Standardized, Quality Assured Time-Kill Curve Analysis and Pharmacodynamic Functions of Different Antibiotics for *in-vitro* Evaluation of Treatment Regimens for *Neisseria gonorrhoeae*

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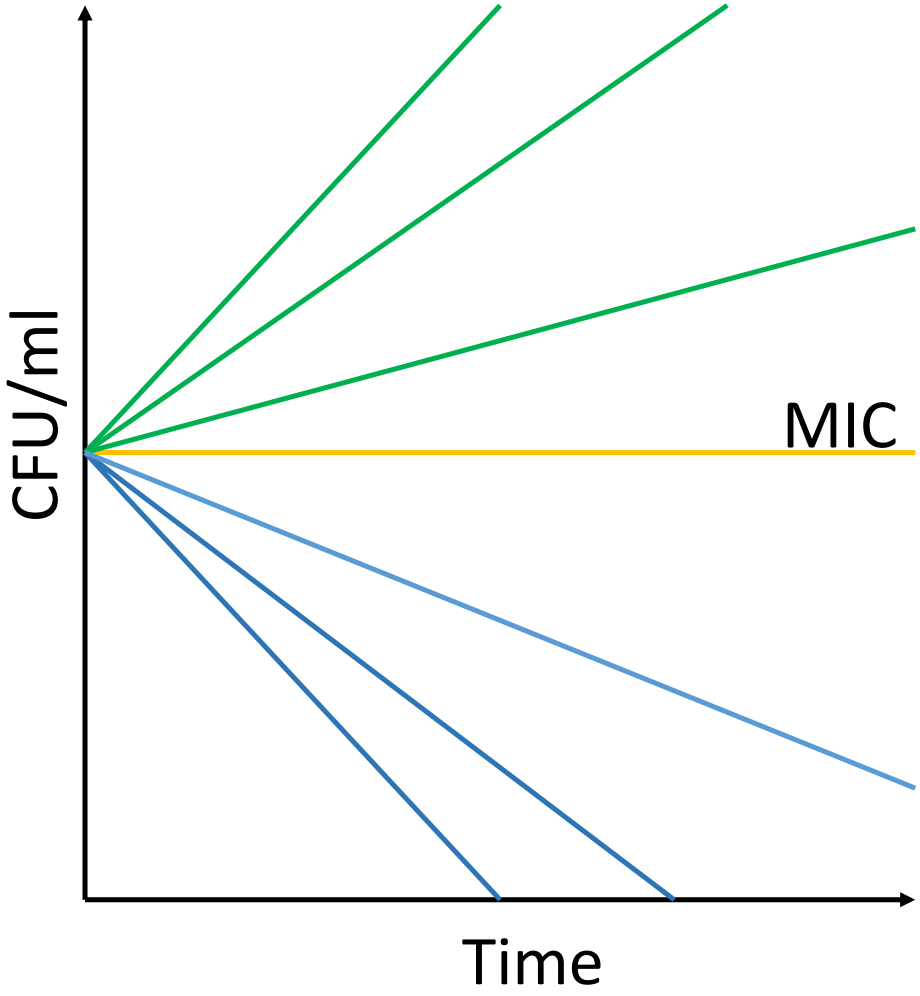
Time-kill curves for *Neisseria gonorrhoeae*

Challenges:

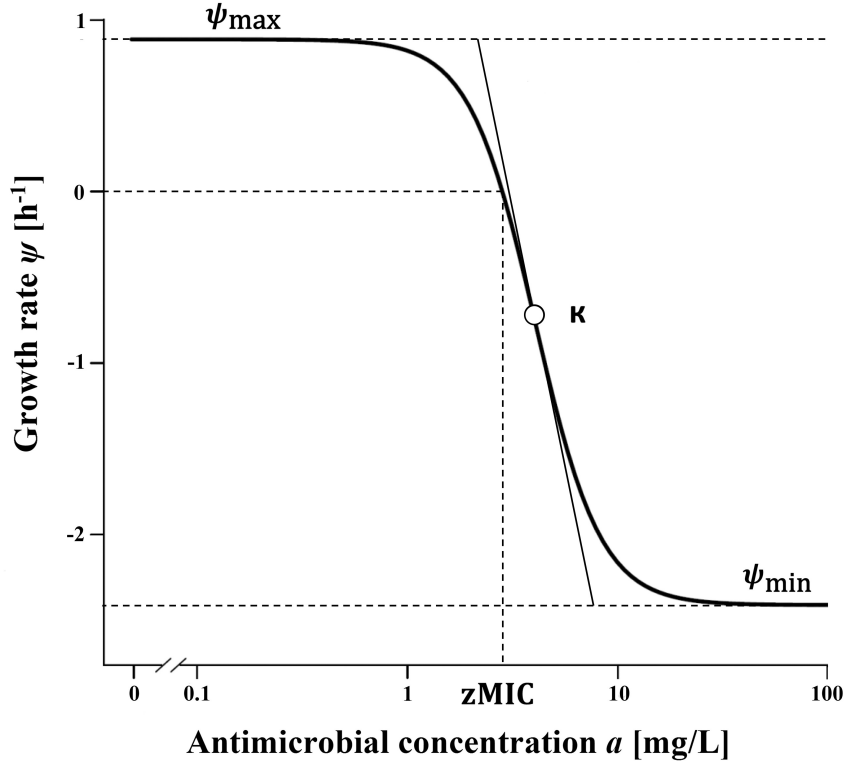
- Fastidious bacteria difficult to grow standardized in liquid broth
- Synchronized growth phase for all strains needed
- Interpretation requires expert knowledge
- Normally very low throughput (colony counting!)



Pharmacodynamic analysis of *in-vitro* time-kill data

Estimating pharmacodynamic parameters from time-kill data (Regoes et al., 2004):

- ψ_{max}: maximal growth in absence of antimicrobial
- κ: slope of Hill function
- ψ_{min}: minimal net growth at high concentrations
- zMIC: concentration that results in zero growth



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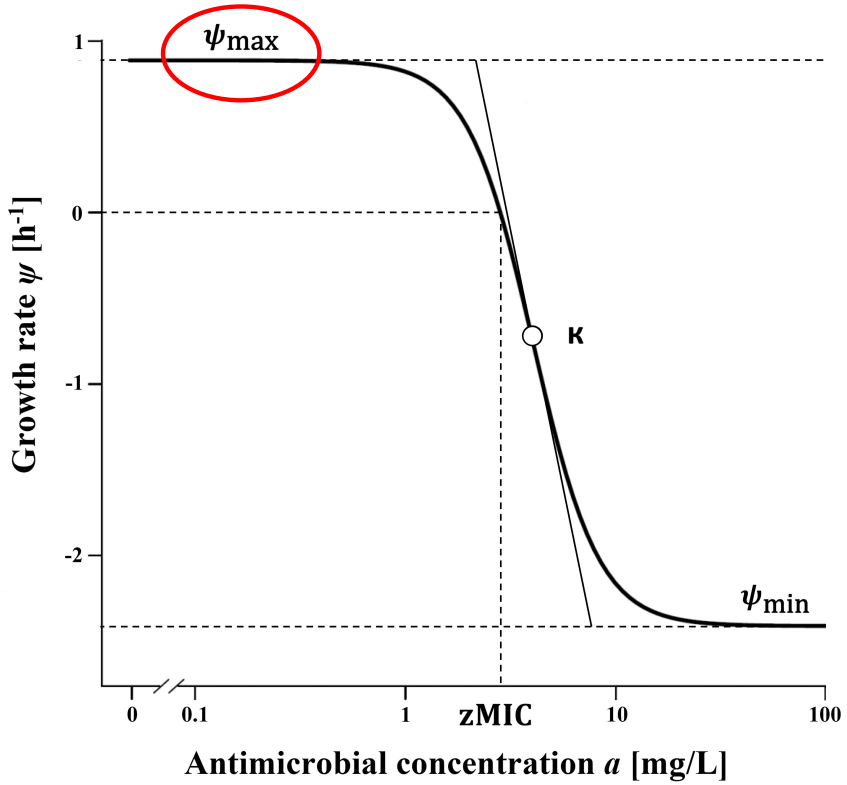

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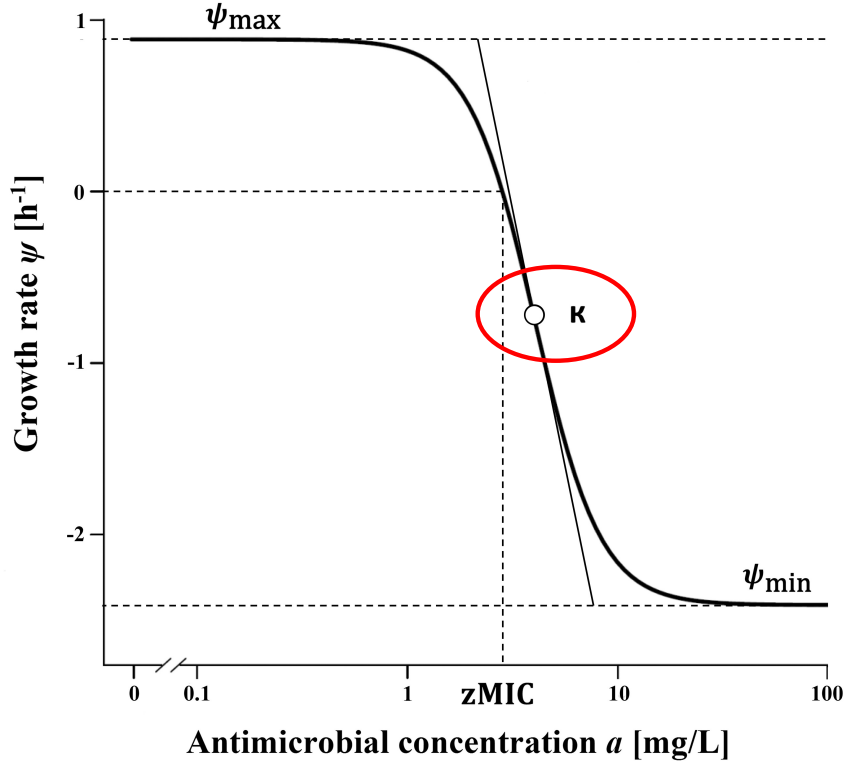

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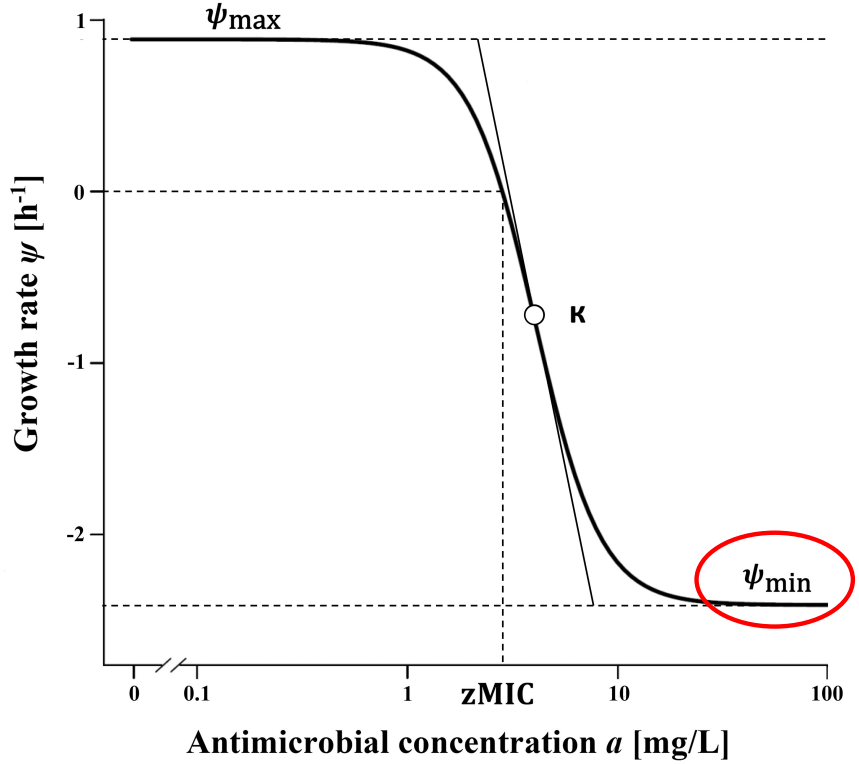

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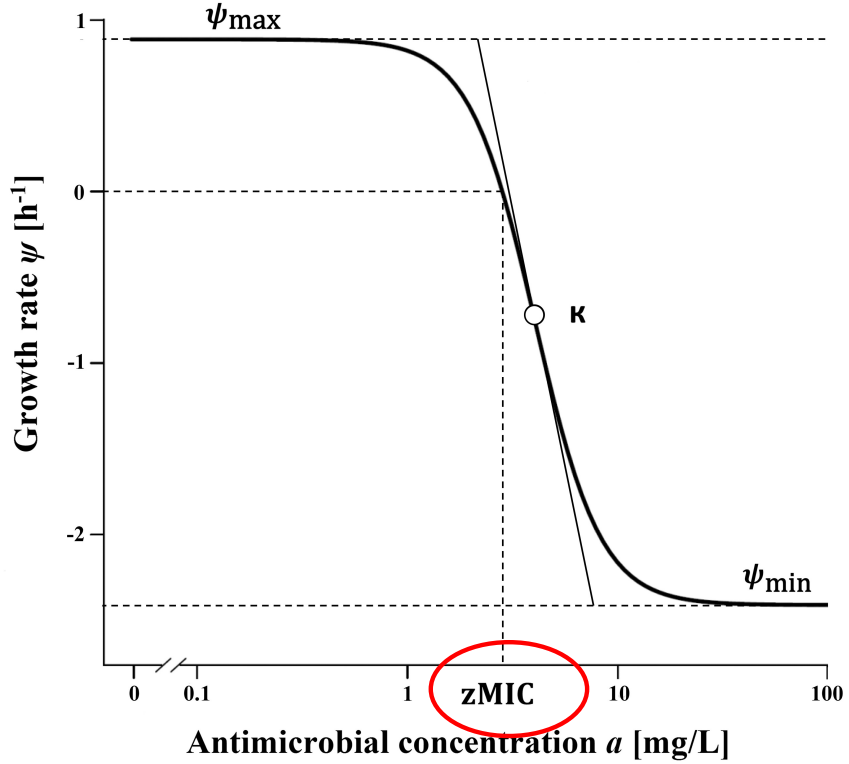
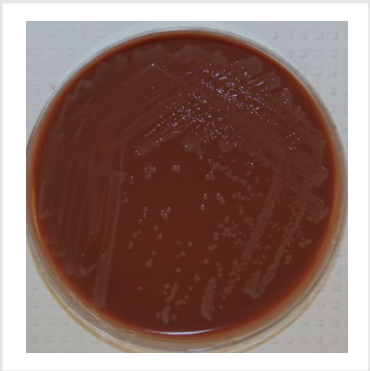
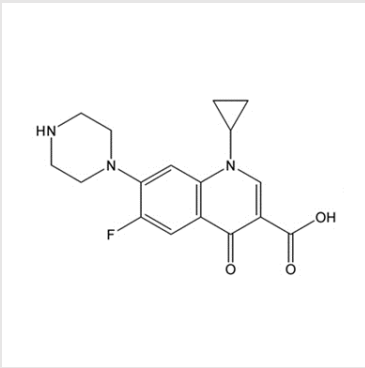
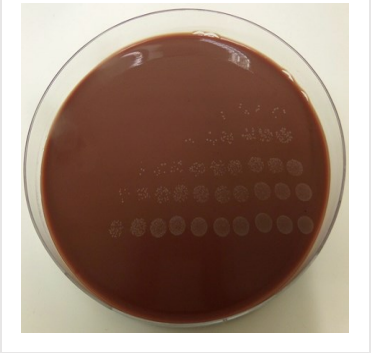
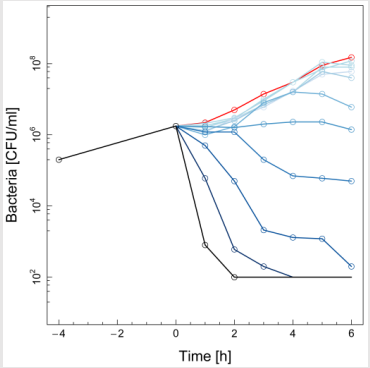


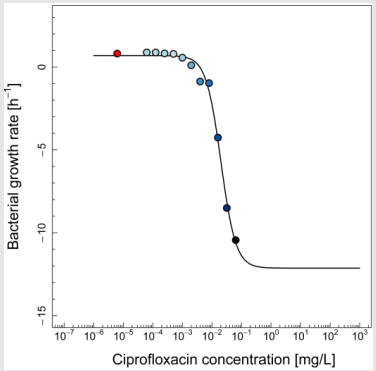
Workflow of the novel time-kill assay











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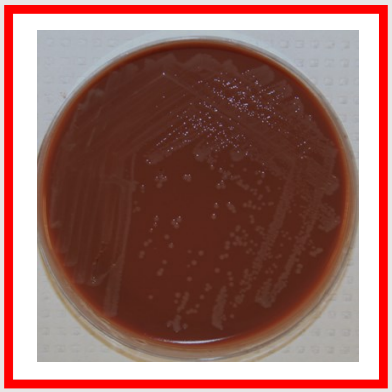

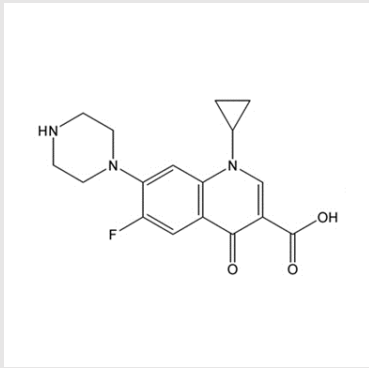

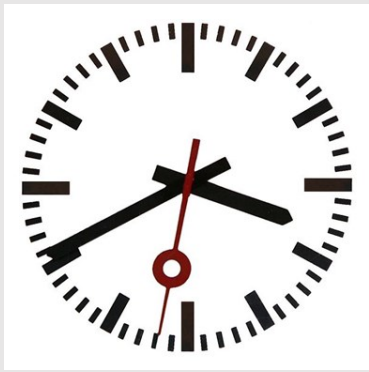

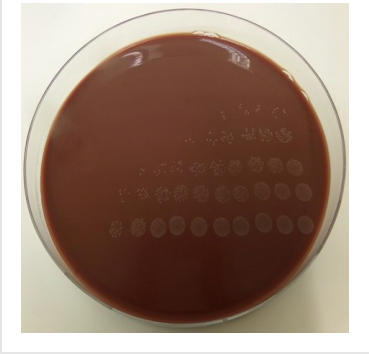

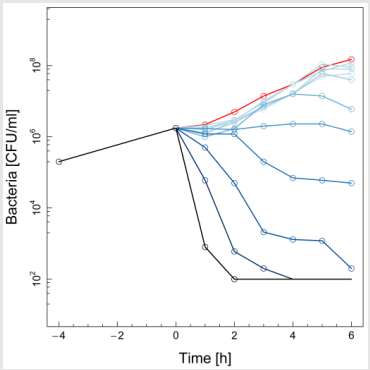

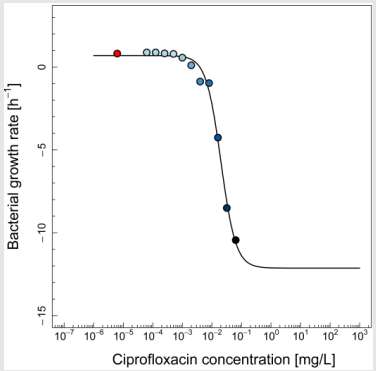

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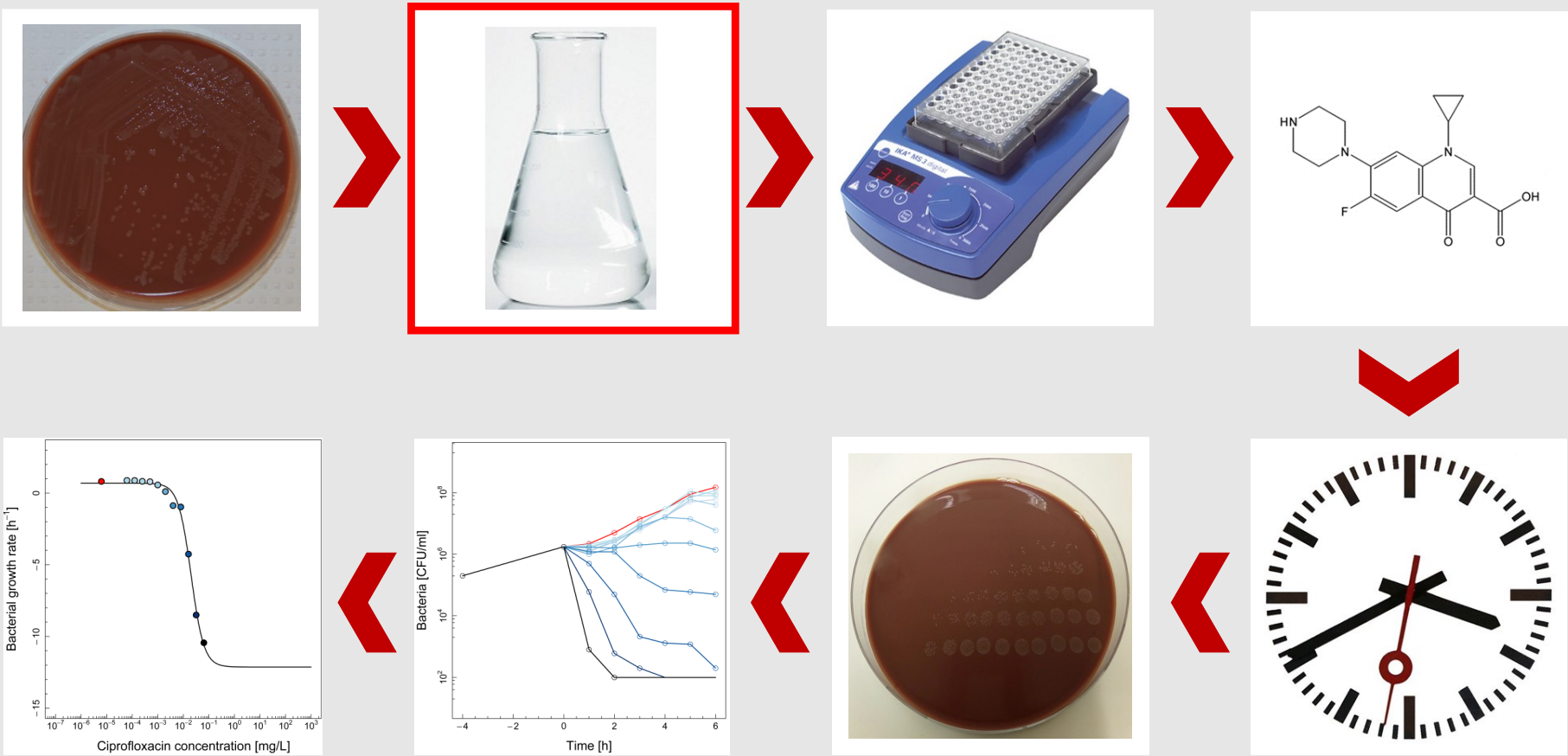

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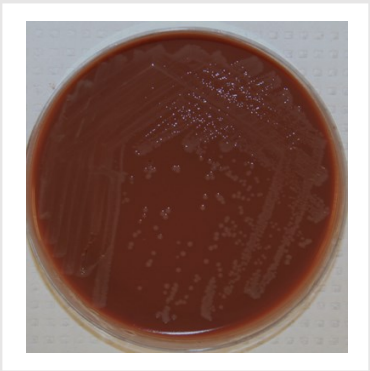

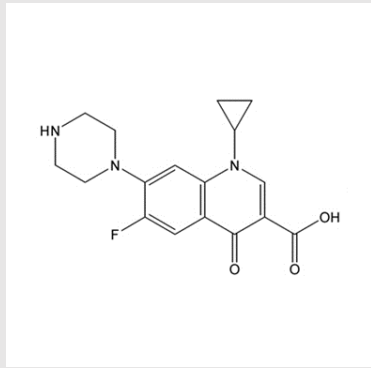

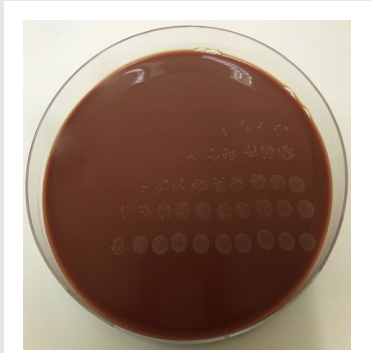

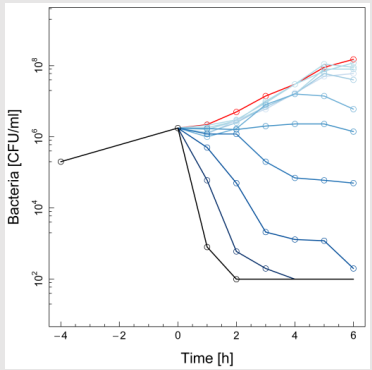

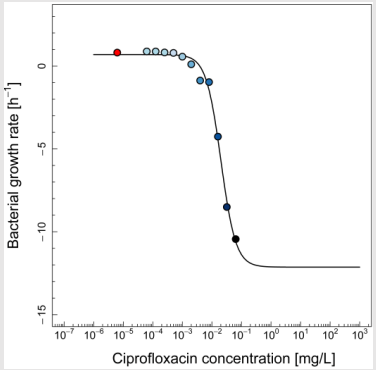

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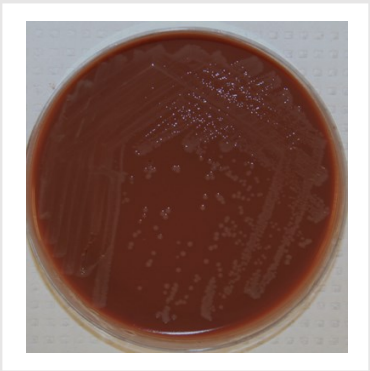

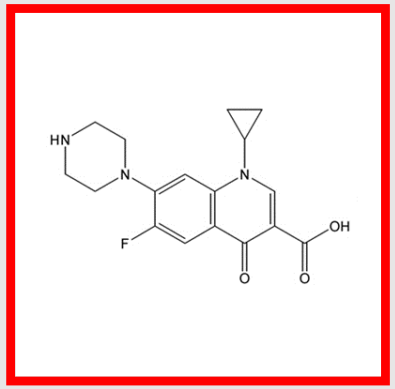

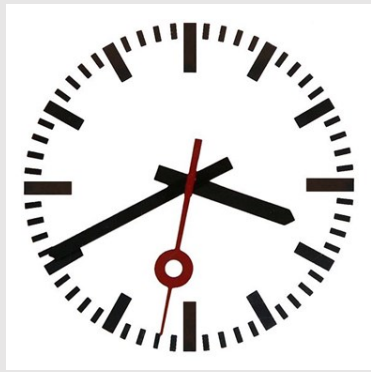

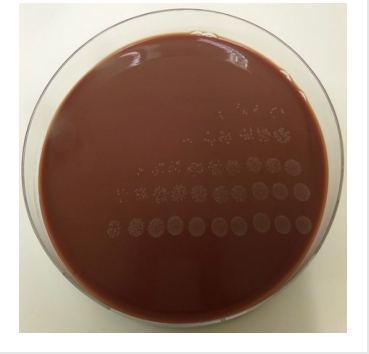

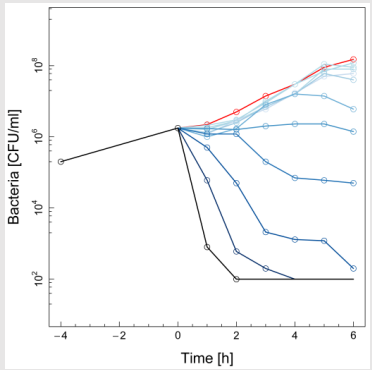

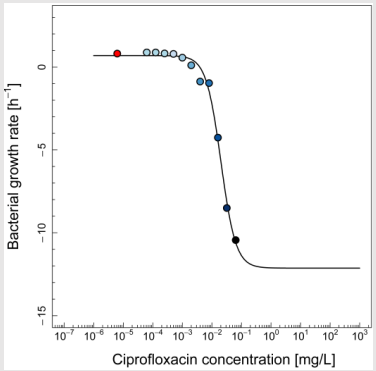

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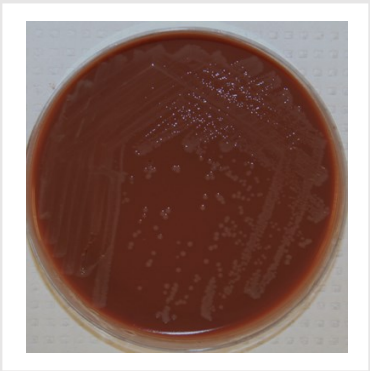

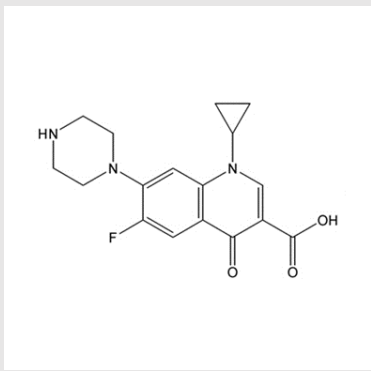

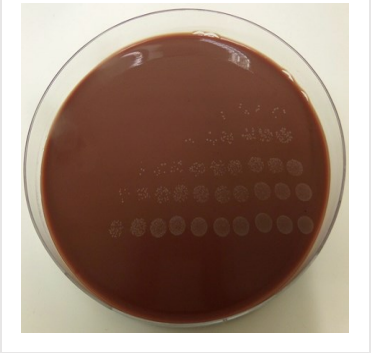

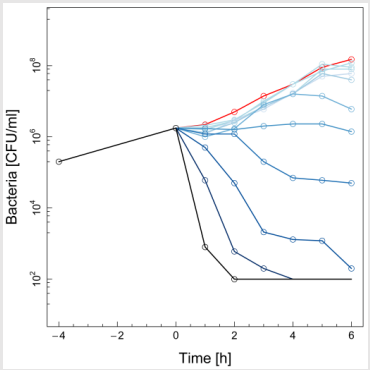

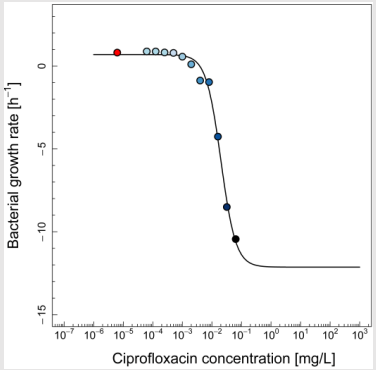

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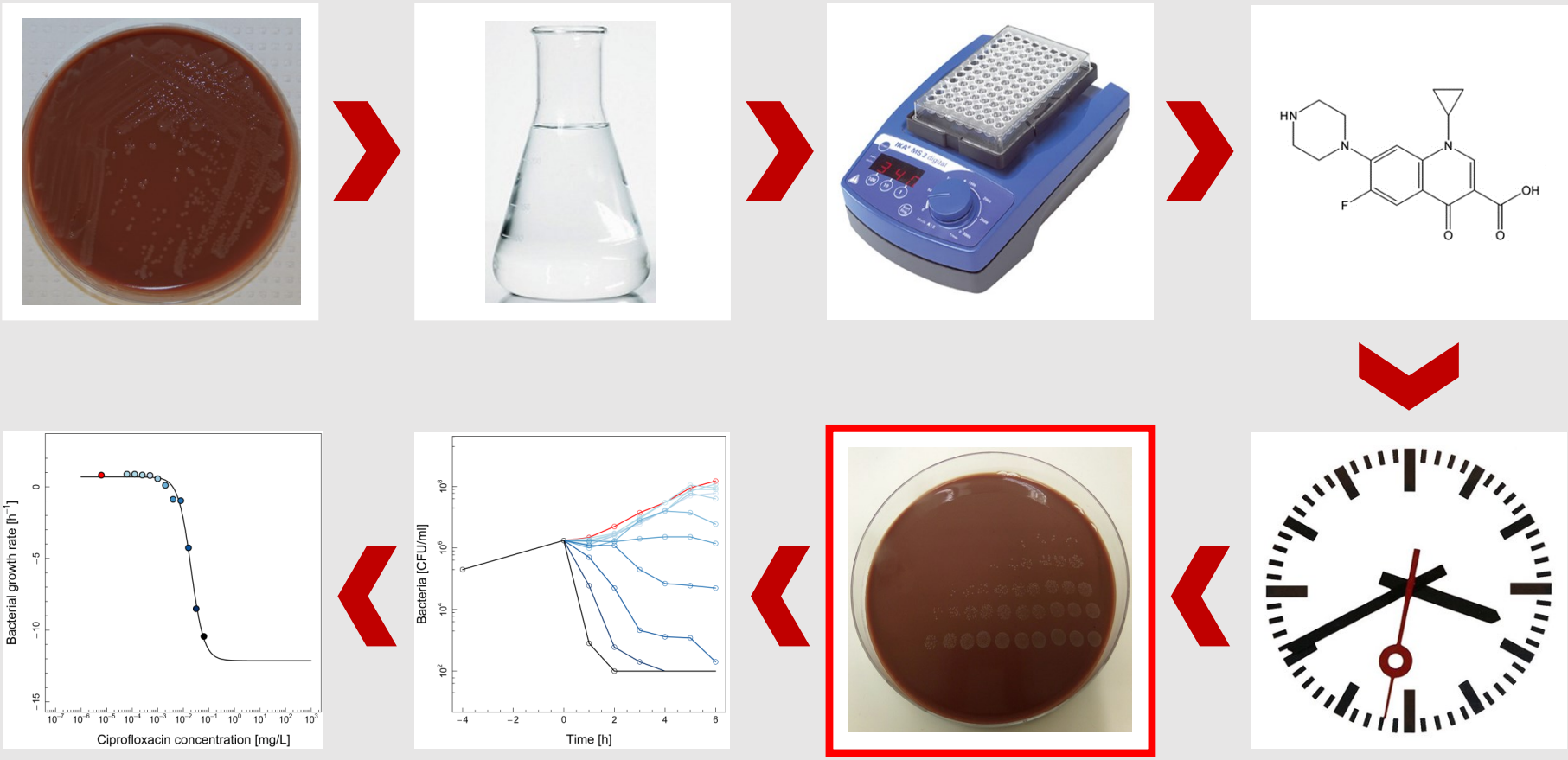

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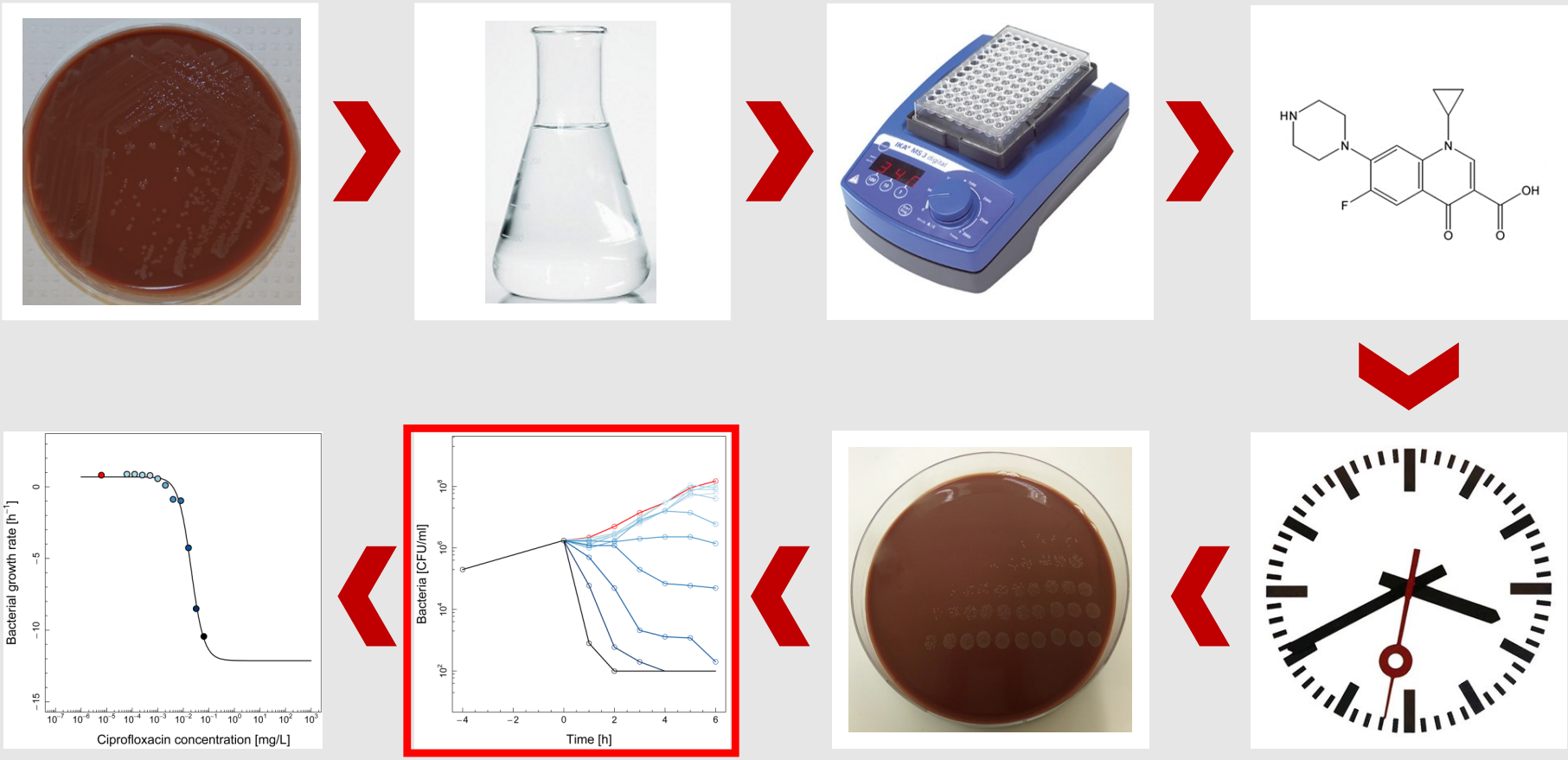

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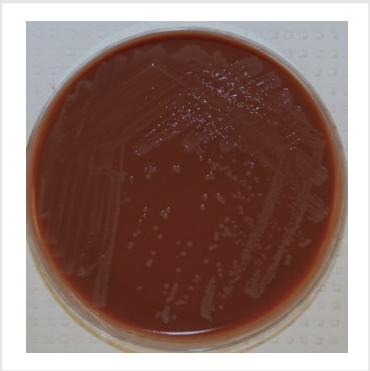
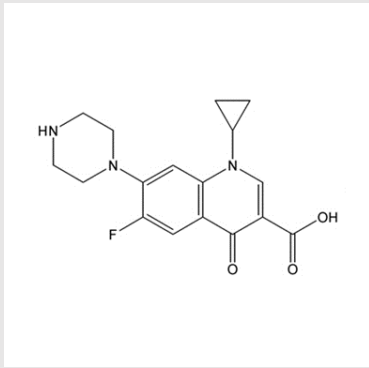
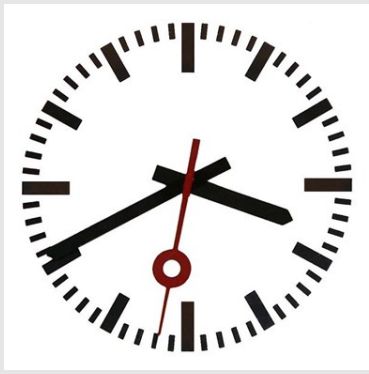
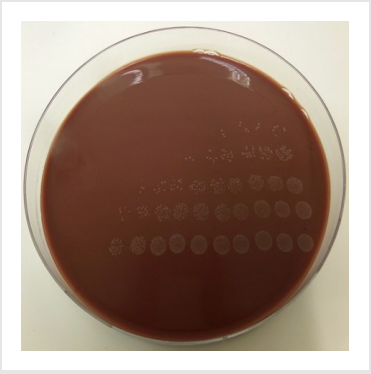
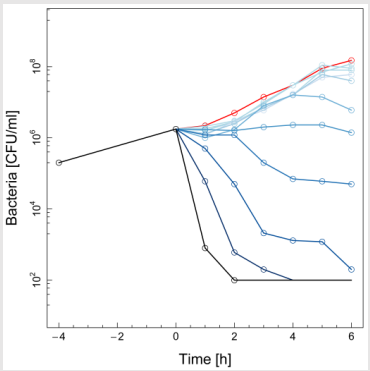
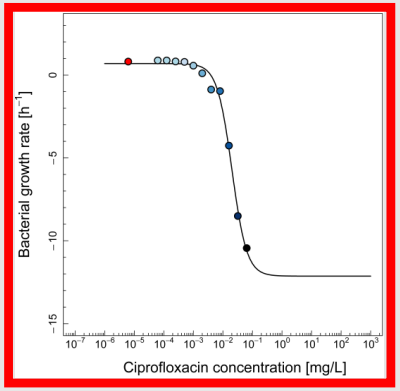




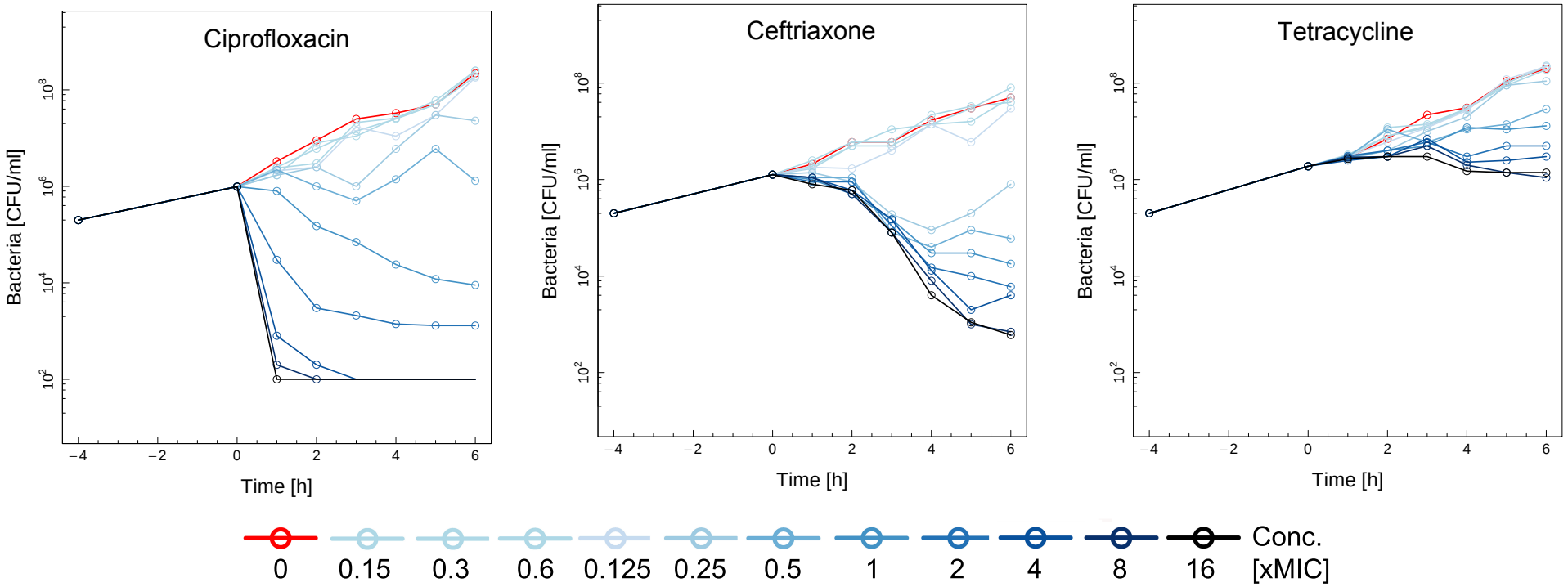








Time-kill curves in a susceptible strain (DOGK18)



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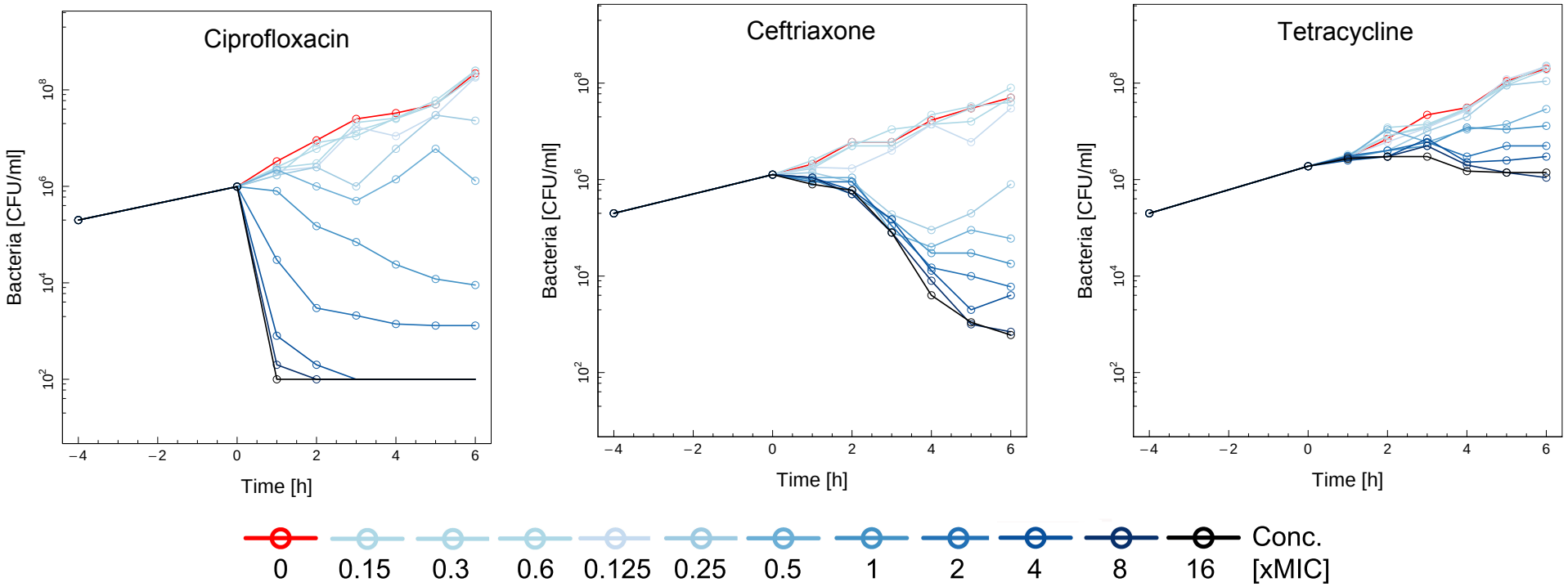
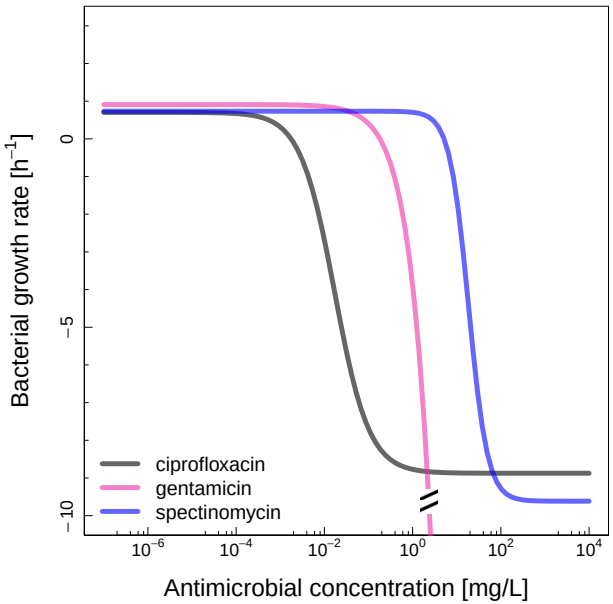
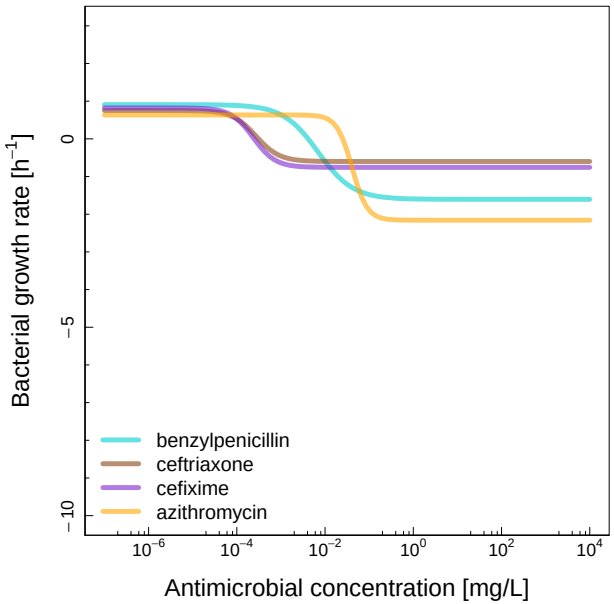
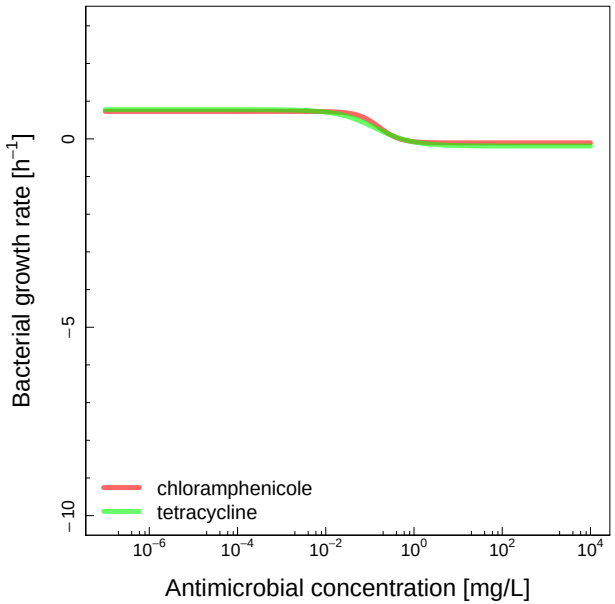


Time-kill assay has improved throughput and distinguishes different antimicrobials

Pharmacodynamic functions for different antimicrobials in DOGK18







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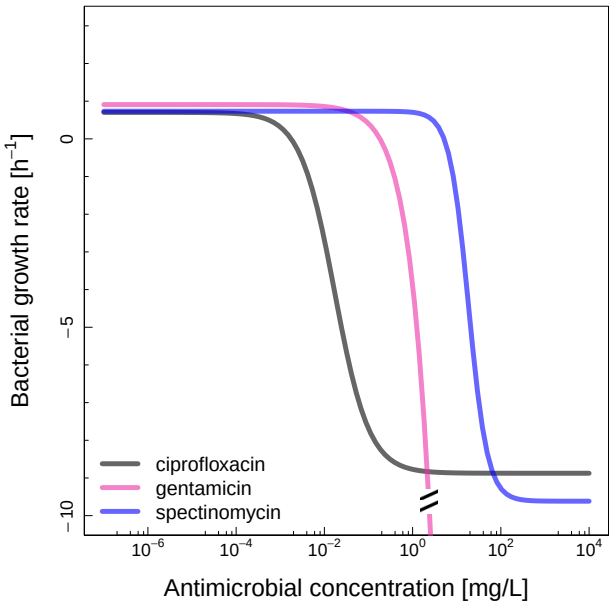
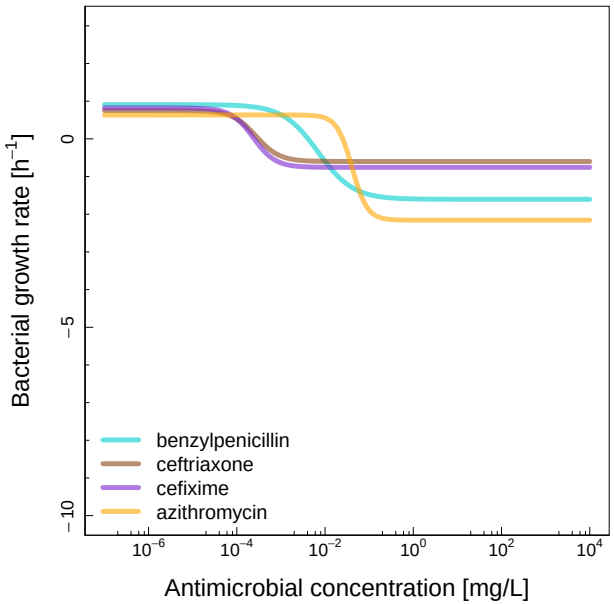
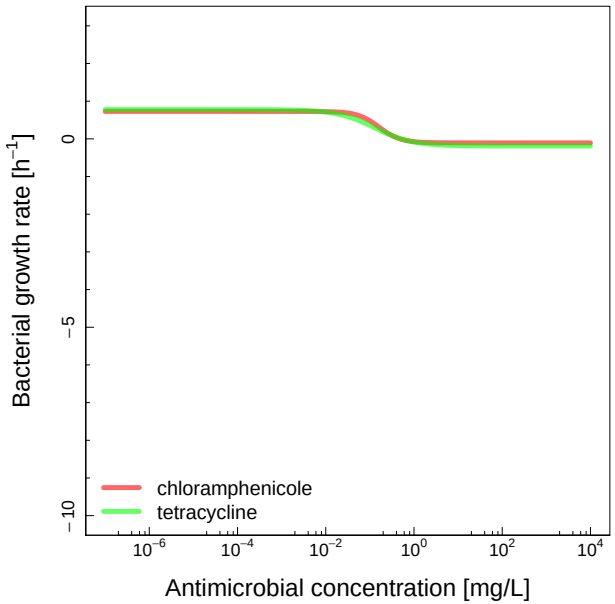






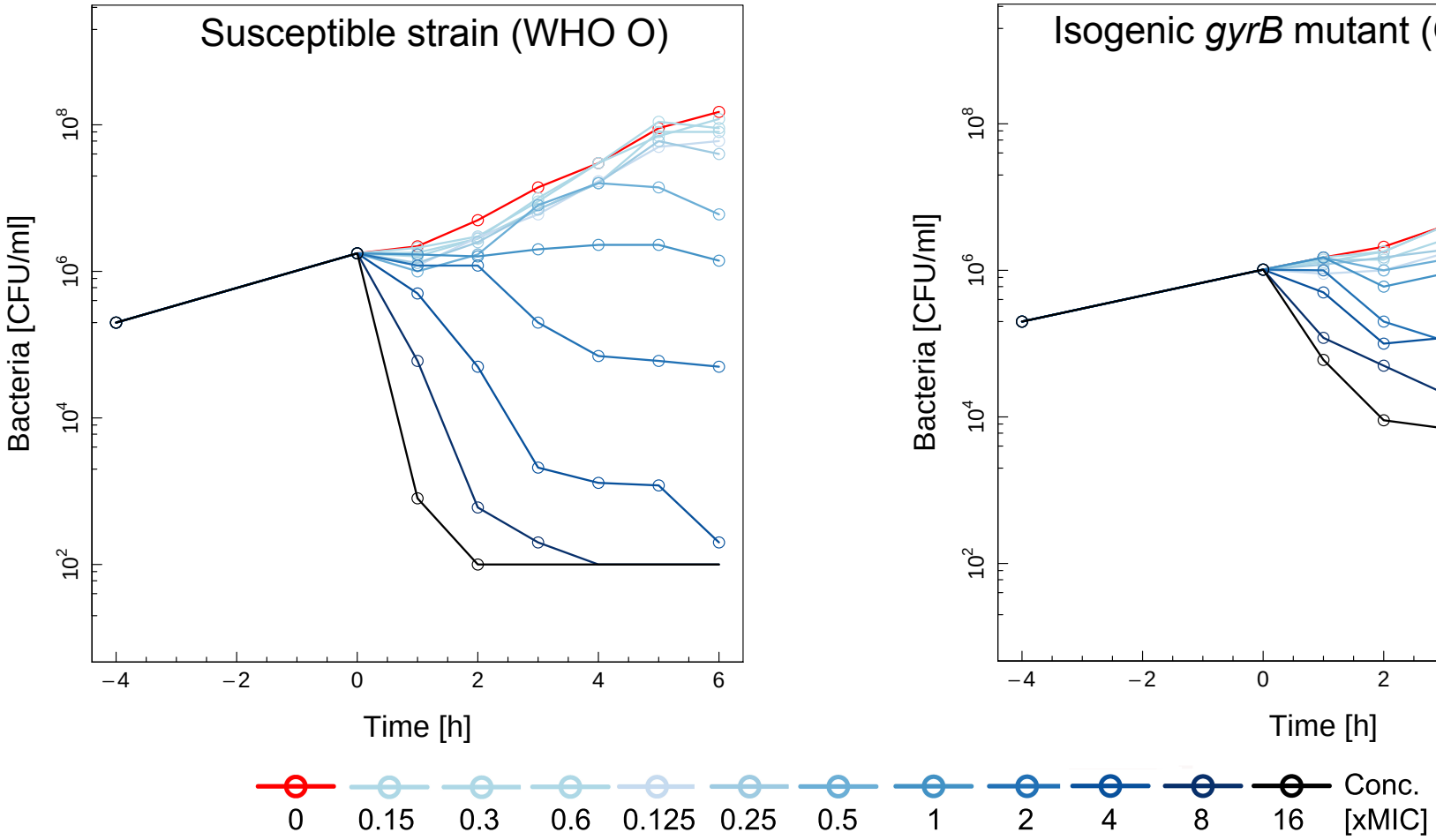
Pharmacodynamic functions quantify the results from rapidly bactericidal to bacteriostatic

Application of the novel assay

Genetic resistance determinants, in vitro time-kill curve analysis and pharmacodynamic functions for the novel topoisomerase II inhibitor ETX0914 (AZD0914) in Neisseria gonorrhoeae

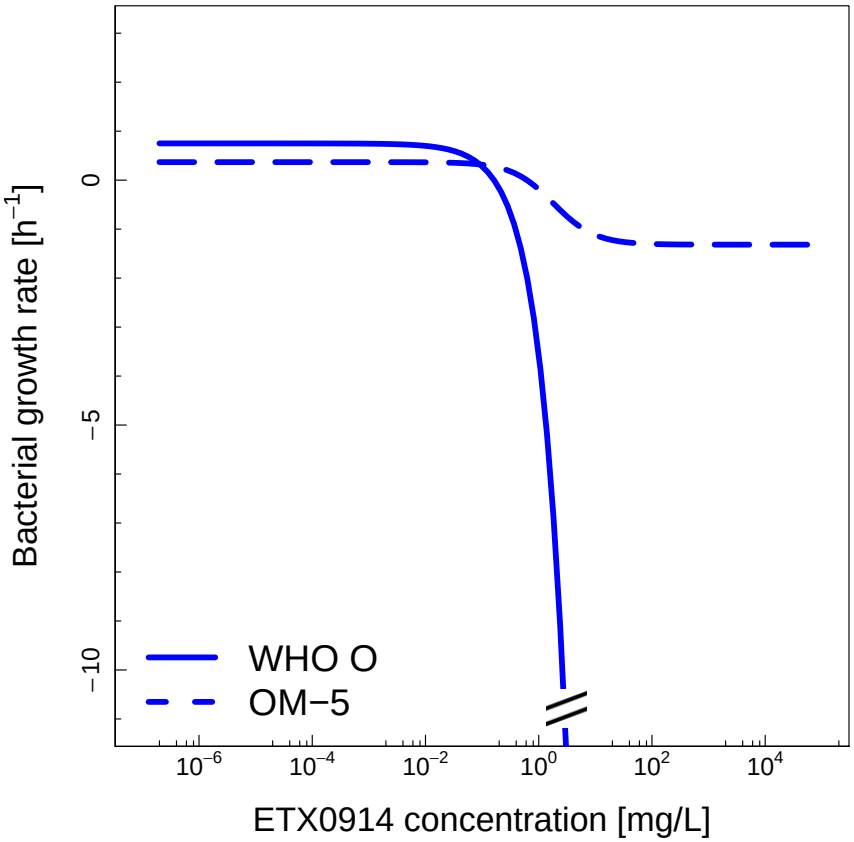
Sunniva Förster, Daniel Golparian, Susanne Jacobsson, Lucy Hathaway, Nicola Low, William Shafer, Christian Althaus and Magnus Unemo

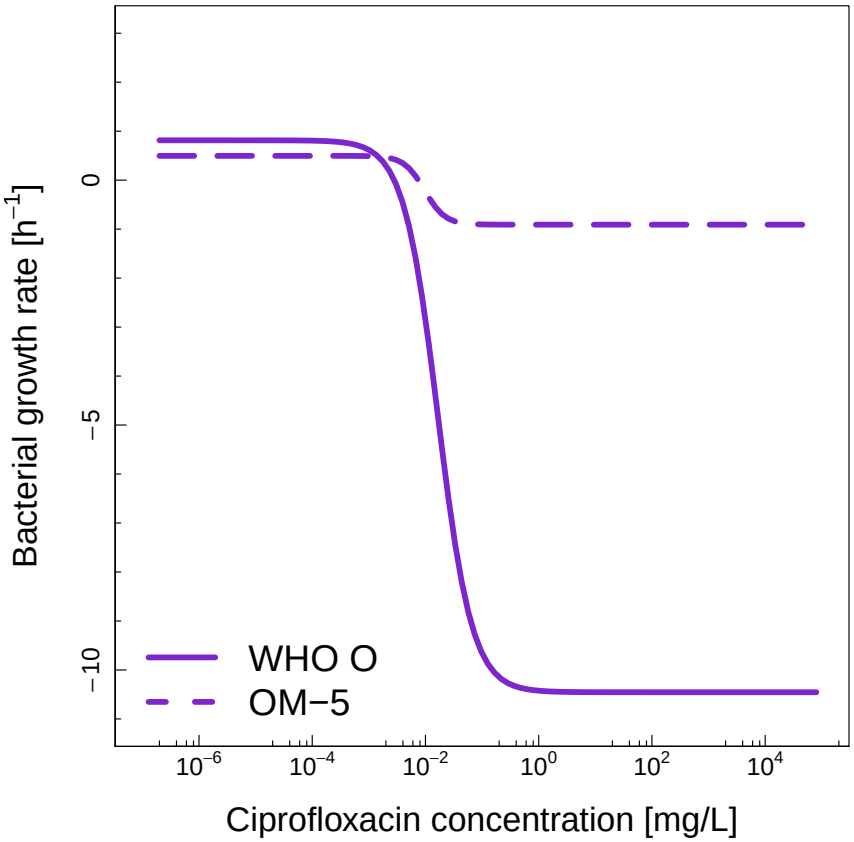
Comparison of mutants resistant to ETX0914



Förster et. al. 2015, submitted

Pharmacodynamic comparison of ETX0914 and ciprofloxacin





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- Evaluation of drug candidates (ETX0914) and mutants (*gyrB*)

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- The time-kill assay works across susceptible strains, resistant mutants and antimicrobial classes
- Pharmacodynamic functions can be used to quantify time-kill data
- Evaluation of drug candidates (ETX0914) and mutants (*gyrB*)
- Estimated parameters can be used for pharmacodynamic modelling

Acknowledgements

University Hospital Örebro

- Daniel Golparian
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- Magnus Unemo

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- Christian Althaus
- Nicola Low

Institute for Infectious Disease (IFIK)

- Lucy Hathaway

References

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