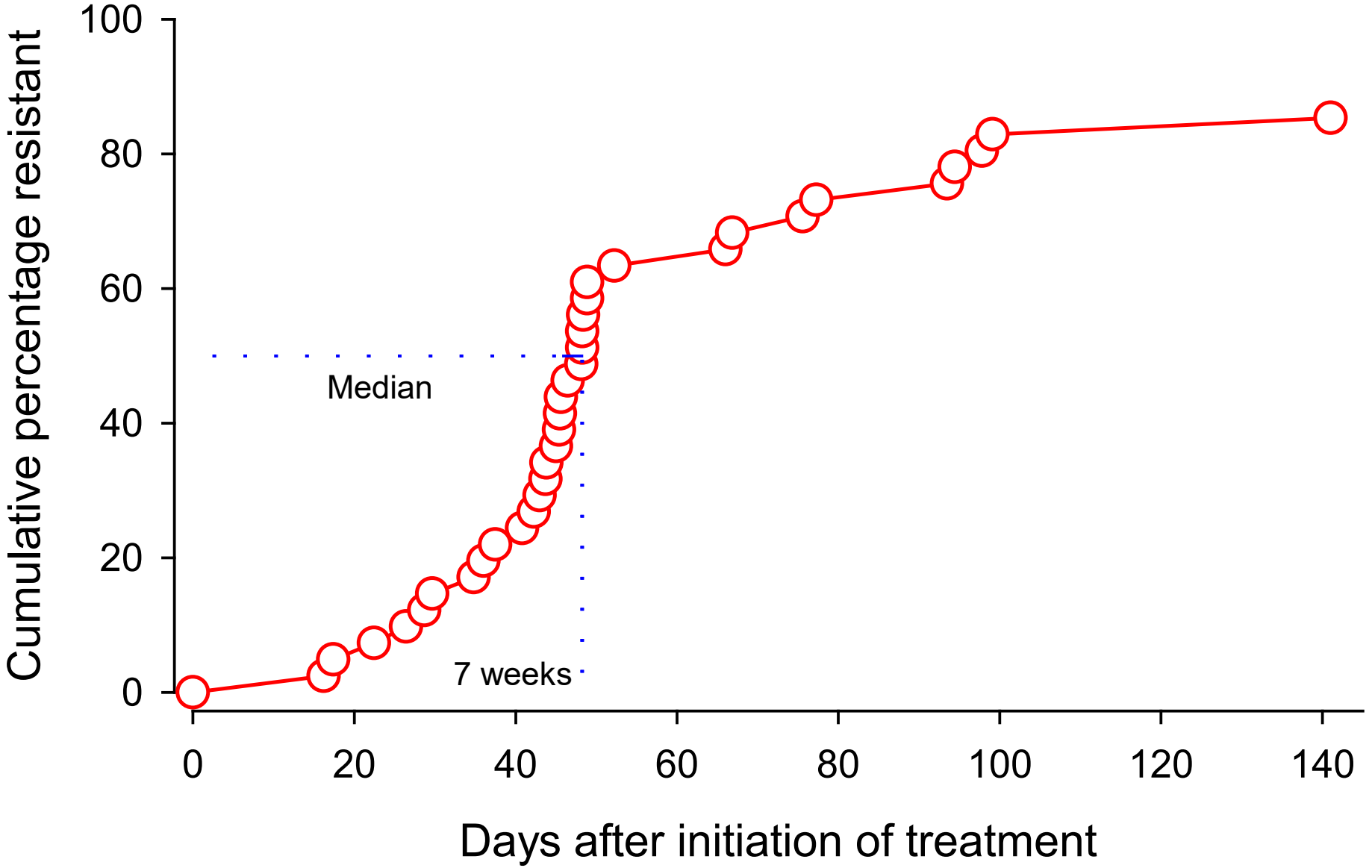
The bumpy road to efficacious, resistance-preventing anti-tuberculosis chemotherapy

Bern, November 22, 2024

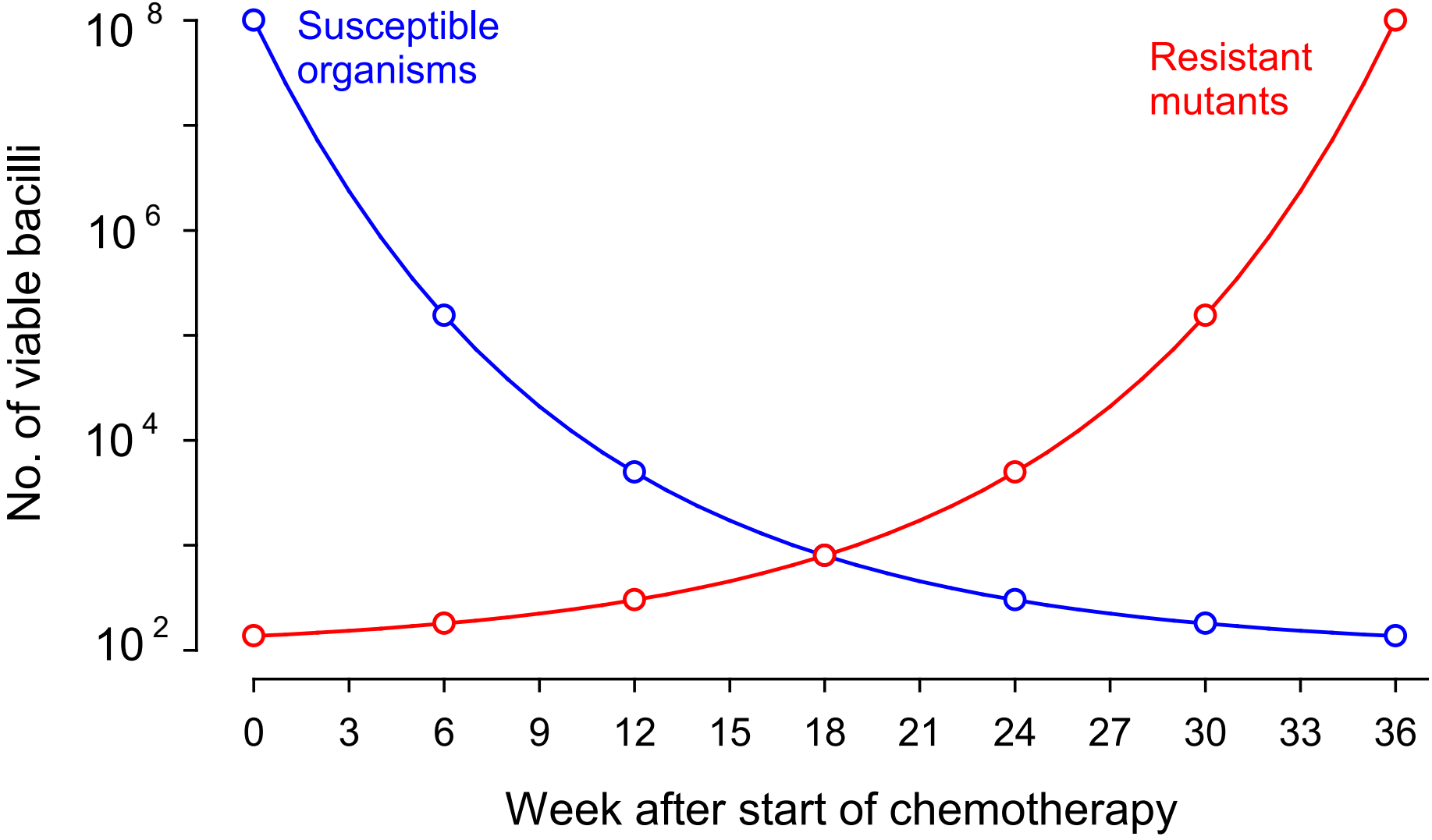
Hans L Rieder

Cumulative percentage of strains resistant to streptomycin, BMRC streptomycin trial, 1947

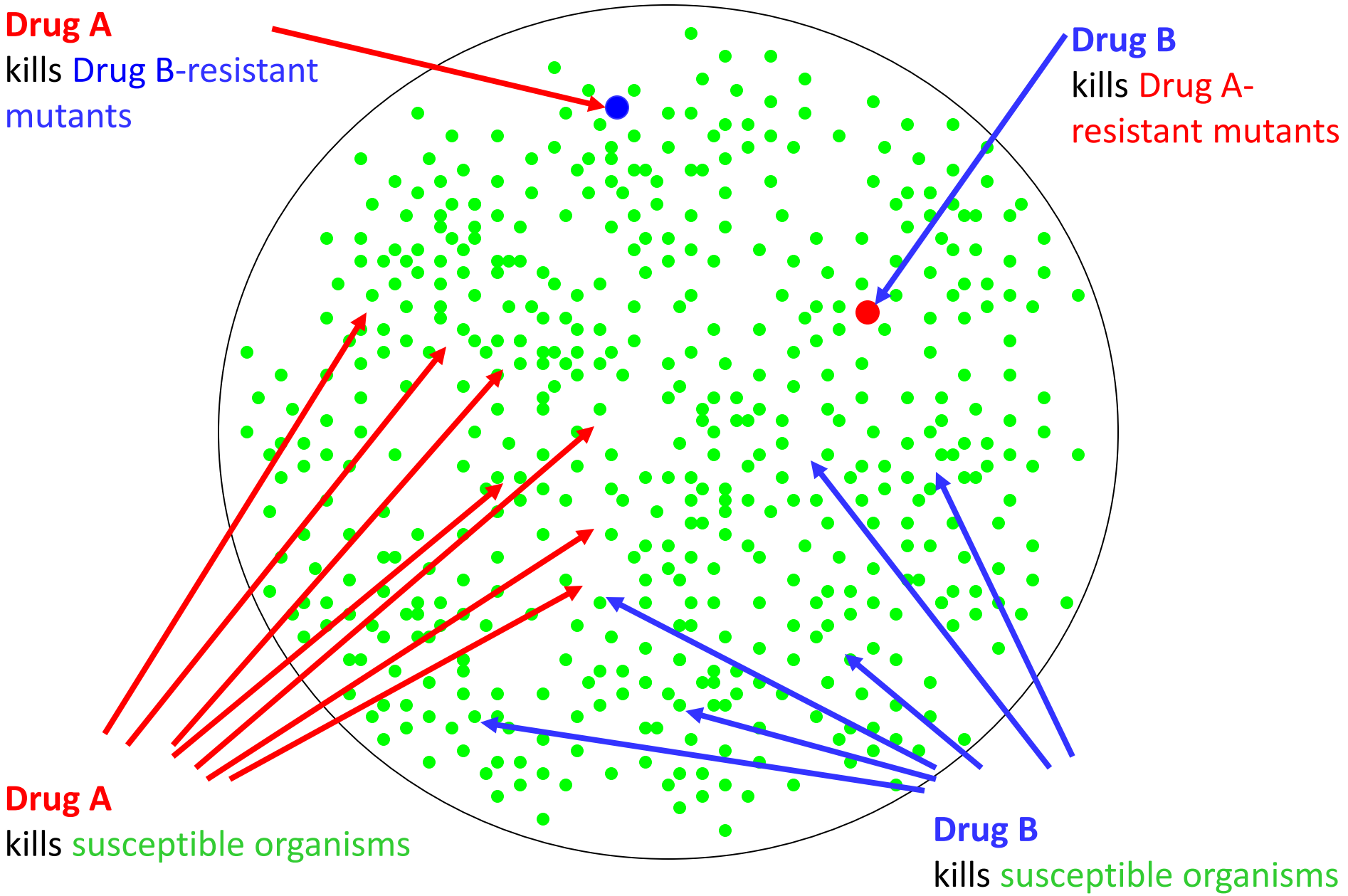


British Medical Research Council. Br Med J 1948;2:769-82

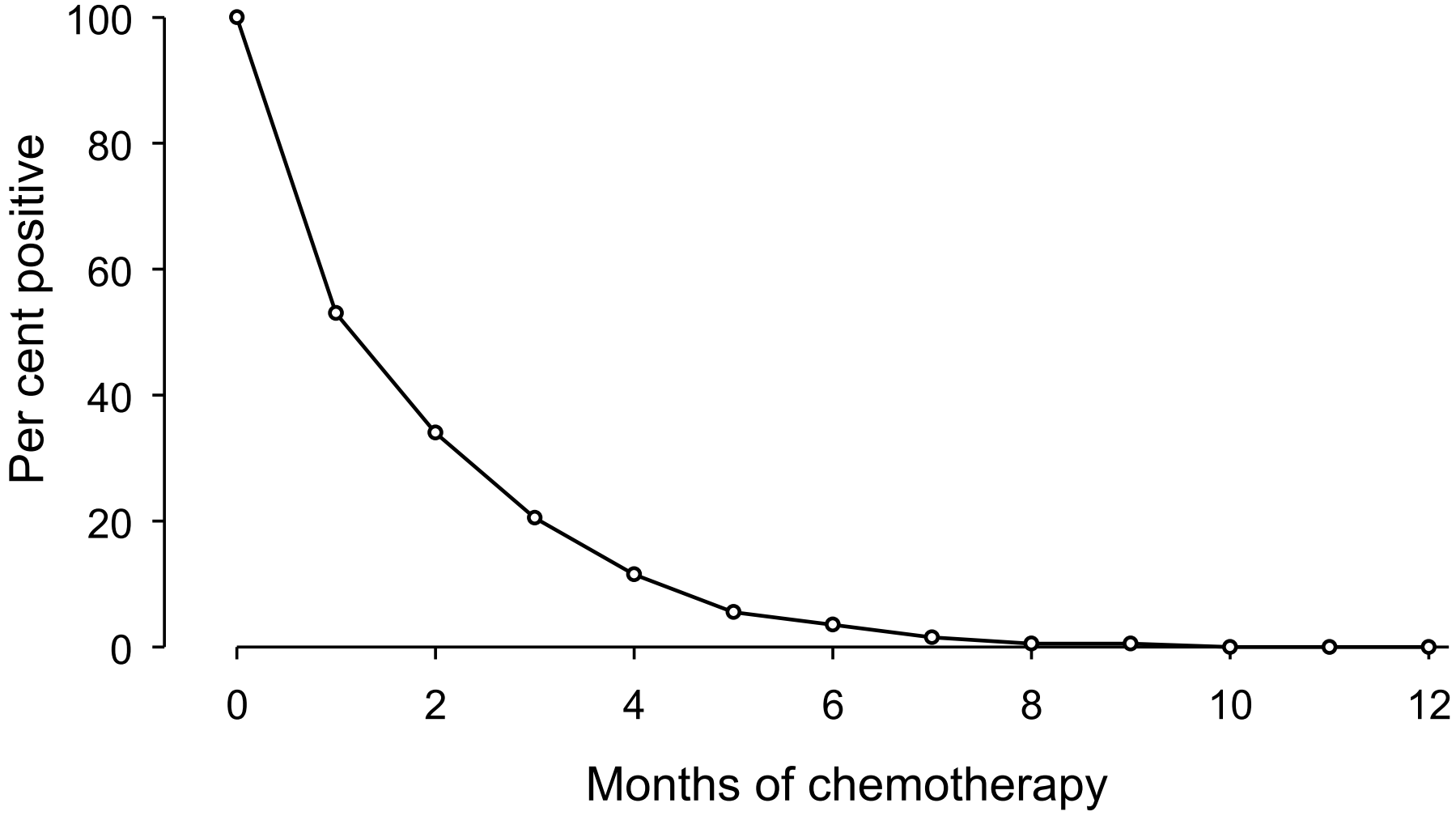
Diagrammatic Representation of the Emergence of Resistance to Isoniazid with Isoniazid - Monotherapy



Modified after Mitchison DA. In: Heaf F, et al. Churchill, London: 1968;Ch 8:160-82


Drug A
kills Drug B-resistant mutants
Drug B
kills Drug A-resistant mutants
Drug A
kills susceptible organisms
Drug B
kills susceptible organisms

Culture conversion of pulmonary tuberculosis in patients with susceptible organisms, receiving SM-INH-PAS



Crofton J. Am Rev Tuberc Pulm Dis 1958;77:869-71

Drug-susceptible tuberculosis is curable with a three-drug combination of isoniazid, streptomycin, and *para*-aminosalicylic acid in 18 months (observational study in Edinburgh, Scotland)

Crofton J. Am Rev Tuberc Pulm Dis 1958;77:869-71

"… it is clear that the bacilli are not eradicated … as a direct consequence of the chemotherapy… …Triple-drug regimens have little place, as judged both on theoretical grounds and from experience in actual trials…"

McDermott W. Bull World Health Organ 1960;23:427-61

Concept of the core drug and its companion drugs in tuberculosis treatment regimens

Core drug

- Contributes most to prevention of failure and relapse
- Is well tolerated and given to every patient throughout treatment
- Without it, the regimen loses substantially or almost entirely its efficacy

Companion drugs

- Ensure that no resistance is acquired by core drug
- Have some essential properties (bactericidal or sterilizing activity)

Van Deun A, et al. Int J Tuberc Lung Dis 2018;22:239-45

The original cascade in Union programs, considering the then worst-case scenario of initial isoniazid resistance, using essential drugs

Among true failures, at point of failure:

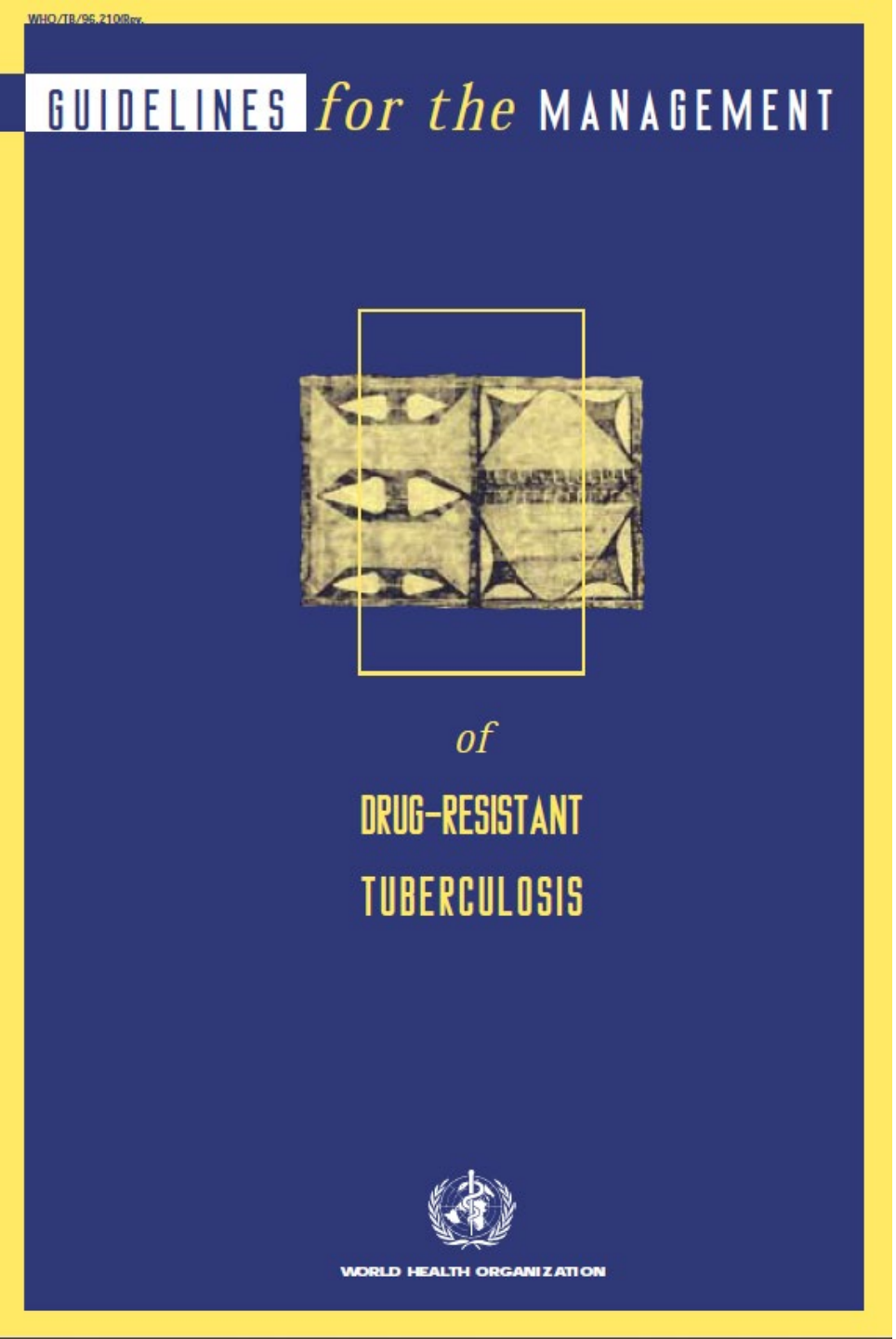
2 S**H**RZ / 6 TH

East African Medical Research Council, British Medical Research Council. Tubercle 1980;61:59-69

Re-treatment regimen:

2 SEH**R**Z / 1 EH**R**Z / 5 HE**R**

Jentgens H, Oberhoffer M, Rouillon A, Styblo K. Tuberculosis guide for high prevalence countries (first edition). Misereor, Aachen 1986:1-56

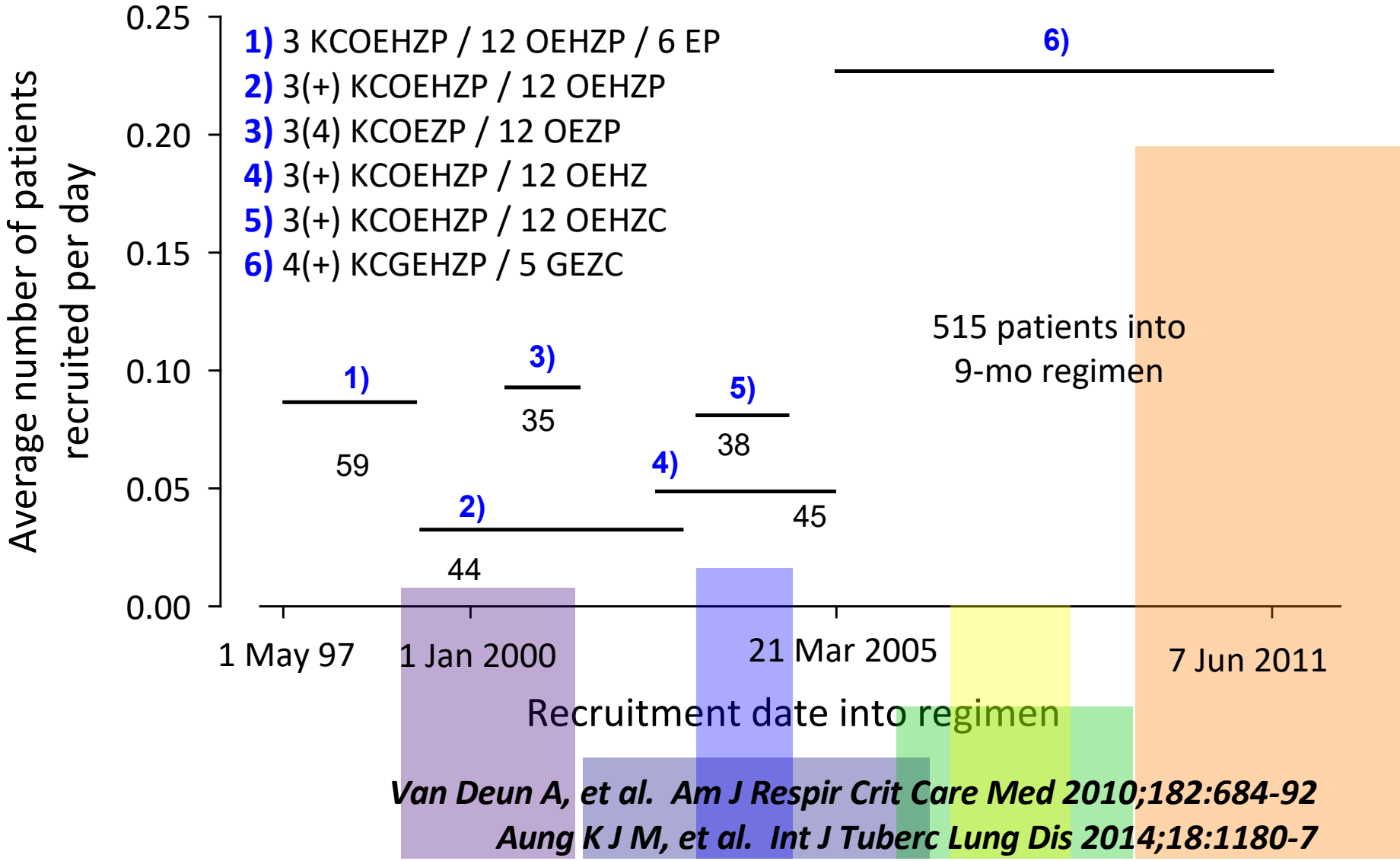


Crofton J, Chaulet P, Maher D, Grosset J, Harris W, Horne N, Iseman M, Watt B.

Guidelines for the management of drug-resistant tuberculosis.

World Health Organization 1997;96.210(Rev. 1):1-40.

Recruitment into sequentially adaptive regimens for MDR tuberculosis, Damien Foundation Projects, Bangladesh

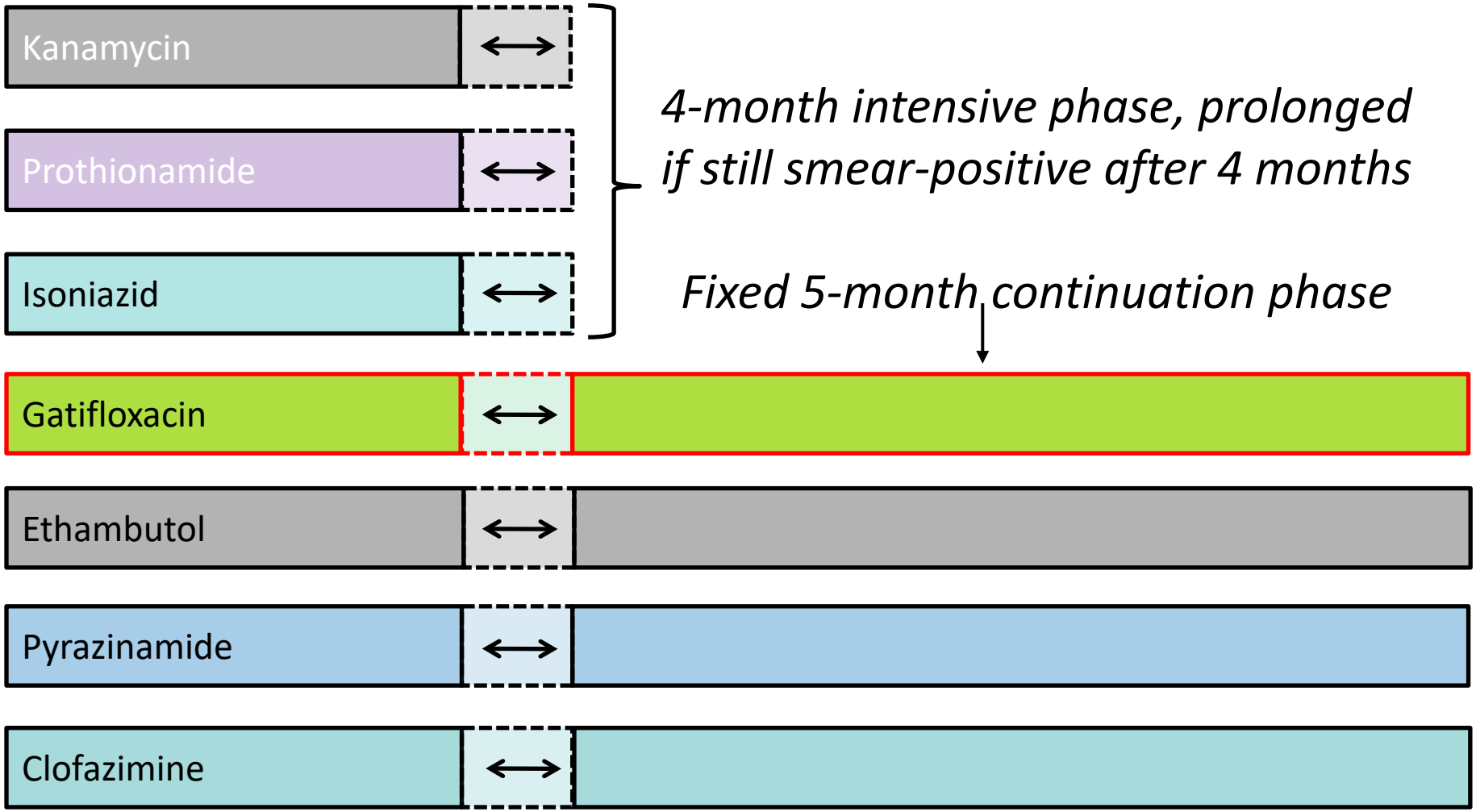


Van Deun A, et al. Am J Respir Crit Care Med 2010;182:684-92

Aung K J M, et al. Int J Tuberc Lung Dis 2014;18:1180-7

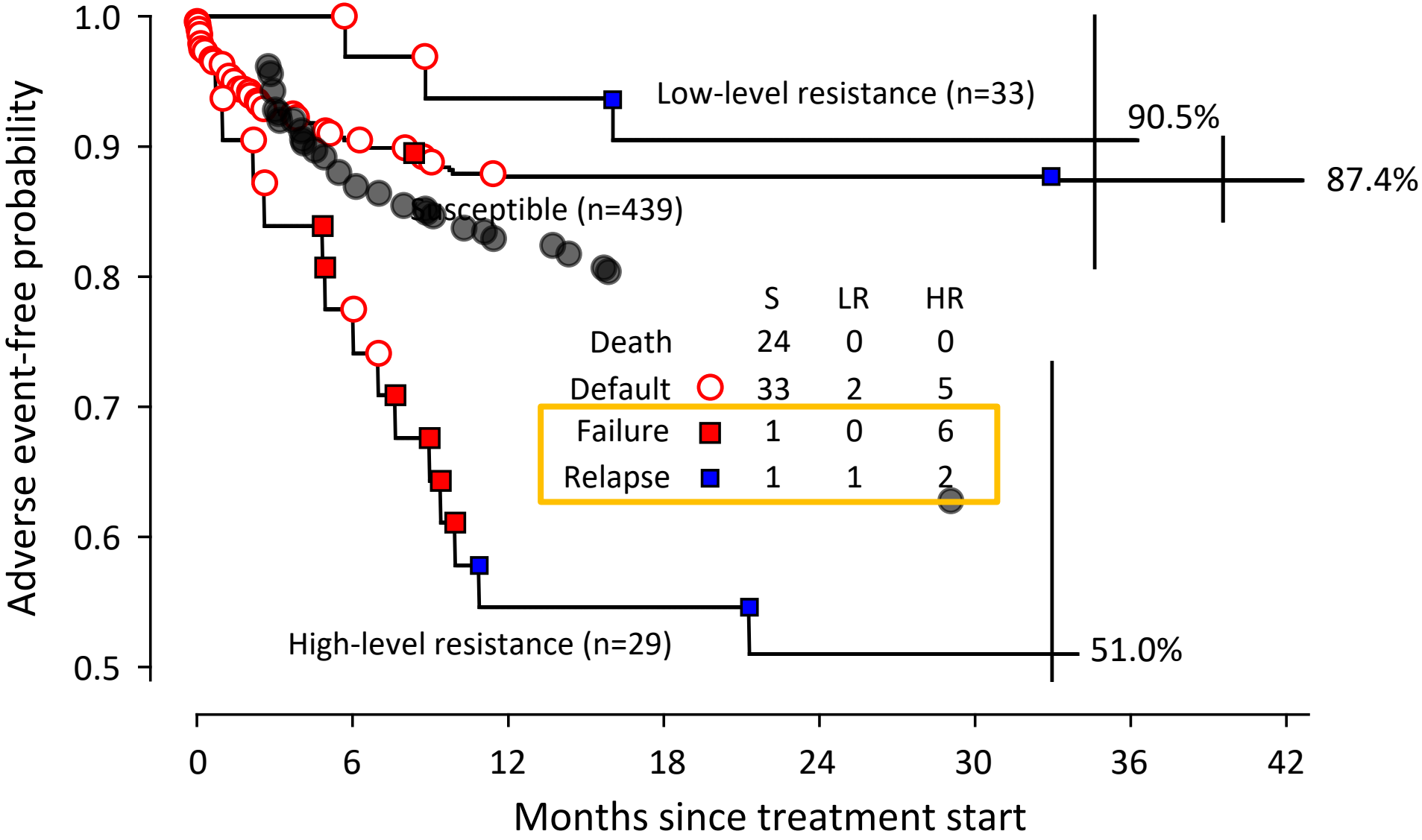
Van Deun A, et al. Unpublished details, October 2014

The (minimum) 9-month regimen for MDR in Bangladesh (220 €)



Aung K J M, et al. Int J Tuberc Lung Dis 2014;18:1180-7

MDR treatment outcome, stratified by fluoroquinolone resistance level, enrolled March 2005 to June 2011, Bangladesh



Aung K J M, et al. Int J Tuberc Lung Dis 2014;10:1180-7

Failures of failures of f…

11 of 515 patients had bacteriological failure (7) or relapse (4):

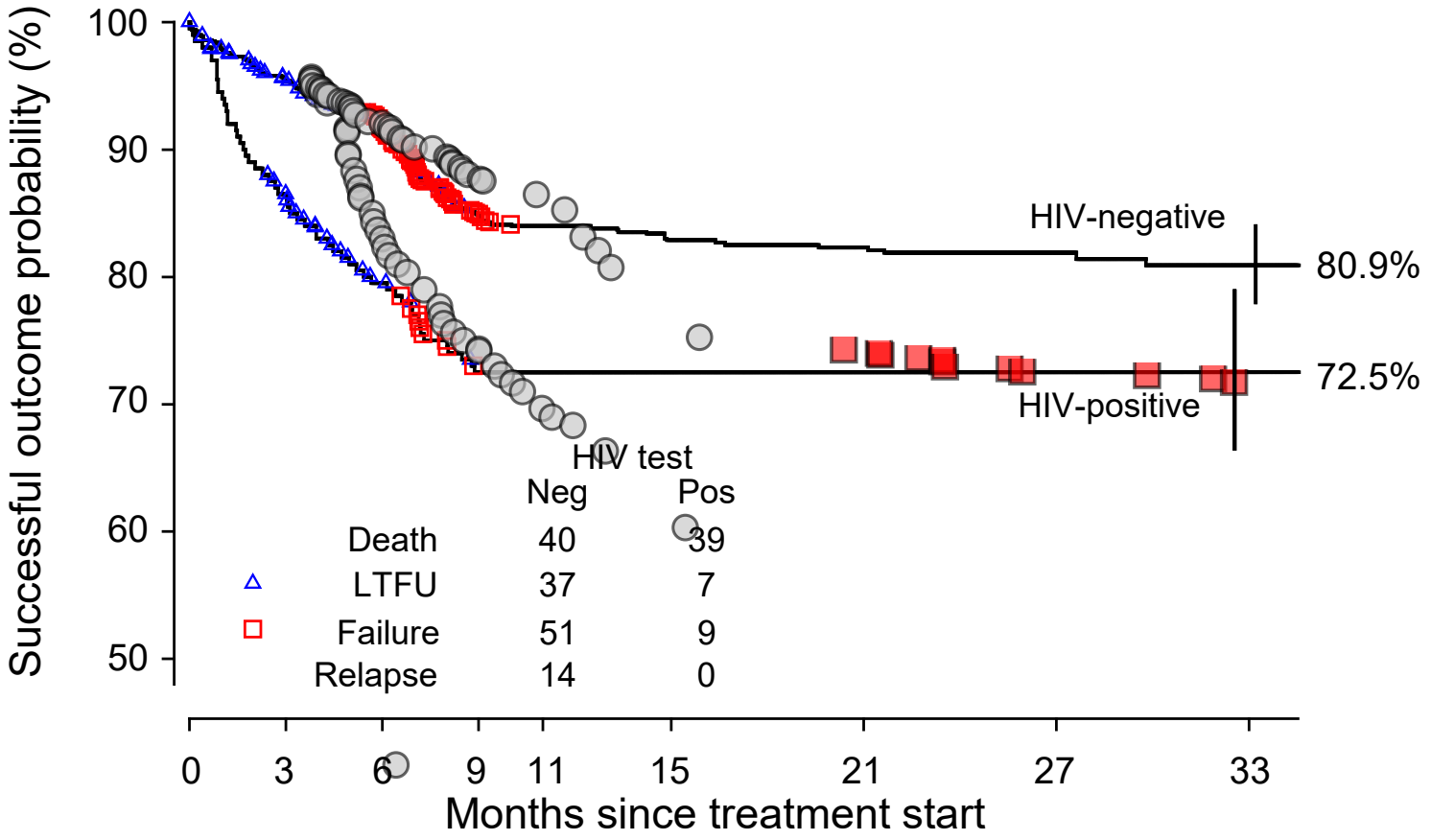
- Only 1 case had acquired drug resistance (to kanamycin) but the strain remained susceptible to amikacin
- 1 case had primary XDR (MDR plus fluoroquinolone- plus aminoglycoside-resistant tuberculosis)
- The above 2 and the other 9 were cured with a repeat treatment of the original regimen or a bedaquiline-containing salvage regimen

=> *Not a single patient in the cohort remained a chronic excreter with MDR or XDR tuberculosis*

Note: Do you know of any other clinical trial that assessed the penultimate epidemiologically relevant outcome of "**Failures of failures of failures of failures**"?

Aung K J M, et al. Int J Tuberc Lung Dis 2014;10:1180-7

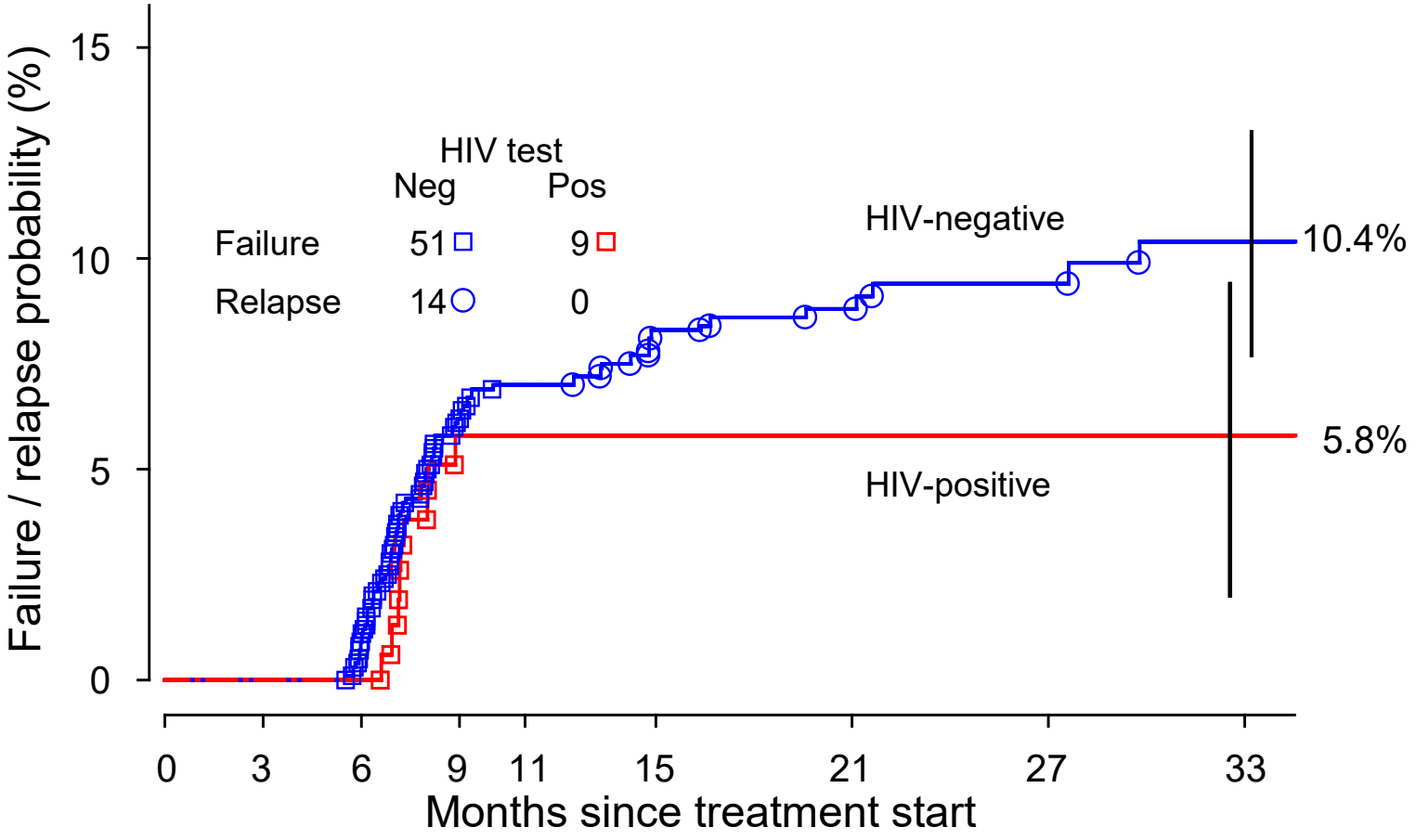
Treatment outcome up to two years after treatment cessation among 1006 patients with rifampicin-resistant tuberculosis, nine African countries



HIV-negative	At risk	806	769	741	667	551	514	381	211	84
	Events	2	37	67	122	128	135	138	140	142
	Censored	0	0	0	17	127	157	287	455	580
HIV-positive	At risk	200	173	159	139	119	118	94	47	22
	Events	1	27	41	55	55	55	55	55	55
	Censored	0	0	0	6	26	27	51	98	123

Schwœbel V, et al. Lancet EClinicalMedicine 2020;20:100268

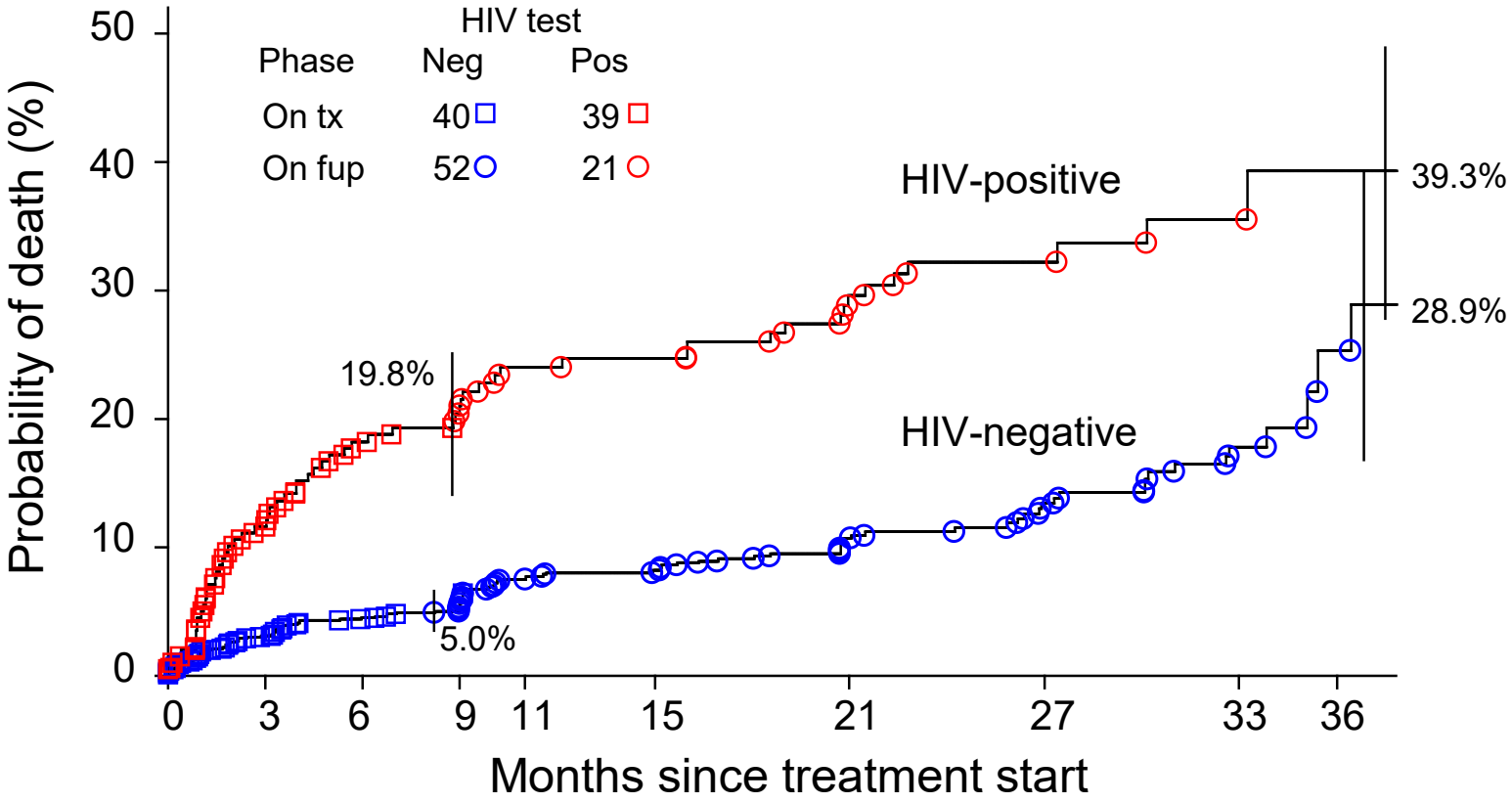
Failure plus relapse probability (all other events censored) among 1006 patients with rifampicin-resistant tuberculosis, nine African countries



HIV-negative	At risk	806	769	741	667	551	514	381	211	84
	Events	0	0	7	46	51	58	61	63	65
	Censored	0	37	58	93	204	234	364	532	657
HIV-positive	At risk	200	173	159	139	119	118	94	47	22
	Events	0	0	0	9	9	9	9	9	9
	Censored	0	27	41	52	72	73	97	144	169

Schwœbel V, et al. Lancet EClinicalMedicine 2020;20:100268

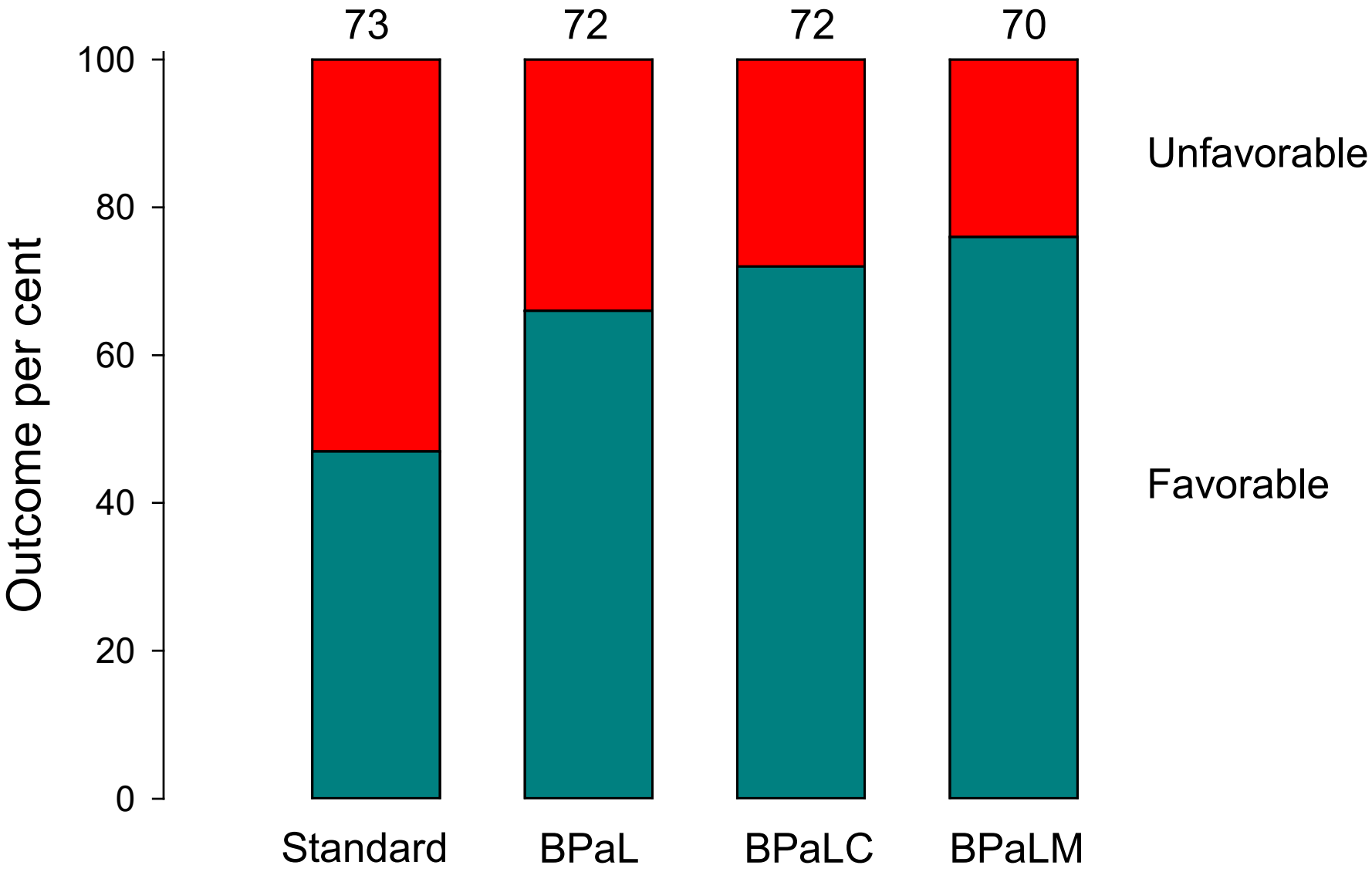
Death probability (all other events censored) among 1006 patients with rifampicin-resistant tuberculosis, nine African countries



	At risk	806	769	741	667	551	514	381	211	84	21
HIV negative	Events	1	25	36	44	56	60	72	80	88	92
	Censored	0	12	29	95	199	232	353	515	634	693
	At risk	200	173	159	139	119	118	94	47	22	4
HIV positive	Events	1	23	36	41	46	47	54	57	59	60
	Censored	0	4	5	20	35	35	52	96	119	136

Schwœbel V, et al. Lancet EClinicalMedicine 2020;20:100268

Intention-to-treat outcome with a 24-wk all-oral BPaL treatment regimen for rifampicin-resistant tuberculosis

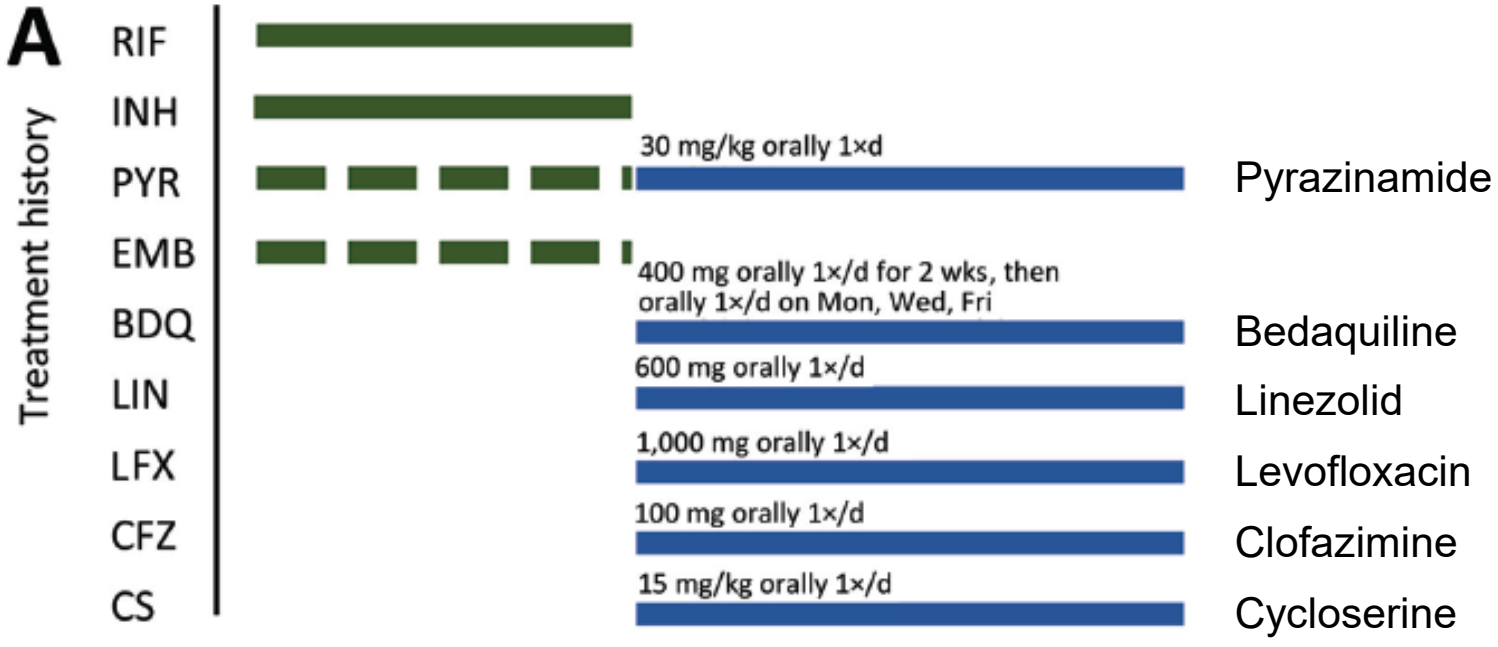


Nyang'wa BT. N Engl J Med 2022;387:2331-43

Put all your eggs in one basket. Then you're less likely to drop that basket

David Haye

https://quotefancy.com/quote/1788097/David-Haye-Put-all-your-eggs-in-one-basket-Then-you-re-less-likely-to-drop-that-basket
Accessed: 16 Oct 2024



B

DST (phenotpyic/genotypic)

RIF	Unknown	R/L430P	R/L430P	Rifampicin
INH	Unknown	R/S315T	R/S315T	Isoniazid
PYR	Unknown	S/WT	S/WT	
EMB	Unknown	R/I306T	R/I306T	
BDQ	ND	**S/WT**	**R/*rv0678* frameshift**	Bedaquiline
LIN	ND	S/WT	S/WT	
FQ	ND	S/WT	S/WT	Clofazimine
CFZ	ND	**S/WT**	**R/*rv0678* frameshift**	
CS	ND	S/WT	S/WT	
AMI	ND	S/WT	S/WT	

Günther G, et al
Emerg Infect Dis
2024;30:568-71

The temptation of a “pan-tuberculosis” regimen (one regimen for both drug-susceptible and -resistant tuberculosis)

Example: Cevik M, et al (funding: TB Alliance): 4mo for susceptible or 6mo for resistant tuberculosis of a BPaMZ regimen vs the current international standard 2 RHEZ / 4 RH regimen for drug-susceptible tuberculosis: *Lancet Infect Dis 2024;24:1003-14*.

The experimental regimen:

- met the primary efficacy endpoint of sputum culture conversion at 8 weeks
- did not meet the secondary efficacy endpoint of unfavorable treatment outcome at 52 weeks due to an excess of adverse drug events (drug-induced liver injury)

Basic principles

Resistant mutants are only selected by a drug taken (selection pressure)

=> Do not risk losing a core drug by giving it unless needed (a “pan-tuberculosis” regimen does that by definition)

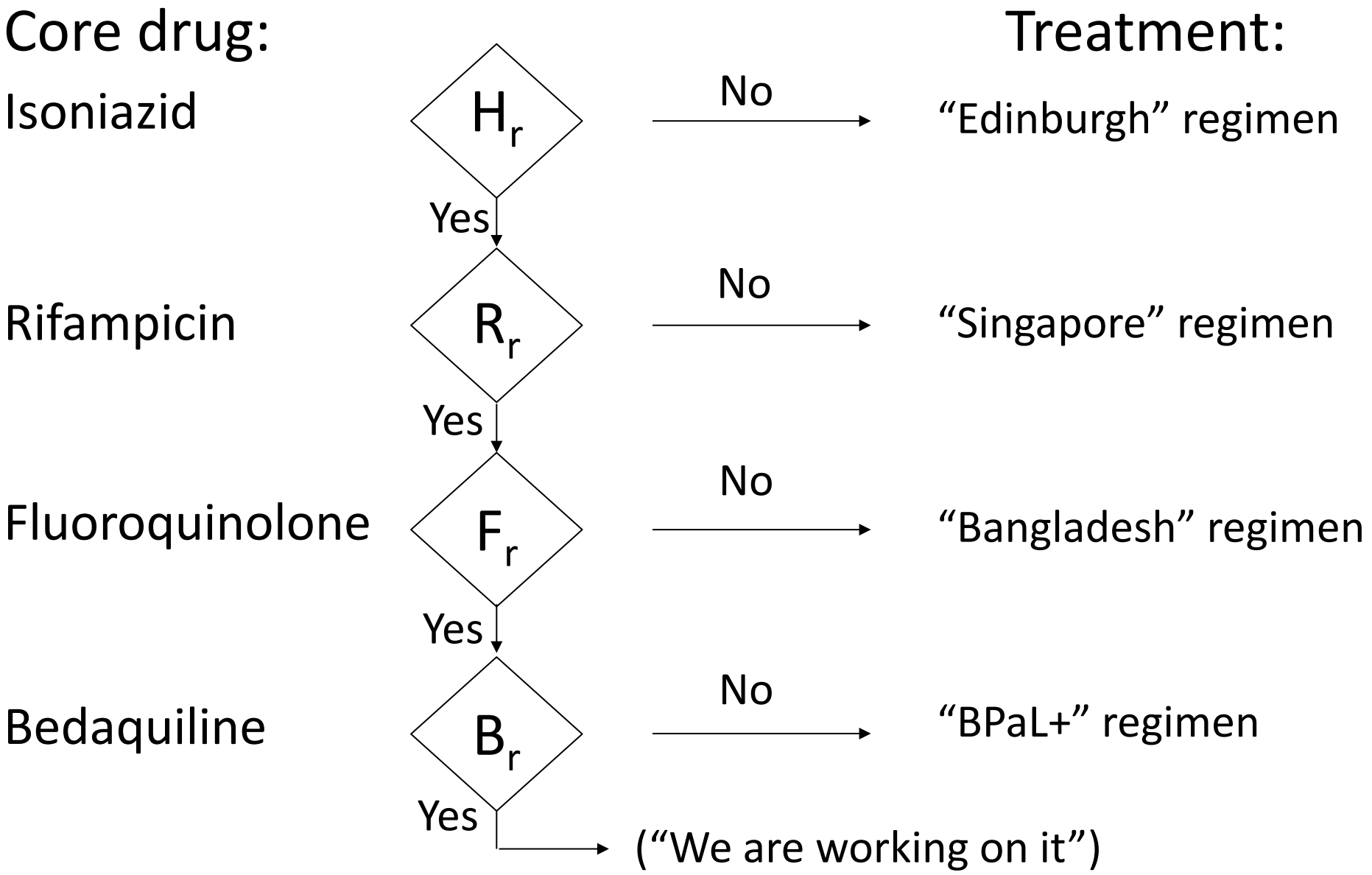
A standardized, clinical-trial-tested regimen is a solid basis

=> “Personalized medicine” in tuberculosis chemotherapy has mostly been an euphemism for a chaotic approach. It should be reserved for “salvage regimens” when no standardized approach has (yet) been defined.

Solution to both challenges:

=> Cascade of regimens approach

Allow patients to fail treatment: Cascade of regimens



Or is it?

Allow patients to fail treatment: Cascade of regimens