

Need for action to contain environmental AMR (The Environmental Dimension of AMR)

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Three main issues associated with the environment highlighted in WHO / EU Action plans

- Role of pharmaceuticals in the environment driving emergence of AMR



WHO, 2015

- Circulation of AMR in the environment
- Environmental transmission of AMR

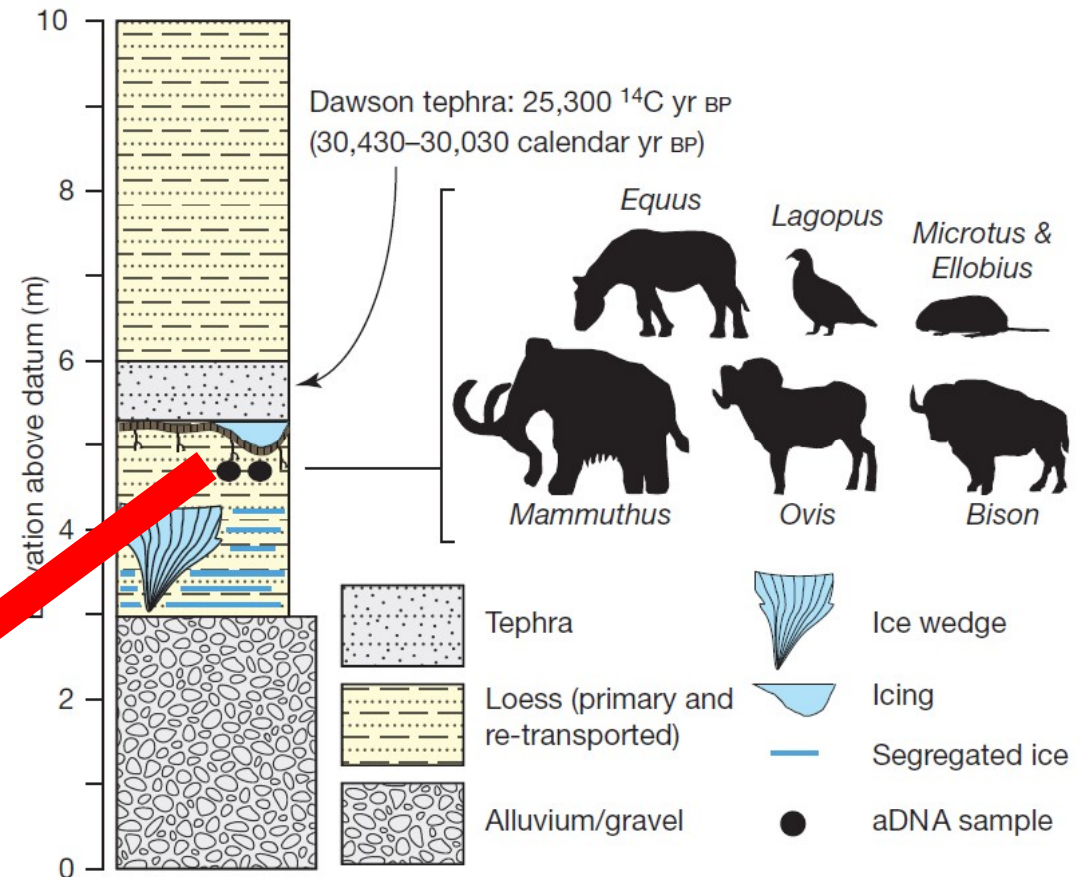
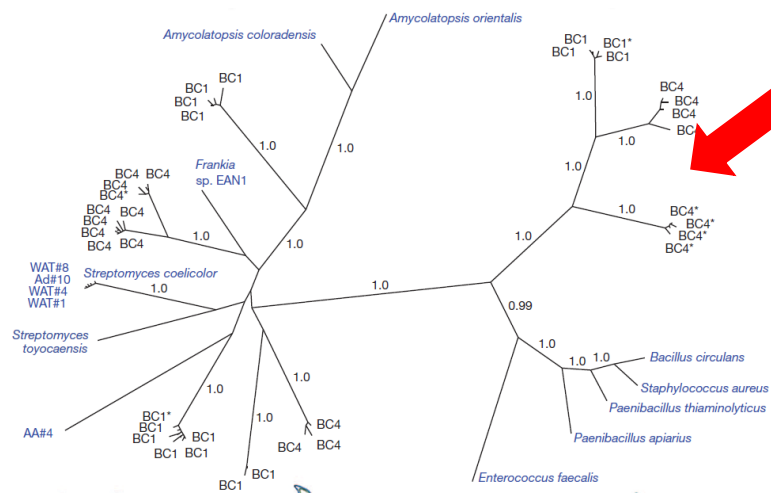


AMR action plan 2017

Antibiotic resistance: an ancient phenomenon

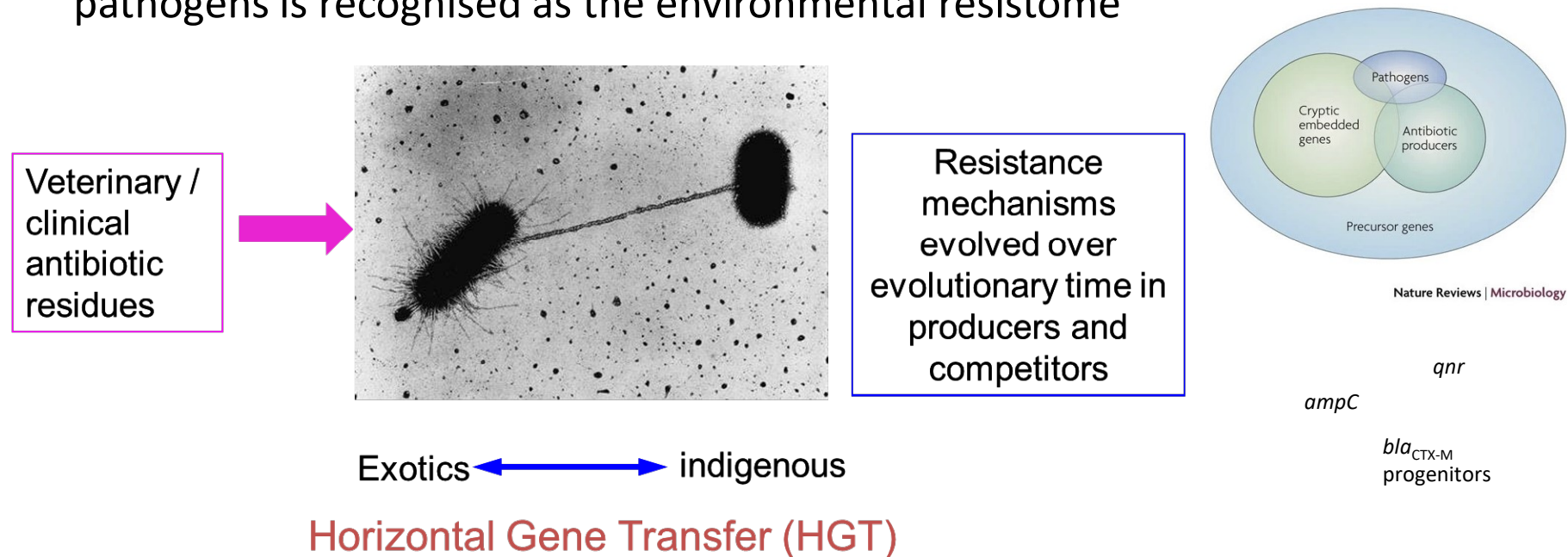
Samples from permafrost before the "Age of Antibiotics"

➔ Enormous variety of resistance genes against modern antibiotics



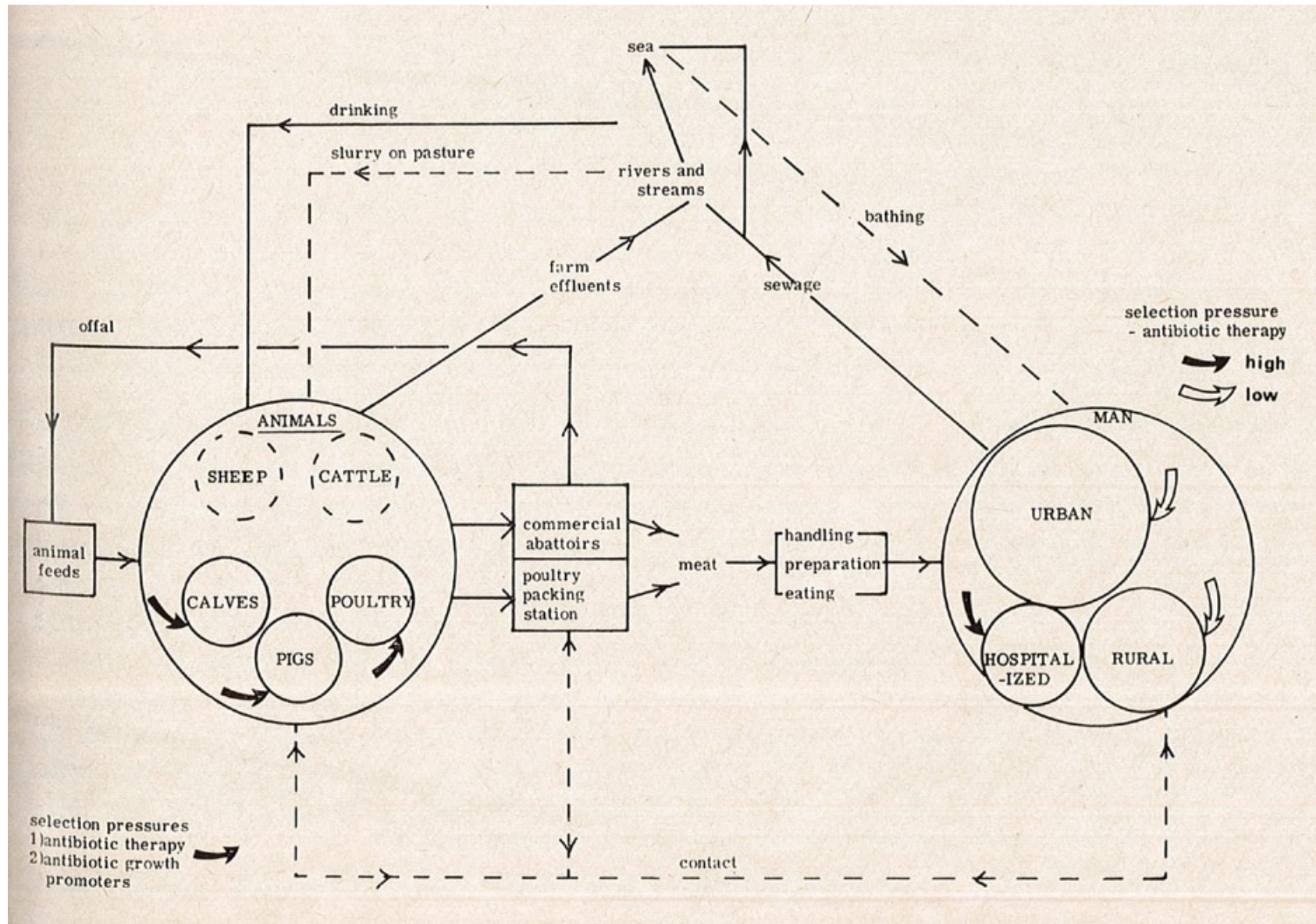
Mobility of antibiotic resistance genes and their bacterial hosts from the natural and farmed environment to humans

- Rare gene transfer events that lead to new genetic combinations – rare but can be extremely important – origin of genes in previously susceptible human pathogens is recognised as the environmental resistome



- Acute transmission events. Relatively common, introduction of human and animal associated AMR bacteria to aquatic and soil systems and human exposure to these bacteria/genes in environmental settings.

Antibiotic resistance: the present situation reviewed. Linton et al, 1977.



Role of pharmaceuticals in the environment
driving emergence of AMR

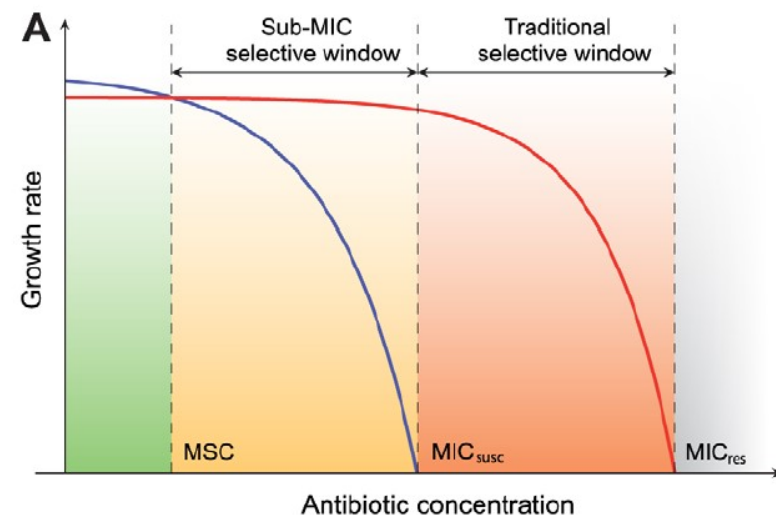
Selection of Resistant Bacteria at Very Low Antibiotic Concentrations

Erik Gullberg^{1¶}, Sha Cao^{1¶}, Otto G. Berg², Carolina Ilbäck¹, Linus Sandegren¹, Diarmaid Hughes¹, Dan I. Andersson^{1*}

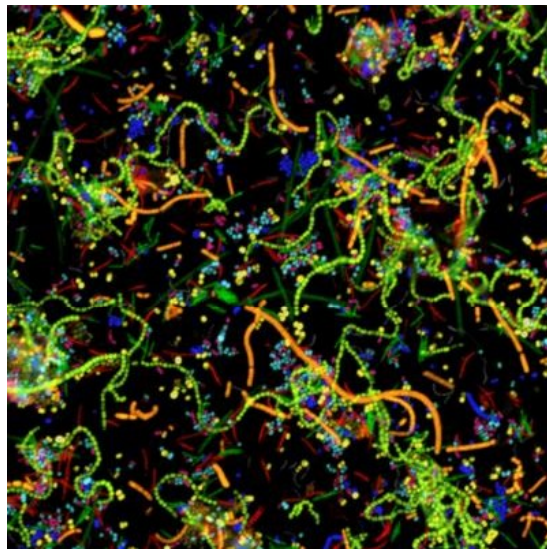
¹ Department of Medical Biochemistry and Microbiology, Uppsala University, Uppsala, Sweden, ² Department of Molecular Evolution, Uppsala University, Uppsala, Sweden

Chromosomal mutation in single species competition assays

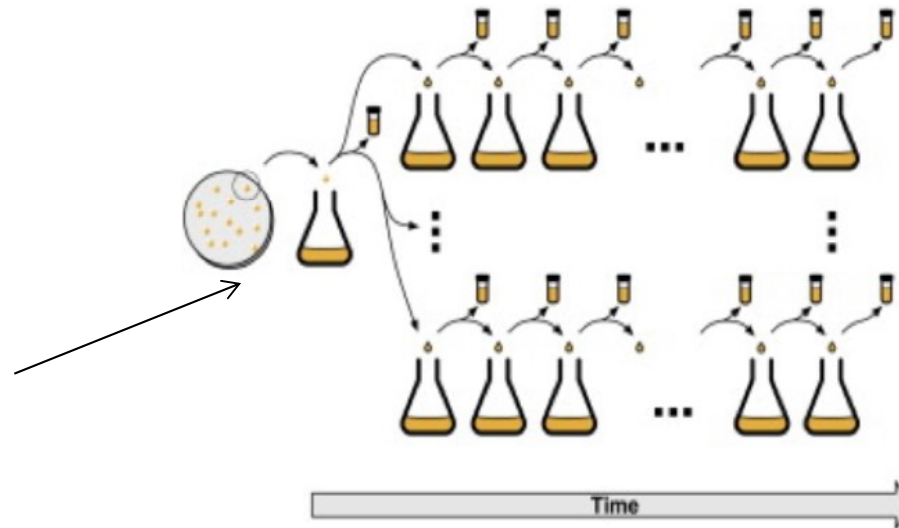
- Streptomycin MSC was $\frac{1}{4}$ of MIC
1 mg / L
- Tetracycline MSC was $\frac{1}{100}$ of MIC
15 μ g / L
- Ciprofloxacin MSC was between $\frac{1}{10}$ and $\frac{1}{230}$ of MIC
2.5 μ g – 100 ng / L



Antibiotic selection in complex microbial communities at sub-therapeutic concentrations



Alex Valm



A schematic of a serial transfer experiment
(from Sprouffske et al., 2012)

Competition between 100s-1000s of species (susceptible, acquired resistant and intrinsically resistant)

The 'SElection End points in Communities of bacTeria' (SELECT) Method: A Novel Experimental Assay to Facilitate Risk Assessment of Selection for Antimicrobial Resistance in the Environment

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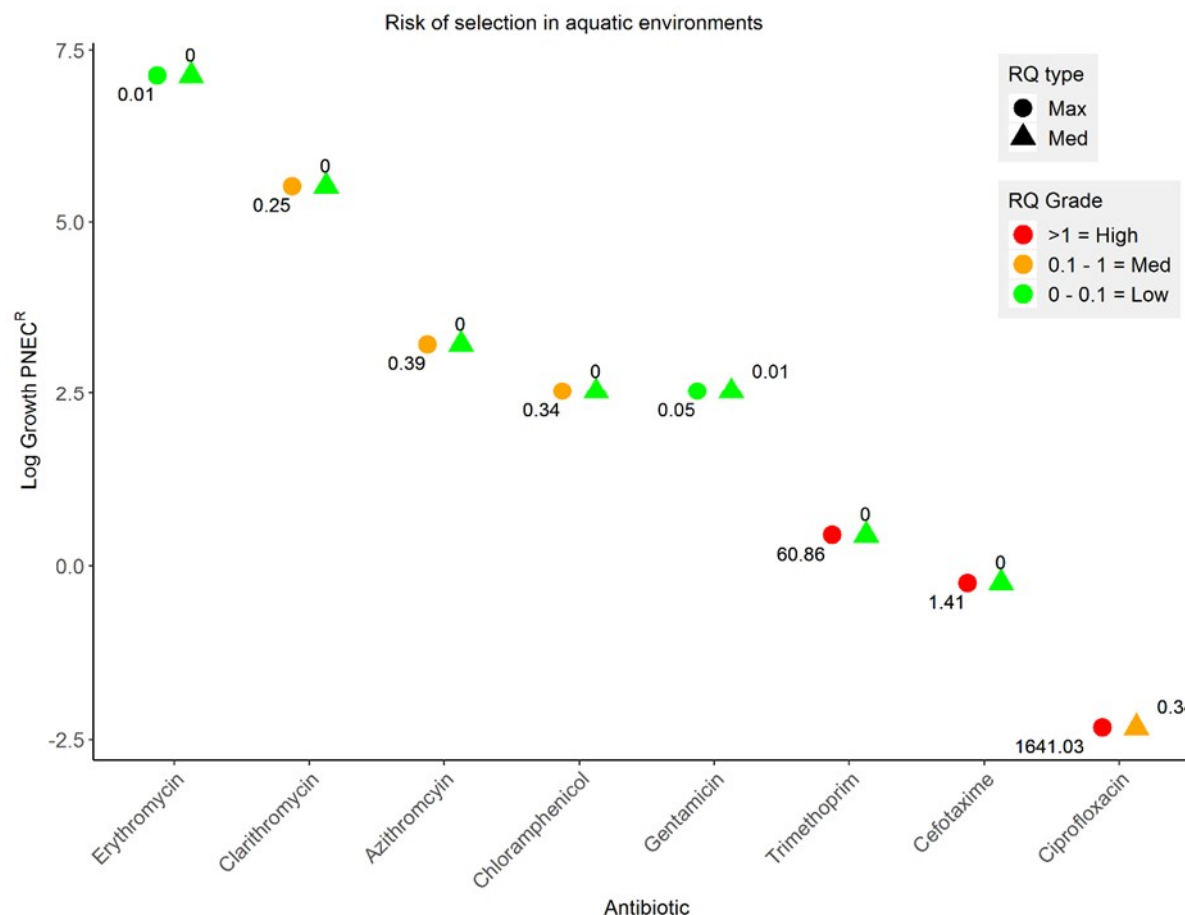
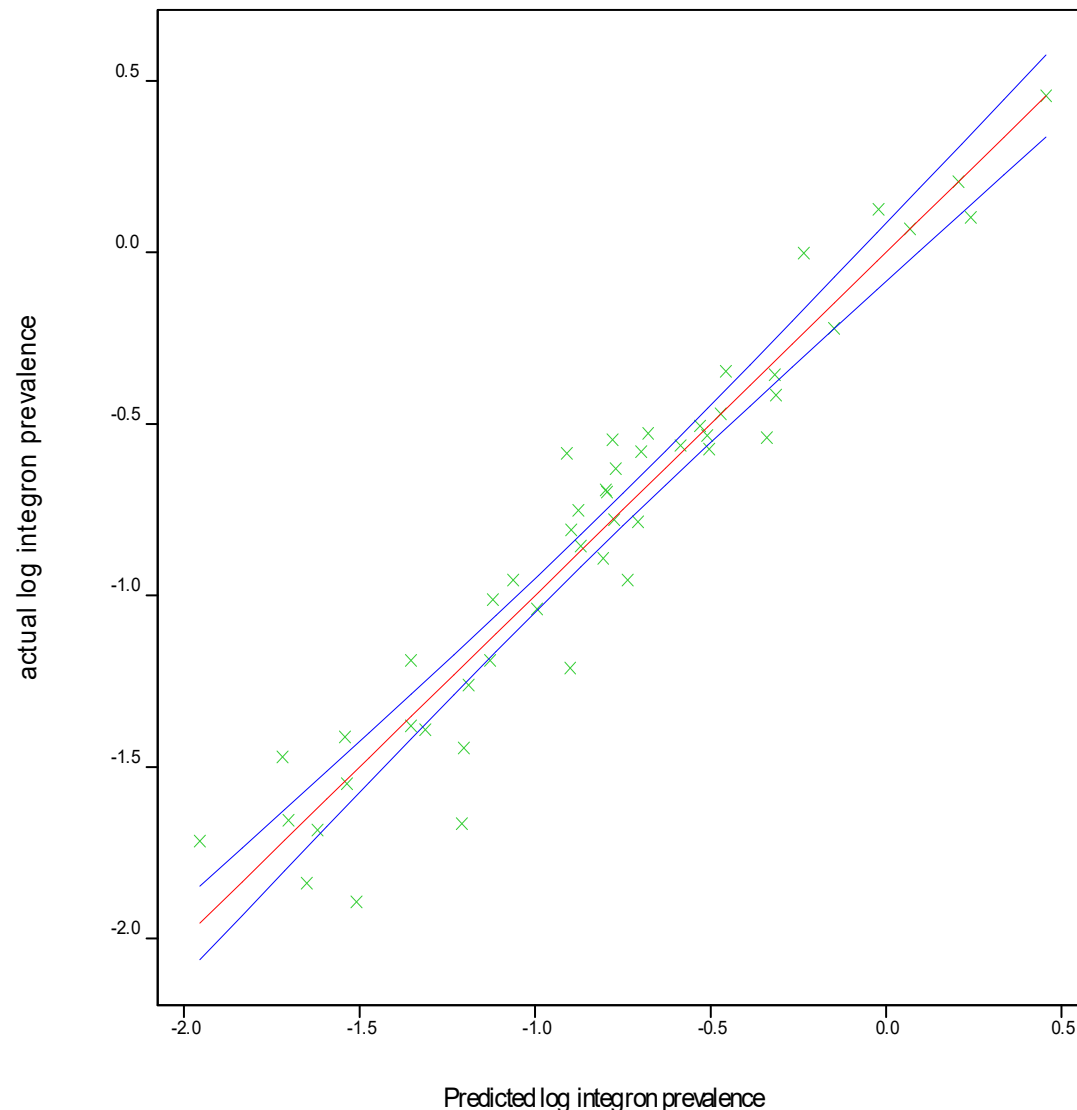


Figure 3. Risk Quotients (RQs) = $PNEC^R$ /maximum measured environmental concentration ('MEC', circles) or median MEC (triangles). MECs were extracted from the Umweltbundesamt (UBA) pharmaceuticals in the environment database freely available online, for hospital effluent, wastewater influent and wastewater effluent samples. Risk was broadly classified in a traffic light system: low (green) risk, $RQ = 0 - <0.1$, medium (orange) risk, $RQ = >0.1$ and <1 , high (red) risk, $RQ = >1$. Exact RQ values are also reported. NB gentamicin RQ based on PEC data.

Circulation of AMR in the environment

model includes WWTP and land use 2km from river

Fitted and observed relationship with 95% confidence limits



Linear regression models accounted for 82.9 % of the variance seen in log integron prevalence at different sites in the Thames River Basin.

50% of variance associated with point source and 30% with diffuse pollution

Amos, G.C.A., Singer, A.C., Bowes, M.J., Gaze, W.H., Wellington, E.M.H. *et al.*, (2015) Identifying the drivers for antibiotic resistance dissemination in the environment. *ISME J.*

Environmental transmission of AMR

Anthropological and socioeconomic factors contributing to global antimicrobial resistance: a univariate and multivariable analysis



Peter Collignon, John J Beggs, Timothy R Walsh, Sumanth Gandra, Ramanan Laxminarayan



Summary

Background Understanding of the factors driving global antimicrobial resistance is limited. We analysed antimicrobial resistance and antibiotic consumption worldwide versus many potential contributing factors.

Lancet Planet Health 2018;
2: e398-405

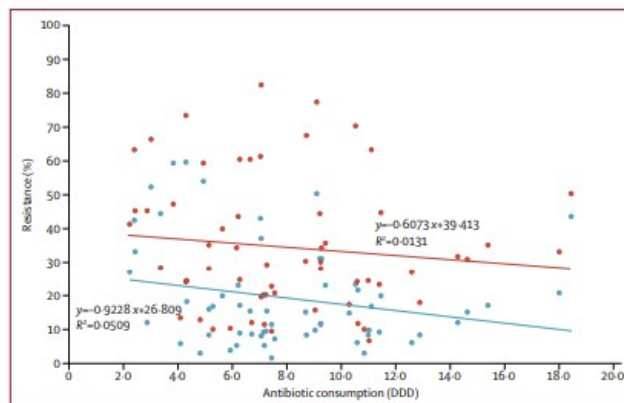


Figure 2: *Escherichia coli* resistance levels for fluoroquinolones and third-generation cephalosporins compared with antibiotic consumption

Figure shows data for percentage of resistance versus defined daily dose (DDD) of antibiotic, plotted only for countries with data for DDD and both measures of resistance. Blue circles indicate *Escherichia coli* resistance to third-generation cephalosporins (%). Red circles indicate *E coli* resistance to fluoroquinolones (%). The blue line shows the linear measure of *E coli* resistance to third-generation cephalosporins. The red line shows the linear measure of *E coli* resistance to third-generation fluoroquinolones. R^2 =coefficient of determination.

“Surprisingly, we found that antibiotic consumption was poorly correlated with antimicrobial resistance levels”

“a high prevalence of antimicrobial resistance can be more likely attributed to the dissemination of antimicrobial resistance, especially via poor sanitation and contaminated potable water”

	Effect on resistance rate of 1 SD increase in each explanatory variable (logit)	p value
Usage (standardised)	-0.88	0.64
Governance index	-7.89	0.025
Health expenditure index	-5.54	0.093
GDP per capita (standardised)	6.62	0.030
Education index	7.93	0.058
Infrastructure index	-16.84	0.014
Climate index	2.01	0.33
R^2	0.54	..

GDP=gross domestic product. R^2 =coefficient of determination.

Table 2: Effect of changes in indices on the resistance of *Escherichia coli* to third-generation cephalosporins and fluoroquinolones



Contents lists available at ScienceDirect

Environment International

journal homepage: www.elsevier.com/locate/envint



Human recreational exposure to antibiotic resistant bacteria in coastal bathing waters



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journal homepage: www.elsevier.com/locate/envint



Exposure to and colonisation by antibiotic-resistant *E. coli* in UK coastal water users: Environmental surveillance, exposure assessment, and epidemiological study (Beach Bum Survey)



Anne F.C. Leonard^{a,*}, Lihong Zhang^{a,*}, Andrew J. Balfour^a, Ruth Garside^a, Peter M. Hawkey^b, Aimee K. Murray^a, Obioha C. Ukoumunne^c, William H. Gaze^{a,*}

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Summary

- Evidence suggests selection for AMR at sub-therapeutic concentrations is likely to occur in all animal, human and environmental compartments
- Most antibiotics used end up in the environment, with diverse bacteria from multiple sources increasing the likelihood of emergence of novel resistance genes from the environmental resistome
- AMR in aquatic systems correlates with pollution sources from both human and animal sources
- There is significant evidence of transmission of AMR associated with WASH in LMICs and HICs

Research Needs

- Accurate MSCs for single compounds and complex mixtures to understand selective potential in the environment
- Models to predict emergence / evolution of AMR in impacted environments
- Understanding “acute” risk of environmental transmission (colonisation and infection) to human populations living around and utilising impacted environments
- Prioritisation by cost : benefit for interventions and mitigation strategies to reduce evolution and transmission of AMR

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