# A pharmacometric multistate model for predicting long-term treatment outcomes of patients with drug-resistant tuberculosis

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## Background

- Studying treatment outcomes of tuberculosis (TB) requires a long follow-up which is costly and difficult. An early and reliable biomarker reflecting treatment response is urgently needed
- Classical time-to-event analysis only focuses on one primary outcome of the interest, whereas the multistate modelling approach can evaluate several outcomes at the same time and incorporate covariates without losing information from intermediate events

### Aim

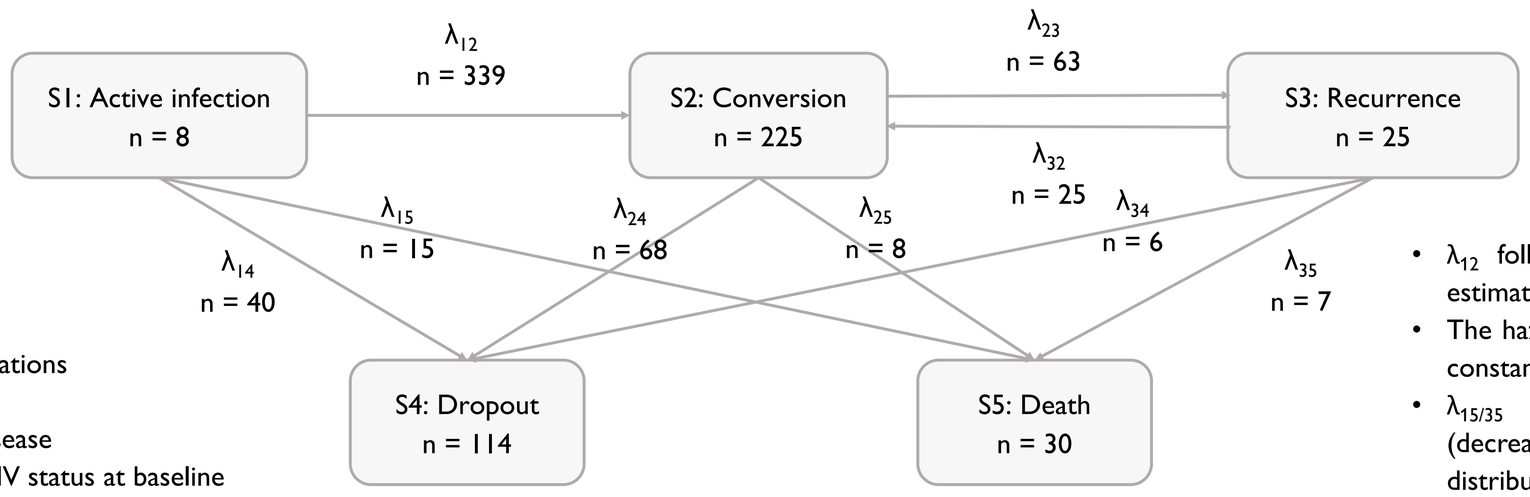
- Develop a general pharmacometric multistate model framework for TB
- Evaluate the link between long-term outcomes and early treatment response

## Methods

- Data were obtained from two phase II clinical trials (C208 and C209) of bedaquiline (BDQ) on top of a multi-drug background regimen [1,2]
- A multistate model consisting of five states (S1 - active infection, S2 - conversion, S3 - recurrence, S4 - dropout, and S5 - death) was developed
- Parametric hazard functions including a surge function [3], constant and Weibull distributions were tested for each transition rate from state *i* to state *j* ($\lambda_{ij}$)
- Evaluated predictors included individual characteristics, baseline disease severity (e.g., time-to-positivity [TTP], types of drug-resistant TB), and observed or model-derived on-treatment biomarkers (e.g., half-life of bacterial clearance [HL], predicted mycobacterial load [MBL]) [4-7]

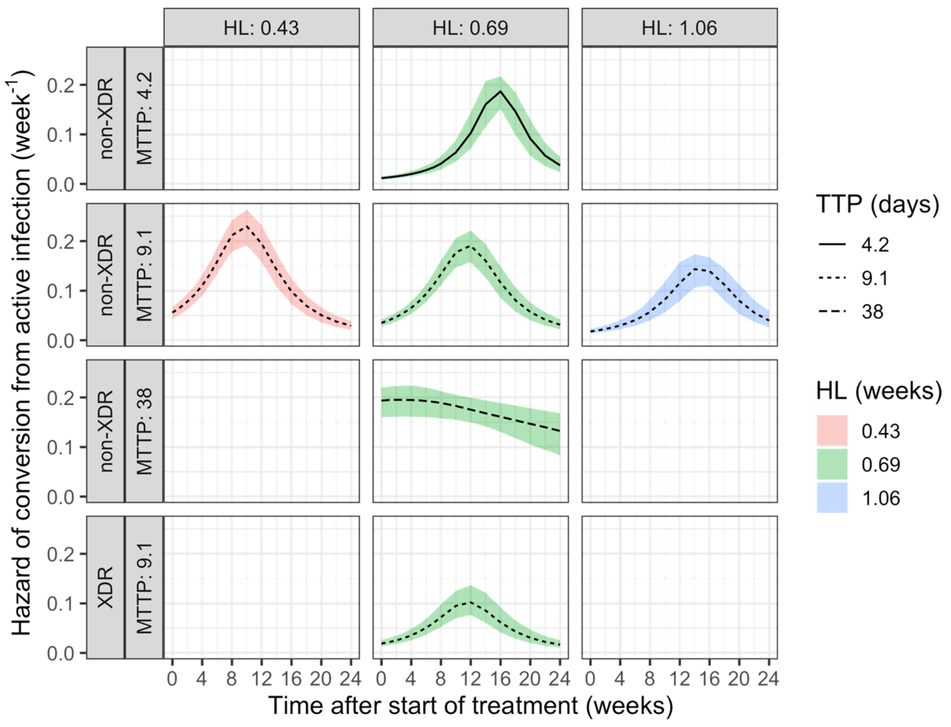
## Results

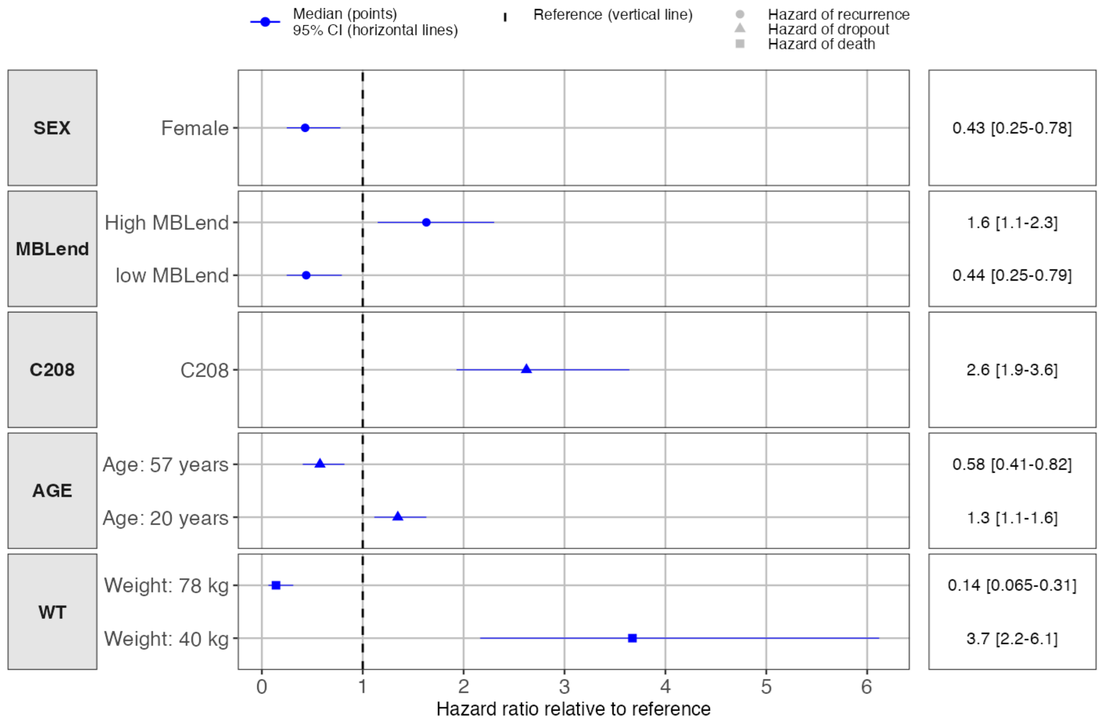
Parameter estimates and example NONMEM code




- 402 patients with 6984 observations were included in the analysis
- 96% of patients had cavitary disease
- 91% of patients had negative HIV status at baseline

- $\lambda_{12}$ followed a surge function with estimated peak at 11 weeks
- The hazard of $\lambda_{14}$, $\lambda_{25}$, $\lambda_{23}$, and $\lambda_{32}$ was constant over time
- $\lambda_{15/35}$ (increasing hazard), $\lambda_{24/34}$ (decreasing hazard) followed Weibull distributions

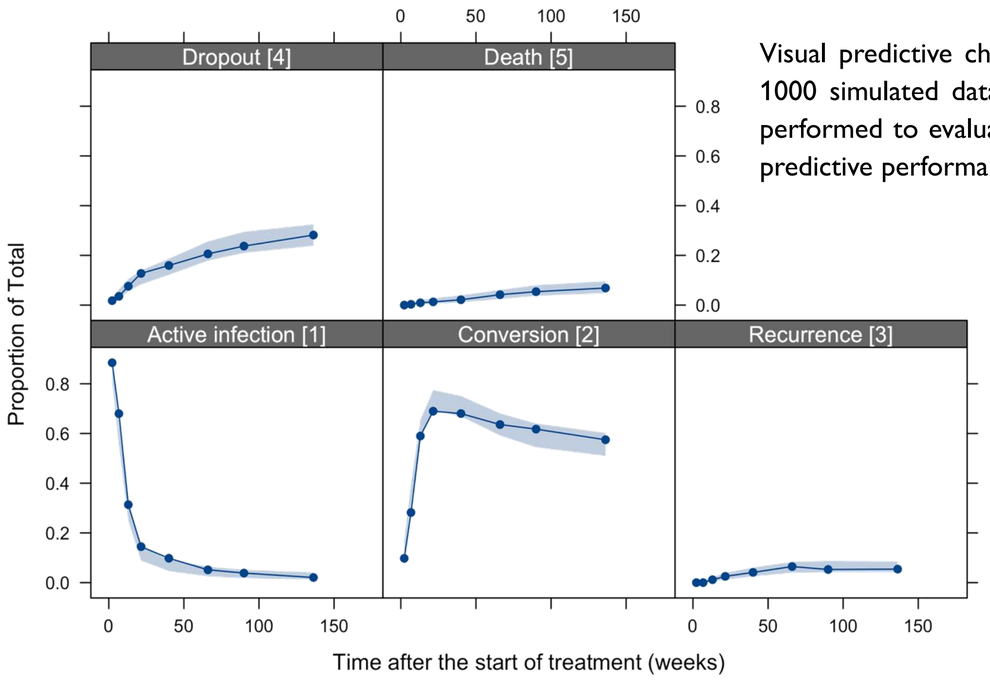



- Patients having higher probability to reach earlier sputum culture conversion (SCC):
  1. Long baseline TTP (i.e., low TB disease burden)
  2. Short HL in the first two weeks (i.e., faster bacterial clearance)
  3. Not infected with extensively drug-resistant TB (XDR-TB) strain

- Being male or having high MBL at the end of BDQ treatment increased the risk of recurrence
- Enrolled in the C208 study or younger ages were associated with a higher risk of dropout from any state
- Lower baseline weight was correlated with a higher risk of death from any state

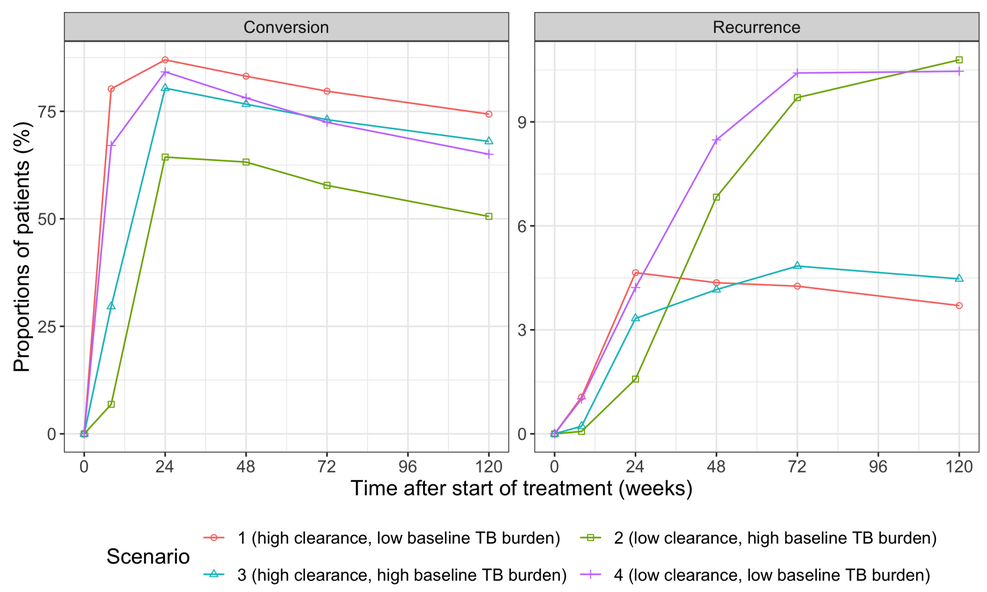
### Evaluation of model predictive performance




Visual predictive checks with 1000 simulated dataset were performed to evaluate model predictive performance

### Simulations based on TB disease severity and treatment response

- Patients with low baseline TB burden can achieve earlier SCC regardless of the speed of bacterial clearance
- The risk of recurrence increased sharply in patients with slow bacterial clearance




## Conclusion

- The developed multistate model enables prediction of possible outcomes longitudinally in patients with various TB disease severity and on-treatment responses
- Model-derived early on-treatment biomarkers (HL of bacterial clearance in the first two weeks and predicted MBL at the end of BDQ treatment) were identified as significant predictors on treatment outcomes, providing opportunities for future applications in other TB regimens

### List of references

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