



NATIONAL HEALTH
LABORATORY SERVICE

GeneXpert MTB/RIF

Progress Report

August 2014





Table of Contents

Background to project	3
Assays performed to date	5
Rif Concordance	8
Errors	9
Monthly uptake since implementation started	10
Specific GeneXpert Site Progress	10
Training: Laboratory and Clinical	11
Challenges identified during the course of the project to date	11
Literature Update	11
Update on Research Projects	13
Funding	14
Recent Campaigns	14



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, 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.



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 4,189,455 specimens have been processed to date (31 August 2014). In August 241,561 specimens were processed. The total % of *Mycobacterium tuberculosis* complex (MTBC) detected in this cohort was 9.31% (22,499). 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	3252	15235	549	19 036	17,1
EASTERN CAPE	2012	15880	84755	2862	103 497	15,3
EASTERN Cape	2013	43908	308311	9859	362 078	12,1
EASTERN CAPE	2014	31692	246074	5860	283 626	11,2
FREE STATE	2011	2811	14532	35	17 378	16,2
FREE STATE	2012	11660	76863	288	88 811	13,1
FREE STATE	2013	14545	136631	1274	152 450	9,5
FREE STATE	2014	9316	86569	789	96 674	9,6
GAUTENG	2011	3094	18881	443	22 418	13,8
GAUTENG	2012	11120	72979	2305	86 404	12,9
GAUTENG	2013	30693	210680	7769	249 142	12,3
GAUTENG	2014	25584	204129	5131	234 844	10,9
KWAZULU-NATAL	2011	820	3347	56	4 223	19,4
KWAZULU-NATAL	2012	2754	13657	768	17 179	16,0
KWAZULU-NATAL	2013	6171	40657	2174	49 002	12,6
KWAZULU-NATAL	2014	4731	35645	1286	41 662	11,4
KWAZULU-NATAL	2011	6726	27228	840	34 794	19,3
KWAZULU-NATAL	2012	21209	122316	5147	148 672	14,3
KWAZULU-NATAL	2013	36259	251540	12980	300 779	12,1
KWAZULU-NATAL	2014	34345	311360	10600	356 305	9,6
LIMPOPO	2011	1973	17253	173	19 399	10,2
LIMPOPO	2012	4004	30924	689	35 617	11,2
LIMPOPO	2013	13819	186281	6110	206 210	6,7

5 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.



LIMPOPO	2014	9815	147079	4945	161 839	6,1
MPUMALANGA	2011	2629	12683	1100	16 412	16,0
MPUMALANGA	2012	4035	22226	1133	27 394	14,7
MPUMALANGA	2013	10169	60955	2336	73 460	13,8
MPUMALANGA	2014	9961	75896	2590	88 447	11,3
NORTH WEST	2011	3429	14557	644	18 630	18,4
NORTH WEST	2012	5499	29977	2052	37 528	14,7
NORTH WEST	2013	12835	96815	4872	114 522	11,2
NORTH WEST	2014	11489	101914	4399	117 802	9,8
NORTHERN CAPE	2011	2727	15527	712	18 966	14,4
NORTHERN CAPE	2012	3830	21728	1038	26 596	14,4
NORTHERN CAPE	2013	7670	51607	2491	61 768	12,4
NORTHERN CAPE	2014	5819	40989	1988	48 796	11,9
WESTERN CAPE	2011	2173	9897	47	12 117	17,9
WESTERN CAPE	2012	13206	68045	689	81 940	16,1
WESTERN CAPE	2013	30709	165219	2871	198 799	15,4
WESTERN CAPE	2014	24322	128511	1406	154 239	15,8
TOTAL		496 683	3 579 472	113 300	4 189 455	11,9

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

Province	MTB Detected	MTB Not Detected	Test Unsuccessful	Grand Total	% MTB Detected
Eastern Cape	4 428	40 952	993	46 373	9,55
Free State	1 274	12 481	122	13 877	9,18
Gauteng	3 329	28 935	575	32 839	10,14
Kwa-Zulu Natal	5 478	57 048	1 855	64 381	8,51
Limpopo	1 303	22 747	862	24 912	5,23
Mpumalanga	1 256	10 894	565	12 715	9,88
North West	1 431	14 282	619	16 332	8,76
Northern Cape	748	6 437	178	7 363	10,16
Western Cape	3 252	19 350	167	22 769	14,28
Grand Total	22 499	213 126	5 936	241 561	9,31



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

Province	Inconclusive	Resistant	Sensitive	No Rif Results	Grand Total	% RIF Resistance
Eastern Cape	63	266	4 097	2	4 428	6,01
Free State	35	73	1 166		1 274	5,73
Gauteng	54	184	3 090	1	3 329	5,53
Kwa-Zulu Natal	95	441	4 927	15	5 478	8,05
Limpopo	35	64	1 190	14	1 303	4,91
Mpumalanga	28	118	1 109	1	1 256	9,39
North West	37	69	1 325		1 431	4,82
Northern Cape	19	29	700		748	3,88
Western Cape	57	177	3 018		3 252	5,44
Grand Total	423	1 421	20 622	33	22 499	6,32

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	2919	52	3 252	7,6
EASTERN CAPE	2012	213	1077	14456	134	15 880	6,8
EASTERN CAPE	2013	1237	2884	39638	149	43 908	6,6
EASTERN CAPE	2014	943	1952	28766	31	31 692	6,2
FREE STATE	2011	28	155	2626	2	2 811	5,5
FREE STATE	2012	162	755	10717	26	11 660	6,5
FREE STATE	2013	368	802	13353	22	14 545	5,5
FREE STATE	2014	295	537	8481	3	9 316	5,8
GAUTENG	2011	25	179	2889	1	3 094	5,8
GAUTENG	2012	136	766	10142	76	11 120	6,9
GAUTENG	2013	896	1989	27738	70	30 693	6,5
GAUTENG	2014	572	1541	23451	20	25 584	6,0
KWAZULU-NATAL	2011	5	77	737	1	820	9,4
KWAZULU-NATAL	2012	20	241	2449	44	2 754	8,8
KWAZULU-NATAL	2013	139	523	5308	201	6 171	8,5
KWAZULU-NATAL	2014	151	455	4106	19	4 731	9,6
KWAZULU-NATAL	2011	59	515	6138	14	6 726	7,7
KWAZULU-NATAL	2012	397	1925	18679	208	21 209	9,1
KWAZULU-NATAL	2013	931	3173	31924	231	36 259	8,8
KWAZULU-NATAL	2014	1031	2979	30175	160	34 345	8,7
LIMPOPO	2011	25	148	1775	25	1 973	7,5



LIMPOPO	2012	52	268	3609	75	4 004	6,7
LIMPOPO	2013	296	716	12698	109	13 819	5,2
LIMPOPO	2014	234	481	9062	38	9 815	4,9
MPUMALANGA	2011	30	207	2386	6	2 629	7,9
MPUMALANGA	2012	57	401	3501	76	4 035	9,9
MPUMALANGA	2013	228	1006	8906	29	10 169	9,9
MPUMALANGA	2014	316	910	8717	18	9 961	9,1
NORTH WEST	2011	39	303	3083	4	3 429	8,8
NORTH WEST	2012	75	414	5000	10	5 499	7,5
NORTH WEST	2013	306	705	11795	29	12 835	5,5
NORTH WEST	2014	369	612	10501	7	11 489	5,3
NORTHERN CAPE	2011	28	186	2511	2	2 727	6,8
NORTHERN CAPE	2012	50	236	3536	8	3 830	6,2
NORTHERN CAPE	2013	171	410	6799	290	7 670	5,3
NORTHERN CAPE	2014	182	268	5361	8	5 819	4,6
WESTERN CAPE	2011	15	107	2050	1	2 173	4,9
WESTERN CAPE	2012	153	653	12397	3	13 206	4,9
WESTERN CAPE	2013	690	1529	28488	2	30 709	5,0
WESTERN CAPE	2014	480	1296	22546		24 322	5,3
Total		11 437,00	33 629,00	449 413,00	2 204,00	496 683	6,8

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

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



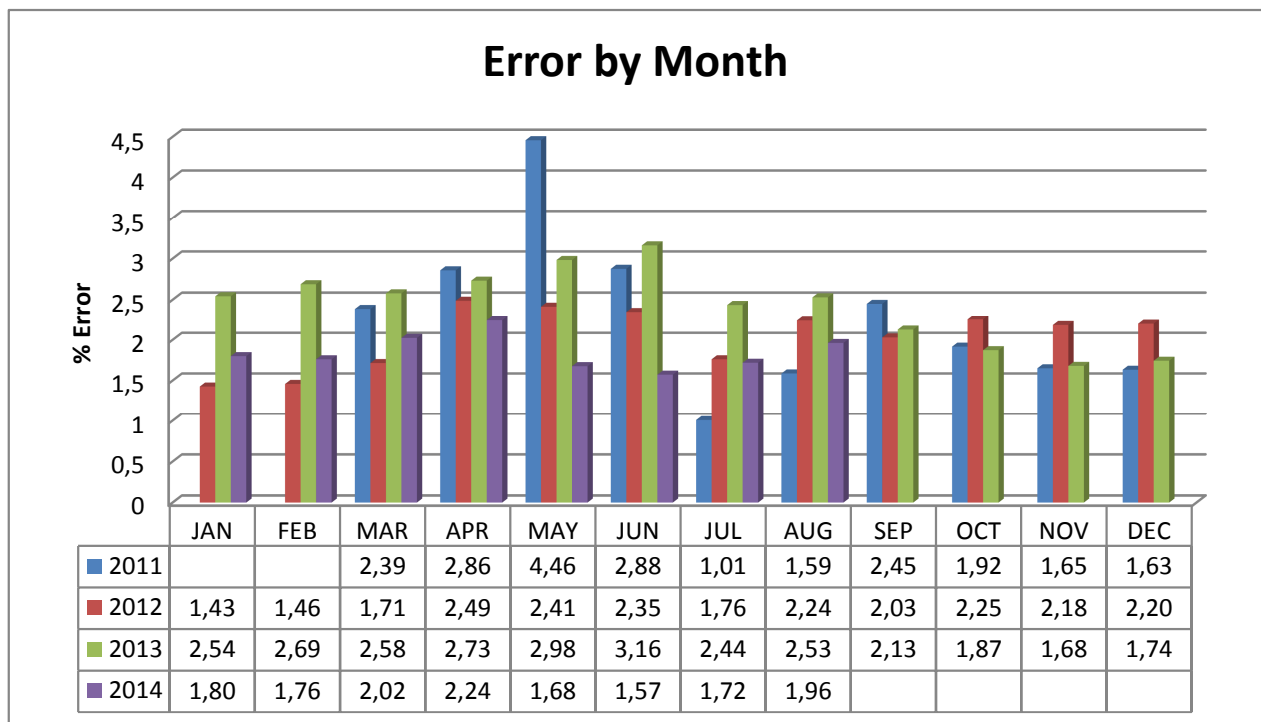
4. Errors

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 August 2014)

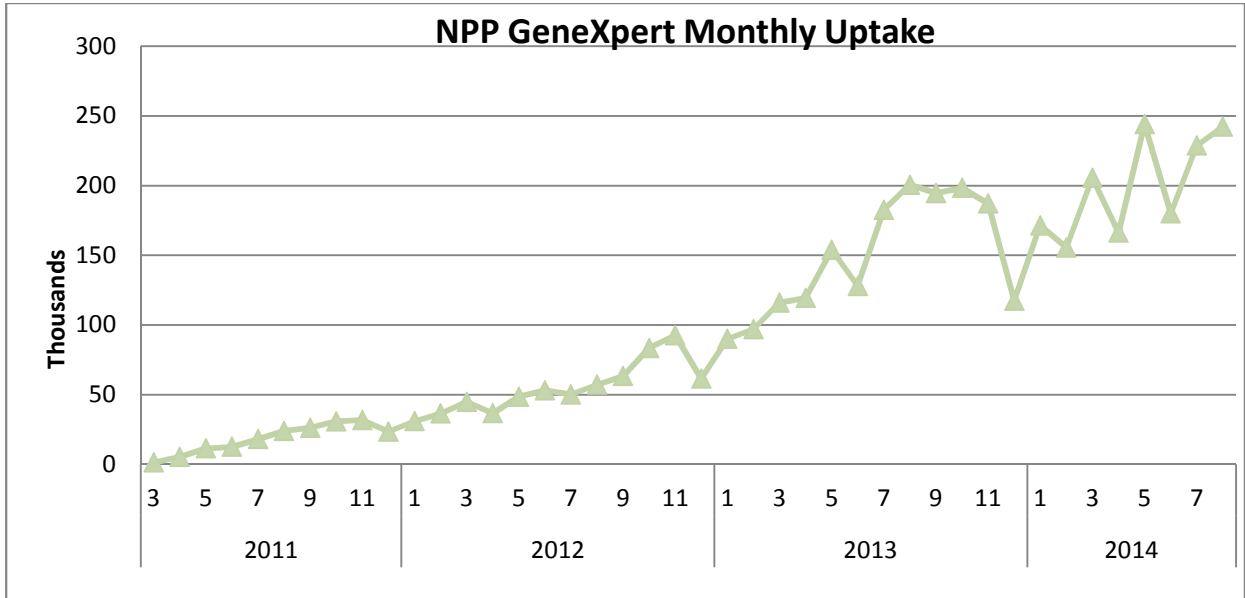
Province	ERRORS	INVALIDS	NO RESULTS	MTB Results	Grand Total	% Error
Eastern Cape	784	169	40	45 488	46 481	1,69
Free State	93	27	2	13 828	13 950	0,67
Gauteng	481	47	47	32 445	33 020	1,46
Kwa-Zulu Natal	1 502	246	107	62 678	64 533	2,33
Limpopo	745	100	17	24 068	24 930	2,99
Mpumalanga	504	32	29	12 167	12 732	3,96
North West	541	31	47	15 769	16 388	3,30
Northern Cape	119	59		7 185	7 363	1,62
Western Cape	116	32	19	23 131	23 298	0,50
Grand Total	4 885	743	308	236 759	242 695	2,01

Figure 1: GeneXpert Error by Month



5. Monthly uptake since implementation started

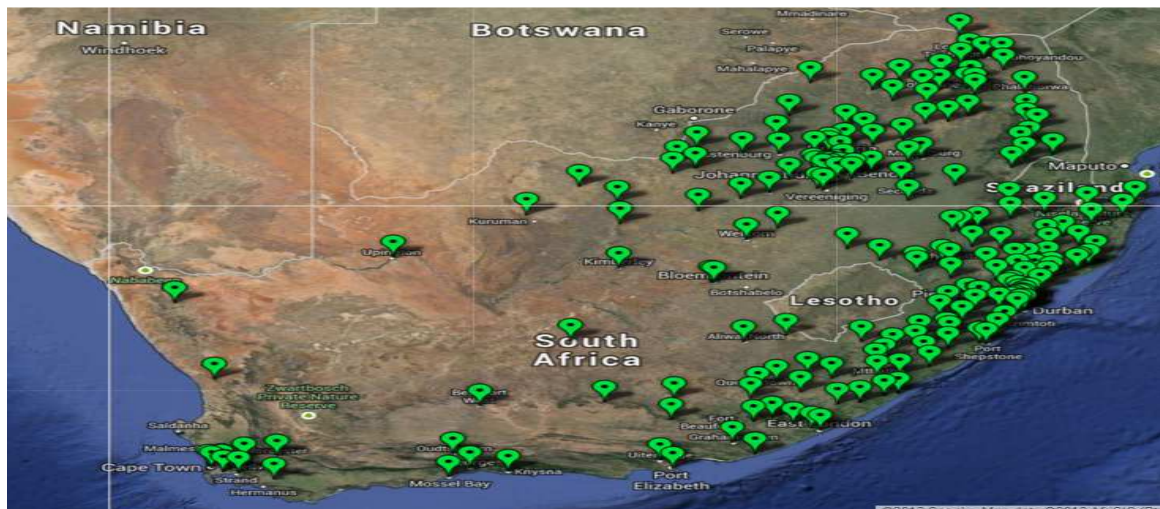
Figure 2: GeneXpert Monthly Uptake



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





7. Training: Laboratory and Clinical

A total of 1,569 laboratory staff and 7,077 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
- 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
Le Palud et al, BMC Pulm Med. 2014	Retrospective review of clinical, radiological, and microbiological characteristics of TB-suspects requiring diagnostic FOB (bronchial aspirate or bronchoalveolar lavage) with Gx assay • N=175	<ul style="list-style-type: none"> • Compared to culture, sensitivity values were 80.0% for the Xpert MTB/RIF, and 25.0% smear 	<ul style="list-style-type: none"> • Compared to culture, specificity values were 98.6% for the Xpert MTB/RIF assay, and 95.8% for smear
Dlamini-Mvelase, BMC Infect Dis, 2014	Retrospective data collection of all patients with rifampicin resistance on Xpert performed between March 2011 and April 2012 in KZN, SA. Xpert results were compared with those of phenotypic and/genotypic drug susceptibility testing • N=637	<ul style="list-style-type: none"> • Of 637 patients tested by Xpert, 50% had confirmatory results, of which a third were sent on the same day as Xpert test. • rifampicin discordance and mono-resistance was 8.8% and 13.4% respectively 	
Raizada N et al, PloS One, 2014	Pediatric presumptive PTB cases	<ul style="list-style-type: none"> • 590 (12.8%, CI 11.8-13.8) pediatric PTB were diagnosed. 	

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	(both TB and Drug Resistant TB (DR-TB)) accessing any public health facilities in India were prospectively enrolled and tested on Xpert MTB/RIF N=4600	<ul style="list-style-type: none"> Overall 10.4% (CI 9.5-11.2) of presumptive PTB cases had positive results by Xpert MTB/RIF, compared with 4.8% (CI 4.2-5.4) who had smear-positive results. Upfront access to Xpert MTB/RIF testing in pediatric presumptive PTB cases was associated with a two-fold increase in bacteriologically-confirmed PTB, and increased detection of rifampicin-resistant TB cases 	
Yin et al, Biomed Res Int. 2014	Evaluated the diagnostic accuracy of the Xpert MTB/RIF assay on childhood pulmonary tuberculosis (PTB) using bronchoalveolar lavage fluid (BALF) , smear and culture in comparison to Chinese clinical composite reference standard N=255	The sensitivity of AFB microscopy, MTB culture, and Xpert MTB/RIF assay was 8.4%, 28.9%, and 53.0%, respectively.	The specificity of three assays was all 100%.
Durovni B et al, Bull World Health Organ, 2014	A pilot implementation study was conducted in two Brazilian cities to explore the replacement of sputum smear microscopy with Xpert.	<ul style="list-style-type: none"> Of the tested sputum samples, 7.3% were too scanty for Xpert and had to be examined microscopically. 10% of Xpert equipment needed replacement, but spare parts were not readily available in the country. Absence of patient identification numbers led to the introduction of errors in the medical information system. 	
Myneedu et al, Int J Tuberc Lung Dis, 2014	Performance of the Xpert® MTB/RIF assay and compare Xpert results with solid and MGIT 960 liquid culture system in an Indian setting.	<ul style="list-style-type: none"> Xpert correctly identified all Mycobacterium tuberculosis isolates. The sensitivity and specificity of the Xpert assay for the detection of rifampicin resistance was respectively 98.2% and 97.0% when compared with MGIT 960 results. 	

10. Update on GeneXpert Research projects:

10.1. 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
 - Submissions dates have closed
 - Analysis and reporting underway
- TBGxMonitor™ (www.tbgxmonitor.com) upgrade specification finalized.
 - Seriun continue to publish updated components which are undergoing verification and validation.



- Development validation to begin from 1 September.

10.2. 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.

10.3 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 and the initial mock data exchange was successful. An additional mHealth pilot, funded by the CDC, will commence before the end of 2014. The pilot will be conducted at MDR-TB treatment initiation sites within two districts of Gauteng, namely; City of Johannesburg and Ekurhuleni. It is an “APP to Tablet” project. The name of the APP is “Treat TB”.

11. Update on other projects

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

- The study is complete. Data analysis and cost analysis is still underway

Sub-studies within GCC

- **Evaluation of the GeneXpert to Diagnose Paediatric 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 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.
- **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 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. 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.

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 August