



PanACEA

# Prediction of increase in time-to-positivity after higher doses of rifampicin based on PKPD modelling

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# High dose rifampicin for tuberculosis (TB)

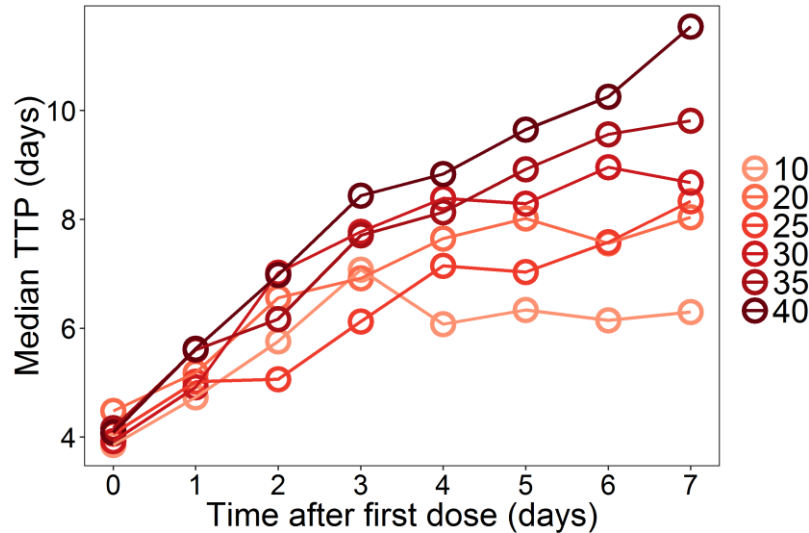
- Rifampicin used at 10 mg/kg to treat TB
- Higher doses may be more effective
- PanACEA HIGHRIF1<sup>1</sup> evaluated up to 40 mg/kg daily rifampicin
  - Antibacterial activity measured using time-to-positivity (TTP) in liquid culture medium (MGIT, Becton-Dickinson)
- No significant exposure-response using conventional statistical methods<sup>1</sup>

Objectives: To explore exposure-response of increasing doses of rifampicin for 7 days of TTP using PKPD modelling  
...and predict TTP for 50 mg/kg rifampicin!



# Study design and data

Median TTP vs time<sup>1</sup>



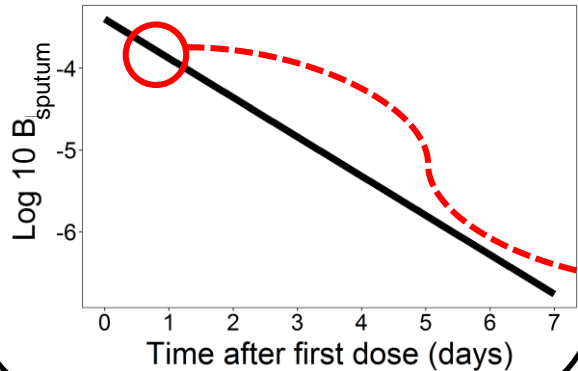
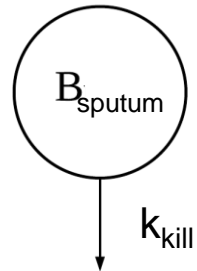
- 83 adult pulmonary TB patients<sup>1</sup>
  - 10 (n=8), 20, 25, 30, 35, 40 (n=15/arm) mg/kg
- TTP = time from start of incubation of sputum specimen in liquid culture until a positive signal
  - Time-to-event data
- Signals positive at low oxygen level
  - High bacterial burden = short TTP and vice versa

<sup>1</sup>Boeree MJ *et al.* Am J Respir Crit Care 2015 (=HIGHRI1)



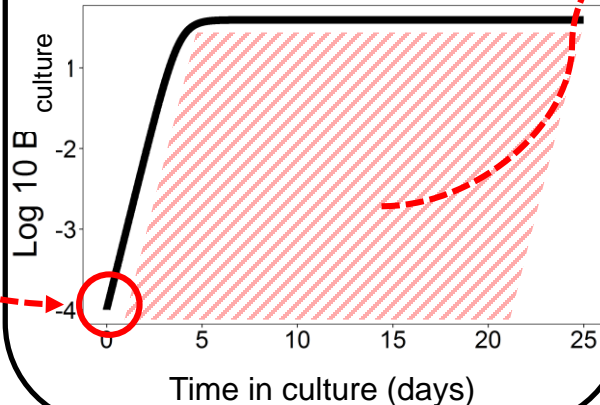
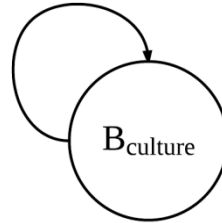
# Model structure

## Sputum model



## Mycobacterial growth model

$$k_G \times (B_{\text{max}} - B_{\text{culture}})$$

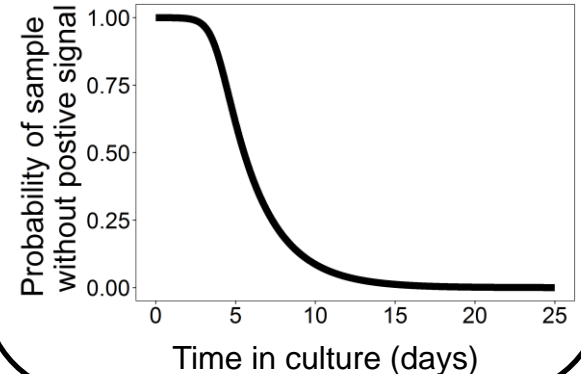


## Hazard model

$$h(t) = B_{\text{culture}}(t)$$

$$H(t) = \int_0^t h(t) dt$$

$$S(t) = e^{-H(t)}$$



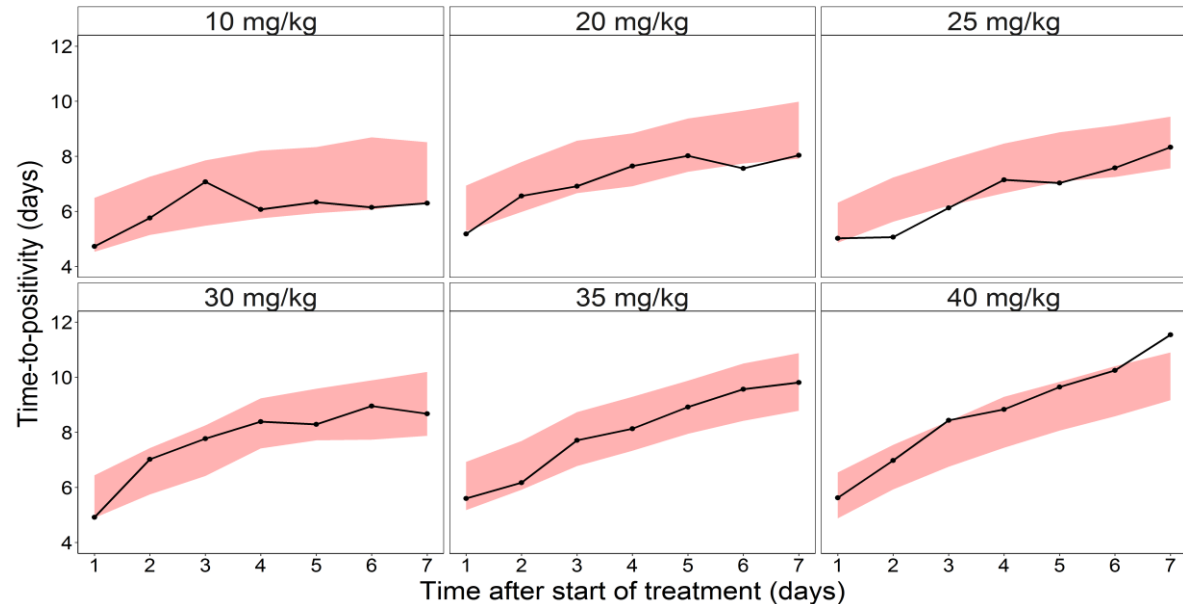
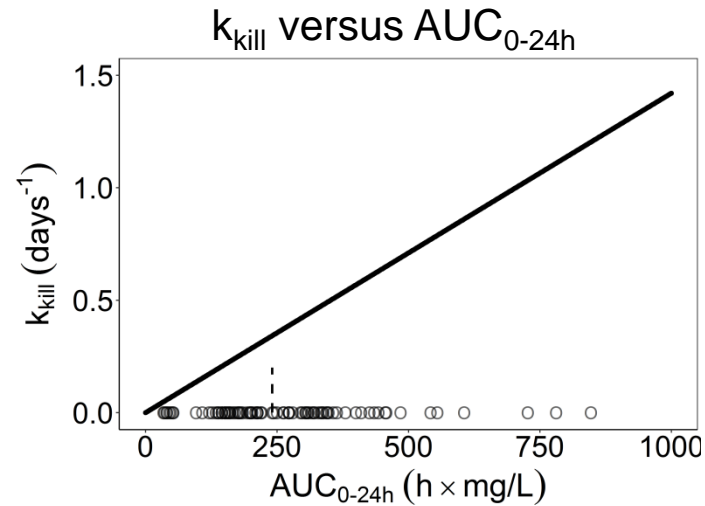
$B$  = number of bacteria



# Exposure-response

- Rifampicin day 7  $AUC_{0-24h}$  - significant covariate on  $k_{kill}$

Predicted and observed median TTP



Predicted:  Observed:  5

# Prediction of 50 mg/kg

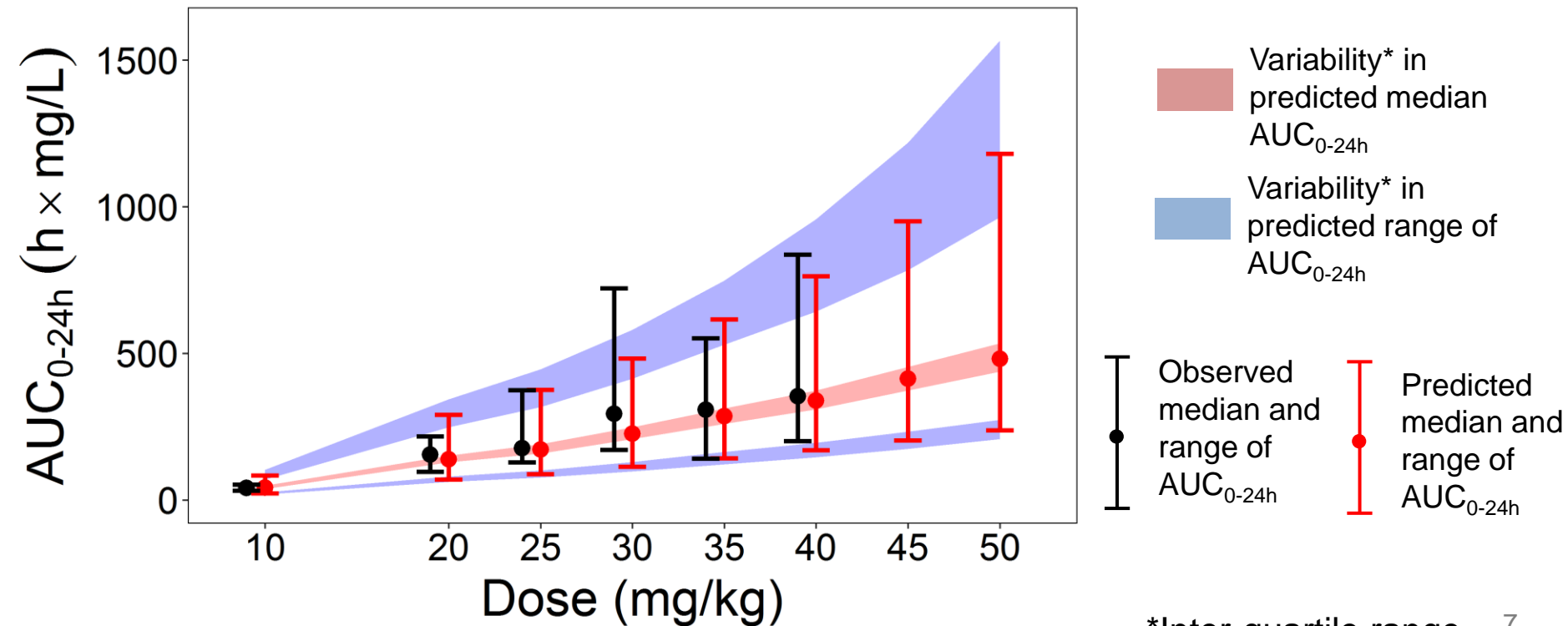
- Simulation of 1000 new trials
  - Same protocol as HIGHRIF1
  - 10, 20, 25, 30, 35, 40, 45 and 50 mg/kg
- Day 7  $AUC_{0-24h}$  simulated from PK model<sup>1</sup>
  - Re-sampling of covariates from HIGHRIF1
  - Simulate full PK curve and calculate  $AUC_{0-24h}$  using ncappc<sup>2</sup>

<sup>1</sup>Svensson RJ *et al.* CPT 2017

<sup>2</sup>Acharya C *et al.* Comput Methods Programs Biomed 2016

# Simulated day 7 $AUC_{0-24h}$

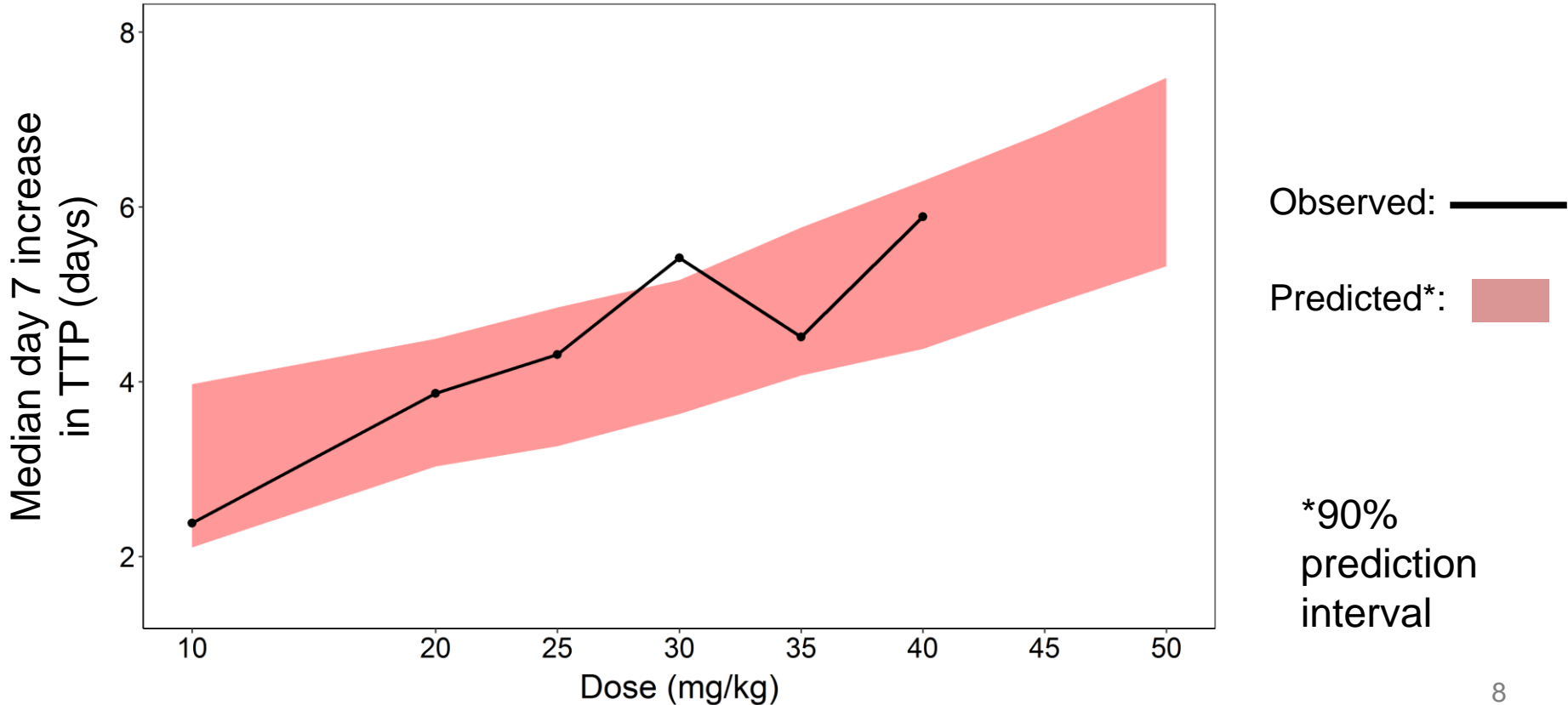
Day 7  $AUC_{0-24h}$  vs dose





# TTP day 7 change from baseline

Median day 7 increase in TTP vs dose





# Conclusions

- PKPD-modelling using a time-to-event model allowed detection of significant exposure-response
  - Not possible using conventional statistical methods
  - Increased confidence and supports testing higher doses of rifampicin in longer and larger settings
- Clinical trial simulations show increased response for a 50 mg/kg dose
  - Supports testing 50 mg/kg from drug effect perspective



# Acknowledgements

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