NATIONAL HEALTH LABORATORY SERVICE

GeneXpert MTB/RIF

Progress Report

September 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 242011. 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, 296 GeneXpert instruments of varying sizes (GX4: 98; GX16:190; GX48: 1; GX80:7) have been placed in 216 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.

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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)

2. Assays performed to date

In summary, a total of 4,411,399 specimens have been processed to date (30 September 2014). In September 221,944 specimens were processed. The total % of *Mycobacterium tuberculosis* complex (MTBC) detected in this cohort was 9.76% (21,661). 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	3 252	15 235	549	**19 036**	**17,08**
EASTERN CAPE	2012	15 880	84 755	2 862	**103 497**	**15,34**
EASTERN Cape	2013	43 908	308 311	9 859	**362 078**	**12,13**
EASTERN CAPE	2014	36 211	283 754	8 219	**328 184**	**11,03**
FREE STATE	2011	2 811	14 532	35	**17 378**	**16,18**
FREE STATE	2012	11 660	76 863	288	**88 811**	**13,13**
FREE STATE	2013	14 545	136 631	1 274	**152 450**	**9,54**
FREE STATE	2014	10 589	97 832	877	**109 298**	**9,69**
GAUTENG	2011	3 094	18 881	443	**22 418**	**13,80**
GAUTENG	2012	11 120	72 979	2 305	**86 404**	**12,87**
GAUTENG	2013	30 693	210 680	7 769	**249 142**	**12,32**
GAUTENG	2014	29 110	232 018	5 776	**266 904**	**10,91**
KWAZULU-NATAL	2011	7 546	30 575	896	**39 017**	**19,34**
KWAZULU-NATAL	2012	23 963	135 973	5 915	**165 851**	**14,45**
KWAZULU-NATAL	2013	42 430	292 197	15 154	**349 781**	**12,13**
KWAZULU-NATAL	2014	44 121	396 477	13 945	**454 543**	**9,71**
LIMPOPO	2011	1 973	17 253	173	**19 399**	**10,17**
LIMPOPO	2012	4 004	30 924	689	**35 617**	**11,24**
LIMPOPO	2013	13 819	186 281	6 110	**206 210**	**6,70**
LIMPOPO	2014	11 100	168 105	5 959	**185 164**	**5,99**
MPUMALANGA	2011	2 629	12 683	1 100	**16 412**	**16,02**
MPUMALANGA	2012	4 035	22 226	1 133	**27 394**	**14,73**

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MPUMALANGA	2013	10 169	60 955	2 336	**73 460**	**13,84**
MPUMALANGA	2014	11 258	86 662	3 121	**101 041**	**11,14**
NORTH WEST	2011	3 429	14 557	644	**18 630**	**18,41**
NORTH WEST	2012	5 499	29 977	2 052	**37 528**	**14,65**
NORTH WEST	2013	12 835	96 815	4 872	**114 522**	**11,21**
NORTH WEST	2014	13 018	116 742	5 165	**134 925**	**9,65**
NORTHERN CAPE	2011	2 727	15 527	712	**18 966**	**14,38**
NORTHERN CAPE	2012	3 830	21 728	1 038	**26 596**	**14,40**
NORTHERN CAPE	2013	7 670	51 607	2 491	**61 768**	**12,42**
NORTHERN CAPE	2014	6 558	47 168	2 248	**55 974**	**11,72**
WESTERN CAPE	2011	2 173	9 897	47	**12 117**	**17,93**
WESTERN CAPE	2012	13 206	68 045	689	**81 940**	**16,12**
WESTERN CAPE	2013	30 709	165 219	2 871	**198 799**	**15,45**
WESTERN CAPE	2014	26 770	141 788	1 587	**170 145**	**15,73**
TOTAL		**518 344**	**3 771 852**	**121 203**	**4 411 399**	**11,75**

Table 2: GeneXpert MTB Results by province (01-30 September 2014)

Province	MTB Detected	MTB Not Detected	Test Unsuccessful	Grand Total	% MTB Detected
Eastern Cape	4 468	37 417	2 350	44 235	10,10
Free State	1 295	11 422	89	12 806	10,11
Gauteng	3 619	29 103	717	33 439	10,82
Kwa-Zulu Natal	5 044	49 448	2 061	56 553	8,92
Limpopo	1 285	21 021	1 014	23 320	5,51
Mpumalanga	1 260	10 507	526	12 293	10,25
North West	1 453	13 779	700	15 932	9,12
Northern Cape	680	5 764	251	6 695	10,16
Western Cape	2 557	13 919	195	16 671	15,34
Grand Total	**21 661**	**192 380**	**7 903**	**221 944**	**9,76**

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Table 3: Provincial GeneXpert RIF Results in MTB detected cases (01-30 September 2014)

Province	Inconclusive	Resistant	Sensitive	No RIF Result	Grand Total	% Rif Resistant
Eastern Cape	60	239	4 157	12	4 468	5,35
Free State	16	77	1 202		1 295	5,95
Gauteng	49	212	3 356	2	3 619	5,86
Kwa-Zulu Natal	61	359	4 606	18	5 044	7,12
Limpopo	12	69	1 197	7	1 285	5,37
Mpumalanga	13	98	1 149		1 260	7,78
North West	25	85	1 343		1 453	5,85
Northern Cape	5	45	630		680	6,62
Western Cape	31	138	2 388		2 557	5,40
Grand Total	**272**	**1 322**	**20 028**	**39**	**21 661**	**6,10**

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	248	2 919	52	**3 252**	**7,63**
EASTERN CAPE	2012	213	1 077	14 456	134	**15 880**	**6,78**
EASTERN CAPE	2013	1 237	2 884	39 638	149	**43 908**	**6,57**
EASTERN CAPE	2014	1 003	2 194	32 971	43	**36 211**	**6,06**
FREE STATE	2011	28	155	2 626	2	**2 811**	**5,51**
FREE STATE	2012	162	755	10 717	26	**11 660**	**6,48**
FREE STATE	2013	368	802	13 353	22	**14 545**	**5,51**
FREE STATE	2014	311	614	9 661	3	**10 589**	**5,80**
GAUTENG	2011	25	179	2 889	1	**3 094**	**5,79**
GAUTENG	2012	136	766	10 142	76	**11 120**	**6,89**
GAUTENG	2013	896	1 989	27 738	70	**30 693**	**6,48**
GAUTENG	2014	618	1 750	26 721	21	**29 110**	**6,01**
KWAZULU-NATAL	2011	64	592	6 875	15	**7 546**	**7,85**
KWAZULU-NATAL	2012	417	2 166	21 128	252	**23 963**	**9,04**
KWAZULU-NATAL	2013	1 070	3 696	37 232	432	**42 430**	**8,71**
KWAZULU-NATAL	2014	1 243	3 793	38 888	197	**44 121**	**8,60**
LIMPOPO	2011	25	148	1 775	25	**1 973**	**7,50**
LIMPOPO	2012	52	268	3 609	75	**4 004**	**6,69**
LIMPOPO	2013	296	716	12 698	109	**13 819**	**5,18**
LIMPOPO	2014	246	550	10 259	45	**11 100**	**4,95**
MPUMALANGA	2011	30	207	2 386	6	**2 629**	**7,87**
MPUMALANGA	2012	57	401	3 501	76	**4 035**	**9,94**

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MPUMALANGA	2013	228	1 006	8 906	29	**10 169**	**9,89**
MPUMALANGA	2014	329	1 010	9 901	18	**11 258**	**8,97**
NORTH WEST	2011	39	303	3 083	4	**3 429**	**8,84**
NORTH WEST	2012	75	414	5 000	10	**5 499**	**7,53**
NORTH WEST	2013	306	705	11 795	29	**12 835**	**5,49**
NORTH WEST	2014	397	699	11 914	8	**13 018**	**5,37**
NORTHERN CAPE	2011	28	186	2 511	2	**2 727**	**6,82**
NORTHERN CAPE	2012	50	236	3 536	8	**3 830**	**6,16**
NORTHERN CAPE	2013	171	410	6 799	290	**7 670**	**5,35**
NORTHERN CAPE	2014	187	313	6 050	8	**6 558**	**4,77**
WESTERN CAPE	2011	15	107	2 050	1	**2 173**	**4,92**
WESTERN CAPE	2012	153	653	12 397	3	**13 206**	**4,94**
WESTERN CAPE	2013	690	1 529	28 488	2	**30 709**	**4,98**
WESTERN CAPE	2014	511	1 430	24 829		**26 770**	**5,34**
Total		**11 709**	**34 951**	**469 441**	**2 243**	**518 344**	**6,74**

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**		**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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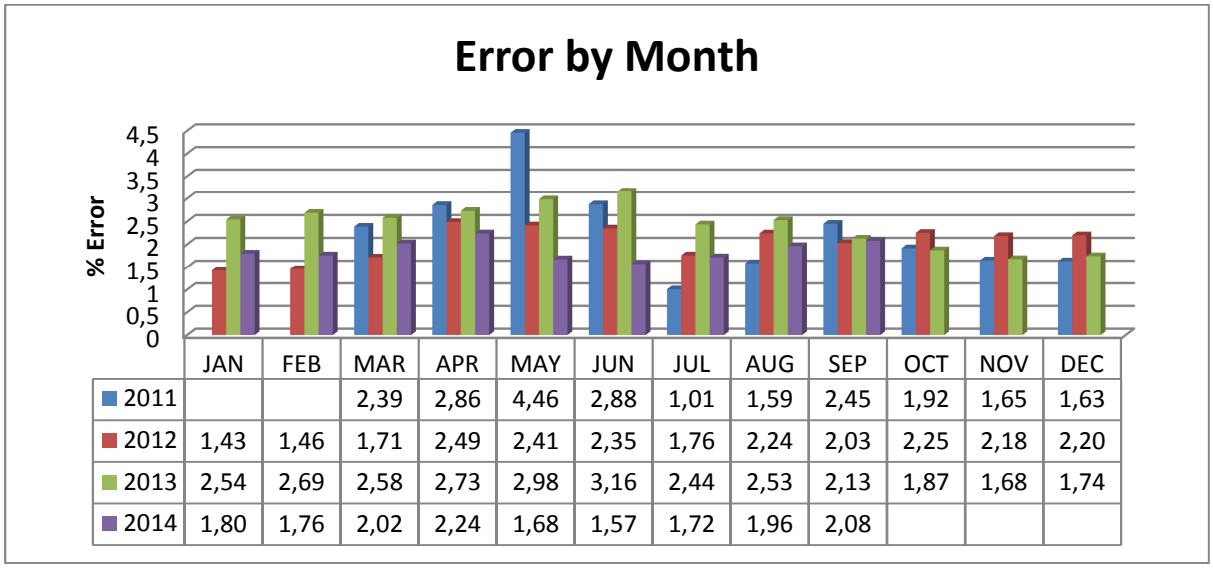
Table 6: Number of Unsuccessful Tests and Reasons (1-30 September 2014)

Province	ERROR	INVALD	NO RESULTS	MTB RESULTS	Grand Total	% ERROR
Eastern Cape	1 009	1 257	84	41 975	44 325	2,28
Free State	66	23		12 787	12 876	0,51
Gauteng	556	148	13	32 831	33 548	1,66
Kwa-Zulu Natal	1 310	693	58	54 643	56 704	2,31
Limpopo	528	456	30	22 378	23 392	2,26
Mpumalanga	399	108	19	11 790	12 316	3,24
North West	504	164	32	15 289	15 989	3,15
Northern Cape	142	108	1	6 453	6 704	2,12
Western Cape	98	94	3	16 928	17 123	0,57
Grand Total	**4 612**	**3 051**	**239**	**215 074**	**222 977**	**2,07**

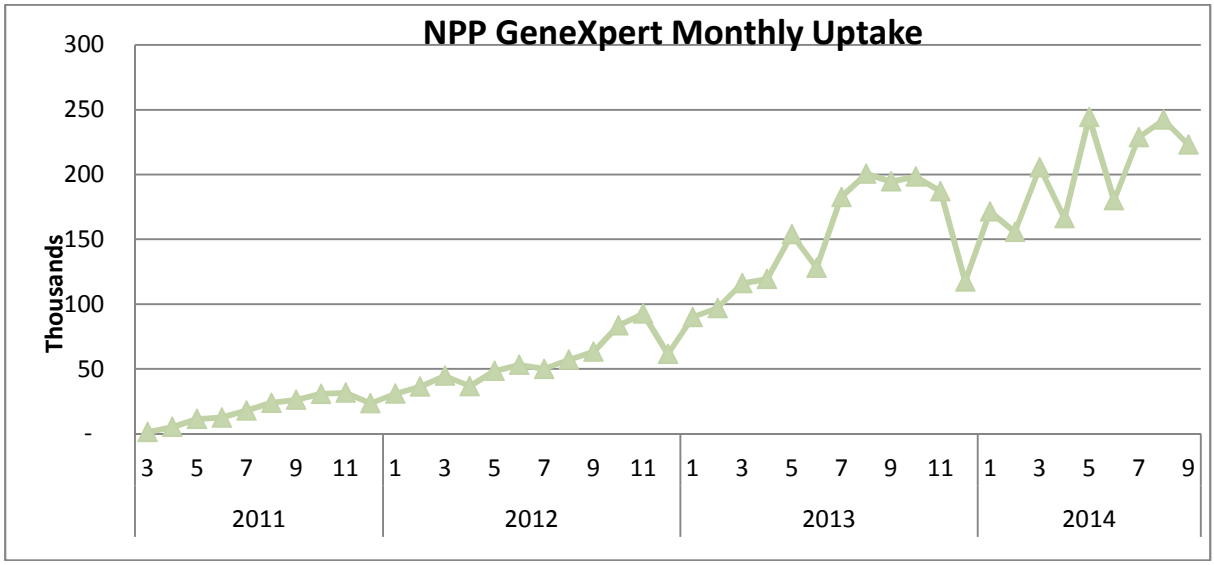
Figure 1: GeneXpert Error by Month



	JAN	FEB	MAR	APR	MAY	JUN	JUL	AUG	SEP	OCT	NOV	DEC
2011			2,39	2,86	4,46	2,88	1,01	1,59	2,45	1,92	1,65	1,63
2012	1,43	1,46	1,71	2,49	2,41	2,35	1,76	2,24	2,03	2,25	2,18	2,20
2013	2,54	2,69	2,58	2,73	2,98	3,16	2,44	2,53	2,13	1,87	1,68	1,74
2014	1,80	1,76	2,02	2,24	1,68	1,57	1,72	1,96	2,08			

5. Monthly uptake since implementation started

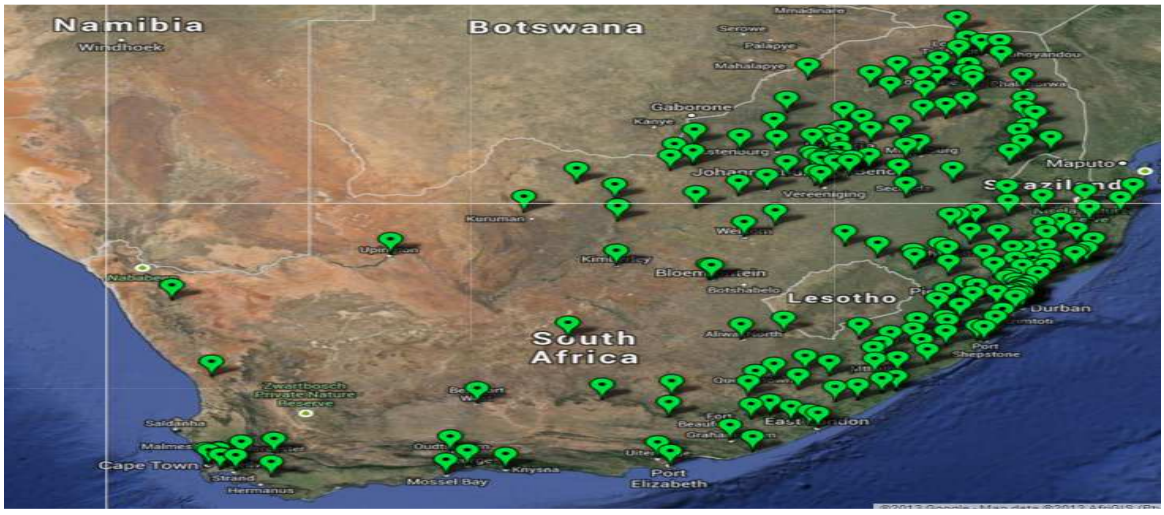
Figure 2: GeneXpert Monthly Uptake



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 1,584 laboratory staff and 7,348health 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
Mboowa G et al, BMC Infec Dis, 2014	• Determined the frequency of MDR-TB in Kampala using Xpert® MTB/RIF in comparison with the agar proportion method (APM) • Determined the frequency of probes for different rpoB gene mutations using Xpert® MTB/RIF assay in the 81 bp RRDR • n=1501	• Xpert® MTB/RIF assay detected 313 MTB positive specimens • n= 12 specimens had both MTB and rifampicin- resistance • n=1/12 found to be rifampicin mono-resistant on APM while the 11 were found to be MDR-TB • E (7/12), B (3/12), A (1/12), D (1/12) and no rif-resistance was associated with probe C	
Ssengooba Wet al, PLoS One, 2014	Compared the diagnostic gain of the Xpert add-on strategy with Xpert replacement strategy for pulmonary tuberculosis diagnosis among HIV-infected adults to inform its implementation • N=424	• Add-on strategy Xpert showed an incremental sensitivity of 44.7% (35.7-53.9%) when added to Direct Zhiel Neelsen, 42.3% (33.4-51.5%) to direct fluorescent microscopy and 35.0% (26.5-44.0%) to concentrated fluorescent microscopy. • Doing smear microscopy prior to Xpert assay in add-on fashion only identifies a	

		few additional TB cases.	
Coetzee L et al, Peadiat Infec Dis, 2014	Prospective hospital-based study of children <13 years referred for FNAB at Tygerberg hospital and Dora Nginza hospital, South Africa • N=72	XpertMTB/RIF identified 32 of 40 cases as positive with a sensitivity of 80%	Specificity of 93.8%

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

11.2. *Connectivity solutions for the GeneXpert*

- Connectivity: Collaboration with Cepheid ongoing
  - i. Remote connectivity – old dashboard still up to collect routine data ~ 2.3mil results to date

11.3 mHealth solutions for MDR-TB

A 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. A pilot (proof-of-concept) interface (Treat TB) has been developed and is due to be implemented at MDR-TB treatment initiation sites in two districts of Gauteng (City of Johannesburg and Ekurhuleni) at the end of November 2014. Two facilities in the Eastern Cape have also requested its implementation (date to be confirmed). The Treat TB interfaced has been designed to be fully interoperable, and will eventually be absorbed, with the emocha interface. Emocha is due to be launched at Murchison Hospital in Kwa-Zulu Natal in January 2015.

11. Update on other projects

Grand Challenges Canada project: Multiple POC HIV/TB integration feasibility project

- Study is complete, data analysis and costing analysis is still ongoing

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 of the study to determine appropriate stool processing protocol is continuing. A second phase has been included to test two different buffers.
- **Longitudinal follow up of Dried Blood Spotsfor 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.
- **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). Publication has been drafted, under review.
- **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 Quantassay for VL was performed on a 42 member plasma HIV-1 subtype C panel versus the CAP/CTMv2 (Roche) and RealTi*m*e HIV-1 (Abbott). 2). A laboratory validation is planned to test the Cepheid HIV-1 Quantitative VL cartridge on plasma, DBS and whole blood. The protocol is in development and ethics has been obtained. 3.) A laboratory evaluation of the new Alere q POC HIV viral instrument is planned. Protocol is being developed.
- **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. Additional data analysis underway.

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

The NHLS Ladysmith Laboratory and National Priority Programmes (NPP) teamed up with National and Provincial Department of Health and provided services including screening and testing TB and HIV, CD4 Count and Pap Smears at the Eskom Ingula HCT campaign on 23 September 2014.The NHLS provided Xpert TB testing in a mobile laboratory from which the NHLS National Priority Programmes team tested Xpert TB samples on-site, using a GeneXpert 16 instrument installed in NHLS Mobile Laboratory. The campaign was successful and received 197 sputum samples for Xpert TB testing, 80 samples received for CD4 count analysis and 33 samples received for Pap Smears