NATIONAL HEALTH LABORATORY SERVICE

GeneXpert MTB/RIF

Progress Report

November 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, 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 4,833,487 specimens have been processed to date (30 November 2014). In November 191,427 specimens were processed. The total % of *Mycobacterium tuberculosis* complex (MTBC) detected in this cohort was 9.99% (19,132). 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**
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**
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**
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**
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**
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**
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**
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**

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NORTHERN CAPE	2013	7 912	53 728	2 529	**64 169**	**12,3**
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**
EASTERN CAPE	2014	45 396	360 434	10 661	**416 491**	**10,9**
FREE STATE	2014	12 958	118 208	909	**132 075**	**9,8**
GAUTENG	2014	35 767	285 002	7 030	**327 799**	**10,9**
KWAZULU-NATAL	2014	53 084	487 233	17 499	**557 816**	**9,5**
LIMPOPO	2014	13 283	200 412	7 208	**220 903**	**6,0**
MPUMALANGA	2014	13 562	105 765	3 945	**123 272**	**11,0**
NORTH WEST	2014	15 795	142 328	6 299	**164 422**	**9,6**
NORTHERN CAPE	2014	8 088	59 135	2 719	**69 942**	**11,6**
WESTERN CAPE	2014	30 117	163 047	1 797	**194 961**	**15,4**
TOTAL		**559 033**	**4 142 964**	**131 490**	**4 833 487**	**11,6**

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

Province	MTB Detected	MTB Not Detected	Test Unsuccessful	Grand Total	% MTB Detected
Eastern Cape	3 872	32 589	889	37 350	10,37
Free State	1 179	10 198	97	11 474	10,28
Gauteng	2 973	23 804	656	27 433	10,84
Kwa-Zulu Natal	4 470	45 939	1 673	52 082	8,58
Limpopo	1 080	15 354	564	16 998	6,35
Mpumalanga	1 204	9 783	391	11 378	10,58
North West	1 227	10 630	467	12 324	9,96
Northern Cape	683	5 070	184	5 937	11,50
Western Cape	2 444	13 876	131	16 451	14,86
Grand Total	**19 132**	**167 243**	**5 052**	**191 427**	**9,99**

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

Province	Inconclusive	Resistant	Sensitive	No Rif Result	Grand Total	% Rif Resistant
Eastern Cape	80	255	3 536	1	3 872	6,59
Free State	15	74	1 090		1 179	6,28
Gauteng	62	167	2 740	4	2 973	5,62
Kwa-Zulu Natal	115	411	3 939	5	4 470	9,19
Limpopo	23	48	1 008	1	1 080	4,44
Mpumalanga	24	107	1 073		1 204	8,89
North West	49	62	1 116		1 227	5,05
Northern Cape	4	29	650		683	4,25

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Western Cape	75	140	2 229		2 444	5,73
Grand Total	**447**	**1 293**	**17 381**	**11**	**19 132**	**6,76**

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	2626	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	1 197	2 786	41 369	44	**45 396**	**6,14**
FREE STATE	2014	352	778	11 824	4	**12 958**	**6,00**
GAUTENG	2014	764	2 140	32 836	27	**35 767**	**5,98**
KWAZULU-NATAL	2014	1 434	4 596	46 854	200	**53 084**	**8,66**
LIMPOPO	2014	315	650	12 272	46	**13 283**	**4,89**
MPUMALANGA	2014	366	1 196	11 981	19	**13 562**	**8,82**
NORTH WEST	2014	487	856	14 443	9	**15 795**	**5,42**
NORTHERN CAPE	2014	194	398	7 486	10	**8 088**	**4,92**
WESTERN CAPE	2014	633	1 584	27 899	1	**30 117**	**5,26**
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**

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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		**12 660**	**37 626**	**506 482**	**2 265**	**559 033**	**6,73**

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	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.

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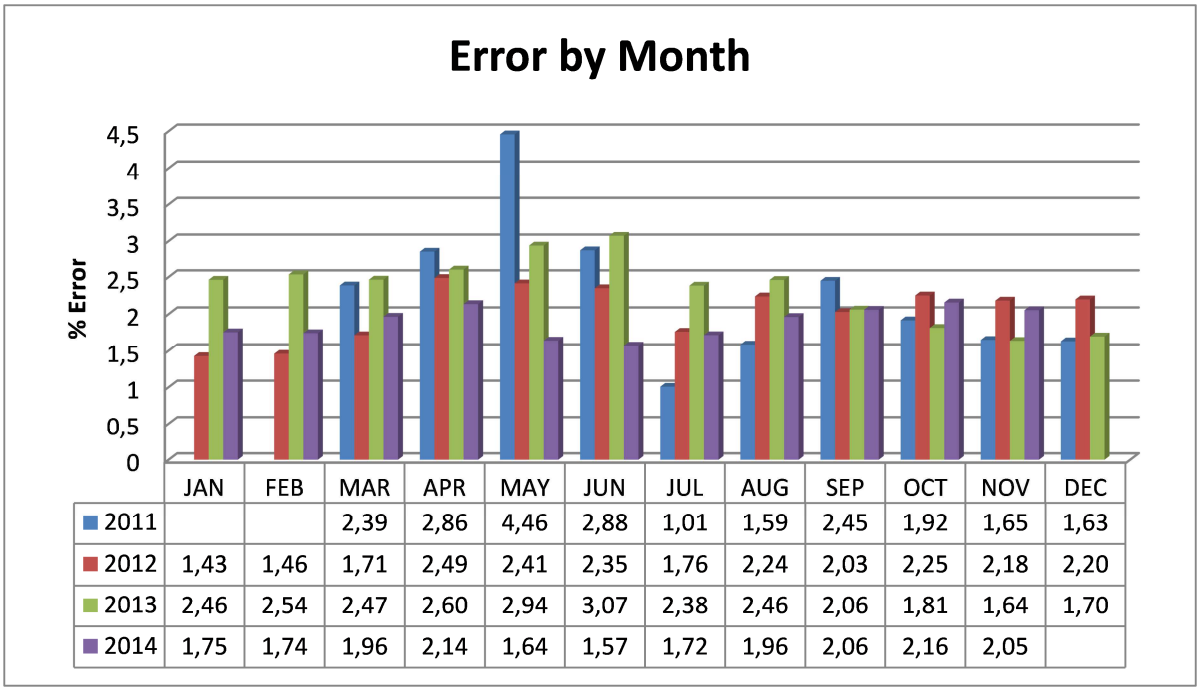
Table 6: Number of Unsuccessful Tests and Reasons (1-30 November 2014)

Province	ERROR	INVALIDS	NO RESULTS	MTB Results	Grand Total	% Error
Eastern Cape	743	109	37	36 503	37 392	1,99
Free State	61	32	3	11 433	11 529	0,53
Gauteng	552	73	31	26 889	27 545	2,00
Kwa-Zulu Natal	1 266	310	97	50 636	52 309	2,42
Limpopo	428	103	33	16 464	17 028	2,51
Mpumalanga	317	52	22	11 006	11 397	2,78
North West	355	84	28	11 895	12 362	2,87
Northern Cape	102	80	2	5 758	5 942	1,72
Western Cape	107	20	4	16 703	16 834	0,64
Grand Total	**3 931**	**863**	**257**	**187 287**	**192 338**	**2,04**

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	2,46	2,54	2,47	2,60	2,94	3,07	2,38	2,46	2,06	1,81	1,64	1,70
2014	1,75	1,74	1,96	2,14	1,64	1,57	1,72	1,96	2,06	2,16	2,05	

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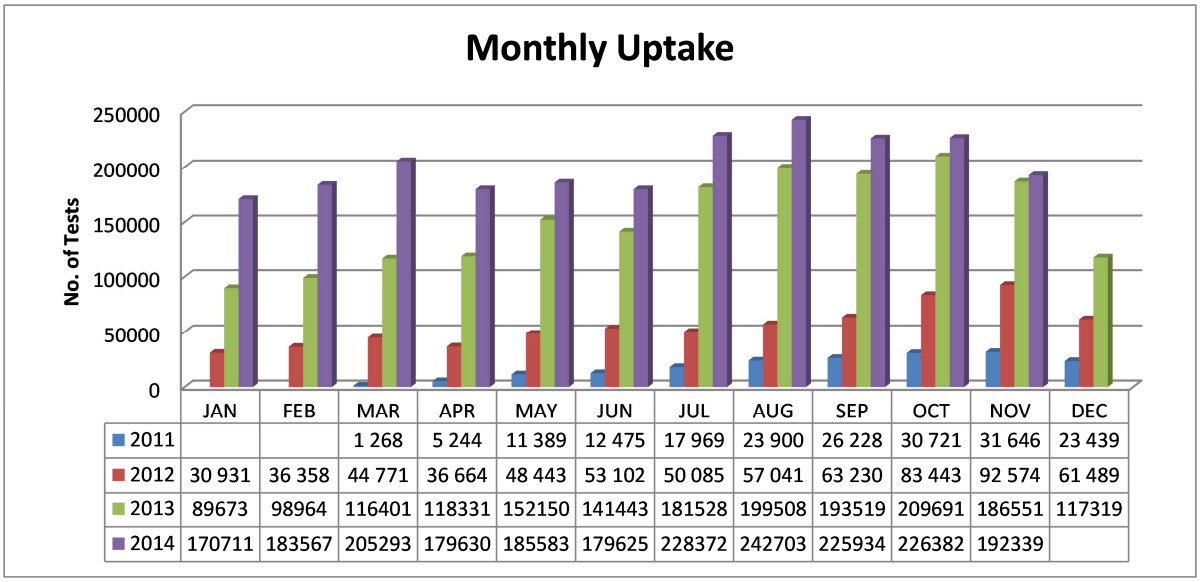
5. Monthly uptake since implementation started

Figure 2: GeneXpert Monthly Uptake

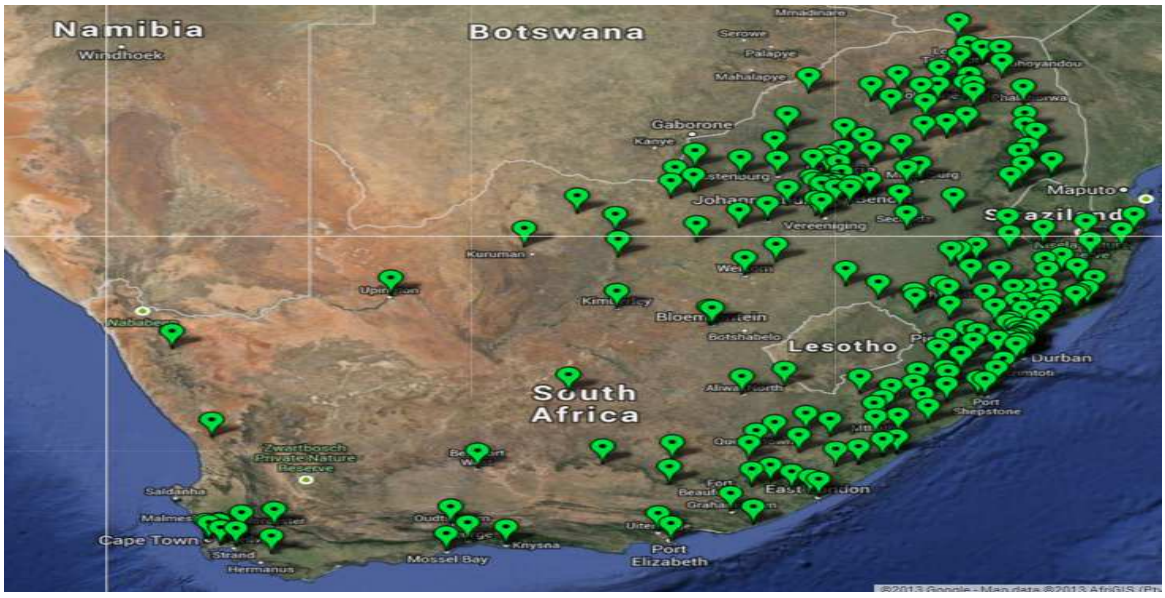


	JAN	FEB	MAR	APR	MAY	JUN	JUL	AUG	SEP	OCT	NOV	DEC
2011			1 268	5 244	11 389	12 475	17 969	23 900	26 228	30 721	31 646	23 439
2012	30 931	36 358	44 771	36 664	48 443	53 102	50 085	57 041	63 230	83 443	92 574	61 489
2013	89673	98964	116401	118331	152150	141443	181528	199508	193519	209691	186551	117319
2014	170711	183567	205293	179630	185583	179625	228372	242703	225934	226382	192339	

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



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7. Training: Laboratory and Clinical

A total of 1,693 laboratory staff and 7,937 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
Cox et al, PloS 2014	A pragmatic prospective cluster-randomised trial of Xpert for all individuals with presumptive (symptomatic) TB compared to the routine diagnostic algorithm of sputum microscopy and limited use of culture in a large TB/HIV primary care clinic N=1,985	• 13% (32/257) of individuals with bacteriologically confirmed TB (smear, culture, or Xpert) did not initiate treatment by 3 mo after presentation in the Xpert arm, compared to 25% (41/167) in the routine arm • The yield of bacteriologically confirmed TB cases among patients with presumptive TB was 17% (167/1,003) with routine diagnosis and 26% (257/982) with Xpert diagnosis • Higher rates of treatment initiation in the Xpert arm: 23% (229/1,003) and 28% (277/982) in the routine and Xpert arms, respectively • There was no difference in 6-mo mortality with Xpert versus routine diagnosis	
Huh et al, BMC Infect Dis. 2014	Evaluated the performance of the	• Sensitivity of the Xpert assay for MTB	

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	Xpert assay with respect to its clinical application at a tertiary care hospital in Korea, a country with an intermediate tuberculosis burden and high-resource N=303	detection in category 1 (patients with a high probability of pulmonary tuberculosis) was 89.8% but 66.7% in category 2 (exclusion of tuberculosis in clinically indeterminate patients for pulmonary tuberculosis)	
Hu et al, China med J, 2014	The performance of Xpert MTB/RIF investigated in two county-level laboratories in Hunan Province, China	Sensitivity of Xpert MTB/RIF was 100% for smear- and culture-positive TB and 88.6% for smear-negative and culture-positive TB Overall sensitivity was 94.5% for all culture-positive patients. For the detection of rifampin resistance, the sensitivity of MTB/RIF was 92.9%.	The specificity was 99.8%. For the detection of rifampin resistance, the specificity of MTB/RIF was 98.7%.

10. Update on GeneXpert Research projects:

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

- Panel 3 of the 2014 EQA program was prepared and shipped to all participating sites.
- New countries joining the EQA program: Swaziland and Namibia
- TBGxMonitor™ (www.tbgxmonitor.com) upgrade specification finalized.
    - Seriun continue to publish updated components which are undergoing verification and validation.
    - Validation underway

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 three 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 interface between CDW and emocha (app developers) has been secured. A "Treat TB" app is currently being developed for implementation into eight MDR-TB treatment initiation sites in two districts of Gauteng (Ekurhuleni and City of Johannesburg).

11. Update on other projects

- **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. 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 started – 25 spiked TB positive specimens completed.
- **Longitudinal follow up of Dried Blood Spots for viral load monitoring**: Longitudinal collection of DBS from n=100 HIV-positive patients on ARV's. V0, V1, V2, V3, V5 collected and tested. Outstanding V7.
- **Development of DCS EQA for LPA:** A short form paper has been accepted to Journal Clinical Microbiology.
- **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=91 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:** Two new HIV VL evaluations of POC diagnostics are planned: 1). A pilot evaluation of the new Alere q VL POC instrument (Alere Inc) on whole blood which provides a VL result in 52 min - Testing has begun 2). A laboratory evaluation of the Cepheid HIV-1 Quantitative VL cartridge on plasma, DBS and whole blood - patient recruitment has started at Helen Joseph Hospital.
- **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 November