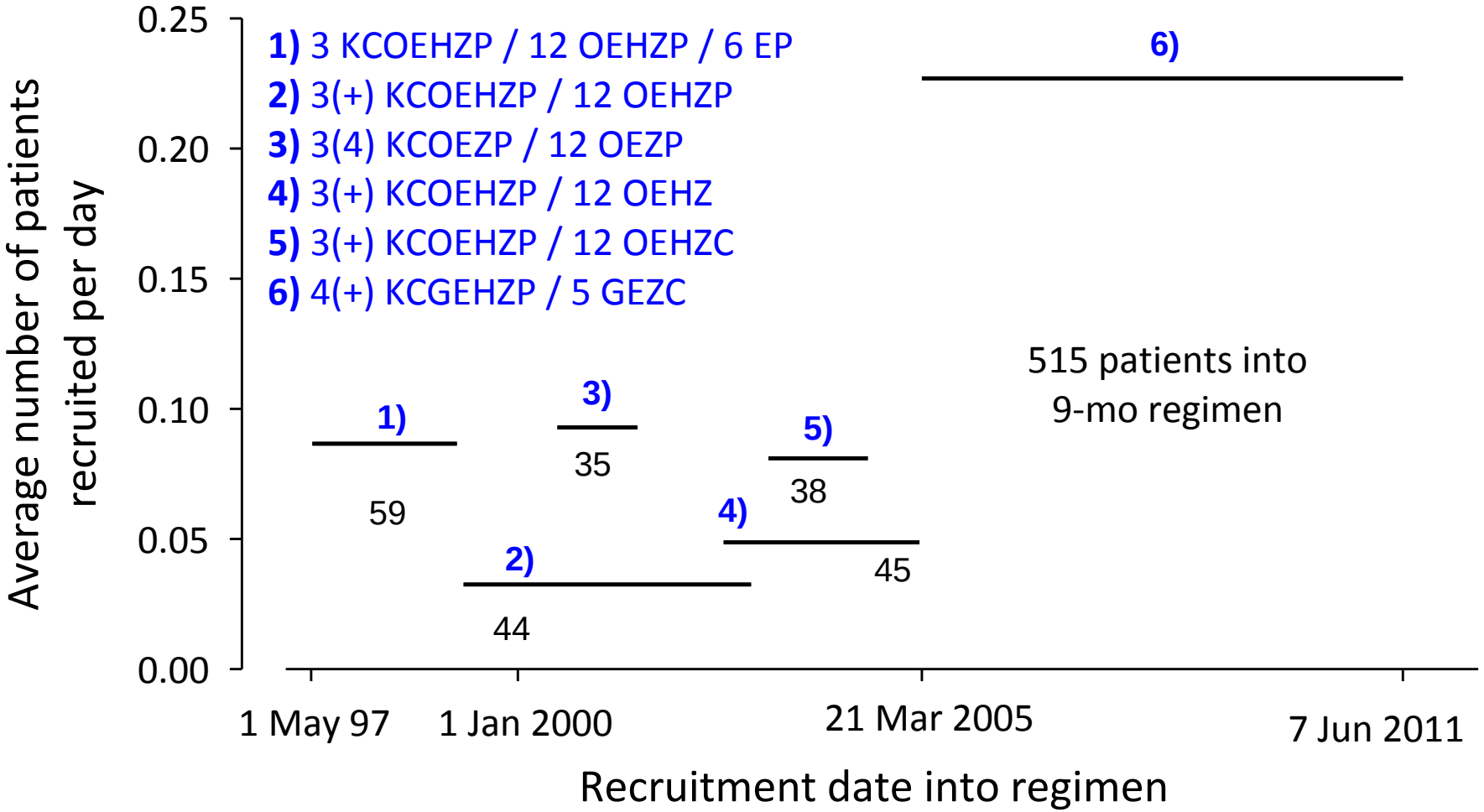
Successful MDR-TB treatment regimens – are 9 months long enough?

Hans L Rieder

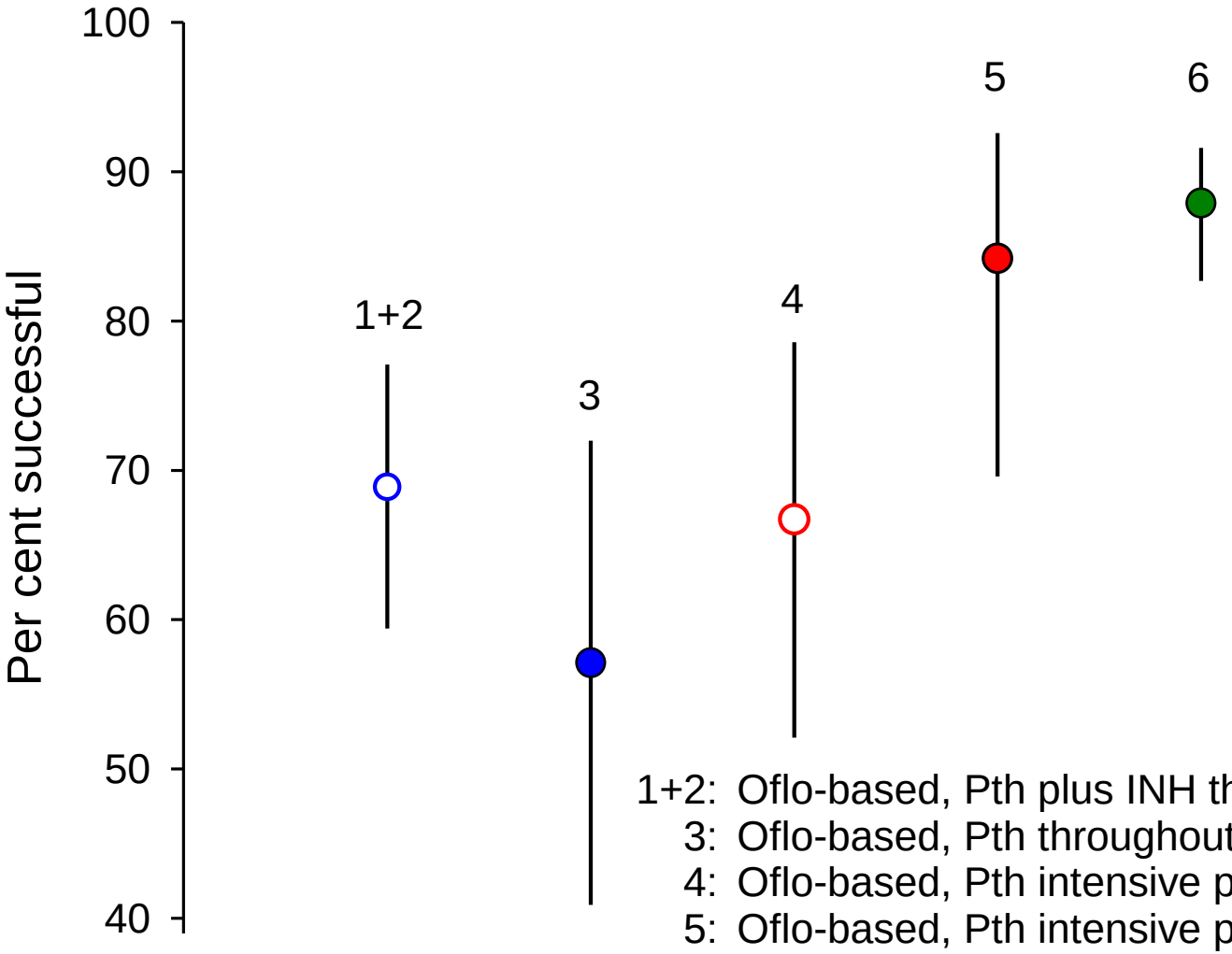
Magglingen / Macolin, 23 March 2017

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, Rieder HL. Unpublished details

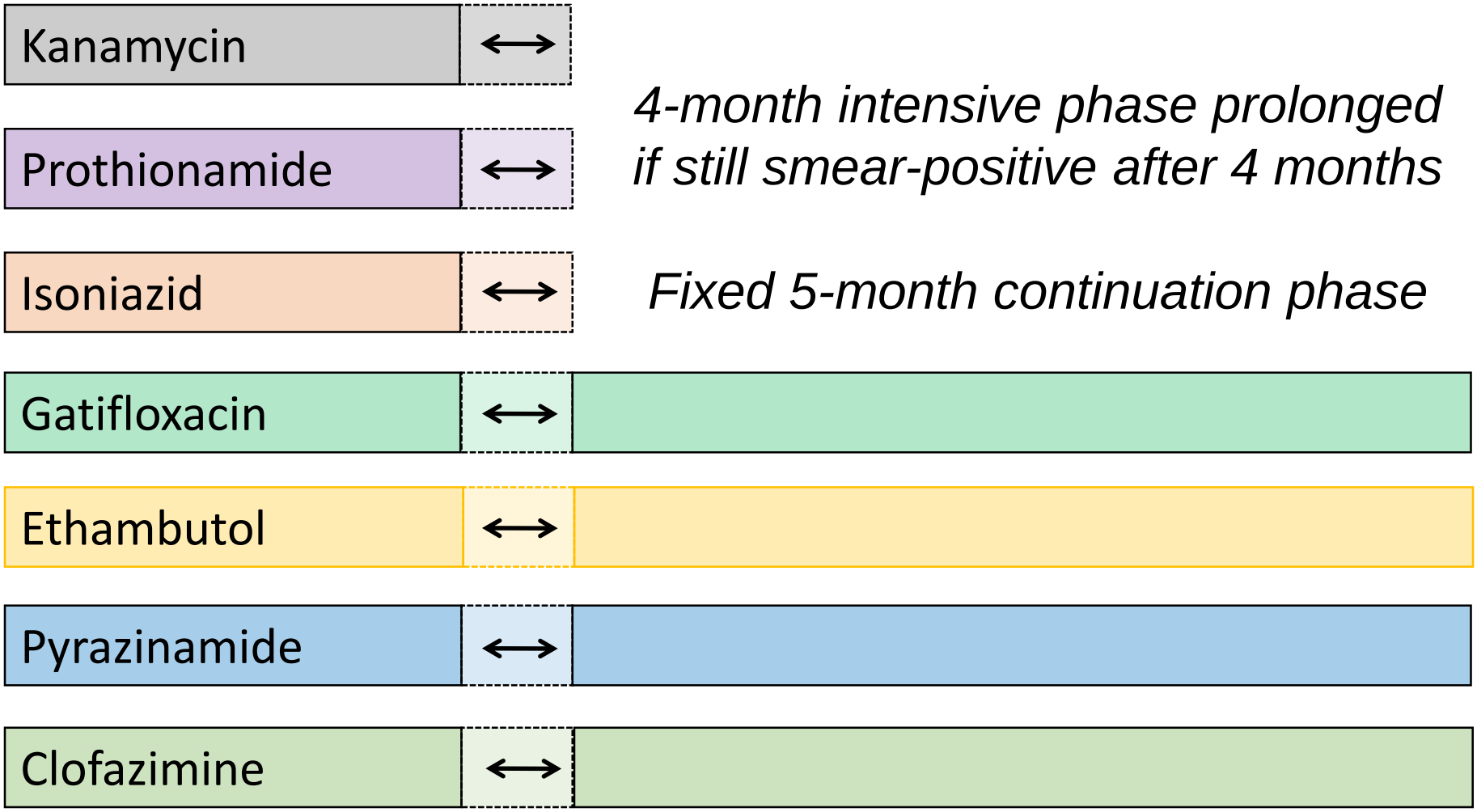
Proportion with successful treatment outcome with the six sequential MDR treatment regimens, Damien Foundation projects, Bangladesh



1+2: Oflo-based, Pth plus INH throughout
3: Oflo-based, Pth throughout, no INH
4: Oflo-based, Pth intensive phase, INH throughout
5: Oflo-based, Pth intensive phase, INH and Clo throughout
6: Gati-based, Pth and INH intensive phase, Clo throughout

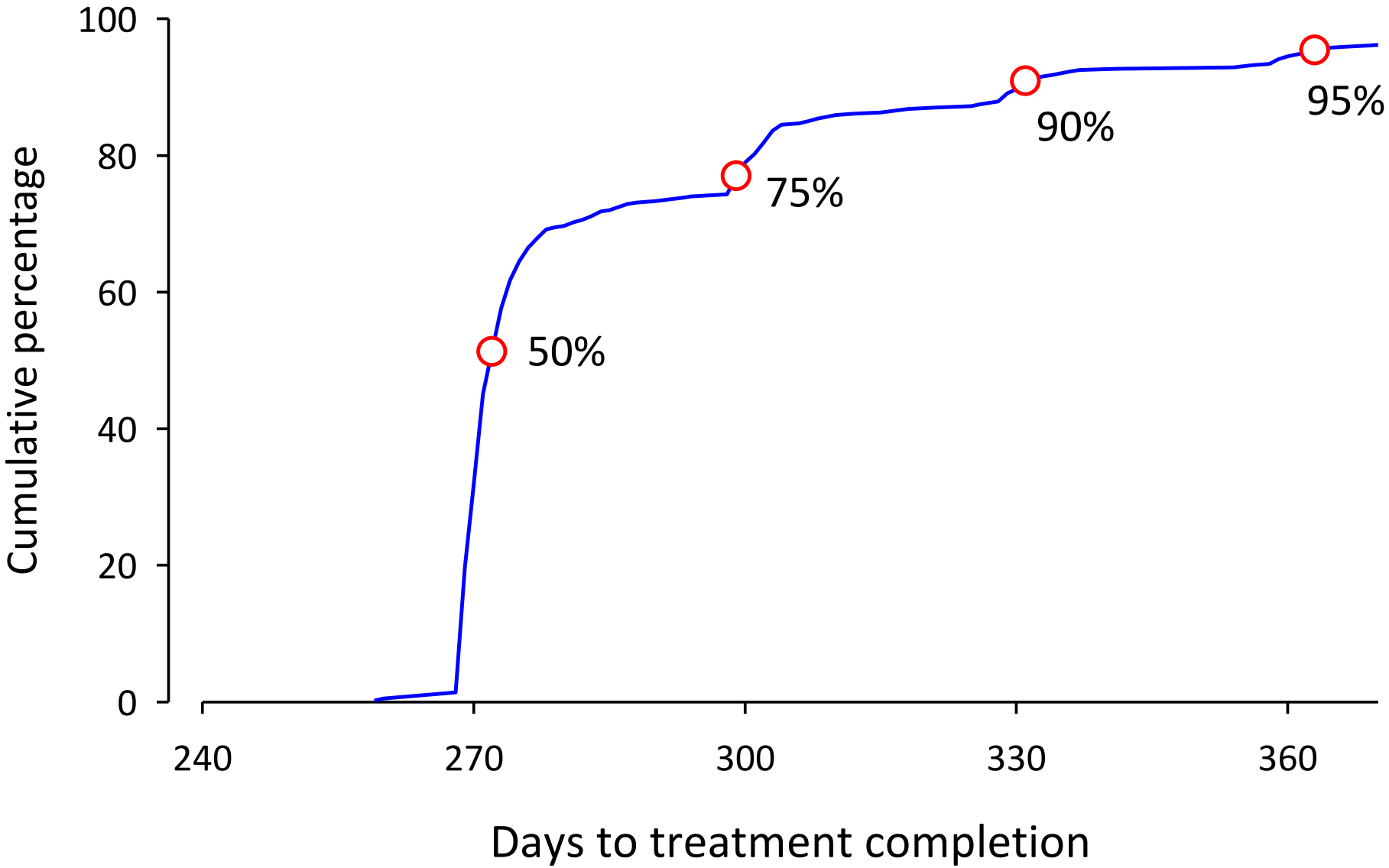
Van Deun A, et al. Am J Respir Crit Care Med 2010;182:684-92

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



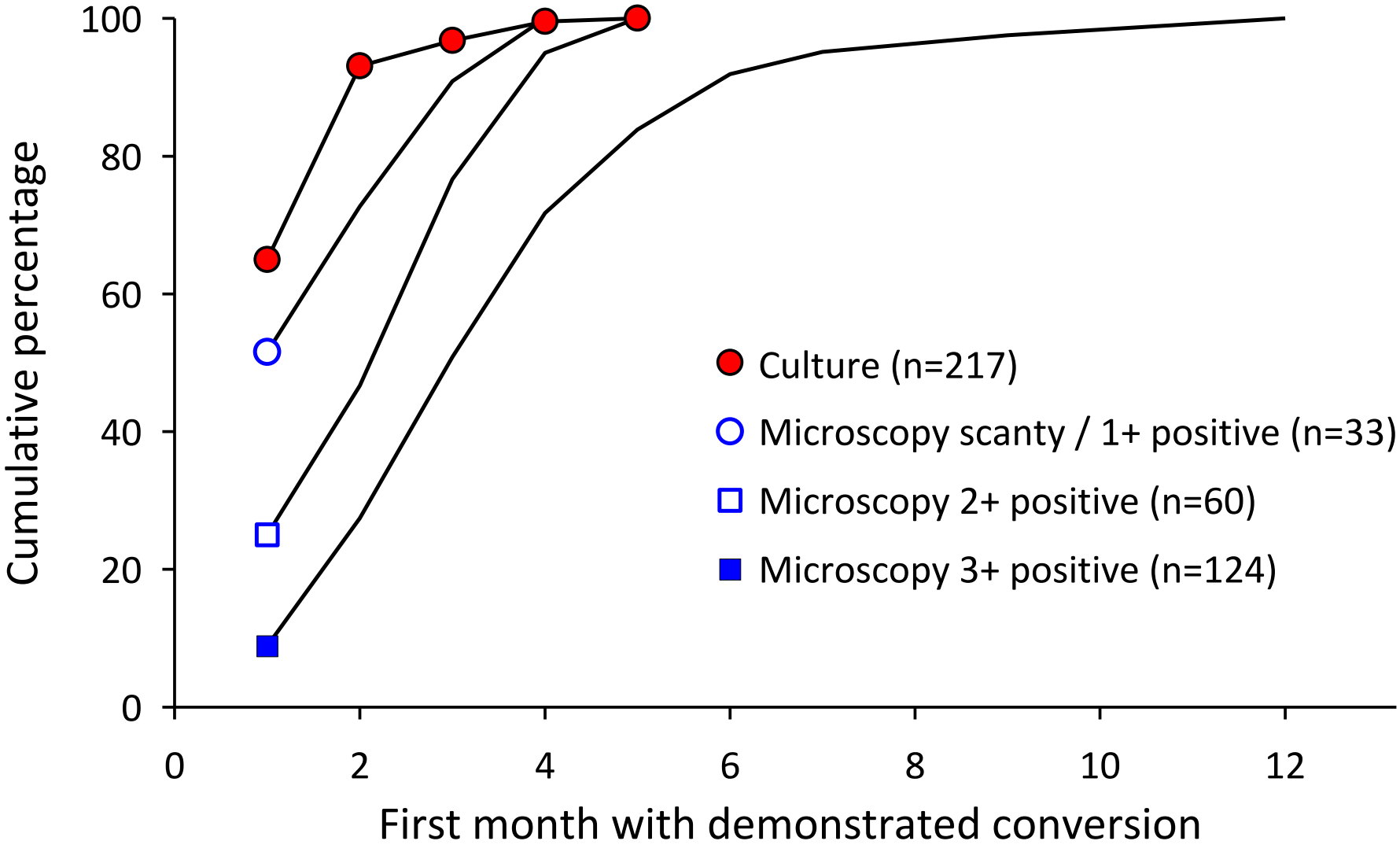
Aung K J M, et al. Int J Tuberc Lung Dis 2014;18:1180-7

Time to completion of MDR treatment among 439 patients without unfavorable event during treatment, Bangladesh



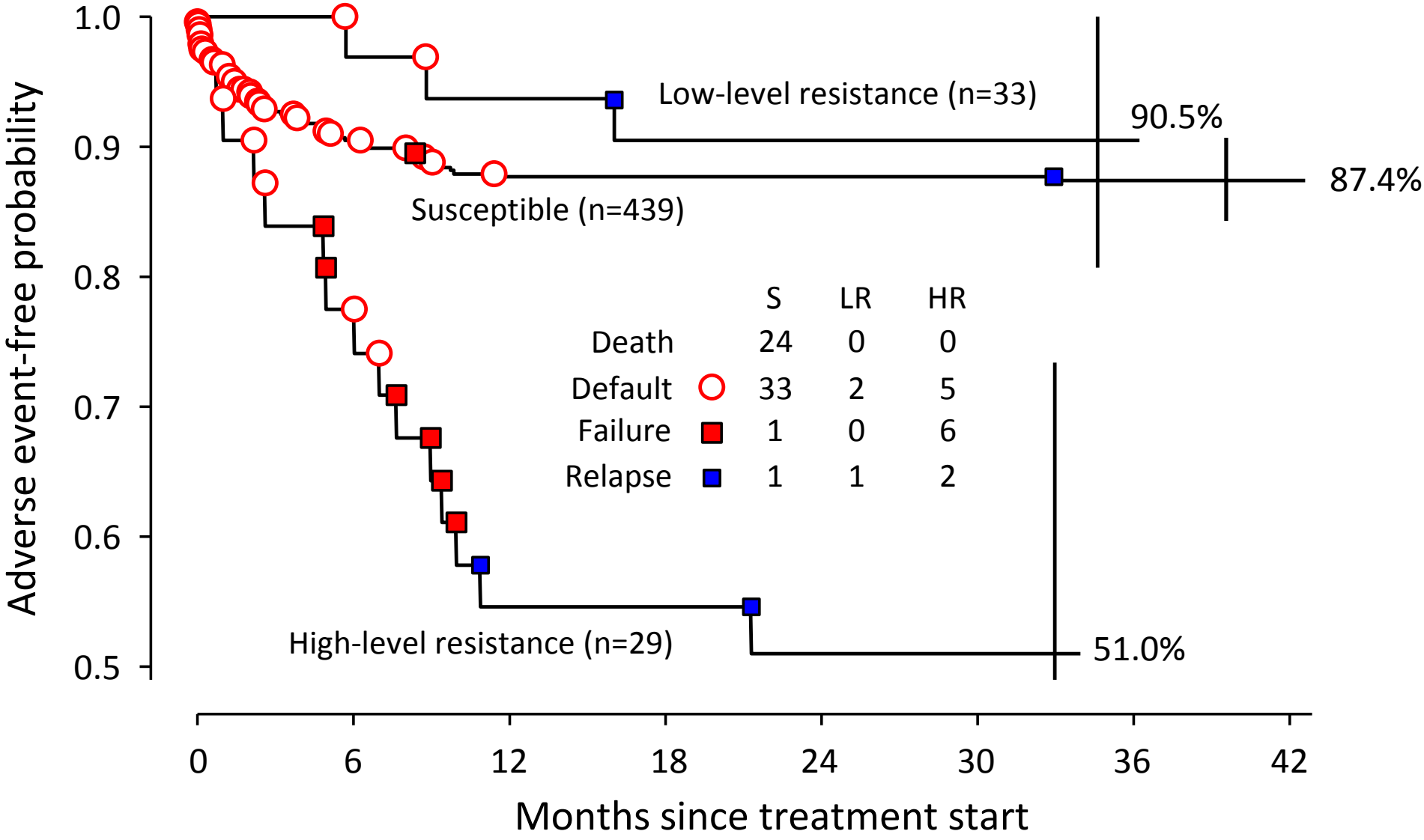
Aung K J M, et al. Int J Tuberc Lung Dis 2014;18:1180-7

Cumulative proportion of patients on MDR treatment with conversion by culture and microscopy, Bangladesh, 2005-2011



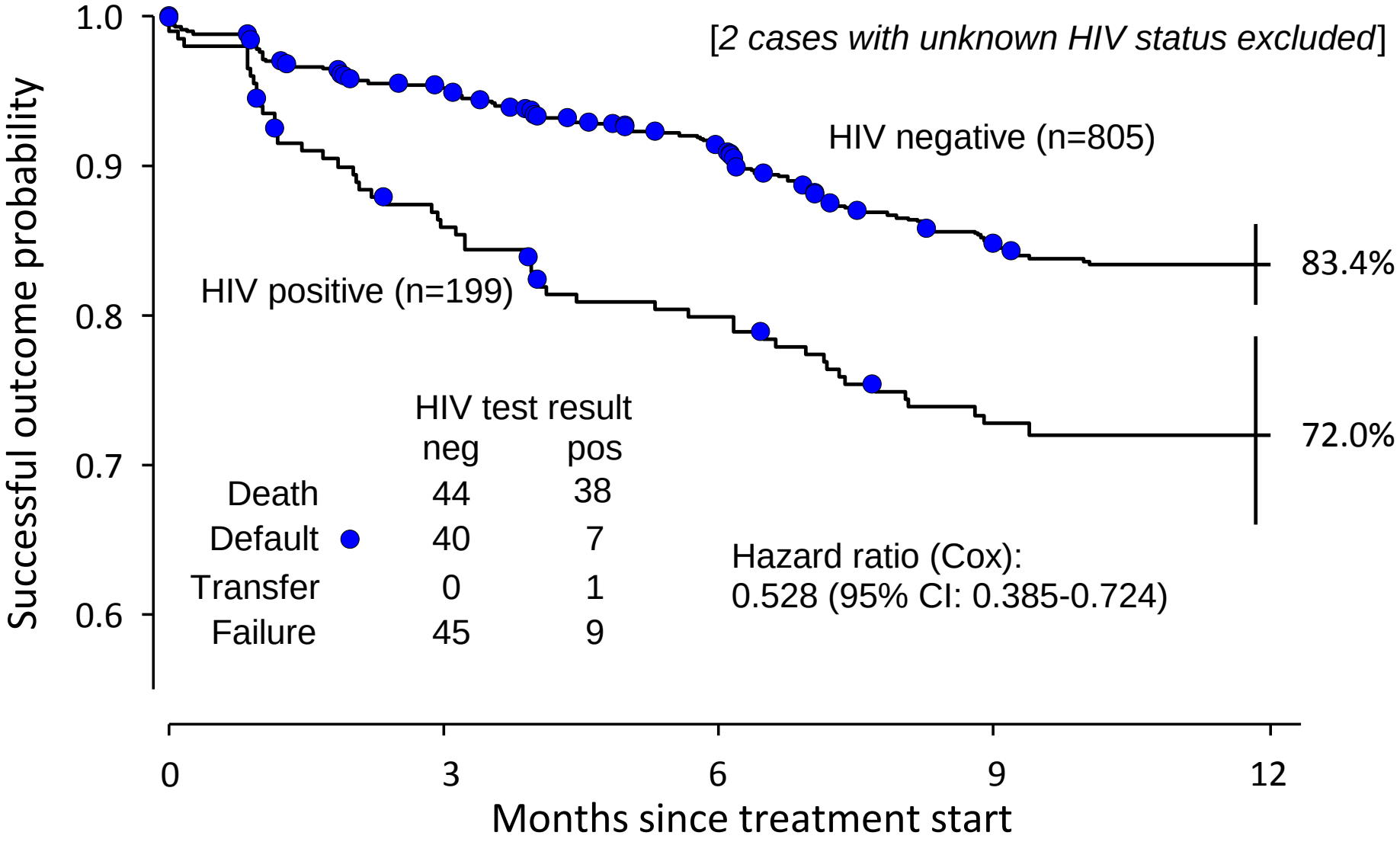
Aung K J M, et al. Int J Tuberc Lung Dis 2014;18:1180-7

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



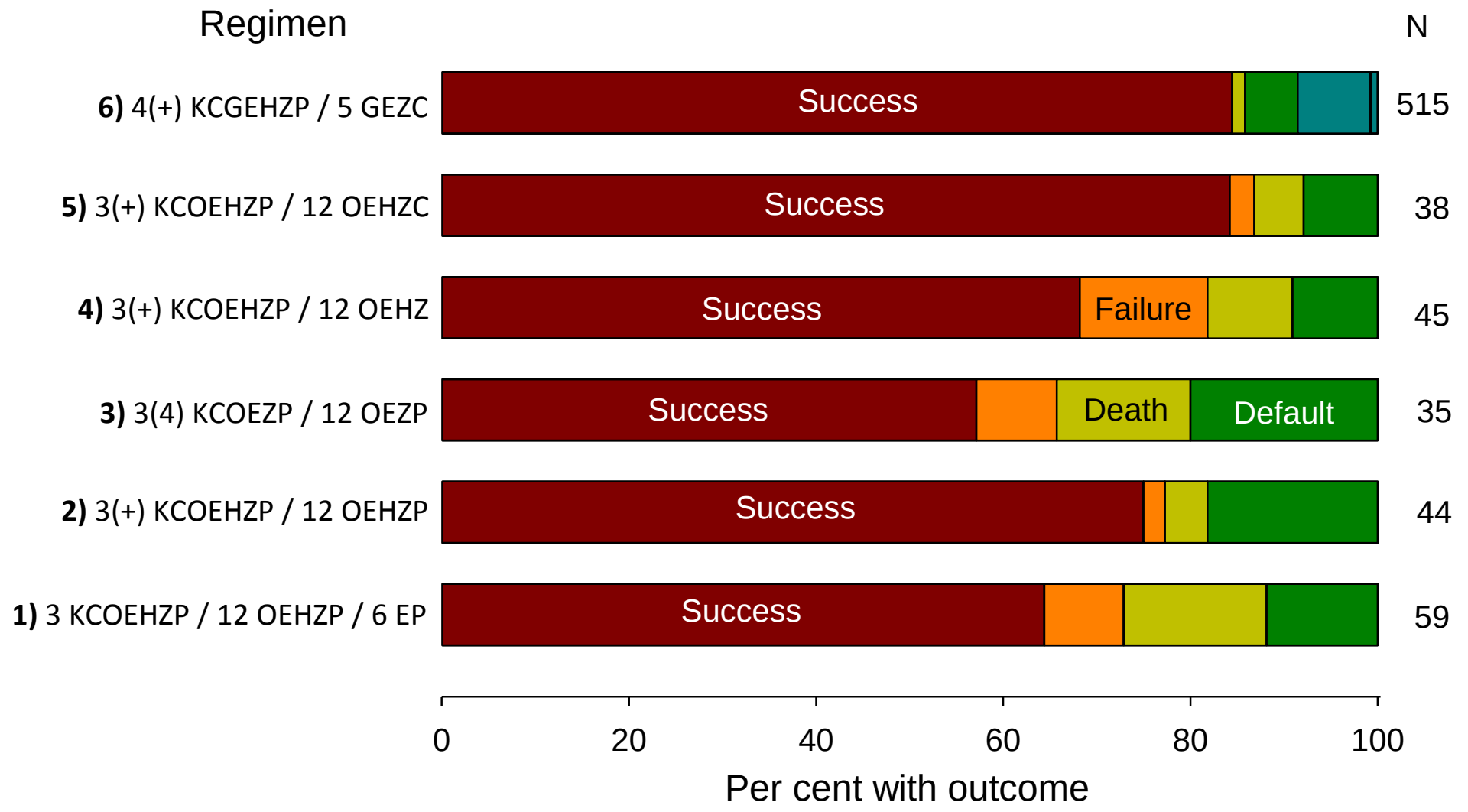
Aung K J M, et al. Int J Tuberc Lung Dis 2014;10:1180-7

Kaplan-Meier successful MDR on-treatment outcome probability, Africa, enrolled through April 1, 2015



Trébucq A, et al. Preliminary analysis of unpublished data Union World Conference, Liverpool, Oct 2016

Treatment outcome with 6 sequential MDR regimens, Bangladesh, 1997-2011

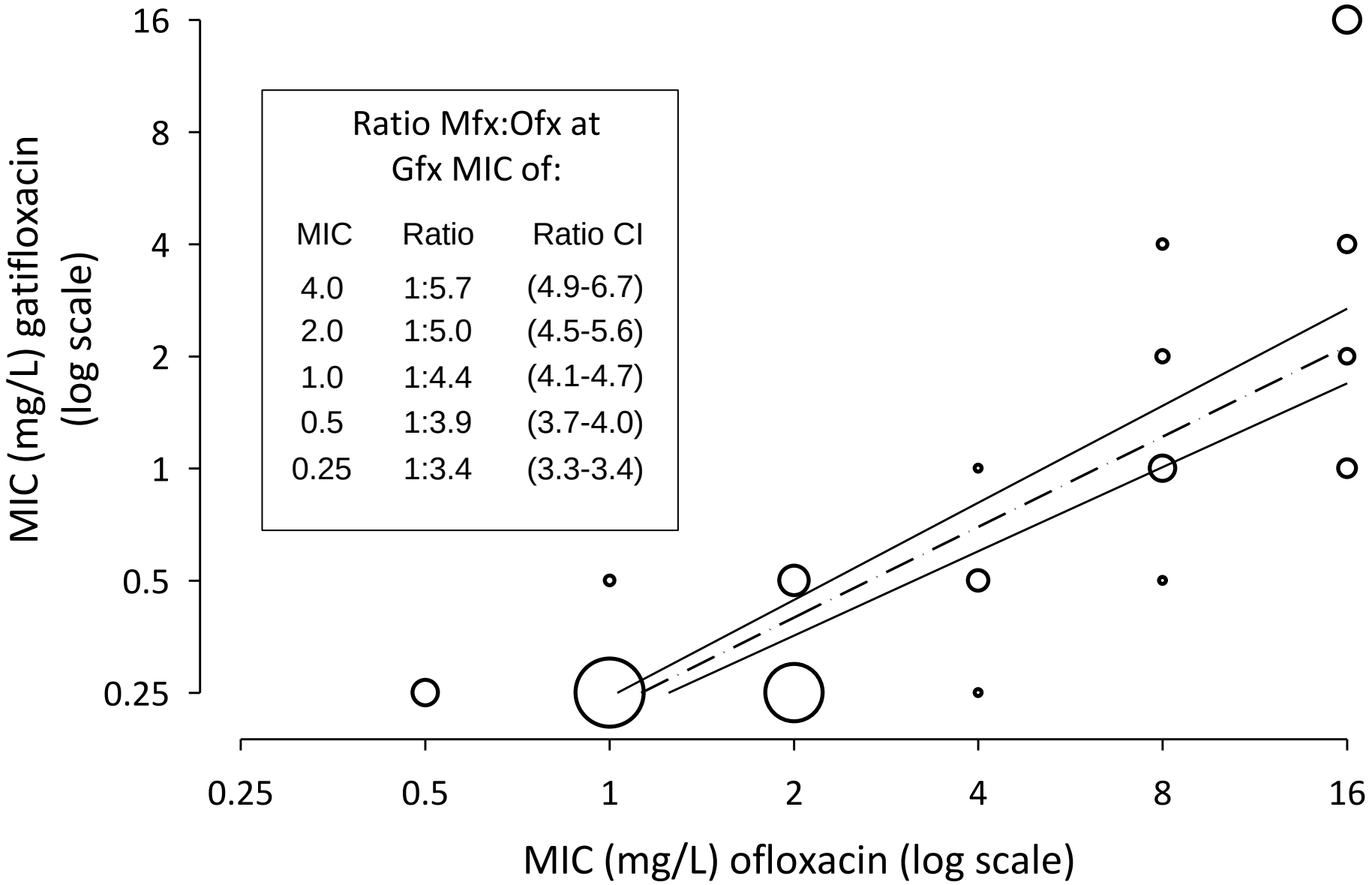


Van Deun A, et al. Am J Respir Crit Care Med 2010;182:684-92
Aung K J M, et al. Int J Tuberc Lung Dis 2014;18:1180-7

Drugs in the regimen and rationale for their use and high dosage where applicable

- High-dose [400-800 mg] gatifloxacin
- Thioamide plus high-dose [300-600 mg] isoniazid
- Pyrazinamide
- Ethambutol
- Clofazimine
- Kanamycin

MIC of ofloxacin versus gatifloxacin for *M tuberculosis*

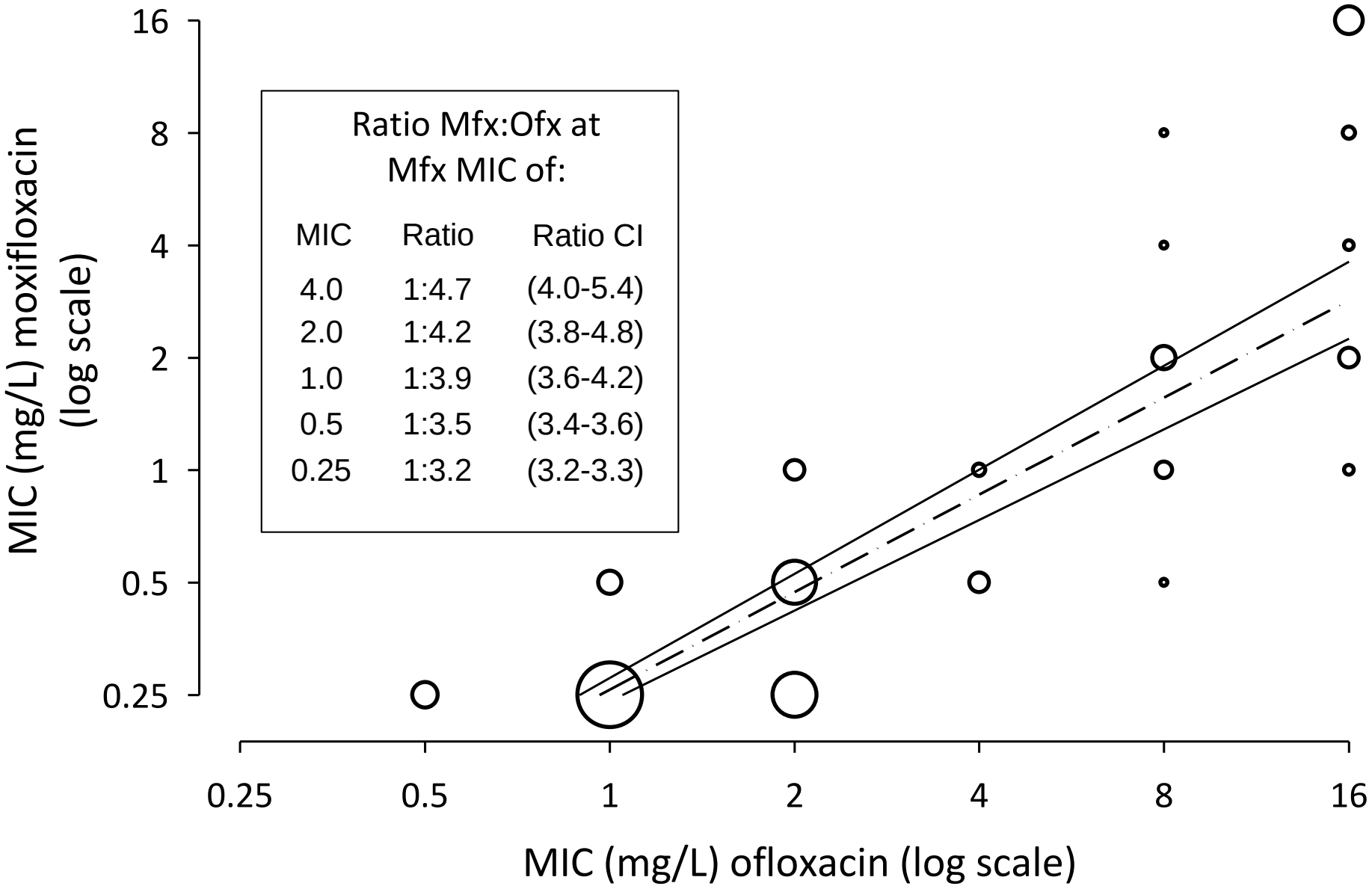


Ratio Mfx:Ofx at Gfx MIC of:

MIC	Ratio	Ratio CI
4.0	1:5.7	(4.9-6.7)
2.0	1:5.0	(4.5-5.6)
1.0	1:4.4	(4.1-4.7)
0.5	1:3.9	(3.7-4.0)
0.25	1:3.4	(3.3-3.4)

Rigouts L, et al. J Antimcrob Chemother 2016;71:314-23

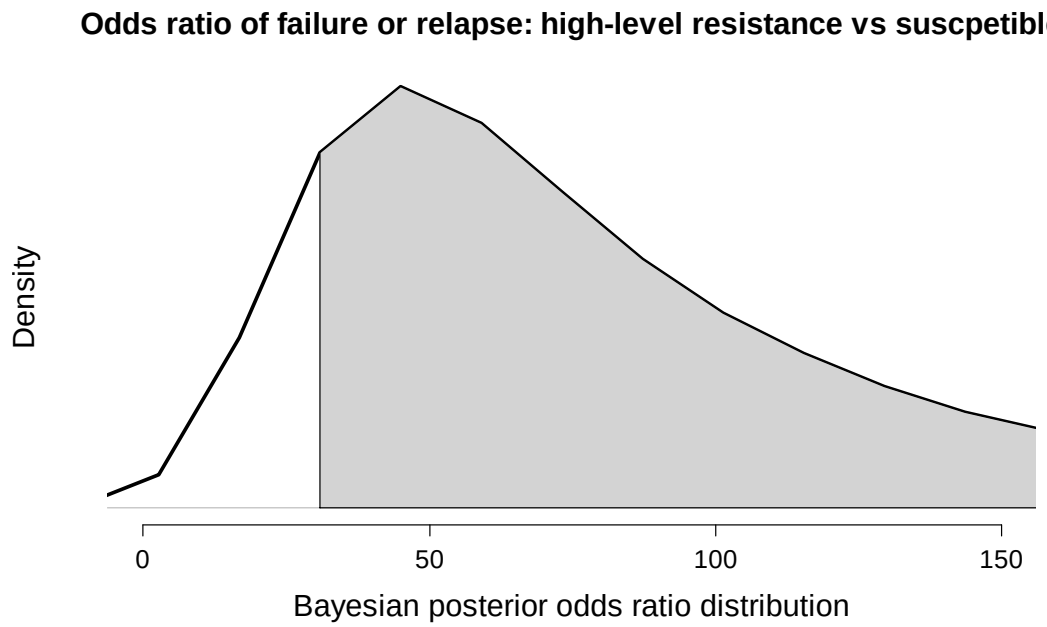
MIC of ofloxacin versus moxifloxacin for *M tuberculosis*



Rigouts L, et al. J Antimcrob Chemother 2016;71:314-23

Bangladesh results to the point: study offers internally an indirect, unbiased estimator of efficacy

By fluoroquinolone-resistance	Failure or relapse	Total in cohort
High-level resistance	8 (27.6% [13.4-47.4])	29
Susceptible or low-level resistance	3 (0.6% [0.2-2.0])	472



Mutations in *katG* gene

Mid-level / high-level resistance

Mutations in *inhA* gene

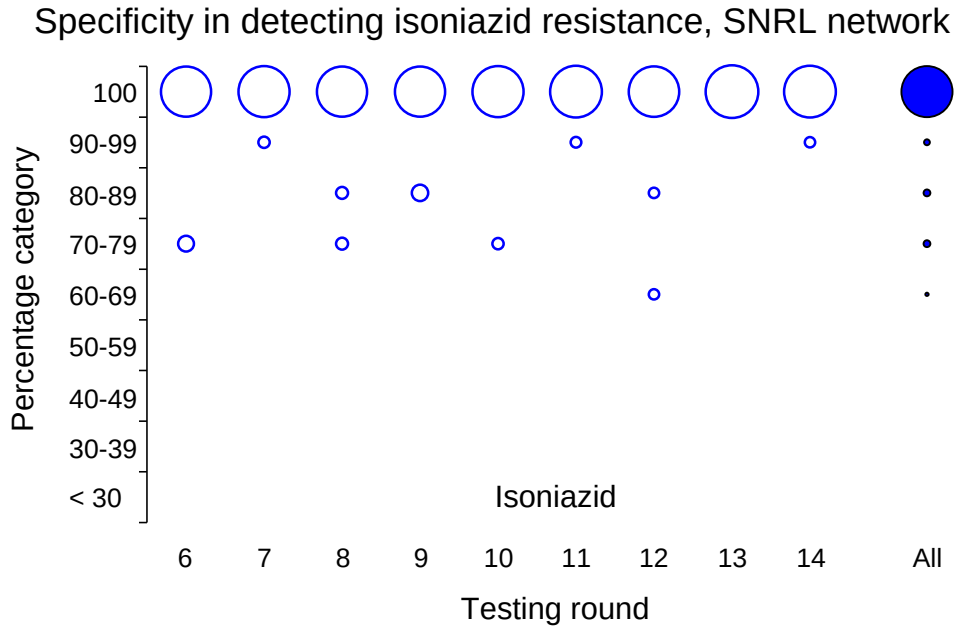
Low-level resistance

Isoniazid resistance

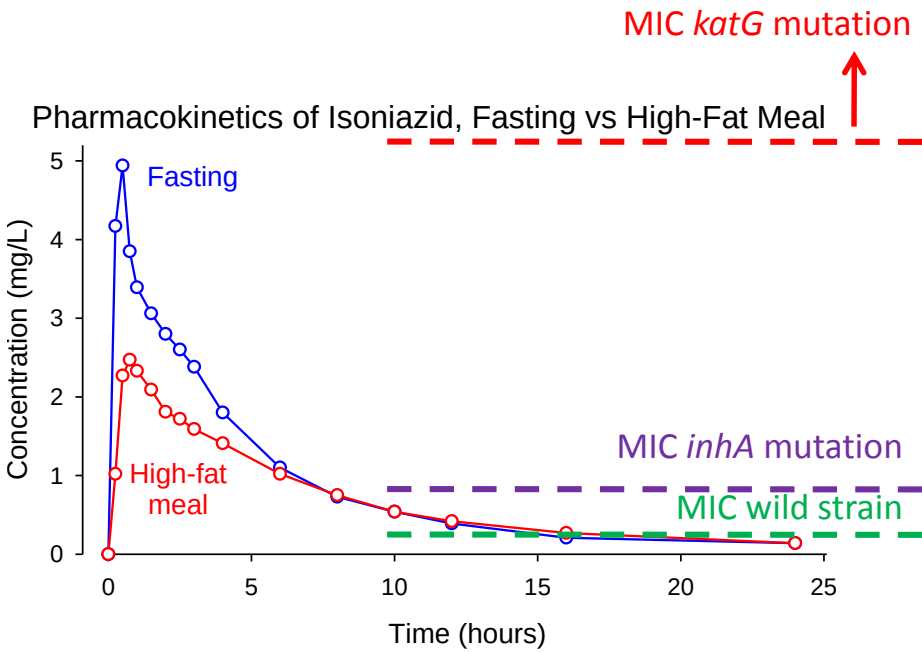
INH often useless, strains often susceptible to thioamides

INH useful, strains often resistant to thioamides

Banerjee A, et al. Science 1994;263:227-30

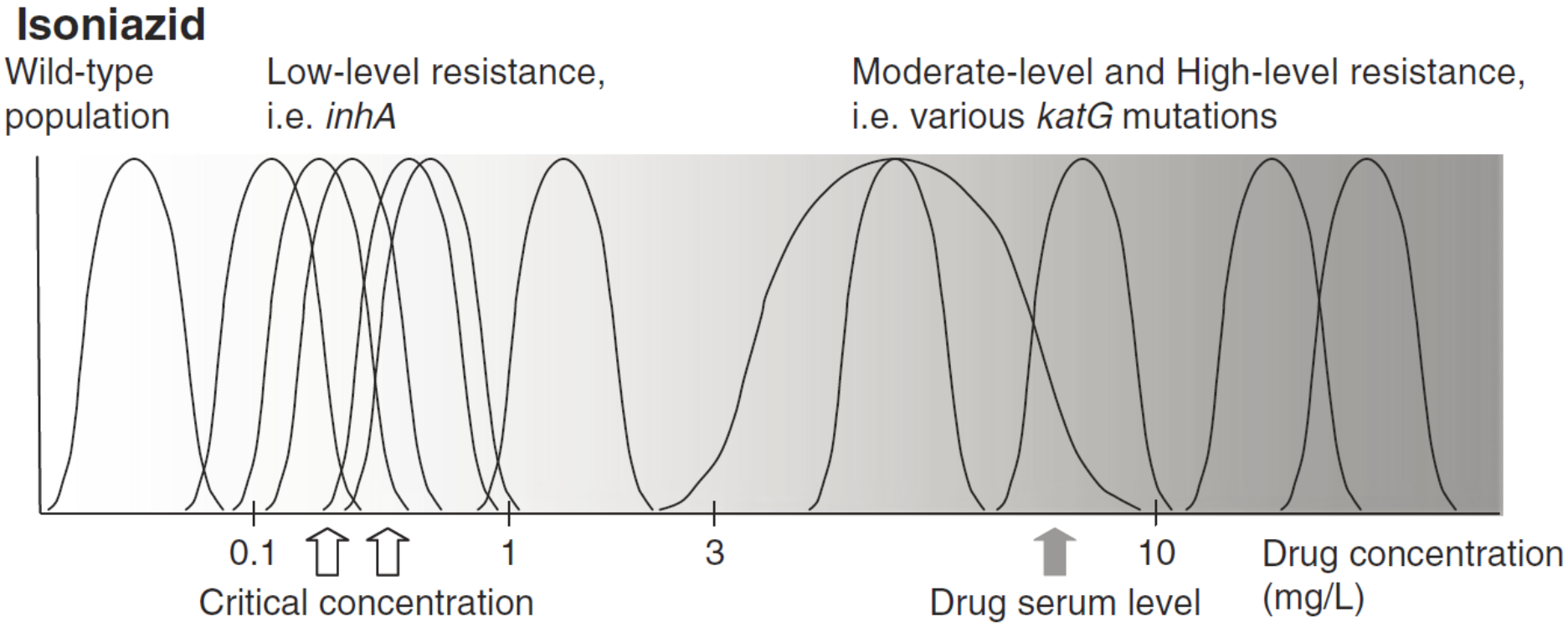


Van Deun A, et al. Int J Tuberc Lung Dis 2011;15:116-24



Peloquin CA, et al. Int J Tuberc Lung Dis 1999;3:703-10

Rationale for high-dose isoniazid is because of certain *katG* gene mutations, not because of resistance due to mutations in the *inhA* promoter gene!



Böttger EC. Clin Microbiol Infect 2011;17:1128-34

Very frequent *katG* 315Thr mutation is an example for wide MIC variation

Influence of level of fluoroquinolone resistance and pyrazinamide resistance on treatment outcome of MDR treatment, Bangladesh

All, not stratified

FQ resistance	Bacteriological outcome		
	Success	Non-success	Total
Low-level	30	1	31
High-level	14	8	22
Total	44	9	53

Common MH odds ratio: 12.6 (1.3-118.6)

(*Excluding 9 deaths / lost to follow-up*)

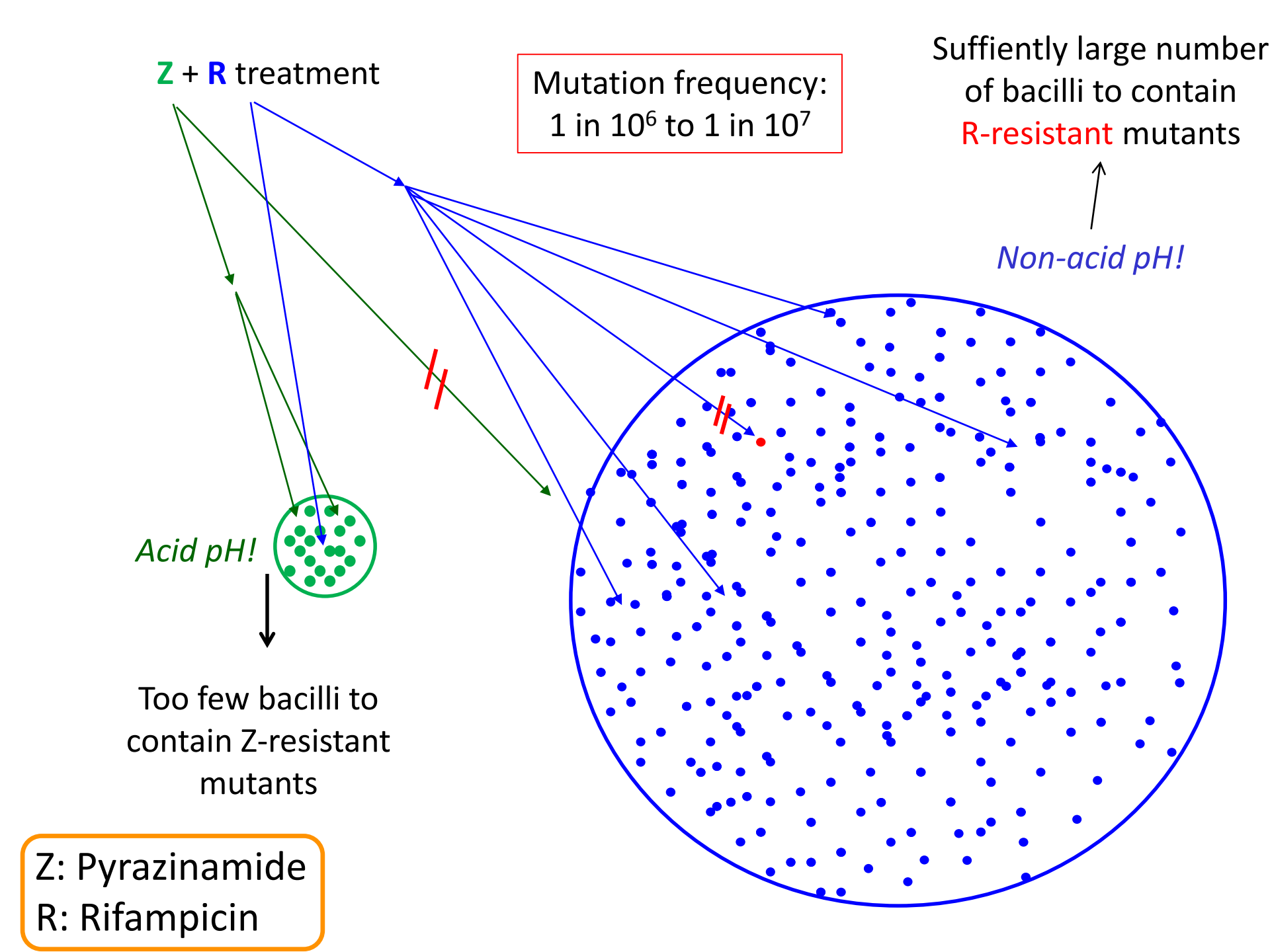
FQ resistance	**Pyrazinamide-resistant** Bacteriological outcome			**Not pyrazinamide-resistant** Outcome		
	Success	Non-success	Total	Success	Non-success	Total
Low-level	10	1	11	20	0	20
High-level	7	**7**	14	7	**1**	8
Total	17	8	25	27	1	28

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

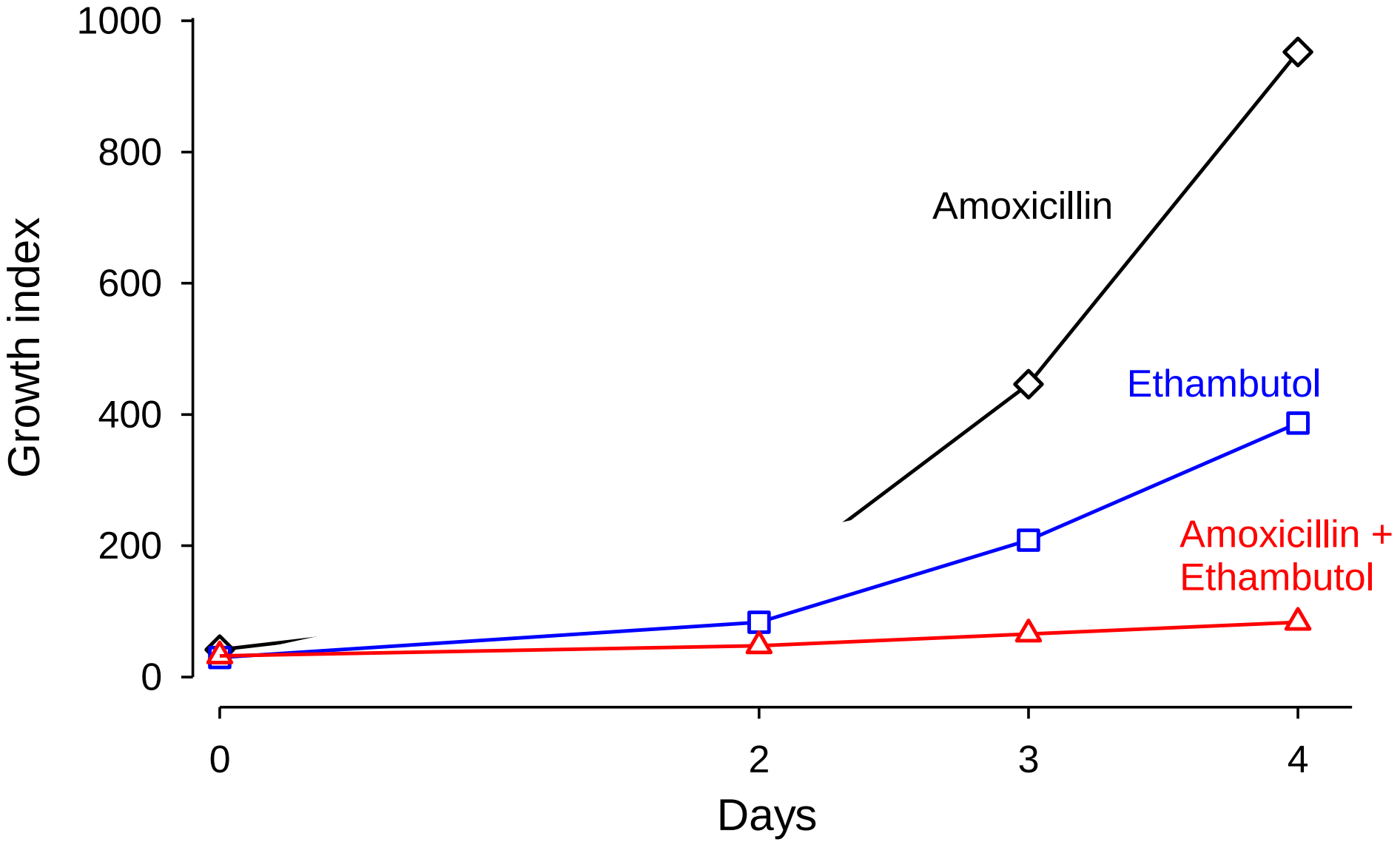
Not all patients with MDR have pyrazinamide resistance!

"... Given the high specificity (94%–98%) of *pncA* ... for pyrazinamide resistance, we estimate that [strains from] at least 56%–66% of MDR TB and 90%–95% of XDR TB cases from these settings [South Africa and Georgia] are likely to be resistant to pyrazinamide ..."

Allana S, et al. Emerg Infect Dis 2017;23:491-5

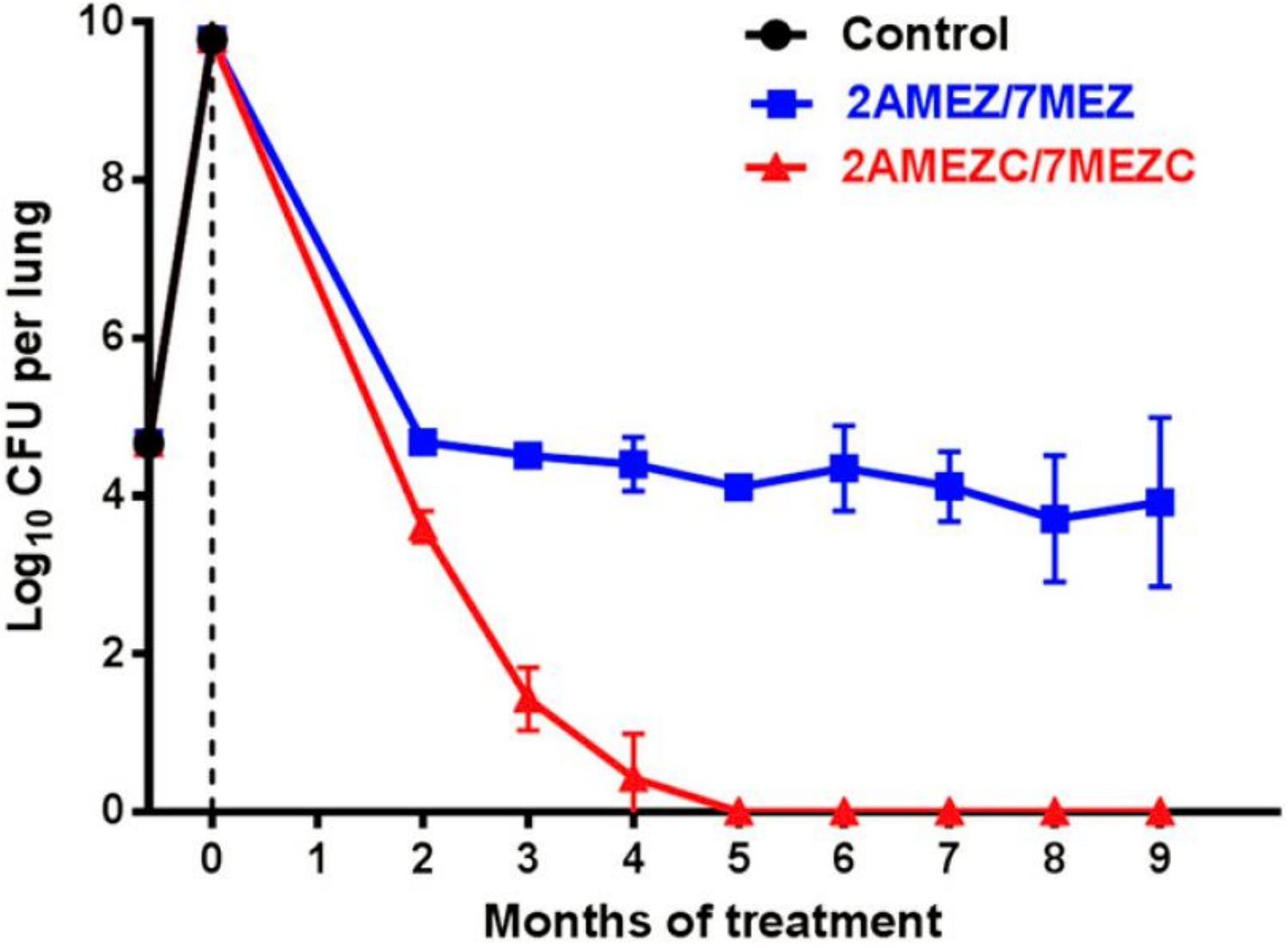

Z + R treatment
Mutation frequency:
1 in 10^6 to 1 in 10^7
Suffiently large number of bacilli to contain R-resistant mutants
Non-acid pH!
Acid pH!
Too few bacilli to contain Z-resistant mutants
Z: Pyrazinamide
R: Rifampicin

In vitro effect of ethambutol at 1/4 of its MIC on amoxicillin



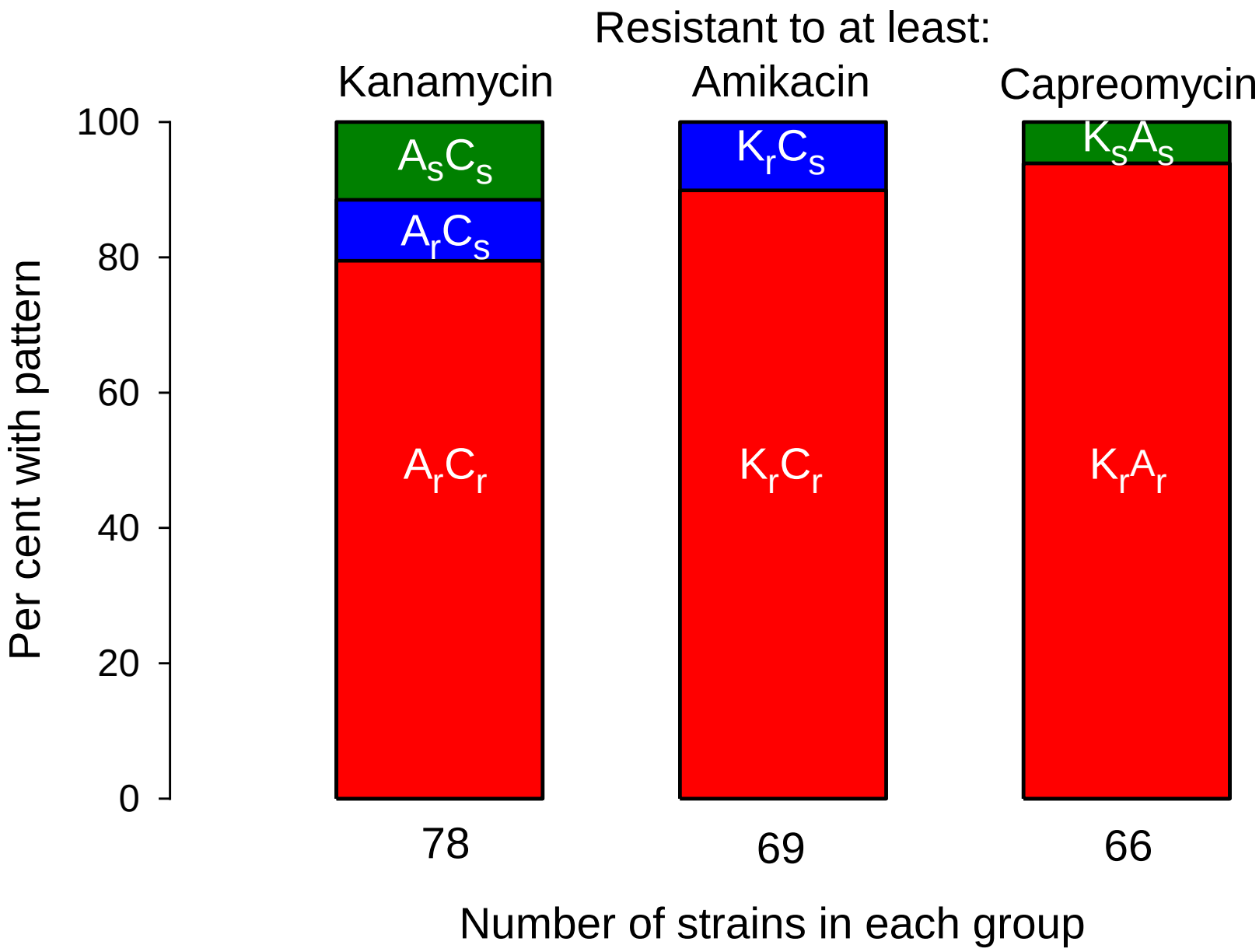
Abate G, Mjörner H. J Antimicrob Chemother 1998;42:735-40

Clofazimine in MDR treatment in the murine model



Grosset JH, et al. Am J Respir Crit Care Med 2013;188:608-12

Cross-resistance among second-line injectable drugs, Georgia



Jugheli L, et al. Antimicrob Agents Chemother 2009;53:5064-8

Conclusions

- The main issue in MDR treatment is not as much lack of efficacy (failure / relapse) as lack of effectiveness (loss to follow-up)
- The rationale for the choice of individual drugs is important. Much remains, however, unknown about the role of interplay between drugs. It thus might be unwarranted to be selective in choosing a drug solely because of its perceived appeal
- Developing an equally effective regimen without thioamides and aminoglycosides / polypeptides is imperative (STREAM 2)
- Affordability of MDR regimens for low-income countries must be assured to reduce dependence on external donors for effective tuberculosis control

If interested, you may obtain the presentation as an MP4 file:

Access **www.tbrieder.org**, open "**Presentations**" to watch / listen to online or offline after downloading it.