



NATIONAL HEALTH
LABORATORY SERVICE

GeneXpert MTB/RIF

Progress Report

June 2014





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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 which stated 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. 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 24 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.

Since then, 295 GeneXpert instruments of varying sizes (GX4: 98; GX16:189; GX48: 1; GX80:7) have been placed in 207 sites – both urban and rural settings, by the National Priority Programmes of the NHLS and the NDoH, the progress of which is described in point 6 below.

The programme is being further expanded to directly support the annual screening for TB and HIV of a quarter of a million people in special risk populations in correctional centres and in peri-mining communities. There are 6 districts with high proportion of mines in South Africa that have been identified for focused attention.



1.1. Correctional Services

In order to improve TB control in all 242 correctional facilities in South Africa, the NHLS is working in partnership with the Department of Correctional Services (DCS), NDoH, Aurum Institute, TB/HIV Care Association and Right to Care to ensure access to regular HIV- and TB-related screening, testing and treatment of up to 150,000 offenders through the Global Fund programme. Xpert MTB/Rif testing is being provided either on-site, or at the nearest referral laboratory. During 2014, Xpert MTB/RIF testing facilities have been established on-site at the following Correctional Facilities:

- KgošiMampuru Management Area II
- Barberton Management Area
- Johannesburg Management Area
- Groenpunt Management Area
- Pollsmoor Management Area
- St Albans Management Area
- Durban-Westville Management Area

1.2. Peri-Mining Communities

NHLS, together with the Aurum Institute, has been appointed by NDoH (under the Global Fund grant) to provide services to implement interventions aimed at improving TB and HIV/AIDS management for vulnerable peri-mining communities (estimated at around 600,000 people) in 6 main mining districts. Six staffed and GeneXpert-equipped mobile TB units will be provided within the communities to undertake Xpert MTB/RIF testing for TB. In addition, persons newly identified as HIV-infected through the clinical partner will be staged for HIV-treatment using CD4 tests provided by the closest NHLS lab in the district. The 6 districts with a high proportion of mines in South Africa that have been identified for focused attention are:

- Lejweleputswa (Free State),
- Dr K K Kaunda & Bojanala Districts (North West),
- West Rand (Gauteng)
- Waterberg & Sekhukhune (Limpopo)



2. Assays performed to date

In summary, a total of 3,794,651 specimens have been processed to date (30 June 2014). In June 178,755 specimens were processed. The total % of *Mycobacterium tuberculosis* complex (MTBC) detected in this cohort was 9.93% (17,759). As a reflection of Xpert MTB/RIF's superior sensitivity over microscopy, the average national TB positivity rate among suspects was found to be 8% using microscopy but up to 16-18% in the first year and 13-14% in the second and third year, and has remained constantly around 12% in the fourth year, after introduction of Xpert® MTB/RIF assay. To date Kwa-Zulu Natal (KZN) has performed the greatest number of tests which is probably as a result of the number of instruments placed (refer to tables 1 & 2). Average Rifampicin resistance detection rates have remained around 7% since project inception (Refer to tables 3 & 4).

Table 1: GeneXpert MTB Results by province (cumulative)

Province	Year	MTB Detected	MTB Not Detected	Test Unsuccessful	Total	% MTB Detected
Eastern Cape	2011	3 295	15 341	551	19 187	17.17
Eastern Cape	2012	16 051	85 592	2 891	104 534	15.35
Eastern Cape	2013	44 578	314 296	10 045	368 919	12.08
Eastern Cape	2014	22 592	171 847	4 048	198 487	11.38
Free State	2011	2 806	14 568	33	17 407	16.12
Free State	2012	11 615	77 012	280	88 907	13.06
Free State	2013	14 844	140 297	1 312	156 453	9.49
Free State	2014	6 662	63 227	650	70 539	9.44
Gauteng	2011	3 752	23 820	583	28 155	13.33
Gauteng	2012	12 680	84 598	2 569	99 847	12.70
Gauteng	2013	33 241	230 727	8 540	272 508	12.20
Gauteng	2014	18 912	151 146	4 323	174 381	10.85
Kwa-Zulu Natal	2011	11 579	44 638	1 647	57 864	20.01
Kwa-Zulu Natal	2012	23 922	135 810	5 913	165 645	14.44
Kwa-Zulu Natal	2013	43 051	297 748	15 428	356 227	12.09
Kwa-Zulu Natal	2014	27 675	233 471	8 314	269 460	10.27
Limpopo	2011	1 975	17 257	174	19 406	10.18
Limpopo	2012	3 992	30 704	689	35 385	11.28
Limpopo	2013	13 969	189 190	6 215	209 374	6.67
Limpopo	2014	6 802	100 151	3 372	110 325	6.17
Mpumalanga	2011	2 622	12 653	1 104	16 379	16.01
Mpumalanga	2012	4 021	21 867	1 118	27 006	14.89



Mpumalanga	2013	10 228	62 018	2 367	74 613	13.71
Mpumalanga	2014	6 796	50 930	1 645	59 371	11.45
North West	2011	3 411	14 603	644	18 658	18.28
North West	2012	5 156	28 923	1 966	36 045	14.30
North West	2013	12 146	90 862	4 623	107 631	11.28
North West	2014	7 698	67 088	3 078	77 864	9.89
Northern Cape	2011	3 248	16 044	738	20 030	16.22
Northern Cape	2012	4 459	23 665	1 194	29 318	15.21
Northern Cape	2013	8 091	53 385	2 682	64 158	12.61
Northern Cape	2014	3 914	26 565	1 598	32 077	12.20
Western Cape	2011	2 189	9 953	44	12 186	17.96
Western Cape	2012	13 264	68 290	661	82 215	16.13
Western Cape	2013	31 649	169 782	2 922	204 353	15.49
Western Cape	2014	17 592	90 998	1 147	109 737	16.0
Total		460 477	3 229 066	105 108	3 794 651	12.1

Table 2: GeneXpert MTB Results by province (01-30 June 2014)

Province	MTB Detected	MTB Not Detected	Test Unsuccessful	Grand Total	% MTB Detected
Eastern Cape	3 284	27 963	652	31 899	10.29
Free State	862	8 229	90	9 181	9.39
Gauteng	2 733	24 029	500	27 262	10.02
Kwa-Zulu Natal	4 332	40 735	1 288	46 355	9.35
Limpopo	988	16 989	550	18 527	5.33
Mpumalanga	1 109	9 356	280	10 745	10.32
North West	1 135	9 628	262	11 025	10.29
Northern Cape	555	3 854	214	4 623	12.01
Western Cape	2 761	16 220	157	19 138	14.43
Grand Total	17 759	157 003	3 993	178 755	9.93



Table 3: Provincial GeneXpert RIF Results in MTB detected cases (01-30 June 2014)

Province	Inconclusive	Resistant	Sensitive	No Rif Results	Grand Total	% Rif Resistance
Eastern Cape	117	193	2 971	3	3 284	5.88
Free State	31	48	782	1	862	5.57
Gauteng	54	144	2 534	1	2 733	5.27
Kwa-Zulu Natal	124	408	3 786	14	4 332	9.42
Limpopo	22	50	915	1	988	5.06
Mpumalanga	55	104	950		1 109	9.38
North West	39	58	1 037	1	1 135	5.11
Northern Cape	13	23	517	2	555	4.14
Western Cape	67	133	2 561		2 761	4.82
Grand Total	522	1 161	16 053	23	17 759	6.54

Table 4: Provincial GeneXpert RIF Results in MTB detected cases (cumulative)

Province	Year	Inconclusive	Resistant	Sensitive	No RIF Result	Total	% RIF Resistant
Eastern Cape	2011	33	251	2 955	56	3 295	7.62
Eastern Cape	2012	213	1 097	14 603	138	16 051	6.83
Eastern Cape	2013	1 257	2 923	40 239	159	44 578	6.56
Eastern Cape	2014	659	1 385	20 522	26	22 592	6.13
Free State	2011	28	152	2 625	1	2 806	5.42
Free State	2012	162	735	10 692	26	11 615	6.33
Free State	2013	377	814	13 631	22	14 844	5.48
Free State	2014	226	390	6 043	3	6 662	5.85
Gauteng	2011	29	218	3 504	1	3 752	5.81
Gauteng	2012	159	874	11 566	81	12 680	6.89
Gauteng	2013	974	2 107	30 085	75	33 241	6.34
Gauteng	2014	465	1 172	17 255	20	18 912	6.20
Kwa-Zulu Natal	2011	106	879	10 537	57	11 579	7.59
Kwa-Zulu Natal	2012	417	2 164	21 089	252	23 922	9.05
Kwa-Zulu Natal	2013	1 093	3 756	37 767	435	43 051	8.72
Kwa-Zulu Natal	2014	887	2 507	24 144	137	27 675	9.06
Limpopo	2011	25	148	1 777	25	1 975	7.49
Limpopo	2012	52	267	3 598	75	3 992	6.69
Limpopo	2013	302	724	12 833	110	13 969	5.18
Limpopo	2014	160	338	6 286	18	6 802	4.97
Mpumalanga	2011	30	207	2 379	6	2 622	7.89
Mpumalanga	2012	57	401	3 487	76	4 021	9.97



Mpumalanga	2013	235	1 017	8 947	29	10 228	9.94
Mpumalanga	2014	217	650	5 924	5	6 796	9.56
North West	2011	39	301	3 067	4	3 411	8.82
North West	2012	66	390	4 687	13	5 156	7.56
North West	2013	283	673	11 165	25	12 146	5.54
North West	2014	246	415	7 033	4	7 698	5.39
Northern Cape	2011	29	204	3 011	4	3 248	6.28
Northern Cape	2012	64	275	4 109	11	4 459	6.17
Northern Cape	2013	180	431	7 190	290	8 091	5.33
Northern Cape	2014	119	193	3 593	9	3 914	4.93
Western Cape	2011	15	107	2 066	1	2 189	4.89
Western Cape	2012	150	666	12 445	3	13 264	5.02
Western Cape	2013	711	1 589	29 347	2	31 649	5.02
Western Cape	2014	359	947	16 285	1	17 592	5.38
Total		10 424	31 367	416 486	2 200	460 477	6.81

3. Rif Concordance

Rifampicin concordance is good for both LPA and culture. The data is skewed by reporting the GeneXpert immediately, but still have to wait for MGIT and LPA results.

Table 5: Rif Concordance by LPA or DST

		GeneXpert Confirmation & Rif Concordance									
Province	Rif Resistant Cases	Cultures					LPA				
		Confirmed		Rif Concordance		Pre-analytical	Confirmed		Rif Concordance		Indeterminate
		#	%	#	%		#	%	#	%	
Eastern Cape	4 511	133	2.9%	78	58.6%	3	963	21%	661	68.6%	2
Free State	1 614	130	8.1%	71	54.6%	0	500	31%	393	78.6%	123
Gauteng	3 325	136	4.1%	98	72.1%	4	731	22%	643	88.0%	16
Kwazulu-Natal	7 504	1 676	22.3%	1 548	92.4%	0	1 544	21%	1 337	86.6%	42
Limpopo	1 157	79	6.8%	61	77.2%	1	234	20%	178	76.1%	1
Mpumalanga	1 812	376	20.8%	365	97.1%	0	606	33%	523	86.3%	3
North West	1 748	75	4.3%	43	57.3%	0	450	26%	241	53.6%	14
Northern Cape	839	149	17.8%	104	69.8%	4	275	33%	204	74.2%	22
Western Cape	2 648	61	2.3%	13	21.3%	1	2 009	76%	1 825	90.8%	2
National	25 158	2 815	11.2%	2 381	84.6%	13	7 312	29%	6 005	82.1%	225



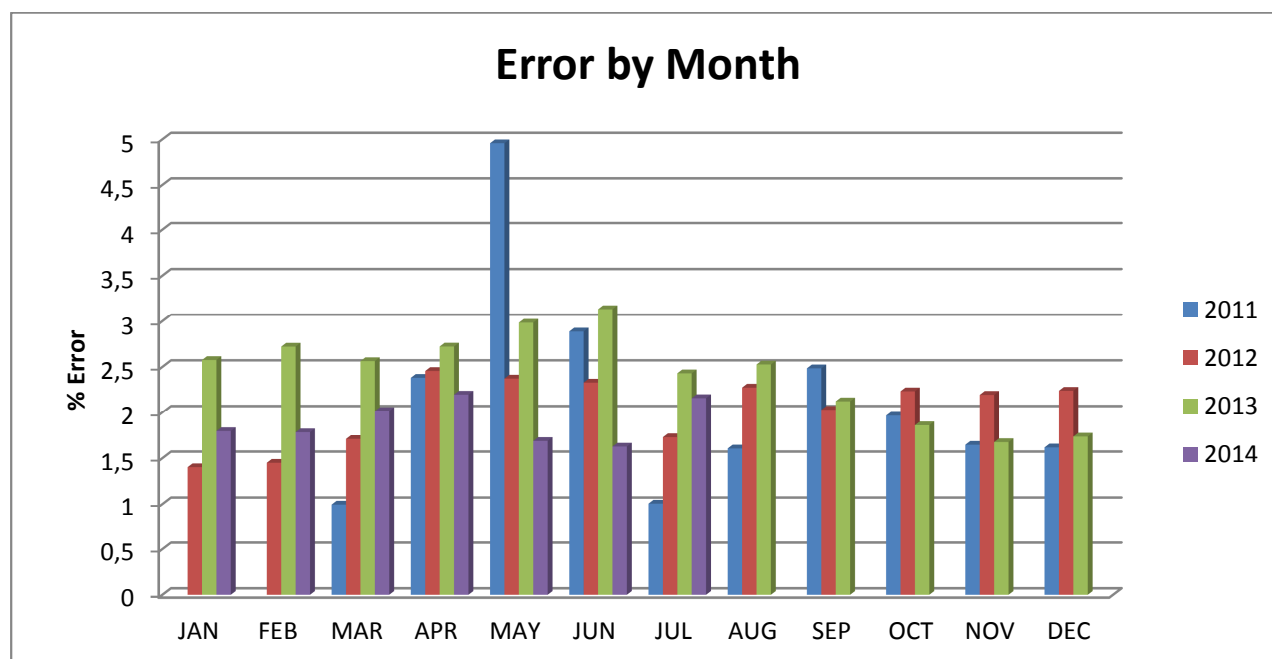
4. Errors

Average error rate has ranged consistently below 3% and none of the provinces reported error rates above 3%. Details of the invalid results, which likely represent sample issues remains below 1%. These are being monitored regularly and corrective action implemented where necessary.

Table 6: Number of Unsuccessful Tests and Reasons (1-30 June 2014)

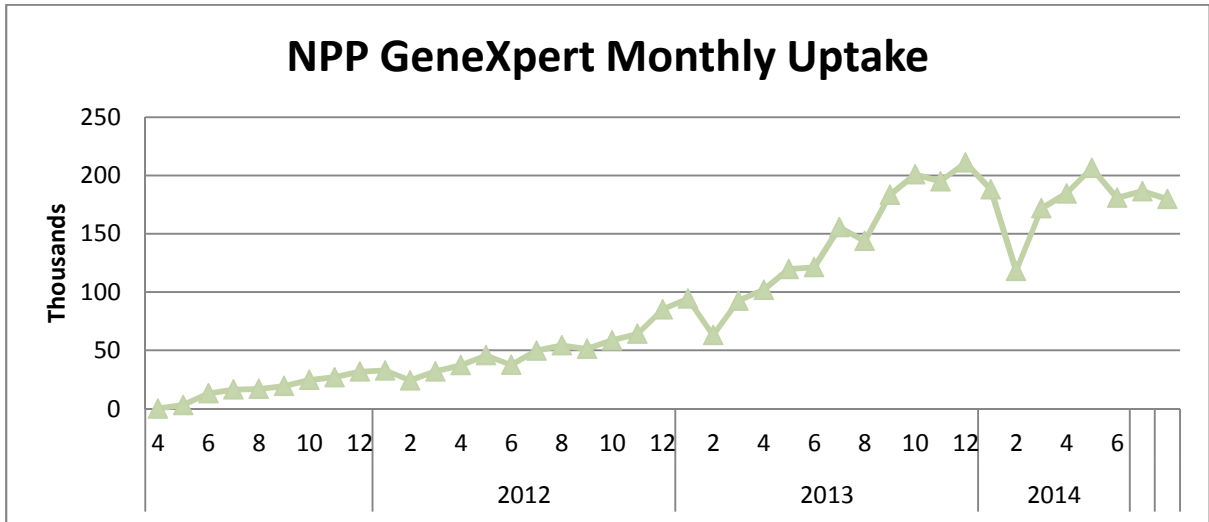
Province	ERRORS	INVALIDS	NO RESULTS	MTB Results	Grand Total	% Error
Eastern Cape	487	122	43	31 395	32 047	1.52
Free State	48	19	23	9 131	9 221	0.52
Gauteng	345	105	50	26 867	27 367	1.26
Kwa-Zulu Natal	988	207	93	45 215	46 503	2.12
Limpopo	399	129	22	18 047	18 597	2.15
Mpumalanga	213	33	34	10 510	10 790	1.97
North West	216	23	23	10 833	11 095	1.95
Northern Cape	98	110	6	4 429	4 643	2.11
Western Cape	113	29	14	19 295	19 451	0.58
Grand Total	2 907	777	308	175 722	179 714	1.62

Figure 1: GeneXpert Error by Month



5. Monthly uptake since implementation started

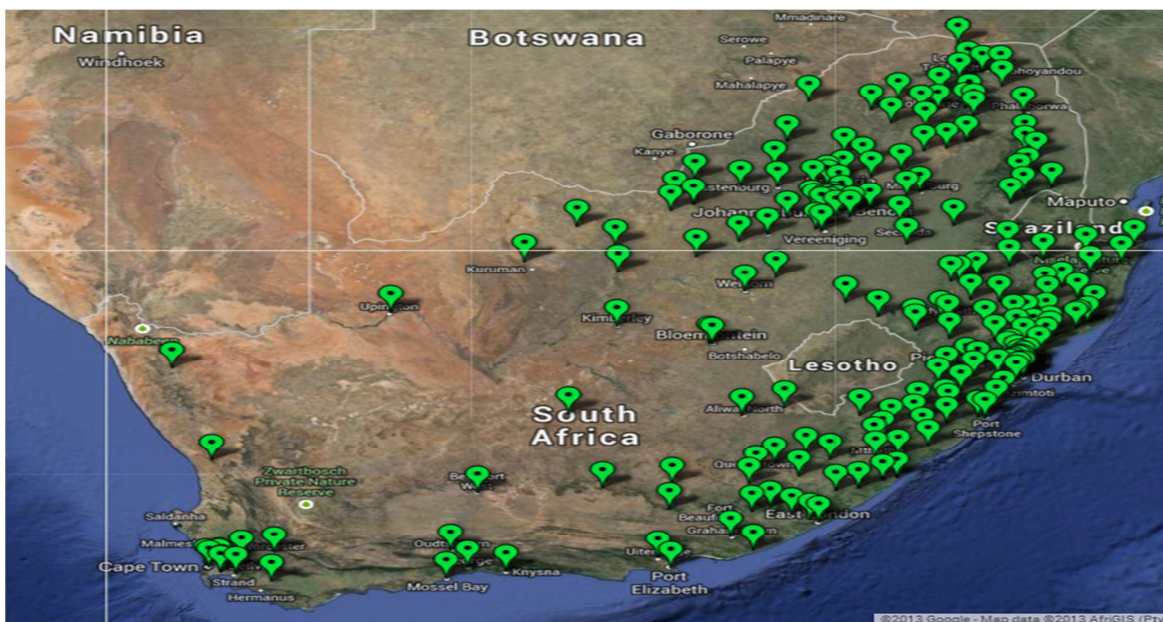
Figure 2: GeneXpert Monthly Uptake



Monthly uptake increased steadily since program inception. The main reason for interruptions is due to the variation in work practices which is expected during the December period.

6. Phased Implementation Progress

Figure 3: Current GeneXpert Placement (207 testing centers, 295analysers, Gx4: 98; Gx16-8: 1; Gx16: 188; GX48:1; GX80-80: 7) *20 clinic placements *7 Correctional Facilities



10 Disclaimer: This is a dynamic specimen dataset requiring regular update and it should be noted that figures may change as linkages to individuals tested are updated.



7. Training: Laboratory and Clinical

A total of 1,136 laboratory staff and 6,395 health care workers have been trained since December 2011. This will be an ongoing process to support NDoH training on clinical algorithm. Laboratory staff received both clinical and technical training.

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

- Rollout of EGK to avoid duplications
- Implementing WHO recommended guidelines for Xpert testing on EPTB and paediatric samples: being addressed
- Hospital staff not complying to the GXP testing algorithm because trainings has not been conducted in most of the hospitals- being addressed
- Staff rotation in hospital wards posing a challenge in the implementation and compliance to the TB algorithms resulting to delay in initiating patients on TB Treatment
- Delays in installation of some equipment, renovations and cabling to allow for network installations which hampered the ‘go live’ date of four correctional facilities namely St Albans Management Area, Durban-Westville Management Area, Barberton Management Area and Groenpunt Management Area. All sites will be up and running by the 01 August 2014.

9. Literature Update For GeneXpert

There has been an expansion of the literature with respect to the assay performance. The highlights are summarized in the table below:

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

Manuscript	Aim/Sample population and specimen type (n=...)	Results	
		Sensitivity	Specificity
Davis et al, Am J RespirCrit Care Med	A prospective, cross-sectional study with 2-month follow-up comparing Xpert with standard strategies for evaluating outpatients for active pulmonary TB from a low-burden country, between May 2010 and June 2011.	<ul style="list-style-type: none"> • 156 patients underwent Xpert testing. • 59 (38%) received empiric TB treatment. • 13 (8%) had culture-positive TB. • Xpert-guided management would have hypothetically decreased overtreatment by 94%, eliminating a median of 44 overtreatment days per patient and 2,169 total overtreatment days annually. 	
Pandie et al, BMC Med 2014	Evaluated the diagnostic accuracy of the XpertMTB/RIF test compared to	<ul style="list-style-type: none"> • Xpert-MTB/RIF had a sensitivity 	<ul style="list-style-type: none"> • Xpert-MTB/RIF had a specificity

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	pericardial adenosine deaminase (ADA) and unstimulated interferon-gamma (uIFN γ) in suspected Tuberculous pericarditis; n=151	of 63.8%	of 100%
		Concentration of pericardial fluid by centrifugation and using standard sample processing did not improve XpertMTB/RIF accuracy	
Kim et al, J Thoracic Dis 2014	XpertMTB/RIF assay compared to MTB nested PCR, as well as AFB smear and culture, on 198 clinical samples (160 pulmonary and 38 non-pulmonary specimens)	<ul style="list-style-type: none"> • Xpert sensitivity = 86.1% • MTB nested PCR sensitivity = 69.4% for MTB culture-positive pulmonary TB 	<ul style="list-style-type: none"> • XpertMTB/RIF specificity = 97.8% • MTB nested PCR = 94.1%

10. Update on GeneXpert Research projects:

11.1. GeneXpert Verification and EQA program using Dried Culture spots (DCS)

- Panel 2 of the 2014 EQA program has been sent to all participating NHLS sites
 - i. Submissions are still pending
 - ii. Awaiting NHLS and international site submissions. Deadline is 31 August.
- TBGxMonitor™ (www.tbgxmonitor.com) upgrade specification finalized.
 - Seriucontinue to publish updated components which are undergoing verification and validation.
 - Development validation to being from 1 September.

11.2. Connectivity solutions for the GeneXpert

- Connectivity: Collaboration with Cepheid ongoing
 - i. Remote connectivity – old dashboard still up to collect routine data.
 - ii. Awaiting feedback on the data generated from the beta trial.

11.3 mHealth solutions for MDR-TB

An mHealth project together with the John Hopkins University (JHU) group and funded through the Global Fund has commenced. It was agreed that the data sharing will be conducted through the CDW Initial review of the web-service interface being discussed. Additional options for possible mHealth applications for pilot are currently being investigated.



11. Update on other projects

Grand Challenges Canada project: Multiple POC HIV/TB integration feasibility project

Patient follow-up on the GCC randomized controlled trial is continuing: Only 10 patients on the SOC and 10 on the POC arms outstanding follow-up visits before study close.

- A full data analysis of all results has begun and will be presented at the GCC meeting in Seattle in August. This will include:
 - An analysis of clinic workflow to assess the place for POC in clinic workflow.
 - A full costing analysis of POC versus SOC by HER20.
 - A qualitative analysis of all challenges experienced in the clinics

Sub-studies within GCC

- **Evaluation of the GeneXpert to Diagnose Paediatric TB using stool specimens:** (In collaboration with David Alland and FIND). The laboratory R&D component to determine appropriate stool processing protocol has started. n=20 TB positive and n=20 TB negative specimens will be tested using various protocols before clinical component of the study.
- **Longitudinal follow up of Dried Blood Spots for viral load monitoring:** Longitudinal collection of DBS from n=100 HIV-positive patients on ARV's over 60 weeks. Outstanding final visit (V5) DBS for testing.
- **Clinic validation of EPOC Blood gas analysis system (Alere):** A new chemistry POC device has been evaluated at ThembaLethu clinic by a nurse. n=125 patients were recruited into the study. Creatinine measurements on the EPOC versus creatinine on Reflotron and routine laboratory results are being compared for precision and accuracy analysis. Study complete. Data analysis underway.
- **Development of DCS EQA for LPA:** EQA test panels consisting of DCS have been provided to 4 routine labs (x3 panels each) as a pilot evaluation of the format on the MTBDR_{plus}LPA (HainLifeScience). Results are being written up for publication. Data analysis software and automated reporting for the National LPA EQA program is under development.



- **Laboratory validation of new TB diagnostics:** 1). A validation protocol is underway for evaluation of the updated Abbott NM high throughput TB assay. The R&D component of the study has begun to assess the biosafety of the Abbott inactivation buffer. This will be followed by a clinical evaluation.
- **Laboratory validation of new HIV diagnostics:**1). A pilot to investigate the performance of the new Xpert® HIV-1 Quantassay for VL was performed on a 42 member plasma HIV-1 subtype C panel versus the CAP/CTMv2 (Roche) and RealTime HIV-1 (Abbott). 2). A laboratory validation is planned to test the Cepheid HIV-1 Quantitative VL cartridge on plasma, DBS and whole blood. Protocol under development.
- **GCC Connectivity**
 - No specific update. The connectivity solutions are not being used at present since the study is not recruiting any further patients or performing new tests.

12. Funding

Table 9: Total and Percentage Contribution to date by Donor

Donor	% Contribution
NDoH	24.04
Bill & Melinda Gates Foundation	7.20
TB Reach	1.42
MSF	0.90
FIND	0.45
USAID	2.45
CDC NHLS 2010/11	14.78
CDC NDoH	0.72
CDC NHLS 2011/12	1.39
Dr. Niebauer	0.20
Gobal Fund NDOH	40.91
Global Fund RTC	2.78
CDC NDoH	2.77
Subtotal	100

CDC has contributed 19, 65% towards the program to date.

13. Recent Campaigns

None in the month of June