



Bedaquiline's exposure-response relationship confirmed with data from the observational study C209

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Objective

- To prospectively evaluate two models previously developed [1] for bedaquiline (BDQ) effect on mycobacterial load (MBL), quantified by culture time to positivity (TTP).
- To further explore the impact of design- and patient-related characteristics.

Data and model

- For the evaluation, data only from TMC207-C209 study was used, which is a phase IIb clinical trial (single-arm, open-label) enrolling *newly diagnosed or treatment-experienced* multi-drug resistant (MDR) TB subjects, including patients with (pre-) extensively-drug resistant (XDR) TB.
- The evaluated models were developed with data from the TMC207-C208 study enrolling exclusively *newly diagnosed* MDR-TB patients.
- TTP from mycobacterial growth incubator tubes (MGIT) is a quantitative measure of mycobacterial load in sputum samples.
- The structure of the evaluated models (Fig. 1) consists of :
 - a longitudinal representation of mycobacterial load in patients
 - the probability of bacterial presence in sputum sample
 - a time-to-event model for TTP in MGIT
 with baseline bacterial load (mTTP) and drug-resistance type (2 subgroups) as covariates.

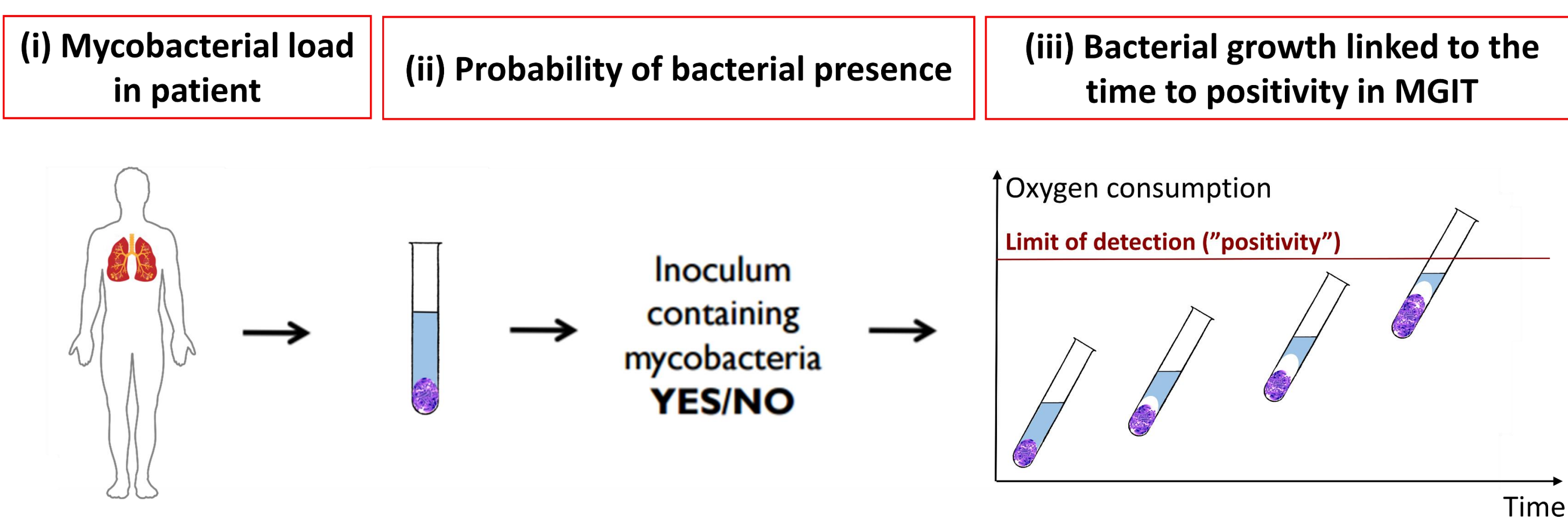


Figure 1. Schematic representation of the model. Adapted from [1]

Method

- Evaluation of BDQ exposure-response relationship :
- Tested with a set of 500 bootstrapped datasets of individual profiles, stratified by the TB type.
- Performed by using fixed population parameters from the TMC207-C208 study.
- Comparison of two previously defined models :
 - A “treatment effect” model with a fixed BDQ effect regardless of individual concentration
 - An “exposure-response” model with an Emax type concentration dependence
- Relative predictive performance between the two models was evaluated using the objective function value (OFV)
- Re-estimation of model parameters and additional covariates analysis :
- New considered covariates (Table 1) :

Variable [unit]		n (%) or median (range)
TB type	MDR	126 (61.1%)
	Pre-XDR	44 (21.4%)
	XDR	36 (17.5%)
Previous TB treatment - presence	Yes	185 (89.8%)
	No	21 (10.2%)
Previous TB treatment - duration [days]		48 (4,2638)

Table 1. Summary of patient characteristics tested in this analysis (i.e. considered covariates).

Results

- The model including the exposure-response relationship described the data markedly better than a model with only a treatment effect (Fig. 2) : The mean difference in OFV was -17 (bootstrapped 95%PI = -45 to 10)

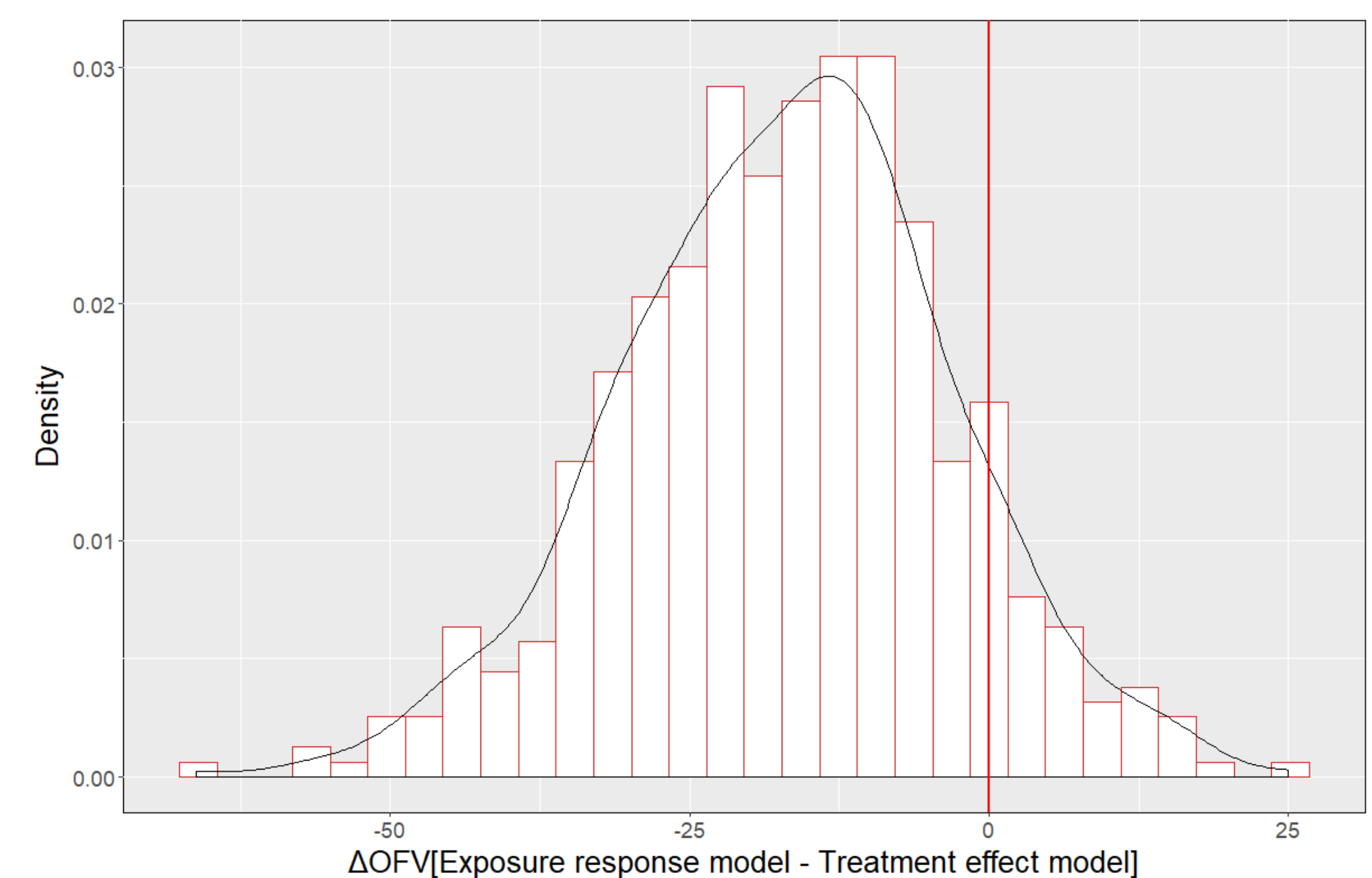


Figure 2. Distribution of the difference in OFV between the model with the exposure-response effect and the model with the treatment effect. The data are better described with the exposure-response model in 89% of the cases. Abbreviation: OFV, Objective Function Value.

- Significant impact of the type of drug resistance : XDR and pre-XDR patients have 141% (RSE 37%) and 44% (RSE 59%) longer MBL half-life than MDR patients, respectively (Fig.3)

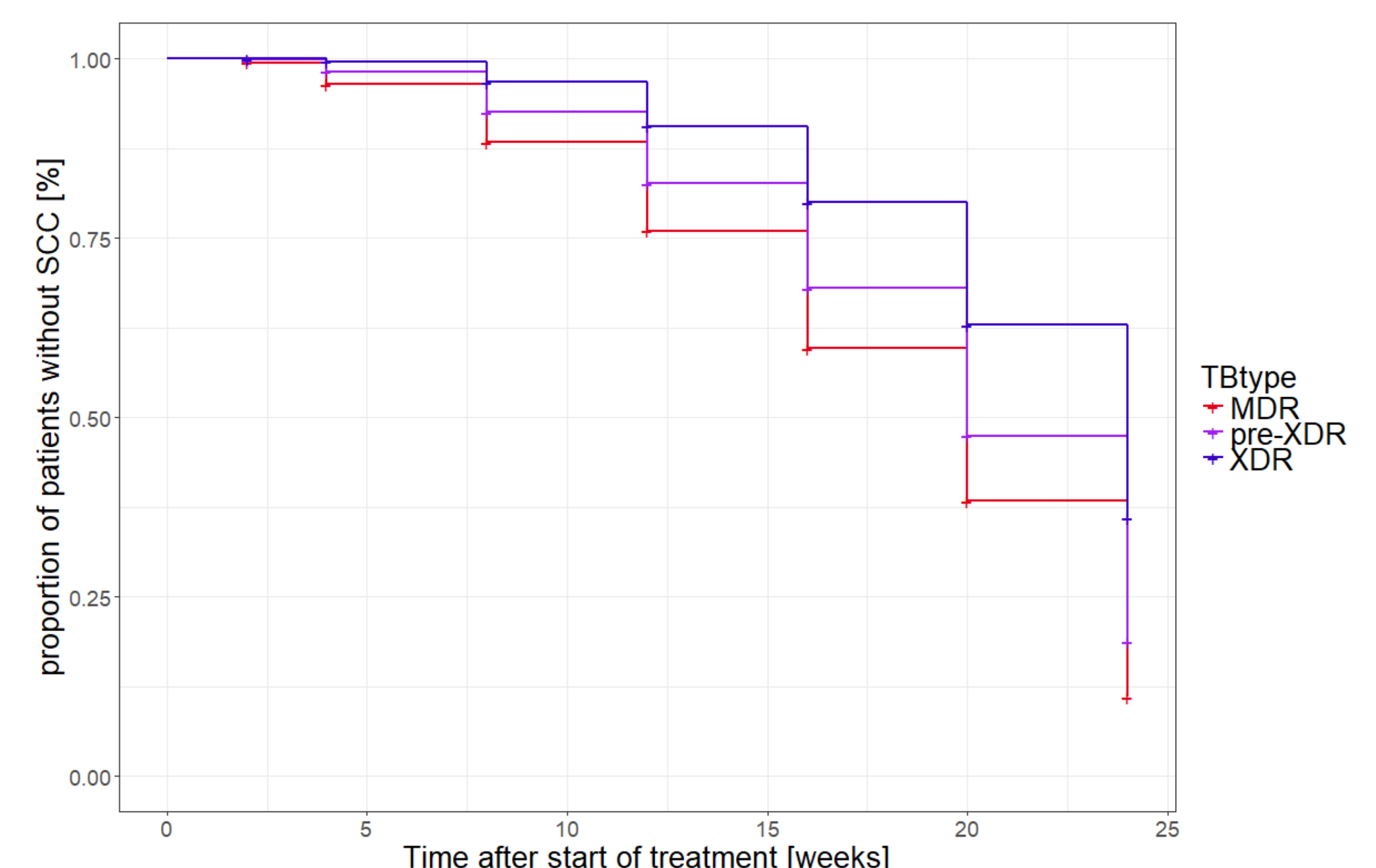


Figure 3. Survival plot: proportion of patients without sputum culture conversion (SCC) vs time after start of treatment. SCC is a marker used to predict therapeutic efficacy

Conclusion

- The previously developed model including the exposure-response effect has been shown to prospectively provide better description of data compared to a treatment effect model.
- Patients with pre-XDR TB and XDR TB showed to slower clear the bacteria than MDR patients.
- Further investigations are ongoing to explore the benefit of a merged analysis of both TMC207-C208 and TMC207-C209 data.
- This work supports the use of the model for potential BDQ dose optimizations.

References

[1] E. M. Svensson & M. O. Karlsson, 'Bedaquiline's exposure-response relationship revealed through modeling of mycobacterial load', PAGE 25 (2016) Abstr 5937 [www.page-meeting.org/?abstract=5937]

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