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### **Influence of Tissue Distribution and Protein Binding on Resistance**

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#### **Abstract**

Most infections occur in the tissues and body fluids rather than in the blood. The site of infection is usually the extracellular compartment of tissues or body fluids such as epithelial lining fluid, bronchial secretion or middle ear fluid. Antibiotic concentrations at the site of infection may be reduced due to high protein binding or patient-related factors. The exposure of active (unbound) drug at the site of infection, where high numbers of bacteria multiply, is not only responsible for efficacy but also drives the selection pressure for resistance. To predict the propensity of antibiotic concentrations to select resistant subpopulations, pharmacokinetic and pharmacodynamic (PK/PD) parameters have been adapted. In general, additional PK/PD indices and higher values are needed to suppress resistant subpopulations than reduce the general population. The information derived from PK/PD modelling allows to optimize dosage regimens and minimize the preferential killing of the susceptible majority, leaving a selected drug-resistant subpopulation intact. Better understanding about the influence of protein binding, PK/PD principles at tissue sites versus blood, and interaction between antibiotic treatment and commensal flora is needed to improve dosing regimens that may be less likely to promote resistance selection pressure at the site of infection.