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The changing and challenging landscape of drug-resistant tuberculosis

Presented by:

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Drug-resistant tuberculosis: a vocabulary

Term	Meaning
Susceptible	Susceptible to all first-line anti-TB drugs: (HRZES)
Monoresistant	Resistant to any one of the first-line anti-TB drugs
Polyresistant	Resistant to two or more first-line drugs, but not both isoniazid and rifampin
Multidrug resistant (MDR)	Resistant to at least INH and rifampin
Extensively drug resistant (XDR)	Resistant to at least INH, rifampin, fluouroquinolones, and injectables
Pre-XDR	Resistant to at least INH, rifampin, and either fluouroquinolones or injectables
Highly resistant	XDR or treatment intolerant/non-responsive MDR TB

BRITISH MEDICAL JOURNAL

LONDON SATURDAY OCTOBER 30 1948

STREPTOMYCIN TREATMENT OF PULMONARY TUBERCULOSIS

A MEDICAL RESEARCH COUNCIL INVESTIGATION

The following gives the short-term results of a controlled investigation into the effects of streptomycin on one type of pulmonary tuberculosis. The inquiry was planned and directed by the Streptomycin in Tuberculosis Trials Committee, composed of the following members: Dr. Geoffrey Marshall (chairman), Professor J. W. S. Blacklock, Professor C. Cameron, Professor N. B. Capon, Dr. R. Cruickshank, Professor J. H. Gaddum, Dr. F. R. G. Heaf, Professor A. Bradford Hill, Dr. L. E. Houghton, Dr. J. Clifford Hoyle, Professor H. Raistrick, Dr. J. G. Scadding, Professor W. H. Tytler, Professor G. S. Wilson, and Dr. P. D'Arcy Hart (secretary). The centres at which the work was carried out and the specialists in charge of patients and pathological work were as follows:

Brompton Hospital, London.—Clinician: Dr. J. W. Crofton, Streptomycin Registrar (working under the direction of the honorary staff of Brompton Hospital); Pathologists: Dr. J. W. Clegg, Dr. D. A. Mitchison.

Collindale Hospital (L.C.C.), London.—Clinicians: Dr. J. V. Hurford, Dr. B. J. Douglas Smith, Dr. W. E. Snell; Pathologists (Central Public Health Laboratory): Dr. G. B. Forbes, Dr. H. D. Holt.

Harefield Hospital (M.C.C.), Harefield, Middlesex.—Clinicians: Dr. R. H. Brent, Dr. L. E. Houghton; Pathologist: Dr. E. Nassau.

Bangour Hospital, Bangour, West Lothian.—Clinician: Dr. I. D. Ross; Pathologist: Dr. Isabella Purdie.

Killingbeck Hospital and Sanatorium, Leeds.—Clinicians: Dr. W. Santon Gilmour, Dr. A. M. Reevie; Pathologist: Professor J. W. McLeod.

Northern Hospital (L.C.C.), Winchmore Hill, London.—Clinicians: Dr. F. A. Nash, Dr. R. Shoulman; Pathologists: Dr. J. M. Alston, Dr. A. Mohun.

Sully Hospital, Sully, Glam.—Clinicians: Dr. D. M. E. Thomas, Dr. L. R. West; Pathologist: Professor W. H. Tytler.

The clinicians of the centres met periodically as a working subcommittee under the chairmanship of Dr. Geoffrey Marshall; so also did the pathologists under the chairmanship of Dr. R. Cruickshank. Dr. Marc Daniels, of the Council's scientific staff, was responsible for the clinical co-ordination of the trials, and he also prepared the report for the Committee, with assistance from Dr. D. A. Mitchison on the analysis of laboratory results. For the purpose of final analysis the radiological findings were assessed by a panel composed of Dr. L. G. Blair, Dr. Peter Kerley, and Dr. Geoffrey S. Todd.

Introduction

When a special committee of the Medical Research Council undertook in September, 1946, to plan clinical trials of streptomycin in tuberculosis the main problem faced was that of investigating the effect of the drug in pulmonary tuberculosis. This antibiotic had been discovered two years previously by Waksman (Schatz, Bugie, and Waksman, 1944); in the intervening period its power of inhibiting tubercle bacilli *in vitro*, and the results of treatment in experimental tuberculous infection in guinea-pigs, had been reported; these results were strikingly better than those with any previous chemotherapeutic agent in tuberculosis. Preliminary results of trials in clinical tuberculosis had been published (Hinshaw and Feldman, 1945; Hinshaw, Feldman, and Pfuetze, 1946; Keefer *et al.*, 1946); the clinical results in pulmonary tuberculosis were encouraging but inconclusive.

The natural course of pulmonary tuberculosis is in fact so variable and unpredictable that evidence of improvement or cure following the use of a new drug in a few cases cannot be accepted as proof of the effect of that drug. The history of chemotherapeutic trials in tuberculosis is filled with errors due to empirical evaluation of drugs (Hart, 1946); the exaggerated claims made for gold treatment, persisting over 15 years, provide a spectacular example. It had become obvious that, in future, conclusions regarding the clinical effect of a new chemotherapeutic agent in tuberculosis could be considered valid only if based on adequately controlled clinical trials (Hinshaw and Feldman, 1944). The one controlled trial of gold treatment (and the only report of an adequately controlled trial in tuberculosis we have been able to find in the literature) reported negative therapeutic results (Amberson, McMahon, and Pinner, 1931). In 1946 no controlled trial of streptomycin in pulmonary tuberculosis had been undertaken in the U.S.A. The Committee of the Medical Research Council decided then that a part of the small supply of streptomycin allocated to it for research purposes would be best employed in a rigorously planned investigation with concurrent controls.

The many difficulties of planning and conducting a trial of this nature are important enough to warrant a full description here of the methods of the investigation.

Plan and Conduct of the Trial

Type of Case

A first prerequisite was that all patients in the trial should have a similar type of disease. To avoid having to make allowances for the effect of forms of therapy other than bed-rest, the type of disease was to be one not suitable for other forms of therapy. The estimated chances of spontaneous regression must be small. On the other hand, the type of lesion should be such as to offer some prospect of action by an effective chemotherapeutic agent; for this reason old-standing disease, and disease with thick-walled

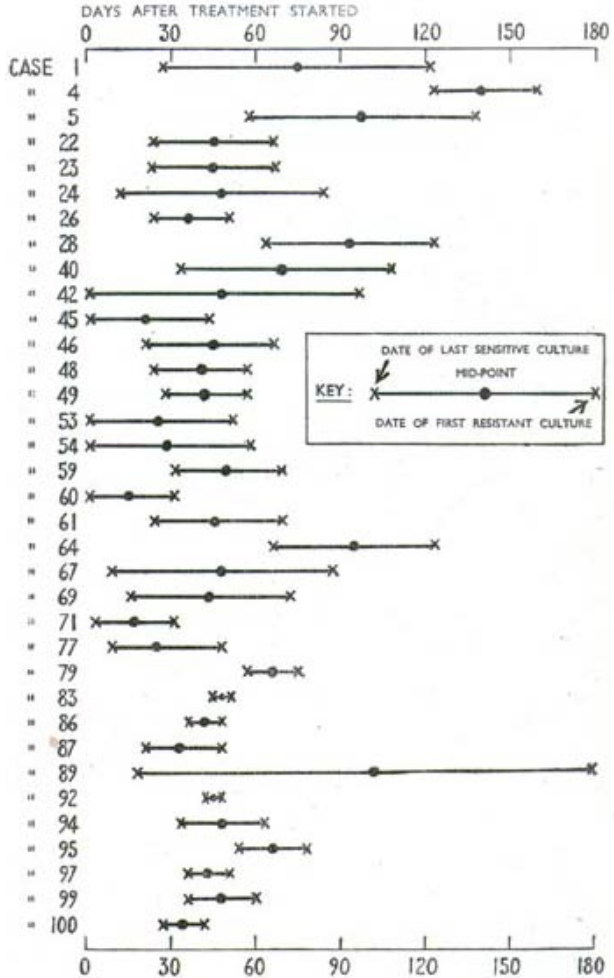


CHART V.—Showing date of emergence of streptomycin resistance (over 10 times that of H37Rv)

The emergence of MDR-TB in New York City

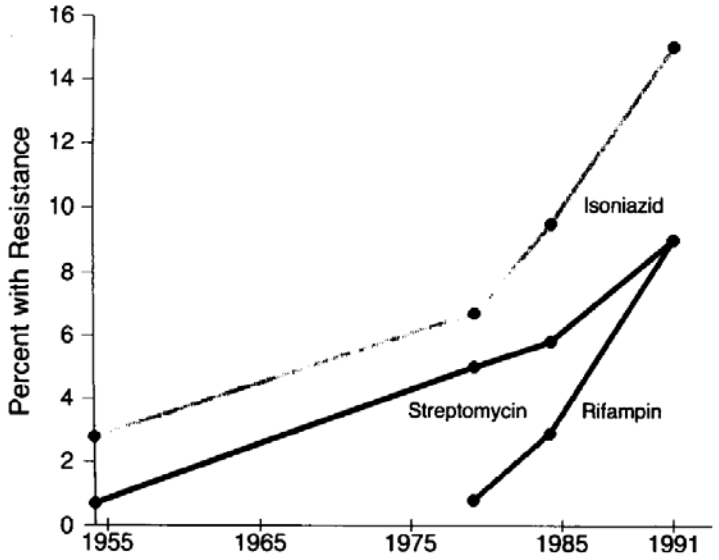


Figure 2. Percentages of Patients in New York City Who Had Never Been Treated for Tuberculosis and Who Had Isolates Resistant to One or More Antituberculosis Medications, 1953 to 1991.

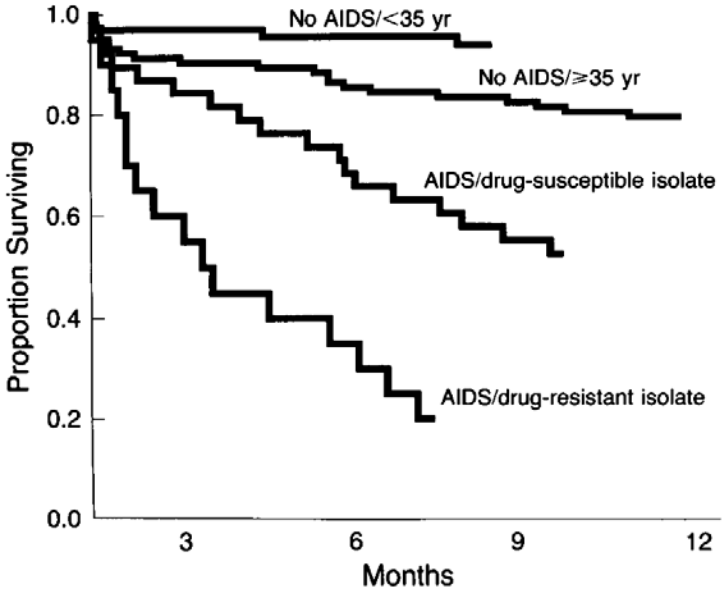


Figure 1. Survival among Patients Who Had Not Previously Received Antituberculosis Medications and Who Had Cultures That Grew *M. tuberculosis* in April 1991.

Frieden et al. New Engl J Med 1993; 328: 521-526

Country or Region	No. of Patients	Drug Susceptibility	Drug Resistance						Multidrug Resistance (95% CI)*
			Any Drug	One Drug	Two Drugs	Three Drugs	Four Drugs	>1 Drug	
			percentage of patients						
Argentina	606	87.5	12.5	6.6	2.5	1.8	1.7	5.9	4.6 (3.1–6.7)
Benin	333	91.6	8.4	6.0	2.1	0.3	0	2.4	0.3 (0–1.9)
Bolivia	498	74.5	25.5	20.1	5.2	0.2	0	5.4	1.2 (0.5–2.7)
Botswana	407	96.3	3.7	3.4	0.2	0	0	0.2	0.2 (0–1.6)
Brazil	2,095	91.4	8.6	6.4	2.1	0	0	2.1	0.9 (0.6–1.4)
Cuba	763	91.7	8.3	7.2	0.5	0.5	0	1.0	0.7 (0.2–1.6)
Czech Republic	199	98.0	2.0	1.0	0	0	1.0	1.0	1.0 (0.2–4.0)
Dominican Republic	303	59.4	40.6	25.7	10.9	2.6	1.3	14.9	6.6 (4.2–10.2)
England and Wales	2,742	93.1	6.9	4.6	1.9	0.4	0	2.3	1.1 (0.7–1.5)
Estonia	266	71.8	28.2	11.3	7.1	5.3	4.5	16.9	10.2 (6.9–14.6)
France	1,491	91.8	8.2	5.6	2.1	0.5	0.1	2.6	0.5 (0.2–1.1)
Ivory Coast	320	86.6	13.4	5.3	6.3	1.6	0.3	8.1	5.3 (3.2–8.5)
Kenya	445	93.7	6.3	5.4	0.9	0	0	0.9	0 (0–1.1)
Latvia	347	66.0	34.0	7.5	12.4	9.5	4.6	26.5	14.4 (11.0–18.7)
Lesotho	330	91.2	8.8	6.1	2.4	0.3	0	2.7	0.9 (0.2–2.9)
Nepal	787	90.2	9.8	5.7	2.8	0.6	0.6	4.1	1.1 (0.6–2.2)
New Zealand	418	95.2	4.8	3.6	0.7	0.5	0	1.2	0.7 (0.2–2.3)
Northern Ireland	59	96.6	3.4	1.7	1.7	0	0	1.7	1.7 (0.1–10.3)
Peru	1,500	84.6	15.4	10.1	3.9	1.0	0.4	5.3	2.5 (1.8–3.4)
Portugal	815	86.3	13.7	8.3	3.9	1.2	0.2	5.4	1.7 (1.0–2.9)
Puerto Rico	369	90.0	10.0	7.0	1.4	1.4	0.3	3.0	1.9 (0.8–4.0)
Republic of Korea	2,486	89.6	10.4	6.9	2.3	1.0	0.2	3.5	1.6 (1.1–2.2)
Romania	1,636	90.3	9.7	5.3	2.6	1.7	0	4.3	2.8 (2.0–3.7)
Russia (Ivanovo Oblast)	248	71.8	28.2	15.3	6.5	2.8	3.6	12.9	4.0 (2.1–7.5)
Scotland	290	97.2	2.8	2.4	0	0	0.3	0.3	0.3 (0–2.2)
Sierra Leone	463	71.9	28.1	16.6	10.2	1.1	0.2	11.4	1.1 (0.4–2.7)
Spain (Barcelona)	218	90.4	9.6	8.7	0.9	0	0	0.9	0.5 (0–2.9)
Swaziland	334	88.3	11.7	6.6	3.9	1.2	0	5.1	0.9 (0.2–2.8)
Thailand	131	63.4	36.6	21.4	11.5	3.1	0.8	15.3	3.8 (1.4–9.1)
United States	13,511	87.7	12.3	8.2	2.8	0.7	0.6	4.1	1.6 (1.4–1.9)
Vietnam	640	67.5	32.5	19.1	11.6	0.9	0.9	13.4	2.3 (1.4–3.9)
Zimbabwe	676	96.7	3.3	1.3	1.2	0.1	0.6	1.9	1.9 (1.1–3.4)
Median	431.5	90.1	9.9	6.6	2.5	0.6	0.2	3.8	1.4 (0.5–3.0)
Minimum	59	59.4	2.0	1.0	0	0	0	0.2	0 (0–1.1)
Maximum	13,511	98.0	40.6	25.7	12.4	9.5	4.6	26.5	14.4 (11.0–18.7)

*Multidrug resistance was defined as resistance to at least isoniazid and rifampin. CI denotes confidence interval.

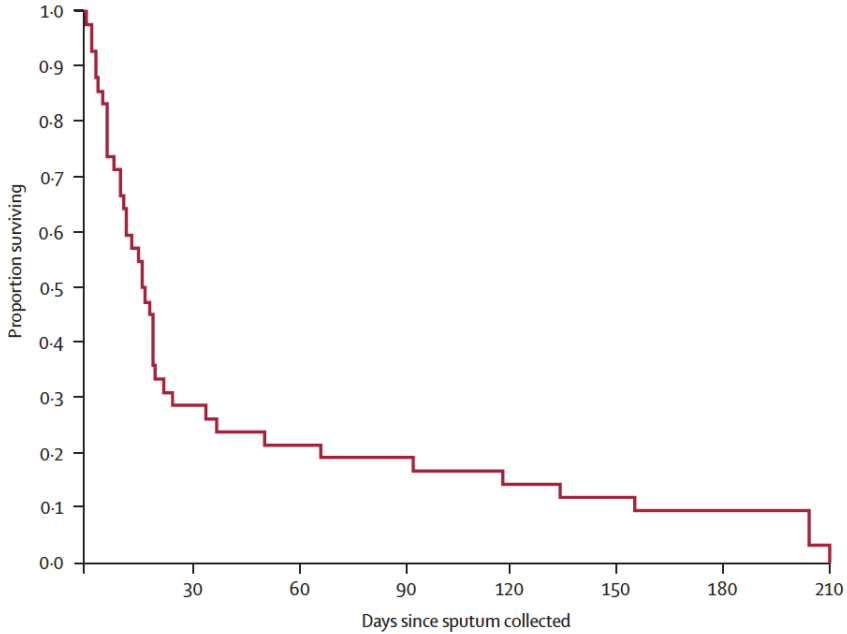
Pablos Mendez et al. New Engl J Med 1998; 338: 1641-1649

Prevalence and survival of MDR/XDR TB in KwaZulu Natal

	Group 1	Group 2	Group 3†	Total
Total tested	86	25	1428	1539
Culture-positive	45	22	475	542
MDR tuberculosis*	26	10	185	221
XDR tuberculosis	17	6	30	53

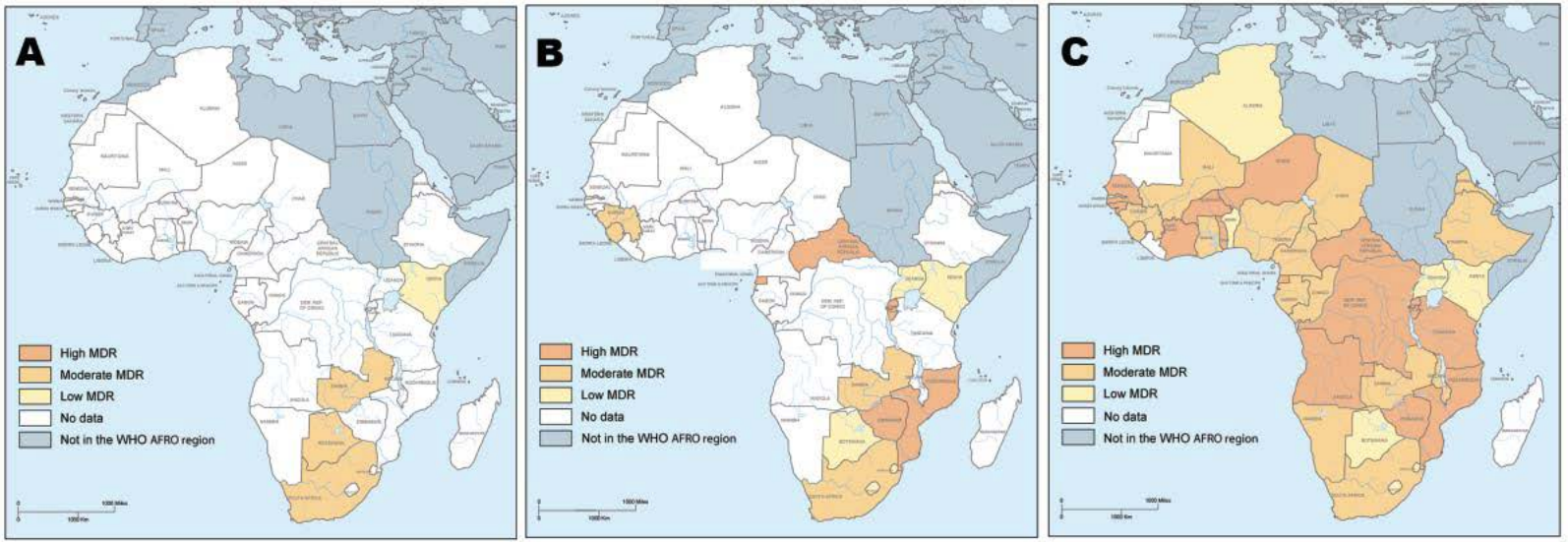
Data are number of patients. *Includes cases of XDR tuberculosis.

Table 1: **Distribution of culture results and drug-resistance categories by group for all patients (n=1539) for whom sputum culture was done**



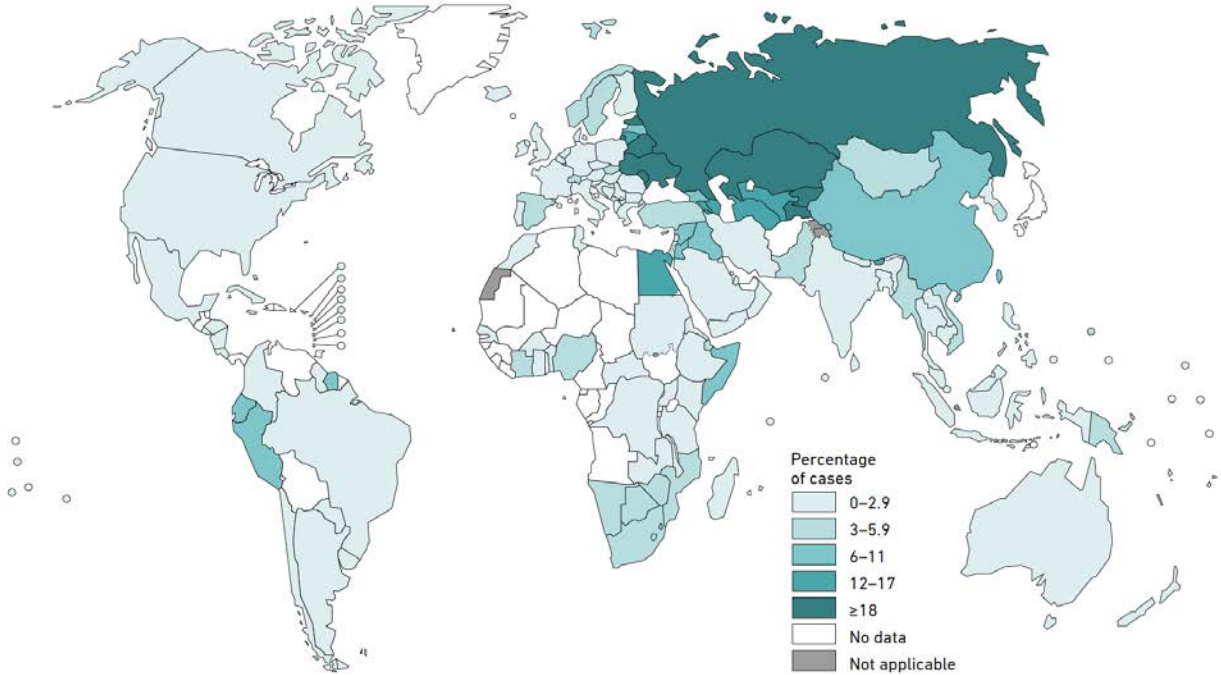
Gandhi et al. Lancet 2006; 368: 1575-1580

MDR-TB in Africa



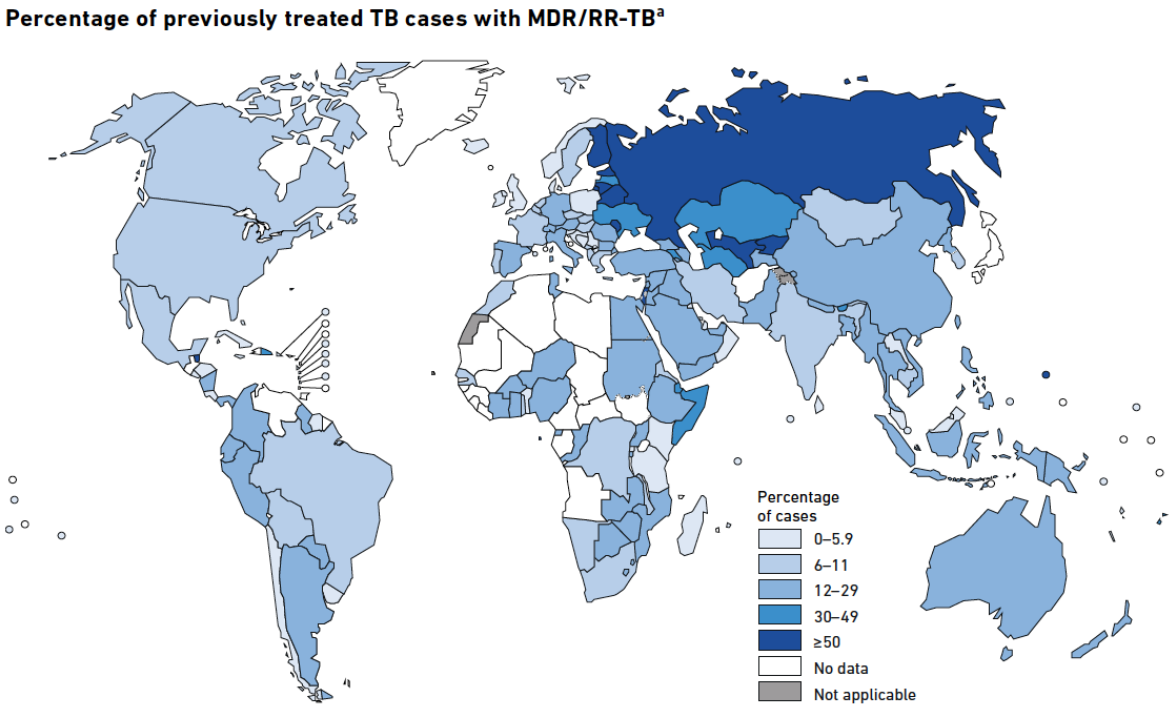
Ben Amor, Schluger Emerg Inf Dis 2008

Percentage of new TB cases with multidrug resistant or rifampin monoresistant (MDR/RR) TB



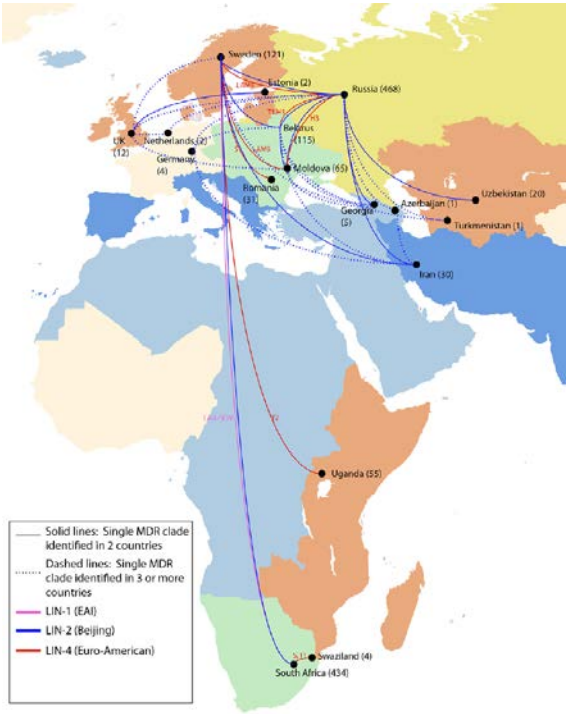
WHO Global TB Report 2018

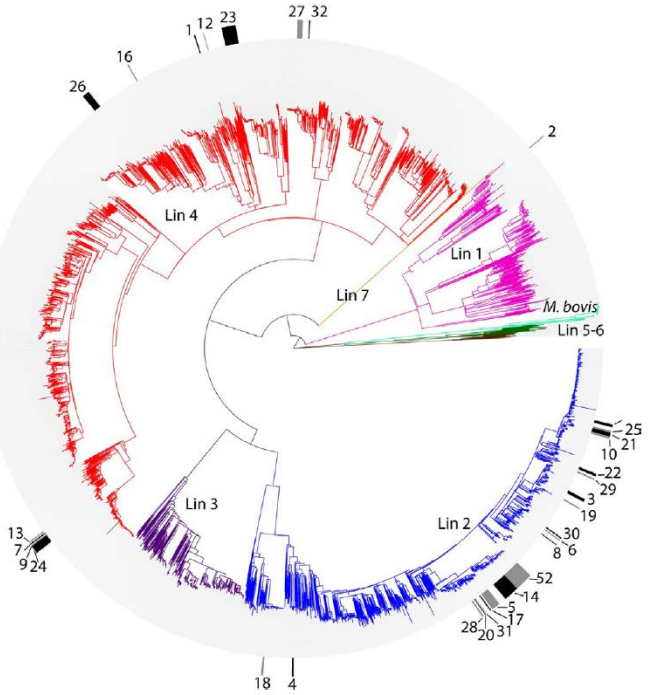
Percentage of new TB cases with multidrug resistant or rifampin monoresistant (MDR/RR) TB



WHO Global TB Report 2018

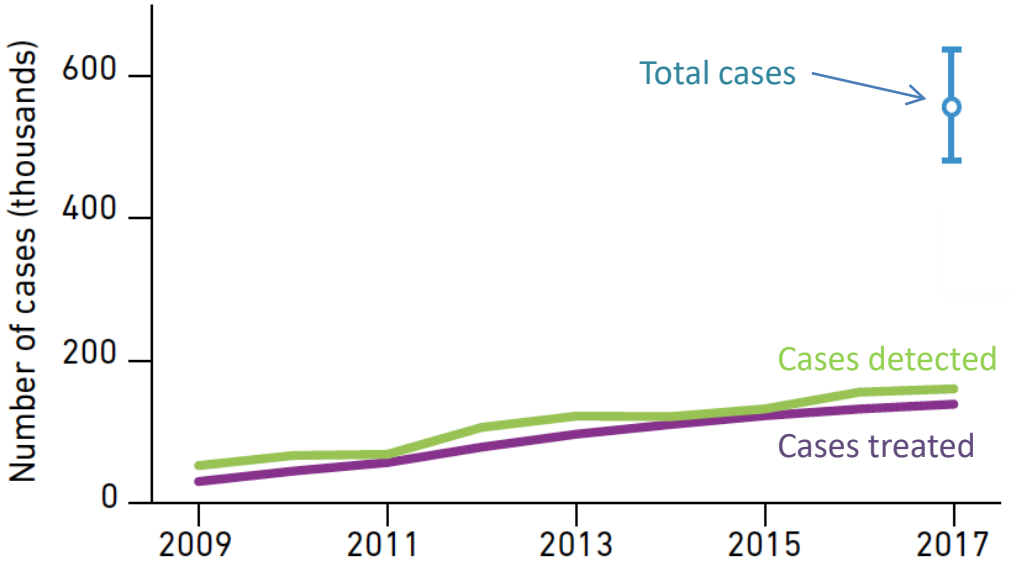
Global migration of MDR-TB strains





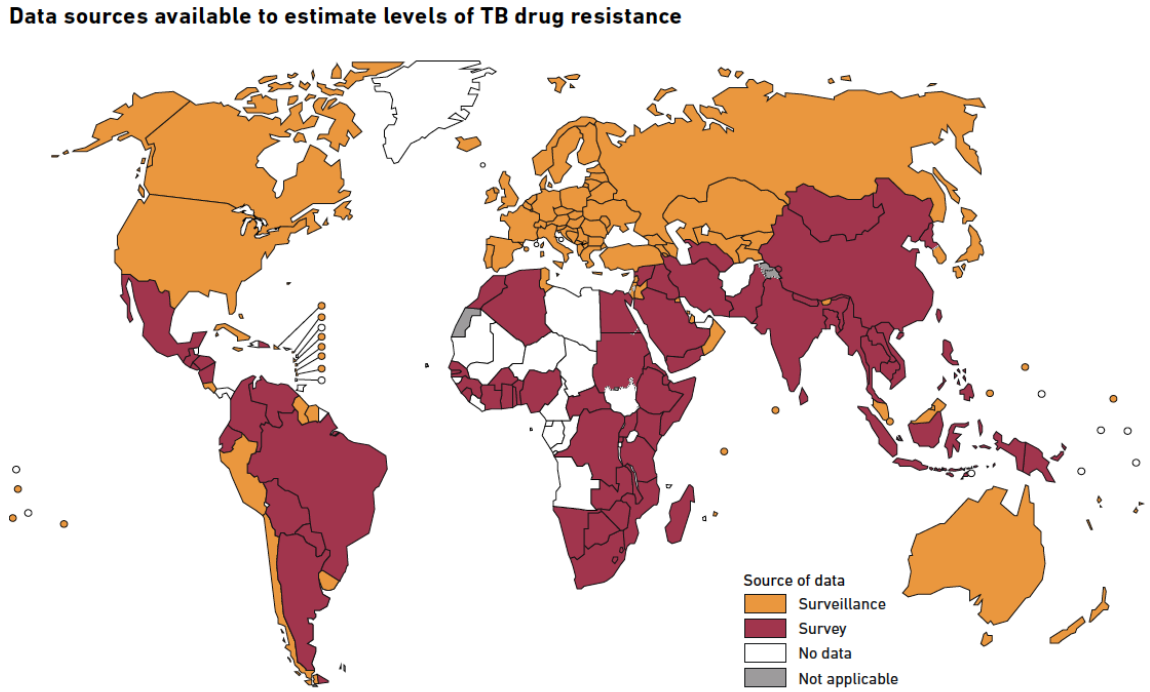
Cohen et al. Thorax 2019

Eighty percent of those with MDR/RR-TB are neither detected or treated

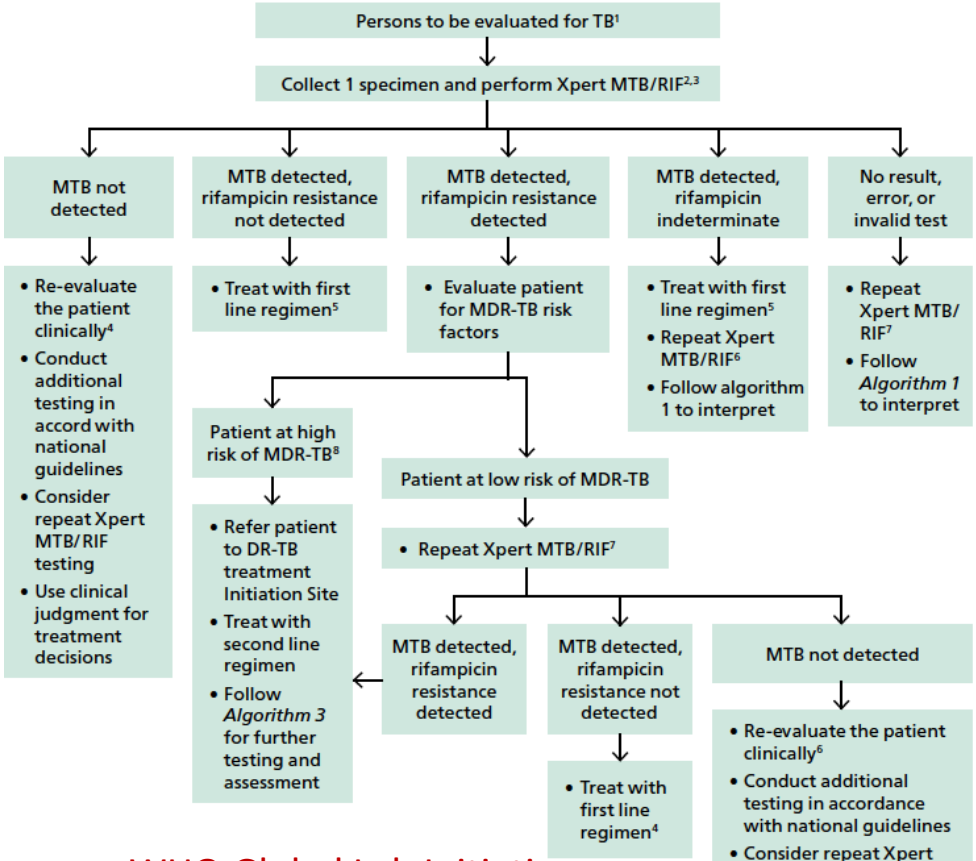


WHO Global TB Report 2018

Measuring TB drug resistance in the world

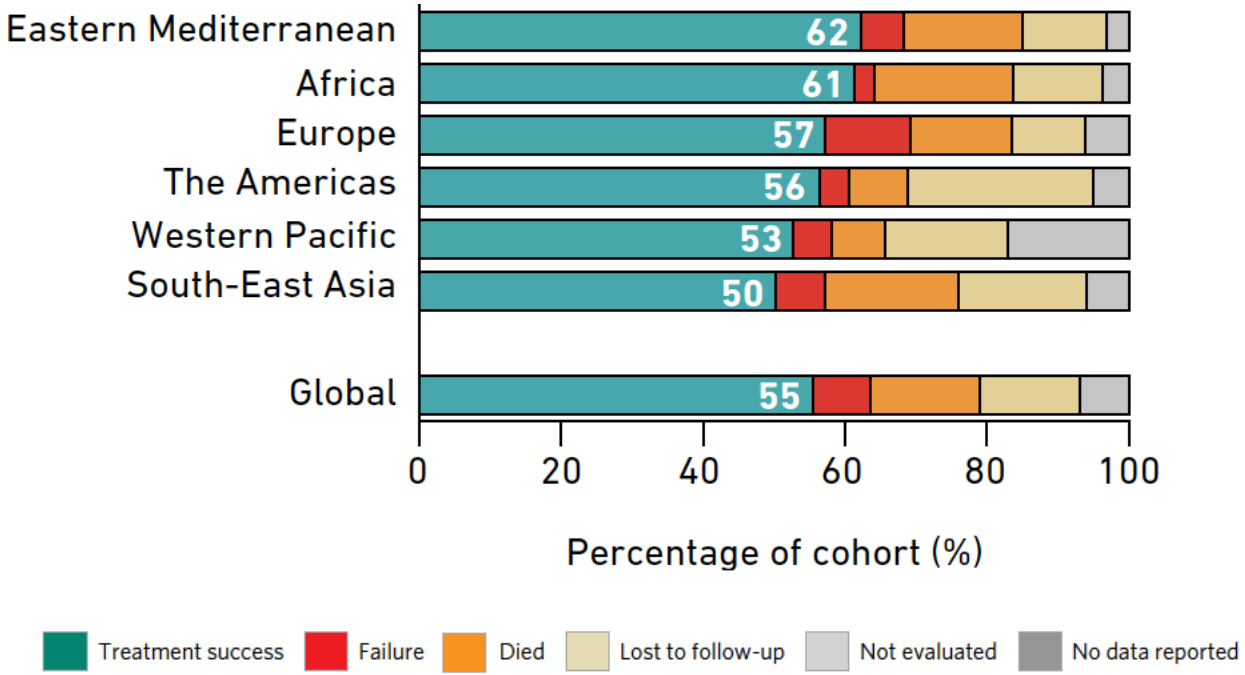


WHO Global TB Report 2018



WHO Global Lab Initiative
Model Diagnostic Algorithm
Revised June 2018

Outcomes of patients treated for RR and MDR-TB

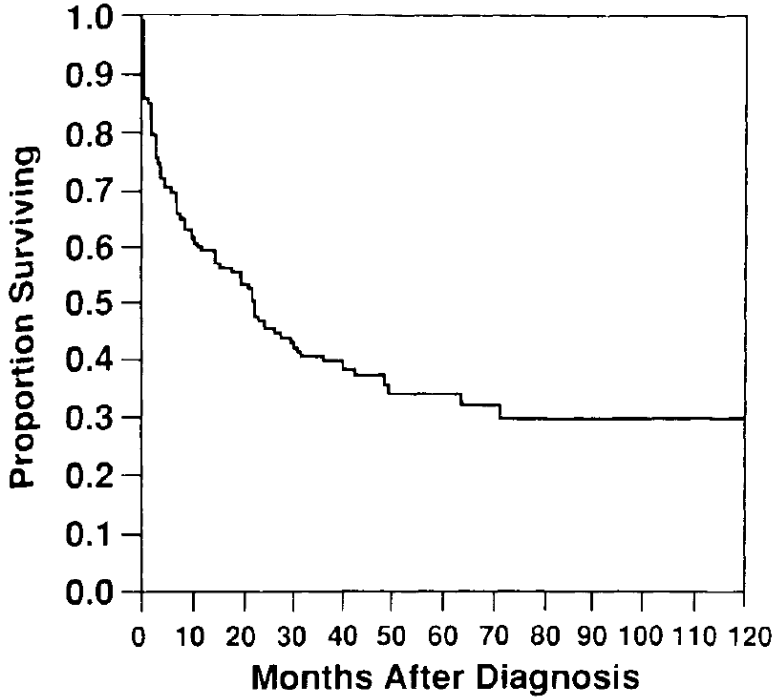


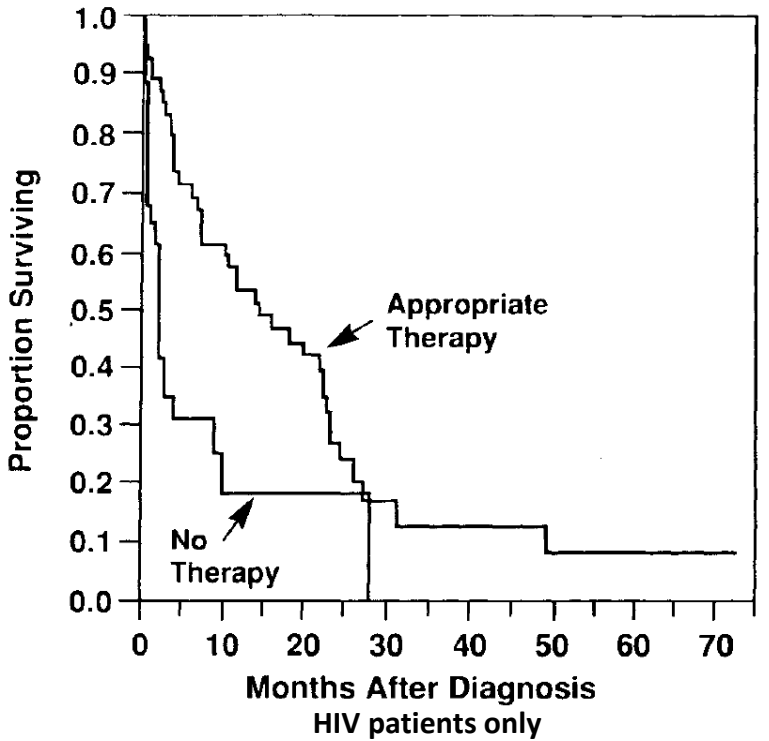
WHO Global TB Report 2018

Drug-resistant TB continues to be a public health crisis…Urgent action is required to improve the coverage and quality of diagnosis, treatment and care for people with drug-resistant TB.

WHO Global TB Report 2018

Survival of patients with MDR-TB, Bellevue Hospital, 1983-1993





Park, Davis, Schluger. Am J Resp Crit Care Med 1996; 153: 317-324

WHO 2011 recommendations for constructing an MDR regimen

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

- WHO: use at least 5 effective drugs, including PZA (D1)
  - One from group A
  - One from group B
  - Two from group C
  - If a regimen can't be composed from the above, use drugs from D2 or D3
- Treat for 18-24 months

The Bangladesh short-course regimen for MDR-TB

		Drug doses by weight group		
Drug	**Weeks**	**< 33 kg**	**33 - 50 kg**	**> 50 kg**
Kanamycin*	1 - 16	15 mg per kilogramme body weight		
Isoniazid (H)	1 - 16	300 mg	400 mg	600 mg
Prothionamide	1 - 16	250 mg	500 mg	750 mg
Clofazimine	1 - 40	50 mg	100 mg	100 mg
Moxifloxacin	1 - 40	400 mg	600 mg	800 mg
Ethambutol	1 - 40	800 mg	800 mg	1200 mg
Pyrazinamide	1 - 40	1000 mg	1500 mg	2000 mg

- Kanamycin 3 times/week after week 12

The intensive phase may be extended by 4 or 8 weeks if smear conversion has not occurred by 16 or 20 weeks

Comparison of WHO recommended 18-24 month regimen with a shorter regimen: STREAM

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

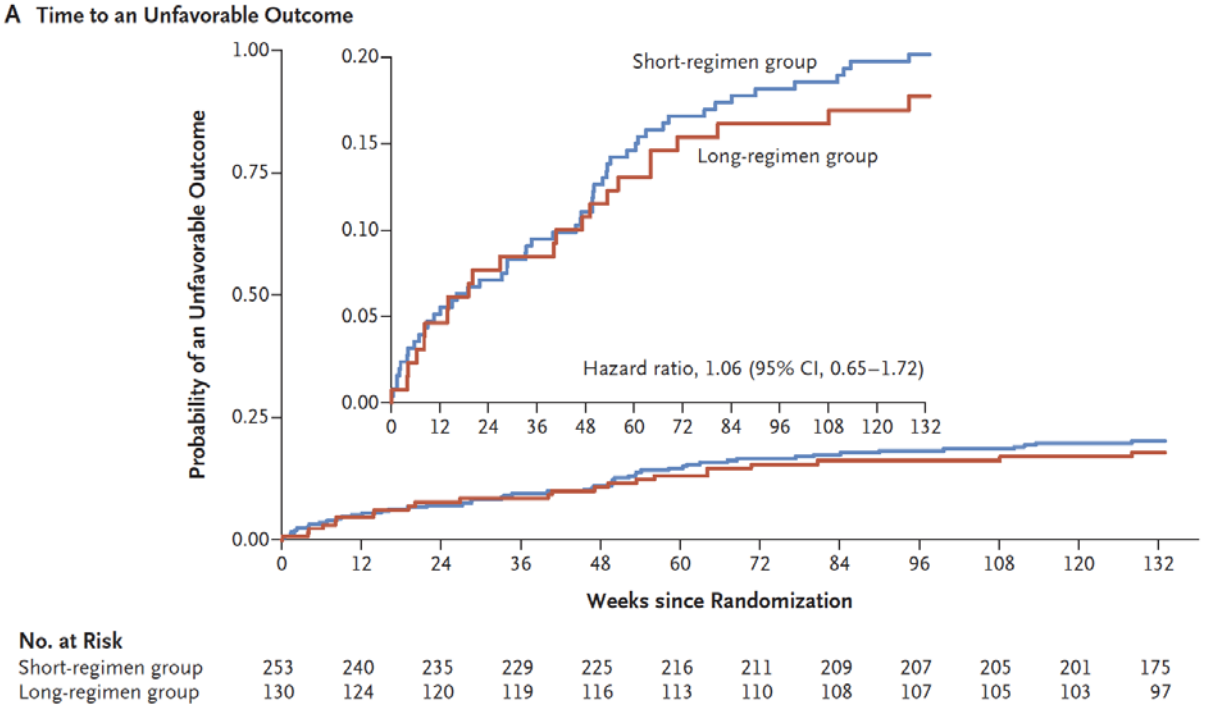
A Trial of a Shorter Regimen for Rifampin-Resistant Tuberculosis

A.J. Nunn, P.P.J. Phillips, S.K. Meredith, C.-Y. Chiang, F. Conradie, D. Dalai, A. van Deun, P.-T. Dat, N. Lan, I. Master, T. Mebrahtu, D. Meressa, R. Moodliar, N. Ngubane, K. Sanders, S.B. Squire, G. Torrea, B. Tsogt, and I.D. Rusen, for the STREAM Study Collaborators*

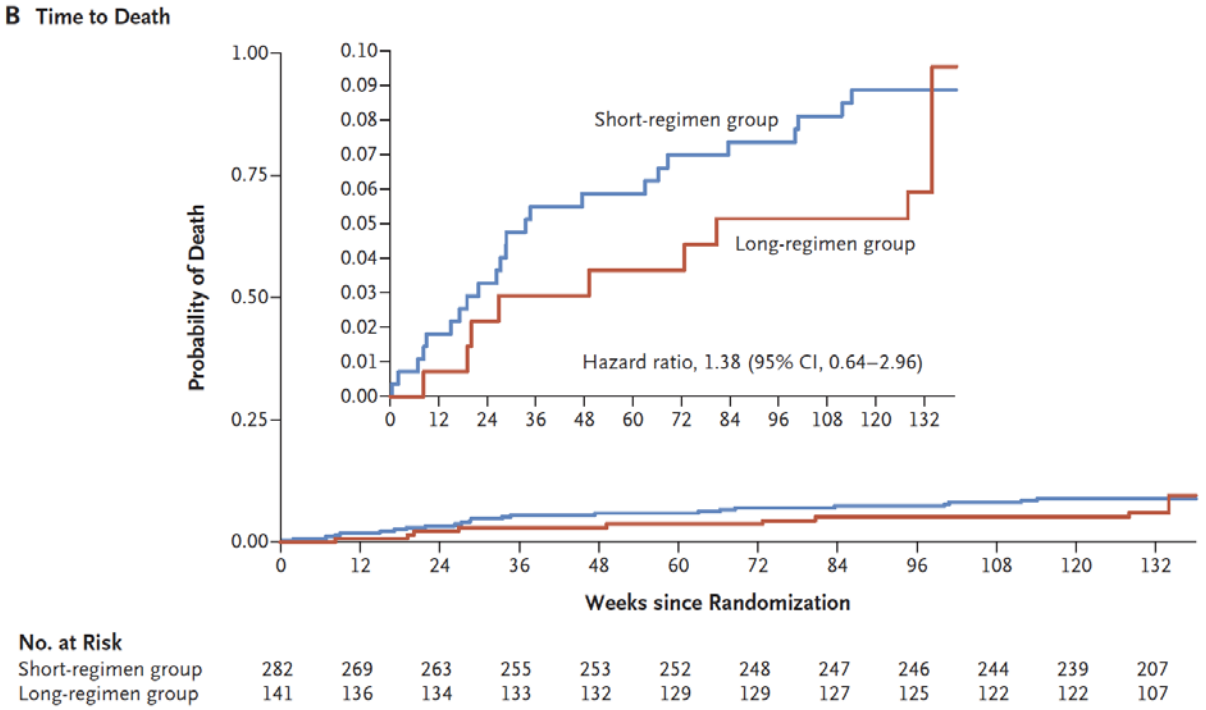
STREAM results: efficacy

Variable	Modified Intention-to-Treat Population			Per-Protocol Population		
	Long Regimen	Short Regimen	Total	Long Regimen	Short Regimen	Total
Disposition of the participants						
Underwent randomization — no.	142	282	424	142	282	424
Were included in the population — no.	130	253	383	87	234	321
Were considered not able to be assessed — no.						
Had reinfection with a different strain	1	7	8	1	6	7
Had a negative culture at 76 weeks but lost to follow-up thereafter	5	1	6	3	1	4
Were included in primary outcome analysis — no.	124	245	369	83	227	310
Outcome						
Attained favorable status — no. (%)†	99 (79.8)	193 (78.8)	292 (79.1)	67 (80.7)	186 (81.9)	253 (81.6)
Had an unfavorable outcome — no. (%)	25 (20.2)	52 (21.2)	77 (20.9)	16 (19.3)	41 (18.1)	57 (18.4)

STREAM results: efficacy



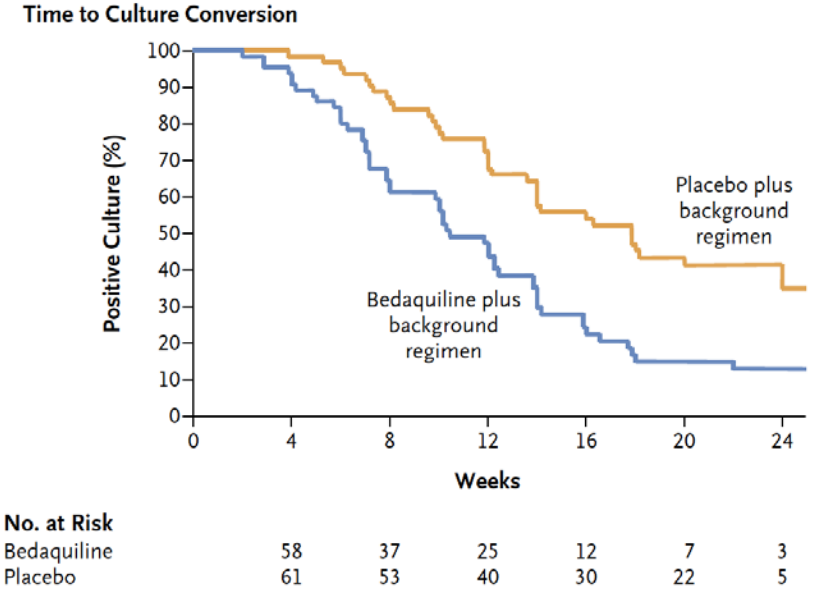
STREAM results: efficacy

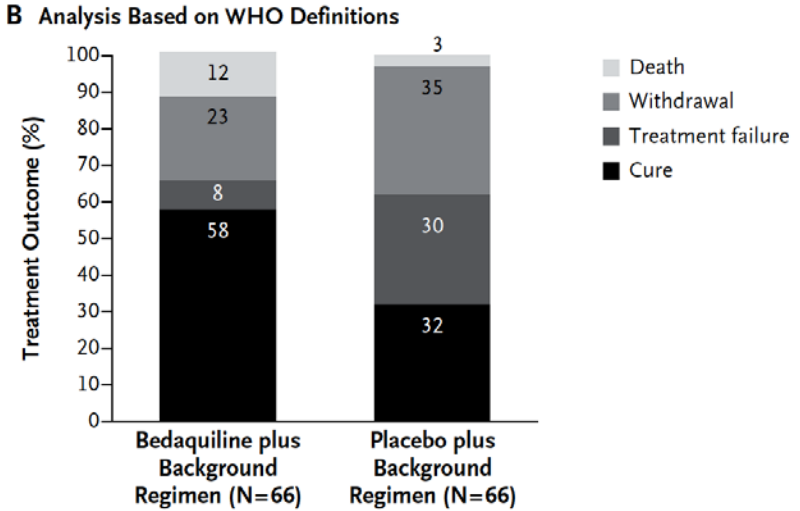


STREAM results: safety

Outcome	Long Regimen (N=141)	Short Regimen (N=282)	Total (N=423)
Grade 3 to 5 adverse event — no. (%)	64 (45.4)	136 (48.2)	200 (47.3)
Serious adverse event — no. (%)	53 (37.6)	91 (32.3)	144 (34.0)
Death — no. (%)	9 (6.4)	24 (8.5)	33 (7.8)
Related to tuberculosis	2	7	9
Related to tuberculosis treatment	1	1	2
Related to HIV or HIV treatment	3	6	9
Other or uncertain	3	10	13

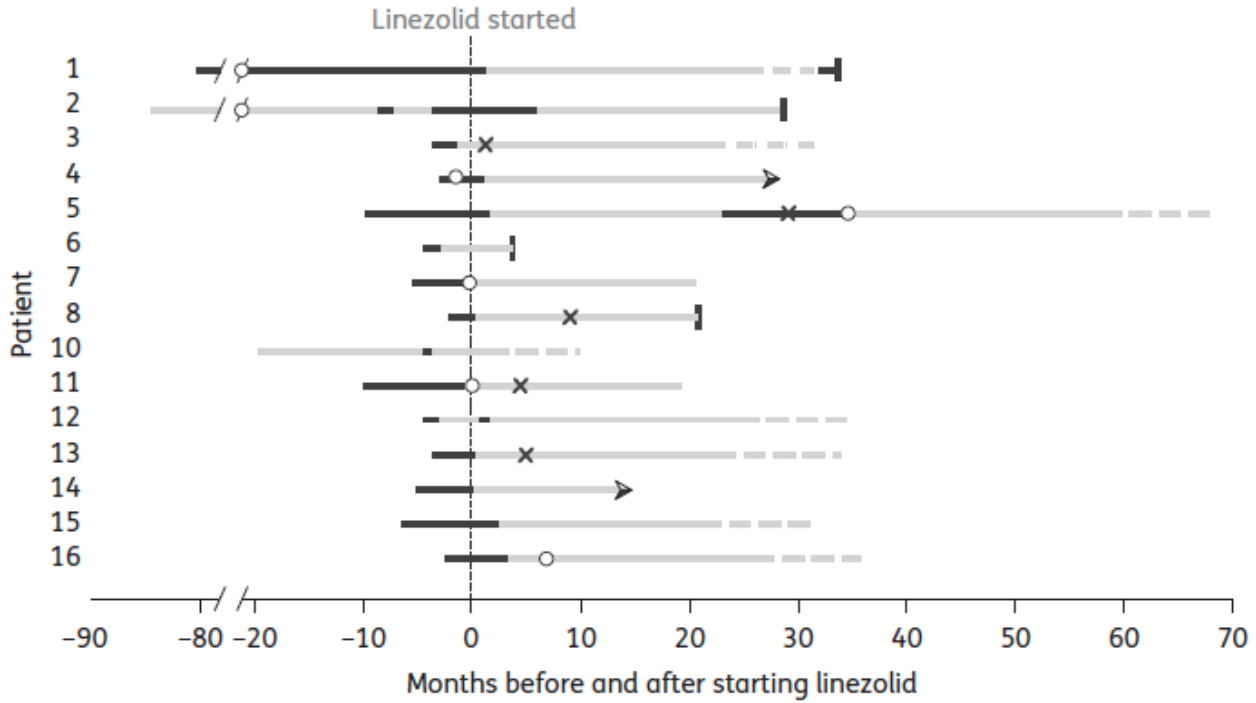
Bedaquiline (TMC207), an ATP synthase inhibitor, in the treatment of MDR-TB





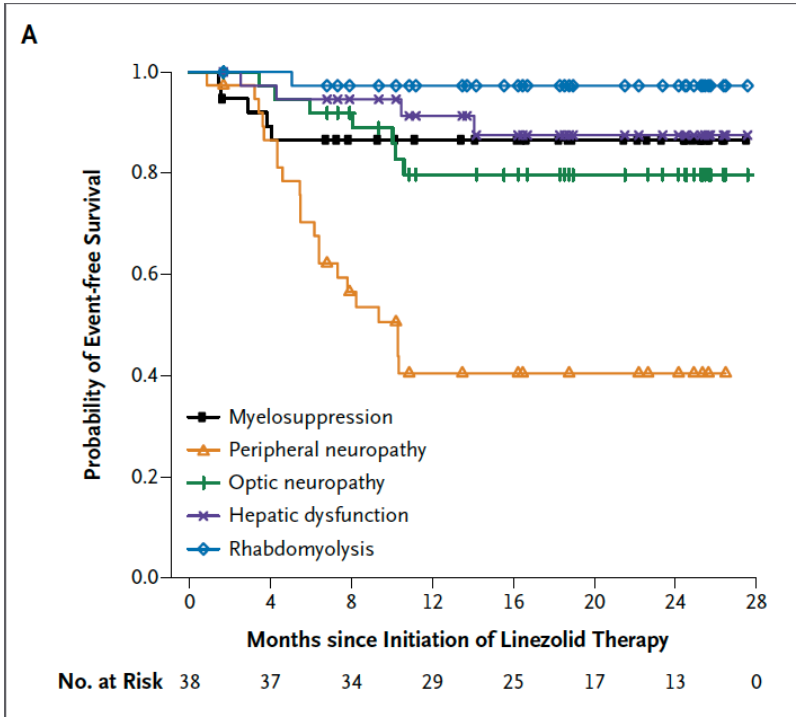
Diacon et al. N Engl J Med 2014; 371: 723-732

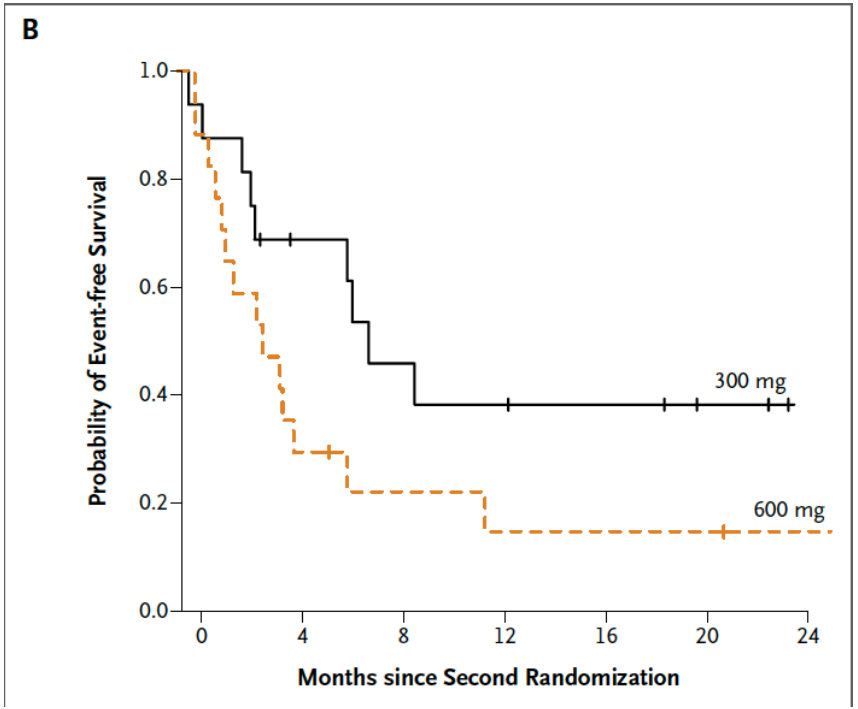
Utility of linezolid in the treatment of MDR and XDR TB: New York City experience



Anger et al. J Antimicrob Chemother 2010; 65:775-783

Adverse effects associated with administration of linezolid for tuberculosis





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

Delaminid in the treatment of MDR-TB

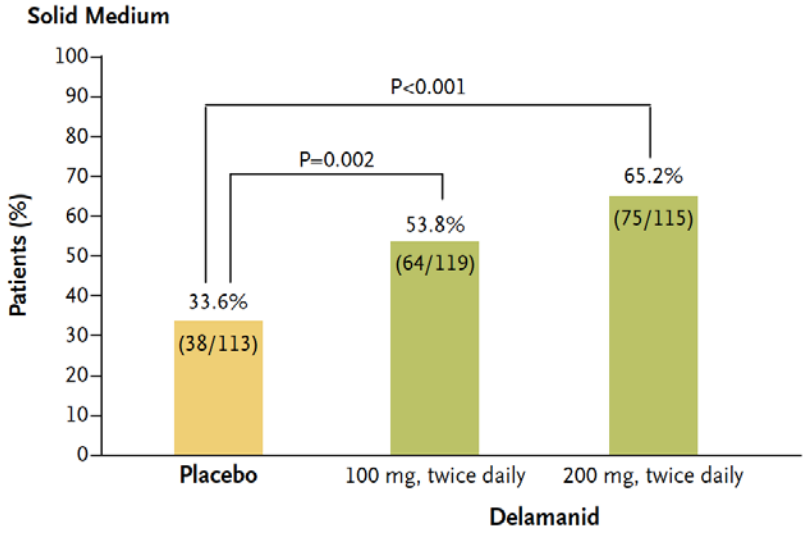
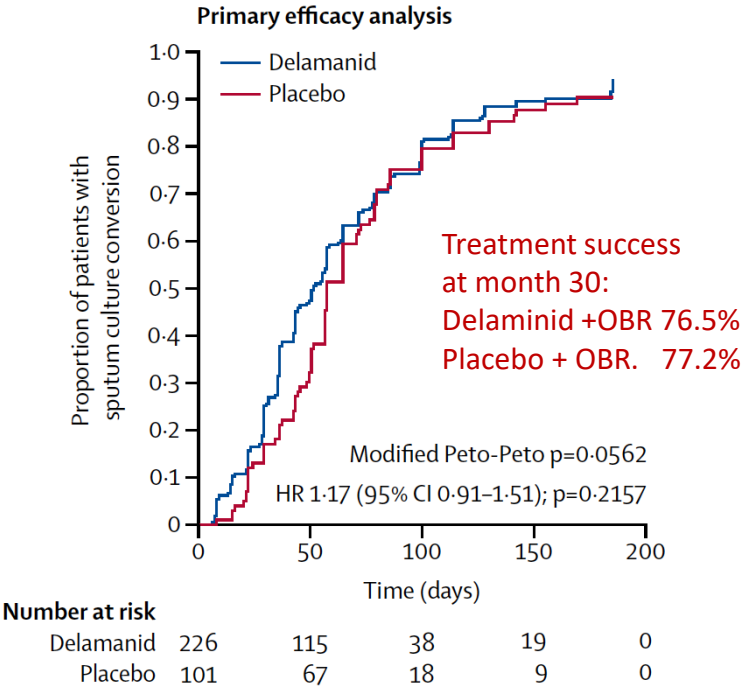


Figure 2. Proportion of Patients with Sputum-Culture Conversion by Day 57.



Gler et al. New Engl J Med 2012; 366: 2151-2160

Groote-Bidlingmaier et al. Lancet Respir Med 2019; 7; 249-259

Drugs associate with success or failure in the treatment of MDR-TB

- Individual patient-level meta-analysis of 12030 patients reported in clinical trials of MDR-TB
- Overall treatment success 61%
- Treatment success positively correlated with use of linezolid, levofloxacin, carbapenems, moxifloxacin, clofazimine or bedaquiline
- Reduction in mortality associated with use of levofloxacin or moxifloxacin, linezolid, or bedaquiline
- Increased mortality associated with use of kanamycin or capreomycin

Injectables						
Amikacin*						
Success	62/69	384/551	68	2·5 (0·9–6·6)	NC	0·09 (–0·04 to 0·22)
Death	15/84	395/946	83	0·4 (0·2–0·8)	NC	–0·16 (–0·30 to –0·03)
Kanamycin†						
Success	52/74	394/546	73	0·9 (0·5–1·9)	15·1%	–0·01 (–0·16 to 0·14)
Death	19/93	391/937	93	0·9 (0·5–1·9)	40·5%	–0·01 (–0·13 to 0·10)
Capreomycin (all patients)						
Success	217/338	229/282	332	0·5 (0·4–0·7)	3·7%	–0·14 (–0·20 to –0·07)
Death	354/692	56/338	675	3·4 (2·7–4·3)	NC	0·25 (0·20 to 0·30)
Capreomycin (sensitive patients only)						
Success	72/91	229/282	91	0·8 (0·4–1·7)	6·0%	–0·04 (–0·16 to 0·08)
Death	25/116	56/338	115	3·8 (1·6–8·9)	NC	0·16 (0·07 to 0·25)
Other drugs						
Levofloxacin or moxifloxacin‡						
Success	279/360	119/182	359	1·2 (0·8–1·6)	7·7%	0·01 (–0·05 to 0·06)
Death	122/482	253/435	482	0·6 (0·4–0·8)	NC	–0·07 (–0·12 to –0·02)
Linezolid						
Success	255/281	221/392	280	6·6 (4·1–10·6)	7·3%	0·31 (0·24 to 0·38)
Death	33/314	418/810	314	0·2 (0·1–0·3)	7·5%	–0·29 (–0·36 to –0·23)
Clofazimine						
Success	141/173	335/500	173	1·5 (0·9–2·6)	NC	0·04 (–0·04 to 0·13)
Death	43/216	408/908	216	0·4 (0·2–0·6)	19·7%	–0·18 (–0·27 to –0·10)
Bedaquiline						
Success	126/145	350/528	139	2·5 (1·3–4·8)	NC	0·12 (0·03 to 0·21)
Death	18/163	433/961	155	0·5 (0·2–0·9)	NC	–0·09 (–0·17 to –0·02)

Lancet 2018; 392: 821-834

2019 consolidated WHO guidelines for treatment of MDR and RR TB: grouping of medicines to be used in longer 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

2019 WHO consolidated guidelines for MDR-TB

- Longer regimens
  - All three group A agents and at least one Group B agent should always be included
  - Kanamycin and capreomycin should not be included
  - Treatment duration shoud be 18-20 months
  - Treatment duration should be 15-17 months after culture conversion
- Shorter regimen
  - Suitable for patients who have not been previously treated for more than 1 month with second-line drugs used in the shorter regimen or in patients in whom resistance to quinolones and second-line injectables has been excluded

Outcomes of MDR-TB patients treated with bedaquiline-containing regimens in South Africa

	Bedaquiline	Non-bedaquiline	p-value
Patients n	68	204	
Age years	34.5 (26–55)	33.5 (18–73)	0.42
Male	41 (60.3)	120 (58.8)	0.89
Body weight at admission kg	51.8 (33.3–78.1)	51.9 (21.0–89.9)	0.76
Patients weighing >50 kg	39 (57.4)	115 (56.4)	0.89
Previous TB treatment	33 (48.5)	171 (83.8)	<0.001
HIV-infected	35 (51.5)	99 (48.5)	0.81
HIV-infected on ARV therapy	35 (100)	90 (90.9)	0.11
Median CD4 count at admission $\mu L \cdot mL^{-1}$	146 (57–271)	198 (71–302)	0.51
Anti-TB drugs received# n	8 (7–8)	9 (8–10)	<0.001
Patients in whom at least one drug was withdrawn due to adverse events	40 (58.8)	78 (38.2)	0.005
Days of admission n	158 (102–221)	199 (77–329)	0.05
Outcomes			
Favourable (cured/completed treatment)	45 (66.2)	27 (13.2)	<0.001
Unfavourable outcome	23 (33.8)	175 (85.8)	
Deceased	10 (14.7)	69 (33.8)	0.004
Failed	4 (5.9)	53 (26)	<0.001
LTFU	8 (11.8)	22 (10.8)	1
Defaulted	1 (1.5)	31 (15.2)	<0.001
On treatment	0 (0)	2 (1)	
Patients with favourable outcome despite drug withdrawal due to adverse events¶	23 (57.5)	10 (12.8)	<0.001
HIV-infected patients with a favourable outcome	24 (68.6)	18 (18.2)	<0.001

Olayanju et al. Eur Respir J 2018; 51: 1800544

Bedaquiline companion drugs

Drugs	Bedaquiline		Non-bedaquiline		p-values (comparing proportions of patients who received drug)
	Patients who received drug	Patients in whom drug was withdrawn due to adverse events (grade ≥3)	Patients who received drug	Patients in whom drug was withdrawn due to adverse events (grade ≥3)	
Patients n		68		204	
Capreomycin	7 (10.3)	6 (85.7)	196 (95.6)	43 (21.9)*	<0.001
Kanamycin	1 (1.5)	1 (100)	110 (53.9)	12 (10.9)	<0.001
Amikacin	0	0	2 (1.0)	0	N/A
Any aminoglycoside#	8 (11.8)	0	202 (99.0)	47 (23.0)	<0.001
Para-amino salicylic acid	64 (94.1)	10 (15.6)	194 (95.1)	13 (6.7)	0.75
Pyrazinamide	66 (97.1)	3 (4.5)	201 (98.5)	10 (5.0)	0.60
Terizidone	61 (89.7)	8 (13.1)	201 (98.5)	10 (5.0)	0.003
Moxifloxacin	13 (19.1)	1 (7.7)	101 (49.5)	3 (3.0)	<0.001
Ofloxacin	0	0	127 (62.3)	3 (2.4)	N/A
Levofloxacin	67 (98.5)	0	0	0	N/A
Ciprofloxacin	0	0	1 (0.5)	0	N/A
Third- or fourth-generation fluoroquinolone¶	68 (98.5)	0	101 (49.5)	0	<0.001
Clofazimine	67 (98.5)	1 (1.5)	65 (31.9)	2 (3.1)	<0.001
Linezolid	55 (80.9)	18 (32.7)	0	0	N/A
Ethambutol	26 (38.2)	5 (19.2)	189 (92.7)	15 (7.9)	<0.001
Ethionamide	15 (22.1)	6 (40)	198 (97.1)	12 (6.1)	<0.001
High-dose isoniazid	22 (32.4)	3 (13.6)	133 (65.2)	13 (9.8)	<0.001
Dapsone	0	0	34 (16.7)	0	N/A
Co-amoxiclavulanate	2 (2.9)	0	79 (38.7)	0	<0.001
Clarithromycin	0	0	43 (21.1)	0	N/A
Amoxicillin	0	0	13 (6.4)	0	N/A
Azithromycin	0	0	1 (0.5)	0	N/A
Meropenem	1 (1.5)	0	0 (0.0)	0	N/A
Bedaquiline	68 (100)	0	0 (0.0)	0	N/A

Olayanju et al. Eur Respir J 2018; 51: 1800544

Pretomanid (Pa-824) in the treatment of XDR and hrMDR-TB: Nix-TB

- Open-label trial for patients with highly-resistant TB: XDR-TB or treatment intolerant or non-responsive MDR-TB
- Patients enrolled at 3 sites in South Africa
- Daily regimen for 6 months:
  - Bedaquiline
  - Pretomanid (PA-824, nitroimidazole)
  - Linezolid (1200mg/day)

- 109 patients enrolled
  - 62% XDR, 38% MDR
  - 51% HIV infected
  - Results available for 101 patients:
    - To date, durable cure has been achieved in 90% of patients
    - Most patients required linezolid dose reduction

TB Alliance, presented at The Union meeting, Oct. 2018

NiX-TB: patient characteristics

Variable	Safety population B-L-Pa (n = 109)	MITT population B-L-Pa (n = 80)
HIV Status		
Negative	53/109 (48.6%)	41/80 (51.2%)
Positive	56/109 (51.4%)	39/80 (48.8%)
Duration Since HIV Diagnosis (months)		
Mean	4	4
SD	4	4
Minimum	0	0
Median	4	4
Maximum	14	14
Original TB Diagnosis		
DS	11/109 (10.1%)	9/80 (11.2%)
MDR	76/109 (69.7%)	58/80 (72.5%)
XDR	21/109 (19.3%)	12/80 (15.0%)
Not available	1/109 (0.9%)	1/80 (1.2%)
Duration Since Original TB Diagnosis (months)		
Mean	24	22
SD	28	27
Minimum	0.5	0.5
Median	12	17
Maximum	141	141
Current TB Diagnosis		
XDR-TB	71/109 (65.1%)	55/80 (68.8%)
MDR-TB Non-Responsive	19/109 (17.4%)	12/80 (15.0%)
MDR-TB Intolerant	19/109 (17.4%)	13/80 (16.2%)
Duration Since Current TB Diagnosis (months)		
Mean	11	10
SD	16	14
Minimum	0.4	0.4
Median	3	3
Maximum	90	90
Duration Since Positive TB Culture (days)		
Mean	52	55
SD	24	24
Minimum	16	16
Median	49	61

- Mean age: 36 years
- Mean CD4+ t-cell count of HIV infected patients: 394
- Patients with cavities: 85%
- BMI:
  - Mean: 21
  - Median: 20

Nix-TB: efficacy

	Total	XDR	TI/NR MDR
N expected	**81**	**56**	**25**
Unassessable	1	1	0
Total Assessable	**80**	**55**	**25**
Favorable	**72 (90%)**	**49 (89%)**	**23 (92%)**
Unfavorable	**8 (10%)**	**6 (11%)**	**2 (8%)**
95% CI for Favorable	81% to 96%	78% to 96%	74% to 99%

NiX-TB: safety

TEAEs by Preferred Term	B-L-Pa (N=109)
Peripheral neuropathy*	87 (79.8)
Anemia	40 (36.7)
Nausea	40 (36.7)
Vomiting	37 (33.9)
Headache†	30 (27.5)
ALT/AST increased§	27 (24.8)
Dyspepsia	26 (23.9)
Rash‡	26 (23.9)
Dermatitis acneiform	26 (23.9)
Decreased appetite	24 (22.0)
Pleuritic pain	20 (18.3)
Upper respiratory tract infection	20 (18.3)
Abdominal pain¶	18 (16.5)
Gamma-Glutamyltransferase increase	18 (16.5)
Amylase increased/ Hyperamylasemia	17 (15.6)

NiX-TB: safety

Treatment Emergent Adverse Events (TEAEs)	B-L-Pa regimen, n (%)
Any TEAE	***109 (100%)***
Serious TEAE	19 (17.4%)
TEAE by severity	
Life-threatening	17 (15.6%)
Severe	41 (37.6%)
Moderate	43 (39.4%)
Mild	8 (7.3%)
TEAEs leading to discontinuation of any study drug	33 (30.3%)

Treatment Emergent Adverse Events (TEAEs)	B-L-Pa regimen, n (%)
TEAEs leading to discontinuation of linezolid	27 (24.8%)
TEAEs leading to discontinuation of B-L-Pa	6 (5.5%)
TEAEs leading to death	6 (5.5%)

TEAEs by Preferred Term	B-L-Pa (N=109)
Peripheral neuropathy*	87 (79.8)
Anemia	40 (36.7)
Nausea	40 (36.7)
Vomiting	37 (33.9)
Headache†	30 (27.5)
ALT/AST increased§	27 (24.8)

Clinical trials with newer agents

- STREAM-2:
  - randomized trial of modified Bangladesh regimen vs. fully oral modified Bangladesh regimen (bedaquiline substituted for kanamycin)
- ZeNix-TB:
  - 4-arm trial of the Nix-TB regimen (BPaL), with varying dose and duration of linezolid
    - Linezolid 600 mg X 9 weeks
    - Linezolid 600 mg X 26 weeks
    - Linezolid 1200 mg X 9 weeks
    - Linezolid 1200 mg X 26 weeks

Multidrug-resistant TB 2019

- An ongoing global public health crisis
- Newer diagnostics should allow faster and more widespread diagnosis and use of more effective drug regimens early in the treatment course
- Treatment approaches are rapidly evolving as new drugs have been introduced
- Overall favorable outcome rates with WHO recommended longer regimens can reach 80% in best circumstances
- Shorter regimen (‘Bangladesh’) achieves good cure rates in less time for eligible patients, but with similar adverse effects as longer regimens
- Regimens containing bedaquiline and linezolid seem to be associated with high rates of favorable outcomes
- Optimal make-up of regimens both in drugs and duration to provide best outcomes (most efficacy, least toxicity) has not been defined
- NiX-TB regimen (BPaL) achieves very high cure in 6 months; requires careful management of side effects

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