NATIONAL HEALTH LABORATORY SERVICE

GeneXpert MTB/RIF

Progress Report

January 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 4 below.

2. Assays performed to date

In summary, a total of 966,033 specimens have been processed to date (31 January 2013). In January 89,993 specimens were processed. The total % of *Mycobacterium tuberculosis* complex (MTBC) detected in this cohort was 16.18% (14,563). 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 9 (refer to tables 1 & 2).

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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 January 2013)

Province	MTB Detected	MTB Not Detected	Test Unsuccessful	Total	% MTB Detected
Eastern Cape	3,032	13,375	456	**16,863**	**17.98**
Free State	1,254	8,064	38	**9,356**	**13.40**
Gauteng	1,704	10,317	331	**12,352**	**13.80**
Kwa-Zulu Natal	3,480	16,884	1,138	**21,502**	**16.18**
Limpopo	1,009	6,219	229	**7,457**	**13.53**
Mpumalanga	453	2,141	105	**2,699**	**16.78**
North West	875	4,670	268	**5,813**	**15.05**
Northern Cape	748	3,017	213	**3,978**	**18.80**
Western Cape	2,008	7,809	156	**9,973**	**20.13**
Total	**14,563**	**72,496**	**2,934**	**89,993**	**16.18**

Table 2: Cumulative GeneXpert MTB Results by province (1 March 2011 – 31 January 2013)

Province	MTB Detected	MTB Not Detected	Test Unsuccessful	Total	% MTB Detected
Eastern Cape	22 419	114 570	3 904	**140 893**	**15.91**
Free State	15 765	99 988	351	**116 104**	**13.58**
Gauteng	15 681	101 287	3 019	**119 987**	**13.07**
Kwa-Zulu Natal	42 429	208 638	9 101	**260 168**	**16.31**
Limpopo	7 333	55 547	1 102	**63 982**	**11.46**
Mpumalanga	7 151	36 930	2 334	**46 415**	**15.41**
North West	9 525	48 560	2 902	**60 987**	**15.62**
Northern Cape	8 044	42 786	2 140	**52 970**	**15.19**
Western Cape	17 414	86 329	784	**104 527**	**16.66**
Total	**145 761**	**794 635**	**25 637**	**966 033**	**15.09**

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

Province	Inconclusive	Resistant	Sensitive	No Rif Result	Total	% RIF Resistant
Eastern Cape	46	212	2,729	45	**3,032**	**6.99**
Free State	20	59	1,175	0	**1,254**	**4.70**
Gauteng	25	134	1,544	1	**1,704**	**7.86**
Kwa-Zulu Natal	55	302	3,117	6	**3,480**	**8.68**
Limpopo	15	86	901	7	**1,009**	**8.52**
Mpumalanga	8	60	384	1	**453**	**13.25**
North West	16	59	795	5	**875**	**6.74**
Northern Cape	14	36	697	1	**748**	**4.81**
Western Cape	25	114	1,869	0	**2,008**	**5.68**
Grand Total	**224**	**1,062**	**13,211**	**66**	**14,563**	**7.29**

Table 4: Cumulative Provincial GeneXpert RIF Results in MTB detected cases (1 March 2011 to 31 January 2013)

Province	Inconclusive	Resistant	Sensitive	No Rif Result	Total	% RIF Resistant
Eastern Cape	292	1560	20335	232	**22419**	**6.96**
Free State	211	952	14575	27	**15765**	**6.04**
Gauteng	185	1064	14360	72	**15681**	**6.79**
Kwa-Zulu Natal	631	3557	37787	454	**42429**	**8.38**
Limpopo	99	532	6595	107	**7333**	**7.25**
Mpumalanga	96	680	6292	83	**7151**	**9.51**
North West	122	753	8627	23	**9525**	**7.91**
Northern Cape	106	506	7419	13	**8044**	**6.29**
Western Cape	190	877	16344	3	**17414**	**5.04**
Total	**1 932**	**10 481**	**132 334**	**1 014**	**145761**	**7.19**

3. Rif Concordance

Rifampicin concordance is good for both LPA and culture. There is significant regional variation in Rifampicin mono-resistance. The national average is 89.4% for DST and 86.7% 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

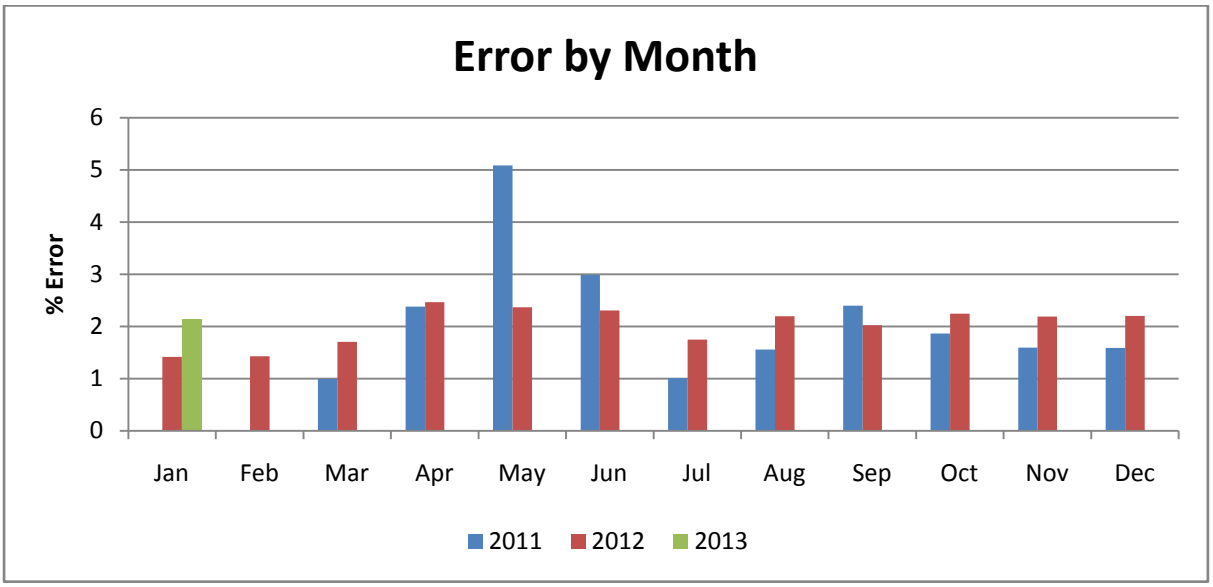
4. Errors

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

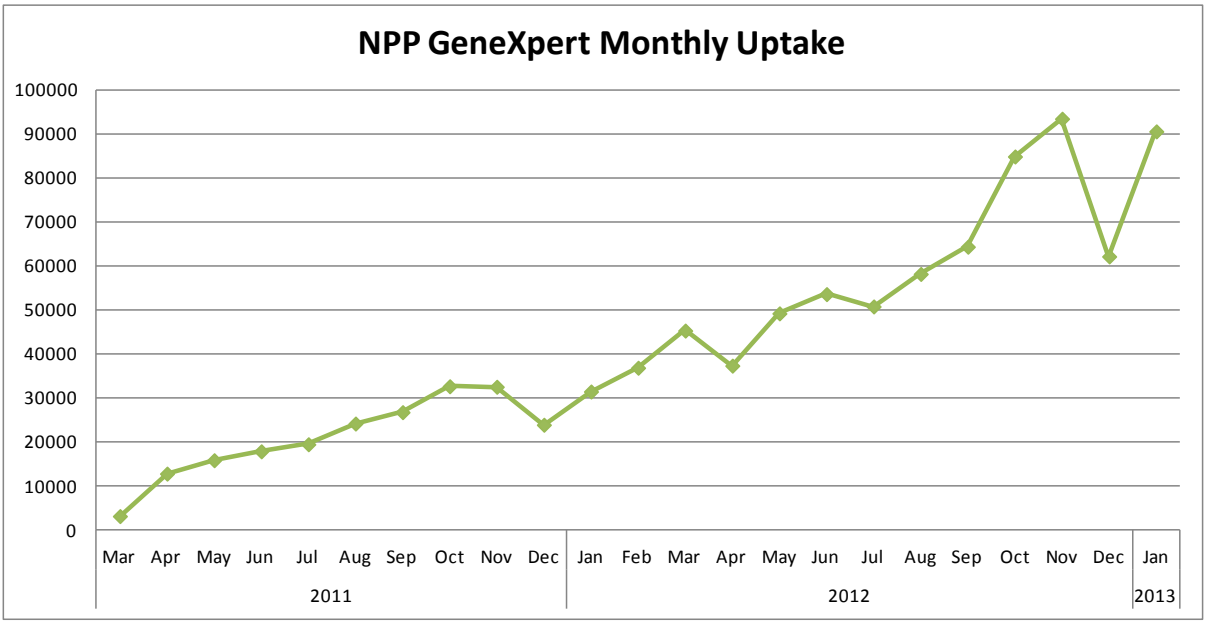
Province	ERR	INV	NORES	No Raw Result	MTB Result	Total	% Error
Eastern Cape	3,369	292	225	18	136,989	**140,893**	**2.39**
Free State	289	25	27	10	115,753	**116,104**	**0.25**
Gauteng	2,680	250	89		116,968	**119,987**	**2.23**
Kwa-Zulu Natal	7,200	1,276	621	4	251,067	**260,168**	**2.77**
Limpopo	911	165	25	1	62,880	**63,982**	**1.42**
Mpumalanga	2,162	148	23	1	44,081	**46,415**	**4.66**
North West	2,615	199	88		58,085	**60,987**	**4.29**
Northern Cape	714	253	37	1,136	50,830	**52,970**	**1.35**
Western Cape	712	53	19		103,743	**104,527**	**0.68**
Total	**20,652**	**2,661**	**1,154**	**1,170**	**940,396**	**966,033**	**2.14**

Figure 1: GeneXpert Error rate 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. 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

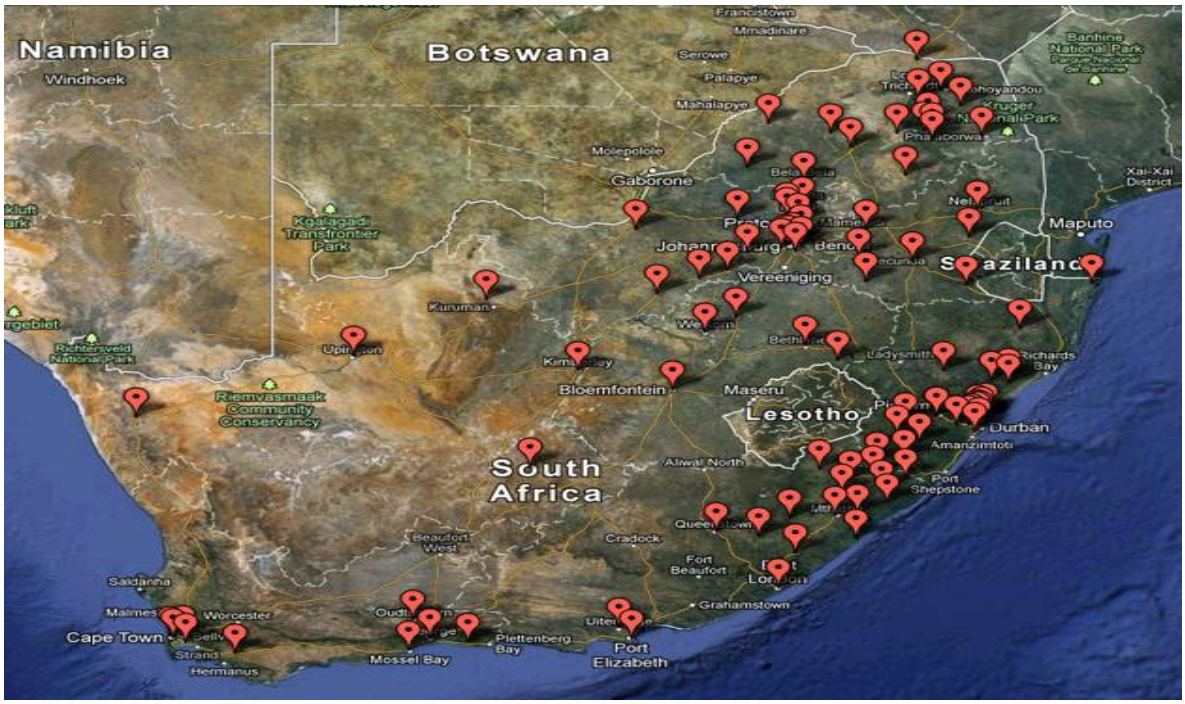
7. Phased Implementation Progress

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	15	44
Phase 3d	41	83	0	124	28	23
TOTAL	**81**	**185**	**2**	**268**	**153**	**57**

To date implementation is 57% complete. Forty four additional instruments will be installed by the end of March. This will increase coverage to 74%.

Figure 3: Current GeneXpert Placement (108 testing centers, 152 analysers, Gx4: 56; Gx16: 94; GX48:2) ***20 clinic placements**



8. Training: Laboratory and Clinical

A total of 264 laboratory staff and 1421 health care workers have been trained since December 2011. This will be an ongoing process to support NDoH training on clinical algorithm. Laboratory staff will receive 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
- Site readiness assessment for the 125 instruments to be placed- will require help from the regional CCMT coordinators
- Plan for additional interface licenses
- Global shortage of GXP cartridges: resolved
- 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
    - 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 8 below:

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

Manuscript	Sample population and specimen type (n=…)	Results	
		Sensitivity	Specificity
Munoz et al, DiagnMicrobiol Infect Dis. 2012	Performed a retrospective analysis of costs and time to treatment (TT) of 150 culture-confirmed TB cases: 100 sputum smear (SS) (+) and 50 SS(-). This group underwent GeneXpert® (GX) assay.	Expenditures and TT of SS(-)/GX(+) cases were inferred from the SS(+) group. GX detected 68% of SS(-) cases.	
Nguyen et al, BMC Infectious Diseases. 2012	Performed an evaluation on stored paediatric specimens comparing the MODsassay to the GeneXpert, in a cohort of Vietnamese children.	The sensitivity of MODS vsXpert were 51.7% and 50.0% respectively. The PPv and NPV were higher for Xpert than for MODS.	

Steingart K.R. et al Cochrane Systematic Review	Systematic Review, pooling data from multiple studies to assess the Xpert MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults, against replacing smear, then phenotypic DST in people with and without HIV	Identified 18 eligible studies, about half from low-income countries. Alone pooled sensitivity = 88% and pooled specificity = 98%; as an add on to negative smear pooled sensitivity and specificity were67% and 98%, respectively. Pooled sensitivity of 68% for sm-vecult+ve TB; 80% pooled sensitivity in those with HIV. Regarding rifampicin resistance, pooled sensitivity of 94% and specificity of 98%. Assay showed very high accuracy to distinguish between NTM and MTBC.

11. Update on GeneXpert Research projects:

- Dried Culture Spot (DCS)for verification of GeneXperts to be rolled out for quarter 1 of 2013: ~700 DCS ready to be shipped
- The following potential EQA materials are being investigated through a pilot, feasibility study (n=11 sites):
    - **i.** DCS EQA panel
    - **ii.** Liquid EQA panel (Vircell)
    - **iii.** Lyophilised EQA panel from the CDC
    - **iv.** Liquid EQA panel from WHO-

  The feasibility pilot is complete. At present the data is being analysed and results written up for publication as well as, more importantly, presentation to QAD in order to choose the most suitable panel.
- DCS EQA & verification program development - ACTG (6 sites) and MSF included in program: first batch of verification and pilot EQA material have been shipped to ACTG sites. n=2 site results have been returned. 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. Expected to be switched live 28 Feb, 2013. Phase 4 scope of work has been generated. Awaiting finalization of specification.

- Alternative specimen preparation protocols:
  - Protocols being developed for Extra-pulmonary TB diagnosis
  - Protocols under development for EPTB: A GeneXpert room has been refurbished at the Braamfontein TB referral lab for the study. A laboratory technician has been recruited and trained. The R&D GeneXpert has been placed for study commencement. The study commenced in the last week of August, investigating 0.5ml of un-centrifuged or concentrated residual EPTB specimens. The activity is ongoing. Thus far about a 20% positivity has been observed on just over 700 unprocessed specimens. Analysis regarding comparison to culture is underway. The phenotypic DST culture confirmation is waiting for about ¾ of the results.
- Connectivity: Collaboration with Cepheid ongoing
  - Remote connectivity – System deployed on more than 100 sites by Cepheid and the NHLS. More than 334,445 results reported to date. The pilot has reached maximum capacity and no further routine sites will be added until the full product launch. The current pilot system cannot handle the additional testing capacity which will be addressed in the full product version.
  - 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 ThembaLethu clinic (n=326) complete.
  - Site visits completed (n=12) and three sites are operational (Grace Mokgomo, North West Province), staff trained for randomized controlled trial (RCT)
  - Four new staff members have been employed: 1x nurse and 3x counselors
  - RCT: ~n=383 patients (POC arm =191; SOC =192) recruited into the study. Prelim results show that of study patients, 64% on the POC arm and 47% on the SOC arm

where eligible for ART initiation, of which 80% on POC and 61% on SOC where initiated.

- A sub-study to investigate feasibility and patient acceptance of multiple finger sticks for POC testing has been completed at Tshwane District Hospital (n=300). Interim results show that multiple POCT can feasibly be performed on multiple or a single finger-stick for all tests, CD4, hemoglobin, ALT and creatinine measurements. Patients prefer to receive multiple finger sticks over a venepuncture. Results presented at ASLM, Cape Town 2012. Results are being written up for publication.
- A 2nd sub study protocol to investigate various blood specimen storage and transport options is being developed. 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 card.

- 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. The system is currently running without remote access due to the lack of GPRS signal. Antennae being installed to assist in signal gain for full system functionality, should the antennae not be sufficient to boost the signal to acceptable levels, the site will likely be switched to satellite connectivity.

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. RecentCampaigns

None in January