Role of the Laboratory in Use of Newer TB Regimens

Keynote Address –
12th National Conference on Laboratory Aspects of Tuberculosis

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Lisa Armitige, MD, PhD has the following disclosures to make:

- No conflict of interests
- No relevant financial relationships with any commercial companies pertaining to this educational activity
- I do profess shameless affection for my state lab in Texas……


WARNING
MAY SPONTANEOUSLY
START TALKING ABOUT
MICROBIOLOGY

Rifampin

Every TB treatment decision starts with whether or not one can use rifampin

Rifampin resistance (or omission)

Standard Short-Course Chemotherapy for Drug-Resistant Tuberculosis

Treatment Outcomes in 6 Countries

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Sang Jae Kim, ScD
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Table 3. Mantel-Haenszel Weighted Relative Risks for Treatment Outcome of New and Retreatment Tuberculosis (TB) Cases With Drug Resistance*

	Weighted Relative Risk (95% Confidence Interval)		
	Treatment Success	Mortality	Failure
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JAMA, May 17, 2000—Vol 283, No. 19

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Regarding the Laboratory and Rifampin

- Early rifampin detection sets the trajectory of all other treatment decisions for both TB disease and TB infection (LTBI)
- Nucleic acid-based tests that detect Mtb ***and*** offer information on rifampin resistance/susceptibility are highly coveted
- Clinically, susceptibility to rifampin is used interchangeably for susceptibility to rifampin, rifabutin and rifapentine so, this one finding, opens a whole chest of treatment options

A Clinician's View of First Line TB Drug Susceptibilities

- A patient with an INH and rifampin susceptible organism can be cured with just those two drugs, these results are most important
- Resistance to each of the first line drugs has different implications, clinically and epidemiologically
- Rifampin is the most important
- PZA monoresistance implies *M. bovis* infection which has different implications for contact investigation
- EMB resistance is only relevant to clinicians if other drugs show resistance

New Treatment Regimens for Drug-Susceptible TB Disease

SHINE Trial

Shorter Treatment for Minimal Tuberculosis (TB) in Children

SHINE Trial Design

- Children ages 0-16 years old
- Multicenter, open-label, parallel-group, non-inferiority, randomized controlled, two-arm trial
- Comparing a 4-month vs the standard 6-month regimen
- Endpoint: favorable outcome; TB-free survival at 72 weeks
- Margin of Inferiority set at 6%

Exclusion Criterion

1. Smear-positive respiratory sample TB
   (note: smear-positive peripheral lymph node sample is allowed)
2. Premature (<37 weeks) **and** aged under 3 months
3. Miliary TB, spinal TB, TB meningitis, osteoarticular TB, abdominal TB, congenital TB
4. Pre-existing non-tuberculous disease likely to prejudice the response to, or assessment of, treatment e.g. liver or kidney disease, peripheral neuropathy, cavitation
5. Any known contraindication to taking anti-TB drugs
6. Known contact with drug resistant adult source case (including mono- resistant TB)
7. Known drug resistance in the child
8. Severely sick
9. Pregnancy

Laboratory Support for SHINE Regimen

- As is frequently the case in children, susceptibilities for the source case guide the treatment course
- Use of this regimen is dependent on any organisms collected from the source case being susceptible to at least INH, rifampin and PZA
- Shorter treatment courses dictate a need for early detection of possible resistance

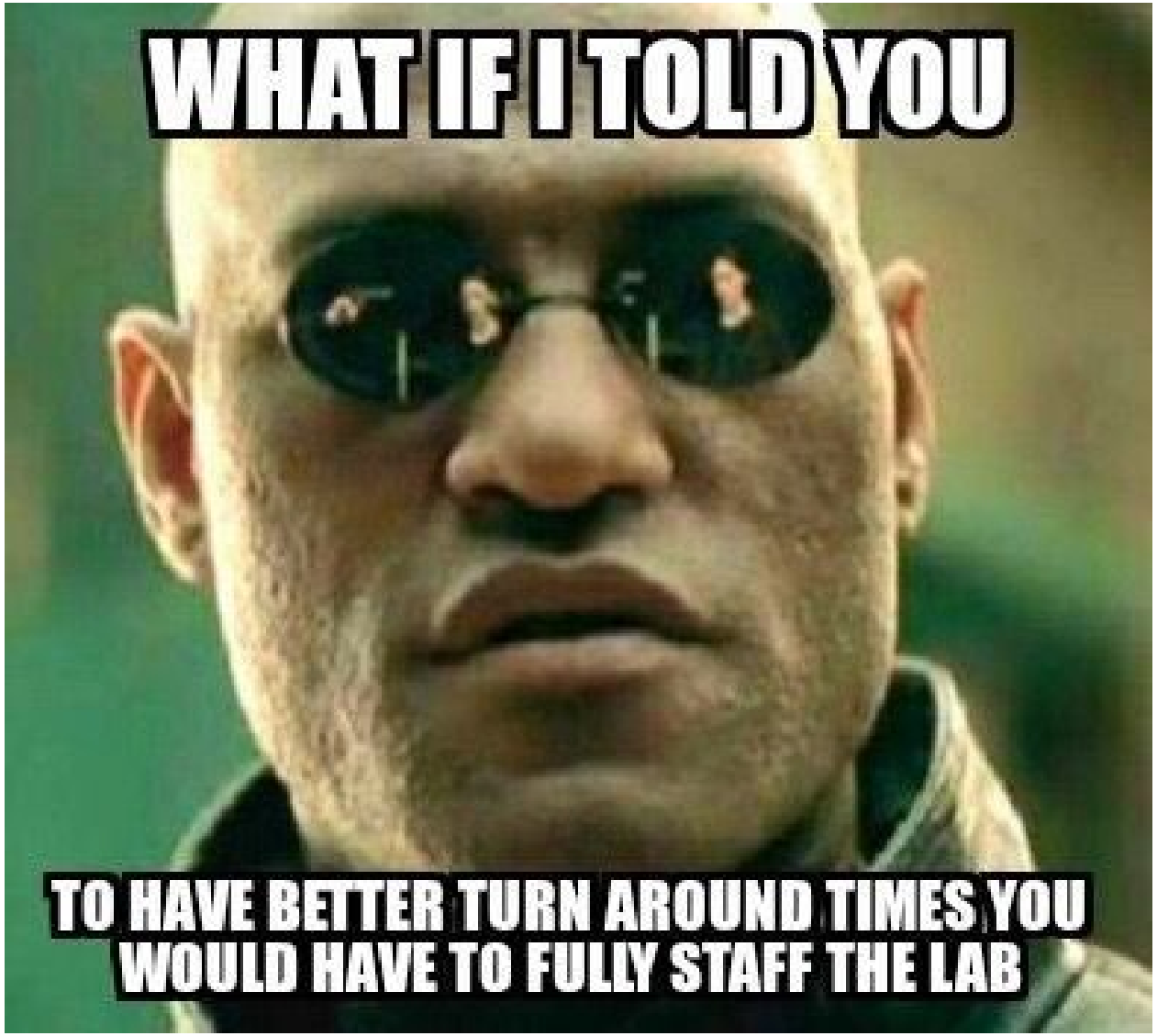
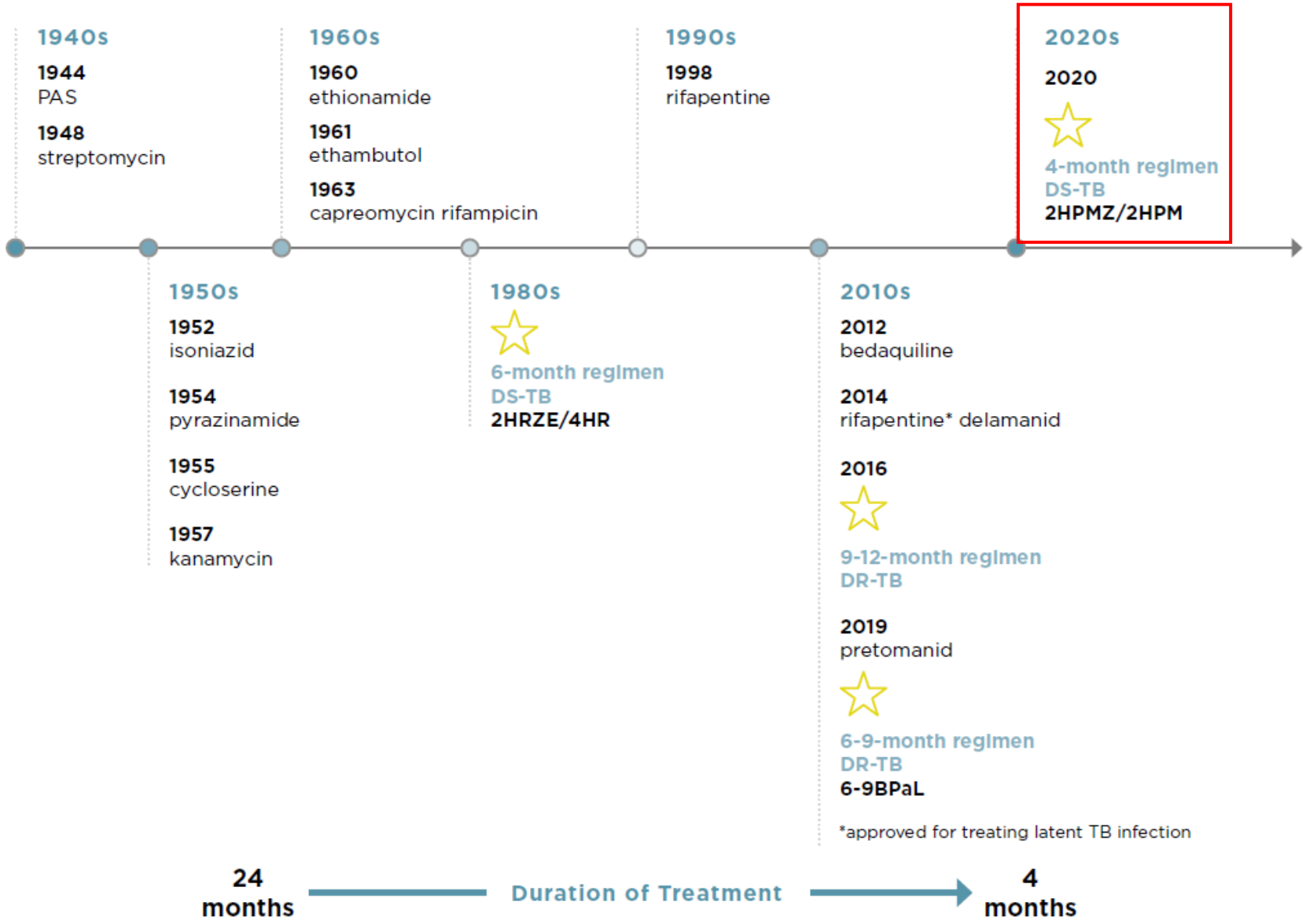

WHAT IF I TOLD YOU
TO HAVE BETTER TURN AROUND TIMES YOU WOULD HAVE TO FULLY STAFF THE LAB

FIGURE 1: TUBERCULOSIS TREATMENT SHORTENING MILESTONES



https://www.treatmentactiongroup.org/publication/an-activists-guide-to-shorter-treatment-for-drug-sensitive-tuberculosis/

Treatment shortening regimen (TBTC Study 31) – Drug Sensitive TB

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Four-Month Rifapentine Regimens with or without Moxifloxacin for Tuberculosis

S.E. Dorman, P. Nahid, E.V. Kurbatova, P.P.J. Phillips, K. Bryant, K.E. Dooley, M. Engle, S.V. Goldberg, H.T.T. Phan, J. Hakim, J.L. Johnson, M. Lourens, N.A. Martinson, G. Muzanyi, K. Narunsky, S. Nerette, N.V. Nguyen, T.H. Pham, S. Pierre, A.E. Purfield, W. Samaneka, R.M. Savic, I. Sanne, N.A. Scott, J. Shenje, E. Sizemore, A. Vernon, Z. Waja, M. Weiner, S. Swindells, and R.E. Chaisson, for the AIDS Clinical Trials Group and the Tuberculosis Trials Consortium

2234 participants (194 PLHIV, 1703 with cavity on CXR)
Randomized 1:1:1 to 3 arms
Noninferiority study

N Engl J Med 2021;384:1705-18.

Study 31 - Laboratory

- Inclusion criterion:
  - Diagnosed pulmonary tuberculosis confirmed on culture to be susceptible to INH, rifampin and fluroquinolones
  - At least one sputum specimen positive for
    - AFB on smear microscopy
    - Xpert MTB/RIF (with a medium or high semiquantitative result)

- 2 sputum specimens were collected at all scheduled visits at or after week 17
  - Smear microscopy and culture by MGIT obtained at baseline
  - Phenotypic testing at baseline and any Mtb positive cultures after week 17
  - WGS on any positive cultures collected after week 17 (compared to baseline)

Study 31 Laboratory

Schedule of procedures/evaluations.

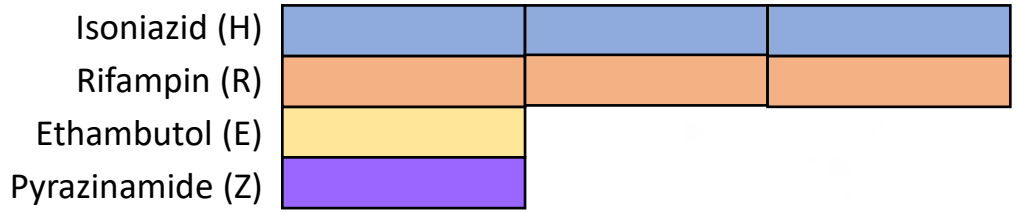
Visit window	Screen	Up to 7 days after screen	+/− three (3) days						+/− seven (7) days					Possible poor treatment response	Post early termination visit[f]
Visit		Baseline	WK 2	WK 4	WK 8	WK 12	WK 17	WK 22	WK 26	MO 9	MO 12	MO 15	MO 18		
Informed consent	X														
Inclusion/Exclusion	X	X													
Demographics, medical history	X														
Contact information	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Symptoms		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events			X	X	X	X	X	X	X						X
Interval medical history										X	X	X	X	X	
Height	X														
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chest radiograph	X						X[e]		X[e]					X	
Visual tests		X		X											
HIV test	X														
CD4, HIV viral load (if HIV-pos)	X[a]														
Pregnancy testing	X														
Randomization		X													
Sputum for smear and culture[b]	X	X	X	X	X	X	XX	XX	XX	XX	XX[c]	XX	XX[c]	XXX	
Sputum for rapid molecular test, if available at site	X														
Storage of Mtb bacterial isolate	X	X					X	X	X	X	X	X	X	X	
Diabetes screen[d]	X														
ALT, bilirubin, creatinine, hemoglobin, WBC with differential, platelets	X		X	X	X	X	X	X							X

Table S2. Schedule of participant evaluations

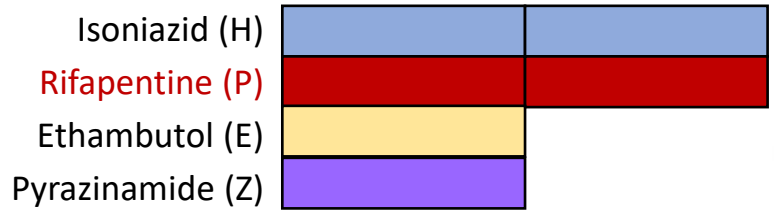
Supplement to: N Engl J Med 2021;384:1705-18.

Study 31 – Treatment Arms

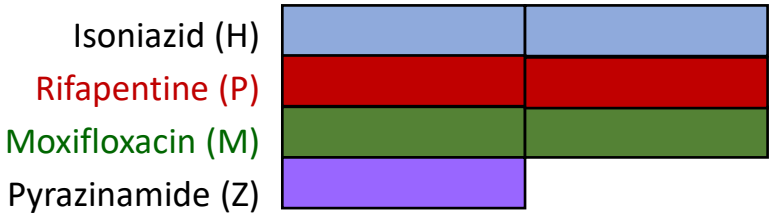
Control
(2HRZE/4HR)



RPT
(2HPZE/2HP)



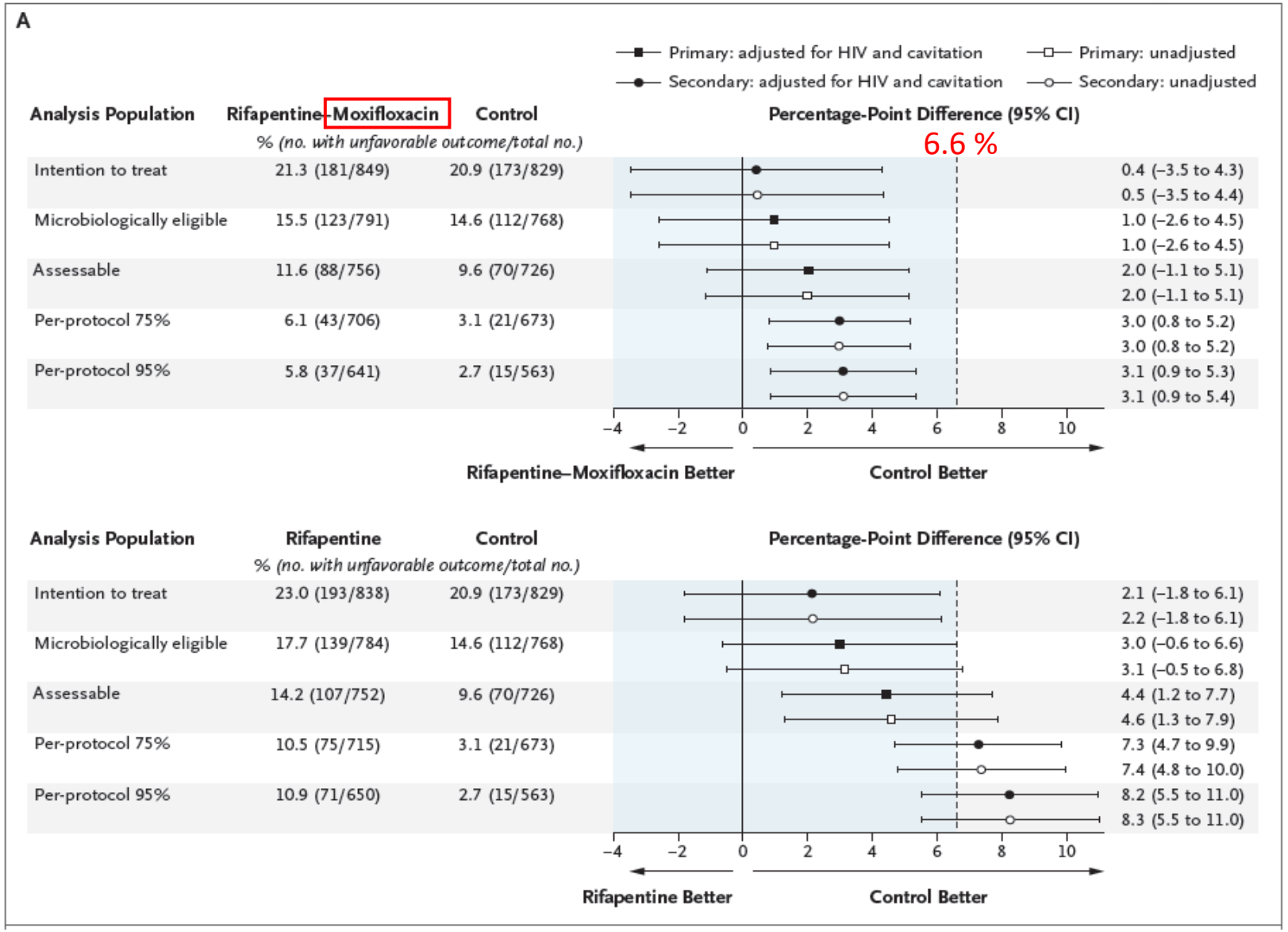
Control
(2HPZM/4HPM)



Notes:

- HRZE dosed at standard doses
- Dosed daily, 7 days/week, observed 5 days/week
- Rifapentine 1200 mg (8 tablets)
- Moxifloxacin 400 mg

Study 31 - Results



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Study 31 Microbiologic Outcomes

Table 2. Primary Efficacy Analysis in the Microbiologically Eligible and the Assessable Populations.*

Outcome	Microbiologically Eligible Population				Assessable Population			
	Control (N=768)	Rifapentine–Moxifloxacin (N=791)	Rifapentine (N=784)	Total (N=2343)	Control (N=726)	Rifapentine–Moxifloxacin (N=756)	Rifapentine (N=752)	Total (N=2234)
Favorable								
Participants with outcome — no. (%)	656 (85.4)	668 (84.5)	645 (82.3)	1969 (84.0)	656 (90.4)	668 (88.4)	645 (85.8)	1969 (88.1)
Adjusted difference from control — percentage points (95% CI)	NA	1.0 (–2.6 to 4.5)	3.0 (–0.6 to 6.6)	NA	NA	2.0 (–1.1 to 5.1)	4.4 (1.2 to 7.7)	NA
Participant had negative culture at month 12 — no. (%)	643 (83.7)	656 (82.9)	636 (81.1)	1935 (82.6)	643 (88.6)	656 (86.8)	636 (84.6)	1935 (86.6)
Participant was seen at month 12 but no sputum was produced or cultures were contaminated but without evidence of *M. tuberculosis* — no. (%)	13 (1.7)	12 (1.5)	9 (1.1)	34 (1.5)	13 (1.8)	12 (1.6)	9 (1.2)	34 (1.5)
Unfavorable								
Participants with outcome — no. (%)	112 (14.6)	123 (15.5)	139 (17.7)	374 (16.0)	70 (9.6)	88 (11.6)	107 (14.2)	265 (11.9)
Outcome related to tuberculosis — no. (%)	24 (3.1)	45 (5.7)	75 (9.6)	144 (6.1)	24 (3.3)	45 (6.0)	75 (10.0)	144 (6.4)
Two consecutive positive cultures at or after week 17†	11 (1.4)	34 (4.3)	63 (8.0)	108 (4.6)	11 (1.5)	34 (4.5)	63 (8.4)	108 (4.8)
Participant not seen at month 12 but had positive culture when last seen	11 (1.4)	3 (0.4)	4 (0.5)	18 (0.8)	11 (1.5)	3 (0.4)	4 (0.5)	18 (0.8)
Clinical diagnosis of tuberculosis recurrence and treatment restarted	2 (0.3)	8 (1.0)	8 (1.0)	18 (0.8)	2 (0.3)	8 (1.1)	8 (1.1)	18 (0.8)

1 case with exogenous reinfection confirmed by WGS

CDC Recommendations for Laboratory Assessment - 4 Month Rifapentine-Moxifloxacin Regimen

Centers for Disease Control and Prevention
MMWR
Morbidity and Mortality Weekly Report
Weekly / Vol. 71 / No. 8
February 25, 2022

Interim Guidance: 4-Month Rifapentine-Moxifloxacin Regimen for the Treatment of Drug-Susceptible Pulmonary Tuberculosis — United States, 2022

Wendy Carr, PhD[1]; Ekaterina Kurbatova, MD[1]; Angela Starks, PhD[1]; Neela Goswami, MD[1]; Leeanna Allen, MPH[1]; Carla Winston, PhD[1]

TABLE 2. Baseline and follow-up evaluations for patients treated with a 4-month rifapentine-moxifloxacin regimen — United States, 2022*

Evaluation	Baseline	Week 4	Week 8 (end of intensive phase)	Week 12	Week 17 (end of treatment)
Microbiology					
Sputum for rapid molecular test†	Y	NA	NA	NA	NA
Sputum for AFB smear and culture§	Y	Y	Y	Y¶	Y¶
Drug susceptibility testing**	Y	NA	Y¶	NA	NA

† At least one baseline specimen is advised to be tested using a rapid molecular test for susceptibility to INH, PZA, RIF, and fluoroquinolones.
§ Sputa for AFB smear and culture should be obtained at baseline, then monthly until two consecutive specimens are AFB smear- and culture-negative.
¶ These activities are optional or contingent on other information.
** Drug susceptibility at least for INH, RIF, PZA, and fluoroquinolones (preferred fluoroquinolone is MOX) should be obtained. Drug susceptibility testing (rapid molecular preferred) should be repeated if patient's culture remains positive after completing 2 months (8 weeks) of treatment.

https://www.cdc.gov/mmwr/volumes/71/wr/mm7108a1.htm

Should the Fluoroquinolones be considered in first line drug testing……..?

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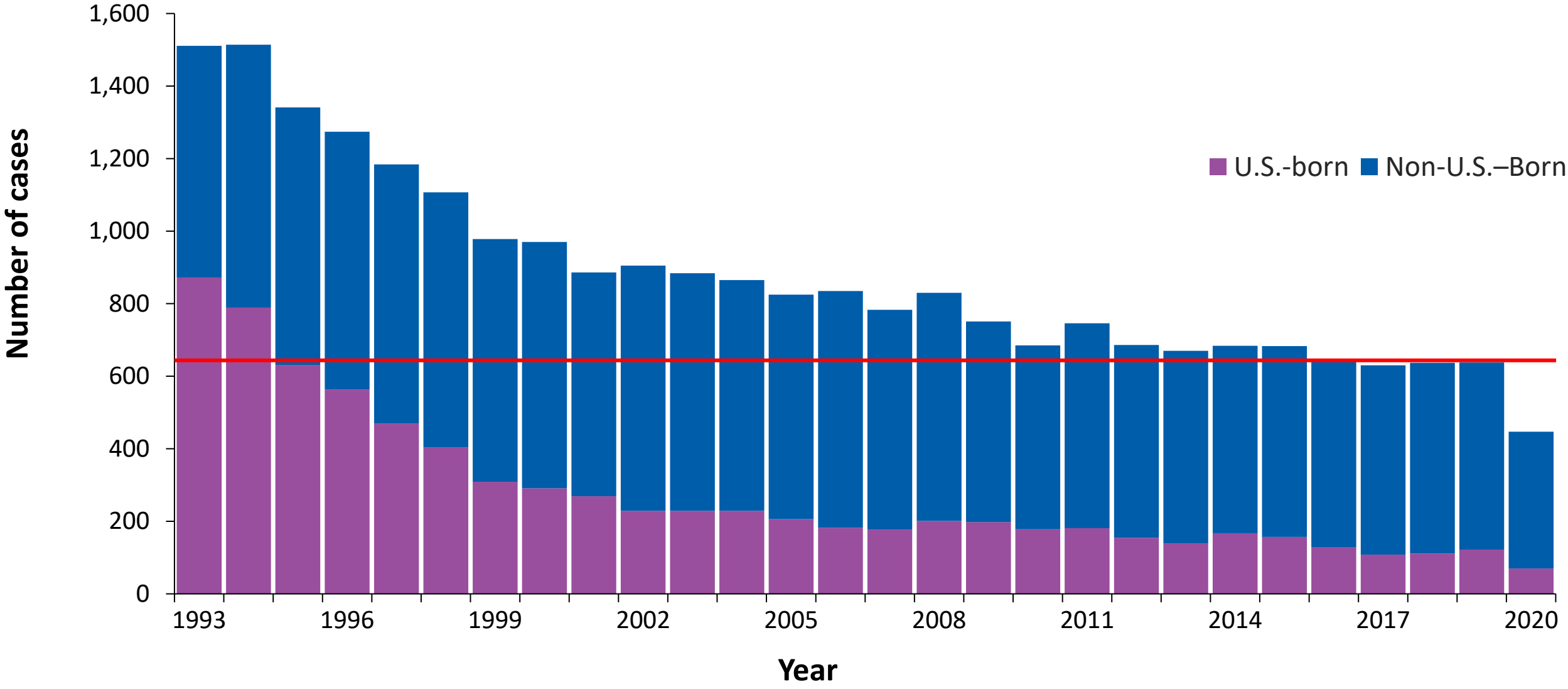
JAMA, May 17, 2000—Vol 283, No. 19

TB Cases by Isoniazid Resistance and Origin of Birth, United States, 1993–2020



Treating INH-resistant Disease

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

Lancet Respir Med 2018; 6: 265–75

	Regimen	Number of datasets included	Number of events/number of patients on treatment	I^{2}**	Number of pairs used†	Propensity score matched analysis‡	
						aOR (95% CI)	Risk difference per 1000 patients treated (95% CI)
Analyses in all patients (with or without isoniazid)							
Mortality (all durations)	(H)REZ + FQ	15	25/524	12%	522	0·7 (0·4 to 1·1)	−20 (−50 to 0)
Mortality (all durations)	(H)REZ	NA	97/2174	NA	NA	1 (ref)	0 (ref)
Success	≥6(H)REZ + FQ	15	245/251	36%	248	2·8 (1·1 to 7·3)	50 (0 to 90)
Success	≥6(H)REZ	NA	1253/1350	NA	NA	1 (ref)	0 (ref)
Success (restricted to later generation FQ: Moxi/Levo/Gati)	≥6(H)REZ + FQ	15	161/165§	44%	164	2·9 (0·9 to 9·3)	60 (−20 to 140)
Success (restricted to later generation FQ: Moxi/Levo/Gati)	≥6(H)REZ	NA	1253/1350	NA	NA	1 (ref)	0 (ref)
Acquired rifampicin resistance	≥6(H)REZ + FQ	10	1/221¶	2%‖	220	0·1 (0·0 to 1·2)	−30 (−60 to 0)
Acquired rifampicin resistance	≥6(H)REZ	NA	44/1160¶	NA	NA	1 (ref)	0 (ref)
Patients who received isoniazid excluded							
Mortality	REZ + FQ	14	8/219	0	205	0·4 (0·2 to 1·1)	−20 (−60 to 20)
Mortality	REZ	NA	41/1054	NA	NA	1 (ref)	0 (ref)
Success	≥6REZ + FQ	14	131/135	33%	127	5·4 (1·8 to 16·6)	130 (−40 to 230)
Success	≥6REZ	NA	837/927	NA	NA	1 (ref)	0 (ref)
Acquired rifampicin resistance	≥6REZ + FQ	9	1/111	NE**	107	0·1 (0·0 to 1·0)	−70 (−140 to 0)
Acquired rifampicin resistance	≥6REZ	NA	43/813	NA	NA	1 (ref)	0 (ref)

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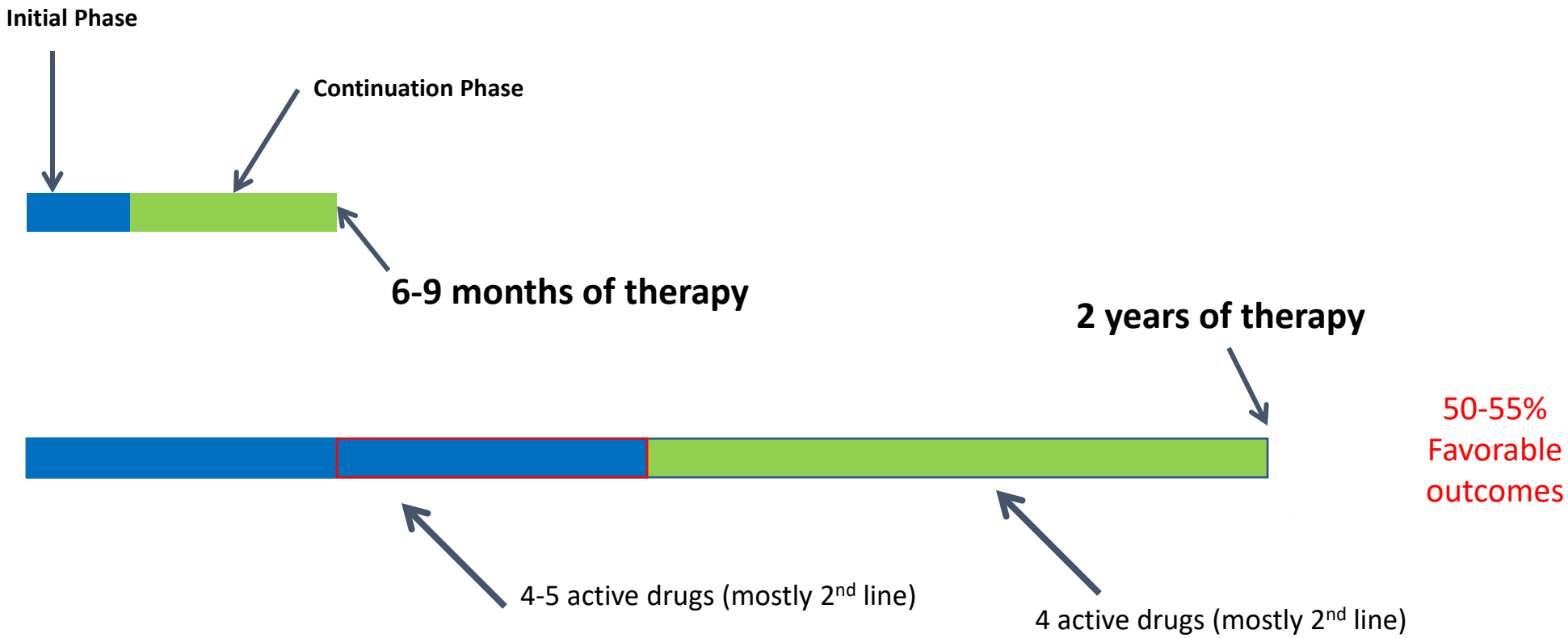
Analyses in all patients (with or without isoniazid)							
Mortality (all durations)	(H)REZ + FQ	15	25/524	12%	522	0·7 (0·4 to 1·1)	−20 (−50 to 0)
Mortality (all durations)	(H)REZ	NA	97/2174	NA	NA	1 (ref)	0 (ref)
Success	≥6(H)REZ + FQ	15	245/251	36%	248	2·8 (1·1 to 7·3)	50 (0 to 90)
Success	≥6(H)REZ	NA	1253/1350	NA	NA	1 (ref)	0 (ref)
Success (restricted to later generation FQ: Moxi/Levo/Gati)	≥6(H)REZ + FQ	15	161/165§	44%	164	2·9 (0·9 to 9·3)	60 (−20 to 140)
Success (restricted to later generation FQ: Moxi/Levo/Gati)	≥6(H)REZ	NA	1253/1350	NA	NA	1 (ref)	0 (ref)
Acquired rifampicin resistance	≥6(H)REZ + FQ	10	1/221¶	2%‖	220	0·1 (0·0 to 1·2)	−30 (−60 to 0)
Acquired rifampicin resistance	≥6(H)REZ	NA	44/1160¶	NA	NA	1 (ref)	0 (ref)
Patients who received isoniazid excluded							
Mortality	REZ + FQ	14	8/219	0	205	0·4 (0·2 to 1·1)	−20 (−60 to 20)
Mortality	REZ	NA	41/1054	NA	NA	1 (ref)	0 (ref)
Success	≥6REZ + FQ	14	131/135	33%	127	5·4 (1·8 to 16·6)	130 (−40 to 230)
Success	≥6REZ	NA	837/927	NA	NA	1 (ref)	0 (ref)
Acquired rifampicin resistance	≥6REZ + FQ	9	1/111	NE**	107	0·1 (0·0 to 1·0)	−70 (−140 to 0)
Acquired rifampicin resistance	≥6REZ	NA	43/813	NA	NA	1 (ref)	0 (ref)

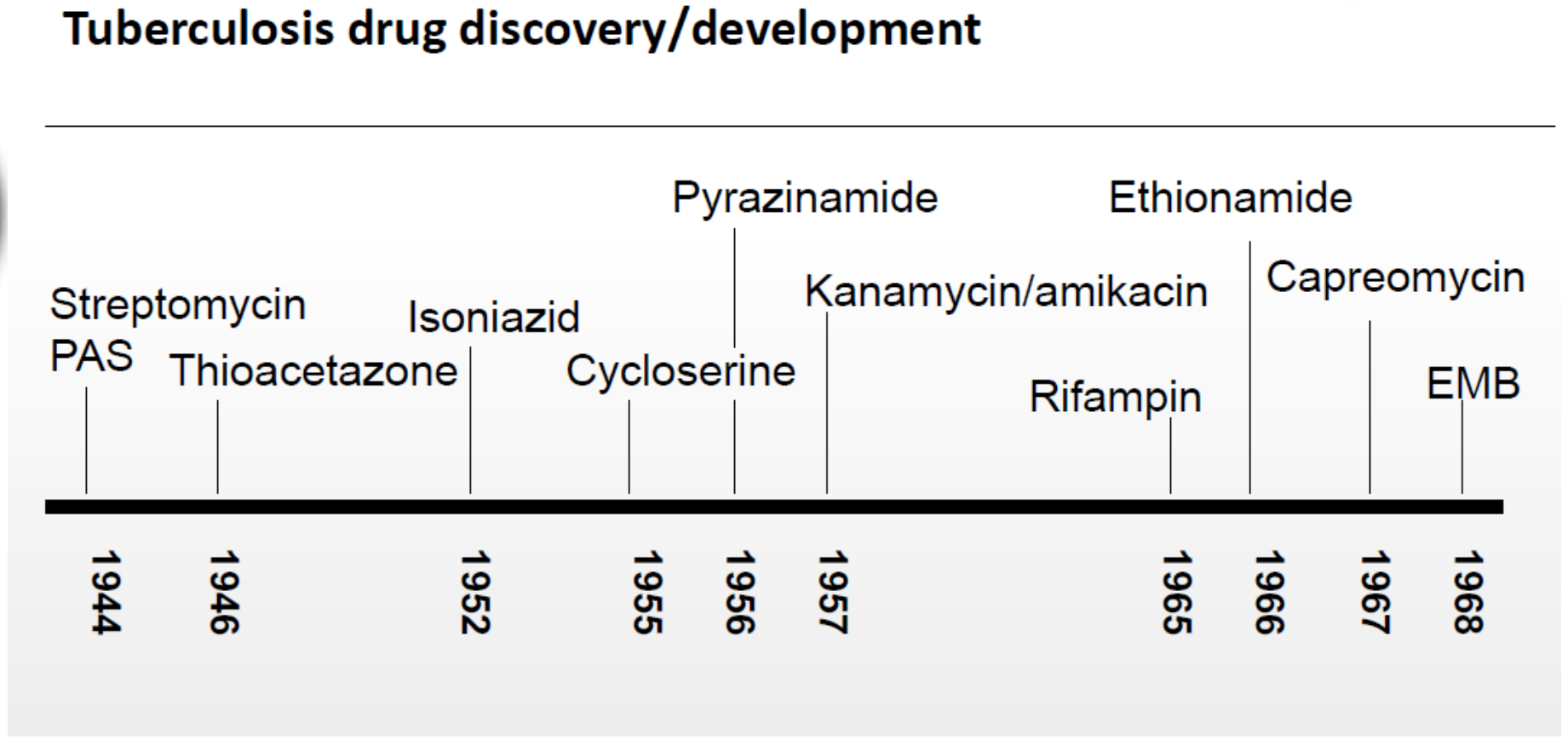
INH-Resistant TB Disease

- INH resistant TB in the US:
  - 643 cases in 2019, 419 cases in 2020
  - 8-9% treatment naïve patients, 13-19% in patients with previous TB
  - Similar rates in US-born and non-US born
- Clear improvement in treatment outcomes with addition of a fluoroquinolone
- Treatment is considered adequate once the FQ is added. Treatment prior to FQ addition is not counted toward length of treatment

Historical Treatment for Drug Susceptible versus MDR TB



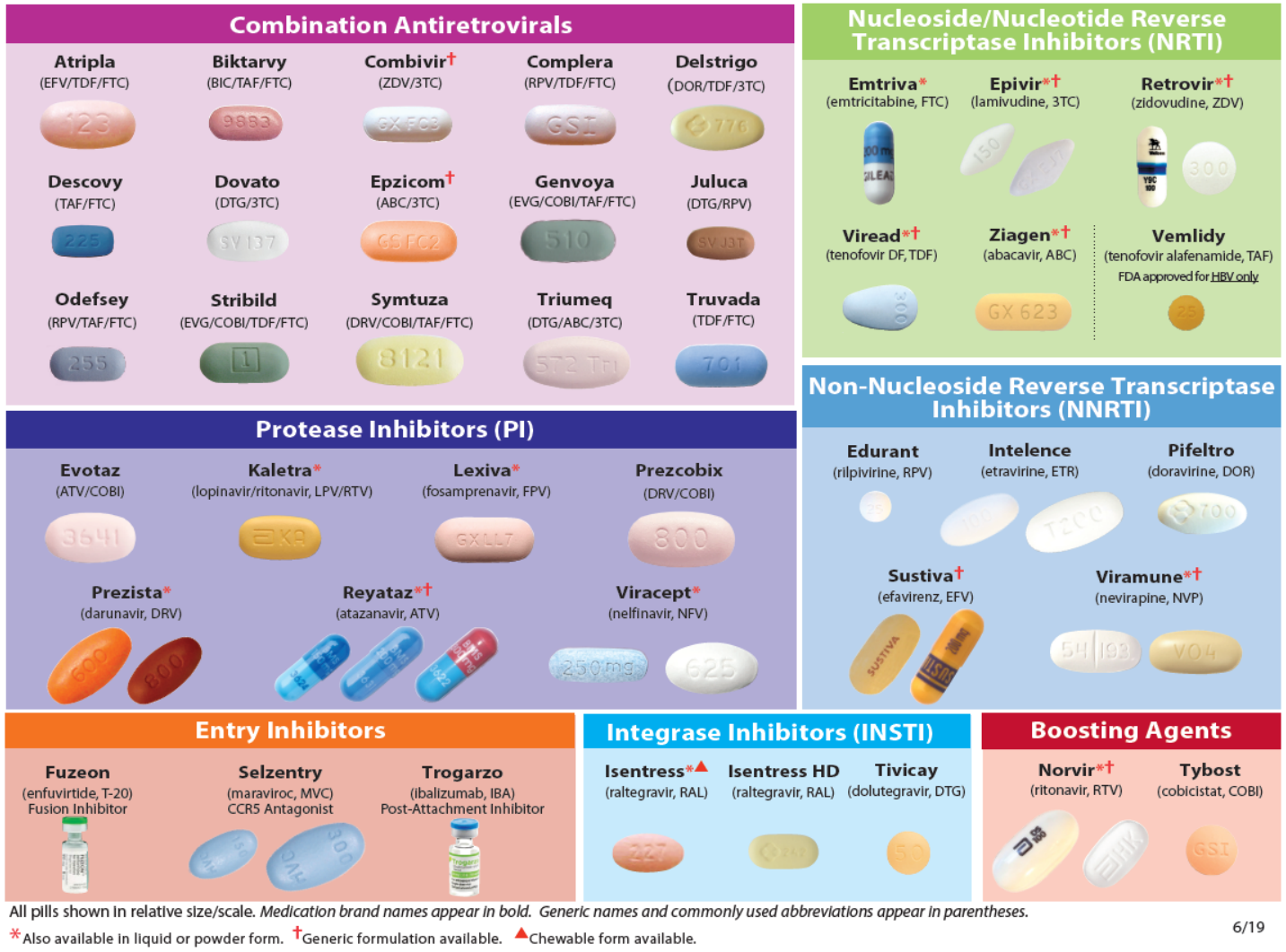
Drugs for TB


Tuberculosis drug discovery/development
Streptomycin
PAS
Thioacetazone
Isoniazid
Cycloserine
Pyrazinamide
Kanamycin/amikacin
Rifampin
Ethionamide
Capreomycin
EMB
1944
1946
1952
1955
1956
1957
1965
1966
1967
1968

HIV Medications

(Developed since 1968)

HIV Medication Chart

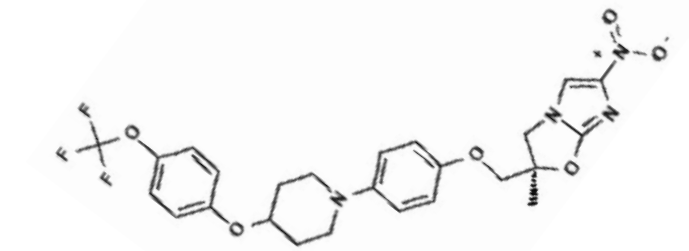


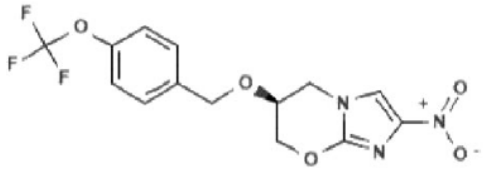
https://anthc.org/wp-content/uploads/2015/12/HIV_MedChart_052016.pdf

TB Medications

(Developed since 1968)

- Bedaquiline in 2012
- Delamanid in 2014 (but not in US)
- Pretomanid 2019





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

Am J Respir Crit Care Med Vol 200, Iss 10, pp e93–e142, Nov 15, 2019

	Drugs	Comments
Group A	Levofloxacin or moxifloxacin; bedaquiline; linezolid	Include all three medicines (unless they cannot be used)
Group B	Clofazimine; cycloserine or terizidone	Add both medicines (unless they cannot be used)
Group C	Ethambutol; delamanid; pyrazinamde; imipenem-cilastatin or meropenem (both must be given with clavulanic acid); amikacin or streptomycin; ethionamide or prothionamide; para-aminosalicylic acid	Add to complete a four-drug to five-drug regimen and when medicines from groups A and B cannot be used

Table 2: 2018 WHO grouping of medications for second-line drug-resistant tuberculosis[130]

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 determined the revised XDR-TB definition will need to:

- Consider the key role of FQNs in the treatment of MDR/RR-TB
- Disregard the 2nd line injectable agents
- Consider the important role of the new or repurposed drugs in Group A especially bedaquiline and linezolid as part of the longer regimens, and the BPaL regimen
- Be feasible for implementation by NTPs
- Be practical and useful for making clinical decisions and when deciding on eligibility while designing treatment regimens
- Identify a resistance pattern that signals the need for an important change in the treatment options

Courtesy of Barbara Seaworth, MD

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

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

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

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

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

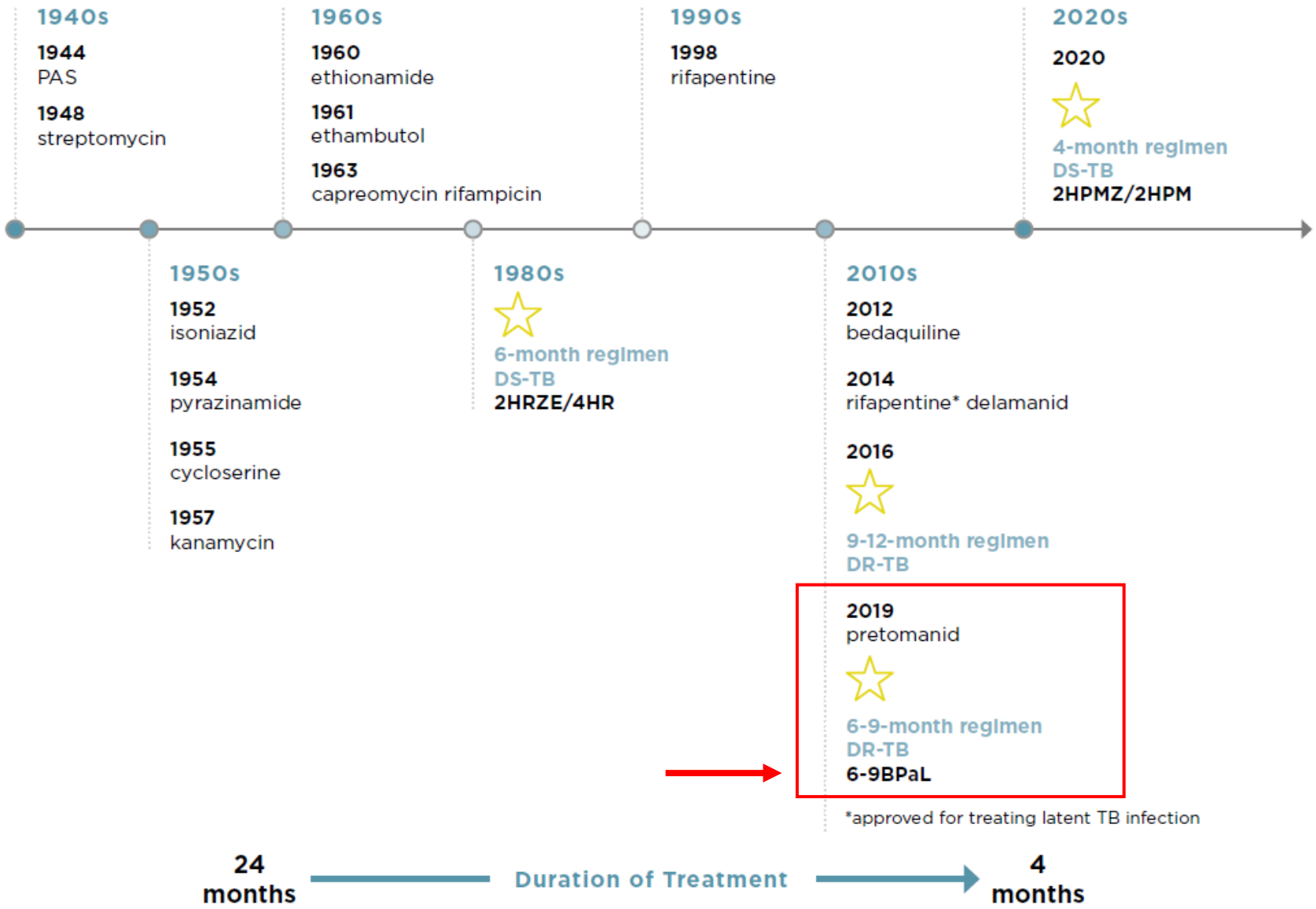
Group A drugs are currently levofloxacin or moxifloxacin, bedaquiline and linezolid; therefore, XDR-TB is MDR/RR-TB that is resistant to a fluoroquinolone and either bedaquiline or linezolid (or both). The Group A drugs may change in the future; therefore, the terminology "Group A will apply to any Group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

Annex 1: Grouping of medicines recommended for use in longer MDR-TB regimens[a]

Groups & steps	Medicine	
Group A: Include all three medicines	levofloxacin *OR*	Lfx
	moxifloxacin	Mfx
	bedaquiline[b,c]	Bdq
	linezolid[d]	Lzd
Group B: Add one or both medicines	clofazimine	Cfz
	cycloserine *OR*	Cs
	terizidone	Trd
Group C: Add to complete the regimen and when medicines from Groups A and B cannot be used	ethambutol	E
	delamanid[c,e]	Dlm
	pyrazinamide[f]	Z
	imipenem–cilastatin *OR*	Ipm–Cln
	meropenem[g]	Mpm
	amikacin *OR*	Am
	streptomycin[h]	(S)
	ethionamide *OR*	Eto
	prothionamide[i]	Pto
	p-aminosalicylic acid[f]	PAS

Courtesy of Barbara Seaworth, MD

FIGURE 1: TUBERCULOSIS TREATMENT SHORTENING MILESTONES



https://www.treatmentactiongroup.org/publication/an-activists-guide-to-shorter-treatment-for-drug-sensitive-tuberculosis/

BPaL Study - Laboratory

- Primary endpoint: unfavorable outcome, defined as treatment failure (bacteriologic or clinical)
- All patients were categorized as having XDR or MDR TB (WHO definition?)
- 2 sputum samples were obtained for smear microscopy and culture
  - Baseline, weeks 1, 2, 4, 6, 8, them monthly through week 26
  - Follow up months 1,2,3 and every 3 months through month 24
- Median number of 29 cultures (range, 20-40) collected to determine the primary endpoint
- Mtb isolates were identified by ‘molecular methods’
- Mtb isolates were sent to a central lab for
  - MIC of bedaquiline, pretomanid and linezolid
  - MGIT testing of rifampin, isoniazid, streptomycin, ethambutol, moxifloxacin, kanamycin

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THERE ARE 2 TYPES OF TECHS...
THOSE WHO CAN DEAL WITH SPUTUM
AND THEN...
THERE'S EVERYONE ELSE.

BPaL Regimen - Results

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 5, 2020 VOL. 382 NO. 10

Treatment of Highly Drug-Resistant Pulmonary Tuberculosis

Francesca Conradie, M.B., B.Ch., Andreas H. Diacon, M.D., Nosipho Ngubane, M.B., B.Ch., Pauline Howell, M.B., B.Ch., Daniel Everitt, M.D., Angela M. Crook, Ph.D., Carl M. Mendel, M.D., Erica Egizi, M.P.H., Joanna Moreira, B.Sc., Juliano Timm, Ph.D., Timothy D. McHugh, Ph.D., Genevieve H. Wills, M.Sc., Anna Bateson, Ph.D., Robert Hunt, B.Sc., Christo Van Niekerk, M.D., Mengchun Li, M.D., Morounfolu Olugbosi, M.D., and Melvin Spigelman, M.D., for the Nix-TB Trial Team*

Table 2. Primary Efficacy Analysis.*

Outcome	XDR	MDR	Overall
Intention-to-treat population†			
No. of patients	71	38	109
Favorable outcome			
No. of patients	63	35	98
Percent of patients (95% CI)	89 (79–95)	92 (79–98)	90 (83–95)
Unfavorable outcome — no. (%)	8 (11)	3 (8)	11 (10)
Deaths — no.	6	1	7
Withdrawal during treatment — no.	1	0	1
Lost to follow-up after end of treatment — no.	0	1	1
Relapse — no.	1	1	2‡
Modified intention-to-treat population†			
No. of patients	70	37	107
Favorable outcome			
No. of patients	63	35	98
Percent of patients (95% CI)	90 (80–96)	95 (82–99)	92 (85–96)
Unfavorable outcome — no. (%)	7 (10)	2 (5)	9 (8)
Deaths — no.	5	1	6
Withdrawal during treatment — no.	1	0	1
Relapse — no.	1	1	2‡
Per-protocol population			
No. of patients	68	37	105
Favorable outcome			
No. of patients	62	35	97
Percent of patients (95% CI)	91 (82–97)	95 (82–99)	92 (86–97)
Unfavorable outcome — no. (%)	6 (9)	2 (5)	8 (8)
Deaths — no.	5	1	6
Relapse — no.	1	1	2‡

- 57/109 patients had baseline MICs to all 3 study drugs
  - All had Pretomanid MICs ≤ 1 µg/ml
  - 54 had BDQ and LZD MICs ≤ 1 µg/ml (WHO recommended CC)
  - 2 had BDQ MICs of 2 µg/ml
  - 1 had BDQ MIC of 4 µg/ml

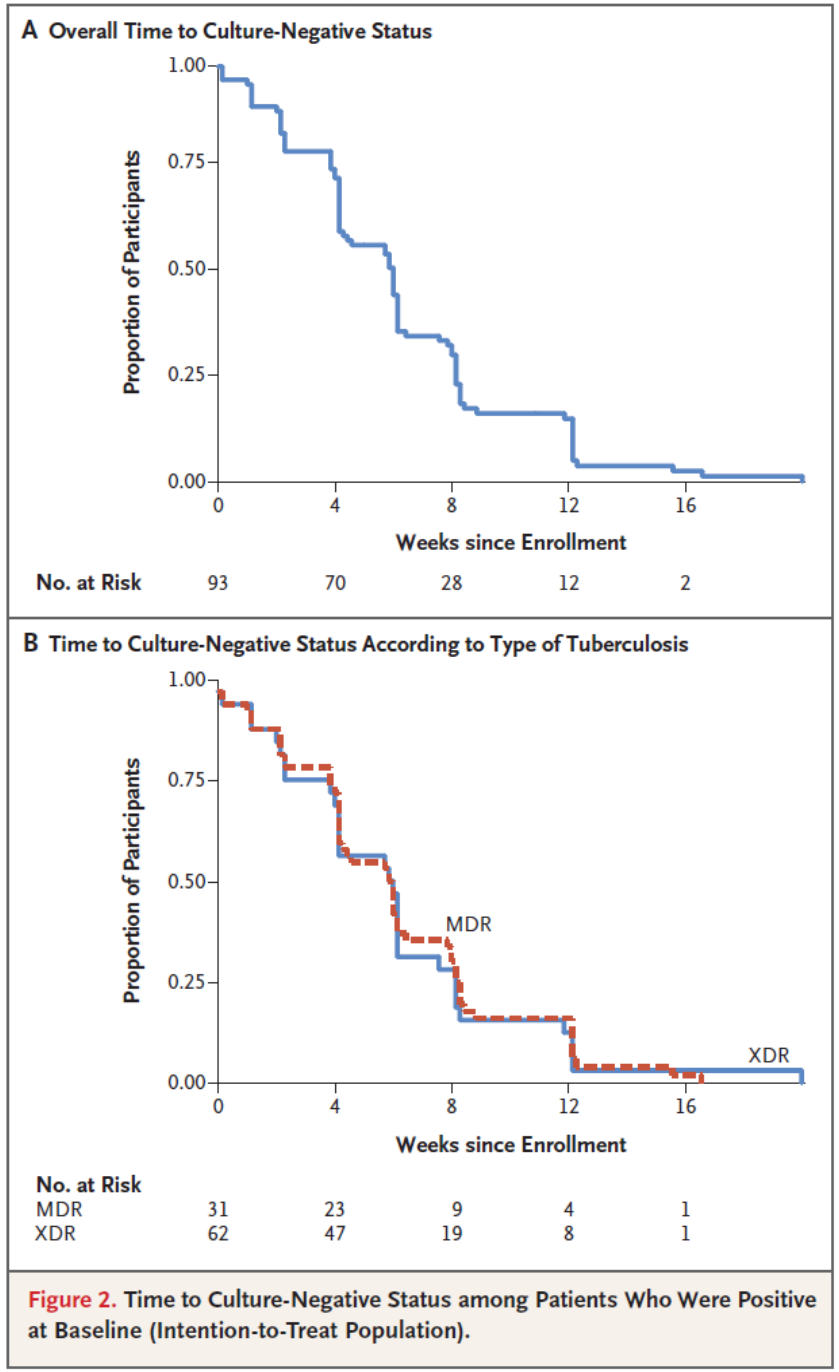

Figure 2. Time to Culture-Negative Status among Patients Who Were Positive at Baseline (Intention-to-Treat Population).

N Engl J Med 2020;382:893-902.

Future MDR studies (Randomized, Controlled Trials) - TB PRACTECAL

- Relevant Inclusion
  - Microbiological test (molecular or phenotypic) confirming the presence of *M. tuberculosis* in sputum;
  - Resistant to at least rifampicin by either molecular or phenotypic drug susceptibility test
- Relevant Exclusion
  - Known resistance to bedaquiline, pretomanid, linezolid or delamanid

- Particpants with TB isolates resistant to rifampicin by rapid molecular tests will be evaluated by MGIT DST (MGIT 960)

- 2 sputum specimens will be collected at least once monthly during treatment, every 2 months during follow up

- DSTs will be performed on pure cultures from baseline/16 weeks forward
  - MGIT DST for H,R, E, Z, Sm, Km, Cm, Mfx and/or Ofx
  - MICs for bedaquiline, pretomanid, linezolid, clofazimine +/- Mfx (when indicated)

- Mycobacterial DNA stored at baseline (D0, D7, W4 if D0/D7 unavailable)
  - Patients with culture reversion or recurrent TB will have genotyping

MDR Studies in Progress

Table 1. Clinical Trials for the Evaluation of Novel Multidrug-resistant Tuberculosis/Rifampicin-Resistant Tuberculosis Treatment Regimens

Name	Regimen	Location	Status 2/2002	Clinical Trials Number
TRUST	Levofloxacin, linezolid, cycloserine, and pyrazinamide (or clofazimine if resistant to pyrazinamide)	China	Recruiting	NCT03867136
MDR-END	Delamanid, linezolid, levofloxacin, and pyrazinamide	Korea	Fully enrolled; in follow-up	NCT02619994
STREAM Stage 2	Bedaquiline, clofazimine, ethambutol, levofloxacin, pyrazinamide, isoniazid, and prothionamide	Ethiopia, Georgia, India, Moldova, Mongolia, South Africa, and Uganda	Fully enrolled; in follow-up	NCT02409290
InDEX	Gene-derived individualized DR-TB regimen	South Africa	Recruiting	NCT03237182
endTB	Bedaquiline, moxifloxacin, linezolid, and pyrazinamide; or bedaquiline, clofazimine, levofloxacin, linezolid, and pyrazinamide; or bedaquiline, delamanid, levofloxacin, linezolid, and pyrazinamide; or delamanid, clofazimine, levofloxacin, linezolid, and pyrazinamide; or delamanid, clofazimine, moxifloxacin, and pyrazinamide	Georgia, India, Kazakhstan, Lesotho, Pakistan, Peru, and South Africa	Fully enrolled; in follow-up	NCT02754765
SimpliciTB	Bedaquiline, pretomanid, moxifloxacin, and pyrazinamide	Africa, Asia, Europe, and South America	Fully enrolled; in follow-up	NCT03338621
BEAT-Tuberculosis	Bedaquiline, delamanid, and linezolid plus levofloxacin or clofazimine	South Africa	Recruiting	NCT04062201
GRACE-TB	Individualized regimen guided by rapid molecular drug susceptibility tests	China	Not yet recruiting	NCT03604848
DRAMATIC	Levofloxacin, bedaquiline, linezolid, delamanid, and clofazimine	Vietnam, The Philippines	Recruiting	NCT03828201
BEAT-TB	Bedaquiline, delamanid, linezolid, and clofazimine	India	Fully enrolled	CTRI/2019/01/017310

Definition of abbreviation: DR-TB = drug-resistant TB.
Adapted from Reference 16.

INT J TUBERC LUNG DIS 26(7):590–591

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INT J TUBERC LUNG DIS 26(7):590–591

When do we worry about bedaquiline resistance?

Assessment of epidemiological and genetic characteristics and clinical outcomes of resistance to bedaquiline in patients treated for rifampicin-resistant tuberculosis: a cross-sectional and longitudinal study

Lancet Infect Dis 2022; 22: 496–506

Nazir Ahmed Ismail, Shaheed Vally Omar*, Harry Moultrie*, Zaheda Bhyat, Francesca Conradie, M Enwerem, Hannetjie Ferreira, Jennifer Hughes, Lavania Joseph, Yulene Kock, Vancy Letsaolo, Gary Maartens, Graeme Meintjes, Dumisani Ngcamu, Nana Okozi, Xavier Padanilam, Anja Reuter, Rodolf Romero, Simon Schaaf, Julian te Riele, Ebrahim Variava, Minty van der Meulen, Farzana Ismail†, Norbert Ndjeka†*

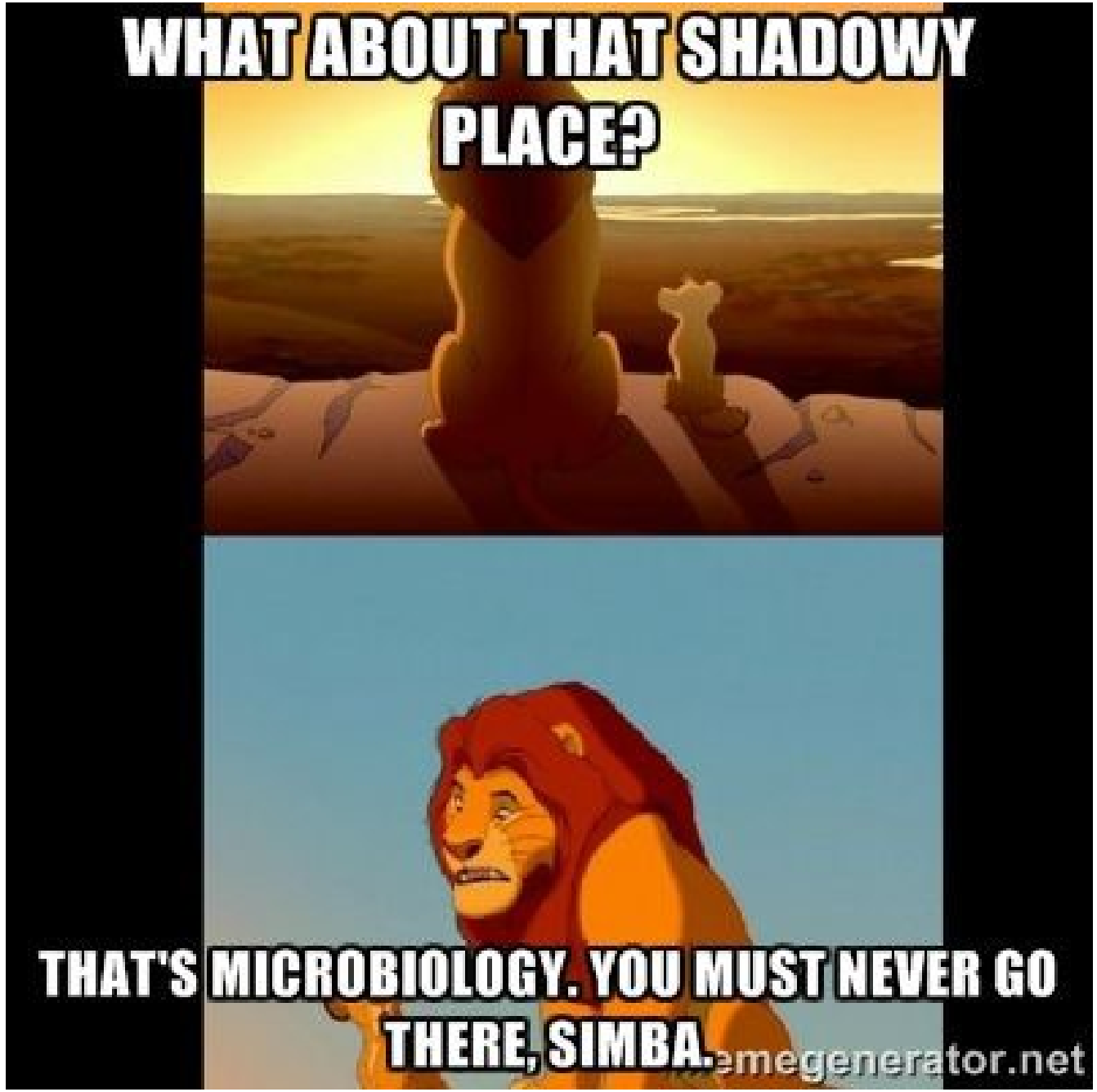
- 8041 patients starting bedaquiline-based treatment had samples collected at baseline, month 2, month 6
- Baseline BDQ resistance was 3.8%
  - BDQ naïve 72/2023, 3.6%
  - Prior BDQ or clofazimine, 4/19, 21.1%
- BDQ resistance was associated with previous exposure to bedaquiline or clofazimine (OR 7.1)
- Rv0678 mutations were associated with resistance
- Resistance emerged in 12/695 (2.3%) of patients on treatment with median time to emergence of 90 days (range 21-654 days)
- Successful treatment outcomes were lower in patients with bedaquiline resistance

Conclusions

- Treatment regimens for TB are shortening, turnaround time for susceptibility testing should shorten as well

- Fluoroquinolones are playing a larger role in TB treatments for both drug susceptible and drug resistant TB. It may be time to consider them first line drugs

- TB treatment regimens for drug resistant TB in the US and worldwide increasingly contain bedaquiline, fluoroquinolones and linezolid. Mechanisms for testing and surveillance need to grow in the direction the treatment regimens are taking us


WHAT ABOUT THAT SHADOWY PLACE?
THAT'S MICROBIOLOGY. YOU MUST NEVER GO THERE, SIMBA.
emegenerator.net

Thank you for attention and for all that you do for our patients

Questions?

Lisa Y Armitige, MD, PhD

Lisa.Armitige@dshs.texas.gov