NATIONAL HEALTH LABORATORY SERVICE
National Priority Programmes

Operational realities of the South African TB molecular diagnostic multiplatform approach

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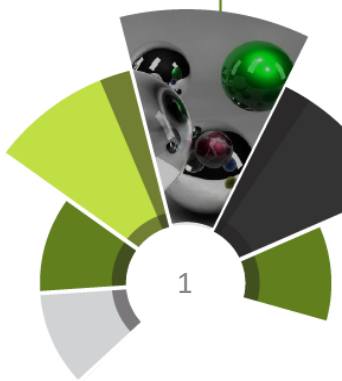
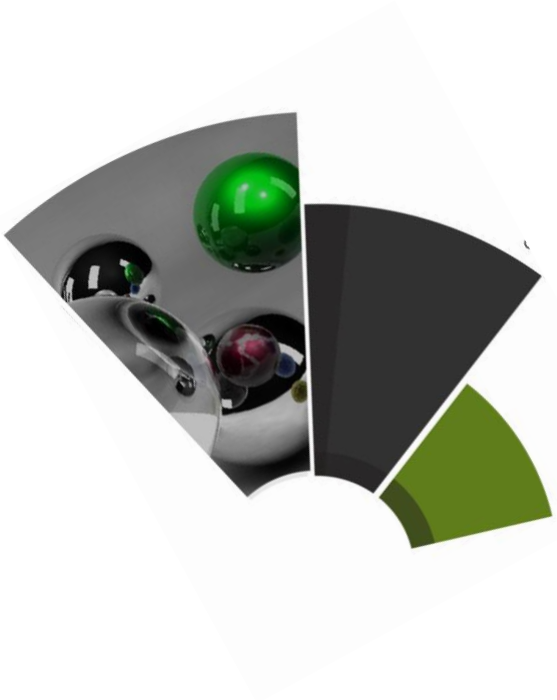
National Priority Programs of the National Health Laboratory Service





Overview:

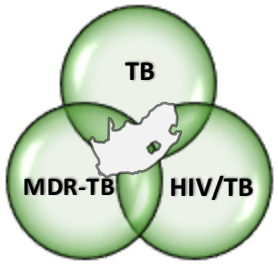
- Background and the South African context.
- Evolution of molecular diagnostics in the TB program.
- Key steps in diversification – implementation overview.
- Programmatic considerations:
  - Procurement and supply chain management.
  - Implementation.
  - Pre-analytic considerations.
  - Analytic considerations.
  - Post-analytic considerations.
- Concluding remarks.

Situation

High-burden TB, TB/HIV co-infection, and MDR-TB:

	2009	2023
Population estimates:	50 million	63 million
TB incidence:	970 per 100’000	427 per 100’000
TB incidence in PLHIV:	577 per 100’000	230 per 100’000

Change in TB incidence (2015-2023): **↓ 57%**



Large gap between diagnosed TB persons and estimated TB incidence

Treatment success rate:

– RR-TB/pre-XDR-TB/XDR-TB: Room for improvement

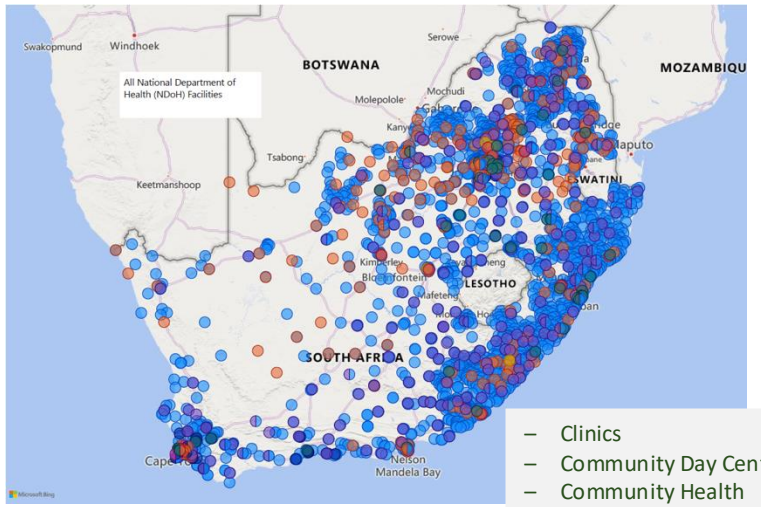
WHO Global tuberculosis report 2010
WHO Global tuberculosis report 2023

Laboratory Services

National Health Laboratory Service:

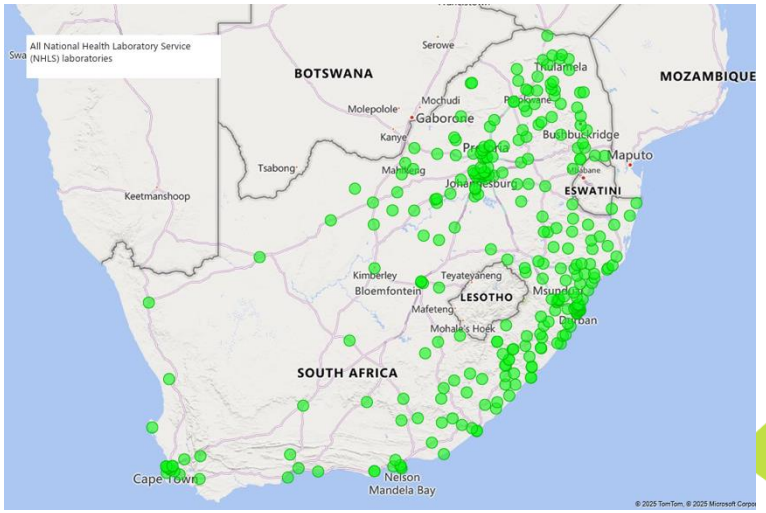
– Parastatal entity providing pathology services to the Ministry of Health on a fee-for-service basis.

– Servicing 4’997 healthcare facilities (state sector) ~85% of the population:



– Clinics
– Community Day Centers
– Community Health
– District & national central hospitals
– Provincial tertiary hospitals
– Regional hospitals.

– 233 laboratories:



Laboratory Services

National Health Laboratory Service:

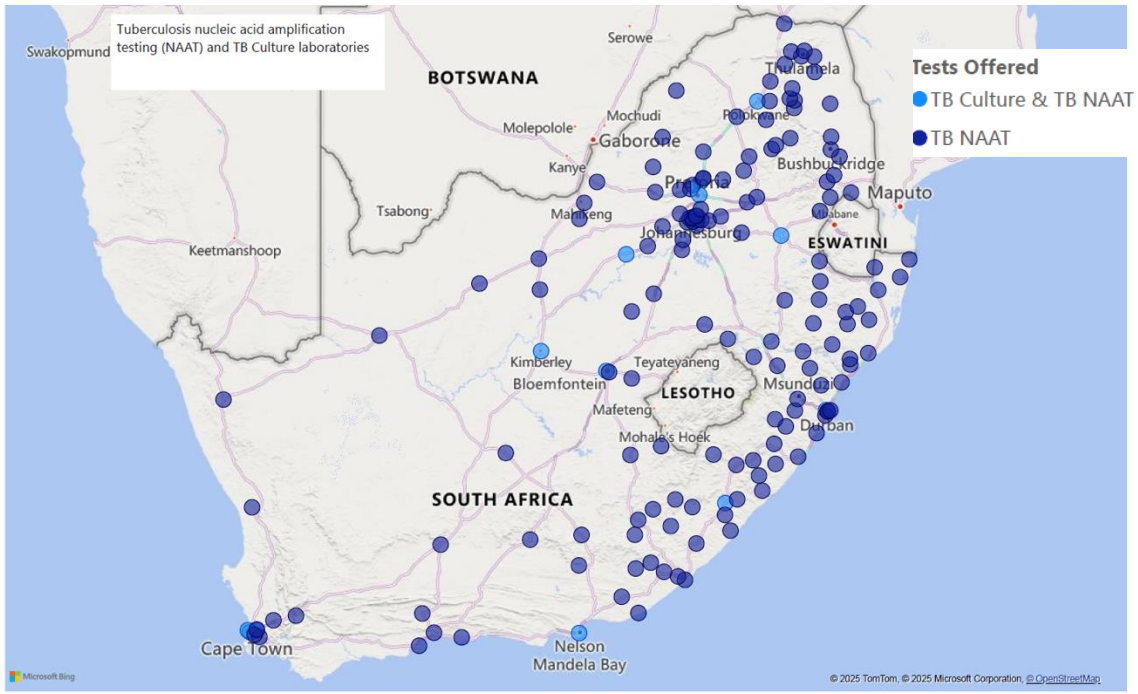
- Fully integrated service across all pathology disciplines [including forensics].
- ~114 million tests conducted annually [all pathology tests].
- HIV- & TB-related diagnostic and disease monitoring tests: ~20% of all tests.
- HIV viral load and TB-NAAT among the top ten tests by volume.

Program	Test		Annual volumes	Laboratory footprint
TB	TB-NAAT	Initial diagnostic (RIF and/or INH)	>3 million	165
		Additional resistance (FLQs, INH)	25'000	15
	TB-culture		600'000	15
	pDST		10'000	6
HIV	CD4-count		2.2 million	49
	Reflexed CrAg		300'000	49
	EID PCR		650'000	12
	HIV viral load		6.7 million	27
	Sequencing for HIV drug resistance		3'000	5
All tests conducted by the NHLS (including TB & HIV): [Chemistry; microbiology; virology; anatomical; histopathology; cytology; haematology; genetics; immunology; forensics, etc.]			**>114 million**	**233**

Laboratory Services: tuberculosis

TB diagnostic services:

- Mixed decentralised and centralised offering.
- Diagnostic programs:
  - Diagnosis and detection of resistance to RIF with/out INH:
    - Xpert® MTB/RIF Ultra [RIF only].
    - Becton Dickinson (BD) MAX™ MDR-TB [RIF and INH].
    - Roche cobas® MTB and MTB/RIF-INH [RIF and INH].
  - Detection of resistance to FLQ and INH:
    - Xpert® MTB/XDR.
  - Culture and pDST.
  - tNGS/WGS.



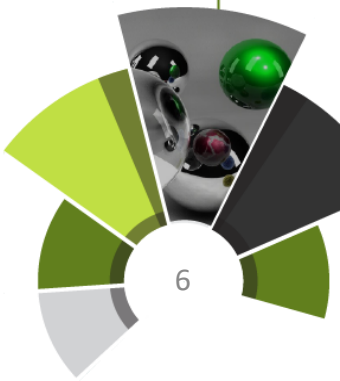
Tiered services:

Tier 4: NTBRL/SRL: 1
- TB-NAAT, Xpert MTB/XDR,
- pDST (incl. MIC) BMD + Agar + MGIT
- tNGS/WGS

Tier 3: 6 laboratories
- TB-NAAT, Xpert MTB/XDR,
- Microscopy and culture,
- pDST, MOTT PCR

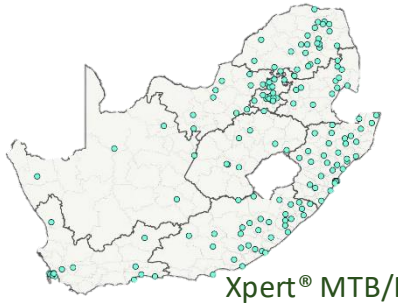
Tier 2: 15 laboratories
- TB-NAAT, Xpert® MTB/XDR,
- Microscopy and culture

Tier 1: 173 laboratories
- TB-NAAT and microscopy



Evolution of molecular diagnostics in the South African TB program

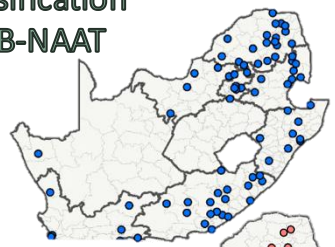
Pre-2023:



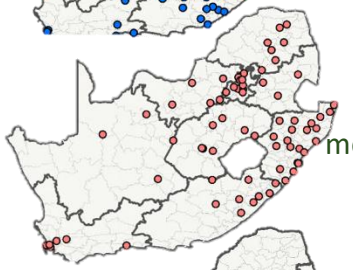
Xpert® MTB/RIF Ultra sites, n=165
Low-/medium-/high-/very high-volume

2023:

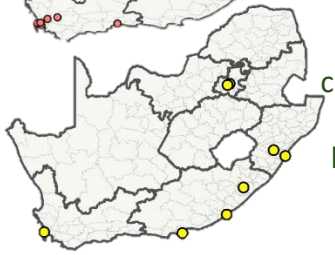
Diversification of TB-NAAT



Xpert® MTB/RIF Ultra, n=82
low-volume throughput



BD MAX™ MDR-TB n=75
medium-volume throughput



cobas® MTB MTB/RIF-INH n=8
high-volume throughput

Reasons for diversification:

- **Risks of having a single supplier servicing a large program**
  - Inability of sole supplier to meet testing demands (post-COVID-19, 2022) of the national TB-recovery plan.
- **Procurement must follow tender processes**:
  - Introduction of competition and alternate suppliers into the market based on WHO-recommendations for moderate complexity platforms.
  - Outcome:
    - Xpert® MTB/RIF Ultra only at low-volume testing sites.
    - Medium-volume testing sites were assigned to BD MAX™ MDR-TB.
    - High-volume testing sites were assigned to cobas® MTB MTB/RIF-INH.

Key steps in diversification - implementation overview

In-country platform evaluations → Initial engagements with suppliers, NHLS IT and operations → Engagement with NDoH: guiding algorithm & results output → Site assessments: structural; space; benches; network points; air-conditioning; refrigeration; storage; waste → Moving of Xpert® systems to create space for new placements → Renovations in preparation for instrument placements

Develop blueprint for new tests on LIMS → Shipping schedules of new instruments → Commencement of instrument placements → Super user training for NHLS master trainers → Compilation of the supplier specific SOPs → Reagent forecasting with suppliers

Ongoing change management: information sessions → Source and distribute verification material → Initial basic training by suppliers → Interface and system verification testing → Site go-live based on verification success & user competency → Training reinforced internally

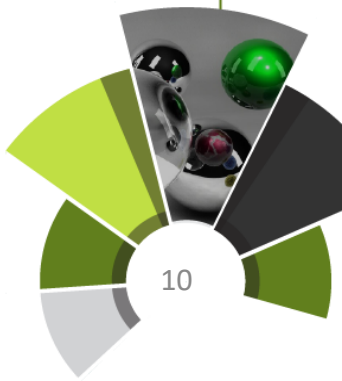
Enrolment in proficiency testing scheme → Monitoring performance indicators → Ongoing engagements with suppliers

Procurement & supply chain management

Challenges/lessons learnt	Implemented solutions/interventions
• Risks in single suppliers servicing large programs.	• Diversification process to introduce additional suppliers. • However, too many suppliers (servicing the same program) may pose other challenges.
• Cheaper assays may require additional resources with more complex workflows. • More complex workflows (less automation) may increase TAT, impacting patient care.	• SOPs which streamline workflows, e.g., interleaving with the BD MAX™ platform. • TAT has progressively improved across the moderate-complexity platforms as the program matured, and users became more comfortable with the newer technologies.
• Indirect implementation costs: – Renovations to accommodate larger instruments (e.g., cobas® platforms). – Procurement of wider laboratory benches to accommodate the BD MAX™ platform. – Refrigeration capacity (e.g., for cobas® reagents). – Interface developments between instruments and the LIMS. – Other IT-related costs.	• Provision of budget to allow for renovations and additional procurements.
• Forecast planning: – 3-to-4-month manufacturing lead time (depending on the supplier).	• Modeling projections to plan forecasts. • Insisting on in-country reserve of buffer stock to accommodate testing surges/fluctuations. • Planning around phase out stock (of the outgoing supplier) during transitions.

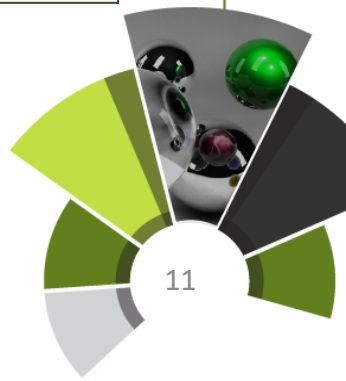
Procurement & supply chain management

Challenges/lessons learnt	Implemented solutions/interventions
• Relationships: – Relationship building with appointed suppliers for successful implementation. – Define roles and responsibilities. – Define the escalation pathway.	• Regularization of meetings between implementer and suppliers. • Service level agreements established: – Defines the procedure for issue logging and supplier response times. – Number of in-country support engineers and expected travel time. – Defines what happens when resolution cannot be found for an issue within 12hrs, 24hrs, >24hrs, etc. – Specifies that majority of spare parts should be accommodated in-country no minimise downtime. – Platform servicing schedules. – Reporting and monitoring requirements (e.g., supplier dashboards for error rates, etc.)



Implementation

Challenges/lessons learnt	Implemented solutions/interventions
• Remote access for programmatic monitoring: – Compatibility with the existing LIMS. – Transmission of assay testing parameters: cycle thresholds, melting points, etc.	• Ongoing developments.
• Proficiency testing: – Differences in limits of detection. – Differences in target detection between assays. – Variation in how MTB is detected and non-wild type sequence detection. – Not all assays reporting isoniazid susceptibility.	• Determined compatibility of existing proficiency testing scheme for newly included assays. • Ongoing revision of performance on proficiency testing across suppliers.
• National guiding algorithm: – Required revision as supplier centric to Xpert MTB/RIF Ultra.	• Referred to all assays as 'TB-NAAT'. • National algorithm revised. • Dissemination of algorithm and training.

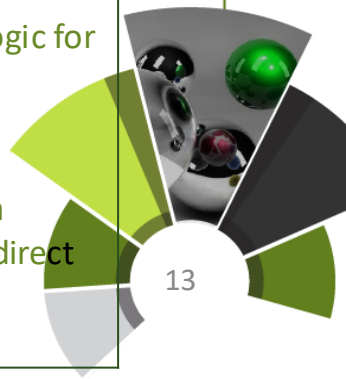


Pre-analytic considerations

Challenges/lessons learnt	Implemented solutions/interventions
• Variation in pre-analytical specimen processing. • Different duration in pre-analytical processing (e.g., sonication required for the cobas® MTB assay).	• Internal super-user training with workflow assessments, for the implementation team. • Development of supplier specific SOPs. • Supplier-initiated training for laboratories. • Reinforcement of training across all testing sites by the implementer. • Change management through information sessions.
• Different processing reagents between suppliers. • Depending on the supplier, >1 reagent type kit required for pre-processing. • Reagent type kits differ in quantities of components.	• Development of a reagent calculator per supplier which factors existing stock of individual components and anticipated testing numbers. • Reinforcement through information sessions.
• Different reagent storage requirements, i.e., some require refrigeration. • Increased storage space requirements and refrigeration.	• Site assessments were completed (space, storage, workflow, etc.). • Procurement of additional refrigeration units, where required.
• Different workflows between assays.	• Development of supplier specific SOPs. • Supplier-initiated training • Reinforcement of training across all testing sites. • Ongoing monitoring of performance indicators.

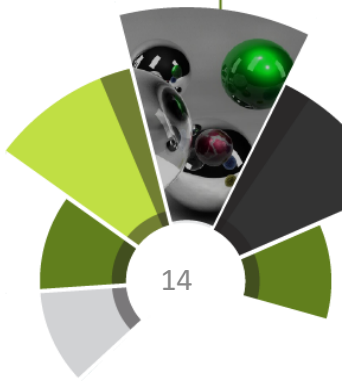
Analytic considerations

Challenges/lessons learnt	Implemented solutions/interventions
• Not all systems are 'closed': With Xpert® Ultra, processed specimen is loaded into a contained cartridge with subsequent testing steps happening within the cartridge. This differs for cobas® MTB MTB/RIF-INH and BD MAX™ MDR-TB assays.	• Introduction of environmental sampling and controls for both moderate-complexity assays.
• Increased waste generation (solid) with both adopted moderate complexity platforms; and specifically liquid waste for cobas® MTB MTB/RIF-INH.	• Consider laboratory storage space. • Adaption of the existing waste logistics to accommodate increased waste generation (including provision for liquid waste).
• Variation in platform complexity. • Lack of full automation, i.e., cobas® MTB MTB/RIF-INH (sorting for susceptibility testing is a manual process following on from the MTB-detection assay).	• Development of supplier specific SOPs. • Supplier-initiated training. • Reinforcement of training across all testing sites. • Change management through information sessions.
• Variation in target detection (e.g., *katG* mutation detection) and supplier interpretive result algorithms. • Discrepant results between assays where the same client may have been tested using different assays at different time points. • Unique result categories per assay: 'MTB trace detected' for Xpert® MTB/RIF Ultra and 'MTB low positive' for the BD MAX™ MDR-TB assay.	• Supplier engagement to better understand algorithm logic for defining MTB detection and resistance calls. • Post-implementation assessment and monitoring of performance indicators across assays (ongoing). • Conversion of specific instrument generated results, via developed interfaces, to 'standardise' and guide more direct clinical management.



Analytic considerations

Challenges/lessons learnt	Implemented solutions/interventions
• Sensitivity to environmental temperatures, e.g., PCR-heater warnings on BD MAX™ MDR-TB assay.	• Environmental temperature monitoring. • Procurement of air-conditioning units to control temperature.
• Recommendations for moderate-complexity platforms exclude testing of extra-pulmonary specimen types.	• At cobas® MTB MTB/RIF-INH and BD MAX™ MDR-TB testing sites, Xpert® platforms were retained to specifically conduct testing of specimens of extra-pulmonary origin: two separate workflows.
• Increased sensitivity for detection with TB-NAAT assays: – Importance of maintaining good laboratory practice to avoid contamination.	• Strict adherence to SOPs and good lab practice. • Performance monitoring through proficiency testing.



Post-analytic considerations

Challenges/lessons learnt	Implemented solutions/interventions
• Result reporting: – Xpert® MTB/RIF Ultra [RIF only]. – BD MAX™ MDR-TB [RIF and INH]. – Roche cobas® MTB and MTB/RIF-INH [RIF and INH].	• Where RIF R is detected (irrespective of TB-NAAT used), further centralised testing on 2nd specimen: Xpert® MTB/XDR and TB-culture. – Higher sensitivity for isoniazid resistance detection with Xpert® MTB/XDR (inclusion of *fabG1* and *oxyR-ahpC*, in addition to *katG* and *inhA*) – possible discordance. • Standardised approach adopted since isoniazid not reported by all assays: – Suppress isoniazid susceptible results (not released). – Only release isoniazid where resistance is detected (released).

DECENTRALISED testing

– **Xpert® MTB/RIF Ultra, or**
– **BD MAX™ MDR-TB, or**
– **Roche cobas® MTB MTB/RIF-INH testing**

Result:
MTBC/RIF R

CENTRALISED testing

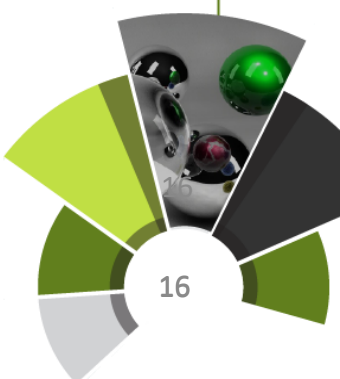
Digest/decontaminate

Xpert® MTB/XDR **(sediment)** and/or

Xpert® MTB/XDR **(cultured isolate)**

Concluding remarks

- Diversification of TB-NAAT testing in South Africa required specific considerations and implementation strategies.
- Diversification may not be applicable in certain settings.
- Consider potential impact of increased algorithm complexity.
- Programmatic transitions take time: ours spanned 19 months.
- Consider the suitability of the supplier's workflow to your setting/infrastructure/individual laboratory level.
- Each setting is unique and may require adaptions for what is best suited.



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