French Agency for Food, Environmental and Health Safety

# Challenges related to the environmental dimension of AMR

**Jean-Yves MADEC**

Antimicrobial resistance and virulence Unit, Head, Anses Lyon
Scientific Director on AMR, Anses
jean-yves.madec@anses.fr

# The story of NDM-1

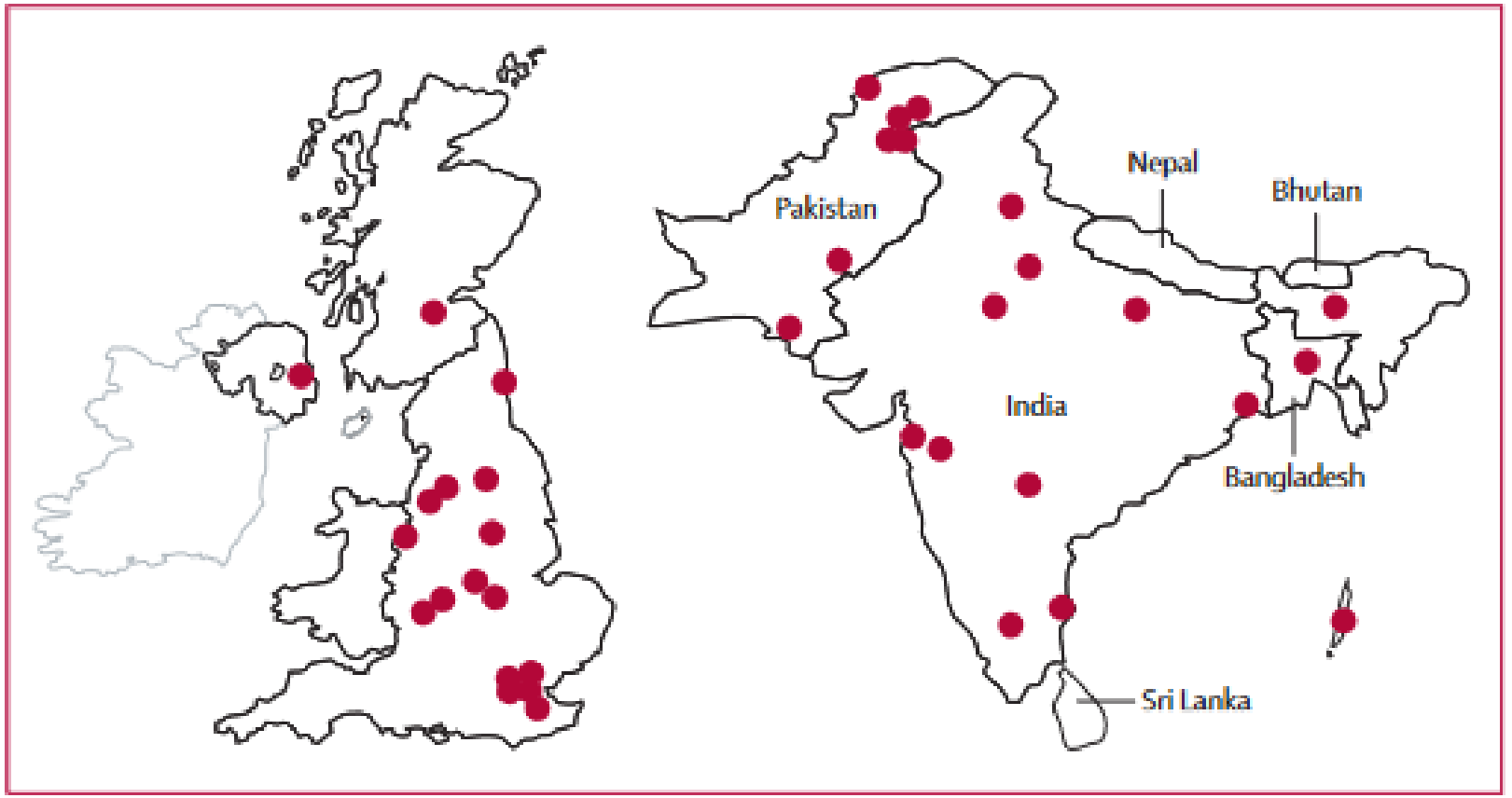



*Figure 5*: Distribution of NDM-1-producing Enterobacteriaceae strains in Bangladesh, Indian, Pakistan, and the UK

Kumarasamy et al, Lancet Infectious Dis 2010

New Delhi Metallo-Beta-Lactamase-1 (NDM-1)

Has emerged in 2008 in the Indian subcontinent

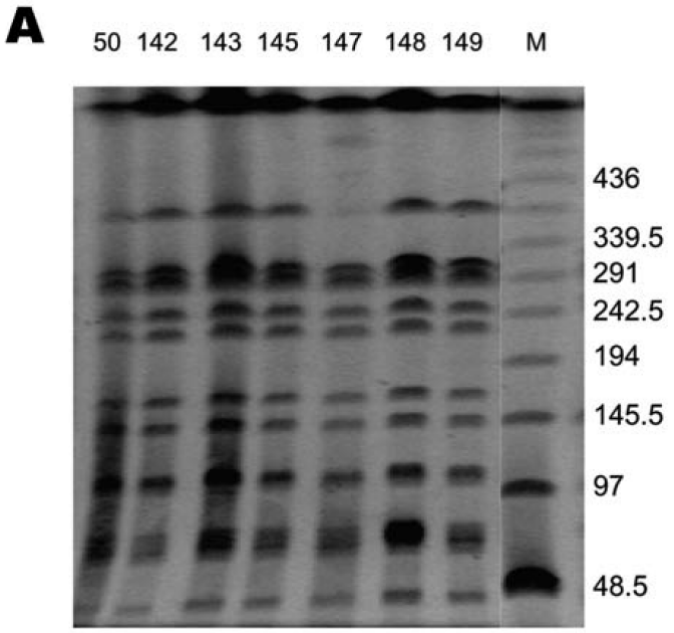
Spread to UK (medical tourism) and worldwide

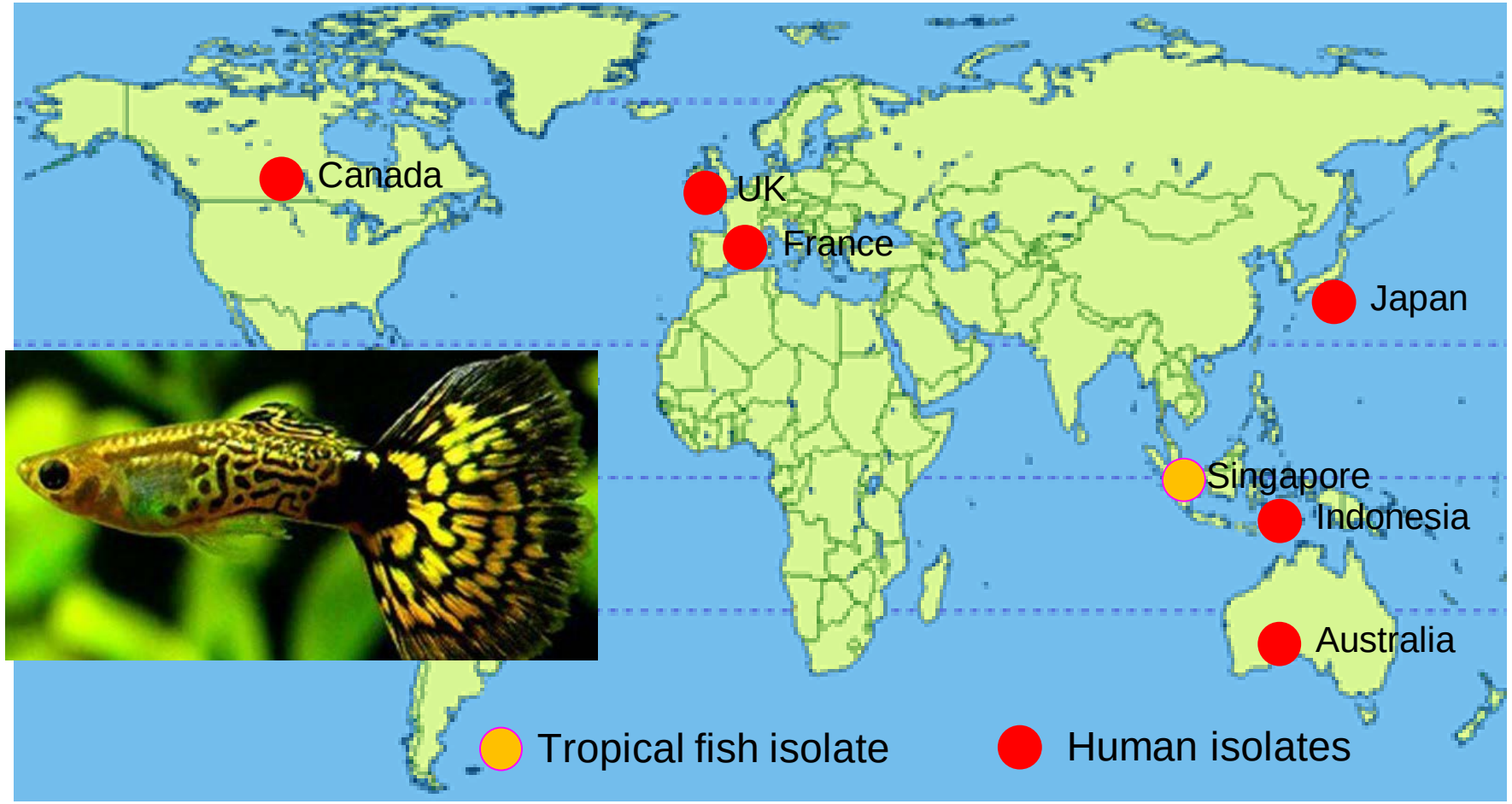
NDM-1 genes found in **surface and tap waters** in 2010 in India, and **in the environment** in Bangladesh

In 2019, NDM-1 found in **nutrient-rich Artic soil** of a remote Norwegian archipelago

# The story of *Poecilia reticulata* (guppy)

Aquariums as reservoirs of multidrug resistant *Salmonella* Paratyphi B




Levings et al, Emerg Infect Dis 2006

# The story of *mec*C-MRSA

**Meticillin-resistant *Staphylococcus aureus* with a novel *mecA* homologue in human and bovine populations in the UK and Denmark: a descriptive study**

2011

*Laura García-Álvarez, Matthew T G Holden, Heather Lindsay, Cerian R Webb, Derek F J Brown, Martin D Curran, Enid Walpole, Karen Brooks, Derek J Pickard, Christopher Teale, Julian Parkhill, Stephen D Bentley, Giles F Edwards, E Kirsty Girvan, Angela M Kearns, Bruno Pichon, Robert L R Hill, Anders Rhod Larsen, Robert L Skov, Sharon J Peacock, Duncan J Maskell, Mark A Holmes*

www.thelancet.com/Infection Published online June 3, 2011 DOI:10.1016/S1473-3099(11)70126-8

theguardian

## New strain of MRSA superbug may have spread from cattle to humans

Newly discovered MRSA strain found in cattle on 3% of dairy farms in the UK and caused 12 infections in people last year

**Ian Sample**, science correspondent
The Guardian, Friday 3 June 2011

# The story of *mec*C-MRSA

2013

**Detection of *mecC*-Positive *Staphylococcus aureus* (CC130-MRSA-XI) in Diseased European Hedgehogs (*Erinaceus europaeus*) in Sweden**

Stefan Monecke[1,2*], Dolores Gavier-Widen[3,4], Roland Mattsson[3], Lena Rangstrup-Christensen[3], Alexandros Lazaris[5], David C. Coleman[5], Anna C. Shore[5,6], Ralf Ehricht[1]

2017

High occurrence of *mecC*-MRSA in wild hedgehogs (*Erinaceus europaeus*) in Sweden

Björn Bengtsson[a,*], Lotta Persson[b], Kerstin Ekström[a], Helle Ericsson Unnerstad[a], Henrik Uhlhorn[a], Stefan Börjesson[a]

2019

European hedgehogs (*Erinaceus europaeus*) as a natural reservoir of methicillin-resistant *Staphylococcus aureus* carrying *mecC* in Denmark

Sophie Lund Rasmussen[1*], Jesper Larsen[2], Rien E. van Wijk[3], Owen R. Jones[4], Thomas Bjørneboe Berg[1,5], Øystein Angen[2], Anders Rhod Larsen[2]

# The story of *mec*C-MRSA

## Emergence of methicillin resistance predates the clinical use of antibiotics

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Received: 12 May 2021
Accepted: 18 November 2021
Published online: 5 January 2022
Open access
Check for updates

Jesper Larsen[1,55], Claire L. Raisen[2,55], Xiaoliang Ba[2], Nicholas J. Sadgrove[3], Guillermo F. Padilla-González[3], Monique S. J. Simmonds[3], Igor Loncaric[4], Heidrun Kerschner[5], Petra Apfalter[5], Rainer Hartl[5], Ariane Deplano[6], Stien Vandendriessche[6,46], Barbora Černá Bolfíková[7], Pavel Hulva[8,9], Maiken C. Arendrup[1], Rasmus K. Hare[1], Céline Barnadas[1,10], Marc Stegger[1], Raphael N. Sieber[1], Robert L. Skov[11], Andreas Petersen[1], Øystein Angen[1], Sophie L. Rasmussen[12,13], Carmen Espinosa-Gongora[14], Frank M. Aarestrup[15], Laura J. Lindholm[16], Suvi M. Nykäsenoja[17], Frederic Laurent[18], Karsten Becker[19], Birgit Walther[20,47], Corinna Kehrenberg[21], Christiane Cuny[22], Franziska Layer[22], Guido Werner[22], Wolfgang Witte[22], Ivonne Stamm[23], Paolo Moroni[24,48], Hannah J. Jørgensen[25], Hermínia de Lencastre[26,27], Emilia Cercenado[28], Fernando García-Garrote[28,49], Stefan Börjesson[29,50], Sara Hæggman[30], Vincent Perreten[31], Christopher J. Teale[32], Andrew S. Waller[33,51,52], Bruno Pichon[34], Martin D. Curran[35], Matthew J. Ellington[35,53], John J. Welch[36], Sharon J. Peacock[37], David J. Seilly[2], Fiona J. E. Morgan[2,54], Julian Parkhill[2], Nazreen F. Hadjirin[2], Jodi A. Lindsay[38], Matthew T. G. Holden[39], Giles F. Edwards[40], Geoffrey Foster[41], Gavin K. Paterson[42], Xavier Didelot[43], Mark A. Holmes[2,56], Ewan M. Harrison[37,44,45,56] & Anders R. Larsen[1,56]

*mec*C-MRSA was driven by natural selection by dermatophyte *Trichophyton erinacei* producing penicillin and colonizing hedgehogs

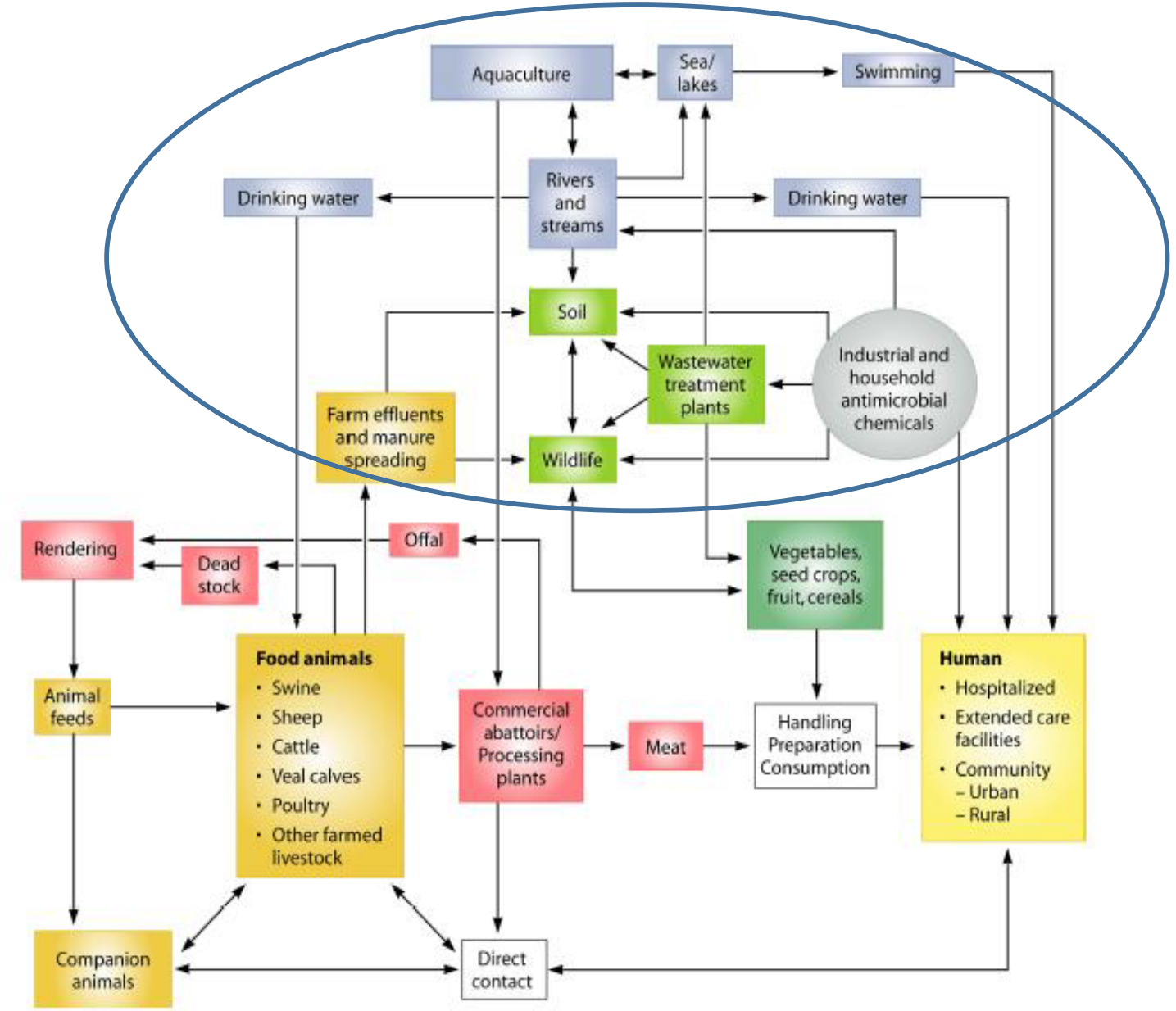
Larsen et al, Nature 2022

# AMR is One Health

Need for an integrated and holistic multi-sectoral approach

# AMR is One Health

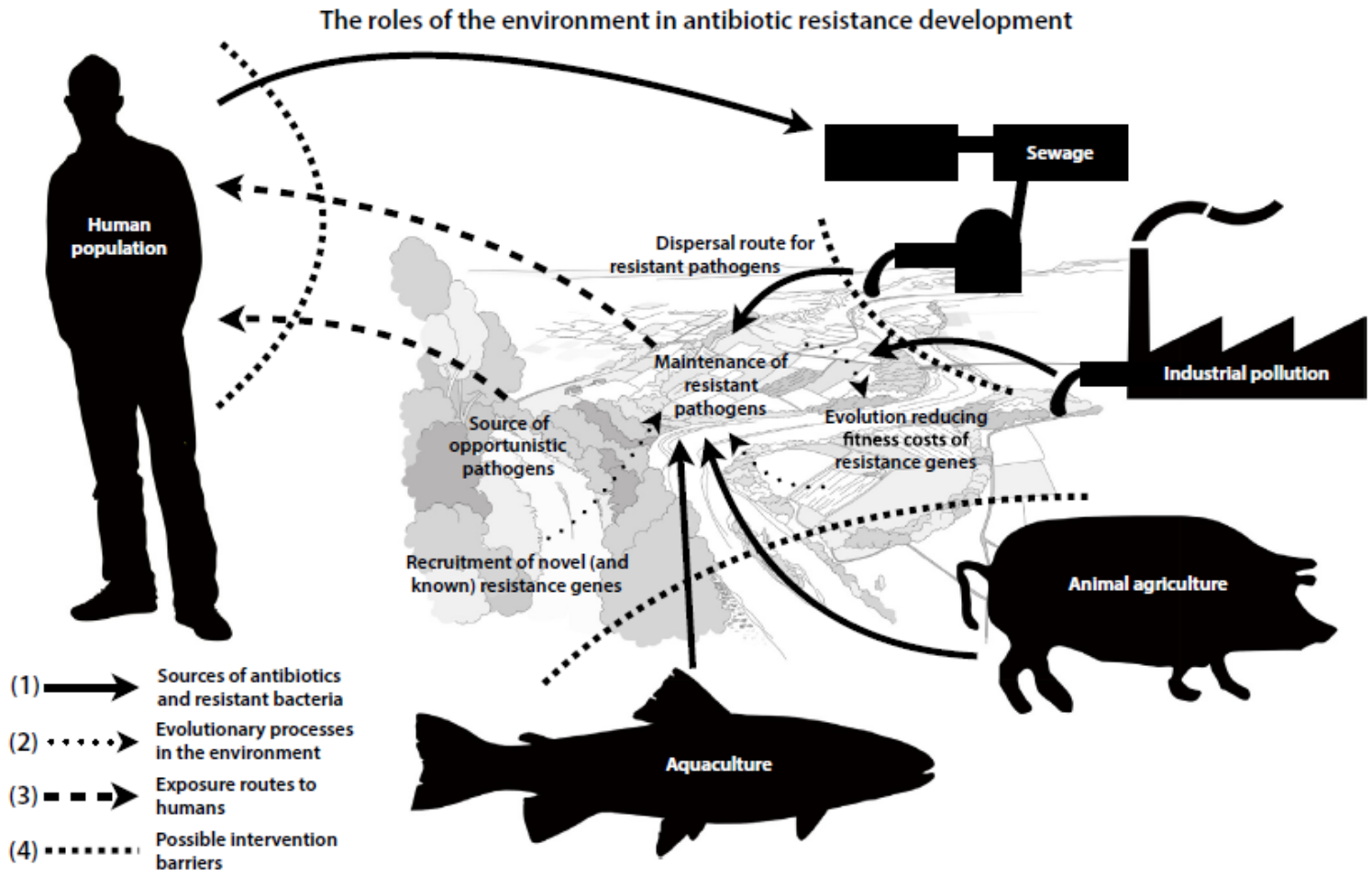
What definition for “the environment “ ?




The complex interplay between different sectors in the spread of antimicrobial resistance (from Davies & Davies, Microbiol Mol Biol Rev. 2010)

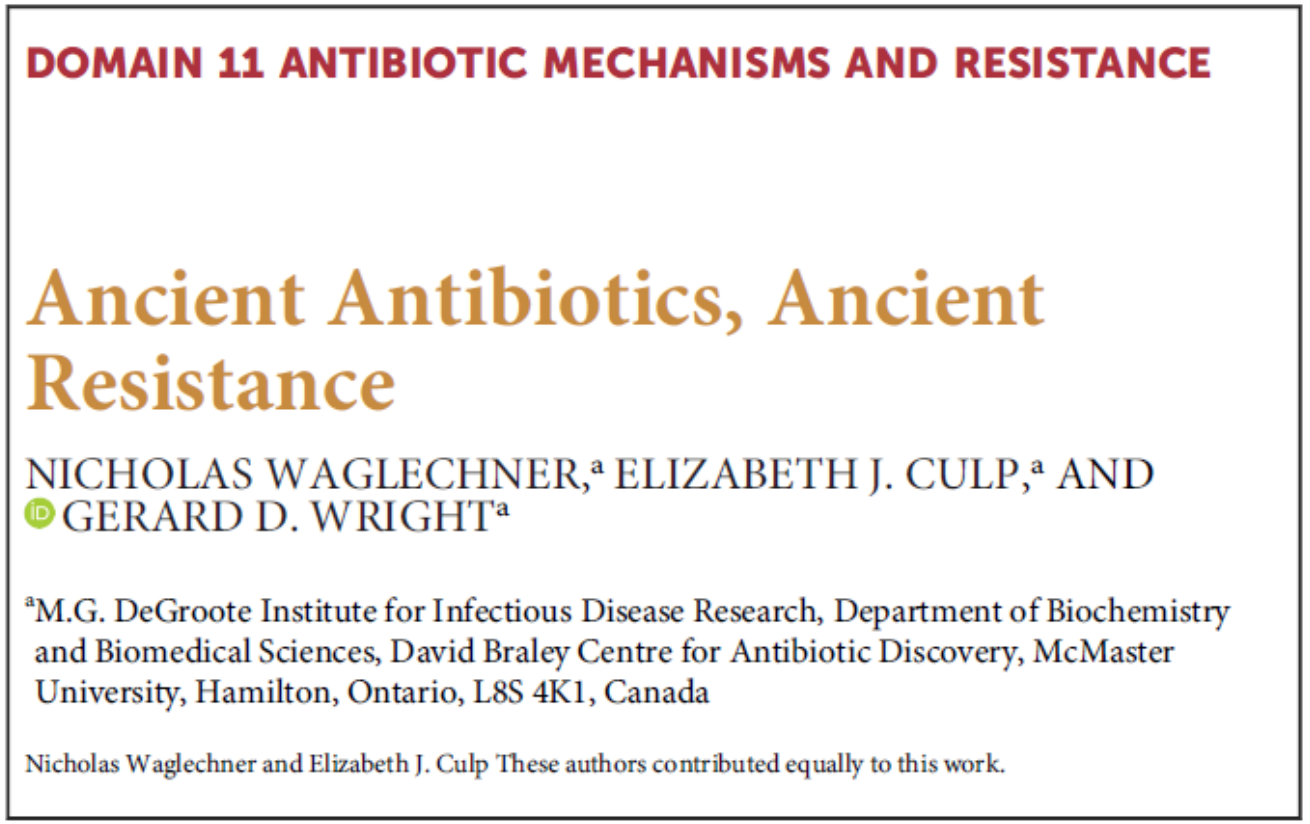
# Dual aspect of the environment

Source of …
Polluted by …




(from Larsson et al, Environment International, 2018)

# Antibiotics and AMR were present in the environment well before anthropogenic use



DOMAIN 11 ANTIBIOTIC MECHANISMS AND RESISTANCE

## Ancient Antibiotics, Ancient Resistance

NICHOLAS WAGLECHNER,[a] ELIZABETH J. CULP,[a] AND GERARD D. WRIGHT[a]

[a]M.G. DeGroote Institute for Infectious Disease Research, Department of Biochemistry and Biomedical Sciences, David Braley Centre for Antibiotic Discovery, McMaster University, Hamilton, Ontario, L8S 4K1, Canada

Nicholas Waglechner and Elizabeth J. Culp These authors contributed equally to this work.

The role of antibiotics in nature

What concentrations of antibiotics are bacteria exposed to in nature ?

Dating the origin of antibiotics

AMR in environmental isolates is far more diverse than that observed in pathogens

# Antibiotics and AMR were present in the environment well before anthropogenic use

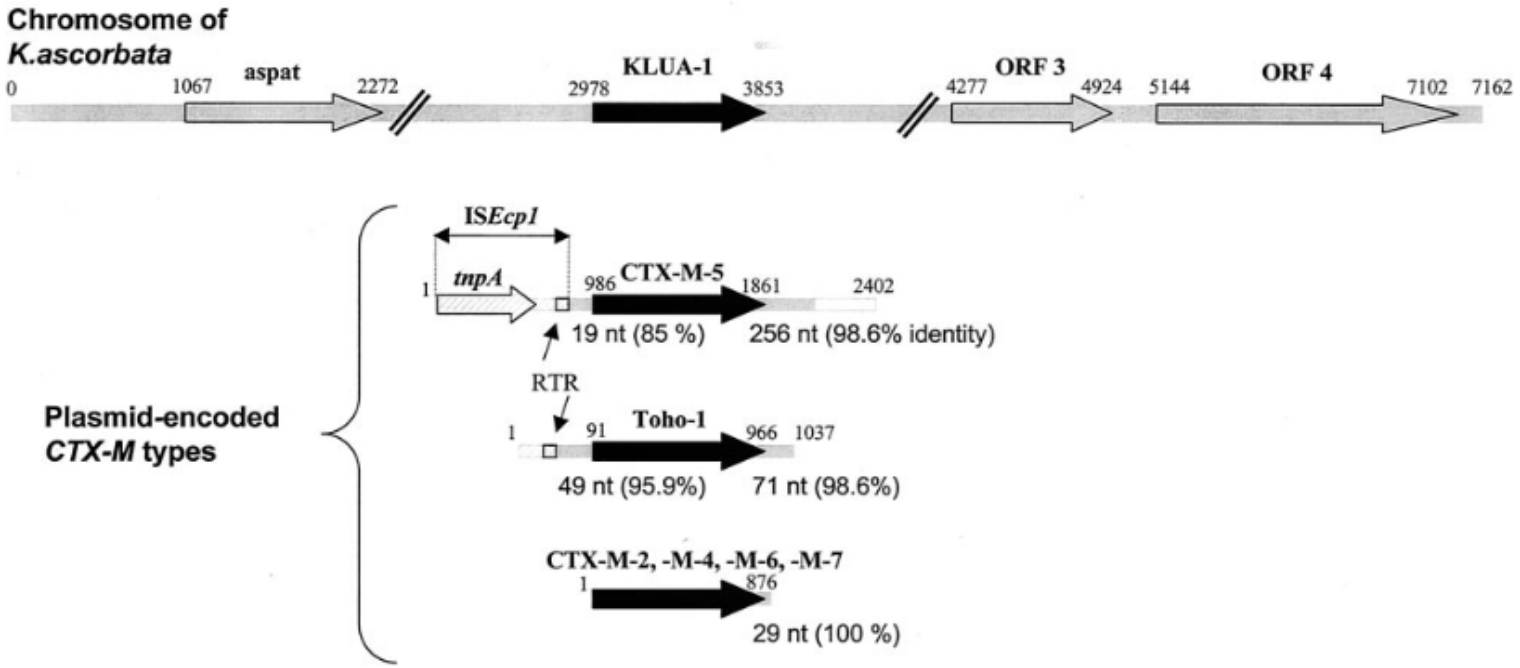
Antimicrobial peptide from frog skin

Rollins-Smith et al, Bioch Bioph Research Comm 2002

Teixobactin produced by *Eleftheria terrae*

Ling et al, Nature 2015

# AMR genes in clinics have progenitors in nature




ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Sept. 2002, p. 3045–3049
0066-4804/02/$04.00+0 DOI: 10.1128/AAC.46.9.3045–3049.2002

Vol. 46, No. 9

β-Lactamases of *Kluyvera ascorbata*, Probable Progenitors of Some Plasmid-Encoded CTX-M Types

Christel Humeniuk,[1] Guillaume Arlet,[2] Valerie Gautier,[2] Patrick Grimont,[3] Roger Labia,[4] and Alain Philippon[1]*

The epidemic spread of CTX-M beta-lactamases

AMR genes are actually pleiotropic in environmental isolates

It also questions the commonly held notion that AMR genes mobilization is in response to human antibiotic use

Coevolution of antibiotics and AMR genes in a co-evolutionary setting

# The pandemic expansion of CTX-M enzymes

Contents lists available at SciVerse ScienceDirect

International Journal of Medical Microbiology

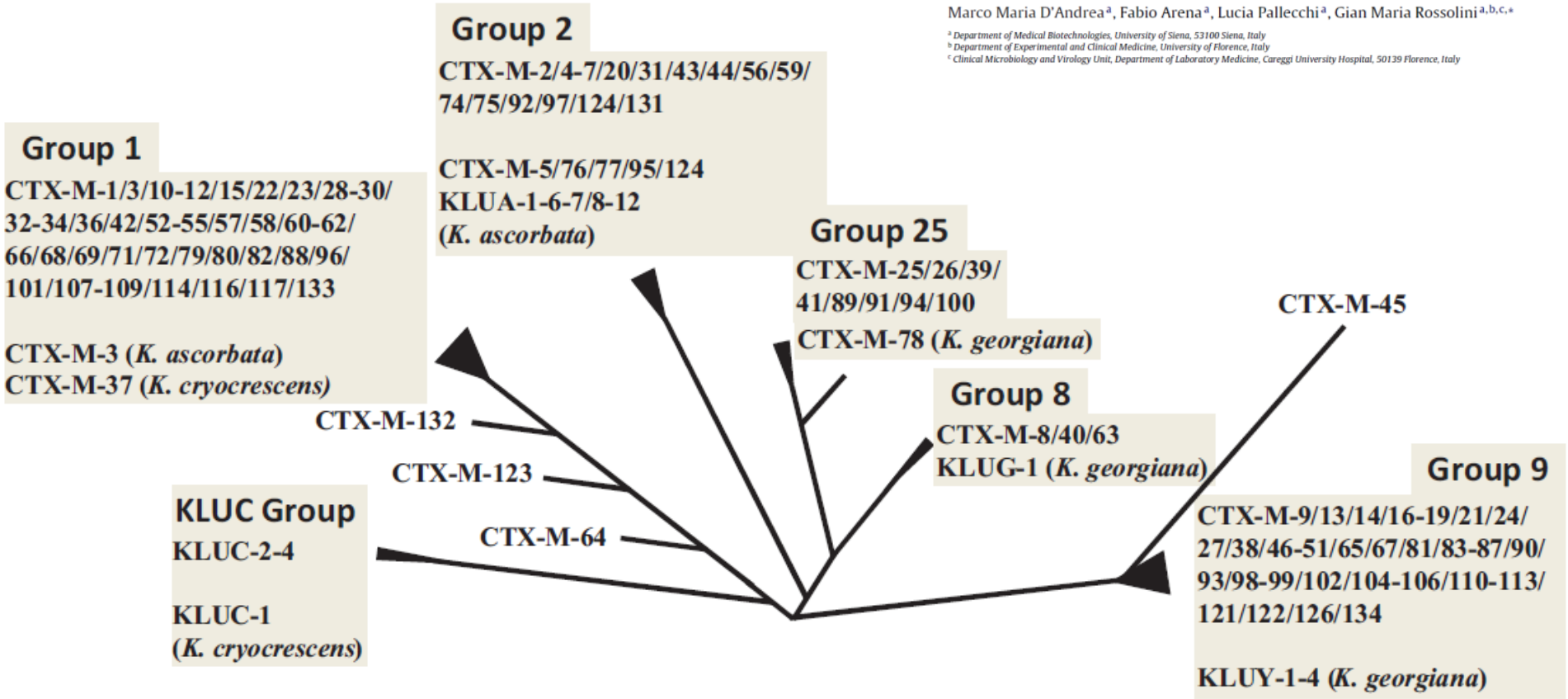
journal homepage: www.elsevier.com/locate/ijmm

Mini review

CTX-M-type β-lactamases: A successful story of antibiotic resistance

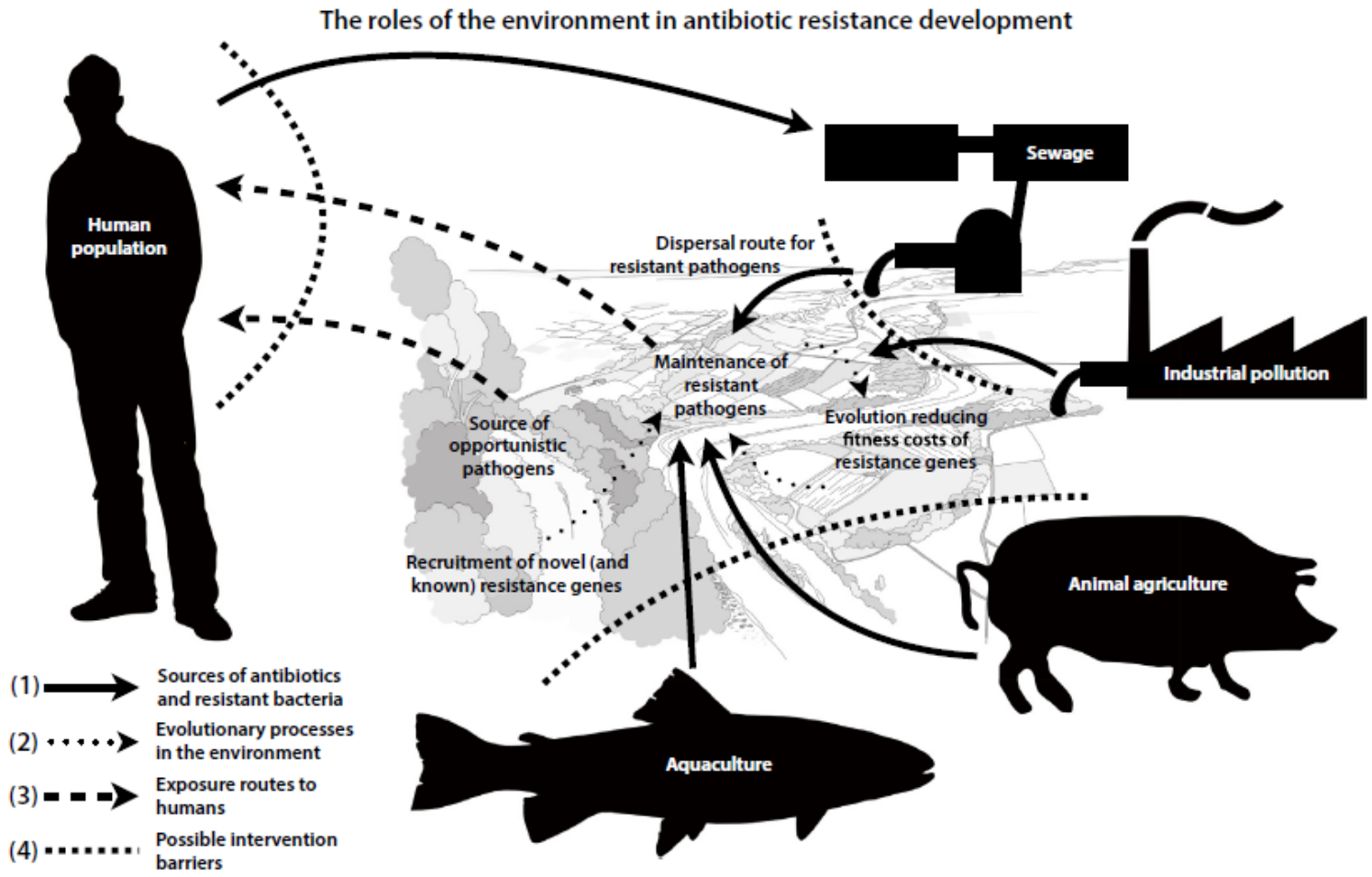
Marco Maria D'Andrea[a], Fabio Arena[a], Lucia Pallecchi[a], Gian Maria Rossolini[a,b,c,*]

[a] Department of Medical Biotechnologies, University of Siena, 53100 Siena, Italy
[b] Department of Experimental and Clinical Medicine, University of Florence, Italy
[c] Clinical Microbiology and Virology Unit, Department of Laboratory Medicine, Careggi University Hospital, 50139 Florence, Italy



# Dual aspect of the environment

Source of …
Polluted by …




(from Larsson et al, Environment International, 2018)

# Pollution with (anthropogenic-related) AMR

ESBL *E. coli*

***Hernandez PLoS One 2013***

***Blaak AEM 2014***

***Bréchet CID 2014***

***Hartmann Frontiers 2012***

***Mani AAC 2018***

***Yaici JAC 2017***

***Kola JAC 2012***

***Van Hoek IJFM 2015***

# Pollution with (anthropogenic-related) AMR


Bizerte Lagoon

**KPC-3-producing ST167 *Escherichia coli* from mussels bought at a retail market in Tunisia**

Yosra Mani[1]†, Wejdene Mansour[1,2]†, Hedi Mammeri[3–5], Erick Denamur[4–6], Estelle Saras[7], Noureddine Boujaafar[1,8], Olfa Bouallègue[1,9], Jean-Yves Madec[7]* and Marisa Haenni[7]

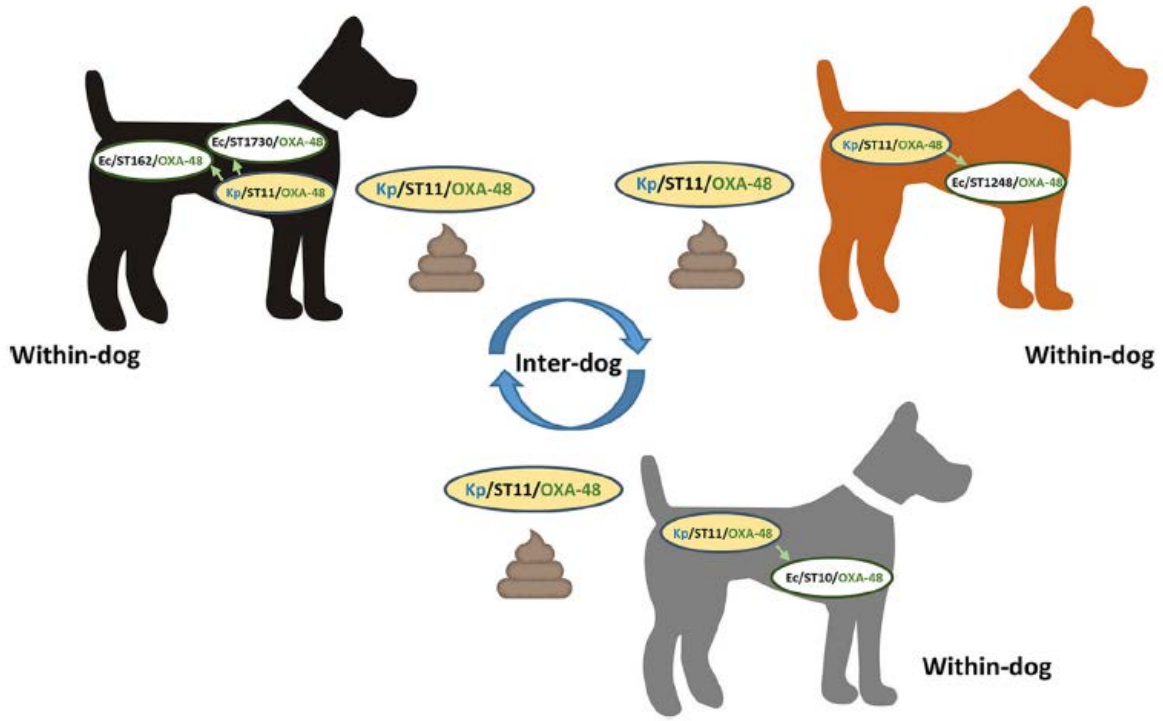
*JAC 2017*

**Spread of *bla*$_{\text{CTX-M-15}}$-Producing *Enterobacteriaceae* and OXA-23-Producing *Acinetobacter baumannii* Sequence Type 2 in Tunisian Seafood**

Yosra Mani,[a] Wejdene Mansour,[a,b] Agnese Lupo,[c] Estelle Saras,[c] Olfa Bouallègue,[a,d] Jean-Yves Madec,[c] Marisa Haenni[c]

*AAC 2018*

# Pollution with (anthropogenic-related) AMR




AMERICAN SOCIETY FOR MICROBIOLOGY | Microbiology Spectrum

*Microbiology Spectrum 2022*

## Spread of the *bla*$_{OXA-48}$/IncL Plasmid within and between Dogs in City Parks, France

Marisa Haenni,[a] Véronique Métayer,[a] Agnese Lupo,[a] Antoine Drapeau,[a] Jean-Yves Madec[a]

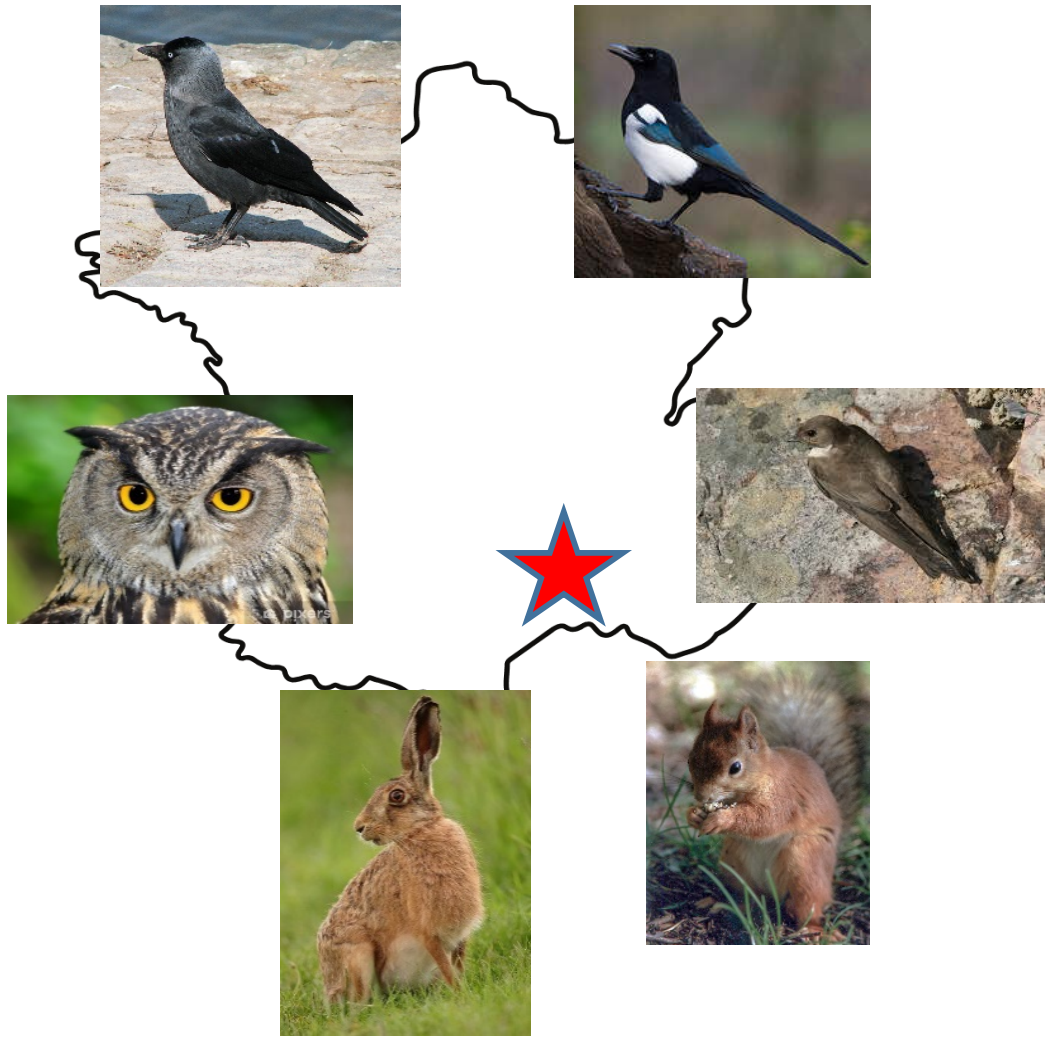
# Pollution with (anthropogenic-related) AMR

Over 400 wild animals at wildlife rescue center (France)

25% of animals acquired ESBL during their stay

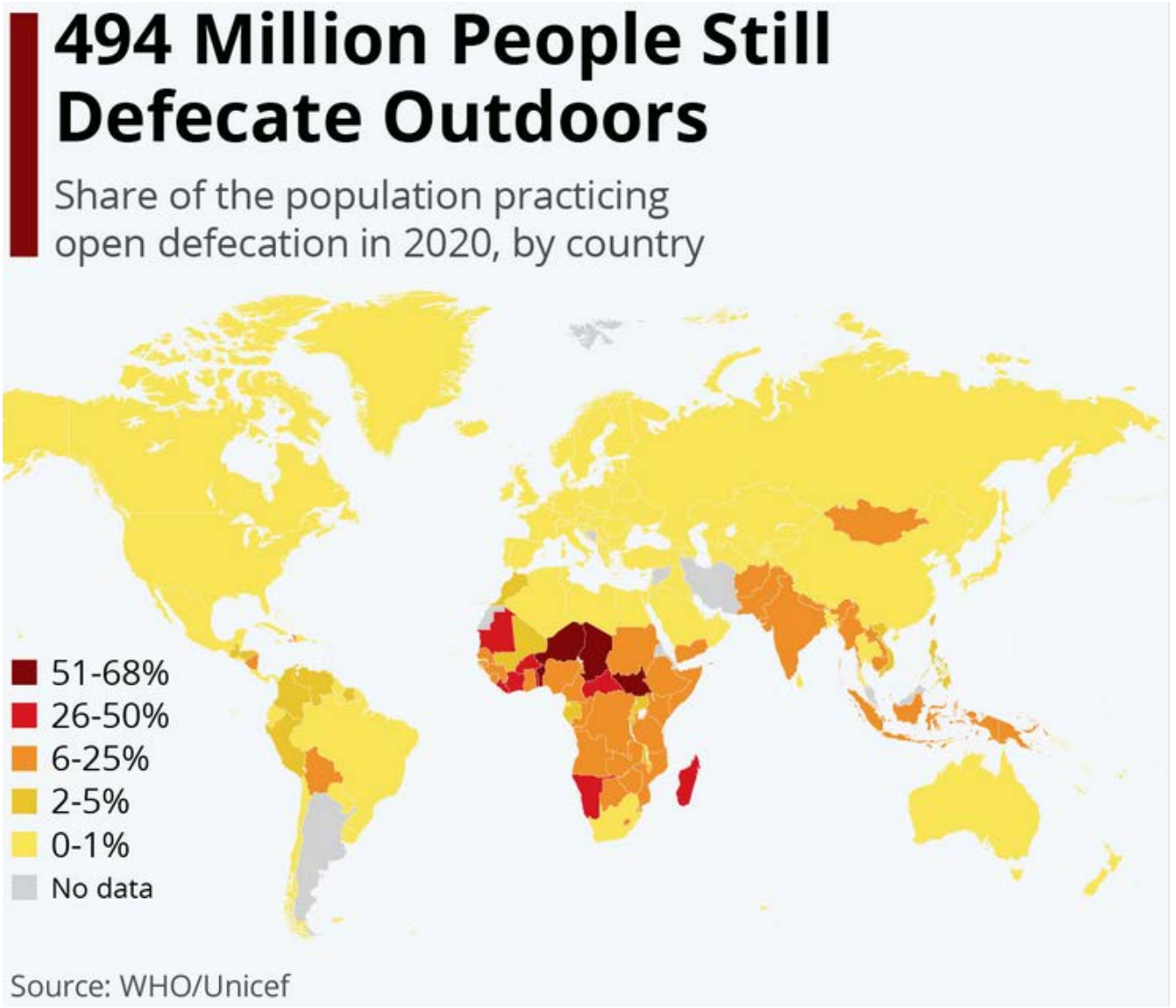
Limited number of ESBL clones, one dominant ESBL plasmid

It questions the ecological impact **when animals are released in nature** after recovery



*Haenni Frontiers 2020*

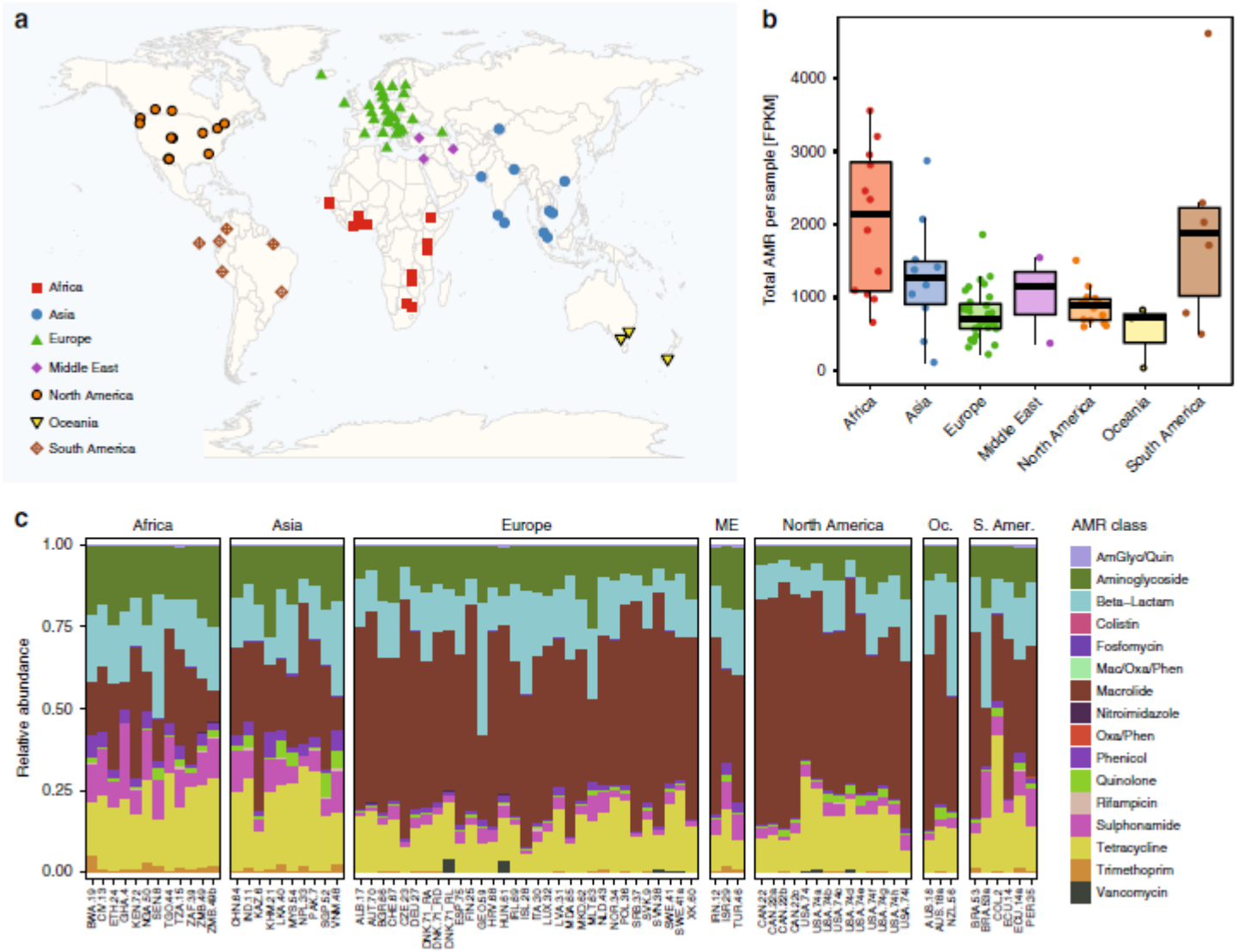
# Wastewater is a major issue for AMR



# Global monitoring of AMR in urban sewage

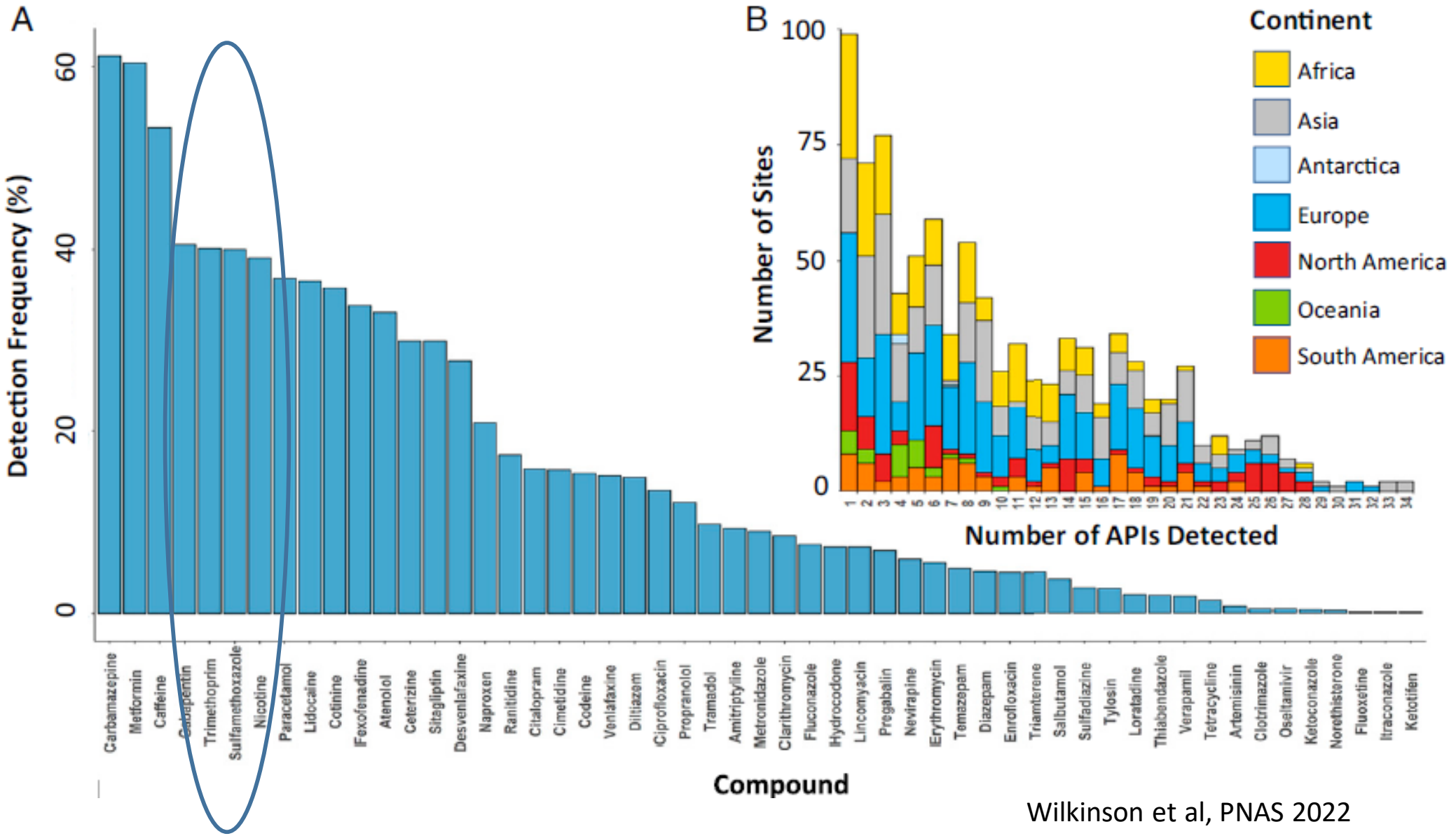
Metagenomic analyses

Differences observed between regions




Hendriksen et al, Nature Com, 2019

# Pollution with pharmaceuticals




Wilkinson et al, PNAS 2022

# Pollution with pharmaceuticals

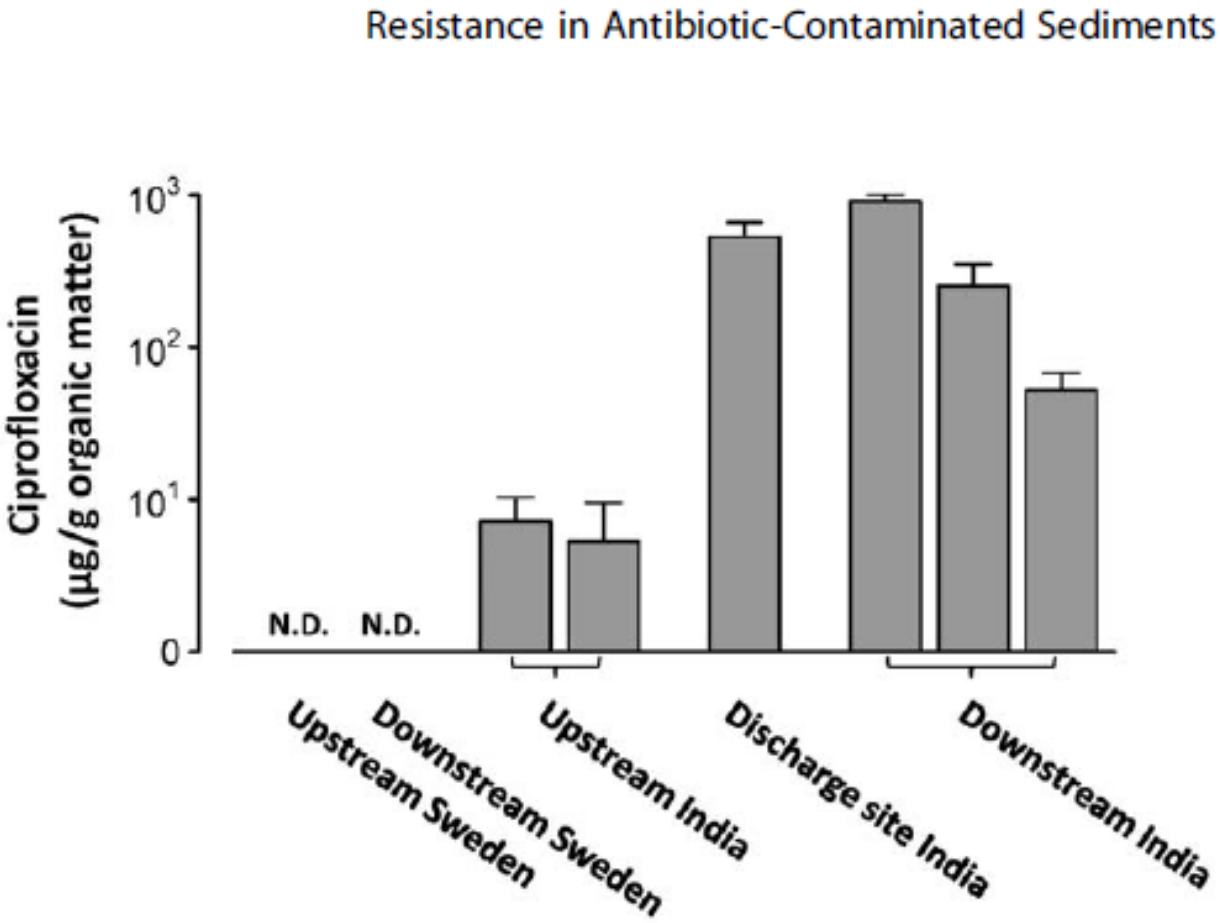

Sulfonamides dominant in sewage in tropical Asia

Sulfamethazine and oxytetracyclines dominant in livestock and aquaculture waste

12 tons/year of sulfamethoxazole is supplied from Mekong river to South China sea

Shimizu et al, Sci of the Total Environment, 2013

# Pollution with pharmaceuticals


Kristiansson et al, PLoS One, 2021

# Pollution with pharmaceuticals

Contents lists available at ScienceDirect

Environment International

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

Environmental contamination in a high-income country (France) by antibiotics, antibiotic-resistant bacteria, and antibiotic resistance genes: Status and possible causes

Marisa Haenni [a], Christophe Dagot [b], Olivier Chesneau [c], Delphine Bibbal [d], Jérôme Labanowski [e], Michèle Vialette [f], Damien Bouchard [g], Fabrice Martin-Laurent [h], Louisiane Calsat [i], Sylvie Nazaret [j], Fabienne Petit [k,l], Anne-Marie Pourcher [m], Anne Togola [n], Morgane Bachelot [o], Edward Topp [p], Didier Hocquet [q,r,*]

Fluoroquinolones and trimethoprime at higher risk of AMR selection

Effluents of wastewater treatment plants as a major source of antibiotics pollution

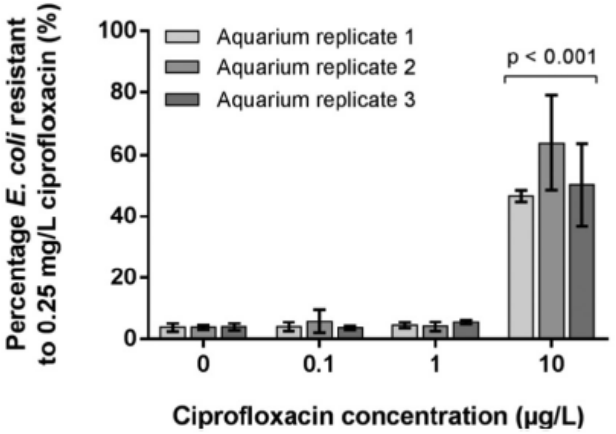
Proposed list of indicators

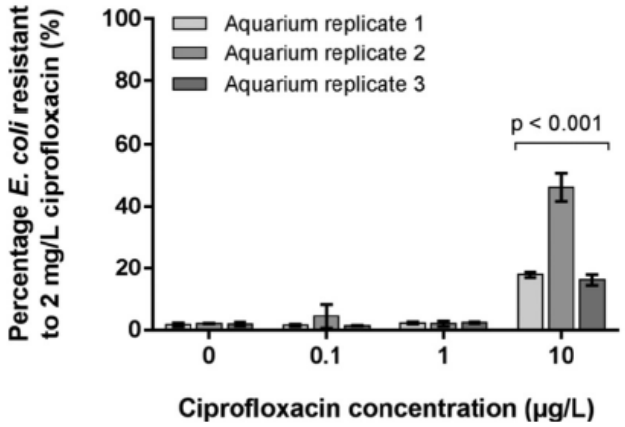
Harmonization of methods and sampling strategies

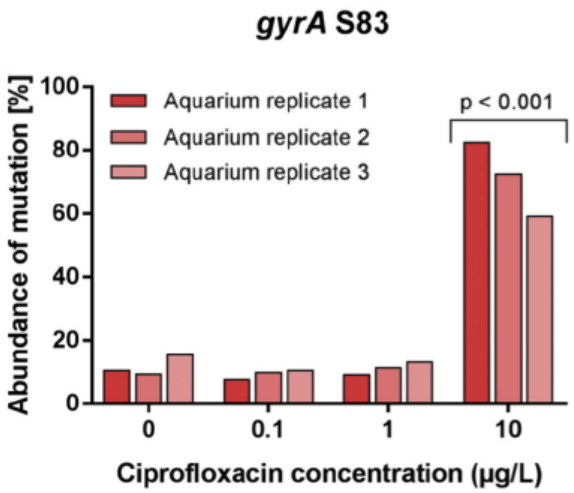
# Pollution with pharmaceuticals

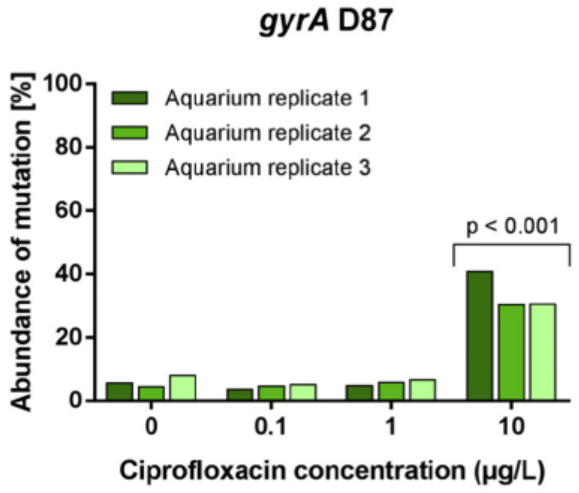
**What levels of antibiotics are needed to select AMR in complex bacterial communities ?**

CIP-R *E. coli* grown in complex aquatic biofilms with different CIP concentrations



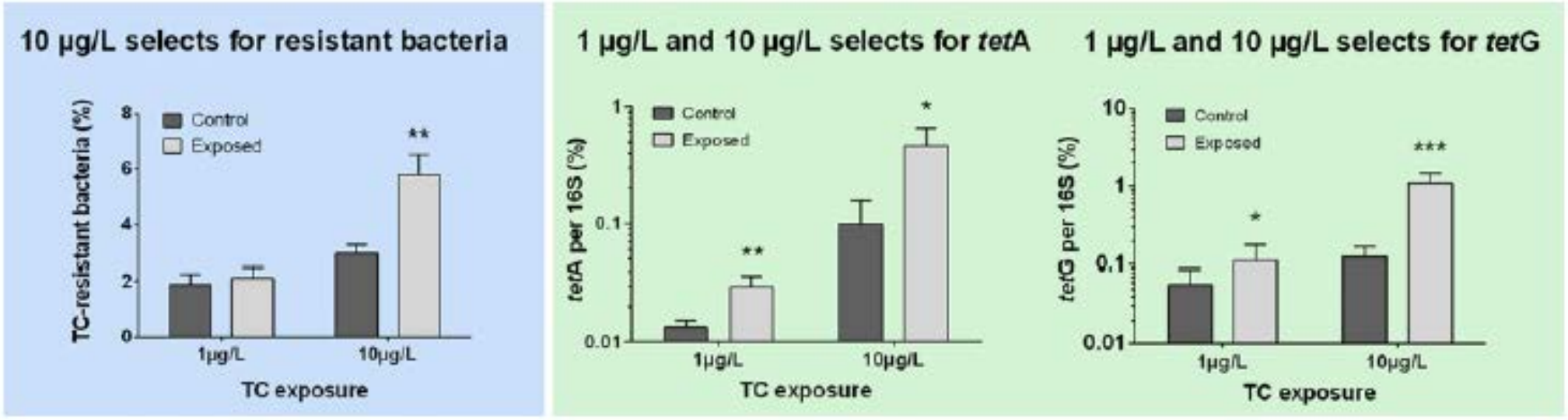




Kraupner et al, Environment International 2018

# Pollution with pharmaceuticals

**What levels of antibiotics are needed to select AMR in complex bacterial communities ?**

One μg/mL of tetracycline selects *tet*A and *tet*G genes in freshwater biofilms
Ten μg/mL of tetracycline selects for phenotypic resistance
Selective concentrations overlap with those reported in sewage treatment plants

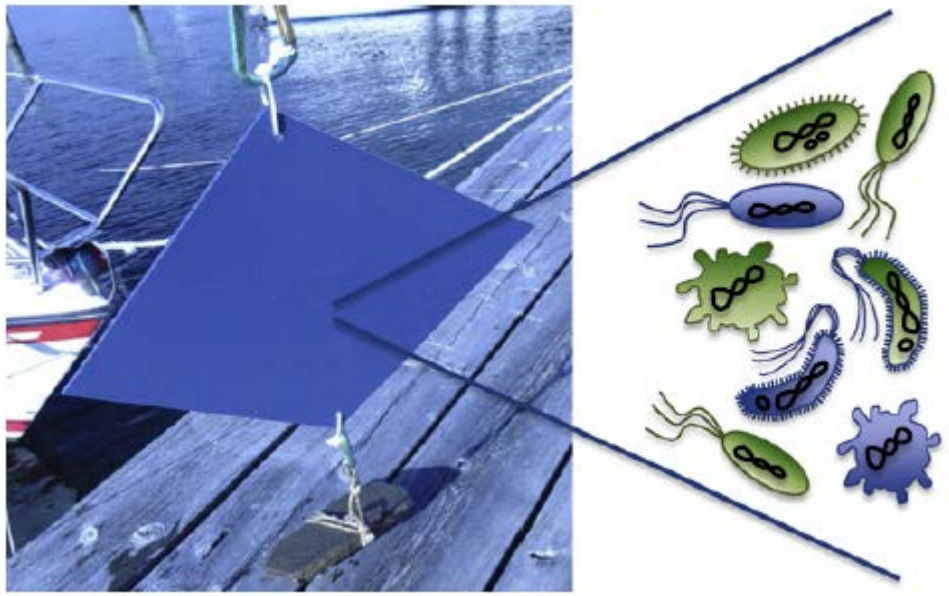


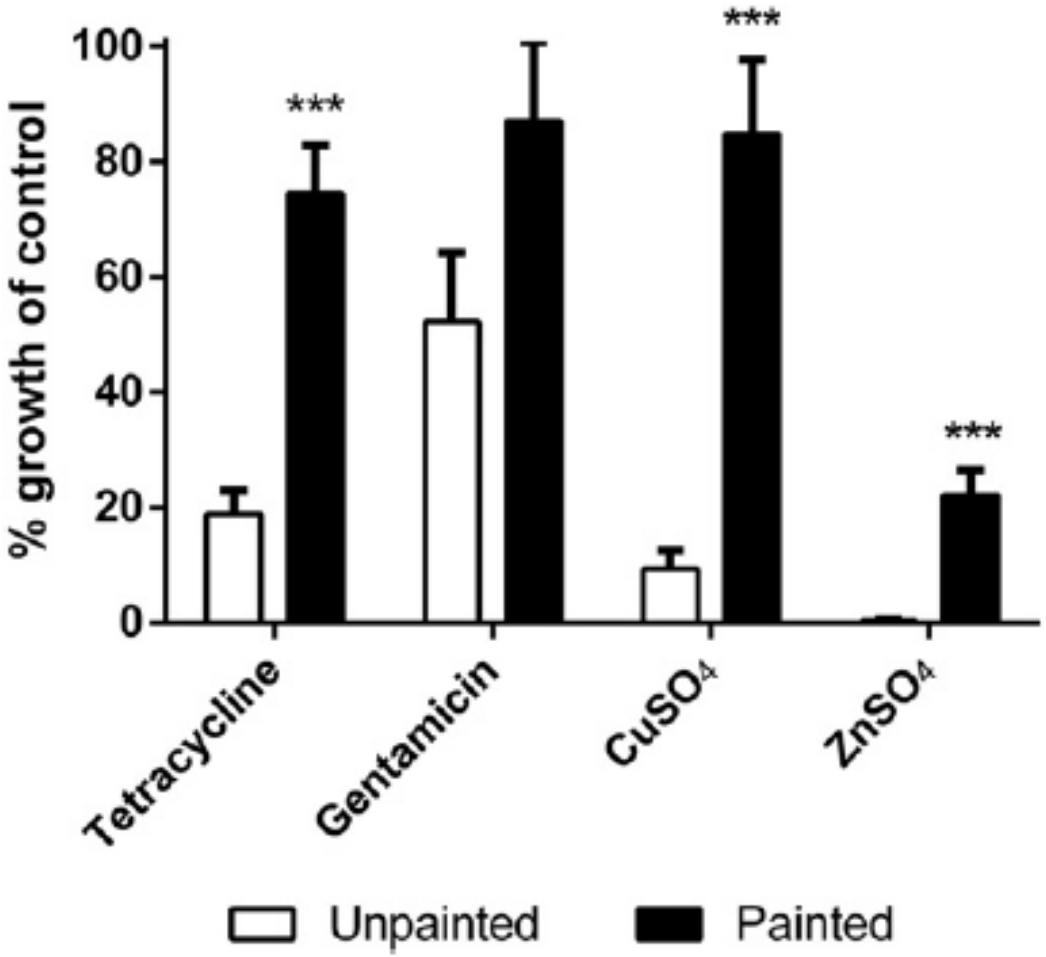

Lundström et al, Sci of the Total Environment 2016

# Pollution with pharmaceuticals

**Do other chemical compounds than antibiotics select AMR ?**

AMR from marine biofilms on **painted** and unpainted surfaces



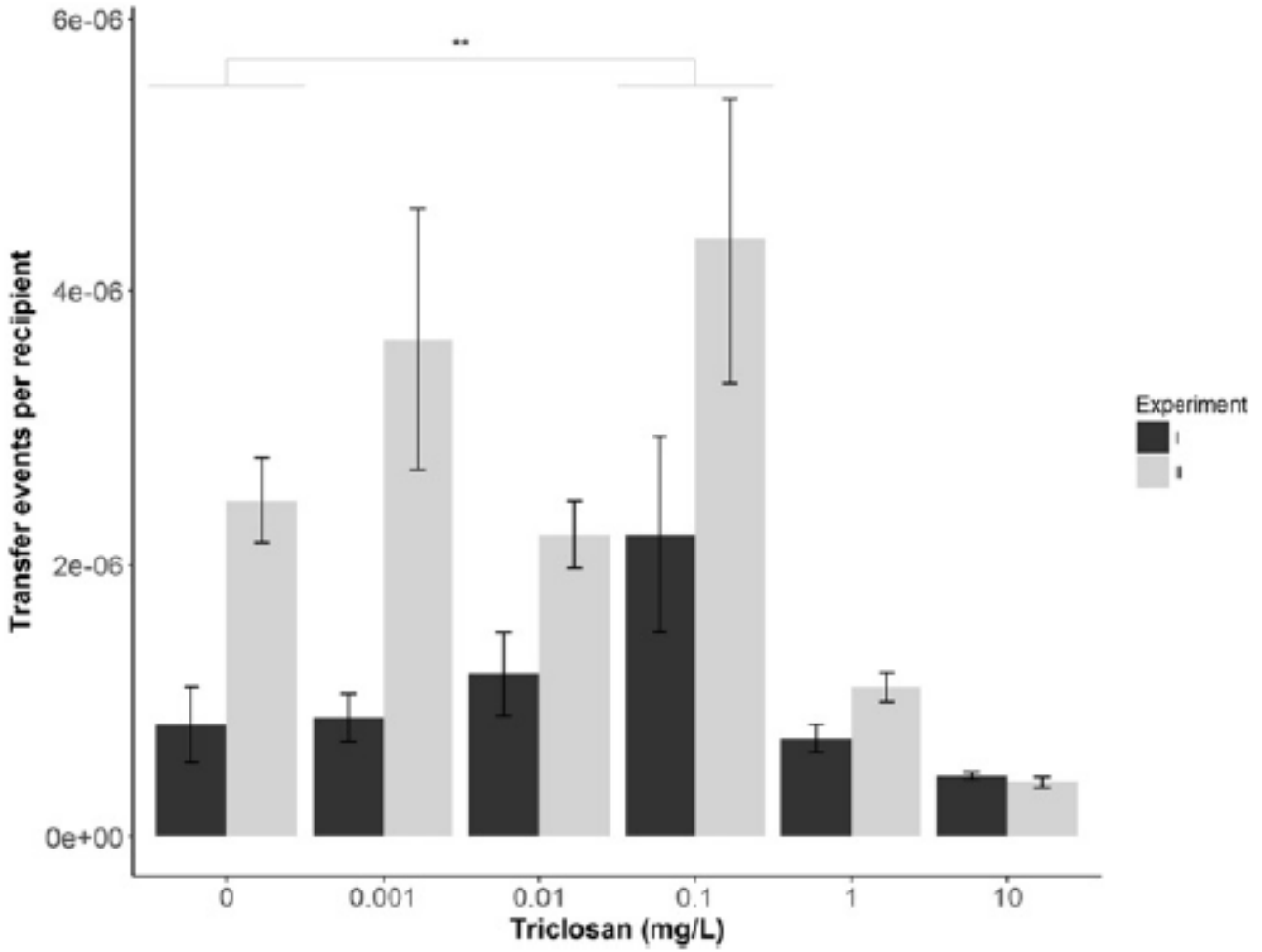



Carl et al, Sci of the Total Environ 2017

# Pollution with pharmaceuticals

**Do other chemical compounds than antibiotics select AMR ?**

Effect of **triclosan** on conjugative transfer of **sulfonamide resistance** from a complex sewage community effluent to an *E. coli* recipient

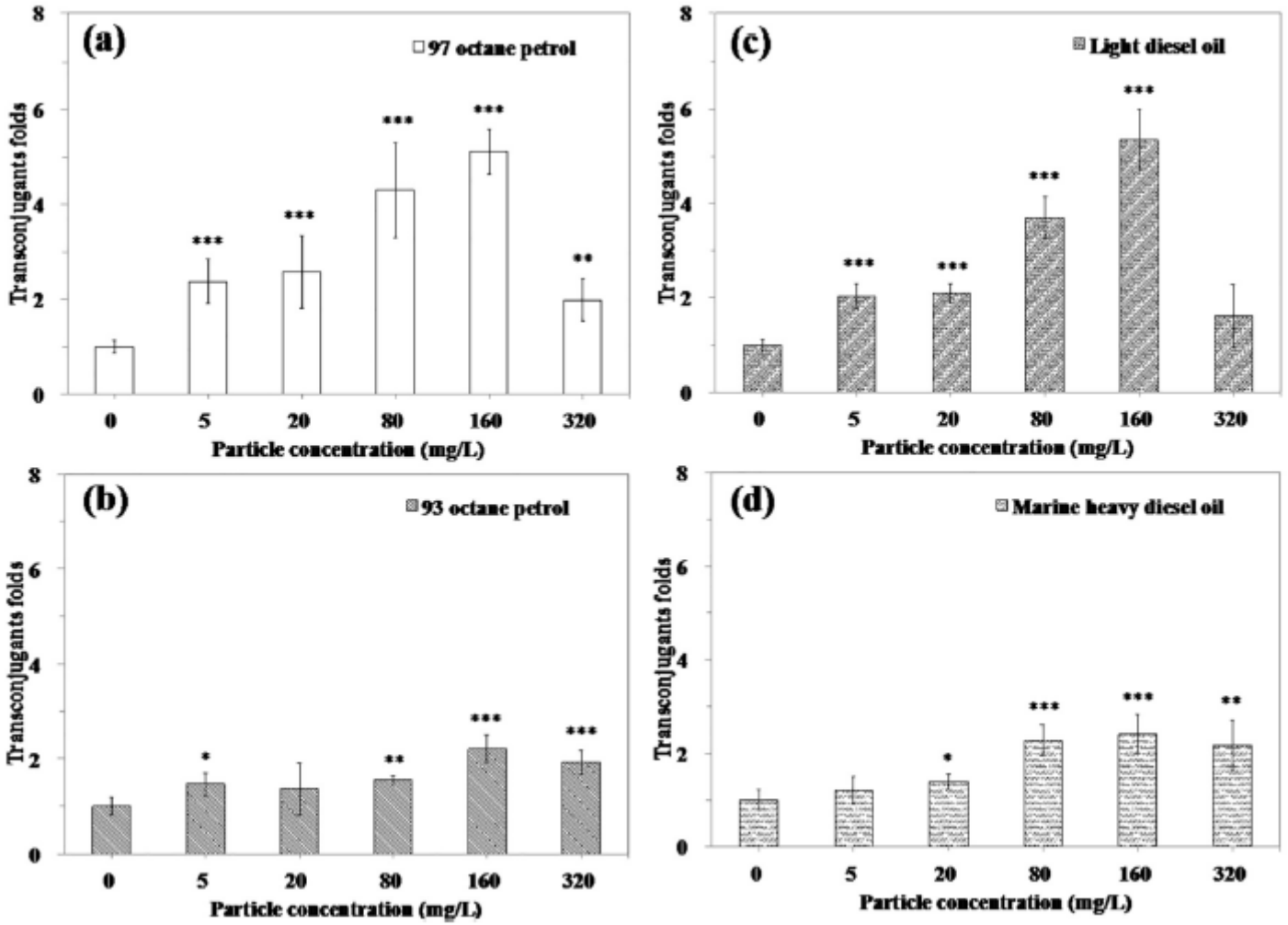



Jutkina et al, Sci of the Total Environ 2018

# Pollution with pharmaceuticals

**Do other chemical compounds than antibiotics select AMR ?**

**Petrol** and **diesel** exhaust particles induces concentration-dependent increase in conjugative transfer rates of AMR genes

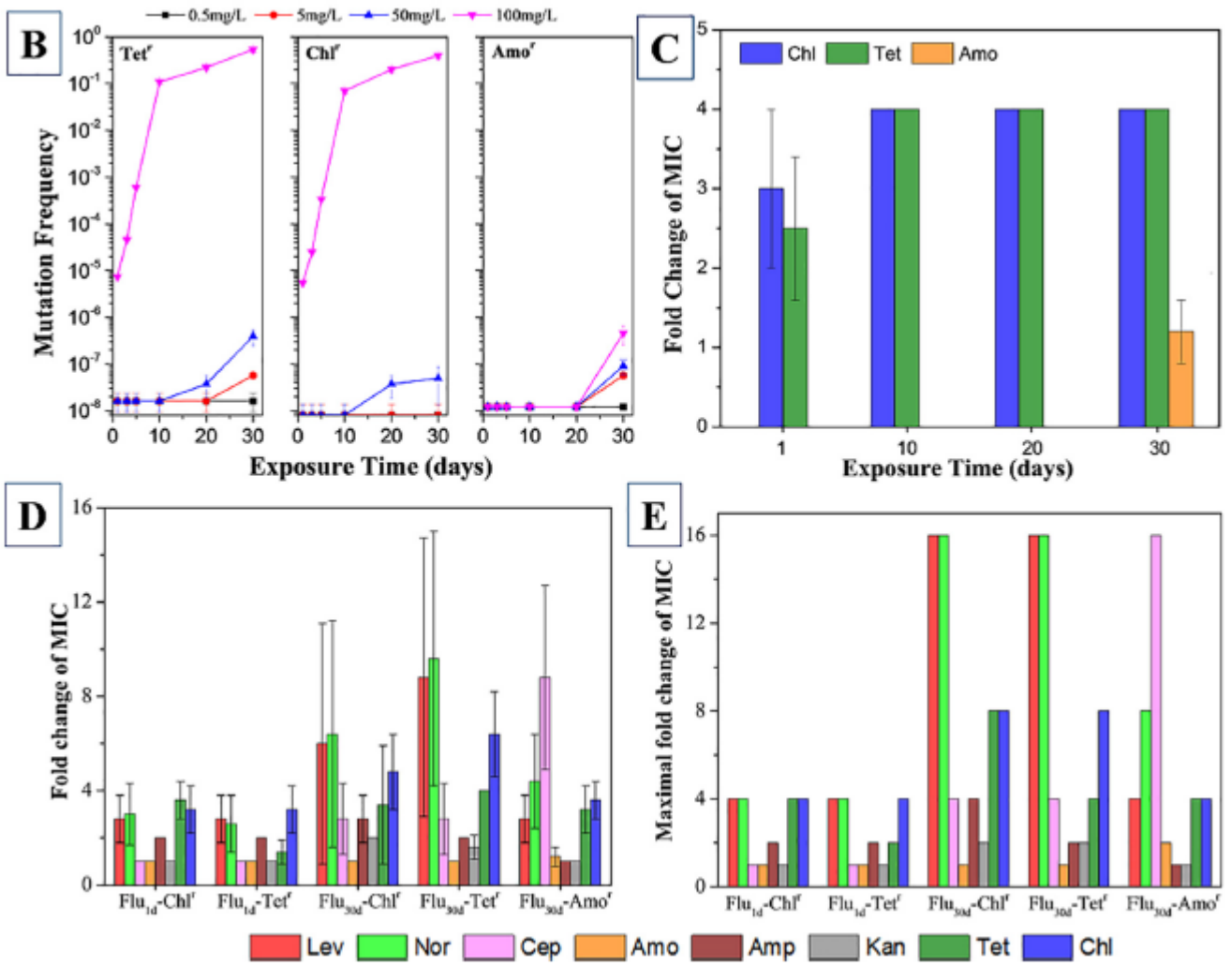



Zhang et al, Environ International 2018

# Pollution with pharmaceuticals

**Do other chemical compounds than antibiotics select AMR ?**

Antidepressant **fluoxetin** induces resistance to multiple antibiotics in *E. coli* through chromosome mutagenesis

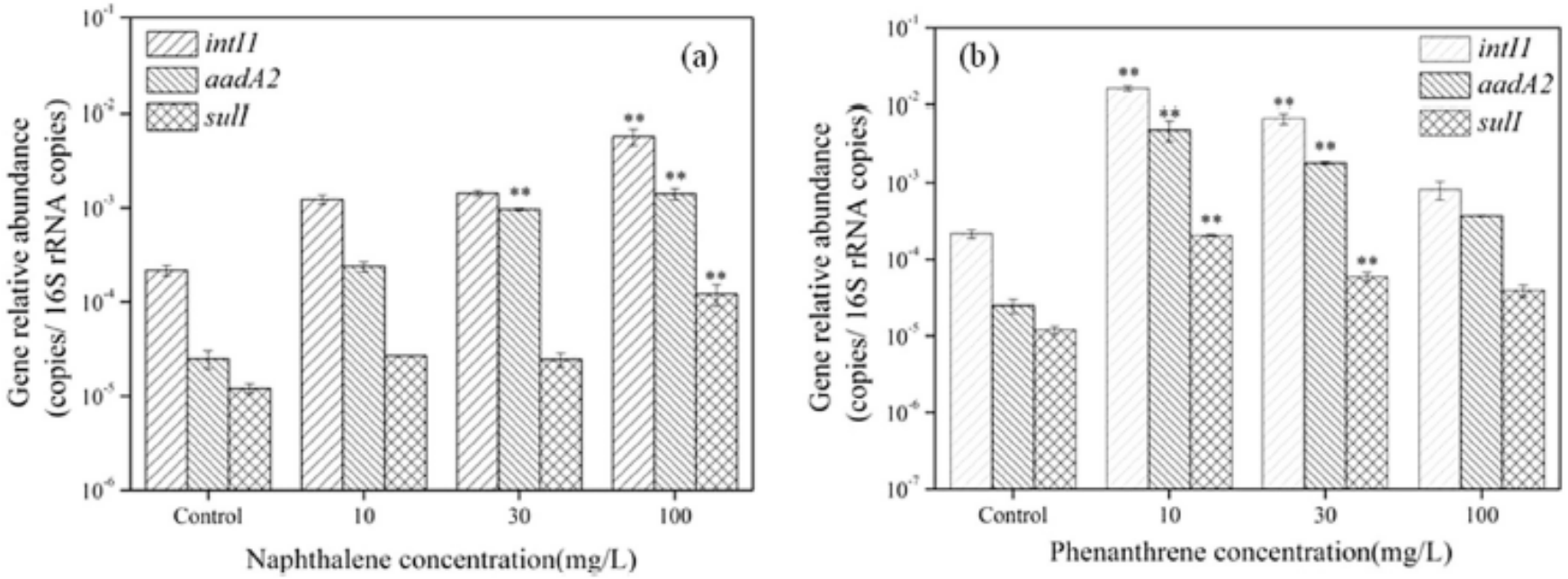



Jin et al, Environ International 2018

# Pollution with pharmaceuticals

**Do other chemical compounds than antibiotics select AMR ?**

**Polycyclic aromatic hydrocarbons (PAH)**
accelerate the propagation of AMR genes in coastal water microbial communities

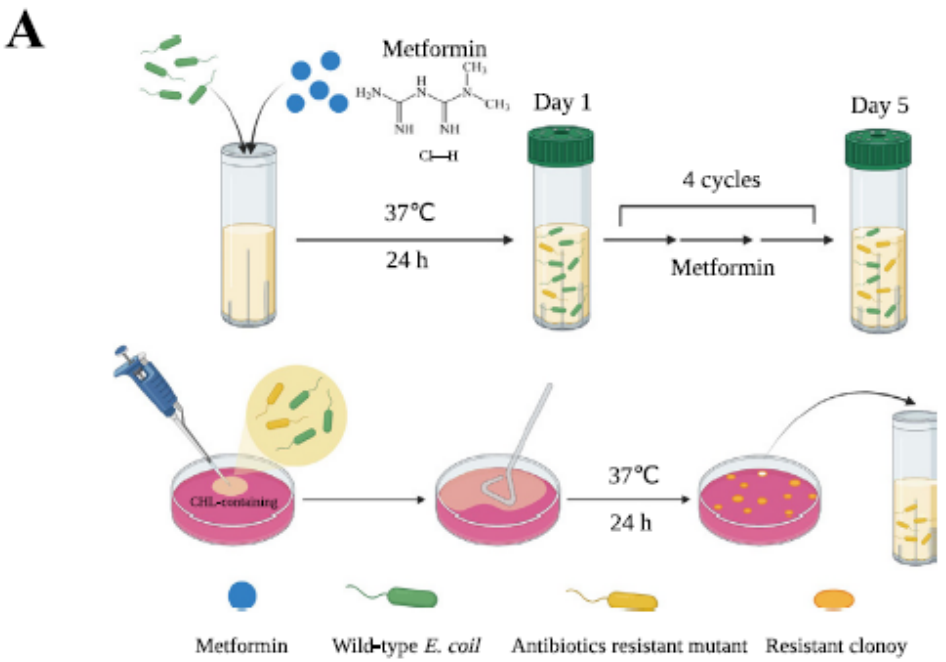


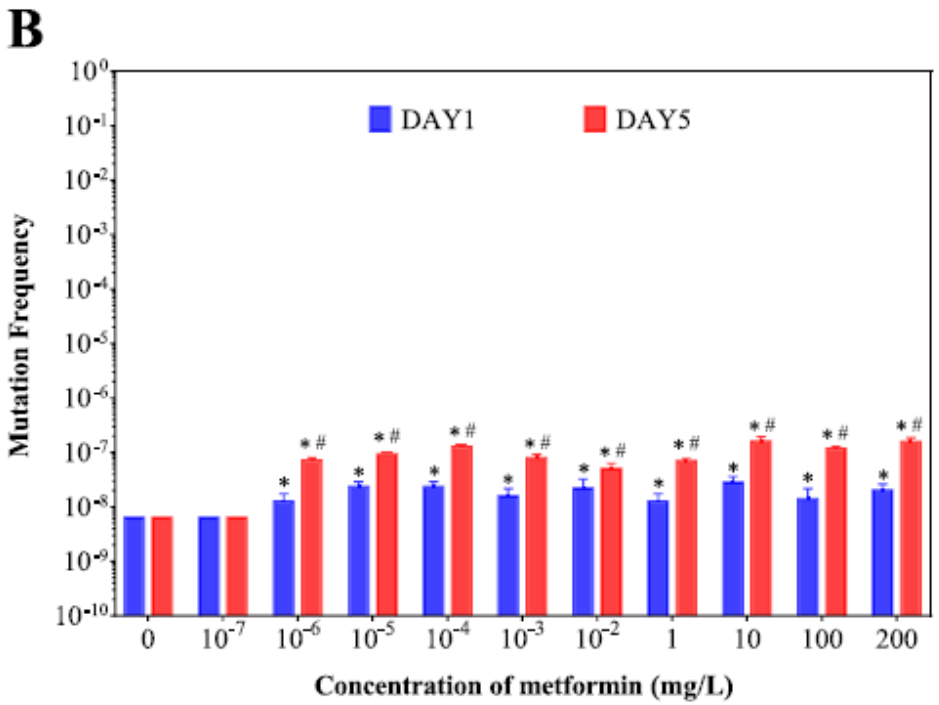

Wang et al, Environmental pollution 2017

# Pollution with pharmaceuticals

**Do other chemical compounds than antibiotics select AMR ?**

**Metformin** promotes AMR development in *E. coli* through chromosome mutagenesis




Wei et al, Journal of Hazardous Materials 2022

# What about risk assessment related to AMR in the environment ?

# Arguments for immediate human exposure ?

**Table 3**
The number (%) of surfers and controls colonised by antibiotic-resistant *E. coli*.

| | 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 $bla_{CTX\text{-}M}$-bearing *E. coli* | 9 (6.3%) | 2 (1.5%) | 4.09 (1.02 to 16.4) | 0.046 |

Leonard et al, Environment International, 2018

# Immediate human exposure ?

Environmental Science & Technology

Critical Review

pubs.acs.org/est

## Role of the Environment in the Transmission of Antimicrobial Resistance to Humans: A Review

Patricia M. C. Huijbers,[†,‡] Hetty Blaak,[*,‡] Mart C. M. de Jong,[†] Elisabeth A. M. Graat,[†] Christina M. J. E. Vandenbroucke-Grauls,[§] and Ana Maria de Roda Husman[‡,∥]

Huijbers et al, Environmental Sci Technol 2015

## Attributable sources of community-acquired carriage of *Escherichia coli* containing β-lactam antibiotic resistance genes: a population-based modelling study

*Lapo Mughini-Gras, Alejandro Dorado-García, Engeline van Duijkeren, Gerrita van den Bunt, Cindy M Dierikx, Marc J M Bonten, Martin C J Bootsma, Heike Schmitt, Tine Hald, Eric G Evers, Aline de Koeijer, Wilfrid van Pelt, Eelco Franz, Dik J Mevius*, Dick J J Heederik*, on behalf of the ESBL Attribution Consortium*

| | Mean (95% CrI) | Median | SD |
|---|---|---|---|
| Food consumption and preparation | 18·9% (7·0–38·3) | 17·6% | 8·1 |
| Seafood | 6·6% (0·3–21·6) | 5·1% | 5·8 |
| Chicken meat | 4·5% (0·2–13·1) | 3·7% | 3·5 |
| Bovine meat | 3·6% (0·1–12·5) | 2·7% | 3·3 |
| Turkey meat | 1·8% (0·6·1) | 1·3% | 1·6 |
| Raw vegetables | 1·1% (0·3·9) | 0·8% | 1·1 |
| Pork | 0·9% (0·3·3) | 0·6% | 0·9 |
| Sheep or goat meat | 0·4% (0·1·6) | 0·3% | 0·4 |
| Animals | | | |
| Contact with companion animals | 7·9% (1·4–19·9) | 7·0% | 4·9 |
| Dogs | 5·1% (0·2–16·3) | 3·9% | 4·4 |
| Cats | 2·4% (0·1–8·0) | 1·9% | 2·2 |
| Horses | 0·5% (0–1·7) | 0·3% | 0·5 |
| Non-occupational contact with farm animals | 3·6% (0·6–9·9) | 3·0% | 2·5 |
| Chickens | 2·8% (0·1–9·0) | 2·1% | 2·4 |
| Cattle | 0·4% (0·1·4) | 0·3% | 0·4 |
| Sheep or goats | 0·3% (0–1·1) | 0·2% | 0·3 |
| Pigs | 0·1% (0–0·5) | 0·1% | 0·1 |
| Environment | 2·6% (0·2–8·7) | 1·9% | 2·3 |
| Swimming in surface freshwater | 2·3% (0·1–8·4) | 1·6% | 2·3 |
| Contact with wild birds | 0·3% (0–1·1) | 0·2% | 0·3 |

The percentage attributions of intestinal carriage of ESBL or pAmpC gene detections in *E coli* isolates from individuals of the open community (n=454) to the different human and non-human sources. ESBL=extended-spectrum β-lactamase. pAmpC=plasmid-mediated AmpC. CrI=credible interval.

**Table:** Estimated attributions of each considered source of intestinal carriage of ESBL or pAmpC gene-carrying *Escherichia coli* detected in the open community in the Netherlands, 2005–17

Mughini-Gras et al, Lancet Planet Health 2019

# Arguments for immediate human exposure ?

Increased use of reclaimed wastewater as an alternative for crop irrigation

Environmental Science & Technology

Article

pubs.acs.org/est

## Human Exposure to Wastewater-Derived Pharmaceuticals in Fresh Produce: A Randomized Controlled Trial Focusing on Carbamazepine

Ora Paltiel,[*,†,‡,§] Ganna Fedorova,[§,∥] Galit Tadmor,[†,§,∥] Geffen Kleinstern,[†,§] Yehoshua Maor,[§] and Benny Chefetz[§,∥]

Paltiel et al, Environmental Sci Technol 2015

# Is manure application at risk to spread AMR ?

Tetracycline resistance genes abundance in soils after 6 years with manure
*tet* genes were present in all soil layers (0-5 cm, 5-10 cm, 10-20 cm)
*tet*O was introduced by manure, and *tet*G, *tet*L abundance increased after fertilization

Science of the Total Environment 506–507 (2015) 279–286

Contents lists available at ScienceDirect

Science of the Total Environment

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

## Long-term application of fresh and composted manure increase tetracycline resistance in the arable soil of eastern China

Shuang Peng [a,b], Yiming Wang [a], Beibei Zhou [a,b], Xiangui Lin [a,*]

# Is manure application at risk to spread AMR ?

Macrolide exposure of soils for 8 years at a dose from 0.1 to 10 mg/kg soil
Several AMR genes were enriched at the 10 but not the 0.1 mg/kg soil
Exposure at realistic concentrations did not increase AMR genes abundance


Ho-Fung Lau et al, Sci of the Total Environment 2020

# Minimal environmental targets for antibiotic manufacturers ?

UN High-Level Meeting on AMR (2016)
13 pharmaceutical companies
Roadmap with 4 key commitments to reduce AMR

## Science-based Targets for Antibiotics in Receiving Waters from Pharmaceutical Manufacturing Operations

*Joan Tell,*† Daniel J Caldwell,‡ Andreas Häner,§ Jutta Hellstern,|| Birgit Hoeger,|| Romain Journel,# Frank Mastrocco,††** Jim J Ryan,‡‡ Jason Snape,§§ Jürg Oliver Straub,§ and Jessica Vestel†*

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*‡‡GlaxoSmithKline, Ware, United Kingdom*
*§§AstraZeneca, Cheshire, United Kingdom*

Tell et al, Integrated Environmental Assessment and Management, 2019

# Is the environmental risk assessment (ERA) appropriate to protect against AMR ?

Environment International 109 (2017) 155–169

Contents lists available at ScienceDirect

Environment International

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

Review article

Integrating human and environmental health in antibiotic risk assessment: A critical analysis of protection goals, species sensitivity and antimicrobial resistance

Gareth Le Page[a], Lina Gunnarsson[a], Jason Snape[b,c], Charles R. Tyler[a,*]

Water Research 200 (2021) 117233

Contents lists available at ScienceDirect

Water Research

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

Dawning of a new ERA: Environmental Risk Assessment of antibiotics and their potential to select for antimicrobial resistance

Aimee K. Murray[a,*], Isobel Stanton[a], William H. Gaze[a], Jason Snape[b]

In Europe, an ERA is required for a medicine if the predicted environmental concentration exceeds 10 ng/L
It leads to the calculation of a Predictable No Effect Concentration (PNEC)

There is a concern that ERA is biaised for antibiotics

# Modelling approaches to estimate the risks of AMR development in the environment

*Environmental Toxicology and Chemistry*—Volume 41, Number 3—pp. 648–662, 2022
Received: 11 December 2020 | Revised: 18 January 2021 | Accepted: 31 March 2021



Hazard/Risk Assessment

## Ecological Risk Assessment of Pharmaceuticals in the Transboundary Vecht River (Germany and The Netherlands)

Daniel J. Duarte,[a,*,1] Gunnar Niebaum,[b,1] Volker Lämmchen,[b,1] Eri van Heijnsbergen,[c] Rik Oldenkamp,[d] Lucia Hernández-Leal,[c] Heike Schmitt,[c,e,f] Ad M. J. Ragas,[a,g] and Jörg Klasmeier[b]

OPEN

The ISME Journal (2015) 9, 1467–1476

www.nature.com/ismej

ORIGINAL ARTICLE

## Validated predictive modelling of the environmental resistome

Gregory CA Amos[1,7], Emma Gozzard[2], Charlotte E Carter[1], Andrew Mead[1,3], Mike J Bowes[2], Peter M Hawkey[4,5], Lihong Zhang[1,8], Andrew C Singer[2], William H Gaze[6,9,10] and Elizabeth MH Wellington[1,9]

# United Nations Environment Programme (UNEP)

**United Nations Environment Programme's work on AMR**

UN environment programme

## Tackling Environmental Antimicrobial Resistance

United Nations Environment Programme (UNEP)

an authoritative advocate for the global environment

UN environment assembly

United Nations Environment Assembly (UNEA):

- World's highest-level decision-making body on the environment.

The Assembly is the governing body of the United Nations Environment Programme (UNEP).

- UNEP sets the global environmental agenda

**UNEP's mission is to provide leadership and encourage partnership in caring for the environment by inspiring, informing, and enabling nations and peoples to improve their quality of life without compromising that of future generations.**

# Final remarks

Environment International 117 (2018) 132–138

Contents lists available at ScienceDirect

Environment International

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

Critical knowledge gaps and research needs related to the environmental dimensions of antibiotic resistance

D.G. Joakim Larsson[a,b,*], Antoine Andremont[c,d], Johan Bengtsson-Palme[a,b], Kristian Koefoed Brandt[e], Ana Maria de Roda Husman[f,g], Patriq Fagerstedt[h], Jerker Fick[i], Carl-Fredrik Flach[a,b], William H. Gaze[j], Makoto Kuroda[k], Kristian Kvint[a,b], Ramanan Laxminarayan[l], Celia M. Manaia[m], Kaare Magne Nielsen[n], Laura Plant[h], Marie-Cécile Ploy[o], Carlos Segovia[p], Pascal Simonet[q], Kornelia Smalla[r], Jason Snape[s,t], Edward Topp[u], Arjon J. van Hengel[v], David W. Verner-Jeffreys[w], Marko P.J. Virta[x], Elizabeth M. Wellington[t], Ann-Sofie Wernersson[y]

1. What are the **relative contributions** of different sources of antibiotics and AMR into the environment ?
2. What is the role of the environment (as affected by anthropogenic inputs) **on the evolution of AMR** ?
3. How significant is the exposure of humans to AMR via different environmental routes, and **what is the impact on human health** ?
4. What technological, social, economic, behavioral interventions are effective **to mitigate the spread of AMR** via the environment ?

*'In India'*


*'Are you sure water is safe ?'*

*'Of course ! It's full of antibiotics !'*