Epidemiology, Treatment and Prevention of MDR-TB

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Objectives

- To document the extent of the global MDR-TB epidemic and suggest where it is headed
- To describe the drugs available for MDR-TB treatment and define their toxicities
- To provide guidance on using these drugs together in combination regimens
- To review potential strategies for prevention of MDR-TB and outline research needs

Outline

- What is MDR-TB and why does it threaten global TB control?
- Improving diagnosis of MDR-TB
- Improving treatment of MDR-TB
- New Drugs for MDR-TB treatment
- Prevention of MDR-TB

Multidrug-Resistant TB (MDR-TB)

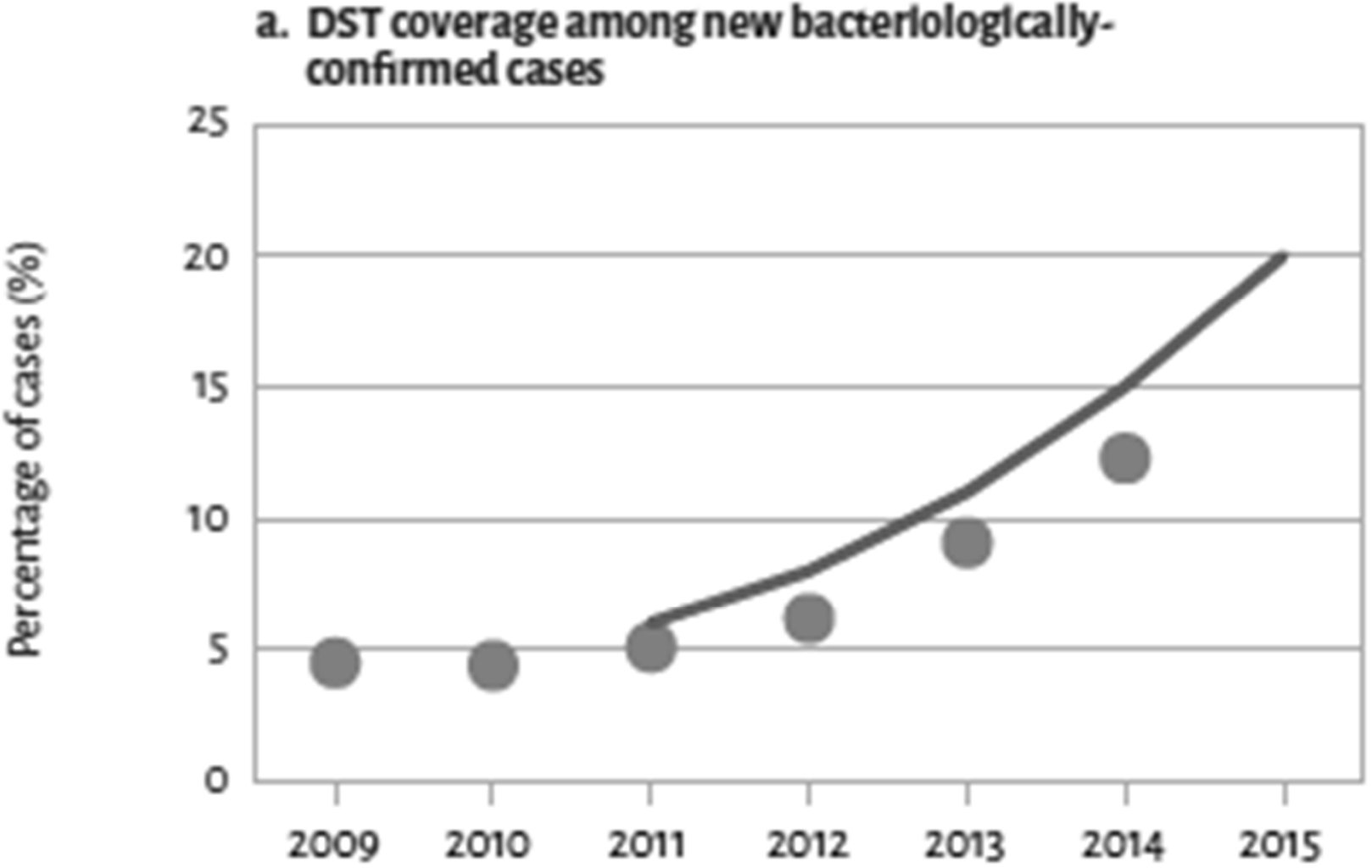
Tuberculosis disease caused by *M. tuberculosis* resistant to Isoniazid and Rifampin (+/- other drugs)

FIGURE 4.1

Global coverage of surveillance data on drug resistance, 1994–2015

2015 Global TB Report

MDR-TB Diagnostic Trends Over Time



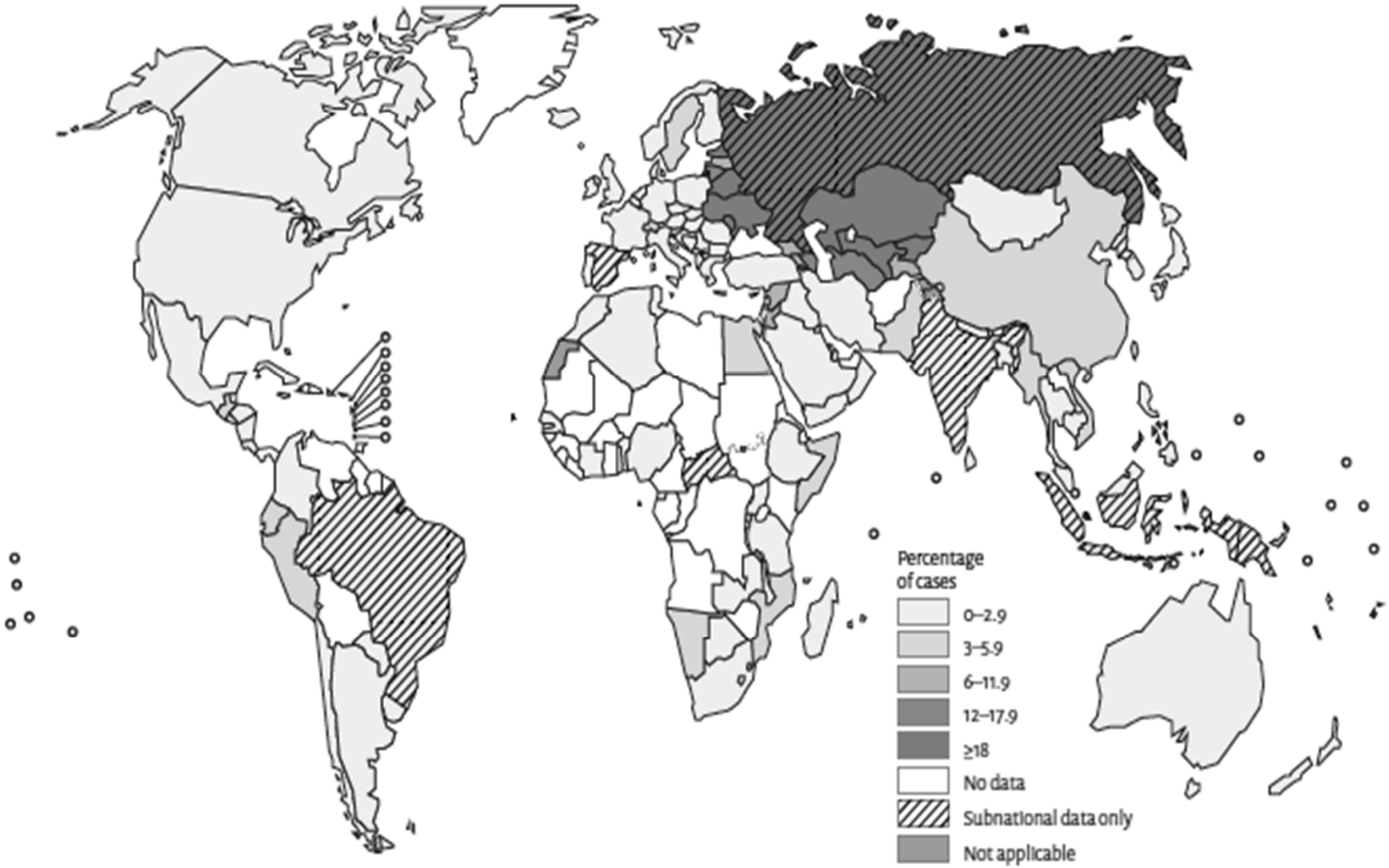
2015 Globnal TB Report

MDR-TB Epidemiology

- Estimated 480,000 new cases last year
- Created by inappropriate treatment, interruption of drug supply and patient nonadherence
- Main mechanism is selection of naturally occurring mutations
- No evidence of transposition with other bacteria
- Also can be primary spread

FIGURE 4.2

Percentage of new TB cases with MDR-TB[a]



2015 Global TB Report

FIGURE 4.3

Percentage of previously treated TB cases with MDR-TB[a]

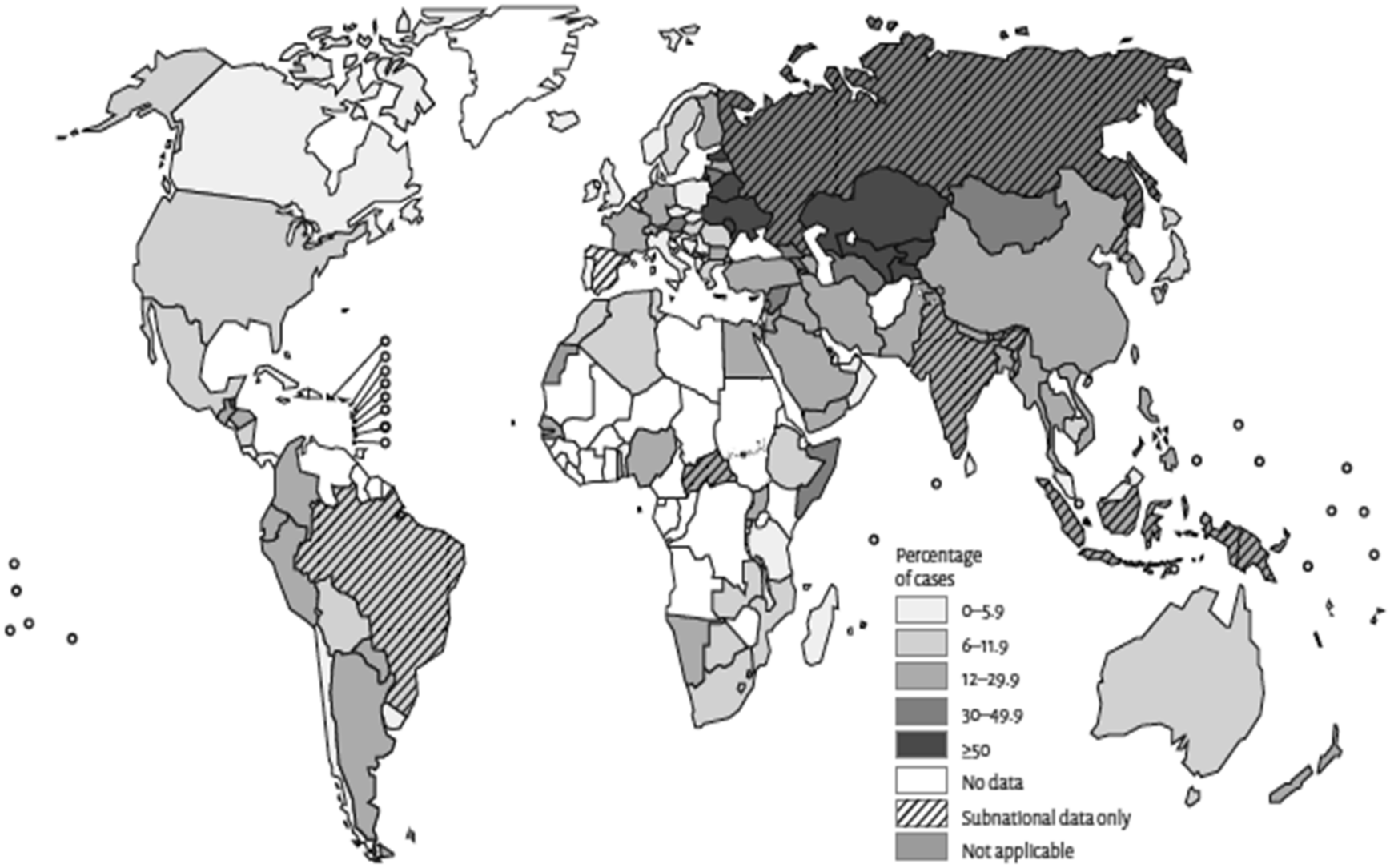


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FIGURE 4.6

Number of MDR–TB cases estimated to occur among notified pulmonary TB cases, 2014

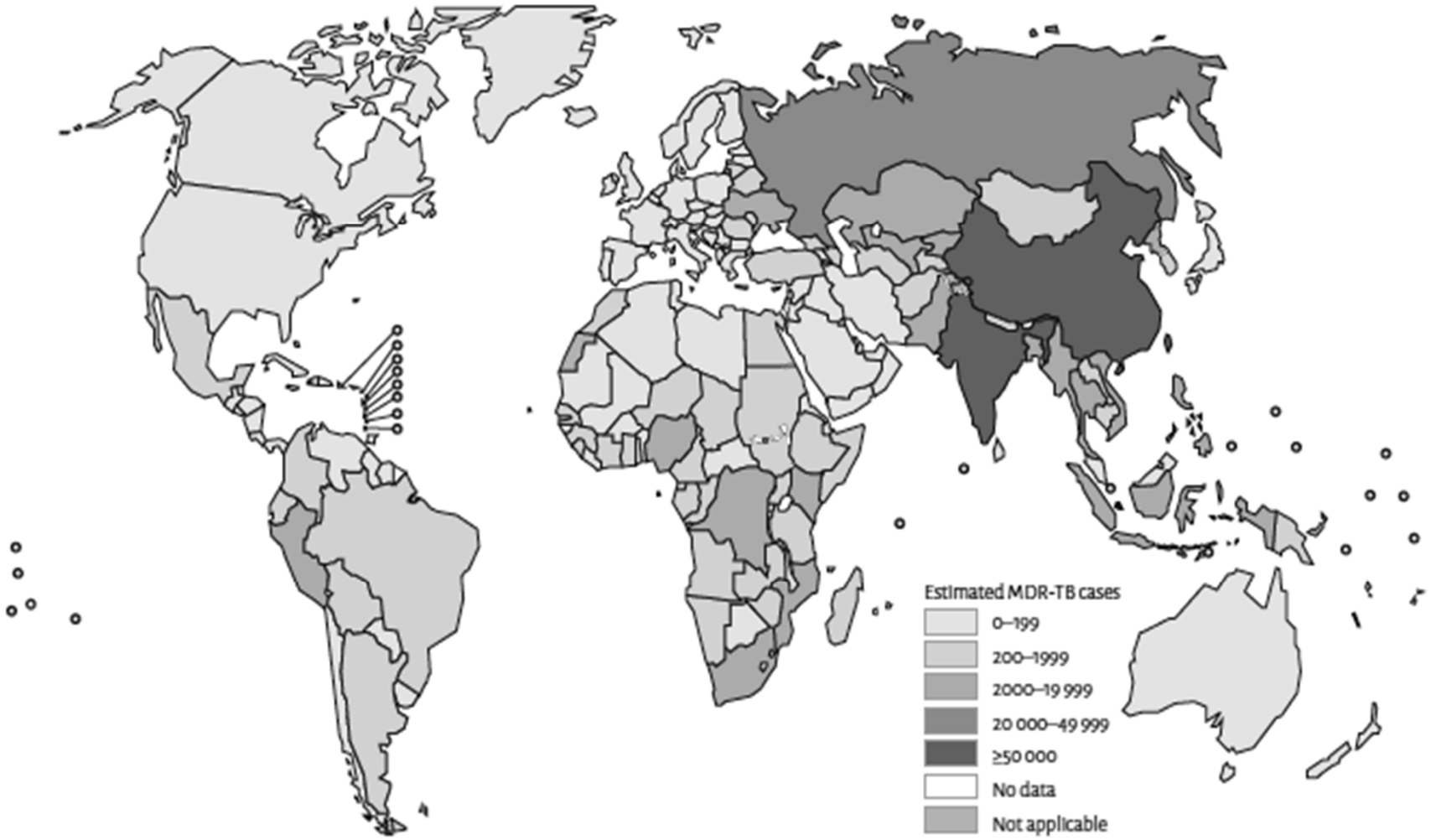

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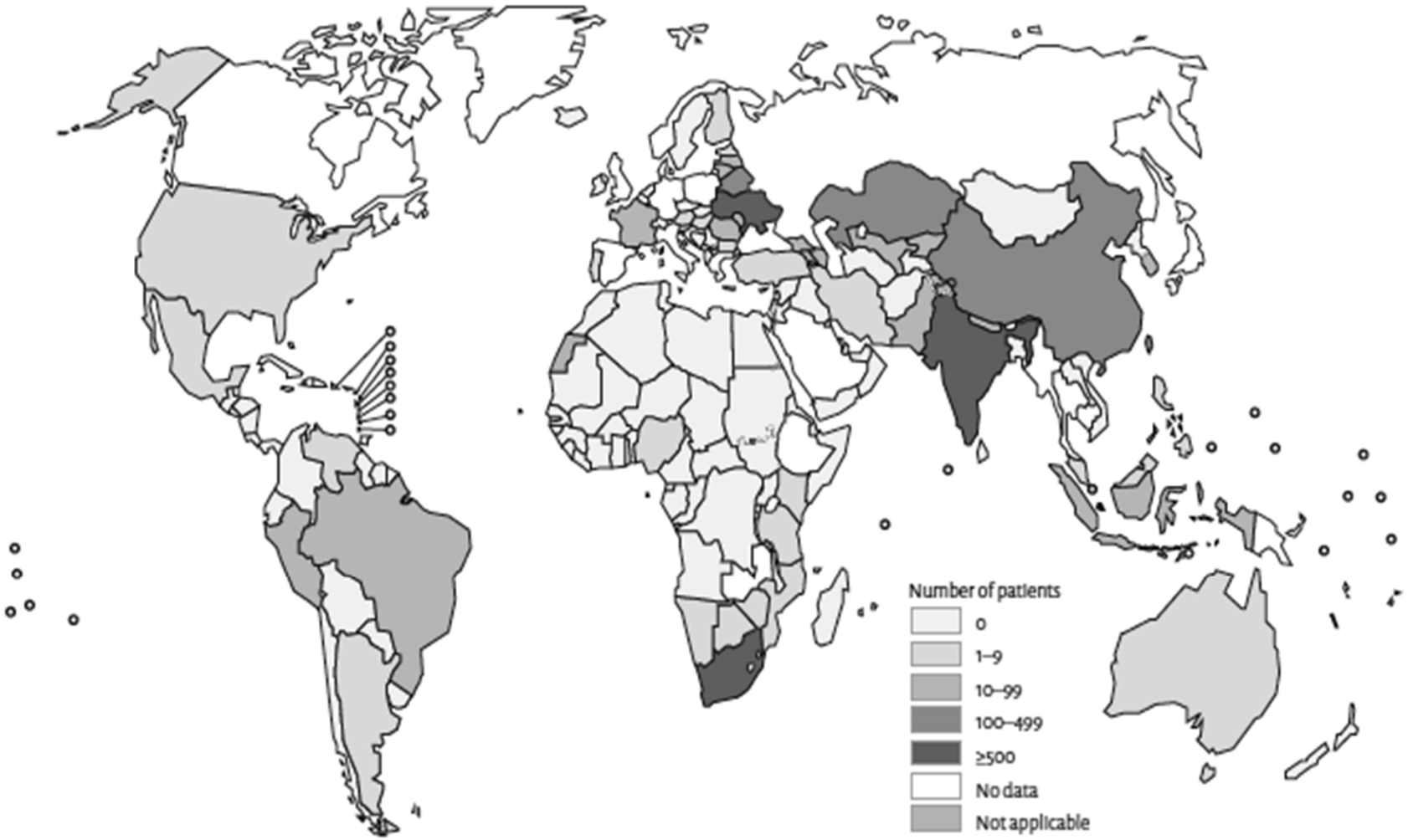
FIGURE 4.8

Number of patients with laboratory-confirmed XDR-TB started on treatment in 2014



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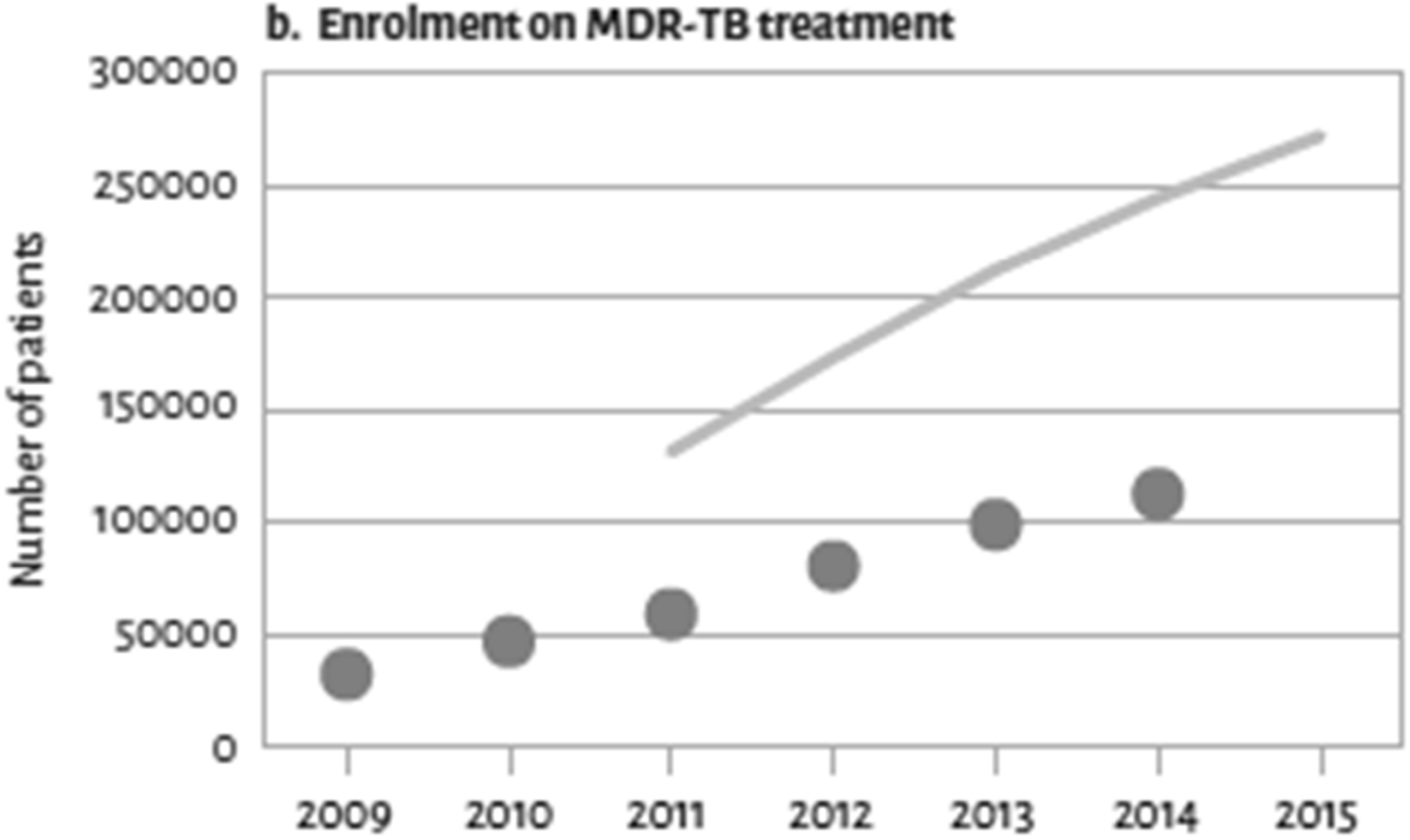
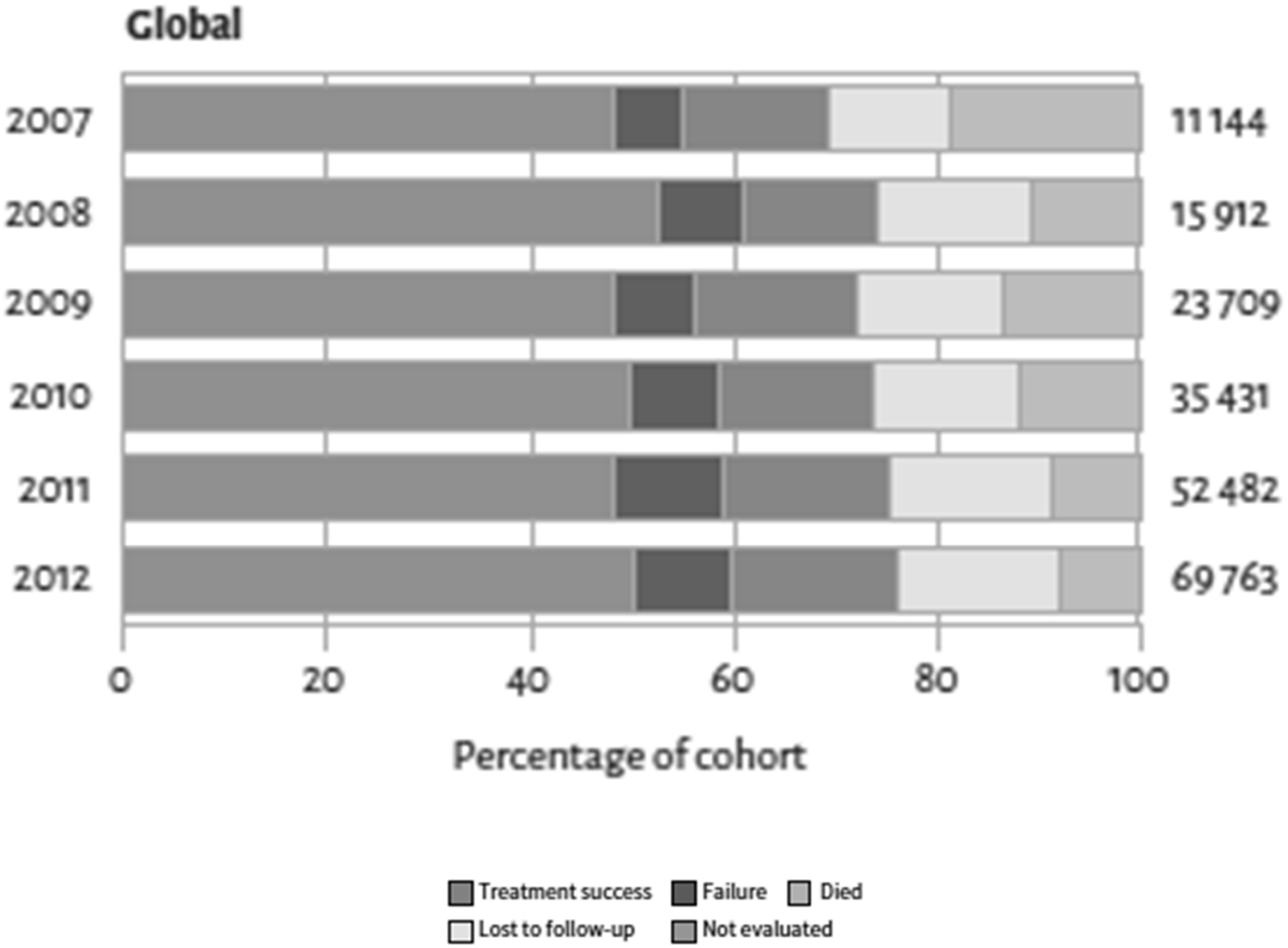
Trends Over Time in MDR-TB Treatment



2015 Global TB Report

MDR-TB Treatment Outcomes, 2007-12



Emergence of Additional DR on MDR-TB Treatment

- Cohort study of 832 patients with MDR-TB treated with WHO recommended regimens
- Of those without baseline resistance to specific SLDs:
  - 79 (11.2%) acquired fluoroquinolone (FQ) resistance
  - 56 (7.8%) acquired resistance to second-line injectable drugs (SLIs)
  - 68 (8.9%) acquired extensively drug-resistant (XDR) tuberculosis

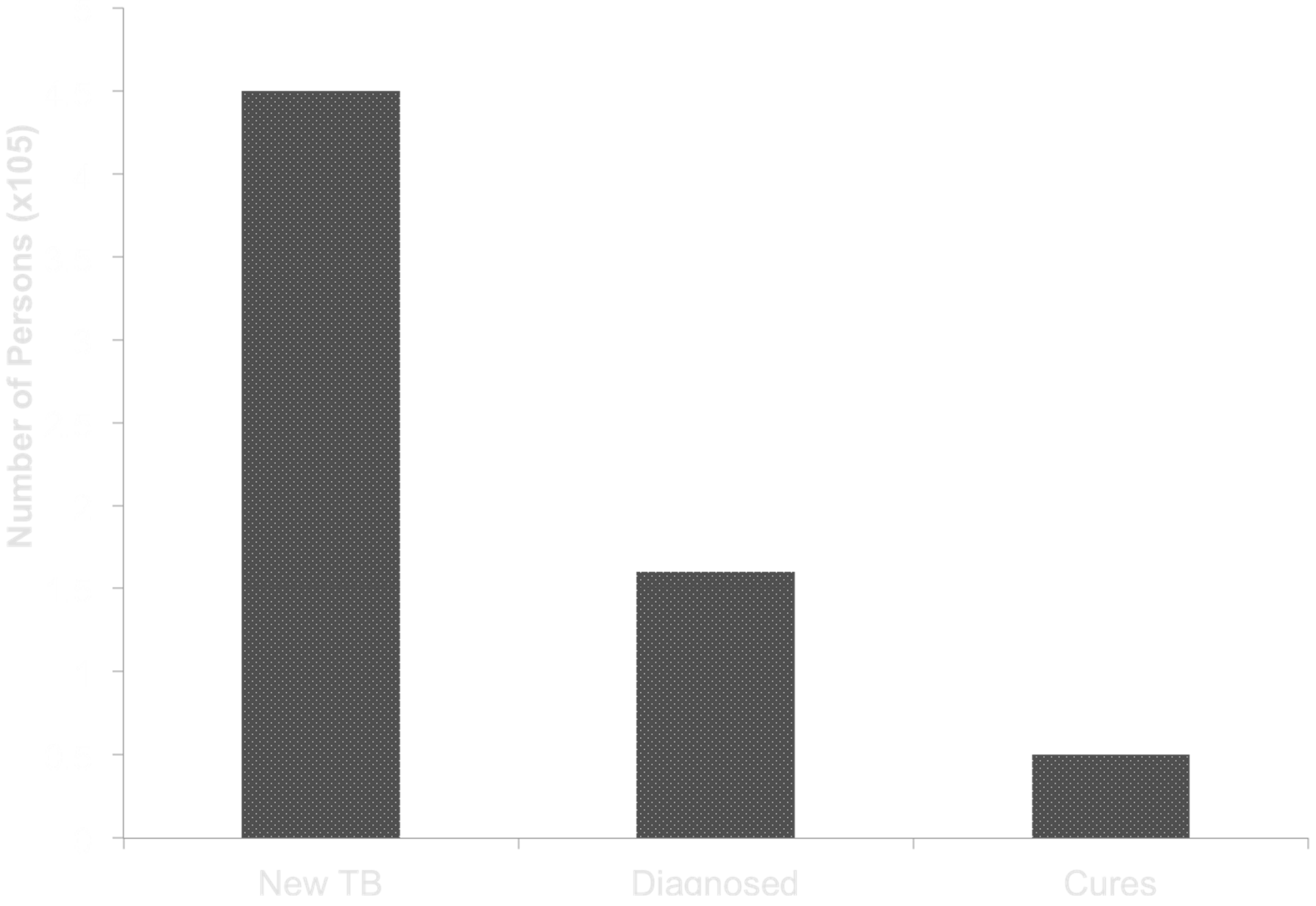
Clin Infect Dis 2014;59:1049

FIGURE 5.8

Number of patients with laboratory-confirmed XDR-TB started on treatment in 2013

2014 Global TB Report

Annual Incident Global MDR-TB



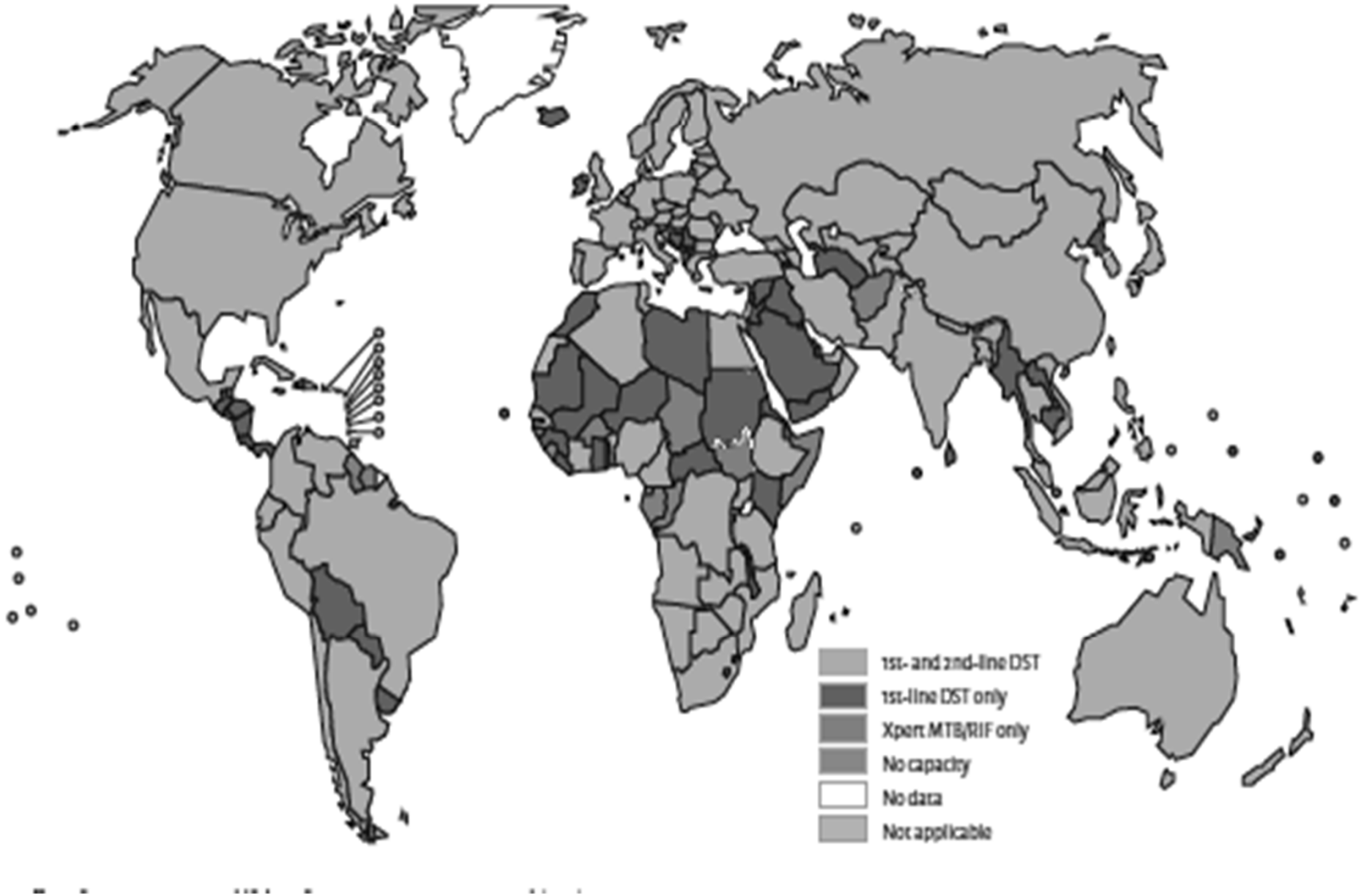
Can we Improve MDR-TB Diagnosis?

WHO Endorses GeneXpert MTB/RIF December 2010

- Xpert MTB/RIF-molecular test, detects TB and rifampin resistance directly from sputum
- Provides diagnosis in < 2 hours
- Sensitivity
  - sm-pos: 98% (95% CI: 97%-99%)
  - sm-neg: 68% (95% CI: 61%-74%)
  - HIV-pos: 79% (95% CI: 70%-86%)
  - RIF-R: 95% (95% CI: 90%-97%)

FIGURE 5.1

Global capacity for drug-susceptibility testing (DST), 2014[a]



2015 Global TB Report

WHO MDR-TB Treatment Recommendations

- 4 second-line antituberculosis drugs likely to be effective as well as PZA, should be included in the intensive phase
- 3rd generation FQ, ETO, CS preferred over PAS
- Intensive phase 8 months
- Drop injectable after intensive phase
- Total duration 20 months or 12 months after culture conversion

WHO MDR-TB Treatment Guidelines, 2011

Can we Improve MDR-TB Treatment Success?

Old and Repurposed Drugs for MDR-TB Treatment

- PZA
- Fluoroquinolones
- Clofazimine
- Linezolid
- Meropenem + Clavulinic acid

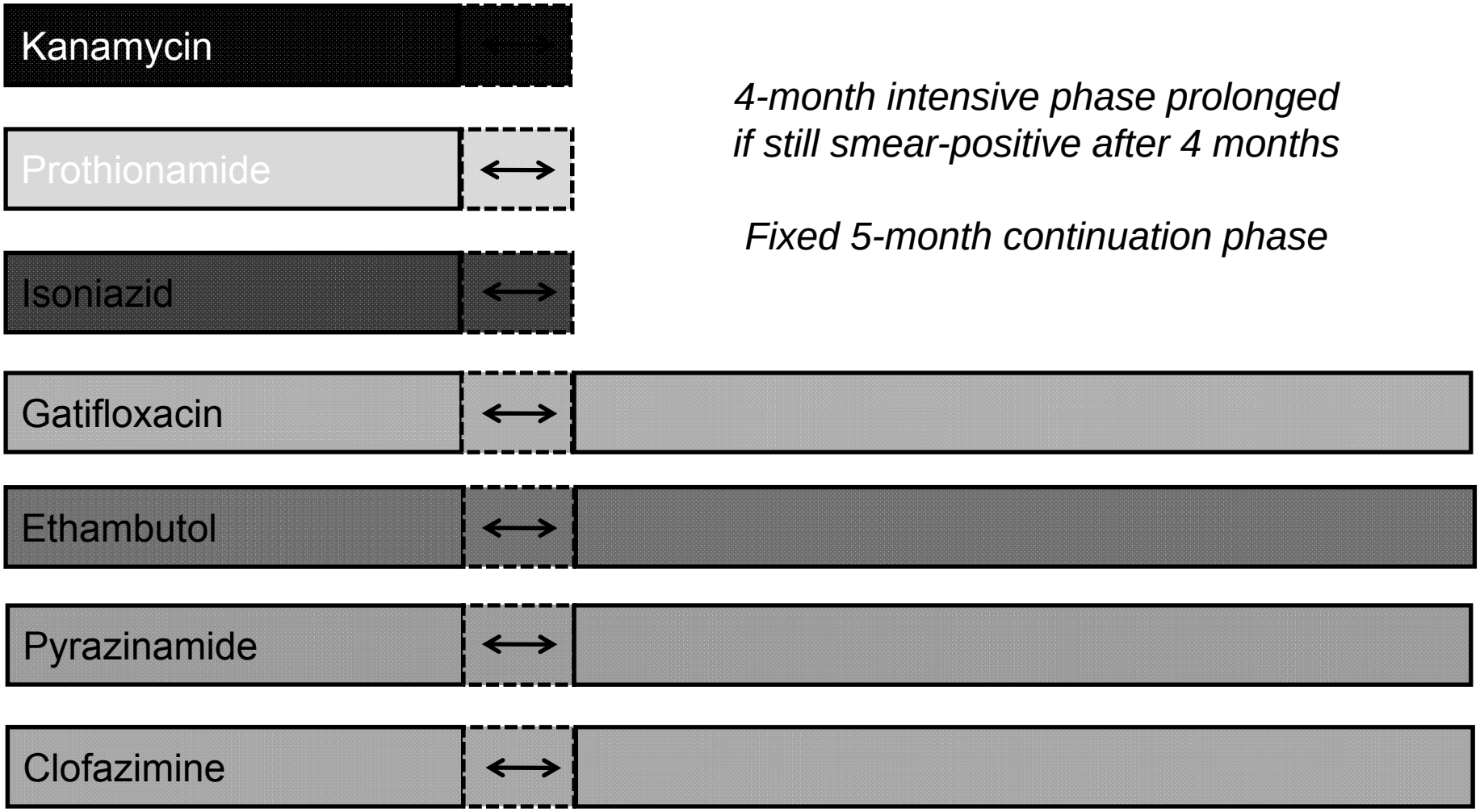
Pyrazinamide for MDR-TB

- Shortens duration of DS-TB therapy
- Synergistic with new and repurposed drugs in murine models
- Substantial hepatotoxicity
- 40-60% of MDR-TB isolates are resistant to PZA

“Third Generation” Fluoroquinolones

- Levofloxacin, Moxifloxacin and Gatifloxacin
- Gatifloxacin not widely available
- Moxifloxacin causes QT prolongation
- Optimal doses of Levofloxacin and Moxifloxacin for TB remain to be determined
- Global resistance to Levo and Moxi ~ 0-9% of MDR-TB

A 9-month regimen for MDR-TB in Bangladesh



4-month intensive phase prolonged if still smear-positive after 4 months

Fixed 5-month continuation phase

AJRCCM 2010:182:684-92

Bangladesh Regimen: Efficacy

515 patients

- 435 Cures/completions (84.5%)
- 29 Deaths (5.6%)
- 40 Defaults (7.8%)
- 7 Failures (1.4%)
- 4 Relapses (0.8%)

IJTLD 2014:18:1180-8

Bangladesh Regimen: Tolerability

515 patients

- 111 Vomiting (21.6%)
- 8 Diabetes/glycosuria (1.5%)
- 50% completion in 9m; 95% in 12m
- Risk factors for failure: FQ or PZA resistance

IJTLD 2014:18:1180-8

STREAM Study

- Description: Modified Bangladesh regimen (with moxifloxacin in place of gatifloxacin) compared to "standard" MDR-TB regimen
- Regimens: 7-drug regimen (9 months)
  4-5 drugs (18-24 months)
- Sponsors: IUATLD, USAID
- Target population: smear+ MDR-TB, adults
- Outcome: Failure, relapse, default or death
- Size: 400 patients – 100% enrolled
- Sites: Ethiopia, Vietnam, South Africa
- Expected completion: 2017

Tolerability of Clofazimine

- Skin discoloration (75-100%)
- Gastrointestinal intolerance (40-50%)
- Eosinophilic enteritis
- Interstitial nephritis
- Rash, dry skin, ichthyosis
- QT prolongation

Clofazimine in TB Treatment

- Use for treatment of Leprosy since 1969
- Effective against *M. tuberculosis* in murine studies
- Early trials of use against TB were not successful
- Little activity in EBA study (days 1-14)
- Part of the “Bangladesh” regimen for MDR-TB
- Persists in tissues for 6-12 months after being given

Clofazimine in MDR-TB Treatment

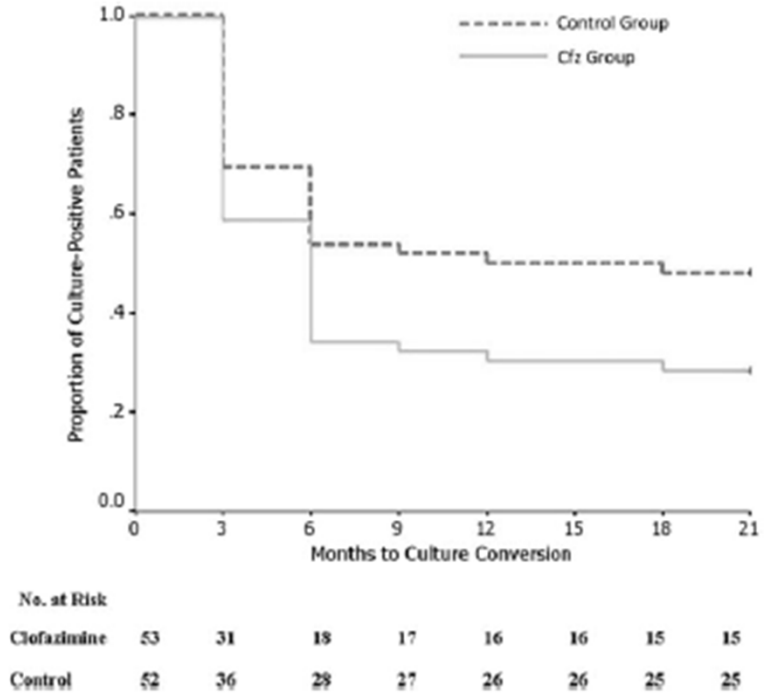


Figure 2. Kaplan–Meier plots of the proportion of patients with positive sputum cultures and time to conversion. Sputum culture conversion to negative was earlier in patients who received clofazimine (Cfz) vs controls ($P = .042$ by log-rank test).

Table 2. Treatment Outcomes

Treatment Outcomes	Cfz Group (n = 53), No. (%)	Control Group (n = 52), No. (%)	*P* Value
Treatment success	39 (73.6)	28 (53.8)	.04
Cure	27 (50.9)	20 (38.5)	.20
Treatment completion	12 (22.6)	8 (15.4)	.34
Poor treatment outcomes	14 (26.4)	24 (46.2)	.04
Death	4 (7.5)	4 (7.7)	1
Failure	6 (11.3)	15 (28.8)	.03
Default	4 (7.5)	5 (9.6)	.74

Abbreviation: Cfz, clofazimine.

105 patients randomized to
OBT+CFZ vs. OBT+Placebo

Clin Infect Dis 2015;60:1361

Clofazimine Trial – Phase 3

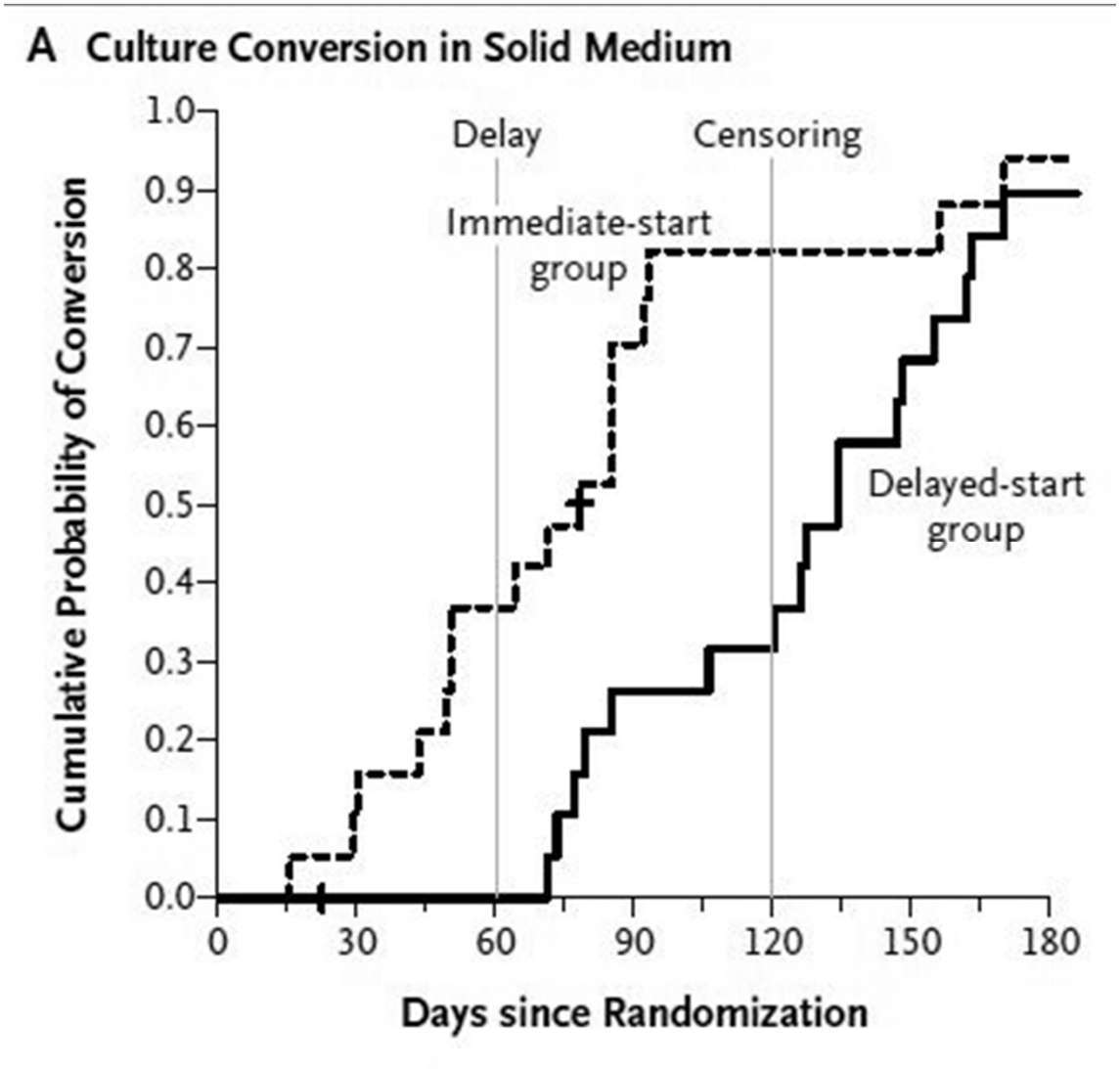
- Description: WHO standard regimen +/- Clofazimine
- Regimens: WHO Standard + $CFZ_{200/100}$ (20-24 months)
  WHO Standard + Placebo (20-24 months)
- Sponsor: Novartis
- Target population: Xpert+ MDR-TB, adults,+/-HIV
- Outcomes: Time to negative sputum culture, cure, relapse
- Size: 380 patients
- Sites: Global
- Expected results: 2020

Prospective Study of Linezolid in XDR-TB Treatment

- 40 patients with XDR-TB in Korea
- Randomized to 300mg qd or 600mg qd
- Further randomized to immediate versus 2 month delayed linezolid (both with OBR)
- 36/40 converted sputum cultures (mean 90 days)
- 4 failures were all resistant to linezolid

NEJM 2012;367:1508-18

Linezolid in the Treatment of XDR-TB



NEJM 2012;367:1508-18

Tolerability of Linezolid in 72 Patients with MDR-TB*

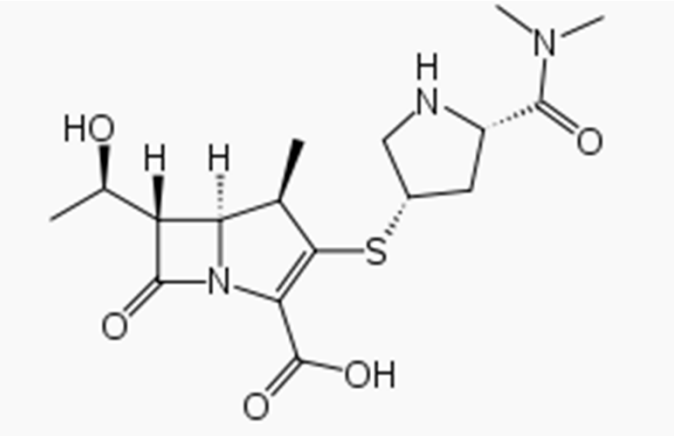
- Peripheral neuropathy (40%)
- Anemia (25%)
- Optic Neuritis (10%)
- Thrombocytopenia (10%)
- GI disorders (8%)
- Neutropenia (2%)

*Dose ≤ 600mg/day

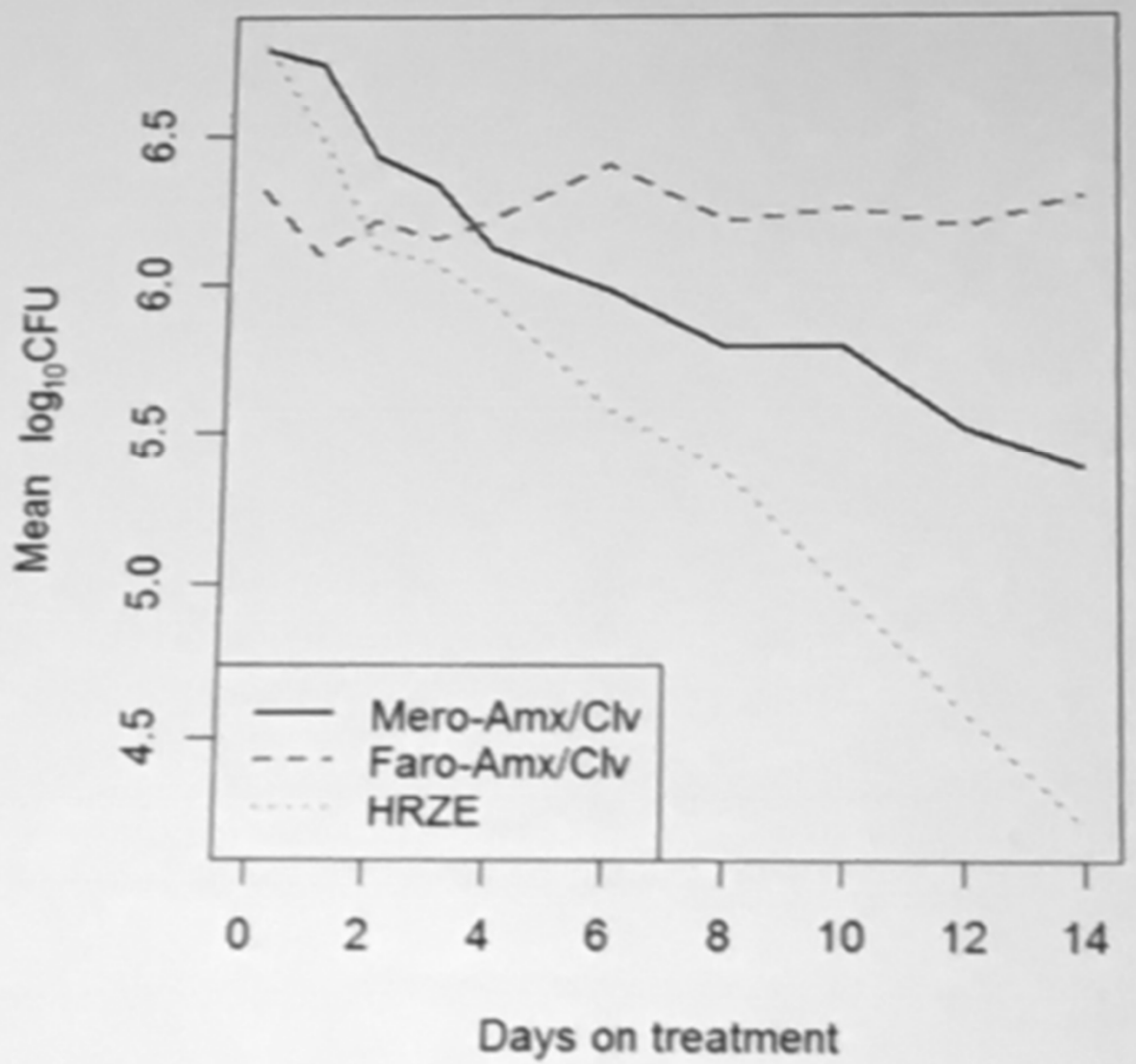
Eur Resp J 2012;40:1437

Meropenem/Clavulinate

- Drug class: Carbapenem (beta-lactam)
- Mode of action: bacterial wall synthesis inhibitor; needs to be given with oral clavulinic acid
- Half life: 1 hour; renal excretion
- Toxicities: headache, diarrhea, nausea, thrombophlebitis
- Chemical Structure:



Observed means of log_{10}CFU



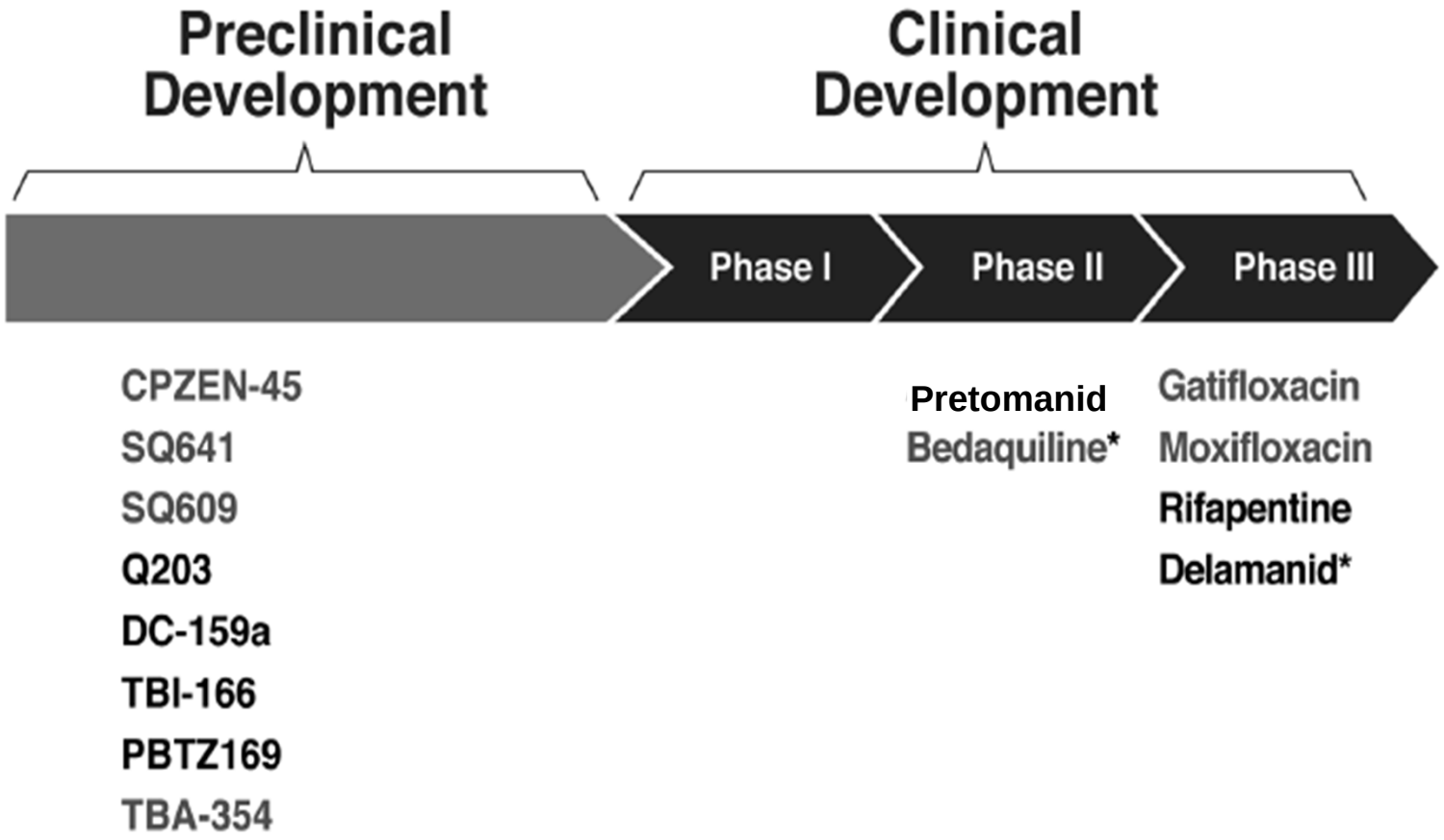
Efficacy and Tolerability of Meropenem

- 37 patients received meropenem 1 gm I.V. tid with clavulanate (125 mg p.o. tid) plus OBT including linezolid
- 61 comparison patients received OBT, most including linezolid
- Sputum-culture conversion in 31/37 (83.8%) versus 15/24 (62.5%) controls (p=0.06)
- 5/37 (13.5%) experienced diarrhea potentially attributed to meropenem–clavulanate
- Two of the five also experienced transient increased liver function tests

Eur J Resp Dis 2013;41:1386

New Drugs for MDR-TB Treatment

Global TB Drug Pipeline



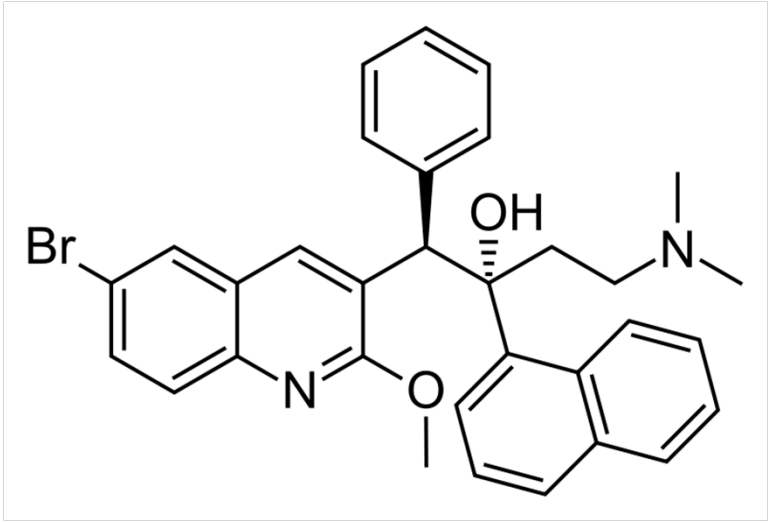
Concepts or candidate drugs to which NIAID has contributed support at some point in development

*Undergoing continued clinical testing to secure full licensure

Updated June 2014. Adapted from Stop TB Partnership http://www.newtbdrugs.org, June 2013.

Bedaquiline (TMC-207)

- Drug class: diarylquinolone
- Mode of action: inhibits proton pump for ATP synthase
- Half life: 24 hours
- Toxicities: Nausea, QT prolongation
- Chemical Structure:

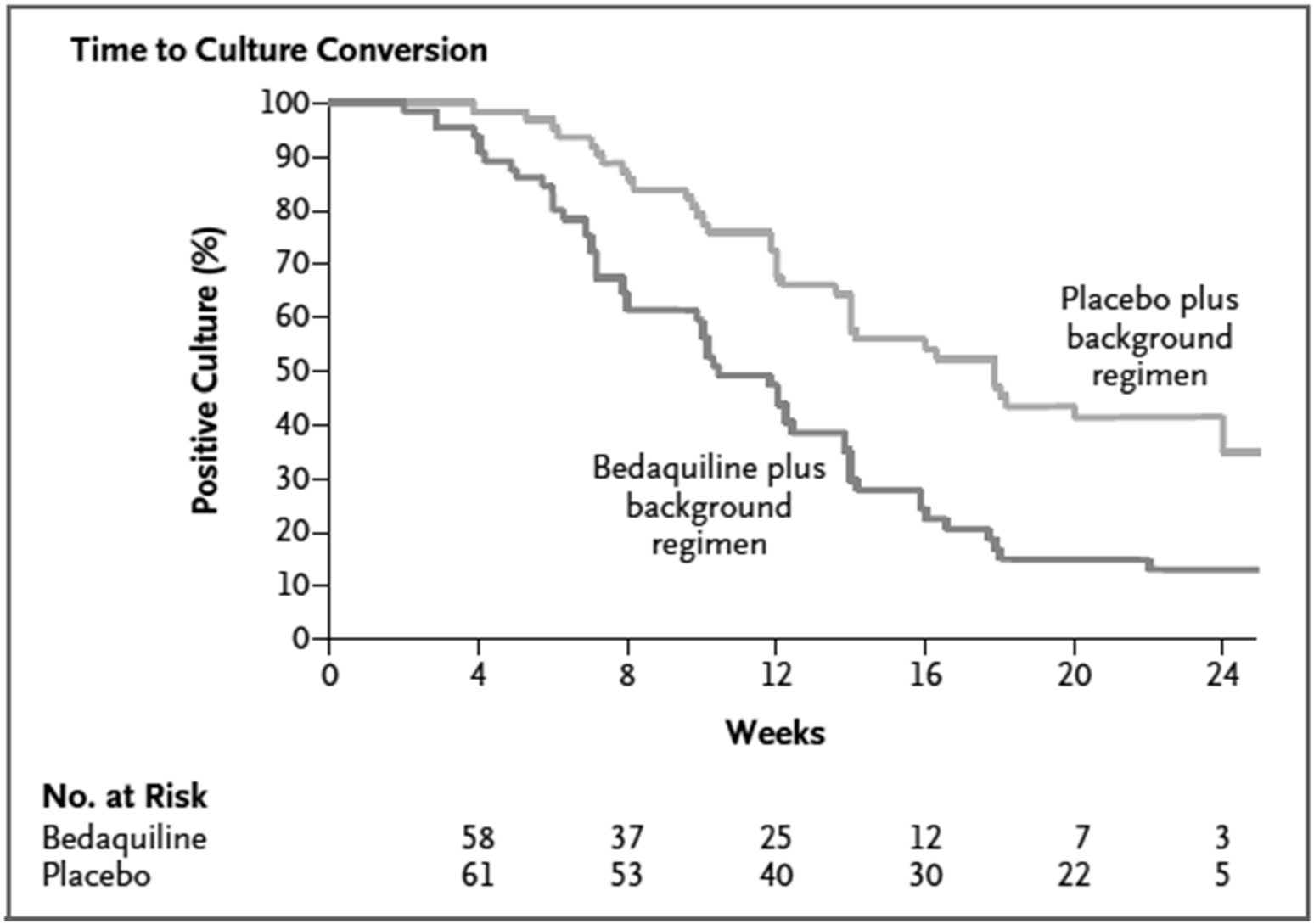


Bedaquiline Phase 2 Study

- Description: Addition of Bedaquiline to OBT for 6 months, followed by OBT for 18 months
- Regimens: OBT+Bedaquiline

  OBT+Placebo
- Sponsor: Janssen
- Target population: newly-diagnosed, smear+ MDR-TB, adults, CD4>300 if HIV+
- Outcome: Time to sputum culture conversion
- Size: 200 patients

Bedaquiline Phase 2 Study
Time to sputum culture conversion



NEJM 2014;371:730

Bedaquiline Phase 2 Study
Final results

	Bedaquiline+OBT	Placebo+OBT
Number	79 patients	81 patients
Median Conversion	12 weeks	18 Weeks*
“Cure” at week 120	58%	32%*
Serious Adverse Events	23%	19%

*p<0.01

NEJM 2014;371:723-32

Tolerability of Bedaquiline

- QT prolongation: +15.4 msec in BDQ vs. +3.3 msec in Placebo
- Increased death at 120 weeks: 10/79 (13%) in BDQ vs. 2/81 (2%) in Placebo
- No other differences between BDQ and Placebo

NEJM 2014;371:730

WHO Bedaquiline Recommendations

- Use for patients with MDR-TB where isolate is resistant to FQ or injectable (or both)
- May also use if patient is intolerant of FQ or injectable
- Give only for first 6 months of regimen
- Continue other drugs for total of 20 months
- Do not use with delamanid

WHO Bedaquiline Recommendations, 2012

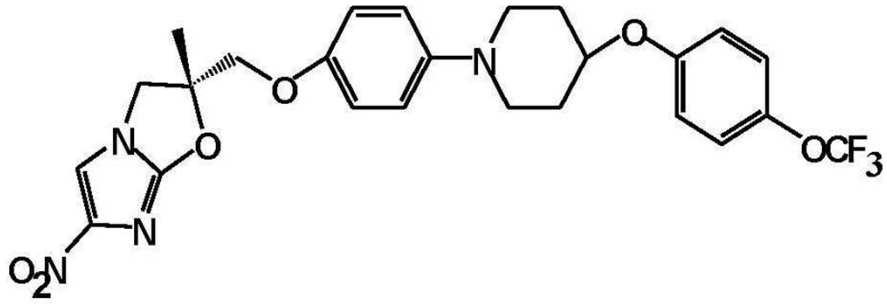
FIGURE 4.10

Countries that had used bedaquiline for the treatment of M/XDR-TB as part of expanded access, compassionate use or under normal programmatic conditions by the end of 2014

2015 Global TB Report

Delamanid (OPC-67683)

- Drug class: nitroimidazo-oxazole
- Mode of action: mycolic acid synthesis inhibitor
- Half life: 20-30 hours
- Toxicities: Nausea, QT prolongation
- Chemical Structure:



Delamanid Phase 2 Study

- Description: Addition of Delamanid (D) to OBT
- Regimens: OBT+D 100 mg bid

  OBT+D 200mg bid

  OBT+Placebo
- Target population: Adults with pulmonary MDR-TB, CD4>350 if HIV+
- Outcome: Sputum conversion at *8 weeks*
- Size: 430 patients

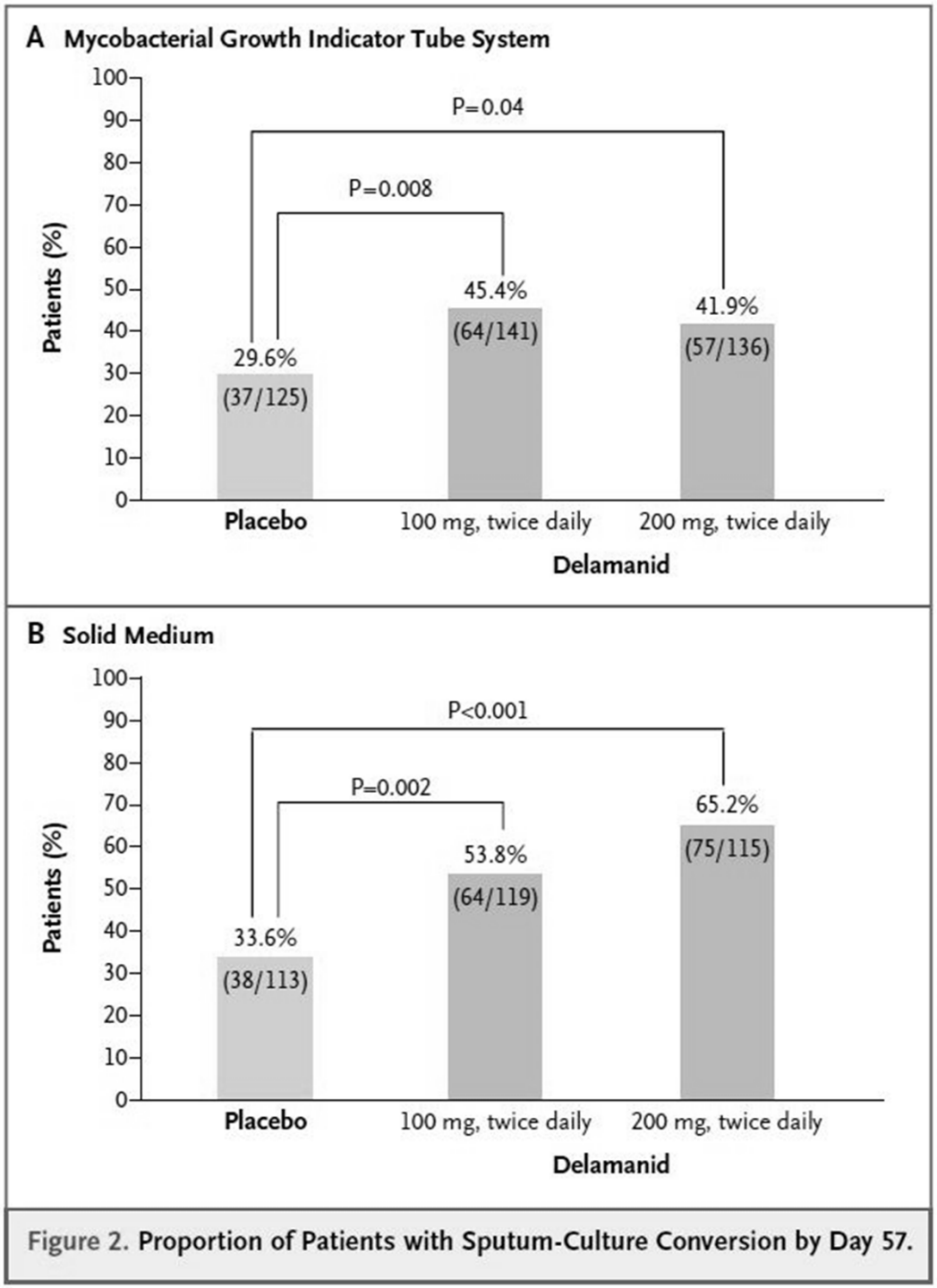


Figure 2. **Proportion of Patients with Sputum-Culture Conversion by Day 57.**

NEJM 2012;366:2158

Tolerability of Delamanid

- Increases in QTcF from baseline were 7.6 ms at 1 month and 12.1 ms at 2 months
- 3% of patients experienced an increase of 60 ms or greater
- 1 patient exhibited a QTcF interval > 500 ms
- No cases of Torsades de Pointes

NEJM 2012;366:2157

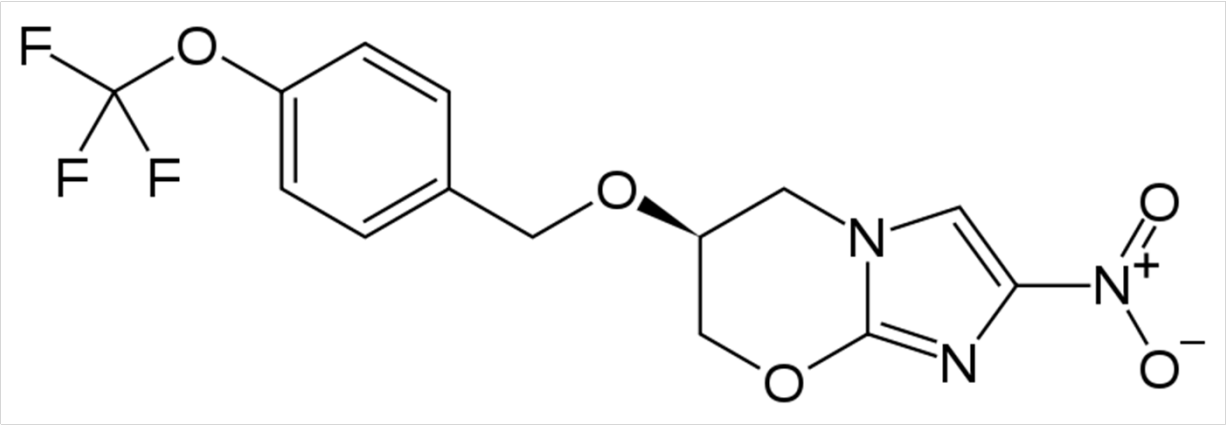
WHO Delamanid Recommendations

- Use for patients with MDR-TB where isolate is resistant to FQ or injectable (or both)
- May also use if patient is intolerant of FQ or injectable
- Give only for first 6 months of regimen
- Continue other drugs for total of 20 months
- Do not use with bedaquiline

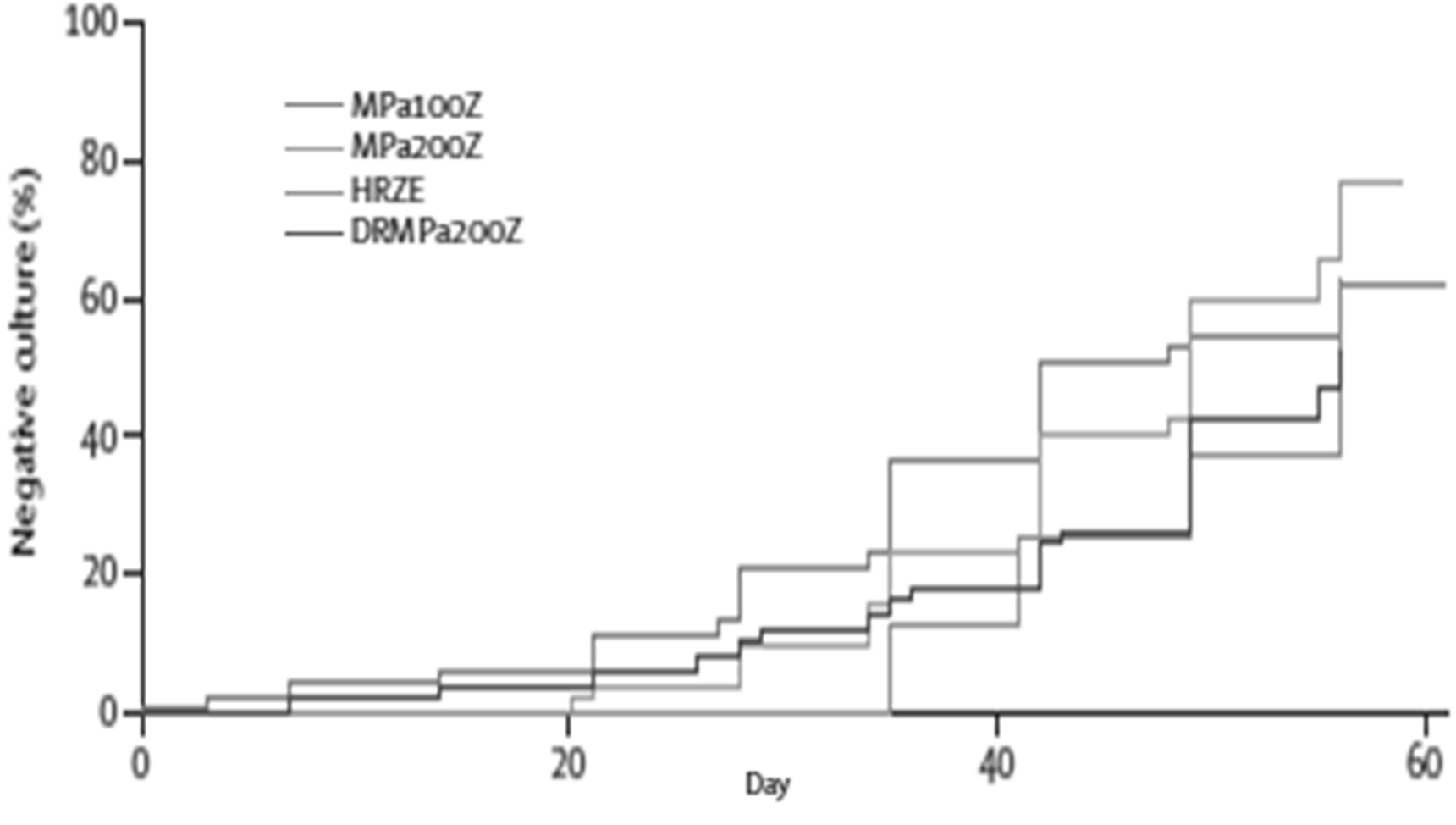
WHO Delamanid Recommendations, 2014

Pretomanid (PA-824)

- Drug class: nitroimidazo-oxazine
- Mode of action: mycolic acid synthesis inhibitor
- Half life: 16-20 hours
- Toxicities: QT prolongation?
- Chemical Structure:



Pretomanid/Moxi/PZA Regimen



Lancet March 18, 2015

MDR-TB Clinical Trials in Progress

- Delamanid - Phase 3
- Opti-Q – Phase 2 (Opti-Q)
- Pretomanid – Phase 3 (STAND)
- Pretomanid+Bedaquiline – Phase 2 (NC-005)
- Pretomanid+Bedaquiline – Phase 3 (NiX-TB)
- NEXT Trial – Phase 3 (BDQ+ oral OBT)

Constructing a new MDR-TB Regimen: Principles

- At least 3 new drug classes
- Avoid overlapping toxicities
- Strive for all-oral regimen
- Estimate duration based on 2 month sputum culture conversion

MDR-TB Drug Menu

Class	
Diarylquinolone:	bedaquiline
Nitroimidazole:	delamanid, PA-824
Oxazolidinone:	linezolid, sutezolid?, others?
Fluoroquinolone:	levofloxacin, moxifloxacin, (gatifloxacin)
Riminophenazine:	clofazimine
Other:	PZA

MDR-TB Clinical Trials in Preparation

- STREAM Stage 2: 6 and 9-month BDQ regimens
- ACTG 5343: Bedaquiline/Delamanid DDI
- MDR-END: 9-month DLM+LZD+LFX+PZA Regimen
- TB-PRACTECAL: PRT+BDQ+LZD+PZA
- EndTB: BDQ, DLM and Combinations
- ACTG 5356: LZD dose optimization with DLM

MDR-TB Prevention

- Ensure that treatment of DS-TB is completed to prevent emergence of DR
- Find and promptly treat MDR-TB cases to reduce primary spread in the community
- Treatment of contacts with MDR-TB?

MDR-TB Household Contact Studies in Preparation

- V-QUIN (levofloxacin)
- TB-CHAMP (levofloxacin)
- Phoenix (delamanid)

Conclusions

- New TB drug classes may increase MDR-TB treatment responses, shorten treatment duration and decrease mortality
- Tolerability of a number of the new and repurposed agents remains to be defined, especially when used in combination
- Combination studies are underway to assess DDI between new agents, other TB drugs and ART

To follow developments in MDR-TB diagnosis and treatment:

RESIST-TB Website

www.resisttb.org