

# Endpoints that may correlate with cure & validation of biomarkers

**Gerry Davies**

Reader in Infection Pharmacology  
Institutes of Infection & Global Health and Translational Medicine

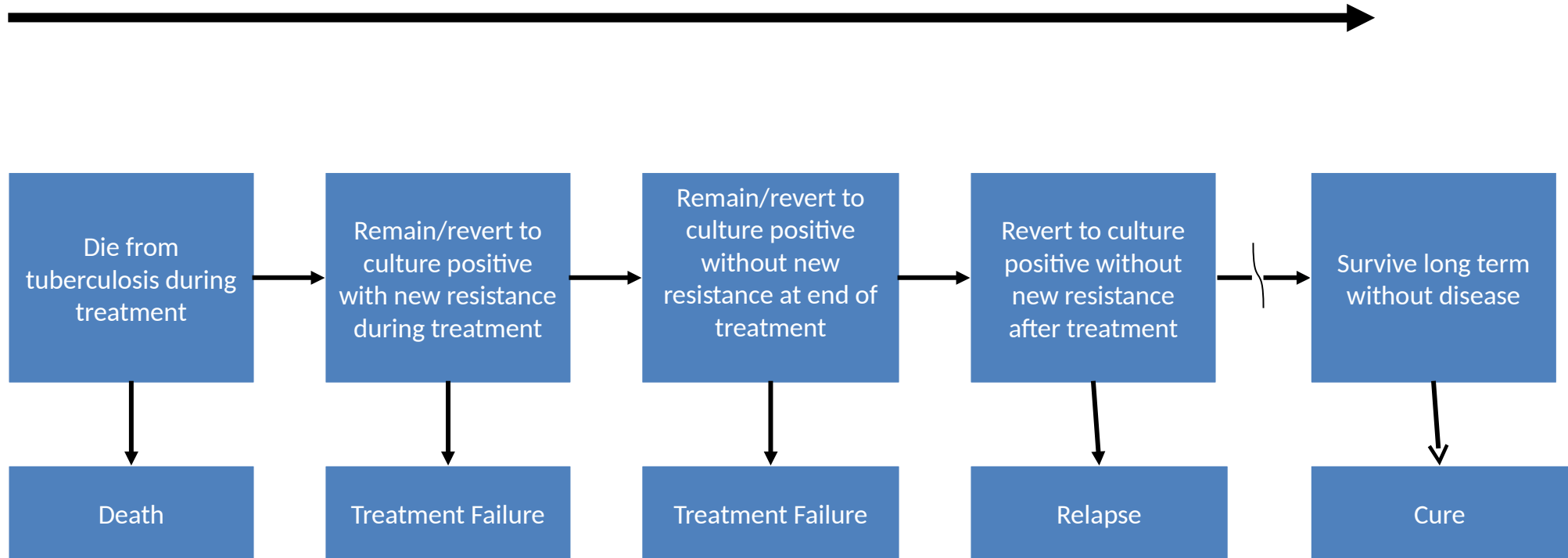


# Overview

- How are endpoints be related to each other ?
- What data are available to us ?
- What do we mean by surrogacy ?
- What does the current evidence show ?
- What do we mean by validation ?
- Which endpoints should we use in the future ?

# Causal linkage of efficacy endpoints

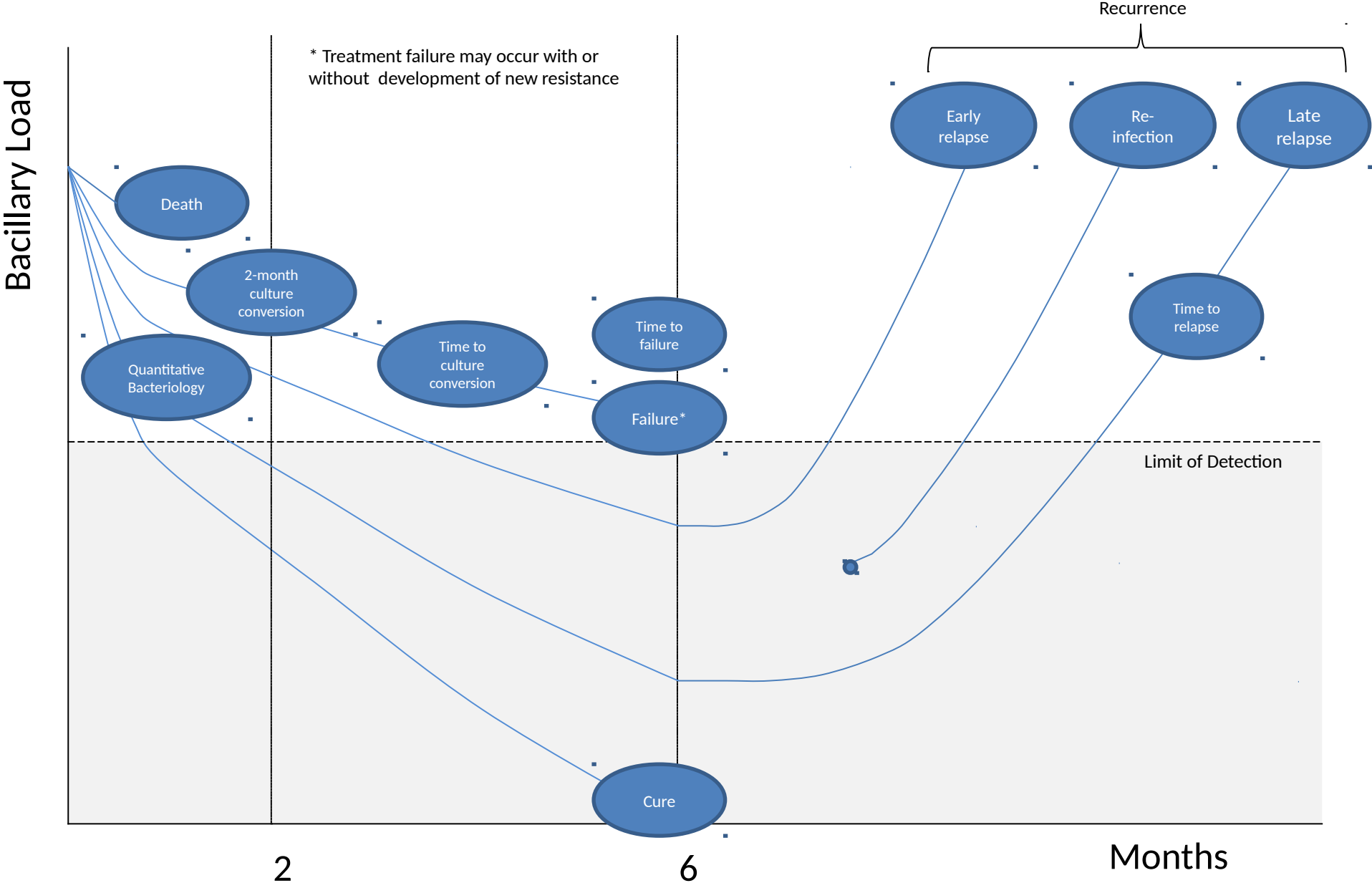
Increasing potency of regimens



“Bactericidal activity”

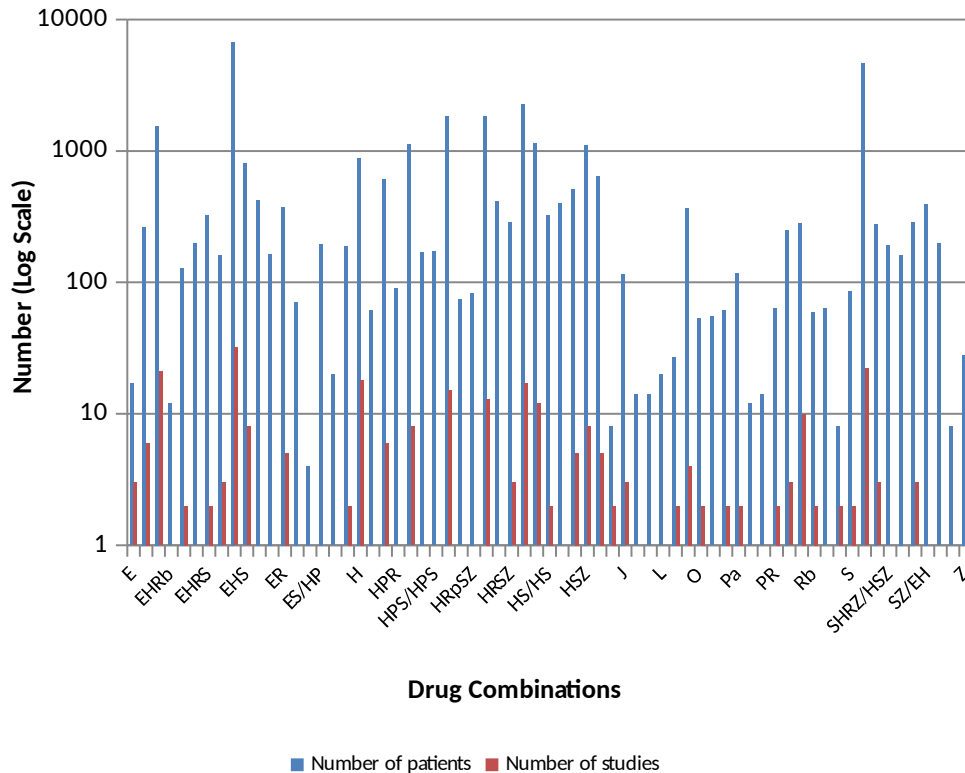
“Sterilizing activity”

# Quantitative basis of efficacy endpoints



# Phase II Systematic Reviews

N=37,173 67 drugs/combinations



133 trials with Phase IIA/B Outcomes

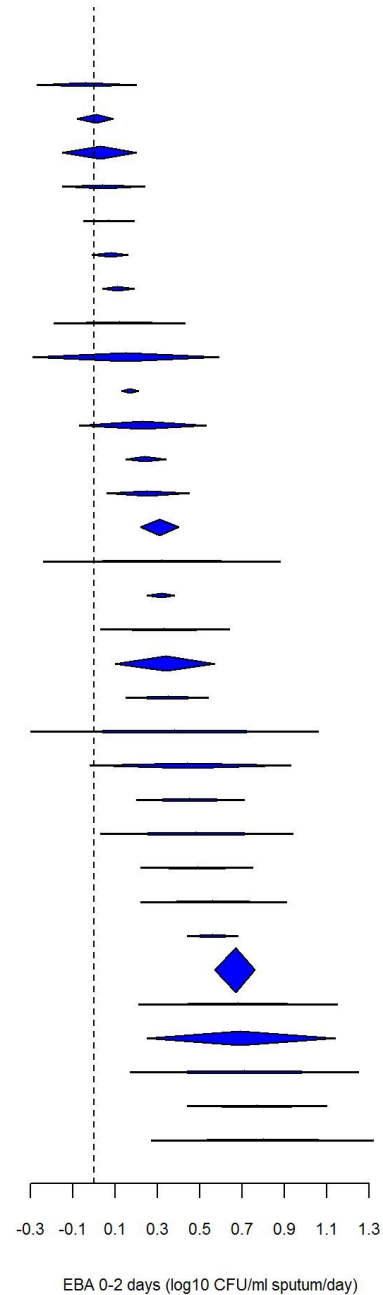
96 Phase III trials with intermediate outcomes

EBA<sub>0-2</sub> and 8w CC most commonly reported endpoints

Inconsistent reporting of other EBA endpoints (EBA<sub>0-7</sub>, EBA<sub>0-14</sub>) and alternative approaches

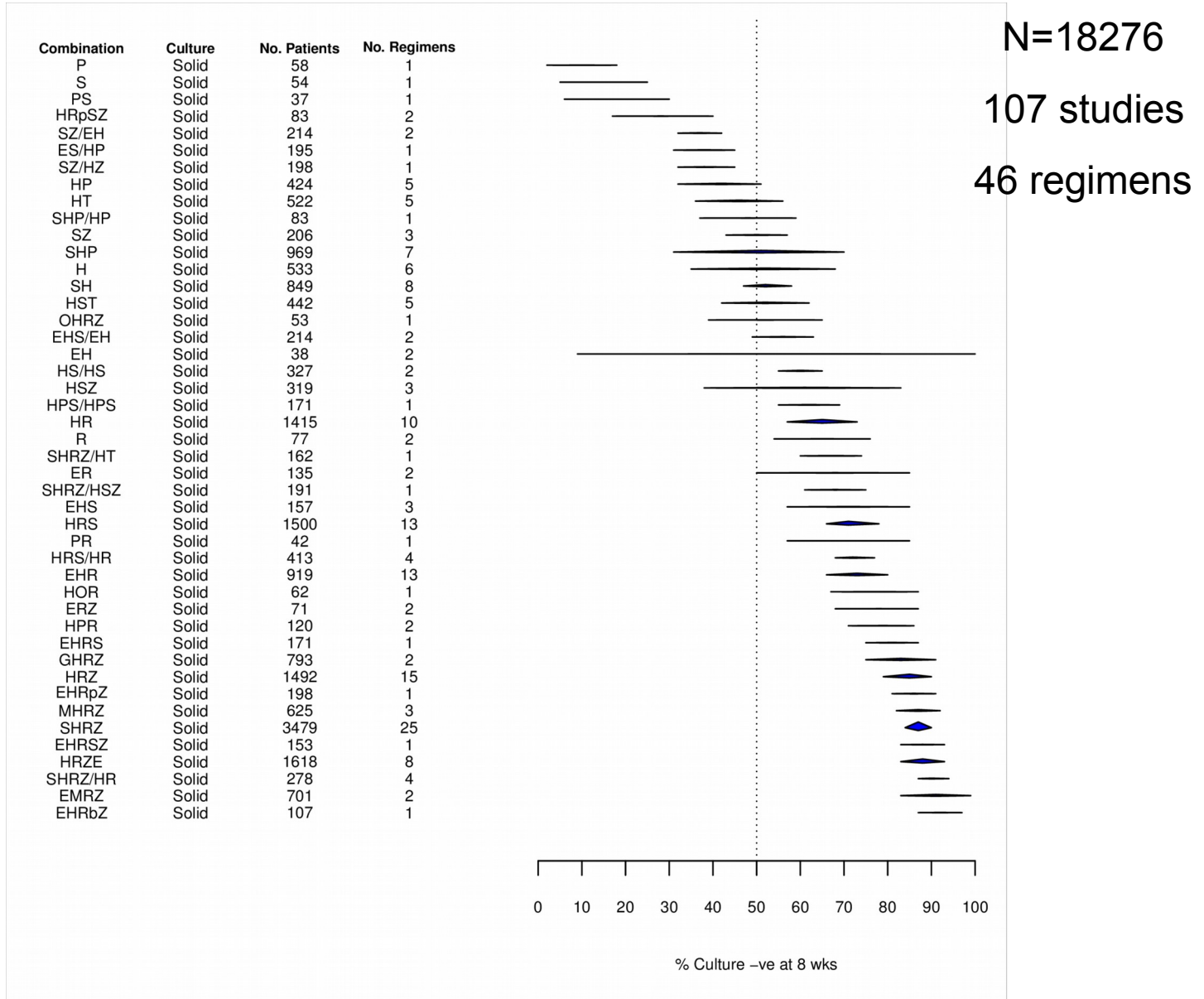
Only 3 regimens with EBA over >2 days and 8w CC data

Combination	Culture	No. Patients	No. Regimens
Rb	Solid	12	1
Z	Solid	27	3
J	Solid	41	3
S	Solid	13	2
ES	Solid	4	1
JZ	Solid	15	1
JPa	Solid	14	1
SZ	Solid	8	2
Pa	Solid	29	2
PaZ	Solid	15	1
R	Solid	28	3
Rp	Solid	16	1
E	Solid	17	3
O	Solid	53	5
HRS	Solid	8	2
PaMZ	Solid	15	1
RS	Solid	8	2
EHRZ	Solid	51	6
G	Solid	10	1
HS	Solid	8	2
M	Solid	18	2
L	Solid	10	1
EHR	Solid	8	2
HZ	Solid	8	2
ER	Solid	8	2
HRZ	Solid	9	1
H	Solid	149	16
ESHRZ	Solid	8	2
SHRZ	Solid	47	4
HR	Solid	8	2
EH	Solid	8	2
HSZ	Solid	8	2

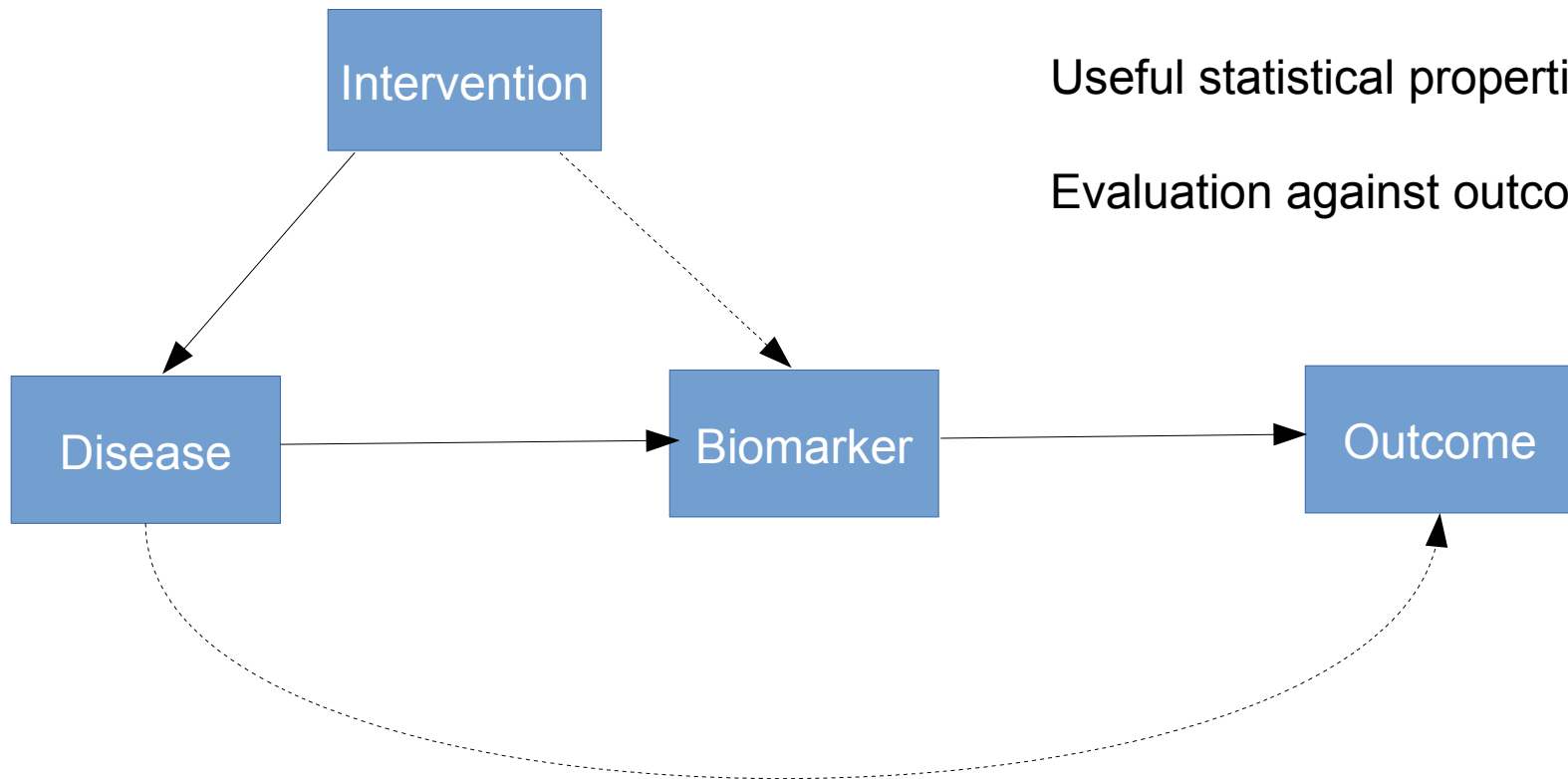


N=681  
24 studies  
141 regimens

# 8w culture conversion



# Concept of surrogacy



Biologically plausible

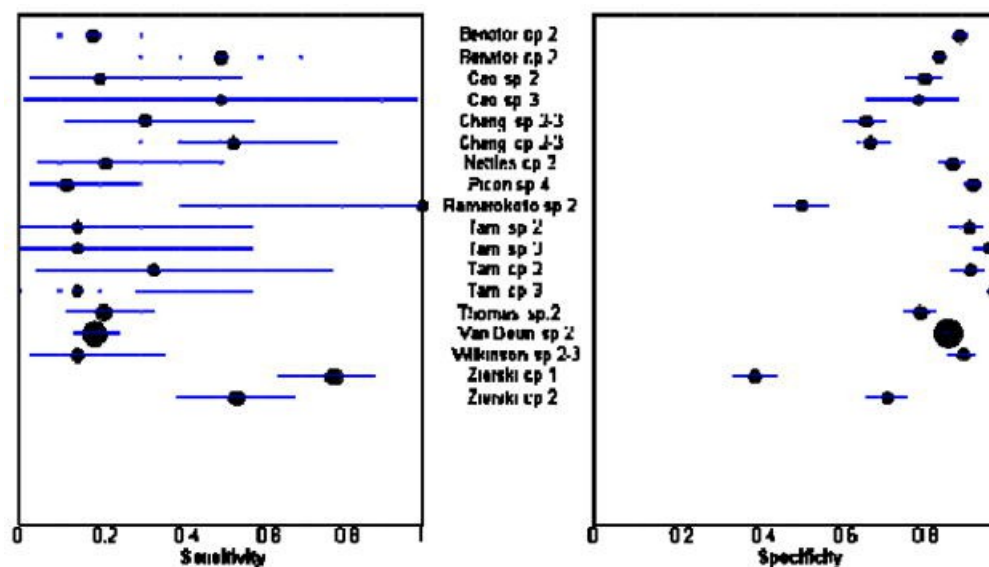
Useful statistical properties

Evaluation against outcome

# Surrogate endpoint

- A biomarker that can replace the reference endpoint
- Trial level : The ability to capture treatment effect on the definitive endpoint ( $\rho_z$ , RE, PTE,  $R^2_{\text{trial}}$ )
- Individual level : The ability to predict an individual's definitive outcome (PPV, NPV, ROC,  $R^2_{\text{individual}}$ )
- These levels are theoretically independent (Simpson's paradox) though in practice often go together

# 8w CC : individual level



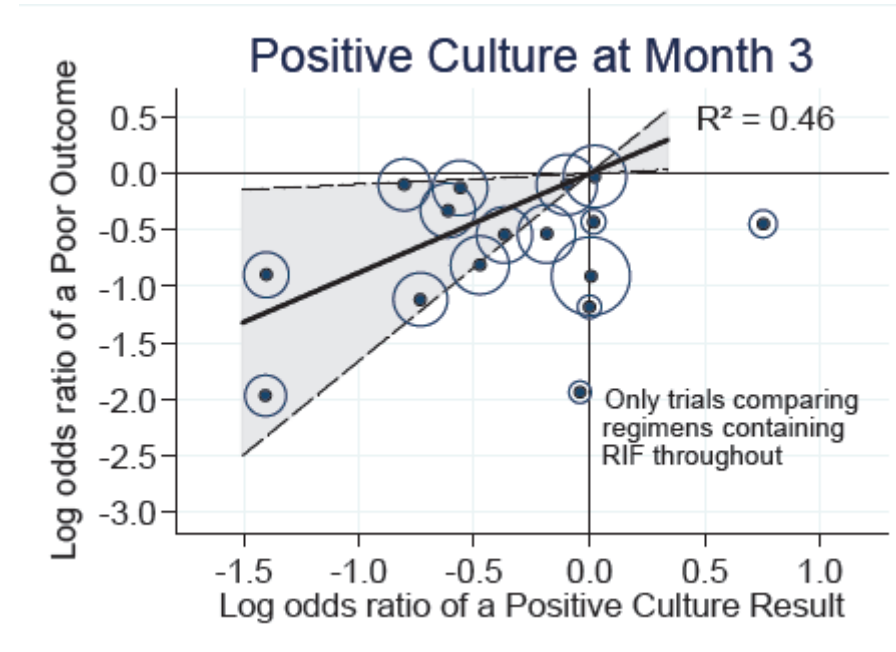
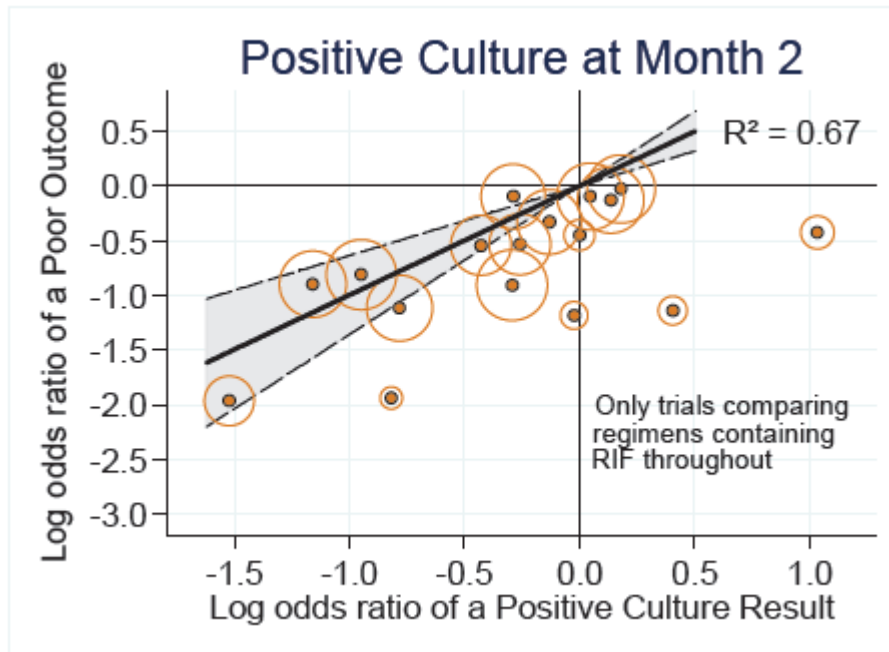
	Studies (n)	Sample size (N)	Hierarchical regression model		Odds ratio (95% CI)	PPV* (95% CI)	NPV* (95% CI)
			Sensitivity (95% CI)	Specificity (95% CI)			
<b>Relapse</b>							
Culture	4	1298	40% (25-56%)	85% (77-91%)	3.8 (2.2-6.8)	18% (14-21%)	95% (95-96%)
Smear	6	9848	24% (12-42%)	83% (72-90%)	1.5 (1.1-2.2)	10% (8-12%)	93% (93-94%)
<b>Failure</b>							
Smear	7	20 062	57% (41-73%)	81% (72-87%)	5.8 (4.3-7.8)	9% (9-10%)	98% (98-98%)

\* Ability of smear to predict poor outcomes, assuming 7% risk of relapse and 3% risk of failure. NPV=negative predictive value; PPV=positive predictive value.

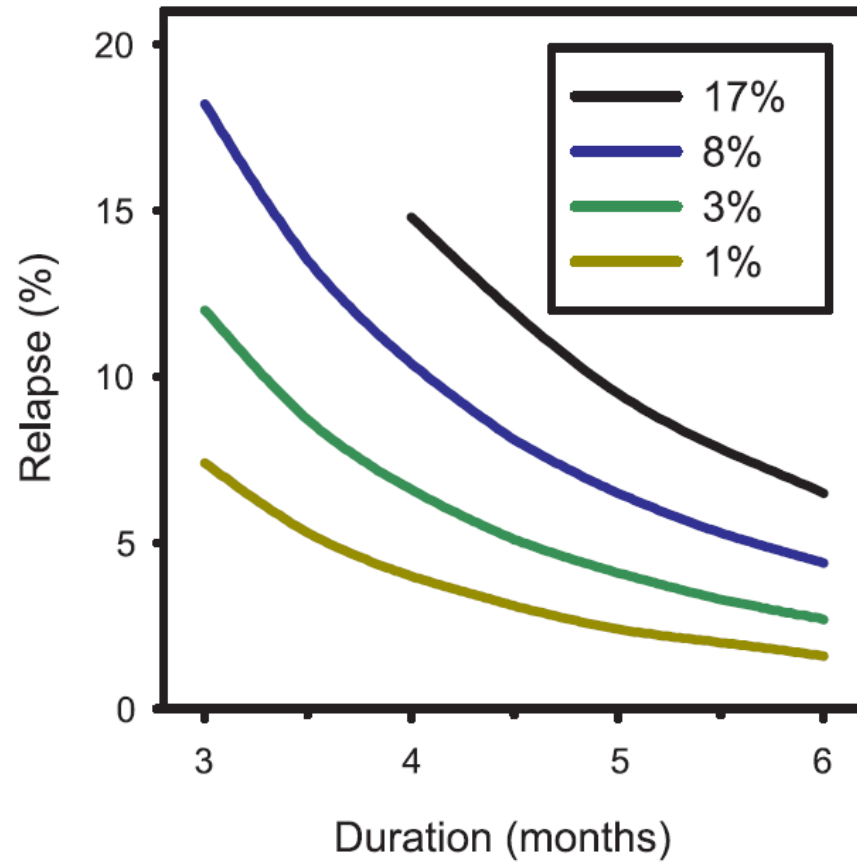
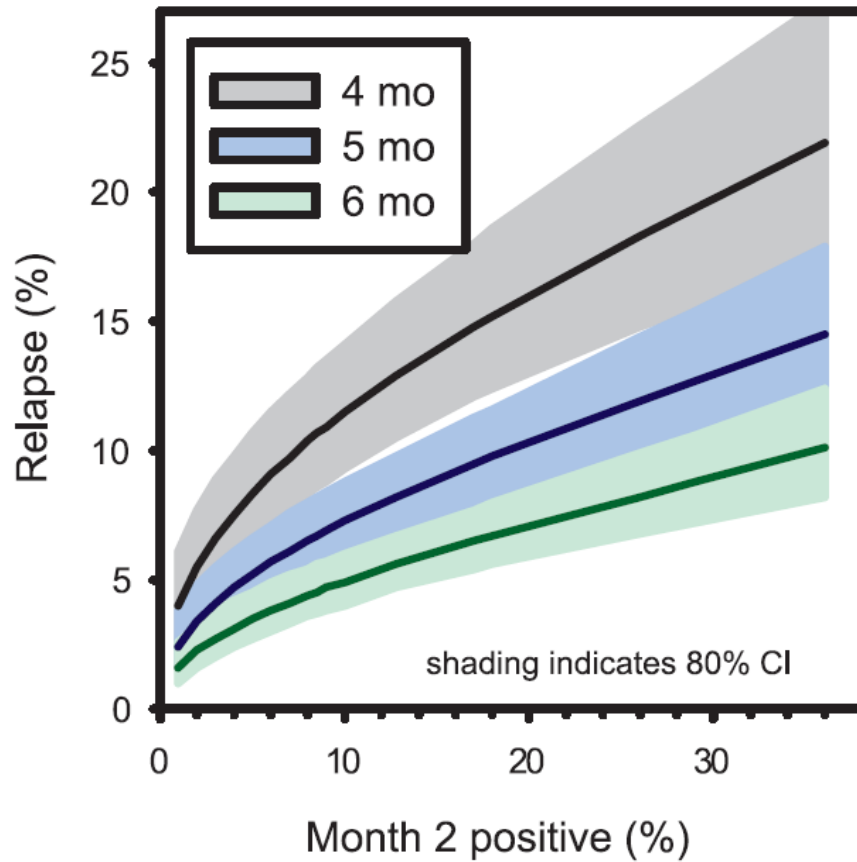
**Table 5: Pooled summary estimates for relapse or failure for patients with a positive sputum culture or smear at 2 months**

# 8w CC : trial level

15 BMRC trials 6974 participants 37 treatment comparisons



# 8w CC : Predicting duration



# Evaluation, Validation, Qualification

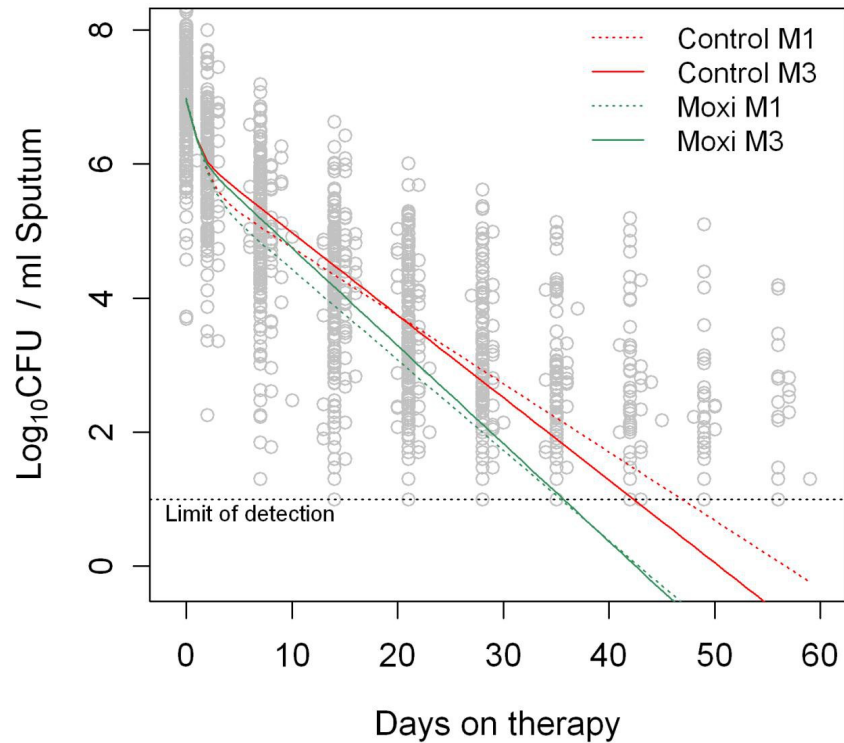
- Prentice criterion
- $R^2_{\text{trial}}$  “sufficiently close to” 1
- Reasonably likely to predict clinical benefit
- Widespread agreement about the significance of the test results
- Can be relied upon to have a specific use and interpretable meaning

# Longitudinal or time-to-event endpoints

- Independent of sampling timepoints
- No need for future ad hoc re-evaluation
- Unrestricted scale of measurement
- Greater statistical power
- Well-adapted to cumulative meta-analysis
- Little trial level evaluation due to design and reporting
- Model choice, LOD, missing data

# Longitudinal endpoints

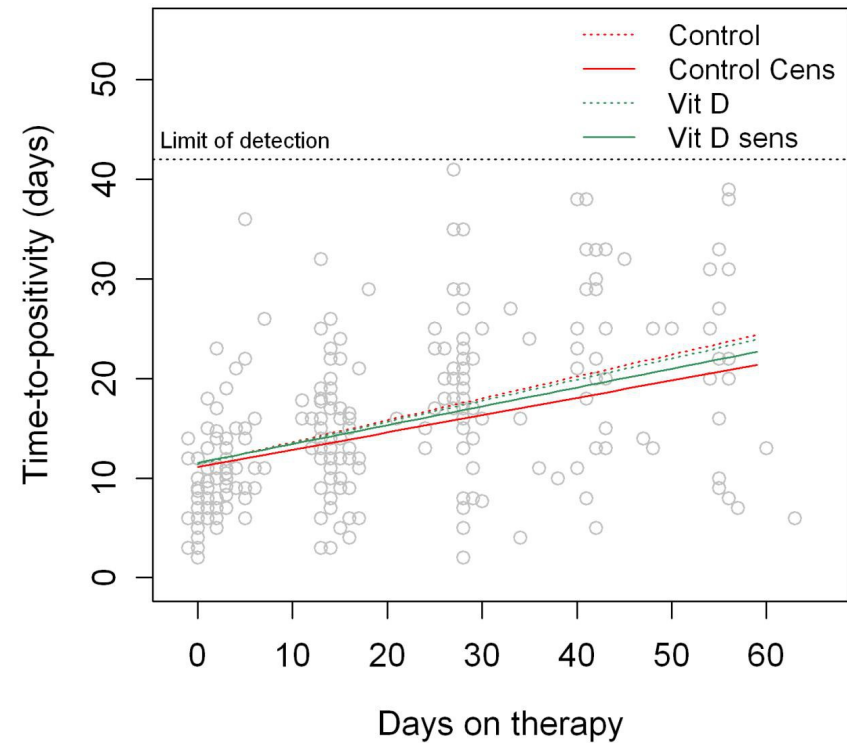
## Oflotub



M3 method in NONMEM

Rustomjee R IJTLD. 2008 12:128-38

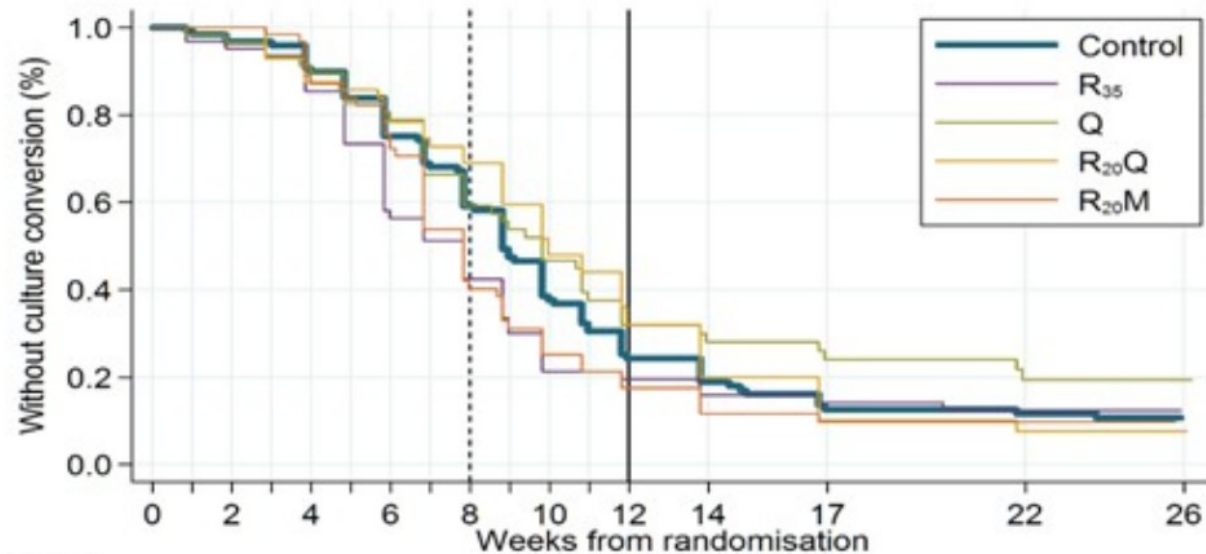
## AdjuVit



I () in WinBUGS

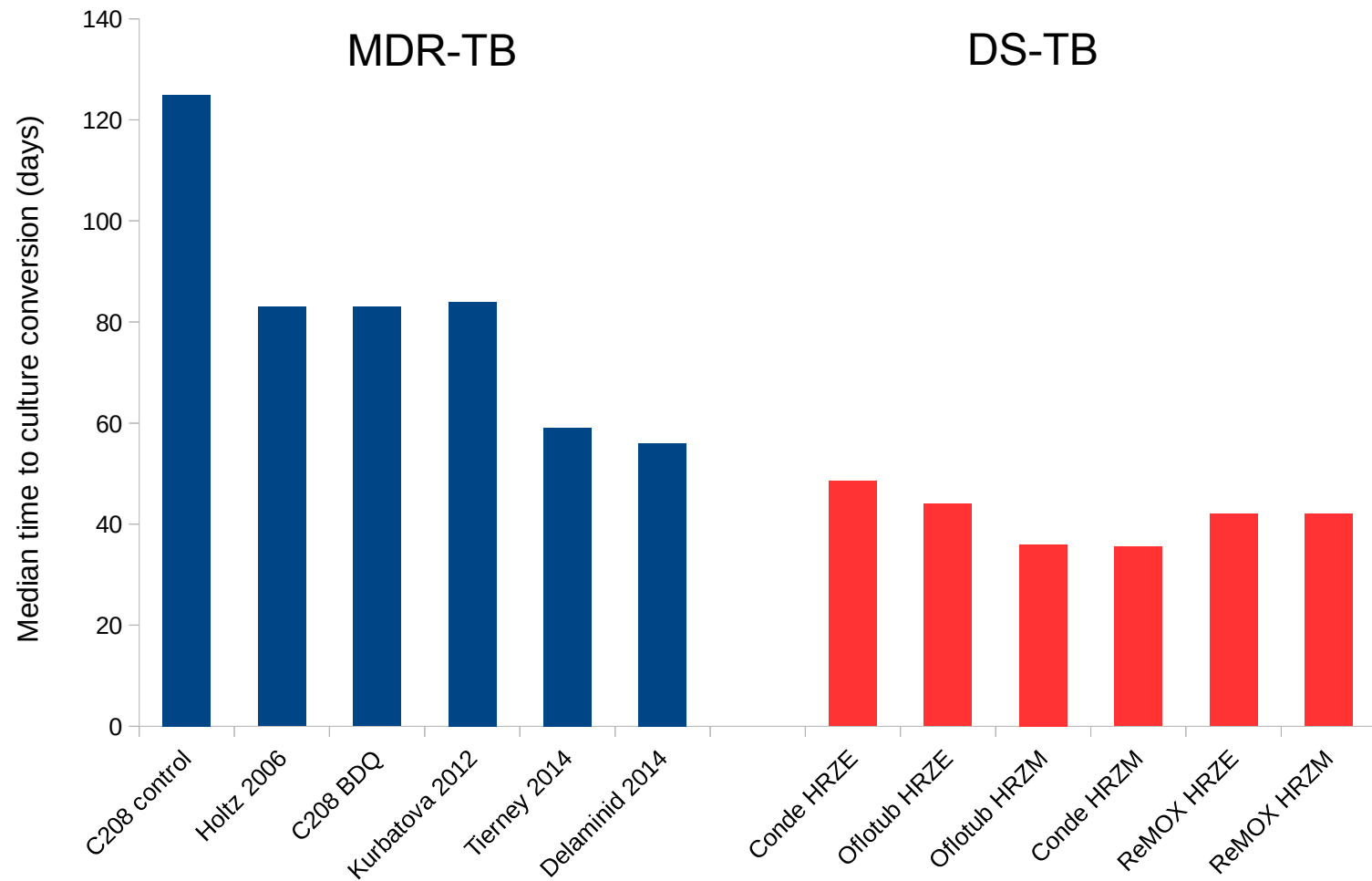
Martineau Lancet. 2012 377:242-50

# Time-to-event endpoints

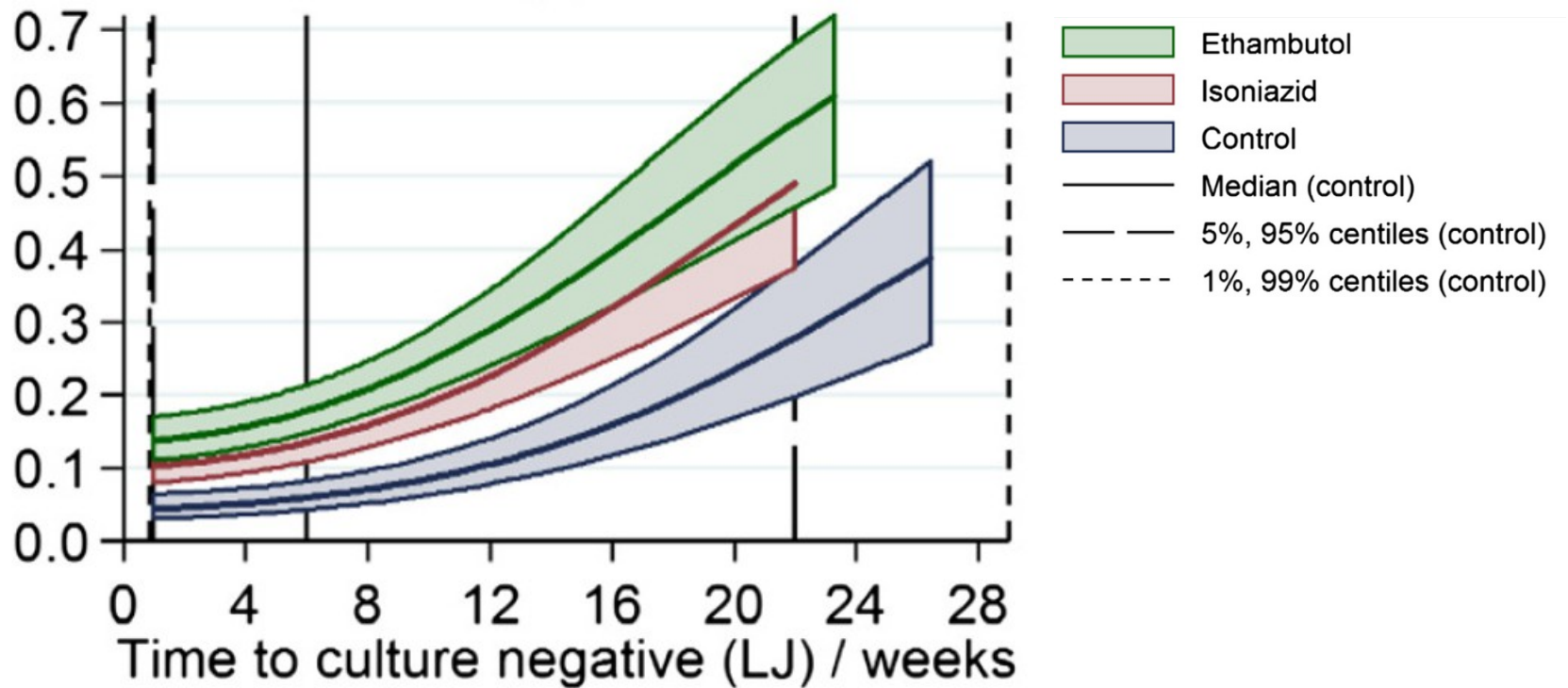


	Control	Q	20RQ	20RM	35R
Included in analysis	123	58	56	63	63
Median time	62 days	63 days	66 days	55 days	48 days
Adj. HR <sup>1</sup> (95% CI)		0.85 (0.57 - 1.27)	0.76 (0.50 - 1.17)	1.42 (0.98 - 2.05)	<b>1.78</b> <b>(1.22 - 2.58)</b>
		p=0.42	p=0.21	p=0.07	<b>p=0.003</b>

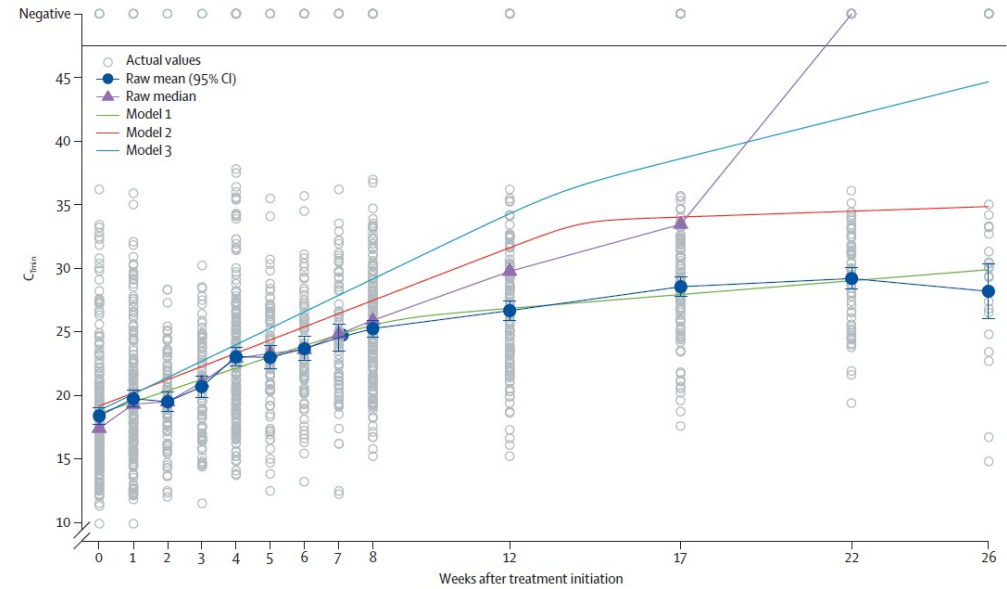
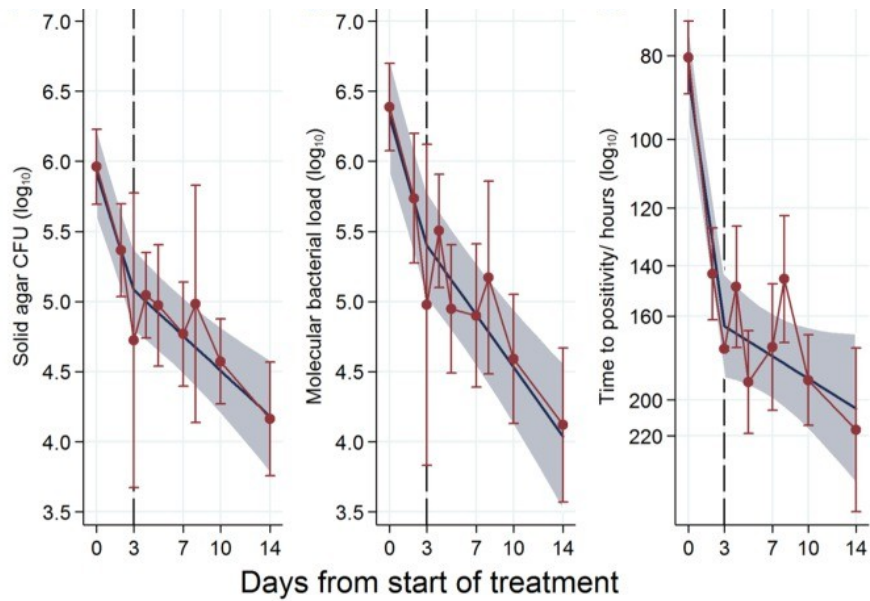
# Scaling of time-to-event endpoints



# Time-to-event : individual level



# Culture-independent methods



Honeyborne I 2014 J Clin Micro 52 : 3064-7

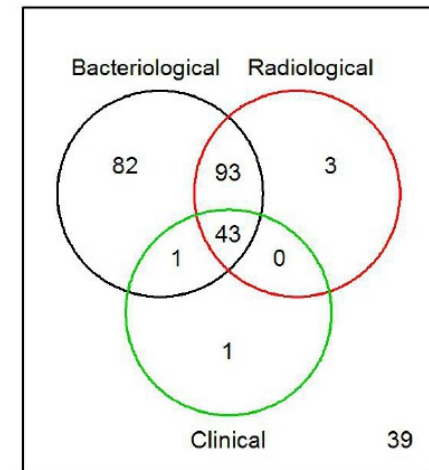
Friedrich S 2013 Lancet Resp Med 1:462

Xavier A 2013 J Clin Micro 51:1894

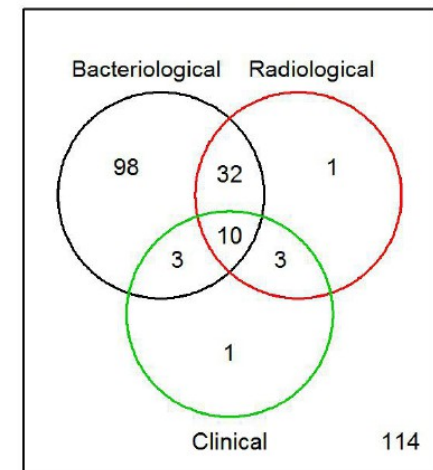
# Alternatives to microbiological endpoints

- Clinical prediction scoring
- Host response (blood/sputum IFN- $\gamma$ )
- Whole blood bactericidal assay
- Host trans/proteo/metabolomic signatures
- Functional imaging (FDG)
- Composite endpoints

On Treatment

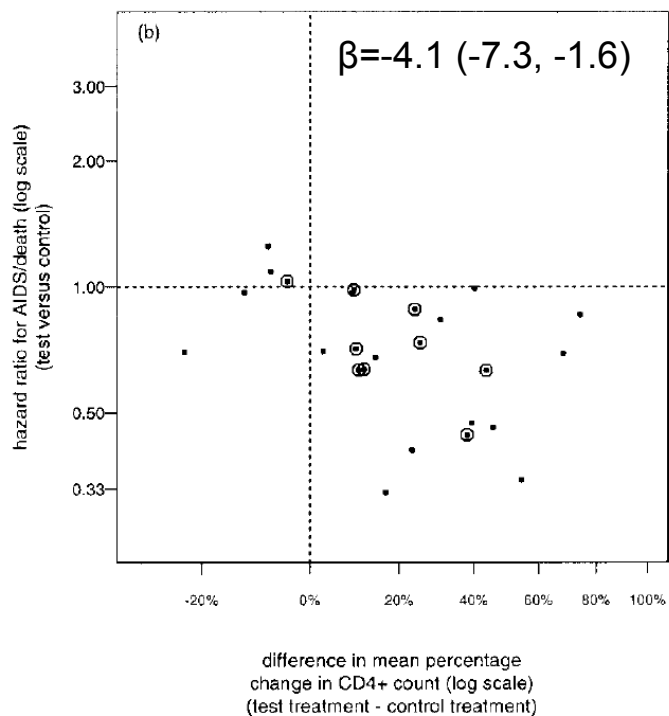


Off Treatment



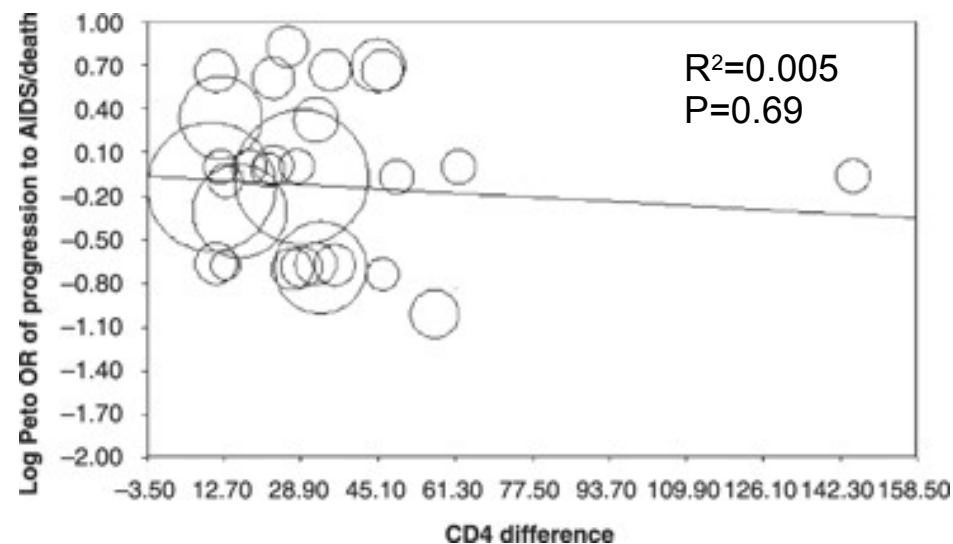
# Evolution of surrogate status

16 trials 13,045 participants  
1987-1997



HSMCG 2000 Aids Hum Retrovir 16 : 1123-33

22 trials 8,363 participants  
1994-2006



Mills EJ 2008 HIV Med 9:849

# Summary

- Biological and causal plausibility of bacteriological endpoints is strong
- Extensive evidence suggests the best-reported (8w CC) is a useful surrogate endpoint and predictive of duration of regimens in DS-TB
- Lack of consensus on outcomes or analytical approaches in Phase II hampers evaluation
- Longitudinal or time-to-event approaches offer many potential advantages and have some individual-level support
- Evaluation is a process not an event and meta-analysis would ideally be curated and cumulative
- A core outcome set would be desirable

# Points for discussion

- What are the best endpoints and approaches to bridge the gap from Phase IIA to Phase IIB ?
- What formal statistical approaches should be favoured for evaluation of early phase endpoints ?
- How will evaluation of longitudinal or time-to-event biomarkers be achieved without a core outcome set or definitions ?
- What are the implications of adaptive approaches for evaluation of novel endpoints and biomarkers ?
- How should the TB trials community support data collection and meta-analytic approaches to address these issues ?