The evolutionary epidemiology of antibiotic resistance evolution

François Blanquart, CNRS
Stochastic Models for the Inference of Life Evolution | CIRB | Collège de France
Quantitative Evolutionary Microbiology | IAME | UFR de médecine Paris Diderot
Resistant and sensitive strains compete for the same hosts
Resistant and sensitive strains compete for the same hosts
Resistant and sensitive strains compete for the same hosts.
Frequency of resistance is intermediate and stable
Frequency of resistance is intermediate and stable

**Streptococcus pneumoniae, ERY**

- France
- Spain
- United Kingdom
- Germany
- Italy

ECDC data
Frequency of resistance is intermediate and stable

Escherichia coli, CTX

- France
- Spain
- United Kingdom
- Germany
- Italy

ECDC data
Frequency of resistance is intermediate and stable

ECDC data
Frequency of resistance is intermediate and stable

Streptococcus pneumoniae 2014

ECDC data

0.0 0.2 0.4 0.6 0.8 1.0

AEB la genciné: Frecuences

consumption of macrolides in Community

0 1 2 3 4 5

Austria
Belgium
Bulgaria
Croatia
Czech Republic
Denmark
Estonia
Finland
France
Germany
Hungary
Iceland
Ireland
Italy
Latvia
Lithuania
Luxembourg
Malta
Netherlands
Norway
Poland
Portugal
Sweden
United Kingdom
Slovakia
Slovenia
Spain

Slovakia
Frequency of resistance is intermediate and stable

*Escherichia coli 2014*

**ECDC data**
Frequency of resistance is intermediate and stable

ECDC data

model
The ‘coexistence problem’

- Lipsitch et al. Epidemics 2009
- Colijn et al. JRSI 2009
- Lehtinen et al. PNAS 2017
- Cobey et al. JRSI 2017
- Davies et al. biorxiv 2018
Short-term fluctuations in the frequency of resistance

Israel, 1401 bacterial isolates from children with acute otitis media

Dagan et al. JID 2008
Short-term fluctuations in the frequency of resistance

total > 200,000 prescriptions (~ 20% prescriptions in the area)
Model linking the frequency of resistance to antibiotic prescriptions

- Emerges from linearisation of any dynamical model around the overall average resistance.
- Two main drivers of the change in resistance:
  - **Stabilising force** (phenomenological)
  - **Antibiotic selection**

\[
\frac{dp}{dt} = -c(p_t - \bar{p}) + \sum_{j=1}^{n} b_j (a_{j,t} - \bar{a}_j)
\]

Because of this, the change in antibiotic use will increase resistance and consequently: resistance multidrug penicillin and sensitivity of the response to antibiotic selection.
No stabilising force

maximal increase at maximal use
= 3 months lag
No stabilising force

maximal increase at maximal use
= 3 months lag

Strong stabilising force

equilibrium between direct and stabilising force
= fluctuations are in phase
Model linking the frequency of resistance to antibiotic prescriptions

- **Strong stabilising force**
- Inference of $b_j / c = \text{change in the frequency of resistance caused by a one unit increase in the prescription of antibiotic } j$
Model linking the frequency of resistance to antibiotic prescriptions

- Strong stabilising force
- Inference of $b_j / c = \text{change in the frequency of resistance caused by a one unit increase in the prescription of antibiotic } j$
- Amoxicillin selects for penicillin resistance only
Model linking the frequency of resistance to antibiotic prescriptions

- Strong stabilising force
- Inference of $b_j / c = \text{change in the frequency of resistance caused by a one unit increase in the prescription of antibiotic } j$
- Amoxicillin selects for penicillin resistance only
- Azithromycin selects for penicillin, erythromycin and multidrug resistance
Model linking the frequency of resistance to antibiotic prescriptions

- Strong stabilising force
- Inference of $b_j / c =$ change in the frequency of resistance caused by a one unit increase in the prescription of antibiotic $j$
  - Amoxicillin selects for penicillin resistance only
  - Azithromycin selects for penicillin, erythromycin and multidrug resistance
  - Cephalosporin counter-selects penicillin, erythromycin and multidrug resistance

$->$ most cephalosporin-resistant strains are penicillin intermediate, a prediction verified in the data (Dagan personal communication)
The model explains 18 to 43% of temporal fluctuations in antibiotic resistance.
The stabilising force implies that any reduction in the consumption of antibiotic has immediate effect on resistance

Frequency of penicillin resistance in France following nationwide prevention campaign in 2002-2007

Reduction in consumption -26.5%

ECDC data
Sabuncu et al. PLOS Med 2009
What explains the coexistence of R and S strains?
What explains the coexistence of R and S strains?
What explains the coexistence of R and S strains?
What explains the coexistence of R and S strains?
What explains the coexistence of R and S strains?
Computing the ‘invasion fitness’ of each strain

= exponential growth rate when rare (with scheme)

Escherichia coli, CTX
Expressions for the invasion fitness

\[ \lambda(S) = \text{natural clearance} + \text{colonisation(untreated)} + \text{antibiotic clearance} \]

\[ \lambda(R) = \text{natural clearance} + \text{colonisation(untreated)} + \text{colonisation(treated)} \]
Pathogen adaptation to a structured host population

inter–class transmission = 0.001

R only
S only

coexistence
What explains the coexistence of R and S strains?
Pathogen adaptation to a structured host population

inter-class transmission = 0.1

R only

S only

coexistence

transmission cost of resistance

average treatment rate per month

frequency of resistance

average treatment rate per month

coexistence
Pathogen adaptation to a structured host population

full inter-class transmission

\[ \tau_{\text{low}} < \tau < \tau_{\text{high}} \]
Pathogen adaptation to a country-structured host population

Evolution of resistance under three forces
1. local selection for resistance under local antibiotic use
2. cost of resistance
3. cross-country transmission
   - flights
   - gravity model
Pathogen adaptation to a country-structured host population: example of erythromycin resistance in *S. pneumoniae* under macrolide consumption

Each year, inference of the **two model parameters**
- cost of resistance
- cross-country transmission rate

median cost = 0.011 per month
median migration rate = 0.0013 per month
Pathogen adaptation to a country-structured host population: example of erythromycin resistance in *S. pneumoniae* under macrolide consumption

- 2-parameters evolutionary model explains the data as well as the 2-parameters linear model
- Drop in correlation in 2005-2010
  - Impact of the PCV vaccine?
Conclusions

Antibiotic resistance is under balancing selection / negative frequency-dependent selection and we do not fully understand why

Host population structure helps maintain coexistence

Fitness interactions with loci themselves under balancing selection also helps

Lehtinen et al. PNAS 2017
Blanquart et al. Proc B 2017
Blanquart et al. J. Roy Soc Interface 2018
Acknowledgements

Christophe Fraser
Sonja Lehtinen
Marc Lipsitch
Ron Dagan