Updated WHO consolidated guidelines on DR-TB treatment 2022

Fuad Mirzayev

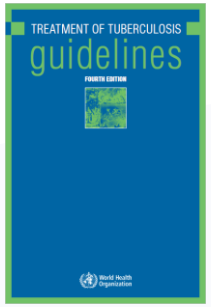
TB treatment team
Global Tuberculosis Programme

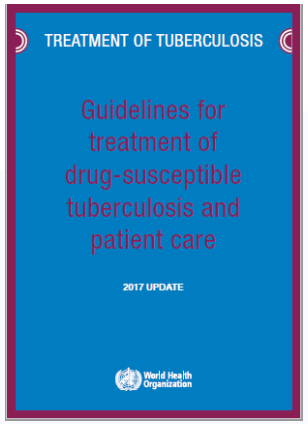
Event
Date 2023

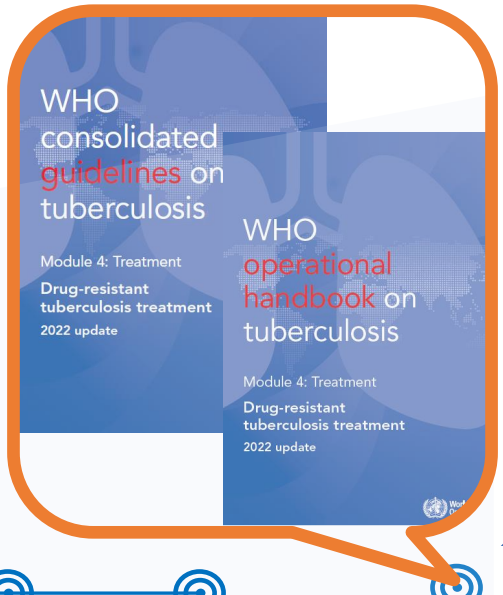
World Health Organization

Guidelines and derivative documents on TB treatment: Guidelines and handbooks

DS-TB

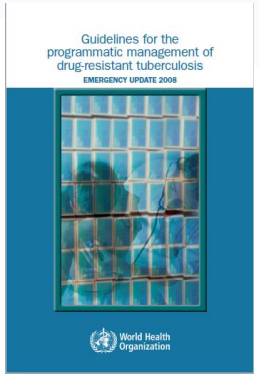






1997 2003 2008 2010 2011 2016 2017 2018 2019 **2020** **2022**

DR-TB



New developments in 2022: Guidelines & Handbooks

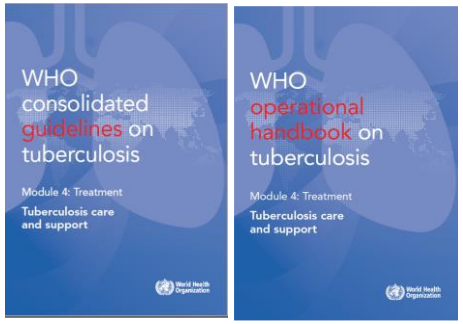
DS-TB

DS-TB guidelines & handbook 2022

- **4-month 2HPMZ/2HPM** regimen
- **4-month 2HRZ(E)/2HR** regimen for children and adolescents
- Consolidating all recommendations on DS-TB (2022)

TB Care & Support

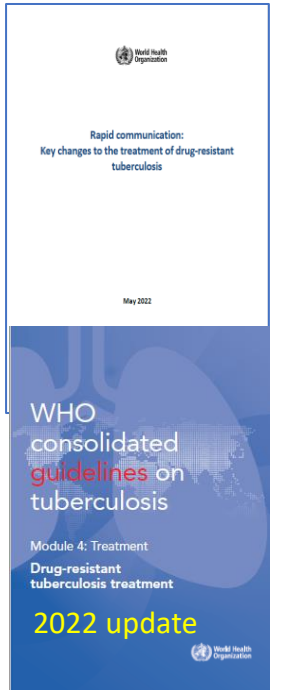
Guidelines & Handbook 2022



DR-TB

Rapid Communication 2022 update

- **6-month BPaLM regimen, comprising bdq, Pa, Lzd (600 mg) & Mfx**, may be used programmatically in place of 9-month or longer (>18 months) regimens, in patients (aged ≥15 years) with MDR/RR-TB
- **9-month, all-oral, bedaquiline-containing regimens*** are preferred over the longer (>18 months) regimen in adults and children with MDR/RR-TB
- Longer regimen for patients with extensive forms of DR-TB (e.g., XDR-TB)



Data reviewed by the WHO Guideline Development Group

GDG meeting in February - March 2022

Data reviewed by the WHO Guideline Development Group

GDG meeting in February - March 2022

1. TB PRACTECAL Trial (sites: Uzbekistan, South Africa, Belarus)

- **Investigational regimens in Stage 1**
  - Arm 1: bedaquiline (B) + pretomanid (Pa) + linezolid (Lzd) + moxifloxacin (Mfx) for 24 weeks (**BPaLM**)
  - Arm 2: bedaquiline + pretomanid + linezolid + clofazimine for 24 weeks (**BPaLC**)
  - Arm 3: bedaquiline + pretomanid + linezolid for (**BPaL**) 24 weeks

- **Investigational regimen in Stage 2** (selected after stage 1)
  - Arm 1: bedaquiline (B) + pretomanid (Pa) + linezolid (Lzd) + moxifloxacin (Mfx) for 24 weeks (**BPaLM**)

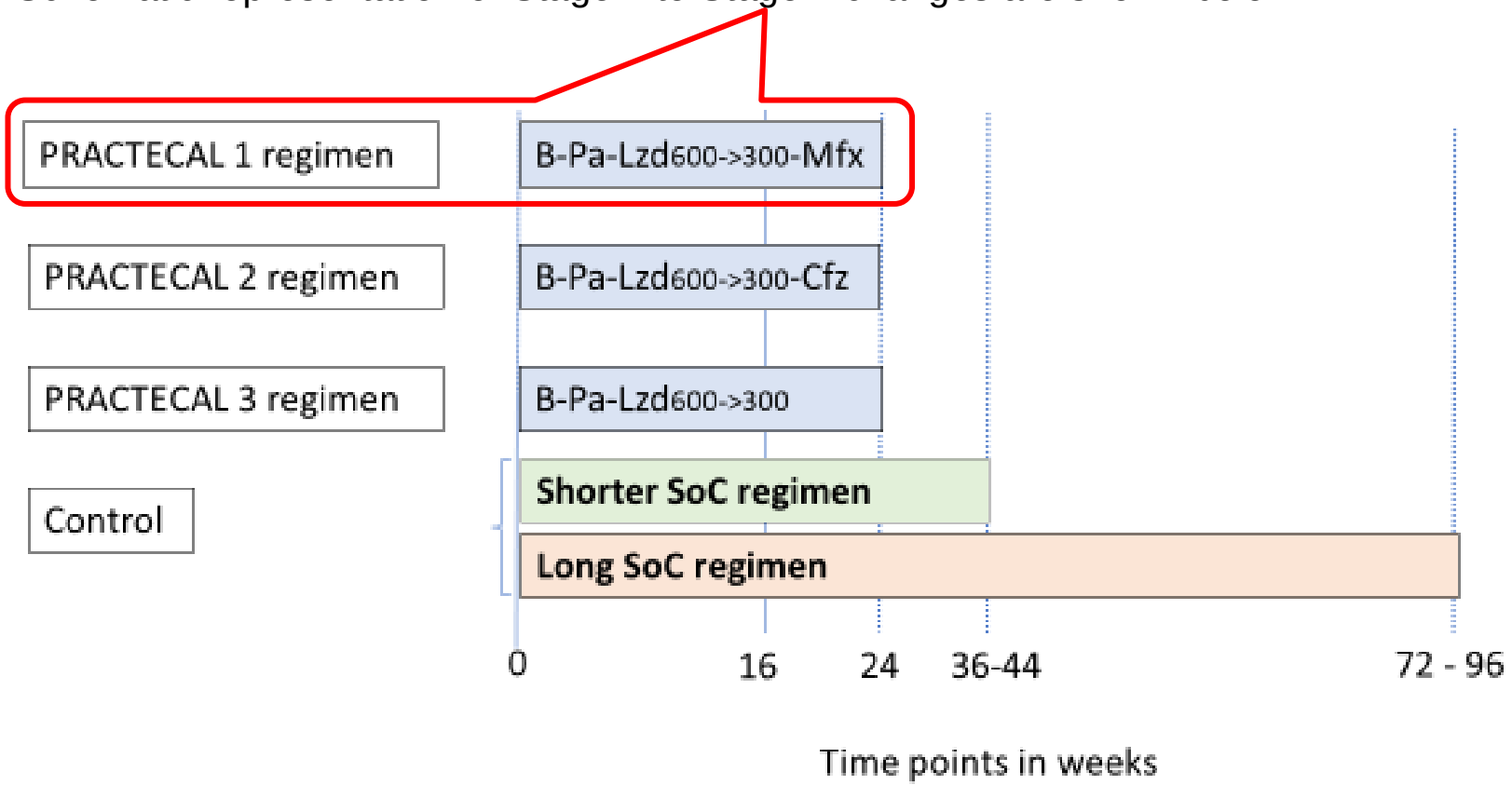
- **Comparator: Standard of care**
  - Locally approved standard of care which is as much as possible consistent with WHO recommendations for RR/MDR-TB (9-month and 18-month regimens depending on the site)

Data reviewed by the WHO Guideline Development Group

GDG meeting in February - March 2022

Schematic of TB PRACTECAL regimens

Schematic representation of Stage 1 to Stage 2 changes are shown below:



Data reviewed by the WHO Guideline Development Group

GDG meeting in February - March 2022

2. ZENIX - trial (sites: Georgia, Moldova, Russia, and South Africa)

BPaL regimen with different doses and duration of linezolid

- Bedaquiline and pretomanid at standard doses
- One of the following oral daily linezolid doses:
  1) 1200mg 26 weeks (primary analysis)
  2) 1200mg 9 weeks
  3) 600mg 26 weeks
  4) 600mg 9 weeks
- No SoC comparator regimen included in the trial

Data reviewed by the WHO Guideline Development Group

GDG meeting in February - March 2022

3. South African - 2019 regimen

- Programmatic data
- 9-month regimen containing linezolid
  - 4-6-month intensive phase: **Lzd(2m)-Bdq(6m)-Lfx-Cfz-Hh-Z-E**
  - 5-month continuation phase: **Lfx-Cfz-Z-E**

- Comparator:
  - 9-month regimen containing Eto: **Bdq(6m)-Lfx/Mfx-Eto-Cfz-Hh-Z-E**
  - WHO recommended longer regimens

Data reviewed by the WHO Guideline Development Group

GDG meeting in February - March 2022

4. Public call - data from multiple countries

- Intended use as external comparators where possible
- Programmatic data on the use of the WHO-recommended 9-month regimen (data from the programmatic implementation in South Africa) and
- Programmatic data on the WHO-recommended longer regimens (data from country programmes in Belarus, Georgia, India, Republic of Moldova, Mozambique, Papua New Guinea, the Russian Federation and Somalia);
- data from fieldwork in multiple countries from Médecins Sans Frontières (MSF); and cohorts from the EndTB project provided by MSF and Partners in Health.

2022 DR-TB Guidelines update

Section 1. **The 6-month bedaquiline, pretomanid, linezolid, and moxifloxacin (BPaLM) regimen for MDR/RR-TB (new)**

Section 2. **The 9-month all-oral regimen for MDR/RR-TB (new)**

Section 3: **Longer regimens for MDR/RR-TB**

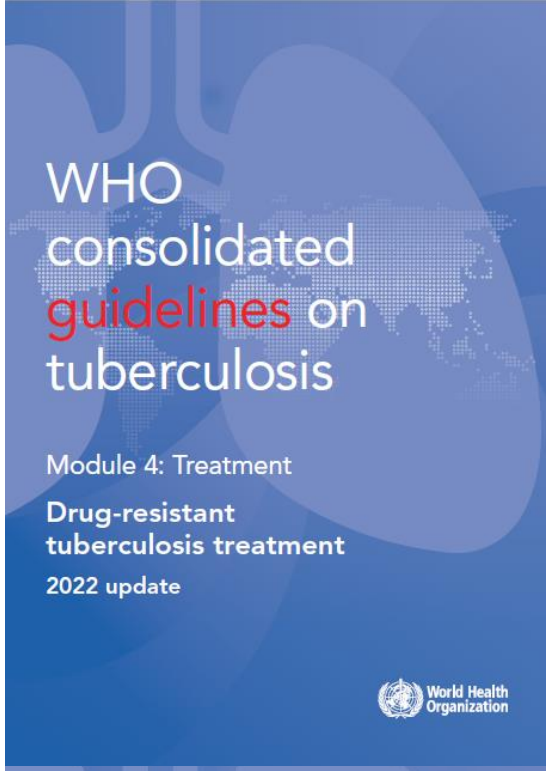
Section 4: **Regimen for rifampicin-susceptible and isoniazid-resistant tuberculosis**

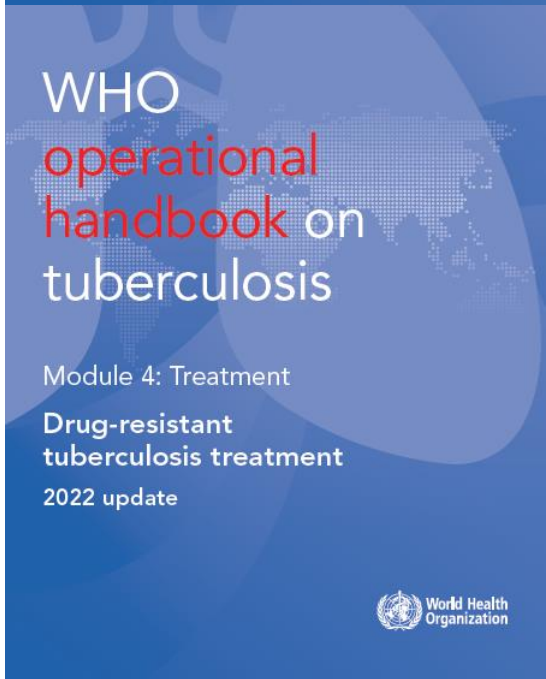
Section 5. **Monitoring patient response to MDR/RR-TB treatment using culture**

Section 6. **Start of antiretroviral therapy in patients on MDR/RR-TB regimens**

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

DR-TB handbook was updated in parallel





2022 DR-TB guidelines - key recommendations

1. The 6-month bedaquiline, pretomanid, linezolid and moxifloxacin (BPaLM) regimen for MDR/RR-TB

2022 DR-TB key recommendations – 6-month BPaLM regimen

PICO questions and decisions of the GDG

#	PICO	Population	Intervention	Comparator [data source]	Sub-PICO	Recommendation
3	Should BPaL regimens with lower linezolid exposure (dose or duration) be used instead of the original BPaL regimen in patients who are eligible for BPaL regimen?	MDR/RR-TB or pre-XDR-TB	BPaL (1200 mg – 9 weeks)	BPaL 1200–26 [ZeNix][a]	3.2	Conditional against the intervention
			BPaL (600 mg – 26 weeks)		3.3	Conditional for the intervention
			BPaL (600 mg – 9 weeks)		3.4	Conditional against the intervention
			BPaL (600 mg then 300 mg)		3.5	No recommendation because the panel felt that comparison of data from different trials was less reliable and indirect
4	Should a 6-month regimen using bedaquiline, pretomanid and linezolid be used in patients with pulmonary pre-XDR-TB (MDR/RR-TB with fluoroquinolone resistance)?	Pre-XDR-TB	BPaL (600 mg – 26 weeks) (FQ-res only)	Longer regimens [IPD][b]	4.1	Conditional for the intervention
5	Should a 6-month regimen using bedaquiline, pretomanid and linezolid be used in patients with pulmonary MDR/RR-TB and without fluoroquinolone resistance?	MDR/RR-TB	BPaL (600 mg – 26 weeks) (FQ-res and FQ-susc)	9-month (Eto)	5.1	Conditional for the intervention
				Longer regimens [IPD][b]	5.2	Conditional for the intervention
				9-month (Lzd)	5.3	Conditional for the intervention
6	Should a 6-month regimen using bedaquiline, pretomanid and linezolid with or without addition of moxifloxacin (BPaLM) or clofazimine be used in patients with pulmonary MDR/RR-TB (with or without fluoroquinolone resistance)?	MDR/RR-TB or pre-XDR-TB	BPaLM	Mix of 9-month and longer regimens [TB-PRACTECAL][c]	6.1	Conditional for the intervention
			BPaLM	BPaL (600 mg then 300 mg) [TB-PRACTECAL][c]	6.2	Conditional for the intervention
			BPaLM	BPaLC [TB-PRACTECAL][c]	6.3	Conditional for the intervention
			BPaLC	Mix of 9-month and longer regimens [TB-PRACTECAL][c]	6.4	Conditional for the intervention
			BPaLC	BPaL (600 mg then 300 mg) [TB-PRACTECAL][c]	6.5	Conditional against the intervention
			BPaL (600 mg then 300 mg)	Mix of 9-month and longer regimens [TB-PRACTECAL][c]	6.6	Conditional for the intervention

The assessment of PICO 3 allowed for the decision on the optimal dosing and duration of linezolid within the BPaLM/BPaL regimen and narrowed down the subsequent comparisons to the intervention regimen with this particular dose and duration of linezolid – BPaL (600 mg – 26 weeks).

2022 DR-TB key recommendations – 6-month BPaLM regimen

PICO questions and decisions of the GDG

#	PICO	Population	Intervention	Comparator [data source]	Sub-PICO	Recommendation
3	Should BPaL regimens with lower linezolid exposure (dose or duration) be used instead of the original BPaL regimen in patients who are eligible for BPaL regimen?	MDR/RR-TB or pre-XDR-TB	BPaL (1200 mg – 9 weeks)	BPaL 1200–26 [ZeNix][a]	3.2	Conditional against the intervention
			BPaL (600 mg – 26 weeks)		3.3	Conditional for the intervention
			BPaL (600 mg – 9 weeks)		3.4	Conditional against the intervention
			BPaL (600 mg then 300 mg)		3.5	No recommendation because the panel felt that comparison of data from different trials was less reliable and indirect
4	Should a 6-month regimen using bedaquiline, pretomanid and linezolid be used in patients with pulmonary pre-XDR-TB (MDR/RR-TB with fluoroquinolone resistance)?	Pre-XDR-TB	BPaL (600 mg – 26 weeks) (FQ-res only)	Longer regimens [IPD][b]	4.1	Conditional for the intervention
5	Should a 6-month regimen using bedaquiline, pretomanid and linezolid be used in patients with pulmonary MDR/RR-TB and without fluoroquinolone resistance?	MDR/RR-TB	BPaL (600 mg – 26 weeks) (FQ-res and FQ-susc)	9-month (Eto)	5.1	Conditional for the intervention
				Longer regimens [IPD][b]	5.2	Conditional for the intervention
				9-month (Lzd)	5.3	Conditional for the intervention
6	Should a 6-month regimen using bedaquiline, pretomanid and linezolid with or without addition of moxifloxacin (BPaLM) or clofazimine be used in patients with pulmonary MDR/RR-TB (with or without fluoroquinolone resistance)?	MDR/RR-TB or pre-XDR-TB	BPaLM	Mix of 9-month and longer regimens [TB-PRACTECAL][c]	6.1	Conditional for the intervention
			BPaLM	BPaL (600 mg then 300 mg) [TB-PRACTECAL][c]	6.2	Conditional for the intervention
			BPaLM	BPaLC [TB-PRACTECAL][c]	6.3	Conditional for the intervention
			BPaLC	Mix of 9-month and longer regimens [TB-PRACTECAL][c]	6.4	Conditional for the intervention
			BPaLC	BPaL (600 mg then 300 mg) [TB-PRACTECAL][c]	6.5	Conditional against the intervention
			BPaL (600 mg then 300 mg)	Mix of 9-month and longer regimens [TB-PRACTECAL][c]	6.6	Conditional for the intervention

The assessment of PICO 4 resulted in the conditional recommendation for use of BPaL (600 mg – 26 weeks) regimen over the currently recommended longer regimens in patients with MDR/RR-TB and additional fluoroquinolone resistance.

2022 DR-TB key recommendations – 6-month BPaLM regimen

PICO questions and decisions of the GDG

#	PICO	Population	Intervention	Comparator [data source]	Sub-PICO	Recommendation
3	Should BPaL regimens with lower linezolid exposure (dose or duration) be used instead of the original BPaL regimen in patients who are eligible for BPaL regimen?	MDR/RR-TB or pre-XDR-TB	BPaL (1200 mg – 9 weeks)	BPaL 1200–26 [ZeNix][a]	3.2	Conditional against the intervention
			BPaL (600 mg – 26 weeks)		3.3	Conditional for the intervention
			BPaL (600 mg – 9 weeks)		3.4	Conditional against the intervention
			BPaL (600 mg then 300 mg)		3.5	No recommendation because the panel felt that comparison of data from different trials was less reliable and indirect
4	Should a 6-month regimen using bedaquiline, pretomanid and linezolid be used in patients with pulmonary pre-XDR-TB (MDR/RR-TB with fluoroquinolone resistance)?	Pre-XDR-TB	BPaL (600 mg – 26 weeks) (FQ-res only)	Longer regimens [IPD][b]	4.1	Conditional for the intervention
5	Should a 6-month regimen using bedaquiline, pretomanid and linezolid be used in patients with pulmonary MDR/RR-TB and without fluoroquinolone resistance?	MDR/RR-TB	BPaL (600 mg – 26 weeks) (FQ-res and FQ-susc)	9-month (Eto)	5.1	Conditional for the intervention
				Longer regimens [IPD][b]	5.2	Conditional for the intervention
				9-month (Lzd)	5.3	Conditional for the intervention
6	Should a 6-month regimen using bedaquiline, pretomanid and linezolid with or without addition of moxifloxacin (BPaLM) or clofazimine be used in patients with pulmonary MDR/RR-TB (with or without fluoroquinolone resistance)?	MDR/RR-TB or pre-XDR-TB	BPaLM	Mix of 9-month and longer regimens [TB-PRACTECAL][c]	6.1	Conditional for the intervention
			BPaLM	BPaL (600 mg then 300 mg) [TB-PRACTECAL][c]	6.2	Conditional for the intervention
			BPaLM	BPaLC [TB-PRACTECAL][c]	6.3	Conditional for the intervention
			BPaLC	Mix of 9-month and longer regimens [TB-PRACTECAL][c]	6.4	Conditional for the intervention
			BPaLC	BPaL (600 mg then 300 mg) [TB-PRACTECAL][c]	6.5	Conditional against the intervention
			BPaL (600 mg then 300 mg)	Mix of 9-month and longer regimens [TB-PRACTECAL][c]	6.6	Conditional for the intervention

The three assessments performed under PICO 5 resulted in the conditional recommendations for the BPaL (600 mg – 26 weeks) regimen over the currently recommended 9-month regimen with ethionamide (sub-PICO 5.1), over longer regimens (sub-PICO 5.2) and over the new 9-month regimen where ethionamide is replaced with 2 months of linezolid (sub-PICO 5.3) in patients with pulmonary MDR/RR-TB without fluoroquinolone resistance.

2022 DR-TB key recommendations – 6-month BPaLM regimen

PICO questions and decisions of the GDG

#	PICO	Population	Intervention	Comparator [data source]	Sub-PICO	Recommendation
3	Should BPaL regimens with lower linezolid exposure (dose or duration) be used instead of the original BPaL regimen in patients who are eligible for BPaL regimen?	MDR/RR-TB or pre-XDR-TB	BPaL (1200 mg – 9 weeks)	BPaL 1200–26 [ZeNix][a]	3.2	Conditional against the intervention
			BPaL (600 mg – 26 weeks)		3.3	Conditional for the intervention
			BPaL (600 mg – 9 weeks)		3.4	Conditional against the intervention
			BPaL (600 mg then 300 mg)		3.5	No recommendation because the panel felt that comparison of data from different trials was less reliable and indirect
4	Should a 6-month regimen using bedaquiline, pretomanid and linezolid be used in patients with pulmonary pre-XDR-TB (MDR/RR-TB with fluoroquinolone resistance)?	Pre-XDR-TB	BPaL (600 mg – 26 weeks) (FQ-res only)	Longer regimens [IPD][b]	4.1	Conditional for the intervention
5	Should a 6-month regimen using bedaquiline, pretomanid and linezolid be used in patients with pulmonary MDR/RR-TB and without fluoroquinolone resistance?	MDR/RR-TB	BPaL (600 mg – 26 weeks) (FQ-res and FQ-susc)	9-month (Eto)	5.1	Conditional for the intervention
				Longer regimens [IPD][b]	5.2	Conditional for the intervention
				9-month (Lzd)	5.3	Conditional for the intervention
6	Should a 6-month regimen using bedaquiline, pretomanid and linezolid with or without addition of moxifloxacin (BPaLM) or clofazimine be used in patients with pulmonary MDR/RR-TB (with or without fluoroquinolone resistance)?	MDR/RR-TB or pre-XDR-TB	BPaLM	Mix of 9-month and longer regimens [TB-PRACTECAL][c]	6.1	Conditional for the intervention
			BPaLM	BPaL (600 mg then 300 mg) [TB-PRACTECAL][c]	6.2	Conditional for the intervention
			BPaLM	BPaLC [TB-PRACTECAL][c]	6.3	Conditional for the intervention
			BPaLC	Mix of 9-month and longer regimens [TB-PRACTECAL][c]	6.4	Conditional for the intervention
			BPaLC	BPaL (600 mg then 300 mg) [TB-PRACTECAL][c]	6.5	Conditional against the intervention
			BPaL (600 mg then 300 mg)	Mix of 9-month and longer regimens [TB-PRACTECAL][c]	6.6	Conditional for the intervention

The assessment of sub-PICO 6.1 resulted in the conditional recommendation for use of the BPaLM regimen of the TB-PRACTECAL trial over the comparator, the mix of SoC regimens under this trial conforming to the WHO recommendations on 9-month or longer regimens, depending on the trial site.

The assessments of sub-PICOs 6.4 and 6.6 resulted in the conditional recommendations for BPaLC and BPaL over the SoC in the TB-PRACTECAL trial; thus all three 6-month BPaL-based regimens were assessed to be preferred over the mix of SoC regimens under this trial.

The assessments of sub-PICOs 6.3 and 6.5 resulted in the conditional recommendations for BPaLM and BPaL over BPaLC; based on these assessments the GDG concluded that BPaLC should not be recommended as a regimen.

The assessment of sub-PICO 6.2 resulted in the conditional recommendations for BPaLM over BPaL; thus, it highlighted the use of the BPaLM regimen as the preferred regimen under the conditions specified in the recommendation and remarks. Compared with BPaL, BPaLM led to more treatment success, fewer failures or recurrences and less emerging drug resistance while showing little difference in adverse events.

2022 DR-TB key recommendations

1. The 6-month bedaquiline, pretomanid, linezolid and moxifloxacin (BPaLM) regimen for MDR/RR-TB

1.1 Recommendation

WHO suggests the use of a 6-month treatment regimen composed of bedaquiline, pretomanid, linezolid (600 mg) and moxifloxacin (BPaLM) rather than the 9-month or longer (18-month) regimens in MDR/RR-TB patients.
(Conditional recommendation, very low certainty of evidence)

Remarks

1. Drug susceptibility testing (DST) for fluoroquinolones is strongly encouraged in people with MDR/RR-TB, and although it should not delay initiation of the BPaLM, results of the test should guide the decision on whether moxifloxacin can be retained or should be dropped from the regimen – in cases of documented resistance to fluoroquinolones, BPaL without moxifloxacin would be initiated or continued.
2. This recommendation applies to the following:
    a. People with MDR/RR-TB or with MDR/RR-TB and resistance to fluoroquinolones (pre-XDR-TB).
    b. People with confirmed pulmonary TB and all forms of extrapulmonary TB except for TB involving the CNS, osteoarticular and disseminated (miliary) TB.
    c. Adults and adolescents aged 14 years and older.
    d. All people regardless of HIV status.
    e. Patients with less than 1-month previous exposure to bedaquiline, linezolid, pretomanid or delamanid. When exposure is greater than 1 month, these patients may still receive these regimens if resistance to the specific medicines with such exposure has been ruled out.
3. This recommendation does not apply to pregnant and breastfeeding women owing to limited evidence on the safety of pretomanid.
4. The recommended dose of linezolid is 600 mg once daily, both for the BPaLM and the BPaL regimen.

2022 DR-TB key recommendations – 6-month BPaLM regimen

Patient selection

High-level summary of main inclusion and exclusion criteria: TB-PRACTECAL and ZeNix trials

	TB-PRACTECAL	ZeNix *(22)*
Inclusion	• Aged 15 years and older • Confirmed TB and RR-TB • Regardless of HIV status	• Aged 14 years and older • Confirmed MDR/RR-TB or pre-XDR-TB • Regardless of HIV status
Exclusion	• Known resistance to Bdq, P, Dlm or Lzd • More than 1 month prior use of Bdq, P, Dlm or Lzd • Pregnant or breastfeeding • Liver enzymes 3 times the upper limit of normal • QTcF >450 ms and other risk factors for QT prolongation (excluding age and gender) or other risk factors for tdp • History of cardiac disease, syncopal episodes, significant symptomatic or asymptomatic arrhythmias (with the exception of sinus arrhythmia) • Moribund • Taking any medications contraindicated with the medicines in the trial • Any baseline laboratory value consistent with Grade 4 toxicity • TB meningoencephalitis, brain abscesses, osteomyelitis or arthritis	• Documented resistance to Bdq, P, Dlm or Lzd • More than 2 weeks of Bdq, Dlm or Lzd • Pregnant • Liver enzymes 3 times the upper limit of normal • BMI <17 • QTcF interval on ECG >500 msec, history of congenital QT prolongation, history of tdp, bradyarrhythmia • Karnofsky score <60 • Peripheral neuropathy of Grade 3–4 • Not expected to survive for more than 6 months • Uncontrolled diabetes or cardiomyopathy, extrapulmonary TB requiring extended treatment, cancer that could affect survival • Abuse of alcohol or illegal drugs • CD4+ count <100 • Use of zidovudine, stavudine or didanosine, use of MAO Inhibitors

6-month regimen BPaLM/BPaL can be used for:

- ✓ People with MDR/RR-TB or with MDR/RR-TB and resistance to fluoroquinolones (pre-XDR-TB)
- ✓ People with confirmed pulmonary TB and all forms of extrapulmonary TB except TB involving the CNS, osteoarticular or disseminated (miliary) TB
- ✓ 14 years and older
- ✓ regardless of HIV status
- ✓ less than 1-month previous exposure to bedaquiline, linezolid, pretomanid or delamanid. When exposure is greater than 1 month, these patients may still receive these regimen if resistance to the specific medicines with such exposure has been ruled out

Not recommended during pregnancy owing to limited evidence on the safety of pretomanid

2022 DR-TB key recommendations – 6-month BPaLM regimen

Subgroup considerations

PLHIV	Use but consider possible DDIs
Children	Restricted to 14 years old and older due to lack of evidence on the use of the regimen and Pretomanid.
Pregnant and breastfeeding	Restricted due to no evidence available
EPTB	Applicable in all forms of extrapulmonary TB except TB involving the CNS, osteoarticular TB and disseminated (miliary) TB

2022 DR-TB key recommendations – 6-month BPaLM regimen

Implementation considerations

<table>
<tr><td>DST needs</td><td>Confirmation of RR-TB
Desirable DST fluoroquinolones</td></tr>
<tr><td>TB disease assessment</td><td>Pulmonary TB patients with radiological evidence of bilateral disease or radiological evidence of cavitation were included in the Nix-TB, ZeNix and TB-PRACTECAL studies.</td></tr>
<tr><td>Regimen composition and dosing</td><td>
<table>
<tr><td>Bedaquiline (100 mg tablet)</td><td>400 mg once daily for 2 weeks, then 200 mg 3 times per week afterwards
OR
200 mg daily for 8 weeks, then 100 mg daily</td></tr>
<tr><td>Pretomanid (200 mg tablet)</td><td>200 mg once daily</td></tr>
<tr><td>Linezolid (600 mg tablet)</td><td>600 mg once daily</td></tr>
<tr><td>Moxifloxacin (400 mg tablet)</td><td>400 mg once daily</td></tr>
</table>
</td></tr>
<tr><td>Regimen duration</td><td>BPaLM - 6 months (26 weeks)
In case of confirmed resistance, Moxifloxacin may be dropped – BPaL
Duration for patients on BPaL can be extended to a total of 9 months (39 weeks)</td></tr>
</table>

2022 DR-TB key recommendations – 6-month BPaLM regimen

Implementation considerations

Modifications of treatment	• if either bedaquiline or pretomanid needs to be permanently discontinued, the entire BPaLM/BPaL regimen should also be discontinued; • if linezolid is permanently discontinued during the initial 9 consecutive weeks of treatment, the entire regimen should be discontinued; • if linezolid is withheld in the later weeks of the regimen, with the total remaining duration of the regimen not exceeding 8 weeks, the regimen can be considered to be completed with the remaining component drugs; and • if moxifloxacin alone is discontinued, the regimen can be continued as the BPaL regimen. Regimen change may be considered when: • more than 2 weeks of consecutive treatment interruption of all medicines in the regimen occurs; or • more than 4 weeks cumulative of nonconsecutive treatment interruption of all medicines in the regimen occurs.
Monitoring	Smear microscopy and culture Same treatment outcome definitions aDSM framework applies

2022 DR-TB guidelines - key recommendations
2. 9-month all-oral regimen for MDR/RR-TB

2022 DR-TB Rapid Communication – 9-month regimen

PICO questions and decisions of the GDG

#	PICO	Population	Intervention	Comparator [data source]	Comparison#	Decision
2-2019	In MDR/RR-TB patients, does an all-oral treatment regimen lasting 9–12 months and including bedaquiline safely improve outcomes when compared with other regimens conforming to WHO guidelines?	MDR/RR-TB	9-month regimen with ethionamide	9-month regimen with injectables; or longer regimens	1	Conditional for intervention
1-2022	Should a shorter all-oral regimen (less than 12 months) containing at least three Group A medicines be used in patients with MDR/RR-TB and fluoroquinolone resistance excluded?	MDR/RR-TB	9-month regimen with linezolid	9-month regimen with ethionamide	1.1	Conditional for either intervention or comparator
				Longer regimens	1.2	Conditional for either intervention or comparator

The main assessment that defined the overall decision was based on sub-PICO 1.1. The background for this decision was provided by the previous review and recommendation for the use of the 9-month regimen with ethionamide agreed during the GDG meeting in November 2019 and reflected in the recommendations published in the 2020 DR-TB treatment guidelines update

2022 DR-TB Rapid Communication – 9-month regimen

PICO questions and decisions of the GDG

#	PICO	Population	Intervention	Comparator [data source]	Comparison#	Decision
2-2019	In MDR/RR-TB patients, does an all-oral treatment regimen lasting 9–12 months and including bedaquiline safely improve outcomes when compared with other regimens conforming to WHO guidelines?	MDR/RR-TB	9-month regimen with ethionamide	9-month regimen with injectables; or longer regimens	1	Conditional for intervention
I-2022	Should a shorter all-oral regimen (less than 12 months) containing at least three Group A medicines be used in patients with MDR/RR-TB and fluoroquinolone resistance excluded?	MDR/RR-TB	9-month regimen with linezolid	9-month regimen with ethionamide	1.1	Conditional for either intervention or comparator
				Longer regimens	1.2	Conditional for either intervention or comparator

The panel judged that the balance of desirable and undesirable consequences favours neither the 9-month regimen with linezolid nor the 9-month regimen with ethionamide in this population. Overall, the panel judged that either regimen could be used and that the flexibility of using either linezolid or ethionamide was helpful to optimize patient care.

2022 DR-TB Rapid Communication – 9-month regimen

PICO questions and decisions of the GDG

#	PICO	Population	Intervention	Comparator [data source]	Comparison#	Decision
2-2019	In MDR/RR-TB patients, does an all-oral treatment regimen lasting 9–12 months and including bedaquiline safely improve outcomes when compared with other regimens conforming to WHO guidelines?	MDR/RR-TB	9-month regimen with ethionamide	9-month regimen with injectables; or longer regimens	1	Conditional for intervention
I-2022	Should a shorter all-oral regimen (less than 12 months) containing at least three Group A medicines be used in patients with MDR/RR-TB and fluoroquinolone resistance excluded?	MDR/RR-TB	9-month regimen with linezolid	9-month regimen with ethionamide	1.1	Conditional for either intervention or comparator
				Longer regimens	1.2	Conditional for either intervention or comparator

The panel judged that although the balance of effects did not favour either the intervention or the comparator, several other evidence-to-decision table criteria (e.g. resources, acceptability, equity and feasibility) favoured the 9-month regimen.

2022 DR-TB key recommendations
2. 9-month all-oral regimen for MDR/RR-TB

2.1 Recommendation

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)

Remarks

1. The 9-month all-oral regimen consists of bedaquiline (used for 6 months), in combination with levofloxacin/moxifloxacin, ethionamide, ethambutol, isoniazid (high-dose), pyrazinamide and clofazimine (for 4 months, with the possibility of extending to 6 months if the patient remains sputum smear positive at the end of 4 months), followed by treatment with levofloxacin/moxifloxacin, clofazimine, ethambutol and pyrazinamide (for 5 months). Ethionamide can be replaced by 2 months of linezolid (600 mg daily).
2. A 9-month regimen with linezolid instead of ethionamide may be used in pregnant women, unlike the regimen with ethionamide.
3. This recommendation applies to :

    a. people with MDR/RR-TB and without resistance to fluoroquinolones.

    b. patients without extensive TB disease and without severe extrapulmonary TB.

    c. patients with less than 1 month exposure to bedaquiline, fluoroquinolones, ethionamide, linezolid and clofazimine; when exposure is greater than 1 month, these patients may still receive this regimen if resistance to the specific medicines with such exposure has been ruled out;.

    d. All people regardless of HIV status.

    e. children (and patients in other age groups) who do not have bacteriological confirmation of TB or resistance patterns but who do have a high likelihood of MDR/RR-TB (based on clinical signs and symptoms of TB, in combination with a history of contact with a patient with confirmed MDR/RR-TB).

2022 DR-TB key recommendations

2. 9-month all-oral regimen for MDR/RR-TB

Patient selection

9-month regimen can be used for:

- ✓ patients with MDR/RR-TB and without resistance to fluoroquinolones;
- ✓ patients without extensive TB disease and without severe extrapulmonary TB;
- ✓ patients with less than 1 month exposure to bedaquiline, fluoroquinolones, ethionamide, linezolid and clofazimine; when exposure is greater than 1 month, these patients may still receive this regimen if resistance to the specific medicines with such exposure has been ruled out;
- ✓ regardless of HIV status;
- ✓ children and patients in other age groups who do not have bacteriological confirmation of TB or resistance patterns but who do have a high likelihood of MDR/RR-TB (based on clinical signs and symptoms of TB, in combination with a history of contact with a patient with confirmed MDR/RR-TB).

- ➢ 9-month regimen with linezolid instead of ethionamide may be used in pregnant women, unlike the regimen with ethionamide.
- ➢ **NEW.** In children with MDR/RR-TB aged below 6 years, an all-oral treatment regimen containing bedaquiline may be used.

2022 DR-TB key recommendations

2. 9-month all-oral regimen for MDR/RR-TB

Subgroup considerations

PLHIV	Use but consider possible DDIs
Children	Applicable for use by extrapolation to all ages. Bedaquiline is recommended for use in all ages
Pregnant and breastfeeding	Ethionamide is usually contraindicated in pregnancy. There is some experience in using linezolid during pregnancy. It is therefore recommended to use the regimen with linezolid instead of ethionamide.
EPTB	Applicable for use except in severe forms of EPTB as for example TB meningitis and disseminated forms of TB

2022 DR-TB key recommendations

2. 9-month all-oral regimen for MDR/RR-TB

Implementation considerations

DST needs	Confirmation of RR-TB Confirmation of fluoroquinolone susceptibility Ideally, genotypic testing for *inhA* and *katG* mutations
TB disease assessment	Serum haemoglobin (if regimen with Lzd is planned to be used) Exclude severe EPTB and advanced TB disease
Regimen composition	<u>Ethionamide variation:</u> 4–6 $Bdq_{(6\ m)}$-Lfx/Mfx-Cfz-Z-E-Hh-Eto / 5 Lfx/Mfx-Cfz-Z-E Initial phase: 4–6 $Bdq_{(6\ m)}$-Lfx/Mfx-Cfz-Z-E-Hh-Eto Continuation phase: 5 Lfx/Mfx-Cfz-Z-E <u>Linezolid variation:</u> 4–6 $Bdq_{(6\ m)}$-Lzd(2 m)-Lfx/Mfx-Cfz-Z-E-Hh / 5 Lfx/Mfx-Cfz-Z-E Initial phase: 4–6 $Bdq_{(6\ m)}$-$Lzd_{(2\ m)}$-Lfx/Mfx-Cfz-Z-E-Hh Continuation phase: 5 Lfx/Mfx-Cfz-Z-E Either Lfx or Mfx can be used Either Eto or Pto can be used
Regimen duration and dosing	9-11 months (initial phase extension decision is taken at month 4) Daily/7 times/week for most of the medicines
Modifications of treatment	Bdq – 6 months, possible extension to 9 months
Monitoring	Smear microscopy and culture Same treatment outcome definitions aDSM framework applies

2022 DR-TB guidelines - key recommendations

3. 18-month all-oral regimen for MDR/RR-TB

2022 DR-TB key recommendations
3. 18-month all-oral regimen for MDR/RR-TB

3.1 Recommendation

In multidrug- or rifampicin-resistant tuberculosis (MDR/RR-TB) patients on longer regimens, all three Group A agents and at least one Group B agent should be included to ensure that treatment starts with at least four TB agents likely to be effective, and that at least three agents are included for the rest of the treatment if bedaquiline is stopped. If only one or two Group A agents are used, both Group B agents are to be included. If the regimen cannot be composed with agents from Groups A and B alone, Group C agents are added to complete it.
(Conditional recommendation, very low certainty of evidence)

2022 DR-TB key recommendations

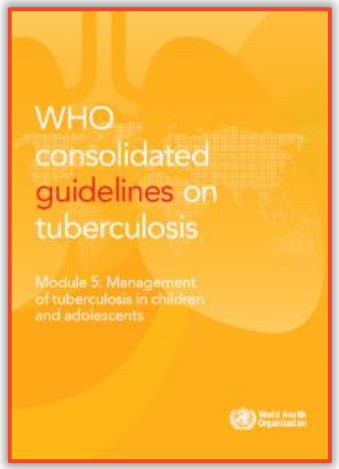
3. 18-month all-oral regimen for MDR/RR-TB

Grouping of medicines recommended for use in longer MDR-TB regimens

Groups and steps	Medicine	Abbreviation
Group A: Include all three medicines	Levofloxacin *or* moxifloxacin	Lfx Mfx
	Bedaquiline[b,c]	Bdq
	Linezolid[d]	Lzd
Group B: Add one or both medicines	Clofazimine	Cfz
	Cycloserine *or* terizidone	Cs Trd
Group C: Add to complete the regimen and when medicines from Groups A and B cannot be used	Ethambutol	E
	Delamanid[e]	Dlm
	Pyrazinamide[f]	Z
	Imipenem–cilastatin *or* meropenem[g]	Ipm–Cln Mpm
	Amikacin (*or* streptomycin)[h]	Am (S)
	Ethionamide *or* prothionamide[i]	Eto Pto
	P-aminosalicylic acid[i]	PAS

NEW. In children with MDR/RR-TB aged below 6 years, an all-oral treatment regimen containing bedaquiline may be used.

NEW. In children with MDR/RR-TB aged below 3 years delamanid may be used as part of longer regimens.



MDR/RR-TB regimen selection

BPaLM/BPaL regimen (MDR/RR-TB and pre-XDR-TB)

- in patients (aged ≥14 years) with MDR/RR-TB who have not had previous exposure to bedaquiline, pretomanid and linezolid (defined as >1 month exposure).
- This regimen may be used without moxifloxacin (BPaL) in the case of documented resistance to fluoroquinolones (in patients with pre-XDR-TB).
- DST to fluoroquinolones is strongly encouraged, but DST should not delay treatment initiation.
- Cannot be used during pregnancy
- if DST confirms susceptibility can be used in those exposed to B, Pa, or L for more than 1 month
- no TB meningitis, osteoarticular or disseminated TB

9-month regimens (MDR/RR-TB)

- 2 months of linezolid (600 mg) can be used as an alternative to 4 months of ethionamide.
- no previous exposure to second-line treatment (including bedaquiline),
- no fluoroquinolone resistance and
- no extensive pulmonary TB disease or severe extrapulmonary TB.
- rapid DST for ruling out fluoroquinolone resistance is required.
- can be used in all age groups
- regimen with linezolid can be used in pregnant women

Longer regimens (18-month, individualized, mostly in XDR-TB)

- Last resort regimen
- Those who failed or not eligible for two shorter regimens
- XDR-TB patients
- Individualized based on current recommendations

MDR/RR-TB regimen selection and factors to be considered

Regimen	MDR/RR-TB fluoroquinolone susceptible	Pre-XDR-TB	XDR-TB	Extensive pulmonary TB	Extrapulmonary TB	Age <14 years
6-month BPaLM/BPaL	Yes (BPaLM)	Yes (BPaL)	No	Yes	Yes – except TB involving CNS, miliary TB and osteoarticular TB	No
9-month all-oral	Yes	No	No	No	Yes – except TB meningitis, miliary TB, osteoarticular TB and pericardial TB	Yes
Longer individualized 18-month	Yes[a]/No	Yes[a]/No	Yes	Yes	Yes	Yes
Additional factors to be considered if several regimens are possible	Drug intolerance or adverse events					
	Treatment history, previous exposure to regimen component drugs or likelihood of drug effectiveness					
	Patient or family preference					
	Access to and cost of regimen component drugs					

BPaL: bedaquiline, pretomanid and linezolid; BPaLM: bedaquiline, pretomanid, linezolid and moxifloxacin; CNS: central nervous system; MDR/RR-TB: multidrug- or rifampicin-resistant TB; TB: tuberculosis; XDR-TB: extensively drug-resistant TB.

[a] When 6-month BPaLM/BPaL and 9-month regimens could not be used.

In summary:

- New and shorter treatment regimens for MDR/RR-TB treatment – BPaLM/BPaL and the 9-month regimen
- Longer, 18-20 months regimen – the “last resort” individualized regimen
- The duration of MDR/RR-TB treatment can be the same as of DS-TB treatment
- DST, age and other factors to be considered for MDR/RR-TB regimen selection

Android -

https://play.google.com/store/apps/details?id=com.whotbksp

iOS -

https://apps.apple.com/us/app/who-tb-guide/id1569546750

https://extranet.who.int/tbknowledge

Acknowledgements

- Experts participating in the guideline development groups and global consultation meetings
- NTPs, researchers and partners who shared data for the WHO guideline updates
- Fuad Mirzayev, Medea Gegia, Linh Nguyen, Samuel Schumacher, Zignol Matteo and other colleagues in Global Tuberculosis Programme, WHO

Thank you

World Health Organization

20, Avenue Appia
1211 Geneva

Switzerland