



NATIONAL HEALTH
LABORATORY SERVICE

GeneXpert MTB/RIF

Progress Report

February 2015





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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, 309 GeneXpert instruments of varying sizes (GX4: 110; GX16:190; GX48: 1; GX80:8) 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.

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:

- Kgošimampuru 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 5 353 517 specimens have been processed to date (28 February 2015). In January 194,940 specimens were processed. The total % of *Mycobacterium tuberculosis* complex (MTBC) detected in this cohort was 9.39% (18,296). 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 11% 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	17.1
EASTERN CAPE	2012	15,880	84,755	2,862	103,497	15.3
EASTERN CAPE	2013	45,469	320,022	10,046	375,537	12.1
EASTERN CAPE	2014	48,900	382,954	11,369	443,223	11.0
EASTERN CAPE	2015	8,147	60,844	1,859	70,850	11.5
FREE STATE	2011	2,811	14,532	35	17,378	16.2
FREE STATE	2012	11,660	76,863	288	88,811	13.1
FREE STATE	2013	14,758	139,299	1,020	155,077	9.5
FREE STATE	2014	14,030	125,556	998	140,584	10.0
FREE STATE	2015	2,181	18,281	216	20,678	10.5
GAUTENG	2011	3,094	18,881	443	22,418	13.8
GAUTENG	2012	11,120	72,979	2,305	86,404	12.9
GAUTENG	2013	31,432	215,064	7,690	254,186	12.4
GAUTENG	2014	38,537	303,875	7,433	349,845	11.0
GAUTENG	2015	6,190	51,730	1,268	59,188	10.5
KWAZULU-NATAL	2011	7,546	30,575	896	39,017	19.3
KWAZULU-NATAL	2012	23,963	135,973	5,915	165,851	14.4
KWAZULU-NATAL	2013	42,294	293,200	15,003	350,497	12.1
KWAZULU-NATAL	2014	57,322	519,673	18,686	595,681	9.6
KWAZULU-NATAL	2015	9,208	84,129	3,263	96,600	9.5
LIMPOPO	2011	1,973	17,253	173	19,399	10.2
LIMPOPO	2012	4,004	30,924	689	35,617	11.2



LIMPOPO	2013	13,927	188,932	6,086	208,945	6.7
LIMPOPO	2014	14,376	211,955	7,688	234,019	6.1
LIMPOPO	2015	2,022	28,285	1,177	31,484	6.4
MPUMALANGA	2011	2,629	12,683	1,100	16,412	16.0
MPUMALANGA	2012	4,035	22,226	1,133	27,394	14.7
MPUMALANGA	2013	10,406	63,030	2,210	75,646	13.8
MPUMALANGA	2014	14,650	112,752	4,211	131,613	11.1
MPUMALANGA	2015	2,162	16,774	851	19,787	10.9
NORTH WEST	2011	3,429	14,557	644	18,630	18.4
NORTH WEST	2012	5,499	29,977	2,052	37,528	14.7
NORTH WEST	2013	13,301	100,512	4,926	118,739	11.2
NORTH WEST	2014	17,001	150,582	6,638	174,221	9.8
NORTH WEST	2015	2,666	22,212	912	25,790	10.3
NORTHERN CAPE	2011	2,727	15,527	712	18,966	14.4
NORTHERN CAPE	2012	3,830	21,728	1,038	26,596	14.4
NORTHERN CAPE	2013	7,912	53,728	2,529	64,169	12.3
NORTHERN CAPE	2014	8,685	63,062	2,891	74,638	11.6
NORTHERN CAPE	2015	1,385	9,241	330	10,956	12.6
WESTERN CAPE	2011	2,173	9,897	47	12,117	17.9
WESTERN CAPE	2012	13,206	68,045	689	81,940	16.1
WESTERN CAPE	2013	28,653	155,003	2,343	185,999	15.4
WESTERN CAPE	2014	33,718	180,293	1,992	216,003	15.6
WESTERN CAPE	2015	4,796	27,503	252	32,551	14.7
TOTAL		616,959	4,591,101	145,457	5,353,517	11.5

Table 2: GeneXpert MTB Results by province (01-28 February 2015)

Province	MTB Detected	MTB Not Detected	Test Unsuccessful	Grand Total	% MTB Detected
Eastern Cape	3 746	32 466	997	37 209	10,07
Free State	995	9 313	120	10 428	9,54
Gauteng	3 176	28 881	832	32 889	9,66
Kwa-Zulu Natal	4 494	44 683	1 769	50 946	8,82
Limpopo	946	15 774	616	17 336	5,46
Mpumalanga	998	8 796	492	10 286	9,70
North West	1 253	11 410	440	13 103	9,56
Northern Cape	621	4 515	155	5 291	11,74
Western Cape	2 067	15 289	96	17 452	11,84
Grand Total	18 296	171 127	5 517	194 940	9,39

Table 3: Provincial GeneXpert RIF Results in MTB detected cases (01-28 February 2015)

Province	Inconclusive	Resistant	Sensitive	Grand Total	% Rif Resistant
Eastern Cape	42	229	3 470	3 741	6,12
Free State	10	59	925	994	5,94
Gauteng	43	191	2 941	3 175	6,02
Kwa-Zulu Natal	100	343	4 044	4 487	7,64
Limpopo	6	51	887	944	5,40
Mpumalanga	14	90	892	996	9,04
North West	16	75	1 162	1 253	5,99
Northern Cape	10	25	586	621	4,03
Western Cape	24	101	1 942	2 067	4,89
Grand Total	265	1 164	16 849	18 278	6,37

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	1 274	2 969	41 073	153	45 469	6,53
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	372	800	13 564	22	14 758	5,42
GAUTENG	2011	25	179	2 889	1	3 094	5,79
GAUTENG	2012	136	766	10 142	76	11 120	6,89
GAUTENG	2013	921	2 008	28 433	70	31 432	6,39
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	1 076	3 704	37 079	435	42 294	8,76
LIMPOPO	2011	25	148	1 775	25	1 973	7,50
LIMPOPO	2012	52	268	3 609	75	4 004	6,69
LIMPOPO	2013	299	715	12 803	110	13 927	5,13
MPUMALANGA	2011	30	207	2 386	6	2 629	7,87
MPUMALANGA	2012	57	401	3 501	76	4 035	9,94
MPUMALANGA	2013	238	1 024	9 116	28	10 406	9,84
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	325	730	12 219	27	13 301	5,49
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	175	422	7 025	290	7 912	5,33
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	636	1 409	26 606	2	28 653	4,92
EASTERN CAPE	2014	1 248	2 983	44 620	49	48 900	6,10
EASTERN CAPE	2015	79	478	7 582	8	8 147	5,87
FREE STATE	2014	367	816	12 843	4	14 030	5,82
FREE STATE	2015	23	125	2 032	1	2 181	5,73
GAUTENG	2014	818	2 293	35 399	27	38 537	5,95
GAUTENG	2015	87	364	5 737	2	6 190	5,88
KWAZULU-NATAL	2014	1 512	4 962	50 646	202	57 322	8,66
KWAZULU-NATAL	2015	185	723	8 279	21	9 208	7,85
LIMPOPO	2014	328	706	13 294	48	14 376	4,91
LIMPOPO	2015	10	107	1 898	7	2 022	5,29
MPUMALANGA	2014	380	1 281	12 969	20	14 650	8,74
MPUMALANGA	2015	29	193	1 938	2	2 162	8,93
NORTH WEST	2014	504	909	15 579	9	17 001	5,35
NORTH WEST	2015	45	151	2 469	1	2 666	5,66
NORTHERN CAPE	2014	200	448	8 022	15	8 685	5,16
NORTHERN CAPE	2015	13	73	1 299		1 385	5,27
WESTERN CAPE	2014	678	1 766	31 273	1	33 718	5,24
WESTERN CAPE	2015	52	234	4 510		4 796	4,88
Total		13 476	41 254	559 907	2 322	616 959	6,69

3. Rif Concordance

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
		#	%	#	%		#	%	#	%	
Eastern Cape	5 514	213	3,9%	138	64,8%	3	1 393	25%	1 290	92,6%	5
Free State	1 903	166	8,7%	95	57,2%	0	643	34%	523	81,3%	146
Gauteng	4 116	160	3,9%	109	68,1%	4	1 067	26%	968	90,7%	20
Kwazulu-Natal	9 673	2 221	23,0%	2 069	93,2%	0	2 117	22%	1 857	87,7%	80
Limpopo	1 451	85	5,9%	69	81,2%	2	335	23%	260	77,6%	9
Mpumalanga	2 369	532	22,5%	523	98,3%	0	870	37%	749	86,1%	2
North West	2 506	143	5,7%	103	72,0%	0	799	32%	681	85,2%	31
Northern Cape	962	202	21,0%	152	75,2%	3	367	38%	281	76,6%	22
Western Cape	3 281	96	2,9%	26	0,0%	0	2 583	79%	2 403	93,0%	2
National	31 775	3 818	12,0%	3 284	86,0%	12	10 174	32%	9 012	88,6%	317

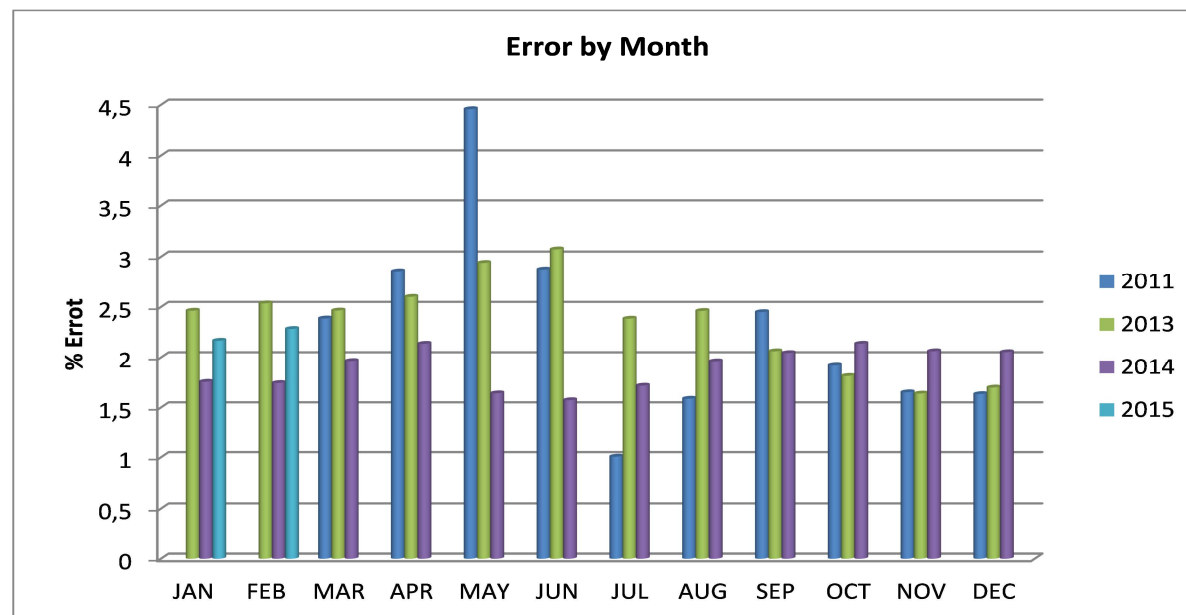
4. Errors

Average error rate has ranged consistently below 3%, however Limpopo and Mpumalanga 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 (1-28 February 2015)

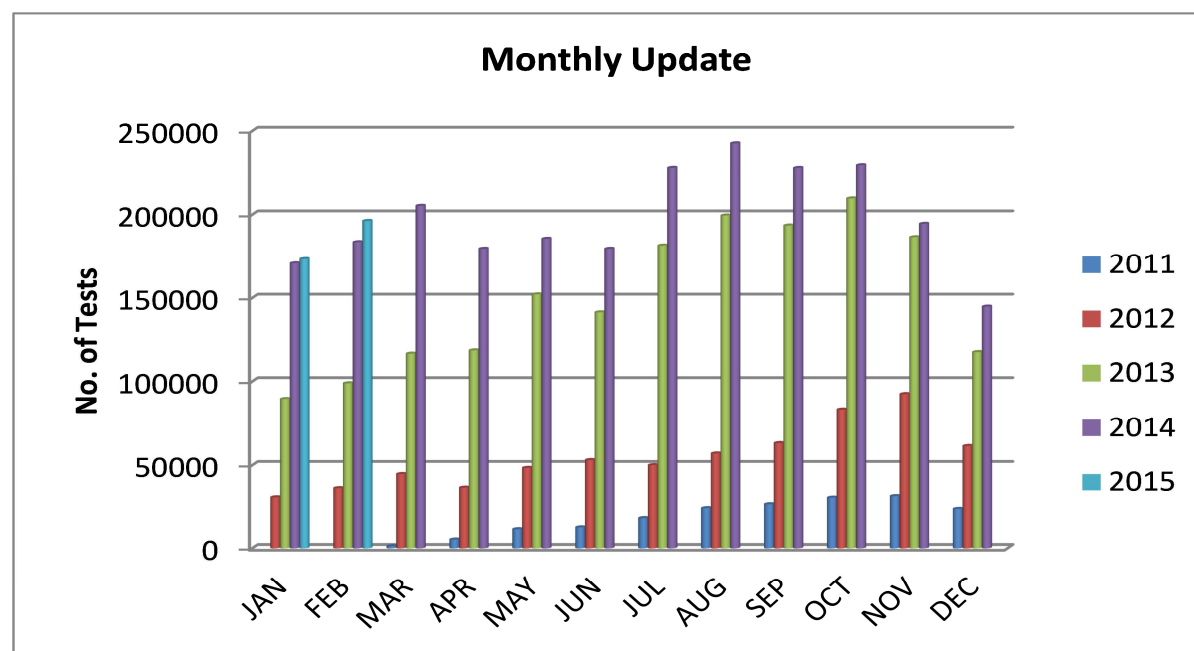
Province	Error	Invalid	No Results	MTB Results	Grand Total	% Error
Eastern Cape	783	128	85	36 227	37 223	2,10
Free State	96	20	4	10 379	10 499	0,91
Gauteng	716	98	18	32 244	33 076	2,16
Kwa-Zulu Natal	1 402	252	115	49 319	51 088	2,74
Limpopo	474	132	10	16 753	17 369	2,73
Mpumalanga	441	39	12	9 800	10 292	4,28
North West	363	60	17	12 679	13 119	2,77
Northern Cape	99	56		5 137	5 292	1,87
Western Cape	88	7	1	17 695	17 791	0,49
Grand Total	4 462	792	262	190 233	195 749	2,28

Figure 1: GeneXpert Error by Month



5. Monthly uptake since implementation started

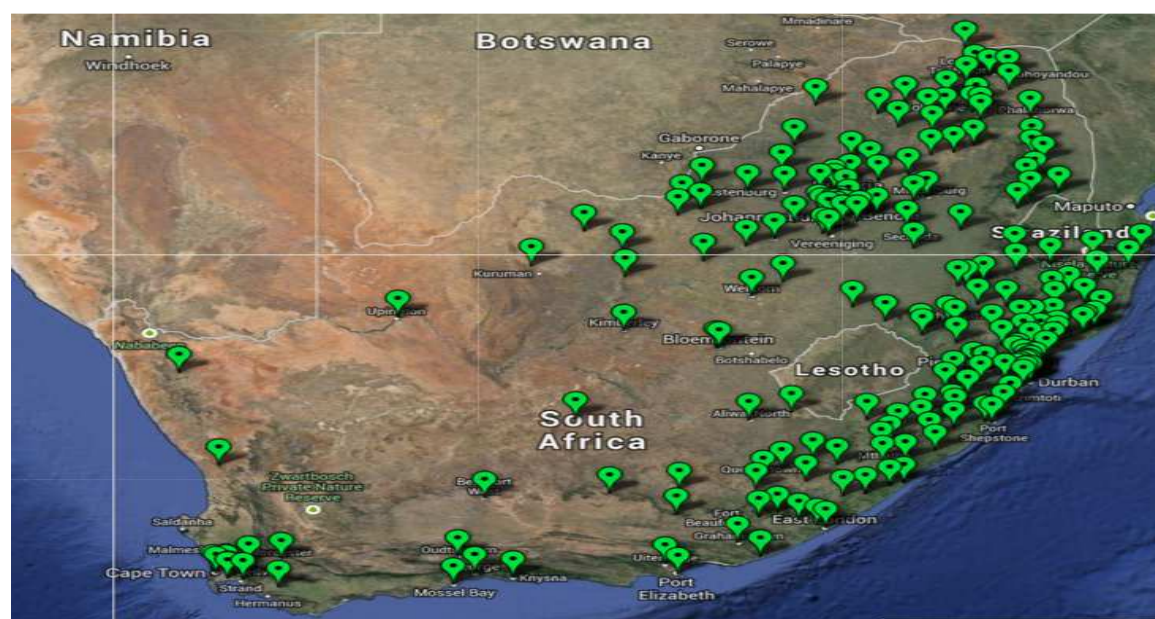
Figure 2: GeneXpert Monthly Uptake



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 (221 testing centers, 310 analysers, Gx4: 110; Gx16-8: 1; Gx16: 188; GX48:1; GX80-80: 7) *20 clinic placements *7 Correctional Facilities *6 Mobile Vans



7. Training: Laboratory and Clinical

A total of 1,710 laboratory staff and 8,198 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 paediatric samples: being addressed
- EPTB training to be expanded to correctional facilities to ensure compliance
- 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
You et al, J Infec, 2015	Evaluated the cost-effectiveness of rapid diagnosis with Xpert in patients hospitalized for suspected active pulmonary tuberculosis in Hong Kong	• Xpert was more effective with higher QALYs gained and a lower mortality rate when compared with smear plus Xpert • A conventional diagnostic approach was the least preferred option with the highest cost, lowest QALYs gained and highest mortality rate. • Sensitivity analysis showed that Xpert would be the most cost-effective option if the sensitivity of sputum AFB smear microscopy was $\leq 74\%$.	
Mokaddas et al, JCM 2015	Investigated Discordance between Xpert MTB/RIF and BACTEC MGIT 960 culture system for detection of rifampin-resistant Mycobacterium tuberculosis isolates in a low TB incidence country N=452	• N=440 Mycobacterium tuberculosis were detected as rifampin-susceptible. • N=10 Mycobacterium tuberculosis were detected rifampin-resistant • Two rifampin-susceptible isolates by MGIT were rifampin-resistant by Xpert. • rpoB sequencing identified a silent (CTG521TTG) mutation in one and a missense (GAC516TAC) mutation in another isolate.	
Kim et al, Ann Clin LabSci, 2015	Evaluated the performance of Xpert MTB/RIF in identifying MTB and resistance to RIF in patients with suspected TB who were hospitalized at a secondary hospital in Korea N=444	• The sensitivity, specificity, PPV, and NPV of the Xpert MTB/RIF assay were 73.85%, 99.03%, 94.12%, and 94.72%, respectively. • Among five patients with RIF resistance determined by the Xpert MTB/RIF assay, four (80%) were confirmed as suffering from multidrug-resistant (MDR) TB by DST.	



10. Update on GeneXpert Research projects:

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

- EQA panel report summaries has been sent to relevant program co-ordinators.
- TBGxMonitor™ (www.tbgxmonitor.com) upgrade specification finalized.
 - o Developments partially complete. Completed components have been validated and will published live 1 April.
 - o Continued developments will be published at a later stage.
- EQA panel 1 for 2015 is being prepared

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. New trial commencing on the version likely to be made commercial.

11.3.mHealth solutions for MDR-TB

PHC, Linkage and MDR-TB APPs (emocha)

The first 3 sites in Port Shepstone (Murchison Hospital, Gateway Clinic and Gamalakhe) will receive their first training on the 18th of March 2015 at the Ugu District Offices in Kwa-Zulu Natal. The training will be led by NHLS and Jhpiego South Africa. The implementation of the mHealth system will commence on 19 March 2015 and will be supervised at each facility until 27 March 2015. Thereafter, regular monitoring visits will be planned.

Treat TB APP

The Treat TB app was developed and implemented into the first pilot site, Charlotte Maxeke Johannesburg Academic Hospital, on 4 December 2014. Training was performed on the app to two clinicians, one data capturer, two nurses and one social worker. The app development was proven to be successful, with a further software upgrade to refine it. The next seven sites for implementation are; South Rand Hospital, Helen Joseph Hospital, Baragwanath Hospital, Phulusong, Thembisa, Germiston (Bertha Gxawa) and Thambo. The MDR-TB Coordinator (Portia Madumo) has been granted permission by the Deputy MDR-TB Director for the Gauteng Province, to attend all TB meetings for the districts of Ekurhuleni and City of Johannesburg.



11. Update on other projects

- **Evaluation of the GeneXpert to Diagnose Paediatric TB using stool specimens:** (In collaboration with David Alland and FIND). The laboratory R&D component to determine appropriate stool processing protocol has started. Phase 1a completed and involved 30 spiked TB positive and 30 TB negative specimens tested using 6 different stool processing and filtration protocols. Phase 1b completed (25 positive and 25 negative specimens processed). Phase IIA has started – 50 patients enrolled.
- **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 72 weeks. Outstanding final visit (V7) DBS for testing.
- **Laboratory validation of new TB diagnostics:** 1). A validation protocol is underway for evaluation of the updated Abbott MTB-RT high throughput TB assay. The clinical study has begun: n=153 patients have been recruited to date and tested on the new Abbott assay for comparison to MGIT culture and smear.
- **Laboratory validation of new HIV diagnostics:**
 - A pilot evaluation of the new Alere q VL POC instrument (Alere, Inc) on a longitudinal cohort of whole blood specimens. Performance will be compared to plasma VL on Abbott and DBS VL on Abbott to determine the place for POC.
 - A laboratory evaluation of the Cepheid HIV-1 Quantitative VL cartridge on plasma, DBS and whole blood. n=85 patients have been recruited into the study and plasma, whole blood and DBS tested on the Cepheid platform. Comparison will be made to Roche plasma VL.
- **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 February 2015.