NATIONAL HEALTH LABORATORY SERVICE

GeneXpert MTB/RIF

Progress Report

September 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 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, 283 GeneXpert instruments of varying sizes (GX4: 95; GX16:186; GX48: 1; GX80:1) 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 2,144,333 specimens have been processed to date (30 September 2013). In August 194,648 specimens were processed. The total % of *Mycobacterium tuberculosis* complex (MTBC) detected in this cohort was 10.95% (21,309). 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
	2011	3294	15413	556	**19 263**	**17.10**
	2012	16040	85575	2892	**104 507**	**15.35**
Eastern Cape	2013	31755	222334	7430	**261 519**	**12.14**
	2011	2844	14830	33	**17 707**	**16.06**
	2012	11631	77087	280	**88 998**	**13.07**
Free State	2013	10926	105256	918	**117 100**	**9.33**
	2011	3049	18727	424	**22 200**	**13.73**
	2012	10960	72349	2267	**85 576**	**12.81**
Gauteng	2013	20902	149289	6054	**176 245**	**11.86**
	2011	12226	45944	1730	**59 900**	**20.41**
	2012	24446	138967	6116	**169 529**	**14.42**
Kwa-Zulu Natal	2013	29876	206950	12413	**249 239**	**11.99**
	2011	1975	17261	172	**19 408**	**10.18**
	2012	3993	30710	688	**35 391**	**11.28**
Limpopo	2013	9993	141469	4936	**156 398**	**6.39**
	2011	2639	12763	1107	**16 509**	**15.99**
	2012	4044	21959	1118	**27 121**	**14.91**
Mpumalanga	2013	6650	39805	1694	**48 149**	**13.81**
	2011	3476	14887	657	**19 020**	**18.28**
	2012	5174	29005	1976	**36 155**	**14.31**
North West	2013	8828	67781	3703	**80 312**	**10.99**
	2011	2864	16117	735	**19 716**	**14.53**
	2012	4440	23653	1192	**29 285**	**15.16**
Northern Cape	2013	5899	38392	2042	**46 333**	**12.73**
	2011	2204	10093	31	**12 328**	**17.88**
	2012	13202	68427	596	**82 225**	**16.06**
Western Cape	2013	22233	119619	2348	**144 200**	**15.42**
Total		**275 563**	**1 804 662**	**64 108**	**2 144 333**	**12.85**

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Table 2: GeneXpert MTB Results by province (01-30 September 2013)

Province	MTB Detected	MTB Not Detected	Test Unsuccessful	Grand Total	% MTB Detected
Eastern Cape	4 298	32 428	795	37 521	11.45
Free State	1 354	14 118	121	15 593	8.68
Gauteng	3 362	23 715	647	27 724	12.13
Kwa-Zulu Natal	4 526	33 948	1 783	40 257	11.24
Limpopo	1 326	23 094	498	24 918	5.32
Mpumalanga	1 269	8 385	265	9 919	12.79
North West	1 245	10 415	495	12 155	10.24
Northern Cape	770	5 286	220	6 276	12.27
Western Cape	3 159	16 899	227	20 285	15.57
Grand Total	**21 309**	**168 288**	**5 051**	**194 648**	**10.95**

Table 3: Provincial GeneXpert RIF Results in MTB detected cases (01-30 September 2013)

Province	Inconclusive	Resistant	Sensitive	No Rif Results	Grand Total	% Rif Resistant
Eastern Cape	187	242	3 868	1	4 298	5.63
Free State	85	78	1 191		1 354	5.76
Gauteng	158	226	2 968	10	3 362	6.72
Kwa-Zulu Natal	160	407	3 908	51	4 526	8.99
Limpopo	33	72	1 212	9	1 326	5.43
Mpumalanga	52	110	1 107		1 269	8.67
North West	49	66	1 130		1 245	5.30
Northern Cape	37	42	689	2	770	5.45
Western Cape	137	184	2 838		3 159	5.82
Grand Total	**898**	**1 427**	**18 911**	**73**	**21 309**	**6.70**

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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
	2011	33	251	2957	53	**3 294**	**7.62**
	2012	213	1096	14597	134	**16 040**	**6.83**
Eastern Cape	2013	908	2114	28609	124	**31 755**	**6.66**
	2011	28	154	2661	1	**2 844**	**5.41**
	2012	162	736	10707	26	**11 631**	**6.33**
Free State	2013	316	626	9969	15	**10 926**	**5.73**
	2011	25	174	2849	1	**3 049**	**5.71**
	2012	135	760	9995	70	**10 960**	**6.93**
Gauteng	2013	603	1366	18895	38	**20 902**	**6.54**
	2011	107	923	11134	62	**12 226**	**7.55**
	2012	434	2207	21553	252	**24 446**	**9.03**
Kwa-Zulu Natal	2013	795	2612	26260	209	**29 876**	**8.74**
	2011	25	148	1777	25	**1 975**	**7.49**
	2012	52	267	3599	75	**3 993**	**6.69**
Limpopo	2013	256	541	9101	95	**9 993**	**5.41**
	2011	31	210	2392	6	**2 639**	**7.96**
	2012	57	407	3504	76	**4 044**	**10.06**
Mpumalanga	2013	169	689	5771	21	**6 650**	**10.36**
	2011	40	304	3128	4	**3 476**	**8.75**
	2012	66	390	4704	14	**5 174**	**7.54**
North West	2013	222	493	8084	29	**8 828**	**5.58**
	2011	28	197	2637	2	**2 864**	**6.88**
	2012	64	273	4093	10	**4 440**	**6.15**
Northern Cape	2013	140	308	5164	287	**5 899**	**5.22**
	2011	15	106	2082	1	**2 204**	**4.81**
	2012	150	657	12393	2	**13 202**	**4.98**
Western Cape	2013	549	1129	20554	1	**22 233**	**5.08**
Total		**5 623**	**19 138**	**249 169**	**1 633**	**275 563**	**6.95**

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

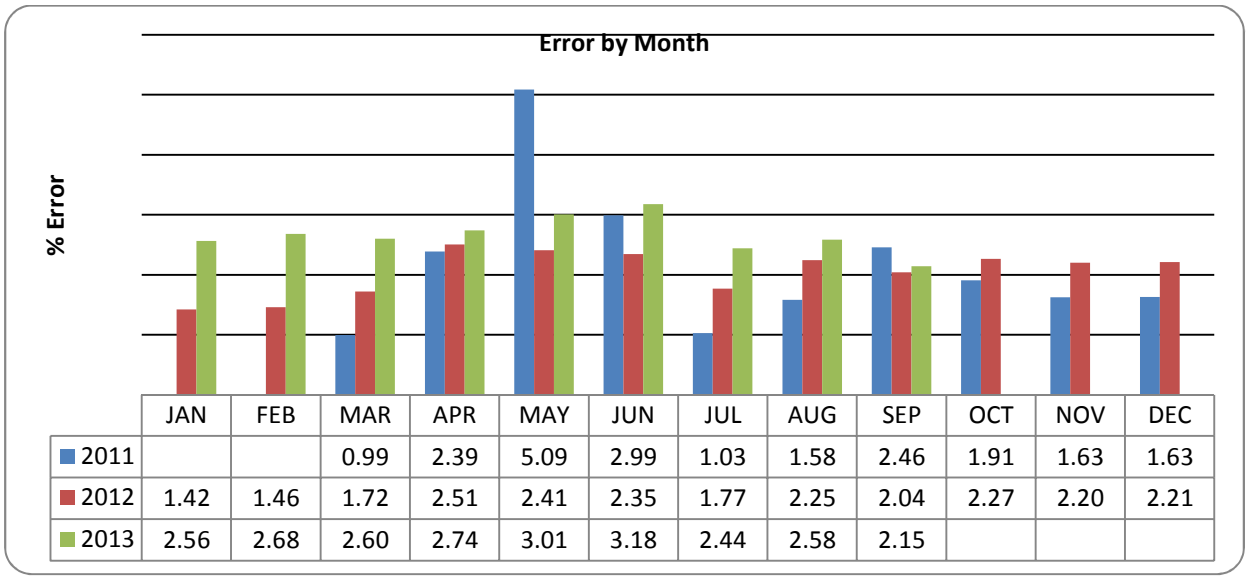
4. Errors

Average error rate has ranged consistently below 3%, however 2/9 provinces reported error rates above 3% in the month of September. 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 (1-30 September 2013)

Province	ERR	INV	NORES	MTB Results	Grand Total	% Error
Eastern Cape	656	89	50	36756	37551	1.75
Free State	116	4	1	15476	15597	0.74
Gauteng	539	79	29	27112	27759	1.94
Kwa-Zulu Natal	1477	206	100	38558	40341	3.66
Limpopo	405	69	24	24424	24922	1.63
Mpumalanga	206	52	7	9656	9921	2.08
North West	430	57	8	11660	12155	3.54
Northern Cape	91	127	2	6057	6277	1.45
Western Cape	204	17	5	20438	20664	0.99
Grand Total	**4124**	**700**	**226**	**190137**	**195187**	**2.11**

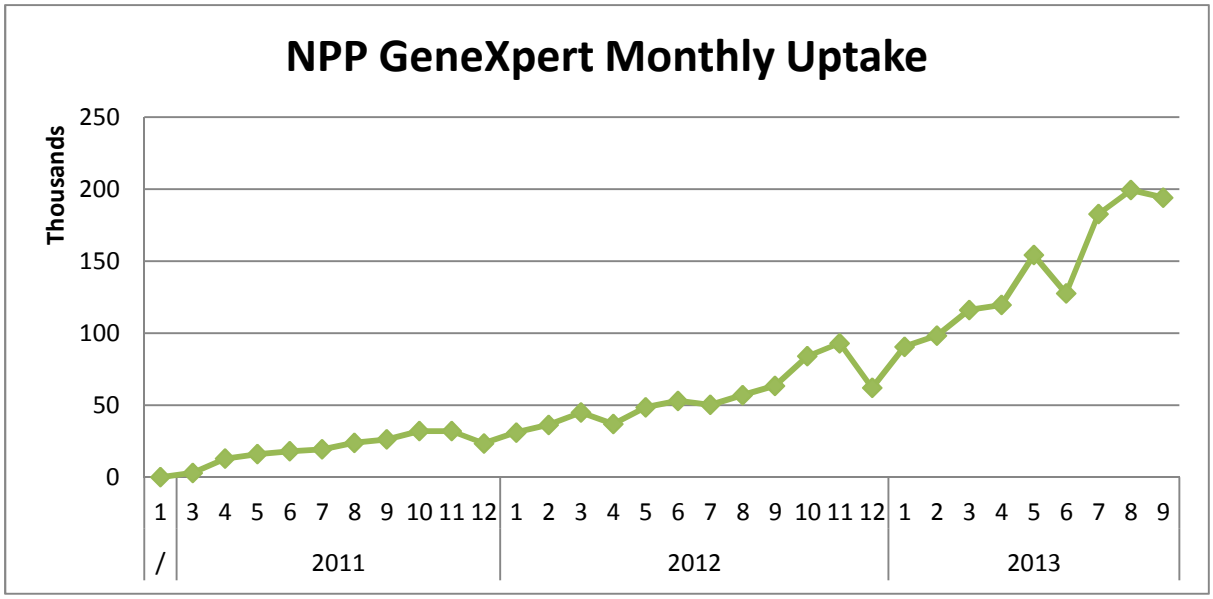
Figure 1: GeneXpert Error by Month



	JAN	FEB	MAR	APR	MAY	JUN	JUL	AUG	SEP	OCT	NOV	DEC
2011			0.99	2.39	5.09	2.99	1.03	1.58	2.46	1.91	1.63	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	3.01	3.18	2.44	2.58	2.15			

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.

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

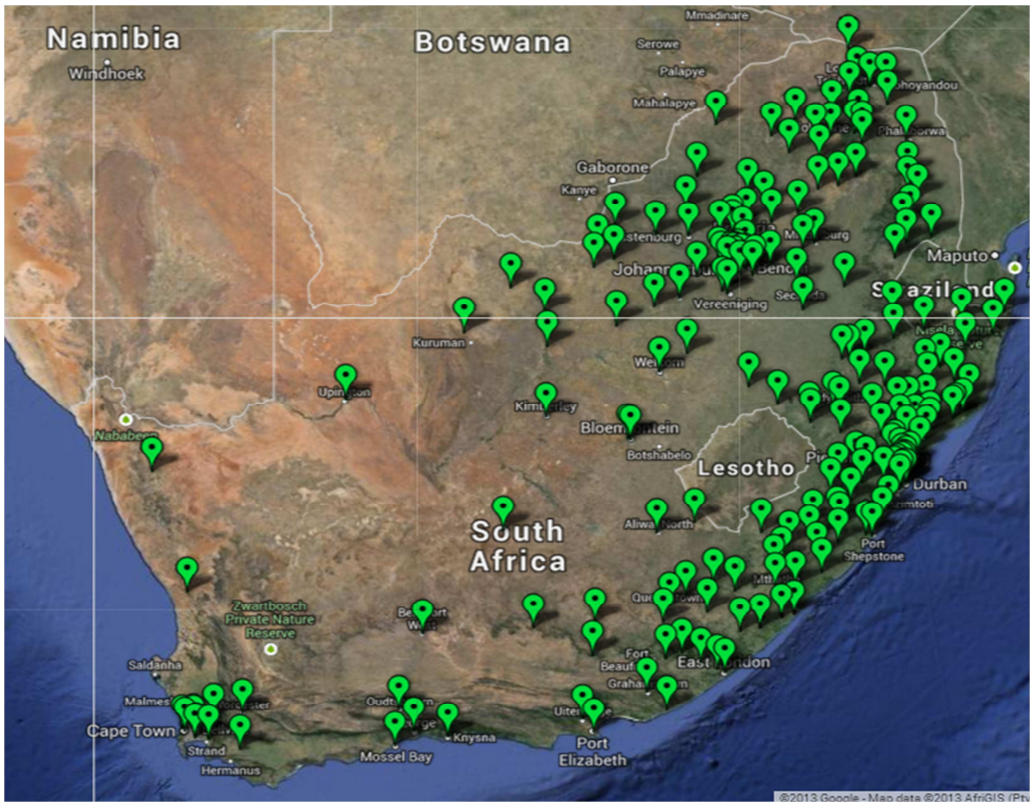
Phase IIIa and b: Gates funded study (Gauteng, EC and Free State). Completed

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, 283 **analysers, Gx4:** 95; Gx16-8: 1**; Gx16:** 185; GX48:1; GX80-80: 1) *20 clinic placements



8. Training: Laboratory and Clinical

A total of 943 laboratory staff and 4,601 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	Aim/Sample population and specimen type (n=…)	Results	
		Sensitivity	Specificity
Asencio Egea et al, 2013 Rev Esp Salud Publica (abstract only)	To estimate the economic and health care impact after the introduction of the Xpert MTB/RIF® assay	Estimated a minimum cost of 3217 euros per False positive Each False negative required an extension of hospitalization from 7 days on average (62229 euros) FP and FN translated into a global cost of 62229 euros. Hospital would have saved 45979 euros overall in five years	
Shenai et al, 2013, JCM	N=26 Exhaled breath condensate (EBC) N=26 saliva N=26 urine N=24 blood	Sensitivity: EBC = 0.0% saliva = 38.5% urine =3.8% blood =8.3%	
Jafari et al, 2013, Int J Tuberc Lung Dis. 2013	Xpert and (bronchoalveolar lavage) BAL T-SPOT tests were compared in 96 patients suspected of having sputum smear-negative pulmonary TB	Xpert sensitivity =60.0% in culture-confirmed cases and 42.1% in all TB patients. BAL T-SPOT sensitivity = 80.0%, in culture-confirmed cases and 89.4% in all	Xpert specificity = 97.4% in culture-confirmed cases and 97.4% in all TB patients. BAL T-SPOT specificity = 62.6% in culture-confirmed cases and 62.6% in all

		TB patients	TB patients
CDC, 2013,MMWR Morb Mortal Wkly Rep.	Centers for Disease Control and Prevention (CDC) Report on use of the Xpert MTB RIF in the US	CDC continues to recommend the Xpert MTB/RIF assay in the prompt diagnosis of TB and RMP-resistant disease	

11. Update on GeneXpert Research projects:

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

- DCS are being produced for verification of the India GeneXpert program.
- Phase 3 of the national NHLS GeneXpert EQA is being manufactured for November roll-out.
- 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 finalized and will be implemented in November along with a number of system upgrades to automate the reporting process for EQA.

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

A study 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: approximately 170 EPTB clear watery fluids have been tested.

11.3. ***Connectivity solutions for the GeneXpert***

- Connectivity: Collaboration with Cepheid ongoing
    i. Remote connectivity – System deployed on 180 instruments to date with over 1,089,000 results live on the dashboard. The NHLS are currently underway with completing the national enrolment of laboratories on the dashboard.
    ii. Cepheid are currently entering discussions with the NPP about a trial of the release version of the online dashboard which will take form in Q1 2014.

iii. 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 is complete and patients are being followed-up 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: Patient recruitment complete.
    - **Laboratory validation** of a rapid strip based test for **HIV/Syphilis** (SD Bioline):
        - n=130 syphilis samples tested
        - n=120 HIV samples tested

      Results will be compared to routine lab testing.
    - **Laboratory validation** of a new POC chemistry system the **Epoc** (Alere): Protocol complete and ethics obtained.
    - **Clinical validation** of nurse operated **Liat (IQuum)** VL testing at POC on finger stick specimens: Protocol is complete and ethics obtained. n=~50 patients have been recruited into the study and tested on-site. Awaiting laboratory VLresults for comparison.
    - **Laboratory validation of Primestore technology with flocked swabs** to determine the ease and accuracy of flocked swab technology for collecting and transporting finger stick blood specimens for centralized VL testing. Study ongoing.
    - **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 which is currently underway.
  - 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.
  - The evaluation of the captured data will take place in November and form 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