Update on Draft American Thoracic Society /
Centers for Disease Control / European Respiratory Society / Infectious Diseases Society of America
Clinical Practice Guidelines:

Treatment of Drug-Resistant Tuberculosis

On behalf of the writing committee

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Dr. Seaworth has:

No conflicts of interest to declare.

She will discuss the follow medications approved by the FDA for TB:

Isoniazid (INH), rifampin (RIF), Rifapentine, Pyrazinamide (PZA), Ethambutol (EMB), Streptomycin, Cycloserine, Ethionamide, Para-aminosalicyclate (PAS), Bedaquiline.

All other drugs discussed are NOT FDA approved for TB:

Fluoroquinolones, linezolid, delamanid, amikacin, clofazimine, meropenem, amox/clavulanate

Objectives

- Identify treatment regimens and individual drugs leading to the best patient outcomes for treatment of MDR and XDR TB
- Discuss the evidence base behind the ATS, CDC, ERS, IDSA recommendations
- Discuss the importance of patient centered care for MDR TB including toxicity monitoring patient education and choice.

AMERICAN THORACIC SOCIETY DOCUMENTS

Treatment of Drug-Resistant Tuberculosis

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

Payam Nahid, Sundari R. Mase, Giovanni Battista Migliori, Giovanni Sotgiu, Graham H. Bothamley, Jan L. Brozek, Adithya Cattamanchi, J. Peter Cegielski, Lisa Chen, Charles L. Daley, Tracy L. Dalton, Raquel Duarte, Federica Fregonese, C. Robert Horsburgh, Jr., Faiz Ahmad Khan, Fayez Kheir, Zhiyi Lan, Alfred Lardizabal, Michael Lauzardo, Joan M. Mangan, Suzanne M. Marks, Lindsay McKenna, Dick Menzies, Carole D. Mitnick, Diana M. Nilsen, Farah Parvez, Charles A. Peloquin, Ann Raftery, H. Simon Schaaf, Neha S. Shah, Jeffrey R. Starke, John W. Wilson, Jonathan M. Wortham, Terence Chorba, and Barbara Seaworth; 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, THE EUROPEAN RESPIRATORY SOCIETY, AND THE INFECTIOUS DISEASES SOCIETY OF AMERICA SEPTEMBER 2019, AND WAS CLEARED BY THE U.S. CENTERS FOR DISEASE CONTROL AND PREVENTION SEPTEMBER 2019

Background: The American Thoracic Society, U.S. Centers for Disease Control and Prevention, European Respiratory Society, and Infectious Diseases Society of America jointly sponsored this new practice guideline on the treatment of drug-resistant tuberculosis (DR-TB). The document includes recommendations on the treatment of multidrug-resistant TB (MDR-TB) as well as isoniazid-resistant but rifampin-susceptible TB.

was judged to be very low, because the data came from observational studies with significant loss to follow-up and imbalance in background regimens between comparator groups. Good practices in the management of MDR-TB are described. On the basis of the evidence review, a clinical strategy tool for building a treatment regimen for MDR-TB is also provided.

Grateful Thanks to:

- Dr. Payam Nahid
- Dr. “Tommy” Lan
- Dr. Dick Menzies

…”Guidelines are intended to help providers identify the therapeutic options associated with improved outcomes and in the context of individual patient values and preferences”

…”Guidelines are intended for settings in which treatment is individualized and where mycobacterial cultures, molecular and culture-based and radiographic facilities are available”

Treatment of Drug-Resistant Tuberculosis
Guideline Leadership and GRADE Methodology Group

- **Chairs:** Payam Nahid (ATS), Barbara Seaworth (IDSA) GB Migliori and Giovanni Sotgui (ERS), Sundari Mase and Terry Chorba (CDC)
- **GRADE Methodology Group:** R. Menzies, MD, F. Fregonese, MD, Z. Lan, MD, and F. A. Khan, MD, McGill University, Quebec, Canada; P. Nahid, MD, MPH, University of California, San Francisco, CA, USA; G. Sotgiu, MD, University of Sassari, Sassari, Italy; J. Brozek, MD, PhD, McMaster University, Ontario, Canada.

*All authors have submitted ICMJE Form for Disclosure of Potential Conflicts of Interest to American Thoracic Society. Conflicts will be disclosed in print.

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Treatment of Drug-Resistant Tuberculosis

- The guideline is intended as a companion to the 2016 ATS/CDC/IDSA Treatment of Drug-Susceptible Tuberculosis Practice Guidelines.
- 21 PICO questions relevant to the care for DR-TB patients were addressed. Of these 19 address MDR/XDT-TB and 2 address INH-R TB
- Strength of recommendations were based on Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach.
- Evidence profiles to address PICOs were based on two individual-patient level meta-analyses, published in Lancet and Lancet Respiratory Disease

Evidence-base supporting the guidelines:

The Collaborative Group for Meta-Analysis of Individual Patient Data in MDR-TB treatment

Articles

Treatment correlates of successful outcomes in pulmonary multidrug-resistant tuberculosis: an individual patient data meta-analysis

The Collaborative Group for the Meta-Analysis of Individual Patient Data in MDR-TB treatment–2017; Nafees Ahmad, Shama D Ahuja, Onno W Akkerman, Jan-Willem C Alffenaar, Laura F Anderson, Parvaneh Baghaei, Didi Bang, Pennan M Barry, Mayara L Bastos, Digamber Behera, Andrea Benedetti, Gregory P Bisson, Martin J Boeree, Maryline Bonnet, Sarah K Brode, James C M Brust, Ying Cai, Eric Caumes, J Peter Cegielski, Rosella Centis, Pei-Chun Chan, Edward D Chan, Kwok-Chiu Chang, Macarthur Charles, Andra Cirule, Margareth Pretti Dalcolmo, Lia D'Ambrosio, Gerard de Vries, Keertan Dheda, Aliasgar Esmail, Jennifer Flood, Gregory J Fox, Mathilde Fréchet-Jachym, Geisa Fregona, Regina Gayoso, Medea Gegia, Maria Tarcela Gler, Sue Gu, Lorenzo Guglielmetti, Timothy H Holtz, Jennifer Hughes, Petros Isaakidis, Leah Jarlsberg, Russell R Kempker, Salmaan Keshavjee, Faiz Ahmad Khan, Maia Kipiani, Serena P Koenig, Won-Jung Koh, Afranio Kritski, Liga Kuksa, Charlotte L Kvasnovsky, Nakwon Kwak, Zhiyi Lan, Christoph Lange, Rafael Laniado-Laborín, Myungsun Lee, Vaira Leimane, Chi-Chiu Leung, Eric Chung-Ching Leung, Pei Zhi Li, Phil Lowenthal, Ethel L Maciel, Suzanne M Marks, Sundari Mase, Lawrence Mbuagbaw, Giovanni B Migliori, Vladimir Milanov, Ann C Miller, Carole D Mitnick, Chawangwa Modongo, Erika Mohr, Ignacio Monedero, Payam Nahid, Norbert Ndjeka, Max R O'Donnell, Nesri Padayatchi, Domingo Palmero, Jean William Pape, Laura J Podewils, Ian Reynolds, Vija Riekstina, Jérôme Robert, Maria Rodriguez, Barbara Seaworth, Kwonjune J Seung, Kathryn Schnippel, Tae Sun Shim, Rupak Singla, Sarah E Smith, Giovanni Sotgiu, Ganzaya Sukhbaatar, Payam Tabarsi, Simon Tiberi, Anete Trajman, Lisa Trieu, Zarir F Udwadia, Tjip S van der Werf, Nicolas Veziris, Piret Viiklepp, Stalz Charles Vilbrun, Kathleen Walsh, Janice Westenhouse, Wing-Wai Yew, Jae-Joon Yim, Nicola M Zetola, Matteo Zignol, Dick Menzies

N. Ahmad, et al., Lancet, 2018

Articles

Comparison of different treatments for isoniazid-resistant tuberculosis: an individual patient data meta-analysis

Federica Fregonese, Shama D Ahuja, Onno W Akkerman, Denise Arakaki-Sanchez, Irene Ayakaka, Parvaneh Baghaei, Didi Bang, Mayara Bastos, Andrea Benedetti, Maryline Bonnet, Adithya Cattamanchi, Peter Cegielski, Jung-Yien Chien, Helen Cox, Martin Dedicoat, Connie Erkens, Patricio Escalante, Dennis Falzon, Anthony J Garcia-Prats, Medea Gegia, Stephen H Gillespie, Judith R Glynn, Stefan Goldberg, David Griffith, Karen R Jacobson, James C Johnston, Edward C Jones-López, Awal Khan, Won-Jung Koh, Afranio Kritski, Zhi Yi Lan, Jae Ho Lee, Pei Zhi Li, Ethel L Maciel, Rafael Mello Galliez, Corinne S C Merle, Melinda Munang, Gopalan Narendran, Viet Nhung Nguyen, Andrew Nunn, Akihiro Ohkado, Jong Sun Park, Patrick P J Phillips, Chinnaiyan Ponnuraja, Randall Reves, Kamila Romanowski, Kwonjune Seung, H Simon Schaaf, Alena Skrahina, Dick van Soolingen, Payam Tabarsi, Anete Trajman, Lisa Trieu, Velayutham V Banurekha, Piret Viiklepp, Jann-Yuan Wang, Takashi Yoshiyama, Dick Menzies

F. Fregonese, et al., Lancet Resp, 2018

The Collaborative Group for Meta-Analysis of Individual Patient Data in MDR-TB treatment

(members in alphabetic order)

Nafees Ahmad, Shama D. Ahuja, Onno W. Akkerman, Jan W. C. Alffenaar, Laura F. Anderson, Parvaneh Baghaei, Didi Bang, Pennan M. Barry, Mayara L. Bastos, Digamber Behera, Andrea Benedetti, Greg P. Bisson, Martin Boeree, Maryline Bonnet, Sarah K. Brode, James C. M. Brust, Ying Cai, Geisa F. Carlessso, Eric Caumes, J. Peter Cegielski, Rosella Centis, Pei-Chun Chan, Edward D. Chan, Kwok-Chiu Chang, Macarthur Charles, Andra Cirule, Margareth Pretti Dalcolmo, Lia D'Ambrosio, Gerard de Vries, Keertan Dheda, Aliasgar Esmail, Jennifer Flood, Gregory Fox, Regina Gayoso, Medea Gegia, Maria Tarcela Gler, Sue Gu, Lorenzo Guglielmetti, Timothy H. Holtz, Jennifer Hughes, Petros Isaakidis, Mathilde Frechet-Jachym, Leah Jarlsberg, Russell R. Kempker, Salmaan Keshavjee, Faiz Ahmad Khan, Maia Kipiani, Serena P. Koenig, Won-Jung Koh, Afranio Kritski, Liga Kuksa, Charlotte L. Kvasnovsky, Nakwon Kwak, **Zhiyi Lan**, Christoph Lange, Rafael Laniado-Laborín, Myungsun Lee, Vaira Leimane, Chi-Chiu Leung, Eric Chung-Ching Leung, Pei Zhi Li, Phil Lowenthal, Ethel L. Maciel, Suzanne M. Marks, Sundari Mase, Lawrence Mbuagbaw, **Dick Menzies**, Giovanni B. Migliori, Vladimir Milanov, Ann C. Miller, Carole Mitnick, Chawangwa Modongo, Erika Mohr, Ignacio Monedero, Payam Nahid, Norbert Ndjeka, Max R. O'Donnell, Nesri Padayatchi, Domingo Palmero, Jean William Pape, Laura J. Podewils, Ian Reynolds, Vija Riekstina, Jérôme Robert, Maria Rodriguez, Barbara Seaworth, Kwonjune J. Seung, Kathryn Schnippel, Tae Sun Shim, Rupak Singla, Sarah E. Smith, Giovanni Sotgiu, Ganzaya Sukhbaatar, Payam Tabarsi, Simon Tiberi, Anete Trajman, Lisa Trieu, Zarir F. Udwadia, Tjip S. van der Werf, Nicolas Veziris, Piret Viiklepp, Stalz Charles Vilbrun, Kathleen Walsh, Janice Westenhouse, Wing-Wai Yew, Jae-Joon Yim, Nicola M. Zetola, Matteo Zignol

PRISMA of IPD in MDR-TB

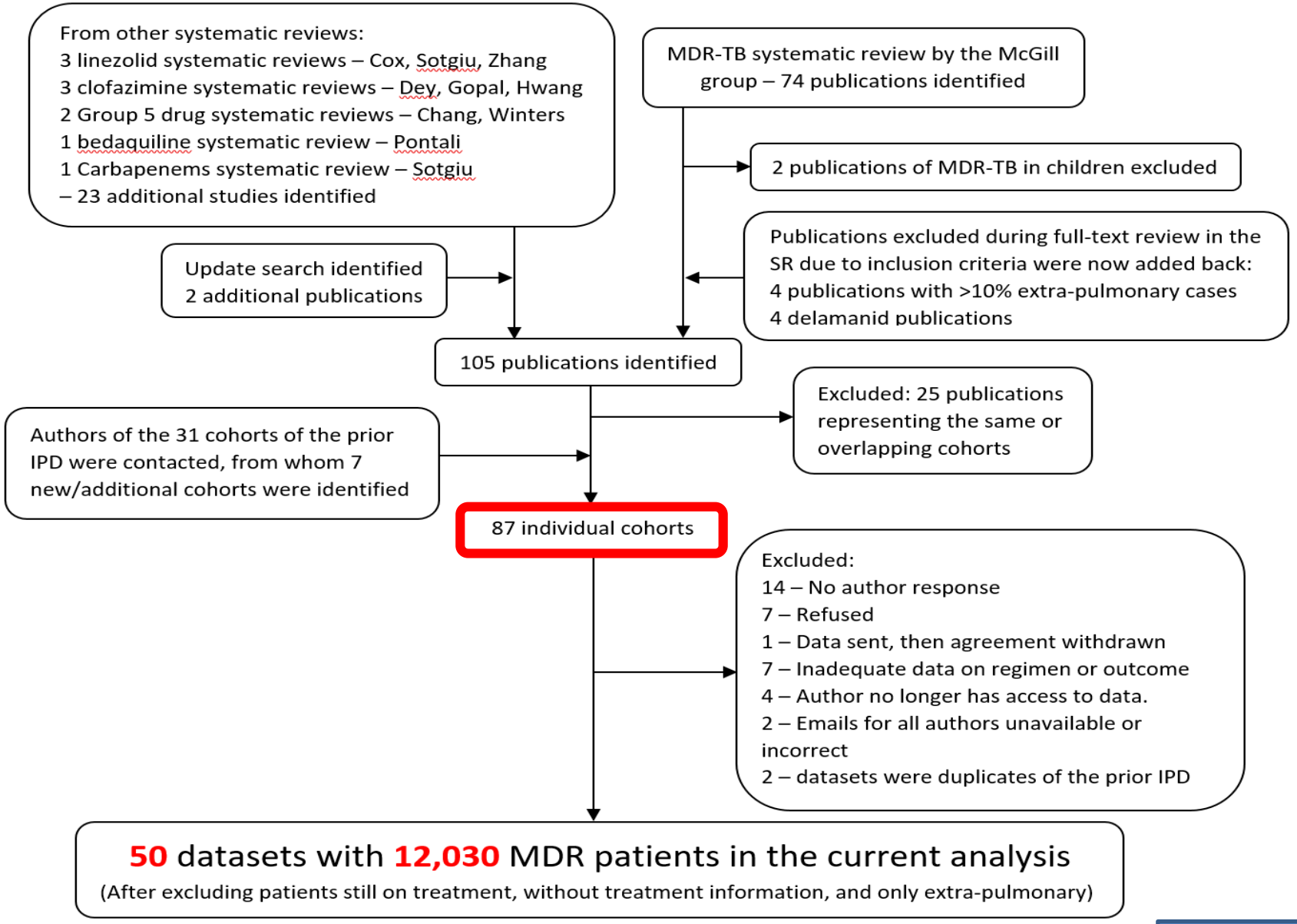
- Studies from Jan 2009, to April 2016 with original results, end of treatment outcomes in cohorts of at least 25 adults (aged >18 years).
- Obtained **anonymized individual patient data** provided by study investigators, regarding **clinical characteristics, treatment, and outcomes.**
- Using **propensity score-matched** generalized mixed effects logistic, or linear regression, **calculated adjusted odds ratios and adjusted risk differences for success or death during treatment.**
- Analyses conducted by Dick Menzies and McGill University Group

PRISMA (Preferred Reporting Items for Systematic Reviews)

Study selection

- Data source:
  - 74 studies included in systematic review (Bastos, ERJ 2017)
  - New data from authors in the 2010 IPD
- Data availability:
  - Authors contacted successfully
  - Investigators willing and able to share their data
  - Data available for treatment regimen and end of treatment outcomes
- Minimum number of patients:
  - 25 - to avoid very small series with unusual events
  - But for Lzd, or Bdq or Dlm – accept if >=10

PRISMA of IPD in MDR-TB



N. Ahmad, et al., Lancet, 2018

What is an Individual Patient Data (IPD) Meta-analysis (IPDMA)?

- Direct collection of the original data for each patient from all the relevant studies
- Meta-analyses based on individual level data rather than aggregated study level data. Allows adjustment for confounders, or stratified analyses (e.g. by HIV, or added resistance)
- Improved quality of both the data and the analysis
- Considered to be a “gold standard” of systematic reviews
- More work, Relies on extensive collaboration between researchers

Cochrane Handbook for Systematic Reviews of Interventions, 2011

Strength and limitations

Strength:

- Large sample size
- Availability of information on key covariates is in most studies, allowing control of confounders
- Availability of drug susceptibility testing

Limitation:

- Observational design
- Individualized treatment policies in most centers
- Uncontrolled confounders
- Adverse events (included in the WHO guidance)

Analysis methods

Drug efficacy - propensity score matching (PSM)

- PSM: generate treatment *vs* control group, that are balanced on a large number of covariates
- Treatment efficacy assessed in 2 ways:
  - Success vs Fail/ Relapse
  - Death vs Success/ Fail/ Relapse

    (Success = Cure + Complete)
- Effect estimate in 2 types:
  - Adjusted odds ratios (aOR)
  - Adjusted risk differences (aRD)

Data collection

Patient and clinical factors (covariates):

- Age, Gender, HIV
- AFB smear results, Cavitation on chest X-ray
- Prior TB treatment with 1st and/or 2nd-line drugs
- Drug sensitivity testing results

Intervention (treatment regimen):

- Drug used: a drug was used for at least one month, at any time during therapy.

Outcome:

- End of treatment outcome, using Laserson / WHO 2013 definitions

Patient Characteristics

	% with characteristic
Age (years)	38.3 ± 13.8
Sex (male)	63.1 %
HIV positive	18.3 %
On ART	49.4 %
AFB positive	77.4 %
Cavitation on chest radiograph	76.4 %
Past TB treatment	78.5 %
First line drugs	74.3 %
Second line drugs	25.7 %
Resistance to any SLI on DST	25.5 %
Resistance to FQ on DST	23.8 %

	N	Percent *
Total	12030	
Success	7346	65 %
Fail/Relapse	1017	6 %
Death	1729	11 %
Did not complete **	1938	12 %

* Pooled percentage using random effect at study level

** Include loss to follow-up, transfer and unknown

Association of covariates with outcomes

	Success vs Fail/Relapse		Death vs Success/Fail/Relapse		Did not complete vs Success/Fail/Relapse /Death	
	aOR	95% CI	aOR	95% CI	aOR	95% CI
Age (per 1 year older)	1.0	(0.99, 1.01)	**1.02**	**(1.01, 1.02)**	**0.99**	**(0.99, 0.99)**
Sex (reference: female)	1.0	(0.9, 1.1)	1.1	(1.0, 1.3)	**1.4**	**(1.3, 1.6)**
HIV positive	0.9	(0.7, 1.2)	**3.1**	**(2.6, 3.7)**	1.2	(1.0, 1.4)
AFB positive	**0.5**	**(0.4, 0.6)**	**1.5**	**(1.2, 1.8)**	1.0	(0.9, 1.2)
Cavitation on chest radiograph	**0.6**	**(0.5, 0.7)**	**1.4**	**(1.2, 1.6)**	1.0	(0.9, 1.2)
Prior TB treatment with 1st line drugs	**0.6**	**(0.5, 0.8)**	1.1	(0.9, 1.3)	1.1	(0.9, 1.3)
Prior TB treatment with 2nd line drugs	**0.6**	**(0.5, 0.8)**	1.1	(0.9, 1.4)	0.9	(0.8, 1.1)
Resistance to any SLI on DST	**0.6**	**(0.5, 0.8)**	**1.6**	**(1.3, 1.9)**	1.0	(0.9, 1.2)
Resistance to FQ on DST	**0.3**	**(0.2, 0.4)**	**1.4**	**(1.2, 1.8)**	1.0	(0.8, 1.2)

PICO (Population, Intervention, Comparators, Outcomes) **Questions**

Population	Drug A + Background regimen	Without Drug A (Control) + Background regimen	Outcomes
Patients with confirmed MDR-TB Patients with XDR-TB	Pyrazinamide	Without Pyrazinamide	End of treatment outcome: Success *vs* Failure/Relapse Death *vs* Success/Failure/ Relapse
	Ethambutol	Without Ethambutol	
	Injectable agent	Without Injectable agent	
	Later generation FQ	Without Later generation FQ (no FQ or older FQ)	
	linezolid - Overall - 600 mg/day dosage	Without Linezolid	
	Clofazimine	Without Clofazimine	
	Bedaquiline	Without Bedaquiline	
	Carbapenem	Without Carbapenem	

Quality Assessment - summary

Quality of evidence	Study design	Lower if…	Higher if…
High	Randomized trial	Study limitations	Large effect (e.g., RR 0.5) Very large effect (e.g., RR 0.2)
Moderate		Inconsistency	Evidence of dose-response gradient
Low	Observational study	Indirectness	All plausible confounding would reduce a demonstrated effect
Very low		Imprecision	
		Publication bias	

Strength of Recommendation

- **Strong:** confident that benefits > harms
  - Patients: should expect recommended course of action
  - Providers: should follow recommended course of action
  - Policy makers: recommendation can be adopted as policy

  *"We **recommend** using/against using…."*

- Conditional: benefits likely outweigh harms, but less confident
  - Patients: most but not all would want recommended course of action
  - Providers: different choices may be appropriate for some patients
  - Policy makers: policy making will require substantial debate

  *"We **suggest** using/against using…."*

Treatment of Drug-Resistant Tuberculosis
Guideline Contents

1. Amoxicillin-clavulanate (AMX/CLV)
2. Bedaquiline (BDQ)
3. Carbapenems with clavulanic acid
4. Clofazimine (CFZ)
5. Cycloserine (Cs)
6. Delamanid (DLM)
7. Ethambutol (EMB)
8. Ethionamide (ETO) and Prothionamide (PTO)
9. Fluoroquinolones: Levofloxacin (LFX), Moxifloxacin (MFX), Ciprofloxacin (CFX) and Ofloxacin (OFX)
10. Injectables: Amikacin (Am), Capreomycin (Cm), Kanamycin (Km) and Streptomycin (S)
11. Linezolid (LZD)
12. Macrolides: azithromycin and clarithromycin
13. P-Aminosalicylic Acid (PAS)
14. Pyrazinamide (PZA)

BUILDING A TREATMENT REGIMEN FOR MDR/XDR-TB TUBERCULOSIS

Contents

Results

ATS, CDC, ERS and IDSA Preferred Drugs for MDR TB Longer Regimen

INCLUDE:

Levofloxacin or Moxifloxacin **strong** recommendation

Bedaquiline **strong** recommendation

Linezolid conditional recommendation

Clofazimine conditional recommendation

Cycloserine conditional recommendation

Include when one of more preferred drugs cannot be given:

Injectable; amikacin conditional recommendation

Ethambutol conditional recommendation

PZA conditional recommendation

Carbapenem (always with amoxicillin-clavulanic acid) conditional

Delamanid “no” recommendation; defer to WHO

BETTER

Drug / Drug Class	Recommendation		Certainty in the evidence	Relative (95% CI) Death	Relative (95% CI) Success
	FOR	AGAINST			
Bedaquiline	Strong		Very Low	aOR 0.4 (0.3 to 0.5)	aOR 2.0 (1.4 to 2.9)
Fluoroquinolone: Moxifloxacin	Strong		Very Low	aOR 0.5 (0.4 to 0.6)	aOR 3.8 (2.8 to 5.2)
Fluoroquinolone: Levofloxacin	Strong		Very Low	aOR 0.6 (0.5 to 0.7)	aOR 4.2 (3.3 to 5.4)
Linezolid	Conditional		Very Low	aOR 0.3 (0.2 to 0.3)	aOR 3.4 (2.6 to 4.5)
Clofazimine	Conditional		Very Low	aOR 0.8 (0.6 to 1.0)	aOR 1.5 (1.1 to 2.1)
Cycloserine	Conditional		Very Low	aOR 0.6 (0.5 to 0.6)	aOR 1.5 (1.4 to 1.7)
Injectables: Amikacin	Conditional		Very Low	aOR 1.0 (0.8 to 1.2)	aOR 2.0 (1.5 to 2.6)
Injectables: Streptomycin	Conditional		Very Low	aOR 0.8 (0.6 to 1.1)	aOR 1.5 (1.1 to 2.1)
Ethambutol	Conditional		Very Low	aOR 1.0 (0.9 to 1.2)	aOR 0.9 (0.7 to 1.1)
Pyrazinamide	Conditional		Very Low	aOR 0.7 (0.6 to 0.8)	aOR 0.7 (0.5 to 0.9)
Injectables: Carbapenems w/ clavulanic acid	Conditional		Very Low	aOR 1.0 (0.5 to 1.7)	aOR 4.0 (1.7 to 9.1)
Delamanid	Concur with WHO conditional recommendation				

ATS, CDC, ERS and IDSA Selected Drugs Previously Included in MDR TB Longer Regimens

We suggest NOT including:

Ethionamide if more effective drugs are available to contract a regimen with at least 5 effective drugs

P-aminosalicylic acid if more effective drugs are available to contract a regimen with at least 5 effective drugs

Kanamycin or capreomycin

We recommend Not including:

Amoxicillin-clavulanate with exception of when patient is receiving a carbapenem **strong**

Macrolides azithromycin and clarithromycin **strong**

Drug / Drug Class	Recommendation		Certainty in the evidence	Relative (95% CI) Death	Relative (95% CI) Success
	FOR	AGAINST			
Ethionamide Prothionamide		Conditional	Very Low	aOR 0.9 (0.8 to 1.0)	aOR 0.8 (0.7 to 0.9)
Injectables: Kanamycin		Conditional	Very Low	aOR 1.1 (0.9 to 1.2)	aOR 0.5 (0.4 to 0.6)
P-Aminosalicylic Acid		Conditional	Very Low	aOR 1.2 (1.1 to 1.4)	aOR 0.8 (0.7 to 1.0)
Injectables: Capreomycin		Conditional	Very Low	aOR 1.4 (1.1 to 1.7)	aOR 0.8 (0.6 to 1.1)
Macrolides: Azithromycin Clarithromycin		Strong	Very Low	aOR 1.6 (1.2 to 2.0)	aOR 0.6 (0.5 to 0.8)
Amoxicillin-clavulanate		Strong	Very Low	aOR 1.7 (1.3 to 2.1)	aOR 0.6 (0.5 to 0.8)

ATS CDC, ERS, IDSA Groupings

Drug / Drug Class	Recommendation		Certainty in the evidence	Relative (95% CI) Death	Relative (95% CI) Success
	FOR	AGAINST			
Bedaquiline	Strong		Very Low	aOR 0.4 (0.3 to 0.5)	aOR 2.0 (1.4 to 2.9)
Fluoroquinolone: Moxifloxacin	Strong		Very Low	aOR 0.5 (0.4 to 0.6)	aOR 3.8 (2.8 to 5.2)
Fluoroquinolone: Levofloxacin	Strong		Very Low	aOR 0.6 (0.5 to 0.7)	aOR 4.2 (3.3 to 5.4)
Linezolid	Conditional		Very Low	aOR 0.3 (0.2 to 0.3)	aOR 3.4 (2.6 to 4.5)
Clofazimine	Conditional		Very Low	aOR 0.8 (0.6 to 1.0)	aOR 1.5 (1.1 to 2.1)
Cycloserine	Conditional		Very Low	aOR 0.6 (0.5 to 0.6)	aOR 1.5 (1.4 to 1.7)
Injectables: Amikacin	Conditional		Very Low	aOR 1.0 (0.8 to 1.2)	aOR 2.0 (1.5 to 2.6)
Injectables: Streptomycin	Conditional		Very Low	aOR 0.8 (0.6 to 1.1)	aOR 1.5 (1.1 to 2.1)
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Pyrazinamide	Conditional		Very Low	aOR 0.7 (0.6 to 0.8)	aOR 0.7 (0.5 to 0.9)
Injectables: Carbapenems w/ clavulanic acid	Conditional		Very Low	aOR 1.0 (0.5 to 1.7)	aOR 4.0 (1.7 to 9.1)
Delamanid	Concur with WHO conditional recommendation				
Ethionamide Prothionamide		Conditional	Very Low	aOR 0.9 (0.8 to 1.0)	aOR 0.8 (0.7 to 0.9)
Injectables: Kanamycin		Conditional	Very Low	aOR 1.1 (0.9 to 1.2)	aOR 0.5 (0.4 to 0.6)
P-Aminosalicylic Acid		Conditional	Very Low	aOR 1.2 (1.1 to 1.4)	aOR 0.8 (0.7 to 1.0)
Injectables: Capreomycin		Conditional	Very Low	aOR 1.4 (1.1 to 1.7)	aOR 0.8 (0.6 to 1.1)
Macrolides: Azithromycin Clarithromycin		Strong	Very Low	aOR 1.6 (1.2 to 2.0)	aOR 0.6 (0.5 to 0.8)
Amoxicillin-clavulanate		Strong	Very Low	aOR 1.7 (1.3 to 2.1)	aOR 0.6 (0.5 to 0.8)

Figure 1. Summary of recommendations on drugs for use in a treatment regimen for patients with multidrug-resistant tuberculosis, including strength of recommendation, certainty in the evidence, and relative effects on death and treatment success. Additional details and other outcomes of interest are provided in the section on Drugs and Drug Classes, and in Appendix B: Evidence Profiles in the online supplement. Success is defined as end of treatment cure or treatment completion. aOR = adjusted odds ratio; CI = confidence interval; WHO = World Health Organization.

WHO Grouping

GROUP	MEDICINE	Abbreviation
Group A: Include all three medicines (unless they cannot be used) Strong	Levofloxacin OR Moxifloxacin	Lfx Mfx
	Bedaquiline[1,4]	Bdq
	Linezolid[2]	Lzd
Group B: Add both medicines (unless they cannot be used)	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[3,4]	Dlm
	Pyrazinamide[5]	Z
	Imipenem-cilastatin OR Meropenem[6]	Ipm-Cln Mpm
	Amikacin (OR Streptomycin)[7]	Am (S)
	Ethionamide OR Prothionamide	Eto Pto
	p-aminosalicylic acid	PAS

Best Practices

- Consultation should be requested with a TB expert when there is suspicion of or confirmation of DR-TB.
  - **“The responsibility for successful treatment of TB is placed primarily on the provider or program initiating therapy rather than on the patient.”**

- Molecular DSTs should be obtained for rapid detection of mutations associated with resistance.
  - **When rifampin resistance is detected**, additional DST should be performed immediately for first-line drugs, and at least fluoroquinolones, and aminoglycosides.
  - Resistance to fluoroquinolones should be excluded whenever isoniazid resistance is found.

Best Practices

- Regimens should include only drugs to which the patient's *M. tuberculosis* isolate has documented or high likelihood of susceptibility (efficacy).
  - **Drugs known to be ineffective** based on *in vitro* growth-based or molecular resistance **should NOT be used**.
    - This applies to all drugs and treatment regimens, unless reliable methods of testing susceptibility for a drug have yet to be developed.
  - Resistance of 1% or greater identifies a drug which should not be used.

Best Practices

- Treatment response should be **monitored clinically, radiographically and bacteriologically**
  - Cultures obtained at least monthly for pulmonary TB.
  - When cultures remain positive > three months of treatment, susceptibility tests for drugs should be repeated.
  - Weight and other measures of clinical response should be recorded monthly.

Best Practices

- Patients should be educated and asked about adverse effects at each visit.
  - Adverse effects should be ***investigated*** and ***ameliorated.***

- Patient-centered case management helps patients understand their diagnosis, understand and participate in their treatment, and discuss potential barriers to treatment.
  - Patient-centered strategies and interventions should be used to minimize barriers to treatment.
-

Number of possibly effective drugs

Duration of therapy

Number of possibly effective drugs

Duration of therapy

For success:

Better outcome : aOR > 1, aRD > 0 (increase success)

The higher, the better

For death:

Better outcome : aOR < 1, aRD < 0 (decrease death)

The lower, the better

Bold green: significantly better

Bold red: significantly worse

Number of Drugs in the Intensive Phase of Treatment

We suggest using at least **five** drugs in the intensive phase of treatment of MDR-TB

conditional recommendation- very low certainty of evidence.

Table 3. Propensity Score–matched Analysis of the Number of Drugs in the Intensive Phase of Treatment and the Adjusted Odds Ratio of Treatment Success versus Failure or Relapse

No. of Drugs	No. of Patients		Propensity Score–matched Analysis	
	Success/Total (%)	Death/Total (%)	aOR (95% CI)	Risk Difference (95% CI) (%)
For the analysis of success vs. fail*/relapse†				
0–2 drugs	1,097/1,236 (88.8)	—	1.0 (reference)	
3 drugs	1,257/1,407 (89.3)	—	1.7 (1.4 to 2.0)	6 (4 to 7)
4 drugs	1,657/1,847 (89.7)	—	1.2 (1.4 to 2.0)	8 (6 to 9)
5 drugs	926/986 (93.9)	—	3.0 (2.3 to 3.9)	8 (7 to 10)
⩾6 drugs	523/568 (92.1)	—	2.3 (1.6 to 3.1)	4 (1 to 7)
For the analysis of death vs. success/fail*/relapse†				
0–2 drugs	—	205/1,441 (14.2)	1.0 (reference)	
3 drugs	—	233/1,640 (14.2)	0.9 (0.8 to 1.1)	−1 (−3 to 1)
4 drugs	—	345/2,192 (15.7)	1.1 (0.9 to 1.2)	−3 (−5 to −1)
5 drugs	—	104/1,090 (9.5)	0.6 (0.5 to 0.7)	−2 (−3 to 0)
⩾6 drugs	—	54/622 (8.6)	0.5 (0.4 to 0.7)	2 (−0 to 5)

Definition of abbreviations: aOR = adjusted odds ratio; CI = confidence interval.

*World Health Organization definitions: fail = treatment terminated or need for permanent regimen change of at least two antituberculosis drugs because of: lack of conversion by the end of the intensive phase, bacteriological reversion in the continuation phase after conversion to negative, evidence of additional acquired resistance to fluoroquinolones or second-line injectable drugs or adverse drug reactions.

†Relapse was defined as a positive bacteriological culture in the 12 months after treatment completion.

Number of Drugs in the Continuation Phase of Treatment

We suggest using at least **four** drugs in the continuation phase of treatment of MDR-TB

conditional recommendation, very low certainty of evidence

Table 4. Propensity Score–matched Analysis of the Number of Drugs in the Continuation Phase of Treatment and the aOR of Treatment Success versus Failure or Relapse

No. of Drugs	No. of Patients		Propensity Score–matched Analysis	
	Success/Total (%)	Death/Total (%)	aOR (95% CI)	Risk Difference (95% CI) (%)
For the analysis of success vs. fail*/relapse†				
0–1 drug	1,017/1,144 (88.9)	—	1.0 (reference)	
2 drugs	1,272/1,425 (89.2)	—	1.1 (0.9 to 1.3)	1 (−1 to 3)
3 drugs	1,623/1,810 (89.7)	—	1.2 (1.0 to 1.4)	3 (1 to 5)
4 drugs	816/864 (94.4)	—	2.3 (1.7 to 3.1)	3 (1 to 5)
⩾5 drugs	346/383 (90.3)	—	1.2 (0.9 to 1.8)	−4 (−8 to −1)
For the analysis of death vs. success/fail*/relapse†				
0–1 drug	—	187/1,331 (14.0)	1.0 (reference)	
2 drugs	—	193/1,618 (11.9)	0.8 (0.6 to 0.9)	−3 (−5 to −1)
3 drugs	—	307/2,117 (14.5)	1.0 (0.8 to 1.1)	−4 (−5 to −2)
4 drugs	—	78/942 (8.3)	0.5 (0.4 to 0.7)	−1 (−4 to 1)
⩾5 drugs	—	37/420 (8.8)	0.5 (0.4 to 0.8)	5 (1 to 8)

Definition of abbreviations: aOR = adjusted odds ratio; CI = confidence interval.

*World Health Organization definitions: fail = treatment terminated or need for permanent regimen change of at least two anti-tuberculosis drugs because of: lack of conversion by the end of the intensive phase, bacteriological reversion in the continuation phase after conversion to negative, evidence of additional acquired resistance to fluoroquinolones or second-line injectable drugs or adverse drug reactions.

†Relapse was reported as a positive bacteriological culture in the 12 months after treatment completion.

For this analysis all “effective” drugs were considered as equals; likely impacts analysis of number needed as BDQ≠PAS

WHO Consolidated Guidelines on MDR TB Therapy, 2019

The Number of Drugs

At treatment start

Continuation phase

PICO 3

- **In contemporary longer MDR-TB regimens, the risk of treatment failure, relapse and death was comparable when:**
  - the treatment started with **four, five or six** medicines likely to be effective.
- **Also showed that patients who took three agents in the continuation phase-the situation expected when starting with four agents and stopping one drug after 6 months**
  - fared no worse than those who took four agents in the continuation phase

- **Recommendation:** In patients with MDR-TB we suggest an **intensive phase duration** of treatment of **between 5 and 7 months after culture conversion**(conditional)

Intervals from Sputum Culture Conversion to End of Intensive-Phase Treatment (*mo*)	No. of Patients		Propensity Score–matched Analysis			
	Treatment Success	Total	No. of Pairs	aOR	95% CI	Risk Difference (95% CI)
0–1.0	239	251		1.0	Reference	
1.01–3.0	668	695	694	1.5	1.0 to 2.3	0.02 (0.00 to 0.03)
3.01–5.0	878	917	906	1.4	1.0 to 2.0	0.02 (0.00 to 0.03)
5.01–7.0	1,158	1,179	1,179	3.3	2.1 to 5.2	0.04 (0.03 to 0.05)
7.01–15.0	1,025	1,080	1,079	1.1	0.8 to 1.5	0.01 (−0.01 to 0.02)

Definition of abbreviations: aOR = adjusted odds ratio; CI = confidence interval.

Recommendation: In patients with MDR-TB, we suggest a **total treatment duration** of **between 15-21 months after culture conversion** (conditional)

Table 9. Adjusted Estimates of Treatment Success by Duration of Treatment Interval between Sputum Culture Conversion and End of Treatment, All Forms of Multidrug Resistance (*N* = 4,691)

Interval from Sputum Culture Conversion to End of Treatment (*mo*)	No. of Patients		Propensity Score–matched Analysis			
	Treatment Success	Total	No. of Pairs	aOR	95% CI	Risk Difference (95% CI)
0.1–12.0	360	396	394	0.5	0.4 to 0.7	−0.04 (−0.07 to −0.01)
12.01–15.0	565	593		1.0	Reference	
15.01–18.0	1,206	1,235	1,223	2.1	1.4 to 3.1	0.02 (0.01 to 0.04)
18.01–21.0	1,122	1,158	1,154	1.6	1.1 to 2.3	0.02 (0.00 to 0.03)
21.01–24.0	858	893	889	1.2	0.9 to 1.8	0.01 (−0.01 to 0.02)
24.01–69	386	416	413	0.7	0.4 to 1.0	−0.02 (−0.05 to 0.00)

…”Our analyses and recommendations for the **duration** of intensive and continuation phases of therapy are **anchored to the timing of culture conversion** as this approach factors in that treatment response may vary by patient, resistance patterns and regimen composition and potency, among other factors”.

…”**Optimal total duration of treatment for MDR-TB using injectable free, all-oral regimens cannot be determined** from these datasets, but clinical trials evaluating newer drugs and all-oral regimens for MDR-TB are underway”.

For the selection of an effective MDR-TB treatment regimen and duration of MDR-TB treatment:

- **SUMMARY OF RECOMMENDATIONS:**

- We suggest using **at least five drugs in the intensive phase** of treatment and **four drugs in the continuation phase** of treatment (conditional recommendation, very low certainty in the evidence).

- We suggest an **intensive-phase duration of treatment of between 5 and 7 months after culture conversion** (conditional recommendation, very low certainty in the evidence).

- We suggest a **total treatment duration of between 15 and 21 months after culture conversion** (conditional recommendations, very low certainty in the evidence).

- In patients with pre-extensively drug-resistant TB (**pre-XDR-TB**) and extensively drug-resistant TB (**XDR-TB**), which are both subsets of MDR-TB, we suggest a **total treatment duration of between 15 and 24 months after culture conversion** (conditional recommendations, very low certainty in the evidence).

Association of Individual Drugs with Outcomes

SUCCESS (CURE AND TREATMENT COMPLETION)
DEATH (MORTALITY)

Association of FQ use with Success and Death

	N pairs	aOR (95% CI)	aRD (95% CI)
Ofloxacin (susceptible) vs No FQ			
Success	1865	1.0 (0.8, 1.2)	-0.01 (-0.04, 0.01)
Death	2285	**0.6 (0.5, 0.7)**	**-0.08 (-0.11, -0.06)**
Levofloxacin (susceptible) vs No FQ			
Success	1450	**4.2 (3.3, 5.4)**	**0.15 (0.13, 0.18)**
Death	1632	**0.6 (0.5, 0.7)**	**-0.06 (-0.09, -0.04)**
Moxifloxacin (susceptible) vs No FQ			
Success	1031	**3.8 (2.8, 5.2)**	**0.11 (0.08, 0.14)**
Death	1145	**0.5 (0.4, 0.6)**	**-0.07 (-0.10, -0.04)**
Lfx/Mfx vs Ofx (resistant to Ofx but not tested or Sens to Lfx/Mfx)			
Success	715	**1.7 (1.3, 2.2)**	**0.08 (0.04, 0.13)**
Death	927	0.9 (0.8, 1.2)	0.02 (-0.01, 0.06)

New & Repurposed Drugs

– Linezolid (Lzd)

– Clofazimine (Cfz)

– Bedaquiline (Bdq)

Association of Bedaquiline use with Success and Death

BDQ vs No BDQ	N pairs	aOR (95% CI)	aRD (95% CI)
All patients			
Success	490	**2.0 (1.4, 2.9)**	**0.10 (0.05, 0.14)**
Death	548	**0.4 (0.3. 0.5)**	**-0.14 (-0.19, -0.10)**
High income countries			
Success	85	3.0 (0.9, 10.1)	0.05 (-0.05, 0.15)
Death	93	0.6 (0.2, 1.9)	-0.03 (-0.11, 0.05)

Usual BDQ dosage: 400 mg/day for 2 weeks, then 200 mg/day three times weekly for 22 weeks; 1 study used prolonged BDQ treatment (>24 weeks)

Use of BDQ associated with more resistance, XDR, but also other newer drugs

Enhanced Activity of Bedaquiline In Combination

- Adjusted Odds Ratio of Success / Mortality:
  - Bedaquiline vs no Bedaquiline **2.0 / 0.4**
  - Bedaquiline and Linezolid vs no Bedaquiline and Linezolid **2.7 / 0.3**
  - Bedaquiline and Clofazimine vs no Bedaquiline and Clofazimine **5.0 / 0.3**

- Combination of Bedaquiline with Linezolid and Clofazimine is especially active
  - All three should be included in regimen
  - Linezolid had conditional recommendation due to higher toxicity risk

Association of Linezolid use with Success and Death

LZD vs No LZD	N pairs	aOR (95% CI)	aRD (95% CI)
All patients			
Success	799	**3.4 (2.6, 4.5)**	**0.15 (0.11, 0.18)**
Death	883	**0.3 (0.2, 0.3)**	**-0.20 (-0.23, -0.16)**
600 mg/day patients (80% of all patients)			
Success	529	**3.1 (2.2, 4.3)**	**0.15 (0.11, 0.20)**
Death	578	**0.2 (0.2, 0.3)**	**-0.19 (-0.23, -0.14)**
High income countries			
Success	516	**3.9 (2.6, 5.8)**	**0.12 (0.08, 0.16)**
Death	556	1.3 (0.8, 2.2)	0.01 (-0.01, 0.04)

Usual LZD dosage: 600 mg/day (80%); 1200 mg/day (10%); 300 mg/day (10%)

Use of LZD associated with more resistance, XDR, but also other newer drugs

WHO Consolidated Guidelines on MDR TB Therapy 2019

- The 2018 IPD data base included experience from over 300 patients treated with Linezolid for at least 1 month, mostly at a dose of 600 mg daily
  - 30% received linezolid for 1-6 months
  - >30% received linezolid for more than 18 months – these patients had the lowest frequency of treatment failure, loss to follow up and death.
  - A plot of linezolid duration and treatment failure suggests that the optimal duration of use would be around 20 months

Association of Clofazimine use with Success and Death

Cfz vs No Cfz	N pairs	aOR (95% CI)	aRD (95% CI)
All patients			
Success	564	**1.5 (1.1, 2.1)**	**0.06 (0.01, 0.10)**
Death	679	0.8 (0.6, 1.0)	-0.04 (-0.08, 0.00)
High income countries			
Success	212	1.3 (0.7, 2.5)	0.03 (-0.03, 0.09)
Death	233	1.4 (0.7, 2.7)	0.04 (-0.01, 0.09)

Usual Cfz dosage: 100 mg/day

Use of Cfz associated with more resistance, XDR, but also other newer drugs

XDR – New/Repurposed Drugs

	N pairs	aOR (95% CI)	aRD (95% CI)
Lfx/Mfx vs No FQ			
Success	359	1.2 (0.8, 1.6)	0.01 (-0.05, 0.06)
Death	482	**0.6 (0.4, 0.8)**	**-0.07 (-0.12, -0.02)**
Lzd vs No Lzd			
Success	280	**6.6 (4.1, 10.6)**	**0.31 (0.24, 0.38)**
Death	314	**0.2 (0.1, 0.3)**	**-0.29 (-0.36, -0.23)**
Cfz vs No Cfz			
Success	173	1.5 (0.9, 2.6)	0.04 (-0.04, 0.13)
Death	216	**0.4 (0.2, 0.6)**	**-0.18 (-0.27, -0.10)**
Bdq vs No Bdq			
Success	139	**2.5 (1.3, 4.8)**	**0.12 (0.03, 0.21)**
Death	155	**0.5 (0.2, 0.9)**	**-0.09 (-0.17, -0.02)**

Pyrazinamide (PZA)

Association of PZA use with Success and Death

Use vs No Use	N pairs	aOR (95% CI)	aRD (95% CI)
PZA vs No PZA - Strains susceptible to PZA			
Success	1818	**0.7 (0.5, 0.9)**	**-0.03 (-0.04, -0.01)**
Death	1986	**0.7 (0.6, 0.8)**	**-0.03 (-0.05, -0.01)**
PZA vs No PZA - Strains resistant to PZA			
Success	1064	**0.5 (0.4, 0.7)**	**-0.05 (-0.08, -0.03)**
Death	1262	**1.5 (1.2, 1.9)**	**0.05 (0.02, 0.07)**

Cycloserine, Ethambutol, Ethionamide and PAS

Use of Cycloserine/Terizidone:

- When susceptible – Beneficial
  - aOR for success 1.5
  - aOR for mortality 0.6
- When resistant – No benefit

Use of Ethambutol:

- When susceptible – No benefits
  - aOR for success 0.9
  - aOR for mortality 1.0
- When resistant – Worse outcomes

Use of Ethionamide/Prothionamide or PAS:

- When susceptible – No benefits
- When resistant – Worse outcomes

Injectable drugs

Association of Injectable use with Success and Death

	N pairs	aOR (95% CI)	aRD (95% CI)
Streptomycin (susceptible) vs No injectable			
Success	1017	**1.5 (1.1, 2.1)**	0.02 (-0.00, 0.04)
Death	1121	0.8 (0.6, 1.1)	-0.02 (-0.04, 0.01)
Amikacin (susceptible) vs No injectable			
Success	1393	**2.0 (1.5, 2.6)**	**0.06 (0.04, 0.08)**
Death	1644	1.0 (0.8, 1.2)	-0.00 (-0.03, 0.02)
Kanamycin (susceptible) vs No injectable			
Success	2523	**0.5 (0.4, 0.6)**	**-0.07 (-0.08, -0.05)**
Death	2958	1.1 (0.9, 1.2)	0.01 (-0.01, 0.02)
Capreomycin (susceptible) vs No injectable			
Success	938	0.8 (0.6, 1.1)	-0.03 (-0.06, -0.00)
Death	1114	**1.4 (1.1, 1.7)**	**0.04 (0.01, 0.07)**

XDR – Capreomycin

	N pairs	aOR (95% CI)	aRD (95% CI)
Capreomycin vs No Capreomycin			
Success	332	**0.5 (0.4, 0.7)**	**-0.14 (-0.20, -0.07)**
Death	675	**3.4 (2.7, 4.3)**	**0.25 (0.20, 0.30)**
Capreomycin (susceptible) vs No Capreomycin			
Success	91	0.8 (0.4, 1.7)	-0.04 (-0.16, 0.08)
Death	115	**3.8 (1.6, 8.9)**	**0.16 (0.07, 0.25)**

Injectable Drug Summary

- **If sensitive:** Overall effect of injectables – modest benefit
  - Amikacin appears to be the best
  - Streptomycin may still be useful (if sensitive)
  - Capreomycin and kanamycin appear to have no benefit and possible harm

- **If resistant:** Use of all injectable drugs associated with worse outcomes or no benefit

- Capreomycin has no benefit in XDR treatment, even for susceptible isolates

- Cumulative dose and duration predicted toxicity as did older age, dehydration/hypovolemia/hypotension, prior SLID treatment, coexisting hepatic or renal disease and concomitant medications.

Association of Carbapenems use with Success and Death

Cpm vs No Cpm	N pairs	aOR (95% CI)	aRD (95% CI)
All patients			
Success	138	**4.0 (1.7, 9.1)**	**0.14 (0.06, 0.21)**
Death	168	1.0 (0.5, 1.7)	-0.00 (-0.09, 0.08)
Imipenem only			
Success	71	**5.1 (1.3, 19.3)**	**0.13 (0.02, 0.24)**
Death	91	0.8 (0.4, 1.6)	-0.04 (-0.17, 0.08)
Meropenem only			
Success	69	2.7 (0.9, 7.6)	0.12 (0.00, 0.23)
Death	79	0.8 (0.3, 2.0)	-0.02 (-0.13, 0.09)

Conclusions

Drug	aOR ↑success	aOR ↓death
Moxifloxacin	**3.8**	**0.5**
Levofloxacin	**4.2**	**0.6**
Bedaquiline	**2.0**	**0.4**
Linezolid	**3.4**	**0.3**
Clofazimine	**1.5**	0.8
Carbapenems	**4.0**	1.0
Pyrazinamide	**0.7**	**0.7**
Amikacin	**2.0**	1.0
Cycloserine	1.5	0.6

Table 5. Clinical Strategy to Build an Individualized Treatment Regimen for MDR-TB

- Build a regimen **using five or more drugs to which the isolate is susceptible (or has low likelihood of resistance)**, preferably with drugs that have not been used to treat the patient previously.
- Choice of drugs is contingent on capacity to appropriately monitor for significant adverse effects, patient comorbidities, and preferences/values (choices therefore subject to program and patient safety limitations).
- In children with TB disease who are contacts of infectious MDR-TB source cases, the source case's isolate DST result should be used if an isolate is not obtained from the child.
- **TB expert medical consultation is recommended (ungraded good practice statement).**

Step 1: Choose one later-generation fluoroquinolone	Levofloxacin Moxifloxacin
Step 2: Choose both of these prioritized drugs	Bedaquiline Linezolid
Step 3: Choose both of these prioritized drugs	Clofazimine Cycloserine
Step 4: If a regimen cannot be assembled with five effective oral drugs, *and the isolate is susceptible*, use one of these injectable agents*	Amikacin Streptomycin
Step 5: If needed or if oral agents preferred over injectable agents in STEP 4, use the following drugs†	Delamanid‡ Pyrazinamide Ethambutol
Step 6: If limited options and cannot assemble a regimen of five effective drugs, consider use of the following drugs	Ethionamide or prothionamide§ Imipenem–cilastatin/clavulanate or meropenem/clavulanate‖ *p*-Aminosalicylic acid¶ High-dose isoniazid**

ATS CDC, ERS, IDSA Groupings

Drug / Drug Class	Recommendation		Certainty in the evidence	Relative (95% CI) Death	Relative (95% CI) Success
	FOR	AGAINST			
Bedaquiline	Strong		Very Low	aOR 0.4 (0.3 to 0.5)	aOR 2.0 (1.4 to 2.9)
Fluoroquinolone: Moxifloxacin	Strong		Very Low	aOR 0.5 (0.4 to 0.6)	aOR 3.8 (2.8 to 5.2)
Fluoroquinolone: Levofloxacin	Strong		Very Low	aOR 0.6 (0.5 to 0.7)	aOR 4.2 (3.3 to 5.4)
Linezolid	Conditional		Very Low	aOR 0.3 (0.2 to 0.3)	aOR 3.4 (2.6 to 4.5)
Clofazimine	Conditional		Very Low	aOR 0.8 (0.6 to 1.0)	aOR 1.5 (1.1 to 2.1)
Cycloserine	Conditional		Very Low	aOR 0.6 (0.5 to 0.6)	aOR 1.5 (1.4 to 1.7)
Injectables: Amikacin	Conditional		Very Low	aOR 1.0 (0.8 to 1.2)	aOR 2.0 (1.5 to 2.6)
Injectables: Streptomycin	Conditional		Very Low	aOR 0.8 (0.6 to 1.1)	aOR 1.5 (1.1 to 2.1)
Ethambutol	Conditional		Very Low	aOR 1.0 (0.9 to 1.2)	aOR 0.9 (0.7 to 1.1)
Pyrazinamide	Conditional		Very Low	aOR 0.7 (0.6 to 0.8)	aOR 0.7 (0.5 to 0.9)
Injectables: Carbapenems w/ clavulanic acid	Conditional		Very Low	aOR 1.0 (0.5 to 1.7)	aOR 4.0 (1.7 to 9.1)
Delamanid	Concur with WHO conditional recommendation				
Ethionamide Prothionamide		Conditional	Very Low	aOR 0.9 (0.8 to 1.0)	aOR 0.8 (0.7 to 0.9)
Injectables: Kanamycin		Conditional	Very Low	aOR 1.1 (0.9 to 1.2)	aOR 0.5 (0.4 to 0.6)
P-Aminosalicylic Acid		Conditional	Very Low	aOR 1.2 (1.1 to 1.4)	aOR 0.8 (0.7 to 1.0)
Injectables: Capreomycin		Conditional	Very Low	aOR 1.4 (1.1 to 1.7)	aOR 0.8 (0.6 to 1.1)
Macrolides: Azithromycin Clarithromycin		Strong	Very Low	aOR 1.6 (1.2 to 2.0)	aOR 0.6 (0.5 to 0.8)
Amoxicillin-clavulanate		Strong	Very Low	aOR 1.7 (1.3 to 2.1)	aOR 0.6 (0.5 to 0.8)

Figure 1. Summary of recommendations on drugs for use in a treatment regimen for patients with multidrug-resistant tuberculosis, including strength of recommendation, certainty in the evidence, and relative effects on death and treatment success. Additional details and other outcomes of interest are provided in the section on Drugs and Drug Classes, and in Appendix B: Evidence Profiles in the online supplement. Success is defined as end of treatment cure or treatment completion. aOR = adjusted odds ratio; CI = confidence interval; WHO = World Health Organization.

WHO Grouping

GROUP	MEDICINE	Abbreviation
Group A: Include all three medicines (unless they cannot be used) Strong	Levofloxacin OR Moxifloxacin	Lfx Mfx
	Bedaquiline[1,4]	Bdq
	Linezolid[2]	Lzd
Group B: Add both medicines (unless they cannot be used)	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[3,4]	Dlm
	Pyrazinamide[5]	Z
	Imipenem-cilastatin OR Meropenem[6]	Ipm-Cln Mpm
	Amikacin (OR Streptomycin)[7]	Am (S)
	Ethionamide OR Prothionamide	Eto Pto
	p-aminosalicylic acid	PAS

Conclusions

Benefit of each individual drug		
Pyrazinamide	No clear benefit	“Bad”
Capreomycin	No benefit	“Worse”
Later generation FQ	Significant benefit	“Better”
Linezolid	Significant benefit	“Better”
Bedaquiline	Significant benefit	“Better”
Clofazimine	Weak benefit	“Good”

Dr. Tommy Lan McGill NAR 2018

Shorter Course Standardized Regimen

Judged by the guidelines committee to have:

minimal desirable effects (on treatment success, mortality and culture conversions) and

small to moderate undesirable effects (adverse events, limited applicability, and use of kanamycin) and

includes drugs for which there is documented or high likelihood of resistance.

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PICO Question 18—Shorter-course, standardized regimen: In patients with MDR-TB, does treatment with a standardized MDR-TB regimen for ⩽12 months lead to better outcomes than treatment with an MDR-TB regimen for 18–24 months?

Recommendation 18: The shorter-course regimen is standardized with the use of kanamycin (which the committee recommends against using) and includes drugs for which there is documented or high likelihood of resistance (e.g., isoniazid, ethionamide, pyrazinamide). Although the STREAM Stage 1 randomized trial found the shorter-course regimen to be noninferior to longer injectable-containing regimens with respect to the primary efficacy outcome (7), the guideline committee cannot make a recommendation either for or against this standardized shorter-course regimen, compared with longer individualized all-oral regimens that can be composed in accordance with the recommendations in this practice guideline. We make a research recommendation for the conduct of randomized clinical trials evaluating the efficacy, safety, and tolerability of modified shorter-course regimens that include newer oral agents, exclude injectables, and include drugs for which susceptibility is documented or highly likely.

"…the guideline committee cannot make a recommendation either for or against this standardized shorter-course regimen, compared with the longer individualized all-oral regimens…"

WHO Rapid Communication 2019

Key Changes to the treatment of drug-resistant TB

- Injectable agents should be phased out as a matter of priority in all treatment regimens and replaced by Bedaquiline

- A shorter (9-12 months) all-oral Bedaquiline-containing treatment regimen of 9-12 months durations is the preferred option for eligible MDR/RR-TB patients
  - 4-6 months: BDQ, LFX/MFX, Ethion, EMB, PZA, High INH, Clofazimine
  - 5 months: LFX/MFX, Clofazimine, PZA, EMB

Children

Nearly 1 million cases of TB in children;

230,000 deaths

35,000 cases of MDR and XDR-TB

Special Considerations in children:

Bacterial burden is smaller than that in most adults – most drug resistance is primary not acquired.

Paucibacillary nature makes diagnosis harder

Little is known about pharmacokinetics, safety, and tolerability of drugs in neonates, infants and toddlers.

Children more prone to disseminated TB, including meningitis

Drugs that penetrate well into CSF, , may have an advantage

Most children can avoid the injectables

- **Our PS-matched IPDMA did not include sufficent numbers of children to allow the formultation of GRADE-based recommendations.**

- **However on the basis of a recent IPDMA of 975 children with MDR TB from 18 countries, recent pharmacokinetic studies in children and several observational studies showing good outcomes, the recommendations noted on choice of drugs, composition of regimens, and durations of treatment for adults can also be applied to children with MDR-TB**

MDR-TB and Pregnancy

Conclusions:

Despite low cure rates reported in the literature, we believe that the benefits of treatment to mother, child, and the community outweigh the harms.

No evidence to support one particular regimen over another

Most experts avoid ethionamide and the SLIDs

Most drugs are FDA Category C

Bedaquiline and meropenem Category B

Aminoglycosides Category D

- **Systematic Review of Literature to Support Guidelines**
  - Treatment regimens were individualized according to drug susceptibility and tolerability
  - 65 pregnant women, treatment outcome data available:
    - 49% cured
    - 20% completed
    - 14% died
    - Failure 9%
  - Fetal Outcomes
    - 78.5% healthy births
    - 12% medical abortions
    - 3% spontaneous abortions
    - 1.5% stillbirth
    - 3% born with HIV

EDITOR'S CHOICE

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

Suzanne M Marks ✉, Sundari R Mase, Sapna Bamrah Morris

Clinical Infectious Diseases, Volume 64, Issue 12, 15 June 2017, Pages 1670–1677,
https://doi.org/10.1093/cid/cix208

Published: 14 March 2017 **Article history ▾**

We selected studies that compared treatment vs nontreatment outcomes and performed a meta-analysis to estimate the relative risk of TB incidence and its 95% confidence interval

Results

We abstracted data from 21 articles that met inclusion criteria. Six articles presented outcomes for contacts who were treated compared with those not treated for MDR-LTBI; 10 presented outcomes only for treated contacts, and 5 presented outcomes only for untreated contacts. The estimated MDR-TB incidence reduction was 90% (9%–99%) using data from 5 comparison studies. We also found high treatment discontinuation rates due to adverse effects in persons taking pyrazinamide-containing regimens. Cost-effectiveness was greatest using a fluoroquinolone/ethambutol combination regimen.

Conclusions

Few studies met inclusion criteria, therefore results should be cautiously interpreted. We found a reduced risk of TB incidence with treatment for MDR-LTBI, suggesting effectiveness in prevention of progression to MDR-TB, and confirmed cost-effectiveness. However, we found that pyrazinamide-containing MDR-LTBI regimens often resulted in treatment discontinuation due to adverse effects.

Management of Contacts of MDR TB

Systematic Review of 21 published studies:

Using data from 5 non-registry-matched comparison studies included in the review of observational studies:

MDR-TB incidence occurred in 2 of 190 **(1.1%) compared to 14.3%** in those who received no MDR LTBI treatment.

Estimated MDR-TB **incidence reduction was 90%**

PICO Question 21—Treatment of Contacts Exposed to MDR-TB: Should contacts exposed to an infectious patient with MDR-TB be offered LTBI treatment versus followed with observation alone?

Recommendation 21: For contacts with presumed MDR LTBI due to exposure to an infectious patient with MDR-TB, we suggest offering treatment for LTBI (conditional recommendation, very low certainty in the evidence). We suggest 6 to 12 months of treatment with a later-generation fluoroquinolone alone or with a second drug, on the basis of drug susceptibility of the source-case *M. tuberculosis* isolate. On the basis of evidence of increased toxicity, adverse events, and discontinuations, pyrazinamide should not be routinely used as the second drug.

Evidence-base supporting the guidelines:

The Collaborative Group for Meta-Analysis of Individual Patient Data in MDR-TB treatment

Treatment correlates of successful outcomes in pulmonary multidrug-resistant tuberculosis: an individual patient data meta-analysis

The Collaborative Group for the Meta-Analysis of Individual Patient Data in MDR-TB treatment–2017; Nafees Ahmad, Shama D Ahuja, Onno W Akkerman, Jan-Willem C Alffenaar, Laura F Anderson, Parvaneh Baghaei, Didi Bang, Pennan M Barry, Mayara L Bastos, Digamber Behera, Andrea Benedetti, Gregory P Bisson, Martin J Boeree, Maryline Bonnet, Sarah K Brode, James C M Brust, Ying Cai, Eric Caumes, J Peter Cegielski, Rosella Centis, Pei-Chun Chan, Edward D Chan, Kwok-Chiu Chang, Macarthur Charles, Andra Cirule, Margareth Pretti Dalcolmo, Lia D'Ambrosio, Gerard de Vries, Keertan Dheda, Aliasgar Esmail, Jennifer Flood, Gregory J Fox, Mathilde Fréchet-Jachym, Geisa Fregona, Regina Gayoso, Medea Gegia, Maria Tarcela Gler, Sue Gu, Lorenzo Guglielmetti, Timothy H Holtz, Jennifer Hughes, Petros Isaakidis, Leah Jarlsberg, Russell R Kempker, Salmaan Keshavjee, Faiz Ahmad Khan, Maia Kipiani, Serena P Koenig, Won-Jung Koh, Afranio Kritski, Liga Kuksa, Charlotte L Kvasnovsky, Nakwon Kwak, Zhiyi Lan, Christoph Lange, Rafael Laniado-Laborín, Myungsun Lee, Vaira Leimane, Chi-Chiu Leung, Eric Chung-Ching Leung, Pei Zhi Li, Phil Lowenthal, Ethel L Maciel, Suzanne M Marks, Sundari Mase, Lawrence Mbuagbaw, Giovanni B Migliori, Vladimir Milanov, Ann C Miller, Carole D Mitnick, Chawangwa Modongo, Erika Mohr, Ignacio Monedero, Payam Nahid, Norbert Ndjeka, Max R O'Donnell, Nesri Padayatchi, Domingo Palmero, Jean William Pape, Laura J Podewils, Ian Reynolds, Vija Riekstina, Jérôme Robert, Maria Rodriguez, Barbara Seaworth, Kwonjune J Seung, Kathryn Schnippel, Tae Sun Shim, Rupak Singla, Sarah E Smith, Giovanni Sotgiu, Ganzaya Sukhbaatar, Payam Tabarsi, Simon Tiberi, Anete Trajman, Lisa Trieu, Zarir F Udwadia, Tjip S van der Werf, Nicolas Veziris, Piret Viiklepp, Stalz Charles Vilbrun, Kathleen Walsh, Janice Westenhouse, Wing-Wai Yew, Jae-Joon Yim, Nicola M Zetola, Matteo Zignol, Dick Menzies

N. Ahmad, et al., Lancet, 2018

Articles

Comparison of different treatments for isoniazid-resistant tuberculosis: an individual patient data meta-analysis

Federica Fregonese, Shama D Ahuja, Onno W Akkerman, Denise Arakaki-Sanchez, Irene Ayakaka, Parvaneh Baghaei, Didi Bang, Mayara Bastos, Andrea Benedetti, Maryline Bonnet, Adithya Cattamanchi, Peter Cegielski, Jung-Yien Chien, Helen Cox, Martin Dedicoat, Connie Erkens, Patricio Escalante, Dennis Falzon, Anthony J Garcia-Prats, Medea Gegia, Stephen H Gillespie, Judith R Glynn, Stefan Goldberg, David Griffith, Karen R Jacobson, James C Johnston, Edward C Jones-López, Awal Khan, Won-Jung Koh, Afranio Kritski, Zhi Yi Lan, Jae Ho Lee, Pei Zhi Li, Ethel L Maciel, Rafael Mello Galliez, Corinne S C Merle, Melinda Munang, Gopalan Narendran, Viet Nhung Nguyen, Andrew Nunn, Akihiro Ohkado, Jong Sun Park, Patrick P J Phillips, Chinnaiyan Ponnuraja, Randall Reves, Kamila Romanowski, Kwonjune Seung, H Simon Schaaf, Alena Skrahina, Dick van Soolingen, Payam Tabarsi, Anete Trajman, Lisa Trieu, Velayutham V Banurekha, Piret Viiklepp, Jann-Yuan Wang, Takashi Yoshiyama, Dick Menzies

F. Fregonese, et al., Lancet Resp, 2018

Treatment of Isoniazid-Resistant TB

Recommendation:

We suggest adding a later-generation fluoroquinolone to a 6-month regimen of daily rifampin, ethambutol and pyrazinamide for patients with INH-resistant TB

Conditional recommendation

Recommendation:

In patients with INH-resistant TB treated with a daily regimen of a later-generation fluoroquinolone, rifampin, ethambutol, and PZA, we suggest that the duration of PZA can be shortened to 2 months in selected situations

Non-cavitary and lower-burden disease or toxicity from PZA

Conditional recommendation

Not included by WHO

Duration of REZ (6 vs 8-9 months)

Success versus failure/relapse *(mortality not analyzable)*

Comparison	N Success/N on regimen	Propensity score	
		Odds ratio aOR (95% CI)	Risk Difference aRD (95% CI)
All Patients			
6REZ (±INH)	254/262	**2.4 (1.0 – 5.5)**	+4% (0 to +8%)
>6REZ (±INH)	999/1088	1.0 (reference)	Reference
Only if no INH			
6REZ	136/142	2.5 (0.9; 7.5)	+5% (-1% to +8%)
>6REZ	701/785	1.0 (reference)	Reference

Acquired RIF resistance: Non-significant – but **lower** with 6REZ than 8-9REZ

Adding a Fluoroquinolone to ≥6(H)REZ: **Success** versus failure/relapse

Comparison	N Success/ N on regimen	Propensity score	
		Odds ratio aOR (95% CI)	Risk Difference aRD (95% CI)
All Patients			
≥6(H)REZ **&FQ** *	245/251	**2.8 (1.1; 7.3)**	+5% (0 to +9%)
≥6 (H)REZ	1253/1350	1.0 (reference)	Reference
FQ are only moxifloxacin/levofloxacin/gatifloxacin			
≥6(H)REZ &**FQ**	161/165	2.9 (0.9; 9.3)	+6% (-2% to +14%)
≥6 (H)REZ	1253/1350	1.0 (reference)	Reference

Median duration of FQ: 6 months
Acquired RIF resistance: **Significantly lower if received a FQ**
Findings virtually identical in patients who did not receive any INH

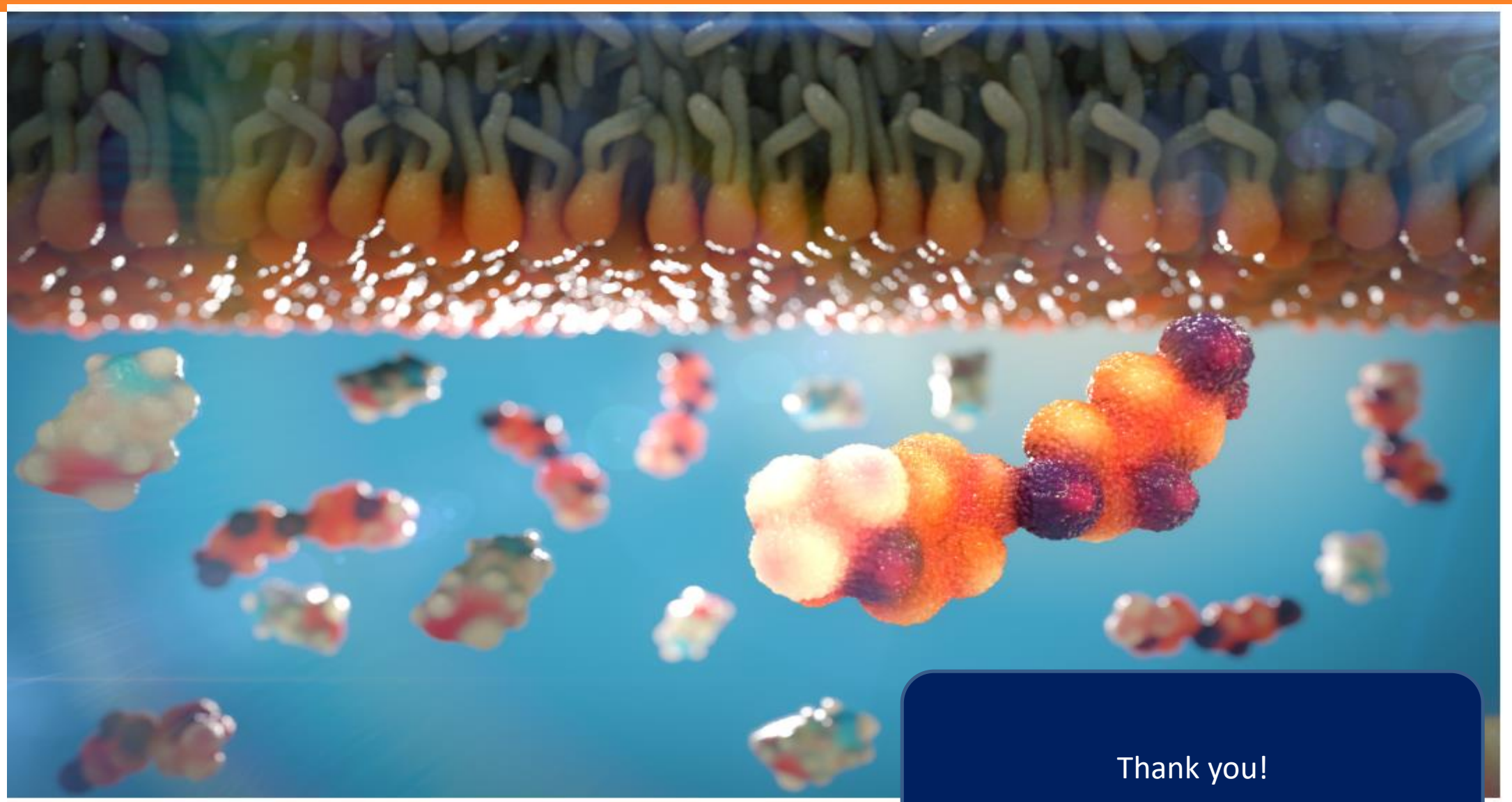
Adding a Fluoroquinolone to (H)REZ. **Only 1-3 months PZA. Success** versus failure/relapse

Comparison	N Success/ N on regimen	Propensity score	
		Odds ratio aOR (95% CI)	Risk Difference aRD (95% CI)
All Patients			
≥6RE **1-3Z & FQ** (±INH)	117/118	5.2 (0.6; 46.7)	+4% (-2% to +9%)
≥6REZ (±INH)	1253/1350	1.0 (reference)	reference
FQ are only moxifloxacin/levofloxacin/gatifloxacin			
≥6RE **1-3Z & FQ** (+INH)	104/105	5.2 (0.6, 47.2)	+5% (-3% to +12%)
≥6REZ (+INH)	1253/1350	1.0 (reference)	reference

Acquired RIF resistance: **No patient who received a FQ developed MDR**
Median Duration of FQ: 7 months

What is Not Covered

- Rifampin mono-resistant tuberculosis
- Specifics regarding when a patient with MDR-TB or XDR-TB or even INH-R TB can be released from isolation
- How do new drugs impact the:
  - Number of drugs in the regimen
  - The duration of therapy



Artist's rendering of the pretomanid compound.

Thank you!