

The immune system's significance in Tuberculosis (TB) drug development is often underestimated due to experimental complexities. We use an integrated in silico approach to understand how the immune system influences therapy effectiveness in managing the infection and reducing relapse risk. Our model reproduced realistic disease outcomes and highlighted that IS deficiencies lead to short-term relapse and death.

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# Integrating PKPD and Agent-Based Modeling to Explore Tuberculosis Relapse after Treatment

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## Methods

## IN SILICO EXPERIMENT

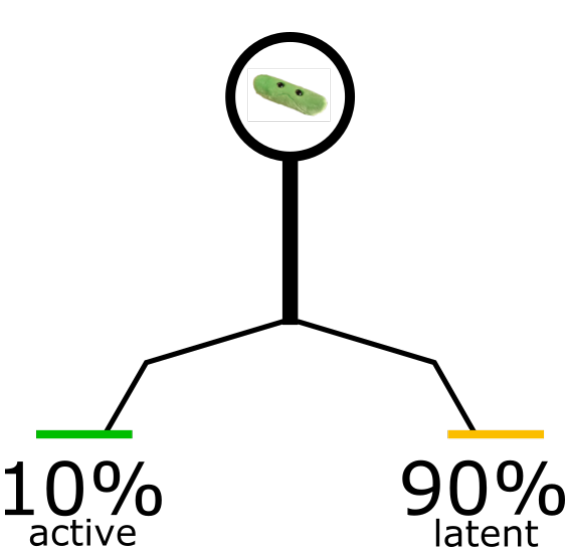
### STEP 1

Create a virtual cohort using the C-Immsim Agent Based Model. A virtual patient is a simulation of the Immune System (IS) response to Mtb infection. Each one is a disease trajectory representing a real epidemiological outcome.



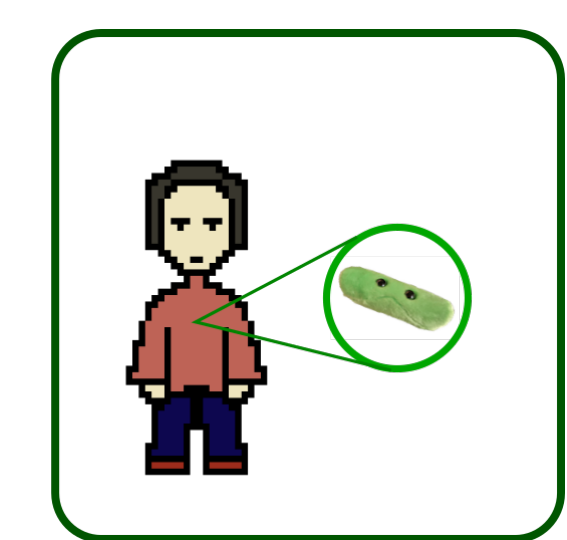
### STEP 2

Calibrate model parameters using estimated frequency of disease outcomes from epidemiological data. We build an epidemiological tree from real data and classified our simulations trajectories according to possible disease outcomes.



### STEP 3

Select active patients. From the set of simulated disease trajectories we choose those that we classified as active.



### STEP 4

Administer standard therapy to active patient. Drug quantity is specified by plasma concentration instead that in clinical administered dose. We use data from literature to simulate a plasma drug concentration consistent with the administered dose in real treatments.



C-Immsim is an Agent Based Model able to represent both the innate immune and the adaptive immune response.

We modified C-Immsim to model the IS response to Mtb infection, specifically we added rules to represent interaction between Mtb and Macrophages.

theoretical trajectories

simulated trajectories

Real Outcomes

Virtual

Real-world frequencies of the main possible outcomes associated with TB from aggregated data. The epidemiological tree, serves as the first and main target in calibrating our model.

Disease outcome	Real observable		Virtual observable	
	2Y	50Y	2Y	50Y
primary	5%	5%	5.7%	5.7%
post-primary	0%	5%	0%	5.4%
latent4life	90%	80%	85%	74.8%
latent	4%	8%	2.2%	3.6%
cleared	1%	2%	7.1%	10.5%

This table presents population-level disease outcome statistics extrapolated from the literature, used as ground truth for model calibration (Real Observable). It also shows the corresponding values obtained from our 50-year simulations using parameters inferred with pyABC (Virtual Observable). The values for the "2 Years (Y)" column were obtained by cutting the TB epidemiology tree just after the first branching, coinciding with the transition from the primary to the post-primary stage.

We ran a single 50-years virtual cohort accounting 1000 virtual patients, with parameters sampled from the various posterior obtained, in order to validate the parameter values inferred with pyABC.

Daily for 2 months: Rifampin 600 mg, Isoniazid 300 mg, Pyrazinamide 1500 mg, Ethambutol 1200 mg

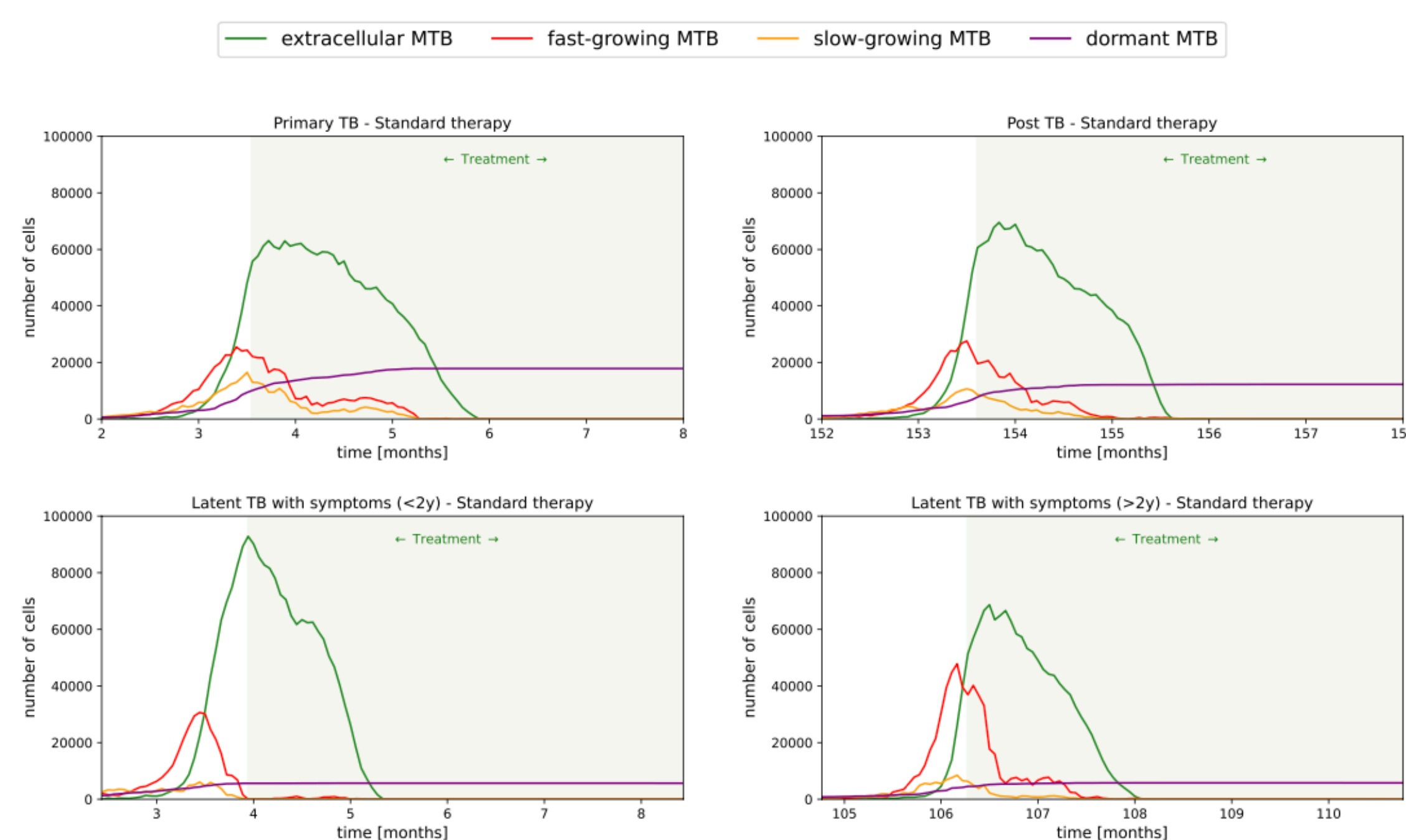
Daily for 4 months: Rifampin 600 mg, Isoniazid 300 mg

Drug therapy is implemented as a set of stochastic processes acting on single entities such as Mtb and macrophages, whose probabilities of occurrence are estimated from pharmacokinetics (PK) and pharmacodynamics (PD) data.

$$E(c) = \frac{E_{max}}{1 + (\frac{EC_{50}}{c})^h}$$

## RESULTS

- Following drug therapy, most patients successfully cleared tuberculosis.
- Dormant bacteria could sporadically reactivate.
- Short-term relapses were not observed.

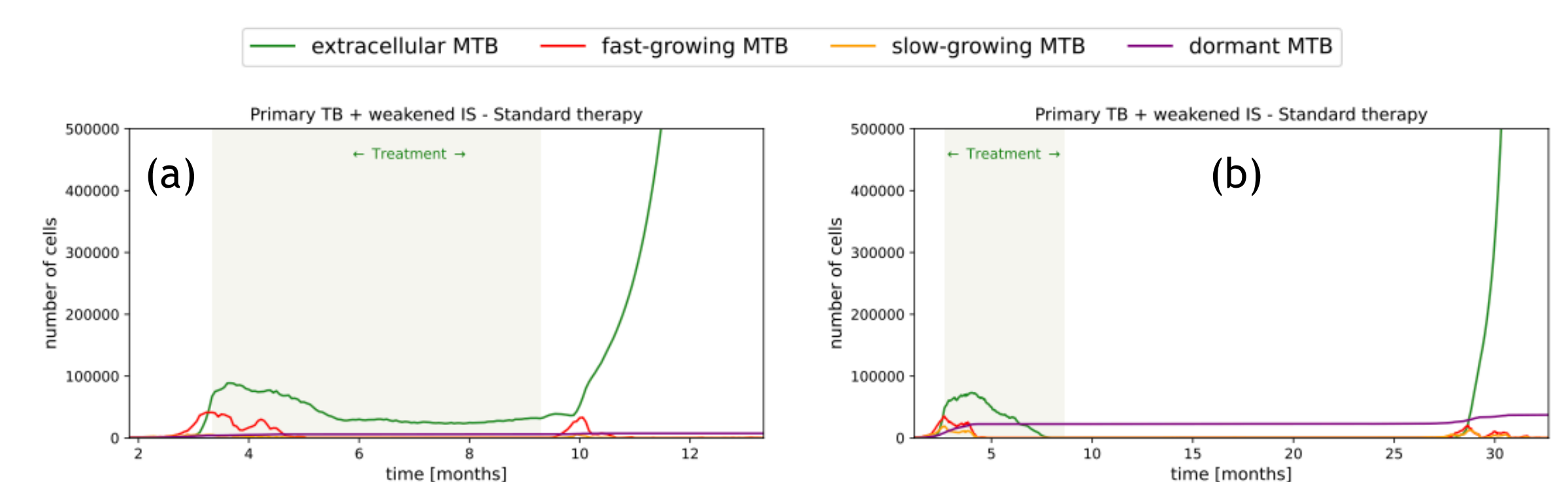


Disease state	Simulations with therapy (%)
Death within 2 years after therapy	0
Death at least 2 years after therapy	1
Symptoms without death	4
Latent	95
Cleared	0

Table 2: Simulated disease outcome in presence of drug therapy.

## INDUCING RELAPSE

- We simulated compromised IS in the final months of therapy.
- Around 20% of patients experienced disease reactivation, leading to death without further treatment.



We presented initial findings from our study using a computational approach which integrates an Agent-Based Simulator and PKPD modeling to understand how the IS influences tuberculosis treatment outcomes. Our model reproduced realistic disease outcomes and highlighted that IS deficiencies lead to short-term relapse and death. Our results suggest that computational methods can advance tuberculosis understanding and inform drug development and treatment strategies.