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Introduction

- Antibiotic PK/PD targets inform antibiotic dose selection and include Time (%) above the minimum inhibitory concentration (%T>MIC) for time-dependent antibiotics, and AUC/MIC for concentration-dependent antibiotics.
- Dose fractionation studies in immune suppressed animal infection models are commonly used to derive PK/PD targets
- The effect of immune suppression on PK/PD targets and associated dosing strategies is uncertain.
- For treatment of bacteriemia, neutrophils and monocytes play a key role in the innate immune response

Mechanism-based model development

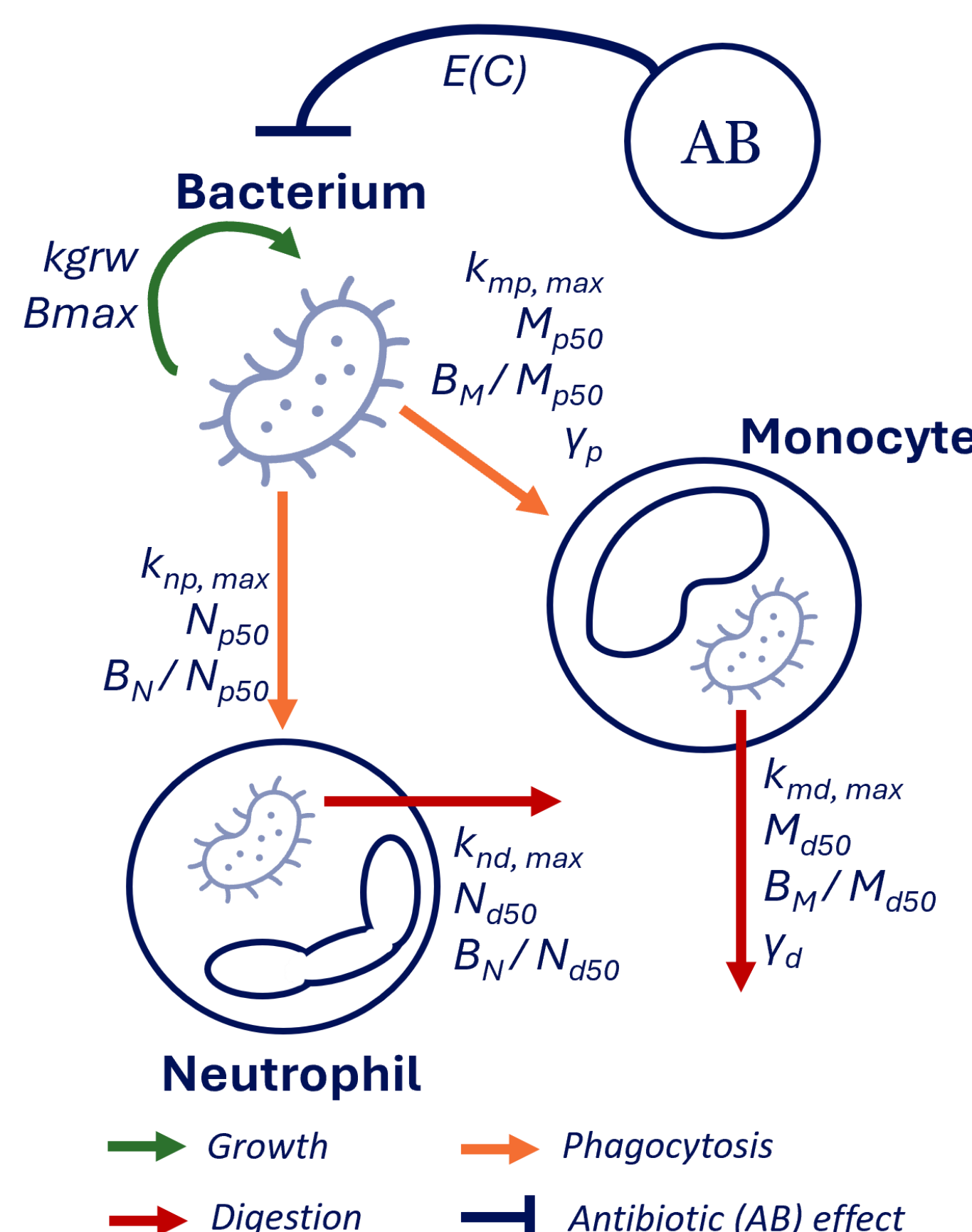


Figure 2. Model schematic of the developed mechanism-based model.

- Bacterial dynamics were modelled with a capacity-limited growth rate ($kgrw$, $Bmax$) and clearance via phagocytosis by the innate immune cells (I): neutrophils (N) and monocytes (M)
- Phagocytosis (p) and digestion (d) rates were modelled as maximum rates ($k_{i,max}$) which are concentration-dependent (I_{50}) and saturable processes (B/I_{50} , γ).

Parameter	Value
$kgrw$	0.5885 /h
$Bmax$	$2.5 \cdot 10^9$ CFU/mL
knp,max	1.90 /h
N_{p50}	$6.92 \cdot 10^5$ cell/mL
B_N/N_{p50}	3.92 CFU/cell
knd,max	5.61 /h
N_{d50}	$3.98 \cdot 10^6$ cell/mL
B_N/N_{d50}	2.84 CFU/cell
kmp,max	1.77 /h
M_{p50}	$2.73 \cdot 10^5$ cell/mL
B_M/M_{p50}	1.25 CFU/cell
γ_p	5.54
kmd,max	6.23 /h
M_{d50}	$3.98 \cdot 10^6$ cell/mL
B_M/M_{d50}	1.05 CFU/cell
γ_d	14
$kgmin$	-1 /h (bacteriostatic) or -3 /h (bactericidal)
H	0.5 (time dependant) or 3 (concentration dependant)

Table 1. Model parameters with their estimated or set values.

Aim

To evaluate how immune impairment impacts PK/PD targets using a mechanism-based model of innate immune response during bacteraemia

Methods

Model development

- A mechanism-based model was developed, incorporating phagocytosis and digestion by neutrophils and monocytes. Parameters were based on published experimental studies.

Sensitivity analysis and parameter calibration

- A global sensitivity analysis using Sobol was used to identify key drivers of bacterial dynamics, assessed by the AUC, for two immune competent species: (A) mice and (B) humans
- The most sensitive parameters were calibrated using *in vivo* data of immune competent mice.

Antibiotic PK/PD model and simulations

- The model was extended with PK/PD models for bacteriostatic and bactericidal antibiotics, covering both time- and concentration dependency (Eq. 1)

$$E(C) = kgrw - \left(\frac{(kgrw - kgmin) \cdot \frac{C}{MIC}}{\frac{C}{MIC} - \frac{kgmin}{kgrw}} \right)$$

Equation 1. Antibiotic effect on kgrw

- A dose fractionation study was simulated to determine PK/PD targets, based on achieving $\geq 2 \log_{10}$ CFU/mL reduction at 24 hours

Model evaluation and *in vivo* calibration

- Shown is which parameters most influenced bacterial dynamics across two species
- The first order index indicates the importance of a single parameter, while the total effect index includes also the interactions between various parameters
- The most influential were the maximum phagocytosis rates of neutrophils and monocytes (knp,max , kmp,max), which were estimated to be 78% lower *in vivo* than *in vitro*

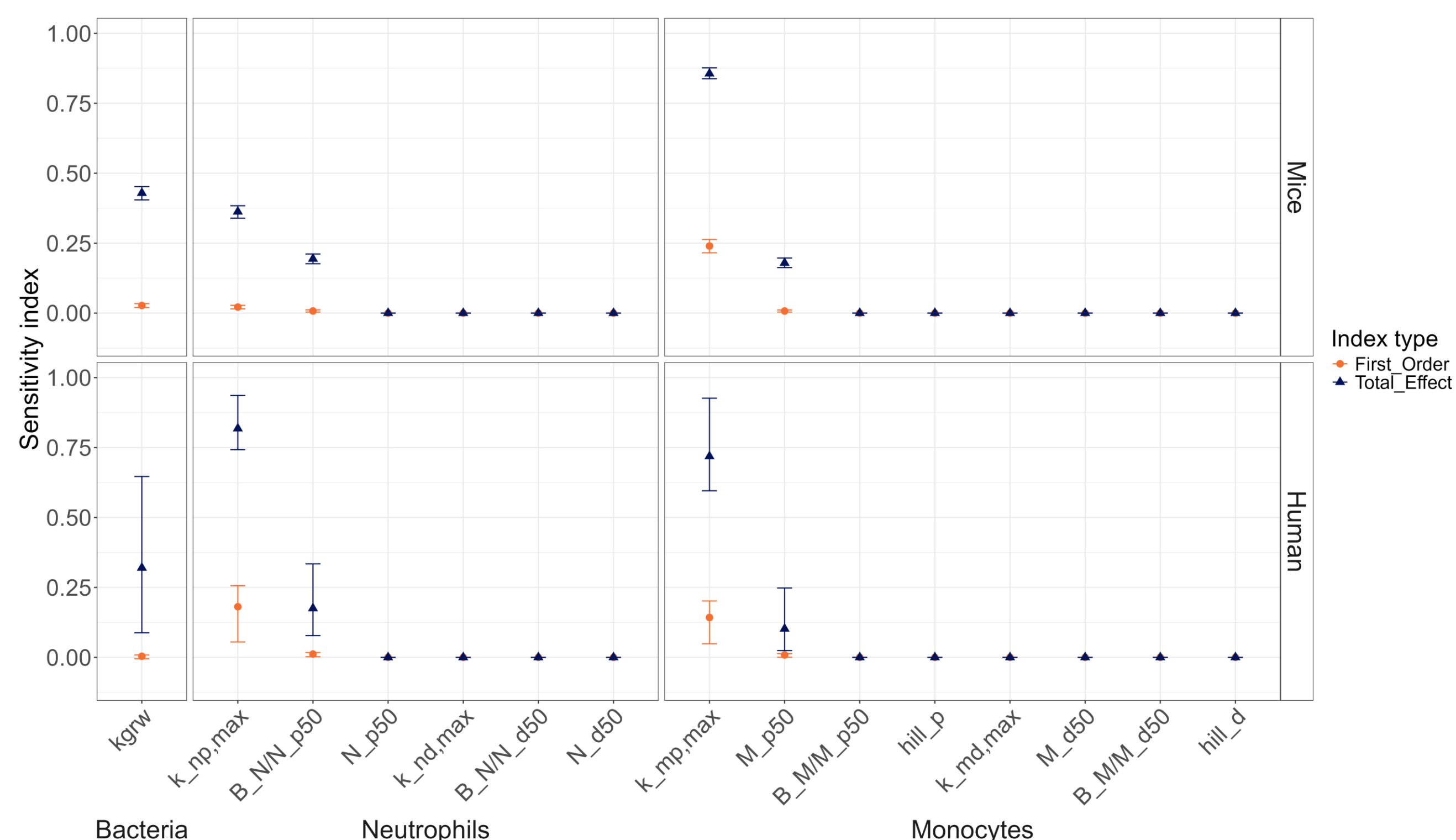


Figure 3. Global sensitivity analysis for two species. Parameters are deemed sensitive if the sensitivity index is higher or equal to 0.05. Two scenarios are studied, where variables are set to reflect immune competent mice (top row) and immune competent humans (bottom row).

Impact of immune deficiency on antibiotic PK/PD targets

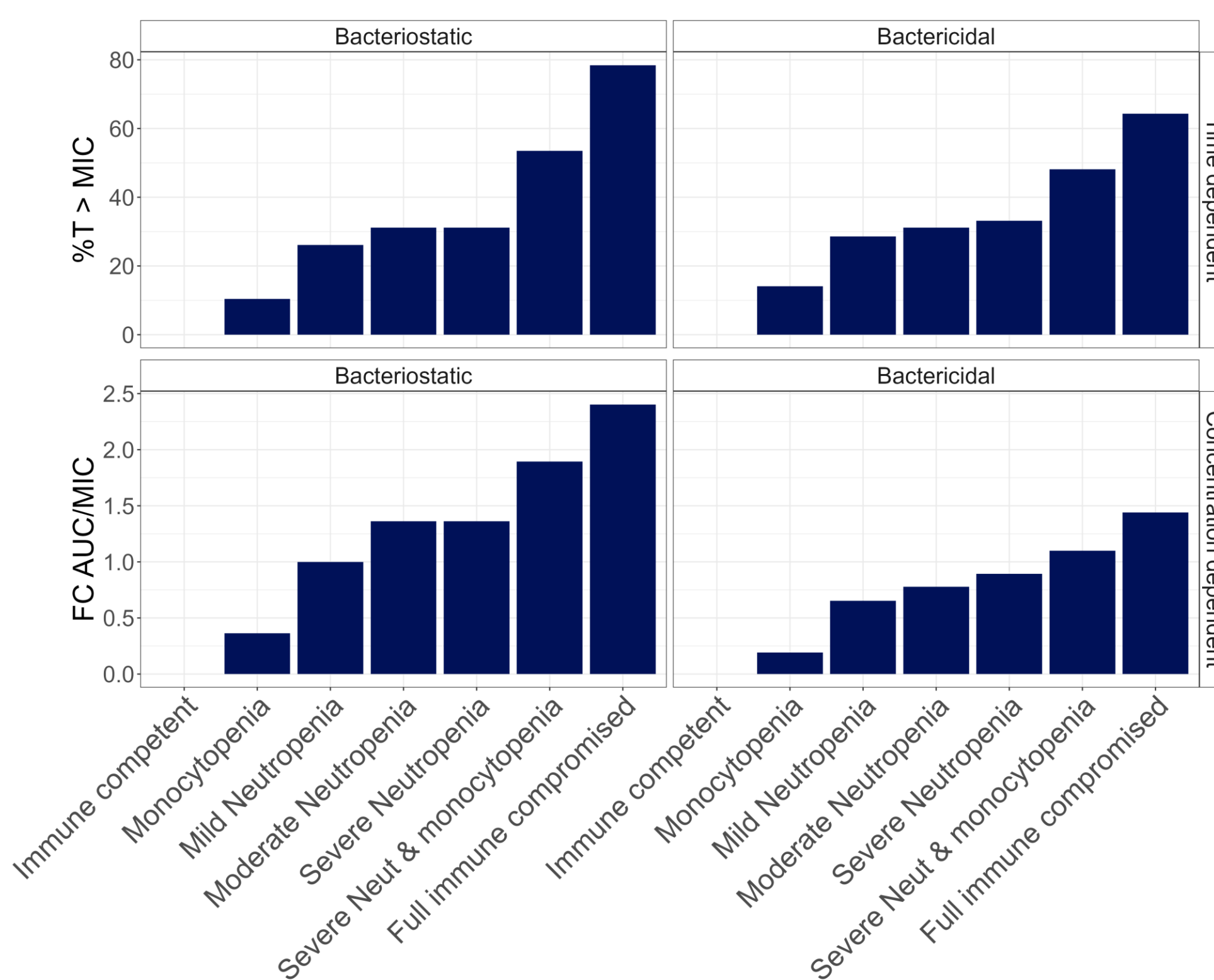


Figure 4. The impact of immune deficiencies on PK/PD targets of both time- and concentration dependent antibiotics on both bacteriostatic and bactericidal antibiotics. The fold change in AUC/MIC is calculated as the $\log_2$ fold change of AUC/MIC compared to the immune competent individual.

Conclusions

- The developed mechanism-based model captures the effects of innate immunity during bacteraemia on bacterial clearance
- Increasing levels of immune deficiency were associated with higher PK/PD targets, underscoring the role of host immunity in determining effective antibiotic exposure.