Model-Informed Drug Development

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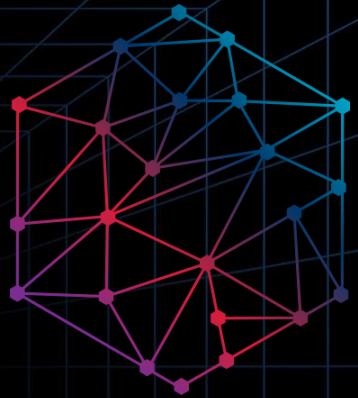

Model-Based Meta-Analysis of Anti-Tuberculosis Regimen Efficacy in Relapsing Mouse Model Studies

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Tuberculosis remains a global health challenge

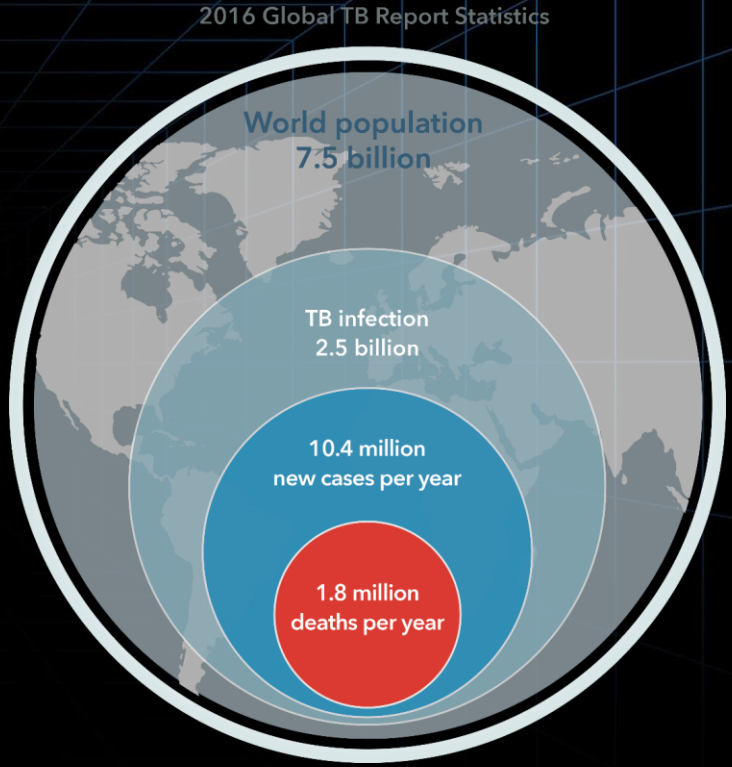
Although temporarily eclipsed by the COVID-19 pandemic, tuberculosis (TB) remains the leading infectious disease-related cause of death in the world

Drugs are effective but regimens are difficult

- **Long duration**
- **Lack of "forgiveness" to poor adherence**
- **High comorbidity with HIV**

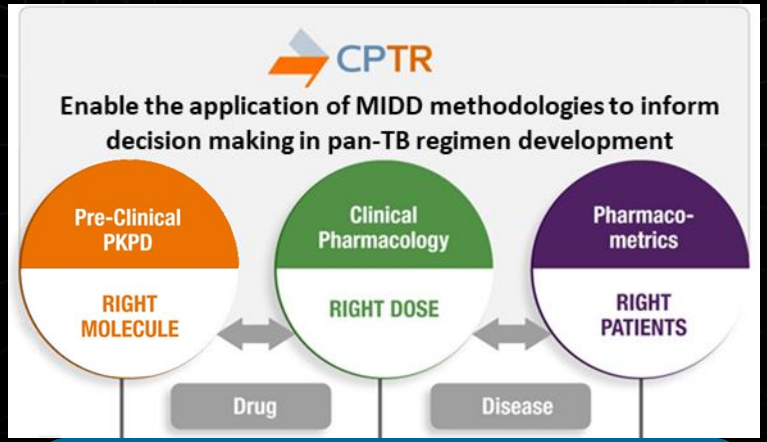
  → ***drug interactions and high bill burden***

A regimen that is simpler, shorter in duration, safer, as well as highly effective in both drug susceptible and resistant strains, is required to bring TB under control as an endemic disease.



CPTR Initiative

The Critical Path to TB Drug Regimens (CPTR) Initiative was established as a global, cross-sector consortium that aimed to accelerate the development of safer and shorter duration anti-TB drug regimens



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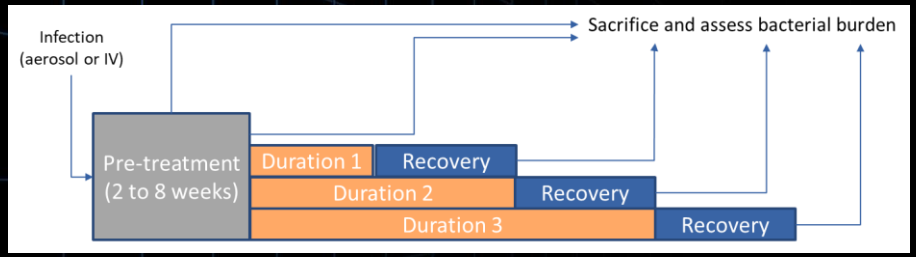
Relapsing Mouse Model Studies

The curative potential of novel anti-TB drugs and regimens is often assessed via "relapsing mouse model" (RMM) studies in BALB/c mice



- **Interpretation of RMM studies relies on evaluating raw data tables comparing proportions of mice exhibiting relapse following treatment with selected regimens at limited treatment durations**

<u>Why is this important</u>?

→ **RMM studies are highly influential in regimen prioritization for further study and often inform regimen selection for clinical evaluation**

Treatment	Proportion of mice relapsing after treatment for:			
	1 month	1.5 months	2 months	2.5 months
Regimen A	--	--	7/15 (47%)	2/15 (47%)
Regimen B	--	14/15 (93%)	10/15 (47%)	8/15 (53%)
Regimen C	--	5/15 (33%)	0/15 (0%)	--
Regimen D	--	8/15 (53%)	6/15 (40%)	--
Regimen E	4/15 (27%)	0/15 (0%)	--	--

RMM Studies → We can do better!

The focus on assessing relative regimen efficacy based on proportions of relapsing mice at limited treatment durations *does not* provide answers to key questions such as:

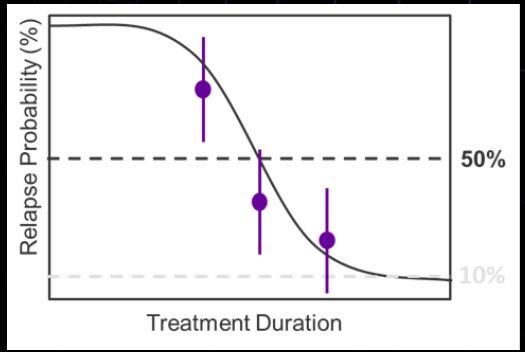
"How long do we need to treat with Regimen A to achieve a high probability of cure?"

"How does the time to X% relapse probability compare for novel regimens vs. established regimens?"

We need to shift from raw tables of *proportions* . . .

Treatment	Proportion of mice relapsing after treatment for:			
	1 month	1.5 months	2 months	2.5 months
Regimen A	--	--	7/15 (47%)	2/15 (47%)
Regimen B	--	14/15 (93%)	10/15 (47%)	8/15 (53%)
Regimen C	--	5/15 (33%)	0/15 (0%)	--
Regimen D	--	8/15 (53%)	6/15 (40%)	--
Regimen E	4/15 (27%)	0/15 (0%)	--	--

. . . to model-informed estimates of *probabilities* based on all relevant data!



Model-Based Meta Analysis

A model-based meta-analysis (MBMA) was performed to convert treatment duration-dependent relapse proportions observed in BALB/c mouse RMM studies into probabilities for regimens of interest

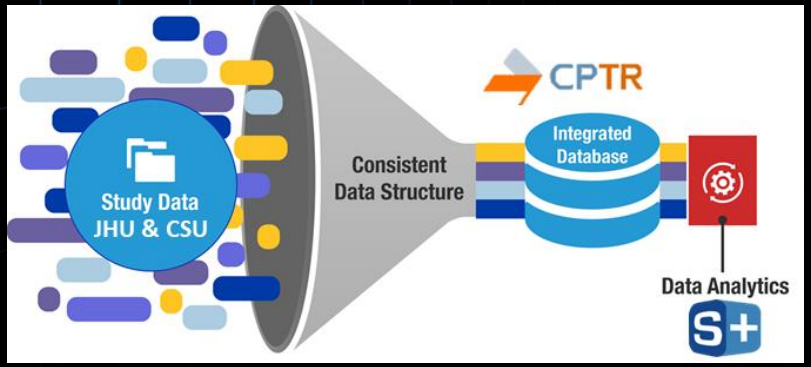
Objectives:

- Develop a statistical model describing observed relapse proportion vs. treatment duration data and inter-study variability;
- Assess key study-level variables contributing to inter-study variability in regimen efficacy; and
- Estimate metrics of interest (e.g., time to 10% relapse probability) from derived profiles for comparison of regimen performance

Source Data

The CPTR Initiative database of RMM studies was used for this analysis

- Standardized dataset of 1,592 mice across 28 studies contributed by Dr. Eric Nuermberger (Johns Hopkins) and Dr. Anne Lenaerts (Colorado State)
- A total of 17 unique regimens based on Isoniazid (H), Rifampin (R), Pyrazinamide (Z), Ethambutol (E), Moxifloxacin (M), Bedaquiline (B), Pretomanid (Pa), and Linezolid (L)



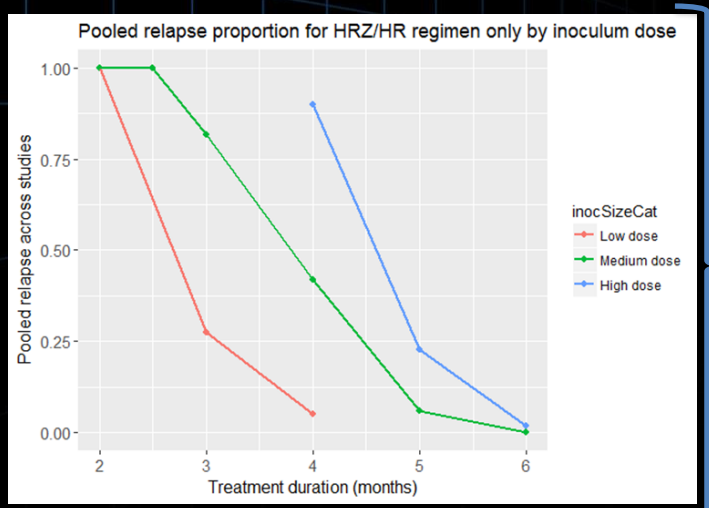
[a]Regimen	Number of Studies	Number of Mice	Months of Treatment
BPa	3	79	2, 3, 4
BPaL	4	139	2, 3, 4
HE	1	30	6, 9
HRE	1	31	3, 6
HRE/HR	1	45	3, 4.5, 6
HRZ/HR	15	531	2, 2.5, 3, 4, 5, 6
HRZE	5	105	2, 3, 4
HRZE/HR	9	199	3, 4, 4.5, 5, 6
HRZE/HRZ	1	15	3
HRZM	2	40	2, 3
HRZM/HRM	2	23	3, 6
HZE	1	29	3, 6
RMZ	1	36	3, 4, 5
RMZ/RM	5	215	3, 4, 5, 6
[b]RMZ/RM_BIDM	1	15	2.5
RMZE	2	45	2, 3
RMZE/RM	1	15	3

[a]Regimens with a continuation phase starting at 2 months denoted with a "/"
[b]Moxifloxacin 100 mg/kg dosed twice daily for a total daily dose of 200 mg/kg

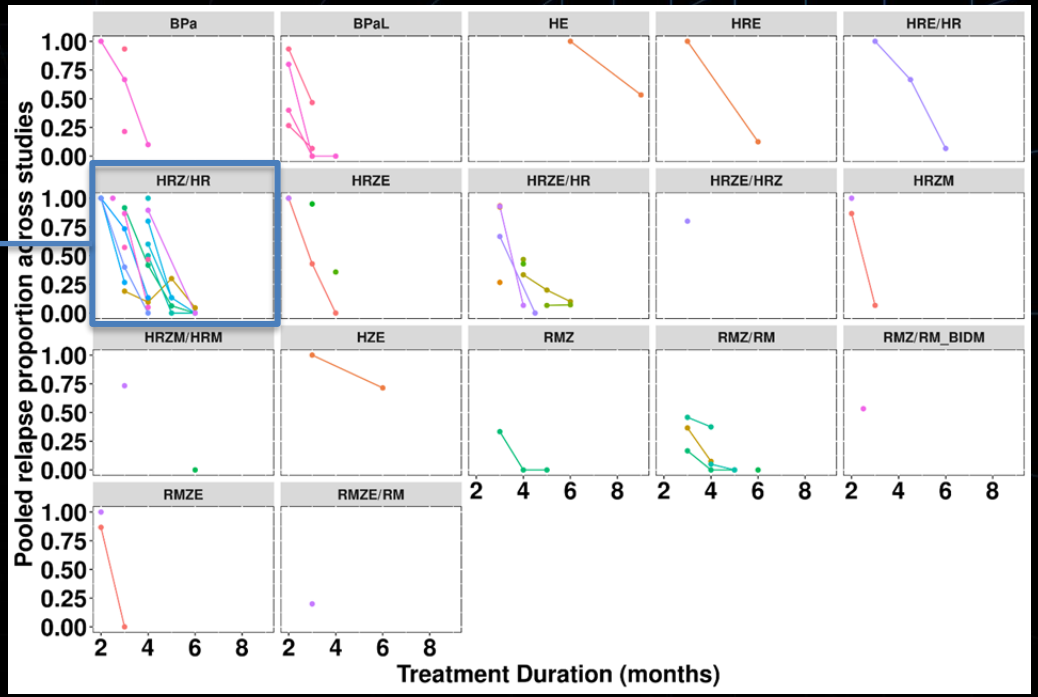
Exploratory Data Analysis

EDA showed significant inter-study variability in regimen efficacy

- Variability attributed in part to study-level differences in covariates



Proportion of mice relapsing versus treatment duration by regimen and study



Statistical Model

A mixed effects logistic regression model was applied to account for inter-study variability, differential regimen response, and effects of study-level covariates

$$logit(p_{i,j,k}) = INT_{i,j} + SLP_{i,j} * (TIME_k - 2)$$

$$INT_{i,j} = INT_{TRT} + INT_{CAT} + INT_{CONT} + \eta_{INT,j}$$

$$SLP_{i,j} = SLP_{TRT} + SLP_{CAT} + SLP_{CONT} + \eta_{SLP,j}$$

Where:

- $p_{i,j,k}$ is the probability of relapse for a given treatment/covariate combination *i* in study *j* at treatment duration *k*
- $INT_{i,j}$ is logit relapse probability at 2 months for the *i*th regimen in the *j*th study with a study-level covariate effect
- $SLP_{i,j}$ slope of the logit relapse probability vs. treatment duration for the *i*th regimen in the *j*th study with a study-level covariate effect
- TRT is categorical treatment indicator
- CAT denotes a categorical covariate effect
- CONT denotes a continuous covariate effect
- η is the random effect of the *j*th study for intercept and slope, assumed $N(0,\omega^2)$

A note on the model structure:

- Treatment duration (TIME) was offset by 2 months to account for regimens with distinct intensive and continuation phases
  - Regimens that were identical up to the start of the continuation phase shared the same INT value → therefore assumed to have the same probability of relapse at 2 months duration
    - Example: HRZE, HRZE/HRZ and HRZE/HR

Model Development

Model development followed standard practices and will be described in detail in a forthcoming manuscript

Model Description	OFV	AIC
Naïve model	1131	1141
"Full" regimen fixed effects, no covariates	987.1	1033
"Reduced" regimen fixed effects	990.1	1018
Reduced regimen fixed effects + covariates	899.2	931.2
Current model	**882.4**	**920.4**

Key notes from model development:

- Regimen fixed effects were simplified to promote model stability by grouping regimen-specific parameters prior to covariate assessment
- Consistent with EDA findings, inoculum amount (INOC) and lung bacterial burden in control animals at baseline (BASE) were identified as statistically significant covariates via stepwise covariate modeling
- Current model includes covariate effects and as many regimen-specific fixed effects as could be supported while maintaining model stability to support goal of comparing relative regimen performance

Current Model Summary:

$$logit(p_{i,j,k}) = INT_{i,j} + SLP_{i,j} * (TIME_k - 2)$$

$$INT_{i,j} = INT_{TRT} + 1.40 \times (INOC_j - 3.29) + \eta_{INT,j}$$

$$SLP_{i,j} = SLP_{TRT} + 0.497 \times (BASE_j - 6.79) + \eta_{SLP,j}$$

Regimen-specific fixed effects estimates:

Regimen	INT_{TRT}	SLP_{TRT}
BPa	2.27	-1.96
BPaL	0.499	-3.77
HE	21.5	-3.00
HRE or HRE/HR	9.58	-3.00
HRZ/HR	4.86	-3.00
HRZE or HRZE/HRZ	4.7	-3.23
HRZE/HR	4.7	-3.00
HRZM	3.61	-4.79
HRZM/HRM	3.61	-3.00
HZE	12.7	-3.00
[a]RMZ/RM_BIDM	0.654	-3.11
RMZ	2.22	-3.54
RMZ/RM	2.22	-3.11
RMZE	2.11	-3.54
RMZE/RM	2.11	-3.11

[a]Moxifloxacin 100 mg/kg dosed twice daily for a total daily dose of 200 mg/kg

Random effects estimates:

$$\omega_{SLP} = 0.636 \quad \omega_{INT} = 1.209$$

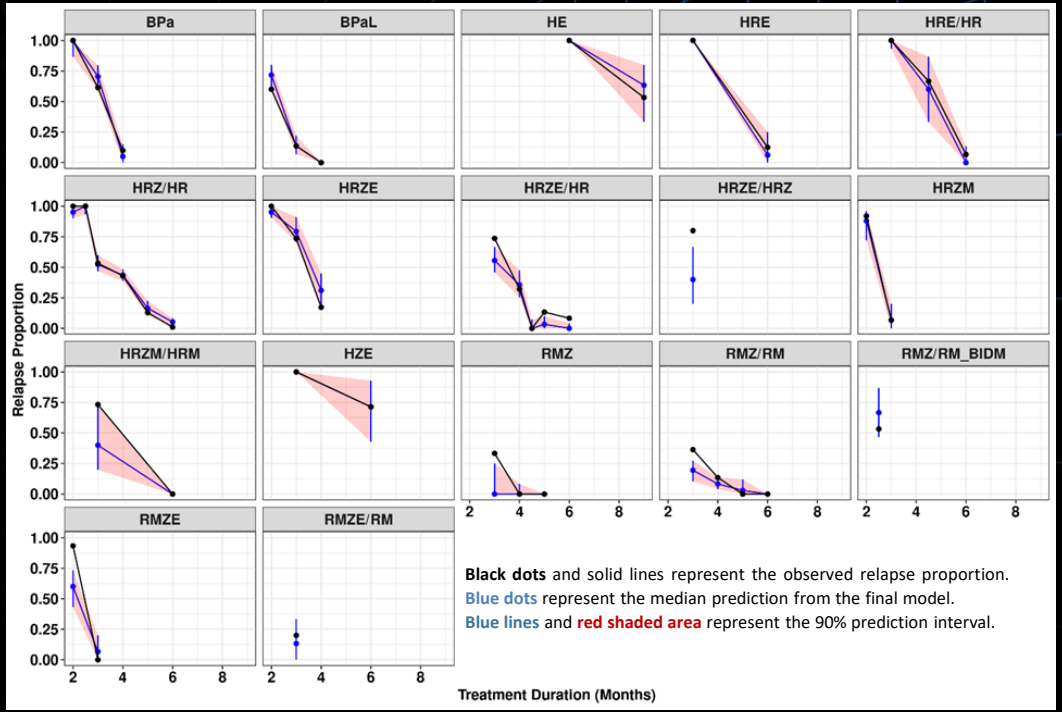
$$CORR_{SLP-INT} = -0.75$$

Visual Predictive Check

Visual Predictive Check (VPC) of the current model shows good agreement between model-based predictions and observed data when stratified by regimen

- Additional VPCs by covariate value and study (not shown) exhibited similar patterns

Visual predictive check for the current model – Stratified by regimen



Covariate Effects

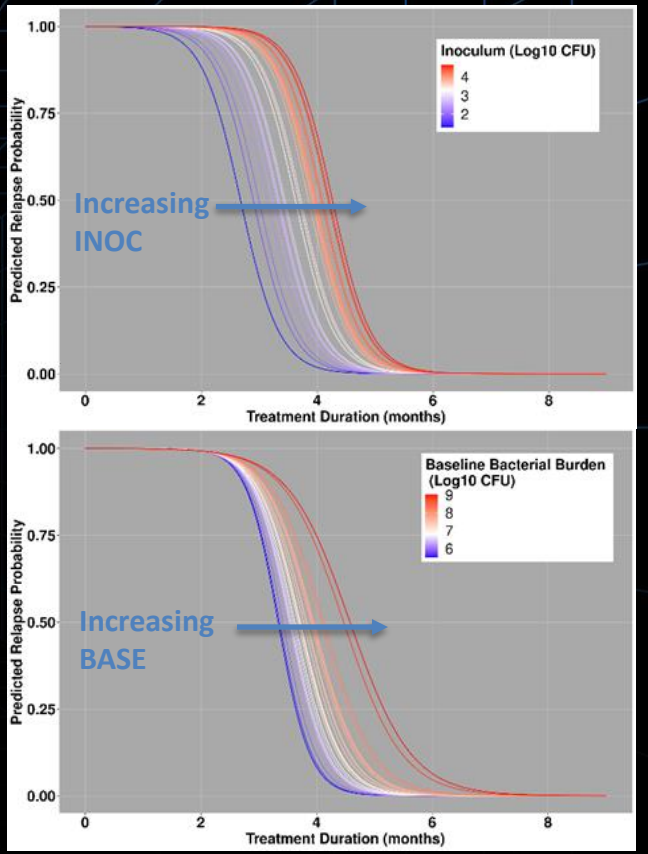
Modeling results indicate that study-level differences in inoculum amount (INOC) and lung bacterial burden in control animals at baseline (BASE) explained a large portion of the observed inter-study variability

- The findings are intuitive as both covariates reflect overall mycobacterial burden and therefore disease severity

  → *higher burden = longer treatment duration to achieve "cure"*

Since inoculum amount is correlated with lung bacterial burden and can be controlled by the study team, this analysis identified a key study variable that can be adjusted in future studies to improve consistency and comparability

Simulated effects of covariates on HRZE/HR regimen

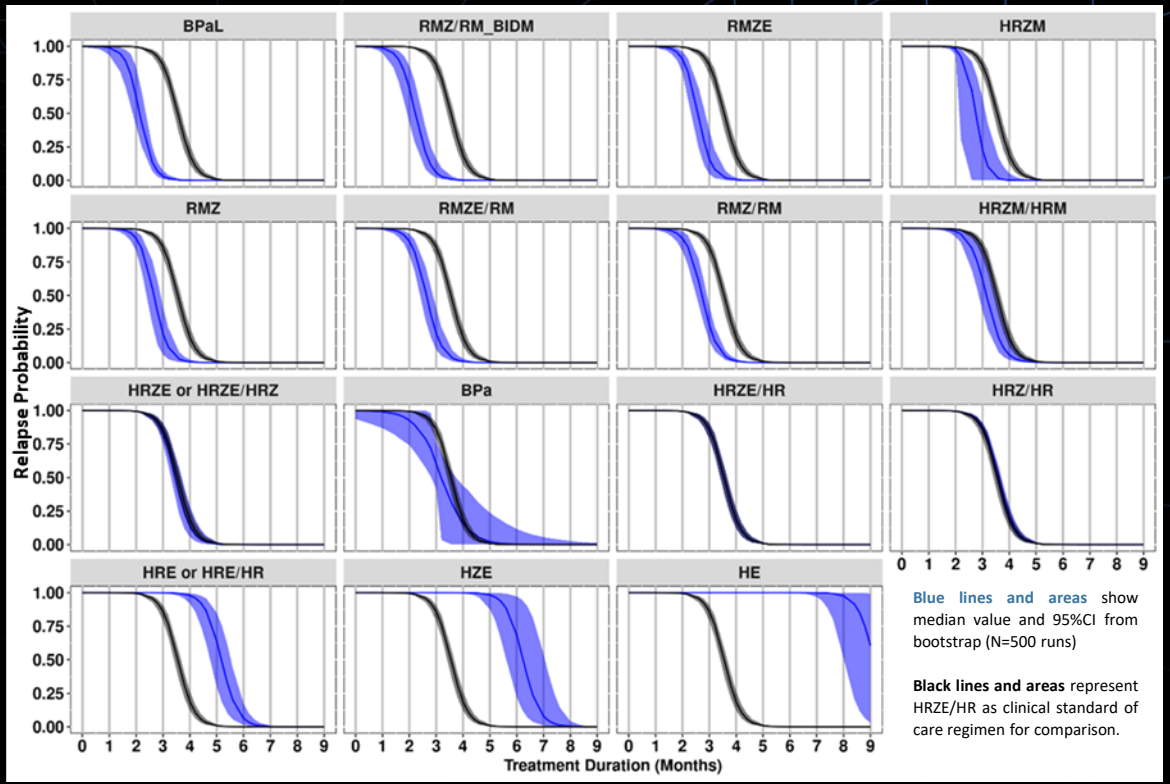


Regimen Comparisons

Covariate-normalized relapse probability vs. treatment duration profiles were obtained by simulation from bootstrap estimates at covariate reference values

- → *Provides an "apples-to-apples" comparison of regimen efficacy*
- → *Enables calculation of metrics of interest including time to 10% relapse probability (T10)*

Covariate-normalized relapse probability vs. treatment duration profiles by regimen



Regimen Comparisons

Covariate-normalized T10 estimates show incremental differences between regimens and three groupings relative to the HRZE/HR standard of care regimen

While findings show expected trends, this MBMA is the first time that these regimens have been simultaneously and quantitatively compared across multiple RMM studies

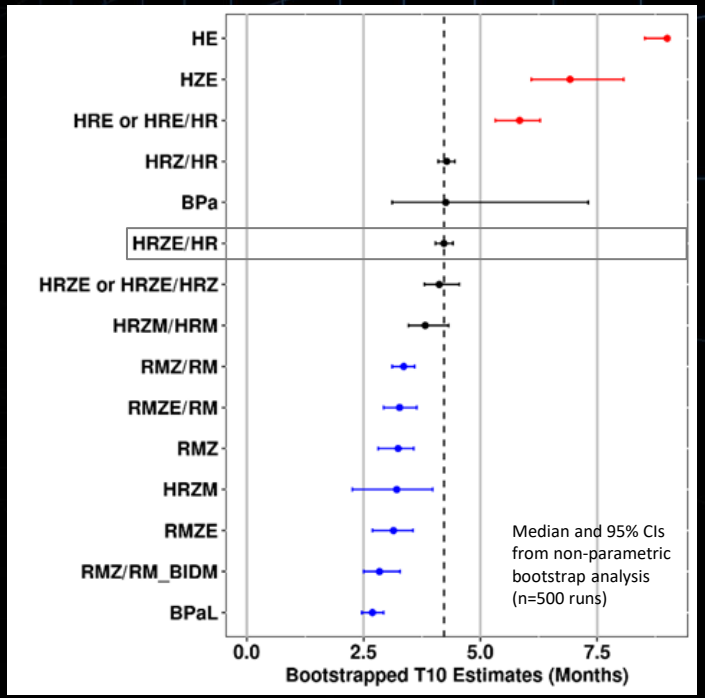
Statistics for covariate-normalized T10 values (months)

Regimen	Median	95%CI	Rank
BPaL	2.69	2.46 - 2.93	1
RMZ/RM_BIDM	2.84	2.5 - 3.28	2
RMZE	3.14	2.69 - 3.56	3
HRZM	3.21	2.26 - 3.98	4
RMZ	3.24	2.81 - 3.57	5
RMZE/RM	3.27	2.93 - 3.64	6
RMZ/RM	3.36	3.11 - 3.59	7
HRZM/HRM	3.82	3.46 - 4.32	8
HRZE or HRZE/HRZ	4.12	3.8 - 4.55	9
HRZE/HR	**4.22**	**4.04 - 4.41**	**10**
BPa	4.26	3.11 - 7.31	11
HRZ/HR	4.28	4.1 - 4.45	12
HRE or HRE/HR	5.84	5.32 - 6.28	13
HZE	6.92	6.09 - 8.07	14
HE	≥9.00	8.52 - ≥9.00	15

Better than standard of care HRZE/HR regimen

Worse than standard of care HRZE/HR regimen

Forest plot of covariate-normalized T10 values (months)



Model Applications

The MBMA approach presented herein provides a framework for improving the design, analysis, and interpretation of RMM studies

- The underlying dataset and model is iteratively updated with emerging BALB/c mouse RMM study data to provide robust estimates of efficacy for candidate regimens relative to current regimens
- In addition to identifying important covariates, the model has been applied in simulation / re-estimation studies to assess alternative study designs
  - *Net result is a marked shift in study design that significantly decreases the number of mice per regimen while providing more informative results*

Bottom Line - This effort has helped to shift RMM studies away from *proportions* and towards *probabilities*, thereby improving the preclinical development and prioritization of candidate anti-TB drug regimens

Q&A

Questions & Answers

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