Pathways for the evolution of antibiotic resistance: From natural ecosystems to hospitals and back

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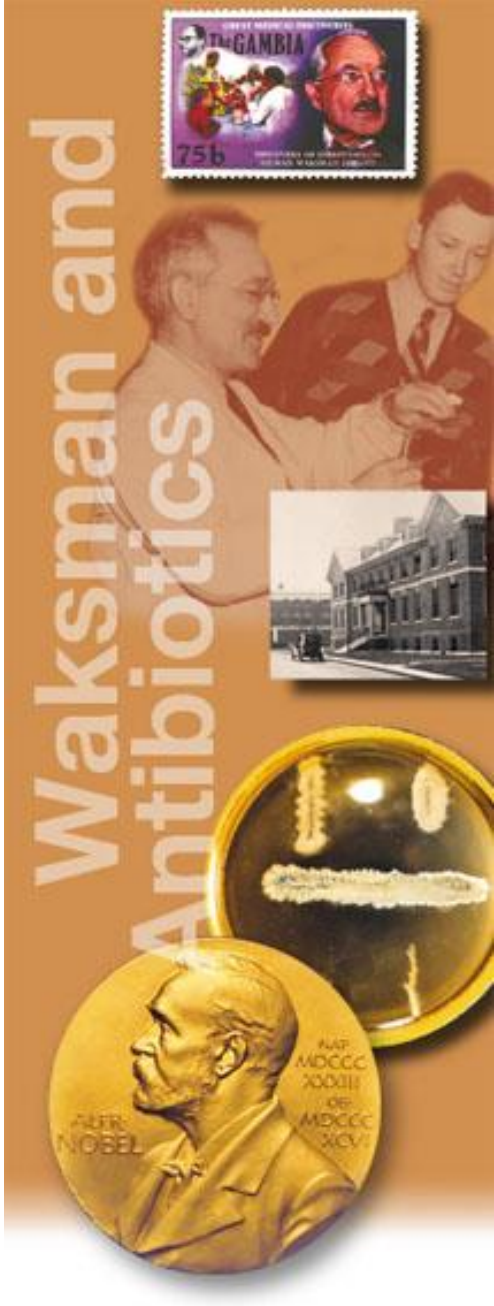
Antibiotics from Nature: Looking for inhibitors

THE SOIL AS A SOURCE OF MICROORGANISMS ANTAGONISTIC TO DISEASE-PRODUCING BACTERIA

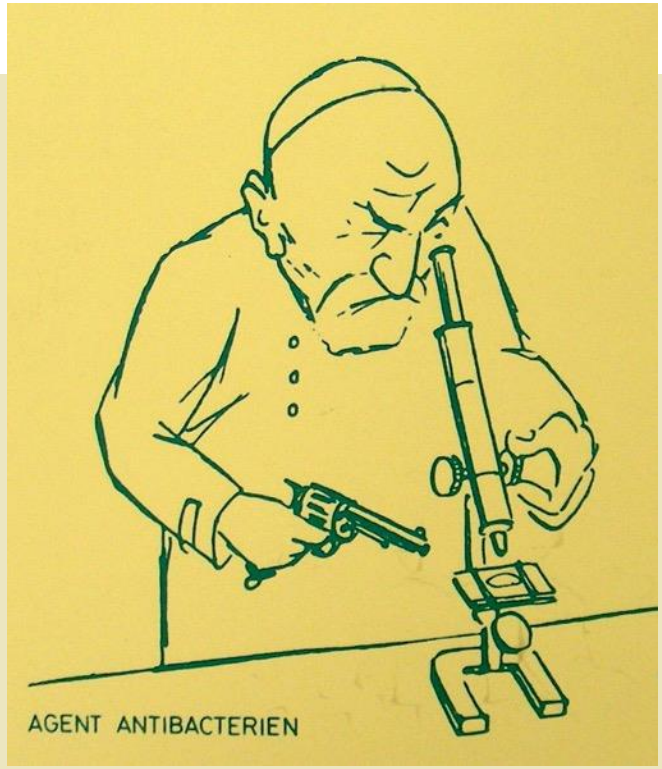
SELMAN A. WAKSMAN AND H. BOYD WOODRUFF

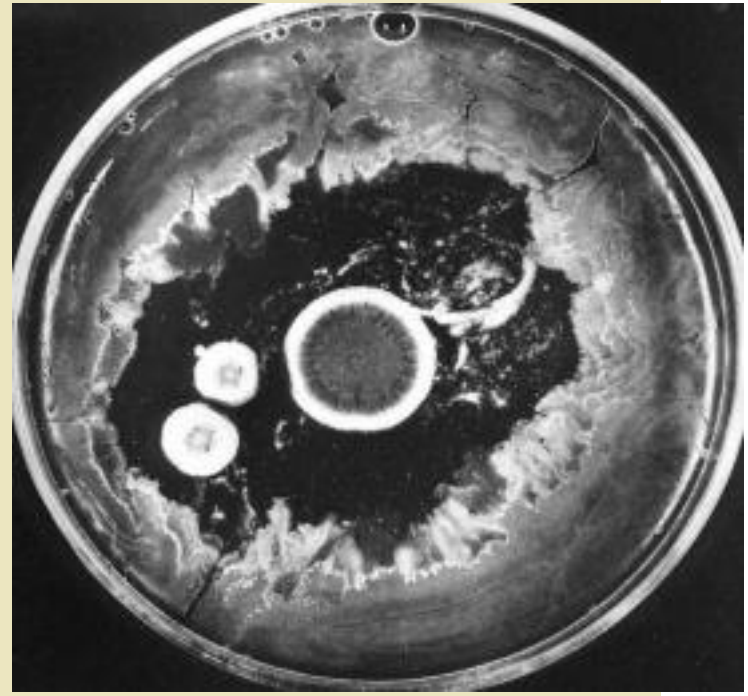
J Bacteriol. 1940 40: 581–600

Bacteria pathogenic for man and animals find their way to the soil, either in the excreta of the hosts or in their remains. If one considers the period for which animals and plants have existed on this planet and the great numbers of disease-producing microbes that must have thus gained entrance into the soil, one can only wonder that the soil harbors so few bacteria capable of causing infectious diseases in man and in animals. One hardly thinks of the soil as a source of epidemics. What has become of all the bacteria causing typhoid, dysentery, cholera, diphtheria, pneumonia, bubonic plague, tuberculosis, leprosy, and numerous others? This question was first raised by medical bacteriologists in the eighties of the last century. The soil was searched for bacterial agents of infectious diseases, until the conclusion was reached that these do not survive long in the soil. It was suggested that the cause of the disappearance of these disease- producing organisms in the soil is to be looked for among the soil-inhabiting microbes, antagonistic to the pathogens and bringing about their rapid destruction in the soil.



Antibiotics: Weapons in a microbial warfare





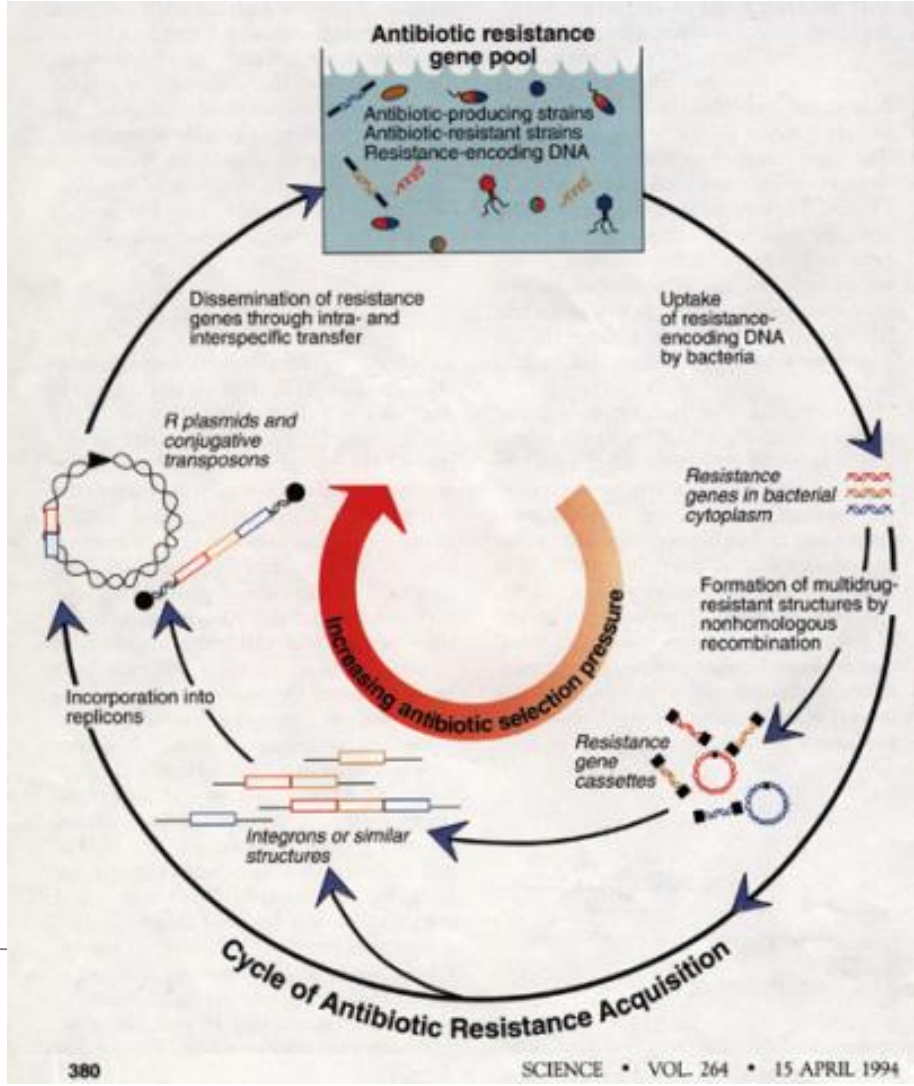
Origin and dissemination of antibiotic resistance genes

Proc. Nat. Acad. Sci. USA Vol. 70 pp. 2276-2280,1973 **Aminoglycoside Antibiotic-Inactivating Enzymes in Actinomycetes Similar to Those Present in Clinical Isolates of Antibiotic-Resistant Bacteria**

RAOUL BENVENISTE AND JULIAN DAVIES

The metabolic role of the aminoglycoside-modifying enzymes in actinomycetes is not known. Miller and Walker have postulated that **phosphorylated streptomycin might be important as a metabolic precursor** of streptomycin or to **detoxify the antibiotic** (7). The enzymes might also be required for transport of these antibiotics in or out of the cell. Alternatively, they may have nothing to do with antibiotic biosynthesis and may play a role in another biosynthetic process.

Nothing is known about the origin of R factors. The Watanabe hypothesis (4) provides a simple molecular mechanism for their origin, but we can only speculate on the environmental and evolutionary factors that play a role in their formation and maintenance. **Their presence does not seem to require the extensive use of a selective antibiotic environment since Gardner et al. (21) have found R factors in an "antibiotic virgin population" in the Solomon Islands.**



Resistance is everywhere: Risks must be ranked

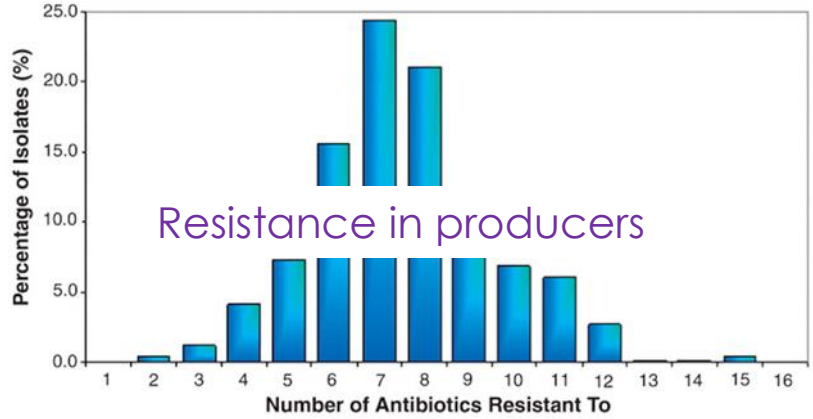
The Shared Antibiotic Resistome of Soil Bacteria and Human Pathogens

Kevin J. Forsberg,[1*] Alejandro Reyes,[1*] Bin Wang,[1,2] Elizabeth M. Selleck,[3] Morten O. A. Sommer,[4,5]† Gautam Dantas[1,2]†

OPEN ACCESS Freely available online

The Culturable Soil Antibiotic of Multi-Drug Resistant Bacte

Fiona Walsh*, Brion Duffy



Resistance in producers

2444–2447
ccess publication 4 August 2011

Journal of Antimicrobial Chemotherapy

as vehicles of the resistome in cystic fibrosis

olain*, Laura Fancello, Christelle Desnues and Didier Raoult

Microb Ecol (2013) 65:975–981
DOI 10.1007/s00248-013-0187-2

MICROBIOLOGY OF AQUATIC SYSTEMS

Marine Sediment Bacteria Harbor Antibiotic Resistance Genes Highly Similar to Those Found in Human Pathogens

Jing Yang · Chao Wang · Chang Shu · Li Liu · Jianing Geng · Songnian Hu · Jie Feng

Sampling the Antibiotic Resistome

Vanessa M. D'Costa,[1] Katherine M. McGrann,[1] Donald W. Hughes,[2] Gerard D. Wright[1*]

LETTER

doi:10.1038/nature12212

Antibiotic treatment expands the resistance reservoir and ecological network of the phage metagenome

Sheetal R. Modi[1], Henry H. Lee[1]†, Catherine S. Spina[1,2,3] & James J. Collins[1,2,3]

Functional Characterization of the Antibiotic Resistance Reservoir in the Human Microflora

Morten O. A. Sommer,*† Gautam Dantas,*†‡ George M. Church

Intrinsic resistome

The intrinsic resistome can be defined as the ensemble of elements that contribute to the characteristic phenotype of susceptibility to antibiotics of a given bacterial species (or clone).

These elements belong to the core genome and has not been recently acquired by HGT as the consequence of the recent use of antibiotics at clinical settings.

The genes contributing to intrinsic resistance in a given species, might contribute to acquired resistance in a different one if they are transferred by HGT. However, only a few have been found in mobile elements

The significant resistome

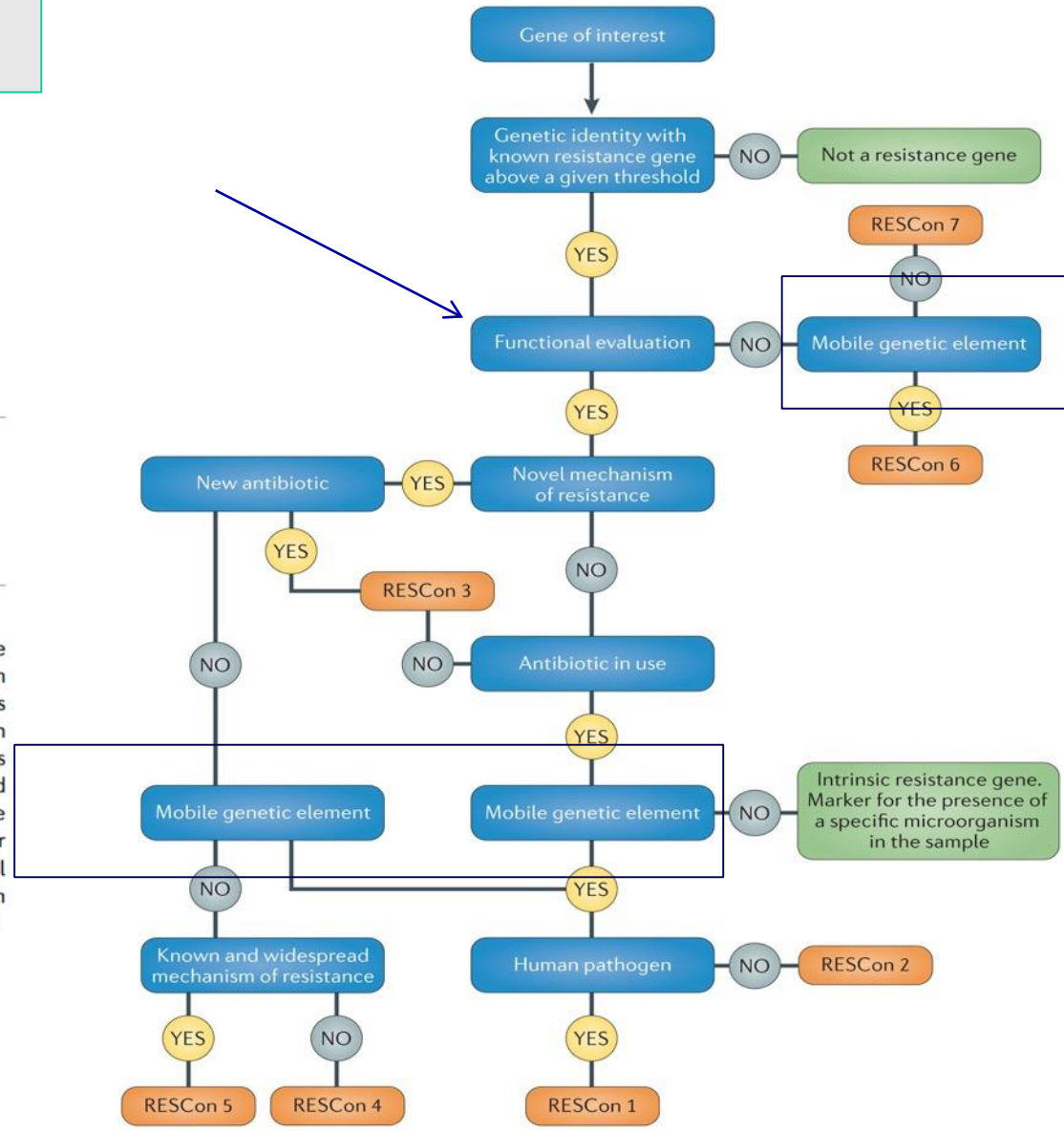
PERSPECTIVES

OPINION

What is a resistance gene? Ranking risk in resistomes

José L. Martínez, Teresa M. Coque and Fernando Baquero

Abstract | Metagenomic studies have shown that antibiotic resistance genes are ubiquitous in the environment, which has led to the suggestion that there is a high risk that these genes will spread to bacteria that cause human infections. If this is true, estimating the real risk of dissemination of resistance genes from environmental reservoirs to human pathogens is therefore very difficult. In this Opinion article, we analyse the current definitions of antibiotic resistance and antibiotic resistance genes, and we describe the bottlenecks that affect the transfer of antibiotic resistance genes to human pathogens. We propose rules for estimating the risks associated with genes that are present in environmental resistomes by evaluating the likelihood of their introduction into human pathogens, and the consequences of such events for the treatment of infections.



Resistance and resilience

Prediction of the intestinal resistome by a three-dimensional structure-based method

Etienne Ruppé[1,2,17]*, Amine Ghozlane[1,3,4,17], Julien Tap[1,16,17], Nicolas Pons[1], Anne-Sophie Alvarez[1], Nicolas Maziers[1], Trinidad Cuesta[5], Sara Hernando-Amado[5], Irene Clares[5], Jose Luís Martínez[5], Teresa M. Coque[6,7,8], Fernando Baquero[6,7,8], Val F. Lanza[6,7], Luis Máiz[9], Tiphaine Goulenok[10], Victoire de Lastours[2,10], Nawal Amor[10], Bruno Fantin[2,10], Ingrid Wieder[11], Antoine Andremont[2,11], Willem van Schaik[12,13], Malbert Rogers[12], Xinglin Zhang[12], Rob J. L. Willems[12], Alexandre G. de Brevern[14], Jean-Michel Batto[1], Hervé M. Blottière[1], Pierre Léonard[1], Véronique Léjard[1], Aline Letur[1], Florence Levenez[1], Kevin Weiszer[1], Florence Haimet[1], Joël Doré[1], Sean P. Kennedy[1,4] and S. Dusko Ehrlich[1,15]

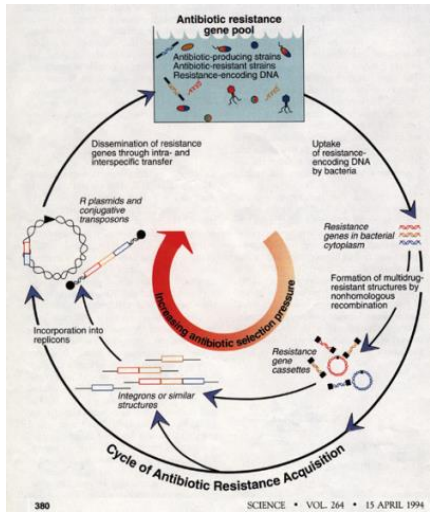
In summary, we developed a method, PCM, which could unveil the diversity of ARDs in the intestinal microbiota. Employing this tool, we gathered evidence that the vast majority of the ARDs we predicted showed no sign of mobility and that their abundance was correlated to gene richness. Together with the protective trait of some intestinal bacteria against antibiotics[33], our results suggest that the ARDs from the intestinal microbiota might be considered as our 'resilience allies'[38] assuring the preservation of the healthy commensal microbiota under antibiotic exposure.

Natural ecosystems as origin, reservoires and vehicles for the dissemination of antibiotic resistance

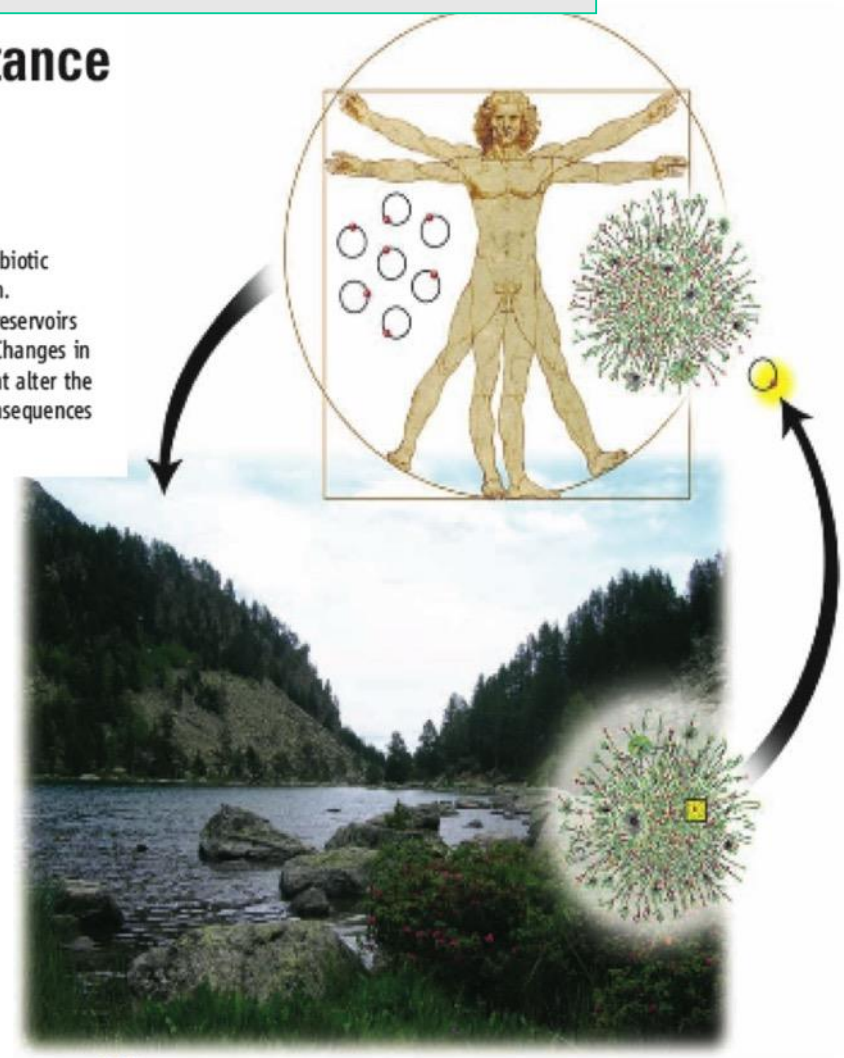
Antibiotics and Antibiotic Resistance Genes in Natural Environments

José L. Martínez*

The large majority of antibiotics currently used for treating infections and the antibiotic resistance genes acquired by human pathogens each have an environmental origin. Recent work indicates that the function of these elements in their environmental reservoirs may be very distinct from the "weapon-shield" role they play in clinical settings. Changes in natural ecosystems, including the release of large amounts of antimicrobials, might alter the population dynamics of microorganisms, including selection of resistance, with consequences for human health that are difficult to predict.



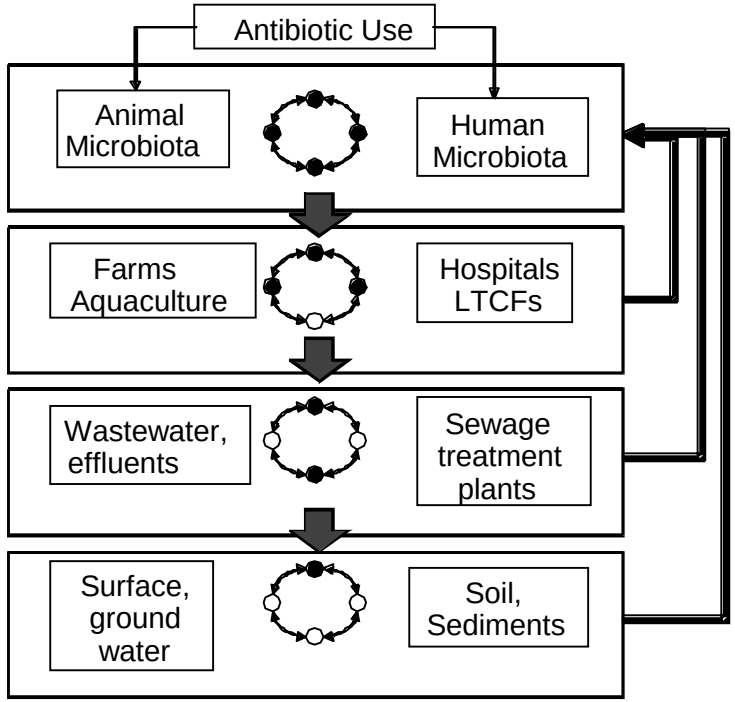
380 SCIENCE • VOL. 264 • 15 APRIL 1994



Ecological connectivity

It was on a short-cut through the hospital kitchens that Albert was first approached by a member of the Antibiotic Resistance.

The reactors for the building up of antibiotic resistance



REVIEW ARTICLE

Lateral genetic transfer and the construction of genetic exchange communities

Elizabeth Skippington & Mark A. Ragan

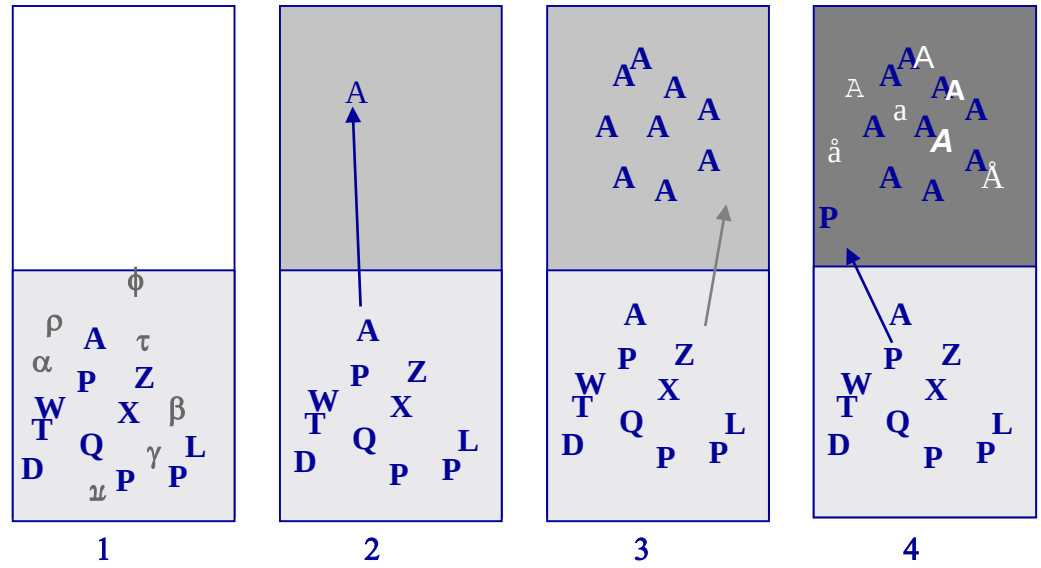
ARC Centre of Excellence in Bioinformatics, Institute for Molecular Bioscience, The University of Queensland, Brisbane, Qld, Australia

Baquero F, Martínez, J. L., Cantón R. (2008). Current Opinion in Biotechnology 19:260-5

Founder effect in the establishment of antibiotic resistance genes

TEM-1 beta-lactamase is the first antibiotic resistance gene described.

Altought several derivatives of TEM-1 (and other plasmid-encoded betalactamases) are selected in pathogenic bacteria, the number of completely different plasmidic beta-lactamases is rather low considering the amount of potential beta-lactamases in environmental bacteria.



Martínez, J.L., Fajardo, A., Garmendia, L., Hernández, A., Linares, J. F., Martínez-Solano, L., Sánchez, M. B. (2009)
FEMS Microbiology Reviews 33: 44-65

SCIENTIFIC REPORTS

OPEN

Multilevel selection of *bcrABDR*-mediated bacitracin resistance in *Enterococcus faecalis* from chicken farms

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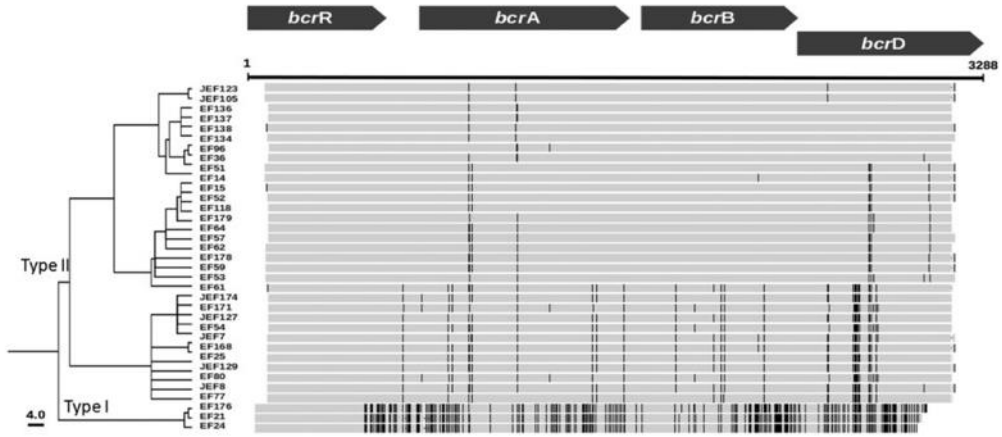
Mu-Ya Chen[1,2], Felipe Lira[3], Hua-Qing Liang[1,2], Rui-Ting Wu[1,2], Jia-Hong Duan[1,2], Xiao-Ping Liao[1,2], José L. Martínez[3], Ya-Hong Liu[1,2] & Jian Sun[1,2]



The figure shows the phylogenetic relationships among the different *bcr*ABDR alleles studied in the present work. As shown, two major branches (Type I and Type II) can be distinguished, with the Type II allele presenting also three different subtypes. This population structure indicates that the acquisition of *bcr*ABDR by *E. faecalis* has a polyphyletic origin. Each black line in the Figure represents a SNP in comparison with the consensous *bcr*ABDR sequence.

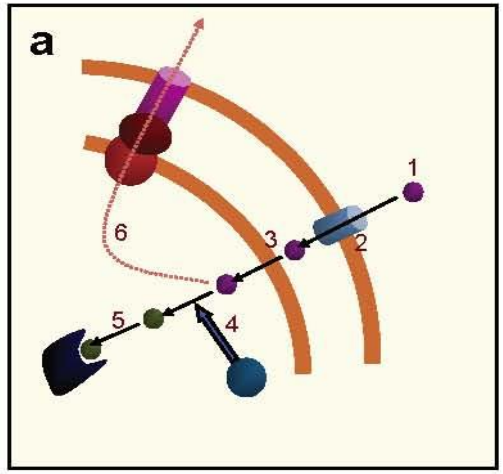
Enterococcus cecorum can be a reservoir of bacitracin resistance in chicken

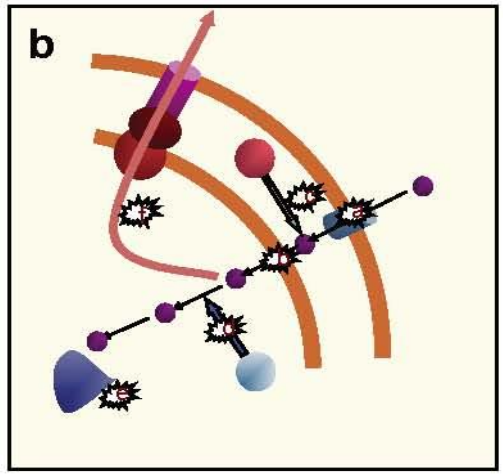
To ascertain the distribution of *bcr*ABDR, the sequence of the cluster and the surrounding IS*Enfa1* was searched at NCBI DNA database. In addition to the aforementioned plasmids, Type II *bcr*ABDR was found to be present in the genome of *Streptocccus pyogenes* NGAS322 as well as in the genomes of different strains of *E. cecorum* (a chicken commensal with some virulent members) isolates[15,16,17], in occasions surrounded by IS*Enfa1*, in other occasions without IS present around. In addition, the genomes of *E. cecorum* also contain upstream and downstream sequences nearly identical to those found in pEF123 and other *bcr*ABDR-containing plasmids. All of these will be powerful to improve *Enterococcus cecorum* can be a reservoir of bacitracin resistance in chicken. Although the whole-genome sequence methods used in this study did not allow distinguishing between chromosomal and plasmidic DNA. Since a route of transmission from *E. cecorum* towards *E. faecalis* or *vice versa* cannot be tracked, we cannot ascertain which is the origin of *bcr*ABDR; however our results indicate that the commensal chicken microbiota can be a reservoir of transferrable bacitracin resistance that may end in relevant human pathogens as *E. faecalis*.

Table 2
Minimum inhibitory concentration (MIC) and *bcr* genotype for each of the studied *Enterococcus* isolates, according to their origin and species.

Origin	Isolate	Species	MIC (mg/L)	bcrAB	bcrABD	bcrABR	bcrABDR	Other[a]
Veterinary	337/03	*E. faecium*	24		x			
	1213/02	*E. faecalis*	>256	x				
	1903/02	*E. gallinarum*	>256	x				
	2151/03	*E. faecalis*	>256				x	
	2479/02	*E. faecalis*	>256			x		
	3031/03	*E. faecalis*	>256				x	
	3179/03	*E. faecium*	>256			x		
	3671/03	*E. avium*	>256	x				

Fitness costs associated to antibiotic resistance





Antibiotic resistance may produce a burden on bacterial metabolism because:

- Target proteins are very important for bacterial physiology, so that antibiotic resistance mutations in this proteins make them less proficient.
-The acquisition of a antibiotic resistance plasmid renders a metablic cost (replication, trasncription, traduction)
-.

-Consequently, antibiotic cycling may reduce antibiotic resistance

-Unfortunately this os not true

J Antimicrob Chemother 2010; **65:** 350–360
doi:10.1093/jac/dkp387 Advance publication 8 November 2009

Journal of Antimicrobial Chemotherapy

Little evidence for reversibility of trimethoprim resistance after a drastic reduction in trimethoprim use

M. Sundqvist[1,2]*§, P. Geli[3,4]†§, D. I. Andersson[5], M. Sjölund-Karlsson[2]‡, A. Runehagen[6], H. Cars[7], K. Abelson-Storby[8], O. Cars[1,9]‖ and G. Kahlmeter[2,10]‖

Objectives: The worldwide rapid increase in antibiotic-resistant bacteria has made efforts to prolong the lifespan of existing antibiotics very important. Antibiotic resistance often confers a fitness cost in the bacterium. Resistance may thus be reversible if antibiotic use is discontinued or reduced. To examine this concept, we performed a 24 month voluntary restriction on the use of trimethoprim-containing drugs in Kronoberg County, Sweden.

Methods: The intervention was performed on a 14 year baseline of monthly data on trimethoprim resistance and consumption. A three-parameter mathematical model was used to analyse the intervention effect. The prerequisites for reversion of resistance (i.e. fitness cost, associated resistance and clonal composition) were studied on subsets of consecutively collected *Escherichia coli* from urinary tract infections.

Results: The use of trimethoprim-containing drugs decreased by 85% during the intervention. A marginal but statistically significant effect on the increase in trimethoprim resistance was registered. There was no change in the clonal composition of *E. coli* and there was no measurable fitness cost associated with trimethoprim resistance in clinical isolates. The frequency of associated antibiotic resistances in trimethoprim-resistant isolates was high.

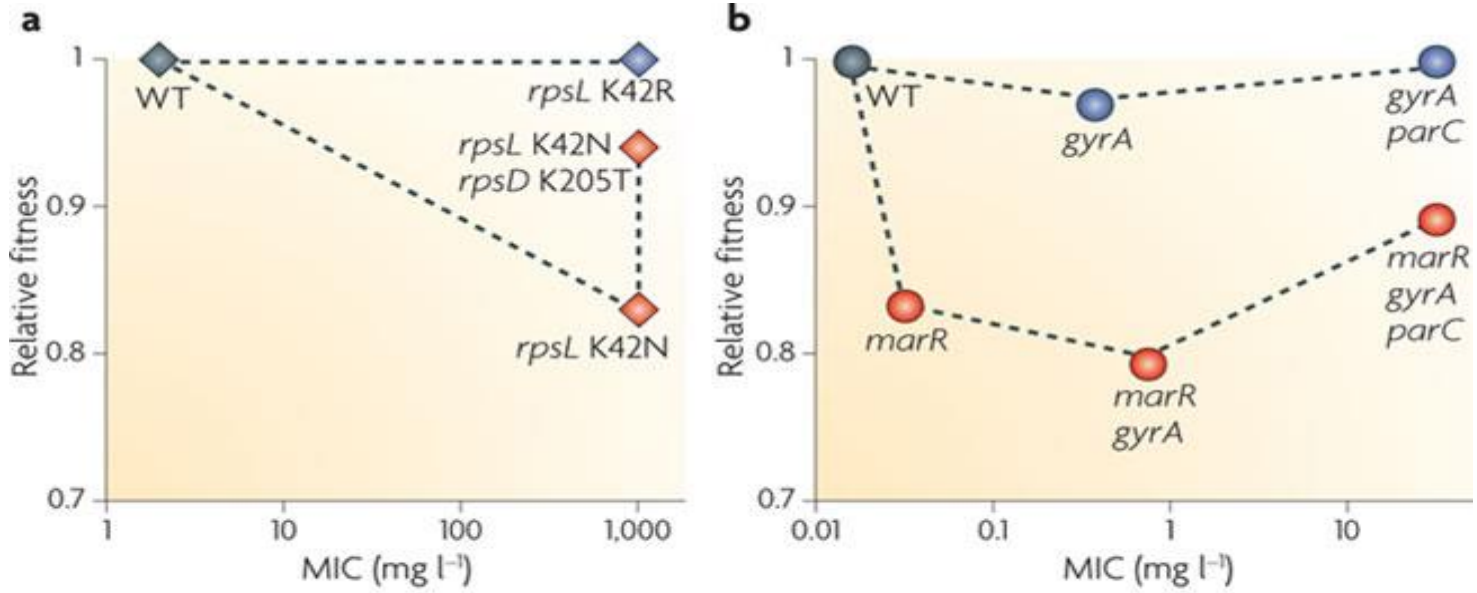
Conclusions: A lack of detectable fitness cost of trimethoprim resistance *in vitro* together with a strong co-selection of other antibiotics could explain the rather disappointing effect of the intervention. The result emphasizes the low possibility of reverting antibiotic resistance once established and the urgent need for the development of new antibacterial agents.

Some mutations produce no cost

Bacteria	Resistance	Cost*	Assay system	Refs
Salmonella enterica subsp. *enterica* serovar Typhimurium	Streptomycin	Variable	Mice and *in vitro*	29,31,88,91
	Rifampicin	Variable	Mice and *in vitro*	29,49
	Nalidixic acid	Yes	Mice and *in vitro*	29
	Ciprofloxacin	Yes	Chickens and *in vitro*	124
	Fusidic acid	Variable	Mice and *in vitro*	40–42,92
	Mupirocin	Yes	Mice, nematodes and *in vitro*	125
	Actinonin	Yes	Mice, nematodes and *in vitro*	96
Escherichia coli	Streptomycin	Variable	*In vitro*	126,127
	Norfloxacin	Variable	Mice and *in vitro*	58
	Rifampicin	Variable	*In vitro*	46
	Fosfomycin	Yes	Urine and *in vitro*	128
Campylobacter jejuni	Ciprofloxacin	Variable	Chickens	34
Mycobacterium tuberculosis	Isoniazid	Yes	Mice	73,99
	Rifampicin	Yes	Macrophages and *in vitro*	26,129,130
Mycobacterium bovis	Isoniazid	Yes	Mice	72
Mycobacterium smegmatis	Streptomycin	Variable	*In vitro*	30
Staphylococcus aureus	Fusidic acid	Variable	Rats and *in vitro*	39,131,132
	Rifampicin	Variable	Biofilms and *in vitro*	45,47,133
	Mupiricin	No	Mice and *in vitro*	33,134
	Methicillin	Yes	*In vitro*	32
	Vancomycin	Variable	*In vitro*	57
Staphylococcus epidermidis	Fusidic acid	Yes	Humans	135
	Ciprofloxacin	No	Humans	135
Streptococcus pneumoniae	Gemifloxacin	Yes	Mice and *in vitro*	136
Helicobacter pylori	Clarithromycin	Yes	Mice and *in vitro*	25,27
Chlamydia psittaci	Spectinomycin	Yes	*In vitro*	137
Pseudomonas aeruginosa	Fluoroquinolone	Variable	*In vitro*	82,138
Pseudomonas fluorescens	Rifampicin	Yes	Soil	139
Listeria monocytogenes	Class IIa bacteriocin	Yes	*In vitro*	140
Neisseria meningitidis	Sulfonamide	Yes	*In vitro*	141

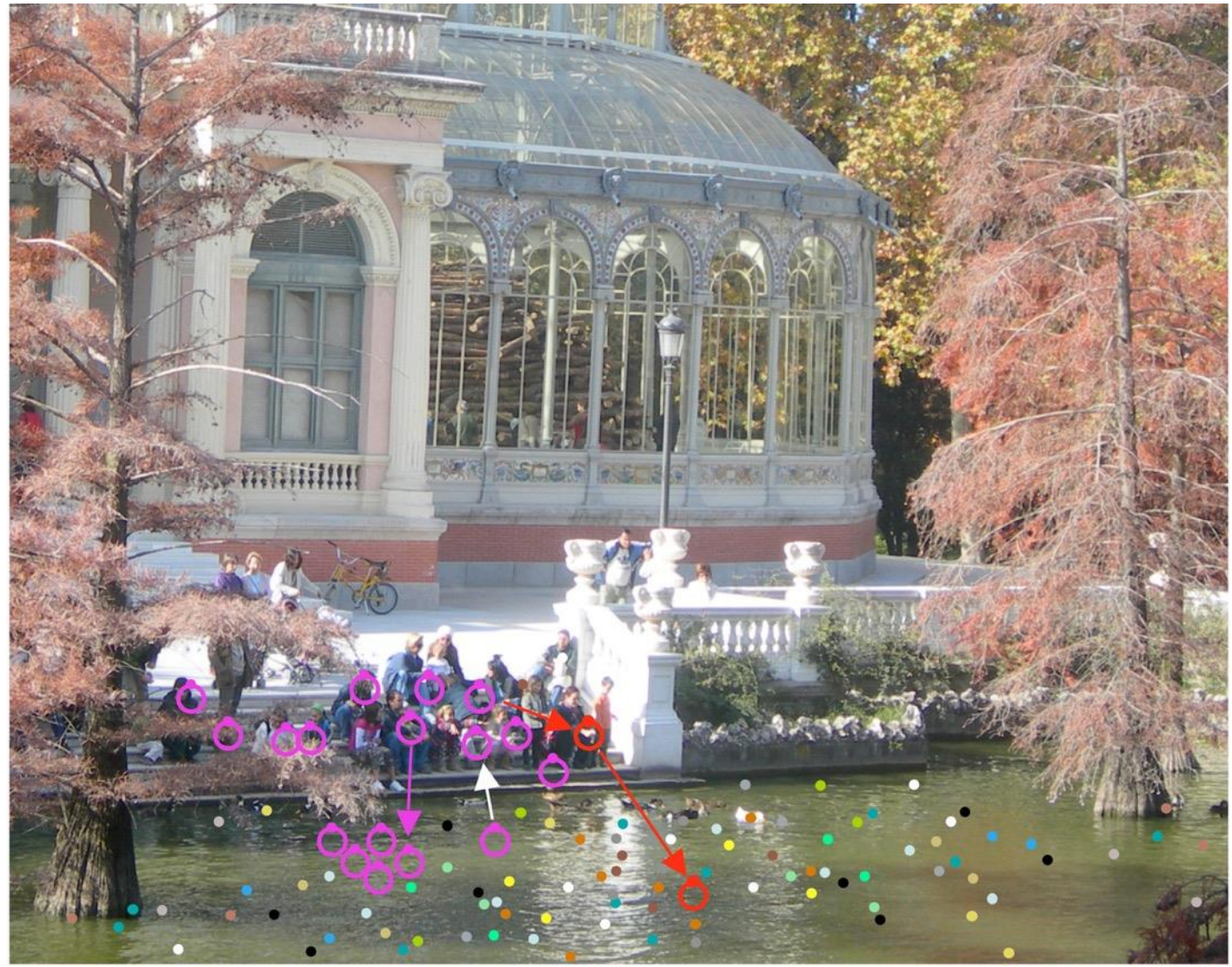
*Yes indicates that the increase in the generation time, which is a measure of the fitness cost, ranges from several percent up to as much as 400%. Variable means that some mutations have an associated fitness cost, whereas others do not.

Acquisition of secondary mechanisms of resistance may compensate fitness costs

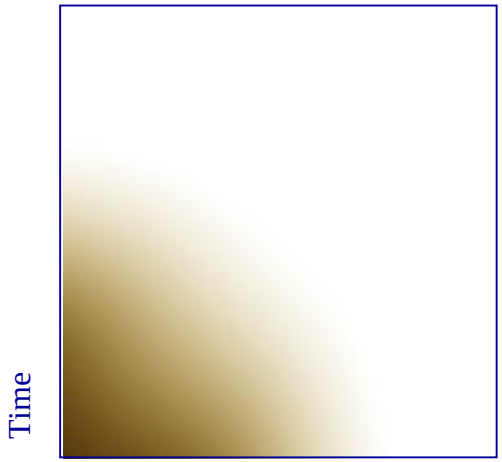


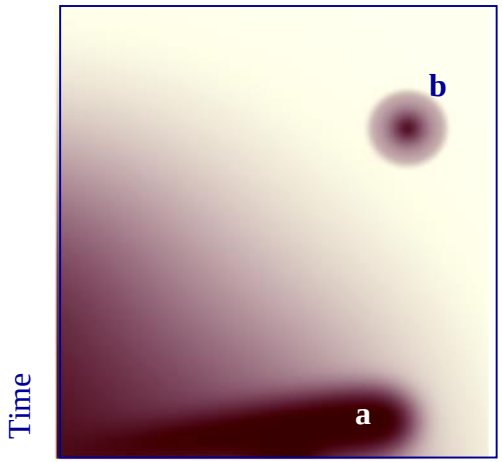
Nature Reviews | Microbiology

Environmental dissemination of resistance: Going back to natural ecosystems



On the different fate pollution by antibiotics or by resistance genes





Martínez, J.L. (2009) Environmental Pollution 157:2893-902

Unexpected Occurrence of Plasmid-mediated Quinolone Resistance Determinants in Environmental *Aeromonas* spp.

Vincent Cattoir,*†‡ Laurent Poirel,*† Camille Aubert,*† Claude-James Soussy,‡ and Patrice Nordmann*†

Emerging Infectious Diseases • www

Journal of Antimicrobial Chemotherapy (2008) **62**, 948–950
doi:10.1093/jac/dkn341
Advance Access publication 3 September 2008

JAC

Plasmid-mediated quinolone resistance in *Aeromonas allosaccharophila* recovered from a Swiss lake

Renata Cristina Picão[1,2], Laurent Poirel[1], Antonella Demarta[3], Carla Sofia Ferreira Silva[1], Anna Rita Corvaglia[4], Orlando Petrini[3] and Patrice Nordmann[1]*

[1]*Service de Bactériologie-Virologie, INSERM U914 'Emerging Resistance to Antibiotics', Hôpital de Bicêtre, Assistance Publique/Hôpitaux de Paris, Faculté de Médecine et Université Paris Sud, K.-Bicêtre, France;* [2]*Laboratório ALERTA, Universidade Federal de São Paulo, São Paulo, Brazil;* [3]*Istituto Cantonale di Microbiologia, Bellinzona, Switzerland;* [4]*Centre Médical et Universitaire, Université de Genève, Geneva, Switzerland*

suggests that these genes may spread silently. In addition, the fact that the same mobile insertion cassette-associated *qnrS2* structure has been found in different *Aeromonas* species from aquatic environments from distantly related geographical areas may indicate that these PMQR determinants are widespread, at least in Europe. Our findings strengthen the possible role of *Aeromonas* spp. and of mobile insertion cassette-type structures as vehicles for the dissemination of quinolone resistance markers. They may be the link between the progenitor of QnrS proteins (Vibrionaceae) and enterobacterial clinical species such as *Salmonella*.

environmental microbiology

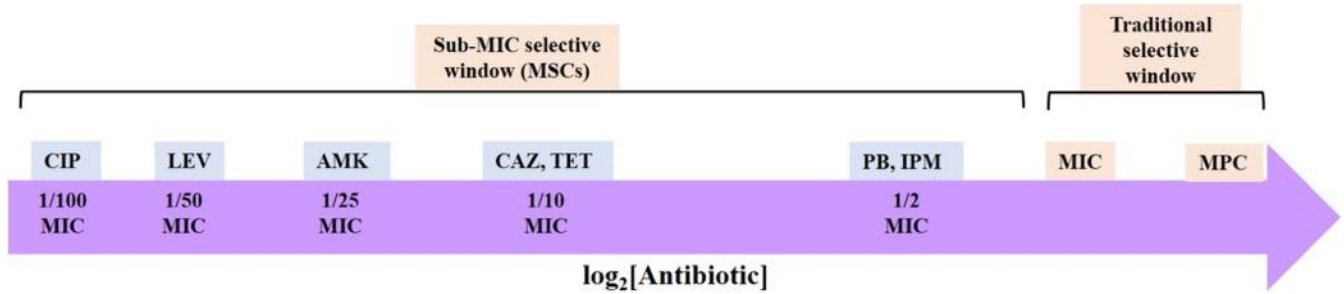
Environmental Microbiology (2021) **00**(00), 00–00 doi:10.1111/1462-2920.15806

Special Issue Article

Evolution under low antibiotic concentrations: a risk for the selection of *Pseudomonas aeruginosa* multidrug-resistant mutants in nature

Fernando Sanz-García, Sara Hernando-Amado and José Luis Martínez*

Centro Nacional de Biotecnología, CSIC, Madrid 28049, Spain.



Selection requires long time because is not lethal. Maybe not important at clinical settings but highly relevant in antibiotic polluted environments as hospital waste-waters©©

Waste Water Treatment Plants as epidemiological markers for early detection of antibiotic resistance

SCIENCE ADVANCES | RESEARCH ARTICLE

HEALTH AND MEDICINE

Antibiotic resistance in European wastewater treatment plants mirrors the pattern of clinical antibiotic resistance prevalence

Katariina M. M. Pärnänen[1]*, Carlos Narciso-da-Rocha[2]*, David Kneis[3]*, Thomas U. Berendonk[3], Damiano Cacace[3], Thi Thuy Do[4], Christian Elpers[5], Despo Fatta-Kassinos[6], Isabel Henriques[7], Thomas Jaeger[8], Antti Karkman[1], Jose Luis Martinez[9], Stella G. Michael[6], Irene Michael-Kordatou[6], Kristin O'Sullivan[10], Sara Rodriguez-Mozaz[11], Thomas Schwartz[8], Hongjie Sheng[12,13], Henning Sørum[10], Robert D. Stedtfeld[13], James M. Tiedje[14], Saulo Varela Della Giustina[11], Fiona Walsh[4], Ivone Vaz-Moreira[2], Marko Virta[1†], Célia M. Manaia[2†]

Integrated antibiotic resistance (AR) surveillance is one of the objectives of the World Health Organization global action plan on antimicrobial resistance. Urban wastewater treatment plants (UWTPs) are among the most important receptors and sources of environmental AR. On the basis of the consistent observation of an increasing north-to-south clinical AR prevalence in Europe, this study compared the influent and final effluent of 12 UWTPs located in seven countries (Portugal, Spain, Ireland, Cyprus, Germany, Finland, and Norway). Using highly parallel quantitative polymerase chain reaction, we analyzed 229 resistance genes and 25 mobile genetic elements. This first trans-Europe surveillance showed that UWTP AR profiles mirror the AR gradient observed in clinics. Antibiotic use, environmental temperature, and UWTP size were important factors related with resistance persistence and spread in the environment. These results highlight the need to implement regular surveillance and control measures, which may need to be appropriate for the geographic regions.

Pollution is the major source of significant resistome in natural ecosystems

Fecal pollution can explain antibiotic resistance gene abundances in anthropogenically impacted environments

Antti Karkman [1,2,3], Katariina Pärnänen[4] & D.G.Joakim Larsson [1,2]

Discharge of treated sewage leads to release of antibiotic resistant bacteria, resistance genes and antibiotic residues to the environment. However, it is unclear whether increased abundance of antibiotic resistance genes in sewage and sewage-impacted environments is due to on-site selection pressure by residual antibiotics, or is simply a result of fecal contamination with resistant bacteria. Here we analyze relative resistance gene abundance and accompanying extent of fecal pollution in publicly available metagenomic data, using crAssphage sequences as a marker of human fecal contamination (crAssphage is a bacteriophage that is exceptionally abundant in, and specific to, human feces). We find that the presence of resistance genes can largely be explained by fecal pollution, with no clear signs of selection in the environment, with the exception of environments polluted by very high levels of antibiotics from manufacturing, where selection is evident. Our results demonstrate the necessity to take into account fecal pollution levels to avoid making erroneous assumptions regarding environmental selection of antibiotic resistance.

NATURE COMMUNICATIONS | (2019)10:80 | https://doi.org/10.1038/s41467-018-07992-3 | www.nature.com/naturecommunications

Neverthess, environmental bacteria (non-producers) are in several cases the original source of antibiotic resistance

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Aug. 2005, p. 3523–3525 Vol. 49, No. 8
0066-4804/05/$08.00+0 doi:10.1128/AAC.49.8.3523–3525.2005

Origin of Plasmid-Mediated Quinolone Resistance Determinant QnrA

Laurent Poirel,[1] Jose-Manuel Rodriguez-Martinez,[1,2] Hedi Mammeri,[1] Alain Liard,[1] and Patrice Nordmann[1]*

Service de Bactériologie-Virologie, Hôpital de Bicêtre, Assistance Publique/Hôpitaux de Paris, Faculté de Médecine Paris-Sud, Université Paris XI, 94275 K.-Bicêtre, France,[1] and University Hospital Virgen Macarena, University of Sevilla, Sevilla, Spain[2]

Received 15 March 2005/Returned for modification 19 April 2005/Accepted 21 May 2005

Plasmid-mediated resistance to quinolones is increasingly reported in studies of *Enterobacteriaceae*. Using a PCR-based strategy, a series of gram-negative species were screened for *qnrA*-like genes. *Shewanella algae*, an environmental species from marine and fresh water, was identified as its reservoir. This is a one of the very few examples of progenitor identification of an acquired antibiotic resistance gene.

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Sept. 2011, p. 4405–4407 Vol. 55, No. 9
0066-4804/11/$12.00 doi:10.1128/AAC.00681-11

Origin of OXA-181, an Emerging Carbapenem-Hydrolyzing Oxacillinase, as a Chromosomal Gene in *Shewanella xiamenensis*∇

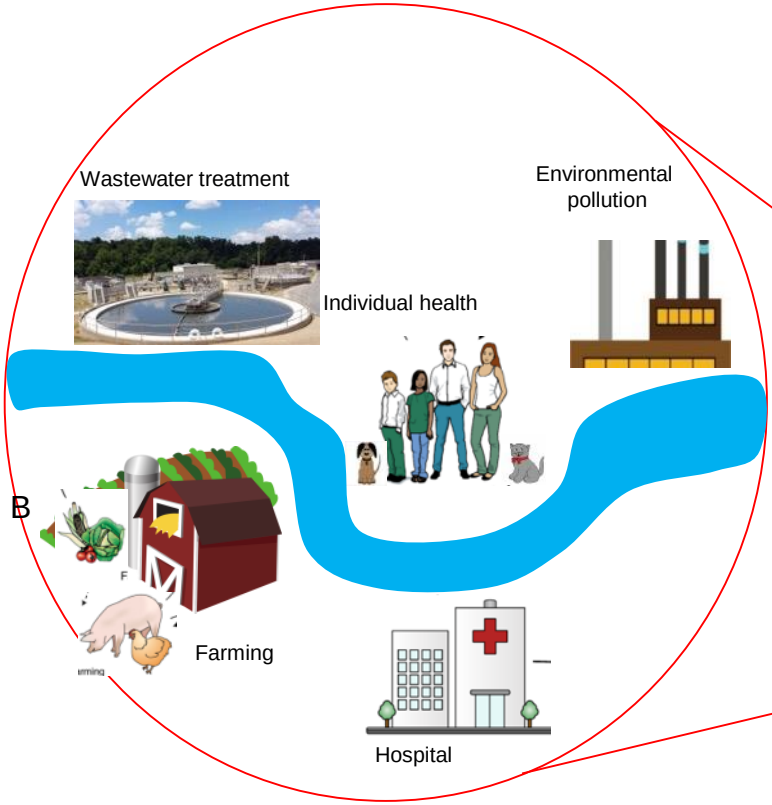
Anaïs Potron, Laurent Poirel, and Patrice Nordmann*

Service de Bactériologie-Virologie, INSERM U914, Emerging Resistance to Antibiotics, Hôpital de Bicêtre, Assistance Publique/Hôpitaux de Paris, Faculté de Médecine, and Université Paris-Sud, 84275 Le Kremlin-Bicêtre, France

Received 17 May 2011/Returned for modification 22 June 2011/Accepted 26 June 2011

Plasmid-mediated carbapenem-hydrolyzing β-lactamases are becoming emerging threats with *Enterobacteriaceae*. In particular, the carbapenem-hydrolyzing class D β-lactamase OXA-48 and its derivative OXA-181 have been reported increasingly worldwide. Using a PCR-based strategy, environmental samples were screened for bla_{OXA-48}-like genes. *Shewanella xiamenensis*, an environmental species from marine and freshwater, was identified as the progenitor of the $bla_{OXA-181}$ gene. This work identifies the reservoir of an emerging carbapenemase gene that is clinically significant.

One Health and Global Health: Similar concepts, but not exactly the same



One Health(s)

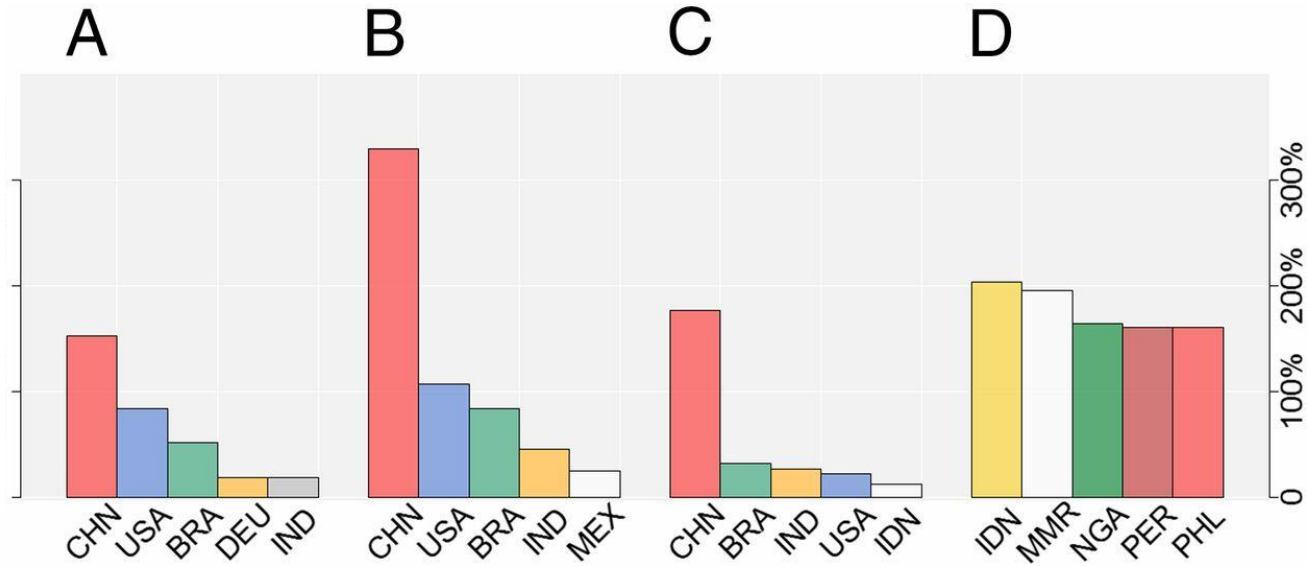
Global Health

NATURE MICROBIOLOGY | VOL 4 | SEPTEMBER 2019 | 1432–1442 | www.nature.com/naturemicrobiology

Global trends in antimicrobial use in food animals

Thomas P. Van Boeckel[a,1], Charles Brower[b], Marius Gilbert[c,d], Bryan T. Grenfell[a,e,f], Simon A. Levin[a,g,h,1], Timothy P. Robinson[i], Aude Teillant[a,e], and Ramanan Laxminarayan[b,e,j,1]

Demand for animal protein for human consumption is rising globally at an unprecedented rate. Modern animal production practices are associated with regular use of antimicrobials, potentially increasing selection pressure on bacteria to become resistant. Despite the significant potential consequences for antimicrobial resistance, there has been no quantitative measurement of global antimicrobial consumption by livestock. We address this gap by using Bayesian statistical models combining maps of livestock densities, economic projections of demand for meat products, and current estimates of antimicrobial consumption in high-income countries to map antimicrobial use in food animals for 2010 and 2030. We estimate that the global average annual consumption of antimicrobials per kilogram of animal produced was 45 mg·kg^{-1}, 148 mg·kg^{-1}, and 172 mg·kg^{-1} for cattle, chicken, and pigs, respectively. Starting from this baseline, we estimate that between 2010 and 2030, the global consumption of antimicrobials will increase by 67%, from 63,151 ± 1,560 tons to 105,596 ± 3,605 tons. Up to a third of the increase in consumption in livestock between 2010 and 2030 is imputable to shifting production practices in middle-income countries where extensive farming systems will be replaced by large-scale intensive farming operations that routinely use antimicrobials in subtherapeutic doses. For Brazil, Russia, India, China, and South Africa, the increase in antimicrobial consumption will be 99%, up to seven times the projected population growth in this group of countries. Better understanding of the consequences of the uninhibited growth in veterinary antimicrobial consumption is needed to assess its potential effects on animal and human health.

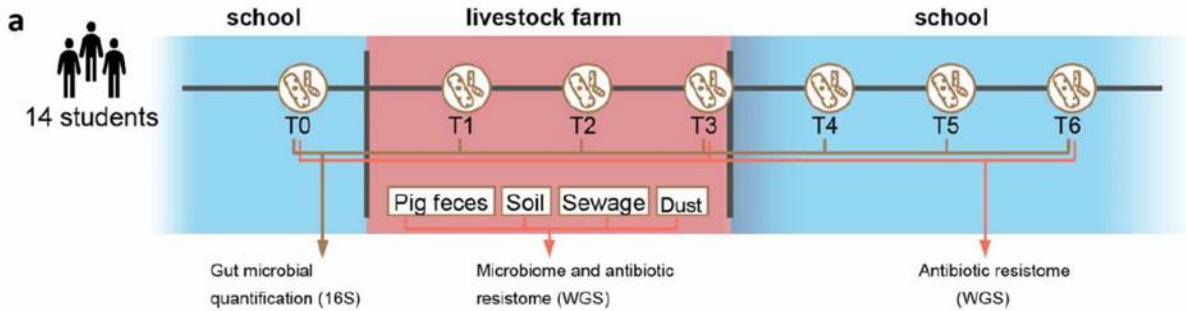


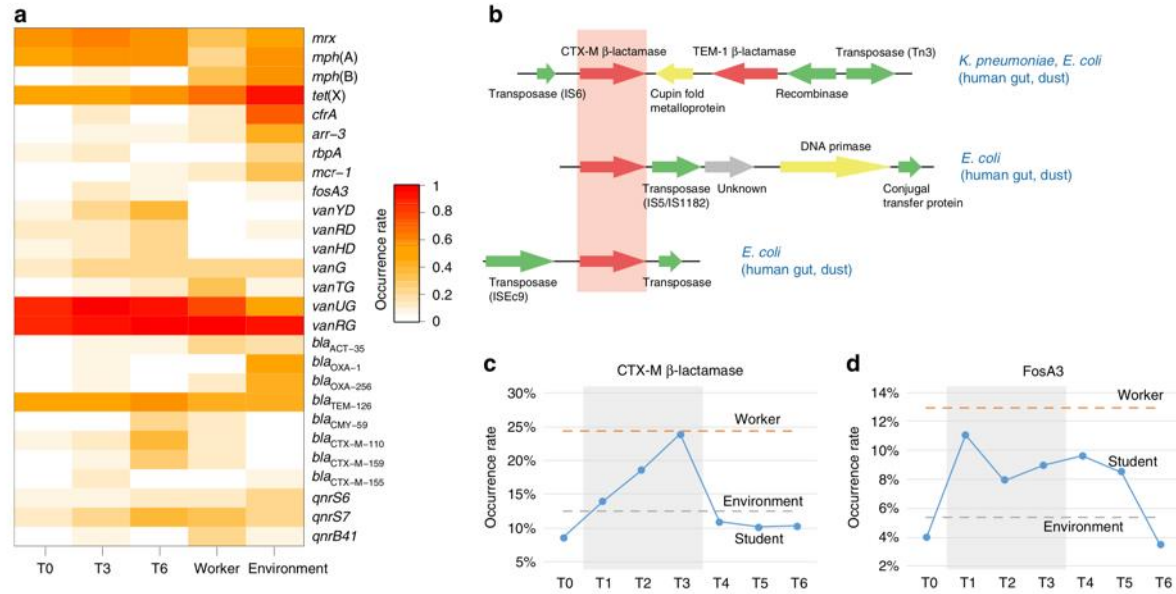
(*A*) Largest five consumers of antimicrobials in livestock in 2010. (*B*) Largest five consumers of antimicrobials in livestock in 2030 (projected). (*C*) Largest Increase in antimicrobial consumption between 2010 and 2030. (*D*) Largest relative increase in antimicrobial consumption between 2010 and 2030.

Thomas P. Van Boeckel et al. PNAS 2015;112:18:5649-5654

Environmental remodeling of human gut microbiota and antibiotic resistome in livestock farms

Jian Sun[1,2,10], Xiao-Ping Liao[1,2,10], Alaric W. D'Souza[3,10], Manish Boolchandani[3,10], Sheng-Hui Li[1,4,10], Ke Cheng[1,2], José Luis Martínez[5], Liang Li[1,2], You-Jun Feng[1,2], Liang-Xing Fang[1,2], Ting Huang[1,2], Jing Xia[1,2], Yang Yu[1,2], Yu-Feng Zhou[1,2], Yong-Xue Sun[1,2,6], Xian-Bo Deng[2], Zhen-Ling Zeng[1,2,6], Hong-Xia Jiang[1,2,6], Bing-Hu Fang[1,2,6], You-Zhi Tang[1,2,6], Xin-Lei Lian[1,2], Rong-Min Zhang[1,2], Zhi-Wei Fang[4], Qiu-Long Yan[4], Gautam Dantas[3,7,8,9]✉ & Ya-Hong Liu[1,2,6]✉



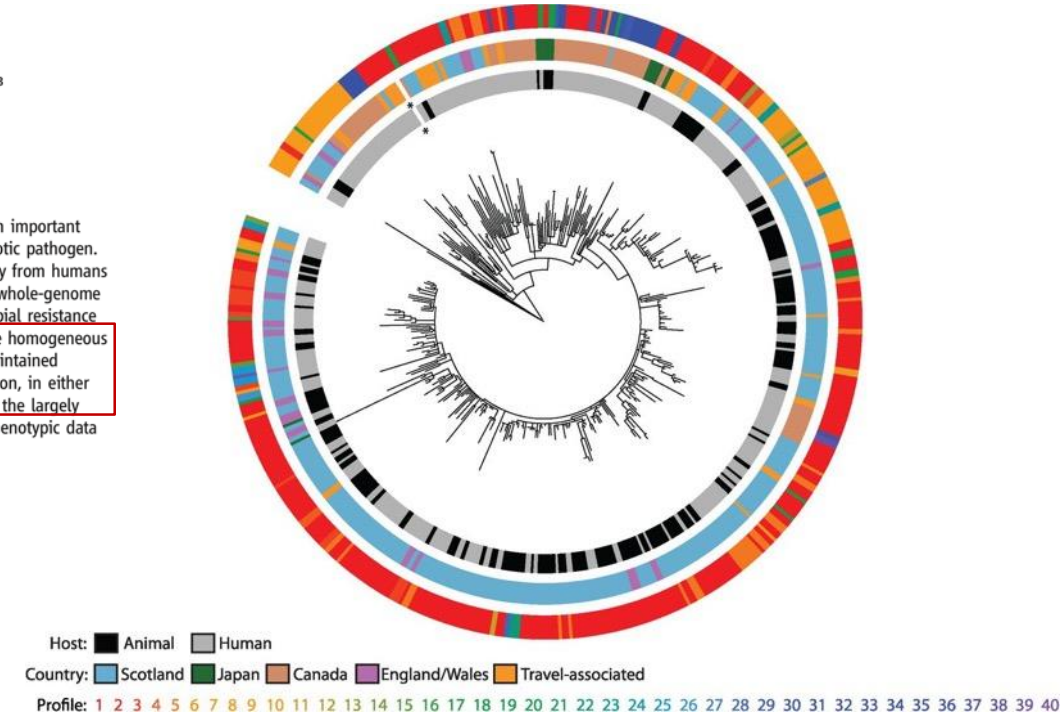


Antibiotic resistance in humans and in other animals: Non all strains are eco-equivalent

Distinguishable Epidemics of Multidrug-Resistant *Salmonella* Typhimurium DT104 in Different Hosts

A. E. Mather,[1] S. W. J. Reid,[2]‡ D. J. Maskell,[3] J. Parkhill,[1] M. C. Fookes,[1] S. R. Harris,[1] D. J. Brown,[4] J. E. Coia,[4] M. R. Mulvey,[5] M. W. Gilmour,[5]* L. Petrovska,[6] E. de Pinna,[7] M. Kuroda,[8] M. Akiba,[9] H. Izumiya,[10] T. R. Connor,[1]† M. A. Suchard,[11] P. Lemey,[12] D. J. Mellor,[13] D. T. Haydon,[13] N. R. Thomson[1]‡

The global epidemic of multidrug-resistant *Salmonella* Typhimurium DT104 provides an important example, both in terms of the agent and its resistance, of a widely disseminated zoonotic pathogen. Here, with an unprecedented national collection of isolates collected contemporaneously from humans and animals and including a sample of internationally derived isolates, we have used whole-genome sequencing to dissect the phylogenetic associations of the bacterium and its antimicrobial resistance genes through the course of an epidemic. Contrary to current tenets supporting a single homogeneous epidemic, we demonstrate that the bacterium and its resistance genes were largely maintained within animal and human populations separately and that there was limited transmission, in either direction. We also show considerable variation in the resistance profiles, in contrast to the largely stable bacterial core genome, which emphasizes the critical importance of integrated genotypic data sets in understanding the ecology of bacterial zoonoses and antimicrobial resistance.



A. E. Mather et al. Science 2013;341:1514-1517

Science
AAAS

Antibiotic resistance in humans and in other animals: Transfer bi-directionality

Staphylococcus aureus CC398: Host Adaptation and Emergence of Methicillin Resistance in Livestock

Lance B. Price,[a] Marc Stegger,[b] Henrik Hasman,[c] Maliha Aziz,[a] Jesper Larsen,[b] Paal Skytt Andersen,[b] Talima Pearson,[d] Andrew E. Waters,[a] Jeffrey T. Foster,[d] James Schupp,[a] John Gillece,[a] Elizabeth Driebe,[a] Cindy M. Liu,[a,d] Burkhard Springer,[e] Irena Zdovc,[f] Antonio Battisti,[g] Alessia Franco,[g] Jacek Żmudzki,[h] Stefan Schwarz,[i] Patrick Butaye,[j,k] Eric Jouy,[l] Constanca Pomba,[m] M. Concepción Porrero,[n] Raymond Ruimy,[o] Tara C. Smith,[p] D. Ashley Robinson,[q] J. Scott Weese,[r] Carmen Sofia Arriola,[s] Fangyou Yu,[t] Frederic Laurent,[u] Paul Keim,[a,d] Robert Skov,[b] and Frank M. Aarestrup[c]

IMPORTANCE Modern food animal production is characterized by densely concentrated animals and routine antibiotic use, which may facilitate the emergence of novel antibiotic-resistant zoonotic pathogens. Our findings strongly support the idea that livestock-associated MRSA CC398 originated as MSSA in humans. The jump of CC398 from humans to livestock was accompanied by the loss of phage-carried human virulence genes, which likely attenuated its zoonotic potential, but it was also accompanied by the acquisition of tetracycline and methicillin resistance. Our findings exemplify a bidirectional zoonotic exchange and underscore the potential public health risks of widespread antibiotic use in food animal production.

Review Article | Published: 04 July 2018

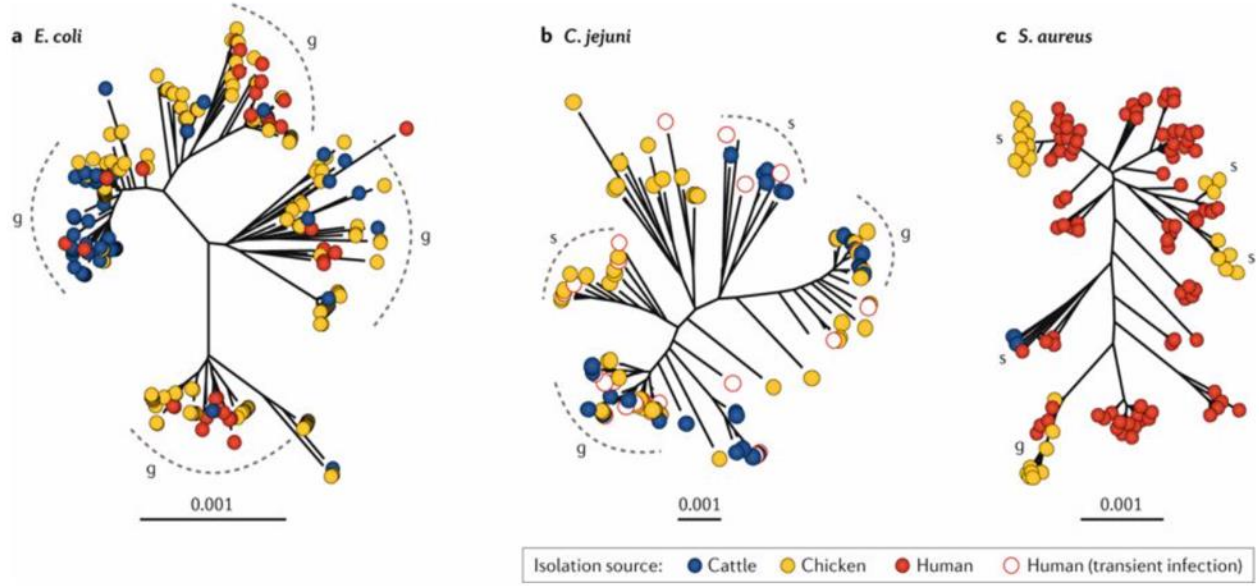
Population genomics of bacterial host adaptation

Samuel K. Sheppard, David S. Guttman & J. Ross Fitzgerald

Nature Reviews Genetics **19**, 549–565 (2018) | Download Citation

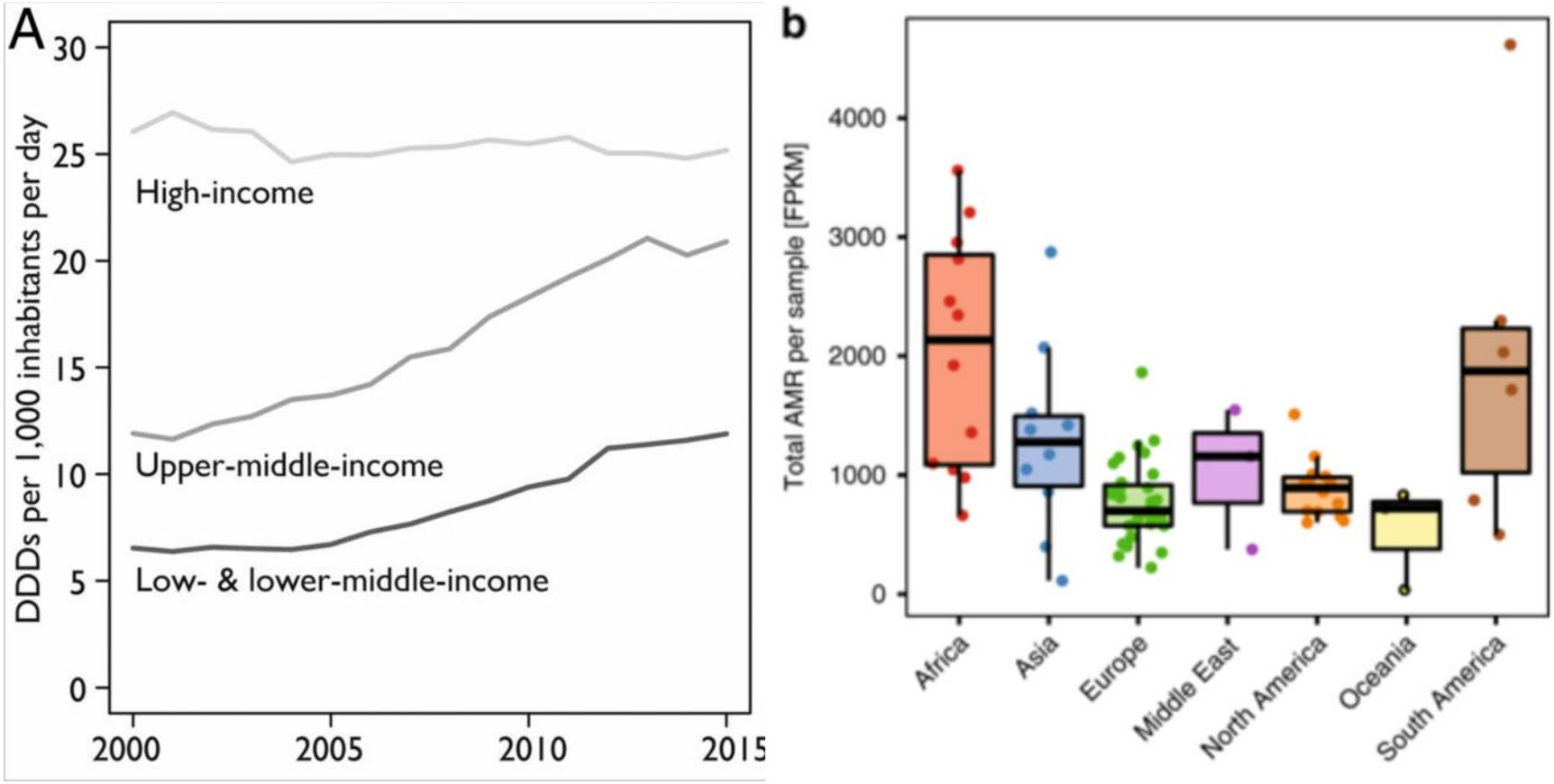
Fig. 1: Host-associated genetic structure in bacterial populations.

From: Population genomics of bacterial host adaptation



The degree to which lineage structure is related to host source varies between multi-host pathogen species. Neighbour-joining trees (constructed from 52 concatenated ribosomal protein gene sequences) are shown for three different bacterial species from three different host sources. **a** | For *Escherichia coli*, it is difficult to link host niche with genotype because isolates from all major phylogroups are represented in multiple isolate sources. **b** | For *Campylobacter jejuni*, there are host-restricted (specialist) lineages, but some lineages are found in multiple hosts and can be termed generalists. **c** | For *Staphylococcus aureus*, lineages are largely host restricted, but generalist lineages can occur. The scale bar represents a genetic distance of 0.001. s, specialist; g, generalist.

Economy and the use of antibiotics: Antibiotic selective pressure is not the main reason for inter-country differences in antibiotic resistance



PNAS | vol. 115 | no. 15 | E3463–E3470

Nat Commun. 2019; 10: 1124.

Reduction of antibiotic resistance genes at Waste Water Treatment Plants: Impact in the dissemination of antibiotic resistance

Dissemination of NDM-1 positive bacteria in the New Delhi environment and its implications for human health: an environmental point prevalence study

Timothy R Walsh, Janis Weeks, David M Livermore, Mark A Toleman

Summary

Background Not all patients infected with NDM-1-positive bacteria have a history of hospital admission in India, and extended-spectrum β-lactamases are known to be circulating in the Indian community. We therefore measured the prevalence of the NDM-1 gene in drinking water and seepage samples in New Delhi.

Methods Swabs absorbing about 100 µL of seepage water (ie, water pools in streets or rivulets) and 15 mL samples of public tap water were collected from sites within a 12 km radius of central New Delhi, with each site photographed and documented. Samples were transported to the UK and tested for the presence of the NDM-1 gene, bla_{NDM-1}, by PCR and DNA probing. As a control group, 100 µL sewage effluent samples were taken from the Cardiff Wastewater Treatment Works, Tremorfa, Wales. Bacteria from all samples were recovered and examined for bla_{NDM-1} by PCR and sequencing. We identified NDM-1-positive isolates, undertook susceptibility testing, and, where appropriate, typed the isolates. We undertook Inc typing on bla_{NDM-1}-positive plasmids. Transconjugants were created to assess plasmid transfer frequency and its relation to temperature.

Findings From Sept 26 to Oct 10, 2010, 171 seepage samples and 50 tap water samples from New Delhi and 70 sewage effluent samples from Cardiff Wastewater Treatment Works were collected. We detected bla_{NDM-1} in two of 50 drinking-water samples and 51 of 171 seepage samples from New Delhi; the gene was not found in any sample from Cardiff. Bacteria with bla_{NDM-1} were grown from 12 of 171 seepage samples and two of 50 water samples, and included 11 species in which NDM-1 has not previously been reported, including *Shigella boydii* and *Vibrio cholerae*. Carriage by enterobacteria, aeromonads, and *V cholera* was stable, generally transmissible, and associated with resistance patterns typical for NDM-1; carriage by non-fermenters was unstable in many cases and not associated with typical resistance. 20 strains of bacteria were found in the samples, 12 of which carried bla_{NDM-1} on plasmids, which ranged in size from 140 to 400 kb. Isolates of *Aeromonas caviae* and *V cholerae* carried bla_{NDM-1} on chromosomes. Conjugative transfer was more common at 30°C than at 25°C or 37°C.

Interpretation The presence of NDM-1 β-lactamase-producing bacteria in environmental samples in New Delhi has important implications for people living in the city who are reliant on public water and sanitation facilities. International surveillance of resistance, incorporating environmental sampling as well as examination of clinical isolates, needs to be established as a priority.

Lancet Infect Dis 2011; 11: 355–62

Published Online
April 7, 2011
DOI:10.1016/S1473-3099(11)70059-7

See Comment page 334

Department of Infection, Immunity and Biochemistry, School of Medicine, Cardiff University, Heath Park, Cardiff, UK (Prof T R Walsh PhD, J Weeks BSc, M A Toleman PhD); **University of Queensland Centre for Clinical Research, University of Queensland, Brisbane, Australia** (Prof T R Walsh); **and Health Protection Agency Microbiology Services, Colindale, London, UK** (D M Livermore PhD)

Correspondence to:
Prof Timothy R Walsh, Centre for Clinical Research (UQCCR) I Level 8, Building 71/918 Royal Brisbane Hospital, Herston QLD 4006, Australia
t.r.walsh@uq.edu.au

International transmission of antibiotic resistance

Reference(s)	Resistant organism	Antibiotic resistance	Route of importation	Likely mode of importation
[57]	*Escherichia coli*	β-Lactams, mediated by plasmid-borne SHV-5 β-lactamase gene	Indian subcontinent to United Kingdom	Human travel
[58, 59]	*Salmonella typhi*	Multiple antibiotics	Developing countries (mainly South Asia) to United States and Canada	Human travel
[31]	MRSA	Multiple antibiotics	Great Britain to The Netherlands	Human travel (health workers)
[60]	MRSA	Multiple antibiotics	Brazil to Portugal	Unknown
[45]	*Shigella sonnei*	Ampicillin, TMP-SMX, streptomycin	Mexico to United States	Imported food (parsley)
[4]	*Campylobacter jejuni*	Quinolones	Europe and Asia to United States	Human travel
[61]	*Streptococcus pneumoniae* 6B	Multiple antibiotics	Spain to Iceland	Unknown

NOTE. MRSA, methicillin-resistant *Staphylococcus aureus;* SHV-5, sulphydryl variable-5; TMP-SMX, trimethoprim-sulfamethoxazole.

Clinical Infectious Diseases, Volume 33, Issue 3, 1 August 2001, Pages 364–369, https://doi.org/10.1086/321877

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Apr. 1990, p. 515–518
0066-4804/90/040515-04$02.00/0

Vol. 34, No. 4

Emergence of Resistant Fecal *Escherichia coli* in Travelers Not Taking Prophylactic Antimicrobial Agents

BARBARA E. MURRAY,* JOHN J. MATHEWSON, HERBERT L. DuPONT, CHARLES D. ERICSSON, AND RANDALL R. REVES

International transmission of antibiotic resistance: The path from high-incidence to low incidence countries

Tuberculosis in migrants moving from high-incidence to low-incidence countries: a population-based cohort study of 519 955 migrants screened before entry to England, Wales, and Northern Ireland

Robert W Aldridge, Dominik Zenner, Peter J White, Elizabeth J Williamson, Morris C Muzyamba, Poonam Dhavan, Davide Mosca, H Lucy Thomas, Maeve K Lalor, Ibrahim Abubakar, Andrew C Hayward**

Interpretation Migrants from countries with a high incidence of tuberculosis screened before being granted entry to low-incidence countries pose a negligible risk of onward transmission but are at increased risk of tuberculosis, which could potentially be prevented through identification and treatment of latent infection in close collaboration with a pre-entry screening programme.

International transmission of antibiotic resistance: The path from high-incidence to low incidence countries

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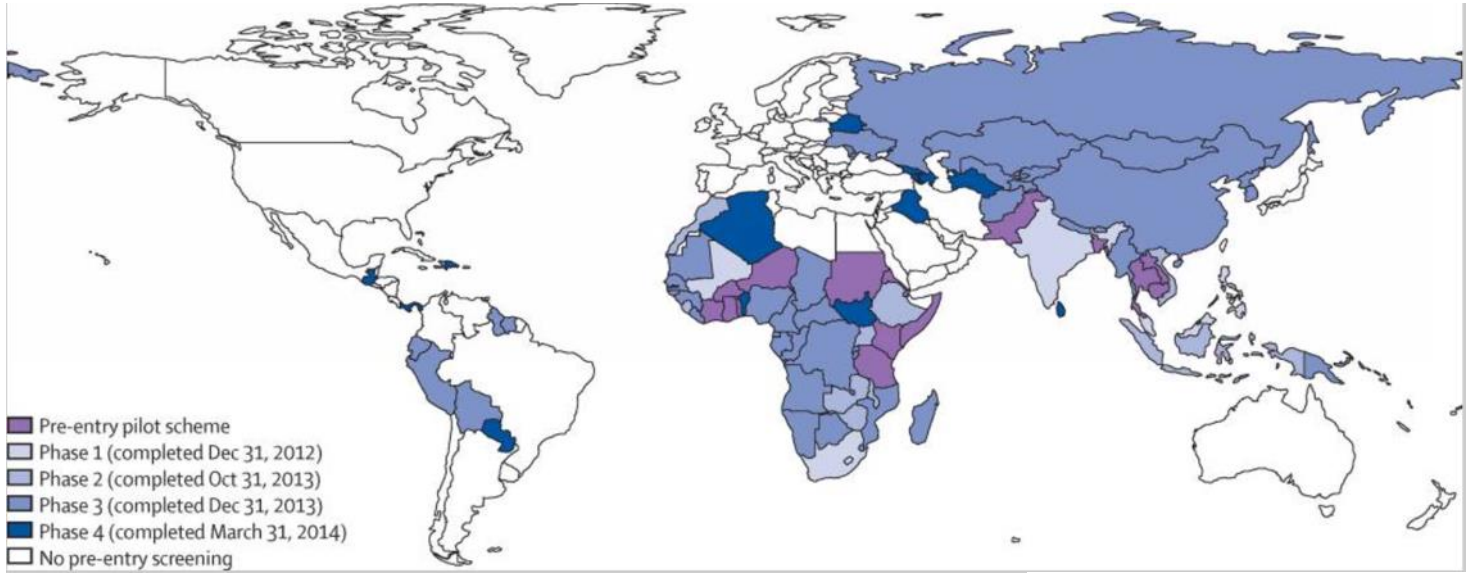
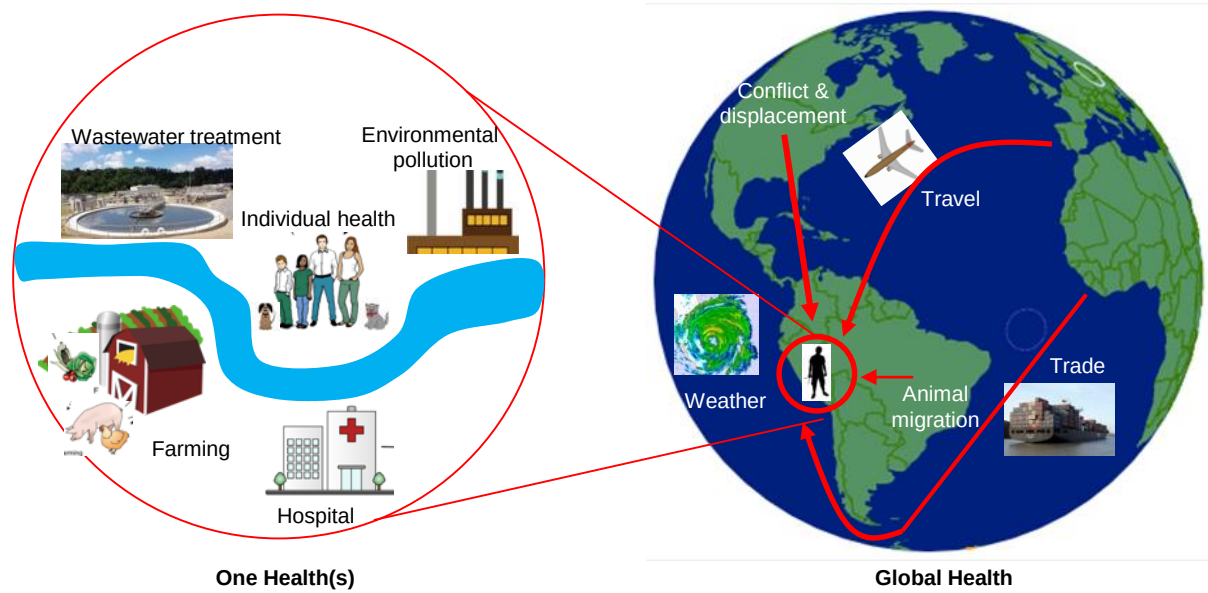


Different levels for fighting antibiotic resistance



Individual Health: Direct therapeutic actions

One-Health: Direct actions and regulations that require the approval of local (national) authorities.

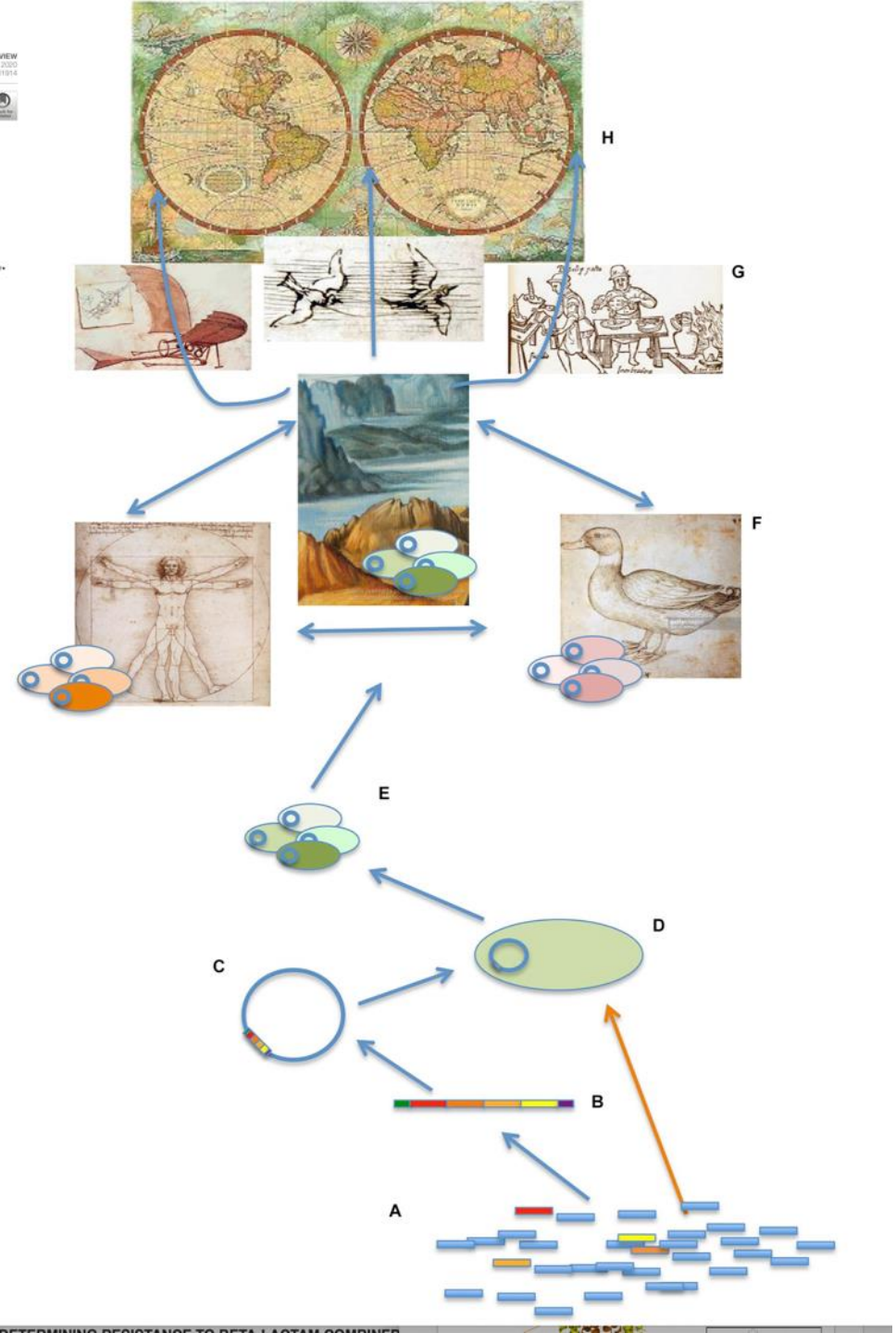
Global Health: Mainly recommendations: Soft power (UN, WHO) important. Hard power is over for Health issues that have ethical, political and economical consequences.

frontiers in Microbiology

REVIEW
published: 28 August 2020
doi: 10.3389/fmicb.2020.01914

Antibiotic Resistance: Moving From Individual Health Norms to Social Norms in One Health and Global Health

*Sara Hernando-Amado[1], Teresa M. Coque[2], Fernando Baquero[2] and José L. Martínez[1]**



frontiers in Microbiology

REVIEW
published: 28 August 2020
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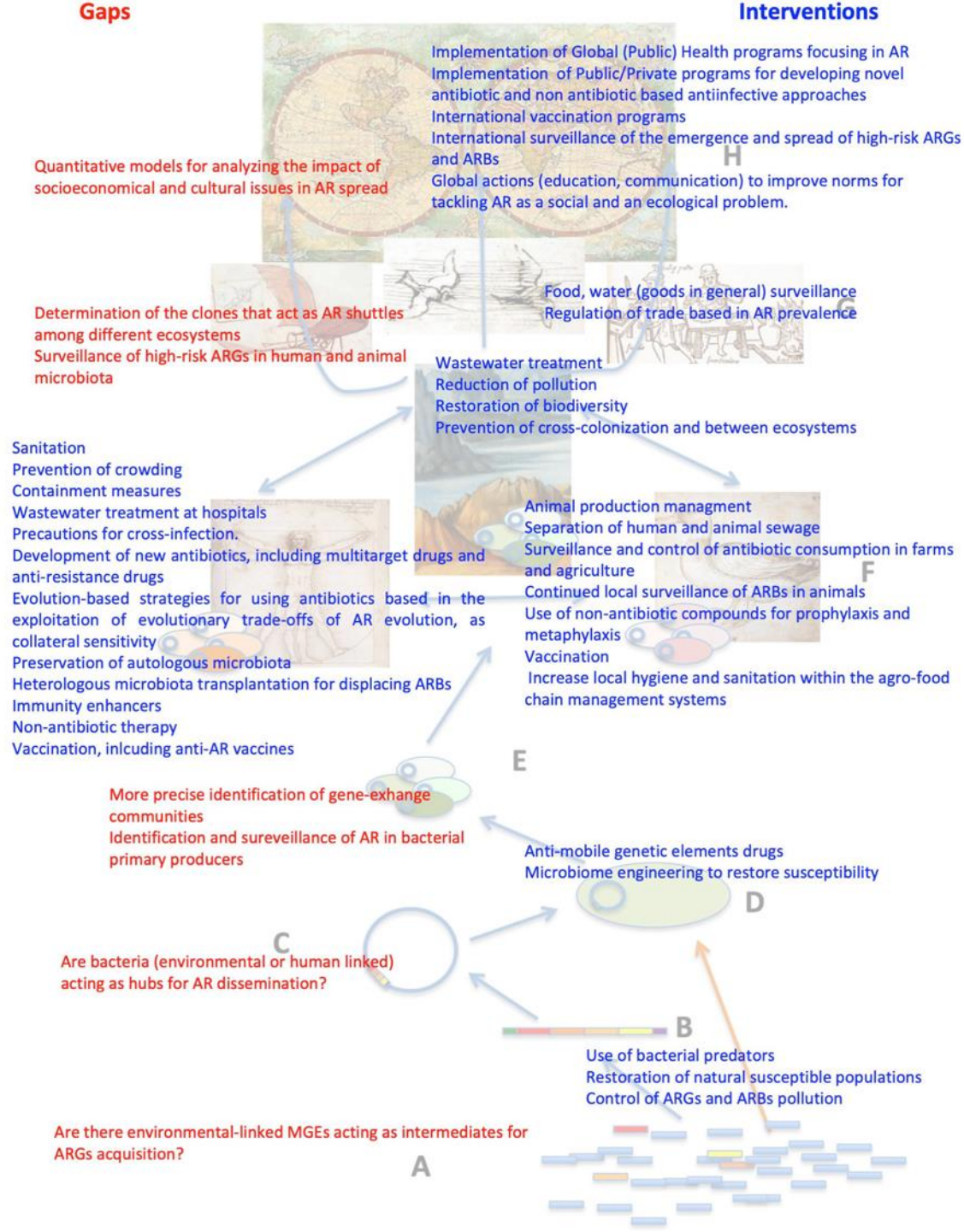
Antibiotic Resistance: Moving From Individual Health Norms to Social Norms in One Health and Global Health

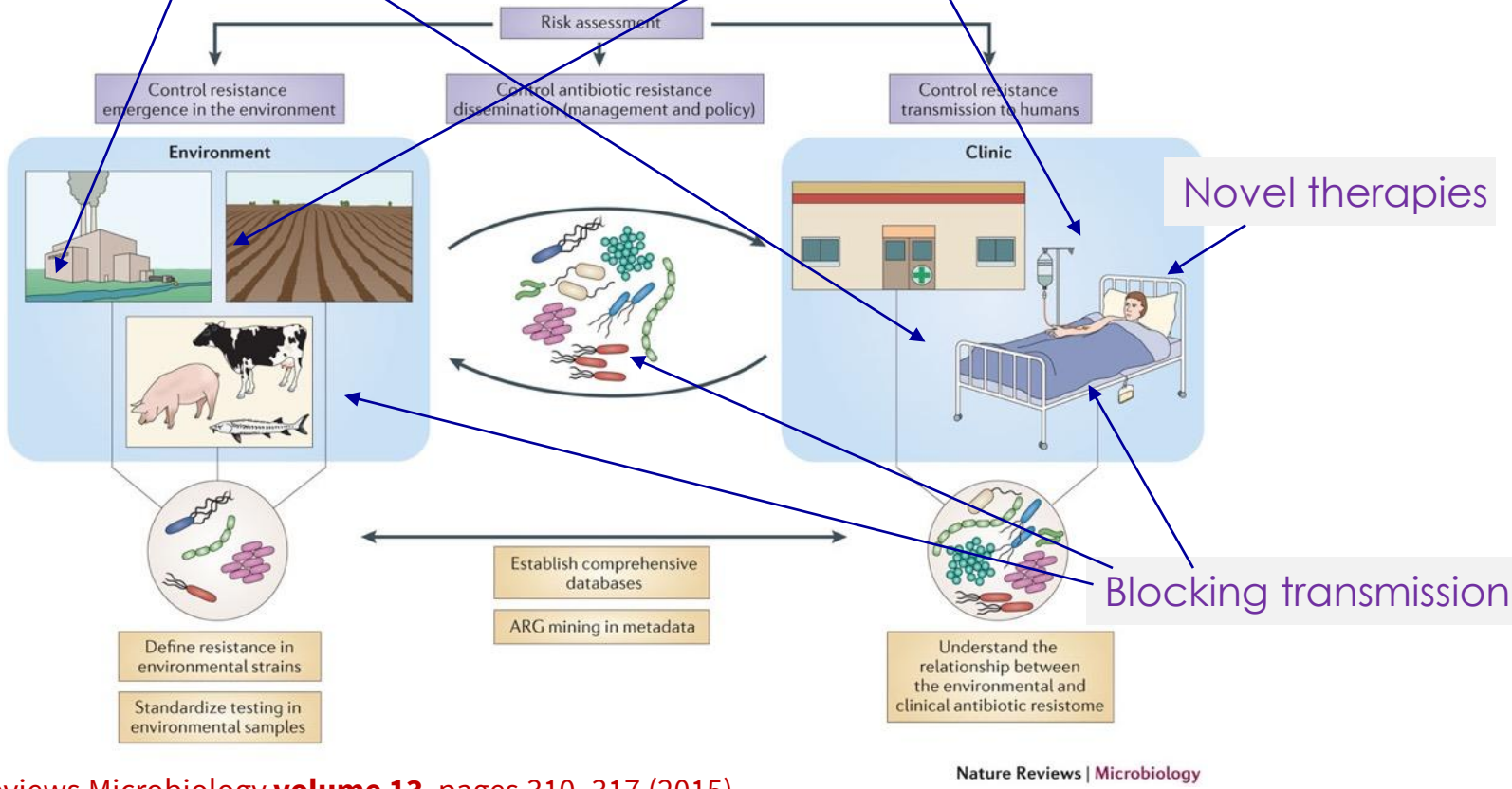
*Sara Hernando-Amado[1], Teresa M. Coque[2], Fernando Baquero[2] and José L. Martinez[1]**



Breaking transmission of antibiotic resistance: The resistance entities

Restoring susceptible populations

Reduction of selection pressure



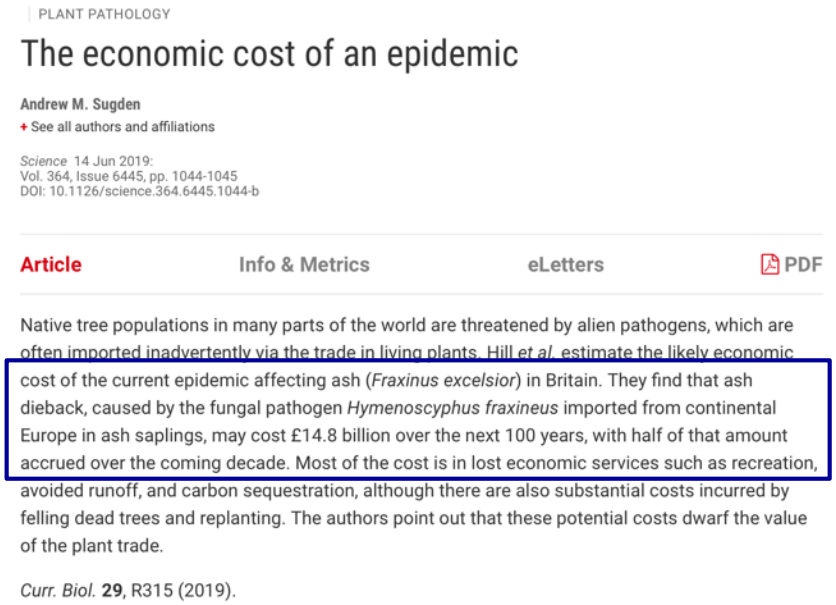
Novel therapies

Blocking transmission

Nature Reviews Microbiology **volume 13**, pages 310–317 (2015)

The need of Universal Health Services: What Public Health means?

The current focus in the political, economical and ethical aspects.
We need moving to technical issues



PLANT PATHOLOGY

The economic cost of an epidemic

Andrew M. Sugden
+ See all authors and affiliations

Science 14 Jun 2019:
Vol. 364, Issue 6445, pp. 1044-1045
DOI: 10.1126/science.364.6445.1044-b

Native tree populations in many parts of the world are threatened by alien pathogens, which are often imported inadvertently via the trade in living plants. Hill *et al.* estimate the likely economic cost of the current epidemic affecting ash (*Fraxinus excelsior*) in Britain. They find that ash dieback, caused by the fungal pathogen *Hymenoscyphus fraxineus* imported from continental Europe in ash saplings, may cost £14.8 billion over the next 100 years, with half of that amount accrued over the coming decade. Most of the cost is in lost economic services such as recreation, avoided runoff, and carbon sequestration, although there are also substantial costs incurred by felling dead trees and replanting. The authors point out that these potential costs dwarf the value of the plant trade.

Curr. Biol. **29**, R315 (2019).

Cancer is an individual disease. If someone is not treated, this does not affect the health of others.

Infection is a social disease: anything that happens in a given host impacts the health of all of us.

No man is an *Iland*, intire of it selfe; every man is a peece of the *Continent*, a part of the *maine*; if a *Clod* bee washed away by the *Sea*, *Europe* is the lesse, as well as if a *Promontorie* were, as well as if a *Mannor* of thy *friends* or of *thine owne* were; any mans *death* diminishes *me*, because I am involved in *Mankinde*; And therefore never send to know for whom the *bell* tolls; It tolls for *thee*.

JOHN DONNE

DEVOTIONS

VPON

Emergent Occasions, and seuerall steps in my Sicknes:

Digested into

1. MEDITATIONS *vpon our Humane Condition.*
2. EXPOSTVLATIONS, *and Debatements with God.*
3. PRAYERS, *vpon the seuerall Occasions, to him.*

By IOHN DONNE, Deane of *S. Pauls*, London.

LONDON,
Printed by *A. M.* for THOMAS IONES. 1624.

Thanks