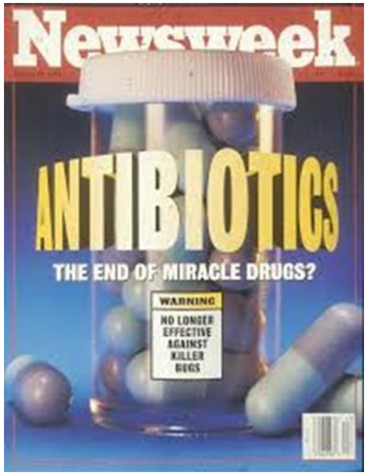


L'approccio "One Health" in Italia: fact checking

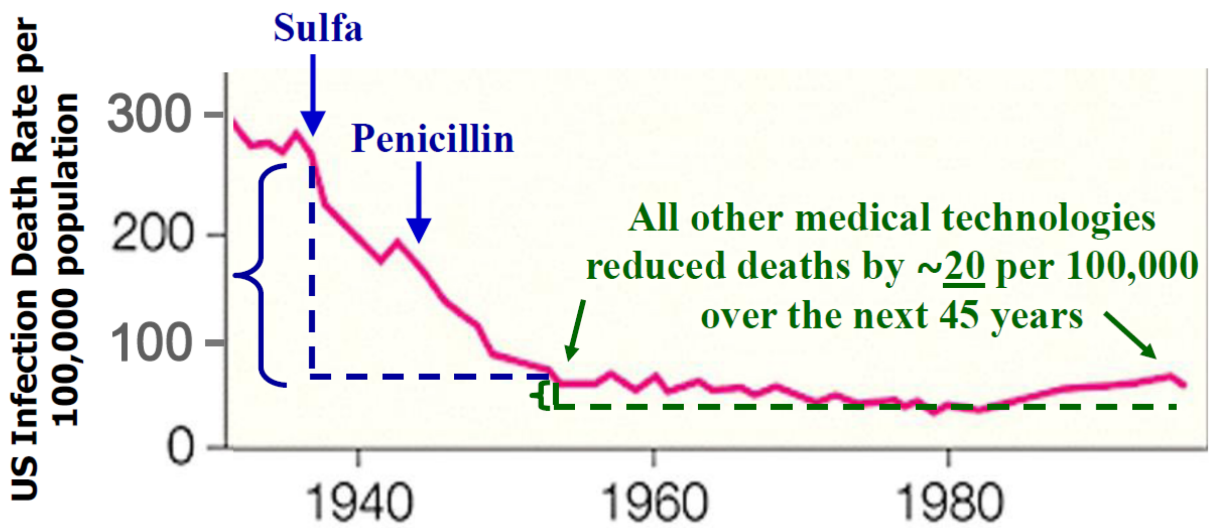
Leonardo Pagani, MD

Lead, Antimicrobial Stewardship Program
Infectious Diseases Branch, Bolzano Central Hospital, Italy

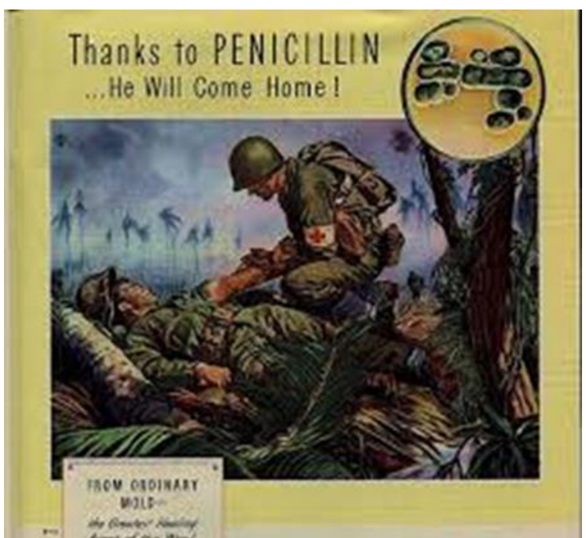
Executive Board of "Global Alliance for Infections in Surgery"

Padua, May 25, 2022

Antibiotics caused US deaths to decline by ~220 per 100,000 in 15 years

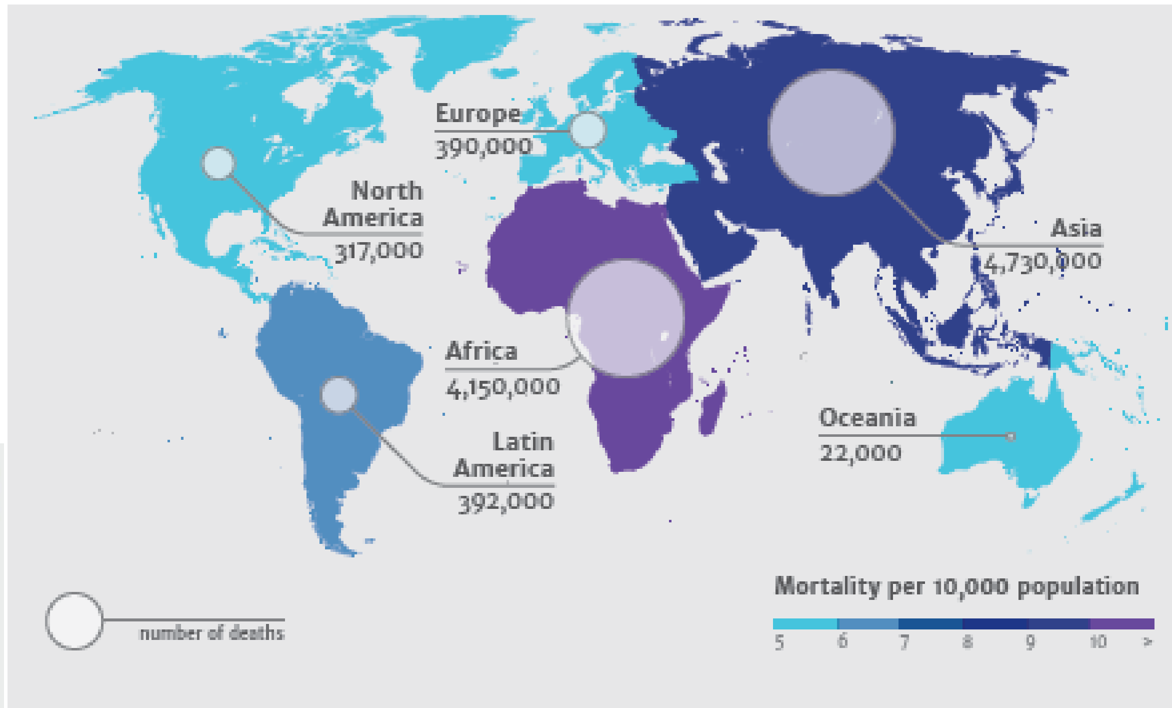


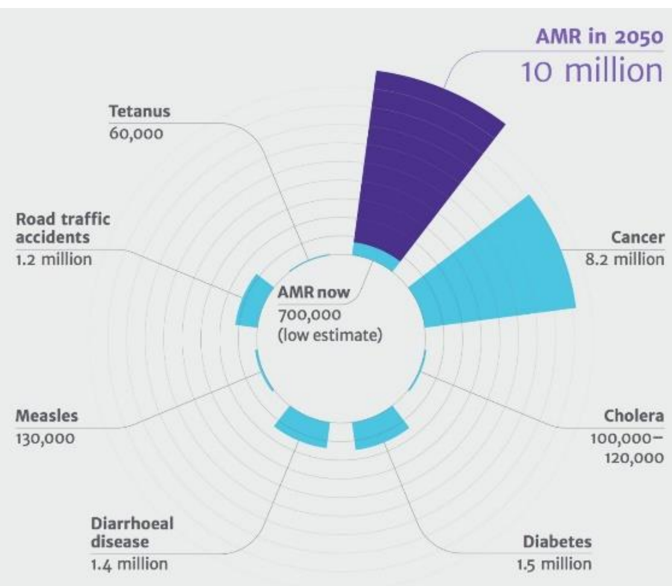
Armstrong, G. L. et al. JAMA 1999;281:61-66.



The perfect storm is approaching..

Deaths attributable to AMR every year by 2050

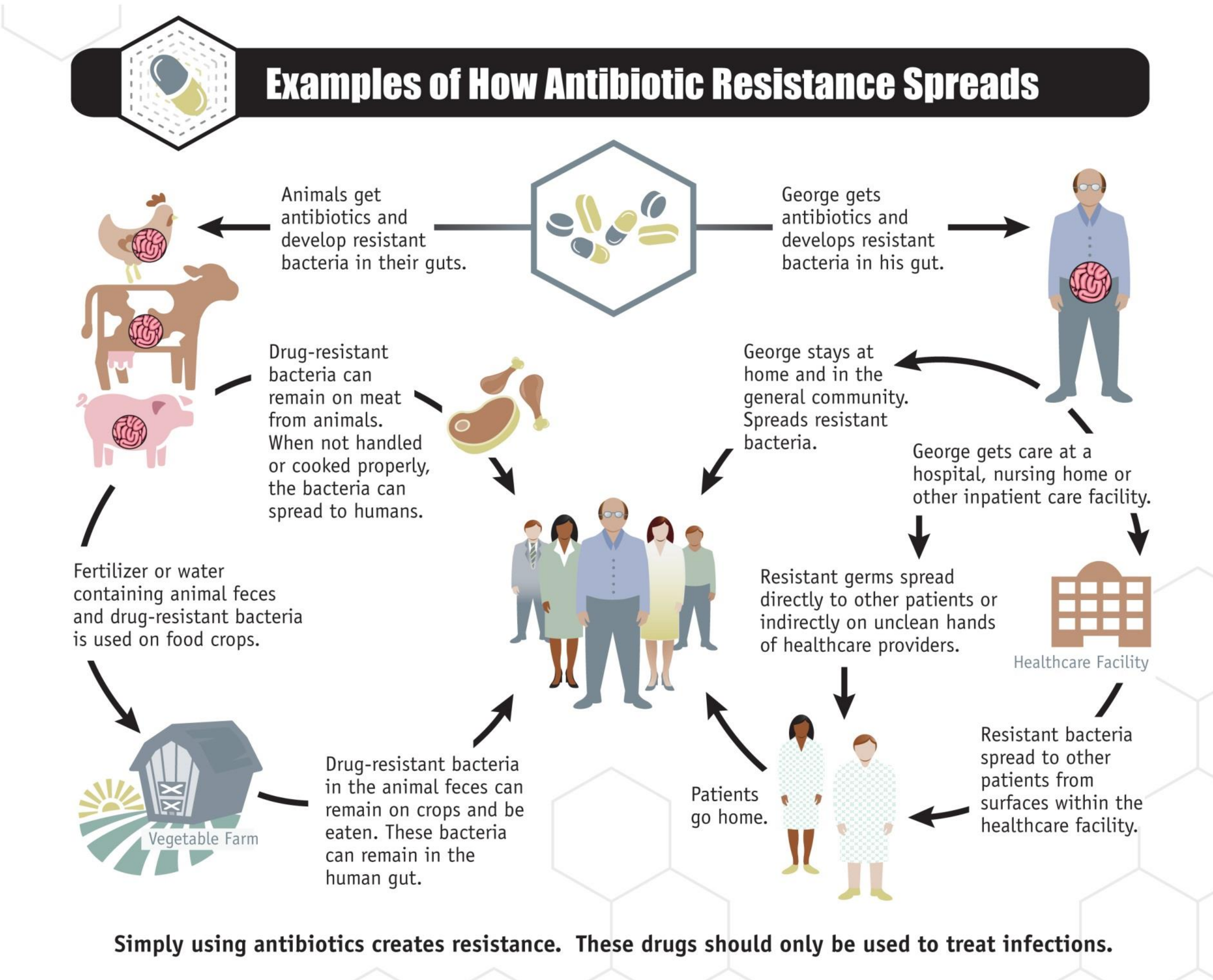




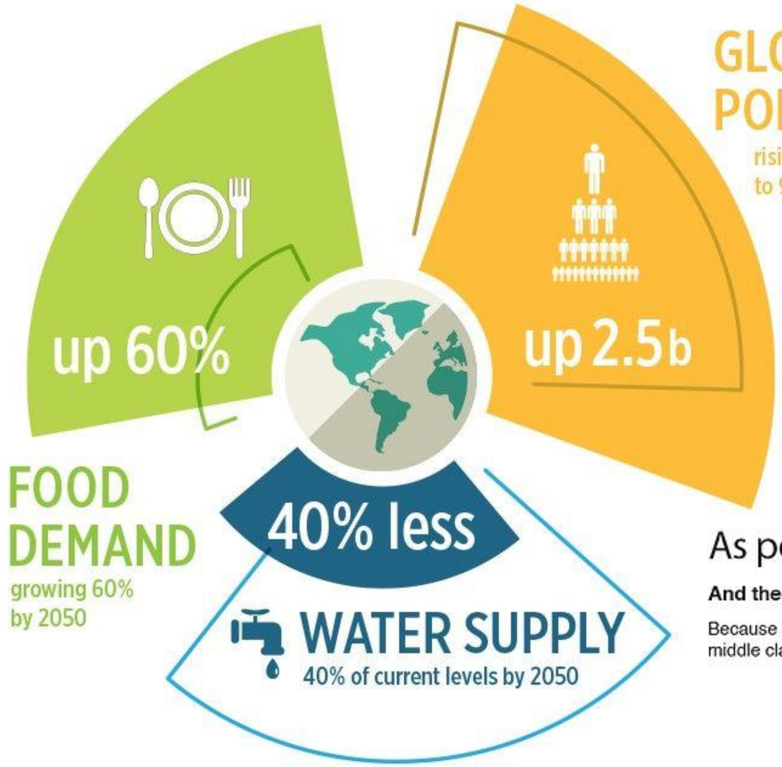
...and this scenario did not even take into account the upcoming pandemic "era"...

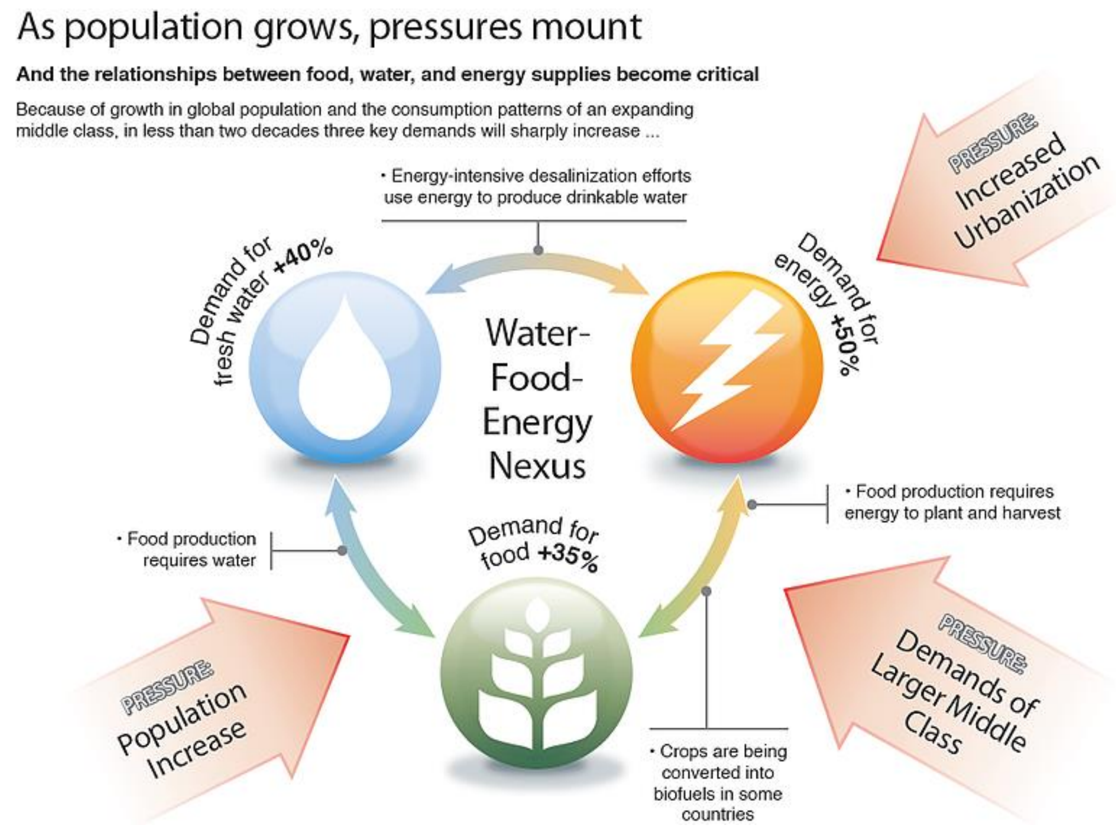
Consequences of resistance

- Even simple infections will become impossible to treat
- Many medical achievements are only possible with effective antimicrobials

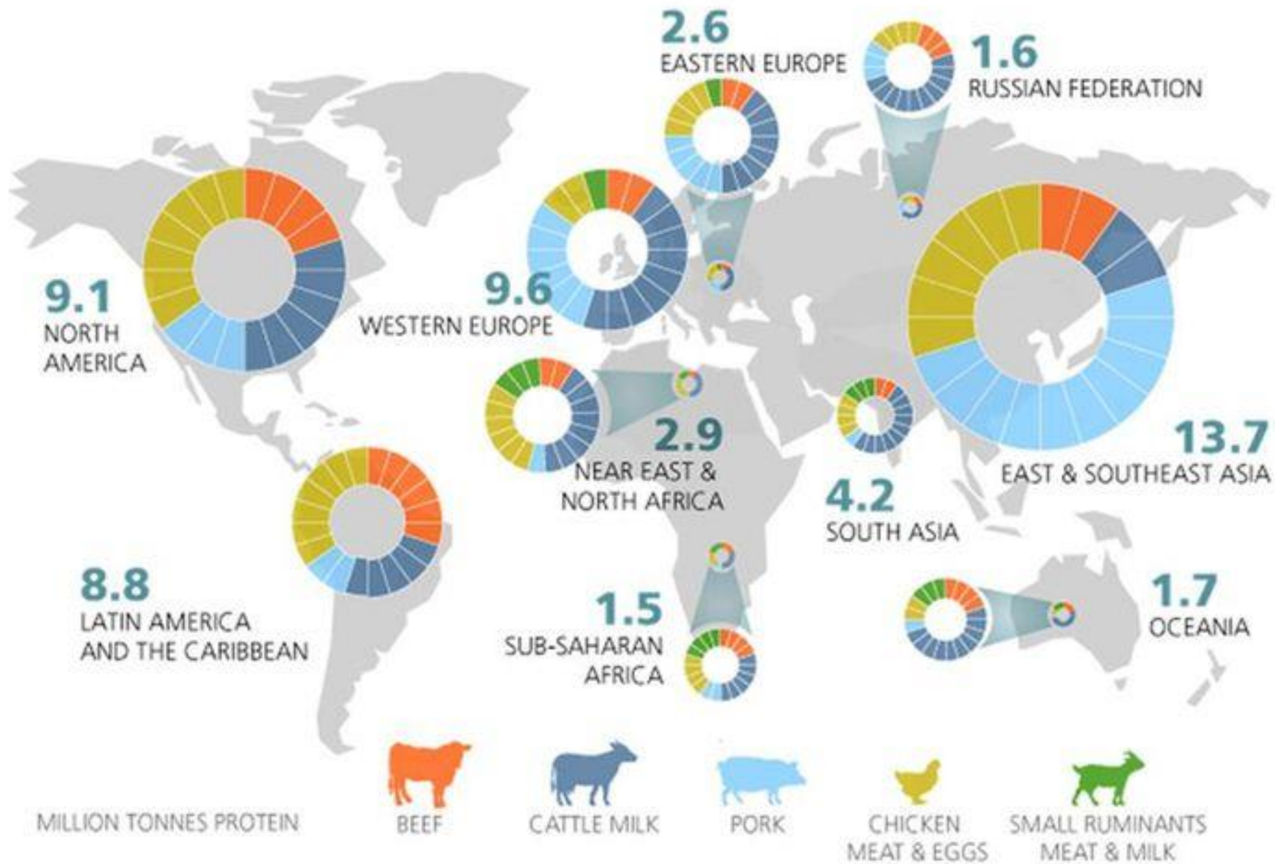


Source: www.washingtonpost.com


GLOBAL POPULATION
rising from 7.2 billion to 9.7 billion by 2050
up 2.5b
up 60%
FOOD DEMAND
growing 60% by 2050
40% less
WATER SUPPLY
40% of current levels by 2050


As population grows, pressures mount
And the relationships between food, water, and energy supplies become critical
Because of growth in global population and the consumption patterns of an expanding middle class, in less than two decades three key demands will sharply increase ...
• Energy-intensive desalinization efforts use energy to produce drinkable water
Demand for fresh water +40%
Water-Food-Energy Nexus
Demand for energy +50%
PRESSURE: Increased Urbanization
• Food production requires energy to plant and harvest
• Food production requires water
Demand for food +35%
PRESSURE: Population Increase
• Crops are being converted into biofuels in some countries
PRESSURE: Demands of Larger Middle Class

LIVESTOCK PRODUCTION



***Regional production**. Regional total production and their profile by commodity are shown. Meat production in protein basis was calculated by using data on dressing percentages, carcass to bone-free meat and average bone-free meat protein content. Milk from all species was converted into fat and protein corrected milk. Eggs production is also expressed in protein terms.*

Intensive (factory) farming:
emergence and spread of AMR

- Failure of Infection Control
  - Crowding
  - Lack of hygiene
- Exposure to Antibiotics
  - Widespread
  - Prolonged
  - Sub-lethal doses
- Stress reaction
  - Increased shedding

GLOBAL HEALTH ACTION
2019, VOL. 12, 1697541
https://doi.org/10.1080/16549716.2019.1697541

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SHORT COMMUNICATION

OPEN ACCESS

Check for updates

Excessive use of medically important antimicrobials in food animals in Pakistan: a five-year surveillance survey

Mashkoor Mohsin [a], Thomas P. Van Boeckel [b,c], Muhammad Kashif Saleemi [d], Muhammad Umair [a], Muhammad Noman Naseem [d], Cheng He [e], Ahrar Khan [f] and Ramanan Laxminarayan [c,g]

[a]Institute of Microbiology, University of Agriculture, Faisalabad, Pakistan; [b]Institute for Environmental Decisions, ETH Zurich, Zurich, Switzerland; [c]Center for Disease Dynamics, Economics & Policy, Washington, DC, USA; [d]Department of Pathology, University of Agriculture, Faisalabad, Pakistan; [e]College of Veterinary Medicine, China Agricultural University, Beijing, China; [f]Shandong Vocational Animal Science and Veterinary College, Weifang, China; [g]Princeton Environment Institute, Princeton, NJ, USA

ABSTRACT
Demand for poultry meat is rising in low- and middle-countries, driving the expansion of large commercial farms where antimicrobials are used as surrogates for hygiene, good nutrition. This routine use of antimicrobials in animal production facilitates the emergence and spread of antibiotic-resistant pathogens. Despite potentially serious consequences for the animal industry, few studies have documented trends in antimicrobial use (AMU) at the farm-level in low- and middle-income countries. The objective of this study was to estimate

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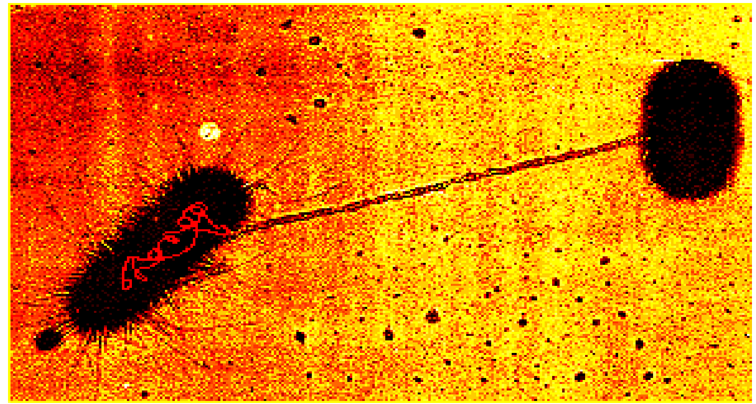
RESPONSIBLE EDITOR
Stig Wall, Umeå University, Sweden

(41.71 mg/fPU), doxycycline (81.81 mg/fPU), and enrofloxacin (26.19 mg/fPU) were the most frequently used antimicrobials for prophylactic or therapeutic use. Lincomycin was the most frequently used antimicrobial used in-feed (29.09 mg/fPU). Our findings suggest that the annual consumption of antimicrobials in the broiler sector in Pakistan could be as high as 568 tons. This alarmingly high consumption estimate is the first baseline study on antimicrobial use in animals in Pakistan. Our findings call for immediate actions to reduce antimicrobial use in Pakistan, and countries with comparable farming practices.

Transfer of resistance

- Bacteria (with resistance) may transfer between animals and to humans
  - Pathogens:
    - *Salmonella*
    - *Listeria*
    - *Campylobacter*



Plasmids encoding resistance to several antibiotic classes

  - Commensals (gut-flora = reservoir of resistance genes)
    - *E. coli (ESBL in chickens)*

Taylor and Reeder *CABI Agric Biosci* (2020) 1:1
https://doi.org/10.1186/s43170-020-00001-y

CABI Agriculture and Bioscience
CABI

RESEARCH **Open Access**

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Antibiotic use on crops in low and middle-income countries based on recommendations made by agricultural advisors

Philip Taylor* and Robert Reeder

Table 6 Ten crops on which antibiotics were most frequently recommended

Crop	Cases in which antibiotic was included on that crop
Rice	974
Tomato	143
Citrus	117
Paprika	61
Potato	36
Cabbage	35
Eggplants	25
Pumpkin	23
Onions	15
Maize	14

Crop names were grouped and harmonised to allow analysis e.g. "Citrus" is an amalgamation of all named citrus crops

Fungicide for spoilage control of citrus fruit; for treatment of dutch elm disease in trees; for control of fungal diseases of seed potatoes… to warrant **“shelf-life”**

Budavari, S. (ed.). The Merck Index - An Encyclopedia of Chemicals, Drugs, and Biologicals. Whitehouse Station, NJ: Merck and Co., Inc., 1996., p. 1585

Thiabendazole is a fungicide and parasiticide.
Thiabendazole is also a chelating agent, which means that it is used medicinally to bind metals in cases of metal poisoning, such as lead poisoning, mercury poisoning or antimony poisoning.
Thiabendazole is vermicidal and/or vermifugal against *Ascaris lumbricoides* ("common roundworm"), *Strongyloides stercoralis* (threadworm), *Necator americanus*, *Ancylostoma duodenale* (hookworm), *Trichuris trichiura* (whipworm), *Ancylostoma braziliense* (dog and cat hookworm), *Toxocara canis*, *Toxocara cati* (ascarids), and *Enterobius vermicularis* (pinworm).
Thiabendazole also suppresses egg and/or larval production and may inhibit the subsequent development of those eggs or larvae which are passed in the feces.

Sanitation and AMR

WASH

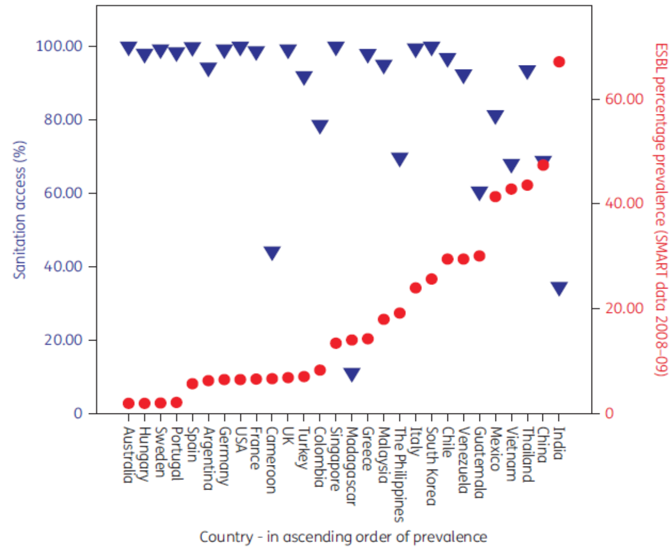
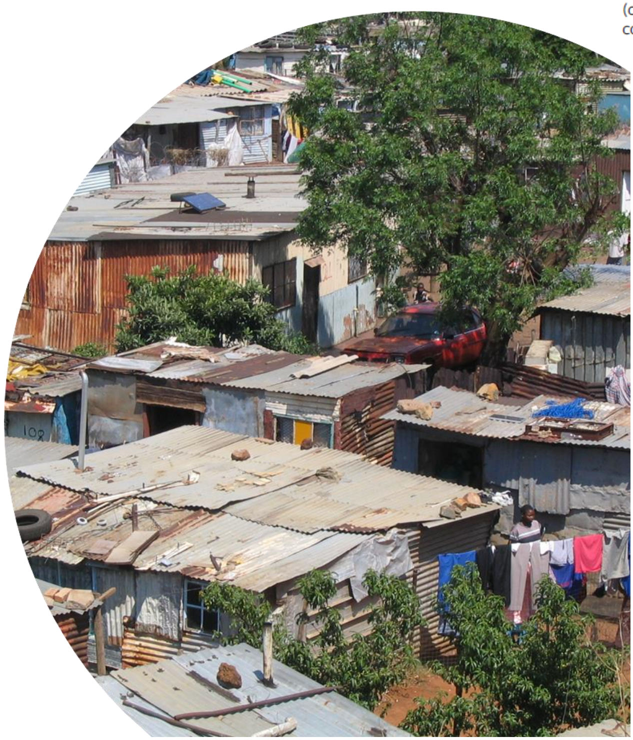


Figure 2. Sanitation access and ESBL prevalence. Sanitation access is access to improved sanitation facilities, 2008–09, as defined by WHO/UNICEF (data.worldbank.org/indicator/SH.STA.ACSN). ESBL prevalence is for 2008–09 and is derived from SMART study data.[111,147,148] This figure appears in colour in the online version of *JAC* and in black and white in the print version of *JAC*.



frontiers in Microbiology

ORIGINAL RESEARCH
published: 10 November 2017
doi: 10.3389/fmicb.2017.02232

Occurrence of Extended Spectrum β-Lactamases, KPC-Type, and MCR-1.2-Producing *Enterobacteriaceae* from Wells, River Water, and Wastewater Treatment Plants in Oltrepò Pavese Area, Northern Italy

Mariasofia Caltagirone[1], Elisabetta Nucleo[1], Melissa Spalla[1], Francesca Zara[1], Federica Novazzi[1], Vittoria M. Marchetti[1], Aurora Piazza[1,2], Ibrahim Bitar[1,3], Marica De Cicco[1], Stefania Paolucci[4], Giorgio Pilla[5], Roberta Migliavacca[1] and Laura Pagani[1]*

TABLE 5 | Phenotipical and molecular characteristics of 3GCs-resistant transconjugants; comparison with *E. coli* and *Klebsiella* spp. donors resistance and β-lactamases.

Isolates	Resistance[a]	Enzyme	Inc (Replicon)[b]
1T *E. coli*	**AMP**, **CAZ**, **CTX**, **FEP**, **CIP**, **PIP**, **LEV**, **MOXI**, **NOR**, TOB, **TMS**.	**CTX-M-1**	IncF (FIB)
3T *E. coli*	AMC, **AMP**, CAZ, **CTX**, **FEP**, **PIP**, ERT, MEM, TZP, **CIP**, **CL**, **MOXI**, **NOR**.	**CTX-M-28**, **TEM-1**	IncP (P), IncF(FIB)
7T *E. coli*	AMC, AMP, CAZ, PIP, TMS, **CO**.	CTX-M-1, **MCR-1.2**, SHV-12	IncX4 (X4)
11T *E. coli*	**AMC**, AMP, CAZ, **CTX**, FEP, **PIP**, TZP.	**SHV-12**	IncF (FIB)
1TP *E. coli* Broni	AMC, **AMP**, **CTX**, CAZ, **FEP**, **PIP**, **CIP**, **LEV**, **MOXI**, **NOR**, TOB, **CL**, FOS.	**CTX-M-28**	IncHI2 (HI2), IncF (FIA, FIB)
2TP *E. coli* Broni	**AMP**, CAZ, **CTX**, **FEP**, **PIP**, CIP, **LEV**, MOXI, NOR, CL.	**CTX-M-14**	IncX1(X1)
1TP *E. coli* Varzi	**AMP**, **CTX**, **FEP**, **PIP**, TMS.	**CTX-M-15**	IncT (T)
2TP *E. coli* Varzi	**AMP**, **CTX**, **CIP**, **LEV**, **MOXI**, **NOR**, PI, TMS.	**CTX-M-15**	IncF (FIA)
3TP *E. coli* Varzi	**AMP**, **CTX**, CAZ, FEP, PIP.	**CTX-M-15**, TEM-1	IncF (FIA, FIB)
6TP *E. coli* Varzi	**AMP**, **CTX**, **CAZ**, **PIP**, **CIP**, **LEV**, **MOXI**, **NOR**, **TOB**, **TMS**.	**CTX-M-1**, **SHV-5**	IncF (FIA, FIB)
1TP *E. coli* Stradella	**AMP**, **CTX**, **FEP**, CIP, CO,GM, MOXI, NOR, LEV, **TMS**, TOB.	**CTX-M-1**	IncF (FIA, FIB)
1TP *K. pneumoniae* Varzi	**AMP**, **CTX**, **FEP**, **PIP**.	**CTX-M-15**	IncF (FIA)
3TP *K. pneumoniae* Varzi	**AMP**, CAZ, **CTX**, FEP, PIP, TMS.	**CTX-M-28**	IncN (N)
5TP *K. pneumoniae* Varzi	**AMC**, **AMP**, **CTX**, CAZ, FEP, MEM, **ERT**, **TZP**, CIP, NOR, MOXI, FOS, CL, GM, TMS.	**TEM-1**, **KPC-2**	IncFIIk (FIIk, FIBKQ)
9T *K. oxytoca*	**AMP**, **CTX**, **FEP**, FOS, **PIP**.	**CTX-M-1**	IncN (N), R (NA[c])

[a]*AMC, amoxicillin/clavulanic acid; AMP, ampicillin; CAZ, ceftazidime; CIP, ciprofloxacin; CL, chloramphenicol; CO, colistin; CTX, cefotaxime; ERT, ertapenem; FEP, cefepime; FOS, fosfomycin; GM, gentamicin; LEV, levofloxacin; MEM, meropenem; MOXI, moxifloxacin; NOR, norfloxacin; PIP, piperacillin; TZP, piperacillin-tazobactam; TOB, tobramycin; TMS, trimetoprim/sulfametoxazol;* [b]*Inc, incompatibility group,* [c]*NA, not assigned.*
The antibiotic resistance and the determinants transferred in the transconjugants are underlined and provided in bold.

and Multi-Locus-Sequence-Typing. During one-year study and taking in account the whole Gram-negative bacterial population, an average percentage of cefotaxime resistance of 69, 32, and 10.3% has been obtained for the wastewater treatment plants, streams, and wells, respectively. These results, of concern for public health, highlight the need to improve hygienic measures to reduce the load of discharged bacteria with emerging resistance mechanisms.

Keywords: water ecosystems, Gram-negative bacteria, carbapenemases, colistin resistance, molecular characterization

MDR bacteria do not need passport to cross country borders

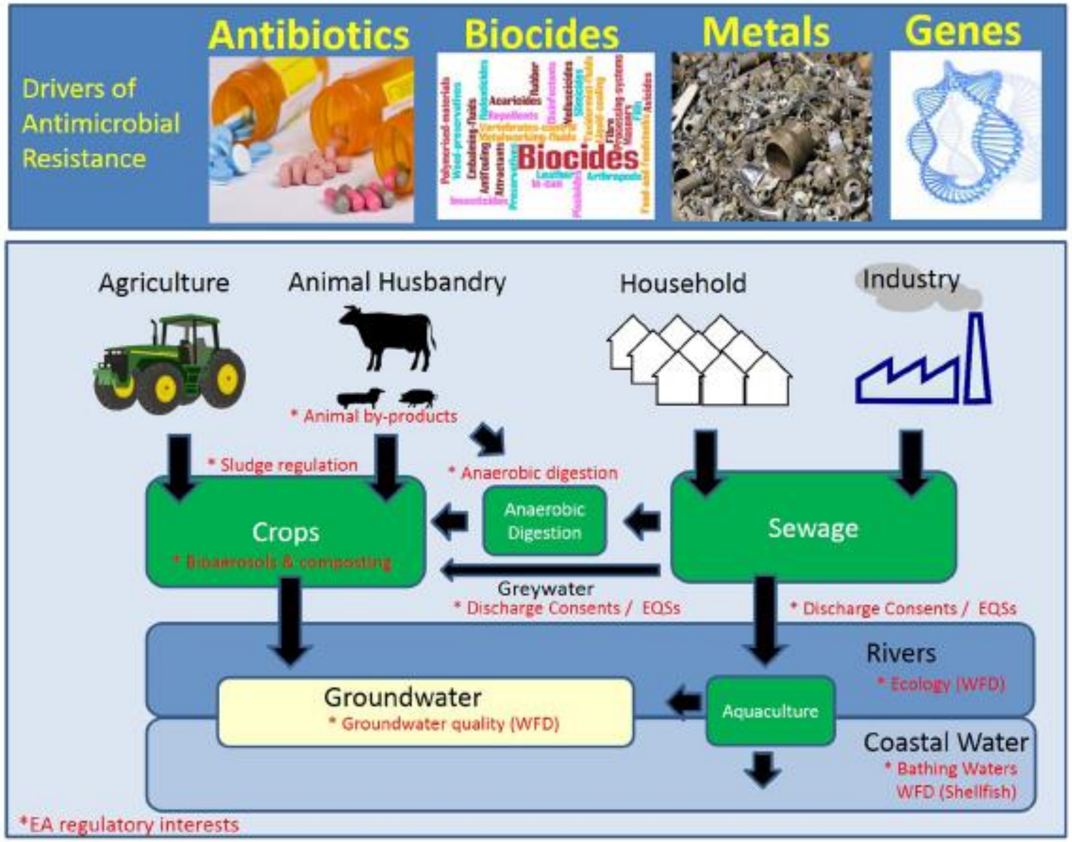
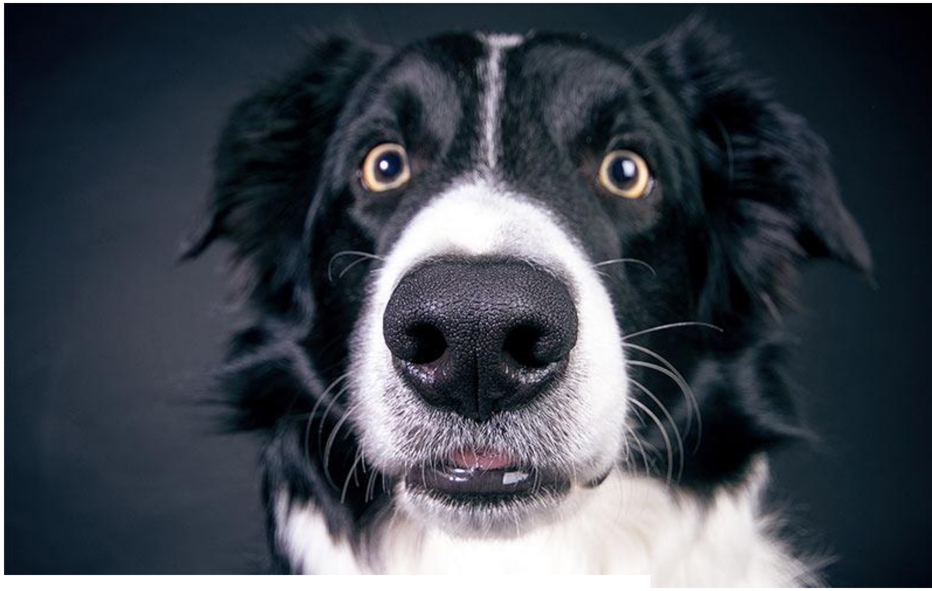


FIGURE 1 | Schematic of the hot-spots and drivers of antimicrobial resistance (AMR). The environmental compartments that are currently monitored or regulated by the Environment Agency (EA; England) are denoted by an asterisk in red. WFD, Water Framework Directive.



New Delhi Metallo-β-Lactamase-5–Producing *Escherichia coli* in Companion Animals, United States

Stephen D. Cole, Laura Peak, Gregory H. Tyson, Renate Reimschuessel, Olgica Ceric, Shelley C. Rankin

Author affiliations: University of Pennsylvania School of Veterinary Medicine, Philadelphia, Pennsylvania, USA (S.D. Cole, S.C. Rankin); Louisiana State University, Baton Rouge, Louisiana, USA (L. Peak); US Food and Drug Administration, Silver Spring, Maryland, USA (G.H. Tyson, R. Reimschuessel, O. Ceric)

DOI: https://doi.org/10.3201/eid2602.191221

We report isolation of a New Delhi metallo-β-lactamase-5–producing carbapenem-resistant *Escherichia coli* sequence type 167 from companion animals in the United States. Reports of carbapenem-resistant *Enterobacteriaceae* in companion animals are rare. We describe a unique cluster of bla_{NDM-5}–producing *E. coli* in a veterinary hospital.

ORIGINAL RESEARCH
published: 16 November 2016
doi: 10.3389/fmicb.2016.01843

High Prevalence of β-lactamase and Plasmid-Mediated Quinolone Resistance Genes in Extended-Spectrum Cephalosporin-Resistant *Escherichia coli* from Dogs in Shaanxi, China

Xiaoqiang Liu[1], Haixia Liu[2], Yinqian Li[1] and Caiju Hao[1]*

[1] Department of Basic Veterinary Medicine, College of Veterinary Medicine, Northwest A&F University, Yangling, China,
[2] Department of Aquaculture, College of Animal Science and Technology, Northwest A&F University, Yangling, China

Objective: The aim of this study was to investigate the occurrence and molecular characterization of extended-spectrum β-lactamases (ESBL), plasmid-mediated AmpC β-lactamase (pAmpC) and carbapenemases as well as plasmid-mediated quinolone-resistant (PMQR) among extended-spectrum cephalosporin-resistant (ESC-R) *Escherichia coli* from dogs in Shaanxi province in China.

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COMMENTARY

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Wildlife Is Overlooked in the Epidemiology of Medically Important Antibiotic-Resistant Bacteria

Monika Dolejska,[a,b] Ivan Literak[a,b]

[a]Department of Biology and Wildlife Diseases, Faculty of Veterinary Hygiene and Ecology, University of Veterinary and Pharmaceutical Sciences Brno, Brno, Czech Republic

[b]CEITEC VFU, University of Veterinary and Pharmaceutical Sciences Brno, Brno, Czech Republic

ABSTRACT Wild animals foraging in the human-influenced environment are colonized by bacteria with clinically important antibiotic resistance. The occurrence of such bacteria in wildlife is influenced by various biological, ecological, and geographical factors which have not yet been fully understood. More research focusing on the human-animal-environmental interface and using novel approaches is required to understand the role of wild animals in the transmission of antibiotic resistance and to assess potential risks for the public health.

KEYWORDS antibiotics, carbapenemase, environment, landfill, transmission, wild animal

Citation Dolejska M, Literak I. 2019. Wildlife is overlooked in the epidemiology of medically important antibiotic-resistant bacteria. Antimicrob Agents Chemother 63:e01167-19. https://doi.org/10.1128/AAC.01167-19.

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Address correspondence to Monika Dolejska, monika.dolejska@gmail.com.

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The views expressed in this article do not necessarily reflect the views of the journal or of ASM.

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Published 25 July 2019

In this issue of Antimicrob Agents Chemother, Ahlstrom et al. (3) provide data on the first detection of CPE isolates in wildlife in the United States. By examining feces of almost 1,000 gulls from seven locations near solid waste sites in Alaska for CPE using antibiotic-supplemented medium, they obtained 7 *Escherichia coli* isolates positive for the carbapenemase genes bla_{KPC-2} or bla_{OXA-48}. Although the overall prevalence of CPE found in wild birds in this study was quite low (<1%), this observation is surprising since the surveillance of carbapenem resistance in Alaska initiated in 2013 has so far revealed only four imported cases of human infections by CPE. Three bla_{KPC-2}-positive *E. coli* isolates from gulls were assigned to sequence type 410 (ST410), a successful clone with reported interspecies transmission between wildlife, humans, and companion animals (4). Four highly related (only two single nucleotide polymorphisms [SNPs]) sequence type 38 (ST38) *E. coli* isolates with chromosomally integrated bla_{OXA-48} were found in the gulls as well. Of note, ST38 is considered a globally dispersed multidrug-

antibiotics

Review

Country Income Is Only One of the Tiles: The Global Journey of Antimicrobial Resistance among Humans, Animals, and Environment

Angela Pieri [1], Richard Aschbacher [2], Giada Fasani [2], Jole Mariella [3], Lorenzo Brusetti [4], Elisabetta Pagani [2], Massimo Sartelli [5] and Leonardo Pagani [1,2,*]

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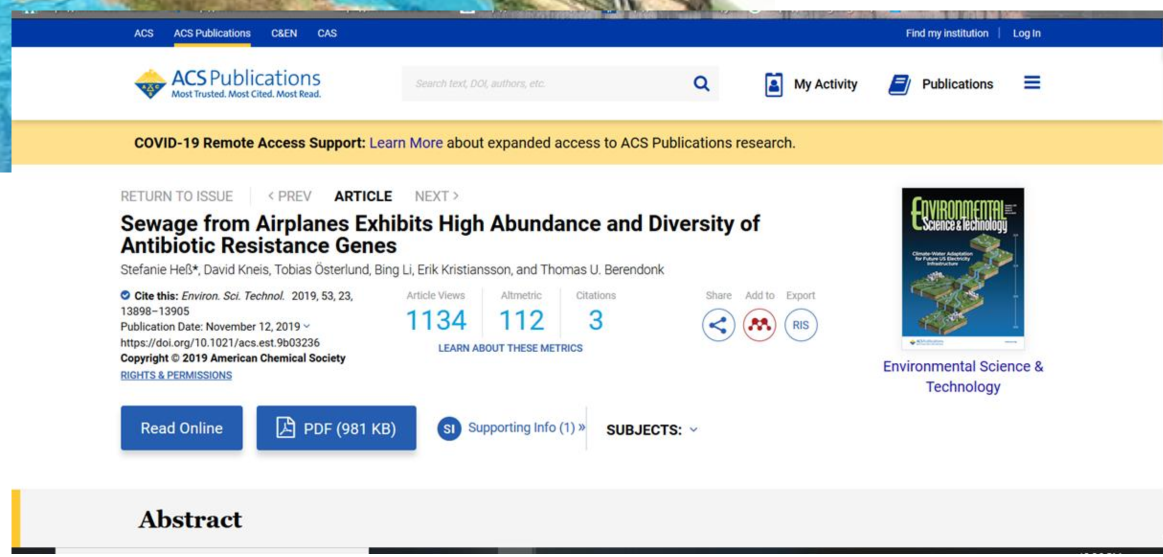
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Sewage from Airplanes Exhibits High Abundance and Diversity of Antibiotic Resistance Genes

Stefanie Heß*, David Kneis, Tobias Österlund, Bing Li, Erik Kristiansson, and Thomas U. Berendonk

Cite this: *Environ. Sci. Technol.* 2019, 53, 23, 13898–13905
Publication Date: November 12, 2019
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Abstract

MDR bacteria do not need passport to cross country borders

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Sewage from Airplanes Exhibits High Abundance and Diversity of Antibiotic Resistance Genes

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Cite this: *Environ. Sci. Technol.* 2019, 53, 23, 13898–13905
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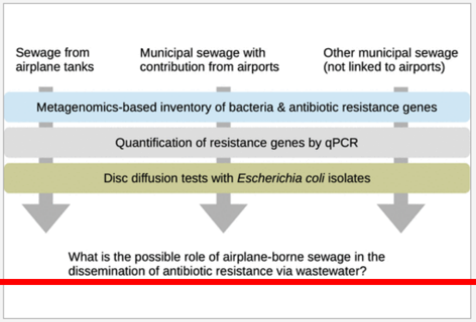
Abstract

Abstract

Airplane sanitary facilities are shared by an international audience. We hypothesized the corresponding sewage to be an extraordinary source of antibiotic-resistant bacteria (ARB) and resistance genes (ARG) in terms of diversity and quantity. Accordingly, we analyzed ARG and ARB in airplane-borne sewage using complementary approaches: metagenomics, quantitative polymerase chain reaction (qPCR), and cultivation. For the purpose of comparison, we also quantified ARG and ARB in the inlets of municipal treatment plants with and without connection to airports. As expected, airplane sewage contained an extraordinarily rich set of mobile ARG, and the relative abundances of genes were mostly increased compared to typical raw sewage of municipal origin. Moreover, combined resistance against third-generation cephalosporins, fluorochinolones, and aminoglycosides was unusually common (28.9%) among *Escherichia coli* isolated from airplane sewage. This percentage exceeds the one reported for German clinical isolates by a factor of 8. Our findings suggest that airplane-borne sewage can effectively contribute to the fast and global spread of antibiotic resistance.



Pal *et al. Microbiome* (2016) 4:54
DOI 10.1186/s40168-016-0199-5

Microbiome

RESEARCH Open Access

The structure and diversity of human, animal and environmental resistomes

Chandan Pal[1,2], Johan Bengtsson-Palme[1,2], Erik Kristiansson[2,3] and D. G. Joakim Larsson[1,2*]

Many ARGs are widespread across environments
Out of the 325 horizontally transferable ARG types analysed, 203 ARG types were detected at least once in this

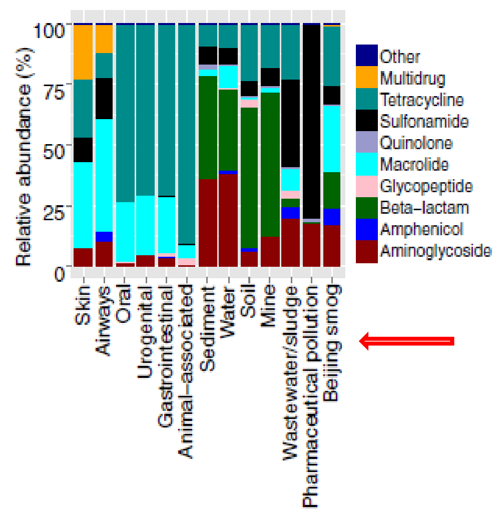


Fig. 3 *Bar graph* showing the relative abundance of resistance genes to different classes of antibiotics across environments

14 % of the detected ARGs were found in both humans and at least one external environment.

Biocide and metal resistance genes are most common in external environments
The relative abundances of biocide and metal resistance genes were, in contrast to ARGs, higher in most external environments than in human and animal microbiomes (Fig. 1b). Similarly, the richness of biocide and metal resistance genes was higher in all investigated external environments than in human body sites and animals, with Beijing smog having the highest richness of biocide and metal resistance genes (Fig. 1e). Within the human microbiome, oral and skin habitats showed higher richness of biocide/metal resistance genes than other body sites did. There was a strong correlation between the richness of biocide/metal resistance genes and the genus richness (Spearman's correlation coefficient = 0.469, $p < 0.001$) (Fig. 2c). We observed no correlation between the richness of ARGs and biocide/metal resistance genes (Spearman's correlation coefficient = −0.015, $p = 0.645$), even after controlling for the effect of taxonomic richness (partial correlation coefficient = −0.056, $p = 0.097$) (Additional file 1: Figure S4).

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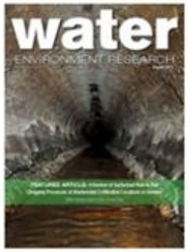

Survival and antibiotic resistance of bacteria in artificial snow produced from contaminated water

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Abstract References Citations Supplementary Data Data/Media Metrics

This study shows microbiological contamination of water in two main Podhale rivers, whose resources are used for artificial snowing, and the resulting snow contamination. 31 E. coli strains were isolated from snow at two ski stations in the studied region, their antimicrobial resistance was determined and the presence of extended-spectrum β-lactamase (ESBL) genes was searched for. The results indicate that waters of both rivers are severely contaminated, resulting in contamination of artificial snow, with among others thermotolerant E. coli. E. coli isolated from snow were most frequently resistant to ampicillin (74.19%) and amoxicillin/clavulanate (51.61% isolates). Aminoglycosides and 3rd generation cephalosporins were most efficient among the tested antimicrobials. Some bacterial strains were multi-drug resistant and three strains exhibited ESBL mechanism. Molecular analyses showed the presence of ESBL genes in the same three strains. Genetic variation among E. coli indicates that only some genotypes are able to survive the artificial snowing process.

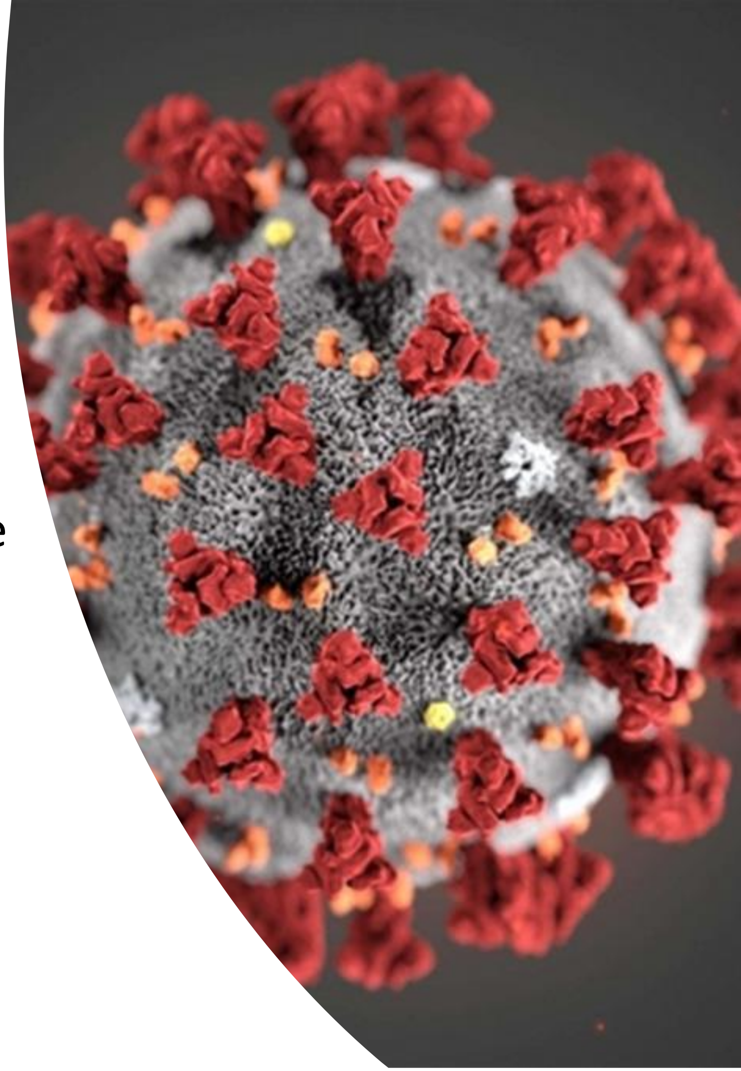
Keywords: antimicrobial resistance; artificial snow; ESBL; Escherichia coli

Integrated Surveillance System Data/Information for Action

- Prevalence of AMR in different reservoirs
- AMR trends over time
- Association between AMR and Use of antimicrobial agents
- Guide evidence-based policies and guidelines to control antimicrobial use in human and animals
- Identify and evaluate the effectiveness of interventions to contain the emergence and spread of resistant bacteria, or even new viruses or threats

How surveillance can improve health outcomes

- Locally: allow healthcare professionals to make better informed clinical decisions to ensure better patients outcomes
  - ASP, PRP, PPP
- Nationally: guide policy and ensure appropriate and timely public health interventions
  - PNCAR, scientific societies,
- Globally: provide early warnings of emerging threats and data to identify and act on long-term trends
  - WHO, CDC



Infections caused by resistant bacteria are associated with increased morbidity, mortality, length of hospital stay, and costs.[9] If unrelenting attention to infection control practices is crucial, the administration of antimicrobials should no longer be considered a single's pledge, as clearly demonstrated by these recent Italian experiences. AMPs are rightly aimed at a more appropriate prescription of antimicrobials and trigger a virtuous circle through tight collaborative efforts and ever-improving educational plans: we are bound to be geared up in helping caregivers avoid collateral damage related to antimicrobial misuse while ultimately improving patient safety. In Italy, we should really start thinking about effective antimicrobial policies rather than deeming antimicrobial resistance and inappropriate antimicrobial therapy as our inescapable fate.

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Conclusions

Observations from this ECDC country visit confirm that the AMR situation in Italian hospitals and regions poses a major public health threat to the country. The levels of carbapenem-resistant *Enterobacteriaceae* (CRE) and *Acinetobacter baumannii* have now reached hyper-endemic levels and, together with meticillin-resistant *Staphylococcus aureus* (MRSA), this situation causes Italy to be one of the Member States with the highest level of resistance in Europe.

During conversations in Italy, ECDC often gained the impression that these high levels of AMR appear to be accepted by stakeholders throughout the healthcare system, as if they were an unavoidable state of affairs.

The factors that contribute negatively to this situation seem to be:

- Little sense of urgency about the current AMR situation from most stakeholders and a tendency by many stakeholders to avoid taking charge of the problem;
- Lack of institutional support at national, regional and local level;
- Lack of professional leadership at each level;
- Lack of accountability at each level;
- Lack of coordination of the activities between and within levels.

If the current trends of carbapenem resistance and colistin resistance in gram-negative bacteria such as *Klebsiella pneumoniae* and *A. baumannii* are not reversed, key medical interventions will be compromised in the near future. Untreatable infections following organ transplantation, intensive care or major surgical interventions are now a significant possibility in many Italian hospitals.

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