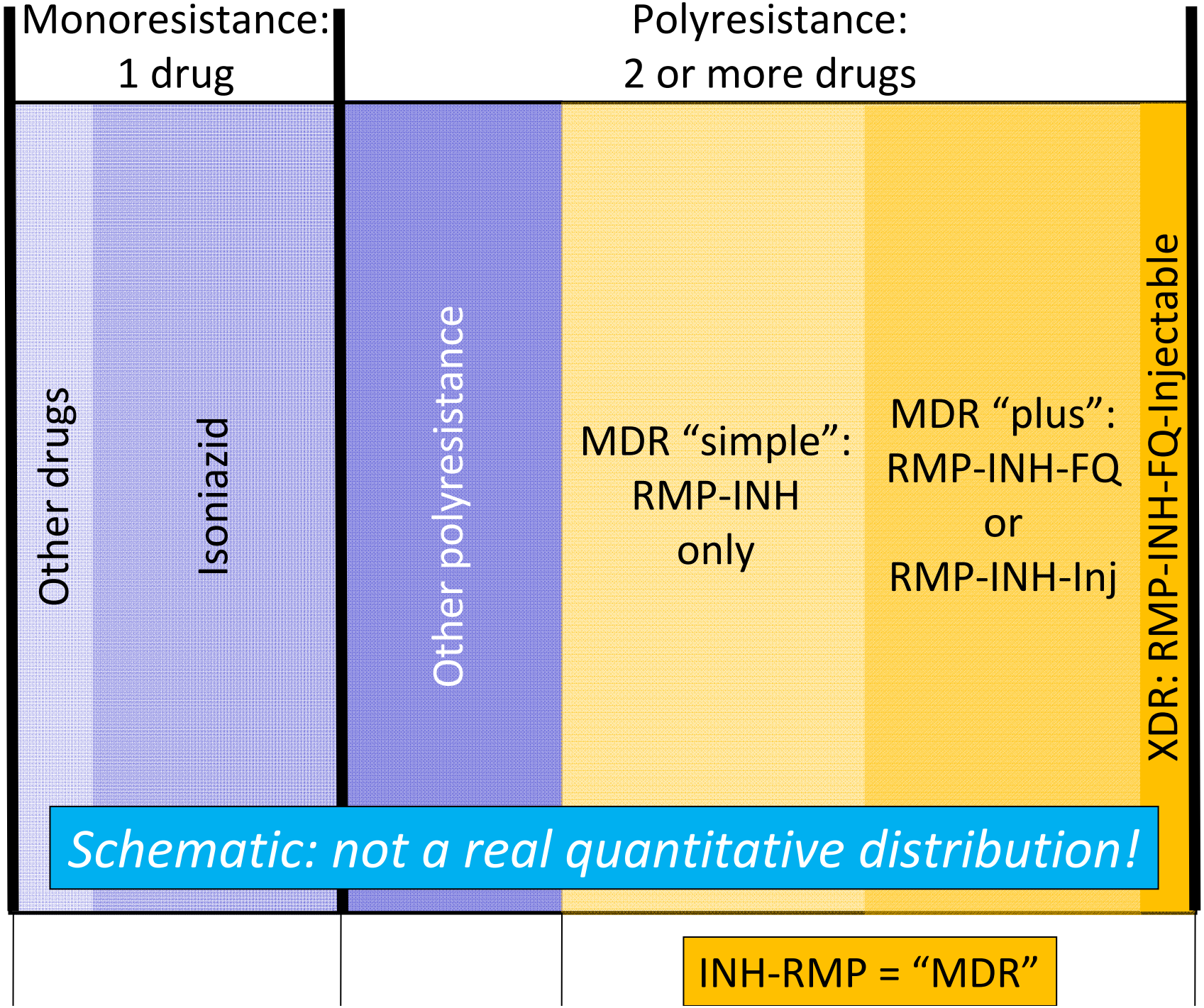
Management of MDR-TB: A terrible problem or an easy one?

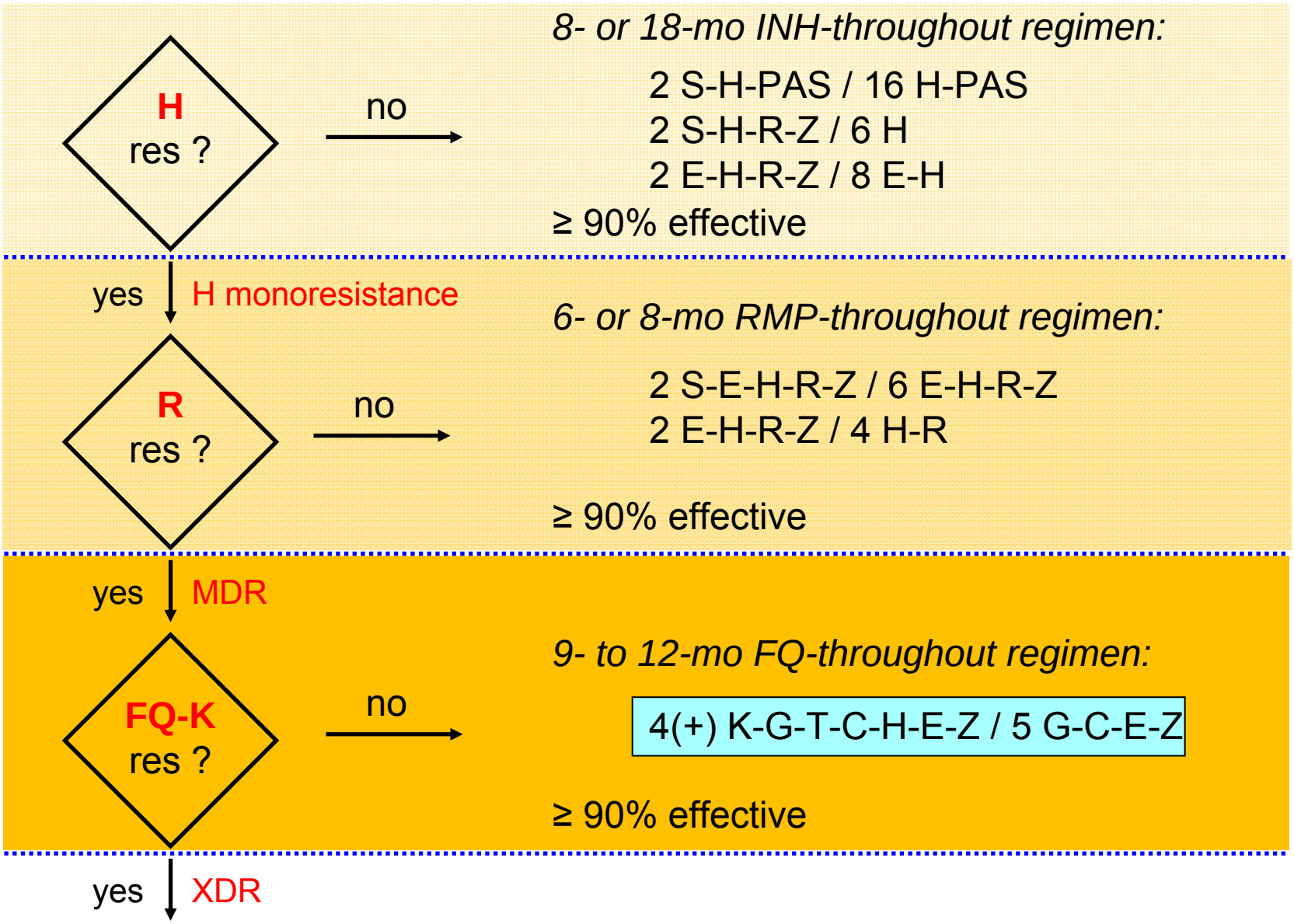
20e symposium tuberculose de Münchenwiler, 24 mars 2011

Hans L Rieder

International Union Against Tuberculosis and Lung Disease

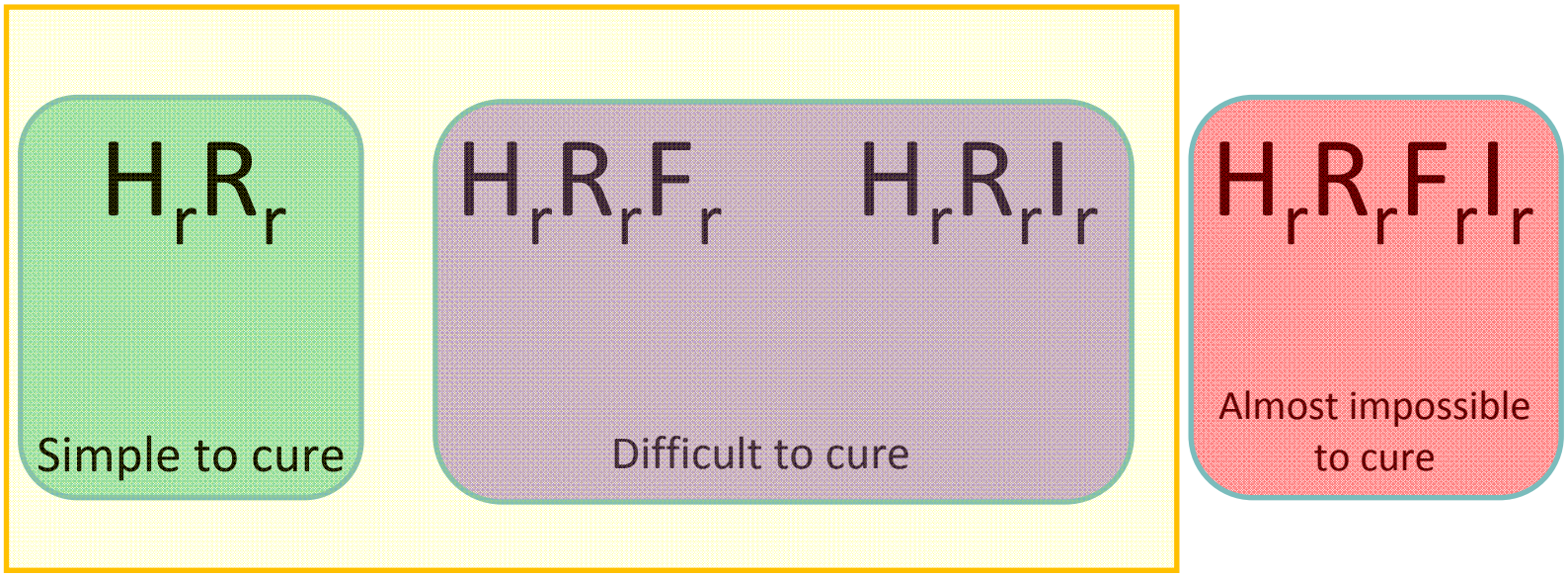

Monoresistance:
1 drug
Polyresistance:
2 or more drugs
Other drugs
Isoniazid
Other polyresistance
MDR "simple":
RMP-INH
only
MDR "plus":
RMP-INH-FQ
or
RMP-INH-Inj
XDR: RMP-INH-FQ-Injectable
Schematic: not a real quantitative distribution!
INH-RMP = "MDR"

The Regimen Cascade



Complex! Toxic! 21-mo regimen – poor effectiveness (50%)

Establish the frequency of MDR subsets



? 70%-90%

?

?

1%-15% [1]

[1] *Centers for Disease Control and Prevention. Morb Mortal Wkly Rep 2006;55:301-5*

Sequential development of an effective MDR treatment regimen in Bangladesh

Regimen		Problem	Change for next cohort
No	In "TB-speak" letters		
1	3 KCOEHZP / 12 OEHZP / 6 EP	Too long	Drop 3rd phase
2	3(+) KCOEHZP / 12 OEHZP	Usefulness of H?	Drop H
3	3(4) KCOEZP / 12 OEZP	Failures, toxicity	Re-intro H, drop P from CP
4	3(+) KCOEHZP / 12 OEHZ	Failures	Add C throughout
5	3(+) KCOEHZP / 12 OEHZC	Still too long	Prolong IP, switch FQ, drop H from CP
6	4(+) KCGEHZP / 5 GEZC	Satisfactory	New standard found!

Abbreviations for drugs and treatment phases

K:	Kanamycin	H:	Isoniazid	IP:	Intensive phase
C:	Clofazimine	Z:	Pyrazinamide	CP:	Continuation phase
O:	Ofloxacin	P:	Prothionamide		
E:	Ethambutol	G:	Gatifloxacin		

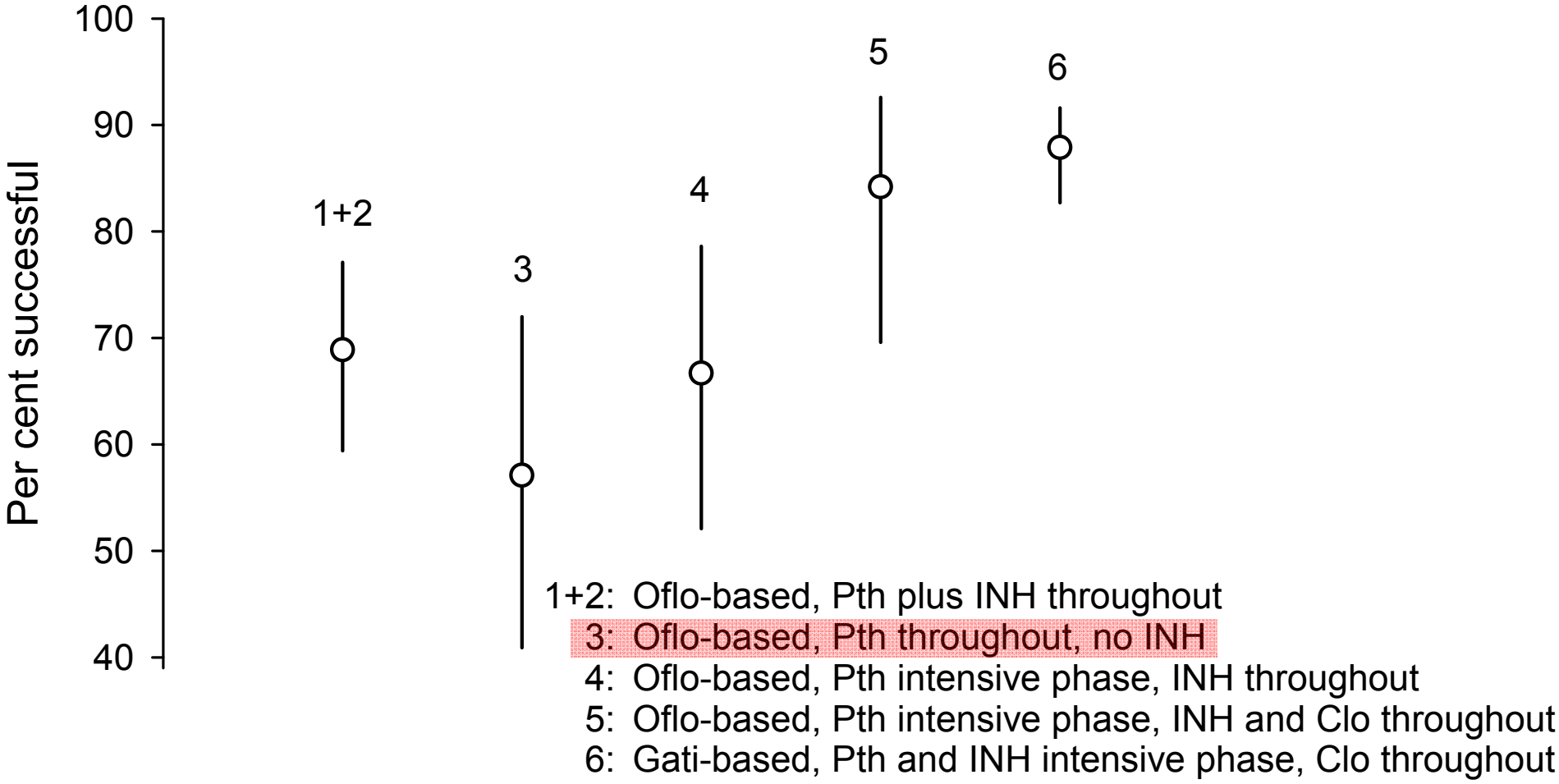
Van Deun A, et al. Am J Respir Crit Care Med 2010;182:684-92

Treatment of MDR tuberculosis in Damien Foundation Projects, Bangladesh, 1997-2007

Adverse reaction	Regimens 1+2		Regimen 3		Regimen 4		Regimen 5		Regimen 6		Total	
	n	%	n	%	n	%	N	%	n	%	N	%
Patients	103		35		45		38		206		427	
Vomiting	75	72.8	23	65.7	14	31.1	14	36.8	44	21.4	170	39.8
Dysglycemia	1	1.0	0	0.0	1	2.2	0	0.0	8	3.9	10	2.3
Neurologic	9	8.7	1	2.9	0	0.0	0	0.0	0	0.0	10	2.3
Mental	9	8.7	1	2.9	0	0.0	1	2.6	1	0.5	12	2.8
Ataxia	0	0.0	0	0.0	1	2.2	0	0.0	8	3.9	9	2.1
Hearing	5	4.9	0	0.0	1	2.2	0	0.0	13	6.3	19	4.4
Arthralgia	18	17.5	4	11.4	4	8.9	2	5.3	2	1.0	30	7.0
Jaundice	2	1.9	0	0.0	1	2.2	0	0.0	0	0.0	3	0.7

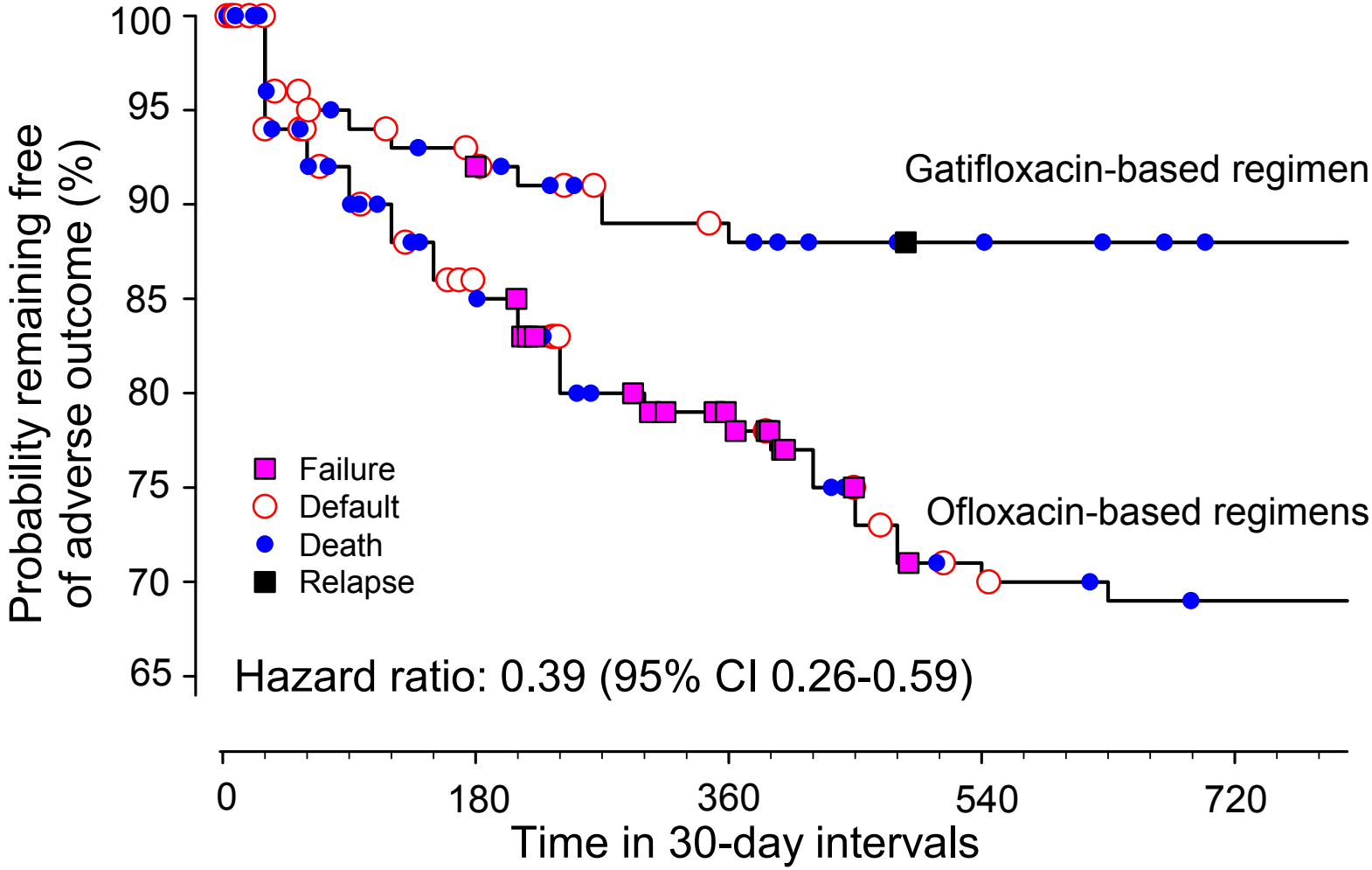
Van Deun A, et al. Am J Respir Crit Care Med 2010;182:684-92

Proportion of patients with a successful treatment outcome for multidrug-resistant tuberculosis, by regimen, Bangladesh



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

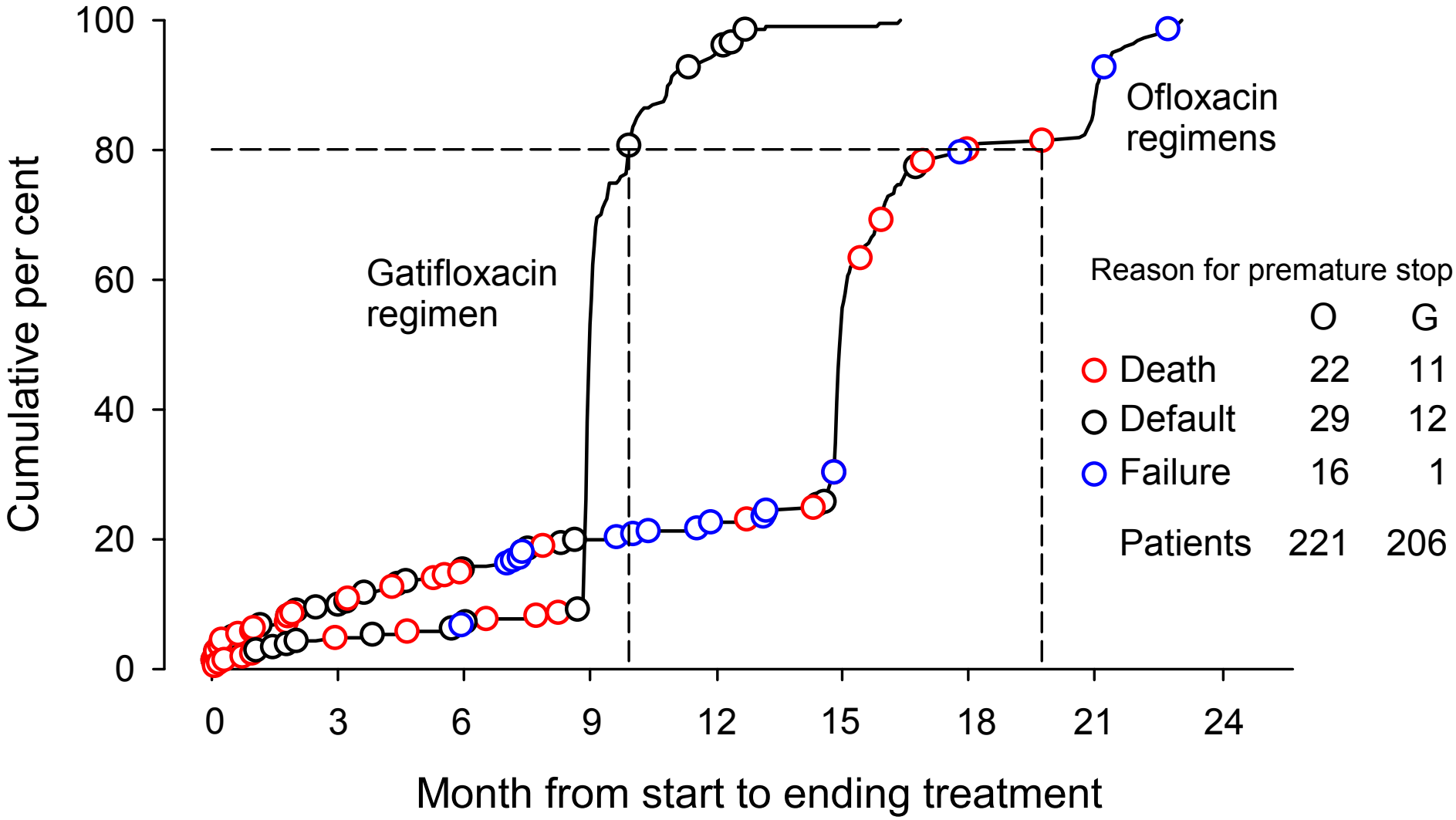
Kaplan-Meier analysis of primary adverse endpoint



Ofloxacin	221	208	203	200	195	191	188	184	177	*177*	175	172	171	167	164	160	158	157	156	*156*	152	151	*151*	149	*149*					
Gatifloxaxin	206	198	195	193	192	191	190	187	186	182	179	177	176	175	*175*	172	168	166	165	*165*	164	163	139	131	128					

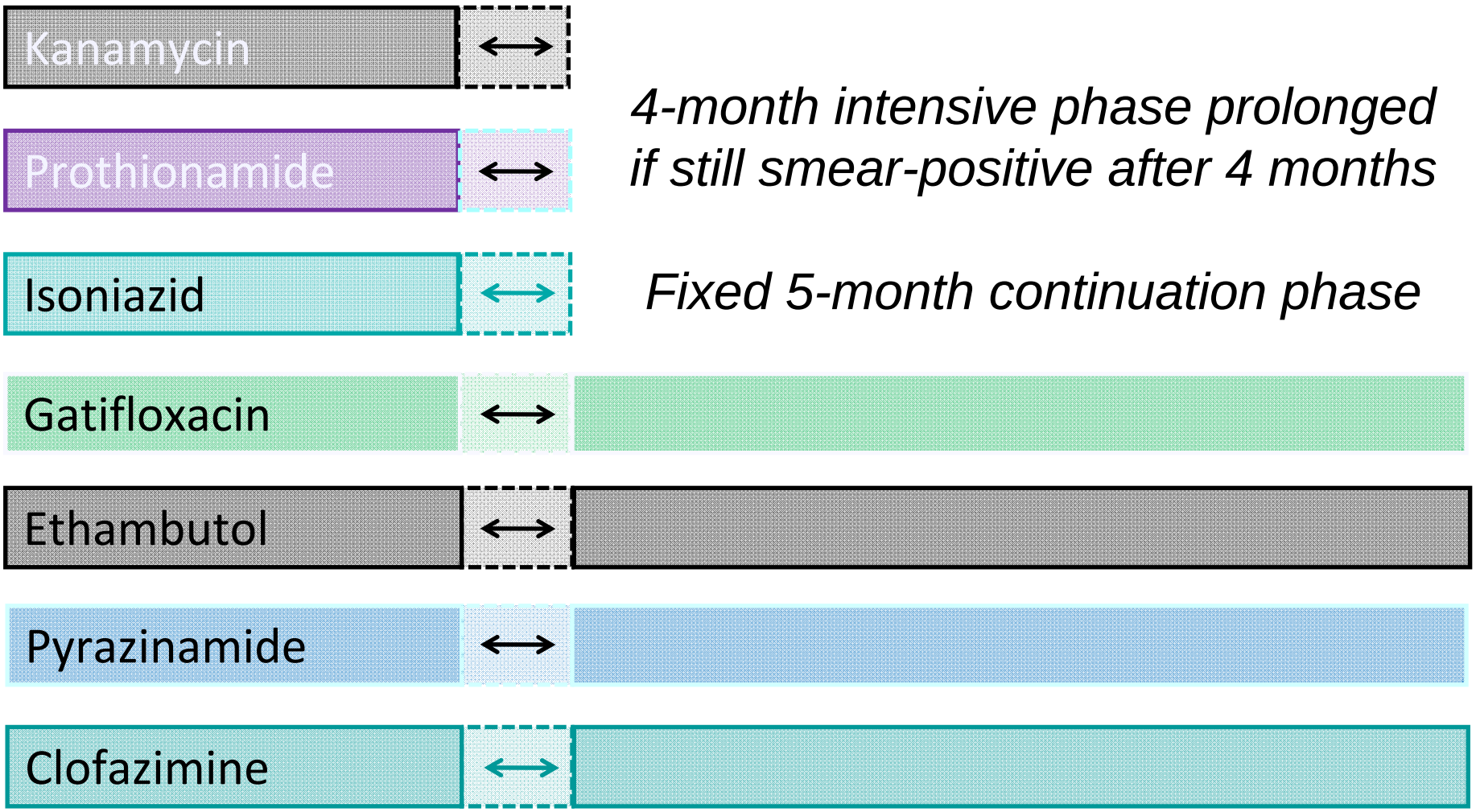
Van Deun A, et al. Am J Respir Crit Care Med 2010;182:684-92

Time from treatment start to treatment stop of MDR treatment



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 €)

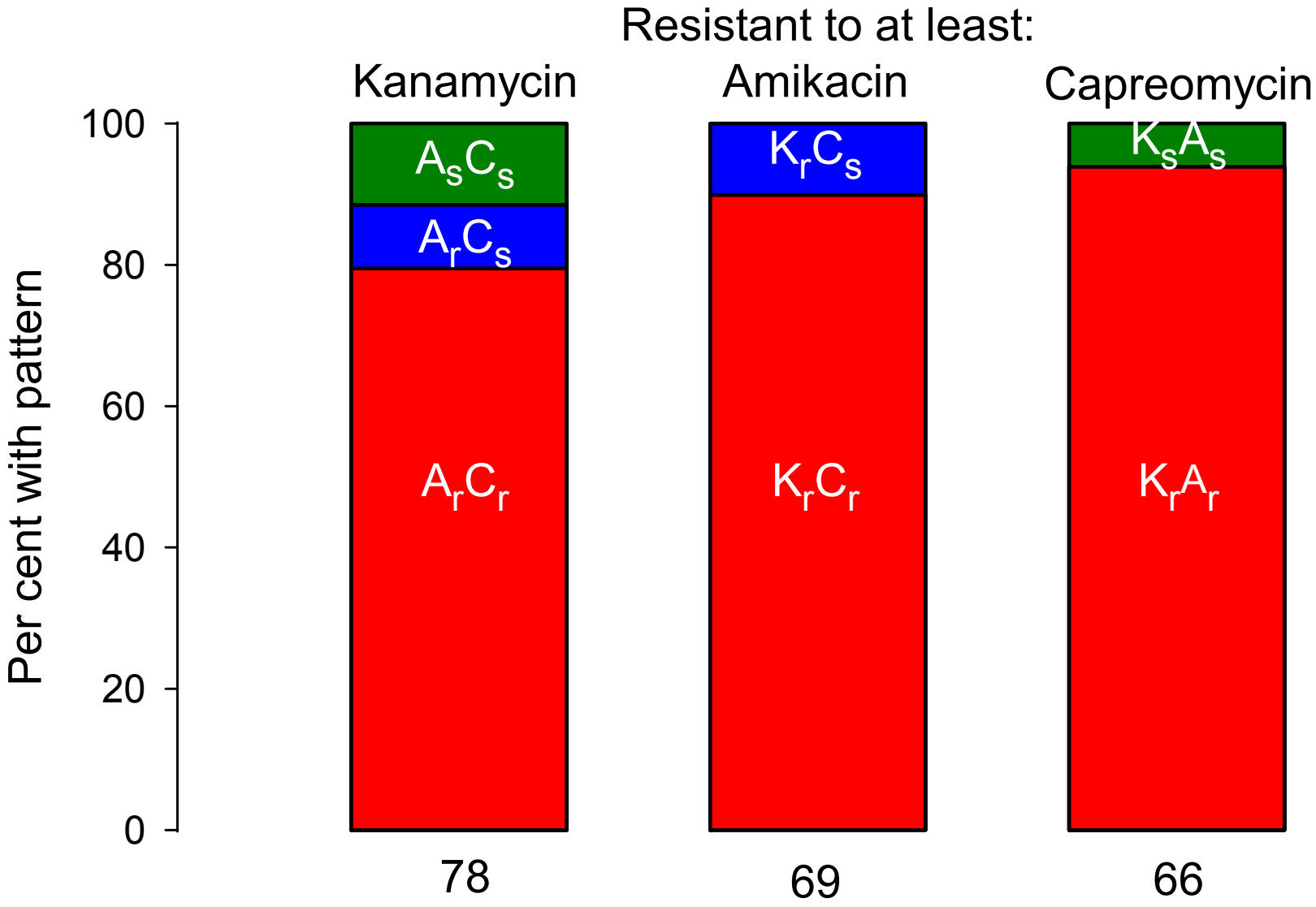


4-month intensive phase prolonged if still smear-positive after 4 months

Fixed 5-month continuation phase

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

Cross-resistance among second-line injectable drugs, Georgia



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

Mutations in *katG* gene

High-level resistance

Mutations in *inhA* gene

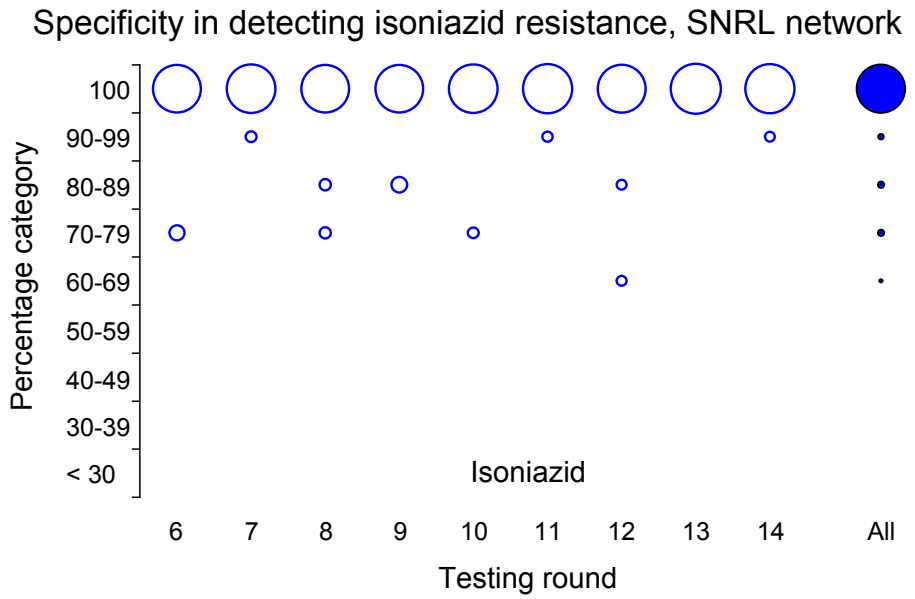
Low-level resistance

Isoniazid resistance

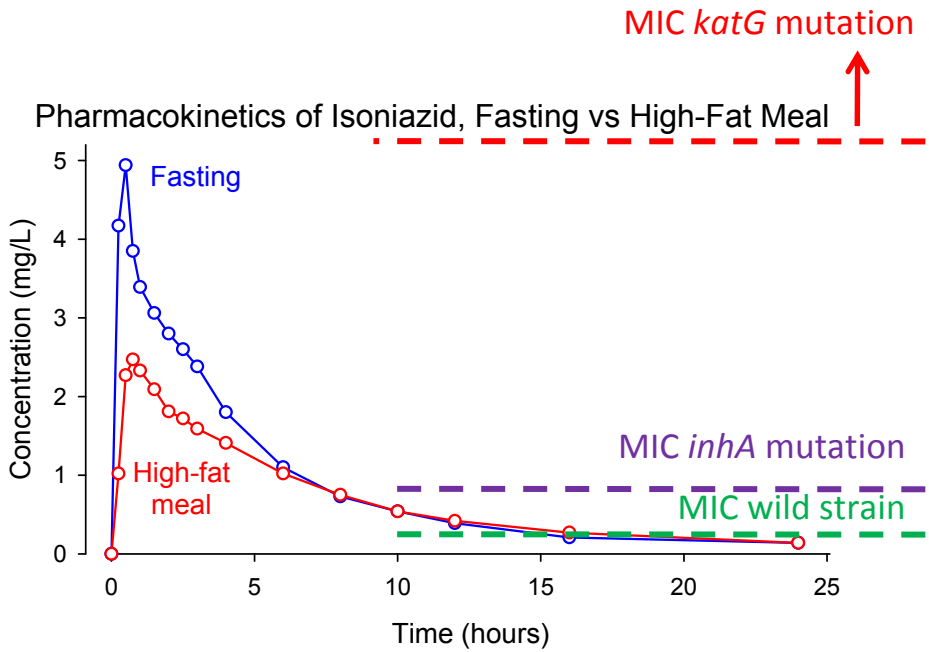
INH useless, strains often susceptible to thioamides

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: in press



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

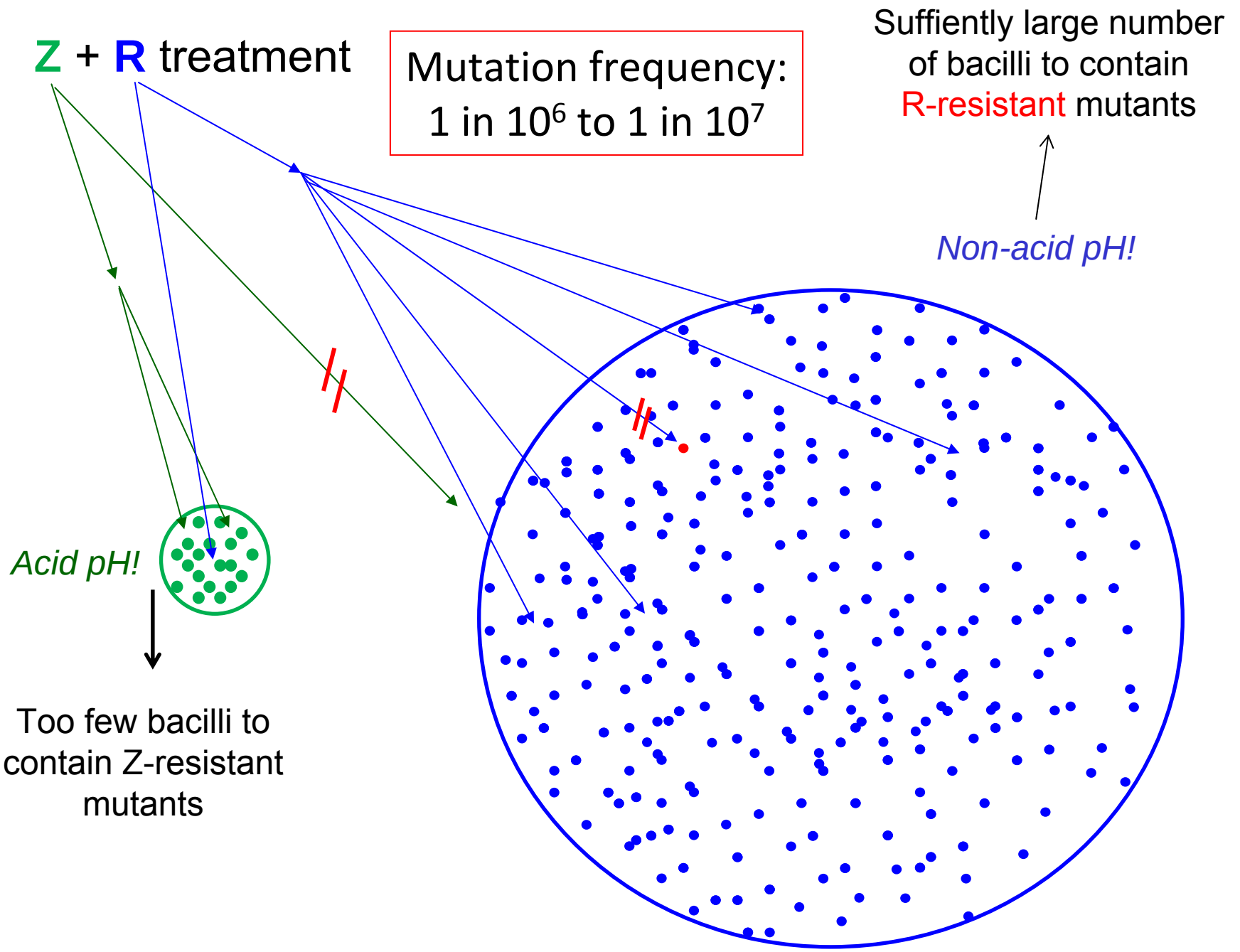
Fluoroquinolone generations

Generation	Selected examples
1	Cinoxacin, oxolinic acid (mostly obsolete and withdrawn)
2	Ofloxacin, ciprofloxacin, norfloxacin
3	Levofloxacin, sparfloxacin
4	Gatifloxacin (removed by FDA), moxifloxacin

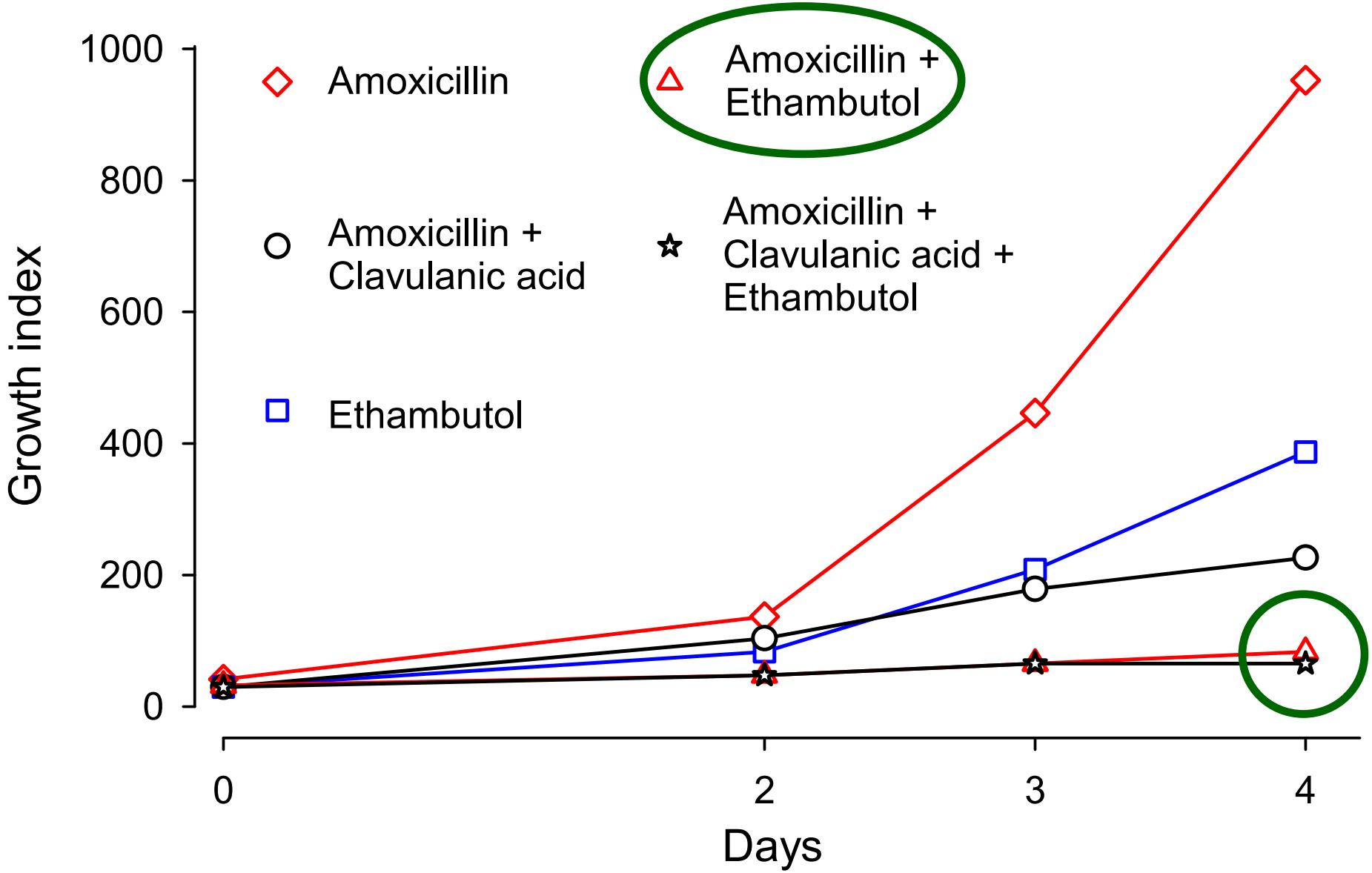
* Outpatient Gatifloxacin Therapy and Dysglycemia in Older Adults (Mean age: 78yrs)

Laura Y. Park-Wyllie, Pharm.D., David N. Juurlink, M.D., Ph.D., Alexander Kopp, B.A., Baiju R. Shah, M.D., Ph.D., Therese A. Stukel, Ph.D., Carmine Stumpo, Pharm.D., Linda Dresser, Pharm.D., Donald E. Low, M.D., and Muhammad M. Mamdani, Pharm.D., M.P.H.

* *Park-Wyllie L Y, et al. N Engl J Med 2006;354:1352-61*


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

In vitro effect of ethambutol at 1/4 of its MIC on increasing the effect of a weak companion drug



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

Conclusions

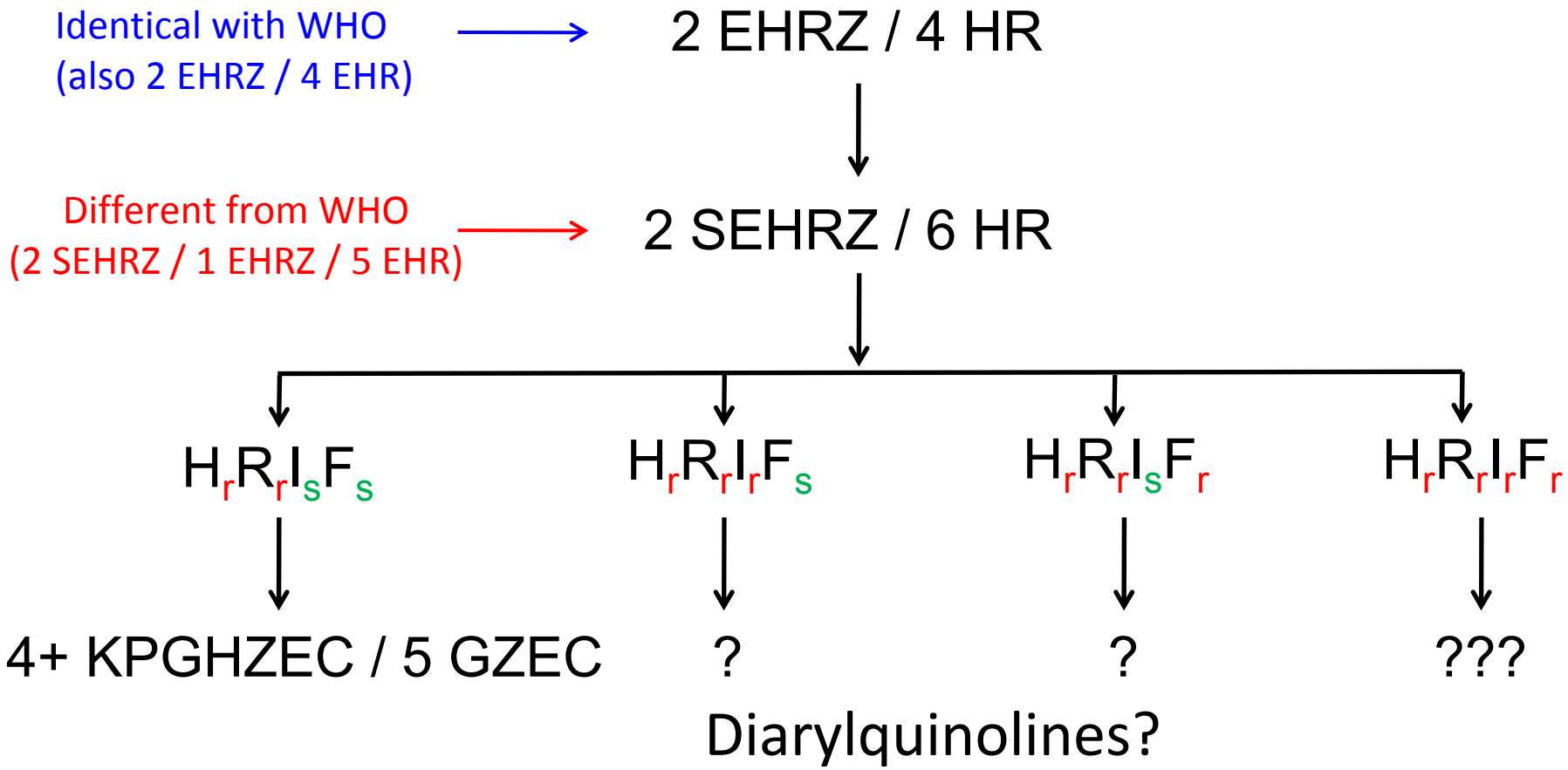
- A well-tolerated, effective treatment regimen for MDR tuberculosis has been developed over an 11-year period in Bangladesh among patients without HIV infection, naïve to prior use of second-line drugs
- The regimen is affordable (220 €) for low-income countries
- The regimen is simple enough to be prescribed, observed, and managed at regional or even peripheral level

Where to go from here?

1) **Apply the regimen** in multiple settings in which success is likely, to alleviate quickly the sorry state of affairs that only 2% of patients with MDR are estimated to currently obtaining treatment

2) **Implement the** appropriate **research agenda**:
   - Sufficiently powered clinical trials to confirm or refute findings (funding?)
   - Observational studies in other countries with and without HIV infection among their tuberculosis patients (in progress)
   - Development of sequentially adaptive regimens in settings which have lost fluoroquinolone or injectable drug activity
   - Any new regimen must retain drug affordability for the owners of the national programs

The Union's proposed revised cascade of regimens



Aït-Khaled N, Alarcón E, Armengol R, Bissell K, Boillot F, Caminero J A, Chiang C Y, Clevenbergh P, Dlodlo R, Enarson D A, Enarson P, Fujiwara P I, Harries A D, Heldal E, Hinderaker S G, Monedero I, Rieder H L, Rusen I D, Trébucq A, Van Deun A, Wilson N.
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Paris: International Union Against Tuberculosis and Lung Disease, 2010.

World Health Organization. Word Health Organization Document 2010;WHO/HTM/TB/2009.420:1-147