Mathematical Modeling of Pulmonary Tuberculosis Therapy: Development of a First Prototype Model with Rifampin

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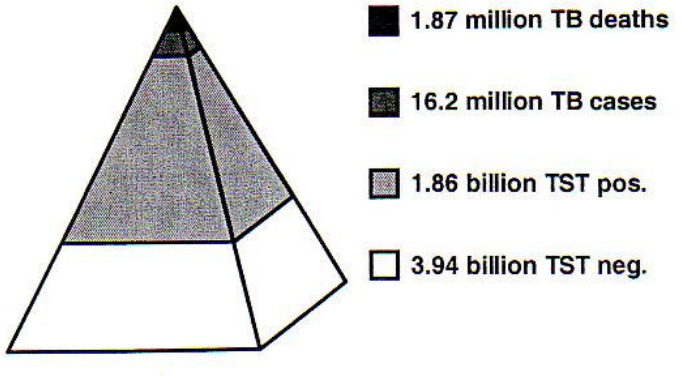
Tuberculosis Burden and Issues

- TB remains one of the biggest killers among infectious diseases: 1.8 million deaths in 2008

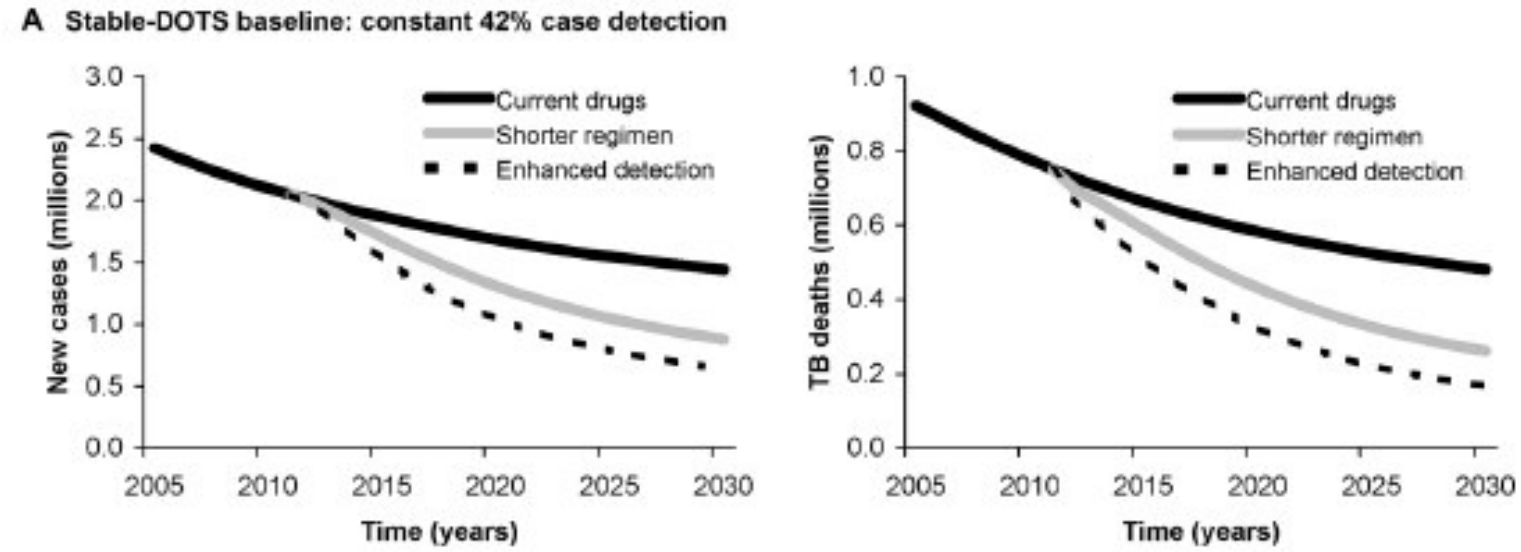


- Short-course chemotherapy (3-4 drugs) is effective when well conducted, but…
- TB treatment is long (min 6 months) and difficult (drug interactions, adverse effects)
- Full Patients' compliance is hard to achieve
- Emergence of resistant *M. tuberculosis* (MDR, XDR)

Rom and Garay (Ed.). Tuberculosis 2nd ed., LWW 2004

The Need for a Shorter TB therapy

- A shorter TB therapy could greatly reduce morbidity and mortality, by reducing transmission, failure, and drug resistance

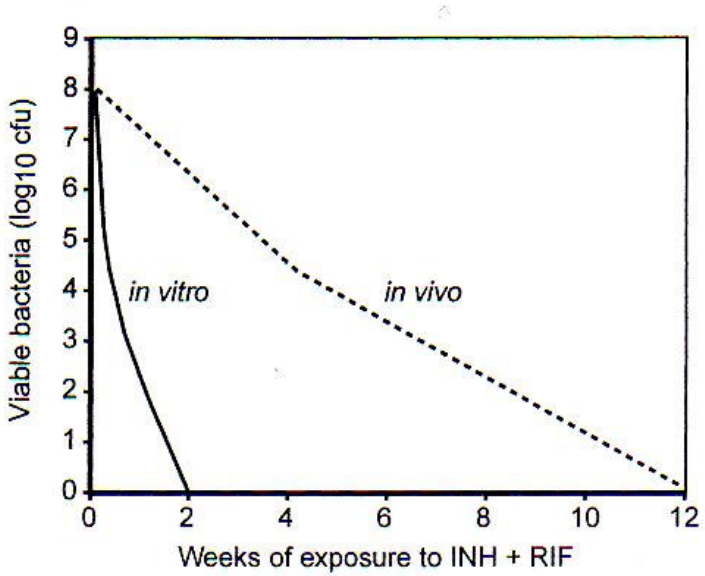


- Two ways: new TB drugs and/or optimal use of current agents

Salomon et al. PLoS Med 2006

The Need for New Models

- Both drug development and optimization require predictive models
- *In vitro* models are poorly predictive of the clinical effect of anti-TB drugs
- Animal models do not fully mimic the human disease and are expensive



The objective of our study was to build a descriptive prototype mathematical model of TB treatment by rifampin

Rom and Garay (Ed.). Tuberculosis 2nd ed., LWW 2004

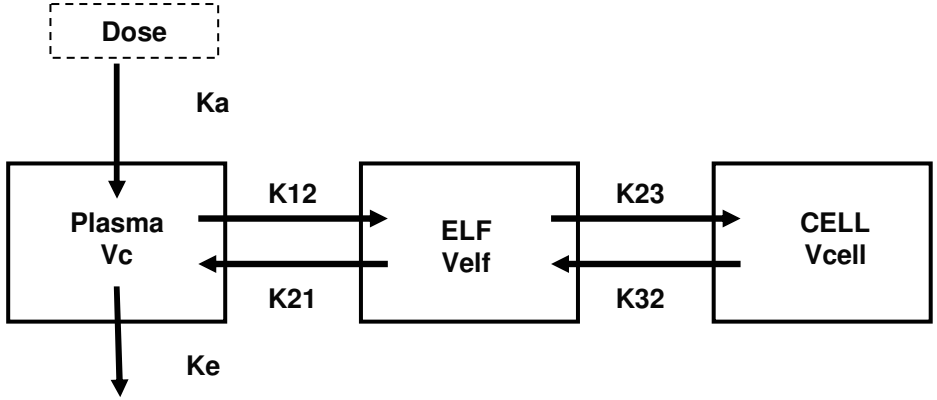
Model Structure

- Only one drug : rifampin
- Full model based on 3 submodels:

  - **PK model**: dose → pulmonary concentrations
  - **PD model**: antibacterial effect in lungs
  - **Physiological** / **disease model**: bacterial dynamics and immune response during TB infection

PK and PD Models

- PK data from non-infected subjects
- PK model outputs = RIF concentrations in extracellular (ELF) and intracellular (AC) lung compartments *(Goutelle)*



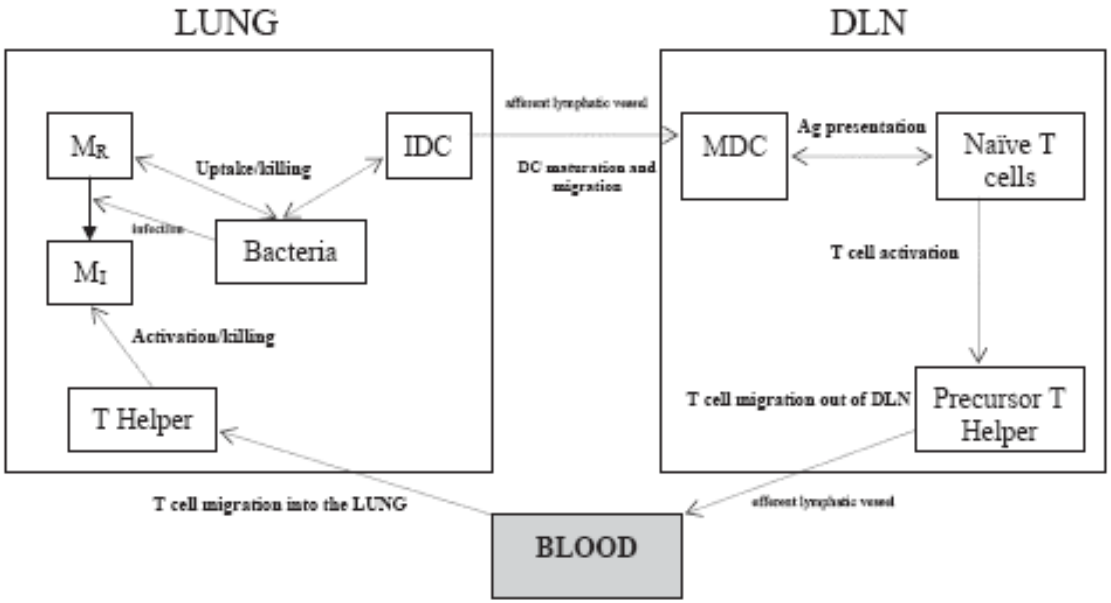
- PD model based on the Hill equation
- PD parameter values derived from experimental data *(Jayaram, Gumbo)*
- PD model outputs = number of intraC (BI) and extraC (BE) bacteria in lungs

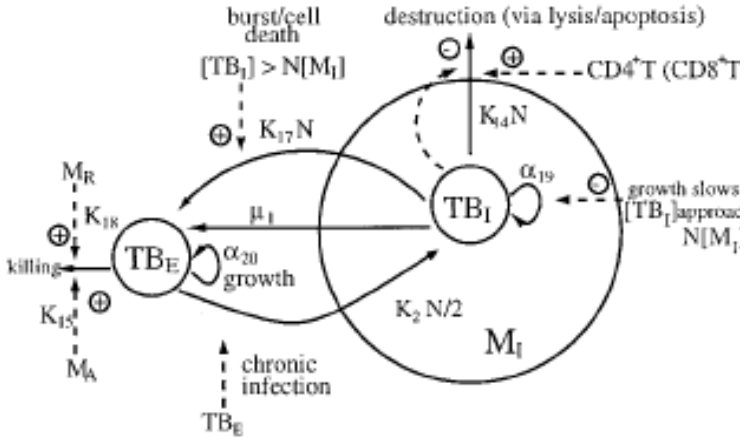
Goutelle et al. AAC 2009

Jayaram et al. Antimicrob Agents Chemother 2003
Gumbo et al. Antimicrob Agents Chemother 2007

Disease Model

- Mathematical model of the human immune response and bacterial dynamics during TB infection
- Previously published by Denise Kirschner's group (Michigan Univ)
- Lung and lymph node system
- Dynamics of cells, cytokines and two populations of bacteria (extraC and intraC)
- Can simulate *M. tuberculosis* growth in lungs from the first day of infection
- 17 ODE





"Conservative" B_I growth

From B_I to B_E (M_I-bursting)

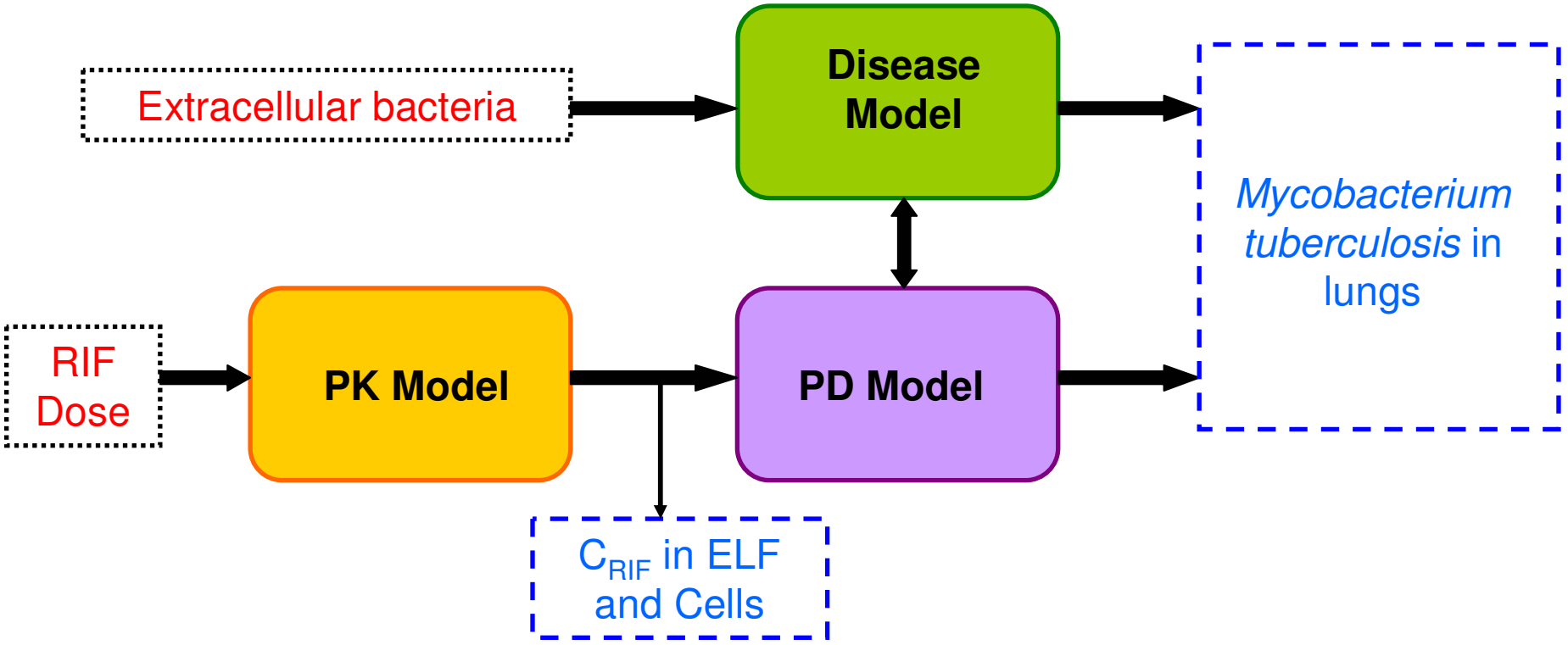
$$\frac{dB_I}{dt} = \alpha_{19} B_I \left(1 - \frac{B_I^m}{B_I^m + (NM_I)^m}\right) - k_{17} N M_I \left(\frac{B_I^m}{B_I^m + (NM_I)^m}\right) \qquad (1.12)$$

$$+ k_2 \left(\frac{N}{2}\right) M_R \left(\frac{B_E}{B_E + c_9}\right) - k_{14} N_1 M_I \left(\frac{\frac{T_1}{M_I}}{\frac{T_1}{M_I} + c_4}\right)$$

T-cell mediated killing

Wigginton et al. J Immunol 2001
Marino et al.J Theor Biol 2004

Full Model Building



Full Model Building

Extracellular bacterial dynamics

$$\frac{dB_E}{dt} = a_{20}B_E \cdot (1-\frac{B_E}{B_{E\max}}) \cdot (1-\frac{C_{ELF}^{\alpha_g}}{EC_{50g}^{\alpha_g} + C_{ELF}^{\alpha_g}}) - k_{k\max(E)} \frac{C_{ELF}^{\alpha_k}}{EC_{50k}^{\alpha_k} + C_{ELF}^{\alpha_k}} \cdot B_E$$

$$- k_{15}M_A B_E - k_{18}M_R B_E + k_{14}N_1 M_I (\frac{T_1/M_I}{T_1/M_I + c_4})$$

$$+ k_{17}NM_I (\frac{B_I^m}{B_I^m + (NM_I)^m}) - k_2 (\frac{N}{2}) M_R (\frac{B_E}{B_E + c_9}) - d_{12}B_E IDC$$

PK model outputs

PD model

Immune response model

Intracellular bacterial dynamics

$$\frac{dB_I}{dt} = a_{19}B_I \cdot (1-\frac{B_I^m}{B_I^m + (NB_I)^m}) \cdot (1-\frac{C_{CELL}^{\alpha_g}}{EC_{50g}^{\alpha_g} + C_{CELL}^{\alpha_g}}) - k_{k\max(I)} \frac{C_{CELL}^{\alpha_k}}{EC_{50k}^{\alpha_k} + C_{CELL}^{\alpha_k}} \cdot B_I$$

$$- k_{17}NM_I (\frac{B_I^m}{B_I^m + (NM_I)^m}) + k_2 (\frac{N}{2}) M_R (\frac{B_E}{B_E + c_9})$$

$$- k_{14}N_1 M_I (\frac{T_1/M_I}{T_1/M_I + c_4})$$

Model Features and Settings

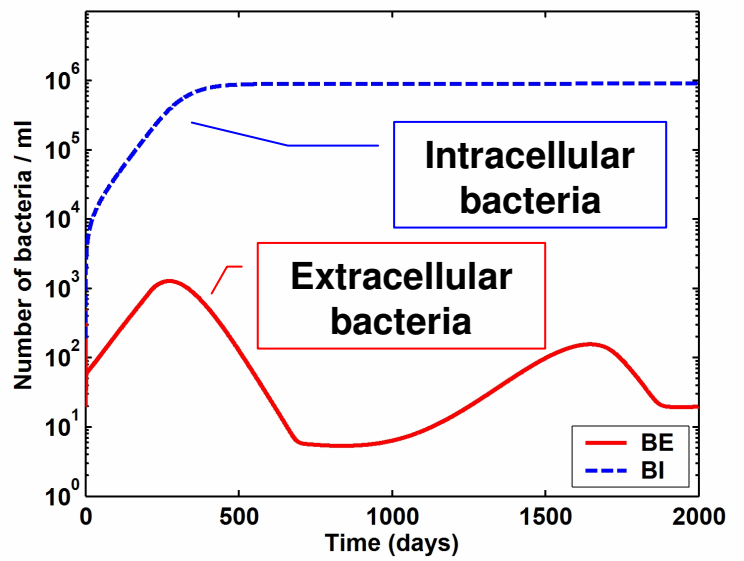
- System of 21 ODE solved in Matlab®
- Therapeutic simulations up to 6 months
- For each simulation, 2 successive periods:
  - No drug therapy: disease model only – no variability
  - RIF therapy: individual PK parameters from the PK study – various PK/PD profiles (n=34)
- Bacterial dynamics from Day 1 of infection to the last day of RIF therapy

Analysis of the Results

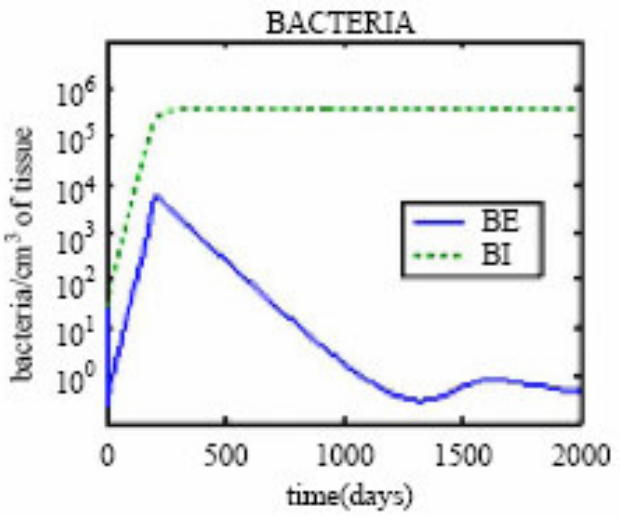
- Reproduction of Kirschner's model
- Qualitative analysis: shape of time-kill curves
- Quantitative analysis:
  - bactericidal activities (BE) simulated over the first days for various dosage regimens
  - comparison with clinical data = Early Bactericidal Activities (EBA)

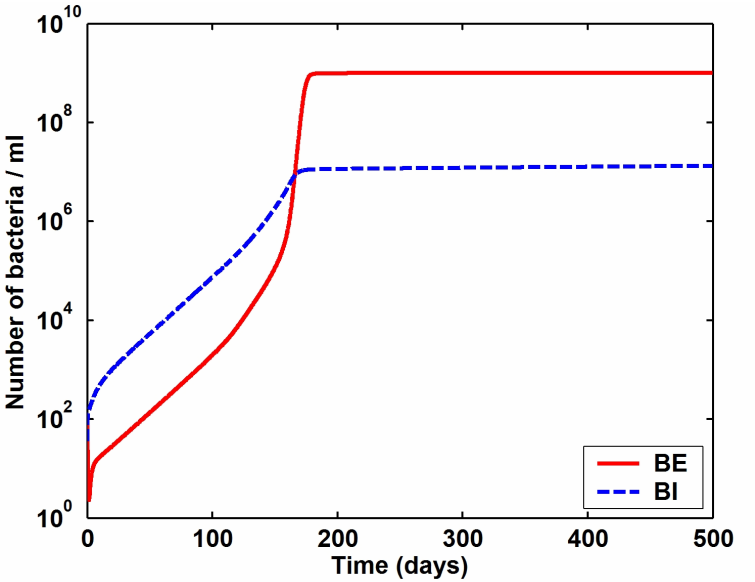
$$EBA\ (0-2j) = \frac{\log_{10} N_{(0)} - \log_{10} N_{(2)}}{2}$$

Simulations With No Drug

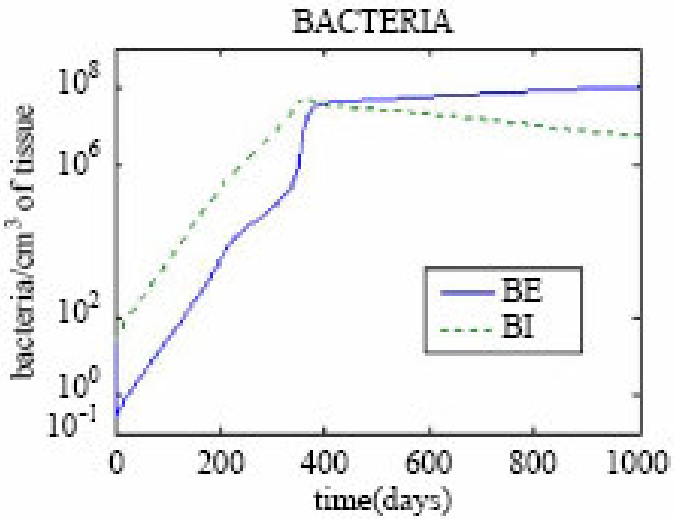


Latent TB





Active Disease



Marino et al.J Theor Biol 2004

Simulations with Rifampin

Disease model

No drug

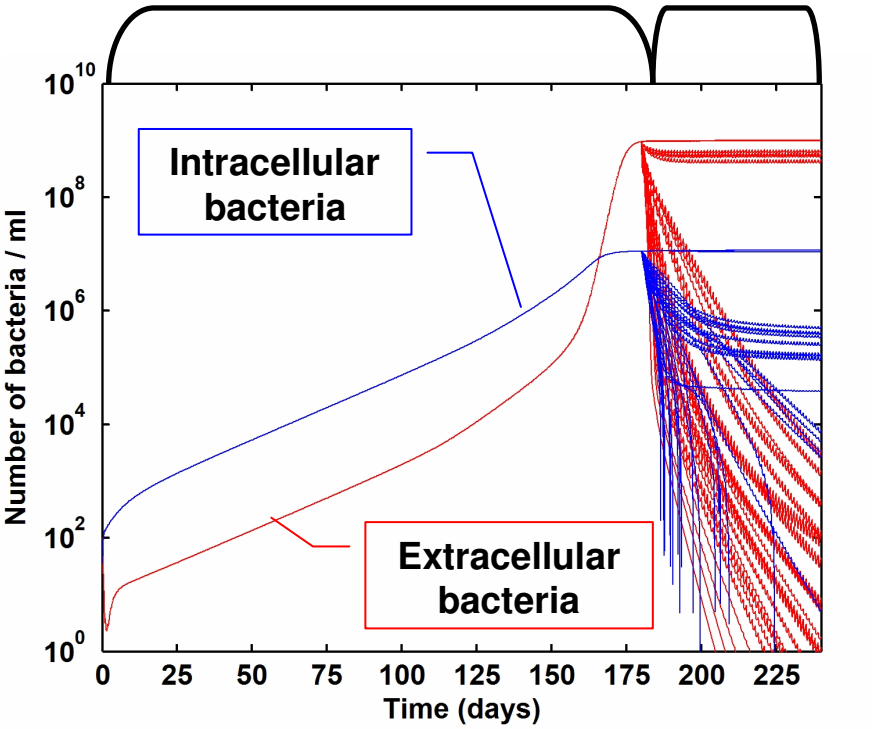
180 days

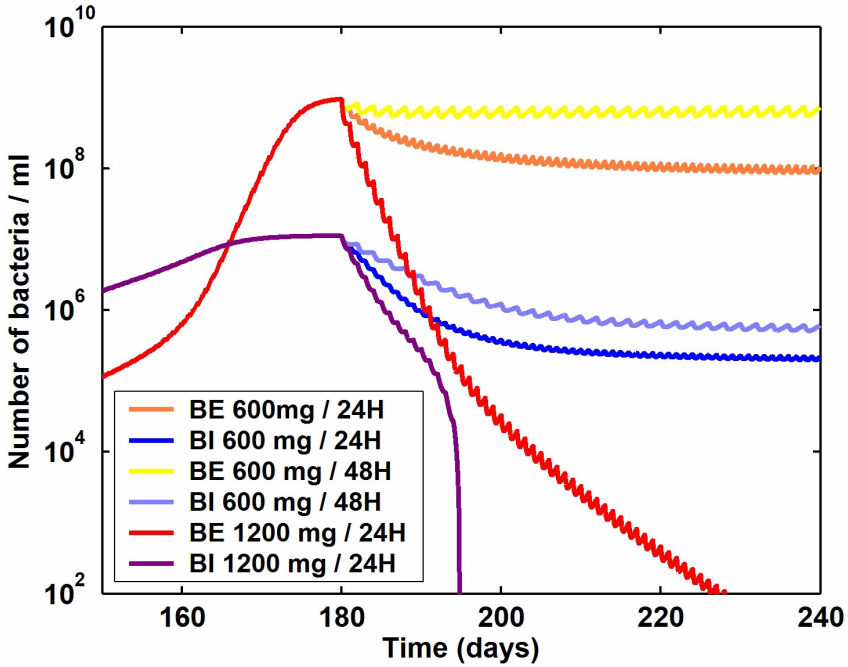
RIF 600 mg

60 days

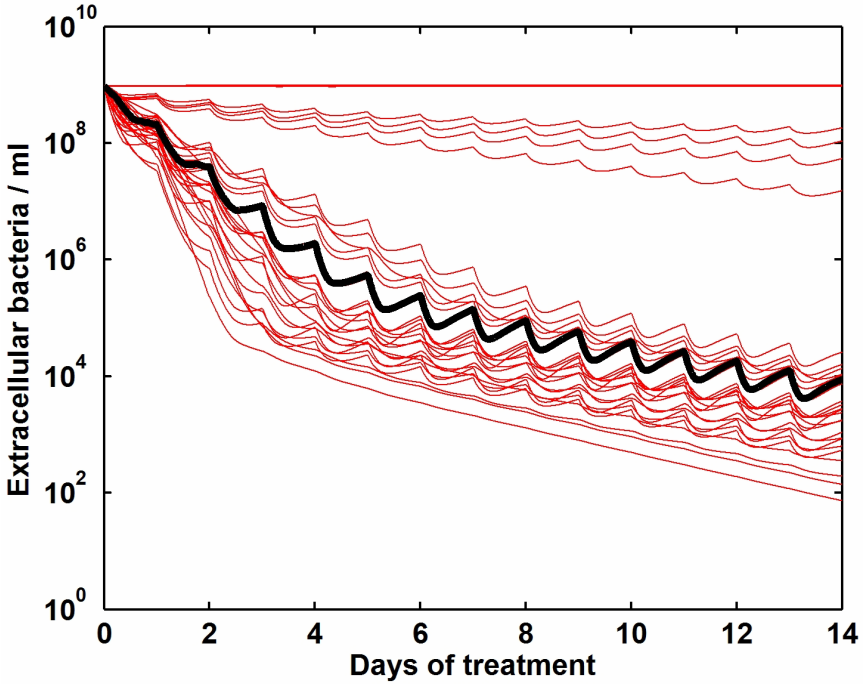
34 subjects

Median effect of various RIF dosage regimens





Antibacterial Effect



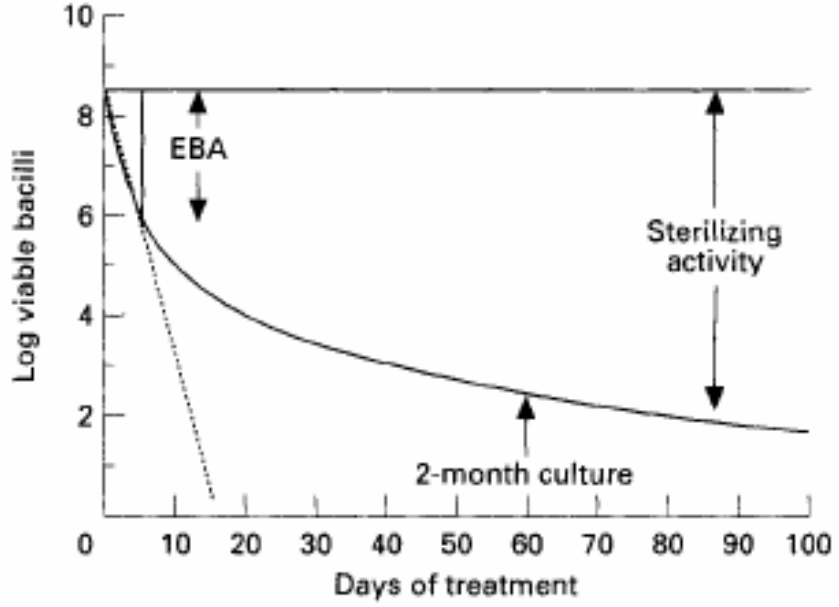


Fig. 1 Counts of viable tubercle bacilli in sputum during treatment

- Model shows a biphasic decline of B_E: killing slows down between days 2-10
- This result is in agreement with clinical data
- The biphasic shape of EBA has not been elucidated yet

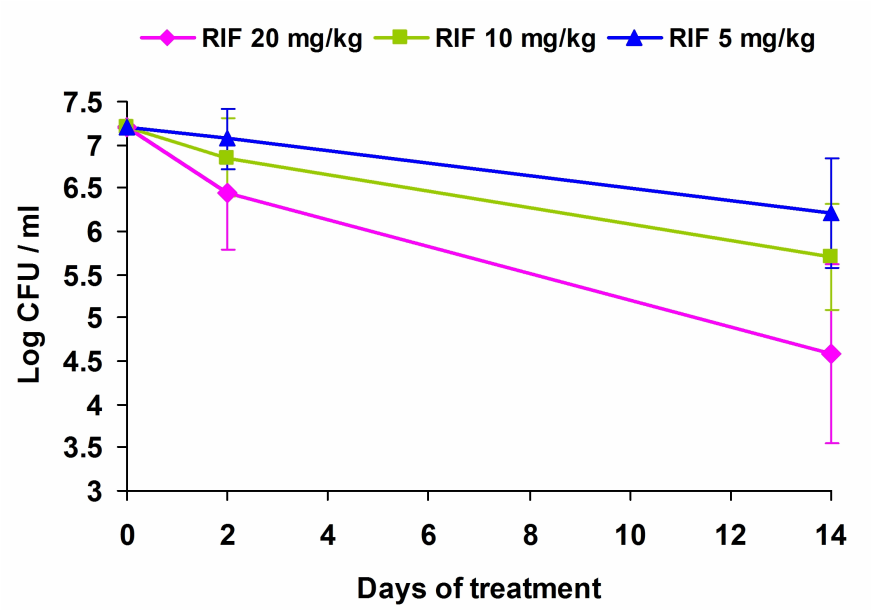
Mitchison. J Applied Bacteriol 1996;81:72S-80S

Antibacterial Effect

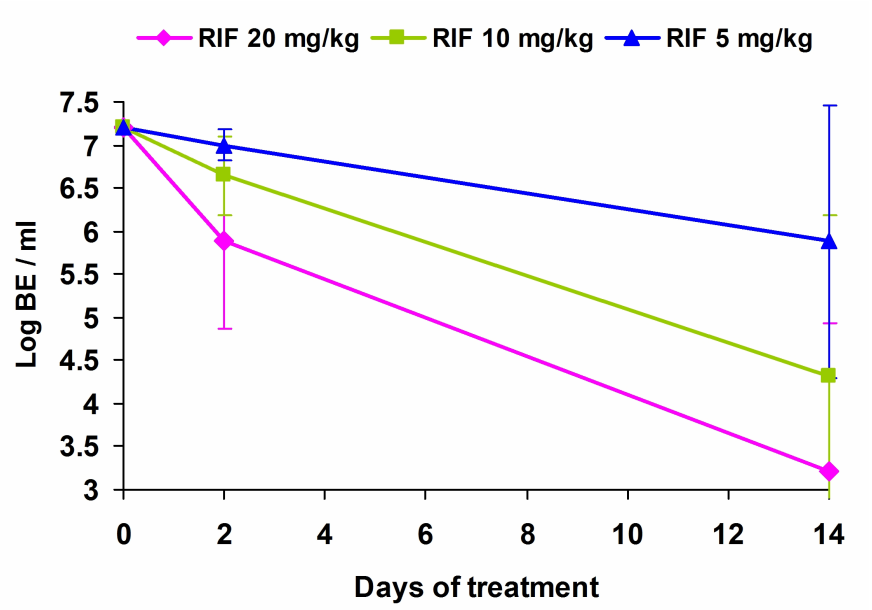
RIF dose	Period	Bactericidal activities simulated (log_{10} B_E /ml/j) Mean (SD)	EBA reported in literature	
			Mean (SD)	Référence
300 mg or 5 mg /kg	0-2 j	**0.102 (0.090)**	**0.121 (0.130)**	Sirgel *et al.* (2005)
	0-5 j	**0.117 (0.156)**	**0.111 (0.072)**	Sirgel *et al.* (2005)
	2-14 j	**0.093 (0.132)**	**0.072 (0.052)**	Jindani *et al.* (1980, 2003)
600 mg or 10 mg/kg	0-2 j	**0.277 (0.229)**	**0.174 (0.228)** **0.221 (0.247)** **0.29 (0.30)** **0.28 (0.21)**	Jindani *et al.* (1980, 2003) Sirget *et al.* (2005) Chan *et al.* (1992) Gosling *et al.* (2003)
	0-5 j	**0.302 (0.279)**	**0.226 (0.144)**	Sirgel *et al.* (2005)
	2-14 j	**0.194 (0.156)**	**0.096 (0.051)**	Jindani *et al.* (1980, 2003)
1200 mg or 20 mg/kg	0-2 j	**0.659 (0.512)**	**0.383 (0.326)** **0.44 (0.24)**	Jindani *et al.* (1980, 2003) Diacon *et al.* (2007)
	0-5 j	**0.537 (0.372)**	**0.30 (0.11)**	Diacon *et al.* (2007)
	2-14 j	**0.222 (0.142)**	**0.154 (0.086)**	Jindani *et al.* (1980, 2003)

Antibacterial Effect

EBA from Jindani (2003) (n=8)



Simulated Killing effect (n=34)



- The simulated antibacterial effects are in agreement with EBA data for low RIF doses (300, 600 mg)
- The model seems to overestimate the effect of high RIF doses (1200 mg)

Jindani et al. Am J Resp Crit Care Med 2003

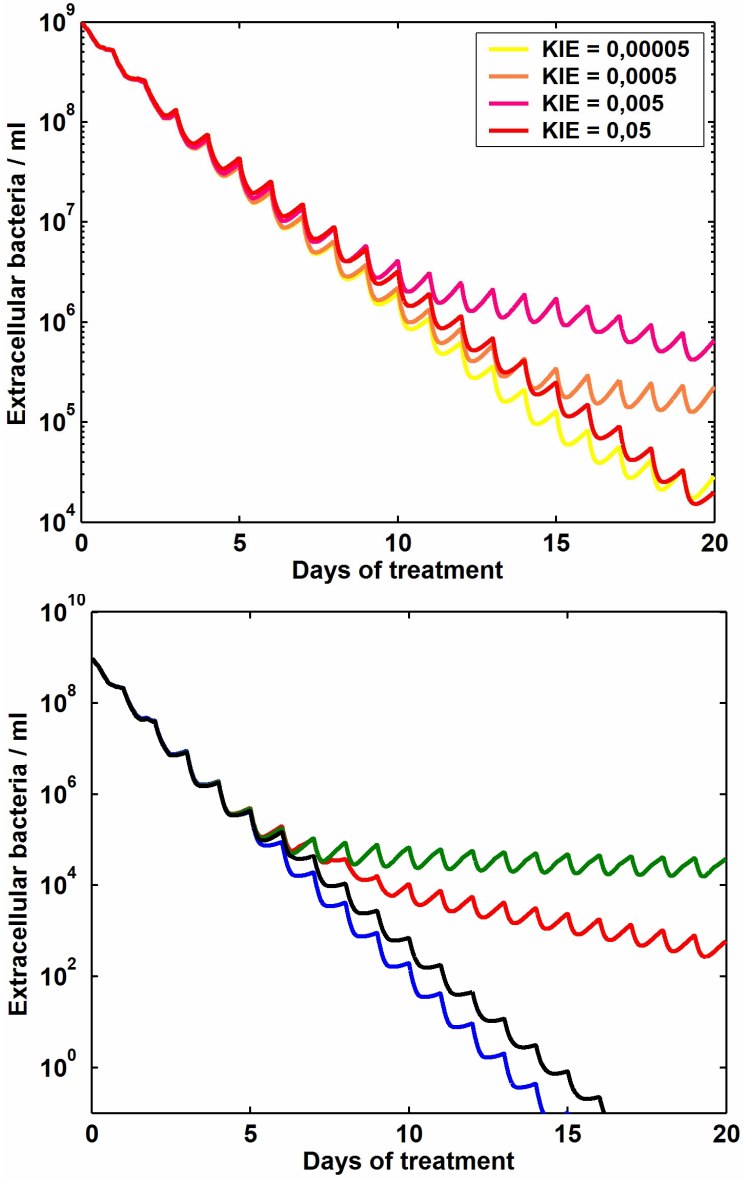
Model Reduction

- Model reduction was explored with 2 objectives:
  - To assess the relevance of the full model
  - To analyse the factors conditionning the shape of the killing effect
- PK/PD model with no disease model
- Simulation under various assumptions:
  - Exchange or no exchange between BE and BI
  - Concentration / effect parameters identical or different between extraC and intraC compartments

$$\frac{dB_E}{dt} = a_{20} B_E \left(1 - \frac{B_E}{B_{E\max}}\right)\left(1 - \frac{C_1^{\alpha_g}}{EC_{50g}^{\alpha_g} + C_1^{\alpha_g}}\right) - k_{k\max(E)} \frac{C_1^{\alpha_k}}{EC_{50k}^{\alpha_k} + C_1^{\alpha_k}} \cdot B_E$$

$$- k_{EI} B_E + k_{IE} B_I$$

Insights from Model Reduction



- Intercomparment transfer rate constants KEI and KIE influence the shape of the killing effect
- **No biphasic killing** observed when:
  - No exchange between BE and BI, kEI = kIE = 0, (blue curve)
  - Similar PD effect of RIF in extraC and intraC compartment, Kkmax(E) = Kkmax(I), (black curve)
  - fast transfer from intraC to extraC compartment (high values of KIE)

A New Hypothesis

- 2 hypothesis have been proposed to explain the slow down of the antibacterial effect and the requirement for long therapy *in vivo*
  - **Persistent** subpopulations of bacilli
  - Genetically **resistant** subpopulations
- No such special populations included in the model
- A new hypothesis: role of a protected / reservoir compartment of intracellular bacteria (Antia 1996)
- In the simulations, this reservoir appears to be due to:
  - Reciprocal transfer between BE and BI
  - Slow transfer from intraC to extraC compartment
  - Drug less effective in intraC conditions (PD parameters)

Antia Proc R Soc Lob B 1996

Conclusion and Perspective

- A very preliminary effort towards a complete mathematical description
- Many limits / assumptions:
  - Only one anti-TB drug
  - PD data from in vitro / animal studies
  - No PD variability
  - No drug resistant subpopulation
  - No post antibiotic effect
  - No autoinduction

- The model is able to reproduce some qualitative and quantitative properties of the effect of RIF observed in human TB patients
- A descriptive tool to study, analyse and explore complex drug-pathogen-host interactions during TB infection