NATIONAL HEALTH LABORATORY SERVICE

GeneXpert MTB/RIF

Progress Report

August 2013

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 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 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.

Since then, 278 GeneXpert instruments of varying sizes (GX4: 90; GX16:187; GX48: 2) 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.

2. Assays performed to date

In summary, a total of 1,899,822 specimens have been processed to date (31 August 2013). In August 150,941 specimens were processed. The total % of *Mycobacterium tuberculosis* complex (MTBC) detected in this cohort was 10.47% (15,806). 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,

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
	/	1			**1**	
	2011	3294	15413	555	**19 262**	**17.10**
	2012	16040	85575	2892	**104 507**	**15.35**
Eastern Cape	2013	26187	179185	6388	**211 760**	**12.37**
	2011	2844	14830	33	**17 707**	**16.06**
	2012	11631	77087	280	**88 998**	**13.07**
Free State	2013	9102	85811	746	**95 659**	**9.52**
	2011	3116	19017	424	**22 557**	**13.81**
	2012	11057	72748	2285	**86 090**	**12.84**
Gauteng	2013	16609	118294	5173	**140 076**	**11.86**
	/	11	33	1	**45**	
	2011	12215	45911	1729	**59 855**	**20.41**
	2012	24446	138967	6116	**169 529**	**14.42**
Kwa-Zulu Natal	2013	24626	167258	10217	**202 101**	**12.18**
	2011	1975	17261	172	**19 408**	**10.18**
	2012	3993	30710	688	**35 391**	**11.28**
Limpopo	2013	8274	110835	4205	**123 314**	**6.71**
	2011	2639	12763	1107	**16 509**	**15.99**
	2012	4044	21959	1118	**27 121**	**14.91**
Mpumalanga	2013	4978	28774	1290	**35 042**	**14.21**
	2011	3476	14887	657	**19 020**	**18.28**
	2012	5174	29005	1976	**36 155**	**14.31**
North West	2013	7196	53950	3025	**64 171**	**11.21**
	2011	2864	16117	735	**19 716**	**14.53**
	2012	4440	23653	1192	**29 285**	**15.16**
Northern Cape	2013	4880	31281	1715	**37 876**	**12.88**
	2011	2204	10093	31	**12 328**	**17.88**
	2012	13202	68426	596	**82 224**	**16.06**
Western Cape	2013	19102	102888	2125	**124 115**	**15.39**
Total		**249 620**	**1 592 731**	**57 471**	**1 899 822**	**13.14**

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Table 2: GeneXpert MTB Results by province (01-31 August 2013)

Province	MTB Detected	MTB Not Detected	Test Unsuccessful	Grand Total	% MTB Detected
Eastern Cape	3 035	24 451	888	28 374	10.70
Free State	942	10 619	76	11 637	8.09
Gauteng	2 268	16 859	590	19 717	11.50
Kwa-Zulu Natal	3 562	26 630	1 680	31 872	11.18
Limpopo	942	18 692	550	20 184	4.67
Mpumalanga	844	5 620	253	6 717	12.57
North West	885	7 453	330	8 668	10.21
Northern Cape	506	3 744	213	4 463	11.34
Western Cape	2 822	16 144	343	19 309	14.61
Grand Total	**15 806**	**130 212**	**4 923**	**150 941**	**10.47**

Table 3: Provincial GeneXpert RIF Results in MTB detected cases (01-31 August 2013)

Province	Inconclusive	Resistant	Sensitive	No Results	Grand Total	% Rif Resistance
Eastern Cape	130	197	2 704	4	3 035	6.49
Free State	36	50	854	2	942	5.31
Gauteng	90	144	2 034		2 268	6.35
Kwa-Zulu Natal	150	305	3 064	43	3 562	8.56
Limpopo	41	42	852	7	942	4.46
Mpumalanga	17	82	744	1	844	9.72
North West	24	41	820		885	4.63
Northern Cape	19	23	464		506	4.55
Western Cape	109	130	2 583		2 822	4.61
Grand Total	**616**	**1 014**	**14 119**	**57**	**15 806**	**6.42**

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

Province	Year	Inconclusive	Resistant	Sensitive	No RIF Result	Total	% RIF Resistant
	/			1		**1**	
	2011	33	251	2957	53	**3 294**	**7.62**
	2012	213	1096	14597	134	**16 040**	**6.83**
Eastern Cape	2013	670	1778	23618	121	**26 187**	**6.79**
	2011	28	154	2661	1	**2 844**	**5.41**
	2012	162	736	10707	26	**11 631**	**6.33**
Free State	2013	213	517	8358	14	**9 102**	**5.68**
	2011	27	177	2911	1	**3 116**	**5.68**
	2012	137	765	10085	70	**11 057**	**6.92**
Gauteng	2013	406	1089	15088	26	**16 609**	**6.56**
	/		2	9		**11**	
	2011	107	921	11125	62	**12 215**	**7.54**
	2012	434	2207	21553	252	**24 446**	**9.03**
Kwa-Zulu Natal	2013	602	2133	21733	158	**24 626**	**8.66**
	2011	25	148	1777	25	**1 975**	**7.49**
	2012	52	267	3599	75	**3 993**	**6.69**
Limpopo	2013	207	450	7530	87	**8 274**	**5.44**
	2011	31	210	2392	6	**2 639**	**7.96**
	2012	57	407	3504	76	**4 044**	**10.06**
Mpumalanga	2013	101	552	4305	20	**4 978**	**11.09**
	2011	40	304	3128	4	**3 476**	**8.75**
	2012	66	390	4704	14	**5 174**	**7.54**
North West	2013	153	403	6611	29	**7 196**	**5.60**
	2011	28	197	2637	2	**2 864**	**6.88**
	2012	64	273	4093	10	**4 440**	**6.15**
Northern Cape	2013	96	254	4245	285	**4 880**	**5.20**
	2011	15	106	2082	1	**2 204**	**4.81**
	2012	150	657	12393	2	**13 202**	**4.98**
Western Cape	2013	412	948	17741	1	**19 102**	**4.96**
Total		**4 529**	**17 392**	**226 144**	**1 555**	**249 620**	**6.97**

3. Rif Condordance

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

Province	Rif Resistant Cases	GeneXpert Confirmation & Rif Concordance								
		MGIT				LPA				
		Confirmed		Rif Concordance		Confirmed		Rif Concordance		Inderterminate
		#	%	#	%	#	%	#	%	
Eastern Cape	2,500	40	1.6%	13	32.5%	222	9%	209	94.1%	1
Free State	1,105	51	4.6%	24	47.1%	230	21%	187	81.3%	45
Gauteng	1,729	68	3.9%	48	70.6%	328	19%	303	92.4%	9
Kwazulu-Natal	4,104	824	20.1%	781	94.8%	806	20%	719	89.2%	26
Limpopo	686	32	4.7%	27	84.4%	94	14%	68	72.3%	0
Mpumalanga	905	157	17.3%	152	96.8%	235	26%	210	89.4%	2
North West	714	33	4.6%	26	78.8%	133	19%	123	92.5%	8
Northern Cape	561	53	9.4%	38	71.7%	98	17%	81	82.7%	10
Western Cape	1,359	21	1.5%	2	0.0%	976	72%	927	95.0%	4
National	13,663	1,279	9.4%	1,111	86.9%	3,122	23%	2,827	90.6%	105

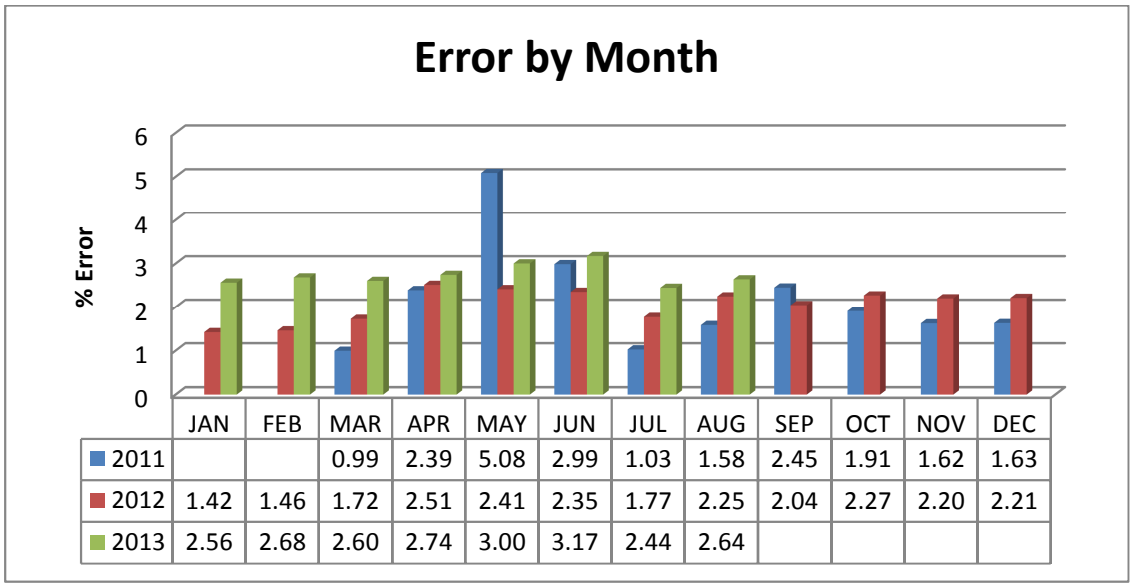
4. Errors

Average error rate has ranged consistently below 3%, however 2/9 provinces reported error rates above 3% in the month of August. Fewer laboratories reported an increase in the number of errors due to hardware failures of the modules. 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 (1-31 August 2013)

Province	ERR	INV	NORES	MTB Results	Grand Total	% Error
Eastern Cape	742	73	73	27 497	28 385	2.61
Free State	62	11	3	11 564	11 640	0.53
Gauteng	518	55	17	19 132	19 722	2.63
Kwa-Zulu Natal	1 430	166	84	30 235	31 915	4.48
Limpopo	420	101	29	19 636	20 186	2.08
Mpumalanga	180	65	8	6 467	6 720	2.68
North West	275	37	18	8 340	8 670	3.17
Northern Cape	73	140		4 250	4 463	1.64
Western Cape	283	41	19	19 136	19 479	1.45
Grand Total	**3 983**	**689**	**248**	**146 257**	**151 180**	**2.63**

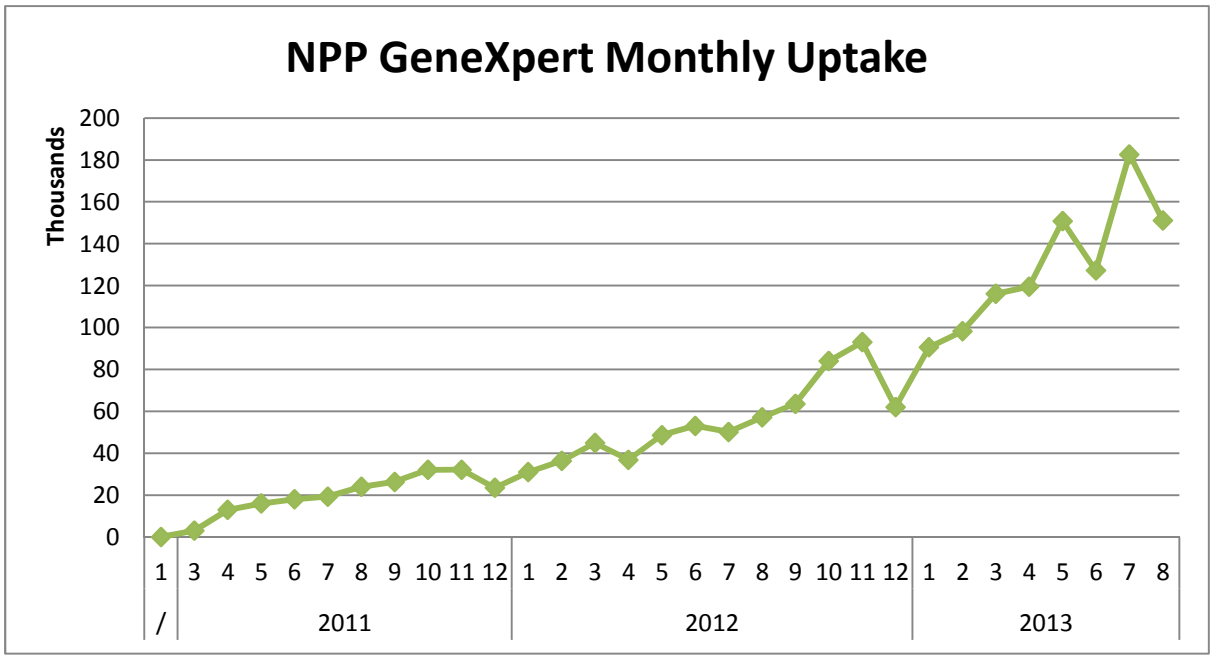
Figure 1: GeneXpert Error by Month



	JAN	FEB	MAR	APR	MAY	JUN	JUL	AUG	SEP	OCT	NOV	DEC
2011			0.99	2.39	5.08	2.99	1.03	1.58	2.45	1.91	1.62	1.63
2012	1.42	1.46	1.72	2.51	2.41	2.35	1.77	2.25	2.04	2.27	2.20	2.21
2013	2.56	2.68	2.60	2.74	3.00	3.17	2.44	2.64				

5. Monthly uptake since implementation started

Figure 2: GeneXpert Monthly Uptake



Monthly uptake increased steadily since program inception. There was a significant decrease in the number of tests conducted in the month of August. The cause is being investigated. The main reason for interruptions is due to the variation in work practices which is expected during the December

period. In addition, there was a global shortage in the supply of Xpert MTB/RIF® cartridges in the months of July, October and November 2012. This was resolved in December 2012. Another shortage was experienced in March. The stock supply was stabilized in April. In addition Cepheid re-introduced the supply of 50 kit cartridges to high volume sites.

6. Further project phases as defined in the NTCM model

Phase I completed and reported on in the section above.

Phase IIa involves full capacitation of existing labs: Completed

Phase IIb: Full capacitation of high burden districts. Completed

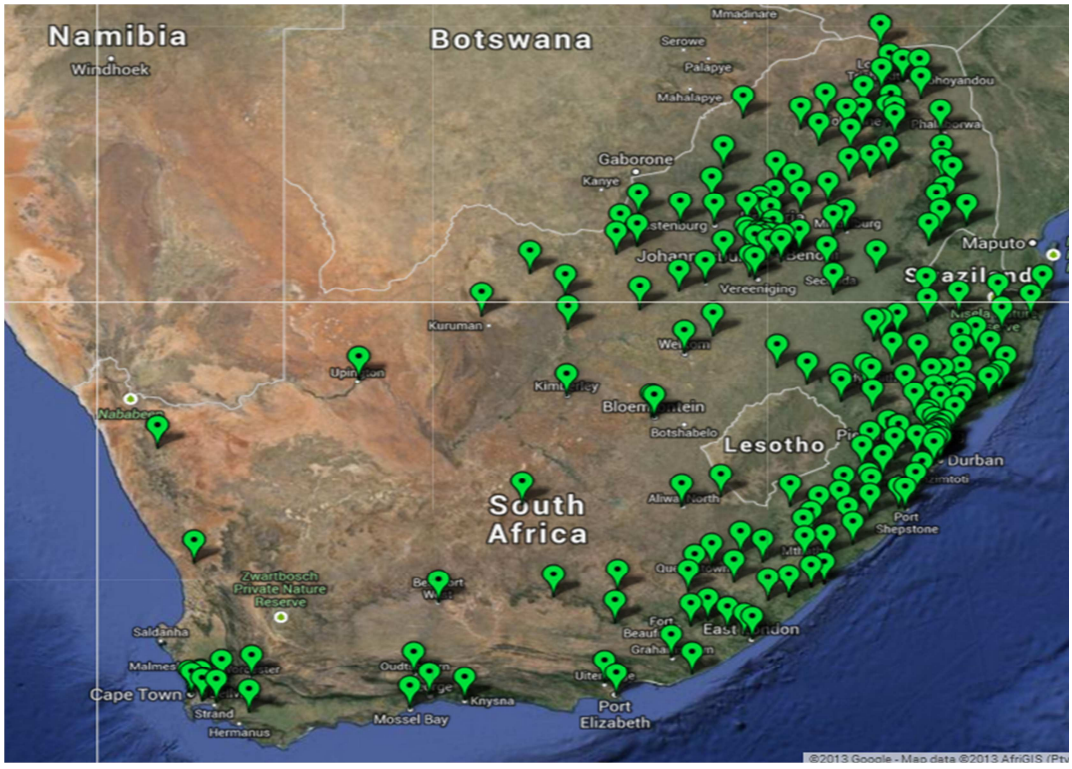
Phase IIIa and b: Gates funded study (Gauteng, EC and Free State). Completed

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

Phase IIId: Completion of all current microscopy and clinic sites: Completed

7. Phased Implementation Progress

Figure 3: Current GeneXpert Placement (207 testing centers, 278 **analysers, Gx4:** 90; Gx16-8: 1**; Gx16:** 186; GX48:1; Gx80-48: 1) *20 clinic placements



8. Training: Laboratory and Clinical

A total of 916 laboratory staff and 3,968 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.

9. 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
- Rollout of EGK to avoid duplications
- Multiple specimens submitted for initial diagnosis using the GeneXpert in the Free State: being addressed with the provincial coordinator.

10. 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	Sample population and specimen type (n=…)	Results	
		Sensitivity	Specificity
Gous et al, 2013 JCM	Comparison of the performance of the DCS verification program across different bulk batches, testing settings/cadre of staff and Xpert® MTB/RIF assay version	The proportion of variability (R-squared) in Ct values explained by batch =14%; by setting/cadre of staff =5.6% and by assay version =4.2%.	
Al-Darraji et al, 2013, PloS One	N=125 HIV-infected prisoners provided two early-morning sputum specimens to be examined using fluorescence smear microscopy, BACTEC MGIT 960 liquid culture and a single Xpert	53.3% (95% CI 30.12-75.2%)	100% (95% CI 96.6-100%)
Choi et al, 2013, Int J Tuberc Lung Dis.	Determined cost-effectiveness of implementing Xpert in settings with low TB prevalence, such as the United States using a decision-analysis model comparing current TB	Xpert testing of a single sputum sample from TB suspects is expected to result in lower total health care costs per patient (US2673) compared to diagnostic algorithms using only sputum microscopy	

	diagnostic algorithms in the United States to algorithms incorporating Xpert	and culture (US2728) and improved health outcomes (6.32 QALYs gained per 1000 TB suspects).
Dhana et al, 2013, BMC Case reports	Case report of a 35-year-old man presenting with dyspnoea and constitutional symptoms of tuberculosis	The new Xpert MTB/RIF (Xpert) assay detected rifampicin-sensitive Mycobacterium tuberculosis in pericardial as well as sputum samples. Smear of the pericardial sample was negative

11. Update on GeneXpert Research projects:

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

- Preparation of verification DCS for the 3rd quarter of Gx implementation are complete and in the process of being sent to sites.
- EQA Panels for round two have been sent to sites. Results are in the process of being collected
- TBGxMonitor™ (www.tbgxmonitor.com) is about to undergo an upgrade to include EQA reporting functionality for national and international EQA programs along with a minor functionality upgrade.
    - The first of the minor updates has been completed.
    - The national reporting template has been received for comment and review and the update should begin in October.

11.2. *Diagnosis of Extrapulmonary TB (EPTB) using the GeneXpert MTB/RIF*

A study to develop protocols for diagnosing EPTB from alternative specimen types has been completed. Finding showed good sensitivity for the Xpert on purulent specimens but poor sensitivity for clear watery fluids (publication under review by PLoSMedicine). Based on these findings, a new study is underway:

- To determine whether a modified GeneXpert protocol which will not involve addition of SR buffer, can be used to increase the diagnostic sensitivity of the Xpert MTB/Rif assay for clear watery fluid types among aspirates and fluids.
- To date: 42 pleural fluids/aspirates have been tested and n=17 CSF samples

11.3. *Connectivity solutions for the GeneXpert*

- Connectivity: Collaboration with Cepheid ongoing

i. Remote connectivity – System deployed on more than 110 sites and the first phase of the upgrade is completed. The site list for remaining instruments is currently being compiled to include 100% coverage of all instruments and sites.

ii. The Cepheid remote calibration is currently fully functional and sites are performing the calibration procedure without any manual uploading and retrieval of files.

12. Update on other projects

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

GCC is a three year project to investigate the feasibility of integrating multiple POC testing for HIV and TB (using the Xpert MTB/RIF test) integration of services in an active ARV treatment clinic. This will involve a randomized controlled trial at 3 clinic sites to compare standard of care and Point of care. Enrolment for the study will be completed by end of September and follow-up of patients will continue for one year.

- *Sub-studies within GCC*
    - Investigating **alternative media** (Hemaform plates, Primestore tubes and a thicker DBS cards) **for blood specimen collection/storage and transport** to centralized laboratories for VL testing: Study ongoing.
    - **Laboratory validation** of a rapid strip based test for **HIV/Syphilis** (SD Bioline): Protocol is complete/ethics has been obtained.
    - **Validation** of a new POC chemistry system. A laboratory validation of the new POC blood analysis system, the **Epoc** (Alere) will begin in Oct.
    - **Clinical validation** of nurse operated VL testing at POC: A clinical validation of the **Liat (IQuum)** POC VL instrument will begin in Oct. The objective of this validation is to ensure that a nurse can perform VL testing at POC on finger whole blood specimens. Protocol is under review.
    - **Laboratory validation of Primestore technology with flocked swabs** will be begin in Oct. The objective is to determine the ease and accuracy of flocked swab technology for collecting and transporting finger stick blood specimens for centralized VL testing.

- **Laboratory Comparison of Genotype MTBDRplus versions 1 and 2 using DCS.** This comparison will be performed using DCS material in order to determine the reproducibility of results using either version of the MTBDRplus assay. This will be initiated during October.
- **DNAGenotek Evaluation.** A novel liquification, storage and nucleic acid extraction reagent set for sputa will be evaluated in the laboratory and clinically, beginning in October.

- GCC Connectivity
  - The connectivity component has been altered to include a user-based review of both connectivity options.
  - Both AegisPOC and Conworx have been moved to a single site in the North West (Botshabelo) with a user capturing information on both systems to compare the ease of use, time of use and user preference of the systems.
  - This evaluation will form part of a review on the connectivity as part of a publication.

13. 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.

14. Recent Campaigns

None in August