastern Cape				2	7	9	22.22
	ALFRED NZO	2	4	14	88	108	12.96
	AMATHOLE	7	2	29	207	245	11.84
	CHRIS HANI			2	19	21	9.52
	GERT SIBANDE				1	1	-
	LEJWELEPUTSWA		1	3	21	25	12.00
	O R TAMBO	23	56	203	2,666	2,948	6.89
	OVERBERG				1	1	-
	UKHAHLAMBA	1		1	25	27	3.70
Free State					4	4	-
	FEZILE DABI	10		43	1,090	1,143	3.76
	GERT SIBANDE				9	9	-
	LEJWELEPUTSWA	19	1	106	1,601	1,727	6.14
	SEDIBENG				19	19	-
	THABO MOFUTSANYANA			6	20	26	23.08
Gauteng	CITY OF JOHANNESBURG	24	1	173	2,793	2,991	5.78
	EKURHULENI METRO	2		4	118	124	3.23
	N/A				1	1	-
Kwa-Zulu Natal	AMAJUBA				4	4	-
	ETHEKWINI METRO	100	44	741	10,146	11,031	6.72
	ILEMBE			5	2	7	71.43
	N/A	3		36	343	382	9.42
	UGU		3	4	153	160	2.50
	UMGUNGUNDLOVU			1	3	4	25.00
	UMZINYATHI			1	2	3	33.33
	UTHUNGULU	1	4	77	422	504	15.28
	ZULULAND			41	135	176	23.30
LIMPOPO	ETHEKWINI METRO				6	6	-
	GREATER SEKHUKHUNE			5	21	26	19.23
	MOPANI	21	22	125	1,643	1,811	6.90
	N/A	6	3	22	243	274	8.03
	VHEMBE			1	9	10	10.00
	WATERBERG				12	12	-
MPUMALANGA	EHLANZENI			2	6	8	25.00
	ETHEKWINI METRO	8	1	74	883	966	7.66
	GERT SIBANDE	28	4	204	2,291	2,527	8.07
	NKANGALA	3		7	84	94	7.45
North West					1	1	-
	BOJANALA				1	1	-
	CITY OF TSHWANE				1	1	-
	DR KENNETH KAUNDA	29		189	2,018	2,236	8.45
	DR RUTH SEGOMOTSI MOMPATI	1		9	102	112	8.04
	ETHEKWINI METRO		6	14	165	185	7.57
	GERT SIBANDE	1	1	5	51	58	8.62
	NGAKA MODIRI MOLEMA			3	103	106	2.83
	VHEMBE				1	1	-
Northern Cape					8	8	-
	AMATHOLE				1	1	-
	DR KENNETH KAUNDA				1	1	-
	DR RUTH SEGOMOTSI MOMPATI			2	19	21	9.52
	EKURHULENI METRO			6	51	57	10.53
	FRANCES BAARD	16	1	77	1,397	1,491	5.16
	JOHN TAOLO GAETSEWE	6	1	58	972	1,037	5.59
	N/A	1			16	17	-
	NAMAKWA			4	11	15	26.67
	PIXLEY KA SEME	2		37	223	262	14.12
	SIYANDA	5		16	304	325	4.92
	XHARIEP				3	3	-
Western Cape	CAPE WINELANDS			13	141	154	8.44
	CITY OF CAPE TOWN	15		89	1,938	2,042	4.36
	CITY OF JOHANNESBURG				10	10	-
	OVERBERG	1		6	151	158	3.80
Grand Total		**335**	**155**	**2,460**	**32,787**	**35,737**	6.88

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 3: Number of Unsuccessful Tests and Reasons

Province	Error	Invalid	No Result	MTB Result	Total	% Error Total
Eastern Cape	525	47	6	19,007	19,585	2.68
Free State	26			18,085	18,111	0.14
Gauteng	380	47	8	22,146	22,581	1.68
Kwa-Zulu Natal	1,045	486	36	56,263	57,830	1.81
LIMPOPO	136	30	10	20,150	20,326	0.67
MPUMALANGA	1,131	119	11	19,901	21,162	5.34
North West	510	41		16,013	16,564	3.08
Northern Cape	547	127	15	19,281	19,970	2.74
Western Cape	37	7		12,926	12,970	0.29
Grand Total	**4,337**	**904**	**86**	**203,772**	**209,099**	**2.07**

3. Utilization rates of instruments within the field



Instrument utilization has decreased significantly at some sites from November to December due to shortage of cartridge suppply.

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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. Specific GeneXpert Progress

- **Phase 2a:** Completed

- **Phase 2b:** Global Fund funding for phase 2b has been approved. Singing of contracts between the primary recipients and sub-recipients is underway. Phase 2b is projected to roll-out in April 2012.

Table 4: Phase 2b

Province	District	Lab	Capacity Per Day	Instruments			Donor
				GX4	GX16	GX48	
EC	Amathole	EAST LONDON TB	576	0	0	1	Global Fund RTC
EC	Nelson Mandela Bay Metro	PORT ELIZABETH TB	576	0	0	1	Global Fund RTC
EC	O.R. Tambo	ST ELIZABETH	64	0	1	0	Global Fund DOH
EC	O.R. Tambo	ST LUCY	16	1	0	0	Global Fund DOH
EC	O.R. Tambo	ZITULELE	32	0	1	0	Global Fund DOH
GP	City of Johannesburg	CENTRAL TB	80	1	1	0	Global Fund DOH
GP	City of Johannesburg	NJH ROUTINE	16	1	0	0	Global Fund DOH
KZN	eThekwini	Addington	32	0	1	0	Global Fund DOH
KZN	eThekwini	Charles James MC	32	0	1	0	Global Fund DOH
KZN	eThekwini	Clairwood	16	1	0	0	Global Fund DOH
KZN	eThekwini	Dbn Chest Clinic MC	64	0	1	0	Global Fund DOH
KZN	eThekwini	Don Mackenzie MC	16	1	0	0	Global Fund DOH
KZN	eThekwini	FOSA MC	16	1	0	0	Global Fund DOH
KZN	eThekwini	Hlengisizwe MC	16	1	0	0	Global Fund DOH
KZN	eThekwini	Inanda C MC	32	0	1	0	Global Fund DOH
KZN	eThekwini	KwaDabeka MC	32	0	1	0	Global Fund DOH
KZN	eThekwini	Mahatma Ghandi	48	0	1	0	Global Fund DOH
KZN	eThekwini	Osindisweni	16	1	0	0	Global Fund DOH
KZN	eThekwini	PineTown MC	48	0	1	0	Global Fund DOH
KZN	eThekwini	RK Khan	64	0	1	0	Global Fund DOH
KZN	eThekwini	Verulam MC	16	1	0	0	Global Fund DOH
KZN	eThekwini	Wentworth	32	0	1	0	Global Fund DOH
KZN	Sisonke	Kokstad	32	2	0	0	50% Global Fund DOH and TB/HIV Care
KZN	Sisonke	Pholela HCC	16	1	0	0	TB/HIV Care
KZN	Sisonke	Rietvlei	48	0	1	0	Global Fund DOH
KZN	Sisonke	St. Appolinaris	16	1	0	0	TB/HIV Care
KZN	Uthungulu	Eshowe	16	1	0	0	MSF
KZN	Uthungulu	Mbongolwana	16	1	0	0	MSF
KZN	Zululand	Benedictine	48	0	1	0	Global Fund DOH
LP	Mopani	KGAPANE	32	0	1	0	Global Fund DOH
LP	Mopani	PHALABORWA	32	0	1	0	Global Fund DOH
LP	Mopani	SEKORORO	16	1	0	0	Global Fund DOH
MP	Gert Sibande	EMBHULENI	32	0	1	0	Global Fund DOH
NC	Siyanda	UPINGTON	64	0	1	0	Global Fund DOH
NW	Dr Kenneth Kaunda (Southern)	POTCHEFSTROOM	48	0	1	0	Global Fund DOH
WC	City of Cape Town	GROOTE SCHUUR CLINICAL PATH	48	0	1	0	Global Fund DOH

Table 5: Phase 3a Progress

Province	Lab	GX4	GX16	Date of Installation	Installer	Training	Trainer	Status	EQA Verification Results	Interfacing	Comments
EC	MARY THERESA		1	9-Jan-12	Trevor	11 &12 Jan	Max	In Progress	Pending	18-Jan-12	
EC	MT AYLIFF		1	9-Jan-12	Trevor	10 & 11 Jan	Max	In Progress	Received	18-Jan-12	All modules of the instrument passed verification, except for module D4
EC	ALL SAINTS		1	10-Jan-12	Trevor	11 & 12 Jan	Trevor	In Progress	Received	19-Jan-12	All modules of the instrument passed verification
FS	BETHLEHEM		1	Awaiting							
GP	PRETORIA WEST		1	12-Dec-11	Jurie	10-Jan-12	Sheila & Sebaka	Complete	Received	Complete	All modules of the instrument passed verification
GP	BOKSBURG BENONI	1	1	13-Dec-11	Donovan	12-Jan-12	Sheila & Sebaka	Complete	Received	Complete	All modules of the instrument passed verification
GP	TEMBISA		1	12-Dec-11	Jurie	15-Dec-11	Sheila & Sebaka	Complete	Received	Complete	All modules of the instrument passed verification
EC	ST PATRICK		1	12-Jan-12	Trevor	12 & 13 Jan	Trevor		Pending	17-Jan-12	
GP	HELEN JOSEPH		1	13-Dec-11	Donovan	18-Jan-12	Sheila & Sebaka		Pending	Complete	
MP	WITBANK		1	14-Dec-11	Donovan	16-Jan-12	Sheila & Sebaka		Received	13-Jan-12	All modules of the instrument passed verification

Table 6: Phase 3b

The remaining 10 machines will be placed in July 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

6. Training: Laboratory and Clinical

A total of 57 laboratory staff have been trained since December 2011 as summarized in table 8. This will be an ongoing process to support NDoH training on clinical algorithm. Laboratory staff will receive both clinical and technical training.

Table 8: Laboratory Training

Venue	DATE	Trainer	TOTAL # OF DELEGATES	Outcomes
Christ the King	15 December 11	Veeresh	4	GeneXpert Operation, Maintenance, Troubleshooting and Data Entry
Kokstad	22 December 11	Trevor	4	GeneXpert Operation, Maintenance, Troubleshooting and Data Entry
St. Apollinaris	19 December 11	Veeresh	2	GeneXpert Operation, Maintenance, Troubleshooting and Data Entry
Tembisa	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
Tambo Memorial	12 January 12	Sebaka/Sheila	13	GeneXpert Operation, Maintenance, Troubleshooting and Data Entry
Witbank	16 January 12	Sheila	8	GeneXpert Operation, Maintenance, Troubleshooting and Data Entry
Mary Theresa	11/12 Jan 12	Maxine	4	GeneXpert Operation, Maintenance, Troubleshooting and Data Entry
Mt Ayliff	10/11 Jan 12	Maxine	4	GeneXpert Operation, Maintenance, Troubleshooting and Data Entry
St Patrick	12/13 Jan 12	Trevor	3	GeneXpert Operation, Maintenance, Troubleshooting and Data Entry
All Saints	11/12 Jan 12	Trevor	4	GeneXpert Operation, Maintenance, Troubleshooting and Data Entry

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

- Alignment of enthusiastic donors to support one plan
- Implement fee for service from 1 February 2012 (R220.00)
- Finalization of the request forms: The GXP assay and confirmatory tests are to be added to the CCMT form.
- Finalization of signing of the Global Fund contract
- Expert TB working group within Microbiology expert committee established
- New cartridge change GX3 to GX4

- Separate Rif lists to be generated, once MDR confirmed will be placed formally on register
- 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 9 below:

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

Manuscript	Sample population and specimen type (n=…)	Results	
		Sensitivity	Specificity
Tortoli et al, Eur Resp J, 2012	1,476 EPTB specimens (biopsies, urines, pus, cerebrospinal fluids, gastric aspirates) including paediatric (n=494)	Adult - 81.3% Paed - 86.9%	Adult - 99.8% Paed - 99.7%
Van Rie et al, Int J Tuber Lung Dis, 2012	Case study of a false positive Rif resistant sample	Probe B a potential cause. The revised assay should result in fewer false Rif cases.	
Van Zyl-Smit, PloSONE, 2011	Comparison of the turn-around-time, detection-threshold, dynamic range, reproducibility, relative discriminative ability, of 4 mycobacterial load determination techniques: automated liquid culture (BACTEC-MGIT-960), [^{3}H]-uracil incorporation assays, luciferase-reporter construct bioluminescence, and Xpert -MTB/RIF	Xpert-MTB/RIF correlated well with mycobacterial load, had a rapid turn-around-time (2 hours), was user friendly, but had a detection limit of 100 organisms.	
Safianowska, Pneumonol Alergol Pol, 2012	Comparison of 1875 samples for AMPLICOR MTB (104 were inhibited), and 213 samples for Xpert MTB/RIF	81.9% for AMPLICOR MTB and 81.8% for Xpert MTB/RIF	AMPLICOR - 97.2% Xpert - 99.5%
Williamson et al, Int J Tuber Lung Dis, 2011	M. tuberculosis isolates were screened for mutations in the rpoB gene using the Cepheid Gene-Xpert®	Demonstrate a significant association between the presence of rpoB gene mutations that are	

	MTB/RIF assay. Clinical correlation was made by reviewing patient case notes. Isolates from 94 patients were found to have INH-resistant, RMP-susceptible profiles. Clinical information was available for 52 patients	not detected at the current RMP critical concentration and treatment failure
Theron et al, Clin Infec Dis, 2012	Xpert MTB/RIF-generated cycle-threshold (C(T)) values have poor clinical utility as a rule-in test for smear positivity (cut-point ≤20.2; sensitivity 32.3%, specificity 97.1%) but moderately good rule-out value (cut-point >31.8; negative predictive value 80.0%). Thus, 20% of individuals with C (T) values >31.8 were erroneously ruled out as smear-negative. This group had a significantly lower sputum bacillary load relative to correctly classified smear-positive patients (C (T) ≤ 31.8; P < .001).	

9. Update on GeneXpert Research projects:

- DCS Verification – all phase 2a instruments verified.
- Cepheid Liquid EQA pilot prepared for 20 sites with questionnaire.
- DCS EQA & verification program development - ACTG (3 sites) and MSF included in program.
- 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. Protocols under development for solid tissue, gastric aspirates etc
    iii. Sputum heat inactivation: to determine whether heat inactivation can be used prior to Xpert testing to render it safe for further manipulation – ongoing
- Evaluation of G4 cartridge:
    i. 500 samples processed at Baragwanath. No significant performance differences between G3 and G4.
    ii. Further evaluation ongoing using MGIT concentrates.
- Connectivity: Collaboration with Cepheid ongoing
    i. Remote connectivity – System demo (5 Jan)

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).
    - Site visits completed (n=12) and selection being finalized.
    - Finalization of RCT protocol.
- Connectivity:
    - Conworx (POCcelerator) and LDS (AegisPOC) to be trialed in 2 sites during RCT
    - Awaiting NHLS feedback for HemoCue project at CMJAH

11. Grants submitted

None

12. Funding issues

None