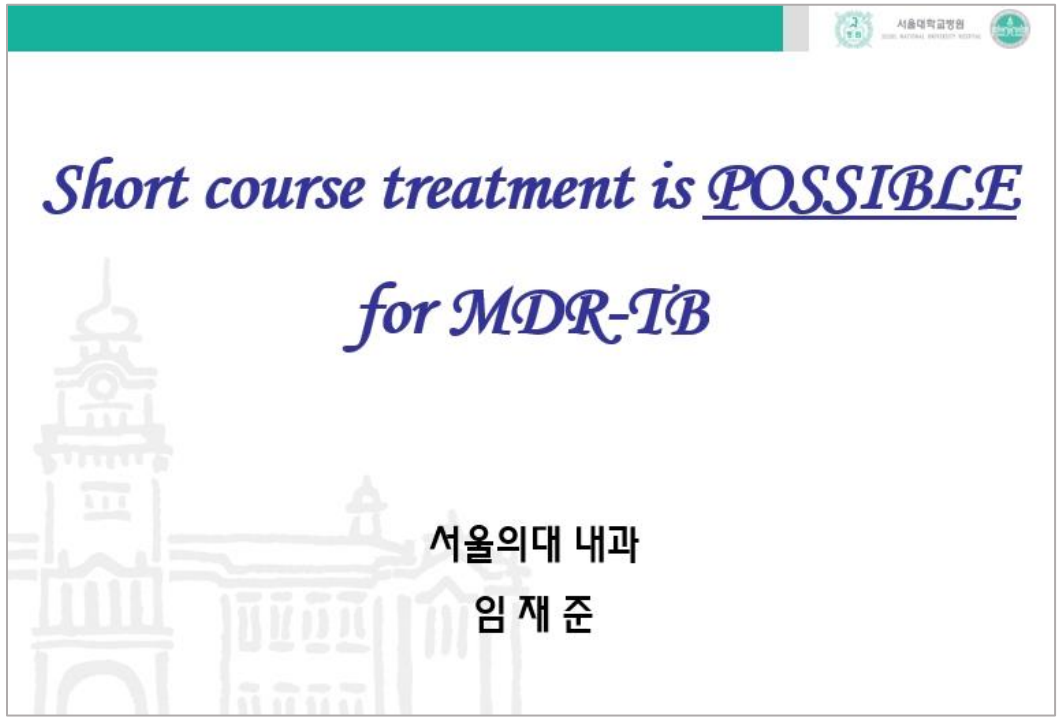
Shorter treatment for MDR-TB with oral drugs is possible in South Korea

서울대학교병원 호흡기내과

곽 낙 원

Debate for shorter treatment of MDR-TB



Daejeon Convention Center, April 6, 2013

Changes in MDR-TB treatment

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)

Groups and steps	Medicine and abbreviation	
Group A: **Include all three medicines**	Levofloxacin *or* moxifloxacin	Lfx Mfx
	Bedaquiline[b,c]	Bdq
	Linezolid[d]	Lzd
Group B: **Add one or both medicines**	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[c,e]	Dlm
	Pyrazinamide[f]	Z
	Imipenem-cilastatin *or* meropenem[g]	Ipm-Cln Mpm
	Amikacin (*or* streptomycin)[h]	Am (S)
	Ethionamide *or* prothionamide[i]	Eto Pto
	P-aminosalicylic acid[i]	PAS

World Health Organization

THE SHORTER MDR-TB REGIMEN

4-6 Km-Mfx-Pto-Cfz-Z-$H_{high\text{-}dose}$-E / 5 Mfx-Cfz-Z-E

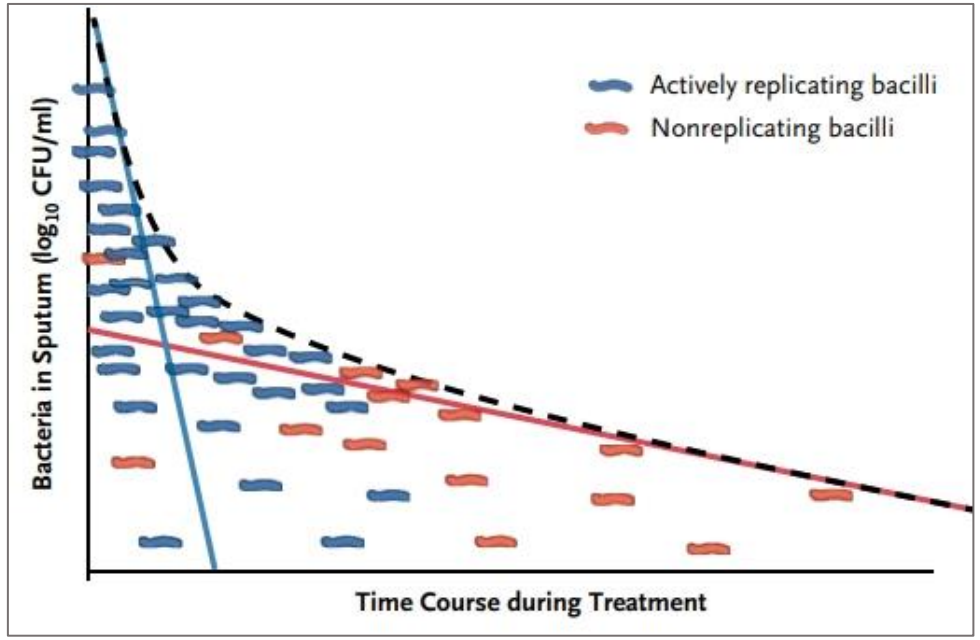
Km=Kanamycin; Mfx=Moxifloxacin; Pto=Prothionamide;
Cfz=Clofazimine; Z=Pyrazinamide;
$H_{high\text{-}dose}$= high-dose Isoniazid; E=Ethambutol

Drug	Dose
Bedaquiline (100 mg tablet)	400 mg once daily for 2 weeks, then 200 mg 3 times per week afterwards OR 200 mg daily for 8 weeks, then 100 mg daily
Pretomanid (200 mg tablet)	200 mg once daily
Linezolid (600 mg tablet)	600 mg once daily
Moxifloxacin (400 mg tablet)	400 mg once daily

Contents

Contents

Why we need longer treatment in MDR/RR-TB



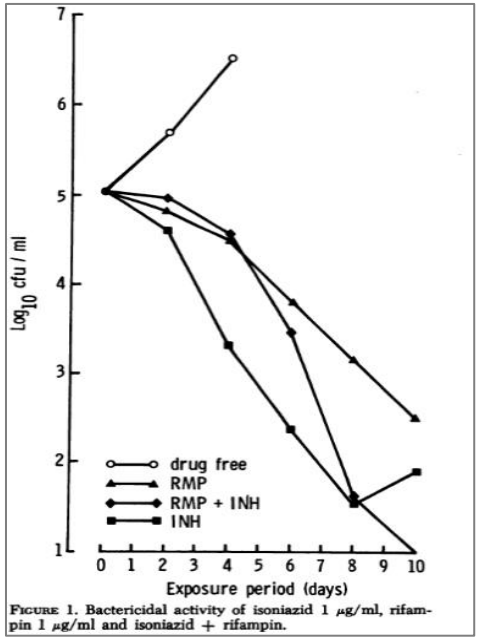


FIGURE 1. Bactericidal activity of isoniazid 1 μg/ml, rifampin 1 μg/ml and isoniazid + rifampin.

Regimen	CFU	
	1 month	4 month
INH+ SM+ RFP	3,000	7.5
INH+ SM	11,000	336

Early bactericidal activity: killing rapidly multiplying bacteria - INH

Sterilizing acitivity: killing persistent, or nonreplicating bacteria- RFP/PZA

Horsburgh et al. N Engl J Med 2015

Mitchison. Chest 1979

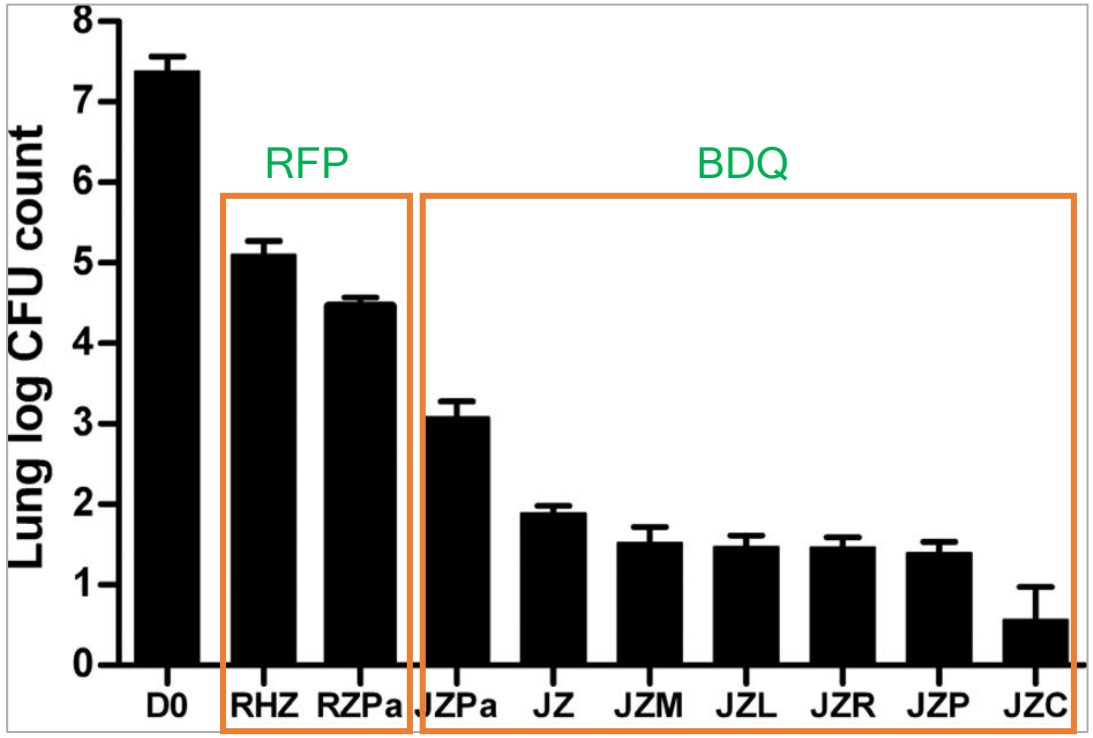
If we have drugs as effective as rifampicin,

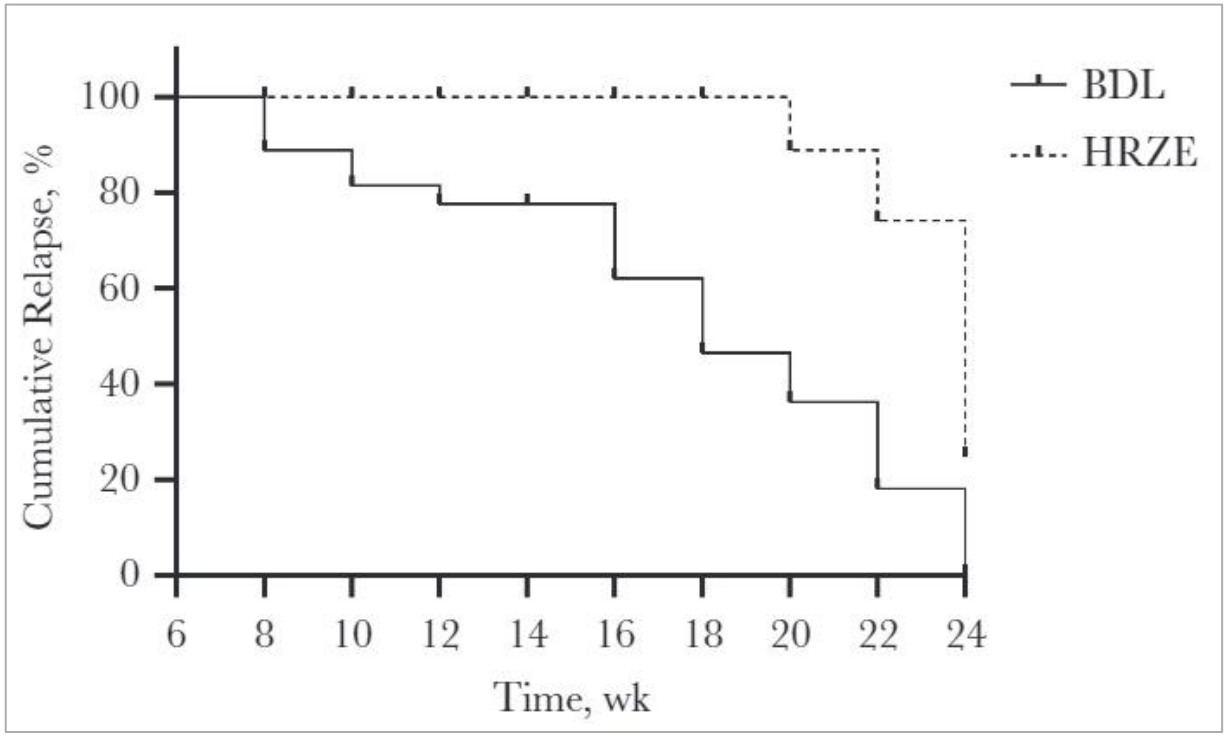
	Bactericidal activity	Sterilizing activity	Resistance prevention	Core drug
RFP	High	High	High	Y
PZA	Low	High	Low	
FQ	High	High	High	Y
DLM	High	High?	High	?
BDQ	High	High	High	Y
LZD	High	Low	High	
CFZ	Low	High	High	
2nd line injectables	High	Low	High	

Core drug: high bactericidal activity, sterilizing activity and resistance prevention
Companion drug: high bactericidal activity to reduce the high bacillary load and limit the core drug-resistance

van Deun et al. Int J Tuberc Lung Dis 2018

New core drugs' effects in animal model





In mice, BDQ or DLM-based regimens showed superior efficacy
in terms of sterilizing effect and relapse prevention than RFP-based regimens

Tasneen et al. Antimicrob Agent Chemother 2011

Pietmann et al. J Infect Dis 2021

Contents

Oral regimens for MDR-TB in RCTs

	BDQ	Pa	DLM	FQ	LZD	PZA	CFZ	EMB	ETH	INH (high)
MDR-END			O	O	O	O				
NExT	O			O	O	O			Δ	Δ
Nix/ZeNix	O	O			O					
TB-PRACTECAL	O	O		O	O					
STREAM-2	O			O		O	O	O	O	O
endTB	Δ		Δ	O	Δ	O	Δ			
SimpliciTB	O	O		O		O				

Oral regimens vs conventional longer treatment

MDR-END

	Conventional (=89)	Interventional (n=79)
Favorable outcomes at 24-months	60 (71%)	54 (75%)
Failed to culture conversion	0	1 (1%)
2 or more drugs changes	10 (12%)	4 (6%)
Loss to follow-up	4 (5%)	1 (1%)

Interventional arm- 9-12 months DLM, LZD, LFX, and PZA

Conventional arm- 20-24 months regimens according to 2014 WHO guideline

Mok et al. Lancet 2022

Oral regimens vs injectable-containing regimens

NExT

	Conventional	Interventional	P-value
2-months conversion	70.7%	86.1%	0.113
6-months conversion	95.1%	95.4%	0.999
Favorable outcomes (24-months)	22.7%	51.0%	0.006
Adeverse events (discontinuation)	56.4%	30.3%	0.007

Interventional arm- 6-9 months BDQ, LZD, LFX, PZA and TZD/PTH/INH (high-dose)

Conventional arm- 18-20 months or 9-11 months KM containing regimens

Esmail et al. Am J Respir Crit Care Med 2022

Oral regimens vs novel drugs-containing regimens

TB-PRACTECAL

	Conventional (=66)	Interventional (n=62)
Favorable outcome	34 (52%)	55 (89%)
Unfavorable outcome	32 (48%)	7 (11%)
Early discontinuation	28 (42%)	5 (8%)
Adherence issues	3/28 (11%)	0
Adverse events	17/28 (61%)	5/5 (100%)
Treatement failure	0	0

Interventional arm- 6 months BDQ, Pa, LZD and MFX

Conventional arm- 9-20 months standard-care (BDQ in 94.9%, LZD in 97.4%, DLM in 12.8%)

Nyang'wa et al. N Engl J Med 2022

Contents

Loss to follow-up in public sector

Data from National Mokpo TB hospital/ Masan TB hospital and Seobuk hospital

	Never treated (n=41)	First-line drugs only (n=88)	Second-line drugs (n=73)	Total (n=202)
Treatment failure, n (%)	1 (2.4)	1 (1.1)	1 (1.4)	3 (1.5)
Transfer out, n (%)	4 (9.8)	20 (22.7)	16 (21.9)	40 (19.8)
Default, n (%)	14 (34.1)	27 (30.7)	34 (46.6)	75 (37.1)
Death, n (%)	0	2 (2.3)	7 (9.6)	9 (4.5)

About half of unfavorable outcomes are due to loss to follow-up in real clinical practice

Jeon et al. J Korean Med Sci 2011

Loss to follow-up in private sector

	2001-2005 (n=125)	2006-2010 (n=123)	2011-2015 (n=84)
Treatment duration, months	31.5	24.4	19.8
Favorable outcomes, n (%)	84 (67.2)	103 (83.7)	74 (88.1)
Unfavorable outcomes, n (%)	41 (32.8)	20 (16.3)	10 (11.9)
Microbiologic failure, n (%)	18 (14.4)	7 (5.8)	4 (4.8)
Loss to follow-up, n (%)	10 (8.0)	6 (4.8)	5 (5.9)

About half of unfavorable outcomes are due to loss to follow-up in real clinical practice

Kwak et al. Int J Tuberc Lung Dis 2019

Longer duration, more loss to follow-up

	Shorter regimens (n=2,625)	Longer regimens (n=2,717)
Treatment success, n (%)	2,164 (80.0)	1,814 (75.3)
Failure or relapse, n (%)	118 (3.6)	112 (2.7)
Death during treatment, n (%)	201 (7.6)	265 (4.6)
Loss to follow-up, n (%)	142 (4.2)	526 (14.6)

In IPD meta-analysis (9-12 months shorter [Bangladesh] regimens vs > 20 months regimens), treatment success was higher with shorter regimen than with longer regimen due to less loss to follow-up.

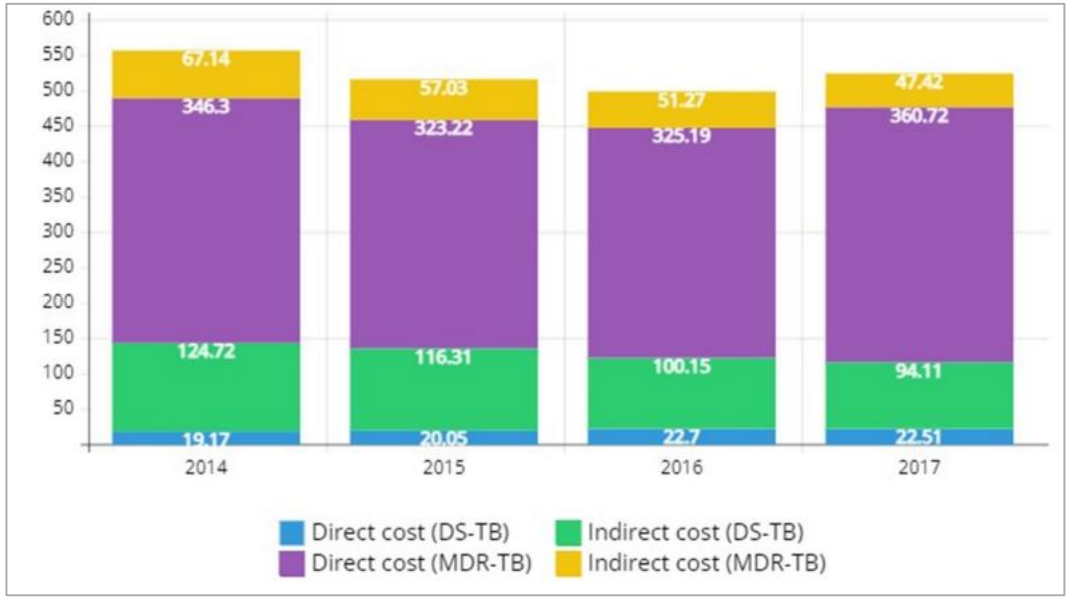
Abidi et al. Eur Respir J 2020

Contents

Cost of MDR-TB treatment in South Korea

	DS-TB	MDR-TB
Direct cost	516	4,000
Drug cost	32	1,860
Indirect cost	1,663	12,941
Total cost	2,166	15,856

Medical cost per person (1999-2004) (unit: $1)



Total medical cost in Korea (2014-2017) (unit: $1M)

The cost of MDR-TB is burdensome at the individual and national levels

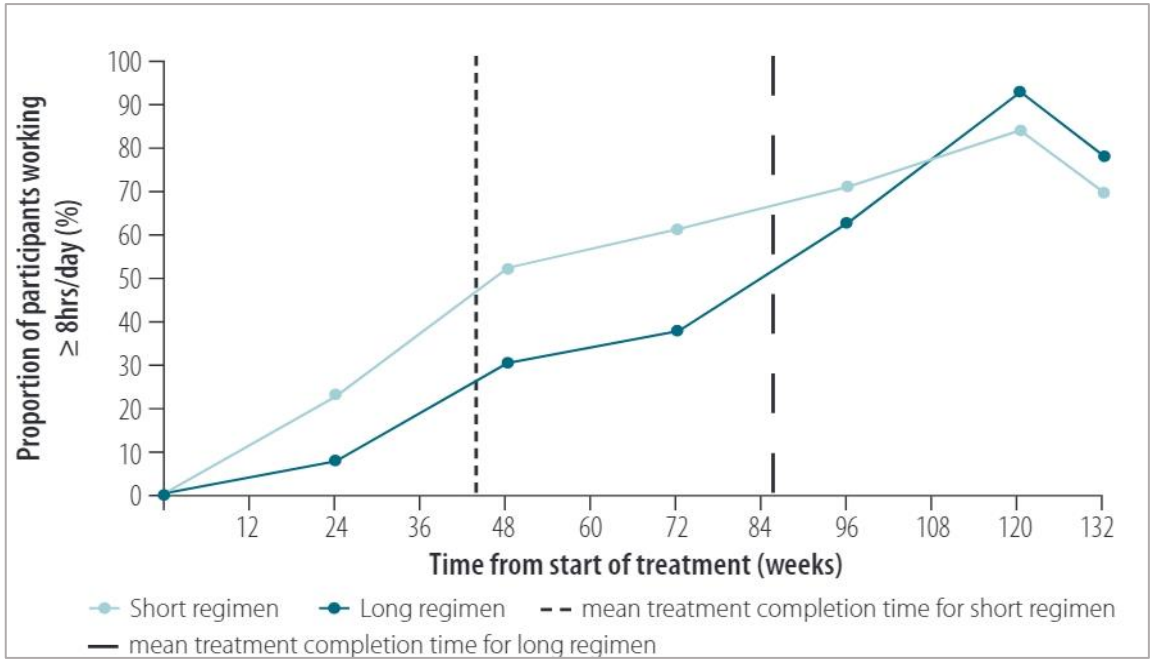
Kang et al. Respirology 2006

Lee et al. Front Public Health 2022

Cost saving through treatment shortening

Cost and working pattern of Ethiopian patients enrolled in STREAM trial

	Longer regimen	Shorter regimen
Total cost ($)	6,096.6	4,523.3
Cardiac safety monitoring	0	149.6
Medication cost	1663.0	1361.3
Social support	799.6	254.4
Consumables	408.0	183.6



Treatment shortening → Medication cost ↓, working hour ↑, consumables ↓

Madan et al. World Health Organ 2020

Cost saving through expensive drug

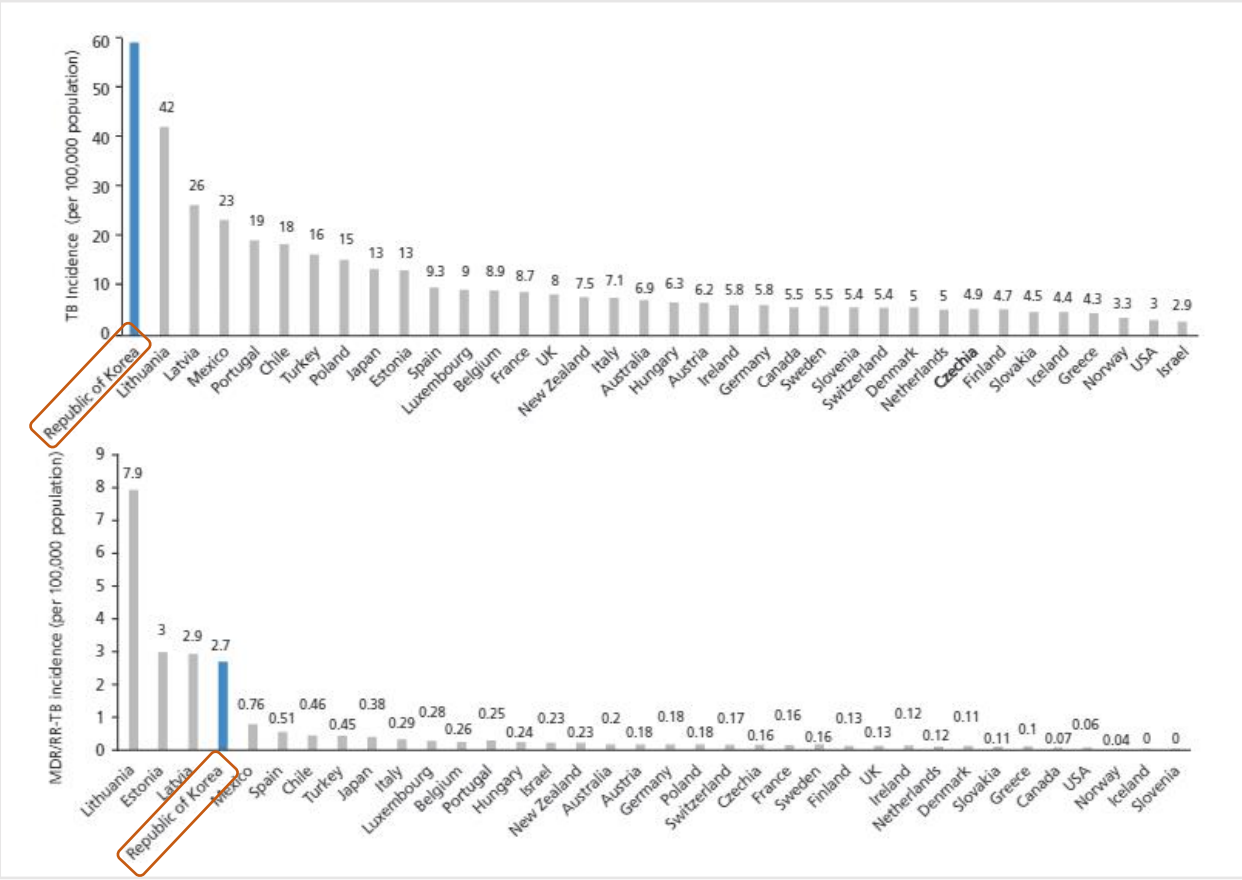
Treatment	Cost, KRW		Effectiveness, QALY		ICUR (KRW/QALY)
	Total	Incremental	Overall	Incremental	
Standard treatment	72,082,172	-	3.80	-	-
Standard treatment + BDQ	86,043,831	13,961,659	5.00	1.20	11,638,656

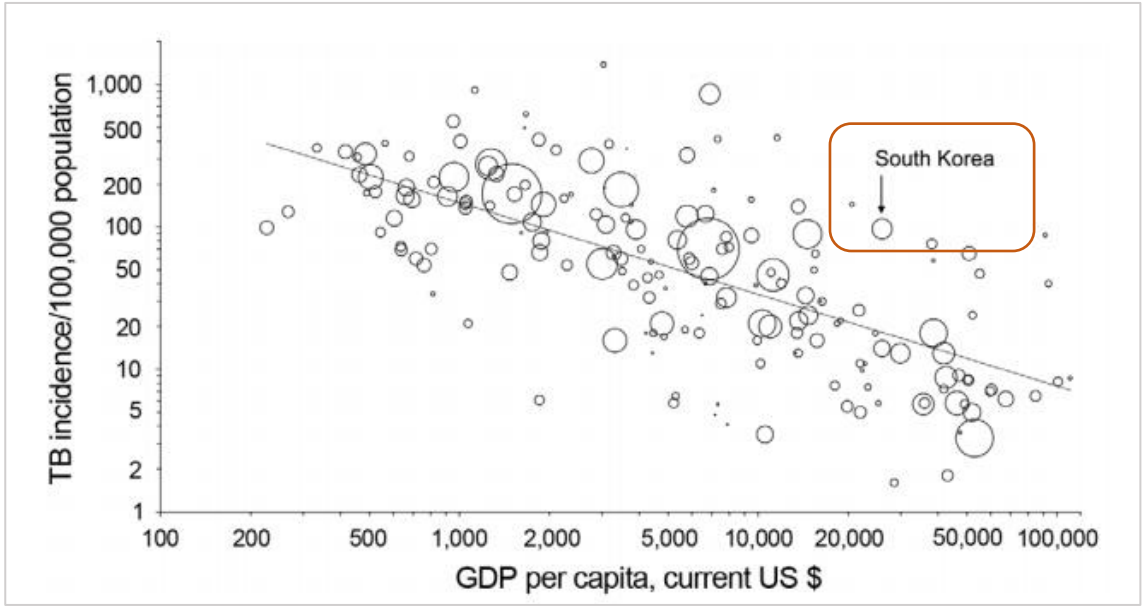
According to a cohort-based decision-analytic model,
addition of bedaquiline had an 80% of probability of being cost-effective,
at wiliness-to-pay threshold of 26,000,000 KRW.

Park et al. Clin Ther 2016

Contents

High burden of TB in South Korea

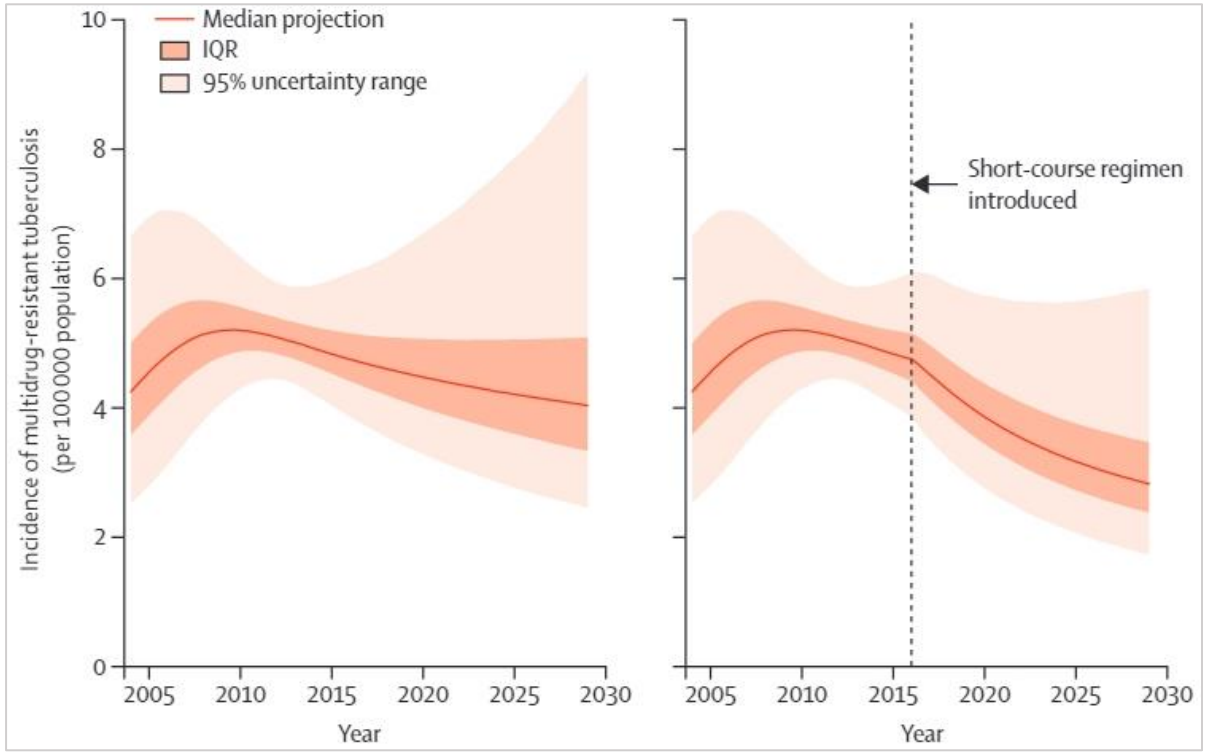


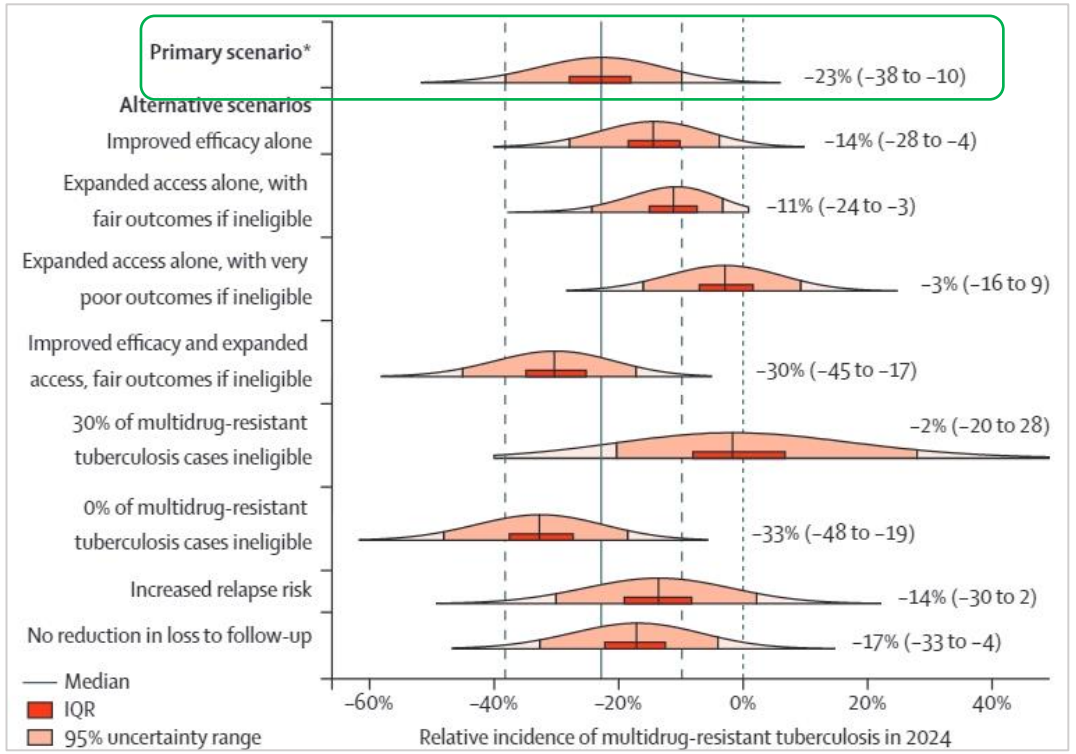


Son et al. J Korean Med Assoc 2021

Kim et al. Emerg Infect Dis 2015

Decreased incidence with shorter duration



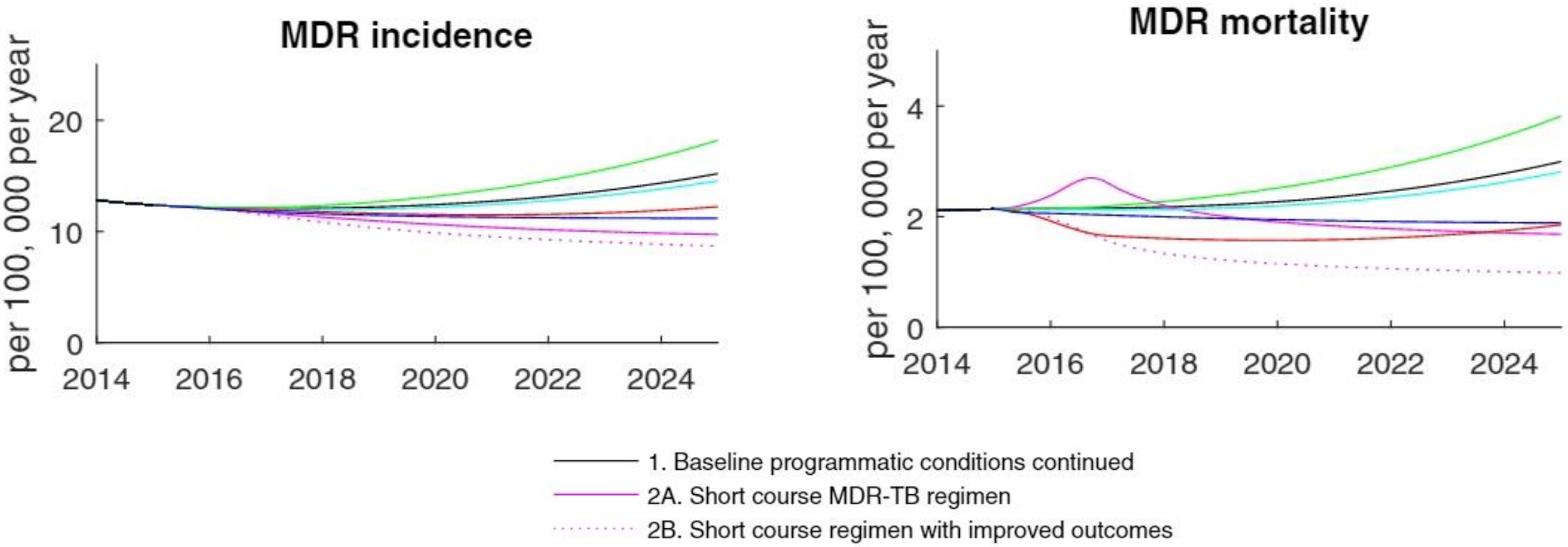


When we shortened the treatment duration from 20 to 9 months,

incidence will be changed from 4.3 [2.9-7.6] (2014) to 3.3 [2.2-5.6] (2023) per 100,000 population

Kendall et al.Lancet Respir Med 2017

Decrased mortality with shorter duration



The shorter regimen reduced MDR-TB incidence and mortality, achieving greater gains than the alternative interventions (such as improvement of TB detection, identification and treatment avaliability)

Trauer et al.BMC Med 2016

Contents

Why shorter-oral regimens are possible in South Korea

1. Experienced and well-trained medical staff
2. Affordable cost of newer drugs
3. Availability of laboratories for DST
4. Administrative capacitiy
5. Low barrier to medicial facilities

Suggested regimens for MDR-TB

1. MDR-TB without FQ resistance or FQ exposure

- BPaLM (6-9 months)

- DLM, LZD, LFX and PZA (9-12 months)

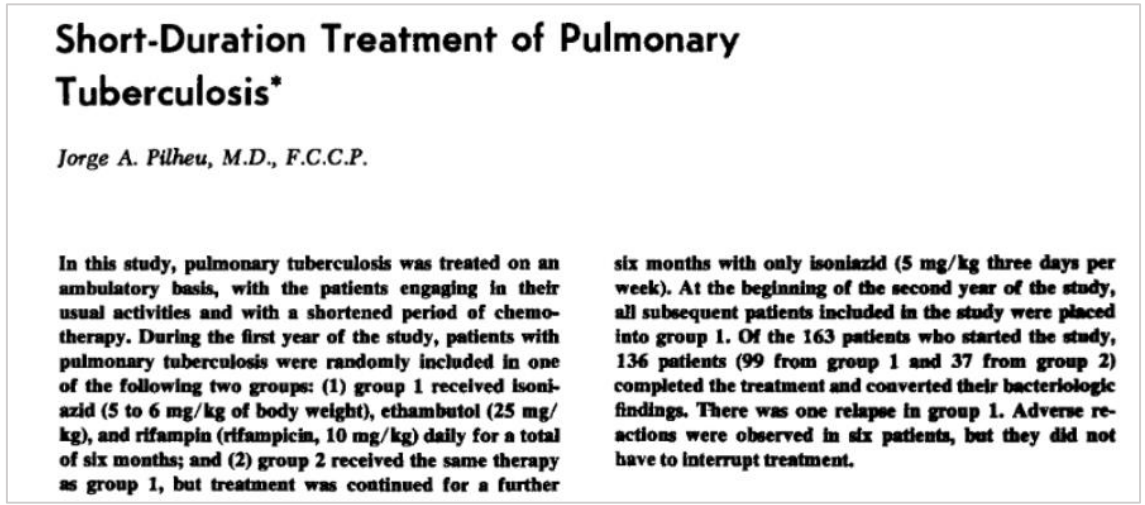
2. MDR-TB with FQ resistance or FQ exposure

- BPaL (6-9 months)

3. Unavailability of BDQ, LZD, DLM

- Individualized longer regimens

Déjà vu

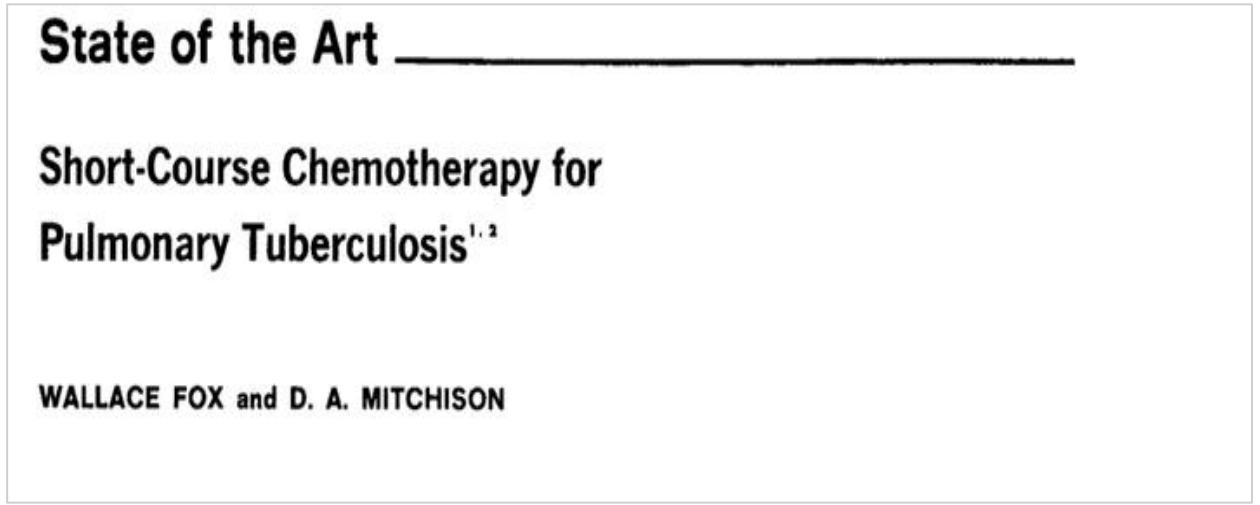


Short-Duration Treatment of Pulmonary Tuberculosis*

Jorge A. Pilheu, M.D., F.C.C.P.

In this study, pulmonary tuberculosis was treated on an ambulatory basis, with the patients engaging in their usual activities and with a shortened period of chemotherapy. During the first year of the study, patients with pulmonary tuberculosis were randomly included in one of the following two groups: (1) group 1 received isoniazid (5 to 6 mg/kg of body weight), ethambutol (25 mg/kg), and rifampin (rifampicin, 10 mg/kg) daily for a total of six months; and (2) group 2 received the same therapy as group 1, but treatment was continued for a further six months with only isoniazid (5 mg/kg three days per week). At the beginning of the second year of the study, all subsequent patients included in the study were placed into group 1. Of the 163 patients who started the study, 136 patients (99 from group 1 and 37 from group 2) completed the treatment and converted their bacteriologic findings. There was one relapse in group 1. Adverse reactions were observed in six patients, but they did not have to interrupt treatment.

Phileu. Chest 1977



State of the Art

Short-Course Chemotherapy for Pulmonary Tuberculosis[1,2]

WALLACE FOX and D. A. MITCHISON

Fox et al. Am Rev Respir Dis 1975

"At the present moment, we cannot be certain if the period of six months of chemotherapy is sufficient for all tuberculosis patients"

Phileu. Chest 1977

"The high cost of rifampin remains problem that, it is hoped, may to some extent be solved with mass production"

Spinosa et al. N Engl J Med 1970

Thank you for your attention