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Introduction

- Acute and severe infections are often treated with **empirical antibiotic combinations** to expand coverage.
- Aminoglycoside + beta-lactam combinations are common in **neonatal sepsis** in low- and middle-income countries (LMICs).
- Empirical treatments are often based on guidelines that do not consider **regional differences** in antibiotic resistance profiles.

Aims

- Develop a workflow to **identify effective empirical antibiotic combinations** for specific regions and indications.
- Apply the methodology to combinations for treatment of neonatal sepsis in LMICs.

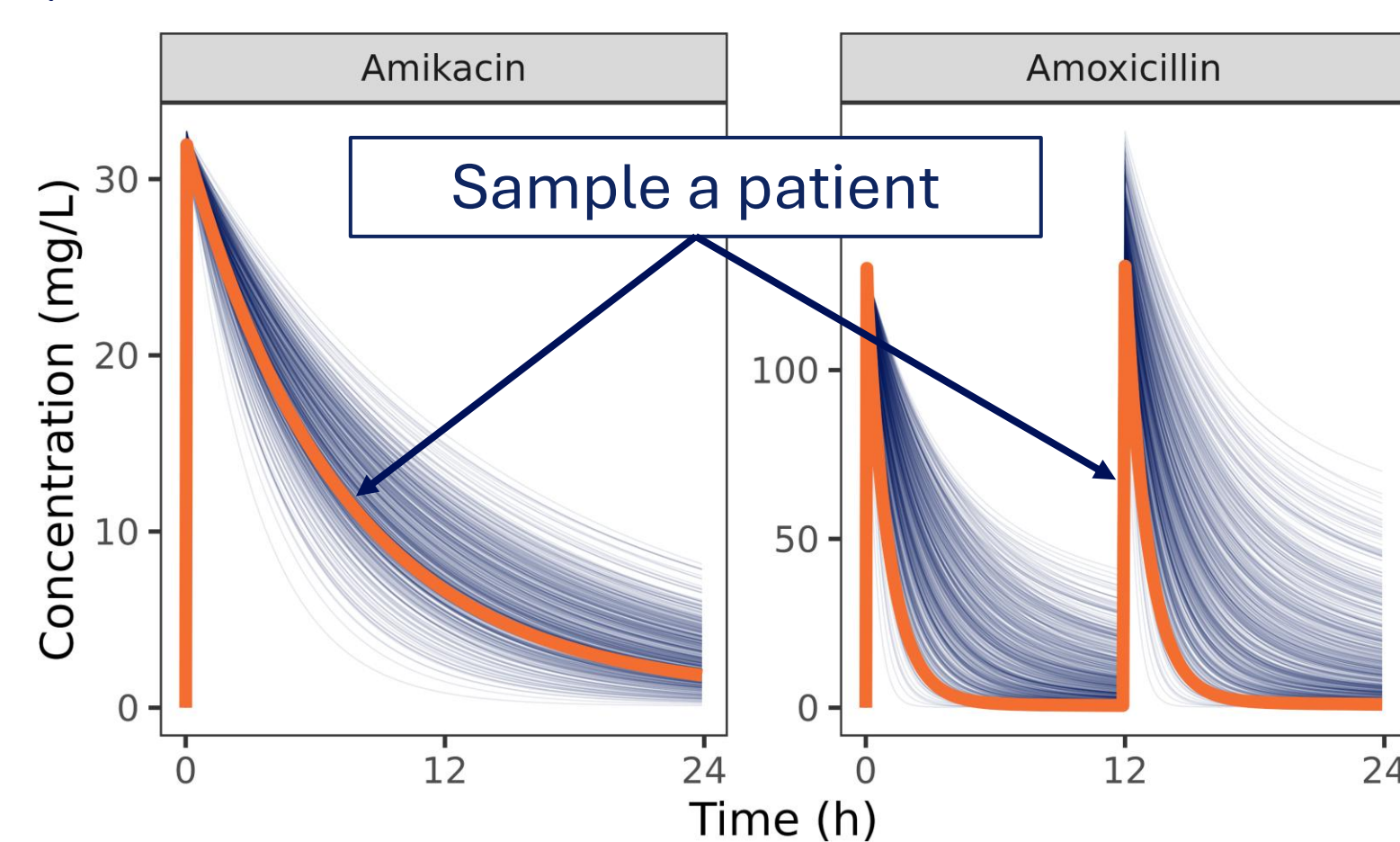
Methods

- Probability of PK/PD target attainment (PTA) was evaluated for **aminoglycoside (3) + beta-lactam (6) combinations**.
- The workflow is illustrated below for amikacin + amoxicillin.
- 1,000 neonate-pathogen pairs were simulated per site.

Generate a virtual population of neonates

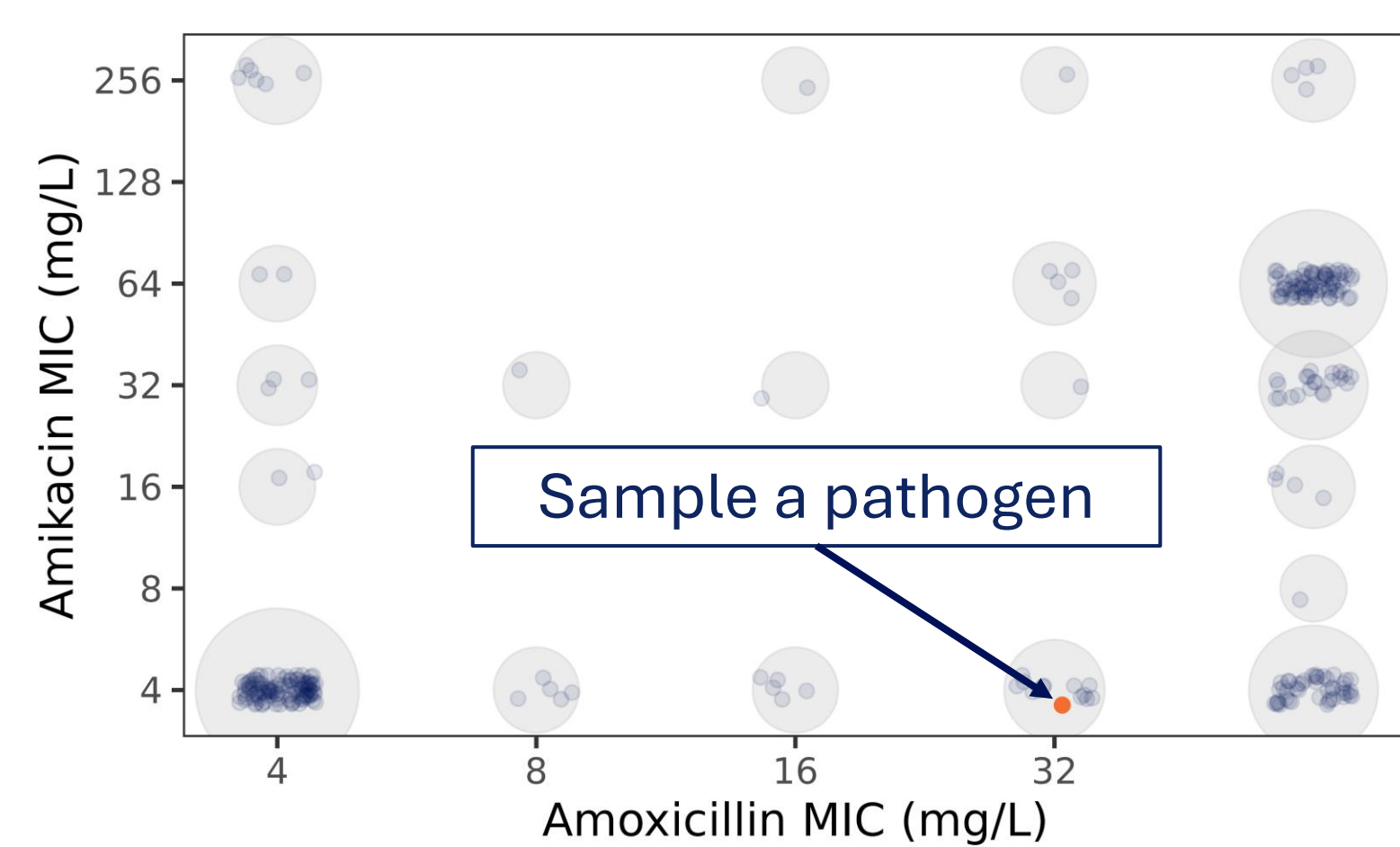
- Example:* early-onset sepsis (postnatal age ≤ 3 days) in preterm neonates (gestational age 32-36 weeks).
- Realistic covariate sets: weight and serum creatinine based on postnatal age, gestational age and sex.¹⁻³

Simulate PK profiles



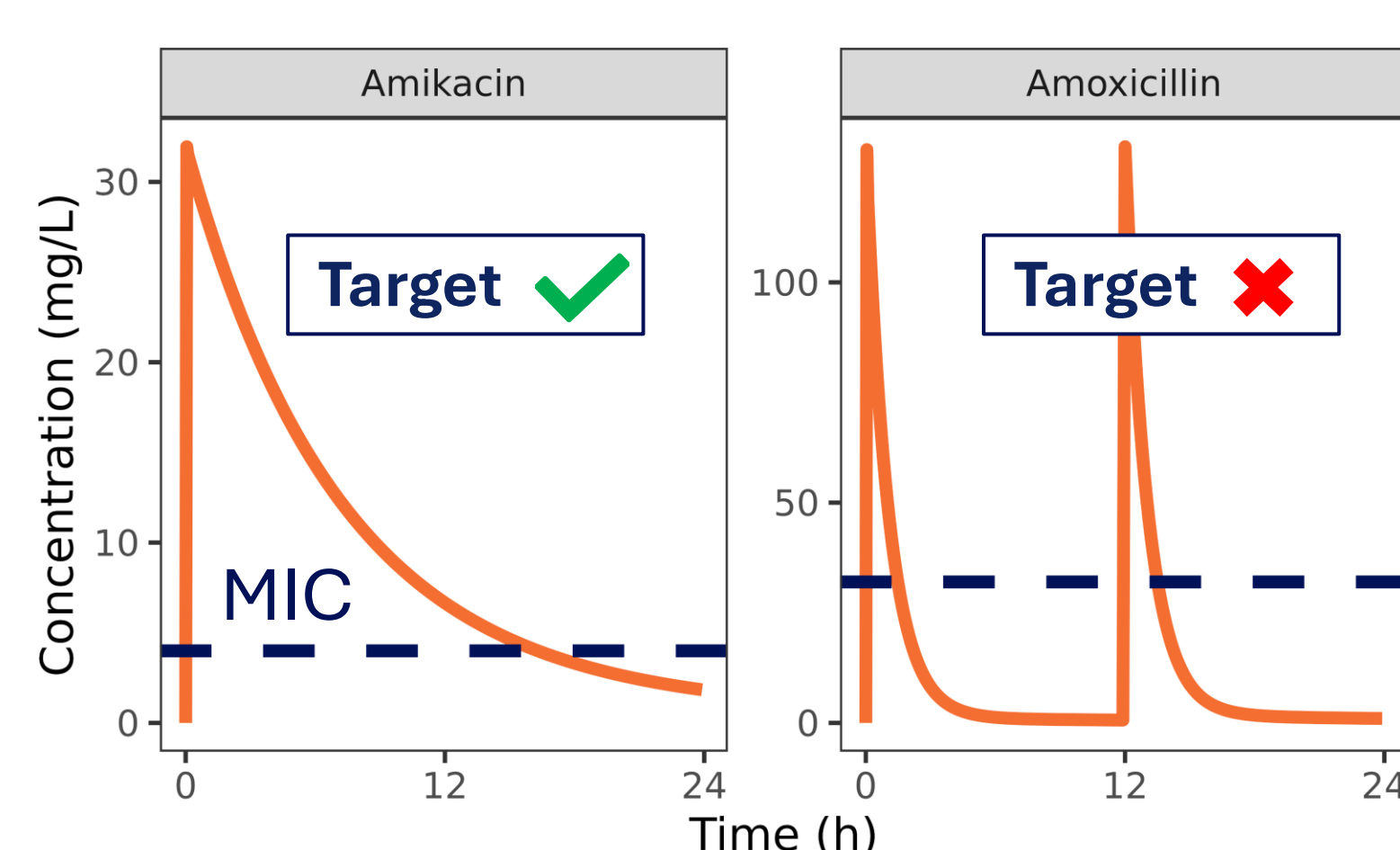
- Using published neonatal PK models⁴⁻¹² in RxODE.¹³
- Guideline-based dosing¹⁴ dependent on weight, gestational age and postnatal age.

Sample realistic combinations of MIC values



- Site-specific, multivariate** MIC distributions from a neonatal sepsis trial.¹⁵
- MIC: minimum inhibitory concentration, standard susceptibility metric.

Determine PK/PD target attainment



References

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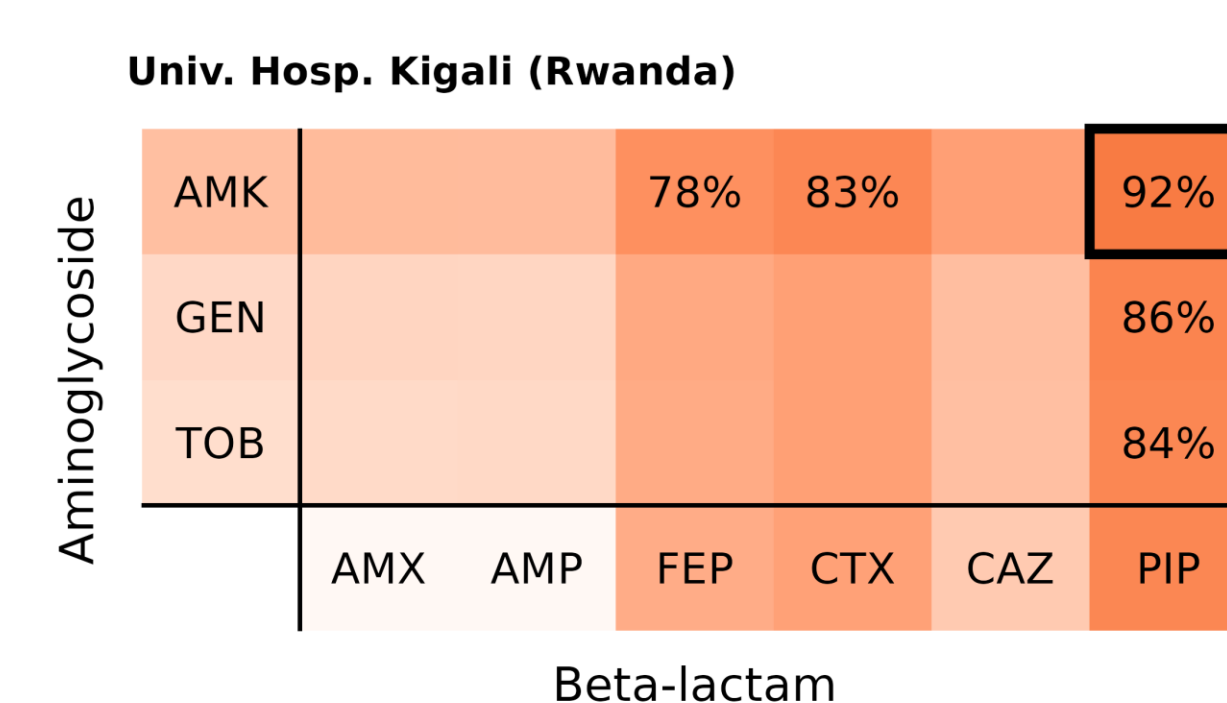
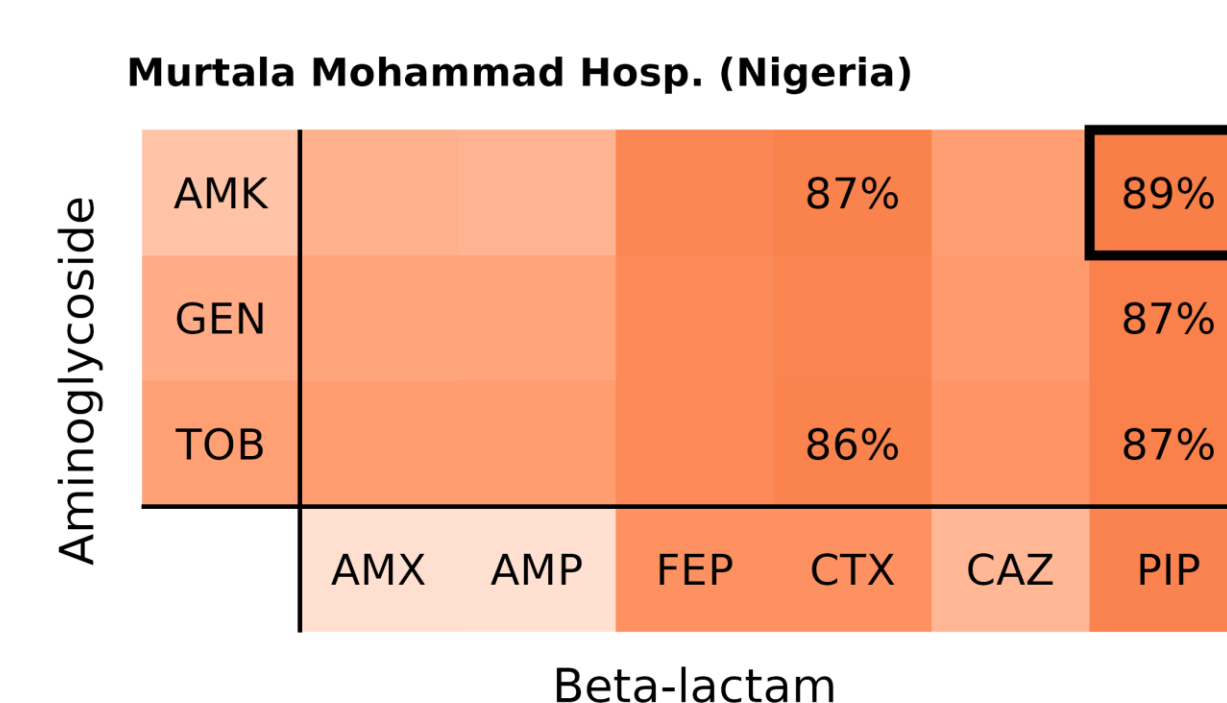
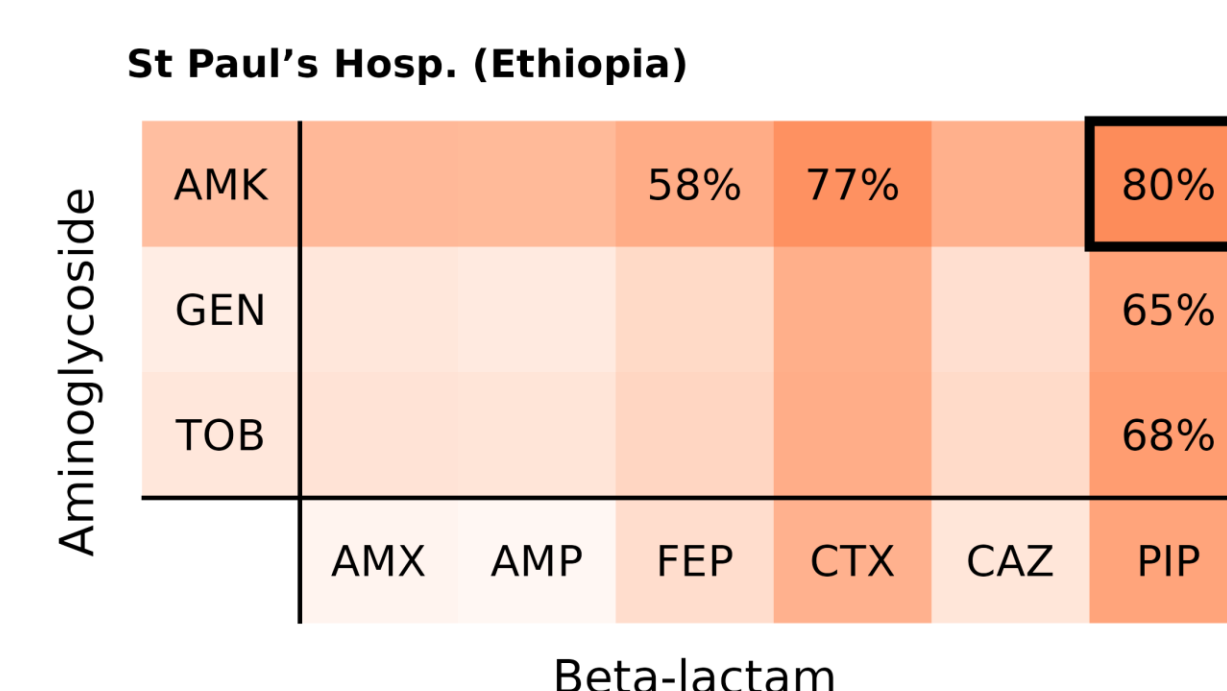
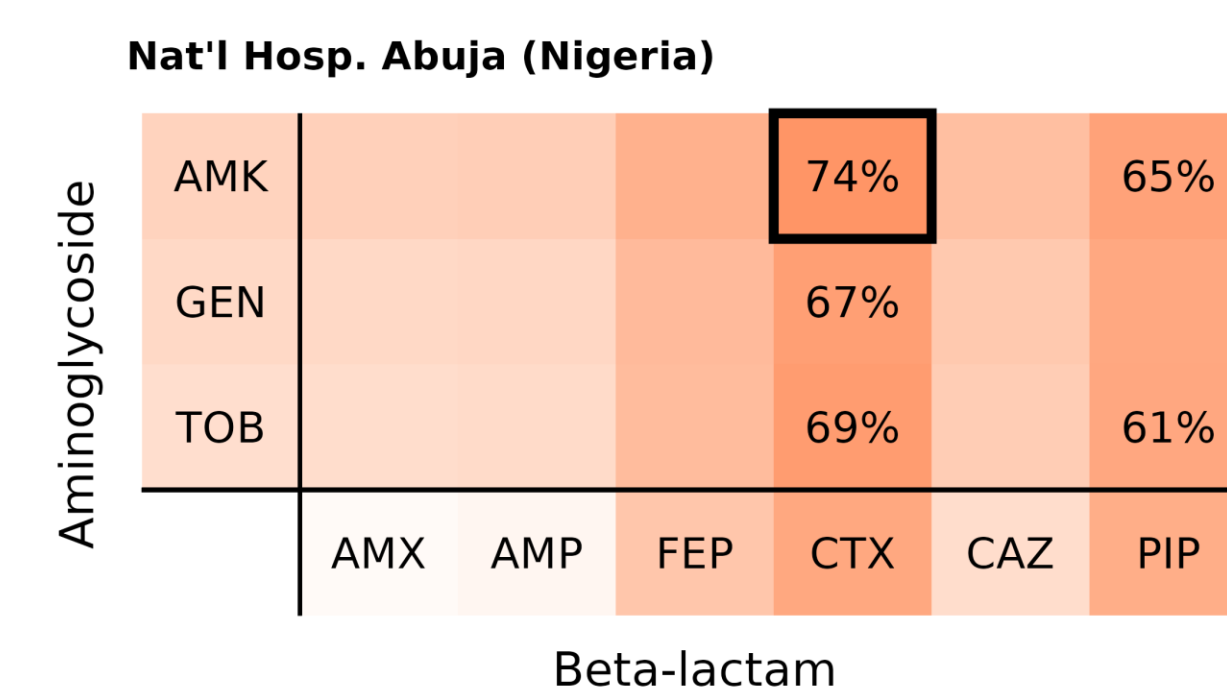
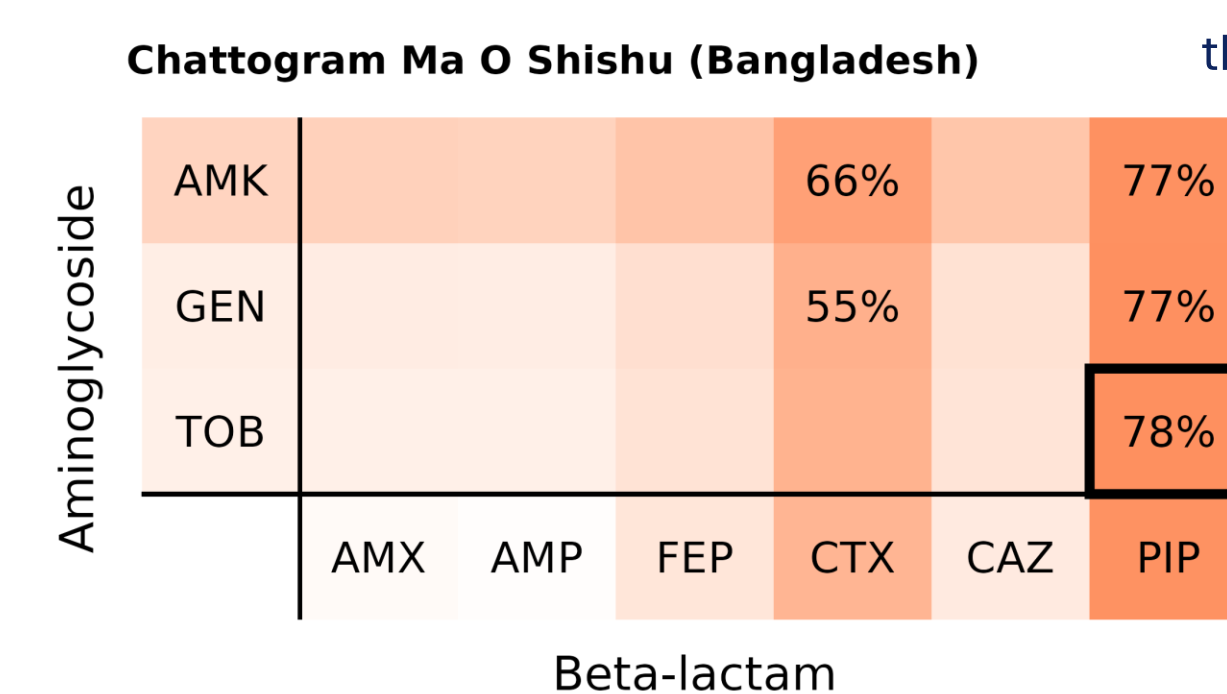
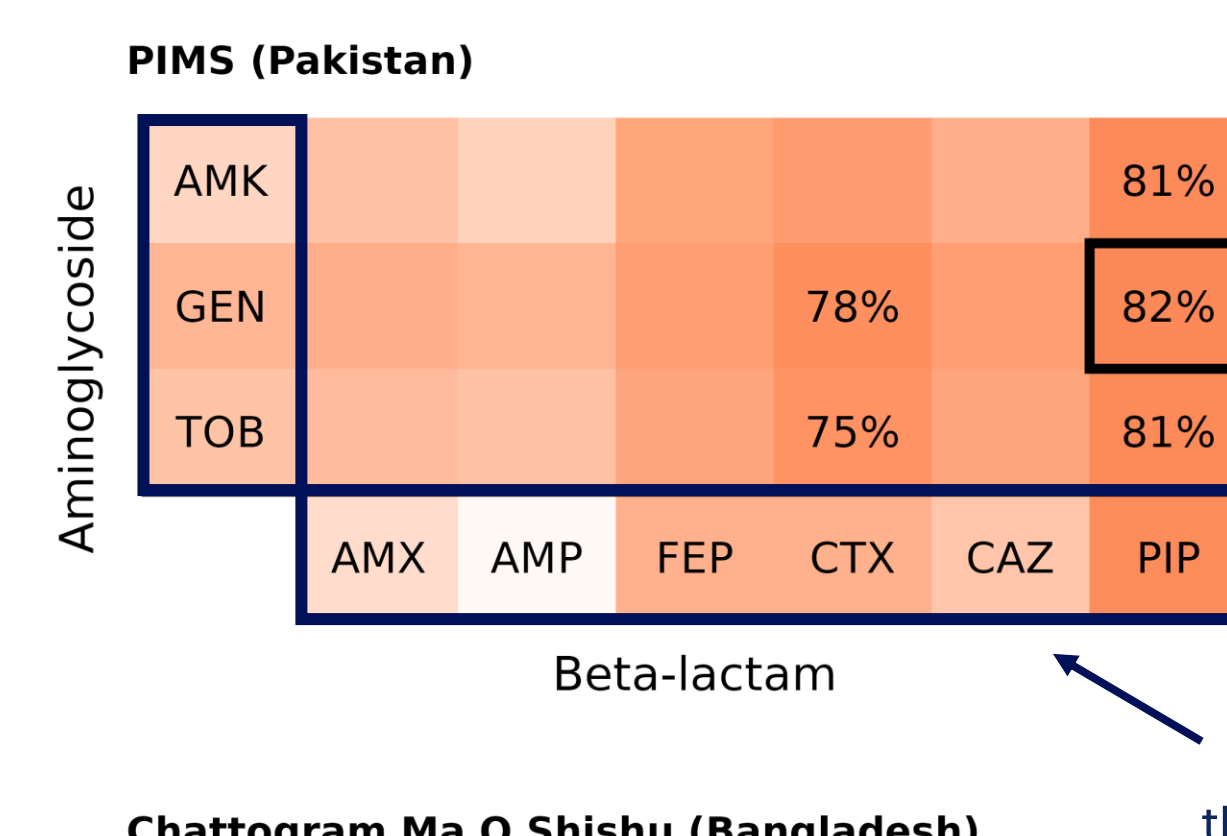
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Results

- PTA and **optimal combinations vary by site**.
- Coverage can be complementary: combining top single antibiotics does not always yield optimal PTA.
- When multiple combinations yield similar coverage, selection can focus on optimizing dual target attainment.

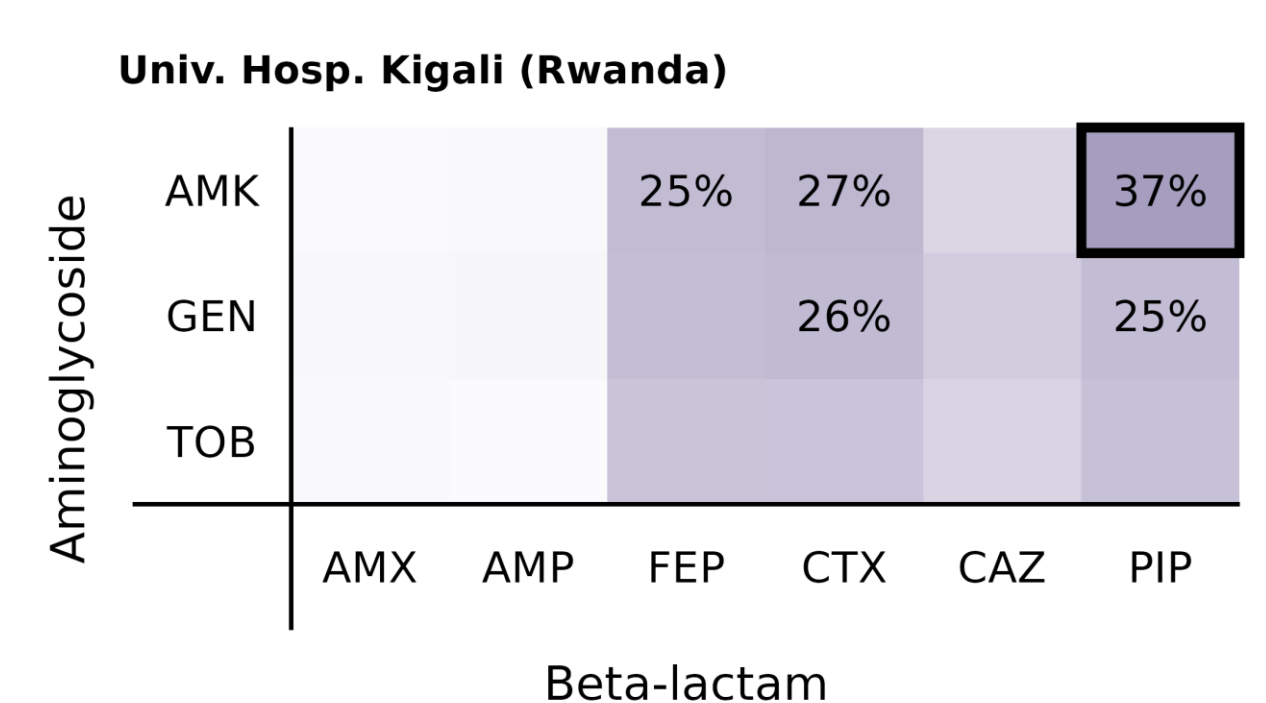
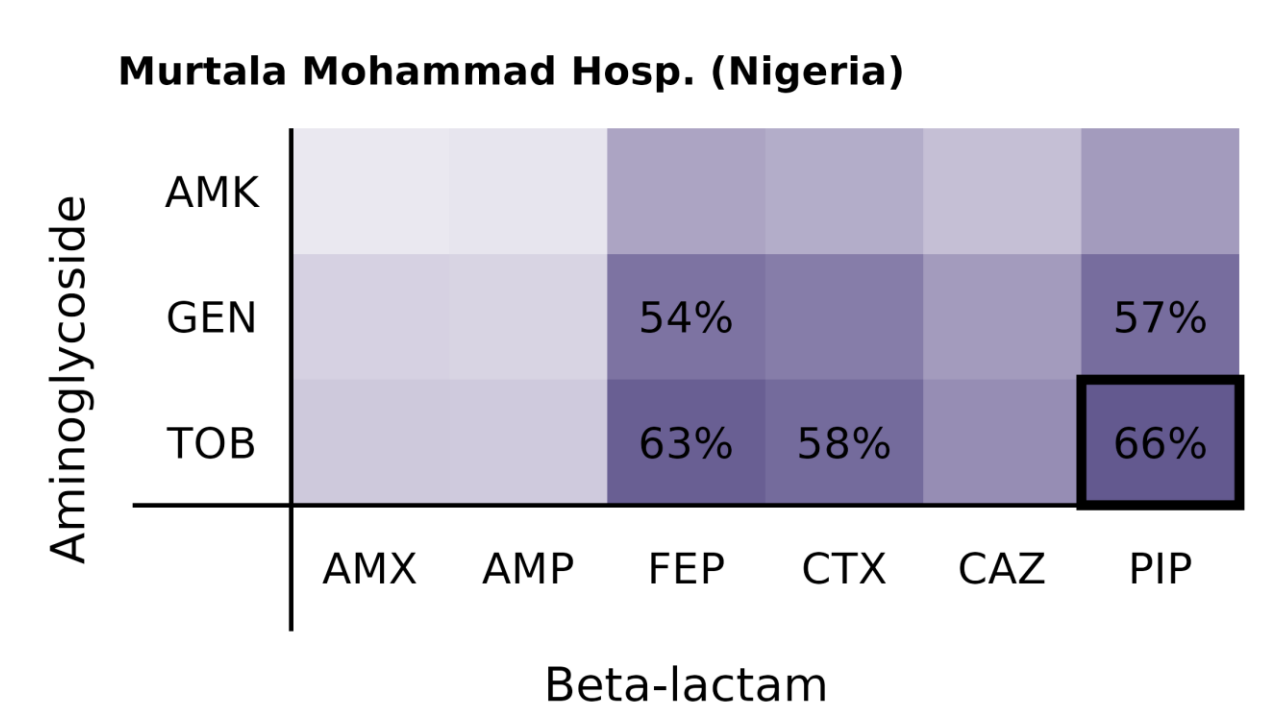
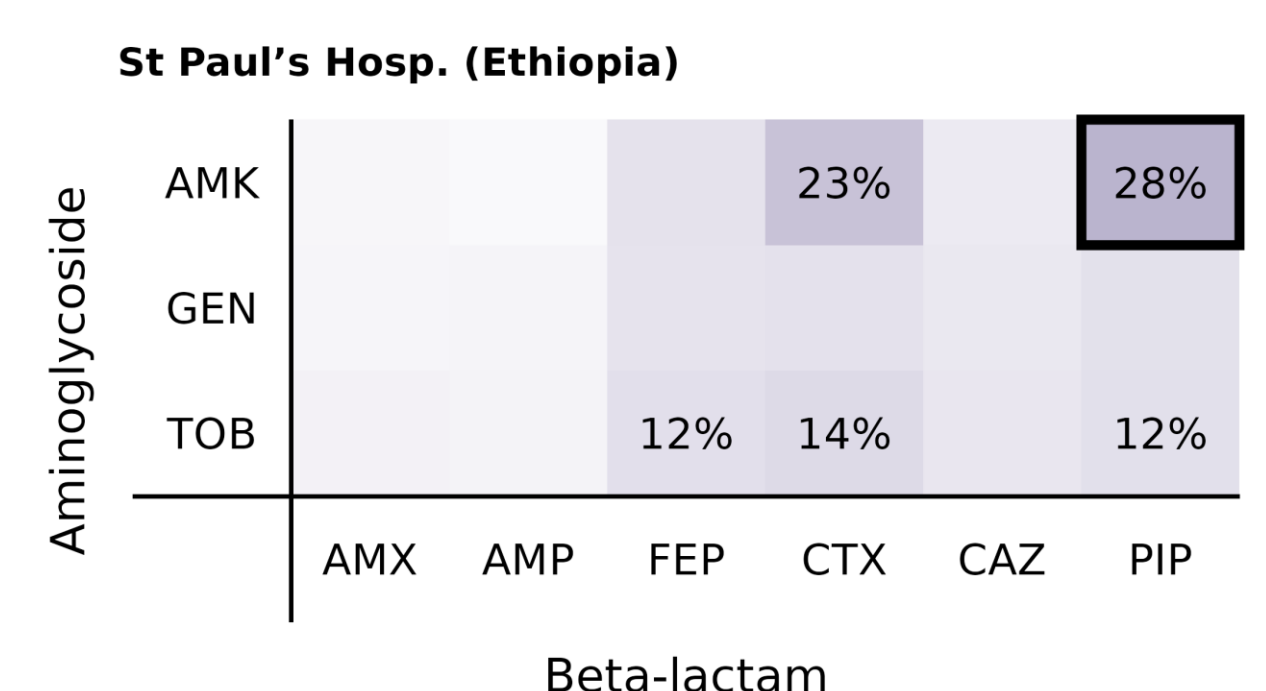
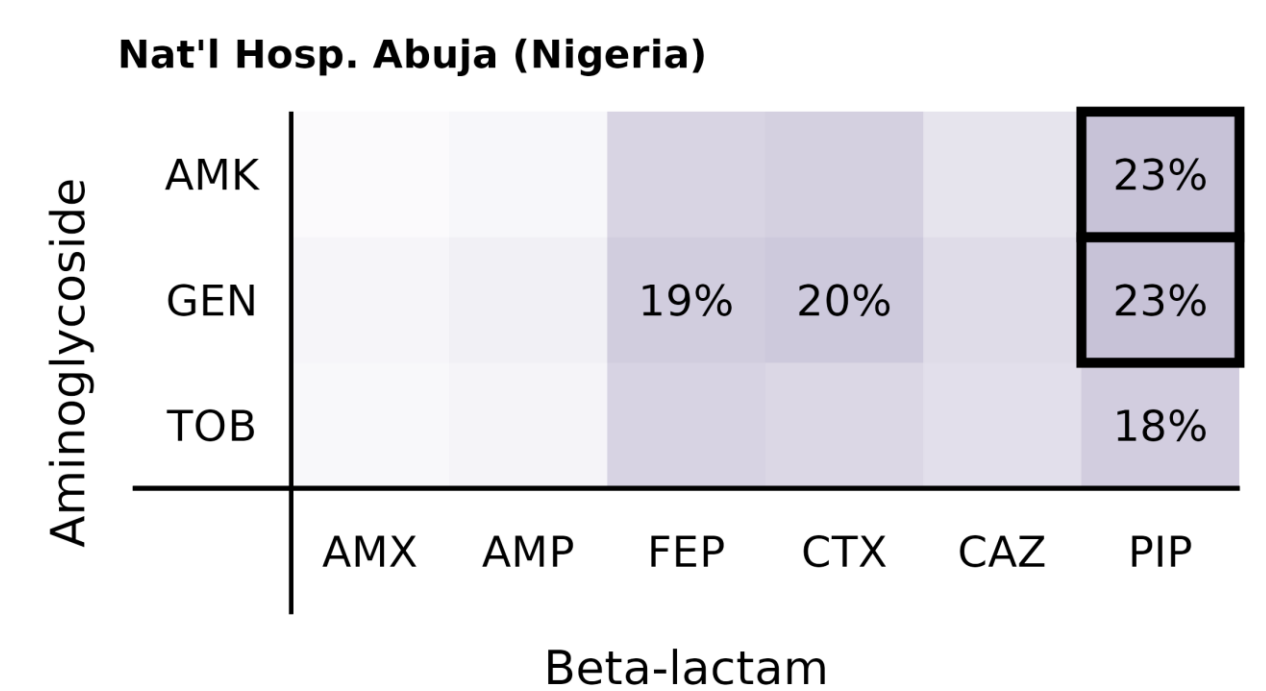
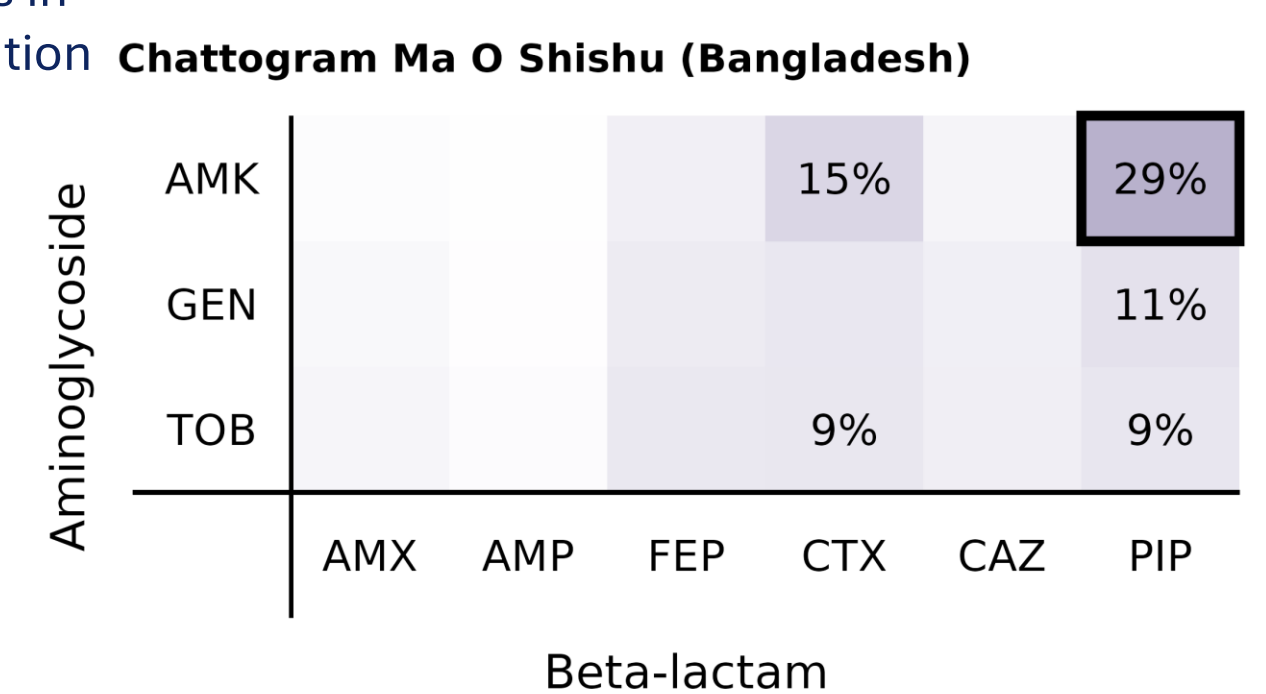
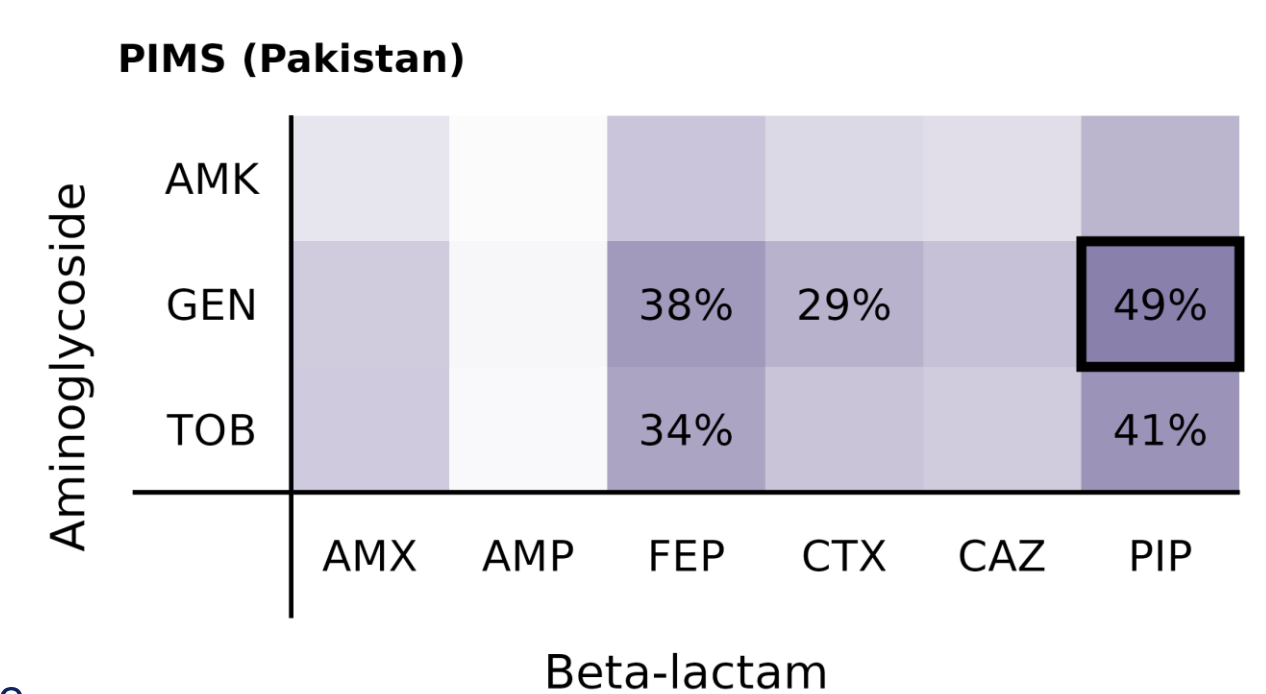
Probability of achieving at least one PK/PD target



Attaining ≥ 1 PK/PD target (%)

0 25 50 75 100

Probability of achieving both PK/PD targets



Attaining both PK/PD targets (%)

0 25 50 75 100

Aminoglycosides: AMK = amikacin, GEN = gentamicin, TOB = tobramycin
Beta-lactams: AMX = amoxicillin, AMP = ampicillin, FEP = cefepime, CTX = cefotaxime, CAZ = ceftazidime, PIP = piperacillin

Conclusion

This workflow can aid the **rational selection** of antibiotics for empirical combination treatment, based on local, multivariate MIC distributions and the PK in the target population.