PAGE 2025 – Thessaloniki, Greece

Model-based characterisation of antibiotic activity in the presence of immune response: towards improved preclinical-to-clinical translation

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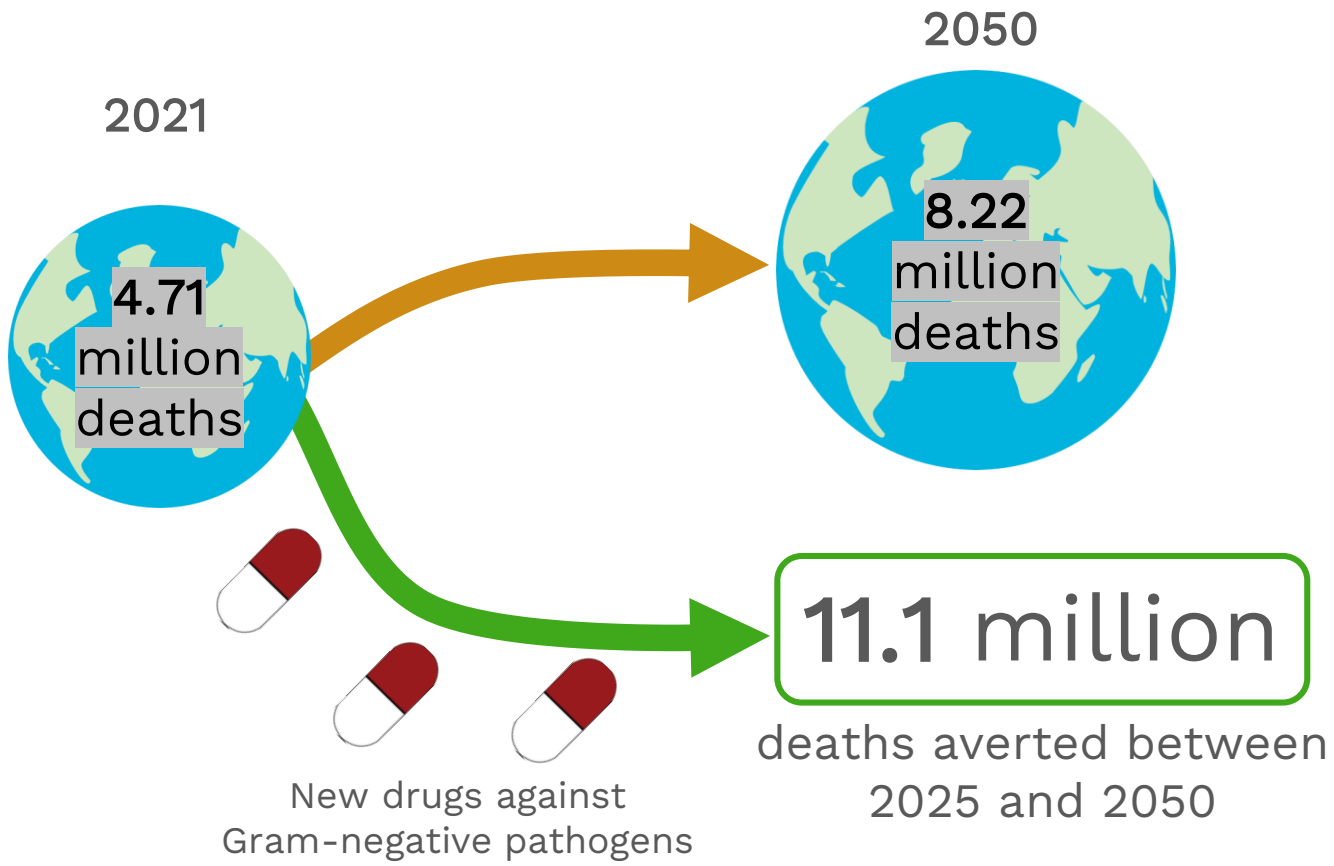
Antimicrobial resistance (AMR): a global threat

Global deaths per year associated with AMR[1]:



→ **New antibiotics are needed!**

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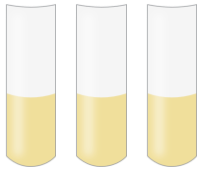
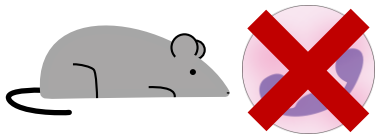
[1]GBD 2021 Antimicrobial Resistance Collaborators. Lancet 2024:S0140-6736(24)01867-1.

Preclinical evaluation of antibiotic PKPD



In vitro time-kill



In vivo
Neutropenic mouse thigh/lung infection

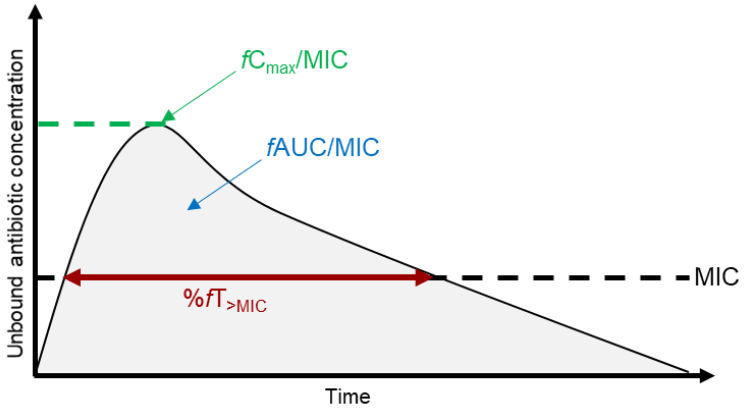
Clinical use?

- Bacteria not quantifiable in patients

→ **Reliance on preclinical data**

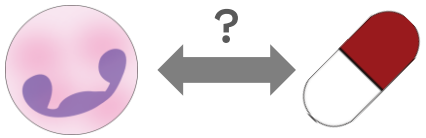
Translation?

- PK/PD indices: standard approach
- Limitations: single time point, summary metrics

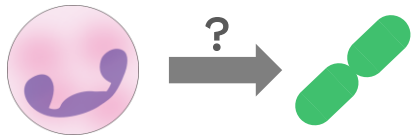


Immune response?

Preclinical settings are **neutropenic**:



interactions?



quantitative killing?

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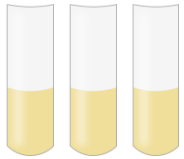
Evaluated antibiotics

Afabicin

- Fatty acid synthesis inhibitor (FabI enzyme)
- Phase II development (NCT02426918, NCT03723551)[2]
- Available data (drug development):



In vitro time-kill

Neutropenic mouse thigh infection

Immunocompetent mouse thigh infection

Meropenem

- Carbapenem (inhibition of cell wall synthesis)
- Study design:

Neutropenic mouse lung infection

Intermediate suppression mouse lung infection

Immunocompetent mouse lung infection

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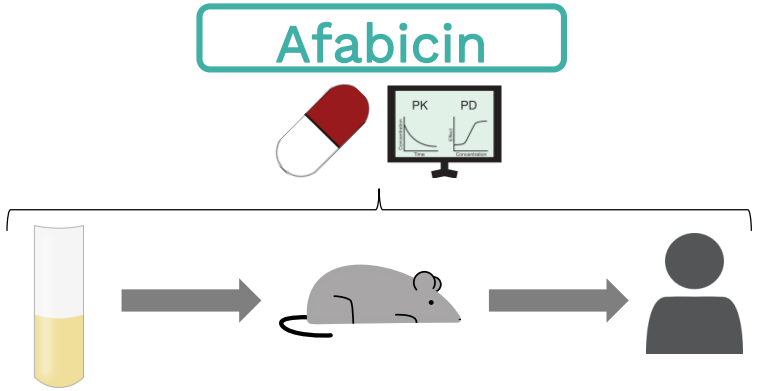
[2]Wittke F, et al. Antimicrobial agents and chemotherapy 2020;64,10: e00250-20

Aims

- To translate antibiotic activity from *in vitro* to *in vivo* and subsequently to clinical settings using PKPD modelling approaches



- To quantify the relative contribution of antibiotics and immune response to bacterial killing

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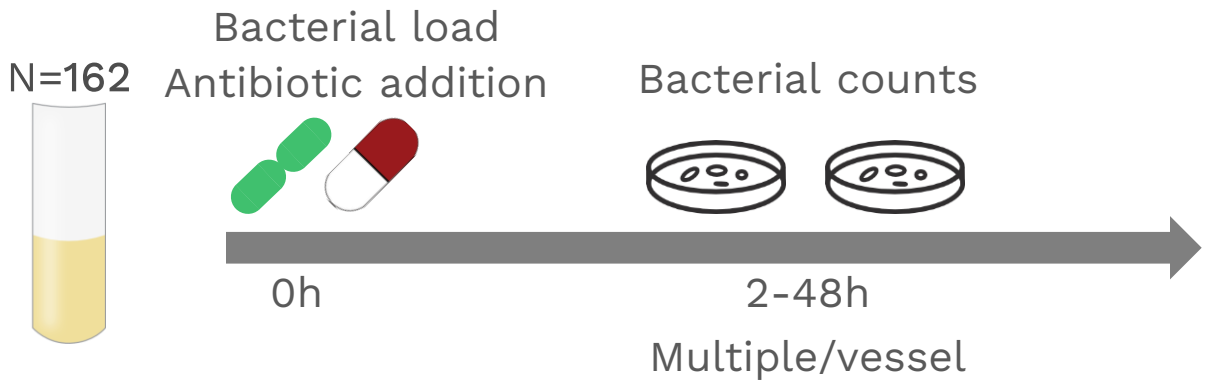
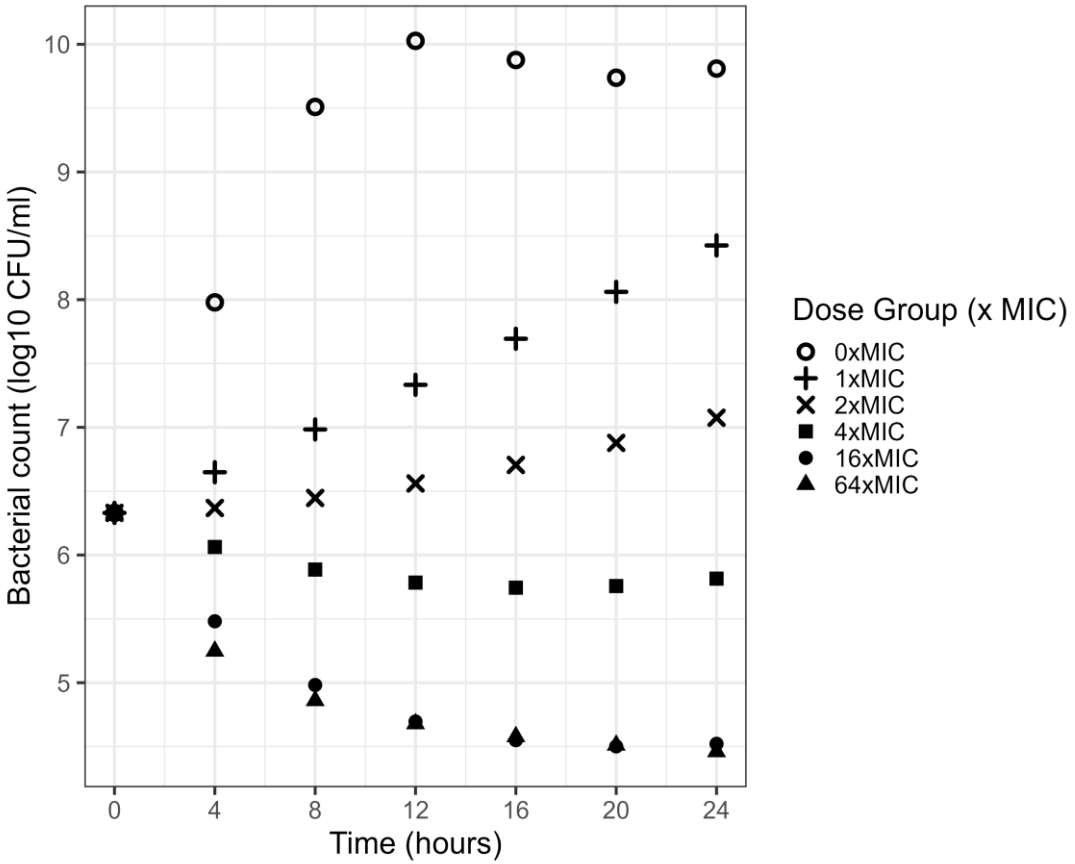
In vitro time-kill experiments



21 *Staphylococcus aureus* strains
Minimum Inhibitory Concentration (MIC): 0.004 – 0.03 mg/L

Afabicin desphosphono (active metabolite)
Static concentrations: 0.004 – 1 mg/L

Bacterial dynamics over time



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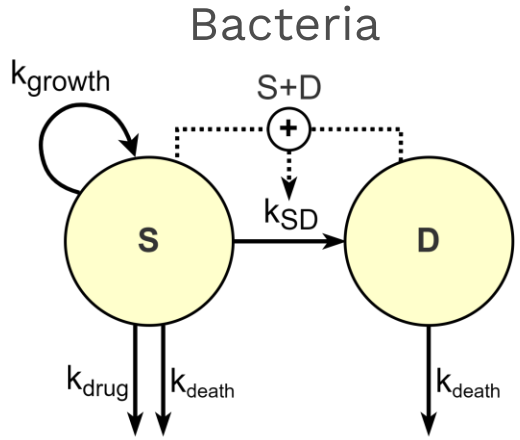
In vitro PKPD model

Afabicin

Susceptible bacteria (**S**):
Growing, drug-susceptible



Dormant bacteria (**D**):
Non-growing, non-drug-susceptible

S → D transfer dependent on bacterial count and maximal system capacity

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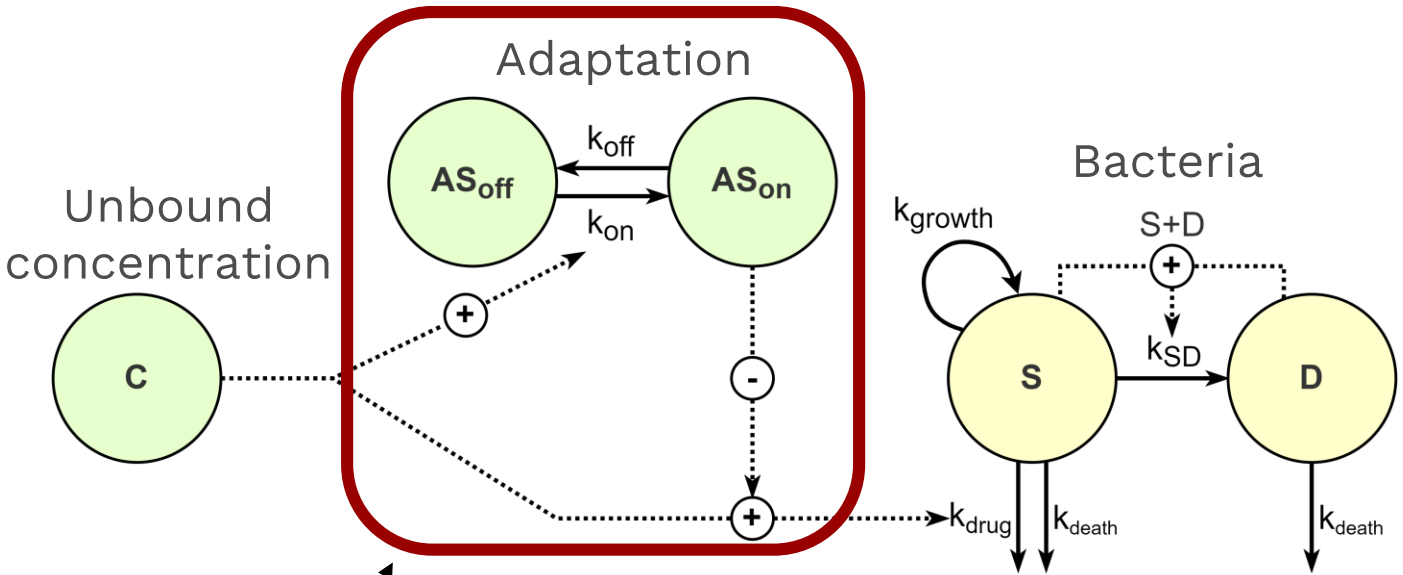
In vitro PKPD model

Afabicin



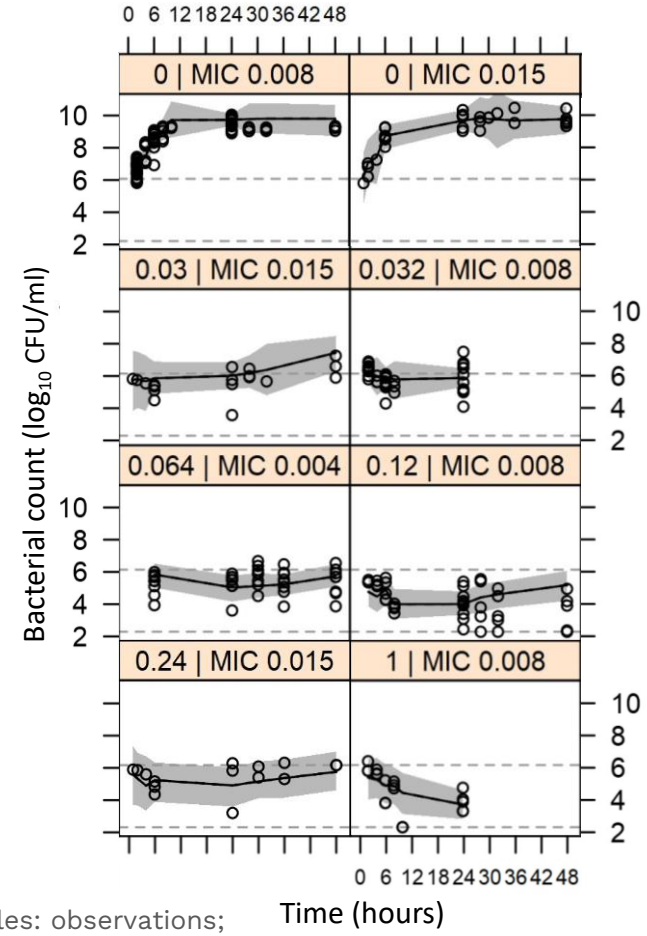
$$k_{drug}(t) = \frac{E_{max}(t) \cdot C^{hill}}{C^{hill} + EC_{50}^{hill}}$$

Reversible **adaptation** under drug exposure lowering E_{max}

Strain differences:
MIC scaling of drug effect

$$EC_{50} = MIC^{\gamma}$$

Example subset of strains/concentrations:



Circles: observations;
solid lines (areas): median (95% CI) of model predictions;
dashed lines: median start inoculum, limit of quantification

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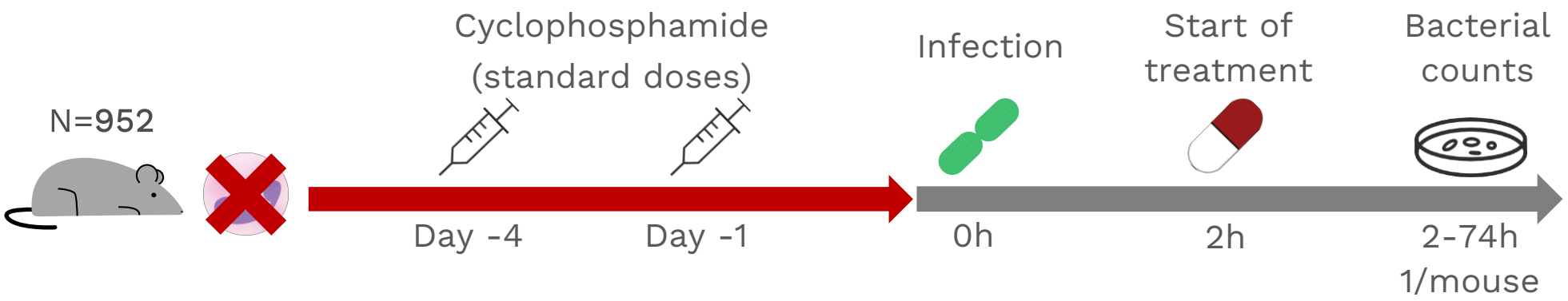
MIC: Minimum Inhibitory Concentration S: susceptible bacteria D: dormant bacteria

Neutropenic mouse thigh infection

Afabicin



9 *Staphylococcus aureus* strains
MIC: 0.004 – 0.06 mg/L
8/9 strains not evaluated *in vitro* → translation across bacterial strains

Afabicin 0.01 – 190 mg/kg q6h

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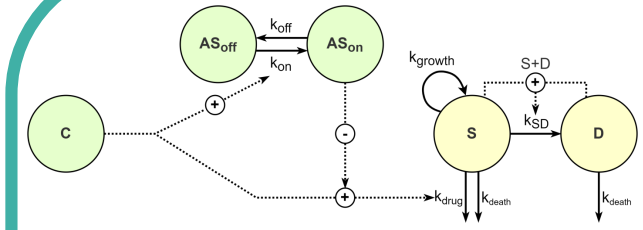
MIC: Minimum Inhibitory Concentration

Translation from *in vitro* to *in vivo*

Afabicin

Can *in vivo* study outcomes be predicted using insights from *in vitro* studies?



In vitro
PKPD model

+

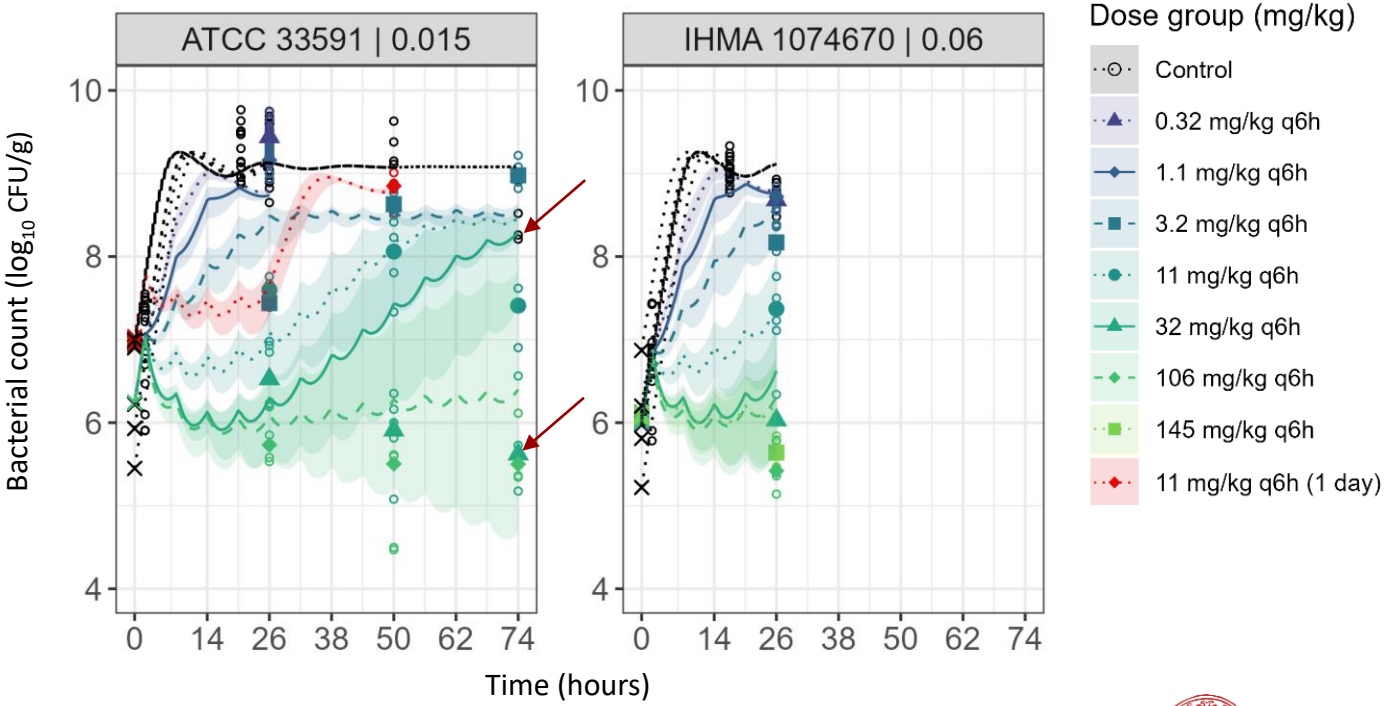
Afabicin mouse
PK model

+

Growth parameters
(control data)

Predictions with PKPD parameter uncertainty

Example strains:



Symbols: median of observations; open circles: observations;
lines: median of model predictions;
areas: 95% confidence interval of predictions (uncertainty)

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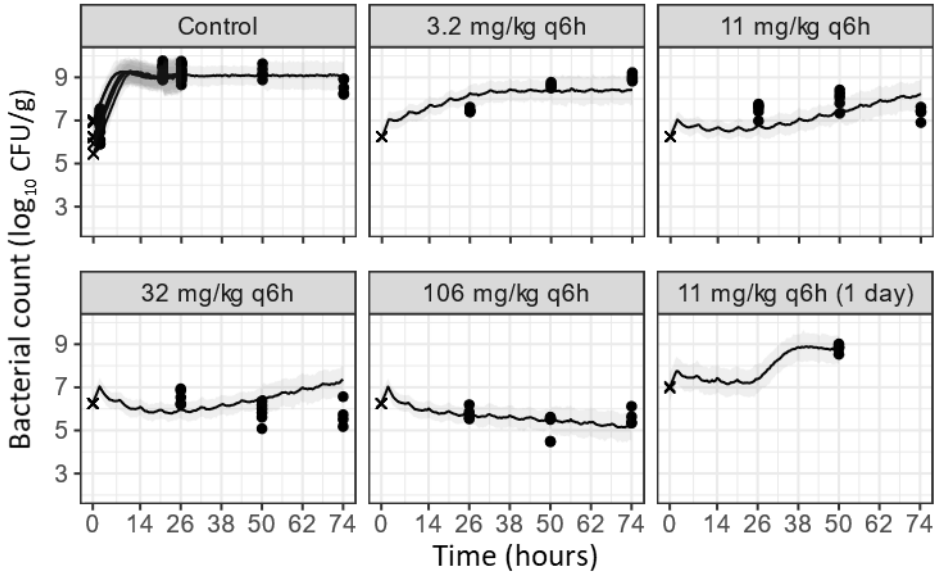
Re-estimation with *in vivo* data

Afabicin

- Joint model estimation with *in vitro* and neutropenic mouse thigh infection data
- **$EC_{u,50}$ 38 to 45% lower *in vivo***, other drug effect parameters shared with *in vitro*

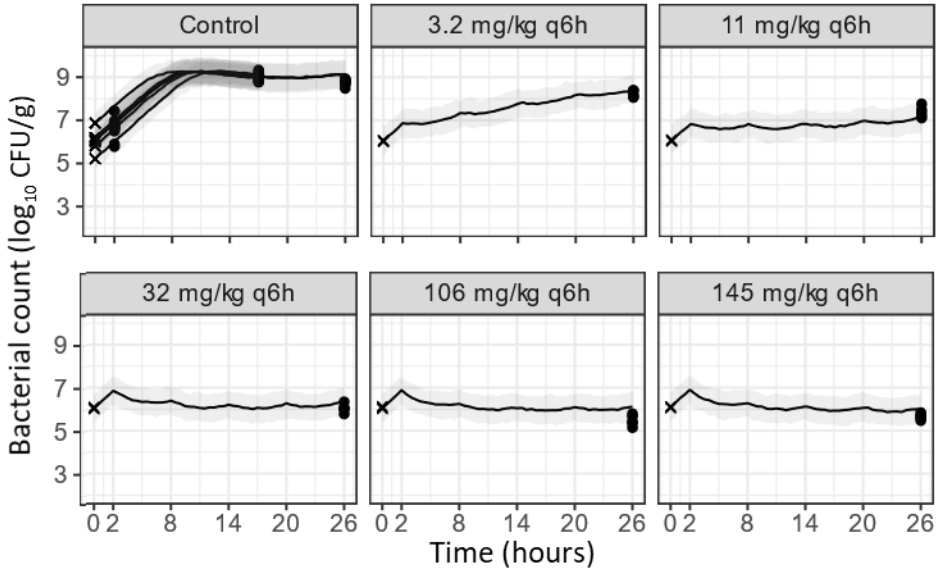
Example strains:

S. aureus ATCC33591 (MIC=0.015 mg/L)



Circles: observations; crosses: start inoculum;
solid lines (areas): median (95% CI) of model predictions

S. aureus IHMA1074670 (MIC=0.06 mg/L)



All results in **open-access article**
Saporta R, et al. Journal of Antimicrobial Chemotherapy. 2024;79(12):3150-59

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MIC: Minimum Inhibitory Concentration

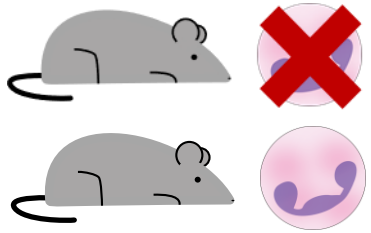
What about the immune system?

Afabicin

Meropenem

Influence of the immune system on antibiotic PK?

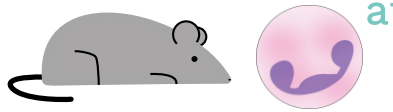
N=60



Meropenem PK study in infected mice (40 & 300 mg/kg)

Influence of the immune system on antibiotic effect?

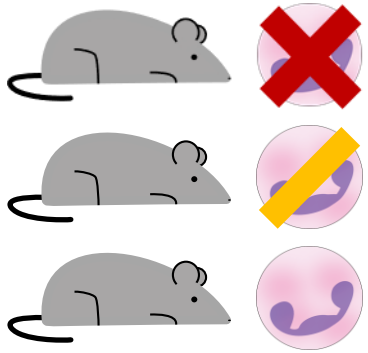
N=819



Inclusion of immunocompetent afabicin data in translation framework

4 *S. aureus* strains (studied in neutropenic mice)

N=180



Meropenem efficacy study in mice with various immune states

40 or 300 mg/kg q4h

K. pneumoniae DSM116099

MIC = 0.032 mg/L

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MIC: Minimum Inhibitory Concentration

Immunocompetent mouse infection

Afabicin

Meropenem

Neutropenic

Cyclophosphamide
(standard doses)

Day -4 Day -1

Intermediate

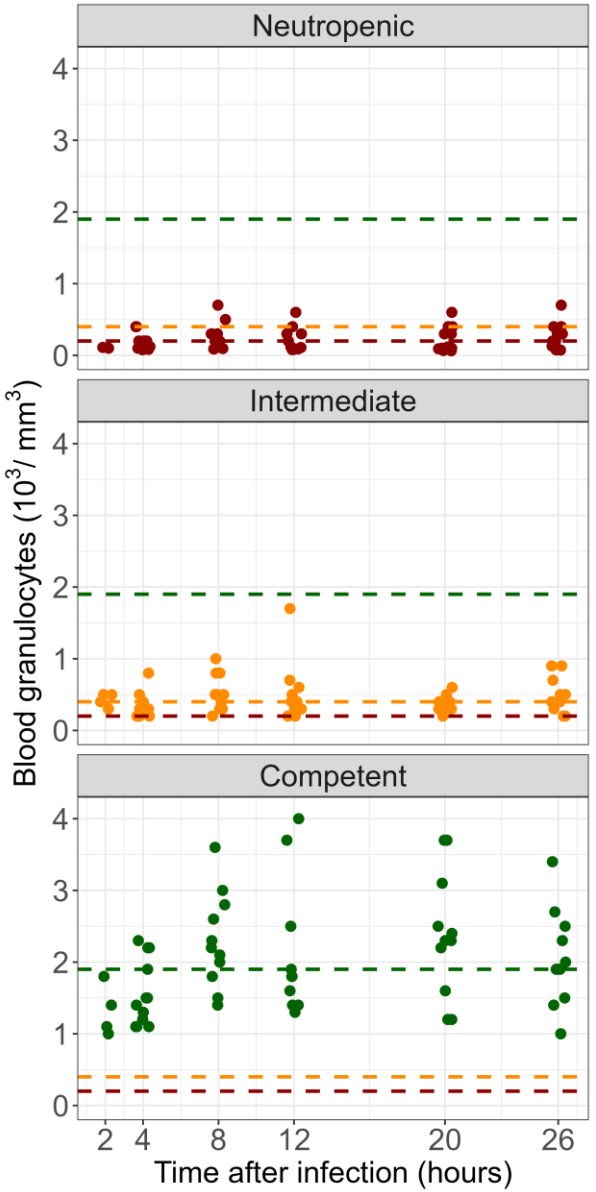
Cyclophosphamide
(lowered doses)

Day -4 Day -1

Competent

No cyclophosphamide

Day -4 Day -1



Blood granulocytes in meropenem PD study (1 observation/mouse)

Circles: observations; dashed lines: medians of observations per immune status (all times)

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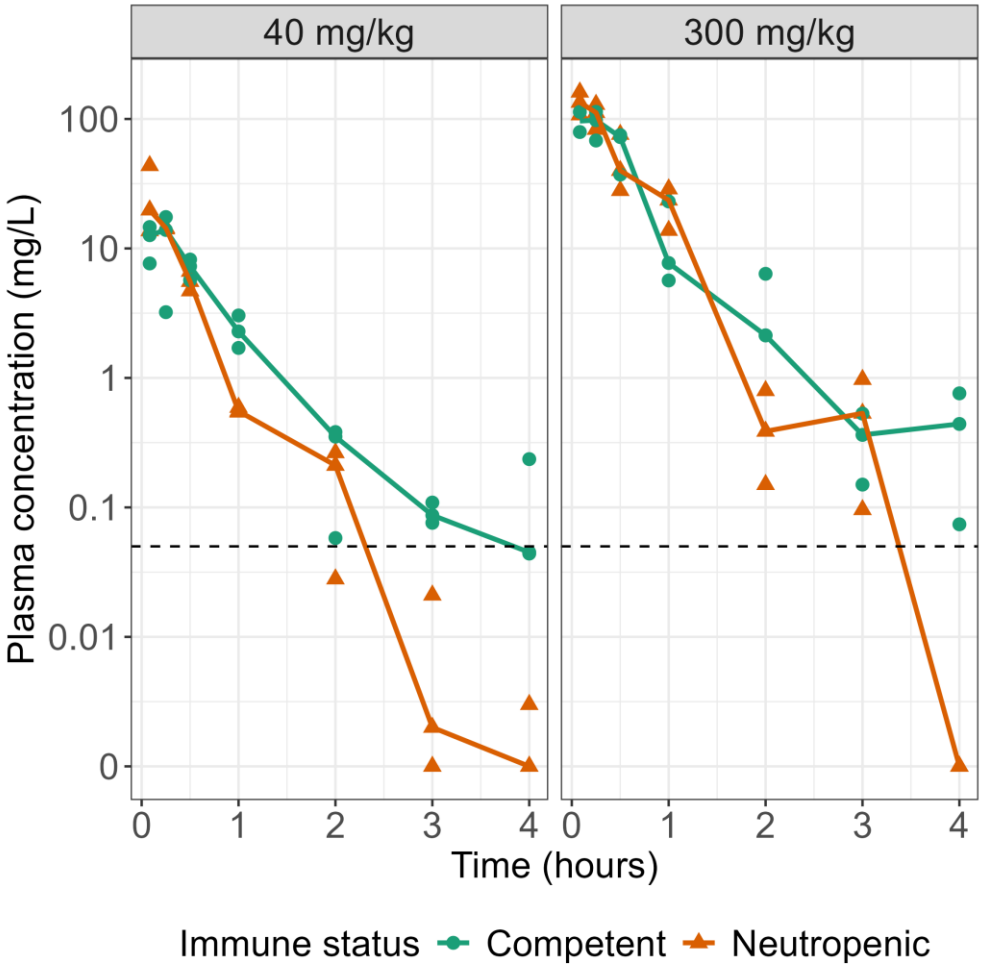
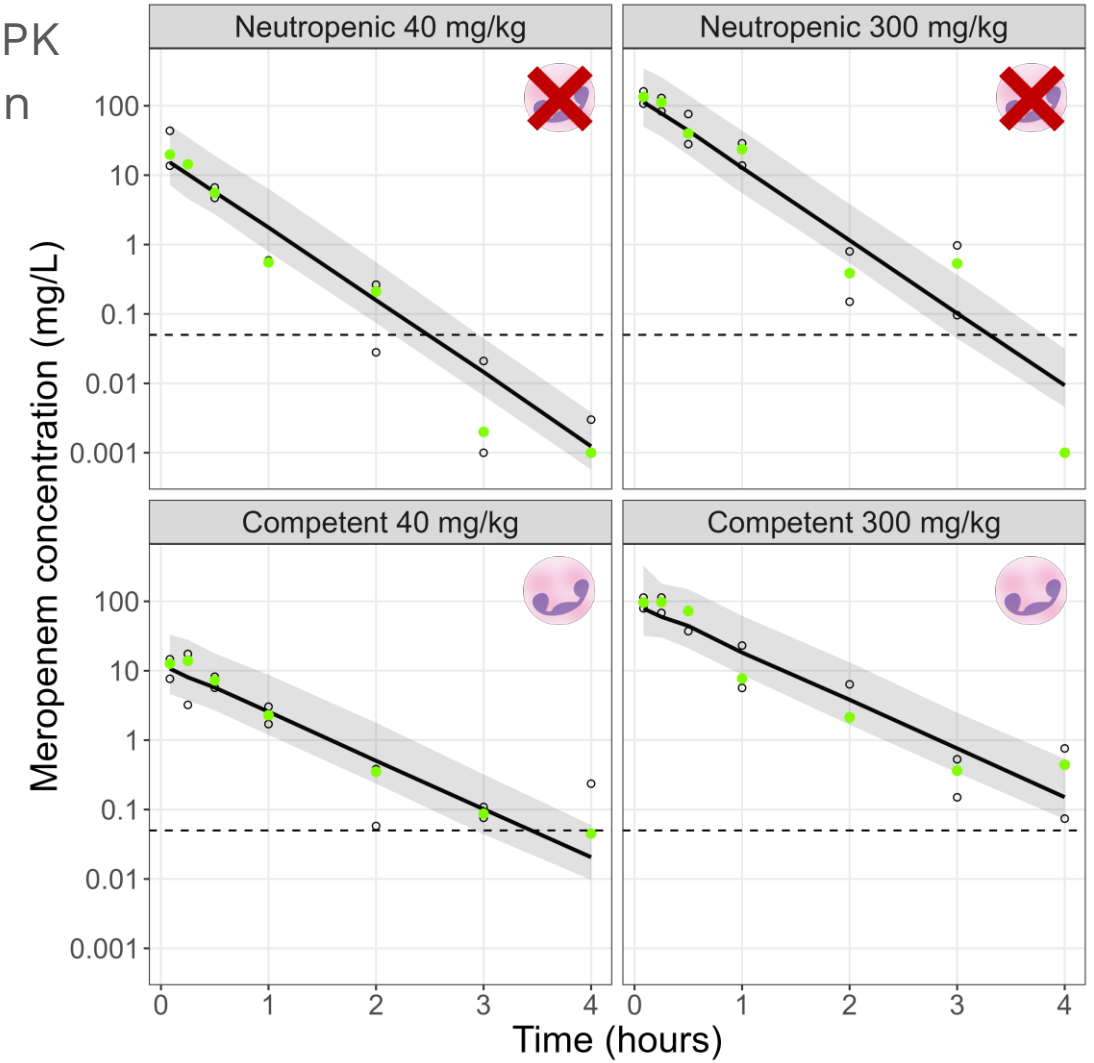
Immune status influences meropenem PK

Meropenem



Symbols: observations; lines: median of observations;
horizontal dashed line: limit of quantification (LOQ)

1 compartment PK
≠ in distribution volume



(Green) circles: (median) observations;
solid lines (areas): median (95% CI) of model predictions;
horizontal dashed line: LOQ

Immune response modelling

Afabicin

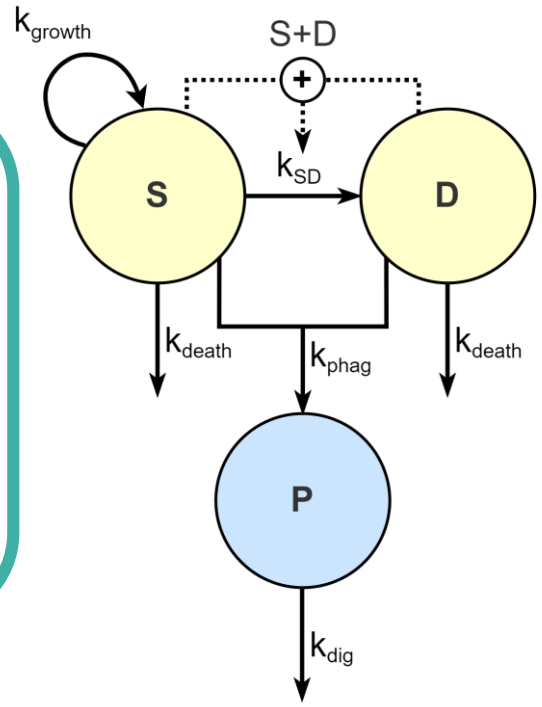
Meropenem

Afabicin

- Neutrophil dynamics fixed from literature[3]
- Saturable phagocytosis rate:

$$k_{phag} = k_{phag,max} \cdot \left(1 - \frac{P/N^H}{P/N^H + P/N_{50,phag}^H}\right)$$

Phagocytosis and digestion process



Meropenem

- Immune status: covariate for k_{phag} and k_{dig}

	Neutropenic	Intermediate	Competent
k_{phag} (h^{-1})	0 (Fixed)*	0.187	0.321

*Non-differentiable from k_{growth}

[3]Thorsted A, et al. CPT Pharmacometrics Syst Pharmacol. 2023;12(12):1972-1987

S: susceptible bacteria
P: phagocytosed bacteria
D: dormant bacteria
N: thigh neutrophils

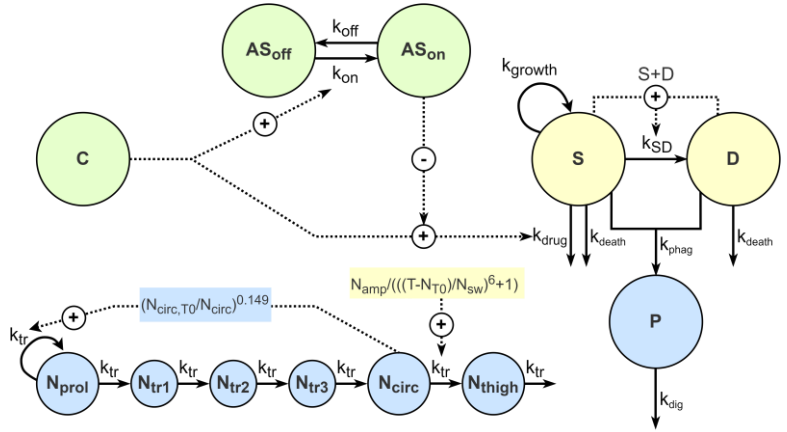
Drug effect in presence of immune response

Afabicin

Meropenem

→ Lower contribution of antibiotics to bacterial killing in immunocompetent conditions

Afabicin

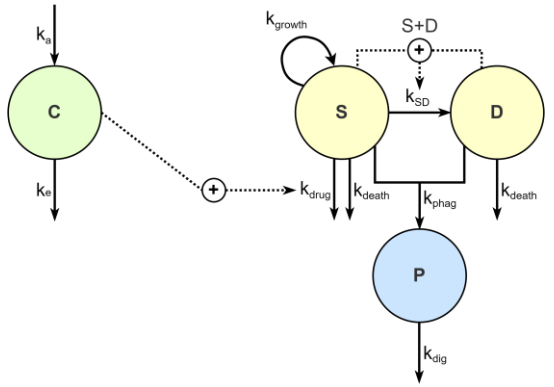


- Model for *in vitro* and neutropenic data expanded with killing by immune cells
- Reduced E_{max} and EC_{50} in immunocompetent vs neutropenic mice

E_{max} (h^{-1})	3.37	0.238
$EC_{u,50}$ (mg/L)	0.264	0.074

Example for MIC=0.008 mg/L

Meropenem



- Same E_{max} model parameters for all immune states

E_{max} (h^{-1})	0.922
EC_{50} (mg/L)	1.58

- Reduced effect attributed to a lower fraction of S bacteria due to phagocytosis

Available data did not support an intracellular drug effect on P bacteria

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MIC: Minimum Inhibitory Concentration

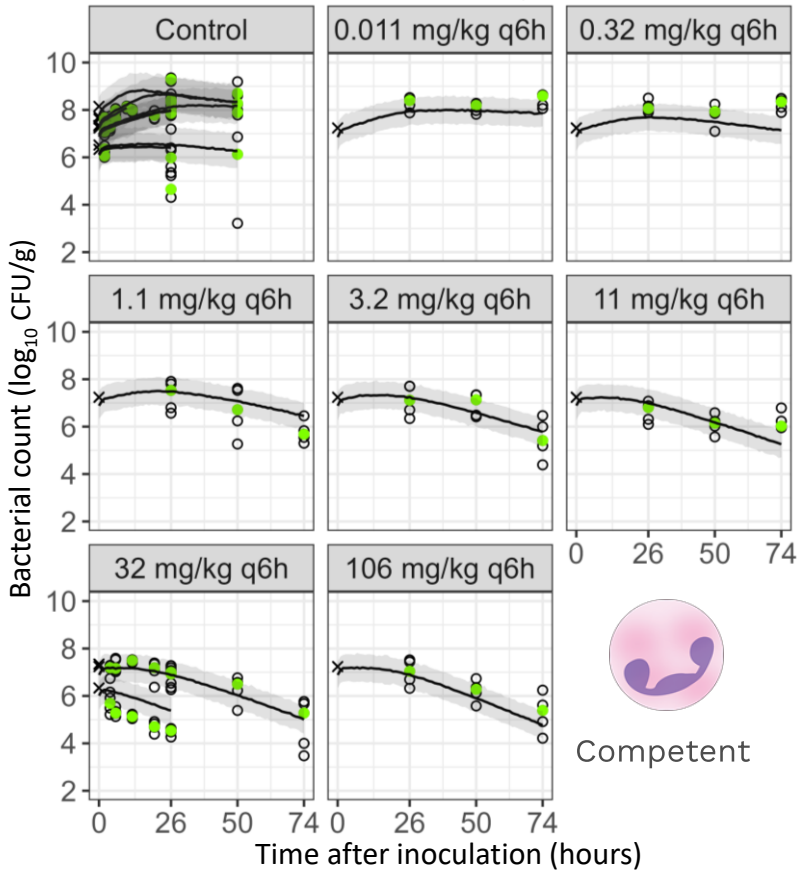
The PKPD models described the time course of antibiotic effects and immune response

Afabicin

Meropenem

Afabicin

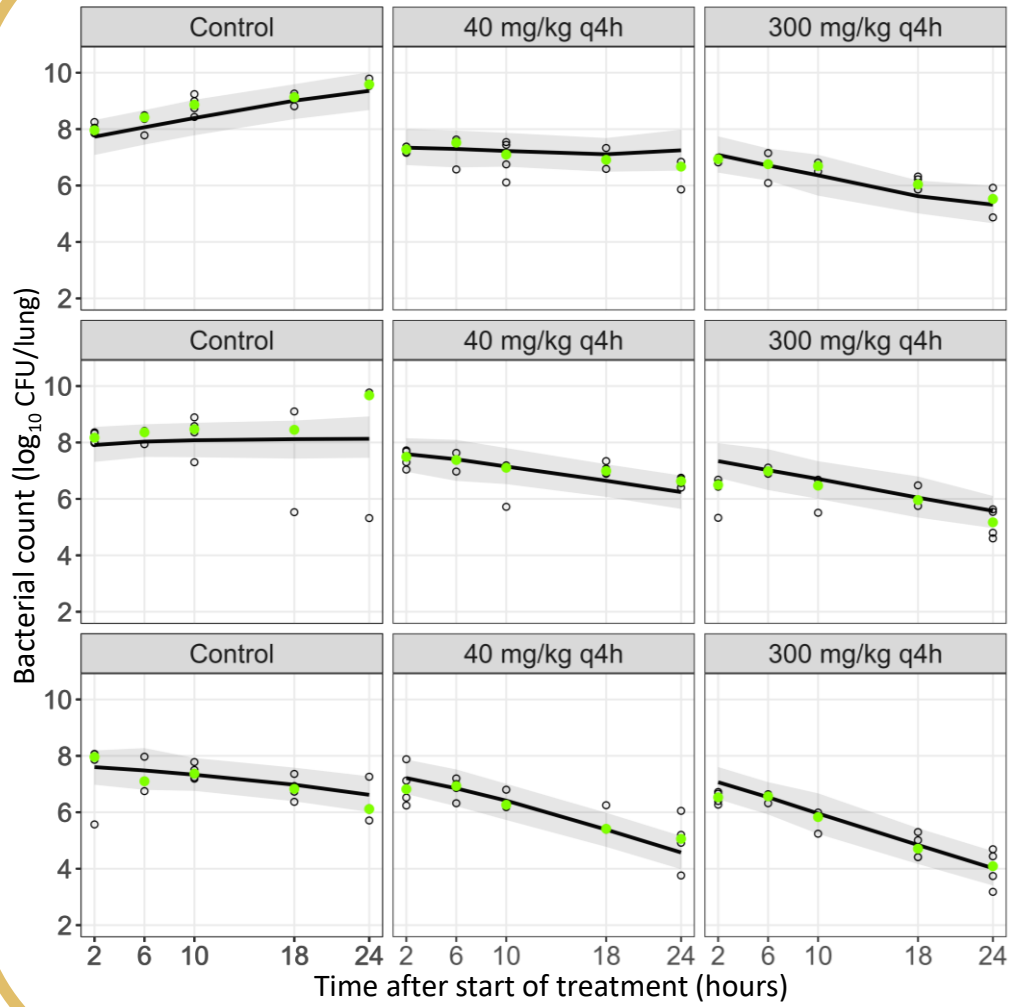
Example strain: *S. aureus* ATCC33591
MIC=0.015 mg/L



Competent

(Green) circles: (median) observations; crosses: inoculum; solid lines (areas): median (95% CI) of model predictions

Meropenem



Neutropenic

Intermediate

Competent

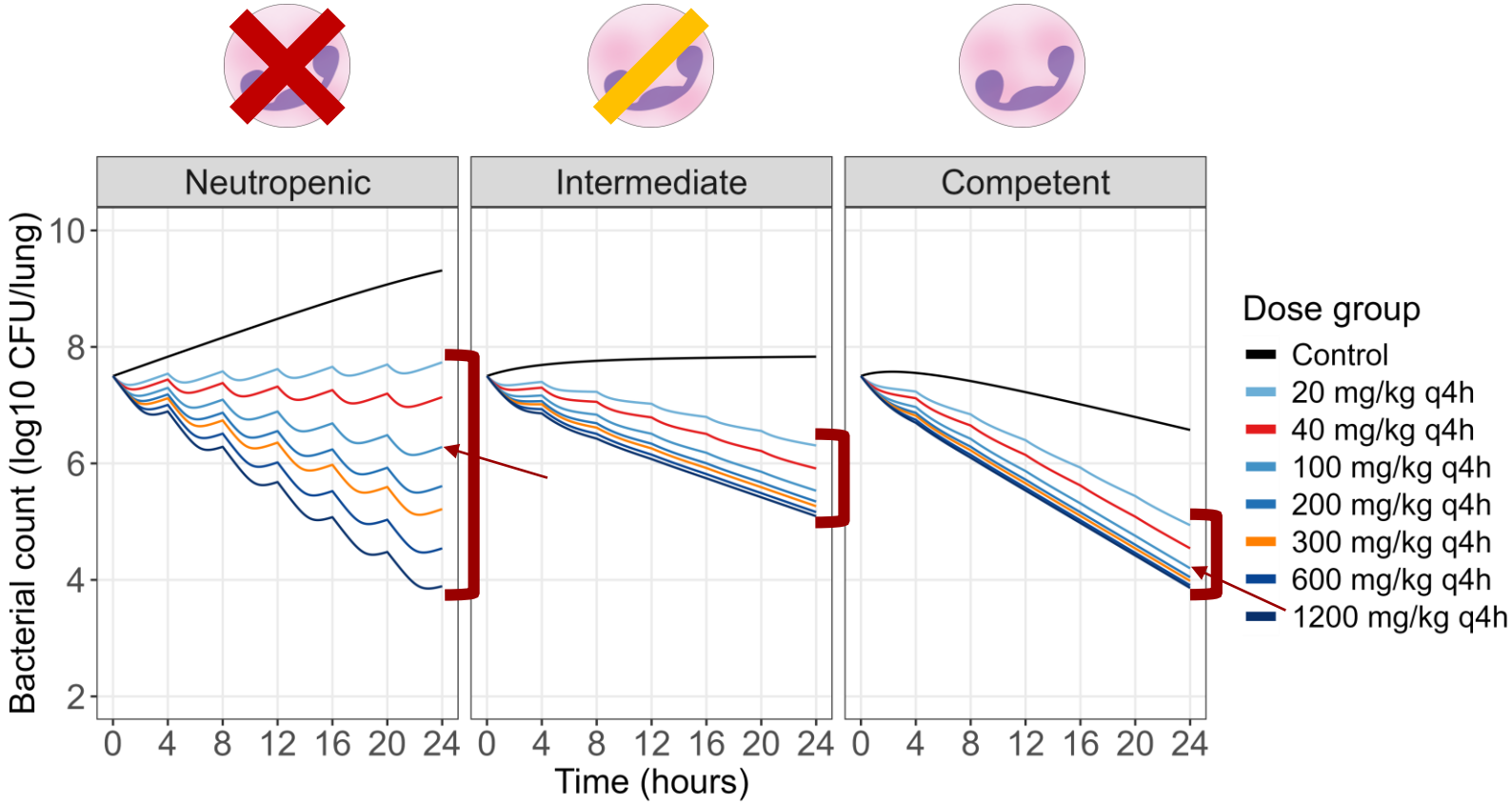
(Green) circles: (median) observations; solid lines (areas): median (95% CI) of model predictions; dashed lines: median of observations

MIC: Minimum Inhibitory Concentration

Implications for dose-response relationships?

Meropenem

- Simulated meropenem dose-ranging study in mice with various immune states



Lines: Model predictions (typical values)

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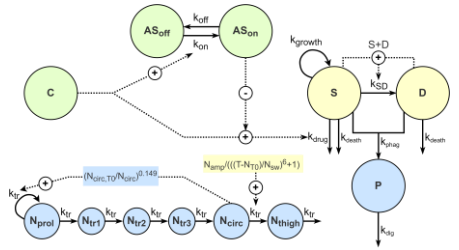
Preclinical-to-clinical translation?

Afabicin

Simulation settings

- Immunocompetent PKPD model



- Human PK model (Phase I data)
- **Phase II dosing regimens**
- Covariates: sampled from distribution in NHANES database (adults)[4]
- Neutrophil levels:
  - 1.69 x 10^6/ml (equivalent to mice)
  - 5 x 10^6/ml (within normal range)

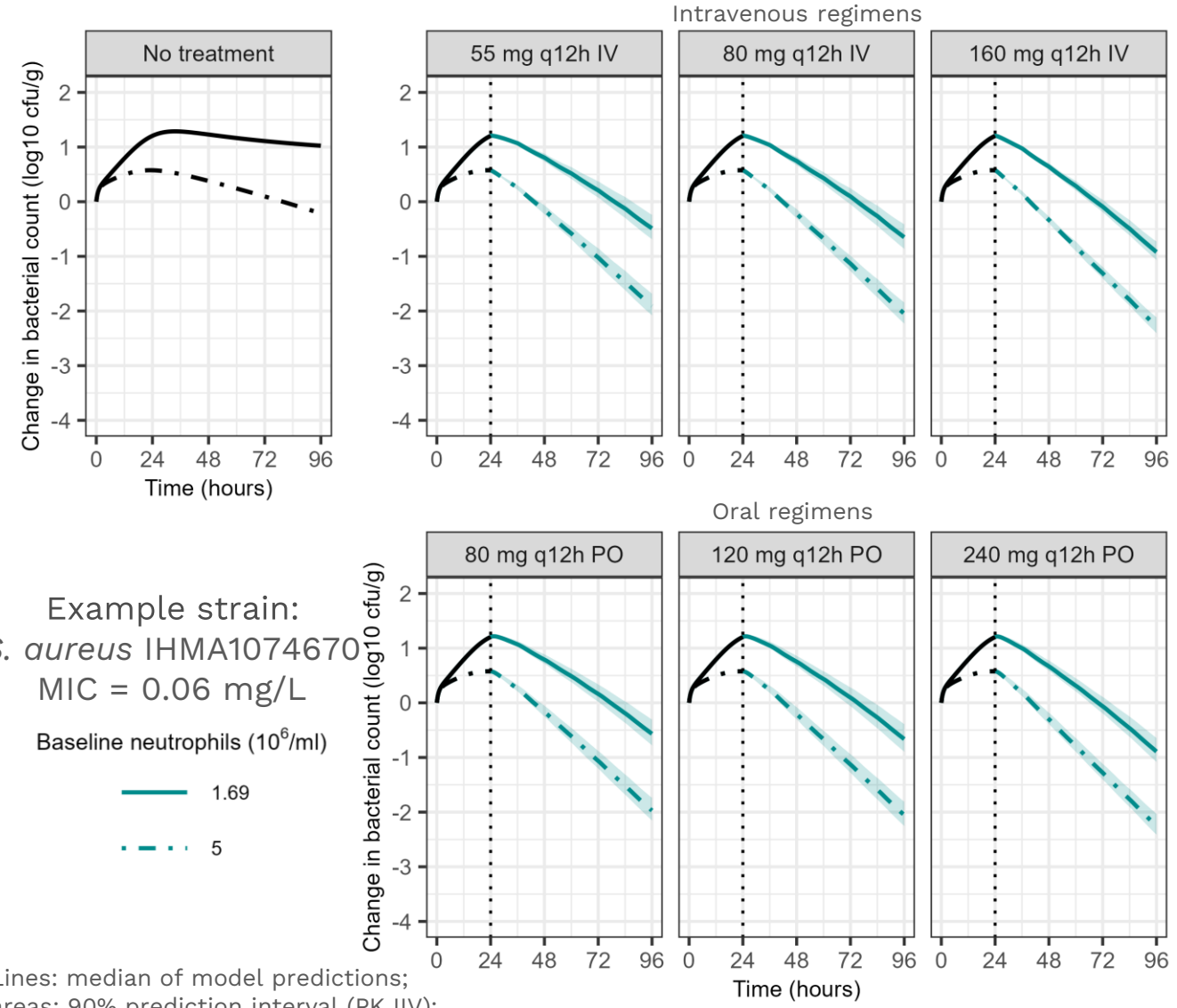
N=500 per group

Phase II results in ABSSSI[2]

>90% early clinical responders

→ Agreement of model-predicted bacterial dynamics and clinical response rates

ABSSSI: acute bacterial skin and skin structure infections



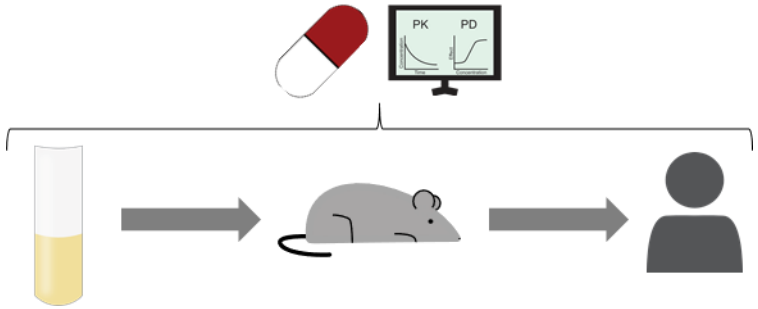
Lines: median of model predictions;
areas: 90% prediction interval (PK IIV);
vertical dashed line: start of treatment

[2]Wittke F, et al. Antimicrobial agents and chemotherapy 2020;64,10: e00250-20

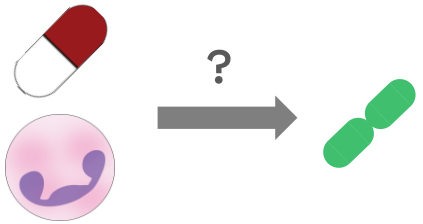
[4]Centers for Disease Control and Prevention. National Center for Health Statistics. National Health and Nutrition Examination Survey Data 08/2021-08/2023.

Conclusions

Model-based approaches demonstrated an ability to translate antibiotic PKPD across bacterial strains and experimental settings



Antibiotic PK and/or efficacy were impacted by the immune system, leading to potential differences in dose-response



→ Quantifying the time course of bacterial killing by the antibiotic and the immune system with model-based approaches may improve translation and dose selection

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Acknowledgements

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