MDR TB

Dr. Sandeep Sharma

DM- Seminar

Global and national magnitude of DR-TB problem

- Globally, estimated 450 000 incident cases MDR/RR-TB in 2021
- New TB cases with MDR/RR-TB 3.6% & previously treated cases was 18%
- The countries with the largest share of incident cases of MDR/RR-TB in 2021 were India (26% of global cases), the Russian Federation (8.5% of global cases) and Pakistan (7.9% of global cases)
- The estimated proportion of MDR/RR-TB cases with pre-XDR (i.e. resistance to any fluoroquinolone for which testing was done) was 20%

WHO Global TB report

Global and national magnitude of DR-TB problem

- Estimated number of MDR/RR-TB cases in India is 124 000 (9.1/lakh population)

NDRS (INDIA)	All	New	Previously treated TB
Resistant to any drugs	28%	22%	36.82%
MDR-TB	6.19%	2.84%	11.62%
Isoniazid (H) resistance	16%	11.6%	25%

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No.	Indicator	Achievement in 2022
1	No. of notified bacteriological confirmed TB patients	12,32,149 (51%)
2	No. of bacteriologically confirmed TB patients with valid rapid DRT result for at least Rifampicin (RS/RR)	9,38,217 (76%)
3	No. of Rifampicin resistant TB patients diagnosed (MDR/ RR-TB)	63,801
4	No. of Rifampicin resistant TB patients with a valid DST result available for at least fluoroquinolone	23,846 (37%)
5	No. of Rifampicin resistant TB patients with FQ resistance diagnosed (Pre-XDR-TB)	12,002
6	No. of Rifampicin resistant TB patients with FQ resistance with a DST result available for Bedaquiline/ Linezolid	1187 (10%)
7	No. of Rifampicin resistant TB patients with FQ resistance diagnosed with resistant to Bedaquline/ Linezolid or both (XDR-TB)	85
8	No. of bacteriologically confirmed patients (with Rifampicin resistance not detected) with a DST result available for at least Isoniazid	2,04,034 (23%)
9	No. of Rifampicin resistance not detected patients with Isoniazid resistance diagnosed (H Mono-poly DR-TB)	15,953

Definitions

5 categories of drug-resistant TB

1. **Isoniazid (INH)-resistant TB**
2. **RR TB**- whose biological specimen is resistant to R, detected using phenotypic or genotypic methods, with or without resistance to other anti-TB drugs. It includes any resistance to R, in the form of mono-resistance, poly-resistance, MDR or XDR
3. **MDR-TB** -RR and INH resistant
4. **Pre-XDRTB** (Pre-extensively drug-resistant TB) -resistant to rifampicin (MDR/RR-TB) and any fluoroquinolone
5. **XDR-TB** -TB that is resistant to rifampicin (MDR/RR-TB), plus any fluoroquinolone, plus at least one of the group A drugs, bedaquiline and linezolid or both

- *Roelens M, et al. Am J Respir Crit Care Med Vol 204, Iss 6, pp 713–722, Sep 15, 2021*
- *WHO consolidated guidelines on tuberculosis. Module 4: treatment - drug-resistant tuberculosis treatment, 2022 update. Geneva: World Health Organization; 2022*
- *Meeting report of the WHO expert consultation on the definition of extensively drug-resistant tuberculosis, 27-29 October 2020. Geneva: World Health Organization; 2021*

Detection of drug resistance/susceptibility

- **Genotypic tests**-Rapid molecular diagnostic method for Drug Resistance Testing (DRT)- These are genotypic tests that detect specific genetic mutations that are associated with drug resistance
- **Phenotypic tests** -Growth based Drug Susceptibility Testing (DST) ,wherein bacilli are grown and subsequently tested for drug susceptibility using various drug containing and drug-free media

Rapid molecular drug resistance testing (genotypic tests)

- Xpert MTB/RIF is a cartridge-based NAAT (CB-NAAT)
- The Xpert MTB/XDR
- Truenat MTB and Truenat MTB-Rif Dx
- Line probe assays (LPA)
- Genetic sequencing

Cartridge-based NAAT (CB-NAAT)

	GeneXpert MTB/RIF	Xpert ULTRA
MTB Detection and RIF determination	Semi-Quantitative hemi-nested PCR Cycle threshold probe comparison	Semi-Quantitative nested PCR High Resolution Melt technology
Targets	Detection of a single copy target: rpoB gene (5 probes)	Detection of a single copy target: rpoB gene (4 probes), Detection of 2 different multi-copy targets: IS6110 & IS1081 (2 probes)
Turn around Time (TAT)	110 min	< 80 min
RIF resistance detection	false-positive results for strains that carry phenotypically silent mutations (synonymous mutations), or for paucibacillary specimen	low specificity
Limit Of Detection	131 cfu/ml	11.8 cfu/ml
Semi-Quantification	High, Medium, Low, and Very Low	High, Medium, Low, Very Low, and Trace

Xpert Ultra versus Xpert MTB/RIF for pulmonary tuberculosis and rifampicin resistance in adults with presumptive pulmonary tuberculosis (Review)

Zifodya JS, Kreniske JS, Schiller I, Kohli M, Dendukuri N, Schumacher SG, Ochodo EA, Haraka F, Zwerling AA, Pai M, Steingart KR, Horne DJ

Aim- To determine how accurate Xpert Ultra is compared with Xpert MTB/RIF for diagnosing pulmonary tuberculosis and rifampicin resistance in adults

Method- compared the diagnostic accuracy of Xpert Ultra and Xpert MTB/RIF with results primarily measured **against culture** (detection of pulmonary tuberculosis) and **DST and LPA** (detection of rifampicin resistance)

Studies- 9 studies (n=3500) compared Xpert Ultra to Xpert MTB/RIF for diagnosing pulmonary tuberculosis, and 5 studies (n=930) compared Xpert Ultra to Xpert MTB/RIF for rifampicin resistance.

Cochrane Database of Systematic Reviews 2021, Issue 2. Art. No.: CD009593.

Xpert Ultra versus Xpert MTB/RIF for pulmonary tuberculosis and rifampicin resistance in adults with presumptive pulmonary tuberculosis

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Pulmonary tuberculosis detection	Xpert Ultra		Xpert MTB/RIF	
	Pooled sensitivity	Pooled specificity	Pooled sensitivity	Pooled specificity
PTB detection against culture	90.9% (86.2 to 94.7	95.6% (93.0 to 97.4)	84.7% (78.6 to 89.9	98.4% (97.0 to 99.3
Smear-negative, culture-positive participants	77.5% (67.6 to 85.6)	95.8% (92.9 to 97.7)	60.6% (48.4 to 71.7)	98.8% (97.7 to 99.5)
People living with HIV	87.6% (75.4 to 94.1)	92.8% (82.3 to 97.0)	74.9% (58.7 to 86.2)	99.7% (98.6 to 100.0)
Participants with a history of TB	84.2% (72.5 to 91.7)	88.2% (70.5 to 96.6)	81.8% (68.7 to 90.0)	97.4% (91.7 to 99.5)

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Xpert Ultra versus Xpert MTB/RIF for pulmonary tuberculosis and rifampicin resistance in adults with presumptive pulmonary tuberculosis

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Rifampicin resistance detection	Xpert Ultra		Xpert MTB/RIF	
	Pooled sensitivity	Pooled specificity	Pooled sensitivity	Pooled specificity
Rifampicin resistance detection	94.9% (88.9 to 97.9)	99.1% (97.7 to 99.8)	95.3% (90.0 to 98.1)	98.8% (97.2 to 99.6)
smear-positive specimens	93.9% (84.4 to 97.7)	99.3% (97.8 to 99.9)	95.5% (88.4 to 98.6)	99.1% (97.3 to 99.9)
smear-negative specimens	92.0% (75.0 to 95.8)	99.4% (96.2 to 100)	95.4% (82.3 to 99.3)	99.2% (94.8 to 100

Pooled proportion of indeterminate rifampicin resistance results for XpertUltra was 7.6% (2.4 to 21.0) & Xpert MTB/RIF was low, at 0.8% (0.2 to 2.4).

Cochrane Database of Systematic Reviews 2021, Issue 2. Art. No.: CD009593.

Xpert Ultra versus Xpert MTB/RIF for pulmonary tuberculosis and rifampicin resistance in adults with presumptive pulmonary tuberculosis

Figure 12. Forest plots of repeated Xpert Ultra sensitivity and specificity for detection of pulmonary tuberculosis in adults with initial trace result, culture reference standard. The squares represent the sensitivity and specificity of one study, the black line its confidence interval (CI). TP = true positive; FP = false positive; FN = false negative; TN = true negative

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Dorman 2018	9	10	4	9	0.69 [0.39, 0.91]	0.47 [0.24, 0.71]
Mishra 2020a	1	0	0	3	1.00 [0.03, 1.00]	1.00 [0.29, 1.00]
Piersimoni 2019	1	0	0	3	1.00 [0.03, 1.00]	1.00 [0.29, 1.00]

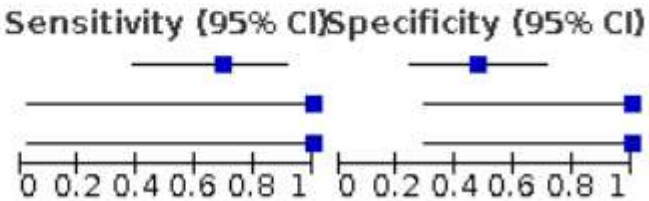

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Table 7. Selected systematic reviews on the diagnostic accuracy of Xpert Ultra and Xpert MTB/RIF for pulmonary tuberculosis and rifampicin resistance

Author, year (see descriptions of systematic reviews in footnotes)	Date searched up to	No. of studies (participants)	Test	Pulmonary tuberculosis, summary estimates (95% CI)*		No. of studies	Rifampicin resistance, summary estimates (95% CrI)*	
				Sensitivity	Specificity		Sensitivity	Specificity
Chang 2012	October 2011	15 (8117)	Xpert MTB/RIF	90% (89 to 91)	98% (98 to 99)	7	See footnote for this study	See footnote for this study
Walusimbi 2013 (smear-negative)	May 2012	15 (2046)	Xpert MTB/RIF	67% (62 to 71)	98% (97 to 99)	N/A	N/A	N/A
Steingart 2014	December 2013	27 (6026)	Xpert MTB/RIF	89% (85 to 92)	99% (98 to 99)	Sensitivity: 17 Specificity: 24	95% (90 to 97)	98% (97 to 99)
Yan 2016	Not reported	12 (8122)	Xpert MTB/RIF	89% (87 to 90)	98% (98 to 99)	N/A	N/A	N/A
Li 2017	June 2015	24 (2486)	Xpert MTB/RIF	87% (83 to 90)	97% (96 to 98)	N/A	N/A	N/A
Alvis-Zakzuk 2017	December 2015	N/A	Xpert MTB/RIF	N/A	N/A	8	See footnote for this study	See footnote for this study
Horne 2019	January 2018	85 (41,965)	Xpert MTB/RIF	85% (82 to 87)	98% (97 to 98)	48 (8020)	96% (94 to 97)	98% (98 to 99)
Zhang 2019	May 2019	10 (not reported)	Xpert Ultra	89% (82 to 94)	97% (95 to 98)	4 (856)	95% (92 to 97)	99% (98 to 100)
Jiang 2020	April 2020	19 (5855)	Xpert Ultra and Xpert MTB/RIF	Xpert MTB/RIF: 69% (57 to 78) Xpert Ultra: 84% (76 to 90)	Xpert MTB/RIF: 99% (98 to 99) Xpert Ultra: 97% (96 to 98)	N/A	N/A	N/A

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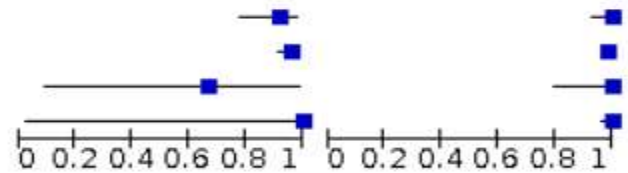
Figure 11. Forest plots of Xpert Ultra and Xpert MTB/RIF sensitivity and specificity for the detection of rifampicin resistance by smear status. The squares represent the sensitivity and specificity of one study, the black line its confidence interval (CI). TP = true positive; FP = false positive; FN = false negative; TN = true negative

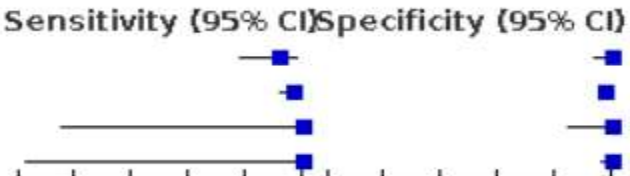
Xpert Ultra for detection of rifampicin resistance, smear-positive

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Chakravorty 2017	34	0	3	50	0.92 [0.78, 0.98]	1.00 [0.93, 1.00]
Dorman 2018	144	6	6	319	0.96 [0.91, 0.99]	0.98 [0.96, 0.99]
Mishra 2020b	2	0	1	16	0.67 [0.09, 0.99]	1.00 [0.79, 1.00]
Piersimoni 2019	1	0	0	104	1.00 [0.03, 1.00]	1.00 [0.97, 1.00]



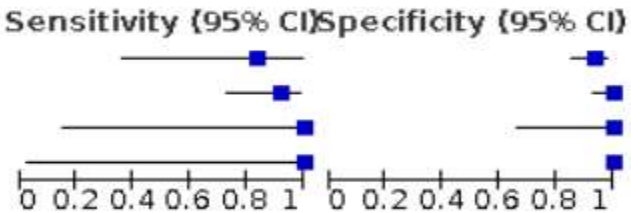
Xpert MTB/RIF for detection of rifampicin resistance, smear-positive

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Chakravorty 2017	34	0	3	57	0.92 [0.78, 0.98]	1.00 [0.94, 1.00]
Dorman 2018	145	7	5	319	0.97 [0.92, 0.99]	0.98 [0.96, 0.99]
Mishra 2020b	2	0	0	22	1.00 [0.16, 1.00]	1.00 [0.85, 1.00]
Piersimoni 2019	1	0	0	104	1.00 [0.03, 1.00]	1.00 [0.97, 1.00]



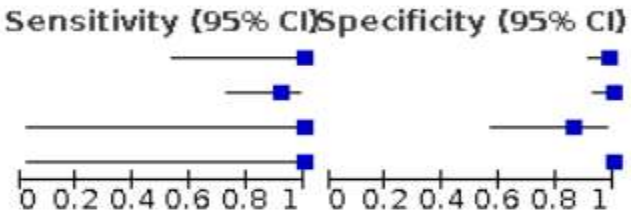
Xpert Ultra for detection of rifampicin resistance, smear-negative

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Chakravorty 2017	5	4	1	62	0.83 [0.36, 1.00]	0.94 [0.85, 0.98]
Dorman 2018	22	0	2	51	0.92 [0.73, 0.99]	1.00 [0.93, 1.00]
Mishra 2020b	2	0	0	9	1.00 [0.16, 1.00]	1.00 [0.66, 1.00]
Piersimoni 2019	1	0	0	253	1.00 [0.03, 1.00]	1.00 [0.99, 1.00]



Xpert MTB/RIF for detection of rifampicin resistance, smear-negative

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Chakravorty 2017	6	1	0	63	1.00 [0.54, 1.00]	0.98 [0.92, 1.00]
Dorman 2018	22	0	2	53	0.92 [0.73, 0.99]	1.00 [0.93, 1.00]
Mishra 2020b	1	2	0	12	1.00 [0.03, 1.00]	0.86 [0.57, 0.98]
Piersimoni 2019	1	0	0	253	1.00 [0.03, 1.00]	1.00 [0.99, 1.00]



Cochrane Database of Systematic Reviews 2021, Issue 2. Art. No.: CD009593.

Xpert MTB/XDR

- Xpert MTB/XDR detects mutations associated with resistance towards isoniazid , fluoroquinolones , second-line injectable drug (SLI) (amikacin, kanamycin, capreomycin) and ethionamide in a single test
- The test uses a semi quantitative nested PCR followed by high resolution melt technology
- Results are available in less than 90 minutes
- It can potentially improve access to rapid drug susceptibility testing, especially for ruling out fluoroquinolone resistance, which is required before starting the shorter oral Bedaquiline-containing MDR/RR-TB regimen

Cao Y, et al . J Clin Microbiol. 2021 Feb 18;59(3):e02314-20

Xpert MTB/XDR for detection of pulmonary tuberculosis and resistance to isoniazid, fluoroquinolones, ethionamide, and amikacin (Review)

Pillay S, Steingart KR, Davies GR, Chaplin M, De Vos M, Schumacher SG, Warren R, Theron G

- Aim – accuracy of Xpert MTB/XDR for detecting pulmonary tuberculosis and resistance to tuberculosis drugs (i.e. isoniazid, fluoroquinolones, ethionamide, and amikacin) in adults
- Method- Xpert MTB/XDR accuracy was assessed against three reference standards
- 2 multicentre studies reporting on 6 separate cohorts (groups of study participants), **1228** participants for pulmonary **tuberculosis detection** and **1141** participants for **drug resistance detection**

Cochrane Database of Systematic Reviews 2022, Issue 5. Art. No.: CD014841

Xpert MTB/XDR for detection of pulmonary tuberculosis and resistance to isoniazid, fluoroquinolones, ethionamide, and amikacin

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Xpert MTB/XDR	sensitivity	specificity	Against	Number
Pulmonary tuberculosis detection	98.3% (96.1 to 99.5) to 98.9% (96.2 to 99.9)	22.5% (14.3 to 32.6) to 100.0% (86.3 to 100.0	solid or liquid culture	1228
People irrespective of rifampicin resistance				
Isoniazid resistance	94.2% (87.5 to 97.4)	98.5% (92.6 to 99.7)	pDST	1083
Fluoroquinolone resistance	93.2% (88.1 to 96.2)	98.0% (90.8 to 99.6)	pDST	1021
People with known rifampicin resistance				
Ethionamide resistance	98.0% (74.2 to 99.9)	99.7% (83.5 to 100.0)	gDST	434
Amikacin resistance	86.1% (75.0 to 92.7)	98.9% (93.0 to 99.8)	pDST	490
Fluoroquinolone resistance irrespective of rifampicin resistance	93.2% (88.1 to 96.2)	98.0% (90.8 to 99.6)	pDST	1021

Cochrane Database of Systematic Reviews 2022, Issue 5. Art. No.: CD014841

Truenat real-time quantitative micro PCR system by Molbio

Molbio Diagnostics (Bangalore, India) developed three assays that utilise chip-based real-time micro PCR:

- **Two for detection of M. tuberculosis** (the **Truenat MTB** assay (including the nrdB single copy target) and the **MTB Plus assay** (including nrdZ and multicopy IS6110 targets) and
- One for the detection of RIF resistance (**the MTB-RIF Dx reflex assay** targeting the rpoB gene) .
- A point-of-care, cost-effective assay with higher performance and/or a robust, battery-operated assay with minimal operational requirements
- Could provide a viable alternative to Xpert and drive greater access for TB testing
- Both the devices are portable, battery operated, and can function at up to 40°C ambient temperature and up to 80% relative humidity

A prospective multicentre diagnostic accuracy study for the Truenat tuberculosis assays

Abstract

Background Bringing reliable and accurate tuberculosis (TB) diagnosis closer to patients is a key priority for global TB control. Molbio Diagnostics have developed the Truenat point-of-care molecular assays for detection of TB and rifampicin (RIF) resistance.

Methods We conducted a prospective multicentre diagnostic accuracy study at 19 primary healthcare centres and seven reference laboratories in Peru, India, Ethiopia and Papua New Guinea to estimate the diagnostic accuracy of the point-of-care Truenat MTB, MTB Plus and MTB-RIF Dx assays for pulmonary TB using culture and phenotypic drug susceptibility testing as the reference standard, compared with Xpert MTB/RIF or Ultra.

Results Of 1807 enrolled participants with TB signs/symptoms, 24% were culture-positive for *Mycobacterium tuberculosis*, of which 15% were RIF-resistant. In microscopy centres, the pooled sensitivity of Truenat MTB and Truenat MTB Plus was 73% (95% CI 67–78%) and 80% (95% CI 75–84%), respectively. Among smear-negative specimens, sensitivities were 36% (95% CI 27–47%) and 47% (95% CI 37–58%), respectively. Sensitivity of Truenat MTB-RIF was 84% (95% CI 62–95%). Truenat assays showed high specificity. Head-to-head comparison in the central reference laboratories suggested that the Truenat assays have similar performance to Xpert MTB/RIF.

Conclusion We found the performance of Molbio's Truenat MTB, MTB Plus and MTB-RIF Dx assays to be comparable to that of the Xpert MTB/RIF assay. Performing the Truenat tests in primary healthcare centres with very limited infrastructure was feasible. These data supported the development of a World Health Organization policy recommendation of the Molbio assays.

Eur Respir J 2021; 58: 2100526

A prospective multicentre diagnostic accuracy study for the Truenat tuberculosis assays

TABLE 2 Performance of Truenat assays for tuberculosis and for rifampicin resistance detection at the primary healthcare centre (microscopy centre) and the reference laboratory

	N	True positive	False positive	False negative	True negative	Sensitivity % (95% CI)	Sensitivity % smear-positive (95% CI)	Sensitivity % smear-negative (95% CI)	Specificity % (95% CI)
Microscopy centre sputum									
Truenat MTB	1356	192	25	71	1068	73.0 (67.3–78.0)	91.0 (85.8–94.4) (n=177)	36.0 (26.7–46.6) (n=86)	97.7 (96.7–98.5)
Truenat MTB Plus	1356	210	40	53	1053	79.8 (74.6–84.2)	96.0 (92.1–98.1) (n=177)	46.5 (36.4–57.0) (n=86)	96.3 (95.1–97.3)
Truenat MTB-RIF Dx	190	16	9	3	162	84.2 (62.4–94.5)	87.5 (64.0–96.5) (n=16)	66.7 (20.8–93.8) (n=3)	94.7 (90.3–97.2)
Reference laboratory sputum									
Truenat MTB	1541	275	27	71	1168	79.5 (74.9–83.4)	95.8 (92.4–97.7) (n=236)	44.5 (35.6–53.9) (n=110)	97.7 (96.7–98.4)
Truenat MTB Plus	1541	295	51	51	1144	85.3 (81.1–88.6)	98.3 (95.7–99.3) (n=236)	57.3 (47.9–66.1) (n=110)	95.7 (94.4–96.7)
Truenat MTB-RIF Dx	332	44	9	8	271	84.6 (72.5–92.0)	86.7 (73.8–93.7) (n=45)	71.4 (35.9–91.8) (n=7)	96.8 (94.0–98.3)

Eur Respir J 2021; 58: 2100526

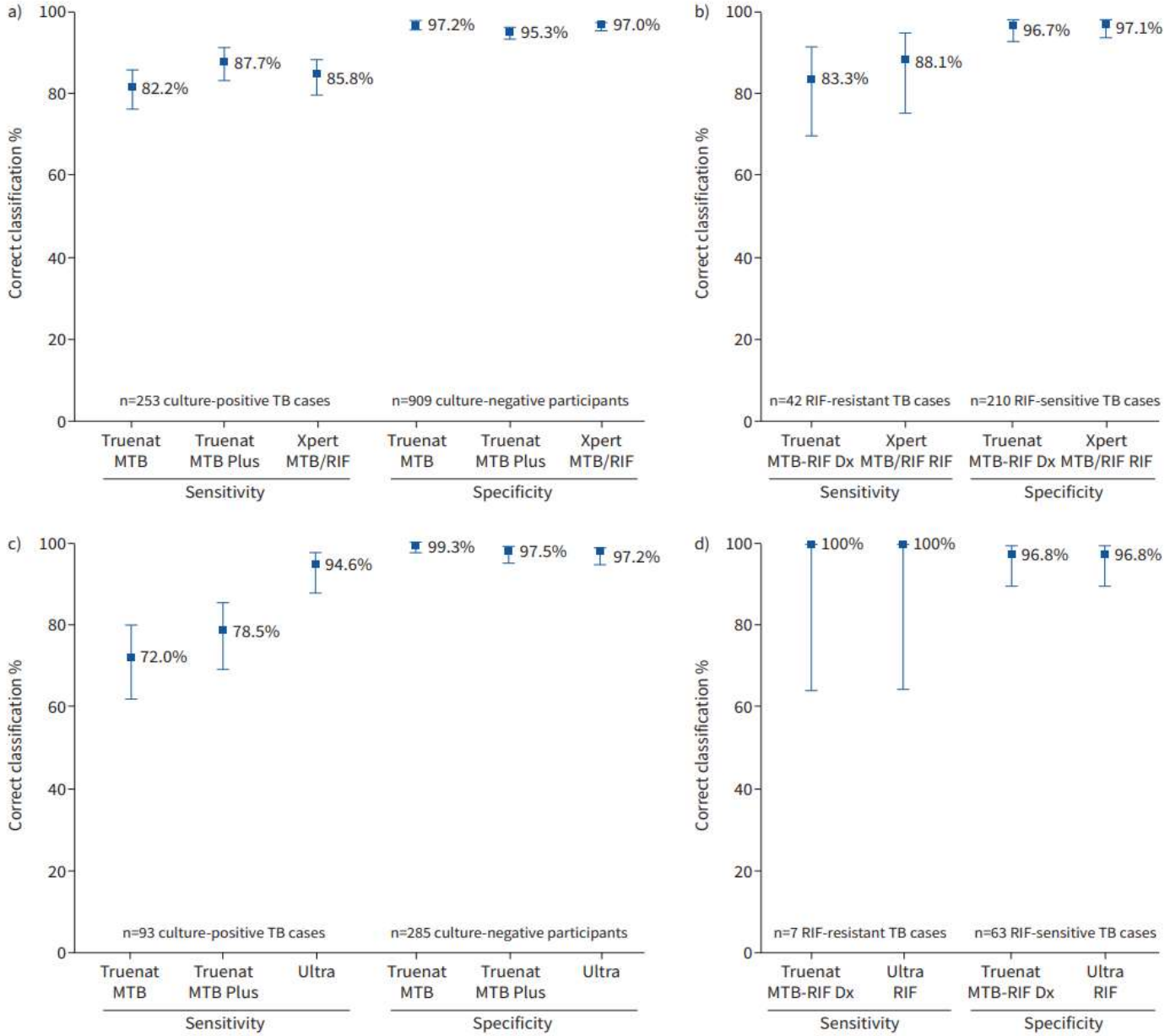
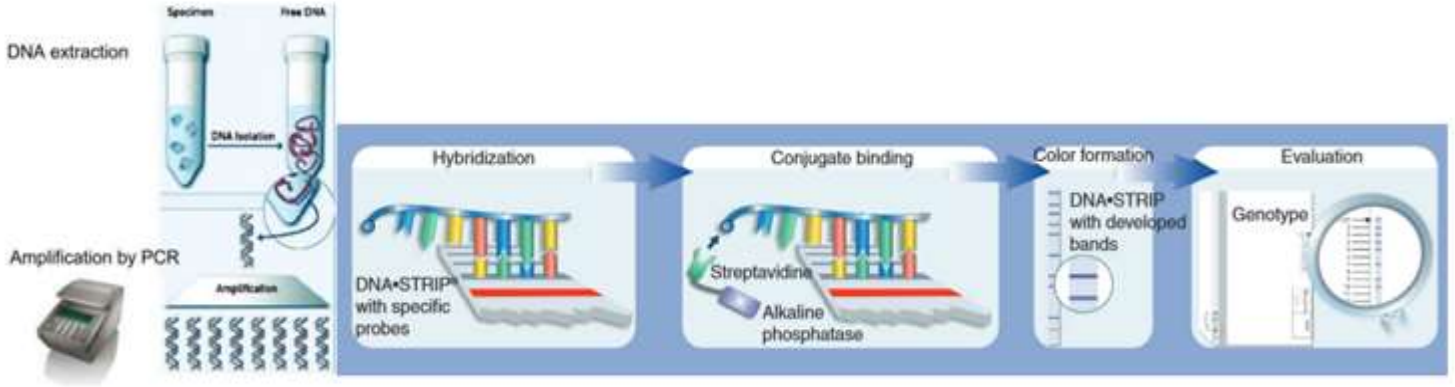


FIGURE 3 Performance of the Truenat, Xpert MTB/RIF and Ultra assays conducted at the reference laboratories. TB: tuberculosis; RIF: rifampicin. a) Performance of Truenat and Xpert MTB/RIF for TB detection (participants from Case Detection Group). b) Performance of Truenat and Xpert MTB/RIF for RIF resistance detection (all participants). c) Performance of Truenat and Ultra for TB detection (participants from Case Detection Group). d) Performance of Truenat and Ultra for RIF resistance detection (all participants).

Eur Respir J 2021; 58: 2100526

LPA



- LPA uses PCR and reverse hybridization methods for detection of mutation associated with drug resistance
- Frist line LPA detects mutations in the rpoB gene for R resistance; in the KatG gene and the InhA promoter region for H [and ethionamide (Eto)] resistance
- second line LPA detects mutations in genes gyrA & gyr B for FQ resistance and rrs and eis (low level kanamycin resistance) for SLID resistance

LPA

- Results of LPA are interpreted based on development/ absence of Wild Type (WT) and Mutant (MUT) bands.
- **Resistance not detected** -When **all WT probes** in the regions of the gene known to confer resistance to the drug are **developed** and **none** of the **MUT probes** in the corresponding region are developed
- **Resistance inferred-** whenever **one or more WT probes** in regions of the gene known to confer resistance to the drug are **not developed** and **none** of the **MUT probes** in the corresponding region are developed
- **Resistance detected-**is used whenever **one or more MUT probes** identifying specific mutations conferring resistance to the drugs are **developed**; regardless of whether WT probes are developed or not

Table 3.1: LPA results and their clinical interpretation for programmatic use

Drug	Gene	Test results	Clinical interpretation
Rifampicin	rpoB	Resistance inferred or detected	R is not effective
Isoniazid	katG	Resistance to high level H inferred or detected	H is unlikely to be effective even at high dose
	InhA	Resistance to low level H inferred or detected	H at high dose is likely effective. Eto/Pto are not effective
Fluoroquinolones	gyrA	Resistance to Lfx and low level Mfx inferred Resistance to Lfx and low level Mfx detected	Lfx is not effective. Mfx could be used at higher dose. The regimen should be reevaluated based on phenotypic DST results to Mfx at clinical breakpoint
		Resistance Lfx and high level Mfx detected (MUT 3B, MUT 3C, MUT 3D)	Lfx / Mfx is not effective
	gyrB	Resistance to Lfx and low level Mfx inferred Resistance to Lfx and low level Mfx detected	Lfx is not effective. Mfx could be used at higher dose. The regimen should be re-evaluated based on phenotypic DST results to Mfx at clinical breakpoint.
Second-line injectable drugs	rrs	Resistance inferred or detected	Am, Km and Cm are not effective
		Resistance to Am inferred (mutation at 1402)	Km and Cm are likely not effective. Phenotypic DST result should guide the choice to use Am in the treatment regimen
	eis	Resistance inferred or detected	Am and Cm are likely effective. Km is not effective

PMDT 2021

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Systematic evaluation of line probe assays for the diagnosis of tuberculosis and drug-resistant tuberculosis

Background: Line probe assays (LPAs) are PCR-based assays used for the rapid diagnosis of *Mycobacterium tuberculosis* (MTB) and drug-resistant tuberculosis (DR-TB). But studies on its performance are insufficient. Thus, in this study, we conducted a systematic review and meta-analysis to evaluate the effect of LPAs in the detection of MTB and drug-resistant TB in comparison with the traditional culture and DST methods.

Methods: A systemic literature search was conducted on the Web of Science, Embase, PubMed, the Cochrane Library, Scopus, and OVID databases. All the included studies were classified according to different detecting objects. Sensitivity, specificity, Positive Likely Ratio (PLR), Negative Likely Ratio (NLR), Diagnostic Odds Ratio (DOR), corresponding 95% confidence interval, Area Under Curve (AUC), Deeks' funnel plot, and Bivariate Boxplot was used to do the evaluation.

Results: 147 studies included 491 datasets, with 182,448 samples, were incorporated into our analysis. The sensitivity (95% CI), specificity (95% CI), PLR, NLR, DOR and AUC for MTB were 0.89 (0.86 to 0.92), 0.94 (0.90 to 0.97), 15.70, 0.11, 139 and 0.96, respectively; for rifampicin-resistant TB were 0.96 (0.95 to 0.97), 0.99 (0.98 to 0.99), 82.9, 0.04, 1994 and 1.00, respectively; for isoniazid-resistant TB were 0.91 (0.89 to 0.93), 0.99 (0.98 to 0.99), 83.4, 0.09, (0.99 to 1.00), 195.7, 0.07, 2783 and 1.00, respectively; for Multi-drug resistant TB (MDR-TB) were 0.93 (0.90 to 0.95), 1.00 (0.99 to 1.00), 195.7, 0.07, 2783 and 1.00, respectively; for extensively drug-resistant TB (XDR-TB) were 0.60 (0.33 to 0.82), 1.00 (0.95 to 1.00), 291.3, 0.4, 726 and 0.95, respectively; for (second-line drug-resistant TB) SLID-TB were 0.83 (0.78 to 0.87), 0.98 (0.97 to 0.99), 44.6, 0.17, 262 and 0.98, respectively. Sensitivity in pre-extensively drug-resistant TB (Pre-XDR-TB) was 0.67, specificity was 0.91. No publication bias existed according to Deeks' funnel plot.

Conclusion: High diagnosis performance was confirmed in LPAs for the diagnosis of MTB and drug-resistant TB. LPAs might be a good alternative to culture and DST in detecting MTB, RR-TB, INH-TB, XDR-TB, SLID-TB, and MDR-TB. While more studies were still needed to explore the diagnosis performance of LPAs for Pre-XDR TB.

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Systematic evaluation of line probe assays for the diagnosis of tuberculosis and drug-resistant tuberculosis

Subgroup of types of TB.

Results	TB					RIF-resistant TB					INH-resistant TB					MDR-TB				SLID-TB		
	PTB [a]	EPTB [b]	Smear Positive TB [c]	Smear Negative TB [d]	Mix [e]	PTB	EPTB	Smear Positive TB	Smear Negative TB	Mix [e]	PTB	EPTB	Smear Positive TB	Smear Negative TB	Mix [e]	PTB	EPTB	Smear Positive TB	Mix [e]	PTB	Smear Positive TB	Mix [e]
Numbers of datasets	2	5	12	4	50	9	6	25	3	88	7	3	23	3	81	1	2	8	31	7	13	98
Sensitivity	0.85	0.77	0.93	0.79	0.9	0.96	0.91	0.96	0.95	0.96	0.88	0.91	0.88	0.79	0.92	1	0.97	0.95	0.92	0.44	0.71	0.86
Septicity	0.76	0.81	0.97	0.98	0.94	0.96	0.98	0.99	0.97	0.99	0.98	0.96	0.99	0.98	0.99	0.98	0.99	1	0.99	0.98	0.99	0.98
Positive LR	5.02	6.10	64.05	/	16.03	54.88	61.5	183.45	47.76	82.83	50.1	34.29	70.79	57.83	122.35	50	778.8	/	185.92	88.79	114.18	46.59
Negative LR	0.21	0.28	0.07	/	0.11	0.05	0.09	0.04	0.06	0.04	0.12	0.09	0.12	0.21	0.08	0	0.03	0.06	0.08	0.58	0.30	0.14

Subgroup of types of LPAs.

Results	TB					RIF-resistant TB					INH-resistant TB
	MTBDRplus	MTBDRsl	MTBDR	INNO-LiPA Rif. TB	LPAs	MTBDRplus	MTBDRsl	MTBDR	INNO-LiPA Rif. TB	LPAs	MTBDRplus
Numbers of datasets	39	12	10	11	2	91	13	20	6	1	19
Sensitivity	0.88	0.90	0.92	0.89	0.82	0.96	0.91	0.98	0.94	1.00	0.94
Septicity	0.93	0.95	0.94	0.93	0.92	0.99	0.99	0.98	0.98	1.00	0.99
Positive LR	15.73	28.59	26.70	17.17	12.38	88.04	104.39	68.17	316.63	/	164.35
Negative LR	0.12	0.10	0.08	0.11	0.20	0.04	0.09	0.02	0.06	/	0.06

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Growth-based drug susceptibility testing (DST) (phenotypic tests)

- **Liquid culture -BACTEC MGIT 960**
  - Automated Liquid Culture System
  - Higher rate of MTB isolation
  - Requires a shorter turnaround time
  - MGIT is the preferred method for DST
  - Used to monitor response to treatment
  - Long-term follow-up of patients on DR TB treatment
- **Solid culture (Lowenstein–Jensen)**
  - Longer turnaround time
  - Due to the higher rate of contamination in liquid culture, an LJ slope is inoculated as a backup for every MGIT culture

Genetic sequencing

- Resistance in MTB is mainly conferred through point mutations in specific gene targets
- Targeted sequencing can be achieved through Pyrosequencing, Sanger sequencing as well as Next-generation sequencing (NGS)
- NGS technology have enabled the routine use of NGS for both targeted NGS and WGS of Mycobacterium tuberculosis complex (MTBC) samples
- WGS can provide the near complete genome of Mycobacterium tuberculosis (MTB)
- Targeted NGS can generate MTB sequence data at specific genetic loci of interest
- NGS offers great promise for rapid diagnosis of DR-TB

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Value of routine whole genome sequencing for *Mycobacterium tuberculosis* drug resistance detection

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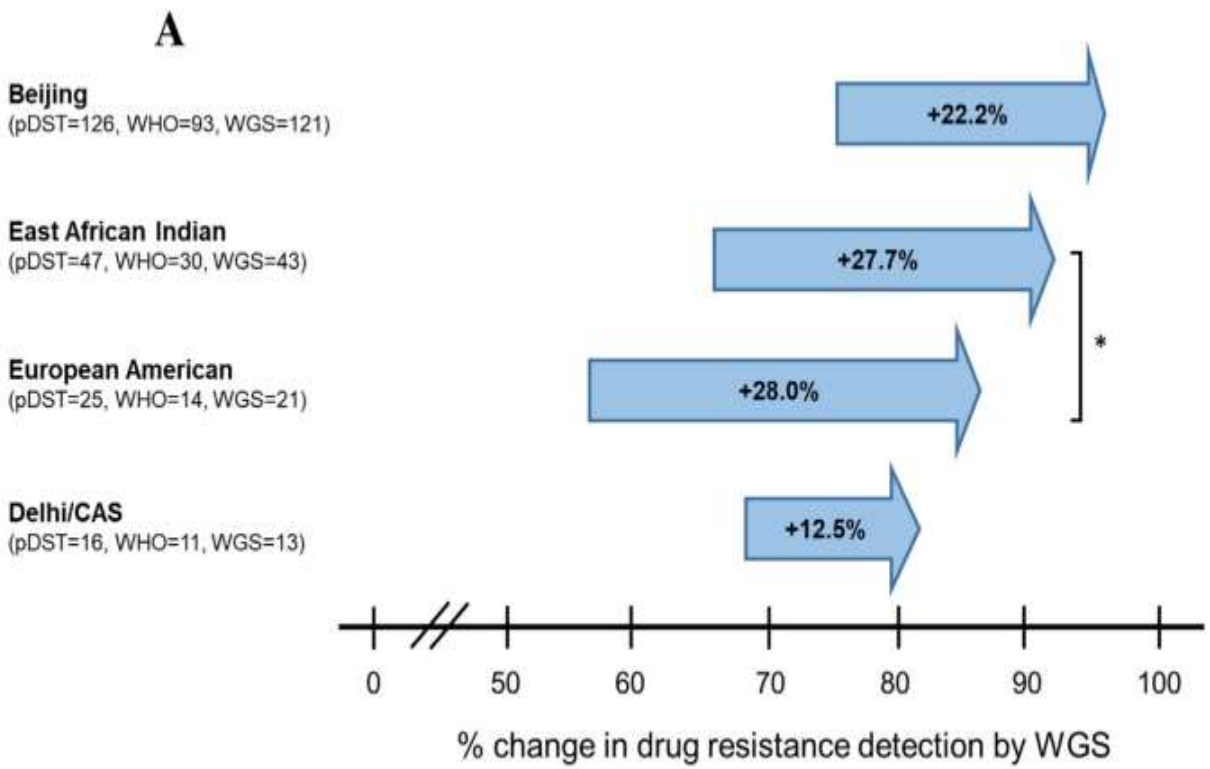
ABSTRACT

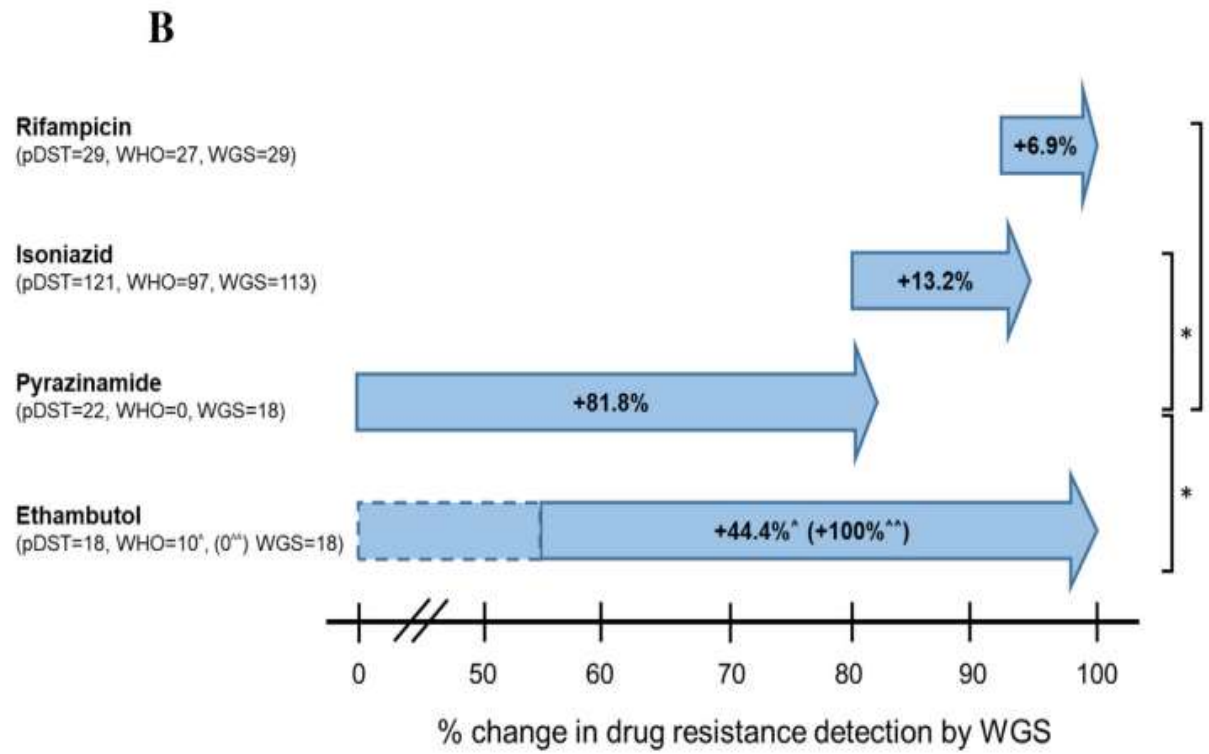
Routine whole genome sequencing (WGS) of pathogens is becoming more feasible as sequencing costs decrease and access to benchtop sequencing equipment and bioinformatics pipelines increases. This study examined the added value gained from implementing routine WGS of all *Mycobacterium tuberculosis* isolates in New South Wales, Australia.

Drug resistance markers inferred from WGS data were compared to commercial genotypic drug susceptibility testing (DST) assays and conventional phenotypic DST in all isolates sequenced between 2016 and 2019. Of the 1107 clinical *M. tuberculosis* isolates sequenced, 29 (2.6%) were multi-drug resistant (MDR); most belonged to Beijing (336; 30.4%) or East-African Indian (332; 30%) lineages. Compared with conventional phenotypic DST, WGS identified an additional 1% of isolates which were likely drug resistant, explained by mutations previously associated with treatment failure and mixed bacterial populations. However, WGS provided a 20% increase in drug resistance detection in comparison with commercial genotypic assays by identifying mutations outside of the classic resistance determining regions in *rpoB*, *inhA*, *katG*, *pncA* and *embB* genes. Gains in drug resistance detection were significant ($p = 0.0137$, paired *t*-test), but varied substantially for different phylogenetic lineages.

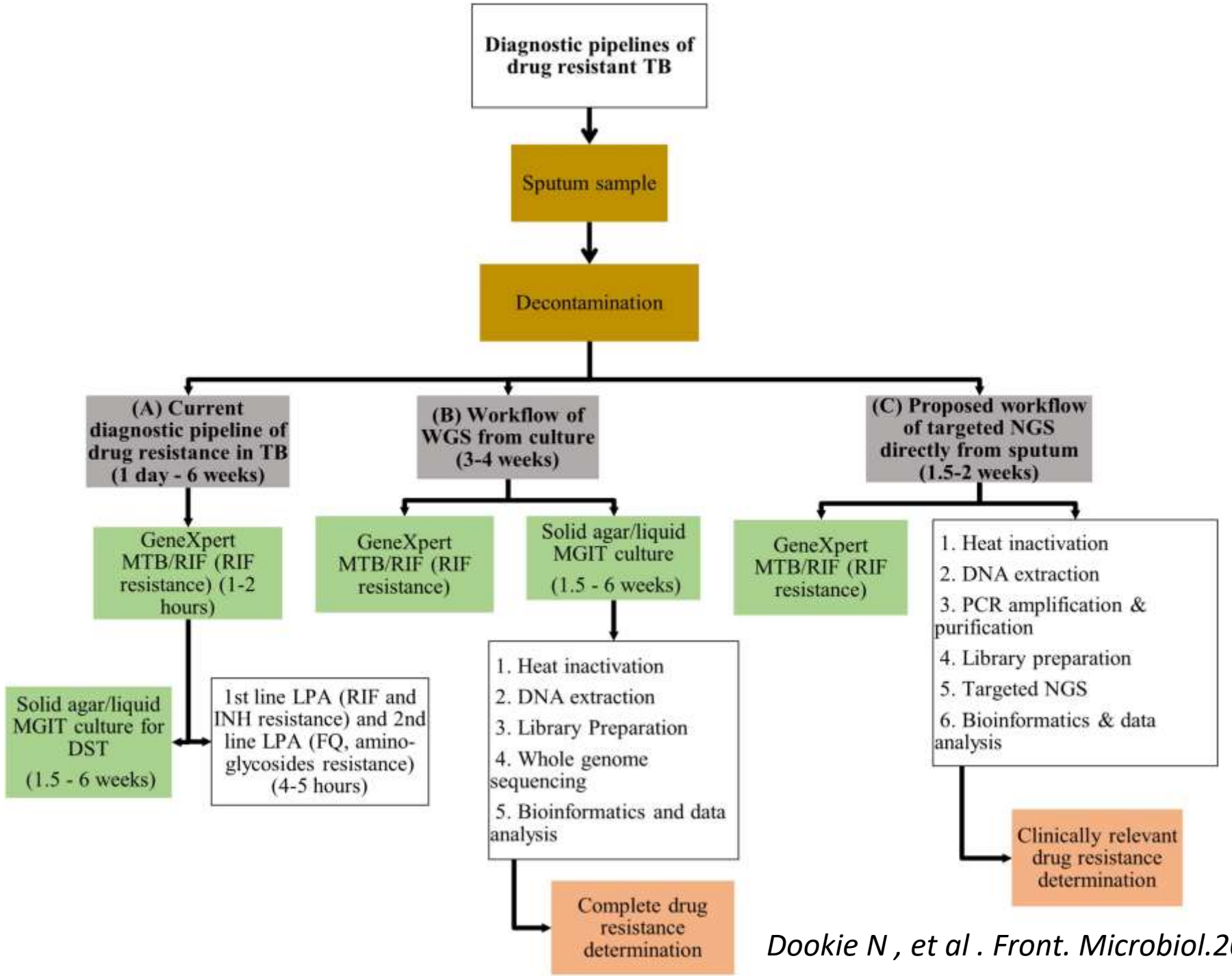
In low incidence settings, routine WGS of *M. tuberculosis* provides better guidance for person-centered management of drug resistant tuberculosis than commercial genotypic assays.

Value of routine whole genome sequencing for *Mycobacterium tuberculosis* drug resistance detection





C. Lam et al. International Journal of Infectious Diseases 113S (2021) S48–S54



Dookie N , et al . Front. Microbiol.2022 , 13:775030

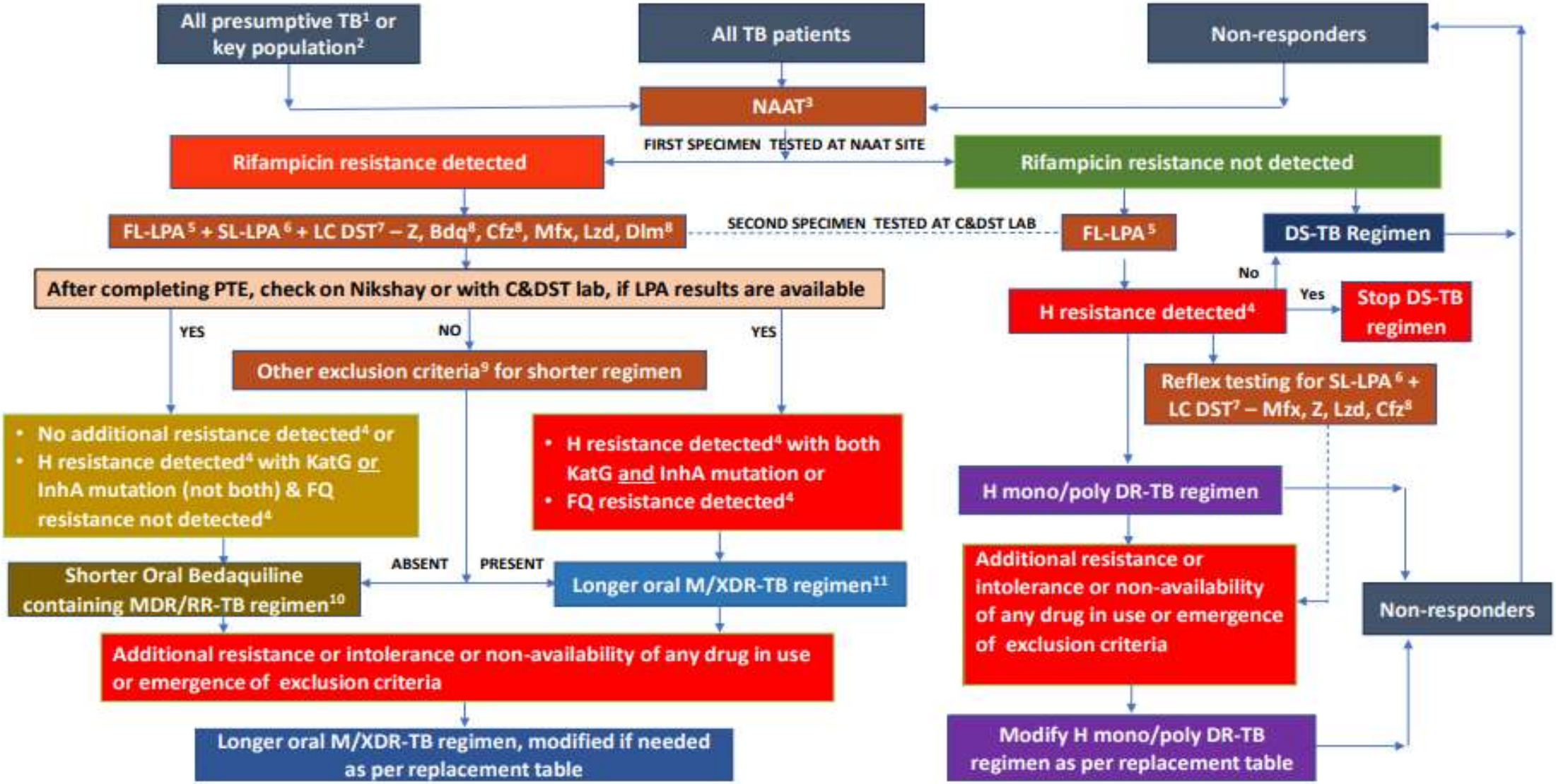
Treatment of MDR TB

Medicine		Treatment failure or relapse versus treatment success		Death versus treatment success	
		Number treated	Adjusted odds ratio (95% confidence limits)	Number treated	Adjusted odds ratio (95% confidence limits)
A	Levofloxacin *OR* moxifloxacin	3 143	0.3 (0.1–0.5)	3 551	0.2 (0.1–0.3)
	Bedaquiline	1 391	0.3 (0.2–0.4)	1 480	0.2 (0.2–0.3)
	Linezolid	1 216	0.3 (0.2–0.5)	1 286	0.3 (0.2–0.3)
B	Clofazimine	991	0.3 (0.2–0.5)	1 096	0.4 (0.3–0.6)
	Cycloserine *OR* terizidone	5 483	0.6 (0.4–0.9)	6 160	0.6 (0.5–0.8)
C	Ethambutol	1 163	0.4 (0.1–1.0)	1 245	0.5 (0.1–1.7)
	Delamanid	289	1.1 (0.4–2.8)*	290	1.2 (0.5–3.0)*
	Pyrazinamide	1 248	2.7 (0.7–10.9)	1 272	1.2 (0.1–15.7)
	Imipenem–cilastatin *OR* meropenem	206	0.4 (0.2–0.7)	204	0.2 (0.1–0.5)
	Amikacin	635	0.3 (0.1–0.8)	727	0.7 (0.4–1.2)
	Streptomycin	226	0.5 (0.1–2.1)	238	0.1 (0.0–0.4)
	Ethionamide *OR* prothionamide	2 582	1.6 (0.5–5.5)	2 750	2.0 (0.8–5.3)
	p-aminosalicylic acid	1 564	3.1 (1.1–8.9)	1 609	1.0 (0.6–1.6)
Other medicines	Kanamycin	2 946	1.9 (1.0–3.4)	3 269	1.1 (0.5–2.1)
	Capreomycin	777	2.0 (1.1–3.5)	826	1.4 (0.7–2.8)
	Amoxicillin–clavulanic acid	492	1.7 (1.0–3.0)	534	2.2 (1.3–3.6)

WHO consolidated guideline on tuberculosis Module 4: Treatment – Drug resistant TB treatment June 2020

Table 4.1: Grouping of anti-TB drugs and steps for designing longer MDR-TB regimen

GROUPS & STEPS	MEDICINE	ABBREVIATION
Group A **Include all three medicines**	Levofloxacin or	Lfx
	Moxifloxacin	Mfx
	Bedaquiline	Bdq
	Linezolid	Lzd
Group B **Add one or both medicines**	Clofazimine	Cfz
	Cycloserine or	Cs
	Terizidone	Trd
Group C **Add to complete the regimen and when medicines from Group A and B cannot be used**	Ethambutol	E
	Delamanid	Dlm
	Pyrazinamide	Z
	Imipenem-cilastatin or	Ipm-Cln
	Meropenem	Mpm
	Amikacin	Am
	(OR Streptomycin)	(S)
	Ethionamide or	Eto
	Prothionamide	Pto
	p-aminosalicylic acid	PAS


All presumptive TB[1] or key population[2]
All TB patients
Non-responders
NAAT[3]
FIRST SPECIMEN TESTED AT NAAT SITE
Rifampicin resistance detected
Rifampicin resistance not detected
FL-LPA[5] + SL-LPA[6] + LC DST[7] – Z, Bdq[8], Cfz[8], Mfx, Lzd, Dlm[8]
SECOND SPECIMEN TESTED AT C&DST LAB
FL-LPA[5]
DS-TB Regimen
After completing PTE, check on Nikshay or with C&DST lab, if LPA results are available
No
Yes
H resistance detected[4]
Stop DS-TB regimen
YES
NO
YES
Other exclusion criteria[9] for shorter regimen
Reflex testing for SL-LPA[6] + LC DST[7] – Mfx, Z, Lzd, Cfz[8]
• No additional resistance detected[4] or
• H resistance detected[4] with KatG or InhA mutation (not both) & FQ resistance not detected[4]
• H resistance detected[4] with both KatG and InhA mutation or
• FQ resistance detected[4]
H mono/poly DR-TB regimen
ABSENT
PRESENT
Shorter Oral Bedaquiline containing MDR/RR-TB regimen[10]
Longer oral M/XDR-TB regimen[11]
Additional resistance or intolerance or non-availability of any drug in use or emergence of exclusion criteria
Non-responders
Additional resistance or intolerance or non-availability of any drug in use or emergence of exclusion criteria
Longer oral M/XDR-TB regimen, modified if needed as per replacement table
Modify H mono/poly DR-TB regimen as per replacement table

PMDT 2021

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Treatment of Highly Drug-Resistant Pulmonary Tuberculosis

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STUDY	Intervention	Outcomes	Results
• Nix-TB Trial • Open-label, single-group study • 3 South African sites • XDR and with MDR tuberculosis patients that not responsive to treatment or for which a second-line regimen had been discontinued because of side effects • N=109	Orally administered treatment as- **bedaquiline** at a dose of 400 mg once daily for 2 weeks followed by 200 mg three times a week for 24 weeks, plus **pretomanid** at a dose of 200 mg daily for 26 weeks and **linezolid** at a dose of 1200 mg daily for up **to 26 weeks** (with dose adjustment depending on the toxic effects)	• The primary end point was the incidence of an **unfavorable outcome**, defined as treatment failure (bacteriologic or clinical) or disease relapse until 6 months after the end of treatment • Secondary end points included the time to an unfavorable outcome and the time to sputum culture conversion through the treatment period	• 11 patients **(10%)** had an unfavorable outcome and 98 patients (**90**%; 95% CI, 83 to 95) had a favorable outcome • 11 unfavorable (7 deaths , 1 withdrawal of consent , 2 relapse , 1 lost to follow up). • The expected linezolid toxic effects of **peripheral neuropathy** (81% of patients) and **myelosuppression** (48%).

N Engl J Med 2020;382:893-902

ORIGINAL ARTICLE

Bedaquiline–Pretomanid–Linezolid Regimens for Drug-Resistant Tuberculosis

STUDY	Intervention	Outcomes	Results
• ZeNix • Partially blind, randomized trial • Pulmonary **(XDR)**, **pre-XDR**, or **rifampin-resistant TB** that was not responsive to treatment or for which a second-line regimen had been discontinued because of side effects • 4 trial sites in South Africa, 1 in of Georgia,1 in Moldova, and 5 in Russia • **N= 181**	participants were randomly assigned, in a 1:1:1:1 ratio, to **one of the four** linezolid regimens (**either 1200 mg or 600 mg daily for either 26 weeks or 9 weeks**) + all participants received 26 weeks of **bedaquiline** (200 mg daily for 8 weeks, followed by 100 mg daily for 18 weeks) and **pretomanid** (200 mg daily for 26 weeks).	• The primary end point - the incidence of an **unfavorable outcome**, defined as treatment failure or disease relapse (clinical or bacteriologic) at **26 weeks** after completion of treatment • Secondary end points- included bacteriologic or clinical treatment failure and relapse at **78 weeks** after the end of treatment and time to sputum **culture conversion**	• Among with linezolid at a dose of 1200 mg for 26 weeks or 9 weeks or 600 mg for 26 weeks or 9 weeks, 93%, 89%, **91**%, and 84%, respectively, had a **favorable outcome** • **Peripheral neuropathy** occurred in 38%, 24%, 24%, and 13%, respectively; • **Myelosuppression** occurred in 22%, 15%, 2%, and 7%, respectively; **linezolid dose was modified** (in 51%, 30%, 13%, and 13%, respectively

N Engl J Med 2022;387:810-23.

ZeNix Trial

A 600-mg, 26-week regimen of linezolid appeared to have the most favorable risk–benefit profile among the regimens studied

Table 3. Safety Analysis.*

Variable	Bedaquiline–Pretomanid–Linezolid Regimen				Total (N=181)
	Linezolid, 1200 mg, 26 wk (N=45)	Linezolid, 1200 mg, 9 wk (N=46)	Linezolid, 600 mg, 26 wk (N=45)	Linezolid, 600 mg, 9 wk (N=45)	
	number of participants (percent)				
≥1 Grade 3 or higher adverse event	14 (31)	11 (24)	9 (20)	11 (24)	45 (25)
≥1 Serious adverse event	3 (7)	4 (9)	1 (2)	3 (7)	11 (6)
Death from any cause	0	1 (2)	0	0	1 (1)
Tuberculosis-related death	0	0	0	0	0
≥1 Episode of optic neuropathy†‡	4 (9)	0	0	0	4 (2)
≥1 Episode of peripheral neuropathy‡§	17 (38)	11 (24)	11 (24)	6 (13)	45 (25)
Severity of event in participants with ≥1 episode of peripheral neuropathy§¶					
Grade 1	10 (22)	7 (15)	10 (22)	6 (13)	33 (18)
Grade 2	7 (16)	4 (9)	1 (2)	0	12 (7)
≥1 Episode of myelosuppression‖	10 (22)	7 (15)	1 (2)	3 (7)	21 (12)
Hemoglobin level					
<8 g/dl and below baseline level	0	1 (2)	0	0	1 (1)
<25% below baseline level	9 (20)	4 (9)	0	0	13 (7)
Absolute neutrophil count <750/mm³ and below baseline level	1 (2)	3 (6)	1 (2)	3 (7)	8 (4)
Platelet count <50,000/mm³ and below baseline level	0	0	0	0	0
Liver-related serious adverse event	0	1 (2)	1 (2)	1 (2)	3 (2)
QTcF interval >60 msec above baseline value	0	2 (4)	0	1 (2)	3 (2)
Maximum QTcF interval ≥500 msec	0	1 (2)	0	1 (2)	2 (1)
Any interruption, dose reduction, or discontinuation of linezolid	23 (51)	14 (30)	6 (13)	6 (13)	49 (27)

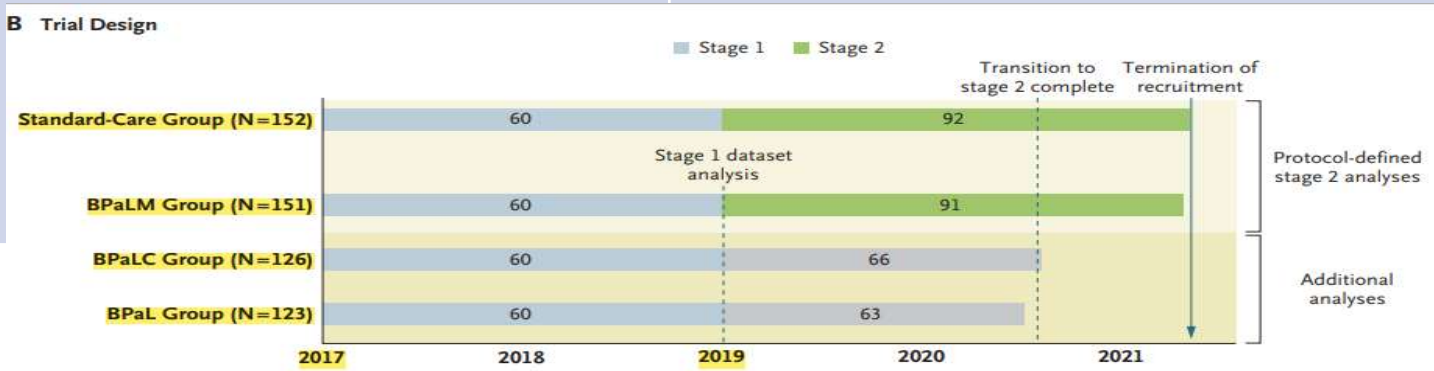
N Engl J Med 2022;387:810-23.

ORIGINAL ARTICLE

A 24-Week, All-Oral Regimen for Rifampin-Resistant Tuberculosis

TB-PRACTECAL study

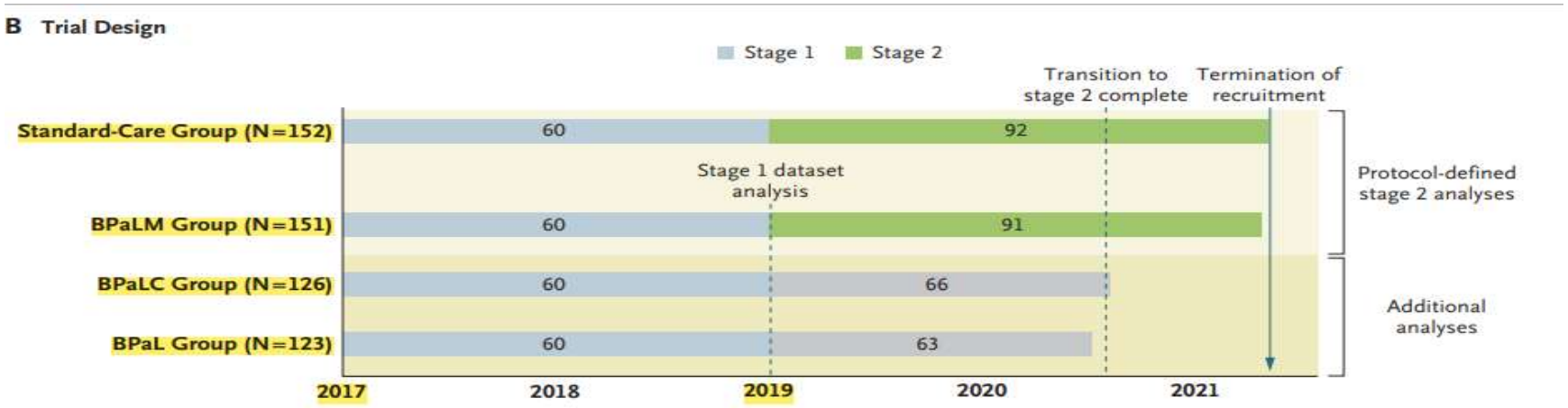
STUDY	Intervention	Regimens
• Open-label, phase 2–3, multicenter, randomized, controlled **noninferiority trial** • Aim- to compare the safety and efficacy of **three investigational 24-week regimens** with those of the **accepted 9-to-20-month** standard-care treatment for **rifampin-resistant pulmonary tuberculosis**	• In stage 1 of the trial, enrolled patients were randomly assigned to the locally accepted standard-care treatment or to one of three investigational regimens • In stage 2 of the trial patients were enrolled either into the standard-care group or into one of two investigational groups. • **N=522**	• **The BPaL** -bedaquiline at a dose of 400 mg daily for 2 weeks, followed by 200 mg three times per week for 22 weeks; pretomanid at a dose of 200 mg daily for 24 weeks; and linezolid at a dose of 600 mg daily for 16 weeks, followed by 300 mg daily for 8 weeks. • **The BPaLM** regimen included BPaL plus moxifloxacin at a dose of 400 mg daily for 24 weeks, • **BPaLC regimen** included BPaL plus clofazimine at a dose of 100 mg daily (or 50 mg if the patient weighed <30 kg)



N Engl J Med 2022;387:2331-43.

TB-PRACTECAL study

- In stage 1 of the trial, the percentages of patients with culture conversion in liquid medium at 8 weeks after randomization were **77%, 67%, and 46%** in the **BPaLM, BPaLC, and BPaL** groups, respectively ; **8%, 6%, and 10%** of the patients, respectively, discontinued treatment or died.
- The BPaLM regimen was selected for analysis in stage 2 of the trial.



TB-PRACTECAL study

Table 2. Primary Efficacy Analysis at 72 Weeks.

Variable	Intention-to-Treat Population		Modified Intention-to-Treat Population		Per-Protocol Population*	
	Standard-Care Group (N=73)	BPaLM Group (N=72)	Standard-Care Group (N=66)	BPaLM Group (N=62)	Standard-Care Group (N=33)	BPaLM Group (N=57)
Favorable outcome — no. (%)	34 (47)	55 (76)	34 (52)	55 (89)	29 (88)	55 (96)
Primary outcome: unfavorable status — no. (%)	39 (53)	17 (24)	32 (48)	7 (11)	4 (12)	2 (4)
Death — no. (%)	2 (3)	0	2 (3)	0	2 (6)	0
Early discontinuation — no. (%)	35 (48)	15 (21)	28 (42)	5 (8)	—	—
Adherence issues — no./total no. (%)	3/35 (9)	0	3/28 (11)	0	—	—
Adverse event — no./total no. (%)	17/35 (49)	5/15 (33)	17/28 (61)	5/5 (100)	—	—
Did not meet inclusion or exclusion criteria, detected after first dose — no./total no. (%)	7/35 (20)	10/15 (67)	0	0	—	—
Withdrew consent while still receiving treatment — no./total no. (%)	6/35 (17)	0	6/28 (21)	0	—	—
Other reason — no./total no. (%)†	2/35 (6)	0	2/28 (7)	0	—	—
Treatment failure — no.	0	0	0	0	0	0
Lost to follow-up at 72 wk — no. (%)	2 (3)	2 (3)	2 (3)	2 (3)	2 (6)	2 (4)
Recurrence — no.	0	0	0	0	0	0
Risk difference for the primary outcome — percentage points (96.6% CI)‡	—	−30 (−46 to −14)	—	−37 (−53 to −22)	—	−9 (−22 to 4)

BPAL plus moxifloxacin (BPaLM) resulted in superior cure rates compared to the longer WHO standard of care regimen (**89% vs 52%)** with less toxicity (**20% vs 59%)**

MITT population, 78 of 99 patients in the standard-care group **(79%)** and 85 of 96 patients in the BPaLM group **(88%)** had culture conversion at **12 weeks**

N Engl J Med 2022;387:2331-43.

Table 3. Outcomes at 72 Weeks in the Standard-Care, BPaLC, and BPaL Groups.*

Variable	Intention-to-Treat Population			Modified Intention-to-Treat Population			Per-Protocol Population		
	Standard-Care Group (N=73)	BPaLC Group (N=72)	BPaL Group (N=70)	Standard-Care Group (N=66)	BPaLC Group (N=64)	BPaL Group (N=60)	Standard-Care Group (N=33)	BPaLC Group (N=58)	BPaL Group (N=52)
Favorable outcome — no. (%)	34 (47)	52 (72)	46 (66)	34 (52)	52 (81)	46 (77)	29 (88)	52 (90)	46 (88)
Primary outcome: unfavorable status — no. (%)	39 (53)	20 (28)	24 (34)	32 (48)	12 (19)	14 (23)	4 (12)	6 (10)	6 (12)
Death — no. (%)	2 (3)	1 (1)	0	2 (3)	1 (2)	0	2 (6)	1 (2)	0
Early discontinuation — no. (%)	35 (48)	14 (19)	18 (26)	28 (42)	6 (9)	8 (13)	—	—	—
Adherence issues — no./total no. (%)	3/35 (9)	2/14 (14)	2/18 (11)	3/28 (11)	2/6 (33)	2/8 (25)	—	—	—
Adverse event — no./total no. (%)	17/35 (49)	4/14 (29)	5/18 (28)	17/28 (25)	4/6 (67)	5/8 (62)	—	—	—
Did not meet inclusion or exclusion criteria, detected after first dose — no./total no. (%)	7/35 (20)	8/14 (57)	10/18 (6)	0	0	1/8 (12)	—	—	—
Did not receive at least one dose of trial medication — no./total no. (%)	0	0	1/18 (6)	—	—	—	—	—	—
Withdrew consent while still receiving treatment — no./total no. (%)	6/35 (17)	0	0	6/28 (21)	0	0	—	—	—
Other reason — no./total no. (%)†	2/35 (6)	0	0	2/28 (7)	0	0	—	—	—
Treatment failure — no. (%)	0	1 (1)	0	0	1 (2)	0	0	1 (2)	0
Lost to follow-up at 72 wk — no. (%)	2 (3)	3 (4)	3 (4)	2 (3)	3 (5)	3 (5)	2 (6)	3 (5)	3 (6)
Recurrence — no. (%)	0	1 (1)	3 (4)	0	1 (2)	3 (5)	0	1 (2)	3 (6)
Risk difference for the primary outcome — percentage points (95% CI)	—	−26 (−41 to −10)	−19 (−36 to −2)	—	−30 (−45 to −14)	−25 (−41 to −9)	—	−2 (−15 to 12)	−1 (−15 to 14)

The percentages of patients with favorable outcomes in the BPaLC group (81%) and the BPaL group (77%) were higher than the percentage in the standard-care group

N Engl J Med 2022;387:2331-43.

Bedaquiline, Delamanid, Linezolid, and Clofazimine for Treatment of Pre-extensively Drug-Resistant Tuberculosis

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Background. Treatment success rates for multidrug-resistant tuberculosis (MDR-TB) remain low globally. Availability of newer drugs has given scope to develop regimens that can be patient-friendly, less toxic, with improved outcomes. We proposed to determine the effectiveness of an entirely oral, short-course regimen with bedaquiline and delamanid in treating MDR-TB with additional resistance to fluoroquinolones (MDR-TB_{FQ+}) or second-line injectable (MDR-TB_{SLI+}).

Methods. We prospectively determined the effectiveness and safety of combining 2 new drugs with 2 repurposed drugs—bedaquiline, delamanid, linezolid, and clofazimine—for 24–36 weeks in adults with pulmonary MDR-TB_{FQ+} and/or MDR-TB_{SLI+}. The primary outcome was a favorable response at end of treatment, defined as 2 consecutive negative cultures taken 4 weeks apart. The unfavorable outcomes included bacteriologic or clinical failure during the treatment period.

Results. Of the 165 participants enrolled, 158 had MDR-TB_{FQ+}. At the end of treatment, after excluding 12 patients due to baseline drug susceptibility and culture negatives, 139 of 153 patients (91%) had a favorable outcome. Fourteen patients (9%) had unfavorable outcomes: 4 deaths, 7 treatment changes, 2 bacteriological failures, and 1 withdrawal. During treatment, 85 patients (52%) developed myelosuppression, 69 (42%) reported peripheral neuropathy, and none had QTc(F) prolongation >500 ms. At 48 weeks of follow-up, 131 patients showed sustained treatment success with the resolution of adverse events in the majority.

Conclusions. After 24–36 weeks of treatment, this regimen resulted in a satisfactory favorable outcome in pulmonary MDR-TB patients with additional drug resistance. Cardiotoxicity was minimal, and myelosuppression, while common, was detected early and treated successfully.

- **Fully oral short-course regimen of BDQ and DLM with other drugs gives a favorable outcome of 91% in patients with MDR-TBFQ+/SLI+ and 69% in those with both FQ and SLI resistance.**
- **The median time to culture conversion was 8 weeks**

Clin Infect Dis. 2022 Jun 29;76(3):e938–46

ORIGINAL ARTICLE

An All-Oral 6-Month Regimen for Multidrug-Resistant Tuberculosis
A Multicenter, Randomized Controlled Clinical Trial (the NExT Study)

STUDY	INTERVENTION	OUTCOMES	RESULTS
• Multicenter RCT • Adults MDR/RR-TB • 93 of 111 randomized participants (44 in the comparator arm and 49 in the interventional arm)	• Randomised (1:1 ratio) to a 6- month all-oral regimen that included levofloxacin, bedaquiline, linezolid and two other group B/C drugs, **vs** • the standard-of-care (SOC) >9-month World Health Organization (WHO)-approved injectable-based regimen	• The primary endpoint was a favorable WHO-defined treatment outcome 24 months after treatment initiation • The trial was stopped prematurely when bedaquiline-based therapy became the standard of care in South Africa.	• Participants in the intervention arm were 2.2 times more likely to experience **a favorable 24-month outcome** than participants in the SOC arm (51% vs22.7%; risk ratio, 2.2 [1.2–4.1]; P=0.006) • **Toxicity-related drug** substitution occurred more frequently in the SOC arm (65.9% vs. 34.7% ; P=0.001)]

Am J Respir Crit Care Med Vol 205, Iss 10, pp 1214–1227, May 15, 2022

MDR/RR-TB patients recruited from 5 sites across South Africa

Conventional Arm
(5 to 6 drug injection-based regimen)

1:1 Randomization

Interventional Arm
(5 drug all-oral regimen)

December 2014 – September 2016
(18–20 months treatment duration)*

Drug	Daily Dose
1. Kanamycin†	500–750mg (40–50kg) 1,000mg (51–90kg)
2. Moxifloxacin	400mg
3. Clofazimine	50mg (<30kg) 100mg (>30kg)
4. Pyrazinamide	1,000–1,750mg (40–50kg) 1,750–2,000mg (51–70kg) 2,000–2,500mg (71–90kg)
5. Terizidone‡ **or** Ethionamide‡ **or** High dose Isoniazid‡	750mg (40–70kg) 750–1,000mg (71–90kg) 500mg (40–50kg) 750mg (51–70kg) 750–1,000mg (71–90kg) 10–15mg/kg

- **Follow-up for 12 months post-treatment completion**

December 2016 – September 2018
(9–11 months treatment duration)*

Drug	Daily dose and Frequency
1. Kanamycin§	15mg/kg (max 1,000mg)
2. Moxifloxacin **or** Levofloxacin	400mg 750mg(≤50kg) 1,000mg (>50kg)
3.Clofazimine	50mg (<30kg) 100mg (>30kg)
4.Pyrazinamide	1,000mg (<30kg) 1,500mg (>30–50kg) 2,000mg (>50kg)
5.Ethambutol	800mg (<30–50kg) 1,200mg (>50kg)
6.Terizidone‡§ **or** Ethionamide‡§ **or** High dose Isoniazid‡§	750mg (40–70kg) 750–1,000mg (71–90kg) 500mg (40–50kg) 750mg (51–70kg) 750–1,000mg (71–90kg) 10–15mg/kg

- **Follow-up for 13–15 months post-treatment completion**

December 2014 – October 2018
(6–9 month treatment duration)*

Drug	Daily dose and Frequency
1. Bedaquiline (Group A)	400mg daily for 2 weeks followed by 200mg 3 times a week for 24 weeks
2. Linezolid (Group A)	600mg
3. Levofloxacin (Group A)	750mg (≤50kg) 1,000mg (>50kg)
4. Pyrazinamide (Group C)	1,000–1,750mg (40–50kg) 1,750–2,000mg (51–70kg) 2,000–2,500mg (71–90kg)
5. Terizidone‖ (Group B) **or** Ethionamide‖ (Group C) **or** High dose Isoniazid‖ (Group C)	750mg (40–70kg) 750–1,000mg (71–90kg) 15mg/kg (maximum of 900mg) 500mg (40–50kg) 750mg (51–70kg) 750–1,000mg (71–90kg)

- **Follow-up for 15–18 months post-treatment completion**

November 2018

Trial terminated due to the inclusion of bedaquiline into the South African National TB Program's MDR-TB treatment regimen

November 2020

Completion of 24-month follow-up post-treatment initiation for all patients

Table 2. Comparison of Primary and Secondary Endpoints in Each Arm Using the Modified Intention-to-Treat Population ($n = 93$) Unless Otherwise Specified

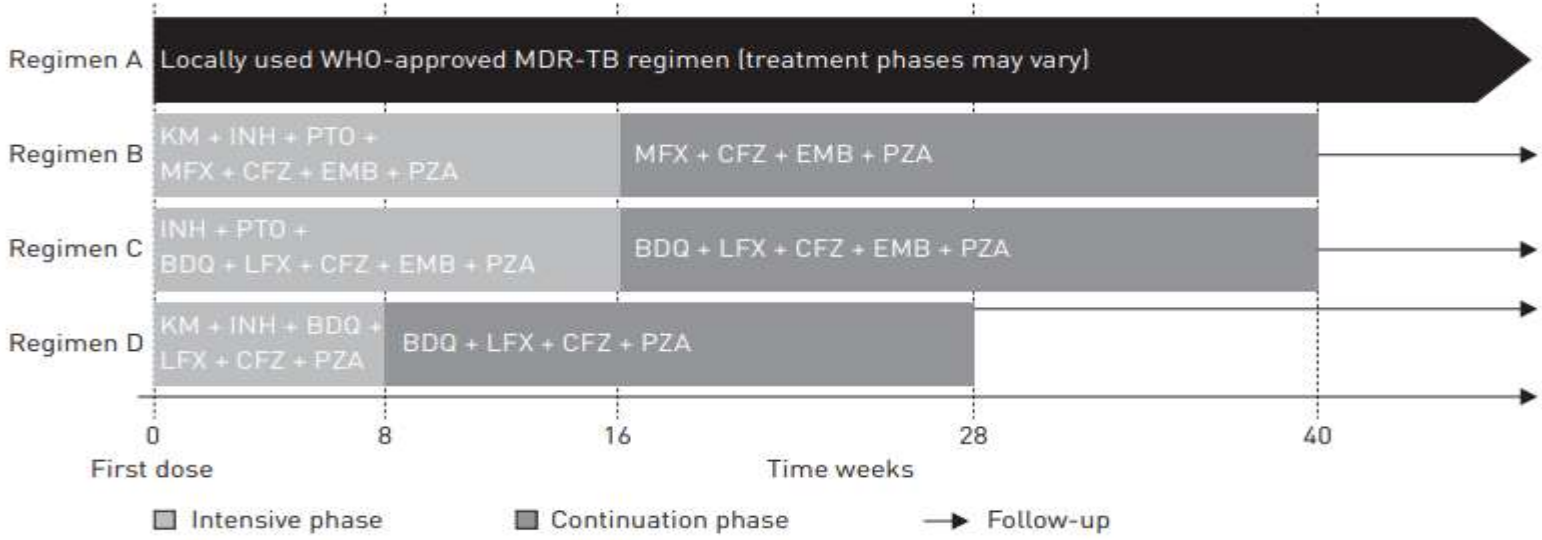
Description of Endpoint	SOC	BDQ/LZD	Relative Risk Ratio (95% CI)	Risk Difference % (95% CI)	*P* Value*
Primary endpoint					
Favorable outcomes at 24 mo after initiation of treatment, *n* (%)	10/44 (22.7)	25/49 (51.0)	2.2 (1.2 to 4.1)	28.3 (9.6 to 47.0)	0.006
Time to unfavorable outcome (event-free survival) over 24-mo	N/A	N/A	Hazard ratio, 0.4 (95% CI, 0.2 to 0.6)		<0.001
Restricted mean time lost, mo†	15.8 (13.0–18.5)†	8.6 (5.9–11.2)	RMTL ratio, 0.5 (95% CI, 0.4 to 0.8)†		0.001†
Secondary endpoints					
Time point–specific WHO-defined favorable outcomes after treatment initiation‡					
Favorable outcomes at 24 mo after treatment initiation in the per-protocol population	10/43 (23.3)	25/44 (56.8)	2.4 (1.3 to 4.5)	33.6 (14.2 to 52.9)	0.002
Favorable outcomes after treatment completion§					
Favorable outcome at treatment completion (specifically at the time point of treatment cessation)					
mITT population	11/44 (25.0)	28/49 (57.1)	1.9 (1.3 to 2.7)	4.0 (1.7 to 9.7)	0.003
Per-protocol population	11/43 (25.6)	27/44 (61.4)	2.0 (1.3 to 3.2)	4.6 (1.9 to 11.5)	0.001
Favorable outcome 12 mo after treatment completion (specifically at the time point of treatment cessation)					
mITT population	10/44 (22.7)	25/49 (51.0)	2.2 (1.2 to 4.1)	28.3 (9.6 to 47.0)	0.006
Per-protocol population	10/43 (23.3)	25/44 (56.8)	2.4 (1.3 to 4.5)	33.6 (14.2 to 52.9)	0.002
Favorable patient-centered outcomes (treatment success or ⩾12-mo relapse-free cure) at 24-mo (i.e., a non–WHO-defined outcome)¶					
Patient-centered outcomes at 24 mo after treatment initiation in the mITT population¶	30/44 (68.2)	33/49 (67.4)	1.0 (0.8 to 1.3)	−0.8 (−19.9 to 18.2)	1
Patient-centered outcomes at 24 mo after treatment initiation in the per-protocol population¶	30/43 (69.8)	33/44 (75.0)	1.1 (0.8 to 1.4)	5.2 (−13.5 to 24.0)	0.637
Culture conversion outcomes (reported for culture-positive participants at baseline)					
2-mo sputum culture conversion	29/41(70.7)‖	37/43 (86.1)‖	1.2 (1.0 to 1.5)	15.3 (−2.0 to 32.7)	0.113
6-mo sputum culture conversion	39/41 (95.1)‖	41/43 (95.4)‖	1.0 (0.9 to 1.1)	0.2 (−8.9 to 9.3)	1
All-cause mortality					
All-cause mortality at 24 mo after initiation of treatment	4/44 (9.0)	4/49 (8.2)	1.0 (0.3 to 3.9)	0.1 (−5.9 to 6.1)	0.91

Am J Respir Crit Care Med Vol 205, Iss 10, pp 1214–1227, May 15, 2022

Short-course treatment for multidrug-resistant tuberculosis: the STREAM trials

Riya Moodley[1] and Thomas R. Godec[1] on behalf of the STREAM Trial Team[2]

- **STREAM stage 1**- noninferiority design, the efficacy and safety of a 9-month regimen based on the one studied in Bangladesh (regimen B) with the WHO-recommended standard of care (regimen A)
- **STREAM stage 2-**primary objectives of programmatic relevance are to assess whether the proportion of patients with a favorable efficacy outcome on regimen C and regimen D is noninferior to that on regimen B at 76 weeks



Eur Respir Rev 2016; 25: 29–35

A Trial of a Shorter Regimen for Rifampin-Resistant Tuberculosis

A.J. Nunn, P.P.J. Phillips, S.K. Meredith, C.-Y. Chiang, F. Conradie, D. Dalai, A. van Deun, P.-T. Dat, N. Lan, I. Master, T. Mebrahtu, D. Meressa, R. Moodliar, N. Ngubane, K. Sanders, S.B. Squire, G. Torrea, B. Tsogt, and I.D. Rusen, for the STREAM Study Collaborators*

STUDY	Intervention	Outcomes	
• Randomized, phase 3, noninferiority trial • Aim- to compare short regimen (9 to 11 months) with a long regimen (20 months) • 10 %points or less was used to determine noninferiority. • **N= 424**	**2:1 ratio randomisation** **short regimen** - moxifloxacin (high dose), clofazimine, ethambutol, and pyrazinamide administered over a 40-week period, supplemented by kanamycin, isoniazid, and prothionamide in the first 16 weeks **vs** **long regimen (20 months)** that followed the 2011 WHO guidelines	**Primary Outcomes-** • **Primary efficacy outcome-** favorable status at 132 weeks-defined by cultures that were negative for M. tuberculosis at 132 weeks after randomization and at a previous occasion during the trial period, with no intervening positive culture or previous unfavorable outcome • **Primary safety outcome-** occurrence of a (severe) adverse event of grade 3 or higher	• **Secondary efficacy outcomes** - times to smear and culture conversions; acquired resistance to fluoroquinolones, aminoglycosides, and pyrazinamide. • **Secondary safety outcomes** - death during the treatment and follow-up periods, an analysis of severe adverse, an analysis of QT interval prolongation, and changes in LFT results.

N Engl J Med 2019;380:1201-13

A Trial of a Shorter Regimen for Rifampin-Resistant Tuberculosis

A.J. Nunn, P.P.J. Phillips, S.K. Meredith, C.-Y. Chiang, F. Conradie, D. Dalai, A. van Deun, P.-T. Dat, N. Lan, I. Master, T. Mebrahtu, D. Meressa, R. Moodliar, N. Ngubane, K. Sanders, S.B. Squire, G. Torrea, B. Tsogt, and I.D. Rusen, for the STREAM Study Collaborators*

Drugs and doses by weight band in the Short regimen are shown below.

Product	Weight group		
	Less than 33 kg	33 kg to 50 kg	More than 50 kg
Moxifloxacin	400 mg	600 mg	800 mg
Clofazimine	50 mg	100 mg	100 mg
Ethambutol	800 mg	800 mg	1200 mg
Pyrazinamide	1000 mg	1500 mg	2000 mg
Isoniazid	300 mg	400 mg	600 mg
Prothionamide	250 mg	500 mg	750 mg
Kanamycin	15 mg per kilogramme body weight (maximum 1g)		

All drugs were given in a single dosage daily (seven days a week) except for kanamycin which was given three times per week from week 12. Doses could be changed at the end of the intensive phase if participants had increased weight.

N Engl J Med 2019;380:1201-13

Table 2. Primary Efficacy Analysis in the Modified Intention-to-Treat and Per-Protocol Populations.*

Variable	Modified Intention-to-Treat Population			Per-Protocol Population		
	Long Regimen	Short Regimen	Total	Long Regimen	Short Regimen	Total
Disposition of the participants						
Underwent randomization — no.	142	282	424	142	282	424
Were included in the population — no.	130	253	383	87	234	321
Were considered not able to be assessed — no.						
Had reinfection with a different strain	1	7	8	1	6	7
Had a negative culture at 76 weeks but lost to follow-up thereafter	5	1	6	3	1	4
Were included in primary outcome analysis — no.	124	245	369	83	227	310
Outcome						
Attained favorable status — no. (%)†	99 (79.8)	193 (78.8)	292 (79.1)	67 (80.7)	186 (81.9)	253 (81.6)
Had an unfavorable outcome — no. (%)	25 (20.2)	52 (21.2)	77 (20.9)	16 (19.3)	41 (18.1)	57 (18.4)
Determined on the basis of bacteriologic findings‡						
Had no negative cultures§	1	5	6	1	5	6
Had bacteriologic reversion during treatment period¶	4	13	17	4	11	15
Had bacteriologic relapse after treatment period and started ≥2 additional drug therapies‖	0	7	7	0	7	7
Had positive culture at last assessment**	2	1	3	2	1	3
Determined on the basis of criteria other than bacteriologic findings						
Had negative culture at last assessment but died during the treatment or follow-up period	5	9	14	5	9	14
Had treatment extended or changed after adverse event	3	4	7	2	3	5
Started ≥2 additional drug therapies owing to decision by the investigator††	3	2	5	2	0	2
Withdrew consent for treatment, was given a different regimen, or was lost to follow-up before 76 weeks	4	8	12	0	3	3
Had treatment extended or changed after poor adherence or loss to follow-up	0	2	2	0	1	1
Had negative culture at last assessment but was lost to follow-up before 76 weeks	3	1	4	0	1	1

Table 3. Summary of Safety Outcomes.*

Outcome	Long Regimen (N=141)	Short Regimen (N=282)
Grade 3 to 5 adverse event — no. (%)	64 (45.4)	136 (48.2)
Serious adverse event — no. (%)	53 (37.6)	91 (32.3)
Death — no. (%)	9 (6.4)	24 (8.5)
Related to tuberculosis	2	7
Related to tuberculosis treatment	1	1
Related to HIV or HIV treatment	3	6
Other or uncertain	3	10
Grade 3 to 5 adverse events according to the five most common MedDRA system organ classes — no. (%)		
Metabolism and nutrition disorders	28 (19.9)	41 (14.5)
Hypokalemia†	10 (7.1)	3 (1.1)
Cardiac disorders	10 (7.1)	30 (10.6)
Conduction disorder†	7 (5.0)	28 (9.9)
Hepatobiliary disorders	8 (5.7)	25 (8.9)
Ear and labyrinth disorders	8 (5.7)	21 (7.4)
Respiratory, thoracic, and mediastinal disorders	6 (4.3)	15 (5.3)

N Engl J Med 2019;380:1201-13

Evaluation of two short standardised regimens for the treatment of rifampicin-resistant tuberculosis (STREAM stage 2): an open-label, multicentre, randomised, non-inferiority trial

STUDY	Intervention	Outcomes	
• Multicentric randomised, phase 3, non-inferiority trial • **Aim**- to compare two bedaquiline-containing regimens with the 9-month STREAM stage 1 regimen • **N= 588** • **non-inferiority** -the upper boundary of the 95% CI should **be < 10%** in both mITT and PP	Participants were randomly assigned **1:2:2:2** to 1) the 2011 **WHO regimen** (terminated early) 2) **9-month control regimen** 3) **9-month oral** with **bedaquiline** (primary comparison) regimen 4) **6-month regimen with bedaquiline and 8 weeks of second-line injectable**	**Primary efficacy outcome-** favourable status at 76 weeks, defined as a negative culture for M tuberculosis at week 76 and on the preceding visit, with no intervening positive culture or previous unfavourable outcome**.**	• **Secondary efficacy outcomes** - times to unfavourable outcome, probable or definite failure or recurrence ,and smear and culture conversion; and frequency of acquired resistance to fluoroquinolones, aminoglycosides, bedaquiline, clofazimine, or pyrazinamide. • **Secondary safety outcomes-** death from any cause; severe adverse events, modification of treatment due to an adverse event. QTcF interval prolongation, and changes in liver function and hearing loss.

Lancet 2022; 400: 1858–68

Oral regimen
9 months
IP -16 weeks

Product	Weight group		
	Less than 33 kg	33 kg to 50 kg	More than 50 kg
Bedaquiline	400 mg once daily for first 14 days/200 mg thrice weekly thereafter		
Levofloxacin	750 mg	750mg	1000 mg
Clofazimine	50 mg	100 mg	100 mg
Ethambutol	800 mg	800 mg	1200 mg
Pyrazinamide	1000 mg	1500 mg	2000 mg
Isoniazid	300 mg	400 mg	600 mg
Prothionamide	250 mg	500 mg	750 mg

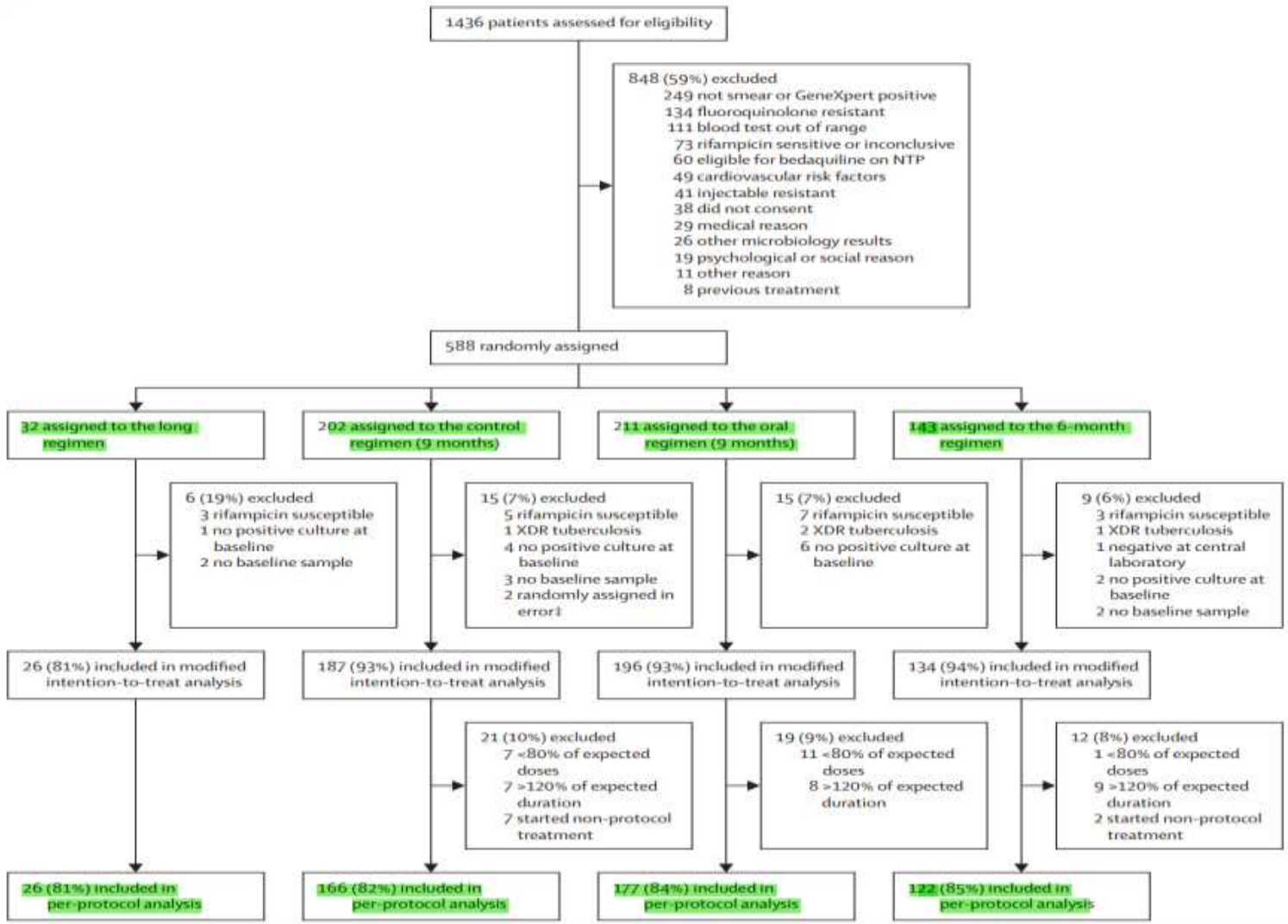
Six-month regimen
IP -8 weeks

Product	Weight group				
	Less than 33 kg	33 kg to less than 40 kg	40 kg to 50 kg	More than 50 kg to 60 kg	More than 60 kg
Bedaquiline	400 mg once daily for first 14 days/200 mg thrice weekly thereafter				
Levofloxacin	750 mg		750 mg		1000 mg
Clofazimine	50 mg		100 mg		100 mg
Pyrazinamide	1000 mg		1500 mg		2000 mg
Isoniazid	400 mg	500 mg	600 mg	800 mg	900 mg
	Daily for the first 14 days, thrice-weekly thereafter for the duration of the intensive phase				
Kanamycin	15 mg per kilogram body weight (maximum 1g)				

A

Long regimen	Control regimen	Oral regimen	6-month regimen
About 20 months	40 weeks 16-week intensive phase*	40 weeks 16-week intensive phase*	28 weeks 8-week intensive phase*
Locally used regimen recommended by WHO in 2011	Moxifloxacin† Clofazimine Ethambutol Pyrazinamide .. Kanamycin (intensive phase) Isoniazid (intensive phase) Prothionamide (intensive phase)	Levofloxacin Clofazimine Ethambutol Pyrazinamide Bedaquiline .. Isoniazid (intensive phase) Prothionamide (intensive phase)	Levofloxacin Clofazimine .. Pyrazinamide Bedaquiline Kanamycin (intensive phase) Isoniazid (intensive phase) ..

B



Lancet 2022; 400: 1858–68

Long regimen	Control regimen	Oral regimen	6-month regimen
About 20 months	40 weeks 16-week intensive phase*	40 weeks 16-week intensive phase*	28 weeks 8-week intensive phase*
Locally used regimen recommended by WHO in 2011	Moxifloxacin† Clofazimine Ethambutol Pyrazinamide .. Kanamycin (intensive phase) Isoniazid (intensive phase) Prothionamide (intensive phase)	Levofloxacin Clofazimine Ethambutol Pyrazinamide Bedaquiline .. Isoniazid (intensive phase) Prothionamide (intensive phase)	Levofloxacin Clofazimine .. Pyrazinamide Bedaquiline Kanamycin (intensive phase) Isoniazid (intensive phase) ..

	Oral regimen vs control regimen			6-month regimen vs control regimen		
	Control	Oral	Difference in favourable response*	Control	6-month	Difference in favourable response*
Total in mITT population	187	196	..	127	134	..
Total with a favourable outcome	133 (71%)	162 (83%)	11·0% (95% CI 2·9–19·0)	87 (69%)	122 (91%)	22·2% (95% CI 13·1–31·2)
Total with an unfavourable outcome	54 (29%)	34 (17%)	..	40 (31%)	12 (9%)	..
Unfavourable outcomes based on bacteriology						
Never achieved culture conversion†	6	2	..	5	1	..
Bacteriological reversion on treatment	11	3	..	8	1	..
Bacteriological recurrence after treatment‡	1	2	..	1	1	..
Culture positive at week 76	2	1	..	2	0	..
Unfavourable outcomes not based on bacteriology						
Died during treatment or follow-up (culture converted)	1	3	..	0	2	..
Lost to follow-up (culture converted)	3	6	..	2	2	..
Treatment changed after adverse event	20	6	..	14	3	..
Treatment extended after adverse event	4	3	..	3	1	..
Treatment extended or changed for other reasons	3	3	..	2	1	..
Participant withdrew consent	3	5	..	3	0	..

Data are n (%), unless otherwise stated. Table presents unfavourable outcomes that led to the primary endpoint, that is, the first unfavourable event that was classified as unfavourable for each participant. mITT=modified intention-to-treat. *Analyses adjusted for randomisation protocol and HIV status. †Includes three early deaths (one in control, two in oral). ‡Includes one patient on the oral regimen who developed an empyema.

***Table 2:* Primary efficacy analysis in modified intention-to-treat population**

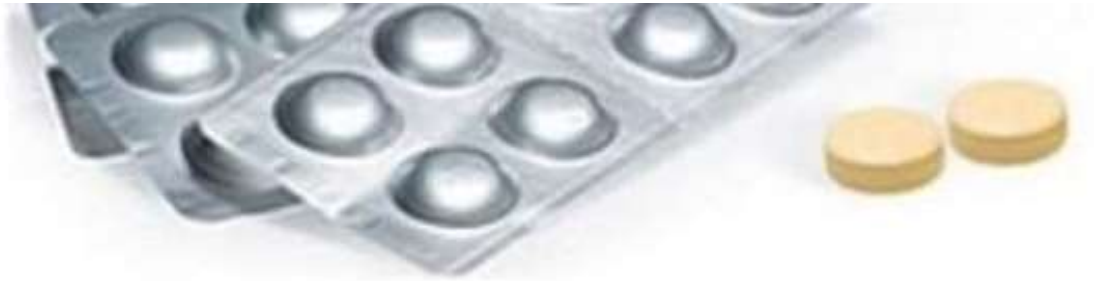
	Oral regimen vs control regimen		6-month regimen vs control regimen	
	Control	Oral	Control	6-month
Total in the safety analysis population	202	211	140	143
Participants with an SAE	35 (17%)	38 (18%)	26 (19%)	27 (19%)
Participants with treatment-related SAE	7 (3%)	4 (2%)	6 (4%)	6 (4%)
Death from any cause	5 (2%)	7 (3%)	2 (1%)	2 (1%)
Any grade 3–4 adverse event	108 (53%)	106 (50%)	75 (54%)	79 (55%)
Any grade 3–5 adverse event	109 (54%)	109 (52%)	76 (54%)	81 (57%)
QTcF >500 ms	12 (6%)	7 (3%)	8 (6%)	4 (3%)
ALT or AST >5-times ULN	28 (14%)	32 (15%)	15 (11%)	13 (9%)
ALT >3-times ULN and total bilirubin >2-times ULN	9 (4%)	14 (7%)	5 (4%)	7 (5%)
Brock grading ≥3 (either ear)	18 (9%)	4 (2%)	11 (8%)	6 (4%)

Data are n (%). ALT=alanine aminotransferase. AST=aspartate aminotransferase. SAE=serious adverse event. QTcF=corrected QT interval calculated with Fridericia's formula. ULN=upper limit of normal.

***Table 3:* Summary of safety outcomes**

Lancet 2022; 400: 1858–68

Delamanid



- Bicyclic nitroimidazooxazole derivative and is a prodrug
- It acts through inhibition of mycolic acid synthesis providing it bactericidal activity , by inhibiting methoxy-mycolic acid and keto-mycolic acid
- Activite against dormant, non-replicating bacilli, as well as those harboured within macrophages
- Resistance to delamanid is rare so far, but when encountered is frequently due to mutations in the nitroreductase that activates it
- Usual dose of 100 mg twice daily
- Bioavailability is increased with fatty food consumption
- The t half is approximately 30 h
- Most excretion is through the feces, with minimal urinary excretion
- Main reported adverse events including mild gastrointestinal symptoms or QTc prolongation

Shetye GS et al.Transl Res. 2020;220:68–97
Nguyen TVA et al. Clin Infect Dis. 2020;71(12):3252–9.

Pretomanid

- Pretomanid is a pro-drug nitroimidazooxazine molecule
- Active against replicating and dormant mycobacteria through inhibition of mycolic acid biosynthesis and nitric oxide release, respectively
- Dose -200 mg OD with food
- Five genes are associated with the emergence of resistance (ddn, fgd1, fbiA, fbiB, and fbiC)
- Crossresistance with delamanid has been observed
- Most common adverse events are gastrointestinal symptoms and vomiting and suggested to be dose related
- Symptoms are not dose related: transaminase increase, hepatotoxicity, and headache.

Nedelman JR, et al. Antimicrob Agents Chemother. 2020;65(1):e01121–20
Haver HL,et al. Antimicrob Agents Chemother. 2015;59(9):5316–23

Bedaquiline

- Class of diarylquinolines inhibiting mycobacterial ATP synthesis by inhibiting F-ATP synthase activity
- Against both replicating and non-replicating bacilli
- Terminal half-life of bedaquiline is extremely long (>5 months)
- Dosing regimen -a loading-phase (2 weeks of 400 mg once daily) and a maintenance phase (200 mg 3 times per week)
- Bedaquiline is metabolized by the cytochrome P450 CPY3A4 enzyme
- Main AEs reported include nausea/vomiting, headache, and arthralgia
- The mean change in QTc has been reported to be between 12 and 15 ms, driven primarily by the exposure to the M2 metabolite
- QT prolongation is generally in combination with other medications that may further prolong the QTc, such as clofazimine and fuoroquinolones

van Heeswijk RPG et al. J Antimicrob Chemother. 2014;69(9): 2310–8
B. D. Edwards, S. K. Field ,Drugs (2022) 82:1695–1715

Drugs	6 months cost (USD)	Rupees
Pretomanid	364	30000
Bedaquilline	400	33000
Delamanid	1700	140000
BPaL	1040	86000

QT EFFECTS OF BEDAQUILINE, DELAMANID OR BOTH IN PATIENTS WITH RIFAMPICIN-RESISTANT-TB: RCT

STUDY	INTERVENTION	OUTCOMES	RESULTS
• **DELIBERATE trial** • Phase 2, open-label trial in which adults with MDR/RR-TB • 84 participants	1:1:1 randomization, using permuted blocks to receive bedaquiline, delamanid, or both for 24 weeks.	The primary endpoint was mean QTcF change from baseline (averaged over weeks 8– 24).	• Patients randomized to bedaquiline (n=28), delamanid (n=27) or both medicines (n=27) - the on-treatment change in **QTcF** from baseline was 11.9 ms, 8.6 ms and 20.7 ms, respectively • Cumulative culture conversion by **Week 8** was 88% (21/24, bedaquiline), 83% (20/24 delamanid), and 95% (19/20, bedaquiline+delamanid) and was 92%, 91%, and 95%, respectively at **24 weeks**

Dooley KE et al. Lancet Infect Dis. 2021 Jul;21(7):975-983

Culture Conversion in Patients Treated with Bedaquiline and/or Delamanid

A Prospective Multicountry Study

- The endTB Observational Study
- Multicountry cohort of patients receiving bedaquiline or delamanid as part of a regimen for RR-TB or MDR-TB
- 1,106 patients

Table 2. Frequency of Sputum Culture Conversion among High-Risk Subpopulations Receiving an MDR-TB Regimen Containing BDQ and/or DLM and Risk Factors for Nonconversion ($N = 1,109$)

Patients	*n/N*	Proportion Converted within 6 mo	Univariable Risk Ratio for Nonconversion [*Ratio (95% Confidence Interval)*]	*P* Value
All patients	939/1,109	0.85	—	—
HIV infection				
Negative	857/990	0.87	Reference	
Positive	82/119	0.69	1.75 (1.16–2.65)	0.007
Hepatitis C infection				
Negative	826/959	0.86	Reference	
Positive	112/144	0.78	1.45 (1.01–2.07)	0.04
Diabetes mellitus or glucose intolerance*				
No	764/908	0.84	Reference	
Yes	161/181	0.89	0.80 (0.52–1.23)	0.31
Baseline resistance*				0.17†
MDR without additional resistance	185/223	0.83	Reference	
MDR without injectable and fluoroquinolone testing	42/50	0.84	0.90 (0.46–1.77)	0.76
Pre-XDR with injectable resistance	87/104	0.84	0.89 (0.53–1.51)	0.67
Pre-XDR with fluoroquinolone resistance	291/328	0.89	0.67 (0.44–1.04)	0.07
XDR	324/389	0.83	1.14 (0.76–1.69)	0.53
Cavitary disease and smear status*				<0.0001†
No cavitary disease, smear <3+	265/292	0.91	Reference	
Cavitary disease, smear <3+	456/520	0.88	1.23 (0.79–1.91)	0.35
No cavitary disease, smear 3+	30/40	0.75	2.72 (1.49–4.95)	0.001
Cavitary disease, smear 3+ (extensive disease)	91/128	0.71	2.94 (1.84–4.68)	<0.0001

Franke, Khan, Hewison, et al.Am J Respir Crit Care Med Vol 203, Iss 1, pp 111–119, Jan 1, 2021

Drug-associated adverse events in the treatment of multidrug-resistant tuberculosis: an individual patient data meta-analysis

*Zhiyi Lan, Nafees Ahmad, Parvaneh Baghaei, Linda Barkane, Andrea Benedetti, Sarah K Brode, James C M Brust, Jonathon R Campbell, Vicky Wai Lai Chang, Dennis Falzon, Lorenzo Guglielmetti, Petros Isaakidis, Russell R Kempker, Maia Kipiani, Liga Kuksa, Christoph Lange, Rafael Laniado-Laborín, Payam Nahid, Denise Rodrigues, Rupak Singla, Zarir F Udwadia, Dick Menzies, and The Collaborative Group for the Meta-Analysis of Individual Patient Data in MDR-TB treatment 2017**

Study	Method	Primary outcomes	Secondary outcomes
• Aim- to estimate the absolute and relative frequency of adverse events associated with different tuberculosis drugs • 35 studies • N= 9178 patients	• Systematic review of the available literature on MDR TB treatment and outcomes published in English, French, Chinese, Portuguese, or Spanish between Jan 1, 2009, and Aug 31, 2015	• Absolute and relative frequency of adverse events leading to permanent discontinuation of each anti-tuberculosis drug	• The association between patient characteristics and the occurrence of at least one adverse event leading to permanent drug discontinuation • The most common types of adverse event for each anti-tuberculosis drug

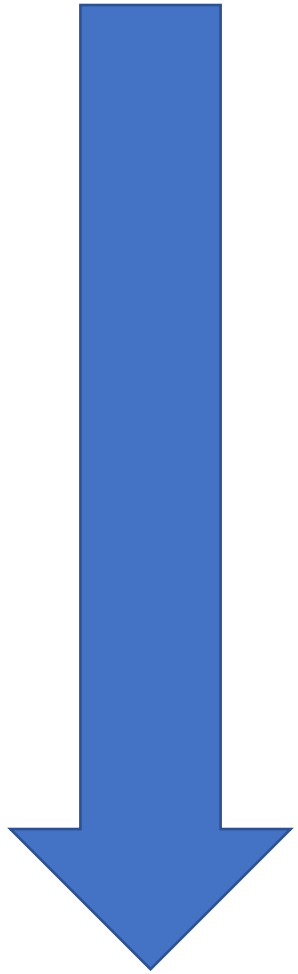
Lancet Respir Med 2020; 8: 383–94

Drug-associated adverse events in the treatment of multidrug-resistant tuberculosis: an individual patient data meta-analysis

	Cohorts using the drug*	Adverse events†/ patients using the drug	Pooled incidence of adverse events, random effect‡ (95% CI)	Pooled incidence of adverse events, fixed effect (95% CI)	Heterogeneity I^2 statistics
Ciprofloxacin	8	4/723	0·6% (0·2–1·5)	0·6% (0·2–1·5)	0·0%
Ofloxacin	22	71/6062	0·9% (0·4–2·1)	1·2% (0·9–1·5)	85·9%
Levofloxacin	20	22/1012	1·3% (0·3–5·0)	2·2% (1·4–3·3)	81·6%
Clofazimine	13	12/1712	1·6% (0·5–5·3)	0·7% (0·4–1·2)	69·4%
Bedaquiline	14§	9/464	1·7% (0·7–4·2)	1·9% (1·0–3·7)	25·7%
Ethambutol	33	124/6089	1·8% (1·0–3·3)	2·0% (1·7–2·4)	84·0%
Streptomycin	17	34/1208	2·9% (1·3–6·2)	2·8% (2·0–3·9)	71·1%
Moxifloxacin	27	30/904	2·9% (1·6–5·0)	3·3% (2·3–4·7)	38·0%
Amoxicillin–clavulanate	23	21/695	2·9% (1·7–4·8)	3·0% (2·0–4·6)	11·5%
Clarithromycin	16	18/457	3·3% (1·5–7·0)	3·9% (2·5–6·2)	47·2%
Imipenem and meropenem	7§	9/158	4·9% (1·0–20·5)	5·7% (3·0–10·6)	14·4%
Pyrazinamide	35	410/5141	5·1% (3·1–8·4)	8·0% (7·3–8·7)	93·4%
Cycloserine and terizidone	40	337/7547	5·7% (4·1–7·8)	4·5% (4·0–5·0)	83·8%
Ethionamide and protionamide	39	376/4627	6·5% (4·1–10·1)	8·1% (7·4–8·9)	92·9%
Kanamycin	25	268/1995	7·5% (4·6–11·9)	13·4% (12·0–15·0)	86·8%
Capreomycin	29	161/1932	8·2% (6·3–10·7)	8·3% (7·2–9·7)	45·1%
Amikacin	23	235/4106	10·2% (6·3–16·0)	5·7% (5·1–6·5)	86·9%
Aminosalicylic acid	35	532/2929	11·6% (7·1–18·3)	18·2% (16·8–19·6)	94·9%
Linezolid	35§	140/783	14·1% (9·9–19·6)	17·9% (15·4–20·7)	67·6%
Thioacetazone	3	103/719	14·3% (12·0–17·1)	14·3% (12·0–17·1)	0·0%

*A study done in a single country was considered as one cohort; a study done in multiple countries was divided into separate cohorts by country. †Adverse events were defined as those that resulted in permanent discontinuation of a drug. ‡Generalised linear mixed model was used to pool the incidence of adverse events. §If a study or cohort only reported adverse events for specific drugs, the cohort was used in the meta-analyses for those drugs.

Table 2: **Pooled incidence of adverse events for each drug using generalised linear mixed model**



Lancet Respir Med 2020; 8: 383–94

	Adverse events*/ patients using the drug	Pooled incidence of adverse events, random effect† (95% CI)	Adverse events with type re-ported‡	Type 1§	Type 2	Type 3	Type 4	Type 5
Ciprofloxacin¶	4/723	0·6% (0·2–1·5)	1	Gynaecomastia (1)	..	..	..	..
Ofloxacin	71/6062	0·9% (0·4–2·1)	12	Musculoskeletal (5, 42%)	Psychiatric (2, 17%)	Gastrointestinal (1, 8%)	Hepatotoxicity (1, 8%)	Rash (1, 8%)
Levofloxacin	22/1012	1·3% (0·3–5·0)	14	Musculoskeletal (9, 64%)	Peripheral neuropathy (2, 14%)	Rash (2, 14%)	Hypoglycaemia (1, 7%)	..
Clofazimine	12/1712	1·6% (0·5–5·3)	12	Cardiovascular (4, 33%)	Hyperpigmentation (5, 42%)	Rash (2, 17%)	Gastrointestinal (1, 8%)	..
Bedaquiline	9/464	1·7% (0·7–4·2)	9	Cardiovascular (5, 56%)	Hepatotoxicity (2, 22%)	CNS toxicity (1, 11%)	Musculoskeletal (1, 11%)	..
Ethambutol	124/6089	1·8% (1·0–3·3)	59	Visual impairment (41, 70%)	Gastrointestinal (10, 17%)	Musculoskeletal (2, 3%)	Rash (2, 3%)	Hepatotoxicity (1, 2%)
Streptomycin	34/1208	2·9% (1·3–6·2)	6	Ototoxicity (5, 83%)	Peripheral neuropathy (1, 17%)	..	..	..
Moxifloxacin	30/904	2·9% (1·6–5·0)	24	Cardiovascular (5, 21%)	Hepatotoxicity (4, 17%)	Gastrointestinal (3, 13%)	Peripheral neuropathy (3, 13%)	Musculoskeletal (2, 8%)
Amoxicillin–clavulanate	21/695	2·9% (1·7–4·8)	9	Gastrointestinal (6, 67%)	Rash (1, 11%)	Musculoskeletal (1, 11%)	Peripheral neuropathy (1, 11%)	..
Clarithromycin	18/457	3·3% (1·5–7·0)	7	Gastrointestinal (4, 57%)	Hepatotoxicity (1, 14%)	Peripheral neuropathy (1, 14%)	Fatigue (1, 14%)	..
Imipenem and meropenem	9/158	4·9% (1·0–20·5)	6	Hepatotoxicity (3, 50%)	Rash (1, 17%)	Fatigue (1, 17%)	Pneumonia (1, 7%)	..
Pyrazinamide	410/5141	5·1% (3·1–8·4)	142	Musculoskeletal (47, 33%)	Gastrointestinal (33, 23%)	Hepatotoxicity (29, 20%)	Rash (18, 13%)	Hyperuricaemia (8, 6%)
Cycloserine and terizidone	337/7547	5·7% (4·1–7·8)	140	Psychiatric (92, 66%)	CNS toxicity (35, 25%)	Gastrointestinal (5, 4%)	Peripheral neuropathy (2, 1%)	Rash (1, 1%)
Ethionamide and protionamide	376/4627	6·5% (4·1–10·1)	108	Gastrointestinal (52, 48%)	Hepatotoxicity (24, 22%)	Psychiatric (6, 6%)	Gynaecomastia (5, 5%)	Musculoskeletal (5, 5%)
Kanamycin	268/1995	7·5% (4·6–11·9)	56	Ototoxicity (42, 75%)	Musculoskeletal (3, 5%)	CNS toxicity (2, 4%)	Gastrointestinal (2, 4%)	Hypotension (2, 4%)
Capreomycin	161/1932	8·2% (6·3–10·7)	71	Nephrotoxicity (36, 51%)	Ototoxicity (12, 17%)	Rash (8, 11%)	Gastrointestinal (5, 7%)	Hypotension (2, 3%)
Amikacin	235/4106	10·2% (6·3–16·0)	211	Ototoxicity (183, 87%)	Nephrotoxicity (22, 10%)	Gastrointestinal (2, 1%)	Intolerance (2, 1%)	Musculoskeletal (1, 1%)
Aminosalicylic acid	532/2929	11·6% (7·1–18·3)	120	Gastrointestinal (95, 79%)	Hypothyroidism (6, 5%)	Hepatotoxicity 5, 4%)	Rash (5, 4%)	Nephrotoxicity (4, 3%)
Linezolid	140/783	14·1% (9·9–19·6)	137	Peripheral neuropathy (87, 64%)	Myelosuppression (30, 22%)	Optic neuritis (7, 5%)	Gastrointestinal (3, 2%)	Rash (3, 2%)
Thioacetazone¶	103/719	14·3% (12·0–17·1)	1	Rash (1)	..	..	..	..

*Adverse events were defined as those that resulted in permanent discontinuation of a drug. †Pooled incidence of adverse events was estimated through meta-analysis of proportions (table 2). ‡This analysis included only studies that reported adverse event types. §For each drug, simple pooling was done to calculate the number of each type of adverse event; the five most common adverse event types with the corresponding proportions were presented. ¶Adverse event types were reported for only one patient.

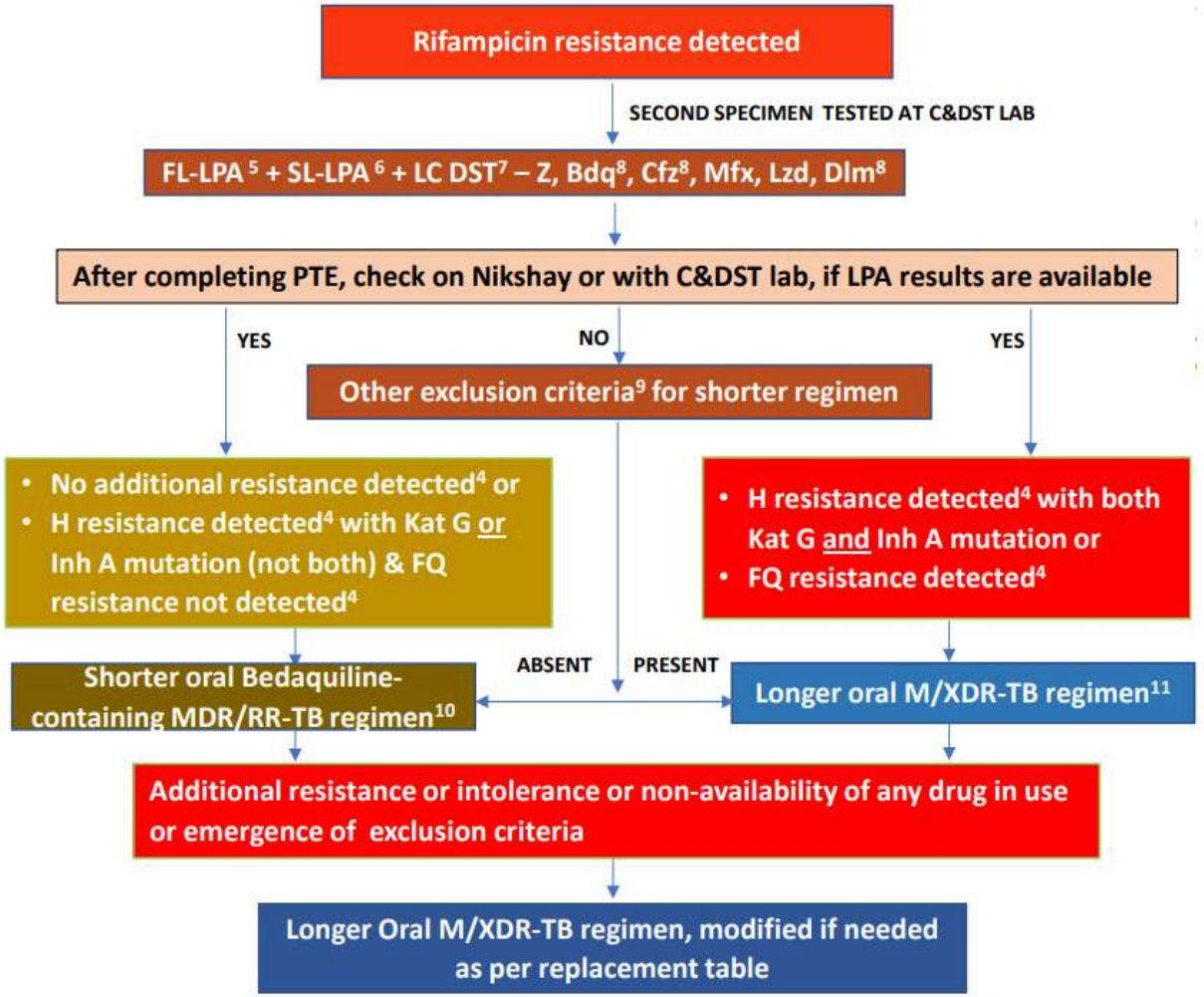
Table 5: **Type of adverse events for each drug**

Lancet Respir Med 2020; 8: 383–94

STUDY	Regimens	Duration	N	Favorable outcomes	ADVERSE EFFECTS
Nix	BPaL	26 wks	105	90 % favorable	neuropathy 81% , myelosuppression 45 %
ZeNix	BPaL (L 1200 & 600 mg for 26 /9 wks)	26 wks	181	Linezolid 1200 mg 26/9 wks- 93 /84 % & **600 mg 26**/9 wks- **91** /84 %	Neuropathy – 1200mg 26 /9 wks- 38 /24 % 600mg – 26/9 wks- 24/13 % Myelosupression 1200 mg 26/9 wk- 22/15 % % 600mg 26/9 wk- 2/7 %
TB PRACTICAL	WHO standard BPaL BPaLM BPaLC	24 wks	522	WHO- 52 % BPaL- 77 % **BPaLM- 89 %** BPaLC- 81 %	BPaLM vs WHO regimen toxicity -20 VS 59 %

Study	Regimens	Duration	N	Favorable outcomes	Adverse effects
Next	all-oral levofloxacin, bedaquiline, and linezolid with two other group B/C drugs vs (WHO)-approved injectable-based regimen	6 months	111	51 vs 22.7 %	More frequently in the SOC arm 65.9% vs. 34.7%
STREAM 1	KM + INH + PTO + **MFX + CFZ + EMB + PZA** for 16 wks MFX + CFZ + EMB + PZA 40wks vs long regimen locally used WHO-approved MDR-TB regimen (20 months)	9-11 months	424	78.8% of those in the short-regimen group vs 79.8% of participants in the long-regimen group	Adverse event of grade >3 occurred in 48.2% in the short-regimen vs 45.4% of participants in the long-regimen group and in
STREAM 2	Control -KM + INH + PTO + **MFX + CFZ + EMB + PZA** **vs** INH + PTO + **BDQ + LFX + CFZ + EMB + PZA (ORAL 9 Months)** **&** KM + INH **+ BDQ + LFX + CFZ + PZA (6 Months)**	9 & 6 months	588	71 % control vs 83 % oral & 69 % control vs 93 % 6 months	Hearing loss in control regimen 9% vs 2% oral vs 4 % in 6 month regimes

Treatment algorithm for MDR/RR-TB



PMDT 2021

Shorter oral Bedaquiline-containing MDR/RR-TB regimen

(4-6) Bdq $_{(6\ m)}$, Lfx, Cfz, Z, E, H^h, Eto	(5) Lfx, Cfz, Z, E,

Inclusion criteria

- Rifampicin resistance detected/inferred
- MDR/RR-TB with H resistance detected/inferred based on InhA mutation only or based on KatG mutation only (not both)
- MDR/RR-TB with FQ resistance not detected
- Children, aged 5 years to less than 18 years of age and weighing at least 15 kg, given their special needs, in consultation with the pediatrician
- No history of exposure to previous treatment with second-line medicines in the regimen (Bdq, Lfx, Eto or Cfz) for more than 1 month (unless susceptibility to these medicines is confirmed)

Exclusion criteria

- MDR/RR-TB patients with H resistance detected with both KatG and InhA mutation
- MDR/RR-TB patients with FQ resistance detected
- If result for FL-LPA, SL-LPA and DST to Z, BDQ* & Cfz* is not available, history of exposure for > 1 month to Bdq, Lfx, Eto or Cfz
- Intolerance to any drug or risk of toxicity from a drug in shorter oral Bedaquiline containing MDR/RR-TB regimen
- Extensive TB disease
- Severe EP-TB disease
- Pregnant and lactating women
- Children below 5 years

PMDT 2021

MDR/RR-TB patients on longer oral M/XDR-TB regimen

- All 3 Group A agents and at least 1 Group B agent should be included to ensure that treatment starts with at least 4 TB agents likely to be effective and that at least 3 agents are included for rest of the treatment if Bdq is stopped
- If the regimen cannot be composed with agents from Groups A and B alone, Group C agents are added to complete it

(18-20) Lfx Bdq $_{\text{(6 month or longer)}}$ Lzd# Cfz Cs

#dose of Lzd will be tapered to 300 mg after the initial 6–8 months of treatment

Bdq will be given for 6 months & extended beyond 6 months as an exception

Pyridoxine to be given to all DR-TB patients as per weight band

For Pre-XDR-TB and XDR-TB patients the duration of longer oral XDR-TB regimen would be for 20 months with appropriate modifications

PMDT 2021

BPaL regimen for MDR-TB with additional FQ resistance

- BPaL research proposal may be considered with flexibility to adapt with anticipated results of ZeNix trial with 4 arms of reduce dosage and duration of Linezolid in BPaL
- In exceptional cases, BPaL can be considered as a last resort by NTEP under prevailing ethical standards in individual patients for whom the design of an effective regimen is not possible as per WHO recommendations
  - Bedaquiline - 400 mg OD for the first 2 weeks and then 200 mg three times a week for 24 weeks
  - Pretomanid - 200 mg OD for 26 weeks
  - Linezolid - 1200 mg once daily for 24 weeks (after 1 month, dose and duration modification for linezolid is permissible), with an option to extend treatment to 39 weeks if they were culture-positive at week 16

PREVENTIVE TREATMENT FOR CONTACTS OF DR-TB

Clinical Infectious Diseases
MAJOR ARTICLE

Systematic Review, Meta-analysis, and Cost-effectiveness of Treatment of Latent Tuberculosis to Reduce Progression to Multidrug-Resistant Tuberculosis

Suzanne M. Marks, Sundari R. Mase, and Sapna Bamrah Morris

Objectives	Study	Outcomes	Results
• Aim- to analyze TB **incidence, treatment completion and discontinuation, and cost-effectiveness** • Persons having **contact to infectious MDR-TB**, who had documented LTBI test reactivity or presumed (for children)	21 articles that met inclusion criteria. 6 articles presented outcomes for contacts who were treated compared with those not treated for MDR-LTBI 10 presented outcomes only for treated contacts 5 presented outcomes only for untreated contacts	• Outcome **of MDR-TB incidence** was verified by culture and drug susceptibility testing, except for some children, who often are culture negative • Contacts with LTBI **effectively treated** if they were on ≥1 medication to which their MDR-TB strain was likely susceptible	• The estimated MDR-TB **incidence reduction was 90% (9%–99%)** using data from 5 comparison studies • High treatment discontinuation rates due to adverse effects in persons taking pyrazinamide-containing regimens. • Cost-effectiveness was greatest using a fluoroquinolone/ethambutol combination regimen

Marks et al. Clin Infect Dis. 2017 June 15; 64(12): 1670–1677

Clinical Infectious Diseases

MAJOR ARTICLE

Systematic Review, Meta-analysis, and Cost-effectiveness of Treatment of Latent Tuberculosis to Reduce Progression to Multidrug-Resistant Tuberculosis

Suzanne M. Marks, Sundari R. Mase, and Sapna Bamrah Morris

Cost-effectiveness of Multidrug-Resistant Latent Tuberculosis Treatment Regimens, 2014 US Dollars. Base Case 3% Tuberculosis Progression.

Treatment	Estimated Regimen Efficacy, %	Estimated Stop Due to AE, %	Estimated Completion, %	Estimated US MDR-TB Cases Over 40 Remaining Years of Life, No.	TB Cases Prevented, No.	Discounted Cases Prevented, No.	Remaining Lifetime QALYs, No.	Estimated Regimen Cost, 2014 $	Discounted Net Cost (Program Cost – Cost of TB Cases Prevented), 2014 $	Incremental Cost (Saving) per Case Prevented, 2014 $
No Tx				480	0	…	23.6915		$16,469,760	
PZA/FQ	90	66	31	346	134	77	23.6311	$1993	$(6,731)	saving
PZA/EMB	62	25	75	257	223	129	23.6730	$1350	$(11,044,074)	saving
FQ alone	62	8	81	239	241	139	23.6899	$1461	$(10,973,136)	saving
FQ/EMB	76	1	79	192	288	167	23.6978	$1893	$(11,486,144)	saving
FQ/ETA	69	0	100	149	331	191	23.6999	$4213	$24,264,686	not cost effective

Marks et al. Clin Infect Dis. 2017 June 15; 64(12): 1670–1677

pathogens

MDPI

Review

Preventive Therapy for Contacts of Drug-Resistant Tuberculosis

Table 1. Characteristics of the main studies assessing the tuberculosis preventive therapy effectiveness in drug-resistant tuberculosis contacts.

Study	Country	Study Design	DR-TB Contacts Included	Adults/ Children	Evidence of a TB Infection (LTBI)	Compared TPT (Months/Drug)	Primary Endpoint	Grade 3 or 4 Adverse Events	Completion Rate
Gureva et al., 2022 [24]	Russia	Prospective cohort study	72	Children ≤ 18 years-old	LTBI was diagnosed in 51 children, some children were treated without any evidence of a LTBI.	9 Mfx OR 9 Ofx OR No treatment	Incidence of TB disease: 0/58 (0%) with TPT 1/14 (7%) without TPT	None	90%
Malik et al., 2020–2021 [23,25,26]	Pakistan	Prospective cohort study	800	Adults & children	LTBI was diagnosed in six subjects, some subjects were treated without any evidence of a LTBI.	6 Lfx + E OR 6 LFx + Eth OR 6 Mfx + E OR 6 MFx+ Eth	Overall effectiveness on TB incidence compared to the historical control cohorts: 65% (95% CI 13–86)	None	70%
Huang et al., 2020 [27]	Peru	Prospective cohort study	652	Children ≤ 19 years-old	LTBI status was assessed in all subjects, the proportion of subjects included with a proven LTBI is not reported.	6–9 H No specific DR-TB contact control group	Incidence of TB disease 26/652 (4%) with TPT	NR	NR
Adler-Shohet et al., 2014 [28]	United States of America	Retrospec-tive cohort study	31	Children	All of the children included in the study had a proven LTBI.	Lfx + Z	Incidence of TB disease: 0/26 (0%) with TPT 0/5 (0%) without TPT	NR	58%
Bamrah et al., 2014 [29]	Federated States of Micronesia	Prospective cohort study	119	Adults & children	All of the subjects included in the study had a proven LTBI.	12 Lfx 12 Lfx + E 12 LFx + Eth 12 Mfx 12 MFx + E No treatment	Incidence of TB disease: 0/104 (0%) with TPT 3/15 (20%) without TPT	None	83–100%
Garcia-Prats et al., 2014 [30]	South Africa	Retrospec-tive cohort study	24	Children ≤ 15 years-old	LTBI was diagnosed in eight subjects, some subjects were treated without any evidence of a LTBI.	6 H + E + Ofx	Incidence of TB disease: 0/24 (0%) with TPT	None	88%

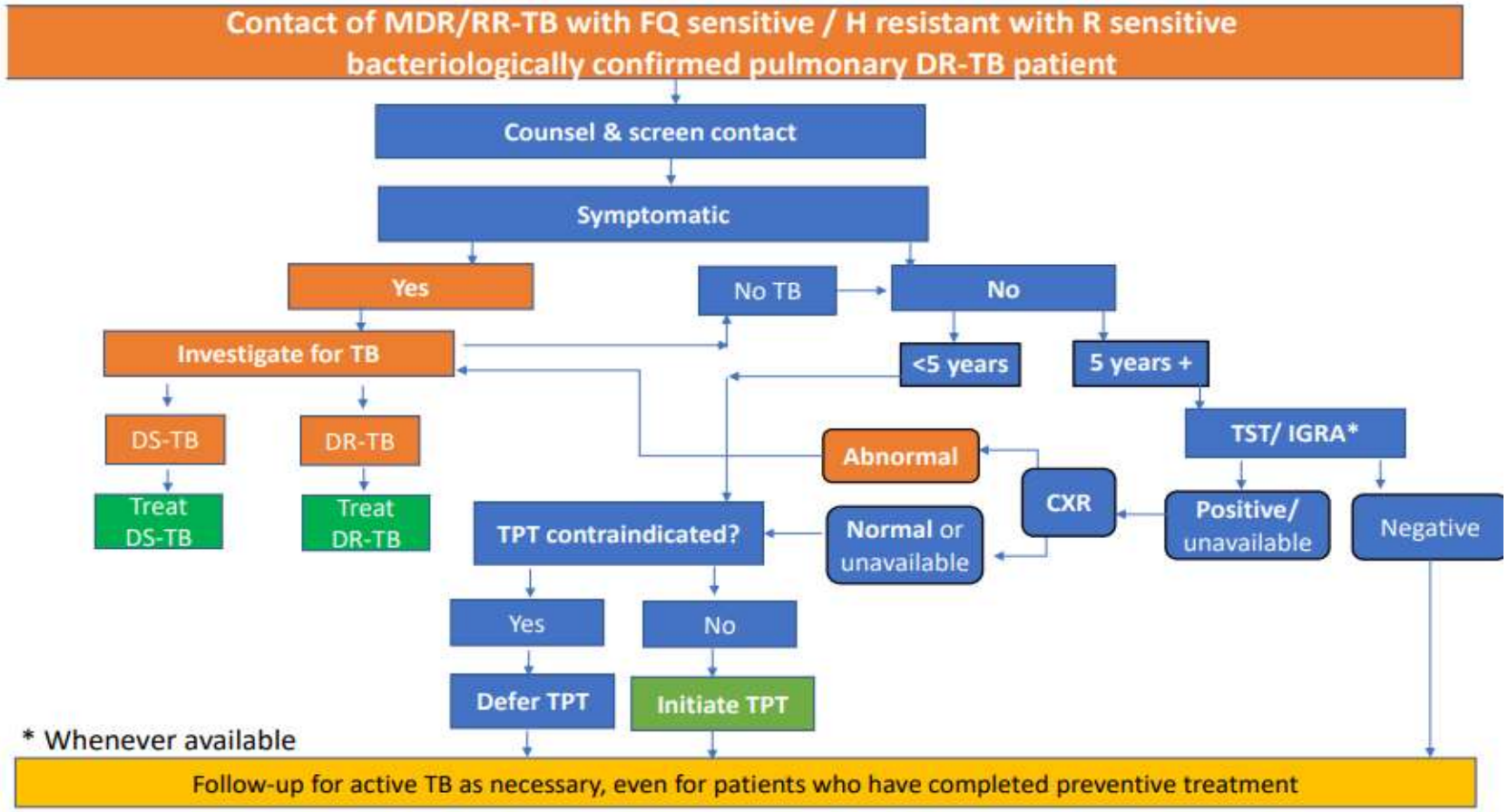
Kherabi, Y.; Tunesi, S.; Kay, A.; Guglielmetti, L. Preventive Therapy for Contacts of Drug-Resistant Tuberculosis. Pathogens 2022, 11, 1189

Study	Country	Study Design	DR-TB Contacts Included	Adults/ Children	Evidence of a TB Infection (LTBI)	Compared TPT (Months/Drug)	Primary Endpoint	Grade 3 or 4 Adverse Events	Comple-tion Rate
Seddon et al., 2013 [31]	South Africa	Prospective cohort study	186	Children ≤ 5 years-old HIV-positive children ≤ 15 years-old	LTBI was diagnosed in 73 children, some children were treated without any evidence of a LTBI.	6 HE + Ofx	Incidence of TB disease: 6/186 (3%) with TPT	7/186 (4%)	76%
Denholm et al., 2012 [32]	Australia	Retrospec-tive cohort study	49	Adults & children	All of the subjects included in the analysis had a proven LTBI.	6–9 Mfx +/− E 6 Cfx +/− Z 6 RZE 9 HZ 6–9 RZ No treatment	Incidence of TB disease: 0/11 (0%) with TPT 2/38 (5%) without TPT	None	82%
Schaaf et al., 2002 [33]	South Africa	Prospective cohort study	105	Children ≤ 5 years-old	LTBI was diagnosed in 70 children, some children were treated without any evidence of a LTBI.	6 HZ + Eth 6 HZE 6 HE + Eth 6 E + Eth 6 HZE + Eth 6 ZE + Eth 6 HZ + Eth	Incidence of TB disease: 2/41 (5%) with TPT 13/64 (20%) without TPT	NR	NR

Source	Year of Publication	Population Addressed	Recommendation to Treat	Watchful Observation Approach	Drug	Ancillary Drugs	Treatment Duration
WHO	2020	General	Yes	Consider	Lfx	E, Eth	6 months
ECDC	2012	General	Yes	Consider	Lfx	No	6 months
ATS/CDC/ ERS/IDSA	2019	General	Yes	Not recommended	Lfx	No	6–12 months
MSF	2022	Pediatric	Yes	Consider	Lfx	No	6 months

Kherabi, Y.; Tunesi, S.; Kay, A.; Guglielmetti, L. Preventive Therapy for Contacts of Drug-Resistant Tuberculosis. Pathogens 2022, 11, 1189

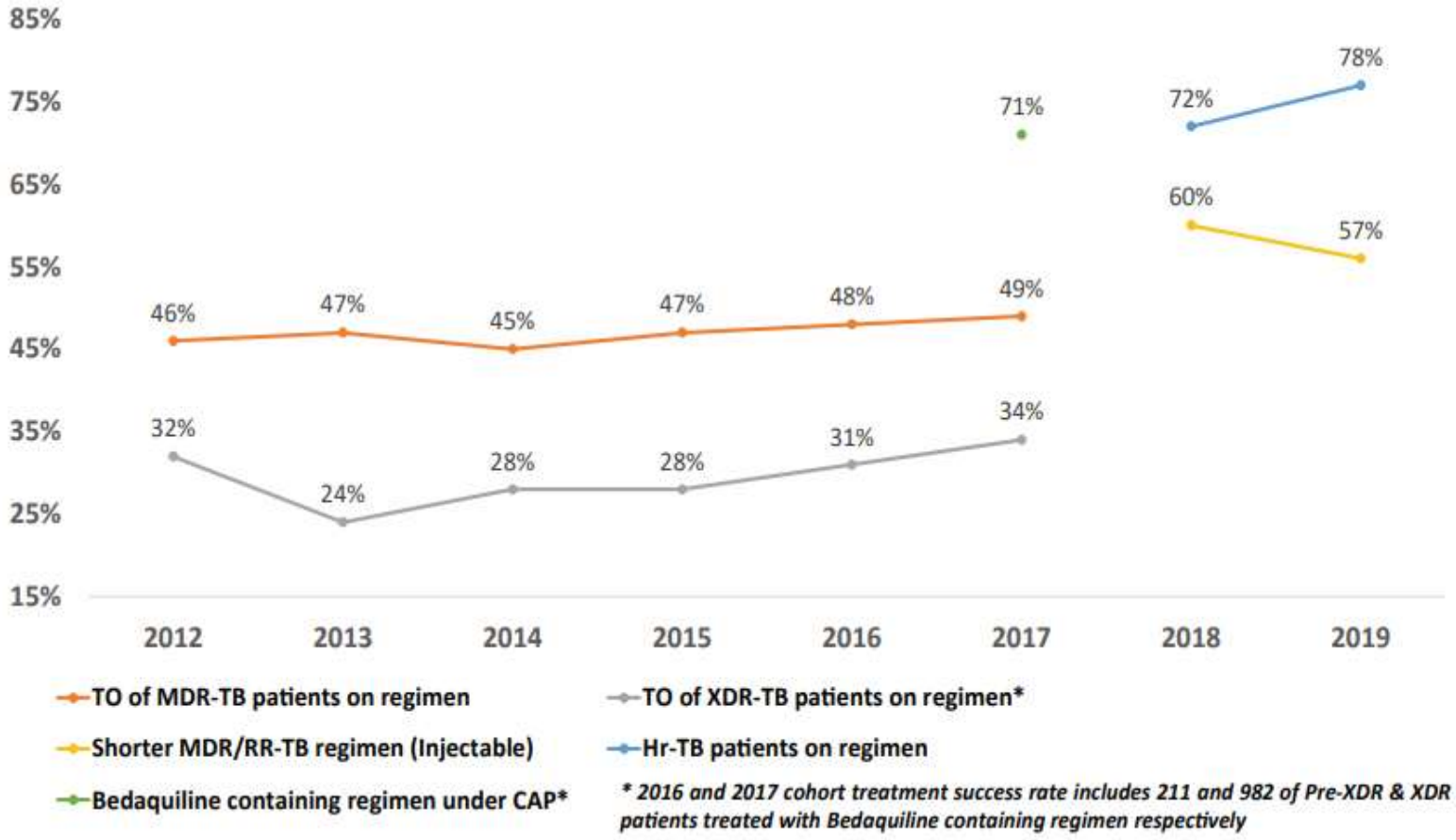
TPT for DR-TB contacts in India



- **Preventive treatment among HHC of MDR-TB index patients (in whom FQ resistance has been ruled out) -6Lfx**
- **HHC of H resistant index patients (in whom R resistance has been ruled out)-4R**
- **Regardless of whether treatment is given or not, clinical follow up should be done for two years and any emergent sing and symptoms of TB**

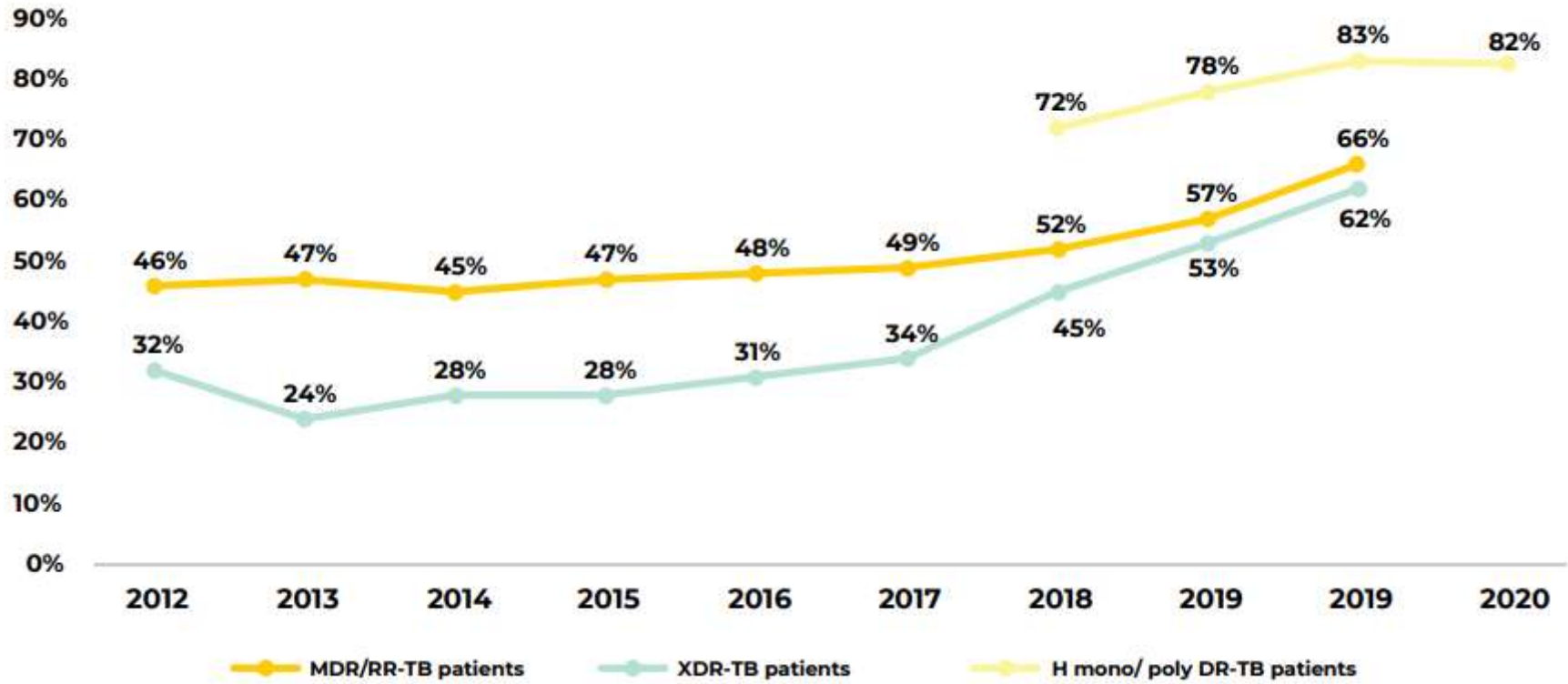
PMDT INDIA 2021

Treatment success rate of M/XDR-TB patients on different regimens



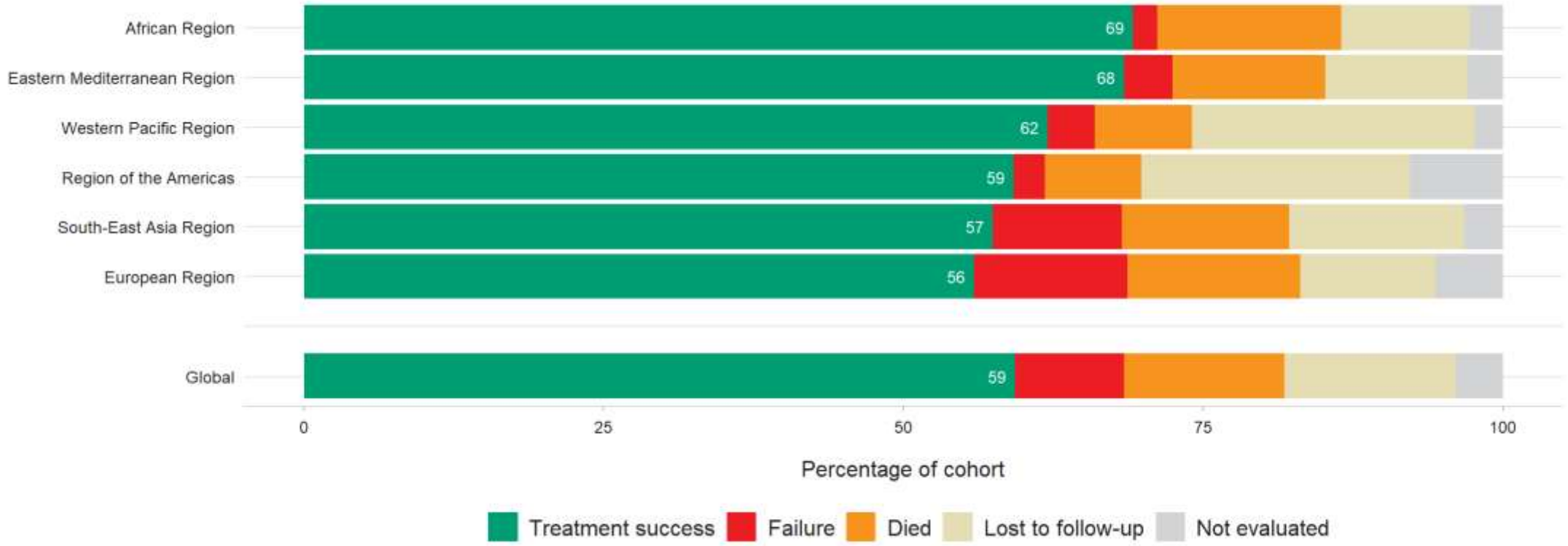
PMDT INDIA 2021

Trend of treatment success rate of M/XDR TB patients



INDIA TB REPORT 2023

Treatment outcomes for MDR/RR-TB cases started on treatment in 2018, WHO regions and globally



Global TB report 2021

2022 Global New TB Drug Pipeline[1] Updated 11/3/2022

Discovery | Preclinical Development | Clinical Development

Lead Optimization → Early Stage Development → GMP / GLP Tox. → Phase 1 → Phase 2 → Phase 3 → Regulatory Market Approvals

Lead Optimization

- Indazole sulfonamides
- Diarylthiazoles
- DprE1 Inhibitors
- Direct InhA Inhibitors
- Mtb energy metabolism
- Gyrase Inhibitors
- Arylsulfonamides
- Inhibitors of MmpL3, Translocase-1, ClpC1, PKS13, F-ATP synthase
- Oxazolidinones
- DnaE1 / Nargenicin analogs

Early Stage Development

- TBD-09, TBD-10 (MK-7762, -3854)
- MPL-447*
- JSF-3285*
- CPZEN-45*
- NTB-3119*
- MBX-4888A (1810)*
- FNDR-10045*, FNDR-20364*

GMP / GLP Tox.

- GSK-839*
- OTB-658

Phase 1

- BVL-GSK098*
- GSK-286*
- TBAJ-876
- TBAJ-587
- TBI-223
- Macozinone* (PBTZ-169)

Phase 2

- Sanfetrinem
- Delpazolid
- Sutezolid
- Sudapyridine (WX-081)
- BTZ-043*
- TBA-7371*
- OPC-167832*
- GSK-656* (070)
- Telacebec*
- Pyrifazimine (TBI-166)
- SPR720*
- SQ-109*

Phase 3

Results Reported / Expected in 2022/23

- TB Practecal
- ZeNix
- Simplici TB (4-month regimen)
- Truncate TB (2-month regimens)
- STREAM 2

Regulatory Market Approvals

- Bedaquiline*
- Delamanid*
- Pretomanid*

*New chemical class. Known chemical classes for any indication are color coded: rifamycin, oxazolidinone, nitroimidazole, diarylquinoline, benzothiazinone, imidazopyridine amide, beta-lactam.

[1] New Molecular Entities not yet approved, being developed for TB or only conditionally approved for TB. Showing most advanced stage reported for each. Details for projects listed can be found at http://www.newtbdrugs.org/pipeline/clinical

Ongoing projects without a lead compound identified: http://www.newtbdrugs.org/pipeline/discovery

Underline = updates since May 2022

WORKING GROUP ON NEW TB DRUGS

www.newtbdrugs.org

Updated: November 2022

Ongoing Trials on preventive therapy for DR-TB contacts

Study	Population Type	Population Size (N)	Structure	Duration of Treatment
V-QUIN	Adults > 15 years	3344	Lfx vs. Placebo	6 months
TB-CHAMP	Children < 5 years	1556	Lfx vs. Placebo	6 months
PHOENIx	Adults > 15 years	5610	Dlm vs. H	6 months

Kherabi Y , et al . Pathogens 2022, 11, 1189

Conclusion

- CBNAAT for diagnosis of MTB and drug resistant needed upfront
- Xpert MTB/XDR improve access to rapid drug susceptibility testing, especially for ruling out fluoroquinolone resistance
- WGS should be offered after clinical , microbiological and DST correlation, WGS still not widely available and costly
- MDR TB shorter regimens has better outcomes as compared to longer regimen , can improve compliance
- For treatment of household contacts of MDR tb index case , data is based on prospective studies , results of RTCs are awaited, no data on XDR tb contact for treatment


WORLD TB DAY 2023
YES! WE CAN END TB
#YesWeCanEndTB #WorldTBDay #EndTB
Stop TB Partnership