



NATIONAL HEALTH
LABORATORY SERVICE

GeneXpert MTB/RIF

Progress Report

February 2014





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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 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, 286 GeneXpert instruments of varying sizes (GX4: 95; GX16:186; GX48: 1; GX80:4) have been placed in 207 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.

2. Assays performed to date

In summary, a total of 2,969,812 specimens have been processed to date (28 February 2014). In February 154,300 specimens were processed. The total % of *Mycobacterium tuberculosis* complex (MTBC) detected in this cohort was 10.97% (16,928). 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, 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	3 295	15 413	555	19 263	17.11
	2012	16 040	85 574	2 892	104 506	15.35
	2013	43 273	301 226	9 497	353 996	12.22
	2014	7 855	48 814	1 108	57 777	13.60
Free State	2011	2 844	14 831	33	17 708	16.06
	2012	11 631	77 087	280	88 998	13.07
	2013	14 595	137 359	1 270	153 224	9.53
	2014	2 364	19 900	175	22 439	10.54
Gauteng	2011	3 049	18 727	424	22 200	13.73
	2012	10 960	72 367	2 267	85 594	12.80
	2013	30 677	210 757	7 583	249 017	12.32
	2014	5 954	40 825	1 190	47 969	12.41
Kwa-Zulu Natal	2011	12 226	45 944	1 730	59 900	20.41
	2012	24 446	138 967	6 116	169 529	14.42
	2013	43 969	304 798	16 051	364 818	12.05
	2014	9 299	69 854	2 215	81 368	11.43
Limpopo	2011	1 975	17 261	172	19 408	10.18
	2012	3 993	30 710	688	35 391	11.28
	2013	13 820	186 834	6 169	206 823	6.68
	2014	2 244	26 247	874	29 365	7.64
Mpumalanga	2011	2 639	12 763	1 107	16 509	15.99
	2012	4 044	21 959	1 118	27 121	14.91



	2013	10 083	60 912	2 330	73 325	13.75
	2014	2 092	12 774	381	15 247	13.72
North West	2011	3 476	14 961	657	19 094	18.20
	2012	5 174	29 005	1 976	36 155	14.31
	2013	12 600	95 991	4 984	113 575	11.09
	2014	2 654	20 959	1 086	24 699	10.75
Northern Cape	2011	2 864	16 117	735	19 716	14.53
	2012	4 440	23 653	1 192	29 285	15.16
	2013	7 921	52 018	2 617	62 556	12.66
	2014	1 333	8 016	487	9 836	13.55
Western Cape	2011	2 204	10 093	31	12 328	17.88
	2012	13 202	68 248	588	82 038	16.09
	2013	31 258	168 252	2 854	202 364	15.45
	2014	6 435	29 902	334	36 671	17.55
Total		376 928	2 509 118	83 766	2 969 812	12.69

Table 2: GeneXpert MTB Results by province (01-28 February 2014)

Province	MTB Detected	MTB Not Detected	Test Unsuccessful	Total	% MTB Detected
Eastern Cape	3 170	23 963	546	27 679	11.45
Free State	912	8 825	91	9 828	9.28
Gauteng	2 514	18 411	567	21 492	11.70
Kwa-Zulu Natal	3 909	33 292	1 054	38 255	10.22
Limpopo	938	13 039	467	14 444	6.49
Mpumalanga	847	5 901	159	6 907	12.26
North West	1 122	10 715	461	12 298	9.12
Northern Cape	544	3 813	238	4 595	11.84
Western Cape	2 972	15 686	144	18 802	15.81
Total	16 928	133 645	3 727	154 300	10.97



Table 3: Provincial GeneXpert RIF Results in MTB detected cases (01-28 February 2014)

Province	Inconclusive	Resistant	Sensitive	No RIF Result	Total	% RIF Resistant
Eastern Cape	75	172	2 922	1	3 170	5.43
Free State	22	51	839		912	5.59
Gauteng	58	162	2 292	2	2 514	6.44
Kwa-Zulu Natal	151	336	3 397	25	3 909	8.60
Limpopo	19	44	872	3	938	4.69
Mpumalanga	22	90	735		847	10.63
North West	30	62	1 030		1 122	5.53
Northern Cape	10	29	504	1	544	5.33
Western Cape	55	174	2 743		2 972	5.85
Total	442	1 120	15 334	32	16 928	6.62

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

Province	Year	Inclusive	Resistant	Sensitive	No RIF	Total	% RIF Resistant
Eastern Cape	2011	33	251	2 958	53	3 295	7.62
	2012	213	1 096	14 597	134	16 040	6.83
	2013	1 216	2 843	39 073	141	43 273	6.57
	2014	156	453	7 238	8	7 855	5.77
Free State	2011	28	154	2 661	1	2 844	5.41
	2012	162	736	10 707	26	11 631	6.33
	2013	372	803	13 400	20	14 595	5.50
	2014	49	142	2 173		2 364	6.01
Gauteng	2011	25	174	2 849	1	3 049	5.71
	2012	135	760	9 995	70	10 960	6.93
	2013	901	1 961	27 750	65	30 677	6.39
	2014	128	371	5 452	3	5 954	6.23
Kwa-Zulu Natal	2011	107	923	11 134	62	12 226	7.55
	2012	434	2 207	21 553	252	24 446	9.03
	2013	1 109	3 791	38 647	422	43 969	8.62
	2014	267	830	8 132	70	9 299	8.93
Limpopo	2011	25	148	1 777	25	1 975	7.49
	2012	52	267	3 599	75	3 993	6.69
	2013	297	720	12 695	108	13 820	5.21
	2014	38	116	2 087	3	2 244	5.17
Mpumalanga	2011	31	210	2 392	6	2 639	7.96



	2012	57	407	3 504	76	4 044	10.06
	2013	227	1 000	8 829	27	10 083	9.92
	2014	44	196	1 851	1	2 092	9.37
North West	2011	40	304	3 128	4	3 476	8.75
	2012	66	390	4 704	14	5 174	7.54
	2013	290	712	11 568	30	12 600	5.65
	2014	57	169	2 428		2 654	6.37
Northern Cape	2011	28	197	2 637	2	2 864	6.88
	2012	64	273	4 093	10	4 440	6.15
	2013	178	423	7 030	290	7 921	5.34
	2014	21	72	1 237	3	1 333	5.40
Western Cape	2011	15	106	2 082	1	2 204	4.81
	2012	150	657	12 393	2	13 202	4.98
	2013	696	1 564	28 996	2	31 258	5.00
	2014	109	339	5 987		6 435	5.27
Total		7 820	25 765	341 336	2 007	376 928	6.84

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
		#	%	#	%		#	%	#	%	
EC	3 814	186	4.9%	109	58.6%	0	648	17%	588	90.7%	2
FS	1 476	78	5.3%	38	48.7%	0	342	23%	233	68.1%	57
GP	2 765	99	3.6%	76	76.8%	0	425	15%	364	85.6%	7
KZN	5 318	1 227	23.1%	1 140	92.9%	0	1 247	23%	981	78.7%	40
LP	998	74	7.4%	66	89.2%	0	184	18%	123	66.8%	2
MP	1 330	232	17.4%	220	94.8%	0	355	27%	286	80.6%	3
NW	1 051	50	4.8%	40	80.0%	0	186	18%	146	78.5%	13
NC	770	65	8.4%	39	60.0%	2	146	19%	100	68.5%	11
WC	1 832	25	1.4%	3	0.0%	0	1 239	68%	1 162	93.8%	4
National	19 354	2 036	10.5%	1 731	85.0%	2	4 772	25%	3 983	83.5%	139

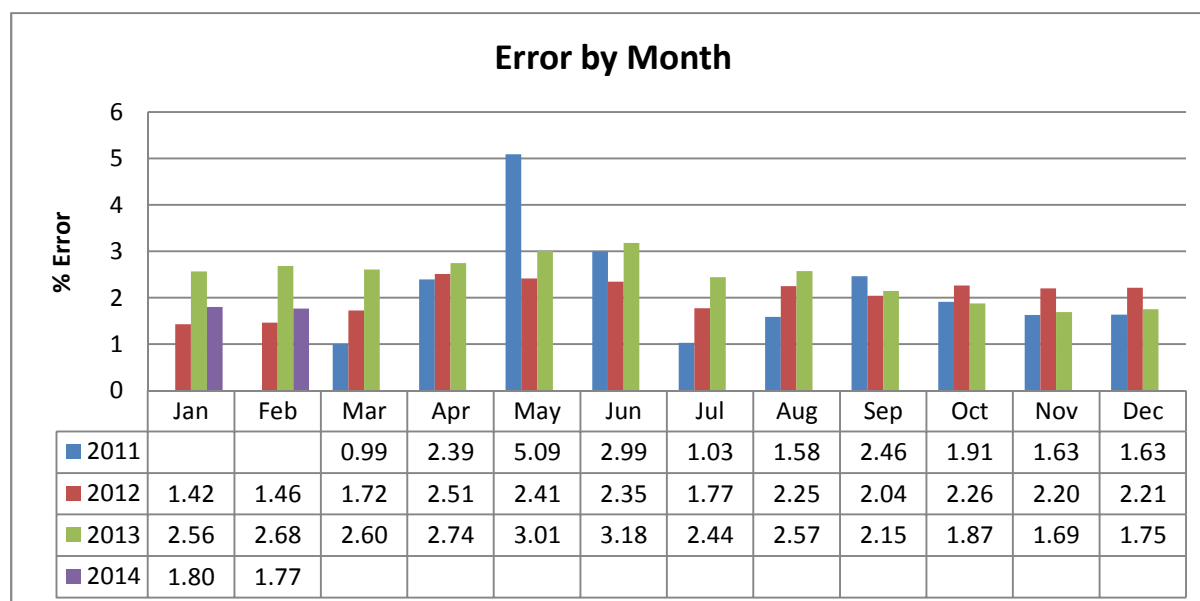
4. Errors

Average error rate has ranged consistently below 3%, however 1/9 provinces reported error rates above 3% in the month of January. 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 (1-28 February 2014)

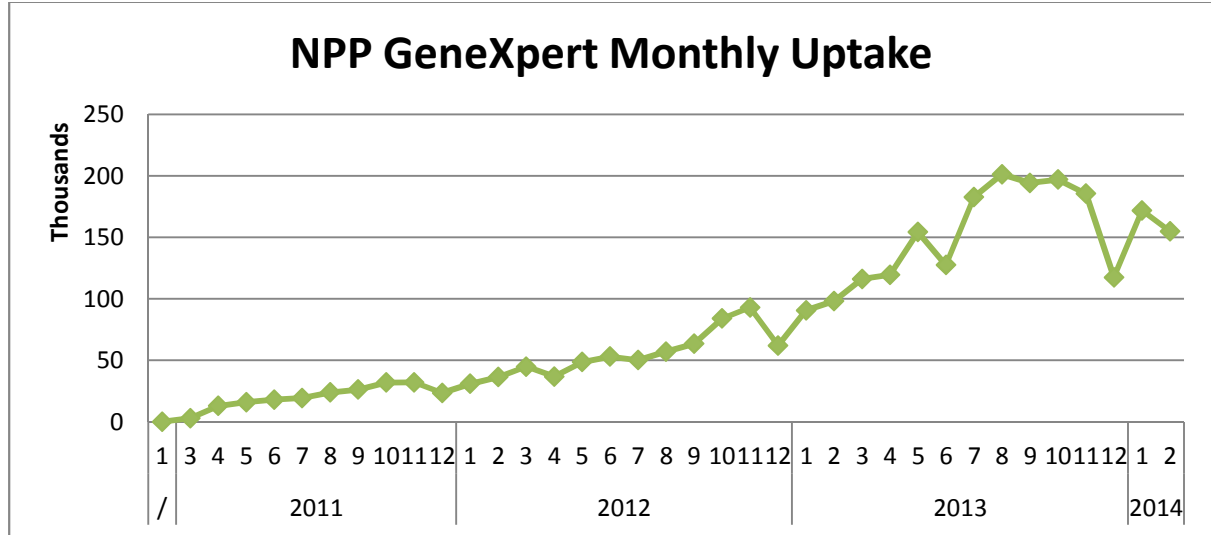
Province	ERR	INV	NORES	MTB Results	Grand Total
EASTERN CAPE	382	144	37	27 955	28 518
FREE STATE	70	18	3	9 690	9 781
GAUTENG	439	95	29	20 561	21 124
KWAZULU-NATAL	782	170	82	36 248	37 282
LIMPOPO	380	83	5	13 991	14 459
MPUMALANGA	122	40	7	7 031	7 200
NORTH WEST	373	62	18	11 913	12 366
NORTHERN CAPE	76	161	3	4 585	4 825
WESTERN CAPE	96	28	13	18 503	18 640
Grand Total	2 720	801	197	150 477	154 195

Figure 1: GeneXpert Error by Month



5. Monthly uptake since implementation started

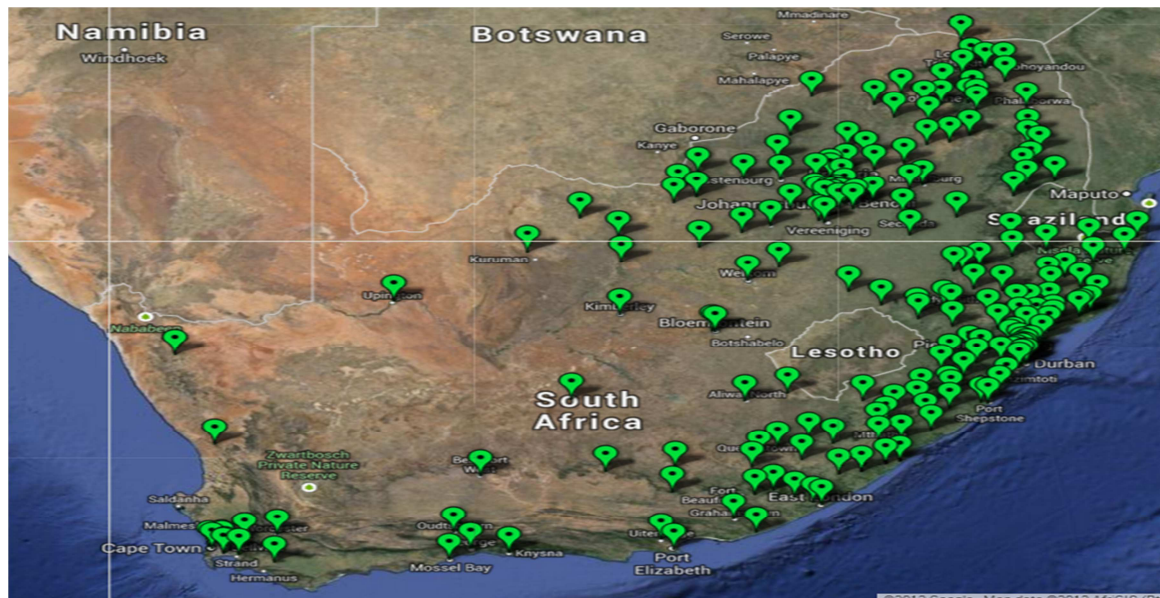
Figure 2: GeneXpert Monthly Uptake



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, 286 analysers, Gx4: 95; Gx16-8: 1; Gx16: 185; GX48:1; GX80-80: 4) *20 clinic placements



7. Training: Laboratory and Clinical

A total of 1,048 laboratory staff and 5,762 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.

21 participants from the QA department of the NHLS all regions, except the Western Cape and Northern Cape region attended a three day HBDC Advanced GeneXpert Training organized by the National Priority Programs of the NHLS in collaboration with Cepheid. The course conducted from 18 to 20 February 2014 at Wits Medical School, Johannesburg, South Africa. Participants included QA coordinators and technical auditors.



The Advanced GeneXpert Training course was intended to give participants knowledge of the GeneXpert technology and its applications in diagnostic and research settings highlighting differences between this technology and the currently available TB diagnostic tools in South Africa.



Topics covered by this comprehensive training course include regulatory compliance and adherence to good laboratory practices, personnel qualifications and responsibilities, establishment and verification of test performance specifications, preparation and processing of clinical molecular samples, quality control practices, proficiency testing and alternative performance assessment, test reports and quality management practices.

We strongly believe that the impact of the information shared between the participants and facilitators will improve the quality of TB testing using the GeneXpert technology within the NHLS. This also highlighted weaknesses in the current communication strategy and the importance of including QA coordinators and technical auditors when new assays are introduced.

In addition, the session addressed progress on oversight and management functions that support information sharing and safeguarding, including the alignment and harmonization of different departments, quality management and 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

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
Wekesa et al, Int J Tuberc Lung Dis, 2014	Cross-sectional analytical study of 123 adults with chronic cough and no previous anti-tuberculosis treatment	<ul style="list-style-type: none"> • The majority of the sputum smear-negative patients did not have TB on single Xpert testing. • CXR gave an overestimate of sputum smear-negative TB cases 	
Kik et al, European Resp J, 2014 Commentary	<ul style="list-style-type: none"> • Outline the desirable test characteristics of new TB diagnostics for use in microscopy centres to assist product developers 		



Raizada et al, PloS One, 2014	Recorded and analysed association between key implementation factors in India and the ability of Xpert MTB/RIF to produce valid results	<ul style="list-style-type: none">• March'12 to January'13, a total of 40,035 suspects were tested by Xpert MTB/RIF• 39,680 (99.1%) received valid results• Overall initial test failure was 2,878 (7.2% (4%-17%))• 2,594 (90.1%) were re-tested and produced valid results• Most frequent reason of test failure was inadequate sample processing or equipment malfunction• Significant variation was observed in failure rates both across instruments and over time
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10. Update on GeneXpert Research projects:

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

- Verification material for new international GeneXpert sites is being manufactured
- Results of Phase 3 of the national NHLS GeneXpert EQA program:
 - i. Two sites (three instruments) were deregistered from the program before panel three which was performed by the remaining 20 sites (instruments: n=25). Two instruments (8%) failed panel 3 (results 50% and 25%). Four instruments (16%) did not submit results and the remaining 19 instruments (76%) all passed (>87.5%).
 - ii. The annual frame score (calculated on the last 3 submitted panel results) shows that of 25 instruments still registered by the end of the third round, seventeen instruments passed (90-100%), one instrument had acceptable results (85-90%) and seven instrument's frame scores are a concern(<85%).
- Panel 1 of the 2014 EQA program has been sent to all participating NHLS sites
 - i. Submissions have started and the closing date for submissions is 30 April 2014.
- A liquid format of the EQA material is also being investigated in terms of composition, stability (at RT, 4°C and 37°C) and feasibility
 - i. Status: stability up to 4 months has been tested



- Commercialization process of EQA DCS material in collaboration with PATH is ongoing. This has the support of both the NHLS and the University of the Witwatersrand, the WHO and the CDC.
- TBGxMonitor™ (www.tbgxmonitor.com) upgrade specification finalized.
 - Seriuin reviewing specification to provide quote on the specification.
 - Additional changes made to the specification to include GX-1 instrument
 - External review for ACTG of Investigation Report forms.
 - Seriuin have begun the update process.

11.2. Connectivity solutions for the GeneXpert

- Connectivity: Collaboration with Cepheid ongoing
 - i. Remote connectivity – old dashboard still up to collect routine data.
 - ii. Testing of the new Cepheid Xpert Monitor is currently underway. Reviews from site and administrative users have been collected and sent to Cepheid for input. Awaiting feedback from Cepheid on these results.

11. Update on other projects

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

Patient follow-up on from the GCC randomized controlled trial is continuing.

- *Sub-studies within GCC*
 - **Paediatric stool protocol:** A study to evaluate the Xpert MTB/RIF assay on paediatric stool specimens (In collaboration with David Alland and FIND). Ethics has been obtained. Stool specimens collection has begun (specimens are being collected from routine residual specimens sent to Microbiology laboratory.)
 - **Longitudinal follow up of Dried blood spots** for viral load monitoring: Longitudinal collection of DBS from n=100 HIV-positive patients over 60 weeks. Sample collection and testing is ongoing.
 - **Clinic validation of EPOCal Blood gas analysis system (Alere):** A new chemistry POC device will be evaluated against routine laboratory results at Themba Lethu



clinic. A nurse will perform the testing on venepuncture specimens for Hb and Creat measurements. Study is due to start Mid-March.

- **Laboratory Comparison of Genotype MTBDRplus v1 and 2 using DCS.** This comparison will be performed using DCS material in order to determine the reproducibility of results using either version of the MTBDRplus assay. Version 1 testing complete. Awaiting version 2 testing. Interim results submitted to SA TB conference 2014.
- **Laboratory validation of new TB diagnostics:** We are also investigating alternative TB assays such as the EasyNat Diagnostic kit for TB (USTAR Biotechnologies)
- **Data analysis is underway on a number of different projects:** Validation of blood collection, storage and transport media; clinic validation of nurse operated Liat POC viral load; laboratory validation of HIV/Syphilis Duo rapid test. Once analysis is complete, results will be written up for publication.
- **GCC Connectivity**
 - The captured data via **TBGxCompanion** has been cleaned based on the initial feedback from the study coordinator and sent to the HERO group for analysis. Additional data capturing and cleaning has been completed based on missing information. The data is ready for analysis.
 - The **SMS-randomization** gateway has been closed down since no further patients are being enrolled.
 - The **AegisPOC-Conworx** user evaluation and transcription error investigation has been completed on the AegisPOC data showing that manual data transcription has a high error rate. Conworx data to be evaluated.



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 February.