The environmental dimension of antimicrobial resistance

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Antibiotic resistance more of threat to world than climate change

Hannah Devlin Science Editor   Dame Sally Davies said

New Science Minister announces 'war cabinet' to tackle antimicrobial resistance on all fronts

16 Jul 2014

For the first time all seven UK research councils unite to fight AMR

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Guidance
UK 5 Year Antimicrobial Resistance Strategy 2013 to 2018

"Environment" in the context of One Health mentioned 5 times

https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/244058/20130902_UK_5_year_AMR_strategy.pdf

WHO AMR Action Plan

GLOBAL ACTION PLAN ON ANTIMICROBIAL RESISTANCE

World Health Organization

WHO, 2015

- This action plan underscores the need for an effective "one health" approach involving coordination among numerous international sectors and actors, including human and veterinary medicine, agriculture, finance, environment, and well informed consumers.

- Drug-resistant bacteria can circulate in populations of human beings and animals, through food, water and the environment, and transmission is influenced by trade, travel and both human and animal migration.

- The potential impact of antimicrobials in the environment is also of concern to many.

1. Understanding how resistance develops and spreads, including how resistance circulates within and between humans and animals and through food, water and the environment, is important for the development of new tools, policies and regulations to counter antimicrobial resistance.

2. Develop, with FAO and OIE communication, education and training materials that can be adapted and implemented regionally and nationally, on subjects that include the need for responsible use of antibiotics, the importance of infection prevention in human and animal health and agricultural practice, and measures to control spread of resistant organisms through food and the environment.

3. Develop standards and guidance (within the tripartite collaboration with FAO and OIE), based on best available evidence of harms, for the presence of antimicrobial agents and their residues in the environment, especially in water, wastewater and food (including aquatic and terrestrial animal feed).

A European One Health Action Plan Against Antimicrobial Resistance

A European One Health Action Plan against Antimicrobial Resistance (AMR)

AMR action plan 2017

"Environment" mentioned 31 times

- Consider options for the harmonised monitoring of AMR in the environment, including through the network of national reference laboratories in the veterinary sector.

2.4
BETTER ADDRESSING THE ROLE OF THE ENVIRONMENT

The environment is increasingly acknowledged as a contributor to the development and spread of AMR in humans and animals, in particular in high risk areas due to human, animal and manufacturing waste streams, but strong evidence is still required to better inform decision-making in this area. Specific actions to improve the knowledge base are considered in section 3. Once relevant monitoring and research data become available, risk assessment methodologies should be developed to evaluate the risks to human and animal health.

The Commission will:

- adopt an EU strategic approach to pharmaceuticals in the environment[31];

- maximise the use of data from existing monitoring, e.g. Watch List monitoring under the Water Framework Directive[32], to improve knowledge of the occurrence and spread of antimicrobials in the environment, including by using the Information Platform for Chemical Monitoring (IPCheM) to access relevant monitoring data[33];

- reinforce the role of the Scientific Committee on Health and Environmental Risks (SCHER) in providing the expertise on environment-related AMR issues.

FRONTIERS 2017

Emerging Issues of Environmental Concern

Three main issues associated with the environment highlighted in EU Action plan

- Circulation of AMR in the environment

- Role of pharmaceuticals in the environment driving AMR

- Environmental transmission of AMR

Antibiotic resistance is on the rise
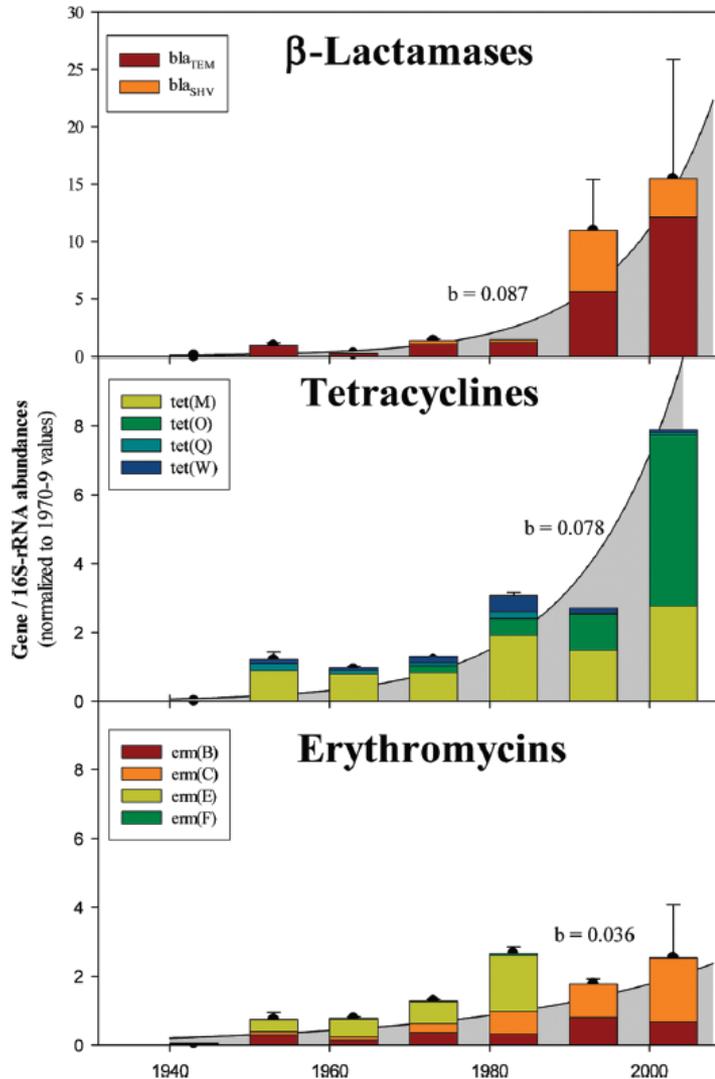
Knapp et al., 2010, PNAS

© http://drsuzanne.net
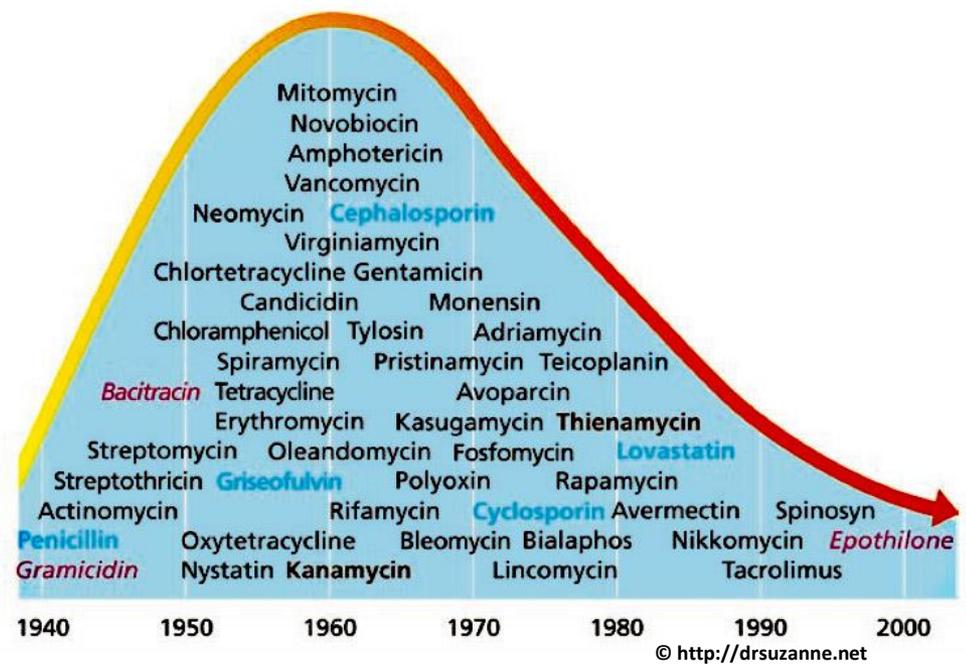
Antibiotic resistance:
An ancient phenomenon

Samples from permafrost before the "Age of Antibiotics"

➜ Enormous variety of resistance genes against modern antibiotics

D'Costa et al., 2011, Nature Letters
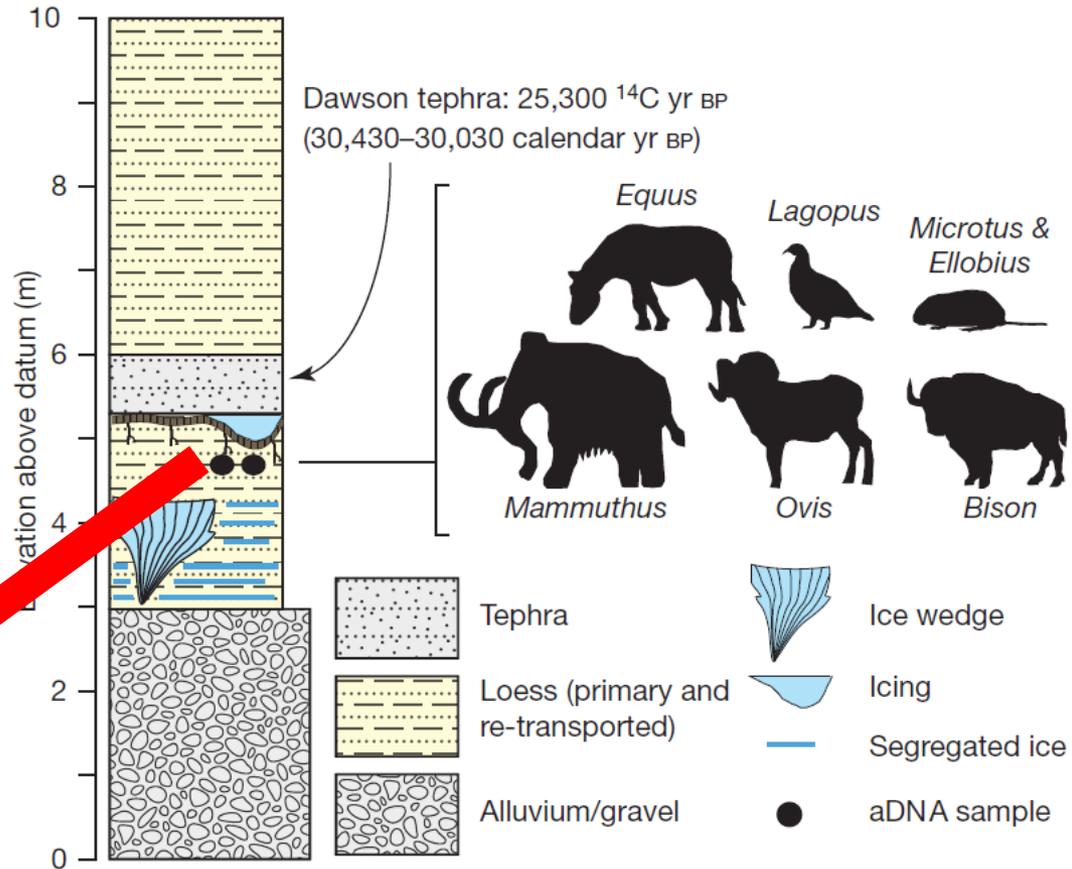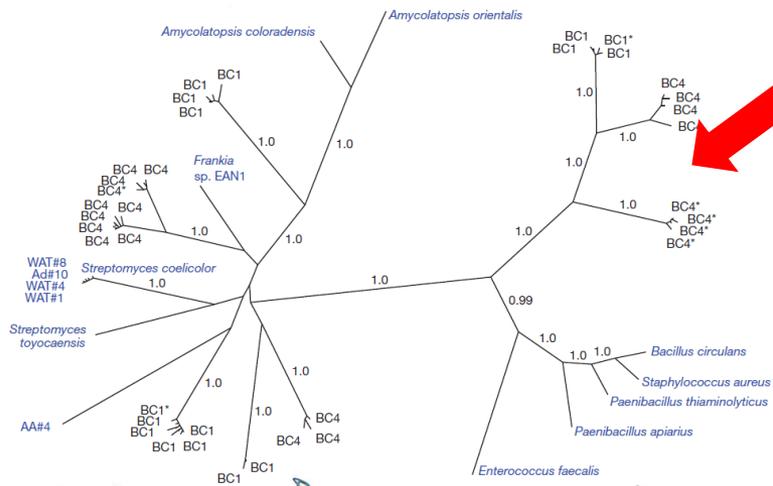
Mobility of antibiotic resistance genes and their bacterial hosts from the natural and farmed environment to humans

- Rare gene transfer events that lead to new genetic combinations – rare but can be extremely important eg. initial mobilisation of CTX-M extended spectrum β-lactamase progenitors – subsequently became associated with human pathogens and were globally distributed.

Veterinary / clinical antibiotic residues

Resistance mechanisms evolved over evolutionary time in producers and competitors

Exotics ⟷ indigenous

Horizontal Gene Transfer (HGT)
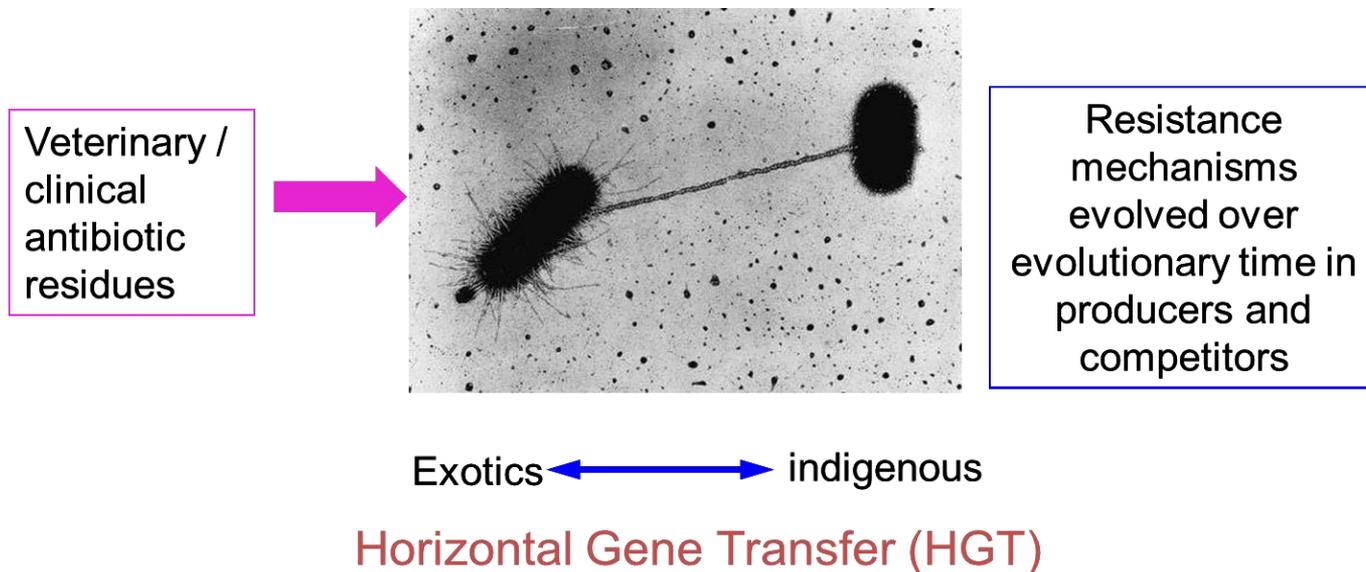
- Acute dissemination / transmission events. Common, introduction of human and animal associated AMR bacteria to aquatic systems and human exposure to these bacteria/genes in environmental settings.
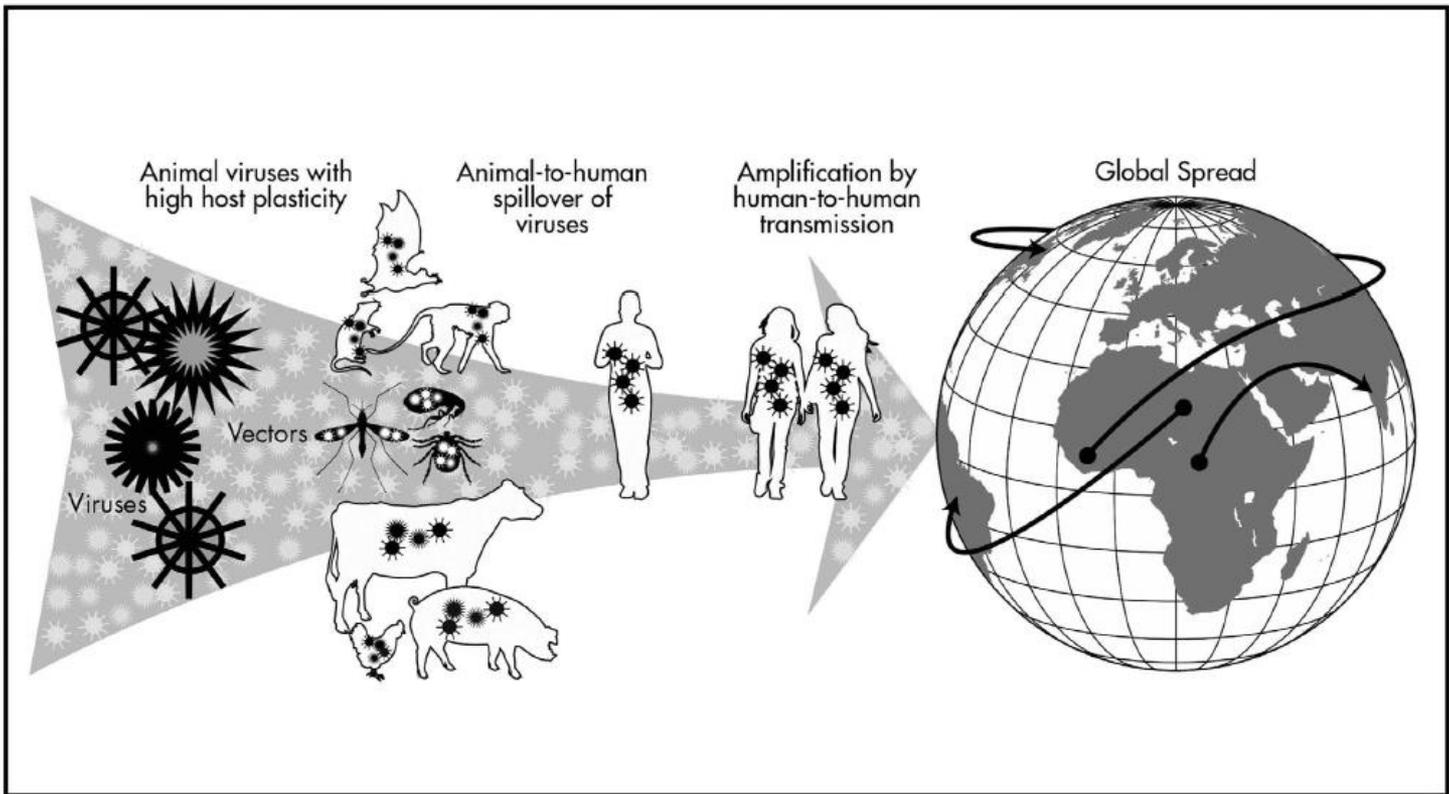
Figure 1. Pandemic properties of zoonotic viruses that spill over from animals to humans and spread by secondary transmission among humans. Key characteristics of pandemic potential that were evaluated for associations with viral traits and high-risk disease transmission interfaces include host plasticity, human-to-human transmissibility, and geographic distribution. Human practices that promote transmission of mutation-prone RNA viruses able to infect a wide range of taxonomically diverse hosts, including wild and domestic animals, act synergistically to facilitate viral emergence, particularly for viruses capable of human-to-human transmission and broad geographic spread (map and illustration created using Adobe Illustrator CS6).

Johnson et al., 2015 Nature Scientific Reports. http://www.nature.com/articles/srep14830

The Human Faecal Resistome: relationship to the environment

Antibiotics
- µg-mg/kg in soils
- ng-µg/L in water

VETERINARY

FOOD ANIMALS

CLINICAL / VETERINARY / PRODUCERS

VETERINARY / CLINICAL

COMMENSALS

WATER

SLURRY / SLUDGE

HUMAN USE

PATHOGENS

SOIL CROPS

VETERINARY / CLINICAL / PRODUCERS

Gene flow

Selection by antimicrobials

Hawkey, P.M.
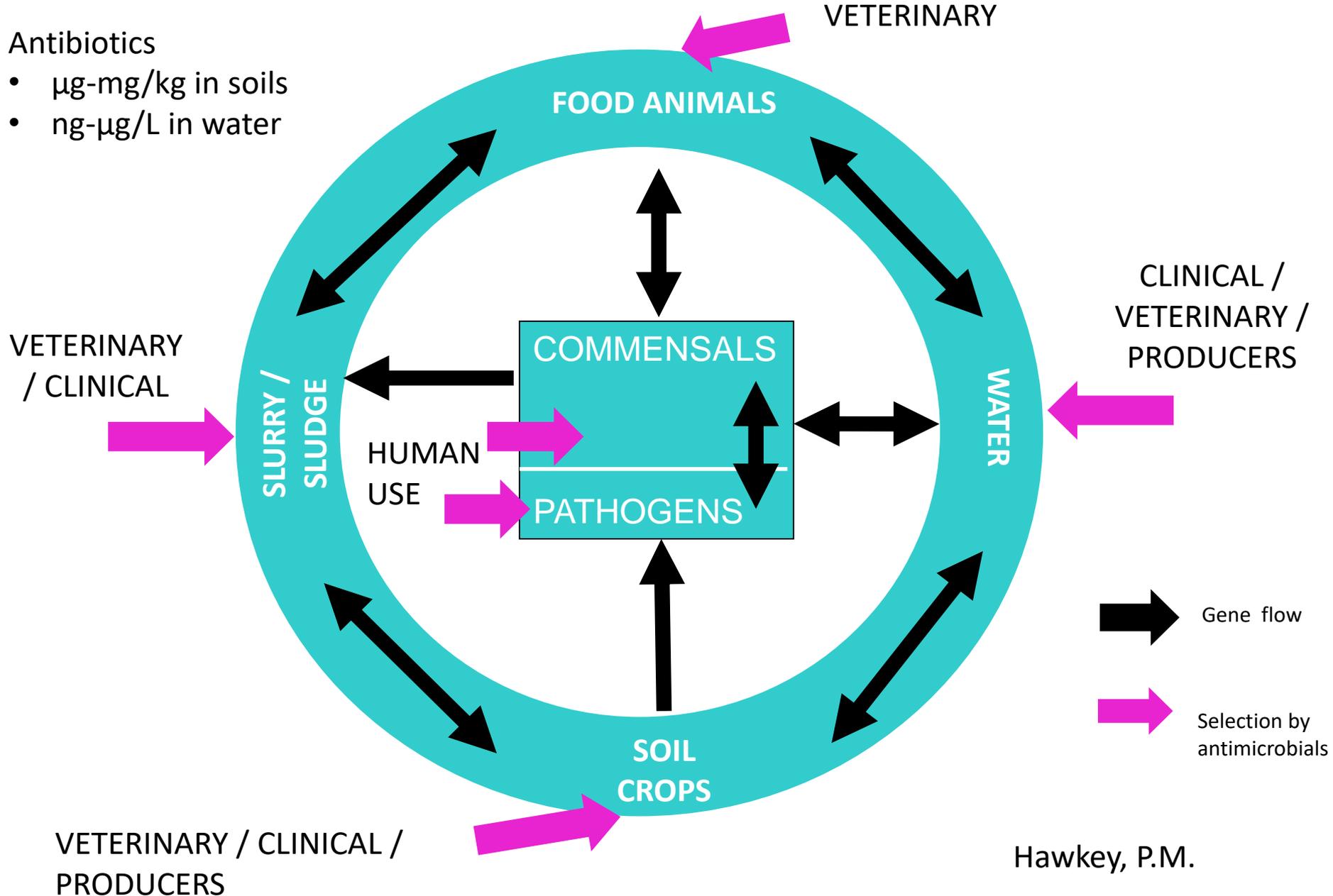
AMU in animals and AMR in humans

Media centre

Stop using antibiotics in healthy animals to prevent the spread of antibiotic resistance

News release

7 NOVEMBER 2017 | GENEVA - WHO is recommending that farmers and the food industry stop using antibiotics routinely to promote growth and prevent disease in healthy animals.

The new WHO recommendations aim to help preserve the effectiveness of antibiotics that are important for human medicine by reducing their unnecessary use in animals. In some countries, approximately 80% of total consumption of medically important antibiotics is in the animal sector, largely for growth promotion in healthy animals.

— WHO guidelines on use of medically important antimicrobials in food-producing animals

Over-use and misuse of antibiotics in animals and humans is contributing to the rising threat of antibiotic resistance. Some types of bacteria that cause serious infections in humans have already developed resistance to most or all of the available treatments, and there are very few promising options in the research pipeline.

"A lack of effective antibiotics is as serious a security threat as a sudden and deadly disease outbreak," says Dr Tedros Adhanom Ghebreyesus, Director-General of WHO. "Strong, sustained action across all sectors is vital if we are to turn back the tide of antimicrobial resistance and keep the world safe."

A systematic review published today in *The Lancet Planetary Health* found that interventions that restrict antibiotic use in food-producing animals reduced antibiotic-resistant bacteria in these animals by up to 39%. This research directly informed the development of WHO's new guidelines.

Related links

— WHO's work on antimicrobial resistance
— Antimicrobial resistance in the food chain
— WHO guidelines on use of medically important antimicrobials in food-producing animals
— Critically important antimicrobials for human medicine
— Fact sheet: antibiotic resistance
— Antimicrobial resistance in the food chain

Feature

— Namibia's ban on antibiotics in healthy animals drives meat exports

Infogrpahics

Restricting the use of antibiotics in food-producing animals and its associations with antibiotic resistance in food-producing animals and human beings: a systematic review and meta-analysis

Karen L Tang, Niamh P Caffrey, Diego B Nóbrega, Susan C Cork, Paul E Ronksley, Herman W Barkema, Alicia J Polachek, Heather Ganshorn, Nishan Sharma, James D Kellner, William A Ghali

Discussion

- 179 identified studies

- An association between interventions that restrict antibiotic use and reduction in the prevalence of antibiotic resistant bacteria in animals and in different human subgroups.

- Overall, reducing antibiotic use decreased prevalence of antibiotic-resistant bacteria in animals by about 15% and multidrug-resistant bacteria by 24–32%.

- The evidence of effect on human beings was more limited and less robust, though meta-analysis of 13 studies showed similar results, with a 24% absolute reduction in the prevalence of antibiotic-resistant bacteria in humans with interventions that reduce antibiotic use in animals.

Antibiotic resistance in the environment

- Dissemination of resistant bacteria, mobile genetic elements and resistance genes

- *In situ* selection by antibiotic residues and co-selecting compounds

- Human exposure to environmental reservoirs of antibiotic resistant organisms / genes

The role of the natural environment in the emergence of antibiotic resistance in Gram-negative bacteria. *Wellington, Gaze* et al. *Lancet ID, 2013.*

Dissemination of AMR at the landscape scale
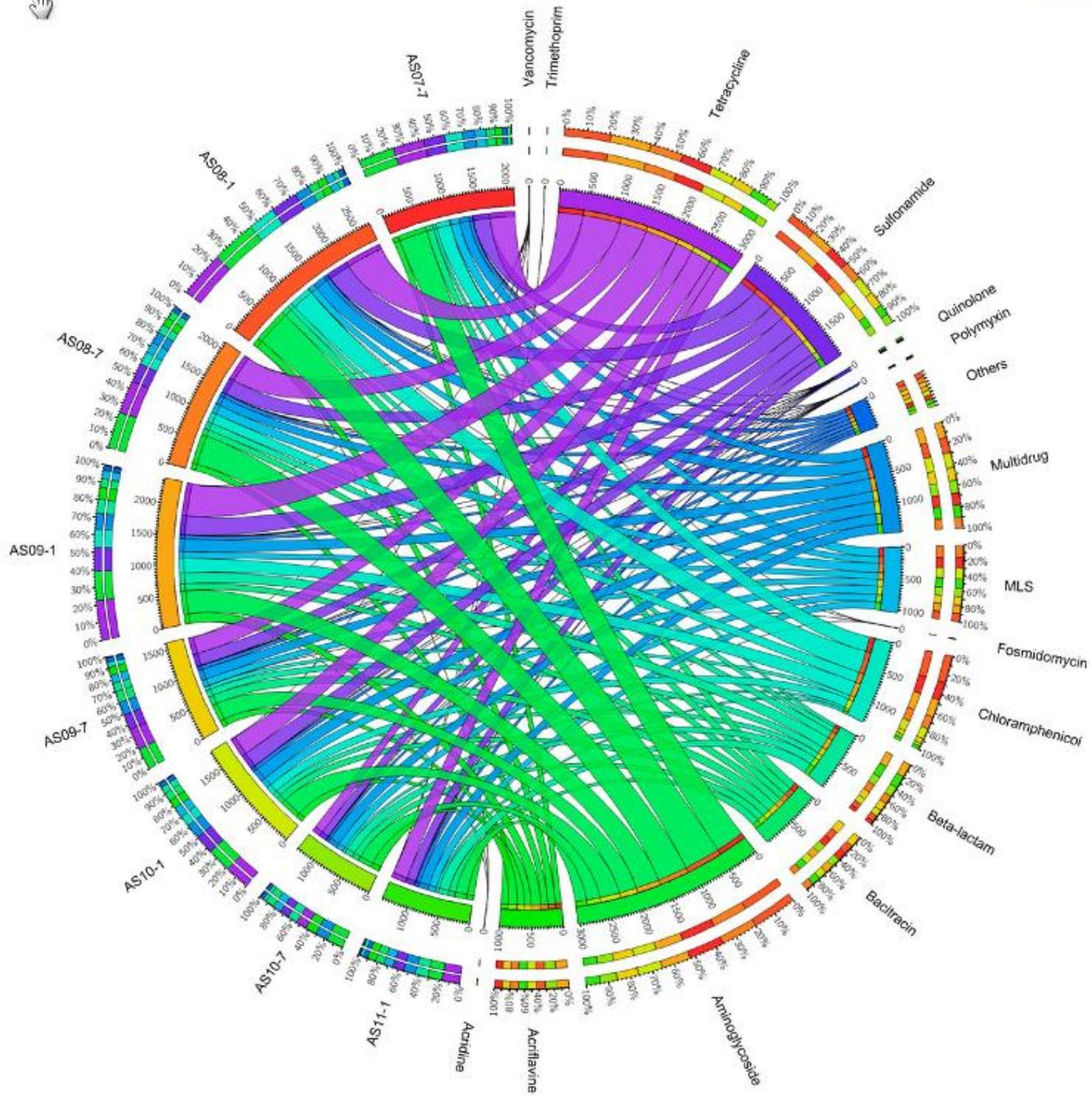
Yang Y, Li B, Ju F, Zhang T. Environ Sci Technol 2013; 47(18): 10197-205.

•11 BILLION LITRES WASTE WATER DISCHARGED
PER DAY IN THE UK

River

The effect of conventional wastewater treatment on the levels of antimicrobial-resistant bacteria in effluent: a meta-analysis of current studies.

Harris S[1], Cormican M, Cummins E.

⊕ Author information

Abstract

Antimicrobial agents in the environment are a cause for concern. Antimicrobial drug residues and their metabolites reach the aquatic and terrestrial environment primarily through wastewater treatment plants (WWTP). In addition to the potential direct negative health and environmental effects, there is potential for the development of antimicrobial-resistant bacteria. Residue levels below the minimum inhibitory concentration for a bacterial species can be important in selection of resistance. There is uncertainty associated with resistance formation during WWTP processing. A meta-analysis study was carried out to analyse the effect of WWTP processing on the levels of antimicrobial-resistant bacteria within bacterial populations. An analysis of publications relating to multiple antimicrobial-resistant (MAR) bacteria (n = 61), single antimicrobial-resistant (SAR) E. coli (n = 81) and quinolone/fluoroquinolone-resistant (FR) bacteria (n = 19) was carried out. The odds-ratio (OR) of MAR (OR = 1.60, $p < 0.01$), SAR (OR = 1.33, $p < 0.01$) and FR (OR = 1.19, $p < 0.01$) bacteria was determined. The results infer that WWTP processing results in an increase in the proportion of resistant bacteria in effluent, even though the overall bacterial population may have reduced (i.e. a reduction in total bacterial numbers but an increase in the percentage of resistant bacteria). The results support the need for further research into the development of antimicrobial-resistant strains and possible selective pressures operating in WWTPs.

[Indexed for MEDLINE]

f ▾ g+

Waste water effluent contributes to the dissemination of CTX-M-15 in the natural environment

G. C. A. Amos[1], P. M. Hawkey[2,3], W. H. Gaze[1]†‡ and E. M. Wellington[1]*‡
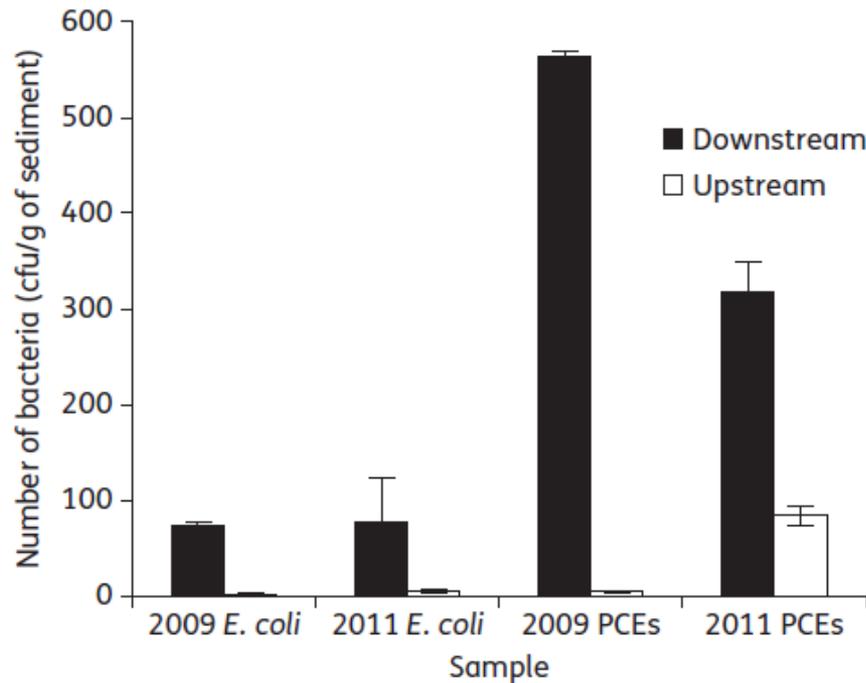
Figure 1. Counts of 3GC-resistant presumptive *E. coli* and PCEs from samples collected downstream and upstream of a WWTP in 2009 and 2011. Error bars are ± standard errors of biological replicates.
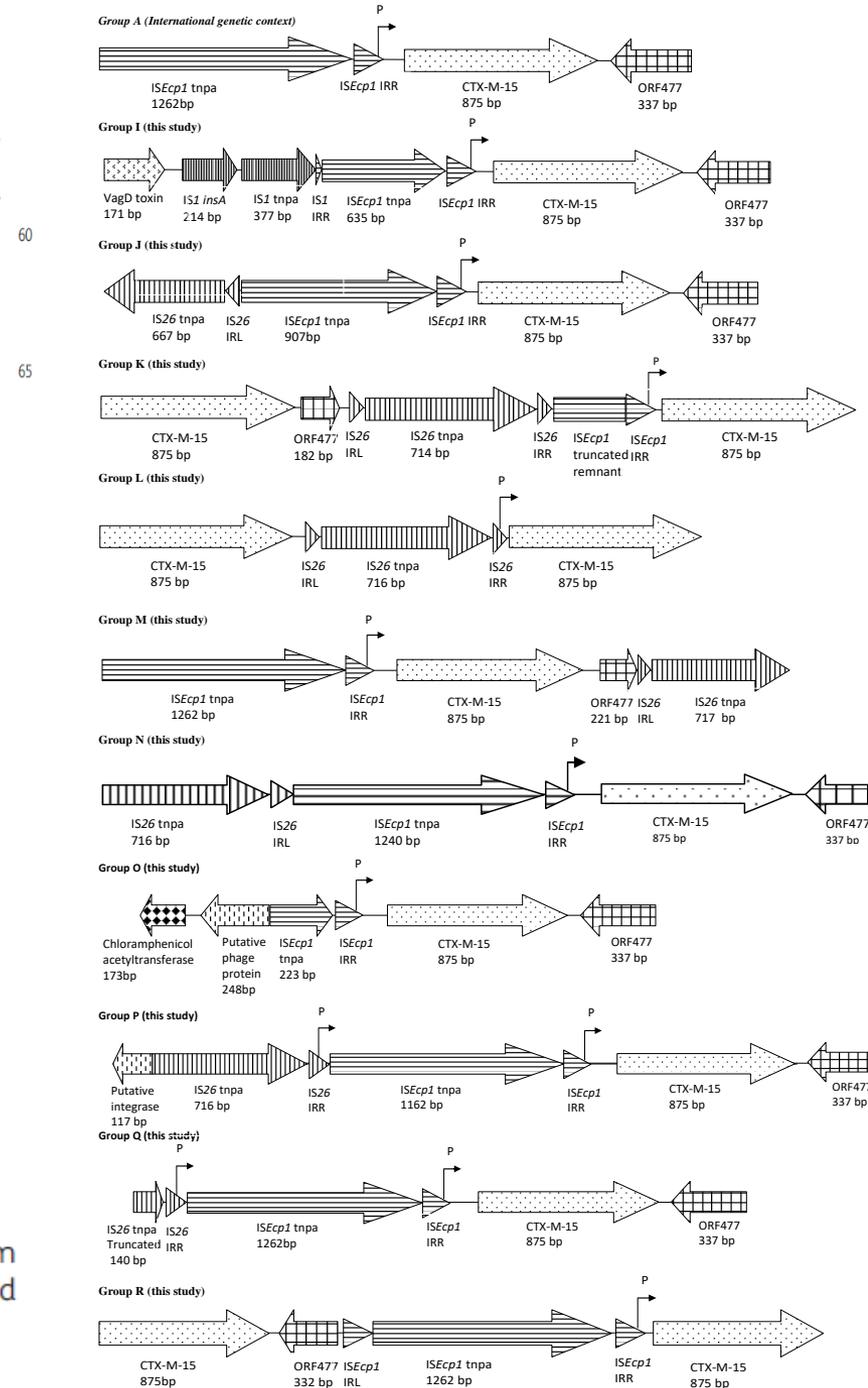
Integron prevalence upstream and downstream of a large WWTP

Amos, Zhang, Hawkey, Gaze, Wellington *et al.,* ISME Journal 2018.

The CEH Thames Initiative

Class 1 integron prevalence in sediments
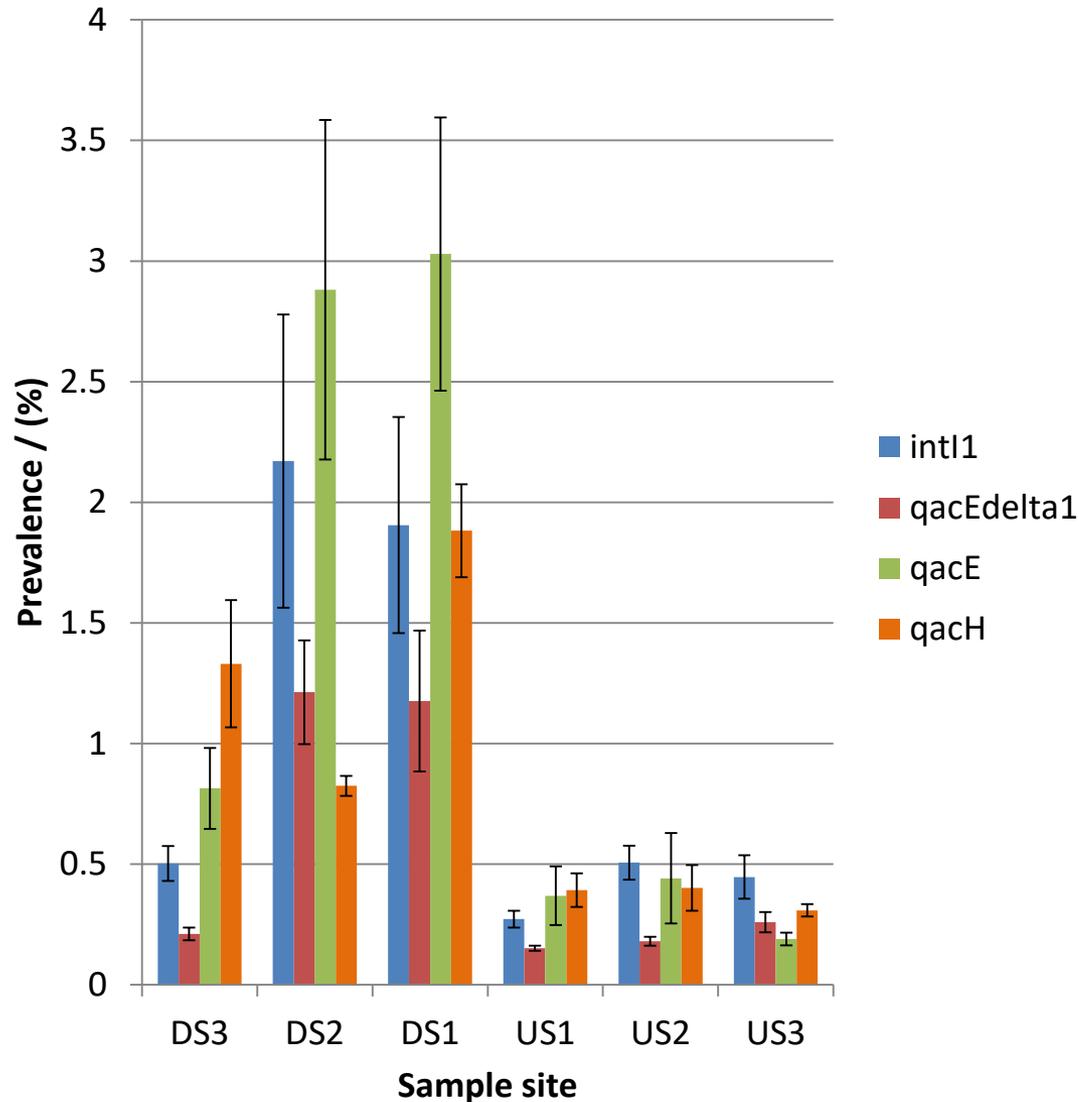
Geospatial analyses of sampling point TC1, Thames at Wheatley
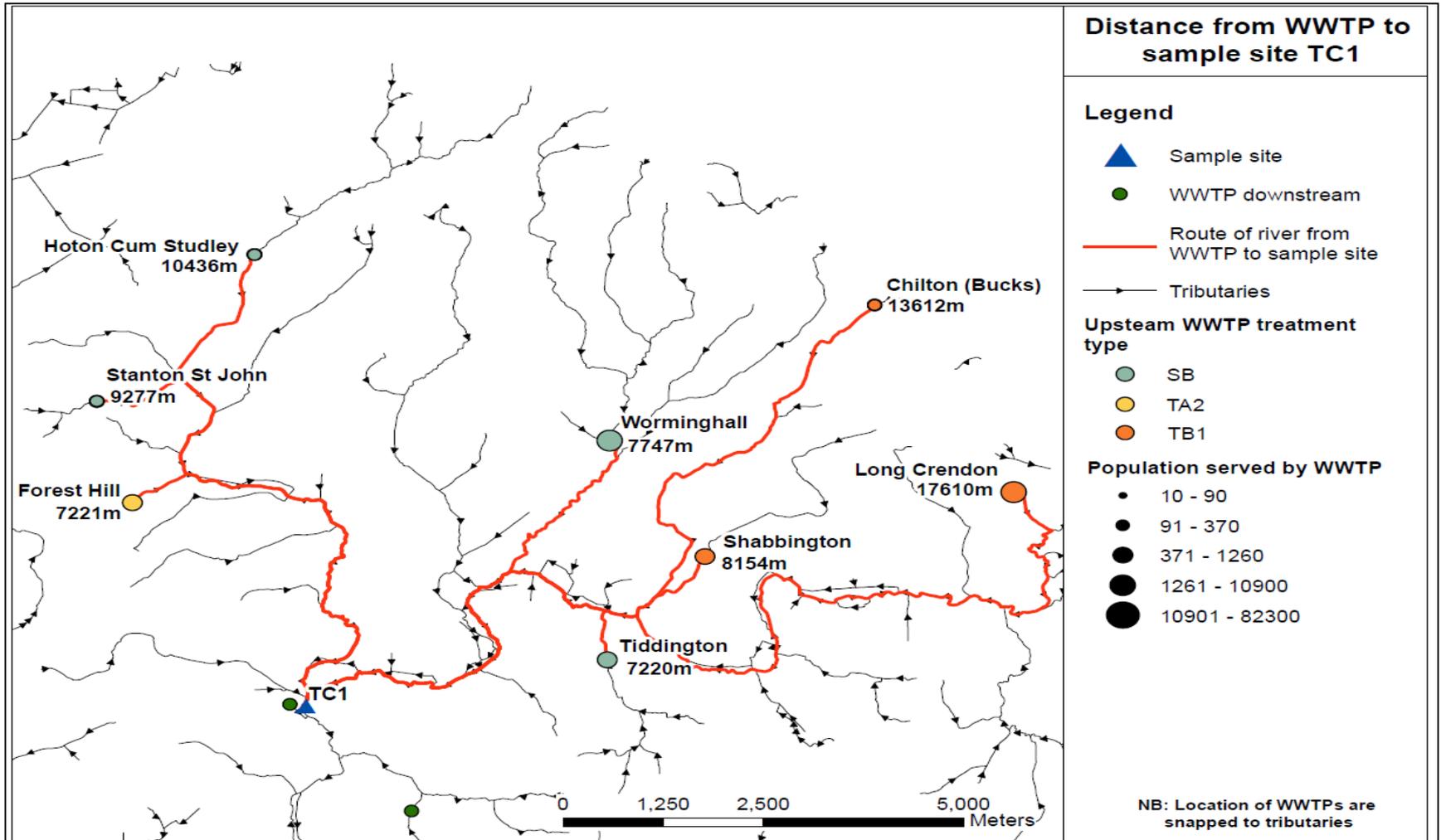
model includes WWTP and land use 2km from river

Fitted and observed relationship with 95% confidence limits

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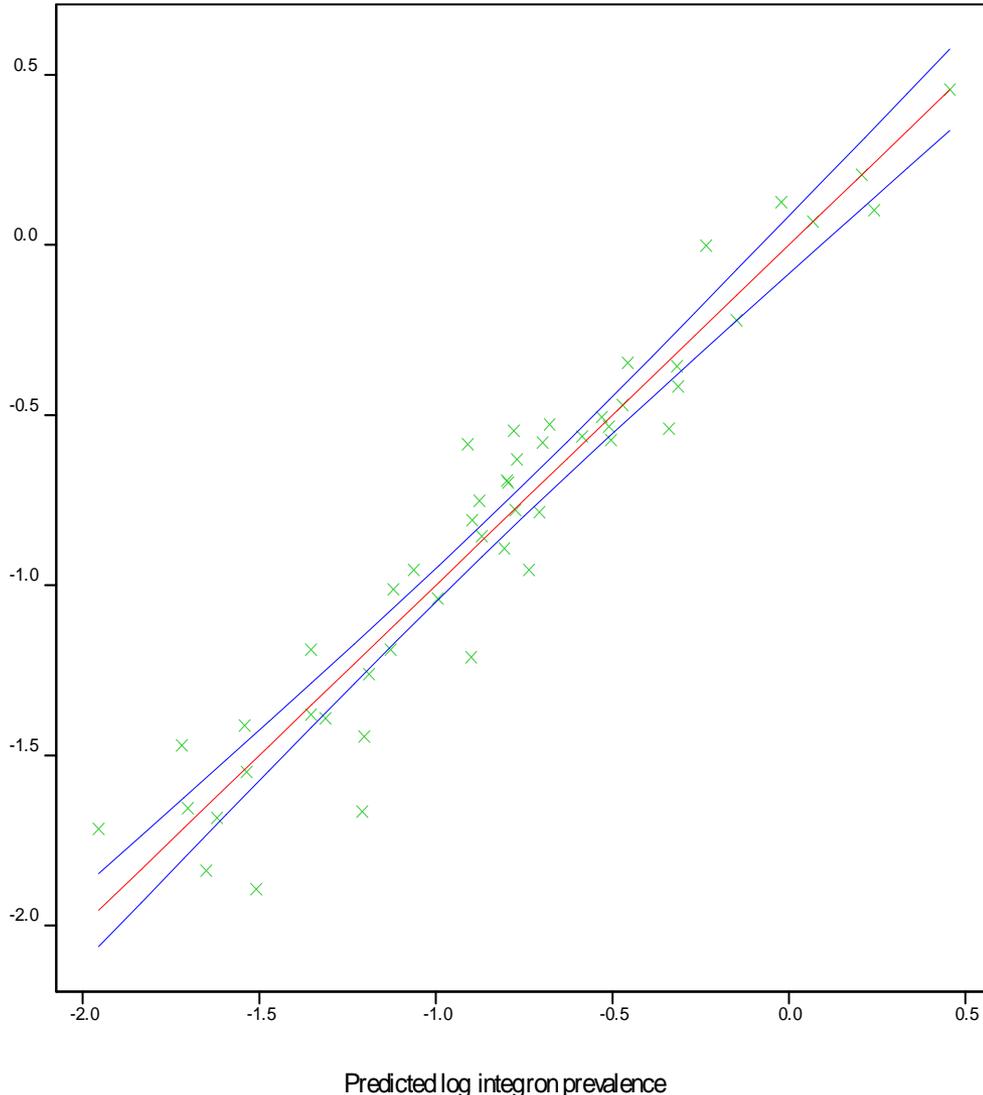
Linear regression models accounted for 82.9 % of the variance seen in log integron prevalence at different sites in the Thames River Basin.

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.*

Using next generation sequencing to reveal human impact on aquatic reservoirs of antibiotic resistant bacteria at the catchment scale

NERC funded directed call on Environmental microbiology and Human Health 2015 – 2018. £1.2 million. Partners: University of Warwick, University of Exeter, Centre for Ecology and Hydrology, Rothamsted Research

Characterise relative abundance and diversity >3,000 AMR genes, chemical and geospatial variables at 70 sites – develop predictive model and high throughput assays for marker genes correlating with specific pollution sources

Stakeholders: AstraZeneca, Thames Water, VMD, PHE, Defra, EA, FSA, Rivers Trusts
Commercial partners: LGC, Advanced Anaerobics, AUT
Overseas HE partners: HKU

NERC SCIENCE OF THE ENVIRONMENT

Selection for AMR in natural and farmed environments

Co-selection of resistance to antibiotics, metals and biocides

Antibiotic residues, e.g. tetracycline, beta lactam, ciprofloxacin

Biocides or chemicals with antimicrobial properties in a wide range of products, e.g. disinfectants, antiseptics, detergent, cosmetics, food preservatives

Cu Pb Zn Ag Cr Heavy metals, e.g. silver, zinc, copper, chromium, lead

Selective pressure from antibiotic residues, biocidal substances and heavy metals on bacterial communities contribute to increased antibiotic resistance in the environment. Bacteria can develop multi-resistance to such substances, and transfer the multi-resistance genes to non-resistant bacteria, and to the next generation.

Disinfectant resistance
Zinc resistance
Ciprofloxacin resistance
Copper resistance
Tetracycline resistance

Coselección para la resistencia a los antibióticos, los metales y los biocidas

Residuos de antibióticos, p. ej. tetraciclina, betalactámico, ciprofloxacina

Biocidas o sustancias químicas con propiedades antimicrobianas presentes en una amplia gama de productos, p. ej. desinfectantes, antisépticos, detergentes, cosméticos, conservantes alimentarios

Cu Pb Zn Ag Cr Metales pesados, p. ej. plata, cinc, cobre, cromo, plomo

La presión selectiva de los residuos de antibióticos, sustancias biocidas y metales pesados en las comunidades bacterianas contribuye a la resistencia a los antibióticos presentes en el medio natural. Las bacterias pueden desarrollar multirresistencia a esas sustancias y transmitir los genes multirresistentes a otras bacterias no resistentes, así como a la generación posterior.

Resistencia a los desinfectantes
Resistencia al cinc
Resistencia a la ciprofloxacina
Resistencia al cobre
Resistencia a la tetraciclina

Environmental antibiotic concentrations

Antibiotic	Effluent conc. µg / L (max)	Surface waters µg / L (max)
Penicillin	0.2	-
Erythromycin	6.0	1.7
Fluoroquinolones (ciprofloxacin, norofloxacin)	0.1	0.1
Sulfamethoxazol	2.0	1.9
Chloramphenicol	0.5	-
Trimethoprim	0.7	0.7

Kummerer 2009

Hospital waste water
Ciprofloxacin 0.70 – 17.3 µg / L, mean 5.12 µg / L (Gomez *et al.,* 2007)
Cefotaxime 0.41 – 150 µg / L, mean 9.52 µg / L

Fluoroquinolones highly enriched in sludge (1.4 to 2.42 mg kg^1). Persistent
in sludge-treated soils months after application. (Golet *et al*. 2007)

Tetracycline and sulfamethazine reported from liquid manure at 66 mg l^{-1} and
40 mg l^{-1} respectively (Kummerer, 2004)

Competition assays can determine Minimal Selective Concentrations (MSCs)
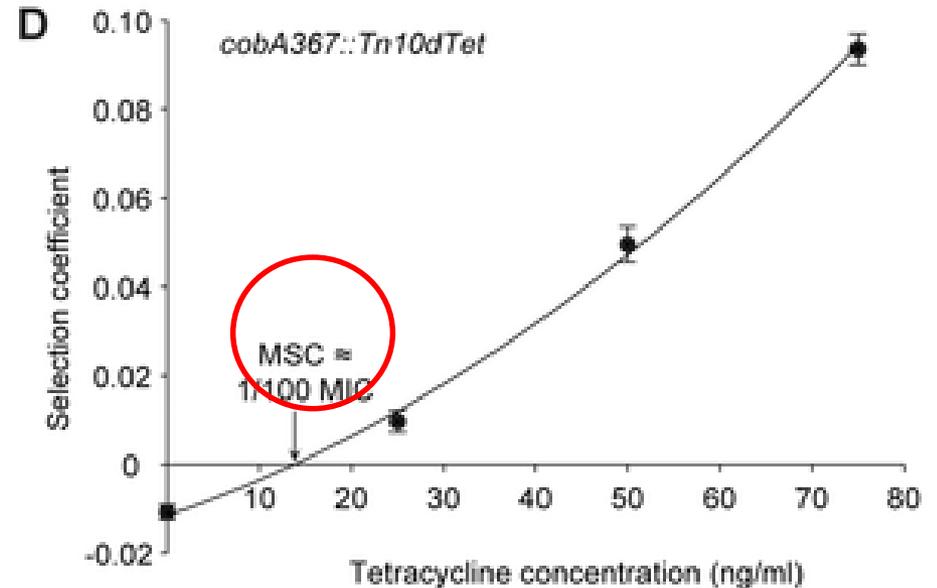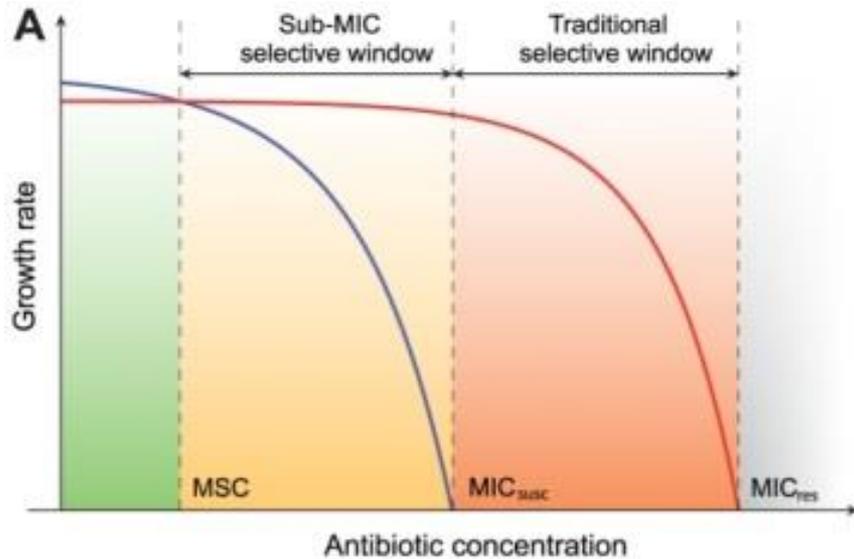
Gullberg *et al.* (2011)

MSCs from Gullberg *et al.,* 2011

Chromosomal mutation in single species competition assays

- Streptomycin MSC was ¼ of MIC   1 mg / L

- Tetracycline MSC was 1/100 of MIC   15 µg / L

- Ciprofloxacin MSC was between 1/10 and 1/230 of MIC   2.5 µg – 100 ng / L

Antibiotic selection in complex microbial communities at sub-therapeutic concentrations
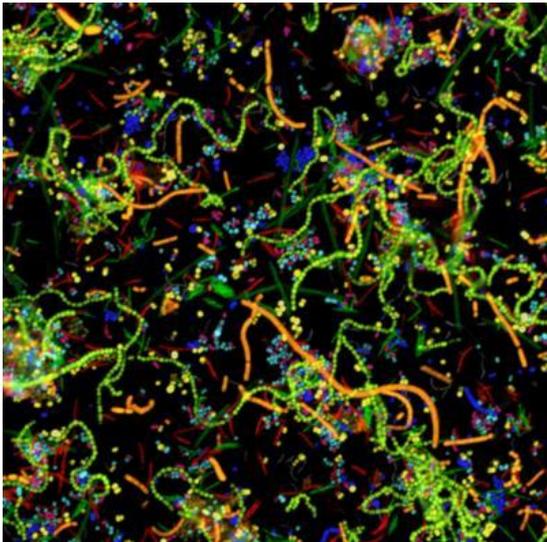
Alex Valm
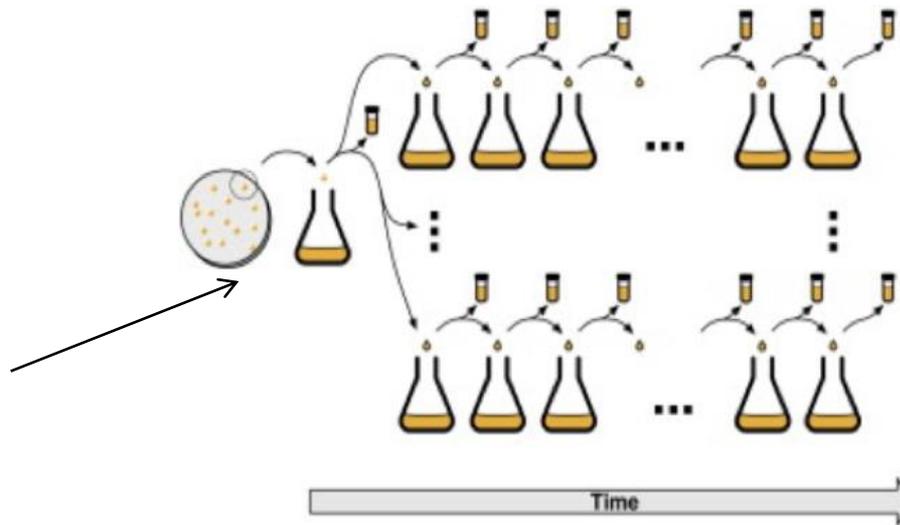
A schematic of a serial transfer experiment
(from Sprouffske et al., 2012)

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

Selection for cefotaxime resistance

CTX-M group specific qPCR after 8 days cefotaxime exposure
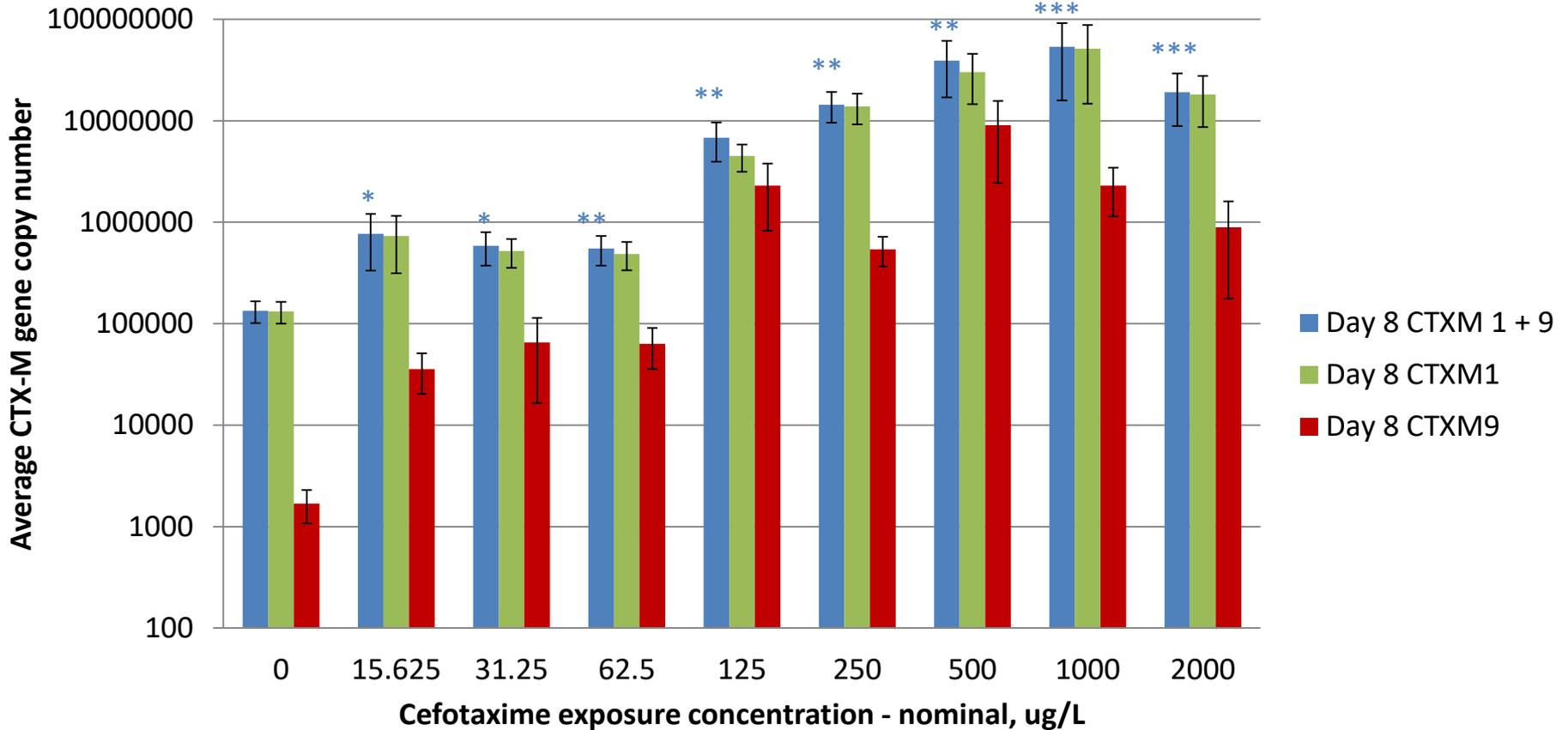
* p <0.1, ** p <0.05, *** p <0.01 significantly different to no antibiotic control according to T-test/ Mann-Whitney U-test with unequal variances, as appropriate.

Is AMR in the Environment Driven by Dissemination of Antibiotics or Antibiotic Resistance Genes?

Cross Council AMR Theme 3 grant, led by Andrew Singer (CEH) with Liz Wellington (Warwick) and Will Gaze (Exeter). £1.5 million.

Area for biofilm growth

Sump to catch river debris

Floats

Flow control gates
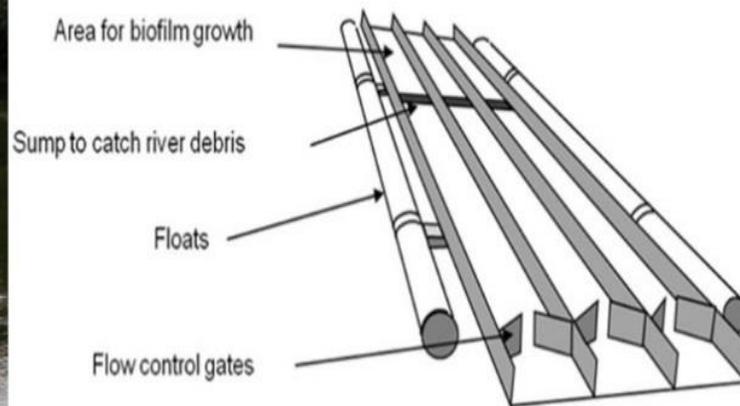
CEH river flume system. Replicated, separate channels (5m long) allow for *in situ* manipulation experiments.

Transmission of environmental AMR to humans & animals

Environmental surveillance - methods

- 97 water samples

- Provided by the Environment Agency

- July 2012 – Sept 2012
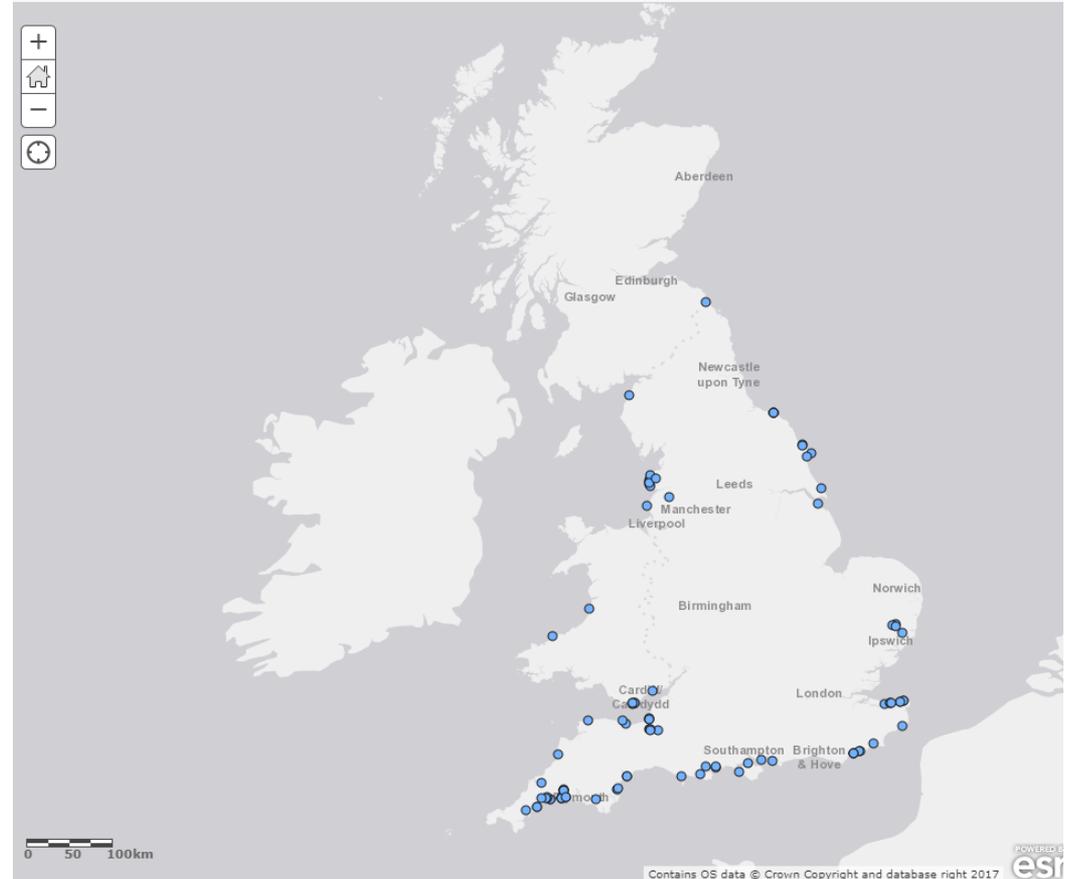
Map of sampling locations

Results – environmental surveillance

- 15/97 (15%) water samples had *E. coli* resistant to cefotaxime/ceftazidime

- On average 0.12% of all *E. coli* were resistant to cefotaxime/ceftazidime

- 0.07% of all *E. coli* were harbouring *bla*$_{CTX-M}$

- The most common *E. coli* phylogroup harbouring CTX-Ms were phylogroup B2

- Most of the B2 *E. coli* harbouring CTX-Ms were confirmed as *E. coli* ST131

Indistinguishable NDM-producing *Escherichia coli* isolated from recreational waters, sewage, and a clinical specimen in Ireland, 2016 to 2017

Bláthnaid M Mahon, [1] Carina Brehony, [1] Elaine McGrath, [2,3] James Killeen, [1] Martin Cormican, [1,2,3] Paul Hickey, [4] Shane Keane, [4] Belinda Hanahoe, [3] Ann Dolan, [5] and Dearbháile Morris [1]

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Abstract

Go to: ☑

In this study, New Delhi metallo-beta-lactamase (NDM)-producing *Enterobacteriaceae* were identified in Irish recreational waters and sewage. Indistinguishable NDM-producing *Escherichia coli* by pulsed-field gel electrophoresis were isolated from sewage, a fresh water stream and a human source. NDM-producing *Klebsiella pneumoniae* isolated from sewage and seawater in the same area were closely related to each other and to a human isolate. This raises concerns regarding the potential for sewage discharges to contribute to the spread of carbapenemase-producing *Enterobacteriaceae*.

Exposure Risk Assessment

- Calculate the number of cefotaxime-resistant *E. coli* and bla_{CTX-M}-bearing *E. coli* water users are likely to ingest

Exposure = *P x D x V*

P= Proportion of resistant (or CTX-M-bearing E. coli)

D= Density of *E. coli* reported in designated waters around England and Wales

V= Volume of water ingested during a particular water sport.

Leonard *et al (*2015), *Environment International*

Results – exposure risk assessment
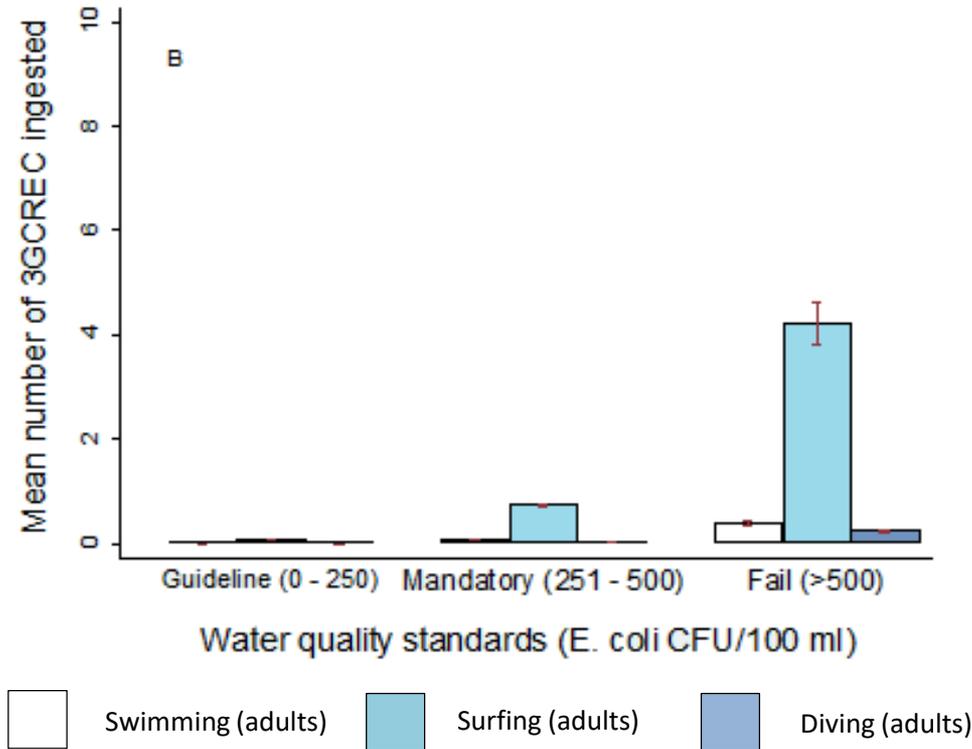
Mean number of phenotypically resistant *E. coli* swimmers (white, surfers (pale blue) and divers (dark blue) typically ingest per session of each activity

- 6.3 million exposure events to phenotypically resistant *E. coli*

- 2.5 million exposure events to bla_{CTX-M}- bearing *E. coli*

- Surfers swallow most water compared to other water users and are therefore at greatest risk of exposure

RESEARCH ARTICLE

A coliform-targeted metagenomic method facilitating human exposure estimates to *Escherichia coli*-borne antibiotic resistance genes

A. F. C. Leonard[1], X. L. Yin[2], T. Zhang[2], M. Hui[3] and W. H. Gaze[1,*]

[1]European Centre for Environment and Human Health, University of Exeter Medical School, Knowledge Spa, Royal Cornwall Hospital, Truro, TR1 3HD, UK , [2]Department of Civil Engineering, The University of Hong Kong, Pokfulam Road, Hong Kong and [3]Department of Microbiology, The Chinese University of Hong Kong, Prince of Wales Hospital, 30-32 Ngan Shing Street, Shatin, New Territories, Hong Kong

*Corresponding author: European Centre for Environment and Human Health, University of Exeter Medical School, Knowledge Spa, Royal Cornwall Hospital, Truro, TR1 3HD, UK. Tel: +44-1872-258149; E-mail: w.h.gaze@exeter.ac.uk

One sentence summary: Assessment of the abundance and diversity of resistance genes in *Escherichia coli*, using a high-throughput sequencing approach to facilitate an estimation of bathers exposure to resistance genes in bathing waters.

Editor: Edward Topp

Table 3. Number of water sports sessions occurring in England in 2016 that resulted in at least 1, 10, 100 or 1000 E. coli-borne ARGs being ingested.

Number of E. coli-borne ARGs ingested	Number of exposures in bathing waters in three different categories of water quality			Total number of exposure events occurring in England in 2016
	E. coli density ≤250 cfu 100 mL^{-1}	E. coli density 251–500 cfu 100 mL^{-1}	E. coli density >500 cfu 100 mL^{-1}	
1	118 028 329	3 072 874	2 083 558	123 184 760
10	36 251 904	3 072 874	2 083 558	41 408 336
100	0	943 820	1 540 037	2 483 857
1000	0	0	373 925	373 925

Here's Why Scientists Are Going To Check Out Surfers' Butts

And it's not because their asses are so fine.

Posted on June 9, 2015, at 6:13 p.m.

Natasha Umer
BuzzFeed Staff

f   ✉   📌   t   More ⌄

Going to the beach is fun! But it might also be a nasty experience.

Ahh! Diapers!

Fox / Via giphy.com

Surfers wanted for 'superbug' study

By Claire Marshall
BBC environment correspondent

🕔 8 June 2015 | Science & Environment   f 🐦 💬 ✉ ◁ Share

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Six Years After Fukushima, Robots Finally Find Reactors' Melted Uranium Fuel   TRILOBITES Rock Carvings of Ancient Dogs Getting Taught New Tricks   A Helping of Science With Your Thanksgiving Dinner   A Close-Up Made of Sto Arabia's Des

SCIENCE

Do Seas Make Us Sick? Surfers May Have the Answer

Surfers, Seawater, Sewage Superbug Study: On World Oceans Day, Researchers Look Into How Antibiotic Resistance Moves From Environment To People

BY ELIZABETH WHITMAN 🐦   ON 06/08/15 AT 10:37 AM

Epidemiological survey - methods

- Cross-sectional study to compare faecal carriage rates of antibiotic resistant *E. coli* in people who surf regularly to people who don't

  - Exposure group: ~150 frequent surfers (surf >once per week)

  - Comparator group: ~150 recruits with limited exposure to seawater

- Worked with local Charity, Surfers Against Sewage, to help with recruitment

Results

	Surfers (N=143)	Controls (N=130)	Risk ratio (95% CI)	P value
Carriage of cefotaxime-resistant *E. coli*	13 (9·1%)	4 (3·1%)	2·95 (1·05 to 8·32)	0·040
Carriage of *bla*$_{CTX-M}$-bearing *E. coli*	9 (6·3%)	2 (1·5%)	4·09 (1·02 to 16·4)	0·046

- CTX-M-15 was the most abundant type of CTX-M found both in *E.coli* isolated from surfers and during the environmental surveillance of *E. coli* in coastal bathing waters in England and Wales.

- 75% of surfers colonised by CTX-M-bearing were colonised by *E. coli* ST131
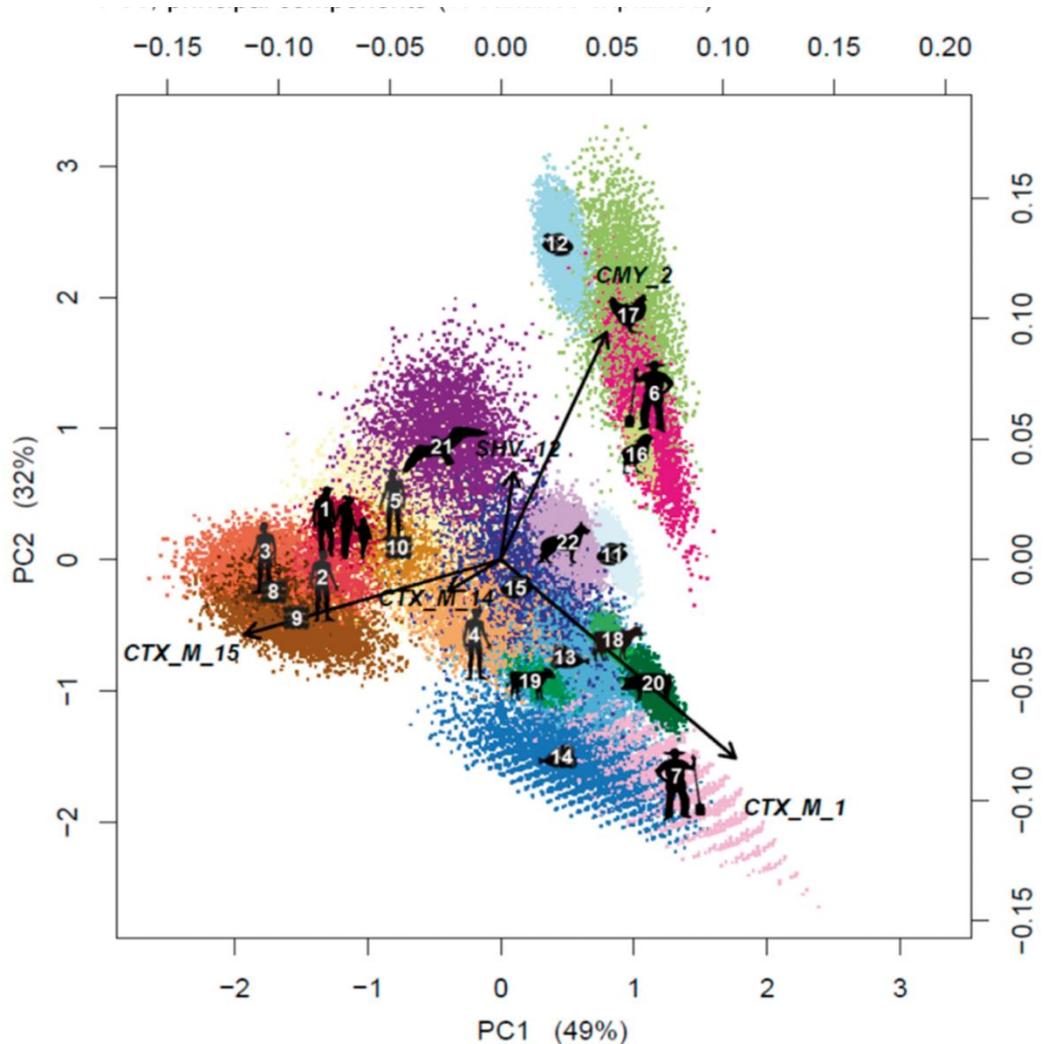
Leonard et al., Env International, in press.

Summary

- Human and animal associated AMR bacteria are introduced into the environment where they mix with indigenous bacteria in the presence of antibiotic residues and other bio-active compounds.

- Levels of AMR are predictable at a river catchment scale.

- Evidence suggests selection for AMR occurs at environmental concentrations for SOME antibiotics.

- Humans are exposed to AMR bacteria in natural environments and new evidence suggests an association with increased risk of gut carriage.

- Colonisation is a known risk factor for infection.

- We do not know the contribution of acute environmental transmission to the overall burden of AMR infections in humans, but we do know mobile resistance genes acquired by previously susceptible human pathogens are likely to have evolved in environmental bacteria.

Group members working on AMR

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