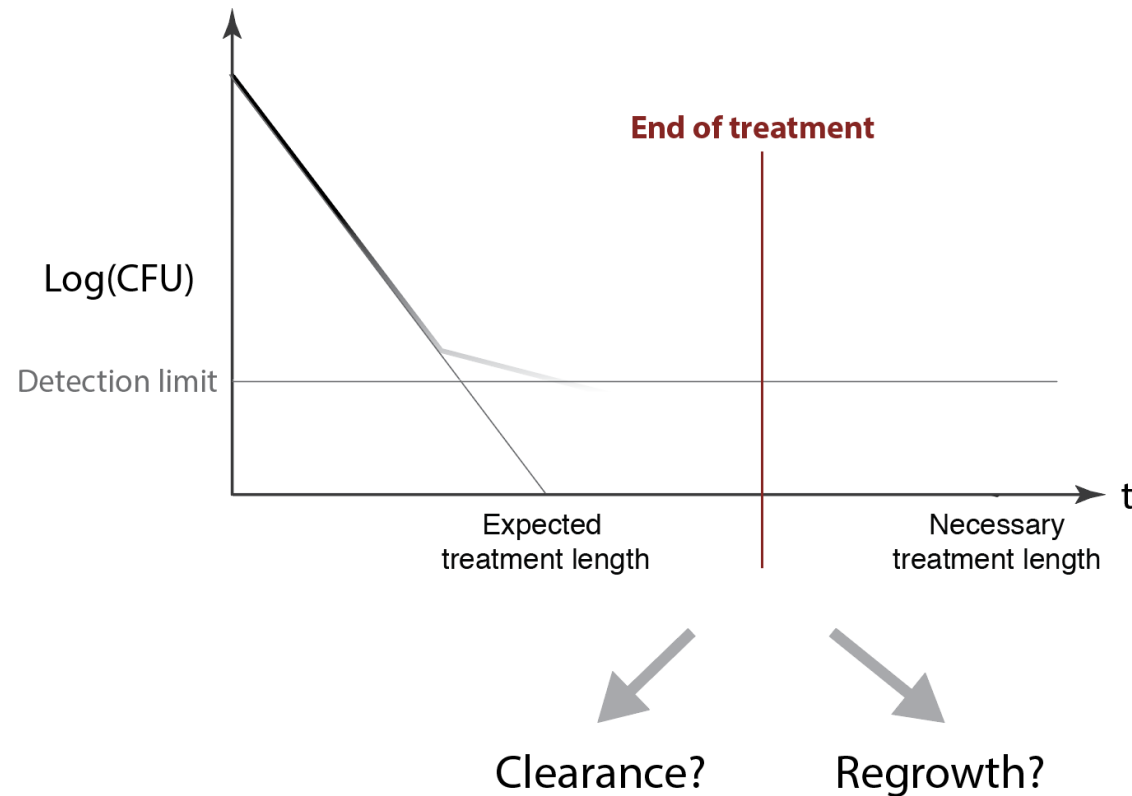


High peak rifampicin concentrations accelerate the slow phase of bacterial elimination in tuberculosis patients

Antal Martinecz, Martin J. Boeree, Andreas H. Diacon, Rodney Dawson, Rob E. Aarnoutse, Pia Abel zur Wiesch

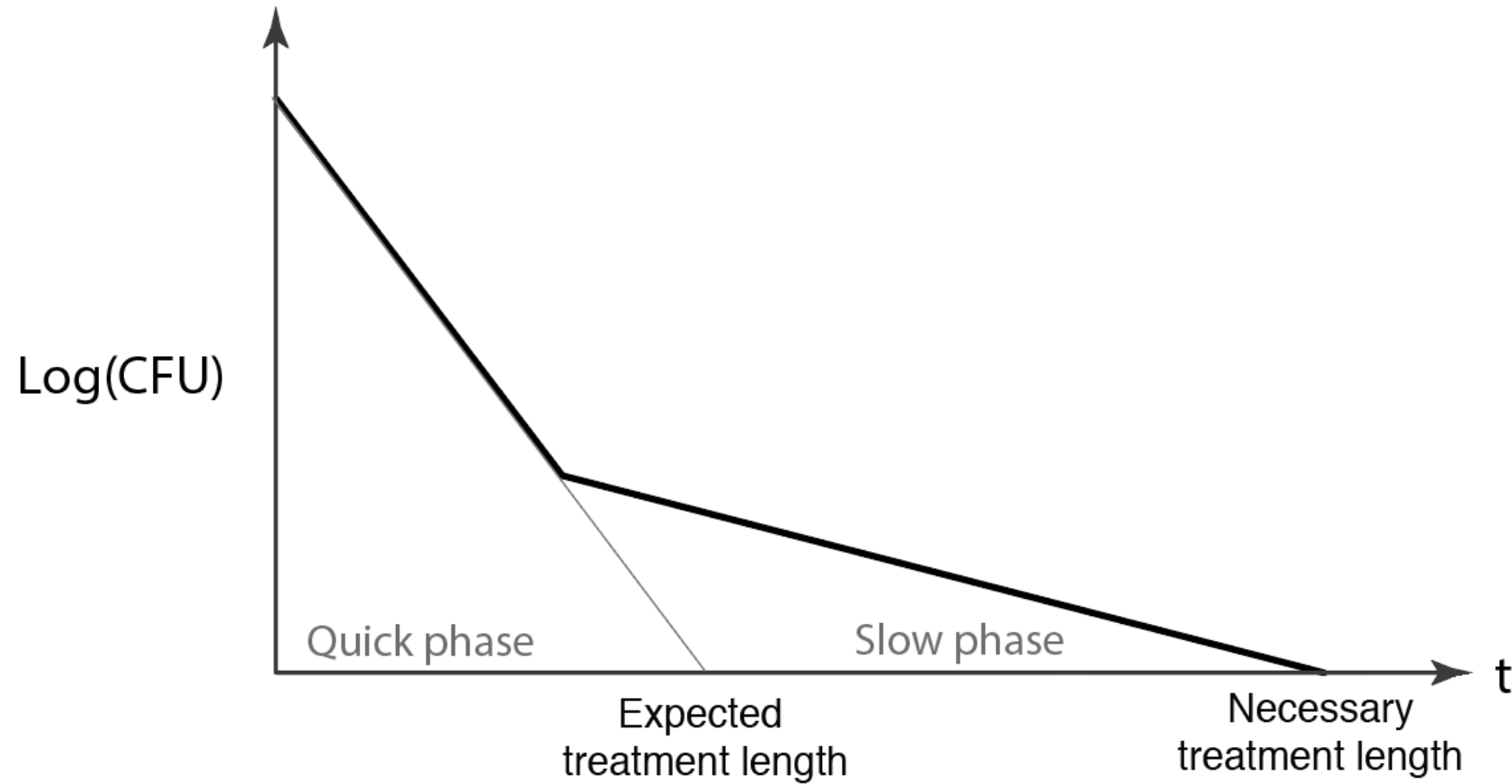


The dataset (NCT01392911)

- EBA trial with 78 TB patients
- 14 days
- Rifampicin in 10,20,30,35,40 mg/kg doses
 - Monotherapy for days 1-7
 - Combination therapy for days 7-14 (isoniazid, pyrazinamide, and ethambutol)

Boeree MJ, Diacon AH, Dawson R *et al.* A dose-ranging trial to optimize the dose of rifampin in the treatment of tuberculosis. *Am J Respir Crit Care Med* 2015

The elimination of bacteria slows down over time, this can be mitigated by higher rifampicin concentrations¹⁻³. How do PK parameters affect this?



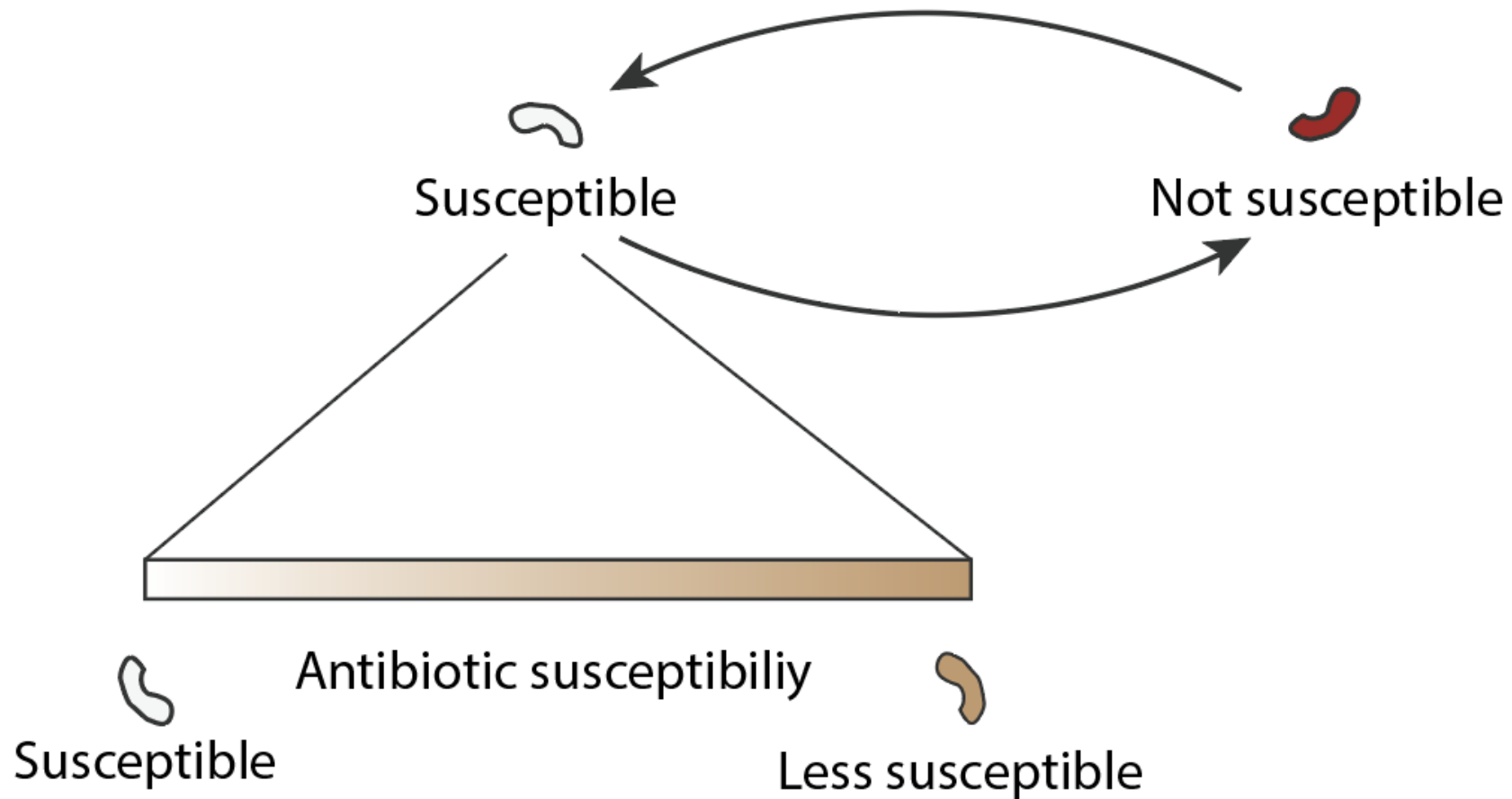
1 Hu, Y. *et al. Front. Microbiol.* (2015)

2 Chigutsa, E. *et al. Antimicrob. Agents Chemother.* (2015)

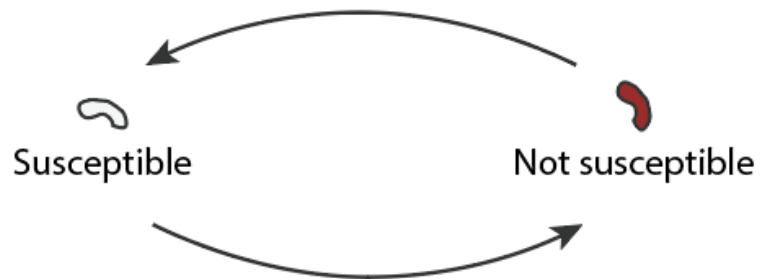
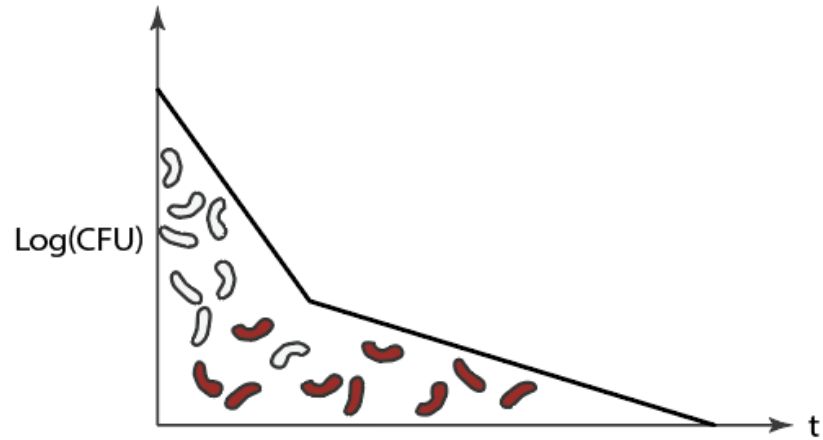
3 Svensson, R. J. *et al. Clin. Pharmacol. Ther.* (2018)

Expectations based on mathematical models

To understand how PK parameters affect the slow phase we have to look at the possible (not mutually exclusive) causes of it



Switching back and forth between a completely non-susceptible (dormant) and susceptible state can cause a slowdown in the elimination



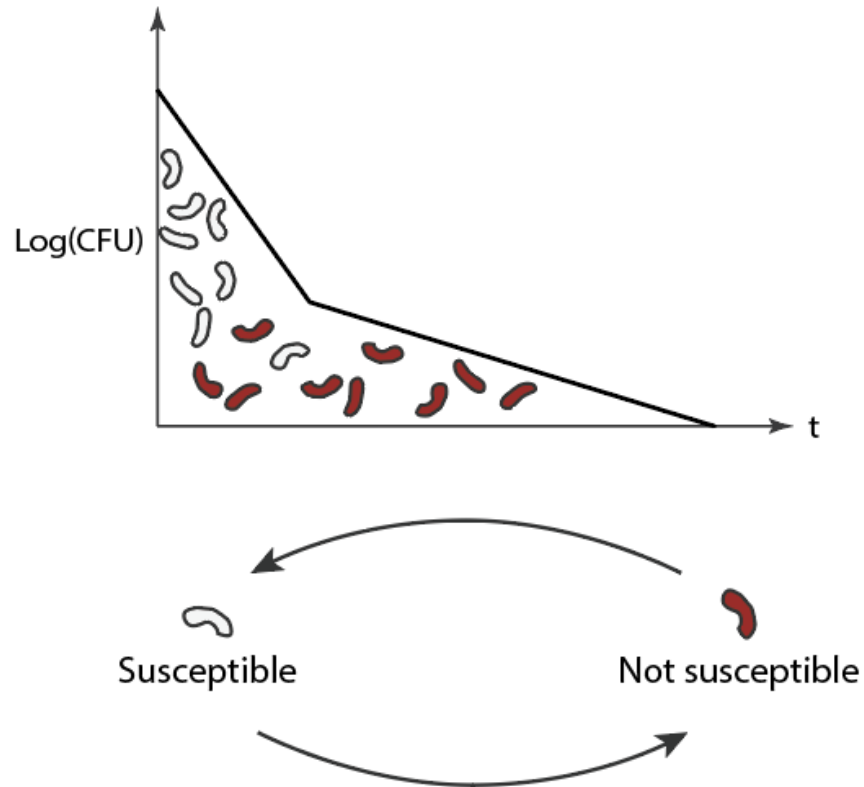
1 Boshoff, H. I. M. *et al. Nat. Rev. Microbiol.* (2005)

2 Hoff, D. R. *et al. PLoS One*, (2011)

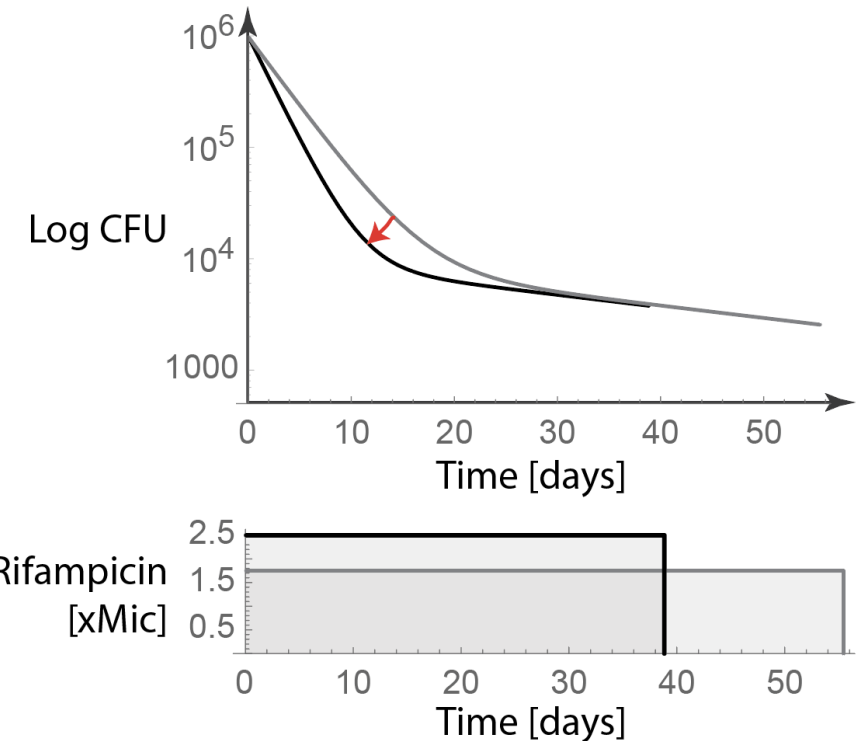
3 Chao, M. C. *et al. Annu. Rev. Microbiol.* (2010)

Figure adapted from: Horsburgh, C. R. *et al. N. Engl. J. Med.* (2015)

Switching back and forth between a completely resistant (dormant) and susceptible state can cause a slowdown in the elimination



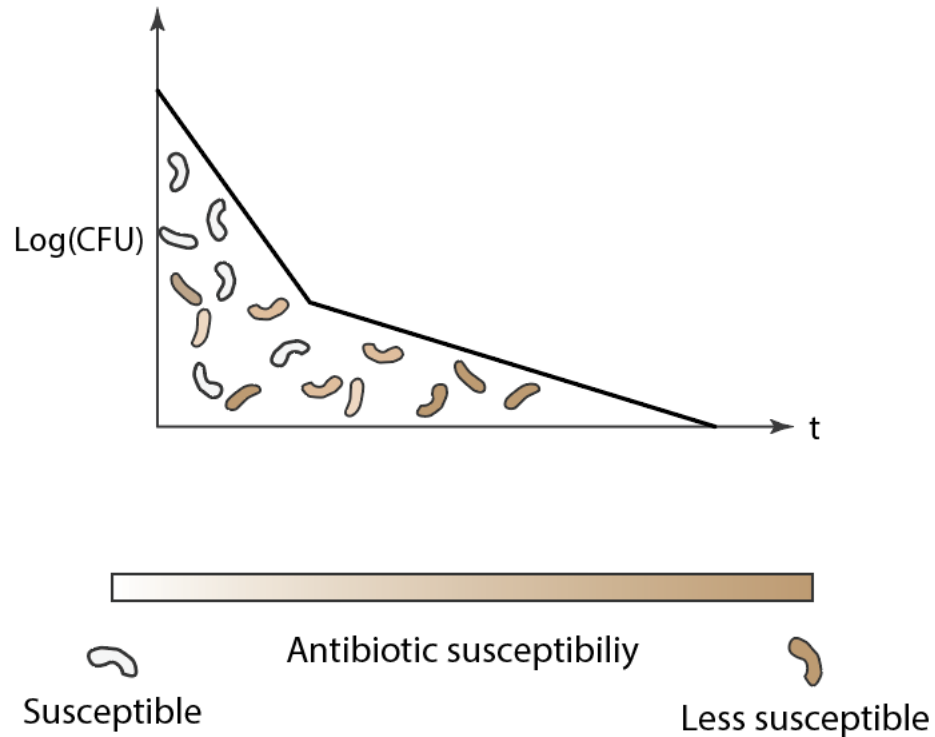
Response to an increase in c_{Max}



- 1 Boshoff, H. I. M. *et al. Nat. Rev. Microbiol.* (2005)
 - 2 Hoff, D. R. *et al. PLoS One*, (2011)
 - 3 Chao, M. C. *et al. Annu. Rev. Microbiol.* (2010)
- Figure adapted from: Horsburgh, C. R. *et al. N. Engl. J. Med.* (2015)

- Plots made using data from:
- 4 Cadosch, D. *et al. PLoS Comput. Biol.* (2016)
 - 5 Hu, Y. *et al. Front. Microbiol.* (2015)
 - 6 de Steenwinkel, J. E. M. *et al. J. Antimicrob. Chemother.* (2010)

Pre-existing heterogeneities in the susceptibility within the population without switching can also cause a slowdown in the elimination¹



1 Abel zur Wiesch, P. *et al. Sci. Transl. Med.* (2015)

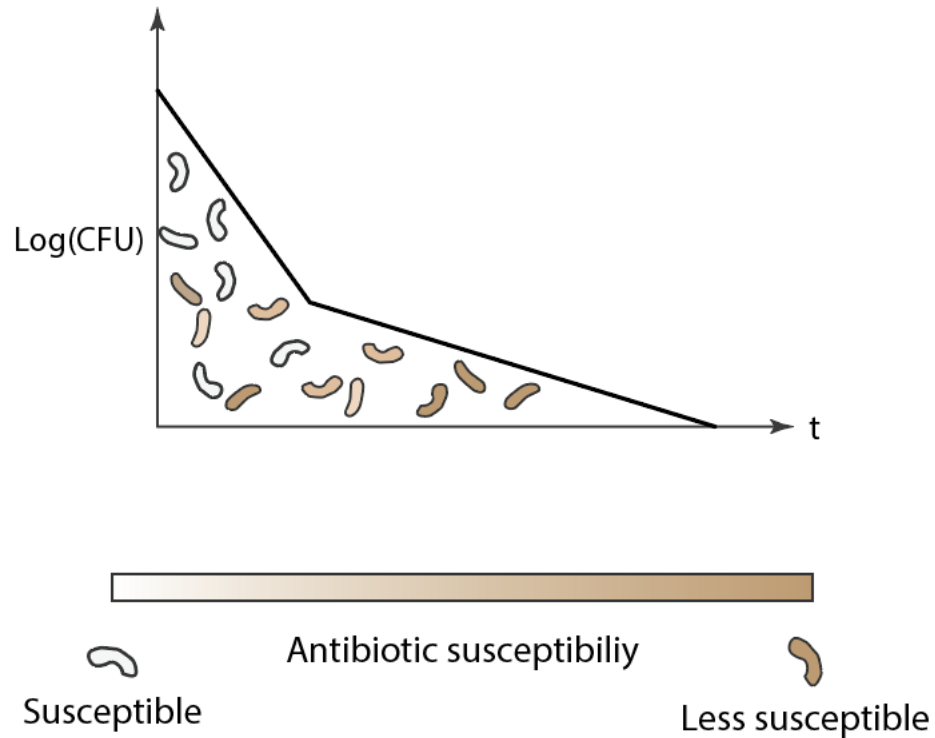
Shown to exist in mycobacteria in:

2 Wakamoto, Y. *et al. Science* (2013)

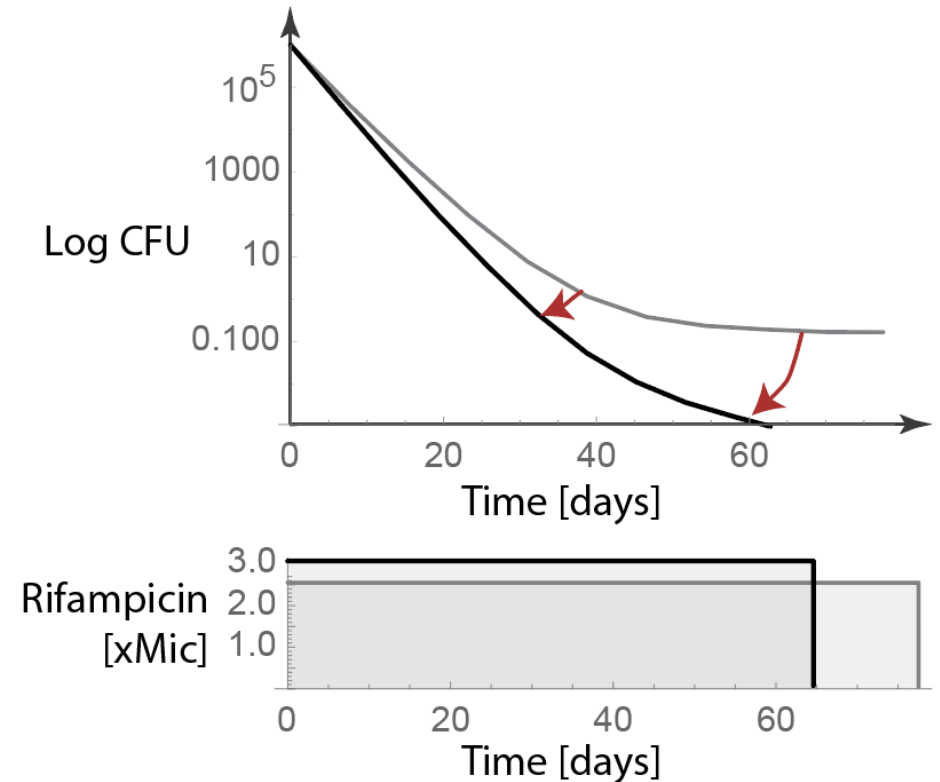
3 Rego, E. H. *et al. Nature* (2017)

4 Aldridge, B. B. *et al. Science* (2012)

Pre-existing heterogeneities in the susceptibility within the population without switching can also cause a slowdown in the elimination



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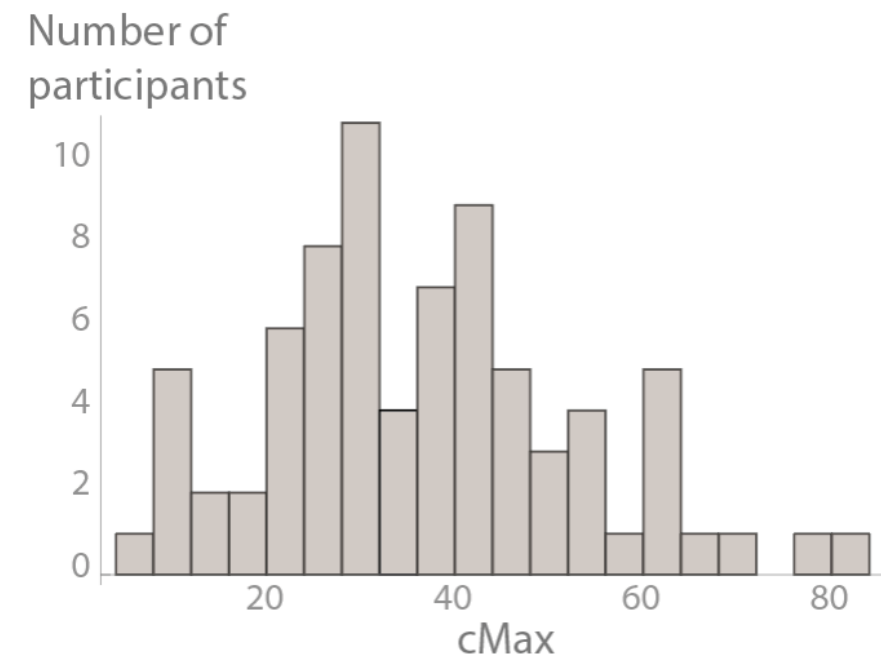
5 Hu, Y. *et al. Front. Microbiol.* (2015)

6 de Steenwinkel, J. E. M. *et al. J. Antimicrob. Chemother.* (2010)

Analysis of clinical trial data

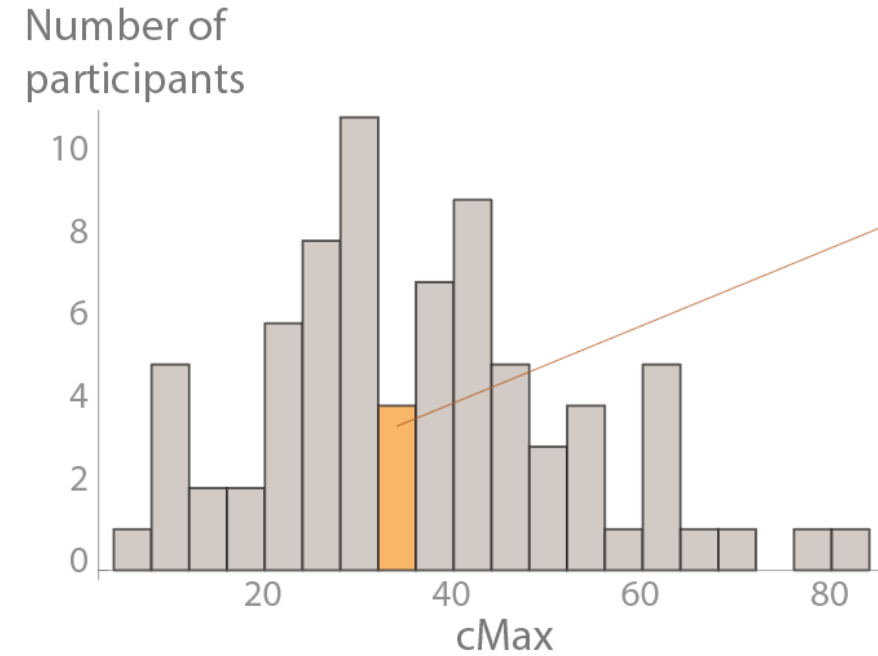
First, we grouped participants together based on their PK measurements

A Histogram of cMax values

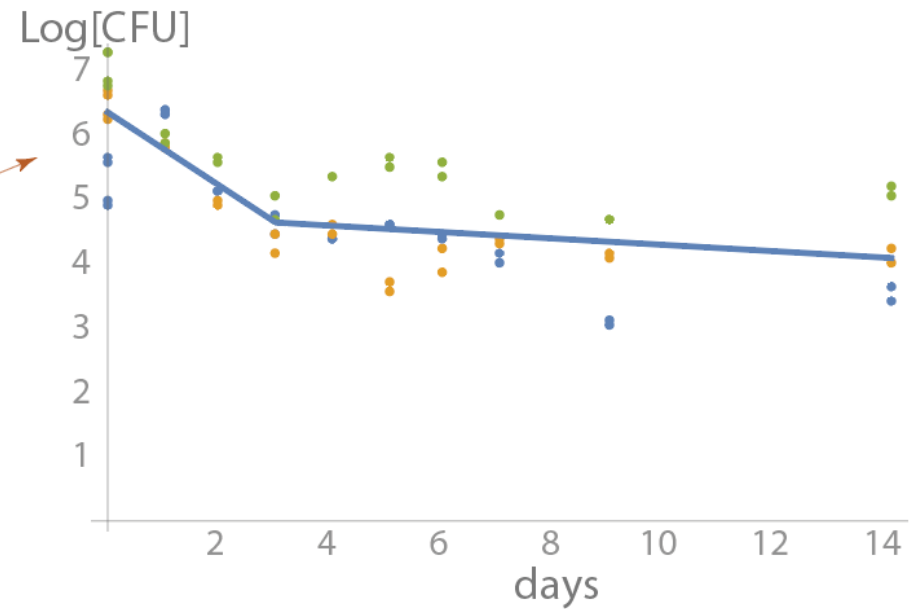


Next, we have fitted biphasic kill curves to the bacterial count measurements

A Histogram of cMax values

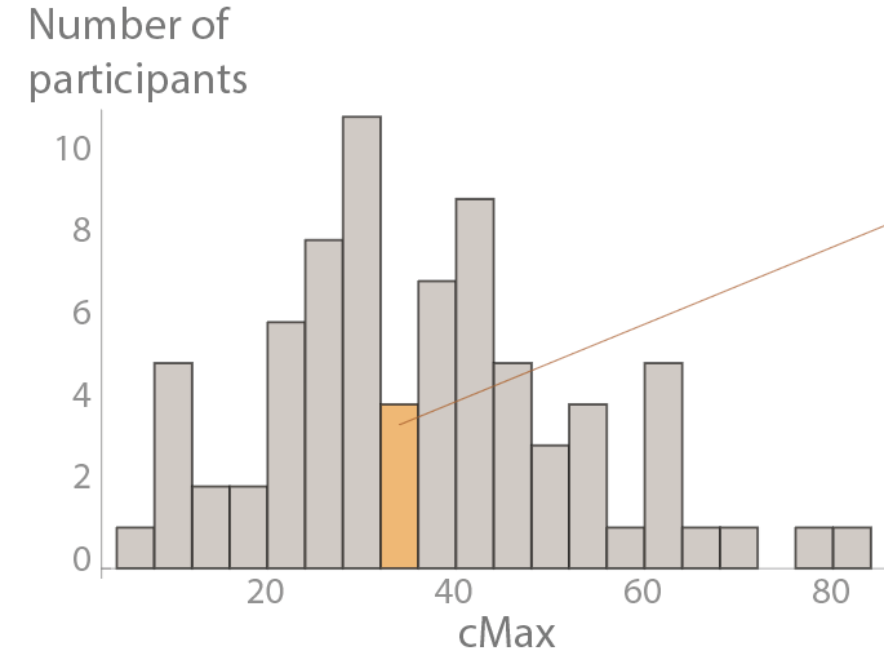


B Measured Log[CFU] for all participants grouped by cMax values

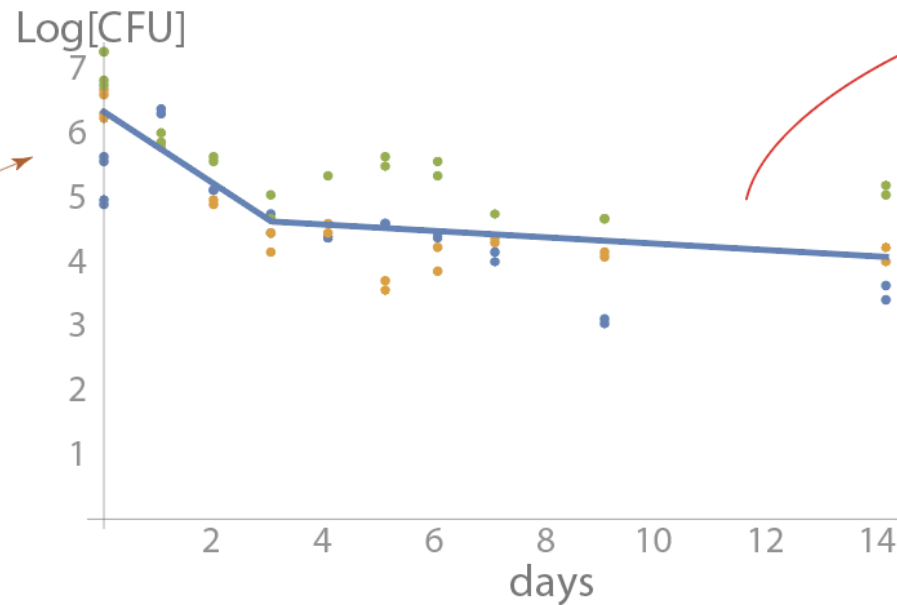


Finally, we plotted the properties of the fitted curves against the PK measures

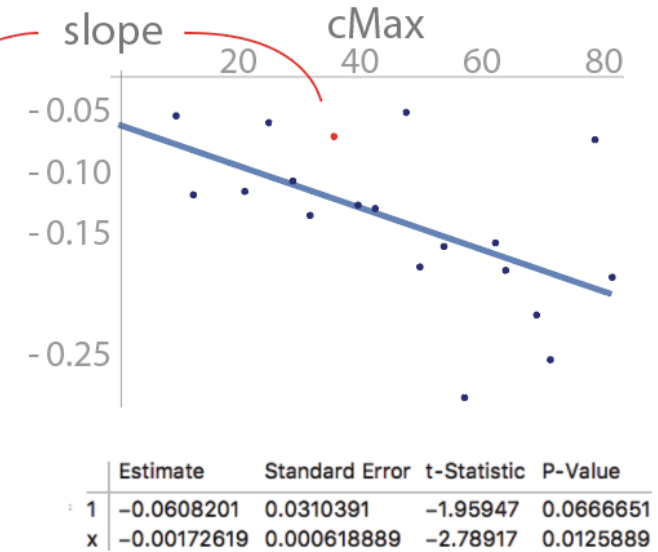
A Histogram of cMax values



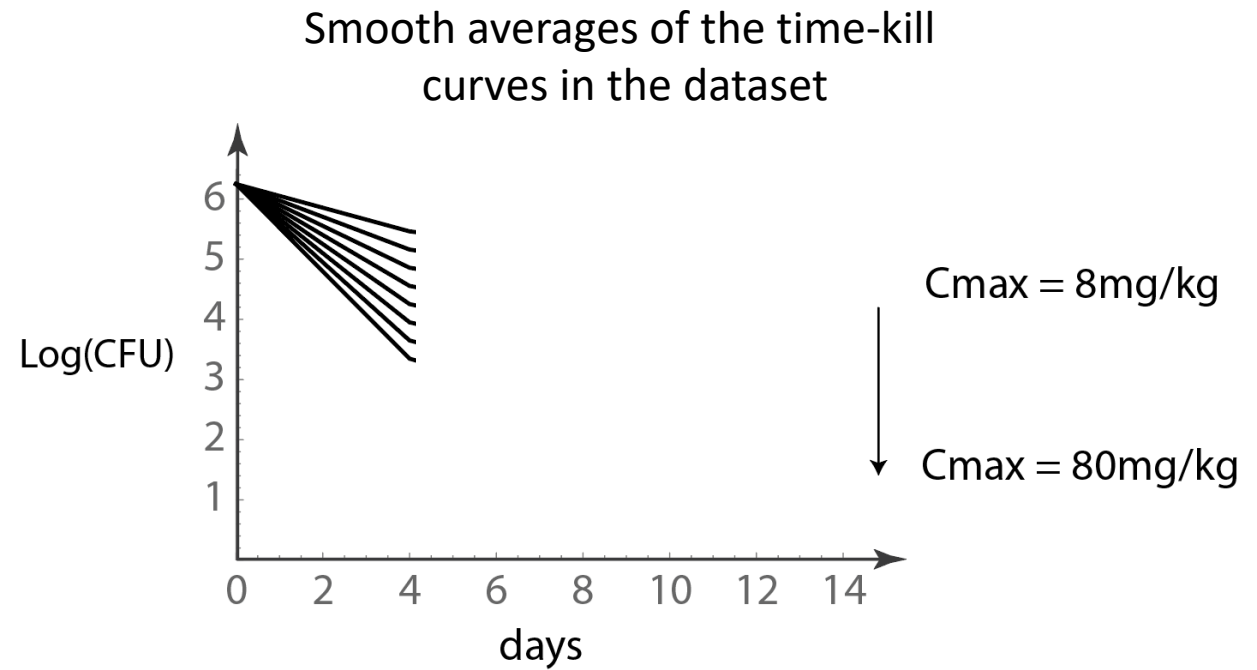
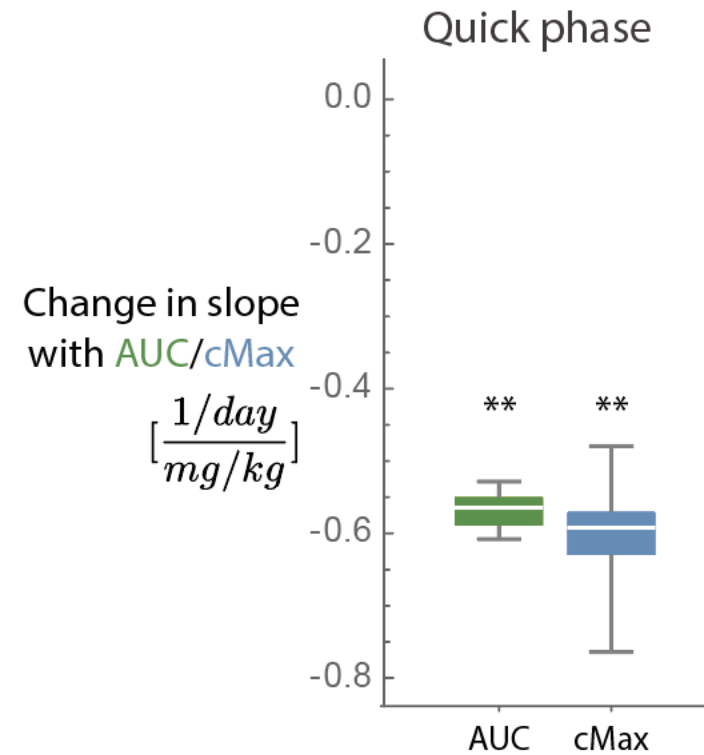
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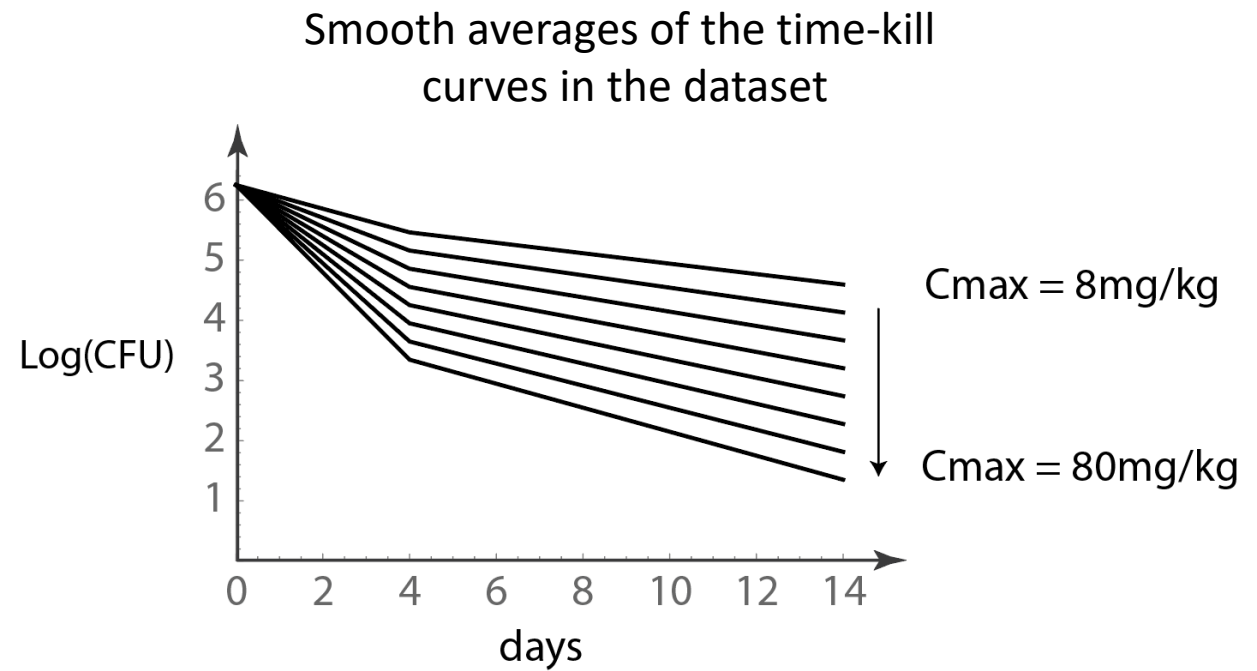
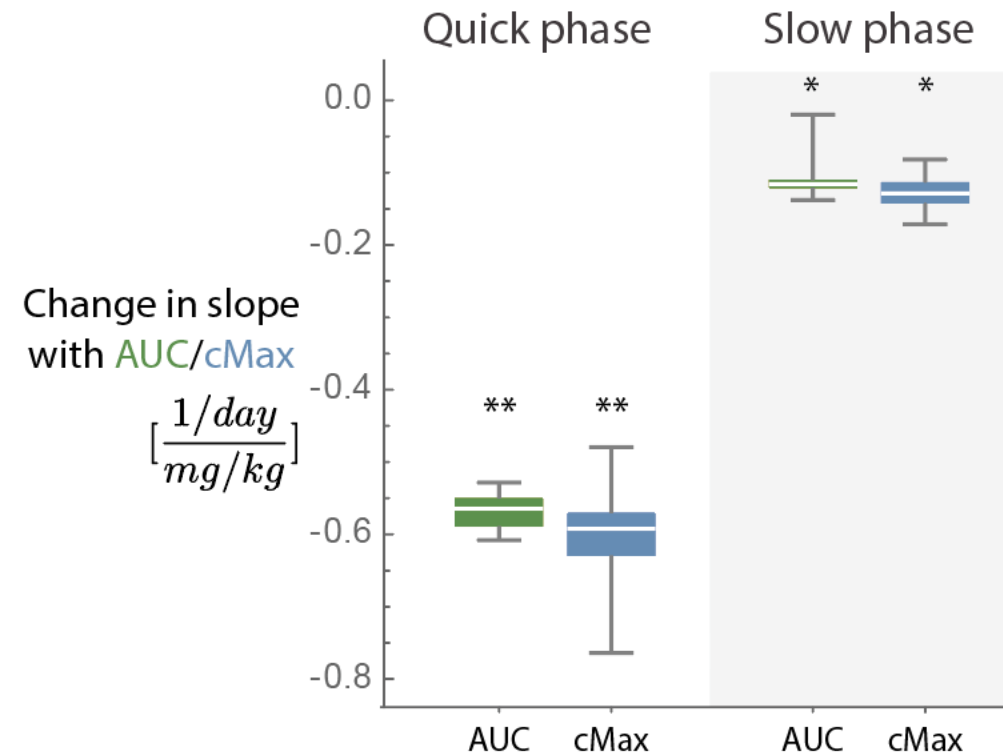
C Slope of the slow phase for each group (by cMax)



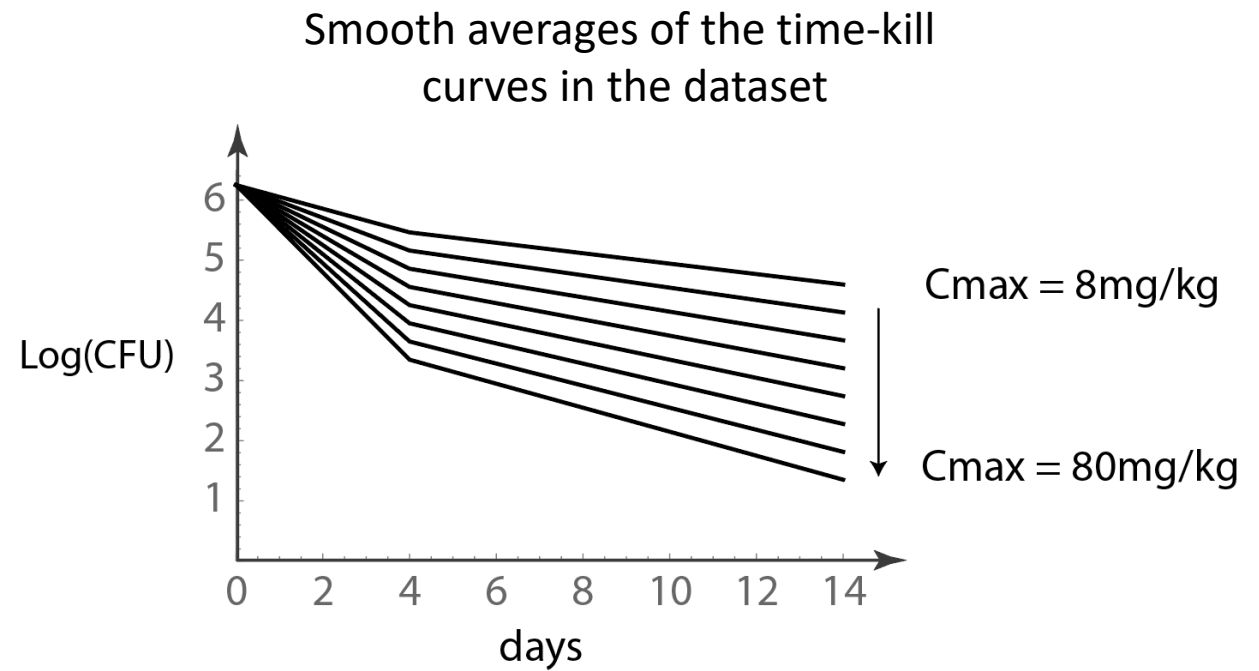
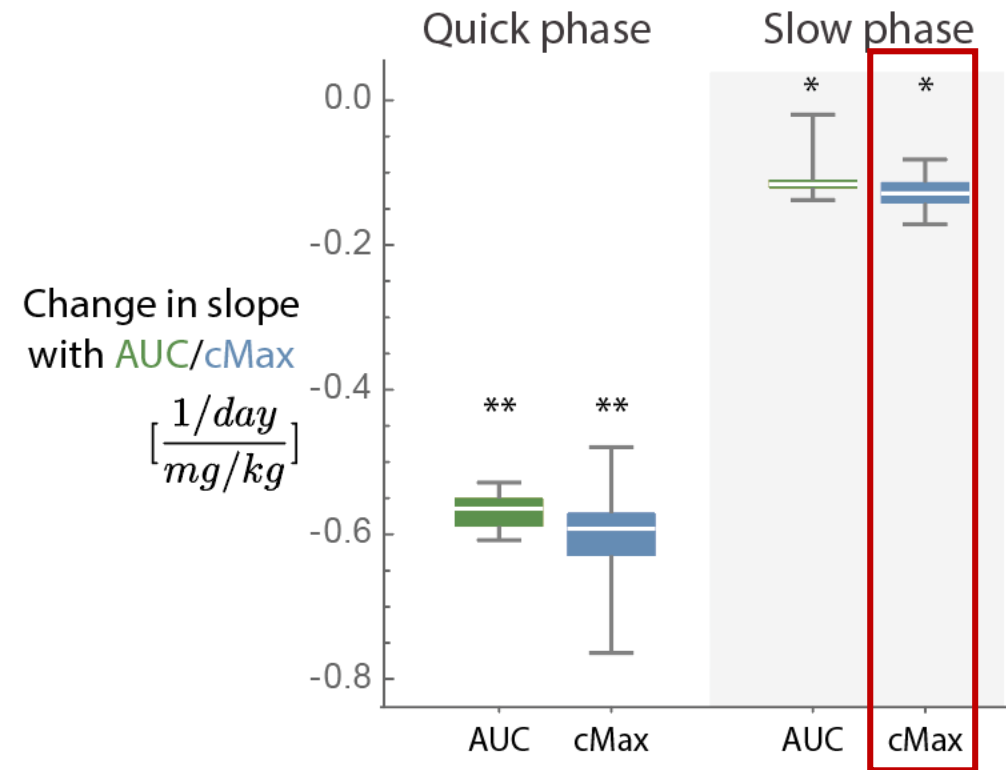
High peak concentrations of rifampicin accelerate the slow phase of bacterial elimination



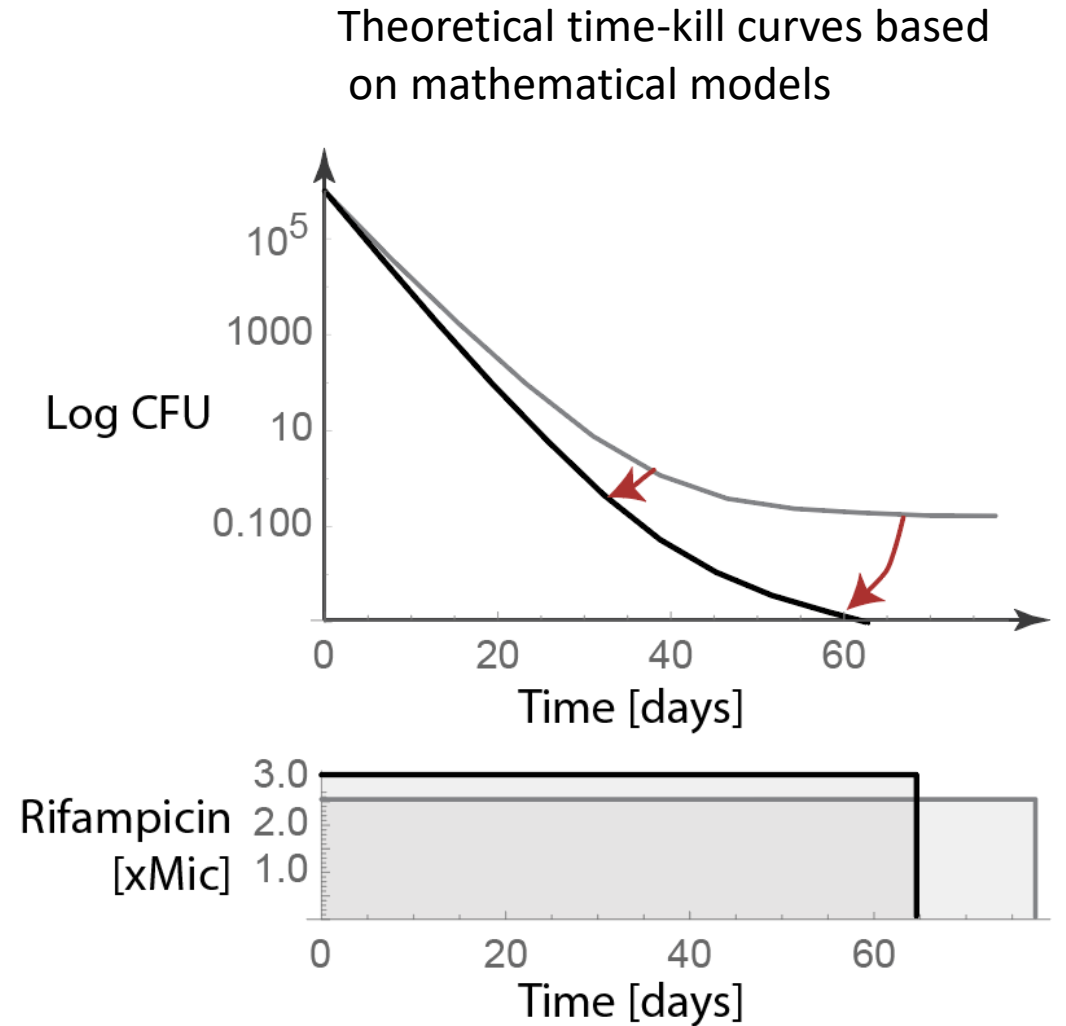
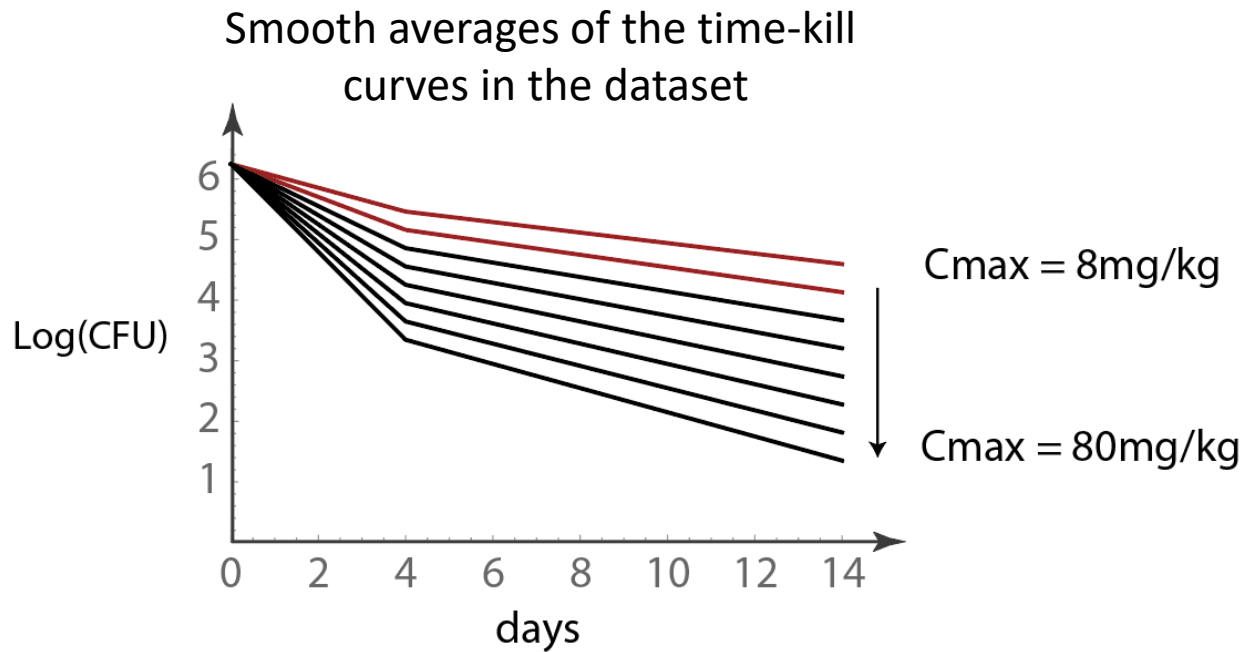
High peak concentrations of rifampicin accelerate the slow phase of bacterial elimination



High peak concentrations of rifampicin accelerate the slow phase of bacterial elimination



Pharmacokinetic parameters can affect bacterial loads at the end of trial (14 days), therefore possibly the chance of relapse



Thank you for your attention

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