The Oflotub trial

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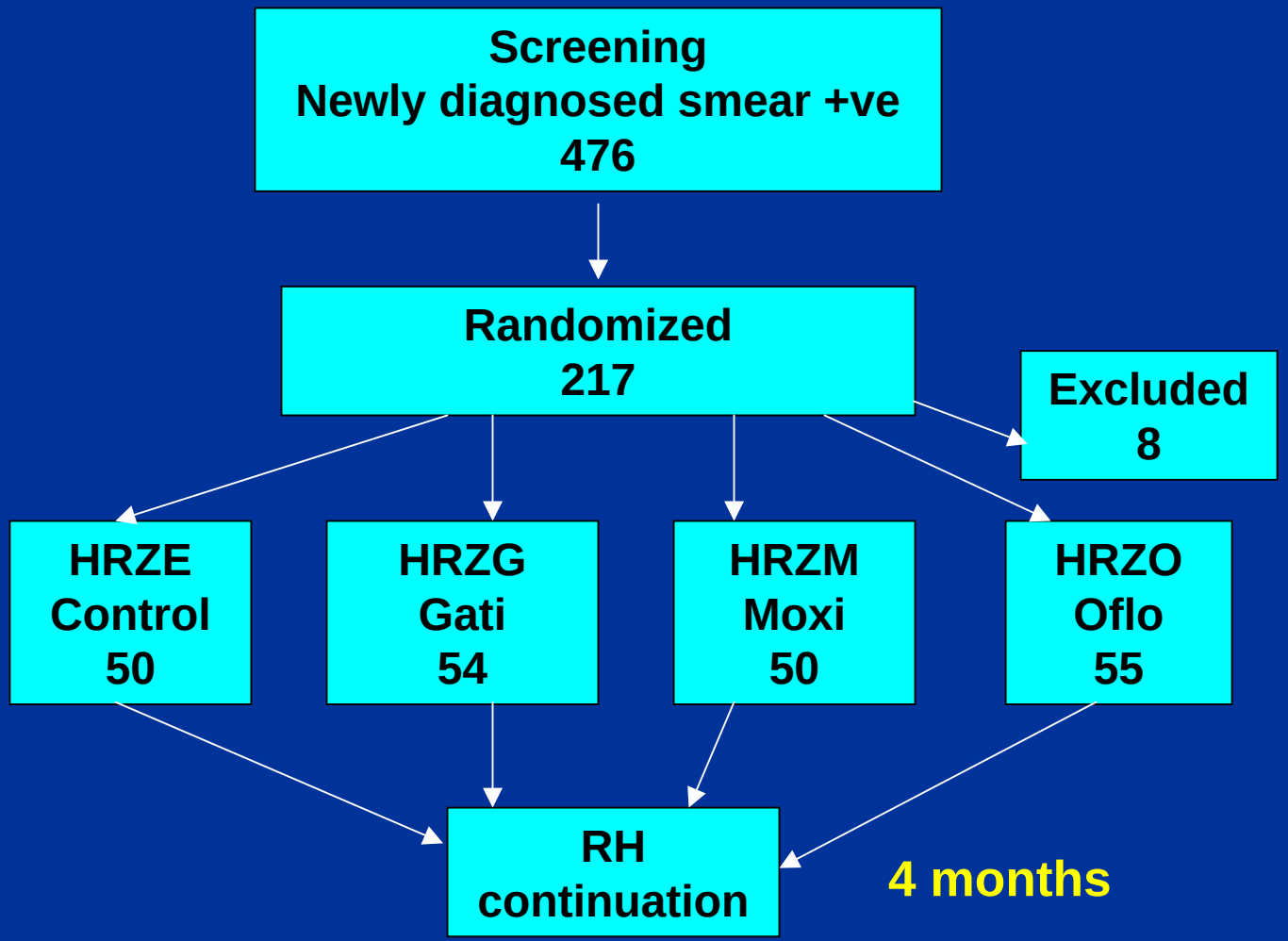
Phase 1	Volunteers: Toxicity in man Human pharmacology
Phase 2 **Oflotub Ph 2** **Sterilising activities of ofloxacin, gatifloxacin & moxifloxacin**	Patients: Proof of principle Increase rate of sterilisation? What drug combinations
Phase 3 **Oflotub Ph 3** **4 mth regimen:2GHRZ/2GHR** **6 mth control: 2EHRZ/4HR**	Patients: Licensing study Shortened test regimen

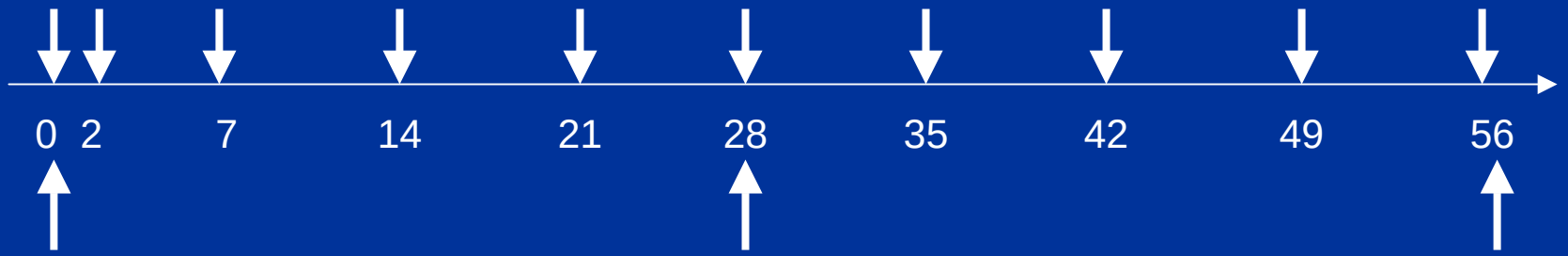
Summary of recruitment to Ph 2 trial



Comparative bactericidal assessments

14 hour sputum collection

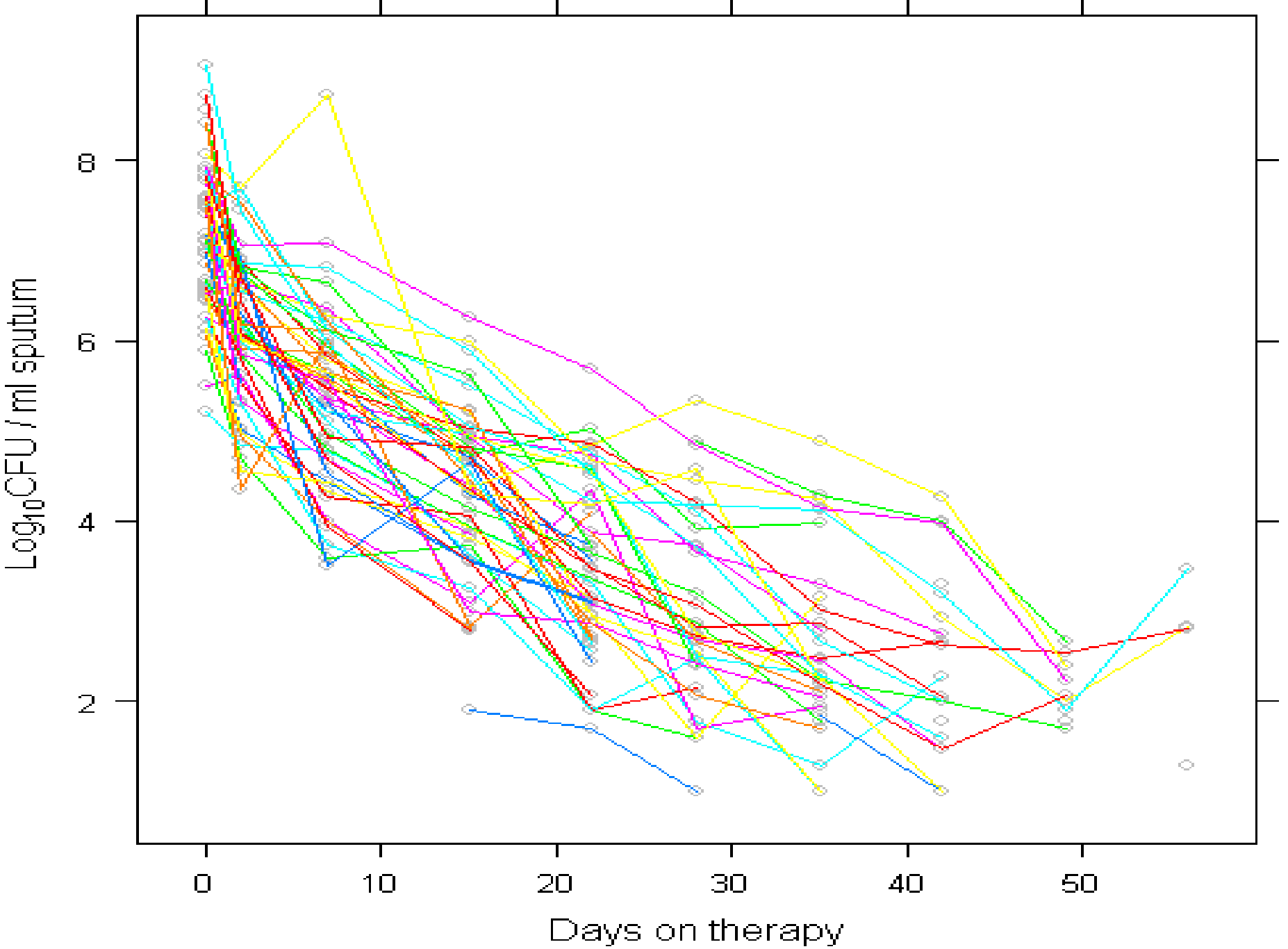
Sputum colony counts on selective 7H11 medium without decontamination at 10 time points during initial 8-week phase

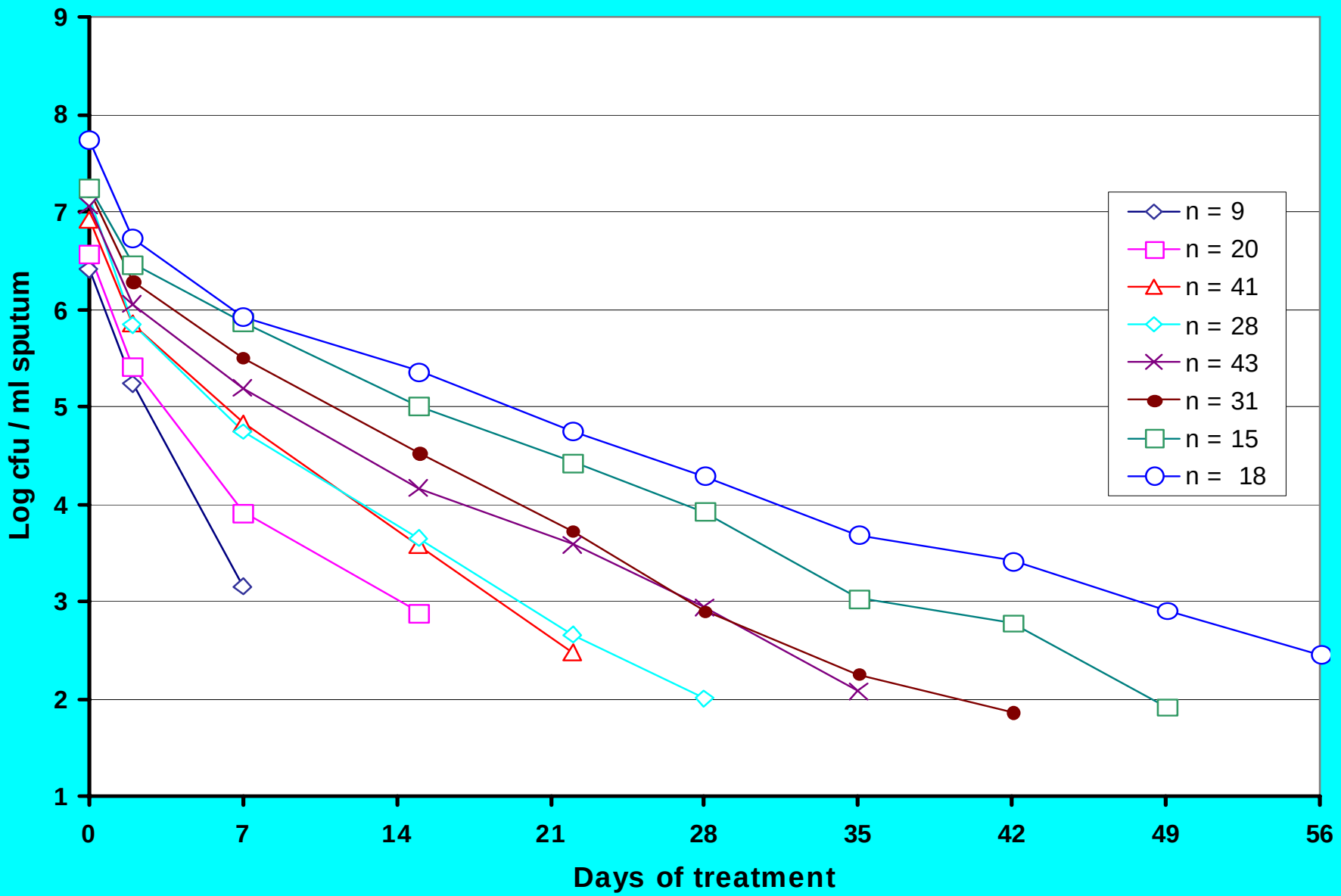


Standard 7H11 culture + indirect susceptibility tests

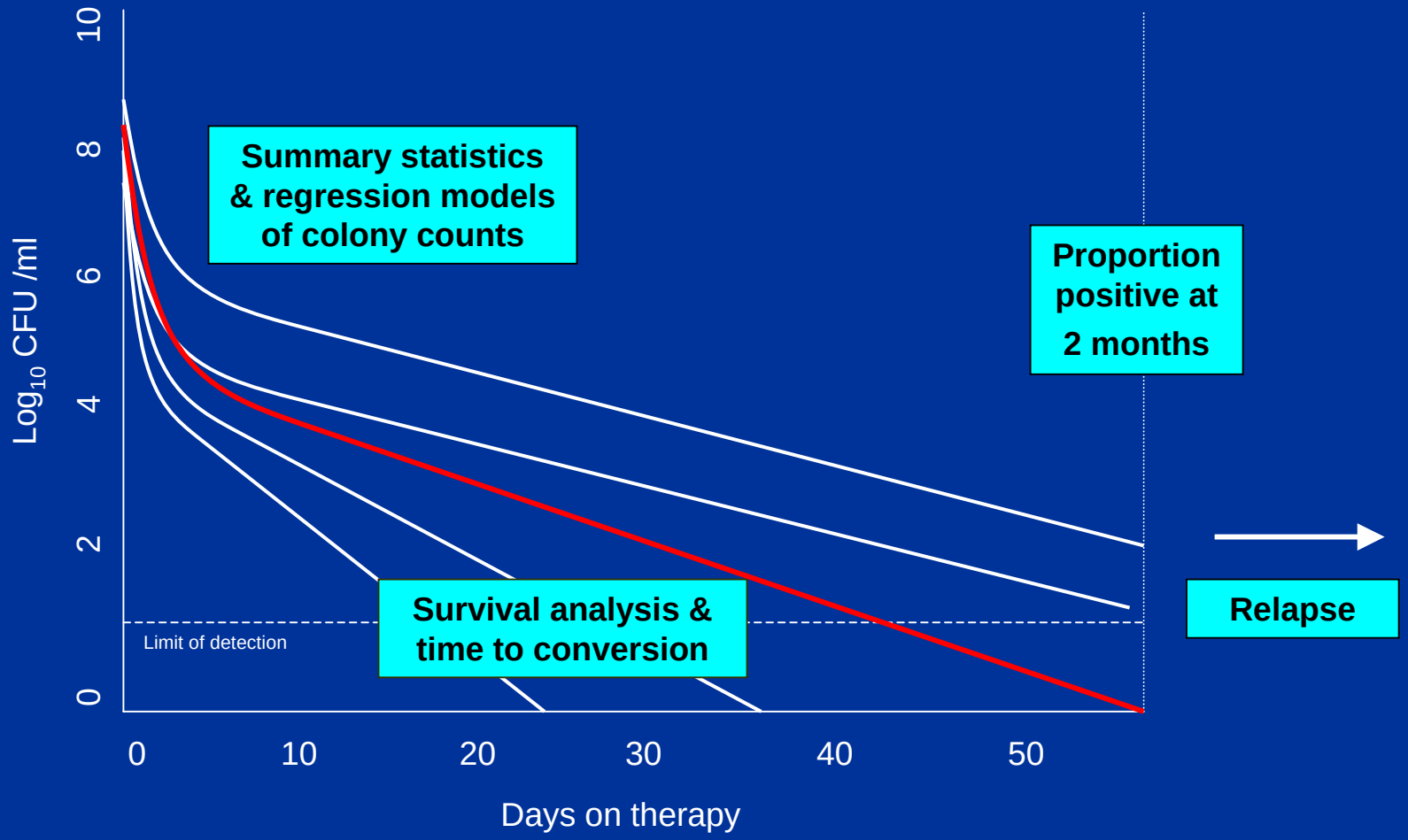
Standard 7H11 culture

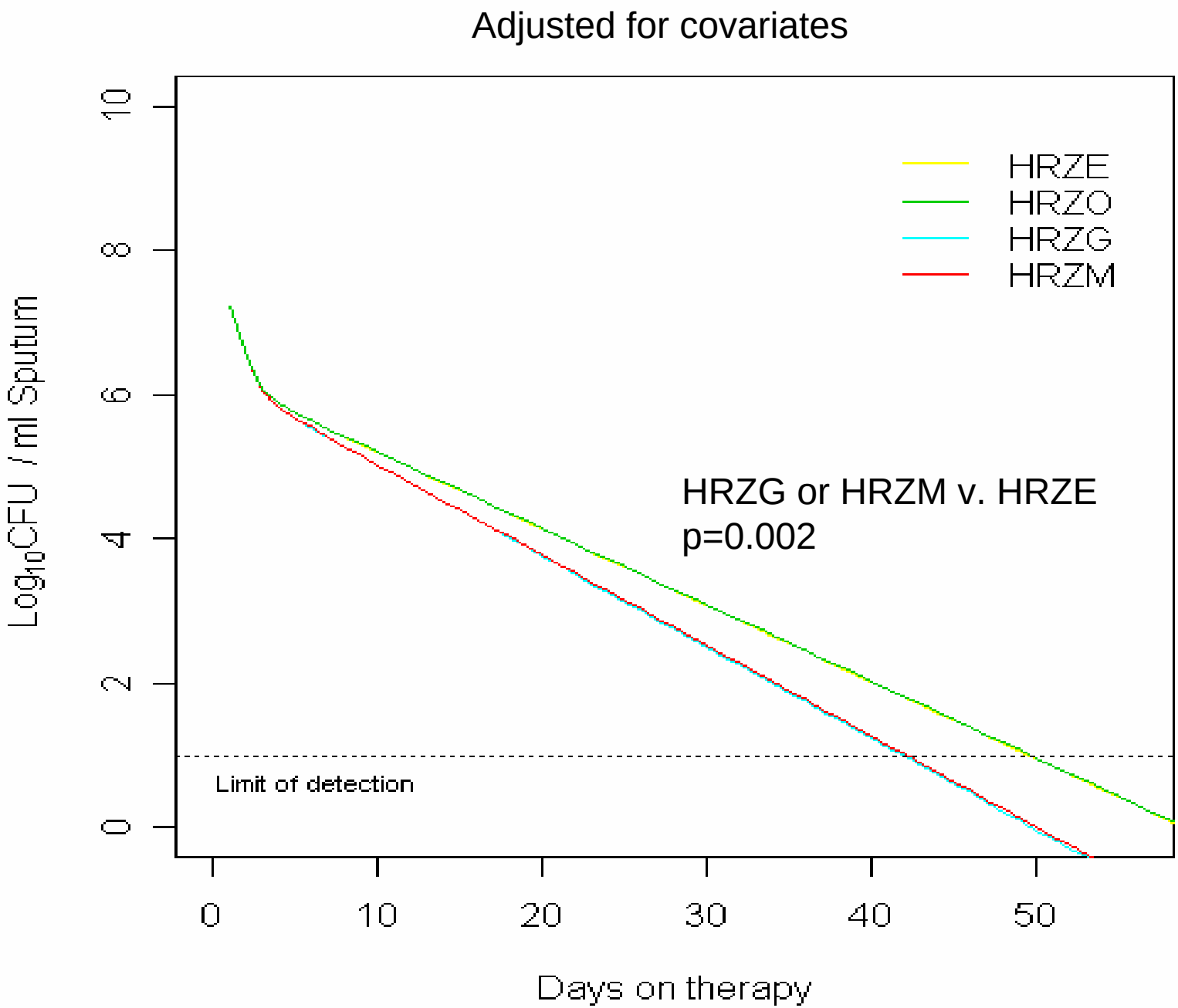
Standard 7H11 culture + Liquid culture (MGIT)

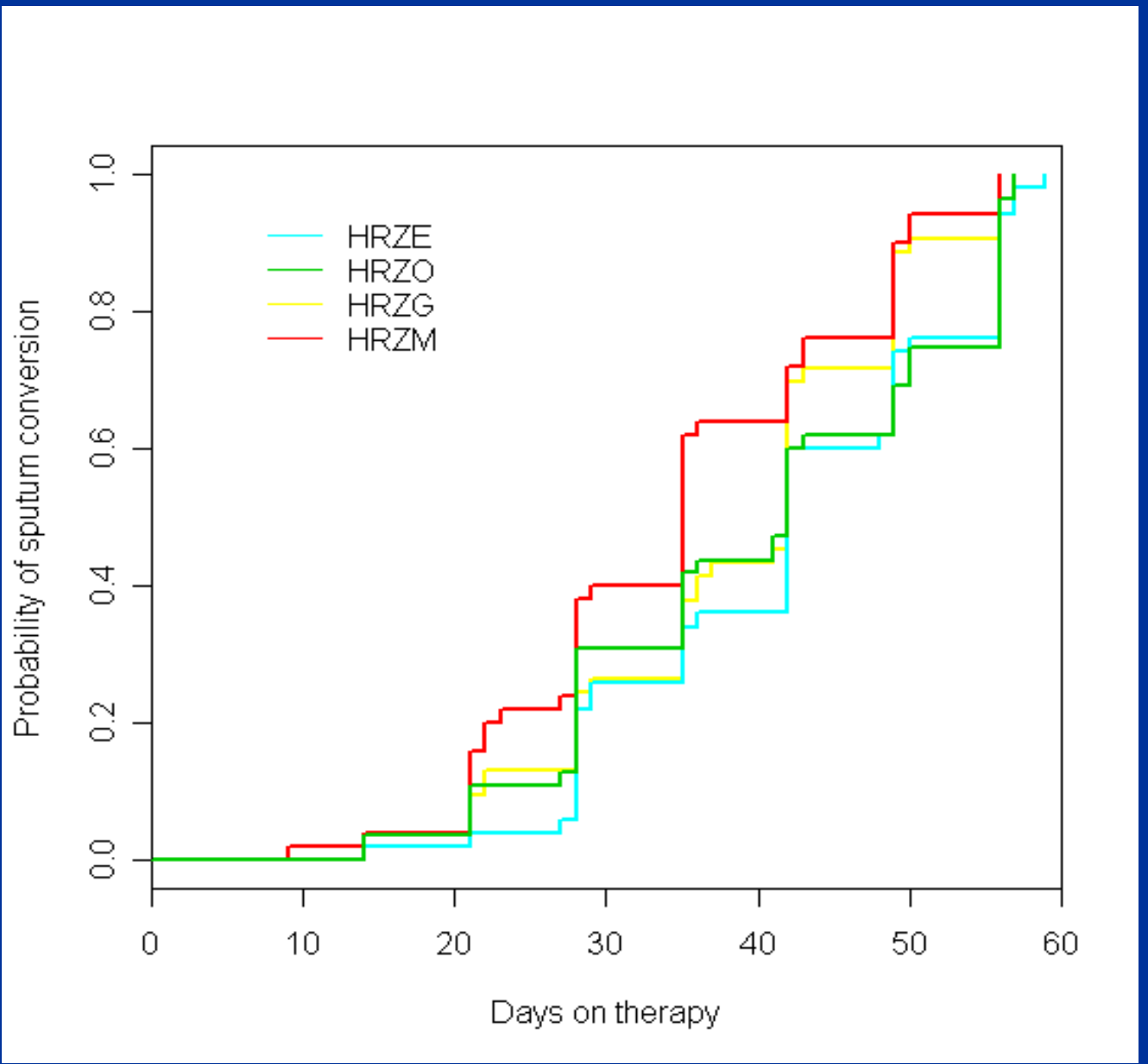

Log10CFU / ml sputum
8
6
4
2
0
10
20
30
40
50
Days on therapy


Log cfu / ml sputum
9
8
7
6
5
4
3
2
1
0
7
14
21
28
35
42
49
56
Days of treatment
n = 9
n = 20
n = 41
n = 28
n = 43
n = 31
n = 15
n = 18

Analytical approaches to Phase II surrogate endpoint studies

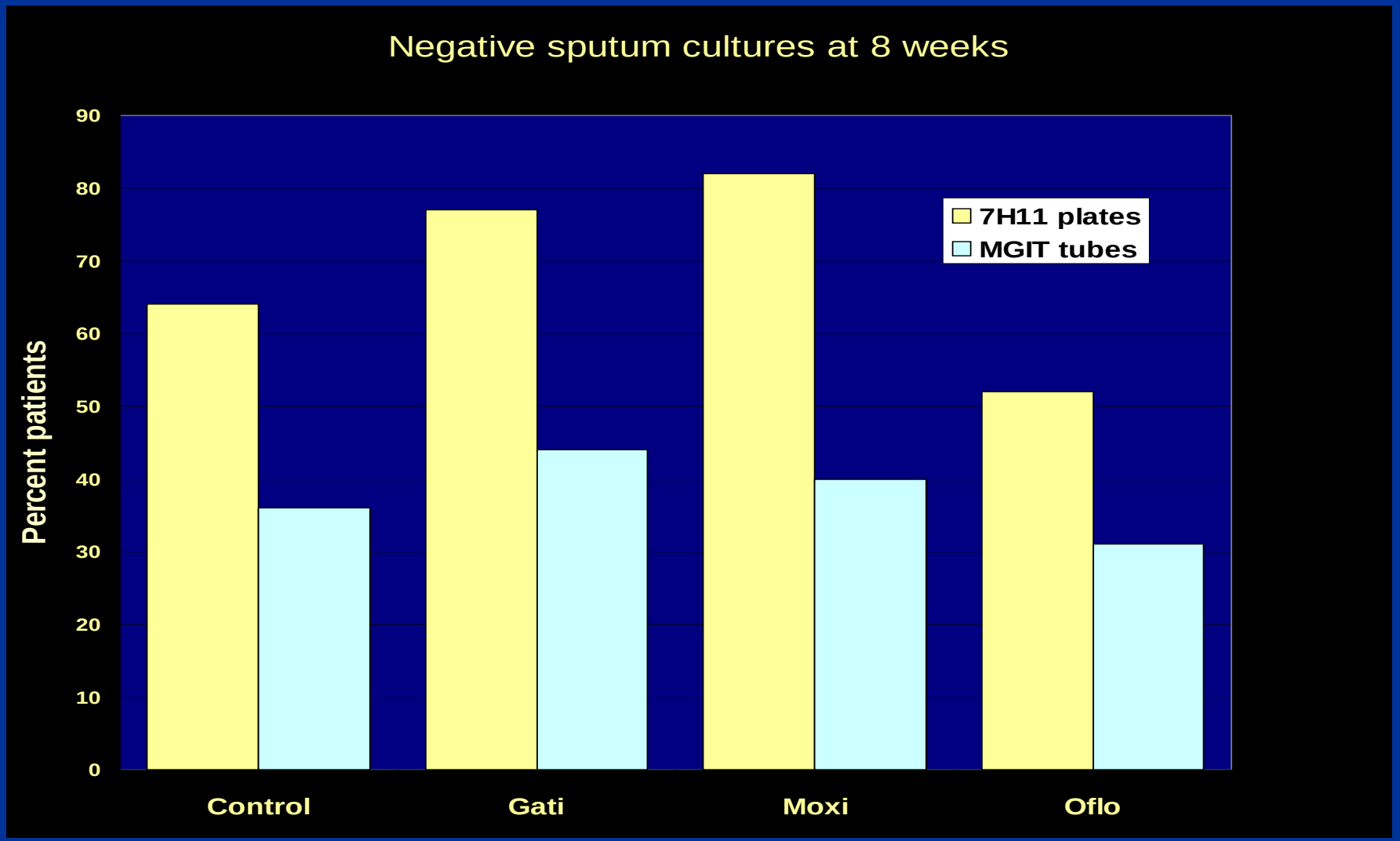



Adjusted for covariates
HRZE
HRZO
HRZG
HRZM
HRZG or HRZM v. HRZE
p=0.002
Limit of detection
Log10CFU / ml Sputum
0
2
4
6
8
10
0
10
20
30
40
50
Days on therapy



Hazard ratios

	P v. control
Gati	0.054
Moxi	0. 017
Oflo	0.4



7H11 $\chi_{[3]}^2 = 7.3$, $p = 0.062$: MGIT $\chi_{[3]}^2 = 1.7$, $p = 0.6$

Conclusions

- When substituted for Ethambutol, both Moxifloxacin and Gatifloxacin cause killing in the late phase significantly faster than in the controls
- Ofloxacin substitution had no effect
- Of the various analytic methods, SSCC was the best with speed of sputum conversion and then proportion of patients with negative cultures at 8 weeks.
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- SSCC methods should be used in future studies.

Collaborators

Clinical trial
(S African MRC)

- Bernard Fourie, Roxana Rustomjee
- Thuli Mthiyane, Karl Reddy
- Wim Sturm, Jenny Allen, Frik Sirgel

Oflotub

- Christian Lienhardt, EU Framework 5
  Tom Kanyok, WHO/TDR

Analysis

- Gerry Davies (Wellcome, Bangkok)
- Jonathan Levin