NATIONAL HEALTH LABORATORY SERVICE

GeneXpert MTB/RIF

Progress Report

March 2013

NATIONAL HEALTH LABORATORY SERVICE

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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 24th 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.

The remainder of the roll-out is being performed in a phased manner by the National Priority Programmes of the NHLS and the NDoH, the progress of which is described in point 6 below.

2. Assays performed to date

In summary, a total of 1,180,669 specimens have been processed to date (31 March 2013). In March 116,089 specimens were processed. The total % of *Mycobacterium tuberculosis* complex (MTBC) detected in this cohort was 11.65% (13,523). The percentage positivity has remained on average between 15 -16% country-wide. 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 (01-31 March 2013)

Province	MTB Detected	MTB Not Detected	Test Unsuccessful	Total	% MTB Detected
Eastern Cape	2 779	17 947	484	**21 210**	**13.10**
Free State	1 075	9 874	111	**11 060**	**9.72**
Gauteng	1 659	11 909	510	**14 078**	**11.78**
Kwa-Zulu Natal	3 183	21 570	1 251	**26 004**	**12.24**
Limpopo	898	11 821	520	**13 239**	**6.78**
Mpumalanga	514	3 089	147	**3 750**	**13.71**
North West	809	6 260	262	**7 331**	**11.04**
Northern Cape	641	4 642	154	**5 437**	**11.79**
Western Cape	1 965	11 823	192	**13 980**	**14.06**
Total	**13 523**	**98 935**	**3 631**	**116 089**	**11.65**

Table 2: GeneXpert MTB Results by province (cumulative)

Province	MTB Detected	MTB Not Detected	Test Unsuccessful	Total	% MTB Detected
Eastern Cape	27 881	147 474	4 765	**180 120**	**15.48**
Free State	17 835	117 802	524	**136 161**	**13.10**
Gauteng	18 963	124 431	4 002	**147 396**	**12.87**
Kwa-Zulu Natal	48 148	247 615	11 332	**307 095**	**15.68**
Limpopo	9 137	76 899	2 125	**88 161**	**10.36**
Mpumalanga	8 084	42 664	2 636	**53 384**	**15.14**
North West	11 132	60 475	3 431	**75 038**	**14.84**
Northern Cape	9 272	50 960	2 516	**62 748**	**14.78**
Western Cape	21 340	107 996	1 230	**130 566**	**16.34**
Total	**171 792**	**976 316**	**32 561**	**1 180 669**	**14.55**

Table 3: Provincial GeneXpert RIF Results in MTB detected cases (01-31 March 2013)

Province	Inconclusive	Resistant	Sensitive	No Rif Result	Total	% RIF Resistant
Eastern Cape	52	219	2 498	10	**2 779**	**7.88**
Free State	26	68	980	1	**1 075**	**6.33**
Gauteng	22	101	1 533	3	**1 659**	**6.09**
Kwa-Zulu Natal	72	270	2 828	13	**3 183**	**8.48**
Limpopo	21	49	820	8	**898**	**5.46**
Mpumalanga	13	68	429	4	**514**	**13.23**
North West	14	59	716	20	**809**	**7.29**
Northern Cape	12	21	476	132	**641**	**3.28**
Western Cape	32	104	1 829		**1 965**	**5.29**
Total	**264**	**959**	**12 109**	**191**	**13 523**	**7.09**

Table 4: Provincial GeneXpert RIF Results in MTB detected cases (cumulative)

Province	Inconclusive	Resistant	Sensitive	No Rif Result	Total	% RIF Resistant
Eastern Cape	409	1 967	25 234	271	**27 881**	**7.05**
Free State	262	1 064	16 476	33	**17 835**	**5.97**
Gauteng	241	1 254	17 389	79	**18 963**	**6.61**
Kwa-Zulu Natal	747	4 037	42 894	470	**48 148**	**8.38**
Limpopo	134	640	8 245	118	**9 137**	**7.00**
Mpumalanga	116	795	7 084	89	**8 084**	**9.83**
North West	150	860	10 075	47	**11 132**	**7.73**
Northern Cape	130	566	8 414	162	**9 272**	**6.10**
Western Cape	254	1 083	20 000	3	**21 340**	**5.07**
Total	**2 443**	**12 266**	**155 811**	**1 272**	**171 792**	**7.14**

3. Rif Condordance

Rifampicin concordance is good for both LPA and culture. There is significant regional variation in Rifampicin mono-resistance. The national average is 12% for DST and 17% for LPA. This could be attributed to a number of factors such as geographical variation, laboratory variation, interpretation of LPA, reliability of gold standard or even strain variation.

Testing and clinical algorithms show variation across provinces, requiring standardisation as this leads to significant confusion in all aspects of the testing cycle, as well as in some cases, being more onerous to the TB patients themselves.

Table 5: Rif Concordance by LPA or DST

Province	Rif Resistant Cases	GeneXpert Confirmation & Rif Concordance									
		DST					LPA				
		Confirmed		Rif Concordance		Pre-analytical	Confirmed		Rif Concordance		Inderterminate
		#	%	#	%		#	%	#	%	
Eastern Cape	1153	47	4.1%	10	21.3%	0	46	4%	45	97.8%	1
Free State	724	15	2.1%	7	46.7%	11	79	11%	64	81.0%	14
Gauteng	895	21	2.3%	16	76.2%	21	90	10%	84	93.3%	2
Kwazulu-Natal	2726	686	25.2%	652	95.0%	0	631	23%	509	80.7%	28
Limpopo	380	28	7.4%	27	96.4%	1	44	12%	39	88.6%	0
Mpumalanga	514	81	15.8%	78	96.3%	1	131	25%	111	84.7%	2
North West	435	8	1.8%	7	87.5%	2	50	11%	47	94.0%	6
Northern Cape	343	24	7.0%	17	70.8%	8	55	16%	47	85.5%	8
Western Cape	782	1	0.1%	0	0.0%	3	235	30%	234	99.6%	0
National	7 952	911	11.5%	814	89.4%	47	1 361	17%	1 180	86.7%	61

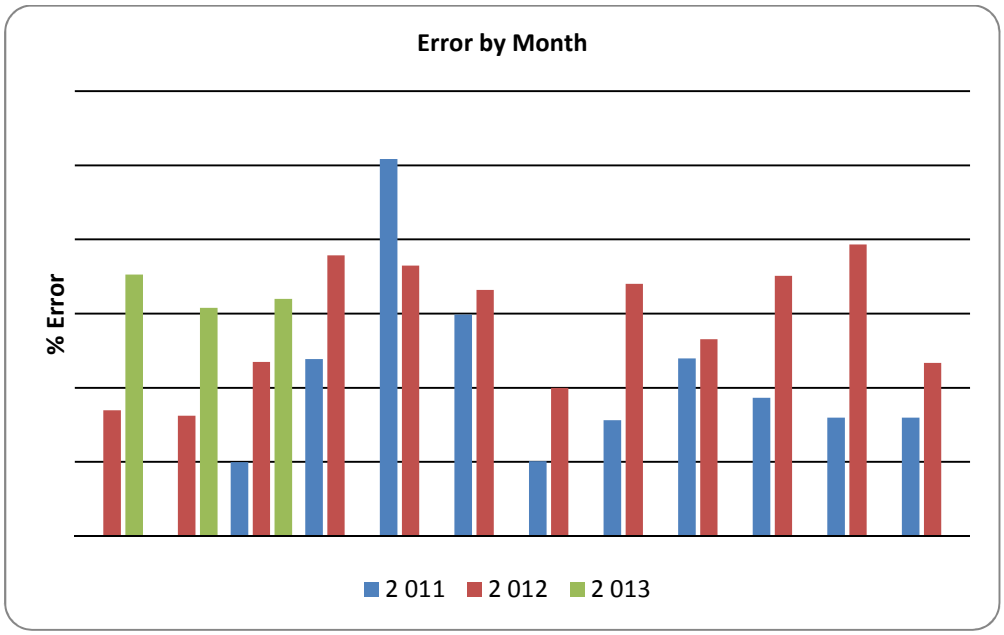
4. Errors

Errors have ranged consistently below 3%. Details of 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

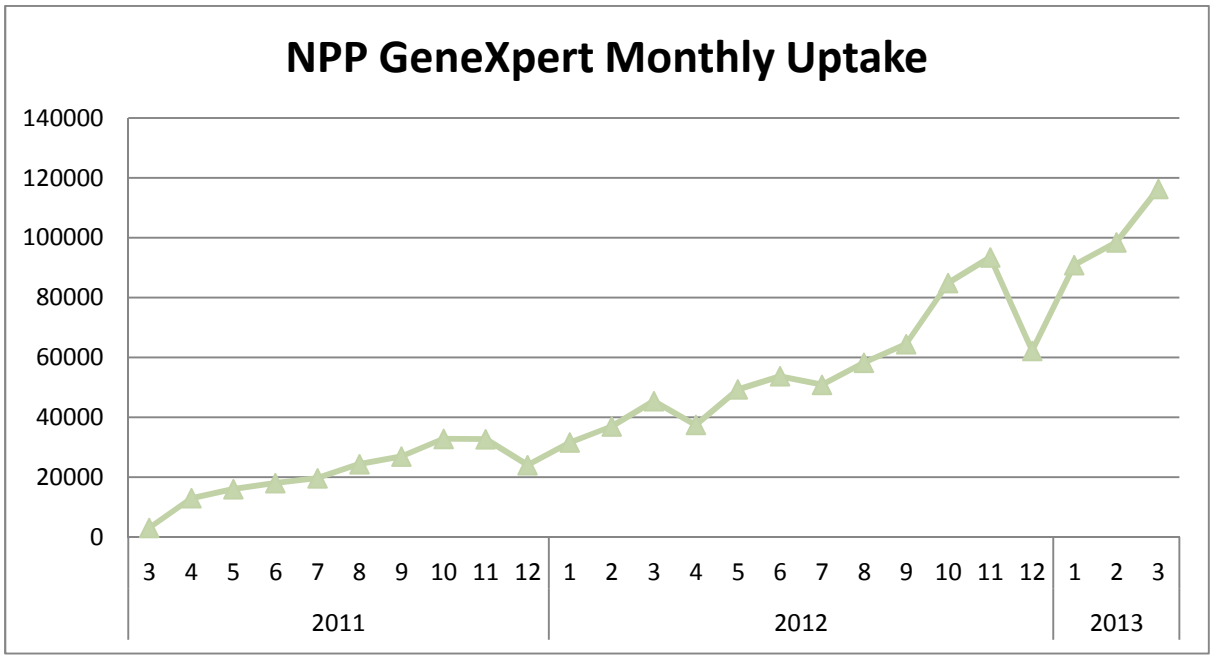
Province	ERR	INV	NORES	No Raw Result	MTB Result	Total	% Error
Eastern Cape	4073	415	259	18	175355	**180 120**	**2.26**
Free State	430	47	37	10	135637	**136 161**	**0.32**
Gauteng	3514	357	131		143394	**147 396**	**2.38**
Kwa-Zulu Natal	8977	1512	839	4	295763	**307 095**	**2.92**
Limpopo	1800	262	62	1	86036	**88 161**	**2.04**
Mpumalanga	2430	173	32	1	50748	**53 384**	**4.55**
North West	3098	235	98		71607	**75 038**	**4.13**
Northern Cape	883	259	39	1335	60232	**62 748**	**1.41**
Western Cape	1113	93	24		129336	**130 566**	**0.85**
Total	**26 318**	**3 353**	**1 521**	**1 369**	**1 148 108**	**1 180 669**	**2.23**

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. In addition, there was a global shortage in the supply of Xpert MTB/RIF® cartridges in the months of July, October and November 2012. This was resolved in December 2012. Another shortage was experienced this month. We have once again been assured that the NHLS has first priority in the manufacturing and procurement process. Cepheid has also provided a weekly delivery schedule for the NHLS until the end of the year based on the projections provided.

6. Further project phases as defined in the NTCM model

Phase I has been completed and has been reported on in the section above.

Phase IIa involves full capacitation of existing labs: Completed

Phase IIb: Full capacitation of high burden districts. Completed

Phase IIIa and b: Gates funded study (Gauteng, EC and Free State). Phase 3a Completed

Phase IIIc: ensuring all districts have a minimum of 1 instrument per district: In Progress

Phase IIId: Completion of all current microscopy and clinic sites: In Progress

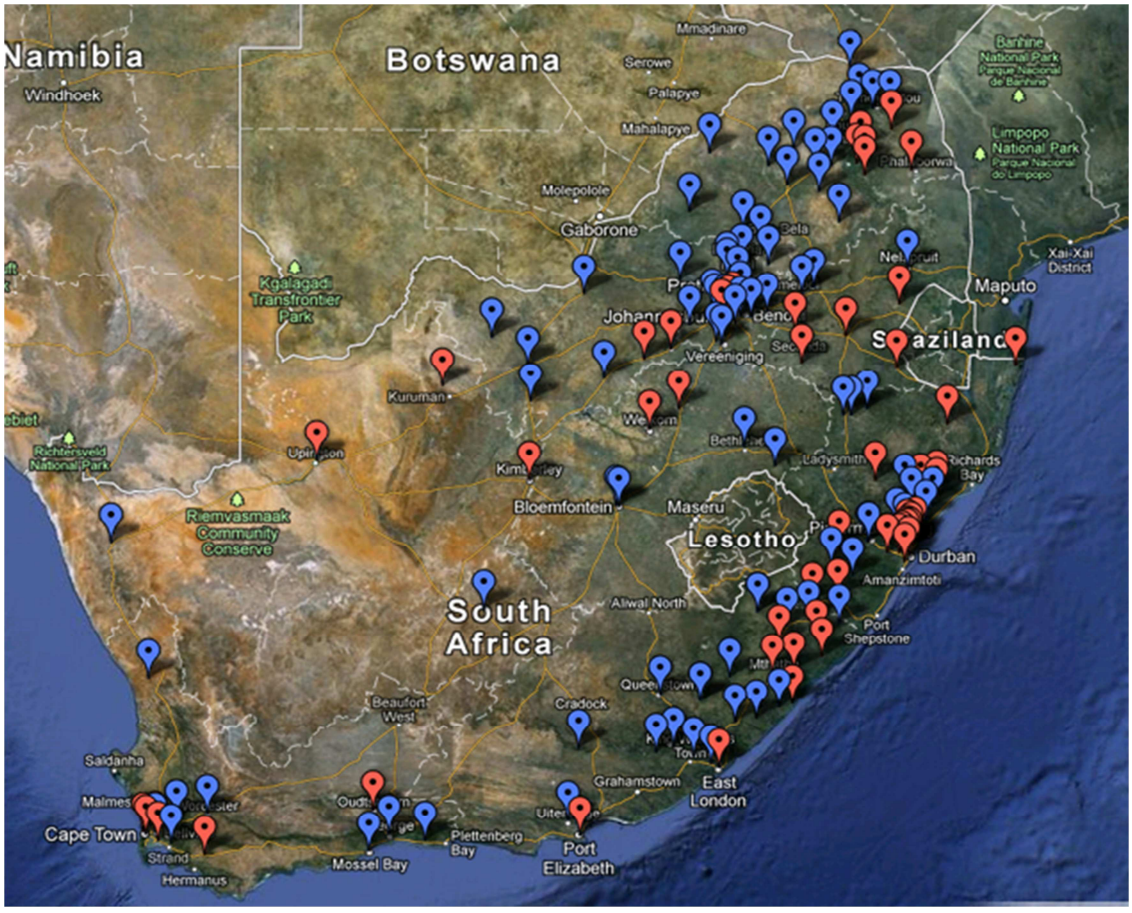
7. Phased Implementation Progress

Table 7: Phased Implementation Progress

Phase	GX4	GX16	GX48	TOTAL	Placed	% Completion
Phase 1/2a	7	30	1	38	38	100
Phase 2b	22	23	1	46	46	100
Phase 3a	3	10	0	13	13	100
Phase 3b	2	11	0	13	13	100
Phase 3c	6	28	0	34	30	88
Phase 3d	41	83	0	124	63	51
TOTAL	**81**	**185**	**2**	**268**	**203**	**76**

To date implementation is 76% complete.

Figure 3: Current GeneXpert Placement (142 testing centers, 203 analysers, Gx4: 65; Gx16: 136; GX48:2) ***20 clinic placements**



8. Training: Laboratory and Clinical

A total of 652 laboratory staff and 2021 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.

9. Challenges identified during the course of the project to date

- Delay in training health care workers, especially doctors whose availability is limited, on clinical algorithm: is being addressed
- Global shortage of GXP cartridges

- Rollout of EGK to avoid duplications
- Laboratories using GXP for monitoring treatment (and not just diagnosis): is being addressed through training
- Under expenditure on the GeneXpert: resolved at the TB/HIV quarterly meeting.
    - Reduction in the price of the cartridge.
    - Delay in release of funds by Global Fund
    - Global shortage of cartridges
    - Delay in implementation of the automated billing system by the NHLS which will only be operation from the 1st of September 2012.
    - Delay in setting up billing accounts: KZN, Northern Cape and Free State

10. Literature Update For GeneXpert

There has been an expansion of the literature with respect to the assay performance. The highlights are summarized in table 11 below:

Table 8: Recent publications (GeneXpert for pulmonary TB and extrapulmonary TB)

Manuscript	Sample population and specimen type (n=…)	Results	
		Sensitivity	Specificity
Nicol, 2013, Clin Infec Dis	N=115 children	Culture positive specimens: 8/17 detected, 47.1% sensitive (26.2-69.0)	97/98 detected, 99.0% specificity (94.4-99.8)
Hella, 2013, BMJ Case Report	Case report: A 31-year-old HIV-negative man presented to theclinic with a 6-month history of back pain and a swelling at the back.	Xpert MTB/RIF assay detected Mycobacterium tuberculosis with no rifampicin resistance in a Paraspinal abscess	

Sekadde, 2013, BMC Infec Dis	N=235 children	Xpert MTB/RIF test had a sensitivity of 79.4% (95% CI 63.2 - 89.7). The Xpert MTB/RIF test identified 13 of the 14 (92.9%) smear positive-culture positive and 14 of the 20 (70%) smear negative -culture positive cases.	Specificity of 96.5% (95% CI 93 - 98.3).
		The median time to TB detection was 49.5 days (IQR 38.4-61.2) for LJ, and 6 days (IQR 5 - 11.5) for MGIT culture and 2 hours for the Xpert MTB/RIF test	

11. Update on GeneXpert Research projects:

- Dried Culture Spot (DCS) for verification of GeneXperts to be rolled out for quarter 2 of 2013: ~600 DCS have been prepared for the next round of Gx implementation.
- DCS for EQA program: n=300 EQA panels have been prepared for the first round of EQA for all NHLS sites and ACTG sites.
- The following potential EQA materials where investigated through a pilot, feasibility study (n=11 sites):
    - **i.** DCS EQA panel
    - **ii.** Lypohilised EQA panel (VIRCELL™)
    - **iii.** Dried Tube Spot EQA panel from the CDC
    - **iv.** Simulated sputum EQA panel from WHO-GLI
    - **v.** Liquid panel from Maine Molecular Diagnostics (MMQCI™)

  The results were presented at the 5th GLI meeting in France and summarized below:

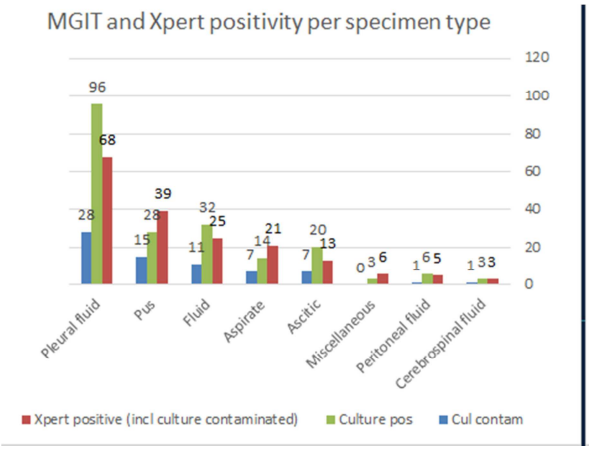
- MMQCI panel, which was the only panel that required cold storage which contributed to a lower score.

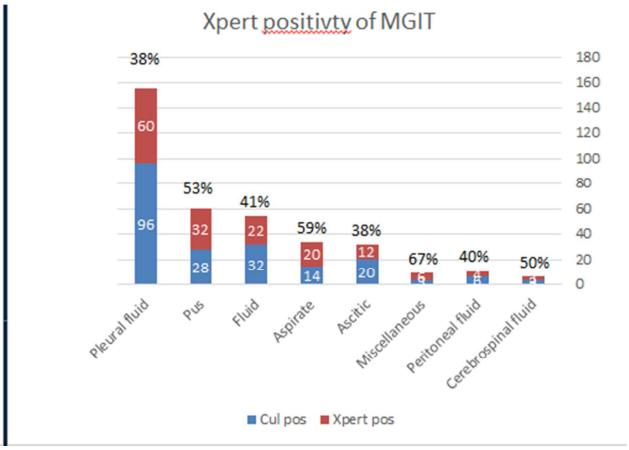
- All panels where received in good condition and therefore good for shipping across distances, and all showed compatibility with the Xpert testing process.
- No panel caused any PCR inhibition.
- Matrix requirement (liquid or dry) did not appear to be a distinguishing criterion as had reduced scores on: insufficient volumes; need for extra consumables; ability to transfer to the Xpert cartridge.
- Minimal variation in probe Ct may be more attractive for monitoring RIF call rates using differences in probe drop out or probe delayed hybridisation.

Factors such as SOP clarity, label bar-code scanning, and use of the web based program highlight the need for any EQA program to be accompanied by training and ongoing improvements.

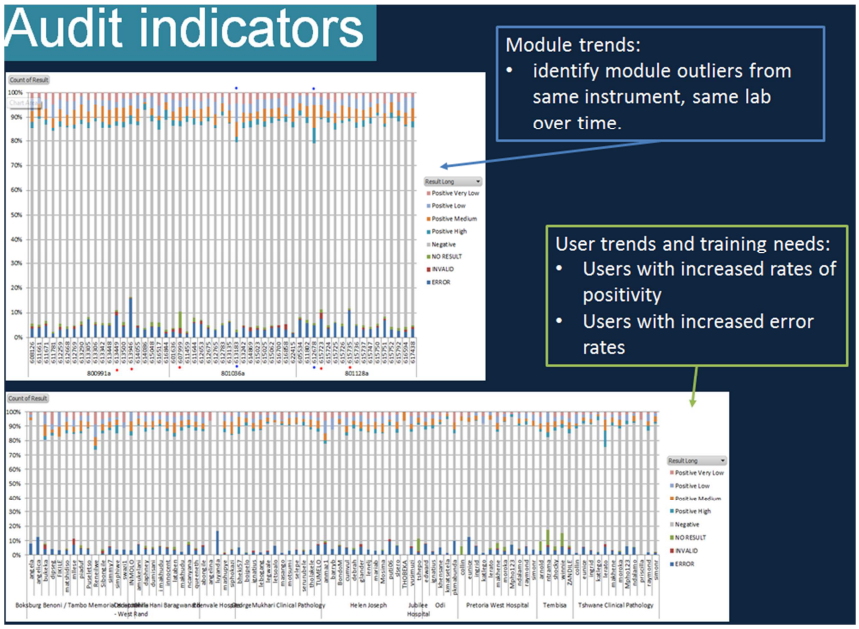
- DCS EQA & verification program development - ACTG (6 sites) and MSF included in the program: first batch of verification and pilot EQA material have been shipped to ACTG sites. All but for 2 ACTG sites returned results: 1 verification from an Infinity site in the USA, due to cost and an EQA panel from Peru, which was lost at Peru Customs due to a strike by airport workers, although it arrived. Rwanda has received both EQA and Verification Material to aid in their initial setup. The Feedback received, was that the DCS performed well according to both users and the providers at that side.
- TBGxMonitor™ (www.tbgxmonitor.com) automated GeneXpert Verification and EQA reporting platform has been upgraded to include full EQA report processing. Both Verification and EQA components have been completed. The next major upgrade Phase 3 has been completed and is currently undergoing validation testing and will be deployed live by 1 May, 2013. Phase 4 scope of work has been generated. Awaiting finalization of specification.
- Alternative specimen preparation protocols:
    i. Protocols being developed for TB diagnosis in children
    ii. Protocols under development for EPTB: Preliminary data has been presented to the NDoH as well as the GLI of the WHO. Preliminary data

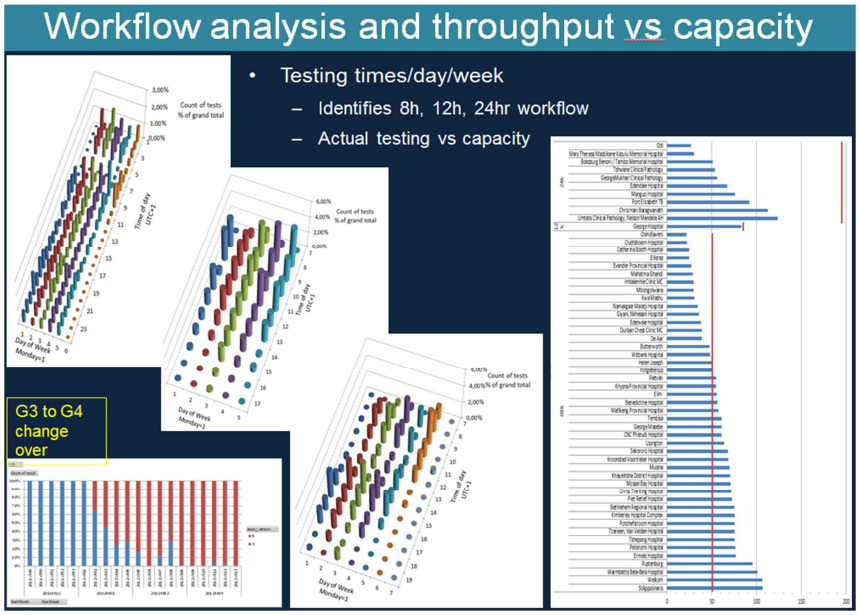
alsohas been submitted to a WHO initiated meta-analysis. Overall sensitivity of Xpert compared to MGIT=55.9% (CI 48.8; 62.8), Absolute number: 159 new cases (18% of total referrals). The bar charts summarise the positivity and culture contamination for various tissue types.





- Connectivity: Collaboration with Cepheid ongoing
    i. Remote connectivity – System deployed on more than 100 sites by Cepheid and the NHLS. More than 340,000 results reported to date. The current pilot system cannot handle the additional testing capacity which will be addressed in the full product version. Discussions are currently under way to include the remainder of the NHLS sites on the system, purge the data and begin monitoring again to assist in the evaluation of the ongoing rollout. The following outputs from the system illustrate some useful tools for the NPP.





ii. The first point of care site (Botshabelo Clinic, North West Province) has gone live on the Cepheid Dashboard with an additional 2 sites to be connected. These sites are using Metacom-sponsored routers (3G) connection for reporting.

12. HIV/TB Integration

- Grand Challenges Canada project: Multiple POC HIV/TB integration feasibility project
    - Phase I complete
    - Phase II: Evaluation of nurse operated POC versus routine lab completed at HJH Themba Lethu clinic (n=326) complete.
        - Manuscript in progress.
    - RCT: ~n=452 patients (POC arm =226; SOC =226) recruited into the study.
    - Sub-study to investigate feasibility and patient acceptance of multiple finger sticks for POC testing: Completed. Awaiting re-submission.
    - Sub-study to investigate various blood specimen storage and transport options: This study will compare viral load testing on Dried Blood Spots (DBS) to new technologies/alternatives such as Hemaform plates, Primestore tubes and a thicker DBS cards.
        - Protocol has been developed. We are awaiting ethics clearance and clinic approvals.
        - An initial pilot to investigate various DBS paper types and sizes is underway to increase sensitivity of HIV viral load testing on DBS.
    - Sub-study to investigate volumes of blood collected from finger stick for point of care testing: This is in collaboration with Northwestern University. A protocol is being developed and ethics approval is being obtained.
- Connectivity:
    - Conworx (POCcelerator) and LDS (AegisPOC) to be trialed in 2 sites during RCT. AegisPOC was installed at the first connectivity on 15 September, 2012. The Conworx solution was installed on the 14th of December, 2012. An antennae was installed and sufficiently boosted the signal. Conworx now running routinely at Tigane Clinic. Internet outage has been experienced at both clinics – the causes for these are currently being investigated.

13. Grants Submitted

None

14. 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.

15. Recent Campaigns

- World TB Day: Pollsmoor Correctional Services
- Gauteng World TB Day