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La gestione della TB MDR

13th ACCP 2023

Meeting on Antimicrobial Chemotherapy in Clinical Practice (ACCP)

Drug-resistant TB (DR-TB): TB disease caused by a strain of *Mycobacterium tuberculosis* complex that is resistant to any TB medicines.

Extensively drug-resistant TB (XDR-TB): TB disease caused by a strain of *M. tuberculosis* complex that is resistant to rifampicin (and may also be resistant to isoniazid), and that is also resistant to at least one fluoroquinolone (levofloxacin or moxifloxacin) and to at least one other "Group A" drug (bedaquiline or linezolid).

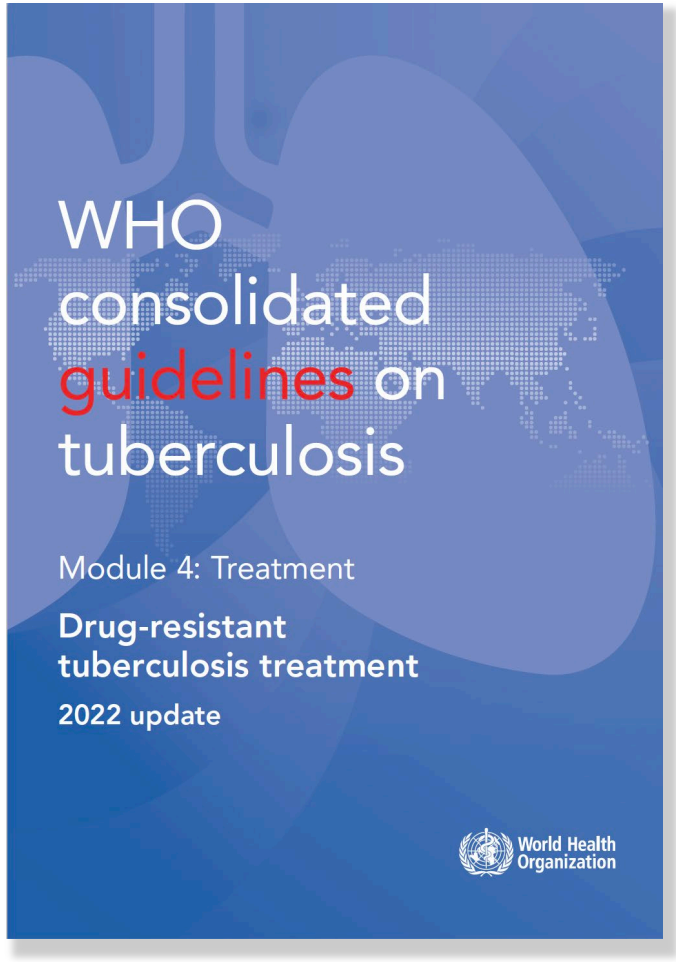
MDR/RR-TB: refers to either multidrug-resistant TB (MDR-TB) or rifampicin-resistant TB (RR-TB).

Multidrug-resistant TB (MDR-TB): TB disease caused by a strain of *M. tuberculosis* complex that is resistant to rifampicin and isoniazid.

Pre-extensively drug-resistant TB (pre-XDR-TB): TB disease caused by a strain of *M. tuberculosis* complex that is resistant to rifampicin (and may also be resistant to isoniazid), and that is also resistant to at least one fluoroquinolone (either levofloxacin or moxifloxacin).

Rifampicin-resistant TB (RR-TB): TB disease caused by a strain of *M. tuberculosis* complex that is resistant to rifampicin. These strains may be susceptible or resistant to isoniazid (i.e. multidrug-resistant TB [MDR-TB]), or resistant to other first-line or second-line TB medicines.

Rifampicin-susceptible, isoniazid-resistant TB (Hr-TB): TB disease caused by a strain of *M. tuberculosis* complex that is resistant to isoniazid but susceptible to rifampicin.



Severe extrapulmonary TB: presence of miliary TB, TB meningitis, osteoarticular or pericardial TB. In children aged below 15 years, extrapulmonary forms of disease other than lymphadenopathy (peripheral nodes or isolated mediastinal mass without compression) are considered severe.

- The detection of multidrug-resistant (**MDR**) tuberculosis (resistance to rifampicin and isoniazid) or rifampicin-resistant tuberculosis has **increased by about 20% annually** over the past decade (2009–2018). Drug-resistant tuberculosis underpins about **15–20% of global tuberculosis mortality**.[1,2]

- In some countries, such as Russia and Belarus, **almost half of all patients with tuberculosis have rifampicin-resistant tuberculosis**.[3]

- Unmet needs and challenges concerning drug-resistant tuberculosis include **suboptimal diagnosis** (about 60% of cases remain undiagnosed), **inadequate access** to effective drugs (about 30% of patients receive appropriate treatment), and **poor treatment outcomes** (treatment success is achieved in only about 60% of patients).[2]

1 Lange C, Dheda K, Chesov D, Mandalakas AM, Udwadia Z, Horsburgh CR Jr. Management of drug-resistant tuberculosis. *Lancet* 2019; **394:** 953–66. 2 WHO. Global tuberculosis report 2021. Geneva: World Health Organization, 2021. 3 WHO, European Centre for Disease Prevention and Control. Tuberculosis surveillance and monitoring in Europe 2022–2020 data. Copenhagen: World Health Organization and the European Centre for Disease Prevention and Control, 2022.

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journal homepage: www.clinicalmicrobiologyandinfection.com

Original article

Availability and costs of medicines for the treatment of tuberculosis in Europe

Gunar Günther [1, 2], Lorenzo Guglielmetti [3, 4], Claude Leu [1], Christoph Lange [5, 6, 7, 8, *], Frank van Leth [9] on behalf of Tuberculosis Network European Trials group[†]

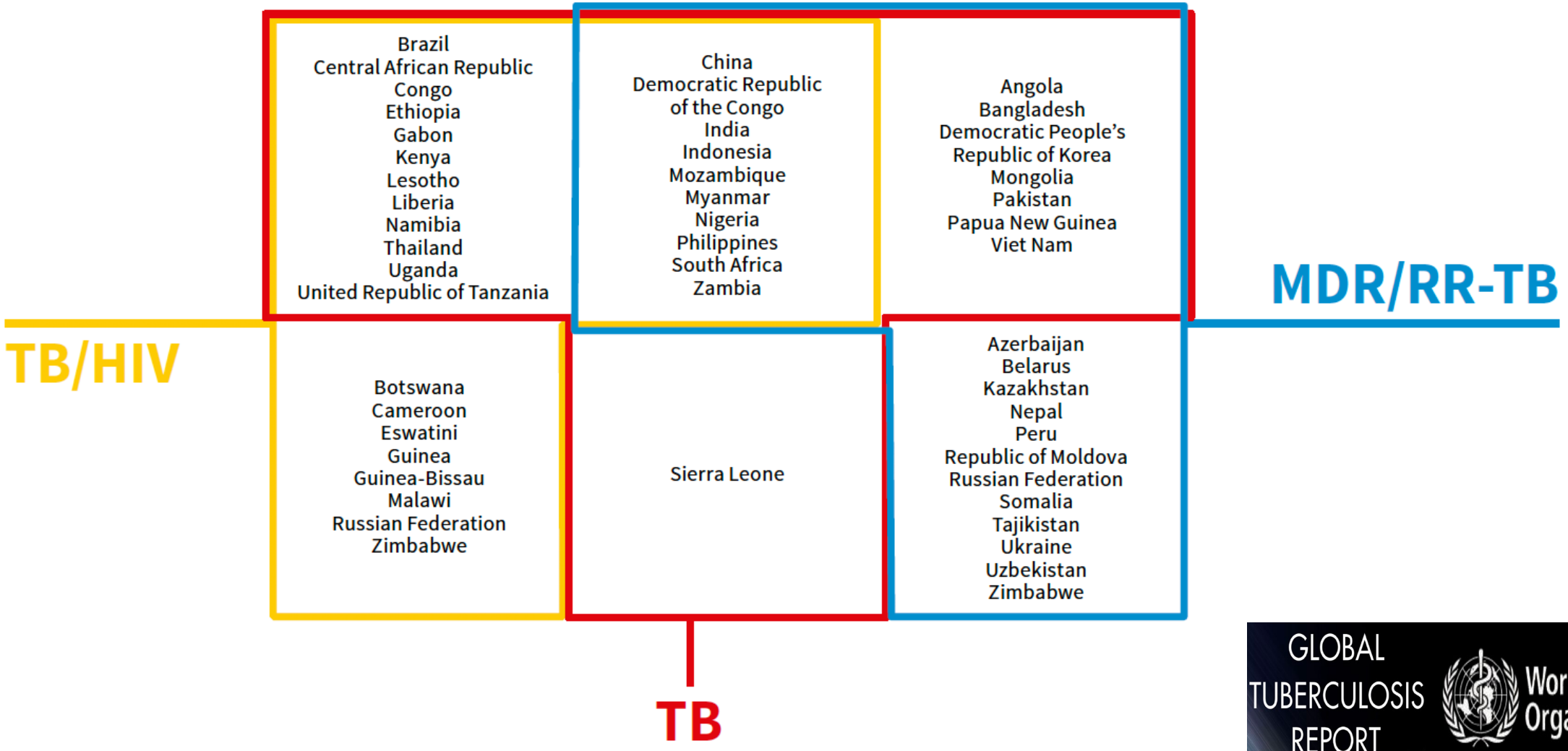
Objectives: To evaluate the access to comprehensive diagnostics and novel antituberculosis medicines in European countries.

Methods: We investigated the access to genotypic and phenotypic *Mycobacterium tuberculosis* drug susceptibility testing and the availability of antituberculosis drugs and calculated the cost of drugs and treatment regimens at major tuberculosis treatment centres in countries of the WHO European region where rates of drug-resistant tuberculosis are the highest among all WHO regions. Results were stratified by middle-income and high-income countries.

Results: Overall, 43 treatment centres from 43 countries participated in the study. For WHO group A drugs, the frequency of countries with the availability of phenotypic drug susceptibility testing was as follows: (a) 75% (30/40) for levofloxacin, (b) 82% (33/40) for moxifloxacin, (c) 48% (19/40) for bedaquiline, and (d) 72% (29/40) for linezolid. Overall, of the 43 countries, 36 (84%) and 24 (56%) countries had access to bedaquiline and delamanid, respectively, whereas only 6 (14%) countries had access to rifapentine. The treatment of patients with extensively drug-resistant tuberculosis with a regimen including a carbapenem was available only in 17 (40%) of the 43 countries. The median cost of regimens for drug-susceptible tuberculosis, multidrug-resistant/rifampicin-resistant tuberculosis (shorter regimen, including bedaquiline for 6 months), and extensively drug-resistant tuberculosis (including bedaquiline, delamanid, and a carbapenem) were €44 (minimum–maximum, €15–152), €764 (minimum–maximum, €542–15152), and €8709 (minimum–maximum, €7965–11759) in middle-income countries ($n = 12$) and €280 (minimum–maximum, €78–1084), €29765 (minimum–maximum, €11116–40584), and €217591 (minimum–maximum, €82827–320146) in high-income countries ($n = 29$), respectively.

Discussion: In countries of the WHO European region, there is a widespread lack of drug susceptibility testing capacity to new and repurposed antituberculosis drugs, lack of access to essential medications in several countries, and a high cost for the treatment of drug-resistant tuberculosis. **Gunar Günther, Clin Microbiol Infect 2022;■:1**

MDR TB, high prevalence Countries



GLOBAL TUBERCULOSIS REPORT

World Health Organization

Are we doing enough for controlling tuberculosis and multi-drug resistance in an epicenter of the current migration emergency (Calabria Region, Southern Italy)?

Salvatore Rotundo[1] · Helen Linda Morrone[1] · Luigia Gallo[2] · Saveria Dodaro[3] · Francesco D'Aleo[4] · Pasquale Minchella[5] · Giovanni Matera[2] · Francesca Greco[3] · Luigi Principe[4] · Enrico Maria Trecarichi[1] · Salvatore Nisticò[5] · Carlo Torti[1] · the Calabria T. B. group

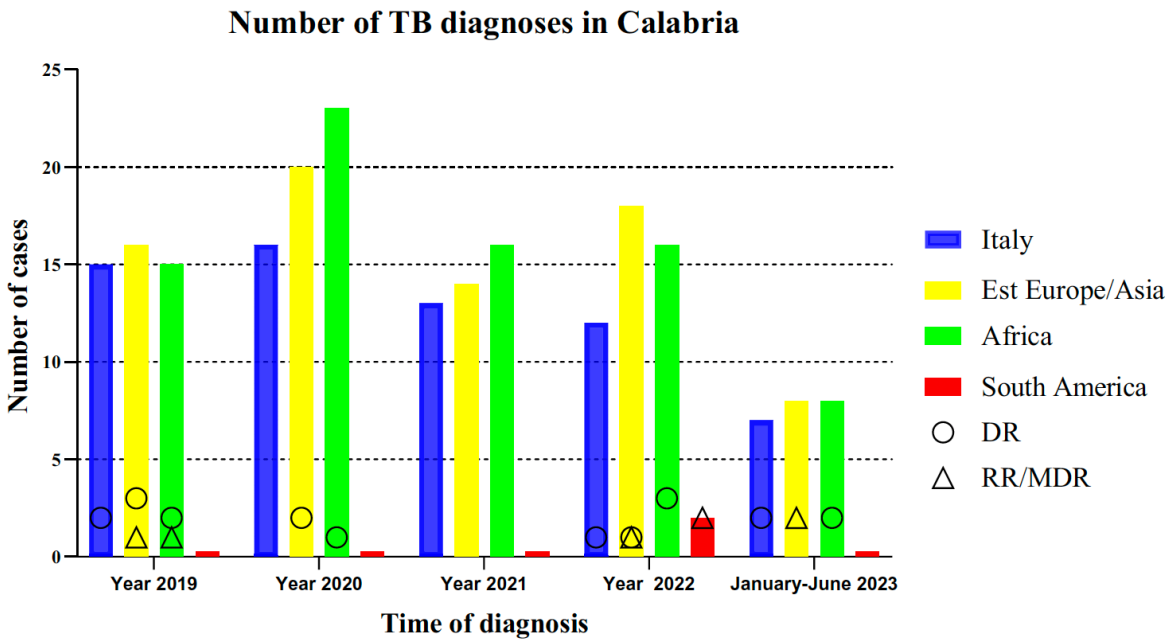
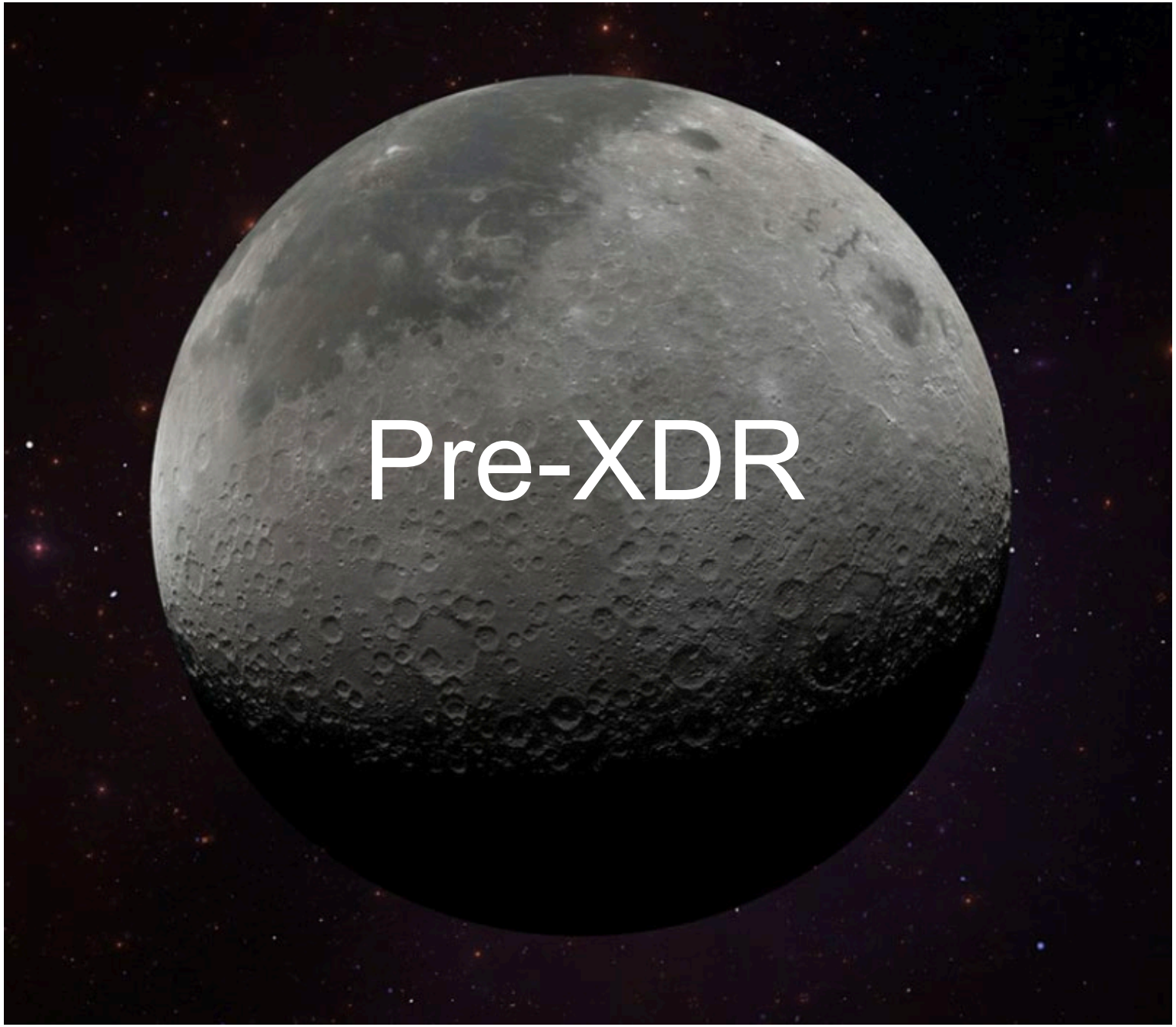


Fig. 1 Number of TB diagnoses in Calabria by year. Colored bars indicate the number of overall patients diagnosed with tuberculosis in each year in Calabria, Italy. DR: strain resistant to at least one first-line anti-tuberculosis drug other than rifampin; RR/MDR: rifampin or multi-drug resistant strain according to World Health Organization[3]. An increase in RR/MDR-TB in the last period of this survey (from January 2022 to June 2023) was observed compared to the period from January 2019 to December 2021 (Fisher's exact test, $p=0.016$). The highest number of MDR-TB cases (5/8) was observed in the last period of this survey (form January 2022 to June 2023) after zero cases detected in 2021.

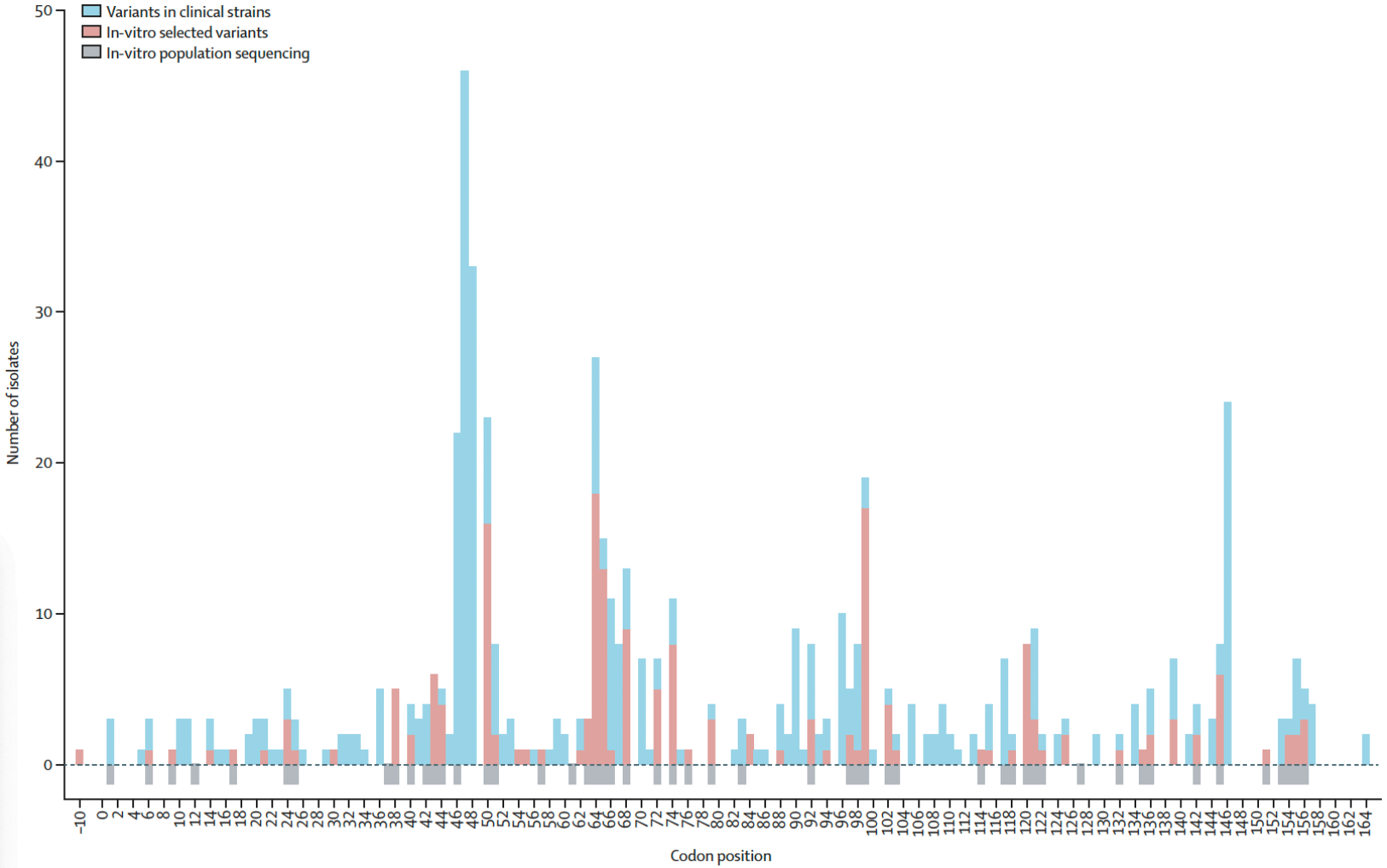
Infection
https://doi.org/10.1007/s15010-023-02106-8

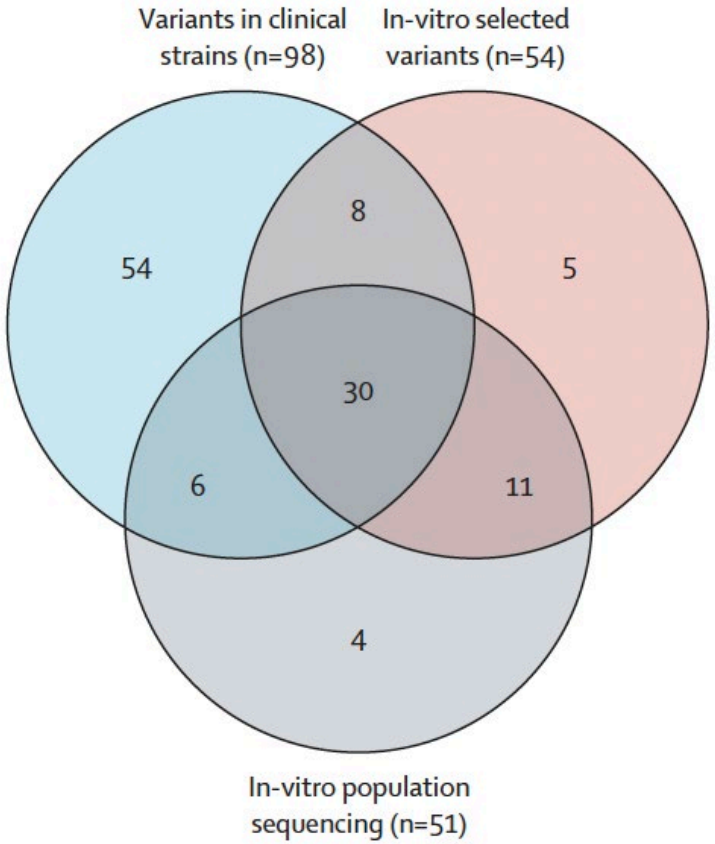

Pre-XDR

Bedaquiline and clofazimine resistance in *Mycobacterium tuberculosis*: an in-vitro and in-silico data analysis

Lancet Microbe 2023; 4: e358–68

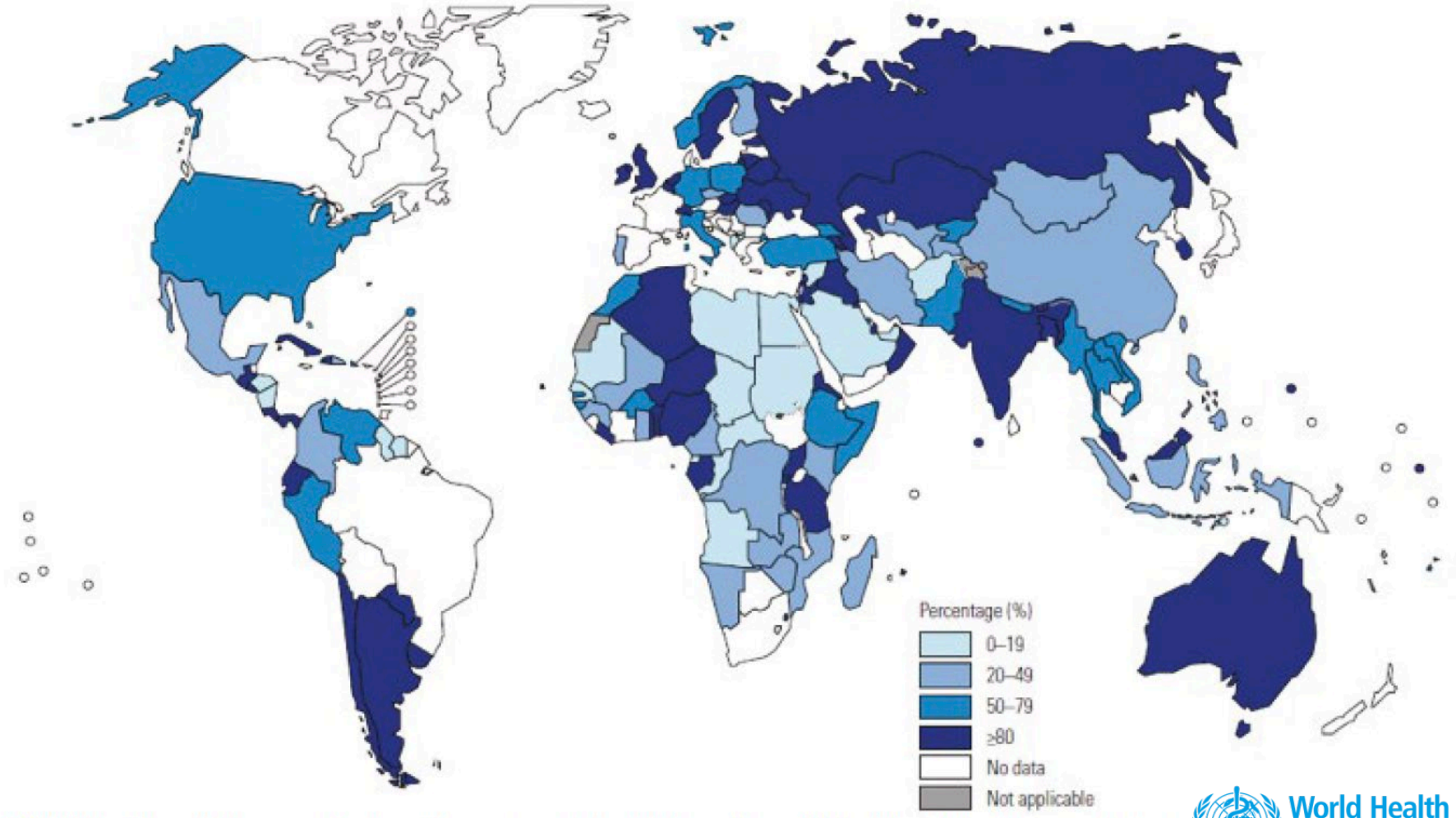
Lindsay Sonnenkalb, Joshua James Carter*, Andrea Spitaleri, Zamin Iqbal, Martin Hunt, Kerri Marie Malone, Christian Utpatel, Daniela Maria Cirillo, Camilla Rodrigues, Kayzad Soli Nilgiriwala, Philip William Fowler†, Matthias Merker†, Stefan Niemann†, on behalf of the Comprehensive Resistance Prediction for Tuberculosis: an International Consortium‡*





Affected codon positions in *Rv0678* leading to bedaquiline resistance in this study and in clinical strains

Percentage of MDR/RR-TB cases tested for susceptibility to fluoroquinolones



MDR/RR-TB: multidrug-resistant or rifampicin-resistant tuberculosis; WHO: World Health Organization.

World Health Organization

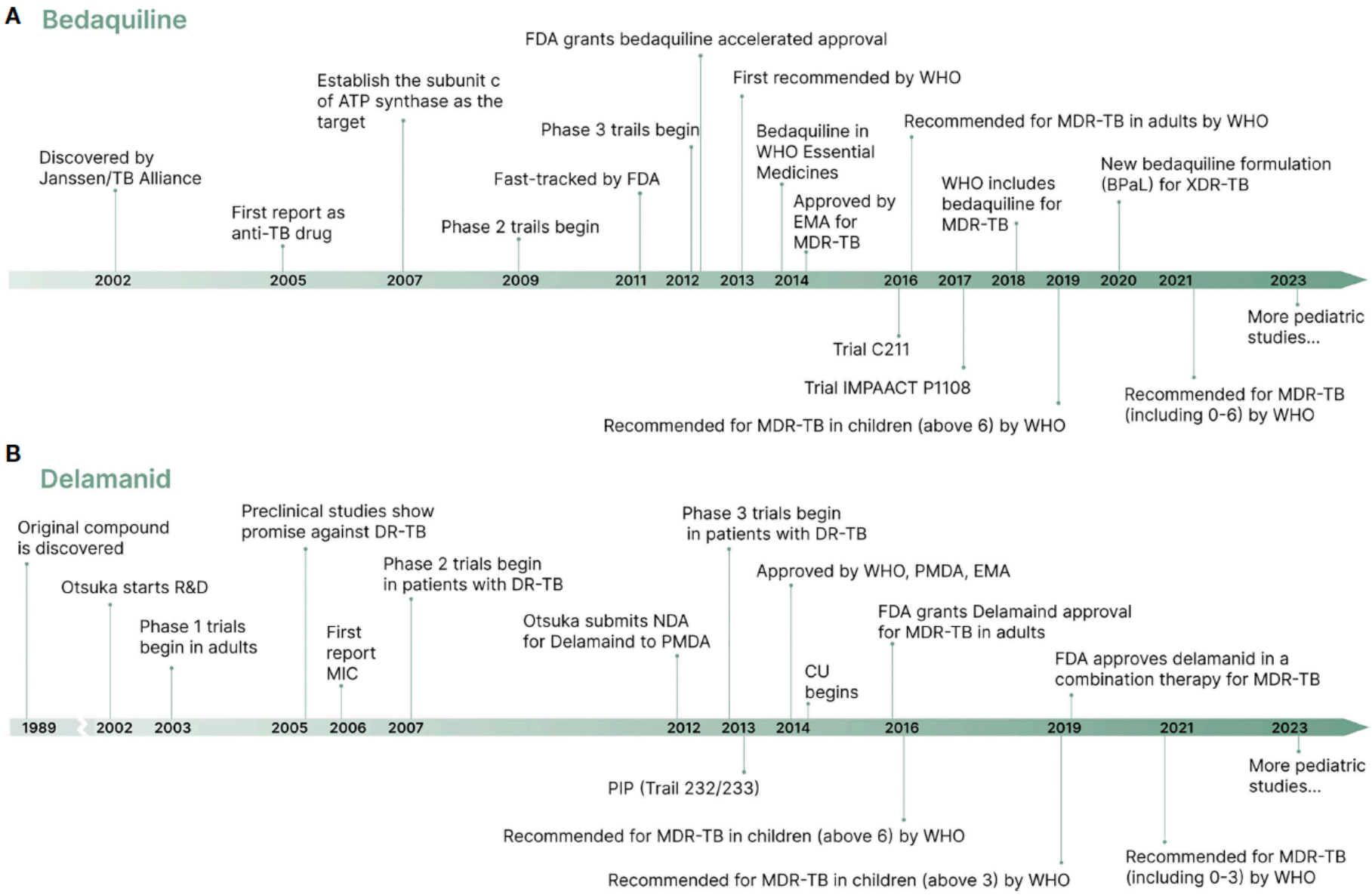
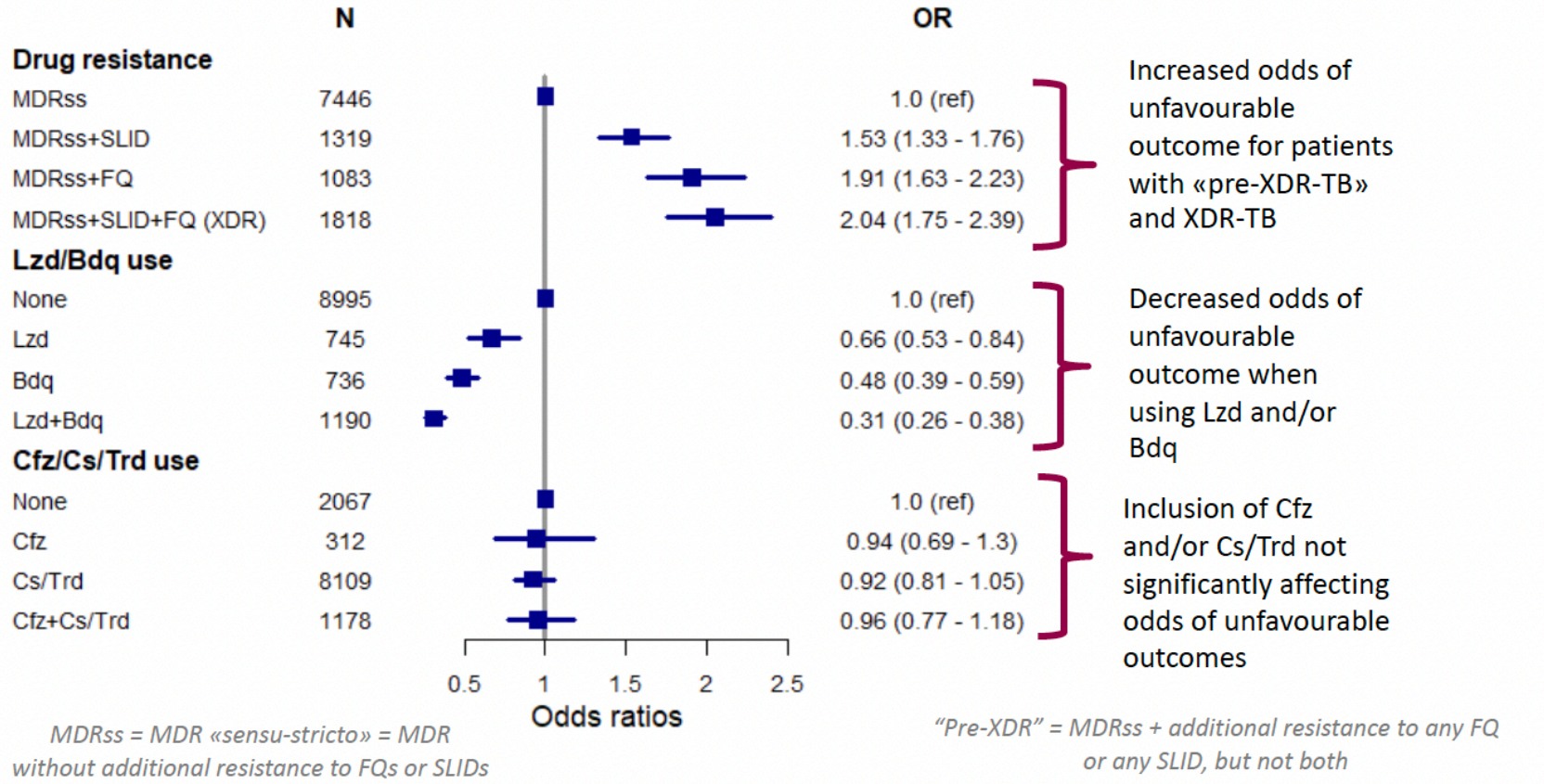


FIGURE 1
A brief timeline of the development of new drugs bedaquiline and delamanid. **(A)** Bedaquiline development timeline. **(B)** Delamanid development timeline.

Association with drug resistance pattern and unfavourable treatment outcome stratified by regimens that include linezolid, bedaquiline, clofazimine, cycloserine and terizidone

N=11,666 patients with MDR-TB; 4,653 (39.9%) had an unfavorable treatment outcome



Bdq: bedaquiline; Cfz: clofazimine; Cs: cycloserine; FQ: fluoroquinolone; Lzd: linezolid; MDR: multidrug resistant; MDRss: multidrug-resistant sensu stricto; N: number; OR: odds ratio; SLID: second-line injectable drug; TB: tuberculosis; Trd; terizidone; XDR: extensively drug resistant.

Roelens et al. Am J Respir Crit Care Med, 2021

Trial (Ref.)	Inclusion/Exclusion criteria
STREAM (NEJM, 2019)	• RR, FQL and aminoglycoside susceptible
Nix-TB (NEJM, 2020)	• XDR (N=71, 65%) • MDR (N=38, 34%) that was not responsive to treatment or for which a second-line regimen had been discontinued because of side effects
NeXT (Am J Respir Crit Care Med, 2022)	• RR/MDR, FQL and aminoglycoside susceptible
MDR-END (Lancet, 2022)	• MDR with FQL susceptible
ZeNix (NEJM, 2022)	• XDR (N=75, 41.4%) • Pre-XDR (N=85, 47%) • RR not responsive or for which a second-line regimen had been discontinued due to side effects (N=21, 11.6%)
STREAM stage 2 (Lancet 2022)	• RR, FQL and aminoglycoside susceptible

ORIGINAL ARTICLE

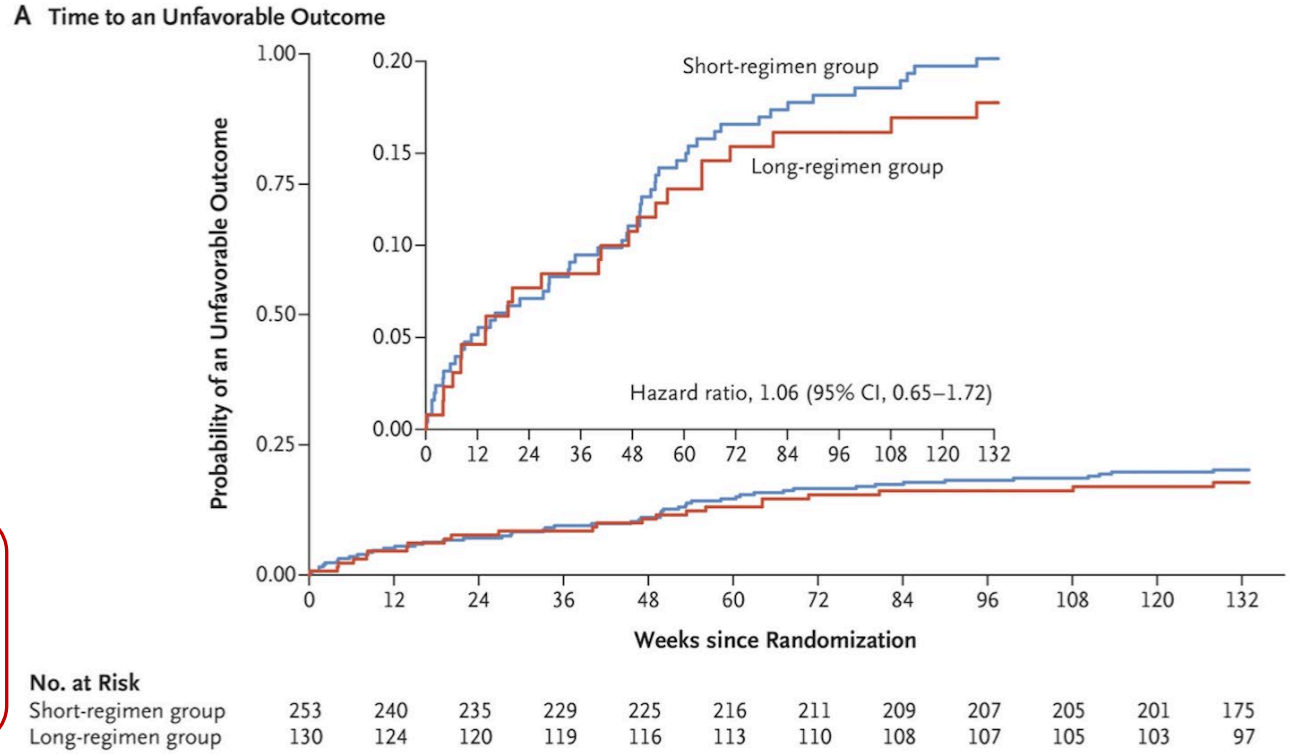
The NEW ENGLAND JOURNAL of MEDICINE

A Trial of a Shorter Regimen for Rifampin-Resistant Tuberculosis

Andrew J. Nunn, M.Sc., Patrick P.J. Phillips, Ph.D., Sarah K. Meredith, M.Sc., Chen-Yuan Chiang, Dr.Philos., Francesca Conradie, M.B., Ch.B., Doljinsuren Dalai, M.D., Armand van Deun, Ph.D., Phan-Thuong Dat, Ph.D., Ngoc Lan, Ph.D., Iqbal Master, M.B., Ch.B., Tesfamarium Mebrahtu, M.D., Daniel Meressa, M.D., et al., for the STREAM Study Collaborators*

The **STREAM trial** randomized 383 participants to receive a STR* (9–11 months) or a long 20-month individualized regimen following the 2011 WHO guidelines. The STR differed from the original Bangladesh regimen only by the substitution of high-dose gatifloxacin by high-dose moxifloxacin.

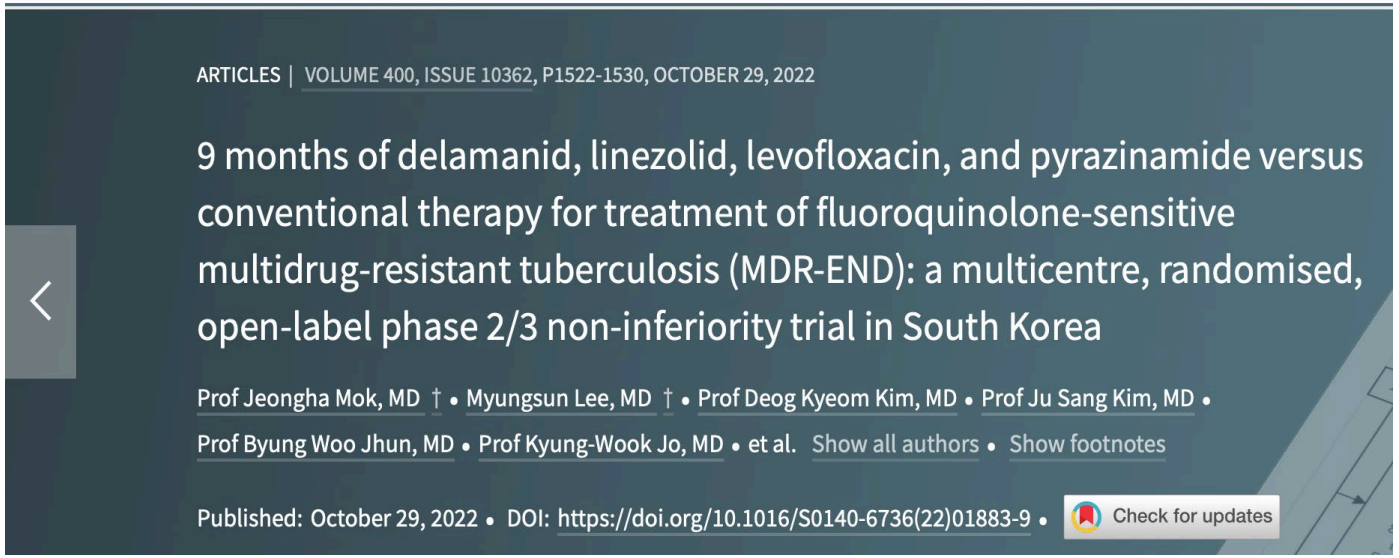
The trial showed **non-inferiority of the STR in persons with rifampicin-resistant but FLQ- and aminoglycoside-susceptible TB.**



***The short regimen consisted of moxifloxacin (high-dose), clofazimine, ethambutol, and pyrazinamide administered over a 40-week period, supplemented by kanamycin, isoniazid, and prothionamide in the first 16 weeks.** The intensive phase could be extended to 20 or 24 weeks for participants who did not have conversion to a negative smear by 16 or 20 weeks, respectively.

NEJM 2019; 380:1201-1213

THE LANCET



ARTICLES | VOLUME 400, ISSUE 10362, P1522-1530, OCTOBER 29, 2022

9 months of delamanid, linezolid, levofloxacin, and pyrazinamide versus conventional therapy for treatment of fluoroquinolone-sensitive multidrug-resistant tuberculosis (MDR-END): a multicentre, randomised, open-label phase 2/3 non-inferiority trial in South Korea

Prof Jeongha Mok, MD † • Myungsun Lee, MD † • Prof Deog Kyeom Kim, MD • Prof Ju Sang Kim, MD • Prof Byung Woo Jhun, MD • Prof Kyung-Wook Jo, MD • et al. Show all authors • Show footnotes

Published: October 29, 2022 • DOI: https://doi.org/10.1016/S0140-6736(22)01883-9 • Check for updates

A multicentre, randomised, open-label phase 2/3 non-inferiority trial (**MDR-END**).

Patients with MDR TB confirmed by phenotypic or genotypic drug susceptibility tests or rifampicin-resistant tuberculosis by genotypic tests, **without FQL resistance.**

The investigational group received **delamanid, linezolid, levofloxacin, and pyrazinamide for 9 months**, and the control group received a conventional 20–24-month regimen, according to the 2014 WHO guidelines.

At 24 months after treatment initiation, 60 **(70·6%)** of 85 participants **in the control group had treatment success**, **as** did 54 **(75·0%)** of 72 participants **in the shorter-regimen group** (between-group difference 4·4% [97·5% one-sided CI –9·5% to ∞]), **satisfying the predefined non-inferiority margin.**

No difference in safety outcomes was identified between the control group and the shorter-regimen group

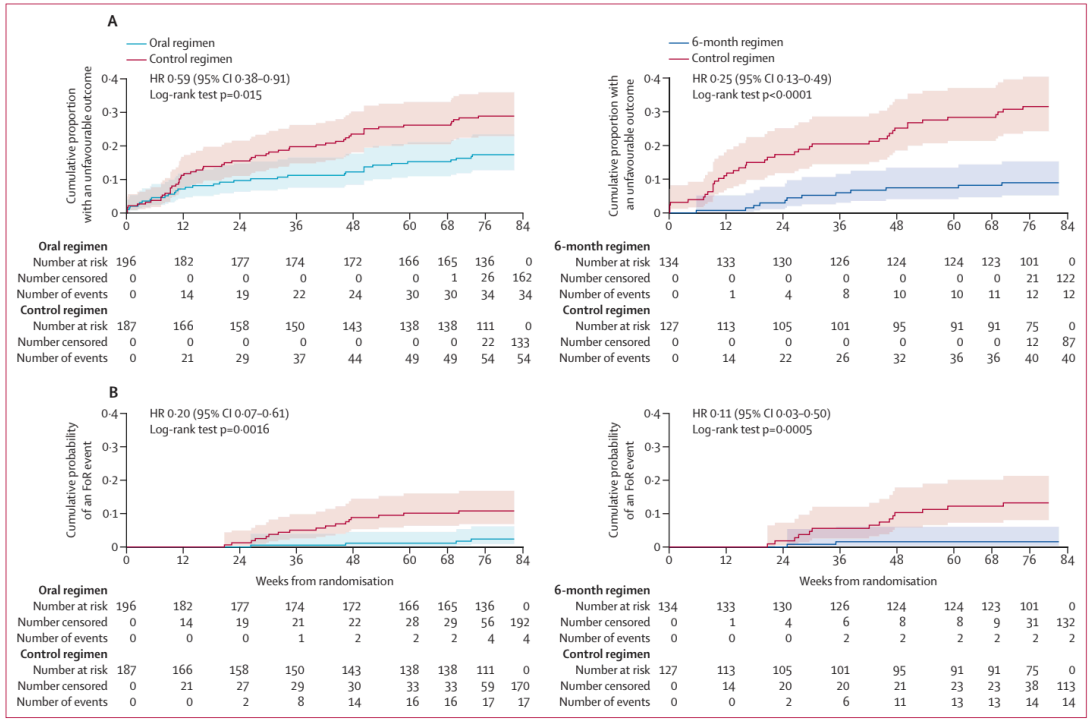
9-month treatment with oral delamanid, linezolid, levofloxacin, and pyrazinamide could represent a new treatment option for patients with fluoroquinolone-sensitive multidrug-resistant tuberculosis

THE LANCET

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

*Ruth L Goodall, Sarah K Meredith, Andrew J Nunn, Adamu Bayissa, Anuj K Bhatnagar, Gay Bronson, Chen-Yuan Chiang, Francesca Conradie, Meera Gurumurthy, Bruce Kirenga, Nana Kiria, Daniel Meressa, Ronelle Moodliar, Gopalan Narendran, Nosipho Ngubane, Mohammed Rassool, Karen Sanders, Rajesh Solanki, S Bertel Squire, Gabriela Torrea, Bazarragchaa Tsogt, Elena Tudor, Armand Van Deun, I D Rusen, for the STREAM study collaborators**

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	0	12	24	36	48	60	68	76	84
Number at risk	196	182	177	174	172	166	165	136	0
Number censored	0	0	0	0	0	0	1	26	162
Number of events	0	14	19	22	24	30	30	34	34
Control regimen									
Number at risk	187	166	158	150	143	138	138	111	0
Number censored	0	0	0	0	0	0	0	22	133
Number of events	0	21	29	37	44	49	49	54	54

6-month regimen	0	12	24	36	48	60	68	76	84
Number at risk	134	133	130	126	124	124	123	101	0
Number censored	0	0	0	0	0	0	0	21	122
Number of events	0	1	4	8	10	10	11	12	12
Control regimen									
Number at risk	127	113	105	101	95	91	91	75	0
Number censored	0	0	0	0	0	0	0	12	87
Number of events	0	14	22	26	32	36	36	40	40

Oral regimen	0	12	24	36	48	60	68	76	84
Number at risk	196	182	177	174	172	166	165	136	0
Number censored	0	14	19	21	22	28	29	56	192
Number of events	0	0	0	1	2	2	2	4	4
Control regimen									
Number at risk	187	166	158	150	143	138	138	111	0
Number censored	0	21	27	29	30	33	33	59	170
Number of events	0	0	2	8	14	16	16	17	17

6-month regimen	0	12	24	36	48	60	68	76	84
Number at risk	134	133	130	126	124	124	123	101	0
Number censored	0	1	4	6	8	8	9	31	132
Number of events	0	0	0	2	2	2	2	2	2
Control regimen									
Number at risk	127	113	105	101	95	91	91	75	0
Number censored	0	14	20	20	21	23	23	38	113
Number of events	0	0	2	6	11	13	13	14	14

Figure 2: **Time to unfavourable outcome (A) and failure or recurrence (B)**
HR=hazard ratio. FoR=failure or recurrence.

	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**

Both bedaquiline-containing regimens, a 9-month oral regimen and a 6-month regimen with 8 weeks of second-line injectable, had superior efficacy compared with a 9-month injectable-containing regimen, with fewer cases of hearing loss.

Lancet 2022; 400: 1858–68

An All-Oral 6-Month Regimen for Multidrug-Resistant Tuberculosis

A Multicenter, Randomized Controlled Clinical Trial (the NExT Study)

Aliasgar Esmail[1,2], Suzette Oelofse[1,2], Carl Lombard[3,4], Rubeshan Perumal[1,2], Linda Mbuthini[1], Akhter Goolam Mahomed[5], Ebrahim Variava[6,7,8], John Black[9], Patrick Oluboyo[10], Nelile Gwentshu[11], Eric Ngam[11], Tertius Ackerman[12], Linde Marais[12], Lynelle Mottay[1,2], Stuart Meier[1,2], Anil Pooran[1,2], Michele Tomasicchio[1,2], Julian Te Riele[13], Brigitta Derendinger[14], Norbert Ndjeka[15], Gary Maartens[16], Robin Warren[14], Neil Martinson[17,18], and Keertan Dheda[1,2,19]

Compared with traditional injectable-containing regimens, in patients with MDR/RR TB without FQL or aminoglycoside resistance, an all-oral 6-month levofloxacin, bedaquiline, and linezolid–containing MDR/RR-TB regimen was associated with a significantly improved 24-month WHO-defined treatment outcome (predominantly owing to toxicity-related drug substitution). **However, drug toxicity occurred frequently in both arms.**

In the modified intention-to-treat event-free survival analysis, participants in the intervention arm were less likely to experience an unfavorable outcome than participants in the SOC arm over a 24-month period (HR=0.4; 95%CI, 0.2–0.6).

This is also supported by an RMTL ratio of 0.5 (95% CI, 0.4–0.8; P=0.001) An exploratory subanalysis including only HIV-infected individuals showed similar results.

Am J Respir Crit Care Med. 2022 May 15;205(10):1214-1227.

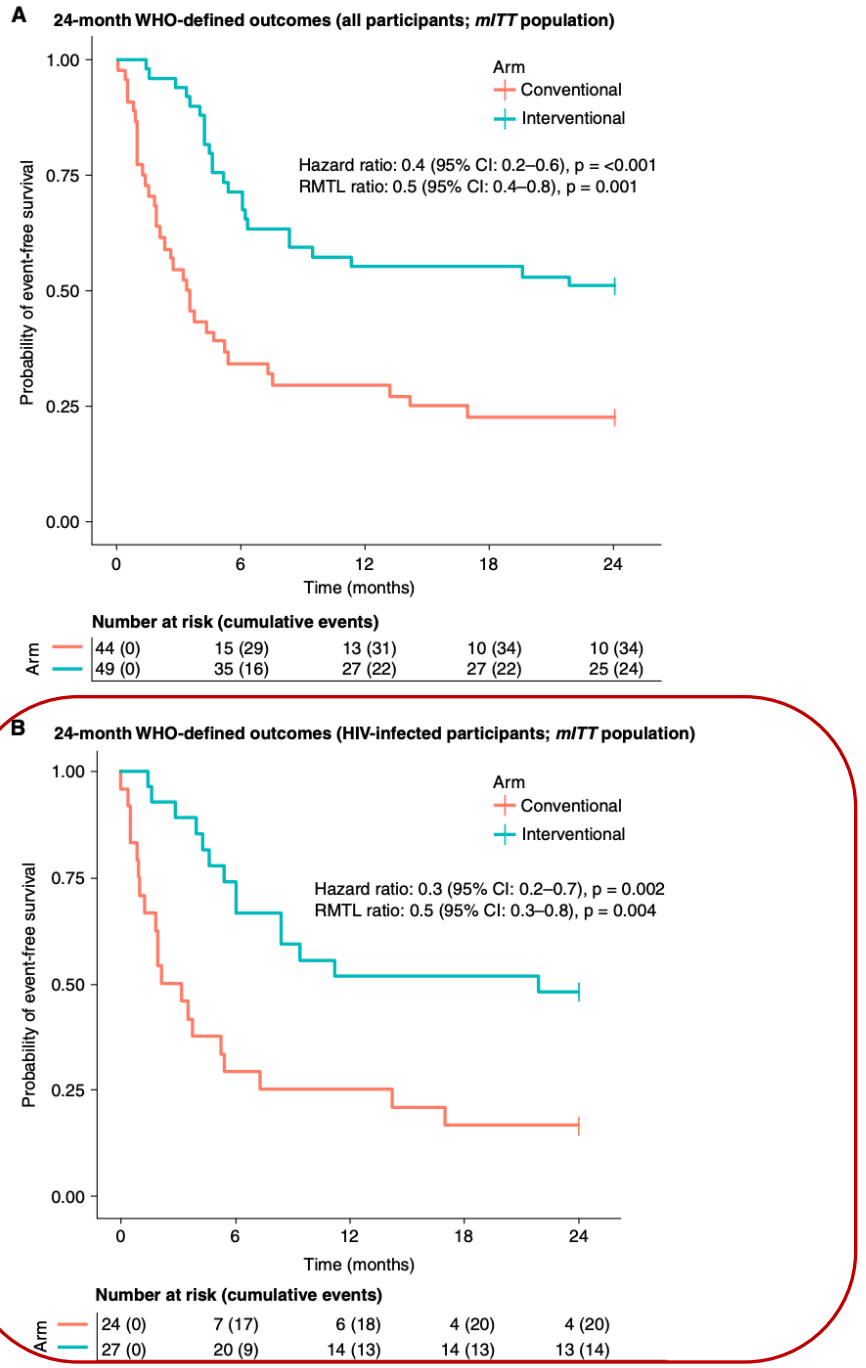


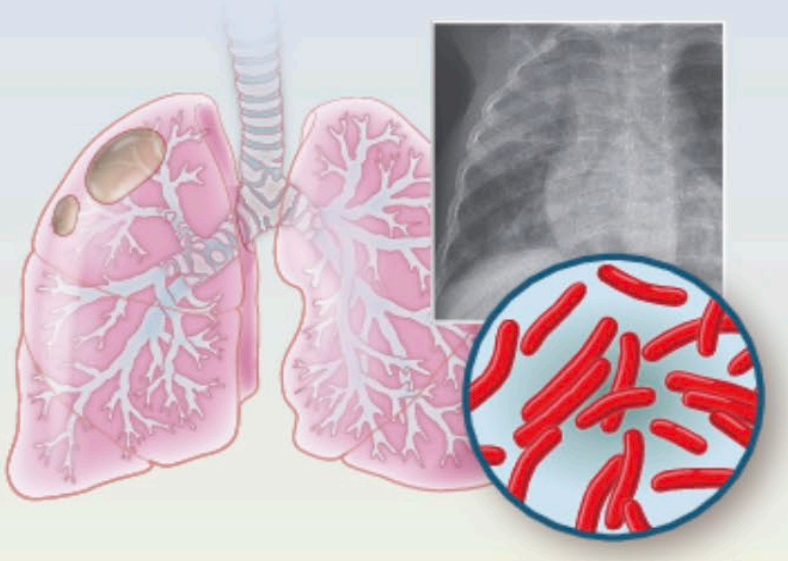
Figure 3. Summary of favorable and unfavorable outcomes in the modified intention-to-treat (mITT; *n* = 93) population. Kaplan-Meier curves indicating the probability of attaining a World Health Organization (WHO)-defined favorable outcome (event-free survival [i.e., absence of an

Treatment of Highly Drug-Resistant Pulmonary TB

F. Conradie et al. 10.1056/NEJMoa1901814

NIX-TB, AN OPEN-LABEL, SINGLE-GROUP STUDY

109 Patients
with confirmed tuberculosis

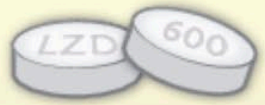


Three-drug regimen (26 wk)

Bedaquiline

Pretomanid
(recently approved)

Linezolid



XDR tuberculosis
N=71
(65%)

Nonresponsive or treatment-intolerant MDR tuberculosis
N=38
(34%)

Clinical resolution at 6 mo after therapy

90% of all patients had favorable outcomes
95% CI, 83–95

89%
95% CI, 79–95

92%
95% CI, 79–98

Linezolid associated with peripheral neuropathy (81%) and myelosuppression (48%)

The NEW ENGLAND JOURNAL of MEDICINE

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Treatment of Highly Drug-Resistant Pulmonary Tuberculosis

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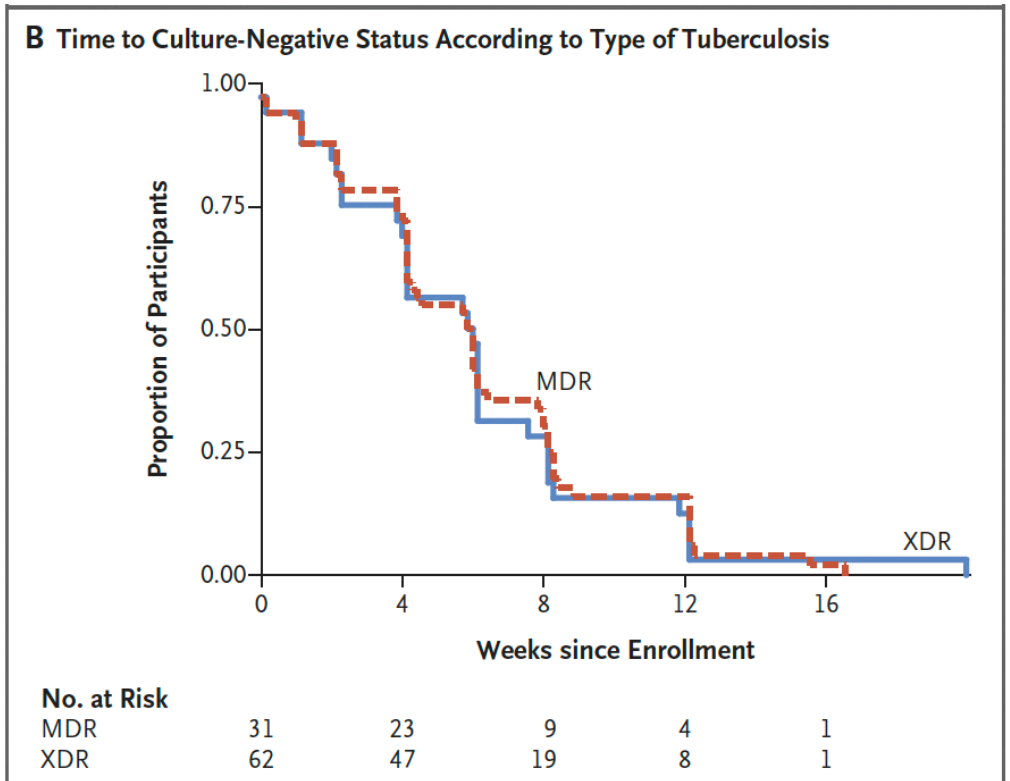

Figure 2. Time to Culture-Negative Status among Patients Who Were Positive at Baseline (Intention-to-Treat Population).

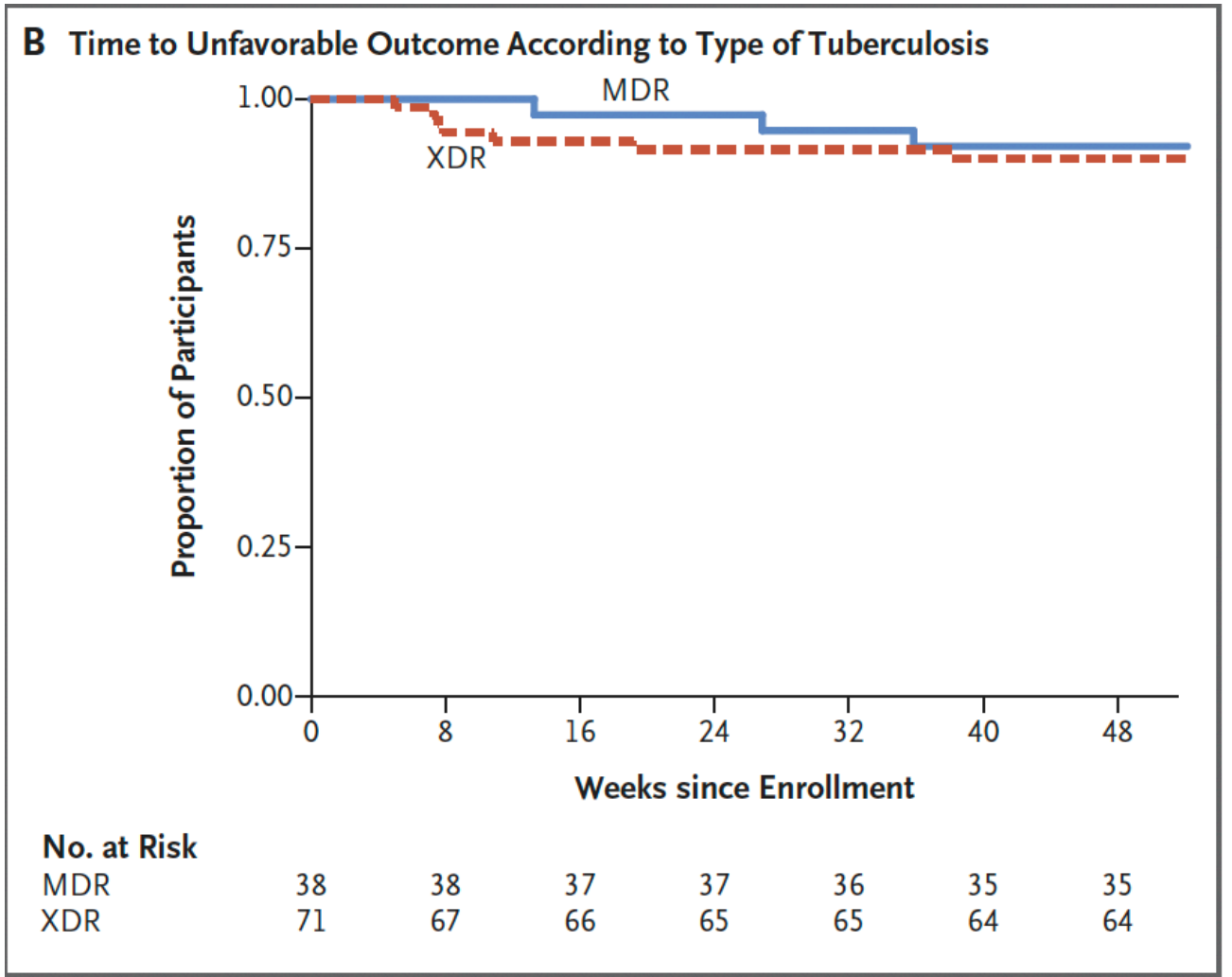

Figure 1. Time to an Unfavorable Outcome (Intention-to-Treat Population).

An unfavorable outcome was defined as treatment failure (bacteriologic or clinical) or disease relapse, with clinical treatment failure defined as a change from the protocol-specified tuberculosis treatment as a result of treatment failure, retreatment for tuberculosis, or tuberculosis-related death through follow-up until 6 months after the end of treatment. MDR denotes multidrug-resistant, and XDR extensively drug-resistant.

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XDR, pre-XDR, RR TB that was not responsive or for which a second-line regimen had been discontinued due to side effects.

Bedaquiline + pretomanid for 26 weeks + linezolid for either 26 weeks or 9 weeks (600 mg OD or 600 mg BID).

RESEARCH SUMMARY

Bedaquiline–Pretomanid–Linezolid Regimens for Drug-Resistant Tuberculosis

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CLINICAL PROBLEM

Bedaquiline–pretomanid–linezolid has had efficacy against highly drug-resistant tuberculosis, but the incidence of adverse events with the 1200-mg daily dose of linezolid has been high. Whether a different dose and duration of linezolid treatment might reduce adverse events while maintaining efficacy is unclear.

CLINICAL TRIAL

Design: A dose-blind, randomized trial assessed the efficacy and safety of four regimens of linezolid as part of bedaquiline–pretomanid–linezolid treatment for highly drug-resistant tuberculosis.

Intervention: 181 participants (≥14 years of age in South Africa and the country of Georgia and ≥18 years of age in Russia and Moldova) with extensively drug-resistant (XDR) tuberculosis, pre-XDR tuberculosis, or rifampin-resistant tuberculosis that was not responsive to treatment or for which a second-line regimen had been discontinued owing to side effects were assigned to receive bedaquiline and pretomanid for 26 weeks, along with linezolid at one of two doses for either 26 weeks or 9 weeks. The primary end point was treatment failure or disease relapse (clinical or bacteriologic) at 26 weeks after completion of treatment. A favorable outcome was maintenance of negative culture status throughout follow-up in participants who had not had an unfavorable outcome previously.

RESULTS

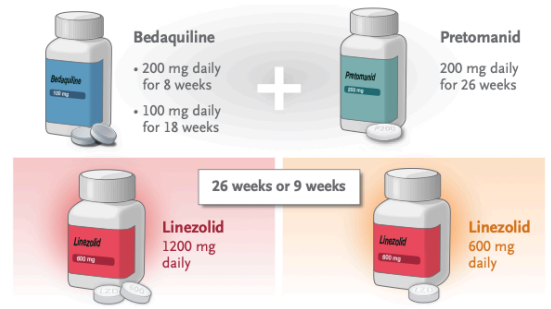
Efficacy: In the four treatment groups, the incidence of treatment failure or disease relapse (the primary end point) ranged from 7 to 16%; the incidence of a favorable outcome ranged from 84 to 93%.

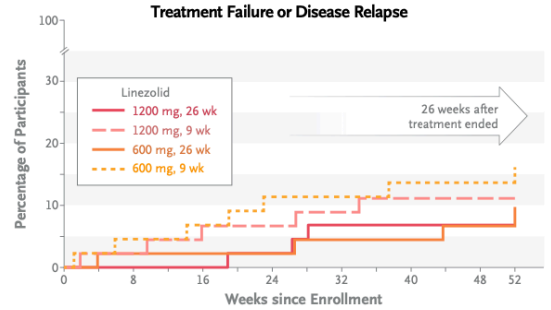
Safety: Fewer linezolid dose modifications, peripheral neuropathy episodes, and myelosuppression events occurred with the lower dose of linezolid than with the higher dose. The higher dose had a poorer safety profile in the 26-week group than in the 9-week group; there was less difference between the two lower-dose groups.

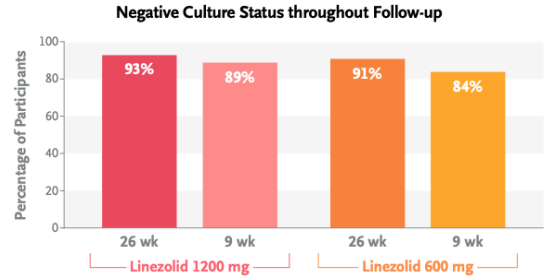
LIMITATIONS AND REMAINING QUESTIONS

- The small sample size limits the precision of estimates of efficacy.
- The trial was not powered for formal comparisons of efficacy among the treatment groups.

Links: Full Article | NEJM Quick Take | Editorial







CONCLUSIONS

In patients with highly drug-resistant tuberculosis, 600 mg of linezolid for 26 weeks resulted in a more favorable risk–benefit profile than other dose–duration regimens tested.

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ORIGINAL ARTICLE

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

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All the investigational agents were administered orally, with food and under observation, 7 days per week. The BPaL regimen consisted of the following: 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, and the BPaLC regimen included BPaL plus clofazimine at a dose of 100 mg daily (or 50 mg if the patient weighed <30 kg) for 24 weeks. In stage 2 of the trial, patients were enrolled either into the standard-care group or into one of two investigational groups.

In patients with rifampin-resistant pulmonary tuberculosis, a 24-week, all-oral regimen was noninferior to the accepted standard-care treatment, and it had a better safety profile.

B Trial Design

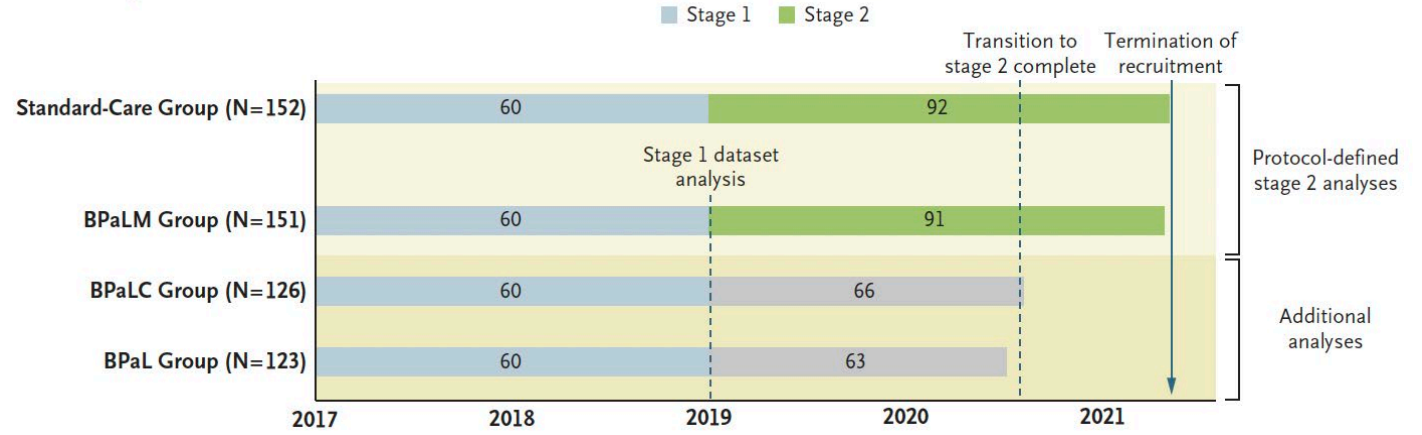


Table 2. Primary Efficacy Analysis at 72 Weeks.

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)

* The per-protocol population included all patients in the modified intention-to-treat population with the exclusion of patients who did not complete a protocol-adherent course of treatment (>80% of doses within 120% of the prescribed duration), other than because of treatment failure or death, and patients who discontinued treatment early because they did not meet the inclusion or exclusion criteria.
† The "other outcome" category included one patient who could not be cared for at a trial site because of local regulations regarding infection control at the site and one patient who could not be cared for because the patient had acute behavioral challenges.
‡ The noninferiority margin was 12 percentage points on the difference scale.

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)

* Confidence intervals for the BPaLC group and BPaL group as compared with the standard-care group are two-sided and were not adjusted for multiplicity and should not be used to infer relative treatment effects.

† The "other outcome" category included one patient who could not be cared for at a trial site because of local regulations regarding infection control at the site and one patient could not be cared for because the patient had acute behavioral challenges.

TB-PRACTECAL	ZeNix (linezolid 600 mg/26-week arm)
24 weeks	26 weeks, extendable to 39 weeks
Bedaquiline (B) 400 mg once daily for the first 2 weeks of treatment followed by 200 mg 3 times per week for 22 weeks (on-label)	Bedaquiline (B) 200 mg once daily for the first 8 weeks of treatment followed by 100 mg once daily for 18 weeks (off-label)
Pretomanid (Pa) 200 mg once daily for 24 weeks	Pretomanid (Pa) 200 mg once daily for 26 weeks
Linezolid (L) 600 mg daily for 16 weeks then 300 mg daily for the remaining 8 weeks	Linezolid (L) 600 mg daily for 26 weeks (could be reduced to 300 mg)
Treatment administered 7 days a week under direct observation or video-supported therapy	Treatment administered 7 days a week. Adherence was monitored by direct observation or by checking medication cards during site visits
Maximum allowed 2 consecutive weeks of treatment interruption	Maximum allowed total of treatment interruptions – 5 weeks (if 26 weeks duration) and 8 weeks (if 39 weeks duration). All treatment interruptions above 7 consecutive days should have been made up by extending treatment duration. Minimum taken total doses of linezolid – at least 9 weeks

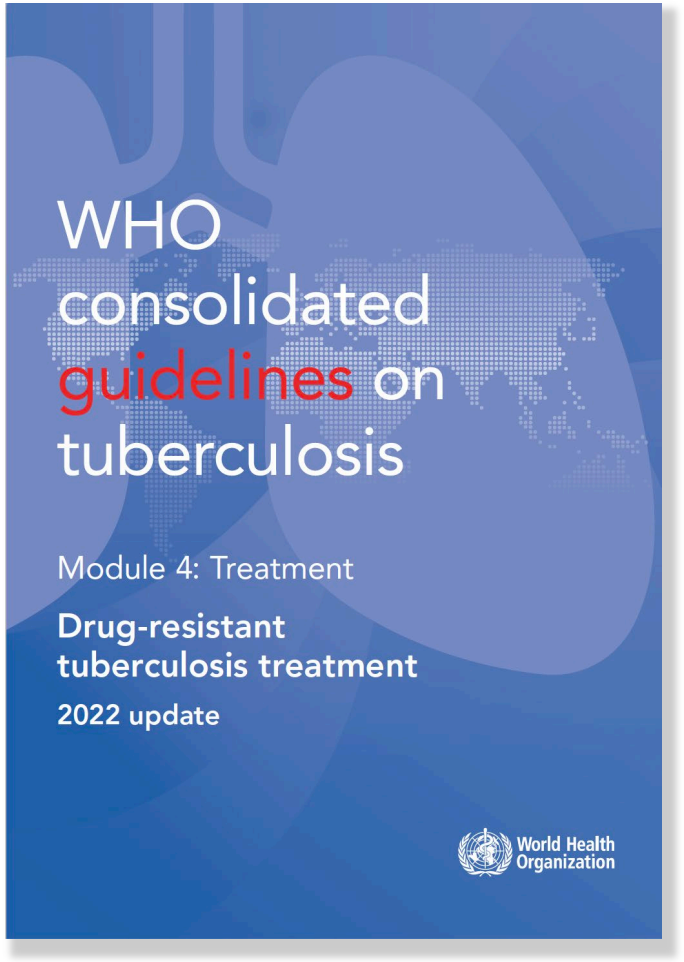
Box 2. Bedaquiline dosing approach in ZeNix trial

A pharmacokinetic simulation study assessed whether a bedaquiline dosing scheme could be devised that would permit daily dosing while maintaining drug exposure levels of the labelled dosing scheme. The key findings from the simulations (23) of the proposed dosing scheme for ZeNix of bedaquiline administered 200 mg daily over 8 weeks followed by 100 mg daily for an additional 16 weeks were as follows:

- The exposures (C_{max}, mean or trough) of the proposed dosing scheme were not expected to exceed the exposures associated with the labelled scheme on Day 14 at the end of the 400 mg daily dose. With the labelled dosing scheme, the highest exposures were on Day 14 at the end of the 400 mg daily loading dose.
- The average daily exposures with the proposed dosing scheme over 6 months were within (or were not substantially different from) the range of exposures over 6 months of the labelled dosing scheme.
- The cumulative exposure, in terms of area under the curve (AUC) over time, is similar between the proposed dosing scheme and the labelled scheme.

World Health Organization

Recommendations in the 2019 update	Recommendations in the 2020 update	NEW RECOMMENDATION Recommendations in the 2022 update
Not included in the 2019 guidelines	**Section 4: The bedaquiline, pretomanid and linezolid (BPaL) regimen for MDR-TB with additional fluoroquinolone resistance**	**Section 1: The 6-month bedaquiline, pretomanid, linezolid and moxifloxacin (BPaLM) regimen for MDR/RR-TB or pre-XDR-TB**
Not included the in 2019 guidelines	**4.1** A treatment regimen lasting 6–9 months, composed of bedaquiline, pretomanid and linezolid (BPaL), may be used under operational research conditions in multidrug-resistant tuberculosis (MDR-TB) patients with TB that is resistant to fluoroquinolones, who have either had no previous exposure to bedaquiline and linezolid or have been exposed for no more than 2 weeks. *(Conditional recommendation, very low certainty in the estimates of effect)* ***(New recommendation)***	**1.1** WHO suggests the use of the 6-month treatment regimen, composed of bedaquiline, pretomanid, linezolid (600 mg) and moxifloxacin (BPaLM), rather than 9-month or longer (18-month) regimens in MDR/RR-TB patients. *(Conditional recommendation, very low certainty of evidence)* ***(New recommendation, replacing 4.1 in the 2020 update)***
Section 4: Use of the standardized shorter MDR-TB regimen	**Section 2: Shorter, all-oral, bedaquiline-containing regimen for multidrug-/rifampicin-resistant tuberculosis**	NEW RECOMMENDATION **Section 2: The 9-month all-oral regimen for MDR/RR-TB**
In MDR/RR-TB patients who have not been previously treated for more than 1 month with second-line medicines used in the shorter MDR-TB regimen or in whom resistance to fluoroquinolones and second-line injectable agents has been excluded, a shorter MDR-TB regimen of 9–12 months may be used instead of the longer regimens. *(Conditional recommendation, low certainty in the estimates of effect)*	2.1 A shorter all-oral bedaquiline-containing regimen of 9–12 months duration is recommended in eligible patients with confirmed multidrug- or rifampicin-resistant tuberculosis (MDR/RR-TB) who have not been exposed to treatment with second-line TB medicines used in this regimen for more than 1 month, and in whom resistance to fluoroquinolones has been excluded. *(Conditional recommendation, very low certainty in the evidence)* *(Updated recommendation)*	**2.1** WHO suggests the use of the 9-month all-oral regimen rather than longer (18-month) regimens in patients with MDR/RR-TB and in whom resistance to fluoroquinolones has been excluded *(Conditional recommendation, very low certainty of evidence)* ***(New recommendation, replacing 2.1 in the 2020 update)***



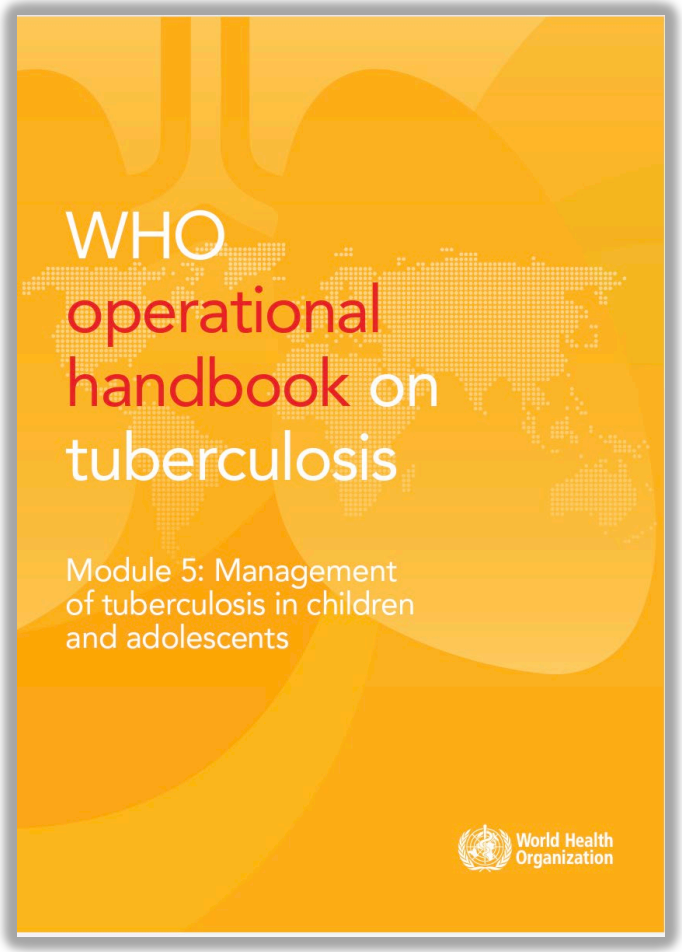
Box 5.16 WHO recommendation on the BPaL regimen

A treatment regimen lasting 6–9 months composed of bedaquiline, pretomanid and linezolid (BPaL) may be used under operational research conditions in multidrug-resistant tuberculosis (MDR-TB) patients with TB that is resistant to fluoroquinolones, who have either had no previous exposure to bedaquiline and linezolid or have been exposed for no more than 2 weeks (conditional recommendation, very low certainty in the estimates of effect).

Source: WHO consolidated guidelines on tuberculosis. Module 4: treatment – drug-resistant tuberculosis treatment. Geneva: World Health Organization; 2022 *(116)*.

Eligibility criteria for treatment with the BPaL regimen are all of the following:

- bacteriologically confirmed PTB and laboratory-confirmed resistance to rifampicin and fluoroquinolones with or without resistance to injectable agents;
- age at least 14 years at the time of enrolment;
- weight 35 kg or over;
- informed consent to be enrolled in the operational research project and to adhere to the follow-up schedule (signed or witnessed consent if the patient is illiterate, or signed or witnessed consent from a child's parent or legal guardian);
- for adolescent girls, no pregnancy or breastfeeding and willingness to use effective contraception;
- no known allergy to any BPaL component medicines;
- no evidence in DST results of resistance to any of the component medicines, or no previous exposure to any of the component medicines for 2 weeks or more;
- no EPTB, including meningitis, other CNS TB or TB osteomyelitis.

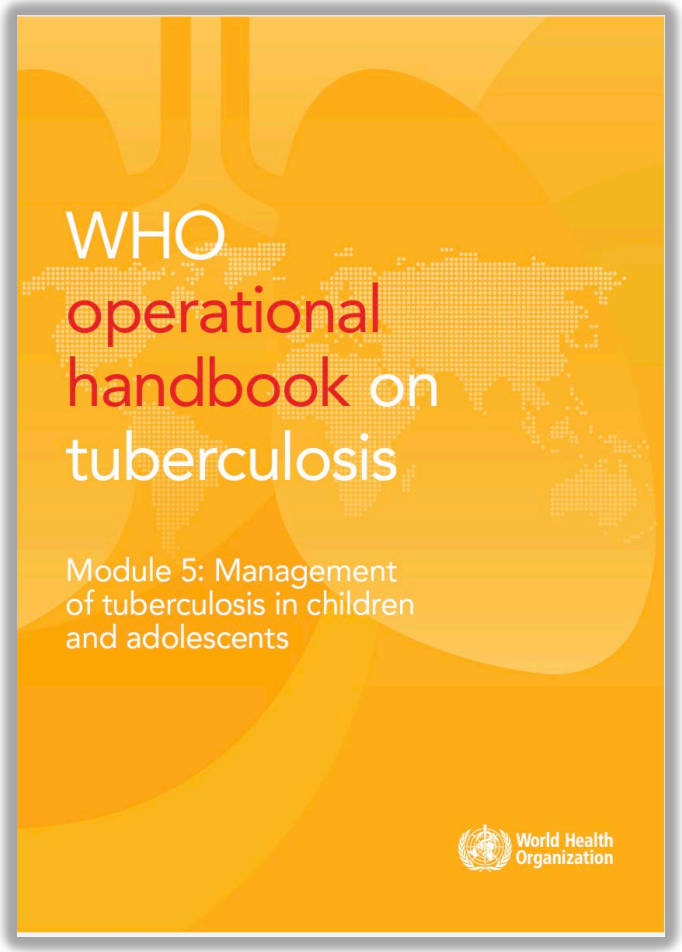


4–6 Bdq (6) – Lfx – Cfz – Z – E – H^h – Eto/5 Lfx – Cfz – Z – E

Month	1	2	3	4	5	6	7	8	9	10	11
Bedaquiline											
High-dose isoniazid											
Ethionamide/ prothionamide											
Levofloxacin											
Clofazimine											
Pyrazinamide											
Ethambutol											

Orange = standardized MDR/RR-TB treatment course.

Blue = added months if still smear-/culture-positive after 4 months of treatment.



Medicine	CSF penetration
Levofloxacin, moxifloxacin, linezolid, cycloserine, ethionamide, meropenem, pyrazinamide	Good penetration
Isoniazid in presence of isoniazid resistance, P-aminosalicylic acid, amikacin	Poor penetration, except in presence of meningeal inflammation
Ethambutol	Poor penetration
Bedaquiline, delamanid, clofazimine	Limited data available

Section 5. Monitoring patient response to MDR/ RR-TB treatment using culture

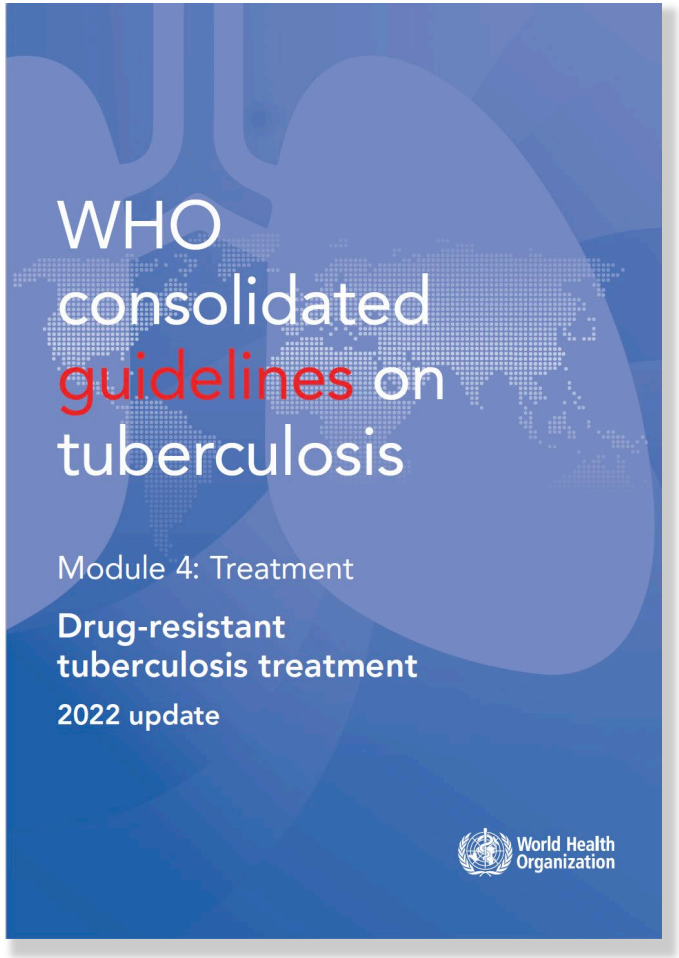
5.1 Recommendation

No.	Recommendation
5.1	In multidrug- or rifampicin-resistant tuberculosis (MDR/RR-TB) patients on longer regimens, the performance of sputum culture in addition to sputum smear microscopy is recommended to monitor treatment response. *(Strong recommendation, moderate certainty in the estimates of test accuracy)* It is desirable for sputum culture to be repeated at monthly intervals.

Table 5.1. Crude odds ratios (95% CLs) of treatment failure in MDR/RR-TB patients without sputum conversion by the end of successive months of treatment compared with patients who converted, by testing method used; IPD meta-analysis for PICO question 7 MDR/RR-TB, 2018 (South Africa, *n*=3 762)

Crude odds ratios according to	Month							
	1	2	3	4	5	6	7	8
Culture	3.6	4.1	5.2	7.4	10.3	16.4	24.7	44.5
	(2.11, 5.97)	(2.76, 6.09)	(3.55, 7.55)	(5.00, 10.80)	(6.88, 15.38)	(10.72, 25.00)	(15.53, 39.20)	(26.53, 74.46)
Smear microscopy	1.9	2.7	3.2	4.2	6.8	10.4	16.5	28.9
	(1.27, 2.73)	(1.82, 3.88)	(2.11, 4.73)	(2.69, 6.48)	(4.19, 10.97)	(6.00, 17.92)	(9.15, 29.77)	(14.87, 56.14)

CL: confidence limits; IPD: individual patient data; MDR/RR-TB: multidrug-resistant or rifampicin-resistant tuberculosis; PICO: population, intervention, comparator and outcome.

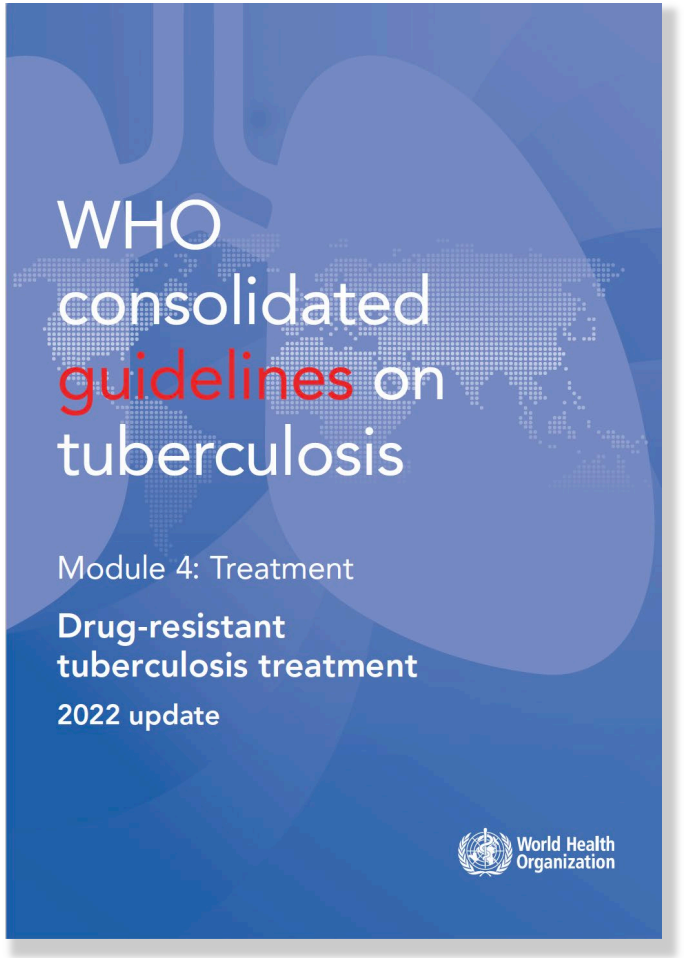


Treatment decisions usually rely upon at least two consecutive positive results (to denote prolonged positivity or reversion) and the effect of one spurious result would last only until the test repeated 1 month later is reported.

Section 7. Surgery for patients on MDR/RR-TB treatment

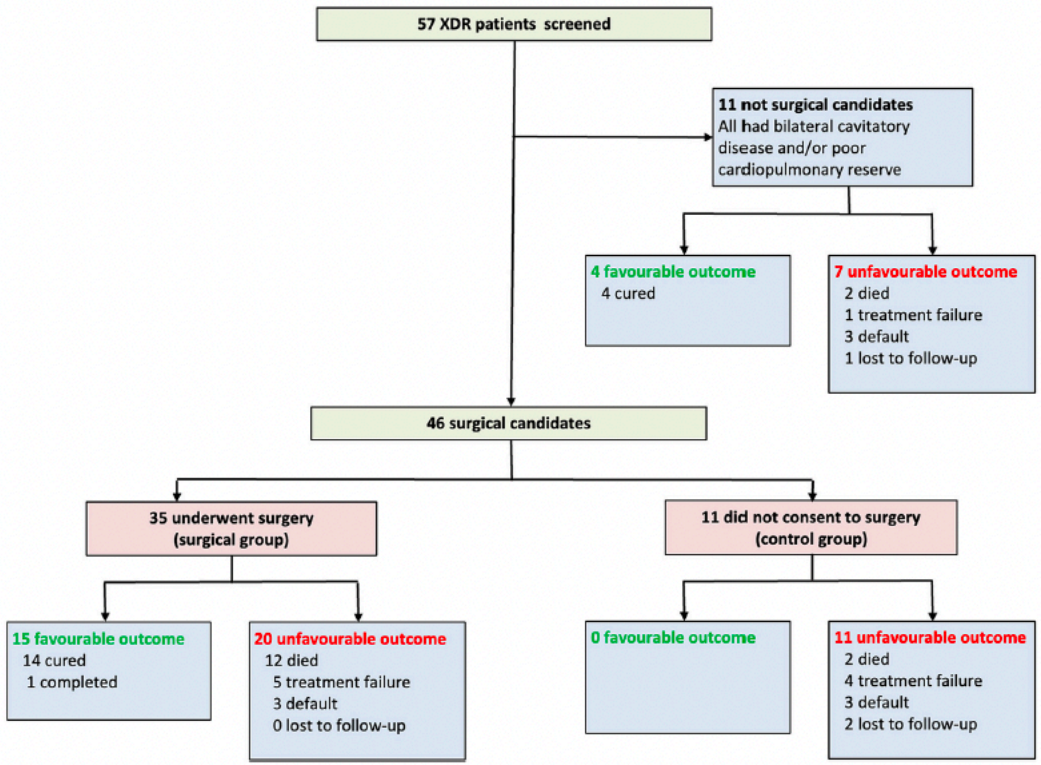
7.1 Recommendation

No.	Recommendation
7.1	In patients with rifampicin-resistant tuberculosis (RR-TB) or multidrug-resistant TB (MDR-TB), elective partial lung resection (lobectomy or wedge resection) may be used alongside a recommended MDR-TB regimen. *(Conditional recommendation, very low certainty of evidence)*



Outcomes of patients undergoing lung resection for drug-resistant TB and the prognostic significance of pre-operative positron emission tomography/computed tomography (PET/CT) in predicting treatment failure

Gregory L. Calligaro,[a,h] Nevadna Singh,[a,h] Timothy C. Pennel,[b,h] Rachelle Steyn,[c] Anita Brink,[c] Aliasgar Esmail,[a] Lynelle Mottay,[a] Suzette Oelofse,[a] Barbara L. Mastrapa,[d] Wisdom Basera,[e,f] Kathryn Manning,[e] Chima Ofoegbu,[b] Anthony Linegar,[b] and Keertan Dheda[a,g,*]



Variable	n	Crude OR (95% CI)	P-value	Adjusted OR (95% CI)[a]	P-value
Age (per year increase)	35	1.03 0.97–1.10)	0.299		
Male sex (vs. female)	35	0.27 (0.07–1.11)	0.069		
HIV status (vs. negative)	9	9.33 (1.02–85.70)	0.048	3.63 (0.39–300.00)	0.280
Current/former smoking status (vs. non-smoking)	14	2.75 (0.65–11.62)	0.169		
XDR status (vs. MDR and pre-XDR)	27	16.63 (1.78–158.09)	0.014	4.89 (0.73–207.03)	0.137
DR-TB treatment (vs. no previous treatment)	20	0.81 (0.21–3.17)	0.767		
Pneumonectomy (vs. lobectomy)	22	1.24 (0.31–4.93)	0.762		
Positive pre-operative sputum culture (vs. negative)	29	3.27 (0.51–20.93)	0.210		
Post-operative bedaquiline (vs. no bedaquiline)	8	0.02 (0.00–0.42)[b]	<0.001	0.06 (0.00–0.50)	0.007
Post-operative linezolid (vs. no linezolid)	10	0.20 (0.04–0.99)	0.049	1.52 (0.09–91.74)	1.00
Post-operative regimen with at least 3 effective drugs	4	0.72 (0.09–5.81)	0.760		

Abbreviations: OR, odds ratio; CI, confidence interval; HIV, human immunodeficiency virus; XDR-TB, extensively drug-resistant tuberculosis; MDR-TB, multidrug-resistant tuberculosis. [a]Adjusted for HIV status, XDR status, post-operative bedaquiline and post-operative linezolid use. [b]No treatment failures in patients treated with bedaquiline; Haldane-Anscombe correction applied.[24]

Table 2: **Predictors of treatment failure in patients who underwent surgery (n = 35).**

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2023;55: 101728

Long-term treatment outcomes in patients with multidrug-resistant tuberculosis

Christina Maier [1, 2, 3], Dumitru Chesov [1, 2, 3, 4], Dagmar Schaub [1, 2, 3], Barbara Kalsdorf [1, 2, 3], Sönke Andres [5], Inna Friesen [5], Maja Reimann [1, 2, 3], Christoph Lange [1, 2, 3, 6, *]

Clinical Microbiology and Infection 29 (2023) 751–757

Objectives: To describe long-term treatment outcomes in patients with multi-drug-resistant/rifampicin-resistant tuberculosis (MDR/RR-TB) and validate established outcome definitions for MDR/RR-TB treatment.

Methods: Among patients with MDR/RR-TB admitted to a German MDR/RR-TB referral centre from 1 September 2002 to 29 February 2020, we compared long-term treatment outcomes derived from individual patient follow-up with treatment outcomes defined by WHO-2013, WHO-2021 and the Tuberculosis Network European Trials Group-2016.

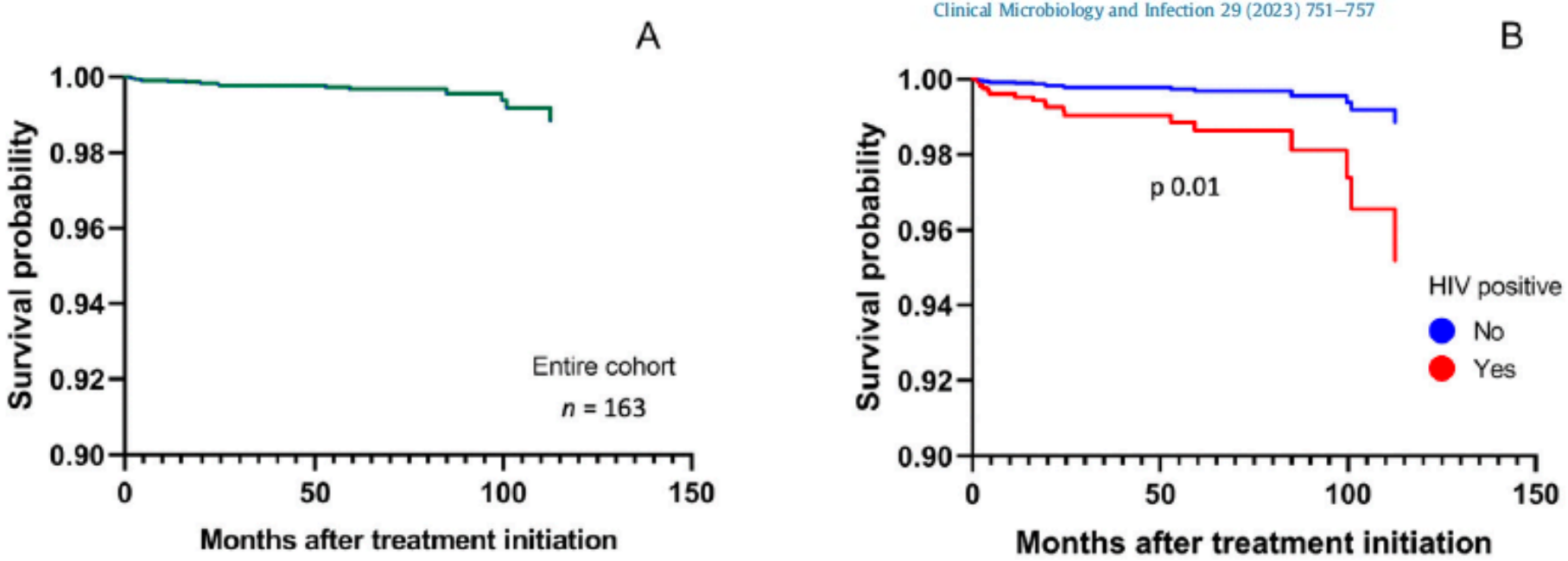
Results: In a total of 163 patients (mean age, 35 years; standard deviation, 13 years; 14/163 [8.6%] living with HIV; 109/163 [66.9%] men, 149/163 [91.4%] migrating to Germany within 5 years), the treatment of culture-confirmed MDR/RR-TB was initiated. Additional drug resistance to a fluoroquinolone or a second-line injectable agent was present in 15 of the 163 (9.2%) *Mycobacterium tuberculosis* strains; resistance against both the drug classes was present in 29 of the 163 (17.8%) strains. The median duration of MDR/RR-TB treatment was 20 months (interquartile range, 19.3–21.6 months), with a medium of five active drugs included. The median follow-up time was 4 years (47.7 months; interquartile range, 21.7–65.8 months). Among the 163 patients, cure was achieved in 25 (15.3%), 82 (50.3%) and 95 (58.3%) patients according to the outcome definitions of WHO-2013, WHO-2021, and the Tuberculosis Network European Trials Group-2016, respectively. The lost to follow-up rate was 17 of 163 (10.4%). Death was more likely in patients living with HIV (hazard ratio, 4.28; 95% confidence interval, 1.26–12.86) and older patients (hazard ratio, 1.08; 95% confidence interval, 1.05–1.12; increment of 1 year). Overall, 101/163 (62.0%) patients experienced long-term, relapse-free cure; of those, 101/122 (82.8%) patients with a known status (not lost to-follow-up or transferred out) at follow-up.

Conclusion: Under optimal management conditions leveraging individualized treatment regimens, long-term, relapse-free cure from MDR/RR-TB is substantially higher than cure rates defined by current treatment outcome definitions. **Christina Maier, Clin Microbiol Infect 2023;29:751**

Long-term treatment outcomes in patients with multidrug-resistant tuberculosis

Christina Maier [1, 2, 3], Dumitru Chesov [1, 2, 3, 4], Dagmar Schaub [1, 2, 3], Barbara Kalsdorf [1, 2, 3], Sönke Andres [5], Inna Friesen [5], Maja Reimann [1, 2, 3], Christoph Lange [1, 2, 3, 6, *]

Clinical Microbiology and Infection 29 (2023) 751–757



Entire cohort	163	155	152	150	150	150	148	148	147	147	145	144	144	144
HIV negative	145	138	136	134	134	134	132	132	132	131	129	128	128	128
HIV positive	14	14	13	13	13	13	12	12	11	11	10	9	9	9
	0	**12**	**24**	**36**	**48**	**60**	**72**	**84**	**96**	**108**	**120**	**132**	**144**	**156**

Months

Fig. 3. Long-term survival of patients with multi-drug-resistant/rifampicin-resistant tuberculosis. (A) Entire cohort. (B) Stratified by HIV infection status.

Primary efficacy outcome in mITT population at 72 weeks post-randomization

Motta I et al. *Efficacy and safety results in participants co-infected with HIV from TB-PRACTECAL Clinical Trial.* 24th International AIDS Conference, Montreal, abstract OAB0402, 2022.

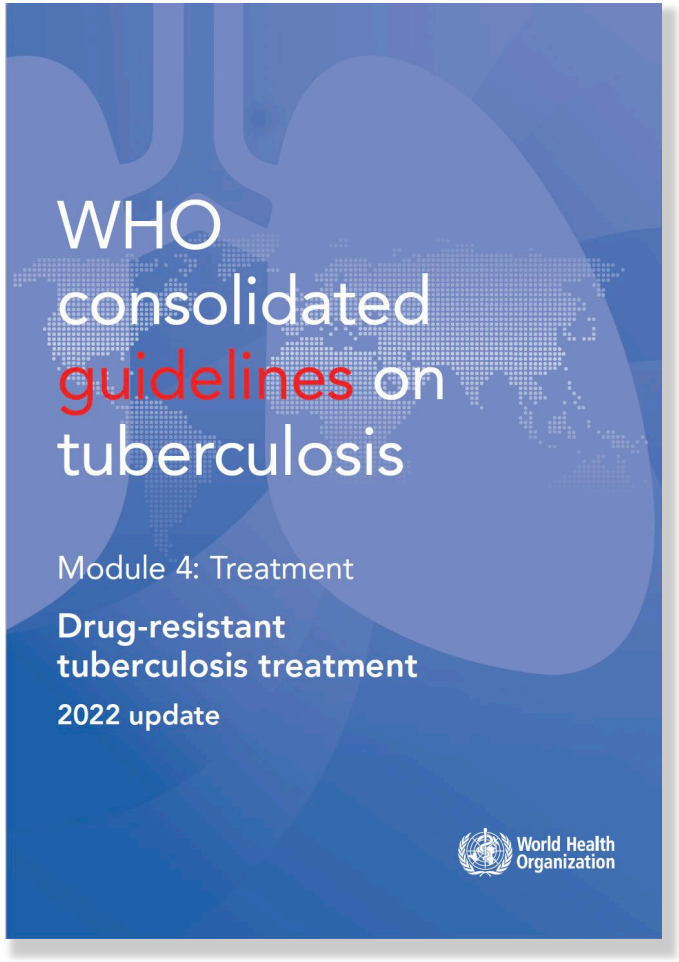
HIV status	SOC n/N (%)	Experimental arm	Risk difference (one-sided 98.3% CI)		Interaction p-value
BPaLM versus control					
Negative	26/51 (51.0)	3/48 (6.3)	-44.7%	(-∞ to -28.1%)	
Positive	6/15 (40.0)	4/14 (28.6)	-11.4%	(-∞ to 25.6%)	p = 0.08
BPaLC versus control					
Negative	26/51 (51.0)	7/50 (14.0)	-37.0%	(-∞ to -18.9%)	
Positive	6/15 (40.0)	5/14 (35.7)	-4.3%	(-∞ to 33.9%)	p = 0.10
BPaL versus control					
Negative	26/51 (51.0)	10/46 (21.7)	-29.2%	(-∞ to -9.6%)	
Positive	6/15 (40.0)	4/14 (28.6)	-11.4%	(-∞ to 25.6%)	p = 0.37

CONCLUSIONS: Current TB-PRACTECAL data supports the use of 24-week regimens irrespective of HIV status. A trend towards the shorter regimens being more efficacious in HIV-negative patients was observed. However, this trend was not seen in the safety outcomes for the BPaL and BPaLM arms. The trial is accruing more data and will update at a later date.

Section 6. Starting antiretroviral therapy in patients on MDR/RR-TB regimens

6.1 Recommendation

No.	Recommendation
6.1	Antiretroviral therapy is recommended for all patients with HIV and drug-resistant tuberculosis requiring second-line antituberculosis drugs, irrespective of CD4 cell count, as early as possible (within the first 8 weeks) following initiation of antituberculosis treatment. *(Strong recommendation, very low certainty of evidence)*



viruses

MDPI

Article

The Effect of HIV and Antiretroviral Therapy on Drug-Resistant Tuberculosis Treatment Outcomes in Eastern Cape, South Africa: A Cohort Study

Brittney van de Water [1,*], Nadia Abuelezam [1], Jenny Hotchkiss [2], Mandla Botha [3] and Limpho Ramangeola [4]

Table 2. Treatment outcomes among patients with DR-TB according to their HIV and ART statuses.

	Everyone (N = 246)	HIV− (N = 89)	HIV+ on ART (N = 137)	HIV+ Not on ART (N = 20)
Success	144 (58.5%)	64 (71.9%)	75 (54.7%)	5 (25.0%)
Cure	118	49	64	5
Completed treatment	26	15	11	0
Non-success	51 (20.7%)	10 (11.2%)	33 (24.1%)	8 (40.0%)
Failed	1	0	1	0
Died	39	6	25	8
Lost to follow-up	11	4	7	0
Transferred out	51 (20.7%)	15 (16.9%)	29 (21.2%)	7 (35.0%)
Censored	21	6	12	3
Still on treatment	10	1	8	1
Missing	8	5	3	0
Moved out	3	0	1	2

Grazie!

BACK-UP

Fluoroquinolone susceptibility	Regimen [a]	Additional medicines
Fluoroquinolone-susceptible	Bdq–Lfx–Lzd–Cfz-(Cs)	Cs, Dlm, PAS, Eto [b,c] (E, Z) [d]
Fluoroquinolone-resistant	Bdq–Lzd–Cfz–Cs–(Dlm) [e]	Dlm [e], PAS, Eto [b,c] (E, Z) [d]
Fluoroquinolone-resistant and bedaquiline (±clofazimine)-resistant	Lzd–Cs–Dlm [e]–E–Z [d]	Mpm/Clav, Eto [b,c], PAS [c]

Bdq: bedaquiline; Cfz: clofazimine; Cs: cycloserine; Dlm: delamanid; E:ethambutol; Eto: ethionamide; FQ: fluoroquinolone; Lfx: levofloxacin; Lzd: linezolid; Mpm/Clav: meropenem–clavulanate; PAS: P-aminosalicylic acid; Z: pyrazinamide.

[a] Medicines in parentheses in this column are suggestions for a fifth medicine when there is severe disease.

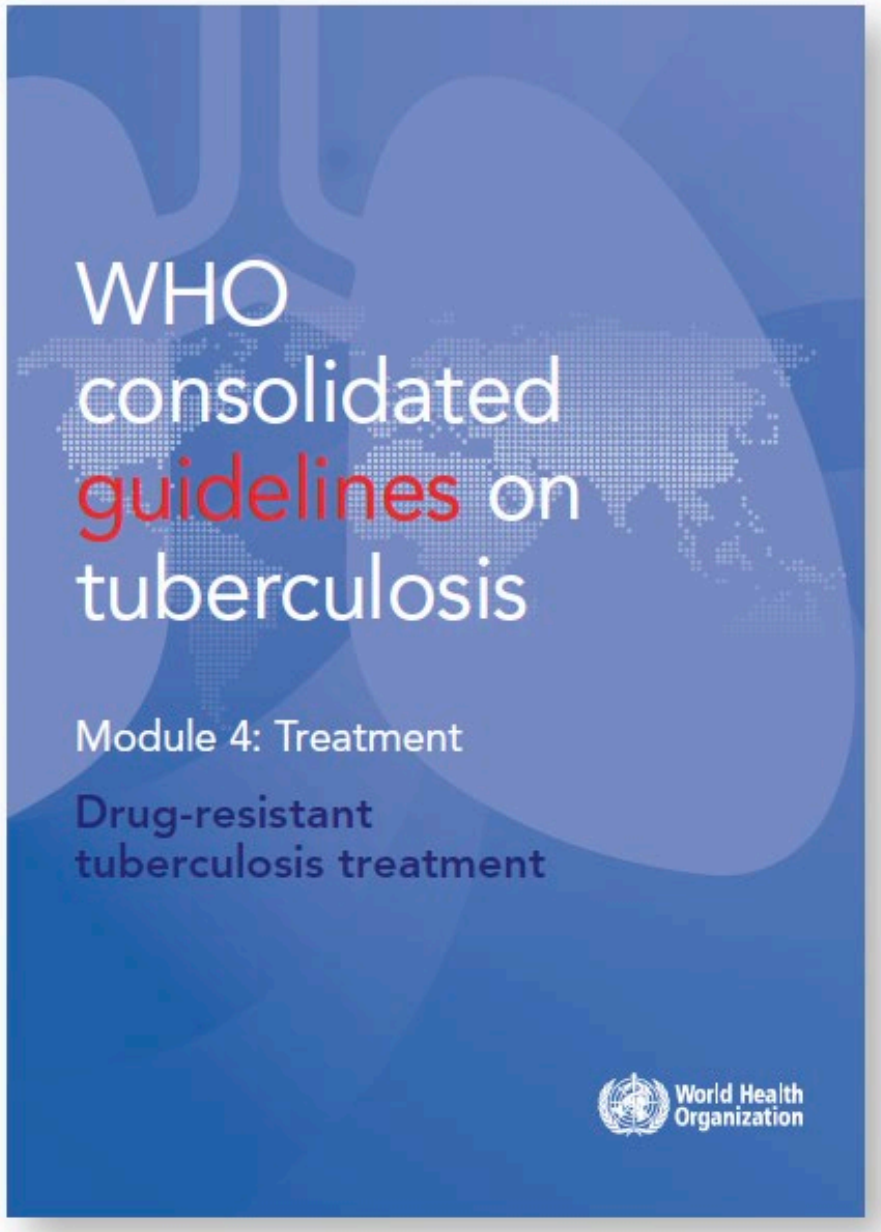
[b] Use ethionamide only if the child or source case does not have a known or suspected *inhA* mutation.

[c] P-aminosalicylic acid and ethionamide showed effectiveness only in regimens without bedaquiline, linezolid, clofazimine or delamanid, and are proposed only when other options to compose a regimen are not possible.

[d] Ethambutol and pyrazinamide should be considered if there is evidence of susceptibility and a regimen with sufficient medicines cannot be composed.

[e] When administering delamanid and cycloserine concurrently, monitoring for neuropsychiatric side-effects is important.

World Health Organization



Based on the discussions during the consultation, and bearing in mind the agreed principles, WHO proposes a new definition for pre-XDR-TB and the revised definition for XDR-TB, outlined in Box 2. The definition of MDR-TB is unchanged and remains as: TB caused by *Mycobacterium tuberculosis (M. tuberculosis)* strains that are resistant to at least both rifampicin and isoniazid.

For reporting purposes, and also considering that both types of drug resistance require the same treatment options, MDR-TB and RR-TB are often grouped together as MDR/RR-TB. This includes patients with isolates that are resistant to rifampicin only and those that fulfil the definition of MDR-TB.

Box 2. Definition of pre-XDR-TB and updated definition of XDR-TB[a]

Pre-XDR-TB: TB caused by *Mycobacterium tuberculosis* (*M. tuberculosis*) strains that fulfil the definition of MDR/RR-TB and that are also resistant to any fluoroquinolone[a]

XDR-TB: TB caused by *Mycobacterium tuberculosis* (*M. tuberculosis*) strains that fulfil the definition of MDR/RR-TB and that are also resistant to any fluoroquinolone[a] and at least one additional Group A drug[b]

MDR/RR-TB: multidrug-resistant or rifampicin-resistant tuberculosis; TB: tuberculosis; XDR-TB: extensively drug-resistant tuberculosis.

[a] The fluoroquinolones include levofloxacin and moxifloxacin, because these are the fluoroquinolones currently recommended by WHO for inclusion in shorter and longer regimens.

[b] The Group A drugs are currently levofloxacin or moxifloxacin, bedaquiline and linezolid; therefore, XDR-TB is MDR/RR-TB that is resistant to a fluoroquinolone and either bedaquiline or linezolid (or both). The Group A drugs may change in the future; therefore, the terminology “Group A” is appropriate here and will apply to any Group A drugs in the future.

New WHO MDR-TB drug classification for building a long MDR-TB regimen

Priority Drug Groups	TB Drug	
Group A: Include all three drugs	levofloxacin *OR*	Lfx
	moxifloxacin	Mfx
	bedaquiline	Bdq
	linezolid	Lzd
Group B: Add one or both drugs	clofazimine	Cfz
	cycloserine *OR*	Cs
	terizidone	Trd
Group C: Add to complete the regimen and when drugs from Groups A and B cannot be used either due to resistance, toxicity or tolerability.	ethambutol	E
	delamanid	Dlm
	pyrazinamide	Z
	imipenem–cilastatin *OR*	Ipm–Cln
	meropenem *WITH* amoxicillin/clavulanate	Mpm
	amikacin	Am
	(*OR* streptomycin)	(S)
	ethionamide *OR*	Eto
	prothionamide	Pto
	p-aminosalicylic acid	PAS

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WHO drug-resistant TB guidelines 2022: what is new?

Table. Core regimens to treat MDR/RR-TB

Regimen	Duration (months)	Indications	Contraindications
BPaLM (BDQ, pretomanid, linezolid, MFX) BPaL (without MFX)	6	MDR/RR-TB patients age 15 years or more; BPaL if documented resistance to FQs	Exposure to any of the drugs composing the regimen for ≥30 days
All-oral, BDQ-containing regimens	9	Adults and children with MDR/RR-TB	Previous exposure to second-line treatment (including BDQ), FQ resistance; extensive pulmonary TB disease; severe extrapulmonary TB
Individualised longer regimen	≥18	Patients with extensive forms of DR-TB (e.g., XDR-TB); or not eligible for the regimens described above or who previously failed shorter treatment regimens	

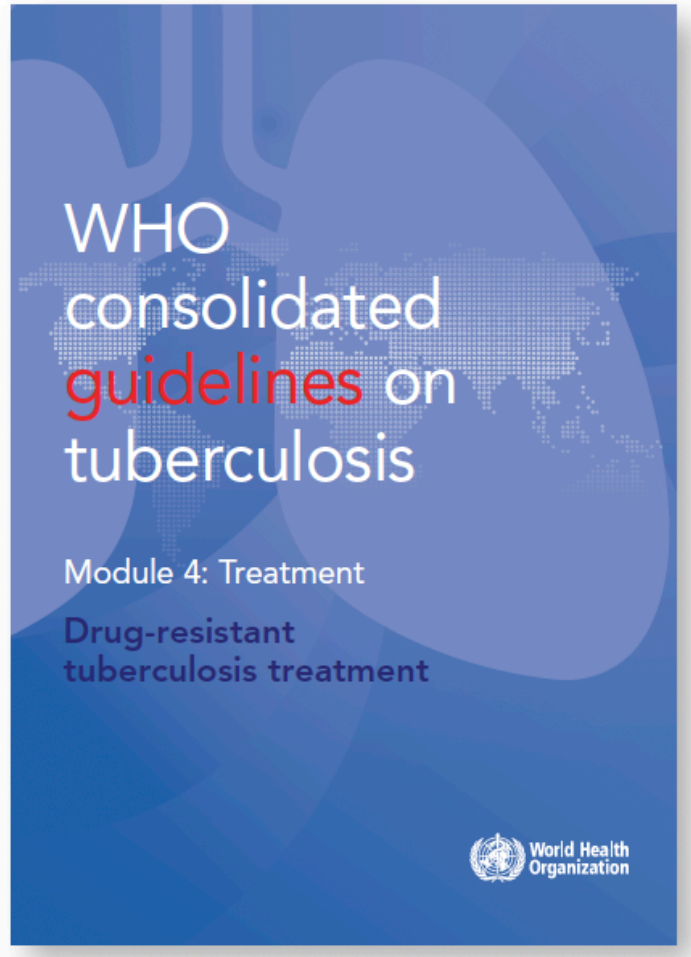
MDR/RR-TB = multidrug-/rifampicin-resistant TB; BDQ = bedaquiline; MFX = moxifloxacin; FQ = fluoroquinolone; DR-TB = drug-resistant TB; XDR-TB = extensively drug-resistant TB.

http://dx.doi.org/10.5588/ijtld.22.0263

All patients with MDR/RR-TB, including those with additional resistance to fluoroquinolones, may benefit from effective all-oral treatment regimens, shorter or longer.

1. For MDR/RR-TB patients without previous exposure to second-line treatment and bedaquiline, without fluoroquinolone resistance and no extensive TB disease or severe extrapulmonary TB, the preferred treatment option is a **shorter, all-oral, bedaquiline-containing regimen**. In this group of patients, national programmes can phase out use of the injectable-containing shorter regimen.

2. For MDR/RR-TB patients with extensive TB disease, severe forms of extrapulmonary TB, those with resistance to fluoroquinolones or who have been exposed to treatment with second-line drugs will benefit from an **individualized longer regimen** designed using the priority grouping of medicines.



3. Novel BPaL regimen for MDR-TB with additional quinolone resistance under operational research conditions.

BPaL: bedaquiline, pretomanid and linezolid; DR-TB: drug-resistant tuberculosis; MDR/RR-TB: multidrug-resistant or rifampicin-resistant tuberculosis; TB: tuberculosis; WHO: World Health Organization; XDR-TB: extensively drug-resistant tuberculosis.

Conclusions

PRACTECAL Arm 1(BPaLM)

1. Current TB-PRACTECAL data supports the use of **24-week regimens** irrespective of HIV status
2. A trend towards the **shorter regimens** being **more efficacious** in HIV-negative patients was observed
3. No differences in trend were observed in the **safety** outcomes for the BPaL and BPaLM arms
4. The trial is accruing more data and will update in the next months

Motta I et al. *Efficacy and safety results in participants co-infected with HIV from TB-PRACTECAL Clinical Trial.* 24th International AIDS Conference, Montreal, abstract OAB0402, 2022.

Long-term treatment outcomes in patients with multidrug-resistant tuberculosis

Christina Maier [1, 2, 3], Dumitru Chesov [1, 2, 3, 4], Dagmar Schaub [1, 2, 3], Barbara Kalsdorf [1, 2, 3], Sönke Andres [5], Inna Friesen [5], Maja Reimann [1, 2, 3], Christoph Lange [1, 2, 3, 6, *]

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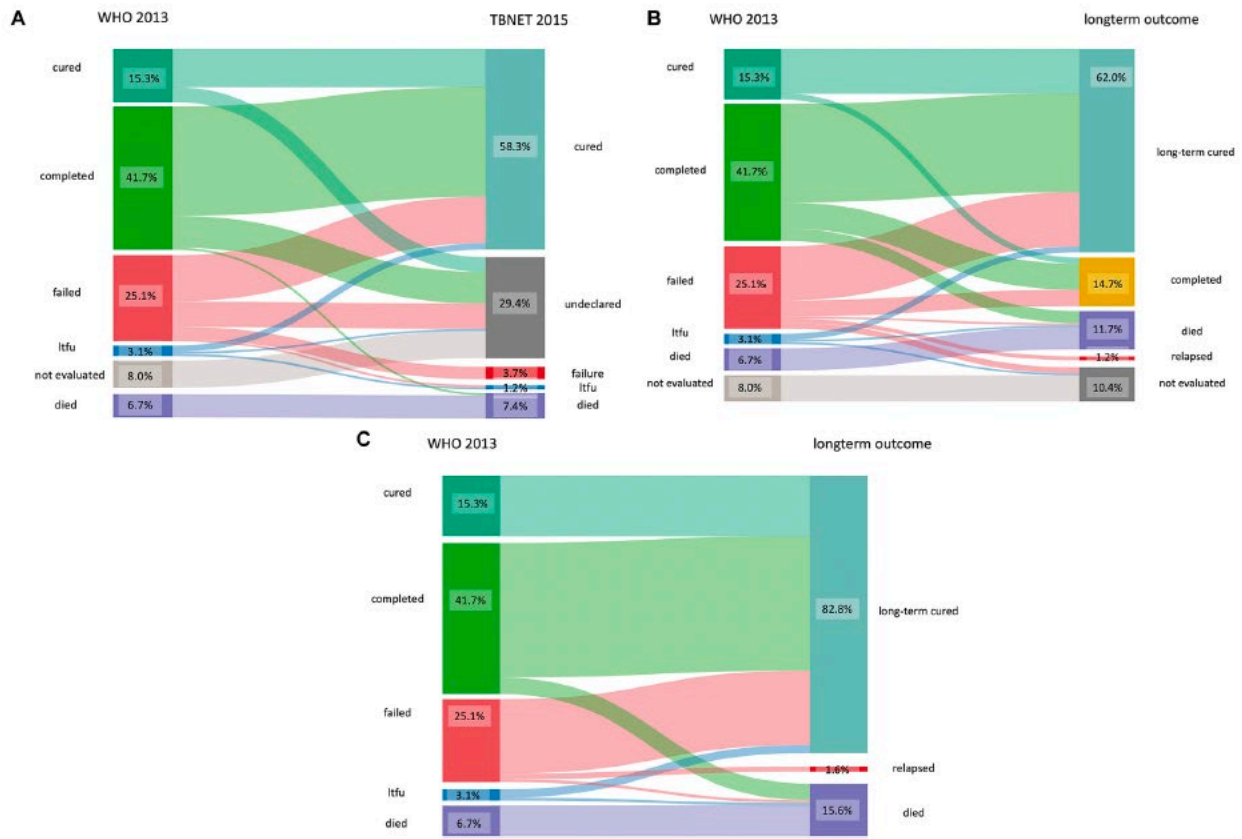

Fig. 2. Outcomes of multi-drug-resistant/rifampicin drug-resistant tuberculosis treatment according to different definitions: (A) WHO 2013 [6] and Tuberculosis Network European Trials Group 2016 [7], (b) WHO 2013 [6] as well as long-term outcomes. (A) and (B) Treatment outcomes for all 163 patients in whom treatment was initiated. (C) Comparison of treatment outcomes based on WHO 2013 [6] definition and long-term outcomes excluding patients with an undeclared outcome who were lost to follow-up, transferred out or finished treatment within 6 months of this analysis. Note that some patients with failure (e.g. because of change of medication in the regimen because of adverse events) or those lost to follow-up (e.g. treatmant interruption) according to WHO definitions still achieve long-term treatment success. LTFU, loss to follow-up; TBNET, Tuberculosis Network European Trials Group.

Update of drug-resistant tuberculosis treatment guidelines: A turning point

Elisa Vanino[1,#], Bianca Granozzi[2,#], Onno W. Akkerman[3], Marcela Munoz-Torrico[4], Fabrizio Palmieri[5], Barbara Seaworth[6], Simon Tiberi[7], Marina Tadolini[2,8,*]

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Indications/contraindications of the shorter and longer MDR/RR-TB treatment regimens

Regimen	6-Month BPaLM/BpaL[a]	9-Month all-oral	Longer individualized 18-month
MDR/RR-TB Fluoroquinolones-susceptible	YES (BPaLM)	YES	YES when 6-month and 9-month regimens could not be used
Pre-extensively DR (Fluoroquinolones resistant)	YES (BPaL only)	NO	YES when 6-month regimen could not be used
Extensively DR-TB	NO	NO	YES
Extensive pulmonary TB	YES	NO	YES
Extrapulmonary TB	YES (except TB involving CNS, miliary TB and osteoarticular TB)	YES (except TB meningitis, miliary TB, pericardial TB and osteoarticular TB)	YES
Age <14 years	NO	YES	YES
People living with HIV	YES	YES	YES
Pregnant/breastfeeding	NO	Ethionamide-sparing regimen is recommended	YES
Exposure to any of the drugs composing the regimen for ≥30 days[b]	NO[b]	NO[b]	YES
History of cardiac disease or concomitant drugs that prolong QTc	YES (but must be monitored closely)	YES	YES
Body mass index <17	YES (but must be monitored closely)	YES	YES
Hemoglobin <8 g/dl or platelet <75.000/mm^3	YES (but prefer other regimes)	Linezolid-sparing regimen is suggested	Linezolid-sparing regimen is suggested
Pre-existing peripheral neuropathy of grade III-IV	YES (but prefer other regimes)	Linezolid-sparing regimen is suggested	Linezolid-sparing regimen is suggested

BpaLM: bedaquiline, pretomanid, linezolid (600 mg) and moxifloxacin; DR-TB: drug-resistant-tuberculosis; MDR/RR-TB, multidrug-resistant/rifampicin-resistant tuberculosis.

[a] When the regimen is BPaL from the start or is changed to BPaL, it can be extended to a total of 9 months (39 weeks) if sputum cultures are positive between months 4 and 6

[b] When exposure is greater than 1 month, resistance to the specific drugs with such exposure must be ruled out before considering the regimen.