NATIONAL HEALTH LABORATORY SERVICE

GeneXpert Implementation Report Update

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1. Background to Project

This project was initiated at the request of the Honorable Minister of Health in early 2011. A pilot study was proposed by the National Department of Health (NDoH) (particularly the TB cluster) while due diligence was being done with respect to project feasibility. This was further prompted by the World Health Organization's strong recommendation in December 2010 that "the new automated DNA test for TB be used as the initial diagnostic test in individuals suspected of MDR-TB or HIV/TB (i.e. all SA TB suspects).

The pilot phase was initiated in microscopy centres in high focus TB areas. The ministry requested that at least 1 instrument be placed in each province, preferably in a district that had a high burden of TB (Selections were made by TB cluster). Twenty-five microscopy centres were selected and a total of 30 instruments placed. The NDoH funded 9 GX16 and 14 GX4 instruments for the project. FIND donated 6 GX4 analysers and the Infinity or GX48 was supported by PEPFAR RTC. All instruments were placed by World TB day March 24th. 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.

2. Assays performed to date

In summary, a total of 181,546 specimens have been processed to date (Nov 2011). The total % of MTB detected in this cohort amounted to 16.74% (30,387 new TB cases). The percentage positivity has remained on average between 16-17% monthly nationally. To date KZN has performed the largest number of tests which is probably as a result of the throughput of the GX48 analyzer (Refer to table 1). Average Rifampicin resistance detection rates have remained around 7% since project inception (Refer to table 2)

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Table 1: GeneXpert MTB Results by province

Province	HEALTH DISTRICT	MTB Detected	MTB Not Detected	Test Unsuccessful	Grand Total	% MTB Detected
Eastern Cape	ALFRED NZO	83	524	13	620	13.39
	AMATHOLE	184	1,362	42	1,588	11.59
	CACADU		14		14	-
	CHRIS HANI	18	112	3	133	13.53
	CITY OF TSHWANE		2		2	-
	GERT SIBANDE	1	15		16	6.25
	LEJWELEPUTSWA	19	17	1	37	51.35
	N/A		1		1	-
	O R TAMBO	2,416	11,141	418	13,975	17.29
	UKHAHLAMBA	14	81	5	100	14.00
	VHEMBE		20		20	-
Eastern Cape Total		**2,743**	**13,303**	**482**	**16,528**	**16.60**
Free State	FEZILE DABI	739	3,671	9	4,419	16.72
	GERT SIBANDE	3	33		36	8.33
	LEJWELEPUTSWA	1,550	8,470	17	10,037	15.44
	N/A		4		4	-
	SEDIBENG	9	19		28	32.14
	THABO MOFUTSANYANA	17	166	1	184	9.24
Free State Total		**2,319**	**12,369**	**27**	**14,715**	**15.76**
Gauteng	CITY OF JOHANNESBURG	2,454	15,638	414	18,506	13.26
	EHLANZENI		1		1	-
	EKURHULENI METRO	96	455	5	556	17.27
	O R TAMBO		1		1	-
	THABO MOFUTSANYANA		1		1	-
Gauteng Total		**2,551**	**16,099**	**419**	**19,069**	**13.38**
Kwa-Zulu Natal	ETHEKWINI METRO	10,766	38,750	1,501	51,017	21.10
	N/A	382	1,664	50	2,096	18.23
	SISONKE		1		1	-
	UGU	116	747	6	869	13.35
	UMGUNGUNDLOVU	4	24	2	30	13.33
	UMZINYATHI	3	5		8	37.50
	UTHUKELA		1		1	-
	UTHUNGULU	386	1,371	17	1,774	21.76
	ZULULAND	126	313	29	468	26.92
Kwa-Zulu Natal Total		**11,784**	**42,877**	**1,605**	**56,266**	**20.94**
Limpopo	CAPRICORN		5		5	-
	GREATER SEKHUKHUNE	22	59		81	27.16
	MOPANI	1,537	12,878	129	14,544	10.57
	N/A	274	3,162	25	3,461	7.92
	NONE		2		2	-
	SEDIBENG		17		17	-
	UMGUNGUNDLOVU		1		1	-
	VHEMBE	10	99	3	112	8.93
	WATERBERG	7	37	3	47	14.89
Limpopo Total		**1,850**	**16,260**	**160**	**18,270**	**10.13**
Mpumalanga	EHLANZENI	6	25	7	38	15.79
	GERT SIBANDE	2,333	11,541	1,025	14,899	15.66
	NKANGALA	86	277	42	405	21.23
	UMKHANYAKUDE		2	2	4	-
Mpumalanga Total		**2,425**	**11,846**	**1,076**	**15,347**	**15.80**
North West	BOJANALA	1	2		3	33.33
	DR KENNETH KAUNDA	1,969	9,908	387	12,264	16.06
	DR RUTH SEGOMOTSI MOMPATI	95	542	16	653	14.55
	NELSON MANDELA BAY METRO		2		2	-
	NGAKA MODIRI MOLEMA	88	316	22	426	20.66
	VHEMBE	1	13	1	15	6.67
North West Total		**2,156**	**10,807**	**428**	**13,391**	**16.10**
Northern Cape	DR RUTH SEGOMOTSI MOMPATI	9	21		30	30.00
	EKURHULENI METRO	54	335	17	406	13.30
	FRANCES BAARD	1,430	8,627	427	10,484	13.64
	JOHN TAOLO GAETSEWE	933	3,446	92	4,471	20.87
	N/A	15	66	1	82	18.29
	NAMAKWA	10	21	1	32	31.25
	PIXLEY KA SEME	259	1,356	73	1,688	15.34
	SIYANDA	323	1,463	86	1,872	17.25
	XHARIEP	3	6		9	33.33
Northern Cape Total		**3,045**	**15,357**	**700**	**19,102**	**15.94**
Western Cape	CAPE WINELANDS	125	357	2	484	25.83
	CITY OF CAPE TOWN	1,294	6,171	14	7,479	17.30
	MOTHEO		1		1	-
	OVERBERG	85	772	14	871	9.76
Western Cape Total		**1,514**	**7,311**	**33**	**8,858**	**17.09**
Grand Total		**30,387**	**146,229**	**4,930**	**181,546**	**16.74**

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Table 2: Provincial GeneXpert RIF Results in MTB detected cases

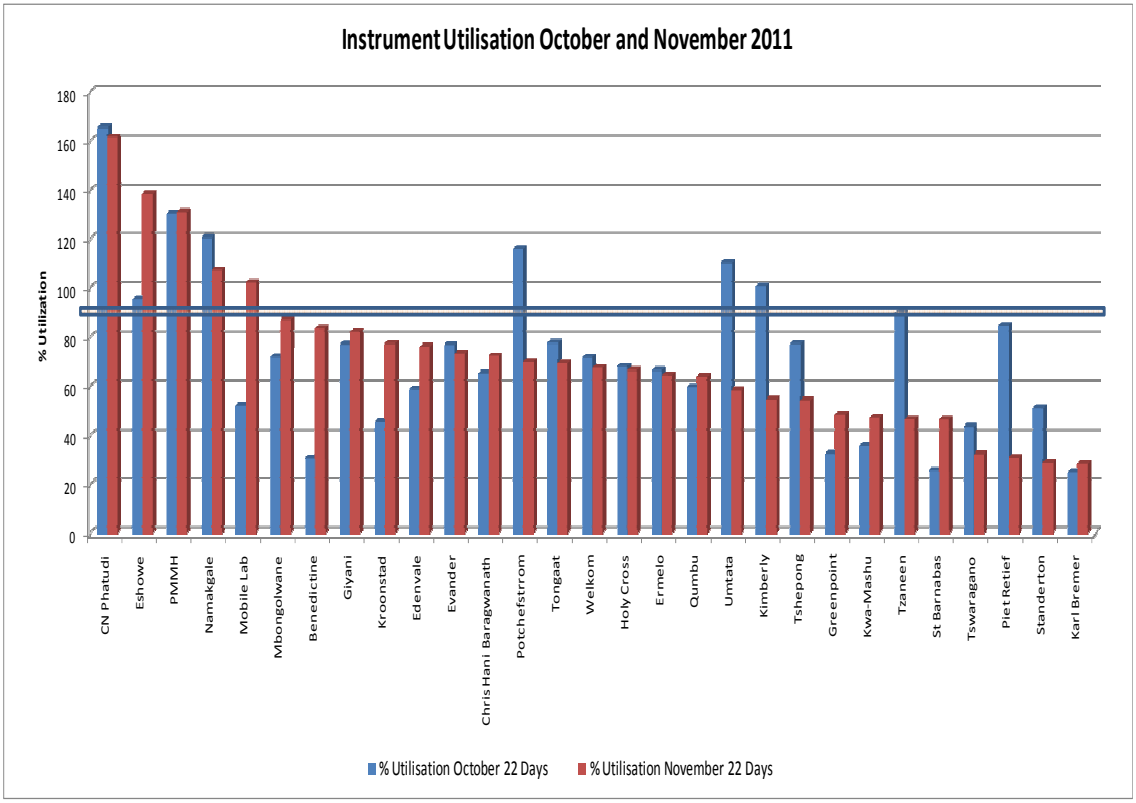
Province	HEALTH_DISTRICT	Inconclusive	Resistant	Sensitive	No Result	Grand Total	% RIF Resistant
Eastern Cape	ALFRED NZO	2	7	71	3	83	8.43
	AMATHOLE	6	21	155	2	184	11.41
	CHRIS HANI		1	17		18	5.56
	GERT SIBANDE			1		1	-
	LEJWELEPUTSWA		2	16	1	19	10.53
	O R TAMBO	17	164	2186	49	2416	6.79
	UKHAHLAMBA	1	1	12		14	7.14
Eastern Cape Total		**26**	**198**	**2464**	**55**	**2743**	7.22
Free State	FEZILE DABI	8	34	697		739	4.60
	GERT SIBANDE			3		3	-
	LEJWELEPUTSWA	17	91	1441	1	1550	5.87
	SEDIBENG			9		9	-
	THABO MOFUTSANYANA		2	15		17	11.76
Free State Total		**25**	**127**	**2166**	**1**	**2319**	5.48
Gauteng	CITY OF JOHANNESBURG	17	148	2288	1	2454	6.03
	EKURHULENI METRO	1	4	91		96	4.17
Gauteng Total		**18**	**152**	**2380**	**1**	**2551**	5.96
Kwa-Zulu Natal	ETHEKWINI METRO	103	724	9890	49	10766	6.72
	N/A	3	36	343		382	9.42
	UGU		3	113		116	2.59
	UMGUNGUNDLOVU		1	3		4	25.00
	UMZINYATHI		1	2		3	33.33
	UTHUNGULU	1	61	320	4	386	15.80
	ZULULAND		29	97		126	23.02
Kwa-Zulu Natal Total		**107**	**855**	**10769**	**53**	**11784**	7.26
Limpopo	GREATER SEKHUKHUNE		5	17		22	22.73
	MOPANI	18	102	1396	21	1537	6.64
	N/A	6	22	243	3	274	8.03
	VHEMBE		1	9		10	10.00
	WATERBERG			7		7	-
Limpopo Total		**24**	**130**	**1672**	**24**	**1850**	7.03
Mpumalanga	EHLANZENI		1	5		6	16.67
	GERT SIBANDE	26	183	2120	4	2333	7.84
	NKANGALA	3	5	78		86	5.81
Mpumalanga Total		**29**	**189**	**2203**	**4**	**2425**	7.79
North West	DR KENNETH KAUNDA	28	162	1779		1969	8.23
	DR RUTH SEGOMOTSI MOMPATI	1	6	88		95	6.32
	NGAKA MODIRI MOLEMA		3	85		88	3.41
North West Total		**29**	**171**	**1956**		**2156**	7.93
Northern Cape	DR RUTH SEGOMOTSI MOMPATI		2	7		9	22.22
	EKURHULENI METRO		6	48		54	11.11
	FRANCES BAARD	16	77	1336	1	1430	5.38
	JOHN TAOLO GAETSEWE	5	56	872		933	6.00
	NAMAKWA		2	8		10	20.00
	PIXLEY KA SEME	2	37	220		259	14.29
	SIYANDA	5	16	302		323	4.95
	XHARIEP			3		3	-
Northern Cape Total		**28**	**196**	**2820**	**1**	**3045**	6.44
Western Cape	CAPE WINELANDS		12	113		125	9.60
	CITY OF CAPE TOWN	12	56	1226		1294	4.33
	OVERBERG		3	80	2	85	3.53
Western Cape Total		**12**	**71**	**1429**	**2**	**1514**	4.69
Grand Total		**298**	**2089**	**27859**	**141**	**30387**	**6.87**

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 3: Number of Unsuccessful Tests and Reasons

Province	Error	Invalid	No Result	MTB Result	Grand Total	% Error Total
Eastern Cape	426	42	6	16,054	16,528	2.58
Free State	21			14,694	14,715	0.14
Gauteng	343	40	4	18,682	19,069	1.80
Kwa-Zulu Natal	1,026	531	34	54,675	56,266	1.82
Limpopo	115	28	10	18,117	18,270	0.63
Mpumalanga	990	69	5	14,283	15,347	6.45
North West	400	28		12,963	13,391	2.99
Northern Cape	542	126	14	18,420	19,102	2.84
Western Cape	17	2		8,839	8,858	0.19
Grand Total	**3,880**	**866**	**73**	**176,727**	**181,546**	2.14

3. **Utilization rates of instruments within the field**



Instrument utilization has decreased significantly at some sites from October to Novembber due to shortage of cartridge suppply by Pro-Gen.

4. **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 October.

Phase IIb : Full capacitation of high burden districts: Subject to Funding

Phase IIIa and b: Gates funded study (Gauteng, EC and Free State)

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

Phase IIId: Completion of all current microscopy and clinic sites

5. Specific GeneXpert Progress

Phase 2a: Completed

Phase 2b, 3a and b

Phase 2b is subject to the release of Global Fund funding. There have been some restrictions on the CDC funding which has also resulted in the delay of part of phase 2b rollout.

20 GXVI analyzers are due for delivery in the third week of November for phase 3a and 3b.

- Five machines will be placed by December 2011 in Helen Joseph, Pretoria West, Tembisa, Boksburg Benoni and Witbank. Five t instruments will be placed in January 2012 at the following sites: ALL SAINTS, MARY THERESA, MT AYLIFF, ST PATRICK and BETHLEHEM.
- The remaining 10 machines should will be placed in July 2012 in the following laboratories: COFIMVABA, QUEENSTOWN, TAYLOR BEQUEST, UITENHAGE, MANAPO, NATALSPRUIT, CARLETONVILLE, JUBILEE, MAMELODI, NELSPRUI

Phase 3c and 3d remain on further release of funding

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Table 5: Phase 2b

Province	District	Lab	Capacity Per Day	Instruments			Donor
				GX4	GX16	GX48	
EC	Amathole	EAST LONDON TB	576	0	0	1	Global Fund RTC
EC	Nelson Mandela Bay Metro	PORT ELIZABETH TB	576	0	0	1	Global Fund RTC
EC	O.R. Tambo	ST ELIZABETH	64	0	1	0	Global Fund DOH
EC	O.R. Tambo	ST LUCY	16	1	0	0	Global Fund DOH
EC	O.R. Tambo	ZITULELE	32	0	1	0	Global Fund DOH
GP	City of Johannesburg	CENTRAL TB	80	1	1	0	Global Fund DOH
GP	City of Johannesburg	NJH ROUTINE	16	1	0	0	Global Fund DOH
KZN	eThekwini	Addington	32	0	1	0	Global Fund DOH
KZN	eThekwini	Charles James MC	32	0	1	0	Global Fund DOH
KZN	eThekwini	Clairwood	16	1	0	0	Global Fund DOH
KZN	eThekwini	Dbn Chest Clinic MC	64	0	1	0	Global Fund DOH
KZN	eThekwini	Don Mackenzie MC	16	1	0	0	Global Fund DOH
KZN	eThekwini	FOSA MC	16	1	0	0	Global Fund DOH
KZN	eThekwini	Hlengisizwe MC	16	1	0	0	Global Fund DOH
KZN	eThekwini	Inanda C MC	32	0	1	0	Global Fund DOH
KZN	eThekwini	KwaDabeka MC	32	0	1	0	Global Fund DOH
KZN	eThekwini	Mahatma Ghandi	48	0	1	0	Global Fund DOH
KZN	eThekwini	Osindisweni	16	1	0	0	Global Fund DOH
KZN	eThekwini	PineTown MC	48	0	1	0	Global Fund DOH
KZN	eThekwini	RK Khan	64	0	1	0	Global Fund DOH
KZN	eThekwini	Verulam MC	16	1	0	0	Global Fund DOH
KZN	eThekwini	Wentworth	32	0	1	0	Global Fund DOH
KZN	Sisonke	Kokstad	32	2	0	0	50% Global Fund DOH and TB/HIV Care
KZN	Sisonke	Pholela HCC	16	1	0	0	TB/HIV Care
KZN	Sisonke	Rietvlei	48	0	1	0	Global Fund DOH
KZN	Sisonke	St. Appolinaris	16	1	0	0	TB/HIV Care
KZN	Uthungulu	Eshowe	16	1	0	0	MSF
KZN	Uthungulu	Mbongolwana	16	1	0	0	MSF
KZN	Zululand	Benedictine	48	0	1	0	Global Fund DOH
LP	Mopani	KGAPANE	32	0	1	0	Global Fund DOH
LP	Mopani	PHALABORWA	32	0	1	0	Global Fund DOH
LP	Mopani	SEKORORO	16	1	0	0	Global Fund DOH
MP	Gert Sibande	EMBHULENI	32	0	1	0	Global Fund DOH
NC	Siyanda	UPINGTON	64	0	1	0	Global Fund DOH
NW	Dr Kenneth Kaunda (Southern)	POTCHEFSTROOM	48	0	1	0	Global Fund DOH
WC	City of Cape Town	GROOTE SCHUUR CLINICAL PATH	48	0	1	0	Global Fund DOH

Table 5: Phase 3a

Serial	Province	District	Lab	GX4	GX16	GX48	Capacity Per Day	Status	Donor
4	EC	Alfred Nzo	MARY THERESA		1		64	Pending	Gates Foundation
5	EC	Alfred Nzo	MT AYLIFF		1		48	Pending	Gates Foundation
23	EC	Chris Hani	ALL SAINTS		1		64	Pending	Gates Foundation
56	FS	Thabo Mofutsanyane	BETHLEHEM		1		48	Pending	Gates Foundation
71	GP	City of Tshwane	PRETORIA WEST		1		48	Pending	Gates Foundation
74	GP	Ekurhuleni	BOKSBURG BENONI	1	1		80	Pending	Gates Foundation
79	GP	Ekurhuleni	TEMBISA		1		64	Pending	Gates Foundation
40	EC	O.R. Tambo	ST PATRICK		1		48	Pending	Gates Foundation
64	GP	City of Johannesburg	HELEN JOSEPH		1		48	Pending	Gates Foundation
148	MP	Nkangala	WITBANK		1		64	Pending	Gates Foundation

Table 6: Phase 3b

Serial	Province	District	Lab	GX4	GX16	GX48	Capacity Per Day	Status	Donor
25	EC	Chris Hani	COFIMVABA		1		64	Pending	Gates Foundation
29	EC	Chris Hani	QUEENSTOWN	1	1		80	Pending	Gates Foundation
33	EC	Nelson Mandela Bay Metro	UITENHAGE		1		64	Pending	Gates Foundation
57	FS	Thabo Mofutsanyane	MANAPO		1		48	Pending	Gates Foundation
68	GP	City of Tshwane	JUBILEE		1		48	Pending	Gates Foundation
69	GP	City of Tshwane	MAMELODI		1		64	Pending	Gates Foundation
77	GP	Ekurhuleni	NATALSPRUIT		1		64	Pending	Gates Foundation
85	GP	West Rand	CARLETONVILLE		1		64	Pending	Gates Foundation
46	EC	Ukhahlamba	TAYLOR BEQUEST	1	1		80	Pending	Gates Foundation
133	MP	Ehlanzeni	NELSPRUIT		2		128	Pending	Gates Foundation

6. **Training: Laboratory and Clinical**

A total of 484 staff have been trained since July 2011 as summarized in table 8 and 9 below. Training was for both laboratory staff and health care professionals in all the nine provinces. This will be an ongoing process to support NDoH training on clinical algorithm. Laboratory staff will receive both clinical and technical training.

Table 8: Laboratory Training

Venue	DATE	Trainer	TOTAL # OF DELEGATES	Outcomes
Greenpoint	14-15 July	Tessa	8	GeneXpert Operation, Maintenance, Troubleshooting and Data Entry
Eshowe	04 August	Floyd	10	GeneXpert Operation, Maintenance, Troubleshooting and Data Entry
Mbongolwana	04 August	Floyd	5	GeneXpert Operation, Maintenance, Troubleshooting and Data Entry
CHB	26 & 30 August	Fimmie	10	GeneXpert Operation, Maintenance, Troubleshooting and Data Entry
Benedictine	06 September	Veeresh	8	GeneXpert Operation, Maintenance, Troubleshooting and Data Entry
Benedictine	14 September	Nico	5	GeneXpert Operation, Maintenance, Troubleshooting and Data Entry
Benedictine	14 September	Nico	8	GeneXpert Overview and Algorithm
Siloah	15 September	Nico	11	GeneXpert Overview and Algorithm
Pholela	22 September	Veeresh	1	GeneXpert Operation, Maintenance, Troubleshooting and Data Entry
Pholela	30 September	Floyd, Sibulele	10	GeneXpert Overview and Algorithm

Venue	DATE	Trainer	TOTAL # OF DELEGATES	Outcomes
Western Cape	23 September	Limenako	26	TB and DR-TB Management Update
Bloemfontein	14 September		51	TB Diagnosis and Algorithm
Forever Resort	27 September		45	TB Diagnosis and Algorithm
Kimberley	21 September	Pamela & Lessie	30	TB Management
Eastern Cape	14 September	T Kunene, O Mokgathle, Ms Mhlope, Dr Erasmus and Dr Mhlongo	65	TB and DR-TB Management Update
North West			37	TB and DR-TB Management Update
Clairwood Hospital	29 September	Lessie, T Kunene, O Mokgathle	60	TB and DR-TB Management Update
Turfontein Race Course	05 September		45	National Tb Guidelines
Mpumalanga	20 September	M Molefe, L Matsoso, T Kunene	49	TB and DR-TB Management Update

7. **Challenges identified during the course of the project to date**

- Alignment of enthusiastic donors to support one plan
- Finalisation of the request forms: The GXP assay and confirmatory tests are to be added to the CCMT form.
- The development of a National TB costing model
- Clinical Algorithm: Understanding of the algorithm still poses a major challenge, however this is being addressed during the clinical training held in the different provinces.
- Error rates which have largely been resolved

8. **Literature Update For GeneXpert**

There has been an expansion of the literature with respect to the assay performance. The highlights are summarized in table 6 below:

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

Manuscript	Sample population and specimen type (n=…)	Results	
		Sensitivity	Specificity
Turnbull et al, 2011 Journal of Pregnancy	Algorithm	Proposed a model for a point of care screening algorithm using GeneXpert in pregnant women.	
Theron et al 2011, ERJ Express	480 TB suspects	When downstream adjunct tests were applied to Xpert-MTB/RIF-negative individuals: (i) radiology ruled-out TB in 24% [56/234; NPV 100%(56/56)]; (ii) smear-microscopy ruled-in TB in 21%(7/24) of culture-positive individuals; (iii) IGRAs were not useful in either context.	
Theron et al 2011, American Journal of Respiratory and Critical Care Medicine	496 South African patients with suspected TB	95% (95% confidence interval [CI], 88–98%; 89 of 94) of smear positive culture-positive cases. Compared with smear microscopy (n = 94), Xpert MTB/ RIF detected an additional 17 cases.	specificity was 94% (91–96%; 320 of 339) smear positive culture-positive cases.
Trebucq et al 2011, Int J Tuberc Lung Dis	Review of GeneXpert for national TUBERCULOSIS programs in low-income countries		
Causse et al 2011, J Clin Micro	340 nonrespiratory samples comparison to Cobas TaqMan MTB	The sensitivity of the Xpert assay was 95% compared to 78% for the Cobas assay.	Xpert = 100% Cobas = 98%

9. Update on GeneXpert Research projects:

- An EQA program based on Dried Culture Spots has been developed
  - Other potential material is being investigated for an EQA program, including inactivated liquid material
  - A pilot study is underway to test the cost and ease of use of liquid EQA material at sites compared to dry EQA material
- Alternative specimen preparation protocols on the GeneXpert:
  - Protocols have been developed for Paediatric TB diagnosis and Extra-pulmonary TB diagnosis

- Protocols are under development for GeneXpert testing on solid tissues, gastric aspirates etc.

- Paediatric study: A study to determine accuracy of diagnosis of paed TB using the GeneXpert is underway at Rahimma Moosa Mother and Child Hospital. N=161 paed patients have been enrolled to date and results will be compared to culture and smear microscopy.

- Sputum heat inactivation: a study to determine whether heat inactivation can be used prior to GeneXpert testing to render it safe for further manipulation, is ongoing

- A study to evaluate the new G4 Xpert cartridge is ongoing – phase I and II are complete, results have been analysed. A phase III study is planned.

- Two abstracts have been accepted to CROI Conference in Seattle 2012:

  - Exploring the value of the Xpert MTB/RIF probe frequencies and cycle threshold data for surveillance purposes.

  - The Reality of Xpert MTB/RIF at Point of Care (POC) for the Diagnosis of Childhood TB using Raw Sputum.

10. **Grants submitted**

None

11. **Funding issues**

- Urgency remains to conclude Global fund negotiations and release funds
- Recurrent assay cost price needs to be agreed upon before new financial year