Ontwikkelingen in de behandeling van tuberculose

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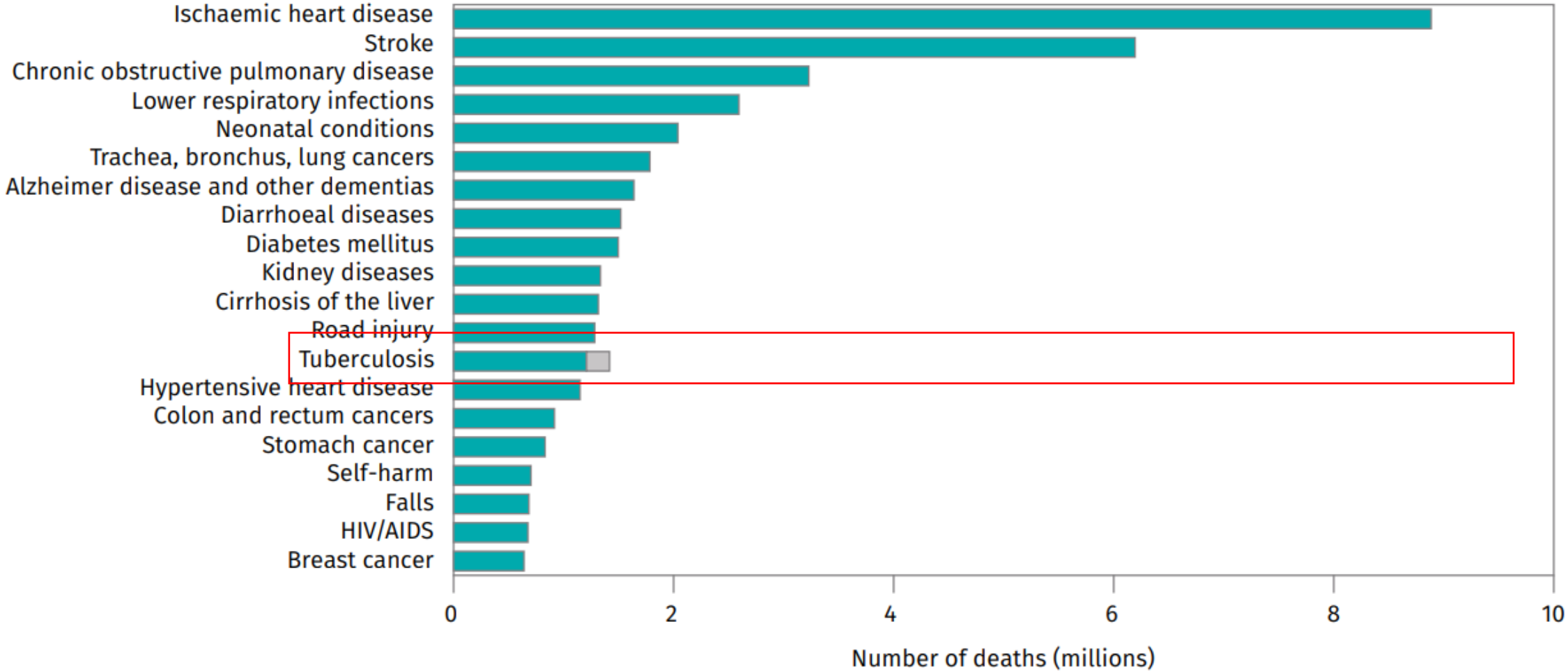
FIG. 7

Top causes of death worldwide in 2019[a,b]

Deaths from TB among HIV-positive people are shown in grey.



FEWER PEOPLE ACCESSED LIFE-SAVING TUBERCULOSIS CARE IN 2021

World Health Organization

END TB

THE COVID-19 PANDEMIC CONTINUES TO HAVE A DAMAGING IMPACT ON ACCESS TO TB SERVICES

In 2021, an estimated **10.6 million** people fell ill with TB

6.4 million people reported to have access to TB care, down from **7.1 million** in 2019

≈4.2 million were undiagnosed or not reported

Better reporting, diagnosis and access to care will close this gap

DRUG-RESISTANT TUBERCULOSIS REMAINS A PUBLIC HEALTH CRISIS

World Health Organization

END TB

IN 2021

450 000 people fell ill with drug-resistant TB

161 746 people accessed treatment

only about **36%** of those in need

of those treated only **60%** were treated successfully in 2019

WHO.org

Behandeling moet beter en korter!

- Verhogen therapietrouw
- Verminderen toxiciteit
- Verminderen van kosten
- Voorkomen van verworven resistentie
- Voor alle vormen van TB
- Betere prestatie TB controle programma's

DS-TB in 4 maanden? MDR-TB in 6-9 maanden?

Inhoud

- Doel en principes van de behandeling
- Ontwikkelingen voor DS-TB
- Ontwikkelingen voor DR-TB

Doel en principes van TB behandeling

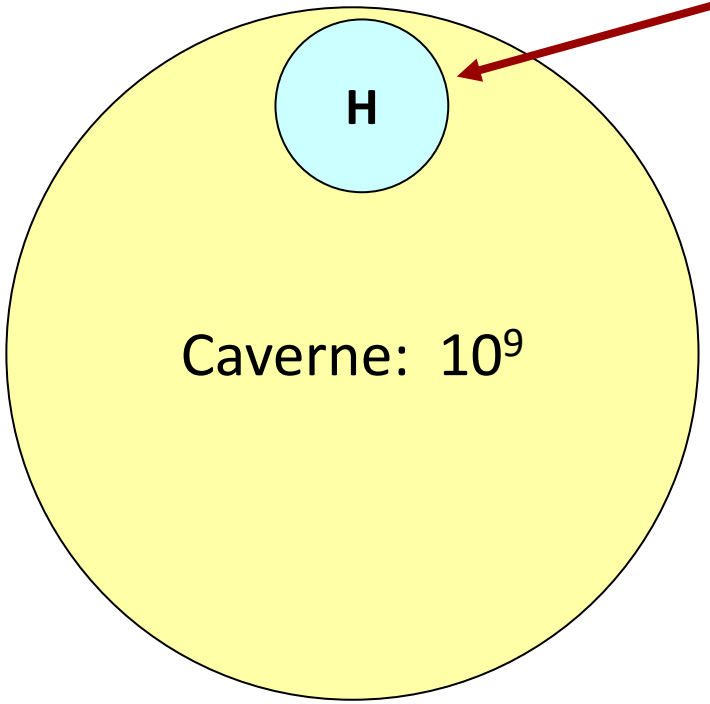
1. Snelle doding bacilli (intensieve fase) → bactericide middelen
   - Voorkomen schade aan de host
   - Afname van besmettelijkheid
   - Verkorting behandelduur?
2. Resistentie voorkomen → combinatie van middelen
   - Inadequate behandeling leidt tot uitgroei van natuurlijk voorkomende resistente bacillen (therapiefalen)
3. Sterilisatie (continuatiefase) → steriliserende middelen
   - Genezing
   - Relapse voorkomen (en dus verdere transmissie en extra zorgkosten)

Three population model

- Populatie A
  - Snel delende bacteriën
    - extracellulair in verkazende granulomen
  - Door grote load en proliferatie meer kans op spontaan ontstaan resistente mutaties
    - Kans hierop voor H bij 10^5-10^6 bacilli
    - Kans hierop voor R bij 10^7-10^9 bacilli
      - deze grote hoeveelheden alleen aanwezig in cavernes of smear positieve patiënten
  - Verantwoordelijk voor symptomen en overlijden (als onbehandeld)
  - Bepaald o.a. de mate van besmettelijkheid

Natuurlijke resistentie

Aantal tbc bacteriën



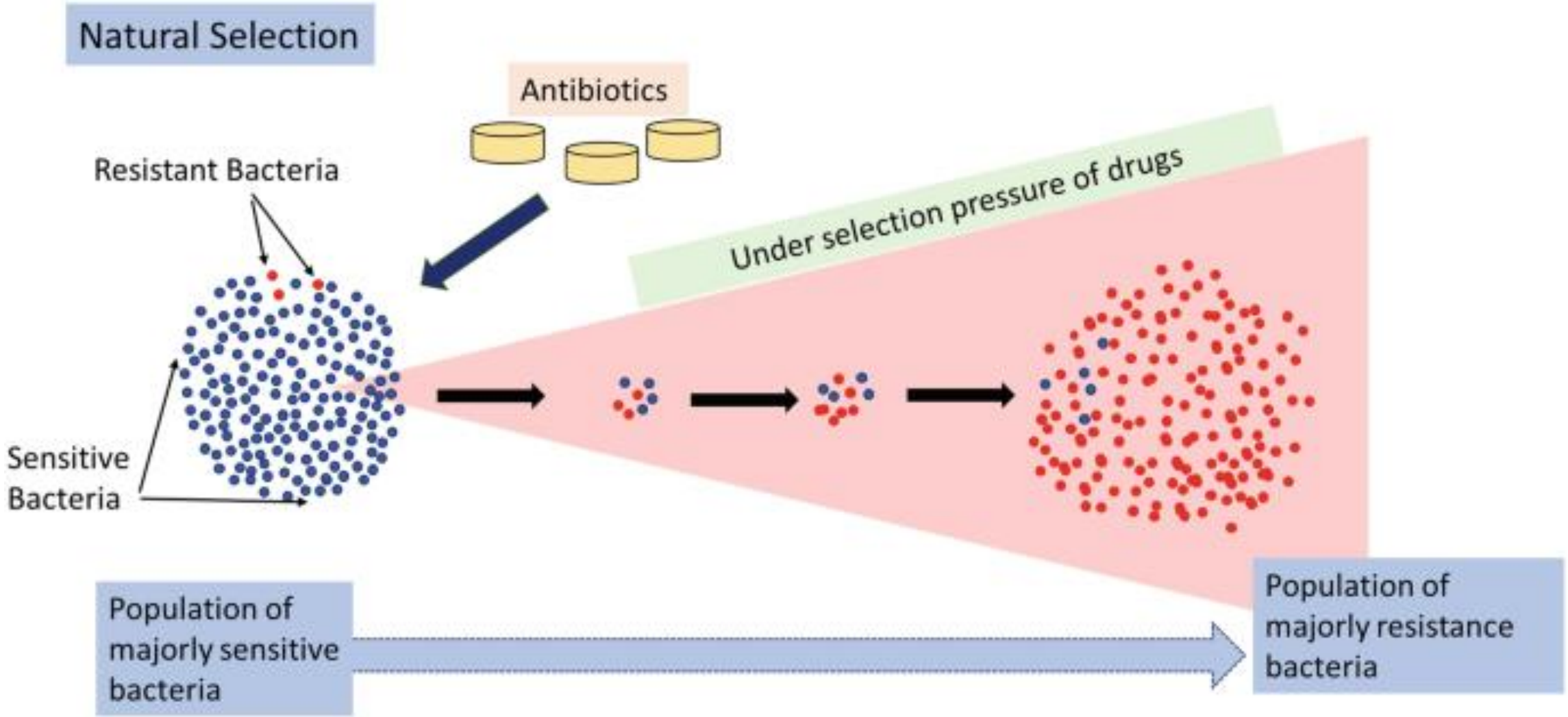
(H) 1: 10^6

resistent → 10^3 = 1000

<u>Conclusie:</u>

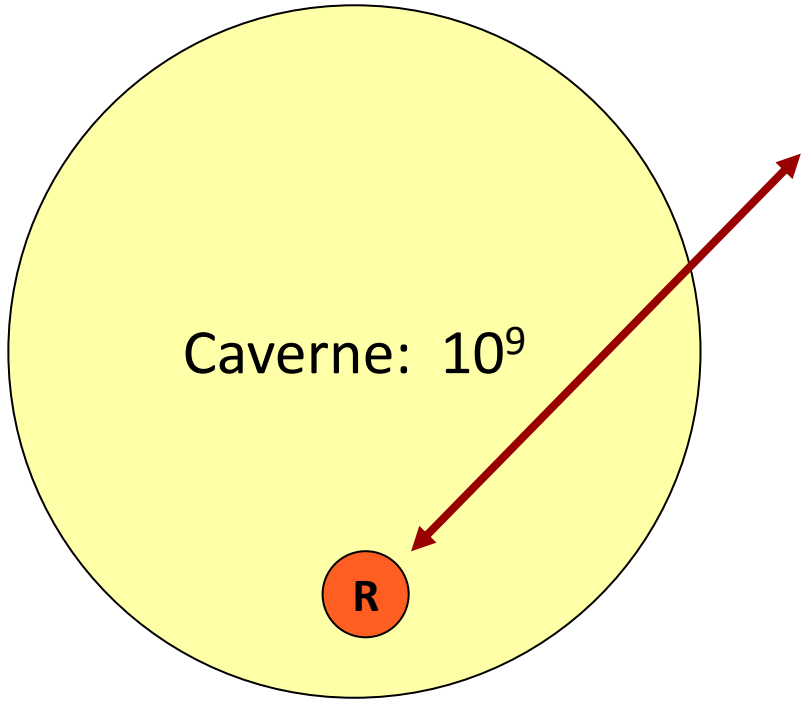
Bij monotherapie (H) selectie van 1000 resistente tbc bacteriën

Waarom je geen monotherapie moet geven



Natuurlijke resistentie

Aantal tbc bacteriën



INH (H) 1: 10^6

resistent $\rightarrow 10^3 = 1000$

Rifampicine (R) 1: 10^9

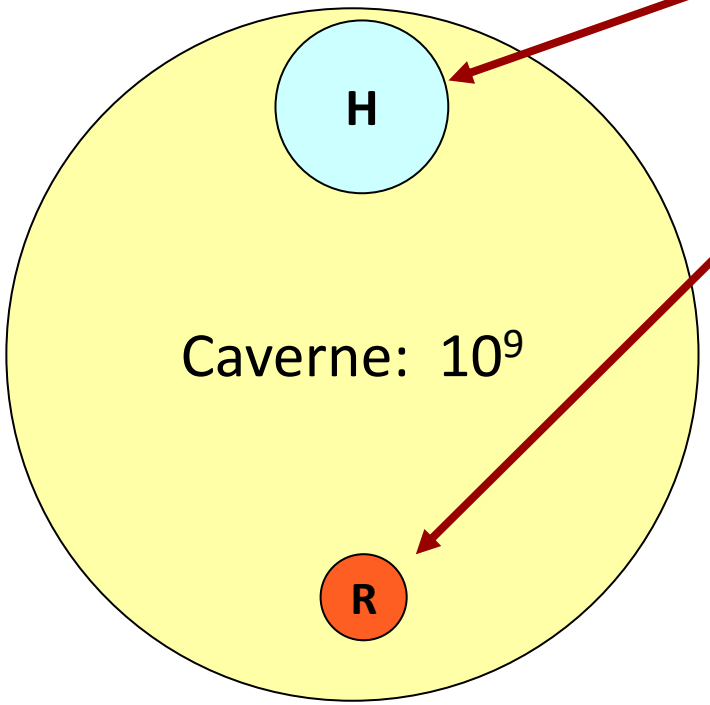
resistent $\rightarrow 10^0 = 1$

<u>Conclusie:</u>

Bij monotherapie (R) selectie van 1 resistente tbc bacterie

Natuurlijke resistentie

Aantal tbc bacteriën



INH (H) 1: 10^6

resistent → 10^3 = 1000

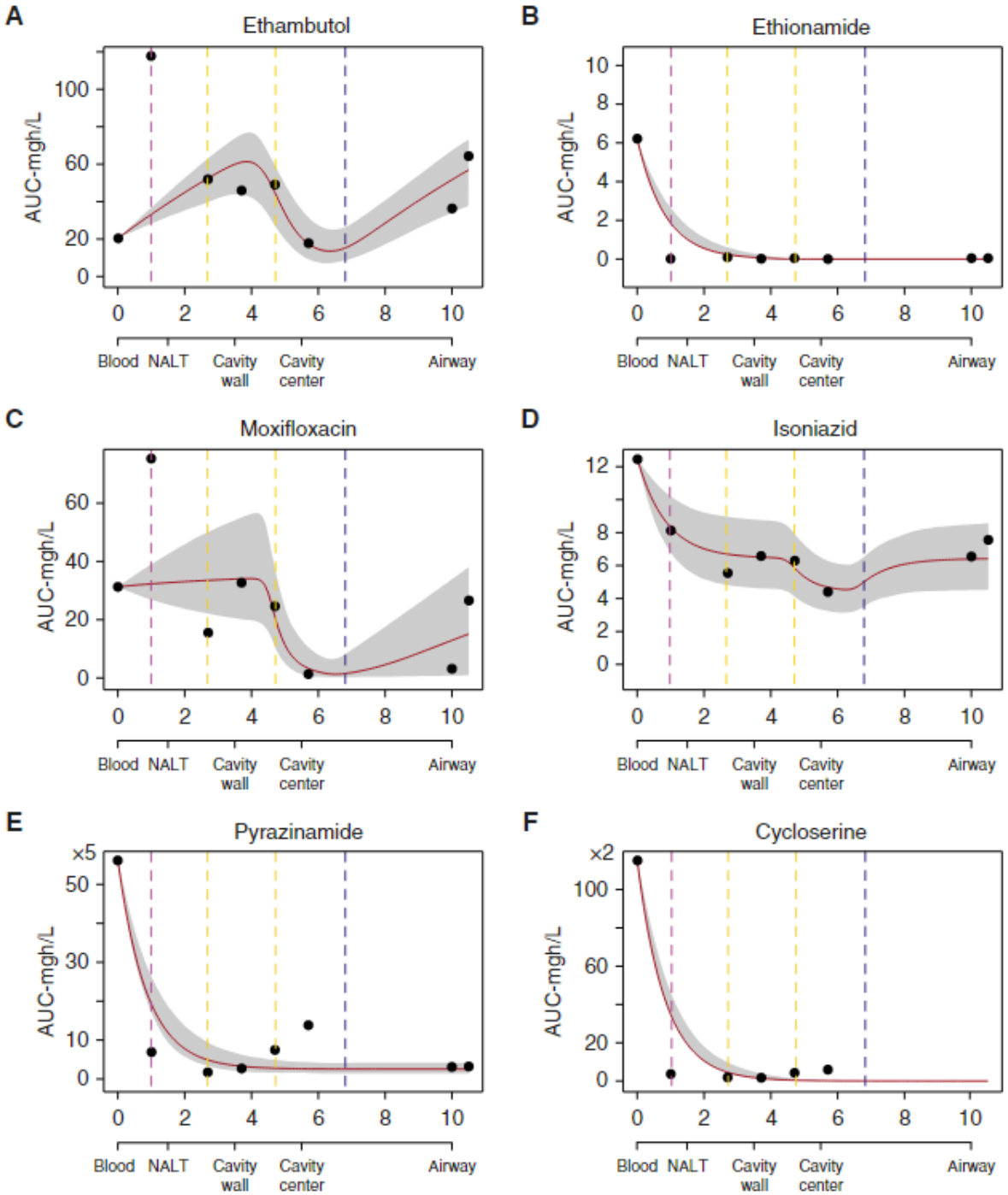
Rifampicine (R) 1: 10^9

resistent → 10^0 = 1

<u>Conclusie:</u> 2 anti-TBC middelen

H (1:10^6) + R (1:10^9) = 1:10^{15}

geeft geen resistentie



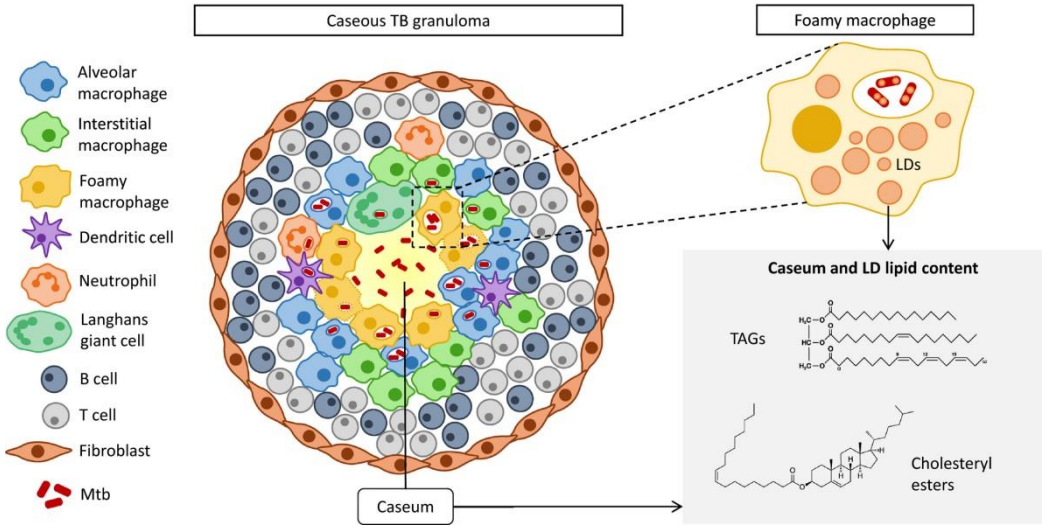
In voldoende hoge concentratie

Op de plaats van infectie

Dheda et al, American Journal of Respiratory and Critical Care Medicine,2018

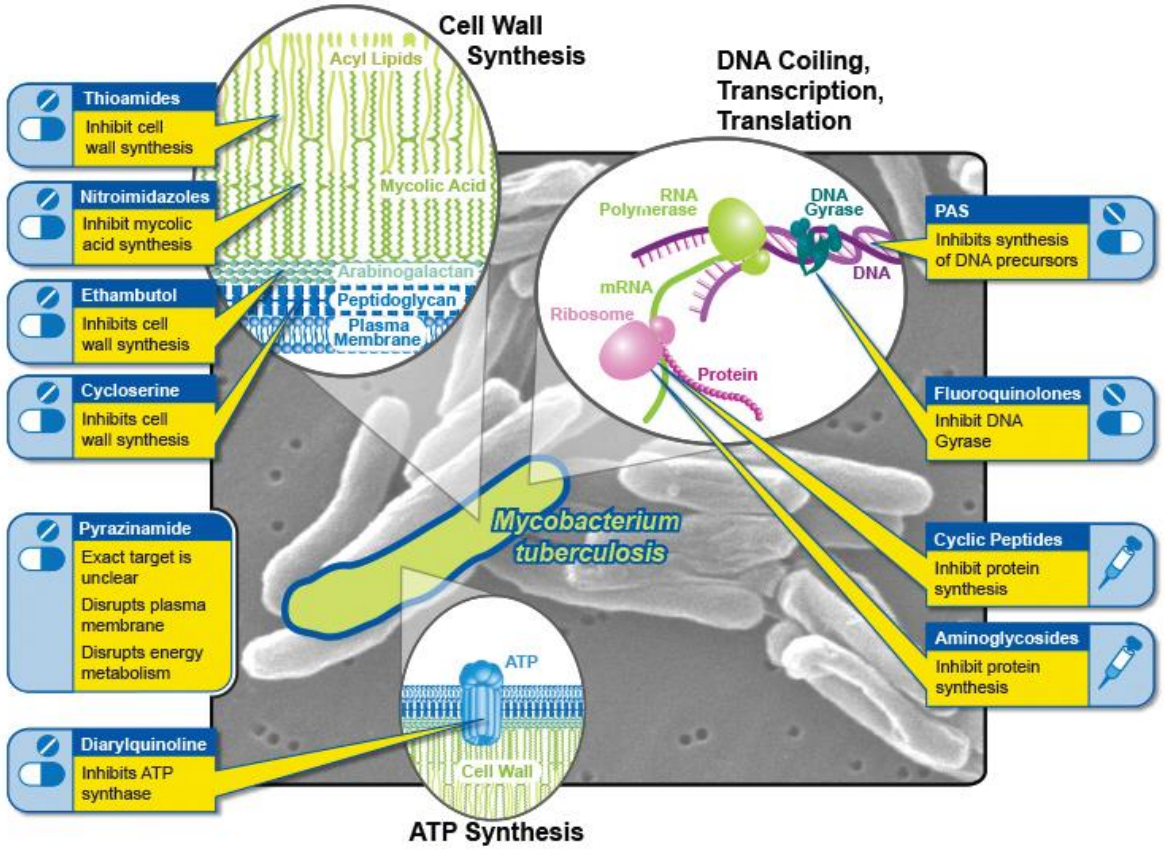
Three population model

- Populatie B
  - langzaam en intermitterend delende bacteriën in lokaal zuur milieu
    - in macrofagen en in necrotisch debris rondom cavernes; $<10^5$ bacilli
  - Indien nog aanwezig aan het einde van de intensieve fase kunnen ze weer actief worden.



Three population model

- Populatie C
  - bacteriën die sporadisch actief metabolisme hebben of repliceren.



Waarom je zo lang moet behandelen

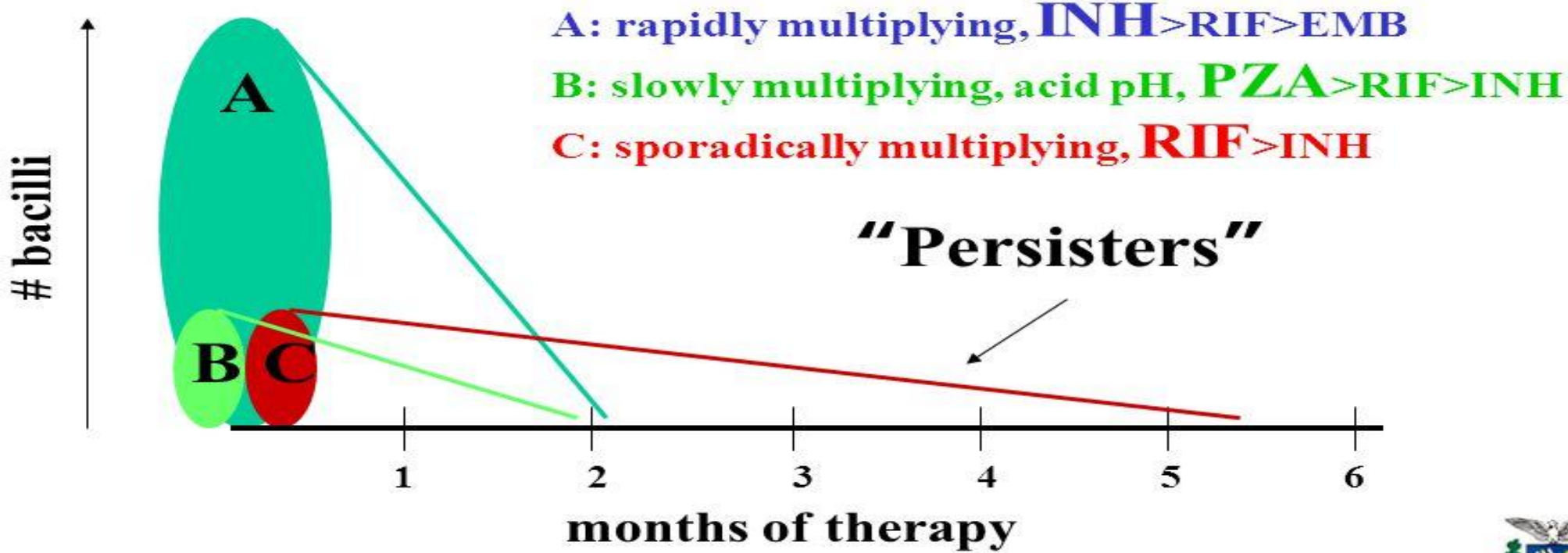
Behandeling verschillende populaties

- Populatie A
  - Tenminste 2 middelen met bactericide activiteit
    - snelheid waarmee sputum microscopie en kweken negatief worden
    - ‘early bactericidal activity’ = drug action in first 48 h
  - Middelen die resistentie moeten voorkomen door groot deel van populatie A te doden
- Populatie B en C
  - Vooral steriliserende middelen
    - Medicatie moet aanwezig zijn op de sporadische momenten dat deze bacteriën delen
    - Reden dat vaak langdurig behandeld moet worden

Hypothetical Model of TB Chemotherapy

M. Iseman, D. Mitchison

3 anatomic/metabolic populations of bacilli in cavitary TB



Box 12.2. Activity and toxicity of anti-tuberculosis drugs

Bactericidal activity	Sterilizing activity	Prevention of resistance	Toxicity
High	*High*	*High*	*Low*
Isoniazid	*Rifampicin*	*Rifampicin*	Ethambutol
Rifampicin	Pyrazinamide	Isoniazid	*Rifampicin*
Levofloxacin/ moxifloxacin	Levofloxacin/ moxifloxacin	Ethambutol	Isoniazide
		Linezolid	Levofloxacin/
		Bedaquiline	Moxifloxacin
		Delamanid	Bedaquiline
		Meropenem	Delamanid
			Meropenem
Moderate	*Moderate*	*Moderate*	*Moderate*
Injectables	Linezolid	Injectables	Pyrazinamide
Linezolid	Clofazimine	Levofloxacin/	Linezolid
Bedaquiline	Bedaquiline	Moxifloxacin	
Delamanid	Delamanid	Ethionamide	
Meropenem	Meropenem	Cicloserine	
		P-aminosalicylic acid	
		Clofazimine	
Low	*Low*	*Low*	*Low*
Ethionamide		Pyrazinamide	Rest
Clofazimine			
Pyrazinamide			

Behandelschema's

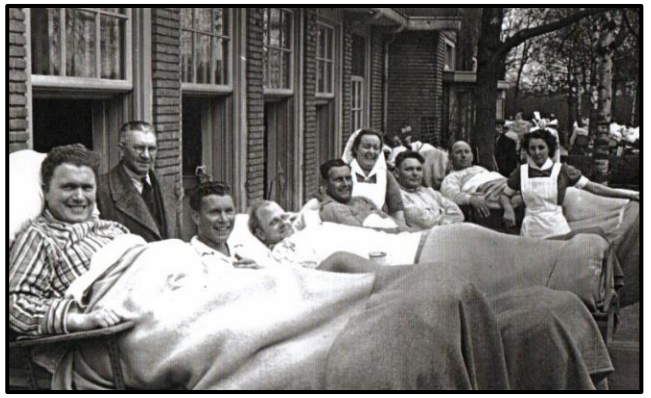
- Bij onbekende gevoeligheid
  - 2HRZE-4HRE
- Bij bewezen normale gevoeligheid
  - 2HRZ(E) – 4HR
- Indien geen pyrazinamide gegeven kan worden
  - 9HR(E)
- Indien geen isoniazide gegeven kan worden (en wel rifampicine gevoelig) = Hr-TB
  - 6 RZ(E) + Lfx
- Bij caverneuze afwijkingen en positieve kweken na 2 maanden
  - Continuatiefase met 3 maanden verlengen

Behandelschema’s

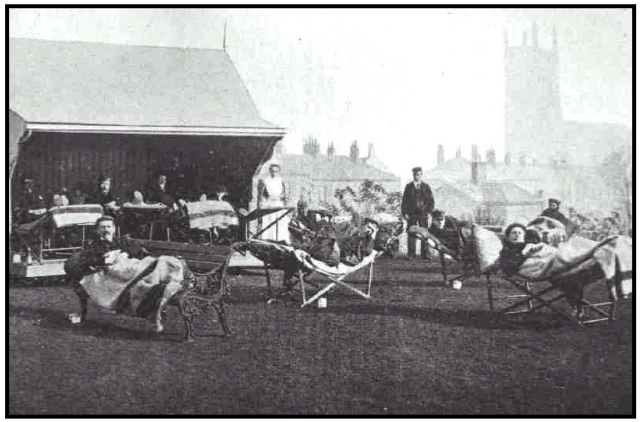
- Bij MDR-TBC (= H en R resistentie)
  - BPALM
- Bij Pre-XDR-TBC (MDR + fluoroquinolonen resistentie)
  - BPAL
- Bij XDR-TBC (Pre-XDR + linezolid of bedaquiline resistentie)
  - Opbouw behandelschema afhankelijk gevoeligheid en volgens schema WHO

Vroeger…

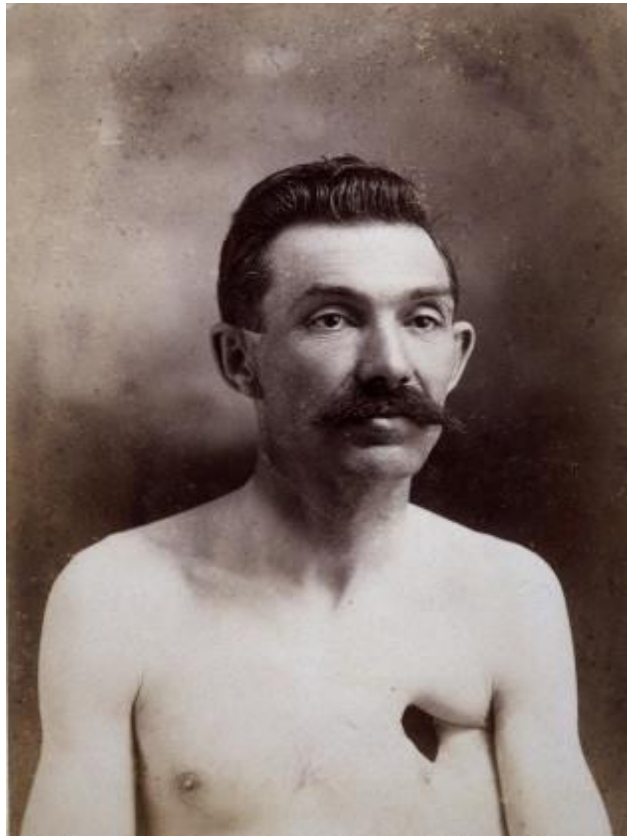
- 1857 eerste Sanatorium (Duitsland):
  - Bedrust
  - Goede voeding
  - Zonlicht en frisse lucht

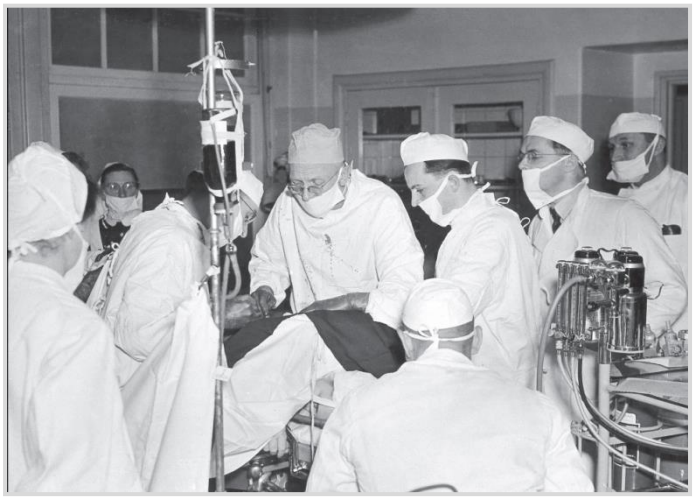


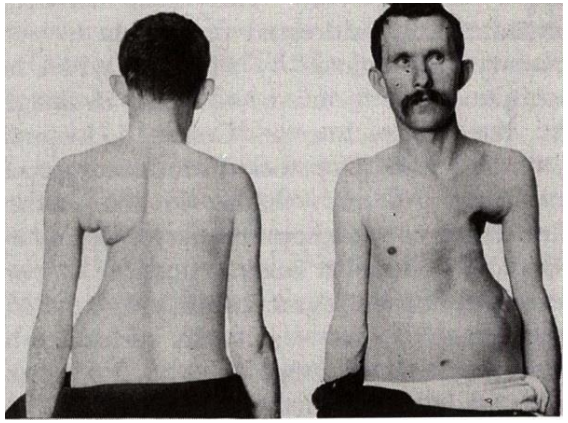
Portion from "Transfusion of a Goat's Blood" (1892) by Jules Adler, which details an attempt to treat tuberculosis with a transfusion of animal blood.

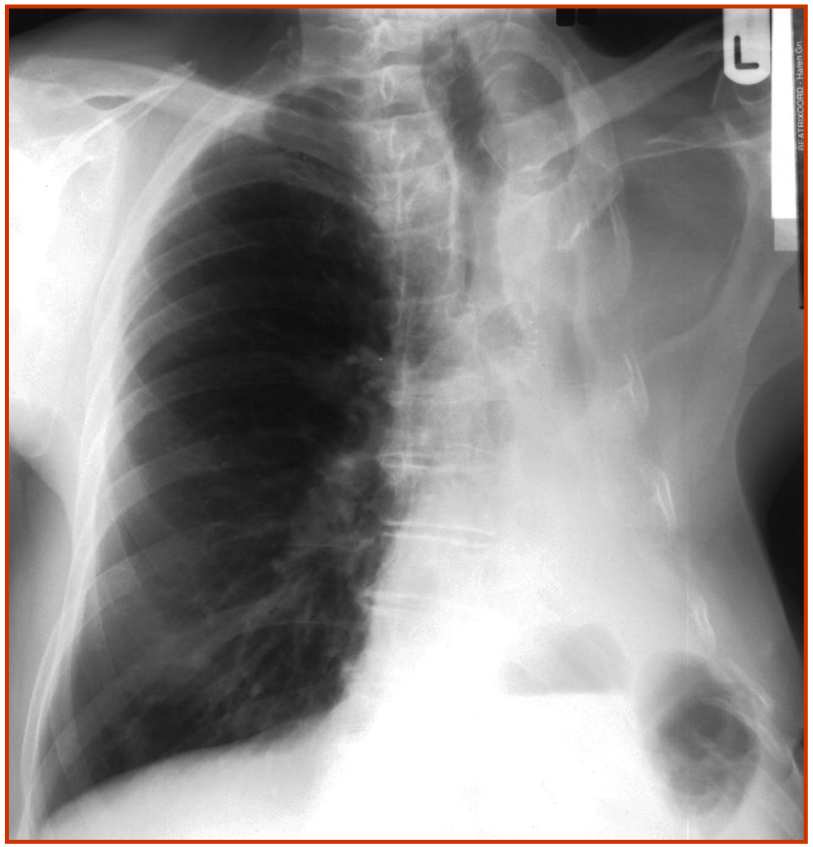


Vroeger…



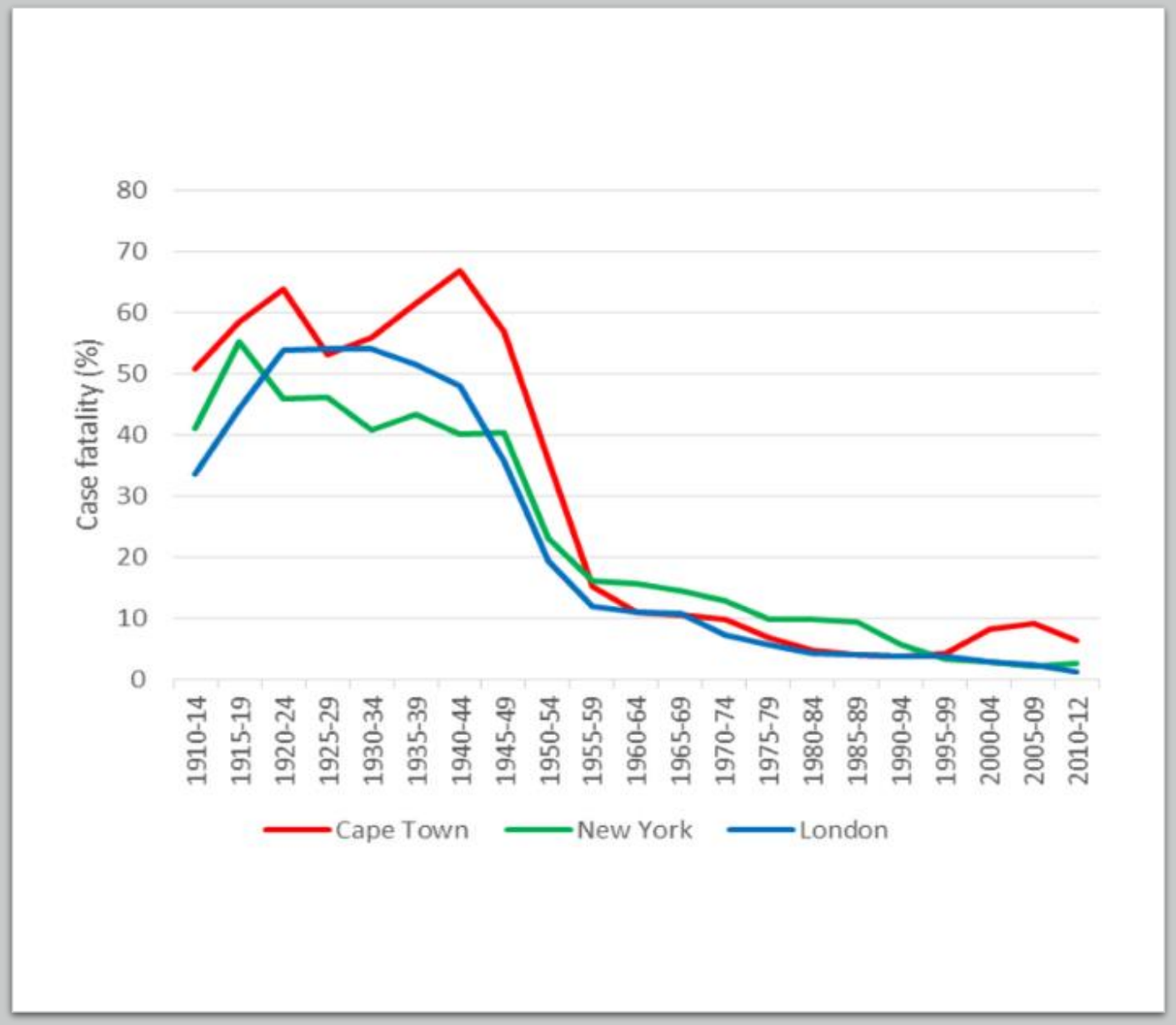




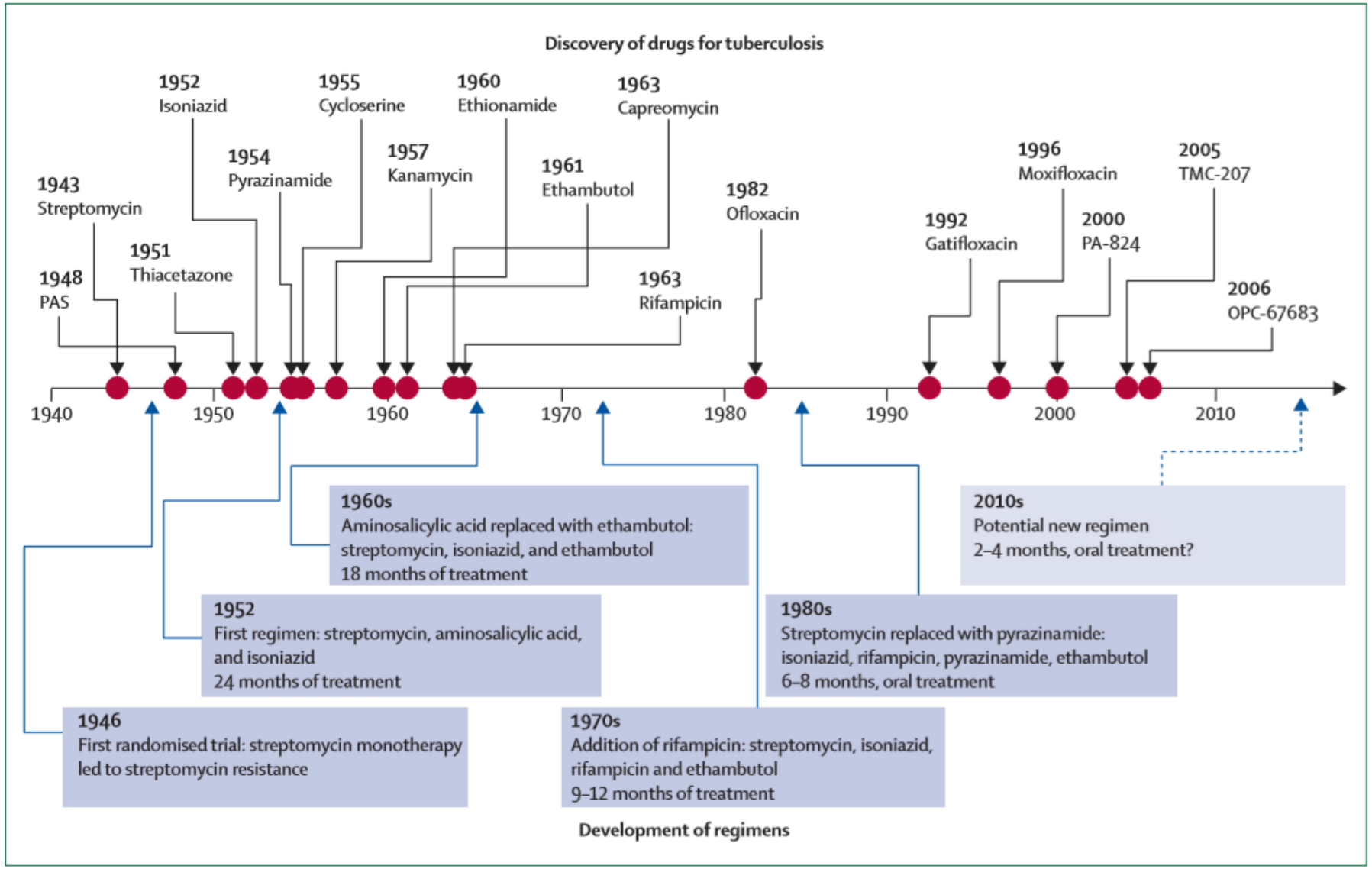


Tot 1945

- Geen medicamenteuze behandeling
  - Gevorderde pulmonale TBC: 50% kans op overlijden in 5 jaar
  - Miliaire, meningitis- en pericarditis tuberculose: overleden vaak binnen enkele weken



Tijdslijn van ontwikkeling anti-TB medicatie



Ma et al . Lancet 2010

Table 1.–Landmarks in tuberculosis (TB) therapy

Date	Landmark
1944	SM and PAS
1948	Randomised trial, SM *versus* PAS *versus* SM/PAS
1952	Triple therapy, isoniazid/SM/PAS, 24 months
1960s	EMB replaces PAS, 18 months
1970s	RIF added to INH/EMB/SM, 9 months
1980s	PZA added to INH/RIF, 6 months

SM: streptomycin; PAS: para-amino salt of salicylic acid; RIF: rifampicin; EMB: ethambutol; INH: isonicotinic acid hydrazide; PZA: pyrazinamide.

Ontwikkeling van de behandeling

1946: Trial met streptomycine in TB meningitis

Respons van 12% bij kinderen < 3 jaar en 36% bij oudere patienten

1947: Streptomycine versus bedrust

minder doden

vaker radiologische en bacteriologische verbetering

veel resistentie: 35 van 41 patienten

na 5 jaar follow-up: nog maar iets lagere mortaliteit

Ontwikkelingen van de behandeling

1948: trial met SM vs PAS vs SM + PAS

Meer kweekconversie en minder SM resistentie in de combinatiegroep

1952 - 1958: de ‘isoniazide studies’

Regimens met isoniazide erin effectiever dan met PAS

Langere behandeling gaf minder relapse

1955 - 1956: primaire drug resistentie

SM: 2.5%

PAS 2.6%

INH: 1.3%

Twee of 3 antibiotica: zelden

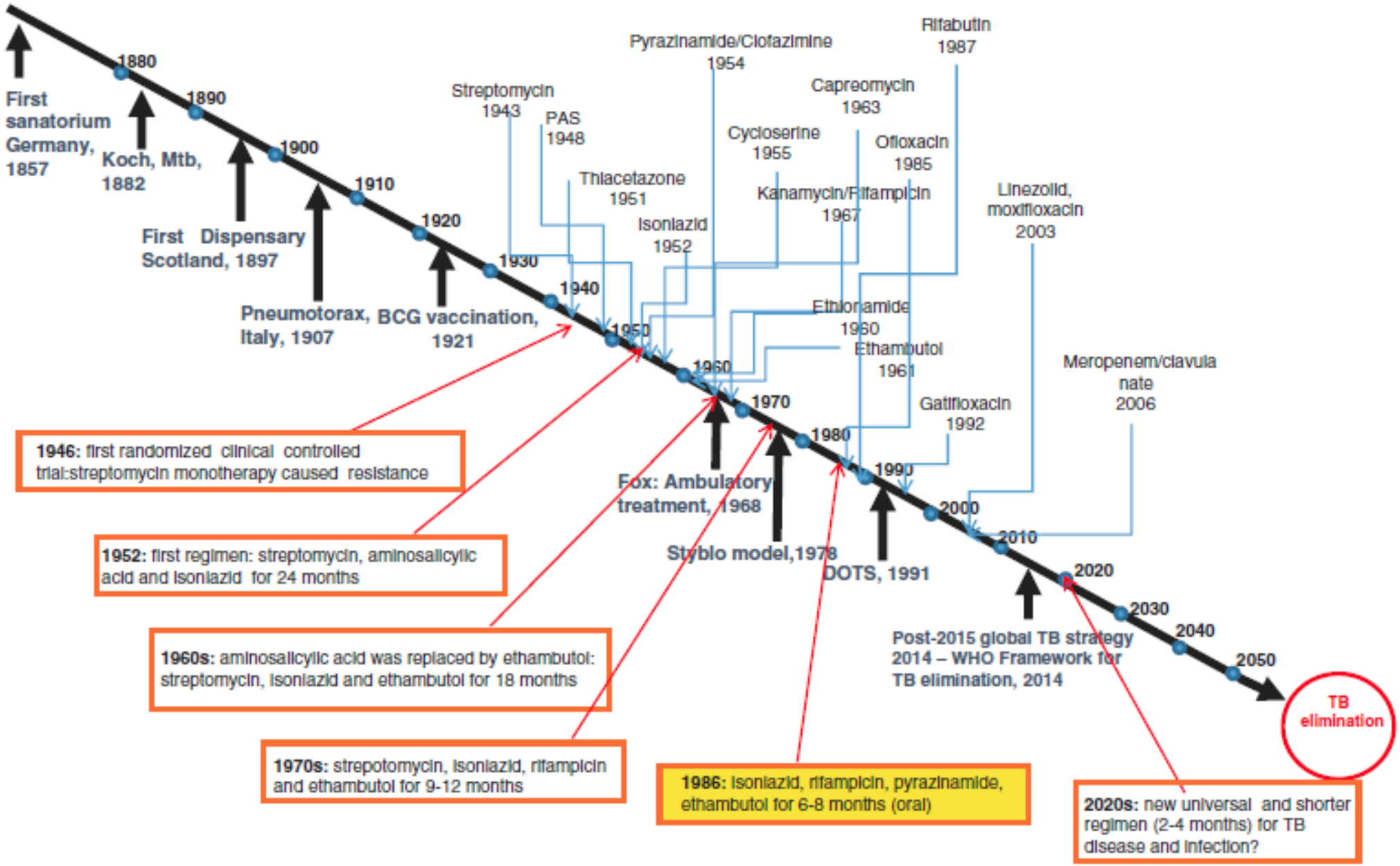
BMRC studies: Oost en Centraal Afrika

Regimen	Duration (Months)	Relapse rate 2 years (percentage)
SH	6	29
SHT	6	22
SHZ	6	8
SHR	6	3
2STH/16TH	18	3

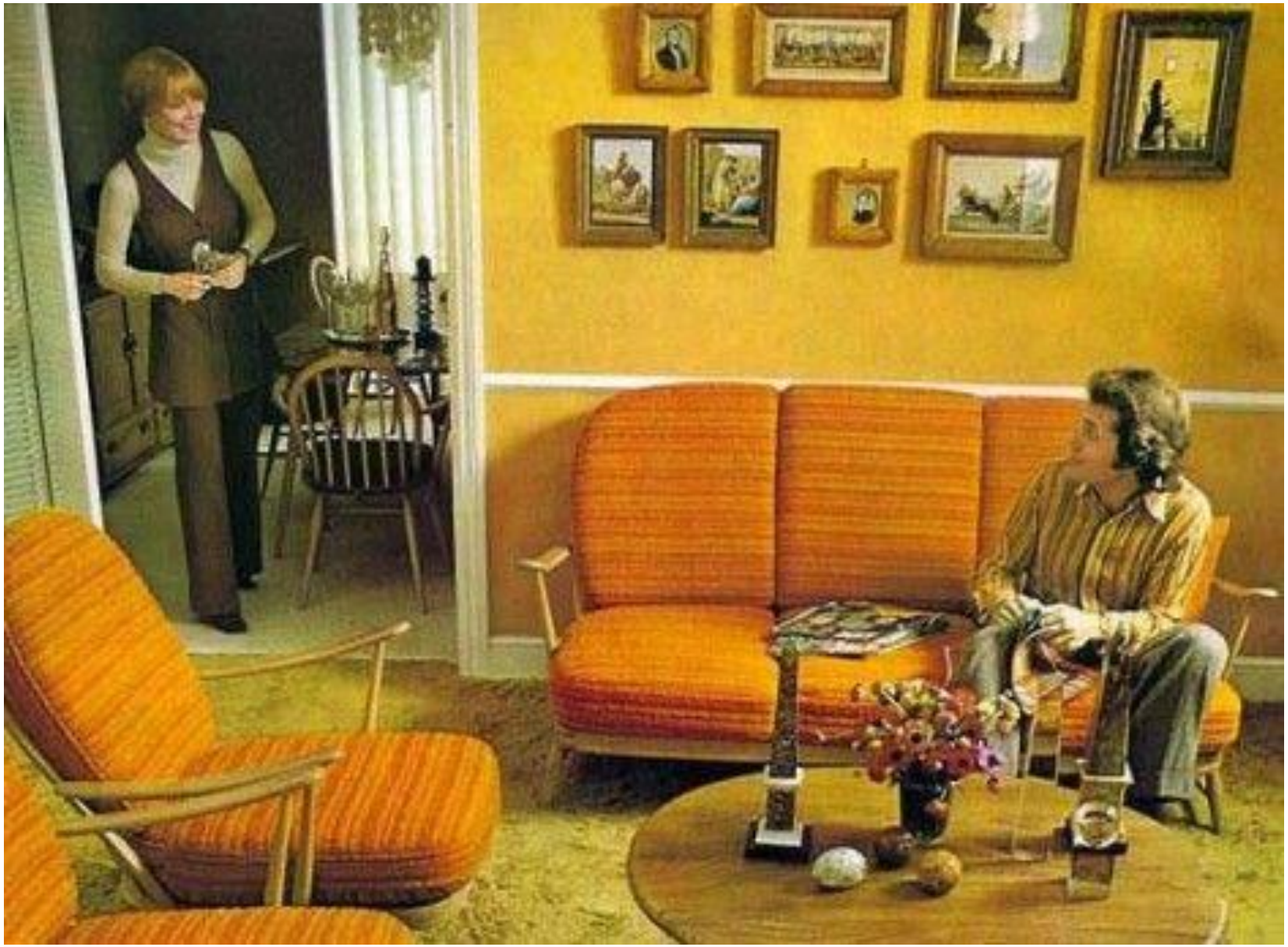
BMRC studies: Zuid-Oost Azië en Hong Kong

Study	Regimen	Duration (Months)	Relapse rate 2 vs 5 years (percentage)
Singapore (1973)	2SHRZ/2SHR	4	8 - 14
Singapore (1973)	2SHRZ/4SHR	6	2 - 3
Hong Kong (1977)	S3H3R3Z3	6 (Z only 2)	3
Hong Kong (1977)	S3H3R3Z3	6 (Z only 4)	5
Hong Kong (1977)	S3H3R3Z3	6 (Z also 6)	3

→ We behandelen de meerderheid te lang om bij een kleine groep relapse te voorkomen



Essential Tuberculosis



Maar er gebeurt van alles!

- 3 nieuwe middelen
  - Bedaquiline, delamanid, pretomanid
- Veelbelovende fase 3 studies t.a.v verkorten behandelduur voor zowel DS-TB als DR-TB
- Dosis optimalisatie studies
- Repurposed drugs
- Host directed therapies
- Individualized treatment

Doseringen rifampicine

- Standaard: 600 mg
  - Farmacokinetiek
  - Toxiciteit
  - Kosten

- Optimale dosis zou bepaald moeten worden o.b.v relatie tussen dosering, exposure, gewenste en ongewenste effecten

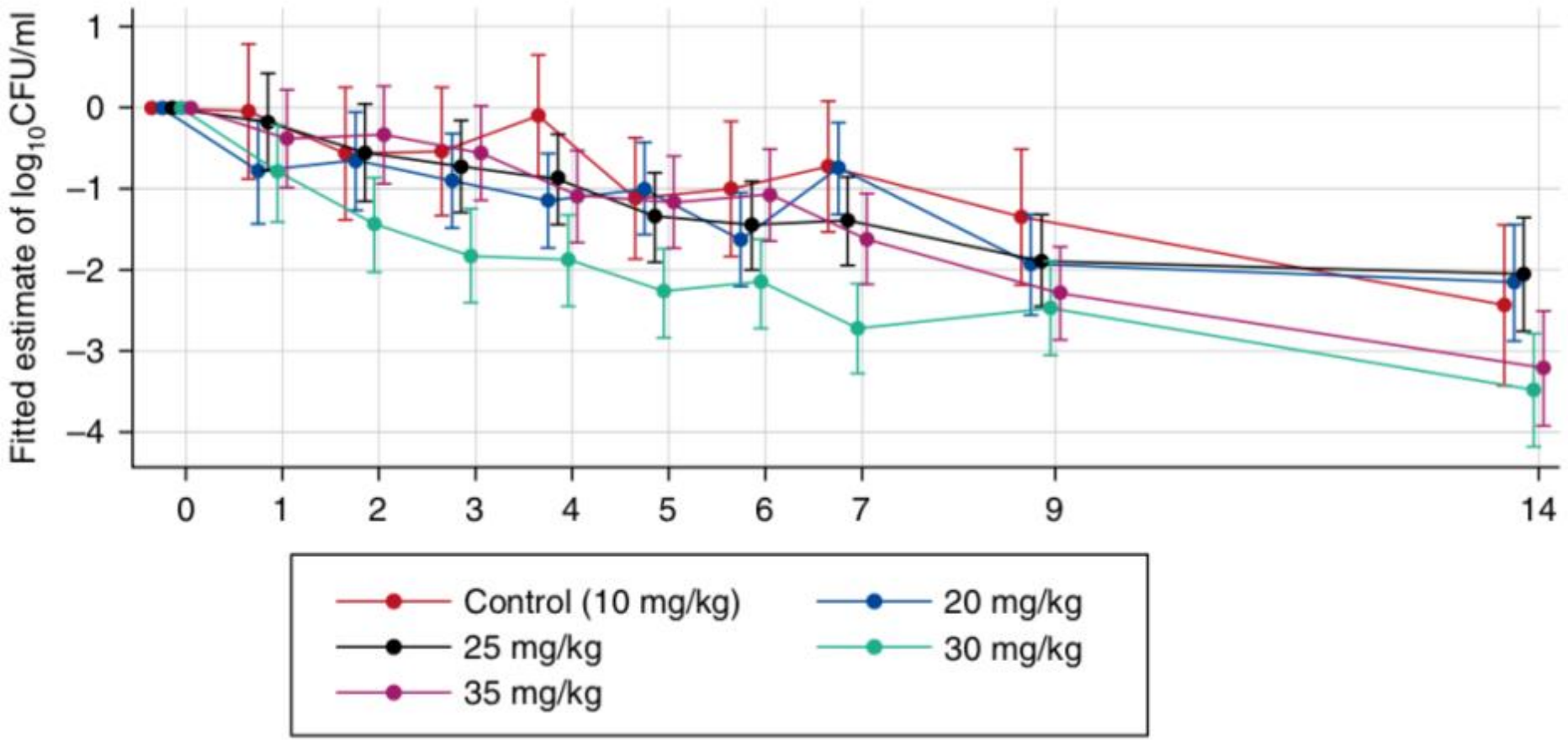
- **Hogere dosis = optimalisatie effectiviteit en verkorten behandelduur?**

Optimized dose rifampicine

Group	AUC_{0-24h} (h · mg/L)	C_{max} (mg/L)*
10 mg/kg (control)	26.3 (21.3–40.9)	7.4 (6.1–9.9)
20 mg/kg	113 (77.5–162)	21.6 (16.0–31.9)
25 mg/kg	135 (91.5–228)	25.1 (16.3–34.6)
30 mg/kg	190 (84.7–436)	33.1 (17.6–55.8)
35 mg/kg	235 (166–321)	35.2 (28.6 –44.2)

Boeree ARJCCM 2015

Optimized dose rifampicine



Hogere doseringen geven betere bacteriële load reductie

Boeree ARJCCM 2015

Optimized dose rifampicine

Group	Total	Grade 1		Grade 2		Grade 3*	
		Possibly Related	Related	Possibly Related	Related	Possibly Related	Related
10 mg/kg RIF (control)	7	0	0	0	0	0	0
20 mg/kg RIF	39	21	1	4	0	2	0
25 mg/kg RIF	24	11	2	2	0	0	0
30 mg/kg RIF	39	21	3	4	0	1	0
35 mg/kg RIF	54	27	2	9	0	0	0
Total	163	80	8	19	0	3	0

Tot 40 mg/kg wordt goed verdragen

Boeree ARJCCM 2015

RIFATOX trial

Table 4 RIFATOX Trial: number of adverse events, other than hepatic, occurring throughout the trial

Toxicity	R10 ($n = 100$)	R15 ($n = 100$)	R20 ($n = 100$)
Haematological	0	0	1
Gastrointestinal	6	3	2
Cutaneous	2	6	3
Arthralgia	8	5	4
Other	4	8	5
Total	20	22	13

Table 3 Grading of ALT values recorded at any time during the trial by study regimen

	ALT units			
Grade[†]	R10* ($n = 600$) *n* (%)	R15* ($n = 600$) *n* (%)	R20* ($n = 600$) *n* (%)	Total ($n = 1800$) *n* (%)
0	553 (92)	501 (84)	518 (86)	1572 (87)
1	29 (5)	51 (9)	42 (7)	122 (7)
2	2 (0.3)	8 (1.3)	8 (1.3)	18 (1)
3	1 (0)	2 (0.3)	4 (0.6)	7 (0.4)
4	0	0	0	0
Results not available	15 (2.5)	38 (6.3)	28 (5)	81 (5)

* R10 = 2EHRZ/4HR; R15 = $2EHR_{15}Z/2HR_{15}/2HR$; R20 = $2EHR_{20}Z/2HR_{20}/2HR$, where numbers before the letters indicate the duration in months of the phase of treatment; numbers in subscript indicate the study regimen.
[†] Based on DAIDS grading as follows:[1] grade 1 = laboratory range 1.25–3.0 × ULN; grade 2 = >3.0–5.0 × ULN; grade 3 = >5.0–10.0 × ULN; grade 4 = >10.0 × ULN.
ALT = alanine transferase; E = ethambutol; H = isoniazid; R = rifampicin; Z = pyrazinamide; DAIDS = Division of AIDS (National Institutes of Health, Bethesda, MD, USA); ULN = upper limit of normal.

Jindani et al, INT J TUBERC LUNG DIS 20(6):832–838, 2016

Optimized dose rifampicine

	Group 1	Group 2	
	(*n* = 26)	(*n* = 57)	
Initial dose and pharmacokinetic parameters		**Initial dose 450 mg**	**Initial dose 600 mg**
		n = 5	*n* = 52
Rifampicin dose (mg/kg)		11.4 (9.6–14.5)	17.7 (7.8–30.0)
C_{max}*		2.8 (0.2–6.6)[5]	5.3 (1.5–13.6)[43]
AUC_{0-24}*		26.5 (20.1–35.0)[2]	27.7 (8.8–65.7)[27]
Adjusted dose and pharmacokinetic parameters			
Rifampicin 900mg	*n* = 4	*n* = 3	*n* = 21
Rifampicin dose (mg/kg)	15.1 (13.1–17.3)	24.9 (21.4–29.0)	15.2 (7.8–20.9)
C_{max}*	18.6[1]	15.6 (12.9–18.7)[3]	11.6 (6.5–22.1)[13]
AUC_{0-24}*	105.0[1]	104.0[1]	58.4 (42.0–119.4)[8]
Rifampicin 1200mg	*n* = 18	*n* = 2	*n* = 28
Rifampicin dose (mg/kg)	18.0 (12.6–27.4)	22.9 (19.2–26.7)	18.6 (12.5–27.7)
C_{max}*	19.3 (13.0–37.3)[8]	19.1[1]	16.8 (8.7–29.7)[13]
AUC_{0-24}*	139.5 (103.0–250.0)[7]	79.0[1]	85.7 (47.0–150.0)[6]
Rifampicin 1500mg	*n* = 1		*n* = 1
Rifampicin dose (mg/kg)	29.4		30.0
Rifampicin 1800mg	*n* = 3		*n* = 1
Rifampicin dose (mg/kg)	30.2 (28.3–32.0)		28.6
C_{max}			17.5
AUC_{0-24}			117.0
Rifampicin 2400mg			*n* = 1
Rifampicin dose (mg/kg)			26.3
C_{max}			37.8
AUC_{0-24}			236

88 patienten

4 hepatoxiciteit (2 tgv INH) met succesvolle herintroductie RIF

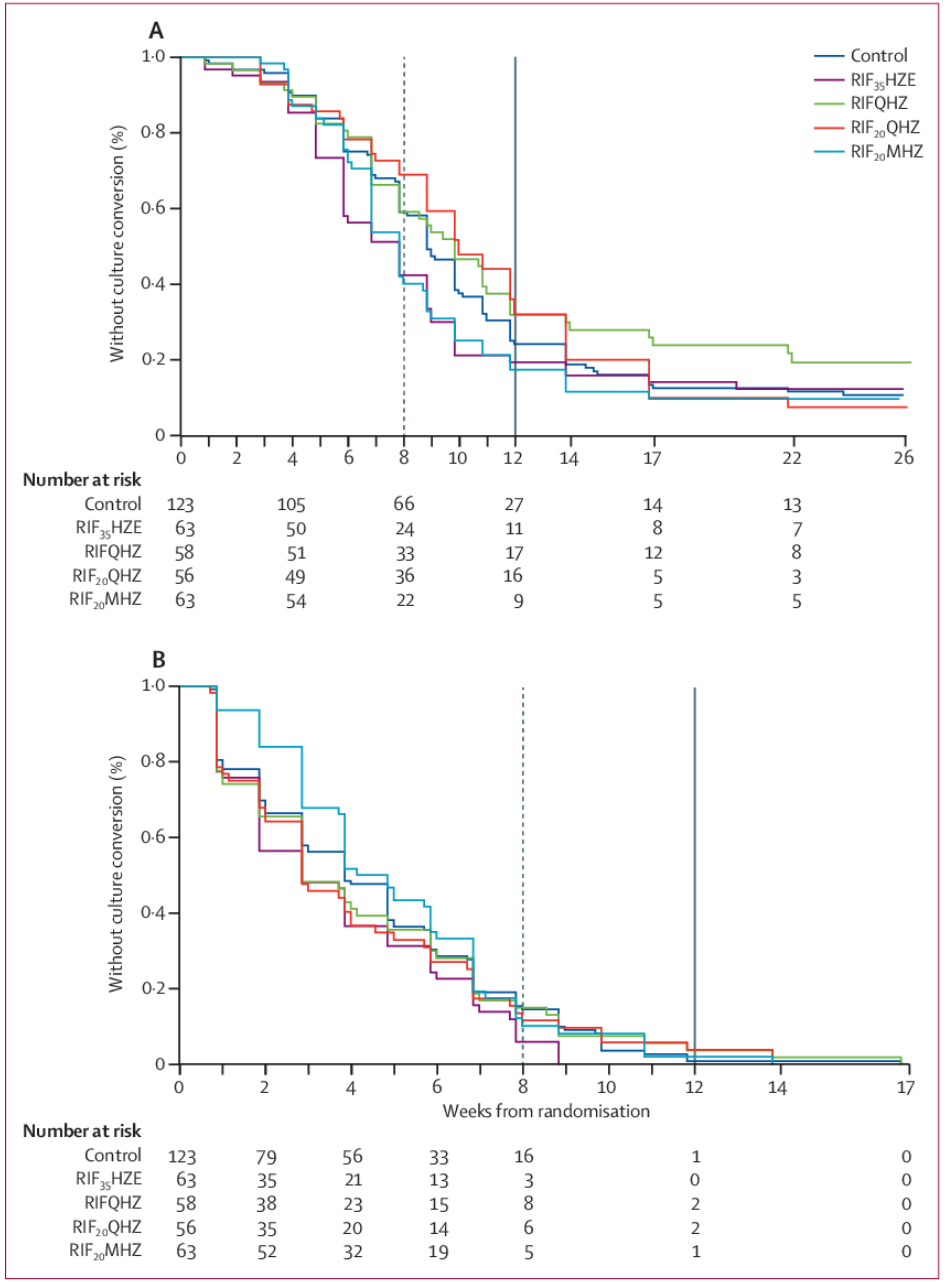
1 patient dosis reductie vanwege gastro-intestinale klachten

Magis PlosOne 2019

PANACEA MAMS trial

- This study showed that 35 mg/kg rifampicin given over 12 weeks was safe and shortened the time to stable culture conversion from 62 to 48 days, showing the potential for an enhanced regimen.

- The other experimental arms, including various combinations of 10 mg/kg or 20 mg/kg of rifampicin, moxifloxacin, and SQ109, did not achieve significant improvements over the control arm.

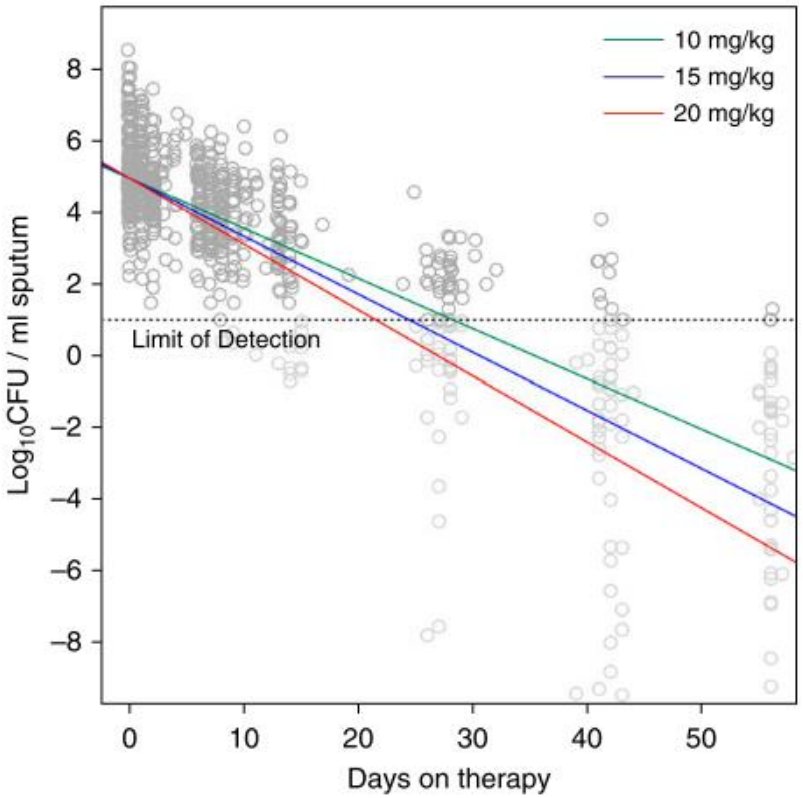


Boeree et al, Lancet infect disease, 2017

HIRIF trial

Table 3. Secondary Efficacy Outcomes*

Outcome	Rifampin Dose			
	10 mg/kg (*n* = 60)	15 mg/kg (*n* = 60)	20 mg/kg (*n* = 60)	Total (*N* = 180)
Culture conversion in Löwenstein-Jensen medium at 8 wk				
Converted	46 (76.7)	44 (73.3)	45 (75.0)	135 (75.0)
Did not convert	3 (5.0)	5 (8.3)	7 (11.7)	15 (8.3)
Contaminated Week 8 cultures	4 (6.7)	1 (1.7)	0 (0)	5 (2.8)
Week 8 cultures not available	7 (11.7)	10 (16.7)	8 (13.3)	25 (13.9)
Early discontinuation	6 (10.0)	9 (15.0)	8 (13.3)	23 (12.8)
Lost to follow-up	1 (1.7)	1 (1.7)	0 (0)	2 (1.1)
Treatment outcome at 12 mo				
Recurrence-free cure	44 (73.3)	46 (76.7)	46 (76.7)	136 (75.6)
Treatment failure	3 (5.0)	1 (1.7)	1 (1.7)	5 (2.8)
Recurrence after cure	3 (5.0)	1 (1.7)	2 (3.3)	6 (3.3)
Relapse†	2 (3.3)	0 (0)	0 (0)	2 (1.1)
Reinfection‡	0 (0)	1 (1.7)	0 (0)	1 (0.6)
Recurrence§	1 (1.7)	0 (0)	2 (3.3)	3 (1.7)
Death	0 (0)	0 (0)	0 (0)	0 (0)
Outcome not evaluable	10 (16.7)	12 (20.0)	11 (18.3)	33 (18.3)
Early discontinuation	8 (13.3)	11 (18.3)	10 (16.7)	29 (16.1)
Lost to follow-up	2 (3.3)	1 (1.7)	1 (1.7)	4 (2.2)



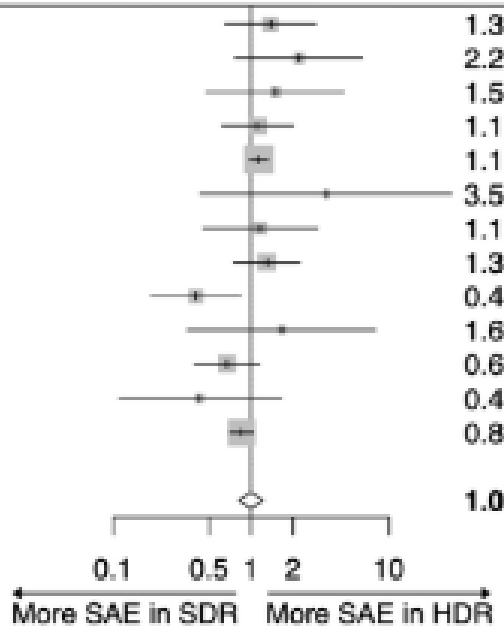
Original research

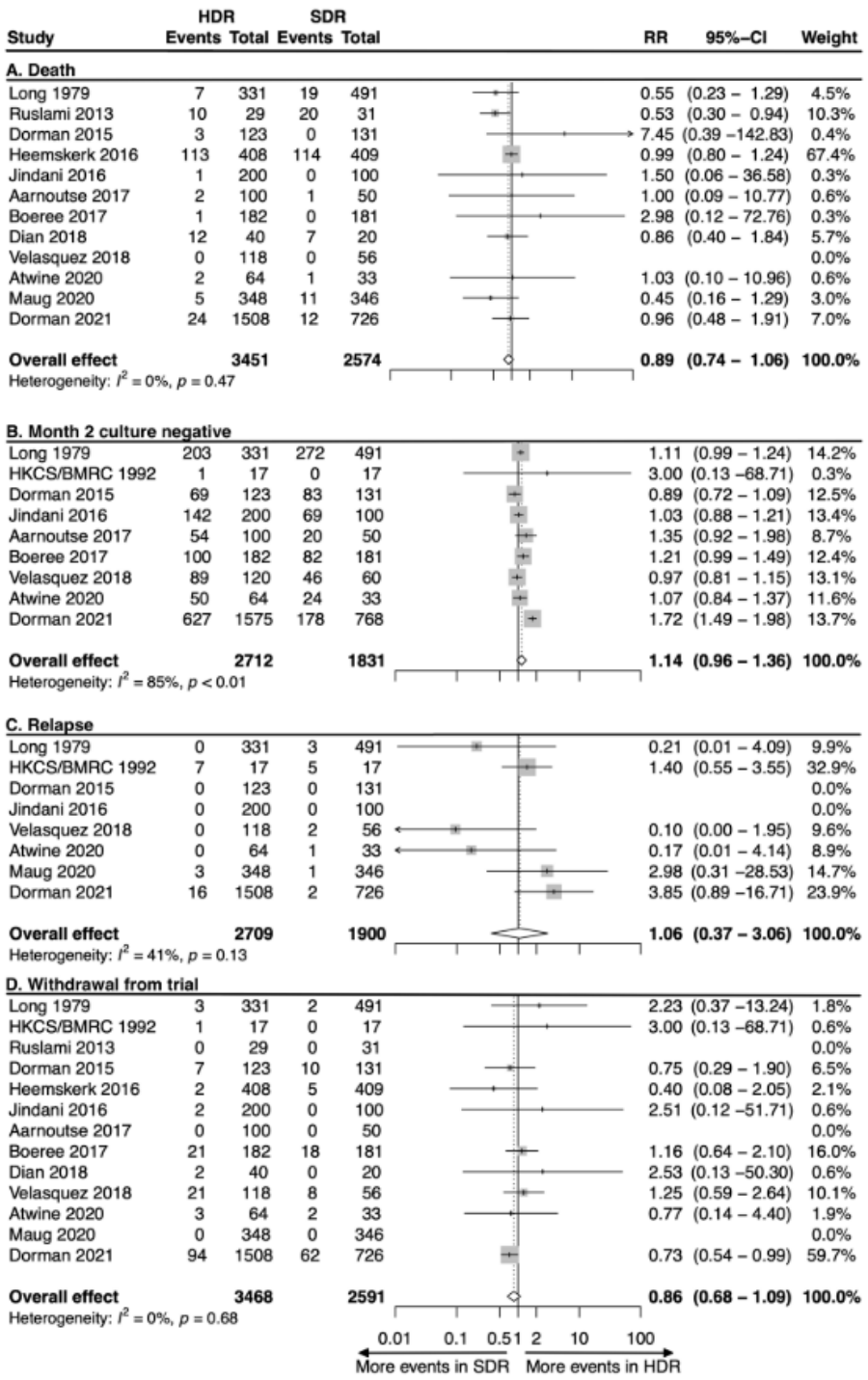
High-dose rifamycins in the treatment of TB: a systematic review and meta-analysis

Omri A Arbiv ,[1] JeongMin M Kim,[1] Marie Yan,[1] Kamila Romanowski,[1,2] Jonathon R Campbell,[3] Anete Trajman ,[3,4] Leyla Asadi,[5] Federica Fregonese,[3] Nicholas Winters,[6] Dick Menzies,[3,6,7] James C Johnston[1,2,3]

Author	HDR SAE	HDR Person–Years	SDR SAE	SDR Person–Years	IRR	95%–CI	Weight
Long 1979	13	993.00	14	1473.00	1.38	(0.65 – 2.93)	5.7%
HKCS/BMRC 1992	11	34.00	5	34.00	2.20	(0.76 – 6.33)	3.3%
Ruslami 2013	7	14.30	5	15.29	1.50	(0.47 – 4.72)	2.8%
Dorman 2015	23	18.87	22	20.10	1.11	(0.62 – 2.00)	8.4%
Heemskerk 2016	404	301.81	357	302.55	1.13	(0.98 – 1.31)	24.8%
Jindani 2016	7	61.37	1	30.68	3.50	(0.43 –28.45)	0.9%
Aarnoutse 2017	14	23.01	6	11.51	1.17	(0.45 – 3.04)	3.9%
Boeree 2017	30	90.75	23	90.25	1.30	(0.75 – 2.23)	9.3%
Dian 2018	12	19.73	15	9.86	0.40	(0.19 – 0.85)	5.7%
Velasquez 2018	7	118.00	2	56.00	1.66	(0.35 – 8.00)	1.6%
Atwine 2020	30	34.37	23	17.72	0.67	(0.39 – 1.16)	9.3%
Maug 2020	3	514.85	7	511.89	0.43	(0.11 – 1.65)	2.1%
Dorman 2021	271	2231.01	152	1074.08	0.86	(0.70 – 1.05)	22.2%
Overall effect					**1.00**	**(0.82 – 1.23)**	**100.0%**

Heterogeneity: $I^2 = 41\%$, $p = 0.06$





- HDRs were not associated with a significant difference in
  - SAEs
  - 2-month culture conversion
  - Death

- Further studies are required to identify specific groups who may benefit from HDR

Lopende trials – optimized dose rifampicine

Table 1
Registered, unpublished clinical trials for the treatment of drug-susceptible tuberculosis (as of 6 July 2023)

Therapeutic approach	Trial (adult patients with TB)	Experimental regimen(s)	Clinical trials registration	Phase	Status
Optimizing rifampicin	IMAGINE-TBM	High-dose R and H for TB meningitis	NCT05382742	II	In preparation
	INTENSE-TBM	High-dose R and high-dose Lzd for TB meningitis	NCT04145258	III	In preparation
	ReDEFINe	High-dose R for TB meningitis	NCT02169882	II	Enrolling
	STEP2C	High-dose R and Mfx for 3 or 4 mo	NCT05807399	IIC	Enrolling
	HARVEST	High-dose R for TB meningitis	ISRCTN15668391	III	Enrolling
	SURE	High-dose R, H, Z + Lfx (± aspirin) for children with TB meningitis	ISRCTN40829906	III	Enrolling
	RIFASHORT	Higher dose R (to 1800 mg/d)—4 mo	NCT0258152	III	Completed
Regimens including new drugs	CRUSH-TB	Bdq + Mfx + Z + Rbt or Dlm—4 mo	NCT05766267	IIC	Final preparation
	DECODE	16 wk of experimental of Delpazolid at different doses associated with Bdq + Dlm + Mfx	NCT04550832	II	Enrolling
	Safety and efficacy of 4-mo regimen of OPC-167832 + Dlm + Bdq		NCT05221502	II	Enrolling
	CLO-FAST (ACTG A5362)	Cfz + Rpt + HZE—13–17 wk	NCT04311502	IIC	Enrolling
	SUDOCU	Bdq + Dlm + Mfx vs. Bdq + Dlm + Mfx + Sutezolid (3 dosages)	NCT03959566	II	Completed
	SimpliciTB	Bdq + Pa + Mfx + Z—4 mo	NCT03338621	III	Completed

Bdq, bedaquiline; Cfz, clofazimine; Dlm, delamanid; H, isoniazid; Lfx, levofloxacin; Lzd, linezolid; Mfx, moxifloxacin; Pa, pretomanid; R, rifampicin; Rbt, rifabutin; TB, tuberculosis; Z, pyrazinamide.

Huidige behandellandschap

DS-TB (85%)	RR/MDR/XDR	TBI
2 HRZE – 4 HR 2 HRZE – 2 HR 2HPZMfx – 2PMfx Hr-TB (10%) 6 RFqZE	4-6 BFqCfzZEHhEto/5FqCfzZE (shorter) 18 BLfqCfz (longer) 6-9 Bpal / Bpalm	3HR 4R 6-9 H 3HP (ATS) FQ(E) voor DR-TBI

4 maanden quinolone bevattende regimes

- NIRT
- OFLOTUB
- REMoxTB
- RIFAQUIN

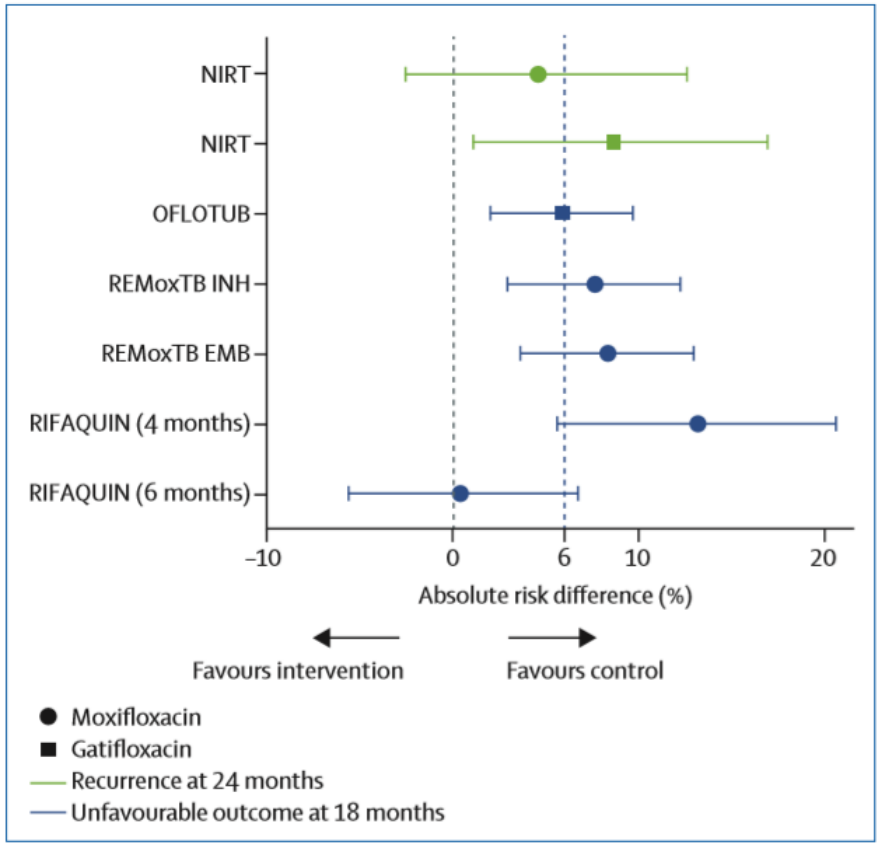


Figure: **Quinolone-containing regimens compared with standard treatment for tuberculosis**

Nimmo et al, the Lancet, 2015

Summary of findings for the main comparison. Moxifloxacin-containing 4-month ATT regimens versus standard 6-month ATT regimen for drug-sensitive pulmonary tuberculosis

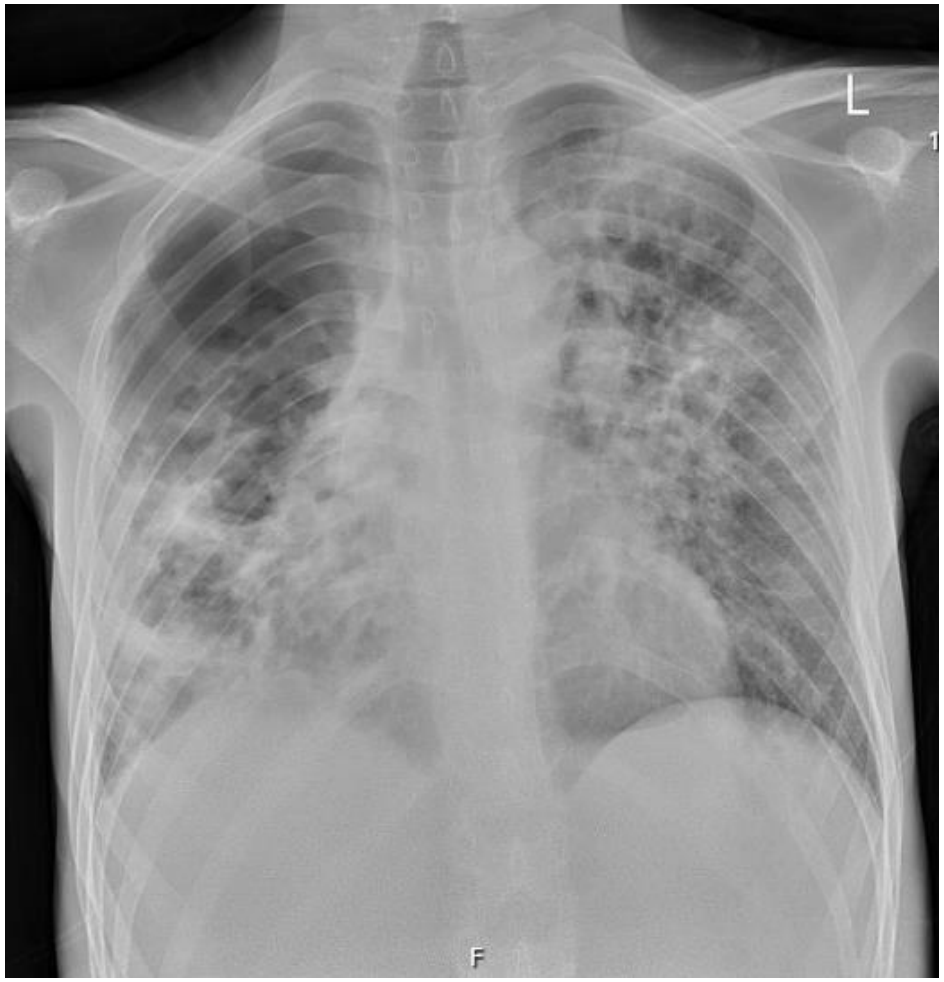
Moxifloxacin-containing 4-month ATT versus standard 6-month ATT regimen for drug-sensitive pulmonary tuberculosis

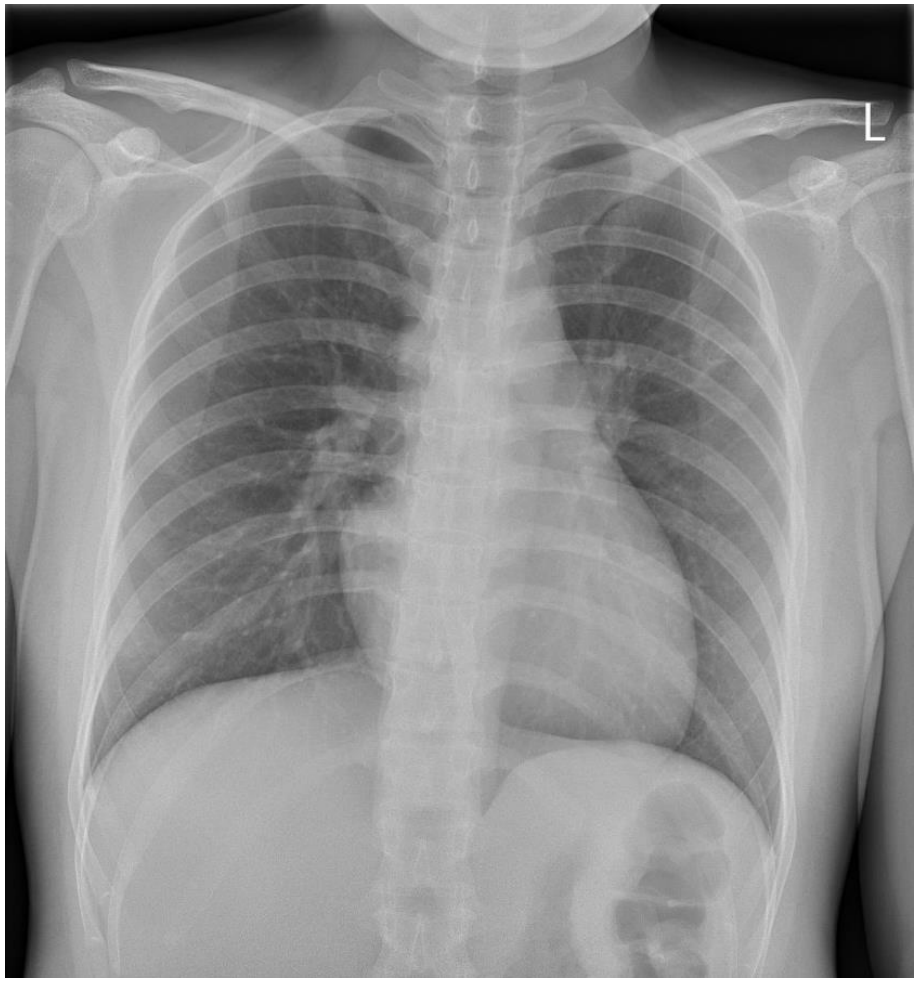
Patient or population: adults with drug-sensitive pulmonary tuberculosis
Setting: low- and middle-income countries in Africa, Asia, and Latin America
Intervention: moxifloxacin-containing 4-month ATT
Comparison: standard 6-month ATT

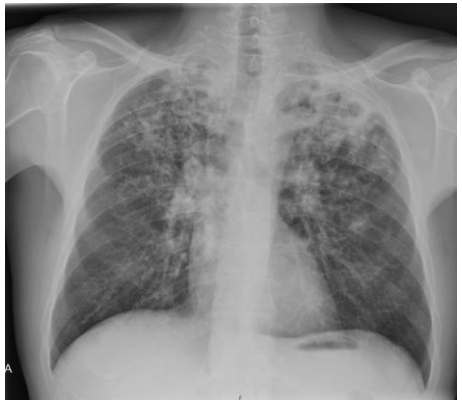
Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with 6-month standard ATT	Risk with 4-month moxifloxacin-containing ATT				
Relapse Follow-up: range 12 to 24 months	32 per 1000	82 more relapses per 1000 (44 more to 140 more)	RR 3.56 (2.37 to 5.37)	2265 (3 RCTs)	⊖⊖⊖⊙ MODERATE[a,b,c] *Due to indirectness*	The 4-month regimen probably increases relapse compared to the 6-month regimen
Death from any cause Follow-up: range 18 to 24 months	21 per 1000	2 more deaths per 1000 (7 fewer to 16 more)	RR 1.06 (0.65 to 1.75)	2760 (3 RCTs)	⊖⊖⊖⊙ MODERATE[a,c,d] *Due to indirectness*	The 4-month regimen probably makes little or no difference in death from any cause compared to the 6-month regimen
Treatment failure	16 per 1000	5 fewer treatment failures per 1000 (11 fewer to 8 more)	RR 0.71 (0.33 to 1.52)	2282 (3 RCTs)	⊖⊖⊖⊙ MODERATE[a,c,d] *Due to indirectness*	The 4-month regimen probably results in little or no difference in treatment failure compared to the 6-month regimen
Acquired drug resistance	7 per 1000	5 fewer with acquired drug resistance per 1000 (6 fewer to 2 more)	RR 0.33 (0.08 to 1.31)	2282 (3 RCTs)[e]	⊖⊖⊙⊙ LOW[c,f,g] *Due to indirectness and imprecision*	The 4-month regimen may be little or no different than the 6-month regimen in the incidence of acquired drug resistance
Serious adverse events Follow-up: range 18 to 24 months	62 per 1000	2 fewer with serious adverse events per 1000 (16 fewer to 16 more)	RR 0.97 (0.74 to 1.27)	3548 (4 RCTs)[g]	⊖⊖⊖⊙ MODERATE[a,c,d,h] *Due to indirectness*	The 4-month regimen probably results in little or no difference in serious adverse events compared to the 6-month regimen

Grace et al, Cochrane review 2019

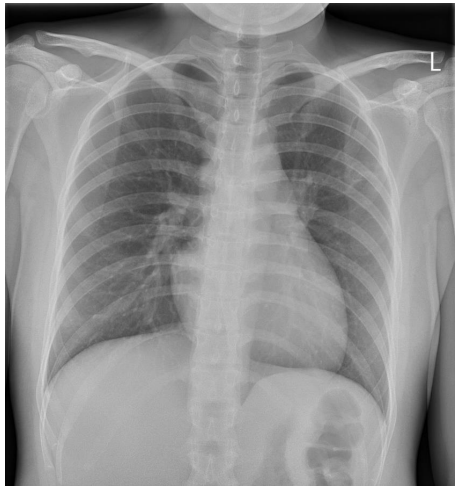
4 maanden behandeling?



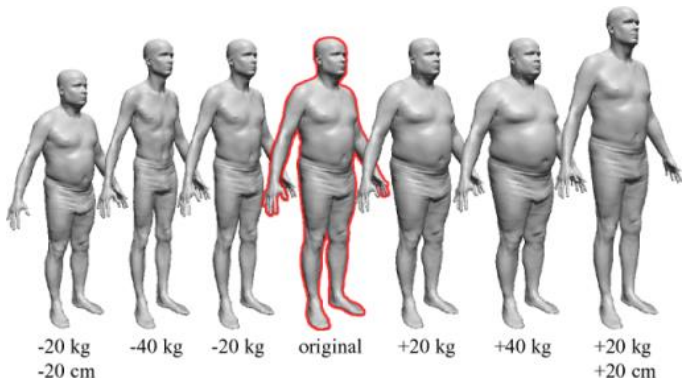




Iedereen even lang?



Iedereen dezelfde dosering?



ARTICLES
https://doi.org/10.1038/s41591-018-0224-2
nature medicine
OPEN
Corrected: Publisher Correction

A patient-level pooled analysis of treatment-shortening regimens for drug-susceptible pulmonary tuberculosis

Marjorie Z. Imperial[1,11], Payam Nahid[1,11], Patrick P. J. Phillips[1], Geraint R. Davies[2], Katherine Fielding[3], Debra Hanna[4,5], David Hermann[5], Robert S. Wallis[6], John L. Johnson[7,8], Christian Lienhardt[9,10] and Rada M. Savic[1*]

- 3411 patiënten uit de modified intention to treat analyse van de OFLOTUB, RIFAQUIN en REMoxTB trial
- Multivariate cox analyse van baseline en on-treatment risicofactoren voor unfavorable outcomes
- Non-inferiority testing o.b.v deze geselecteerde risicogroepen

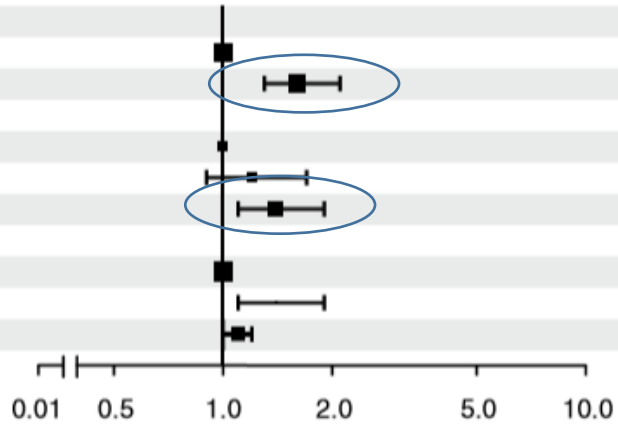
Imperial et al, Nature medicine 2018

4 maanden regimes

Experimental group participants

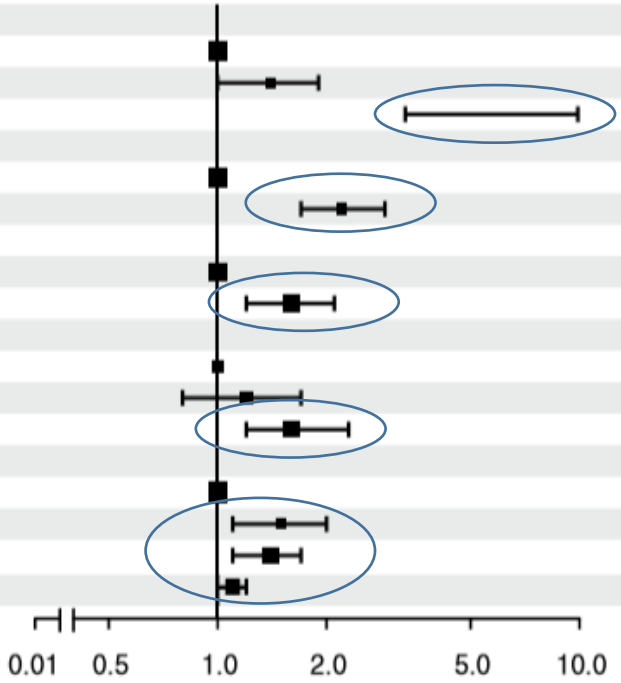
Baseline characteristics

Variable	Number of unfavorable outcomes/ number of study participants (%)	HR (95% CI)
Sex		
Female	90/549 (16)	Reference
Male	326/1,294 (25)	1.6 (1.3–2.1)
Smear grade		
Smear negative or 1+	81/443 (18)	Reference
Smear 2+	104/481 (22)	1.2 (0.9–1.7)
Smear 3+	231/919 (25)	1.4 (1.1–1.9)
HIV status		
Negative	352/1615 (22)	Reference
Positive	64/228 (28)	1.4 (1.1–1.9)
Age (per 10-year increase)	[a]	1.1 (1.0–1.2)



Baseline characteristics, on-treatment culture status and adherence

Variable	Number of unfavorable outcomes/ number of study participants (%)	HR (95% CI)
Adherence		
100%	238/1,348 (18)	Reference
>90 and <100%	64/288 (22)	1.4 (1.0–1.9)
≤90%	15/32 (47)	5.7 (3.3–9.9)
Month 2 culture status		
Negative	212/1,357 (16)	Reference
Positive	105/311 (34)	2.2 (1.7–2.9)
Sex		
Female	64/492 (13)	Reference
Male	253/1,176 (22)	1.6 (1.2–2.1)
Smear grade		
Smear negative or 1+	53/388 (14)	Reference
Smear 2+	72/430 (17)	1.2 (0.8–1.7)
Smear 3+	192/850 (23)	1.6 (1.2–2.3)
HIV status		
Negative	270/1,463 (18)	Reference
Positive	47/205 (23)	1.5 (1.1–2.0)
BMI (per 5 kg m^{-2} decrease)	[b]	1.4 (1.1–1.7)
Age (per 10-year increase)	[b]	1.1 (1.0–1.2)

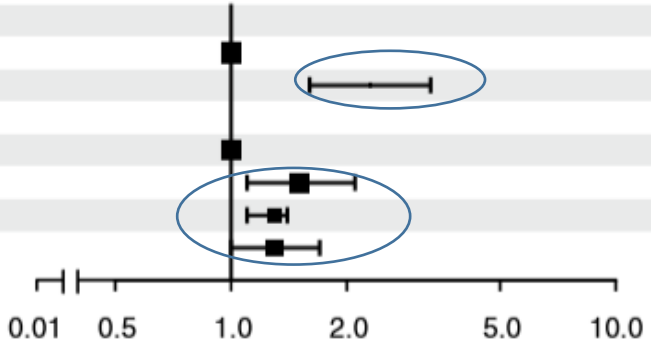


6 maanden controle regimes

Control group participants

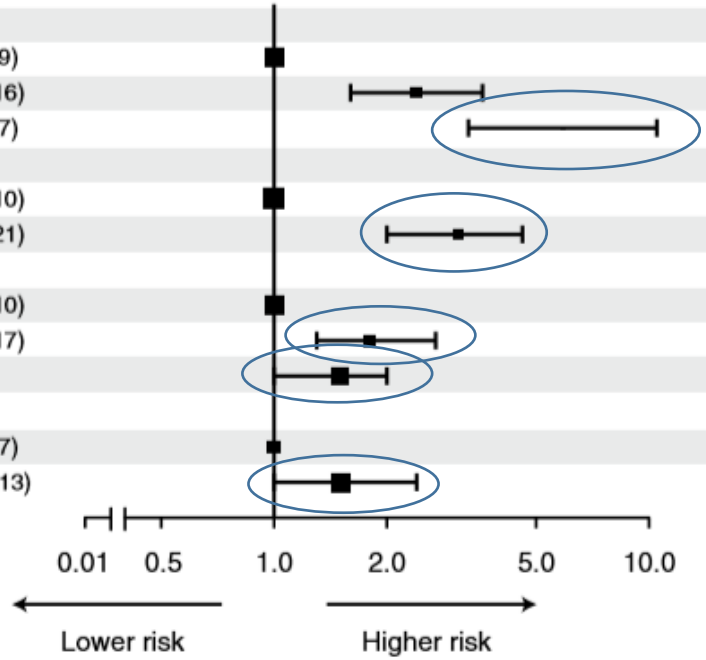
Baseline characteristics

Variable	Number of unfavorable outcomes/ number of study participants (%)	HR (95% CI)
HIV status		
Negative	159/1,103 (14)	Reference
Positive	54/208 (26)	2.3 (1.6–3.3)
Sex		
Female	47/381 (12)	Reference
Male	166/930 (18)	1.5 (1.1–2.1)
Age (per 10-year increase)	[c]	1.3 (1.1–1.4)
BMI (per 5 kg m^{-2} decrease)	[c]	1.3 (1.0–1.7)



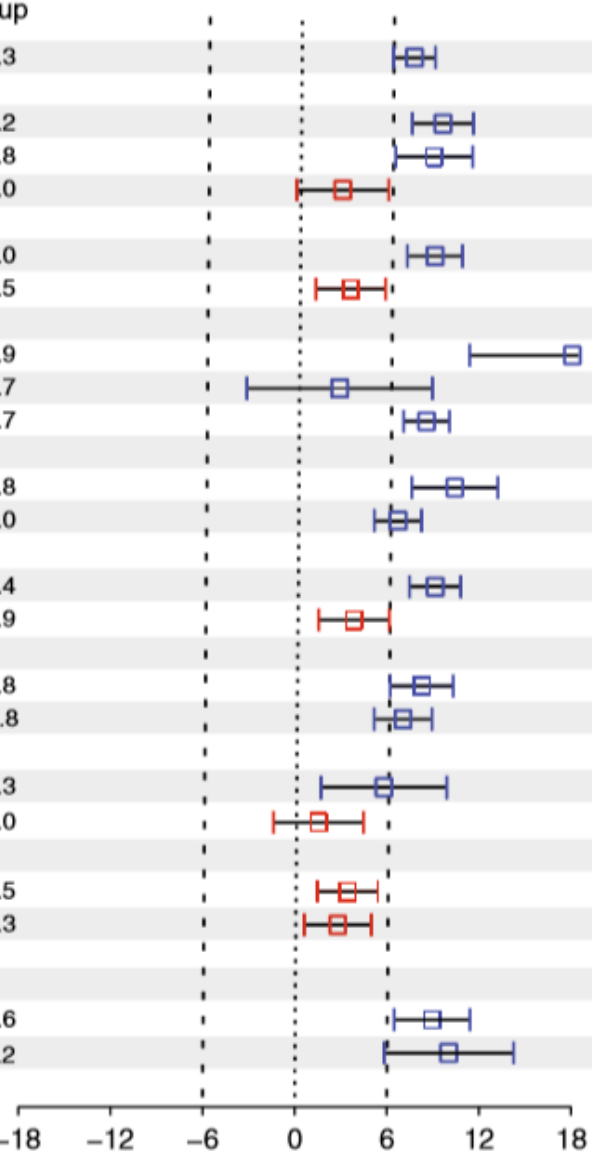
Baseline characteristics, on-treatment culture status and adherence

Variable	Number of unfavorable outcomes/ number of study participants (%)	HR (95% CI)
Adherence		
100%	85/913 (9)	Reference
>90 and <100%	37/230 (16)	2.4 (1.6–3.6)
≤90%	16/43 (37)	5.9 (3.3–10.5)
HIV status		
Negative	98/999 (10)	Reference
Positive	40/187 (21)	3.1 (2.0–4.6)
Month 2 culture status		
Negative	93/922 (10)	Reference
Positive	45/264 (17)	1.8 (1.3–2.7)
BMI (per 5 kg m^{-2} decrease)	[d]	1.5 (1.0–2.0)
Sex		
Female	30/347 (7)	Reference
Male	108/839 (13)	1.5 (1.0–2.4)

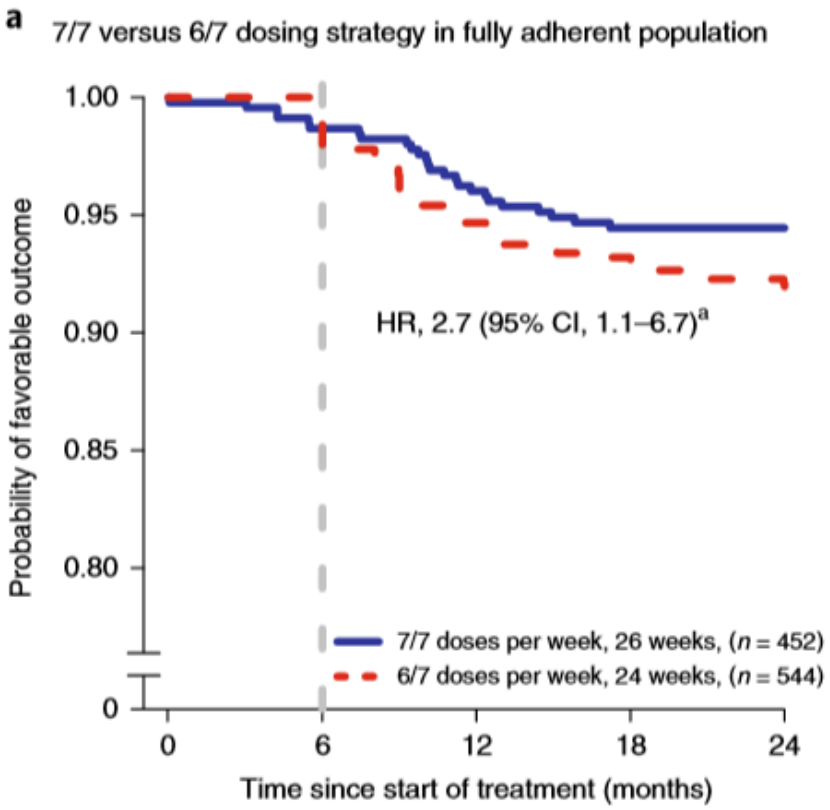


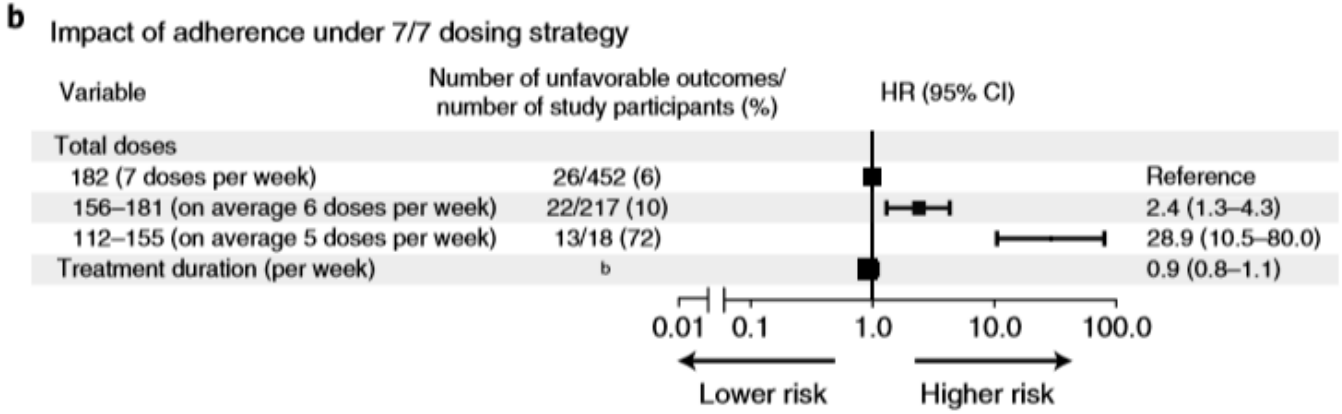
a

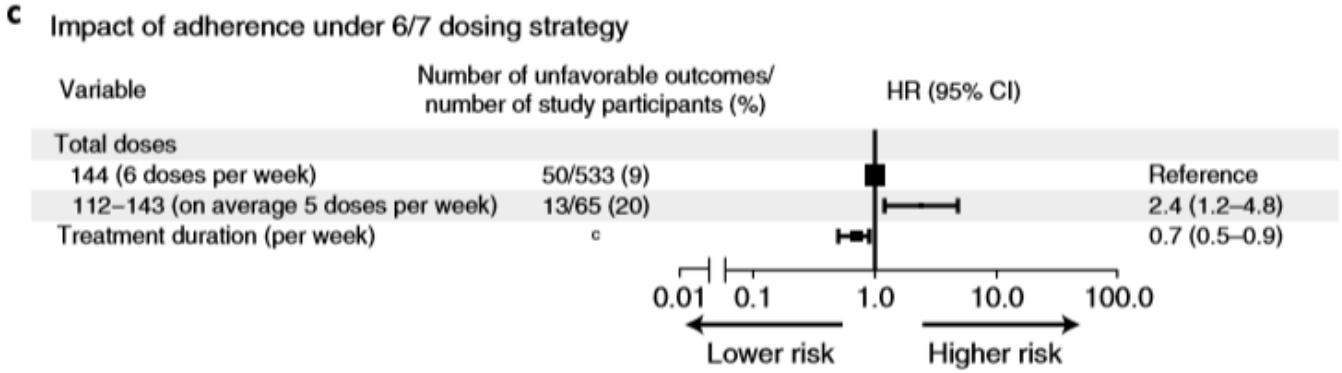
Analysis dataset	Number of participants	Percentage of unfavorable outcome: Experimental group	Percentage of unfavorable outcome: Control group	Percentage point difference, experimental – control (90% CI)	*P*-value for interaction
Overall	3,405	23.6	16.3	7.3 (5.9–8.7)	
Smear status					
Smear 3+	1,655	26.3	17.2	9.2 (7.2–11.1)	
Smear 2+	907	22.4	13.8	8.6 (6.1–11.1)	
Smear negative or 1+	800	19.7	17.0	2.6 (–0.4–5.6)	0.05
Cavitation					
Present	2,094	24.7	16.0	8.6 (6.8–10.4)	
Absent	1,111	20.7	17.5	3.1 (0.9–5.4)	0.06
HIV status					
Positive; CD4$^+$ cell count ≤300	155	33.5	15.9	17.6 (10.9–24.3)	
Positive; CD4$^+$ cell count >300	234	27.1	24.7	2.4 (–3.6–8.5)	
Negative	2,928	22.8	14.7	8.1 (6.6–9.6)	0.14
BMI (kg m^{-2})					
<17	881	27.7	17.8	9.9 (7.1–12.7)	
≥17	2,524	22.3	16.0	6.2 (4.7–7.8)	0.53
Sex					
Male	2,398	26.1	17.4	8.6 (7.0–10.3)	
Female	1,007	17.6	13.9	3.7 (1.4–6.0)	0.33
Age (years)					
≥30	1,702	26.9	18.8	8.1 (6.0–10.1)	
<30	1,698	20.4	13.8	6.6 (4.7–8.4)	0.53
Validation subgroups					
Smear 3+ and non-cavitary disease	394	23.1	17.3	5.8 (1.7–9.9)	0.88
Smear ≤2+ and non-cavitary disease	706	19.6	18.0	1.5 (–1.4–4.5)	0.02
Patient subgroups eligible for 4-month regimens: various definitions					
Smear <2+ or non-cavitary disease	1,591	19.9	16.5	3.4 (1.5–5.4)	0.02
Smear <2+ o smear 2+ and non-cavitary diseaser	1,186	19.1	16.3	2.8 (0.6–5.0)	0.01
Hard-to-treat patient subgroups: various definitions					
Smear 3+ and cavitary disease	1,162	26.4	17.6	8.8 (6.4–11.3)	0.02
Smear 3+ and BMI <17 kg m^{-2}	421	31.2	21.2	10 (5.8–14.1)	0.68



Belang van therapietrouw







Conclusie

- Risicofactoren voor ongunstige uitkomst: 3+ smear baseline, HIV, laag BMI, man, ernst afwijkingen, gemiste dosis (1/10 = 5x hogere kans)

- **47% 'easy to treat phenotype'**
  (lage smear grade (0 of 1+) of geen cavernes)
    - lager risico op unfavourable outcome
    - 4 maanden regimes non-inferior

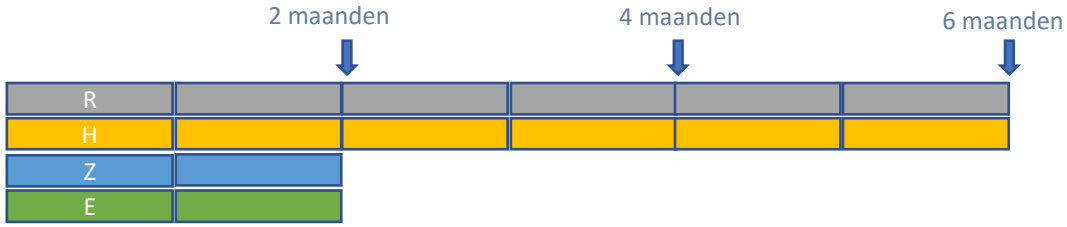
- **34% 'hard-to-treat phenotype'**
  (smear 3+ en cavernes)
    - Mogelijk hogere cure rates met > 6 mnd behandeling

Imperial MZ et al, Nature medicine 2018

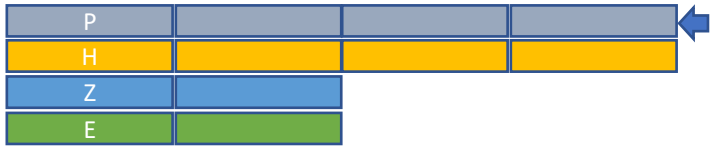
TBTC Study 31: to evaluate rifapentine-containing Tuberculosis Treatment Shortening Regimens

2516 patiënten enrolled in fase 3 open label randomized trial

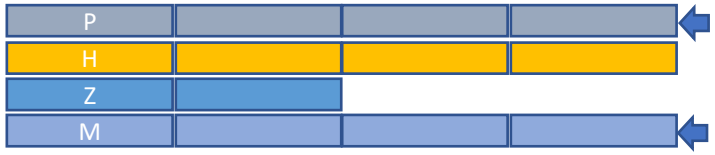
- **Regimen 1 (control): 2RHZE/4RH**



- **Regimen 2 (investigational) 2PHZE/2PH**
  - Rifapentine i.p.v rifampicine
  - Continuatiefase 2 i.p.v 4 maanden



- **Regimen 3 (investigational): 2PHZM/2PHM**
  - Als regimen 2
  - 4 maanden moxifloxacine i.p.v 2 maanden ethambutol



RESEARCH SUMMARY

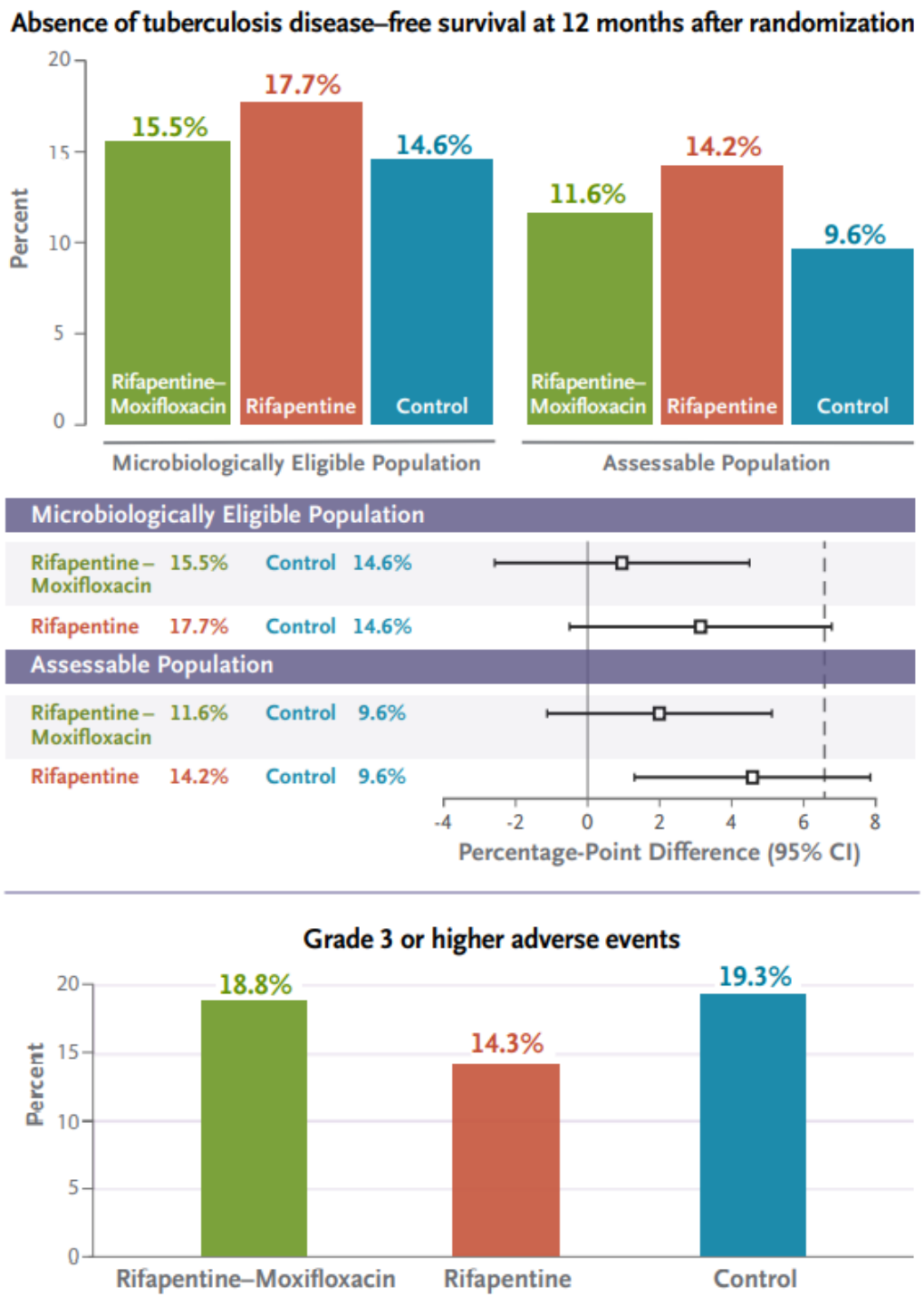
Four-Month Rifapentine Regimens with or without Moxifloxacin for Tuberculosis

Dorman SE et al. DOI: 10.1056/NEJMoa2033400

- Randomized, open-label non-inferiority trial
  - Controle: standaard therapie, 6 mnd
  - Interventie1: rifampicine vervangen door rifapentine, 4 mnd
  - Interventie 2: rifampicine vervangen door rifapentine en ethambutol door moxifloxacine, 4 mnd

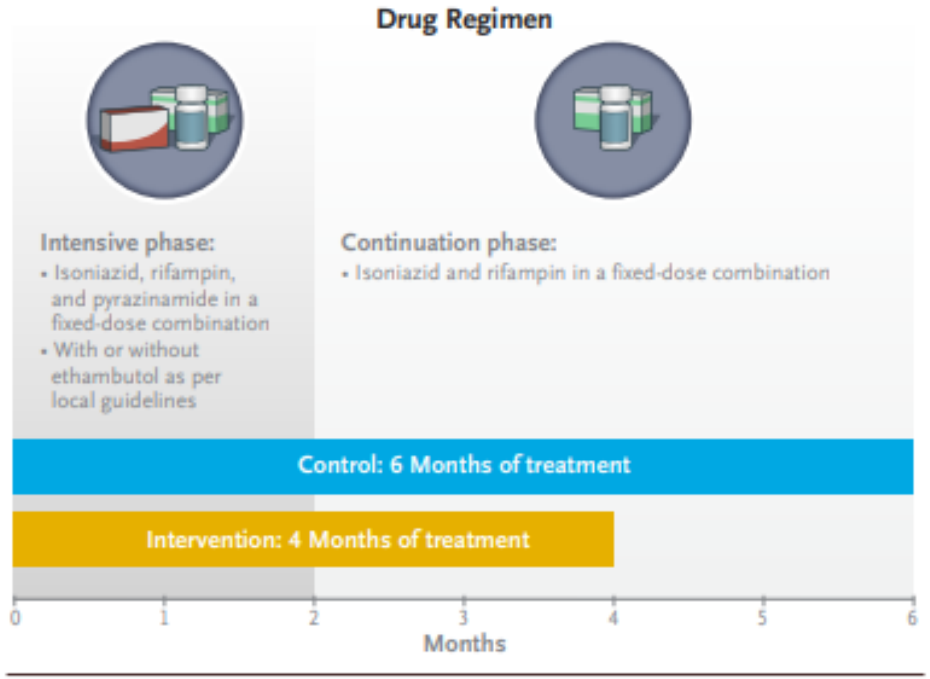
CONCLUSIONS

A 4-month regimen containing rifapentine and moxifloxacin was noninferior in efficacy and similar in safety and premature discontinuation to a standard 6-month antimicrobial regimen for the treatment of tuberculosis.



Kortere behandeling kinderen

- SHINE trial (2020) – Shorter Treatment for Minimal Tuberculosis in Children
  - Fase 3 gerandomiseerde open-label trial bij 1204 kinderen <16 jaar
  - ‘minimal TB’ = microscopie negatief en niet ernstige TB (o.b.v X-thorax),inclusief extra-thoracale lymfeklier TB

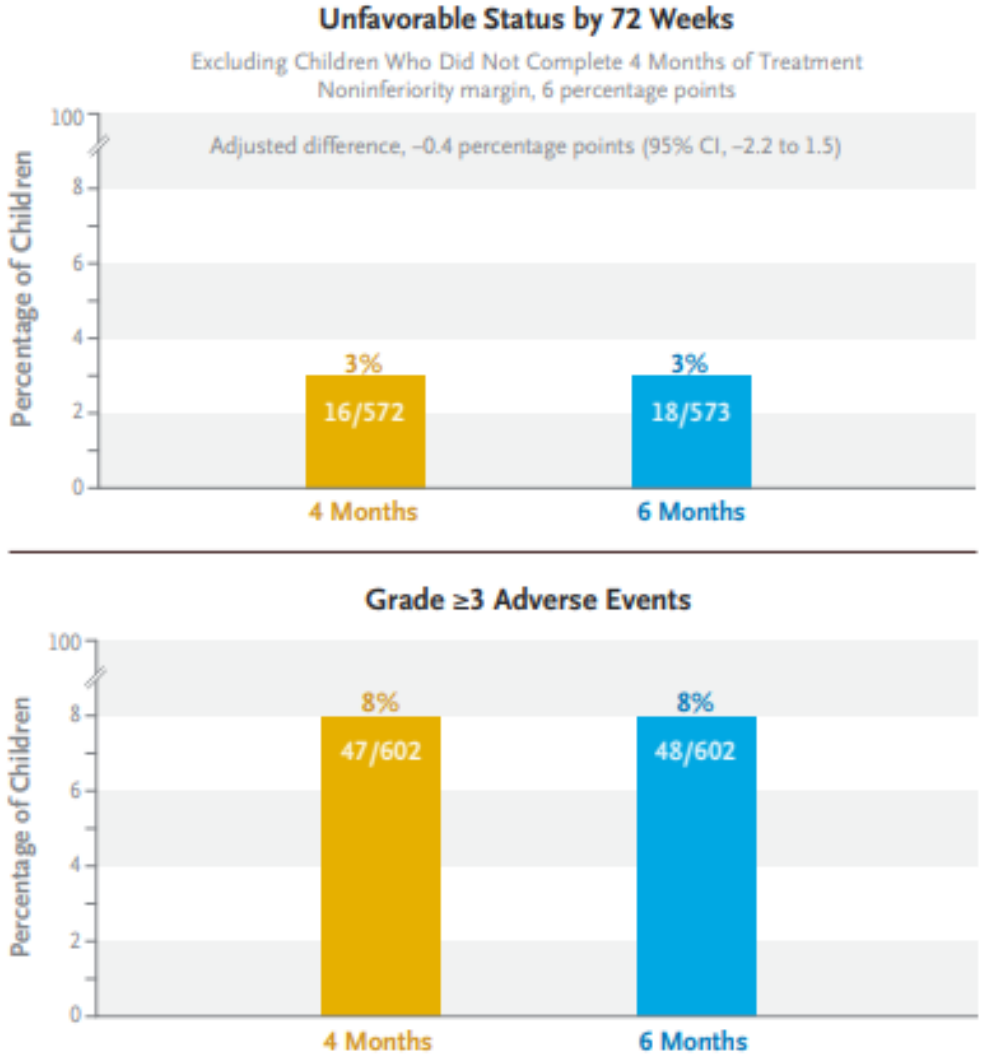


Turkova et al, NEJM, 2022

Kortere behandeling kinderen

- 4 maanden is non-inferior t.o.v 6 maanden behandeling bij kinderen met niet-ernstige, microscopie negatieve TB na 72 weken follow-up

- Unfavourable status = behandelfalen, relapse, mortaliteit, loss-to-follow-up



Turkova et al, NEJM, 2022

Huidige behandellandschap

DS-TB (85%)	RR/MDR/XDR	TBI
2 HRZE – 4 HR 2 HRZE – 2 HR 2HPZMfx – 2PMfx Hr-TB (10%) 6 RFqZE	4-6 BFqCfzZEHhEto/5FqCfzZE (shorter) 18 BLfqCfz (longer) 6-9 Bpal / Bpalm	3HR 4R 6-9 H 3HP (ATS) FQ(E) voor DR-TBI

MDR-TB

MDR-TB meta-analyse

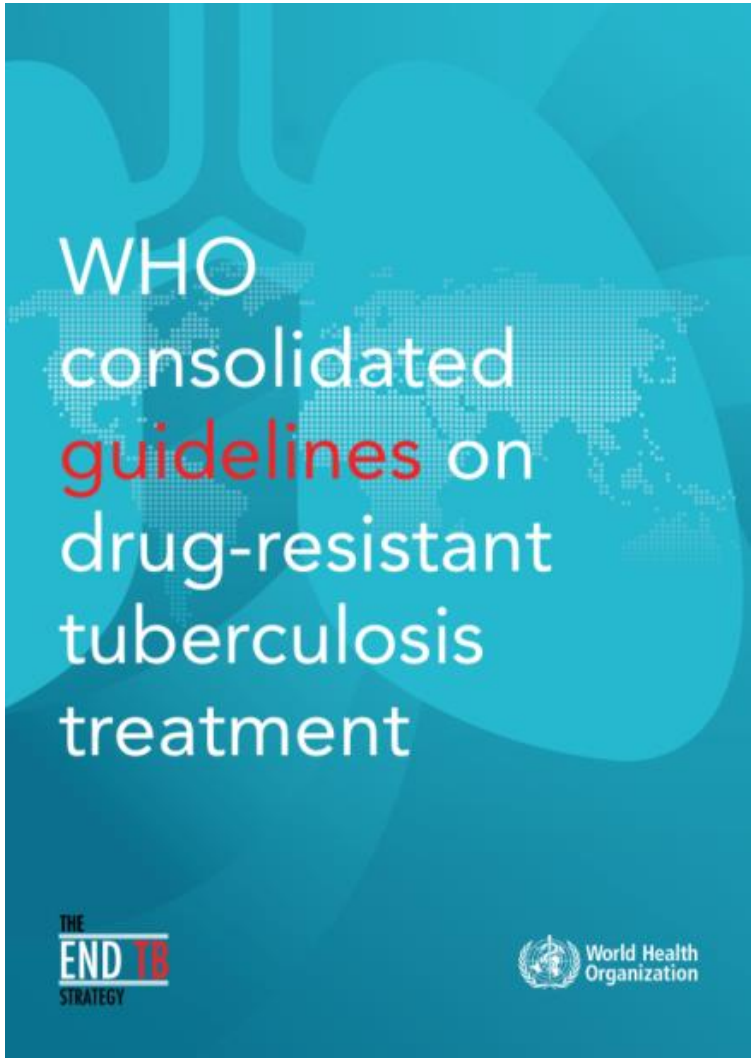
- Landmark paper
- 12.030 patienten
- 25 landen (50 studies)
- 7346 (61%) succesvol
- 1017 (8%) gefaald
- 1729 (14%) overleden

Treatment correlates of successful outcomes in pulmonary multidrug-resistant tuberculosis: an individual patient data meta-analysis

The Collaborative Group for the Meta-Analysis of Individual Patient Data in MDR-TB treatment–2017; Nafees Ahmad, Shama D Ahuja, Onno W Akkerman, Jan-Willem C Alffenaar, Laura F Anderson, Parvaneh Baghaei, Didi Bang, Pennan M Barry, Mayara L Bastos, Digamber Behera, Andrea Benedetti, Gregory P Bisson, Martin J Boeree, Maryline Bonnet, Sarah K Brode, James C M Brust, Ying Cai, Eric Caumes, J Peter Cegielski, Rosella Centis, Pei-Chun Chan, Edward D Chan, Kwok-Chiu Chang, Macarthur Charles, Andra Cirule, Margareth Pretti Dalcolmo, Lia D'Ambrosio, Gerard de Vries, Keertan Dheda, Aliasgar Esmail, Jennifer Flood, Gregory J Fox, Mathilde Fréchet-Jachym, Geisa Fregona, Regina Gayoso, Medea Gegia, Maria Tarcela Gler, Sue Gu, Lorenzo Guglielmetti, Timothy H Holtz, Jennifer Hughes, Petros Isaakidis, Leah Jarlsberg, Russell R Kempker, Salmaan Keshavjee, Faiz Ahmad Khan, Maia Kipiani, Serena P Koenig, Won-Jung Koh, Afranio Kritski, Liga Kuksa, Charlotte L Kvasnovsky, Nakwon Kwak, Zhiyi Lan, Christoph Lange, Rafael Laniado-Laborín, Myungsun Lee, Vaira Leimane, Chi-Chiu Leung, Eric Chung-Ching Leung, Pei Zhi Li, Phil Lowenthal, Ethel L Maciel, Suzanne M Marks, Sundari Mase, Lawrence Mbuagbaw, Giovanni B Migliori, Vladimir Milanov, Ann C Miller, Carole D Mitnick, Chawangwa Modongo, Erika Mohr, Ignacio Monedero, Payam Nahid, Norbert Ndjeka, Max R O'Donnell, Nesri Padayatchi, Domingo Palmero, Jean William Pape, Laura J Podewils, Ian Reynolds, Vija Riekstina, Jérôme Robert, Maria Rodriguez, Barbara Seaworth, Kwonjune J Seung, Kathryn Schnippel, Tae Sun Shim, Rupak Singla, Sarah E Smith, Giovanni Sotgiu, Ganzaya Sukhbaatar, Payam Tabarsi, Simon Tiberi, Anete Trajman, Lisa Trieu, Zarir F Udwadia, Tjip S van der Werf, Nicolas Veziris, Piret Viiklepp, Stalz Charles Vilbrun, Kathleen Walsh, Janice Westenhouse, Wing-Wai Yew, Jae-Joon Yim, Nicola M Zetola, Matteo Zignol, Dick Menzies

Menzies et al., Lancet, sept 2018

WHO DR-TB consolidated guidelines 2020

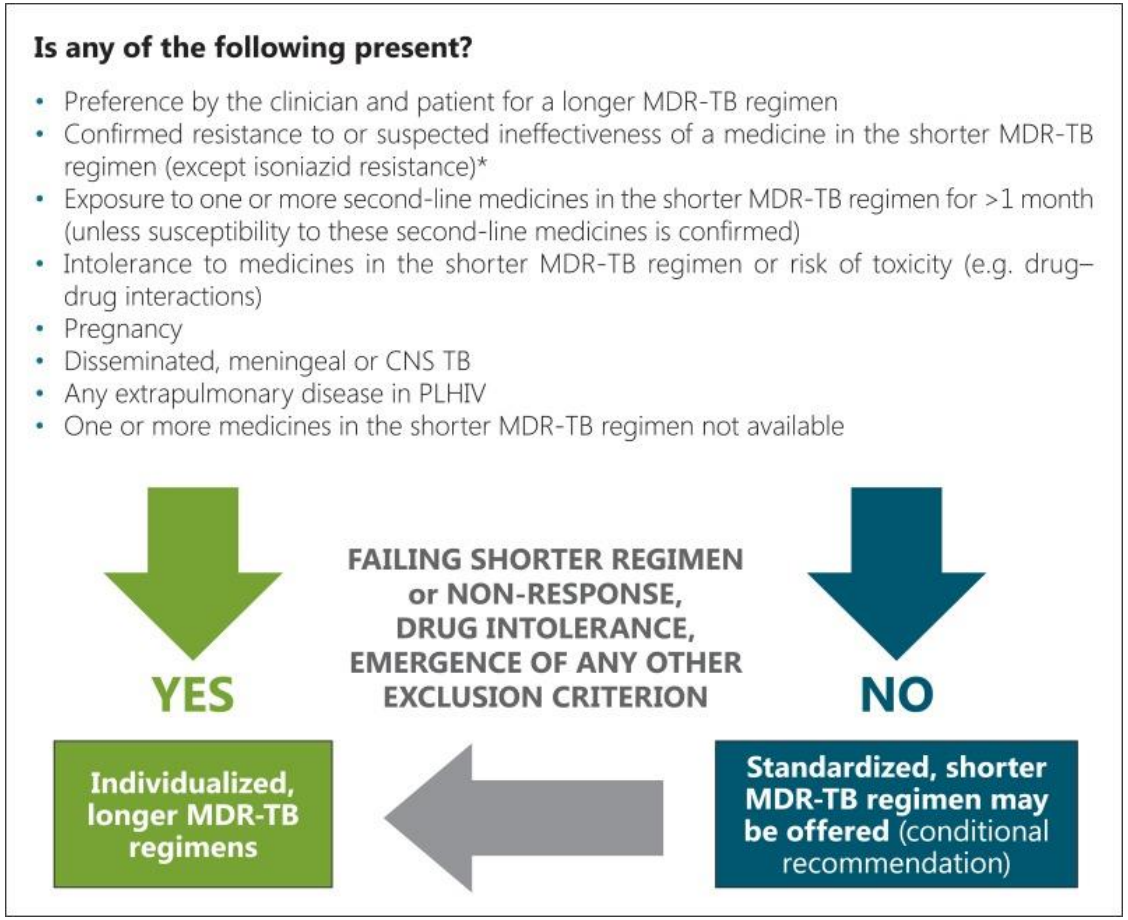


Groups & steps	Medicine	
Group A: Include all three medicines	levofloxacin *OR* moxifloxacin	Lfx Mfx
	bedaquiline[2,3]	Bdq
	linezolid[4]	Lzd
Group B: Add one or both medicines	clofazimine	Cfz
	cycloserine *OR* terizidone	Cs Trd
Group C: Add to complete the regimen and when medicines from Groups A and B cannot be used	ethambutol	E
	delamanid[3,5]	Dlm
	pyrazinamide[6]	Z
	imipenem–cilastatin *OR* meropenem[7]	Ipm–Cln Mpm
	amikacin (*OR* streptomycin)[8]	Am (S)
	ethionamide *OR* prothionamide[9]	Eto Pto
	p-aminosalicylic acid[9]	PAS

MDR behandeling

Longer:

18 Bdq (6 mnd) – LZD – Fq - Cfz



Shorter (9-12 months):

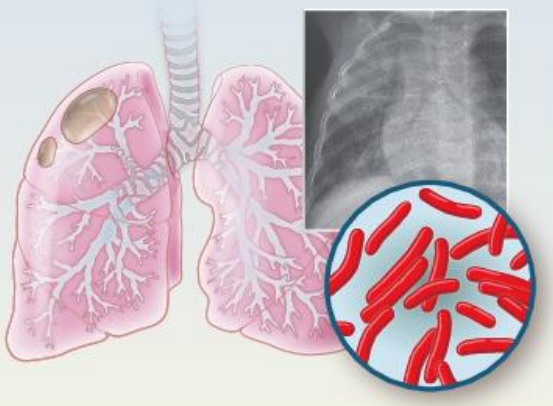
4-6 Bda (6m) Fq-Cfz-Z-E-Hh-Eto / 5 Fq-Cfz-Z-E

The NEW ENGLAND JOURNAL of MEDICINE

Treatment of Highly Drug-Resistant Pulmonary TB

NIX-TB, AN OPEN-LABEL, SINGLE-GROUP STUDY

109 Patients
with confirmed tuberculosis



Three-drug regimen (26 wk)

Bedaquiline

Pretomanid
(recently approved)

Linezolid

XDR tuberculosis
N=71
(65%)

Nonresponsive or treatment-intolerant MDR tuberculosis
N=38
(34%)

Clinical resolution at 6 mo after therapy

90% of all patients had favorable outcomes
95% CI, 83–95

89%
95% CI, 79–95

92%
95% CI, 79–98

Linezolid associated with peripheral neuropathy (81%) and myelosuppression (48%)

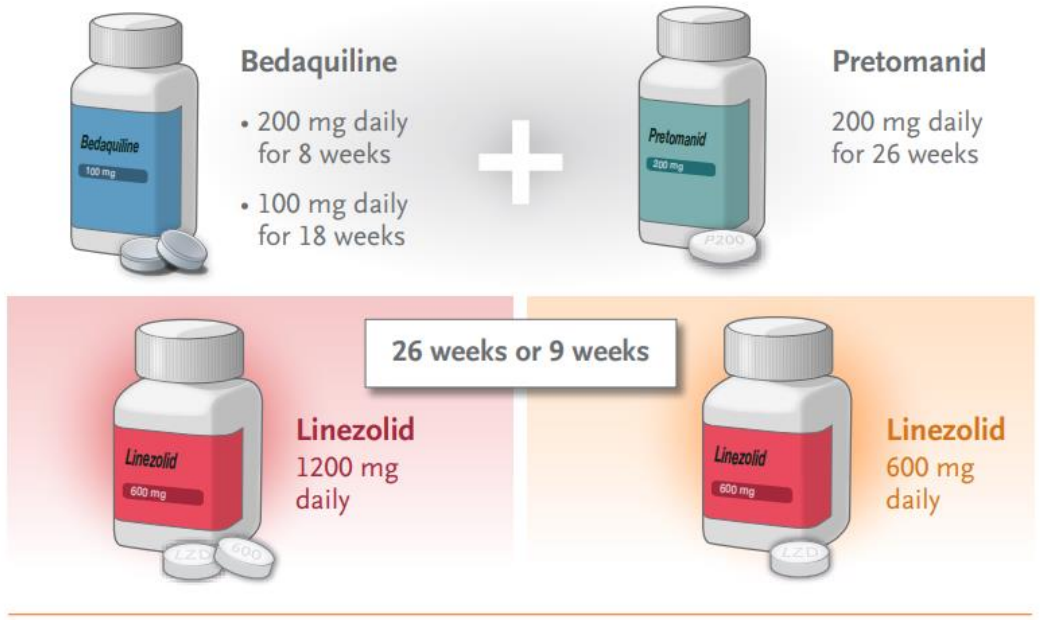
F. Conradie et al. 10.1056/NEJMoa1901814

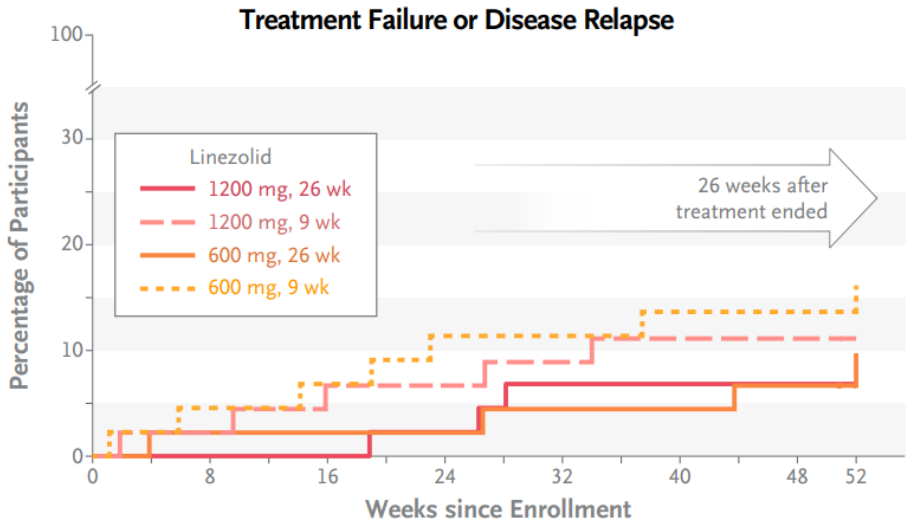
The NEW ENGLAND JOURNAL of MEDICINE

RESEARCH SUMMARY

Bedaquiline–Pretomanid–Linezolid Regimens for Drug-Resistant Tuberculosis

Conradie F et al. DOI: 10.1056/NEJMoa2119430





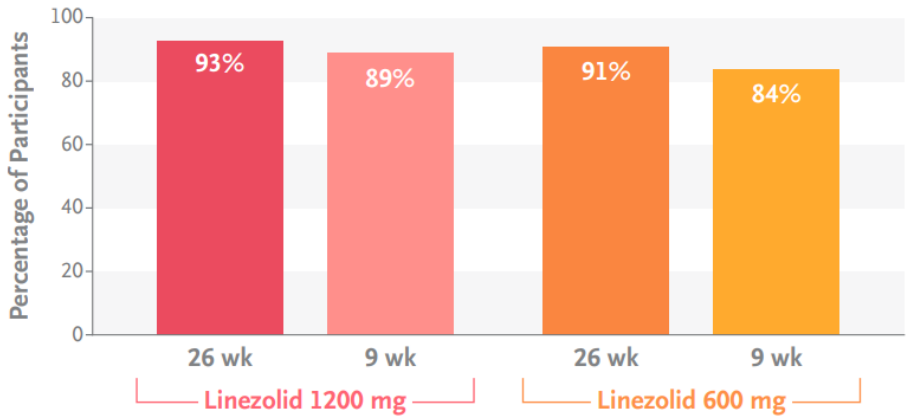


Table 3. Safety Analysis.*

Variable	Bedaquiline–Pretomanid–Linezolid Regimen				Total (N=181)
	Linezolid, 1200 mg, 26 wk (N=45)	Linezolid, 1200 mg, 9 wk (N=46)	Linezolid, 600 mg, 26 wk (N=45)	Linezolid, 600 mg, 9 wk (N=45)	
	number of participants (percent)				
≥1 Grade 3 or higher adverse event	14 (31)	11 (24)	9 (20)	11 (24)	45 (25)
≥1 Serious adverse event	3 (7)	4 (9)	1 (2)	3 (7)	11 (6)
Death from any cause	0	1 (2)	0	0	1 (1)
Tuberculosis-related death	0	0	0	0	0
≥1 Episode of optic neuropathy†‡	4 (9)	0	0	0	4 (2)
≥1 Episode of peripheral neuropathy‡§	17 (38)	11 (24)	11 (24)	6 (13)	45 (25)
Severity of event in participants with ≥1 episode of peripheral neuropathy§¶					
Grade 1	10 (22)	7 (15)	10 (22)	6 (13)	33 (18)
Grade 2	7 (16)	4 (9)	1 (2)	0	12 (7)
≥1 Episode of myelosuppression‖	10 (22)	7 (15)	1 (2)	3 (7)	21 (12)
Hemoglobin level					
<8 g/dl and below baseline level	0	1 (2)	0	0	1 (1)
<25% below baseline level	9 (20)	4 (9)	0	0	13 (7)
Absolute neutrophil count <750/mm³ and below baseline level	1 (2)	3 (6)	1 (2)	3 (7)	8 (4)
Platelet count <50,000/mm³ and below baseline level	0	0	0	0	0
Liver-related serious adverse event	0	1 (2)	1 (2)	1 (2)	3 (2)
QTcF interval >60 msec above baseline value	0	2 (4)	0	1 (2)	3 (2)
Maximum QTcF interval ≥500 msec	0	1 (2)	0	1 (2)	2 (1)
Any interruption, dose reduction, or discontinuation of linezolid	23 (51)	14 (30)	6 (13)	6 (13)	49 (27)

* All participants who received at least one dose of a trial medication were included in the safety analysis population. Listed are adverse events that occurred from the start of treatment through 14 days after the end of treatment. QTcF denotes corrected QT interval calculated with Fridericia's formula.
† The incidence of optic neuropathy was evaluated with the use of the standardized *Medical Dictionary for Regulatory Activities* (MedDRA) query, which included the preferred term optic nerve disorder.
‡ These adverse events were coded with the use of MedDRA, version 23.0.
§ The incidence of peripheral neuropathy was evaluated with the use of the standardized MedDRA query, which included the preferred term peripheral neuropathy.
¶ The highest grade was reported for participants with at least one event that occurred from the start of treatment through 14 days after the end of treatment.
‖ Myelosuppression was determined on the basis of laboratory results.

TO THE EDITOR: We concur with Thwaites and Nahid[1] in their editorial that the landmark study by Conradie et al. offers hope for persons with drug-resistant tuberculosis. However, the fact that peripheral neuropathy, albeit mild and manageable, was reported in 81% of the patients shows that toxic effects associated with these high doses of linezolid are problematic.

Of the 77 patients who were receiving linezolid during their stay in our tuberculosis center between 2007 and 2019, a total of 20 (26%) had polyneuropathy. The linezolid dose was adjusted on the basis of the pharmacokinetic profile and drug susceptibility testing. The median final linezolid dose was 600 mg per day (interquartile range, 300 to 600). In some cases, the linezolid dose was reduced to 150 mg daily.[2]

Bolhuis, NEJM 2020

Table. Core regimens to treat MDR/RR-TB

Regimen	Duration (months)	Indications	Contraindications
BPaLM (BDQ, pretomanid, linezolid, MFX) BPaL (without MFX)	6	MDR/RR-TB patients age 15 years or more; BPaL if documented resistance to FQs	Exposure to any of the drugs composing the regimen for ≥30 days
All-oral, BDQ-containing regimens	9	Adults and children with MDR/RR-TB	Previous exposure to second-line treatment (including BDQ), FQ resistance; extensive pulmonary TB disease; severe extrapulmonary TB
Individualised longer regimen	≥18	Patients with extensive forms of DR-TB (e.g., XDR-TB); or not eligible for the regimens described above or who previously failed shorter treatment regimens	

MDR/RR-TB = multidrug-/rifampicin-resistant TB; BDQ = bedaquiline; MFX = moxifloxacin; FQ = fluoroquinolone; DR-TB = drug-resistant TB; XDR-TB = extensively drug-resistant TB.

WHO drug-resistant TB guidelines 2022: what is new? G. B. Migliori, 1 S. Tiberi2 http://dx.doi.org/10.5588/ijtld.22.0

Table 2
Recently completed and ongoing, unpublished trials on rifampicin-resistant tuberculosis treatment (excluding fluoroquinolone-resistant tuberculosis) (as of 6 July 2023)

Trial	Phase	Control arm	Country	Experimental treatment regimen(s)	Treatment duration (mo)	Notes	Clinicaltrials.gov identifier
Recently completed trials							
OptiQ	II	No	Peru, South Africa	Lfx 11, 14, 17 or 20 mg/kg plus background regimen	6	750–1000 mg Lfx every day achieved target AUC/MIC	NCT01918397
SimpliciTB	II	Yes (only for DS-TB)	8 countries	Bdq, Pa, Z, Mfx	4	Not non-inferior to HRZE; no comparator for MDR-TB arm	NCT03338621
SUDOCU	II	No	South Africa, Tanzania	Sutezolid, Bdq, Dlm, Mfx	3	Regimen well tolerated	NCT03959566
TREAT-TB (India)	III	No	India	Bdq, Dlm, Lzd and Cfz	6–9	91% favourable outcomes	CTRI/2019/01/017310
Ongoing trials							
ACTG A5356	II	No	Multicountry	Bdq, Cfz, Dlm, and Lzd (different posologies)	6	TIW dosing of Lzd	NCT05007821
DECODE	II	No	South Africa, Tanzania	Delpazolid, Bdq, Dlm, Mfx	3	Dose-ranging and tolerability	NCT04550832
DRAMATIC	II	No	Multicountry	Lfx, Bdq, Lzd, Dlm, and Cfz	4–9	Duration-randomized clinical trial	NCT03828201
BEAT tuberculosis	III	Yes	South Africa	Bdq, Dlm, and Lzd, plus Lfx or Cfz	6	Experimental regimen adapted according to rapid molecular testing	NCT04062201
endTB [35]	III	Yes	Multicountry	Bdq, Mfx, Lzd, and Z; or Bdq, Cfz, Lfx, Lzd, and Z; or Bdq, Dlm, Lfx, Lzd, and Z; or Dlm, Cfz, Lfx, Lzd, and Z; or Dlm, Cfz, Mfx, and Z	9	Trial implementing Bayesian adaptive randomization	NCT02754765
TB-TRUST	III	Yes	China	Lfx, Lzd, Cs, and Z (or Cfz if resistant to Z)	6–9	No follow-up available	NCT03867136
TB-TRUST Plus	III	No	China	Bdq, Z, Lzd, Cs, Cfz	6–9	Regimen guided by Z susceptibility testing	NCT04717908
InDEX	IV	Yes	South Africa	Individualized regimens	NS	WGS-derived individualized regimen	NCT03237182
PROSPECT	IV	No	China	Cfz, Cs, Lfx, Lzd, and Pto; or Bdq, Cfz, Cs, Lfx, and Lzd	6 (first regimen), 9 (second regimen)	No follow-up available	NCT05306223
GRACE-TB	NA	Yes	China	Individualized regimens	NS	Individualized regimen guided by rapid molecular tests	NCT03604848
SMARTT	NA	Yes	South Africa	WGS-guided regimen	NS	Individualized regimen guided by rapid molecular tests	NCT05017324

Kanttekening

- Gebrek aan gevoeligheidstesten voor bedaquiline, linezolid, pretomanid en delamanid zijn een bedreiging voor deze nieuwe regimes!

2023 Global New TB Drug Pipeline[1] Updated 11/1/2023

Discovery | Preclinical Development | Clinical Development

Lead Optimization → Early Stage Development → GMP / GLP Tox. → Phase 1 → Phase 2 → Phase 3 → Regulatory Market Approvals

Indazole sulfonamides

Diarylthiazoles

DprE1 Inhibitors

Direct InhA Inhibitors

Mtb energy metabolism

Gyrase Inhibitors

Arylsulfonamides

Inhibitors of MmpL3, Translocase-1, ClpC1, ClpP1P2, PKS13, F-ATP synthase, RNAP

Oxazolidinones

DnaE1 / Nargenicin analogs

FIM-253

TBD10 (MK-3854)

CLB-073*

SPR720*

MPL-447*

JSF-3285*

CPZEN-45*

NTB-3119*

MBX-4888A (1810)*

FNDR-20364*

GSK-839*

OTB-658

TBD09 (MK-7762)

GSK-286*

TBAJ-587

TBI-223

Macozinone* (PBTZ-169)

Telacebec* (Q203)

Alpibectir (BVL-GSK098)*

TBAJ-876

Sanfetrinem

Delpazolid, Sutezolid, Tedizolid

BTZ-043*

TBA-7371*

Quabodepistat (OPC-167832*)

Ganfeborole (GSK-656*/070)

Pyrifazimine (TBI-166)

SQ-109*

Sudapyridine (WX-081)

Bedaquiline*

Delamanid*

Pretomanid*

*New chemical class. Known chemical classes for any indication are color coded: rifamycin, oxazolidinone, nitroimidazole, diarylquinoline, benzothiazinone, imidazopyridine amide, beta-lactam.

[1] New Molecular Entities not yet approved, being developed for TB or only conditionally approved for TB. Showing most advanced stage reported for each. Details for projects listed can be found at http://www.newtbdrugs.org/pipeline/clinical

Ongoing projects without a lead compound identified: http://www.newtbdrugs.org/pipeline/discovery

Underline = updates since November 2022

WORKING GROUP ON NEW TB DRUGS

www.newtbdrugs.org

Updated: November 2023

Conclusie

- Iedereen genezen is beter dan de meerderheid
- One size does not fit all, algoritmes nodig voor betere selectie behandelduur
- 3 nieuwe middelen geregistreerd, ook 8 nieuwe middelen in fase 2
- Veel nieuwe regimes in de pipeline, kortere regimes komen eraan!
  - We kunnen DS-TB behandelen in 4 maanden en DR-TB in 6 maanden
  - Universele schema's voor DS-TB en DR-TB?

Dank voor jullie aandacht!

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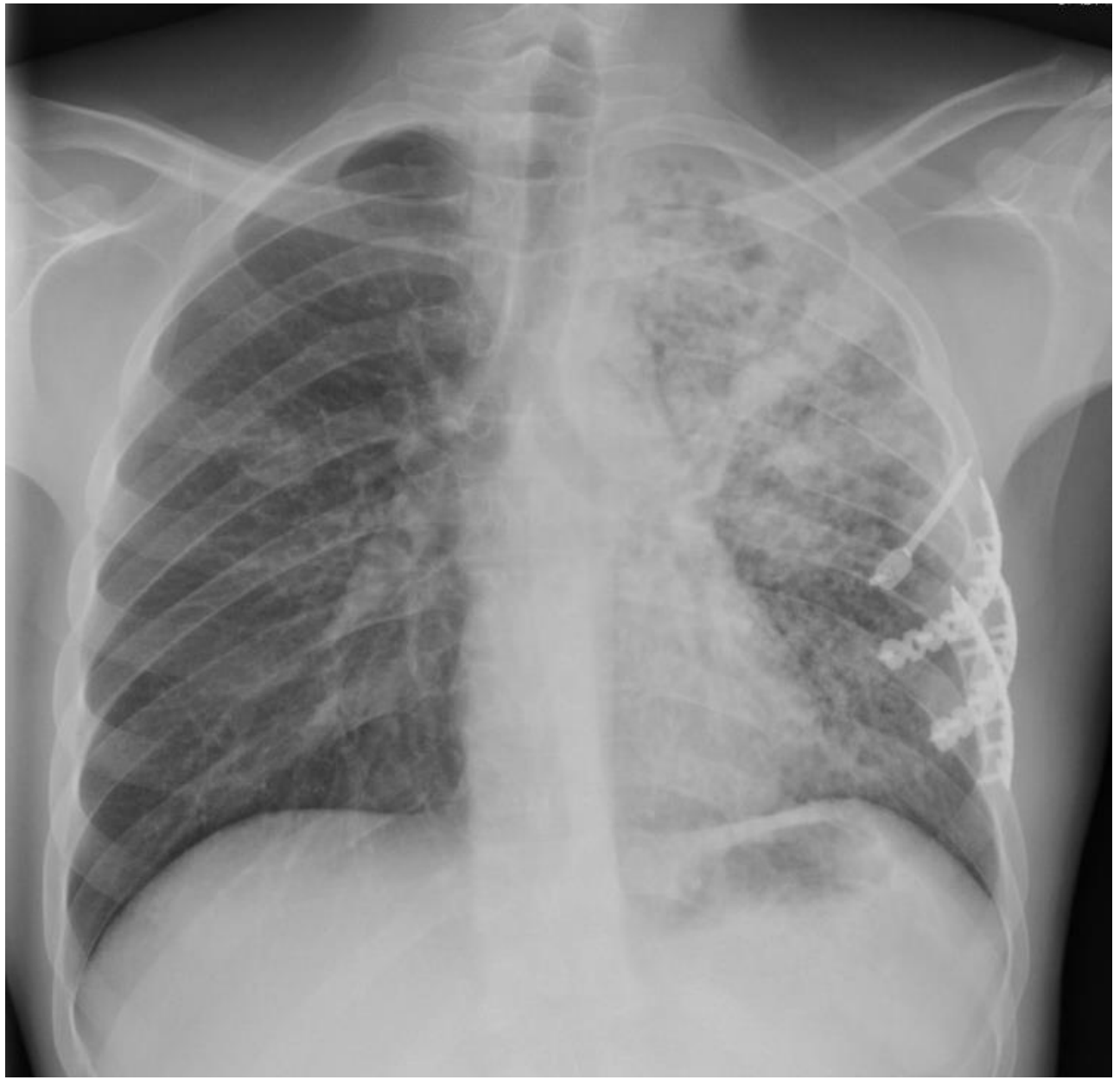
o.w.akkerman@umcg.nl

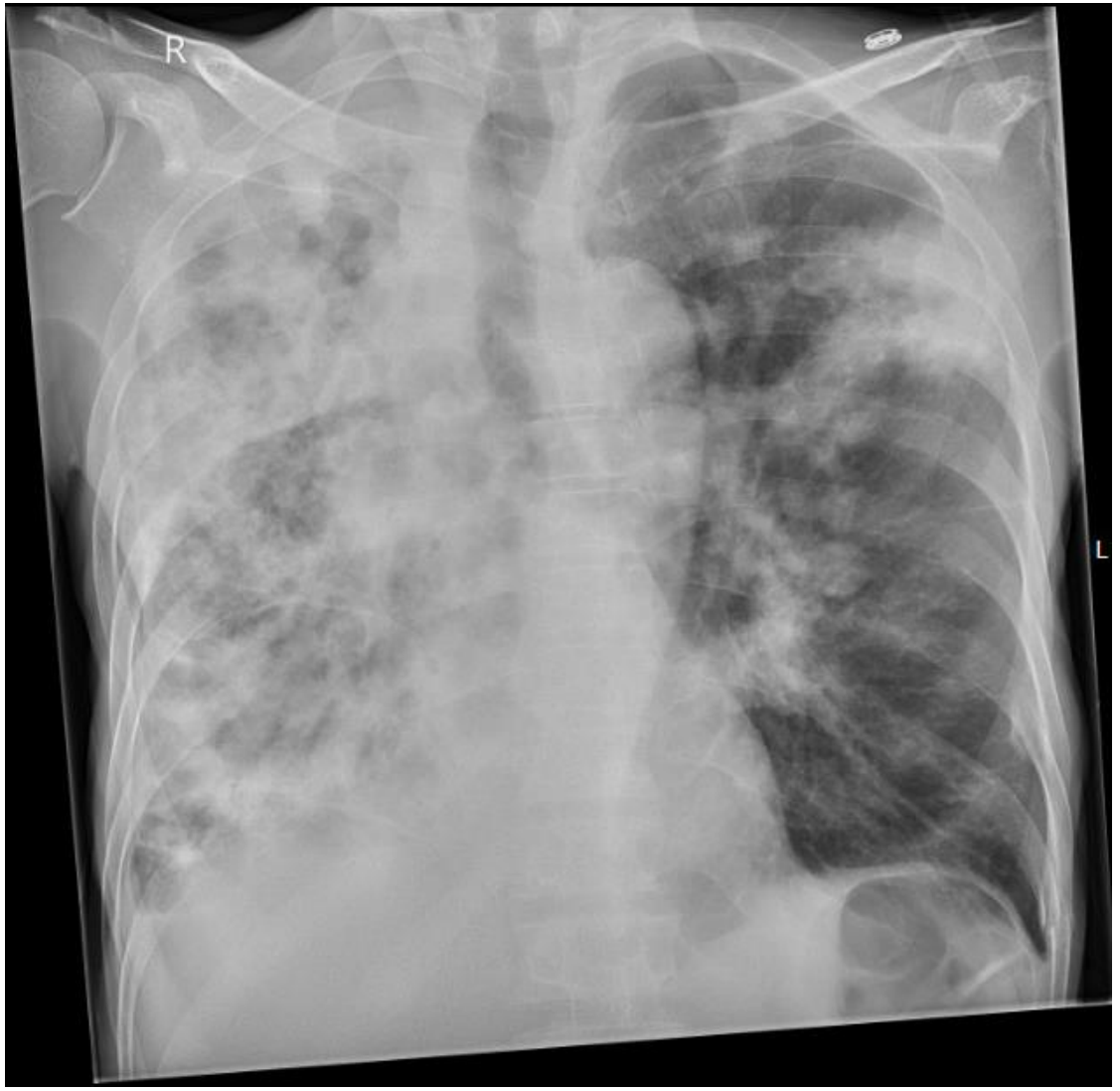
Casus

- VG: schizofrenie, auto ongeval
- Via BCO gevonden, in het cluster INH resistentie
- Auramine 3+. GeneXpert; Mtb, geen rifampicine resistentie.
- 21-12-23 start HRZE
- Psychotische ontregeling
- Beleid?

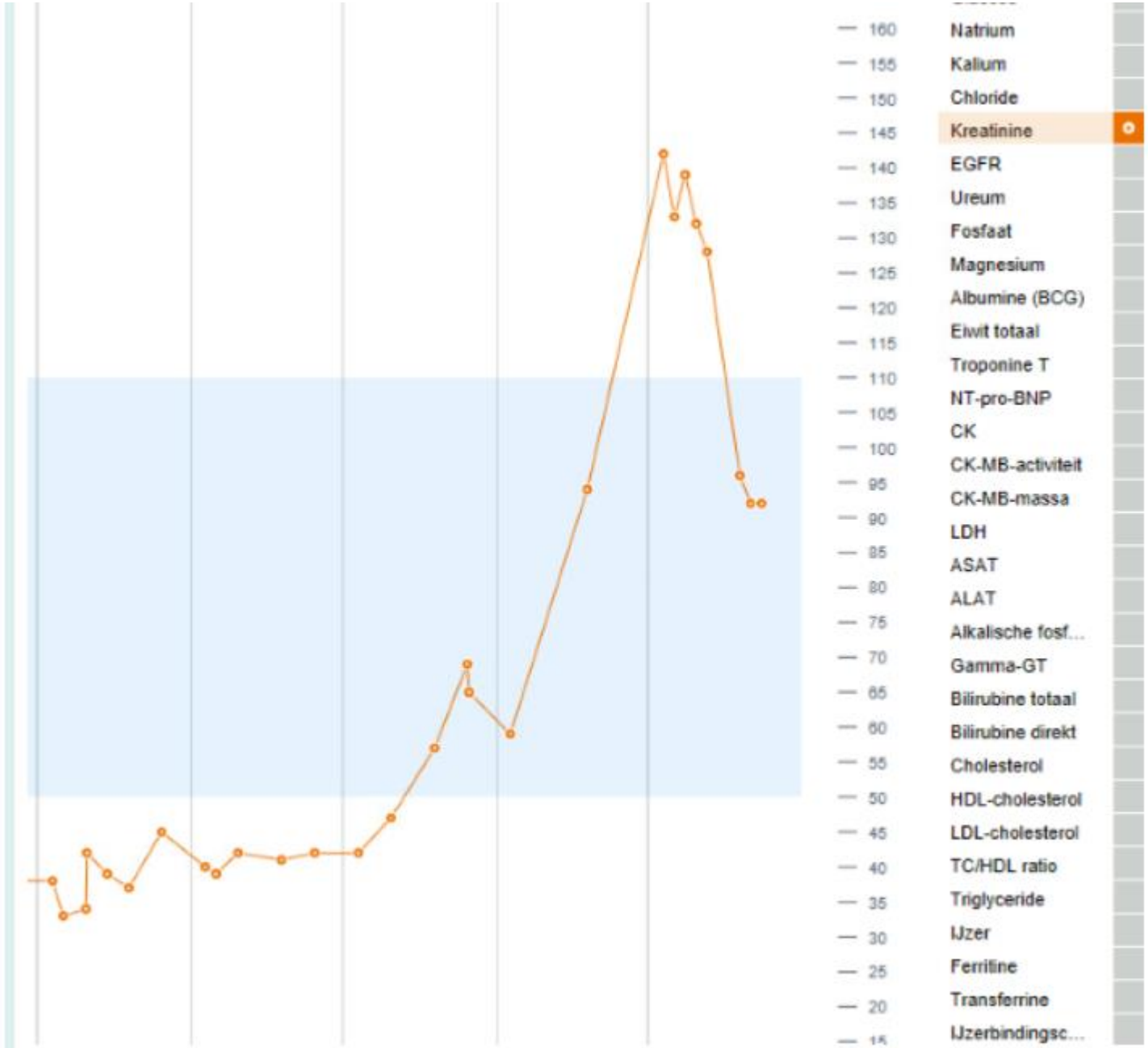


Casus

- WGS: normaal gevoelig
- Start HRZE: 7-9-2023
- Blijft langdurig auramine positief, schaal IV-V.
- Beleid?

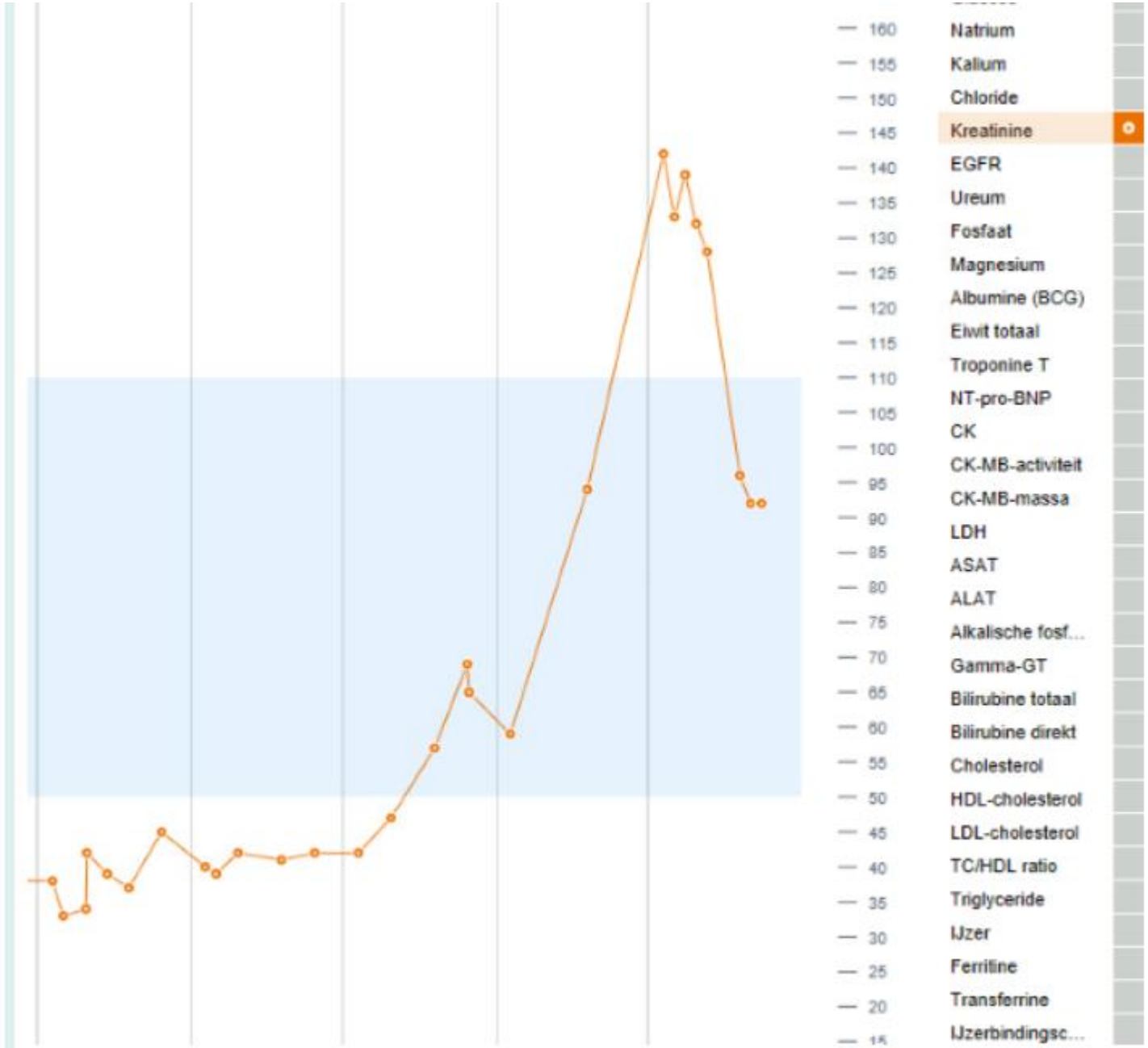


Tijdstempel	Recentste ref.waarden Alle resultaten	2024 5-1-24 00:00	2023 27-12-23 00:00	5-11-23 00:00	26-10-23 00:00	18-10-23 00:00	13-10-23 00:00	4-10-23 00:00	27-9-23 00:00	22-9-23 00:00
CERTE										
SPUTUM CERTE	27-12-23 Geen ref.waarden gevonden		P							



ANI

- Geen eosinofilie (onder steroïden)
- Normaal urine sediment
- Normale echo nieren



TIN

- Verbetering onder prednisolon
- Na afbouwen prednisolon opnieuw kreatinine sprong

- Wat nu?