Multidrug-resistant Tuberculosis

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내용

1. A Trial of a Shorter Regimen for Rifampin-Resistant Tuberculosis. Nunn A.J. et al. N Engl J Med 2019;380:1201-13.
2. Treatment of Highly Drug-Resistant Pulmonary Tuberculosis. Conradied F. et al. N Engl J Med 2020;382:893-902.
3. A regimen containing bedaquiline and delamanid compared to bedaquiline in patients with drug-resistant tuberculosis. Olayanju O. et al. Eur Respir J 2020;55:1901181.
4. Early Bactericidal Activity of Different Isoniazid Doses for Drug Resistant TB (INHindsight): A Randomized Open-label Clinical Trial. Dooley K.E. et al. Dooley K.E. et al. Am J Respir Crit Care Med 2020;201:1416–1424.
5. Global burden of latent multidrug-resistant tuberculosis: trends and estimates based on mathematical modelling. Knight G.W. et al. Lancet Infect Dis 2019;19:903-12.
6. Tuberculosis Preventive Therapy for Individuals Exposed to Drug-resistant Tuberculosis: Feasibility and Safety of a Community-based Delivery of Fluoroquinolone containing Preventive Regimen. Malik A.A. et al. Clinical Infectious Diseases 2020;70(9):1958-65.

1. STREAM

- Observational cohort about Bangladesh regimen, 9-11 months
- Relapse-free cure: 87.9%
  - Van Deun A et al. Am J Respir Crit Care Med 2010;182:684-92.
- A randomized, phase 3, non-inferiority trial
- 9-11 months regimen vs. a long regimen (20 months)
- ≥ 18 years, pulmonary TB
- Exclusion: pre-XDR-TB or XDR-TB
- Regimen
  - 16 weeks Km, H, Pto, high dose Mfx, Cfz, E, Z + 40 weeks High dose Mfx, Cfz, E, Z

- Nunn A.J. et al. N Engl J Med 2019;380:1201-13.

1. STREAM

- Primary: favorable status at 132 weeks

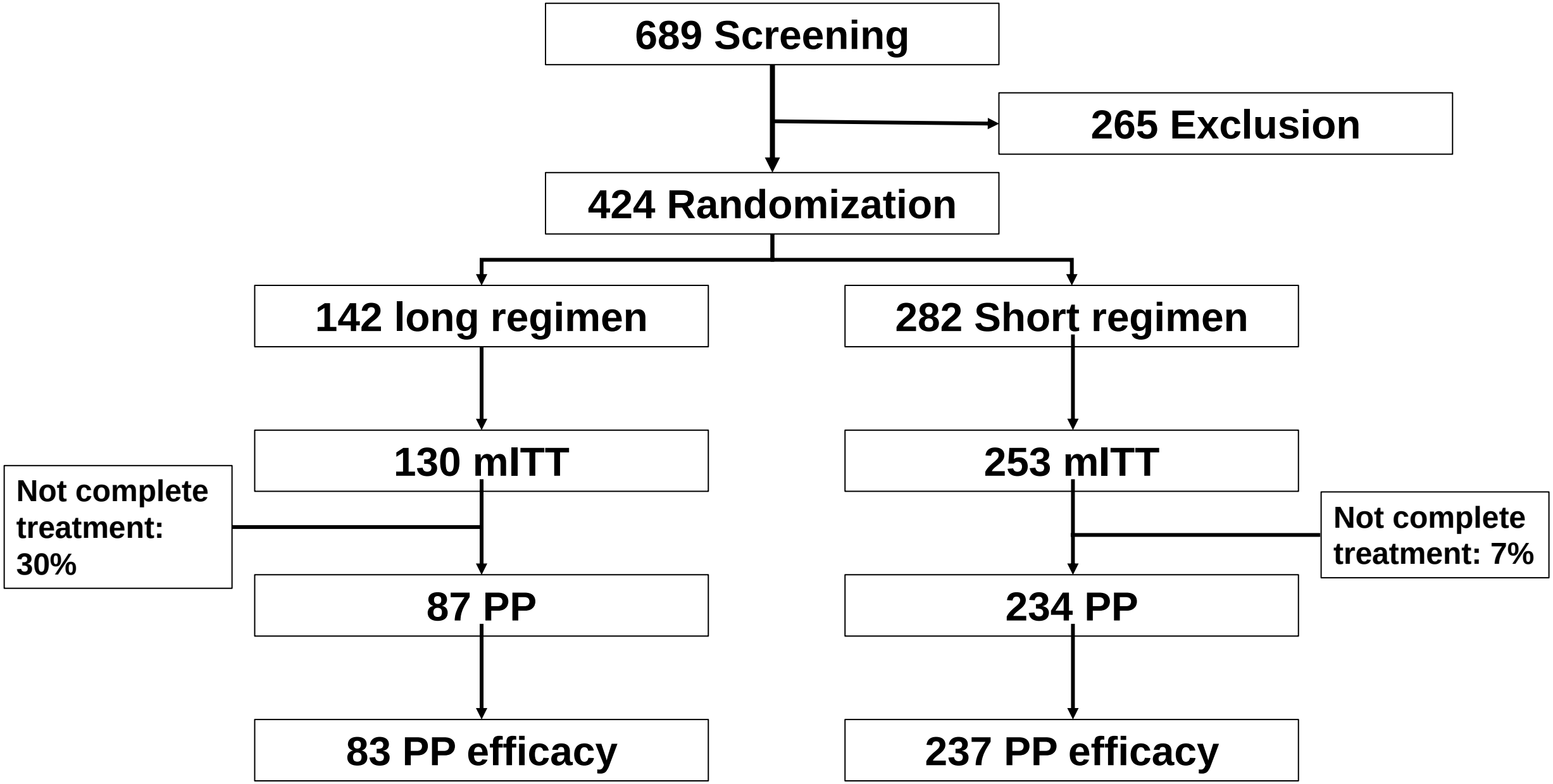
  ADR ≥ 3

- Secondary: times to smear and culture conversions; acquired resistance to FQNs, aminoglycosides, Z

  Death, severe ADR, QT prolongation

- 2:1 randomization

- Nunn A.J. et al. N Engl J Med 2019;380:1201-13.



- Nunn A.J. et al. N Engl J Med 2019;380:1201-13.

1. STREAM

Characteristic	Long (n=130)	Short (n=253)	Total (n=383)
Male	63.8%	59.7%	61.1%
Age, ≥45	16.2%	20.2%	18.8%
Weight>50kg	54.6%	53.8%	54.0%
HIV	30.8%	33.6%	32.6%
Advanced in radiology	31.2%	35.6%	34.1%
Cavity	77.6%	77%	77.2%
QTcF, ≥450	0.8%	2.0%	1.6%

- Nunn A.J. et al. N Engl J Med 2019;380:1201-13.

1. STREAM

Outcome	mITT		PP	
	Long	Short	Long	Short
Favorable	79.8%	78.8%	80.7%	81.9%
Unfavorable	20.2%	21.2%	19.3%	18.1%

Outcomes	Long	Short	Total
ADR, Grade 3-5	45.4%	48.2%	47.3%
Serious ADR	37.6%	32.3%	34.0%
Death	6.4%	8.5%	7.8%

- Nunn A.J. et al. N Engl J Med 2019;380:1201-13.

STREAM stage 2 (NCT02409290)

- Phase 3
- China, Ethiopia, Georgia, India, Indonesia, Republic of Moldova, Mongolia, South Africa, Uganda, Vietnam

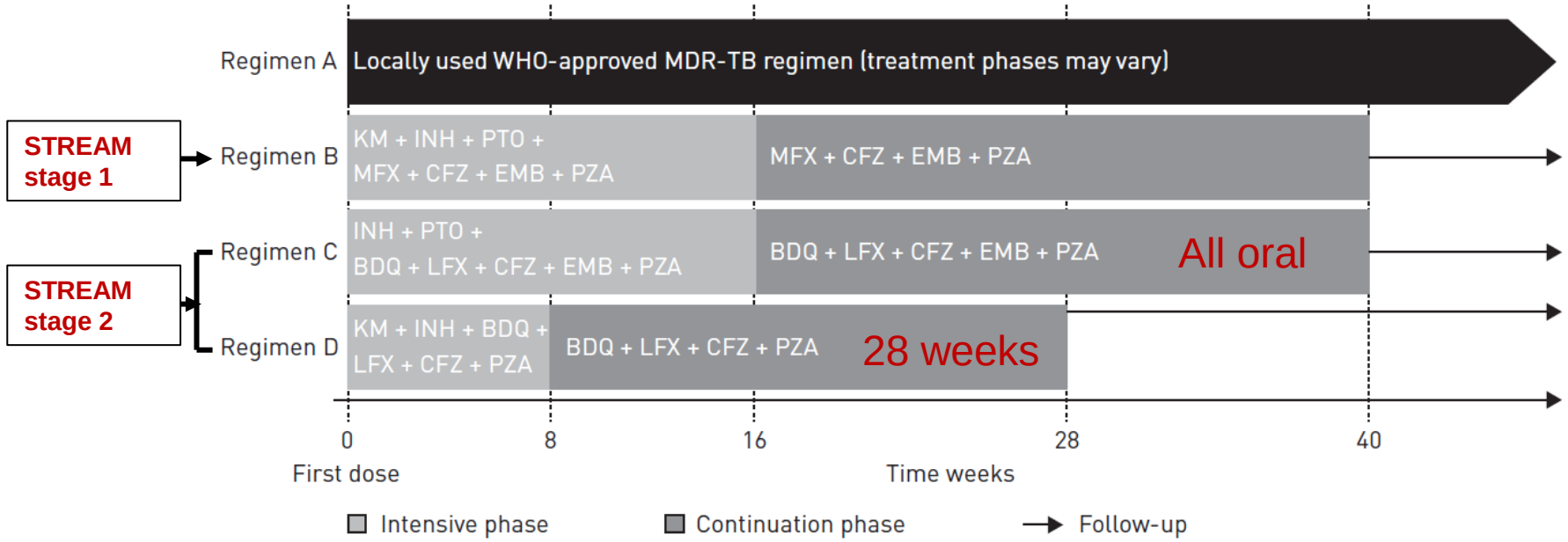


FIGURE 1 STREAM (Evaluation of a Standardised Treatment Regimen of Anti-tuberculosis Drugs for Patients with Multidrug-resistant Tuberculosis) treatment regimens. WHO: World Health Organization; MDR-TB: multidrug-resistant tuberculosis; KM: kanamycin; INH: isoniazid; PTO: prothionamide; MFX: moxifloxacin; CFZ: clofazimine; EMB: ethambutol; PZA: pyrazinamide; BDQ: bedaquiline; LFX: levofloxacin.

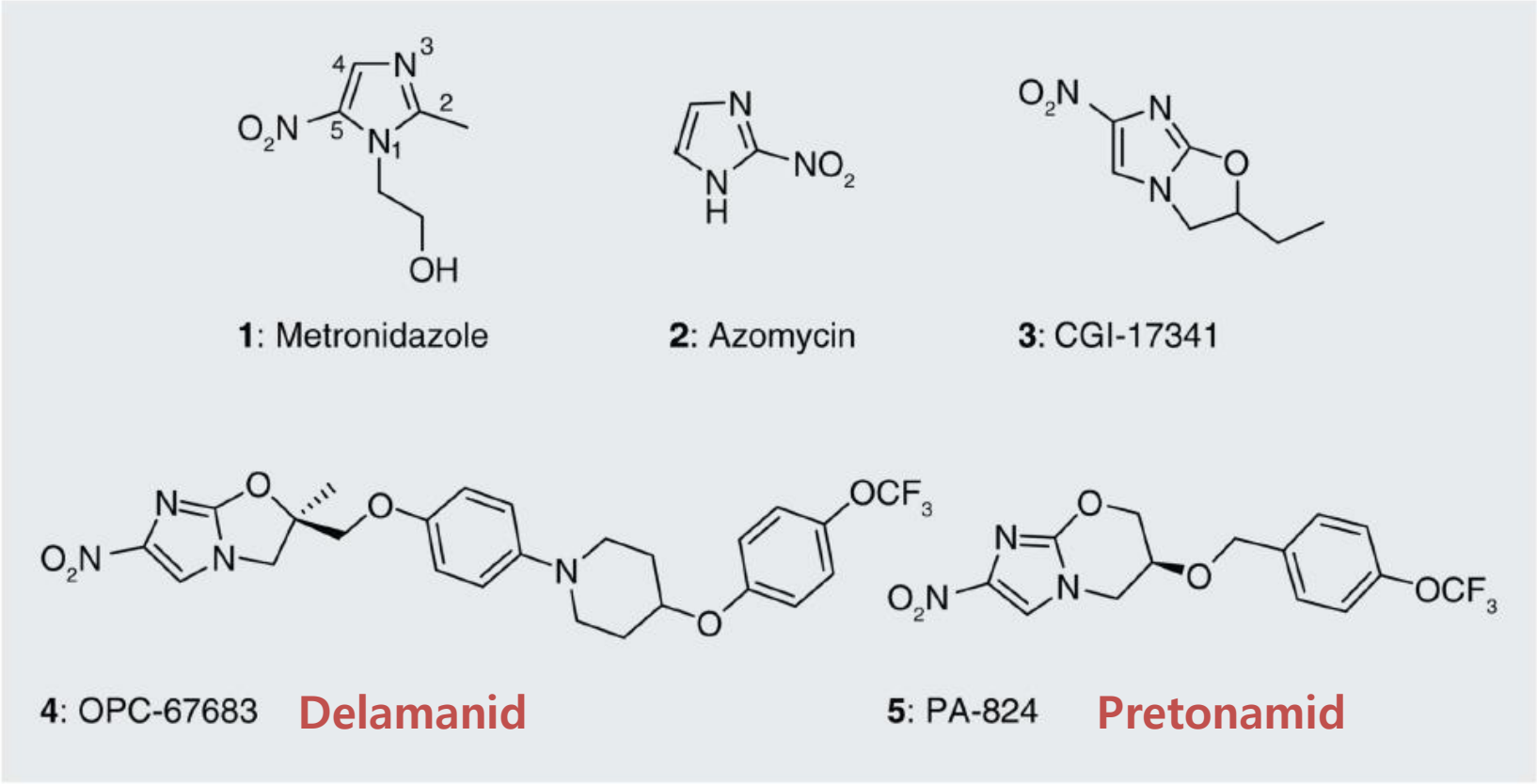
- Moodley R. et al. Eur Respir Rev 2016; 25: 29–35

2. Nix-TB

- BPaL: Bedaquiline + Pretomanid + Linezolid
- Pretonamid
- Novel nitroimidazole
- Inhibit mycolic acid biosynthesis
- NO release under anaerobic conditions → a respiratory poison against nonreplicating bacteria
- Approved by FDA: as part of a combination regimen with Bdq and Lzd for pulmonary XDR- or complicated MDR-TB

- Conradied F. et al. N Engl J Med 2020;382:893-902.

Nitroimidazole

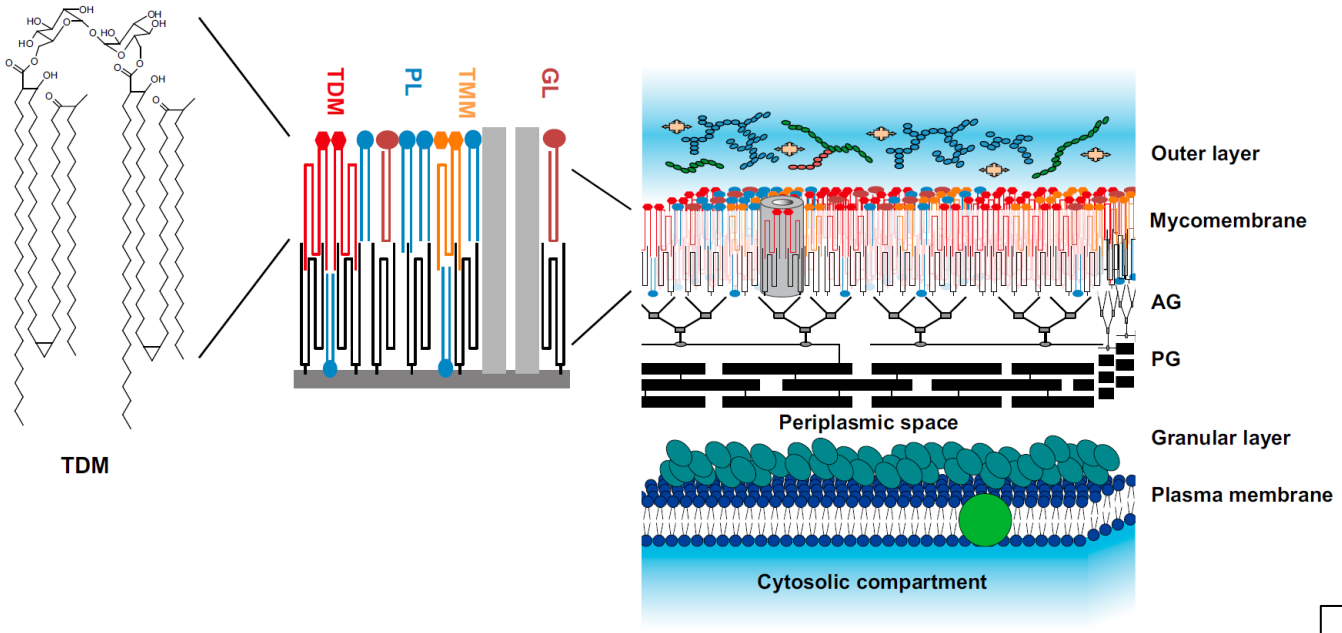


CGI-17341: **bicyclic nitroimidazoles,** active against drug-susceptible as well as MDR Mtb. However, further development was abandoned due to its **mutagenicity**
A few years prior to the discovery of OPC-67683, PathoGenesis (now Novartis) came out with their lead compound PA-824 from a series of over 300 nitroimidazooxazines, which showed increased activity against Mtb with potential to decrease the duration of therapy

Mukherjee, et al. Future Med Chem 2011;3:1427

Mechanism of action

- Mycolic acid
  - 2-alkyl, 3-hydroxy long-chain fatty acids
  - The hallmark of the cell envelope of *Mycobacterium tuberculosis*



Marrakchi et al. Chemistry & Biology 2014;21:67

Activity against Intracellular Mycobacteria in Human Macrophages

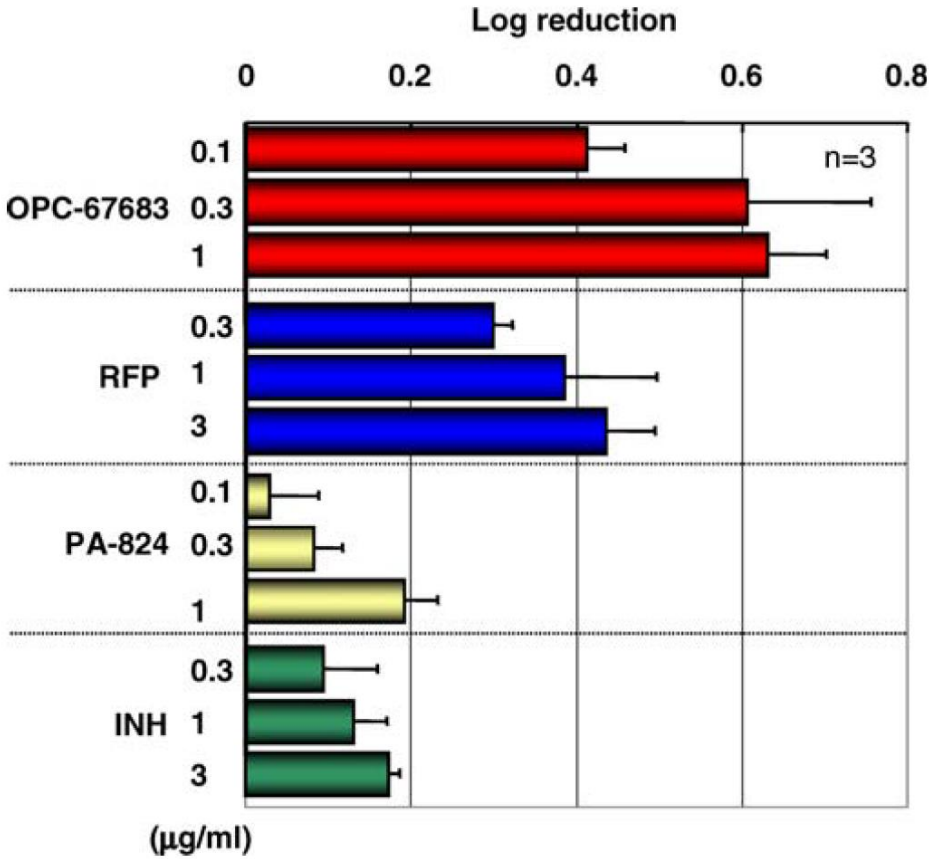


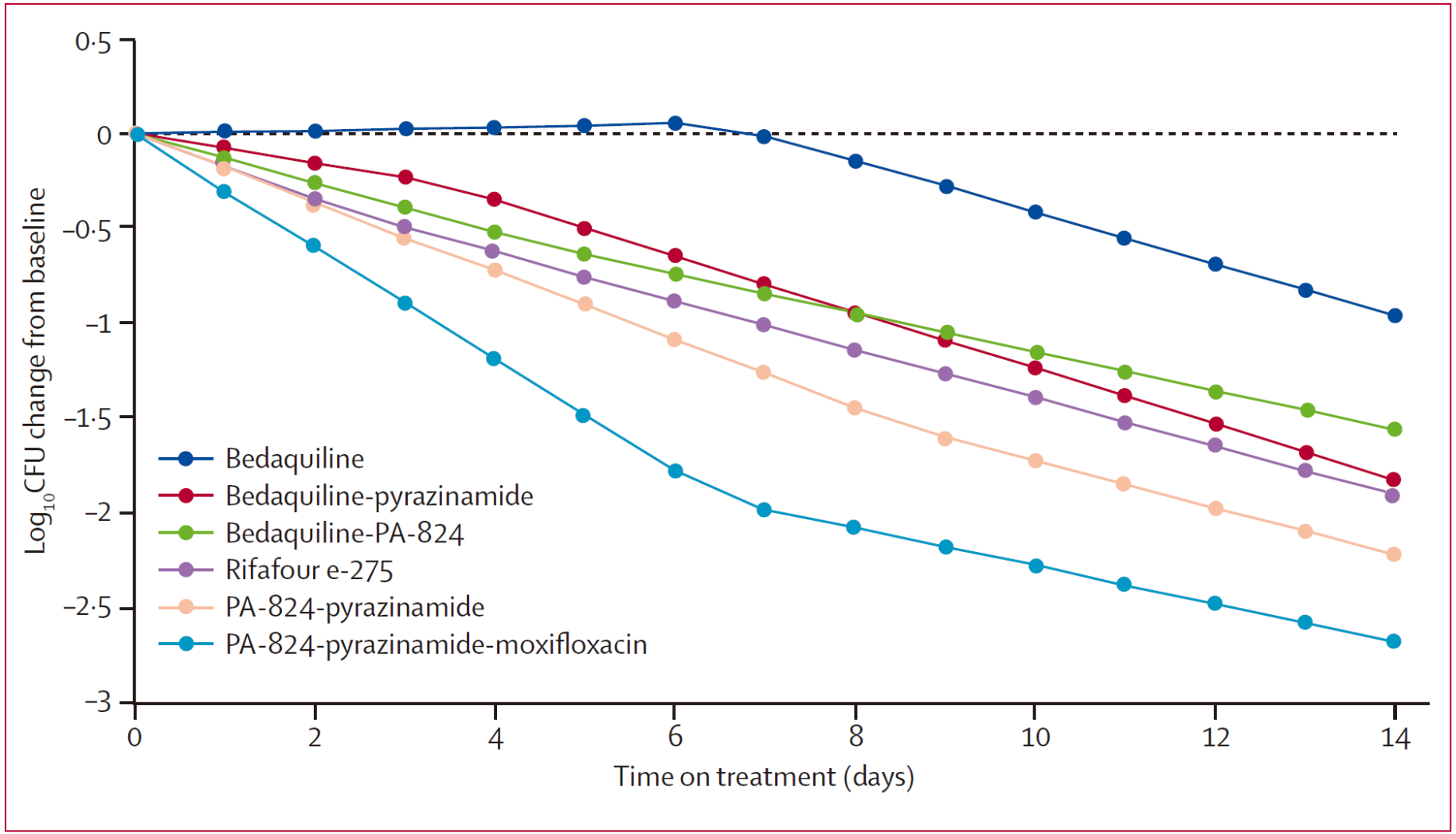
Figure 3. Effect of Pulsed Exposures to OPC-67683, RFP, INH, and PA-824 on the Intracellular Growth of *M. tuberculosis* H37Rv within THP-1 Cells

Infected cells were incubated with the test compound for 4 h, washed, cultured until 68 h at 37 °C, plated on 7H11 agar, and counted for colonies after 16 d of growth at 37 °C. Values represent mean ± S.D ($n = 3$).

doi:10.1371/journal.pmed.0030466.g003

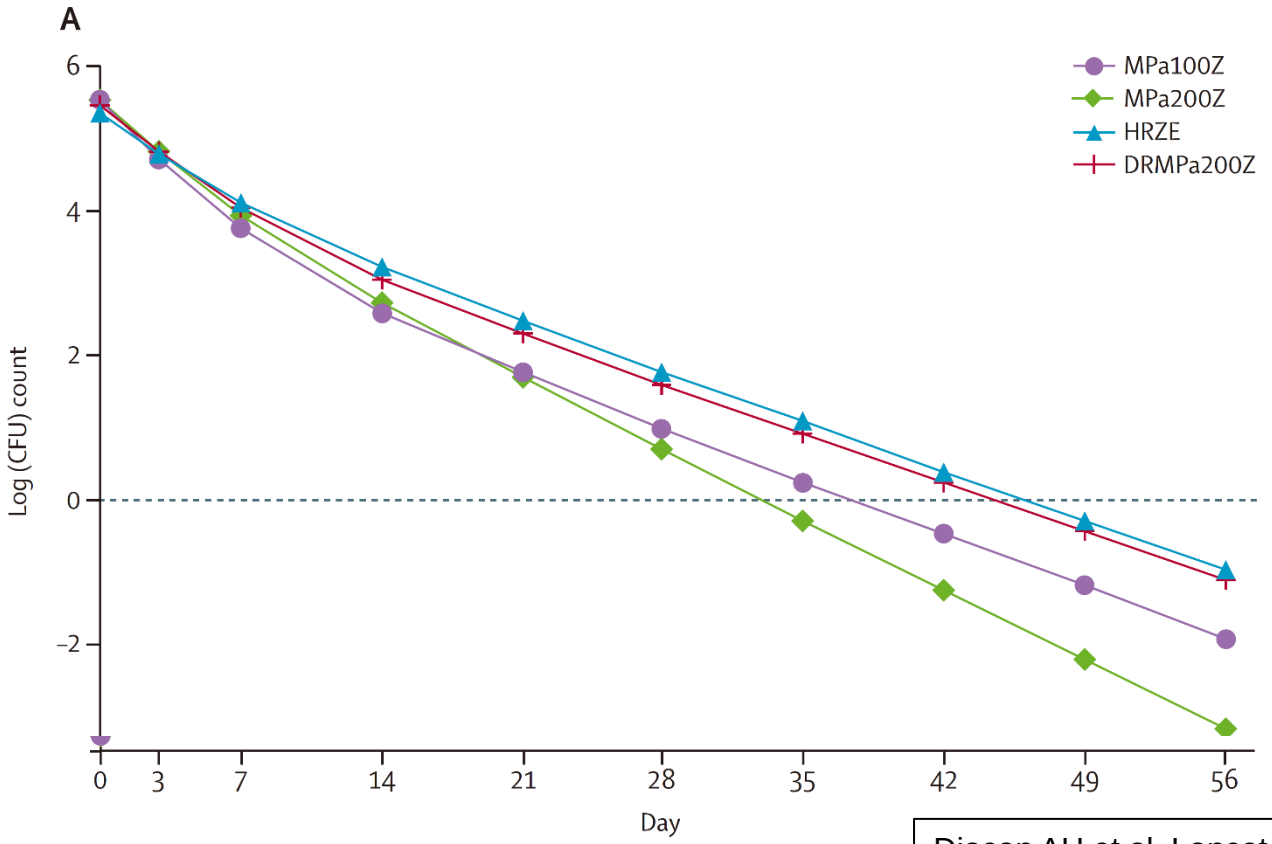
Matsumoto M, et al. PLOS Med 2006;3:e466

- 14 day EBA study, phase IIa
- Smear positive drug susceptible pulmonary TB
- n=85



Diacon AH et al. Lancet 2012;380:986

- Phase 2b study, first 8 weeks treatment
- Smear positive pulmonary TB
- 207 patients: randomized MPa100Z, MPa200Z, HREZ
- 26 MDR-TB: nonradimozed: MPa200Z (DRMPa200Z)
- Primary endpoint: bactericidal activity (change of log_{10}CFU counts)



Diacon AH et al. Lancet 2015;385:1738

2. Nix-TB

- open-label, single-group
- XDR-TB, not responsive to treatment, or second-line regimen discontinued because of side effects
- Duration: 26 weeks, 39 weeks → culture positive at week 16
- three study sites in South Africa
- The primary end point: unfavorable outcome, all-cause mortality, the incidence of ADRs

- Conradied F. et al. N Engl J Med 2020;382:893-902.

2. Nix-TB

Characteristic	Value
Age	35 (17-60)
Male	57 (52)
Black	83 (76)
Median BMI	19.7 (12.4-41.1)
HIV	56 (51)
Cavities	92 (84)
Previous TB drugs	7 (3-13)

- Conradied F. et al. N Engl J Med 2020;382:893-902.

2. Nix-TB

Outcome (ITT population)	XDR	MDR	Total
Favorable	63 (89)	35 (92)	98 (90)
Unfavorable	8 (11)	3 (8)	11 (10)
Relapse	1	1	2

Event	Lzd 600 mg bid	Lzd 1200 mg qd	Overall
ADR	44 (100)	65 (100)	109 (100)
ADR leading to death	4 (9)	2 (3)	6 (6)
Serious ADR	13 (30)	6 (9)	19 (17)
Grade 3 or 4 ADR	27 (61)	35 (54)	62 (57

- 88 patients (81%) were reported to have peripheral neuropathy

- Conradied F. et al. N Engl J Med 2020;382:893-902.

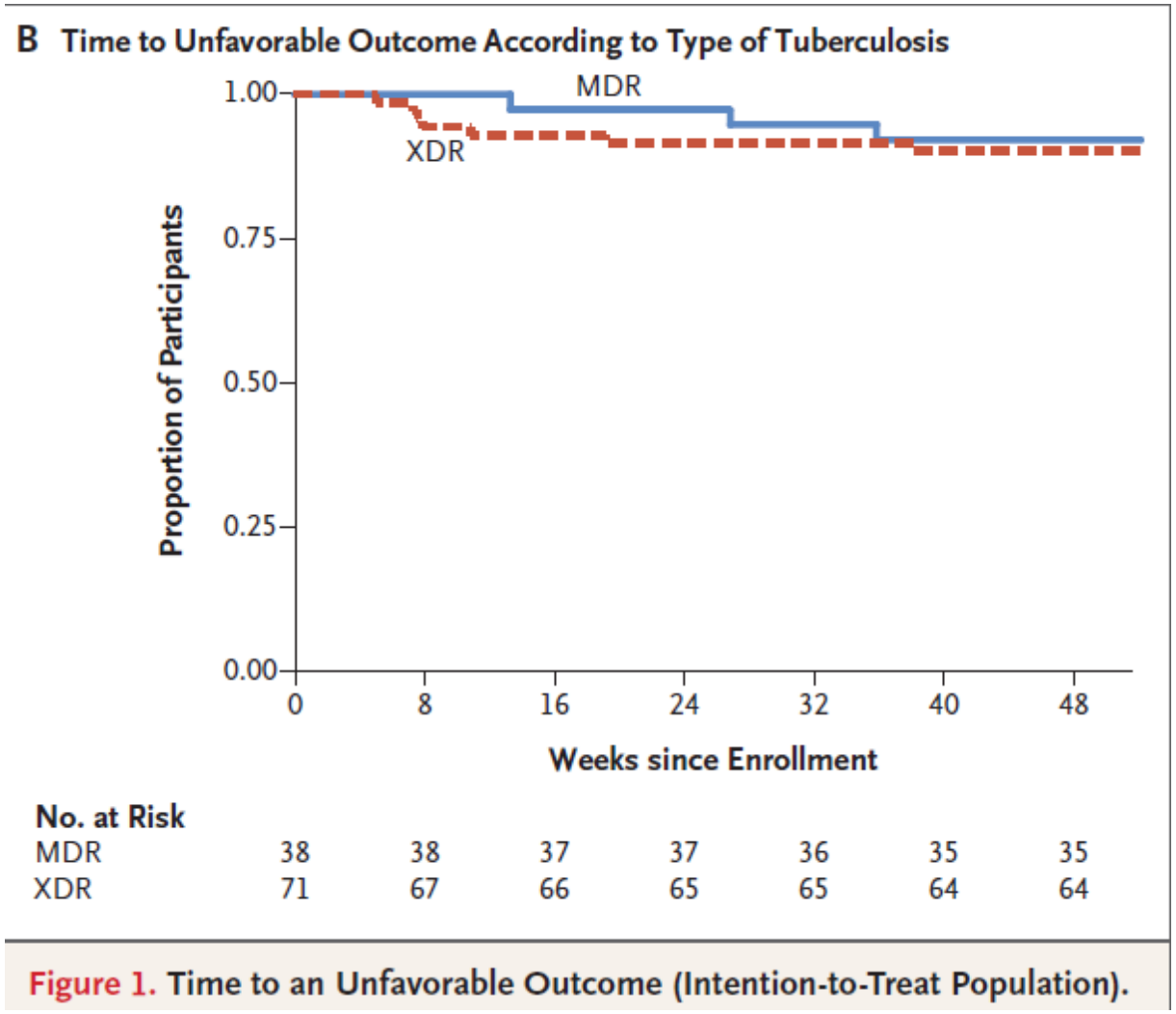


Figure 1. Time to an Unfavorable Outcome (Intention-to-Treat Population).

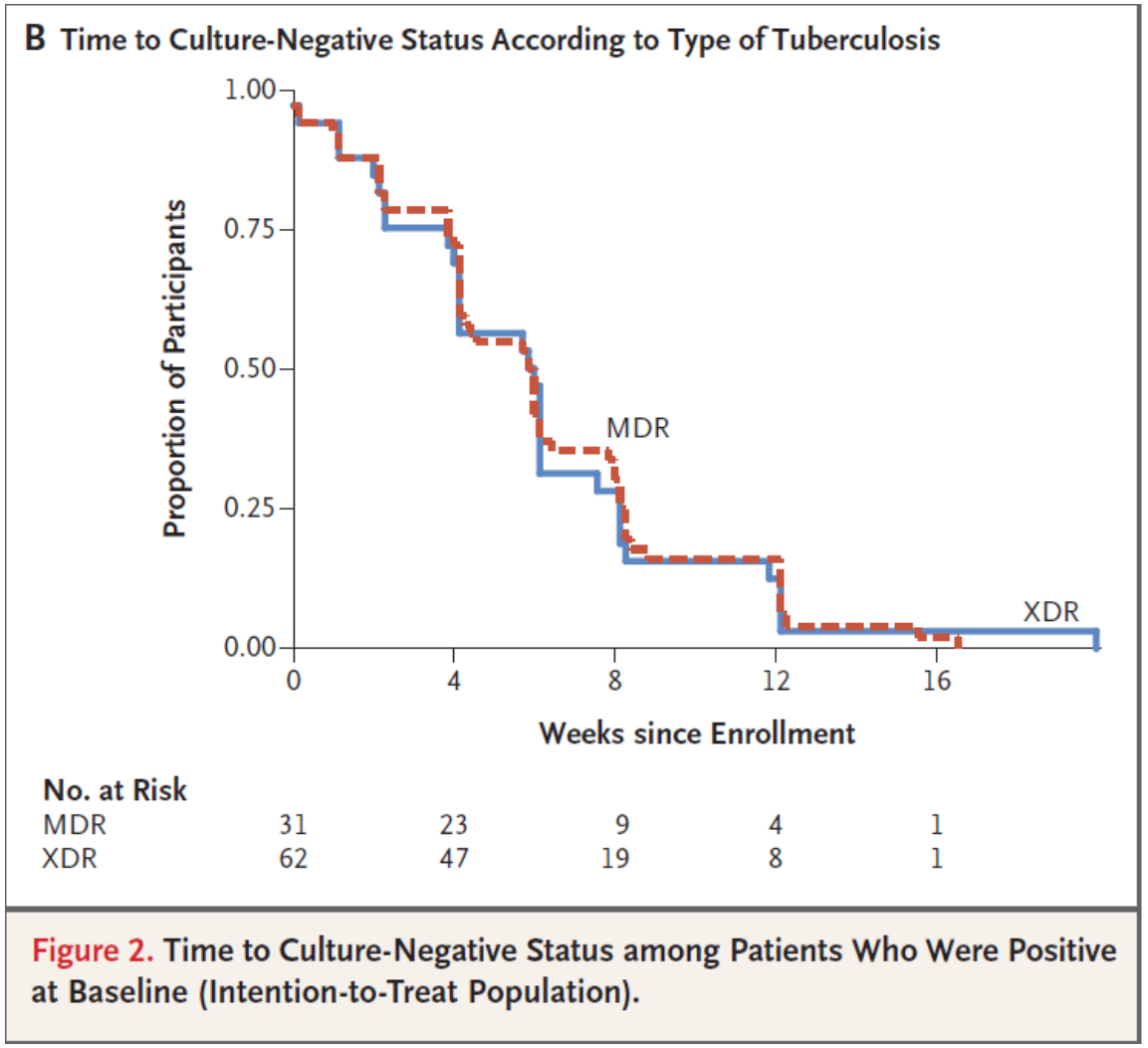


Figure 2. Time to Culture-Negative Status among Patients Who Were Positive at Baseline (Intention-to-Treat Population).

- Conradied F. et al. N Engl J Med 2020;382:893-902.

Zenix

- Zenix tests a version of BPaL with a lower dose and shorter duration of linezolid, to determine whether the efficacy of BPaL can be maintained while reducing toxicity.
- Zenix enrolls participants with XDR-TB at sites in Africa and Eastern Europe.
- https://www.tballiance.org/portfolio/trial/11883

3. Bdq-Dlm combination

- Needs for applying it to FQNs-resistant or XDR-TB
- There has been safety concerns.

Ferlazzo G. et al. Lancet Infect Dis 2018;18:536

	N=28
Median age (IQR)	32.5 (28.5-40.5)
Men	61%
HIV	39%
FQNs-resistant TB	36%
XDR	50%
Use of Lzd	82%
6 m culture negative	79%
Cardiac event	0
Serious ADR	25%

Kim CT et al. Eur Respir J 2018; 51: 1702467

	N=11
Median age (IQR)	50 (39-56)
Men	73%
HIV	0%
FQNs-resistant TB	64%
XDR	36%
Use of Lzd	91%
Culture conversion	64%
Cardiac event	0
Discontinuation due to prolonged QTcF	18%

3. Bdq-Dlm combination

- Prospective observational study
- Brooklyn Chest Hospital in Cape Town, South Africa
- Jan 2014 – April 2018
- Indication of combination therapy: inability having at least 4 effective drugs
- Groups: Bqd based regimen vs. Bdq-Dlm combination regimen
- Outcomes: culture conversion, changes in QTcF, favorable and unfavorable outcomes

- Olayanju O. et al. Eur Respir J 2020;55:1901181.

3. Bdq-Dlm combination

Variables	Bdq-based (n=82)	Bdq-Dlm combination (n=40)
Age	33 (28–42)	34 (27–42)
Males	61%	60%
Number of drugs	8 (7-9)	10 (8-11)
XDR*	81.7%	47.5%
Pre-XDR	12.2%	37.5%
HIV	51.2%	55.0%
Favorable outcome	**63.4%**	**67.5%**
Unfavorable outcome	36.6%	32.5%
QTcF increment > 60ms*	7.3%	20.6%
QTcF > 500 ms	0	0

- Olayanju O. et al. Eur Respir J 2020;55:1901181.

3. Bdq-Dlm combination: ADRs

ADRs	Bdq-based (n=82)	Bdq-Dlm combination (n=40)
Hearing loss	41 (50.0)	18 (45.0)
Anemia	28 (34.1)	15 (37.5)
Elevated liver enzyme	23 (28.0)	13 (32.5)
Peripheral neuropathy	18 (22.0))	12 (30.0
Vomiting	20 (24.4)	8 (20.0)
Deranged renal function	17 (20.7)	9 (22.5)

- Olayanju O. et al. Eur Respir J 2020;55:1901181.

4. EBA of high dose H

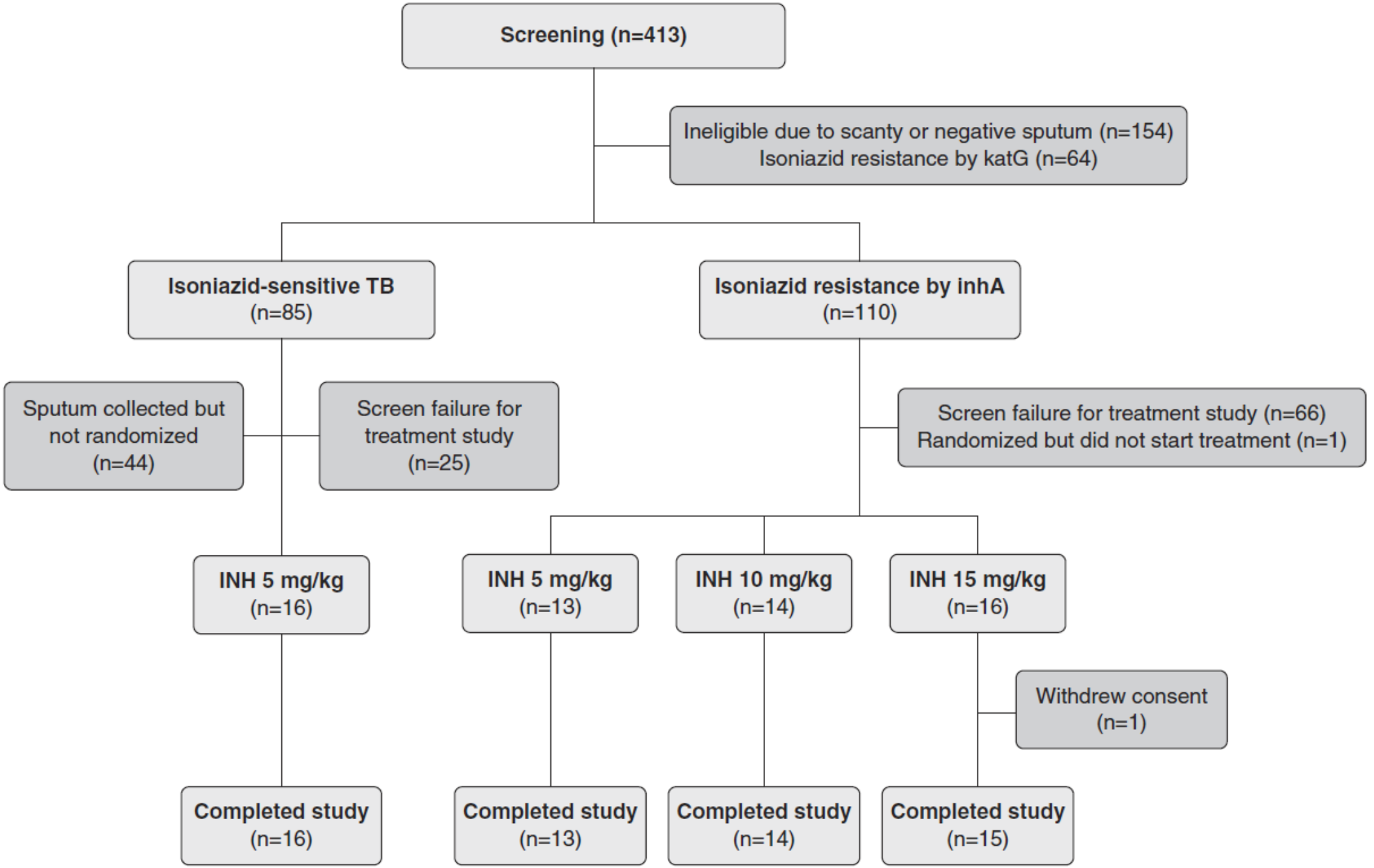
- H > 5mg/kg overcome low-level resistance: mutation in the *inhA*
- Dose-ranging EBA of H
- Phase 2A, single-site, randomized open-label study
- H sensitive or H-resistant PTB
- Adults with smear positive PTB
- Groups
  - *inhA* group: *inhA* promoter or gene mutations but not *katG* mutations
  - Control groups: neither *inhA* nor *katG* mutations

- Dooley K.E. et al. Am J Respir Crit Care Med 2020;201:1416–1424

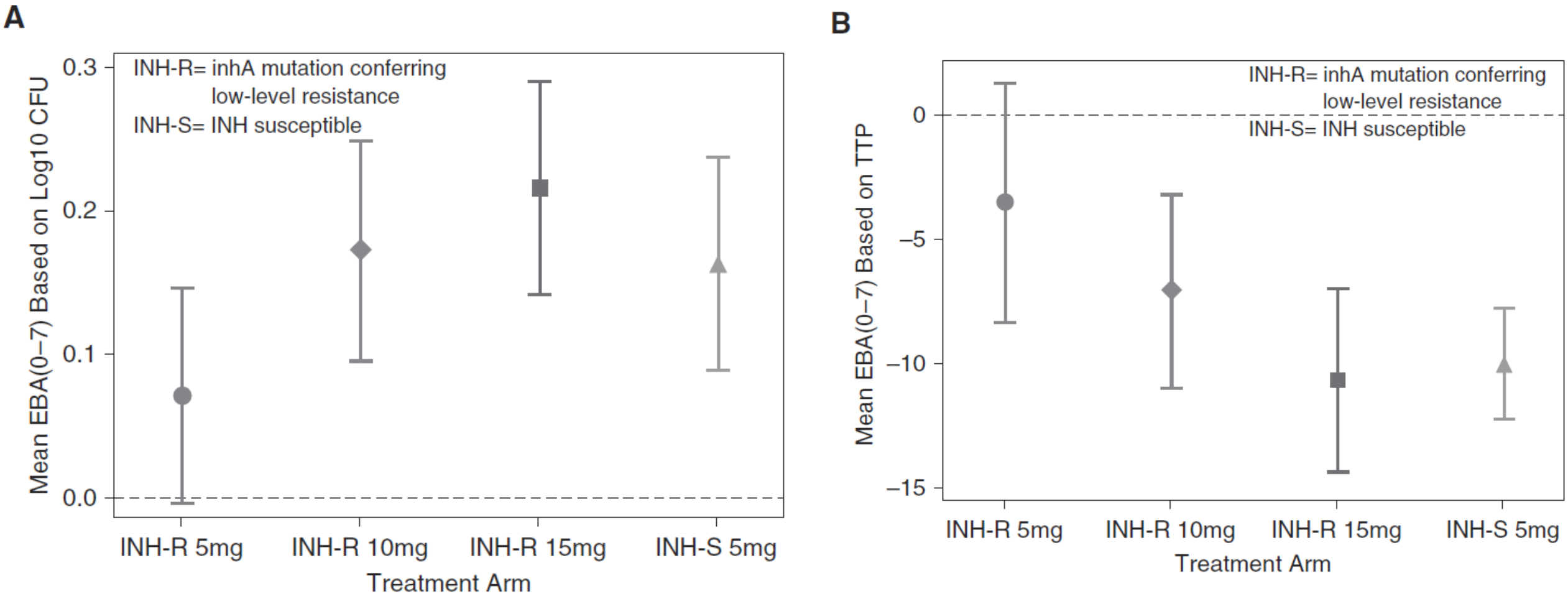
4. EBA of high dose H

- Procedures
  - inhA group: H of 5, 10, or 15 mg/kg daily for 7 days → 1:1:1
  - Control group: 5mg/kg daily
- Daily sputum collections
- Outcomes
  - Daily change in log10 cfu/ml
  - Daily change in TTP
  - ADRs grade ≥2
- Early (EBA0-2) and late (EBA2-7)

- Dooley K.E. et al. Am J Respir Crit Care Med 2020;201:1416–1424



- Dooley K.E. et al. Am J Respir Crit Care Med 2020;201:1416–1424



- Dooley K.E. et al. Am J Respir Crit Care Med 2020;201:1416–1424

Table 2. Mean Isoniazid Pharmacokinetic Data, by Dose and Arm

	Isoniazid-Resistant Tuberculosis			Control Subjects
	5 mg/kg	10 mg/kg	15 mg/kg	5 mg/kg
C_{max}, μg/ml	5.44	9.41	17.1	5.13
$AUC_{0–24}$, μg · h/ml	19.3	45.7	67.7	15.1
CL/F, L/h	24.3	18.0	14.2	26.5

Definition of abbreviations: $AUC_{0–24}$ = area under the concentration–time curve over 24 hours; CL/F = oral clearance; C_{max} = maximum concentration.

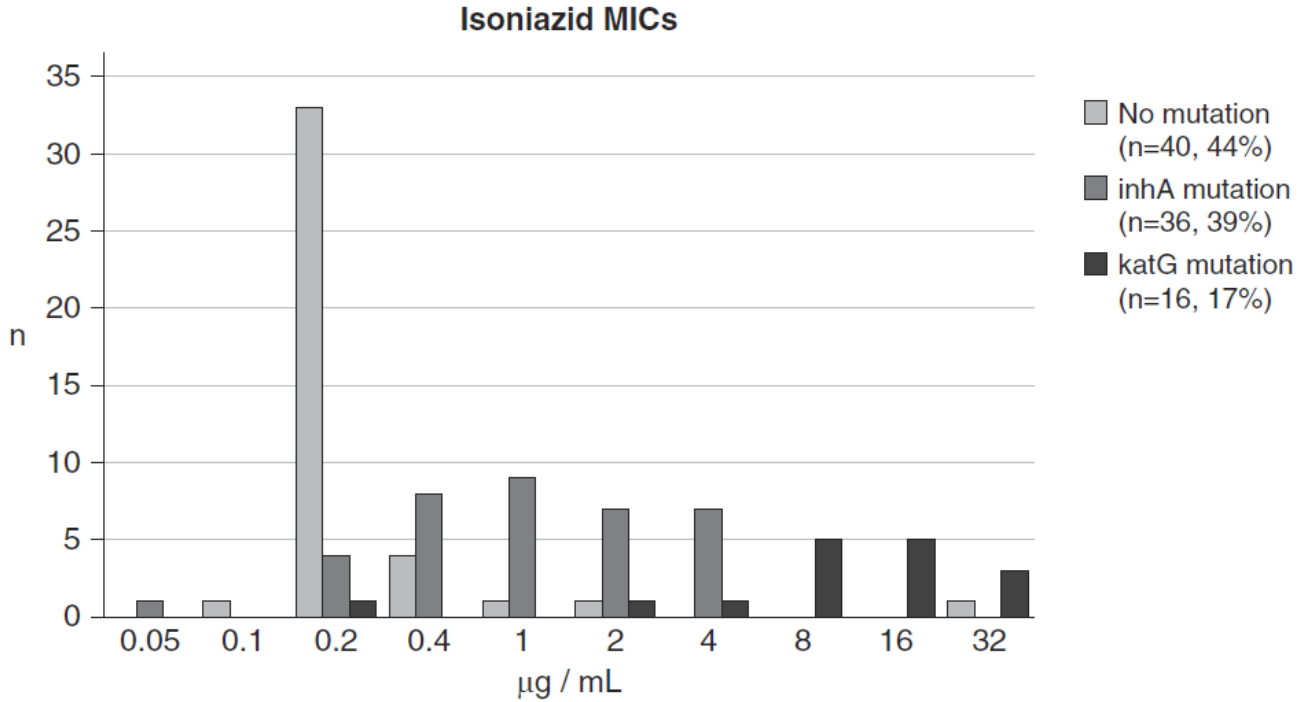


Figure 3. Distribution of minimum inhibitory concentrations (MICs) of isoniazid against strains with no inhA or katG mutations, with inhA mutations, or with katG mutations. Strains are from participants who provided sputum specimens only or who provided specimens and also participated in the treatment trial.

- Dooley K.E. et al. Am J Respir Crit Care Med 2020;201:1416–1424

4. EBA of high dose H

Safety

- 9 grade 3 ADRs.
- All were unrelated or unlikely to be related to study treatments (one each of fever, pain, and dyspnea; two episodes of pneumothorax; and four cases of anemia).
- No grade 4 events or deaths.
- Three participants, all in the inhA group (one in the 5 mg/kg arm and two in the 10 mg/kg arm), developed grade 2 liver enzyme elevations.

- Dooley K.E. et al. Am J Respir Crit Care Med 2020;201:1416–1424

5. Burden of latent MDR-TB

Table 1. Proportion of population with latent TB infection.

WHO region	All LTBI	
	Prevalence (%)	Proportion of infections in children <15 y (%)
AFR	22.4 [20.6–24.6]	13.3 [11.8–14.6]
AMR	11.0 [7.0–20.0]	2.3 [1.3–3.7]
SEA	30.8 [28.3–34.8]	7.4 [6.3–8.2]
EMR	16.3 [13.4–20.5]	7.9 [6.0–9.4]
WPR	27.9 [19.3–40.1]	2.4 [1.7–3.5]
EUR	13.7 [9.8–19.8]	2.0 [1.3–2.7]
GLOBAL	23.0 [20.4–26.4]	5.9 [5.1–6.7]

- Houben RMGJ et al. PLoS Med 2016; 13: e1002152.

- No direct data for the prevalence of latent MDR-TB
- A new mathematical model
- Combined historical annual risks of infection

→Estimate trends in the risk

- Knight GM et al. Lancet Infect Dis 2019;19: 903–12.

5. Burden of latent MDR-TB

	Prevalence (95% uncertainty interval)		Proportion (95% uncertainty interval)	
	Drug-susceptible latent tuberculosis	Multidrug-resistant latent tuberculosis	Latent tuberculosis that is multidrug resistant	Latent tuberculosis that is multidrug resistant in people younger than 15 years
African	22·1% (20·1–25·5)	0·23% (0·19–0·29)	1·0% (0·8–1·3)	2·3% (1·9–2·7)
Americas	10·6% (7·3–19·0)	0·05% (0·04–0·06)	0·5% (0·3–0·8)	3·3% (2·8–4·1)
South-East Asia	30·7% (27·7–34·5)	0·31% (0·23–0·41)	1·0% (0·7–1·3)	2·2% (1·9–2·6)
Eastern Mediterranean	16·4% (13·5–20·9)	0·14% (0·08–0·24)	0·9% (0·5–1·5)	2·9% (1·9–3·8)
Western Pacific	26·8% (17·8–39·2)	0·36% (0·26–0·49)	1·3% (0·7–2·2)	3·7% (3·3–4·1)
European	13·5% (9·9–19·8)	0·38% (0·32–0·44)	2·8% (1·6–3·9)	14·1% (13·1–15·2)
Global	22·9% (20·1–26·1)	0·28% (0·24–0·31)	1·2% (1·0–1·4)	2·9% (2·6–3·1)

Table 1: Prevalence of latent tuberculosis infection, 2014, by WHO region

- Knight GM et al. Lancet Infect Dis 2019;19: 903–12.

5. Burden of latent MDR-TB

	Drug-susceptible latent tuberculosis (thousands)	Multidrug-resistant latent tuberculosis (thousands)
African	155 000 (141 000–179 000)	1590 (1310–2010)
Americas	102 000 (70 700–183 000)	510 (418–624)
South-East Asia	584 000 (527 000–656 000)	5810 (4410–7750)
Eastern Mediterranean	96 000 (78 900–122 000)	837 (481–1410)
Western Pacific	493 000 (326 000–720 000)	6620 (4840–9000)
European	122 000 (90 100–180 000)	3440 (2920–3990)
Global	1 580 000 (1 380 000–1 800 000)	19 100 (16 400–21 700)

Data are n (95% uncertainty interval).

Table 2: Number of people with latent tuberculosis infection, 2014, by WHO region

- Knight GM et al. Lancet Infect Dis 2019;19: 903–12.

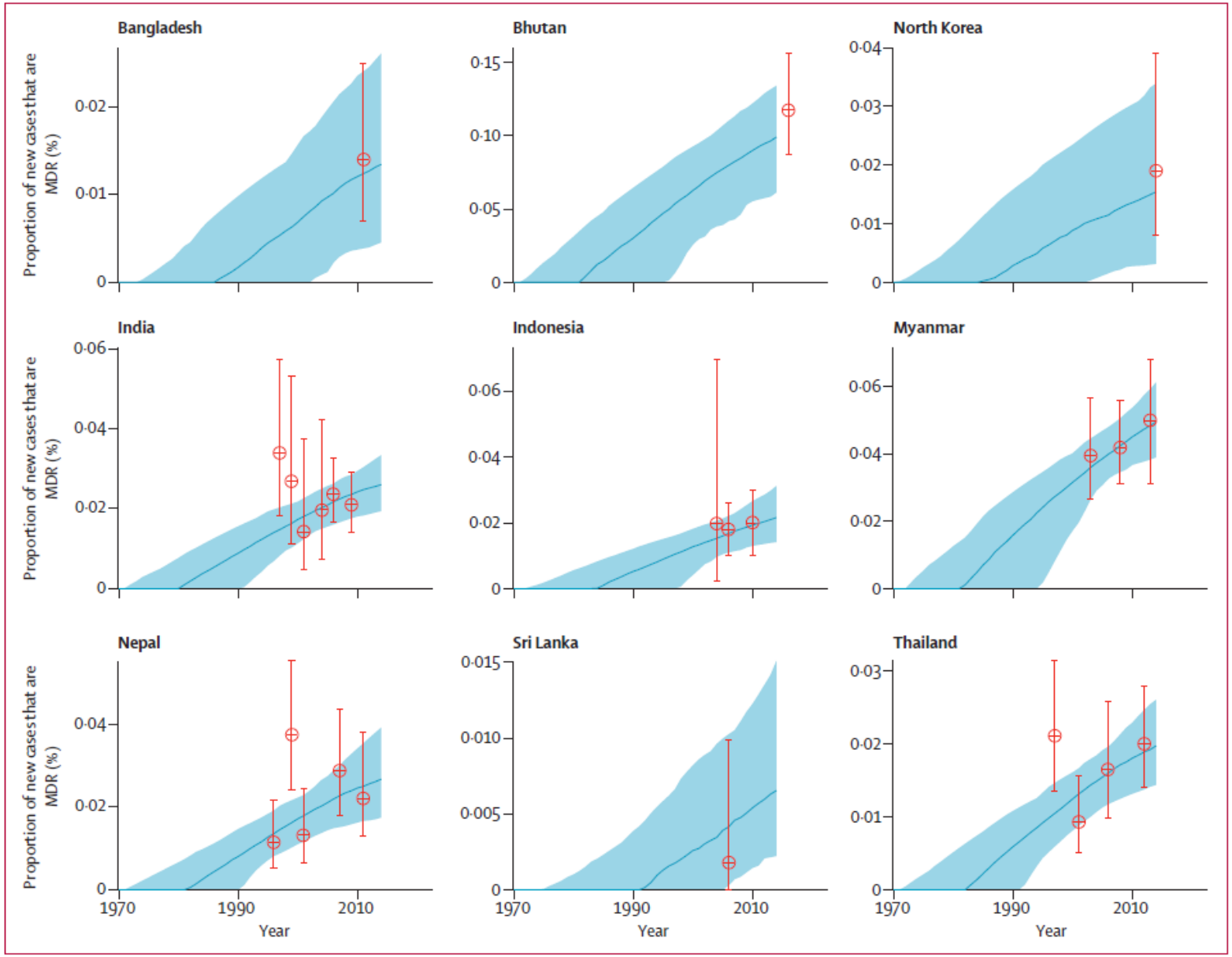


Figure 1: **Proportion of new cases of tuberculosis disease accounted for by MDR tuberculosis in the nine countries in the WHO South-East Asia region included in our model**

The blue lines represent the median proportion from 200 model fits to WHO data (the red datapoints; error bars show 95% CIs). The shaded regions represent the 95% uncertainty intervals. Although we estimated the burden of latent MDR tuberculosis in 2014 (hence the cutoff in this figure) the model trend was fitted to all WHO Drug Resistance Surveillance data. MDR=multidrug resistant.

- Knight GM et al. Lancet Infect Dis 2019;19: 903–12.

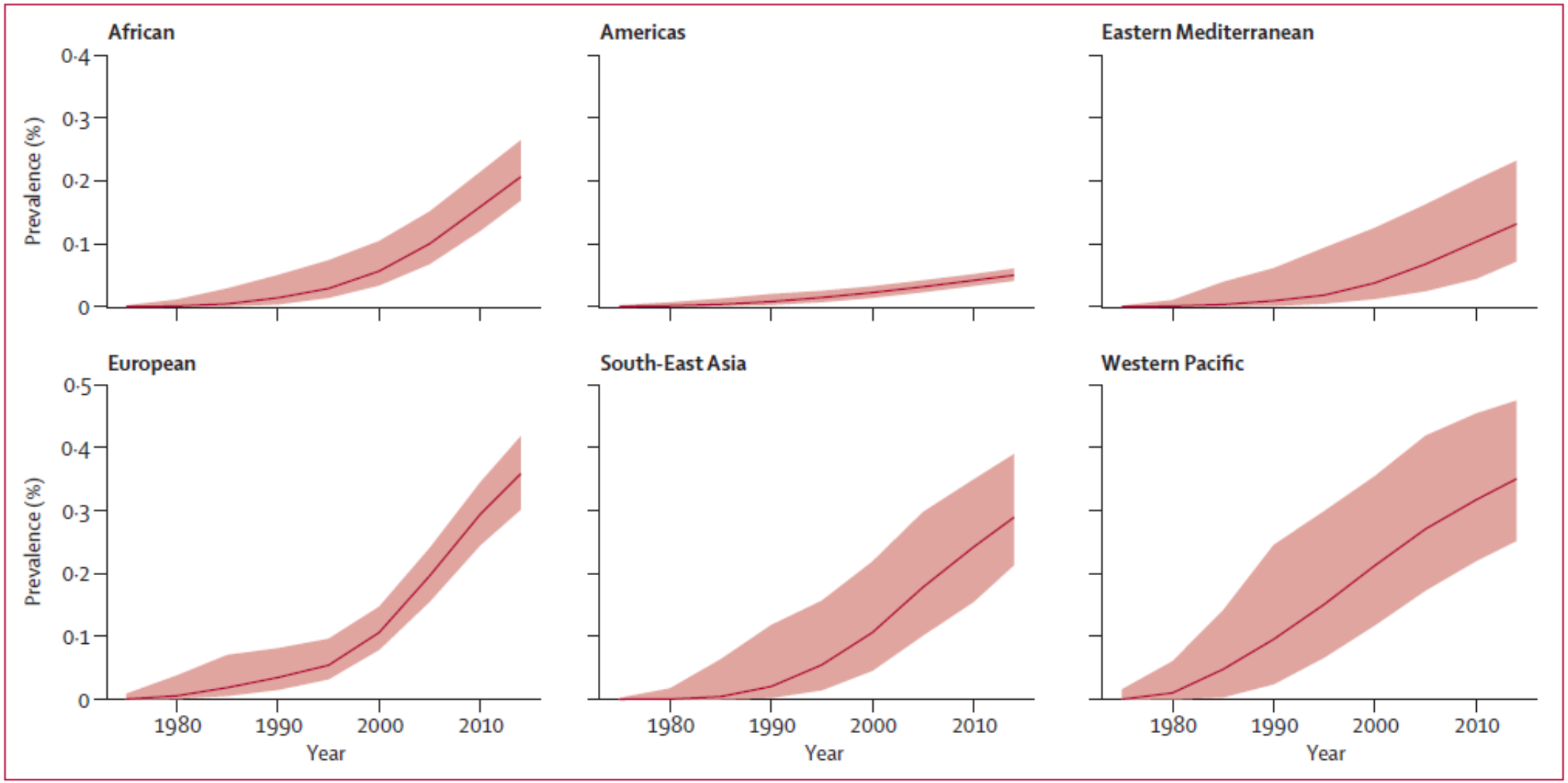


Figure 2: **Prevalence of latent multidrug-resistant tuberculosis infection, by WHO region**
The red line represents the median from 200 model fits. The shaded region represents the 95% uncertainty interval.

- Knight GM et al. Lancet Infect Dis 2019;19: 903–12.

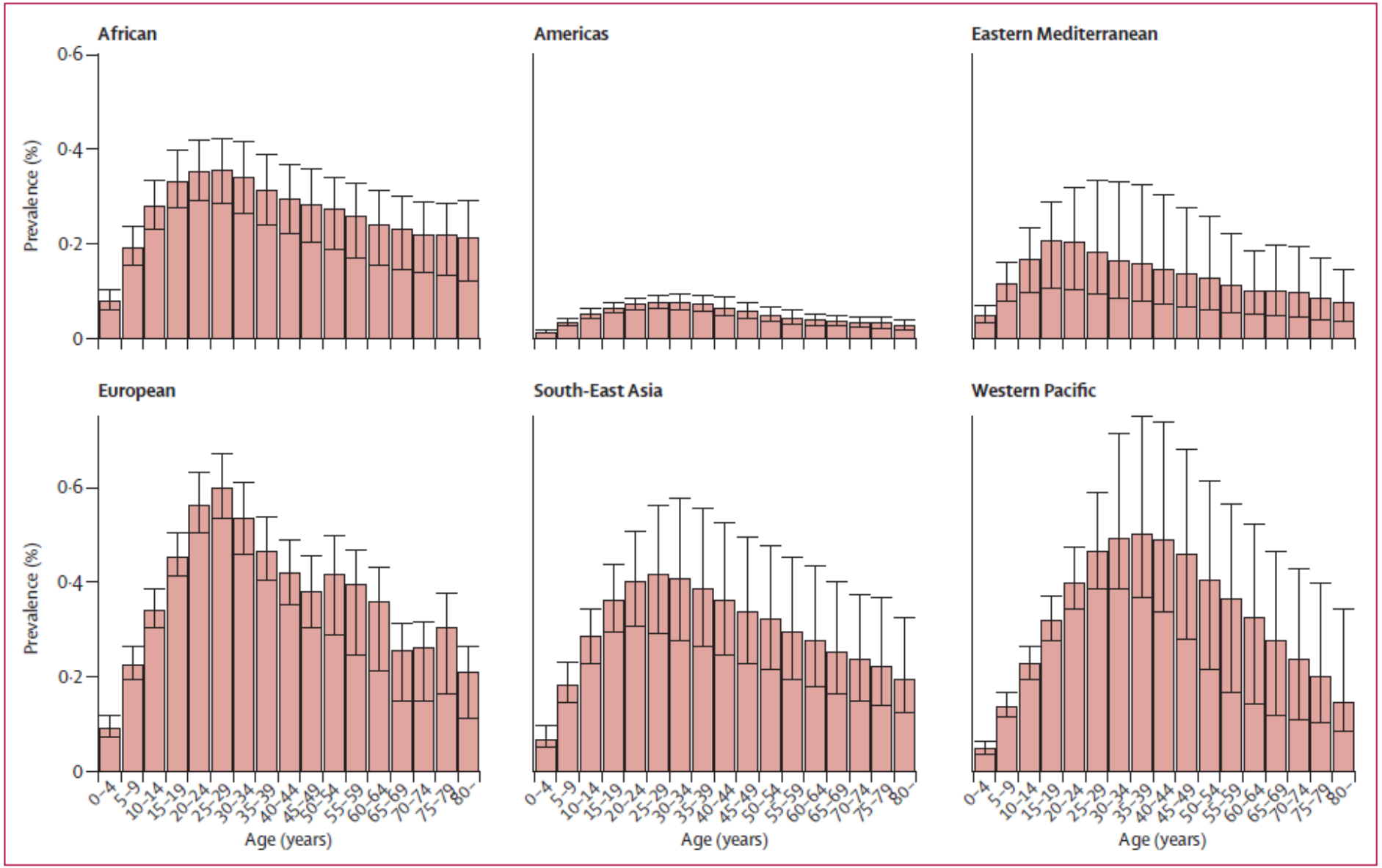


***Figure 4*: Prevalence of latent multidrug-resistant tuberculosis infection in each age group, by WHO region**
Error bars show 95% uncertainty intervals. The prevalence of latent infection with drug-susceptible tuberculosis is shown in the appendix.

- Knight GM et al. Lancet Infect Dis 2019;19: 903–12.

6. Preventive therapy for DR-TB

- Household contacts with MDR-TB
- The preventive treatment should be individualized after a careful assessment of the intensity of exposure, the certainty of the source case, reliable information on the drug resistance pattern of the source case and potential adverse events.
- The drugs should be selected according to the drug susceptibility profile of the source case.

Latent tuberculosis infection: updated and consolidated guidelines for programmatic management. WHO/CDS/TB/2018.4. 2018.

PICO 7: Should preventive treatment be recommended for contacts of patients with multidrug-resistant or rifampicin-resistant TB?

Preventive treatment for contacts of patients with multidrug- or rifampicin-resistant TB

Five studies that included fewer than 20 participants who completed preventive TB treatment were excluded. In addition, the study by Kristi was excluded as only isoniazid monotherapy was given.

Overall quality: very low

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Preventive treatment	No treatment	Relative (95% CI)	Absolute (95% CI)		
INCIDENCE OF ACTIVE TB DISEASE (BOTH DRUG-SUSCEPTIBLE AND DRUG-RESISTANT TB)												
4 *(56–59)*	Observational	Very serious[1]	Not serious	Not serious	Very serious[3]	None	2/41 (4.9%)	13/64 (20.3%)	0.20 (0.04;0.94)[4]	154 fewer per 1000 (273 fewer to 36 fewer)	⨁◯◯◯ Very low	Critical
							0/93 (0%)	3/15 (20%)	0.02 (0.00;0.39)[5]	200 fewer per 1000 (403 fewer to 3 more)		
							0/21 (0%)	0/10 (0%)	-[6]	0 more per 1000 (138 fewer to 138 more)		
							0/30 (0%)	0/166 (0%)	-[7]	0 more per 1000 (45 fewer to 45 more)		
INCIDENCE OF MDR-TB												
3[2] *(56, 57, 59)*	Observational	Very serious[1]	Not serious	Not serious	Very serious[3]	None	0/93 (0%)	3/15 (20%)	0.02 (0.00;0.39)[5]	200 fewer per 1000 (403 fewer to 3 more)	⨁◯◯◯ Very low	Critical
							0/21 (0%)	0/10 (0%)	-[6]	0 more per 1000 (138 fewer to 138 more)		
							0/30 (0%)	0/166 (0%)	-[7]	0 more per 1000 (45 fewer to 45 more)		

Latent tuberculosis infection: updated and consolidated guidelines for programmatic management. WHO/CDS/TB/2018.4. 2018.

6. Preventive therapy for DR-TB

- Prospective cohort study at The Indus Hospital, Karachi, Pakistan
- Subjects: the household contacts of consecutive (index) patients who initiated treatment for DR-TB disease and did not have XDR-TB
  - aged <5: all
  - aged 5–17: a positive TST, diabetes, HIV, or malnutrition (weight for age less than the third percentile)
  - aged ≥18: diabetes, HIV, or malnutrition (BMI, 18.5 kg/m2)
- Treatment: 6 months, 2 drug regimen
  - Lfx (or Mfx) + E (or Eto)

- Malik A.A. et al. Clinical Infectious Diseases 2020;70(9):1958-65.

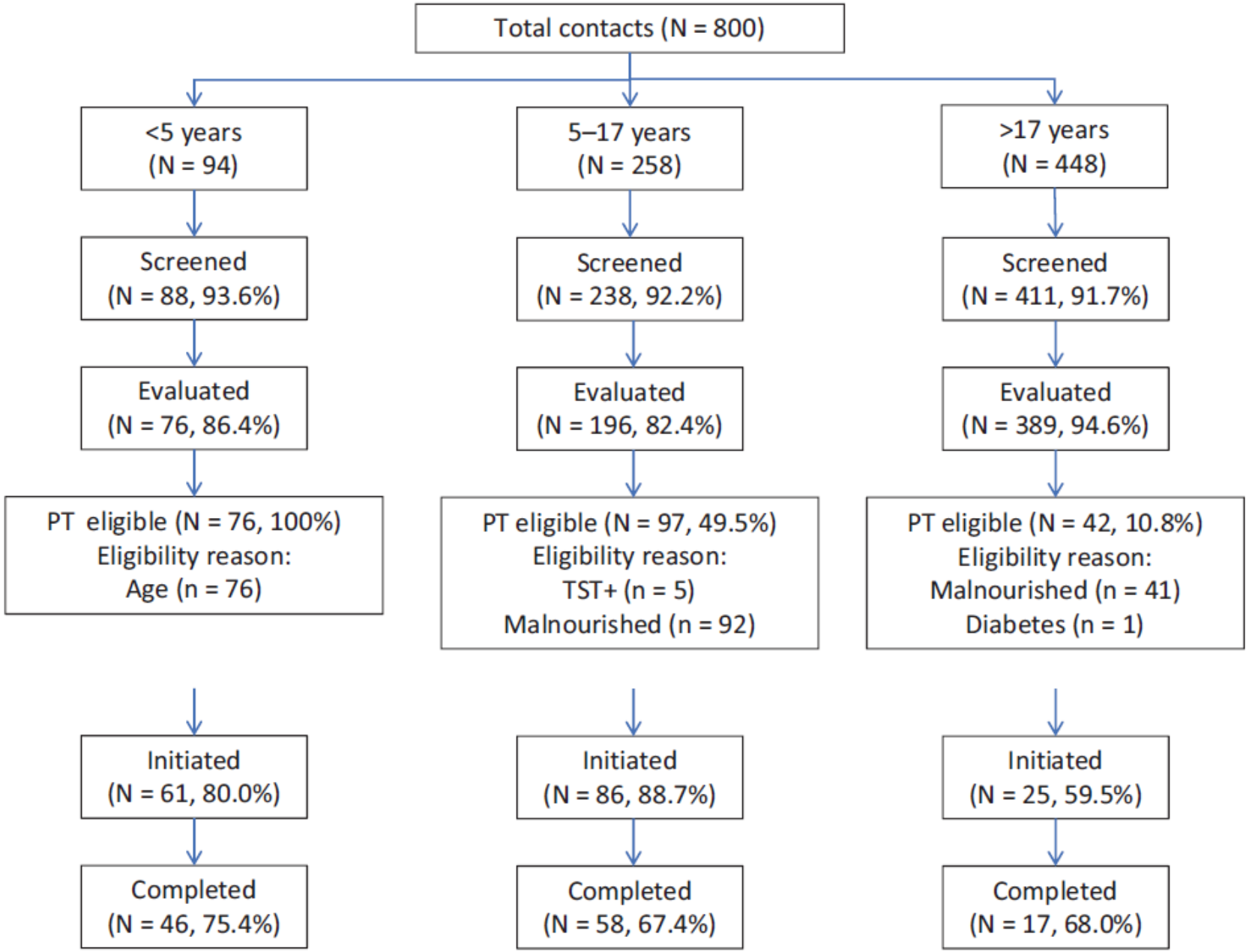
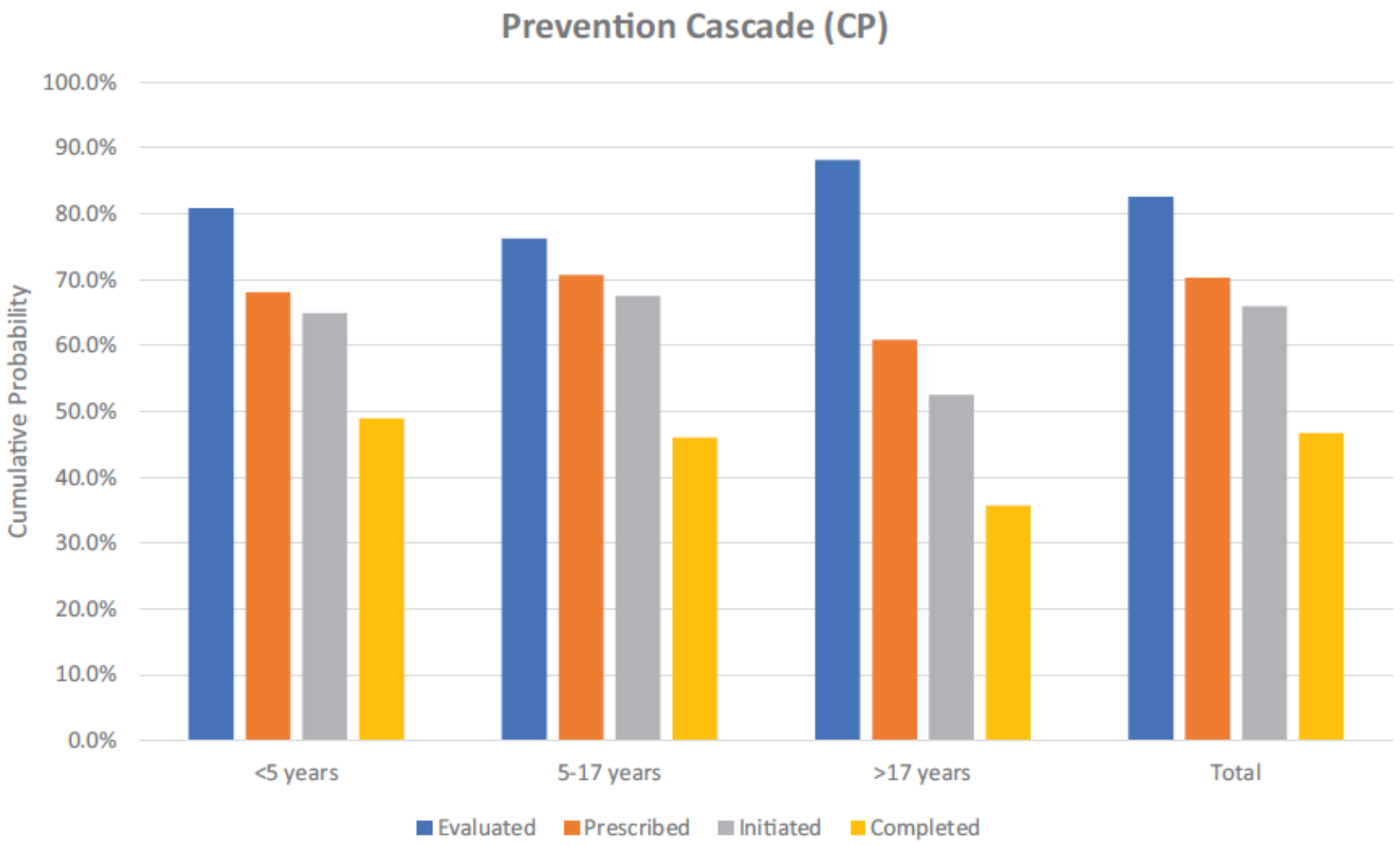


Figure 2. Prevention cascade for drug-resistant tuberculosis household contacts (N = 800). Abbreviations: PT, preventive treatment; TST, tuberculin skin test.

- No TB disease or significant ADRs during 12 months of follow-up



- Malik A.A. et al. Clinical Infectious Diseases 2020;70(9):1958-65.

6. Preventive therapy for DR-TB

Table 3. Adverse Events Profile Experienced by Individuals Treated for Presumed Drug Resistant-tuberculosis Infection, by Companion Drug Received (N = 172)

Adverse Event[a]	Regimen Included Ethambutol, n (%) (n = 113)	Regimen Included Ethionamide, n (%) (n = 59)	Total Who Received Infection Treatment Regimen, n (%) (N = 172)
Gastrointestinal	5 (4.4)	14 (23.7)	19 (11.1)
Jaundice	1 (0.9)	0 (0)	1 (0.6)
Generalized	9 (8.0)	15 (25.4)	24 (14.0)
Rheumatic	3 (2.7)	1 (1.7)	4 (2.3)
Disturbance in menstrual cycle	0 (0)	1 (1.7)	1 (0.6)
Renal	1 (0.9)	0 (0)	1 (0.6)

[a]Not mutually exclusive.

- Malik A.A. et al. Clinical Infectious Diseases 2020;70(9):1958-65.

Summary

- A short regimen was non-inferior to a long regimen.
- The combination of bedaquiline, pretomanid, and linezolid led to a favorable outcome in patients with highly drug-resistant TB.
- A bedaquiline–delamanid combination regimen showed comparable long-term safety compared to a bedaquiline-based regimen in patients with DR-TB.
- Isoniazid 10–15 mg/kg daily had activity against TB strains with *inhA* mutations.
- Three in every 1000 people globally carry latent MDR-TB.
- Fluoroquinolone-based treatment for contacts with presumed DR-TB infection is feasible and well tolerated in a high TB burden setting.