Vuka! Let's unite towards a TB-free world!

9th SA TB Conference
8 – 11 June 2026

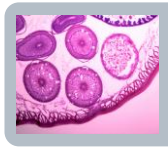
Linezolid interruption and rechallenge in TB

An appraisal of South African programmatic data from 2018 to 2022.

Dr Suzette Oelofse, Aliasgar Esmail, Tahlia Perumal, Jeremi Swanepoel, Stuart Meier, Linda Mbuthini, Shameem Jaumdally, Alex J. Scott, Louié Kühn, Anil Pooran, Norbert Ndjeka, Keertan Dheda , *The Lancet. Global health*

LINEZOLID

A repurposed synthetic oxazolidinone



Stops bacterial growth: inhibiting protein synthesis through binding to mitochondrial rRNA

Recommended as **group A** drug for all RR-TB patients – Critical to the regimen

Clinical trials and systematic reviews show high rates of adverse events leading to drug interruptions (~15-50%) : mainly anaemia and neuropathy

Limited data available on the impact of interruption and NO data on whether LZD can be rechallenged after interruption

F Conradie, NEJM 2020, 2022
Lan, Lancet 2020
Singh, Cochrane, 2019

Study overview

12064

DR-TB patients initiated on LZD

(2018-2020)

Excluded 1962

- 485: Not enough data available for analysis
- 1477: Did not fulfill the eligibility criteria

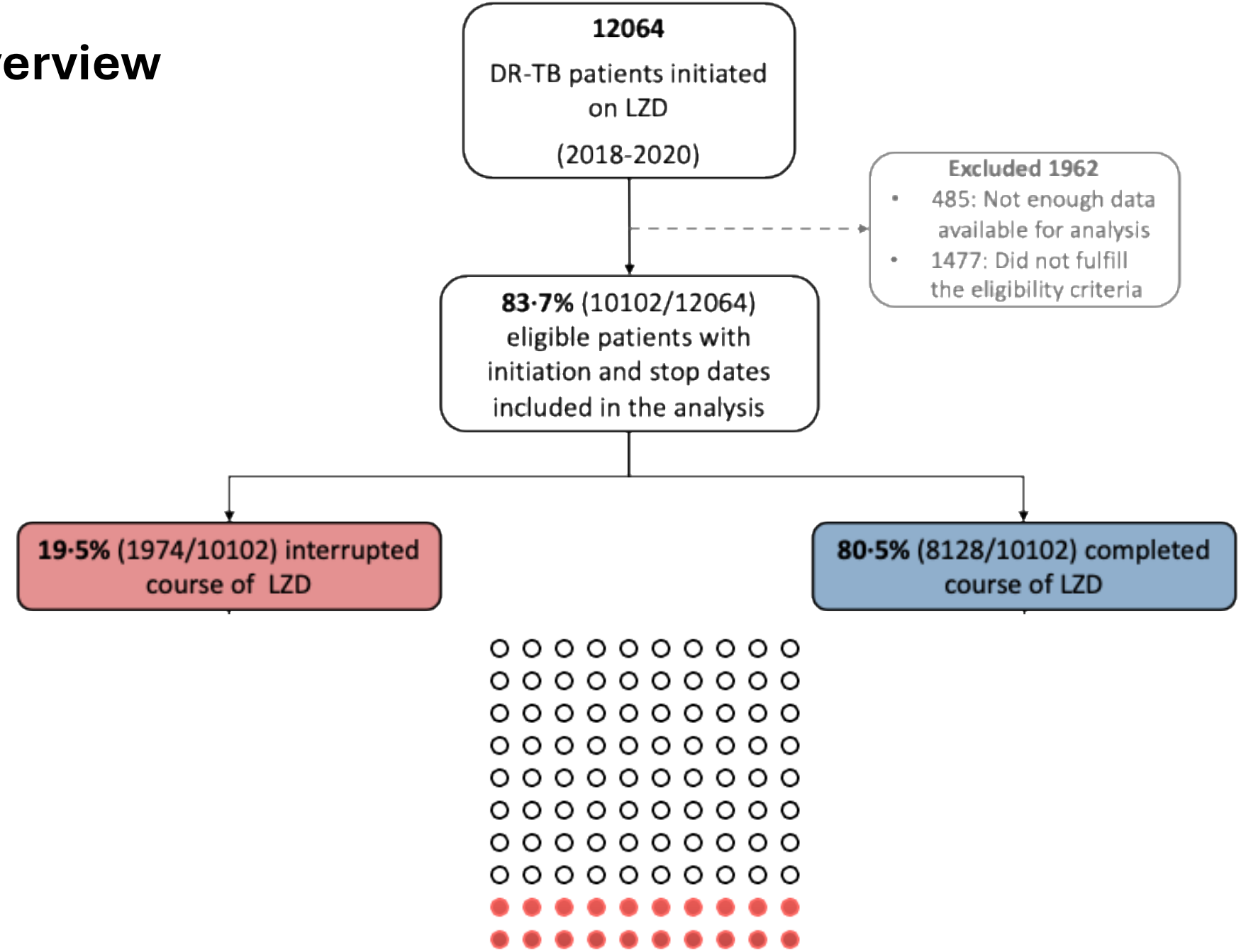
83·7% (10102/12064) eligible patients with initiation and stop dates included in the analysis

EDRWeb
The Electronic Drug-Resistant Tuberculosis Register

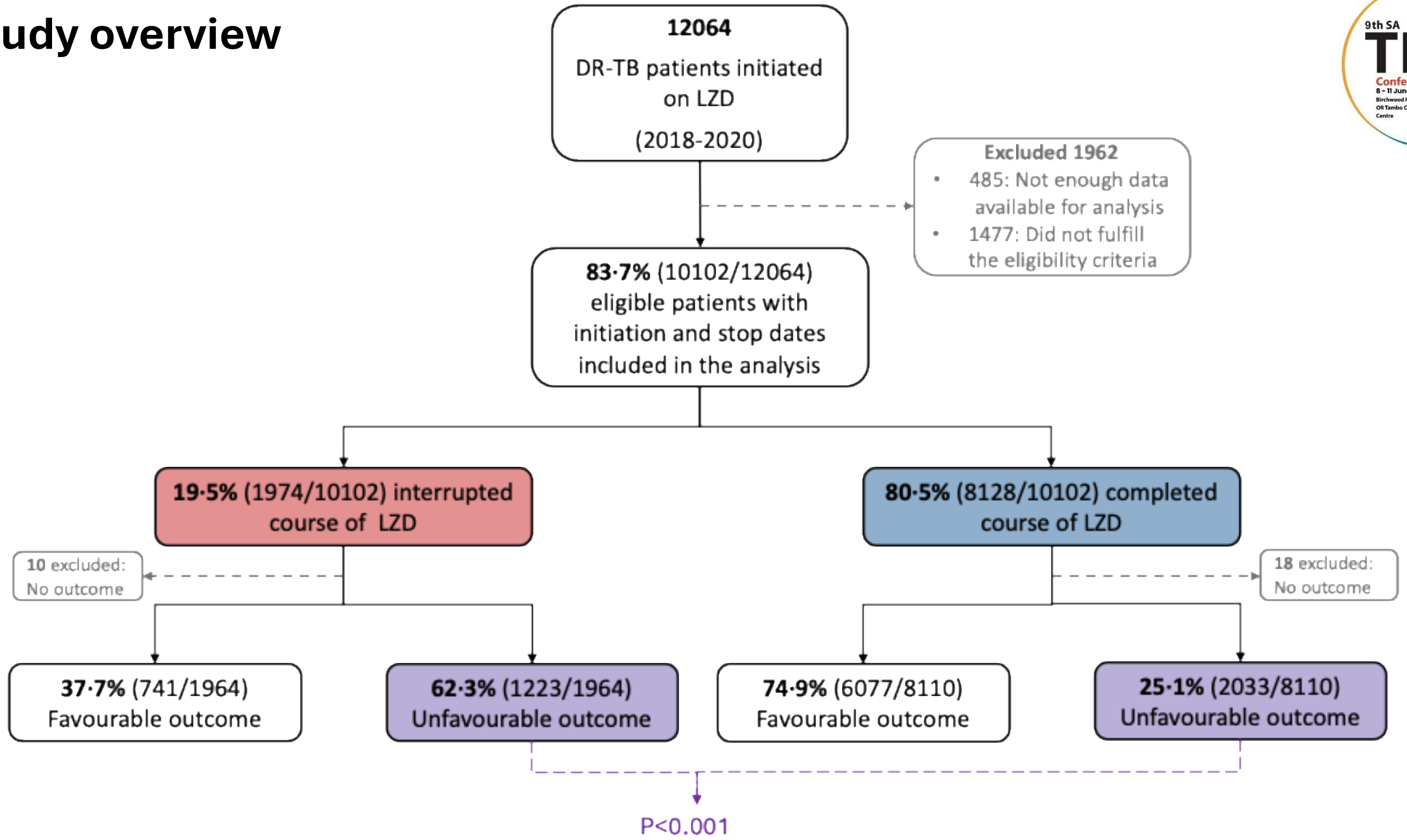
Research questions

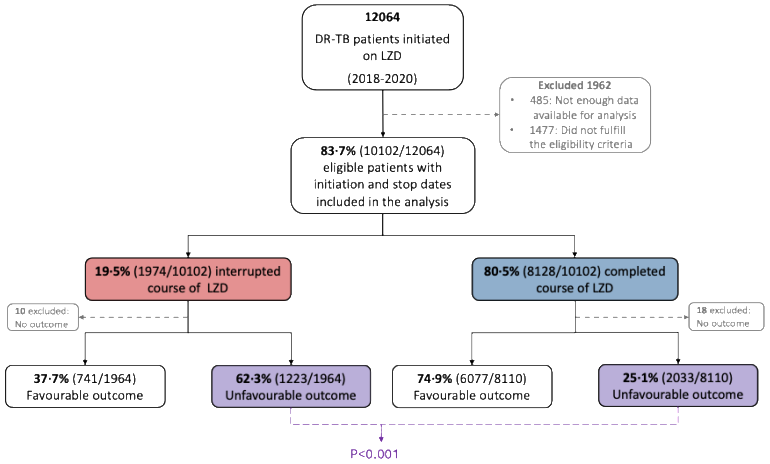
- Who interrupts Linezolid? (how big is the problem?)
- Does interruption impact on outcomes?
- Can LZD be successfully rechallenged after interruption?
- Does rechallenge impact on outcomes?

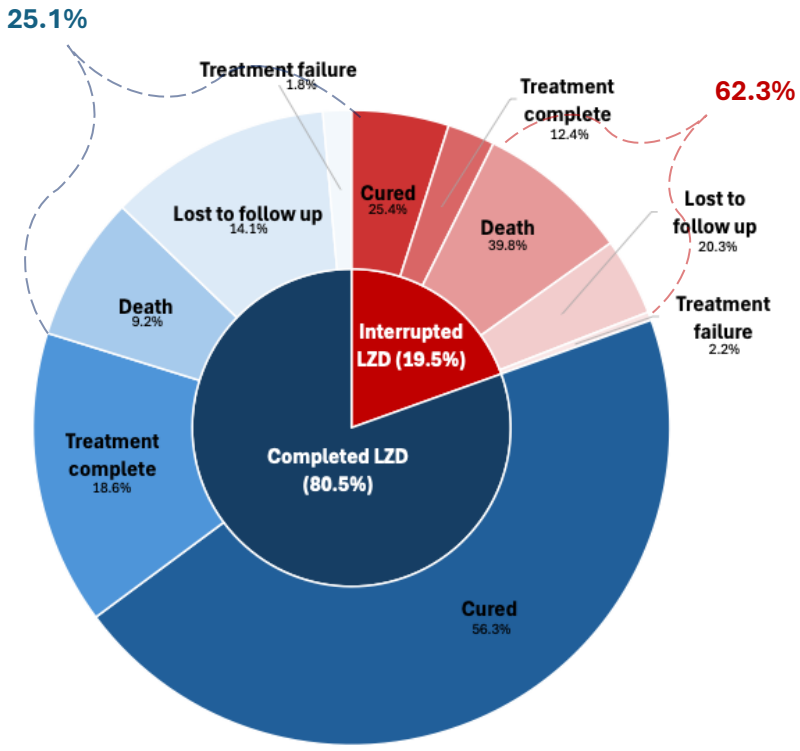
Study overview



Study overview

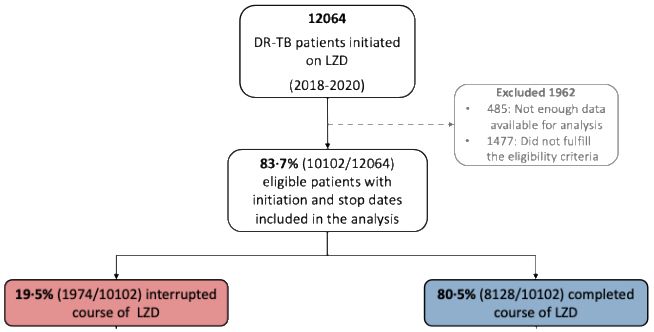




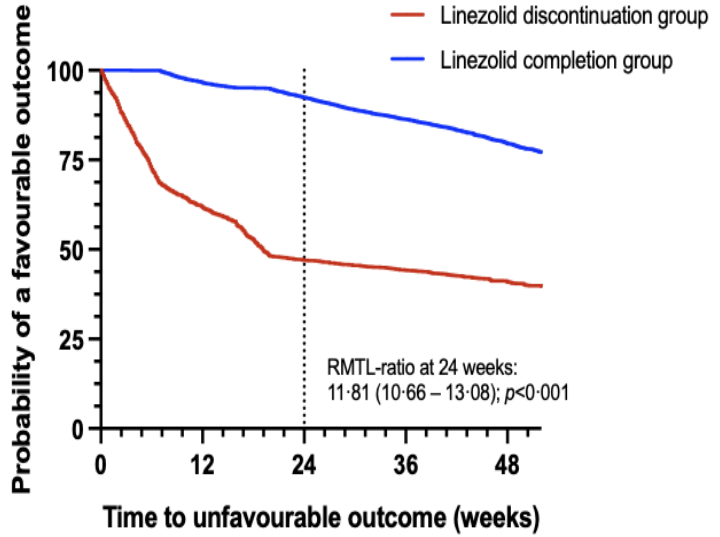


	Unfavourable (n=3256)	Favourable (n=6818)	OR	OR (adjusted)*	P-value
LZD Interruption	1386/3256 (37.6)	741/6818 (10.9)	4·93 (4·45 – 5·48)	3·55 (3·00 – 4·21)	<0·001

	LZD interrupted (n=1974)	LZD completed (n=8128)	P-value	OR
Median age (IQR)	38 (31.0 – 47.0)	37 (30.0 – 46.0)	<0.001	..
Age over 50	**364/1974 (18.4)**	1281/8128 (15·8)	**0.004**	1.21 (1.06-1.37)
Male (%)	1191/1974 (60·3)	4951/8128 (60·9))	0.64	0.98 (0.88 – 1.08)
Weight <50kg	**464/1099 (42·2)**	1639/4619 (35·5)	**<0.001**	1.33 (1.16 – 1.52)
Baseline Hb in g/dl (Median; IQR)	10·6 (8·8 – 12·1)	11·1 (9·5 – 12·8)	<0.001	..
Ward Hb <8g/dl	**107/708 (15·1)**	332/2928 (11·3)	**0.001**	1.45 (1.16 – 1.81)
PLHIV	**1437/1967 (73·1)**	5498/8106 (67·8)	**<0.001**	1.30 (1.17 – 1.45)
ART initiated	1337/1414 (94·6)	**5307/5524 (96·1)**	0.014	0.71 (0.55 – 0.92)
CD4 (Median; IQR)	136 (37·0 – 365·5)	214 (116·5 – 346·5)	0·19	..
CD4 <200	16/26 (61·5)	58/125 (46·4)	0·20	1.51 (0.68 – 3.37)
HIV VL >100	15/25 (60·0)	69/126 (54·8)	0.67	1.10 (0.48 – 2.52)
Diabetes	40/1219 (3·3)	144/4867 (3·0)	0.58	1.21 (0.87 – 1.68)
Previous DR-TB	**269/1974 (13·6)**	915/8128 (11·3)	**0.004**	1.24 (1.08 – 1.43)
Baseline GXP positive	**1672/1694 (98·7)**	6653/6797 (97·9)	0.03	1.63 (1.06 – 2.52)
Baseline Smear positive	**760/1646 (46·2)**	3089/7073 (43·7)	**0.07**	1.13 (1.02 – 1.26)
Baseline Culture positive	**1016/1279 (79·4)**	4421/5983 (73·9)	<0.001	1.35 (1.17 – 1.55)



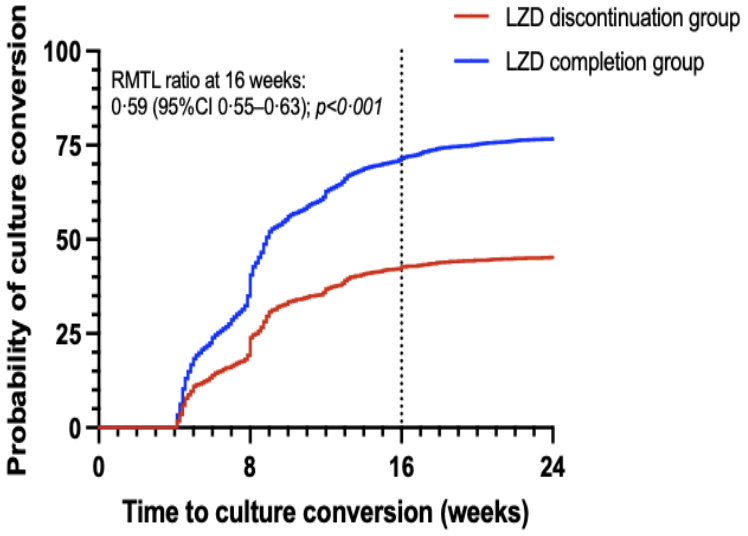
A



Numbers at risk:

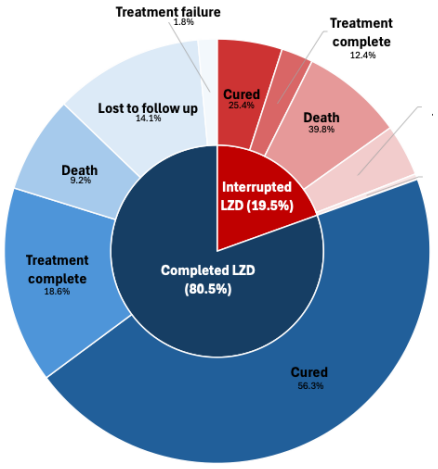
LZD discontinuation group:	1963	1211	913	847	522
LZD completion group:	8110	7842	7481	6800	3475

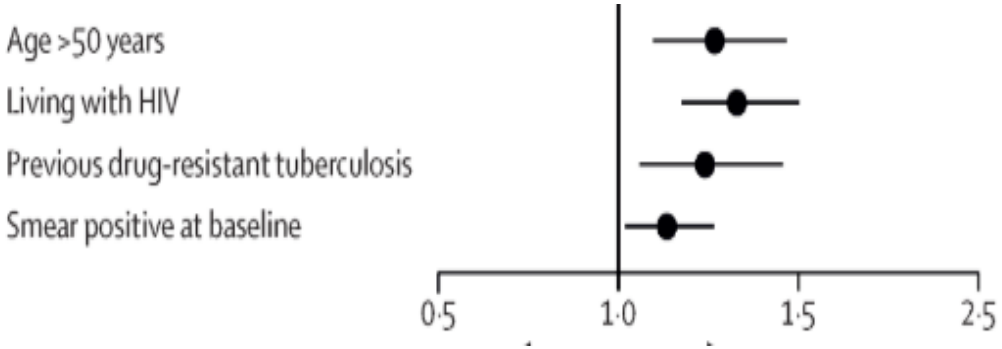
B



Numbers at risk:

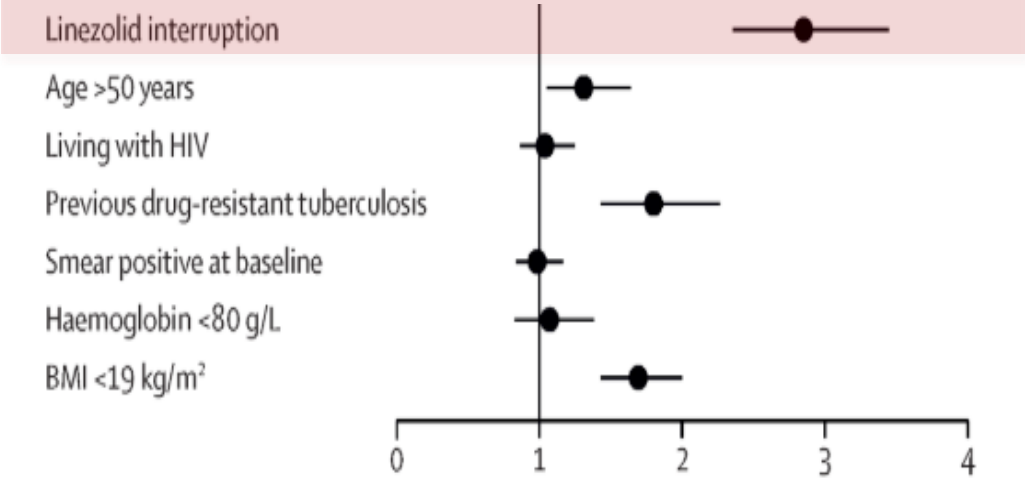
LZD discontinuation group:	1972	1594	1139	1082
LZD completion group:	8122	5284	2348	1897



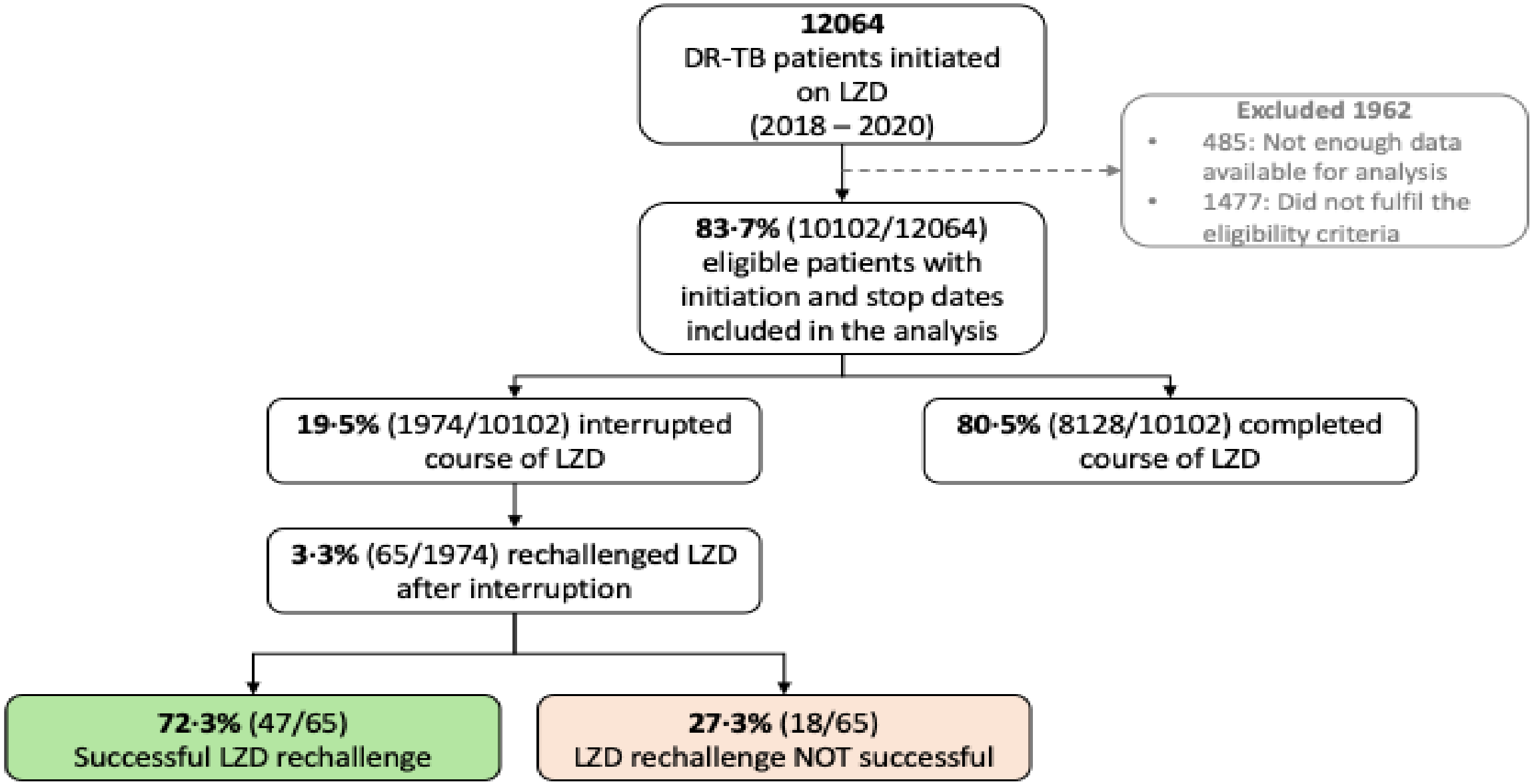


Predictors of LZD interruption

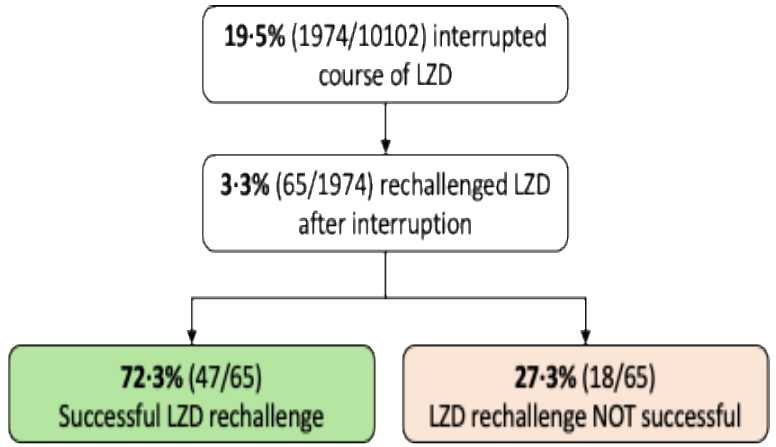
aOR 2·85 (2·36 – 3·45); p< 0·0001

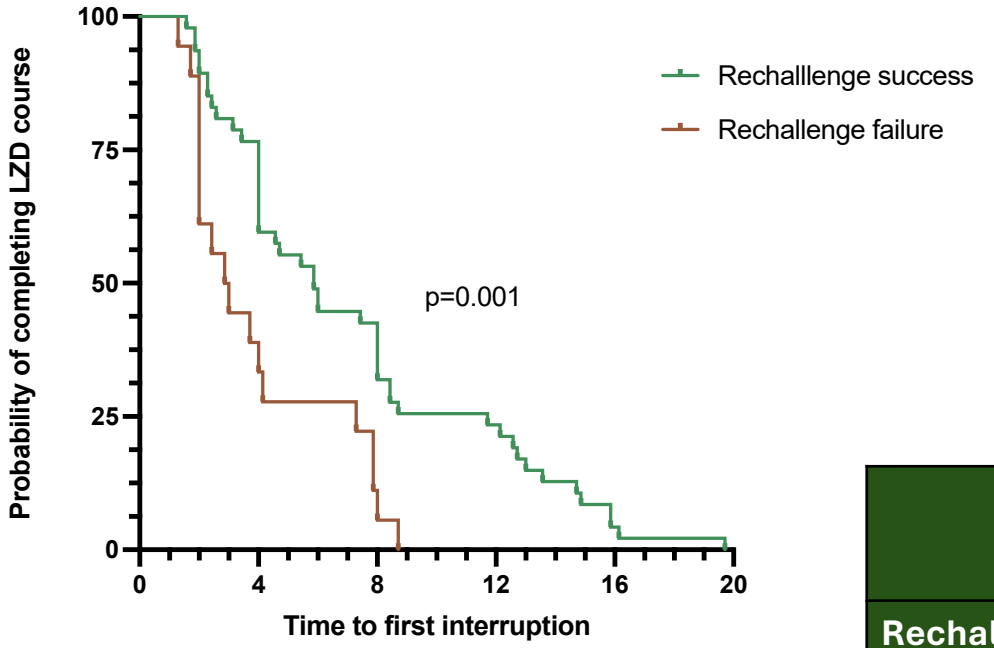


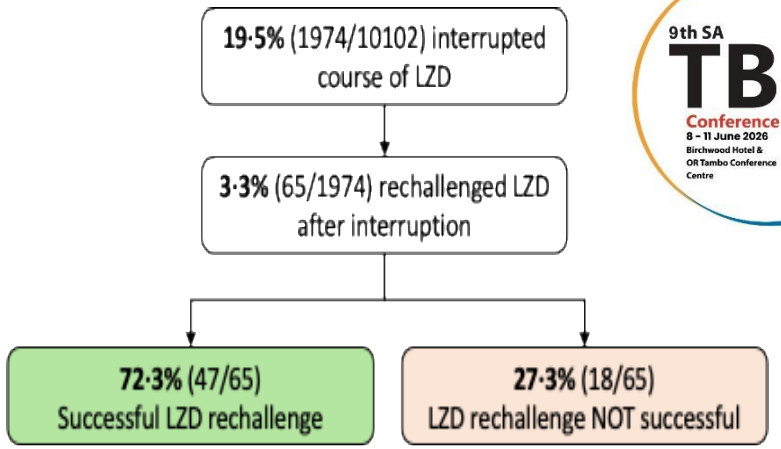
Predictors of unfavourable outcome


12064
DR-TB patients initiated on LZD (2018 – 2020)
Excluded 1962
485: Not enough data available for analysis
1477: Did not fulfil the eligibility criteria
83·7% (10102/12064) eligible patients with initiation and stop dates included in the analysis
19·5% (1974/10102) interrupted course of LZD
80·5% (8128/10102) completed course of LZD
3·3% (65/1974) rechallenged LZD after interruption
72·3% (47/65) Successful LZD rechallenge
27·3% (18/65) LZD rechallenge NOT successful

	Rechallenge successful (n=47)	Rechallenge failed (n=19)	OR (95% CI)	p-value
Age (median; IQR)	36·0 (29·0-48·0)	33·5 (26·3-44·3)	..	0·31
Male (%)	31/47 (66.0)	12/18 (66.7)	0.97 (0.31-3.06)	1.00
Age>50 (%)	11/47 (23.4)	2/18 (11.1)	1.44 (0.48-12.32)	0.33
Weight<50 (%)	7/30 (23.3)	6/13 (46.2)	0.36 (0.09-1.41)	0.16
HIV positive (%)	30/46 (65.2)	12/17 (70.6)	0.78 (0.23-2.61)	0.77
ART initiated (%)	29/31 (93.5)	12/12 (100)	1.07 (0.98-1.17)	1.00
Hb (median; IQR)	11.7 (9.7-12.9)	9.8 (8.1-11.1)	-	0.08
Hb<8 g/dl (%)	2/21 (9.5)	2/9 (22.2)	0.37 (0.04-3.14)	0.56
Previous DR-TB (%)	3/47 (6.4)	1/18 (5.6)	1.16 (0.11-11.93)	1.00
Baseline GXP positive	40/40 (100)	17/17 (100)	1	1
Baseline Smear positive (%)	20/39 (51.3)	5/15 (33.3)	2.11 (0.61-7.30)	0.36
Baseline Culture positive (%)	28/36 (77.8)	8/14 (57.1)	2.63 (0.70-9.81)	0.17
Duration of interruption (median; IQR)	8 (4.6-14.3)	5.65 (4.2-16.6)	..	0.38
Time to first interruption (median; IQR)	5.9 (4.0-11.7)	2.9 (2.0-7.4)	..	0.005

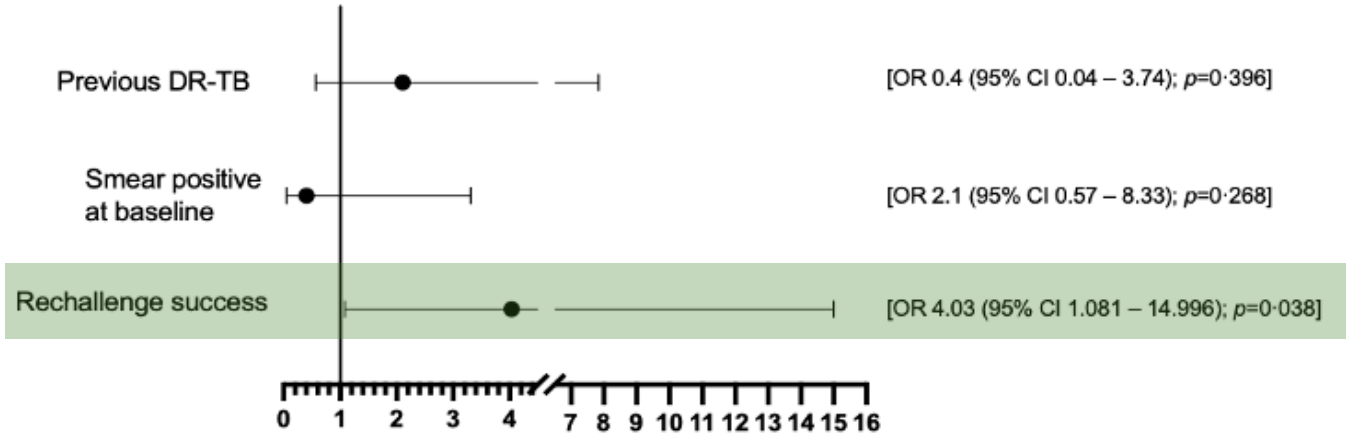




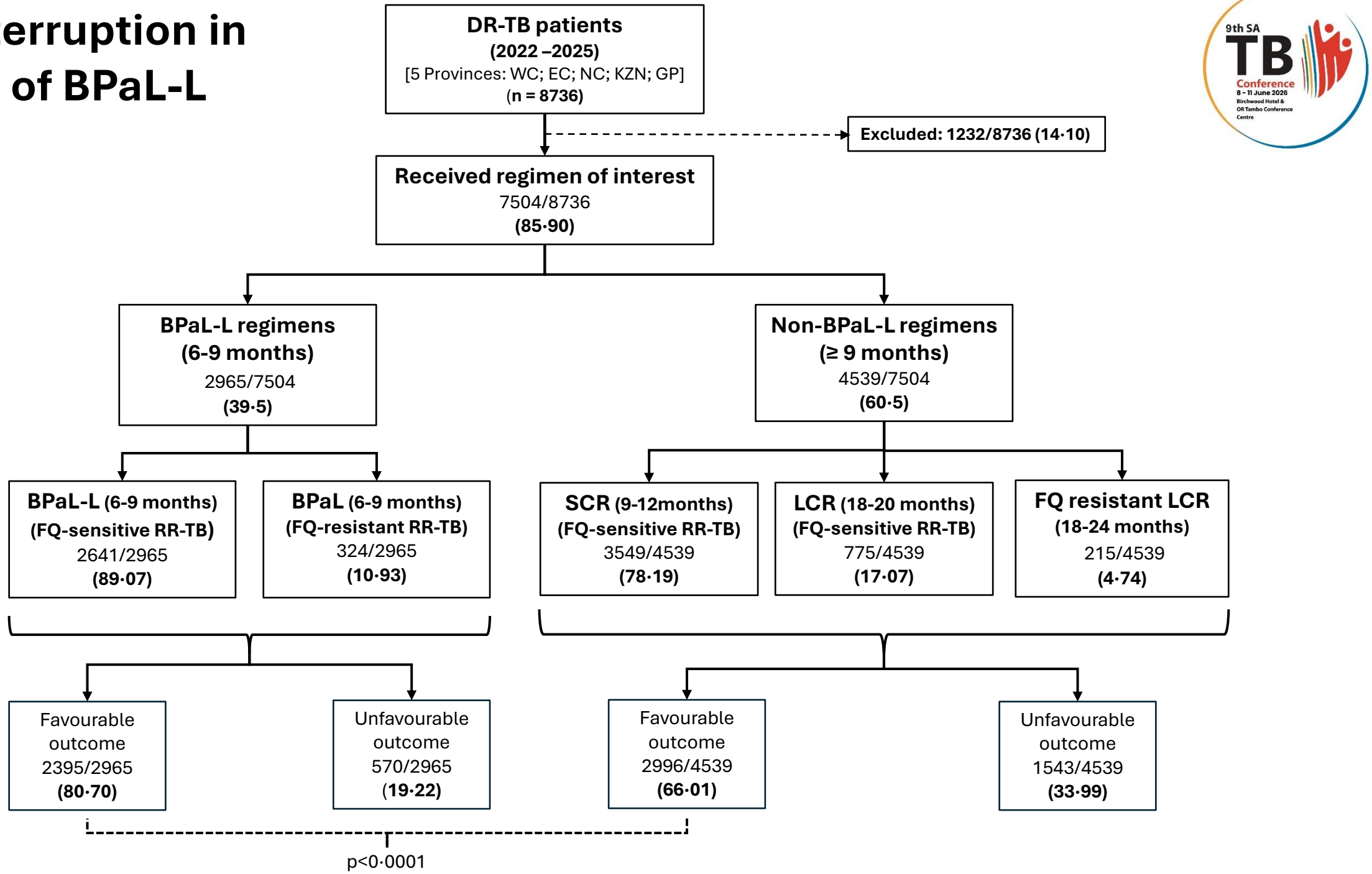


	Favourable outcome (n=47)	Unfavourable outcome (n=17)	OR*	P-value
Rechallenge successful	37/47 (78.7)	9/17 (52.9)	*4.03 (1.03–11.70)	0.04

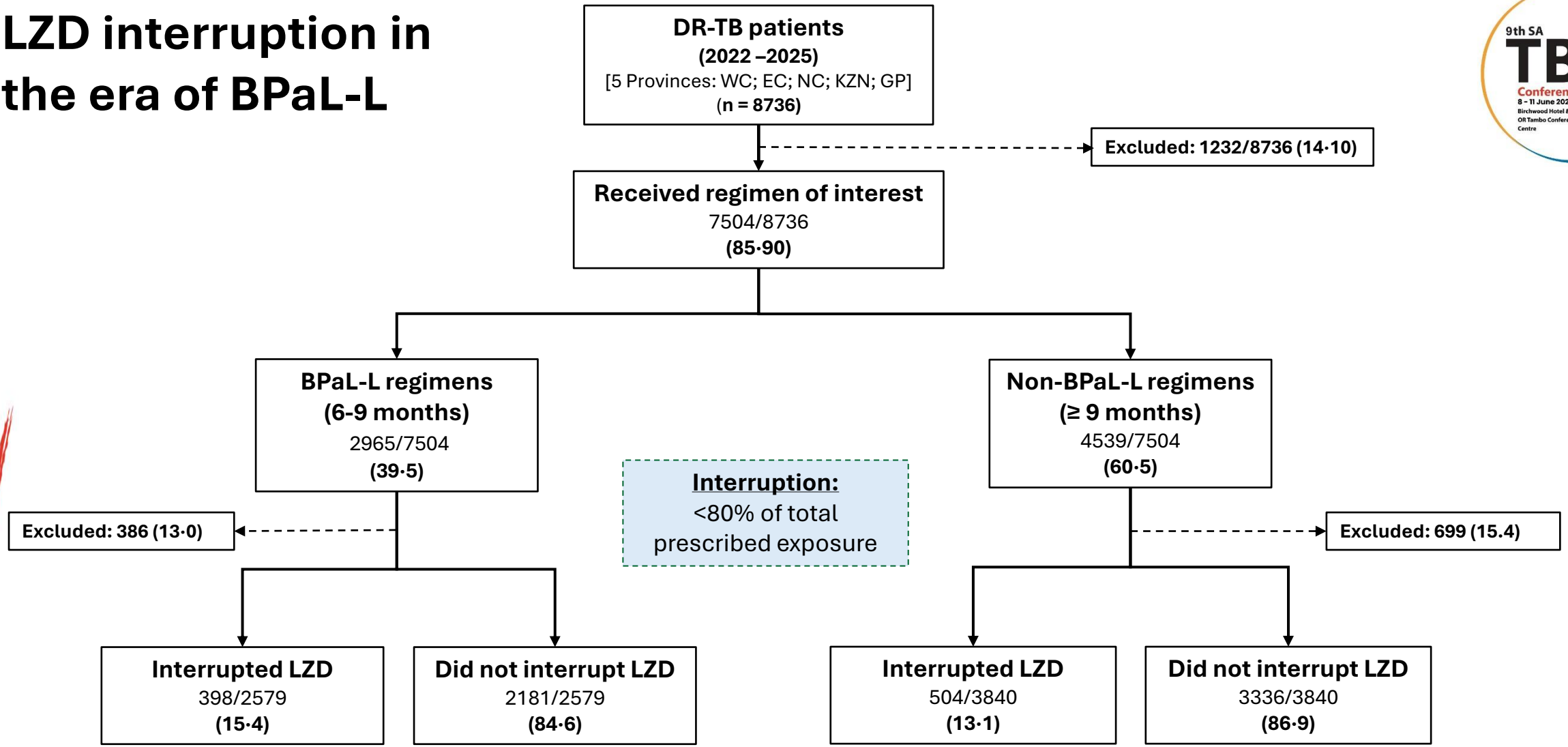
Predictors of favourable outcome – rechallenge group



LZD interruption in the era of BPaL-L



LZD interruption in the era of BPaL-L



Conclusion

LZD interruption is common (occurring in one in five patients)

LZD interruption was independently associated with **an unfavourable clinical outcome.**

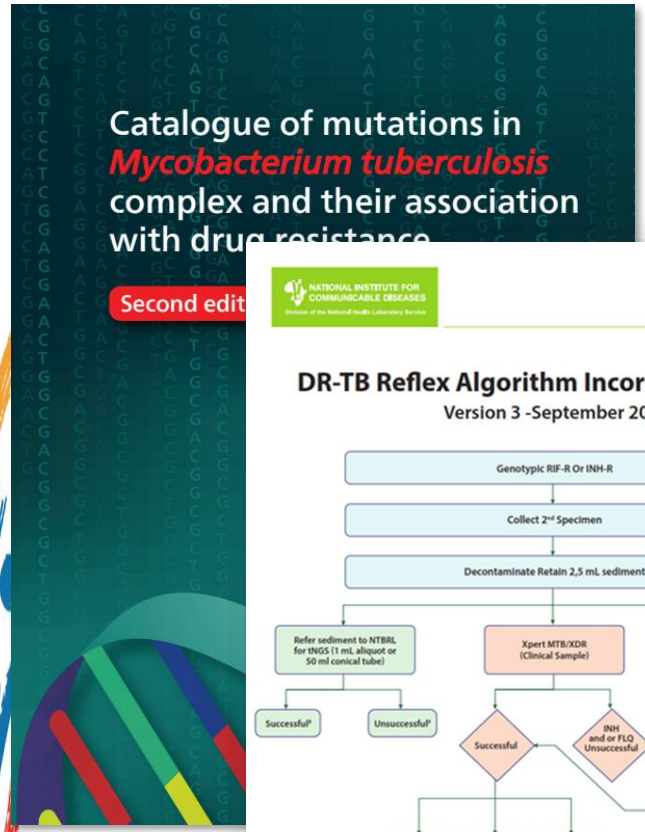
LZD can be successfully rechallenged and is associated with **favourable outcomes.**

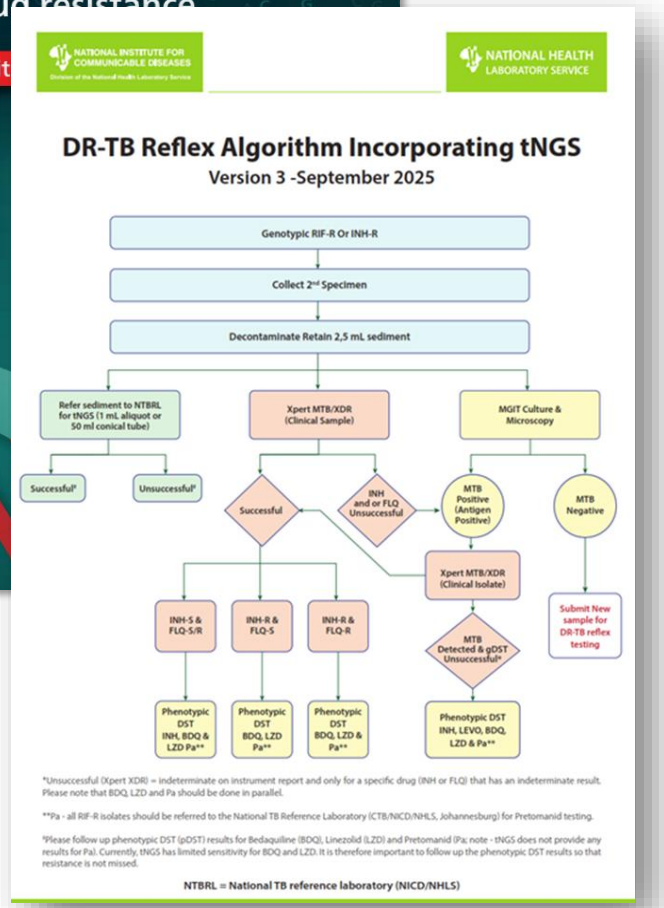
These findings inform clinical practice and have implications for the rollout of newer short course regimens containing LZD.

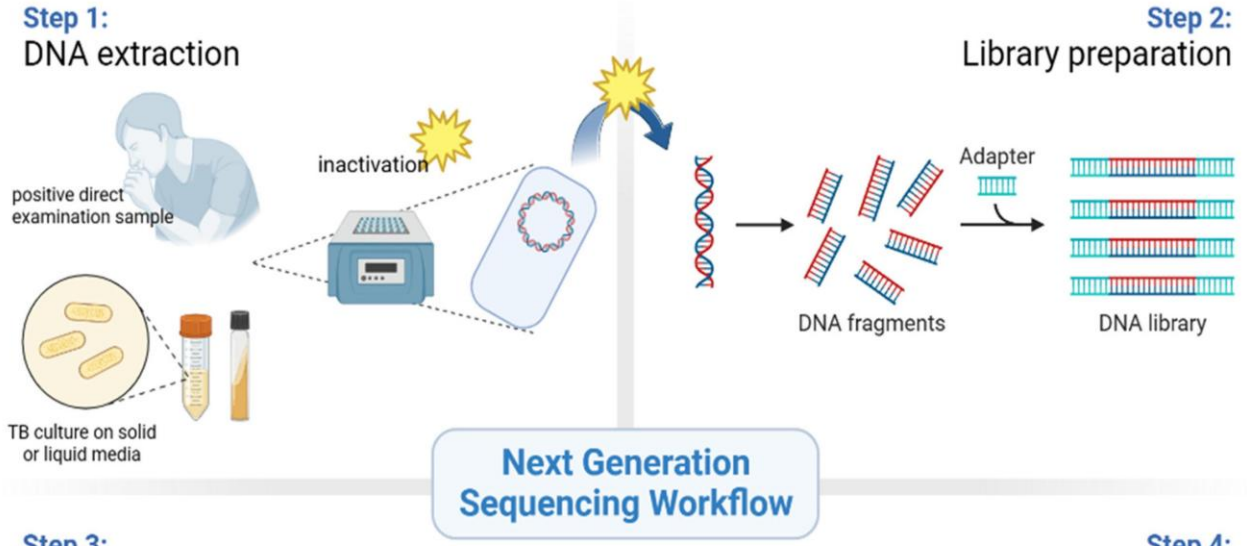
Future considerations:

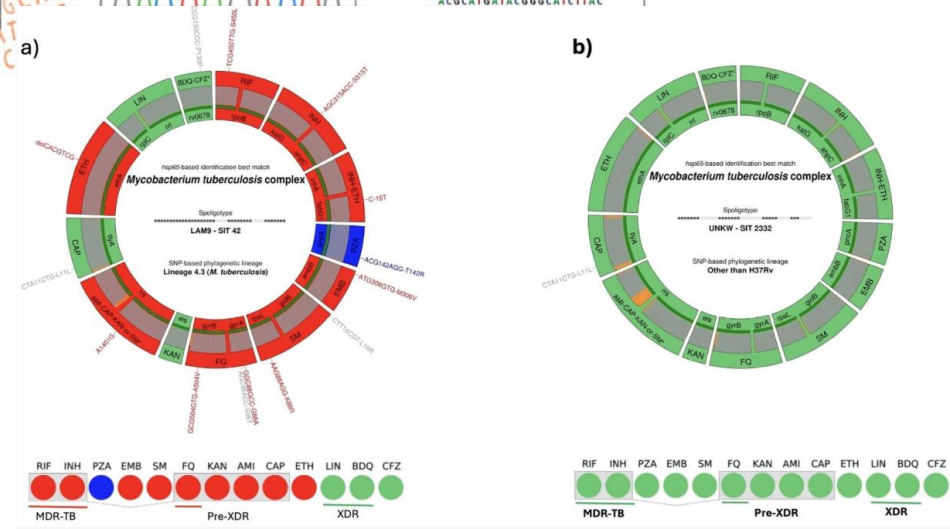
- Utility of LZD therapeutic drug monitoring
- Newer, less toxic drugs
- Protection of current regimens to prevent resistance
- Improved diagnostics

tNGS


Catalogue of mutations in
Mycobacterium tuberculosis
complex and their association
with drug resistance
Second edit


NATIONAL INSTITUTE FOR COMMUNICABLE DISEASES
NATIONAL HEALTH LABORATORY SERVICE
DR-TB Reflex Algorithm Incorporating tNGS
Version 3 -September 2025
Genotypic RIF-R Or INH-R
Collect 2nd Specimen
Decontaminate Retain 2,5 mL sediment
Refer sediment to NTBRL for tNGS (1 mL aliquot or 50 ml conical tube)
Xpert MTB/XDR (Clinical Sample)
MGIT Culture & Microscopy
Successful*
Unsuccessful*
Successful
INH and or FLQ Unsuccessful
MTB Positive (Antigen Positive)
MTB Negative
Xpert MTB/XDR (Clinical Isolate)
Submit New sample for DR-TB reflex testing
INH-S & FLQ-S/R
INH-R & FLQ-S
INH-R & FLQ-R
MTB Detected & gDST Unsuccessful*
Phenotypic DST INH, BDQ & LZD Pa**
Phenotypic DST BDQ, LZD Pa**
Phenotypic DST BDQ, LZD & Pa**
Phenotypic DST INH, LEVO, BDQ, LZD & Pa**
*Unsuccessful (Xpert XDR) = indeterminate on instrument report and only for a specific drug (INH or FLQ) that has an indeterminate result. Please note that BDQ, LZD and Pa should be done in parallel.
**Pa - all RIF-R isolates should be referred to the National TB Reference Laboratory (CTB/NICD/NHLS, Johannesburg) for Pretomanid testing.
*Please follow up phenotypic DST (pDST) results for Bedaquiline (BDQ), Linezolid (LZD) and Pretomanid (Pa; note - tNGS does not provide any results for Pa). Currently, tNGS has limited sensitivity for BDQ and LZD. It is therefore important to follow up the phenotypic DST results so that resistance is not missed.
NTBRL = National TB reference laboratory (NICD/NHLS)


Step 1:
DNA extraction
positive direct examination sample
inactivation
TB culture on solid or liquid media
Step 2:
Library preparation
Adapter
DNA fragments
DNA library
Next Generation Sequencing Workflow
Step 3:
Amplification and Purification
bridge PCR technology
emulsion PCR technology
Step 4:
Sequencing and Analysis
G A C T A G T C T G
Reference Genome
Aligned Sequencing Reads


a)
b)
Mycobacterium tuberculosis complex
LAM9 - SIT 42
Lineage 4.3 (M. tuberculosis)
UNKW - SIT 2332
Other than H37Rv
RIF INH PZA EMB SM FQ KAN AMI CAP ETH LIN BDQ CFZ
MDR-TB
Pre-XDR
XDR

Recruitment

Primary care clinics in and around **Cape Town** (South Africa) - Newly diagnosed and treatment failure associated rifampicin-resistant TB, including pre-XDR and XDR patients (*n* = 250)

1:1 randomization

Study arms

Control arm (*n*=125)
Programmatic **standardised** MDR-TB empiric **treatment regimen**

Intervention arm (*n*=125)
Sequencing-based **individualized treatment regimen** to supplement SOC

Primary Assays

Monthly sample collection resistance amplification rates

Standard of care

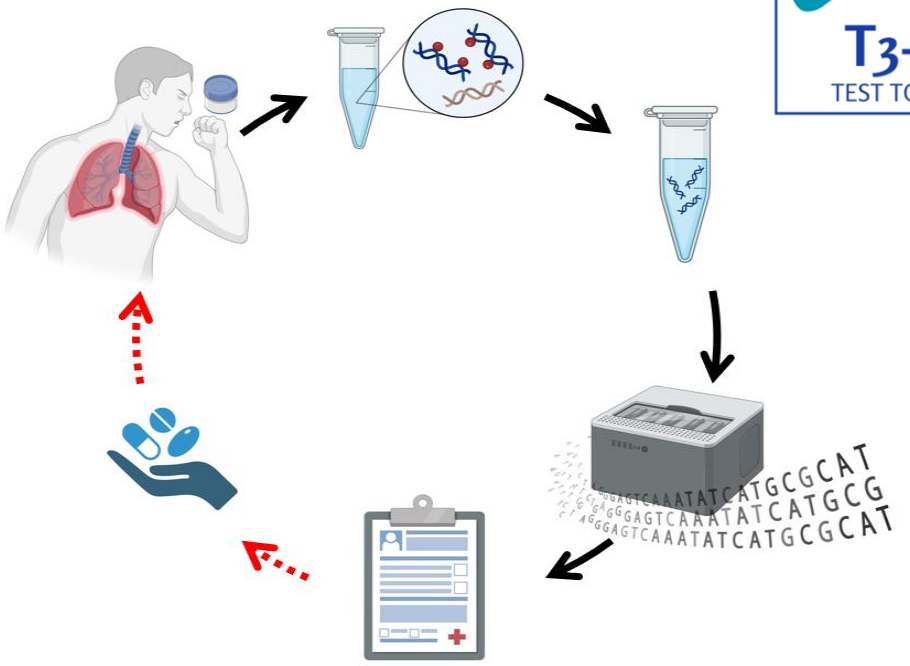
Smear Microscopy

Xpert-XDR

Culture DST

WGS and Epigenetics

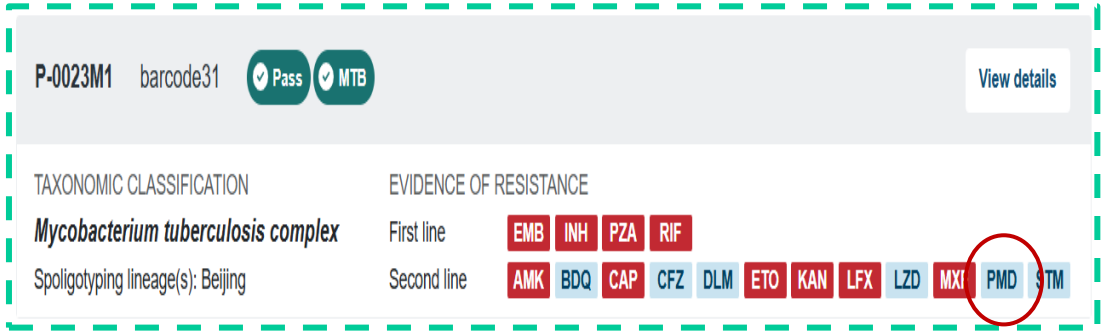
AmPORE-TB test (On-demand tNGS)



Outcomes

Primary outcome: Arm-specific number initiated on ≥4 effective drugs within 14 days of RR-TB diagnosis in each study arm **[n = 125 per arm]***

Secondary outcomes: **(1)** 12-month favourable outcome post treatment initiation **(2)** Time-specific rates of resistance amplification, **(3)** Time-specific rates of culture conversion and clinical outcomes (relapse free survival) **(4)** Prevalence of hetero-resistant bacterial populations **(5)** Adverse event rates **(6)** Feasibility **(7)** Turn-around times **(8)** Cost-effectiveness **(9)** Adjunctive prognostic value of CXR and mycobacterial markers



Thanks and acknowledgements

- Prof. Norbert Ndjeka, A/Prof Ali Esmail, Prof Keertan Dheda, Dr Tahlia Perumal, Dr Jeremi Swanepoel, Dr Alex Scott, Dr Stuart Meier, Dr Shameem Jaumdally, Mr Lind Mbuthini, the whole CLII
- Wamtech – EDRWeb
- The South African Medical Research Council through its Division of Research Capacity Development under the Bongani Mayosi National Health Scholars Programme
- South African MRC/UCT Centre for the Study of Antimicrobial Resistance
- EU (EDCTP), NRF.
- NapkinAI – image generation