Updates on drug resistance patterns, newer drug regimens and TB vaccine

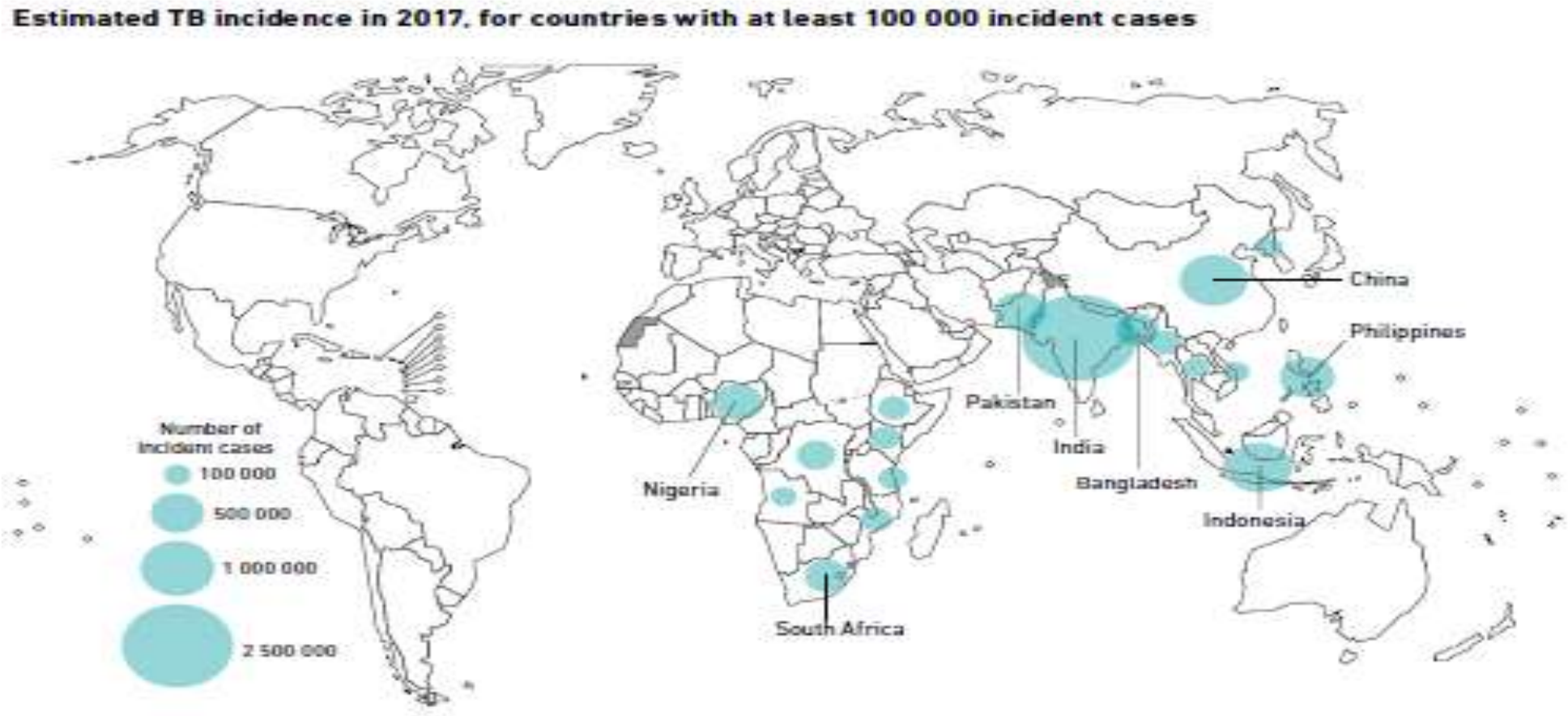
DM Seminar

Harshith Rao

Outline

- Introduction
- Drug resistance: Epidemiology – Risk factors, trends
  - Global
  - Indian
- Molecular mechanisms
- National drug resistance survey
- Newer drug regimens for DR TB : Ongoing trials
- WHO recommendation: Shorter MDR regimen
- TB vaccines

Global TB Incidence 2017



World Health Organization. *Global Tuberculosis Report, 2018.*
Available at: www.who.int/tb/publications/ global_report/en/.

Global Incidence:2016 vs 2017

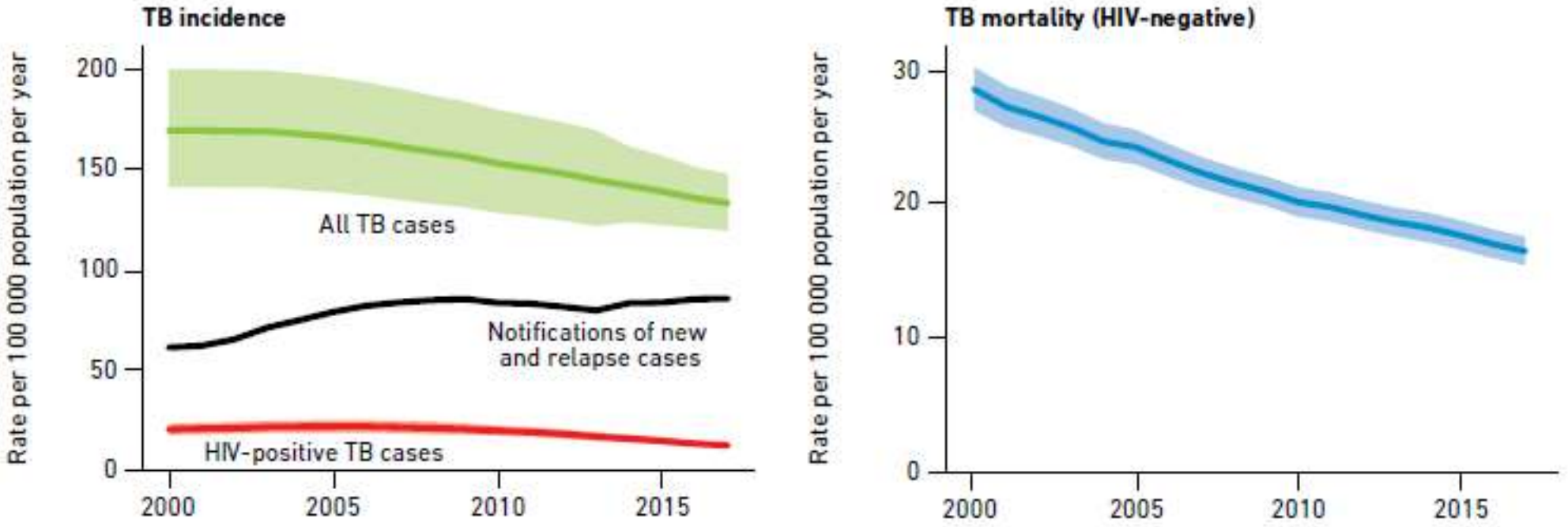
- 10.4 million new cases
- 140 incidence rates

- 10 million new cases
- 133 incidence rates

World Health Organization. *Global Tuberculosis Report, 2017 &2018.*
Available at: www.who.int/tb/publications/ global_report/en/.

Global Trends in Incidence

Global trends in estimated TB incidence and mortality rates, 2000–2017. Shaded areas represent uncertainty intervals.



World Health Organization. *Global Tuberculosis Report, 2018.* Available at: www.who.int/tb/publications/ global_report/en/.

- number of incident cases : falling slowly
- rate of decline (TB incidence rate) : 1.5%pa during 2000−2017

- Incidence Rates (2017)
  - World : 133 (140 in 2016)
  - India : 204 (211 in 2016) ➔ contributing to 27% of the world's TB burden

World Health Organization. *Global Tuberculosis Report, 2018.*
Available at: www.who.int/tb/publications/ global_report/en/.

Definitions

DEFINITIONS

- **Multidrug-resistant (MDR)** refers to TB caused by *Mycobacterium tuberculosis (M. tuberculosis)* that is **resistant to at least isoniazid (INH) and rifampin (RIF).**
- **Pre-extensively drug-resistant (Pre-XDR)** refers to MDR-TB that is **also resistant to *either* a fluoroquinolone *or* a second-line injectable anti-TB drug (kanamycin, capreomycin, or amikacin), but not both.**
- **Extensively drug-resistant (XDR)** refers to MDR-TB that is **also resistant to *both* a fluoroquinolone and a second-line injectable anti-TB drug.**

- Primary Resistance
- Secondary Resistance

2016 vs 2017: Globally MDR-TB

- 600,000 new cases
- 240,000 deaths

- 558,000 new cases
- 230,000 deaths

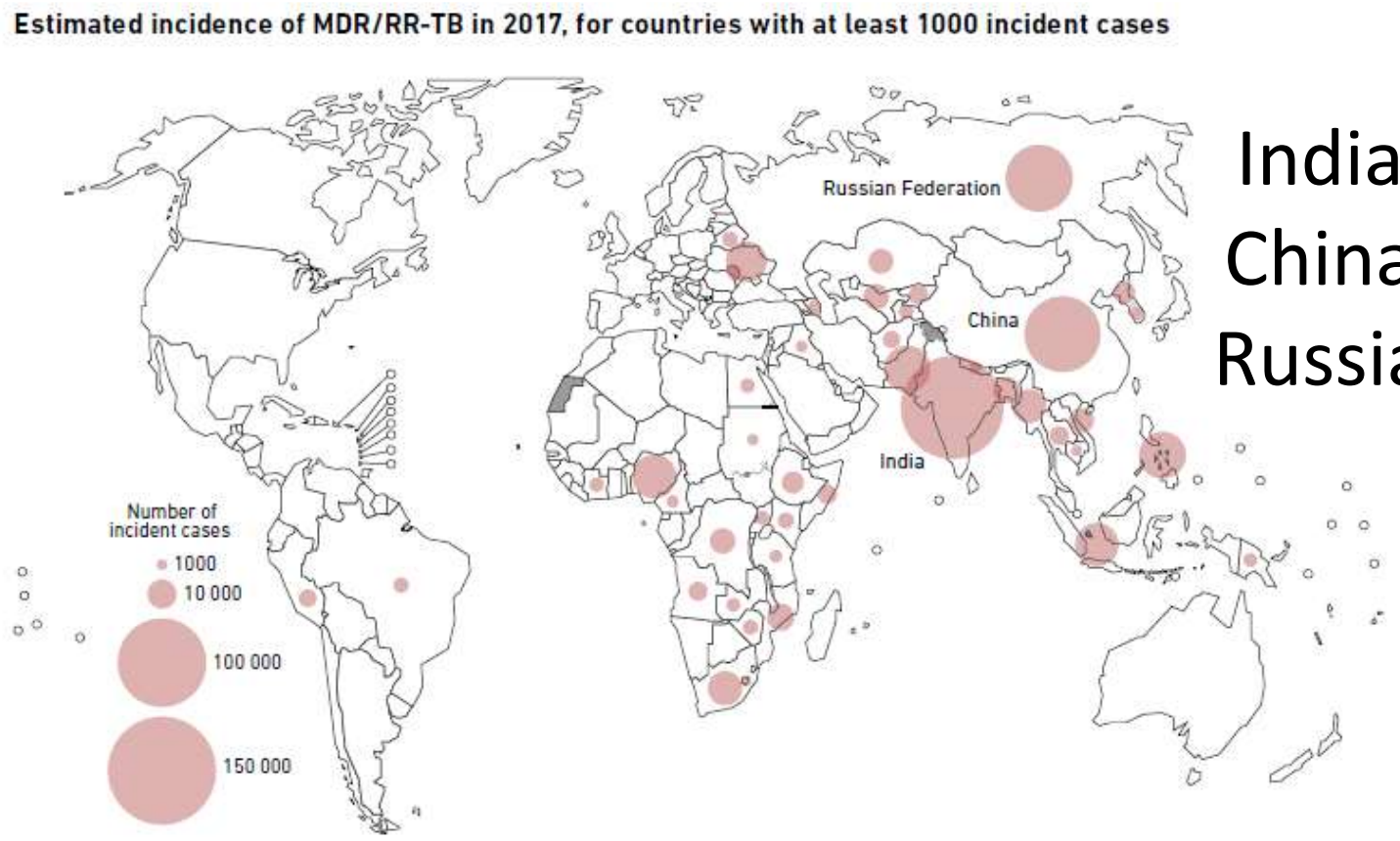
- 4.1% in new cases
- 19% in prev treated cases

- 3.5% in new cases
- 18% in prev treated cases

- The proportion of XDR-TB among MDR-TB patients is 6.2% worldwide

World Health Organization. *Global Tuberculosis Report,2017 & 2018.*
Available at: www.who.int/tb/publications/ global_report/en/.

Global Incidence of MDR TB



India 24%
China 13%
Russia 10%

World Health Organization. *Global Tuberculosis Report, 2018.* Available at: www.who.int/tb/publications/ global_report/en/.

Risk Factors

- **Patients with history of TB (current or past)**
  - Persistent or progressive clinical and/or radiographic findings while on Rx
  - Lack of conversion of cultures to negative during first three months of Rx
  - Non compliance to Rx
  - Lack of directly observed therapy or poorly supervised Rx
  - Documented Rx failure or relapse
  - Inappropriate Rx (few effective drugs or inadequate drug dosing)

Risk Factors

- **Patients without prior history of TB**
  - Exposure to an individual with known or suspected drug-resistant TB
  - Residence in or travel to a region with high prevalence of drug-resistant TB

Single greatest Risk factor
h/o prior treatment (incomplete/ unsupervised)

Isoniazid

- Inhibits synthesis of mycolic acid

- inhA (85-90%)
- katG (10-25%)

- Enoyl acyl carrier protein reductase

Vilchèze C, Wang F, Arai M, et al. Transfer of a point mutation in Mycobacterium tuberculosis inhA resolves the target of isoniazid. Nat Med 2006; 12:1027.
Rozwarski DA, Grant GA, Barton DH, et al. Modification of the NADH of the isoniazid target (InhA) from Mycobacterium tuberculosis. Science 1998; 279:98.

Rifampicin

- Interferes with transcription: binds to RNA polymerase
- rpoB gene (beta chain of mycobacterial RNA polymerase)
- Detected by GenXpert MTB/RIF

Miller LP, Crawford JT, Shinnick TM. The rpoB gene of Mycobacterium tuberculosis. Antimicrob Agents Chemother 1994; 38:805.

Telenti A, Imboden P, Marchesi F, et al. Detection of rifampicin-resistance mutations in Mycobacterium tuberculosis. Lancet 1993; 341:647.

Pyrazinamide

- Prodrug
- Converted to active pyrazinoic acid by pyrazinamidase (pncA gene)

- Less frequent mutation

Scorpio A, Lindholm-Levy P, Heifets L, et al. Characterization of pncA mutations in pyrazinamide-resistant Mycobacterium tuberculosis. Antimicrob Agents Chemother 1997; 41:540.
Kurbatova EV, Cavanaugh JS, Dalton T, et al. Epidemiology of pyrazinamide-resistant tuberculosis in the United States, 1999-2009. Clin Infect Dis 2013; 57:1081.

Ethambutol

- Inhibits mycobacterial cell wall biosynthesis

- embB gene: arabinosyl transferase ➔ arabinogalactan
- Cell wall constituent

Telenti A, Philipp WJ, Sreevatsan S, et al. The emb operon, a gene cluster of Mycobacterium tuberculosis involved in resistance to ethambutol. Nat Med 1997; 3:567.

Streptomycin

- Inhibits mRNA translation
- rpsL/rrs gene: ribosomal protein

Nair J, Rouse DA, Bai GH, Morris SL. The rpsL gene and streptomycin resistance in single and multiple drug-resistant strains of Mycobacterium tuberculosis. Mol Microbiol 1993; 10:521.

Fluroquinolones

- Inhibits DNA gyrase
- gyrA/gyrB gene
- uncommon

Cambau E, Sougakoff W, Jarlier V. Amplification and nucleotide sequence of the quinolone resistance-determining region in the gyrA gene of mycobacteria. FEMS Microbiol Lett 1994; 116:49.

Where does India stands?

- New cases : MDR-TB in India is 147,000 accounting for one fourth of the global burden of MDR-TB
- The treatment success rate in India is 46%(52% globally) and the death rate is 20% (17% globally)
- **PMDT** since 2007

World Health Organization. *Global Tuberculosis Report, 2018.*
Available at: www.who.int/tb/publications/ global_report/en/.

National Anti-TB Drug Resistance Survey (NDRS)

- largest ever NDRS conducted by any country in the world
- DST for 13 anti-TB drugs
- Used MGIT 960

- Period of survey: August 2014 to July 2015

NDRS

- to estimate the prevalence of drug resistance among TB patients with particular focus on MDR-TB among both new and previously treated TB patients

- 5280 sputum smear-positive pulmonary TB patients diagnosed at the DMCs of RNTCP were enrolled in the survey

Ministry of Health & Family Welfare
Government of India

World Health Organization
India

Report of the

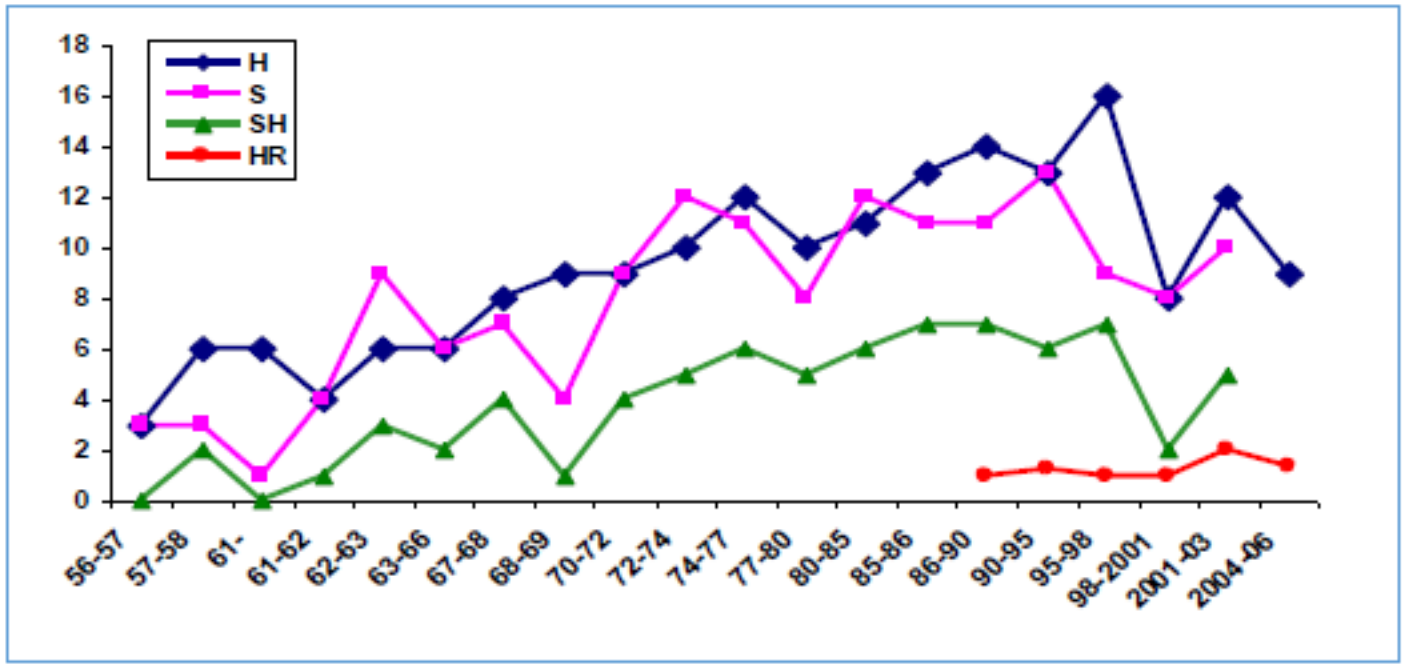
FIRST NATIONAL ANTI-TUBERCULOSIS DRUG RESISTANCE SURVEY

INDIA

2014–16

USAID

Fig. 1: Trend of first-line anti-TB drug resistance from historical surveys



H – Isoniazid; S- Streptomycin; SH – Streptomycin + Isoniazid; HR – Isoniazid + Rifampicin

Rates of MDR/RR-TB reported under RNTCP – India's routine surveillance data	Among new TB patients	Among previously treated patients
2007–2012 (n = 144 326)	NA	19%
2013–2015 (n = 779 300)	5%	11%
2016 (n = 580 438)	4%	9%

RNTCP: National surveillance data 2007-2016

Table 8: MDR-TB/XDR-TB among new and previously treated TB patients

	New TB patients (95% CI)	Previously treated patients (95% CI)	All patients (95% CI)
DST results	3065	1893	4958
Susceptible	2374 (77.46%) (75.93–78.92%)	1196 (63.18%) (60.96–65.36%)	3570 (72.01%) (70.73–73.25%)
Any DR	691 (22.54%) (21.10–24.10%)	697 (36.82%) (34.64–39.04%)	1388 (28.00%) (26.77–29.29%)
MDR	87 (2.84%) (2.28–3.49%)	220 (11.62%) (10.21–13.15%)	307 (6.19%) (5.54–6.90%)
MDR + any SLI	6 (6.90%) (2.57–14.41%)	5 (2.27%) (0.74–5.22%)	11 (3.58%) (1.80–6.32%)
MDR + any FQ	21 (24.14%) (15.60–34.50%)	46 (20.91%) (15.73–26.89%)	67 (21.82%) (17.33–26.87%)
XDR	2 (2.30%) (0.28–8.06%)	2 (0.91%) (0.11–3.25%)	4 (1.30%) (0.36–3.30%)

MDR-TB rate

- 6.19%
- 2.84% among new pts
- 11.60% among previously treated TB patients

Isoniazid resistance

- new 11.06%
- previously treated TB patients was 25.09%

Any drug resistance

- 28.02%
- new TB patients: 22.54%
- 36.82% among previously treated TB patients

- Negligible rifampicin mono-resistance in the survey and isoniazid resistance was invariably associated with rifampicin resistance

- Among MDR-TB patients, additional resistance to any fluoroquinolone was 21% and any second line drug resistance was 3.84%

- Among MDR-TB patients, XDR-TB rate was 1.3%

Economic burden

MDR-TB: A staggering cost for a small percentage of TB cases

A 2014 study by Marks, et al., of MDR-TB patients in the United States in 2005-2007 determined that the direct costs to treat drug-resistant TB averaged $134,000 per MDR-TB patient and $430,000 per XDR-TB patient. In contrast, the estimated cost per non-MDR-TB patient was $17,000.

Marks SM, Flood J, Seaworth B, et al. Treatment practices, outcomes, and costs of multidrug-resistant and extensively drug-resistant tuberculosis, United States, 2005–2007. *Emerg Infect Dis*. 2014;20(5): 812-820.

Molecular Biology of Drug Resistance

- low spontaneous mutation rate, as well as a doubling time (18-24 hrs)
- Thick cell wall made of mycolic acid, precludes horizontal transfer of resistance genes via plasmids or transposon
- All currently known acquired resistances are mediated through chromosomal mutations that arise under selective pressure of antibiotic use

Why combination therapy?

- Mixed population of bacteria with naturally occurring resistance to various drugs
- Replication : spontaneous mutations in genome
- Selection occurs if single drug used

- Chance of an organism to have resistance to 2 drugs is 1 in 10^{14}
- combination therapy : less drug resistance

Why directly observed therapy?

If the patient starts an effective TB regimen and then stops taking all the TB drugs at the same time, the population of bacteria usually remains susceptible.

This is one of the major advantages of directly observed therapy (DOT): either the patient takes all the drugs or none of the drugs. This is also the benefit of combination formulations such as INH/RIF or INH/RIF/PZA in a single product. The patient either takes all drugs or none—reducing risk of development of resistance.

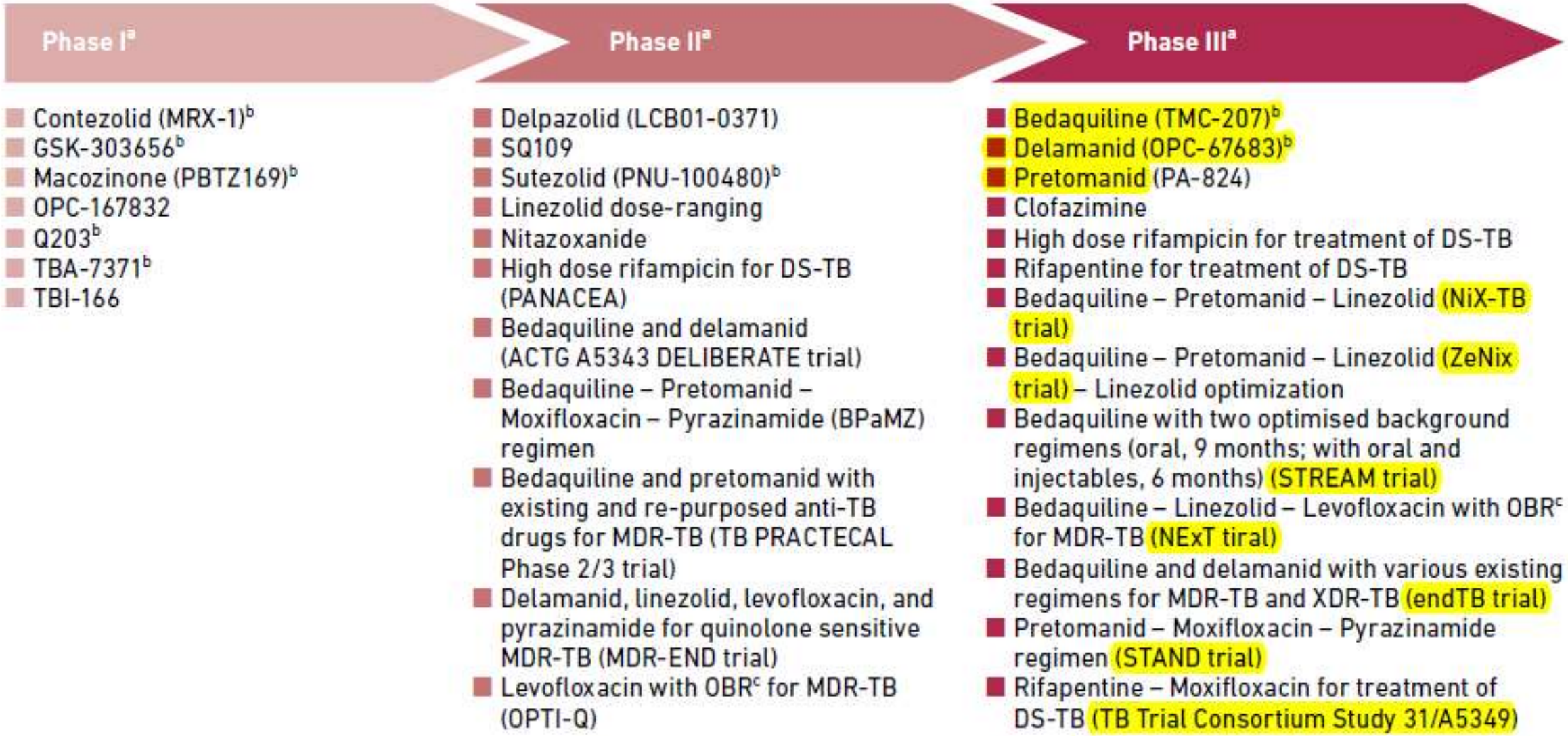
Caminero JA. Multidrug-resistant tuberculosis: epidemiology, risk factors and case finding. *Int J Tuberc Lung Dis*. 2010;14:382-390.

Newer Drug Regimens DR-TB

Why newer drug regimens?

- Long duration of Treatment
- Poor adherence
- Emergence of drug resistant strains
- Drug interaction with ARTs

The global clinical development pipeline for new anti-TB drugs and regimens, August 2018



World Health Organization. *Global Tuberculosis Report, 2018.* Available at: www.who.int/tb/publications/ global_report/en/.

Nix TB Trial

Nix-TB:

Testing a New Potential Treatment for XDR-TB

- The world’s first clinical trial to study an XDR-TB drug regimen
- Injection free regimen
- Open label, single arm 3 RCT
- Bedaquiline + linezolid + pretomanid (triple drug regimen)
- 6 to 9 months

- to evaluate the efficacy, safety, tolerability and pharmacokinetics after 6 months of treatment (option for 9 months for subjects who remain culture positive at month 4) in Subjects with XDR-TB & MDR-TB

- Status: 109 enrolled (target 200)
- Completion Oct 2021

ZeNix Trial

- To evaluate the efficacy, safety and tolerability of various doses and durations of linezolid plus bedaquiline and pretomanid after 26 weeks of treatment in participants with either pulmonary XDR-TB, pre-XDR-TB, or treatment intolerant or non-responsive MDR-TB

- Phase 3, multi-center, partially-blinded, randomized clinical trial in four parallel treatment groups
- Bedaquiline and pretomanid treatment will not be blinded.
- Linezolid treatment dose and duration will be double-blinded.

- randomized to one of the four regimens in a 1:1:1:1 ratio
- will receive 26 weeks of treatment
- If week 16 sample remains culture positive, current treatment is extended to 39 weeks
- will be followed for 78 weeks after end of treatment

- Completion: January 2022

NEXT trial

- to evaluate the impact of a new **injection-free six-to-nine month treatment regimen** of linezolid, bedaquiline, levofloxacin, pyrazinamide (PZA) and ethionamide/high dose isoniazid (INH) compared to the conventional empiric injection-based regimen of 21-24 months treatment

- a Prospective, multisite, Open-label Randomised Controlled Trial
- Completion : January 2019

endTB Trial

- Evaluating Newly Approved Drugs for Multidrug-resistant TB

- Phase III, randomized, controlled, open-label, non-inferiority, multi-country trial evaluating the efficacy and safety of new, all-oral, shortened regimens(including bedaquiline and/or delamanid with existing drugs) for multidrug-resistant tuberculosis (MDR-TB)
- 5 experimental and 1 standard-of-care control arms

- Completion April 2021

Table 1: Regimens tested in recently completed or ongoing clinical trials

Clinical trial	Regimen	Ongoing / completed	All drugs are commercially available
STREAM 1 regimen B	Cfz, E, Z, Mfx, H, Km (16 weeks); followed by Cfz, E, Z, Mfx (24 weeks)	Enrollment completed	Yes
NiX-TB	Bdq, Pa, Lzd (24-36 weeks)	Enrollment completed	No
MDR END	Dlm, Lzd, Lfx, Z (36-52 weeks)	Enrolling	Yes
STREAM 2 regimen C	Bdq, Cfz, E, Z, Lfx, H, Pto (16 weeks); followed by Bdq, Cfz, E, Z, Lfx (24 weeks)	Enrolling	Yes
STREAM 2 regimen D	Bdq, Cfz, Z, Lfx, H, Km (8 weeks); followed by Bdq, Cfz, Z, Lfx (20 weeks)	Enrolling	Yes
PRACTECAL regimen 1	Bdq, Pa, Lzd (24-36 weeks)	Enrolling	No
PRACTECAL regimen 2	Bdq, Pa, Lzd, Cfz (24-36 weeks)	Enrolling	No
PRACTECAL regimen 3	Bdq, Pa, Lzd, Mfx (24-36 weeks)	Enrolling	No
endTB regimen 1	Bdq, Lzd, Mfx, Z (39 weeks)	Enrolling	Yes
endTB regimen 2	Bdq, Cfz, Lzd, Lfx, Z (39 weeks)	Enrolling	Yes
endTB regimen 3	Bdq, Dlm, Lzd, Lfx, Z (39 weeks)	Enrolling	Yes
endTB regimen 4	Dlm, Cfz, Lzd, Lfx, Z (39 weeks)	Enrolling	Yes
endTB regimen 5	Dlm, Cfz, Mfx, Z (39 weeks)	Enrolling	Yes

Bangladesh Regimen

Successful '9-month Bangladesh regimen' for multidrug-resistant tuberculosis among over 500 consecutive patients

K. J. M. Aung,* A. Van Deun,[†‡] E. Declercq,[§] M. R. Sarker,* P. K. Das,* M. A. Hossain,* H. L. Rieder[‡¶]

*Damien Foundation, Dhaka, Bangladesh; [†]Mycobacteriology Unit, Institute of Tropical Medicine, Antwerp, Belgium; [‡]International Union Against Tuberculosis and Lung Disease, Paris, France; [§]Damien Foundation, Brussels, Belgium; [¶]University of Zürich, Zürich, Switzerland

Van Deun A, Maug AKJ, Salim MAH, et al. Short, highly effective and inexpensive standardized treatment of multidrug-resistant tuberculosis. Am J Respir Crit Care Med 2010; 182: 684–692.

- Minimum 4 month intensive phase
- Continuation phase of 5 months

- High dose GFX, EMB, PZA, CFZ through out supplemented by KM, prothionamide and INH in intensive phase

Van Deun A, Maug AKJ, Salim MAH, et al. Short, highly effective and inexpensive standardized treatment of multidrug-resistant tuberculosis. Am J Respir Crit Care Med 2010; 182: 684–692.

Conventional/Other MDR regimens	Bangladesh regimen
meta-analysis of 9153 MDR-TB patients from 32 observational studies conducted in 23 countries showed **a 54% treatment** success rate.	relapse-free cure rate of 87.9%
Costly, € 82 000 approx	Cheap, € 200, with generics
Duration ≥20 months	9 to 11 months
Numerous adverse effects	well tolerated, and serious events requiring a regimen change were rare.

Van Deun A, Maug AKJ, Salim MAH, et al. Short, highly effective and inexpensive standardized treatment of multidrug-resistant tuberculosis. Am J Respir Crit Care Med 2010; 182: 684–692
Diel R, Vandeputte J, de Vries G, et al. Costs of tuberculosis disease in the European Union: a systematic analysis and cost calculation. Eur Respir J 2014; 43: 554–565.

- No RCT’s comparing the Bangladesh regimen with the current standard of care WHO regimen

- STREAM 1 trial aimed to address this issue

STREAM trial

- multicentre randomised controlled trial
- To compare outcomes(efficacy and safety) of a 9-month regimen, based closely on the one developed in Bangladesh, with the current standard of care (the WHO-recommended regimen)

- Difference in GTX and MFX

Nunn AJ, Rusen ID, Van Deun A, et al. Evaluation of a standardized treatment regimen of anti-tuberculosis drugs for patients with multi-drug-resistant tuberculosis (STREAM): study protocol for a randomized controlled trial. Trials 2014; 15: 353

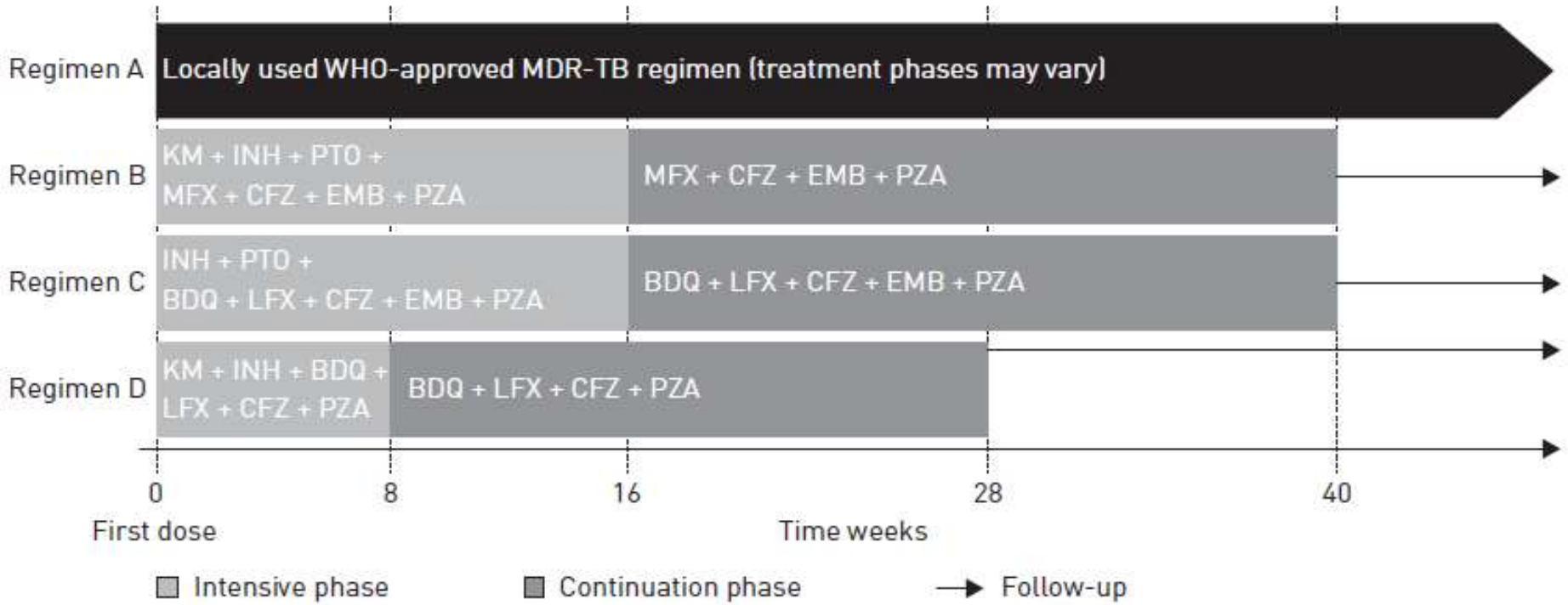


FIGURE 1 STREAM (Evaluation of a Standardised Treatment Regimen of Anti-tuberculosis Drugs for Patients with Multidrug-resistant Tuberculosis) treatment regimens. WHO: World Health Organization; MDR-TB: multidrug-resistant tuberculosis; KM: kanamycin; INH: isoniazid; PTO: prothionamide; MFX: moxifloxacin;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

Nunn AJ, Rusen ID, Van Deun A, et al. Evaluation of a standardized treatment regimen of anti-tuberculosis drugs for patients with multi-drug-resistant tuberculosis (STREAM): study protocol for a randomized controlled trial. Trials 2014; 15: 353

- locally approved current WHO regimen (regimen A)
- the 9-month regimen studied in stage 1 (which becomes the new control regimen for stage 2: regimen B)
- one of the two new study regimens (C or D)

- with a ratio of 1:2:2:2, respectively

Nunn AJ, Rusen ID, Van Deun A, et al. Evaluation of a standardized treatment regimen of anti-tuberculosis drugs for patients with multi-drug-resistant tuberculosis (STREAM): study protocol for a randomized controlled trial. Trials 2014; 15: 353

- Following the release of preliminary results, WHO conducted an expedited review of data provided by the STREAM trial consortium

August 2018

World Health Organization

Rapid Communication:

Key changes to treatment of multidrug- and rifampicin-resistant tuberculosis

(MDR/RR-TB)

Shorter MDR TB drug regimen (STREAM Trial)

- **treatment success** was similar between patients receiving a shorter MDR-TB regimen and longer regimens conforming to prior WHO recommendations

- Shorter MDR TB regimen had an overall comparable **likelihood of treatment success** with longer regimens, with a **lower risk of treatment interruption**

- shorter regimens were associated with **higher risk of treatment failure** and relapse compared to longer regimens, especially when resistance to key medicines in the shorter regimen was present

World Health Organization. WHO issues a position statement on the continued use of the shorter MDR-TB regimen following an expedited review of the STREAM Stage 1 preliminary results. Geneva: WHO; 2018 (http://www.who.int/tb/features_archive/WHO-position-statement- MDRTB-regimen/en/; accessed 12 June 2018).

- 78% of the patients in the STREAM 1 regimen arm experienced a favorable outcome, compared to 81% of the patients in the longer regimen arm
- adverse events were not significantly different in the two arms

World Health Organization. WHO issues a position statement on the continued use of the shorter MDR-TB regimen following an expedited review of the STREAM Stage 1 preliminary results. Geneva: WHO; 2018 (http://www.who.int/tb/features_archive/WHO-position-statement- MDRTB-regimen/en/; accessed 12 June 2018).

- **shorter MDR-TB regimen** refers to a course of treatment lasting 9 to 12 months
- usual structure is as follows:
- 4-6 Km(Am)-Mfx-Pto(Eto)-Cfz-Z-Hhighdose-E
- 5 Mfx-Cfz-Z-E

World Health Organization. WHO issues a position statement on the continued use of the shorter MDR-TB regimen following an expedited review of the STREAM Stage 1 preliminary results. Geneva: WHO; 2018 (http://www.who.int/tb/features_archive/WHO-position-statement- MDRTB-regimen/en/; accessed 12 June 2018).

Longer MDR-TB regimens

- Usually last 18-20 months and may be standardized or individualized.
- Designed to include at least five medicines considered to be effective

- Medicines no longer recommended are kanamycin and capreomycin, given increased risk of treatment failure and relapse associated with their use in longer MDR-TB regimens

- Use of amikacin did not show a similar association

World Health Organization. WHO issues a position statement on the continued use of the shorter MDR-TB regimen following an expedited review of the STREAM Stage 1 preliminary results. Geneva: WHO; 2018 (http://www.who.int/tb/features_archive/WHO-position-statement- MDRTB-regimen/en/; accessed 12 June 2018).

Table 1. Grouping of medicines recommended for use in longer MDR-TB regimens

GROUP	MEDICINE	Abbreviation
Group A: **Include all three medicines (unless they cannot be used)**	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

When shorter MDR TB regimens? Exclusion of

- Resistance or suspected ineffectiveness to a medicine in the shorter MDR-TB regimen (except isoniazid resistance)
- Exposure to one or more 2nd line medicines in the regimen for >1 month (unless susceptibility these 2nd line medicines is confirmed)
- Intolerance to any medicine in the shorter MDR-TB regimen or risk of toxicity
- Pregnancy
- Disseminated, meningeal or central nervous system TB; or any extrapulmonary disease in HIV patients.

World Health Organization. WHO issues a position statement on the continued use of the shorter MDR-TB regimen following an expedited review of the STREAM Stage 1 preliminary results. Geneva: WHO; 2018 (http://www.who.int/tb/features_archive/WHO-position-statement- MDRTB-regimen/en/; accessed 12 June 2018).

Newer TB Vaccines

Current status: BCG vaccination

Protection by BCG Vaccine Against Tuberculosis: A Systematic Review of Randomized Controlled Trials

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[1]Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine; [2]Centre for Infectious Disease Surveillance and Control, Public Health England, London; [3]Centre for Infectious Disease Epidemiology, University College London; [4]School of Social and Community Medicine, University of Bristol; [5]Medical Research Council Human Nutrition Research, University of Cambridge; and [6]Centre for Respiratory Medicine, Royal Free Campus, University College London, United Kingdom

(See the Editorial Commentary by McShane on pages 481–2.)

Background. Randomized trials assessing BCG vaccine protection against tuberculosis have widely varying results, for reasons that are not well understood.

Methods. We examined associations of trial setting and design with BCG efficacy against pulmonary and miliary or meningeal tuberculosis by conducting a systematic review, meta-analyses, and meta-regression.

Results. We identified 18 trials reporting pulmonary tuberculosis and 6 reporting miliary or meningeal tuberculosis. Univariable meta-regression indicated efficacy against pulmonary tuberculosis varied according to 3 characteristics. Protection appeared greatest in children stringently tuberculin tested, to try to exclude prior infection with *Mycobacterium tuberculosis* or sensitization to environmental mycobacteria (rate ratio [RR], 0.26; 95% confidence interval [CI], .18–.37), or infants (RR, 0.41; 95% CI, .29–.58). Protection was weaker in children not stringently tested (RR, 0.59; 95% CI, .35–1.01) and older individuals stringently or not stringently tested (RR, 0.88; 95% CI, .59–1.31 and RR, 0.81; 95% CI, .55–1.22, respectively). Protection was higher in trials further from the equator where environmental mycobacteria are less and with lower risk of diagnostic detection bias. These associations were attenuated in a multivariable model, but each had an independent effect. There was no evidence that efficacy was associated with BCG strain. Protection against meningeal and miliary tuberculosis was also high in infants (RR, 0.1; 95% CI, .01–.77) and children stringently tuberculin tested (RR, 0.08; 95% CI, .03–.25).

Conclusions. Absence of prior *M. tuberculosis* infection or sensitization with environmental mycobacteria is associated with higher efficacy of BCG against pulmonary tuberculosis and possibly against miliary and meningeal tuberculosis. Evaluations of new tuberculosis vaccines should account for the possibility that prior infection may mask or block their effects.

Protection by BCG vaccine against tuberculosis: a systematic review of randomized controlled trial
Clin Infect Dis. 2014 Feb;58(4):470-80

BCG Vaccination: Current status (WHO)

- In countries with high TB burden, single dose of BCG be given to all infants soon after birth(including infants born to women of unknown HIV status)

- Infants with known symptomatic/asymptomatic HIV infection should not receive BCG

World Health Organization. WHO preferred product characteristics for new tuberculosis vaccine. Geneva: WHO; 2018 (http://www.who.int/ immunization/documents/who_ivb_18.06/en/, accessed 30 July 2018)

New evidence

- Provides partial protection against leprosy
- Non specific, beneficial immune modulatory effects

BCG vaccination and leprosy protection: review of current evidence and status of BCG in leprosy control
Expert Rev Vaccines. 2010 Feb;9(2):209-22.
Association of BCG, DTP, and measles containing vaccines with childhood mortality: systematic review
BMJ. 2016 Oct 13;355:i5170

EXPERT REVIEWS

BCG vaccination and leprosy protection: review of current evidence and status of BCG in leprosy control

Expert Rev. Vaccines 9(2), 209–222 (2010)

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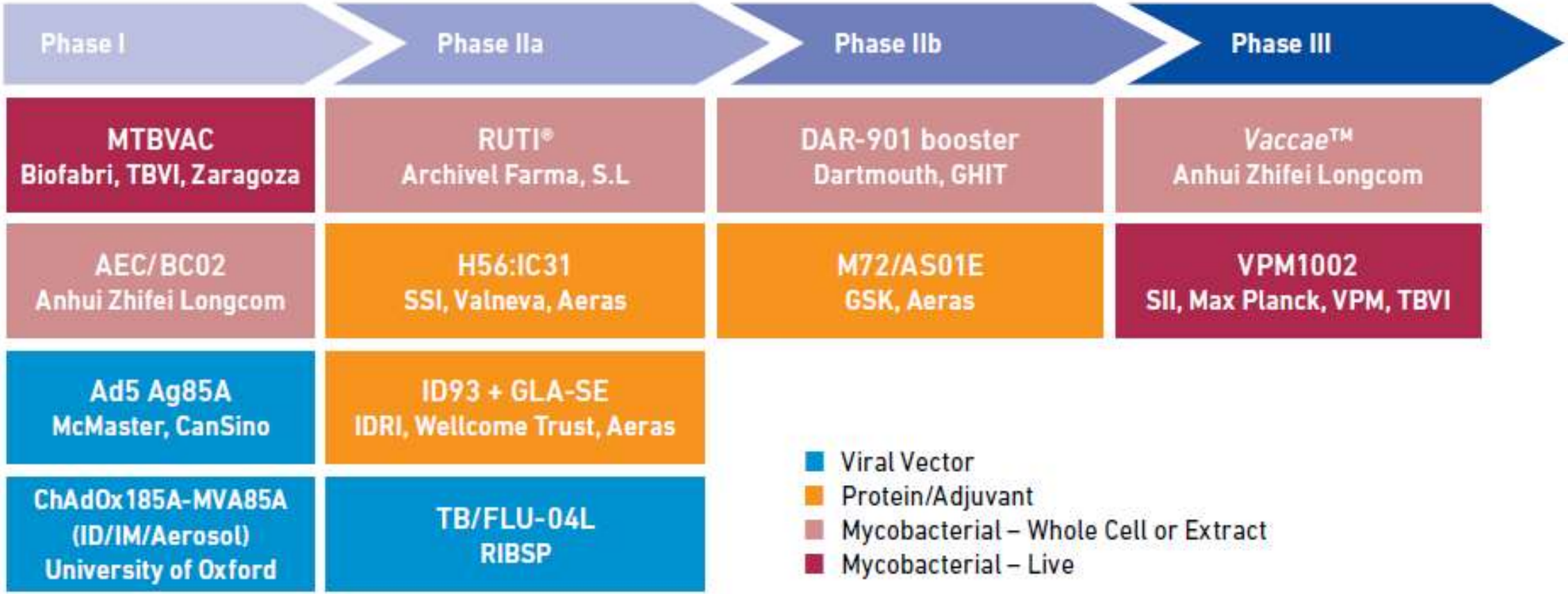
The bacillus Calmette–Guérin (BCG) vaccine, initially developed to provide protection against TB, also protects against leprosy; and the magnitude of this effect varies. Previous meta-analyses did not provide a summary estimate of the efficacy due to the heterogeneity of the results. We conducted a meta-analysis of published data including recently published studies (up to June 2009) to determine the efficacy of BCG protection on leprosy and to investigate whether age at vaccination, clinical form, number of doses, type of study, the latitude of study area and year of publication influence the degree of efficacy and explain the variation. In the light of the results, we argue for more emphasis on the role of BCG vaccination in leprosy control and research.

- 12 new candidates in the pipeline
  - 8 in phase 2/3
  - 4 in phase 1

- unlikely that a new TB vaccine will be available in the immediate future

FIG. 8.3

The global development pipeline for new TB vaccines, August 2018[a]



World Health Organization. *Global Tuberculosis Report, 2018.*
Available at: www.who.int/tb/publications/ global_report/en/.

VPM1002

- live recombinant vaccine
- A Phase II trial is being implemented in South Africa to assess the safety and immunogenicity of the vaccine in HIV-exposed and unexposed neonates
- A Phase II/III trial for prevention of TB recurrence in adults is being implemented in India

World Health Organization. *Global Tuberculosis Report, 2018.*
Available at: www.who.int/tb/publications/ global_report/en/.

Vaccae™ vaccine

- specified lysate that has been licensed by the China Food and Drug Administration as an immunotherapeutic agent to help shorten TB treatment for patients with drug-susceptible TB

- Phase III trial to assess its efficacy and safety in preventing TB disease in people with LTBI has been completed, and data analysis is underway

- The largest TB vaccine trial undertaken in the past decade, involving 10 000 people aged 15–65 years

World Health Organization. *Global Tuberculosis Report, 2018.*
Available at: www.who.int/tb/publications/ global_report/en/.

RUTI®

- non-live, polyantigenic vaccine based on cellwall fragmented *M. tuberculosis* bacteria
- Intended to be used as therapeutic vaccine to be used in conjunction with a short, intensive antibiotic treatment
- A Phase I studyin healthy volunteers and a Phase II study in people with LTBI have demonstrated a good safety profile & found the vaccine to be immunogenic at all studied doses
- main target for RUTI is MDR-TB, and a Phase IIa study in patients with MDR-TB is being implemented

World Health Organization. *Global Tuberculosis Report, 2018.*
Available at: www.who.int/tb/publications/ global_report/en/.

M72/AS01E

- subunit vaccine
- two *M. tuberculosis* antigens (32A and 39A) with an adjuvant (AS01E)

- It is being tested in a Phase IIb efficacy trial in HIV negative adults infected with *M. tuberculosis* in Kenya, South Africa and Zambia

World Health Organization. *Global Tuberculosis Report, 2018.*
Available at: www.who.int/tb/publications/ global_report/en/.

H56:IC31

- Adjuvanted subunit vaccine
- combines three *M. tuberculosis* antigens (Ag85B, ESAT-6 and Rv2660c) with the IC31© adjuvant.
- Three Phase I or I/IIa trials of safety and immunogenicity have been completed

- The trials showed that the vaccine had an acceptable safety profile and was immunogenic at all studied doses.

World Health Organization. *Global Tuberculosis Report, 2018.*
Available at: www.who.int/tb/publications/ global_report/en/.

DAR-901

- whole-cell, heat-inactivated, nontuberculous mycobacterial vaccine booster
- It is now being tested in a Phase IIb preventionof infection trial among BCG-primed adolescents
- The trial is scheduled for completion in 2019

World Health Organization. *Global Tuberculosis Report, 2018.*
Available at: www.who.int/tb/publications/ global_report/en/.