NATIONAL HEALTH LABORATORY SERVICE

GeneXpert MTB/RIF

Progress Report

January 2014

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, 286 GeneXpert instruments of varying sizes (GX4: 95; GX16:186; GX48: 1; GX80:4) 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.

2. Assays performed to date

In summary, a total of 2,815,879 specimens have been processed to date (31 January 2014). In January 171,121 specimens were processed. The total % of *Mycobacterium tuberculosis* complex (MTBC) detected in this cohort was 13.62% (23,306). 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
Eastern Cape	2011	3 295	15 483	555	**19 333**	**17.04**
	2012	16 040	85 574	2 892	**104 506**	**15.35**
	2013	43 273	301 261	9 497	**354 031**	**12.22**
	2014	4 685	24 886	562	**30 133**	**15.55**
Free State	2011	2 844	14 831	33	**17 708**	**16.06**
	2012	11 631	77 087	280	**88 998**	**13.07**
	2013	14 594	137 357	1 270	**153 221**	**9.52**
	2014	1 452	11 075	84	**12 611**	**11.51**
Gauteng	2011	3 049	18 727	424	**22 200**	**13.73**
	2012	10 960	72 367	2 267	**85 594**	**12.80**
	2013	30 677	210 756	7 583	**249 016**	**12.32**
	2014	3 440	22 414	623	**26 477**	**12.99**
Kwa-Zulu Natal	2011	12 226	45 944	1 730	**59 900**	**20.41**
	2012	24 446	138 967	6 116	**169 529**	**14.42**
	2013	43 969	304 798	16 051	**364 818**	**12.05**
	2014	5 388	36 550	1 161	**43 099**	**12.50**
Limpopo	2011	1 975	17 261	172	**19 408**	**10.18**
	2012	3 993	30 710	688	**35 391**	**11.28**
	2013	13 820	186 834	6 169	**206 823**	**6.68**
	2014	1 306	13 208	407	**14 921**	**8.75**
Mpumalanga	2011	2 639	12 763	1 107	**16 509**	**15.99**
	2012	4 044	21 959	1 118	**27 121**	**14.91**

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	2013	10 083	60 912	2 330	**73 325**	**13.75**
	2014	1 245	6 873	222	**8 340**	**14.93**
North West	2011	3 476	14 957	657	**19 090**	**18.21**
	2012	5 174	29 005	1 976	**36 155**	**14.31**
	2013	12 600	95 989	4 984	**113 573**	**11.09**
	2014	1 532	10 242	625	**12 399**	**12.36**
Northern Cape	2011	2 864	16 117	735	**19 716**	**14.53**
	2012	4 440	23 653	1 192	**29 285**	**15.16**
	2013	7 921	52 018	2 617	**62 556**	**12.66**
	2014	789	4 203	249	**5 241**	**15.05**
Western Cape	2011	2 204	10 093	31	**12 328**	**17.88**
	2012	13 202	68 252	588	**82 042**	**16.09**
	2013	31 311	168 413	2 858	**202 582**	**15.46**
	2014	3 469	14 240	191	**17 900**	**19.38**
Total		**360 056**	**2 375 779**	**80 044**	**2 815 879**	**12.79**

Table 2: GeneXpert MTB Results by province (01-31 January 2014)

Province	MTB Detected	MTB Not Detected	Test Unsuccessful	Grand Total	% MTB Detected
Eastern Cape	4 685	24 886	562	30 133	15.55
Free State	1 452	11 075	84	12 611	11.51
Gauteng	3 440	22 414	623	26 477	12.99
Kwa-Zulu Natal	5 388	36 550	1 161	43 099	12.50
Limpopo	1 306	13 208	407	14 921	8.75
Mpumalanga	1 245	6 873	222	8 340	14.93
North West	1 532	10 242	625	12 399	12.36
Northern Cape	789	4 203	249	5 241	15.05
Western Cape	3 469	14 240	191	17 900	19.38
Grand Total	**23 306**	**143 691**	**4 124**	**171 121**	**13.62**

Table 3: Provincial GeneXpert RIF Results in MTB detected cases (01-31 January 2014)

Province	Inconclusive	Resistant	Sensitive	No Rif Results	Grand Total	% Rif Resistant
Eastern Cape	81	281	4 316	7	4 685	6.00
Free State	27	91	1 334		1 452	6.27
Gauteng	70	209	3 160	1	3 440	6.08
Kwa-Zulu Natal	116	494	4 733	45	5 388	9.17
Limpopo	19	72	1 215		1 306	5.51

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Mpumalanga	22	106	1 116	1	1 245	8.51
North West	27	107	1 398		1 532	6.98
Northern Cape	11	43	733	2	789	5.45
Western Cape	54	166	3 249		3 469	4.79
Grand Total	**427**	**1 569**	**21 254**	**56**	**23 306**	**6.73**

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

Province	Year	Inclusive	Resistant	Sensitive	No Rif Results	Total	% RIF Resistant
Eastern Cape	2011	33	251	2959	53	**3 296**	**7.62**
	2012	213	1096	14597	134	**16 040**	**6.83**
	2013	1216	2843	39073	141	**43 273**	**6.57**
	2014	81	281	4316	7	**4 685**	**6.00**
Free State	2011	28	154	2661	1	**2 844**	**5.41**
	2012	162	736	10707	26	**11 631**	**6.33**
	2013	372	803	13399	20	**14 594**	**5.50**
	2014	27	91	1334		**1 452**	
Gauteng	2011	25	174	2849	1	**3 049**	**5.71**
	2012	135	760	9995	70	**10 960**	**6.93**
	2013	901	1961	27750	65	**30 677**	**6.39**
	2014	70	209	3160	1	**3 440**	**6.08**
Kwa-Zulu Natal	2011	107	923	11134	62	**12 226**	**7.55**
	2012	434	2207	21553	252	**24 446**	**9.03**
	2013	1109	3791	38647	422	**43 969**	**8.62**
	2014	116	494	4733	45	**5 388**	**9.17**
Limpopo	2011	25	148	1777	25	**1 975**	**7.49**
	2012	52	267	3599	75	**3 993**	**6.69**
	2013	297	720	12695	108	**13 820**	**5.21**
	2014	19	72	1215		**1 306**	**5.51**
Mpumalanga	2011	31	210	2392	6	**2 639**	**7.96**
	2012	57	407	3504	76	**4 044**	**10.06**
	2013	227	1000	8829	27	**10 083**	**9.92**
	2014	22	106	1116	1	**1 245**	**8.51**
North West	2011	40	304	3128	4	**3 476**	**8.75**
	2012	66	390	4704	14	**5 174**	**7.54**
	2013	290	712	11568	30	**12 600**	**5.65**
	2014	27	107	1398		**1 532**	**6.98**
Northern Cape	2011	28	197	2637	2	**2 864**	**6.88**
	2012	64	273	4093	10	**4 440**	**6.15**

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	2013	178	423	7030	290	**7 921**	**5.34**
	2014	11	43	733	2	**789**	**5.45**
Western Cape	2011	15	106	2082	1	**2 204**	**4.81**
	2012	150	657	12393	2	**13 202**	**4.98**
	2013	697	1569	29043	2	**31 311**	**5.01**
	2014	54	166	3249		**3 469**	**4.79**
Total		**7 379**	**24 651**	**326 052**	**1 975**	**356 588**	**6.91**

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									
		Cultures					LPA				
		Confirmed		Rif Concordance		Pre-analytical	Confirmed		Rif Concordance		Indeterminate
		#	%	#	%		#	%	#	%	
EC	3 814	186	4.9%	109	58.6%	0	648	17%	588	90.7%	2
FS	1 476	78	5.3%	38	48.7%	0	342	23%	233	68.1%	57
GP	2 765	99	3.6%	76	76.8%	0	425	15%	364	85.6%	7
KZN	5 318	1 227	23.1%	1 140	92.9%	0	1 247	23%	981	78.7%	40
LP	998	74	7.4%	66	89.2%	0	184	18%	123	66.8%	2
MP	1 330	232	17.4%	220	94.8%	0	355	27%	286	80.6%	3
NW	1 051	50	4.8%	40	80.0%	0	186	18%	146	78.5%	13
NC	770	65	8.4%	39	60.0%	2	146	19%	100	68.5%	11
WC	1 832	25	1.4%	3	0.0%	0	1 239	68%	1 162	93.8%	4
National	**19 354**	**2 036**	**10.5%**	**1 731**	**85.0%**	**2**	**4 772**	**25%**	**3 983**	**83.5%**	**139**

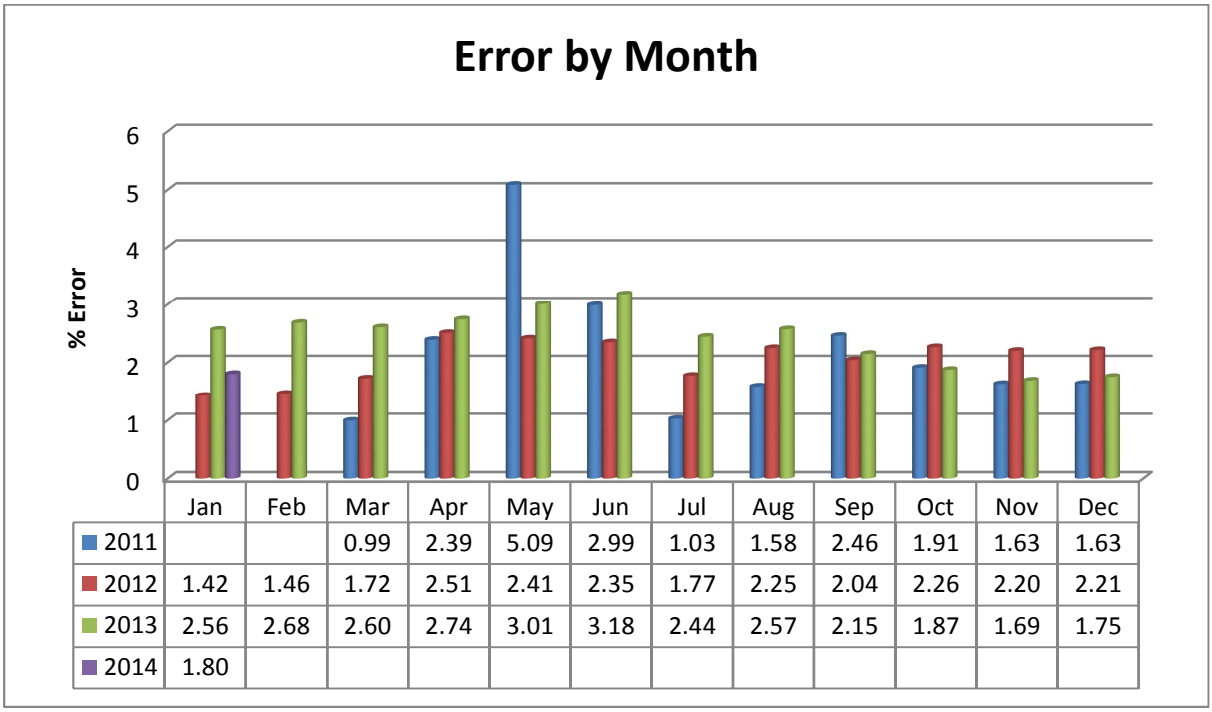
4. Errors

Average error rate has ranged consistently below 3%, however 1/9 provinces reported error rates above 3% in the month of January. 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 January 2014)

Province	ERR	INV	NORES	MTB Results	Grand Total	% Error
Eastern Cape	388	156	18	29 596	30 158	1.29
Free State	49	32	3	12 528	12 612	0.39
Gauteng	497	79	46	25 873	26 495	1.88
Kwa-Zulu Natal	904	198	59	41 944	43 105	2.10
Limpopo	312	78	17	14 514	14 921	2.09
Mpumalanga	158	47	17	8 128	8 350	1.89
North West	517	67	41	11 776	12 401	4.17
Northern Cape	96	152	1	4 992	5 241	1.83
Western Cape	159	19	12	18 406	18 596	0.86
Grand Total	**3 080**	**828**	**214**	**167 757**	**171 879**	**1.79**

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	2.26	2.20	2.21
2013	2.56	2.68	2.60	2.74	3.01	3.18	2.44	2.57	2.15	1.87	1.69	1.75
2014	1.80											

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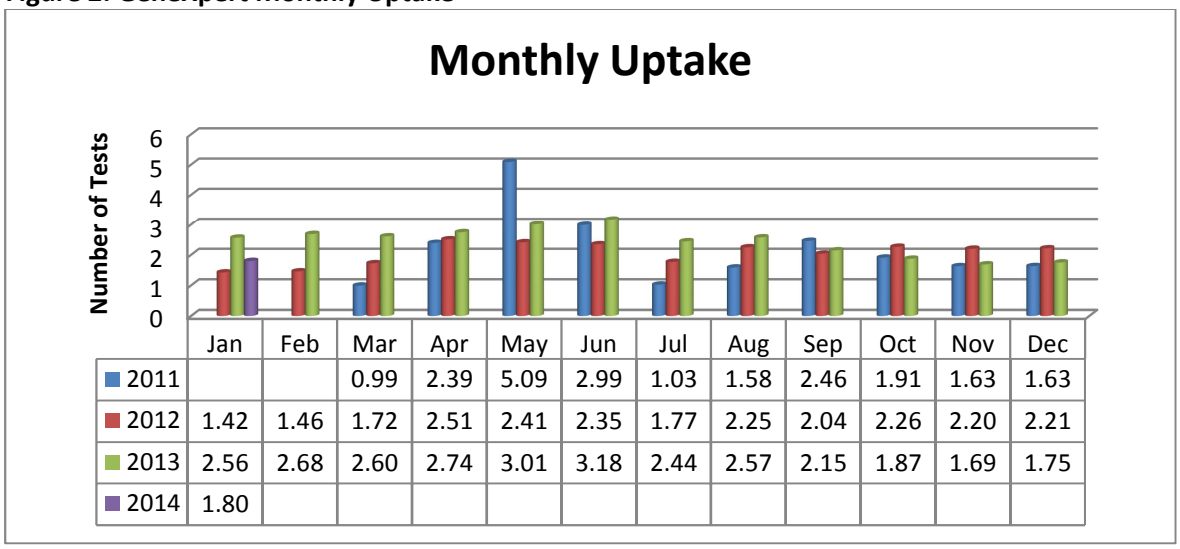
5. Monthly uptake since implementation started

Figure 2: GeneXpert Monthly Uptake

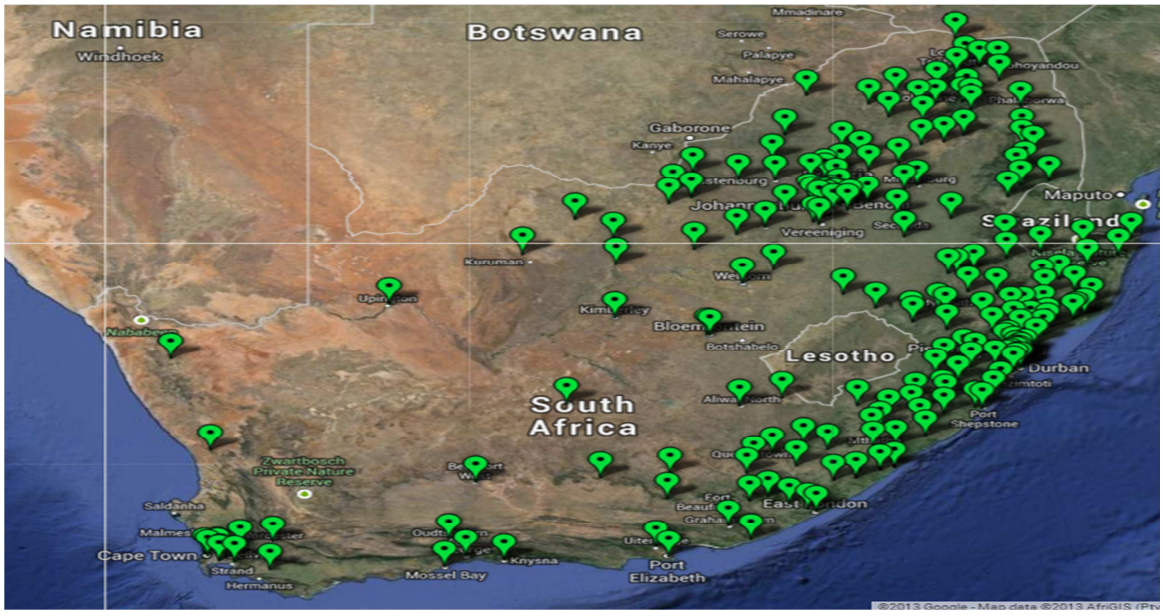


	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
2011			0.99	2.39	5.09	2.99	1.03	1.58	2.46	1.91	1.63	1.63
2012	1.42	1.46	1.72	2.51	2.41	2.35	1.77	2.25	2.04	2.26	2.20	2.21
2013	2.56	2.68	2.60	2.74	3.01	3.18	2.44	2.57	2.15	1.87	1.69	1.75
2014	1.80											

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, 285 **analysers, Gx4:** 95; Gx16-8: 1**; Gx16:** 185; GX48:1; GX80-80: 3) *20 clinic placements



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7. Training: Laboratory and Clinical

A total of 1,035 laboratory staff and 5,332 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

- 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.

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
Creswell et al, BMC Infectious Diseases, 2014	Standard quarterly reports and machine data from the first 12 months of MTB/RIF implementation in 9 TB REACH countries (is a multi-country initiative focusing on innovative ways to improve case notification) were utilized to analyze patient yields, rifampicin resistance, and failed tests	• 65 machines (196 modules) in a variety of facilities • Employed numerous case-finding strategies and testing algorithms. • The projects consumed 47,973 MTB/RIF tests. • Of valid tests, 7,195 (16.8%) were positive for MTB. • A total of 982 rifampicin resistant results were found (13.6% of positive tests). • Of all tests conducted, 10.6% failed. • Considerable heterogeneity in how results were reported and recorded	
Theron et al, Lancet Infect Dis. 2014	• Personal View: Review of emerging data for how empirical treatment is frequently same-day, and might still be the predominant form of treatment in high-burden settings, even after Xpert implementation; and how Xpert might displace so-called true-positive, rather than false-positive, empirical treatment.		

Steingart Cochrane review, 2014	A review of 27 unique studies (integrating nine new studies from 2013) involving n=9557 participants on use of Xpert MTB/RIF	• Xpert® MTB/RIF pooled sensitivity was 89%. • For rifampicin resistance detection, Xpert® MTB/RIF pooled sensitivity was 95%.	• Xpert® MTB/RIF pooled specificity was 99%. • For rifampicin resistance detection, Xpert® MTB/RIF pooled specificity was 98%.
Balcha et al, PLoS One, 2014	N=812 patients from 5 health centres in Ethiopia. Two paired morning sputum samples were obtained. Diagnostic yield of Xpert MTB/RIF in sputum was compared with smear microscopy and liquid culture.	Xpert MTB/RIF increased the TB detection rate by 64 cases (47.4%) compared with smear microscopy. The overall sensitivity of Xpert MTB/RIF was 66.4%, and was not significantly lower when testing one compared with two samples.	

10. Update on GeneXpert Research projects:

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

- Results of Phase 3 of the national NHLS GeneXpert EQA program:
- Manufacture of Phase 1 of the 2014 EQA program is due to start end Jan.
- A liquid format of the EQA material is also being investigated in terms of composition, stability and feasibility.
- In collaboration with PATH we are in the process of commercialization of the verification and EQA material for TB Xpert testing globally. This has the support of both the NHLS and the University of the Witwatersrand, the WHO and the CDC.
- TBGxMonitor™ (www.tbgxmonitor.com) upgrade specification finalized.
    - Seriun reviewing specification to provide quote on the specification.
    - Additional changes made to the specification to include GX-1 instrument
    - External review for ACTG of Investigation Report forms.

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.

- Abstract accepted to CROI.

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

- Connectivity: Collaboration with Cepheid ongoing
    i. Remote connectivity – old dashboard still up to collect routine data.
    ii. Testing of the new Cepheid Xpert Monitor is currently underway. Reviews from site and administrative users are being collected for Cepheid review of the system usability and functionality.

11. 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. As of September 2013, the recruitment target was reached and patient follow-up is continuing.

- *Sub-studies within GCC*
    - **Peadiatric stool protocol**: A study to evaluate the Xpert MTB/RIF assay on peadiatric stool specimens (In collaboration with David Alland and FIND). Protocol and ethics application development underway.
    - **Longitudinal follow up of Dried blood spots** for viral load monitoring: Longitudinal collection of DBS from n=100 HIV-positive patients over 60 weeks. Sample collection is ongoing.
    - **Investigating blood volumes obtained from finger stick**: The study is complete and a publication has been submitted to SAMJ for review.
    - **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. Patient recruitment complete, testing ongoing.
    - **Laboratory Comparison of Genotype MTBDRplus v1 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. Version 1 testing complete. Awaiting version 2 testing. Interim results submitted to SA TB conference 2014.

- GCC Connectivity
  - The captured data via **TBGxCompanion** has been cleaned based on the initial feedback from the study coordinator and sent to the HERO group for analysis. Additional data capturing and cleaning has been completed based on missing information. The data is ready for analysis.
  - The **SMS-randomization** gateway has been closed down since no further patients are being enrolled.
  - The **AegisPOC-Conworx** user evaluation and transcription error investigation has been completed on the AegisPOC data showing that manual data transcription has a high error rate. Conworx data to be evaluated.

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 January.