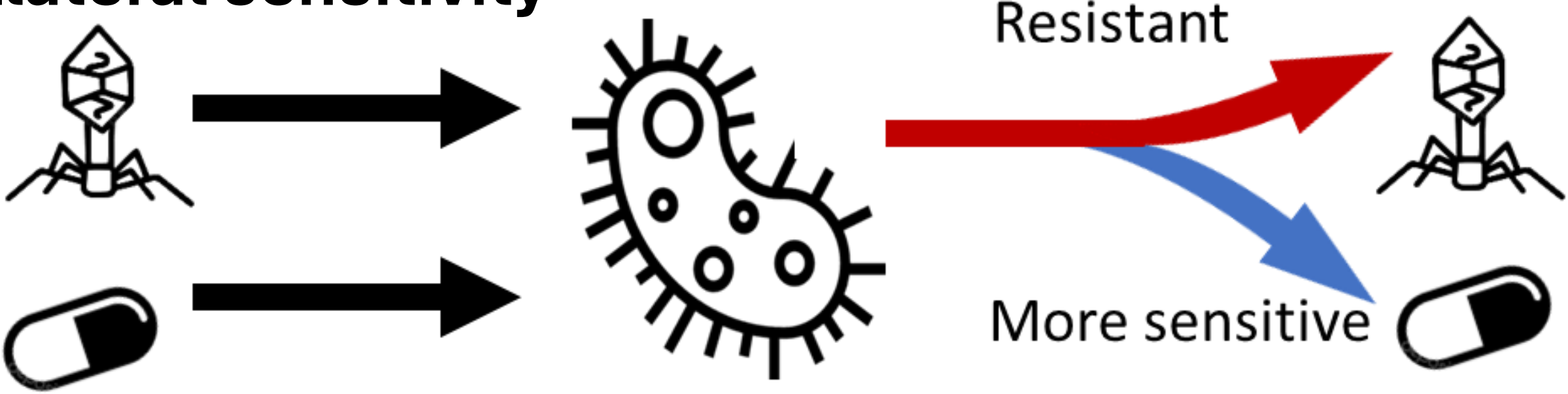


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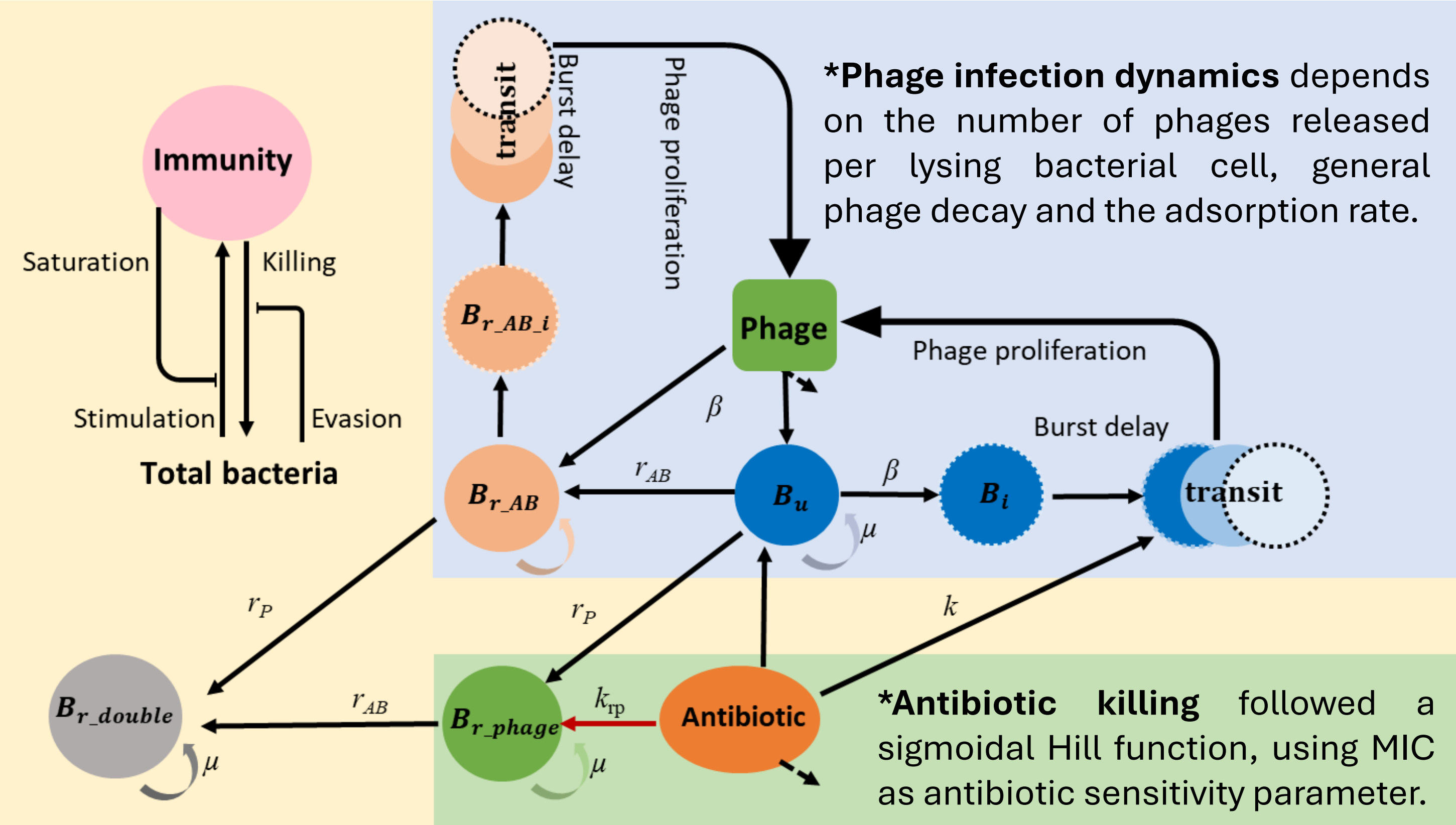
Introduction and Aim

- **Phage-antibiotic combination (PAC)** therapies are key to effective clinical use of phages and resistance prevention.
- **Collateral sensitivity**

- **Aim:** investigate the effect of CS on therapeutic outcomes given different dosing strategies using a mathematical modeling framework.

Methods

Model definition

- **Model compartments:** wildtype bacteria (B_u), infected bacteria (B_i), antibiotic-resistant bacteria (B_{r_AB}), phage-resistant bacteria (B_{r_phage}), antibiotic, phage.



- **Mutation** were defined as first order process.
- **CS:** one directional effect, where B_{r_P} had increased antibiotic susceptibility via reduced MIC.

Simulation scenarios

CS-based phage-antibiotic dosing strategies:

We assess how CS reduces the dose needed to prevent treatment failure ($CFU_{24} > 1$), comparing no, weak, and strong CS conditions.

Delayed antibiotic administration:

To allow phage replication, we tested delayed antibiotic dosing(**0.2-6h**) and evaluated CFU_{24} under strong CS levels to determine the impact on outcomes.

Dose regimens design:

We tested dosing schedules(**QD, BID, TID and infusion**) under CS and antibiotic delay, using **the time to first reach $CFU < 1$** within 72h as a measure of regimen effectiveness.

Initial conditions	Values
B_u (CFU/mL)	10^7
Phage(PFU/mL)	0- 10^8
Antibiotic(mg)(MIC=1)	0-5
Subpopulation	MIC values
Bacteria-resistant and double-resistant	$10 * MIC_{WT}$
Phage-resistant (weak CS)	$0.5 * MIC_{WT}$
Phage-resistant (strong CS)	$0.1 * MIC_{WT}$

Results

CS-based combination allow low antibiotic dose

- For weak CS, the required antibiotic dose for treatment success ($CFU_{24} < 1$) was reduced by 1/3 (from 1.5 mg to 1 mg). (**Figure 1A and 1B**)
- Stronger CS decreased the required antibiotic dose by 1/2 (0.75 mg). (**Figure 1C**)

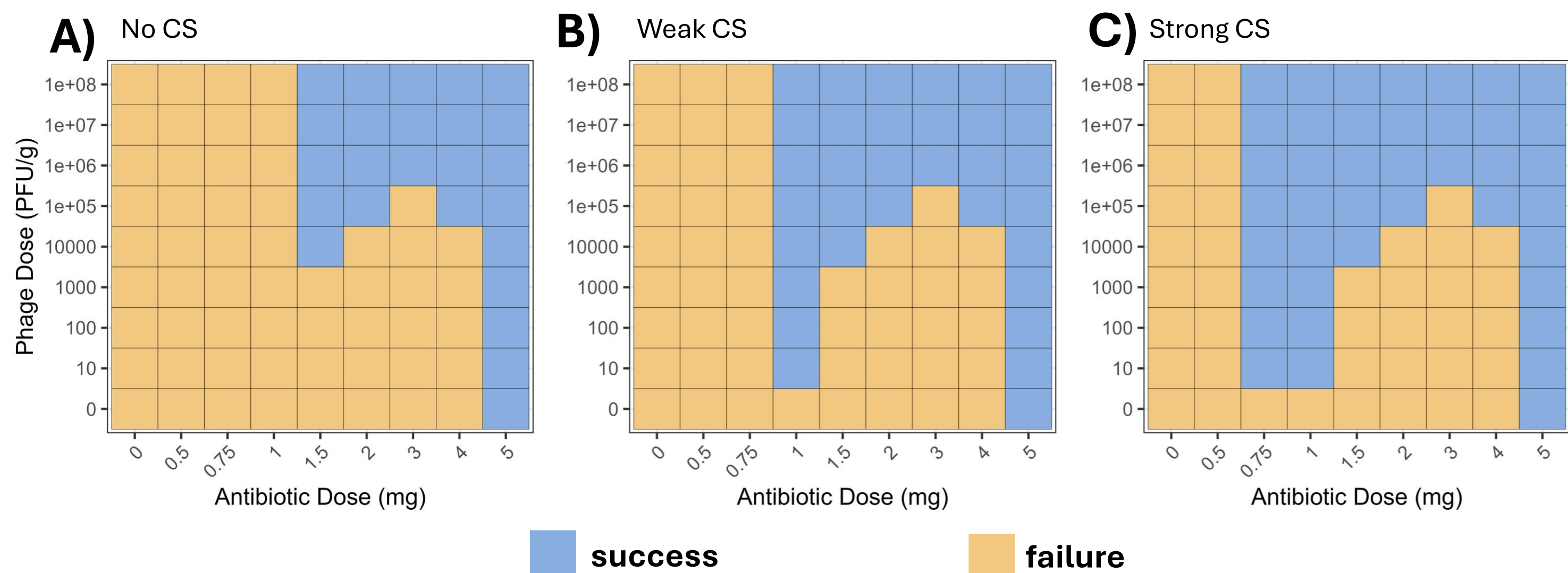


Figure 1. Combination treatment outcome without (A) , and with weak (B) or strong (C) CS.

Delayed antibiotic administration reduces the required phage dose for successful treatment

- Short delay introduce antagonistic effect in high antibiotic dose condition (**Figure 2A and 2B**) which can be compensated by longer delay. (**Figure 2C**)
- With a delay of 2h, the phage dose needed for eradication drops from 10^5 PFU/mL to 10 PFU/mL. (**Figure 2C**)

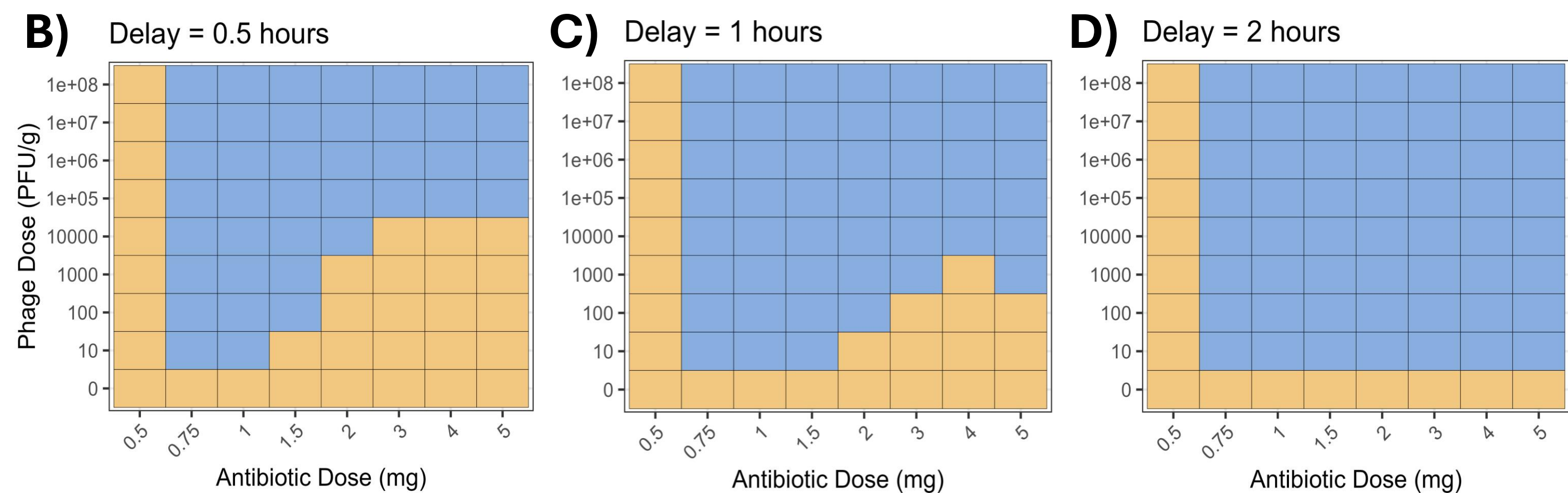


Figure 2. Combination treatment outcome with antibiotic administration delay.

QD perform more efficient bacterial killing effect

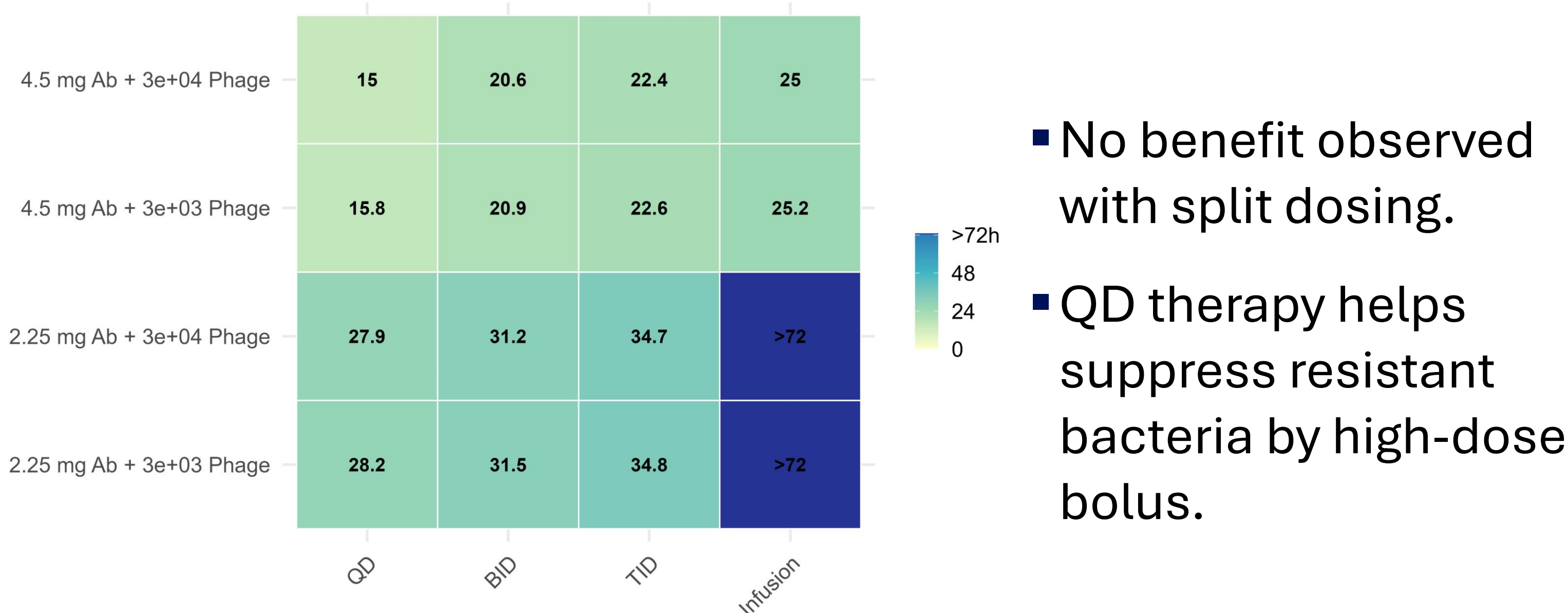


Figure 3. Time at which CFU first falls below the defined threshold($CFU < 1$).

Conclusions

- The presence of CS can lead to **reduced antibiotic dose** required for successful treatment.
- **In the presence of CS, QD with sequential dosing** with phage administrated first appears to be a more optimal strategy.