NATIONAL HEALTH LABORATORY SERVICE

GeneXpert MTB/RIF

Progress Report

July 2014

NATIONAL HEALTH LABORATORY SERVICE

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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, 295 GeneXpert instruments of varying sizes (GX4: 98; GX16:189; GX48: 1; GX80:7) 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.

1.1. Correctional Services

In order to improve TB control in all 242 correctional facilities in South Africa, the NHLS is working in partnership with the Department of Correctional Services (DCS), NDoH, Aurum Institute, TB/HIV Care Association and Right to Care to ensure access to regular HIV- and TB-related screening, testing and treatment of up to 150,000 offenders through the Global Fund programme. Xpert MTB/Rif testing is being provided either on-site, or at the nearest referral laboratory. During 2014, Xpert MTB/RIF testing facilities have been established on-site at the following Correctional Facilities:

- Kgoši Mampuru Management Area II
- Barberton Management Area
- Johannesburg Management Area
- Groenpunt Management Area
- Pollsmoor Management Area
- St Albans Management Area
- Durban-Westville Management Area

1.2. Peri-Mining Communities

NHLS, together with the Aurum Institute, has been appointed by NDoH (under the Global Fund grant) to provide services to implement interventions aimed at improving TB and HIV/AIDS management for vulnerable peri-mining communities (estimated at around 600,000 people) in 6 main mining districts. Six staffed and GeneXpert-equipped mobile TB units will be provided within the communities to undertake Xpert MTB/RIF testing for TB. In addition, persons newly identified as HIV-infected through the clinical partner will be staged for HIV-treatment using CD4 tests provided by the closest NHLS lab in the district. The 6 districts with a high proportion of mines in South Africa that have been identified for focused attention are:

- Lejweleputswa (Free State),
- Dr K K Kaunda & Bojanala Districts (North West),
- West Rand (Gauteng)
- Waterberg & Sekhukhune (Limpopo)

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2. Assays performed to date

In summary, a total of 3,983,810 specimens have been processed to date (31 July 2014). In July 214,266 specimens were processed. The total % of *Mycobacterium tuberculosis* complex (MTBC) detected in this cohort was 10.15% (21,748). 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, and has remained constantly around 12% in the fourth 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	3 294	15 341	551	**19 186**	**17,2**
Eastern Cape	2012	16 051	85 592	2 891	**104 534**	**15,4**
Eastern Cape	2013	44 578	314 296	10 045	**368 919**	**12,1**
Eastern Cape	2014	26 647	204 693	4 936	**236 276**	**11,3**
Free State	2011	2 806	14 567	33	**17 406**	**16,1**
Free State	2012	11 615	77 012	280	**88 907**	**13,1**
Free State	2013	14 844	140 297	1 312	**156 453**	**9,5**
Free State	2014	7 821	73 239	778	**81 838**	**9,6**
Gauteng	2011	3 381	21 079	501	**24 961**	**13,5**
Gauteng	2012	11 477	75 967	2 370	**89 814**	**12,8**
Gauteng	2013	32 411	224 822	8 339	**265 572**	**12,2**
Gauteng	2014	22 295	181 271	4 895	**208 461**	**10,7**
Kwa-Zulu Natal	2011	11 568	44 603	1 646	**57 817**	**20,0**
Kwa-Zulu Natal	2012	23 922	135 810	5 913	**165 645**	**14,4**
Kwa-Zulu Natal	2013	43 054	297 747	15 428	**356 229**	**12,1**
Kwa-Zulu Natal	2014	32 681	281 473	9 841	**323 995**	**10,1**
Limpopo	2011	1 975	17 257	174	**19 406**	**10,2**
Limpopo	2012	3 992	30 704	689	**35 385**	**11,3**
Limpopo	2013	13 969	189 190	6 215	**209 374**	**6,7**
Limpopo	2014	8 113	120 932	3 970	**133 015**	**6,1**
Mpumalanga	2011	2 622	12 653	1 104	**16 379**	**16,0**
Mpumalanga	2012	4 021	21 867	1 118	**27 006**	**14,9**
Mpumalanga	2013	10 228	62 019	2 367	**74 614**	**13,7**

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Mpumalanga	2014	8 043	61 314	1 968	**71 325**	**11,3**
North West	2011	3 411	14 603	644	**18 658**	**18,3**
North West	2012	5 156	28 923	1 966	**36 045**	**14,3**
North West	2013	12 146	90 862	4 623	**107 631**	**11,3**
North West	2014	9 118	78 755	3 531	**91 404**	**10,0**
Northern Cape	2011	3 242	16 028	736	**20 006**	**16,2**
Northern Cape	2012	4 450	23 653	1 194	**29 297**	**15,2**
Northern Cape	2013	8 091	53 385	2 682	**64 158**	**12,6**
Northern Cape	2014	4 616	31 598	1 796	**38 010**	**12,1**
Western Cape	2011	2 142	9 785	44	**11 971**	**17,9**
Western Cape	2012	13 052	67 520	647	**81 219**	**16,1**
Western Cape	2013	31 132	167 526	2 887	**201 545**	**15,4**
Western Cape	2014	20 869	109 183	1 297	**131 349**	**15,9**
Total		**478 833**	**3 395 566**	**109 411**	**3 983 810**	**12,0**

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

Province	MTB Detected	MTB Not Detected	Test Unsuccessful	Grand Total	% MTB Detected
Eastern Cape	4 055	32 848	888	37 791	10,73
Free State	1 159	10 011	128	11 298	10,26
Gauteng	3 383	30 128	572	34 083	9,93
Kwa-Zulu Natal	5 005	47 998	1 527	54 530	9,18
Limpopo	1 311	20 780	598	22 689	5,78
Mpumalanga	1 247	10 381	323	11 951	10,43
North West	1 420	11 667	453	13 540	10,49
Northern Cape	702	5 032	198	5 932	11,83
Western Cape	3 466	18 826	160	22 452	15,44
Grand Total	**21 748**	**187 671**	**4 847**	**214 266**	**10,15**

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

Province	Inconclusive	Resistant	Sensitive	No Rif Result	Grand Total	% Rif Resistant
Eastern Cape	181	251	3 621	2	4 055	6,19
Free State	29	70	1 060		1 159	6,04
Gauteng	81	181	3 119	2	3 383	5,35
Kwa-Zulu Natal	186	418	4 379	22	5 005	8,35
Limpopo	36	64	1 207	4	1 311	4,88
Mpumalanga	52	94	1 092	9	1 247	7,54
North West	42	80	1 296	2	1 420	5,63
Northern Cape	31	31	640		702	4,42
Western Cape	79	184	3 203		3 466	5,31
Grand Total	**717**	**1 373**	**19 617**	**41**	**21 748**	**6,31**

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	2 954	56	**3 294**	**7,6**
Eastern Cape	2012	213	1 097	14 603	138	**16 051**	**6,8**
Eastern Cape	2013	1 257	2 923	40 239	159	**44 578**	**6,6**
Eastern Cape	2014	840	1 636	24 143	28	**26 647**	**6,1**
Free State	2011	28	152	2 625	1	**2 806**	**5,4**
Free State	2012	162	735	10 692	26	**11 615**	**6,3**
Free State	2013	377	814	13 631	22	**14 844**	**5,5**
Free State	2014	255	460	7 103	3	**7 821**	**5,9**
Gauteng	2011	28	198	3 154	1	**3 381**	**5,9**
Gauteng	2012	143	797	10 456	81	**11 477**	**6,9**
Gauteng	2013	951	2 069	29 316	75	**32 411**	**6,4**
Gauteng	2014	546	1 353	20 374	22	**22 295**	**6,1**
Kwa-Zulu Natal	2011	106	877	10 528	57	**11 568**	**7,6**
Kwa-Zulu Natal	2012	417	2 164	21 089	252	**23 922**	**9,0**
Kwa-Zulu Natal	2013	1 093	3 756	37 770	435	**43 054**	**8,7**
Kwa-Zulu Natal	2014	1 073	2 926	28 523	159	**32 681**	**9,0**
Limpopo	2011	25	148	1 777	25	**1 975**	**7,5**
Limpopo	2012	52	267	3 598	75	**3 992**	**6,7**
Limpopo	2013	302	724	12 833	110	**13 969**	**5,2**
Limpopo	2014	196	402	7 493	22	**8 113**	**5,0**
Mpumalanga	2011	30	207	2 379	6	**2 622**	**7,9**
Mpumalanga	2012	57	401	3 487	76	**4 021**	**10,0**
Mpumalanga	2013	235	1 017	8 947	29	**10 228**	**9,9**

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Mpumalanga	2014	269	744	7 016	14	**8 043**	**9,3**
North West	2011	39	301	3 067	4	**3 411**	**8,8**
North West	2012	66	390	4 687	13	**5 156**	**7,6**
North West	2013	283	673	11 165	25	**12 146**	**5,5**
North West	2014	288	495	8 329	6	**9 118**	**5,4**
Northern Cape	2011	28	202	3 008	4	**3 242**	**6,2**
Northern Cape	2012	64	273	4 102	11	**4 450**	**6,1**
Northern Cape	2013	180	431	7 190	290	**8 091**	**5,3**
Northern Cape	2014	150	224	4 233	9	**4 616**	**4,9**
Western Cape	2011	15	105	2 021	1	**2 142**	**4,9**
Western Cape	2012	149	650	12 250	3	**13 052**	**5,0**
Western Cape	2013	698	1 558	28 874	2	**31 132**	**5,0**
Western Cape	2014	437	1 111	19 320	1	**20 869**	**5,3**
Total		**11 085**	**32 531**	**432 976**	**2 241**	**478 833**	**6,8**

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.

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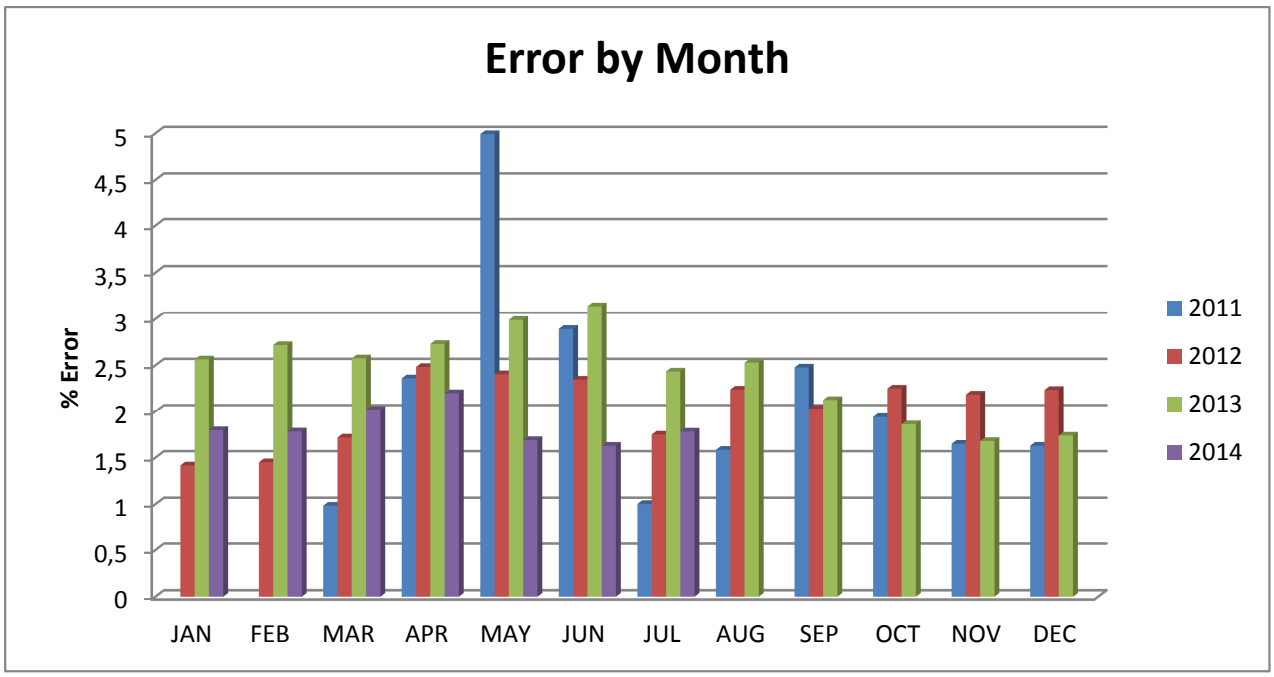
Table 6: Number of Unsuccessful Tests and Reasons (1-31 July 2014)

Province	ERRORS	INVALIDS	NO RESULTS	MTB Results	Grand Total	% ERRORS
Eastern Cape	653	173	62	37 005	37 893	1,72
Free State	92	27	9	11 234	11 362	0,81
Gauteng	468	51	53	33 824	34 396	1,36
Kwa-Zulu Natal	1 235	193	99	53 167	54 694	2,26
Limpopo	455	118	25	22 126	22 724	2,00
Mpumalanga	273	33	17	11 642	11 965	2,28
North West	363	56	34	13 132	13 585	2,67
Northern Cape	150	42	5	5 744	5 941	2,52
Western Cape	126	23	10	22 712	22 871	0,55
Grand Total	**3 815**	**716**	**314**	**210 586**	**215 431**	**1,77**

Figure 1: GeneXpert Error by Month



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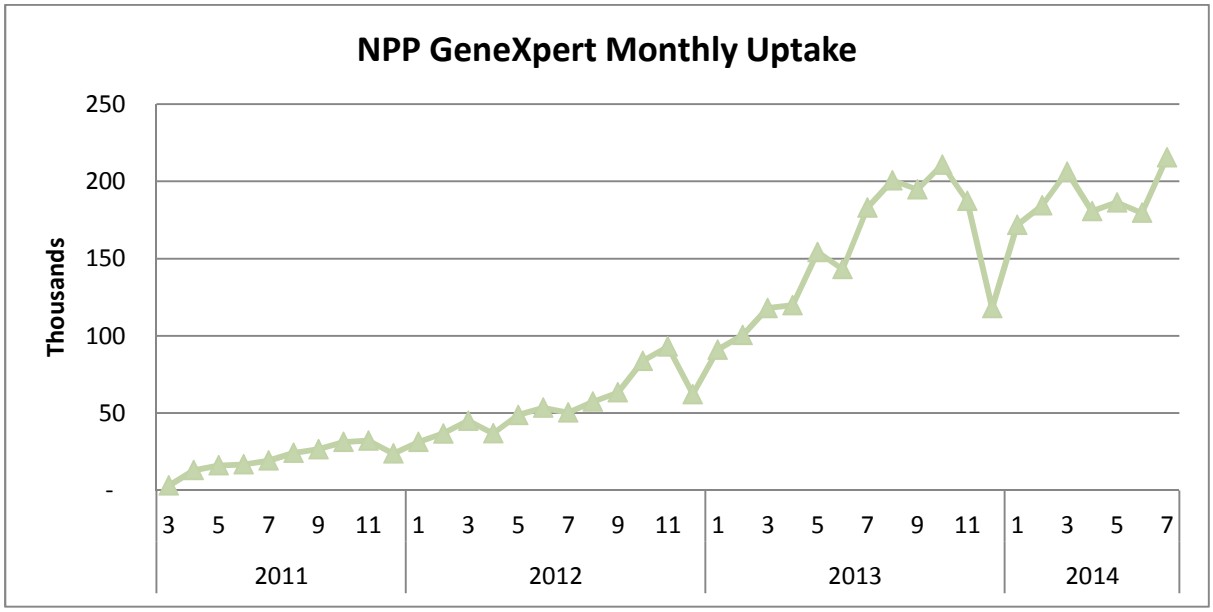
5. Monthly uptake since implementation started

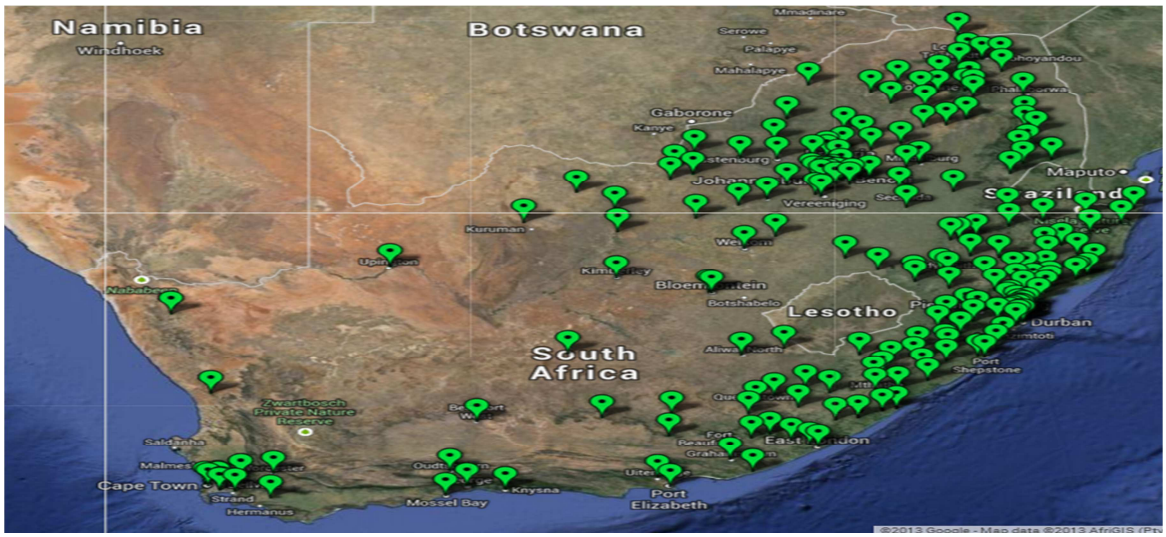
Figure 2: GeneXpert Monthly Uptake



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, 295 **analysers, Gx4:** 98; Gx16-8: 1**; Gx16:** 188; GX48:1; GX80-80: 7) *20 clinic placements *7 Correctional Facilities



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7. Training: Laboratory and Clinical

A total of 1,139 laboratory staff and 6,694 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.

29 participants from the eight provinces, with the exception of the Free State attended a four day HBDC Advanced GeneXpert Training organized by the National Priority Programs of the NHLS in collaboration with Cepheid. The course conducted from 22-25 July 2014 at Wits Medical School, Johannesburg, South Africa.

The Advanced GeneXpert Training course was intended to give participants knowledge of the GeneXpert technology and its applications in diagnostic and research settings highlighting differences between this technology and the currently available TB diagnostic tools in South Africa. Topics covered by this comprehensive training course include regulatory compliance and adherence to good laboratory practices, personnel qualifications and responsibilities, establishment and verification of test performance specifications, preparation and processing of clinical molecular samples, quality control practices, proficiency testing and alternative performance assessment, test reports and quality management practices.

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
- Delays in installation of some equipment, renovations and cabling to allow for network installations which hampered the 'go live" date of four correctional facilities namely St Albans Management Area, Durban-Westville Management Area, Barberton Management Area and Groenpunt Management Area. All sites will be up and running by the 01 August 2014.

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
Theron et al, Sci Rep, 2014	Comparison of culture time-to-positivity (TTP; a surrogate of bacterial load), MTB/RIF TB-specific and internal positive control (IPC)-specific Ct values, and clinical characteristics in patients with suspected TB who provided: • expectorated (n = 438) or induced sputum (n = 128), • tracheal aspirates (n = 71), • BAL fluid (n = 152), • pleural fluid (n = 76), • CSF n = 152, • pericardial fluid (n = 131), • urine (n = 173) specimens.	• Median bacterial load (TTP in days) was the strongest associate of MTB/RIF positivity in each fluid. • TTP correlated with C(T) values in pulmonary specimens but not extrapulmonary specimens • Pulmonary specimens had greater load than extrapulmonary specimens	
Salje et al, PloS Med, 2014	Developed a model of TB transmission, care-seeking behavior, and diagnostic/treatment practices in India and explored the impact of six different rollout strategies.	• Providing Xpert to 40% of public-sector patients with HIV or prior TB treatment reduced TB incidence by 0.2% and MDR-TB incidence by 2.4% • required 2,500 additional MDR-TB treatments and 60 four-module GeneXpert systems at maximum capacity • Improving referrals from informal providers for smear-based diagnosis in the public sector (without Xpert rollout) had substantially greater impact (6.3% reduction) than Xpert scale-up within the public sector.	
Lusiba et al, PloS One, 2014	Evaluated the accuracy of Cepheid's Xpert MTB/Rif test on pleural fluid in the diagnosis of pleural TB in Uganda N=116	The sensitivity of Xpert = 28.7%	Specificity of Xpert =96.6%
Patel et al, JCM, 2014	Comparison of GeneXpert MTB/RIF and Roche-Amplicor for the diagnosis of tuberculous meningitis	Sensitivity (95% CI): Amplicor = 46% (31-60) Xpert MTB/RIF = 50% (33-67)	Specificity (95% CI) Amplicor = 99%(93-100) Xpert MTB/RIF= 94% (84-99)

	(TBM) N=148		
Sharma et al, Eur Resp J, 2014	Reports the performance of Xpert MTB/RIF in EPTB samples from India N=1292 samples	Overall sensitivity specificity of Xpert = 71%	Overall specificity of Xpert =95%,
Naidoo et al, PloS One, 2014	Compared MDR-TB treatment commencement times in MDRTBPlus Line Probe Assay and Xpert MTB/RIF-based algorithms in a routine operational setting.	• Median treatment commencement time in the Xpert algorithm was 17 days (95% CI 13 to 22 days) • Median laboratory turnaround time (to result available in the laboratory) of <1 day • There was a decrease of 25 days (95% CI 17 to 32 days, p<0.001) in median MDR-TB treatment commencement time in the Xpert MTB/RIF-based algorithm	

10. Update on GeneXpert Research projects:

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

- Panel 2 of the 2014 EQA program has been sent to all participating NHLS sites
  - **i.** Submissions dates have closed
  - **ii.** Analysis and reporting underway
- TBGxMonitor™ (www.tbgxmonitor.com) upgrade specification finalized.
  - o Seriun continue to publish updated components which are undergoing verification and validation.
  - o Development validation to begin from 1 September.

11.2. *Connectivity solutions for the GeneXpert*

- Connectivity: Collaboration with Cepheid ongoing
  - i. Remote connectivity – old dashboard still up to collect routine data ~ 2.1mil results to date
  - ii. Awaiting feedback on the data generated from the beta trial.

11.3 mHealth solutions for MDR-TB

An mHealth project together with the John Hopkins University (JHU) group and funded through the Global Fund has commenced. It was agreed that the data sharing will be

conducted through the CDW Initial review of the web-service interface being discussed. Additional options for possible mHealth applications for pilot are currently being investigated.

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 complete.

- Data cleaning and preliminary data analysis completed.
- Initial cost analysis by HE2RO completed.

Sub-studies within GCC

- **Evaluation of the GeneXpert to Diagnose Peadiatric TB using stool specimens**: (In collaboration with David Alland and FIND). The laboratory R&D component to determine appropriate stool processing protocol has started. n=15 spiked TB positive and n=11 TB negative specimens have been tested using 6 different protocols. Results will be analysed by FIND before clinical study commencement.
- **Longitudinal follow up of Dried Blood Spots for viral load monitoring**: Longitudinal collection of DBS from n=100 HIV-positive patients on ARV's over 60 weeks. Outstanding final visit (V5) DBS for testing.
- **Clinic validation of EPOC Blood gas analysis system (Alere):** A new chemistry POC device has been evaluated at Themba Lethu clinic by a nurse. n=125 patients were recruited into the study. Creatinine measurements on the EPOC versus creatinine on Reflotron and routine laboratory results are being compared for precision and accuracy analysis. Study complete. Data analysis underway.
- **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). Results are being written up for publication. development.
- **Laboratory validation of new TB diagnostics:** 1). A validation protocol is underway for evaluation of the updated Abbott NM high throughput TB assay. The clinical study has begun: n=8 patients have been recruited to date.

- **Laboratory validation of new HIV diagnostics:** 1). 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 RealTime HIV-1 (Abbott). 2). A laboratory validation is planned to test the Cepheid HIV-1 Quantitative VL cartridge on plasma, DBS and whole blood. Awaiting kits and training.
- **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 July