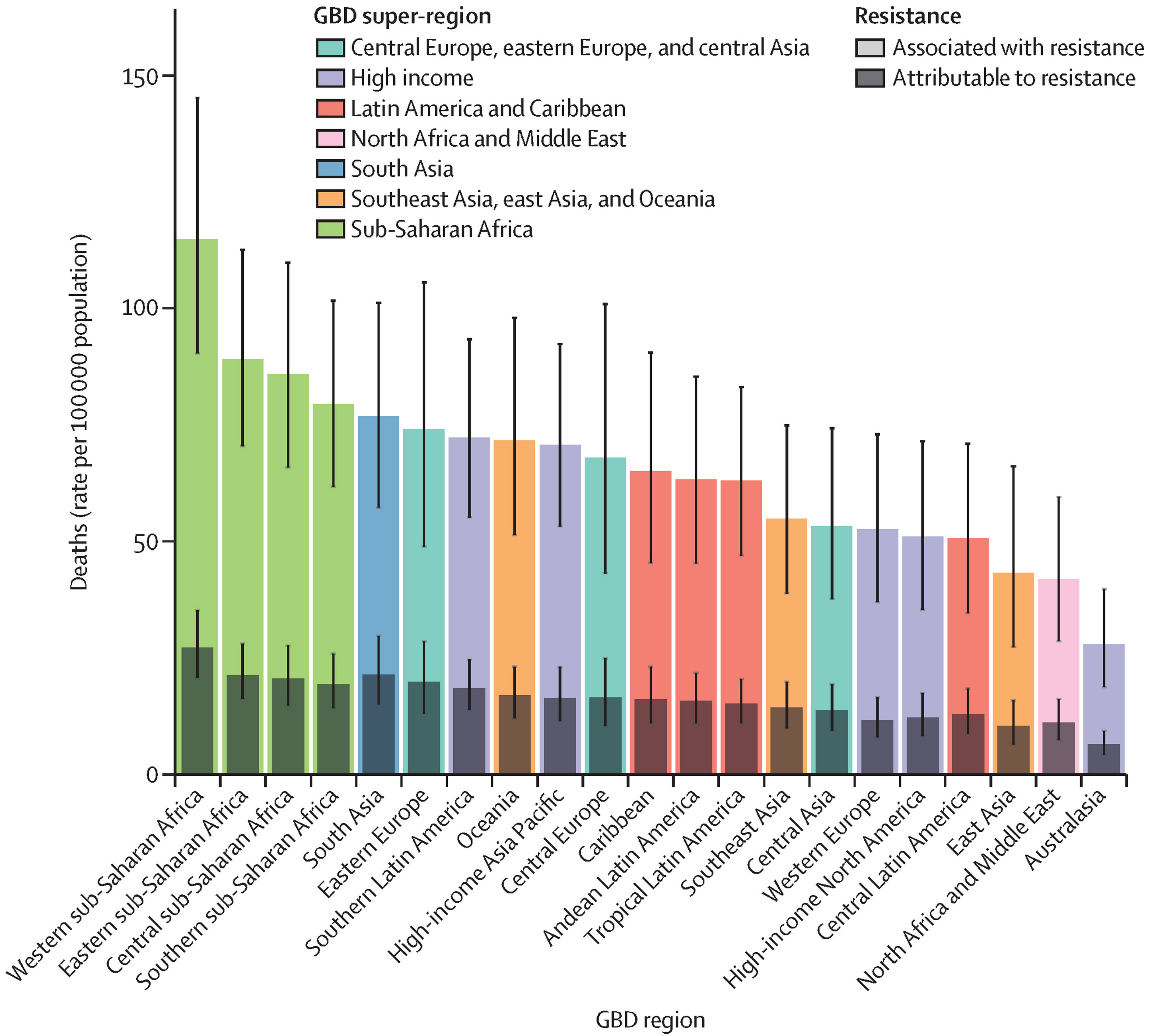
The fitness cost of antibiotic resistance: the role of observational data

Outline

- What is antibiotic resistance, what is fitness cost and why do we care?
- What do experiments tell us and why we need observational data?
- How do we infer fitness cost from observational data?
- Problems with observational approaches.
- What could we do instead.

1. Fitness cost of resistance: why do we care?

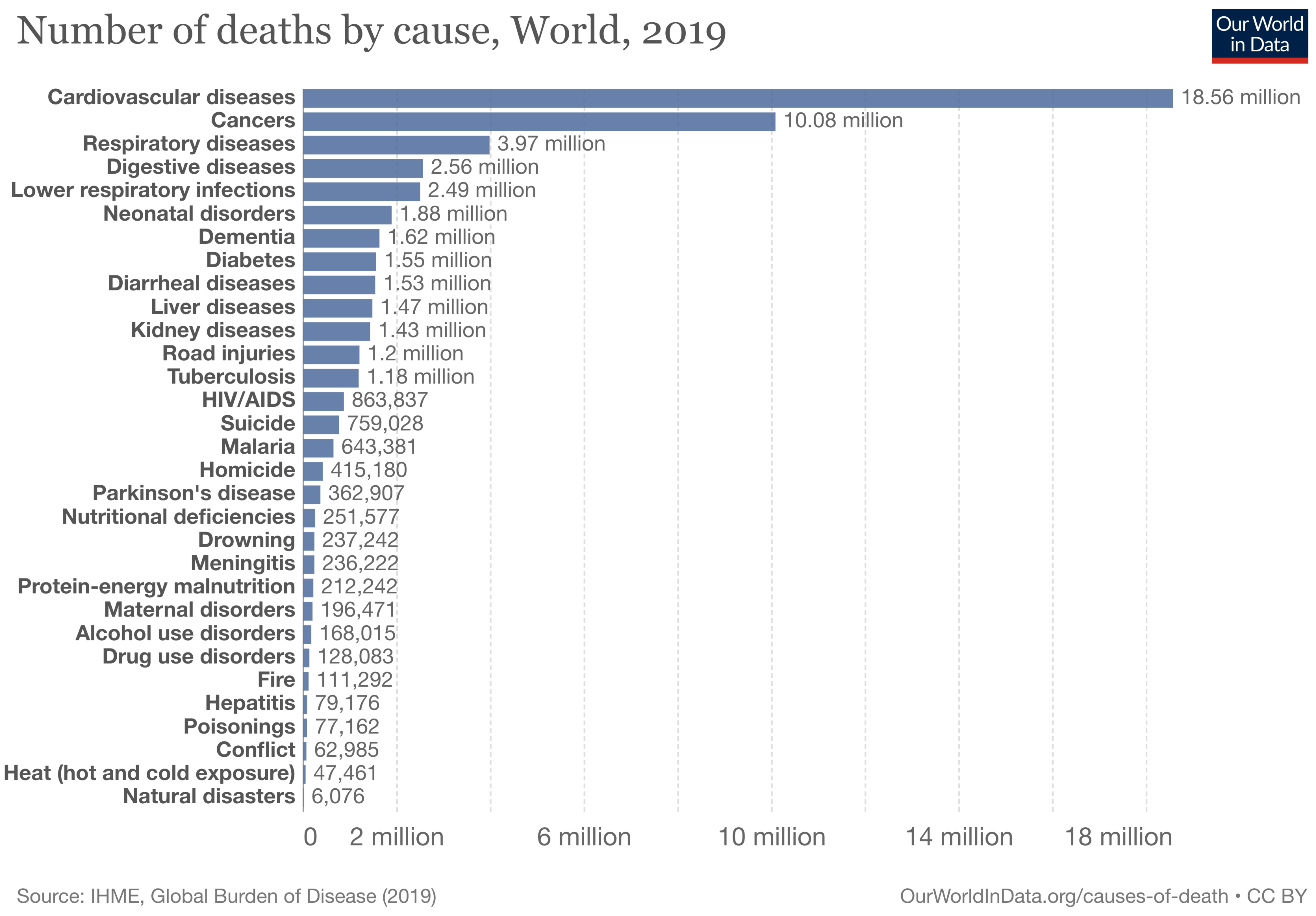
Source: The Economist



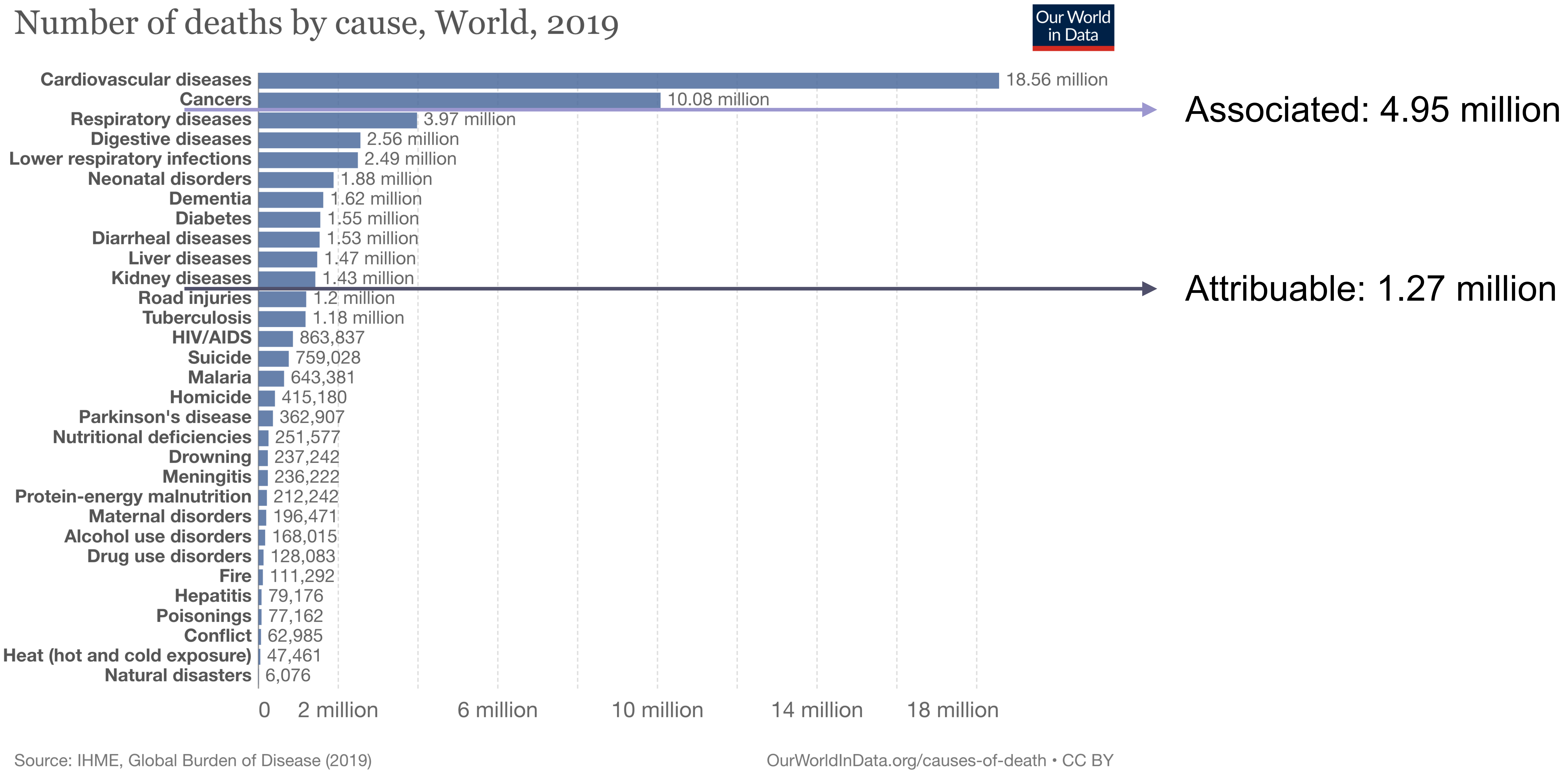
Global deaths 2019:

- 4.95 million (associated)
- 1.27 million (attributable)

Murray et al., The Lancet, 2022

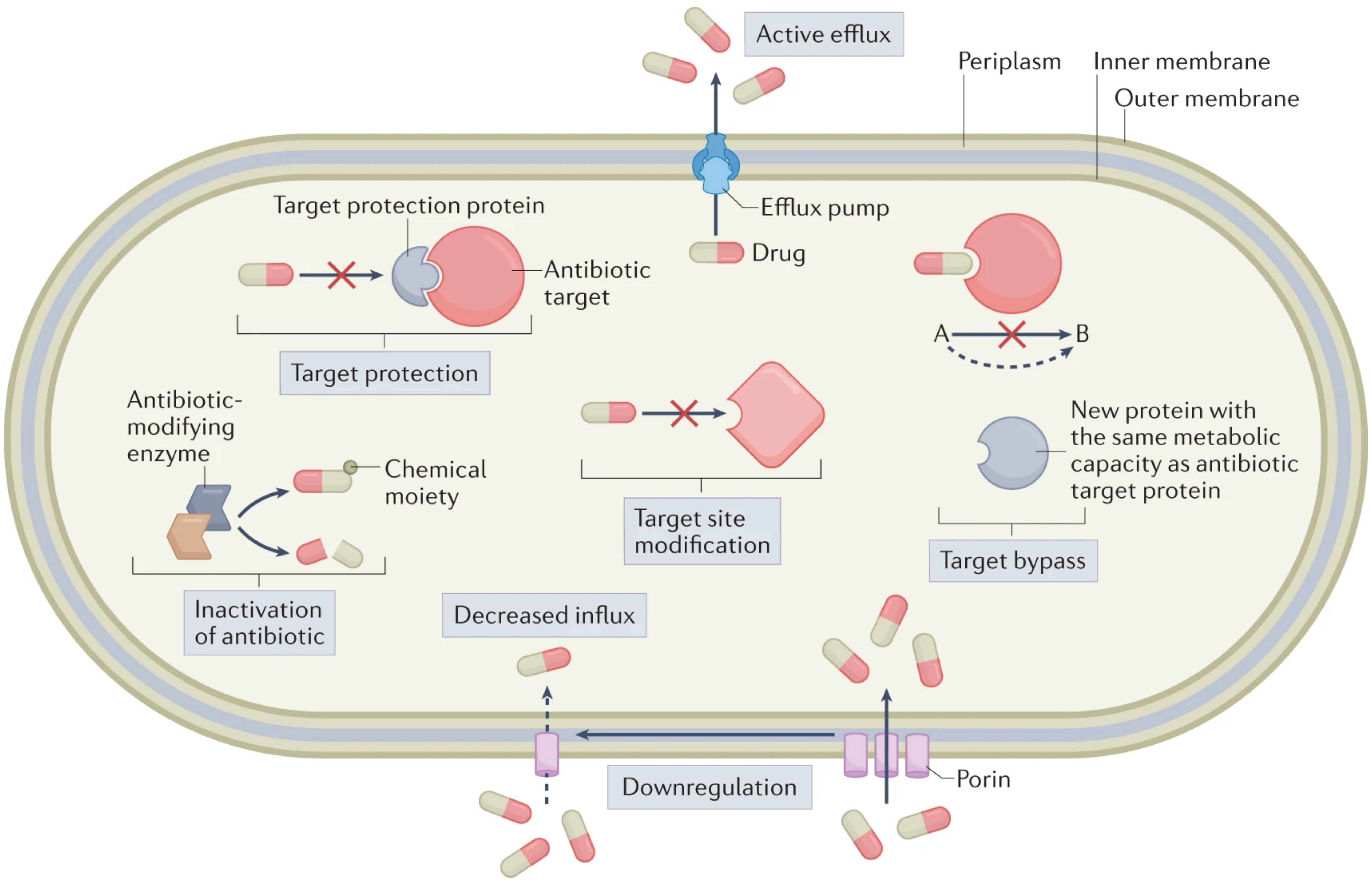


Source: Our world in data



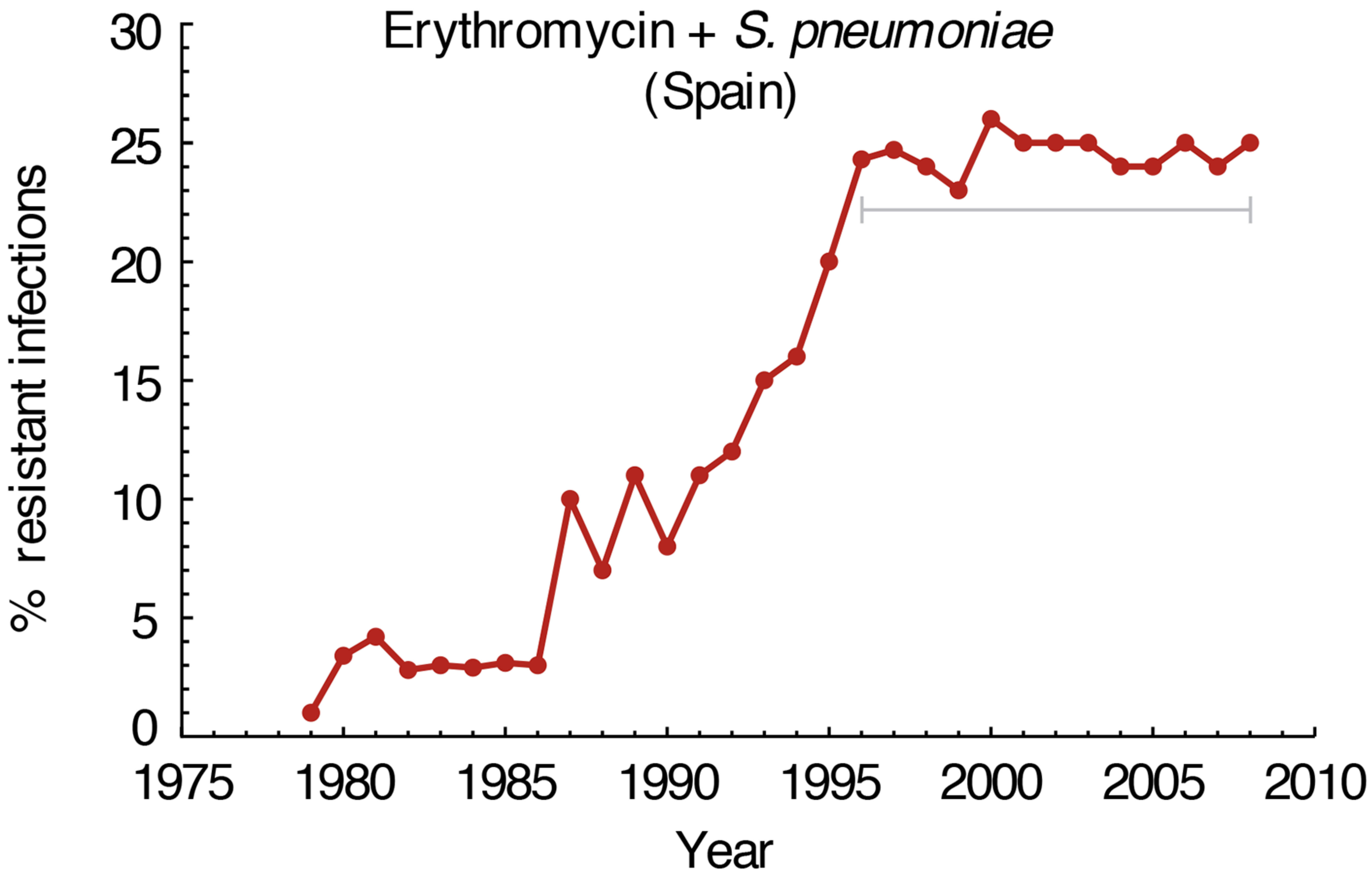
Number of deaths by cause, World, 2019
Our World in Data
Cardiovascular diseases 18.56 million
Cancers 10.08 million
Respiratory diseases 3.97 million
Digestive diseases 2.56 million
Lower respiratory infections 2.49 million
Neonatal disorders 1.88 million
Dementia 1.62 million
Diabetes 1.55 million
Diarrheal diseases 1.53 million
Liver diseases 1.47 million
Kidney diseases 1.43 million
Road injuries 1.2 million
Tuberculosis 1.18 million
HIV/AIDS 863,837
Suicide 759,028
Malaria 643,381
Homicide 415,180
Parkinson's disease 362,907
Nutritional deficiencies 251,577
Drowning 237,242
Meningitis 236,222
Protein-energy malnutrition 212,242
Maternal disorders 196,471
Alcohol use disorders 168,015
Drug use disorders 128,083
Fire 111,292
Hepatitis 79,176
Poisonings 77,162
Conflict 62,985
Heat (hot and cold exposure) 47,461
Natural disasters 6,076
0
2 million
6 million
10 million
14 million
18 million
Associated: 4.95 million
Attribuable: 1.27 million
Source: IHME, Global Burden of Disease (2019)
OurWorldInData.org/causes-of-death • CC BY

Resistance and its cost



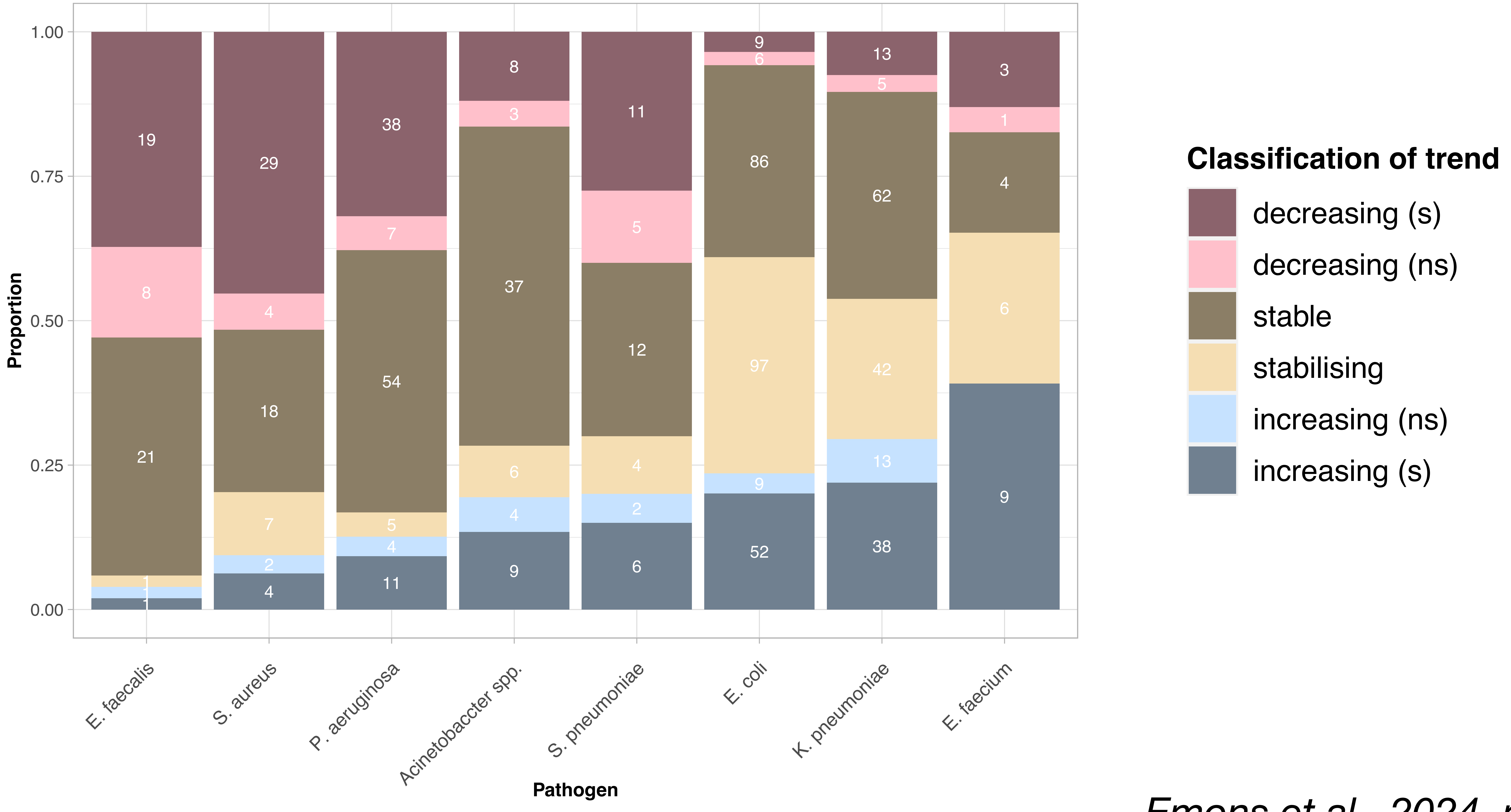
Source: Darby et al., Nature Reviews Microbiology, 2022

Why do we think there is a fitness cost?



Krieger et al., 2020, Plos Computational Biology

Why do we think there is a fitness cost?



Emons et al., 2024, medRxiv

Why does fitness cost matter?

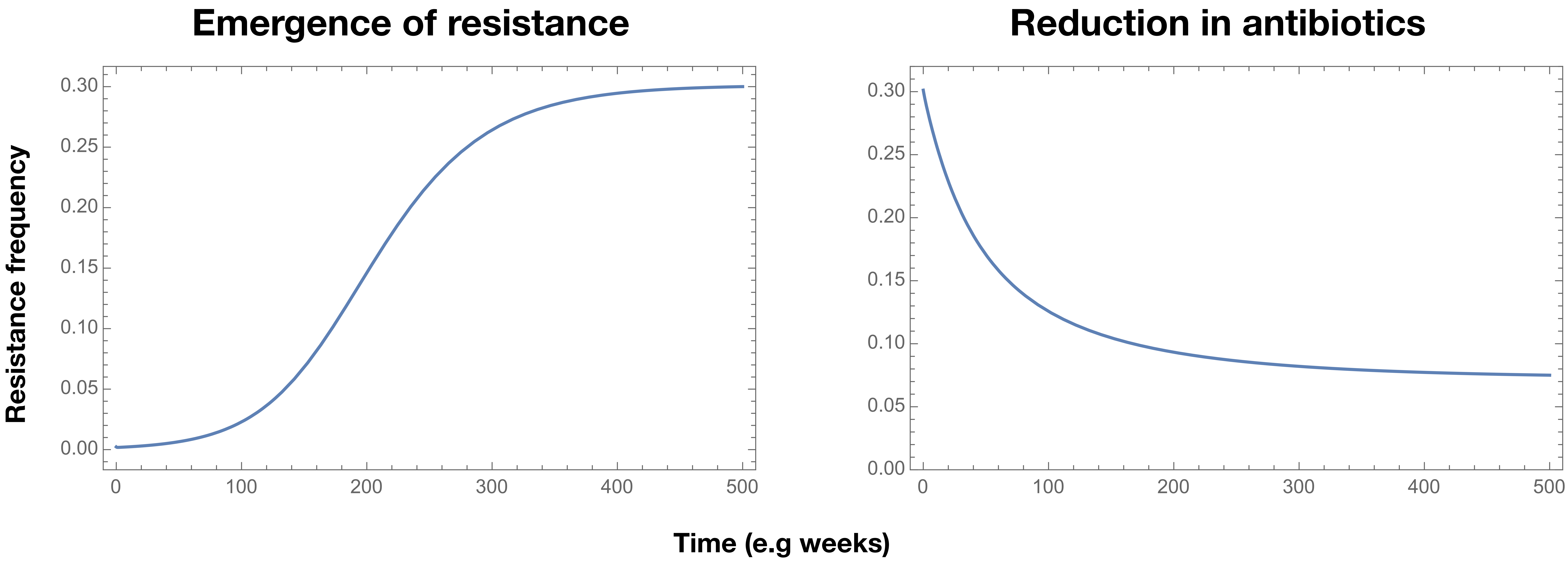
Advantage

Less affected by antibiotics

Disadvantage

Fitness cost

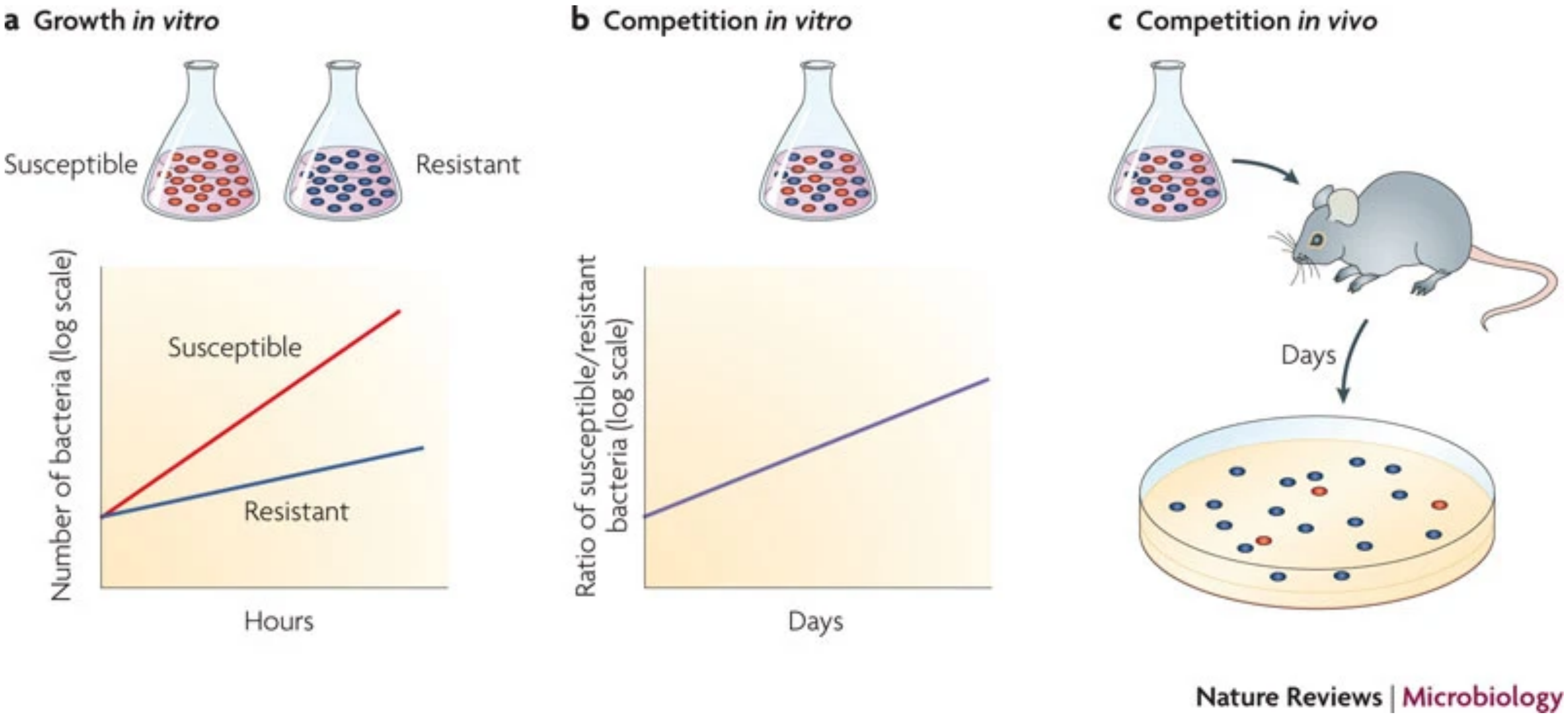
Why does fitness cost matter?



Lipsitch, Trends in Microbiology, 2001

2. What do experiments tell us?

Measuring fitness cost experimentally



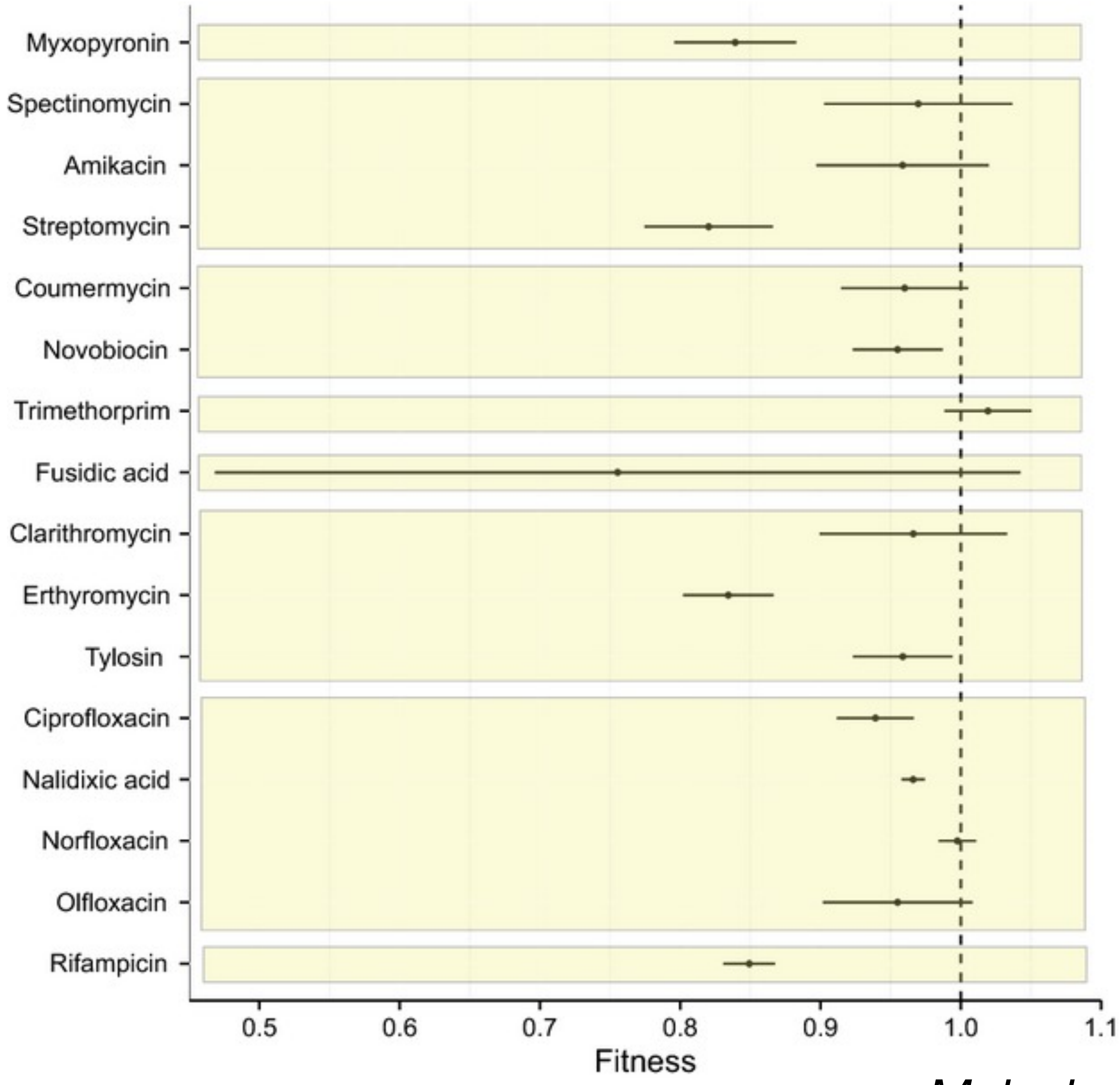
Anderson & Hughes, 2010, Nature Reviews Microbiology

Key insights from experimental work

- Measurable fitness cost often found, but not always.
- Results are sensitive to environmental variation.
- Compensatory evolution is common.

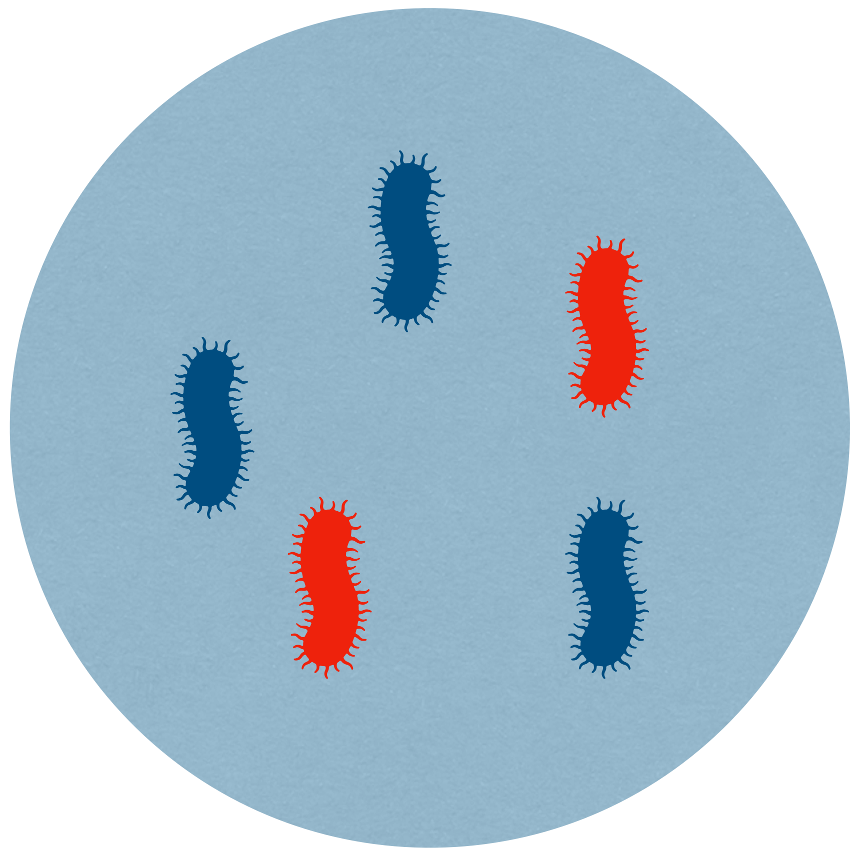
Anderson & Hughes, 2010, Nature Reviews Microbiology

Key insights from experimental work

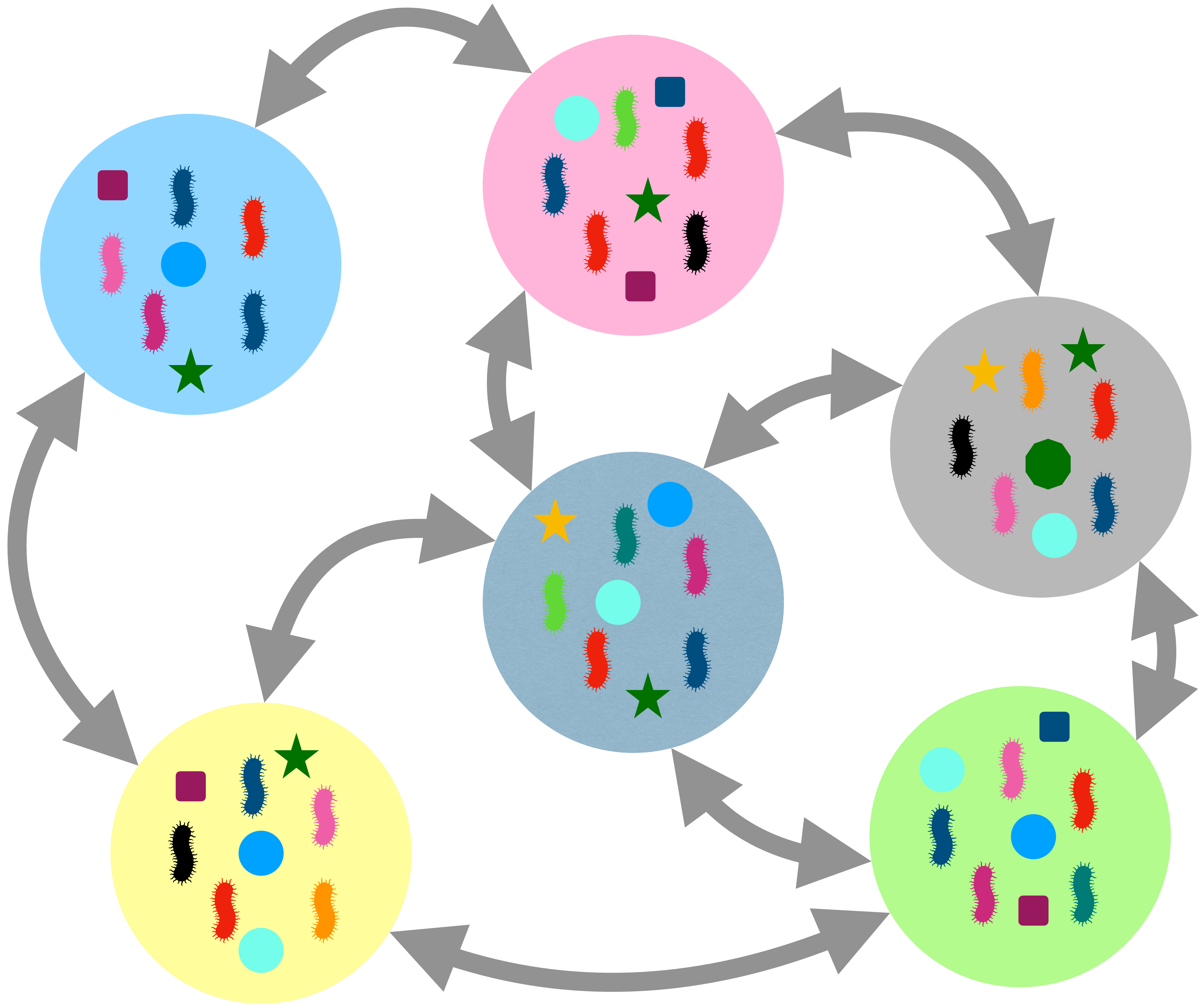


Melnyk, 2014, Evolutionary Applications

Does this translate to epidemiological scale?

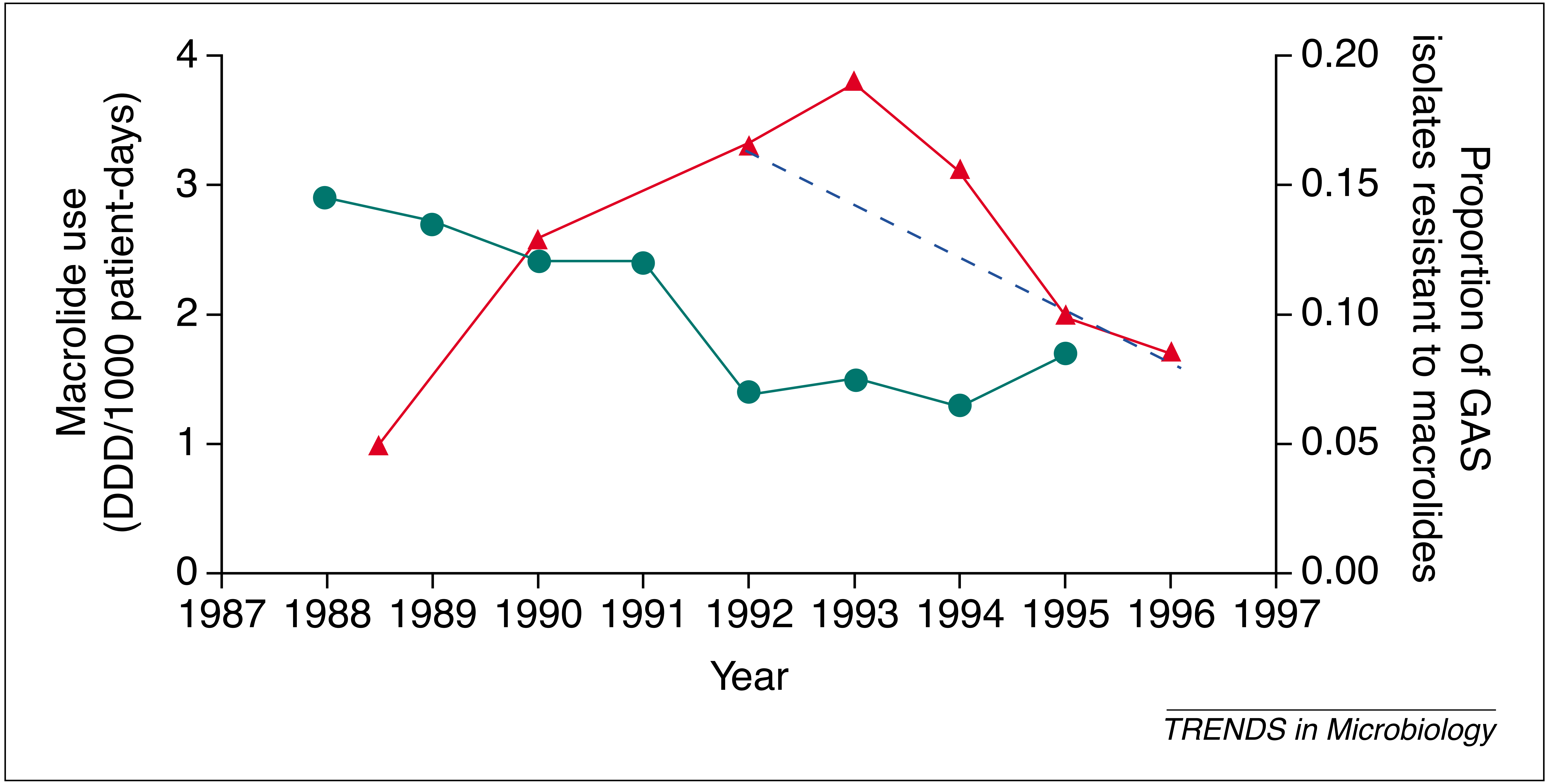


vs



3. Inferring fitness cost from observational data

Qualitative insights



Lipsitch, Trends in Microbiology, 2001

Qualitative insights

Table I. Studies evaluating the effect on resistance rates of large-scale reductions in antibiotic use in the community.

Country (ref.)	Species	Antibiotic(s)	Intervention/evaluation	Study design	Resistance frequency
Finland (21)	*S. pyogenes*	Macrolides	Nationwide/nationwide	Prospective	Decrease
Island (22)	*S. pneumoniae*	β-lactams and more	Nationwide/nationwide	Prospective	Decrease
Great Britain (62,63)	*E. coli*	SXT	Nationwide/local	Retrospective	Increase
Great Britain (64)	*E. coli*	streptomycin	Nationwide/local	Retrospective	No effect
Sweden (59)	*E. coli*	TMP, SXT	County/county	Prospective	Marginal effect
Great Britain (65)	*E. coli*	AMP, TMP, and more	PHC/PHC	Retrospective	Decrease
Israel (66)	*E. coli*	FQX	County/county	Retrospective	Decrease

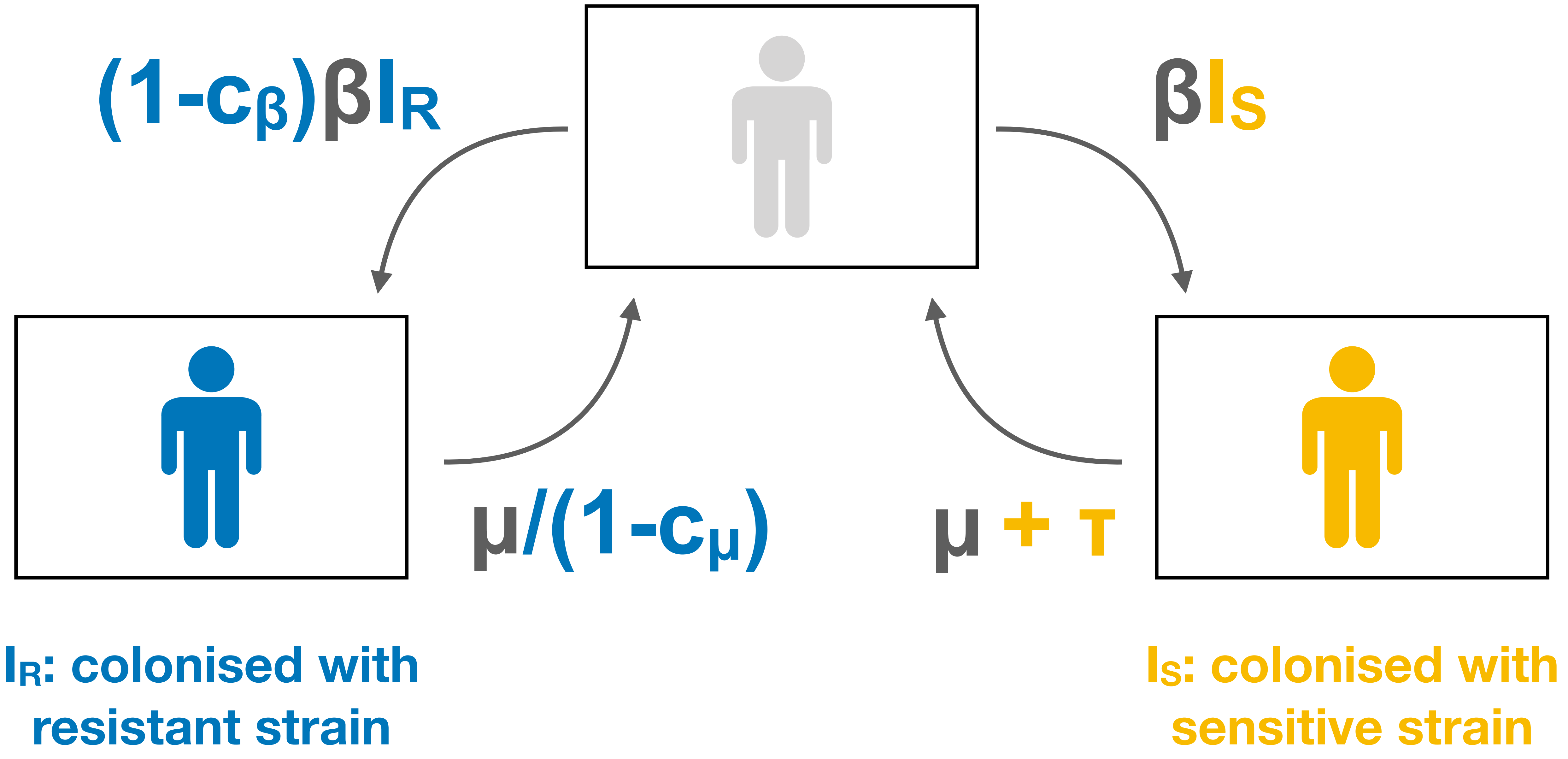
AMP = Ampicillin; FQX = Fluoroquinolones; SXT = Trimethoprim-sulfamethoxazole; TMP = Trimethoprim.

Sundqvist, 2014, *Upsala Journal of Medical Sciences*

Quantitative insights

- Longitudinal data on resistance frequencies.
- (Ideally) longitudinal data on antibiotic consumption.
- A model of transmission.

Estimating fitness cost using a model



β: transmission rate

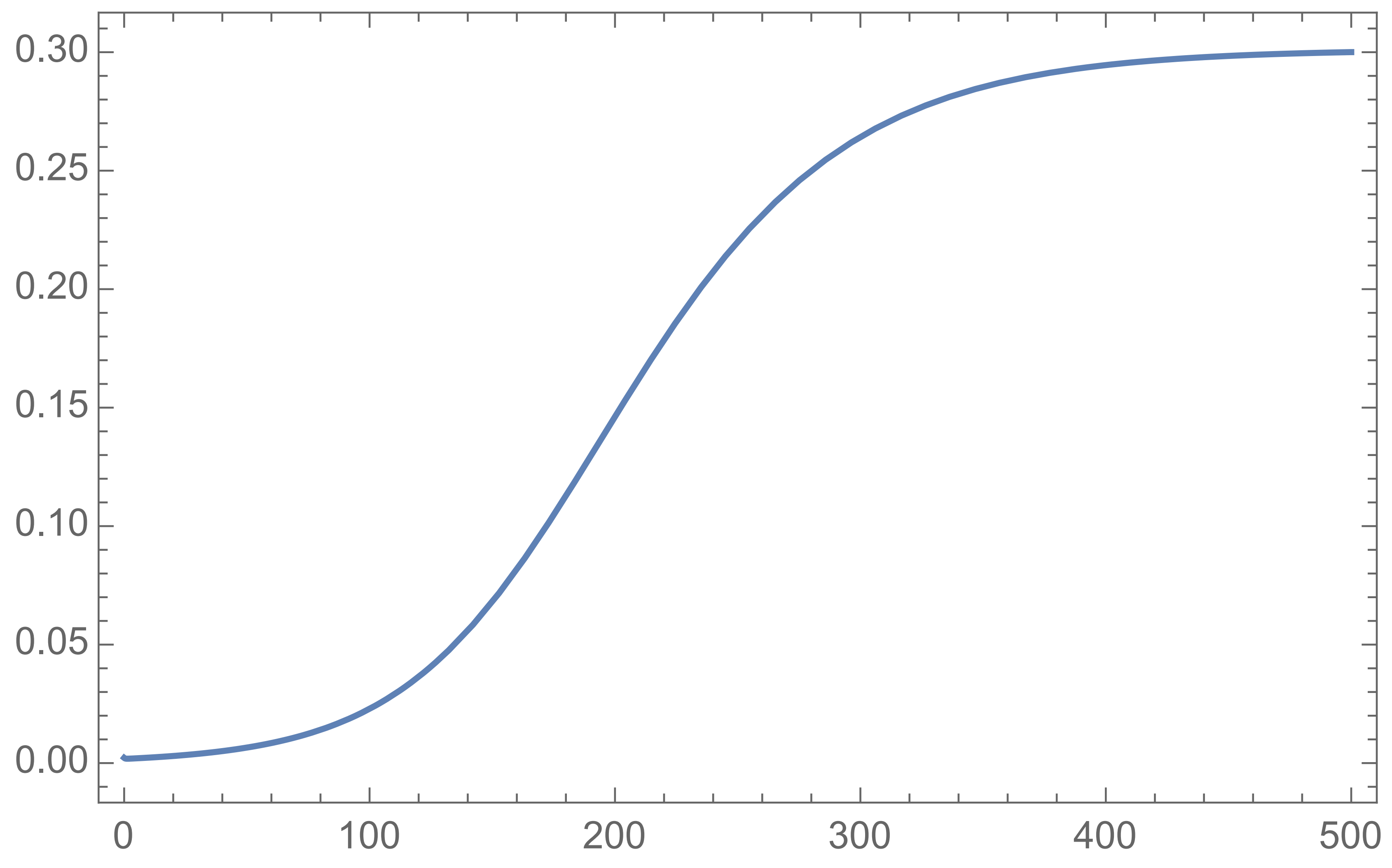
μ: clearance rate

c: cost of resistance

τ: treatment rate

Estimating fitness cost using a model

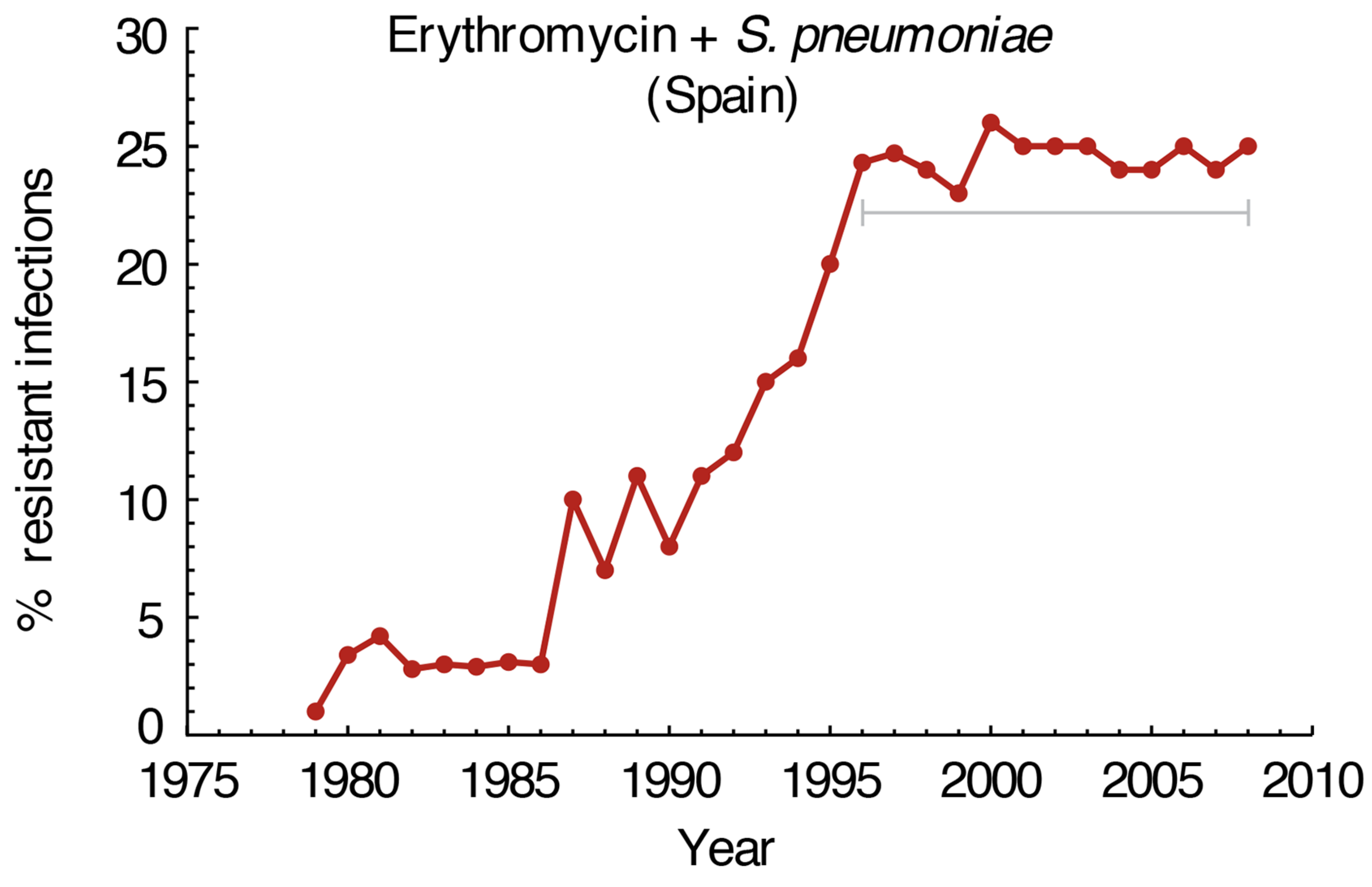
Simulation with set fitness cost



Compare to data

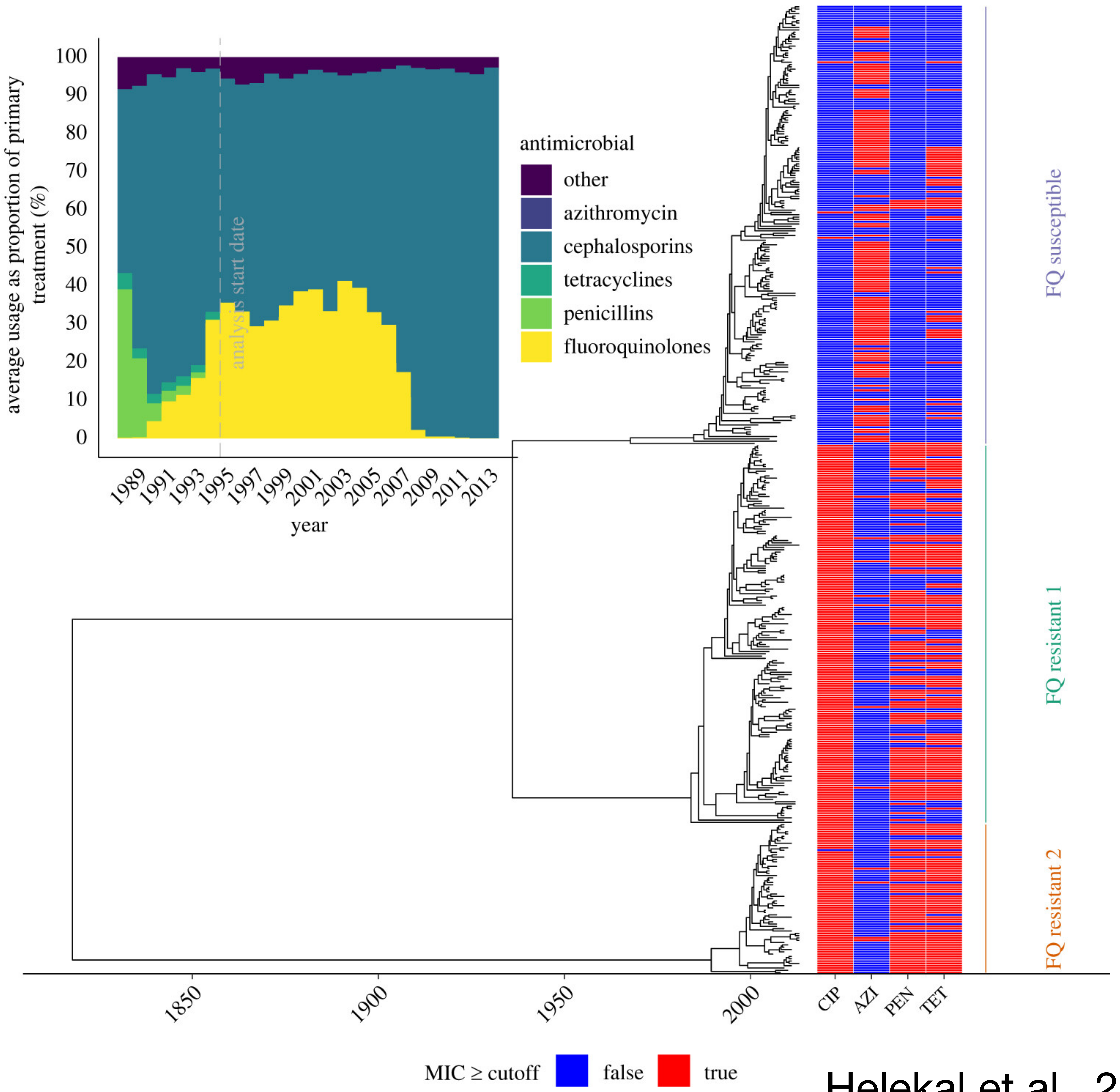
Adjust cost

Observed data



Phylodyamics-based approach

- Phylodynamics aims to infer transmission dynamics from phylogenetic information.
- This approach allows using genetic information instead of longitudinal data on resistance frequencies.



Helekal et al., 2023, *J. R. Soc Interface*

Summary of studies

Study	**Species**	**Drug**	**Approach**	**Cost affects**	**Magnitude**
Luciani et al.	*Mycobacterium tuberculosis*	TB treatment	Population model	Transmission	~ [0 - 0.3]
Knight et al.	*Mycobacterium tuberculosis*	Multi-drug	Household model	Transmission Progression to disease Both	~ 0.7 ~ 0.6 ~ 0.5
Maher et al.	*Streptococcus pneumoniae*	Macrolides	Population model	Transmission	~ [0.05 - 0.2]
Whittles et al.	*Neisseria gonorrhoeae*	Cefixime	Population model	Recovery rate	~ 1.8 (multiplicative)
Helekal et al.	*Neisseria gonorrhoeae*	Fluoroquinolone	Phylodynamics	Recovery rate	> 0
Pečerska et al.	*Mycobacterium tuberculosis*	Multi-drug	Phylodynamics	Transmission	~0.36

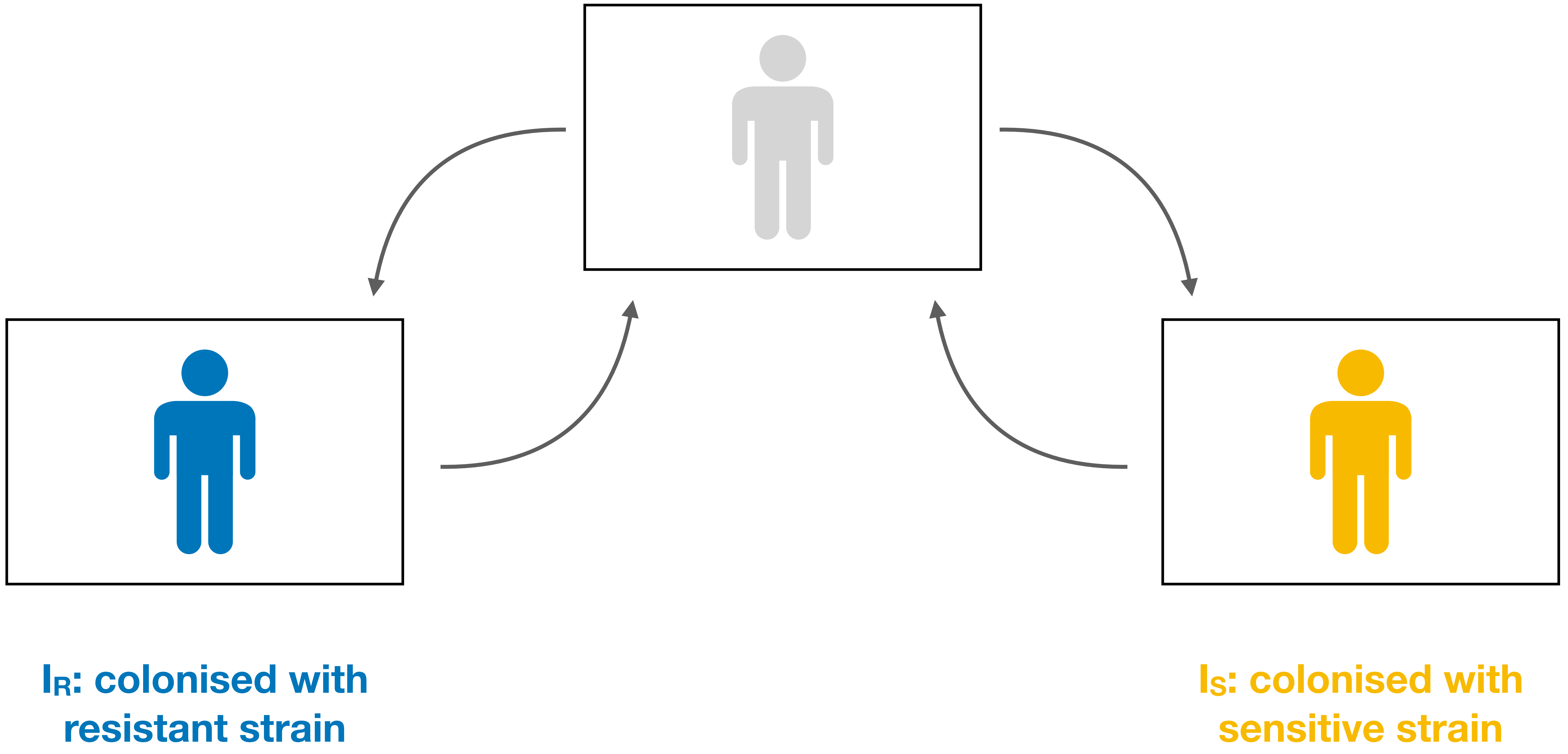
4. Limitations of observational approaches

4. Limitations of observational approaches

- Correlation vs causation:
  - Other factors affecting success of resistant lineages.
  - Was resistance at equilibrium?

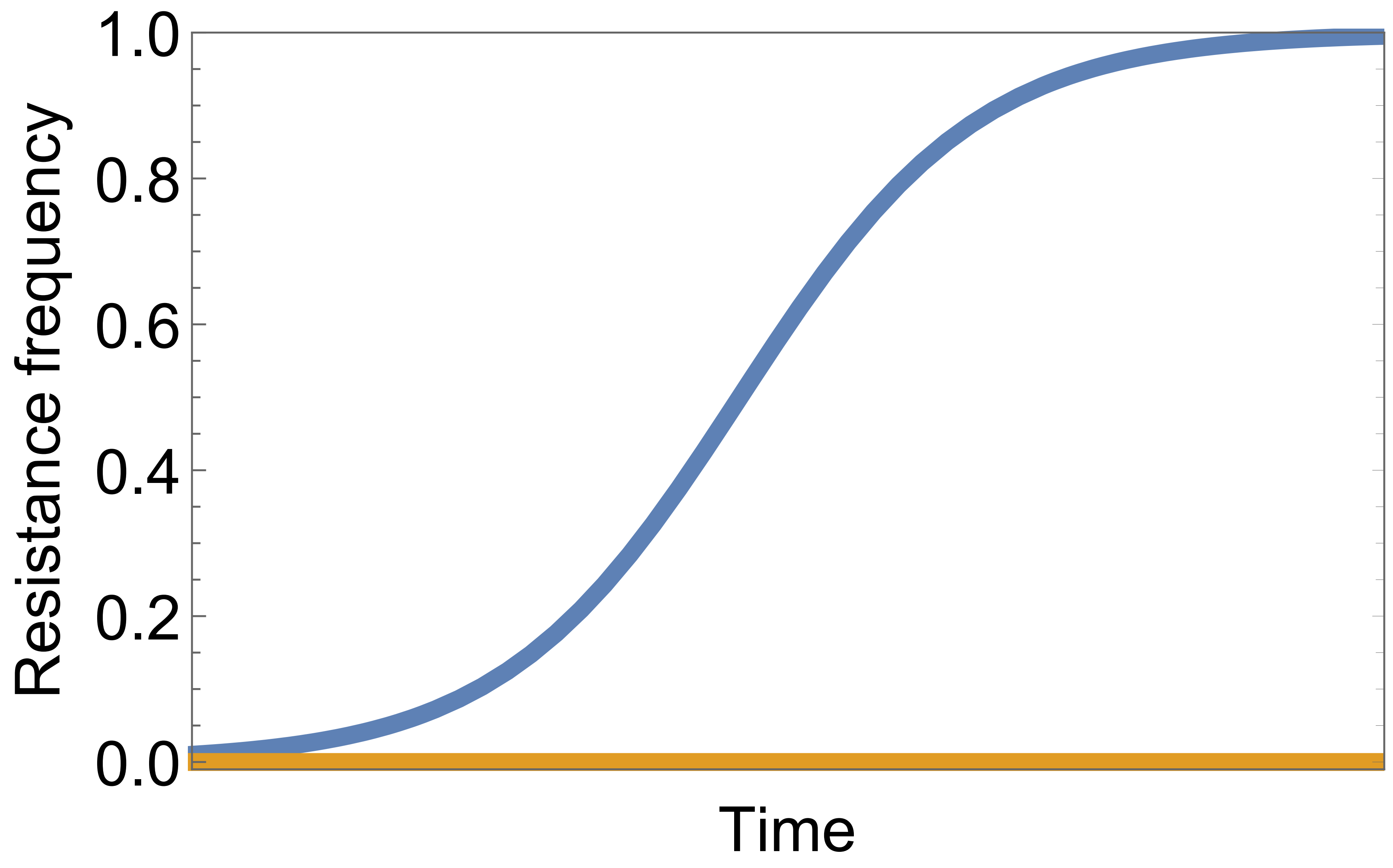
- Need to assume a transmission model

Why model structure in uncertain:
The problem of coexistence

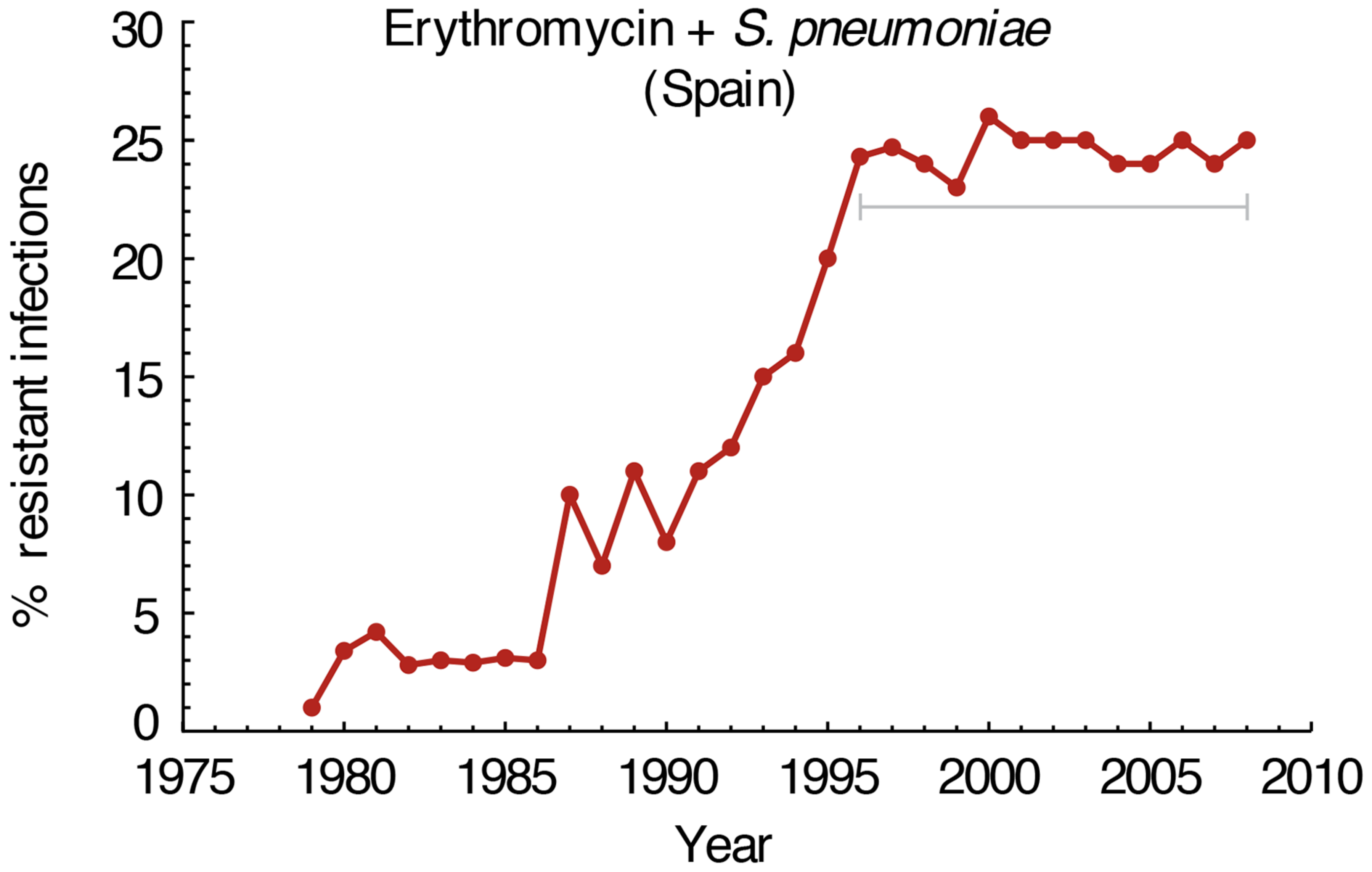


The problem of coexistence

Simulation with set fitness cost



Observed data



Colijn et al., 2010, *J. R. Soc Interface*

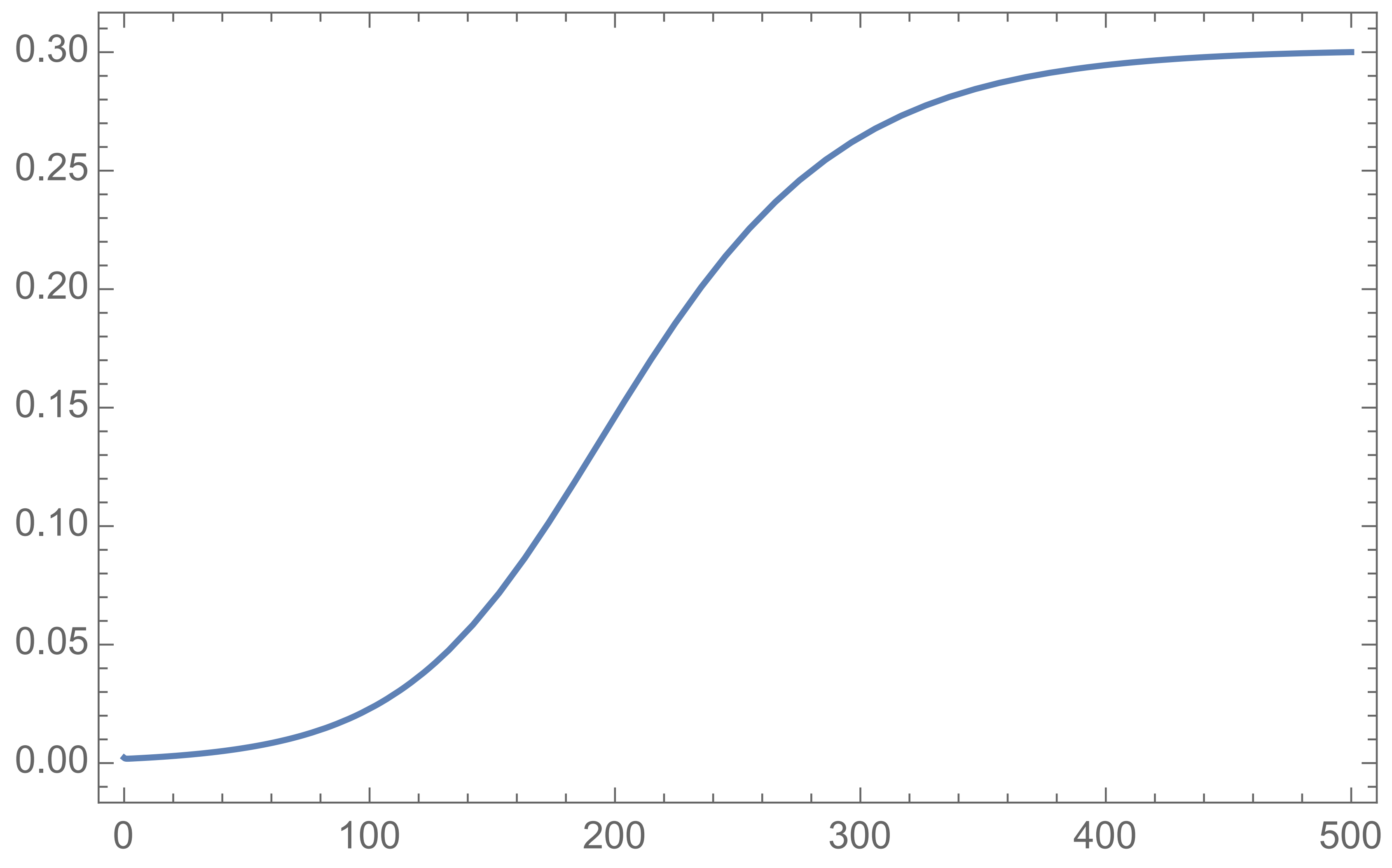
Models that could explain coexistence

- Host population heterogeneity.
- Strain structure.
- Within-host dynamics.
- Mutation-selection balance.

See reference list

Evaluating plausibility of mechanisms is difficult

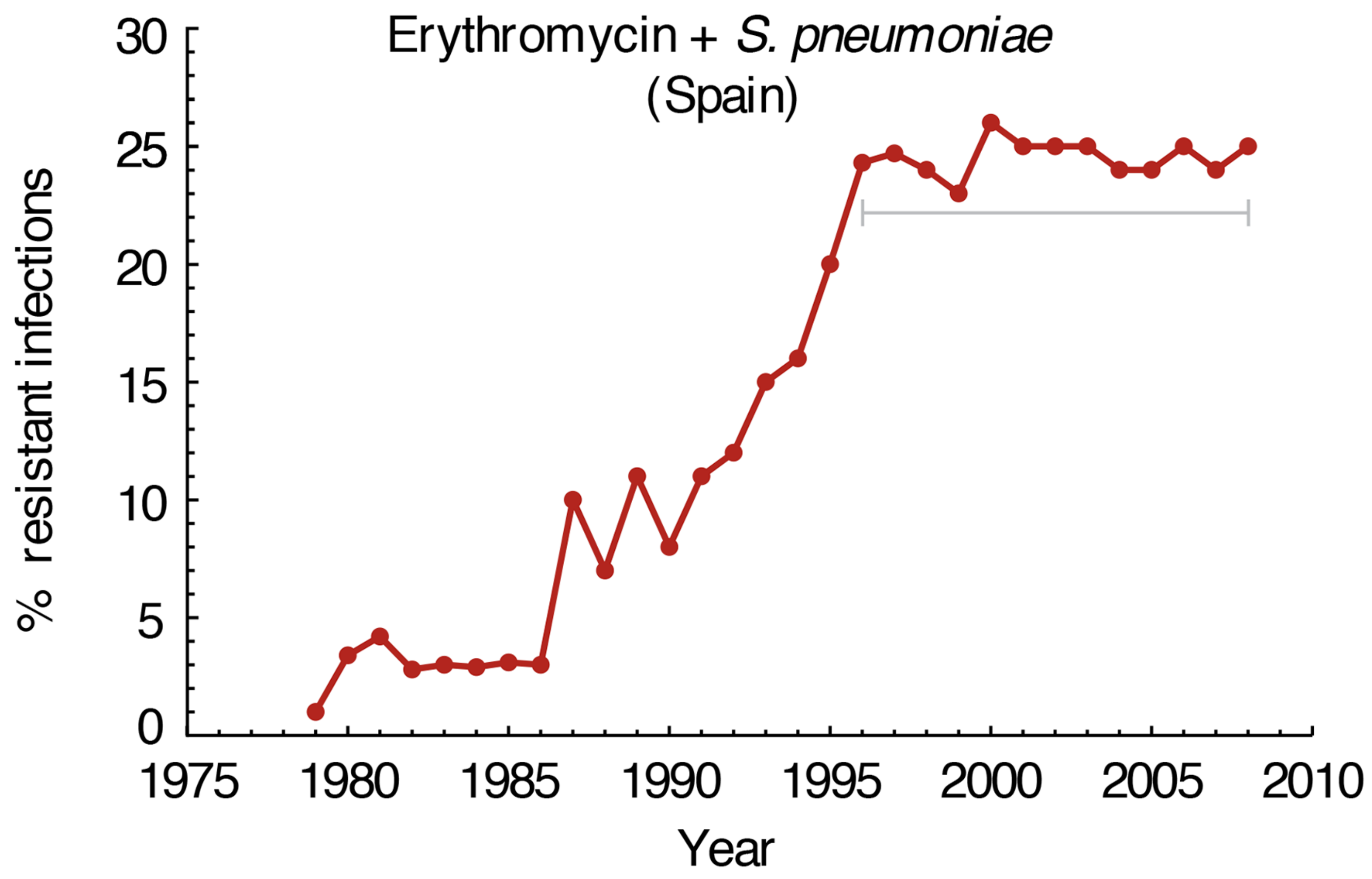
Simulation



Compare to data

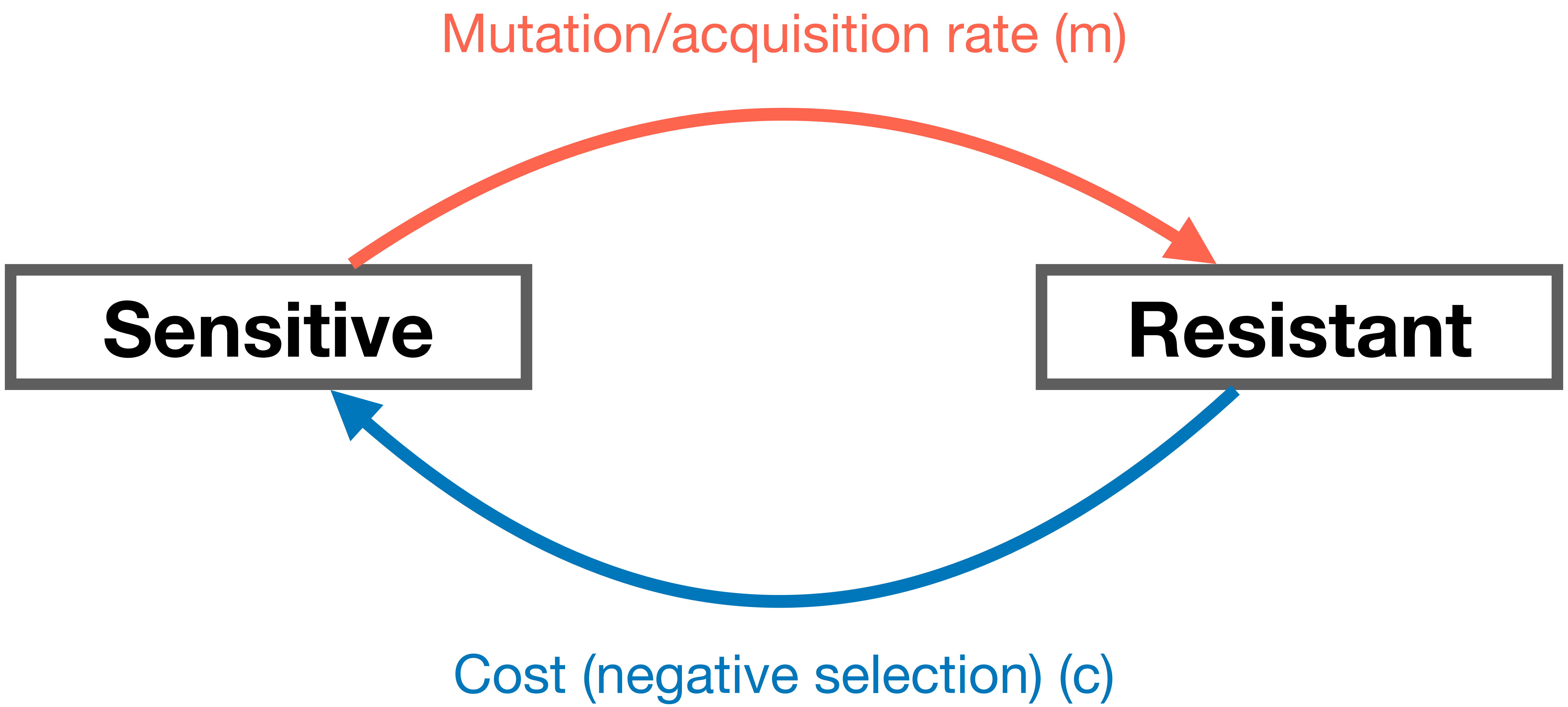
Adjust parameters

Data



See reference list

Example: mutation-selection balance



Frequency of resistance = m/c

Pennings, 2023, medRxiv

Fitness cost: catch 22

- Difficult to infer fitness cost without a good model
- Difficult to infer model without an estimate of fitness cost

5. What could we do instead?

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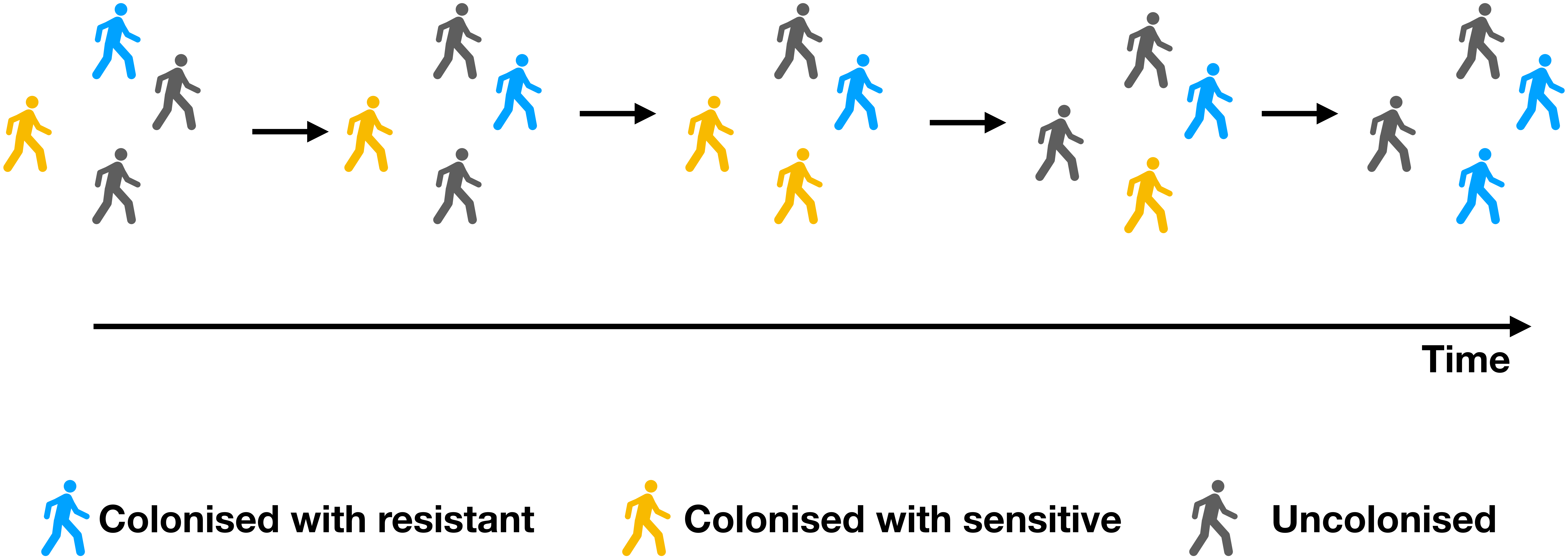

5. What could we do instead?

- Aim is to measure the cost directly from data.
- No need to assume which component of fitness is affected.
- Needs a lot of data; not many examples to be found.
  Grandjean et al., 2015, Plos Medicine

Summary

- Fitness cost of resistance is a key parameter
- Experimental approaches tell us a lot but not enough
- Observational studies are an important complementary approach
- Uncertainty limits model-based approaches
- Need for models that do not depend on transmission model

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Background on resistance

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Murray, C. J., Ikuta, K. S., Sharara, F., Swetschinski, L., Aguilar, G. R., Gray, A., ... & Tasak, N. (2022). Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. *The lancet*, *399*(10325), 629-655.

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-> See also references within these reviews.

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Helekal, D., Keeling, M., Grad, Y. H., & Didelot, X. (2023). Estimating the fitness cost and benefit of antimicrobial resistance from pathogen genomic data. *Journal of the Royal Society Interface*, *20*(203), 20230074

Pečerska, J., Kühnert, D., Meehan, C. J., Coscollá, M., De Jong, B. C., Gagneux, S., & Stadler, T. (2021). Quantifying transmission fitness costs of multi-drug resistant tuberculosis. *Epidemics*, *36*, 100471.

Alternative approaches

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References 2

Models of resistance & problem of coexistence

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Colijn, C., Cohen, T., Fraser, C., Hanage, W., Goldstein, E., Givon-Lavi, N., ... & Lipsitch, M. (2010). What is the mechanism for persistent coexistence of drug-susceptible and drug-resistant strains of Streptococcus pneumoniae?. *Journal of The Royal Society Interface*, *7*(47), 905-919

Kouyos, R., Klein, E., & Grenfell, B. (2013). Hospital-community interactions foster coexistence between methicillin-resistant strains of Staphylococcus aureus. *PLoS pathogens*, *9*(2), e1003134.

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