European Commission

Better Training for Safer Food

Initiative

Antimicrobial Resistance One Health approach

RELEVANCE OF AMR TO THE ENVIRONMENT AND RELATED REGULATORS

BTSF

Food safety

Malaga, Spain – 25-28 November 2019

Relevance of AMR to the Environment and significance to environmental regulators

What is AMR?

- A natural phenomenon but amplified by the environment.
- Not a new phenomenon.
- Inappropriate or over use in human and veterinary medicine.
- Poor hygiene and infection prevention measures in hospitals and farms.
- Transmission of resistant bacteria from animals to humans via the food chain or direct contact.
- Environmental spread caused by contaminated food and water systems and international trade and travel.

"Core" Medicinal Product Legislation

- *Directive 2001/82/EC – Community code relating to veterinary medicinal products – amended by Directive 2004/28/EC*
- *Directive 2001/83/EC – Community code relating to medicinal products for human use – amended by Directive 2004/27/EC*

  - **Environmental risk assessments** (ERA) to be conducted;
  - Member States to ensure that **appropriate collection systems** are in place for unused medicinal products;
  - The summary of product characteristics has to include **special precautions for disposal** of a used medicinal product or derived waste materials, if appropriate.

Study on the environmental risks of medicinal products

- The BIO IS study;
- Global study: scale of the problem, causes, legislative and non-legislative options;
- Contracted by DG SANTE;
- Approach: whole life cycle of pharmaceuticals (Human & Veterinary medicines);
- Gather scientific evidence to inform policy decisions;
- Published in June 2014;
- Stakeholder workshop held in Sept 2014 to discuss options.

Outline of the BIO IS study

- How do medicinal products enter the environment?
- Which molecules are found in the environment and how do they behave?
- Environmental hazards
- Human exposure through the environment and possible impacts
- Factors of influence
- Possible solutions

EU legislation

Risk mitigation is an essential part of the evaluation of antimicrobials.

Risk mitigation can be used to restrict the risk associated with a product to an acceptable level or even to completely remove such a risk.

It is clear that further research is needed in order to estimate exposures and risks associated with environmental pathways of antibiotic resistance.

Nonetheless, certain management options might contribute to the reduction of these risks, acting synergistically with existing policies and goals.

However, there is **no current** provision for assessing the risk of AMR in the environment (e.g. emergence / increase / spread) due to the use of antimicrobials

One Health Approaches Proposals (& Road Map)

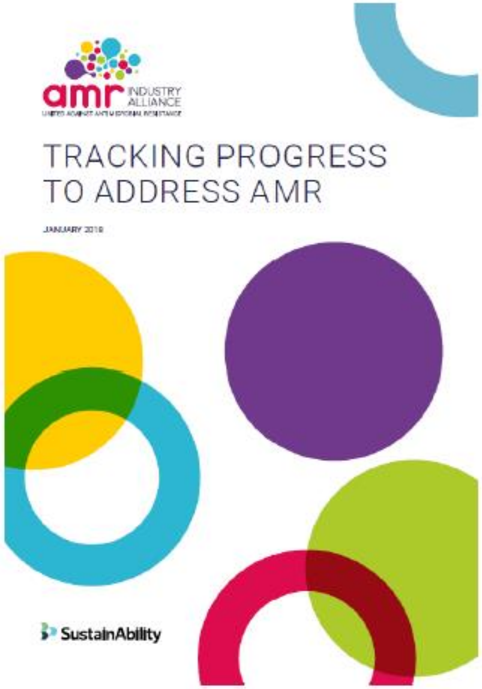
- Better addressing the role of the environment;
- Adopt a strategic approach to pharmaceuticals in the environment;
- Maximise the use of data from existing monitoring; e.g. Watch list monitoring under the Water Framework Directive, to improve knowledge of the occurrence and spread of antimicrobials in the environment, including by using the Information Platform for Chemical Monitoring (IPCheM) to access relevant monitoring data;
- Reinforce the role of the Scientific Committee on Health and Environmental Risks (SCHER) in providing the expertise on environment related AMR issues.

Closing the gaps on AMR

The Commission will:

- Support research into knowledge gaps on the release of resistant microorganisms and antimicrobials into the environment and their spread;
- Explore risk assessment methodologies with the support of scientific agencies and bodies and use them to evaluate the risk to human and animal health from the presence of antimicrobials in the environment;
- Support research into and the development of new tools for monitoring antimicrobials and microorganisms resistant against antimicrobials in the environment;
- Support the development of technologies that enable efficient and rapid degradation of antimicrobials in waste water and the environment to reduce the spread of AMR.

AMR Alliance First Industry Report



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amr INDUSTRY ALLIANCE

UNITED AGAINST ANTIMICROBIAL RESISTANCE

COMMON ANTIBIOTIC MANUFACTURING FRAMEWORK

The Antimicrobial Resistance (AMR) Roadmap Companies recognize and understand concerns raised by stakeholders regarding the presence of pharmaceuticals in the environment (PIE). The major source of pharmaceuticals entering into the environment is via patient excretion following use of medicine that is taken to prevent, cure or alleviate a medical condition. A comparatively smaller contribution to PIE stems from emissions from industry during manufacture of the pharmaceuticals.[1]

While the overall contribution of pharmaceutical manufacturing to PIE is relatively low, there is the potential for localized impacts to be created in cases where manufacturing emissions are inadequately managed. Ensuring the use of appropriate environmental risk management measures to adequately control manufacturing effluent emissions remains an important area of focus for the pharmaceutical industry and is an approach already in place in a number of companies.[2] We are aligned in our intent and are ready to build and share common practices.

Reports of active pharmaceutical ingredients (APIs) in water from pharmaceutical manufacturing indicate concentrations have reached potentially harmful levels when wastewater discharges are not sufficiently controlled at some facilities,[3] highlighting the importance of effective control of API emissions from manufacturing, both in production of the API itself and its formulation into drug products for patient use.

Environmental regulations pertaining to wastewater discharges from manufacturing, already generally apply to pharmaceutical production. However, many socially and environmentally responsible companies go beyond compliance with the basic regulatory requirements for chemical manufacturers (e.g., control of pH, biological oxygen demand, chemical oxygen demand)[4] and establish environmental protection goals to evaluate and reduce potential environmental risk from production of their products.

Currently, most programs focus on potential toxicity to aquatic species, upsets to wastewater treatment plants or potential toxicity in human drinking water. Emission limits, specifically for preventing antimicrobial resistance, are currently under development. The AMR Roadmap signatories are committed to achieving this goal and are reliant on the evolving science as a means to arriving at a consistent methodology for these limits by 2020.

The Antibiotic Manufacturing Framework provides a methodology and set of minimum requirements needed to conduct a site risk evaluation of both macro and micro controls in our supply chains. Company expectations, including this Framework, will be communicated within the AMR Roadmap signatory companies and their supply chains.

Joint Programming Initiative on Antimicrobial Resistance

24 EU and 6 non-EU members.

Aligns collaboration and coordination of research programmes and designs a future research strategy on AMR areas that can benefit from joint efforts across Europe. Those research priorities to be addressed over the next ten years through EU-wide investments and activities are outlined in the JPIAMR Strategic Research Agenda (SRA), launched in Brussels on April 3rd, 2014.

Priorities identified through a series of Scientific Advisory Board workshops and Stakeholder Consultations.

The mission for JPIAMR for the years 2020-2025 is stated as: "To join forces across nations by leading the alignment, coordination, and support to Antimicrobial Resistance One Health collaborative research and global policy activities". Working to address gaps in knowledge on AMR in the environment.

The overarching major goals are:

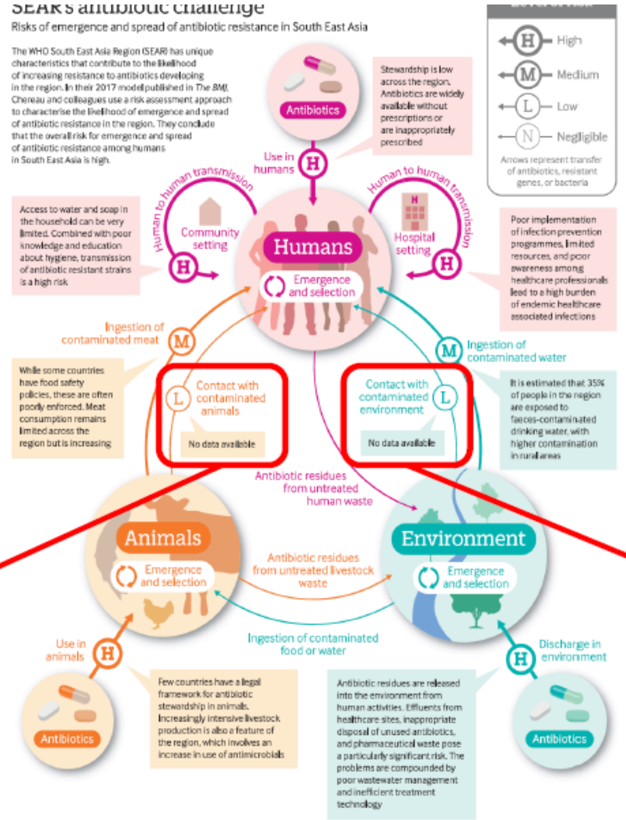
- To align national and international research programmes.
- To support and coordinate transformative research.
- To support and coordinate the JPIAMR Virtual Research Institute.
- To promote innovation and translation of research results.
- To bridge the gap between research and policy.

Lack of understanding of transmission pathways

The extent of transmission of AMR between humans and:

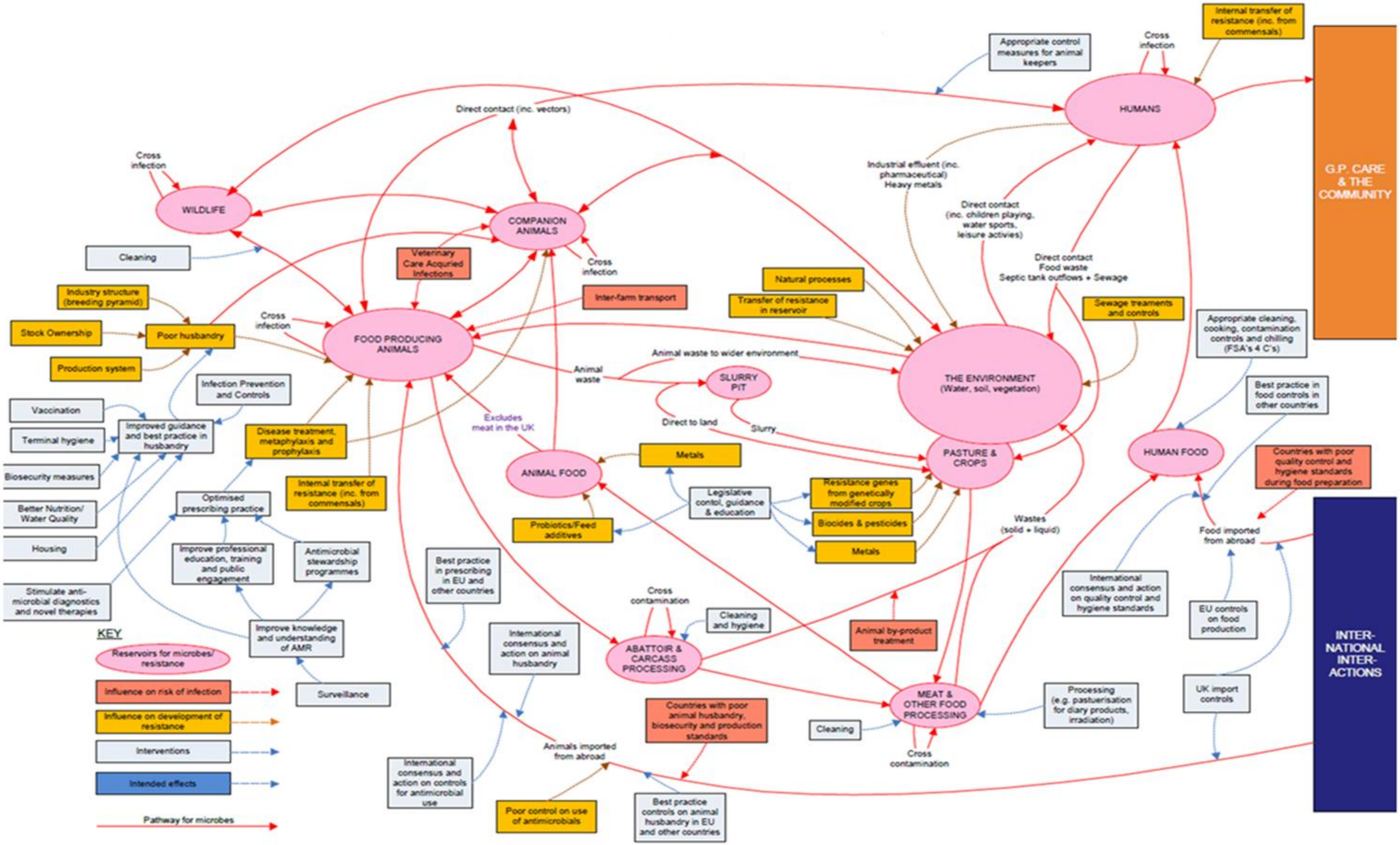
- the environment, and
- the animal sector

is still poorly measured and understood.



BMJ 2017; 358:j3393

http://dx.doi.org/10.1136/bmj.j3393



HUMANS
G.P. CARE & THE COMMUNITY
WILDLIFE
COMPANION ANIMALS
FOOD PRODUCING ANIMALS
THE ENVIRONMENT (Water, soil, vegetation)
SLURRY PIT
PASTURE & CROPS
HUMAN FOOD
ANIMAL FOOD
ABATTOIR & CARCASS PROCESSING
MEAT & OTHER FOOD PROCESSING
INTER-NATIONAL INTER-ACTIONS
Direct contact (inc. vectors)
Cross infection
Cross infection
Cross infection
Cross infection
Cross contamination
Cross contamination
Internal transfer of resistance (inc. from commensals)
Appropriate control measures for animal keepers
Industrial effluent (inc. pharmaceutical) Heavy metals
Direct contact (inc. children playing, water sports, leisure activies)
Direct contact Food waste Septic tank outflows + Sewage
Sewage treaments and controls
Natural processes
Transfer of resistance in reservoir
Appropriate cleaning, cooking, contamination controls and chilling (FSA's 4 C's)
Best practice in food controls in other countries
Countries with poor quality control and hygiene standards during food preparation
Food imported from abroad
EU controls on food production
UK import controls
International consensus and action on quality control and hygiene standards
Processing (e.g. pasteurisation for diary products, irradiation)
Cleaning
Cleaning and hygiene
Animal by-product treatment
Wastes (solid + liquid)
Metals
Metals
Legislative contol, guidance & education
Resistance genes from genetically modified crops
Biocides & pesticides
Probiotics/Feed additives
Animal waste to wider environment
Animal waste
Direct to land
Slurry
Excludes meat in the UK
Inter-farm transport
Veterinary Care Acquried Infections
Cleaning
Industry structure (breeding pyramid)
Stock Ownership
Poor husbandry
Production system
Infection Prevention and Controls
Vaccination
Terminal hygiene
Biosecurity measures
Better Nutrition/ Water Quality
Housing
Stimulate anti-microbial diagnostics and novel therapies
Improved guidance and best practice in husbandry
Disease treatment, metaphylaxis and prophylaxis
Internal transfer of resistance (inc. from commensals)
Optimised prescribing practice
Improve professional education, training and public engagement
Antimicrobial stewardship programmes
Improve knowledge and understanding of AMR
Surveillance
Best practice in prescribing in EU and other countries
International consensus and action on animal husbandry
International consensus and action on controls for antimicrobial use
Animals imported from abroad
Poor control on use of antimicrobials
Best practice controls on animal husbandry in EU and other countries
Countries with poor animal husbandry, biosecurity and production standards
KEY
Reservoirs for microbes/ resistance
Influence on risk of infection
Influence on development of resistance
Interventions
Intended effects
Pathway for microbes

Three major pathways for resistance-driving antimicrobials into the environment

1. Municipal and industrial wastewater;

2. Land spreading of animal manure and sewage sludge, and;

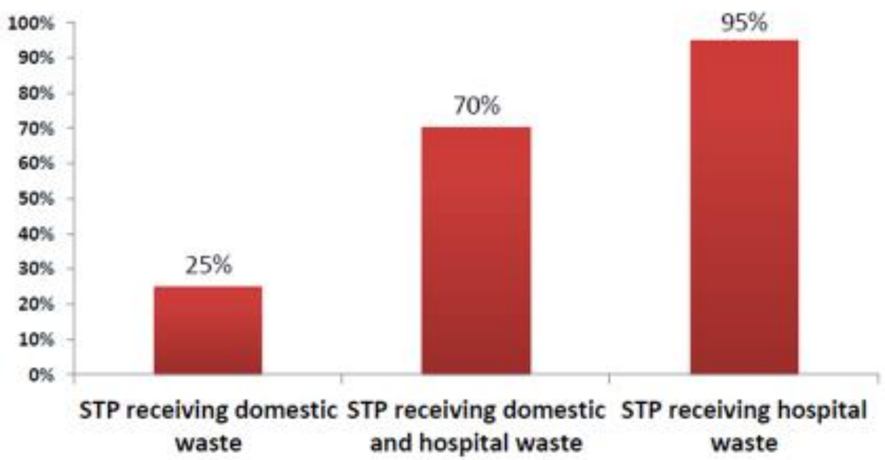
3. Aquaculture

Lets look at some example pathways

Examples taken from recent research

Inability to remove antibiotic resistant bacteria and genes in Sewage treatment Plants (STPs)

E. coli resistance to third-generation cephalosporins among STPs



Frontiers UNEP, 2017

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Antimicrobial residues in water bodies downstream of different sources

Location / source	Country	Antibiotic	Levels	
			PNEC *	Recorded
Hospital wastewater	Thailand	Sulfamethoxazole	16,000 ng/L	1,499 ng/L
Pharmaceutical/industrial wastewater	India	Ciprofloxacin	0.064 µg/L	**31 000 µg/L**
Municipal/community wastewater	India	Ampicillin		21 µg/L
STP/WWTP	Thailand Thailand Thailand	Ciprofloxacin Oxytetracycline Enrofloxacin Roxithromycin	0.064 µg/L 0.500 µg/L	**.20 µg/L** **3 µg/L** 1.6 µg/L Influent – 235 ng/L Effluent – 50 ng/L
Aquaculture	Thailand	Oxytetracycline	500 ng/L	180 ng/L
Water bodies	India	Ciprofloxacin	0.064 µg/L	**6500 µg/L**

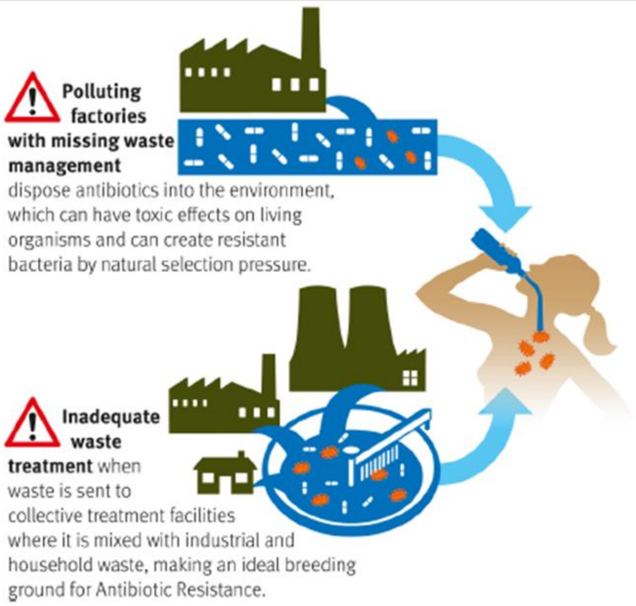
- PNEC = predicted no effect environmental concentrations
- Bengtsson-Palme J, Larsson DGJ. Concentrations of antibiotics predicted to select for resistant bacteria: Proposed limits for environmental regulation. *Environ Int* 2016;86:140-9. doi:10.1016/j. envint.2015.10.015

Antibiotic pollution associated with manufacturing is a significant cause for concern

"…some concentrations of pharmaceuticals we found in surface water samples were higher than the levels in patients that undergo treatment…"

Joakim Larsson, Professor in Environmental Pharmacology, University of Gothenburg

Irresponsible Manufacturing is contributing to AMR…



…but an issue we can tackle!

Reference indications from the final report of the AMR Review, May 2016

30,000 – 70,000 tonnes of waste with antimicrobial activity need appropriate treatment. This does not always happen.

~200 antibiotic factories globally. 80-90% are located in China and India.

Cost of treatment: 0.50 USD/kg API for appropriate waste water treatment.

Drivers outside EU; a comparison

Effluent from pharmaceuticals manufacturers contains extremely high levels of drugs including antibiotics; for example in India;

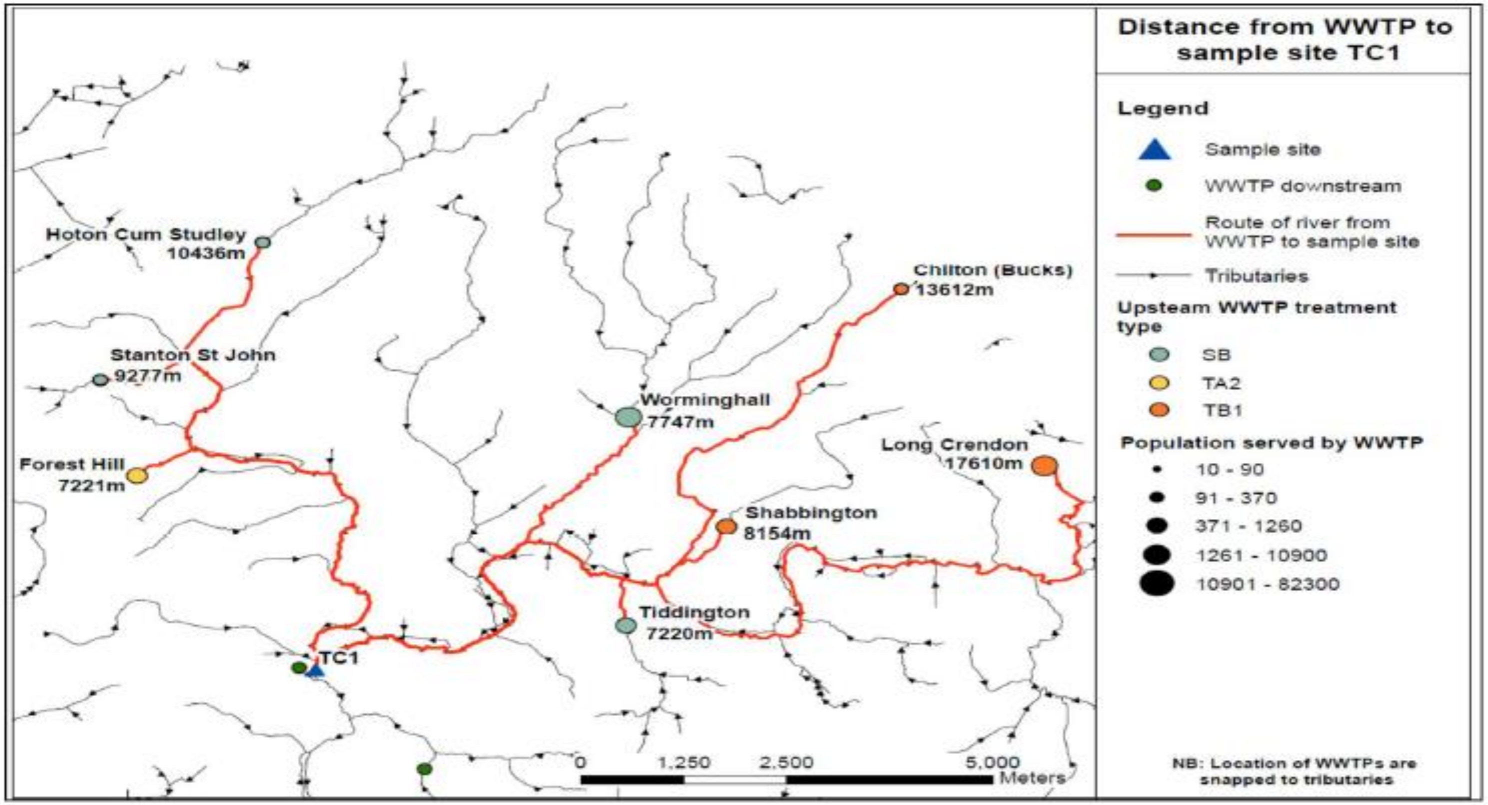
44 kg ciprofloxacin in one day in the effluent

e.g. In Sweden daily consumption is 9 kg total

1g/kg in river sediment

11 BILLION LITRES WASTE WATER DISCHARGED per day in UK alone

Thames at Wheatley



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

Table 3. Chemical properties and fate of selected veterinary antibiotics (modified from Beausse, 2004; Boxall et al., 2004; Tolls, 2001).

Antibiotic	Solubility in water	Log K_{ow}	Log K_{oc}	K_d	pK_a and chemical degradation	Mobility
	g/L			L/kg		
Lincomycin (hydrochloride salt)	freely	ND†	ND	ND	pK_a 7.6 In spiked soil 10 mg/kg undetectable after 11 wk and 80% lost after 7 wk	Immobile especially in high organic matter/clay soil based on manufacturer column tests.
Sulfathiazole	0.6	0.05	2.30	4.9	pK_{a1} 2, pK_{a2} 7.24	Medium mobility based on K_d
Sulfamethazine	1.5	0.89	1.78–2.32	0.6–3.1	pK_{a1} 2.65, pK_{a2} 7.65 Biodegradable but persistent in water phase	High to medium based on K_d
Tylosin	5	3.5	2.74–3.90	8.3–240	pK_a 7.1 Stable at pH 4 to 9, < pH 4 desmycosin is formed.	Low to immobile based on K_d
Virginiamycin	0.054– 0.080	1.5–1.7	2.7–2.8	ND	$T_{1/2}$: 87–173 d 89% inactivated within 18 d and undetectable after 84 d. Activity decreases rapidly in water and increasing temperature. Degrades under alkaline pH.	Immobile due to low water solubility, high lipophilicity and rapid inactivation in soil.
Tetracycline	1.7	−1.19	ND	>400–1620	pK_{a1}-3.30, pK_{a2}-7.68, pK_{a3}-9.69	Immobile based on K_d
Chlortetracycline	0.6	−0.62	ND	282–2608	$T_{1/2}$ in manure 1 wk at 37°C & > 20 d at 4° or 28°C 85% of CTC added to soil was recovered.	Immobile based on K_d
Oxytetracycline	1	−1.22	1.2–5.0	0.3–1030	pK_{a1} 3.27, pK_{a2} 7.32, pK_{a3} 9.11 Stable compared to CTC	Immobile based on K_d
Ciprofloxacin	30	0.4	4.78	430	pK_{a1} 5.9, pK_{a2} 8.89	Immobile based on K_d
Enrofloxacin	130	1.1	4.22–5.89	260–6310	pK_{a1} 6.27, pK_{a2} 8.3	Immobile based on K_d
Penicillin	4	1.87	ND	ND	pK_a 2.79 Unstable, rapidly degrades to penicilloic acid. $T_{1/2}$ < 7 d	Weakly sorbed to soils

† ND = not determined or not found in the literature reviewed.

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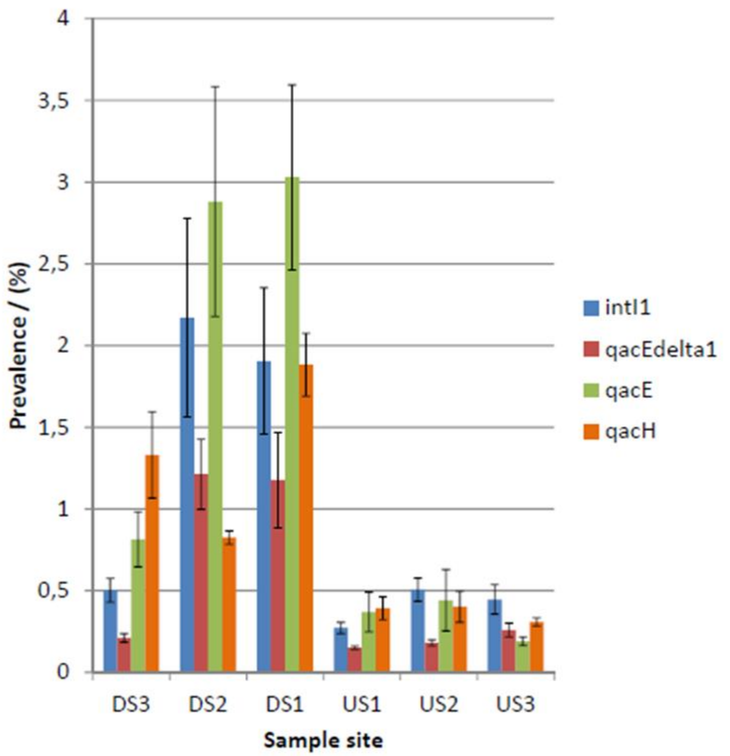
Integron prevalence upstream and downstream of a large WWTP



Amos, Zhang, Hawkey, Gaze, Wellington *et al.*, in prep.

Linus Sandegren. Selection of antibiotic resistance at very low antibiotic concentrations. Upsala Journal of Medical Sciences. 2014; 119: 103–107

- Rate with which resistance mutations (or acquisition of resistance genes through HGT) will arise is expected to be higher at low concentrations of antibiotics. Non-lethal concentrations of antibiotics mean that the bacterial population is not eradicated as with high levels of drug where only pre-existing resistant mutants will survive.

- Low levels of antibiotics have been shown to increase homologous recombination rates, stimulate horizontal gene transfer, and activate integrating genetic elements (29–34).

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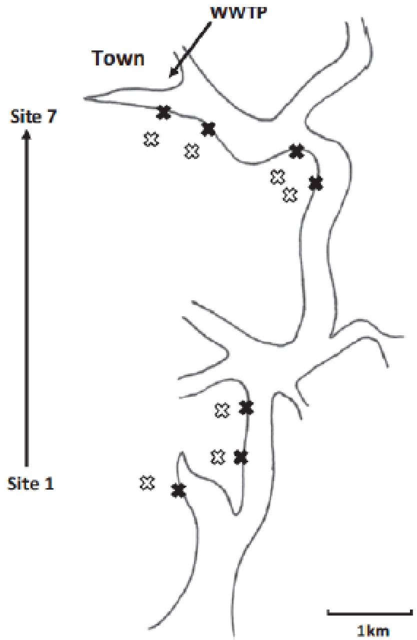
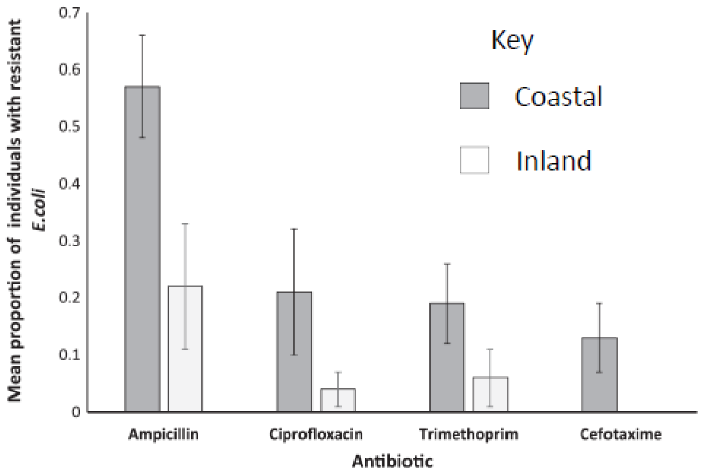
Mitigation costs?

- *Reduction of antibiotics to below the levels of PNECs*
- *Estimated cost for UK WWTPs alone £40Bn*
- *Excluding energy costs*

Indicators of AMR transmission in animals in coastal environments

Exposure to WW effluent increases risk of colonization by AMR bacteria





Furness et al. *Environmental research* 2017: 154 (28 – 34)

	Coastal (N=43)	Inland (N=31)	Risk ratio	P-value
Colonisation by AMR *E. coli*	34 (79%)	11 (35%)	2.23	0.0002

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Environment International 82 (2015) 92–100

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Human recreational exposure to antibiotic resistant bacteria in coastal bathing waters

Anne F.C. Leonard, Lihong Zhang, Andrew J. Balfour, Ruth Garside, William H. Gaze *

European Centre for Environment and Human Health, University of Exeter Medical School, Knowledge Spa, Royal Cornwall Hospital, Truro, Cornwall TR1 3HD, UK

We estimate that over 6 million recreational sessions occurred in 2012 in England and Wales that resulted in the ingestion of 3GC resistant *E. coli.*

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Environment International xxx (xxxx) xxx–xxx

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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,*]

[a] European Centre for Environment and Human Health, University of Exeter Medical School, Truro TR1 3HD, UK
[b] Institution of Microbiology and Infection, University of Birmingham, B15 2TT, UK
[c] National Institute for Health Research Collaboration for Leadership in Applied Health Research and Care South West Peninsula, University of Exeter Medical School,

Mr Ben Dover. Illustration by Martin Bell, Digital Species

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Heavy metals drive AMR development

Environmental Science & Technology

Article

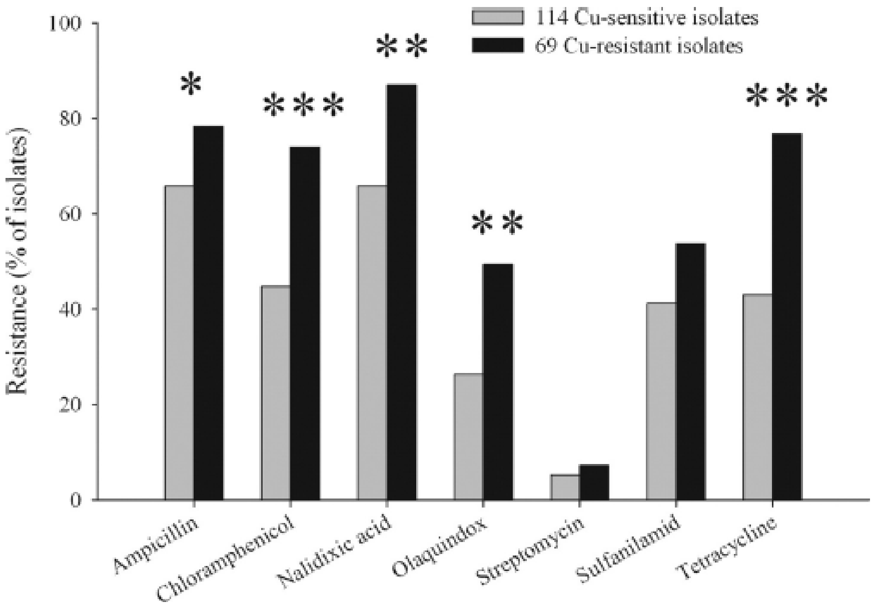
pubs.acs.org/est

Comparison of Metals and Tetracycline as Selective Agents for Development of Tetracycline Resistant Bacterial Communities in Agricultural Soil

Jianxiao Song,[†] Christopher Rensing,[‡] Peter E. Holm,[†] Marko Virta,[§] and Kristian K. Brandt[*,†]

[†]Department of Plant and Environmental Sciences, Faculty of Science, University of Copenhagen, Thorvaldsensvej 40, 1871 Frederiksberg, Denmark

Coupled Cu and antibiotic resistances have now been observed in 4 strain collections generated from Danish soils, but not in strain collection from 'pristine' permafrost



Frequency of resistance to the seven tested antibiotics among 183 bacterial isolates from control soil (94 isolates) and high-Cu soil (89 isolates), of which 114 isolates were Cu-sensitive and 69 Cu-resistant: The level of significance is indicated as follows: *** $P < 0.001$; ** $P < 0.01$; * $P < 0.05$.

Berg et al. *Environ. Sci. Technol.* **2010**, 44, 8724-8728.
DOI: 10.1021/es101798r

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Findings of the Danish study:

- Pig manure harbours a highly diverse antibiotic resistome that should be managed properly.
- Metals such as Cu and Zn may comprise stronger selective agents for antibiotic resistance than antibiotics at environmentally relevant soil concentrations.
- Metal-induced co-selection is probably a common phenomenon, but co-selection processes are hypothesized to become even more important in the future.
- Soil bacterial resistome dynamics is extremely complex and is affected by many interacting factors: concentrations of selecting agents (metals, antibiotics etc.), manure, and time.
- Conjugal plasmid transfer is a powerful vehicle for bacterial evolution and can be modulated by metal stress.

Environmental sources?

"During this cohort study, over 90% of the calves without any previous exposure to prophylactic or therapeutic antibiotics were colonised by CRB during the first year of life. Even though the exact origins of the genes responsible for antibiotic resistance found on this farm remain uncertain, the fact that these cattle have never been given antibiotics, nor has cefotaxime ever been used in animal husbandry, **suggests that these genes were acquired in the environment**."

frontiers
in Microbiology

ORIGINAL RESEARCH
published: 21 March 2018
doi: 10.3389/fmicb.2018.00500

Check for updates

Colonization Dynamics of Cefotaxime Resistant Bacteria in Beef Cattle Raised Without Cephalosporin Antibiotics

*Raies A. Mir[1,2], Thomas A. Weppelmann[3], Lin Teng[1,2], Alexander Kirpich[4], Mauricio A. Elzo[2], Joseph D. Driver[2] and Kwangcheol C. Jeong[1,2]**

[1] Emerging Pathogens Institute, University of Florida, Gainesville, FL, United States, [2] Department of Animal Sciences, Institute of Food and Agricultural Sciences, University of Florida, Gainesville, FL, United States, [3] Herbert Wertheim College of Medicine, Florida International University, Miami, FL, United States, [4] Department of Molecular Genetics and Microbiology, College of Medicine, University of Florida, Gainesville, FL, United States

The emergence of infections caused by antimicrobial resistant microorganisms (ARMs) is currently one of the most important challenges to public health and medicine. Though

Summary - Antimicrobial Resistance (AMR) (I)

- The Commission's 2011 Action Plan against AMR contained 12 actions for implementation by EU Member States
- The Commission published a Road Map with the operational objectives and the deadlines of the 12 Actions of the Action Plan.
- The Roadmap includes the development of the strategic approach to pollution of water by pharmaceutical substance.
- The Roadmap for the new Action Plan against AMR addresses, inter alia, the need for additional information on the presence of antibiotics in the environment, their potentially harmful levels and possible contribution to the development and maintenance of AMR.

Antimicrobial Resistance (AMR) (II)

- The Commission carried out an external evaluation of the AMR action plan, which informed the building of the new EU Action Plan with further policy developments and the need to expand and strengthen environmental action.
- The Commission continues working closely with EMA and the AMR network on strategic objectives in combatting AMR.

Possible solutions are extremely diverse (I)

- Some examples:
  - Improve knowledge by collection of data
  - Creation of database with existing environmental studies
  - Review of ERA guidelines
  - Prioritisation of substances
  - Inclusion of ERA in risk-benefit analysis of medicines for human use
  - Monograph system

Possible solutions are extremely diverse (II)

- More examples:

  - Control of emissions by production sites, hospitals
  - Inclusion in GMP
  - Improvement of waste water treatment
  - Increased collection of unused medicinal products
  - Inclusion in pharmacovigilance – Eco-pharmacovigilance

Why legislation is important for AMR

- Legislations serves to;
- Clarify roles and responsibilities (public/ private)
- Prohibit bad practices and foster good practices
- Provide agreed definitions that clarify interpretation – control, preventive use etc.
- Introduce regulatory mechanisms (licenses, permits, requirements)
- Introduce enforcement actions (sanctions)

Key knowledge Gaps

To be addressed in next section

AENOR INTERNACIONAL

6, Genova street. 28004. Madrid, SPAIN
Tel: +34 91 432 61 25
Mail: 20169607_amr@aenor.com
www.btsf-aenor.com

Better Training for Safer Food
BTSF

European Commission
Consumers, Health, Agriculture and Food Executive Agency
DRB A3/042
L-2920 Luxembourg

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