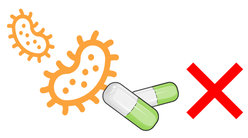
Quantifying the impact of infection on murine antibiotic exposure in the framework of non-conventional treatment modalities within the FAIR study

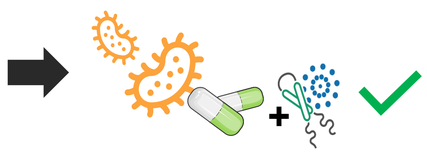
M.S.R. Happ (1,2), L.B.S. Aulin (1), M. Mondemé (3), M. Baldry (3), W. Huisinga (4), C. Faveeuw (3), J.-C. Sirard (3), C. Kloft (1) and R. Michelet (1)

(1) Department of Clinical Pharmacy and Biochemistry, Institute of Pharmacy, Freie Universität Berlin, Germany, (2) Graduate Research Training program PharMetrX, Germany, (3) Institut Pasteur de Lille, Center for Infection and Immunity of Lille, Inserm, France, (4) Institute of Mathematics, University of Potsdam, Germany

Background and Objectives



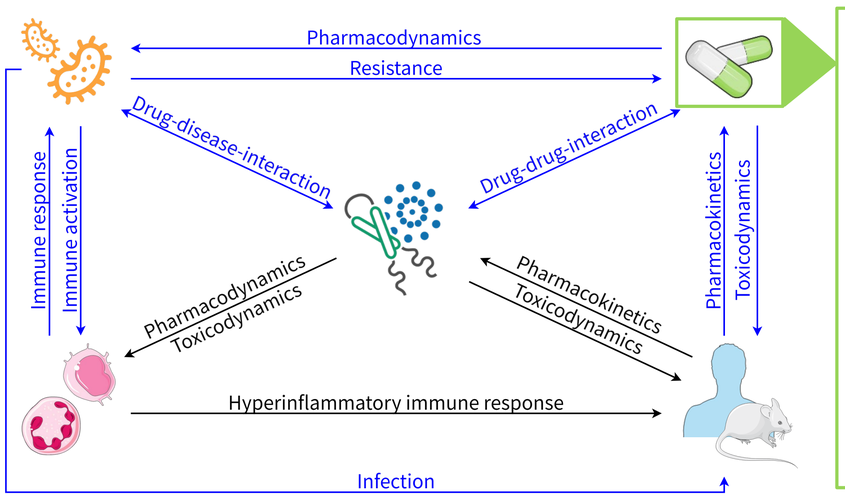
Resistant bacterial pneumonia

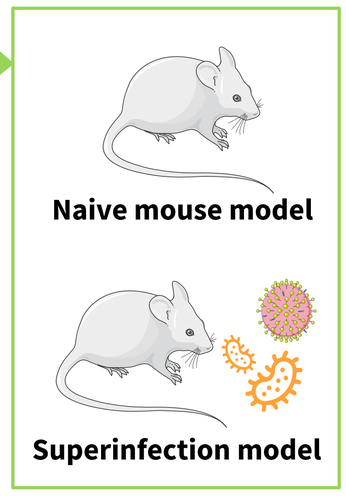


Adding FLAMOD to overcome resistance [1]

Prospective first in human trials: **monotreatment in healthy volunteers (safety)**

Intended indication: **combination treatment, pneumonia patients**





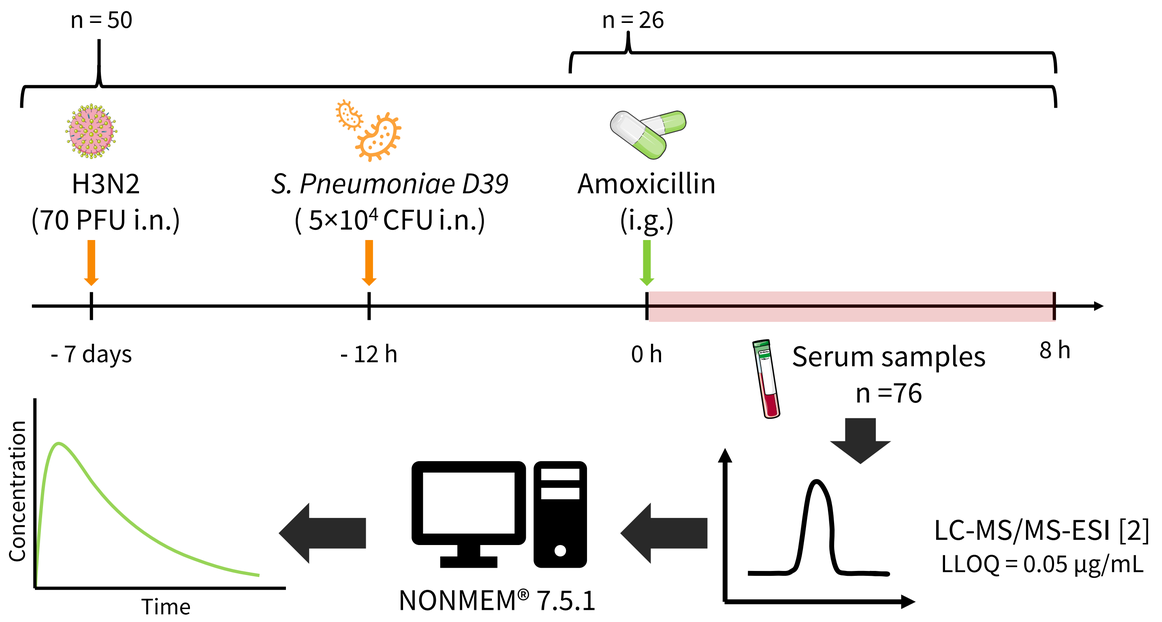
Methods

- C57BL/6J
- Male, 8-week-old
- Dose: 150 µg (n=50)

Superinfection [2]

- C57BL/6J
- Female, 7-week-old
- Dose: 10 µg (n=2), 50 µg (n=22), 350 µg (n=2)

Naive



Results

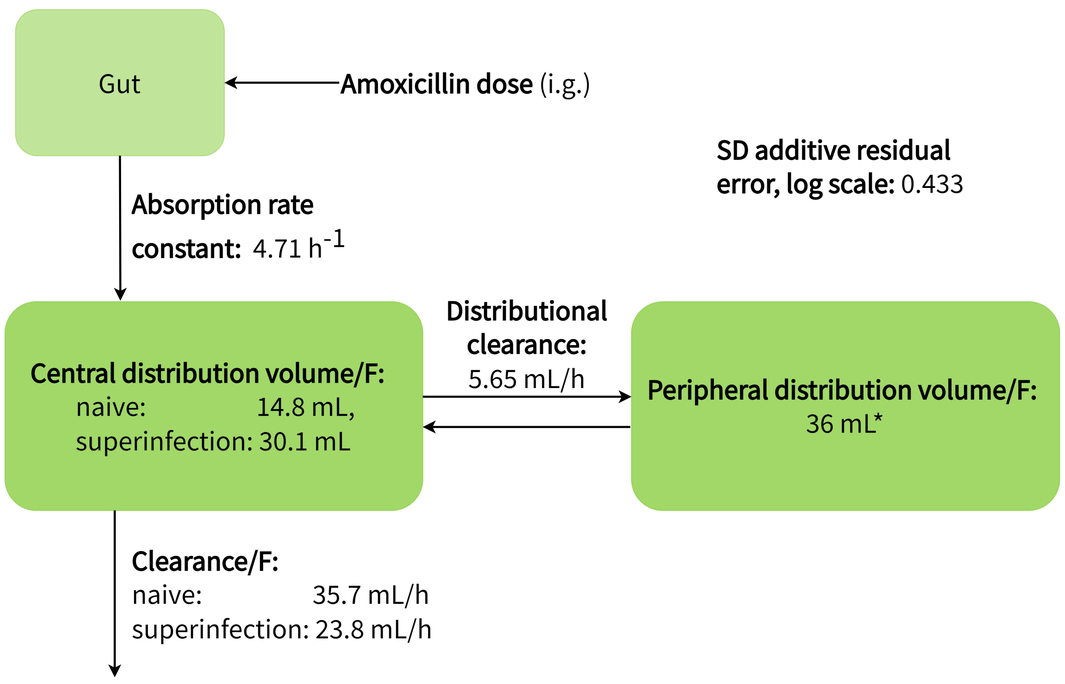
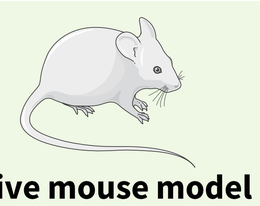


Figure 1: Structure and parameter estimates of murine amoxicillin pharmacokinetic model, based on 76 serum concentrations in naive and superinfected C57BL/6J mice receiving single i.g. doses of 10 to 350 µg amoxicillin. All parameters estimated with RSE<36%. All involved processes follow first order kinetics.
*Parameter was fixed to respective value during model development.



Naive mouse model
$t_{½}$ = 0.290 h
(90% CI 0.198 – 0.357)*

3.1 fold difference in amoxicillin elimination half-life

Superinfection model
$t_{½}$ = 0.874 h
(90% CI 0.720 – 1.07)*

* Elimination half-life estimated by $t_{½}$ = ln(2)*(central Volume/Clearance). Presented are the 5th,50th, and 95th percentiles of the elimination half-life as estimated from 500 bootstrap samples.

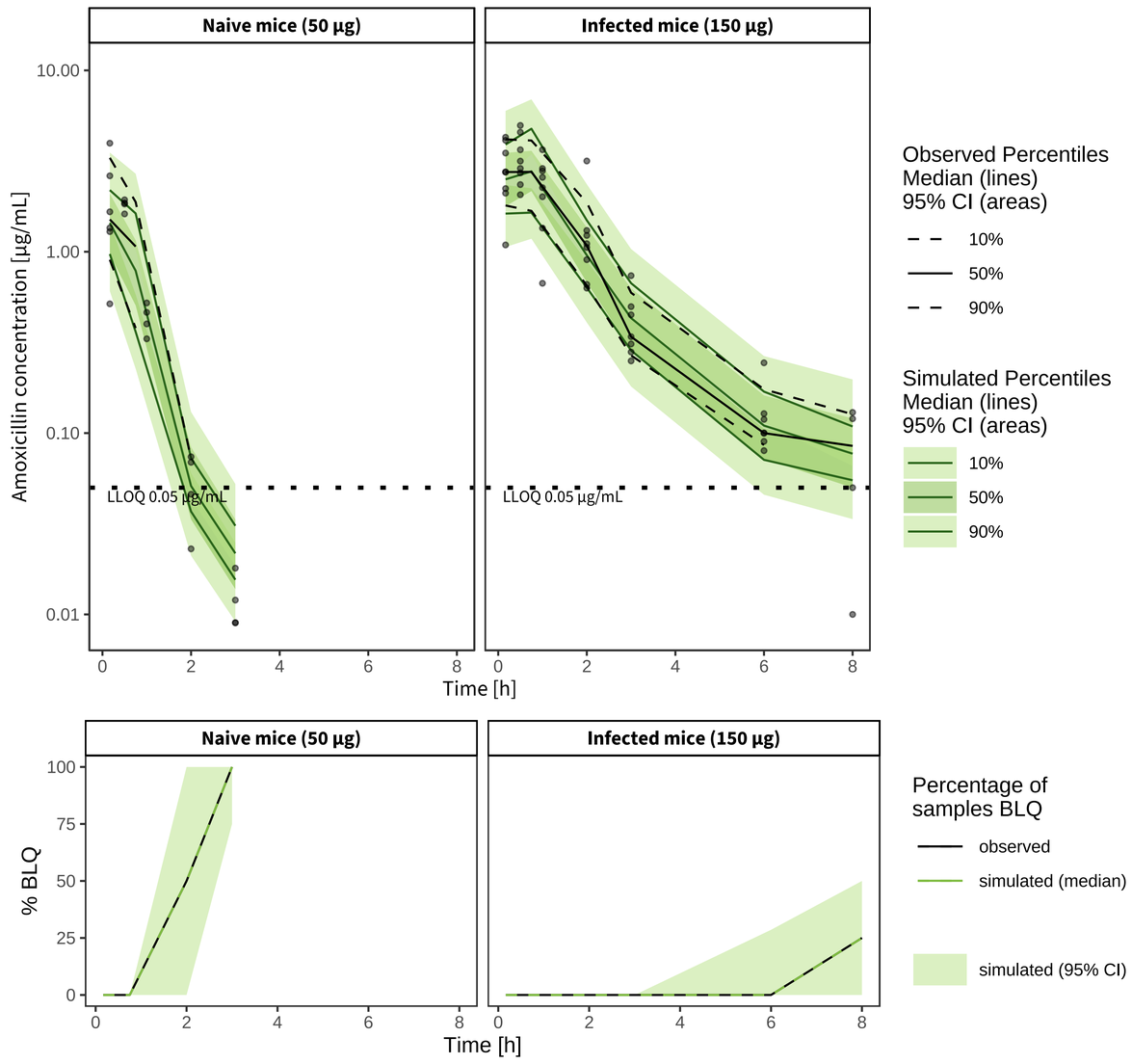


Figure 2: Visual Predictive Check of murine amoxicillin pharmacokinetic model based on 1000 simulations stratified by infection status, including doses of 50 µg for naive (left) and 150 µg superinfected mice (right).

Discussion and Conclusions

- Model revealed **significant differences in amoxicillin PK** between murine naive and superinfection study group
- Previous studies [3] did not indicate saturation of elimination processes in respective dose range
  → **superinfection associated changes e.g. renal impairment** [4] most probable cause
- Accurate description of specific superinfection model **enables future investigation of synergistic effects** of adjunct FLAMOD therapy

Outlook

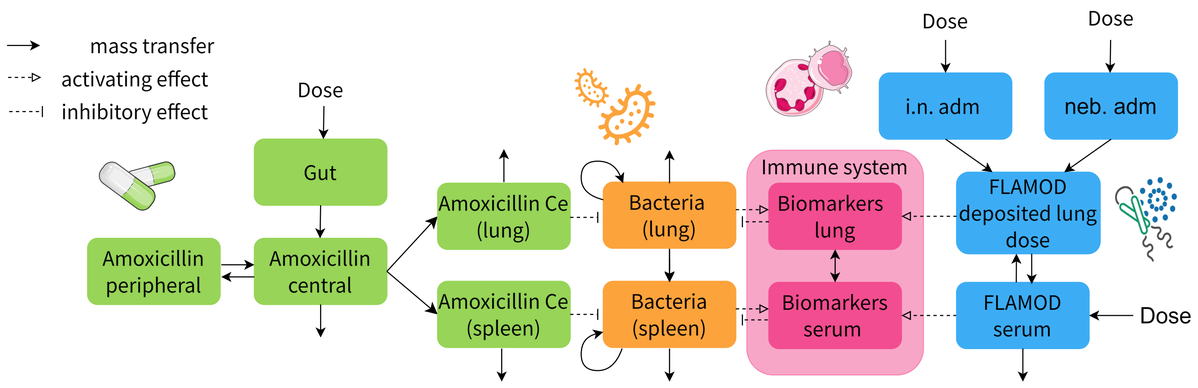


Figure 3: Simplified sketch of comprehensive PKPD model describing host-drug-drug-disease interplay in context of the FAIR proposed FLAMOD + antibiotic combination therapy including processes involved in disposition and effect FLAMOD (blue), immune system (pink), PK and PD of amoxicillin as exemplary antibiotic (green) and bacterial disease submodel (orange).

References

[1] Matarazzo et al., Front. Immunol. (2019)
[2] Mondemé et al., J. Leukoc. Biol. (2024)
[3] Franck et al., Pharmaceutics (2021)
[4] Andonegui et al, SHOCK (2008)

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Abbreviations

BLQ	Below limit of quantification	PD	Pharmacodynamics
CFU	Colony forming units	PK	Pharmacokinetics
CI	Confidence interval	PFU	Plaque forming units
Ce	Effect site concentration	RSE	Relative standard error
F	Bioavailability	$t_{½}$	Elimination half life
i.g.	Intragastric		
i.n.	Intranasal		
LLOQ	Lower limit of quantification		
neb	Nebulised		

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For more information:
Miriam Happ,
miriam.happ@fu-berlin.de
www.clinical-pharmacy.eu

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