

# Drivers of AMR in Aquaculture and the Environment

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**Disclaimer:**

*I attend this conference as an individual expert, and do not represent the CVMP/EMA/ ERAWP/WHO. The views expressed here are my personal views, and may not be understood or quoted as being made on behalf of the CVMP/EMA/ ERAWP/WHO or reflecting the position of the CVMP/EMA/ERAWP/WHO.*

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# Antimicrobial Resistance (AMR) in the Environment

- Lack of current understanding of the issue
- Lack of current regulatory process
- Remains a global priority

# What is AMR:

- A natural phenomenon, but amplified by the environment
- Inappropriate or over-use of antibiotics 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 through direct contact
- Environmental spread caused by contaminated food and water systems and international trade and travel

# European Commission Perspective

- ..”Improving knowledge about the contribution of the environment on AMR by analysing inter-alia the presence of antibiotics in the environment, their potentially harmful levels (no mention of effects) and their possible contribution to the development of AMR, and adopting appropriate monitoring measures...”

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# European Medicines Agency

- EMA and EFSA Joint Scientific opinion on measures to reduce the need to use antimicrobial agents in animal husbandry in the European Union, and the resulting impacts on food safety (RONAFA) published in 24<sup>th</sup> January 2017.
- “...Although an environmental risk assessment is required as part of a MA application, this does not consider the effects of the excreted antimicrobial residues on bacteria in the environment, or the contribution of resistance genes that are excreted and their dissemination throughout the environment. The need to assess this risk is under consultation by CVMP, although further research into this complex topic is required.....” (Sarmah et al., 2006, Wellington et al., 2013)

# CVMP - Veterinary Medicines

- CVMP strategy on antimicrobials 2016-2020, published on 6 October 2016.
- The importance of the environment as a reservoir for antimicrobial resistance genes is now widely recognised ....”The CVMP acknowledges that further consideration should be given to the contribution of veterinary antimicrobials use in the environmental resistome.....”

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# CVMP - Veterinary Medicines



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

1 8 November 2018  
2 EMA/CVMP/ERA/632109/2014  
3 Committee for Medicinal Products for Veterinary Use (CVMP)

4 Reflection paper on antimicrobial resistance in the  
5 environment: considerations for current and future risk  
6 assessment of veterinary medicinal products  
7 Draft

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# 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.
- 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 legislation on environmental risks for antimicrobials



# One Health Approach

- Better addressing and understanding of 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
- Reinforce the role of the Scientific Committees to provide expertise on environment related AMR issues

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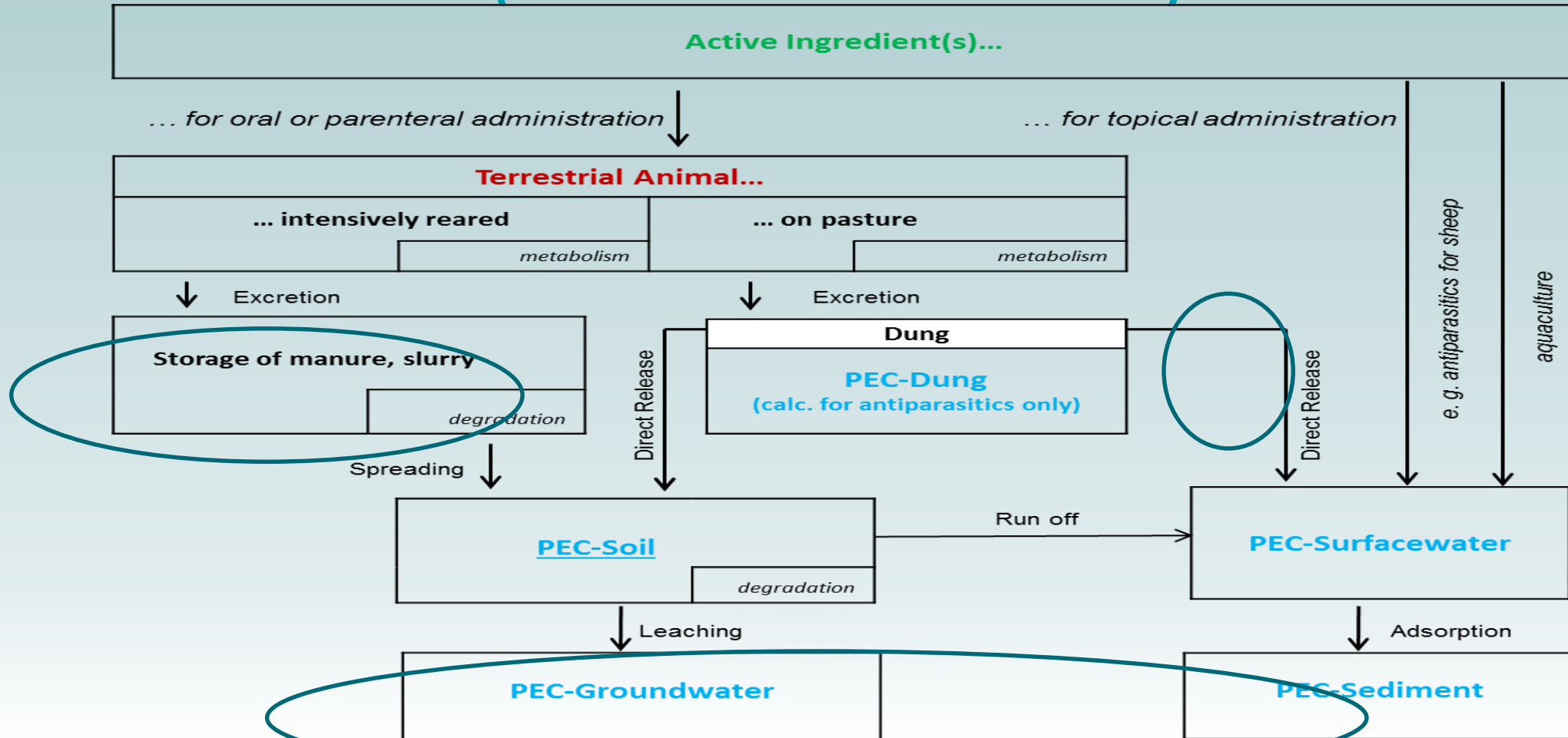


# Environmental Risk Assessment for VMPs

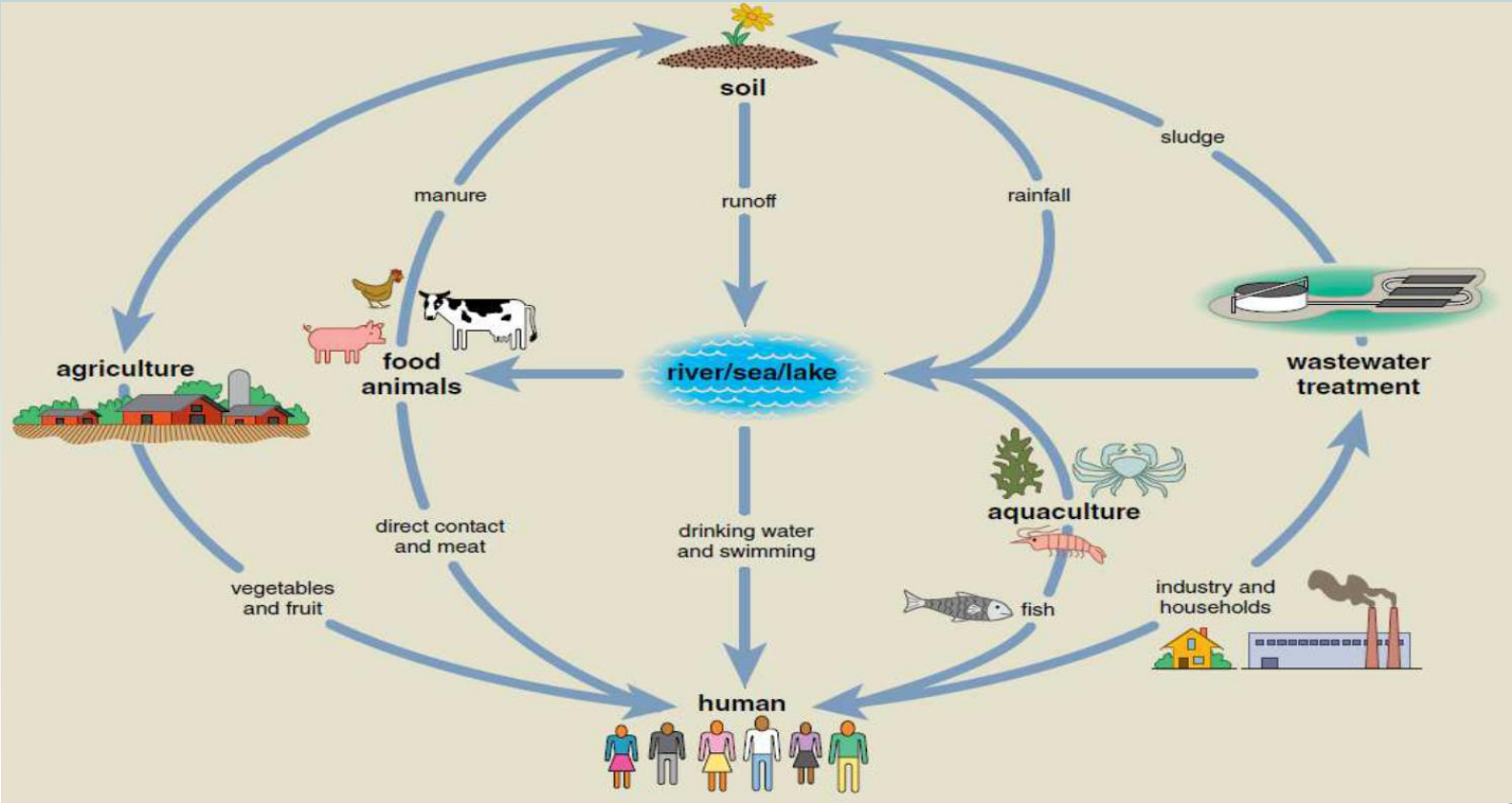
- Entry of VMPs into the environment through:
- Excretion of dung directly onto soil/into surface water
- Spreading of manure on arable land
- Direct/ Indirect entry into surface waters/ sediments in aquaculture
- Spillage at external application and/or direct exposure outdoors
- Contrast to human products where main entry via wastewater and STPs into surface water



# Exposure Pathways for Veterinary Medicines (and antibiotics)



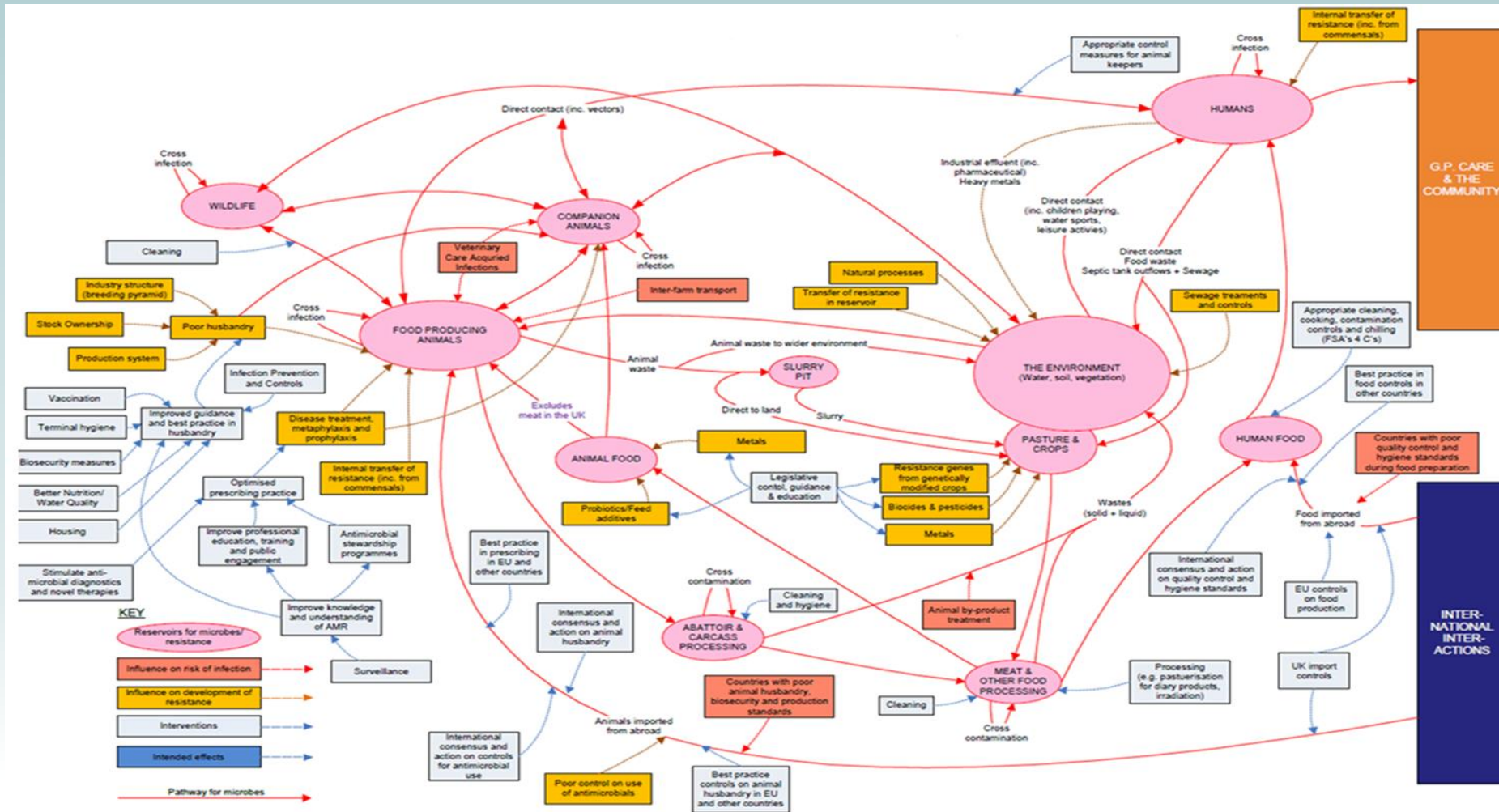
# Stylised Pathway Analysis



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# A complex web of connectivity



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Lets Look at Some Pathways

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# Waste Waters


- AMR transfer between (model) clinical and environmental compartments – a large and diverse fraction of a typical wastewater treatment plant microbial community – can uptake typical plasmids encoding relevant AMRs via HGT (in absence of any type of selection)
- Clearly shows the need to understand the environmental dimension (and processes) better to allow risk assessment/mitigation of AMR.

## Estimating the Transfer Range of Plasmids Encoding Antimicrobial Resistance in a Wastewater Treatment Plant Microbial Community

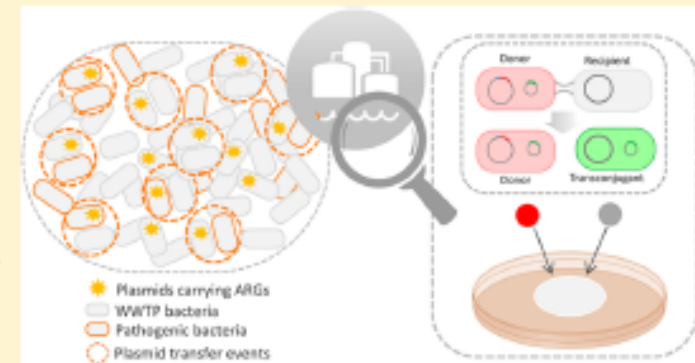
Liguan Li,<sup>†</sup> Amaud Dechesne,<sup>†</sup> Zhiming He,<sup>†</sup> Jonas Stenlökke Madsen,<sup>‡</sup> Joseph Nesme,<sup>‡</sup> Søren J. Sørensen,<sup>‡</sup> and Barth F. Smets<sup>\*,†</sup> 

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<sup>‡</sup>Department of Biology, University of Copenhagen, 2100 Copenhagen, Denmark

 Supporting Information

**ABSTRACT:** Wastewater treatment plants (WWTPs) have been suggested as reservoirs and sources of antibiotic resistance genes (ARGs) in the environment. In a WWTP ecosystem, human enteric and environmental bacteria are mixed and exposed to pharmaceutical residues, potentially favoring genetic exchange and thus ARG transmission. However, the contribution of microbial communities in WWTPs to ARG dissemination remains poorly understood. Here, we examined for the first time plasmid permissiveness of an activated sludge microbial community by utilizing an established fluorescent bioreporter system. The activated sludge microbial community was challenged in standardized



# Heavy Metals Drive AMR Development

**ENVIRONMENTAL**  
Science & Technology

Article

[pubs.acs.org/est](https://pubs.acs.org/est)

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

Jianxiao Song,<sup>†</sup> Christopher Rensing,<sup>‡</sup> Peter E. Holm,<sup>†</sup> Marko Virta,<sup>§</sup> and Kristian K. Brandt<sup>\*,†</sup> 

<sup>†</sup>Department of Plant and Environmental Sciences, Faculty of Science, University of Copenhagen, Thorvaldsensvej 40, 1871 Frederiksberg, Denmark

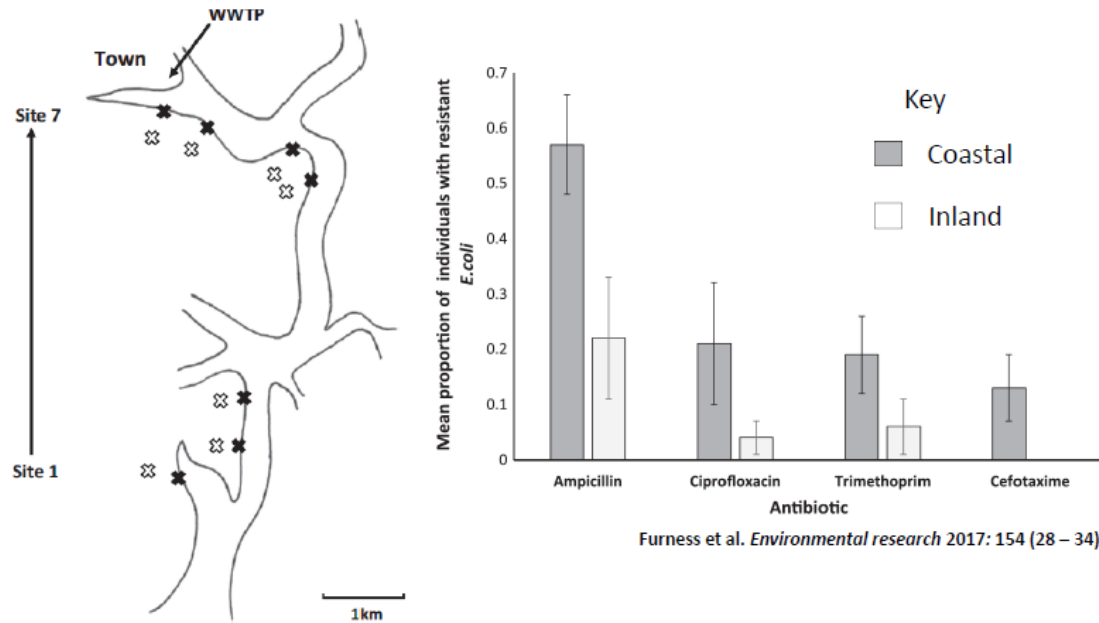
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# Indicators of AMR transmission in animals/ birds in wider environment

Exposure to WW effluent increases risk of colonization by AMR bacteria



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



# 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.**”

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

Raies A. Mir<sup>1,2</sup>, Thomas A. Weppelmann<sup>3</sup>, Lin Teng<sup>1,2</sup>, Alexander Kirpich<sup>4</sup>, Mauricio A. Elzo<sup>2</sup>, Joseph D. Driver<sup>2</sup> and Kwangcheol C. Jeong<sup>1,2\*</sup>

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

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# What next for the ERA?

- ...”It is argued that our inability to answer some of the fundamental questions about AMR in the environment is responsible for the lack of any significant environmental focus in existing AMR Action Plans...”
- ...”It is further argued that without inclusion or consideration of all the drivers and pathways of AMR into the environment, any AMR Action Plans are incomplete and at risk of not achieving the desired goals of ensuring and improving the efficacy of existing and future antibiotics...”
- (pers. comm. Singer)

# How To Address the Issue of AMR in the Environment

Some possible solutions:

- Improve knowledge by collection of data
- Creation of database within existing environmental studies
- Review of ERA guidelines
- Prioritisation of substances
- Inclusion of ERA of AMR in risk-benefit analysis

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# Possible Solutions (II)

More suggestions:

- Control/ understanding of emissions from farms
- Better education and training
- Improvement of waste water treatments
- Increased collection of unused medicinal products
- Inclusion in pharmacovigilance – Eco-pharmacovigilance

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# Risk Mitigation Measures

Mitigation measures should aim to reduce the input of antibiotics into environmental compartments.

For VMPs, this can be done by:

- reducing the quantities of antimicrobials prescribed/used (e.g., prudent use), and by;
- establishing effective barriers (e.g., avoid the release of antibiotic-treated animals into aquatic environments for a determined timespan)

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# Thank you

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