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Antibiothérapie, facteur de risque de colonisation durable par les BMR ou BHRe: Une perspective écologique

Pr. Antoine Andremont

Faculté de Médecine Université Paris-Diderot

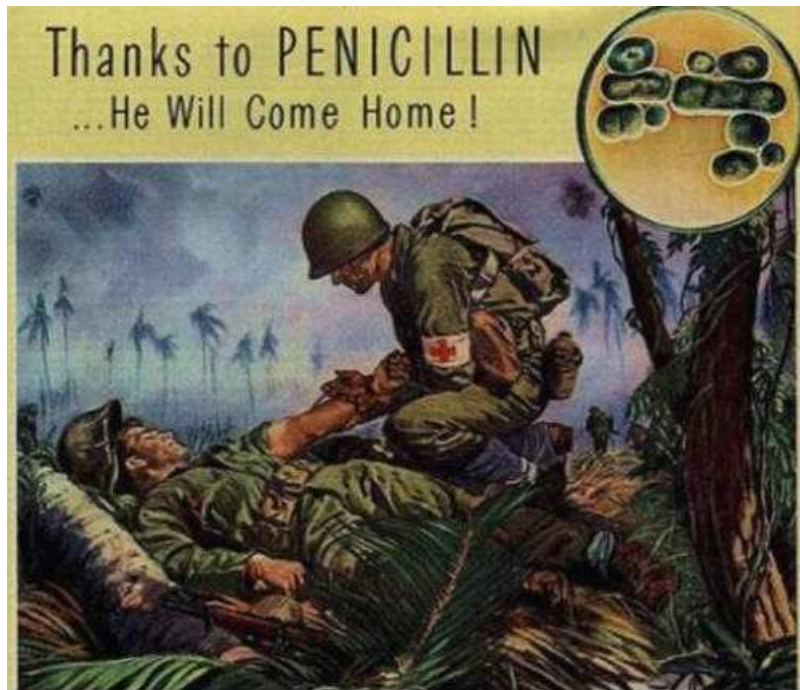
antoine.andremont@aphp.fr

DOI : CS Davolterra (LIR)

Antibiotics are « miracle, *but...* » drugs !



Prof. Alexander Fleming :
the Nobel Price winner
father of the miracle drug



In a 1945 interview with
The New York Times, he
warned that **misuse of
penicillin could lead to
the propagation of
mutant forms of bacteria
that would resist the new
miracle drug.**

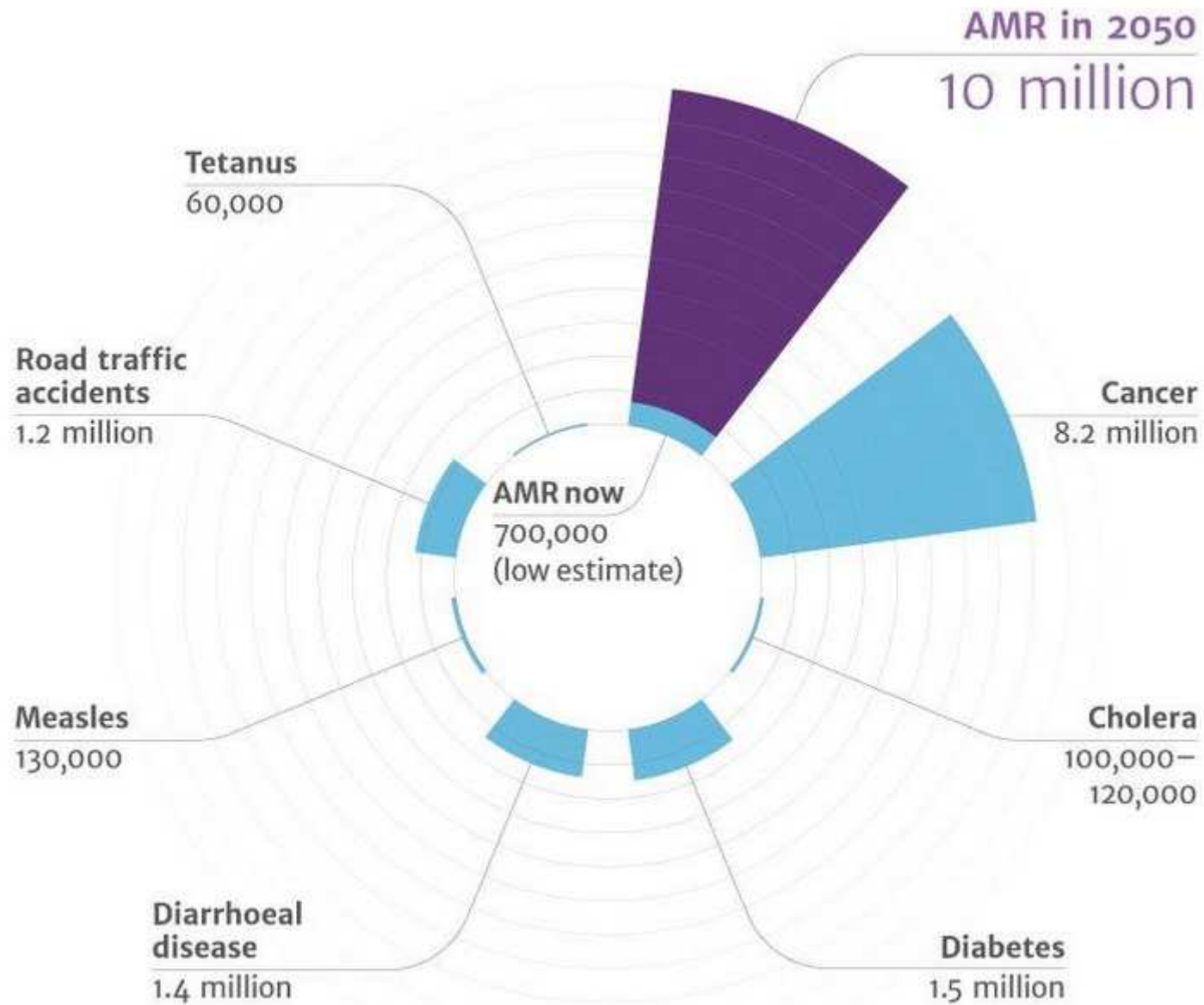
March 11, 2013, G8 Submit UK



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Chief Medical Officer Dame Sally Davies: Resistance to antibiotics risks health 'catastrophe' to rank with terrorism and climate change



Drug resistance

Global action plan on antimicrobial resistance

At the Sixty-eight World Health Assembly in May 2015, the World Health Assembly endorsed a global action plan to tackle antimicrobial resistance - including antibiotic resistance, the most urgent drug resistance trend.

Antimicrobial resistance is occurring everywhere in the world, compromising our ability to treat infectious diseases, as well as undermining many other advances in health and medicine. The goal of the draft global action plan is to ensure, for as long as possible, continuity of successful treatment and prevention of infectious diseases with effective and safe medicines that are quality-assured, used in a responsible way, and accessible to all who need them.

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Global action plan on antimicrobial resistance

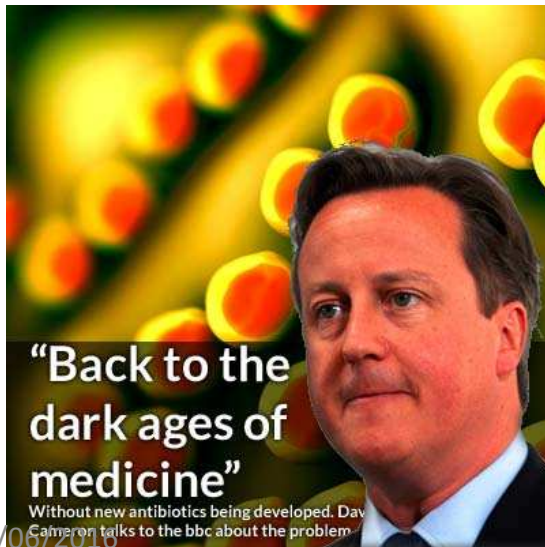
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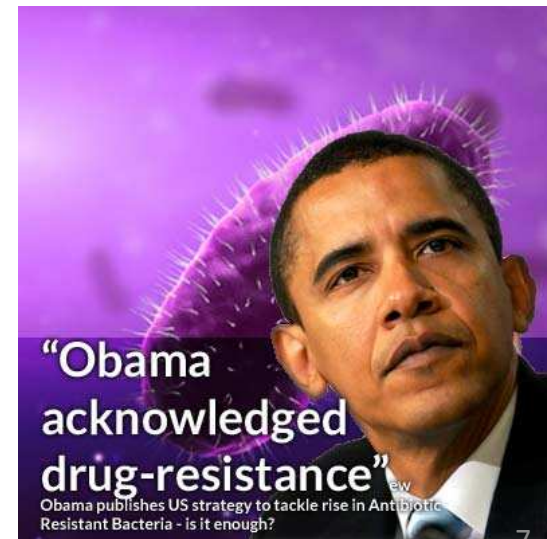
Transatlantic Taskforce on Antimicrobial Resistance (TATFAR)

Antimicrobial resistance (AR) is a public health problem of increasing magnitude and importance recognized by the European Union (EU) the United States (U.S.). Antimicrobial resistance caused:



Without new antibiotics being developed. Dav Cameron talks to the bbc about the problem
22/06/2016

Andremont ARLIN, Juin 2016



Obama publishes US strategy to tackle rise in Antibiotic Resistant Bacteria - is it enough?



Propositions du groupe de travail spécial pour la préservation des antibiotiques



Reporteurs : Dr Jean CARLET et Pierre LE COZ

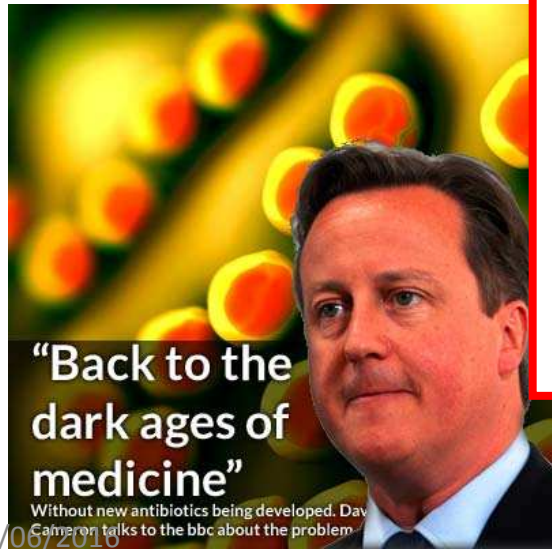


Transatlantic Task Force (TATFAR) Antimicrobial resistance (AR) is a public health problem recognized by the European Union

25,000 deaths EUR 1.5 billion Estimated minimum per year in the U.S.

(TATFAR) Antimicrobial resistance (AR) is a public health problem recognized by the World Health Organization (WHO)

25,000 deaths EUR 1.5 billion Estimated minimum per year in the U.S.



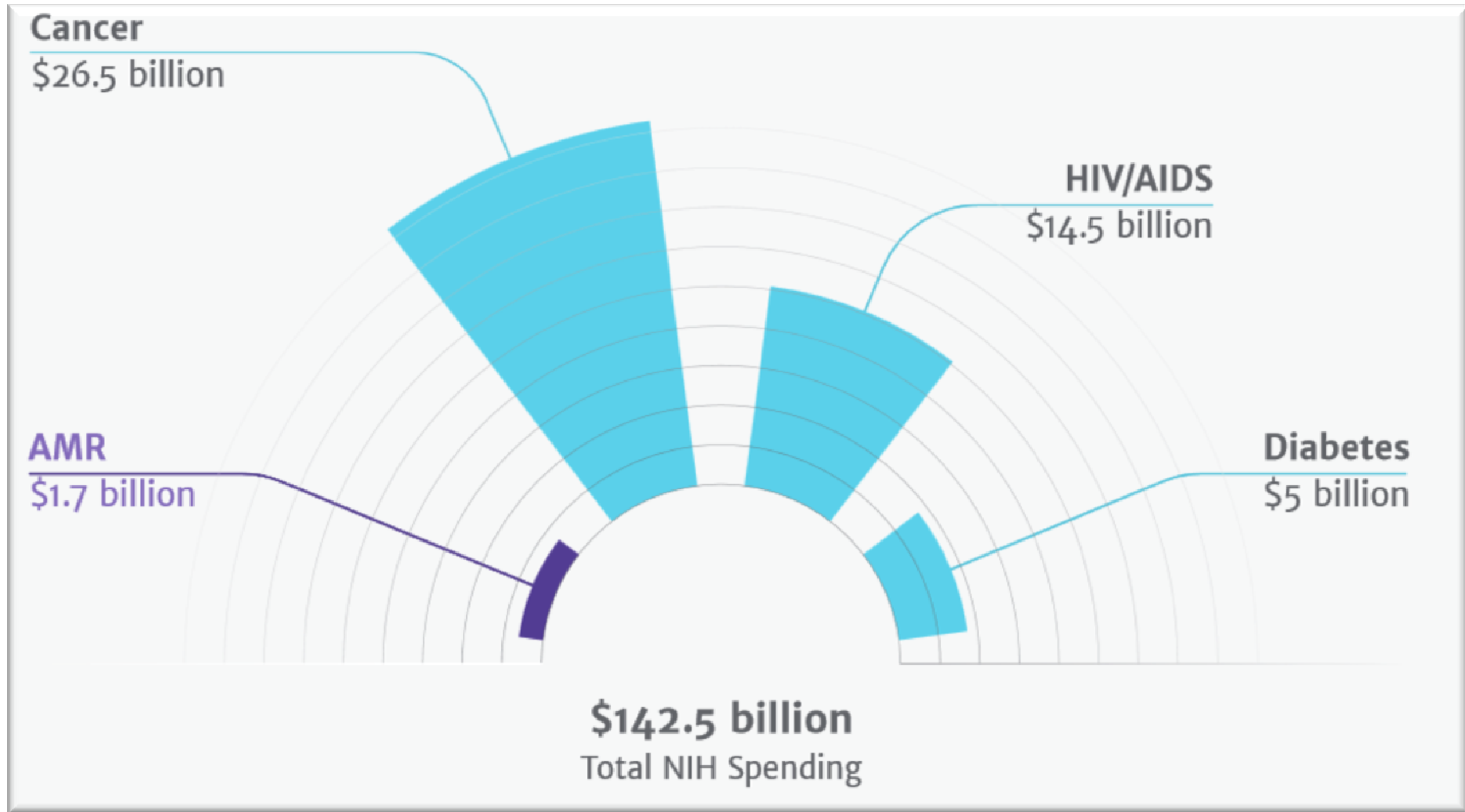
22/06/2016 Without new antibiotics being developed. David Cameron talks to the bbc about the problem

Andremont ARLIN, Juin 2016



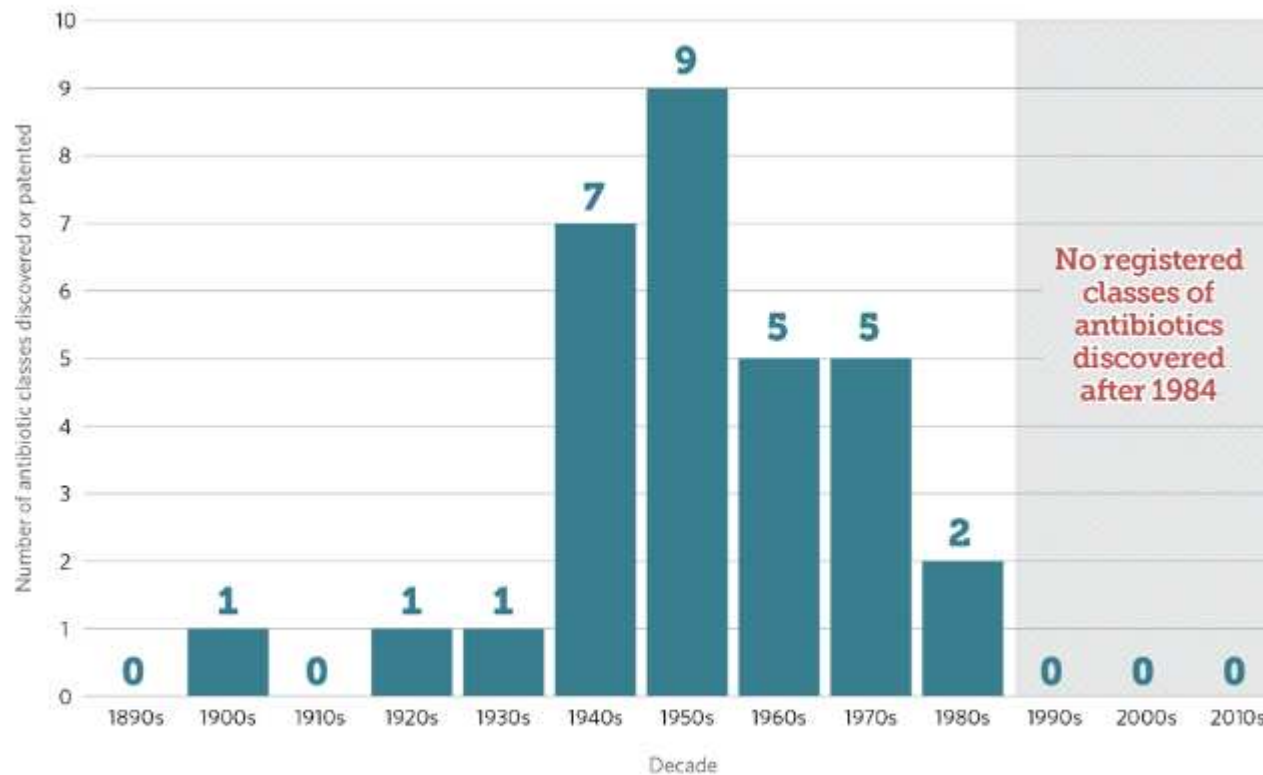
Obama publishes US strategy to tackle rise in Antibiotic Resistant Bacteria - is it enough?

Little money is put in new antibiotics....



Research on new antibiotics stopped in the late 80' while usage continued to increase

Figure 1
More than 30-Year Void in Discovery of New Types of Antibiotics



Source: Adapted from Lynn L. Silver, "Challenges of Antibacterial Discovery," *Clinical Microbiology Review* (2011)

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The crisis is mostly
invisible

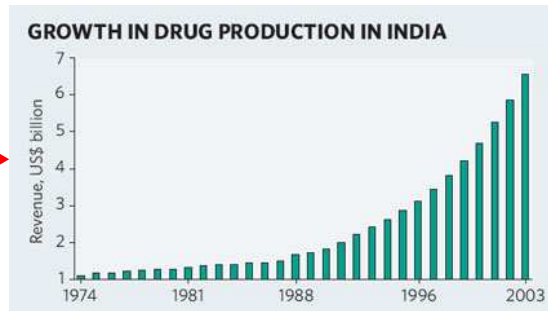
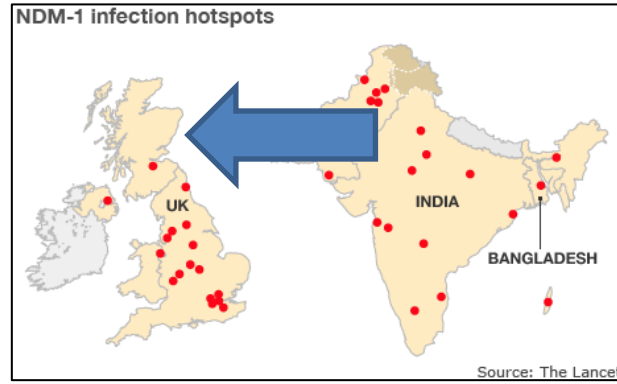
Usually we still do have at
least one antibiotic active
for each patient

But no new
antiotics +
resistance on
the rise

Experts say we can fall anytime!

...An historical interplay between « North » and « south »

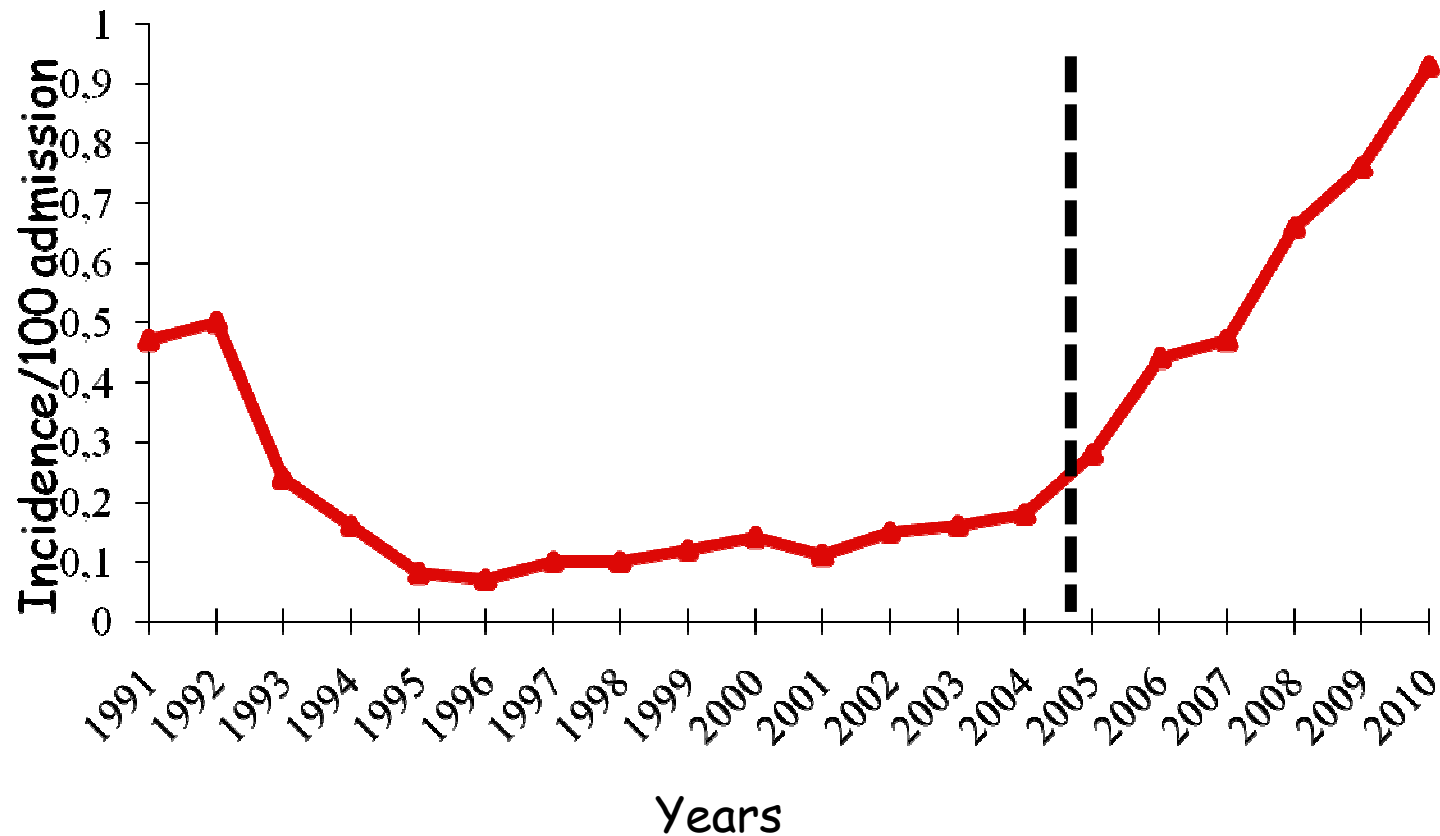
- Antibiotics discovered in Northern industrialised countries
- A new fear from multiresistant bacteria from « South » countries.



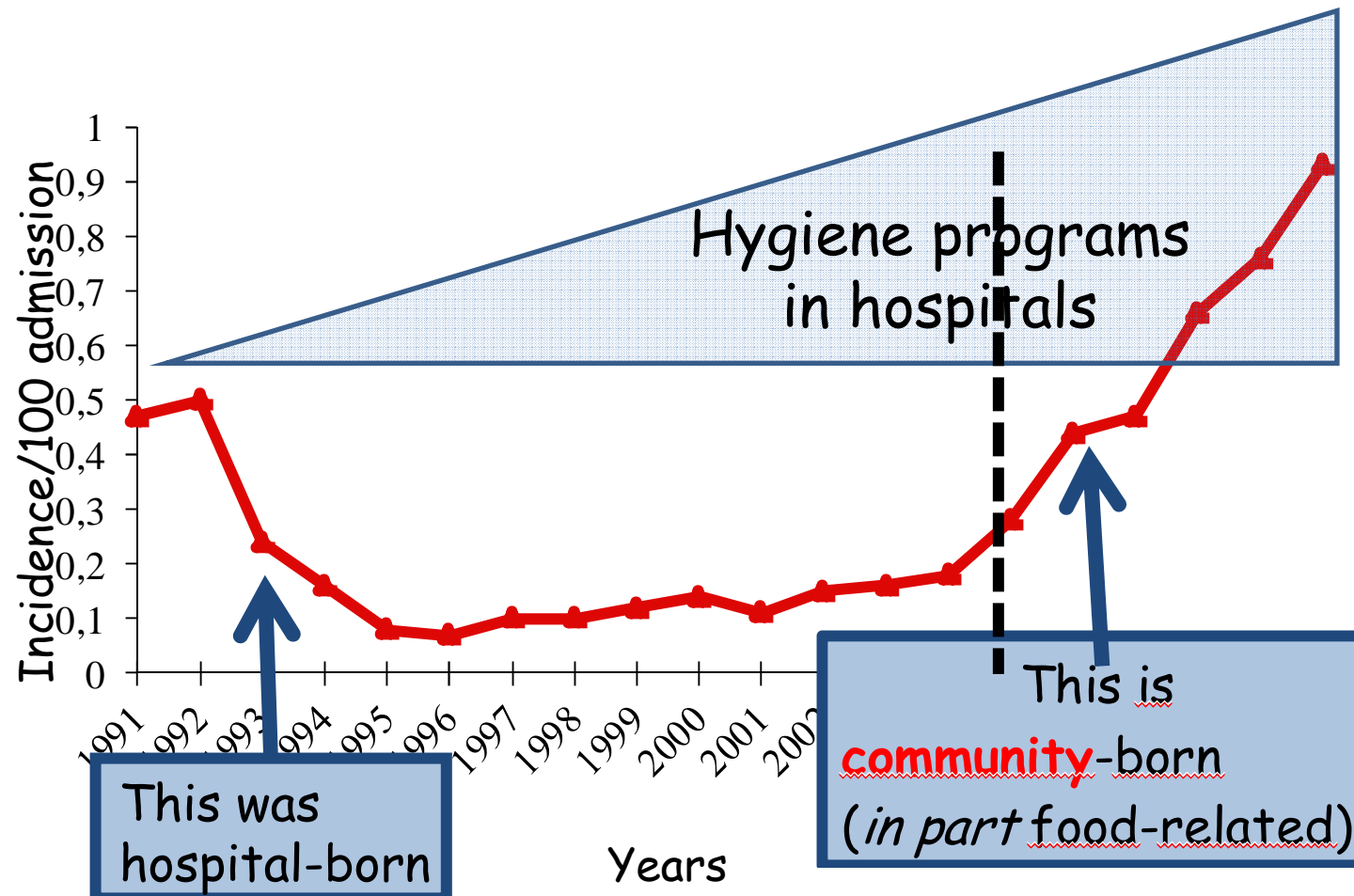
The example of *E. coli*

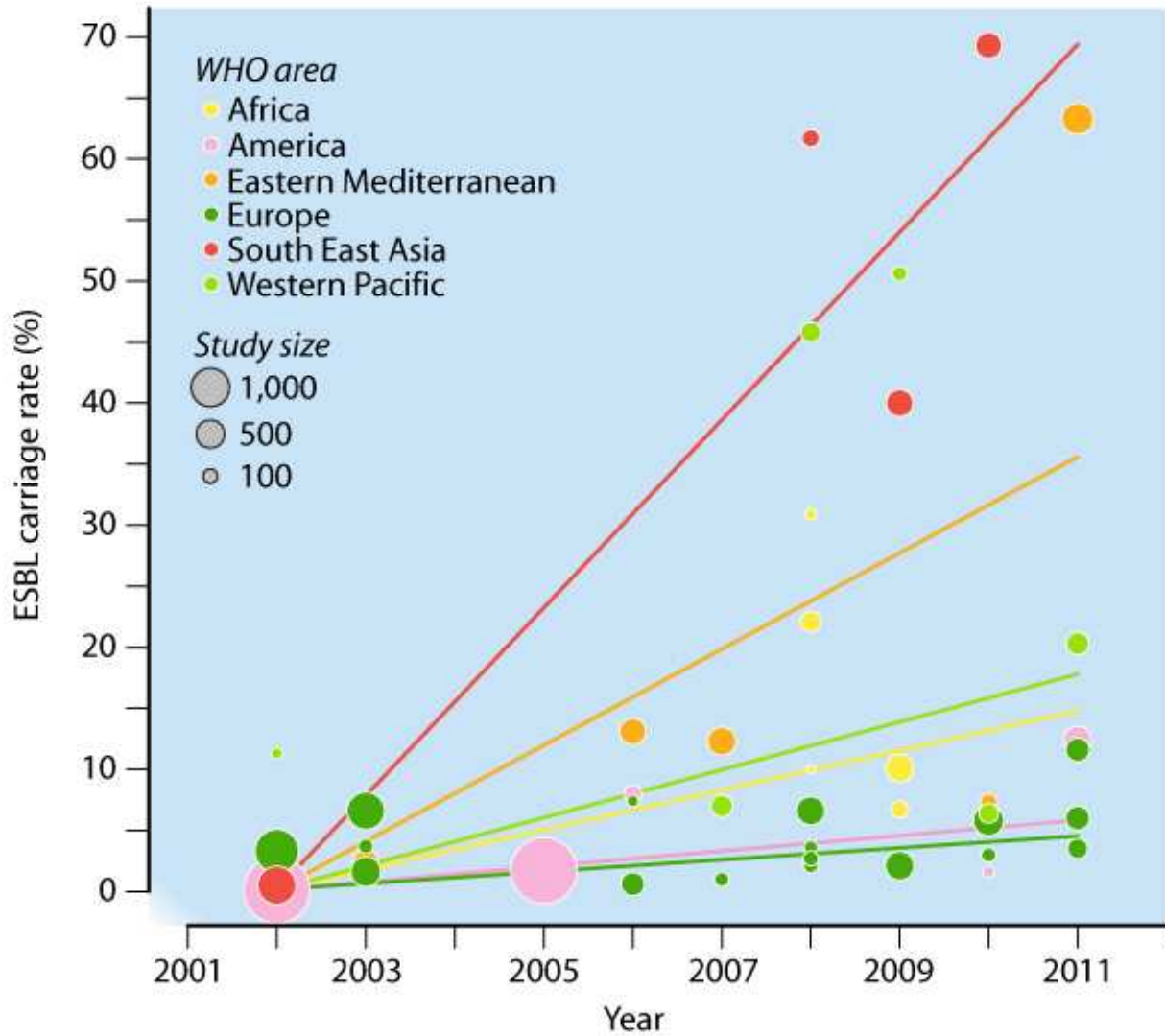
- Normal inhabitants of our intestinal tract
- But also the cause of Urinary tract infections and bacteremia
- Because antibiotics are so effective we have forgotten how serious things can be
- Many *E. coli* have between 2000 and 2015 become resistant to most antibiotics :
 - Third generation cephalosporins ESBL
 - Carbapenems CPE
 - Colistin « Toto-resistance »

ESBL burden of diseases Paris (France) Bichat university hospital



BLSEburden of diseases Paris (France) Bichat university hospital



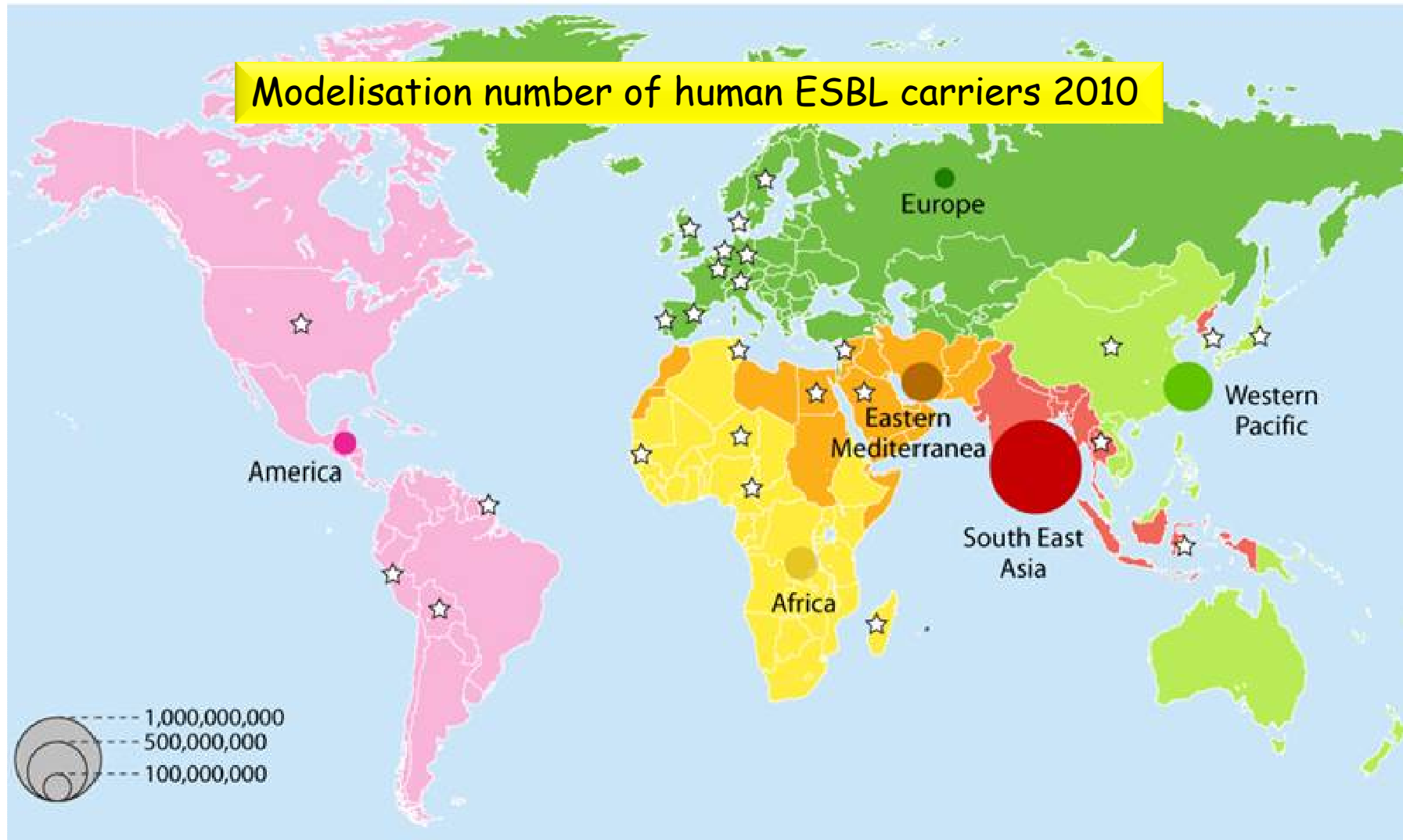


ScEYence Studios
 ASM Journals
 CMR00023-13
 Dr. Woerther
 Figure 01
 2016

Evolution of ESBL carriage rates in the community worldwide

Andremont APJIN, Juin 2016

Modelisation number of human ESBL carriers 2010



icEYence Studios

ISM Journals

MR00023-13

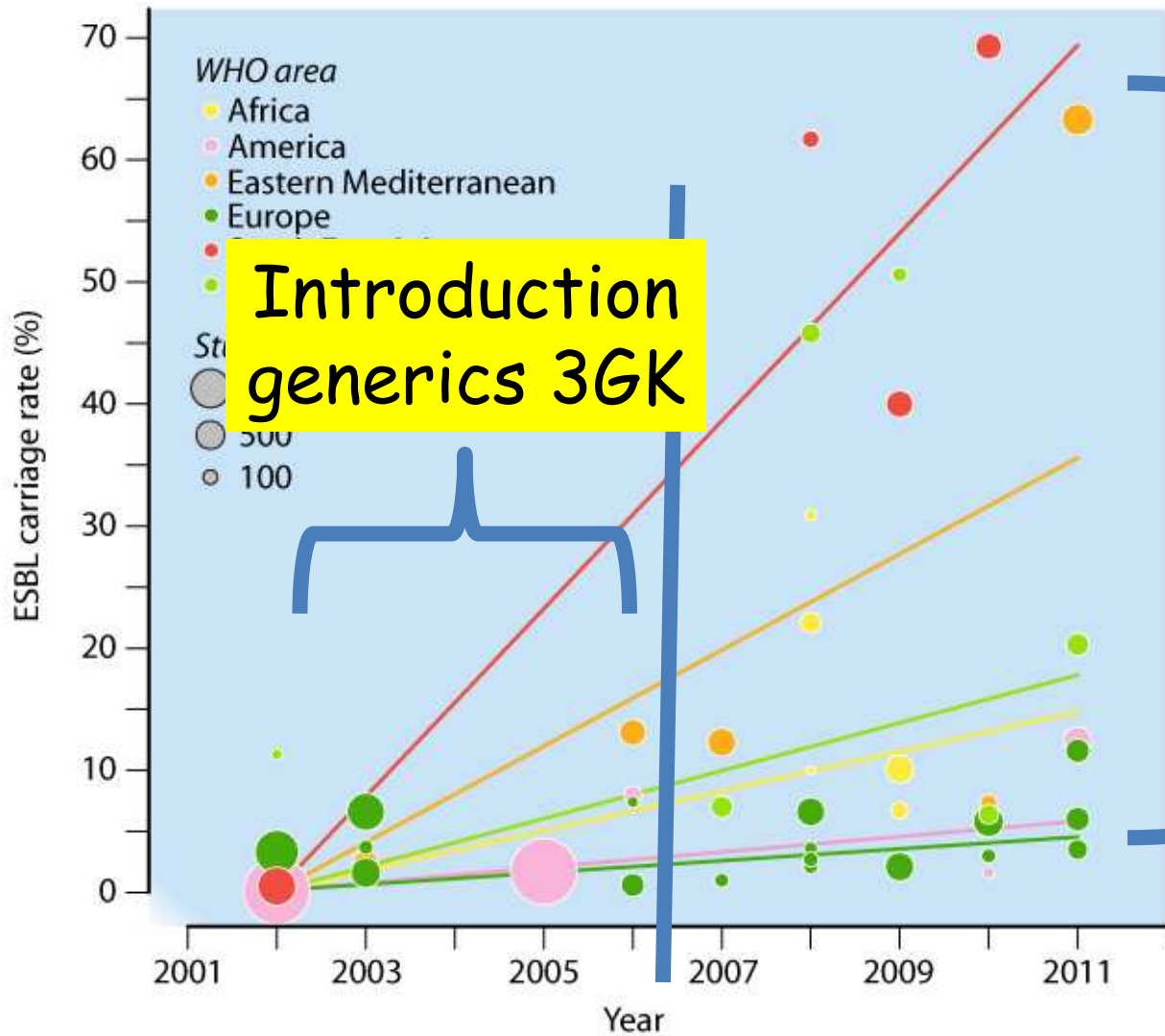
Dr. Woerther

Figure 03

22/06/2016

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18

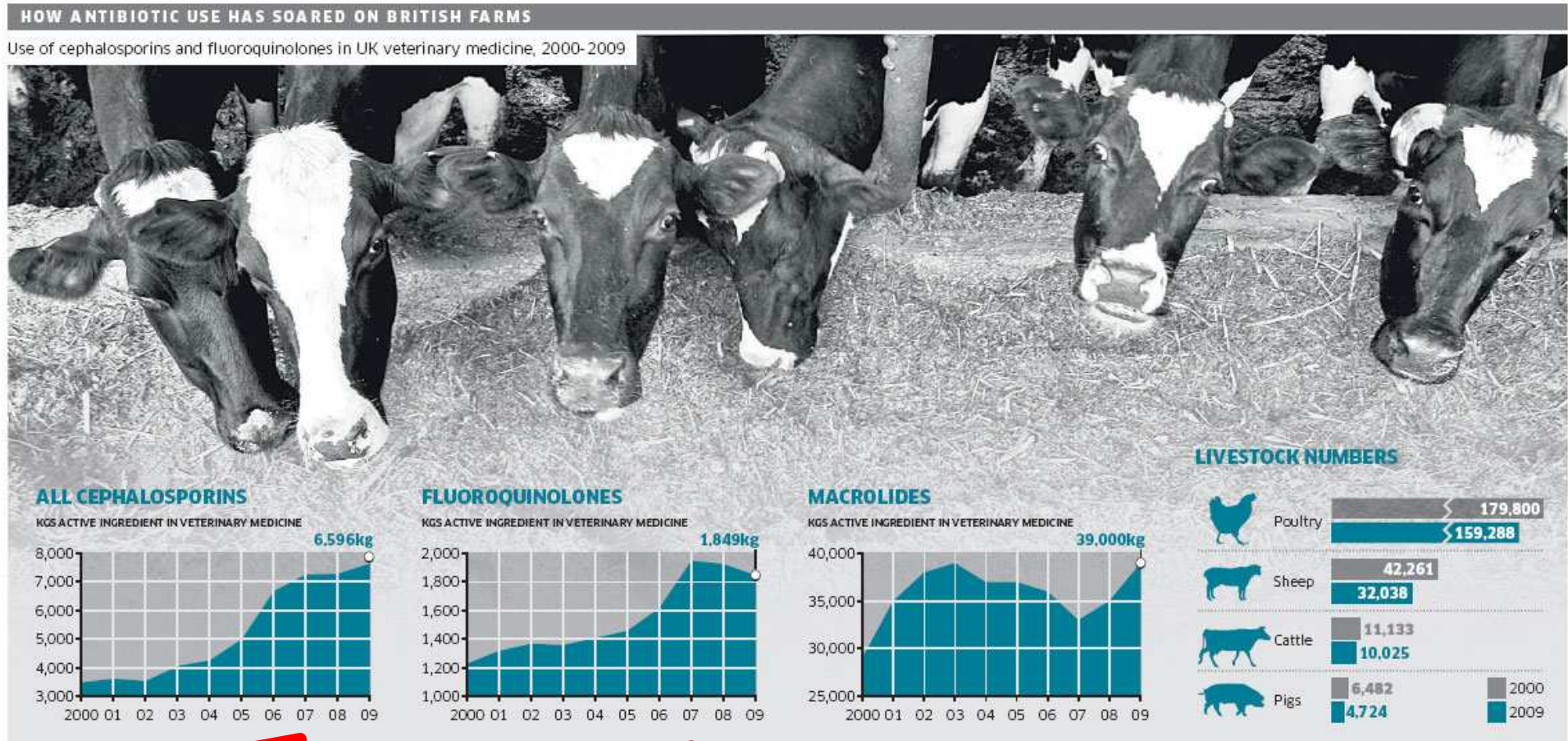


Introduction generics 3GK

Gap between EU and the « South »

Evolution of ESBL carriage rates in the community

La dynamique de la consommation animale : UK



Because E-ESBL are only susceptible to carbapenems....

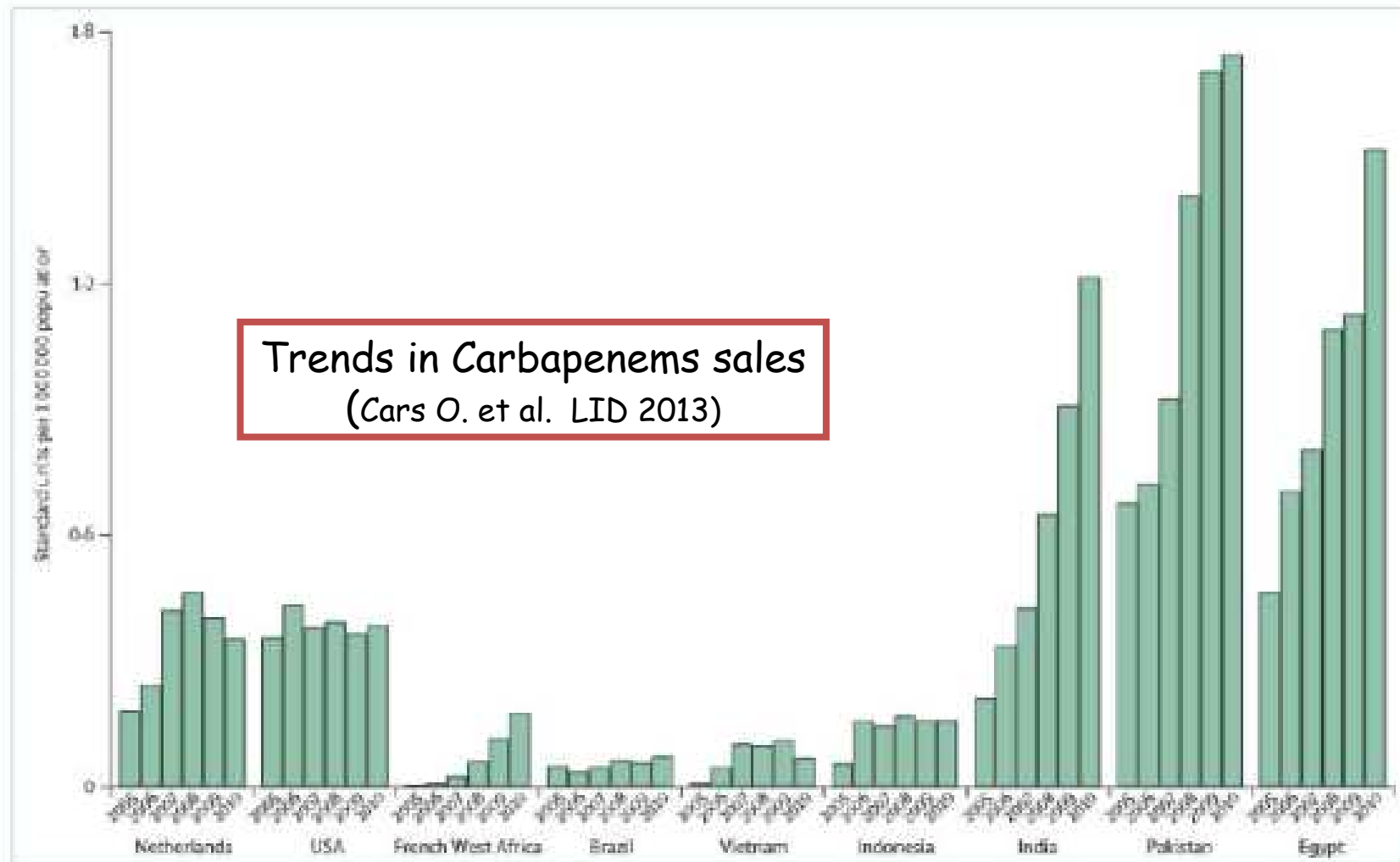
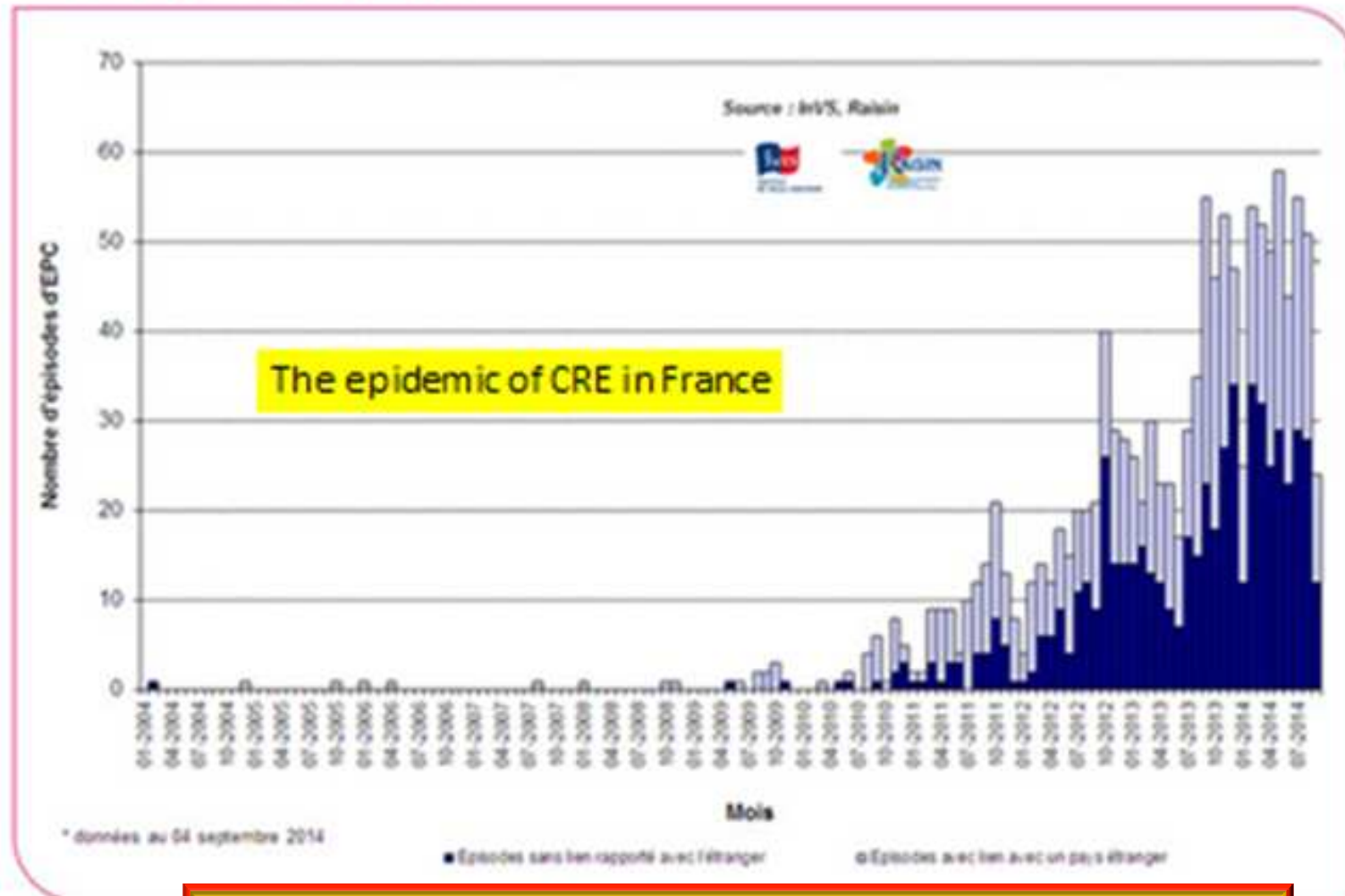


Figure 1 - Nombre d'épisodes impliquant des entérobactéries productrices de carbapénémases en France signalés à l'InVS entre janvier 2004 et le 04 septembre 2014, selon la mise en évidence ou non d'un lien avec un pays étranger (N=1210).



18/09/2

Last line treatment is now colistin

23

Emergence of plasmid-mediated colistin resistance mechanism MCR-1 in animals and human beings in China: a microbiological and molecular biological study



Yi-Yun Liu*, Yang Wang*, Timothy R Walsh, Ling-Xian Yi, Rong Zhang, James Spencer, Yohei Doi, Guobao Tian, Baolei Dong, Xianhui Huang, Lin-Feng Yu, Danxia Gu, Hongwei Ren, Xiaojie Chen, Luchao Lv, Dandan He, Hongwei Zhou, Zisen Liang, Jian-Hua Liu, Jianzhong Shen

Summary

Background Until now, polymyxin resistance has involved chromosomal mutations but has never been reported via horizontal gene transfer. During a routine surveillance project on antimicrobial resistance in commensal *Escherichia coli* from food animals in China, a major increase of colistin resistance was observed. When an *E coli* strain, SHP45,

Lancet Infect Dis 2015
Published Online
November 18, 2015

Colistin resistance: a major breach in our last line of defence



In hospital practice, clinicians have been buoyed by the recent development of new antibiotics active against multidrug resistant Gram-negative bacilli. However, recently approved antibiotics like ceftazidime-avibactam or ceftolozane-tazobactam do not provide activity against all Gram-negative bacilli, with notable gaps in their coverage, including the notorious New Delhi metallo- β -lactamase 1-producing organisms and many strains of carbapenem resistant *Acinetobacter baumannii*. For this reason, the polymyxins (colistin and polymyxin B) remain the last line of defence against

Liu and colleagues¹ present data from China showing that *E coli* from pigs at slaughter and from retail chicken and pork have high rates of plasmid-mediated colistin resistance. The same mechanism was found in *E coli* and *K pneumoniae* isolates from Chinese patients in hospital. These findings suggest that the links between agricultural use of colistin, colistin resistance in slaughtered animals, colistin resistance in food, and colistin resistance in human beings are now complete. One of the few solutions to uncoupling these connections is limitation or cessation of colistin



Lancet Infect Dis 2015
Published Online
November 18, 2015

Discovery of first mcr-1 gene in E. coli bacteria found in a human in United States

MCR-1 causes resistance to colistin, a last-resort drug for treating resistant infections



Media Statement

For Immediate Release: Tuesday, May 31, 2016

Contact: [Media Relations](#),

(404) 639-3286



Et maintenant une bactérie résistante à TOUS les **antibiotiques** :

[Yahoo Actualités](#) - 29 mai 2016

Et maintenant une bactérie résistante à TOUS les **antibiotiques** : à quoi ressemblerait un **monde** sans les traitements qui nous ont protégé ...

[Etats-Unis : premier cas de superbactérie résistante aux antibiotiques](#)

[LINFO.re](#) - 27 mai 2016

[Etats-Unis : découverte d'une nouvelle bactérie résistante à tous les ...](#)

[Le Parisien](#) - 27 mai 2016

[Cette nouvelle super-bactérie signe le début de la fin des antibiotiques](#)

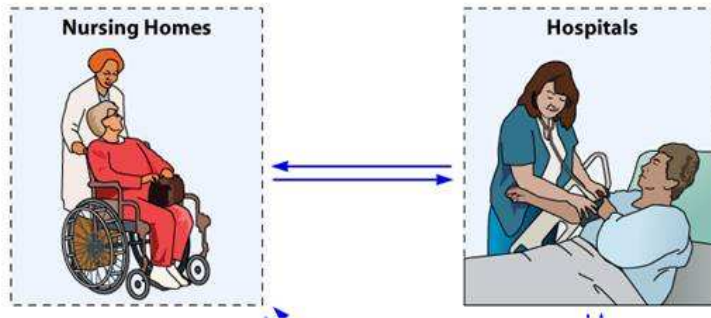
Exhaustif - [Le Huffington Post](#) - 27 mai 2016

[Une bactérie « cauchemardesque » aux États-Unis](#)

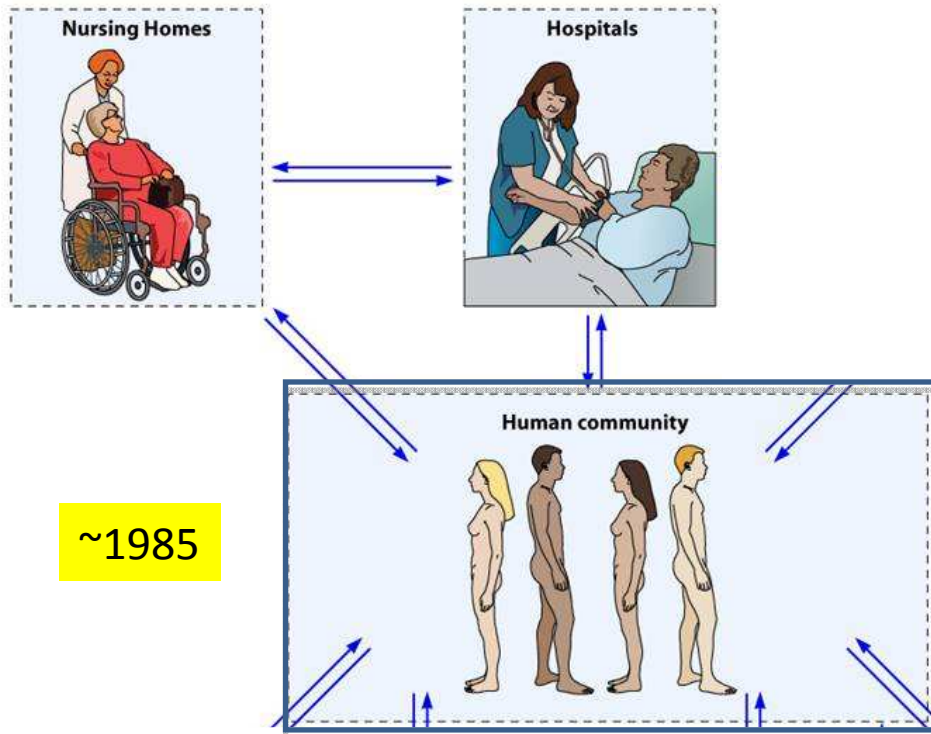
Éditorial - [La Croix](#) - 27 mai 2016

[Le gène de la résistance totale aux antibiotiques apparaît aux États ...](#)

Exhaustif - [Le Figaro](#) - 27 mai 2016



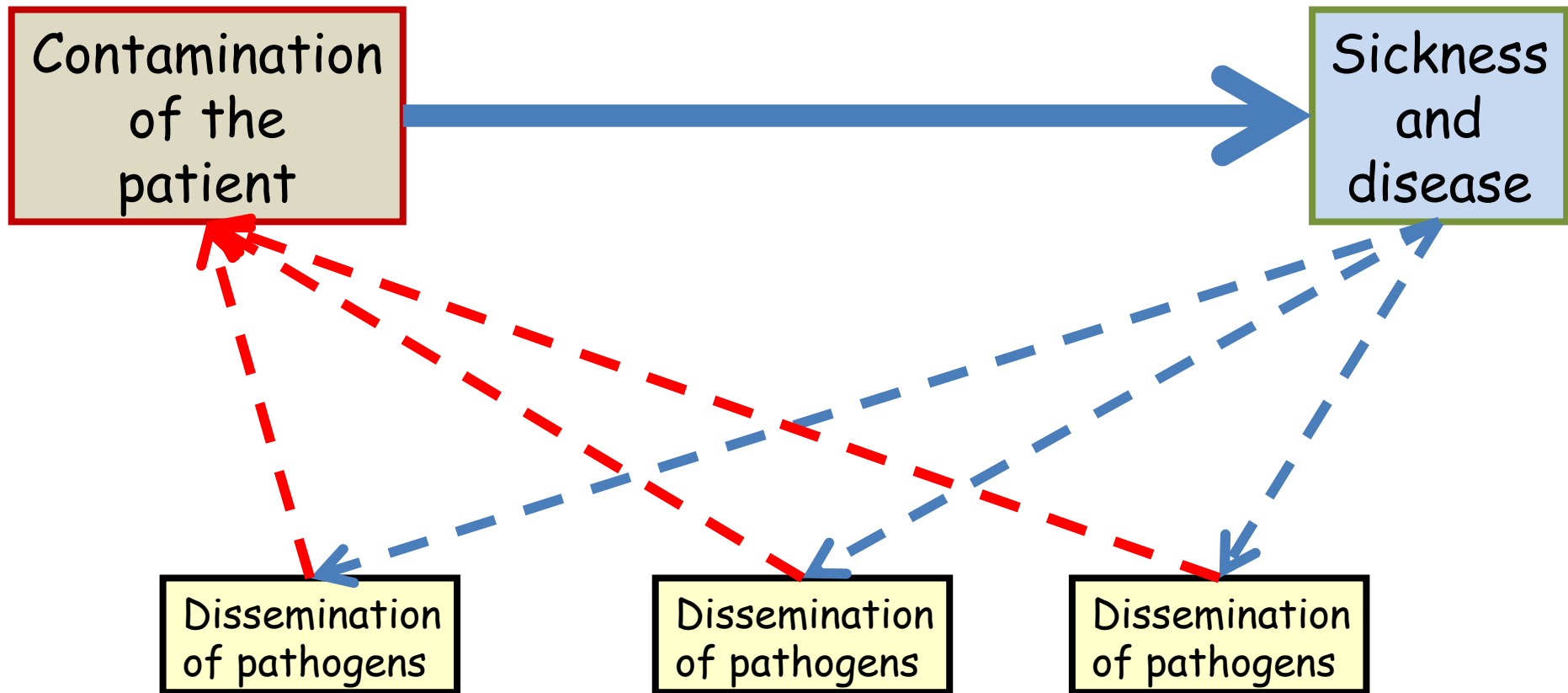
From a medical view of bacterial resistance



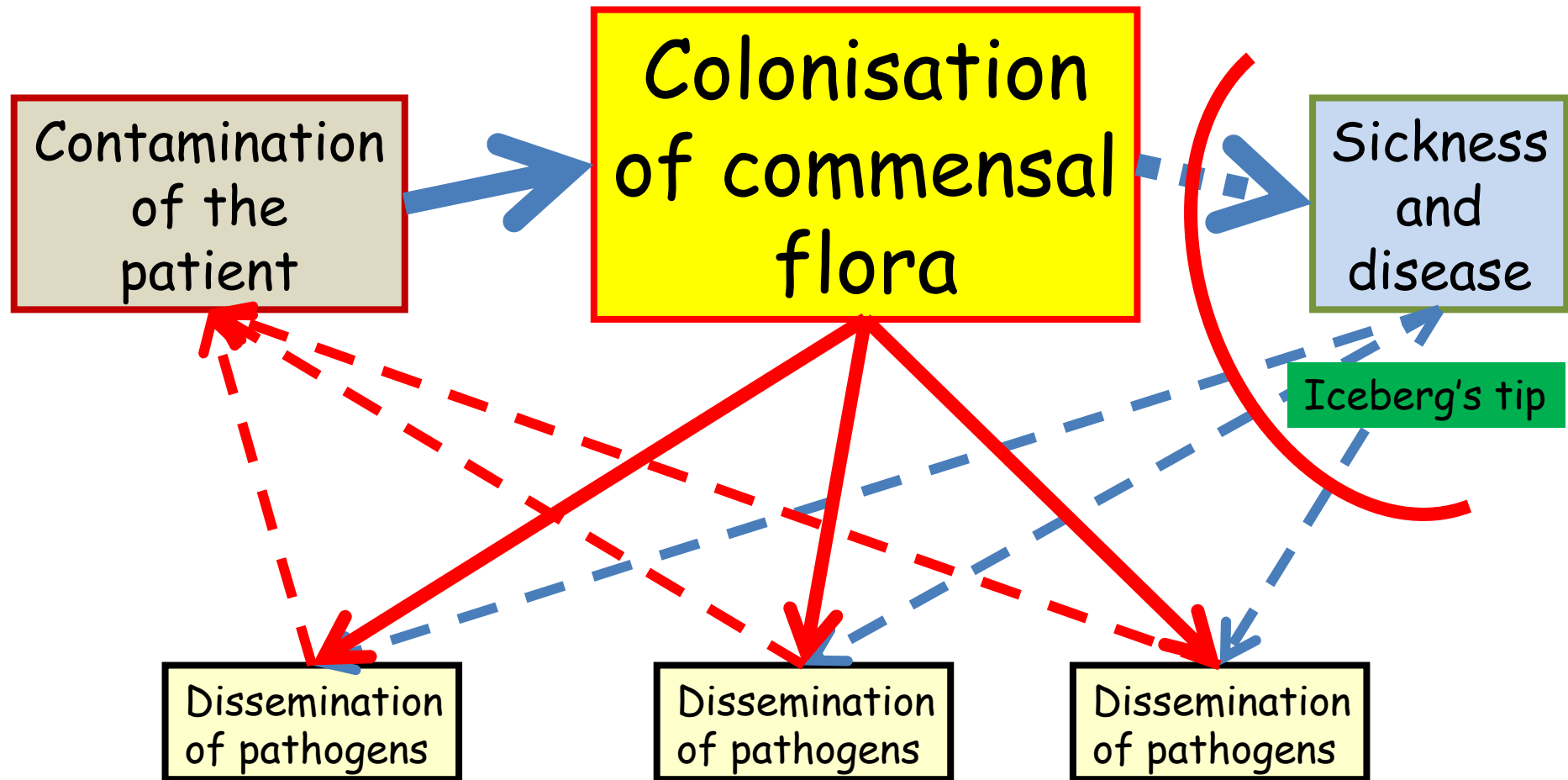
~1985

From a medical view of bacterial resistance

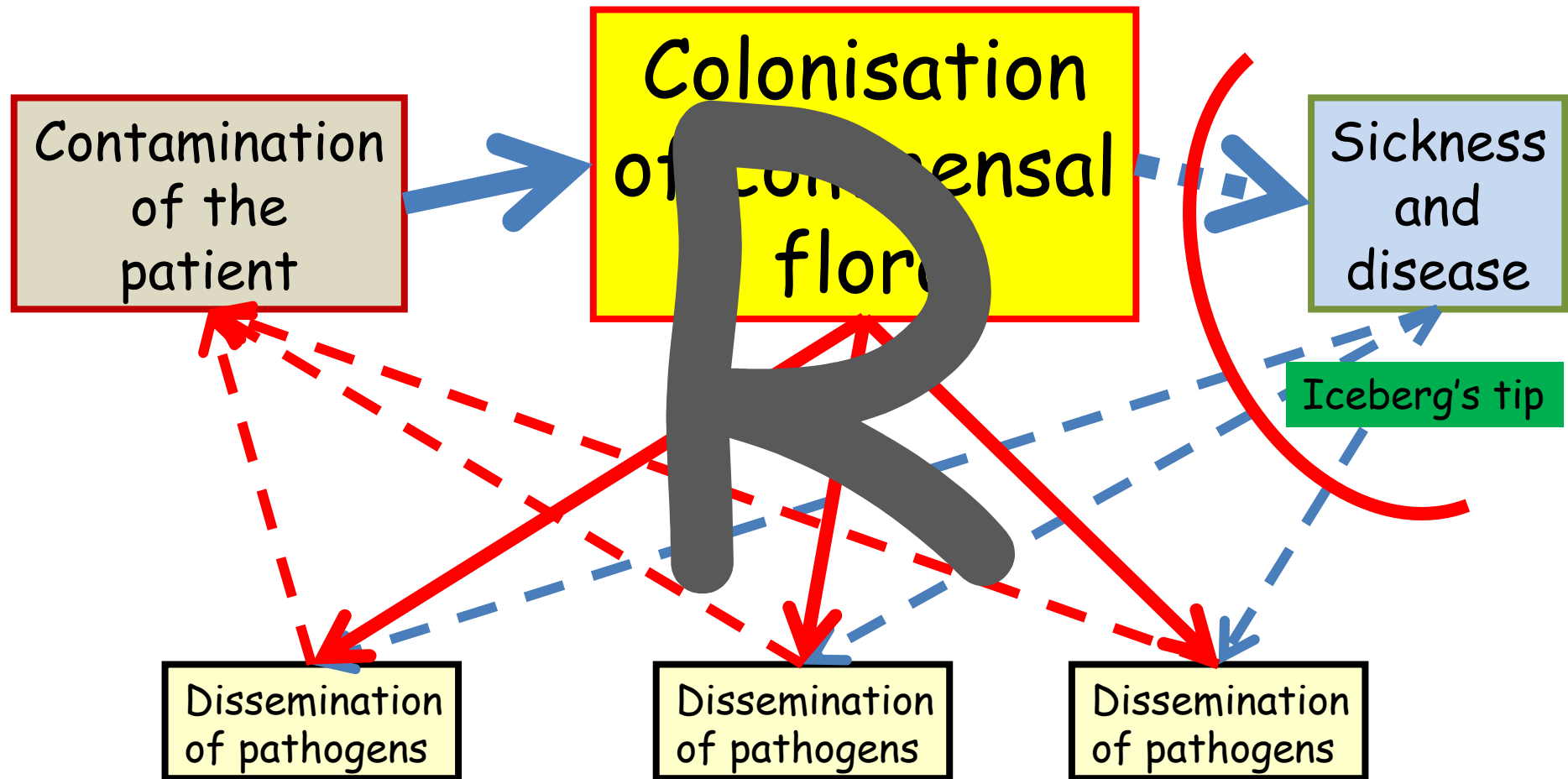
« Classical » natural history of bacterial infections

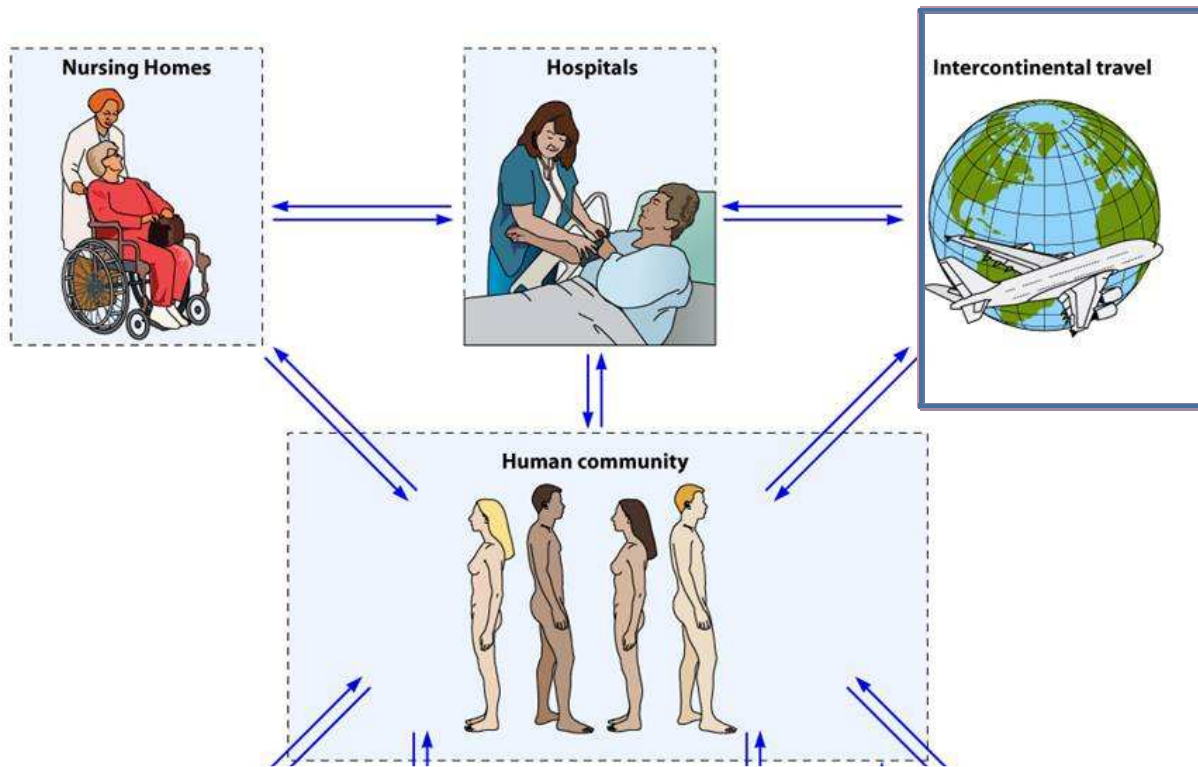


« **New** » natural history of bacterial infections



« **New** » natural history of bacterial infections



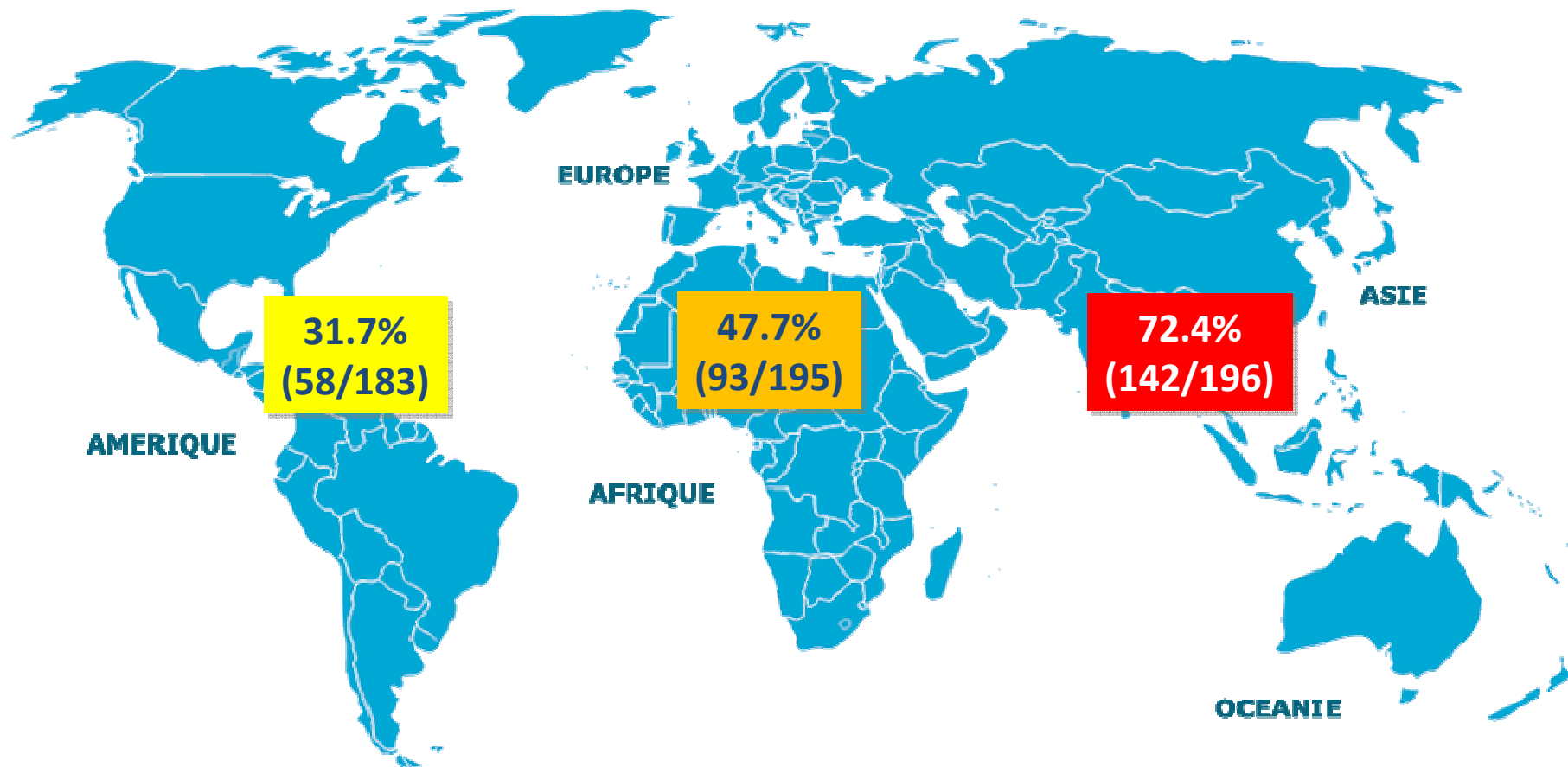


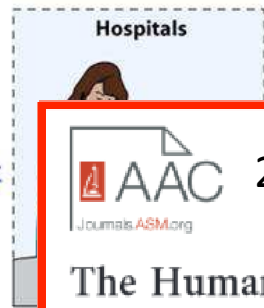
~1990

From a
medical
view of
bacterial
resistance

574 travellers in intertropical zones

Global acquisition rate: 51% (n=293)





Intercontinental travel



AAC 2015
Journals.ASM.org

The Human Gut Microbiome as a Transporter of Antibiotic Resistance Genes between Continents

Johan Bengtsson-Palme,^a Martin Angelin,^b Mikael Huss,^c Sanela Kjellqvist,^c Erik Kristiansson,^d Helena Palmgren,^b D. G. Joakim Larsson,^a Anders Johansson^a

Department of Infectious Diseases, Institute of Biomedicine, The Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden^a; Department of Clinical Microbiology, Infectious Diseases, Umeå University, Umeå, Sweden^b; Science for Life Laboratory, Department of Biochemistry and Biophysics, Stockholm University, Solna, Sweden^c; Department of Mathematical Sciences, Chalmers University of Technology, Gothenburg, Sweden^d; Laboratory for Molecular Infection Medicine Sweden, Department of Clinical Microbiology, Bacteriology, Umeå University, Umeå, Sweden^e

resistance

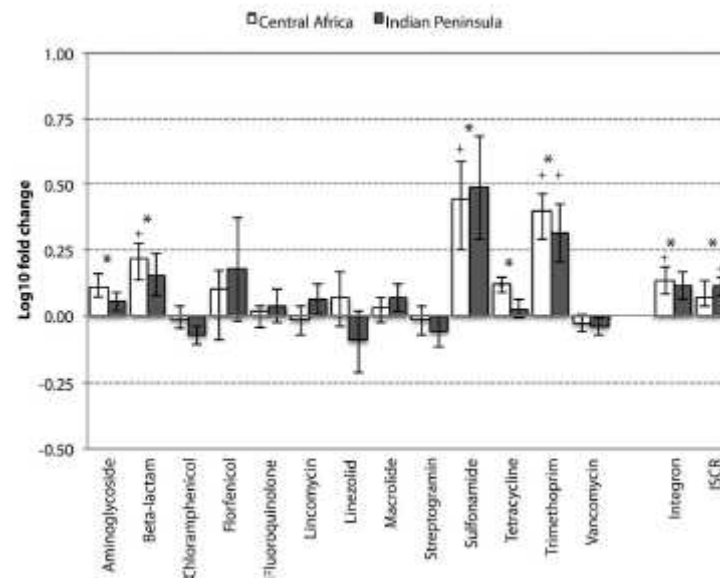
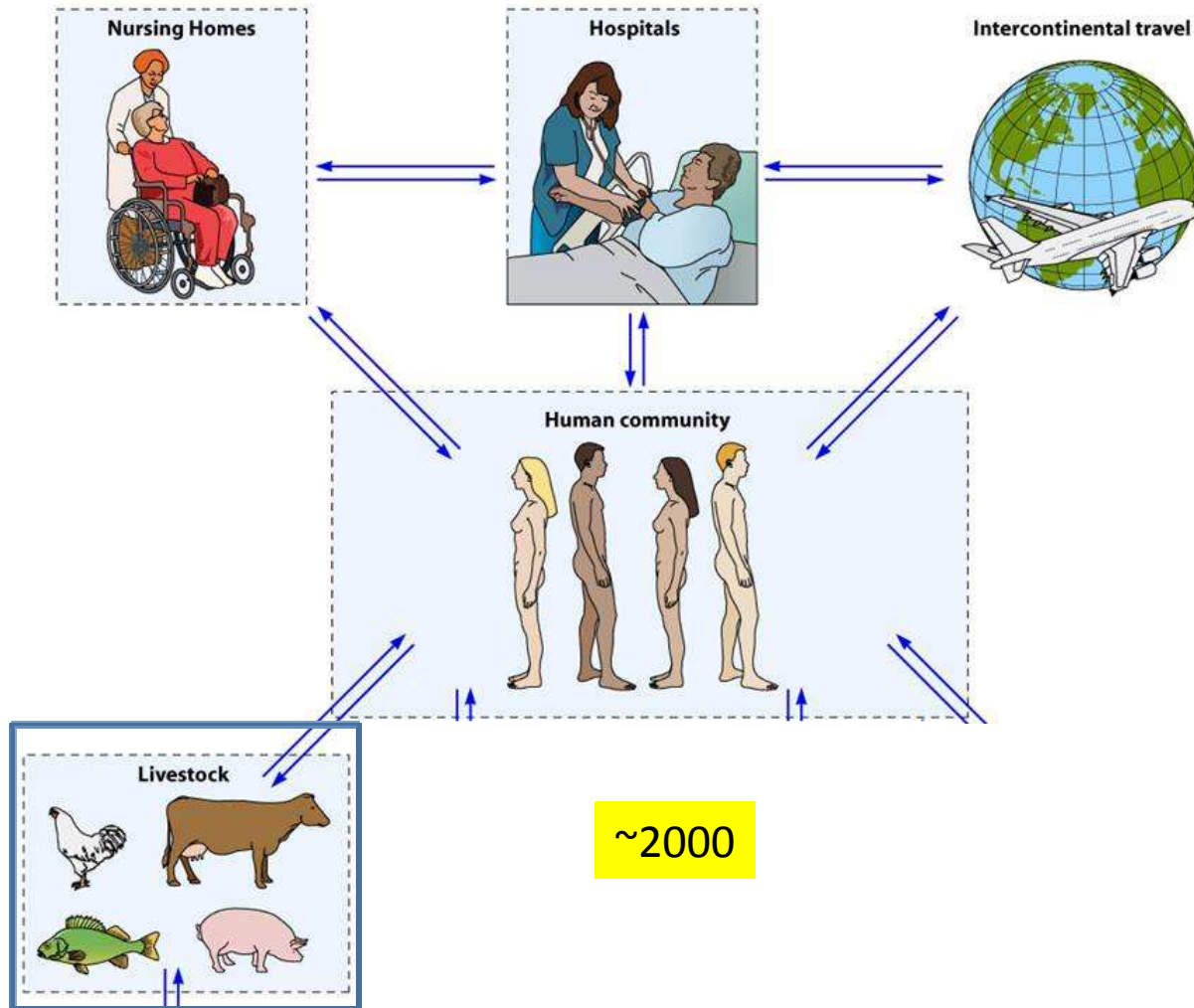


FIG 1 Average fold change of resistance gene categories after travel (\log_{10} scale). Changes in the entire cohort significant after correction for multiple testing are indicated with an asterisk. Significance within the Indian peninsula or the Central Africa group is indicated with a plus sign.



From a medical view of bacterial resistance

To the « one health » approach that includes the animal world

Food Animals and Antimicrobials: Impacts on Human Health

Bonnie M. Marshall^{1,2} and Stuart B. Levy^{1,2,3*}

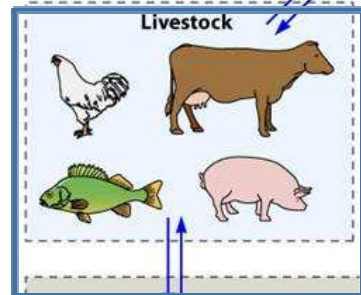
Alliance for the Prudent Use of Antibiotics, Boston, Massachusetts,¹ and Department of Molecular Biology and Microbiology² and Department of Medicine,³ Tufts University School of Medicine, Boston, Massachusetts

bacterial

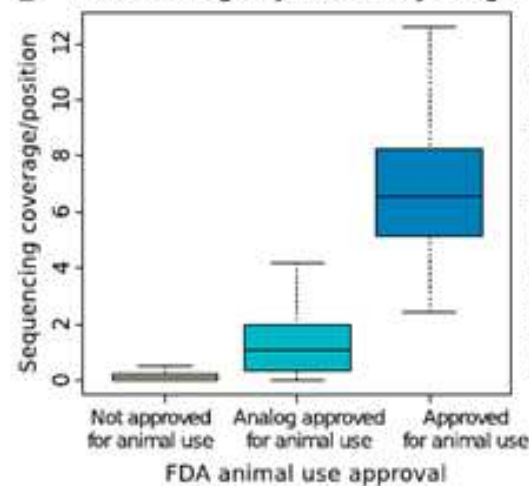
Country-specific antibiotic use practices impact the human gut resistome

Kristoffer Forslund, Shinichi Sunagawa, Jens Roat Kultima, et al.

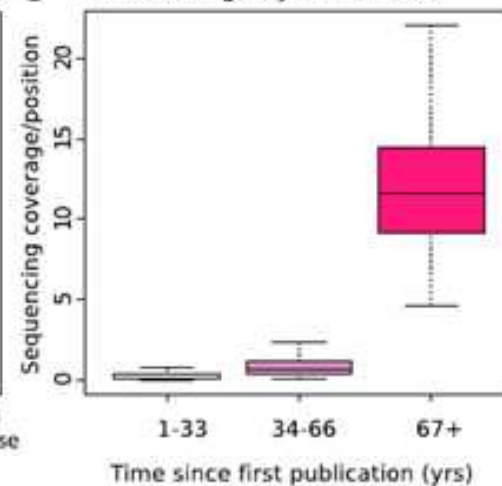
Genome Res. 2013 23: 1163-1169 originally published online April 8, 2013



B ARG carriage by veterinary usage



C ARG carriage by time in use



Food Animals and Antimicrobials: Impacts on Human Health

Bonnie M. Marshall^{1,2} and Stuart B. Levy^{1,2,3*}

FOOD SAFETY

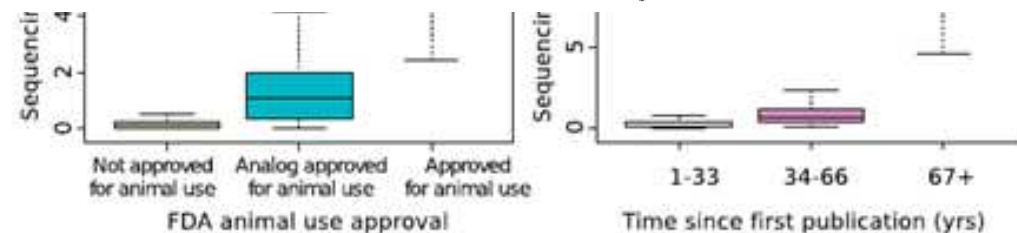
INVITED ARTICLE

Frederick J. Angulo, Section Editor

2009

World Health Organization Ranking of Antimicrobials According to Their Importance in Human Medicine: A Critical Step for Developing Risk Management Strategies for the Use of Antimicrobials in Food Production Animals

Peter Collignon,^{1,2} John H. Powers,^{3,4,5} Tom M. Chiller,⁶ Awa Aidara-Kane,⁷ and Frank M. Aarestrup⁸



Food Animals and Human Health

FOOD SAFETY

Frederick J. Angulo, Section Editor

World Health Organization
According to The
A Critical Step
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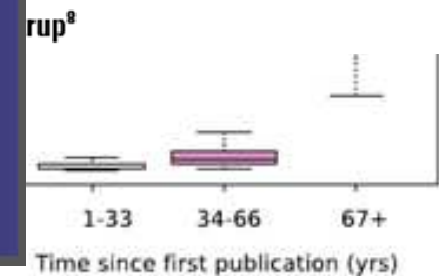
Peter Collignon,^{1,2} John H. Powers

Critically Important Antimicrobials for Human Medicine

3rd Revision 2011



Antimicrobials
Medicine:
Management Strategies
Production Animals





click for updates

Treating cattle with antibiotics affects greenhouse gas emissions, and microbiota in dung and dung beetles

Tobin J. Hammer, Noah Fierer, Bess Hardwick, Asko Simojoki, Eleanor Slade, Juhani Taponen, Heidi Viljanen, Tomas Roslin

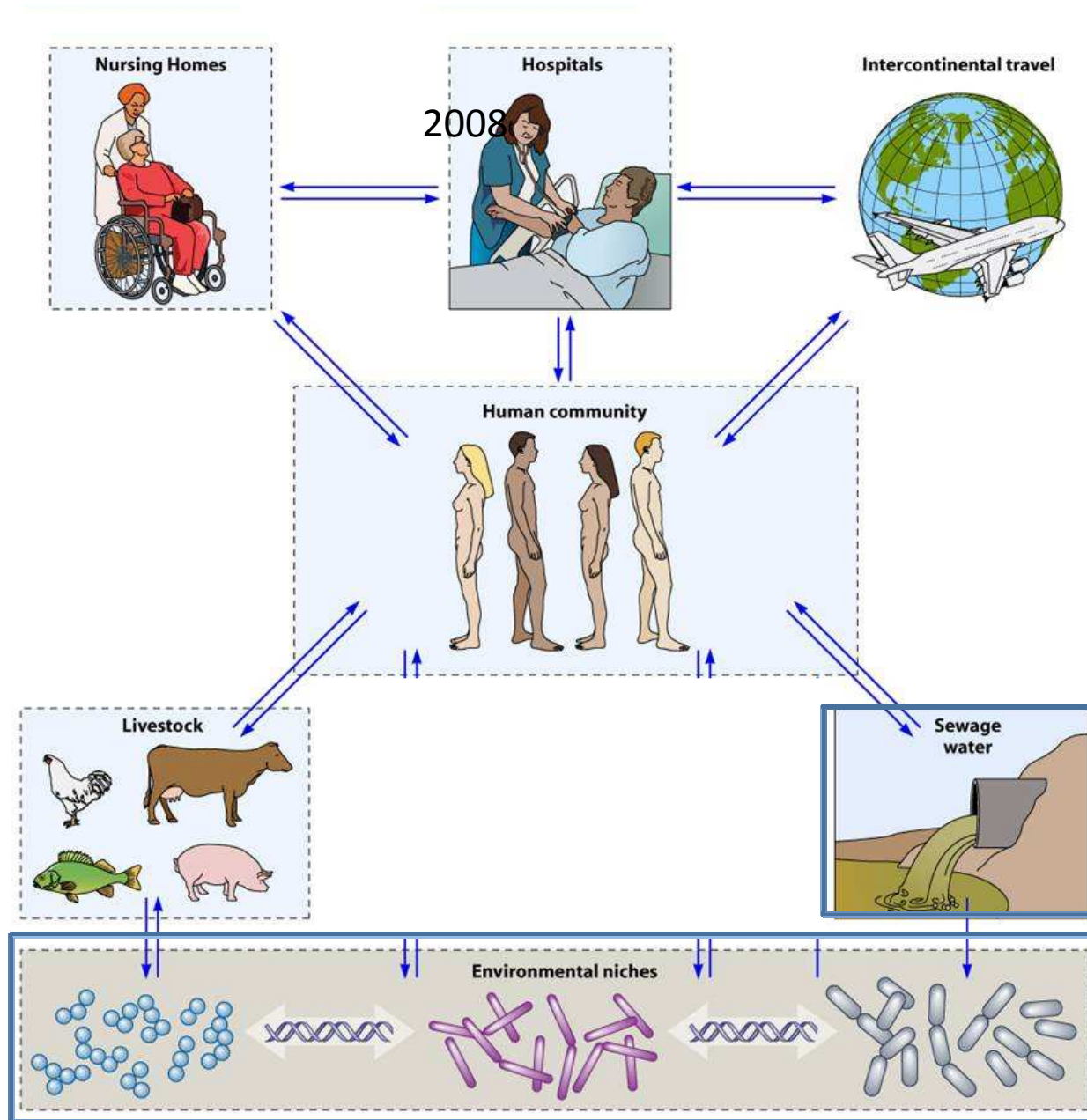
Published 125 May 2016. DOI: 10.1098/rspb.2016.0150



L'administration de tétracyclines à des vaches **augmenterait de 1,8 fois la quantité de méthane** produite !!.

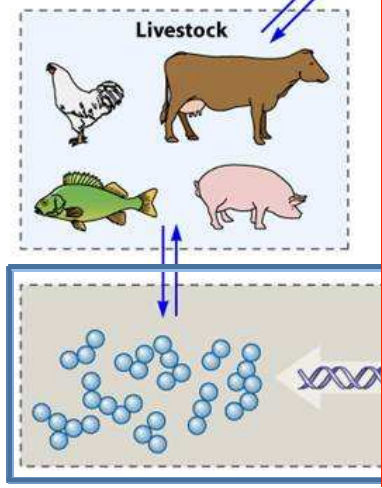
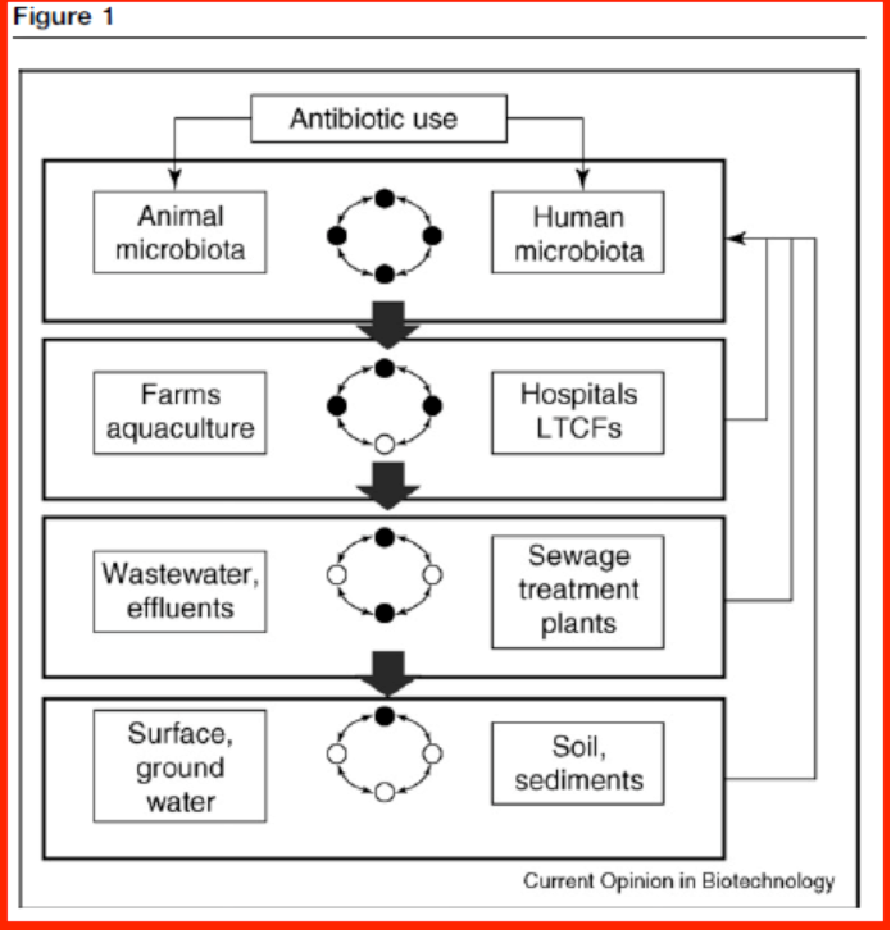
Direct impact on climate change !

"We believe that the tetracycline treatment **favors the growth of methanogenic archaea** in the cows' intestinal tract by reducing the bacteria in the gut."
T.J. Hammer



From a medical view of bacterial resistance

To the « one health » approach that includes the animal world



From a medical view of bacterial resistance

To the « one health » approach that includes the animal world



Effluent from drug manufactures contains extremely high levels of pharmaceuticals

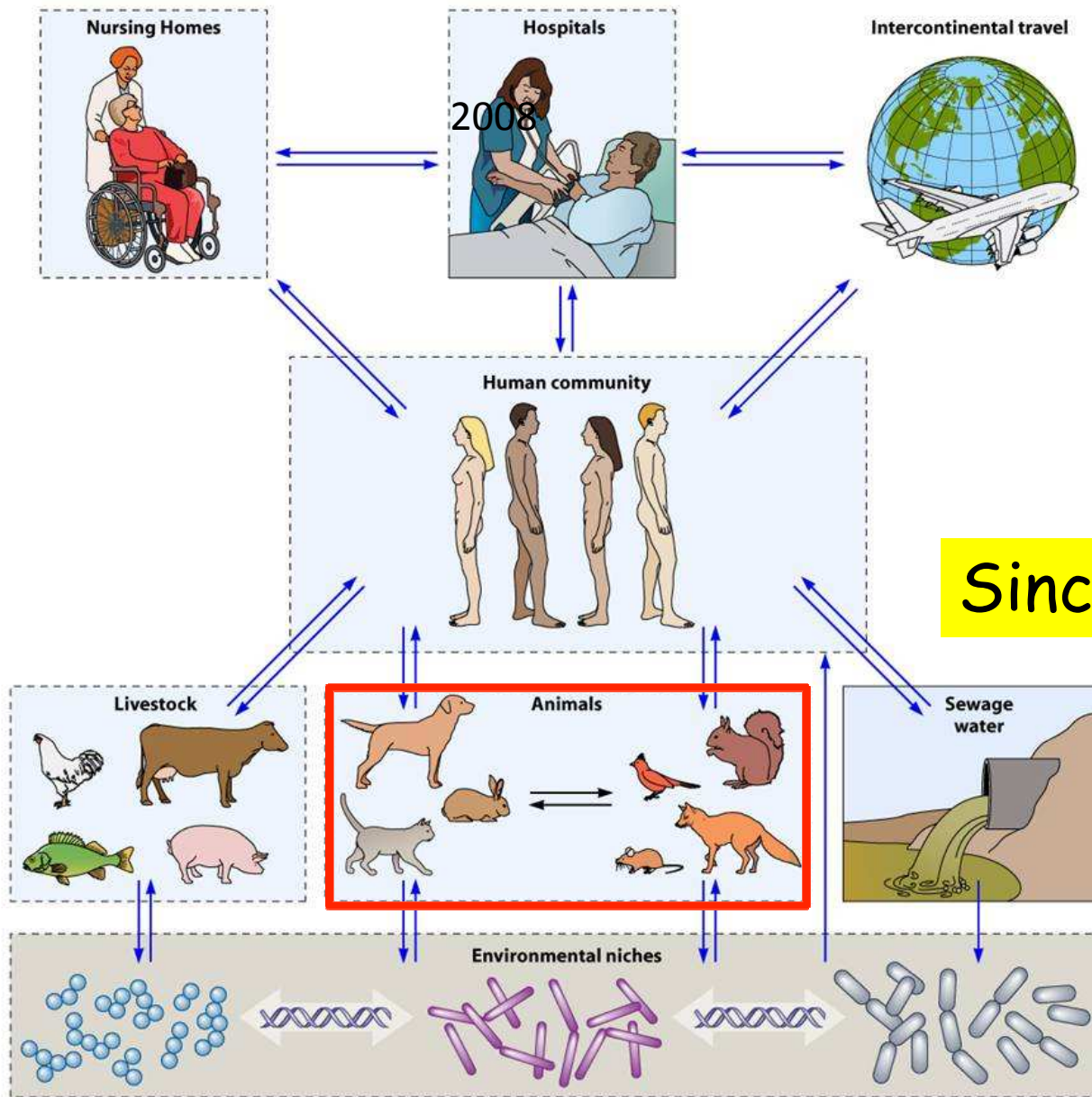
Larsson DG *et al.* J. Haz. Mat. 2007

« La ville d'Inde où la croissance est la plus rapide » (Wikipedia)

Top 11 active pharmaceutical ingredients analysed in effluent samples from PETL, a common effluent treatment plant near Hyderabad serving about 90 bulk drug manufacturers

Active ingredient	Type of drug	Range (µg/L)
Ciprofloxacin	Antibiotic-fluoroquinolone	28,000–31,000
Losartan	Angiotensin II receptor antagonist	2,400–2,500
Cetirizine	H ₁ -receptor antagonist	1,300–1,400
Metoprolol	β ₁ -adrenoreceptor antagonist	800–950
Enrofloxacin	Antibiotic-fluoroquinolone (veterinary use)	780–900
Citalopram	Serotonin reuptake inhibitor	770–840
Norfloxacin	Antibiotic-fluoroquinolone	390–420
Lomefloxacin	Antibiotic-fluoroquinolone	150–300
Enoxacin	Antibiotic-fluoroquinolone	150–300
Ofloxacin	Antibiotic-fluoroquinolone	150–160
Ranitidin	H ₂ -receptor antagonist	90–160

Drugs were analysed using LC–MS/MS monitoring at least two specific fragment ions per substance when possible and quantified using a four-point calibration. Data from two samples taken on consecutive days are presented.



From a medical view of bacterial resistance

Since 2010

To the « one health » approach that includes the animal world



Journal of Applied Ecology



Journal of Applied Ecology 2016, 53, 519–529

doi: 10.1111/1365-2664.12596

REVIEW

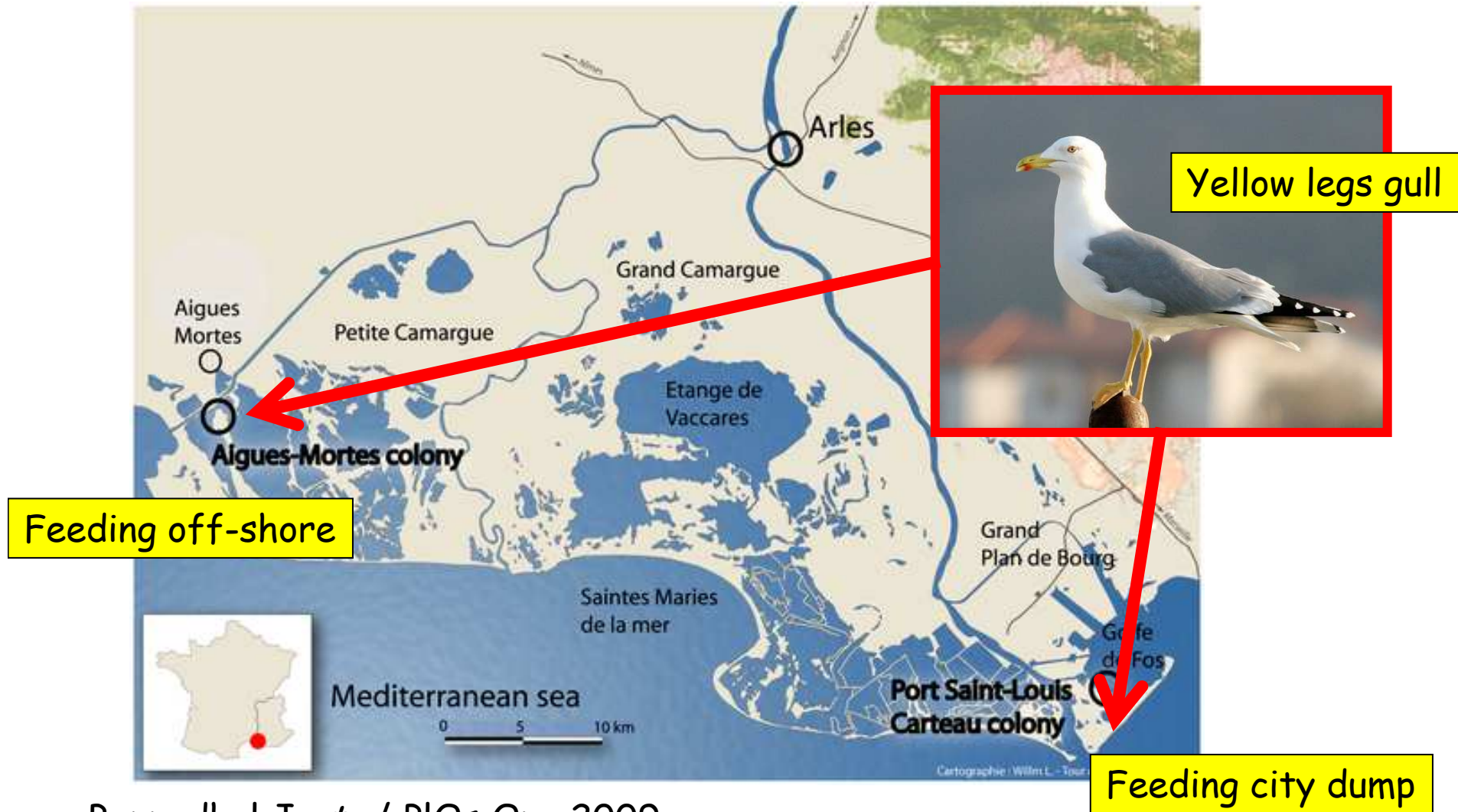
Antimicrobial resistance in wildlife

Marion Vittecoq^{1,2*}, Sylvain Godreuil^{3,4,5}, Franck Prugnotte², Patrick Durand², Lionel Brazier², Nicolas Renaud², Audrey Arnal², Salim Aberkane^{3,5}, H el ene Jean-Pierre^{3,4,6}, Michel Gauthier-Clerc^{1,7}, Fr ed eric Thomas² and Fran ois Renaud²

¹Centre de recherche de la Tour du Valat, Arles, France; ²MIVEGEC (Laboratoire Maladies Infectieuses et Vecteurs, Ecologie, G en etique, Evolution et Contr ole), UMR CNRS 5290/IRD 224, Universit e de Montpellier, Montpellier, France; ³D epartement de Bact eriologie-Virologie, Centre Hospitalier R egional Universitaire (CHRU) de Montpellier, Montpellier, France; ⁴Universit e de Montpellier, Montpellier, France; ⁵Infection by HIV and by agents with mucocutaneous tropism: from pathogenesis to prevention, U 1058, INSERM, Montpellier, France; ⁶UMR 5119 (UM2, CNRS, IRD, IFREMER, UM), Equipe Pathog enes et Environnements, U.F.R. Pharmacie, Montpellier, France; and ⁷D epartement Chrono-Environnement, UMR UFC/CNRS 6249 USC INRA, Universit e de Franche-Comt e, Besan on, France

animal world

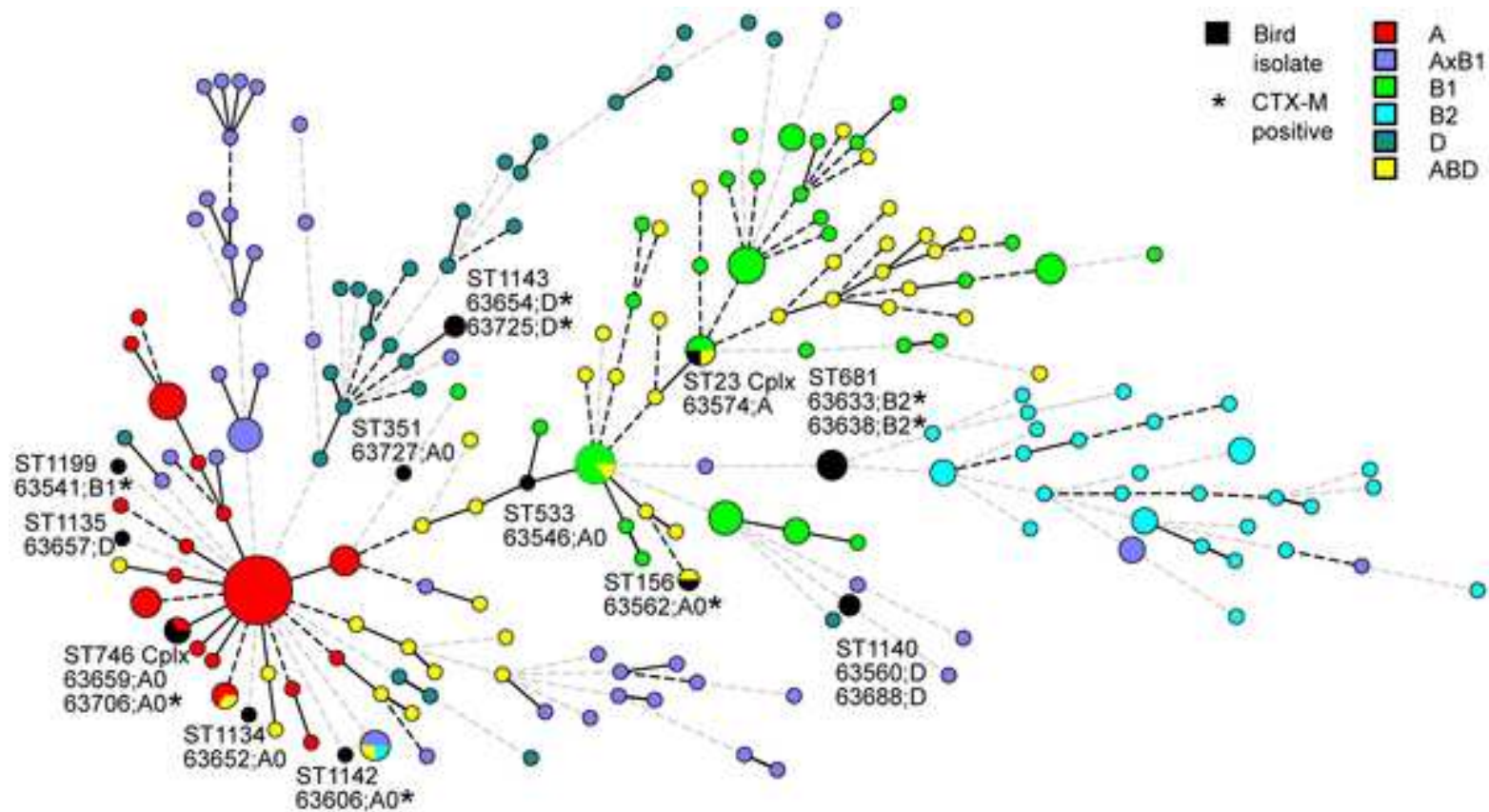
Correspondance between ESBL E. coli of birds and humans (Camargue, France)



Bonnedehal J *et al.* PLOS One 2009

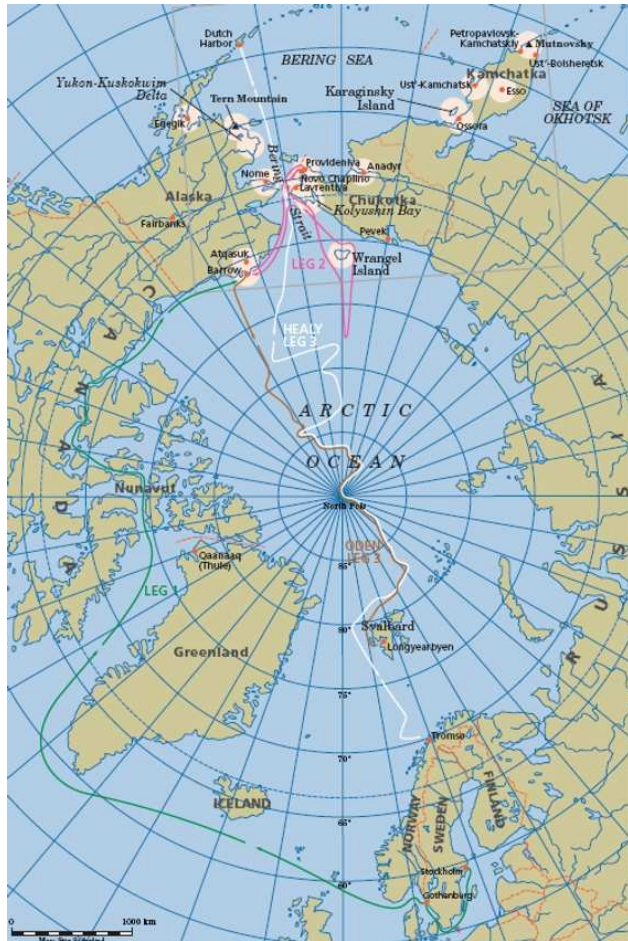
Andréumont ARLIN, Juin 2016

CTX-M E. coli were found in both types of birds and mixed with human strains from the region



Dissemination of MDR into the artic : results of the Beringia expedition 2005

Fecal or cloacal samples from **97 arctic birds** from Northern Siberia, Point Barrow (Alaska) and Northern Greenland



Iceland glaucus gull



Vega glaucus gull



Emperor brent goose



Western sand piper

Sjolund M *et al.* EID 2008

Andrenholt RRLN, Jun 2016

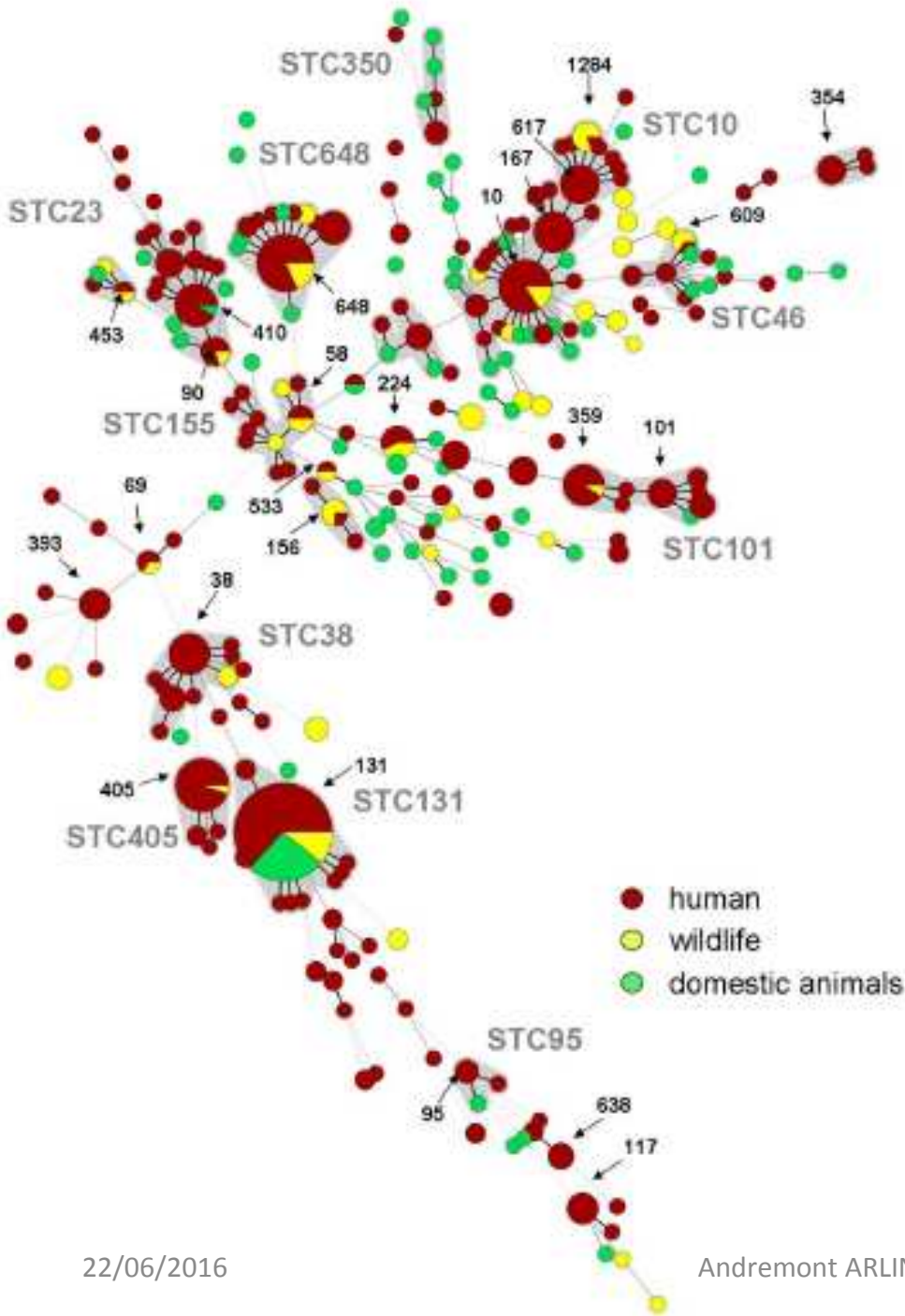
8/97 (8.2%) birds with resistant GNB

Table. Antimicrobial drug resistance phenotypes in 8 *Escherichia coli* isolates from Arctic birds

Isolate	Avian host species	Geographic origin	PhenePlate type*	Drug resistance profile†
2	Western sandpiper	Lorino, Siberia	Si	Amp, Cpd, Cdr, Cxm
18	Vega/Glaucous gull	Novo Chaplino, Siberia	CT3	Amp, Cpd
26	Vega/Glaucous gull	Novo Chaplino, Siberia	Si	Amp, Sul, Chl, Tet, Tri, Nit, Str
35	Vega/Glaucous gull	Novo Chaplino, Siberia	Si	Fos
36	Vega/Glaucous gull	Novo Chaplino, Siberia	Si	Fos
75	Emperor/Brent goose	Kolyuchin, Siberia	CT5	Tet
94	Iceland/Glaucous gull	Thule, Greenland	CT5	Amp, Sul, Chl, Mec, Tet, Tri, Str
97	Iceland/Glaucous gull	Thule, Greenland	Si	Amp, Sul, Chl, Mec, Tri, Str, Nal, Cip

- ✓ Number 2 was a juvenile
- ✓ Some species are migratory birds
- ✓ Most likely theory :
introduction by migration
transfer of resistance between birds

A global analysis



MSTree of 288 human, domestic animals, and wildlife ESBLs in MLSTdatabase

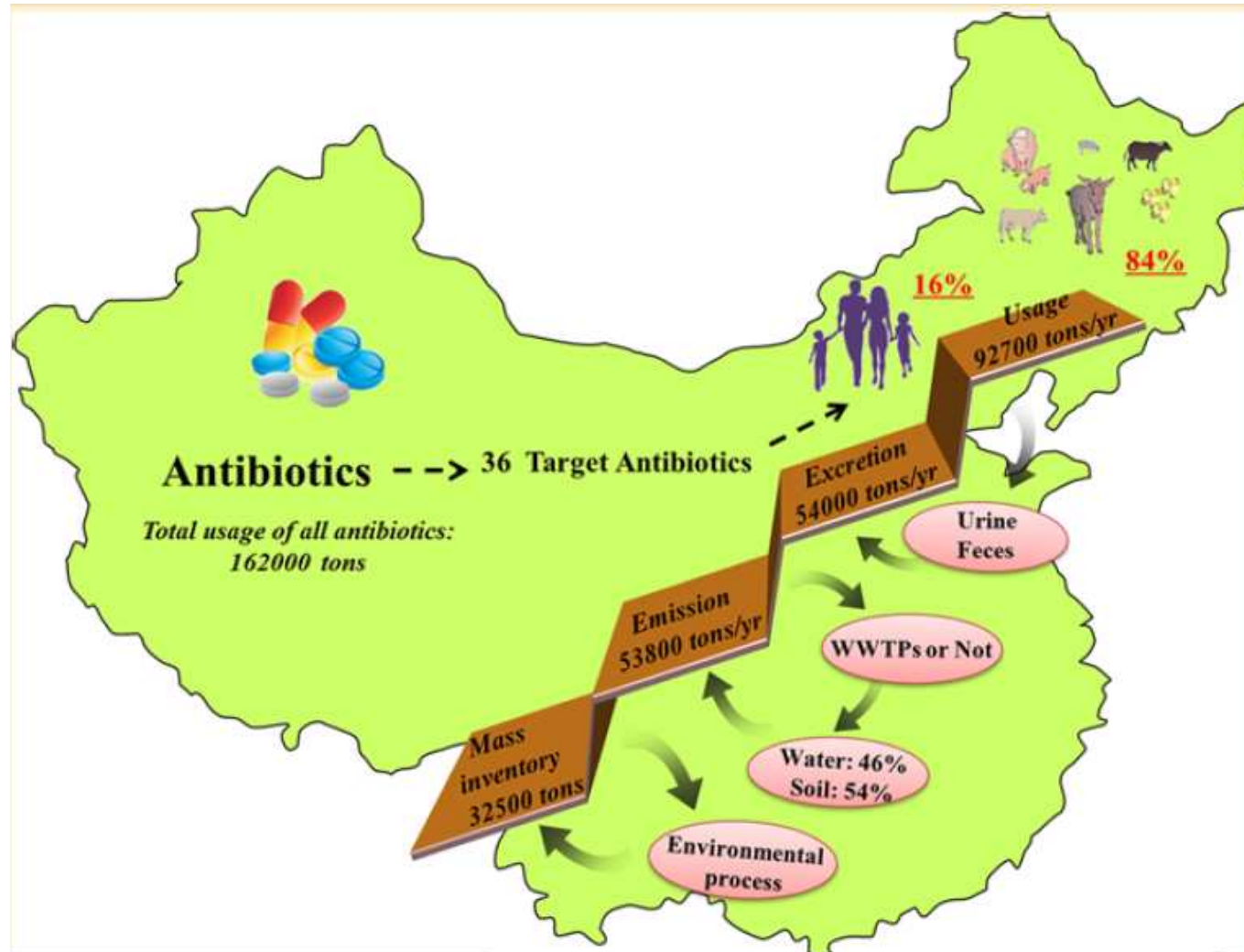
A global picture of the fate of antibiotics after they are produced begins to emerge

Comprehensive Evaluation of Antibiotics Emission and Fate in the River Basins of China: Source Analysis, Multimedia Modeling, and Linkage to Bacterial Resistance

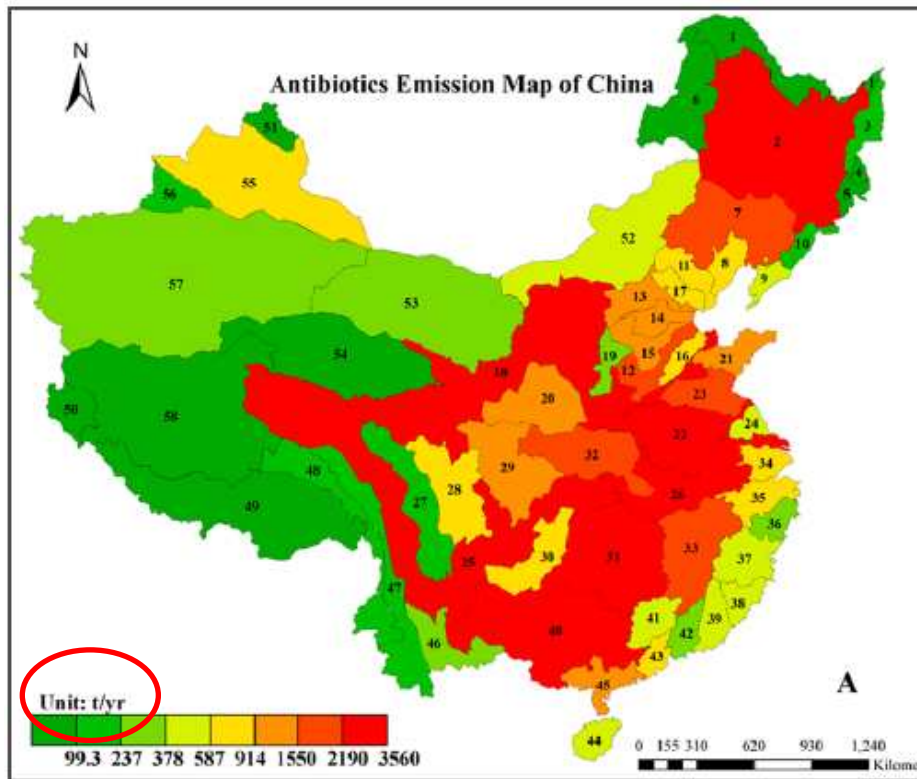
Table 2. Total Usages of All Antibiotics in China and Other Developed Countries

country	year	usage (tons)			DID ^a	ref
		total	human	animals		
China	2013	162000	77760	84240	157	this study
UK	2013	1060	641	420	27.4	56, 57
USA	2011/2012	17900	3290	14600	28.8	58, 59
Canada	2011	<i>b</i>	251	<i>b</i>	20.4	60
Europe	2003	<i>b</i>	3440	<i>b</i>	20.1	32

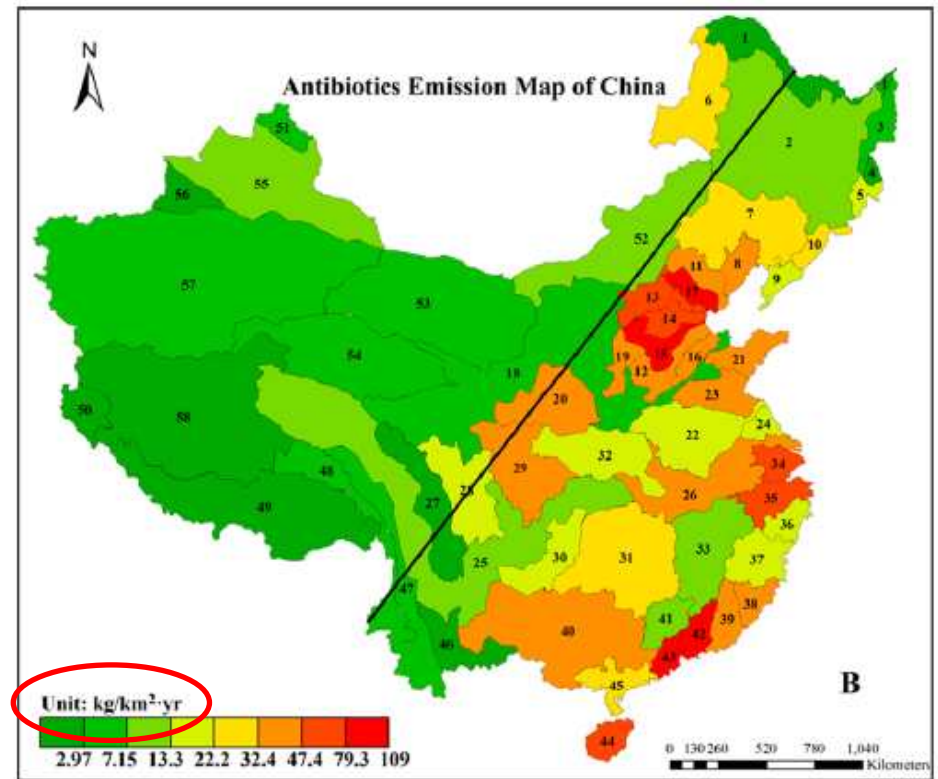
Comprehensive Evaluation of Antibiotics Emission and Fate in the River Basins of China: Source Analysis, Multimedia Modeling, and Linkage to Bacterial Resistance



Map of China showing the total antibiotic emission in each river basin.



t/Y

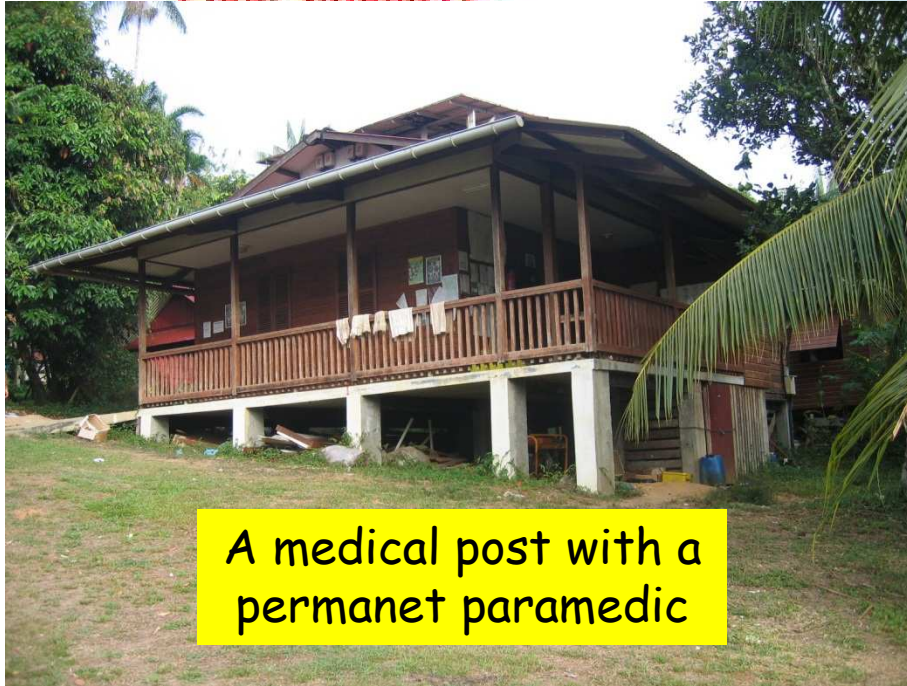


Kg/Km²/Y

What can we do to face AMR

1. Decrease unnecessary use of antibiotics
2. Innovate : New antibiotics, Other means :
 1. Vaccine, bacteriophages
 2. Decrease impact of antibiotics on the intestinal microbiota : **what we try to do**

Four hamlets



~500 amerindians still living in a traditional manner



- Trois-Sauts village
 - South of French Guiana
 - Restricted area

2°15'0.99"N, 52°52'58.99"W

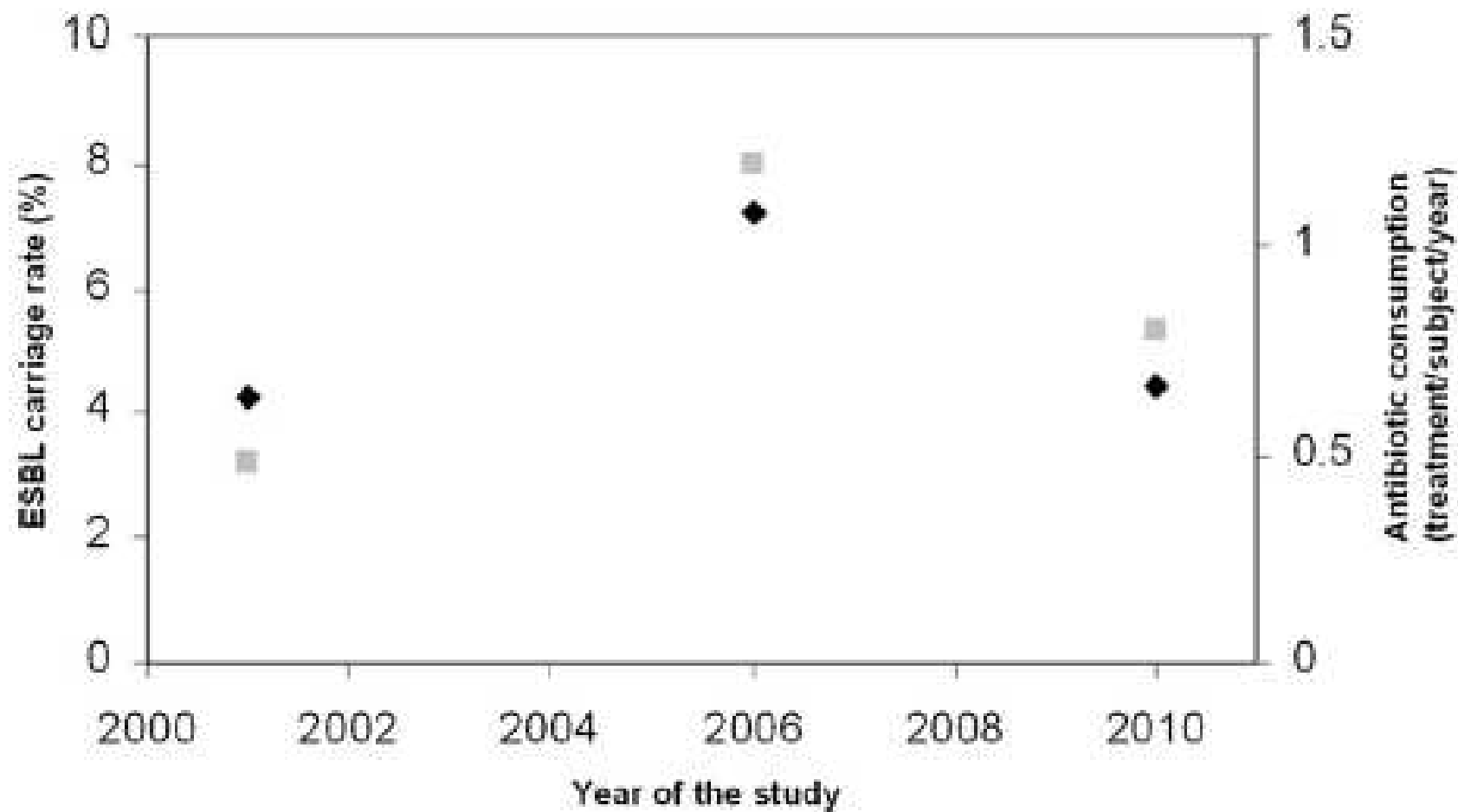


FIG 1 ESBL-E carriage rate in Wayampi volunteers (gray squares) and overall antibiotic exposure of the whole community (black diamonds) in 2001, 2006, and 2010. Linear regression ($y = 8.675x - 1.396$; $R^2 = 0.87$) and Pearson's correlation ($P = 0.24$) were used to evaluate the evolution.

MARAN 2015

Monitoring of Antimicrobial Resistance and Antibiotic Usage in Animals in the Netherlands in 2014

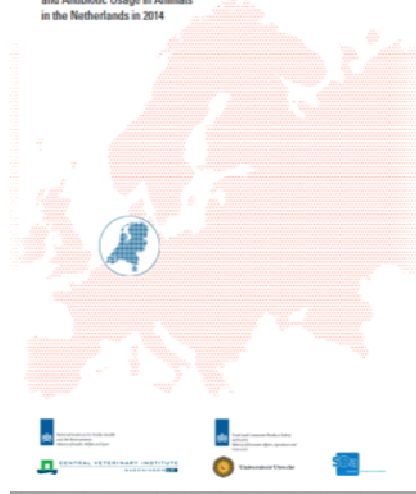


Figure Eco01 Trends in resistance (%) of *E. coli* isolated from broilers, slaughter pigs, veal calves and dairy cattle in the Netherlands from 1998 - 2014.

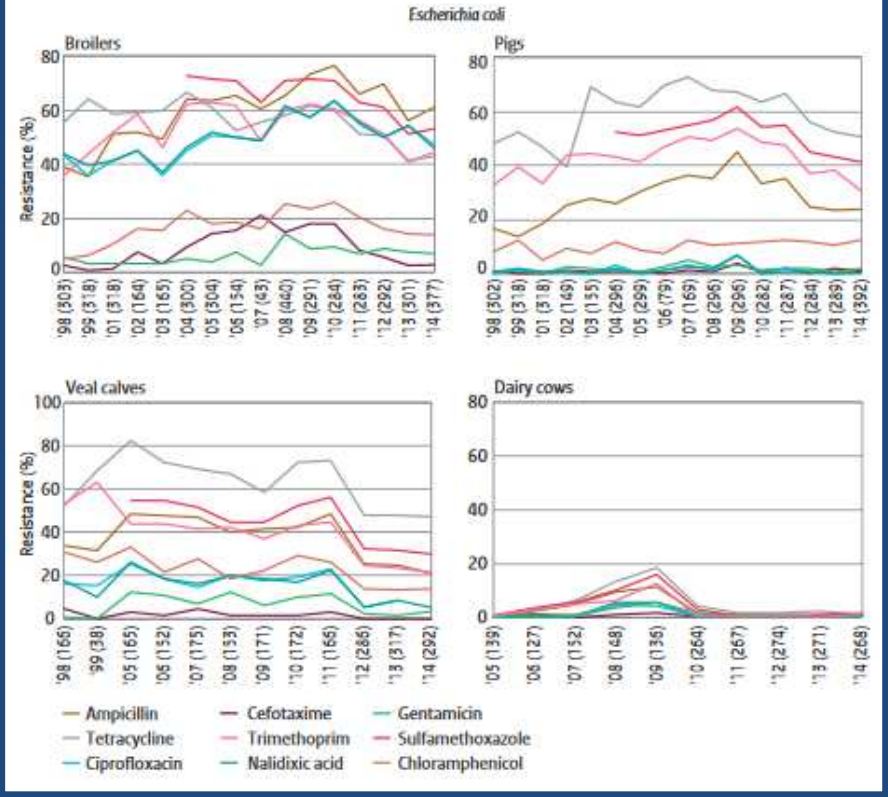
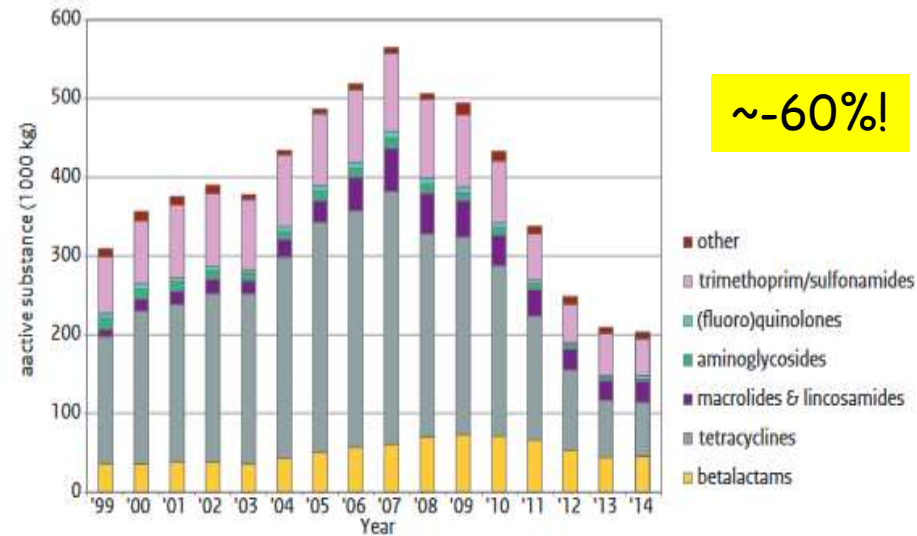


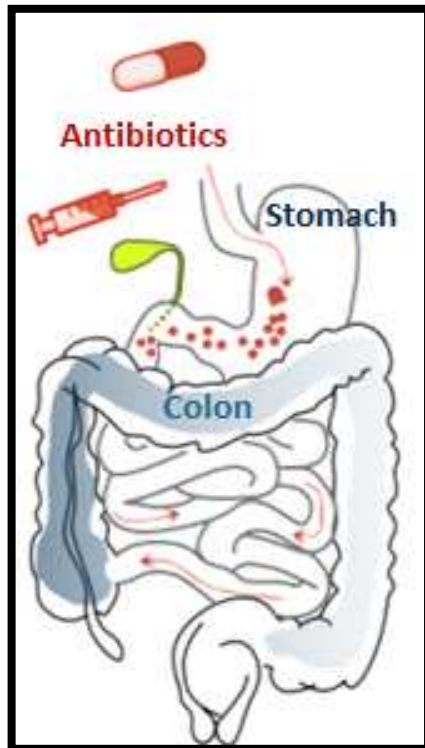
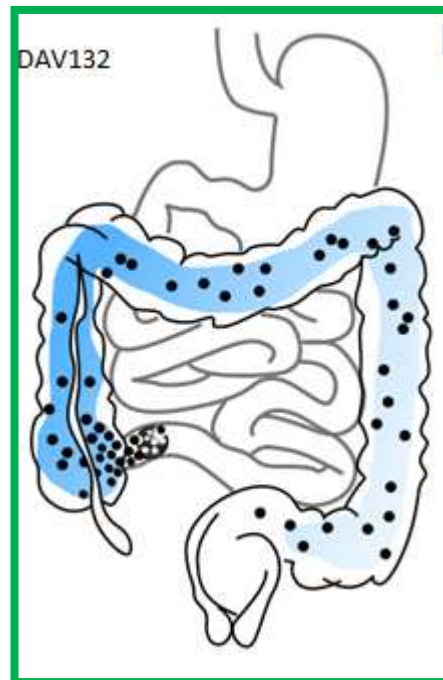
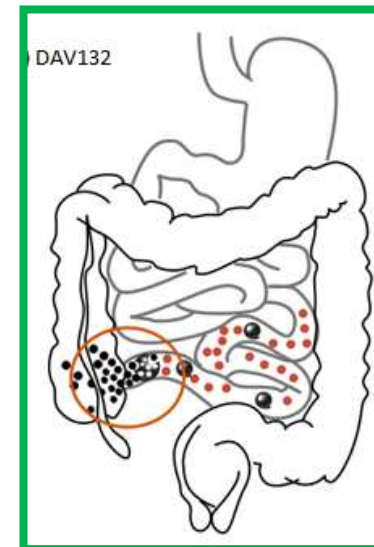
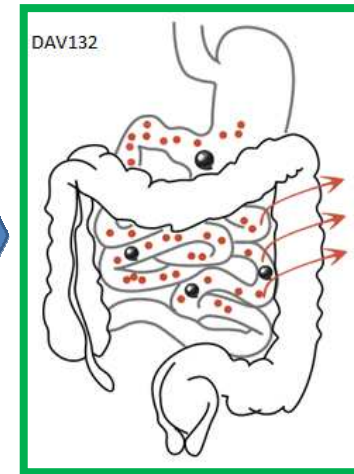
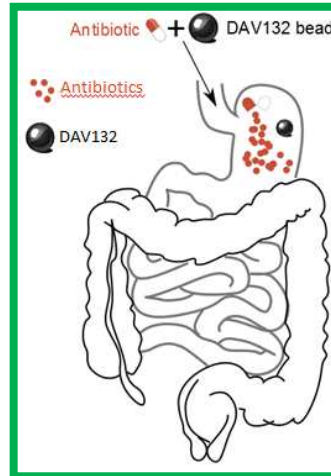
Figure ABuse01 Antimicrobial veterinary medicinal product sales from 1999-2014 in kg (thousands).



What can we do to face AMR

1. Decrease unnecessary use of antibiotics
2. Innovate : New antibiotics, Other means :
 1. Vaccine, bacteriophages
 2. Decrease impact of antibiotics on the intestinal microbiota : **what we try to do**

The concept behind DAV 132



DAV132, an Adsorbent-Based Product, Protects the Gut Microbiome and Prevents *Clostridium difficile* Infections during Moxifloxacin Treatments

Jean de Gunzburg, PhD¹, Amine Ghozlane, PhD², Annie Ducher, MD¹, Xavier Duval, MD, PhD³, Etienne Ruppé, PharmD, PhD², Mark Pulse, MS⁴, Caroline Chilton, PhD⁵, Laurence Armand-Lefevre, PharmD, PhD⁶, Elisabeth Chachaty, PharmD, PhD⁷, Sakina Sayah-Jeanne, PhD², Joël Doré, PhD², Emmanuelle Le Chatelier, PhD², Florence Levenez, BS², Sean Kennedy, PhD², Nicolas Pons, PhD², William Weiss, MS⁴, Mark Wilcox, MD^{4,8}, France Mentré, MD, PhD⁶, Antoine Andremont, MD, PhD⁶ and Stanislav Dusko Ehrlich, PhD^{2,9}
 (1)Da Volterra, Paris, France, (2)Metagenopolis, INRA, Jouy-en-Josas, France, (3)Bichat Claude Bernard Hospital, Paris 7 University, Paris, France, (4)UNT Health Science Center, Fort Worth, TX, (5)University of Leeds, Leeds, UK, (6)University Paris-Diderot Medical School and INSERM, UMR 1137, IAME, Paris, France, (7)Institut Gustave-Roussy, Villejuif Cedex, France, (8)Leeds Teaching Hospitals, Leeds, UK, (9) Center for Host-Microbiome Interactions, King's College London, London, UK

Figure 1: Free MOX fecal concentration (mean ± SD) over D1-D16 (LOQ 40 ng/g; MOX MIC for Enterobacteriaceae 0.5 µg/mL)

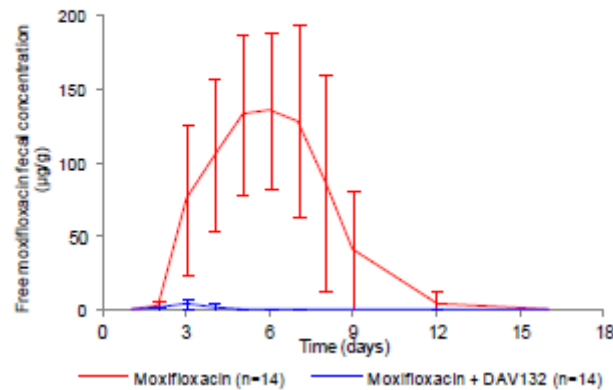


Figure 2: MOX plasma concentration (mean Log ± SD) over 24h on D5 (LOQ 10 ng/ml)

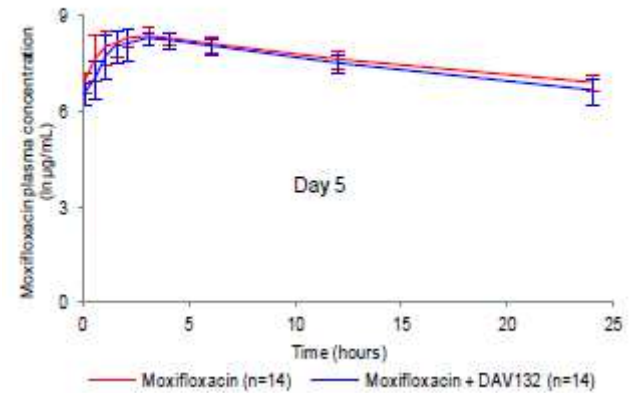
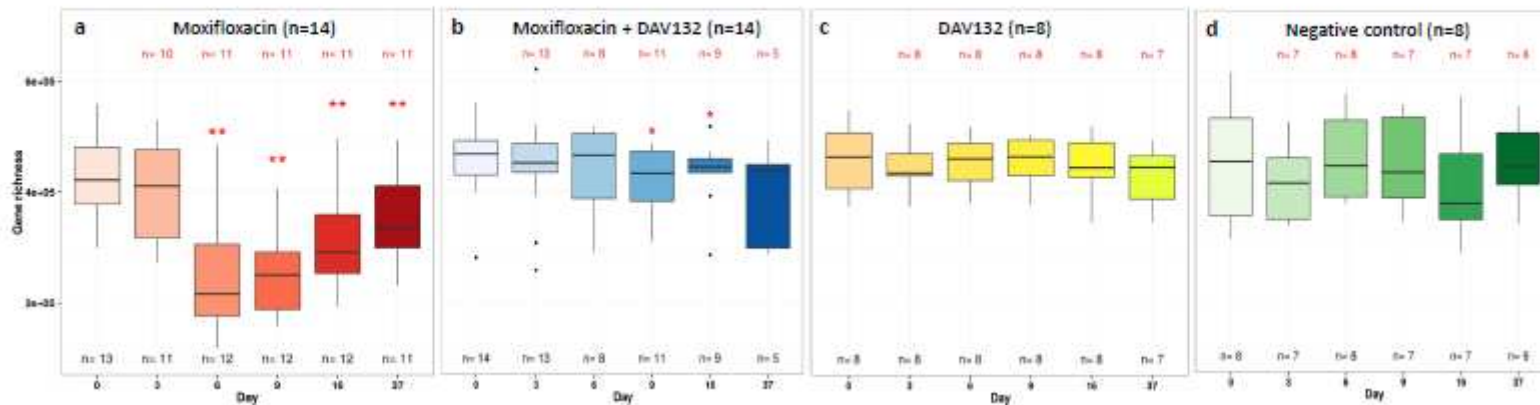


Figure 3: Normalized microbiome gene richness ratio (median, quartiles, 1.5 interquartile range, and outliers) from D1 to D37 in subjects treated with (a) MOX, (b) MOX+DAV132, (c) DAV132, and (d) negative control.



Les messages du jour

- ✓ La résistance bactérienne est un pb MAJEUR
- ✓ C'est un phénomène global et écologique
- ✓ Aucune région ne sera épargnée
- ✓ D'abord diminuent massivement nos utilisations d'antibiotiques
- ✓ Ensuite développer de nouveaux antibiotiques ou d'autres innovation.
- ✓ De l'argent et de la matière grise !

Merci
beaucoup
pour votre
attention!