GeneXpert Implementation in South Africa Public Sector

One year later..Lessons Learnt

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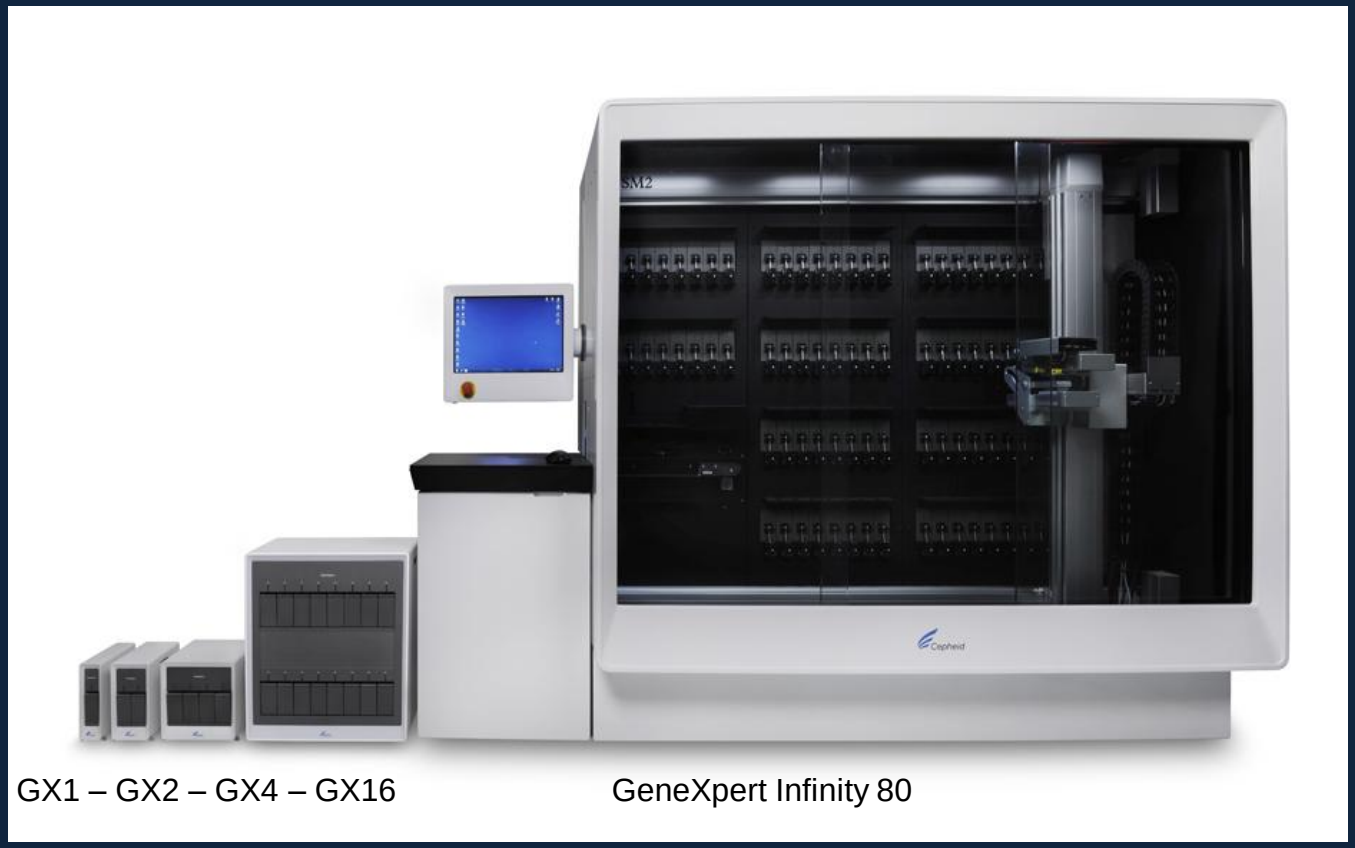
4th WHO/GLI meeting, April 2012

GeneXpert Technology



GX1 – GX2 – GX4 – GX16 GeneXpert Infinity 80

4	8	16	64	320	throughput/8 hr day

WHO Recommendation (2010)

- **WHO Strong Recommendation**: "The new automated DNA test for TB should be used as the initial diagnostic test in individuals suspected of MDR-TB or HIV/TB" *(i.e. Most TB suspects in SA)*
- **Pillars of SA National Strategic Plan: (2012-2017 draft)**
  - Universal testing for HIV and screening for TB – the primary objectives being to ensure that all citizens know their HIV and TB status, and to prevent new HIV and TB infections
  - **Health and wellness** – the primary objective being to ensure access to quality treatment, care and support services for those with HIV and/or TB and to develop programmes to focus on wellness
- **Intention to rollout the GeneXpert in 2-3 year plan**

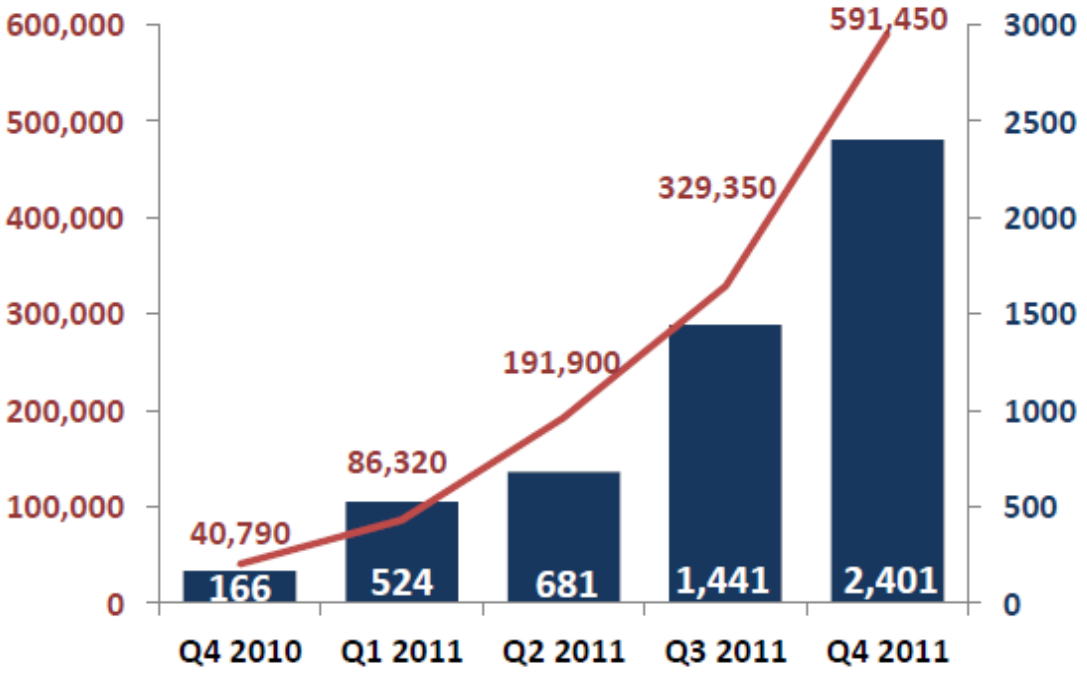
World Health Organization

THE STOP TB DEPARTMENT

- UPDATE -
Implementation and roll-out of Xpert MTB/RIF
February 2012

By the end of 2011, a total of 460 GeneXpert machines (comprising 2,401 modules) and 591,450 Xpe... test cartridges had been procured in 47 countries under concessional pricing.

Cumulative number of GeneXpert modules and Xpert MTB/RIF cartridges procured under concessional pricing



http://www.who.imt/tb/laboratory/

Private sector in SA: ~48 000 non-concessional pricing

Over half of the Xpert MTB/RIF cartridges (330,540 cartridges) have been procured for use in South Africa alone, followed by Pakistan (21,440), Kenya (20,140), the Philippines (17,440) and Swaziland (16,600). Data by country.

Disease Burden in South Africa

- 20% worlds reported HIV-associated TB cases and 4th largest reported numbers of MDR.
- **70% TB suspects infected with HIV**
- Overall TB rates 795/100,000 (2010)
  - Mining populations 2500/100,000
  - Correctional Services 4500/100,0000
- Increasingly smear negative (8-10% positivity) and extra-pulmonary TB(16%), microscopy not helpful for DR detection
- HIV background of 5.7 million infected individuals of which 1.4 million are receiving ARV therapy
- Diagnosis is made to late to avert mortality in HIV co-infected where smear sensitivity drops to 35-40%. Symptomatic screen not useful in 25% cases (*Lawn. JID 2011*)
- Estimated 25-30% of individuals in CT initiating ARV treatment have unrecognisable TB (*Holmes, JAIDS 2006*)

NHLS Laboratory Microscopy Centres: 2010-2012 N=244, serves 87% population

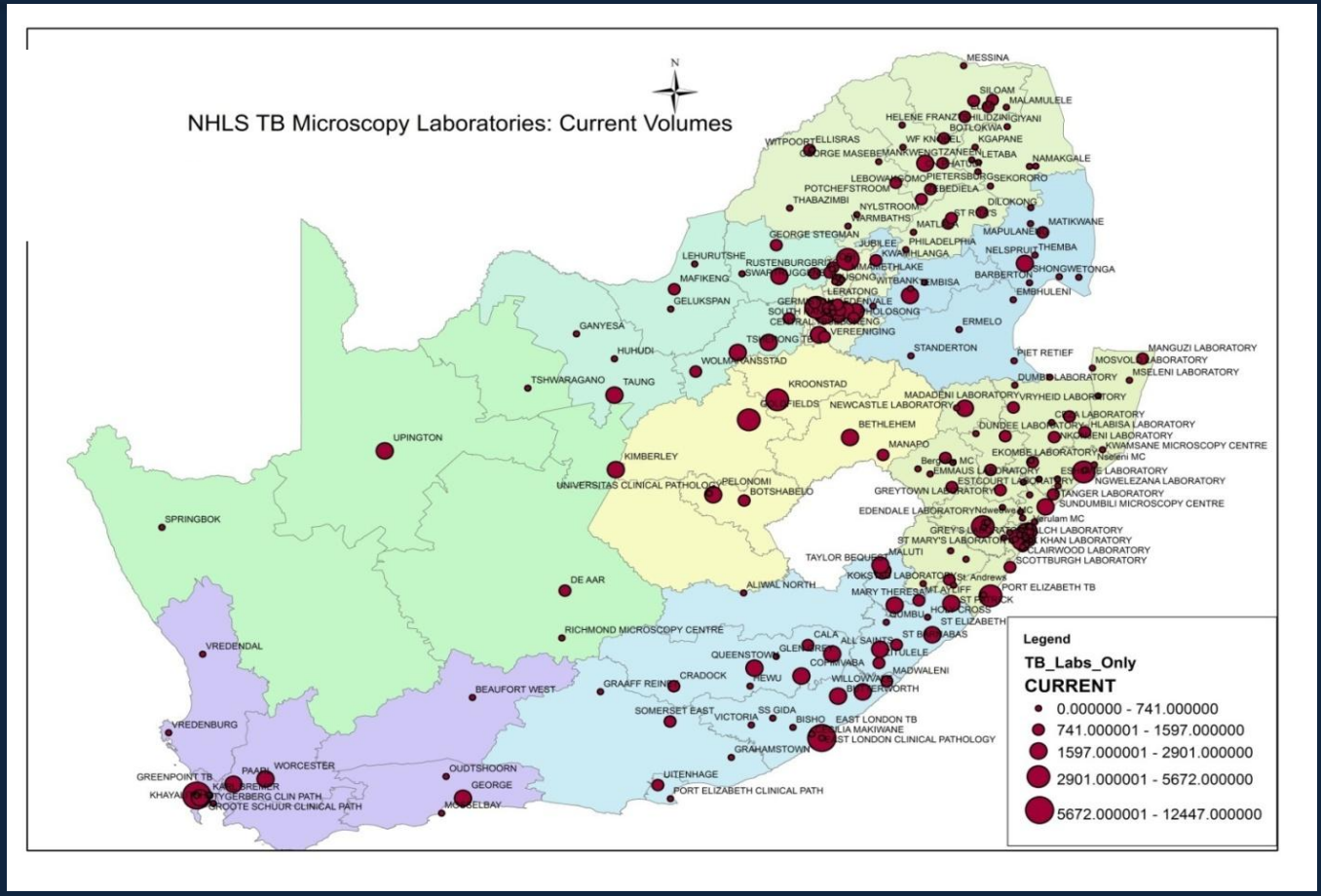
Volumes for 2010

- Smears: 4 ,476 ,271
- Cultures: ~933 179 (22% positive)
- LPA :~90 000

- 16 culture and/or LPA labs
- Initial models based on 2010 volumes

Volumes 2011

Smears: 5,021,166
Culture: 1,174,448 (20% positive)



Situation prior to GeneXpert Rollout

GeneXpert Pilot Implementation

- Minister of Health makes implementation decision in early 2011
- Referred to as phase 1: Limited Pilot in all 9 provinces in SA to establish feasibility
- ≥1 instrument per province in high burden districts (selected by TB cluster)
- Placement in microscopy centres: readiness
- 25 sites, 30 instruments
- 20 GX4, 9 GX16, 1 GX48
- Funding by NDOH, FIND,USAID RTC
- Placement by world TB day: March 24th 2011
- ~10% national coverage based on crude estimate 2010 smears volumes/2

2 smears at diagnosis to be replaced by one Xpert MTB/RIF (Phased approach)

TB SUSPECTS
TB and DR-TB contacts, non-contact symptomatic individuals, re-treatment after relapse, failure and default
Collect one sputum specimen at the health facility under supervision

GXP positive
Rifampicin susceptible

Treat as TB
Start on Regimen 1
Send one specimen for microscopy

Follow up with microscopy

GXP positive
Rifampicin resistant

Treat as MDR-TB
Refer to MDR-TB Unit

Collect one specimen for microscopy, culture and DST for Rifampicin, Isoniazid, fluoroquinolone and Aminoglycoside

Follow up with microscopy and culture

GXP positive
Rifampicin unsuccessful

Treat as TB
Start on Regimen 1
Collect one specimen for microscopy
Culture & DST / LPA

Poor response to antibiotics
Clinically TB
TB on chest x-ray

Treat as TB
Start on Regimen 1
Review culture results

GXP negative

HIV positive

Collect one specimen for culture and LPA or culture and DST (for R and H)
Treat with antibiotics and review after 5 days
Do chest x-ray

LPA/ DST results

Resistant to R and H/ R only

Treat as MDR-TB
Refer to MDR-TB Unit

HIV negative

Treat with antibiotics

Good response

No further follow up
Advise to return when symptoms recur

Poor response

Consider other diagnosis

Refer for further investigation

GXP unsuccessful

Collect one sputum specimen for a repeat GXP

Smith, IJTLD,2011

Methodology for Pilot implementation

Remained the approach with expansion

- **Site needs assessment**: Hoods, space, network points, power, A/C, HR, checklist developed
- **Training & material developed:** intensive 2 day centralised training
  - microscopists were first cadre trained
  - SOP driven, simplified reference charts, incl. safety and GLP
- **LIMS interfacing (pilot)**
  - LIS interface was developed to automatically report results: patient demographics, Lab number, cartridge number, TB detected/not, RIF detected/not, errors and resulting. Transfer to central data warehouse; reporting via sms printers and phones
- A **verification program** ("fit for purpose") for placement and calibration of each module using dried culture spots (*Scott, Stevens et al. JCM 2011)*
- **Widespread Consultation on clinical algorithm**
- **Development of detailed implementation plan, implementation budget and National TB Costing Model (NTCM)**

"**Packaged product/toolbox to facilitate easy implementation**"

Challenges	Lessons Learned in phase I
Algorithm development*	Time to get consensus, ideally before implementation **Changes: TB guidelines, request forms, training etc, resistance reporting** **Challenging to run 2 algorithms in different and/or same regions** **Saturate a region first!**
Training	**Site needs assessment** At least 2 days, several individuals at each site Better on site, follow up required Include GLP, safety, computer literacy **Focus on sample preparation** **Clinician and HCW training critical** **Workflow issues problematic on large instruments** **Regulatory issues?**
Costing implementation & modelling future costs	different modelling approaches : different inputs **Opportunity for costing , reviewing and standardising current TB service** **Cost effective vs. affordable**
Error rates	**3-4%: error codes: 5011 (73%)*** 5006/7 (16%)(insufficient vol), 2008 (10%)
EQA program	Verification program : DCS, liquid pilot Frequency? Per module? **Need for negative controls for larger analysers?**
Electricity, temperature, waste disposal, cartridge storage	UPS, A/C (if>30C); not stable to rescue run cartridges fairly bulky (2-28C) Cartridge switch: software requirements different
Safety	Biohazard hood for infinity and GX16, overkill?

Phased Implementation of GeneXpert in SA

One National Plan

- Phase I: Pilot in high burden districts (HBD)
- Phase II: Completion of high burden districts
  - a. Full capacitation of Phase I labs
  - b. Full capacitation of high burden districts-in progress
- Phase III: XTEND Study* (BMGF)
  - a. Intervention arm- in progress (20 sites)
  - b. Control arm (20 sites)
  - c/d. Completion of all district sites

*Cluster randomised trial to assess cost-effectiveness and impact under routine conditions

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National TB Cost Models

- To estimate implementation costs for NHLS lab network
- To inform national-level budget requirements (2011-2017)
- To estimate the incremental national health service cost of replacing the existing pulmonary TB diagnostic algorithm with a new algorithm incorporating Xpert MTB/RIF molecular technology, under routine care conditions and at costs incurred by the government (*Excel-based population level decision model*) (NTCM)
- Built into Rollout XTEND study (BMGF funded): cluster randomised trial design (phase 3a and b) : to verify modelling and evaluate the cost-effectiveness and assess impact of the Xpert intervention in routine conditions
- For timing reasons alone, decisions were based on NTCM model

Summary of NTCM

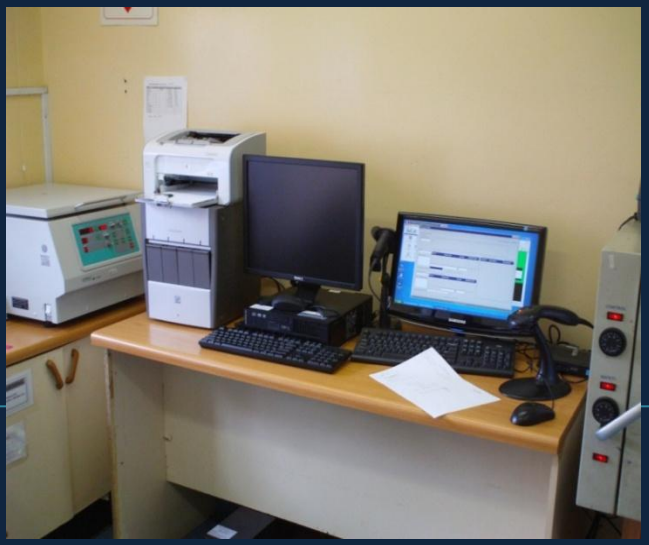
The NTCM model predicted the following:

- Scale- up as planned would require the placement of 65 GX4, 169 GX16 and 4 GX48
  - **Leading to a total national test capacity** of 11,428 tests per day.
- **Total capital cost** (including instruments, additional space, security, and training) between 2011/12 and 2016/17 will be 149 million ZAR (20 million USD)
- **Additional annual budget requirement (53-57%) or USD 48-70 million per year**
- **The NHLS (or laboratory) share of total diagnostic cost increases by**
  - Cost per TB diagnosis per suspect increased by 55% (60 USD)
  - Cost per TB case diagnosed and treated increased by 8% (797-873 USD)
- **Clinic (decentralised placement) is 46% more expensive**, with NDoH investment increasing as a result of additional GX4 instruments, space, air-conditioning and security, and staff time (range 4-7 fold)
- By full scale up: **25-30% increase in TB cases diagnosed, 64% increase in MDR cases detected and 30% more individuals treated**

NHLS staff members in training





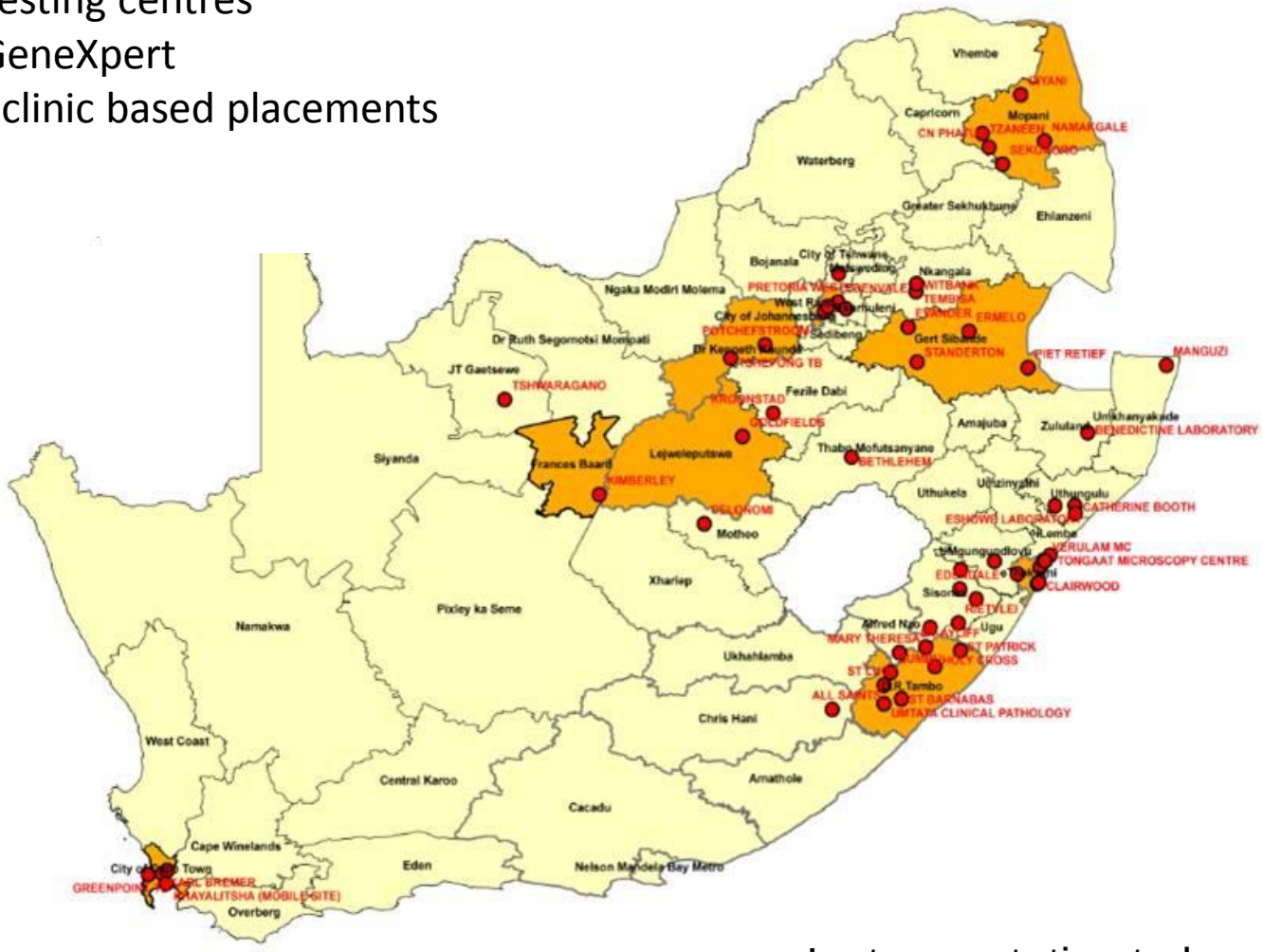



World TB day 2012, mines in Carletonville

10 X GX16 in mobile vehicles

Current GeneXpert Placements in HBD : March 2012

55 Testing centres
79 GeneXpert
*20 clinic based placements



GX4: 38; GX16:40; GX48:1

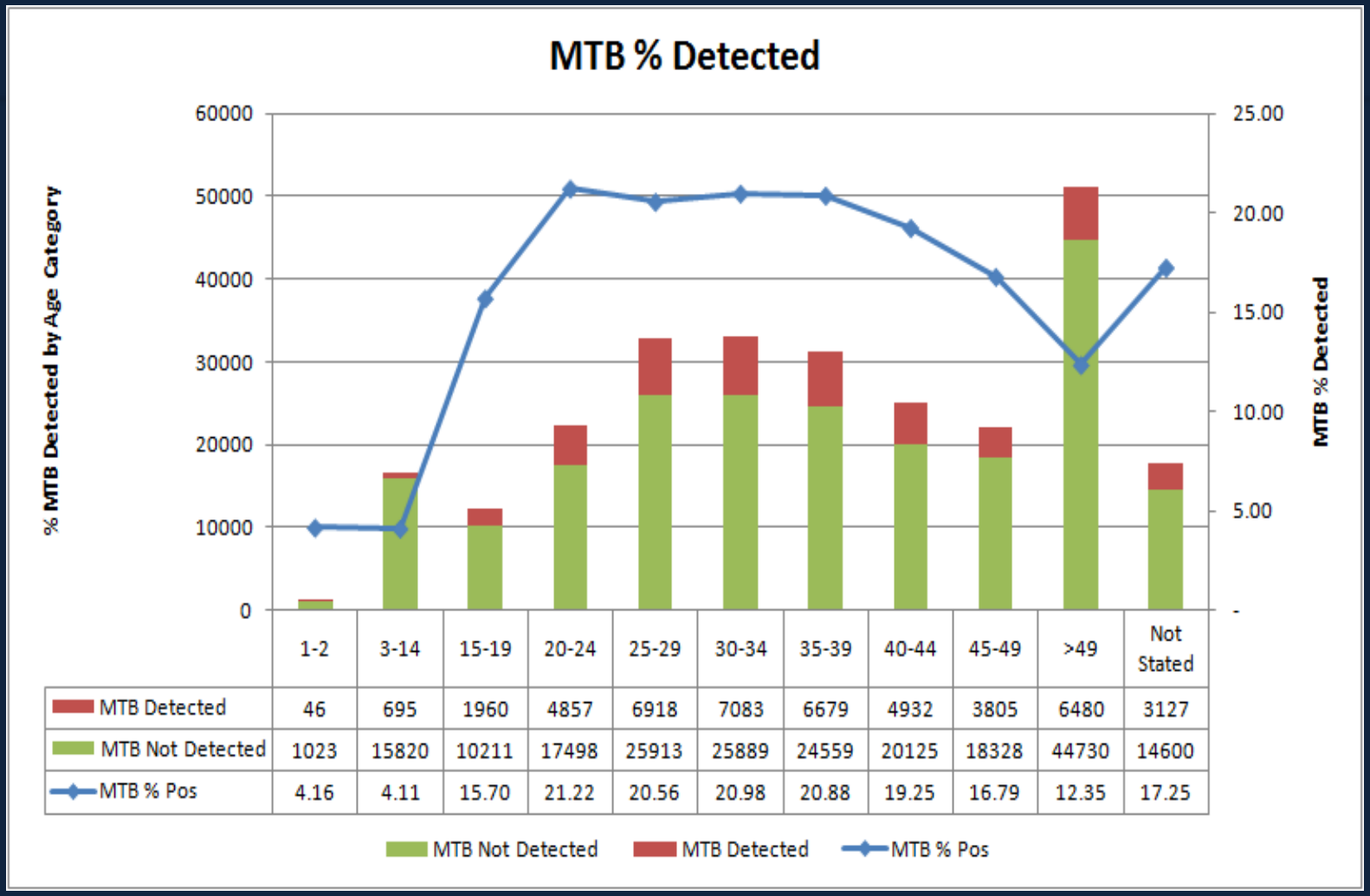
Instrumentation to be placed in all 52 health districts

National MTB Xpert results (01 March 2011 to 27 Mar 2012)

9 Provinces	MTB Detected	MTB Not Detected	Test Unsuccessful	Total	% MTB Detected
Eastern Cape	5936	28135	987	35058	16.93
Free State	5006	27534	64	32604	15.35
Gauteng	4461	28181	601	33243	13.42
Kwa-Zulu Natal	17999	68338	2343	88680	20.30
Limpopo	2776	23271	284	26331	10.54
Mpumalanga	3468	16799	1335	21602	16.05
North West	3292	16376	753	20421	16.12
Northern Cape	4032	20158	751	24941	16.17
Western Cape	5098	23067	72	28237	18.05
Grand Total	**52 068**	**251 859**	**7190 (2.2%)**	**311 117**	**16.74%**

*Note specimens may not equate to patients: de-linked from clinical register
Reflects all comers: new and re-treatment cases, Access may bias current results
Test unsuccessful: errors: 1.88%, invalids: 0.3% : cost: R120 000

Age Distribution in Patients Tested



	1-2	3-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	>49	Not Stated
MTB Detected	46	695	1960	4857	6918	7083	6679	4932	3805	6480	3127
MTB Not Detected	1023	15820	10211	17498	25913	25889	24559	20125	18328	44730	14600
MTB % Pos	4.16	4.11	15.70	21.22	20.56	20.98	20.88	19.25	16.79	12.35	17.25

HIV epidemic influence is very clear

MTB with positive Xpert RIF resistance (March 2011 to 30 March 2012)

Laboratory	Resistant	Sensitive	Inconclusive	No Result	Total	% RIF Resistant
Eastern Cape	454	5315	70	97	5936	7.65
Free State	278	4656	64	8	5006	5.55
Gauteng	270	4145	45	1	4461	6.05
Kwa-Zulu Natal	1405	16265	222	107	17999	7.81
Limpopo	203	2507	40	26	2776	7.31
Mpumalanga	281	3105	50	32	3468	8.10
North West	264	2982	39	7	3292	8.02
Northern Cape	252	3739	38	3	4032	6.25
Western Cape	240	4810	47	1	5098	4.71
Total	**3647**	**47 524**	**615**	**282**	**52068**	**7.00%**
%			**1.18%**	**0.5%**		

***Total Tests may not equate to total patients**
Switch to purchasing G4 in December 2011

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National Concordance of GXP RIF with LPA RIF and DST n=864

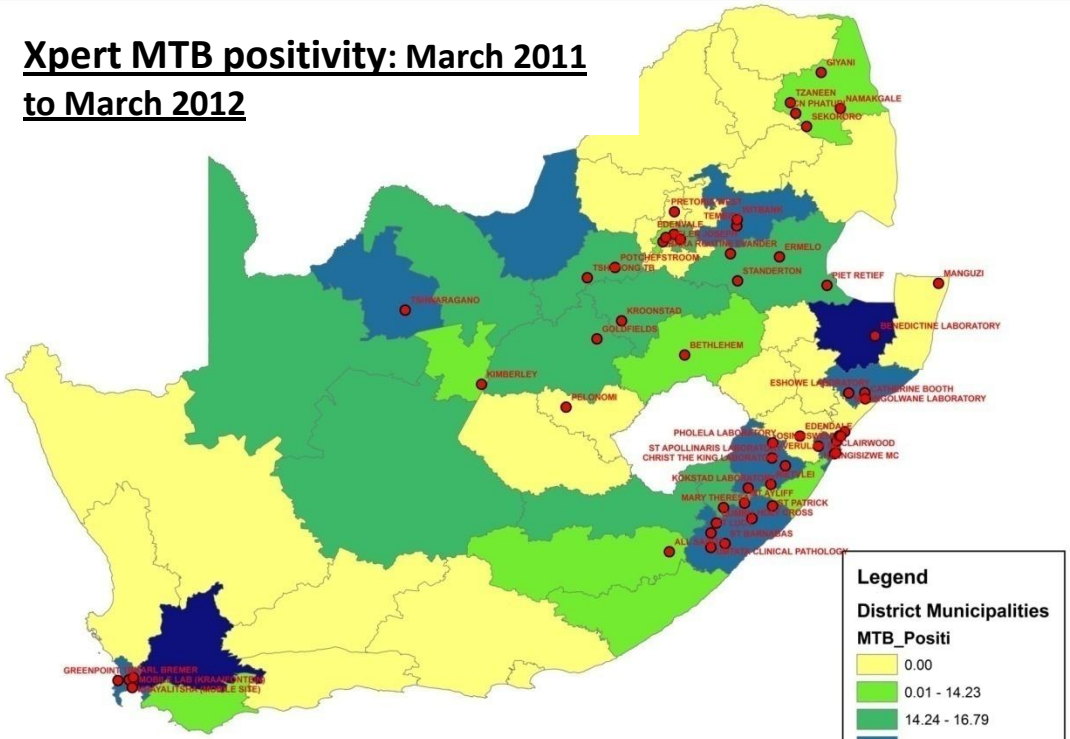
	Concordant LPA (RIF)	Discordant LPA (RIF)	Concordant Culture (RIF)	Discordant Culture (RIF)
Eastern Cape	22	1	1	31
Free State	21	3	3	2
KZN	218	27	219	13
Limpopo	12	2	20	1
Mpumalanga	65	10	55	0
North West	12	1	2	1
Gauteng	48	5	15	3
Northern Cape	49	12	10	5
Western Cape	142	7	2	0
	589	**68**	**327**	**56**
Concordance (%)	**89.6%**		**85.4%**	

- Most LPA assays are done off culture due to low smear positive rates
- **Combination results in Rif Resistance concordance of 83%**
- **Combination of results: INH resistance: 79%**
- **Sites vary : CT: 95% Rif concordance; 83% are INH Resistant**

GeneXpert Rif comparative data to LPA and/or Culture

- Rif concordance is reasonably good for both LPA and culture
- Rif mono-resistance variable: average 20% (5-40%)
  - Geographical variation?
  - Laboratory variation?
  - Interpretation of LPA by staff?
  - How reliable is gold standard?
- Testing and clinical algorithms show variation across provinces: requiring standardisation: TB Expert working committee
- GXP Rif confirmation not conducted for all cases (40%)
  - Algorithm re-inforcement required
  - Increased clinical and laboratory training needed
  - Possibility of Electronic Gatekeeping at LIS
- Repository is essential for collection of relevant isolates
- Unique , single identifier essential

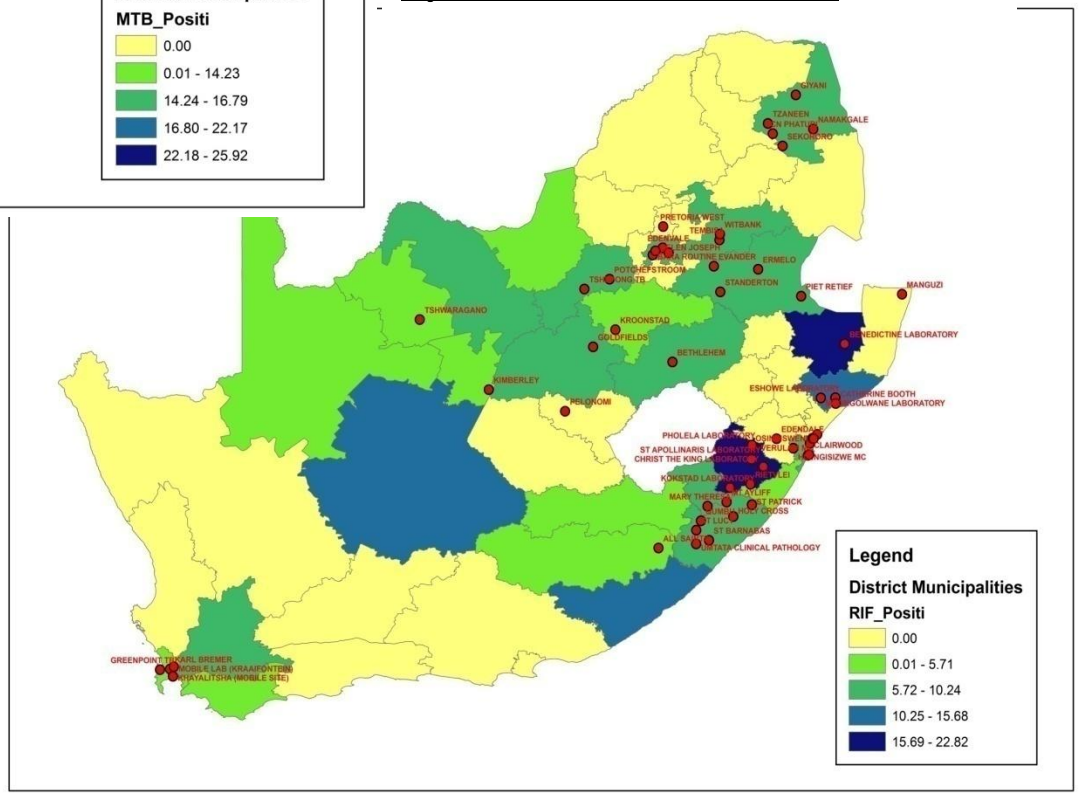
Xpert MTB positivity: March 2011 to March 2012



GeneXpert for the provision of real-time surveillance data?

- Direct interfacing of Gene Xpert instruments to a laboratory information system (LIS) can provide data in near-real time for surveillance

Xpert MTB+ RIF resistant

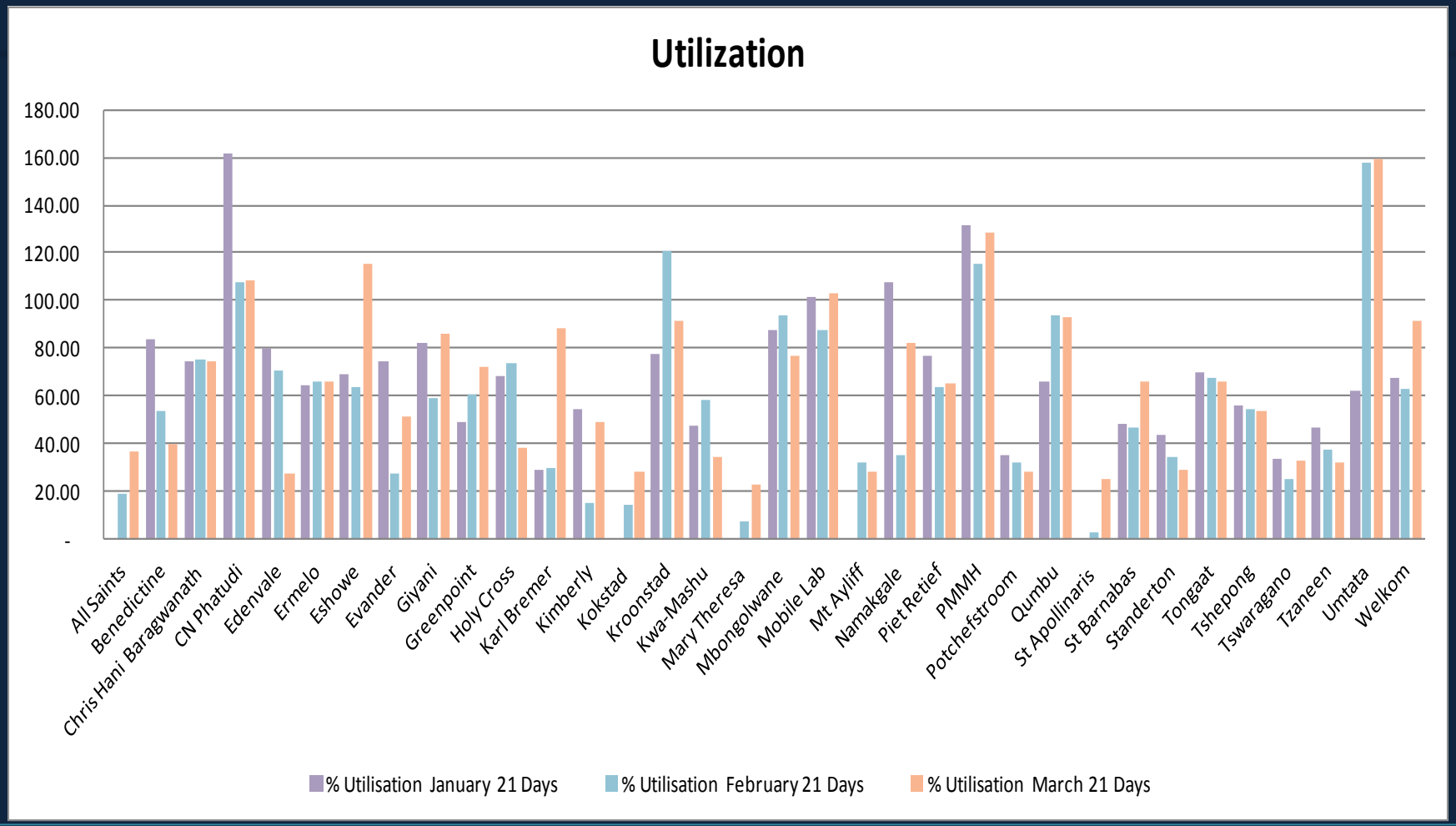


- Are Xpert assay parameters such as probe frequency and median cycle threshold (Ct) values are informative for surveillance purposes?

- The frequency of drop out probes was greater than delayed hybridization. **RIF resistance detection was predominantly based on probe E (~58%), followed by D (~24%).** Rifampicin resistance detection in probes B (~10%), A (7%) and C (~1%) were less frequent.

- The value of monitoring mean **probe Ct values** for determining bacterial load by regions and over time? (*Scott, Stevens et al. CROI 2012)*

Utilization rates of instruments within the field



Variation based on health care centres coming on line
8-10% monthly growth

Expected minimum implementation

2012/2013:NDoH Commitment to cartridges

Province	Number of Instruments			Total Number of Tests
	GX4	GX16	GX48	
EC	6	16	1	424,172
FS	1	5	-	96,279
GP	3	13	-	242,687
KZN	16	13	1	363,061
LP	3	4	-	57,493
MP	2	6	-	102,907
NC	-	4	-	54,684
NW	2	2	-	48,507
WC	4	6	-	125,520
TOTAL	37	69	2	**1,515,310**

NDoH contribution to cartridges: ensure sustainability?

~1,5 million tests to be conducted in new financial year
~ 50 million USD : Capital and recurrent costs
Next 3 months: 49 GX16, 1 infinity

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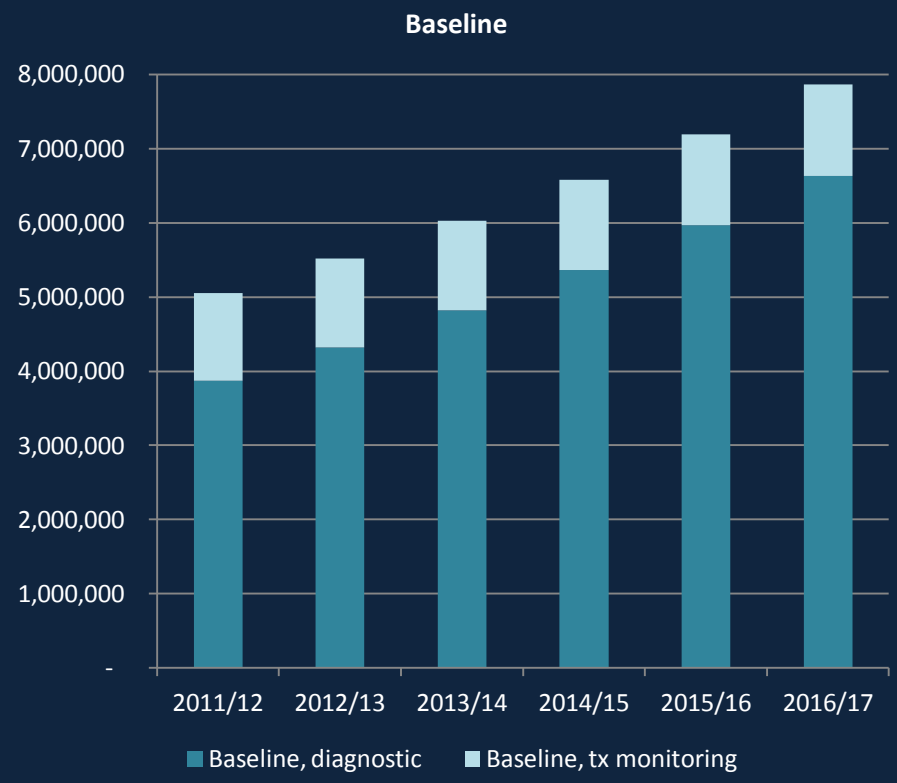
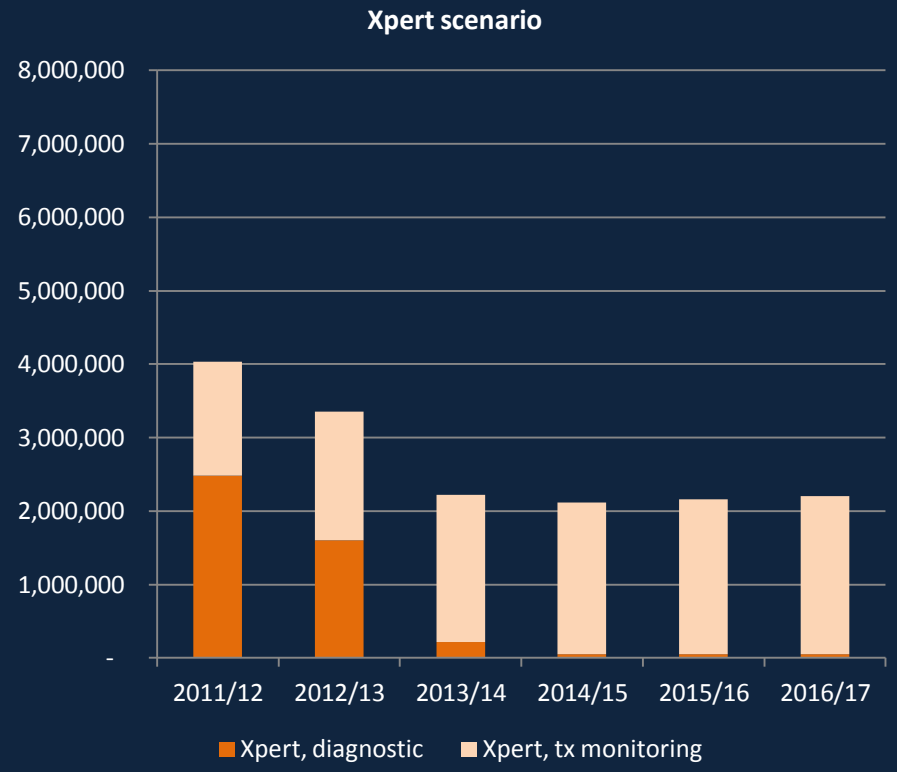
Implications for Laboratories going forward in SA
1. Number of smear microscopies





Results generated from Health Economics & Epidemiology Research Office, National TB Cost Model, 2012 using NHLS data

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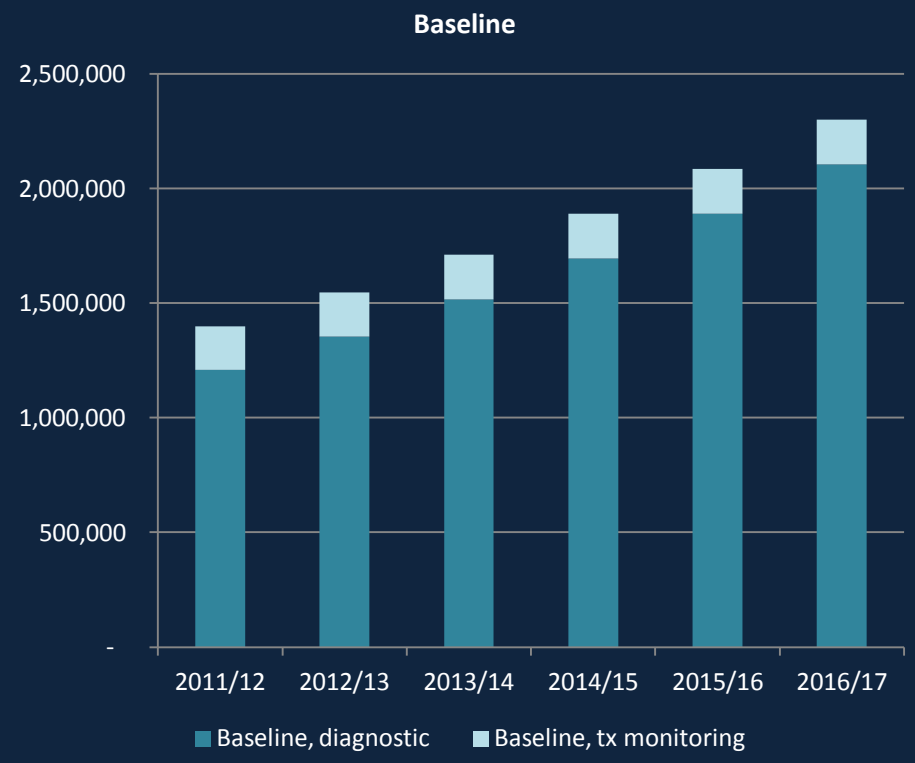
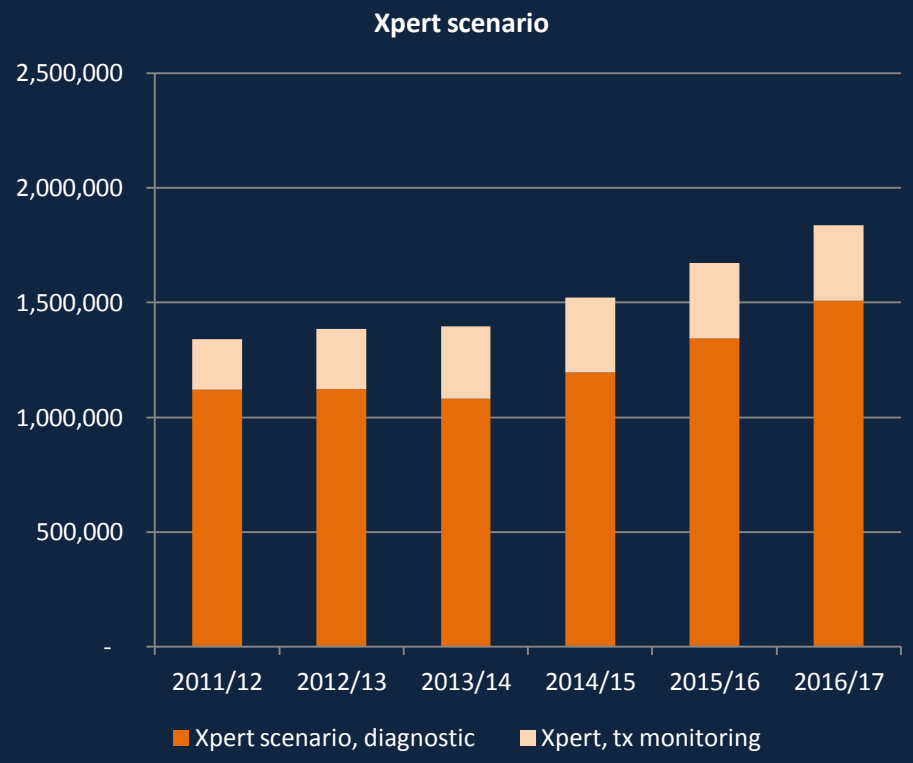
2. Number of cultures





Results generated from Health Economics & Epidemiology Research Office, National TB Cost Model, 2012 using NHLS data and input

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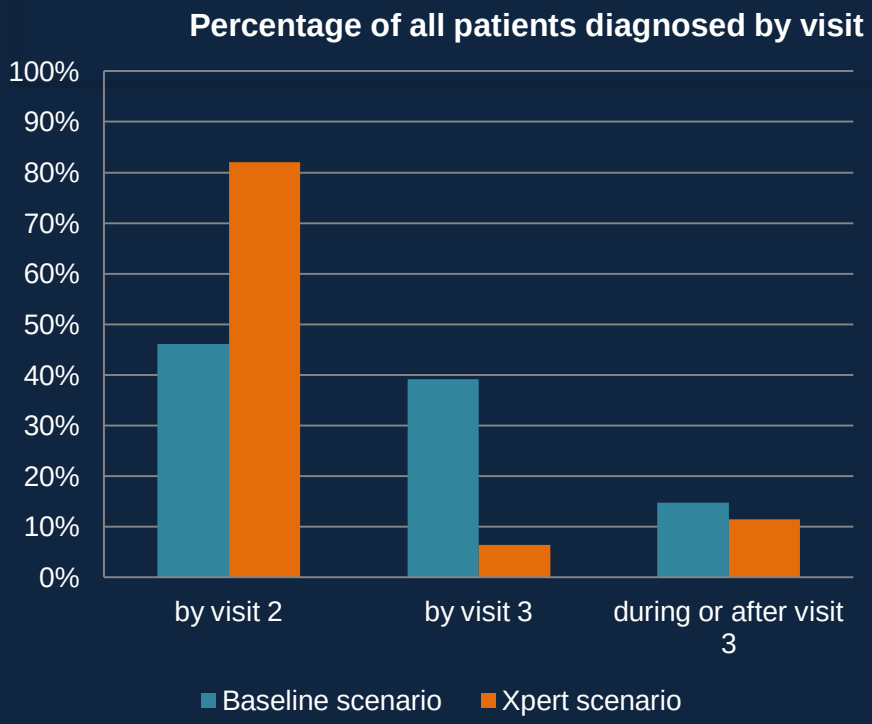
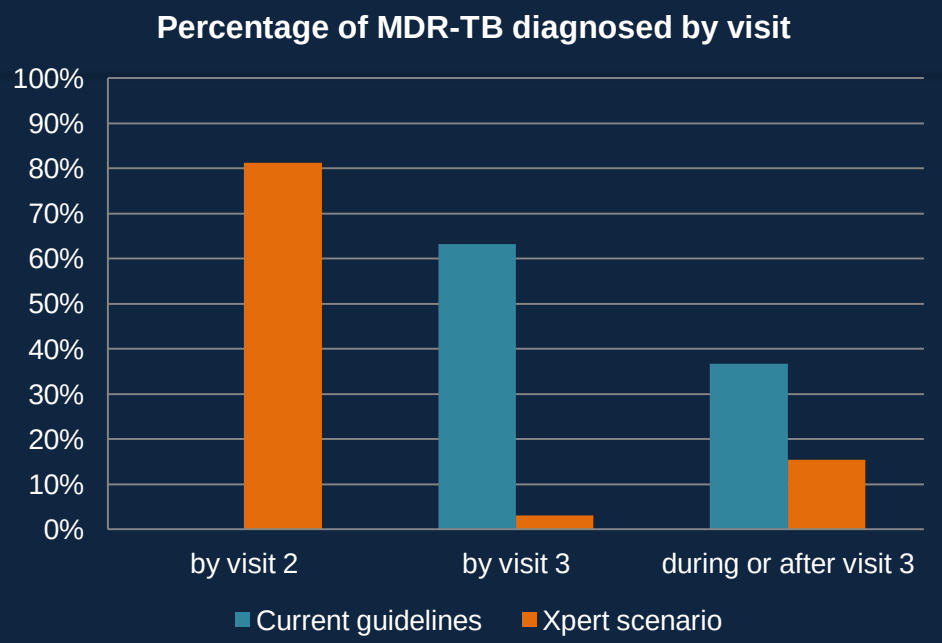
At full placement
Predicted Time to diagnosis





- Currently 46% of cases are diagnosed by visit 2 and a further 40% by visit 3
- Xpert scenario prediction at full coverage: 83% by visit 2 and 89% by visit 3
- By full placement: 87% diagnoses to be made by GeneXpert

Boehme study, 2011. Time to detection: 1 day for Xpert/ smear, 20 days for LPA, 106 days for DST

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1. Ongoing Challenges

- **Paediatric evaluations**:
  - Xpert recommended on 2 induced sputa (*Nichol et al. Lancet 2011*)

    Xpert on 2 induced specimens detected twice as many cases (75.9%) as smear (38%).

    Xpert specificity, 98.8%.
  - Reality routine sample volumes <50% Xpert requirement (*Gous et al. CROI 2012*)
  - Program data showing increased Rif resistance in younger children?
- **Evaluation in extra-pulmonary samples**
- **Remote connectivity:**
  - Connectivity for monitoring instrument performance
  - Remote calibration: 1 million ZAR for annual cartridge calibration
  - POC connectivity instrument management
- **Xpert at clinic sites:**
  - Validation at 20 sites underway (with various clinical partners) *(Scott L, Stevens W et al.)*
  - POC TB Diagnosis: Experience with the Xpert MTB/RIF assay. *(Scott L, Stevens W et al.) SA TB conference, Durban 2010.*
  - (*Clouse et al*.) Witkoppen clinic, feasible, loss to follow up within diagnostic process, needed 2 full time staff members for an average of 16 suspects (range 7-29*). Manuscript accepted)*
  - Grand Challenges Canada grant
- **Validation of new G4 cartridge completed**
- **Evaluation of new technologies as they emerge**
- **Evaluation of routine screening in high risk populations e.g. HIV**
- **Role in monitoring response to Tb treatment**

2. Ongoing implementation challenges

- **Correct Algorithm???**

  What to do with HIV +, Xpert Negatives?(***Rosen et al. Abstract 140 CROI 2012***)

  - **Conclusion: modifying algorithm for the HIV positive individual to include a second Xpert for those who have a first Xpert negative test will speed up results and generate cost savings.**
  - A more sensitive NAAT test in centralized laboratories?
  - Baseline smears and smear monitoring?
  - Reduction in algorithm complexity
  - Routine screening for all HIV positive individuals initiating ART (Lawn
- **Clinical and laboratory training on algorithm: army of trainers is needed**
- **Speed of implementation**
  - NTCM (XICM): expected global volume discounts delayed?
  - Donor fund release delay
- **Level of placement (sub-district labs v clinics)**
  - NTCM (XICM): 46% more expensive per year at full-scale, largely because of economies of scale
- **Rapid Response team needed to evaluate high RIF detection sites**
- **Finalization of appropriate EQA program**
- **Calibration logistics and costs**

Program Summary

- **SA has led** the way for implementation of technology for early diagnosis of TB using Xpert:
  - SA procured **>50% of global** cartridge supply (public sector figures)
  - Rapid increase in test numbers: **311 117** (~8-10% monthly) as of end of March 2012
  - ~48 000 tests done annually in private sector
  - **55 testing** centres established, testing feasible in both urban and remote microscopy centres
  - **79 instruments** of varying capacity installed
  - 20 clinic installations to support various POC projects
  - **~800 staff members** (clinical and laboratory) trained to date
  - **Expert TB working group** within Microbiology expert committee established
  - **EQA program development**

- Detection of MTB is at least doubled for early diagnosis in implementation sites (17% Xpert MTB+ vs. 8% smear+ in 2011)
- Rifampicin resistance detection compared well to reference methodology~6-7%
- 100% diagnostic coverage potential in HBD
- Doubled national coverage since pilot in 2010
- Current national coverage : ~15-20 % to increase to ~60% by March 2013?
- Expenditure in 2011/2012 : ~$5.5 million capital; ~$8 million cartridges

Acknowledgements

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- Right to care: Prof Ian Sanne
- MM&H: Prof Scott, N. Gous, B. Cunningham, Dr E.Prentice
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