

# A semi-mechanistic model of the population pharmacokinetics and bactericidal activity of high-dose isoniazid against multi-drug-resistant tuberculosis

**Kamunhwala Gausi**, Maxwell Chirehwa, Elisa Ignatius, Richard Court, Xin Sun, Laura Moran, Richard Hafner, Lubbe Wiesner, Susan Rosenkranz, Tawanda Gumbo, Susan Swindells, Andreas Diacon, Helen McIlleron, Kelly Dooley, Paolo Denti

**PAGE**

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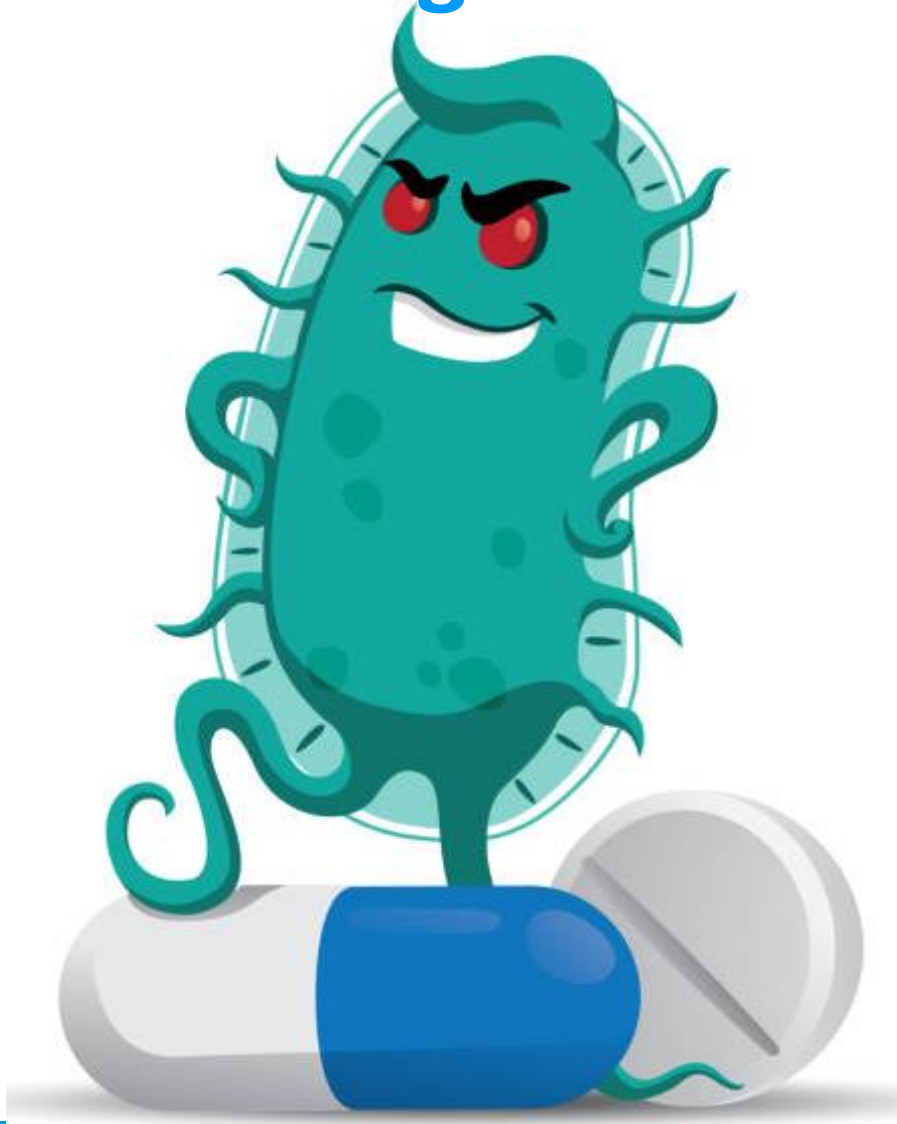


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UCT Pharmacometrics

# Multi-drug resistant tuberculosis



- Higher isoniazid dose effective against low to intermediate **resistant strains**, dose unknown<sup>1,3-4</sup>
- INH resistance<sup>2</sup>
  - **Drug sensitive**, MIC of 0.03 to 0.2 mg/L
  - **InhA mutation**, MIC of 0.2 to 1 mg/L
- PK of isoniazid at higher doses has not been well characterised



# Objectives

- Characterize PK of standard (5 mg/kg) to **high dose isoniazid** (10-15 mg/kg).
- Drug-drug interaction isoniazid and other **multidrug-resistant TB** regimen.
- Early bactericidal activity (EBA) isoniazid against *M.tb* (**drug-sensitive and inhA-mutated**).

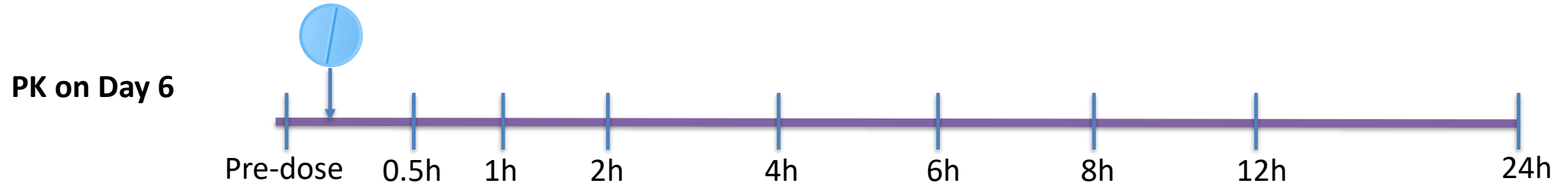


# Isoniazid Pharmacokinetics

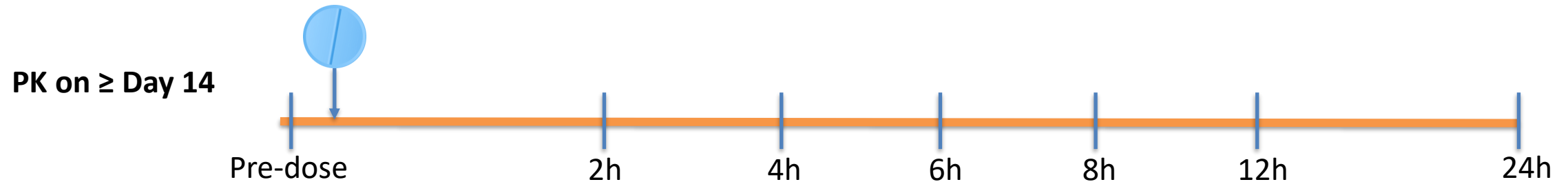


# Method

- Pooled data: **INHindsight** and **PODRtb** study.
- **INHindsight** 7-day EBA of isoniazid monotherapy dose escalation

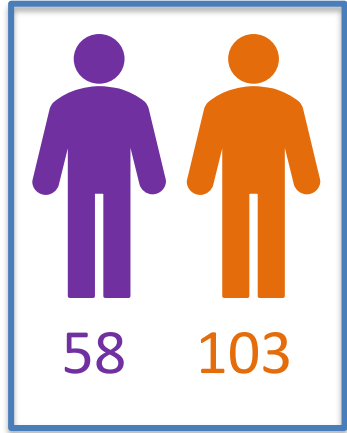


- **PODRtb** observational study of patients on standard treatment for MDR-TB



- N-acetyltransferase 2 (NAT2) genotype captured (rapid, intermediate or slow)<sup>1</sup>
  - When missing, **mixture model** was used to assign phenotype<sup>2</sup>

# Patient characteristics

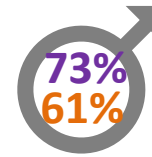


Age: 32 (18-58)

35 (19-69)



18 (16-19)  
17 (16-19)



HIV: +20%/-80%  
+62%/-38%

	5	10	15
mg/kg	52%	24%	25%
	25%	30%	48%



NAT2  
Slow: 26%  
Intermediate: 55%  
Fast: 13%  
Missing: 6% ; 100%

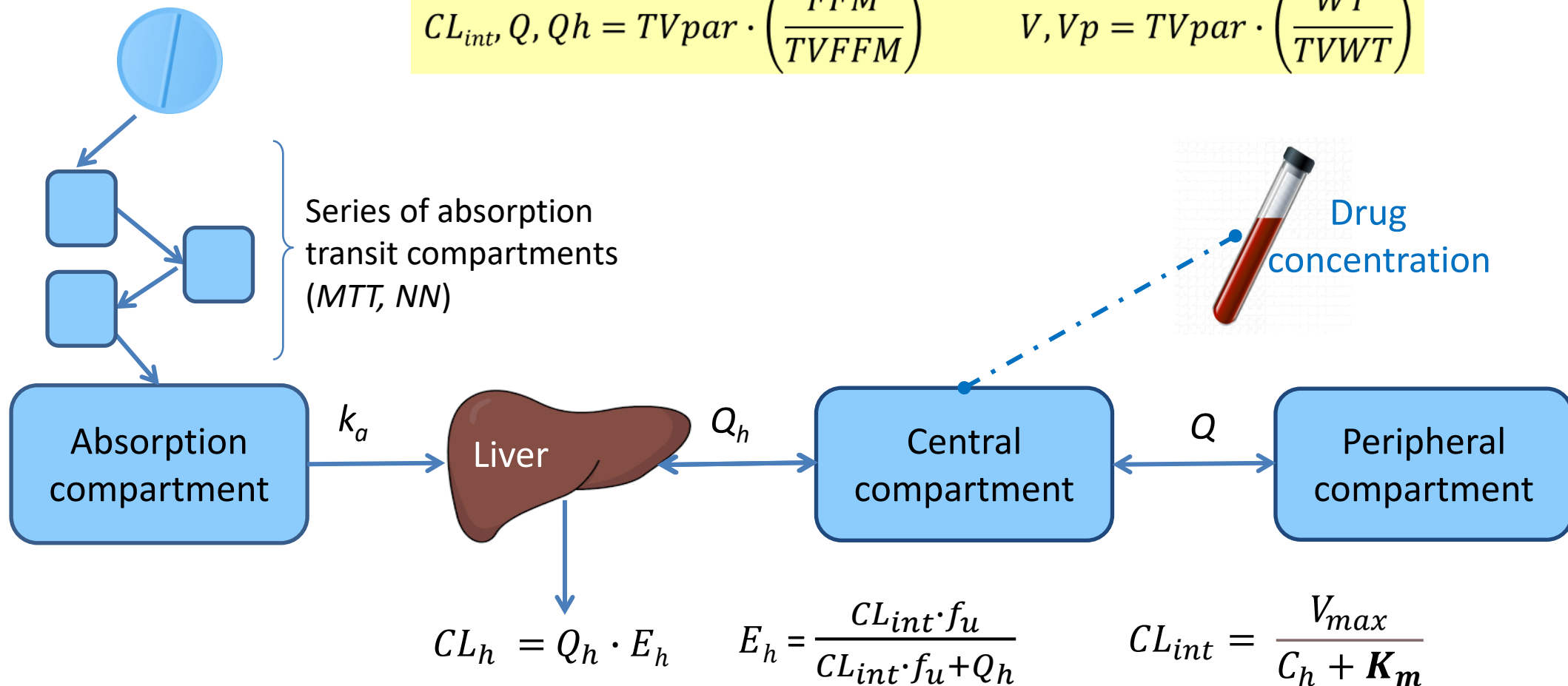


**Concomitant TB drugs - PODRtb**

Ethambutol, Ethionamide,  
kanamycin, Pyrazinamide,  
moxifloxacin, terizidone/cycloserine

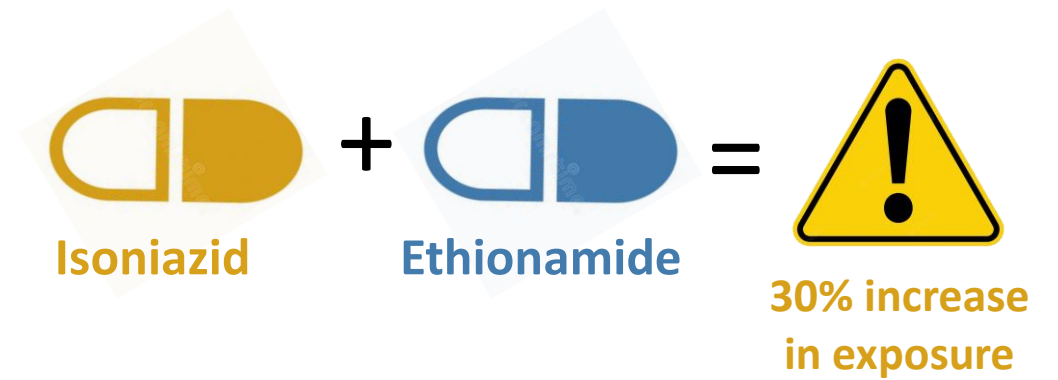
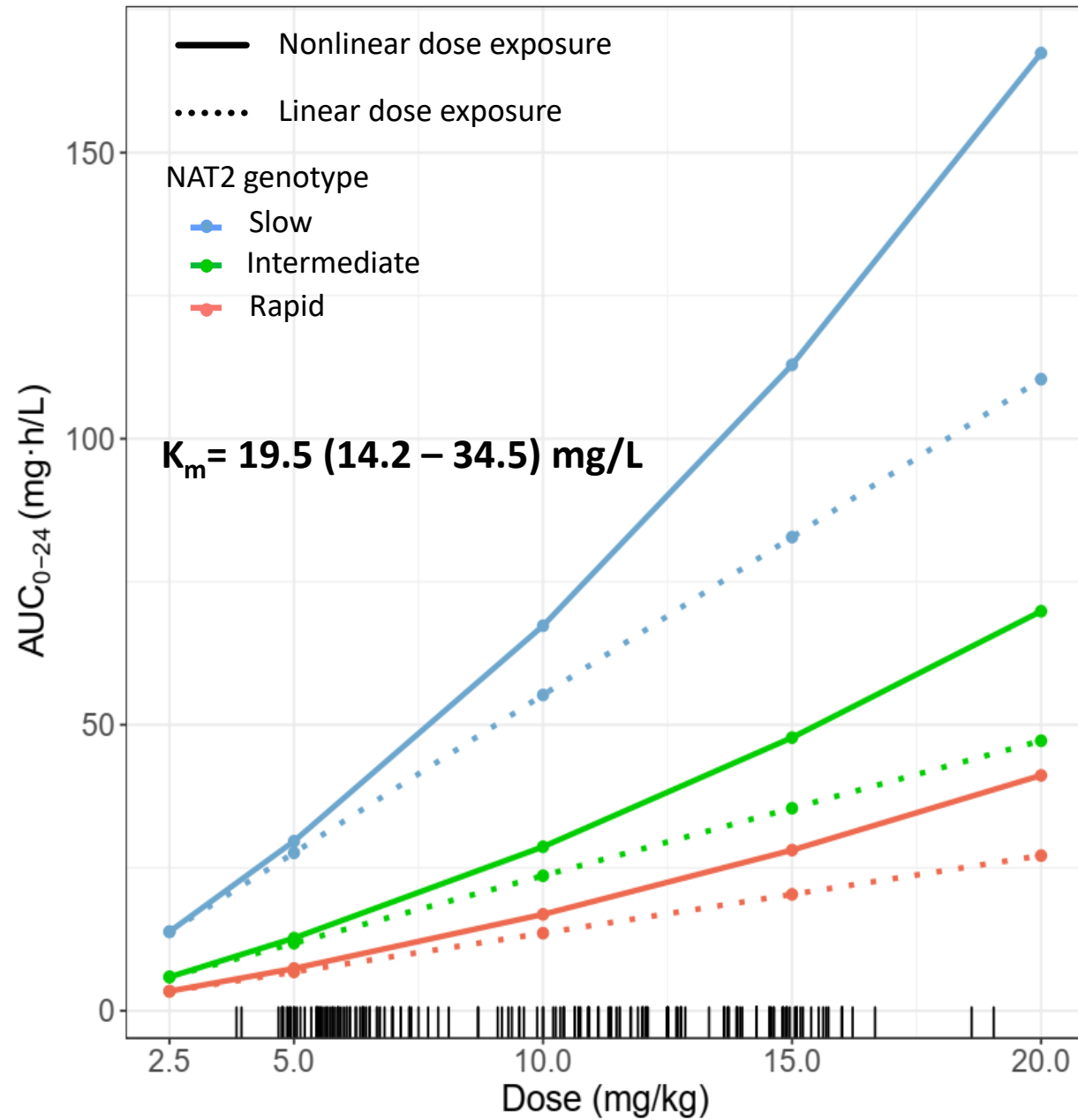
# Pop PK model

$$CL_{int}, Q, Q_h = TV_{par} \cdot \left( \frac{FFM}{TVFFM} \right)^{0.75} \quad V, V_p = TV_{par} \cdot \left( \frac{WT}{TVWT} \right)$$



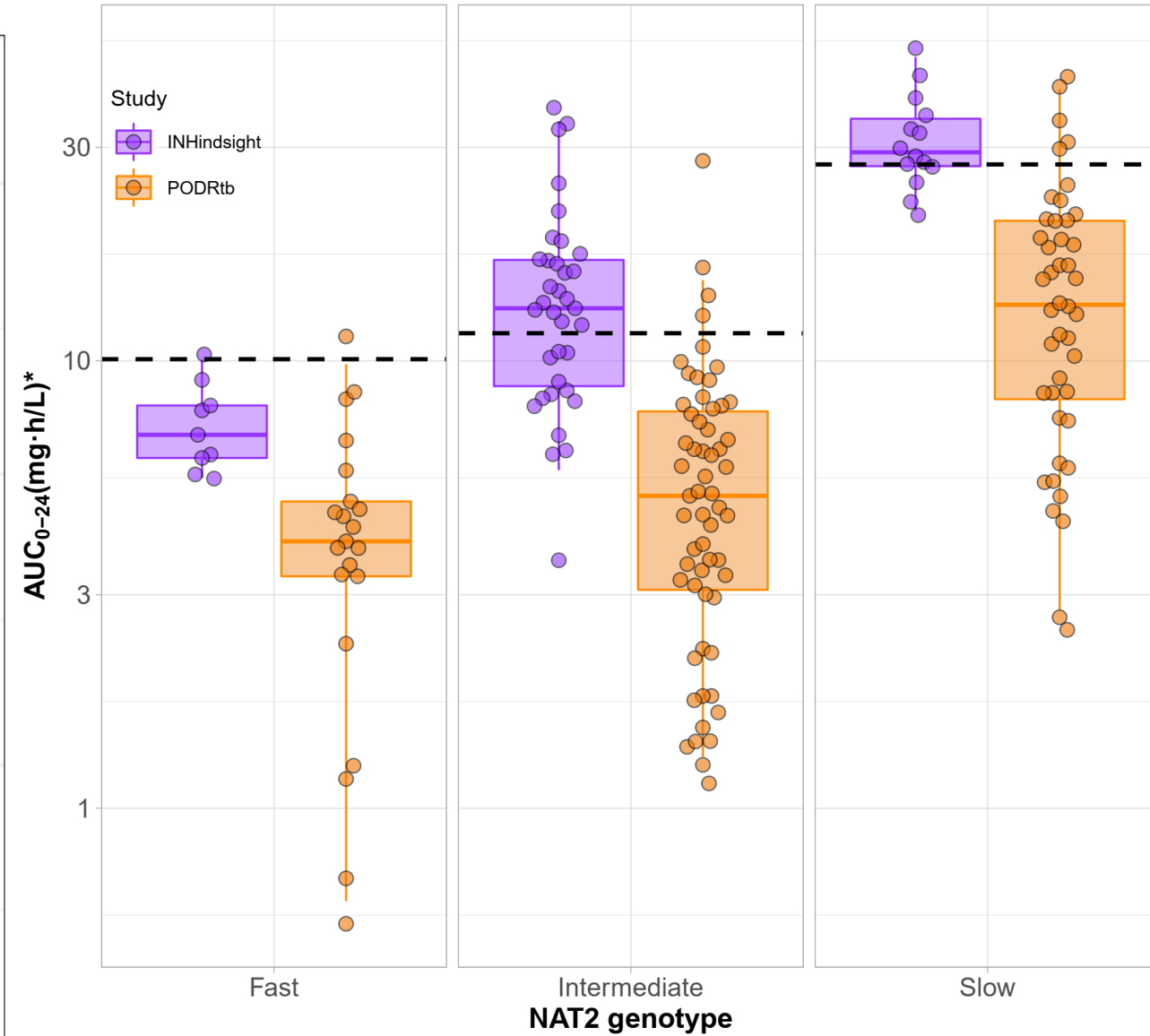
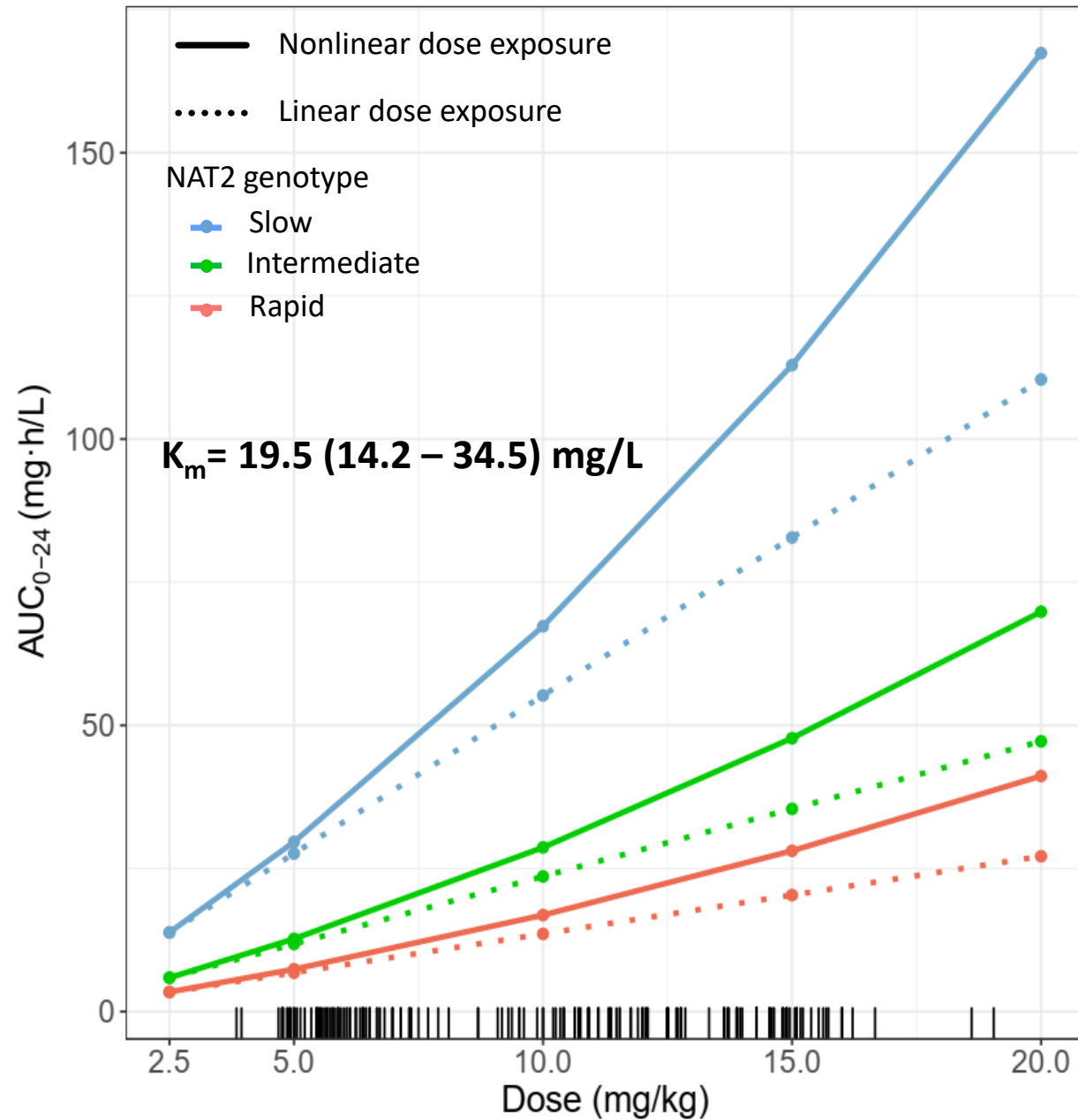
1. Chirehwa et.al. Antimicrob Agents Chemother 2016; 60: 487–94.
2. Gordi et.al. Br J Clin Pharmacol 2005; 59: 189–98.

# Results





# Results



**Pyrazinamide, moxifloxacin, terizidone/cycloserine**

\*Dose normalised to 5 mg/kg

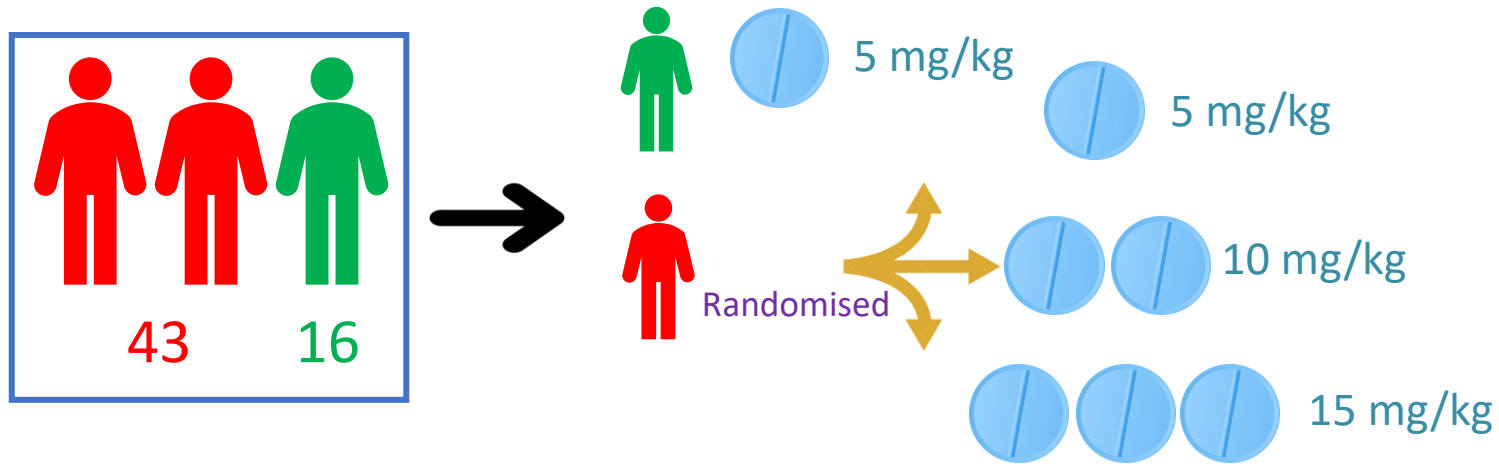
Hong. et al.. Ther. 42, e220–e241 (2020).

Winckler et.al. Int J Tuberc Lung Dis 2021; 25: 896–902.

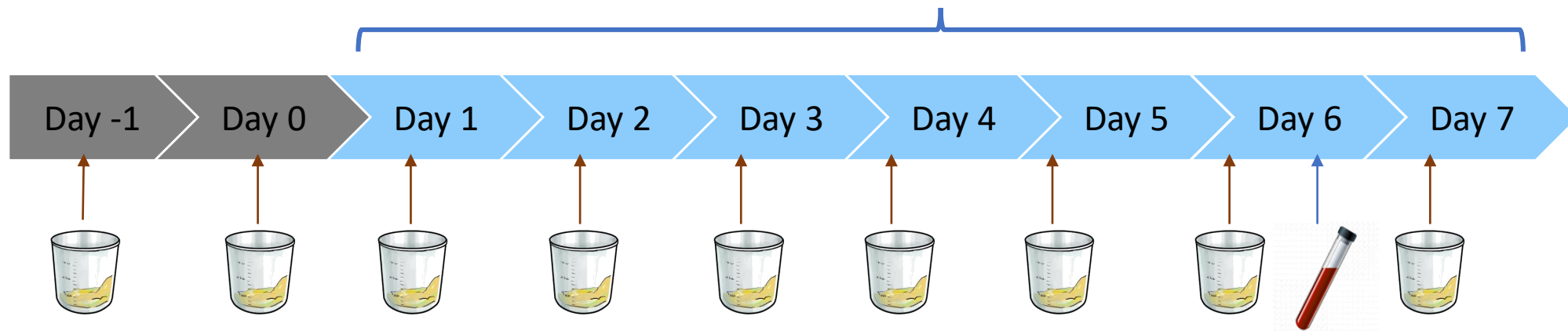
Ranjan et.al. Antimicrob Agents Chemother 2019; 63: e00099-19.

# Isoniazid pharmacokinetics-Pharmacodynamics

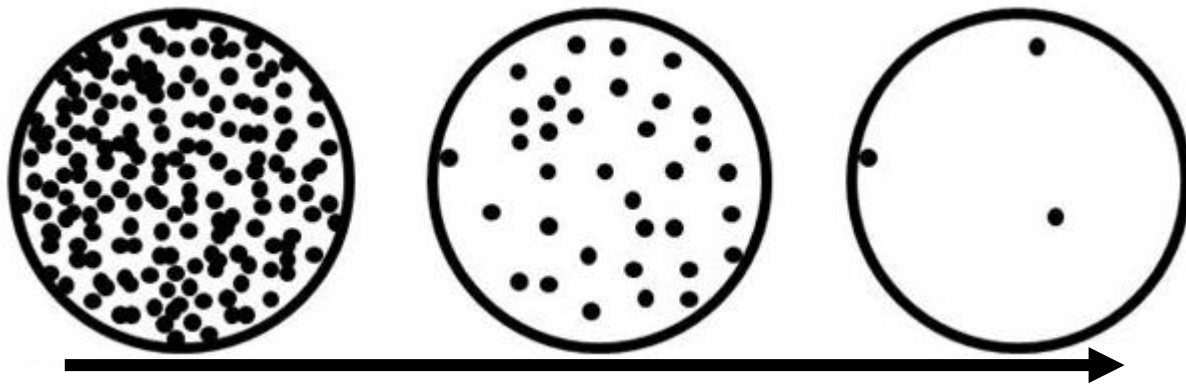
# Study procedure - INHindsight



INH-monotherapy

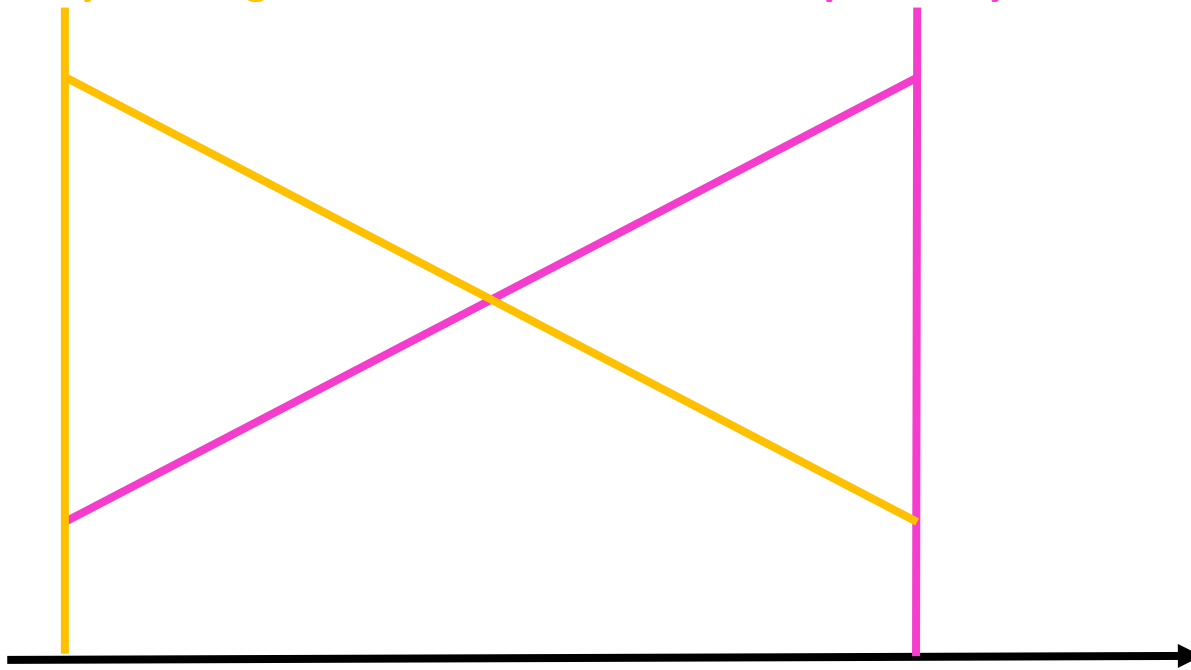


# TB Biomarkers – Bacteria load

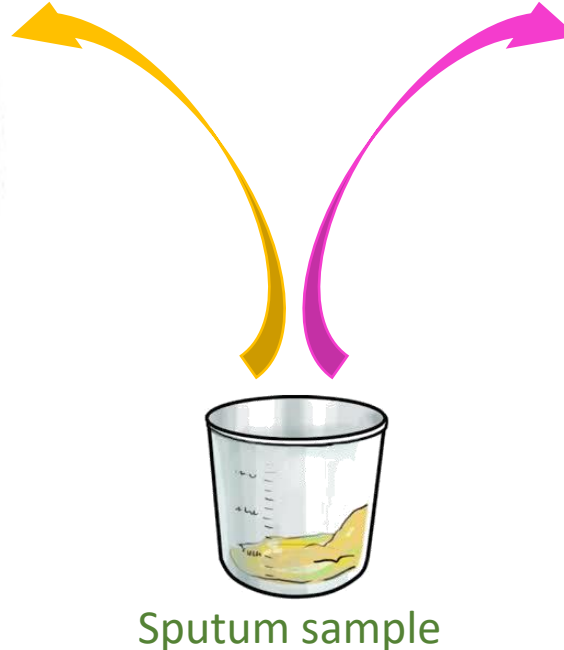


Colony forming units

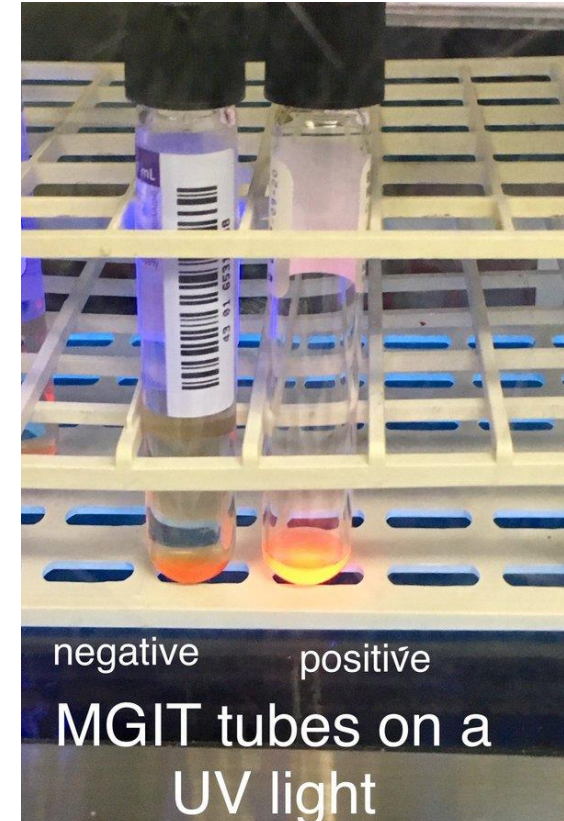
Time to positivity



Time on treatment



Mycobacteria Growth Indicator Tube (MGIT)

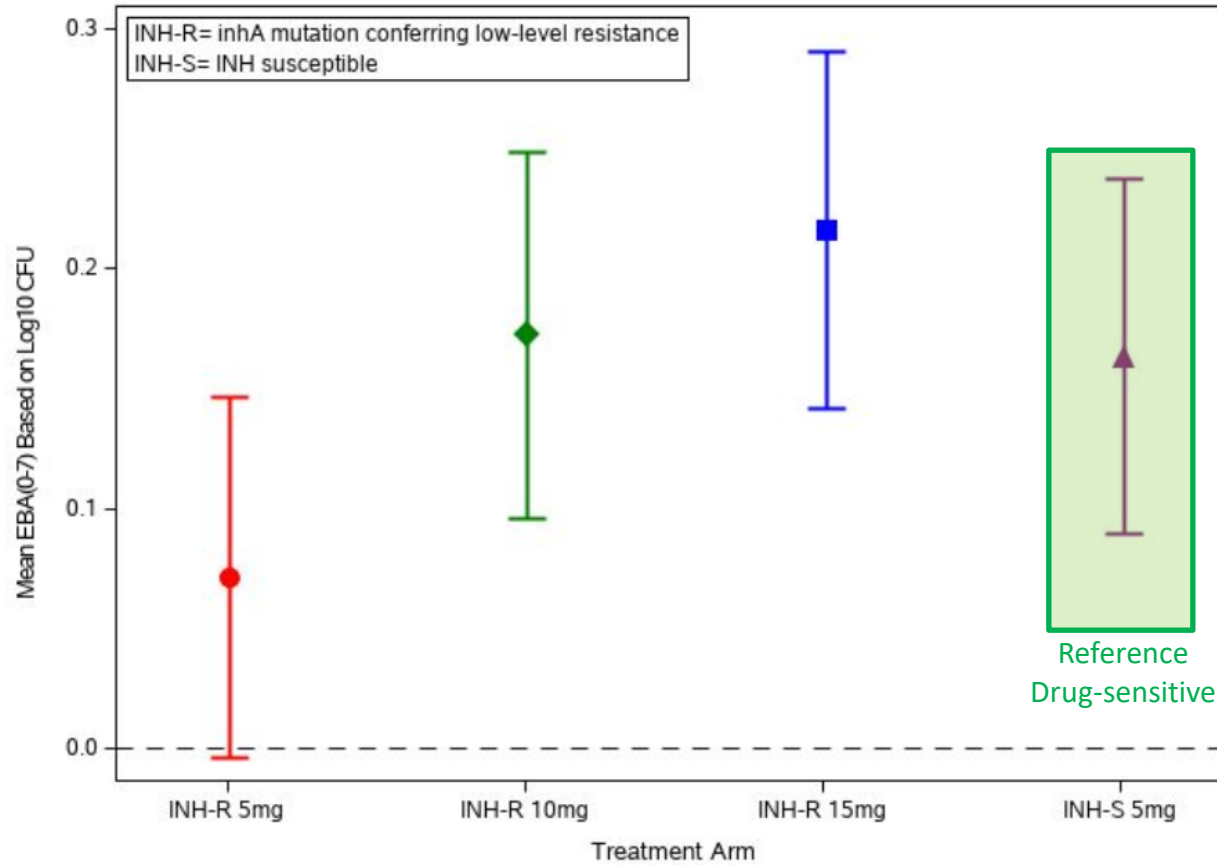


negative positive  
MGIT tubes on a  
UV light

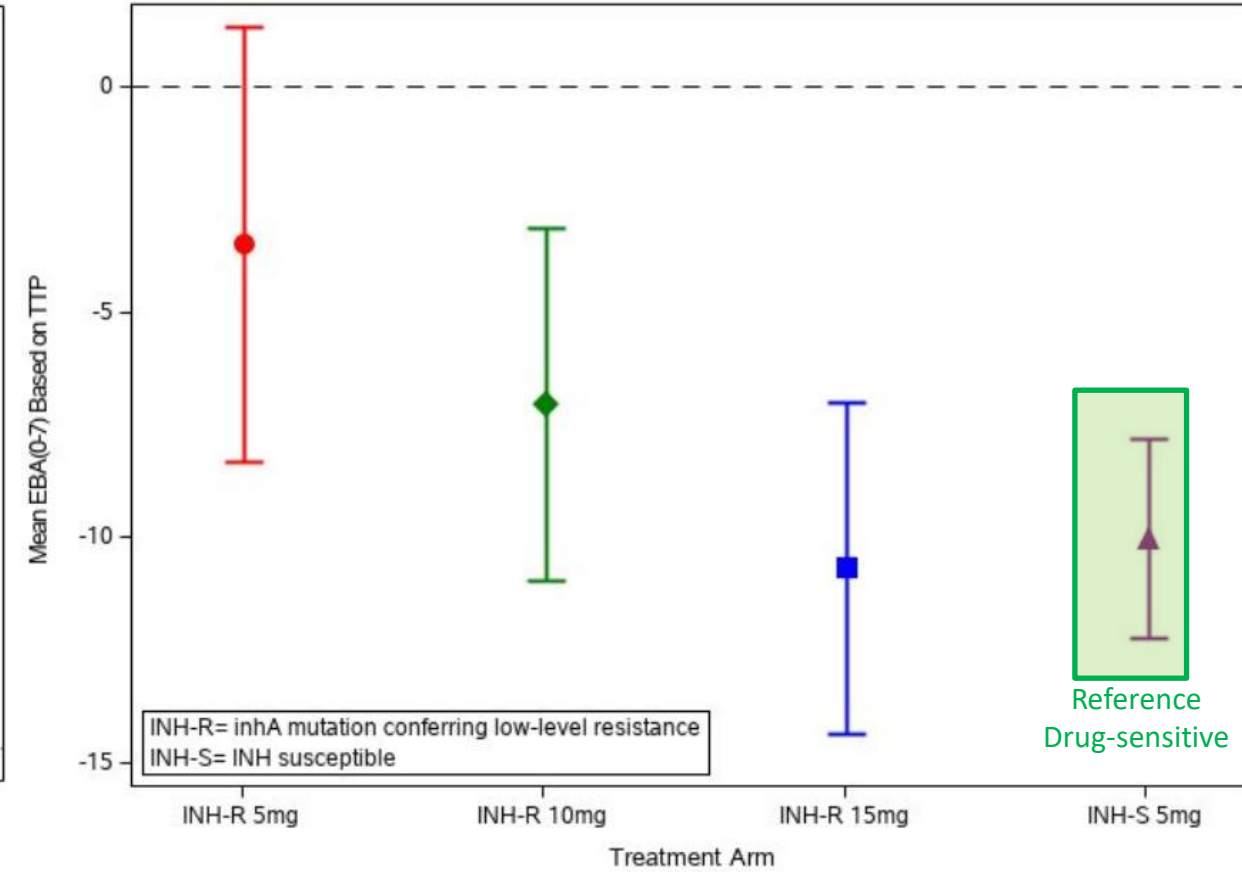
Tweet: @richdavisphd 19/05/2020

# Primary analysis – EBA(0-7) by dose

## Colony forming units



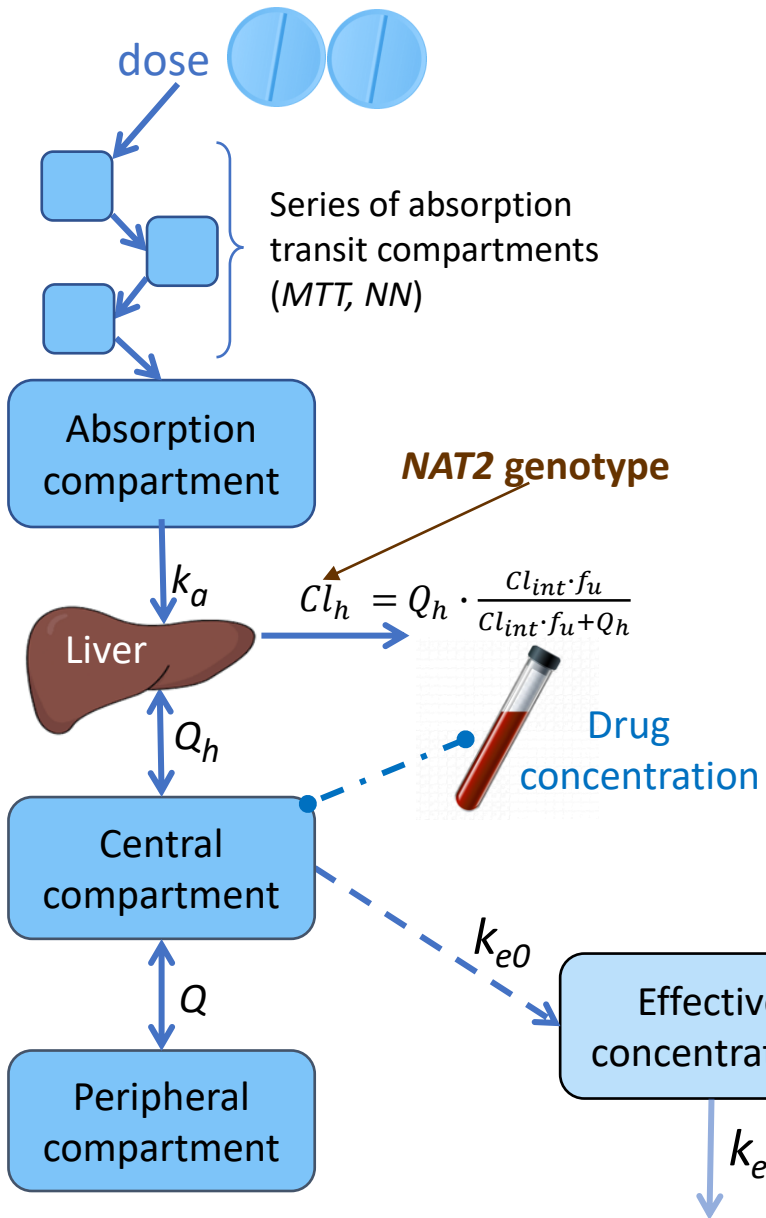
## Time to positivity



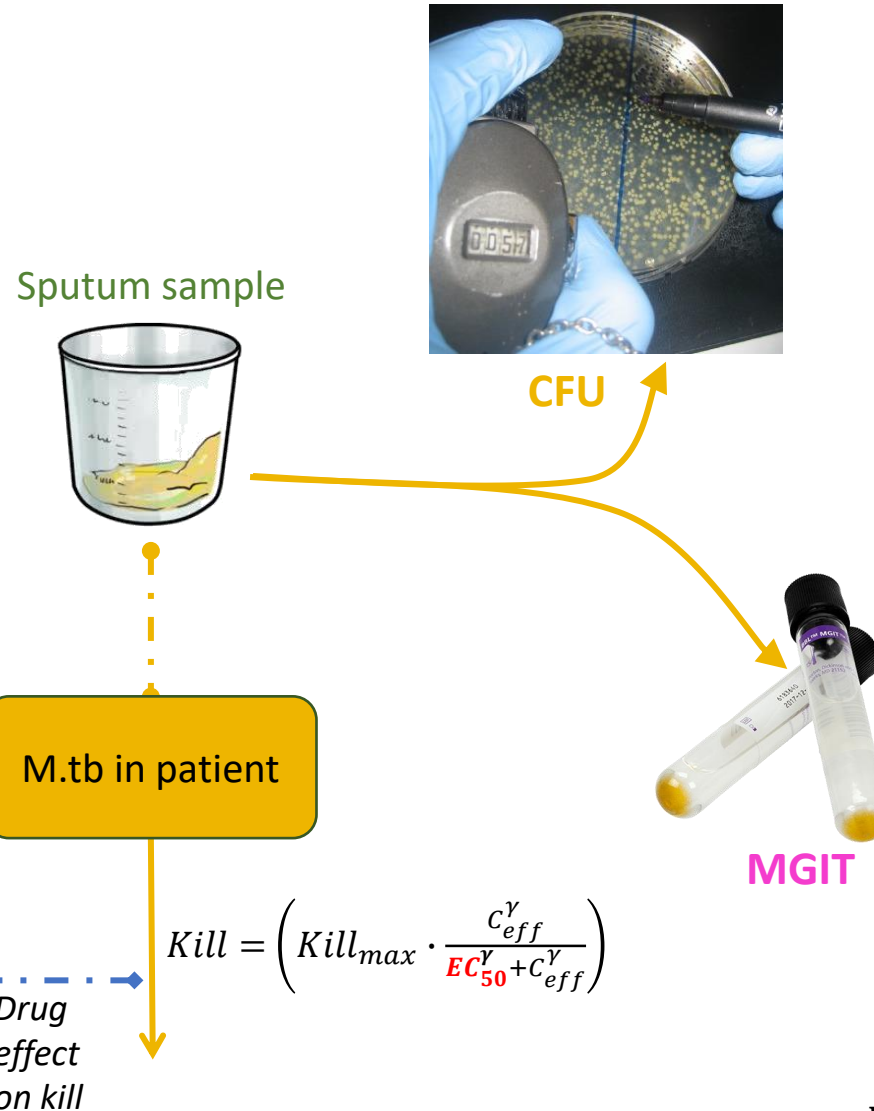




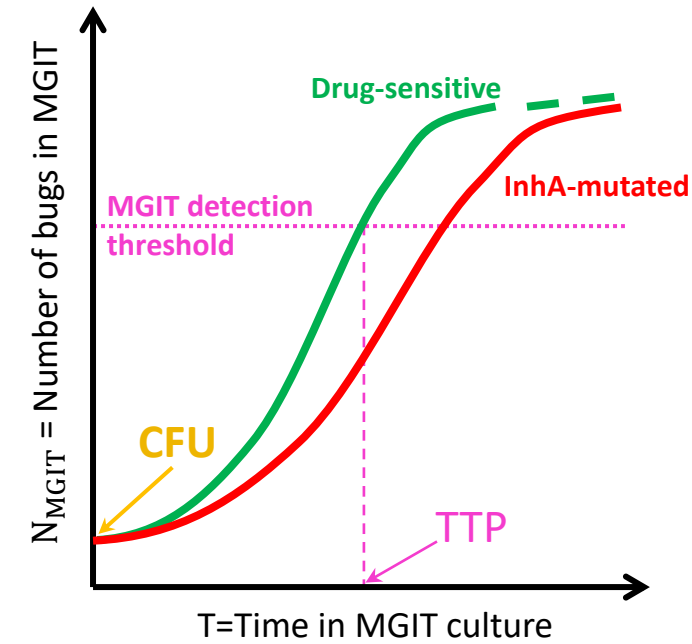
## Pharmacokinetics of isoniazid



## Bacterial kill model

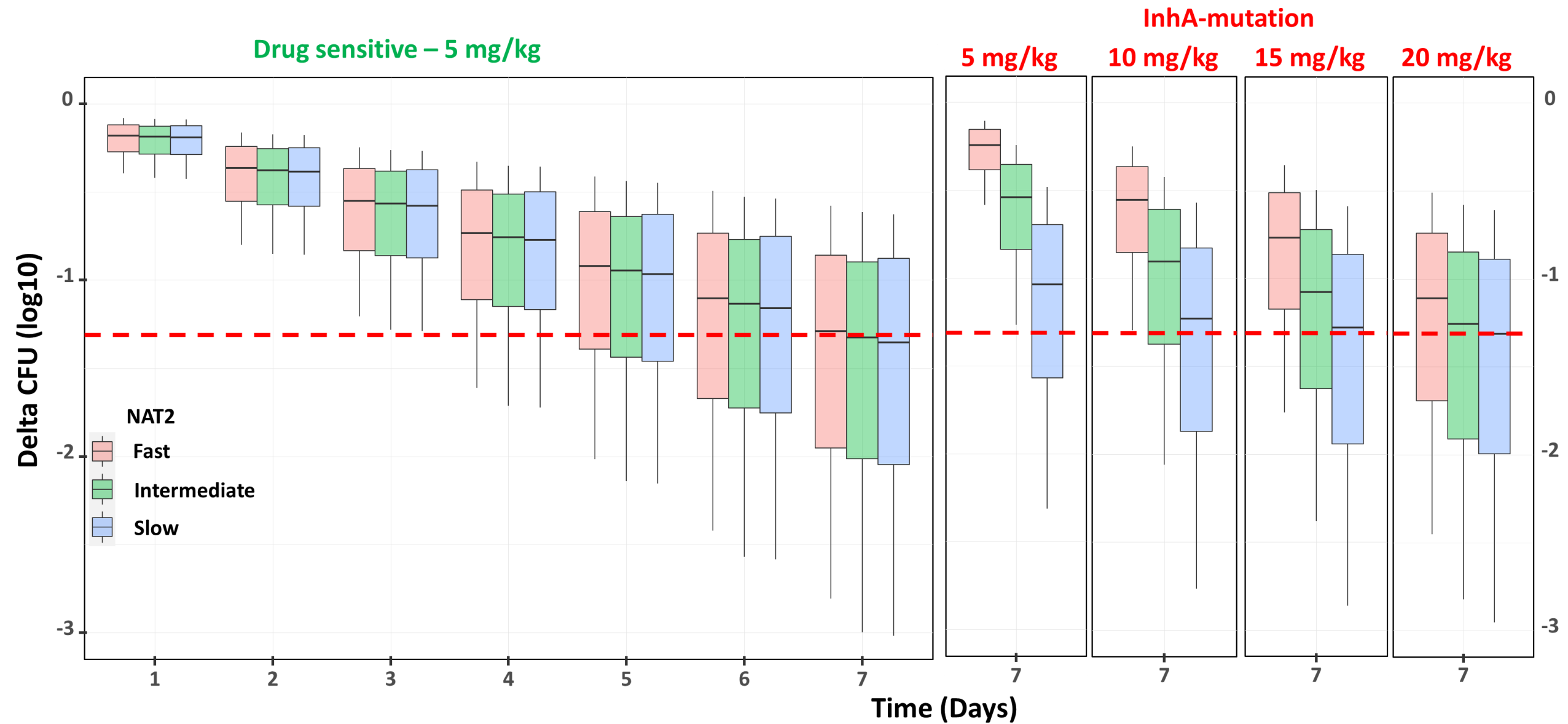


## TTP in MGIT model



$$N_{MGIT}(T) = CFU \cdot e^{k_{growth} \cdot (T - delay)}$$

# Simulation of bacteria kill - Drop in CFU





# Conclusions

EBA

Standard-dose Isoniazid

High-dose isoniazid

VS



VS

Drug-sensitive strain

InhA-mutation strain

NAT2



Dose

10 mg/kg

15 mg/kg

20 mg/kg

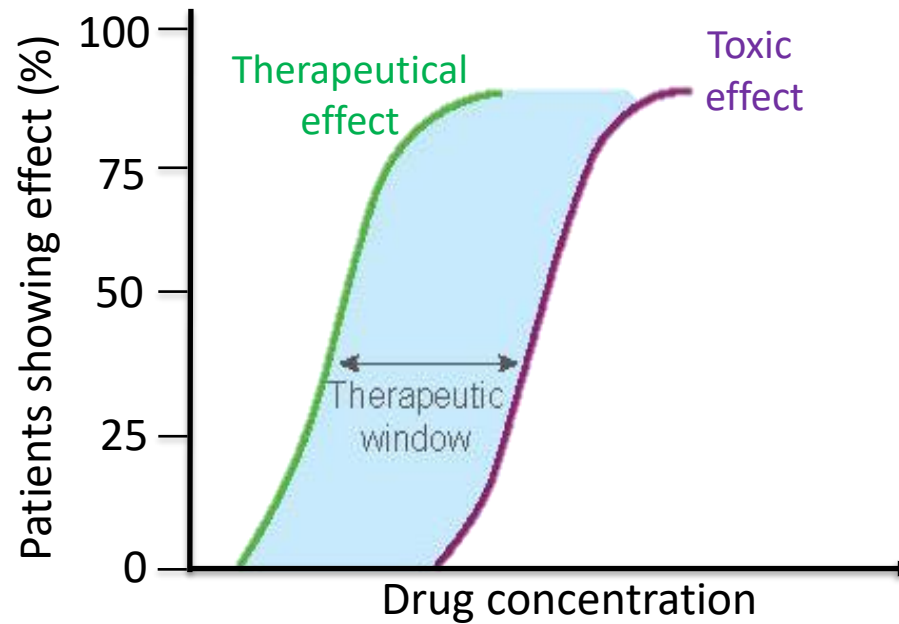


World Health Organization

10 mg/kg dose

VS

MDR-TB

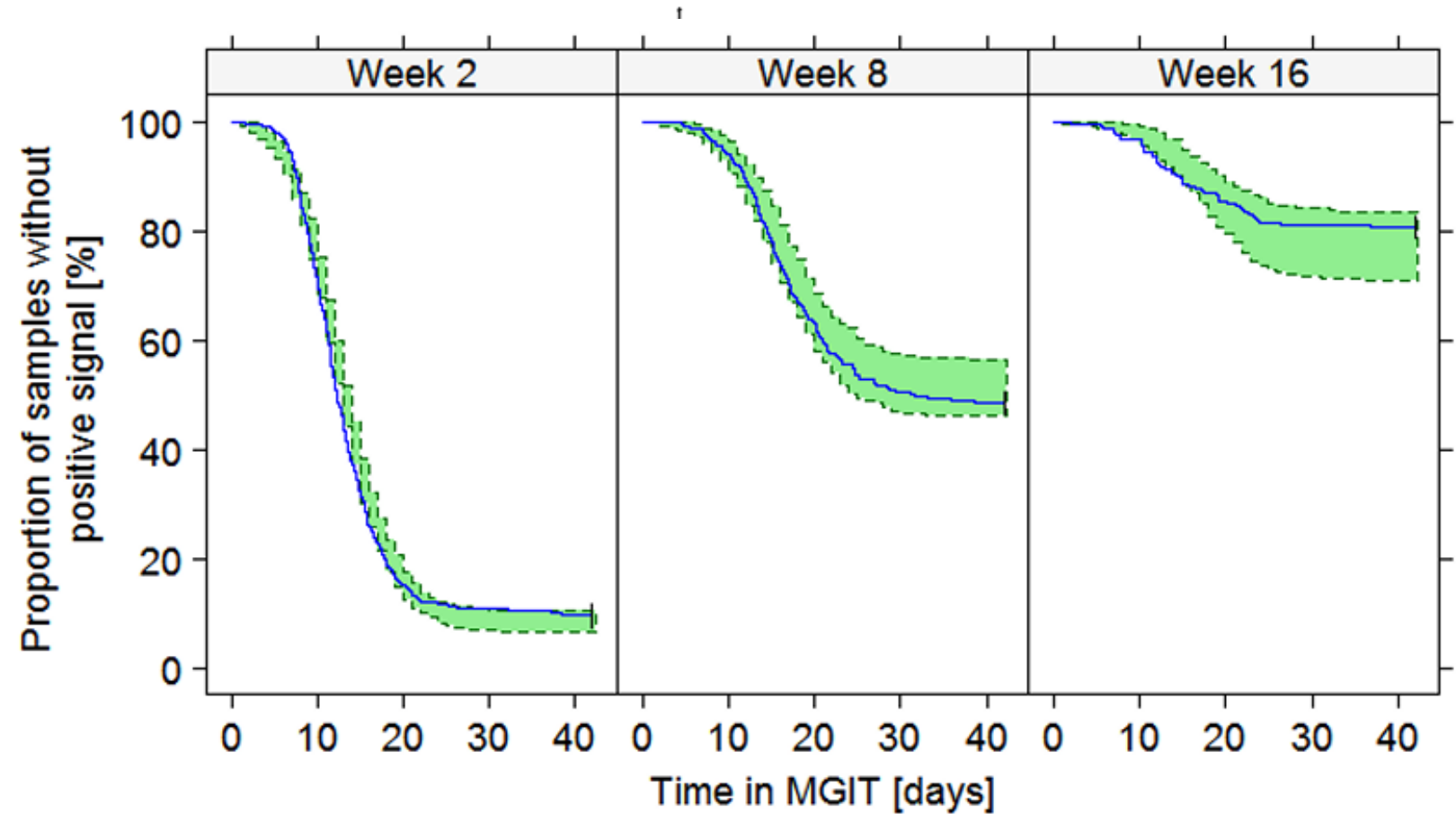


Detect

- MTB DNA
- Resistant strain
- Now – NAT2

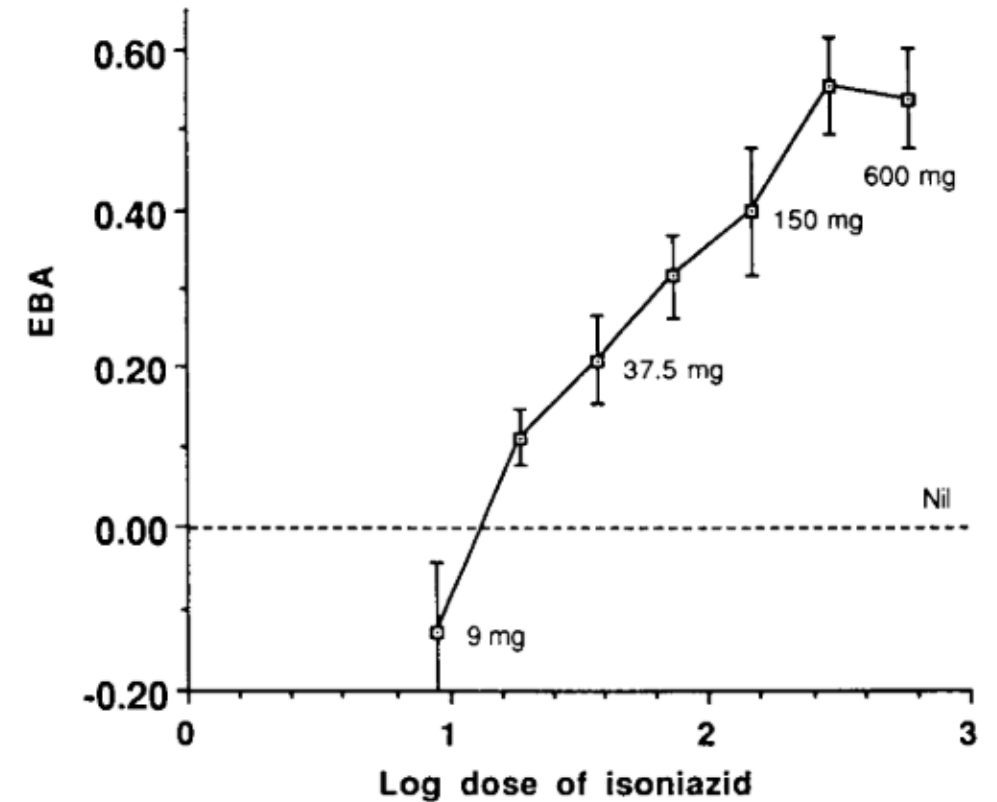
# Challenges

- Time to event models.<sup>1</sup>



# Challenges

- Time to event models.<sup>1</sup>
- Maximum-kill **drug-sensitive strain**.<sup>2,3</sup>

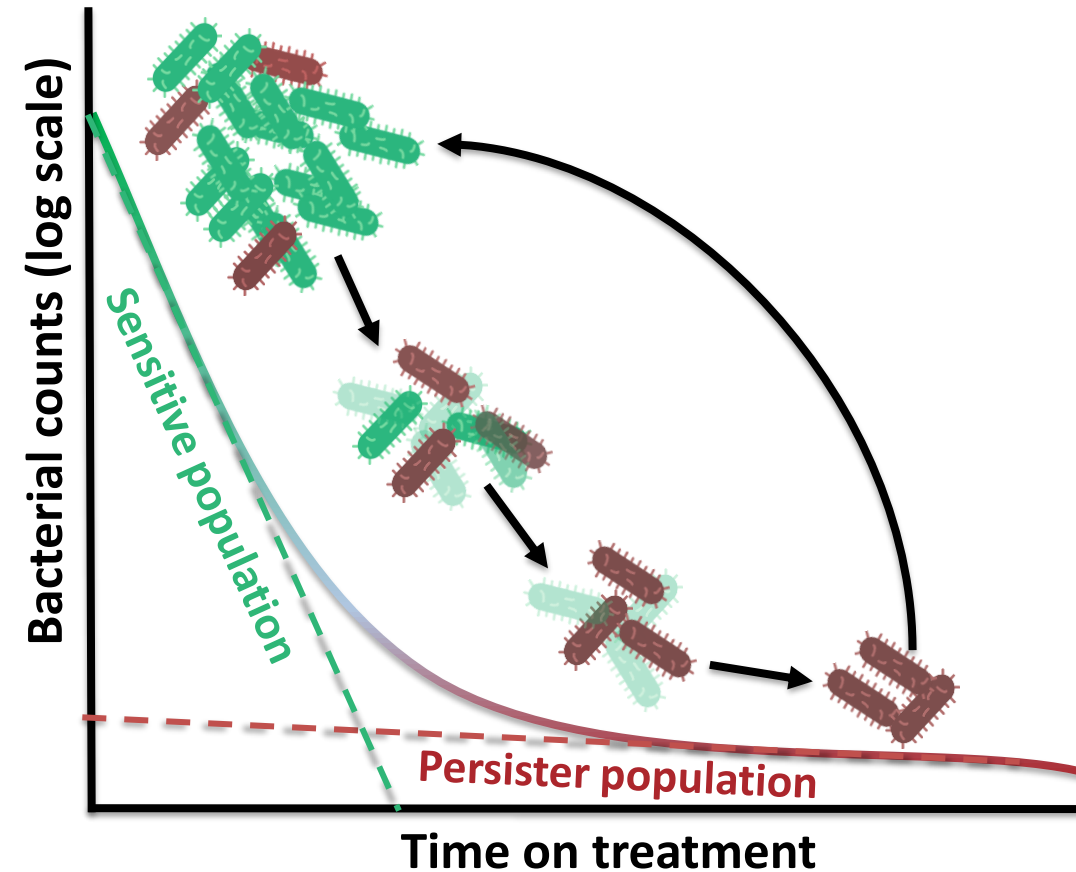


**Figure 1.** Early bactericidal activity (EBA) of isoniazid related to dose size ( $\log_{10}$  mg). Bars indicate SEM.





# Challenges

- Time to event models.<sup>1</sup>
- Maximum-kill **drug-sensitive strain**.<sup>2,3</sup>
- No biphasic kill.<sup>4</sup>



## A Semimechanistic Model of the Bactericidal Activity of High-Dose Isoniazid against Multidrug-Resistant Tuberculosis: Results from a Randomized Clinical Trial

[Previous Article](#)

 Kamunhwala Gausi<sup>1</sup>, Elisa H. Ignatius<sup>2</sup>, Xin Sun<sup>3</sup>, Soyeon Kim<sup>4</sup>, Laura Moran<sup>5</sup>, Lubbe Wiesner<sup>1</sup>, Florian von Groote-Bidlingmaier<sup>6</sup>, Richard Hafner<sup>7</sup>, Kathleen Donahue<sup>8</sup>, Naadira Vanker<sup>6</sup>, Susan L. Rosenkranz<sup>3</sup>, Susan Swindells<sup>9</sup>, Andreas H. Diacon<sup>6</sup>, Eric L. Nuermberger<sup>2</sup>, Kelly E. Dooley<sup>2</sup>, and  Paolo Denti<sup>1</sup>; on behalf of the A5312 Study Team... [Show less](#)

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## Pharmacokinetics of standard versus high-dose isoniazid for treatment of multidrug-resistant tuberculosis

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