

# **Novel TB Drugs**

## **Medical Need & Current Developments**

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Task Applied Science

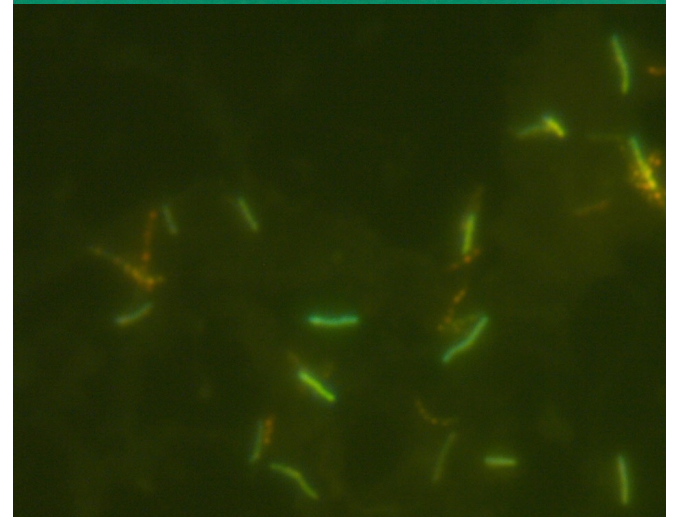


2ND REGULATORY WORKSHOP  
NEW DEVELOPMENTS IN DRUG REGULATION  
PRETORIA 2014



# TB in a nutshell

- TB infection is frequent
  - Only 10% develop active TB disease
  - Two billion people latent TB
- HIV increases TB infection and disease
  - TB #1 cause of death in HIV
- Treatment 6/12 with 4/2-drug combo
- Increasing drug resistance
  - Resistant to RIF & INH = MDR-TB
  - MDR & resistant to inject & FQ = XDR-TB





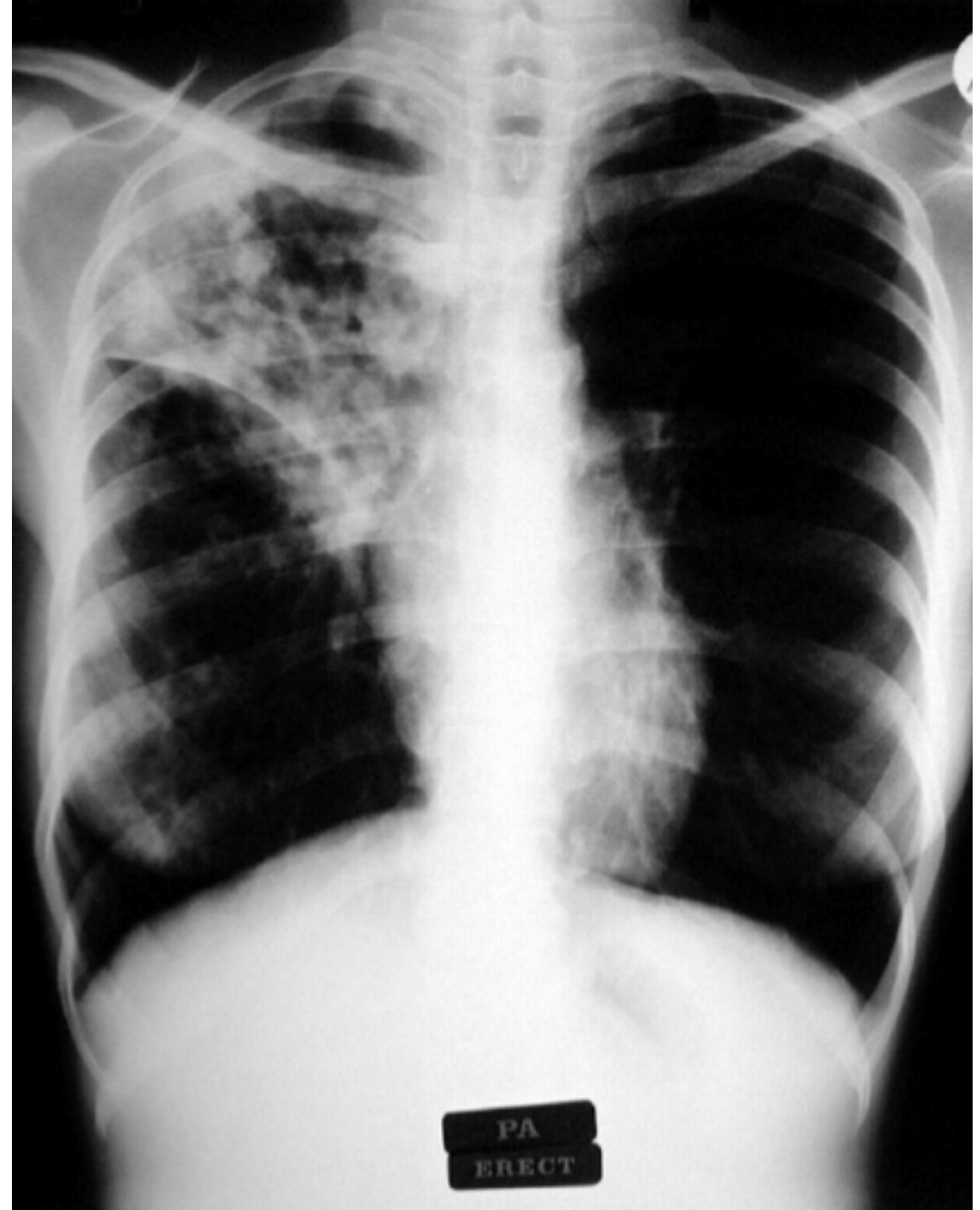


Ernst Ludwig Kirchner. Blick auf Davos. 1924. BündnerKunstmuseumChur, Switzerland



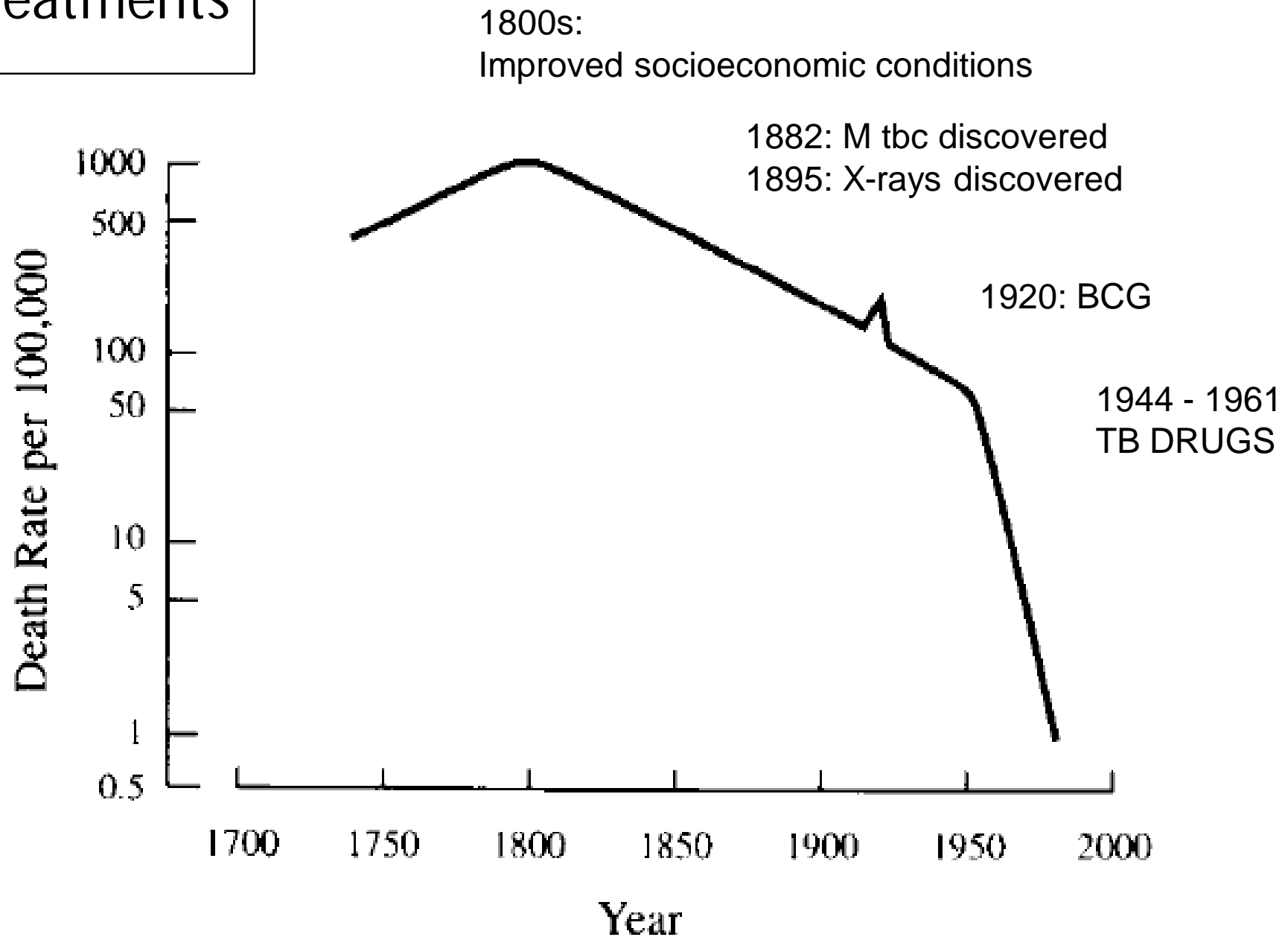
# The Magic Mountain

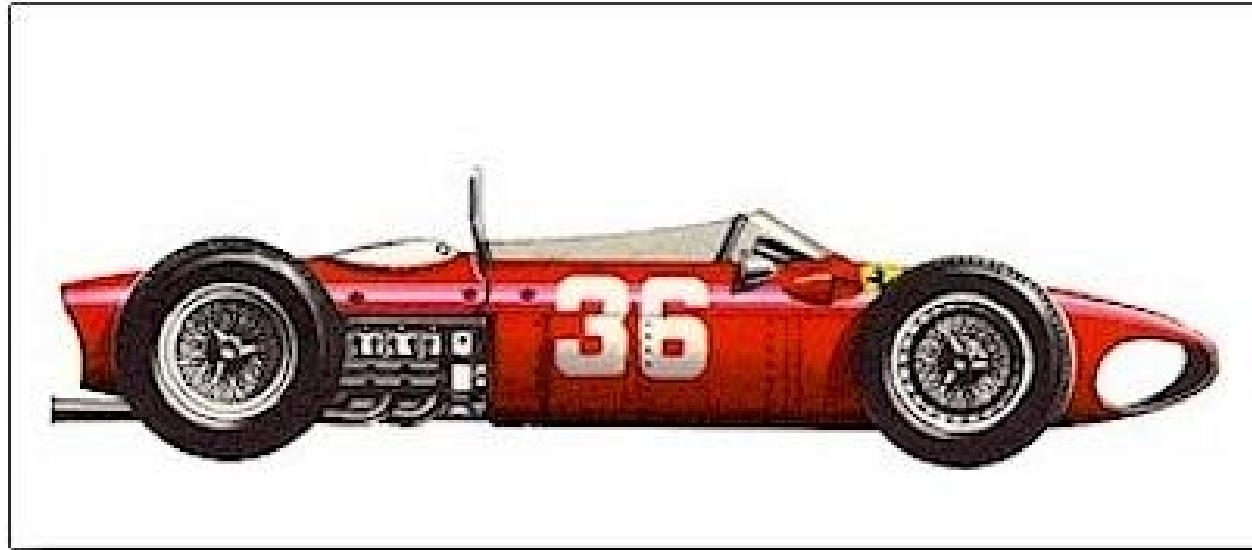
- Sunlight
- Nutrition
- Supine





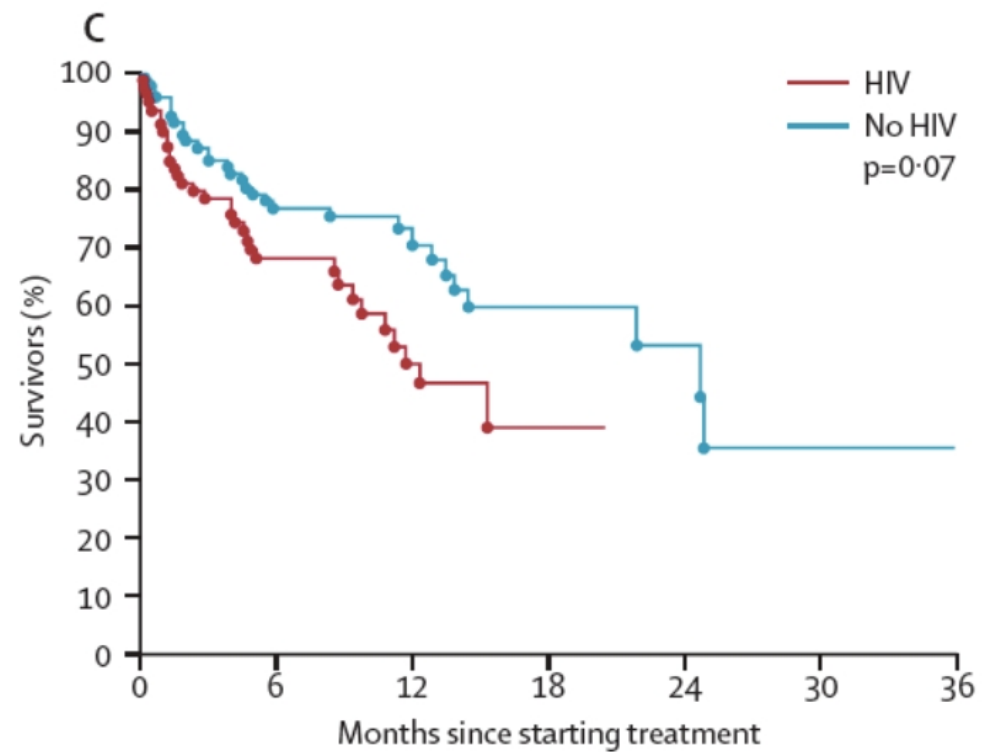
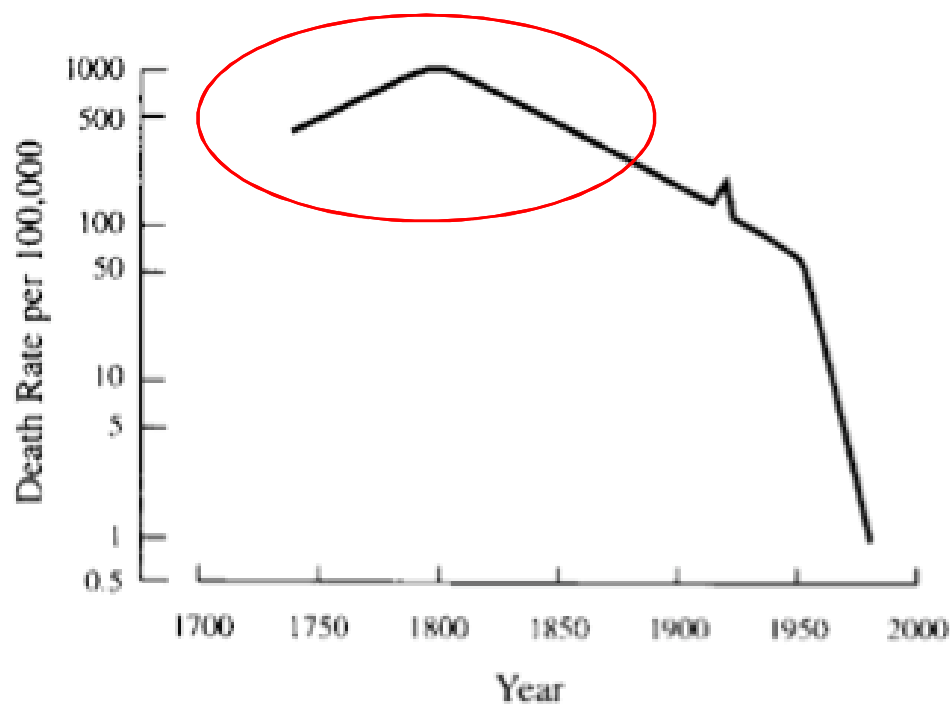
- Vaccines
- Diagnostics
- Treatments





1961





## HIV negative cases with active TB

### Pre-chemotherapy era:

- 10-year fatality rate 70%

### XDR TB Western Cape:

- 3-year fatality rate 60%

Tiemersma EW. 2011. PLoS ONE 6(4): e17601.

Dheda et al. Lancet 2010;375:1798–807

# Consumption



## Switzerland:

- 7/100,000
- EU: 17/100,000 per year

# HIV & XDR TB



## Cape Town:

- 28,000 TB cases pa (24,000 PTB)
- 10% children (<8 years)
- TB notification rate 2012: 990/100,000
- MDR 1,500/year (estimate)
- XDR 100/year (estimate)

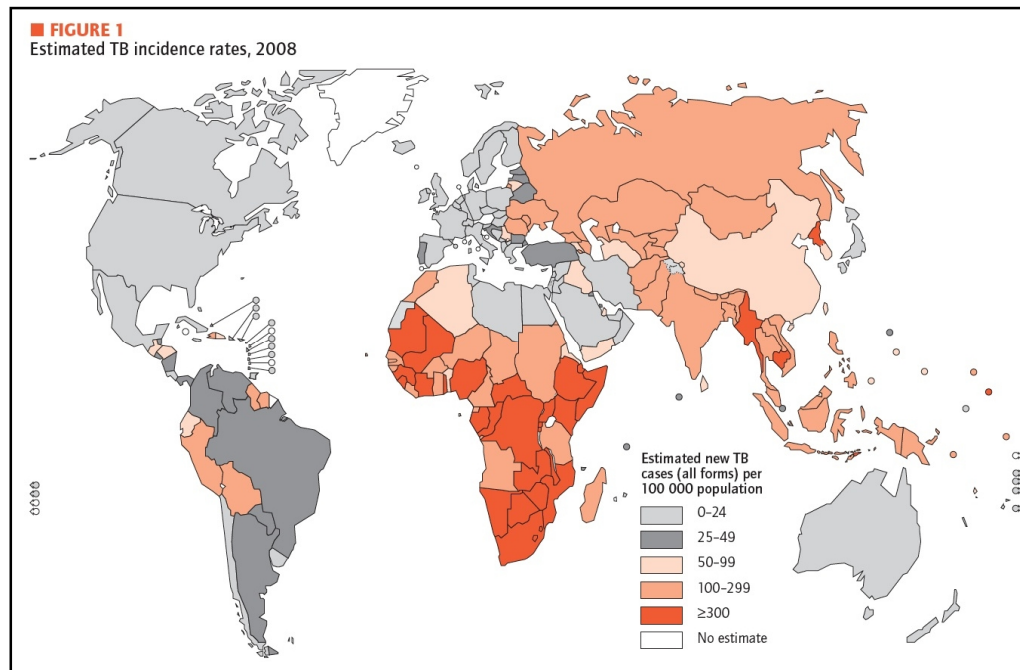




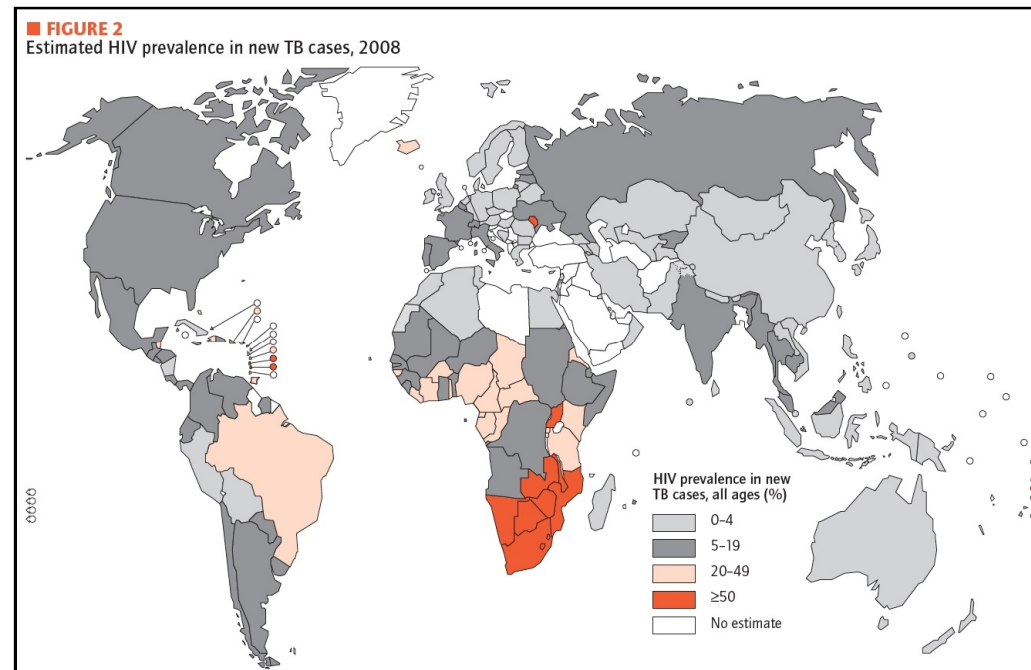




## TB

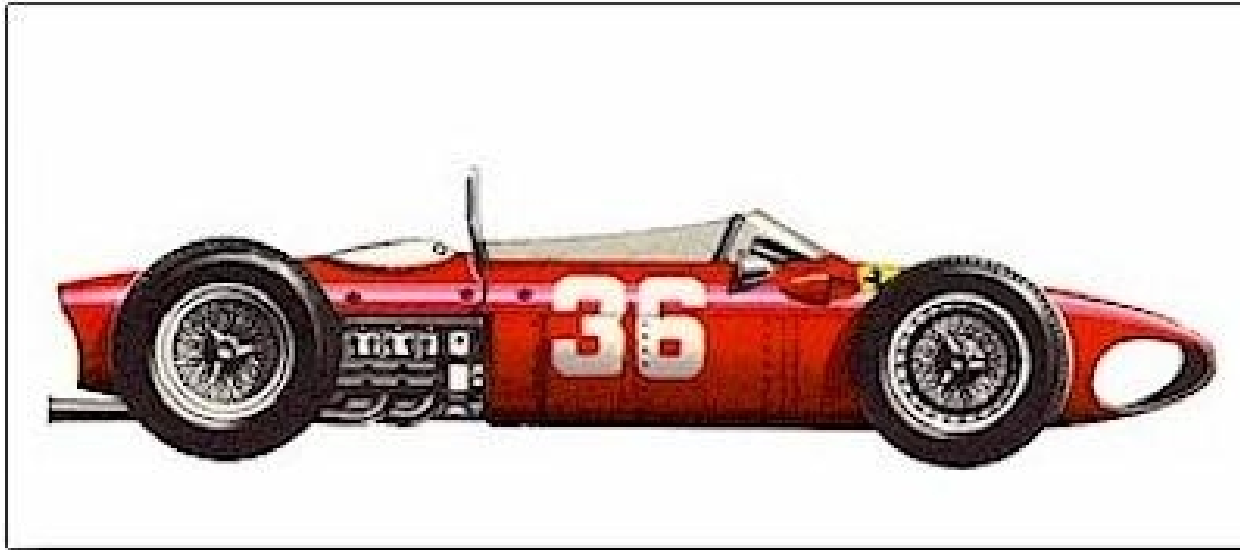


## HIV

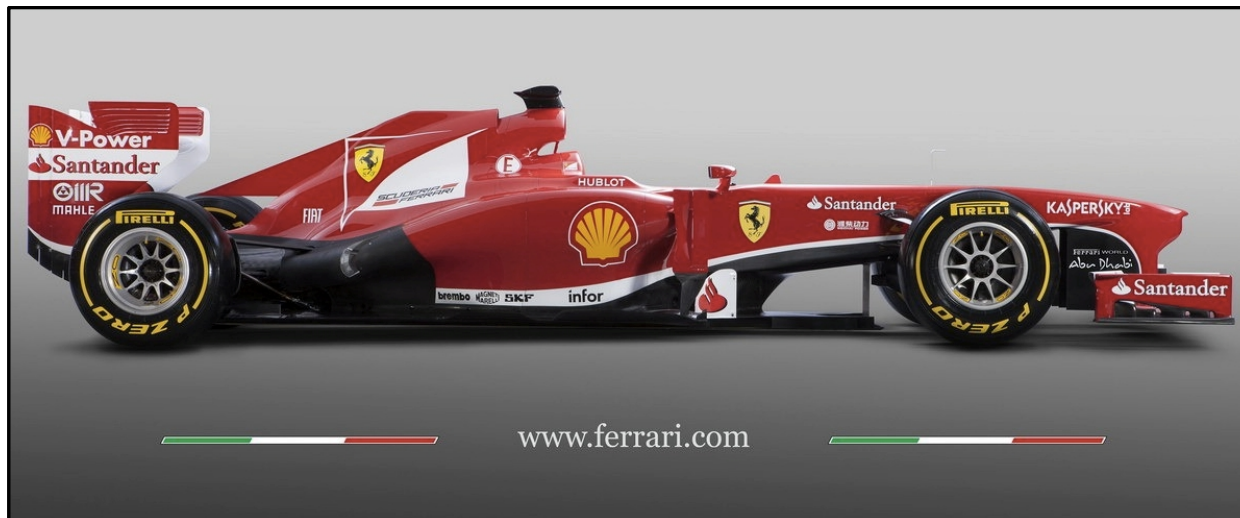




# Need new drugs



1961



2013

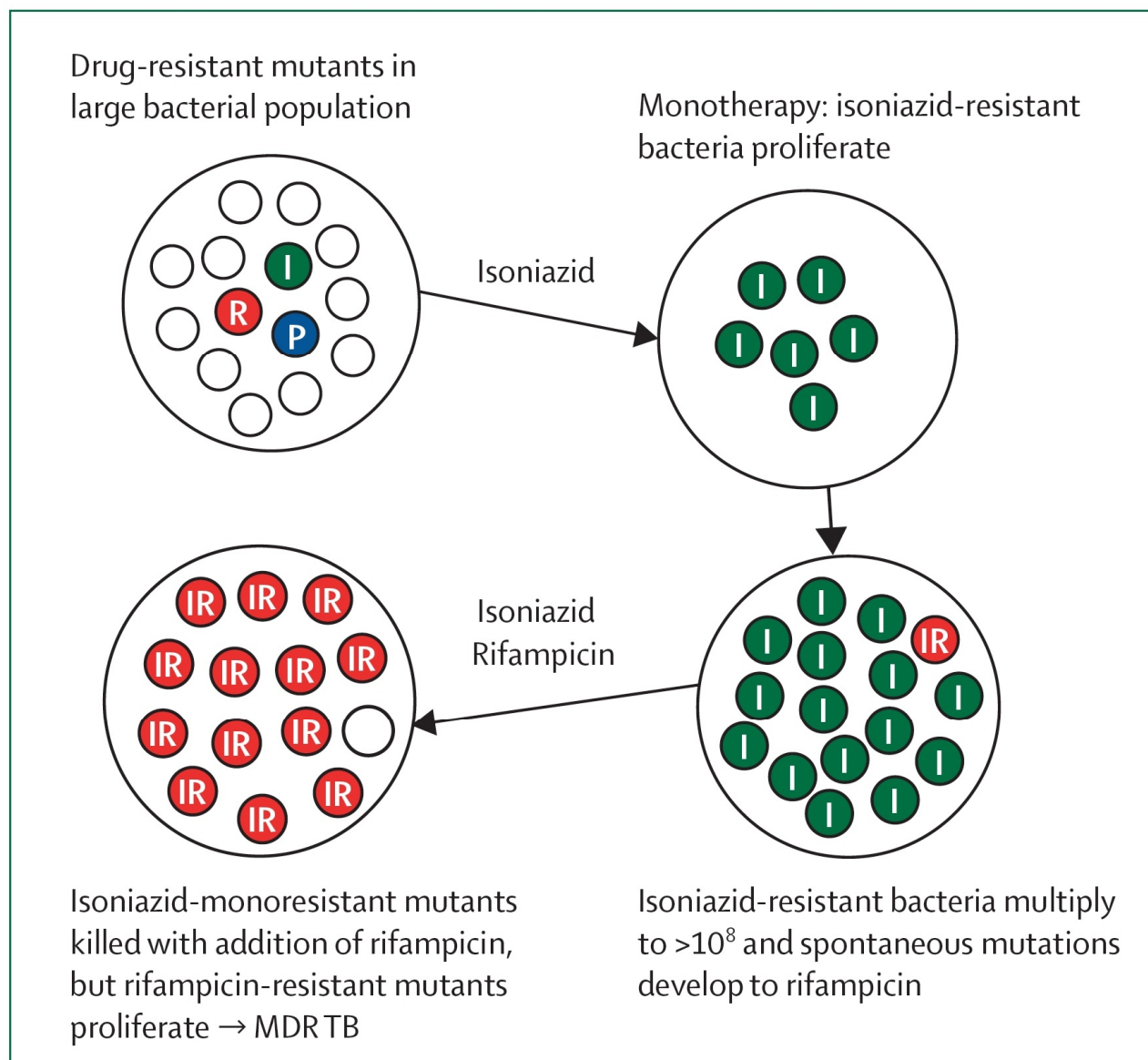
[www.ferrari.com](http://www.ferrari.com)

# continuous process of innovation and testing





# Resistance is always present



Drug	Rate
INH	$1 \times 10^6$
RIF	$1 \times 10^9$
EMB	$1 \times 10^5$
PZA	$1 \times 10^5$

**No monotherapy for active TB!**  
**Acquired -> transmitted resistance**

Gandhi et al Lancet 2010;375:1830

# Combination treatment prevents monotherapy Drug resistance from poor compliance?

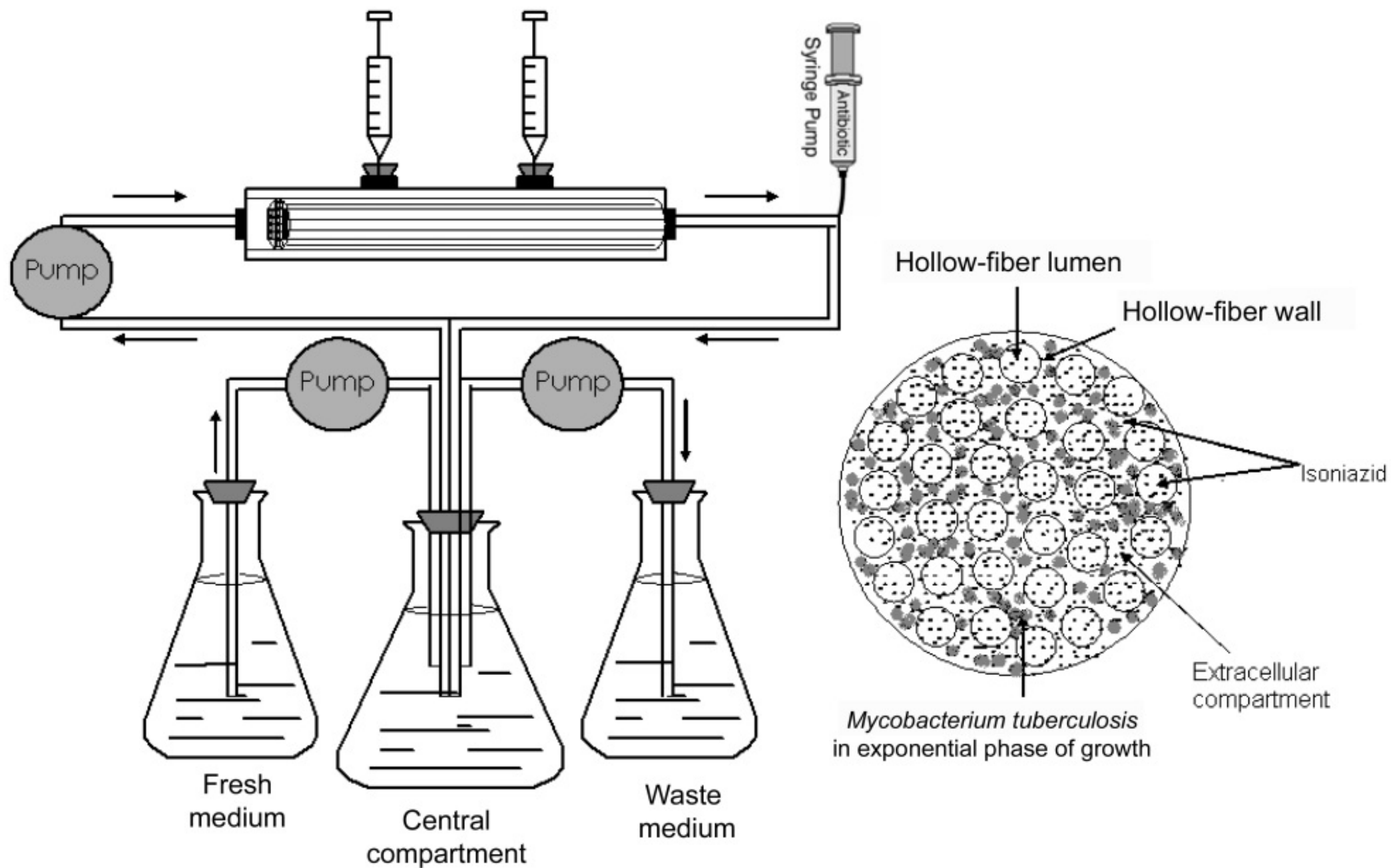


## Hollow Fiber Model

Gumbo et al JID 2007:195;194-201

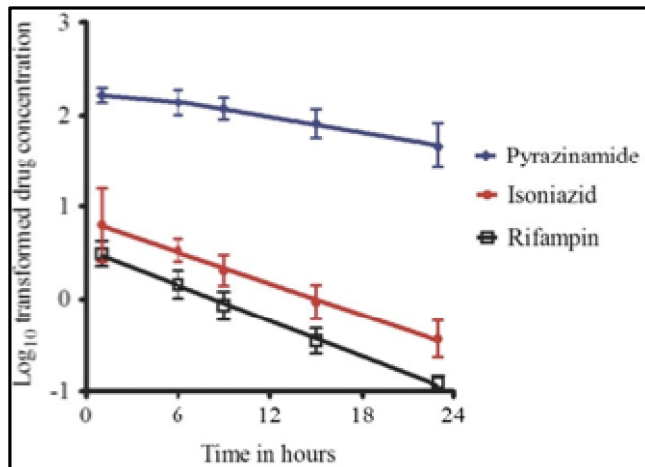
Srivastava et al JID 2011:204; 1951-9



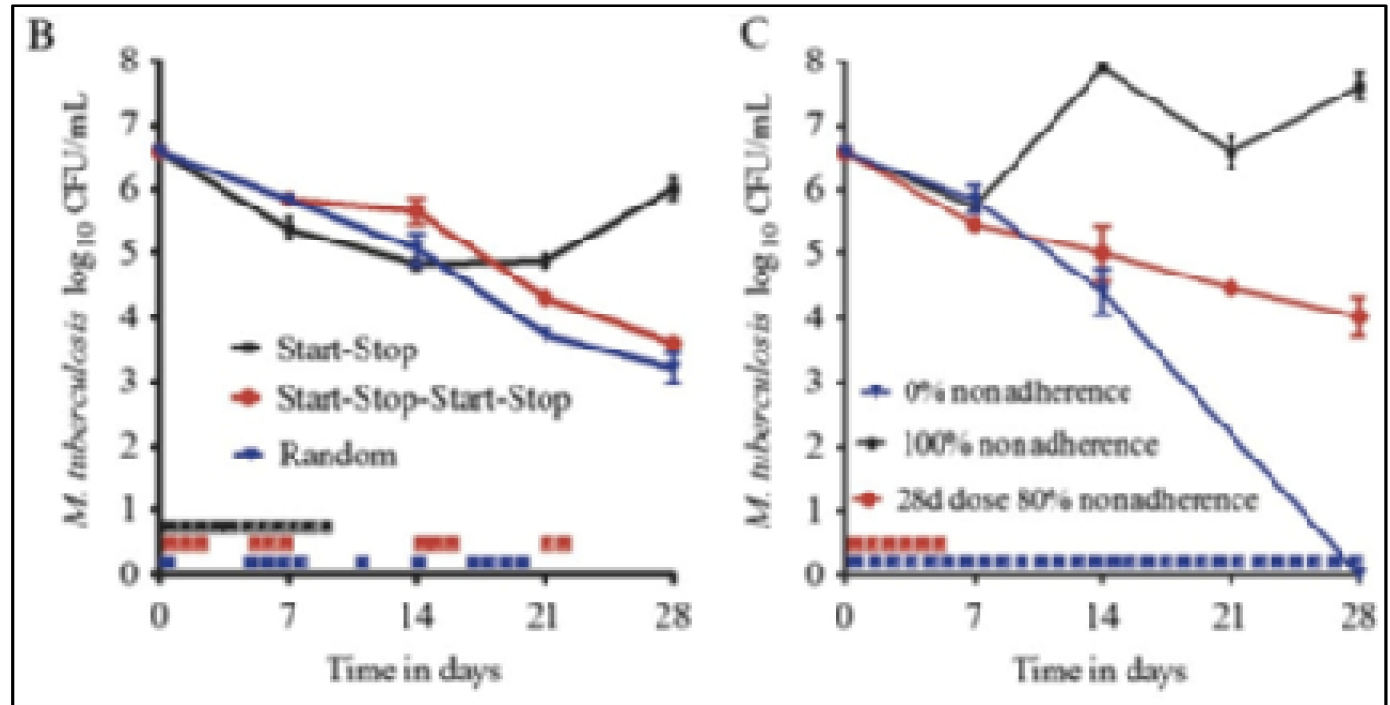


# How quick does non-compliance cause MDR TB?

- Fast and slow growing bacteria
- 0.5% INH-resistant, 0.5% RIF-resistant
- Treated with HRZ at human serum levels
- Poor compliance patterns as seen in practice
- Weekly harvesting to measure resistance



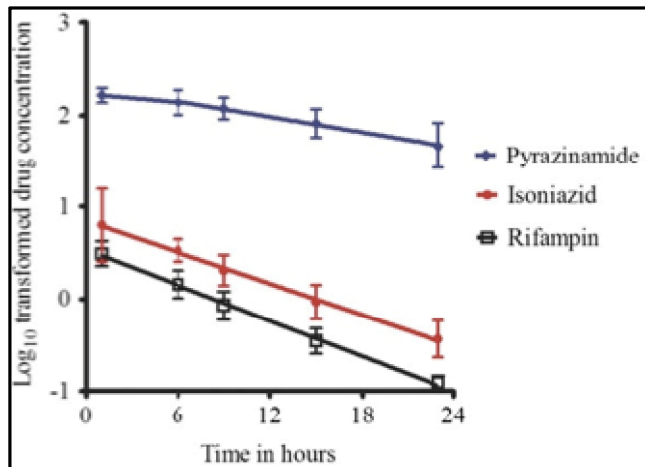
Standard once-daily treatment



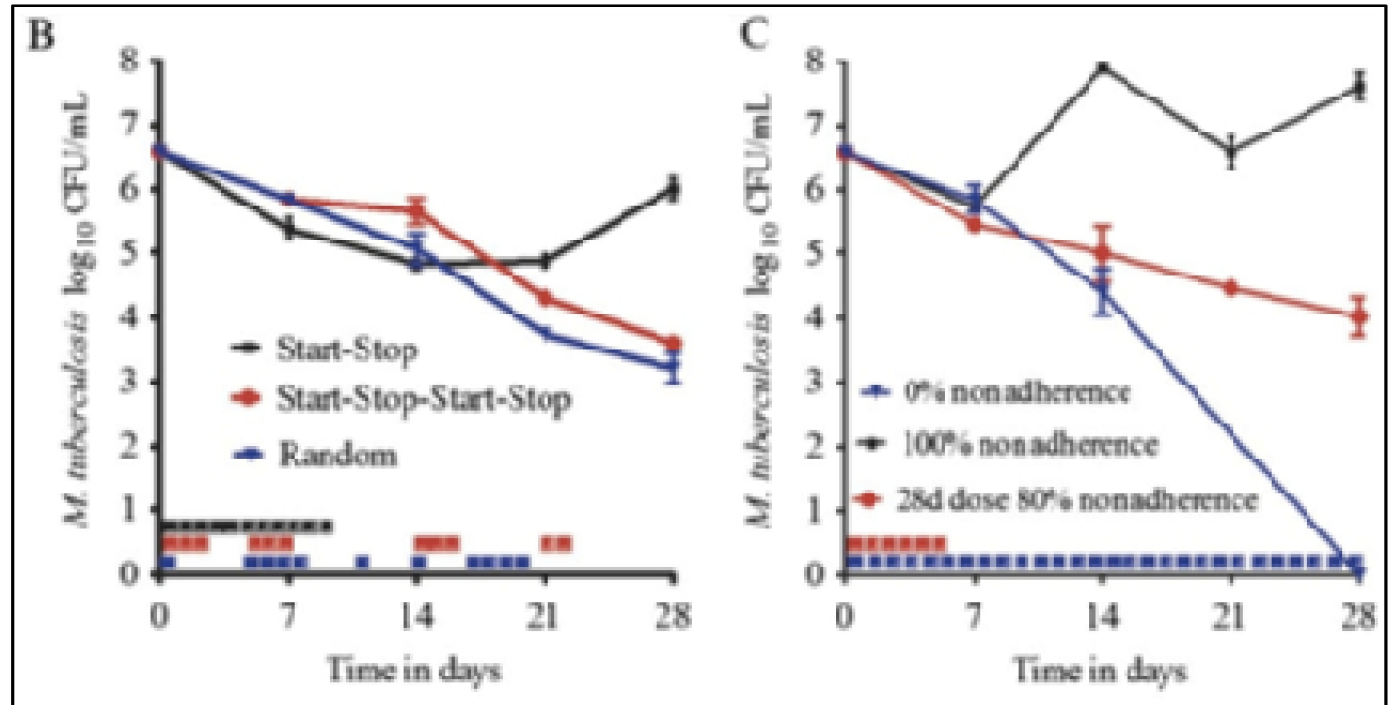


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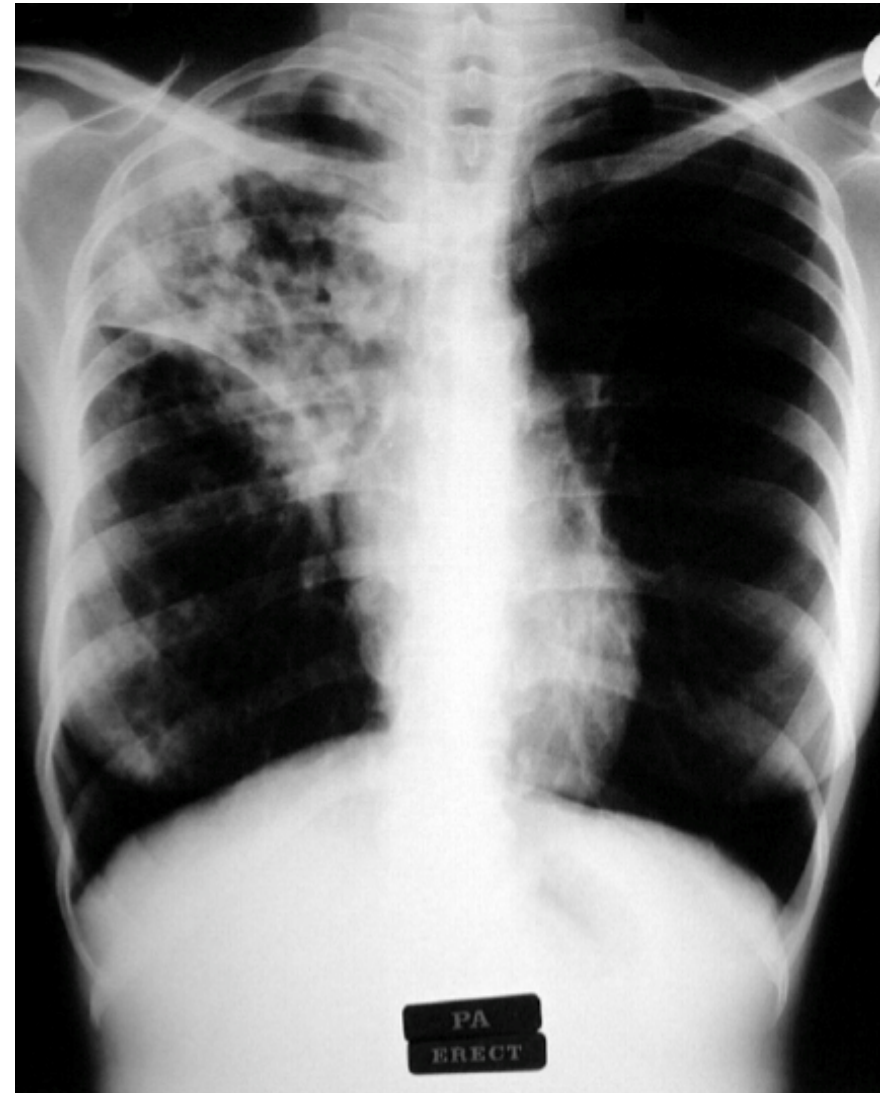
Standard once-daily  
treatment



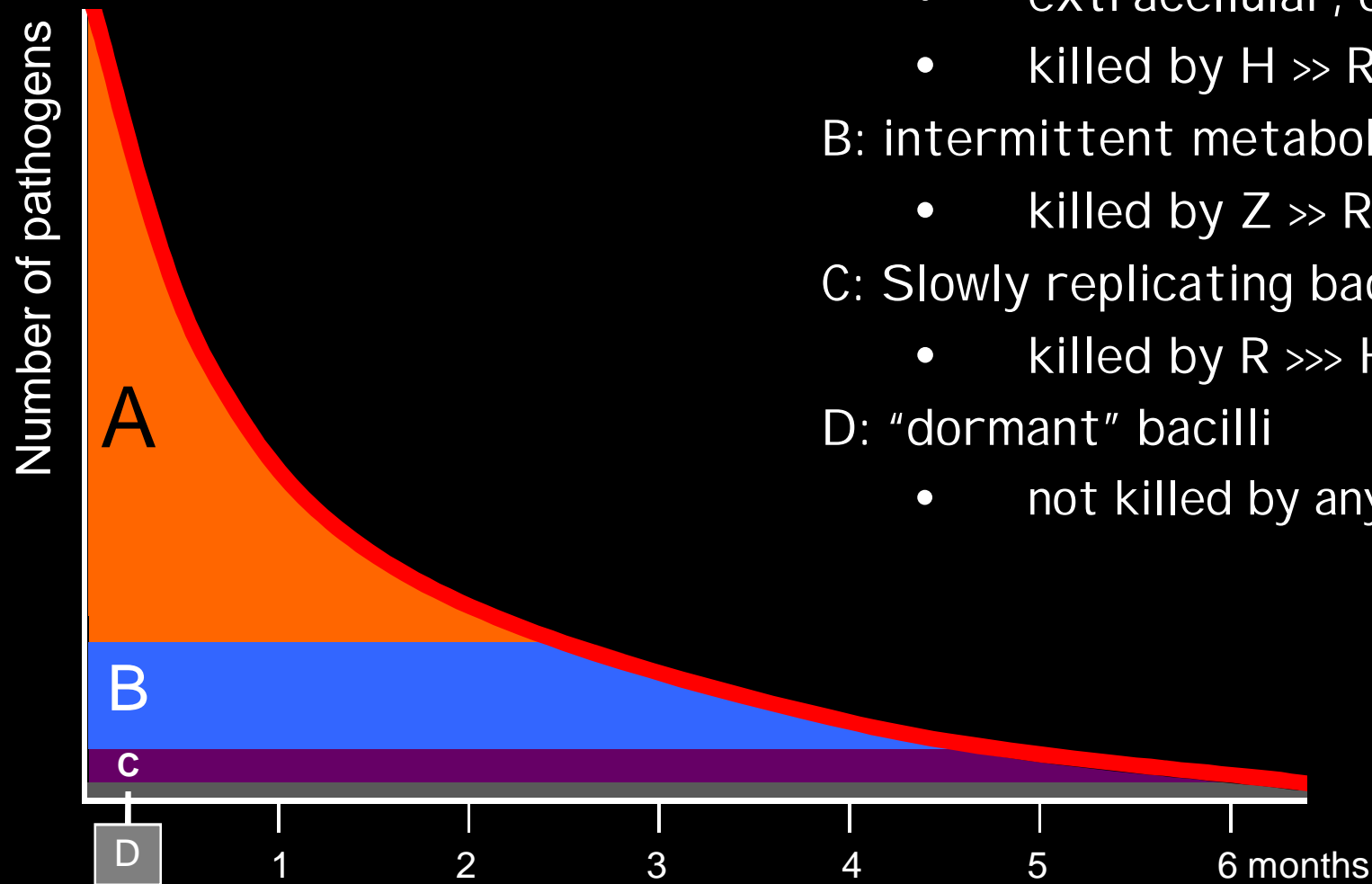
No increase in % resistant bacteria; no MDR-TB

# Other factors

- Within patient variability
  - Cavity walls, fibrosis
  - Drug levels at site of action?
- Between patient variability
  - Absorption/elimination
  - Lower levels in HIV, females
- Bacterial subpopulations
  - Persisters ...



# Different populations killed by different drugs



A: rapidly replicating bacteria

- extracellular, cavity walls
- killed by  $H \gg R > Z$

B: intermittent metabolism

- killed by  $Z \gg R \gg H$

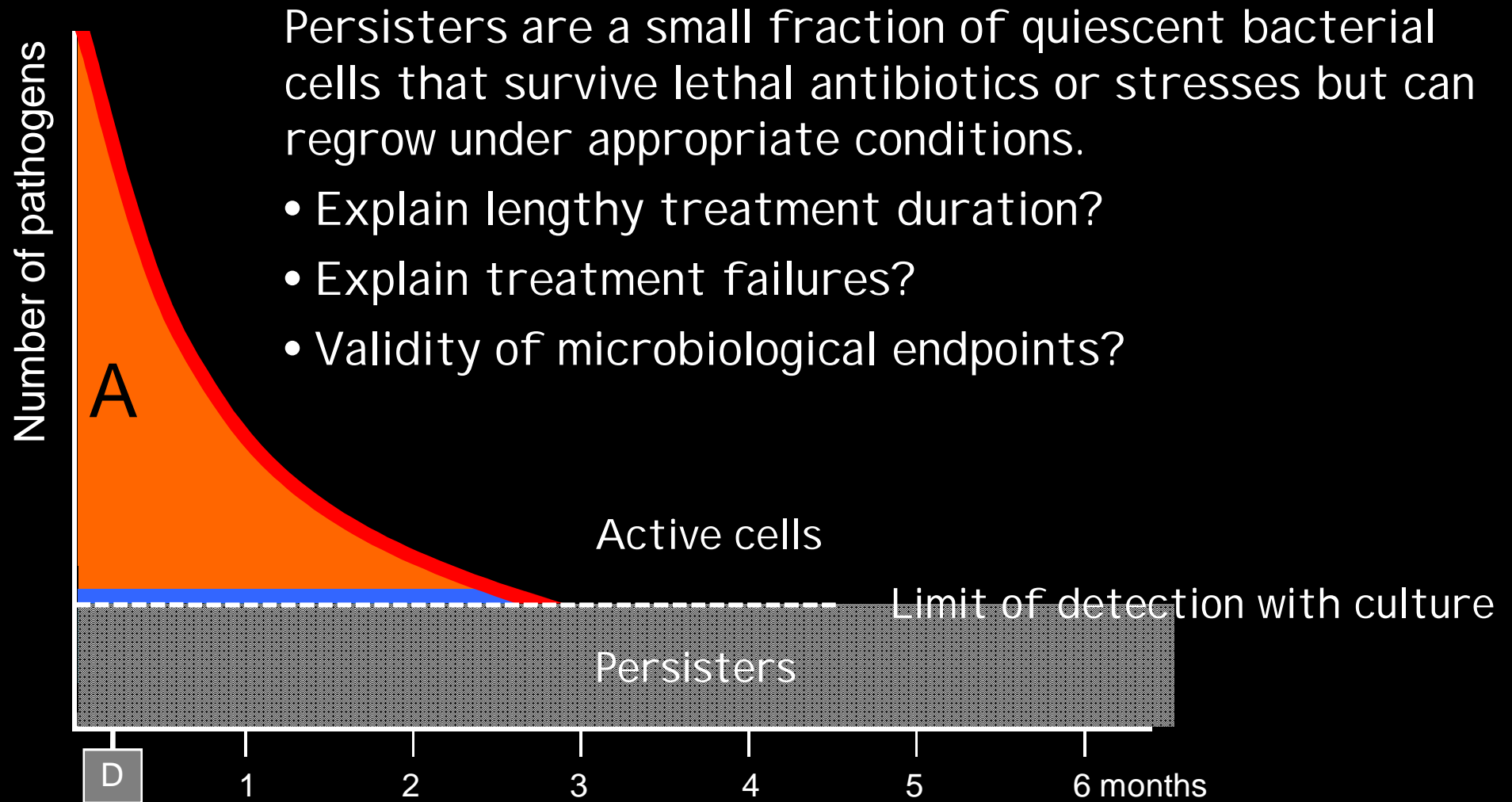
C: Slowly replicating bacteria

- killed by  $R \gg H$

D: "dormant" bacilli

- not killed by any existing drug

# Persisters – the “biofilm form”



Persisters are a small fraction of quiescent bacterial cells that survive lethal antibiotics or stresses but can regrow under appropriate conditions.

- Explain lengthy treatment duration?
- Explain treatment failures?
- Validity of microbiological endpoints?



# TB drugs innovation and testing - Bedaquiline

## Bedaquiline (TMC207, J, Sirturo)

- Unique mechanism of action
- Mycobacterial ATP synthase
- Switches off energy production

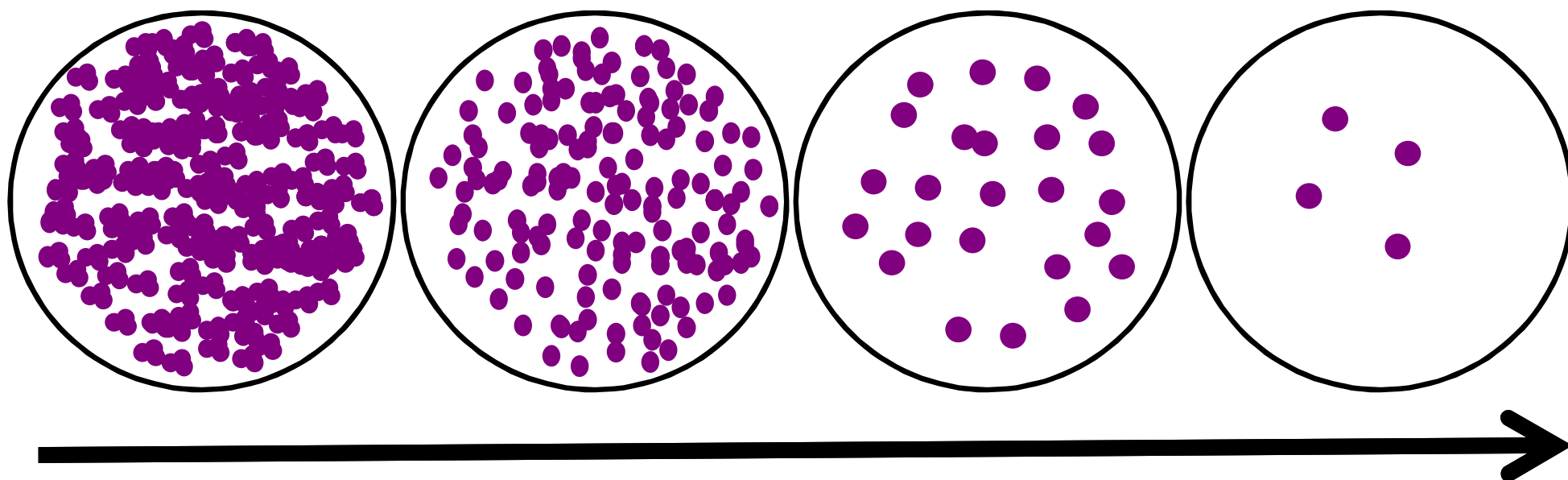
Andries et al. Science 2004.  
A Diarylquinoline Drug Active on the ATP  
Synthase of Mycobacterium tuberculosis



# 28 June 2005

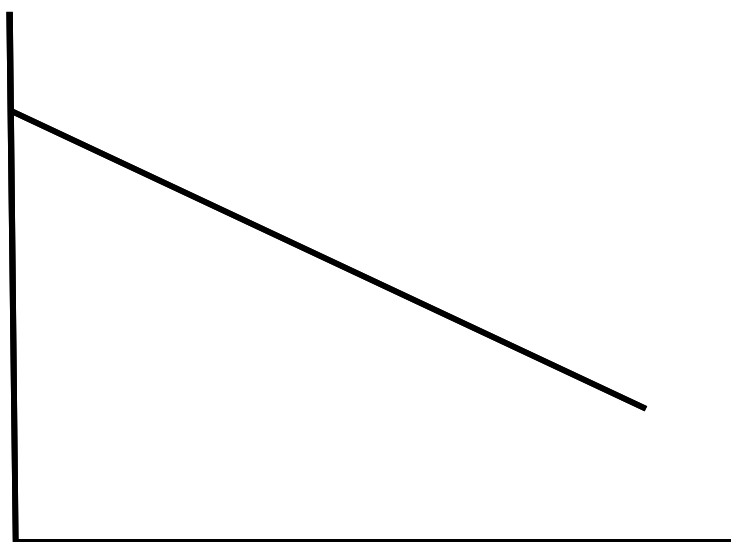
## First TMC207 dose to a TB patient





Up to 14 days

CFU

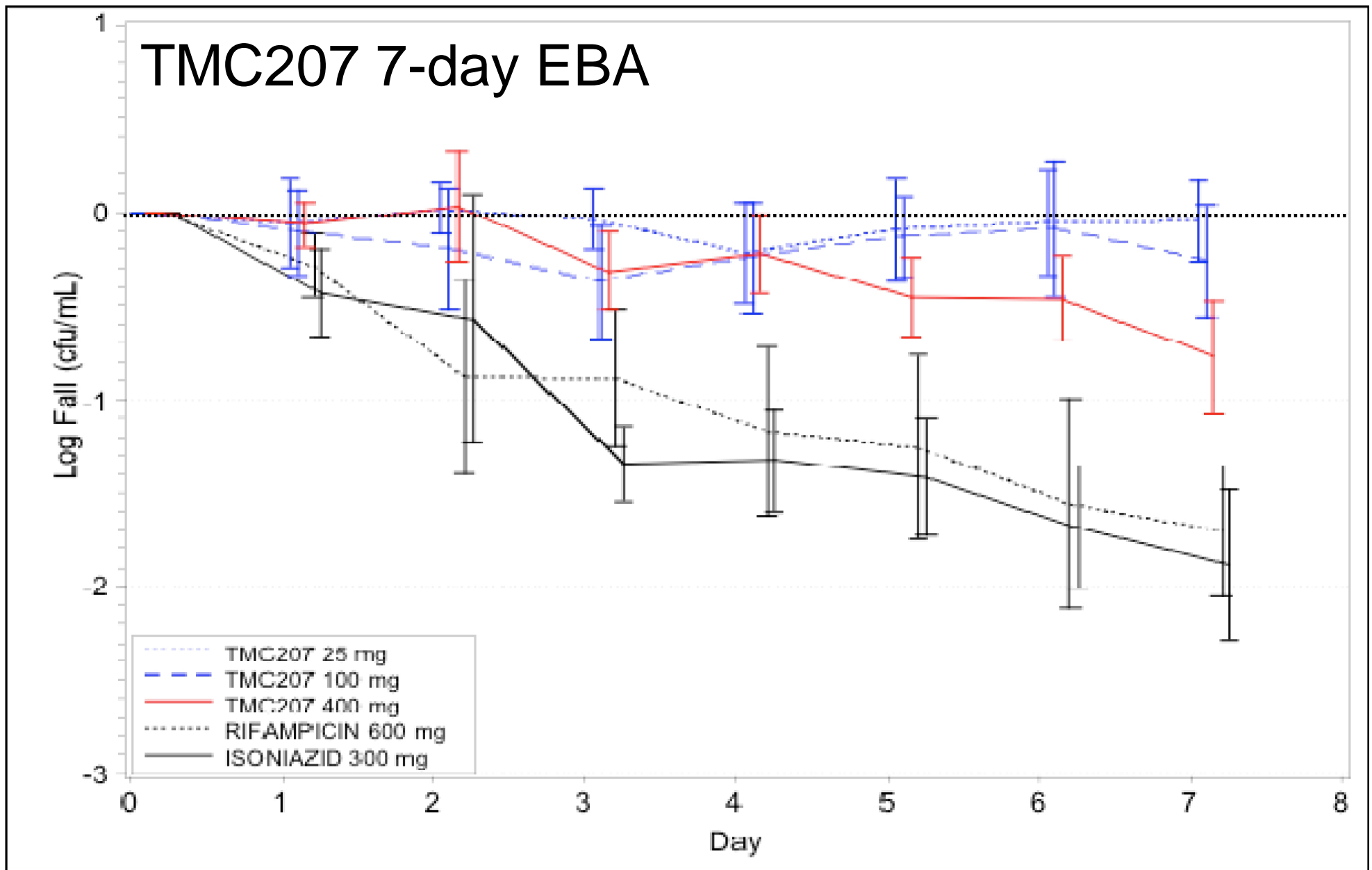


Days

**Early bactericidal activity study:**

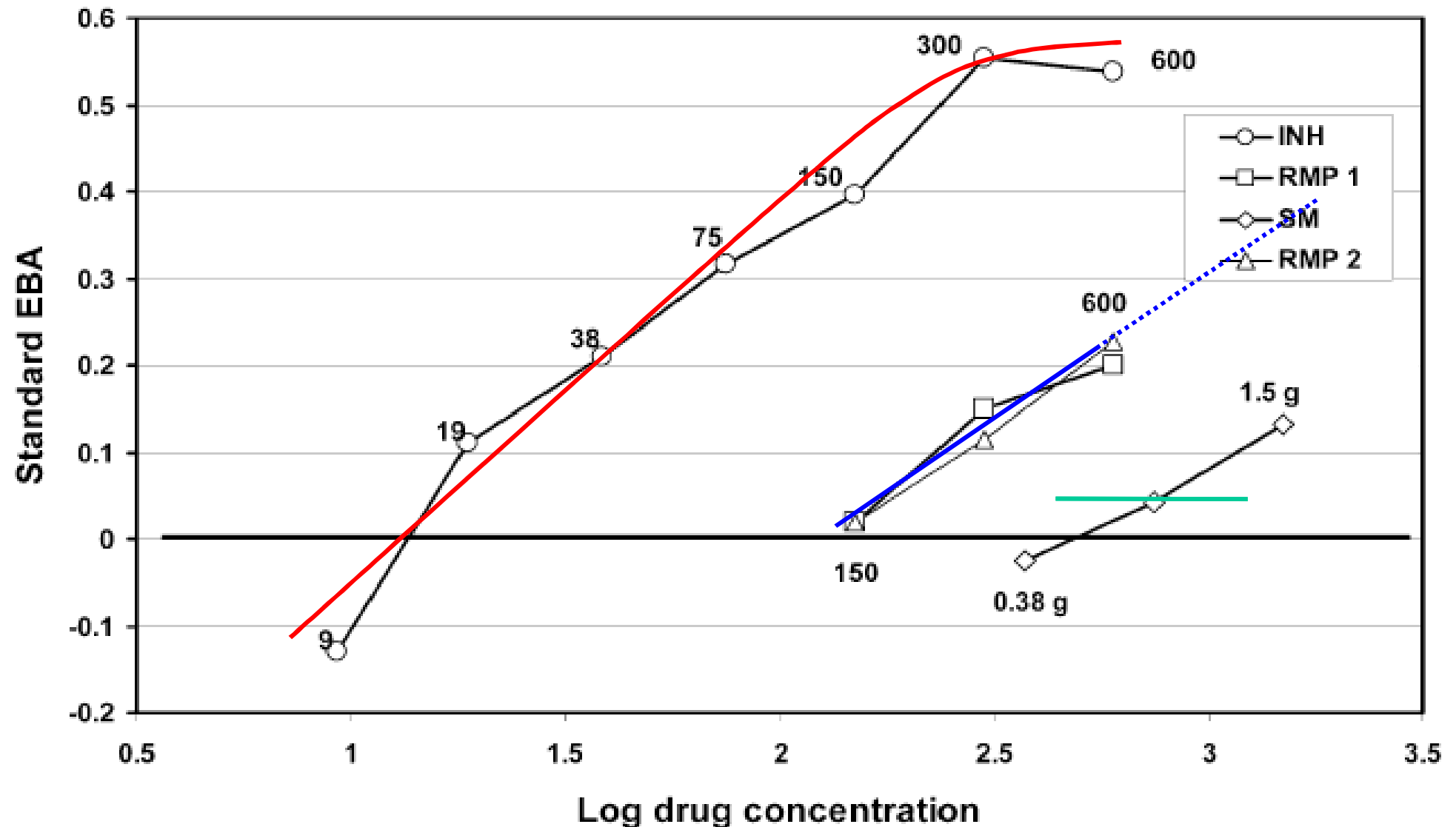
- Fall of logCFU per ml of sputum per day
- Proof of concept for drugs or regimens
- In hospital for safety
- Maximum 7 day run-in phase
- Full course after study

# Proof of concept





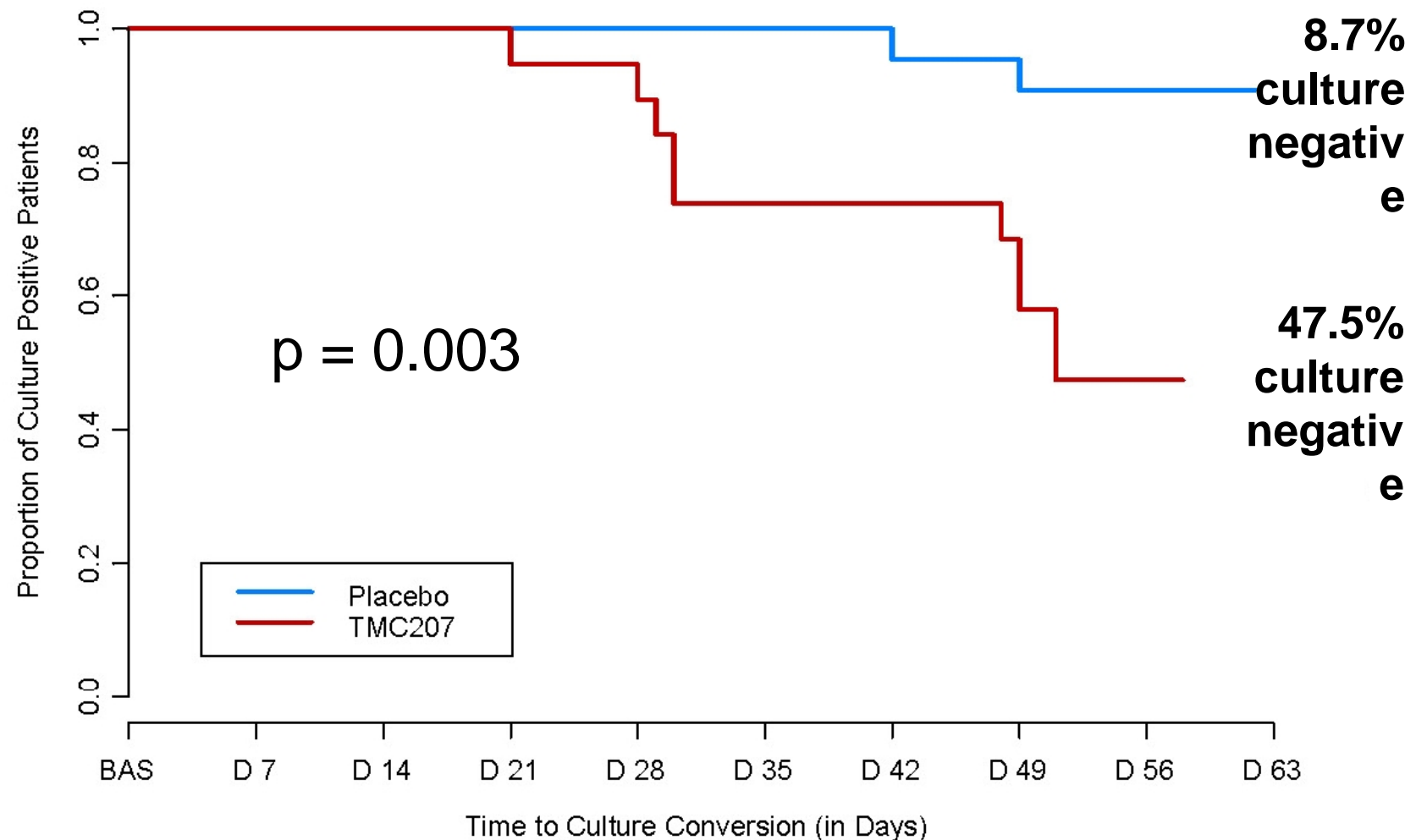
# EBA for dose ranging PK-PD



# TMC207 400mg for 8 weeks

MDR regimen + placebo vs MDR regimen + TMC207

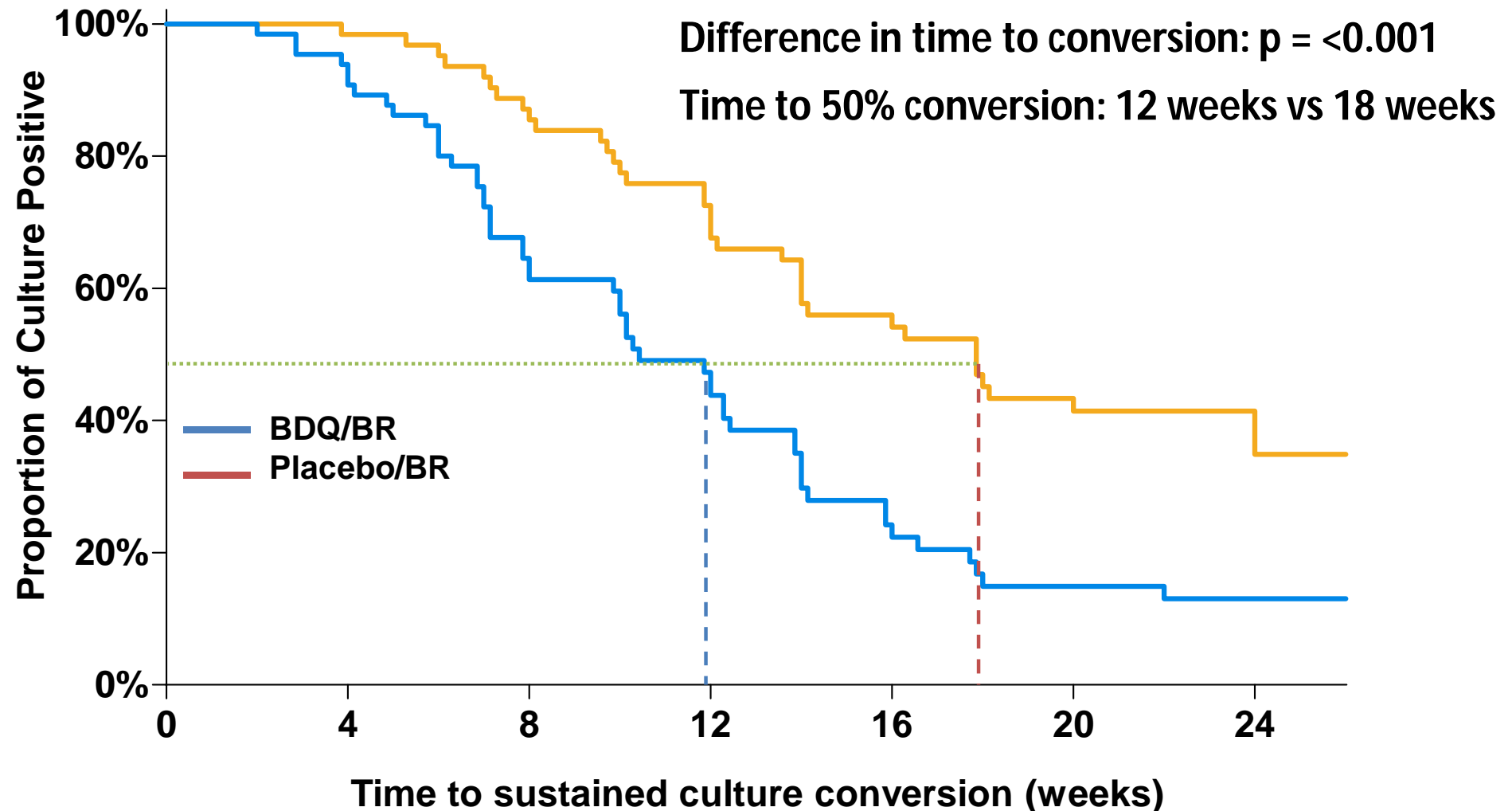
Sustained culture conversion in liquid media, n=44



# TMC207 400mg for 24 weeks

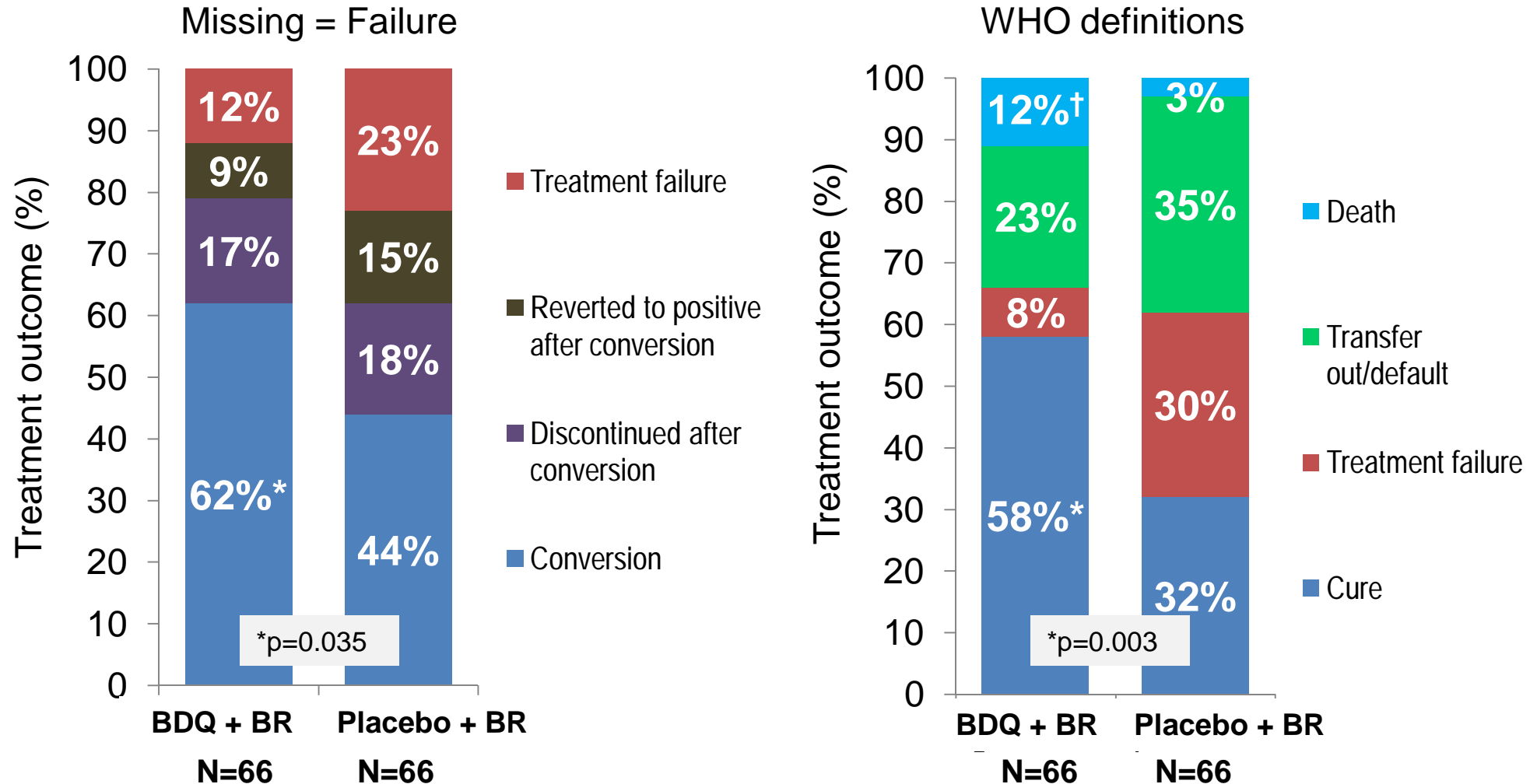
MDR regimen + placebo vs MDR regimen + TMC207

Sustained culture conversion in liquid media, n=132





# Outcome at study end: surrogate vs clinical endpoints



- Median duration of treatment: BDQ 92 weeks, placebo 94 weeks
- 2 vs 16 acquired more resistance
- 0 vs 7 developed pre-XDR or XDR-TB profile
- Unexplained excess deaths in the BDQ group late in follow-up

# Overall deaths (ITT)

**BDQ + BR**  
**10/79 patients**  
(12.7%)

**Placebo + BR**  
**2/81 patients (2.5%)**

**Five deaths due to TB**

Two deaths due  
to TB and  
hemoptysis

## **Causes of five non-TB related deaths**

Alcohol poisoning  
Hepatitis/hepatic cirrhosis  
Septic shock/peritonitis  
Cerebrovascular accident  
Motor vehicle accident

## **Time of death**

9/10 patients died after last BDQ intake (median 49 weeks; range 12–130 weeks)

Deaths not considered related to investigational drug  
Not associated with antecedent QTcF interval  $\geq 500$  ms

Meta-analysis of 9,153 MDR-TB patients: 15% mortality<sup>1</sup>

<sup>1</sup>Ahuja SD, et al. PLoS Med 9: e1001300

# Dec 3 2012 (7y, 5m, 5d later)

FDA hearing – “sufficient proof of efficacy and safety”



BDQ FDA approved for MDR TB 31 Dec 2012

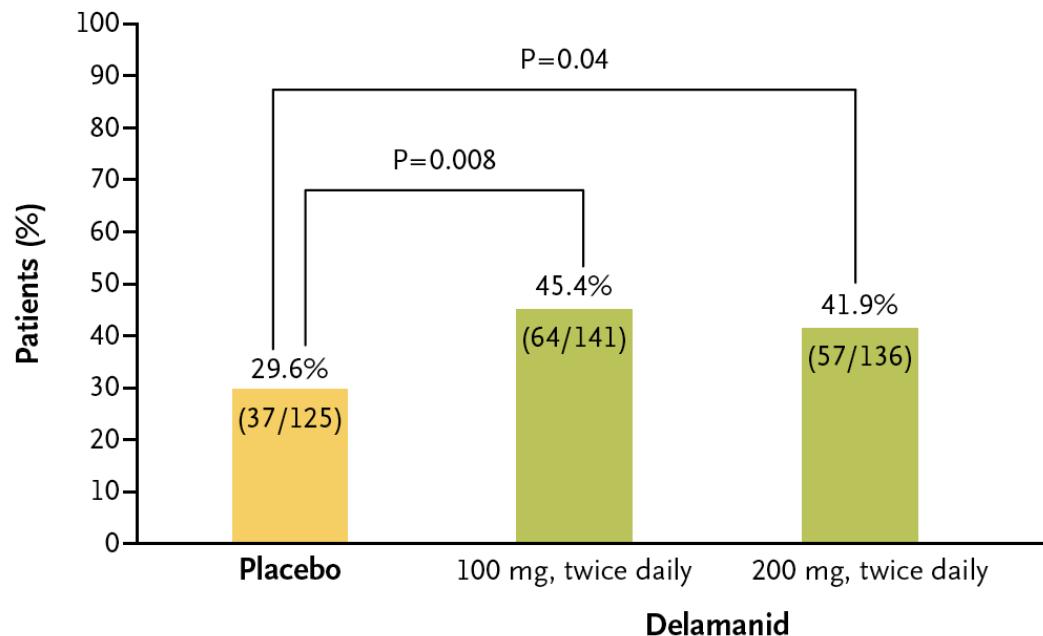
# Phenotypic screening

Fishing mission

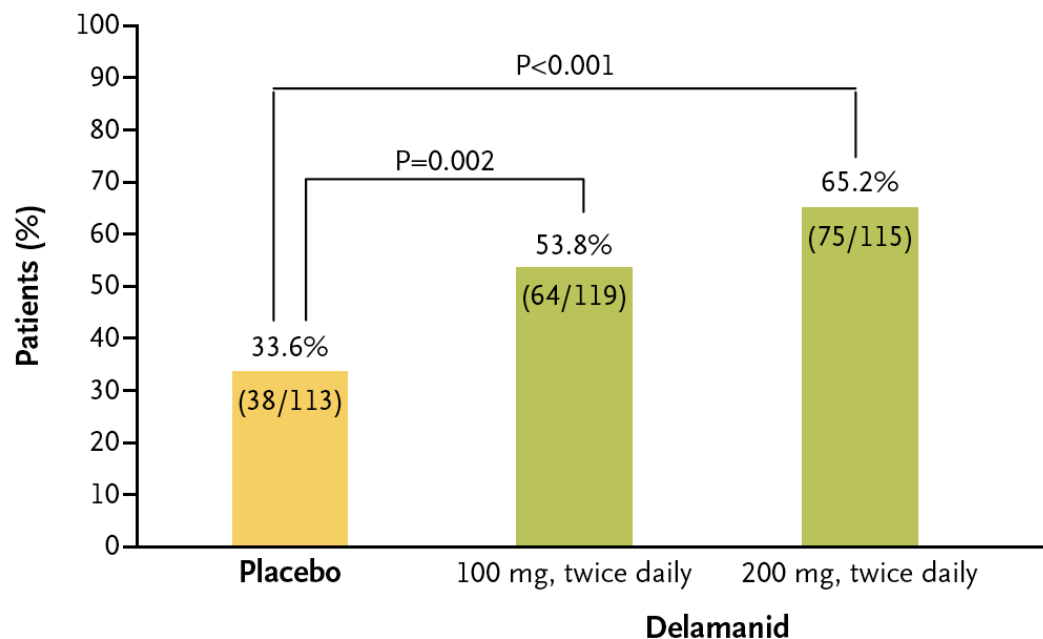




### A Mycobacterial Growth Indicator Tube System



### B Solid Medium



## DELAMANID (Otsuka)

- MDR
  - DLM added for 8 weeks
  - Improved culture conversion
- Subgroup treated for 26 wks
  - Better survival
- Phase 3 results pending
  - Including HIV-MDR
- EMA approval in Nov 2013
- Paediatric study started 2014

Gler et al. NEJM 2012;23:366  
Skripconoka et al. ERJ

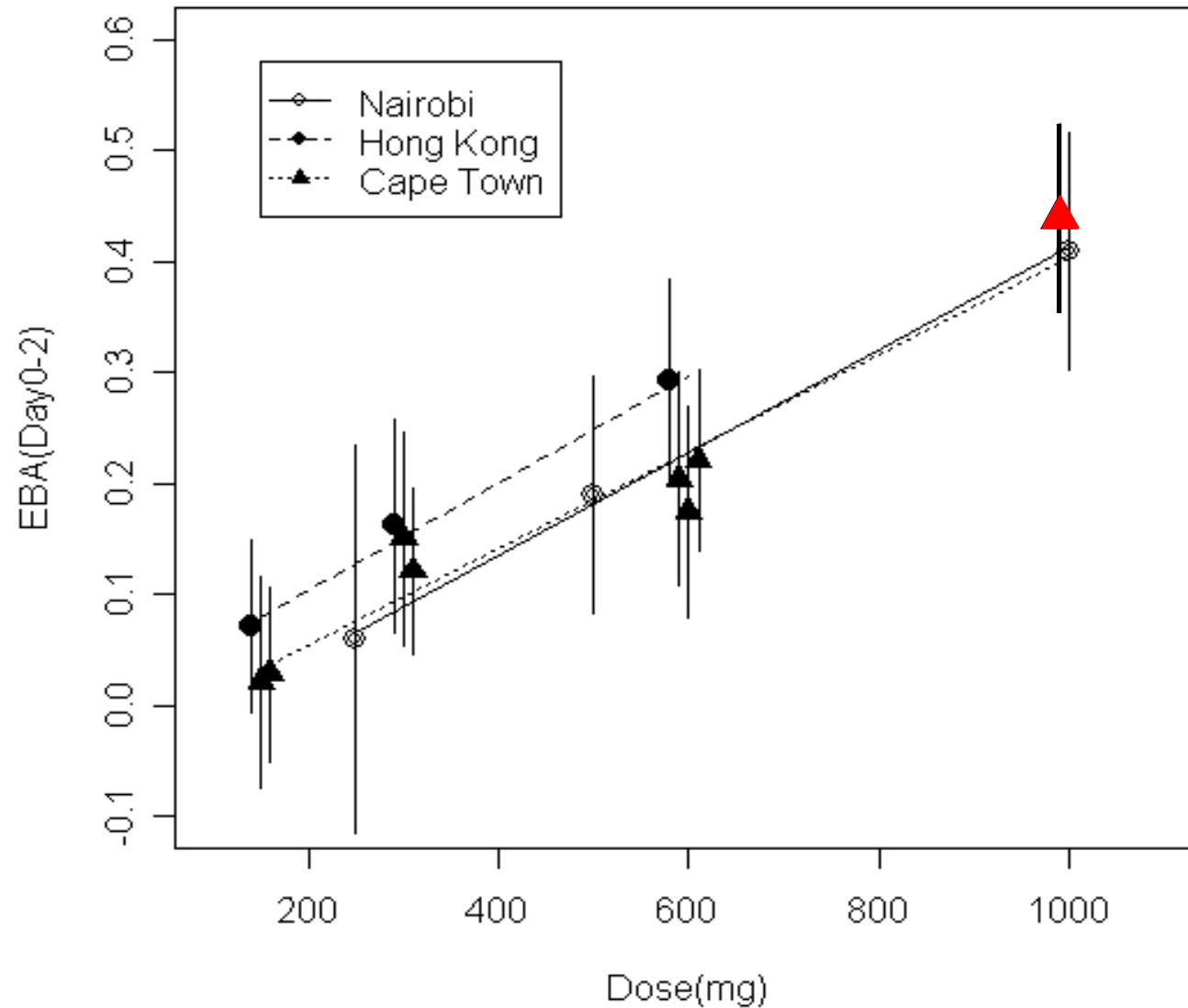
**Figure 2.** Proportion of Patients with Sputum-Culture Conversion by Day 57.

# RIFAMPICIN 1955



## 2-day activity of RIF

Linear dose response curve (consistent results over >30 years)



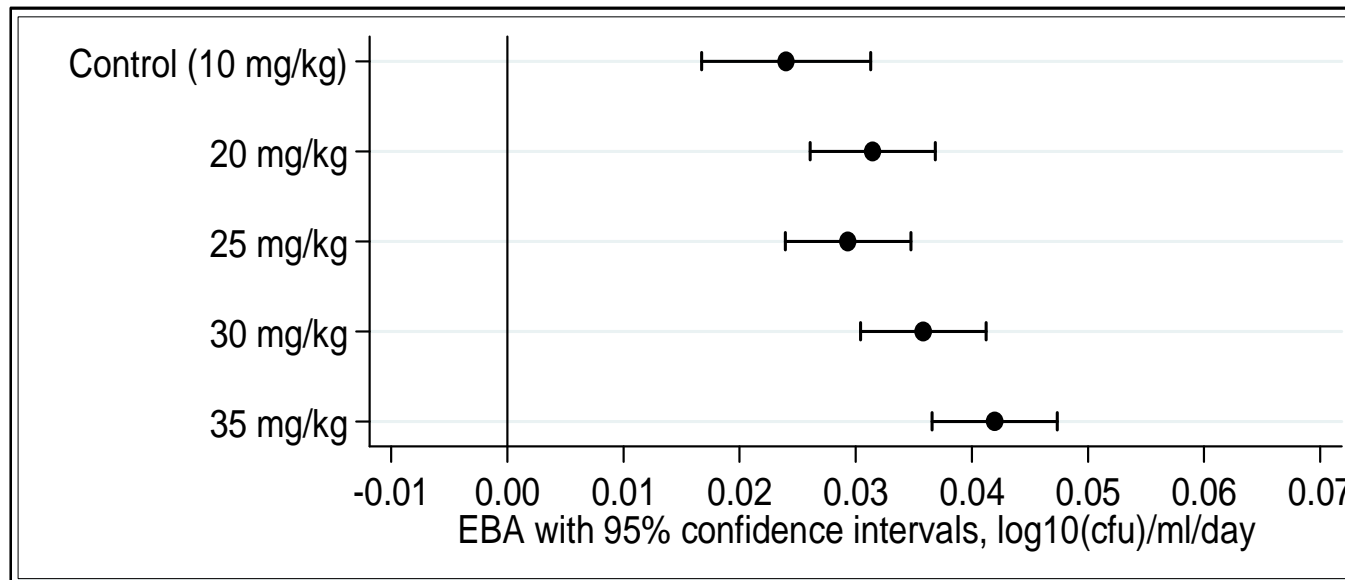
Chan et al, Tuber Lung Dis 1992;73:33; Jindani et al, AJRCCM 1980;121:939; Sirgel et al, JAC 1993;32:867; Sirgel et al, JAC 2000;45:859-70; Sirgel et al, AJRCCM 2005;172:128-35; Diacon et al, AAC 2007;5:2994

## High Dose RIF EBA

- RIF monotherapy for 7 days, then RIF+HZE for 7 days

Group	AUC 0-24 (h* mg/L)	
	Geometric mean	Min - max
10 mg/kg (control)	26	21 – 41
20 mg/kg	113	77 – 162
25 mg/kg	135	92 – 228
30 mg/kg	189	85 – 436
35 mg/kg	254	178 – 355
40 mg/kg	started	

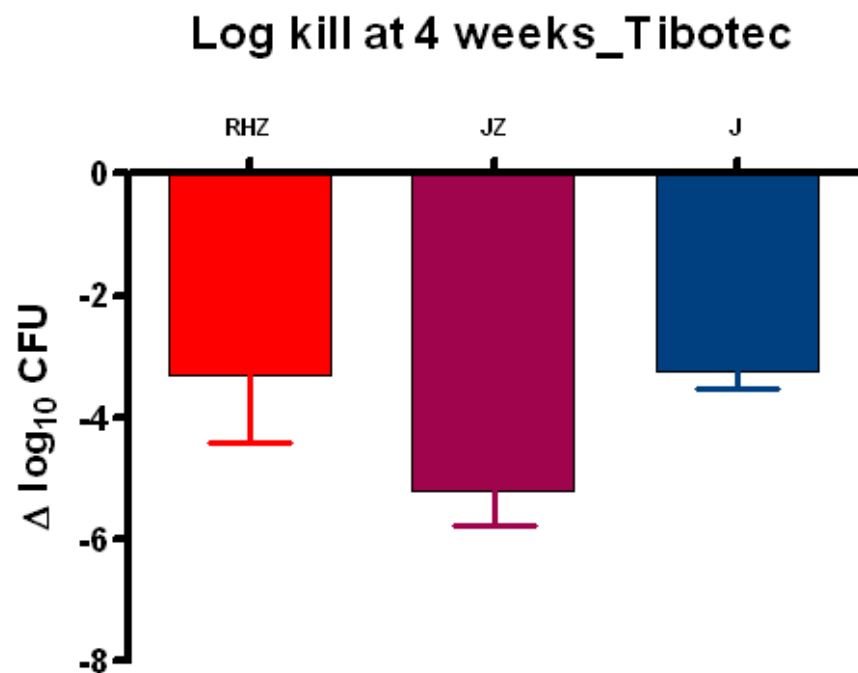
>10-fold increase in mean AUC from 10 to 35 mg/kg



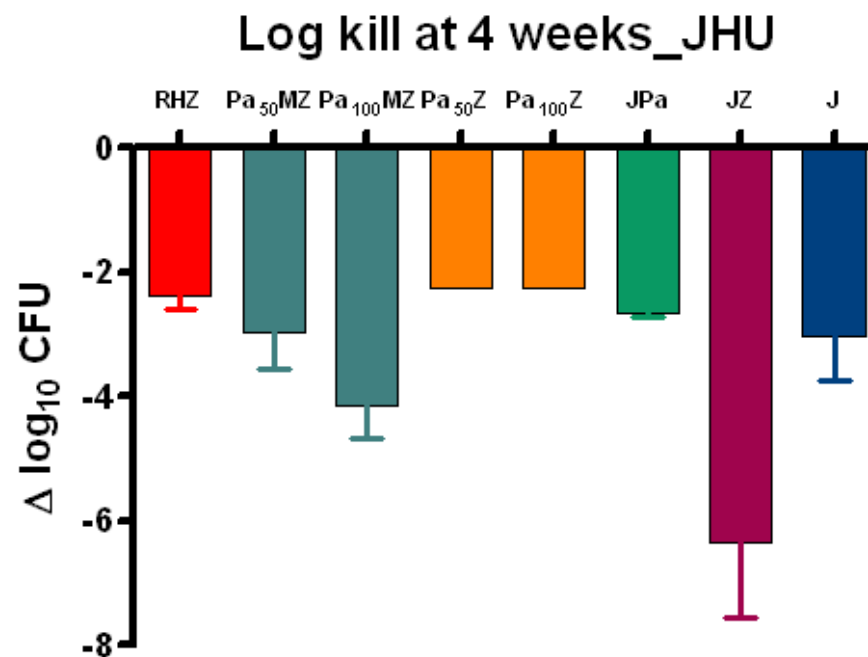
Increasing 14-day activity



# Bactericidal Activity Over 4 Weeks in Mice



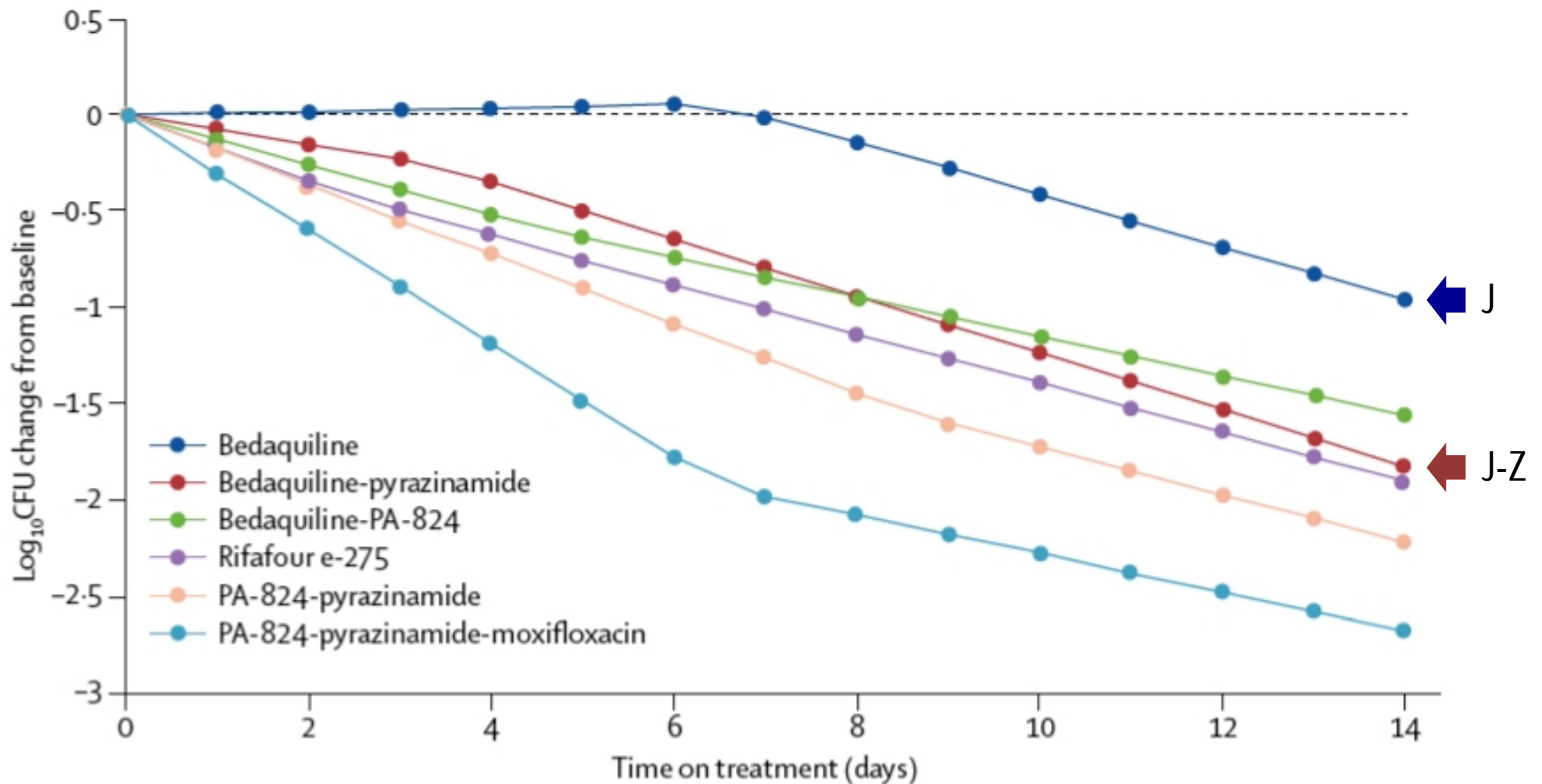
Andries et al, Science (2005); 307:223  
Ibrahim et al, AAC (2007); 51:1011  
Lounis et al, AAC (2008); 52:3568



Nuermberger et al, AAC (2008); 52:1522  
Tasneen et al, AAC (2011); 55:5485-92

# NC-001 Combination 14-day EBA study

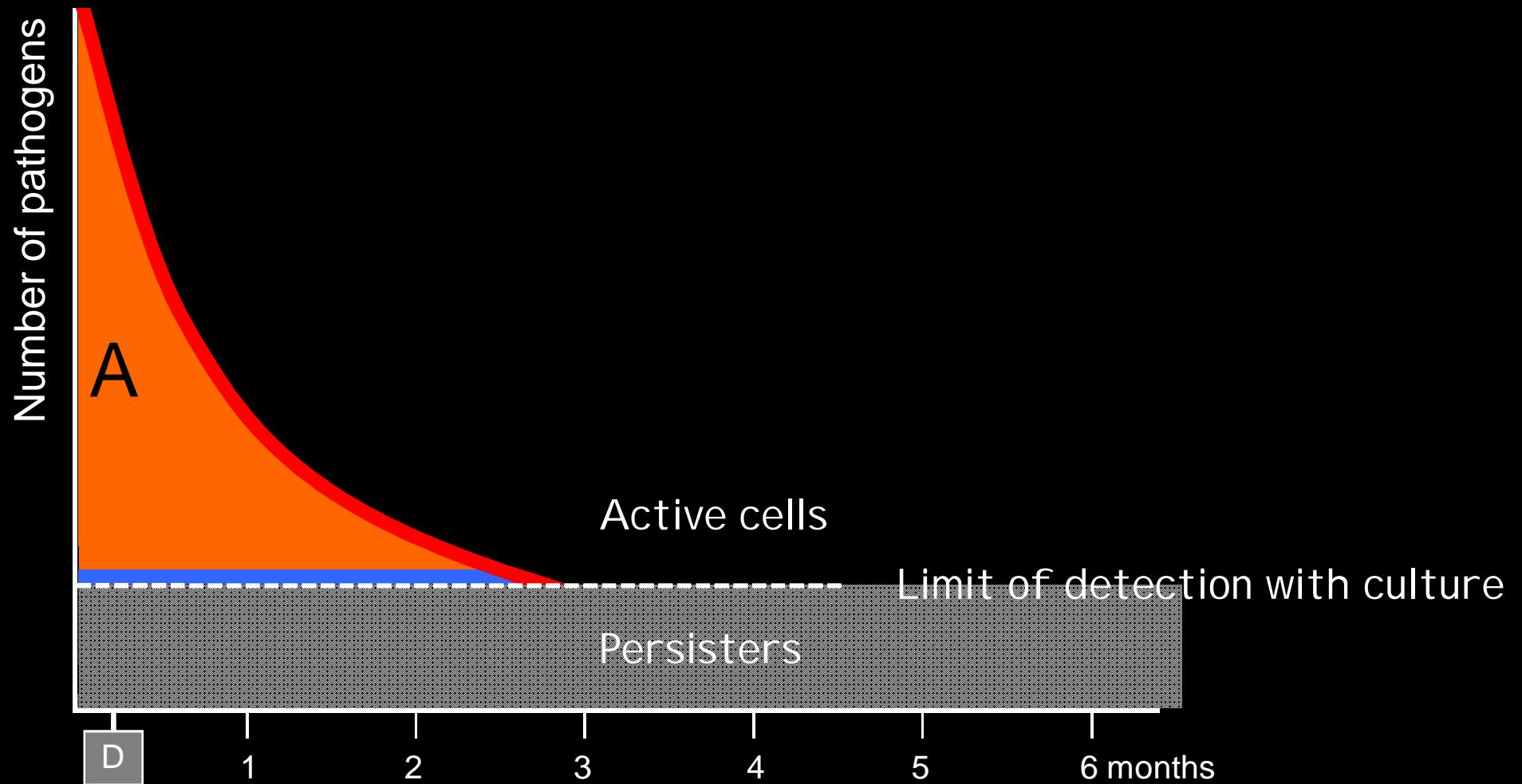
- Confirms murine combination results in humans
- Pa-M-Z at least as good as standard treatment



# Trials

- **Phase 3**
  - Fluoroquinolones to reduce treatment to 4/12 (RemoxTB)
  - Delamanid in MDR TB  $\pm$  HIV
  - Pa-M-Z
  - BDQ Phase III – replace injectable
- **Phase 2**
  - 8-weeks: Rifapentine, SQ109, RIF 20mg/kg, RIF 35mg/kg, BDQ-Pa-Z
  - 2-weeks
    - Linezolid-analogues
    - RIF up to 40mg/kg
    - Betalactams (meropenem, faropenem)
- **Phase 1**
  - Interaction studies with ARVs
  - QT studies of TB drug combinations (BDQ – DEL)
- **PK**
  - Delamanid paediatric program

# Persisters?





# THE FATE OF MYCOBACTERIUM TUBERCULOSIS IN MOUSE TISSUES AS DETERMINED BY THE MICROBIAL ENUMERATION TECHNIQUE

BY ROBERT M. McCUNE, JR.,† M.D., RALPH TOMPSETT, M.D., AND  
WALSH McDERMOTT, M.D.

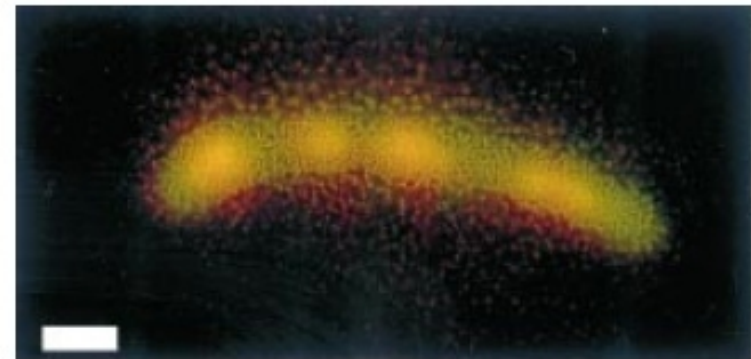
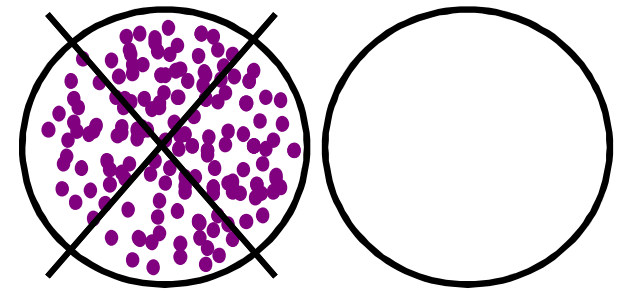
*(From the Departments of Medicine and Public Health and Preventive Medicine, The  
New York Hospital—Cornell Medical Center, New York)*

(Received for publication, July 5, 1956)

- INH/PZA treatment for  $\geq 12$  weeks cured mice with TB
  - nothing could be cultured from tissue
  - no infection could be transmitted to guinea pigs
- Several months later animals were ill again
  - fully sensitive to INH/PZA
- Corticosteroids accelerated relapse

# Persisters

- Drug tolerant, slow metabolizing, non-replicating cells
  - RIF tolerant, can only grow in sensitive liquid culture media
  - Do not grow on agar plates - no CFU
- “Fat and Lazy” (Garton *et al* 2007)
  - Present in sputum
  - Metabolic shift towards accumulating fat
  - Stain with Nile Red (lipid bodies) and Auramine (cell wall)



**Fig. 4.** Image of an acid-fast cell containing intracellular lipid inclusions in a sputum sample from a patient with clinical tuberculosis. The cell is dual-labelled with Auramine O and Nile red. Bar, 2  $\mu$ m.

Dhillon *et al.* JAC 2014;69:437

Dhillon *et al.* BMC Infect Dis 2004;4:51

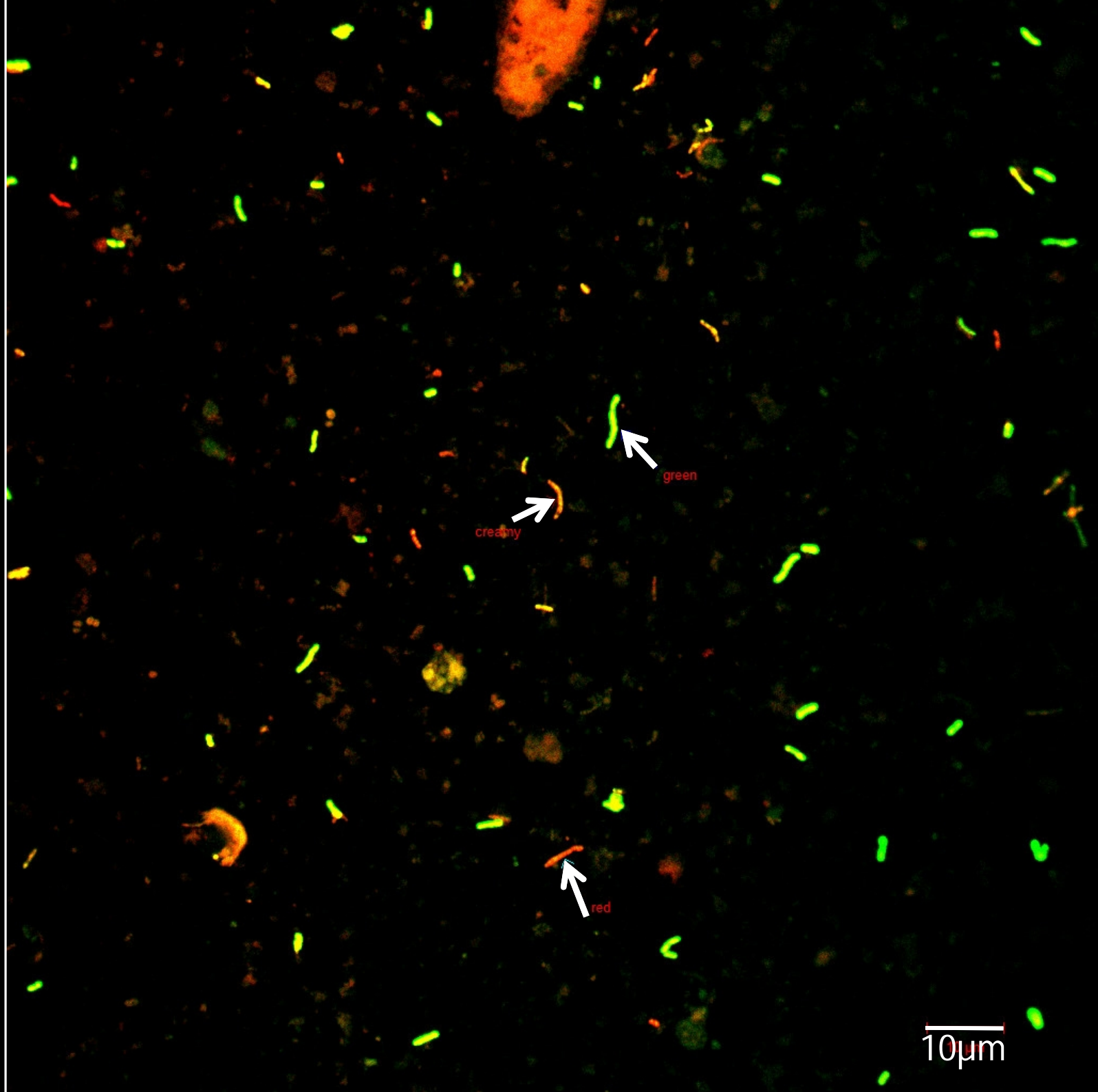
Garton *et al.* PLOS Med 2008;5:e75

Huet *et al.* J Bacteriol 2000;182:6358

Wakamoto *et al.* Science 2013;339:91

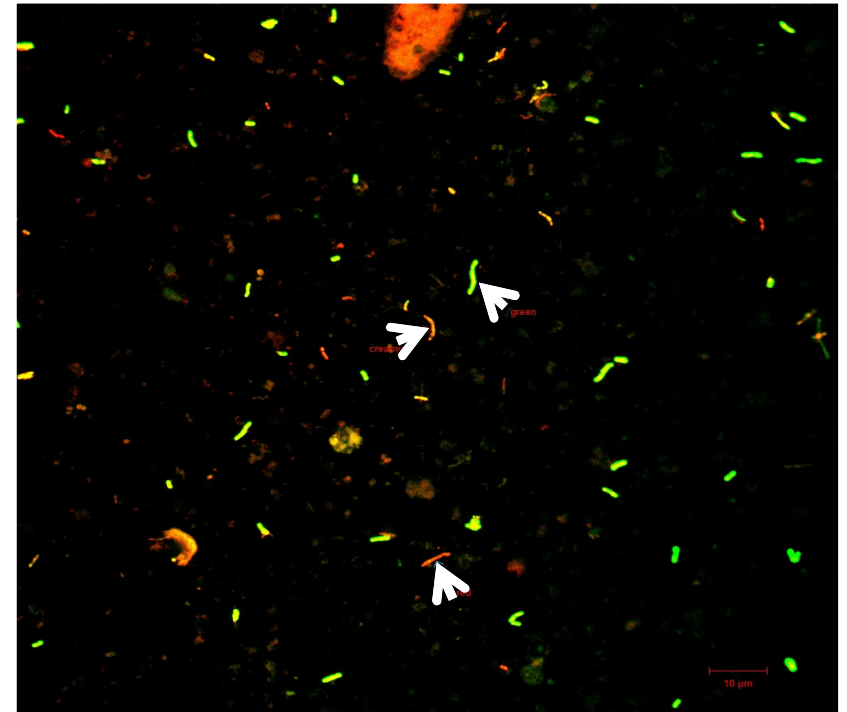
Gomez, McKinney. Tuberculosis 2004;84:29

Dhar, McKinney. Curr Op Microbiol 2007;10:30

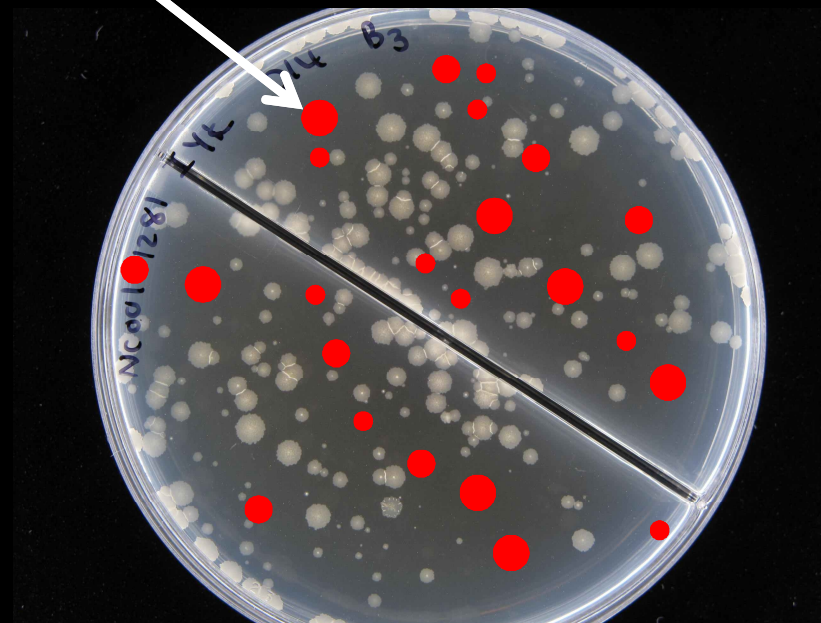
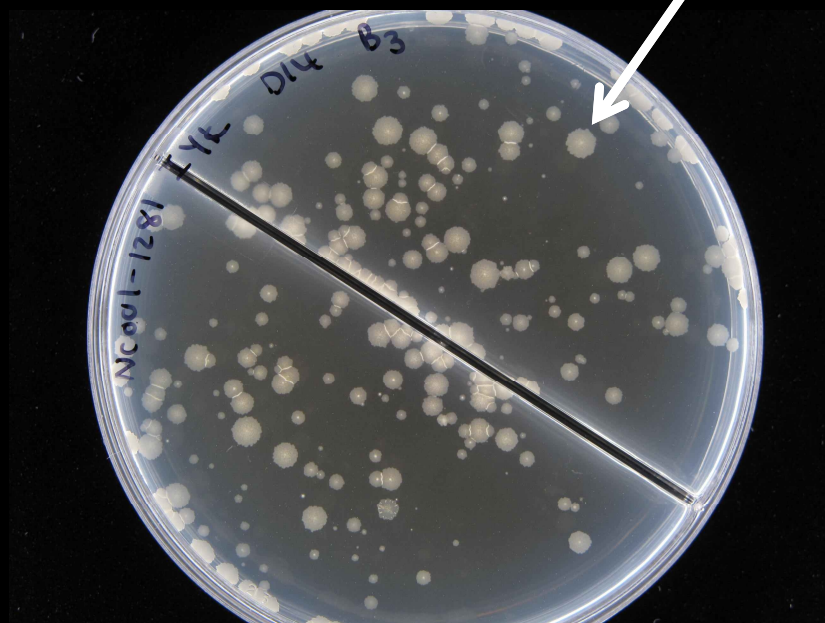
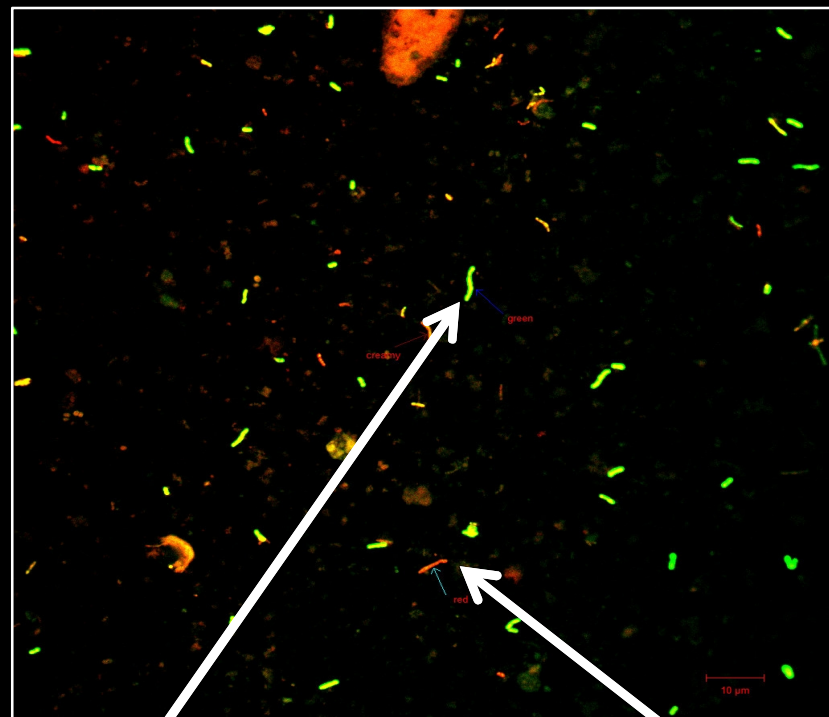


# Rifampicin 10mg/kg for 14 days

- Cell counts and cultures
  - Active bacteria
    - Represented by green cells
    - Produce CFU
    - Killed by RIF
  - Persisters
    - Represented by red cells
    - Do not produce CFU
    - RIF tolerant

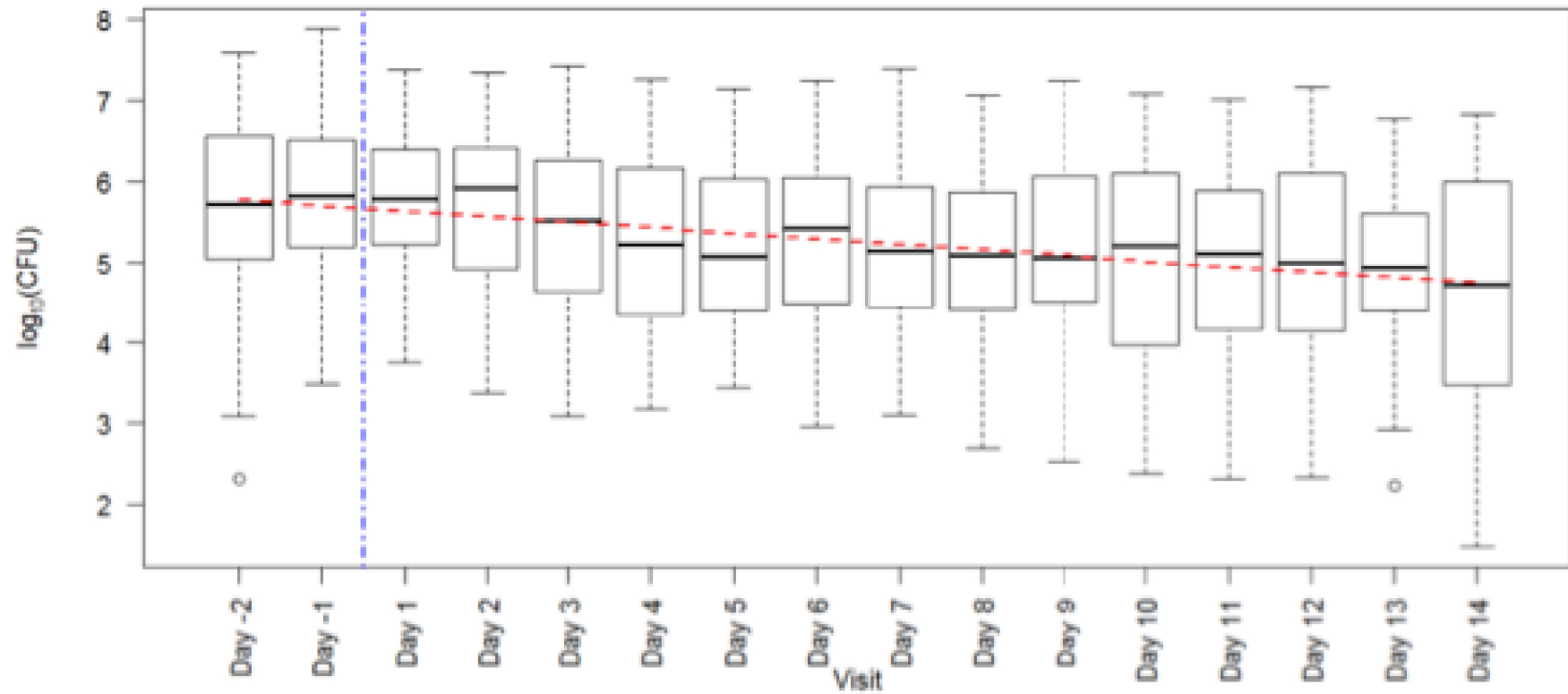




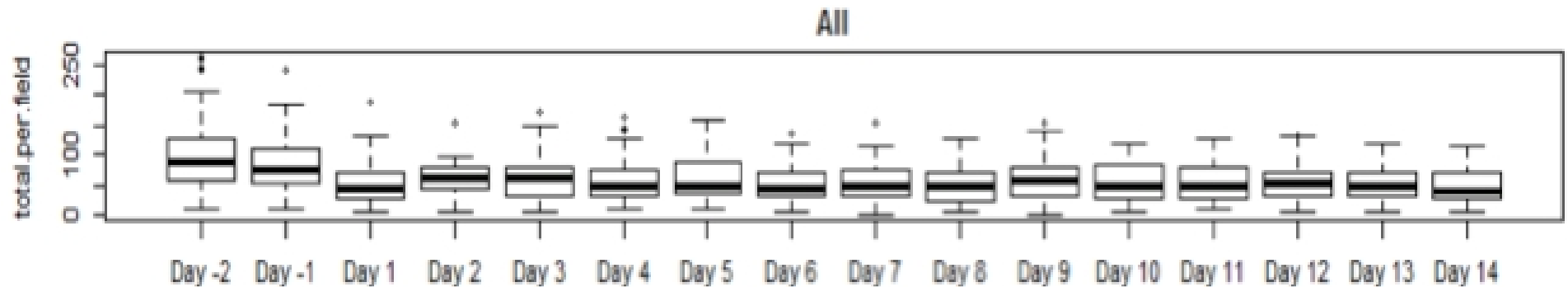


# Unmask the invisible CFU = persisters

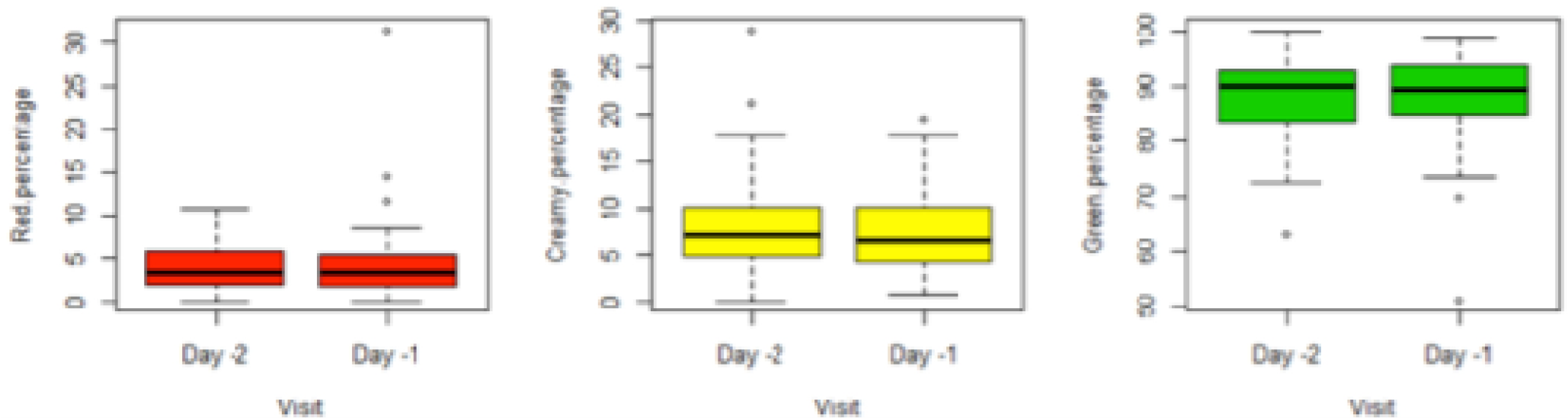
Rifampicin 10mg/kg for 14 days - CFU



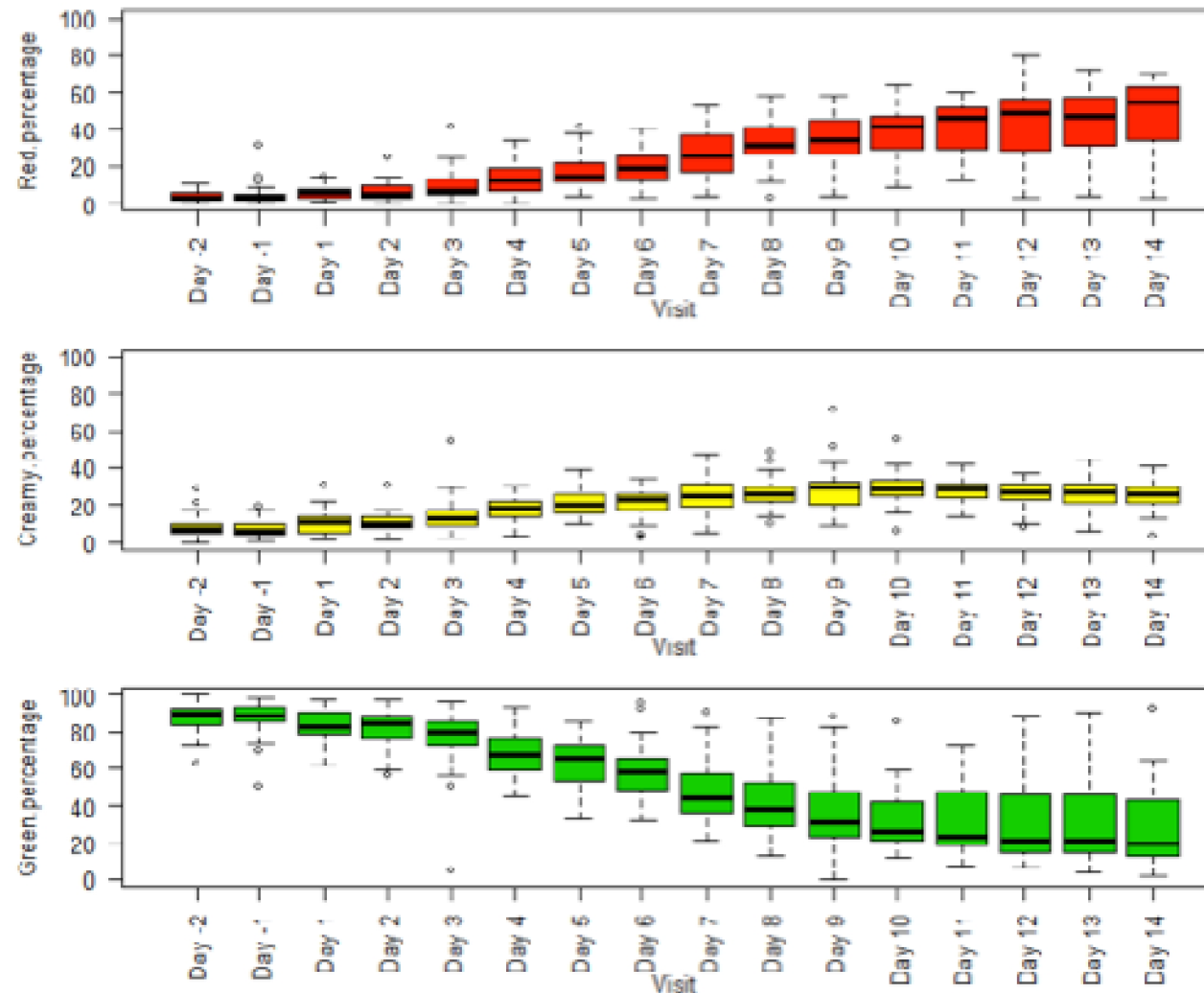
# Cells counted, all (dead or alive)



# Cells counted, without treatment: stable



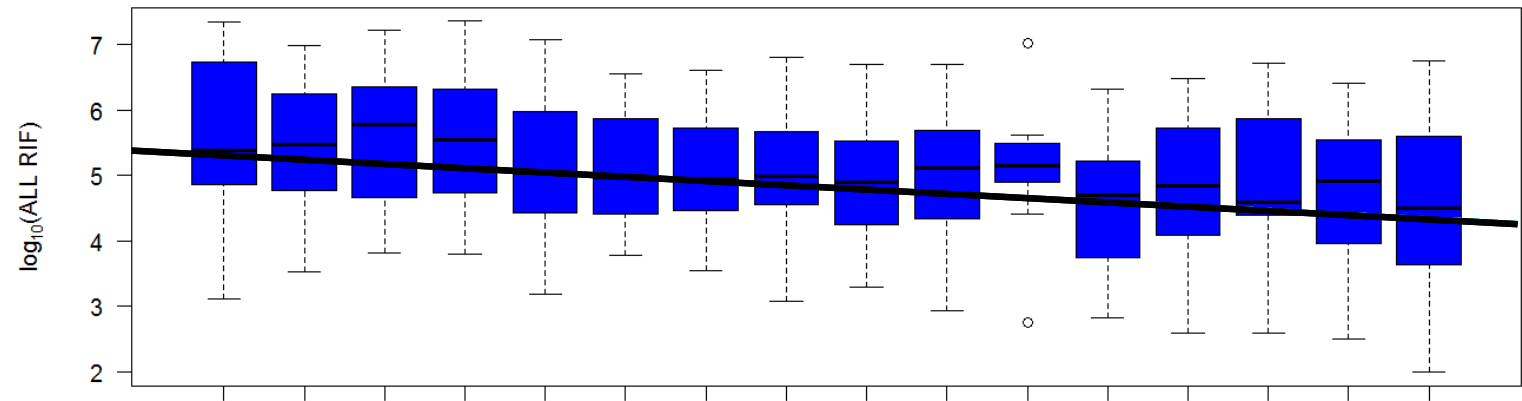
# Percentage of colours (dead or alive)



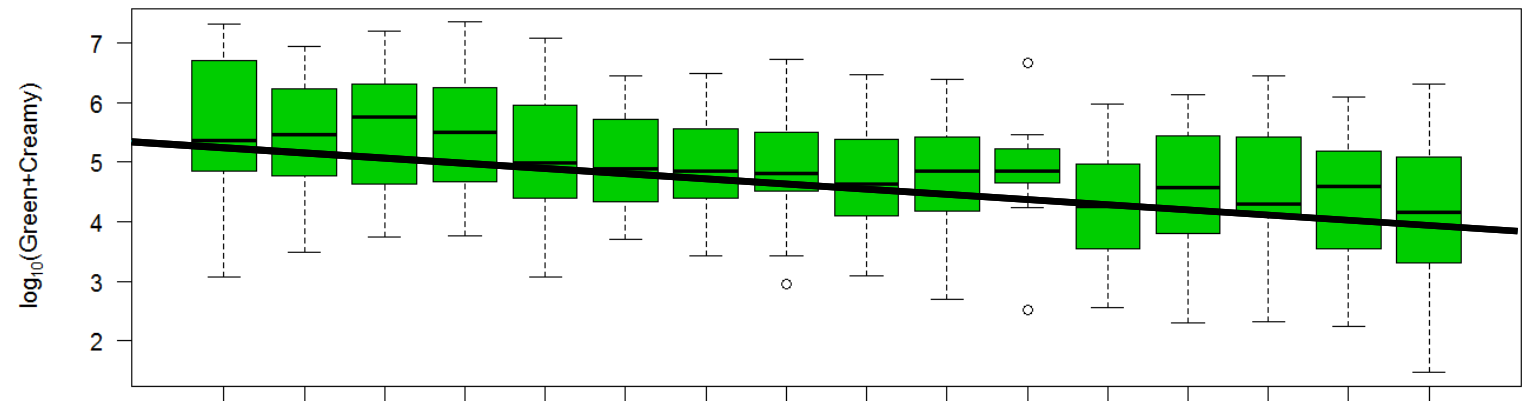


# If all cells made a CFU

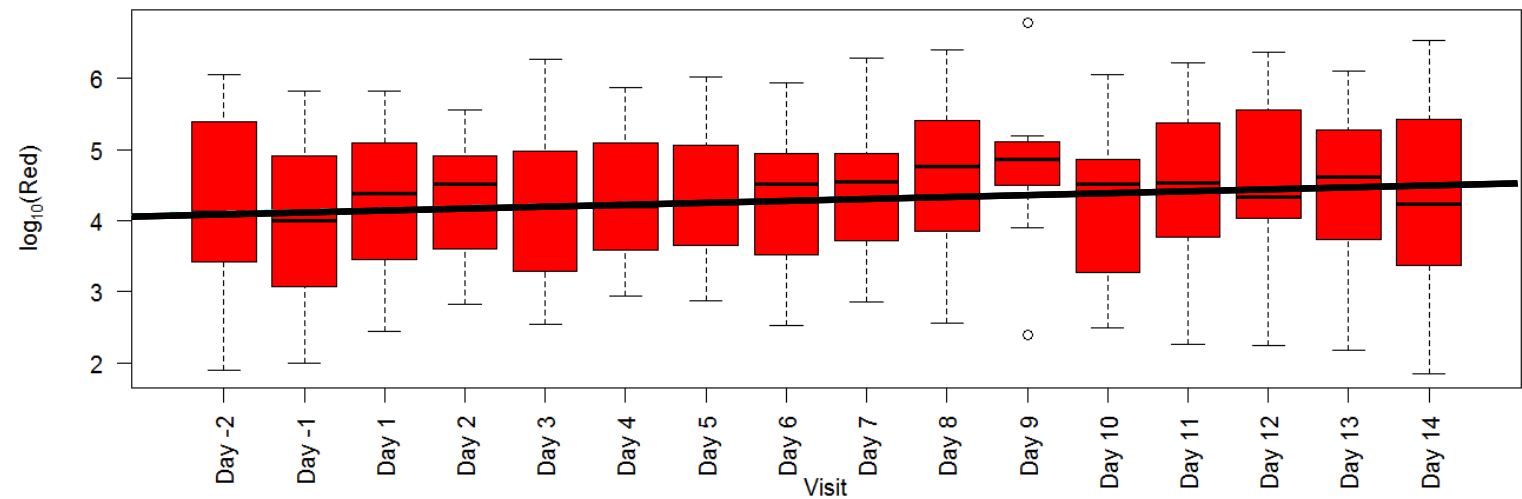
ALL



Visible CFU

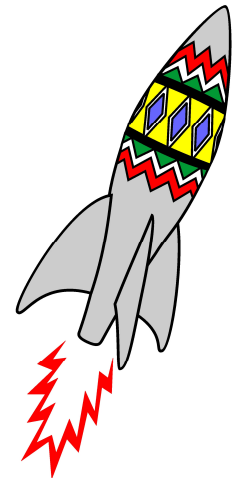


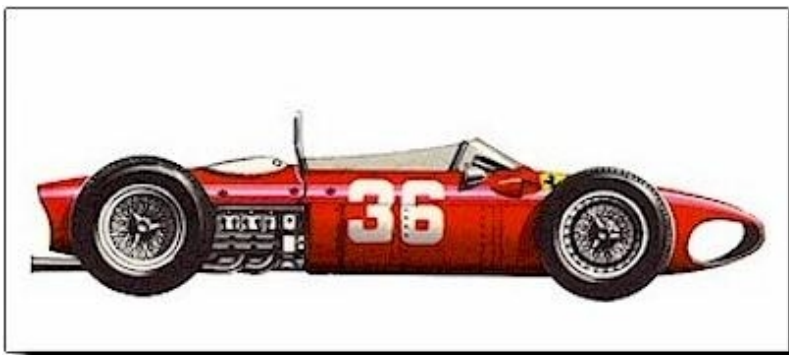
Invisible CFU



# Summary - TB Drug Development

- Two novel drugs approved for MDR TB
- Two 3-drug regimens in Phase III for DS TB
- Pathway for evaluation
  1. Mouse model
  2. 14-day EBA single or combinations
  3. 8-week studies of regimens
  4. Registration trials in MDR or DS TB
- Better biomarker needed





Antituberculosis agents R&D – thanks to all

