Model-based rationale for drug combinations in tuberculosis

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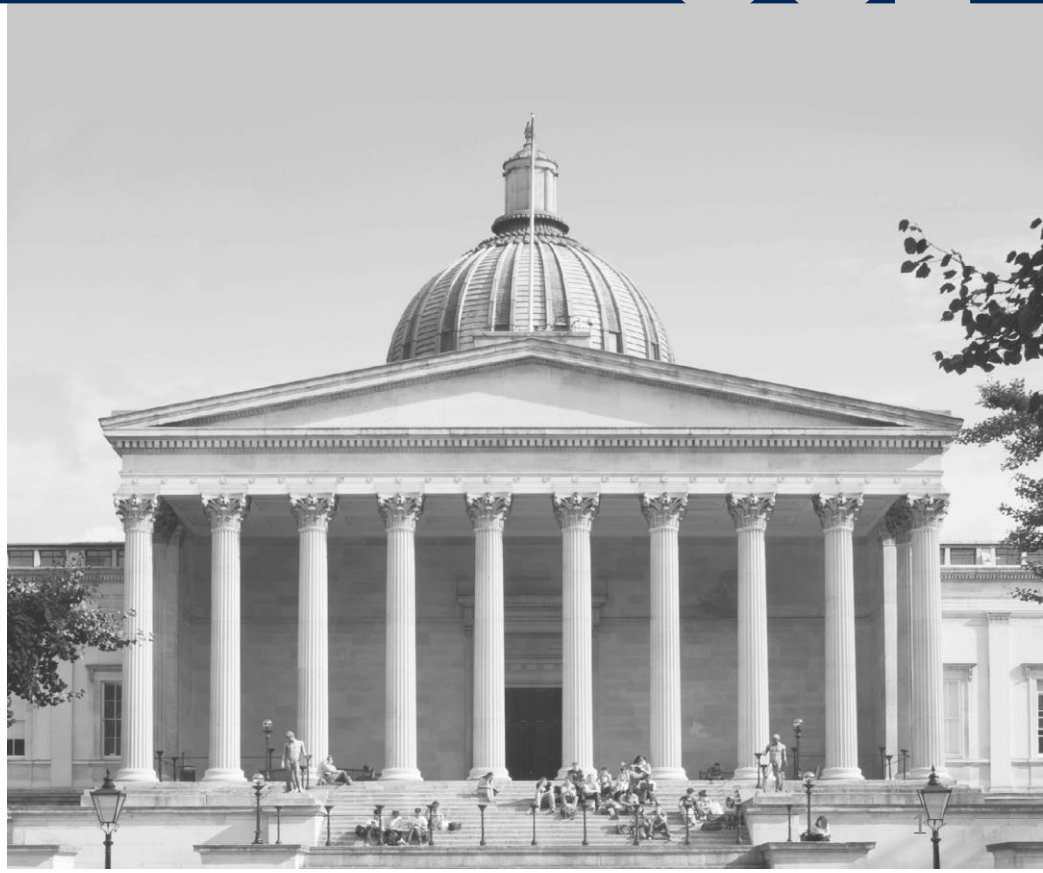
Lewis Sheiner Student Session
PAGE Meeting 2017, Budapest, Hungary



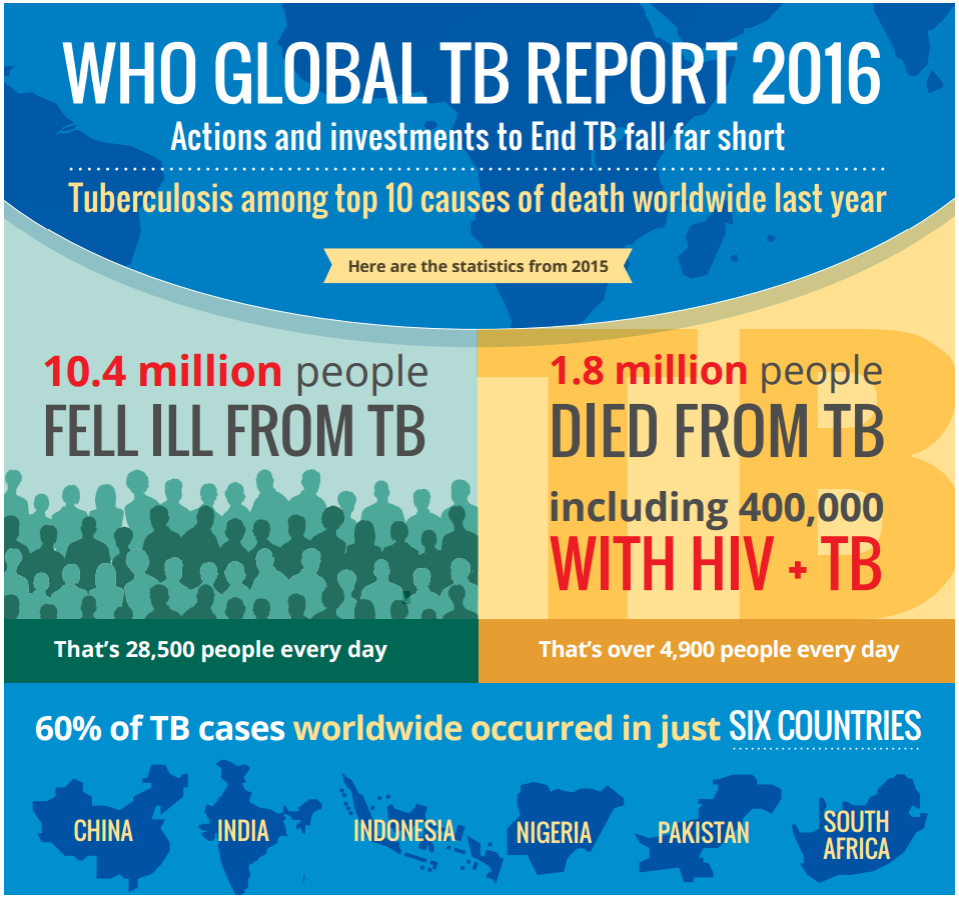
Tuberculosis remains a major burden

Current first-line treatment:

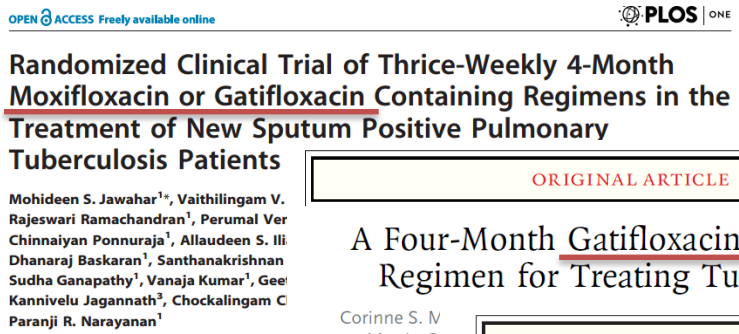
Rifampicin, isoniazid pyrazinamide and ethambutol (2 months) + rifampicin and isoniazid (4 months)

Long, complicated and toxic

Need to replace with shorter regimens



Recent Phase 3 trials in TB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PLOS ONE

Randomized Clinical Trial of Thrice-Weekly 4-Month Moxifloxacin or Gatifloxacin Containing Regimens in the Treatment of New Sputum Positive Pulmonary Tuberculosis Patients

Mohideen S. Jawahar[1]*, Vaithilingam V. Rajeswari Ramachandran[1], Perumal Ver Chinnaiyan Ponnuraja[1], Allaudeen S. Ili Dhanaraj Baskaran[1], Santhanakrishnan Sudha Ganapathy[1], Vanaja Kumar[1], Gee Kannivelu Jagannath[3], Chockalingam C Paranji R. Narayanan[1]

ORIGINAL ARTICLE

A Four-Month Gatifloxacin-Containing Regimen for Treating Tuberculosis

Corinne S. M
Martin G
Joseph Odl
Ferdinand Ka
Bouke C. de Jo
Cha
Piero L.
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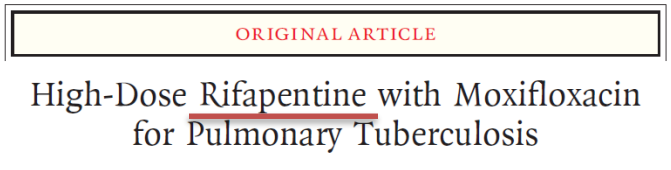
ORIGINAL ARTICLE

High-Dose Rifapentine with Moxifloxacin for Pulmonary Tuberculosis

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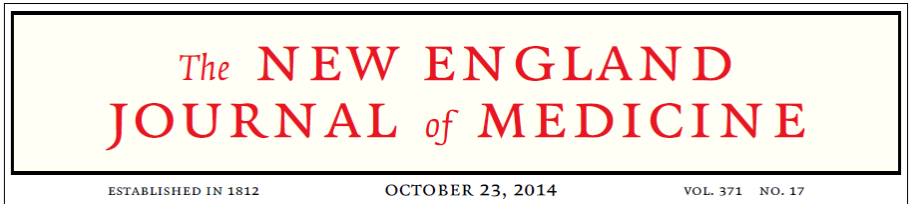

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 23, 2014 VOL. 371 NO. 17

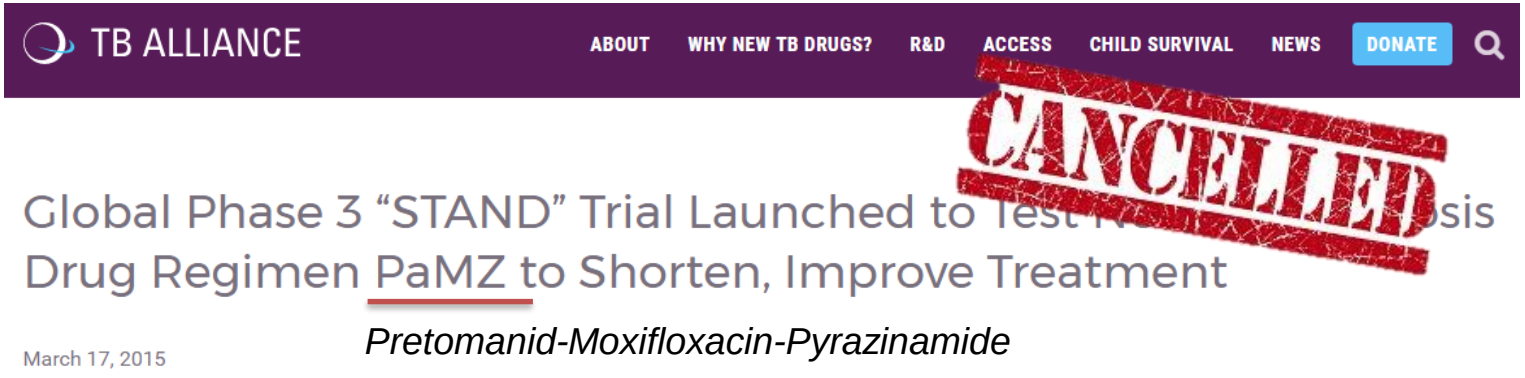
Four-Month Moxifloxacin-Based Regimens for Drug-Sensitive Tuberculosis

Stephen H. Gillespie, M.D., D.Sc., Angela M. Crook, Ph.D., Timothy D. McHugh, Ph.D., Carl M. Mendel, M.D., Sarah K. Meredith, M.B., B.S., Stephen R. Murray, M.D., Ph.D., Frances Pappas, M.A., Patrick P.J. Phillips, Ph.D., and Andrew J. Nunn, M.Sc., for the REMoxTB Consortium*

All shorter regimens **were inferior** to the standard of care regimen

Jawahar et al, 2013
Merle et al, 2014
Jindani et al, 2014
Gillespie et al, 2014

Recent Phase 3 trials in TB



Background

Situation

Development of novel drug combinations in tuberculosis remains challenging.

Target

More effective use of preclinical data to inform selection of dose and drug combinations prior to clinical development.

Proposal

PKPD modelling for integration of preclinical data arising from different experimental protocols.

Research objectives

1. Demonstrate how NLME approach can be used to integrate *in vivo* PKPD data arising from different experimental protocols.

2. Develop a parametric approach to describe the effect of combination treatments on the parameters of interest.

3. Evaluation of different scaling methods for selection of dose and drug combinations in clinical development.

How were novel combinations assessed?

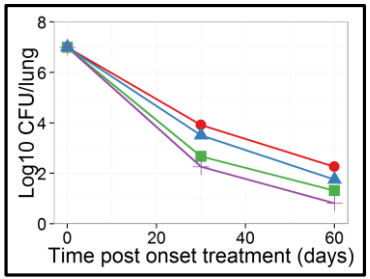
Preclinical stage

Infection

Drug combinations with "standard" dosages

2-6 months

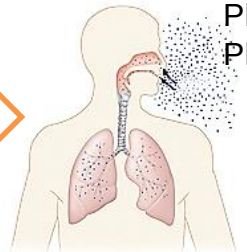
Serial *lung* CFU count



CFU: colony forming unit

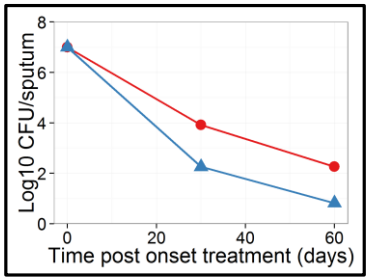
Clinical stage (Phase 2)

Select combination with the highest in vivo efficacy
Use currently approved dosages



Phase 2a (2 wks)
Phase 2b (8 wks)

Serial *sputum* CFU count



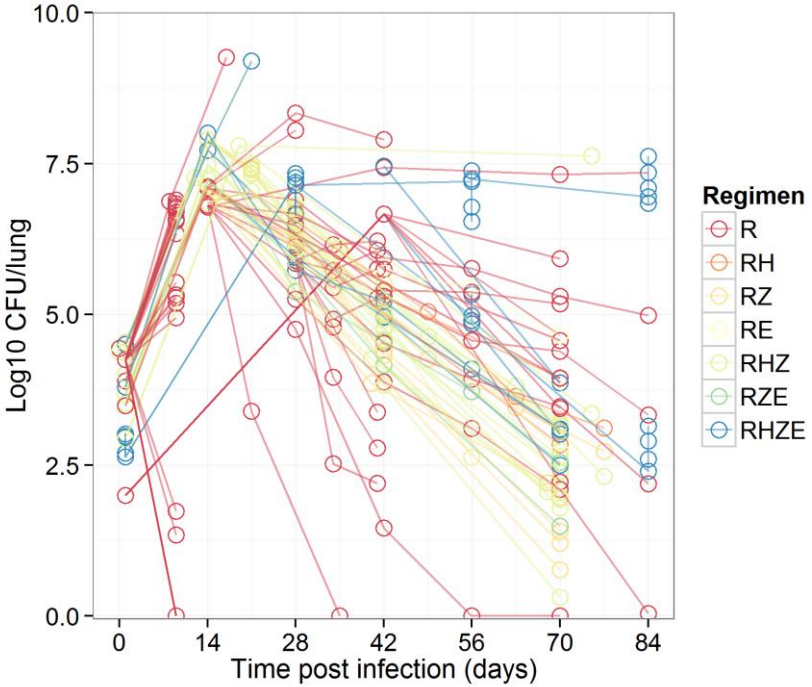
Empirical
Individual drug contribution to overall treatment effect unclear
Little emphasis on dose optimization based on underlying PKPD relationships

Next challenge: systematic data evaluation

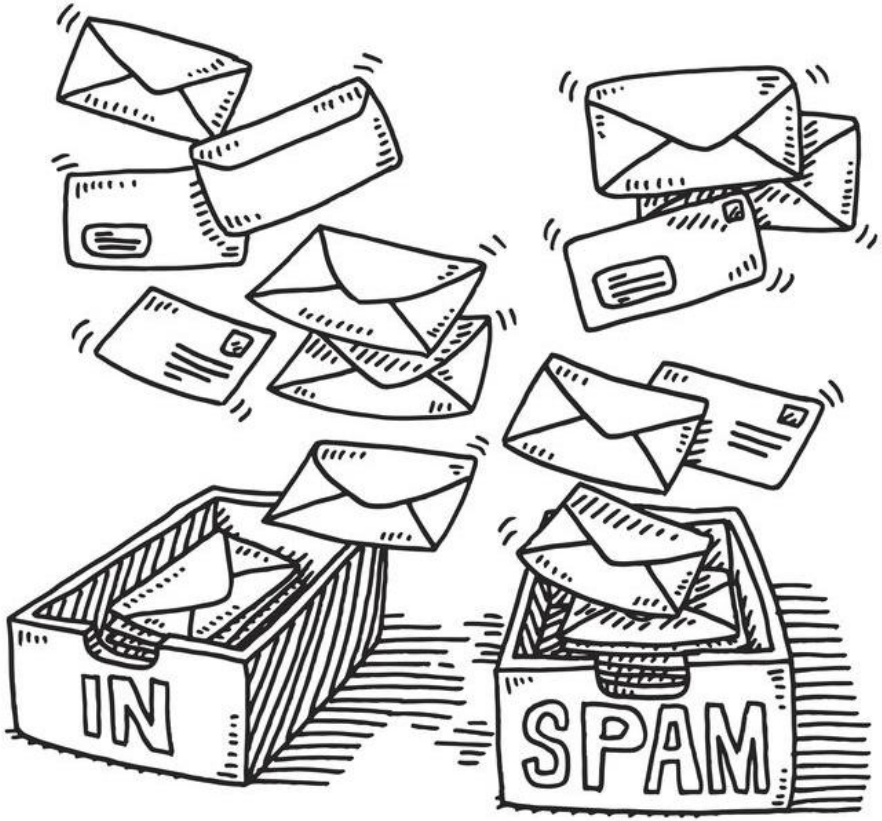
Factorial design to assess drug combinations?

Problems:

1. Large datasets
2. Complex to analyse
3. Results may still not be necessarily translatable to human



How to separate the good from the bad?



Approach: integrated PKPD modelling

Mean generation rate (knet)
Carrying capacity (BMAX)

Potency (IC50)
Maximum killing rate (Emax)

Drug interactions in each combination

Disease

PKPD (backbone drug)

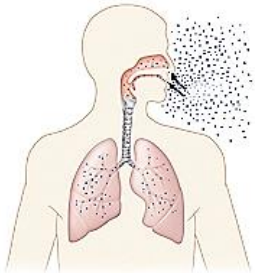
PKPD (drug combinations)

Predict

Predict

External validation

Predict



Disease

PKPD (backbone drug)

PKPD (drug combinations)

Key assumptions in analysis

In vivo

Literature meta-analysis (CFU only)

Simulations (VPCs) performed without inter-individual variability

PK assumed to be constant across experiments

Human

Individual patient data available (demographics and CFU only)

Published PK models used to simulate exposure in patient population

PK variability assumed to be constant between studies

Approach: integrated PKPD modelling

Disease → PKPD (backbone drug) → PKPD (drug combinations)

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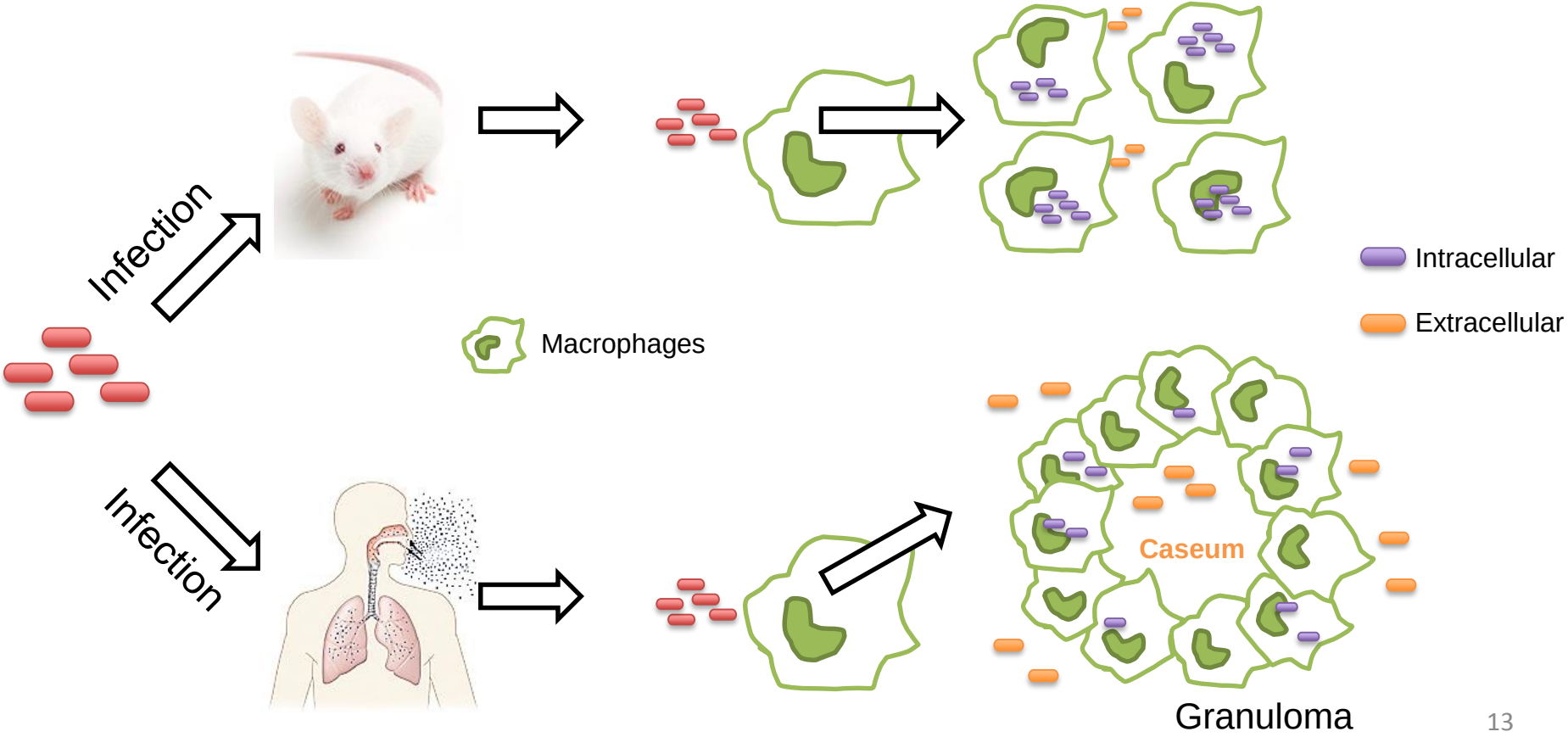
Disease progression in tuberculosis



Key assumptions for disease model

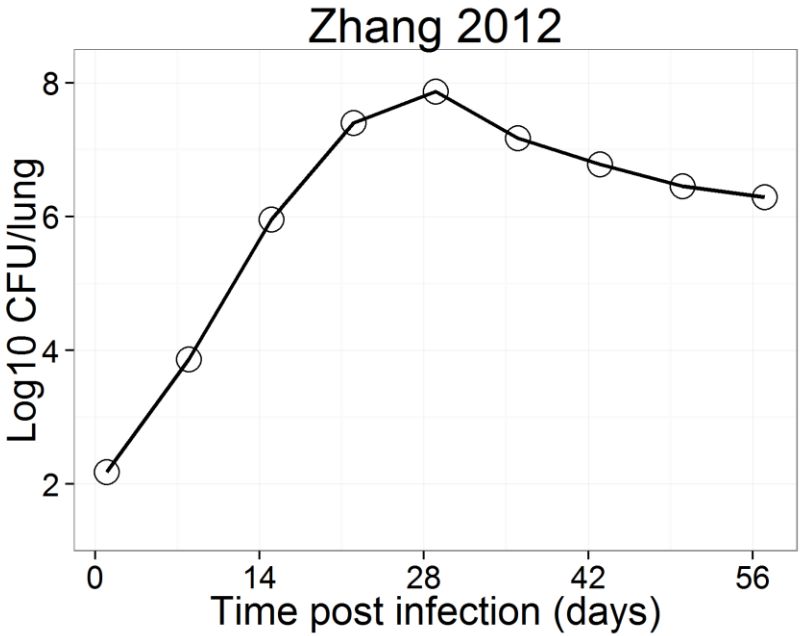
Extracellular and intracellular *M.tuberculosis* were treated as two different populations.

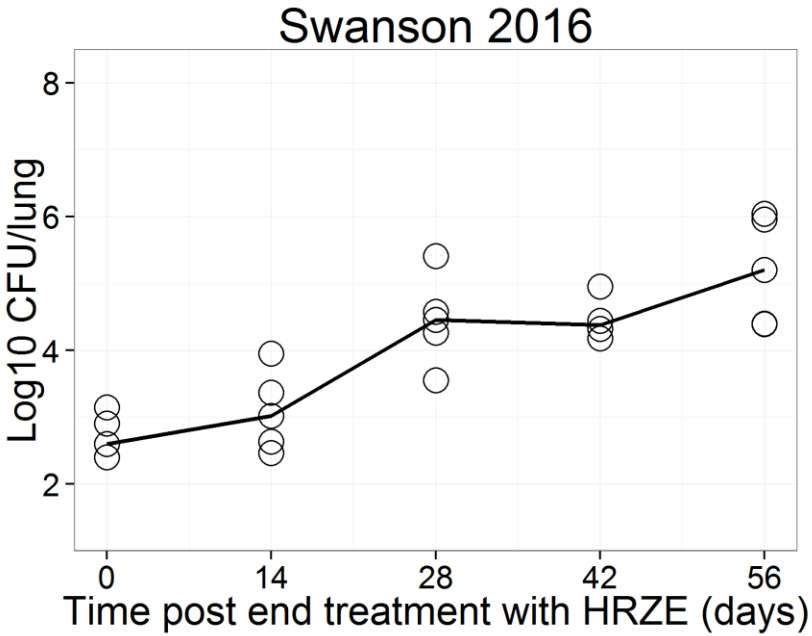
Evidence from preclinical experiments that each population display a different growth rate (fast and slow-growing).[1,2]

A disease model was subsequently developed aiming to describe the equilibration of both populations over time.

1) Beste et al, 2009; 2) Aljayyoussi et al, 2017

Data for in vivo disease model

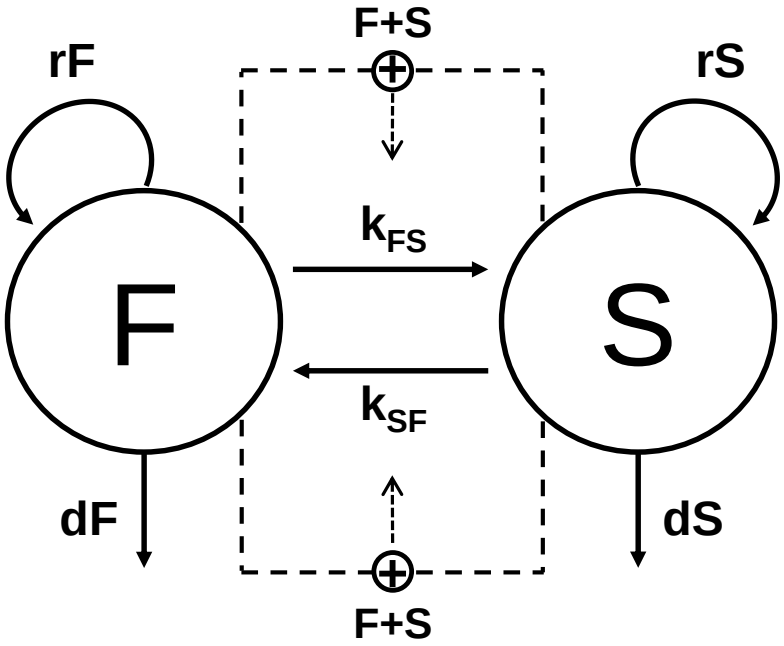




CFU count in **untreated** BALB/c mice

CFU **regrowth** in BALB/c mice after 2 months of treatment

In vivo disease model



$$DADT[F] = GROWTH_F \cdot F - kFS \cdot F + kSF \cdot S$$

$$DADT\ [S] = GROWTH_S \cdot S + kFS \cdot F - kSF \cdot S$$

$$knetF = rF - dF$$

$$knetS = rS - dS$$

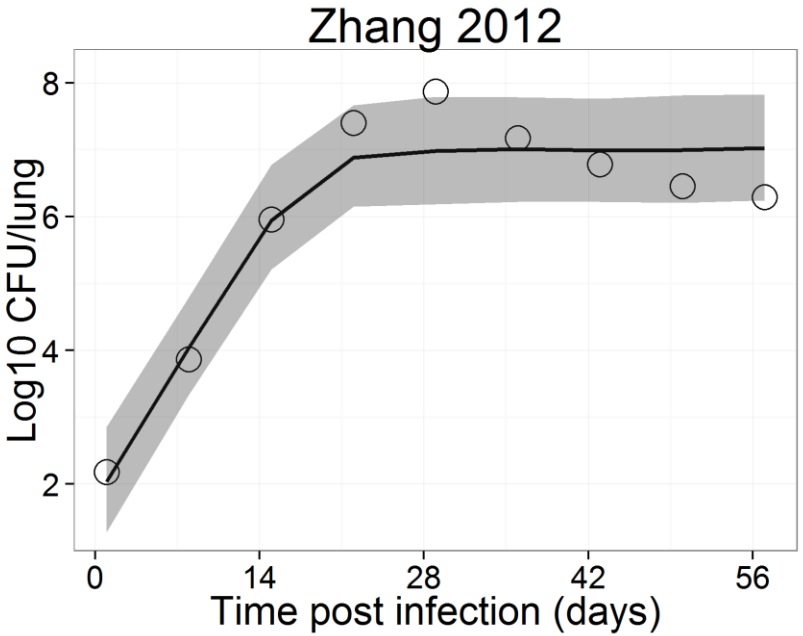
$$GROWTH_F = knetF \cdot \left(1 - \frac{(F+S)}{BMAX}\right)$$

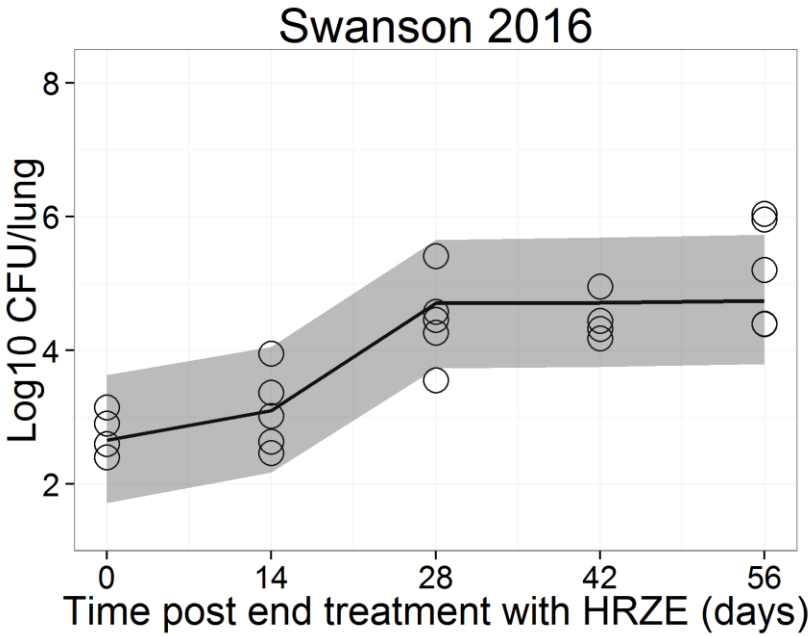
$$GROWTH_S = knetS \cdot \left(1 - \frac{(F+S)}{BMAX}\right)$$

$$kFS = \frac{knetF \cdot (F+S)}{BMAX}$$

$$kSF = \frac{knetS \cdot (F+S)}{BMAX}$$

VPC of in vivo disease model

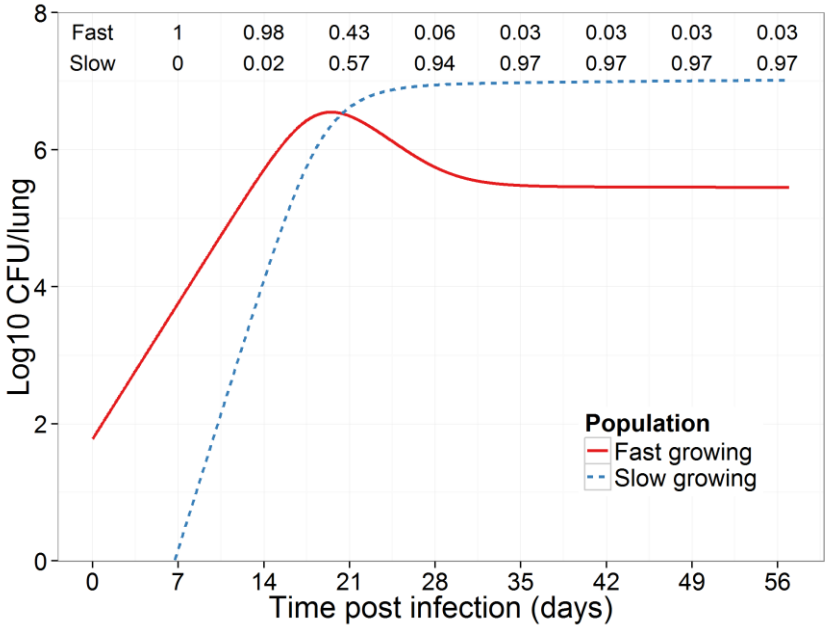




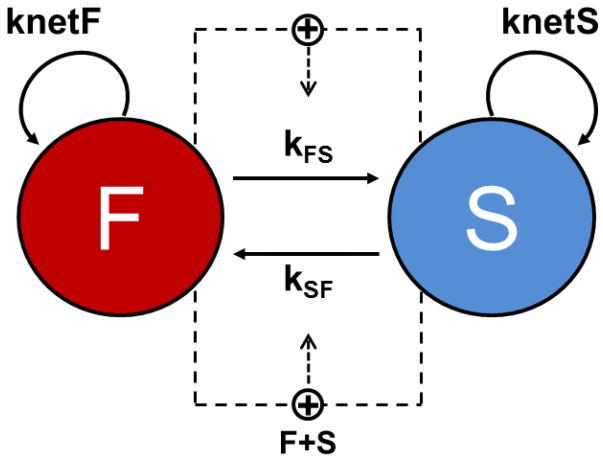
CFU count in **untreated** BALB/c mice

CFU **regrowth** in BALB/c mice after 2 months of treatment

Predicted in vivo disease progression



Predicted fraction from total population



Approach: integrated PKPD modelling

Disease → PKPD (backbone drug) → PKPD (drug combinations)

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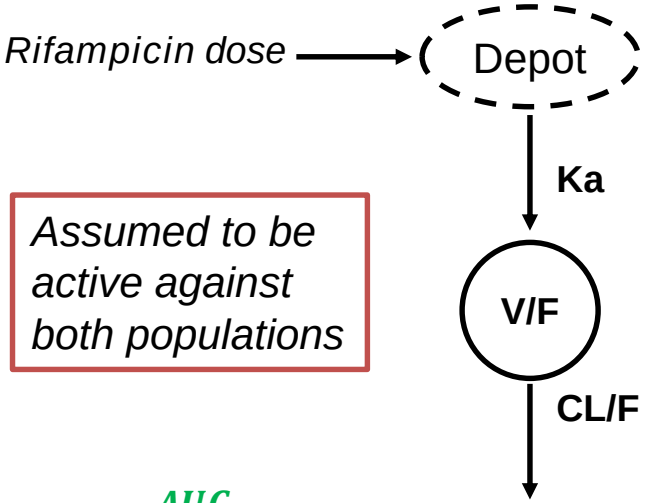
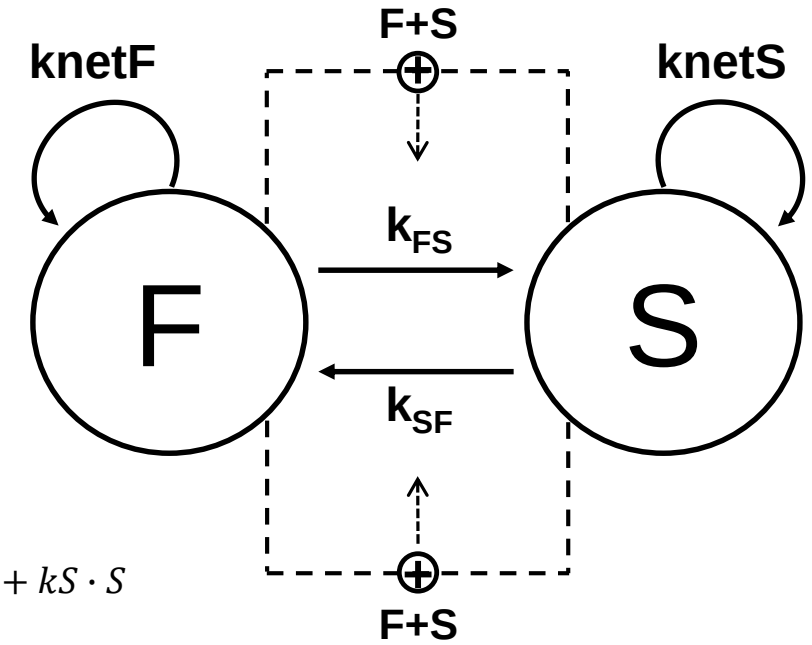
Parameterization of in vivo rifampicin effect



Assumed to be active against both populations

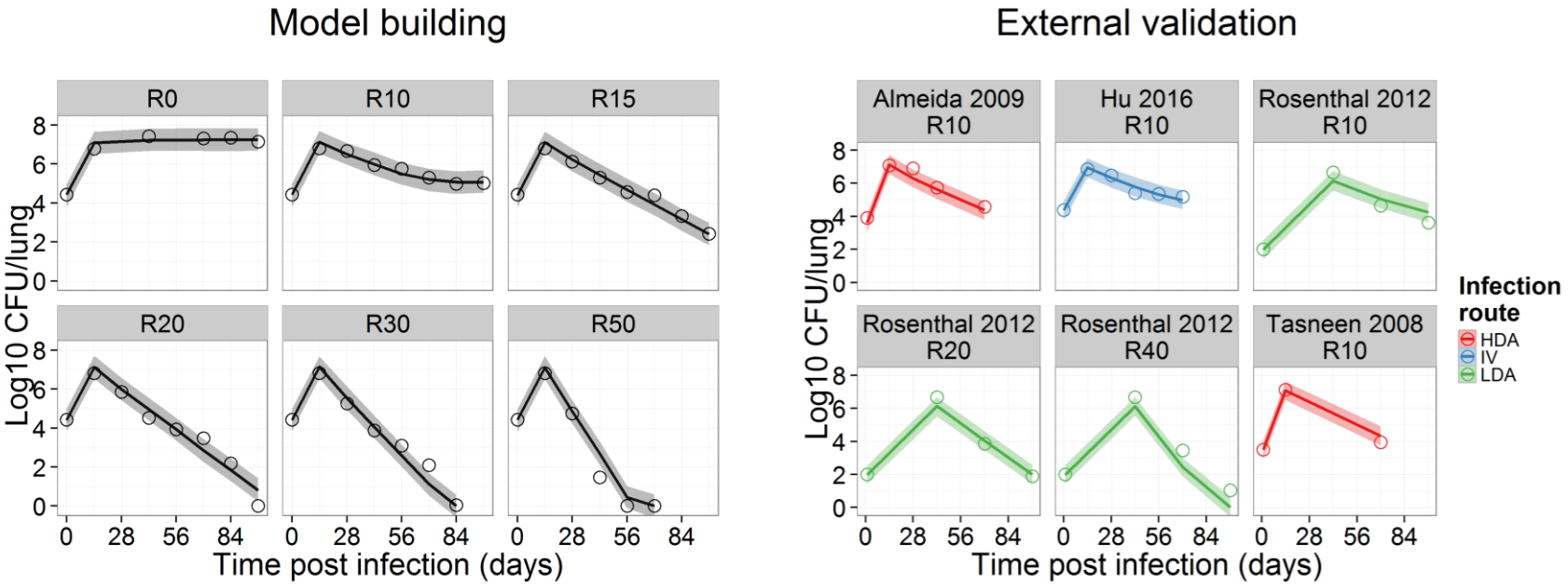


$$C_{ss,av} = \frac{AUC_{0-24}}{24}$$

$$DADT[F] = \left(GROWTH_F - \frac{Emax \cdot C_{ss,av}}{IC50_F + C_{ss,av}}\right) \cdot F - kFS \cdot F + kS \cdot S$$

$$DADT\,[S] = \left(GROWTH_S - \frac{Emax \cdot C_{ss,av}}{IC50_S + C_{ss,av}}\right) \cdot S + kFS \cdot F - kSF \cdot S$$

Model diagnostics and validation



Infection route	IC50, F (mg/L)	IC50, S (mg/L)
Intravenous (IV)	4.87 (reference)	60.2 (reference)
High-dose aerosol (HDA)	3.26	40.3
Low-dose aerosol (LDA)	4.97	61.4

Hu et al 2015

Preliminary conclusions (1)

Longitudinal model to describe growth of fast and slow-growing *Mtb*

Rifampicin IC50 was different between fast and slow growing Mtb

Which companion drug(s) for rifampicin?

Disease → PKPD (backbone drug) → PKPD (drug combinations)

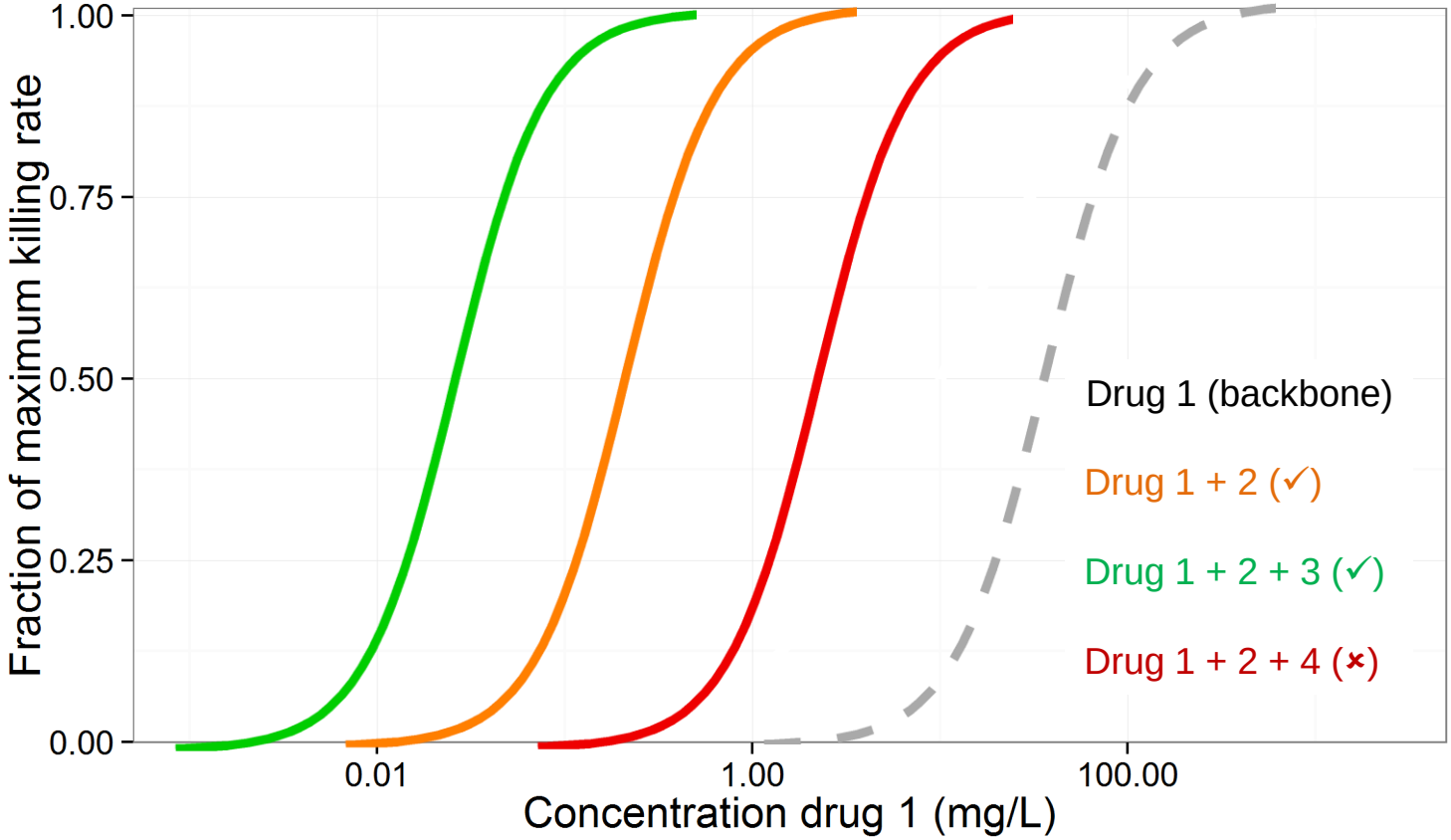
Disease → PKPD (backbone drug) → PKPD (drug combinations)

Which partner drug(s) for rifampicin?

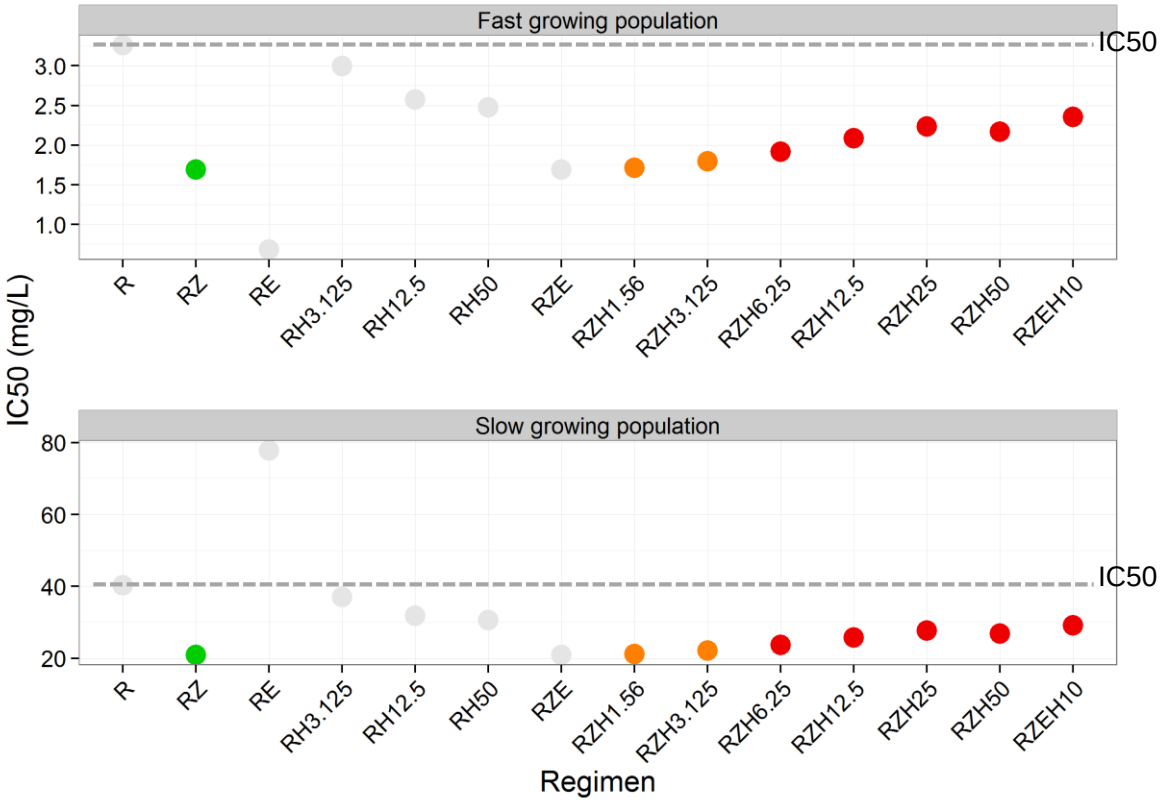
Question: how can we capture the contribution of additional drugs to the overall bacterial clearance, despite **limited** experimental data?

Proposal: treat additional drugs as **discrete covariates** of the potency (IC50) of the backbone drug (rifampicin)

How were drug combinations assessed?



Results with rifampicin as backbone drug



Highest increase in potency with Z

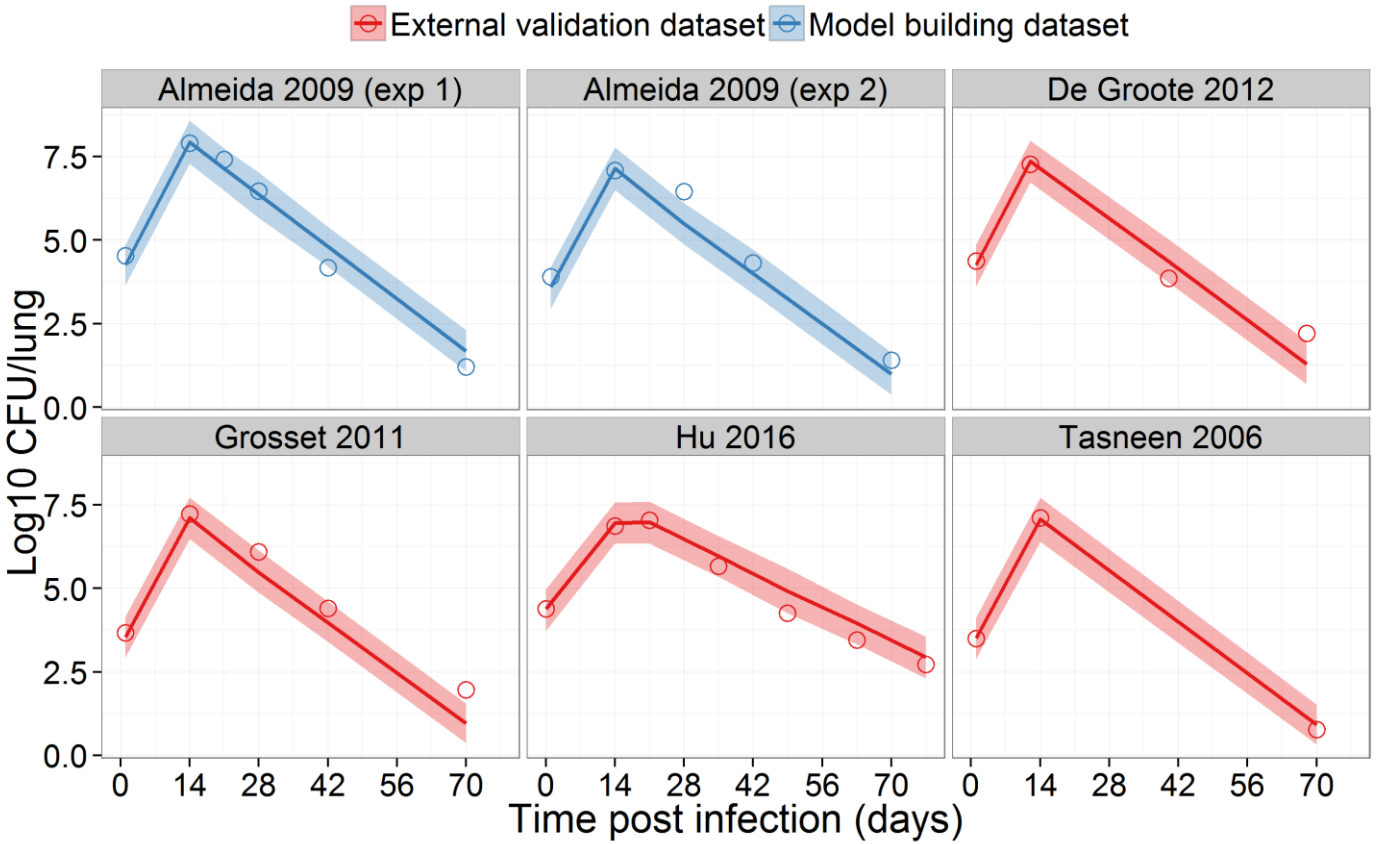
No effect on potency when E added

Reduction in potency if H added

Regimen #1 = RZ

R = rifampicin
H = isoniazid
E = ethambutol
Z = pyrazinamide

Validation of RZ model

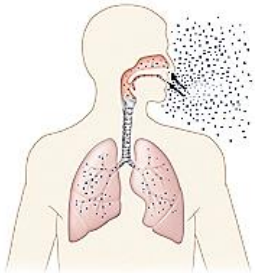


Preliminary conclusion (2)

Our approach allowed parameterization of drug combination(s) as discrete covariates

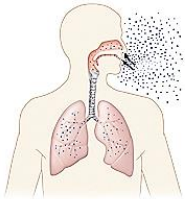
Disease → PKPD (backbone drug) → PKPD (drug combinations)

Predict ↓ Predict ↓ Predict ↓



Disease → PKPD (backbone drug) → PKPD (drug combinations)

Scaling from animal to human



SCALING OF PK

PK model (clearance, volume of distribution, protein binding)

PK model (clearance, volume of distribution, protein binding)

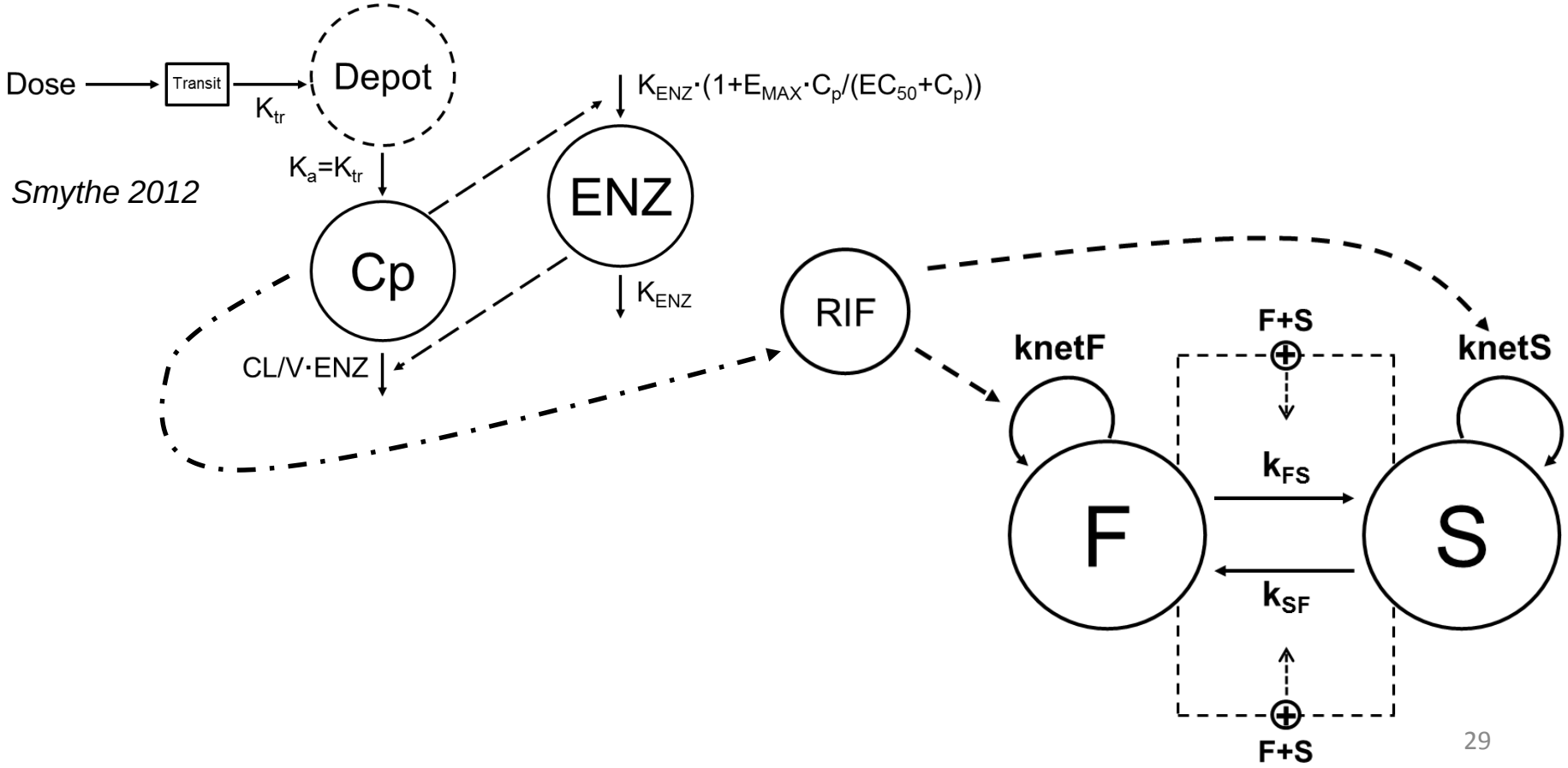
SCALING OF DISEASE

CFU levels and ratio F:S at onset treatment

Disease model (CFU levels)

Disease model (CFU levels)

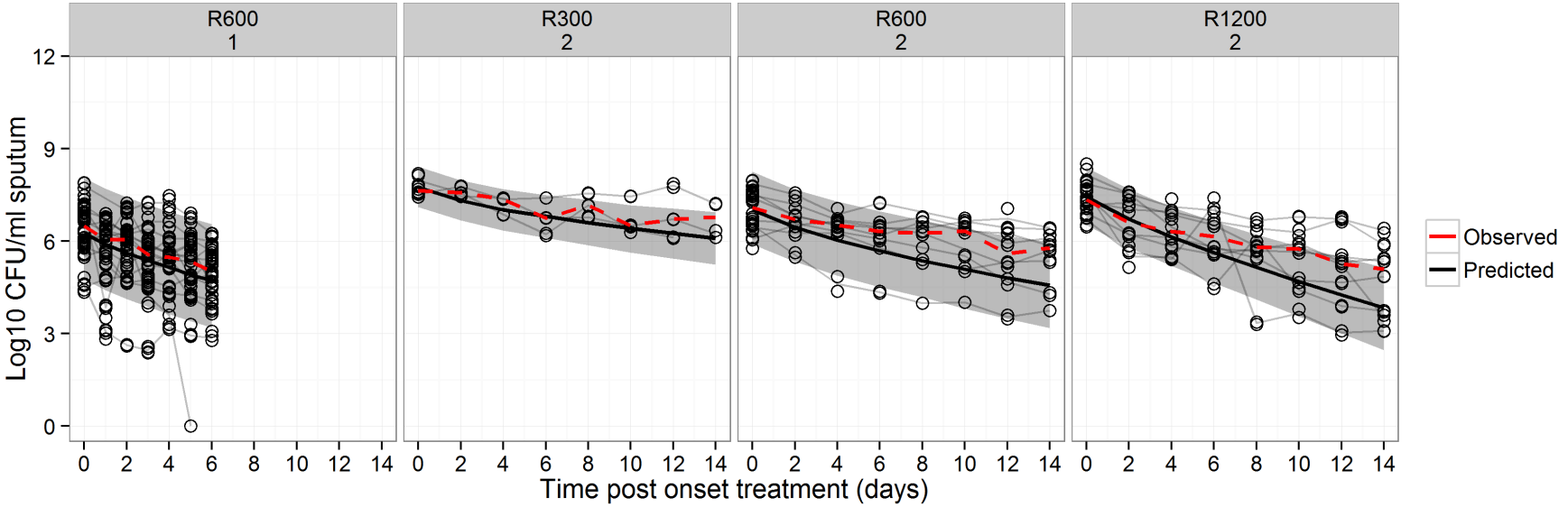
PKPD model of rifampicin in human



Smythe 2012

Predicted EBA of rifampicin in TB patients

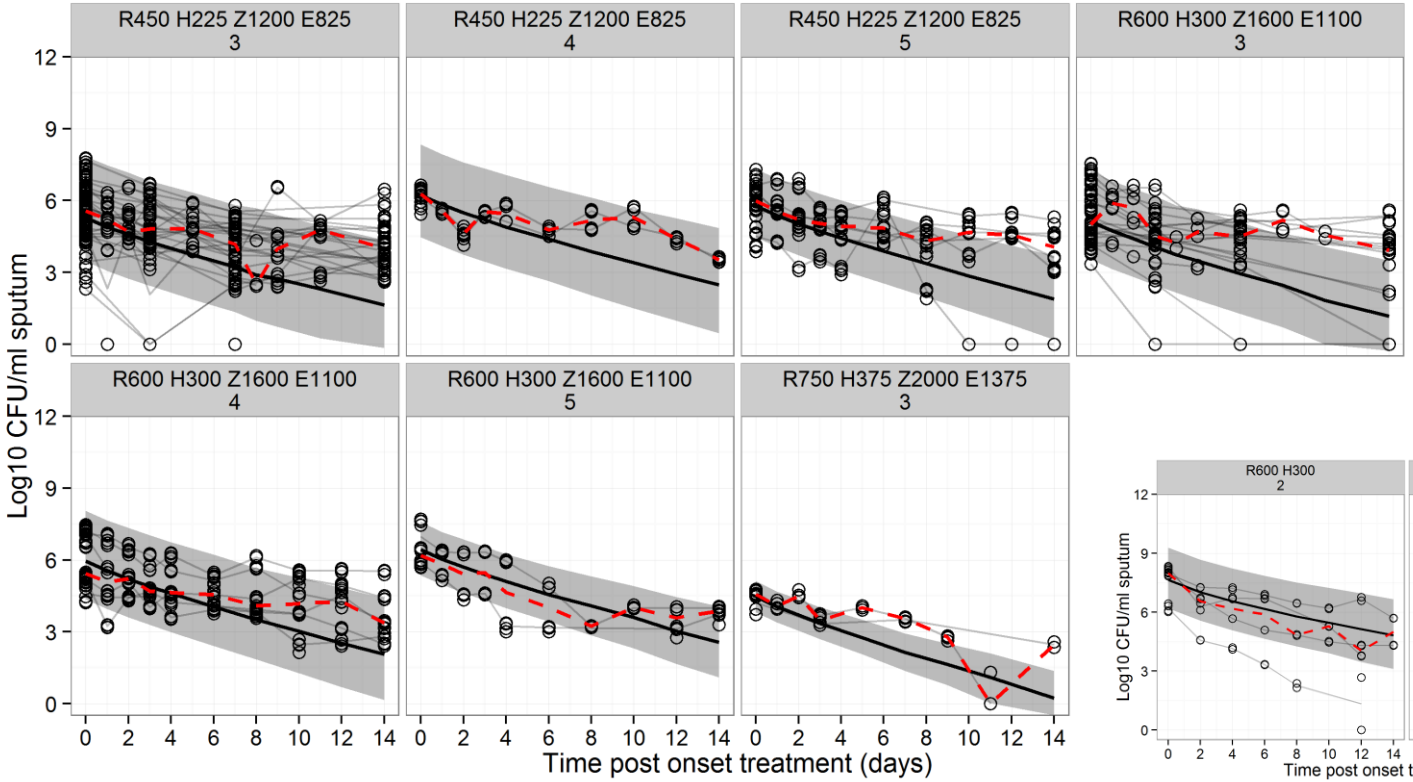
Rustomjee et al 2008 (1)
Jindani et al 1980 (2)



Can we predict EBA following combination treatments too?

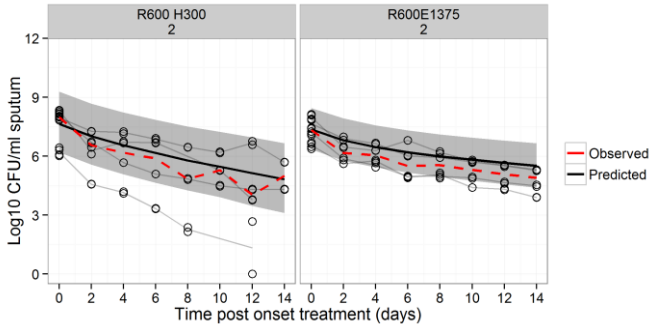
EBA = early bactericidal activity

Predicted EBA of combination treatments



Jindani et al 1980 (2)

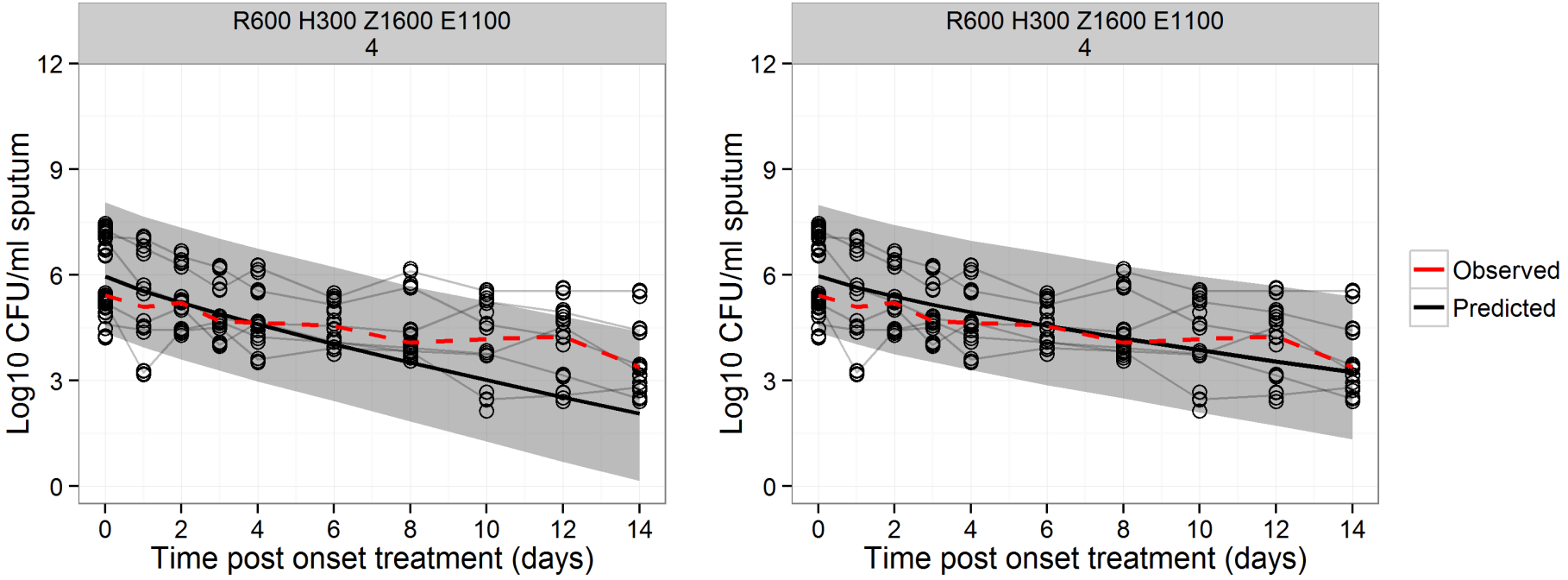
Dawson et al 2015 (3)
Diacon et al 2012 (4)
Diacon et al 2010 (5)



EBA = early bactericidal activity

Sensitivity analysis - pharmacokinetics

Diacon et al 2012 (4)



Conclusions

A longitudinal model describing bacterial growth over time provides insight into the dose rationale for the evaluation of drug combinations.

The proposed parameterization of drug combinations as discrete covariates offers a practical solution for the screening of novel compounds.

Accurate predictions of treatment response in humans require scaling of pharmacokinetics and disease characteristics, which often differ across experimental protocols.

Acknowledgments

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& Therapeutics group

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Appendix

VPC of in vivo rifampicin PK model