ANTIBIOTIC POLLUTION FROM MANUFACTURING

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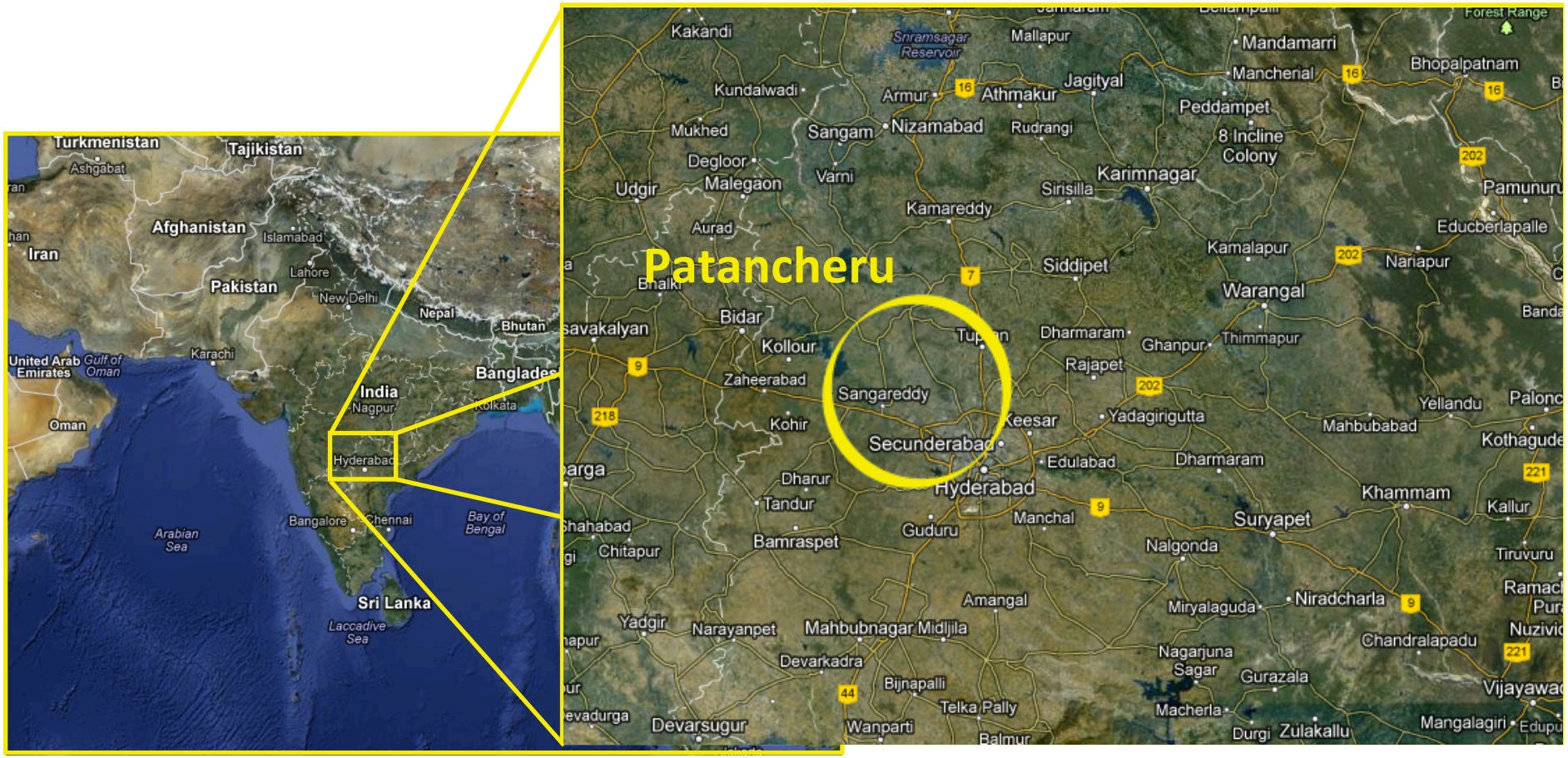
Patancheru, India



Active ingredient	Type of drug	Range (µg/L)
Ciprofloxacin	antibiotic-fluoroquinolone	28,000-31,000
Losartan	angiotensin II receptor antagonist	2,400-2,500
Cetirizine	H_1-receptor antagonist	1,300-1,400
Metoprolol	b_1-adrenoreceptor antagonist	800-950
Enrofloxacin	antibiotic-fluoroquinolone	780-900
Citalopram	serotonin reuptake inhibitor	770-840
Norfloxacin	antibiotic-fluoroquinolone	390-420
Lomefloxacin	antibiotic-fluoroquinolone	150-300
Enoxacin	antibiotic-fluoroquinolone	150-300
Ofloxacin	antibiotic-fluoroquinolone	150-160
Ranitidin	H_2-receptor antagonist	90-160

Based on LC-MS/MS, ESI+, 3-point standard addition, no preconcentration of samples

Larsson DGJ, de Pedro C, Paxeus N. 2007. Effluent from drug manufactures contains extremely high levels of pharmaceuticals. *J Haz Mat. 148 (3), 751-755*

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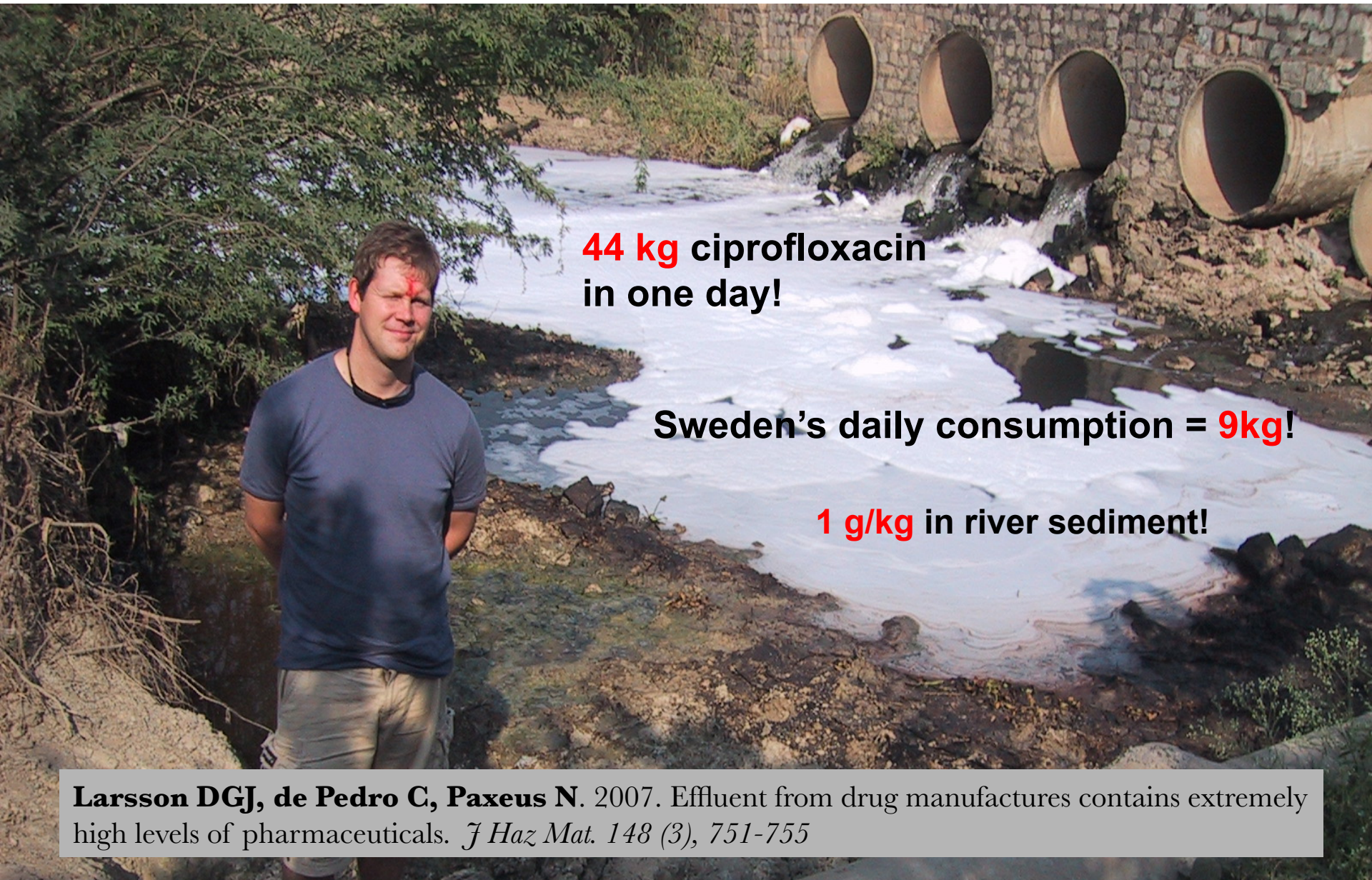

Larsson DGJ, de Pedro C, Paxeus N. 2007. Effluent from drug manufactures contains extremely high levels of pharmaceuticals. *J Haz Mat. 148 (3), 751-755*

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Surface, ground and drinking water highly contaminated with antibiotics and other drugs

Fick J, Söderström H, Lindberg RH, Chau DNP, Tysklind M, Larsson DGJ. 2009. Contamination of surface, ground, and drinking water from pharmaceutical production. *Environmental Toxicology & Chemistry 28:2522–2527*

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IS THE RELEASE OF ANTIBIOTICS INTO THE ENVIRONMENT A PROBLEM?

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Development of Antibiotic Resistance

- Mutations in the existing DNA
- Uptake of entirely new genes from other bacteria
- Bacteria are promiscuous, particularly when stressed!
- Resistance genes present everywhere, in harmless bugs

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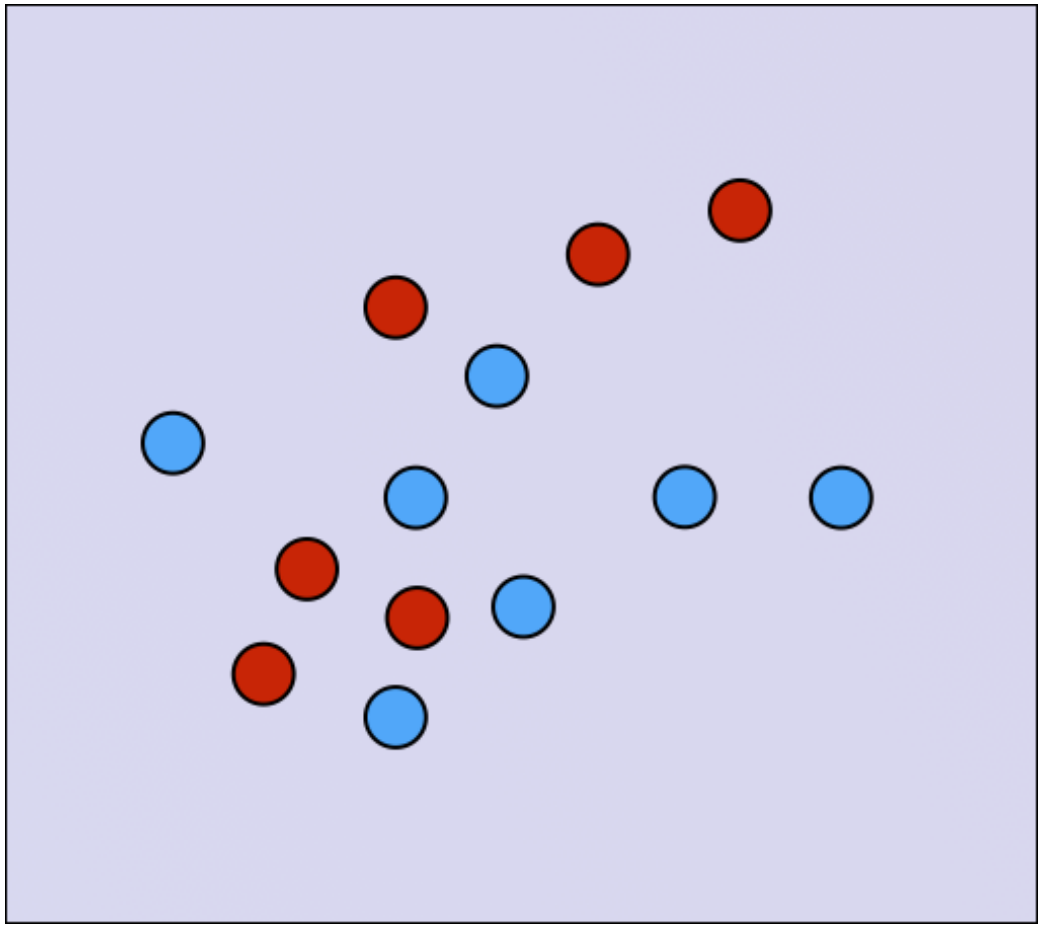
Resistant bacteria outcompete sensitive ones



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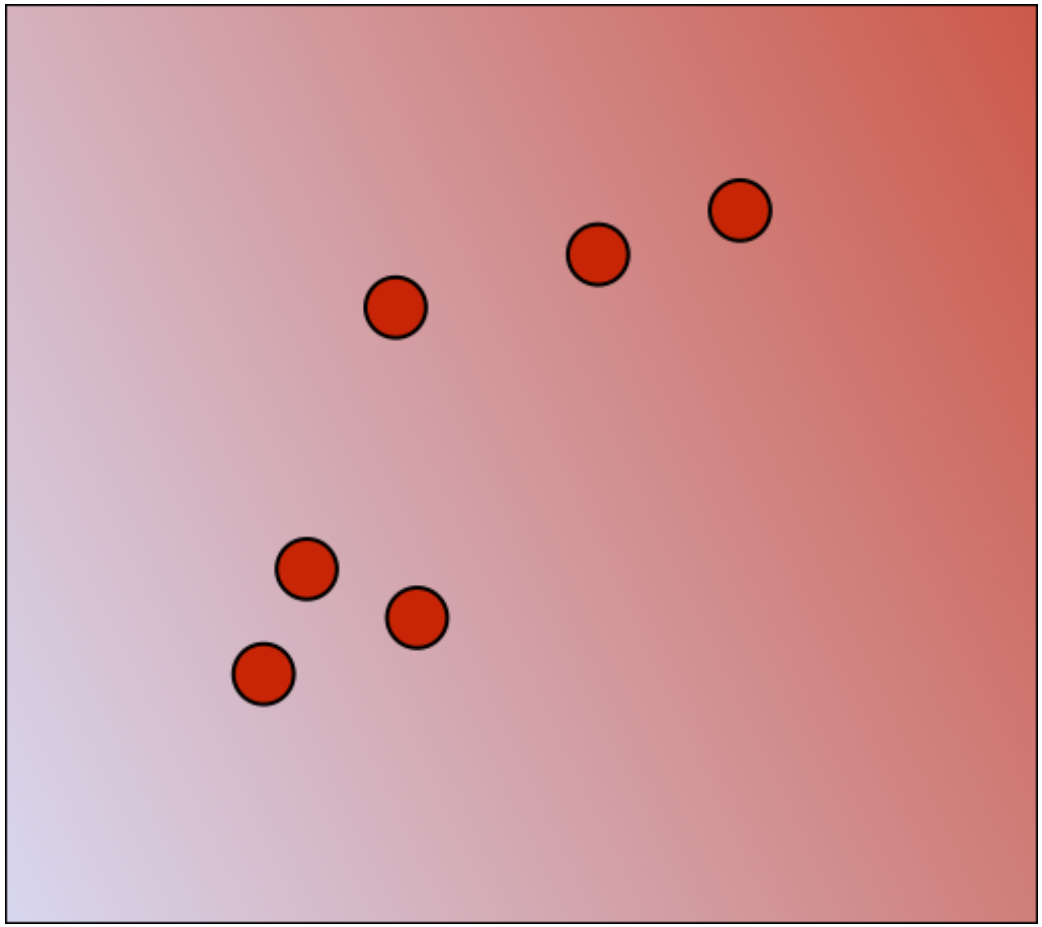
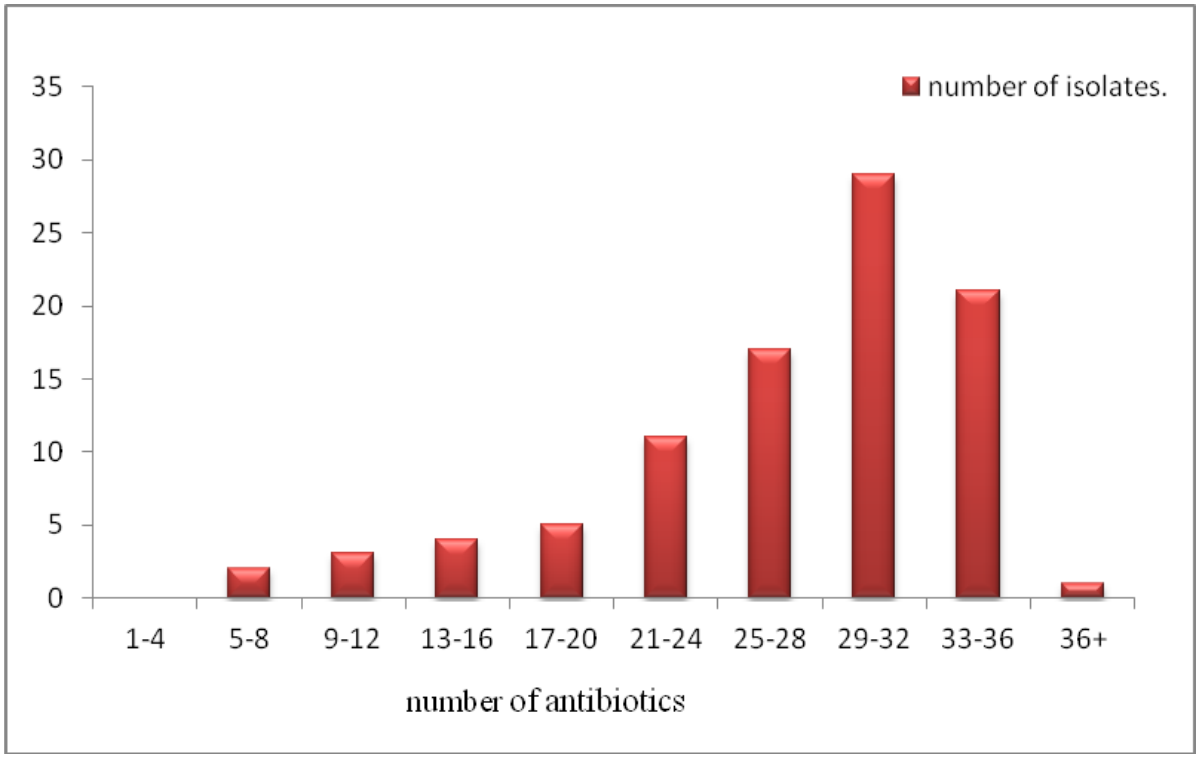
Resistant bacteria outcompete sensitive ones



…which means they can spread and increase in numbers

Highly multi-resistant bacteria within the treatment plant!



Marathe NP, Regina VR, Walujkar SA, Charan SS, Moore ERB, Charan SS, Moore ERB, Larsson DGJ, Shouche YS. 2013. A Treatment Plant Receiving Waste Water from Multiple Bulk Drug Manufacturers Is a Reservoir for Highly Multi-Drug Resistant Integron-Bearing Bacteria. *PLoS ONE 8(10): e77310*

Johnning A, Moore ERB, Svensson-Stadler L, Shouche YS, Larsson DGJ, Kristiansson E. 2013. The acquired genetic mechanisms of a multi-resistant bacterium isolated from a treatment plant receiving wastewater from antibiotic production. *Appl. Environ. Microbiol., 79(23):7256*

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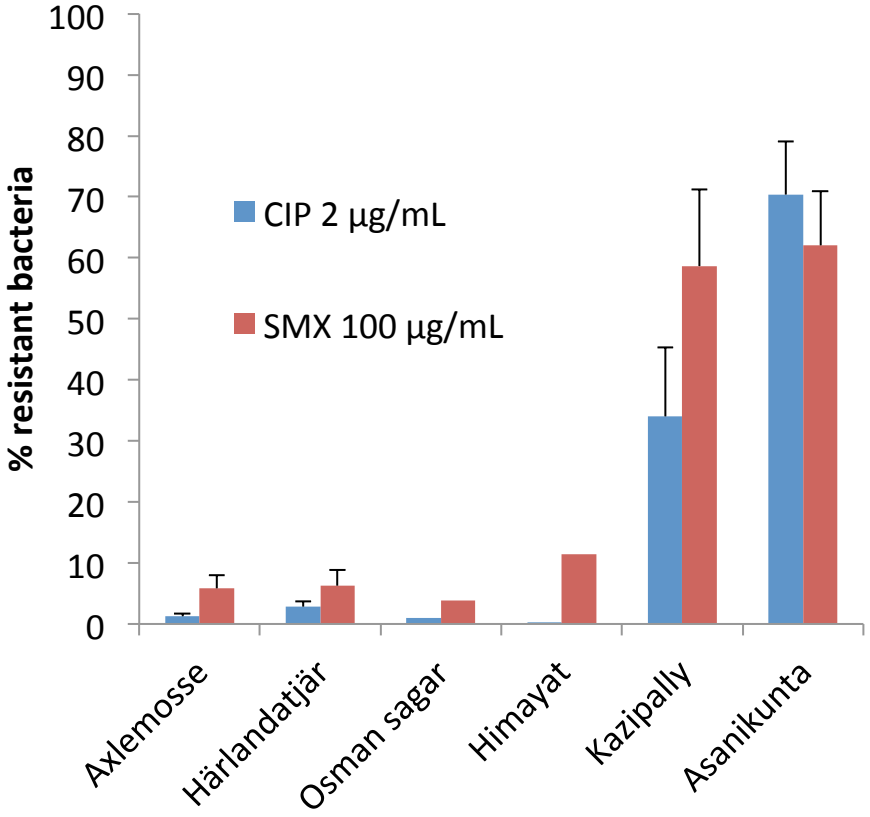
Resistant bacteria thrive in Indian lakes subjected to dumping of pharmaceutical waste



Flach CF, Johnning A, Nilsson I, Smalla K, Kristiansson E, Larsson DGJ. 2015. Isolation of novel IncA/C and IncN fluoroquinolone resistance plasmids from an antibiotic-polluted lake. *Journal of Antimicrobial Chemotherapy, 70, 2709–2717.*

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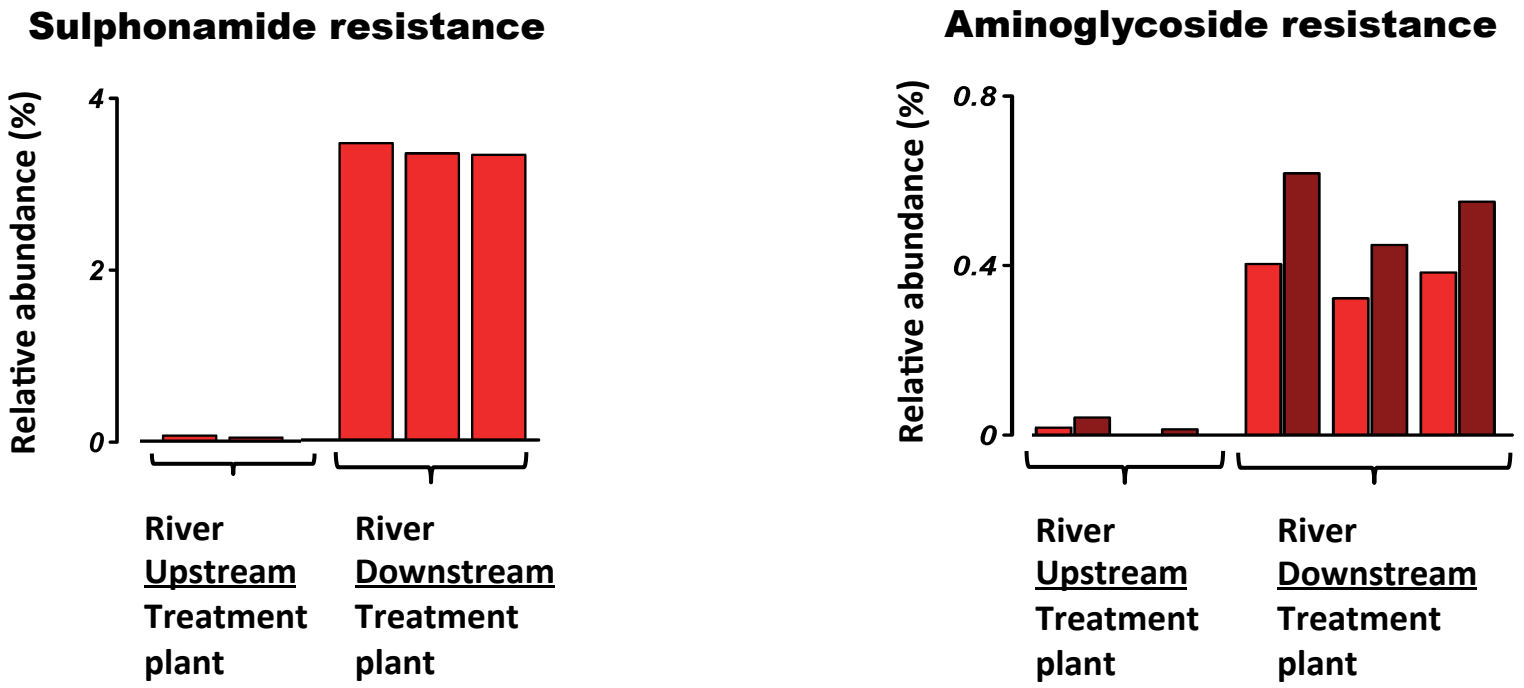
High levels of resistance genes in the polluted river sediments



Kristiansson E, Fick J, Janzon A, Grabic R, Rutgersson C, Weijdegård B, Söderström H, Larsson DGJ. 2011. Pyrosequencing of antibiotic-contaminated river sediments reveals high levels of resistance and gene transfer elements. *PLoS ONE. 6:e17038.*

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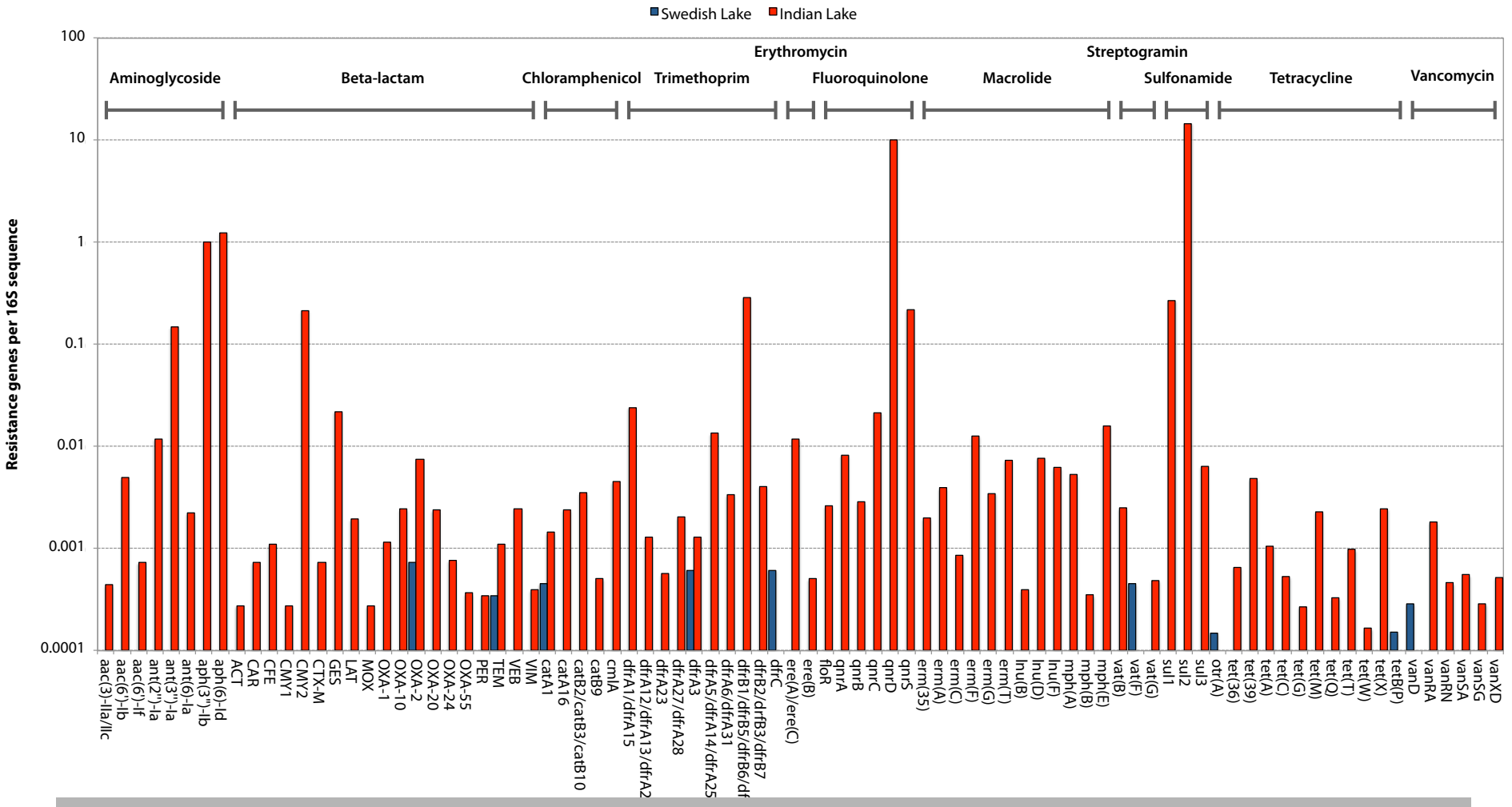
Huge resistance diversity in polluted lake



Bengtsson-Palme J, Boulund F, Fick J, Kristiansson E, Larsson DGJ. 2014. Shotgun metagenomics reveals a wide array of antibiotic resistance genes and mobile elements in a polluted lake in India. *Front Microbiol. 5:648.*

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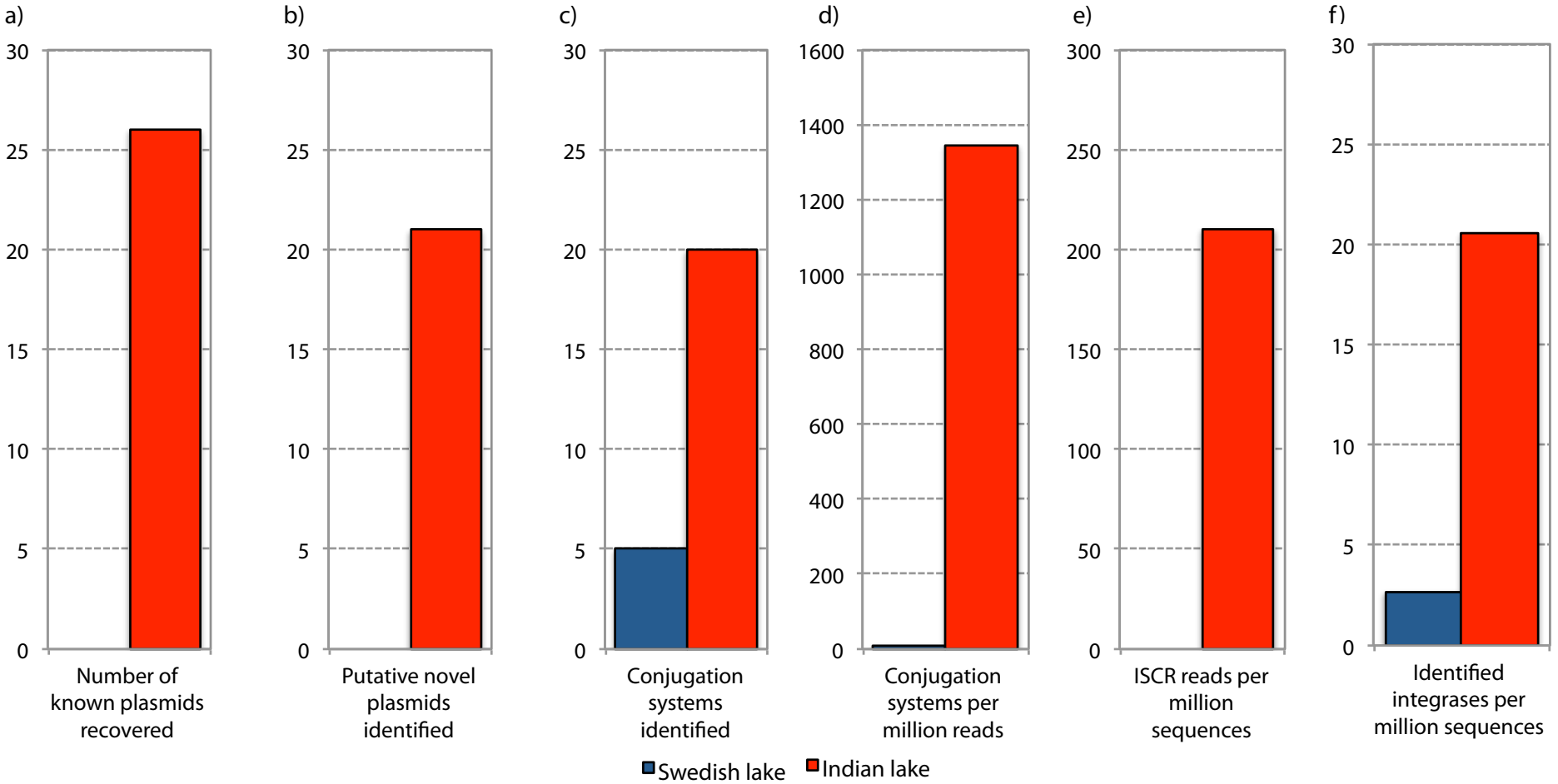
Bengtsson-Palme J, et al. 2014. *Front Microbiol. 5:648.*

...along with dramatically higher abundance of genes facilitating transfer of resistance



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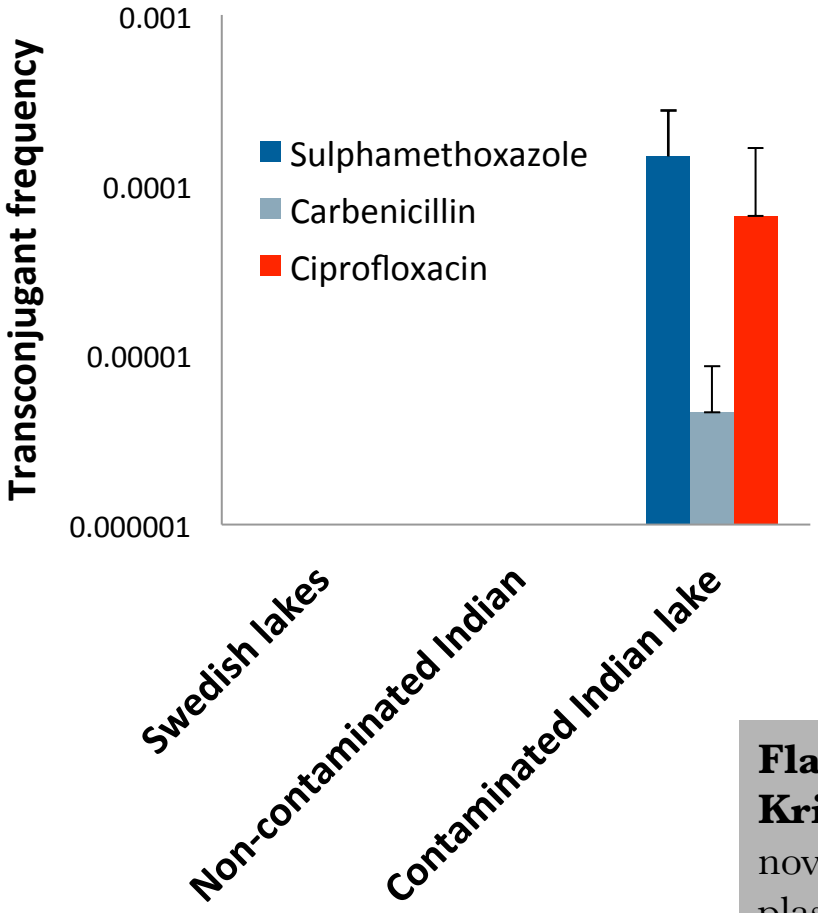
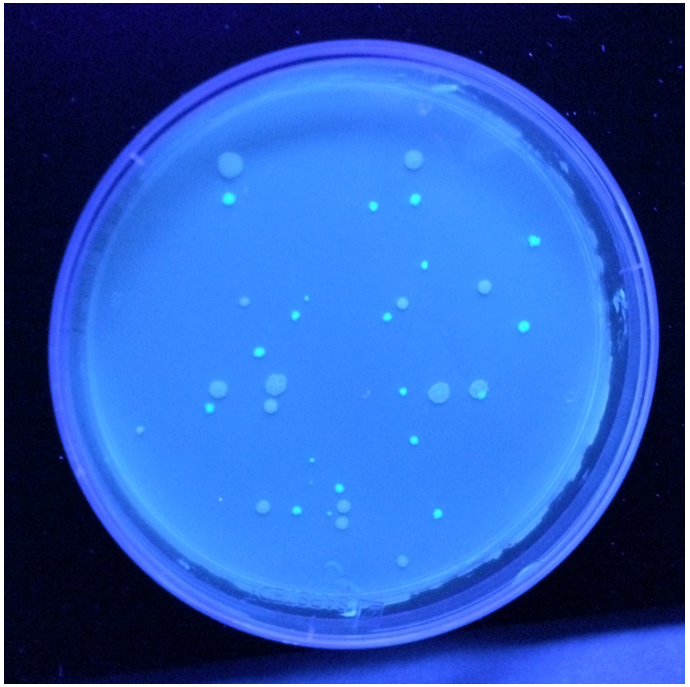
The genes can be transferred to pathogens!





Flach CF, Johnning A, Nilsson I, Smalla K, Kristiansson E, Larsson DGJ. 2015. Isolation of novel IncA/C and IncN fluoroquinolone resistance plasmids from an antibiotic-polluted lake. *Journal of Antimicrobial Chemotherapy, 70, 2709–2717.*

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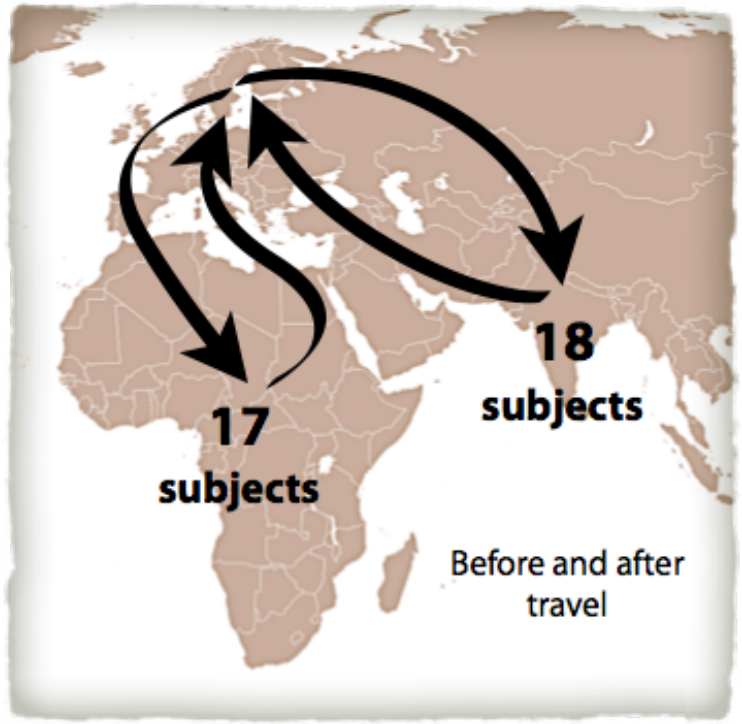
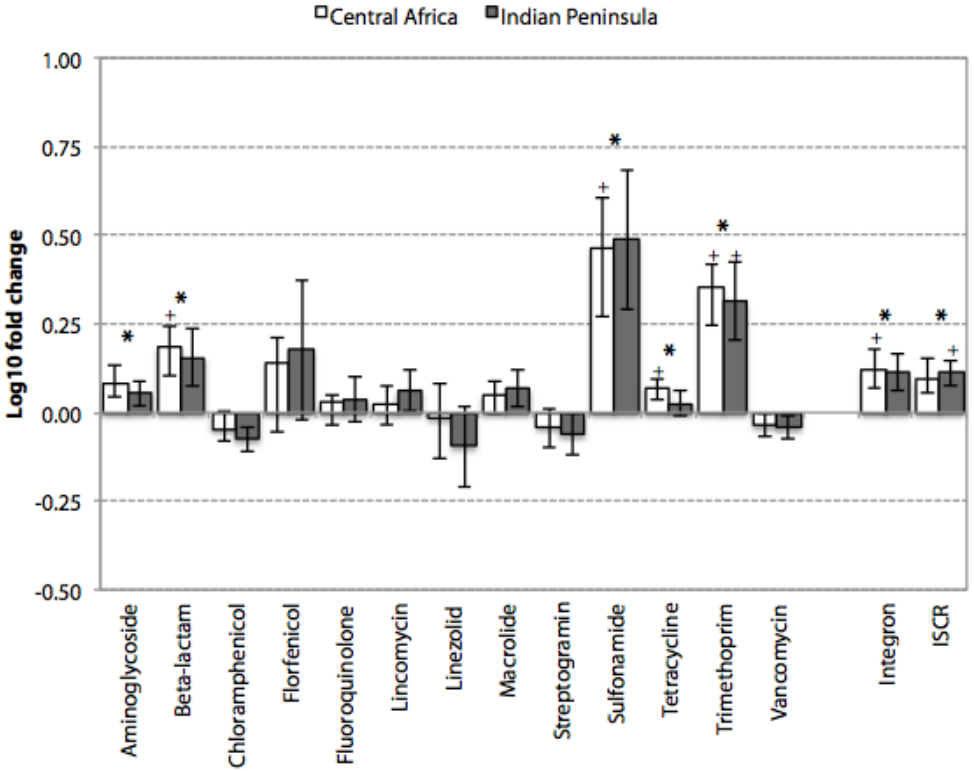
And resistance genes also spread by travel





Bengtsson-Palme J, Angelin M, Huss M, Kjellqvist S, Kristiansson E, Palmgren H, Larsson DGJ, Johansson A. 2015. The Human Gut Microbiome as a Transporter of Antibiotic Resistance Genes between Continents. *Antimicrob Agents Chemother. 59:6551–60.*

”……we argue that risks are greatest in those cases in which the mobilized resistance gene has not yet been detected in pathogenic bacteria..”

Bengtsson-Palme J, Larsson DGJ. 2015. Antibiotic resistance genes in the environment: prioritizing risks. *Nature Reviews Microbiology 13:396.*

What actions are needed?

- Consider resistance development in treatment of antibiotic waste
- Disinfection of effluent
- Non-toxic effluents
- Define discharge limits for antibiotics

Bengtsson-Palme J, Larsson DGJ. 2016. Concentrations of antibiotics predicted to select for resistant bacteria: Proposed limits for environmental regulation. *Environment International. 86:140–9.*

We need minimum standards to improve waste management in antimicrobial production

We need to improve standards of waste management to avoid scenarios where very high concentrations of antibiotics or APIs are released into the environment. There are different ways that this might be achieved. Our preferred route would be to have a minimum regulatory standard. However, while this is established, we believe there is a case for other participants in the supply chain to act now, improving transparency and standards for how antibiotic waste is treated.

A good starting point for such standards might be a recent study[65], which proposed maximum limits for concentrations of common antibiotics in water.

It is true that some companies have already made efforts to improve their environmental management through risk assessment frameworks. However, these do not currently consider the risks associated with rising resistance[66].

65. Bengtsson-Palme J, Larsson DGJ. Concentrations of antibiotics predicted to select for resistant bacteria: Proposed limits for environmental regulation. *Environment International*,2015,86:140-149, doi:10.1016/j.envint.2015.10.015.

66. Murray-Smith RJ, Coombe VT, Grönlund MH, et.al., Managing emissions of Active Pharmaceutical Ingredients from Manufacturing facilities: An Environmental Quality Standard Approach. Integrated *Environmental Assessment and Management*, 2011, 8 (2), 320-330.

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Industry Roadmap for Progress on Combating Antimicrobial Resistance – September 2016

1) We support measures to reduce environmental impact from production of antibiotics, and will:
    i. Review our own manufacturing and supply chains to assess good practice in controlling releases of antibiotics into the environment.
    ii. Establish a common framework for managing antibiotic discharge, building on existing work such as PSCI ‡, and start to apply it across our own manufacturing and supply chain by 2018.
    iii. Work with stakeholders to develop a practical mechanism to transparently demonstrate that our supply chains meet the standards in the framework.
    iv. Work with independent technical experts to establish science-driven, risk-based targets for discharge concentrations for antibiotics and good practice methods to reduce environmental impact of manufacturing discharges, by 2020.

Signatory Companies

Allergan

AstraZeneca

Cipla

DSM Sinochem Pharmaceuticals

F. Hoffman-La Roche Ltd., Switzerland

GSK

Johnson & Johnson

Merck & Co., Inc., Kenilworth, New Jersey, U.S.A.

Novartis

Pfizer

Sanofi

Shionogi & Co., Ltd.

Wockhardt

Can we create incentives to improve environmental standards of production?

- Procurement of medicines
- Pricing and reimbursement
- Good Manufacturing Practice (GMP)

Bengtsson-Palme J, Larsson DGJ. 2016. Time to regulate antibiotic pollution. *The Medicine Maker. Apr:17–8.*

CARe

Centre for Antibiotic Resistance Research at University of Gothenburg

The Vision ***of CARe is to, through research, limit mortality, morbidity and socioeconomic costs related to antibiotic resistance on a global scale.***

Acknowledgements

- Prof. Joakim Larsson
- Current and former members of his research group
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