The impact of weekend dosing holidays on the evaluation of the sterilizing efficacy of different 4-drug combinations in a relapsing mouse model of Mycobacterium tuberculosis infection using a logistic Emax model

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Background and Aim

Tuberculosis (TB) remains a leading infectious disease-related cause of death worldwide. Current treatment options are extremely long and complex, and adherence is supported through programs such as directly observed therapy.

- The performance of drug combinations for TB treatment is commonly assessed preclinically using the relapsing mouse model (RMM), a murine model of TB used to test the overall curative potential of a drug combination. This is done by evaluating the proportion of mice exhibiting relapse (defined as the recurrence of mycobacteria growth in cultures of the lung tissue samples after a post-treatment clearance period) following different treatment durations [1].
- Weekend support is not always available, but at the same time recent studies demonstrated the negative impact of missed doses on the efficacy of the standard of care drug regimen [2; 3].

→ It is crucial to quantitatively assess the impact of weekend dosing holiday on sterilization activity.

The main objective of this work was to apply a model-based analysis using a population nonlinear mixed-effects modelling approach on data coming from a Pilot RMM study, to estimate the time to reach 50% and derive 90% of cure (T50 and T90, respectively) for two common control combinations. The combinations were both tested either 5 or 7 days per week, and the performance of the two schedules was compared.

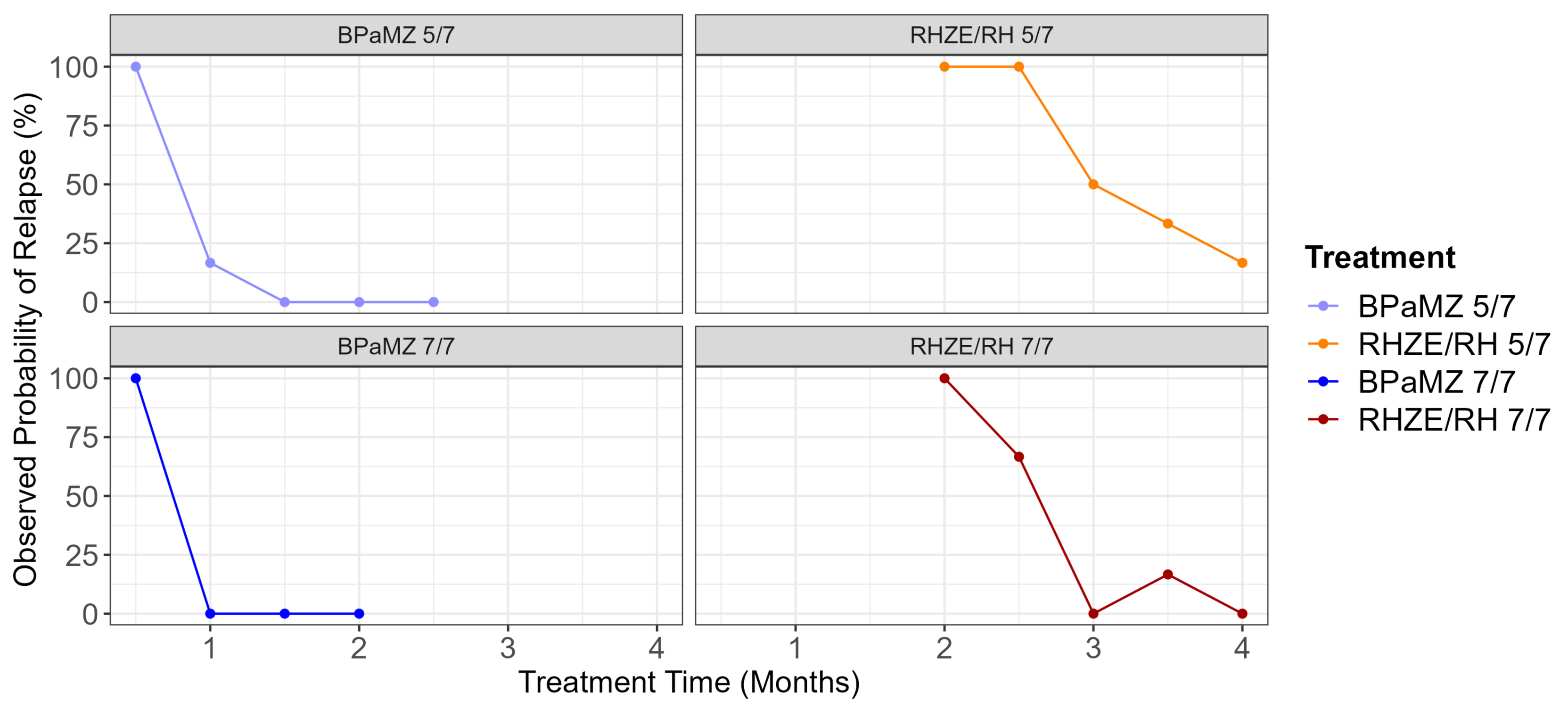
Dataset

The analysis was conducted pooling historical data from previous studies performed in several laboratories together with the Pilot RMM data generated in the current study. In this Pilot study, two drug combinations were tested either 5/7 or 7/7 days at week:

- the standard of care for drug susceptible TB (Rifampicin, Isoniazid, Ethambutol, Pyrazinamide; RHZE/RH)
- the experimental regimen (Bedaquiline, Pretomanid, Moxifloxacin, Pyrazinamide; BPaMZ).

BALB/c mice were intranasally infected with *Mycobacterium tuberculosis* H37Rv. From two weeks post infection, the 4-drugs combinations were daily dosed per oral gavage for 2, 4, 6, 8, 10, 12, 14 or 16 weeks. After each period of treatment, 12 weeks treatment off is used for assessing relapse. Relapse data were treated as a binary endpoint (0 or 1), intended as absence or presence of relapse, respectively.
Collected data are graphically reported in Fig.1.

Fig. 1 Sterilization curves observed. Sterilization curves were drawn using % of relapse determined at the end of 12 weeks treatment off period following each treatment period (0.5, 1, 1.5, 2 months for BPaMZ and 2, 2.5, 3, 3.5, 4 months for RHZE/RH, respectively).



Methods

A population logistic Emax model was developed to predict T50 and derive T90 for TB drug combinations, based on observed percentage of cure/relapse data collected in the Pilot study in addition to 4-drug regimens tested across multiple historical studies of TB combinations' efficacy.

- The probability of relapse over time for each combination of a particular study is modeled according to the classical Emax function.
- A Hill coefficient (γ) is included to represent the steepness of the relapse probability curve over treatment time (equal for the two types of treatment schedule to limit the number of model parameters).
- The inoculum was included as a covariate into the model, as it had been demonstrated to have a meaningful impact on T50 in previous studies [1].
- A random effect was associated with T50 to take into account the remaining unexplained variability. Final model is reported in Fig. 2 along with the details of the different parameters.

Once T50 and γ were estimated for the tested combinations, and thus **T90 could be derived**, a specific **ranking** of the two **controls for the two schedules was drawn up to compare** their **performance**.
The model was developed using NONMEM® 7.5.1 setting the FOCE method for parameters estimation, while data handling was performed through SAS® 9.4.

Fig. 2 Emax model. Logistic Emax model equations characterizing probability of relapse over treatment time duration.

$$P_{ijk} = B - E_{max} \frac{T_j^{\gamma'_i}}{T_j^{\gamma'_i} + T_{50,ik}^{\gamma'_i}}$$

Single treatment of certain study for a given inoculum

Individual parameter | Population parameter | Covariate effect | Variability term

$$T_{50,ik} = (T_{50,i} + \beta * (INOC_k - \overline{INOC})) * \exp(\eta_{1,k})$$

$$\gamma'_i = \exp(\gamma_i)$$

$$T90 = 10^{log10(T50)+(\frac{1}{\gamma'}log10\left(\frac{90}{100-90}\right))}$$

where:

- P_{ijk} is the Probability of Relapse for the i^{th} regimen at the j^{th} month in the k^{th} study
- B is the baseline probability of Relapse at month 0 (fixed to 1)
- E_{max} is the maximum effect for all regimens (fixed to 1)
- $T_{50,i}$ is the time to 50% relapse for the i^{th} treatment (typical value for the i^{th} treatment)
- $T_{50,ik}$ is the time to 50% relapse for the i^{th} treatment in the k^{th} study
- $INOC_k$ is the Inoculum (CFU/ml) for the k^{th} study
- $\overline{INOC}$ is the mean inoculum value across all the studies
- β is the linear effect of the inoculum on T_{50}
- γ'_i is the Hill coefficient for the i^{th} treatment (typical value for the i^{th} treatment)
- η_1 is the random effect of the k^{th} study for T_{50}, assumed to be normally distributed, N(0, σ²)

Therefore, the model can be described and thus evaluated at:

Population level:

- population parameters, i.e. $T_{50,i}$ and γ_i for each regimen (i), considered as the average value across all studies in which that combination was tested and which are thus independent from the effect of covariates added to the model.

Individual level:

- individual parameters, i.e. $T_{50,ik}$ for each regimen i and study k, which incorporate the variability across studies explained by (1) possible covariates (e.g. the inoculum) and (2) a random effect η_1 representing the remaining part of (unexplained) variability.

Results

Both BPaMZ 5/7 and RHZE/RH 5/7 sterilized from 6 and 16 weeks of treatment onwards. A **time-dependent sterilization activity with** an **increased efficacy for** the **7/7 design** was noticed, as expected.
In particular, for BPaMZ, both 5/7 and 7/7, 100% of mice displayed non detectable colonies after 4 and 6 weeks treatment followed by 12 weeks treatment off respectively, while for RHZE/RH, 100% not-detectable colonies were seen after 12 and 14 weeks of treatment with 7/7 and 5/7 dosing regimens, respectively.

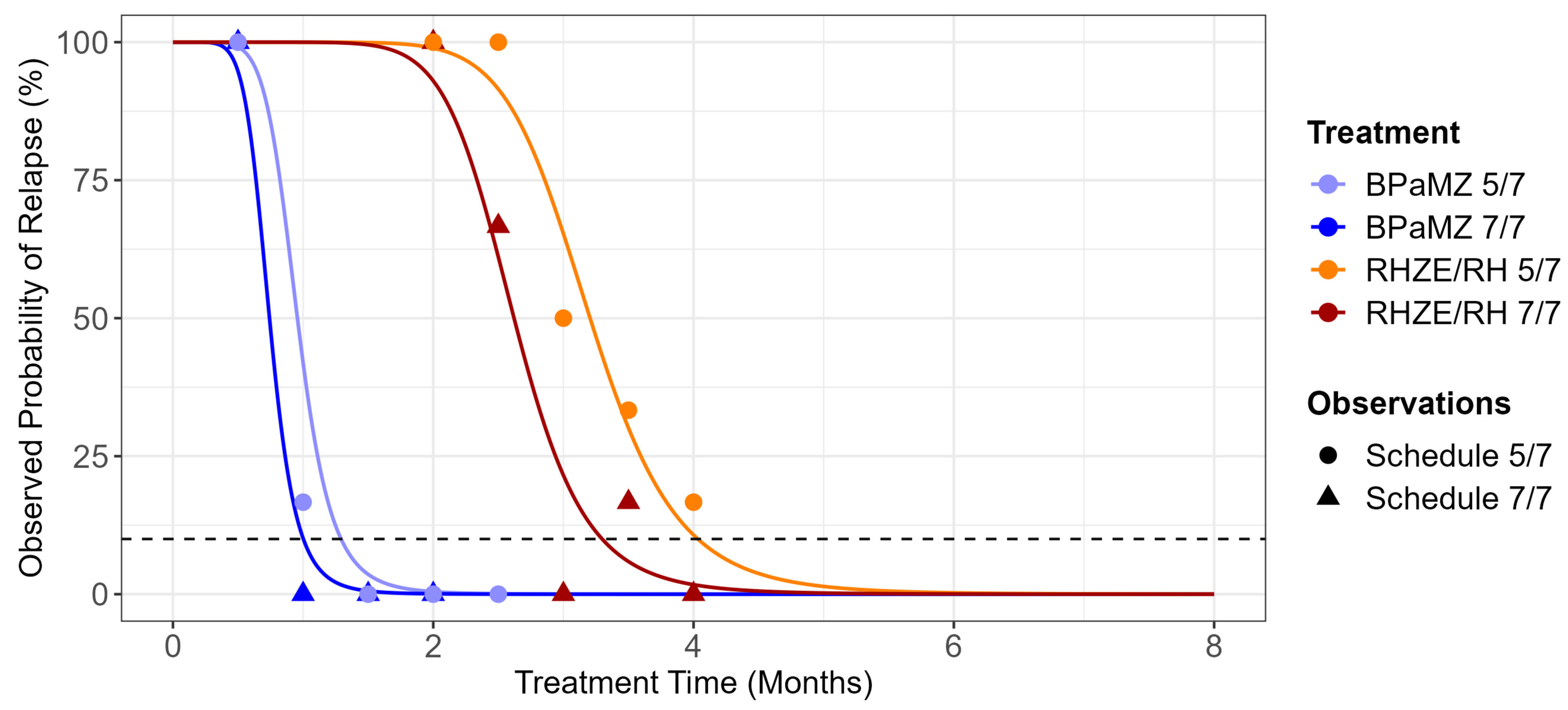
- The developed model was successfully identified with all **T50s and γ parameters estimated with good precision** (Relative Standard Error (**RSE**) **< 25%** for all population parameters).
- The **model** was able to **describe the relapse-time curves** well (Fig. 3), by incorporating inter-study variability as a sum of the inoculum effect (which positively impacts the individual T_{50}) and remaining unexplained variability, which was estimated around 16% (mainly associated with the slightly differences observed in sterilization capability for the control combinations tested in the historical studies).

The **predicted T90s were approximately 20% lower for both combinations when the weekend dosing holiday was in place**: indeed, for BPaMZ 5/7 and RHZE/RH 5/7, individual T90s for the Pilot study were 1.29 and 4.03 months respectively, similar to values found in literature [1; 4], as opposed to 1.00 and 3.29 months for the same combinations dosed 7/7 (Tab. 1).

Tab. 1 Population and individual γ and T50 estimates and derived T90 of sterilization Drug Regimens for PD Pilot Marker study. Model parameters associated with combinations tested in Pilot RMM study are reported with the corresponding precision (RSE %), both in terms of population and individual value. Furthermore, the estimates of the linear effect of the inoculum on T_{50} together with the resulting inter-study variability are provided.

Anti-TB Regimen	γ Population	RSE (%)	T50 (Months) Population	T50 (Months) Individual	RSE (%)	T90 derived (Months) Population	T90 derived (Months) Individual	β	RSE (%)	η1	RSE (%)
BPaMZ 7/7	1.989	8.2	0.390	0.742	23.2	0.526	1.002	0.564	9.2	0.024 (CV = 15.7%)	27.0
BPaMZ 5/7	1.989	8.2	0.684	0.956	11.5	0.923	1.292				
RHZE/RH 7/7	2.258	8.5	2.963	2.621	4.6	3.729	3.298				
RHZE/RH 5/7	2.258	8.5	3.764	3.205	3.3	4.736	4.033				

Fig. 3 Sterilization curves predicted from Emax model. Emax model individual predictions are represented using solid lines, observed % relapse data at each treatment duration are reported using different shapes to distinguish between 5/7 or 7/7 schedule. The grey dashed line indicates the 10% relapse in order to derive the corresponding treatment time needed to reach 90% cure.



- Other than individual estimates, also **population parameters were reported since they allow the characterization of the average time to 50% or 90% cure for a particular regimen shared across studies independently from study-related factors** (as for example the starting inoculum as well as other possible causes, accounted through the inter-study variability term).

Conclusions

The applied **modeling approach** allowed to **quantify** the **different sterilization performance** of the control **combinations**, thereby **enabling** a **comparison** of their efficacy in terms of **T90**. In particular, an improved (i.e., reduced) T90 following dosing 7 days per week treatment vs 5 days per week was demonstrated for both BPaMZ and RHZE/RH.

Indeed, **data suggest that the dosing holidays impact time to cure similarly for differentiated drug combinations in murine TB model**, in fact comparable T90 decrease (in percentage) for both differentiated combinations was observed. Of interest, this improvement corresponds to approximately 20% of the T90 value for both combinations, even though they are composed of drugs with differing pharmacokinetics, pharmacodynamic drivers and mechanisms of action.

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