

Re-thinking the drivers of AMR emergence and spread

The RADAAR Project

(Regional AMR Data Analysis for Advocacy, Response, and Policy)

International Vaccine Institute, Seoul, Korea.

April 12th 2022

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Why worry about antimicrobial
resistance?

Antibiotics are miracle drugs

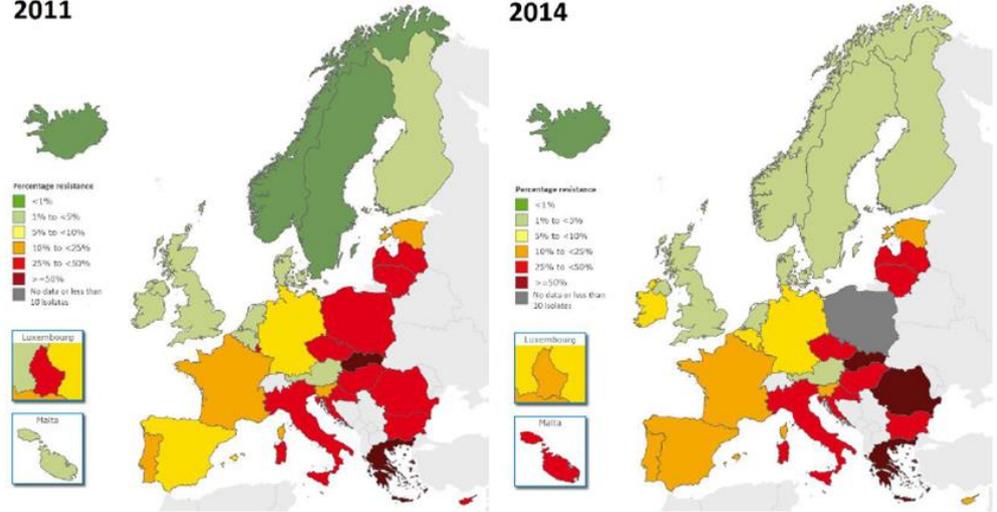
- Resistance is bad!
 - Deaths (mortality)
 - Suffering (morbidity)
- Resistance continues to rapidly rise

Klebsiella Bloodstream infections

Figure 1. *Klebsiella pneumoniae*: percentage of invasive isolates with combined resistance to third-generation cephalosporins, fluoroquinolones and aminoglycosides, EU/EEA, 2011 and 2014

2011

2014



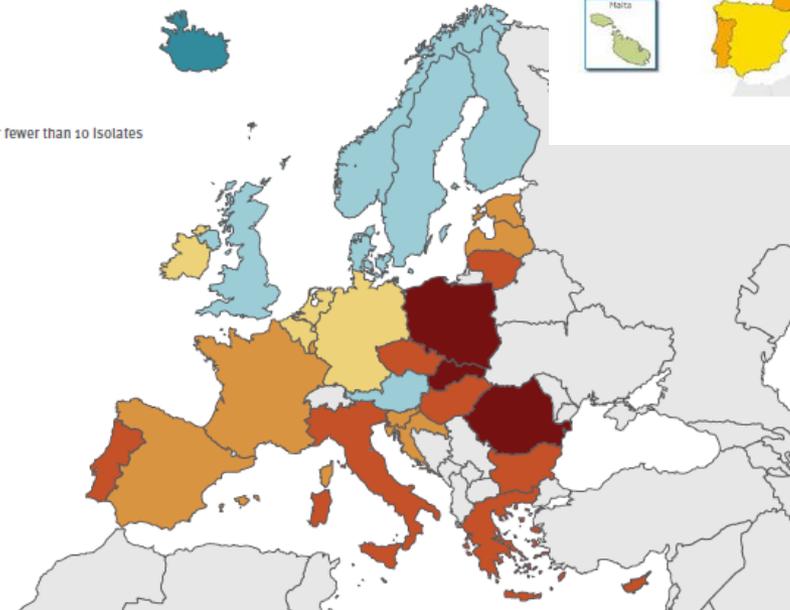
Surveillance of antimicrobial resistance in Europe 2017

Figure 3.12. *Klebsiella pneumoniae*. Percentage (%) of invasive isolates with combined r third-generation cephalosporins and aminoglycosides, by country, EU/EEA countries, 2017



Non-visible countries

- Liechtenstein
- Luxembourg
- Malta



Antibiotic resistance is worse in low and middle income countries - and in many disadvantaged groups



Very High resistance rates in India with E.coli in the community

(e.g. Cipro - Resistance is 73%!)

Indian J Med Res 136, November 2012, pp 842-849

Antibiotic resistance pattern among common bacterial uropathogens with a special reference to ciprofloxacin resistant *Escherichia coli*

Jharna Mandal, N. Srinivas Acharya, D. Buddhapriya & Subhash Chandra Parija

Table II. Antibi

Antibiotics	<i>E. coli</i> n=2671	<i>K. pneu- moniae</i> n=551	<i>P.</i>
Ceftriaxone	1618 (60.5)	327 (59.3)	
Ceftazidime	1526 (57.1)	311 (56.4)	
Gentamicin	1592 (59.6)	337 (61.1)	
Nitrofurantoin	720 (26.9)	323 (58.6)	
Meropenem	264 (9.8)	100 (18.15)	
Ciprofloxacin	1951 (73.04)	302 (54.8)	
Amikacin	621 (23.2)	158 (28.6)	
Ampicillin	2153 (80.6)	-	

Values in parentheses represent percent

Yes – all agree that resistance is bad

But

Isn't it really just all about overuse
and poor use in people??

So then where does spread, water, foods, food
animals and the environment fit in?

AMR is really all about “One Health”

- The One Health concept recognizes that the health of people is connected to the health of animals and the environment.
- Need to have a collaborative “one Health” approach by physicians, veterinarians, ecologists, and many others to monitor and control public health threats and to learn about how diseases spread among people, animals, and the environment (CDC).



SAVING LIVES
BY TAKING A
ONE HEALTH APPROACH

Connecting human, animal, and environmental health

More than half of all infections that people can get can be spread by animals. Diseases like rabies, *Salmonella*, and West Nile virus infections are examples of zoonotic diseases (or zoonoses)—diseases that can be shared between animals and people.



Food and Agriculture
Organization of the
United Nations



WORLD ORGANISATION
FOR ANIMAL HEALTH

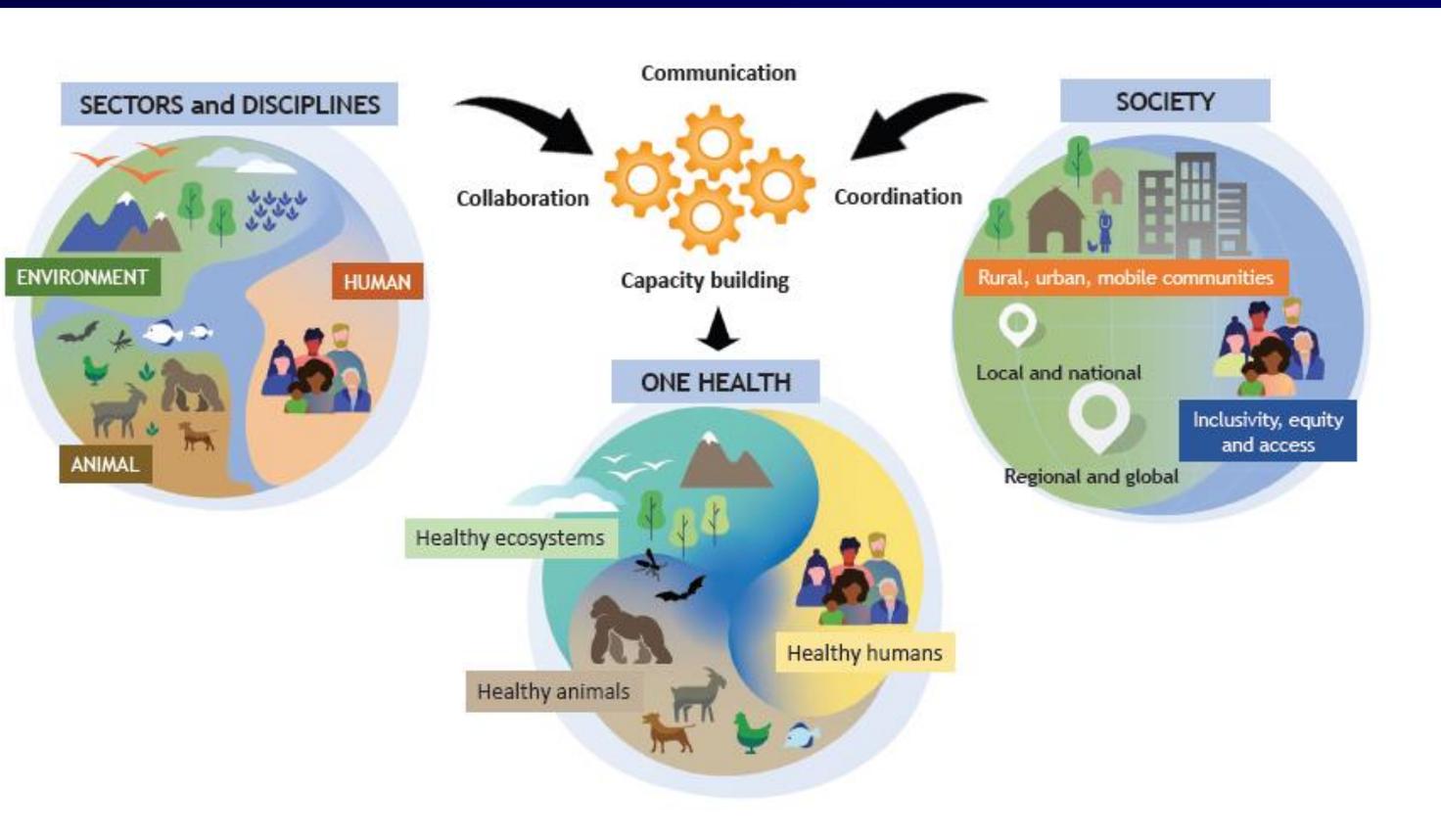


World Health
Organization



UN
environment
programme

**Joint Tripartite (FAO, OIE, WHO) and UNEP Statement
Tripartite and UNEP support OHHLEP's definition of "One Health"**



We are what we eat (and drink)

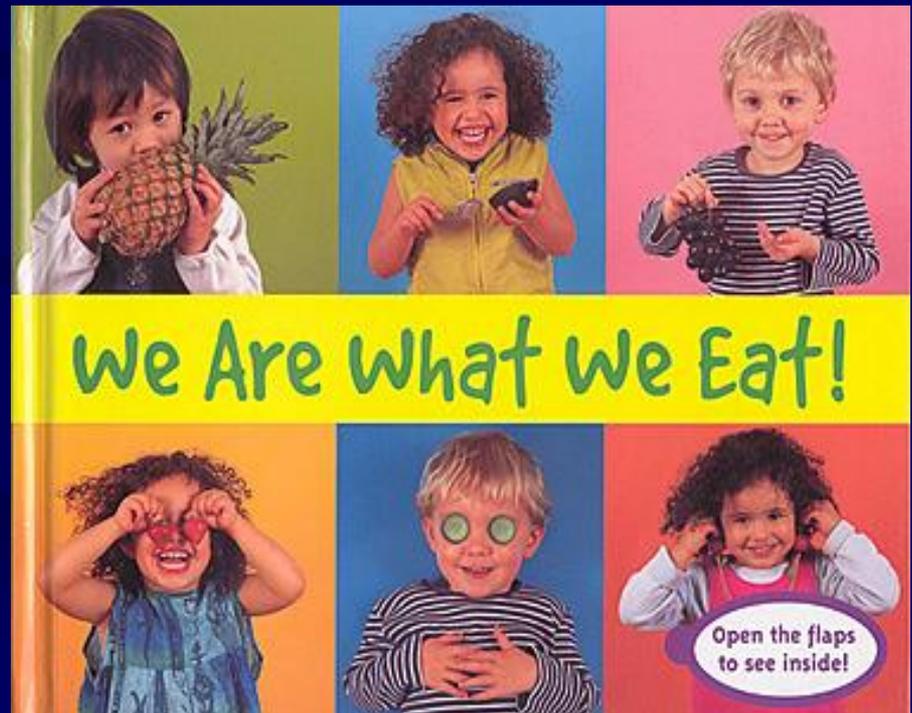
Resistant *Escherichia coli*—We Are What We Eat

Peter Collignon

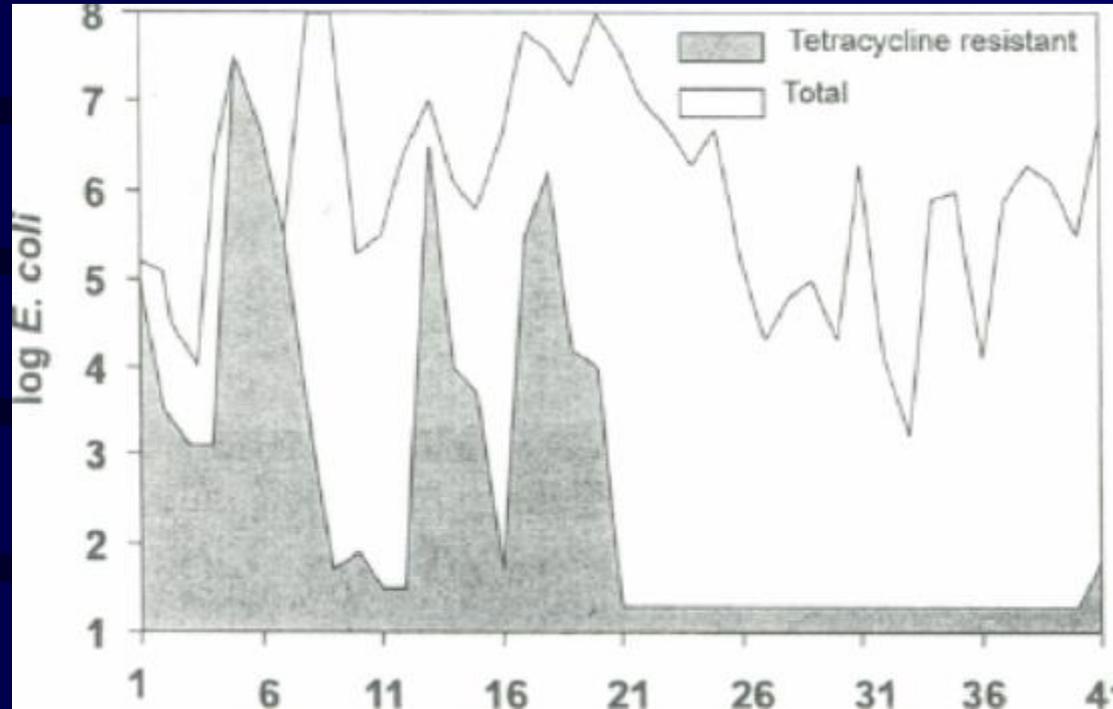
Infectious Diseases Unit and Microbiology Department, The Canberra Hospital, and School of Clinical Medicine, Australian National University, Canberra, Australia

Clinical Infectious Diseases 2009;49:202–4

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Many resistant bacteria are ingested



- A study of tetracycline-resistant E.coli in which volunteers were given sterile food for 20 days after a control period of 21 days showed that most came from food (Corpet 1988, 1993).

Much more resistant *E. coli* via food chain than we think?

Antimicrobial Drug-Resistant *Escherichia coli* from Humans and Poultry Products, Minnesota and Wisconsin, 2002–2004

James R. Johnson,*† Mark R. Sannes,*† Cynthia Croy,*† Brian Johnston,*† Connie Clabots,*†
Michael A. Kuskowski,*† Jeff Bender,‡ Kirk E. Smith,§ Patricia L. Winokur,¶#
and Edward A. Belongia**

Emer Infect Dis Vol.
13, No. 6, June 2007

Many drug-resistant human fecal *E. coli* isolates may originate from poultry, whereas drug-resistant poultry source *E. coli* isolates likely originate from susceptible poultry-source precursors.

Ceftiofur Resistance in *Salmonella enterica* Serovar Heidelberg from Chicken Meat and Humans, Canada

Lucie Dutil, Rebecca Irwin, Rita Finley, Lai King Ng, Brent Avery, Patrick Boerlin, Anne-Marie Bourgault, Linda Cole, Danielle Daignault, Andrea Desruisseau, Walter Demczuk, Linda Hoang, Greg B. Horsman, Johanne Ismail, Frances Jamieson, Anne Maki, Ana Pacagnella, and Dylan R. Pillai

Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 16, No. 1, January 2010

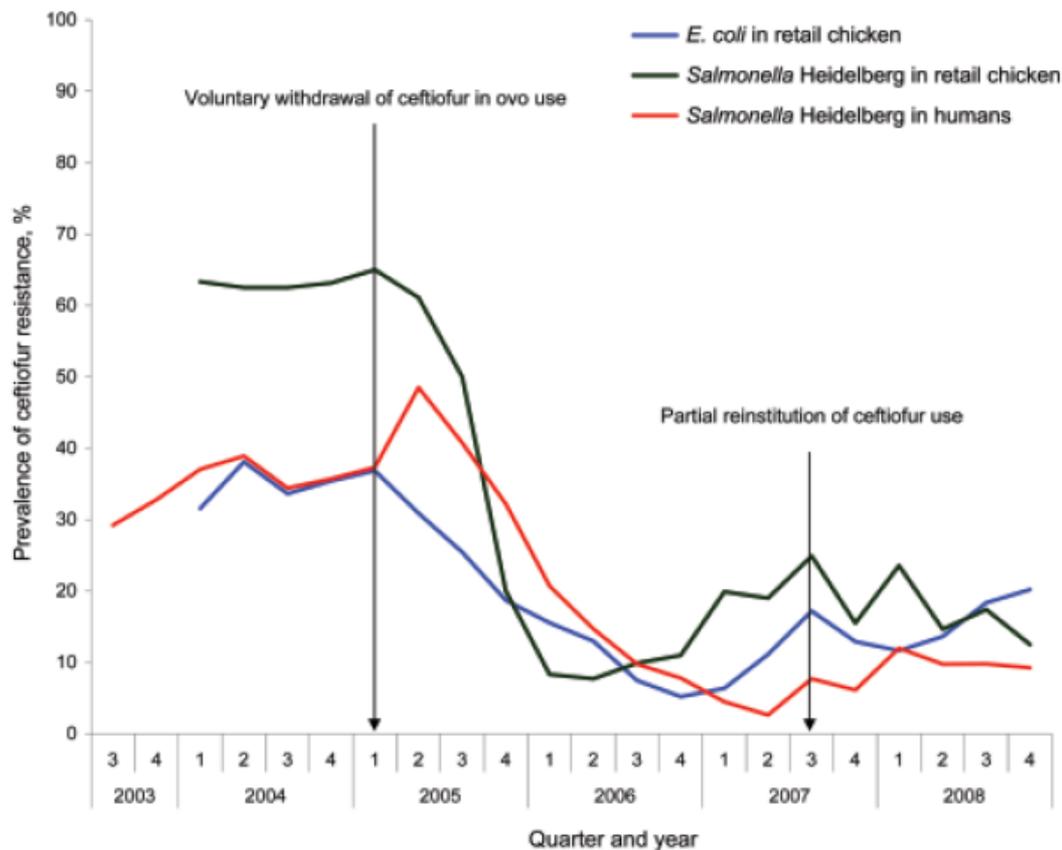


Figure 2. Prevalence of ceftiofur resistance (moving average of the current quarter and the previous 2 quarters) among retail chicken *Escherichia coli*, and retail chicken and human clinical *Salmonella enterica* serovar Heidelberg isolates during 2003–2008 in Québec, Canada.

Genes spread widely

Metagenomic Assembly Reveals Hosts of Antibiotic Resistance Genes and the Shared Resistome in Pig, Chicken, and Human Feces

Liping Ma,[†] Yu Xia,[†] Bing Li,[†] Ying Yang,[†] Li-Guan Li,[†] James M Tiedje,^{*,‡} and Tong Zhang^{*,†}

[†]Environmental Biotechnology Laboratory, The University of Hong Kong, Hong Kong

[‡]Department of Plant, Soil, and Microbial Sciences, Michigan State University, East Lansing, Michigan 48824, United States

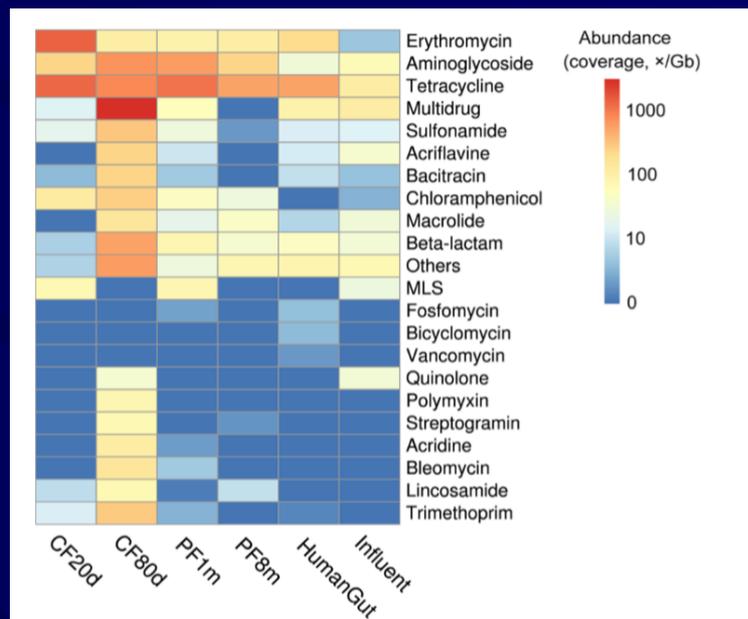
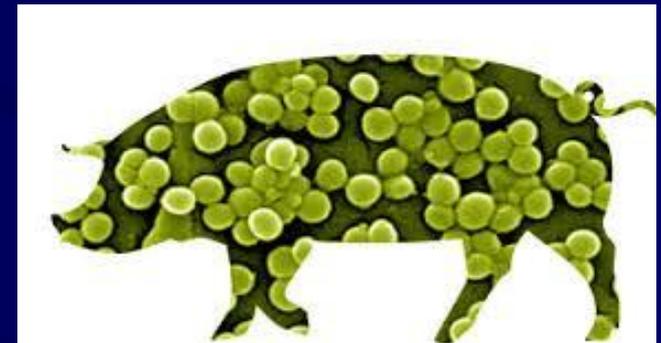


Figure 2. Abundance (coverage of ARG-like ORFs, ×/Gb) of ARG-like ORFs in samples. MLS: Macrolide-lincosamide-streptogramin.

Dose-Response Relationship between Antimicrobial Drugs and Livestock-Associated MRSA in Pig Farming¹

Alejandro Dorado-García, Wietske Dohmen, Marian E.H. Bos, Koen M. Verstappen, Manon Houben, Jaap A. Wagenaar, Dick J.J. Heederik

The farming community can be a vehicle for introduction of livestock-associated methicillin-resistant *Staphylococcus aureus* (LA-MRSA) in hospitals. During 2011–2013, an 18-month longitudinal study aimed at reducing the prevalence of LA-MRSA was conducted on 36 pig farms in the Netherlands. Evaluations every 6 months showed a slight decrease in MRSA prevalence in animals and a stable prevalence in farmers and family members. Antimicrobial use, expressed as defined daily dosages per animal per year, decreased 44% during the study period and was associated with declining MRSA prevalence in pigs. MRSA carriage in animals was substantially higher at farms using cephalosporins. Antimicrobial use remained strongly associated with LA-MRSA in humans regardless of the level of animal contact. A risk factor analysis outlined potential future interventions for LA-MRSA control. These results should encourage animal and public health authorities to maintain their efforts in reducing antimicrobial use in livestock and ask for future controlled intervention studies.



We believe

Resistance is proportional to use

- When you use it, you loose it!
- The more you use then the more resistance
 - cross resistance an issue
 - Volumes are most important
- Need to maintain “last line” or “critically important” antibiotics



If only people used less antibiotics!



STOP
THE **OVERUSE** OF
ANTIBIOTICS

And just as bad or worse - huge volumes are used in food animals (likely >70% of total global use)



Pneumococcal resistance in Children

- Canberra prospective study
 - 461 children followed for over 2 years
- More antibiotics, the more resistance
 - overall 13.6% isolates were penicillin resistant
 - If beta-lactam received OR 2.03
 - if both pen and ceph OR 4.67
 - but resistance dropped with time (after 6 months OR 1)
- 4% increased risk of carriage for each day of beta-lactam therapy



Antibiotic Resistance in the Wild.

If no antibiotic use then little resistance is seen



	kangaroos vs people		
• ampicillin	2.9%	vs	46%
• tetracycline	0.2%		28%
• chloramphenicol	0.4%		14%
• trimethoprim	0.2%		15%

If only people used less antibiotics!

and

Big Pharma developed more antibiotics!!



Antibiotic resistance

What levels you see are dependent on two main factors

- The volumes and types of antibiotics used
- Spread or “Contagion”
 - And contrary to common opinion, this is the main factor!

We seem most concerned about AMR in hospitals
and healthcare settings

BUT

most bacteria and associated AMR is spread in the
community



One Health

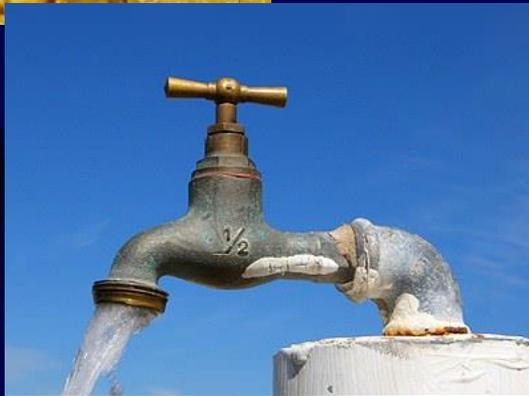
It all goes around, and around, and around



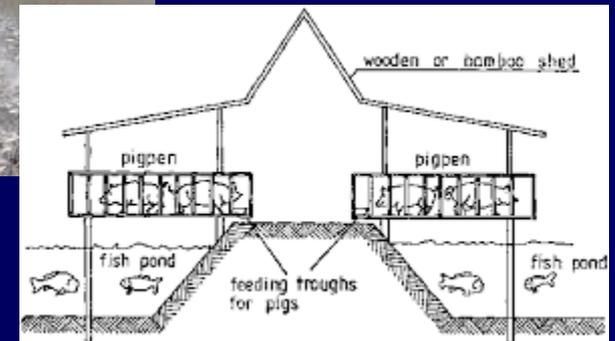
But how and where does the
Environment fit in?

Globally, water is likely the major risk for spread of resistant bacteria.

The environment matters



Aquaculture



Socioeconomic Enablers for Contagion

These are the major Factors responsible for our global
Antimicrobial Resistance Epidemic in people

And its all very related to the One Health concept, especially
the environment component

Antibiotic usage not related to a country's resistance rate



Global antibiotic consumption 2000 to 2010: an analysis of national pharmaceutical sales data

Thomas P Van Boeckel, Sumanth Gandra, Ashvin Ashok, Quentin Caudron, Bryan T Grenfell, Simon A Levin, Ramanan Laxminarayan

Summary

Background Antibiotic drug consumption is a major driver of antibiotic resistance. Variations in antibiotic resistance across countries are attributable, in part, to different volumes and patterns for antibiotic consumption. We aimed to assess variations in consumption to assist monitoring of the rise of resistance and development of rational-use policies and to provide a baseline for future assessment.

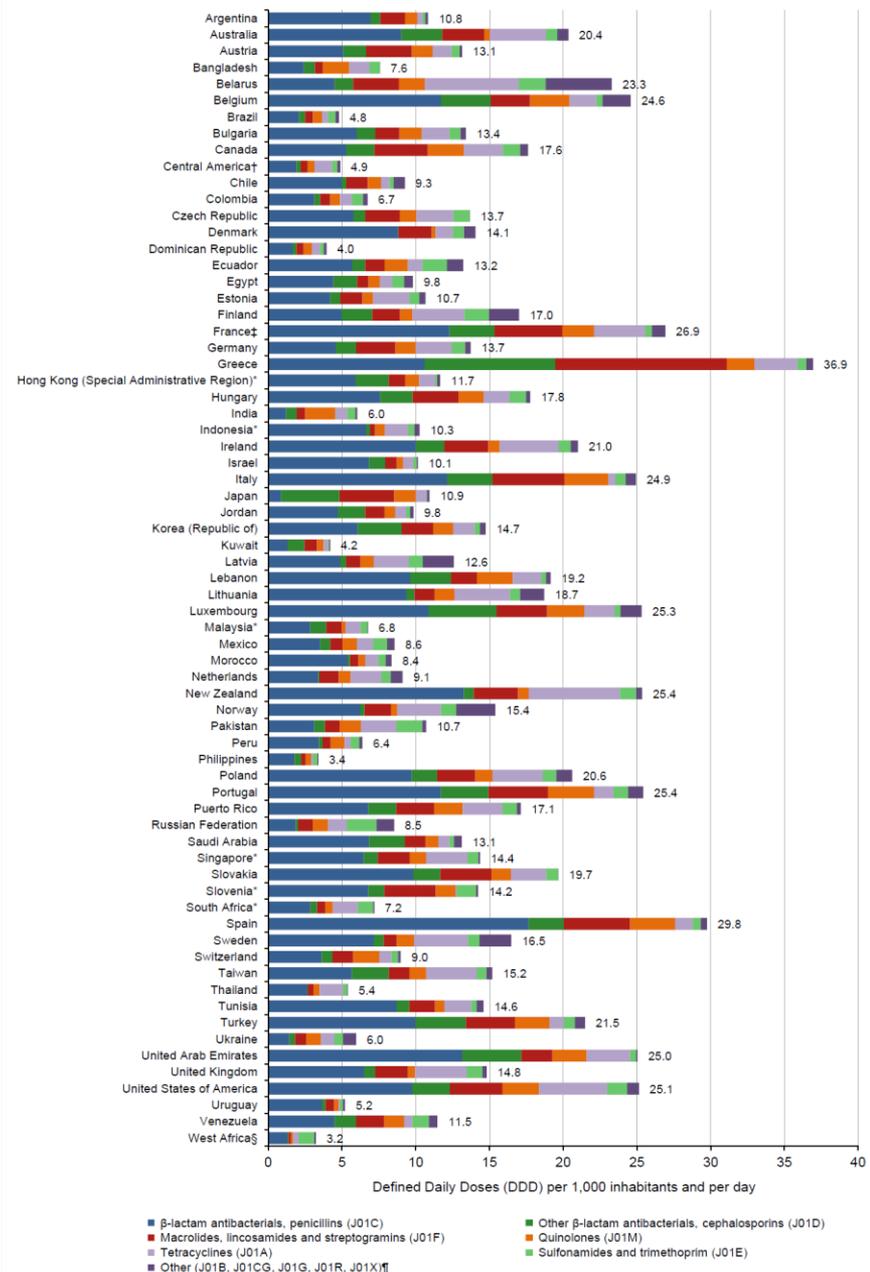
Lancet Infect Dis 2014; 14: 742-50
 Published Online July 10, 2014
[http://dx.doi.org/10.1016/S1473-3099\(14\)70780-7](http://dx.doi.org/10.1016/S1473-3099(14)70780-7)

Supplementary webappendix

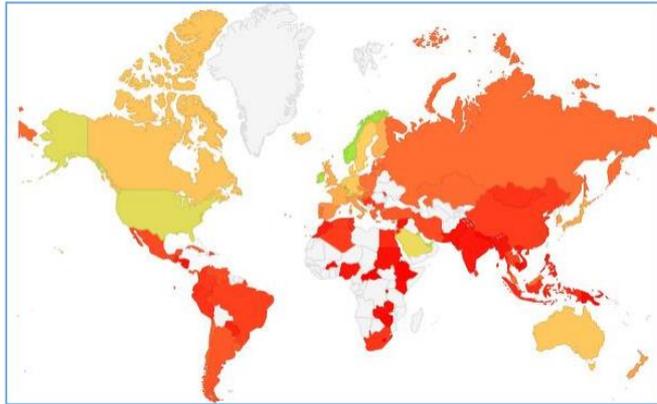
This webappendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Högberg LD, Muller A, Zorzet A, Monnet DL, Cars O. Antibiotic use worldwide. *Lancet Infect Dis* 2014; **12**: 1179-80.

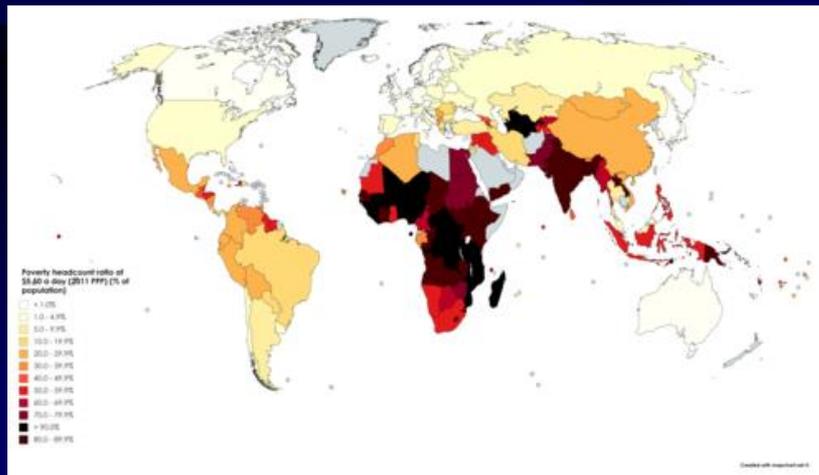
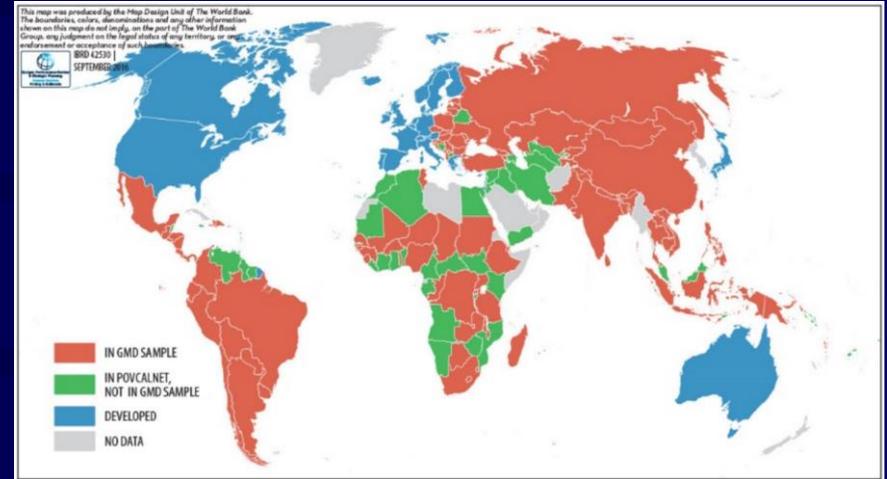
Figure. Antibiotic consumption in 69 countries and regions, 2004.



Poverty levels and AMR



Map 7: GDP



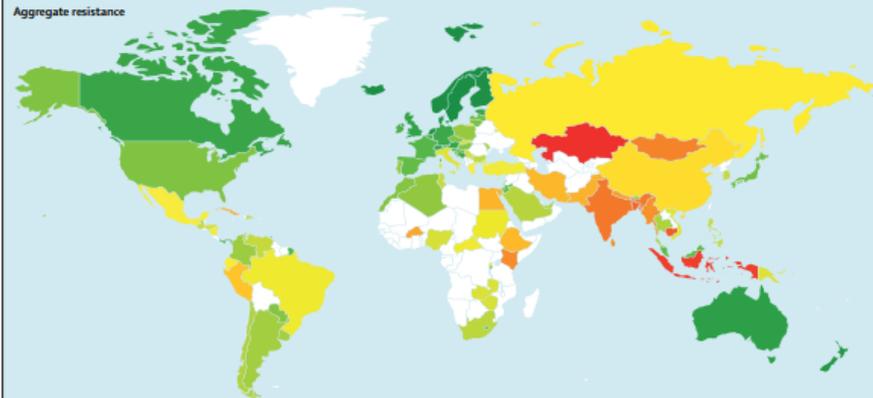
Anthropological and socioeconomic factors contributing to global antimicrobial resistance: a univariate and multivariable analysis

Peter Collignon, John J Beggs, Timothy R Walsh, Sumanth Gandra, Ramanan Laxminarayan

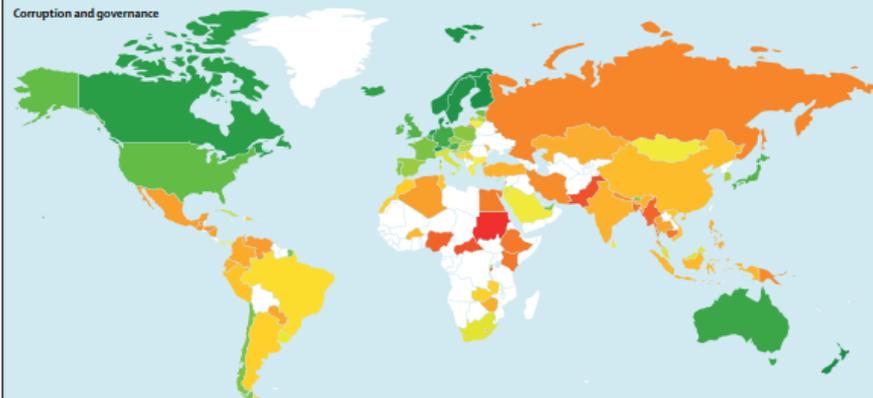
*Lancet Planet Health 2018;
2: e398-405*

Interpretation Reduction of antibiotic consumption will not be sufficient to control antimicrobial resistance because contagion—the spread of resistant strains and resistance genes—seems to be the dominant contributing factor. Improving sanitation, increasing access to clean water, and ensuring good governance, as well as increasing public health-care expenditure and better regulating the private health sector are all necessary to reduce global antimicrobial resistance.

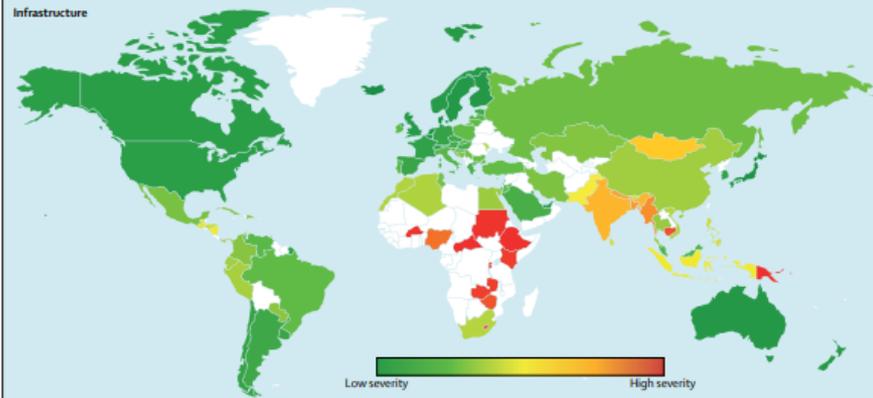
Aggregate resistance



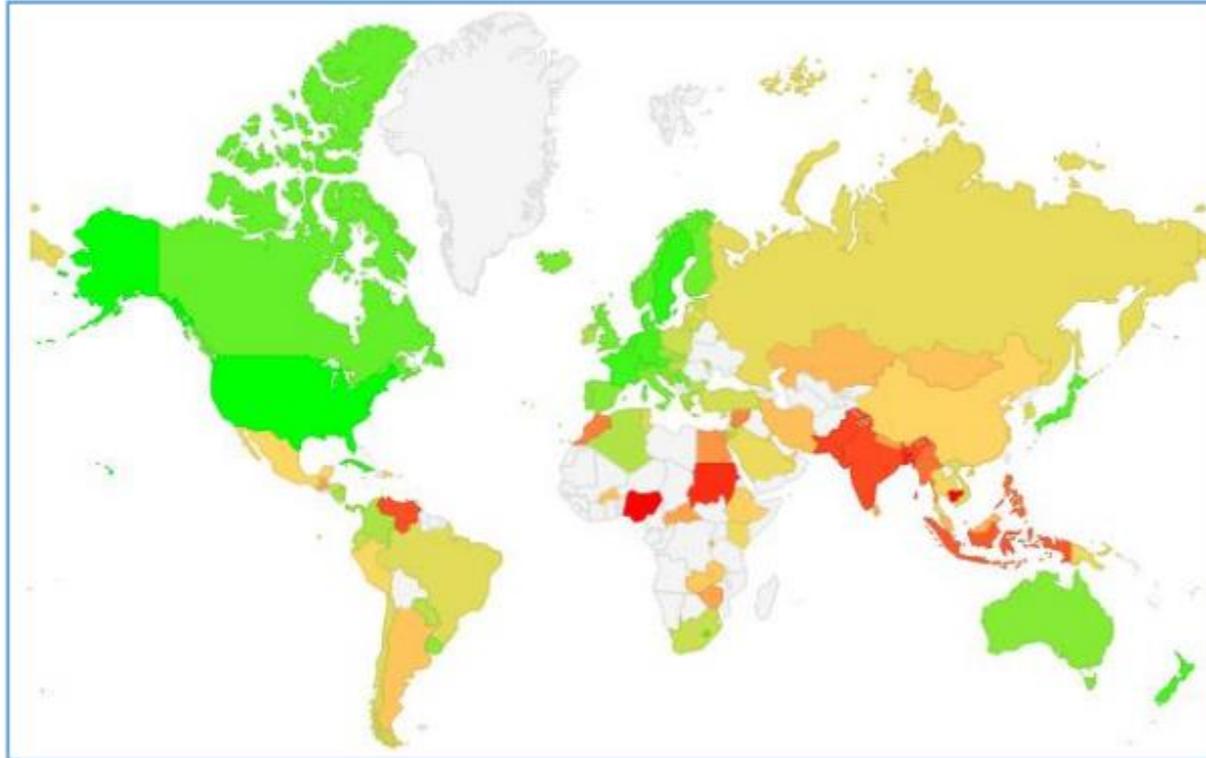
Corruption and governance



Infrastructure



Low severity High severity

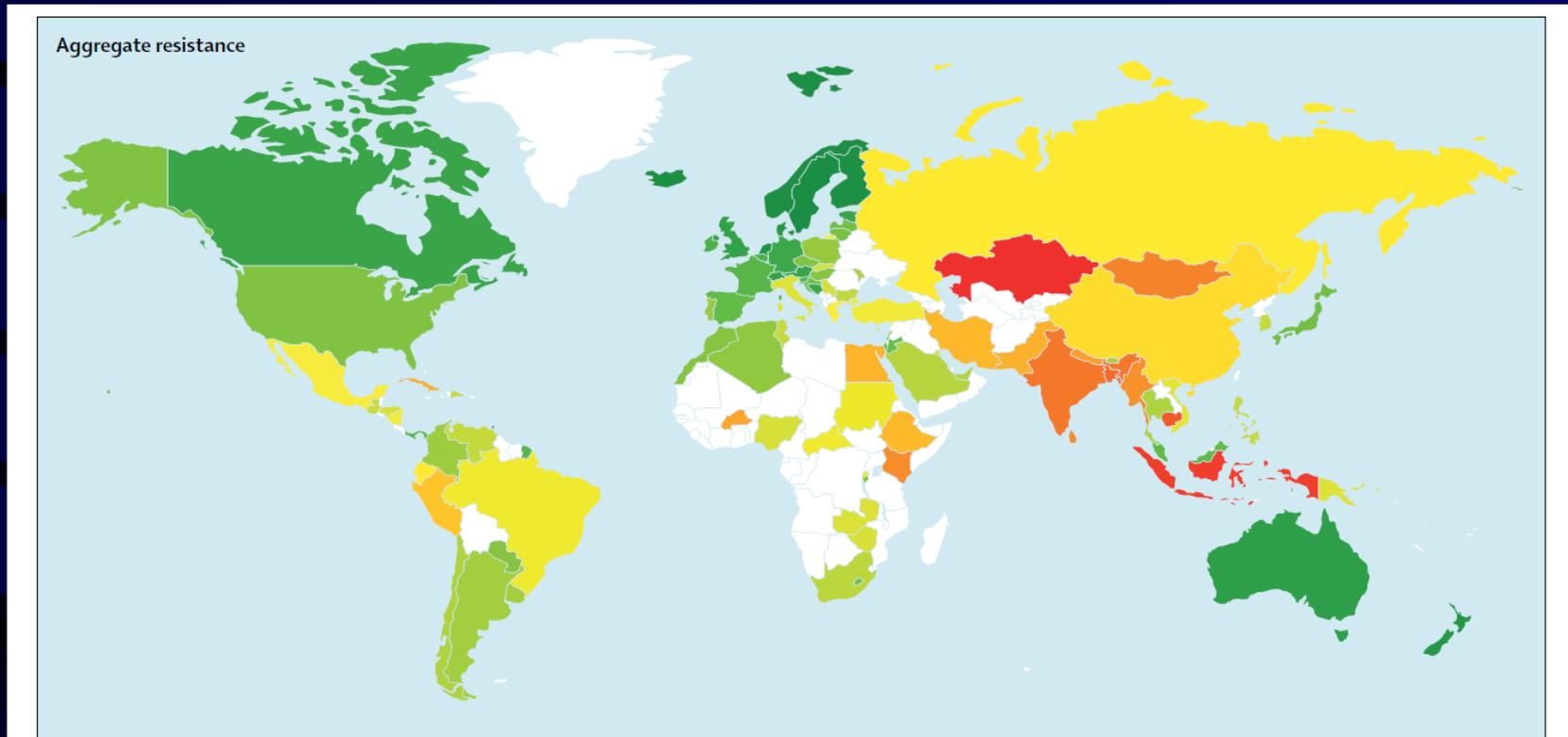


Map 4: Health Spending Index

Anthropological and socioeconomic factors contributing to global antimicrobial resistance: a univariate and multivariable analysis

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AMR and Poverty



Anthropological and socioeconomic factors contributing to global antimicrobial resistance: a univariate and multivariable analysis

Peter Collignon, John J Beggs, Timothy R Walsh, Sumanth Gandra, Ramanan Laxminarayan

International Corruption index is similar to AMR rates



Antibiotic consumption and resistance

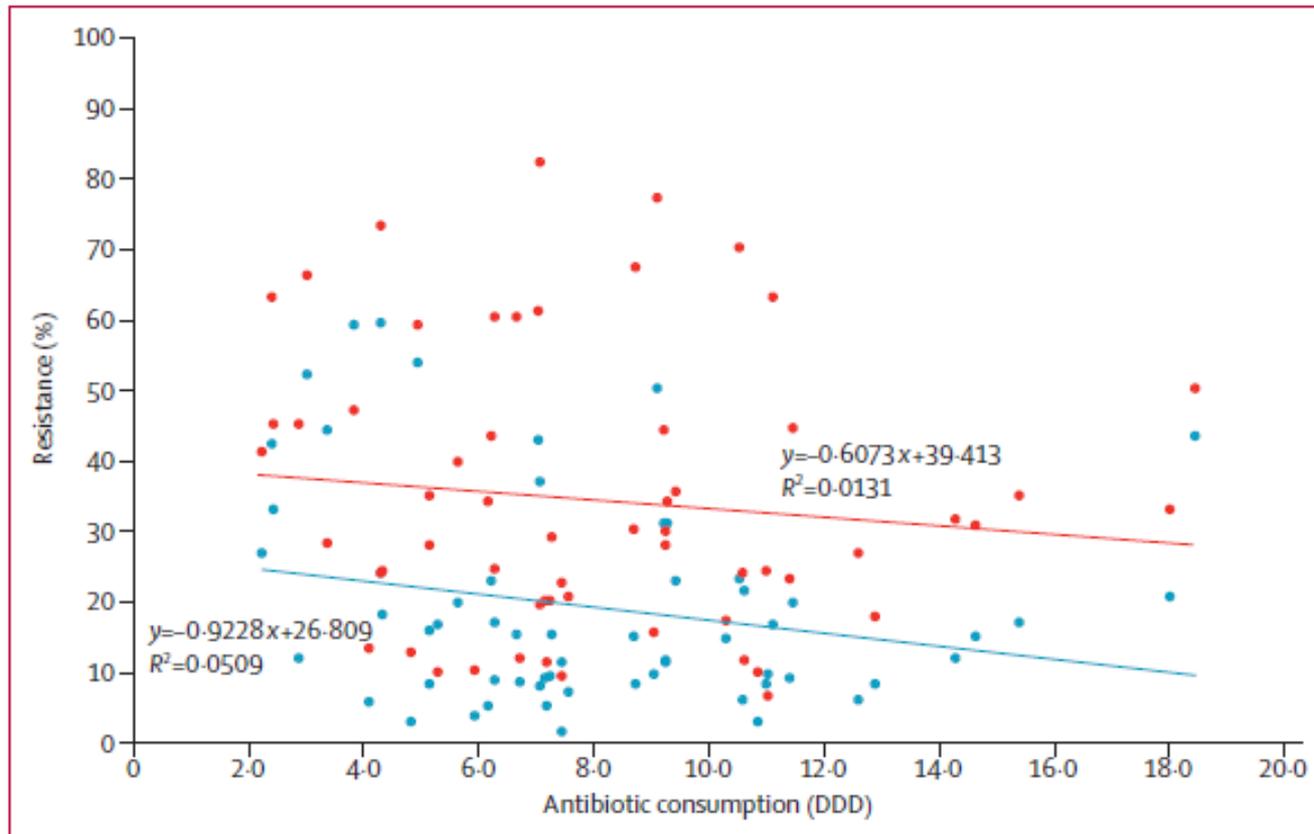


Figure 2: *Escherichia coli* resistance levels for fluoroquinolones and third-generation cephalosporins compared with antibiotic consumption

Figure shows data for percentage of resistance versus defined daily dose (DDD) of antibiotic, plotted only for countries with data for DDD and both measures of resistance. Blue circles indicate *Escherichia coli* resistance to third-generation cephalosporins (%). Red circles indicate *E coli* resistance to fluoroquinolones (%). The blue line shows the linear measure of *E coli* resistance to third-generation cephalosporins. The red line shows the linear measure of *E coli* resistance to third-generation fluoroquinolones. R^2 =coefficient of determination.

Multivariate - *E.coli*

	Effect on resistance rate of 1 SD increase in each explanatory variable (logit)	p value
Usage (standardised)	-0.88	0.64
Governance index	-7.89	0.025
Health expenditure index	-5.54	0.093
GDP per capita (standardised)	6.62	0.030
Education index	7.93	0.058
Infrastructure index	-16.84	0.014
Climate index	2.01	0.33
R ²	0.54	..

GDP=gross domestic product. R²=coefficient of determination.

Table 2: Effect of changes in indices on the resistance of *Escherichia coli* to third-generation cephalosporins and fluoroquinolones

Molecular sewage study



ARTICLE

<https://doi.org/10.1038/s41467-019-08853-3>

OPEN

Global monitoring of antimicrobial resistance based on metagenomics analyses of urban sewage

Rene S. Hendriksen¹, Patrick Munk¹, Patrick Njage¹, Bram van Bunnik², Luke McNally³, Oksana Lukjancenko¹, Timo Röder¹, David Nieuwenhuijse⁴, Susanne Karlsdose Pedersen¹, Jette Kjeldgaard¹, Rolf S. Kaas¹, Philip Thomas Lanken Conradsen Clausen¹, Josef Korbinian Vogt¹, Pimlapas Leekitcharoenphon¹, Milou G.M. van de Schans⁵, Tina Zuidema⁵, Ana Maria de Roda Husman⁶, Simon Rasmussen⁷, Bent Petersen⁷, The Global Sewage Surveillance project co Thomas Sicheritz-Ponten⁹, Heike Schmitt⁶, Jorge Raul Mat Ole Lund⁷, Tine Hald¹, Mark Woolhouse², Marion P. Koop Frank M. Aarestrup¹

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Antimicrobial resistance (AMR) is a serious threat to global public health, but obtaining representative data on AMR for healthy human populations is difficult. Here, we use metagenomic analysis of untreated sewage to characterize the bacterial resistome from 79 sites in 60 countries. We find systematic differences in abundance and diversity of AMR genes between Europe/North-America/Oceania and Africa/Asia/South-America. Antimicrobial use data and bacterial taxonomy only explains a minor part of the AMR variation that we observe. We find no evidence for cross-selection between antimicrobial classes, or for effect of air travel between sites. However, AMR gene abundance strongly correlates with socioeconomic, health and environmental factors, which we use to predict AMR gene abundances in all countries in the world. Our findings suggest that global AMR gene diversity and abundance vary by region, and that improving sanitation and health could potentially limit the global burden of AMR. We propose metagenomic analysis of sewage as an ethically acceptable and economically feasible approach for continuous global surveillance and prediction of AMR.

“Antimicrobial use data .. only explains minor part of variation... However AMR gene abundance strongly correlates with socioeconomic, health and environmental factors”

Conclusion: its complex!

- But factors other than AB usage and New antibiotic development are very important - and more important
 - Water
 - Sanitation
 - Infrastructure
 - Agriculture
 - Animals
 - Environment
 - Governance
 - Corruption
 - Rule of law
 - Health expenditure
 - Government competence
 - education
 - Income
 - Literacy
 - Proportion of Private sector medicine
 - Culture and values of groups and society

One Health

It all goes around, and around, and around

