



NATIONAL HEALTH
LABORATORY SERVICE

GeneXpert MTB/RIF

Progress Report

December 2014





Table of Contents

Background to project	3
Assays performed to date	5
Rif Concordance	8
Errors	8
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	12
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, 308 GeneXpert instruments of varying sizes (GX4: 110; 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 4 974 547 specimens have been processed to date (31 December 2014). In December 140 010 specimens were processed. The total % of *Mycobacterium tuberculosis* complex (MTBC) detected in this cohort was 12.34% (17 278). 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	17,08
EASTERN CAPE	2012	15 880	84 755	2 862	103 497	15,34
EASTERN CAPE	2013	45 469	320 022	10 046	375 537	12,11
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	14 758	139 299	1 020	155 077	9,52
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	31 432	215 064	7 690	254 186	12,37
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	42 294	293 200	15 003	350 497	12,07
LIMPOPO	2011	1 973	17 253	173	19 399	10,17
LIMPOPO	2012	4 004	30 924	689	35 617	11,24
LIMPOPO	2013	13 927	188 932	6 086	208 945	6,67
MPUMALANGA	2011	2 629	12 683	1 100	16 412	16,02
MPUMALANGA	2012	4 035	22 226	1 133	27 394	14,73
MPUMALANGA	2013	10 406	63 030	2 210	75 646	13,76
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	13 301	100 512	4 926	118 739	11,20
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

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.



NORTHERN CAPE	2013	7 912	53 728	2 529	64 169	12,33
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	28 653	155 003	2 343	185 999	15,40
EASTERN CAPE	2014	48 822	382 404	11 341	442 567	11,03
FREE STATE	2014	14 018	125 460	996	140 474	9,98
GAUTENG	2014	38 497	303 721	7 422	349 640	11,01
KWAZULU-NATAL	2014	57 322	519 659	18 686	595 667	9,62
LIMPOPO	2014	14 375	211 955	7 688	234 018	6,14
MPUMALANGA	2014	14 649	112 751	4 211	131 611	11,13
NORTH WEST	2014	16 996	150 519	6 637	174 152	9,76
NORTHERN CAPE	2014	8 665	62 962	2 889	74 516	11,63
WESTERN CAPE	2014	32 111	172 085	1 900	206 096	15,58
TOTAL		576 438	4 262 916	135 193	4 974 547	11,59

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

Province	MTB Detected	MTB Not Detected	Test Unsuccessful	Grand Total	% MTB Detected
Eastern Cape	3 337	21 578	599	25 514	13,08
Free State	1 069	7 308	83	8 460	12,64
Gauteng	2 755	19 005	418	22 178	12,42
Kwa-Zulu Natal	4 219	32 241	1 173	37 633	11,21
Limpopo	1 091	11 501	479	13 071	8,35
Mpumalanga	1 082	6 953	265	8 300	13,04
North West	1 121	7 626	278	9 025	12,42
Northern Cape	553	3 659	166	4 378	12,63
Western Cape	2 051	9 295	105	11 451	17,91
Grand Total	17 278	119 166	3 566	140 010	12,34

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

Province	Inconclusive	Resistant	Sensitive	No Rif Results	Grand Total	% Rif Resistance
Eastern Cape	45	183	3 104	5	3 337	5,48
Free State	16	40	1 013		1 069	3,74
Gauteng	53	151	2 550	1	2 755	5,48
Kwa-Zulu Natal	77	363	3 777	2	4 219	8,60
Limpopo	13	56	1 020	2	1 091	5,13
Mpumalanga	14	85	982	1	1 082	7,86
North West	16	48	1 057		1 121	4,28



Northern Cape	4	46	498	5	553	8,32
Western Cape	22	109	1 920		2 051	5,31
Grand Total	260	1 081	15 921	16	17 278	6,26

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
FREE STATE	2011	28	155	2 626	2	2 811	5,51
FREE STATE	2012	162	755	10 717	26	11 660	6,48
GAUTENG	2011	25	179	2 889	1	3 094	5,79
GAUTENG	2012	136	766	10 142	76	11 120	6,89
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
LIMPOPO	2011	25	148	1 775	25	1 973	7,50
LIMPOPO	2012	52	268	3 609	75	4 004	6,69
MPUMALANGA	2011	30	207	2 386	6	2 629	7,87
MPUMALANGA	2012	57	401	3 501	76	4 035	9,94
NORTH WEST	2011	39	303	3 083	4	3 429	8,84
NORTH WEST	2012	75	414	5 000	10	5 499	7,53
NORTHERN CAPE	2011	28	186	2 511	2	2 727	6,82
NORTHERN CAPE	2012	50	236	3 536	8	3 830	6,16
WESTERN CAPE	2011	15	107	2 050	1	2 173	4,92
WESTERN CAPE	2012	153	653	12 397	3	13 206	4,94
EASTERN CAPE	2014	1 247	2 983	44 543	49	48 822	6,11
FREE STATE	2014	367	815	12 832	4	14 018	5,81
GAUTENG	2014	817	2 289	35 363	28	38 497	5,95
KWAZULU-NATAL	2014	1 512	4 962	50 646	202	57 322	8,66
LIMPOPO	2014	328	706	13 293	48	14 375	4,91
MPUMALANGA	2014	380	1 281	12 968	20	14 649	8,74
NORTH WEST	2014	504	908	15 575	9	16 996	5,34
NORTHERN CAPE	2014	199	448	8 003	15	8 665	5,17
WESTERN CAPE	2014	655	1 691	29 764	1	32 111	5,27
EASTERN CAPE	2013	1 274	2 969	41 073	153	45 469	6,53
FREE STATE	2013	372	800	13 564	22	14 758	5,42
GAUTENG	2013	921	2 008	28 433	70	31 432	6,39
KWAZULU-NATAL	2013	1 076	3 704	37 079	435	42 294	8,76
LIMPOPO	2013	299	715	12 803	110	13 927	5,13
MPUMALANGA	2013	238	1 024	9 116	28	10 406	9,84



NORTH WEST	2013	325	730	12 219	27	13 301	5,49
NORTHERN CAPE	2013	175	422	7 025	290	7 912	5,33
WESTERN CAPE	2013	636	1 409	26 606	2	28 653	4,92
Total		12 927	38 725	522 505	2 281	576 438	6,72

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

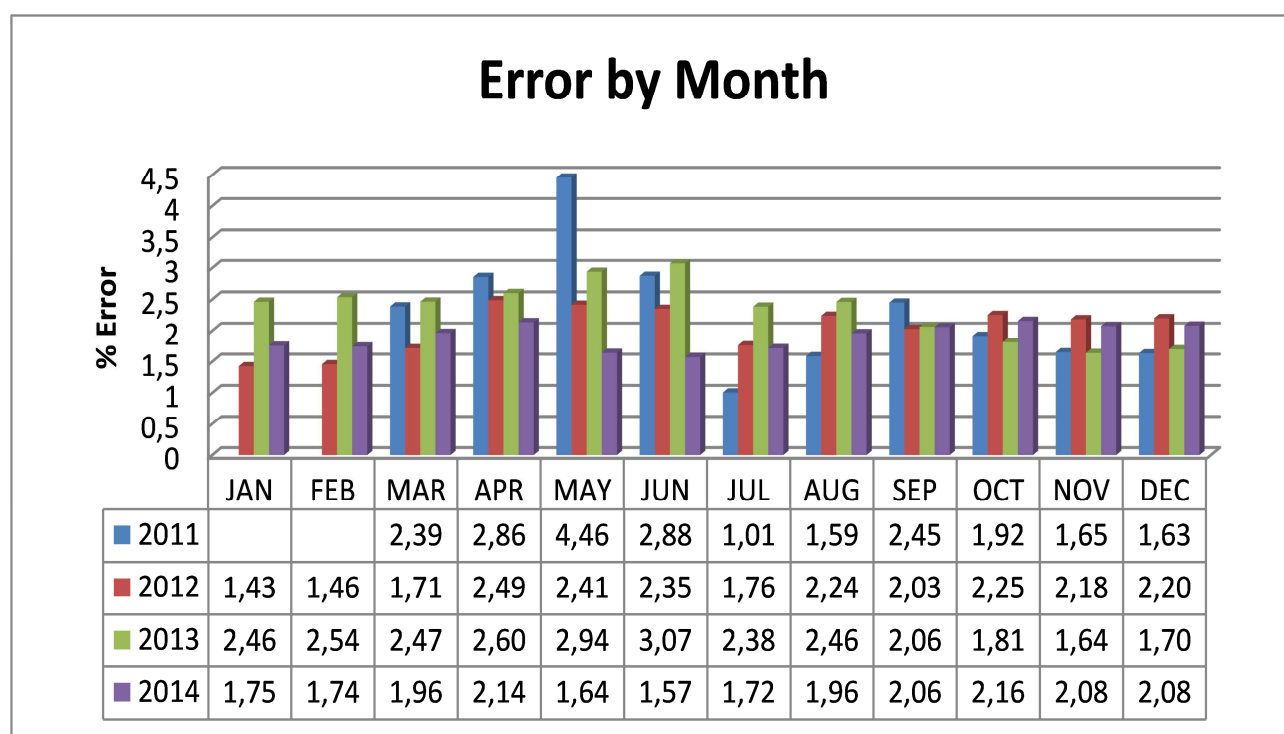
Province	Rif Resistant Cases	GeneXpert Confirmation & Rif Concordance									
		Cultures					LPA				
		Confirmed		Rif Concordance		Pre-analytical	Confirmed		Rif Concordance		Inderterminate
		#	%	#	%		#	%	#	%	
Eastern Cape	5 514	213	3,9%	138	64,8%	3	1 393	25%	1 290	92,6%	5
Free State	1 903	166	8,7%	95	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%. Details of the invalid results, which likely represent sample issues remains below 1%. These are being monitored regularly and corrective action implemented where necessary.

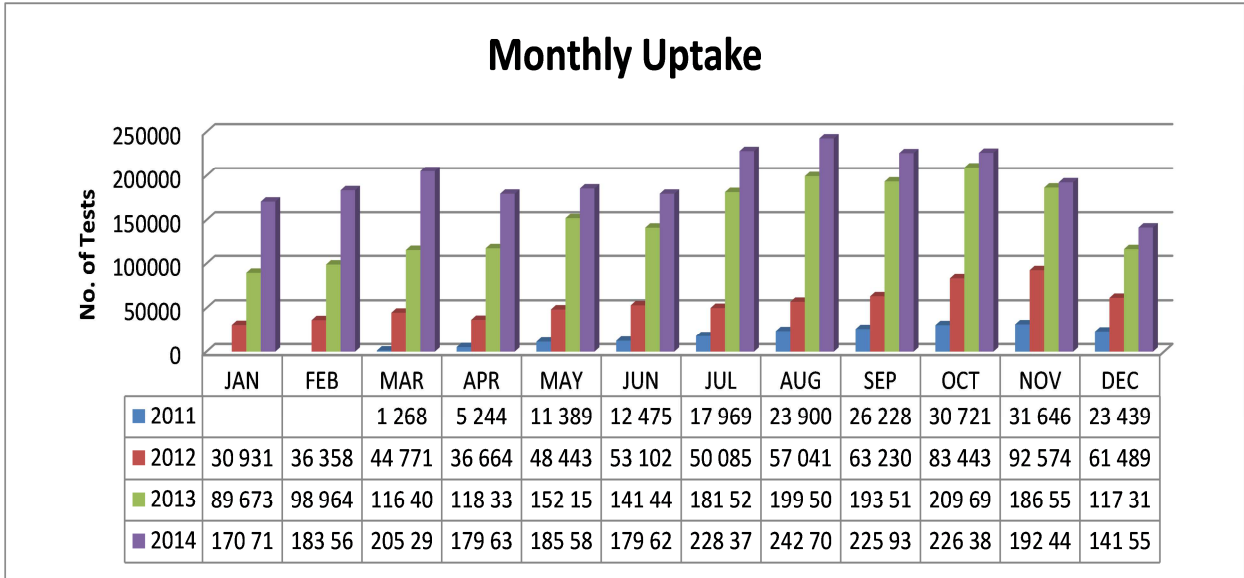
Table 6: Number of Unsuccessful Tests and Reasons (1-31 December 2014)

Province	Error	Invalids	No Results	MTB Results	Grand Total	% Error
Eastern Cape	486	78	35	24 952	25 551	1,90
Free State	49	32	2	8 439	8 522	0,57
Gauteng	362	48	8	21 840	22 258	1,63
Kwa-Zulu Natal	966	148	59	36 584	37 757	2,56
Limpopo	381	86	12	12 608	13 087	2,91
Mpumalanga	224	36	5	8 043	8 308	2,70
North West	233	35	10	8 755	9 033	2,58
Northern Cape	114	50	2	4 214	4 380	0,03
Western Cape	85	17		11 562	11 664	0,73
Grand Total	2 900	530	133	136 997	140 560	2,06

Figure 1: GeneXpert Error by Month


5. Monthly uptake since implementation started

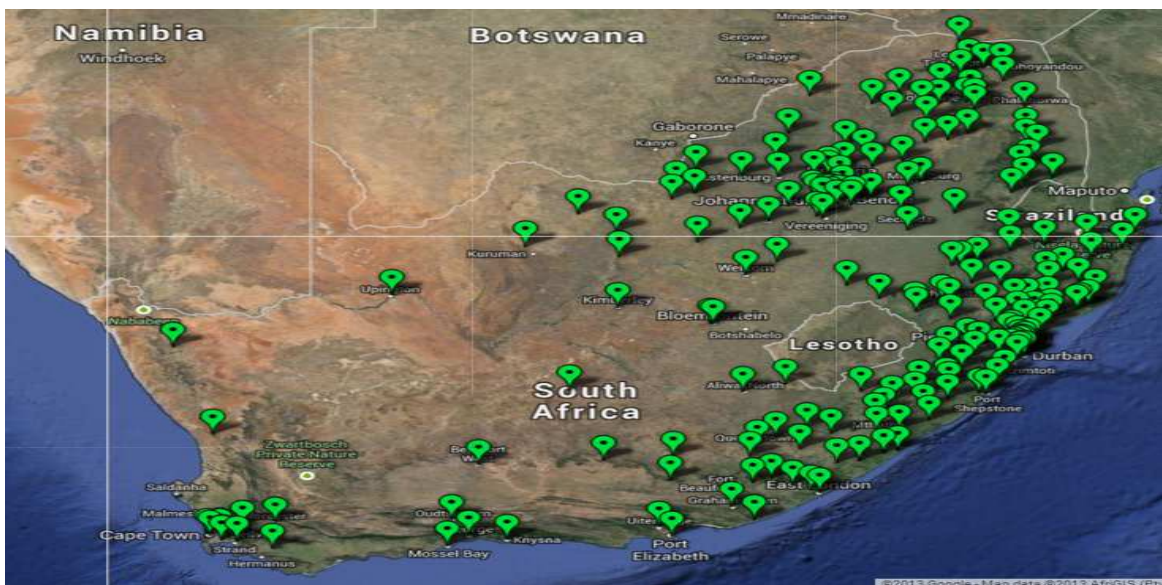
Figure 2: GeneXpert Monthly Uptake



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 1,695 laboratory staff and 7,993 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
Durovni et al, PloS Med, 2014	Assessed the implementation of Xpert MTB/RIF in a stepped-wedge cluster-randomized trial in 14 primary care laboratories in two Brazilian cities N=11,705 baseline (smear microscopy) and n=12,522 intervention (Xpert MTB/RIF) patients	<ul style="list-style-type: none"> • Median time to treatment decreased from 11.4 d (interquartile range [IQR] = 8.5-14.5) to 8.1 d (IQR = 5.4-9.3) (p = 0.04), although not among confirmed cases • Prevalence of rifampicin resistance detected by Xpert was 3.3% (95% CI = 2.4%, 4.3%) among new patients and 7.4% (95% CI = 4.3%, 11.7%) among retreatment patients, • Replacing smear microscopy with Xpert MTB/RIF in Brazil increased confirmation of pulmonary TB 	



<p>Maynard-Smith et al, BMC Infect Dis, 2014</p>	<p>A systematic literature search of 7 electronic databases was conducted to identify studies of the diagnostic accuracy of the Xpert assay when testing non-respiratory samples compared with a culture-based reference standard.</p>	<ul style="list-style-type: none"> • 27 studies with a total of 6,026 non-respiratory samples were included • Pooled summary estimates of sensitivity varied substantially between sample types: • lymph node tissue, 0.96; tissue samples of all types, 0.88; pleural fluid, 0.34; gastric aspirates for diagnosis of sputum-scarce pulmonary TB, 0.78; cerebrospinal fluid and non-pleural serous fluid samples were 0.85 and 0.67 , respectively.
--	--	---

10. Update on GeneXpert Research projects:

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

- Panel 3 of the 2014 EQA submissions finalized and reports sent to participants
- TBGxMonitor™ (www.tbgxmonitor.com) upgrade specification finalized.
 - Developed components undergoing validation.

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

The first 3 sites in Port Shepstone (Murchison Hospital, Gateway Clinic and Gamalakhe) will receive their first training in the second week of February 2015, with the target launch of the mHealth system is end of February 2015. 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. A meeting was held on 12 December 2014 with the Assistant TB Coordinator for the Gauteng Department of Health. At this meeting, the next seven sites for implementation were finalised; South Rand Hospital, Helen Joseph Hospital, Baragwanath Hospital, Phulusong, Thembisa, Germiston (Bertha Gxawa) and Thambo.



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 11A has started – 3 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 60 weeks. Outstanding final visit (V5) DBS for testing.
- **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=59 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: n=46 patient specimens followed longitudinally (V0, V1, V2, V3) have been tested on the Alere q. interim analysis is underway to present at a Alere Symposium at ASLM.
 - A laboratory evaluation of the Cepheid HIV-1 Quantitative VL cartridge on plasma, DBS and whole blood. n=25 patients have been recruited into the study and plasma and blood from each tested on the Cepheid platform. DBS are being stored for later testing.
- **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

The National Health Laboratory Service collaborated with the National Department of Health and other stake holders to offer health care services on 1 December 2014. The event was held at Bronville Park Stadium, Welkom, Free State with the theme “Focus, Partner, Achieve: An AIDS-free Generation.”

A total of 11 sputum samples were received and tested for TB using the GeneXpert technology. In addition 13 samples were received for CD4 testing from clients who tested positive for HIV.