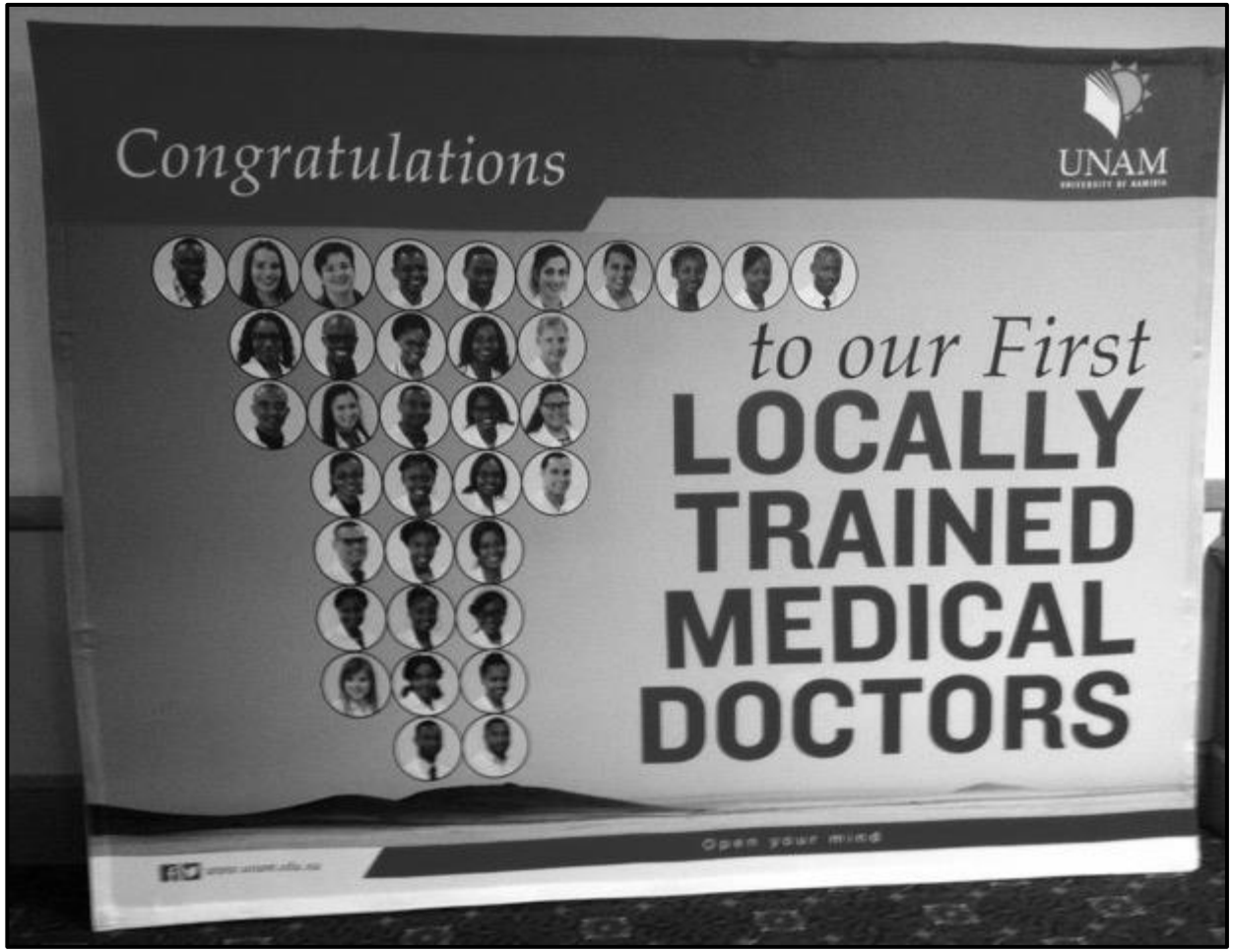
Evolving Bedaquiline resistance in the field – example from Namibia

Gunar Günther

Ministry of Health and Social Services, Namibia
University of Namibia, School of Medicine
Inselspital Bern, Bern University Hospital, Switzerland

Disclosure:



UNAM School of Medicine first graduates in 2016

Namibia – facts

- Population 2,5 Mill
- 45% no electricity
- 65% no sanitation
- life expectancy 63 J.

- HIV prevalence 14%
- TB incidence 450/100.000
- Notification rate 336/100.000
- HIV co-infection 30%
- Est. RR-TB cases 550
- Notified RR-TB cases 250

World Bank 2021
WHO 2023

Katutura hospital

- 800 beds – biggest hospital in the country
- TB hospital – 80 beds
- first pulmonologist in the public sector - since 6 months

Namibian DR- TB Guideline 2020:

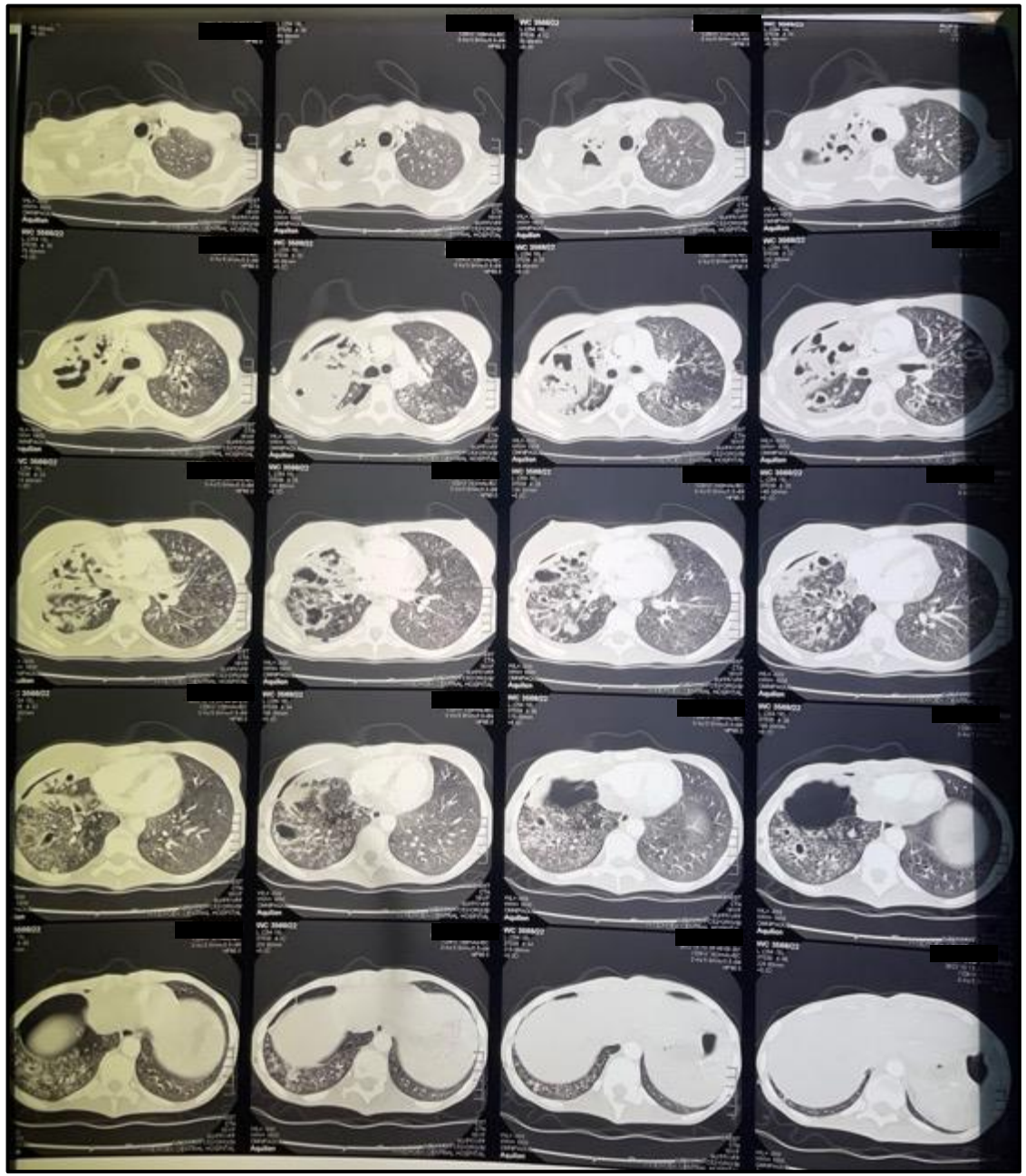
All regimen – all short course and long regimen – contain Bedaquline……..

BPal(M) – available for selected patients in Katutura hospital since end 2021

J.R.

- 17 year old female
- HIV negative (06/06/23)
- Previously treated for drug sensitive TB and failed 1st line treatment 2021 in Angola
- no PMHx
- High school student – highly motivated, highly adherend
- BMI 16 kg/m^2

Imaging - October 2022



Initial diagnostics including targeted NGS

GeneXpert results:

- 06/10/22 MTB detected high
- Rifampicin resistance detected

LPA Results and culture

- Submitted 30/09/22 : Not done due to lack of resources
- Culture also send to Pathcare in SA - and returned for tNGS
- Culture send for extended DST to NICD

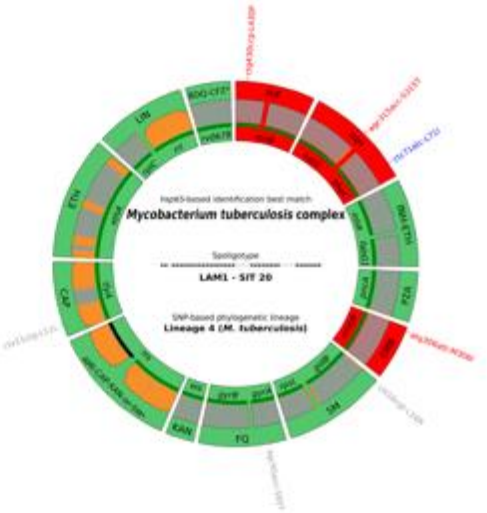
GenoScreen
Innovative Genomics

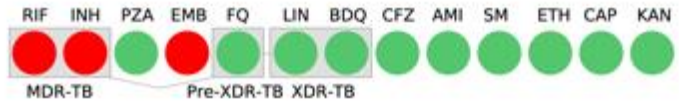
DEEPLEX® Myc-TB Report

from culture

SAMPLE ID: 731822009TM-0922021-lib107

Date of submission	Nov, 28 2022 11:03:58
Analysis mode	Deeplex Myc-TB V3. 0.1 - Extended catalogue
Quality	
Experiment set	IS02NAM0008_25-11-2022





Legend [1]

Drug resistance associated variants[3]

Gene	Genomic position	Codon change	% Variant	Dx-score	AA change	Drug*	Confidence	Resistance level	Reference
embB	4247431	atg306att	100.000	92.25	M306I	EMB	Associated with resistance	Resistant	WHO 2021
katG	2155168	agc315acc	100.000	26.50	S315T	INH	Associated with resistance	Resistant	WHO 2021
rpoB	761095	ctg430ccg	99.980	1217.50	L430P	RIF	Associated with resistance	Resistant	WHO 2021

Uncharacterized and uncertain significance variants[3]

Uncharacterized variants designate sequence variants of as yet unknown association with drug resistance or drug susceptibility. Uncertain significance variants designate variants that could not be characterized yet as either drug resistant or drug susceptible according to the current WHO confidence grading classification.

Gene	Genomic position	Codon change	% Variant	Dx-score	AA change	Drug*	Category	Reference
ahpC	2726403	ctc71atc	99.720	356.25	L71I	n/a	Uncharacterised	n/a

Phenotypic DST – matches tNGS – only first line drug resistance

Mycobacterial Identification - Antigen:

Result	Mycobacterium tuberculosis complex

Antimycobacterial Drug Sensitivity Testing:

Extended Drug Sensitivity Testing - MGIT Culture Based:	
Bedaquiline	Sensitive
Clofazimine	Sensitive
Ethambutol	Sensitive
Isoniazid Low	Resistant
Isoniazid High	Resistant

Submission 17.10.22 / Received 22.12.22

TrakCare Lab Web Results Viewer

NATIONAL INSTITUTE FOR COMMUNICABLE DISEASES
Division of the National Health Laboratory Service

NATIONAL INSTITUTE FOR COMMUNICABLE DISEASES
1 Modderfontein Road, Sandringham, Johannesburg, GP, 2000
Tel: 011 3866466 / 011 5550322, Fax: 011 3866432 / 011 5550495

Practice Number 5200296 pg 2 of 2

Juliana RUFINO LAB NO: **YA 00417606** 17/10/2022 07:00
Namibia Institute of Pathology, Hospital Number 020988540

Antimycobacterial Drug Sensitivity Testing:<Continued>

Levofloxacin	Sensitive
Linezolid	Sensitive
Moxifloxacin Low	Sensitive
Moxifloxacin High	Sensitive
p-aminosalicylic acid	Sensitive
Rifabutin	Sensitive

Linezolid and PAS are being repeated. Results to follow
22/12/2022: PAS and Linezolid results added

Drug Sensitivity - Pyrazinamide Phenotypic Testing

Pyrazinamide 100.0 ug/uL	Sensitive

	Phenotypic DST	Deeplex tNGS
Rif	R	L430P
Inh	R	S315T
Pza	S	WT
Emb	R	I306T
Bdq	S	WT
Lzd	S	WT
Fq	S	WT
Cfz	S	WT
Cs	S	WT
Amk	S	WT

Regimen:

Group A:

- Bedaqulline
- Levofloxacin
- Linezolid

Group B

- Clofazimine
- Cycloserine

First Line

- PZA

October 2022

March 2023

Date	Smear	Culture
30/09/22	2+ positive	Not done/ send to South Africa
28/10/22	1+ positive	Positive after 11 days
30/12/22	2+ positive	Not done
10/01/23	2+ positive	Not done
08/03/23	2+ positive	Not done
01/04/23	negative	no growth after 6 weeks

Big surprise????

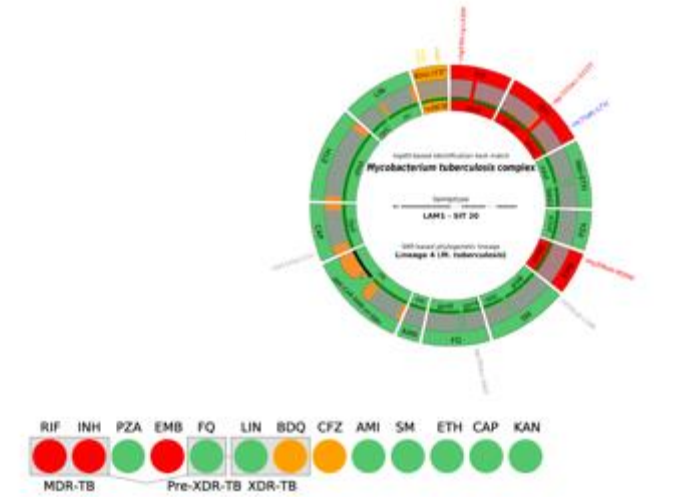
October 2022

March 2023

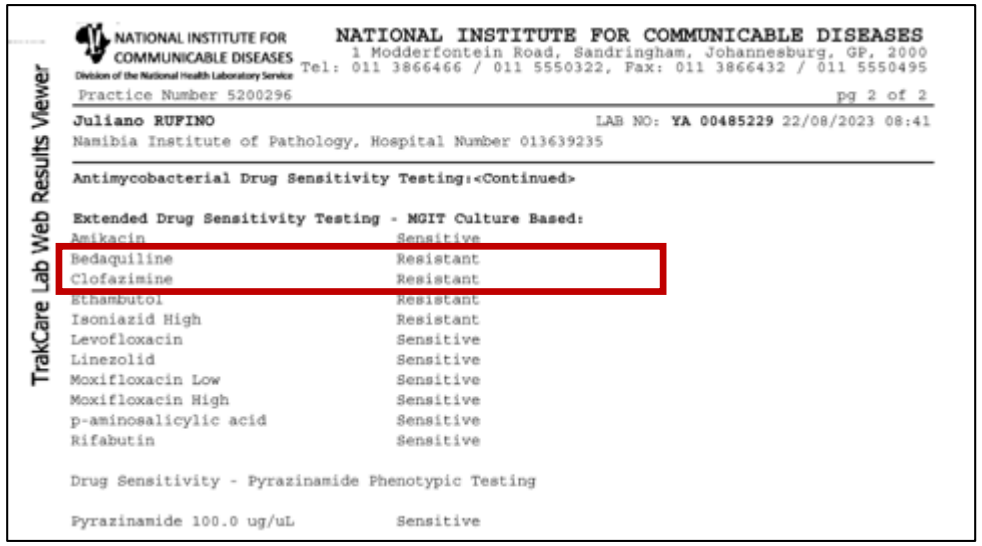
April 2023

Month	Date	Smear	Culture
Month 1	28/10/22	1+ positive	Positive after 11 days
Month 2	30/12/22	2+ positive	Not done
Month 3	10/01/23	2+ positive	Not done
Month 5	08/03/23	2+ positive	Not done
Month 6	**01/04/23**	**negative**	**No growth after 6/12**
Month 7	09/05/23	Scanty	Positive after 7 days
Month 8	08/06/23	1+ positive	Positive after 6 days
Month 9	07/07/23	3+ positive	Positive after 6days
Month 10	12/07/23	2+ positive	Positive after 5 days

Repeat tNGS (Deeplex) – indicates BDQ/CFZ resistance



Gene	Genomic position	Codon change	% Variant	Dx-score	AA change	Drug*	Confidence	Resistance level	Reference
embB	4247431	atg306att	100.000	97.50	M306I	EMB	Associated with resistance	Resistant	WHO 2021
katG	2155168	agc315acc	100.000	26.25	S315T	INH	Associated with resistance	Resistant	WHO 2021
rpoB	761095	ctg430ccg	99.930	679.75	L430P	Rif	Associated with resistance	Resistant	WHO 2021
rv0678	779127	insG	3.570	0.00	frameshift	n/a	n/a	Resistant	n/a
rv0678	779130	insC	16.050	0.00	frameshift	n/a	n/a	Resistant	n/a
rv0678	779407	insG	21.860	0.00	frameshift	n/a	n/a	Resistant	n/a



TrakCare Lab Web Results Viewer

NATIONAL INSTITUTE FOR COMMUNICABLE DISEASES
Division of the National Health Laboratory Service

NATIONAL INSTITUTE FOR COMMUNICABLE DISEASES
1 Modderfontein Road, Sandringham, Johannesburg, GP, 2000
Tel: 011 3866466 / 011 5550322, Fax: 011 3866432 / 011 5550495

Practice Number 5200296 pg 2 of 2

Juliano RUFINO LAB NO: **YA 00485229** 22/08/2023 08:41
Namibia Institute of Pathology, Hospital Number 013639235

Antimycobacterial Drug Sensitivity Testing:<Continued>

Extended Drug Sensitivity Testing - MGIT Culture Based:

Amikacin	Sensitive
Bedaquiline	Resistant
Clofazimine	Resistant
Ethambutol	Resistant
Isoniazid High	Resistant
Levofloxacin	Sensitive
Linezolid	Sensitive
Moxifloxacin Low	Sensitive
Moxifloxacin High	Sensitive
p-aminosalicylic acid	Sensitive
Rifabutin	Sensitive

Drug Sensitivity - Pyrazinamide Phenotypic Testing

Pyrazinamide 100.0 ug/uL	Sensitive

	Phenotypic DST baseline	Deeplex tNGS at baseline	Phenotypic DST at failure	Deeplex tNGS at failure
Rif	R	L430P	R	L430P
Inh	R	S315T	R	S315T
Pza	S	WT	S	WT
Emb	R	I306T	R	I306T
Bdq	S	WT	R	R /Rv0678
Lzd	S	WT	S	WT
Fq	S	WT	S	WT
Cfz	S	WT	R	R /Rv0678
Cs	S	WT	S	WT
Amk	S	WT	S	WT
Pas	S		S	

MIC was not done

Günther et al, EID 2024

New regimen

Regimen:

Group A

~~Bedaqulline~~

Levofloxacin

Linezolid

Group B

~~Clofazimine~~

Cycloserine

Pretomanid

Group C

Amikacin

Meropenem/ Clavulanic acid

(PAS)

First Line

PZA

Now: via port o cath:
Amikacin, Meropenem/Clv +

Culture conversion after 3 months (Nov. 2023)

??? Treatment duration

Questions / uncertainties

- BDQ: raised MIC in Lineage 4[1]
- BDQ: low EBA[2] – do we need i.e. Amikacin at treatment initation
- Could low concentration of BDQ select resistant clones?[3] Would there be a role for high-dose BDQ in Lineage 4 / in general
- Should we give BPaL(M) in extensive disease?
- Is the MDR-END regimen sufficient in BDQ - resistant TB?
- Do we need a new definition for BDQ - resistant TB / FQ – sensitive TB?
- Do we need at least consensus recommendations for management of BDQ – resistant TB

[1]Bateson et al, JAC 2022
[2]Koul et al, Nature Comm 2014
[4]Sonnenkalb et al, Lancet Microbe 2023

tNGS implementation

- started in 2020

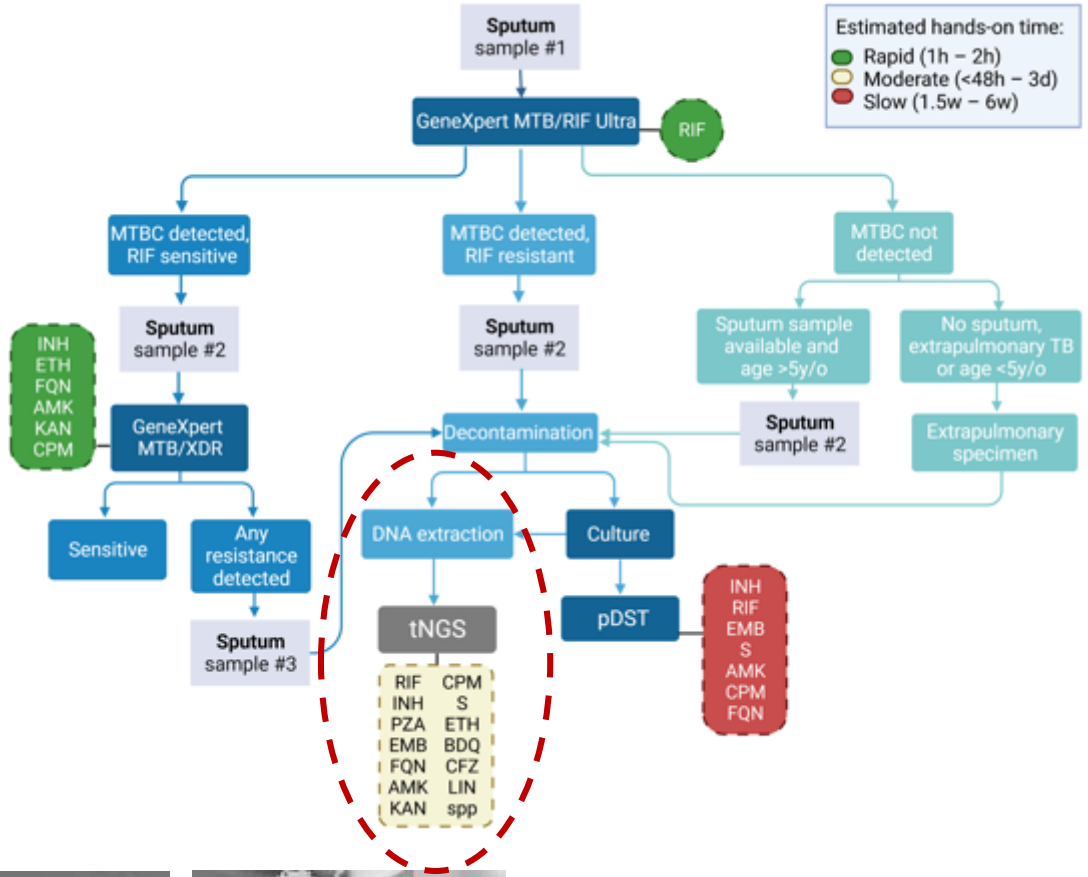
- funded by German government

- initial from culture, now from sputum

- validation currently via WGS

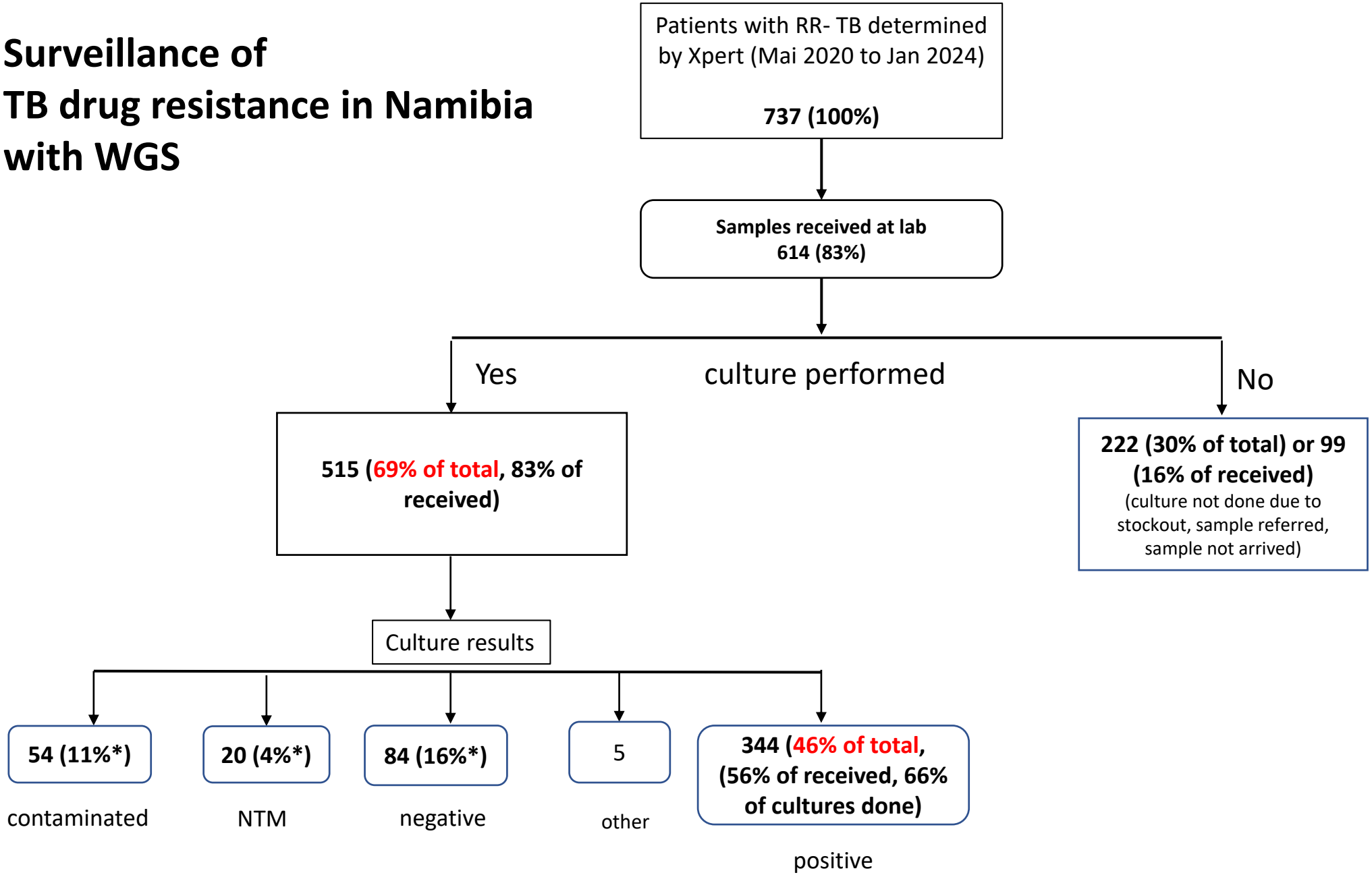
- own culture facility in devlopment for pDST

- biggest challenge: buy-in from MOHSS



de Aurajo et al. Front Public Health 2023

Surveillance of TB drug resistance in Namibia with WGS



* - refers to cultures performed

Status 30.01.2024. 118 samples not yet entered

…..daily battles……

- stock outs – lab: Xpert, culture, DST

- stock out – drugs: currently Pretomanid

- lack of interest/stigma for TB also among HCW

- political support for TB

Summary:

- BDQ RAV also occur under optimal treatment

- Should we really give BPaL(M) also to patients with extensive TB?

- We need DST in our hands, but also recommendations /consensus for clinician how to act upon results

- We need to address sustainability when implementing new diagnostics

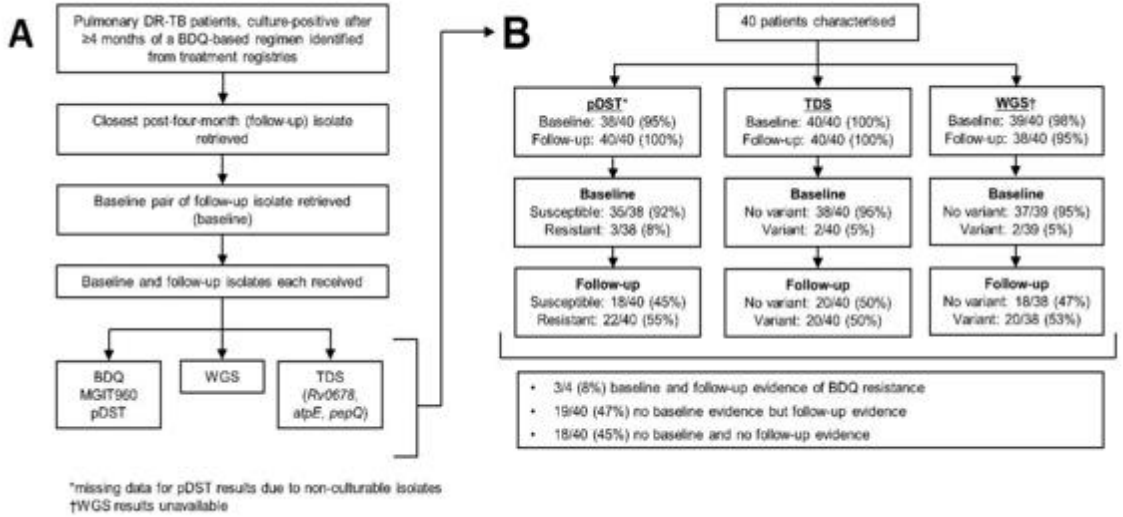
Painting by Papa Shikongeni at Katutura TB hosptial

Special thanks to

- N. Ruswa
- E. Nepolo
- M. Moses
- L. Mhuulu
- S. Niemann
- M. Claassens
- V. Dreyer
- F. Ismail

Risks of the implementation of B(PaLM)

- Bedaquiline: erhöhte MIC bei Lineage 4[2]
- Bedaquiline: langsame Penetration in Kaverne, verglichen mit MXF, LZD and Pretomanid[3]
- Bedaquiline: Exposition mit niedrigen Konzentrationen von BDQ kann Resistenz selektionieren[4]
- Bedaquiline: lange Halbwertszeit kann zu Einzelsubstanzexposition führen[5]
- Bedaquiline und Pretomanid: primäre Resistenz nachgewiesen



[1]Bateson et al, JAC 2022
[2]Rivere et al, AAC 2022
[3]Sarathy et al, ACS Inf Dis 2016
[4]Sonnenkalb et al, Lancet Microbe 2023
[5]De Vos et al, NEJM 2019
Omar et al, NEJM 2022
Derendinger et al. medRxiv 2023