NATIONAL HEALTH LABORATORY SERVICE

GeneXpert MTB/RIF

Progress Report

May 2014

NATIONAL HEALTH LABORATORY SERVICE

Table of Contents

Background to project	3
Assays performed to date	4
Rif Concordance	7
Errors	8
Monthly uptake since implementation started	9
Specific GeneXpert Site Progress	9
Training: Laboratory and Clinical	10
Challenges identified during the course of the project to date	10
Literature Update	10
Update on Research Projects	11
Funding	13
Recent Campaigns	13

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.

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, 287 GeneXpert instruments of varying sizes (GX4: 95; GX16:186; GX48: 1; GX80:5) 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.

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.

2. Assays performed to date

In summary, a total of 3,497,158 specimens have been processed to date (31 May 2014). In May 171,422 specimens were processed. The total % of *Mycobacterium tuberculosis* complex (MTBC) detected in this cohort was 10.86% (18,614). 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	15 341	551	**19 187**	**17.17**
Eastern Cape	2012	16 050	85 592	2 891	**104 533**	**15.35**
Eastern Cape	2013	43 201	300 705	9 485	**353 391**	**12.22**
Eastern Cape	2014	16 855	122 171	2 874	**141 900**	**11.88**
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	14 589	137 328	1 271	**153 188**	**9.52**
Free State	2014	5 506	52 071	546	**58 123**	**9.47**
Gauteng	2011	3 010	18 486	423	**21 919**	**13.73**
Gauteng	2012	10 963	72 328	2 265	**85 556**	**12.81**
Gauteng	2013	30 632	210 372	7 561	**248 565**	**12.32**
Gauteng	2014	15 017	116 706	3 426	**135 149**	**11.11**
Kwa-Zulu Natal	2011	9 782	38 973	1 276	**50 031**	**19.55**
Kwa-Zulu Natal	2012	23 922	135 810	5 913	**165 645**	**14.44**
Kwa-Zulu Natal	2013	43 349	301 505	15 617	**360 471**	**12.03**
Kwa-Zulu Natal	2014	23 369	193 493	7 003	**223 865**	**10.44**
Limpopo	2011	1 975	17 257	174	**19 406**	**10.18**
Limpopo	2012	3 992	30 704	689	**35 385**	**11.28**
Limpopo	2013	13 745	185 438	6 096	**205 279**	**6.70**
Limpopo	2014	5 572	78 513	2 691	**86 776**	**6.42**
Mpumalanga	2011	2 620	12 630	1 102	**16 352**	**16.02**
Mpumalanga	2012	4 021	21 867	1 118	**27 006**	**14.89**

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.

Mpumalanga	2013	10 079	60 897	2 330	**73 306**	**13.75**
Mpumalanga	2014	5 433	39 318	1 310	**46 061**	**11.80**
North West	2011	3 411	14 603	644	**18 658**	**18.28**
North West	2012	5 175	29 004	1 976	**36 155**	**14.31**
North West	2013	12 577	95 838	4 975	**113 390**	**11.09**
North West	2014	6 588	57 497	2 830	**66 915**	**9.85**
Northern Cape	2011	3 242	16 028	736	**20 006**	**16.21**
Northern Cape	2012	4 450	23 653	1 194	**29 297**	**15.19**
Northern Cape	2013	7 916	52 012	2 618	**62 546**	**12.66**
Northern Cape	2014	3 192	21 128	1 285	**25 605**	**12.47**
Western Cape	2011	2 189	9 953	44	**12 186**	**17.96**
Western Cape	2012	13 201	68 191	654	**82 046**	**16.09**
Western Cape	2013	31 326	168 930	2 910	**203 166**	**15.42**
Western Cape	2014	14 681	74 120	979	**89 780**	**16.35**
Total		**429 346**	**2 970 042**	**97 770**	**3 497 158**	**12.28**

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

Province	MTB Detected	MTB Not Detected	Test Unsuccessful	Grand Total	% MTB Detected
Eastern Cape	3 254	25 008	611	28 873	11.27
Free State	950	8 970	92	10 012	9.49
Gauteng	2 930	21 619	596	25 145	11.65
Kwa-Zulu Natal	4 699	39 792	1 315	45 806	10.26
Limpopo	1 066	16 008	472	17 546	6.08
Mpumalanga	1 017	8 032	247	9 296	10.94
North West	1 188	9 917	396	11 501	10.33
Northern Cape	601	4 033	192	4 826	12.45
Western Cape	2 909	15 321	187	18 417	15.80
Grand Total	**18 614**	**148 700**	**4 108**	**171 422**	**10.86**

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.

NATIONAL HEALTH LABORATORY SERVICE

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

Province	Inconclusive	Resistant	Sensitive	No Results	Grand Total	% Rif Resistance
Eastern Cape	100	198	2 952	4	3 254	6.08
Free State	31	48	871		950	5.05
Gauteng	69	160	2 699	2	2 930	5.46
Kwa-Zulu Natal	137	417	4 125	20	4 699	8.87
Limpopo	17	56	984	9	1 066	5.25
Mpumalanga	30	98	887	2	1 017	9.64
North West	32	55	1 101		1 188	4.63
Northern Cape	25	27	549		601	4.49
Western Cape	62	157	2 690		2 909	5.40
Grand Total	**503**	**1 216**	**16 858**	**37**	**18 614**	**6.53**

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	14 602	138	**16 050**	**6.83**
Eastern Cape	2013	1 212	2 843	38 999	147	**43 201**	**6.58**
Eastern Cape	2014	460	1 048	15 326	21	**16 855**	**6.22**
Free State	2011	28	152	2 625	1	**2 806**	**5.41**
Free State	2012	162	735	10 692	26	**11 615**	**6.33**
Free State	2013	373	802	13 392	22	**14 589**	**5.50**
Free State	2014	180	325	4 999	2	**5 506**	**5.90**
Gauteng	2011	25	173	2 811	1	**3 010**	**5.75**
Gauteng	2012	135	760	9 989	79	**10 963**	**6.93**
Gauteng	2013	901	1 960	27 704	67	**30 632**	**6.40**
Gauteng	2014	376	950	13 674	17	**15 017**	**6.33**
Kwa-Zulu Natal	2011	77	746	8 902	57	**9 782**	**7.63**
Kwa-Zulu Natal	2012	417	2 164	21 089	252	**23 922**	**9.05**
Kwa-Zulu Natal	2013	1 101	3 758	38 053	437	**43 349**	**8.67**
Kwa-Zulu Natal	2014	775	2 087	20 383	124	**23 369**	**8.93**
Limpopo	2011	25	148	1 777	25	**1 975**	**7.49**
Limpopo	2012	52	267	3 598	75	**3 992**	**6.69**
Limpopo	2013	295	711	12 630	109	**13 745**	**5.17**
Limpopo	2014	132	275	5 148	17	**5 572**	**4.94**
Mpumalanga	2011	30	207	2 377	6	**2 620**	**7.90**

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.

Mpumalanga	2012	57	401	3 487	76	**4 021**	**9.97**
Mpumalanga	2013	227	1 000	8 823	29	**10 079**	**9.92**
Mpumalanga	2014	157	522	4 749	5	**5 433**	**9.61**
North West	2011	39	301	3 067	4	**3 411**	**8.82**
North West	2012	66	390	4 704	15	**5 175**	**7.54**
North West	2013	290	712	11 543	32	**12 577**	**5.66**
North West	2014	222	374	5 988	4	**6 588**	**5.68**
Northern Cape	2011	28	202	3 008	4	**3 242**	**6.23**
Northern Cape	2012	64	273	4 102	11	**4 450**	**6.13**
Northern Cape	2013	177	422	7 027	290	**7 916**	**5.33**
Northern Cape	2014	101	161	2 924	6	**3 192**	**5.04**
Western Cape	2011	15	107	2 066	1	**2 189**	**4.89**
Western Cape	2012	150	661	12 387	3	**13 201**	**5.01**
Western Cape	2013	702	1 571	29 051	2	**31 326**	**5.02**
Western Cape	2014	289	799	13 592	1	**14 681**	**5.44**
Total		**9 586**	**29 355**	**388 243**	**2 162**	**429 346**	**6.84**

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
		#	%	#	%		#	%	#	%	
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**

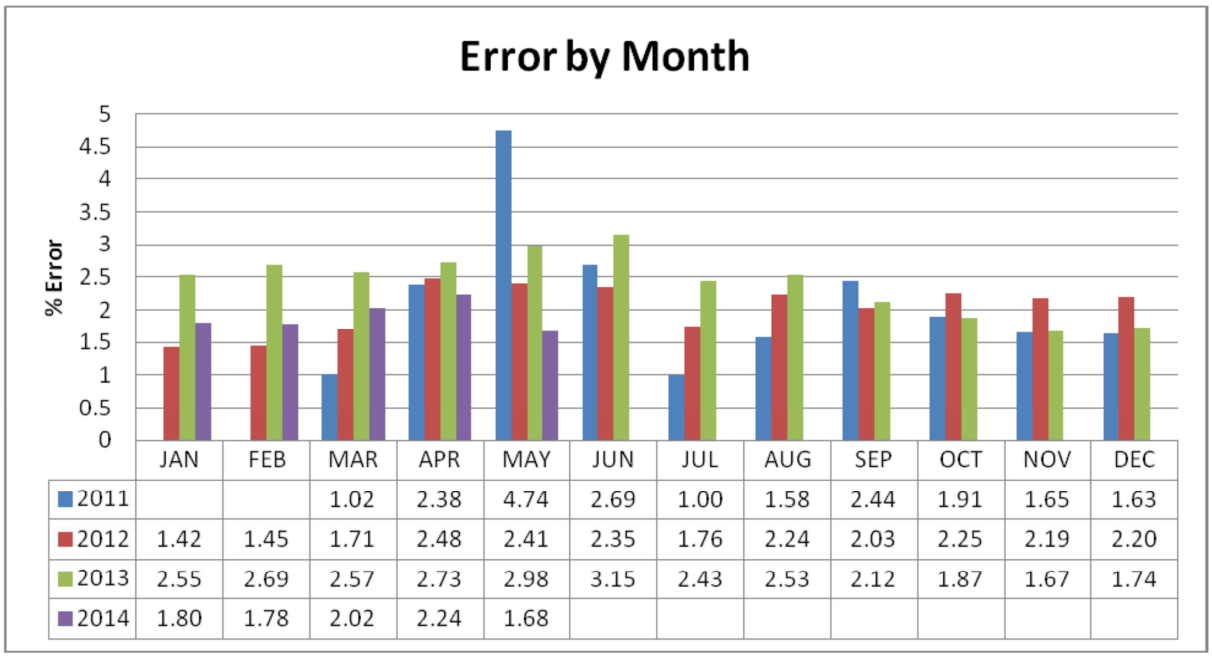
4. Errors

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 (1-31 May 2014)

Row Labels	ERRORS	INVALIDS	NO RESULTS	MTB Results	Grand Total	% Error
Eastern Cape	473	107	31	28 365	28 976	1.63
Free State	57	21	14	9 957	10 049	0.57
Gauteng	406	156	34	24 696	25 292	1.61
Kwa-Zulu Natal	849	374	92	44 605	45 920	1.85
Limpopo	366	89	17	17 091	17 563	2.08
Mpumalanga	188	39	20	9 085	9 332	2.01
North West	326	57	13	11 159	11 555	2.82
Northern Cape	93	93	6	4 643	4 835	1.92
Western Cape	121	42	24	18 532	18 719	0.65
Grand Total	**2 879**	**978**	**251**	**168 133**	**172 241**	**1.67**

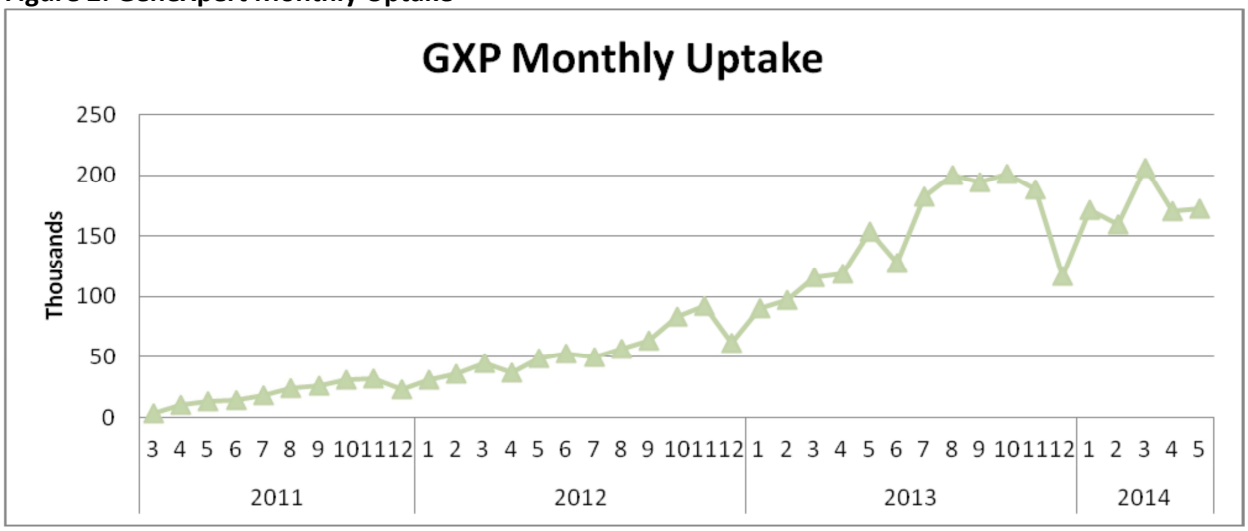
Figure 1: GeneXpert Error by Month



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.

5. Monthly uptake since implementation started

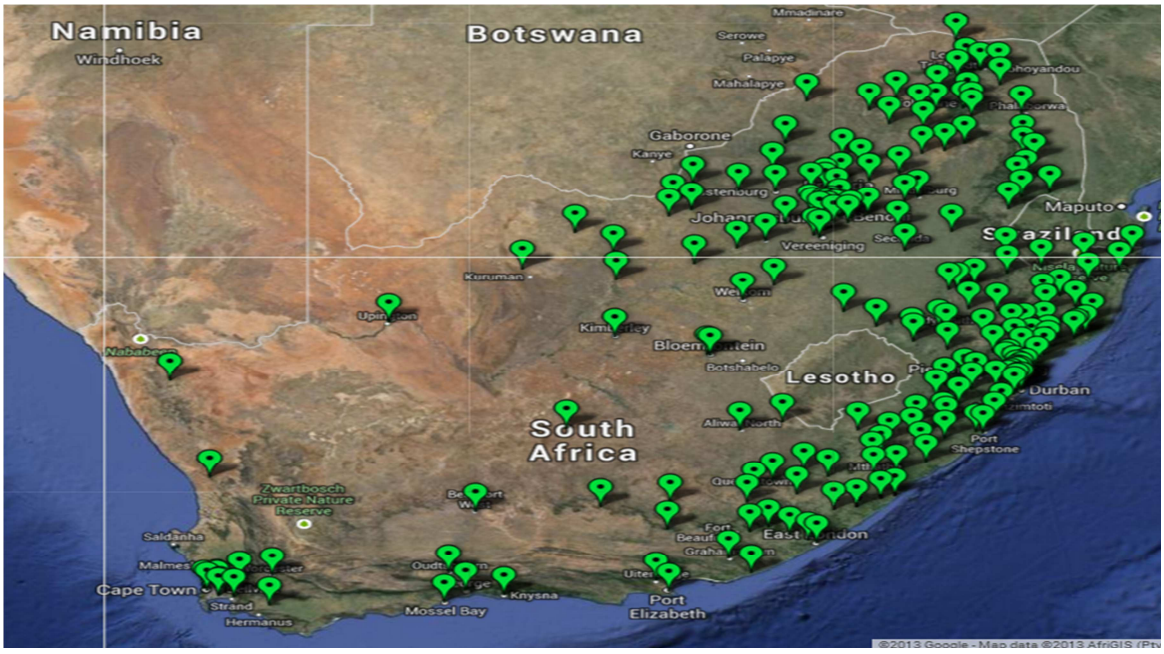
Figure 2: GeneXpert Monthly Uptake



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, 287 **analysers, Gx4:** 95; Gx16-8: 1**; Gx16:** 185; GX48:1; GX80-80: 5) *20 clinic placements



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 1,125 laboratory staff and 6,251 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 paeditric 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

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
Moon et al, J CLin Lab Anal, 2014	N= 100 isolates (50 RIF resistant and 50 RIF susceptible). RIF resistances compared between Xpert MTB/RIF assay, Sacace MTB Real-TM resistance, and AdvanSure MDR-TB GenoBlot assay versus conventional drug-susceptibility test	• Xpert MTB/RIF assay = 94%, • Sacace MTB Real-TM resistance 91.8% • Advansure GenoBlot assay 84%	• Specificity of all assays was 100%
Ozkutuk et al, Mikrobiyol Bul., 2014	Performance evaluation of the Xpert MTB/RIF in a routine laboratory setting in Turkey, on pulmonary and extra-pulmonary clinical samples (intermediate-prevalence setting). n= 2639 clinical specimens (1611 pulmonary; 1028 extra-pulmonary) versus culture	• Overall sensitivity: 73.9% • Pulmonary: 80.8% • Extrapulmonary 58.2%	• Overall specificity: 98.6% • Pulmonary: 98.8% • Extrapulmonary 98.4%

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.

Da Silva Antunes, Int J Tuberc Lung Dis., 2014	Comparison of the cost of Xpert(®) MTB/RIF assay with those of standard care (two smears) in diagnosing TB from the 218 patient's perspective in Brazil	• Median total costs incurred by patients were 54% higher with the smear process than with Xpert (US$25.24 vs. US$16.44, P < 0.000) due to higher indirect and direct costs	
Biadglegne et al, Tuberculosis (Edinb). 2014	Evaluated the performance of Xpert for direct detection of the Mycobacterium tuberculosis complex (MTBC) and rifampicin (RIF) resistance in lymph node aspirates, in northern Ethiopia versus culture	Xpert Sensitivity = 93.5%	Xpert Specificity = 69.2%
		The Xpert test identified the rpoB mutations associated with RIF resistance concordant with GenoType MTBDRplus and phenotypic drug susceptibility testing.	

10. Update on GeneXpert Research projects:

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

- Verification material manufacture for Q2 is in preparation.
- Panel 1 of the 2014 EQA program has been sent to all participating NHLS sites
    i. Submissions have been closed and reports which have not been automatically released (100%) are being reviewed and released.
- TBGxMonitor™ (www.tbgxmonitor.com) upgrade specification finalized.
    - Seriun continue to publish updated components which are undergoing verification and validation.
    - Initial components tested meet specification.
    - Investigation Report form awaiting finalization.

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 Emocha

The Emoch project with the John Hopkins University (JHU) group continues. Emocha team and NHLS IT have agreed that the data sharing will be conducted through the CDW and not the LIS since DisaLab is likely to remain functional for the next couple years at least before the migration to TrackCare is completed. Initial review of the web-service interface being discussed.

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.

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.

- A qualitative study is underway in the clinics to investigate routine workflow in clinics before and after implementation of POC testing.
- A full costing analysis of POC versus SOC will begin in June.

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). Ethics has been obtained. Stool specimen collection has begun (specimens are being collected from routine residual specimens sent to Microbiology laboratory.) Awaiting Xpert kits and consumables.
- **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 and testing is ongoing. Visits V0, V1, V2 and V3 have been tested.
- **Clinic validation of EPOC Blood gas analysis system (Alere):** A new chemistry POC device will be evaluated against routine laboratory results at Themba Lethu clinic. A nurse is performing Creatinine measurements on the EPOC versus creat on Reflotron and routine laboratory results on venepuncture specimens. n=84 patients have been recruited onto the study so far.
- **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 (Hain LifeScience). Three labs have submitted results (2 scored 100%; 1 lab scored 0%). One lab outstanding. 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 through TB assay. Ethics has been approved and awaiting clinic approvals and training. Estimated study start: July.
- **Laboratory validation of new HIV diagnostics:** A pilot to investigate the performance of the new Xpert® HIV-1 Quant assay for VL was performed on a 42 member plasma HIV-1

subtype C panel versus the CAP/CTMv2 (Roche) and RealTi*me* HIV-1 (Abbott). Data analysis is underway and has been submitted to ASLM 2014.

- **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 May