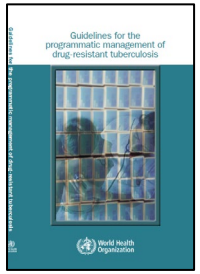
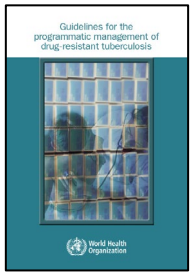
Management of MDR-TB



2006



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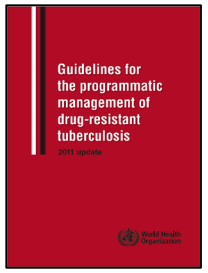

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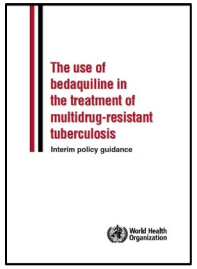
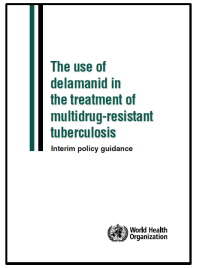


2013



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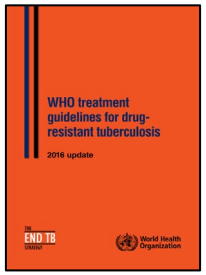

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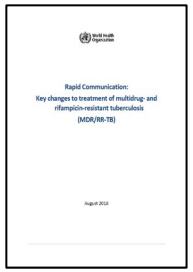
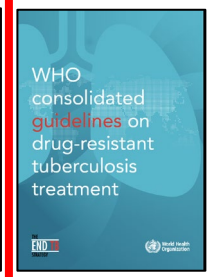
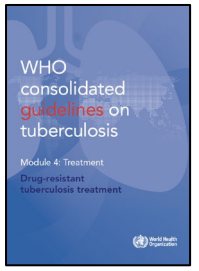


2018

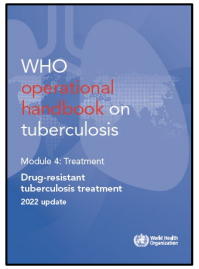
2019



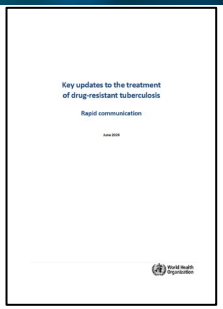
2019



2020



2022



2024

2025

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Financial Disclosures

Advisory Board Member/Consultant: AN2, AstraZeneca, Cepheid, Galapagos, Grifols, Hyfe, Insmed, MannKind, Matinas BioPharma Holdings, Inc., Monaghan, Nob Hill, Paratek Pharmaceuticals, Shionogi, Spero Therapeutics

Data Monitoring Committee: Ostuka Pharmaceutical, Bill and Melinda Gates Foundation

Contracted Research: AN2 Therapeutics, Bugworks, Insmed, Juvabis, Paratek Pharmaceuticals

Management of MDR-TB

- Epidemiology of MDR-TB
- Recommended Treatment Regimens
- Choosing a ”longer” vs. “shorter” regimen
- Building a “longer” regimen
- Evidence for effective ”shorter” regimens
- Evidence for all oral regimens
- Updated US and WHO recommendations for all oral regimens

Definitions for Pre-XDR and XDR-TB

	2006	2021
MDR-TB	Resistance to at least isoniazid and rifampin	Resistance to at least isoniazid and rifampin
Pre-XDR-TB	No definition	MDR plus additional resistance to fluoroquinolones
XDR-TB	MDR plus resistance to fluoroquinolones and one of the second-line injectable drugs (amikacin, kanamycin, or capreomycin)	MDR plus additional resistance to fluoroquinolones and at least one additional Group A drug

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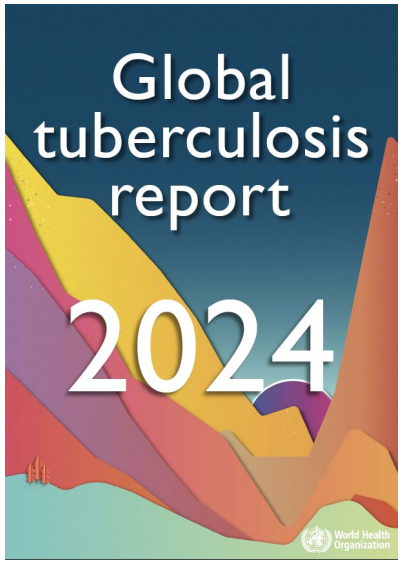
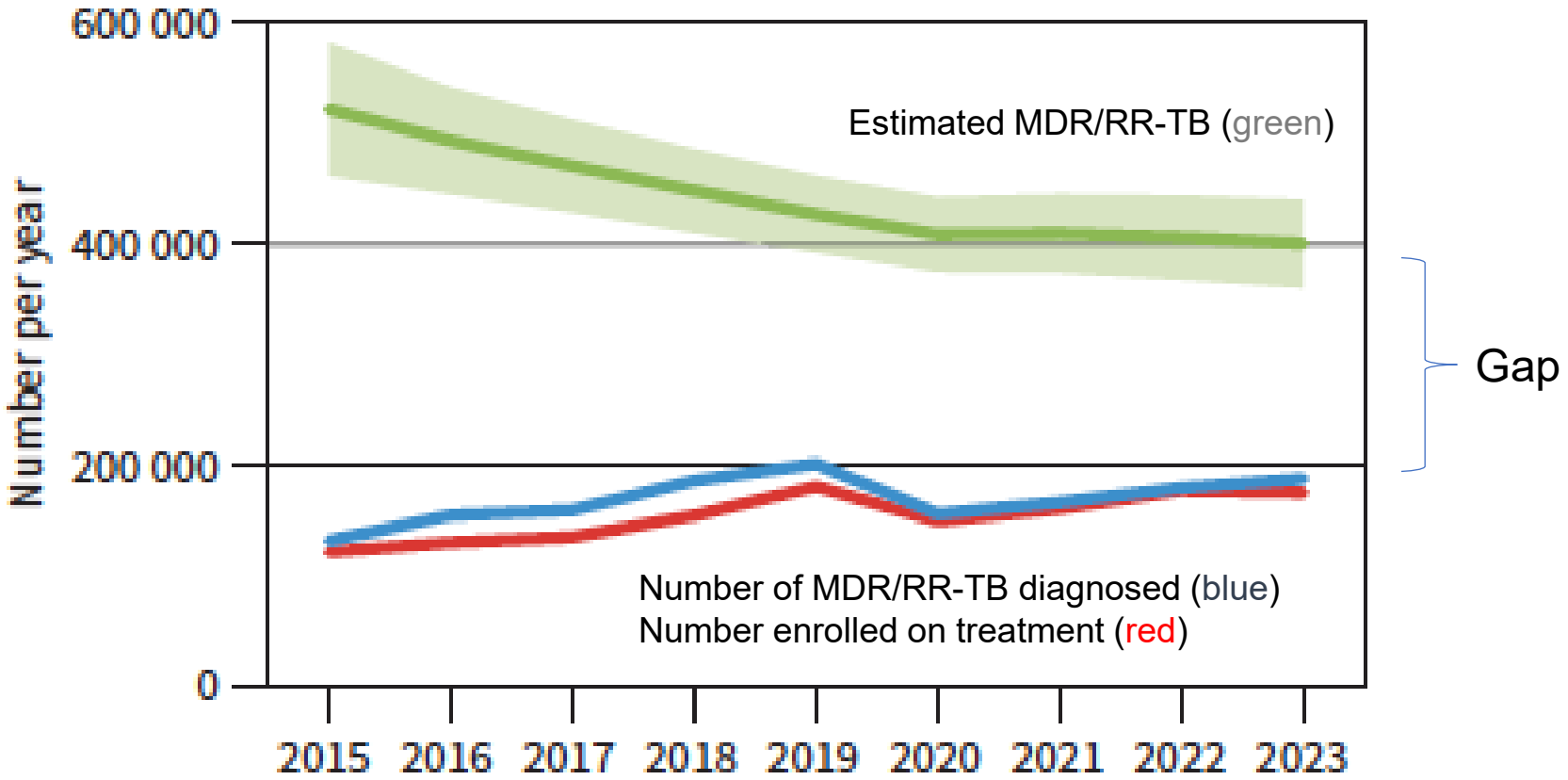
Number of Estimated and Notified MDR/RR-TB Globally, 2015-2023





WHO Global TB Report, 2024

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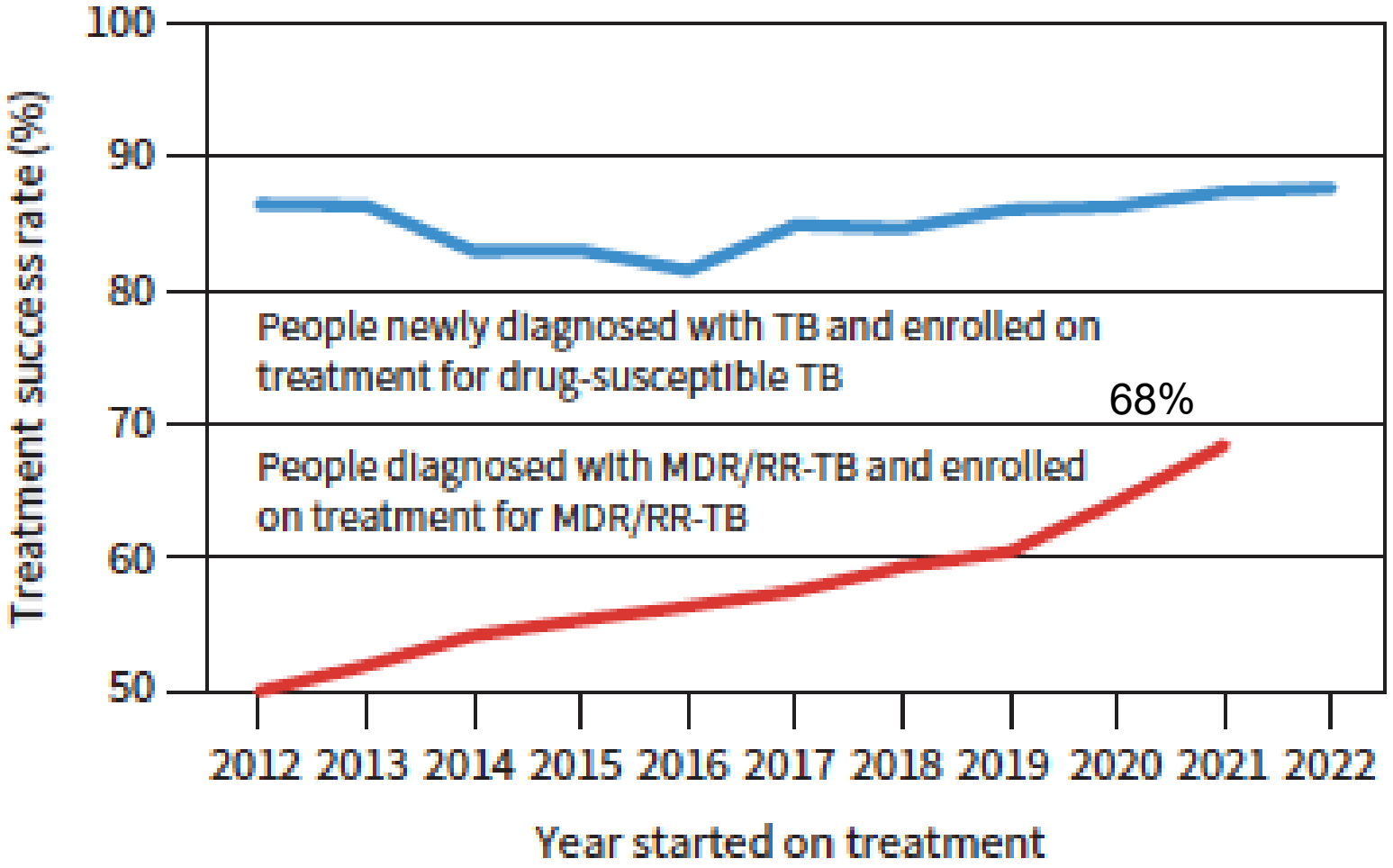
Global Success Rates for People Treated For TB, Including MDR-TB, 2012-2022



WHO Global TB Report, 2024

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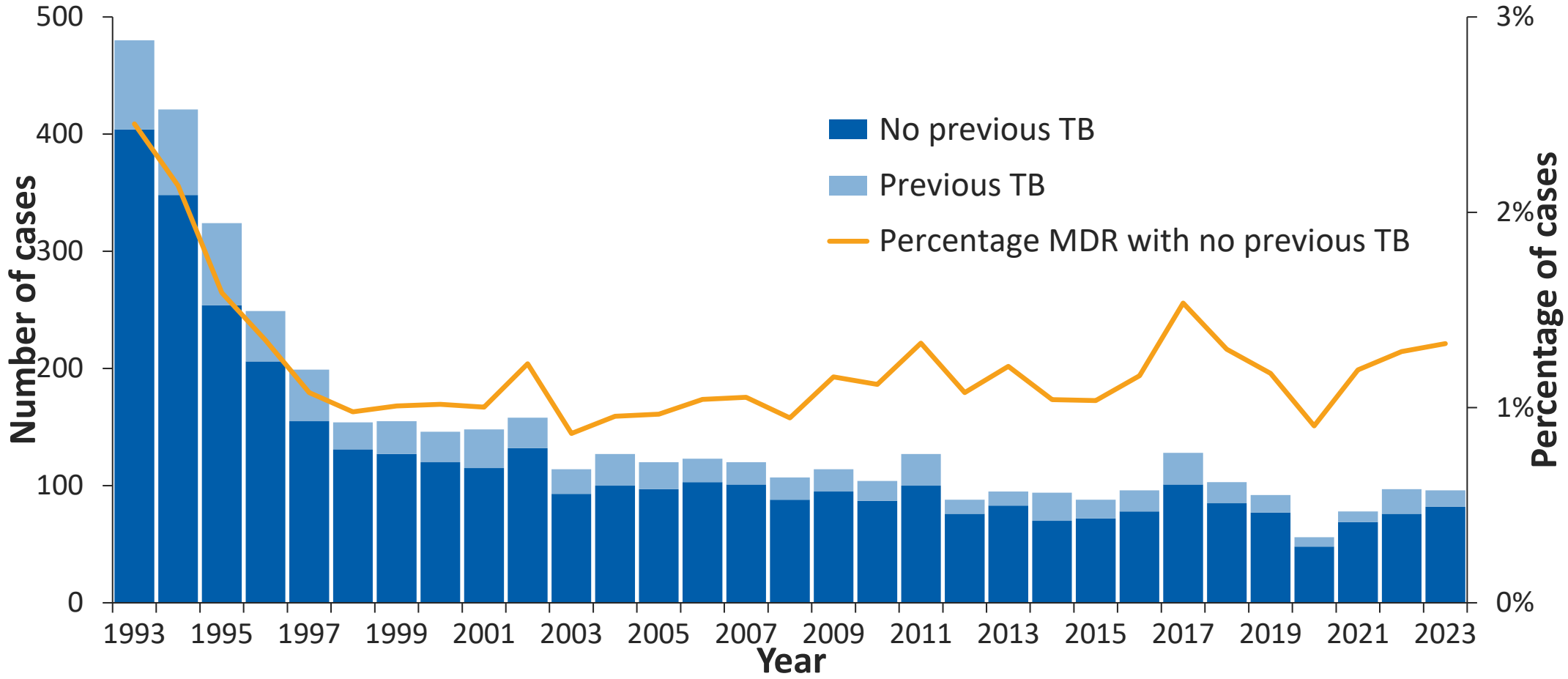
Number and Percentage of Multidrug-Resistant (MDR)* TB Cases† by History of TB, United States, 1993–2023



*Starting in 2023, information on drug resistance included results of molecular drug susceptibility testing in addition to growth-based susceptibility testing for isoniazid and rifampin. An isolate is considered resistant to isoniazid or rifampin if either the growth-based test or molecular test detects resistance.

†Excludes persons with unknown origin of birth.

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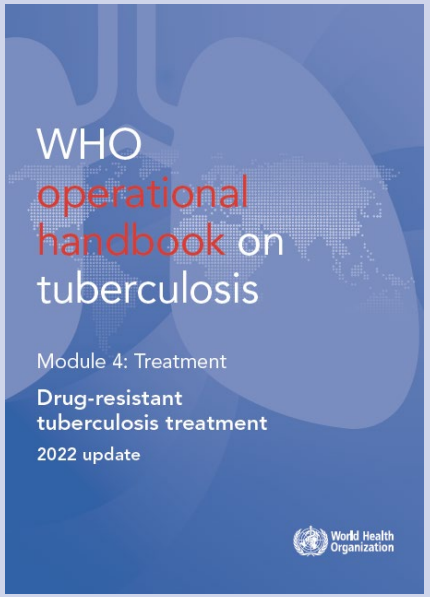
WHO Guidelines For Treatment of MDR-TB

Regimen	Drugs and Duration
✓ BPaLM	6 **Bdq** – **Pa** – **Lzd** - **Mfx**
9-month all oral	4–6 **Bdq**(6 m)-Lfx/**Mfx**-Cfz-Z-E-Hh-Eto or **Lzd**(2 m) / 5 Lfx/**Mfx**-Cfz-Z-E)
Longer individualized	



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[j]	PAS

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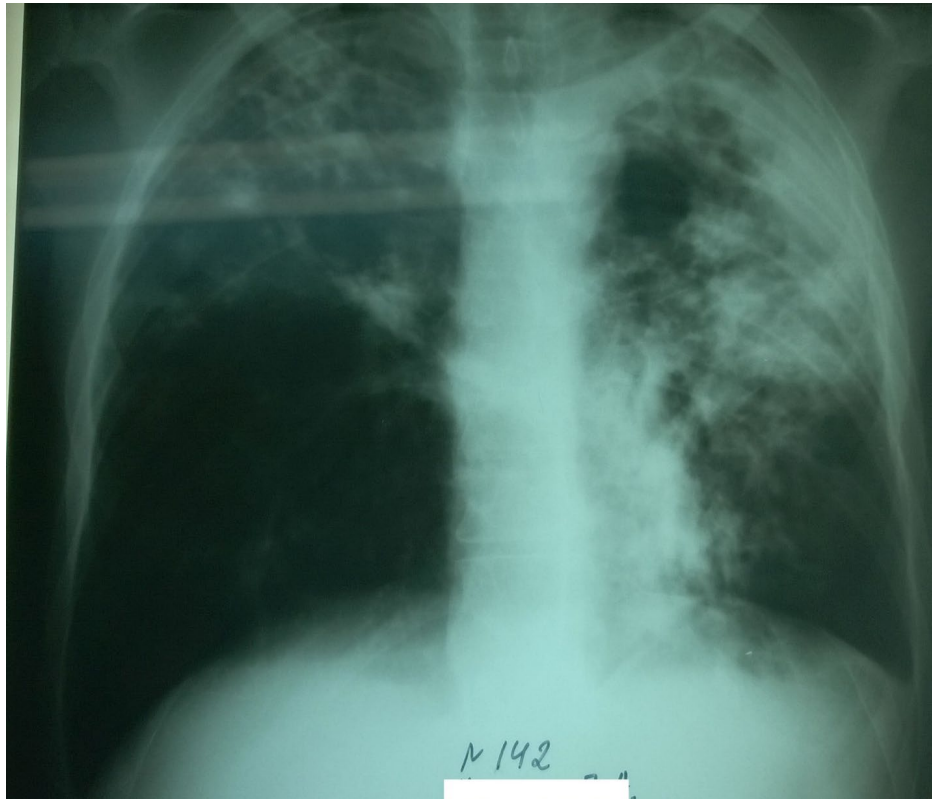
Longer or Shorter MDR-TB Regimen?

- Regimen choice depends on:
  - Fluoroquinolone susceptibility
  - History of second-line drugs received (for > 1 month)
  - Drugs available
  - Drug susceptibility testing available
  - Site of disease
  - Severity of disease
  - Patient preference

Clinical Case

- 36 year old male from former Soviet Republic previously treated for drug-susceptible TB in 2015
- Escaped from prison in 2017 and no treatment until 2018 when presented at local hospital (dyspnea, cough)
- Sputum was AFB smear positive and Xpert MTB/RIF demonstrated likely rifampin resistance
- Treated for MDR-TB with Cm-Mfx-Pto-Cs-Lzd-Imp/Cln (amox-clav) pending DST results
- Had anaphylactic reaction to Imp/Cln, all drugs stopped



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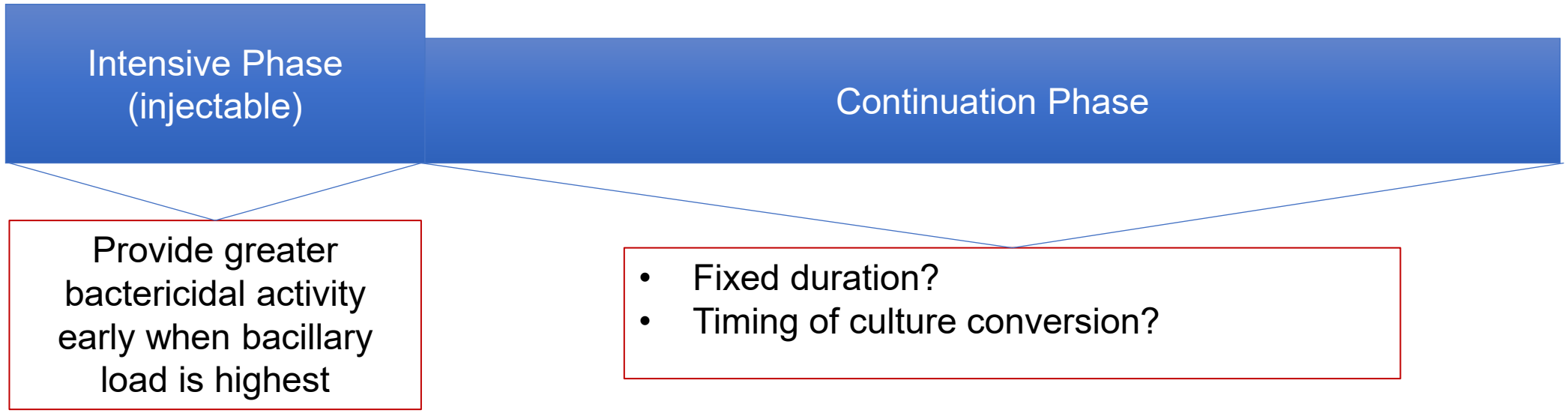
Longer MDR-TB Treatment Regimen
Intensive and Continuation Phases



	Intensive	Total Duration
WHO	6-7 months	18-20 months *or* 15-17 months after culture conversion
ATS/CDC/ ERS/IDSA	5-7 months after culture conversion	15-21 months after culture conversion for MDR-TB 15-24 months after culture conversion for pre-XDR-TB/XDR-TB

WHO Consolidated Guidelines on Tuberculosis, 2020
Nahid P, et al. AJRRCM 2019;200:e93-142

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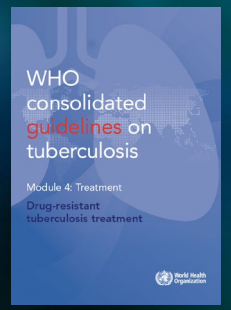

Grouping of Drugs

Build Regimen

WHO	Drugs
Group A	Levofloxacin or moxifloxacin Bedaquiline
	Linezolid
Group B	Clofazimine Cycloserine or terizidone
Group C	Ethambutol Delamanid Pyrazinamide Carbapenems with clavulanic acid Amikacin or streptomycin
	Ethionamide or prothionamide P-aminosalicylic acid
Do not use	Kanamycin Capreomycin
	Macrolides Amox/Clavulanate

WHO Consolidated Guidelines on Tuberculosis, 2020

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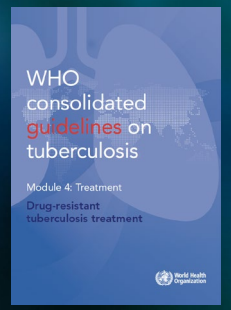

Grouping of Drugs

Build Regimen

WHO	Drugs	ATS/CDC/ERS/IDSA
Group A	Levofloxacin or moxifloxacin Bedaquiline	**Strong recommendation for**
	Linezolid	**Conditional recommendation for**
Group B	Clofazimine Cycloserine or terizidone	
Group C	Ethambutol Delamanid Pyrazinamide Carbapenems with clavulanic acid Amikacin or streptomycin	
	Ethionamide or prothionamide P-aminosalicylic acid	**Conditional recommendation against**
Do not use	Kanamycin Capreomycin	
	Macrolides Amox/Clavulanate	**Strong recommendation against**

WHO Consolidated Guidelines on Tuberculosis, 2020

Nahid P, et al. AJRRCM 2019;200:e93-142

Treatment Success and Adverse Reactions in MDR-TB: individual patient data meta-analysis

50 studies (12,030 patients) from 25 countries

Treatment Failure/relapse vs Treatment Success	
Drug	Adj. OR (95% CI)
Levofloxacin or moxifloxacin	0.3 (0.1, 0.5)
Bedaquiline	0.3 (0.2, 0.4)
Linezolid	0.3 (0.2, 0.5)
Clofazimine	0.3 (0.2, 0.5)
Cycloserine or terizidone	0.6 (0.4, 0.9)

58 studies (9178 patients) from 35 countries

Absolute Risk of Serious AE	
Drug	Median (%) (95% CI)
Bedaquiline	2.4 (0.7, 7.6)
Moxifloxacin	2.9 (1.4, 5.6)
Clofazimine	3.6 (1.3, 8.6)
Levofloxacin	4.1 (1.9, 8.8)
Linezolid	17.2 (10.1, 27.0)

WHO Consolidated Guidelines on Tuberculosis, 2020

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Building a ”Longer” Treatment Regimen For Our Patient

Build Regimen

Drugs	ATS	
	Taken Before	Susceptibility
Levofloxacin or moxifloxacin	Y	**R**
Bedaquiline	N	S
Linezolid	Y	S
Clofazimine	N	S
Cycloserine or terizidone	Y	S
Ethambutol	Y	**R**
Delamanid	N	S
Pyrazinamide	Y	**R**
Carbapenems + clavulanic acid	Y	?
Amikacin or streptomycin	Y	**R**
Ethionamide or prothionamide	N	S
P-aminosalicylic acid		

Nahid P, et al. AJRRCM 2019;200:e93-142

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This patient has..

1. MDR-TB
2. **Pre-XDR-TB**
3. XDR-TB
4. None of the above

Definitions for Pre-XDR and XDR-TB

	2006	2021
MDR-TB	Resistance to at least isoniazid and rifampin	Resistance to at least isoniazid and rifampin
Pre-XDR-TB	No definition	MDR plus additional resistance to fluoroquinolones
XDR-TB	MDR plus resistance to fluoroquinolones and one of the second-line injectable drugs (amikacin, kanamycin, or capreomycin)	MDR plus additional resistance to fluoroquinolones and at least one additional Group A drug

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Building a ”Longer” Treatment Regimen For Our Patient

Build Regimen

Drugs	ATS		
	Taken Before	Susceptibility	Use Drug?
Levofloxacin or moxifloxacin	Y	R	
Bedaquiline	N	S	✓
Linezolid	Y	S	✓
Clofazimine	N	S	✓
Cycloserine or terizidone	Y	S	?
Ethambutol	Y	R	
Delamanid	N	S	✓
Pyrazinamide	Y	R	
Carbapenems + clavulanic acid	Y	?	
Amikacin or streptomycin	Y	R	
Ethionamide or prothionamide	Y	S	✓
P-aminosalicylic acid	N	S	✓

Goal: ≥ 5 likely effective drugs in intensive phase and ≥ 4 in continuation phase

Possible Regimens

1. Bdq-Lzd-Cfz-Dlm-Cs
2. Bdq-Lzd-Cfz-Eto-Cs
3. Bdq-Lzd-Cfz-PAS-Cs

Nahid P, et al. AJRRCM 2019;200:e93-142

Randomized Trials of Shorter Course MDR/RR-TB Regimens – STREAM Trials

Study	Design	Control Regimen	Study Regimens	Duration (wks)	Treatment Success
Stream, Stage 1	Randomized, open label	WHO longer regimen (20 m)	Km+INH+Pto+Mfx+Cfz+E+Z X 16 wks then Mfx+Cfz+E+Z X 24 wks	40	79% v 80% with WHO long regimen

Bdq-bedaquiline, Cfz-clofazimine, E-ethambutol, INH-isoniazid, Km-kanamycin, Lfx-levofloxacin, Mfx-moxifloxacin, Pto-prothionamide, Z-pyrazinamide

Nunn AJ, et al. NEJM 2019;380:1201-1213
Goodall RL, et al. Lancet, 2022;400:1858-1868
WHO. Module 4. 2020

Randomized Trials of Shorter Course MDR/RR-TB Regimens – STREAM Trials

Study	Design	Control Regimen	Study Regimens	Duration (wks)	Treatment Success
Stream, Stage 1	Randomized, open label	WHO longer regimen (20 m)	Km+INH+Pto+Mfx+Cfz+E+Z X 16 wks then Mfx+Cfz+E+Z X 24 wks	40	79% v 80% with WHO long regimen
Stream, Stage 2	Randomized, open label	Stage 1 regimen	Stage 1 regimen vs	40	71%
			Bdq for Km and Lvf for Mfx	40	83%
			Km plus above	28	91%

Bdq-bedaquiline, Cfz-clofazimine, E-ethambutol, INH-isoniazid, Km-kanamycin, Lfx-levofloxacin, Mfx-moxifloxacin, Pto-prothionamide, Z-pyrazinamide

Nunn AJ, et al. NEJM 2019;380:1201-1213
Goodall RL, et al. Lancet, 2022;400:1858-1868
WHO. Module 4. 2020

Randomized Trials of Shorter Course MDR/RR-TB Regimens – Nix and ZeNix

Study	Design	Control Regimen	Study Regimens	Duration (wks)	Treatment Success	Neuropathy
Nix*	Open label	–	Bdq, Pa, Lzd (1200 mg/d)	26	90%	81%

Bdq-bedaquiline, Pa-prothionamide, Lzd-linezolid

*In the Nix trial, only 15% (16/109) of patients completed the starting 1200 mg/day dosing with no interruptions or dose reductions. All completed 4 weeks of the full dose

Conradie F, et al. NEJM 2020;382:893-902
Conradie F, et al. NEJM 2022;387:810-23
WHO. Module 4. 2020

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Randomized Trials of Shorter Course MDR/RR-TB Regimens – Nix and ZeNix

Study	Design	Control Regimen	Study Regimens	Duration (wks)	Treatment Success	Neuropathy
Nix*	Open label	–	Bdq, Pa, Lzd (1200 mg/d)	26	90%	81%
ZeNix	Randomized, open label	Nix regimen	Bdq, Pa, Lzd (1200 mg/d)	26	93%	38%
			Bdq, Pa, Lzd (1200 mg/d)	9	89%	24%
			Bdq, Pa, Lzd (600 mg/d)	26	91%	24%
			Bdq, Pa, Lzd (600 mg/d)	9	84%	13%

Bdq-bedaquiline, Pa-prothionamide, Lzd-linezolid

*In the Nix trial, only 15% (16/109) of patients completed the starting 1200 mg/day dosing with no interruptions or dose reductions. All completed 4 weeks of the full dose

Conradie F, et al. NEJM 2020;382:893-902
Conradie F, et al. NEJM 2022;387:810-23
WHO. Module 4. 2020

CDC BPaL Recommendation

- **August 2019** - FDA approved the use of pretomanid 200mg in combination with bedaquiline and linezolid (BPaL) in adults with pulmonary extensively drug resistant (XDR), treatment-intolerant, or nonresponsive multidrug-resistant (MDR) tuberculosis (TB).

- **February 2022** – CDC provides provisional guidance for the use of BPaL
  - The CDC recommendation for initial linezolid dose within BPaL regimen of 1200 mg

- **February 2024** – CDC updates guidance
  - The CDC recommendation for initial linezolid dose within BPaL regimen changed from 1200 mg to 600 mg, based on results of the ZeNix trial.

https://archive.cdc.gov/#/details?url=https://www.cdc.gov/tb/hcp/treatment/bpal.html

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Demographics and TB Characteristics of First 70 Patients Treated with BPaL in US

Demographics	TB Characteristics

• 70 patients in 12 states
• Median age: 37 yrs (range 14-83)
• Median weight: 58.0 kg (40-132.7 kg)
• Male: 65.7%
• Non US born: 90%
• Nonwhite: 77.9%
• Not Hispanic: 84.3%
	• Pulmonary TB: 75.6%
	• Extrapulmonary TB: 10.0%
	• Both: 14.2%
	• AFB smear: 54.0%
	• Cavitary: 46%
	• Drug resistance:
	  • Rifampin monoresistance: 12.9%
	  • MDR-TB: 61.4%
	  • Pre-XDR-TB: 14.3%
	  • XDR-TB: 1.4%

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Haley CA, et al. Clin Infect Dis 2023;77:1053-62

BPaL Treatment Effectiveness/Adverse Reactions

Effectiveness

Treatment Outcomes	Patient No. (%)
Completed treatment	68 (100)%
Completed 26 wks	55 (80.9%)
Treatment interruption	18 (26.5)
Time to culture conversion	37 days (1-90)
Lost to follow-up	0
Died	0
TB “relapsed”*	2 (2.9%)

*Duration of follow-up ≥ 6 months in 80.9% and ≥ 12 months in 52.9%

Adverse Reactions

Adverse reaction	Patient No. (%)
Hematologic/neurologic events (n=68)	
Linezolid discontinued	3 (4.4)
Linezolid dose change/discontinuation	7 (10.3)
No dose change or discontinuation	5 (7.4)
Gastrointestinal	14 (20.6)
QTc > 500 ms or increase of > 60 ms	0

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Haley CA, et al. Clin Infect Dis 2023;77:1053-62

BPaL Treatment and Linezolid Dosing

Characteristic	Patient No. (%)
Initial BPaL regimen (n=70)	
Initial linezolid dose 600 mg daily	66 (94.3)
Given other TB drugs with PBaL	0
BPaL stopped after rifampin-resistance excluded	2 (2.9)
Linezolid Dose Adjustment (n=68)	
TDM performed	66 (97.1%)
Dose or frequency adjusted	42 (61.8)
Adjusted based on TDM	36 (52.9)
Finished on 600 mg daily	27 (39.7)
Finished on 600 mg tiw	21 (30.9%)

TDM – therapeutic drug monitoring, aiming for trough of < 2

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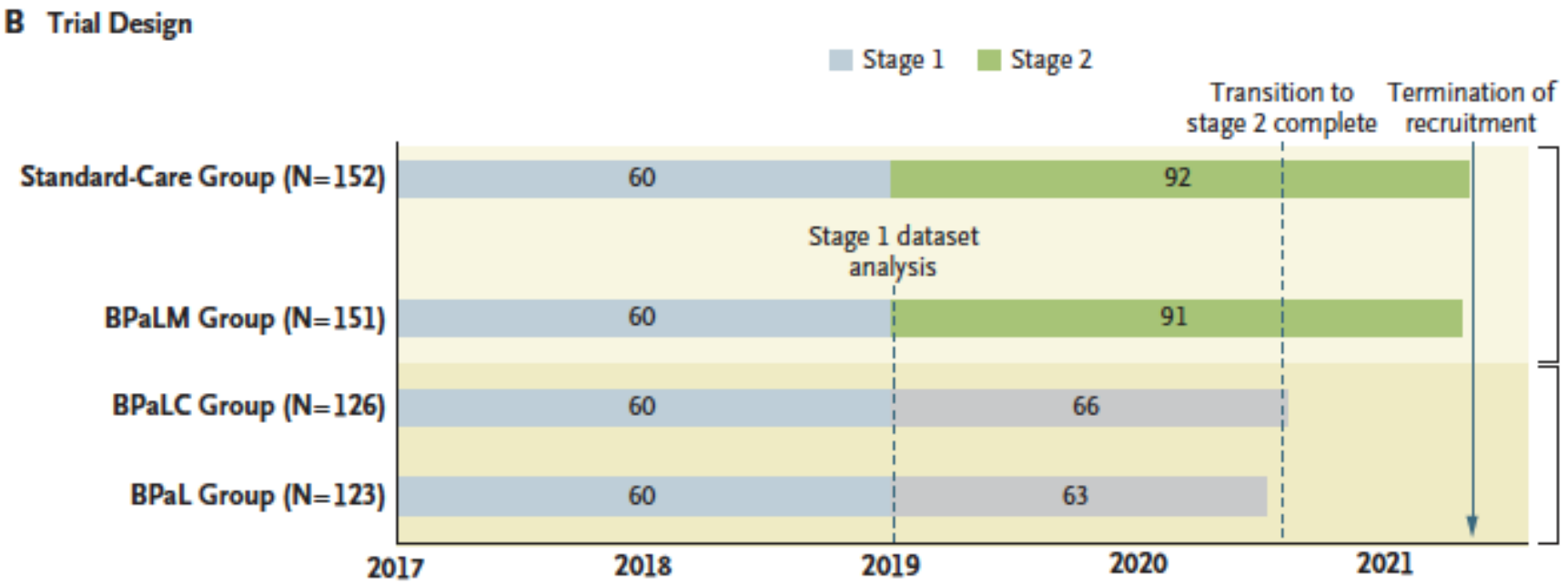
Haley CA, et al. Clin Infect Dis 2023;77:1053-62

TB PRACTECAL: Open-label, phase 2b-3, adaptive multicenter, randomized, controlled noninferiority trial



Culture conversion at 8 wks

77%

67%

46%

SCG – WHO recommended 9-12 month regimen
BPaLM - bedaquiline, linezolid, pretomanid, moxifloxacin
BPaLC - bedaquiline, linezolid, pretomanid, clofazimine
BPaL - bedaquiline, linezolid, pretomanid

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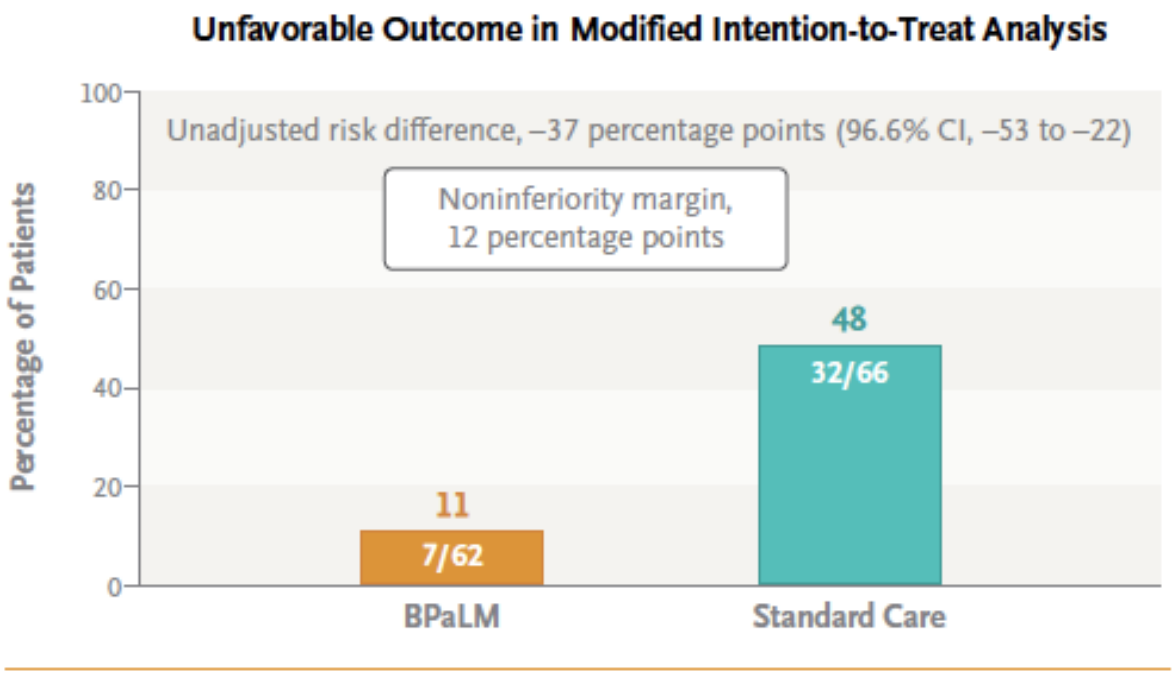
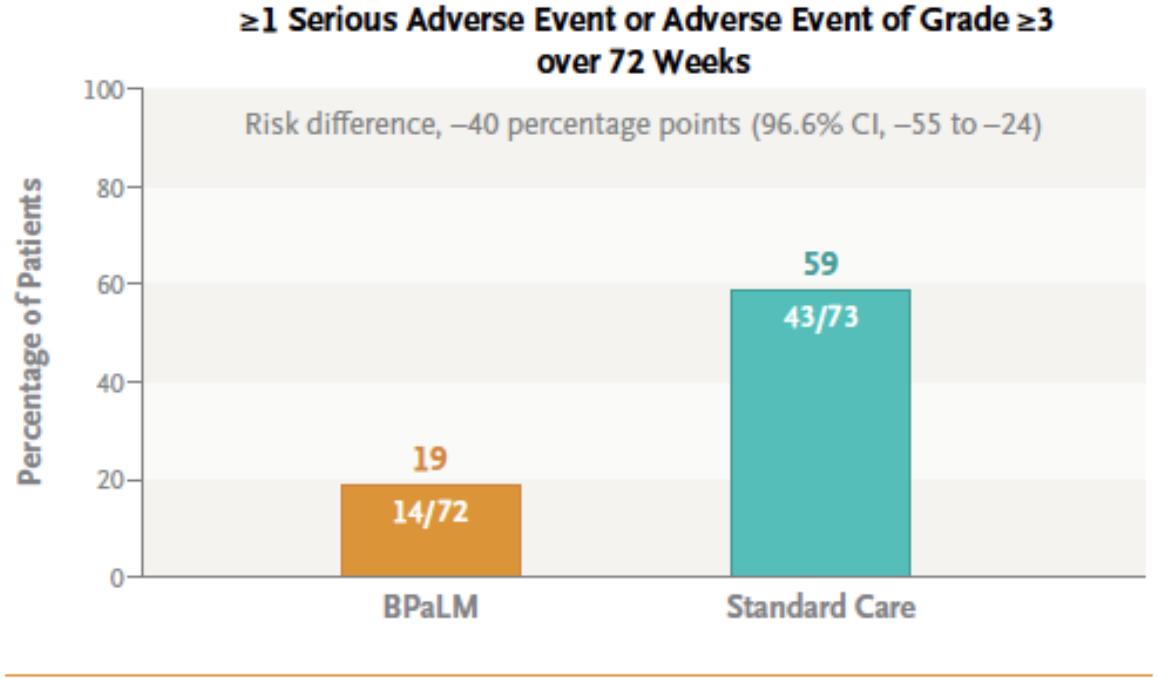
Nyang'wa BT, et al. NEJM 2022;387:25

Stage 2 Treatment Outcomes and Safety Analysis





- BPaLM was noninferior and superior to standard of care and safer
- WHO preferred regimen for fluoroquinolone susceptible MDR-TB

Nyang'wa BT, et al. NEJM 2022;387:2331-43
WHO. Module 4. 2022

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Could Our Patient Receive BPaL or BPaLM?

Build Regimen

Drugs	ATS		
	Taken Before	Susceptibility	Use Drug?
Levofloxacin or moxifloxacin	Y	R	X
Bedaquiline	N	S	✓
Linezolid	Y	S	✓
Clofazimine	N	S	✓
Cycloserine or terizidone	Y	S	✓
Ethambutol	Y	R	X
Delamanid	N	S	✓
Pyrazinamide	Y	R	X
Carbapenems with clavulanic acid	Y	?	X
Amikacin or streptomycin	Y	R	X
Ethionamide or prothionamide	Y	S	✓
P-aminosalicylic acid	N	S	✓

+ Pa = BPaL

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Nahid P, et al. AJRRCM 2019;200:e93-142

Clinical Case

- After several attempts to start a longer MDR-TB regimen he was started on BPaL at the following doses:
  - Bdq 400 mg once daily for two weeks then 200 mg three times a week
  - Pa 200 mg once daily
  - Lzd 600 mg twice daily
- After 2 months, he noticed tingling and numbness in his feet
- What would you do now?

Which of the following would be an appropriate next step?

a) Hold the BPaL regimen and restart when symptoms improve

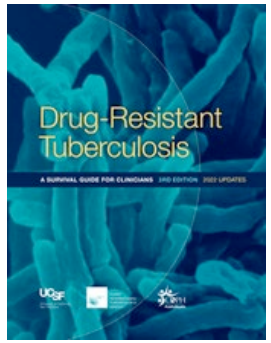
b) Reduce the pretomanid dose

c) **Hold linezolid and restart at reduced dose or frequency**

d) Continue the BPaL regimen and add pyridoxine

Adverse Reactions Associated with Drugs in BPaL/BPaLM

Drug	Adverse effects
Bedaquiline	• QTc prolongation • Hepatitis • Nausea • Joint pain • Headache • Elevated amylase
Pretomanid	• ? • Testicular toxicity was observed in mice and rats but not in non-human primates or in humans to date.
Linezolid*	• Myelosuppression; thrombocytopenia, anemia, and leukopenia • Diarrhea and nausea, including *C.difficile* colitis • Optic and peripheral neuropathy – most resolve, but can be irreversible • Serotonin syndrome



*Mitochondrial toxicity is less common when the serum trough level is < 2 µg/mL

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Pharmacokinetic Considerations

Drug	Metabolism	DDI with ARVs	PK notes
Bedaquiline	CYP3A4/5 substrate Long-terminal half-life	EFV reduces Bdq concentration Bdq exposure increased by boosted PI	Strong PK-PD correlation Black race associated with 30-50% decrease in Bdq exposure QT prolongation driven by M2 metabolite
Pretomanid	CYP3A substrate	EFV reduces Pa concentration	PK studies in children not yet completed
Linezolid	No P450 metabolism	None	Use with caution in renal dysfunction, advanced age Very narrow therapeutic margin Inhibitor of MAO A and B
Moxifloxacin	Glucuronide and sulfate conjugation in liver	None	Do not co-administer with iron, magnesium or calcium

Dheda K, e al. Nature Reviews 2024;10:22

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Updated TB Guidelines

AMERICAN THORACIC SOCIETY DOCUMENTS

Updates on the Treatment of Drug-Susceptible and Drug-Resistant Tuberculosis

An Official ATS/CDC/ERS/IDSA Clinical Practice Guideline

Jussi J. Saukkonen*, Raquel Duarte*, Sonal S. Munsiff*, Carla A. Winston*, Manoj J. Mammen, Ibrahim Abubakar, Carlos Acuña-Villaorduña, Pennan M. Barry, Mayara L. Bastos, Wendy Carr, Hassan Chami, Lisa L. Chen, Terence Chorba, Charles L. Daley, Anthony J. Garcia-Prats, Kelly Holland, Ioannis Konstantinidis, Marc Lipman, Giovanni Battista Migliori, Farah M. Parvez, Adrienne E. Shapiro, Giovanni Sotgiu, Jeffrey R. Starke, Angela M. Starks, Sanket Thakore, Shu-Hua Wang, Jonathan M. Wortham, and Payam Nahid; on behalf of the American Thoracic Society, U.S. Centers for Disease Control and Prevention, European Respiratory Society, and Infectious Diseases Society of America

This official clinical practice guideline was approved by the American Thoracic Society (ATS) and the Infectious Diseases Society of America (IDSA) September 2024, was cleared by the U.S. Centers for Disease Control and Prevention (CDC) September 2024, and was approved by the European Respiratory Society (ERS) October 2024

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Saukkonen JJ, et al. A J Resp Crit Care Med 2025 in press

WHO Treatment Outcomes with BPaL, BPaLM and WHO Long Regimens

WHO Outcomes	TB PRACTECAL BPaL (n=126)	TB PRACTECAL BPaLM (n=128)	ZeNix BPaL (600 mg)	WHO Long with injectables	WHO Long IPD Registry
Duration	24 wk	24 wk	26 wk	9-20 mo	Variable
Success	76.7	88.7	97.7	51.5	73.9
Failure and recurrence	13.3	8.1	2.3	25.8	3.3
Loss to f/u	10.0	8.1	0	19.7	11.8
Adverse events	19.6	21.0	14.0	50.9	4.7
Death	0	0	0	1.9	11.0
Amplified resistance	2.9	0	0	1.9	2.4

Saukkonen JJ, et al. A J Resp Crit Care Med 2025 in press

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ATS/CDC/ERS/IDSA Updated Recommendations

Recommendation #3: In adolescents aged 14 and older and adults with rifampin-resistant pulmonary TB with **resistance or patient intolerance to fluoroquinolones**, who either have had no previous exposure to bedaquiline and linezolid or have been exposed for less than one month, **we recommended the use of the 6-month treatment BPaL regimen rather than more than 15-month regimens** *(strong recommendation, very low certainty of evidence)*

Recommendation #4: In adolescents aged 14 and older and adults with rifampin-resistant, **fluoroquinolone susceptible** pulmonary TB **we recommended the use of the 6-month treatment BPaLM regimen rather than the 15-month or longer regimens in persons with MDR/RR-TB** *(strong recommendation, very low certainly of evidence).*

Saukkonen JJ, et al. A J Resp Crit Care Med 2025 in press

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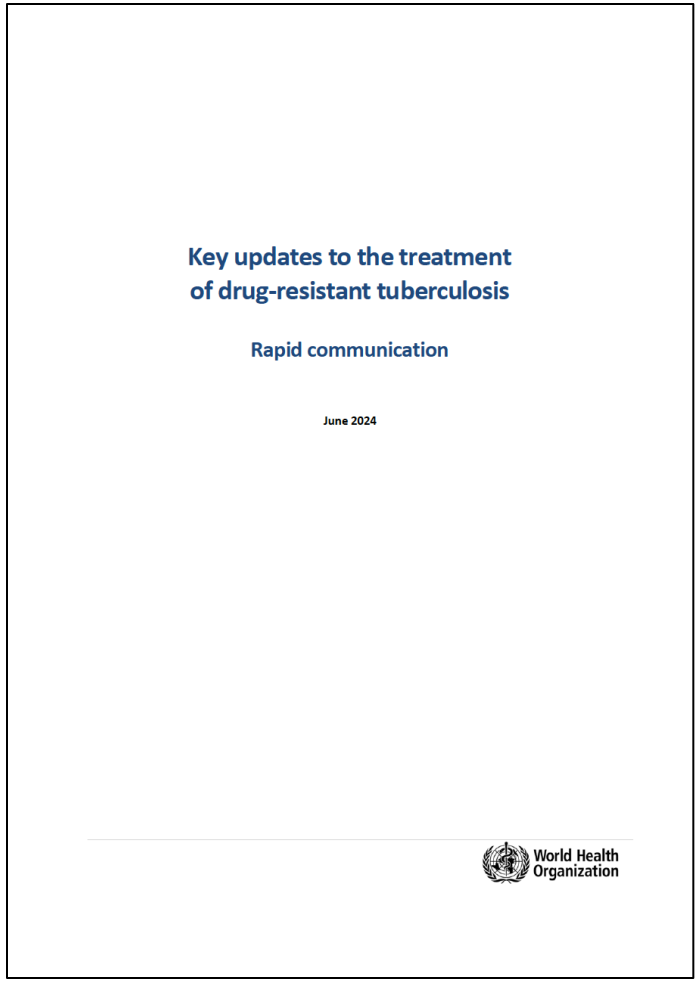
Challenges

- Subgroup Analyses
  - Age – in low incidence settings a greater proportion of patients will be older (more medications and co-morbidities)
  - Children – Longer regimens are recommended for those < 14 yrs as well as pregnant and lactating women
  - People living with HIV – recommended regardless of HIV status or CD4 count
  - Extrapulmonary disease – recommended for non-severe forms
- Availability of rapid drug susceptibility testing
- Availability of therapeutic drug monitoring
- Drug-drug interactions

Key Updates in MDR-TB Treatment from the WHO



- BEAT TB Trial
- endTB Trial

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endTB Trial

- Study Population: 754 adults and adolescents with MDR/RR-TB, including adolescents, HIV infected, and pregnant patients
- Regimens: five different 9-month

Trial Regimens	Bedaquiline	Delamanid	Clofazimine	Linezolid	Quinolone	Pyrazinamide	Duration (months)
endTB 1	Bdq			Lzd	Mfx	Z	
endTB 2	Bdq		Cfz	Lzd	Lfx	Z	
endTB 3	Bdq	Dlm		Lzd	Lfx	Z	9
endTB 4		Dlm	Cfz	Lzd	Lfx	Z	
endTB 5		Dlm	Cfz		Mfx	Z	
Control Arm	Local SOC*						18-24

*Standard of care (SOC) control, composed according to WHO Guidelines, may include Bdq and/or Dlm

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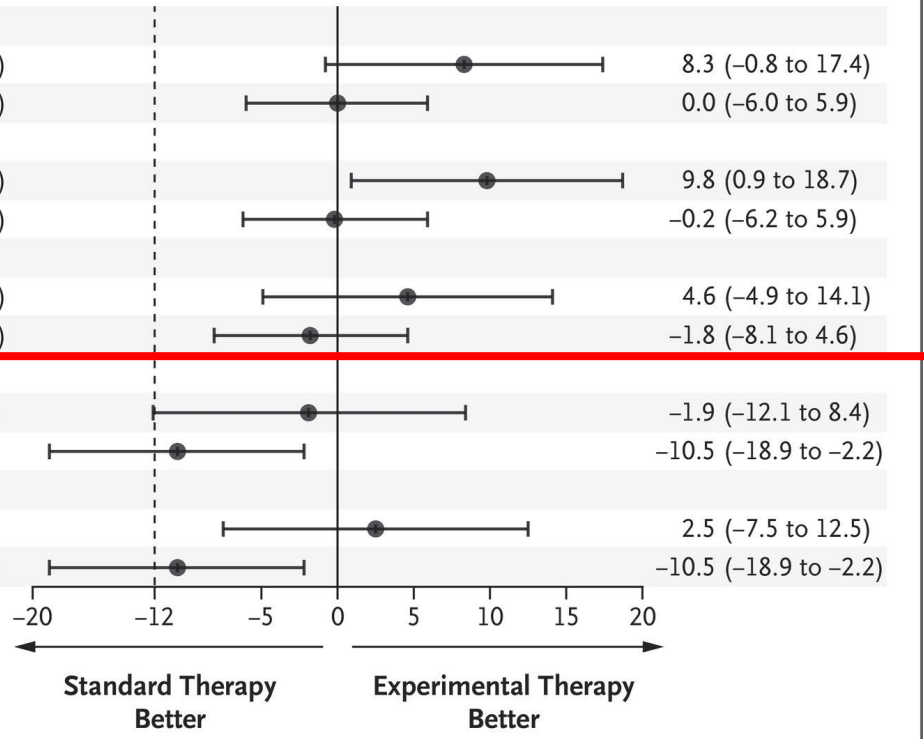
Guglielmetti L, et al. NEJM 2025;392:468-482

endTB Trial Primary Analysis

Analysis Population	Standard Therapy	Experimental Therapy
	no. with favorable outcome/total no. (%)	
Standard therapy vs. BLMZ		
Modified intention-to-treat population	96/119 (80.7)	105/118 (89.0)
Per-protocol population	71/74 (95.9)	94/98 (95.9)
Standard therapy vs. BCLLfxZ		
Modified intention-to-treat population	96/119 (80.7)	104/115 (90.4)
Per-protocol population	71/74 (95.9)	91/95 (95.8)
Standard therapy vs. BDLLfxZ		
Modified intention-to-treat population	96/119 (80.7)	104/122 (85.2)
Per-protocol population	71/74 (95.9)	97/103 (94.2)
Standard therapy vs. DCLLfxZ		
Modified intention-to-treat population	96/119 (80.7)	93/118 (78.8)
Per-protocol population	71/74 (95.9)	82/96 (85.4)
Standard therapy vs. DCMZ		
Modified intention-to-treat population	96/119 (80.7)	89/107 (83.2)
Per-protocol population	71/74 (95.9)	82/96 (85.4)



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Guglielmetti L, et al. NEJM 2025;392:468-482

WHO Key Updates: endTB Trial

- WHO suggests using the **9-month** all-oral regimens (BLMZ, BLLfxCZ, BDLLFxZ*) over the WHO long regimen in patients with MDR/RR-TB in whom resistance to FQNs has been excluded;
  - BLMZ is suggested over using BLLfxCZ
  - BLLfxCZ is suggested over BDLLfxZ
  - CDLLfxZ and CDMZ regimens **are not** recommended due to high rates of treatment failure/relapse and acquired resistance

*BLMZ (Bdq,Lzd,Mxf,Z)
BLLfxCZ (Bdq,Lzd,Lfx,C,Z)
BDLLFxZ (Bdq,Dlm,Lzd,Lfx,Z)

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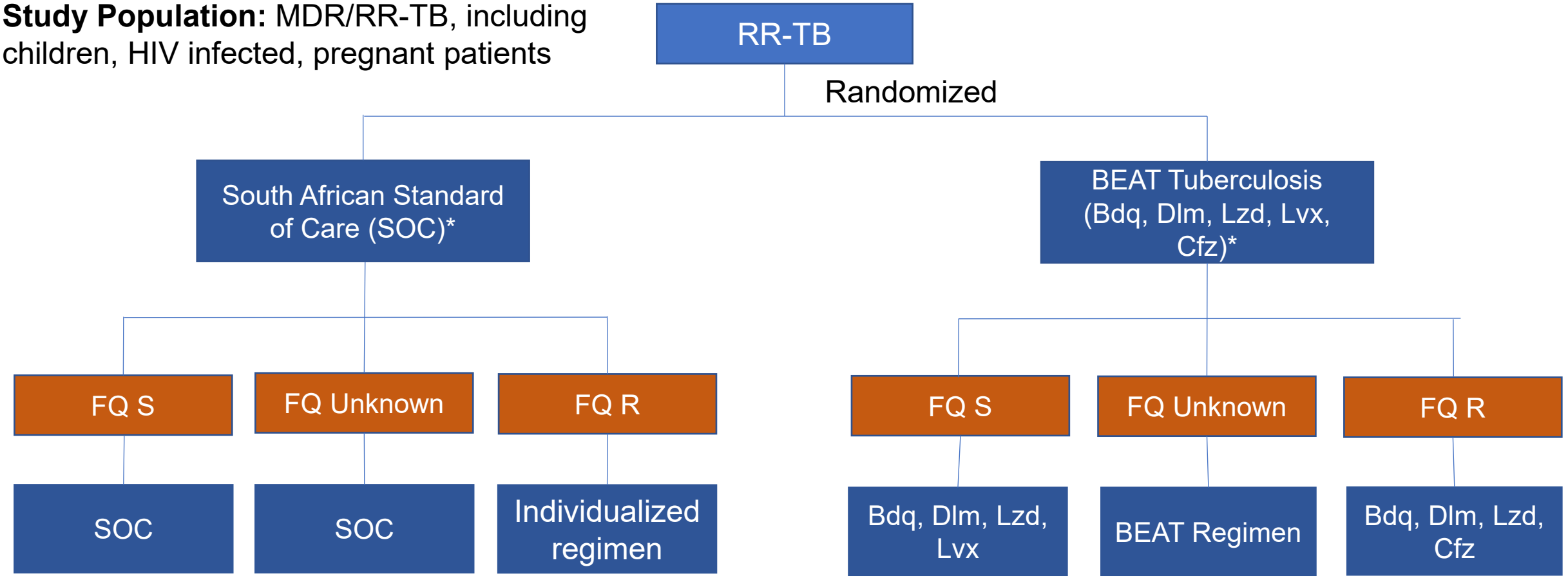
BEAT-Tuberculosis Trial

Study Population: MDR/RR-TB, including children, HIV infected, pregnant patients



*9-month, all oral Bdq regimen, most received Lnz

*6-month regimens

WHO. Rapid Comm 6/2024

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WHO Key Updates: BEAT-Tuberculosis

- **Treatment success:** 86% in both arms
- WHO suggests the use of a 6-month regimen composed of **bedaquiline, delamanid, linezolid (600 mg), levofloxacin, and clofazimine (BDLLfxC)** in MDR/RR-TB patients **with or without FQN resistance** (conditional recommendation, very low certainty of evidence)

WHO. Rapid Comm 6/2024

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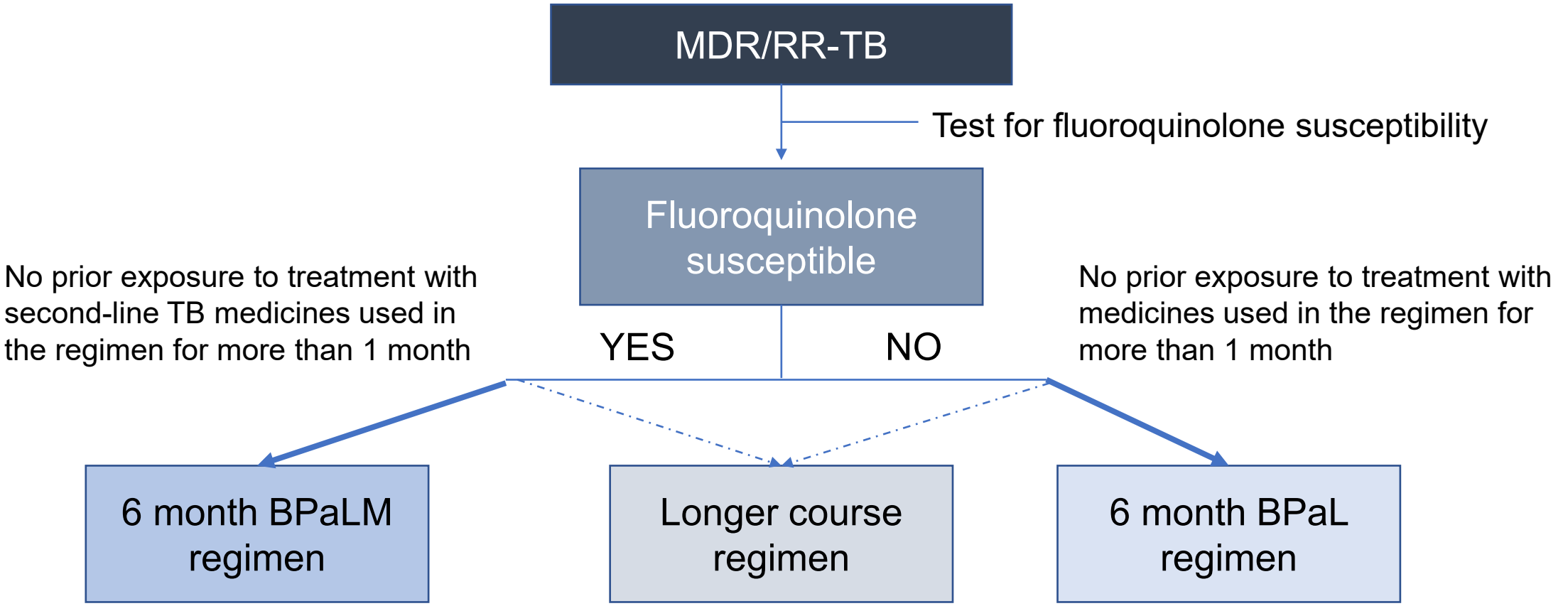
Treatment of MDR-TB: US Regimens



Saukkonen JJ, et al. A J Resp Crit Care Med 2025 in press
Daley CL. Pulmonary TB and its Prevention, 2022

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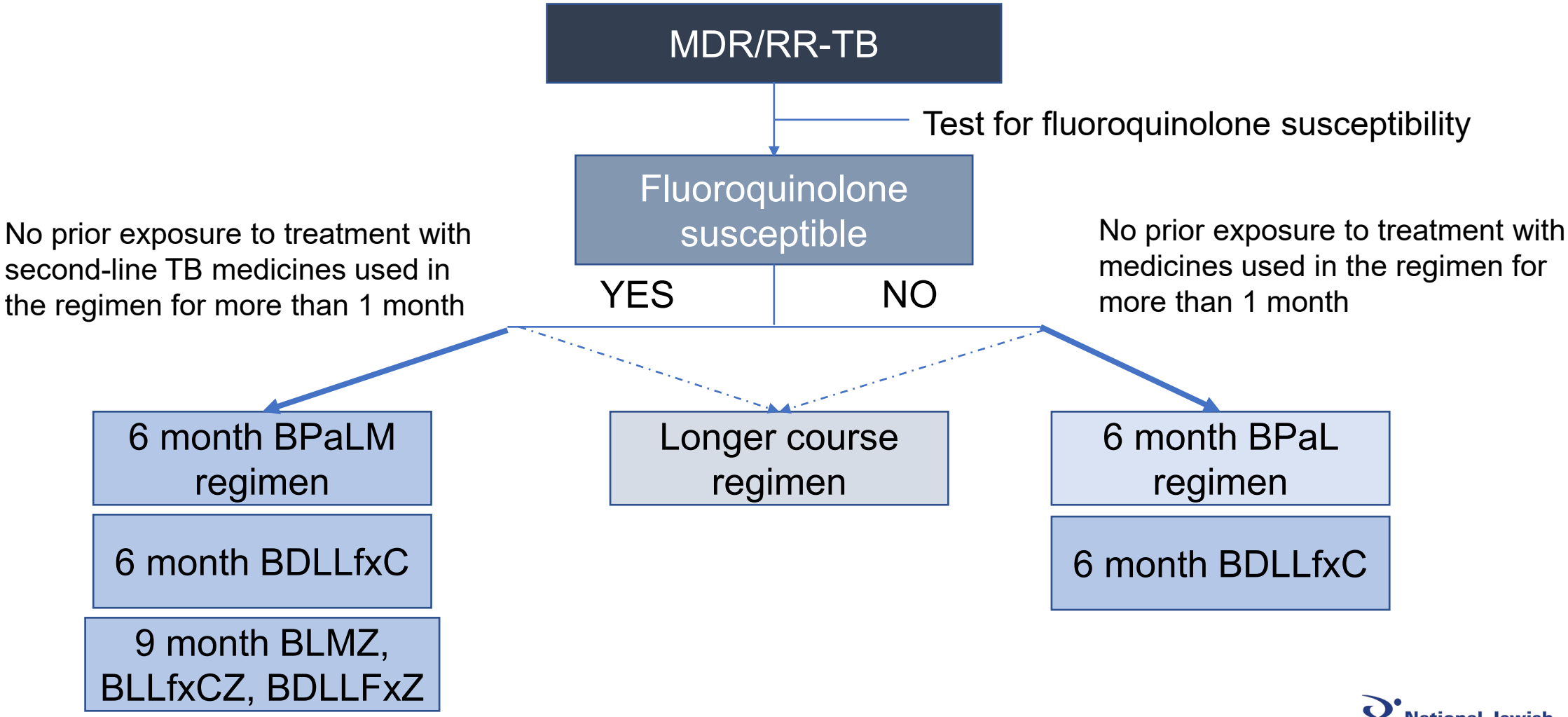
Treatment of MDR-TB: WHO Regimens



Adapted from Daley CL. Pulmonary TB and its Prevention, 2022 WHO. Module 4. 2020

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Emergence of Drug Resistance in Drugs Used for BPaL and BPaLM

Drug	Mutations	Frequency at Baseline	Frequency of Acquired	Cross-resistance
Bedaquiline	Rv0678, atpE gene, and pepQ	0.6%-2.4%	2.1%	Clofazimine (Rv0678, pepQ)
Pretomanid	ddn (Rv3547), fgd1 (Rv0407), fbi A (Rv3361), fbi B (Rv3261), fbi C (Rv1173)	0.7-2.1%	?	Delamanid
Linezolid	*rplC* or *rrl*	19.7% (most had received Lzd previously)	?	Other oxazolidinones
Moxifloxacin	DNA subunits A (*gyrA*) and B (*gyrB*), encode type II DNA topoisomerase	20%	-	Other fluoroquinolones

Perumal R, et al. Eur Resp J 2023;62:2300639
D. Vengurlekar D et al. IJTLD 27(7):567–569; 2023
Moe S, et al. IJTLD 27(5):381–386, 2023
Timm J, et al. PLoS Global Public Health 2023;3:e0002283
WHO Global TB report, 2022

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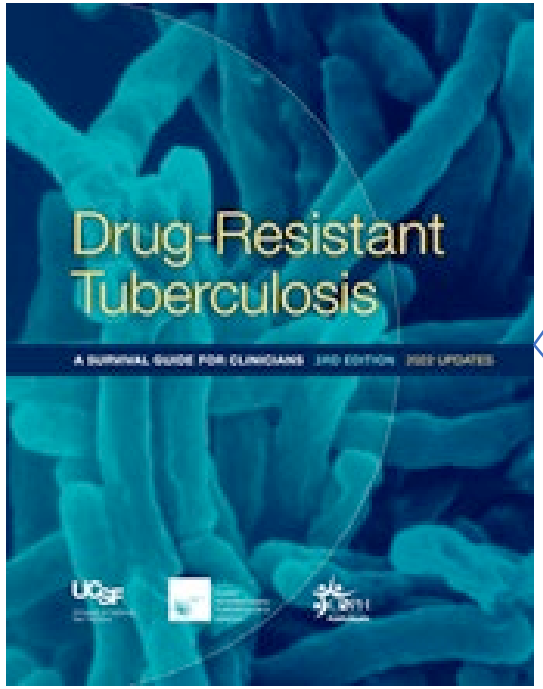
Drug Resistant Tuberculosis: A survival guide for clinicians



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Treatment

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