



香港中文大學
The Chinese University of Hong Kong



香港中文大學醫學院
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Identifying resistome to tackle antibiotic resistance

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Dept of Microbiology

Molecular Diagnosis in ID, HK
11th Nov, 2022

Economic Impact of Selected Infectious Disease Outbreaks

COVID-19 Pandemic

- **\$283 billion to 9.2 trillion** (estimated for 24 industrial nations up to 2020) ¹
- **\$3.5 trillion** (Worldwide COVID-19 mortality costs for >100 countries, upto 2Jul2020)

AMR by 2050

**US\$120
trillion**

¹United Nations Projection for 2021, Best Pract Res Clin Anaesthes 2021 Oct;35:293-306. (doi:10.1016/j.bpa.2020.11.009)

²Viscusi WK. Pricing the global health risks of the COVID-19 pandemic. J Risk Uncertain. 2020;61:1–28.)

³ O'Neill Report, UK2016

Hong Kong Strategy and Action Plan on Antimicrobial Resistance 2017-2022



- Strengthen knowledge through surveillance and research;
- Optimise use of antimicrobials in humans and animals;
- Reduce incidence of infection through effective sanitation, hygiene and preventive measures;
- Improve awareness and understanding of AMR through effective communication, education and training;
- Promote research on AMR;
- Strengthen partnerships and foster engagement of relevant stakeholders.

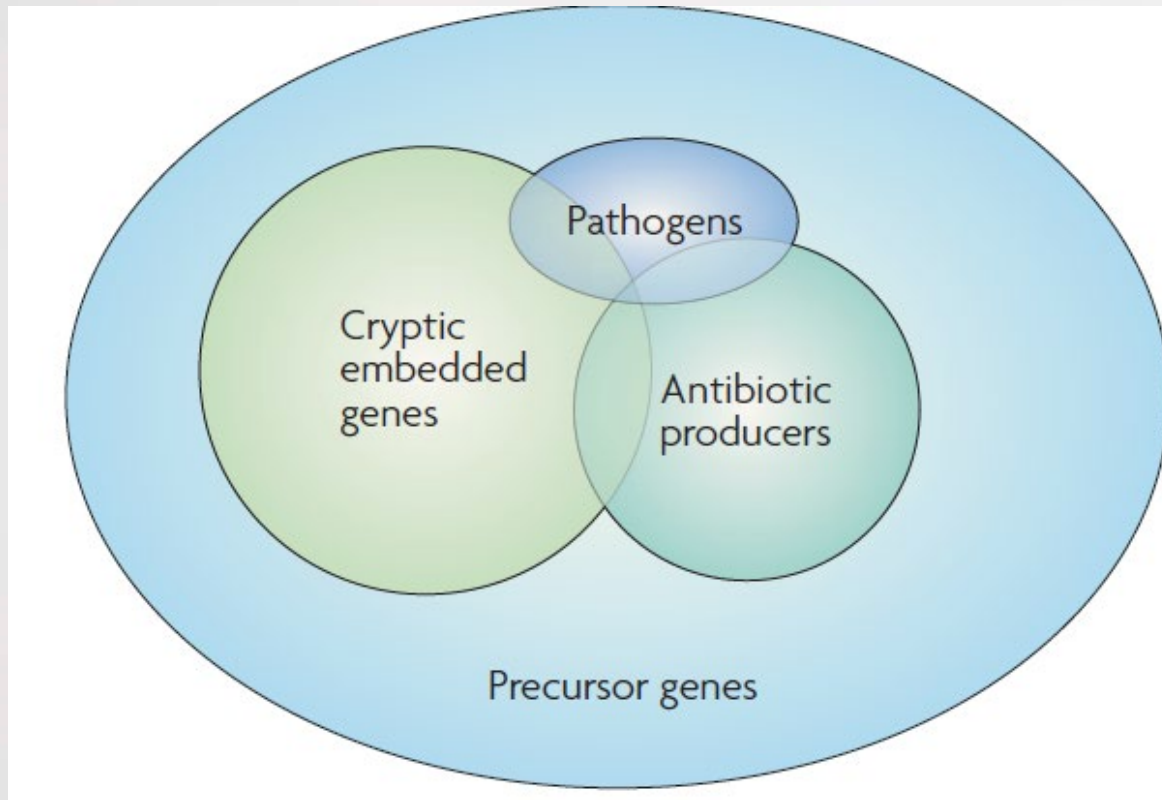




What is Resistome

- All the antibiotic resistance genes in communities of both pathogenic and non-pathogenic bacteria.
- All of the resistance genes in an organism, how they are inherited, and how their transcription levels vary to defend against pathogens like viruses and bacteria.

The Antibiotic Resistome



- Resistance elements found in both pathogenic bacteria and antibiotic-producing bacteria
- Cryptic resistance genes (which are not necessarily expressed) that are present in bacterial chromosomes.
- Encode proteins that can be specific to classes of antibiotics and
- Includes precursor genes that encode proteins with modest antibiotic resistance activity, or affinity to antibiotics, that might evolve into effective resistance genes.

Wright GD. Nat Microbiol 2007

The Soil Resistome

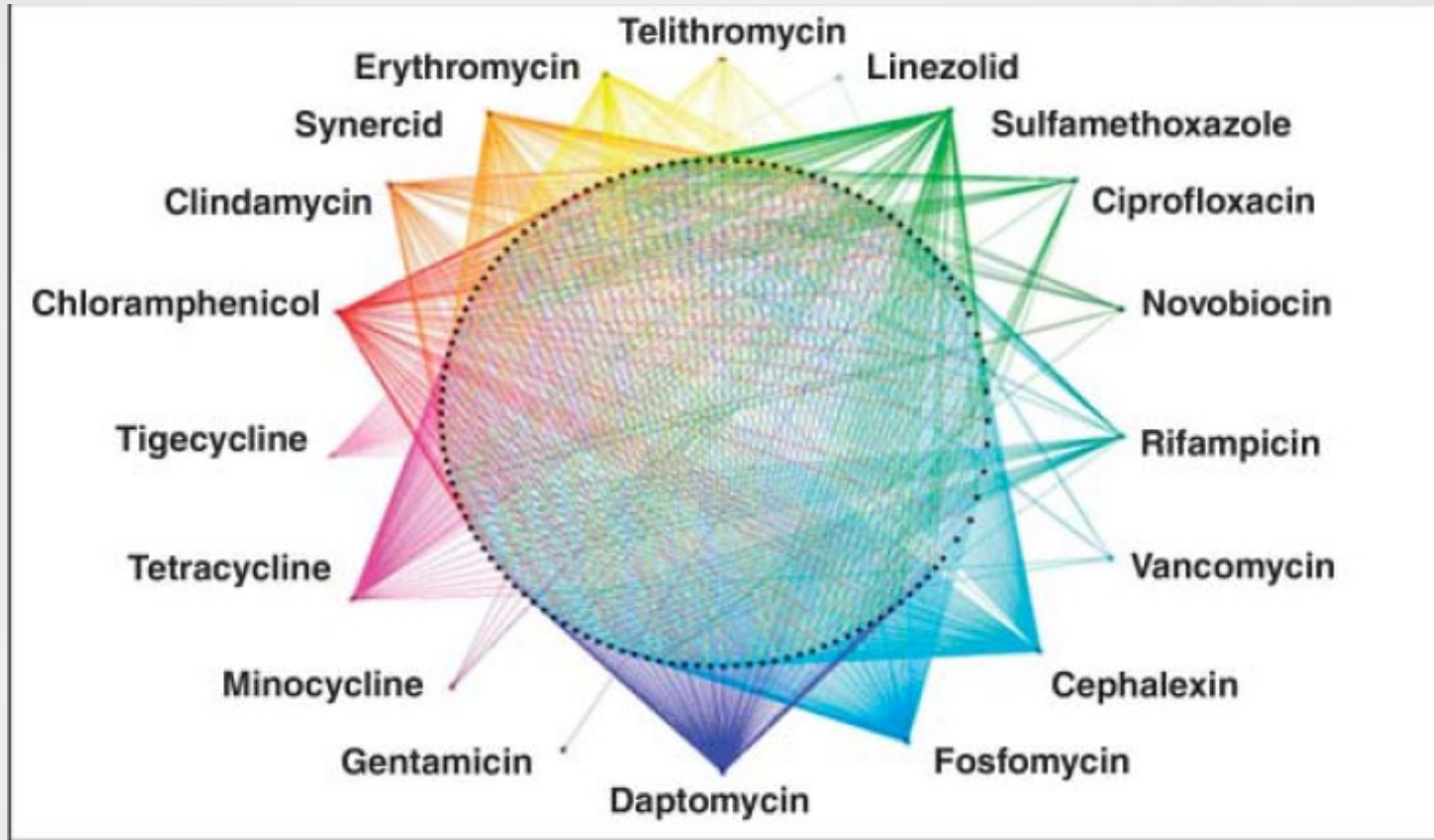
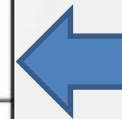
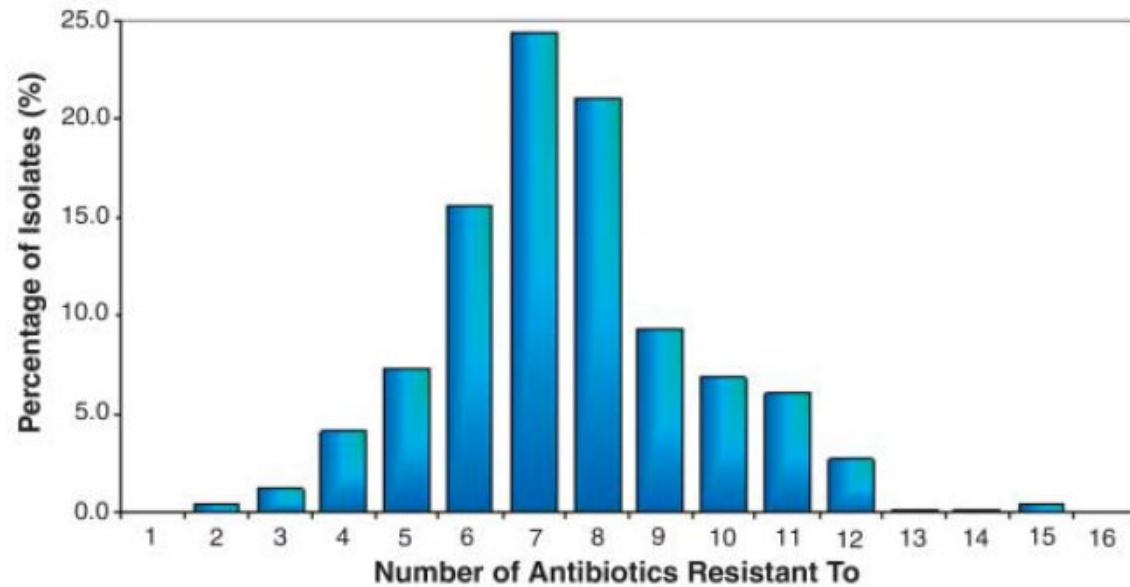
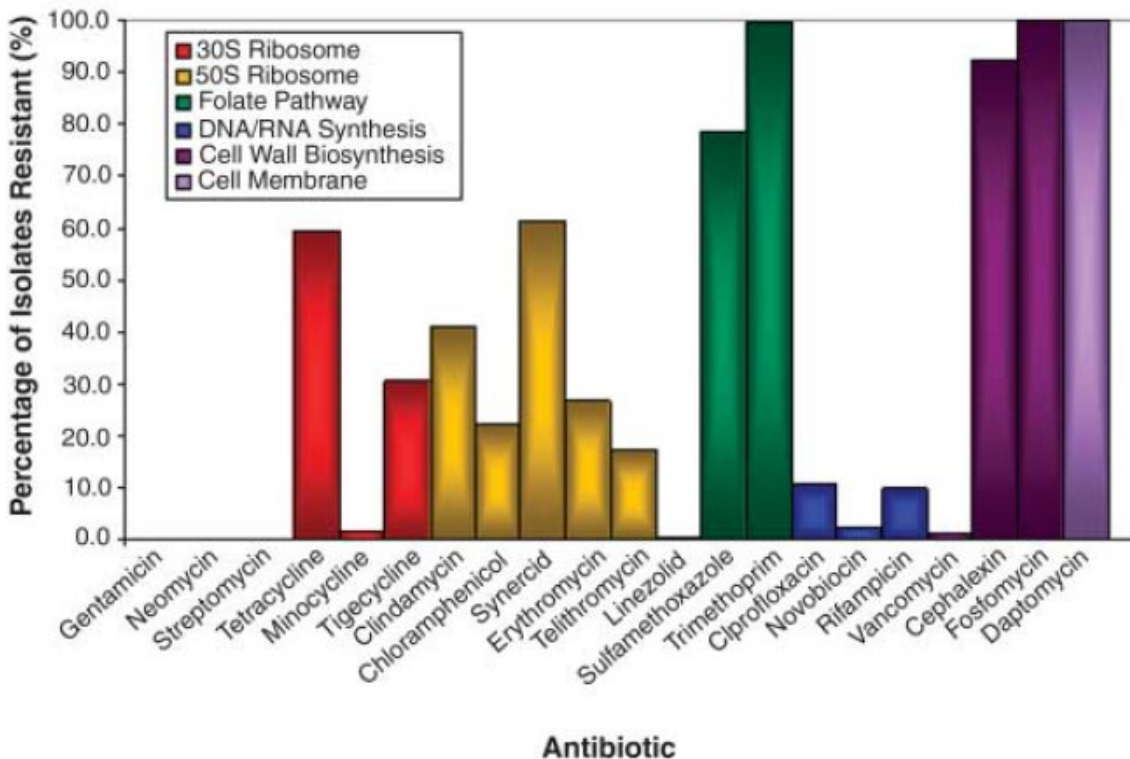


Diagram illustrating phenotypic density and diversity of resistance profiles:
191 dots representing different resistance profiles,
line connecting profile indicates resistance

Antibiotic resistance profiling of 480 soil-derived bacterial isolates.



Upper figure reveals resistance of soil bacteria against 21 antibiotics



Prevalence of resistance against different antibiotics and their classes of mechanisms of action

What does this tell us

- **Prevalence of resistance** from this bacterial community to known antibiotics
- Enables one to elucidate **novel** antimicrobial resistance **mechanisms** that may emerge clinically
- Serves as a foundation for **new antibiotic development**
- Mechanisms eg. enzymatic inactivation may lead to development of inhibitors for **combination therapy** to restore antimicrobial activity



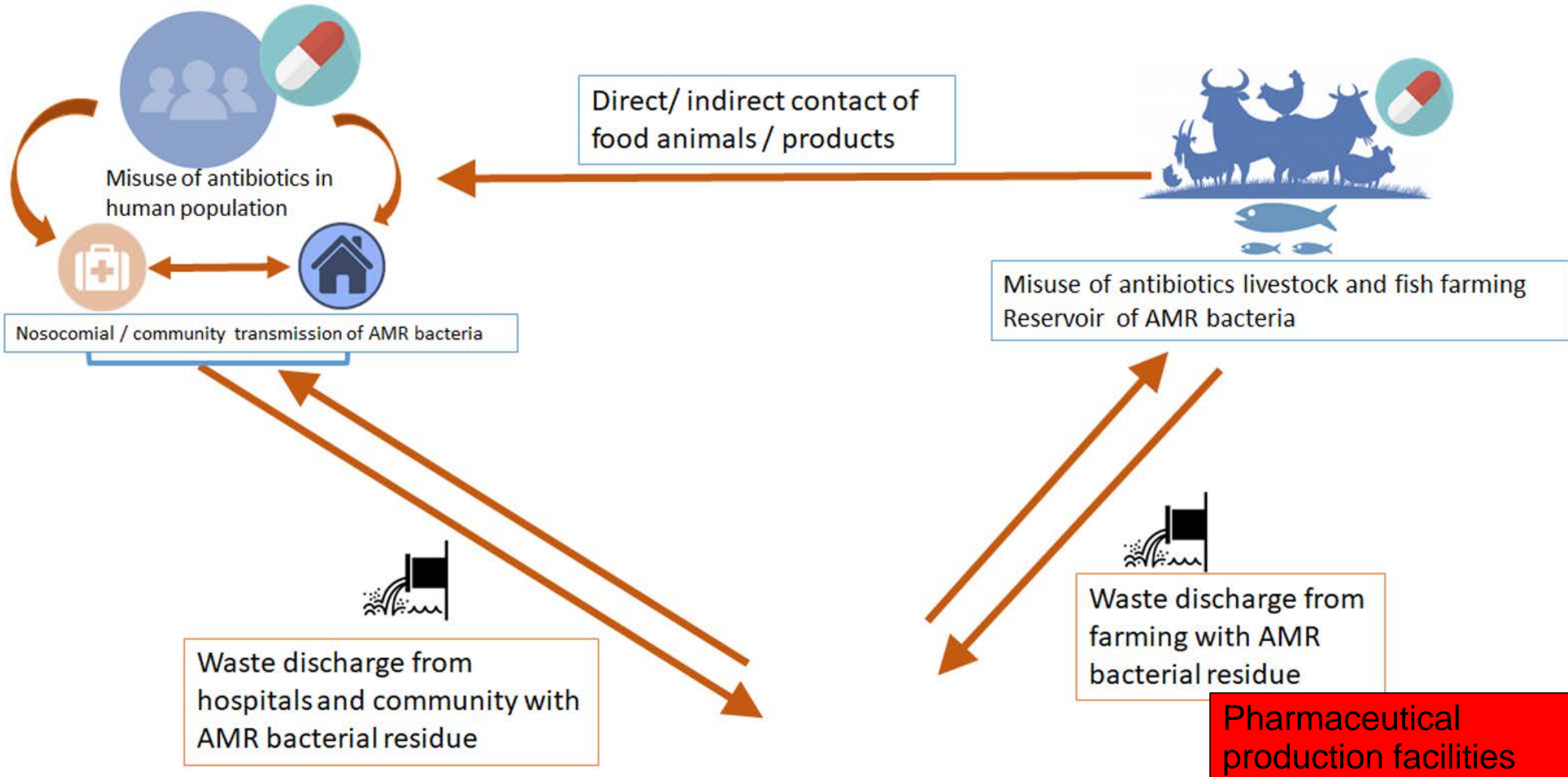
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GLOBAL ACTION PLAN
ON ANTIMICROBIAL
RESISTANCE



Strategic Objectives

1. Improve awareness and **understanding** of AMR
2. Strengthen knowledge through **surveillance and research**
3. Reduce incidence of infection
4. **Optimize** the **use** of antimicrobial agents
5. Ensure sustainable **investment** in countering AMR

Tackling AMR under One Health



Where can we apply Resistome studies to enhance our strategy in containing AMR



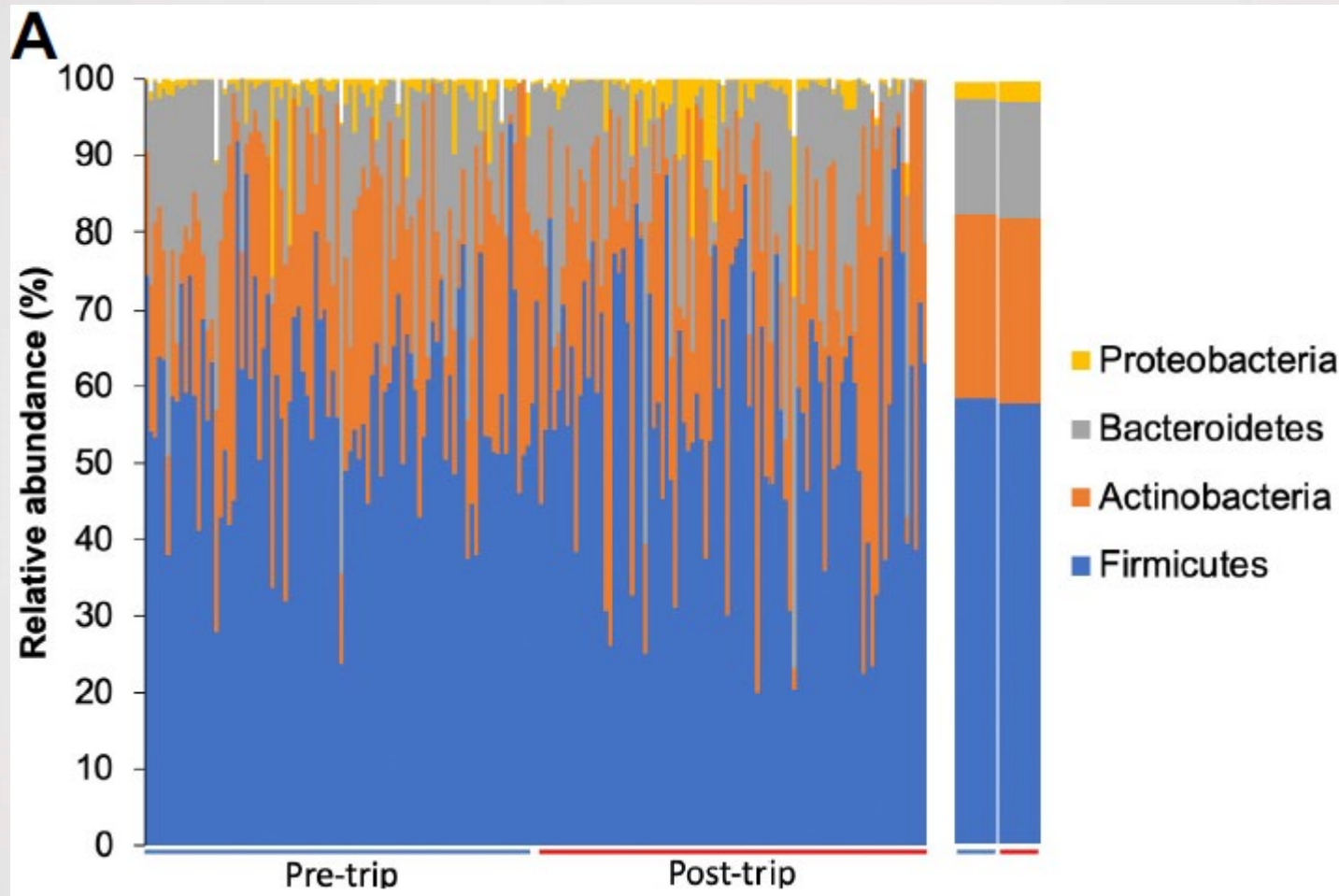
- HUMAN
 - eg. Microbiome, gut
 - Antimicrobial use
 - Transmission routes eg travel
- ANIMAL
 - Farms and reservoirs
 - Antimicrobials / growth hormones
- ENVIRONMENT
 - Reservoirs, soil and water
 - Sewage: municipal, hospital, farms, industries

The Gut Resistome in Travellers: a Pilot study



- International travel increases the risk of acquisition of antibiotic-resistant bacteria and antibiotic resistance genes (ARGs).
- Little information regarding the gut microbiome and resistome of non-Western travellers have been characterized, nor the travel-related risk factors studied
- Study design: prospective observational study of healthy adult residents of Hong Kong
- A questionnaire and stools were collected from the subjects before and after travelling to overseas
- Shotgun metagenomic sequencing was performed on the samples and associated travel-related variables were analysed.
- Microbial diversities and resistome were examined.

Results

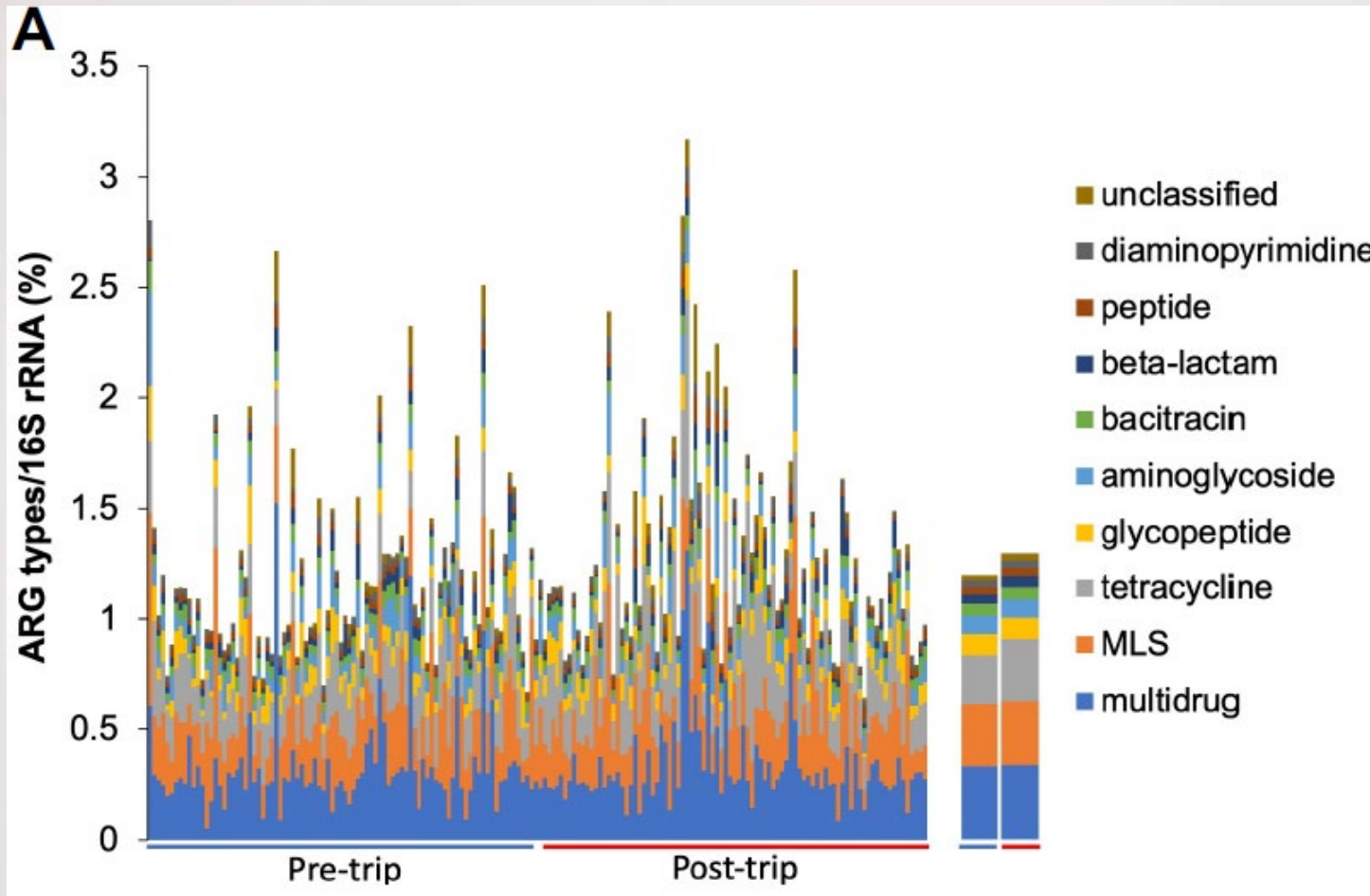


No statistical differences between the alpha diversity with observed species and Shannon diversity index

Taxonomic composition of top four most abundant phyla, before and after travel

(Data unpublished)

Results



No statistical differences between the alpha diversity with observed ARGs and Shannon diversity index

Relative abundance of the top 10 most abundant ARG types, before and after travel

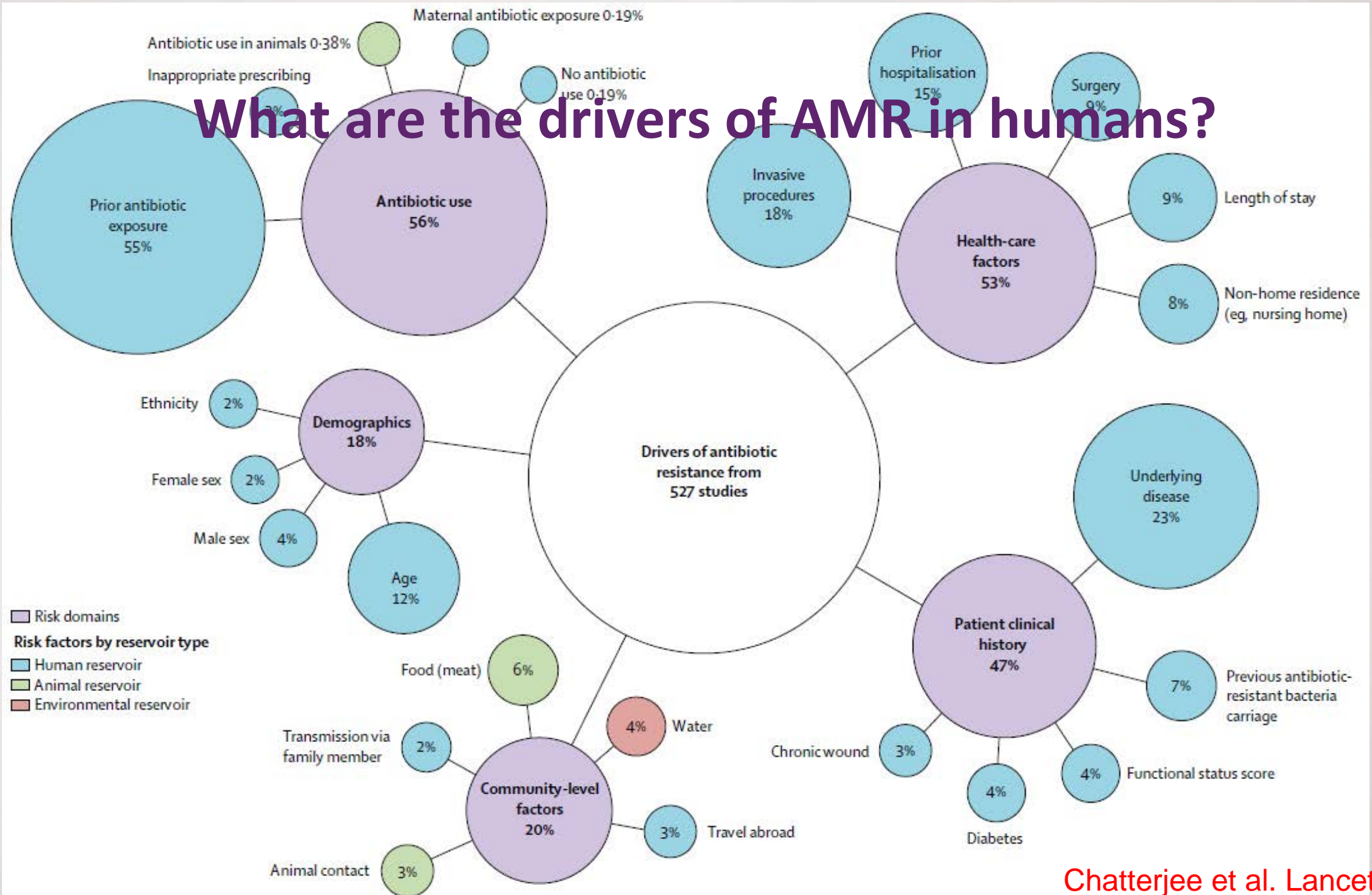
(Data unpublished)



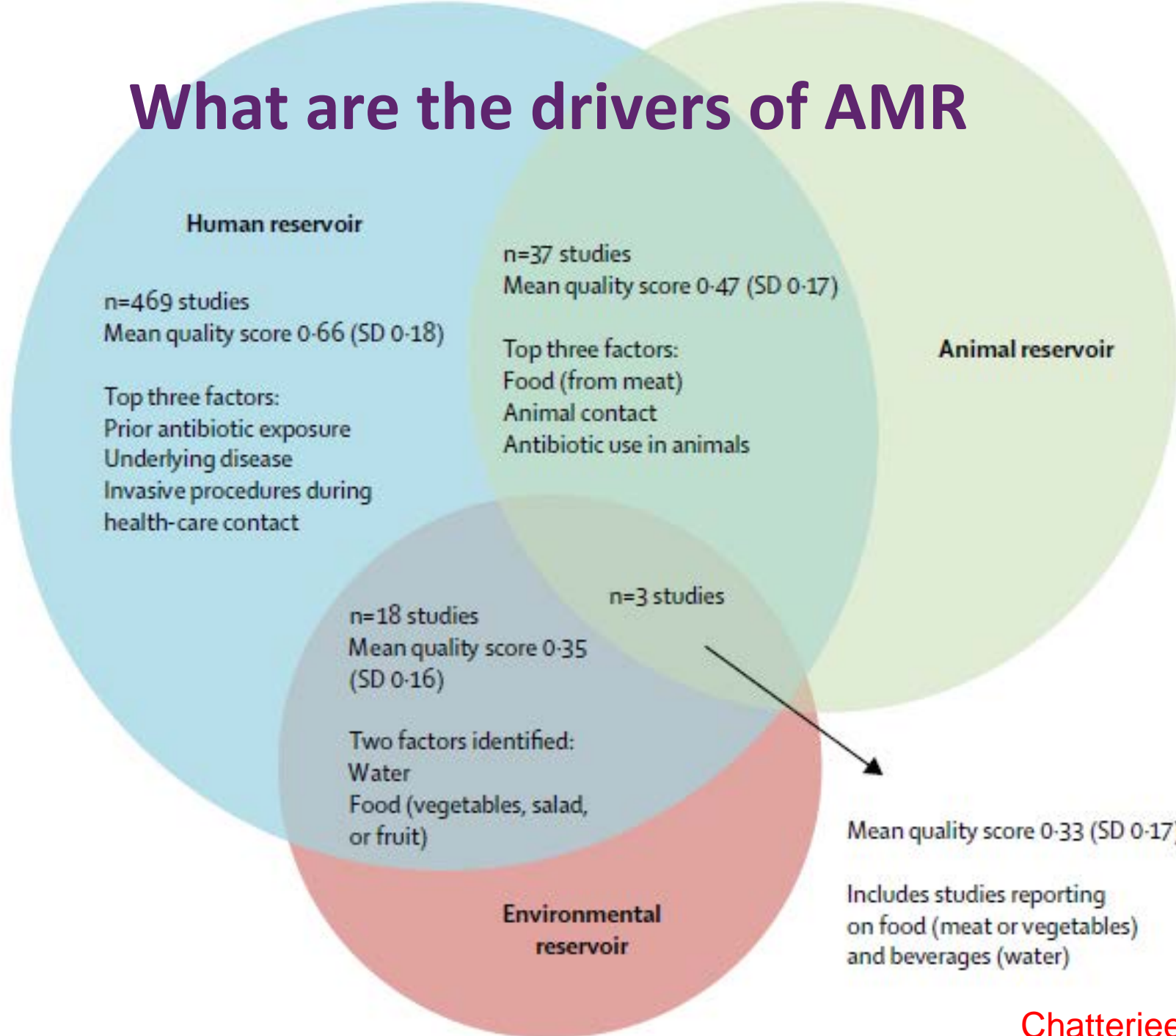
Significant travel-related variables to the alpha and beta diversities of gut resistome

A number of variables eg. Destination (by income of country), destination (by region), purpose of travel etc. are shown to be statistically significant in this cohort

What are the drivers of AMR in humans?




What are the drivers of AMR




Hot-spots and drivers of antimicrobial resistance (AMR)

Drivers of Antimicrobial Resistance


Antibiotics




Biocides

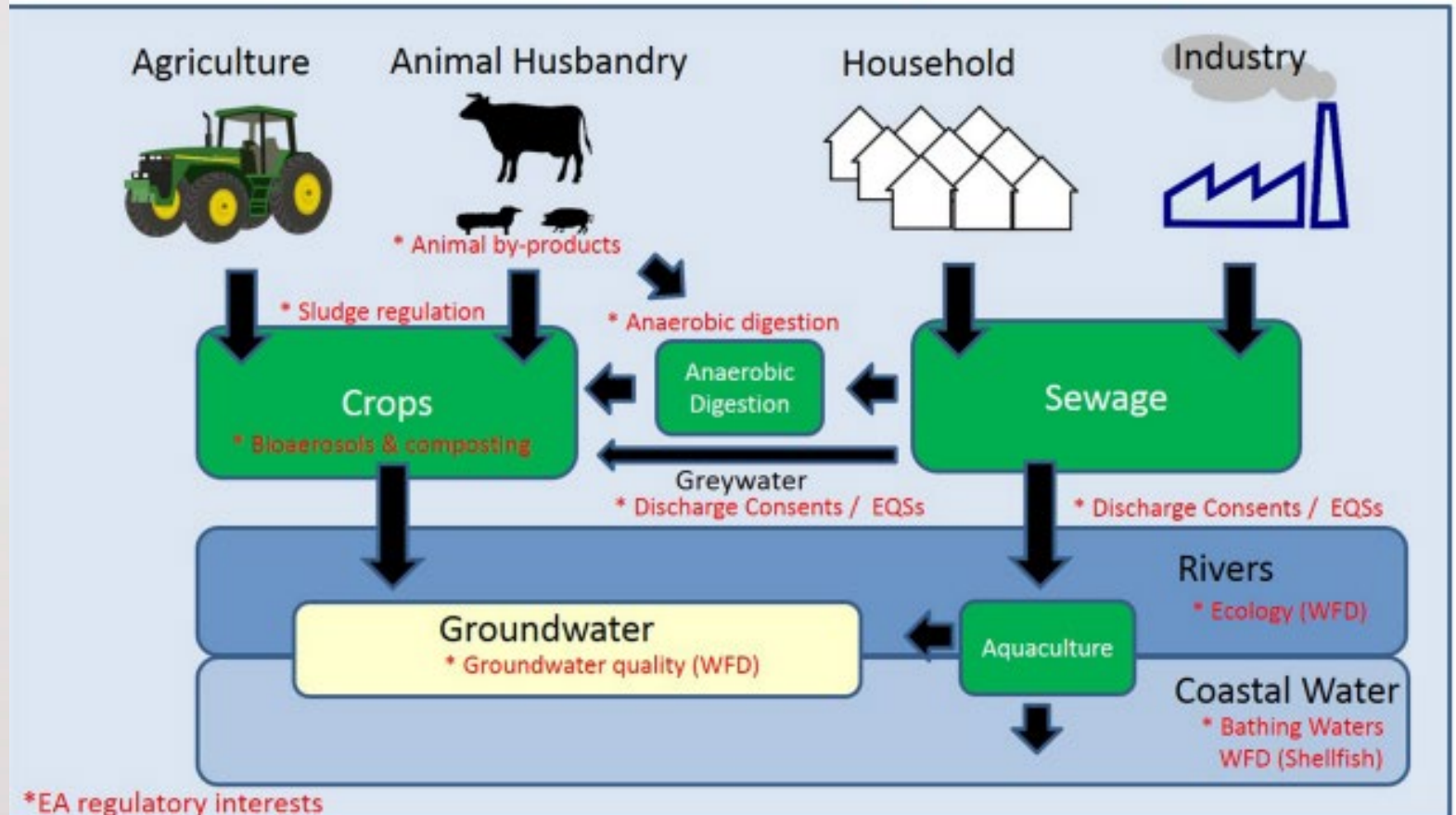


Metals



Genes





The environmental compartments that are monitored or regulated by Environment Agency in UK (in RED*).

Singer et al. Frontiers Microbiol 2016

Resistome in the Environment



Environment International 157 (2021) 106821



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Contents lists available at [ScienceDirect](#)

Environment International

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



A multi-omics study on quantifying antimicrobial resistance in European freshwater lakes

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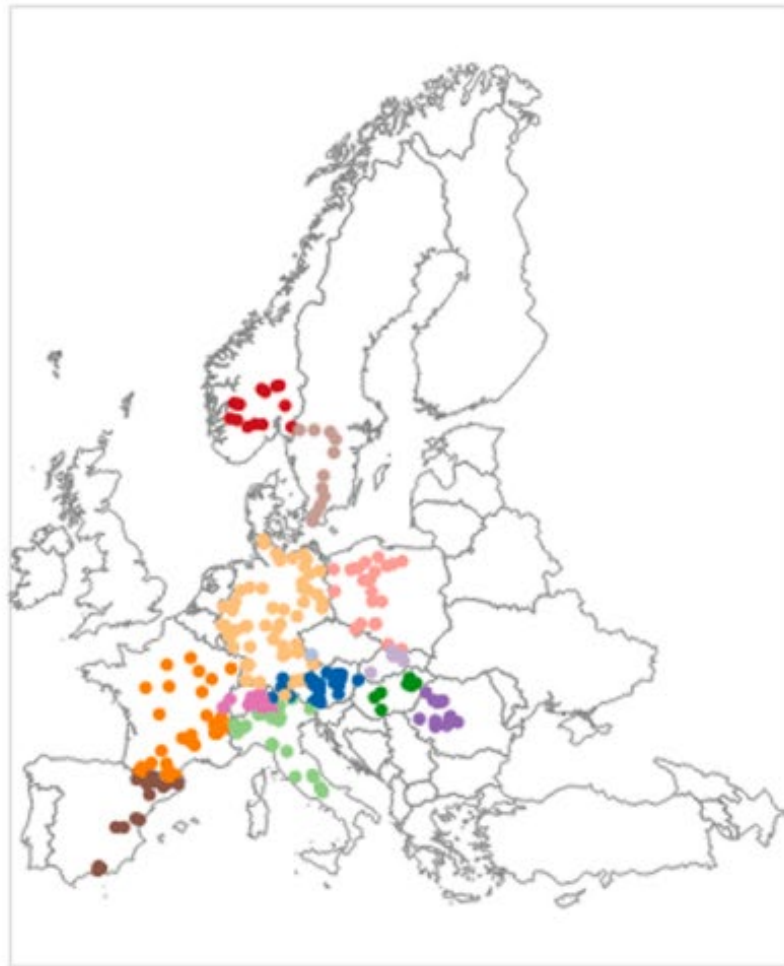
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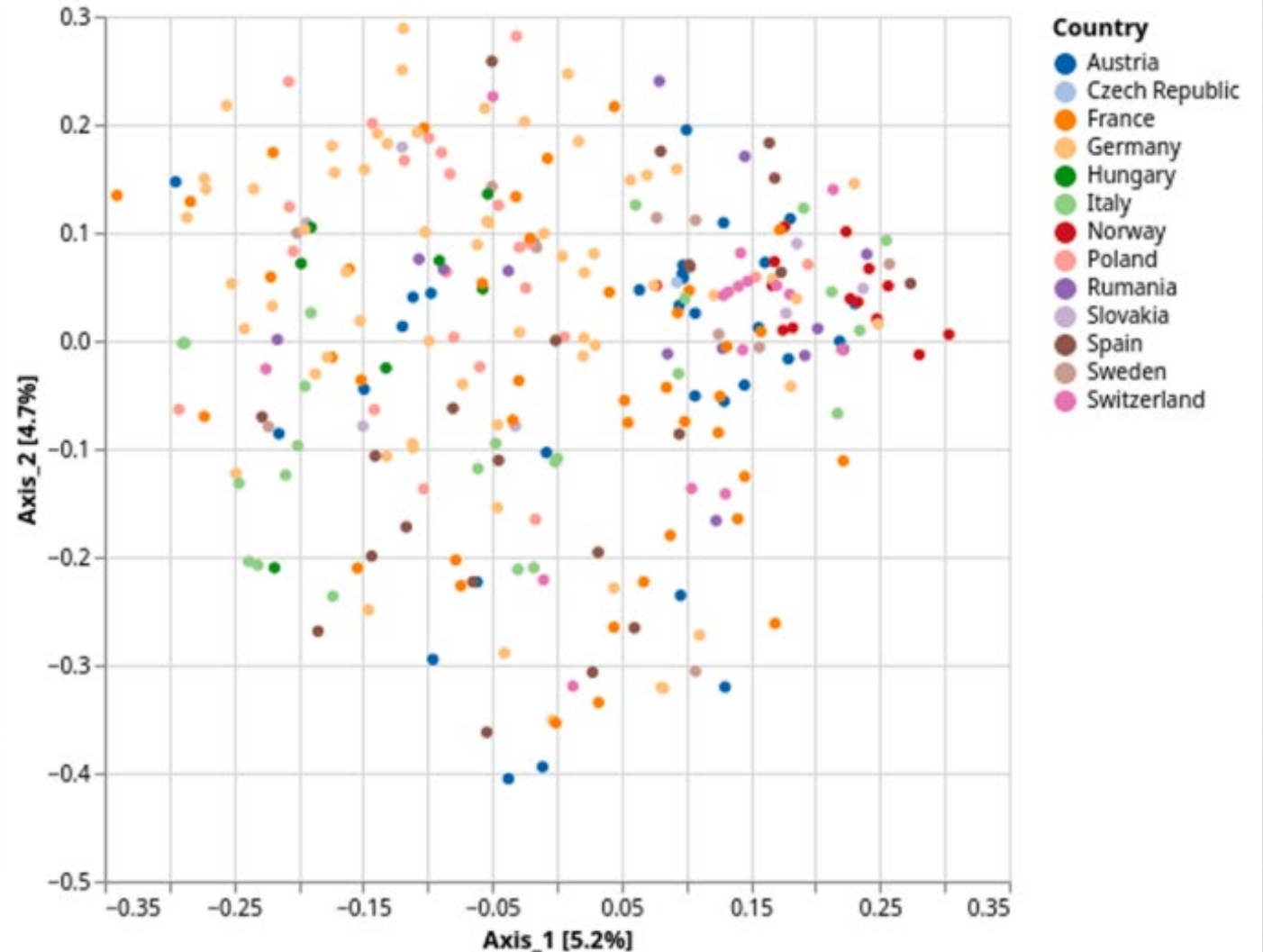


Map of sample sites for 274 freshwater lakes across Europe (a) and PCoA of relative abundance in OTUs (b).

a

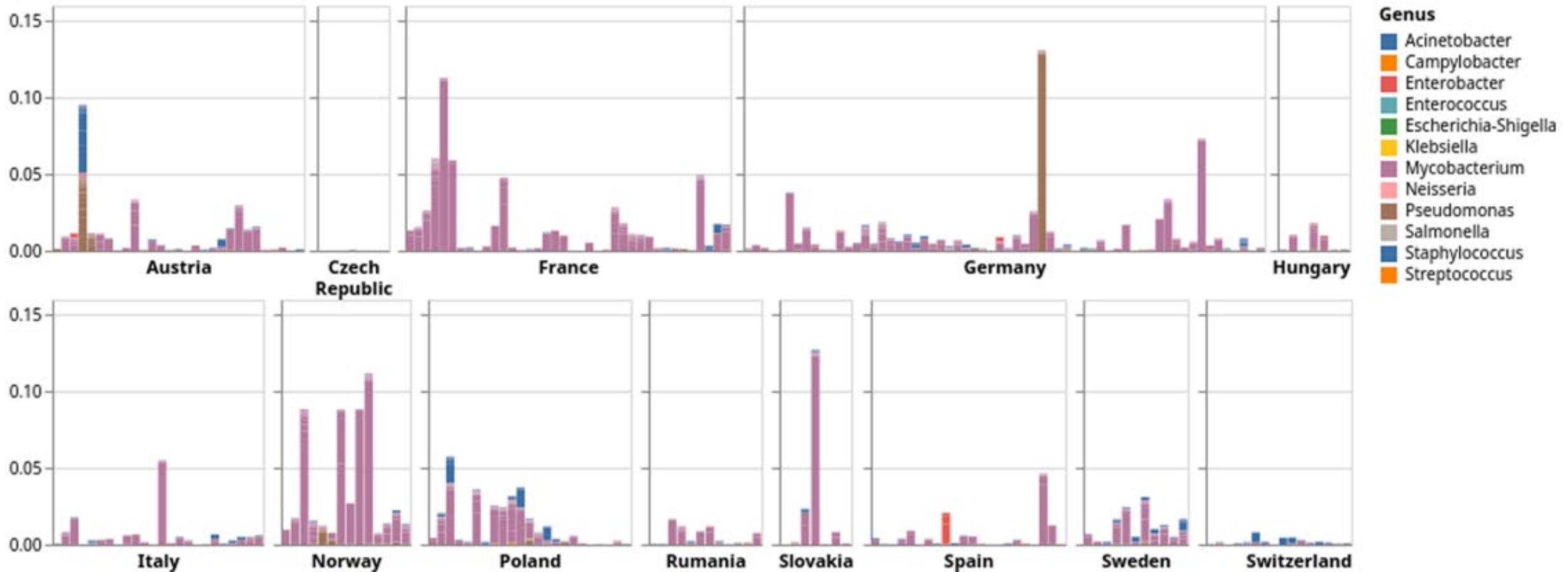


b

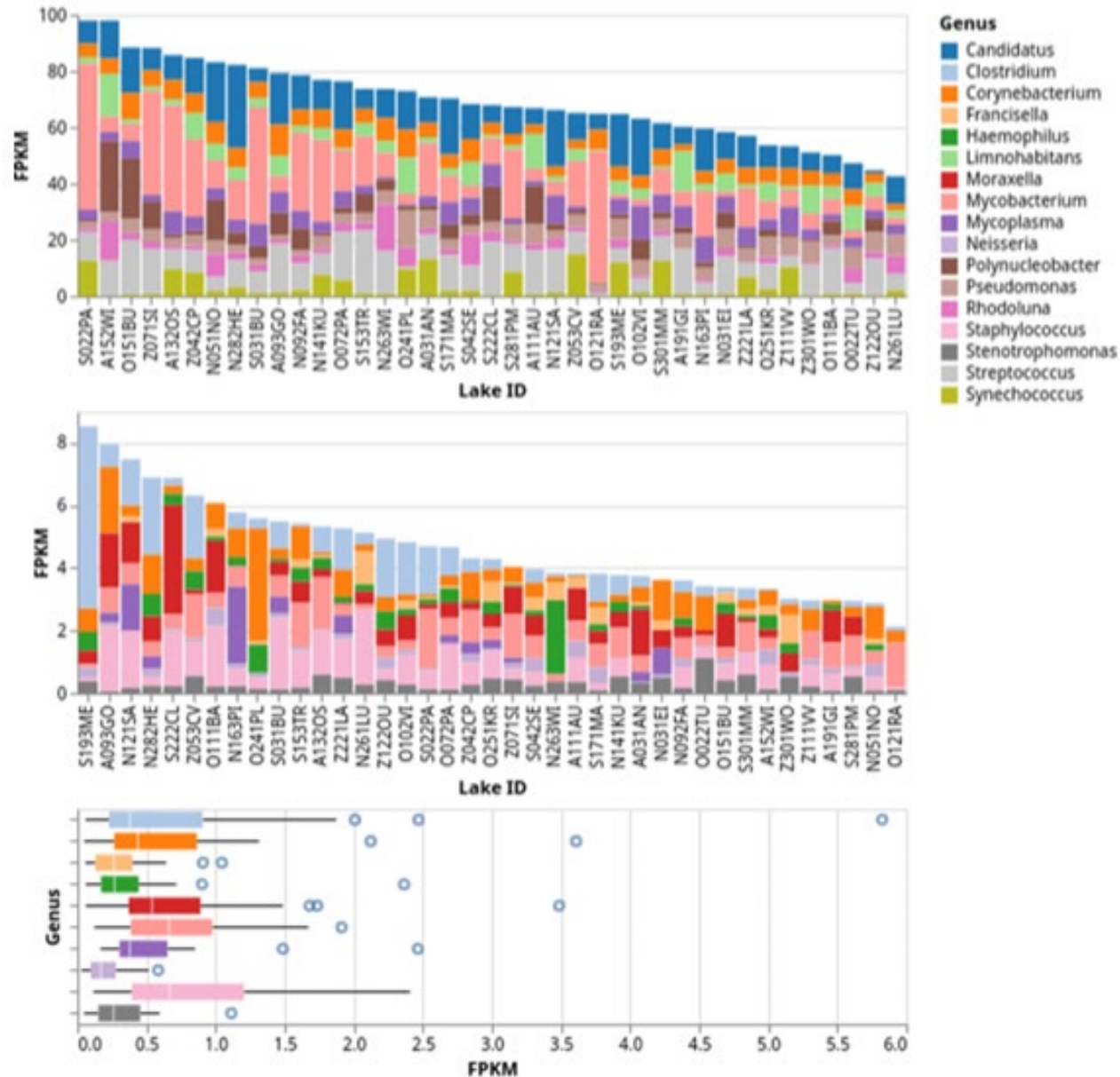


Relative abundance of genera, with known antimicrobial resistance at different sample sites

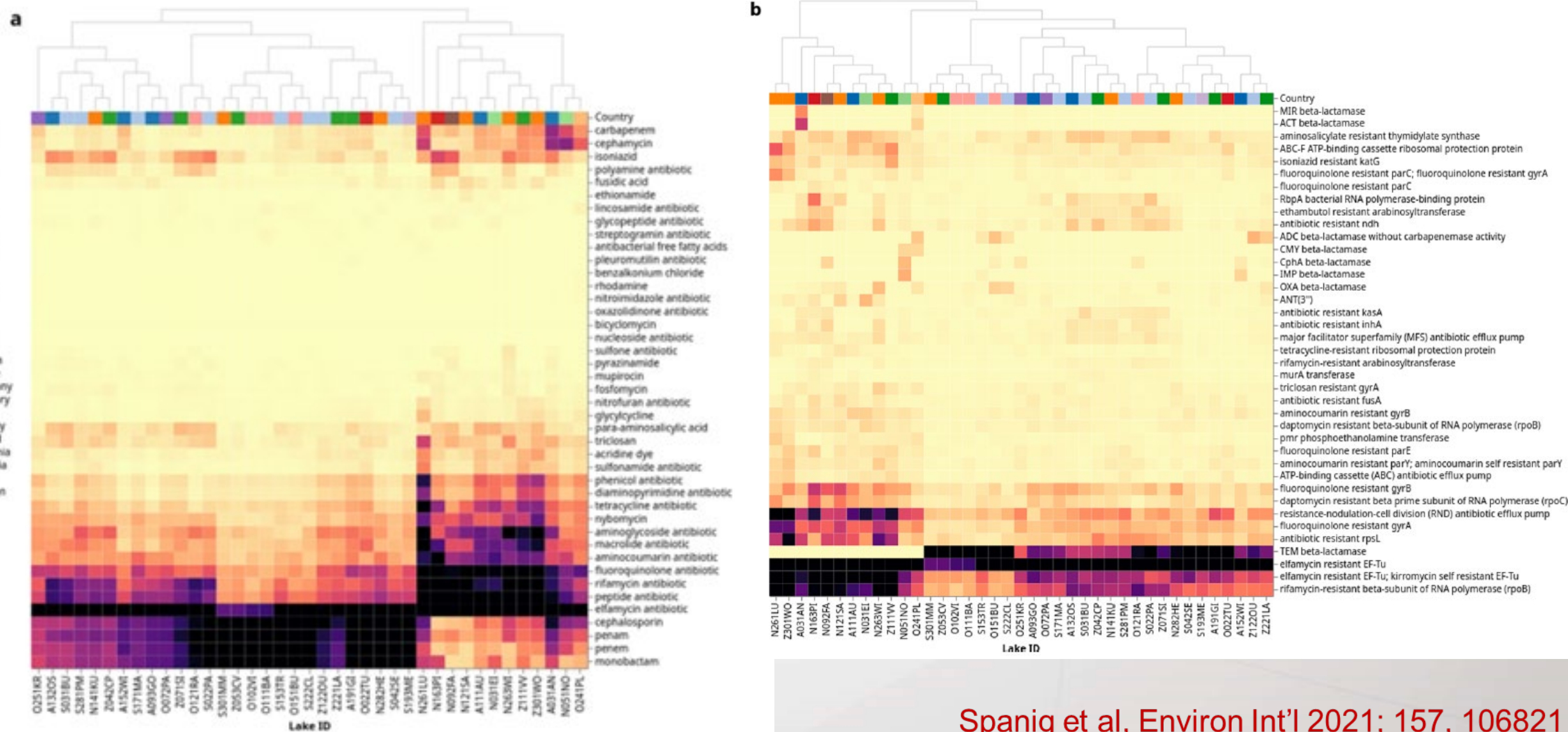
c



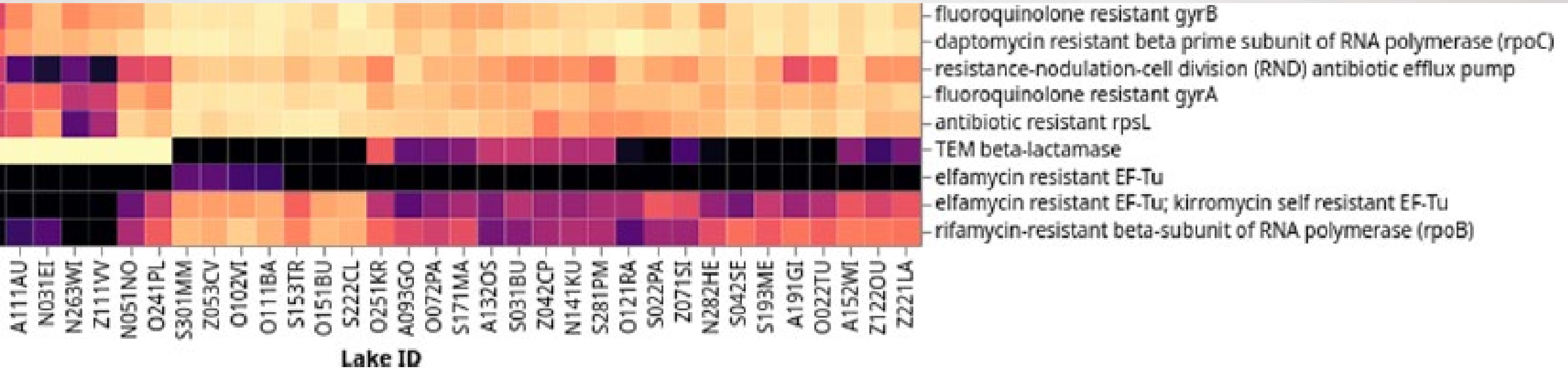
Metagenome taxonomy classification and the top 10 genera of pathogenic relevance



Heatmap of respective lakes (x-axis) and resistance to drug classes and resistance genes



Resistance genes of significance



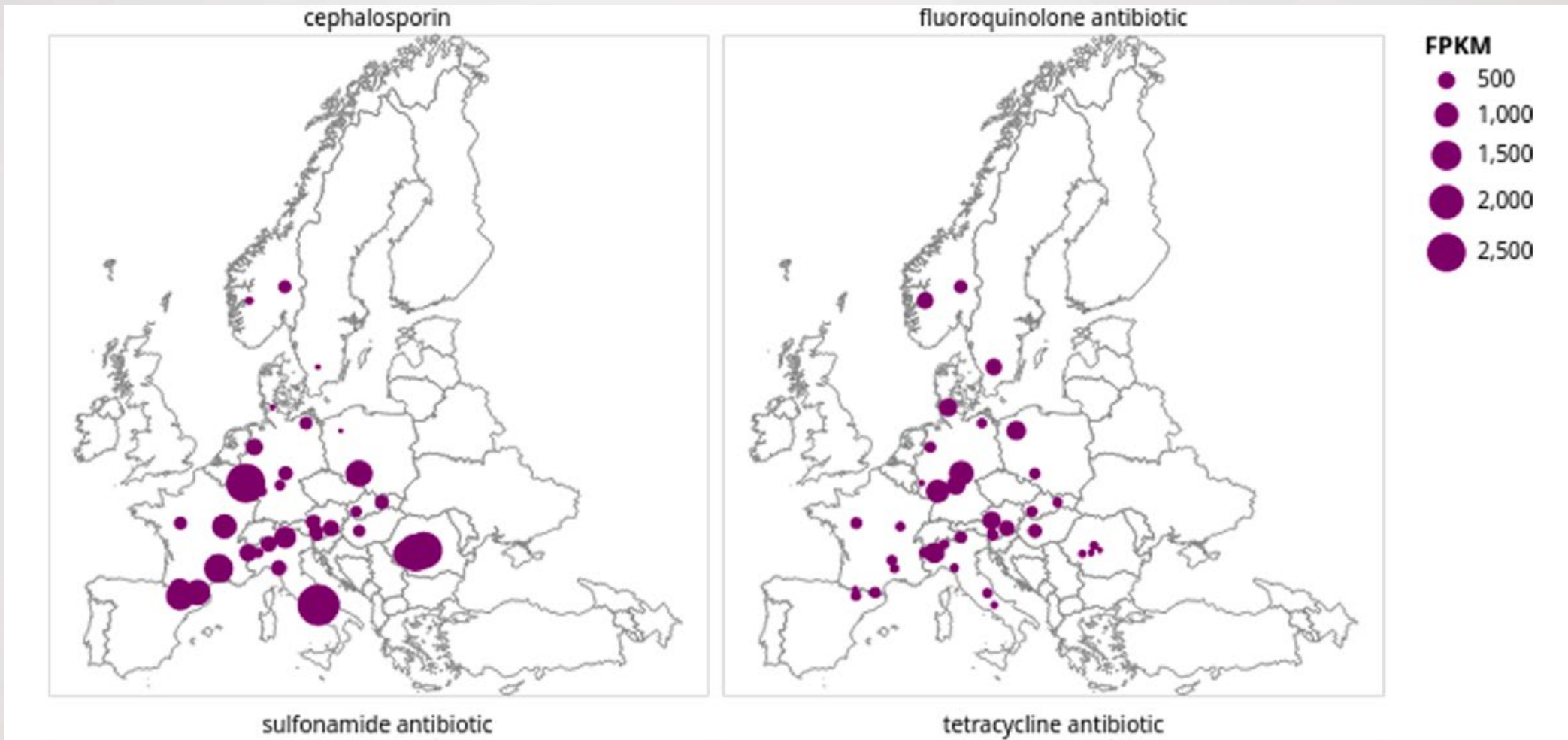
Summary



Boxplot of mapped genes for resistance to drug classes

No. lokes sampled: Austria (5), France (8), Germany (7), Hungary (1), Italy (6), Norway (2), Poland (2), Romania (4), Slovakia (2), Spain (1), Sweden (1).

Density of resistance genes fragments per lake



The larger dot represents more fragments mapped to respective resistance class. Increased fragments mapped to cephalosporin resistance in Romania, Italy, Germany.

How does this compare elsewhere outside Europe?



Ecotoxicology and Environmental Safety 194 (2020) 110443



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Ecotoxicology and Environmental Safety

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



Maharashtra

Shotgun metagenome guided exploration of anthropogenically driven resistomic hotspots within Lonar soda lake of India

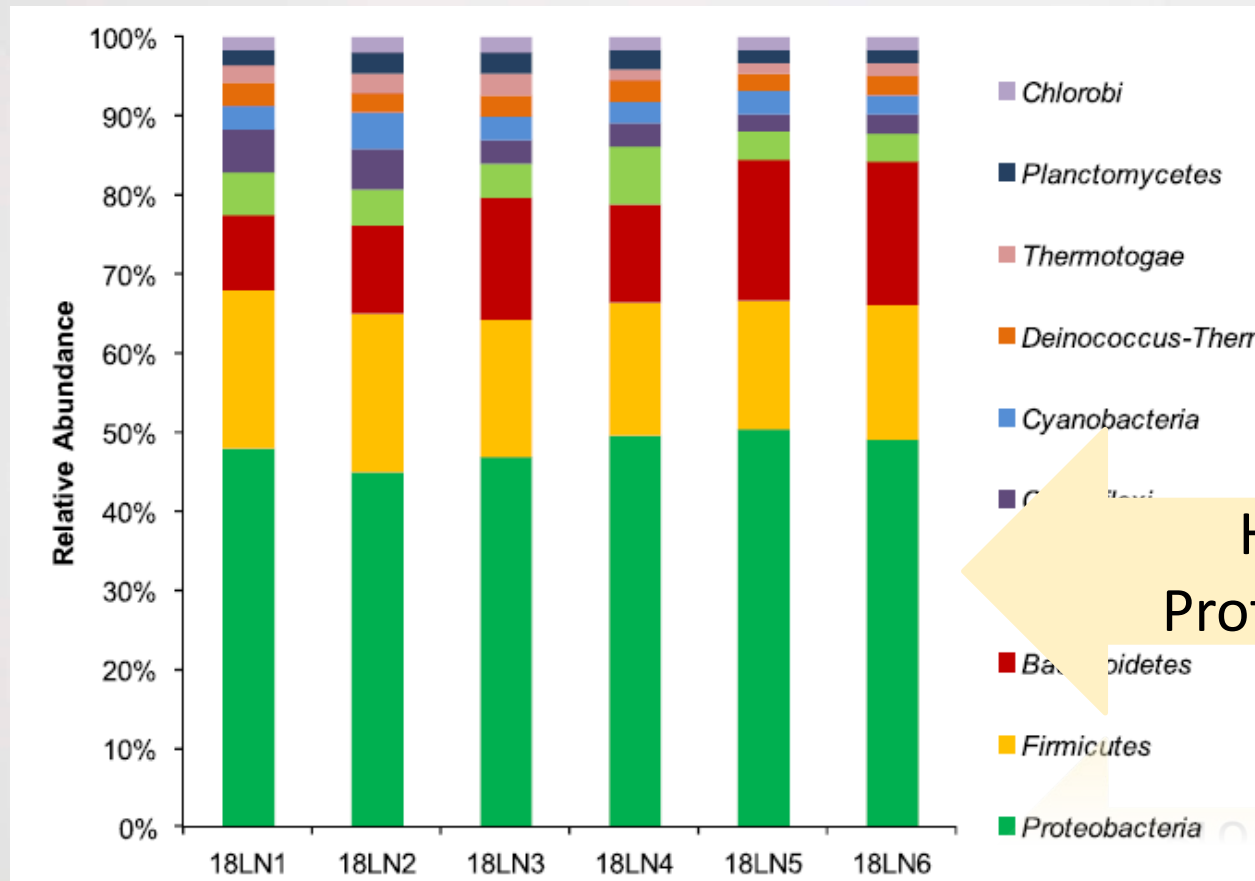
Jaya Chakraborty^{a,1}, Vibhavari Sapkale^{a,b,1}, Vinay Rajput^{a,1}, Manan Shah^a, Sanjay Kamble^c, Mahesh Dharne^{a,b,*}

¹ National Collection of Industrial Microorganisms (NCIM), CSIR-National Chemical Laboratory (NCL), Pune, India

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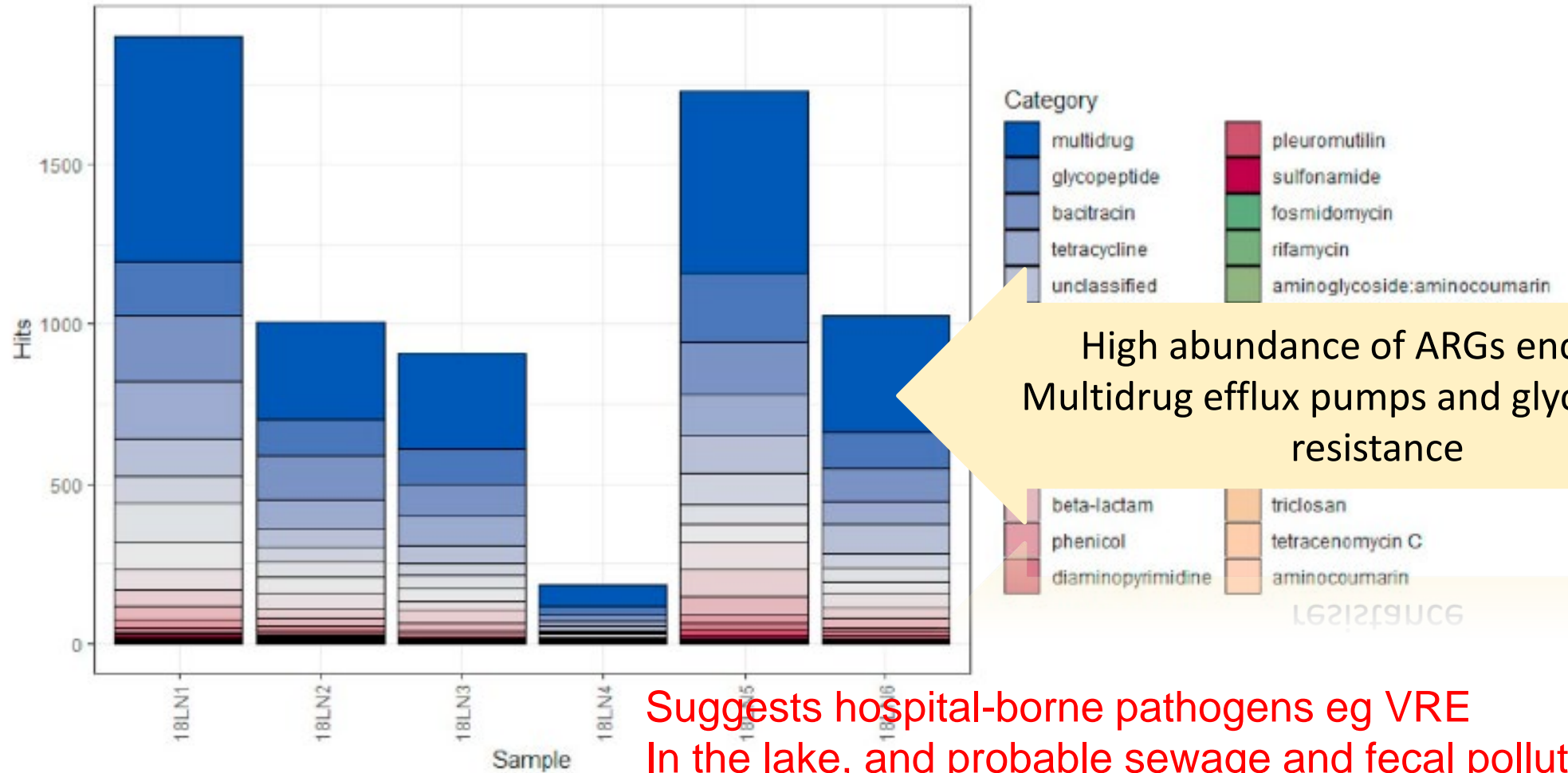
³ Chemical Engineering and Process Development (CEPD) Division, CSIR-National Chemical Laboratory (NCL), Pune, India

Lonar lake of India: Microbial Diversity

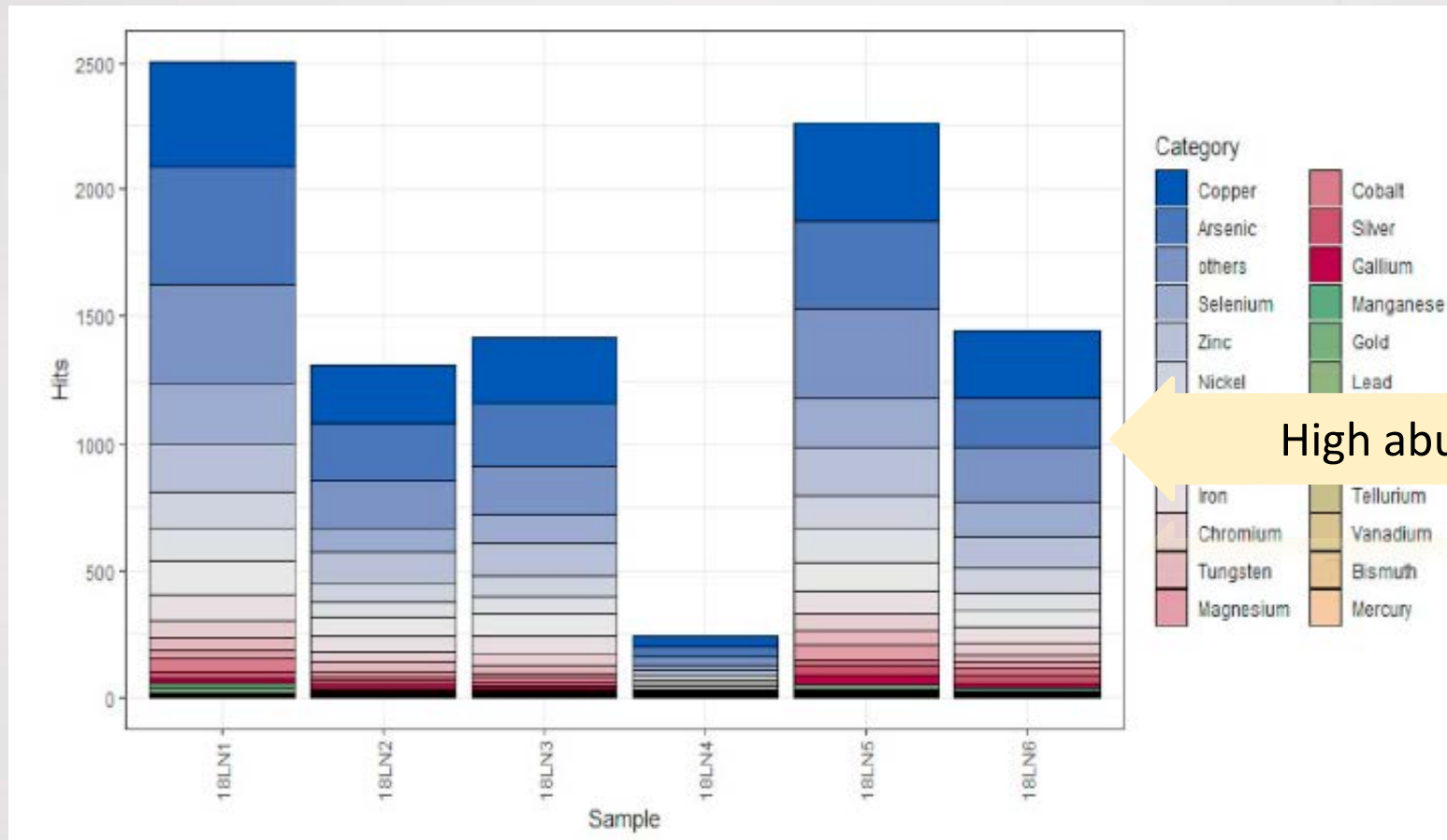


High abundance of Proteobacteria eg. *E. coli*

Lonar lake of India: Antimicrobial resistance genes (ARGs)

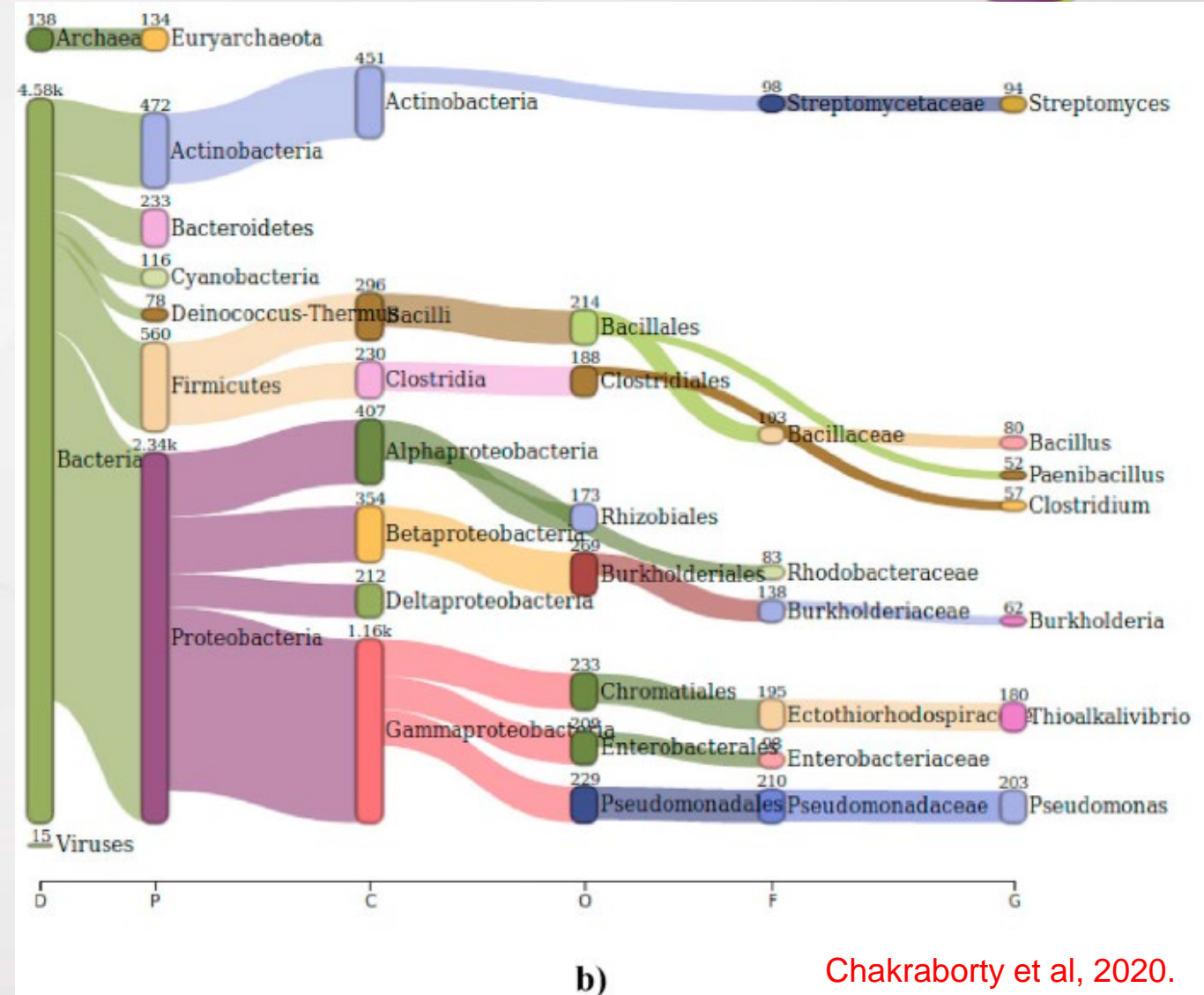
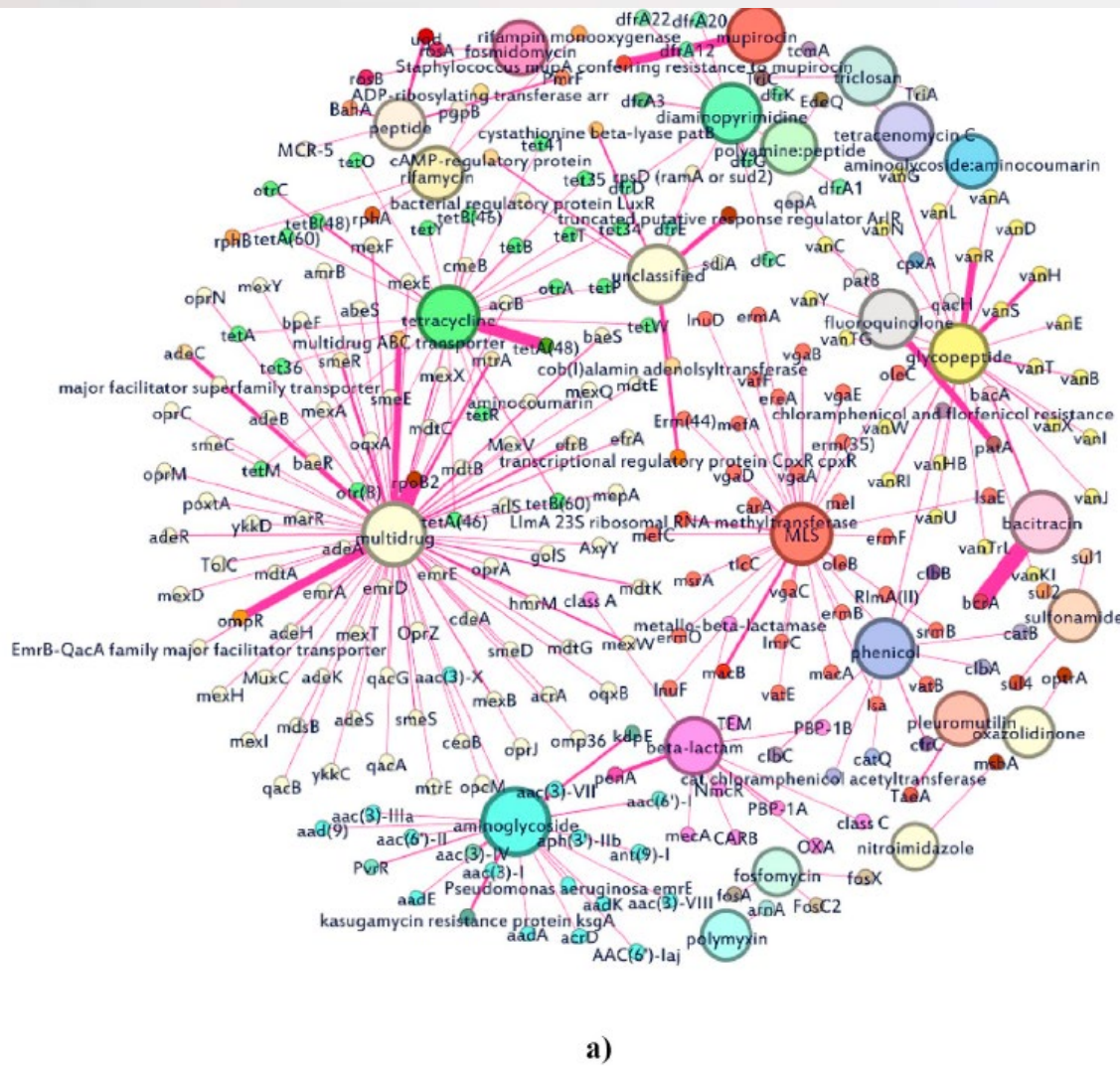


Lonar lake of India: Metal resistance genes (MRGS)



Diverse human microbial communities carrying ARGs and MRGs in the lake support the influence and widespread anthropogenic activities

Network analysis revealing the ARG types (1) and abundance of microbial genera contributing to the Lonar lake samples





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Role of the environment

To develop standards and guidance...for the presence of antimicrobial agents and their residues in the environment, especially in water, wastewater and food (inc. aquatic and terrestrial animal feed)

Drivers and pathways leading to AMR in the Environment



- Selection of resistance genes, beyond antimicrobials, biocides, heavy metals and other chemicals
- Co-selection of genes that confer resistance to chemical hazards (solvents, biocides, antibiotics and metals)
- ARGs themselves may also confer resistance to other chemicals, apart antimicrobials
- 3 major pathways for resistance-driving chemicals into the environment:
 - (1) Municipal and industrial wastewater;
 - (2) Land spreading of animal manure and sewage sludge; and
 - (3) Aquaculture.

Mitigation Strategies to tackle AMR through Resistomes



- Surveillance and monitoring of resistomes on pathways that select AMR
- Regulation and control pathways responsible for release of resistance-driving chemicals into environment
- Understanding and close evidence gaps concerning AMR development pathways
- Understanding selection risks of antibiotics, biocides, metals and other chemicals eg concentrations of antimicrobials
- Others: air transmission (bioaerosols),

Monitor and Control of Environment by Regulators

TABLE 1 | Environment and activities or products monitored or regulated by the Environment Agency of England, which play a potentially important role in the spread and maintenance of AMR in the environment.

Environment	Intersection of Environment Agency with AMR
Wastewater treatment plant (WWTP)	¹ Discharge of treated effluent (from industry and municipal sewage) to land, coast or rivers. ¹ Disposal of sewage sludge ^{1,2,3} Disposal of anaerobic digestate
Agriculture	¹ Land spreading of manure, sewage sludge, and anaerobic digestate as fertilizer or soil conditioner. ¹ Bioaerosols from agriculture (pig and poultry farming) and composting.
Animal husbandry	¹ Disposal of animal by-products ^{1,2} Disposal of animal slurry and manure ^{1,2,3} Disposal of anaerobic digestate
River water quality	^{1,4} Impact of sewage effluent ^{1,4} Impact of diffuse pollution from farm-yard, manure- and biosolid-amended agricultural soil and storm runoff ^{1,4} Freshwater fish farm
Coastal and bathing waters	^{1,4} Impact of farmyard runoff and sewage effluent on bathing water quality, and shellfish bed water quality ^{1,4} Impact of aquaculture on coastal water quality.
Groundwater quality	^{1,5} Leaching of soil amendments (biosolids and manure) and chemical crop treatments

Key regulations: ¹Environmental Permitting (England and Wales) Regulations 2010 (Defra, 2013); ²Animal By-Products (Enforcement) (England) Regulations 2013 (Public Health England, 2013); ³Anaerobic digestate: PAS 110:2014 (BSI, 2014); ⁴Water Framework Directive 2000/60/EC (WFD) (European Commission, 2000); ⁵The Sludge (Use in Agriculture) Regulations 1989 (Public Health England and Wales, and Public Health Scotland, 1989).

Humans **ONE** Animals

- Advancing age
- Diabetes and obesity
- Co-morbidities

- Expanding aquaculture
- Animal husbandry
- Animal health

HEALTH

Environment

- Global warming

AMR and disease surveillance
Prevention and infection control
Reduce AMR in people and animal



Challenges and solution: Containment Strategy and Prompt Response to Emerging Antimicrobial Threats

- Hi-throughput surveillance tool: monitoring trends and identify risks /pathways to AMR
- Appropriate control measures to mitigate and contain spread
- Discovery and characterization of new resistance mechanism(s)
- Development of new drug targets

Acknowledgement

All infection control teams, laboratory staff and healthcare workers in the infection control programmes at the HA hospitals and at CHP

Food and Health Bureau for HMRF Grant on Resistomes

HMRF Commissioned Grant on One Health Approach to Track and Target Antimicrobial Resistance (TnT-AMR)

GRF funding in the study of AMR

Seed funds from Centre of Microbiota Studies, Faculty of Medicine, CUHK

