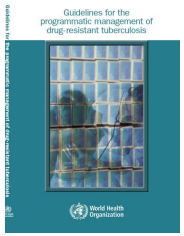
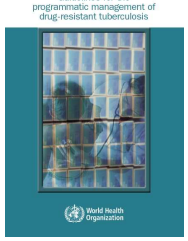
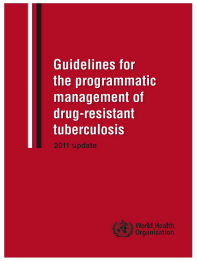
Management of MDR-TB



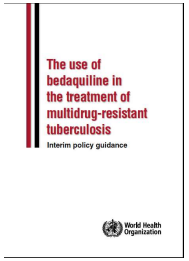
2006



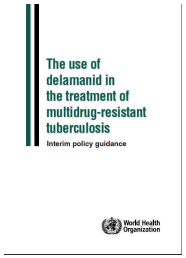
2008



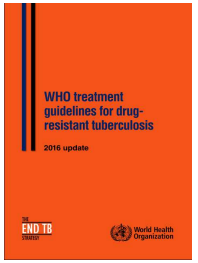
2011



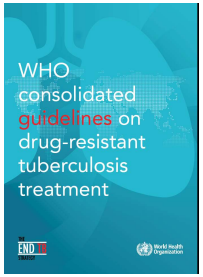
2013



2014

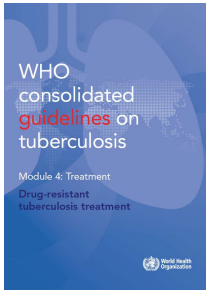


2016

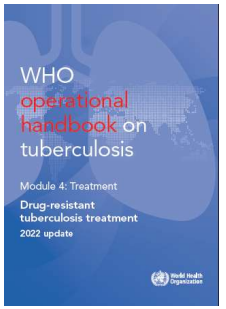


2019

2019



2020



2022

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Disclosures

Consultant: Genentech, Pfizer

Advisory Board Member: AN2, AstraZeneca, Hyfe, Insmed, Juvabis, MannKind, Matinas BioPharma Holdings, Inc., NobHill, Paratek Pharmaceuticals, Spero Therapeutics, Zambon

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

Contracted Research: AN2 Therapeutics, Bugworks, Cystic Fibrosis Foundation, Insmed, Juvabis, Paratek Pharmaceuticals

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Treatment 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
- Emerging resistance

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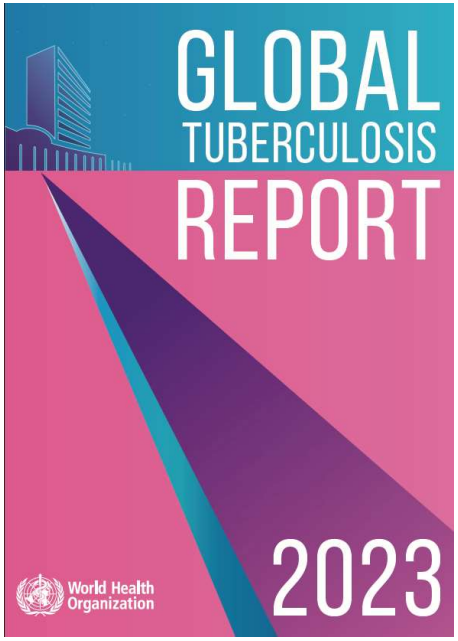
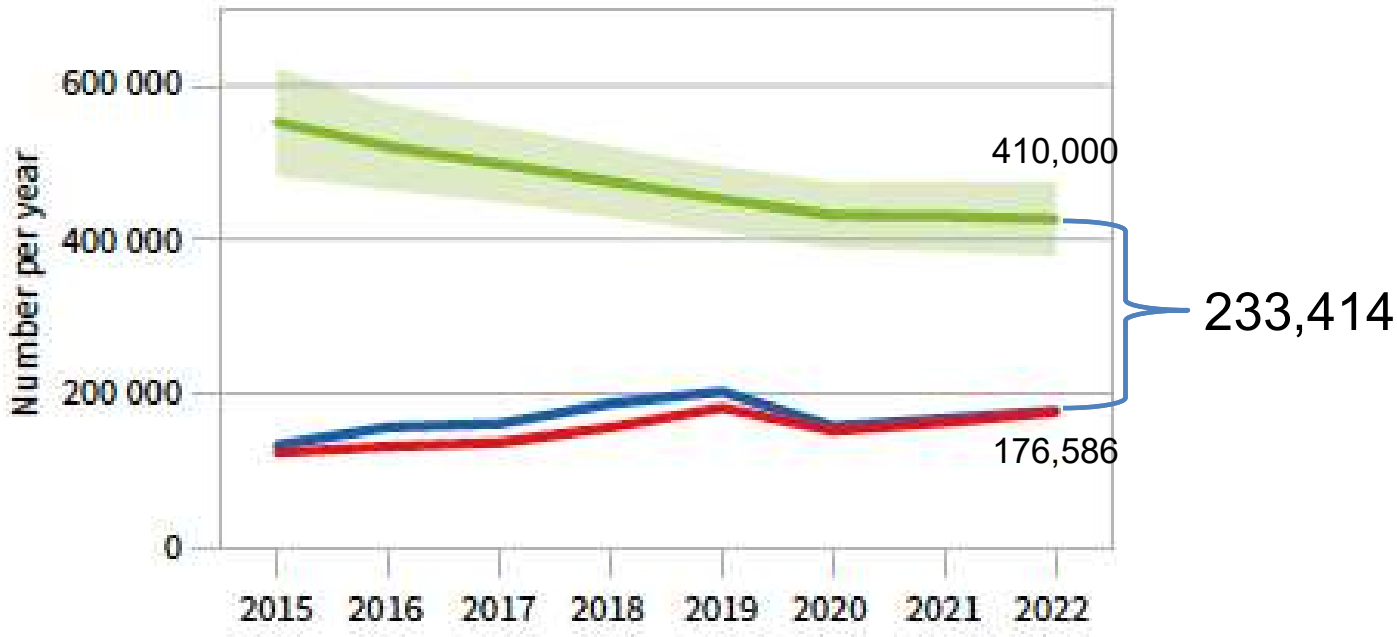
New Definitions for Pre-XDR and XDR-TB

	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

Number of Estimated and Notified MDR/RR-TB Globally, 2015-2022





Estimated MDR/RR-TB (green)
Number of MDR/RR-TB diagnosed (blue)
Number enrolled on treatment (red)

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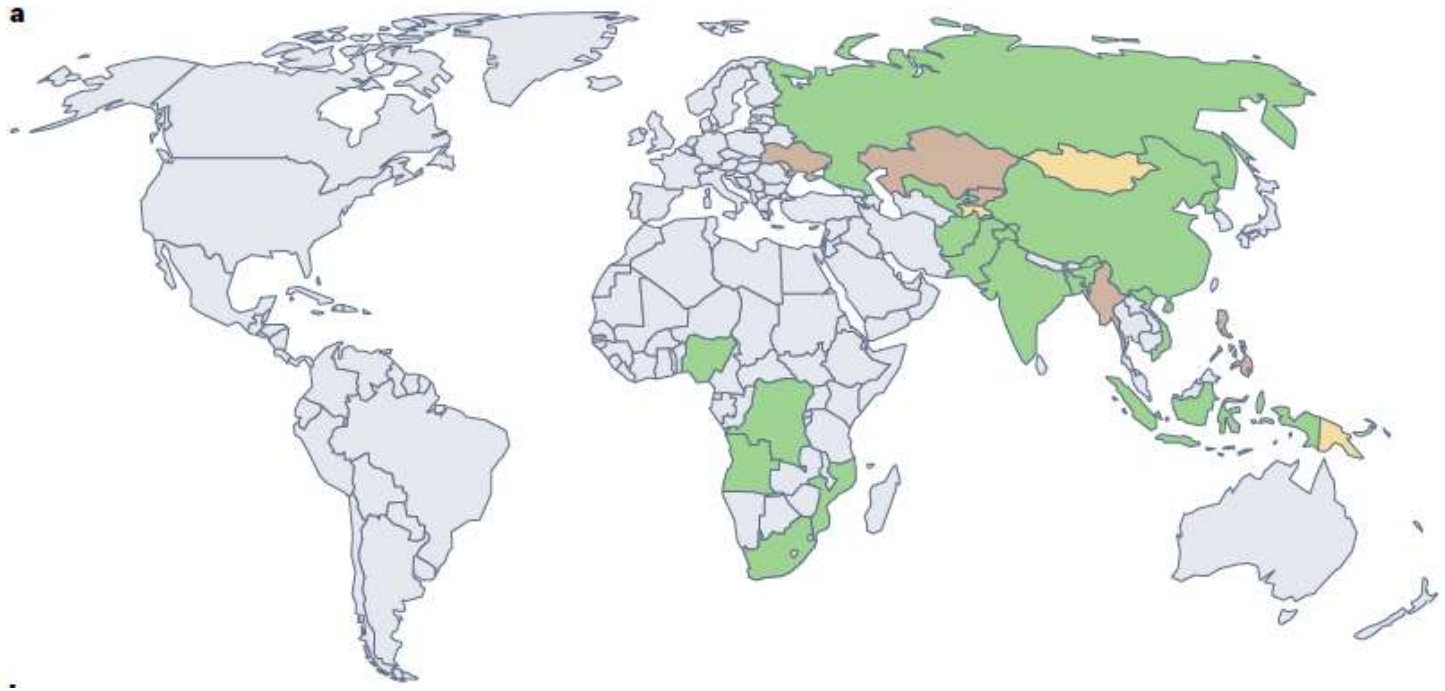
WHO Global TB Report, 2023

Global Epidemiology of MDR/RR-TB



Green – 20 with highest case burden **Yellow – 10 with high rate per 100,000**

Brown – fall into both categories

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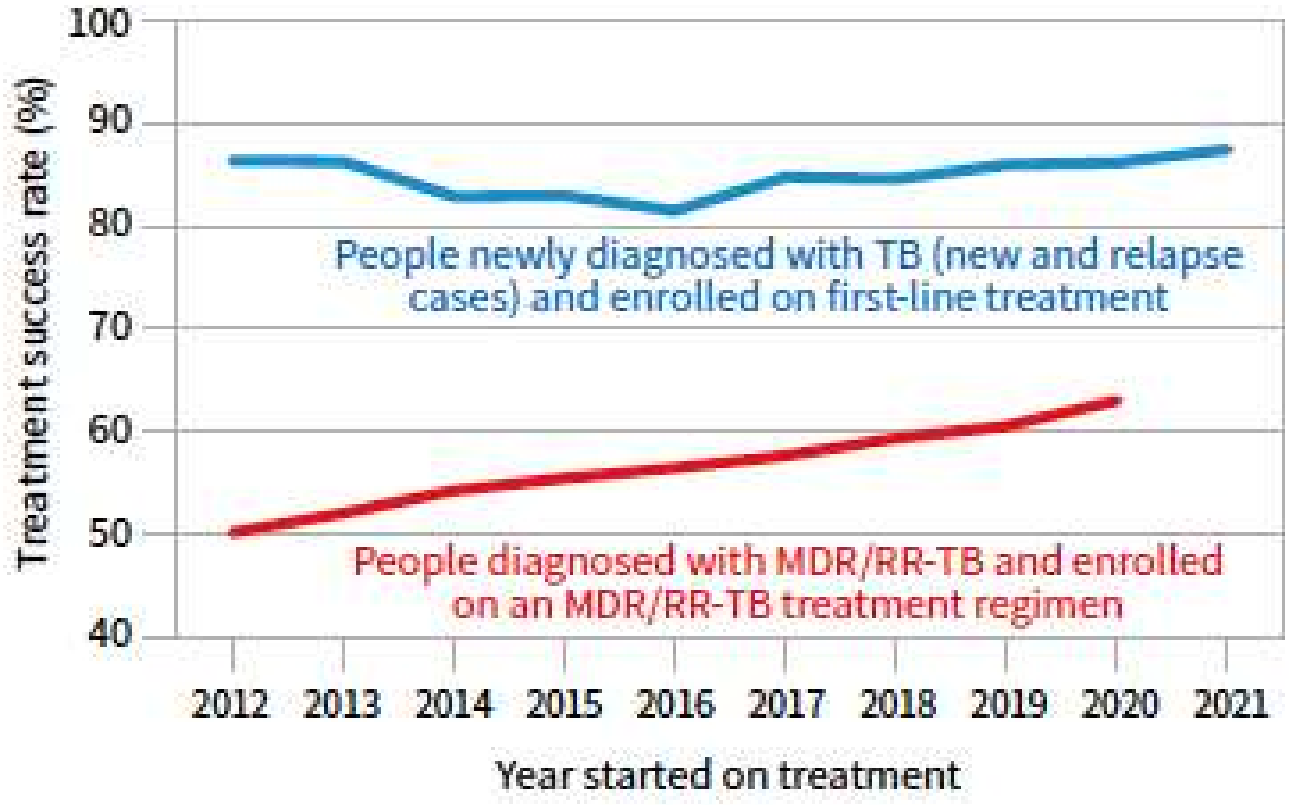
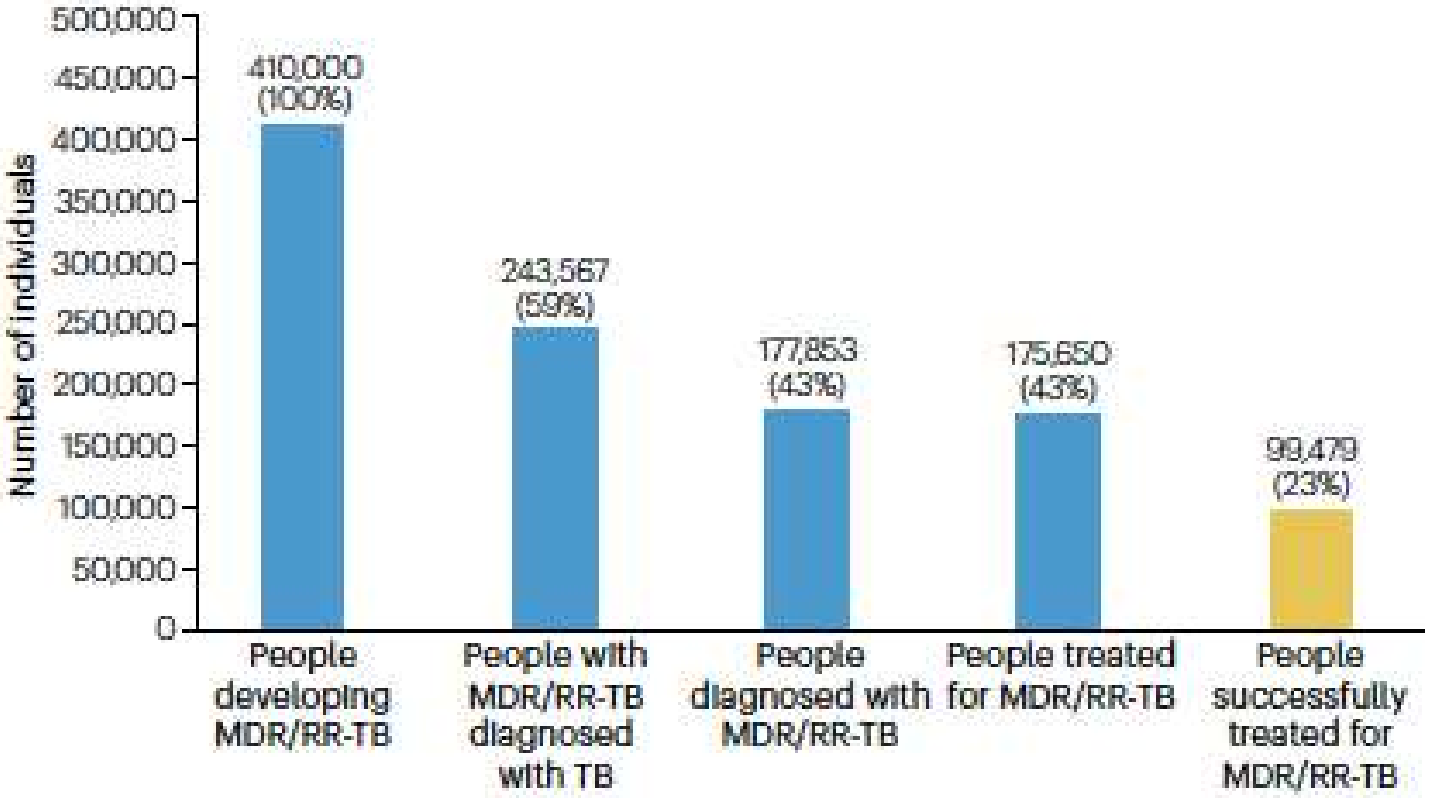
Farhat M, et al. Nat Rev Micro 2024;March 22

Global Success Rates for People Treated For TB, Including MDR-TB, 2012-2021



WHO Global TB Report, 2023

Cascade of Care for MDR/RR-TB



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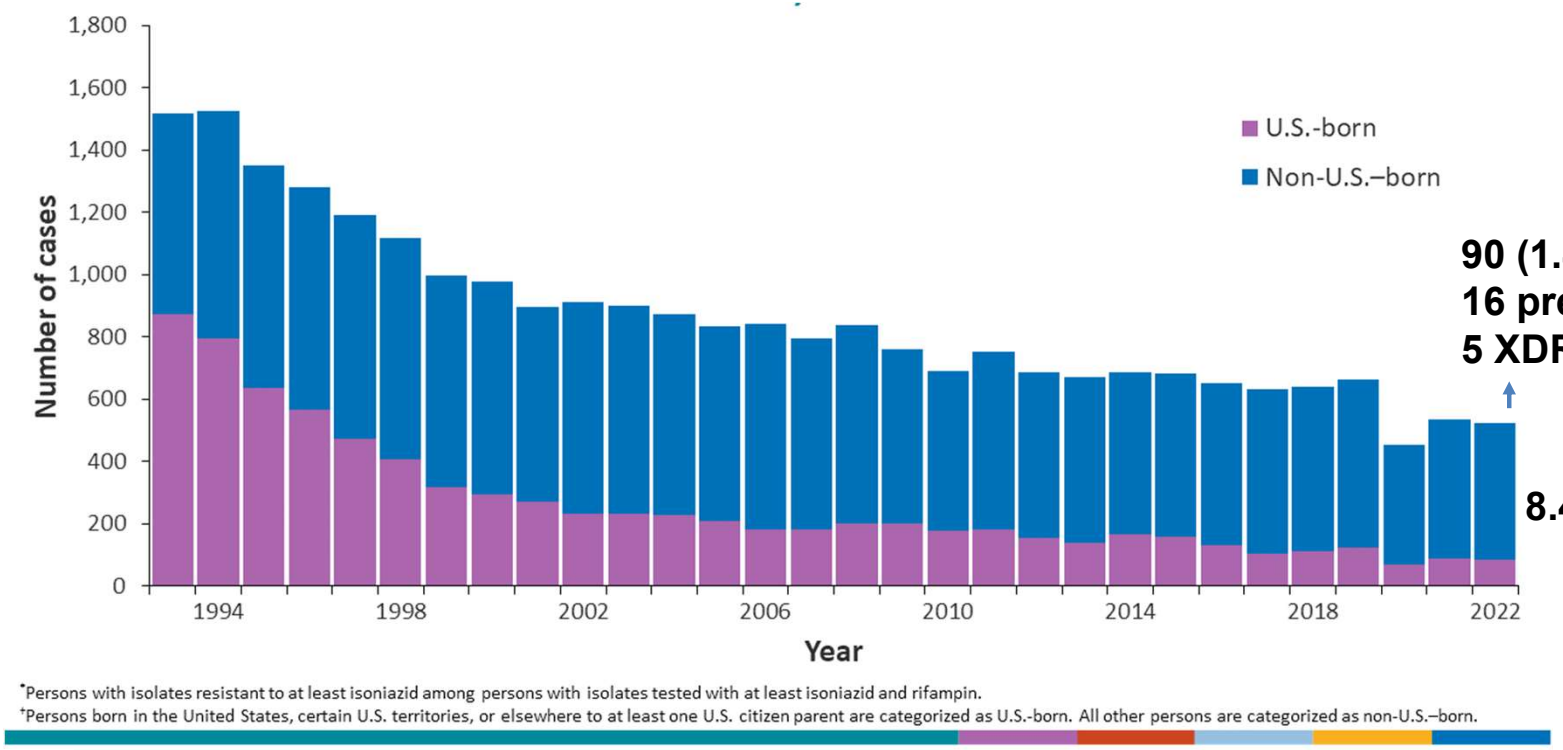
Farhat M, et al. Nat Rev Micro 2024;March 22

Isoniazid Resistant TB in the United States, 1993-2022



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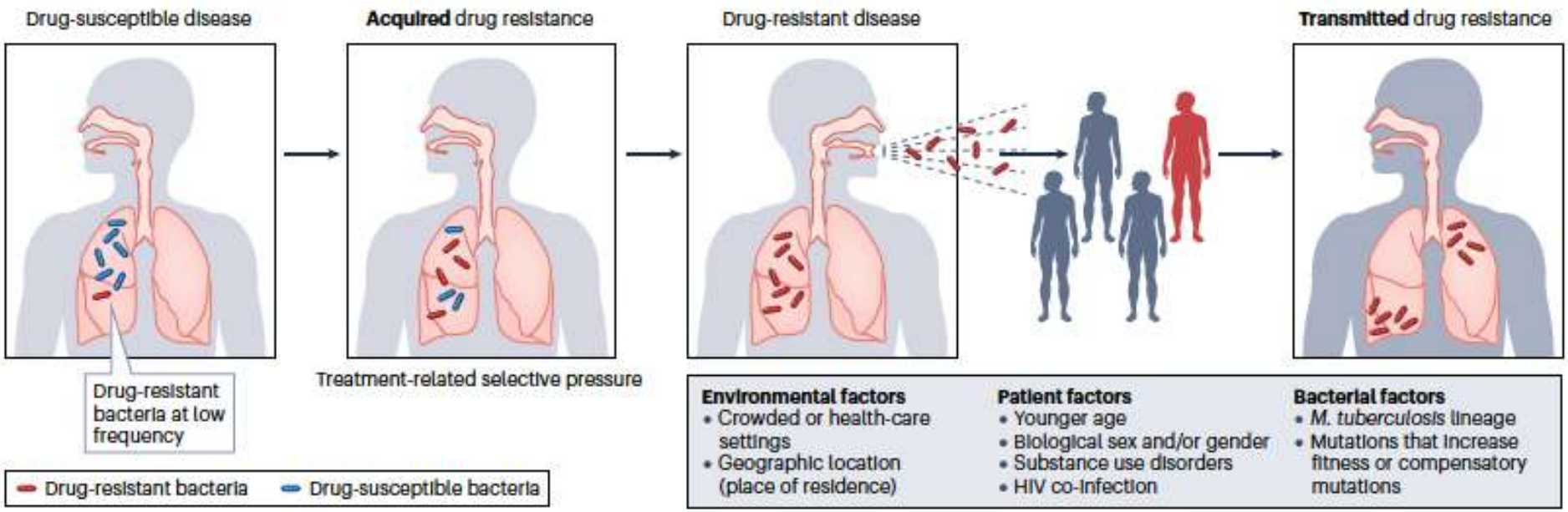
https://www.cdc.gov/tb/statistics/reports/2022/drug_resistant.htm

Acquisition and Transmission of Drug-resistant Tuberculosis



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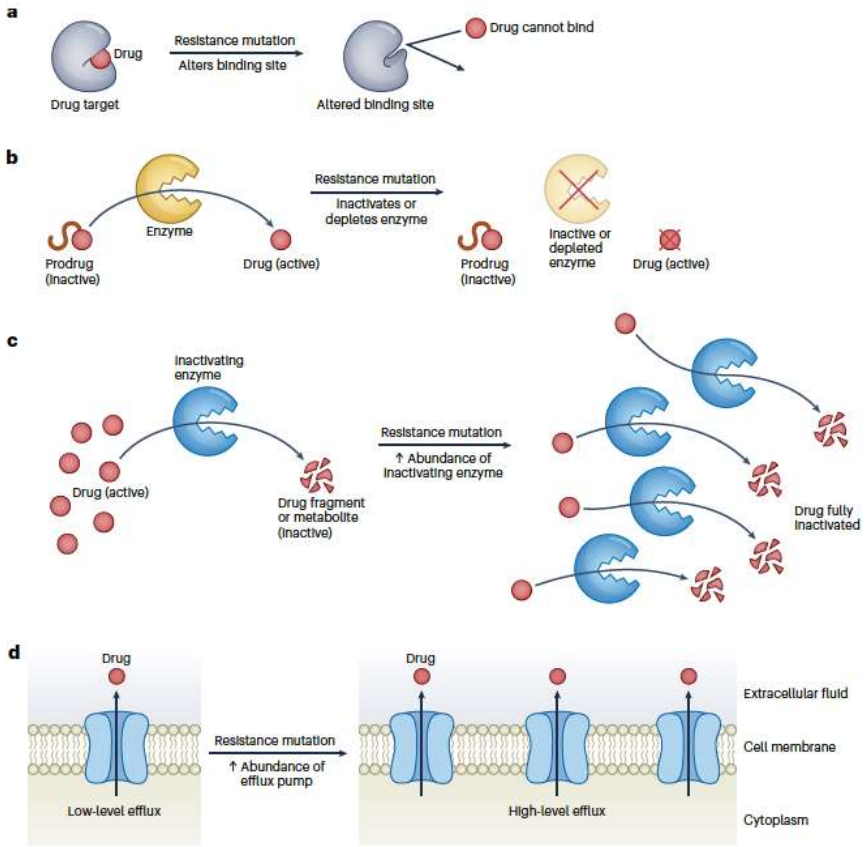
Farhat M, et al. Nat Rev Micro 2024;March 22

Common Mechanisms of Drug Resistance



rifampicin, PZA, linezolid, ethambutol

INH, PZA, ethionamide

amikacin, kanamycin

bedaquiline, clofazimine

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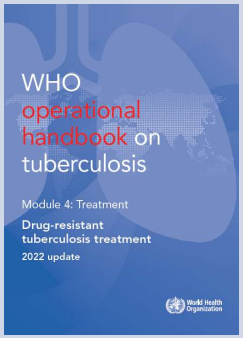
Farhat M, et al. Nat Rev Micro 2024;March 22

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

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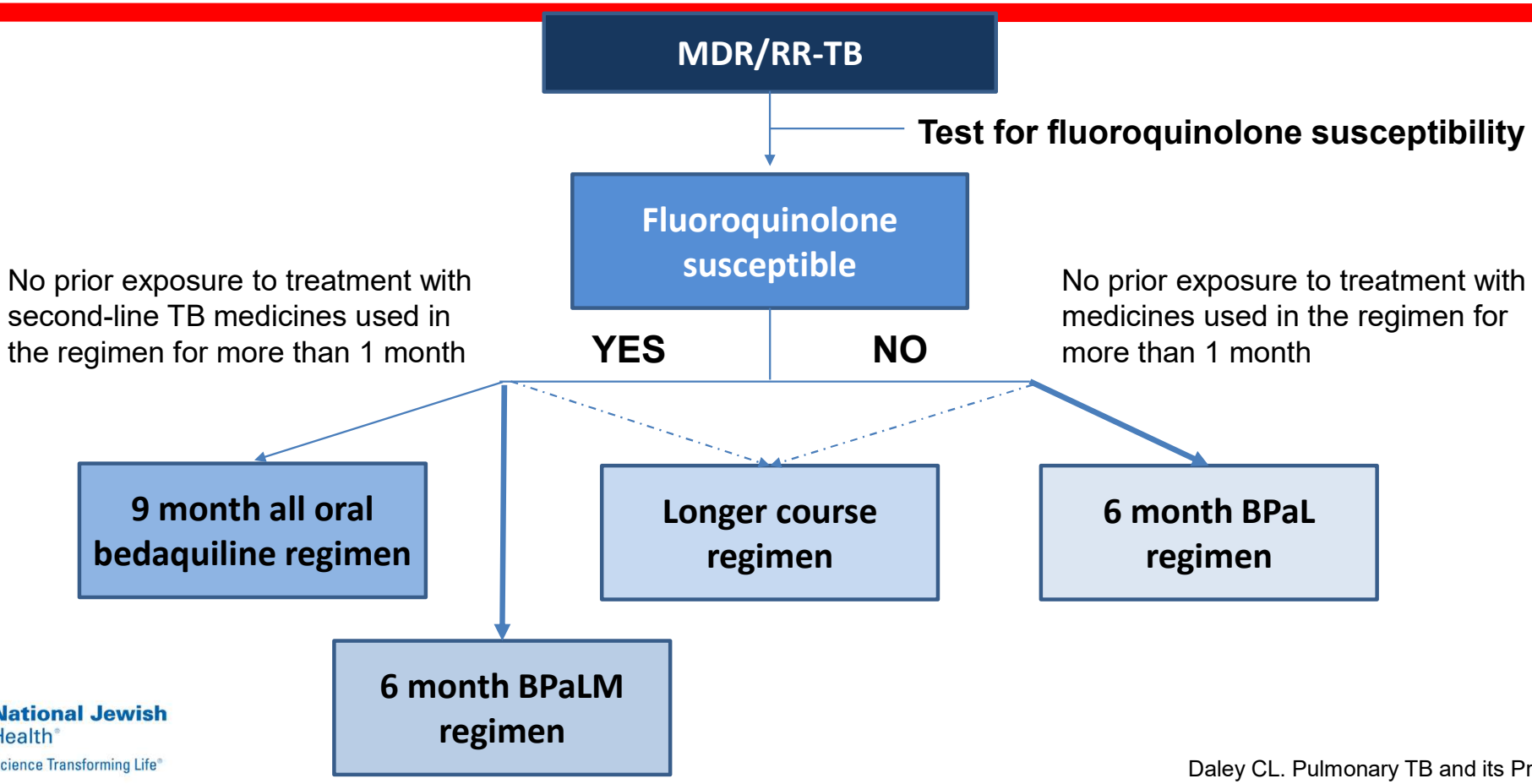
Treatment Algorithm for MDR/XDR-TB



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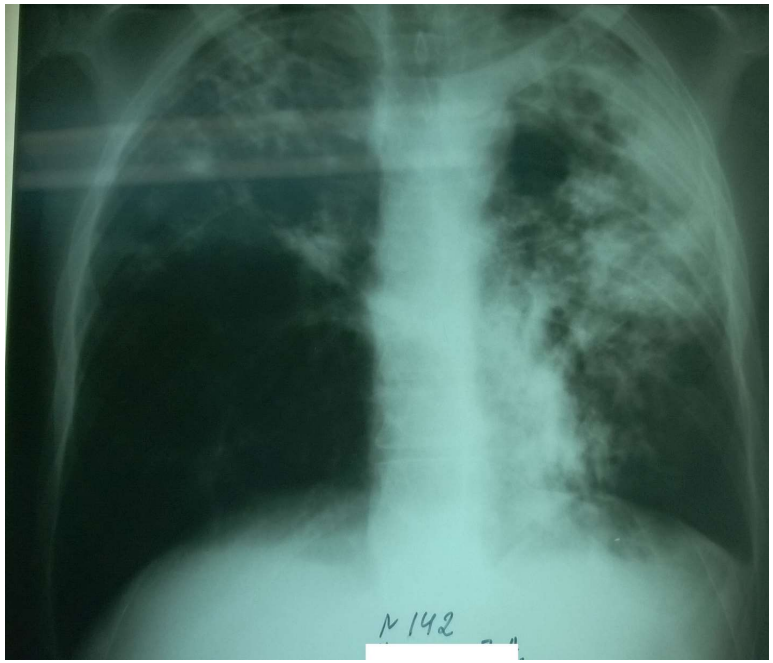
Daley CL. Pulmonary TB and its Prevention, 2022

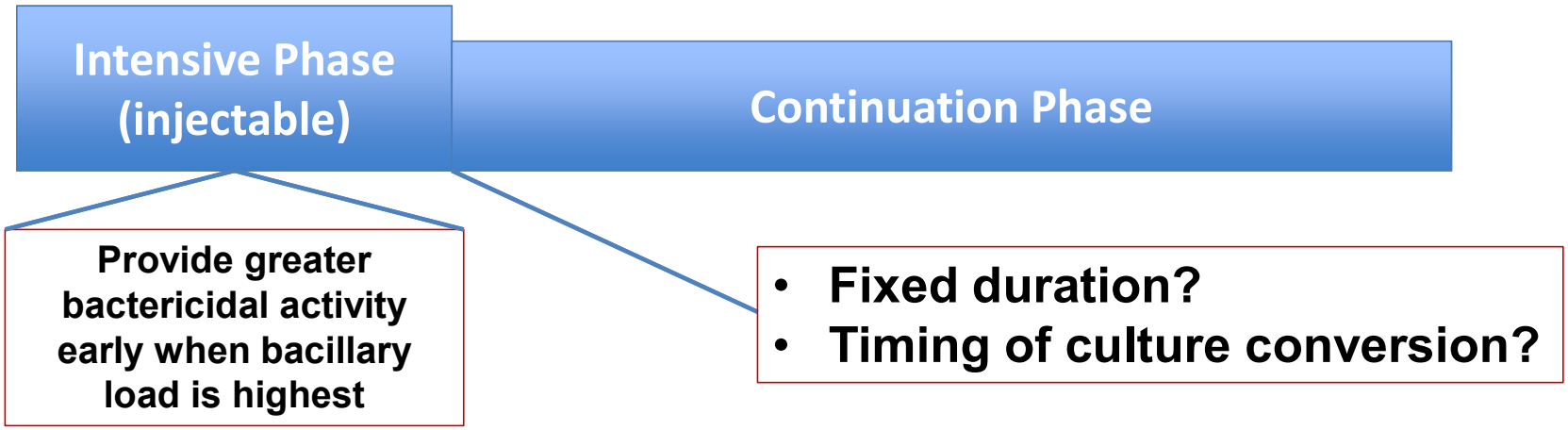
Clinical Case

- 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



Longer MDR-TB Treatment Regimen

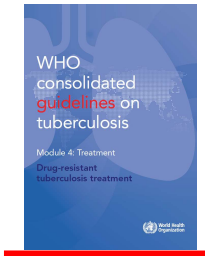
Intensive and Continuation Phases



	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

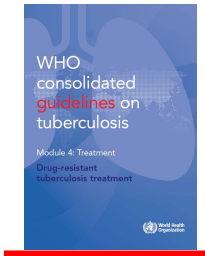


Grouping of Drugs

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



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

58 studies (9178 patients) from 35 countries

Treatment Failure/relapse vs Treatment Success		Absolute Risk of Serious AE	
Drug	Adj. OR (95% CI)	Drug	Median (%) (95% CI)
Levofloxacin or moxifloxacin	0.3 (0.1, 0.5)	Bedaquiline	2.4 (0.7, 7.6)
Bedaquiline	0.3 (0.2, 0.4)	Moxifloxacin	2.9 (1.4, 5.6)
Linezolid	0.3 (0.2, 0.5)	Clofazimine	3.6 (1.3, 8.6)
Clofazimine	0.3 (0.2, 0.5)	Levofloxacin	4.1 (1.9, 8.8)
Cycloserine or terizidone	0.6 (0.4, 0.9)	Linezolid	17.2 (10.1, 27.0)

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WHO Consolidated Guidelines on Tuberculosis, 2020

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	Y	S
P-aminosalicylic acid	N	S

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

New 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

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, Cfz-clofazimine, Emb-ethambutol, INH-isoniazid, Km-kanamycin, Lfx-levofloxacin, Mfx-moxifloxacin, Pa-prothionamide, PZA-pyrazinamide

*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

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

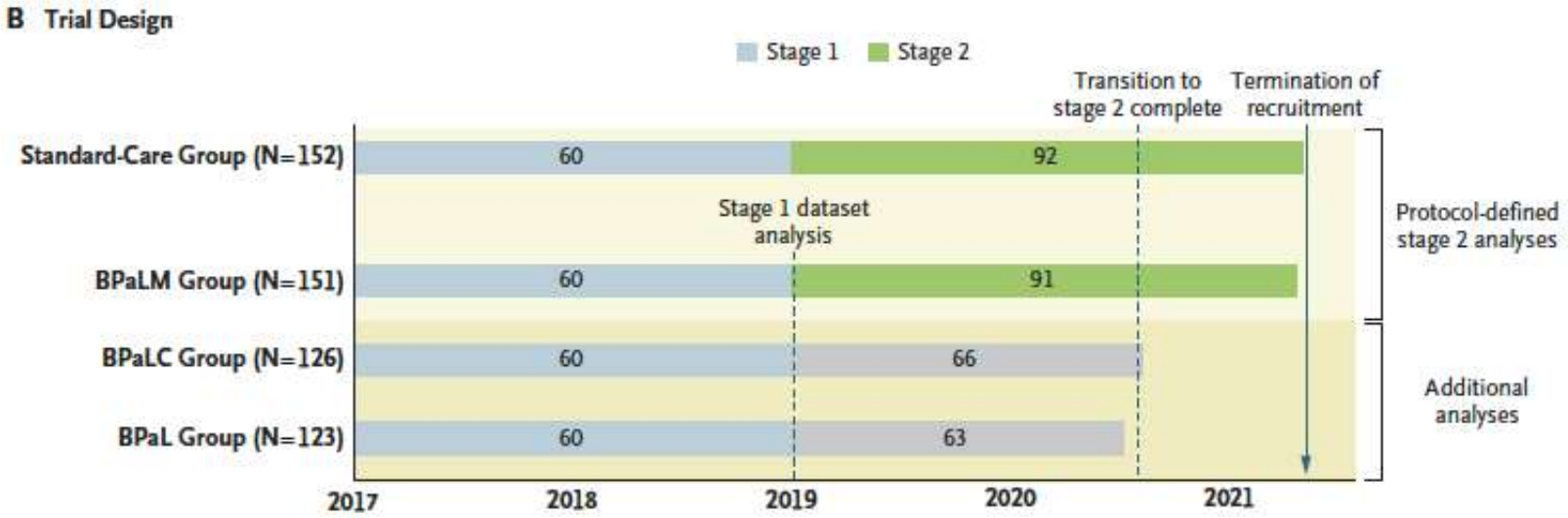
Study	Design	Control Regimen	Study Regimens	Duration (wks)	Treatment Success	Neuropathy
Nix*	Open label	–	Bdq, Pa, Lzd (1200 mg/d)	26	90%	81%
ZeNix	Randomized, open label	Nix regimen	Bdq, Pa, Lzd (1200 mg/d)	26	93%	38%
			Bdq, Pa, Lzd (1200 mg/d)	9	89%	24%
			Bdq, Pa, Lzd (600 mg/d)	26	91%	24%
			Bdq,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

Bdq-bedaquiline, Cfz-clofazimine, Emb-ethambutol, INH-isoniazid, Km-kanamycin, Lfx-levofloxacin, Mfx-moxifloxacin, Pa-prothionamide, PZA-pyrazinamide

*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

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



Culture conversion at 8 wks

77%

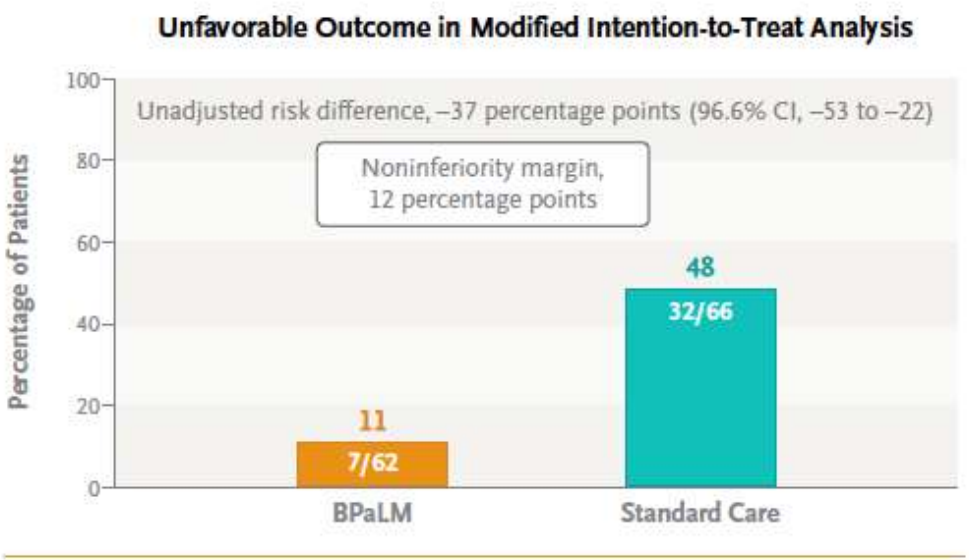
67%

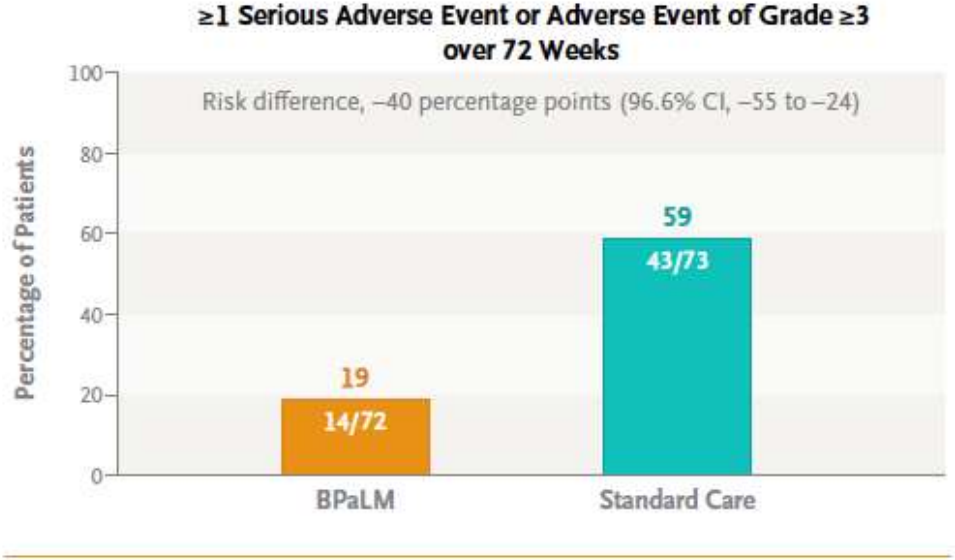
46%

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

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**

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

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

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

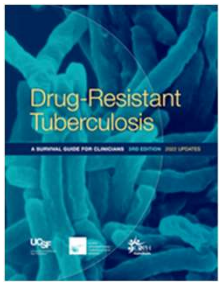
Clinical Case

- 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 notice tingling and numbness in his feet
- What would you do now?

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



Updated CDC Guidelines – November 2023

- CDC recommends use of the BPaL regimen in adults with pulmonary TB that is
  - resistant to isoniazid, rifampin, and at least one fluoroquinolone (e.g., levofloxacin or moxifloxacin) or injectable (i.e., amikacin, kanamycin, capreomycin), or
  - pulmonary TB that is resistant to isoniazid and rifampin among patients who are treatment intolerant or nonresponsive.
- CDC recommends the starting linezolid dose be 600 mg/day

https://www.cdc.gov/tb/topic/drtb/bpal/default.htm

Use of BPaL/BPaLM in the United States

Treatment Outcomes	BPaL (n=116)	BPaLM (n=36)
Completed treatment	84 (72%)	29 (81%)
Lost to follow-up	2 (2%)	0
Continuing treatment	2 (2%)	5 (14%)
Missing completion date	27 (23%)	0
Died from any cause	2 (2%)	2 (6%)
Died from TB	1 (1%)	1 (3%)
TB “relapsed”	3 (3%)	0

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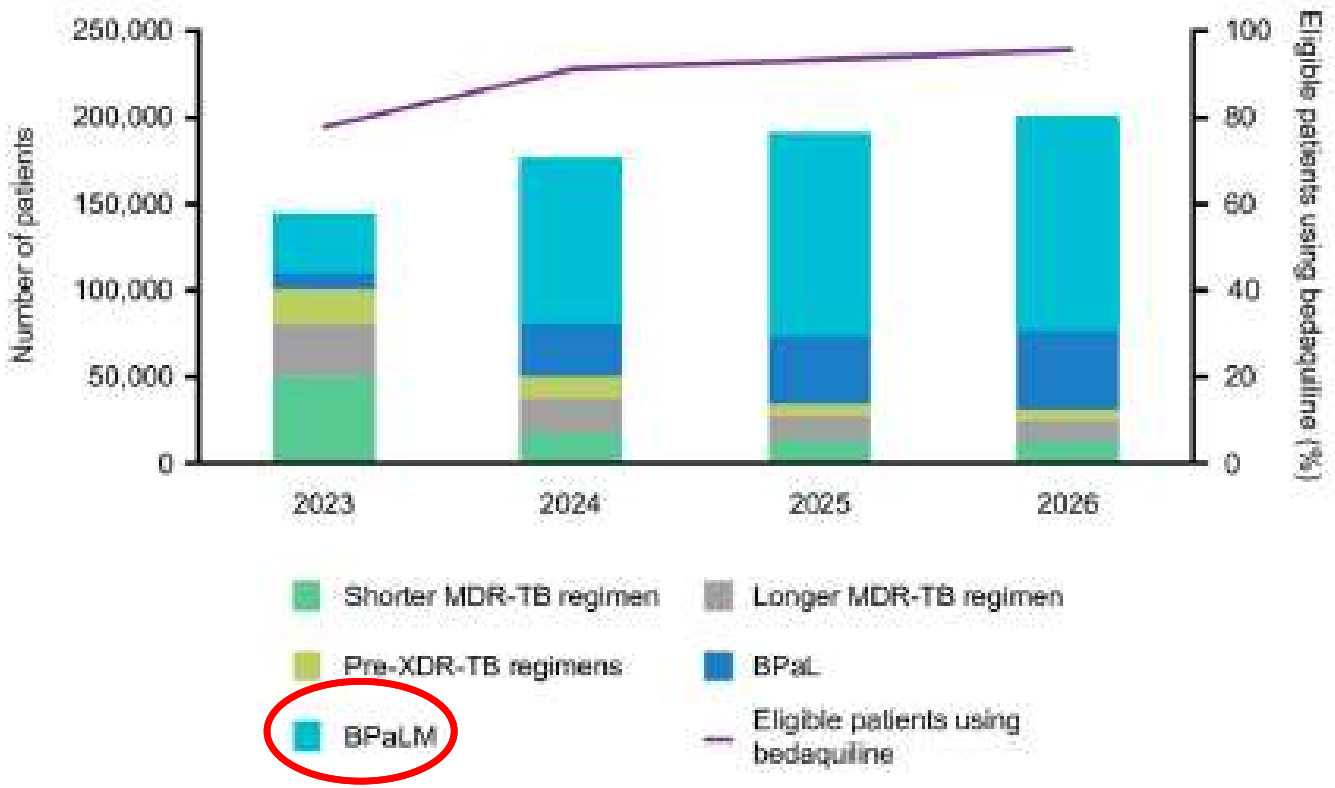
Labuda SM, et al. Lancet Resp Med 2023;387:9: 850-852

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
Delamanid	Low solubility when given with other drugs	None	Higher once-daily dosing is sometimes used after the first 8 wks

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

Projected Use of MDR-TB Treatment Regimens between 2023 and 2026



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Gupta A, et al. PLOS ONE, 2024

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

2024 Global New TB Drug Pipeline[1]

Lead Optimization

- Indazole sulfonamides
- Diarylthiazoles
- DprE1 Inhibitors
- Direct InhA Inhibitors
- Mtb energy metabolism
- Gyrase Inhibitors
- Arylsulfonamides
- Inhibitors of MmpL3, Translocase-1, ClpC1, ClpP1P2, PKS13, F-ATP synthase, RNAP
- Oxazolidinones
- DnaE1 / Nargenicin analogs

Early Stage Development

- FIM-253
- TBD10 (MK-3854)
- CLB-073*
- SPR720*
- MPL-447*
- JSF-3285*
- CPZEN-45*
- NTB-3119*
- MBX-4888A (1810)*
- FNDR-20364*

GMP / GLP Tox.

- GSK-839*
- OTB-658

Phase 1

- TBD09 (MK-7762)
- GSK-286*
- TBAJ-587
- TBI-223
- Macozinone* (PBTZ-169)

Phase 2

- Telacebec* (Q203)
- Alpibectir (BVL-GSK098)*
- TBAJ-876
- Sanfetrinem
- Delpazolid, Sutezolid, Tedizolid
- BTZ-043*
- TBA-7371*
- Quabodepistat (OPC-167832*)
- Ganfeborole (GSK-656*/070)
- Pyrifazimine (TBI-166)
- SQ-109*

Phase 3

- Sudapyridine (WX-081)

Regulatory Market Approvals

- Bedaquiline*
- Delamanid*
- Pretomanid*

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

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

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

Underline = updates since November 2022

WORKING GROUP ON NEW TB DRUGS

www.newtbdrugs.org

Updated: March 2024

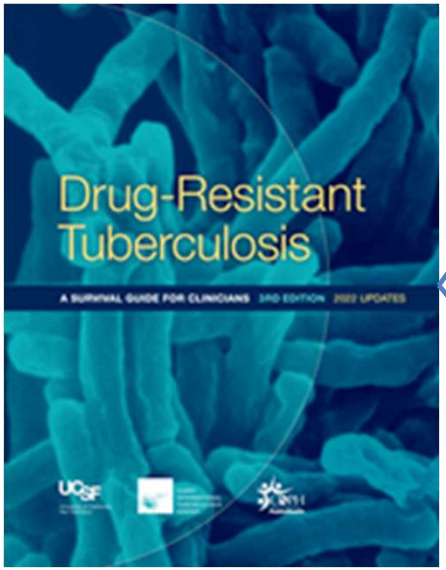
Summary of MDR Regimens

Population	Regimen	Endorsed by:
Fluoroquinolone susceptible		
Nonpregnant, > 14 yrs with pulmonary or non-severe extrapulmonary dz	Preferred: BPaLM Alternative: BPaL, 9 month all oral regimen, or longer regimen	WHO, ATS/IDSA?
Children or pregnant persons with non-advanced pulmonary or non-severe extrapulmonary dz	6-9Bdq-(Lfx/Mfx)-Cfz-Cs(Dlm)	
Flouroquinolone resistant		
Nonpregnant, > 14 yrs with pulmonary or non-severe extrapulmonary dz	Preferred: BPaL Alternative: Longer regimen	WHO, ATS/IDSA
Children or pregnant persons with non-advanced pulmonary or non-severe extrapulmonary dz	6-9Bdq-Cfz-Lzd-Dlm	
Advanced pulmonary dz and ineligible for BPaL/BPaLM or with CNS, bone/joint, or miliary dz or with prior treatment with 2nd-line drugs	Longer regimen	WHO, ATS/IDSA

Bdq-bedaquiline, Cfz-clofazimine, Dlm-delamanid, Lfx-levofloxacin, Mfx-moxifloxacin, P - pretomanid

Farhat M, et al. Nat Rev Micro 2024;March 22

Drug Resistant Tuberculosis: A survival guide for clinicians



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Treatment

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