

Modelling antibiotic PKPD in a lung-mimicking transwell model

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Background

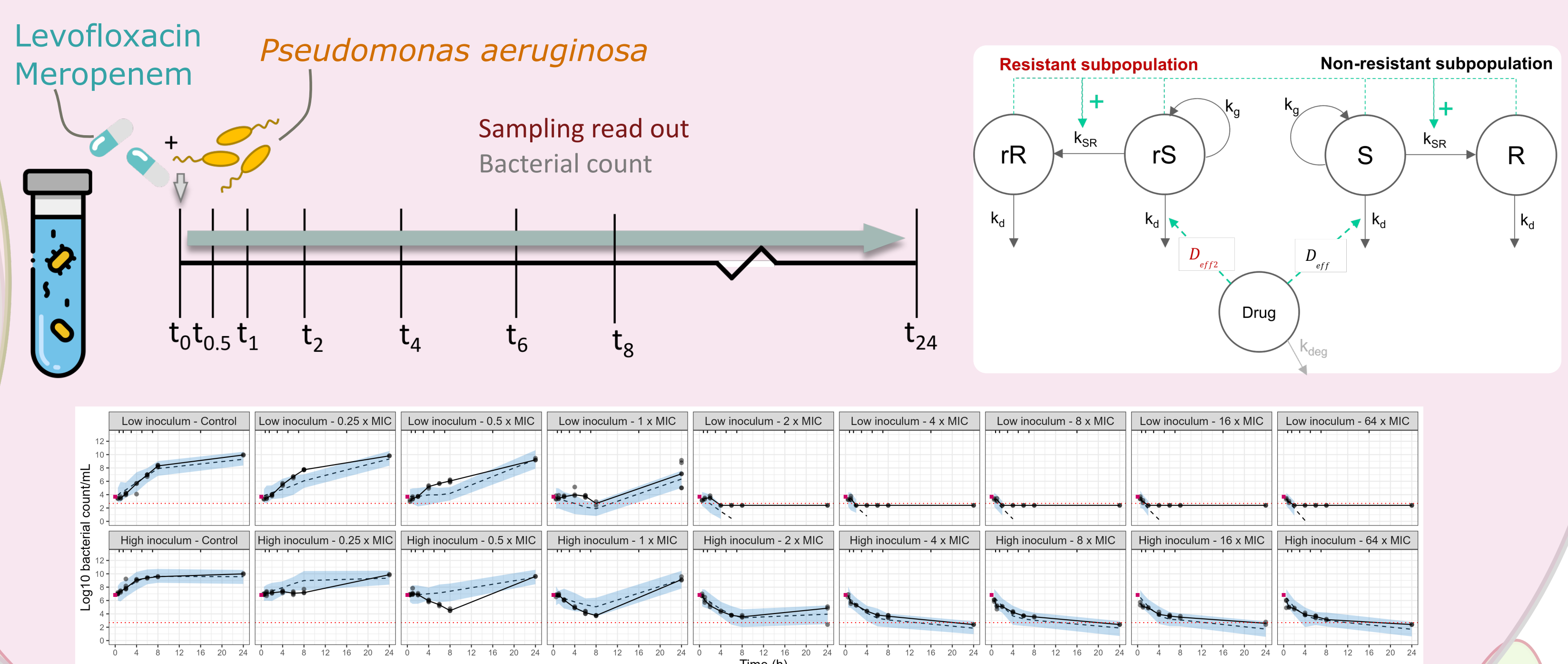
- Traditional *in vitro* time-kill curve (TKC) experiments do not fully replicate the complexity of *in vivo* environments.
- In lung infections, factors like tissue penetration, mucus thickness, pH, and bacterial-induced tissue disruption may influence drug distribution and bacterial dynamics. [1,2]
- Swart et al. [3] developed an *in vitro* human lower airway transwell tissue infection model, offering a physiologically relevant setup for TKC experiments.

Aim

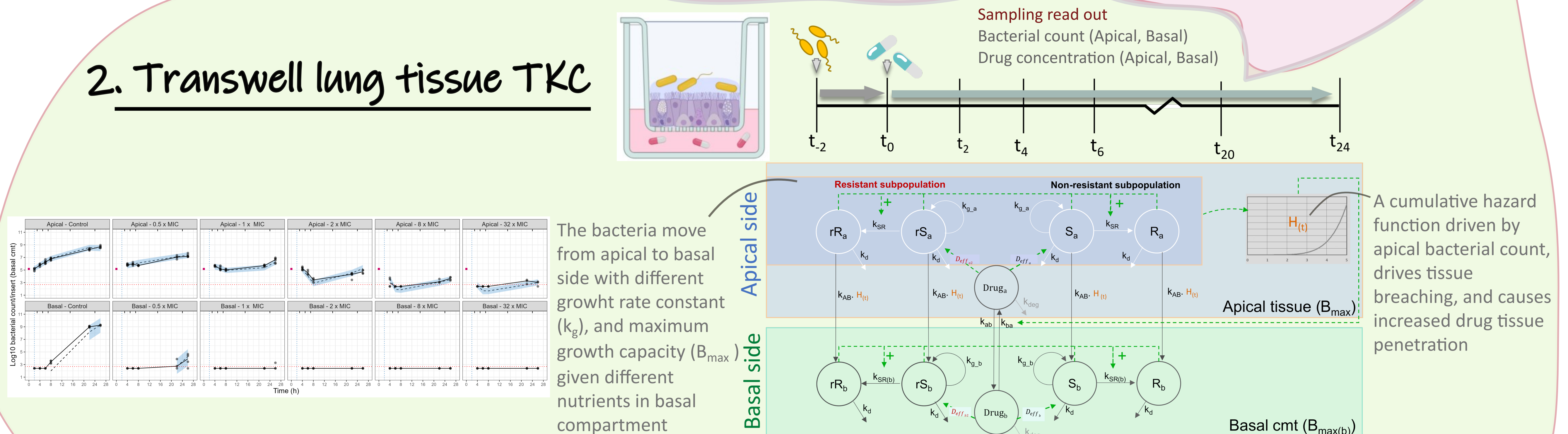
To evaluate the utility of transwell model for antibiotic PKPD assessment, comparing it to broth-based TKC experiments.

Methods and results

1. Conventional broth-based TKC



2. Transwell lung tissue TKC

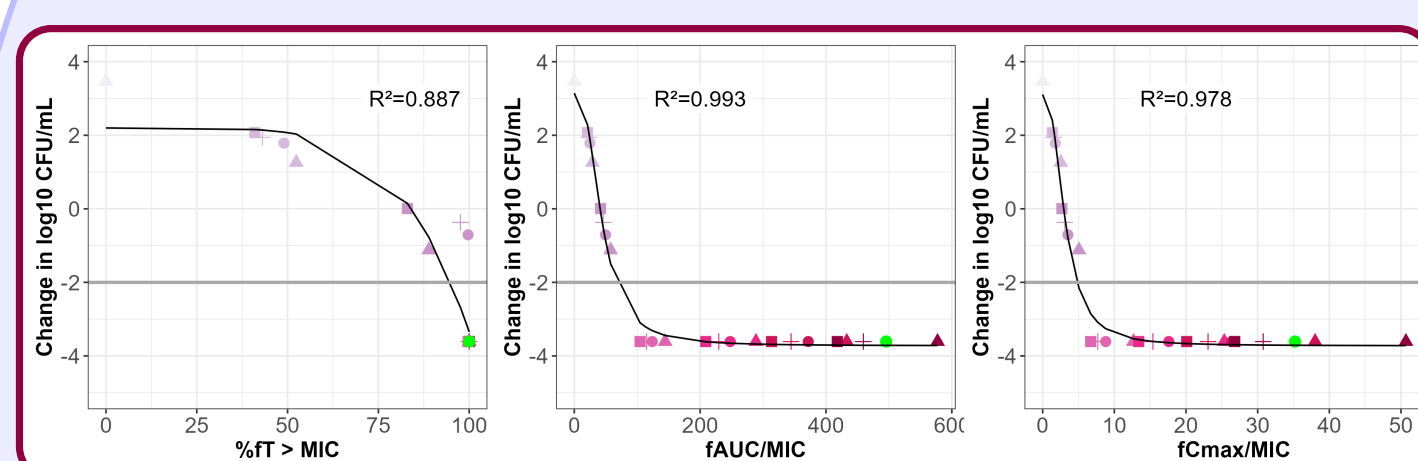


3. PKPD indices simulations

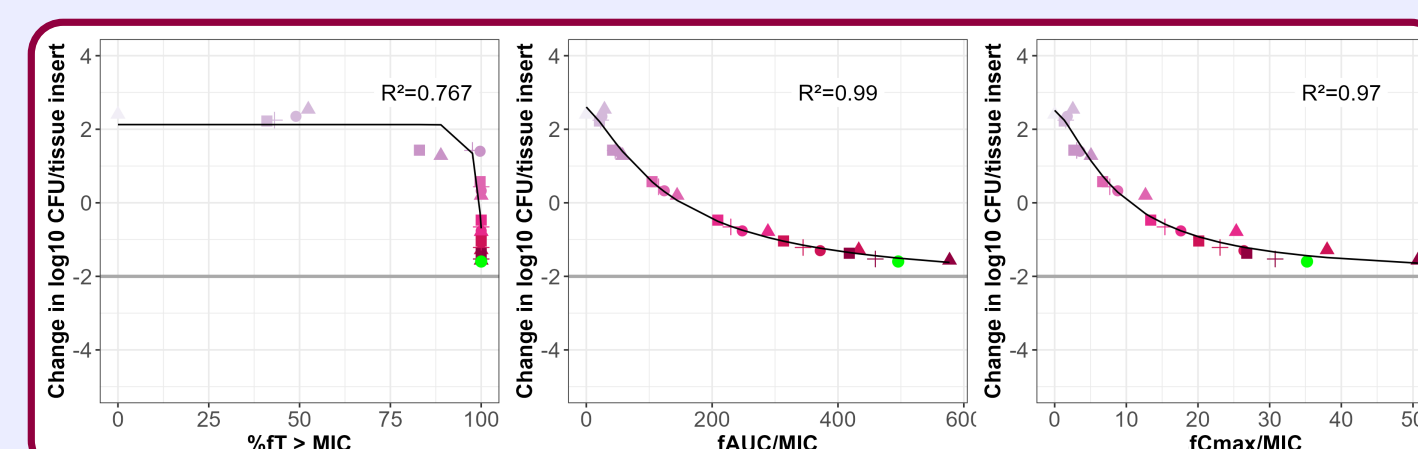
Simulations of dose fractionation studies were performed to evaluate differences in PKPD indices between models. Published human PK models [4,5] were linked to the developed models to predict the epithelial lining fluid concentrations that drive the bacterial killing.

Levofloxacin

Broth model

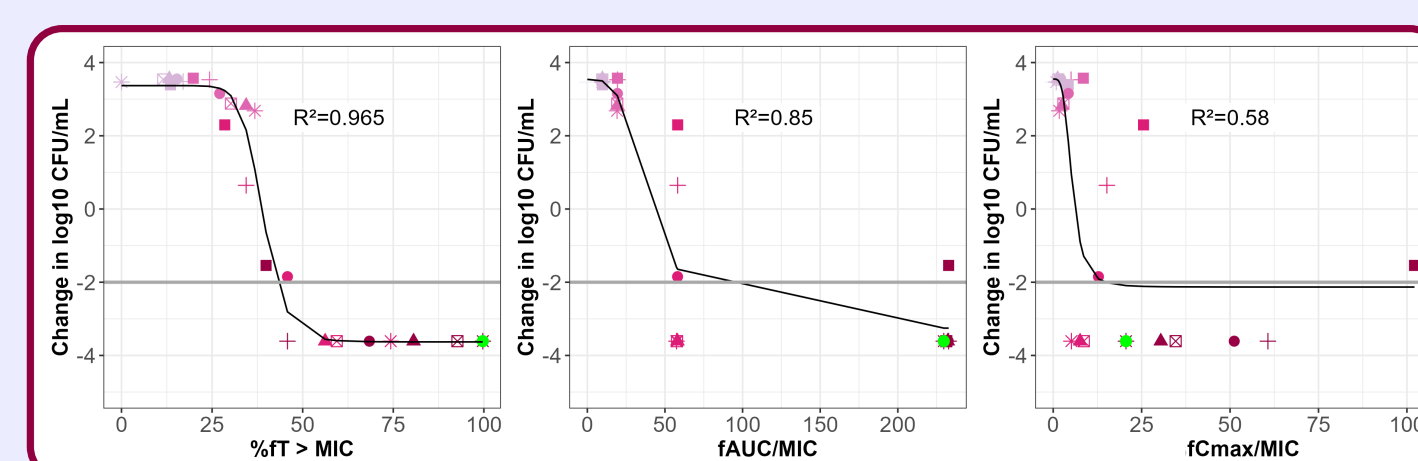


Tissue model

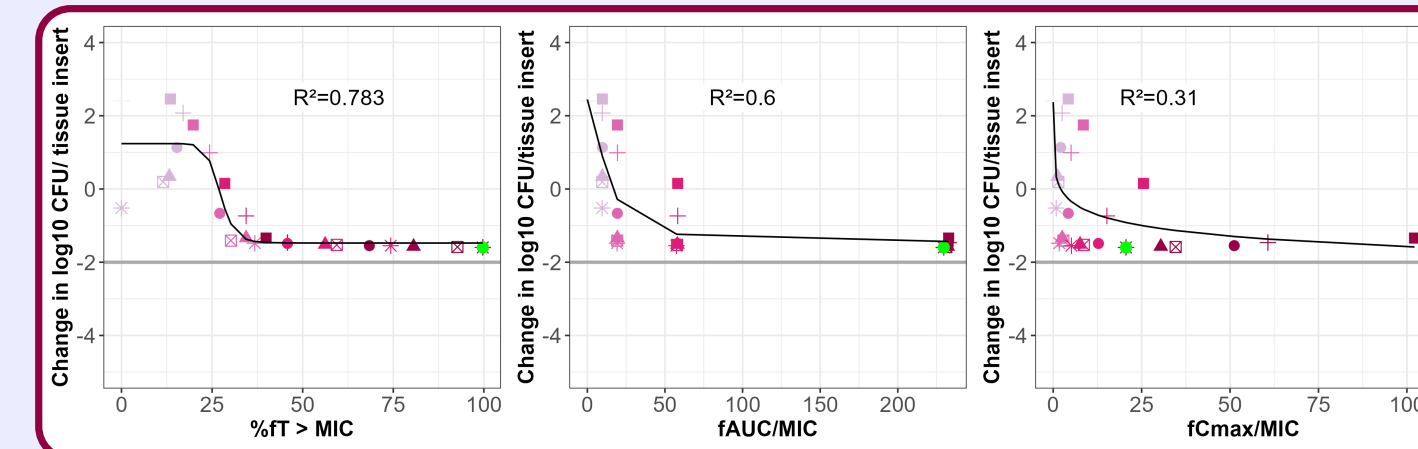


Meropenem

Broth model



Tissue model



Conclusions

- The PKPD modelling revealed slower bacterial growth and killing rates in tissue than broth-based TKC models.
- Impaired tissue integrity led to increased tissue exposure for meropenem, a low-permeability drug, while tissue exposure for levofloxacin remained unchanged.
- The selected PKPD indices for drug efficacy aligned between the models, however different targets were predicted.
- Further research should explore additional pathogen-drug combinations, with dynamic drug concentration.

References

- [1] Satta G et al., Antimicrob Agents Chemother 1988;32:552–60.
- [2] Nielsen EI and Friberg LE. Pharmacol Rev 2013;65:1053–90.
- [3] Nussbaumer-Pröll A and Zeitlinger M. Pharmaceutics 2020;12:773.
- [4] Kuti JL, et al., Int J Antimicrob Agents 2015;45:512–8.
- [5] Lodise TP, et al., Antimicrob Agents Chemother 2011;55:1606–10.



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