Balancing effectiveness and AMR risk

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A novel method to select rational empirical antimicrobial therapy

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Background

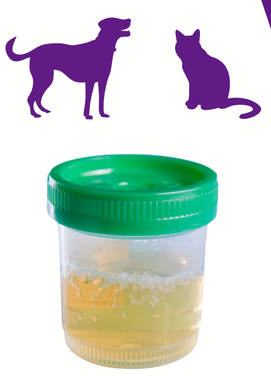
- Pooled antimicrobial culture and susceptibility (C&S) results can be used to recommend optimal empirical therapy in a given clinical condition.
- A previously published method by Blondeau and Tillotson, the **F**ormula for **R**ational selection of empirical **A**ntimicrobial **T**herapy (FRAT) takes into account only pathogen prevalence and susceptibility.
- This results in an 'impact factor' for each antimicrobial, that inherently favours broader-spectrum antimicrobials.
- Good antimicrobial stewardship demands a more nuanced approach that helps clinicians balance expected **effectiveness** with **antimicrobial resistance (AMR) risk.**

Antimicrobial X

	Prevalence (%)	Susceptibility (%)
Bacterium 1	a	b
Bacterium 2	c	d
Bacterium 3	e	f

FRAT:
Impact factor of X = **ab** + **cd** + **ef** ...
until prevalence reaches <2%

Prevalence x Susceptibility



Methods

- De-identified antimicrobial susceptibility results were obtained from culture-positive canine and feline urine samples in Portugal and Australia
- No associated urinalysis or clinical data were obtained, however, since C&S is expensive for pet owners, it is likely that most or all these C&S tests were performed on strong clinical suspicion of a urinary tract infection (UTI)
- To both data sets, we applied:
  - the **FRAT**, resulting in antimicrobial impact factors
  - our own novel method, a **whole-population antimicrobial simulation** that accounts for individual animal infections with multiple pathogens and incorporates local **antimicrobial importance ratings** as a proxy for AMR risk. This resulted in a 'cost per cure' for each antimicrobial

Results

Prevalence x Susceptibility x Antimicrobial Importance

Example of whole-population antimicrobial simulation (Portugal, dogs)

EMA classification
Category D = 1 point
Category C = 2 points
Category B = 3 points

2518 dog UTI cases
- 2473 with single isolates +
- 45 with multiple isolates

1st-line treatment	Expected success (cases cured)	Antimicrobial cost per cure	2nd-line treatment	Expected cumulative success	Cumulative antimicrobial cost per cure
TMS	68% (1708)	1.47	Nitrofurantoin	86% (2177)	1.53
			Amoxycillin	77% (1942)	1.67
			Amox-Clav	83% (2089)	1.98
			Amikacin	83% (2079)	1.99
			Cephalexin	75% (2079)	2.19
			Enrofloxacin	75% (1895)	2.61
			Marbofloxacin	84% (2115)	2.34
Nitrofurantoin	64% (1616)	1.56	TMS	86% (2177)	1.57
			Amoxycillin	76% 1915)	1.78
			Amox-Clav	83% (2098)	2.06
			Amikacin	88% (2222)	1.94
			Enrofloxacin	74% (1873)	2.79
			Marbofloxacin	90% (2257)	2.31
Amox-Clav	59% (1487)	3.39	TMS	83% (2089)	2.94
			Amikacin	83% (2087)	3.40
			Marbofloxacin	86% (2171)	3.74
Amikacin	63% (1580)	3.19	TMS	83% (2079)	2.94
			Amox-Clav	83% (2087)	3.31
			Marbofloxacin	88% (2205)	3.56

- If not tested, an antimicrobial was assumed to be ineffective against that antimicrobial. Intermediate results were also deemed ineffective.
- Infections with multiple isolates were deemed cured when all isolates - aside from any enterococci - had been exposed in that pathway to a drug they were susceptible to.
- Cost per cure was calculated by multiplying the number of animals that needed to be treated empirically, by the antimicrobial importance rating classification points, divided by the number of animals cured

For those antimicrobials routinely tested in both countries, **susceptibility** of the most prevalent urinary isolates **was signicantly lower in Portugal than Australia ($p < 0.001$)**

amoxicillin
TMS
amoxiclav
cephalexin
cefovecin
enrofloxacin

	FRAT highest antimicrobial impact factor	**Whole-population simulation** lowest 'cost per cure'
4990 isolates	Amikacin* 85	TMS 1.47
	Amikacin* 83	TMS 1.47
6196 isolates	Amoxiclav 95	TMS 1.15
	Amoxiclav 95	TMS 1.21

- not registered for animal use in Europe

Conclusions

- Our whole-population antimicrobial simulation method balances expected clinical effectiveness with AMR risk and provides a useful alternative to FRAT
- This method could be used in the development of local antimicrobial treatment guidelines

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