Model-based design of innovative treatment strategies to suppress antimicrobial resistance using collateral sensitivity

PAGE

Online – in the cloud

Lewis Sheiner Student Session 2021

Linda Aulin

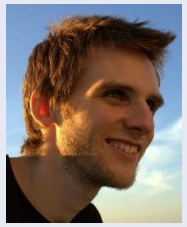
Universiteit Leiden
The Netherlands

Acknowledgments

Universiteit Leiden
The Netherlands

LACDR

Quantitative Pharmacology
PI: Dr Coen van Hasselt



Collaborators:

ibl

Dr. A. Liakopoulos
Dr. D.E. Rozen
M. Buffoni

Funding

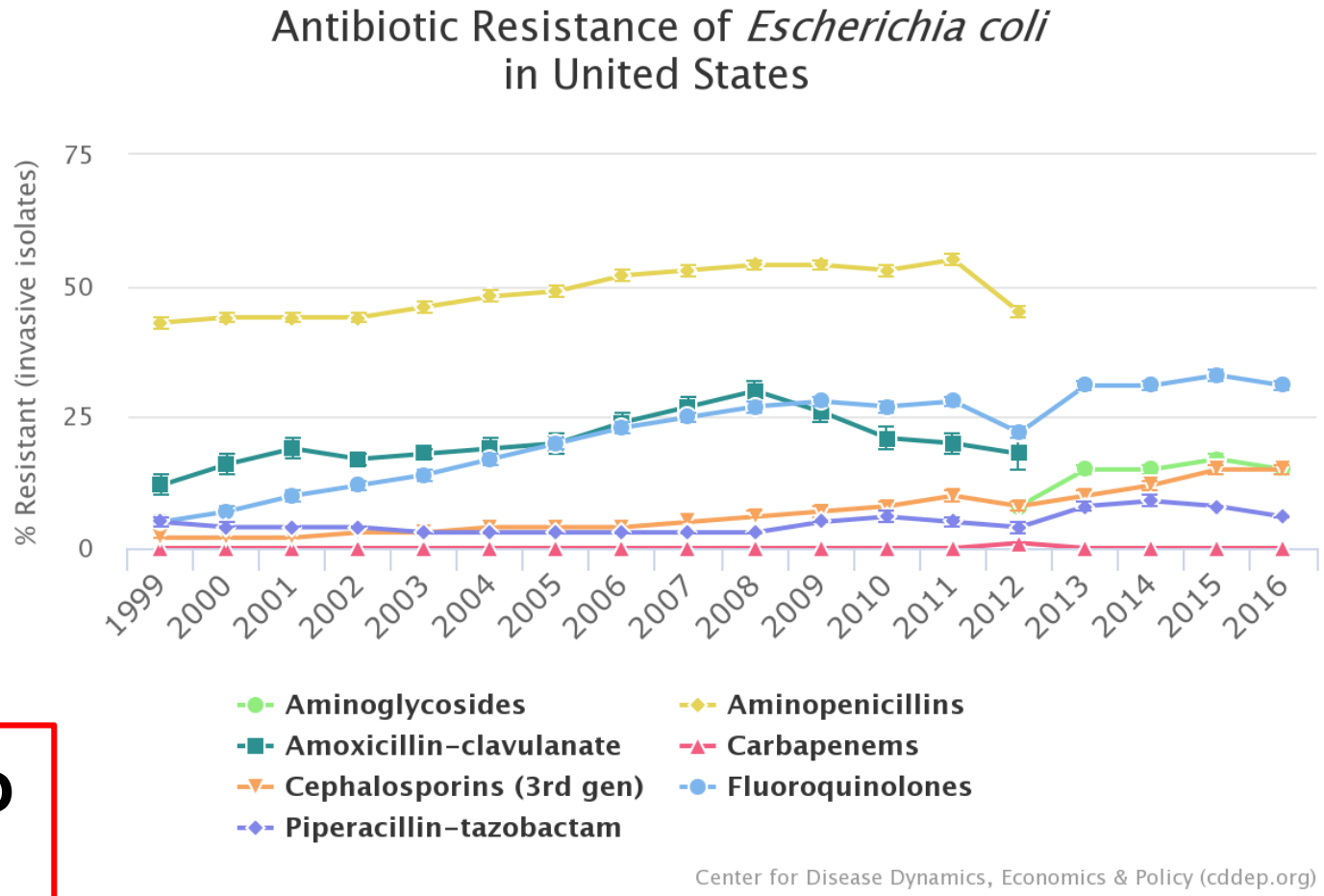
ZonMw

jpiamr

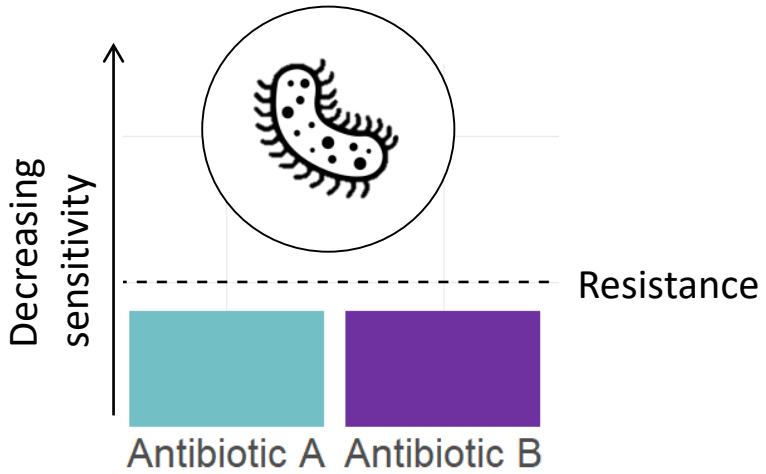
How do we alleviate the threat of antibiotic resistance?

- Increasing resistance is threating treatment efficacy.
- There is a lack of new antibiotics.
- There is a need for innovative treatment strategies using available antibiotics.

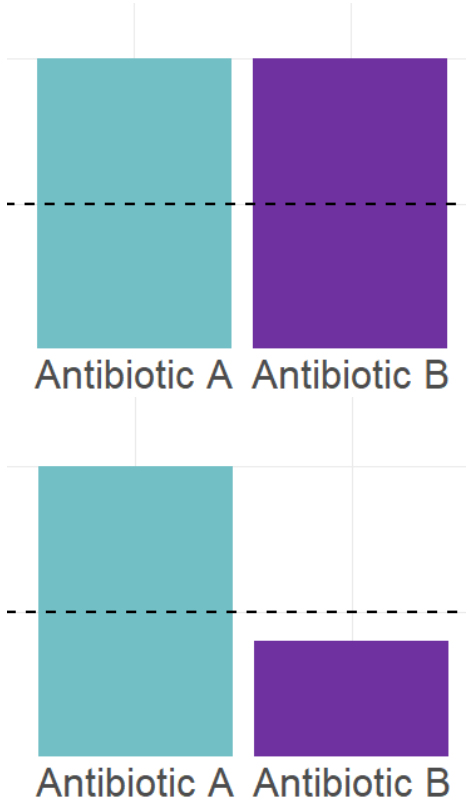
Can we exploit resistance to improve treatments?



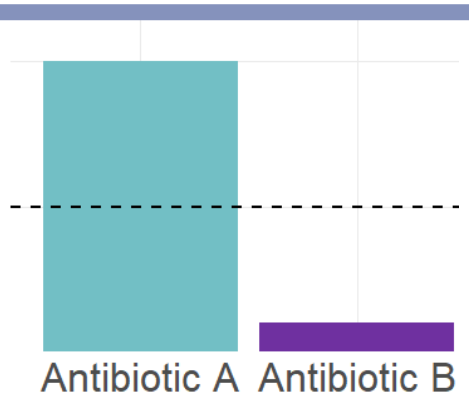
Antibiotic resistance and collateral effects



Antibiotic **A**



Potential to improve treatments



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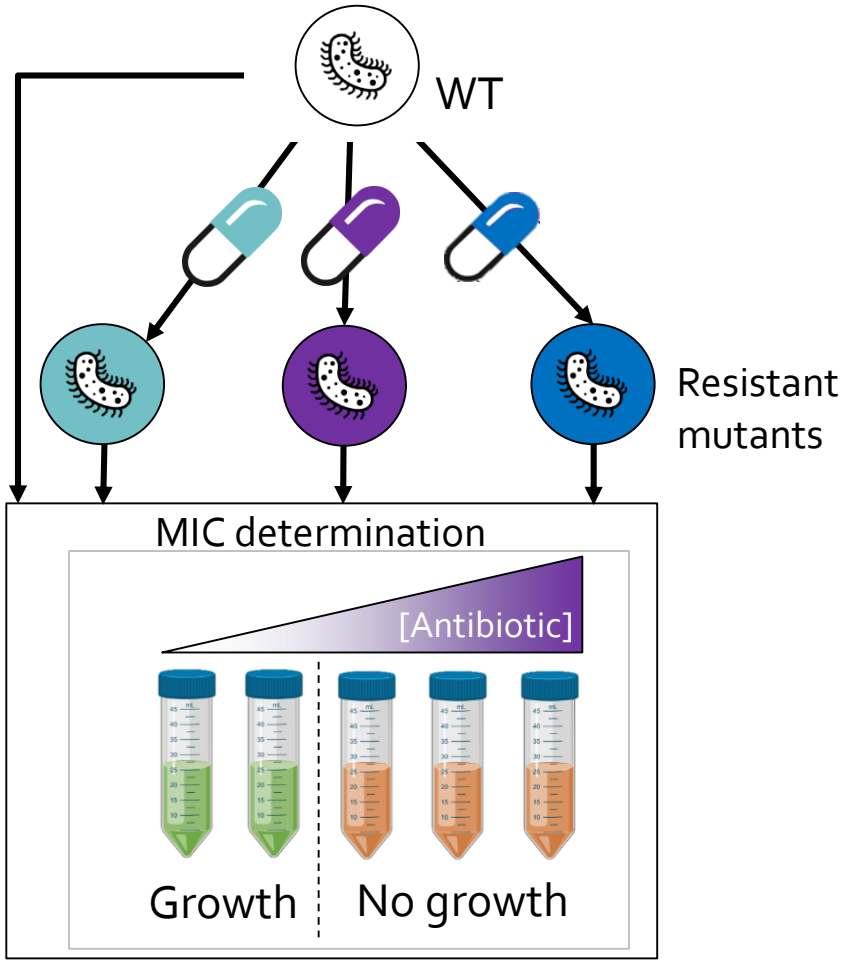
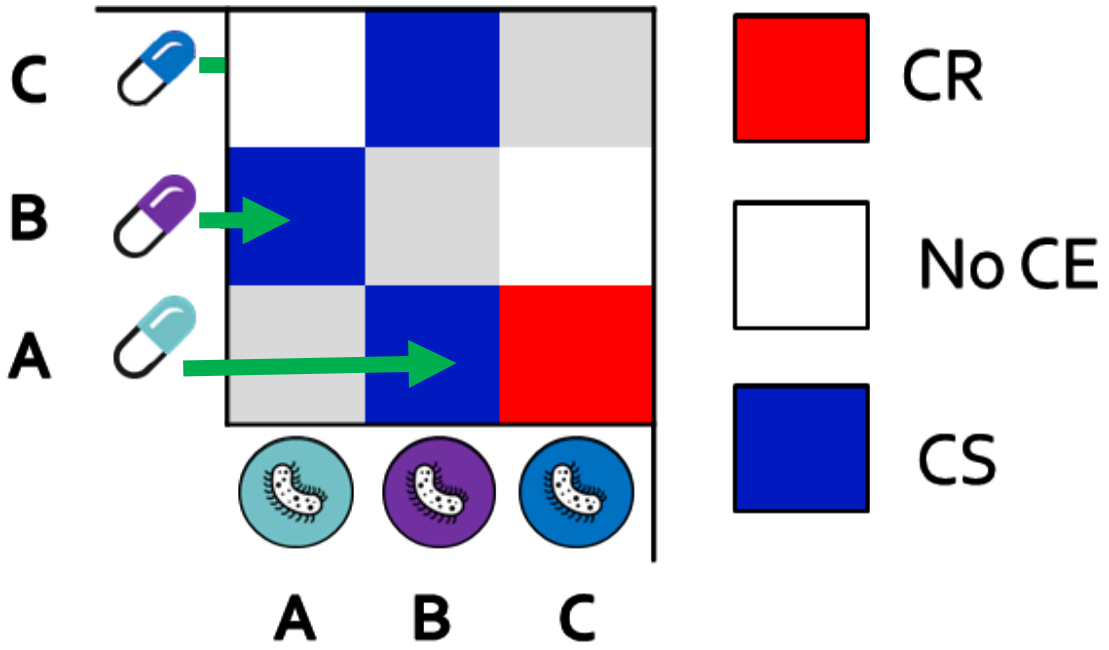
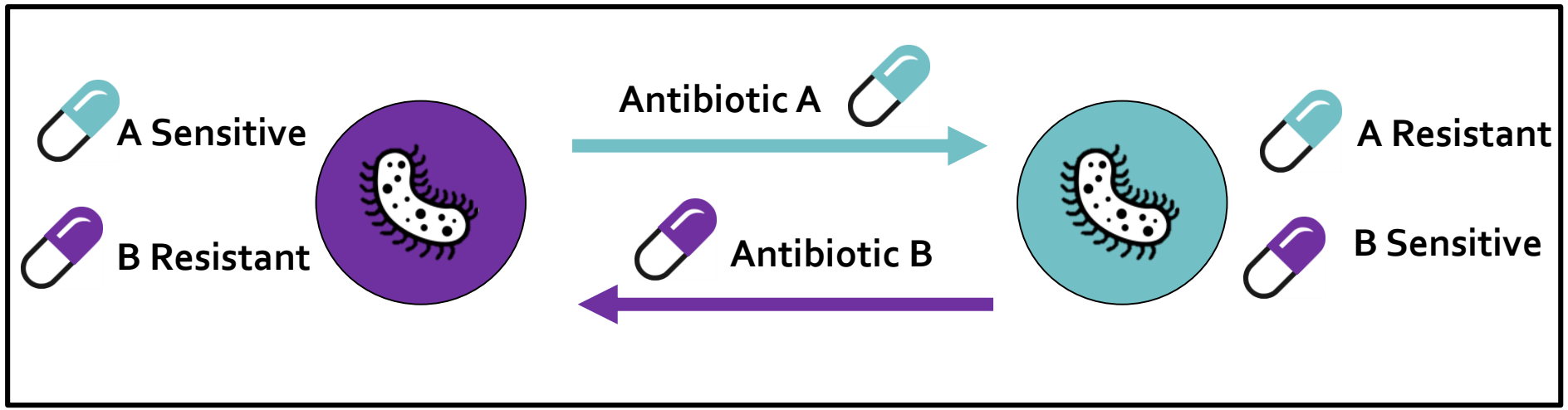
Assessing collateral effects *in vitro*

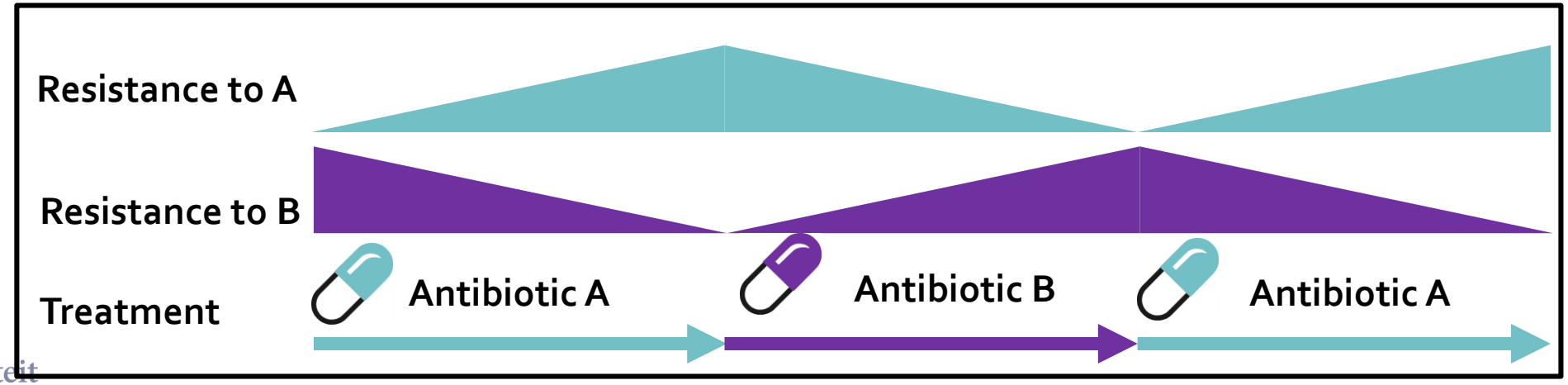


$$\text{collateral effect} = \frac{\text{MIC}_{\text{Mutant}}}{\text{MIC}_{\text{WT}}}$$

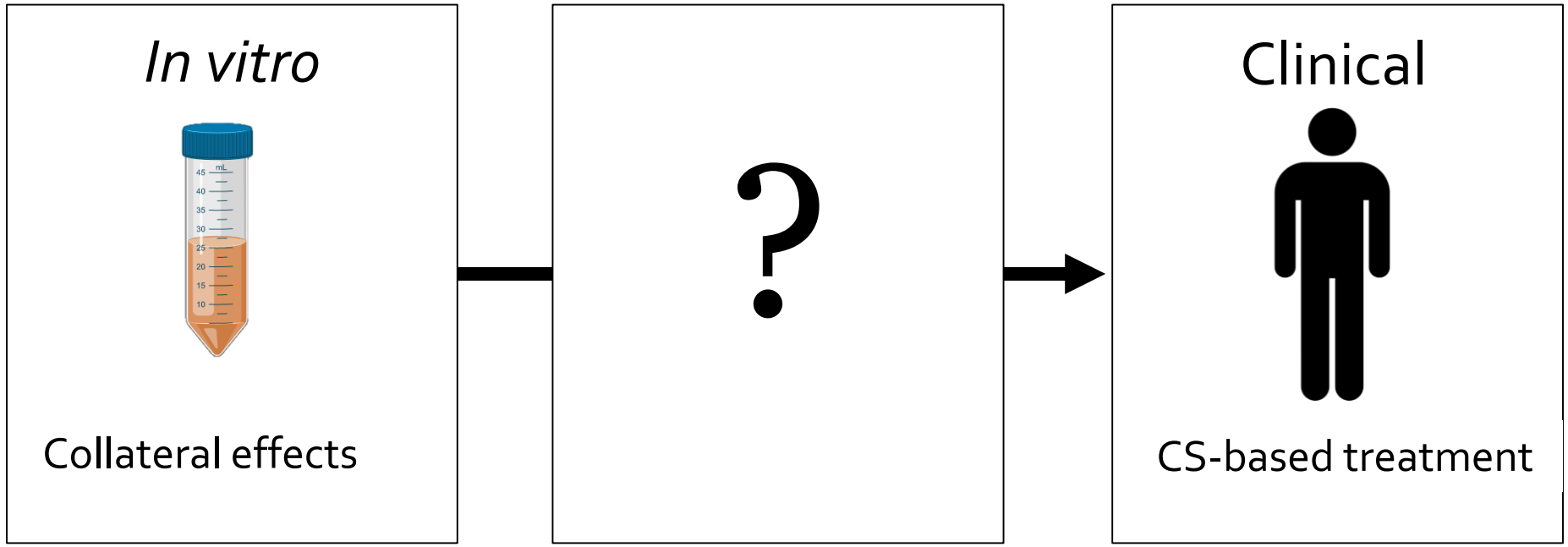


The concept of CS-based treatments

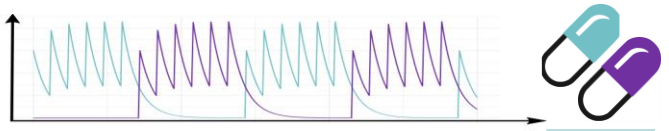




How can CS be translated to clinical treatments?

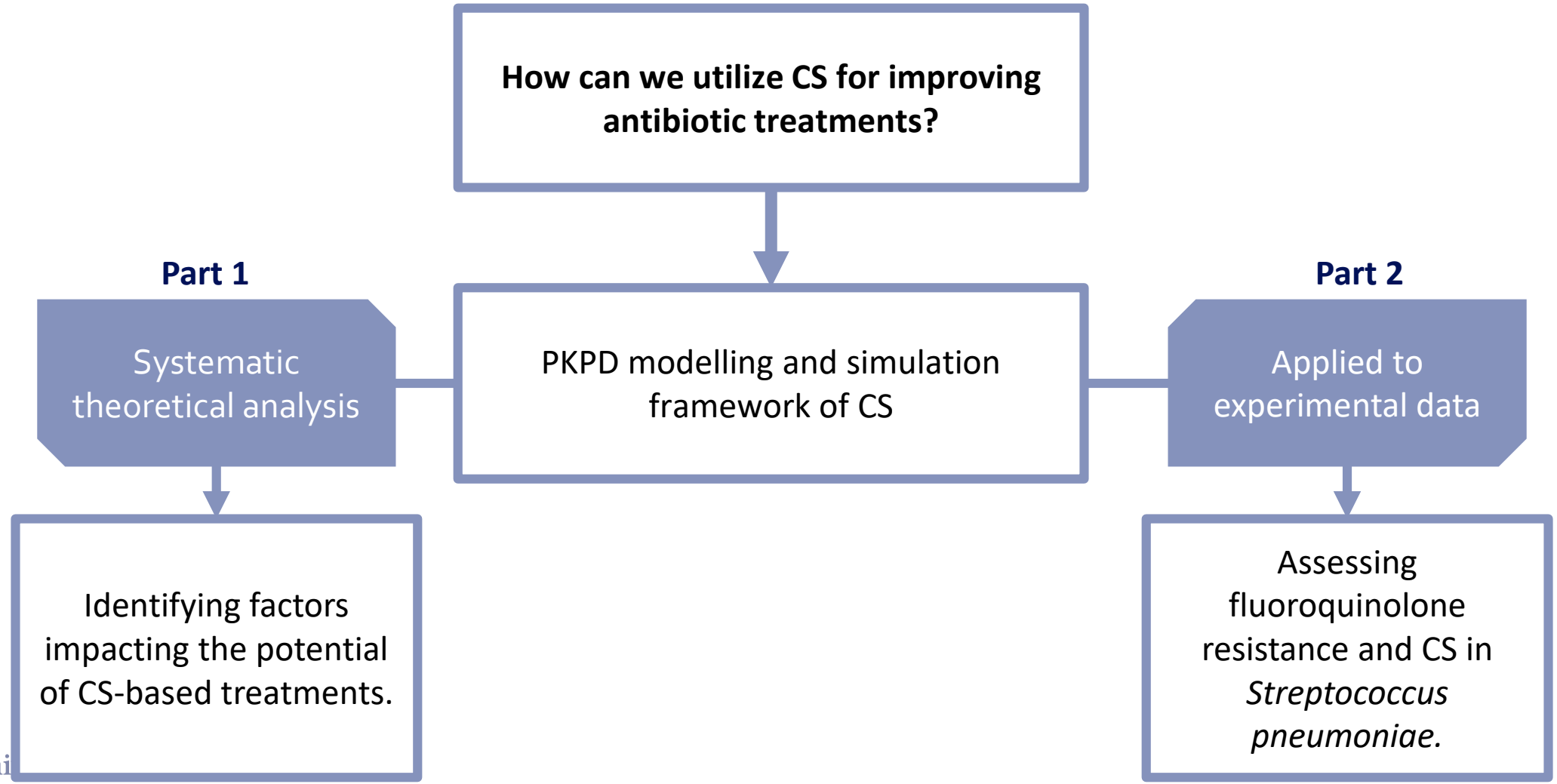


Designing CS-based treatment strategies

Pathogen-specific	Treatment-specific
	
Rate of resistance	Antibiotic type
Directionality of CS	Dosing sequence
Magnitude of CS	Dose amount
Fitness effects	Dosing interval

Optimized CS-based dosing strategy

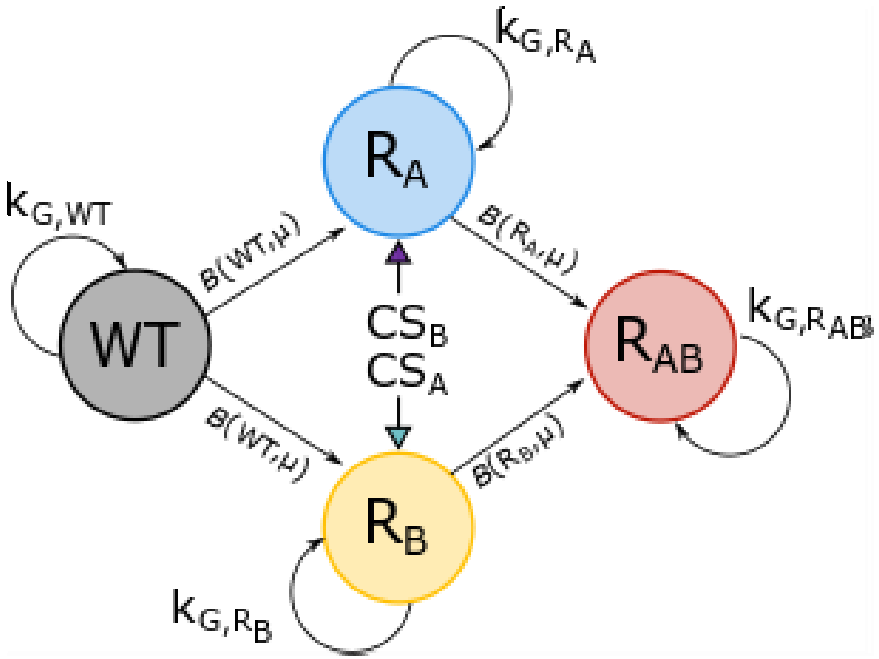
Moving towards CS-based treatments



PKPD modelling and simulation framework

$$k_{G,z} = k_{Gmax,z} \times \left(1 - \frac{WT+R_A+R_B+R_{AB}}{B_{max}}\right)$$

Subpop.	MIC AB_A	MIC AB_B
WT	MIC_S	MIC_S
R_A	MIC_R	MIC_Sx**CS**
R_B	MIC_Sx**CS**	MIC_R
R_{AB}	MIC_R	MIC_R



Bacterial subpopulations

WT Antibiotic sensitive wild type

R_B Resistant to AB_B

R_A Resistant to AB_A

R_{AB} Resistant to AB_A and AB_B

$k_{Gmax,z}$:max growth rate of subpopulation z

μ: mutation rate

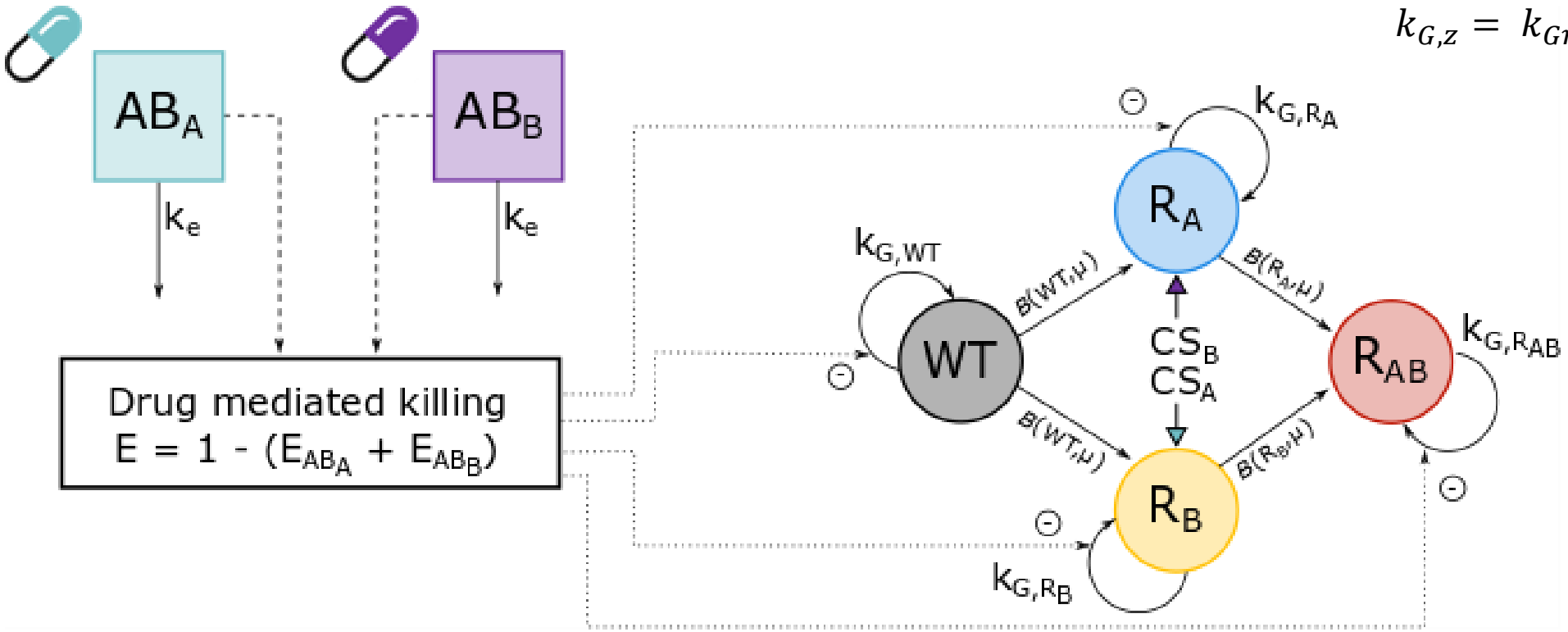
B(z,μ): stochastic mutation

MIC_S= 1 mg/L

MIC_R = 10 mg/L

PKPD modelling and simulation framework

$$k_{G,z} = k_{Gmax,z} \times \left(1 - \frac{WT+R_A+R_B+R_{AB}}{B_{max}}\right)$$



k_e: elimination rate

$k_{Gmax,z}$:max growth rate of subpopulation z

μ: mutation rate

B(z,μ): stochastic mutation

Bacterial subpopulations

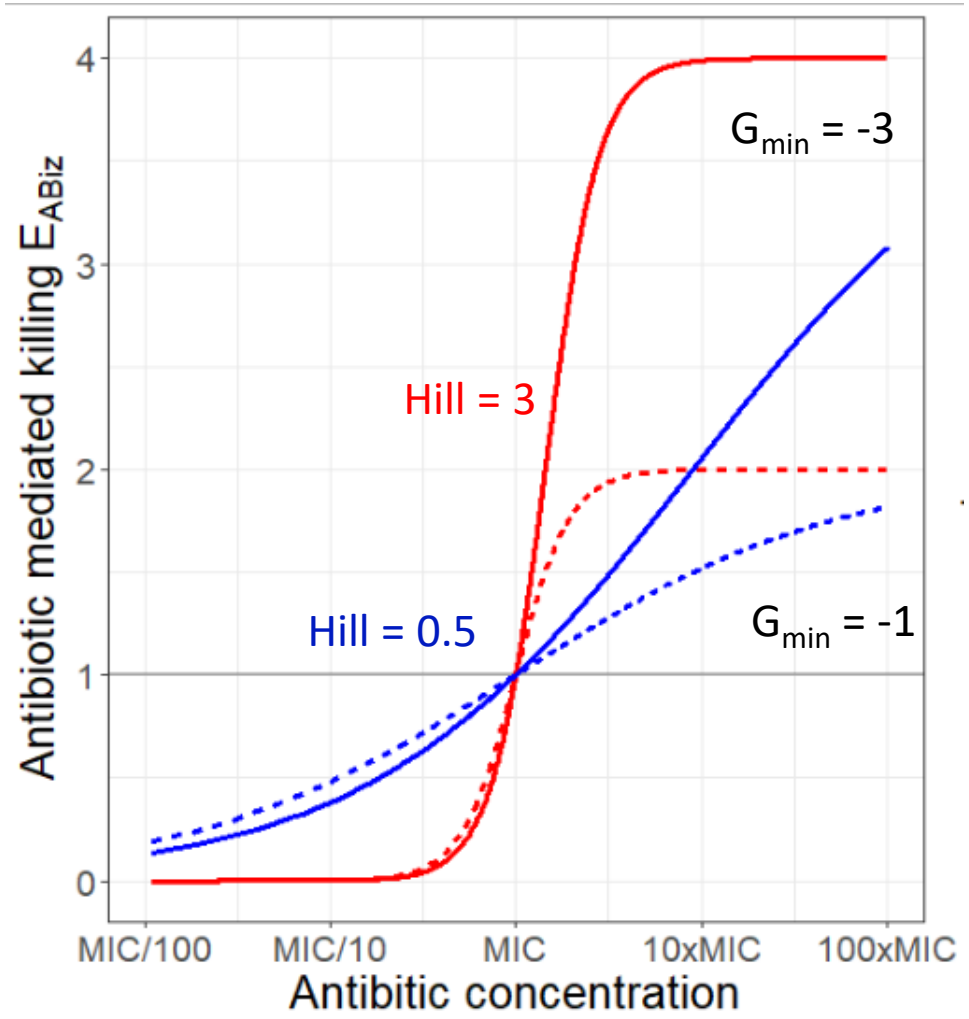
WT Antibiotic sensitive wild type

R_B Resistant to AB_B

R_A Resistant to AB_A

R_{AB} Resistant to AB_A and AB_B

Pharmacodynamic model of antibiotic mediated killing



$$E_{AB_i,z} = \frac{(1 - G_{min,AB_i} / k_{Gmax,z}) \times \left(\frac{C_{AB,i}}{MIC_{AB_i,z}}\right)^{Hill_{AB_i}}}{\left(\frac{C_{D_i}}{MIC_{AB_i,z}}\right)^{Hill_{D_i}} - \frac{G_{min,AB_i}}{k_{Gmax,z}}}$$

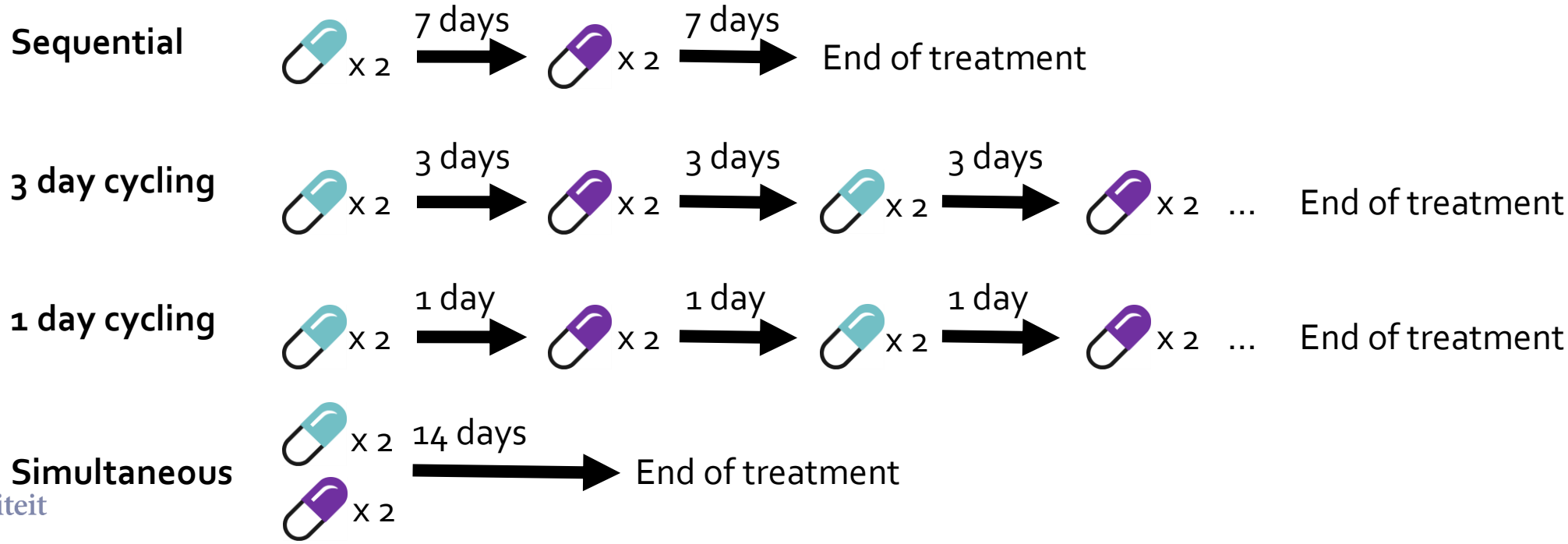
$$E_z = 1 - (E_{AB_A,z} + E_{AB_B,z})$$

$$k_{net,z} = K_{G,z} \times E_z$$

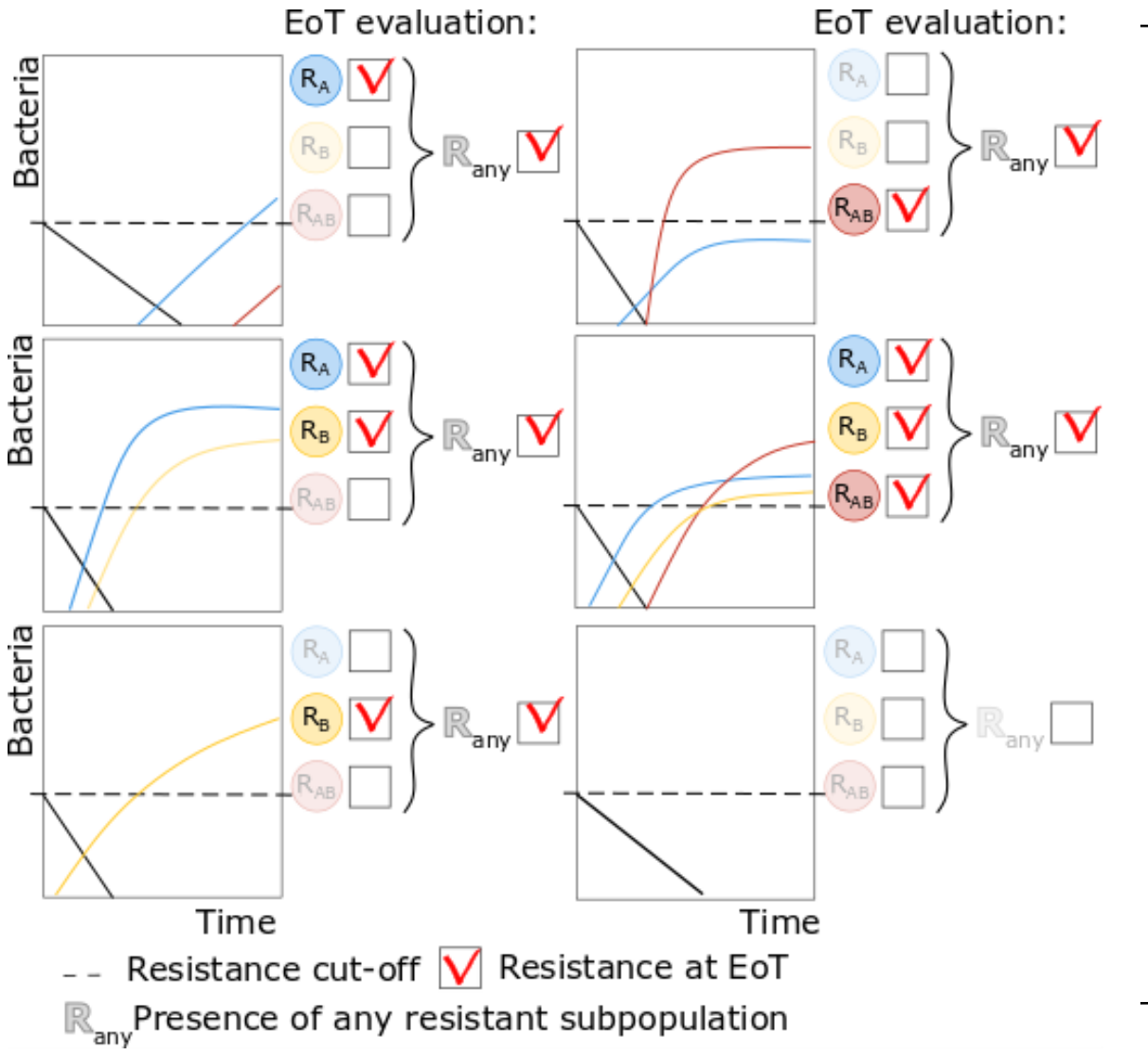
Regoes et al. *Antimicrob Agents Chemother* (2004)

Simulated treatments

- Two week treatments
- Combination treatment using hypothetical antibiotics AB_A and AB_B
- Twice daily i.v. bolus dosing
- Four simulated dosing regimens:



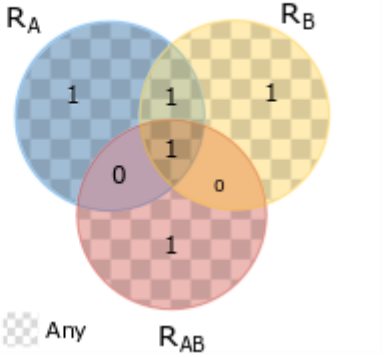
Simulated bacterial dynamics



Evaluation metric: probability of resistance (PoR)

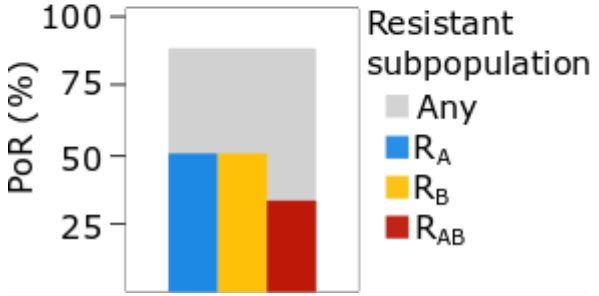
Subjects with resistant infections (n_R)

	n_R
R_A	3
R_B	3
R_{AB}	2
R_{any}	5



Calculating PoR

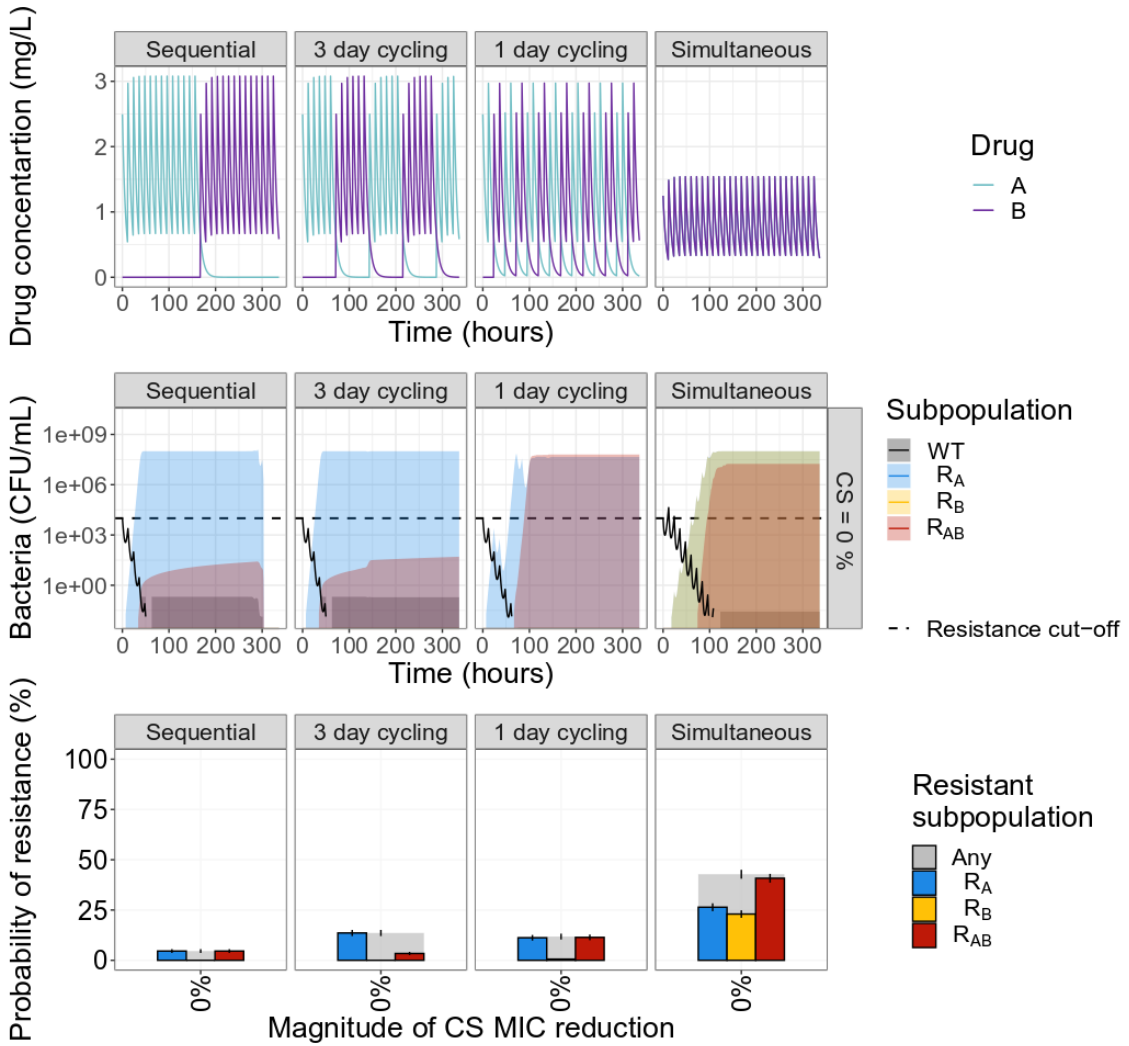
$$PoR = \frac{n_R}{n}$$



Simulated pharmacokinetics and bacterial dynamics

Model input
AB_{effect} = Bacteriostatic AB_{driver} = Concentration-dependent CS = 0%

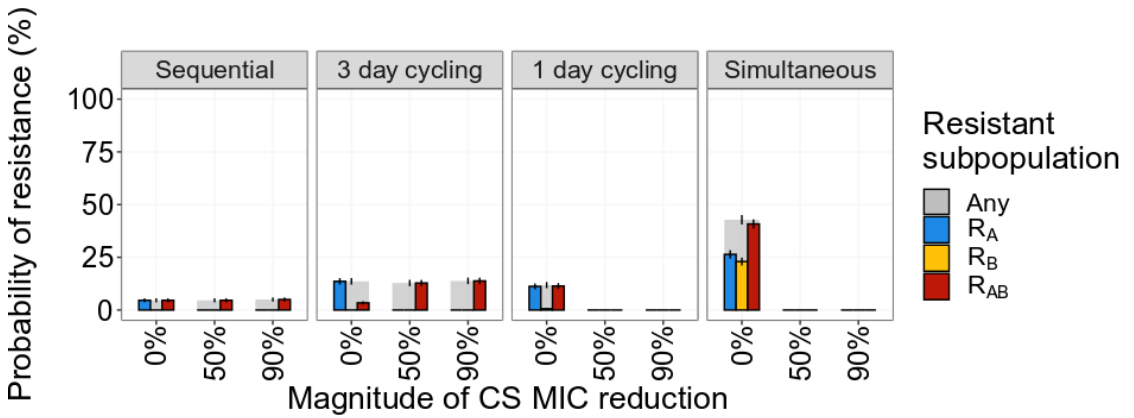
x 500



Can CS be used clinically to suppress resistance?

Model input
AB_{effect} = Bacteriostatic AB_{driver} = Concentration-dependent **CS = 0|50|90%**

x 500



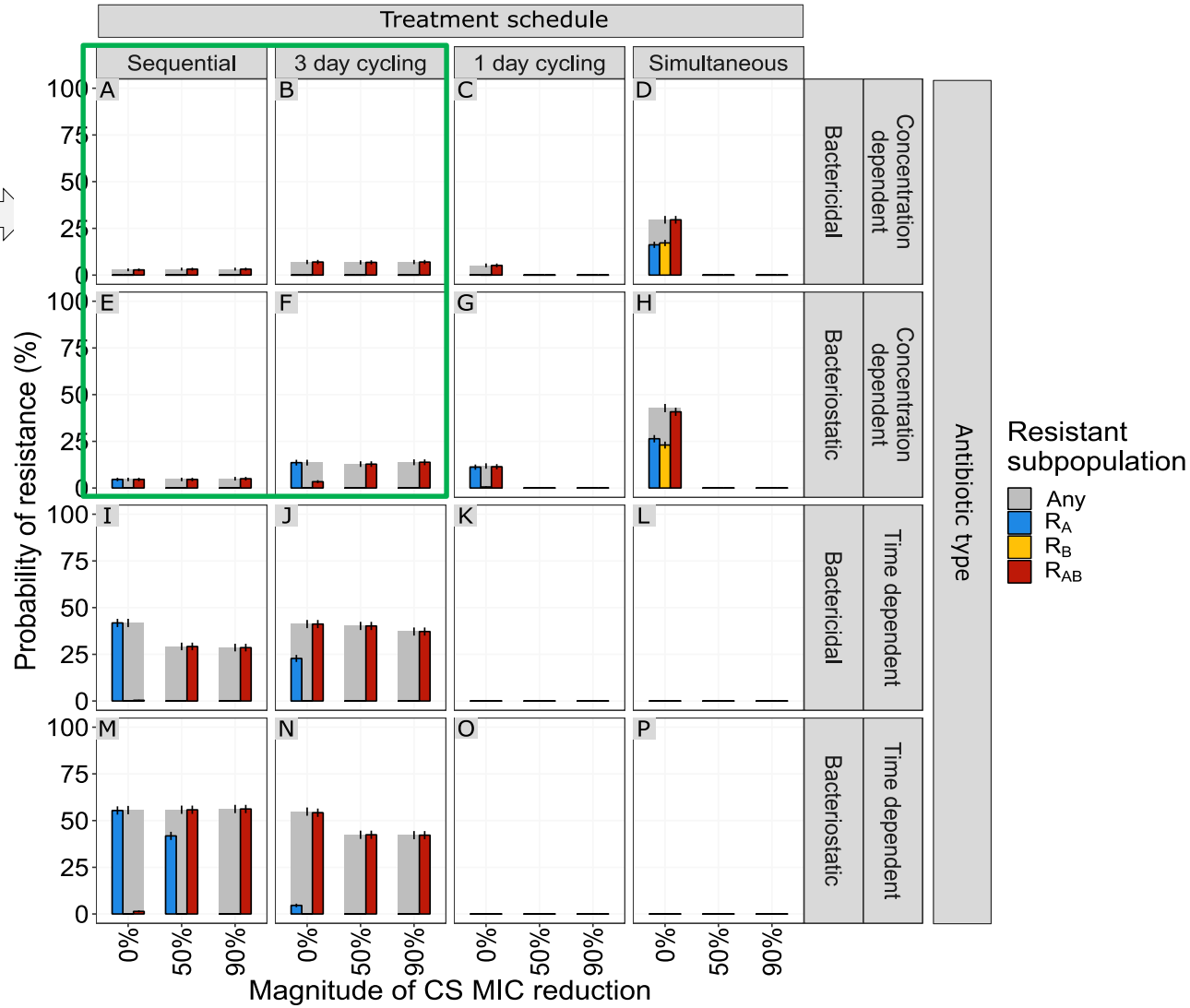
CS ability to suppress resistance depends on the dosing regimen.

How does treatment design affect the utility of CS?

Model input

AB_{effect} = Bacteriostatic| Bactericidal
AB_{driver} = Concentration-dependent | Time-dependent
CS = 0|50|90%

x 500

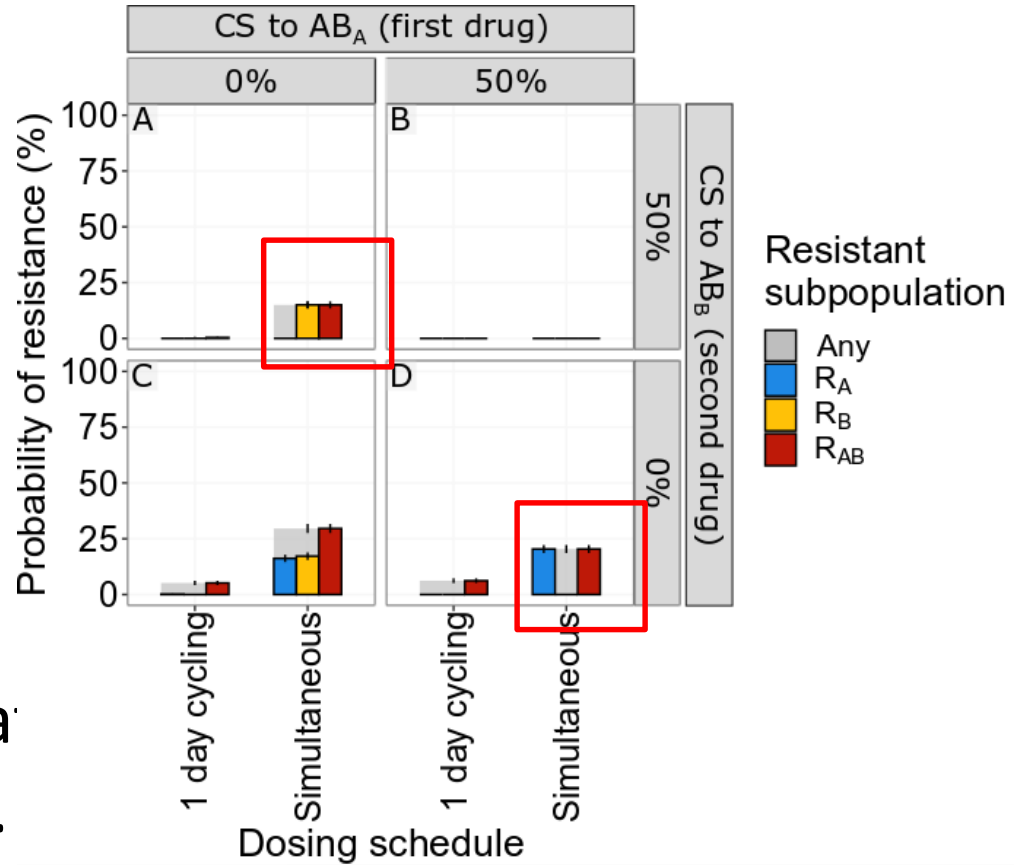


Both drug type and treatment schedule influence the PoR.

Is reciprocal CS needed for resistance suppression?

Model input	
AB_{effect}	= Bactericidal
AB_{driver}	= Concentration-dependent
CS to AB_A	**= 0|50%**
CS to AB_B	**= 0|50%**

x 500

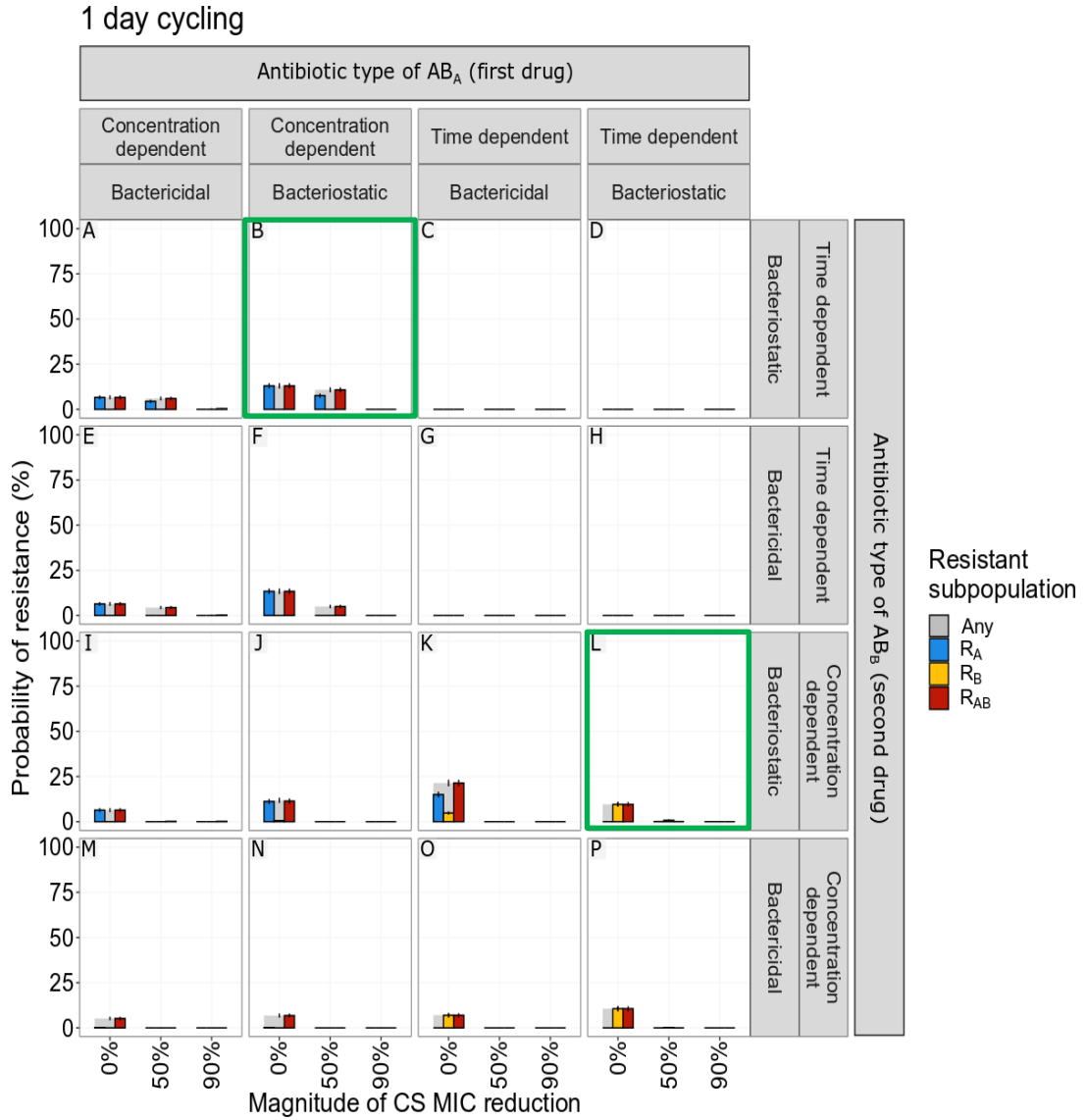


Reciprocal CS is not necessary for cycling trea
Directionality of CS effects influence the PoR.
CS towards the second AB has larger impact.

Can administration order impact resistance ?

Model input
$AB_{A,effect}$ = Bacteriostatic| Bactericidal $AB_{B,effect}$ = Bacteriostatic| Bactericidal $AB_{A,driver}$ = Conc. dep. | Time dep. $AB_{B,driver}$ = Conc. dep. | Time dep. CS = 0|50|90%

x 500



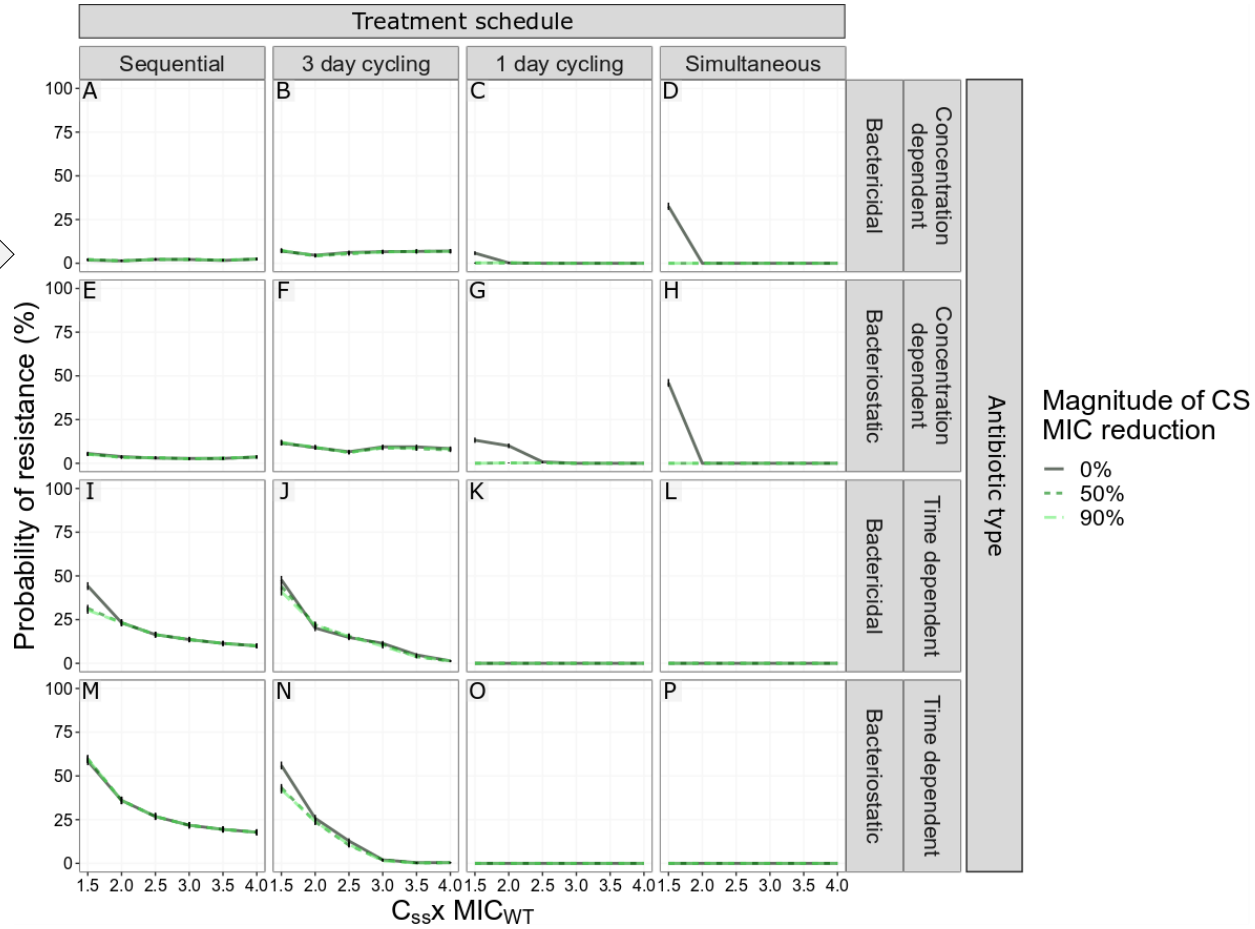
Administration sequence of antibiotic influence PoR.

How does the utility of CS relate to therapeutic window?

Model input

AB_{effect} = Bacteriostatic| Bactericidal
AB_{driver} = Concentration-dependent | Time-dependent
CS = 0|50|90%
Css = 1.5-4xMIC_{WT}

x 500



CS-based treatments show greatest promise for antibiotics with a narrow therapeutic window

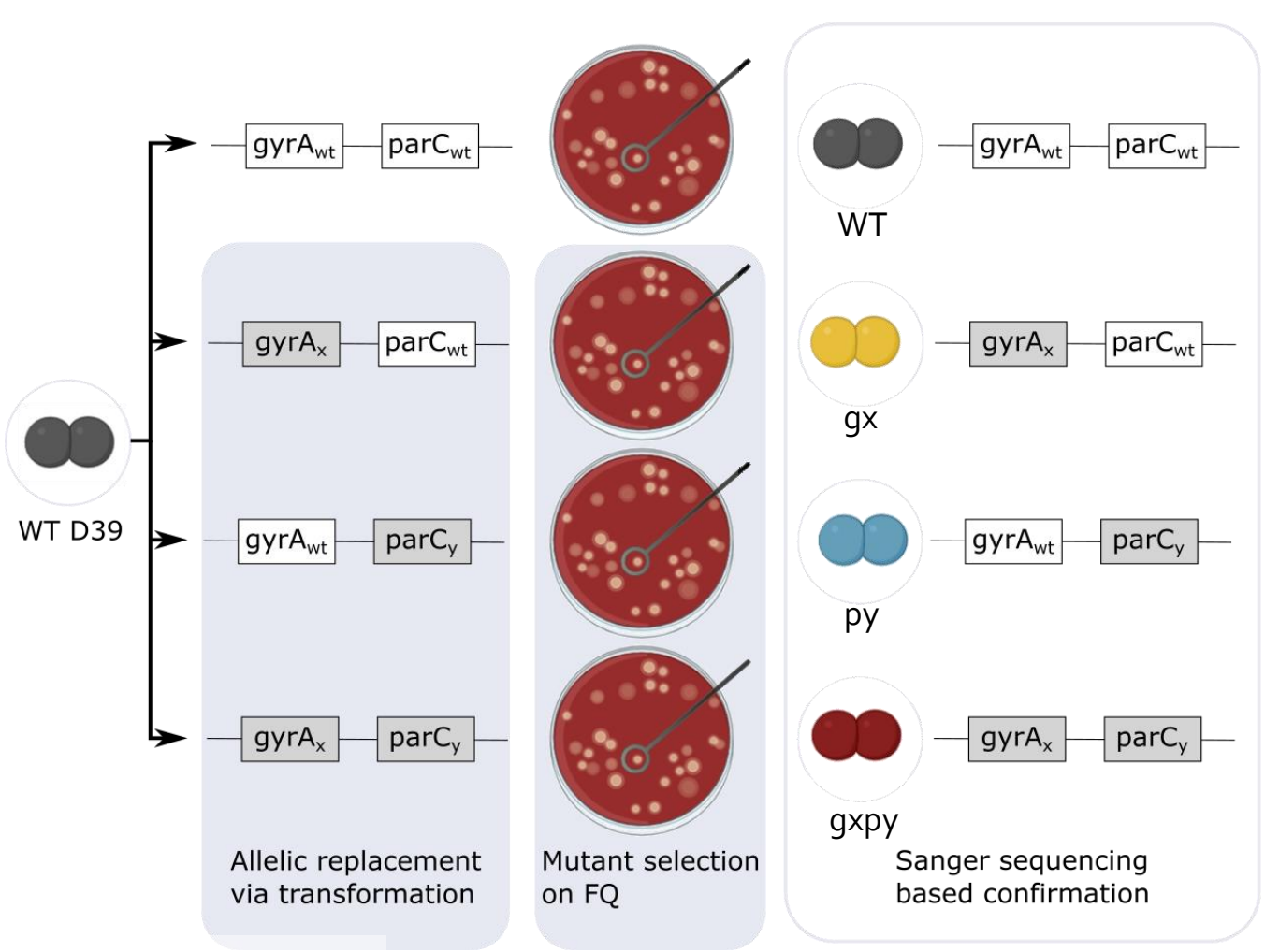
Key design principles for CS-based treatments

Using our framework to simulate theoretical scenarios we show that:

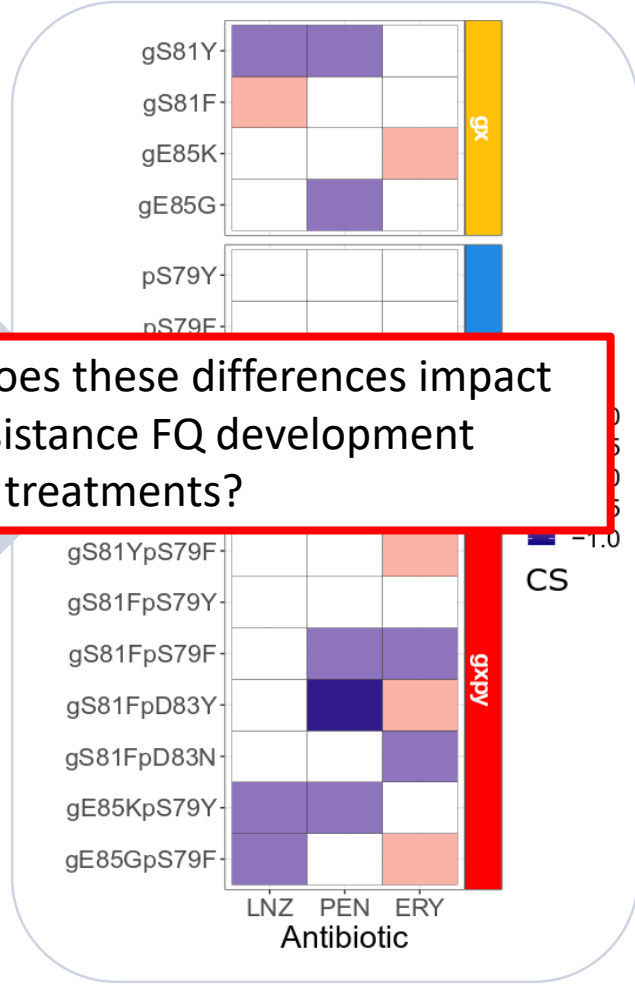
- **simultaneous** or **one-day cycling** treatment were **most effective**.
- the **efficacy of CS-based** cycling therapies **depends the drug sequence**.
- **reciprocal CS is not essential** to suppress resistance.
- CS based treatments are **most relevant** for antibiotics with a **narrow therapeutic window**

Can our general framework can be applied and adapted to specific pathogens and antibiotics?

Fluoroquinolone resistance in *Streptococcus pneumoniae*



How does these differences impact the resistance FQ development during treatments?

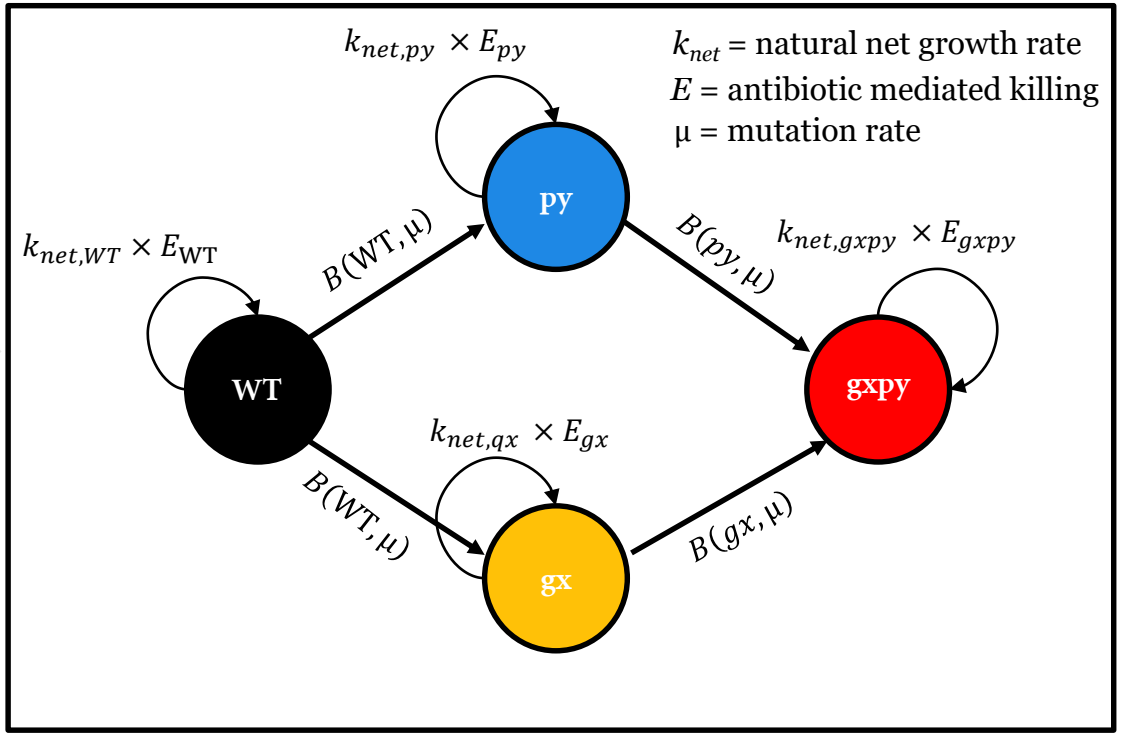


Framework application

Constructing mutational trajectories (MT``) including gyrA, parC and gyrA:parC mutants.

MT	WT	gyrA (gx)	parC (py)	gyrA:parC (gxpy)
1	$g_{wt}p_{wt}$	$g_{S81F}p_{wt}$	$g_{wt}p_{D83N}$	$g_{S81F}p_{D83N}$
2	$g_{wt}p_{wt}$	$g_{S81F}p_{wt}$	$g_{wt}p_{D83Y}$	$g_{S81F}p_{D83Y}$
3	$g_{wt}p_{wt}$	$g_{E85G}p_{wt}$	$g_{wt}p_{S79F}$	$g_{E85G}p_{S79F}$
4	$g_{wt}p_{wt}$	$g_{S81F}p_{wt}$	$g_{wt}p_{S79F}$	$g_{S81F}p_{S79F}$
5	$g_{wt}p_{wt}$	$g_{S81Y}p_{wt}$	$g_{wt}p_{S79F}$	$g_{S81Y}p_{S79F}$
6	$g_{wt}p_{wt}$	$g_{E85K}p_{wt}$	$g_{wt}p_{S79Y}$	$g_{E85K}p_{S79Y}$
7	$g_{wt}p_{wt}$	$g_{S81F}p_{wt}$	$g_{wt}p_{S79Y}$	$g_{S81F}p_{S79Y}$
8	$g_{wt}p_{wt}$	$g_{S81Y}p_{wt}$	$g_{wt}p_{S79Y}$	$g_{S81Y}p_{S79Y}$

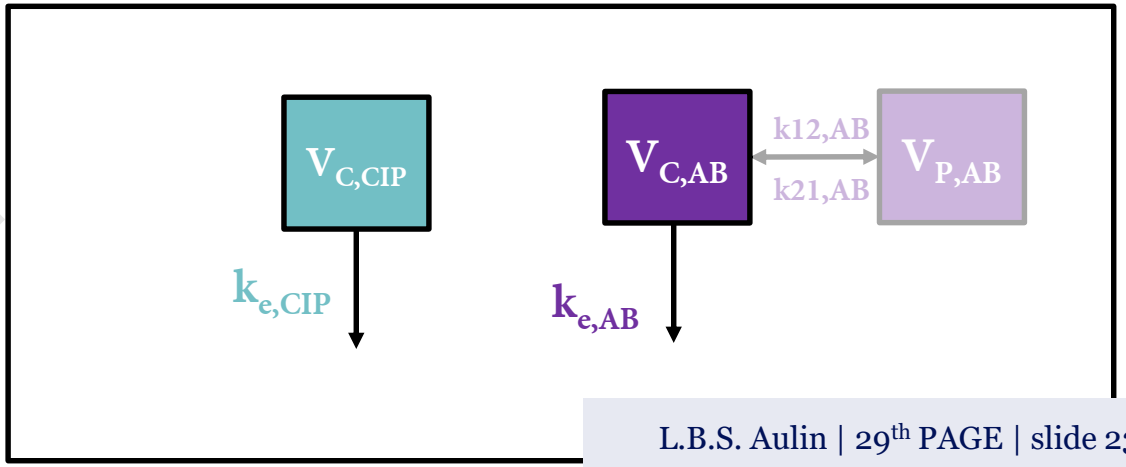
Mutant-specific MICs and fitness



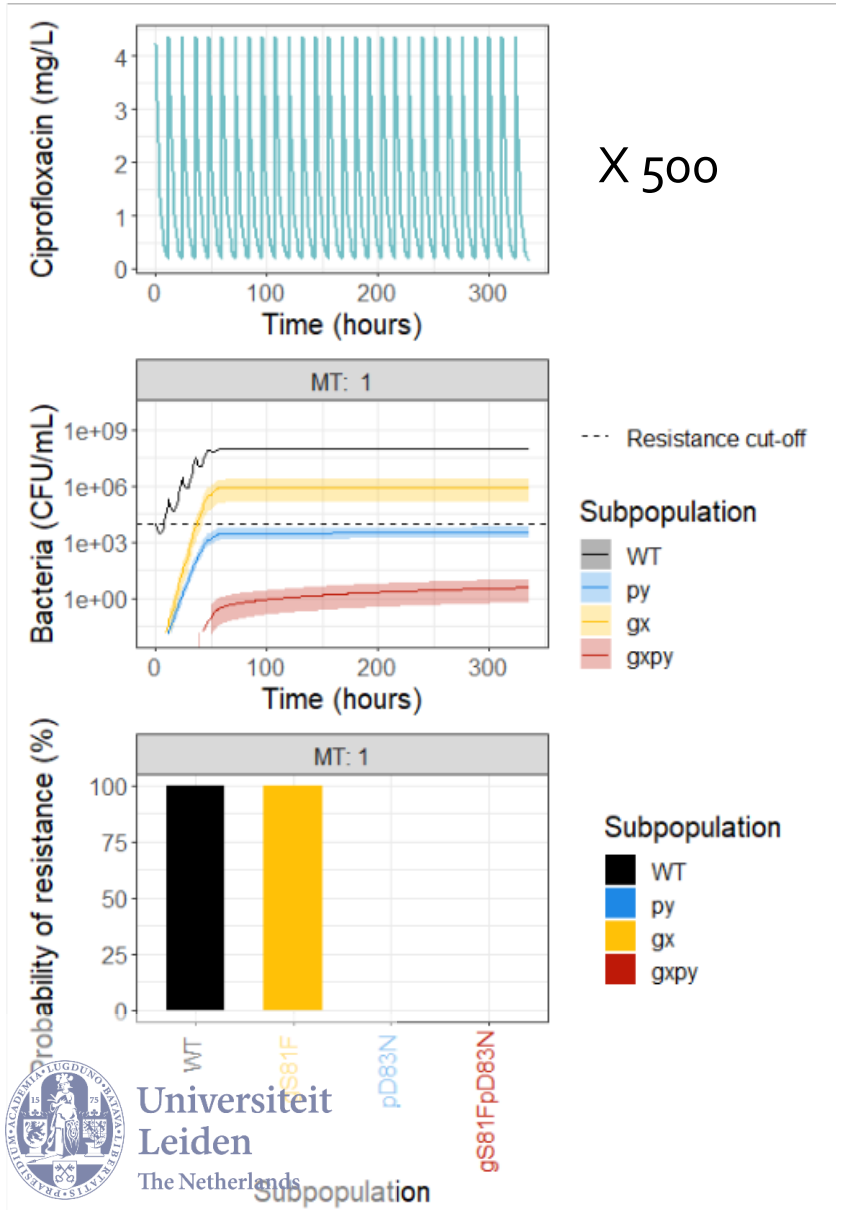
Published human pharmacokinetic (PK) models:

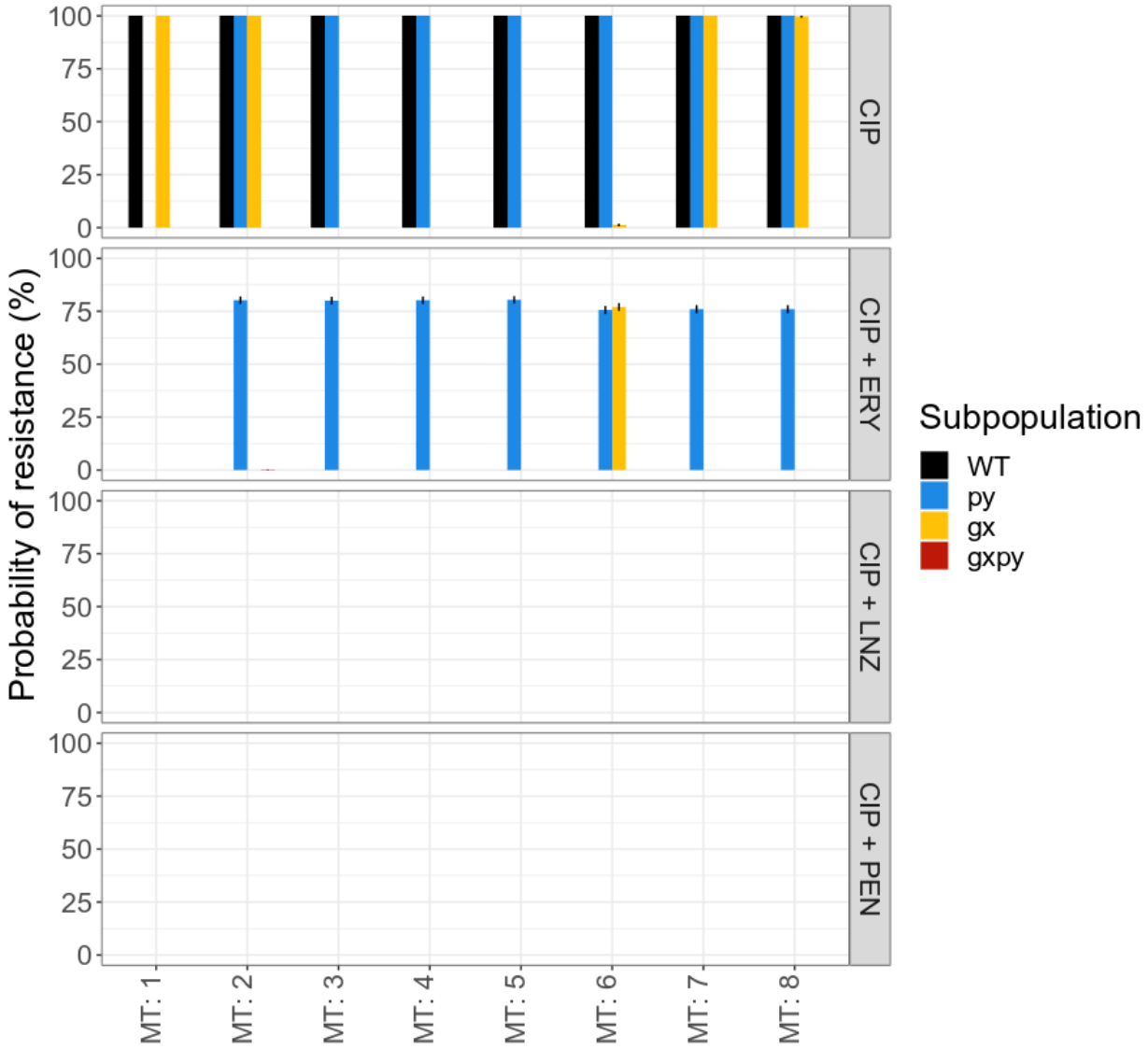
- Ciprofloxacin (CIP)
- Erythromycin (ERY)
- Penicillin (PEN)
- Linezolid (LNZ)

Drug specific PK



Combination treatments could suppress resistance





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Summary

In this analysis we:

- use modelling and simulation to systematically unravel drug- and pathogen-specific factors driving AMR.

- identify key design principles to optimal design of CS-based treatment strategies to suppress AMR.

- illustrate how our framework can be applied to specific pathogens and antibiotics.

Thank you for your attention!

Universiteit Leiden
The Netherlands

l.b.s.aulin@lacdr.leidenuniv.nl

/lindaaulin

@L_Aulin