Environmental Dimensions and Sewage Surveillance of Antibiotic Resistance

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http://gu.se/en/care

Picture by M Kumar, Associated Press

The environment’s role in antibiotic resistance

- <u>**Transmission route**</u> for certain resistant bacteria (human/animal → environment → human/animal)

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MIXING, BOTTLENECKS AND SPREAD
AMR in the environment

Toxin trouble
How Clostridioides *difficile* intoxicates the host

Larsson DGJ, Flach C-F. (2022). Antibiotic resistance in the environment. Nature Reviews Microbiology. DOI: 10.1038/s41579-021-00649-x

Huijbers PMC, Flach C-F, Larsson DGJ. (2019). A conceptual framework for the environmental surveillance of antibiotics and antibiotic resistance. Environ Int. 130:104880.

Bengtsson-Palme J, Kristiansson E, Larsson DGJ. (2018). Environmental factors influencing the development and spread of antibiotic resistance. FEMS Micro Rev. 1;42.

The environment’s role in antibiotic resistance

- **Transmission route** for certain resistant bacteria (human/animal → environment → human/animal)

- **Source and evolutionary ”arena”** for the emergence of new forms of resistance

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The environment’s role in antibiotic resistance

- **Transmission route** for certain resistant bacteria (human/animal → environment → human/animal)
- **Source and evolutionary ”arena”** for the emergence of new forms of resistance
- **Possible indicator of the regional resistance situation**


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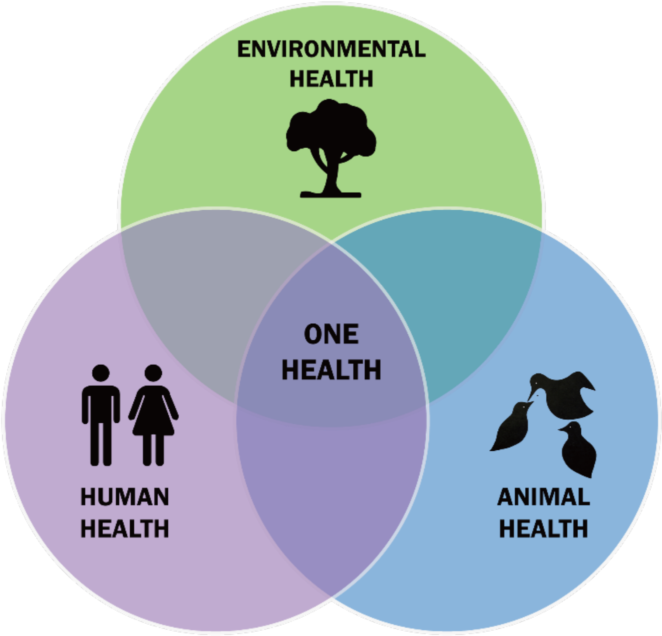
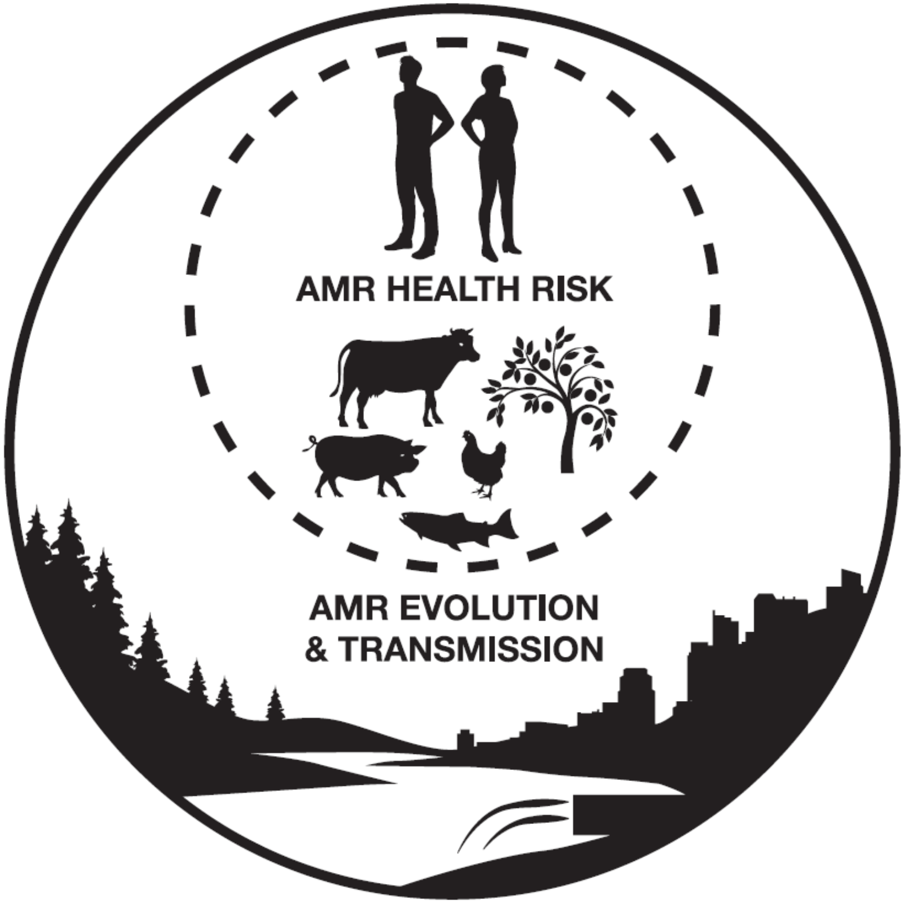
AMR* is **not** a threat to the health of the environment

Common illustration of One Health





**Antibiotics (but not the resistance to antibiotics) <u>can</u> be a direct threat to the health of the environment, but the evidence for that is still very limited*

Larsson DGJ, Gaze WH, Laxminarayan R, Topp R. (2023). AMR, One Health and the environment. ***Nature Microbiology***. https://doi.org/10.1038/s41564-023-01351-9. Read-only link: https://rdcu.be/c8MpY

1. Transmission risks

Environmental Science & Technology

Viewpoint

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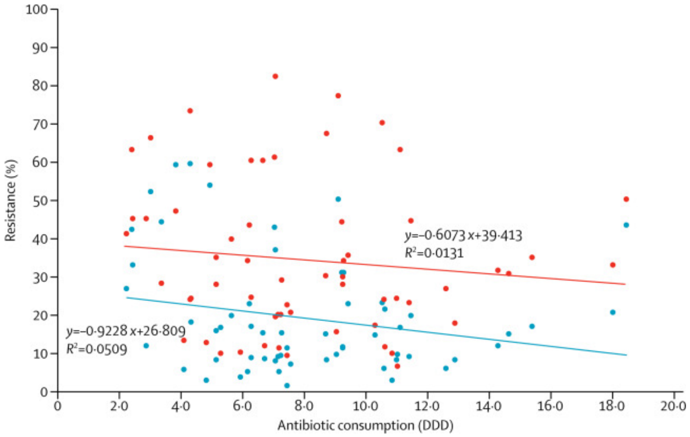
Underappreciated Role of Regionally Poor Water Quality on Globally Increasing Antibiotic Resistance

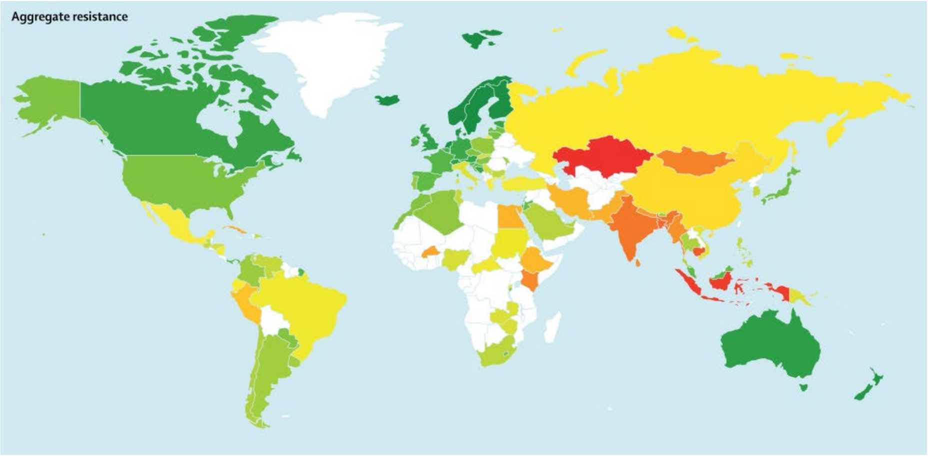
David W. Graham,[*,†] Peter Collignon,[‡] Julian Davies,[§] D. G. Joakim Larsson,[∥] and Jason Snape[⊥]

Globally, antibotic resistance is more strongly linked to lack of sanitation than to reported antibiotic use!

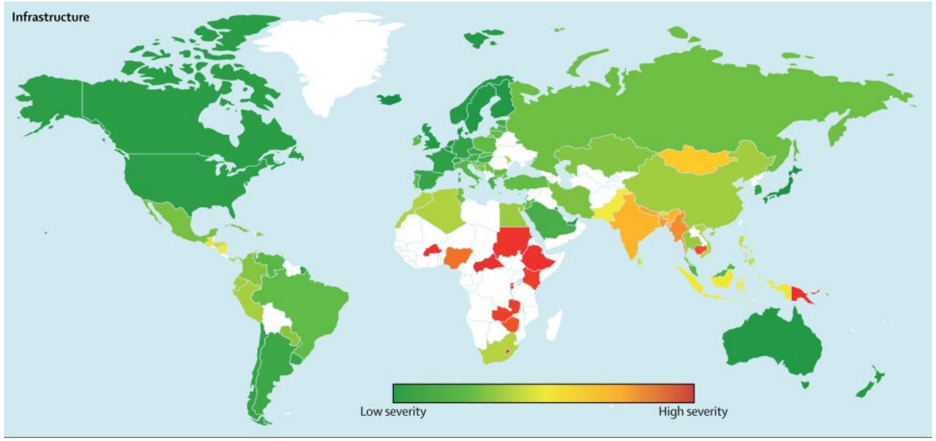


***Escherichia coli* resistance levels for fluoroquinolones and third-generation cephalosporins compared with antibiotic consumption**

Aggregated resistance index



Infrastructure (sanitation control)



Collignon P, Beggs JJ, Walsh TR, Gandra S, Laxminarayan R. Anthropological and socioeconomic factors contributing to global antimicrobial resistance: a univariate and multivariable analysis. Lancet Planet Health. 2018 Sep;2(9):e398-e405

Mendelson M, Laxminarayan R et al. 2024. Antimicrobial resistance and the great divide: inequity in priorities and agendas between the Global North and the Global South threatens global mitigation of antimicrobial resistance. Lancet Global Health. doi.org/10.1016/S2214-109X(23)00554-5

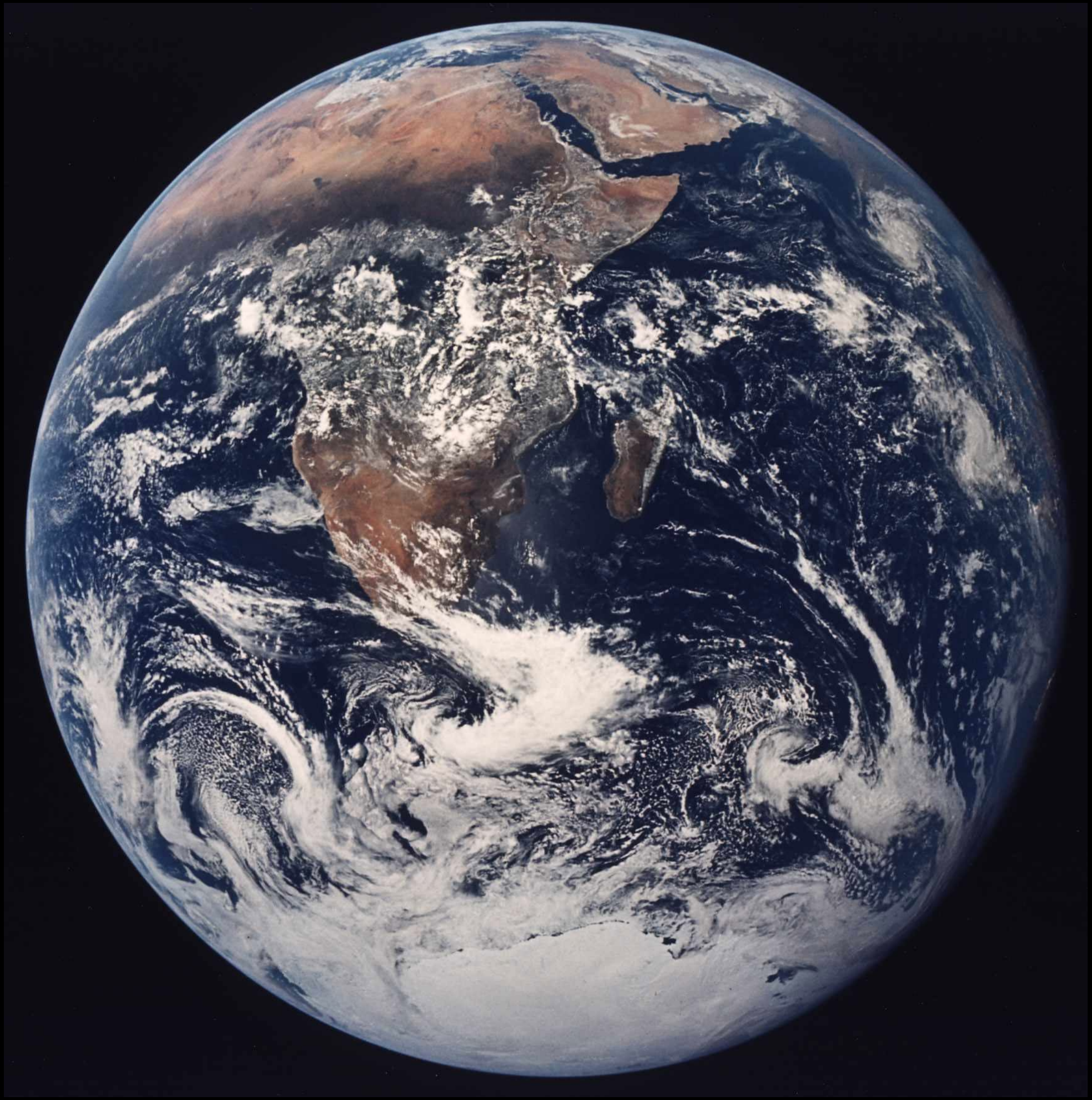
Reduce fecal pollution where human exposure is large!
(and/or reduce human exposure)

Where are risk for transmission of resistant bacteria highest?

- Simply measure *E coli* concentrations
(resistance analyses adds on the margin)!

2. Evolution risks

The environment harbours an enormous reservoir of resistance genes that one by one make their way to pathogens



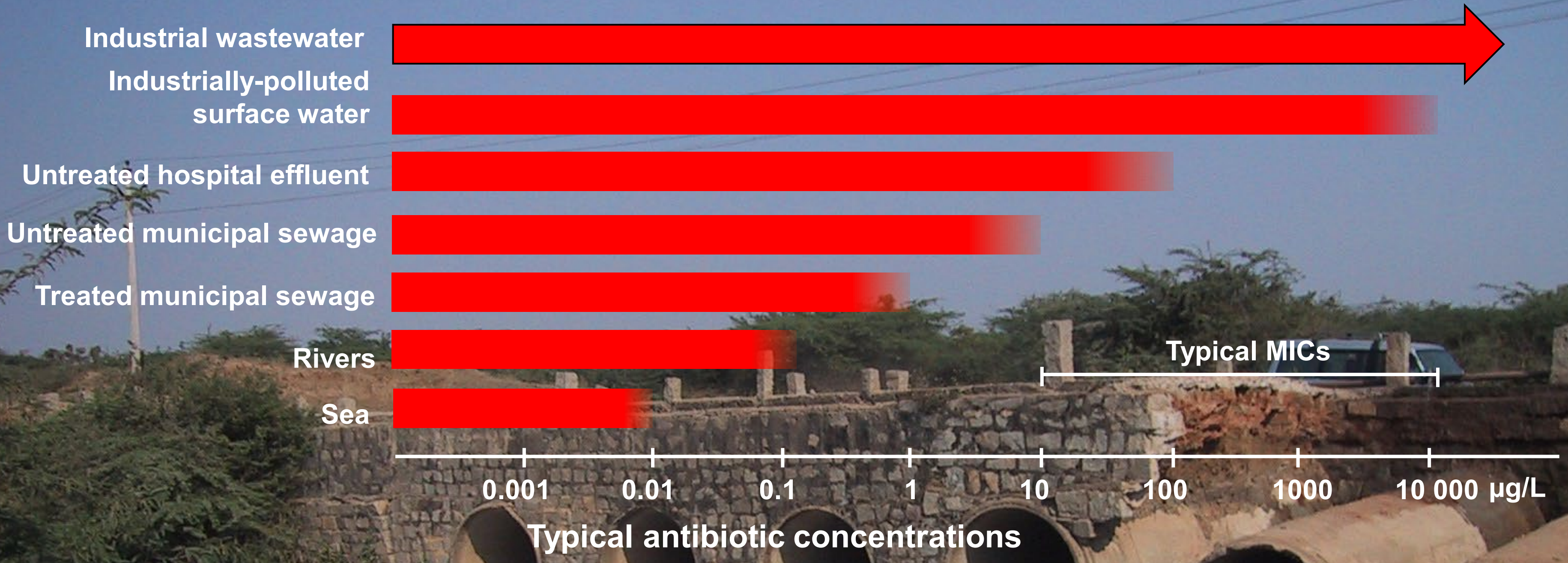
Lund D, Kieffer N, Parras-Moltó M, Ebmeyer S, Berglund F, Johnning A, Larsson DGJ, Kristiansson E. (2022). Large-scale characterization of the macrolide resistome reveals high diversity and several new pathogen-associated genes. Microbial Genomics. 8:000770.

Where do antibiotic resistance genes become mobile?

- unfolding history through comparative genomics points to wastewater as an important environment!

Berglund F, Ebmeyer S, Kristiansson E, Larsson DGJ. (2023).
Evidence for wastewaters as environments where mobile antibiotic resistance genes emerge.
Communications Biology 6: 321. https://doi.org/10.1038/s42003-023-04676-7

Antibiotics concentrations and risks for selection differ vastly between environments!



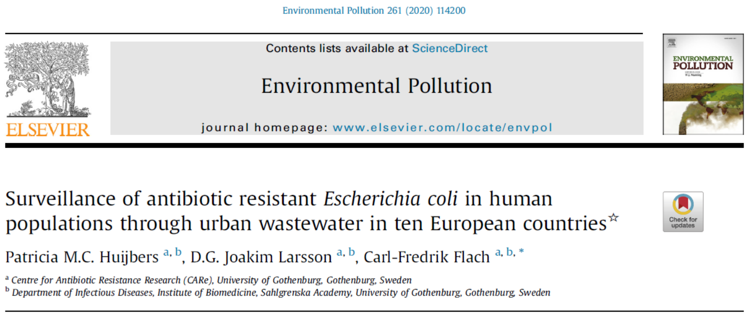
Modified from: Larsson DGJ and Flach CF. 2022.
Antibiotic resistance in the environment.
Nature Reviews Microbiology.
DOI: 10.1038/s41579-021-00649-x

WHO Guidance on waste and wastewater management in pharmaceutical manufacturing with emphasis on antibiotic production

https://www.who.int/teams/environment-climate-change-and-health/water-sanitation-and-health/burden-of-disease/wash-and-antimicrobial-resistance

3. Reflection of the regional resistance situation

Both isolate-based and gene-based sewage data may, to some extent, reflect the regional clinical antibiotic resistance situation



Environmental Pollution 261 (2020) 114200

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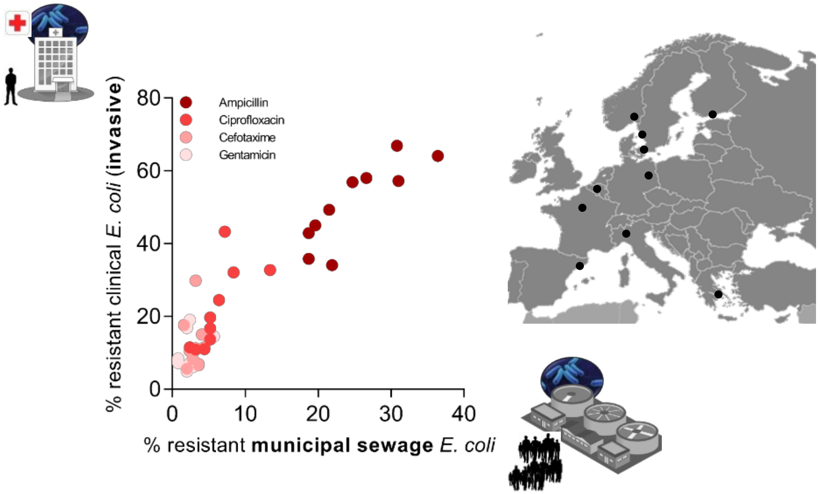
Environmental Pollution

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

Surveillance of antibiotic resistant *Escherichia coli* in human populations through urban wastewater in ten European countries☆

Patricia M.C. Huijbers [a, b], D.G. Joakim Larsson [a, b], Carl-Fredrik Flach [a, b, *]

[a] Centre for Antibiotic Resistance Research (CARe), University of Gothenburg, Gothenburg, Sweden
[b] Department of Infectious Diseases, Institute of Biomedicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

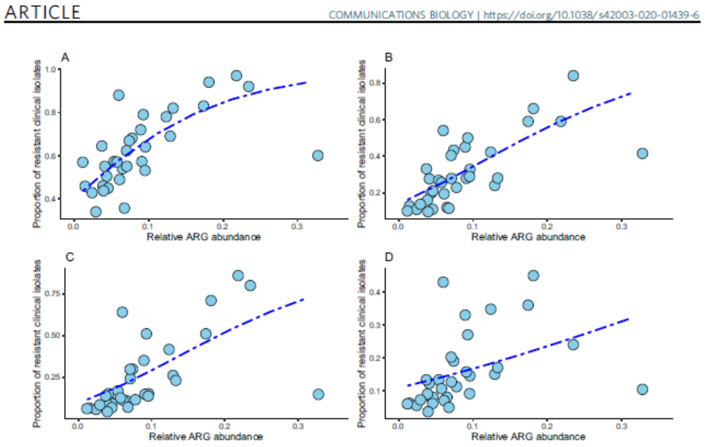


ARTICLE

https://doi.org/10.1038/s42003-020-01439-6 OPEN

Predicting clinical resistance prevalence using sewage metagenomic data

Antti Karkman [1,2], Fanny Berglund [3,4], Carl-Fredrik Flach [3,4], Erik Kristiansson [4,5] &
D. G. Joakim Larsson [3,4]✉

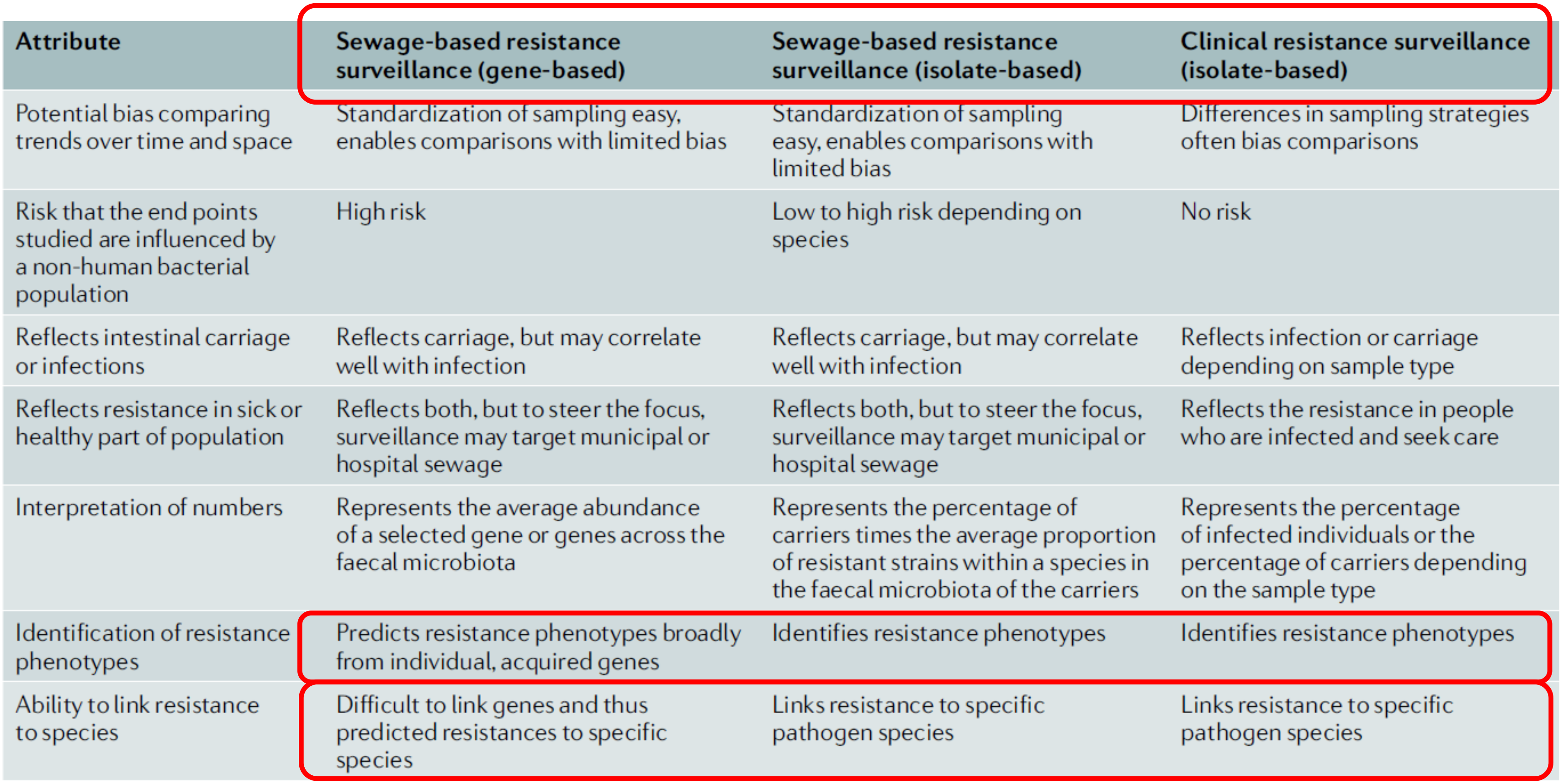


ARTICLE COMMUNICATIONS BIOLOGY | https://doi.org/10.1038/s42003-020-01439-6

Fig. 1 ***E. coli*** **clinical resistance models based on the ten most common ARGs in** ***E. coli*****.** Proportion of resistant invasive *E. coli* clinical isolates to aminopenicillins **a**, fluoroquinolones **b**, third generation cephalosporins **c**, and aminoglycosides **d** against the relative abundance of the 10 most common ARGs in *E. coli*. The blue line shows the fitted clinical resistance from the beta regression model with resistance gene abundance as explanatory variable. Note that for some countries, data on clinical resistance was not available for all classes.

For a conceptual comparison between methods, see:
Larsson DGJ, Flach C-F. (2022). Antibiotic resistance in the environment. Nature Reviews Microbiology. DOI: 10.1038/s41579-021-00649-x

Comparison of sewage-based resistance surveillance* (gene- or isolate-based) with traditional clinical resistance surveillance



Attribute	Sewage-based resistance surveillance (gene-based)	Sewage-based resistance surveillance (isolate-based)	Clinical resistance surveillance (isolate-based)
Potential bias comparing trends over time and space	Standardization of sampling easy, enables comparisons with limited bias	Standardization of sampling easy, enables comparisons with limited bias	Differences in sampling strategies often bias comparisons
Risk that the end points studied are influenced by a non-human bacterial population	High risk	Low to high risk depending on species	No risk
Reflects intestinal carriage or infections	Reflects carriage, but may correlate well with infection	Reflects carriage, but may correlate well with infection	Reflects infection or carriage depending on sample type
Reflects resistance in sick or healthy part of population	Reflects both, but to steer the focus, surveillance may target municipal or hospital sewage	Reflects both, but to steer the focus, surveillance may target municipal or hospital sewage	Reflects the resistance in people who are infected and seek care
Interpretation of numbers	Represents the average abundance of a selected gene or genes across the faecal microbiota	Represents the percentage of carriers times the average proportion of resistant strains within a species in the faecal microbiota of the carriers	Represents the percentage of infected individuals or the percentage of carriers depending on the sample type
Identification of resistance phenotypes	Predicts resistance phenotypes broadly from individual, acquired genes	Identifies resistance phenotypes	Identifies resistance phenotypes
Ability to link resistance to species	Difficult to link genes and thus predicted resistances to specific species	Links resistance to specific pathogen species	Links resistance to specific pathogen species

* Sewage surveillance with the specific objective to predict the resistance situation in humans

Larsson DGJ, Flach C-F. (2022). Antibiotic resistance in the environment. Nature Reviews Microbiology. DOI: 10.1038/s41579-021-00649-x

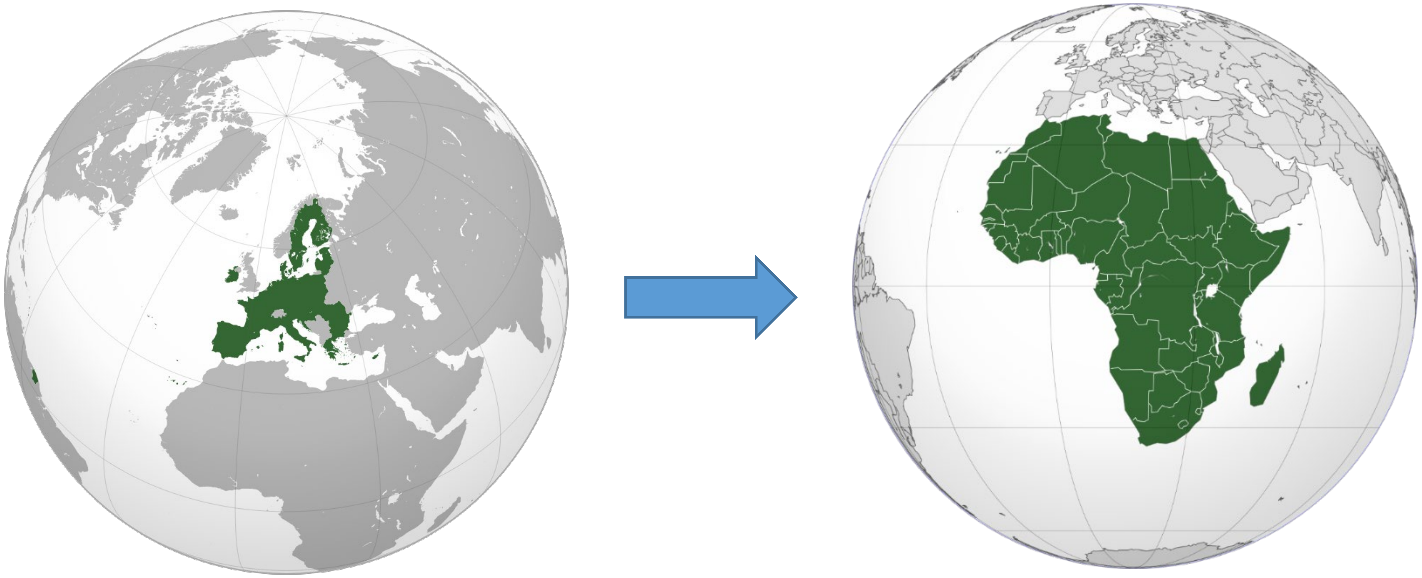
Comparison of sewage-based resistance surveillance* (gene- or isolate-based) with traditional clinical resistance surveillance

Attribute	Sewage-based resistance surveillance (gene-based)	Sewage-based resistance surveillance (isolate-based)	Clinical resistance surveillance (isolate-based)
Ability to identify multiresistance	Does not enable the identification of multiresistance patterns	Identifies multiresistance patterns	Identifies multiresistance patterns
Ability to identify rare types of resistance	Possible via targeted analyses (PCR)	Possible via selective culturing	Challenging
Provides patient-specific information	No	No	Yes
Ability to inform empirical treatment	Unlikely	Possibly, after evaluation	Informs empirical treatment
Prospect for acceptance in clinical community	Very different from current surveillance, major challenges	Different from current surveillance, but also bears similarities, challenging	The accepted standard among the clinical community
Ethical issues	No ethical issues with sampling	No ethical issues with sampling	Ethical issues may arise when carriers are identified
Cost	Inexpensive	Rather inexpensive	Expensive
Simplicity of sample collection and processing	Very simple sampling	Simple, but more elaborate sampling compared with gene-based sewage surveillance	Resource-demanding to process samples from many individual patients
Need for many samples	A single sample can (to some extent) reflect the resistance situation in an entire community	A single sample can (to some extent) reflect the resistance situation in an entire community	A large number of samples are needed to reflect the resistance situation
Need for calibration against clinical resistance prevalence	More calibration against clinical resistance needed	More calibration against clinical resistance needed	Considered 'gold standard' but suffers from, for example, sampling bias
Need for development of sampling protocol	One sampling protocol covers all enteric species (but without separation)	Efficient, specific sampling method evaluated for *Escherichia coli*, not yet for other species	Sampling method exists for almost all bacterial pathogens
Need for local health care infrastructure	No local health care infrastructure needed	No local health care infrastructure needed	Local health care infrastructure needed

* Sewage surveillance with the specific objective to predict the resistance situation in humans

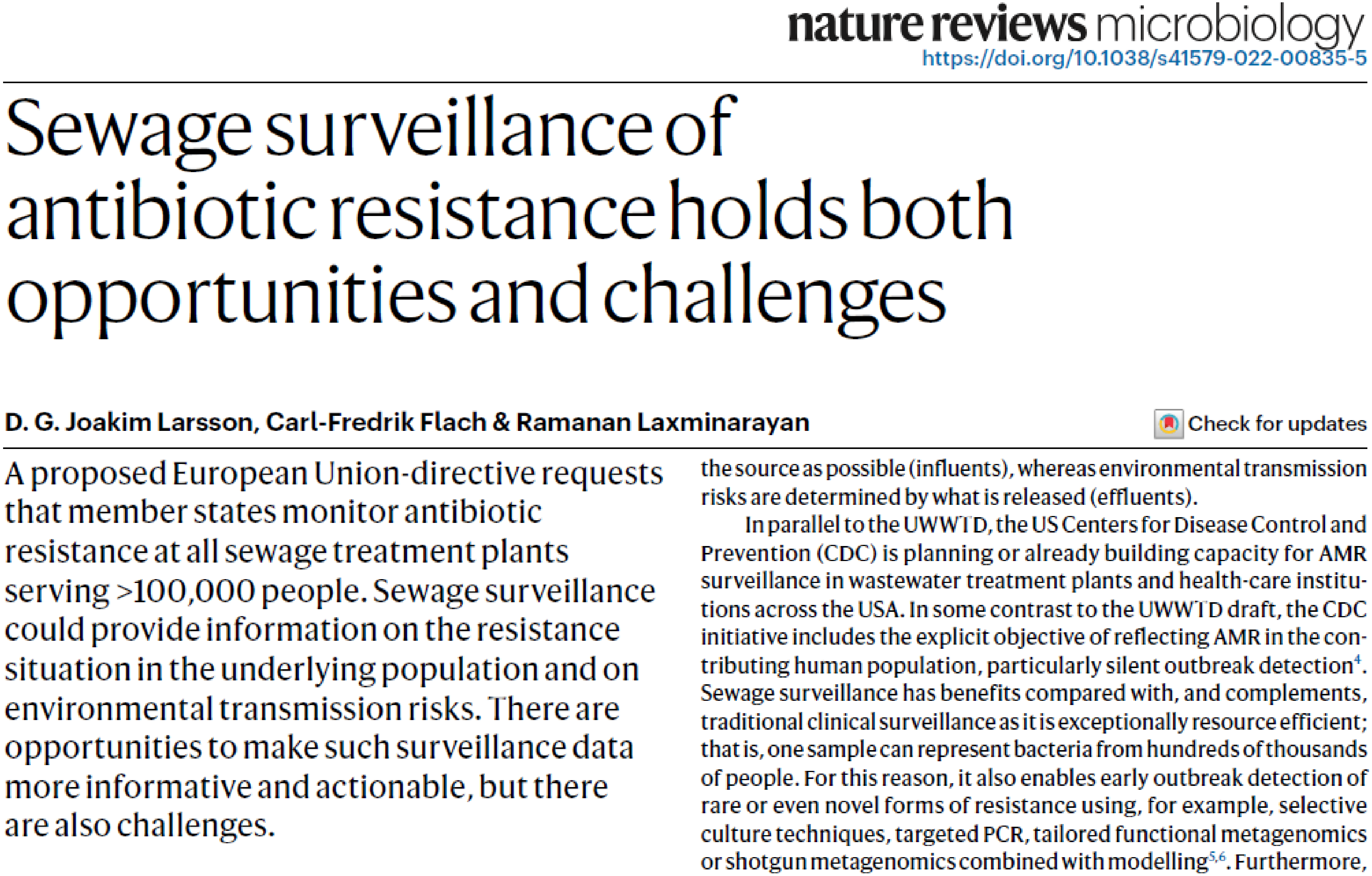
Larsson DGJ, Flach C-F. (2022). Antibiotic resistance in the environment. Nature Reviews Microbiology. DOI: 10.1038/s41579-021-00649-x

Greatest potential value in regions with limited or non-existing, systematic clinical surveillance



..but anywhere as an early warning system for rare or novel forms of resistance

Flach CF, Hutinel M, Razavi M, Åhrén C, Larsson DGJ. (2021). Monitoring of hospital sewage shows both promise and limitations as an early-warning system for carbapenemase-producing Enterobacterales in a low-prevalence setting. Water Research. 200:117261.



nature reviews microbiology

https://doi.org/10.1038/s41579-022-00835-5

Sewage surveillance of antibiotic resistance holds both opportunities and challenges

D. G. Joakim Larsson, Carl-Fredrik Flach & Ramanan Laxminarayan

Check for updates

A proposed European Union-directive requests that member states monitor antibiotic resistance at all sewage treatment plants serving >100,000 people. Sewage surveillance could provide information on the resistance situation in the underlying population and on environmental transmission risks. There are opportunities to make such surveillance data more informative and actionable, but there are also challenges.

the source as possible (influents), whereas environmental transmission risks are determined by what is released (effluents).

In parallel to the UWWTD, the US Centers for Disease Control and Prevention (CDC) is planning or already building capacity for AMR surveillance in wastewater treatment plants and health-care institutions across the USA. In some contrast to the UWWTD draft, the CDC initiative includes the explicit objective of reflecting AMR in the contributing human population, particularly silent outbreak detection[4]. Sewage surveillance has benefits compared with, and complements, traditional clinical surveillance as it is exceptionally resource efficient; that is, one sample can represent bacteria from hundreds of thousands of people. For this reason, it also enables early outbreak detection of rare or even novel forms of resistance using, for example, selective culture techniques, targeted PCR, tailored functional metagenomics or shotgun metagenomics combined with modelling[5,6]. Furthermore,

Flach CF, Hutinel M, Razavi M, Åhrén C, Larsson DGJ. (2021). Monitoring of hospital sewage shows both promise and limitations as an early-warning system for carbapenemase-producing Enterobacterales in a low-prevalence setting. Water Research. 200:117261.

Huijbers P, Bobis Camacho J, Hutinel M, Larsson DGJ, Flach CF. (2023). Sampling considerations for wastewater surveillance of antibiotic resistance in fecal bacteria. International Journal of Environmental Research and Public Health. 20(5):4555

Thank you for listening

Joakim Larsson group

The Larsson group is engaged in research on several aspects of antibiotic resistance, but has a particular expertise in the environmental dimensions, spawning from a long-standing interest in pharmaceuticals in the environment.

Centre for Antibiotic Resistance Research in Gothenburg (CARe)

155 scientists from 18 departments at University of Gothenburg and Chalmers University of Technology

Vetenskapsrådet

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