Modelling antimicrobial de-escalation – when it is superior?

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Background

- Burden of antibiotic resistance (USA, CDC 2013):
  - $35 billion/annually in societal costs
  - 2 million infections/annually
  - 23,000 directly attributable deaths/annually
  - Intensive care units (ICUs) are the epicenters of antibiotic resistance.
- Goal of antimicrobial stewardship programs (ASPs):
  reduce inappropriate use of and resistance to antibiotics without compromising patient outcomes.
- Challenges in assessing ASP interventions:
  - Difficult to set up large multi-center cluster randomized trials
  - Difficult to compare across studies (meta-analysis)
  - Variation in definitions, contexts, outcomes

How does math models help?

- Can improve understandings of:
  - underlying mechanisms
  - sources of uncertainty
- Can assess several factors and hypothetically experiment with scenarios that may be difficult to capture in clinical trials:
  - resistance rates
  - specific drug regimens
- Ultimately, can lead to refined designs, hypotheses, and interpretation of clinical research

Antimicrobial De-escalation in Stewardship Programs

- Switch from broad-spectrum anitbiotics to alternatives based on laboratory susceptibility results.
- Aim to:
  - reduce costs;
  - stop unnecessary or redundant treatment;
  - switch from IV (intravenous) to oral therapy.

Antimicrobial De-escalation in Current Research[1]

	(Kim et al. 2012)	(Leone et al. 2014)
Harms	ICU stay days hospital mortality mortality relative to initial antimicrobial adequacy time to adequate antimicrobials	duration of ICU stays number of ICU-free days Ventilator-free days Catecholamine-free days
Drug use		number of antibiotic days companion antibiotic days antibiotic days for initial episode antipseudomonal agent-free days carbapenem-free days anti-MRSA drug-free days
Resistance	time to development of MDR organisms Methicillin-resistant *S. aureus* Gram-negative non-Enterobacteriaceae	
Not measured	superinfections appropriateness of empiric therapy drug use frequency (empiric, de-escalated, alternative) infection prevalence resistance prevalence	

[1] Tabah A, Cotta M, Garnacho-Montero J, Roborts J, Lipman J, Tacey M, et al. (2016) A systematic review of the definitions, determinants and clinical outcomes of antimicrobial de-escalation in the intensive care unit. Clin Infect Dis.

Antimicrobial De-escalation: Unknowns

From observational studies:

- mortality - unclear;
- resistance strain prevalence - no assessment;
- MDR and superinfections - observed;
- definitions and outcome measurements - differ.

Our questions:

- use of the broad-spectrum drugs? effectiveness of empirical therapy?
- MDR prevalence? resistance prevalence? superinfection?
- mortality?

Antibiotic De-escalation: Modelling

Treatment methods

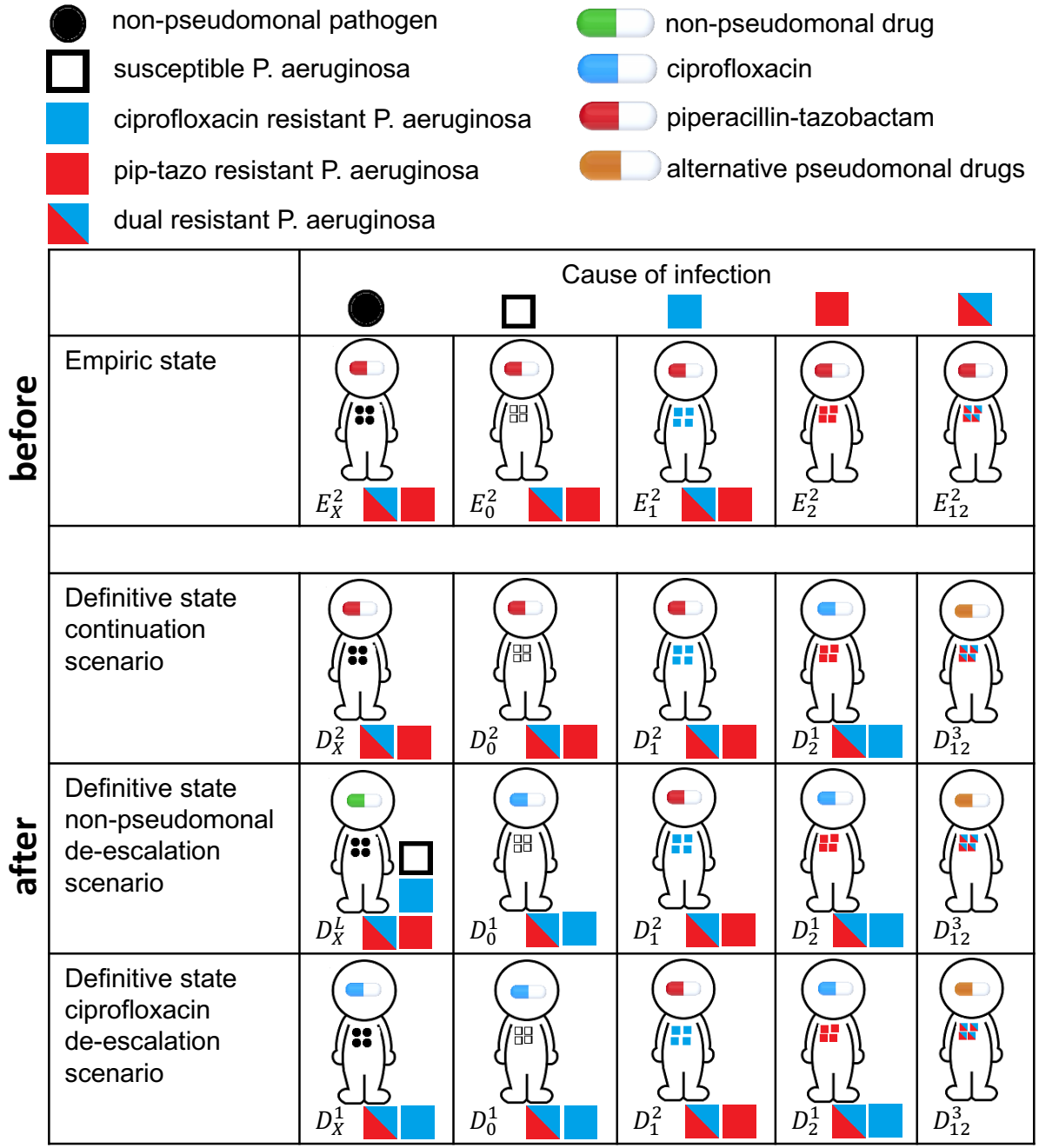
- Continuation:
  infected patient $\rightarrow$ empiric $\rightarrow$ culture results $\rightarrow$ empiric/correction
- De-escalation:
  infected patient $\rightarrow$ empiric $\rightarrow$ culture results $\rightarrow$ definitive/correction

P. aeruginosa

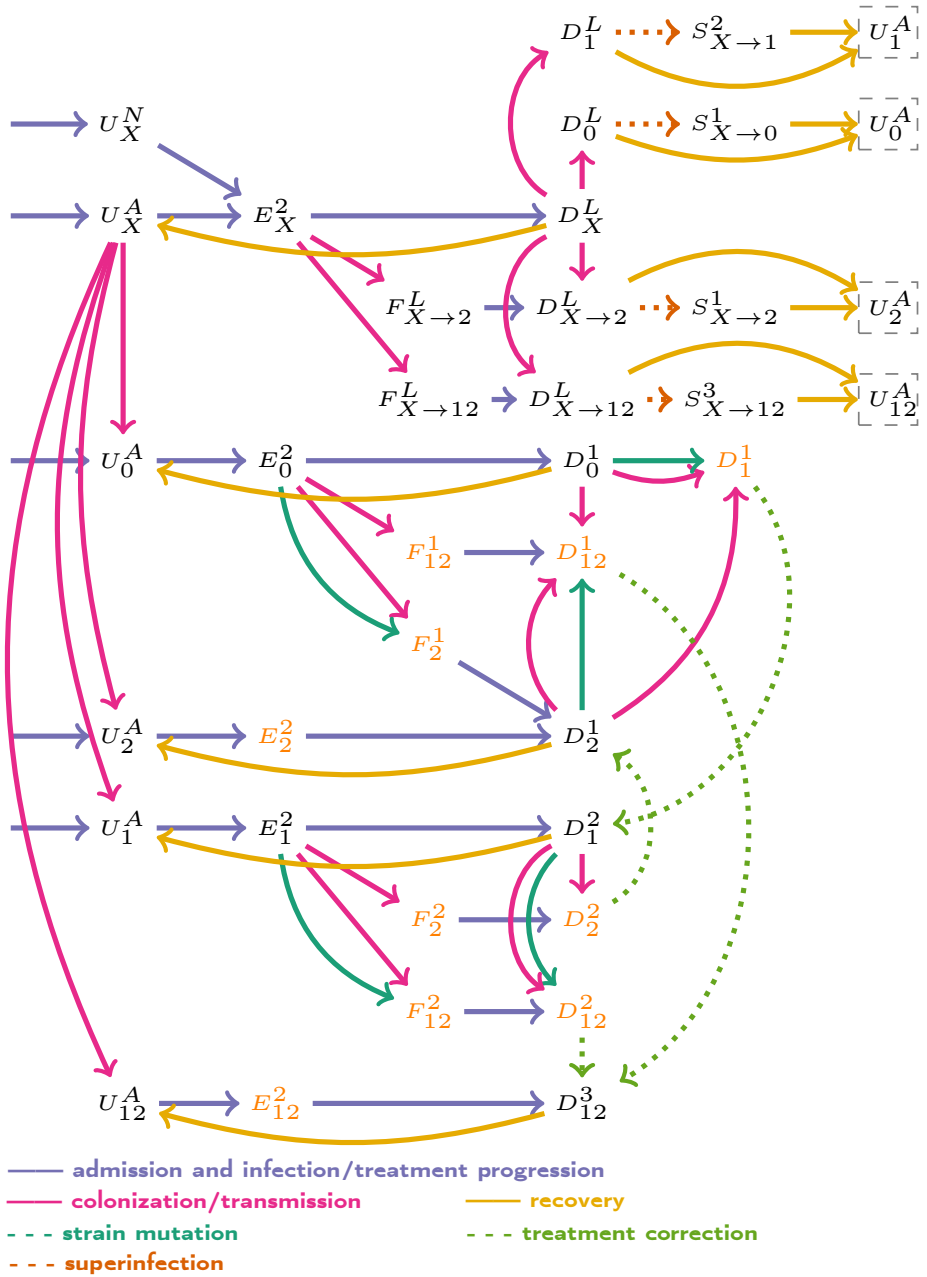
- most often acquired in hospital
- high intrinsic and acquired resistance
- stewardship could have a large impact

Antibiotics

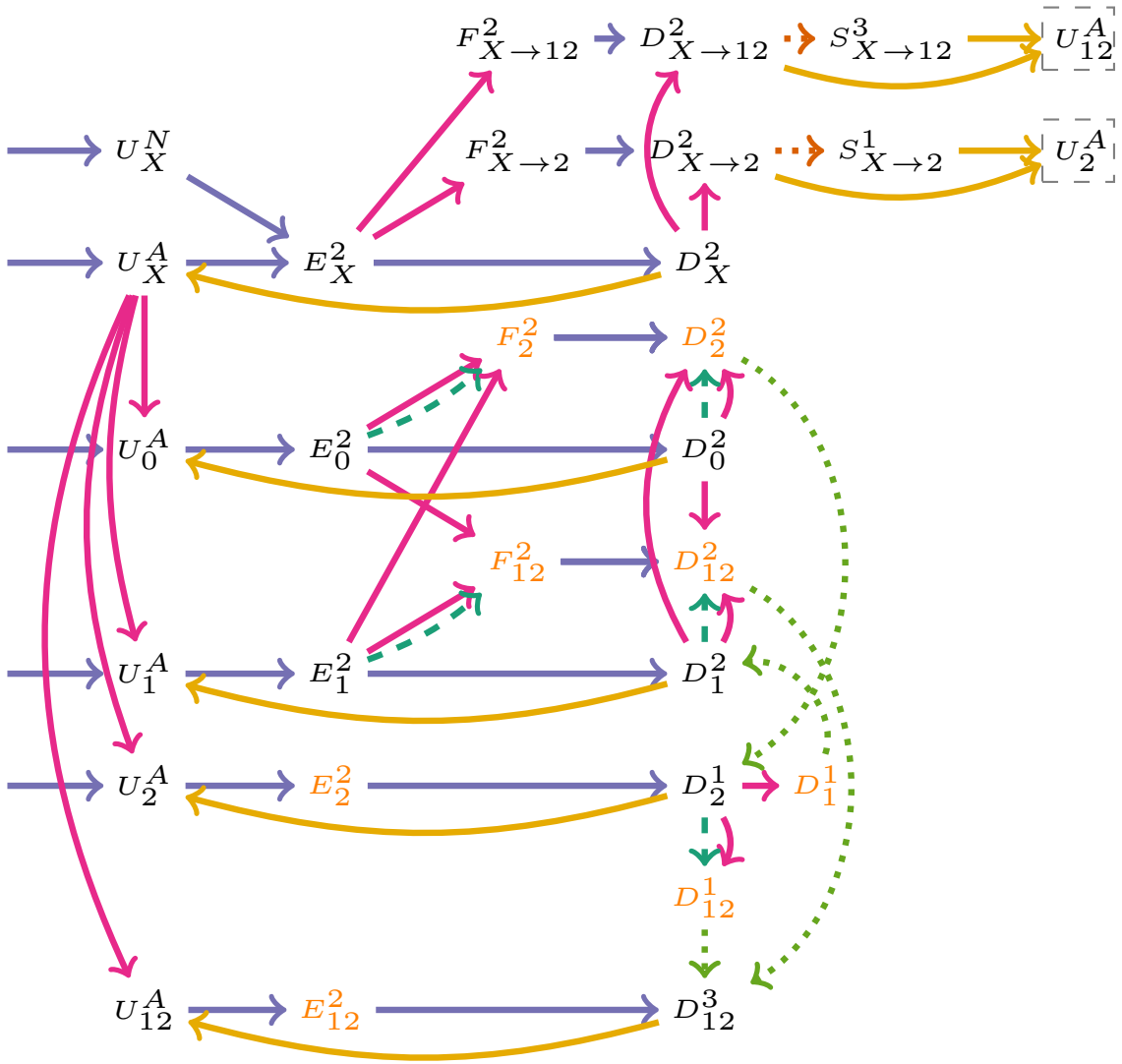
- Empiric drug: pip-tazo - good coverage;
- Definitive drug: ciprofloxacin - poorer but common coverage;
- Last-resort drug: such as a carbapenem or aminoglycoside.


non-pseudomonal pathogen
susceptible P. aeruginosa
ciprofloxacin resistant P. aeruginosa
pip-tazo resistant P. aeruginosa
dual resistant P. aeruginosa
non-pseudomonal drug
ciprofloxacin
piperacillin-tazobactam
alternative pseudomonal drugs
Cause of infection
before
after
Empiric state
Definitive state continuation scenario
Definitive state non-pseudomonal de-escalation scenario
Definitive state ciprofloxacin de-escalation scenario
E_X^2
E_0^2
E_1^2
E_2^2
E_{12}^2
D_X^2
D_0^2
D_1^2
D_2^1
D_{12}^3
D_X^L
D_0^1
D_1^2
D_2^1
D_{12}^3
D_X^1
D_0^1
D_1^2
D_2^1
D_{12}^3

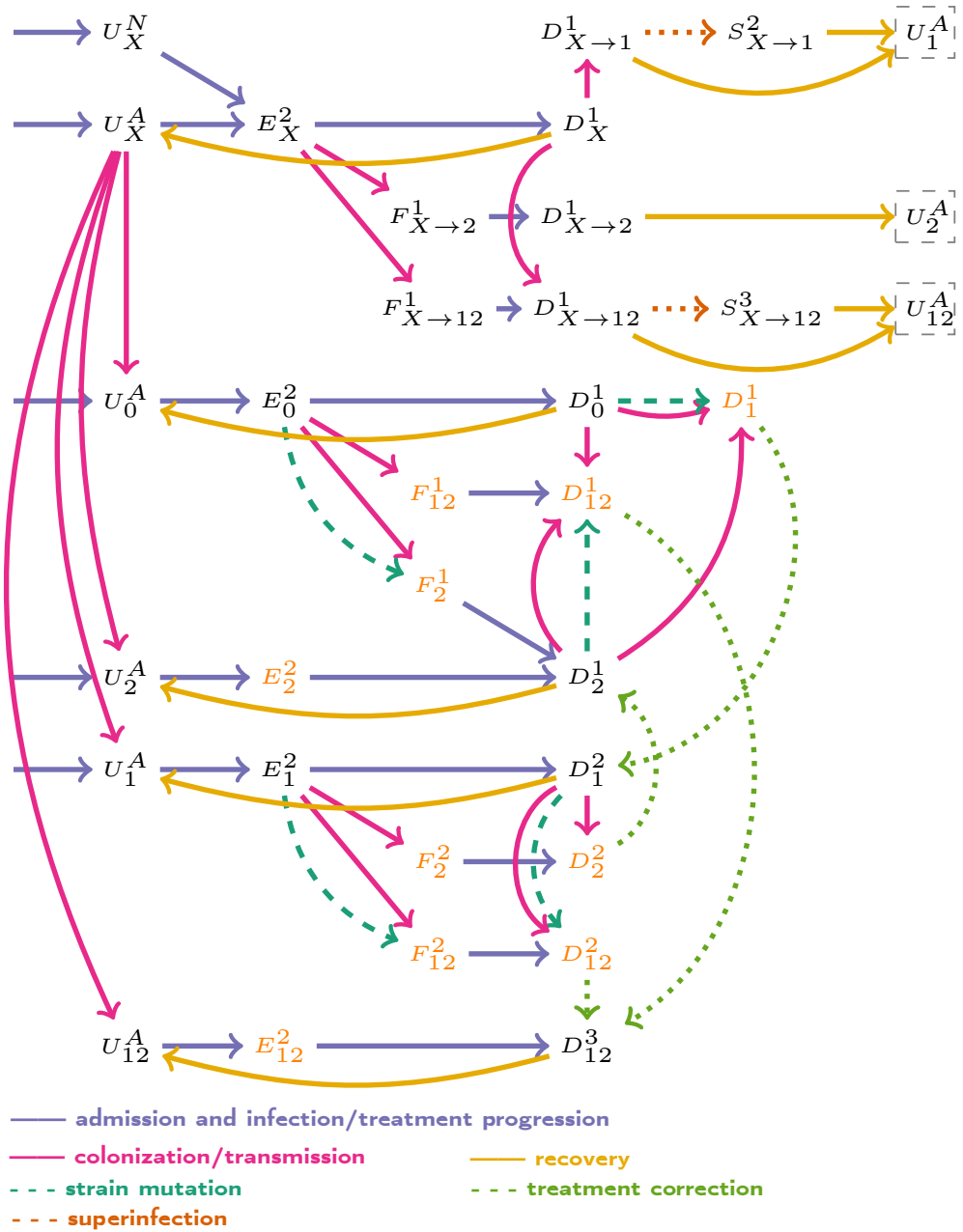
De-escalation



Continuation



Cipro de-escalation

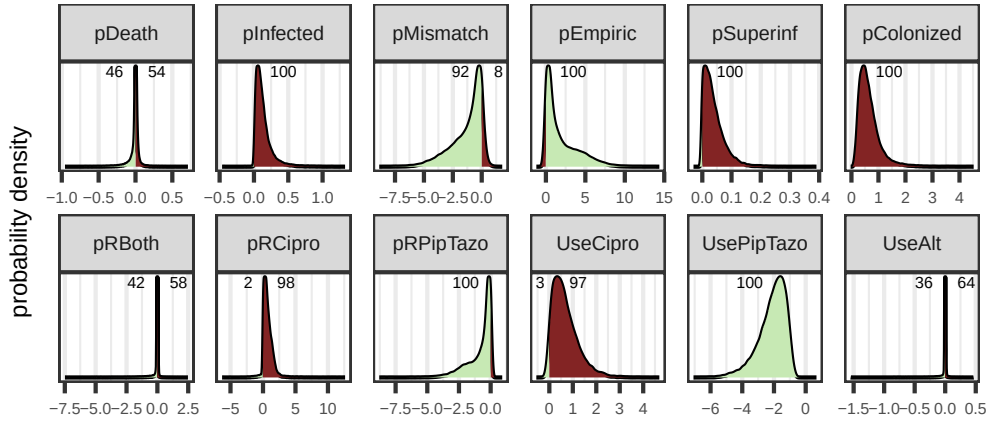


Model parameters.

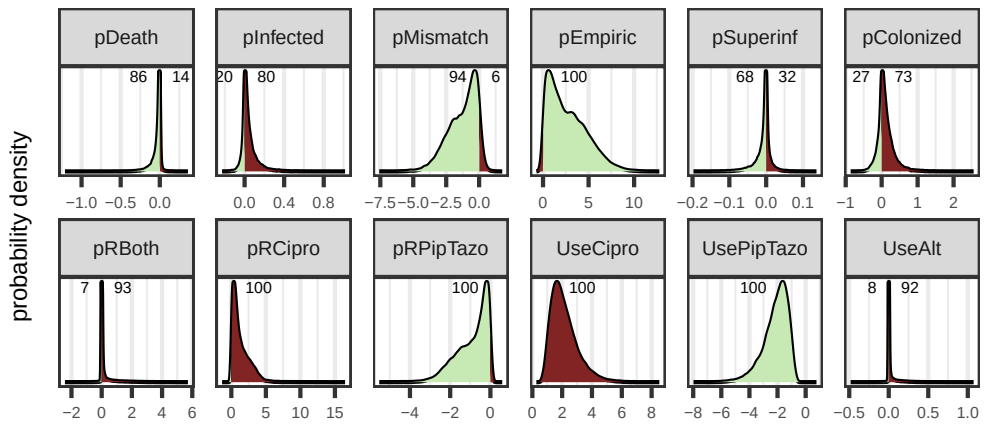
Symbol	Value	Definition
Parameters with fixed values		
N	16	Number of patients in ICU
a	0.6	Fraction of patients admitted with prior exposure to antimicrobials
τ	$1/3$ day^{-1}	Rate of finishing empiric therapy
τ_1	$1/5 \sim 1/3$ day^{-1}	Rate of correcting failed definitive treatment
τ_2	$1/4$ day^{-1}	Rate of finishing an effective definitive treatment
Parameters with clear ranges		
m	$0 \sim 0.1$	Fraction of patients admitted colonized
σ_x	$0.013 \sim 0.0203$ day^{-1}	Infection rate of patients colonized by other species
σ_c	$0.05 \sim 0.14$ day^{-1}	Infection rate of patients colonized by *P.aeruginosa*
τ_3	$\frac{1}{15} \sim \frac{1}{4}$ day^{-1}	Rate of finishing an effective treatment to superinfection
κ_μ	$0.49 \sim 1.0$	Hazard ratio of discharge with nosocomial infection
κ_ν	$1.0 \sim 2.3$	Hazard ratio of death with nosocomial infection
δ	$4\% \sim 40\%$	Difference in probability of death between effective and ineffective empiric therapy after 10 days
Uncertain parameters with large ranges		
β	$0.01 \sim 1$ day^{-1}	Transmission rate
r_1	$0 \sim 0.7$	Fraction of patients admitted colonized with strain 1
r_2	$0 \sim r_1$	Fraction of patients admitted colonized with strain 2
ε_1	$0 \sim 0.03$ day^{-1}	Rate of emergence of ciprofloxacin resistance
ε_2	$0 \sim 0.03$ day^{-1}	Rate of emergence of piperacillin-tazobactam resistance
μ	$0.025 \sim 0.5$ day^{-1}	Discharge rate of patients without nosocomial infection
ν	$0.005 \sim 0.05$ day^{-1}	Death rate of patients without nosocomial infection
η	$0 \sim 100\%$	Probability of emergence of superinfection
ϑ	$0 \sim 100\%$	Hazard ratio of finishing an effective treatment to multi-drug resistant strain infection

Calibration

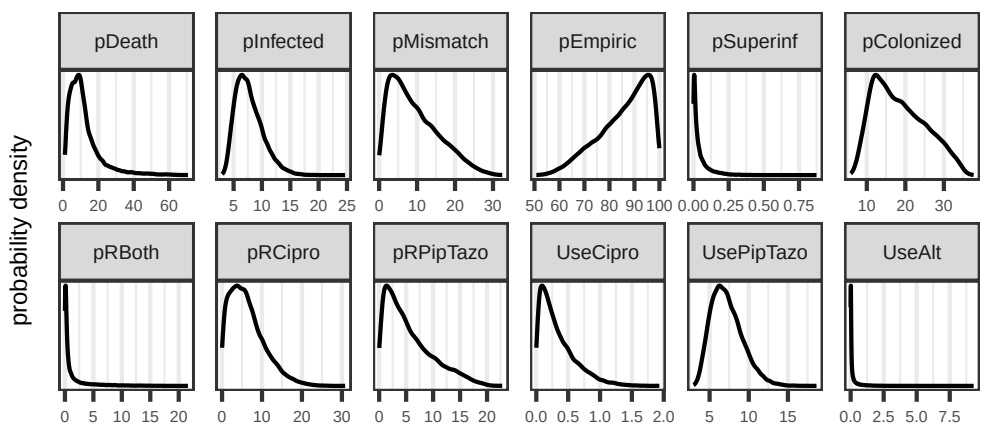
Response	Value	Notes
Resistance to cipro	$0 - 0.29$	Among the intensive care units of Ontario teaching hospitals, 0 to 29% of *P. aeruginosa* isolates are resistant to ciprofloxacin.
Resistance to pip-tazo	$0 - 0.28$	Among the intensive care units of Ontario teaching hospitals, 0 to 28% of *P. aeruginosa* isolates are resistant to piperacillin-tazobactam.
Acquisition prevalence	$0.06 - 0.32$	Prevalence of *P. aeruginosa* acquisition in ICUs varies between 6 and 32%



(a) Differences between non-pseudomonal de-escalation and continuation (%)

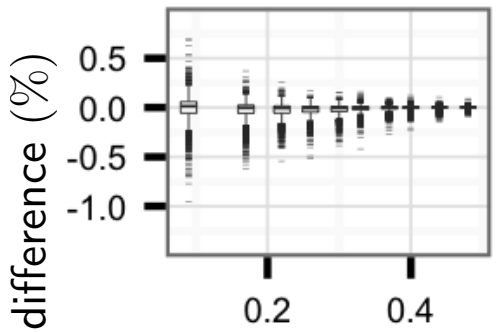


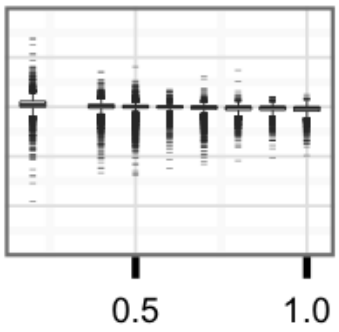
(b) Differences between ciprofloxacin de-escalation and continuation (%)

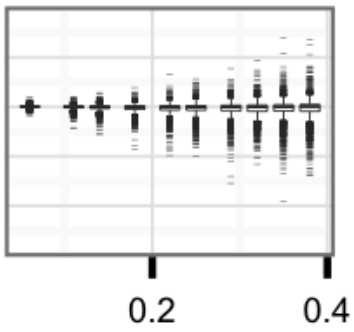


(c) Continuation outcomes (%)

Influence of important parameters on death ratio

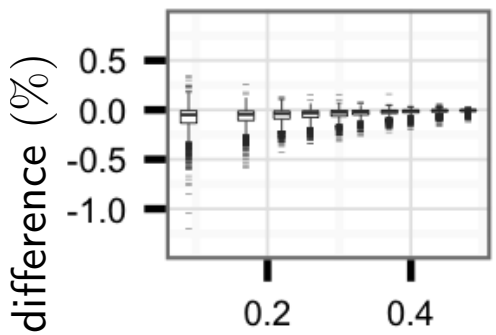


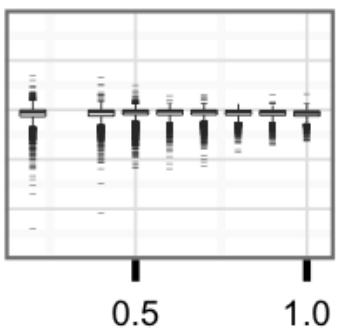


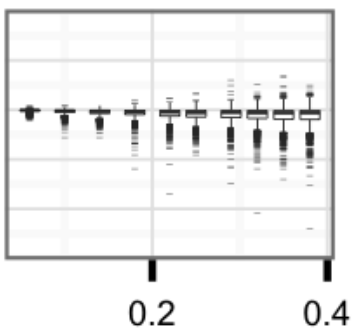


Discharge rate, μ Transmission rate, β Impact of empiric therapy, δ

(a) Non-psuedomonal de-escalation vs continuation



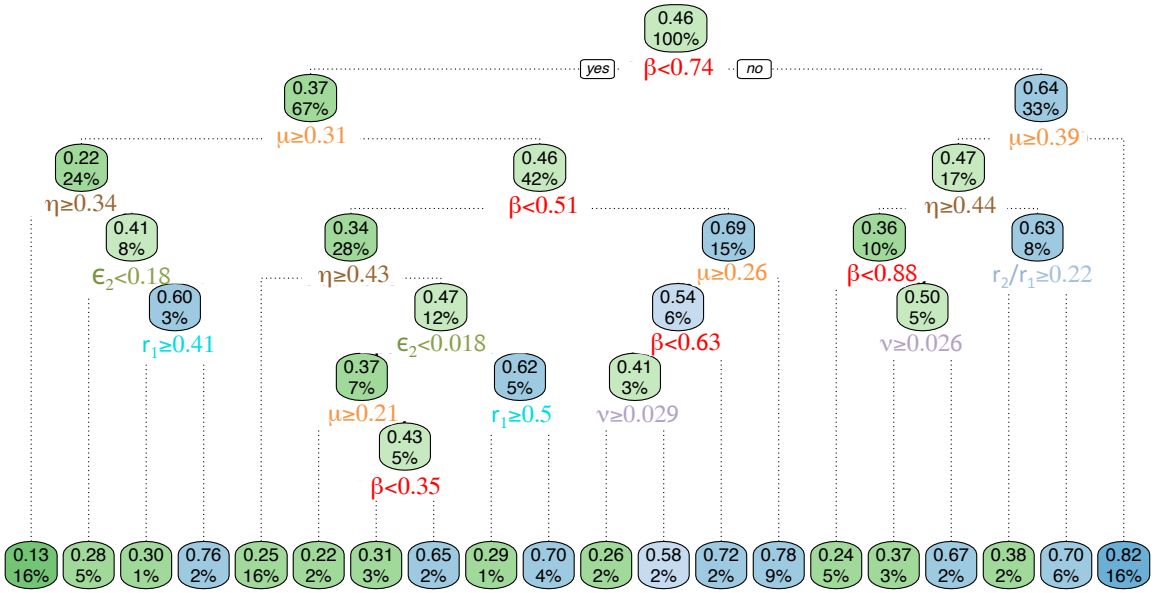




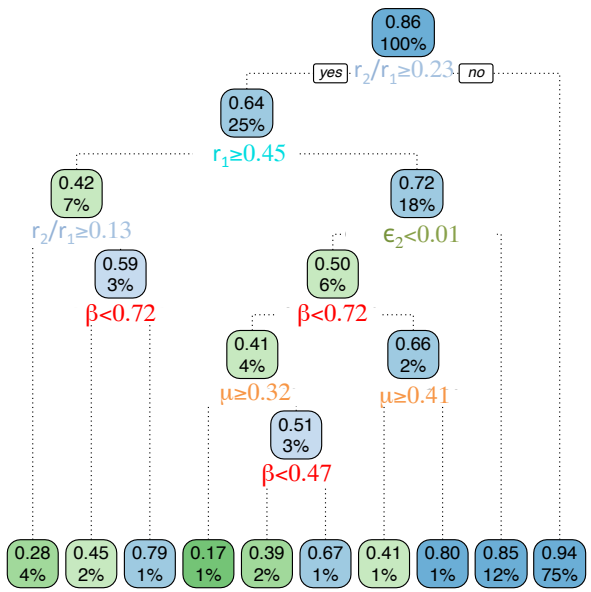
Discharge rate, μ Transmission rate, β Impact of empiric therapy, δ

(a) Ciprofloxacin de-escalation vs continuation

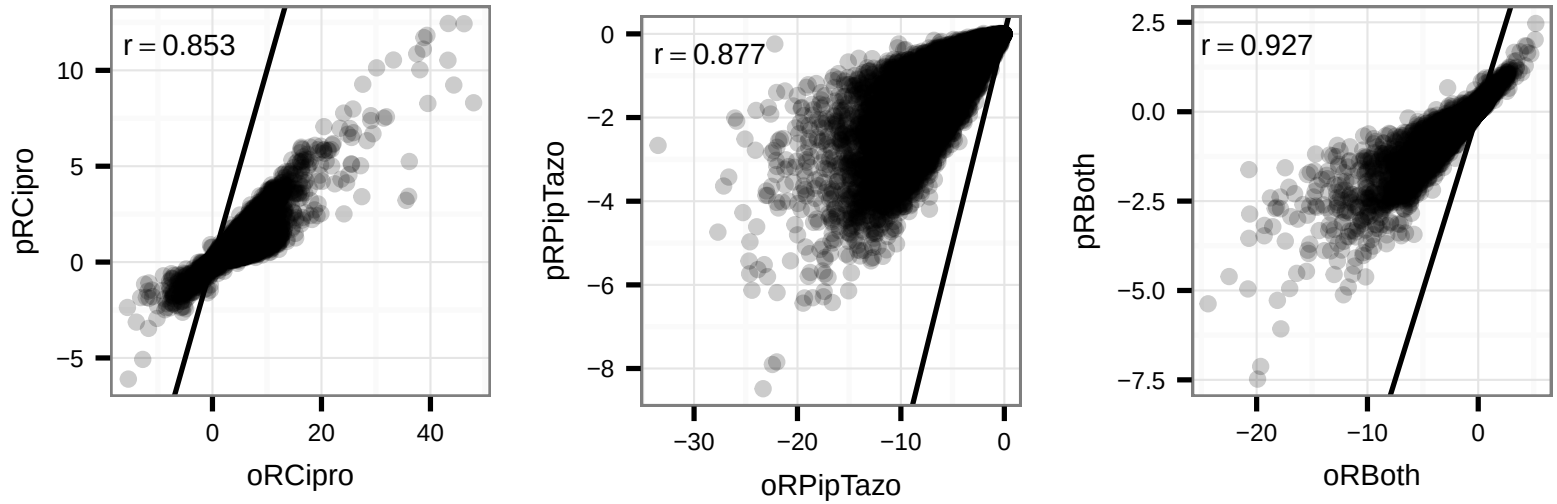
Classification tree



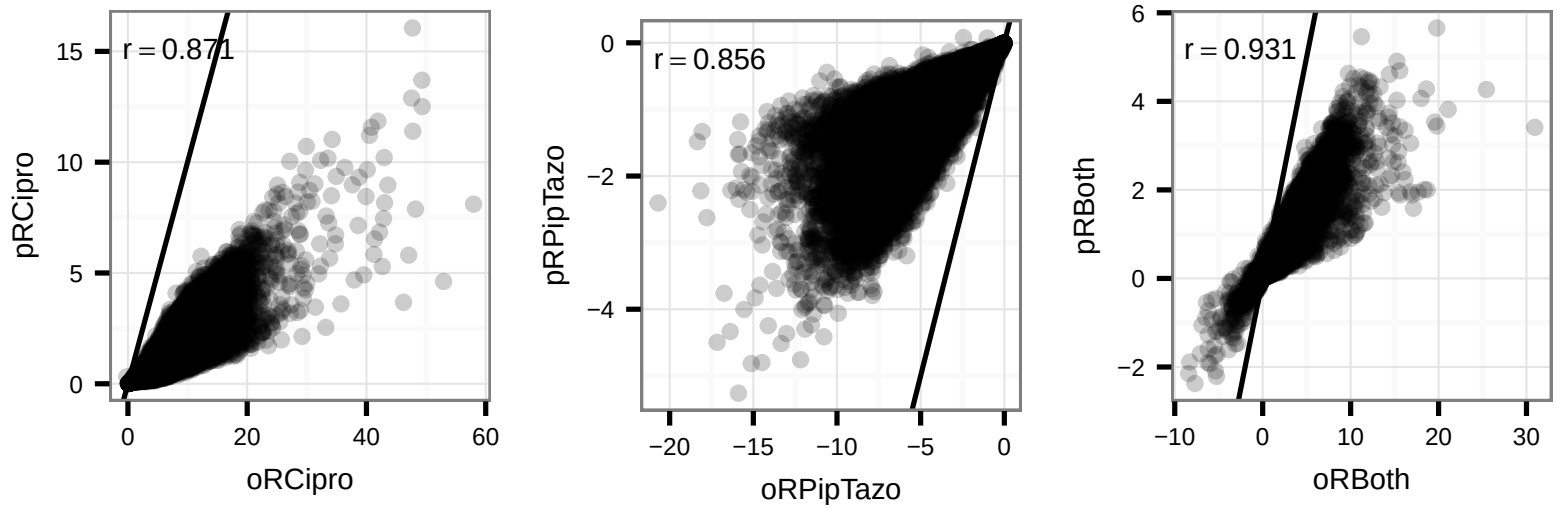
(a) Non-pseudomonal scenario



(b) Ciprofloxacin scenario



(a) Non-pseudomonal scenario



(b) Ciprofloxacin scenario

Clinical measurements overestimate resistance differences compared with ecological measurements.

Collaborators[2]

- Josie Hughes, York University/Mount Sinai Hospital.
- Lindsey Falk, Univeristy of Toronto.
- Amy Hurford, Memorial University of Newfoundland.
- Kunquan Lan, Ryerson University.
- Bryan Coburn, Toronto General Hospital/University of Toronto.
- Andrew Morris, Mount Sinai Hospital/University of Toronto.
- Jianhong Wu, York University.

[2]Hughes J, Huo X, Falk L, Hurford A, Lan K, Coburn B, Morris A, Wu J. (2017) Benefits and unintended consequences of antimicrobial de-escalation: Implications for stewardship programs. PLoS ONE.

- Sensitivity analysis on measurements:
  - ecological and clinical observations are highly correlated
  - clinical observed effects overestimate ecological effects on strain prevalence.
- Sensitivity analysis on parameters: de-escalation is most likely to have a substantial impact when
  - discharge rate is low
  - transmission rate is moderate
  - empiric therapy impact is high
- The need of careful measurements: de-escalation may increase superinfections and multidrug- resistance, while preserving empiric therapy and reducing *C.diff* infections.