NATIONAL HEALTH LABORATORY SERVICE

GeneXpert MTB/RIF

Progress Report

November 2013

NATIONAL HEALTH LABORATORY SERVICE

Table of Contents

Disclaimer: This is a dynamic dataset requiring regular updating and although correct in the vast majority cases, the reader should be aware that the figures reported can change slightly as the linkages are updated

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, 284 GeneXpert instruments of varying sizes (GX4: 95; GX16:186; GX48: 1; GX80:2) 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.

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 2,465,746 specimens have been processed to date (30 November 2013). In November 154,763 specimens were processed. The total % of *Mycobacterium tuberculosis* complex (MTBC) detected in this cohort was 11.26% (17,424). 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	15 461	555	**19 311**	**17.06**
	2012	16 040	85 575	2 892	**104 507**	**15.35**
	2013	38 795	275 430	8 829	**323 054**	**12.01**
Free State	2011	2 844	14 831	33	**17 708**	**16.06**
	2012	11 631	77 087	280	**88 998**	**13.07**
	2013	13 195	126 575	1 155	**140 925**	**9.36**
Gauteng	2011	3 049	18 727	424	**22 200**	**13.73**
	2012	10 960	72 349	2 267	**85 576**	**12.81**
	2013	26 702	188 095	7 073	**221 870**	**12.03**
Kwa-Zulu Natal	2011	12 226	45 944	1 729	**59 899**	**20.41**
	2012	24 446	138 967	6 116	**169 529**	**14.42**
	2013	37 986	267 330	14 613	**319 929**	**11.87**
Limpopo	2011	1 975	17 261	172	**19 408**	**10.18**
	2012	3 993	30 710	688	**35 391**	**11.28**
	2013	12 152	170 503	5 678	**188 333**	**6.45**
Mpumalanga	2011	2 639	12 763	1 107	**16 509**	**15.99**
	2012	4 044	21 959	1 118	**27 121**	**14.91**
	2013	8 628	52 838	2 073	**63 539**	**13.58**
North West	2011	3 476	14 887	657	**19 020**	**18.28**
	2012	5 174	29 005	1 976	**36 155**	**14.31**
	2013	11 004	85 476	4 523	**101 003**	**10.89**
Northern Cape	2011	2 864	16 117	735	**19 716**	**14.53**

	2012	4 440	23 653	1 192	**29 285**	**15.16**
	2013	7 092	47 181	2 444	**56 717**	**12.50**
Western Cape	2011	2 204	10 093	31	**12 328**	**17.88**
	2012	13 202	68 428	596	**82 226**	**16.06**
	2013	28 315	154 501	2 672	**185 488**	**15.27**
Total		**312 371**	**2 081 746**	**71 628**	**2 465 745**	**12.67**

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

Province	MTB Detected	MTB Not Detected	Test Unsuccessful	Total	% MTB Detected
Eastern Cape	3 321	25 516	611	**29 448**	**11.28**
Free State	1 049	10 120	120	**11 289**	**9.29**
Gauteng	2 895	19 942	503	**23 340**	**12.40**
Kwa-Zulu Natal	3 811	29 142	990	**33 943**	**11.23**
Limpopo	990	13 156	352	**14 498**	**6.83**
Mpumalanga	899	6 274	165	**7 338**	**12.25**
North West	1 030	8 590	406	**10 026**	**10.27**
Northern Cape	568	4 258	224	**5 050**	**11.25**
Western Cape	2 861	16 813	157	**19 831**	**14.43**
Total	**17 424**	**133 811**	**3 528**	**154 763**	**11.26**

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

Province	Inconclusive	Resistant	Sensitive	No RIF Result	Total	% RIF Resistant
Eastern Cape	69	231	3 017	4	**3 321**	**6.96**
Free State	10	62	976	1	**1 049**	**5.91**
Gauteng	52	172	2 667	4	**2 895**	**5.94**
Kwa-Zulu Natal	69	300	3 407	35	**3 811**	**7.87**
Limpopo	13	46	929	2	**990**	**4.65**
Mpumalanga	11	78	805	5	**899**	**8.68**
North West	14	55	960	1	**1 030**	**5.34**
Northern Cape	7	25	536		**568**	**4.40**
Western Cape	41	129	2 691		**2 861**	**4.51**
Total	**286**	**1 098**	**15 988**	**52**	**17 424**	**6.30**

NATIONAL HEALTH LABORATORY SERVICE

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	2 958	53	**3 295**	**7.62**
	2012	213	1 096	14 597	134	**16 040**	**6.83**
	2013	1 123	2 595	34 943	134	**38 795**	**6.69**
Free State	2011	28	154	2 661	1	**2 844**	**5.41**
	2012	162	736	10 707	26	**11 631**	**6.33**
	2013	349	743	12 083	20	**13 195**	**5.63**
Gauteng	2011	25	174	2 849	1	**3 049**	**5.71**
	2012	135	760	9 995	70	**10 960**	**6.93**
	2013	809	1 712	24 129	52	**26 702**	**6.41**
Kwa-Zulu Natal	2011	107	923	11 134	62	**12 226**	**7.55**
	2012	434	2 207	21 553	252	**24 446**	**9.03**
	2013	995	3 287	33 376	328	**37 986**	**8.65**
Limpopo	2011	25	148	1 777	25	**1 975**	**7.49**
	2012	52	267	3 599	75	**3 993**	**6.69**
	2013	285	634	11 127	106	**12 152**	**5.22**
Mpumalanga	2011	31	210	2 392	6	**2 639**	**7.96**
	2012	57	407	3 504	76	**4 044**	**10.06**
	2013	198	870	7 533	27	**8 628**	**10.08**
North West	2011	40	304	3 128	4	**3 476**	**8.75**
	2012	66	390	4 704	14	**5 174**	**7.54**
	2013	268	618	10 088	30	**11 004**	**5.62**
Northern Cape	2011	28	197	2 637	2	**2 864**	**6.88**
	2012	64	273	4 093	10	**4 440**	**6.15**
	2013	164	381	6 260	287	**7 092**	**5.37**
Western Cape	2011	15	106	2 082	1	**2 204**	**4.81**
	2012	150	657	12 393	2	**13 202**	**4.98**
	2013	659	1 417	26 238	1	**28 315**	**5.00**
Total		**6 515**	**21 517**	**282 540**	**1 799**	**312 371**	**6.89**

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

		GeneXpert Confirmation & Rif Concordance									
Province	Rif Resistant Cases	Cultures					LPA				
		Confirmed		Rif Concordance		Pre-analytical	Confirmed		Rif Concordance		Inderterminate
		#	%	#	%		#	%	#	%	
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

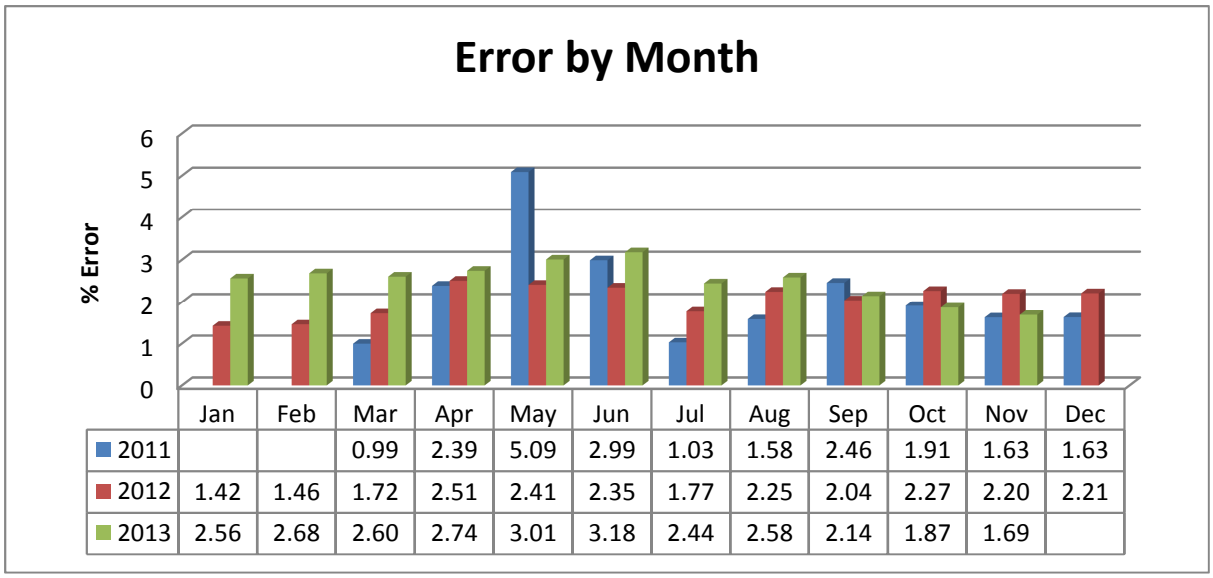
Average error rate has ranged consistently below 3%, however 1/9 provinces reported error rates above 3% in the month of October. There has been a significant improvement in the in the number of errors reported due to hardware failures of the modules reported by laboratories. Details of the invalid results, 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 November 2013)

Province	ERR	INV	NORES	NULL	MTB Results	Grand Total	% Error
Eastern Cape	428	92	91		28 864	29 475	1.45
Free State	106	13	1		11 170	11 290	0.94
Gauteng	361	93	49		22 851	23 354	1.55
Kwa-Zulu Natal	748	195	46	1	32 981	33 971	2.20
Limpopo	255	76	21		14 151	14 503	1.76

Mpumalanga	109	45	11		7 178	7 343	1.48
North West	358	35	13		9 626	10 032	3.57
Northern Cape	131	88	5		4 826	5 050	2.59
Western Cape	119	36	2		20 121	20 278	0.59
Grand Total	**2 615**	**673**	**239**	**1**	**151 768**	**155 296**	**1.68**

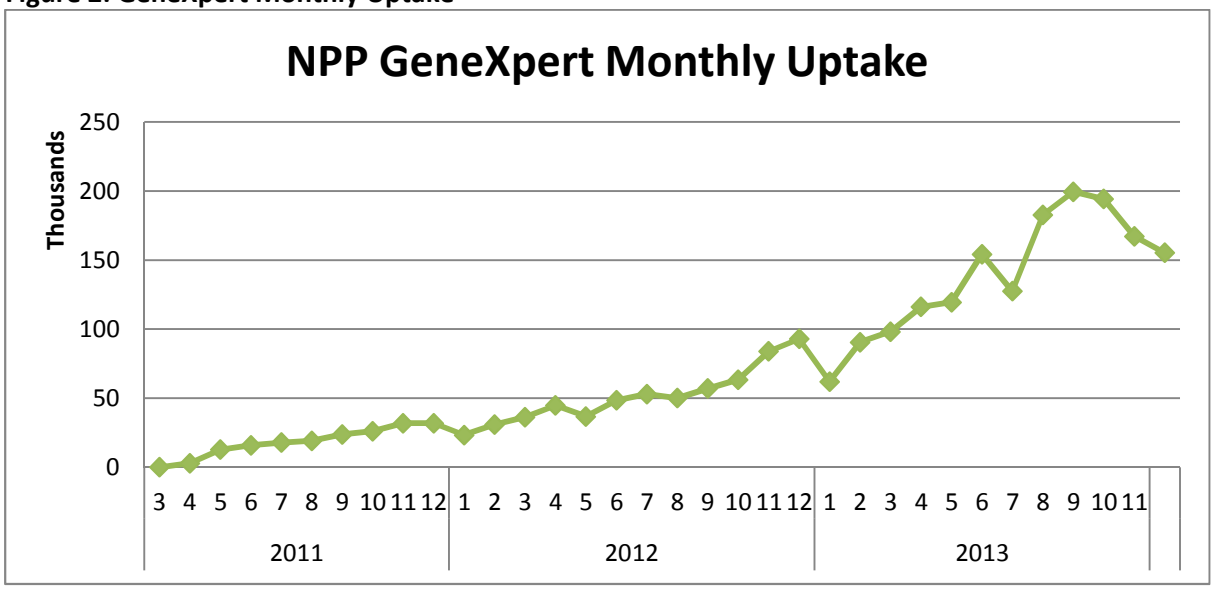
Figure 1: GeneXpert Error by Month



	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	2.14	1.87	1.69	

5. Monthly uptake since implementation started

Figure 2: GeneXpert Monthly Uptake



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Monthly uptake increased steadily since program inception. There was a significant decrease in the number of tests conducted in the month of October and November. CDW experienced problems with data loading from TrakCare Lab since the beginning of November. The problem seems to have not been resolved. Further investigation is required. 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

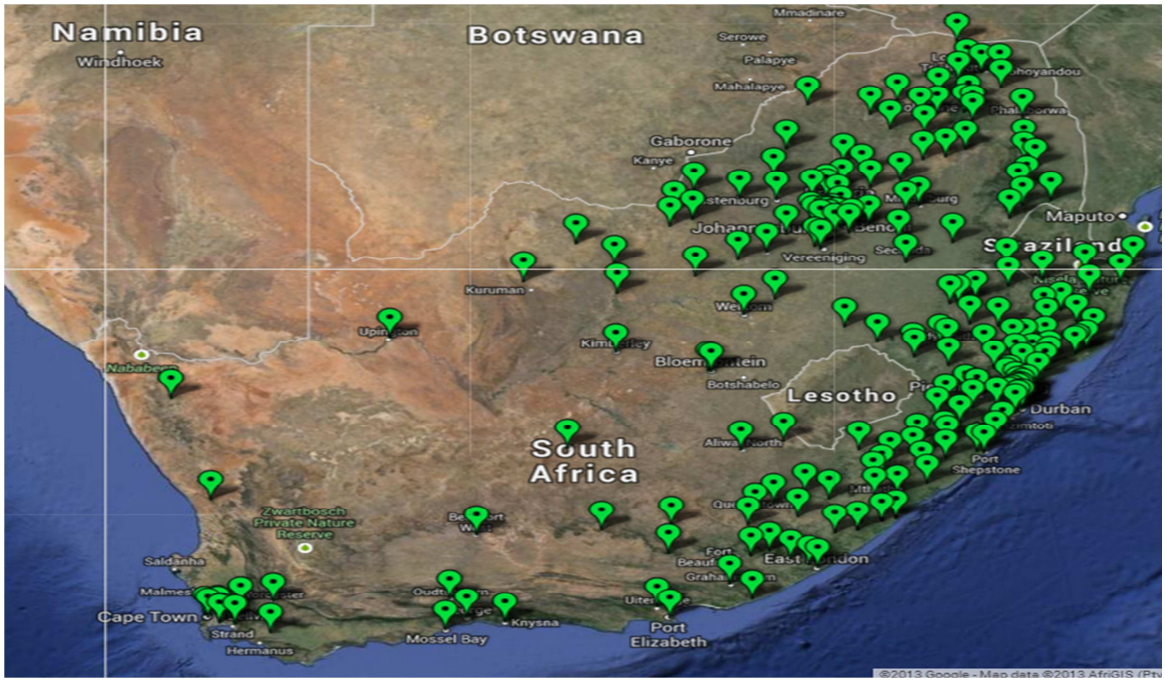
Phase IIIa and b: Gates funded study (Gauteng, EC and Free State). Completed

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, 284 **analysers, Gx4:** 95; Gx16-8: 1**; Gx16:** 185; GX48:1; GX80-80: 2) *20 clinic placements



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8. Training: Laboratory and Clinical

A total of 1,035 laboratory staff and 5,300 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
Nhu et al, J Clin Micro, 2013	N=379 CSF patients presenting with suspected tuberculous meningitis to the Hospital for Tropical Diseases, Ho Chi Minh City	Sensitivities of Xpert, smear and MGIT culture among patients diagnosed with TBM were 59.3% 78.6% and 66.5% respectively	Xpert =99.5% specificity
		Four cases of RIF resistance (n=4/109, 3.7%) were identified by Xpert of which 3 were confirmed to be Multi-drug resistant (MDR) TBM and one was culture negative.	
Millman et al, PloS One, 2013	An incremental cost-benefit analysis comparing the use of a single negative Xpert versus two negative sputum smears to release	Xpert reduced isolation bed utilization from an average of 2.7 to 1.4 days per patient, leading to a 48% reduction in total annual isolation bed usage from 632 to 328 bed-days. Xpert	

	consecutive adult inpatients with presumed TB from respiratory isolation at an urban public hospital in the United States.	saved an average of $2,278 (95% uncertainty range $1582-4570) per admission, or $533,520 per year, compared with smear microscopy
Osman et al, J Clin Micro, 2013-12-12	A retrospective laboratory based record review to measure the positive predictive value of Xpert G4 to detect RiF resistance (n=184)	PPV for Xpert was 99.5% (95% CI 98.5-100)

11. Update on GeneXpert Research projects:

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

- n=250 DCS verification panels have been manufactured for the India GeneXpert program.
- Phase 3 of the national NHLS GeneXpert EQA program has been distributed to sites.
- 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 is currently being finalized for implementation.
    - The first of the minor updates has been completed.
    - The national reporting template has been finalized and will be implemented as part of the finalization of the specification.
    - As of 1 October 2013, the TBGxMonitor platform has processed more than 1,200 report files for both verification and 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. n=17 MTBC by Xpert no SR; N=16 MTBC by Xpert with SR.

11.3. *Connectivity solutions for the GeneXpert*

- Connectivity: Collaboration with Cepheid ongoing

i. Remote connectivity – System deployed on 180 instruments to date with over 1,200,000 results live on the dashboard. Enrolment for all sites, nationally, has been completed. Cepheid and the NHLS are currently resolving instruments which have moved and duplicate enrolments on the system.

ii. Testing of the new Cepheid Xpert Monitor is currently underway. The system is being tested and troubleshooting is commencing through both the WITS and NHLS networks for compatibility for with the proxy servers.

iii. Site selection has been finalized for the pilot trial in January at 10 sites. The pre-trial troubleshooting is to ensure the systems can simply be deployed for trials and evaluated without requiring technical interventions.

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. As of September 2013, the recruitment target was reached with a total of 717patients enrolled into the study; 344 on the POC arm and 373 on the SOC arm. Of the total enrolled patients, n=399 had a CD4<350 (250 on POC; 149 on SOC) and were eligible for ART initiation. Patient follow-up is continuing.

- *Sub-studies within GCC*
    - **Peadiatric stool protocol**: In collaboration with David Alland and FIND, a protocol is being developed and Ethics obtained to evaluate the Xpert MTB/RIF assay on peadiatric stool specimens. A laboratory and clinical validation will be performed in early 2014.
    - **Investigating blood volumes obtained from finger stick**: In collaboration with Northwestern University. Aim of the study is to investigate if 150ul of blood can be obtained from a new finger stick collection device. The study is complete and result being written up for publication to SAMJ. 98% (n=100) of collection

attempts were successful and 86% of cases required only one finger stick to successfully collect 150 ul capillary blood using the developed device.

- 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. Data analysis is underway.
- **Laboratory validation** of a rapid strip based test for **HIV/Syphilis** (SD Bioline): Interim analysis: the assay shows a sensitivity and specificity of 95% and 96% respectively (n=207) for syphilis detection and 100% sensitivity and specificity for HIV detection (n=201). Study ongoing.
- **Laboratory validation** of a new POC chemistry system the **Epoc** (Alere): Protocol complete and ethics obtained. Awaiting instrument from Alere.
- **Clinical validation** of nurse operated **Liat (IQuum)** VL testing at POC on finger stick specimens: Protocol is complete and ethics obtained. n=100 patients have been recruited into the study and tested on-site for VL. Data analysis is underway with comparison to laboratory VL Roche platform.
- **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. N=24 DCS specimens (8 RIF sensitive, 8 RIF resistant and 8 NTM's) have been tested on the LPA version 1 to date and all gave correct TB profiles.
- **DNAGenotek Evaluation.** A novel liquification, storage and nucleic acid extraction reagent set for sputa will be evaluated in the laboratory and clinically. Protocol development is underway.

- 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.
- The SMS-randomization gateway has been closed down since no further patients are being enrolled.
- The AegisPOC-Conworx user evaluation and transcription error investigation is underway.

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 the month of November