New dosing recommendations for anti-tuberculosis therapy in Indian children

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Tuberculosis in **children**
Worldwide in 2016

718 000
New cases

253 000
Deaths

10-60%
HIV coinfection

30%
in India

Pediatric tuberculosis
treatment in **India**

Tuberculosis treatment

Intensive phase — 2 months →

Continuation phase — 4 months →
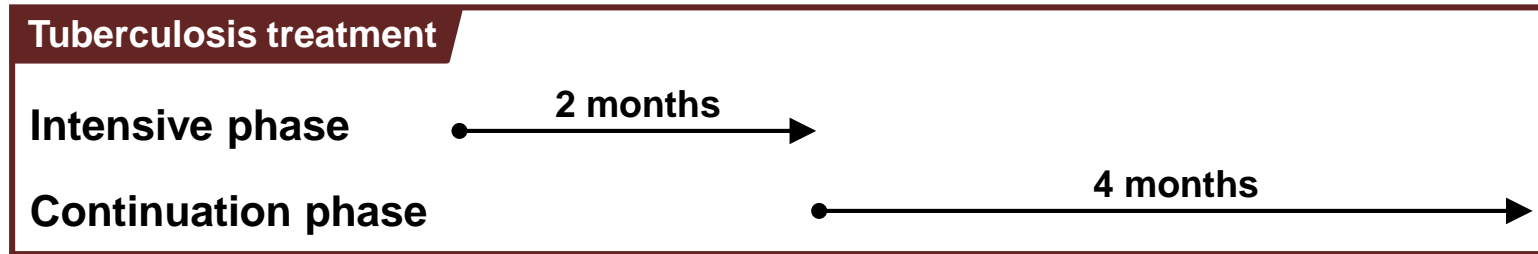
	Previous RNTCP (pre-2012)	**New RNTCP** (Initiated Nov 2017)
Regimen	Thrice-weekly	Once-daily
Isoniazid	10 mg/kg	10 mg/kg
Rifampin	10 mg/kg	15 mg/kg
Pyrazinamide	33 mg/kg	35 mg/kg
Formulation	Single drug formulation	Fixed dose combination

RNTCP: revised national tuberculosis control program

Clinical data
Study design

TB monoinfection
84 children (1-12y)

TB-HIV coinfection
77 children (1-15y)

Covariate Screening
Upon treatment initiation

Demographic
• *weight, age, z-scores, …*
Physiologic
• *acetylator status*
Co-medications
• *Anti-retroviral treatment*

PK study

After 2 weeks

Thrice-weekly dosing

4 weight bands
• *6-10, 11-17, 18-25 and 26-30 kg*
Sampling times
• *0, 2, 4, 6, 8h*

Treatment Outcome
After 6 months

Favorable
• *Cured*
• *Treatment completion*
Unfavorable
• *Death*
• *Treatment failure*

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Ramachandran *et al. Int J Tuberc Lung Di*s (2013) | Ramachandran *et al. AAC* (2015)

Aims

1. To **characterize** the **pharmacokinetics** of **isoniazid**, **rifampin** and **pyrazinamide** in **Indian children** undergoing **thrice-weekly dosing**

2. To **establish** the **relationship** between **drug exposure** and the **probability of unfavorable treatment outcome**

3. To **evaluate** the previous and new **Indian dosing recommendations** and suggest **dose revisions**
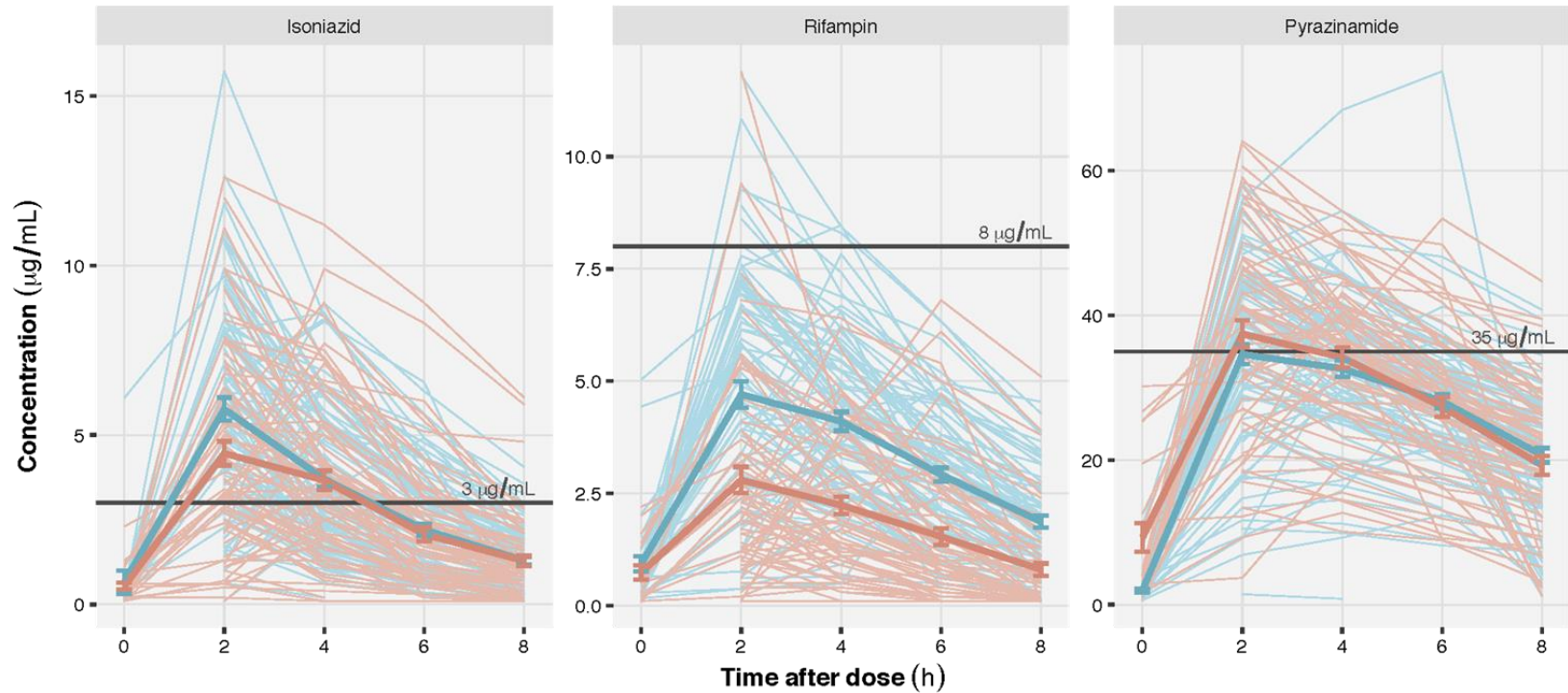
Step 1

Characterize the pharmacokinetics of isoniazid, rifampin and pyrazinamide in Indian children undergoing thrice-weekly dosing

Pharmacokinetic profiles

mean ± standard error of the mean

HIV coinfection had a **strong effect** on the PK of **isoniazid** and **rifampin**
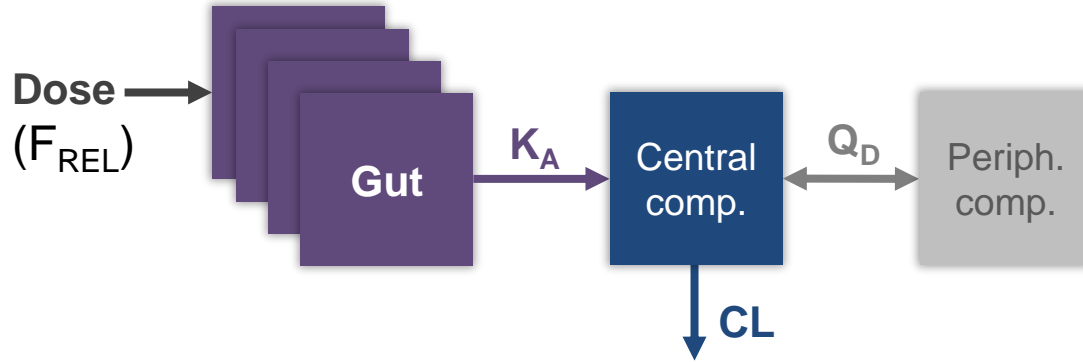
		Isoniazid	Rifampin	Pyrazinamide
Covariates	Body weight	CL, V (allometry) F_{rel} (power)	CL, V (allometry) F_{rel} (power)	CL, V (allometry) F_{rel} (power)
	HIV coinfection	↓ F_{rel} (-20%)	↑ CL (+32%) ↓ F_{rel} (-42%)	–

CL, V: apparent clearance and volume
F_{REL}: relative bioavailability

The **PK models** were **predictive** of AUC_{last}
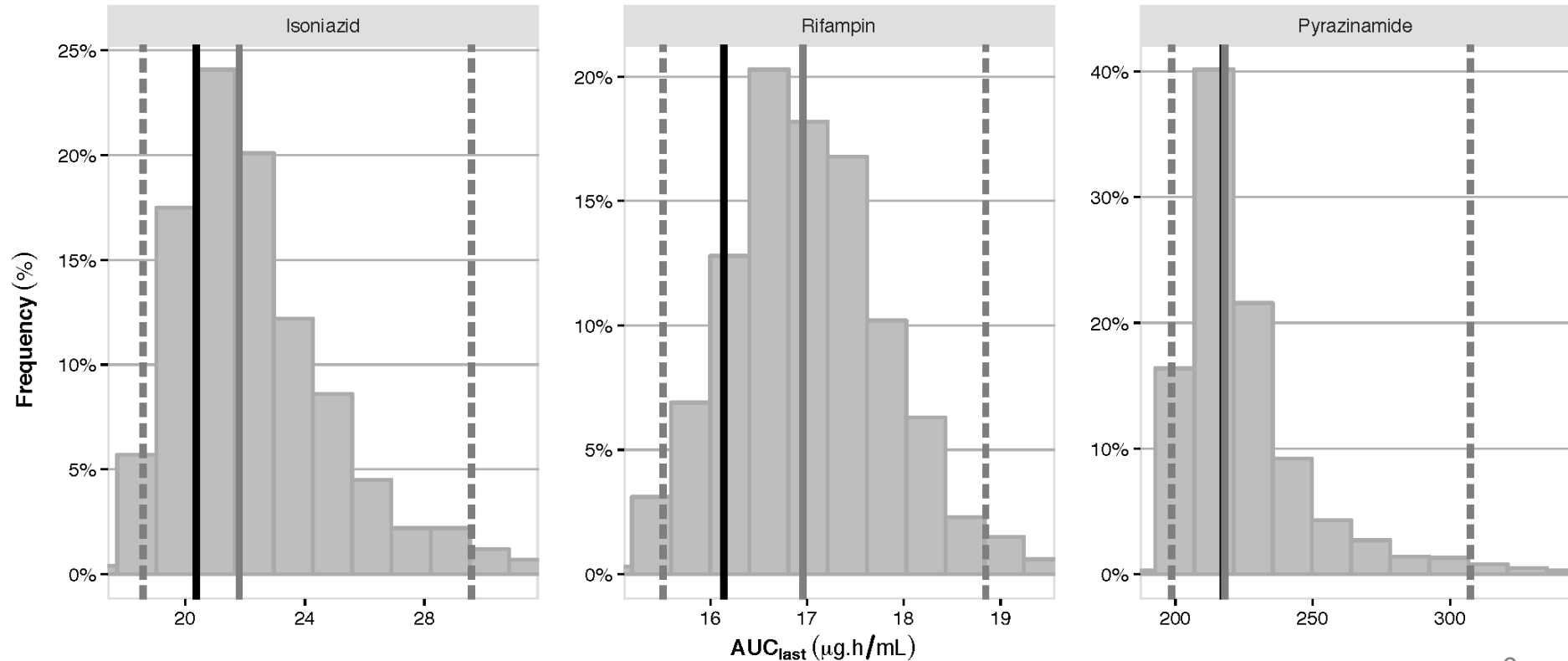
AUC: area under the curve

Step 2

Establish the relationship between drug exposure and the probability of unfavorable treatment outcome
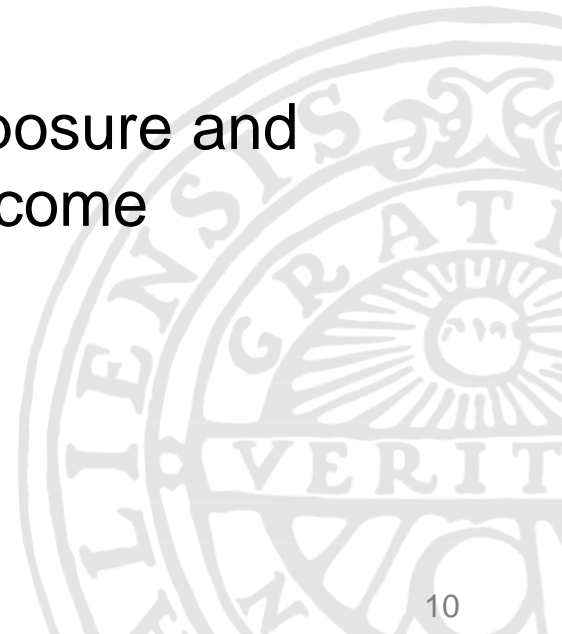
The PK/PD modeling approach

- Treatment outcome evaluated at 6 months
    - 109 favorable (cured/treatment completion)
    - 33 unfavorable (death/treatment failure)
    - 19 unknown

- Probability of unfavorable treatment outcome ($P_{unfavorable}$) modeled using a logistic regression model

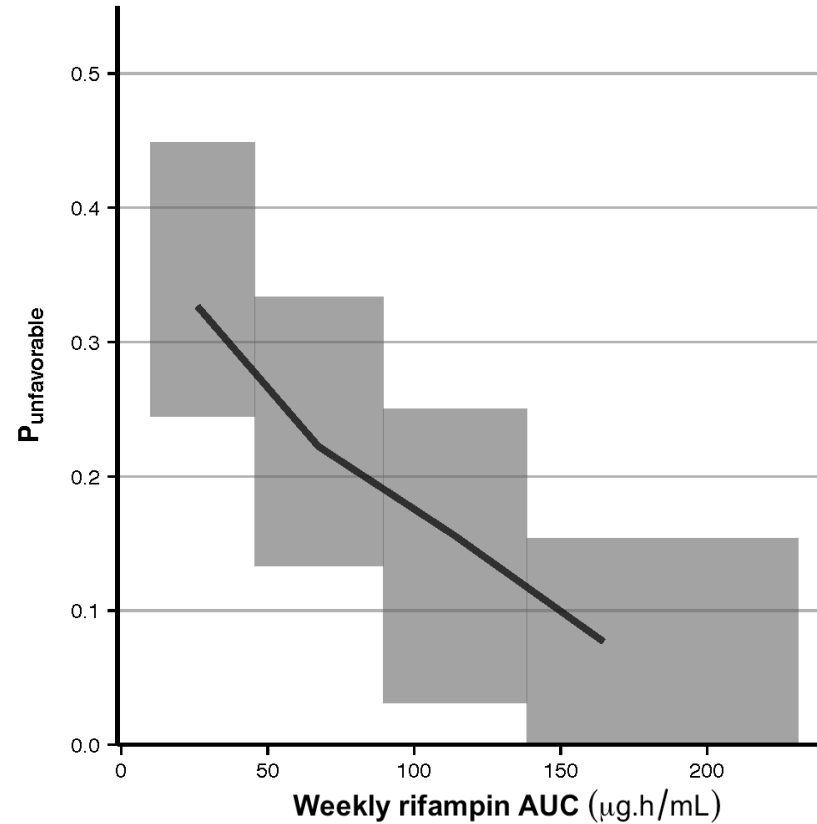- Drug exposure (i.e. weekly AUC) and covariates were tested as predictors of the treatment outcome

Rifampin exposure was the **only predictor** of treatment **outcome**
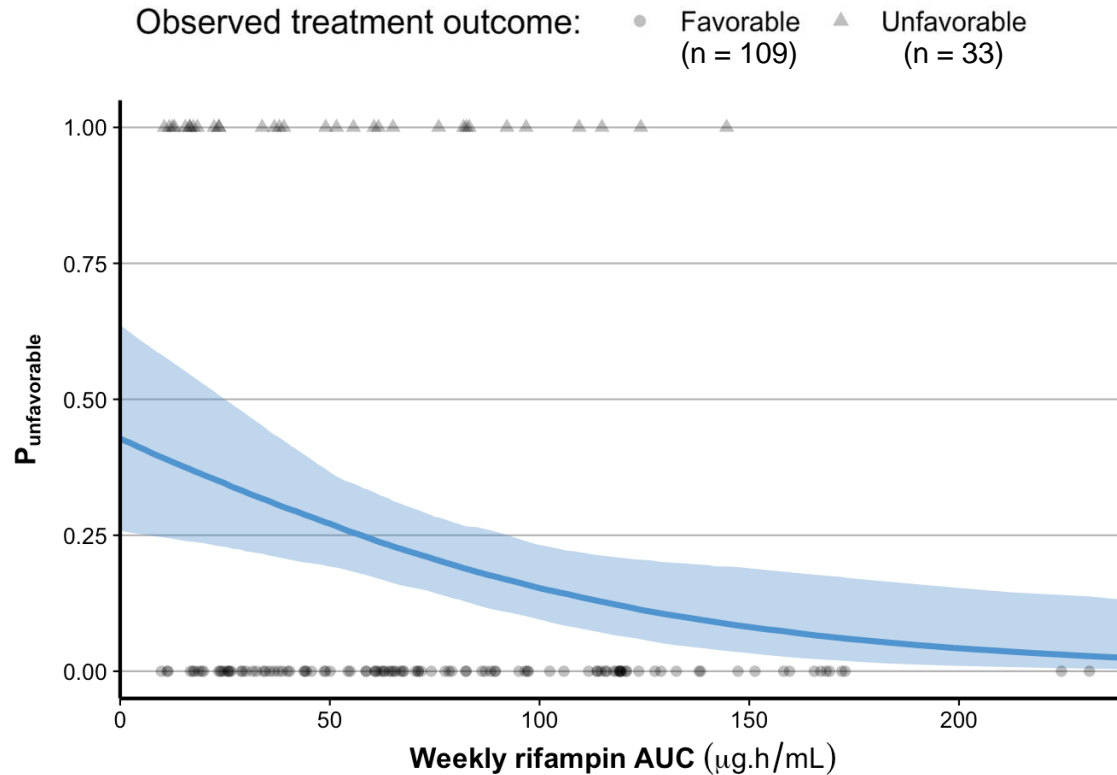
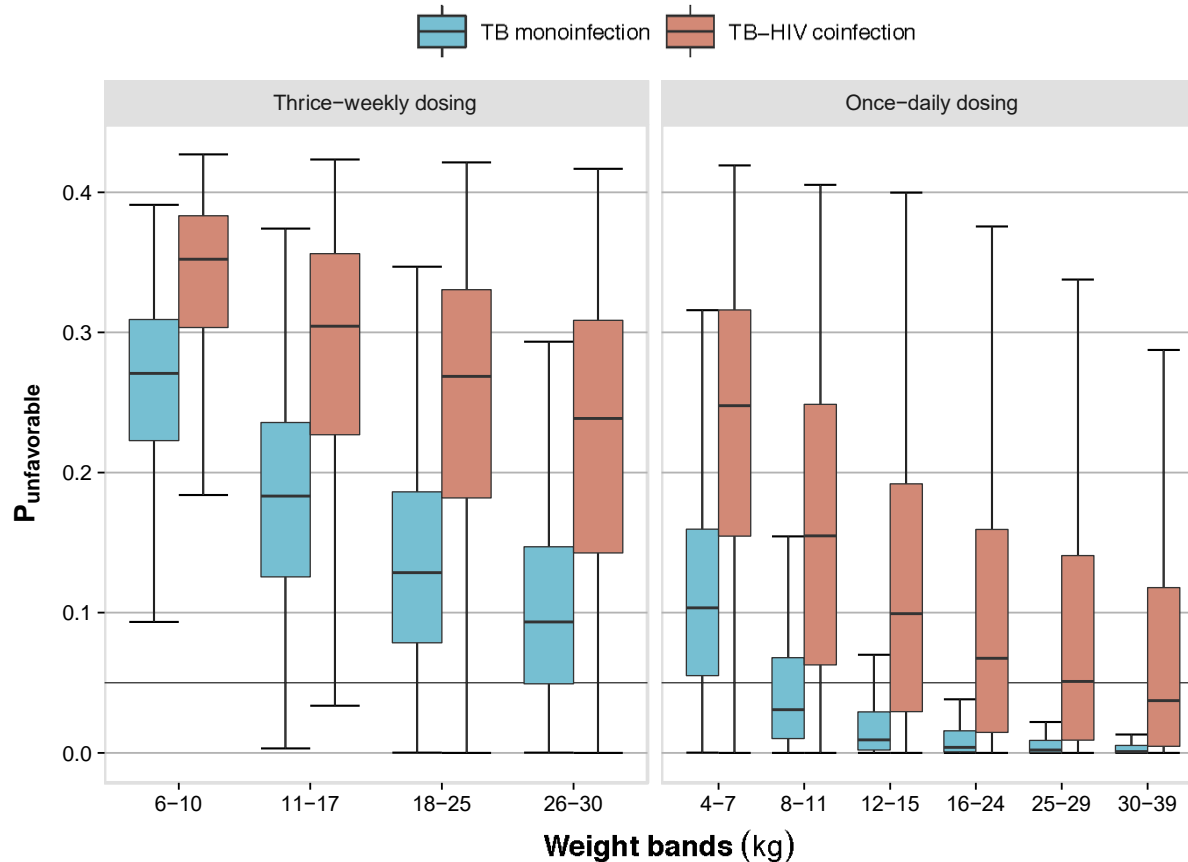# The **PK/PD model** was **predictive** of **treatment outcome**

Step 3

Evaluate the previous and new Indian dosing recommendations and suggest dose revisions

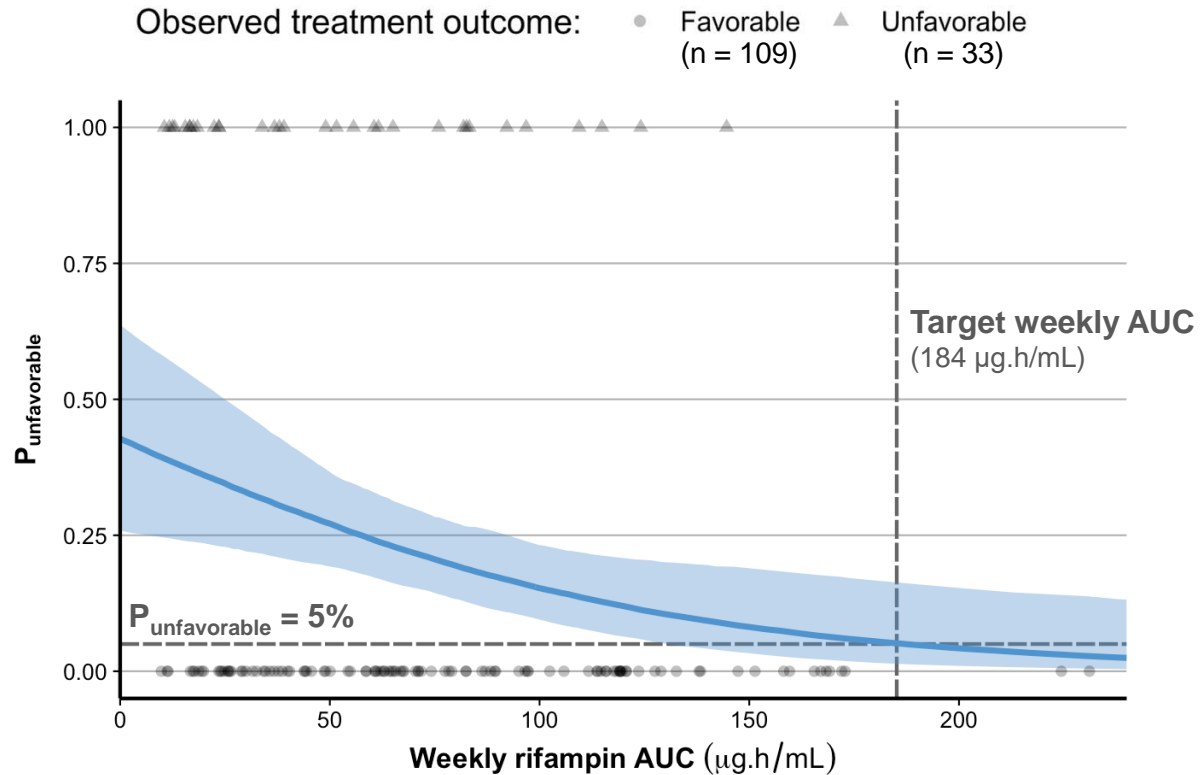# **Small** and **HIV coinfected** children are at **high risk**

First definition of a **target exposure** in **children**
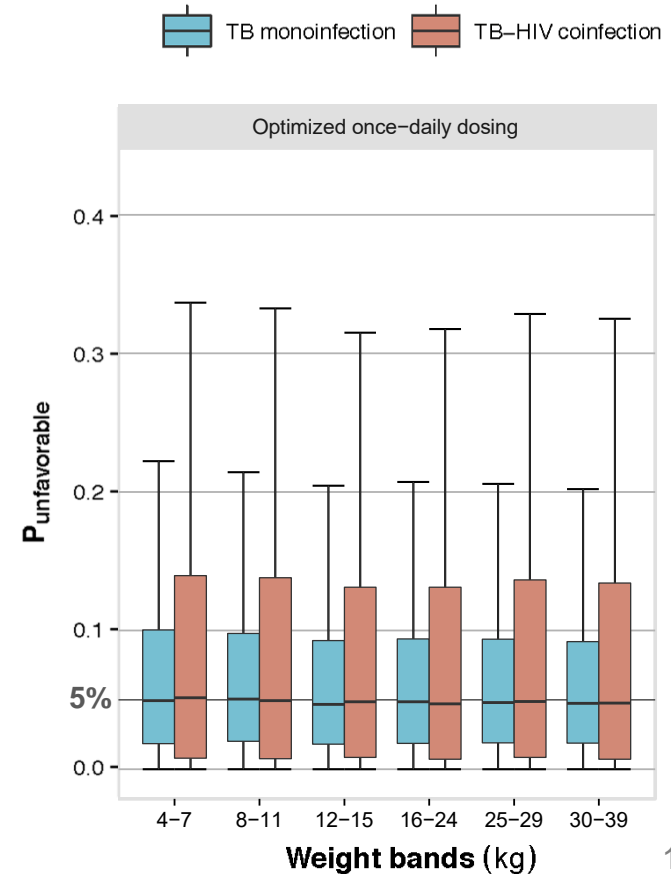
Daily **doses** were **optimized** via a **model-based** approach

Optimized rifampin doses*

Weight band kg	TB monoinfection mg/kg	TB-HIV coinfection mg/kg
4–7	**19.9**	**43.4**
8–11	13.3	**28.9**
12–15	10.3	**23.0**
16–24	7.7	**17.3**
25–29	6.2	14.2
30–39	5.2	11.7

*Currently used dose: 15 mg/kg

The **rifampin** auto **induction**

Dose of 9.8 mg/kg in an HIV- children of 14kg

W. Smytheet et al. (2012)

Conclusions
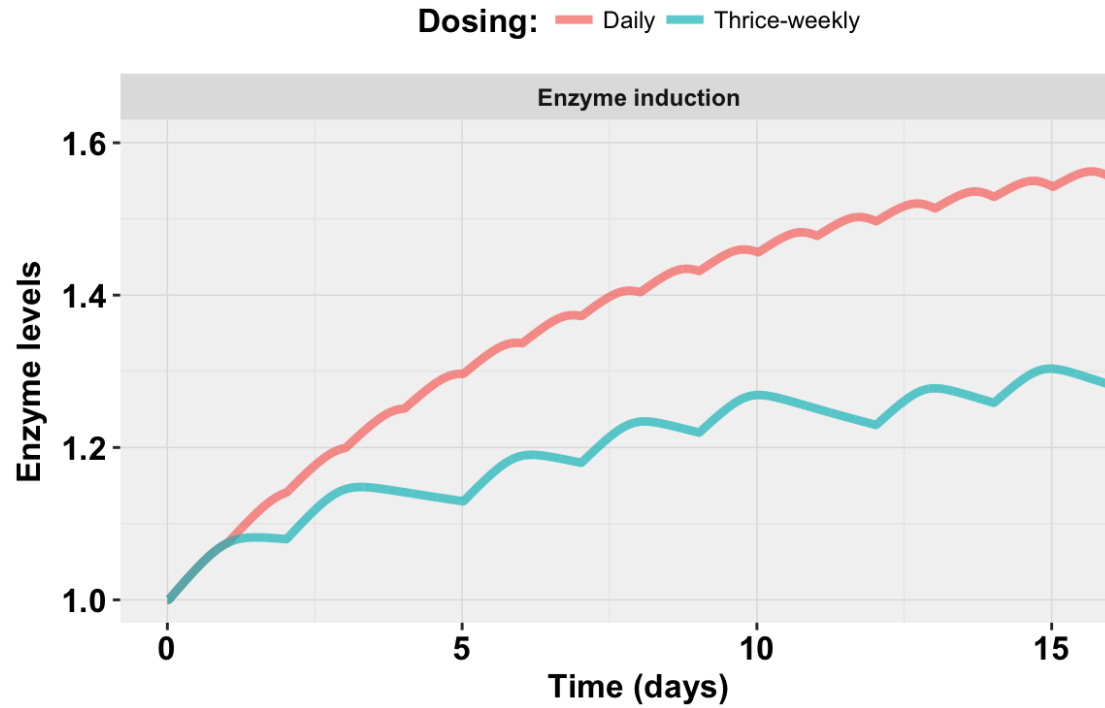
- **Rifampin exposure** was the **lowest** in children with **low body weight** or **HIV** coinfection

- **Low** rifampin **exposures** were linked to an **increased** probability of **unfavorable** treatment **outcome**

- **Optimized** rifampin **doses** were proposed based on a weekly target exposure

- The proposed PK/PD model could be used to **support** the use of **higher** rifampin **doses in children**

Acknowledgements

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