WHO MDR-TB
최신 치료지침 소개

2018.11.9
일선진료의를 위한 결핵강좌
2018 대한결핵 및 호흡기학회 추계학술대회
부산대학교병원 호흡기내과 목정하

UN GENERAL ASSEMBLY HIGH-LEVEL MEETING ON ENDING TB

26 September 2018, New York

FAST FACTS ABOUT UN HLM* ON TB

TB
WORLD'S BIGGEST INFECTIOUS KILLER

KILLING OVER 4500 PEOPLE EVERY DAY

carrying profound economic and social consequences for affected communities and countries

Despite commitments by countries to end TB as part of the UN Sustainable Development Goals (SDGs), the WHO End TB Strategy, and the Global Plan to End TB 2016-2020; The Paradigm Shift (Global Plan),

CURRENT ACTIONS AND INVESTMENTS FALL FAR SHORT OF WHAT IS NEEDED

To address the shortfall,
120 MINISTERS
and other health leaders, and
800 PARTNERS
including civil society,
came together at the First WHO Global Ministerial Conference on Ending TB in November 2017

COMMITTING IN THE MOSCOW DECLARATION TO ACCELERATE EFFORTS TO END TB

These commitments will be elevated to Heads of State at the

FIRST-EVER UN GENERAL ASSEMBLY HIGH-LEVEL MEETING ON TB,

scheduled for September 2018;

The High-Level Meeting on TB should result in an

AMBITIOUS POLITICAL DECLARATION ON TB

that will strengthen action and investments toward the end TB response, saving millions of lives;

ALL

stakeholders - governments, UN agencies, partners, civil society, private sector actors, research and academia, health care providers, and the general public –

CAN AND SHOULD PLAY AN IMPORTANT ROLE IN SECURING COMMITMENT AT THE HIGHEST LEVEL.

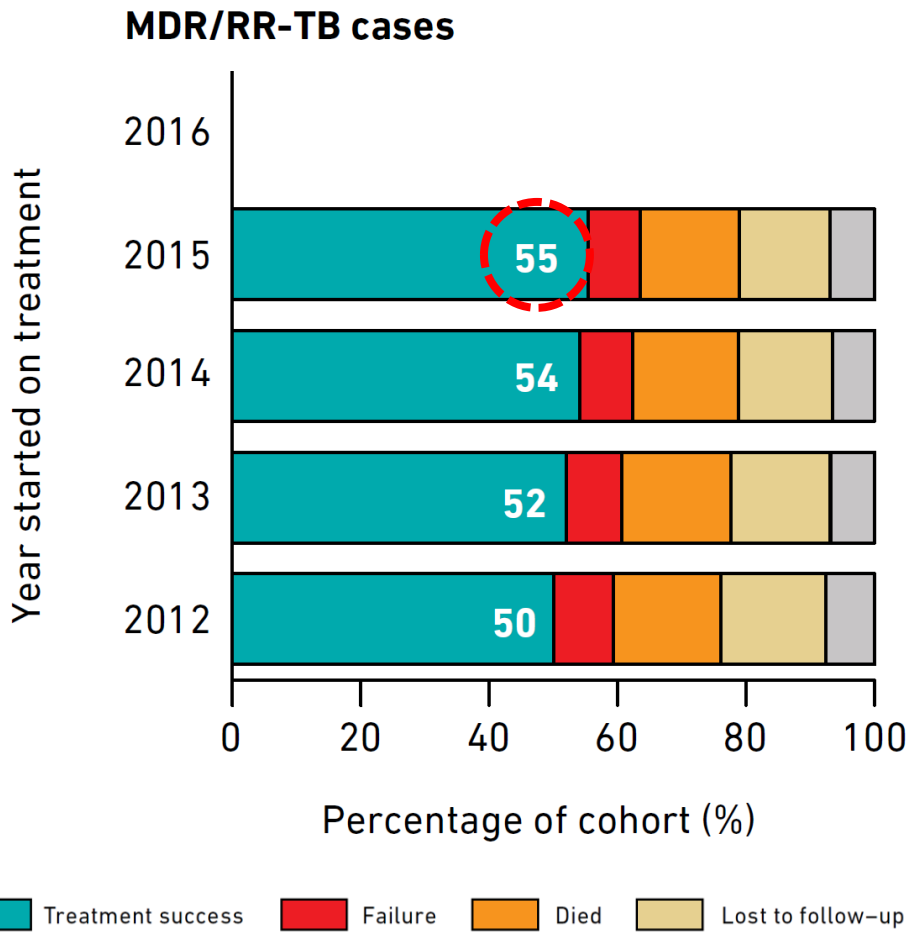
*United Nations High-level Meeting on TB

Stop TB Partnership

World Health Organization

Image from WHO homepage

Global treatment outcomes



XDR-TB : **34%**

WHO. Global tuberculosis report 2018.

Guidelines c

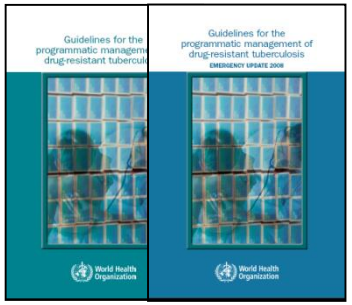
- Regrouping of anti-TB drugs
- Against routinely use of Z
- Shorter regimen

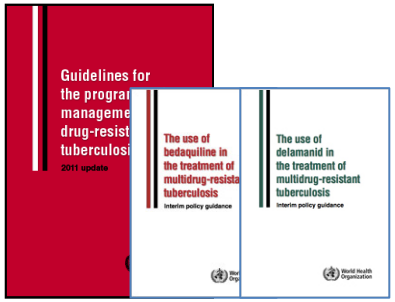
Z - FQ - SLID - Pt

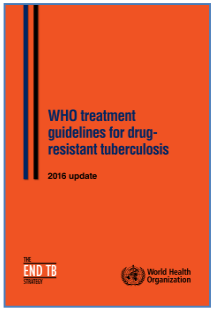
Guide on Bdq, Dlm

2006 2008 2011 2014 2016

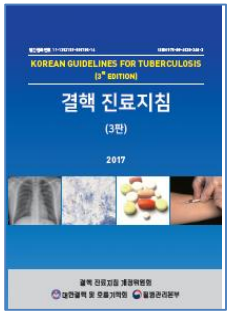
WHO







Korea



2005 2011 2014 2017

Slide: Courtesy of D. Jeon, MD.

2016 WHO guideline

Table 6. Medicines recommended for the treatment of rifampicin-resistant and multidrug-resistant TB[1]

Core	**A. Fluoroquinolones[2]**		Levofloxacin Moxifloxacin Gatifloxacin	Lfx Mfx Gfx
Core	**B. Second-line injectable agents**		Amikacin Capreomycin Kanamycin (Streptomycin)[3]	Am Cm Km (S)
Core	**C. Other core second-line agents[2]**		Ethionamide / Prothionamide Cycloserine / Terizidone Linezolid Clofazimine	Eto / Pto Cs / Trd Lzd Cfz
Add-on	**D. Add-on agents** (not part of the core MDR-TB regimen)	**D1**	Pyrazinamide Ethambutol High-dose isoniazid	Z E H^h
Add-on		**D2**	Bedaquiline Delamanid	Bdq Dlm
Add-on		**D3**	*p*-aminosalicylic acid Imipenem-cilastatin[4] Meropenem[4] Amoxicillin-clavulanate[4] (Thioacetazone)[5]	PAS Ipm Mpm Amx-Clv (T)

WHO. Treatment guidelines for drug-resistant tuberculosis 2016 update.

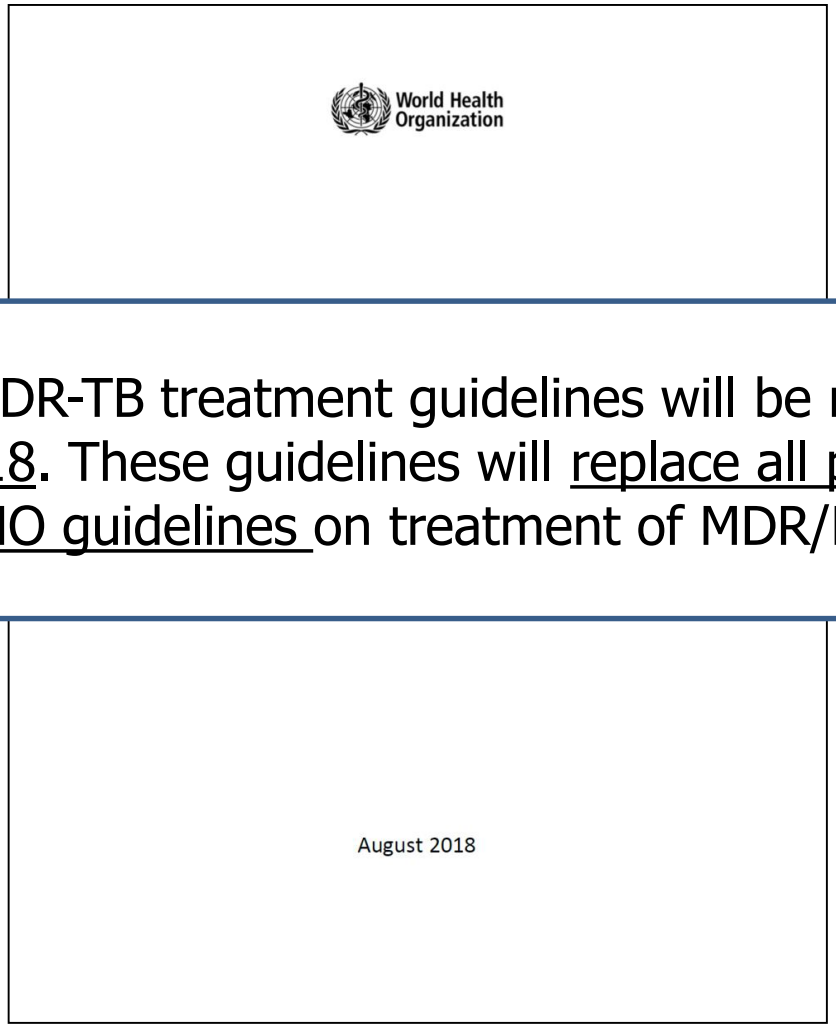
2016 WHO guideline

Table 6. Medicines recommended for the treatment of rifampicin-resistant and multidrug-resistant TB[1]

Core	**A. Fluoroquinolones[2]**	Levofloxacin Moxifloxacin Gatifloxacin	**1**	Lfx Mfx Gfx
Core	**B. Second-line injectable agents**	Amikacin Capreomycin Kanamycin (Streptomycin)[3]	**2**	Am Cm Km (S)
Core	**C. Other core second-line agents[2]**	Ethionamide / Prothionamide Cycloserine / Terizidone	**3,4**	Eto / Pto Cs / Trd
Core		Linezolid Clofazimine		Lzd Cfz
Add-on	**D. Add-on agents** (not part of the core MDR-TB regimen)	**D1** Pyrazinamide Ethambutol High-dose isoniazid	**(5)**	Z E H^h
Add-on		**D2** Bedaquiline Delamanid		Bdq Dlm
Add-on		**D3** *p*-aminosalicylic acid Imipenem-cilastatin[4] Meropenem[4] Amoxicillin-clavulanate[4] (Thioacetazone)[5]		PAS Ipm Mpm Amx-Clv (T)

WHO. Treatment guidelines for drug-resistant tuberculosis 2016 update.

2018 WHO guideline



The new MDR-TB treatment guidelines will be released later in 2018. These guidelines will replace all previous and current WHO guidelines on treatment of MDR/RR-TB.

2018 WHO guideline

Data sources of longer treatment regimens

- Individual patient database (meta-analysis)
- WHO public call data from 26 countries (including Bdq)
- Aggregated results from the phase III RCT of Dlm
- PK and safety data from trials of Bdq and Dlm in children

Key changes of longer regimens

Group	Medicine	Abbreviation
Group A Include all three medicines (unless they cannot be used)	Levofloxacin or Moxifloxacin	Lfx or Mfx
	Bedaquiline ↑	Bdq
	Linezolid ↑	Lzd
Group B Add both medicines (unless they cannot be used)	Clofazimine ↑	Cfz
	Cycloserine or Terizodone	Cs or Trd
Group C Add to complete the regimen and when medicines from Groups A and B cannot be used Km, Cm ✗	Ethambutol	E
	Delamanid	Dlm
	Pyrazinamide	Z
	Imipenem/cilastatin or Meropenem	Ipm-Cln or Mpm
	Amikacin (or Streptomycin) ↓	Am (S)
	Ethionamide or Prothionamide ↓	Eto or Pto
	p-aminosalicylic acid	PAS

WHO. Rapid communication: key changes to treatment of multidrug- and rifampicin-resistant tuberculosis (MDR/RR-TB) 2018.

Key changes of longer regimens

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Group B Add both medicines (unless they cannot be used)	**Clofazimine**	Cfz
	Cycloserine or Terizodone	Cs or Trd
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	Delamanid	Dlm
	Pyrazinamide	Z
	Imipenem/cilastatin or Meropenem	Ipm-Cln or Mpm
	Amikacin (or Streptomycin)	Am (S)
	Ethionamide or Prothionamide	Eto or Pto
	p-aminosalicylic acid	PAS

WHO. Rapid communication: key changes to treatment of multidrug- and rifampicin-resistant tuberculosis (MDR/RR-TB) 2018.

Considerations

1. Evidence on the safety and effectiveness of Bdq beyond 6 months was insufficient for review; extended Bdq use in individual patients will need to follow 'off-label' use best practices.
2. Optimal duration of use of Lzd is not established. Use for at least 6 months was shown to be highly effective,
3. The position of Dlm will be re-assessed once individual patient data from trial 213 has been reviewed; these data were not available for the evidence assessment in July outlined above. Evidence on the safety and effectiveness of Dlm beyond 6 months was insufficient for review; extended use of Dlm in individual patients will need to follow 'off-label' use best practices.
4. Evidence on concurrent use of Bdq and Dlm was insufficient for review.
5. Z is only counted as an effective agent when DST results confirm susceptibility.
6. Amoxicillin-Clavulanic acid is administered with every dose of Imp-Cln or Mpm but is not counted as a separate agent and should not be used as a separate agent.
7. Am and S are only to be considered if DST results confirm susceptibility and high-quality audiology monitoring for hearing loss can be ensured. S is to be considered only if Am cannot be used and if DST results confirm susceptibility (S resistance is not detectable with 2nd line molecular line probe assays and phenotypic DST is required).

WHO. Rapid communication: key changes to treatment of multidrug- and rifampicin-resistant tuberculosis (MDR/RR-TB) 2018.

Considerations

Treatment regimen choice is also determined by

- DST results
- Reliability of existing DST methods
- Population drug resistance levels
- History of previous use of the medicine
- Drug tolerability
- Potential drug-drug interactions

Target of WHO new longer regimen

- All-oral
- More effective
- Less toxic
- Better tolerated
- Reduce the need for hospitalization

Treatm
multidr
meta-a

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PLOS | MEDICINE

Multidrug Resistant Pulmonary Tuberculosis Treatment Regimens and Patient Outcomes: An Individual Patient Data Meta-analysis of 9,153 Patients

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Bdq, Dlm, Lzd, Cfz, Cpm...

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PLoS Med. 2012;9:e1001300.

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Giovanni Sotgiu,
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Lancet. 2018;392:821-34.

IPD meta-analysis

- 50 studies published between Jan, 2009 and April, 2016
- 12,030 patients from 25 countries
  - Children : 2.4%
  - HIV (+) : 18.3%
- Mean age : 38.3 ± 13.8 years
- Resistance levels : Z (51.9%), pre-XDR (about 25%), XDR (10.6%)

- Treatment outcomes
  - Success : 61%
  - Failure or relapse : 8%
  - Died : 14%

Lancet. 2018;392:821-34.

APPENDIX Table S2.3: Treatment received by all 12,030 PATIENTS INCLUDED IN THE IPD ANALYSES

Drugs used in treatment *(% of all patients)*	N	%
Rifabutin (Rfb)	261	2.2 %
Pyrazinamide (PZA)	9669	80.4 %
Ethambutol (EMB)	6072	50.5 %
Fluoroquinolone Used		
Ciprofloxacin (Cfx)	571	4.8 %
Ofloxacin (Ofx)	4413	36.7 %
Levofloxacin (Lfx)	4400	36.6 %
Moxifloxacin (Mfx)	2756	22.9 %
Gatifloxacin (Gfx)	20	0.2 %
Any Later Gen FQN	6779	56.4 %
Any Fluoroquinolone (FQN)	11,296	93.9 %
Injectables used		
Streptomycin (Sm)	2081	17.3 %
Amikacin (Am)	2619	21.8 %
Kanamycin (Km)	4990	41.5 %
Capreomycin (Cm)	2926	24.3 %
Any Second Line Injectable	9863	82.0 %
Group 4 drugs used	N	%
Ethionamide (Eto)	4386	36.5 %
Prothionamide (Pto)	4711	39.2 %
Para-Amino-Salicyclic Acid (PAS)	5239	43.6 %
Cycloserine (Cs)	7131	59.3 %
Terizidone (Trd)	2567	21.3 %
Group 5 and new drugs used:		
Linezolid (Lzd)	1011	8.4 %
Clofazimine (Cfz)	824	6.9 %
Amoxicillin-Clavulanate (AMX – CLV)	1574	13.1 %
Macrolides	1075	8.9 %
Thioacetazone (Thz)	96	0.8 %
Bedaquiline (BDQ)	641	5.3 %
Carbapenem (& clavulanate)	192	1.6 %
Delamanid	29	0.2 %

Lancet. 2018;392:821-34. (suppl.)

Correlates of outcomes

(for susceptible strains)

	Success aOR	**Death** aOR		**Success** aOR	**Death** aOR
E	0.9 (0.7-1.1)	1.0 (0.9-1.2)	**Ofx**	1.0 (0.8-1.2)	0.6 (0.5-0.7)
Z	0.7 (0.5-0.9)	0.7 (0.6-0.8)	**Lfx**	4.2 (3.3-5.4)	0.6 (0.5-0.7)
Eto/Pto	0.8 (0.7-0.9)	0.9 (0.8-1.0)	**Mfx**	3.8 (2.8-5.2)	0.5 (0.4-0.6)
Cs/Trd	1.5 (1.4-1.7)	0.6 (0.5-0.6)	**Lzd**	3.4 (2.6-4.5)	0.3 (0.2-0.3)
PAS	0.8 (0.7-1.0)	1.2 (1.1-1.4)	**Cfz**	1.5 (1.1-2.1)	0.8 (0.6-1.0)
S	1.5 (1.1-2.1)	0.8 (0.6-1.1)	**Bdq***	2.0 (1.4-2.9)	0.4 (0.3-0.5)
Am	2.0 (1.5-2.6)	1.0 (0.8-1.2)	**Cpm***	4.0 (1.7-9.1)	1.0 (0.5-1.7)
Km	0.5 (0.4-0.6)	1.1 (0.9-1.2)	**Amx/Clv***	0.6 (0.5-0.8)	1.7 (1.3-2.1)
Cm	0.8 (0.6-1.1)	1.4 (1.1-1.7)	**Macrolide***	0.6 (0.5-0.8)	1.6 (1.2-2.0)

* No DST testing

Lancet. 2018;392:821-34.

Correlates of outcomes

(for susceptible strains)

	Success aOR	Death aOR		Success aOR	Death aOR
E	0.9 (0.7-1.1)	1.0 (0.9-1.2)	**Ofx**	1.0 (0.8-1.2)	**0.6** (0.5-0.7)
Z	**0.7** (0.5-0.9)	**0.7** (0.6-0.8)	**Lfx**	**4.2** (3.3-5.4)	**0.6** (0.5-0.7)
Eto/Pto	**0.8** (0.7-0.9)	0.9 (0.8-1.0)	**Mfx**	**3.8** (2.8-5.2)	**0.5** (0.4-0.6)
Cs/Trd	**1.5** (1.4-1.7)	**0.6** (0.5-0.6)	**Lzd**	**3.4** (2.6-4.5)	**0.3** (0.2-0.3)
PAS	0.8 (0.7-1.0)	**1.2** (1.1-1.4)	**Cfz**	**1.5** (1.1-2.1)	0.8 (0.6-1.0)
S	**1.5** (1.1-2.1)	0.8 (0.6-1.1)	**Bdq***	**2.0** (1.4-2.9)	**0.4** (0.3-0.5)
Am	**2.0** (1.5-2.6)	1.0 (0.8-1.2)	**Cpm***	**4.0** (1.7-9.1)	1.0 (0.5-1.7)
Km	**0.5** (0.4-0.6)	1.1 (0.9-1.2)	**Amx/Clv***	**0.6** (0.5-0.8)	**1.7** (1.3-2.1)
Cm	0.8 (0.6-1.1)	**1.4** (1.1-1.7)	**Macrolide***	**0.6** (0.5-0.8)	**1.6** (1.2-2.0)

* No DST testing

Lancet. 2018;392:821-34.

XDR-TB

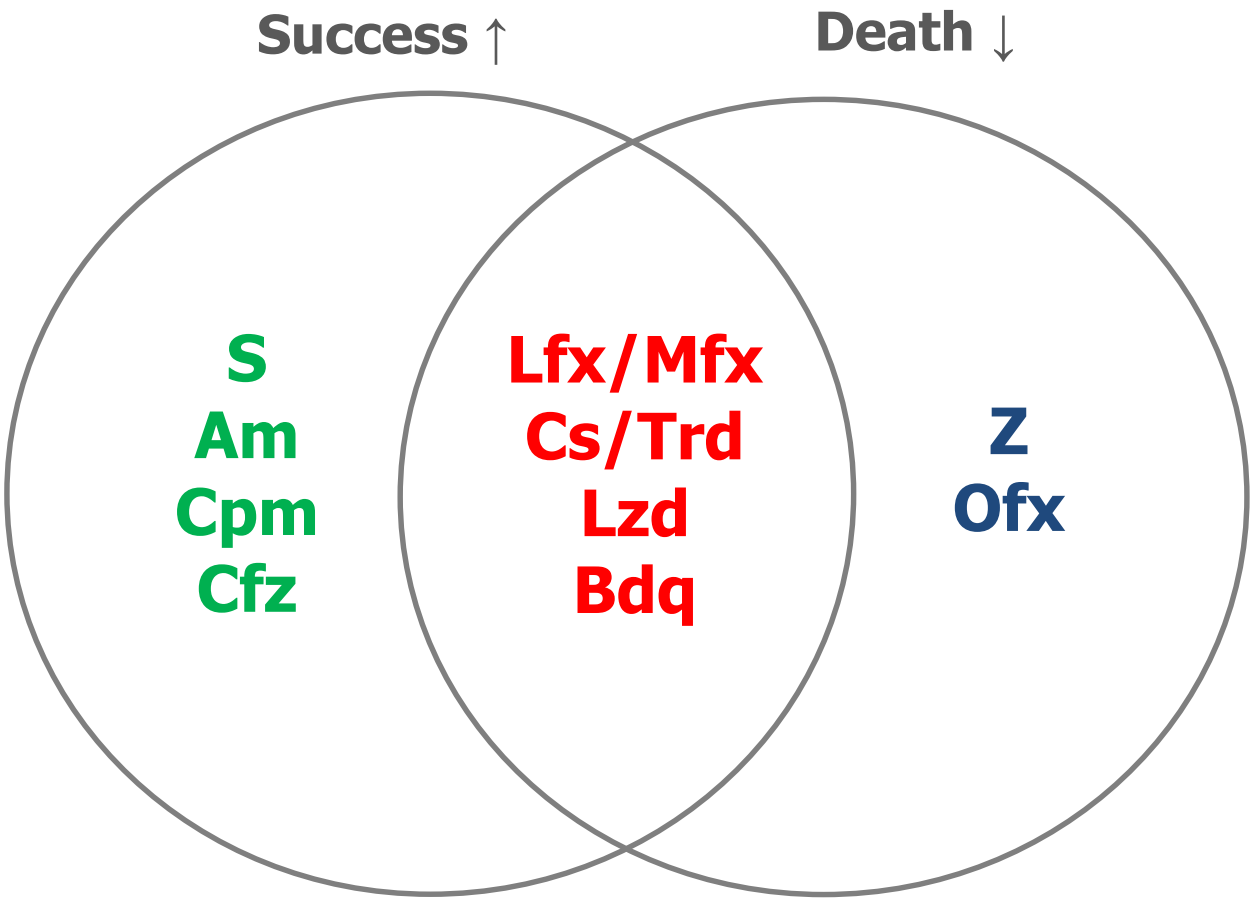
(for all strains)

	Success aOR	**Death** aOR
Am	2.5 (0.9-6.6)	**0.4** (0.2-0.8)
Km	0.9 (0.5-1.9)	0.9 (0.5-1.9)
Cm	**0.5** (0.4-0.7)	**3.4** (2.7-4.3)
Lfx/Mfx	1.2 (0.8-1.6)	**0.6** (0.4-0.8)
Lzd	**6.6** (4.1-10.6)	**0.2** (0.1-0.3)
Cfz	1.5 (0.9-2.6)	**0.4** (0.2-0.6)
Bdq	**2.5** (1.3-4.8)	**0.5** (0.2-0.9)

Lancet. 2018;392:821-34.

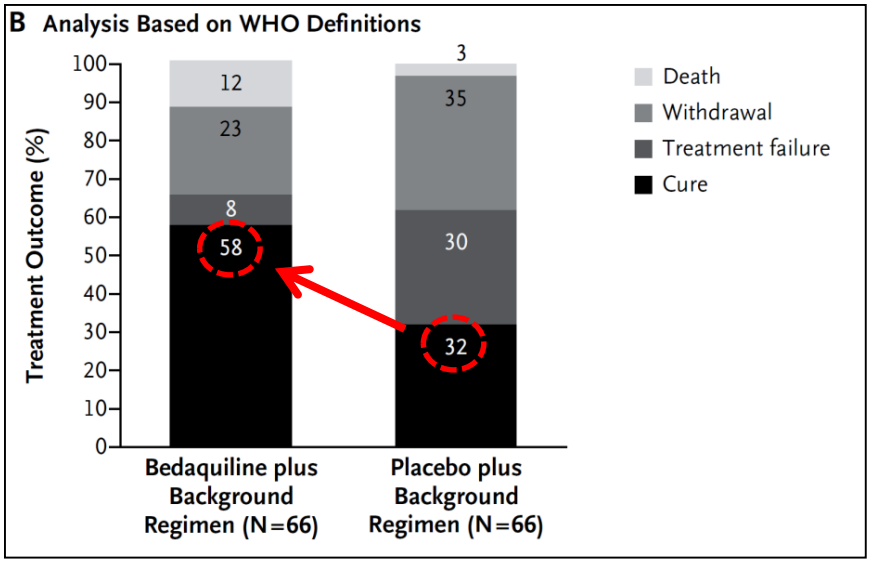
Correlates of outcomes

(for susceptible strains)



Bedaquiline

- Diarylquinoline
- Inhibiting ATP synthase of *M. tuberculosis*
- QT prolongation



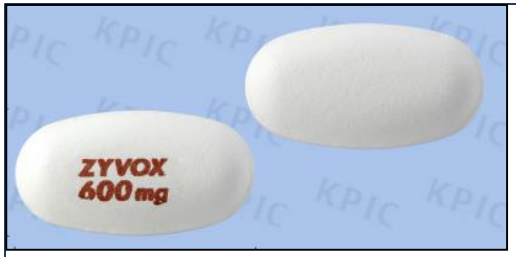
N Engl J Med. 2014;371:723-32.

Bedaquiline

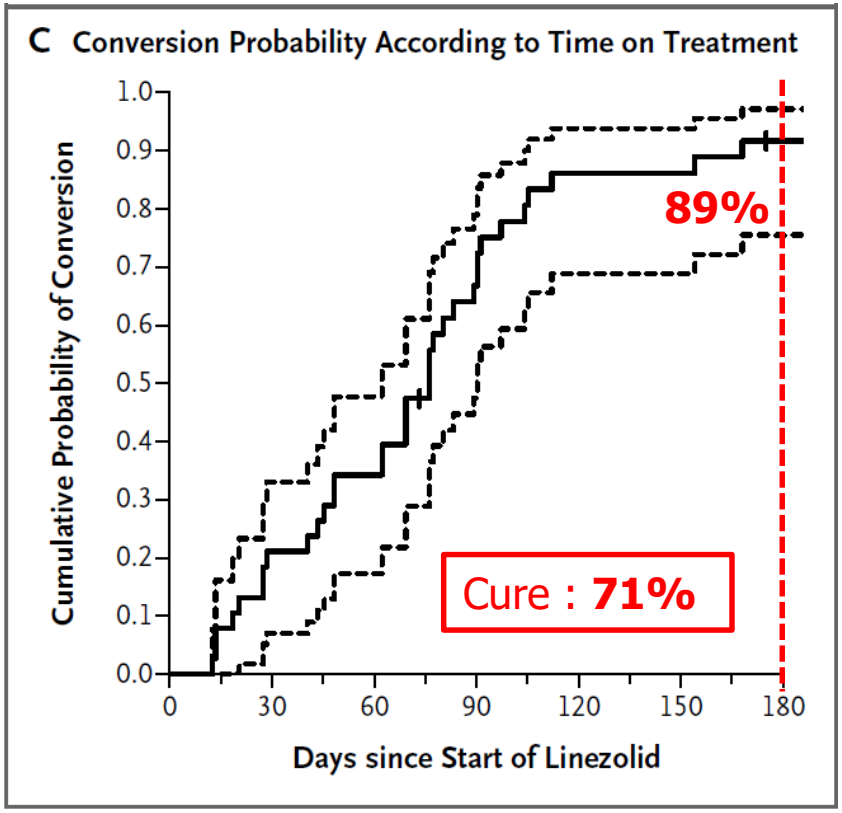
Study	Design	Pt. No.	XDR	Interruption Bdq d/t ADR	QTcF > 500ms	Success	Death
NEJM 2014[1]	RCT (stage 2b)	79	0%		1.3%	58% (vs. 32%)	12% (vs. 3%)
ERJ 2016[2]	Prospective, single arm (stage 2)	233	17%	2.6%	0.4%	62.5%	6.8%
ERJ 2017[3]	Retrospective	428	46%	5.8%	9.7%	71.3%	13.4%
ERJ 2018[4]	Retrospective	68	100%	0%	10.3% (~ 470ms)	66.2% (vs. 13.2%)	14.7% (vs. 33.8%)
Lancet RM 2018[5]	Retrospective (web-based)	1,016	27%			RR/MDR : 49.3% (vs. 42.8%) XDR : 41.1% (vs. 26.2%)	RR/MDR : 12% (vs. 24%) XDR : 14.7% (vs. 39.4%)

[1] N Engl J Med. 2014;371:723-32.
[2] Eur Respir J. 2016;47:564-74.
[3] Eur Respir J. 2017;49. pii: 1700387.
[4] Eur Respir J. 2018;51. pii: 1800544.
[5] Lancet Respir Med. 2018;6:699-706.

Linezolid

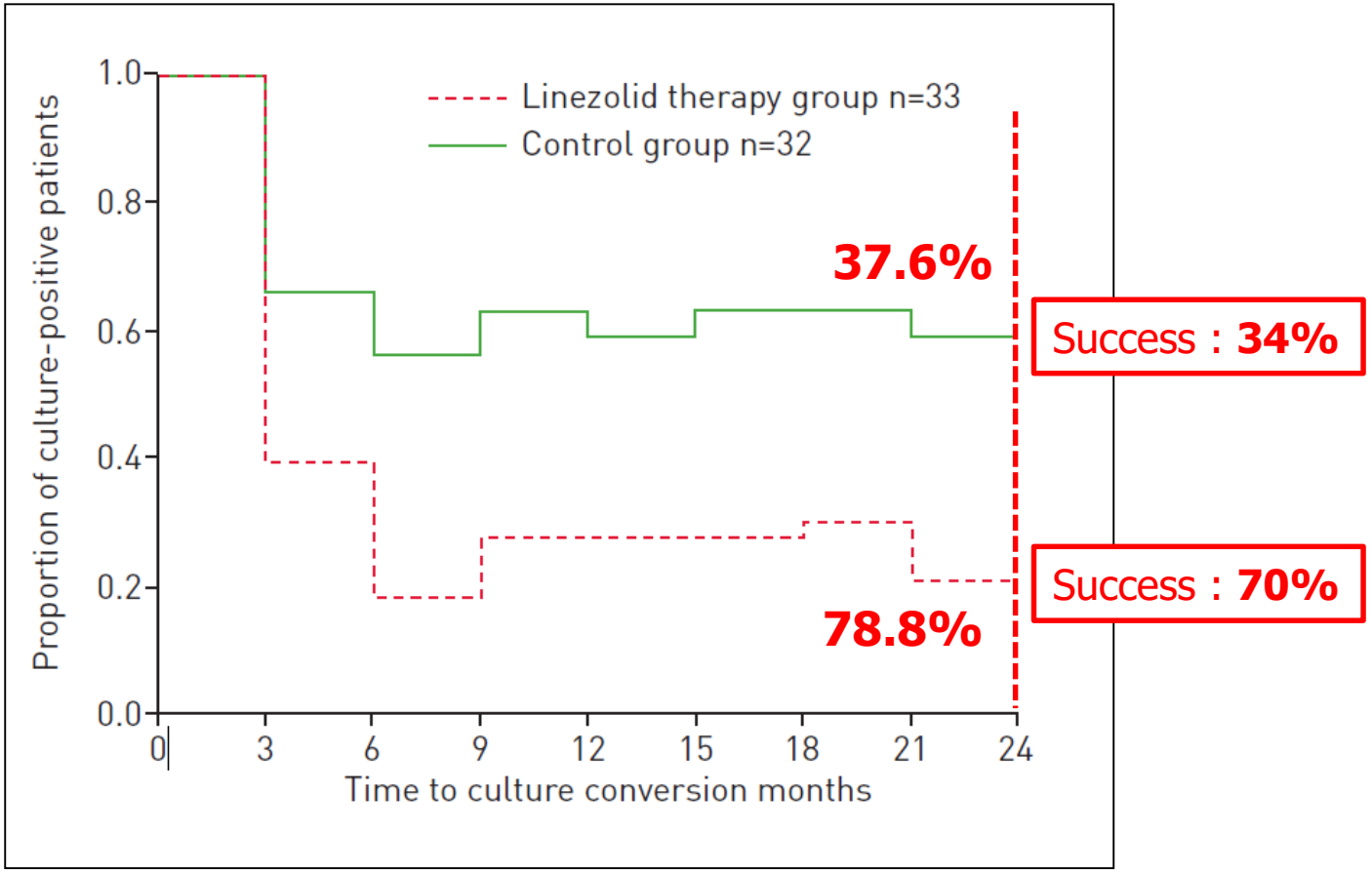


- Oxazolidinone class
- Inhibits protein synthesis by binding the 23S ribosomal RNA
- BM suppression, neuropathy



N Engl J Med. 2012;367:1508-18.

Linezolid



Eur Respir J. 2015;45:161-70.

Linezolid

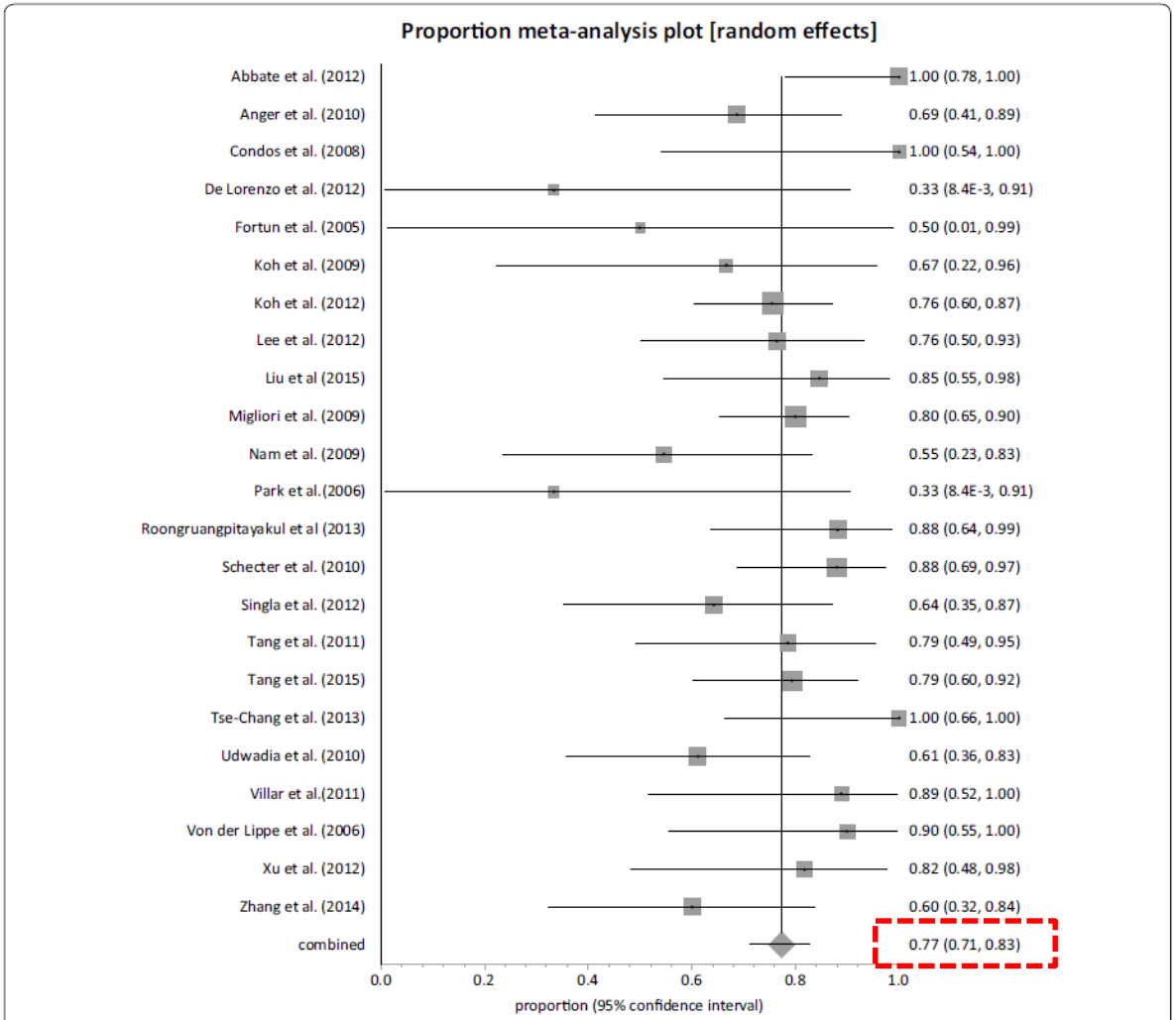
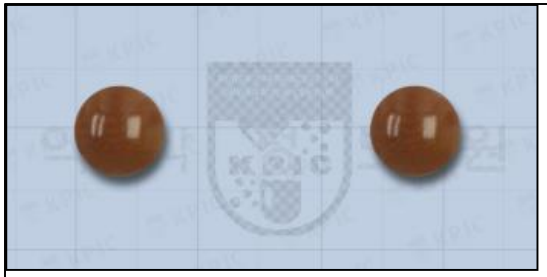


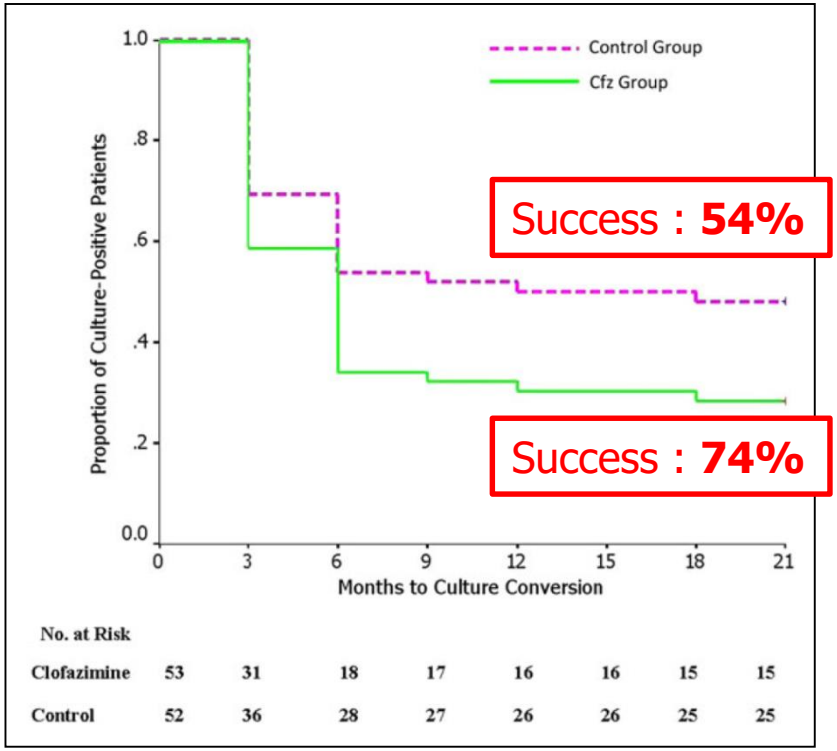
Fig. 3 Forest plot of treatment success, individual and pooled (random effects)

Ann Clin Microbiol Antimicrob. 2016;15:41.

Clofazimine



- Riminophenazine class
- Potent activity against hypoxic, non-replicating *Mycobacterium* (sterilizing drug)
- Bangladesh regimen
- Skin discoloration



Clin Infect Dis. 2015;60:1361-7.

Clofazimine

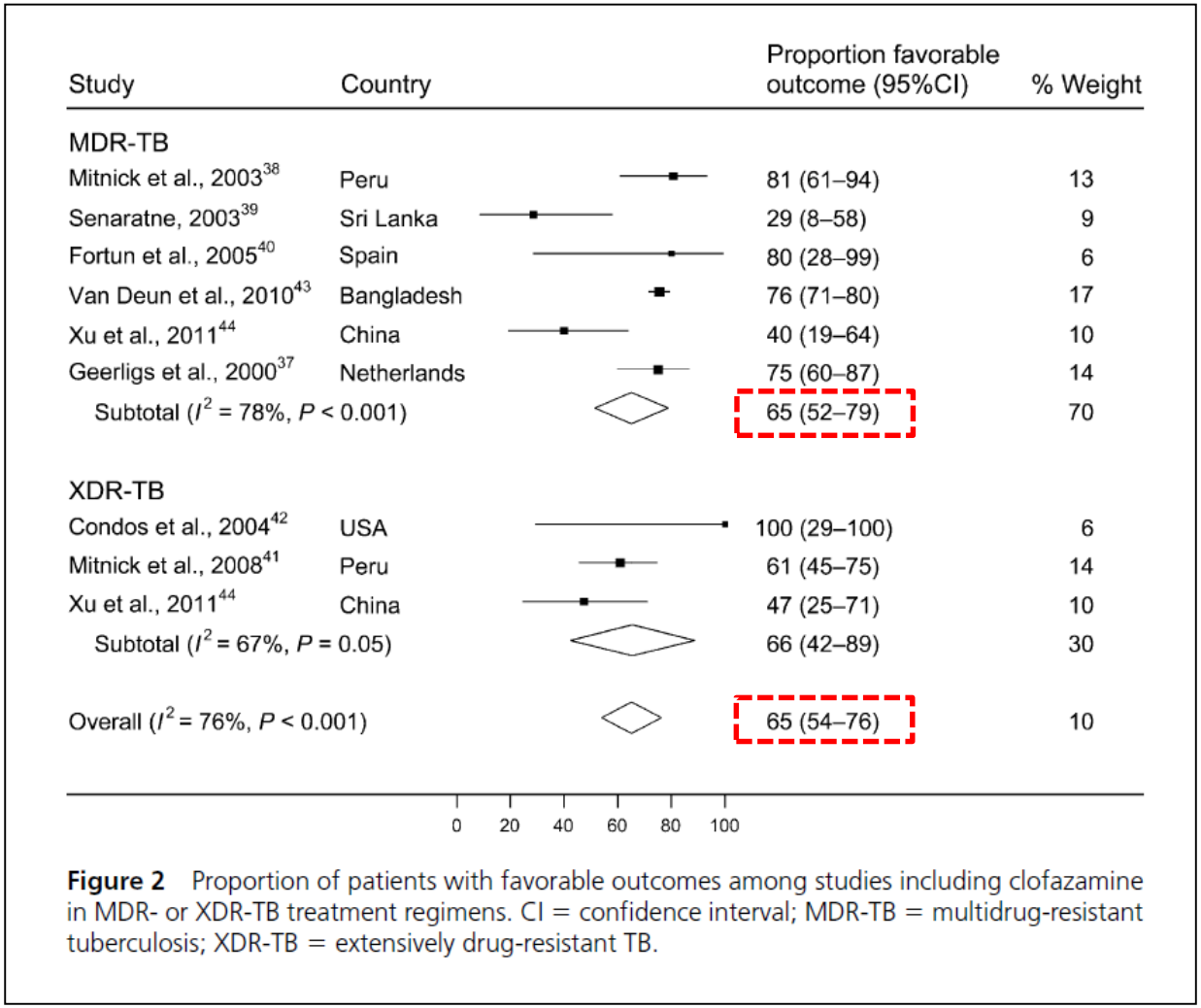
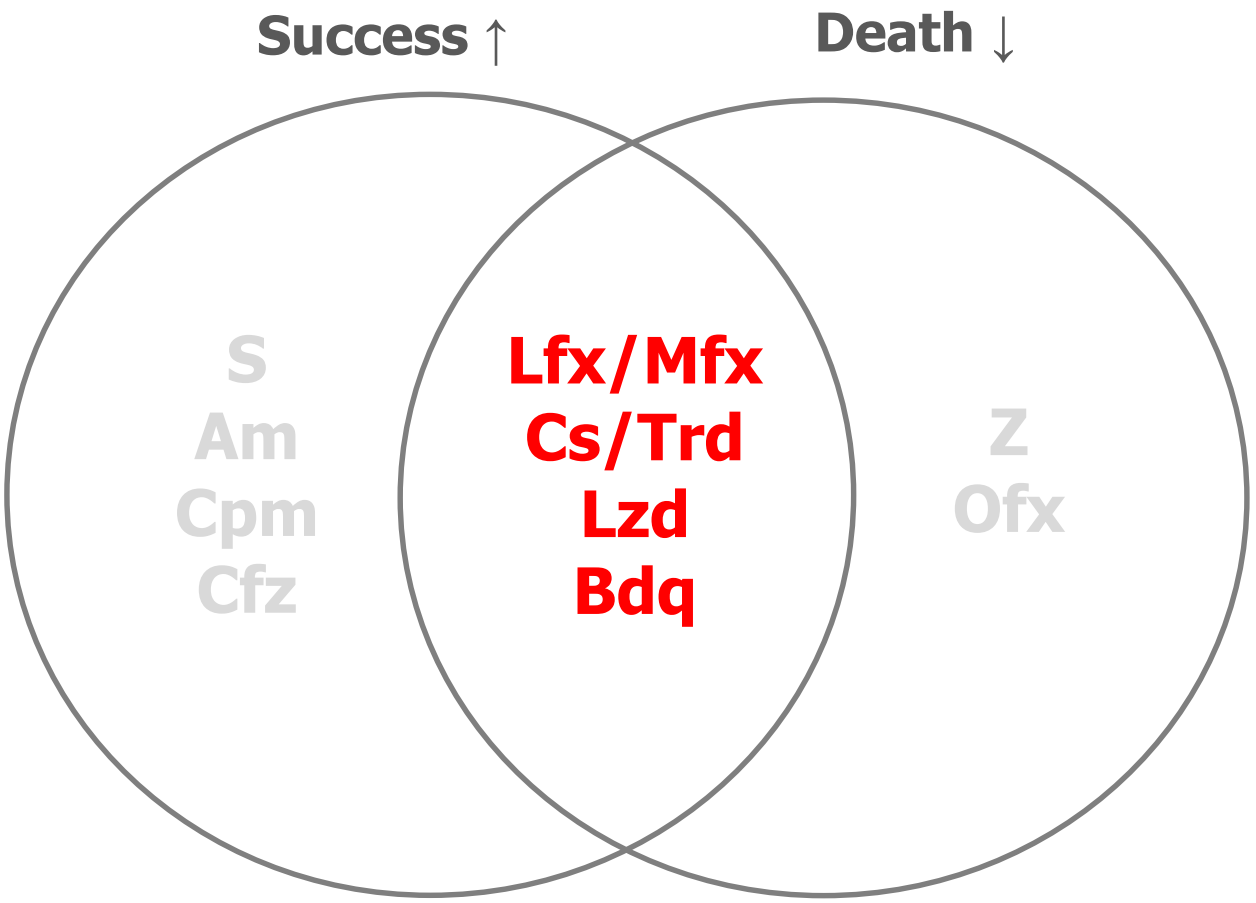
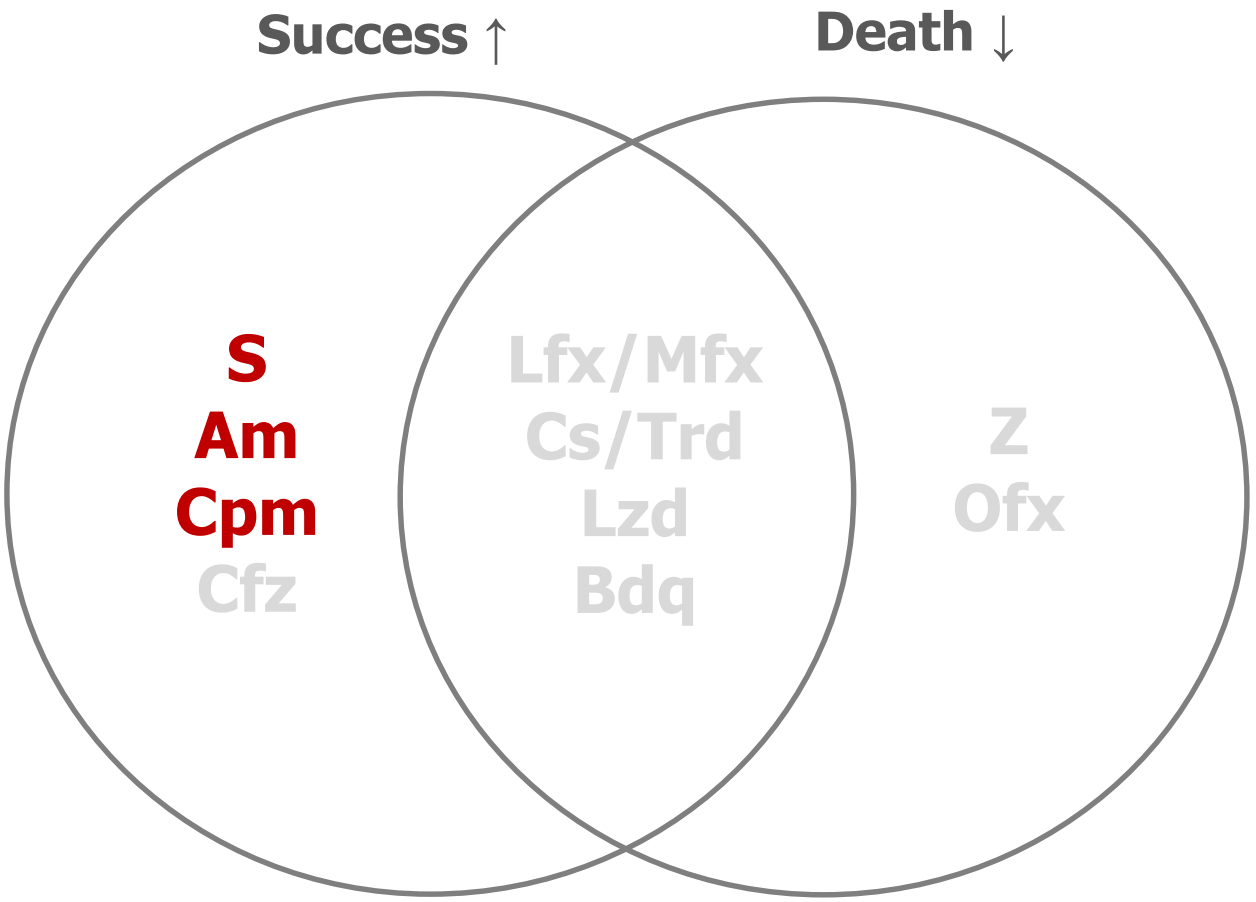


Figure 2 Proportion of patients with favorable outcomes among studies including clofazamine in MDR- or XDR-TB treatment regimens. CI = confidence interval; MDR-TB = multidrug-resistant tuberculosis; XDR-TB = extensively drug-resistant TB.

Int J Tuberc Lung Dis. 2013;17:1001-7.


Success ↑
Death ↓
S
Am
Cpm
Cfz
Lfx/Mfx
Cs/Trd
Lzd
Bdq
Z
Ofx


THE AVENGERS
?
MDR-TB


Success ↑
Death ↓
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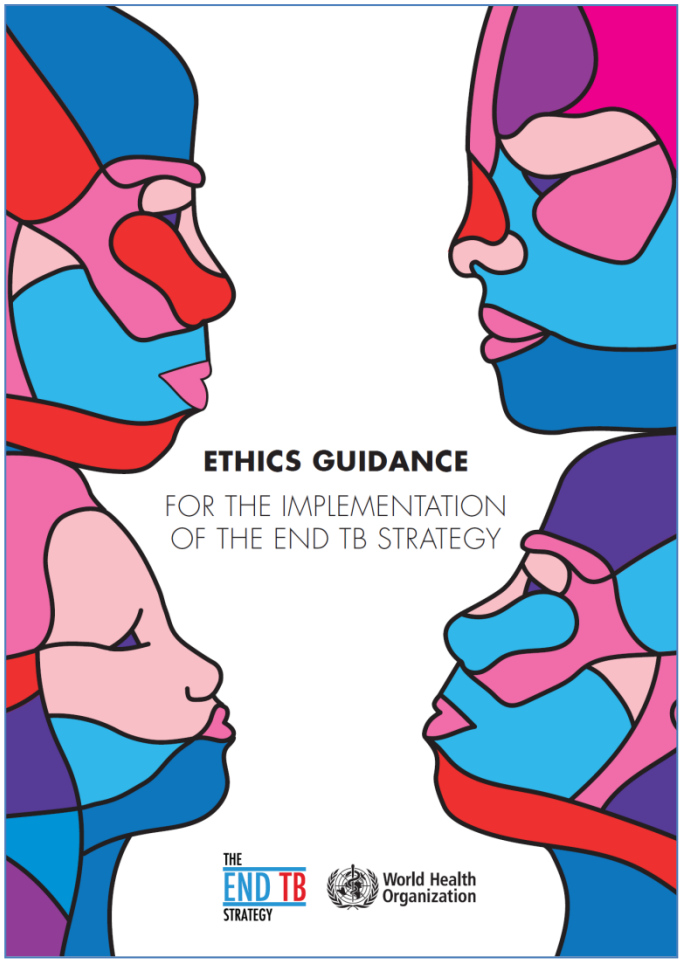
Patient-centred care



Trust and transparency

"These two interrelated values require that communications and decisions at all levels be made in an open manner, through a fair process, and that the said decisions are responsive, factual and evidence-based whenever evidence exists, so as to engender trust by all relevant stakeholders."

Persons with MDR-TB must be 'given information about the risks and benefits of treatment' and that treatment be **'accessible, acceptable, affordable and appropriate'.**

WHO. Ethics guidance for the implementation of the End TB strategy 2017.

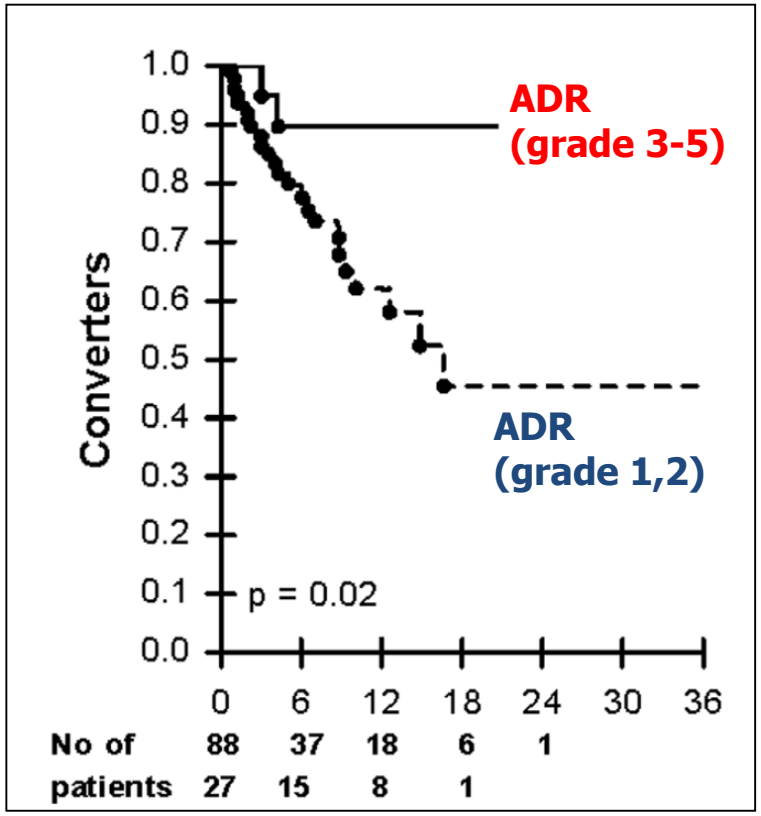
ADR and treatment outcome

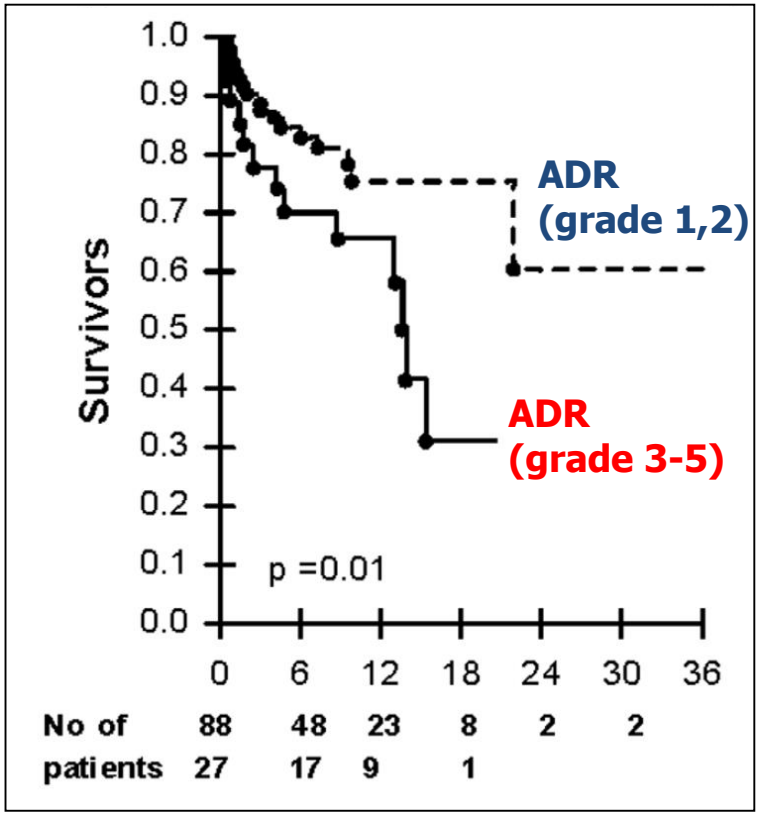
Table 2. Specific drugs, the dosages used in XDR-TB treatment regimens, and the frequency of drug withdrawal due to adverse events relative to the number of patients prescribed the drug.

	Drug dosages used	No. of patients who received a drug as part of the XDR-TB regimen n = 115(%)	Number of patients in whom the drug was withdrawn relative to the total number receiving the drug (%)	Proportion of severe AE [total = 34] due to a specific drug (%)
Isoniazid	4–6 mg/kg/daily	39/115(34)		-
Ethambutol	25 mg/kg/daily	46/115 (40)	1/46(2.2)	1/34(2.9)
Pyrazinamide	30–40 mg/kg/daily	80/115(69.6)	-	-
Amikacin	15–20 mg/kg/daily*	3/115(2.6)	1/3 (33.3)	1/34(2.9)
Kanamycin	15–20 mg/kg/daily*	4/115(3.5)	-	-
Ofloxacin	600–800 mg daily	29/115(25.2)	-	-
Moxifloxacin	400 mg daily	2/115(1.7)	-	-
Ethionamide	15–20 mg/kg/daily	66/115(57.3)	7/66(10.6)	7/34(20.6)
Capreomycin	15–20 mg/kg/daily*	104/115(90.4)	14/104 (13.5)	14/34(41.2)
Para-aminosalicylic acid	8 g (400 mg BD)	101/115(87.8)	7/101(6.9)	7/34(20.5)
Terizidone/Cycloserine	500–750 mg daily	104/115(90.4)	2/104(1.9)	2/34(5.9)
Clarithromycin	1 g (500 mg BD)	77/115(66.9)	-	-
Amoxicillin-clavulanate	375 mg	65/115(56.5)	2/65(3.1)	2/34(5.9)
Clofazimine	200 mg (100 mg BD)	28/115(24.3)	-	-
Dapsone	100–200 mg daily	36/115(31.3)	-	-
Azithromycin	500 mg 3xweekly	11/115(9.6)	-	-
INAT (INH+thiacetazone)	3 tabs daily	2/115(1.7)	-	-
Rifabutin	300 mg daily	1/115(0.87)	-	-

PLoS One. 2013;8:e63057.

ADR and treatment outcome





PLoS One. 2013;8:e63057.

"My world fell silent around me.
I am in front of people,
but I am not here."

Nandita Venkatesan, a survivor of MDR-TB

Lancet. 2018;392:797-8.

The devil we know: is the use of injectable agents for the treatment of MDR-TB justified?

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Int J Tuberc Lung Dis. 2017;21:1114-26.

Mamello Evelyn Moilwa, Lesotho:

January 2014: the month I will never forget in my entire life. I had been in hospital for only 4 months taking MDR-TB treatment when one morning I woke up and I heard a weird noise in my ears. It was exactly the same as the noise made by the air ventilator. I got out of bed to get some fresh air away from the ventilator, hoping to refresh my ears so the noise can go away but it was too late, nothing changed. Later on that day one of the nurses tried speaking to me but I could not comprehend the language. She had to repeat one phrase for many times but to no avail, it was like she was murmuring and I had to read her lips to understand what she was saying. During the pre-treatment counselling, I was warned about all the possible side effects of the treatment and one of them included hearing loss. I still remember that the very first thing I did before taking my first dose of the treatment was to pray and I recall one of the verses I prayed: "Dear Lord, I know I have strength to endure every single pain I am facing throughout this painful journey but I lack courage and strength to sustain just one thing, that of hearing loss, I pray that you let that pass me by". But my prayers were not good enough I guess.

Int J Tuberc Lung Dis. 2017;21:1114-26.

Efficacy of injectables

Table 1 Studies that have examined the efficacy of injectable agents for DR-TB

First author	Year of study	Design	Sample size	Results
Ahuja[20]	2012	Meta-analysis of 32 observational studies	9153 people with MDR-TB assessed	No association between use of any injectable agent and the probability of treatment success
Althomsons[25]	2012	Meta-analysis of data from the national TB surveillance system (USA)	1179 people with MDR-TB assessed	Among persons with MDR-TB, additional resistance to injectable agents was a statistically significant predictor of mortality and poor treatment outcomes ($P < 0.005$, risk ratio not calculated in study)
Bastos[26]	2014	Meta-analysis of data from 31 previously published studies of people with MDR- or XDR-TB	8955 people with XDR- or MDR-TB assessed	OR of treatment success compared with treatment failure or death in persons with susceptibility to an injectable agent (compared with resistance): SM 1.8 (1.2–2.7), AMK or KM 1.8 (1.2–2.8), CPM 1.3 (0.8–2.1)
British Medical Research Council[27]	1948	RCT: patients randomized to receive SM monotherapy (2 g four times a day for 4 months) or no drug treatment; response was assessed clinically and radiologically	107 participants with TB enrolled	51% of participants in the intervention arm (receiving SM) exhibited radiological improvement compared with only 8% in the control group. Clinical improvement was noted in the SM group compared with the control group in the first few months; however, only 15% of the intervention group was bacteriologically negative after 6 months. Study cautioned against using SM in view of the observed vestibular toxicity
Chan[21]	2009	Retrospective cohort study; subanalysis compared long-term treatment outcomes of people with MDR-TB plus SM resistance (susceptible to the three other injectable agents) to people with XDR-TB with resistance to all injectable agents	This was a subanalysis in which 22 people with TB were assessed	75% treatment success rate (95%CI 47–91; $P = 0.04$) for persons with MDR-TB and SM resistance only ($n = 12$) compared with 20% success rate (95%CI 6–51; $P = 0.03$) in persons with XDR-TB ($n = 10$)
Donald[28]	2002	EBA study on SM in humans with pulmonary TB	63 participants randomized; 43 included in the analysis	Minimal EBA (0.133, $P = 0.0009$) only at 30 mg/kg (doses higher than doses used in clinical practice); no EBA at lower doses
Donald[29]	2001	EBA study of AMK in humans with pulmonary TB	7 participants	No significant EBA, 0.041, 0.045 and 0.052 (after 2 days of AMK at 5 mg/kg, 10 mg/kg, 15 mg/kg, respectively)
Falzon[24]	2013	Meta-analysis of data from persons with MDR-TB from 26 centers	6724 people with MDR-TB assessed	Compared with treatment failure, relapse and death, treatment success was 64% in persons with MDR-TB only ($n = 4763$, 95%CI 57–72) compared to persons with MDR-TB with resistance to an injectable agent, which was 56% ($n = 1130$, 95%CI 45–66)
Goerghiou[30]	2017	Observational cohort study in which clinical sputum isolates were analyzed and sequences correlated with clinical details to investigate the relationship between MDR-TB resistance, mutations and mortality	451 clinical isolates sequenced and analyzed	Presence of *rrs* mutation conferring resistance to KM was associated with higher odds of patient mortality (limited study due to lack of follow-up data on 60% of participants)
Kim[22]	2010	Meta-analysis of patient data after 5–8 years of follow-up	1407 people with MDR- or XDR-TB assessed	MDR-TB with resistance to an additional injectable agent was a marginal predictor of poor outcome (hazard ratio of resistance to injectable agent 1.57, 95%CI 1.01–2.44; $P = 0.048$) SM resistance was independently associated with a worse treatment outcome
Migliori[23]	2008	Meta-analysis of data from people with MDR- and XDR-TB with definitive treatment outcomes	288 people with MDR- or XDR-TB included for review	Resistance to CPM yielded a higher proportion of failure and death than CPM-susceptible cases (OR 3.51) Unfavorable outcomes were similar in persons with DR-TB 1) susceptible or 2) resistant to KM or AMK (respectively $P = 0.31$ and $P = 0.78$) Resistance to more than one injectable agent increased the chance of an unfavorable outcome (OR 2.66; $P = 0.024$)

Int J Tuberc Lung Dis. 2017;21:1114-26.

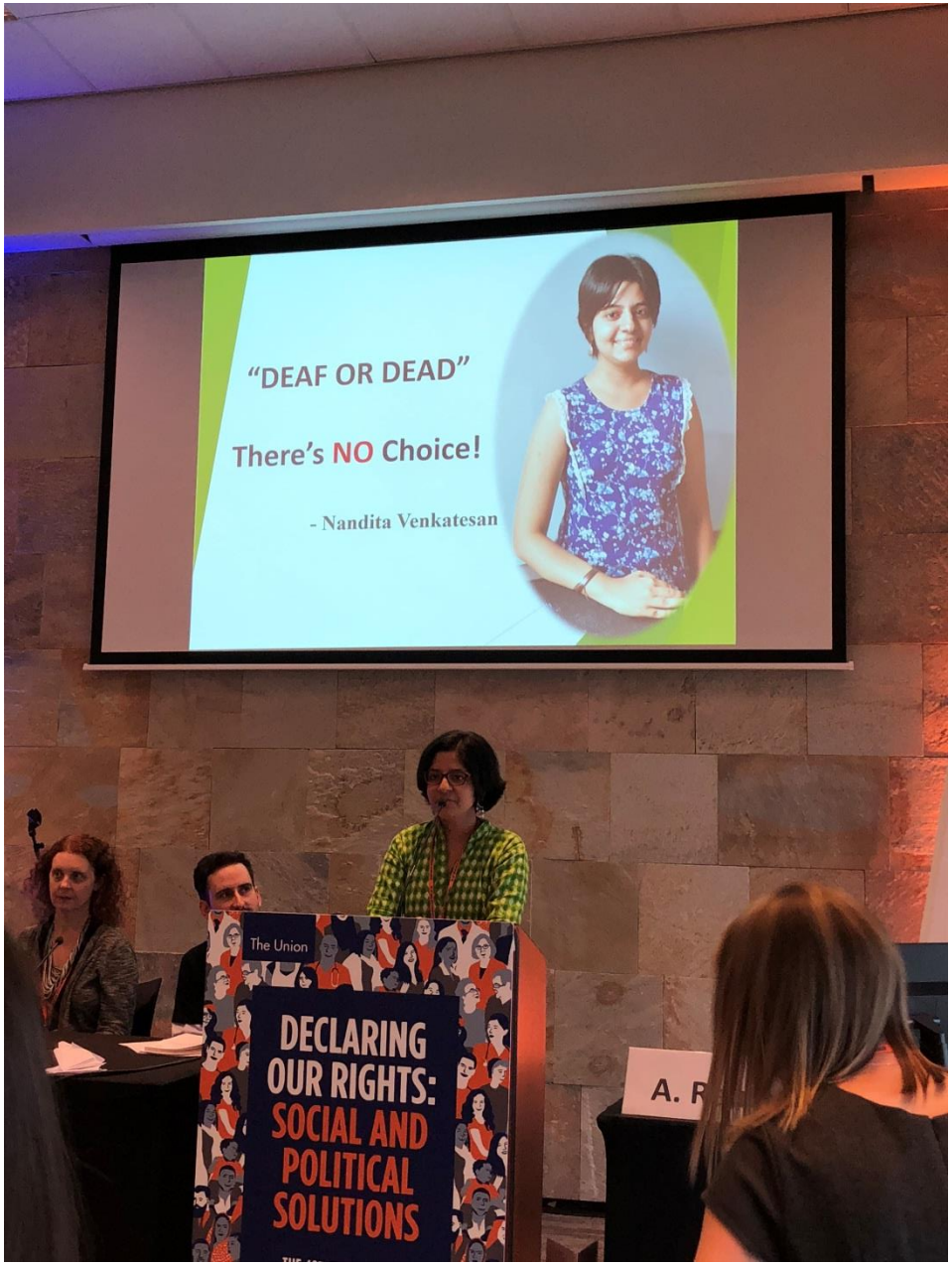
ADRs of injectables

- **Ototoxicity**
  - starting at higher frequencies (higher than those for human speech)
  - can be progressive even after discontinuation
- **Vestibular toxicity**
- **Nephrotoxicity**
- **Electrolyte abnormalities**
- **Pain/injury at the injection site**

- **Health system cost, job problem, etc.**

Table 2 Studies that have examined ototoxicity among patients on treatment for DR-TB (table adapted and updated from References 32 and 38)

First author	Year of study	Study country	Patients with ototoxicity *n* (%)	Age range years	Patients known to be HIV-infected *n* (%)
Baghaei[43]	2006–2009	Iran	8–14 (10.0–17.5)	14–81	4 (5.0)
Bloss[44]	2000–2004	Latvia	195 (19.0)	13–83	32 (3.1)
Burgos[45]	1982–2000	USA	2 (4.2)	22–78	11 (22.9)
Chan[46]	1984–1998	USA	39 (19.0)	2–85	NS
Codecasa[47]	2001–2003	Italy	1 (2.6)	43.6 (17.3)*	2 (5.3)
de Jager[48]	1995–2000	The Netherlands	11 (18.0)	10–83	NS
Dheda[49]	2002–2008	South Africa	10 (6)	⩾16	82/174 (47.1)
Drobac[50]	1999–2003	Peru	2 (6.7)	2–14	2/38 (5.3)
Duggal[51]	2000–2006	India	12 (18.8)	17–65	NS
Furin[52]	1996–1998	Peru	4 (6.7)	12–60	1 (1.7)
Geerligs[53]	1985–1998	The Netherlands	0–6* (0–15)	10–82	0
Ghafar[54]	May–August 2010	South Africa	12 (48)	7 months–16.6 years	12 (40)
Goble[2]	1973–1983	USA	13 (7.6)	17–79	NS
Isaakidis[55]	2007–2011	India	5 (8.6)	11–61	58 (100)
Jacob[56]	2002–2007	Belgium	11 (50.0)	21–76	1/21 (4.8)
Joseph[57]	2006–2007	India	1 (2.6)	⩾18	†
Karagoz[58]	1995–2000	Turkey	24 (22.0)	16–65	0
Keal[6]	2006–2011	UK	5 (27.8)	10–80	1 (5.6)
Kennedy[40]	2004–2009	Ireland	8 (61.5)	24–82	1/7 (14.3)
Keshavjee[59]	2000–2004	Russia	78 (12.8)	XDR-TB: 33.9 ± 11.1† MDR-TB: 35.9 ± 11.3†	5 (0.8)
Kim[60]	1996–2005	Republic of Korea	8 (3.8)	13–91	†
Leimane[61]	2000	Latvia	58 (28.4)	17–78	1/197 (0.5)
Malla[62]	2005–2006	Nepal	12 (9.6)	33.6 ± 12.5†	NS
Masjedi[63]	2002–2006	Iran	20 (46.5)	15–83	0
Modongo[64]	2006–2012	Botswana	270 (62)	⩾15	288 (66%)
Nathanson[65]	1998–2002	Multiple sites	98 (12.0)	NS	NS
Palmero[66]	1996–1999	Argentina	5 (6.8)	<16 excluded 36.0 ± 13.0†	‡
Peloquin[67]	1991–1998	USA	32–28* (36.8–32.2)	19–79	NS
Sagwa[68]	2004–2014		206 (58%)	36.4 (11.7)	164 (46)
Shin[7]	2000–2002	Russia	38 (15.6)	17–65	NS
Sturdy[69]	2004–2009	UK	9 (18.0)	34.6 ± 12.8†	5 (10)
Tahaoğlu[70]	1992–1999	Turkey	45 (28.5)	15–68	‡
Telzak[71]	1991–1994	USA	1 (5.9)	<25: 2 ⩾25: 23	‡
Törün[8]	1992–2004	Turkey	110 (41.8)	14–68	‡
Tupasi[72]	1999–2002	Philippines	22 (18.8)	15–24: 11 ⩾25: 90	Unable to test HIV status
Uffredi[73]	1998–1999	France	2 (4.4)	17–77	9 (20)
van Deun[74]	1997–2007	Bangladesh	19 (4.4)	<25: 108 >25: 319	Not tested
Yew[75]	1990–1997	Hong Kong	9 (14.3)	12–77	0



UNION Conference, 2018

Better deaf than dead ???

Table 3 Comparison between injectable agents, BDQ and DLM

	Injectable agent	BDQ	DLM
Efficacy	EBA trials—only SM has EBA at a high dose of 30 mg/kg[19] Observational cohorts with no clear evidence of benefit[20] No RCT No ongoing RCTs	EBA trials show efficacy (late)[107] Observational cohorts with evidence of benefit[113,116] Phase-IIB RCT data showed improved outcomes[114] Phase-III trial underway[123]	EBA trials show efficacy[108] Observational cohorts with evidence of benefit[101] Phase-IIB RCT data showed improved outcomes[111] Phase-III trial has completed enrollment[123]
Adverse events reported in >5% of patients receiving the drug that are causally linked to the agent	Hearing loss in ⩽61.5% of patients[40] Vestibular toxicity in ⩽9%[31] Renal toxicity and electrolyte abnormalities in ⩽12%[33] Injection site reactions/ abscesses[39]	QTc prolongation >500 msec in 3.9% Hepatitis in 5%[114]	QTc prolongation >500 msec in 2.3%[111]
Logistical considerations	Daily interaction with health care providers required Biohazard and universal precautions required Monthly monitoring for hearing loss required[9]	Monthly monitoring of ECG required[9]	Monthly monitoring of ECG required[9]
Long-term impact	Permanent impact on ability to perform activities of daily living and employment[36] Deafness has been associated with an increased risk of being a victim of physical violence, depression[91]	Arrhythmia, if it occurs, could be fatal	Arrhythmia, if it occurs, could be fatal

More evidences

Less frequent
Easily monitored
Usually reversible

Int J Tuberc Lung Dis. 2017;21:1114-26.

Substituting Bdq for injectables

Table 2. Treatment Outcomes

Variable	Patients, No./Total No. (%)		*P* Value
	Bedaquiline Group (n = 162)	Control Group (n = 168)	
At 12 mo			
Composite unfavorable outcome (primary)[a]	35/146 (23.9)	51/141 (36.2)	.02
Composite unfavorable outcome (secondary)[b]	44/158 (27.9)	58/152 (38.2)	.053
Death	11/145 (7.6)	11/147 (7.5)	.97
Loss to follow-up	17/162 (10.5)	21/168 (12.5)	.57
Treatment failure[c]	7/119 (5.9)	19/109 (17.4)	.006
Modified treatment failure[d]	16/138 (11.6)	29/131 (22.1)	.02
At 18 mo			
Death	13/79 (16.5)	15/100 (15.0)	.79
Failure to achieve sustained culture conversion	3/93 (3.2)	16/81 (19.8)	<.001

Table 3. Predictors of Failure to Achieve Sustained Culture Conversion at 12 Months in the Bedaquiline Group

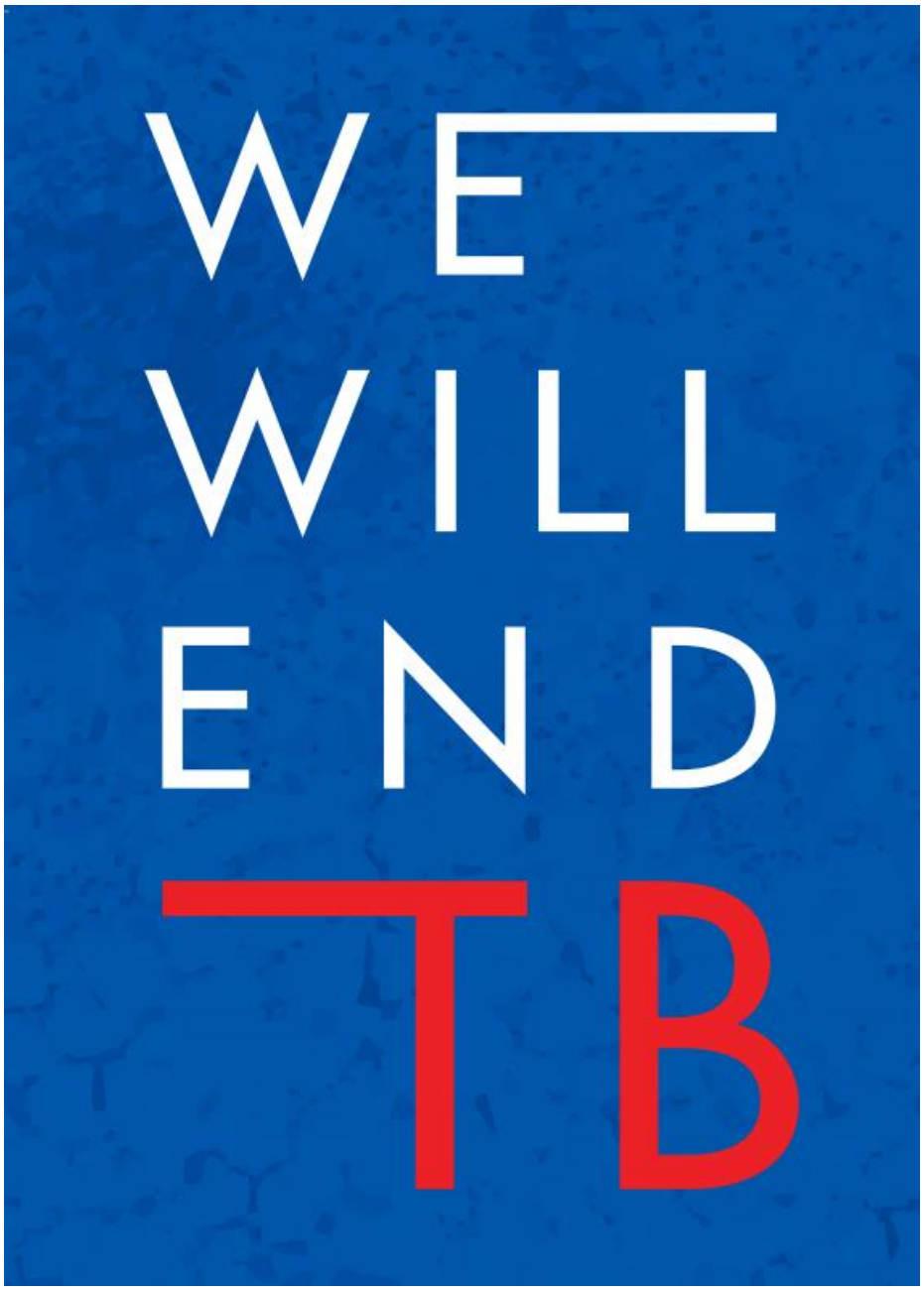
Variable	Univariate OR (95% CI)	*P* Value	Mutivariable OR (95% CI)[a]	*P* Value
Sputum smear positive at baseline	1.4 (.3–7.8)	.67	…	…
Comorbid illness	2.1 (.5–10.2)	.34	1.6 (.3–9.5)	.61
HIV infection	0.3 (.06–1.4)	.12	0.3 (.5–1.7)	.17
Per 30-d delay from start of treatment	1.4 (1.1–1.9)	.007	1.5 (1.1–1.9)	.01

Clin Infect Dis. 2018 [Epub ahead of print]

2018 WHO new longer regimen

L/Mfx - Bdq - Lzd - Cfz - Cs

Accessible ?
Acceptable ?
Affordable ?
Appropriate ?



Thank You !!