« *Le rôle central du microbiote intestinal dans l'évolution et la dissémination de la résistance* »

Antoine Andremont
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CS : DaVolterra

Bactéries environnementales

Bactéries pathogènes

Construction d'outils génétiques
Fonctions nouvelles
Echanges de gènes
Evolutivité et adaptation des bactéries

Bactéries opportunistes

Bactéries commensales

Global use of antibiotics

Animals

Hospitals

Agriculture

Community

L'impact écologique est fonction de la rencontre entre

- Des micro-organismes au sein des écosystèmes

- Des quantités **d'antibiotiques**

« L'universalité » de l'impact

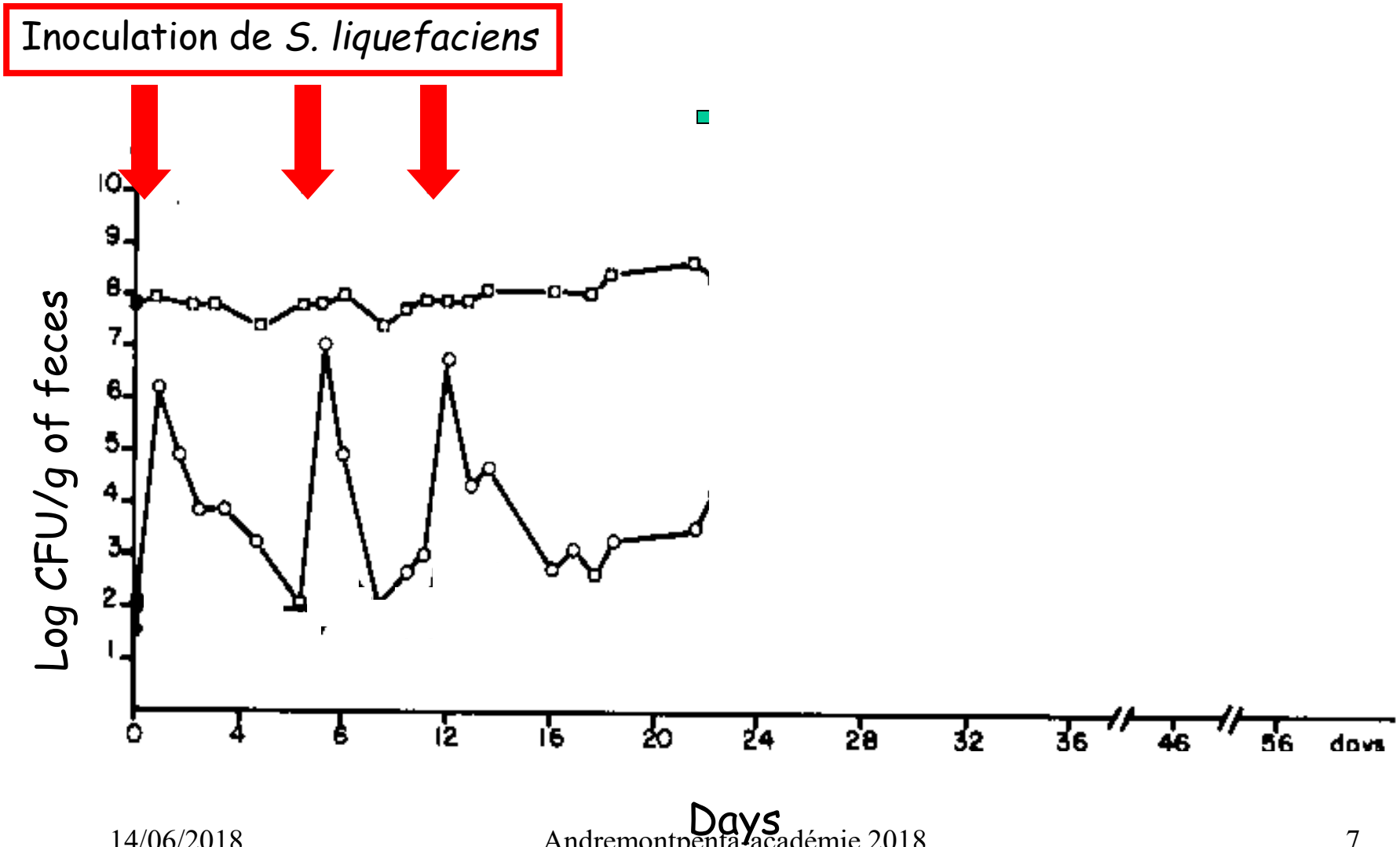
- « ***Bien entendu, l'indication de la prescription n'a rien à voir dans l'affaire…*** »

L'écosystème intestinal est impacté lors de chaque traitement antibiotiqe

Flore colique

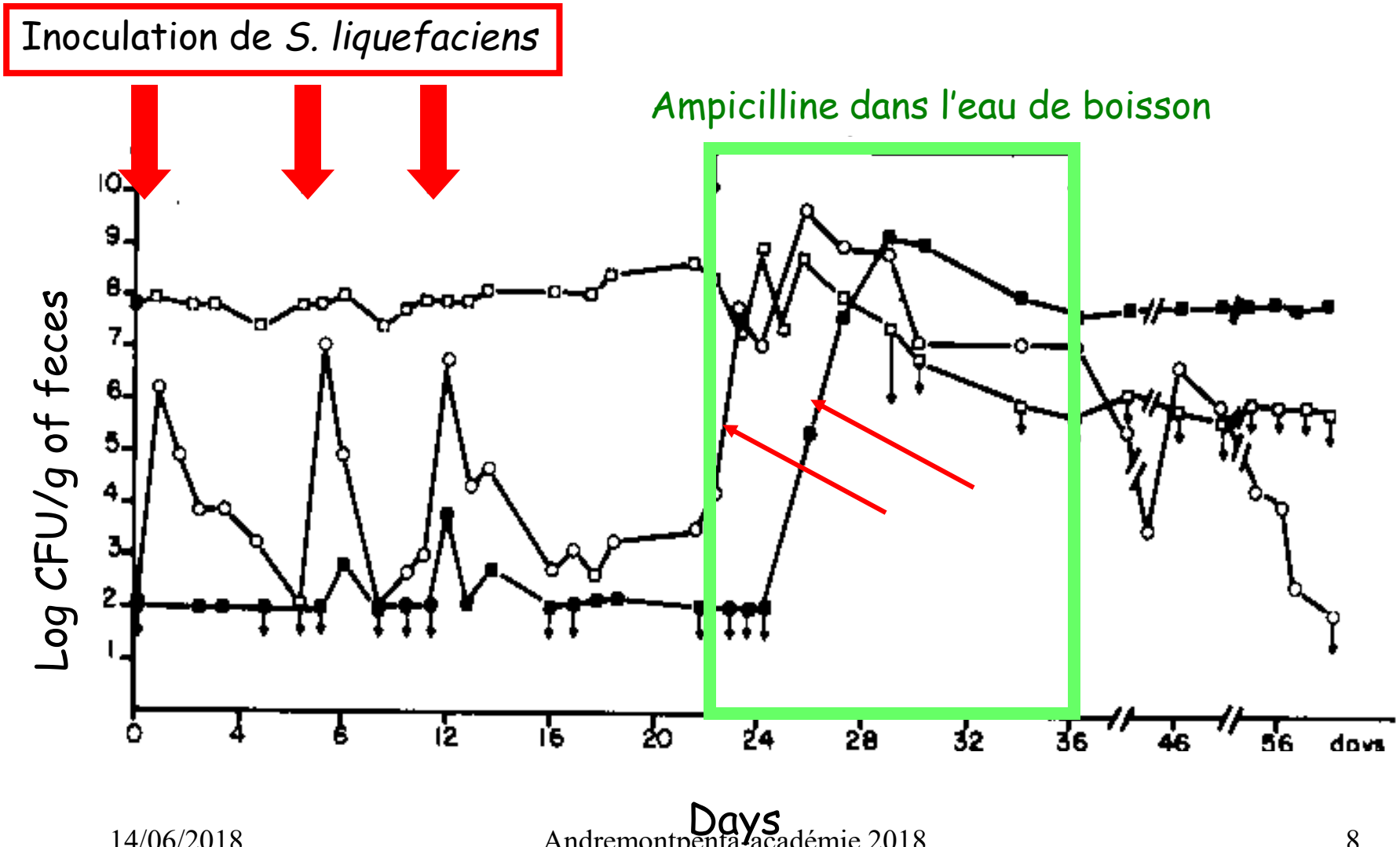
- ✓ 10^{14} CFU
- ✓ Nombreuse espèces (X100)
- ✓ Anaérobies dominantes (10^{12}-10^{14})
- ✓ Enterobacteria et enterococci en faible nombre (10^{8}-10^{10})
- ✓ Très stable
- ✓ Résistante à la colonisation.
- ✓ Très bien décrit en métagénomique

Résistance à la colonisation par *S.liquefaciens multirésistant* (❍) in vivo dans le tube digestif de souris gnotaxéniques associées à une flore humaine [*E. coli* (□)].



From Duval-Yflah Y. *et al.* IAI 1980; 28 :981

Tranfert plasmidique *in vivo* entre une souche de *S.liquefaciens multirésistante* (❍) à *E. coli* commensal (□) dans le tube digestif de souris gnotoxéniques à flore humaine. Transconjugants (■).



From Duval-Yflah Y. *et al.* IAI 1980; 28 :981

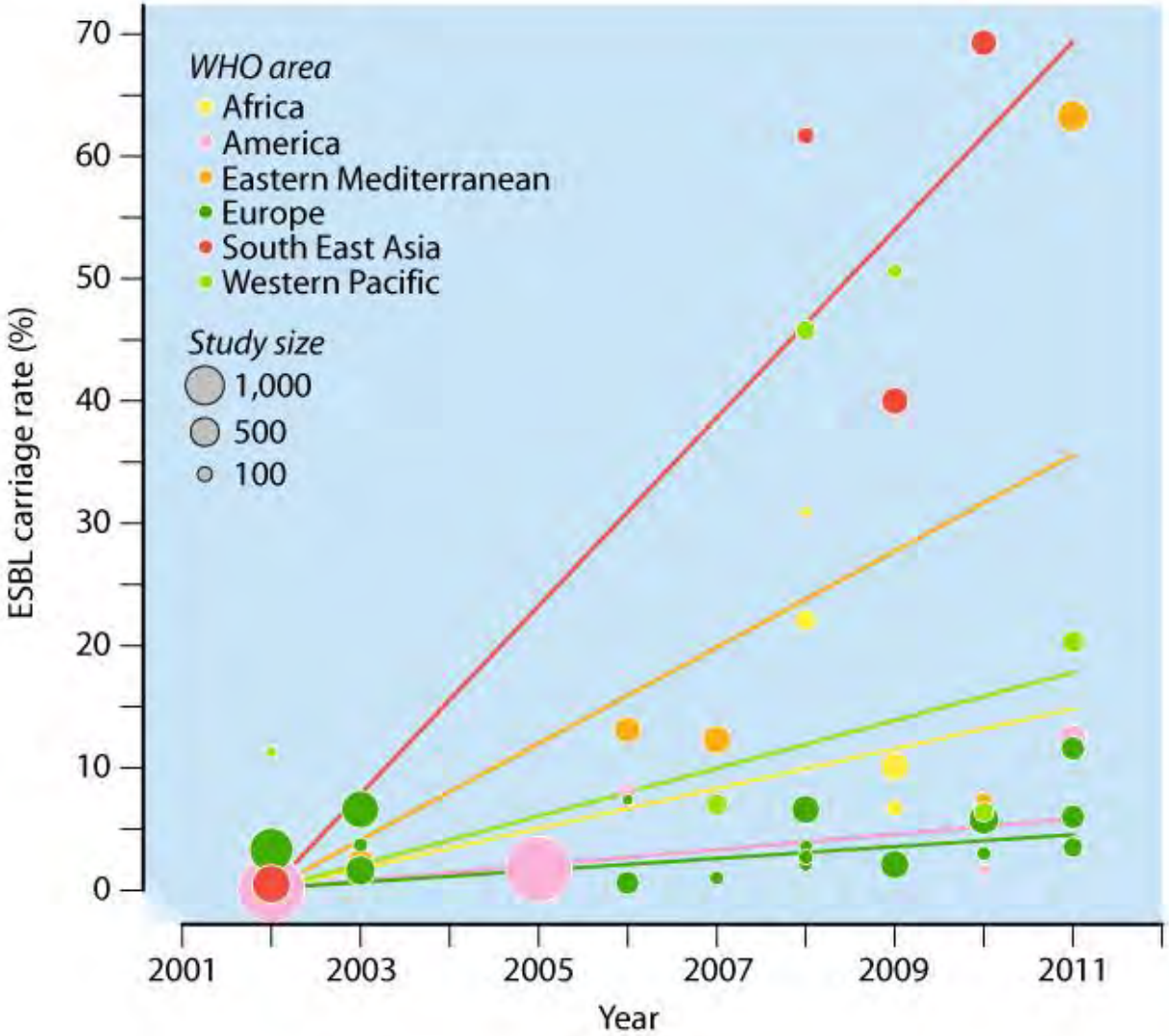


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Figure: 01

Evolution of ESBL carriage rates in the community worldwide

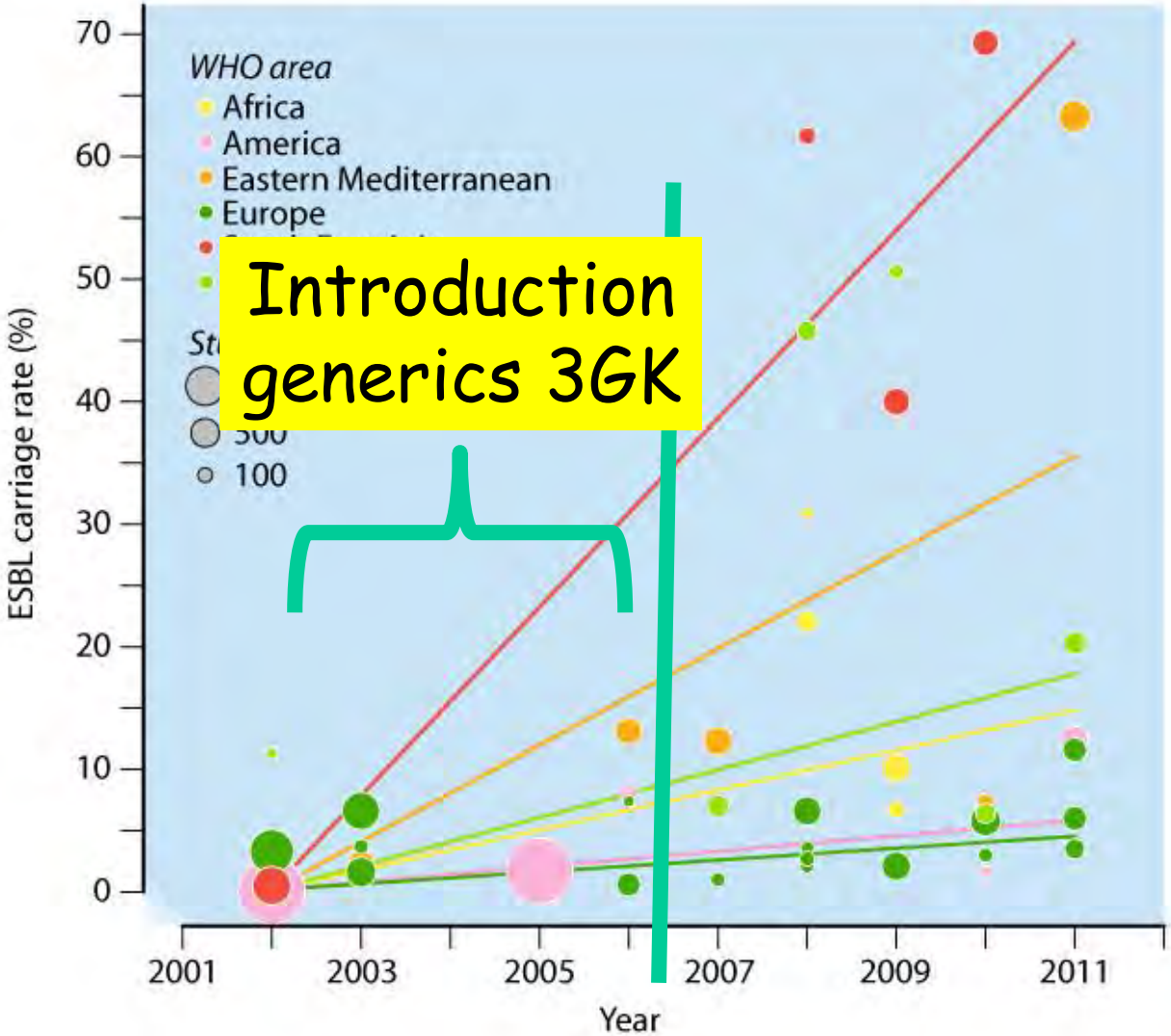

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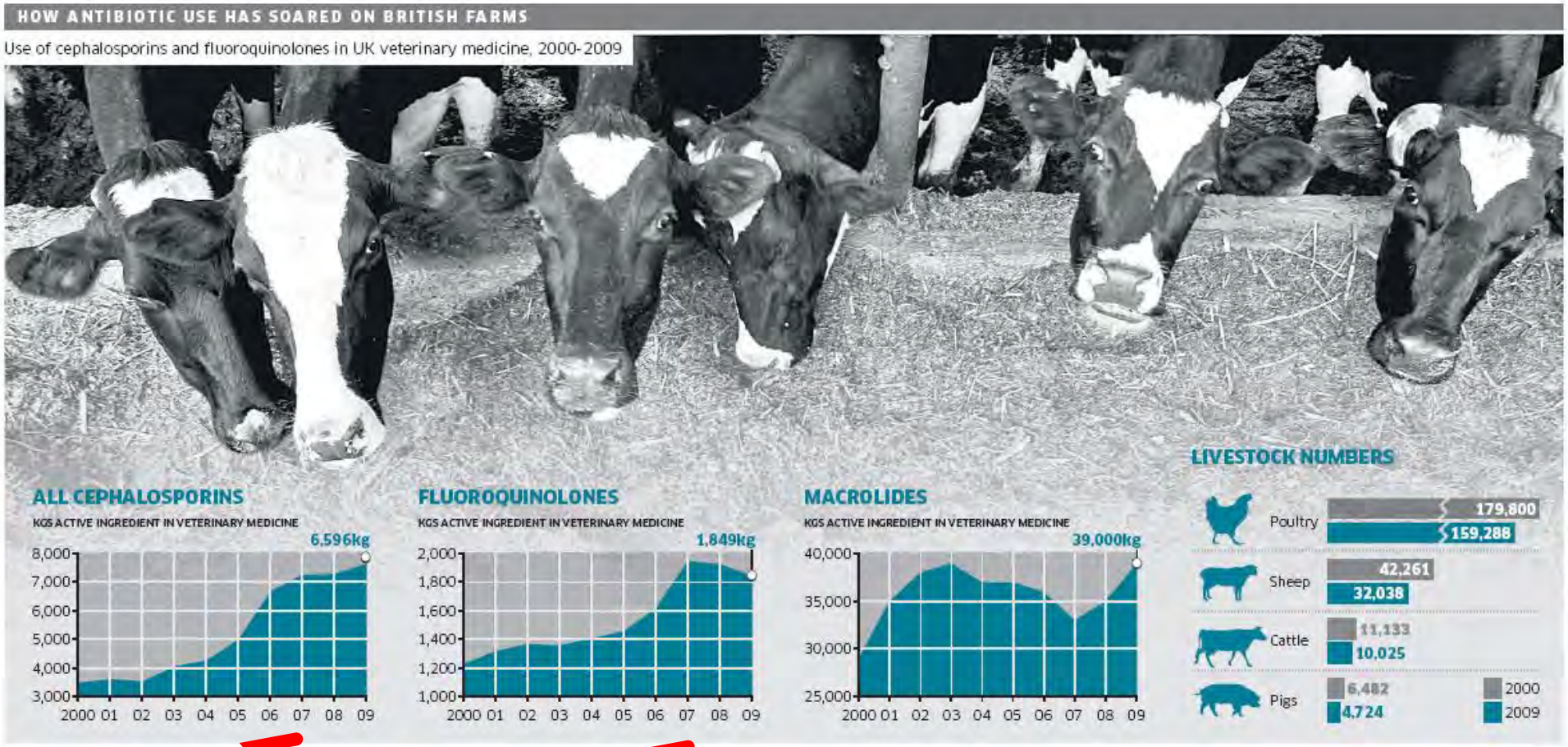
Figure: 01

Evolution of ESBL carriage rates in the community

La dynamique de la consommation animale : UK



THE INDEPENDENT

June 17, 2011

Global increase and geographic convergence in antibiotic consumption between 2000 and 2015

Eili Y. Klein[a,b,c,1], Thomas P. Van Boeckel[d], Elena M. Martinez[a], Suraj Pant[a], Sumanth Gandra[a], Simon A. Levin[e,f,g,1], Herman Goossens[h], and Ramanan Laxminarayan[a,f,i]

[a]Center for Disease Dynamics, Economics & Policy, Washington, DC 20005; [b]Department of Emergency Medicine, Johns Hopkins School of Medicine, Baltimore, MD 21209; [c]Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD 21205; [d]Institute of Integrative Biology, ETH Zürich, CH-8006 Zürich, Switzerland; [e]Department of Ecology and Evolutionary Biology, Princeton University, Princeton, NJ 08544; [f]Princeton Environmental Institute, Princeton University, Princeton, NJ 08544; [g]Beijer Institute of Ecological Economics, SE-104 05 Stockholm, Sweden; [h]Laboratory of Medical Microbiology, Vaccine & Infectious Diseases Institute, University of Antwerp, 2610 Antwerp, Belgium; and [i]Department of Global Health, University of Washington, Seattle, WA 98104

Contributed by Simon A. Levin, February 23, 2018 (sent for review October 3, 2017; reviewed by Bruce R. Levin and Dominique L. Monnet)

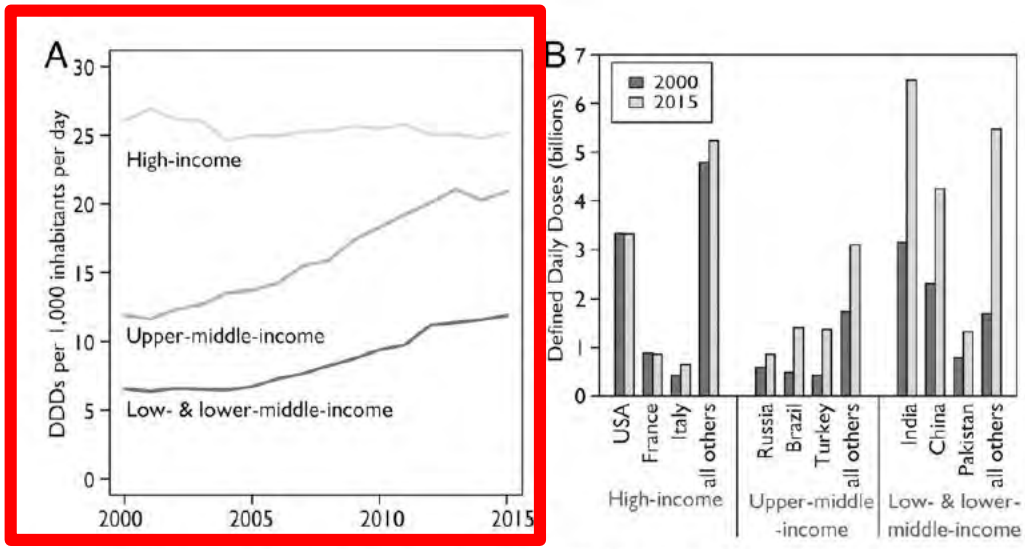


Fig. 2. Global antibiotic consumption by country income classification: 2000–2015. (*A*) Graph showing how the antibiotic consumption rate in DDDs per 1,000 inhabitants per day has rapidly increased for LMICs, while remaining nearly constant for HICs. However, as shown in *B*, the larger population sizes in many LMICs result in greater total antibiotic consumption (DDDs) in LMICs even though their consumption rate (and thus per capita use) is lower. In *B*, each bar reflects total consumption in the specified year for that country or group of countries. Data source: IQVIA MIDAS, 2000–2015, IQVIA Inc. All rights reserved (https://www.iqvia.com/solutions/commercialization/geographies/midas).

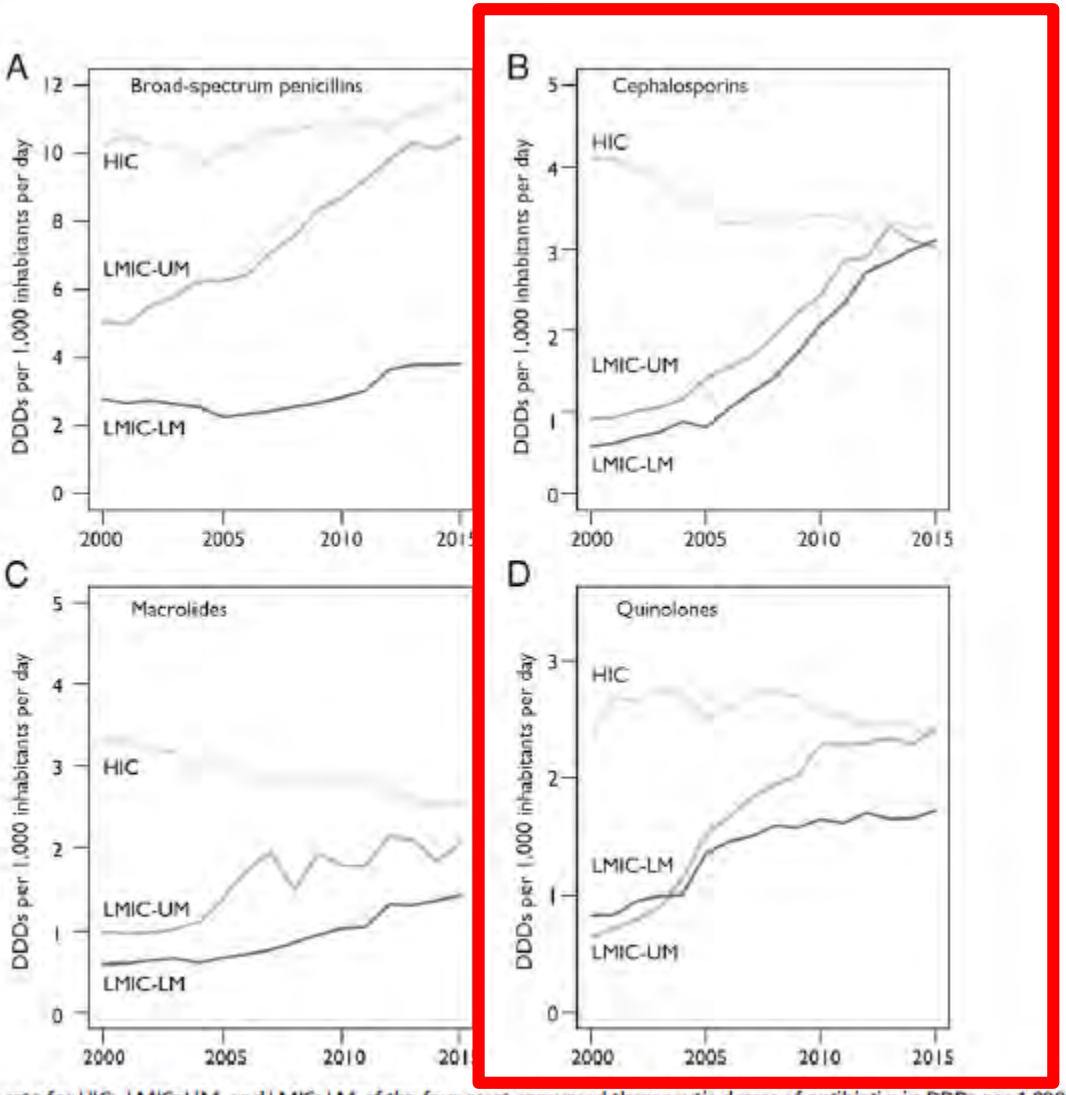


Fig. 3. Antibiotic consumption rate for HICs, LMICs-UM, and LMICs-LM of the four most-consumed therapeutic classes of antibiotics in DDDs per 1,000 inhabitants per day. (*A*) Broad-spectrum penicillins, which correspond to the Anatomical Therapeutic Chemical (ATC) classification of penicillins with extended spectrum (J01CA) excluding carbenicillins. (*B*) Cephalosporins, which correspond to the ATC classification codes J01DB, J01DC, J01DD, and J01DE for the four generations of cephalosporins. (*C*) Macrolides, which correspond to the ATC classification for macrolides, lincosamides, and streptogramins (J01F). (*D*) Quinolones, which correspond to the ATC classification for quinolone antibacterials (J01M). Data source: IQVIA MIDAS, 2000–2015, IQVIA Inc. All rights reserved (https://www.iqvia.com/solutions/commercialization/geographies/midas).

Because E-ESBL are only susceptible to carbapenems

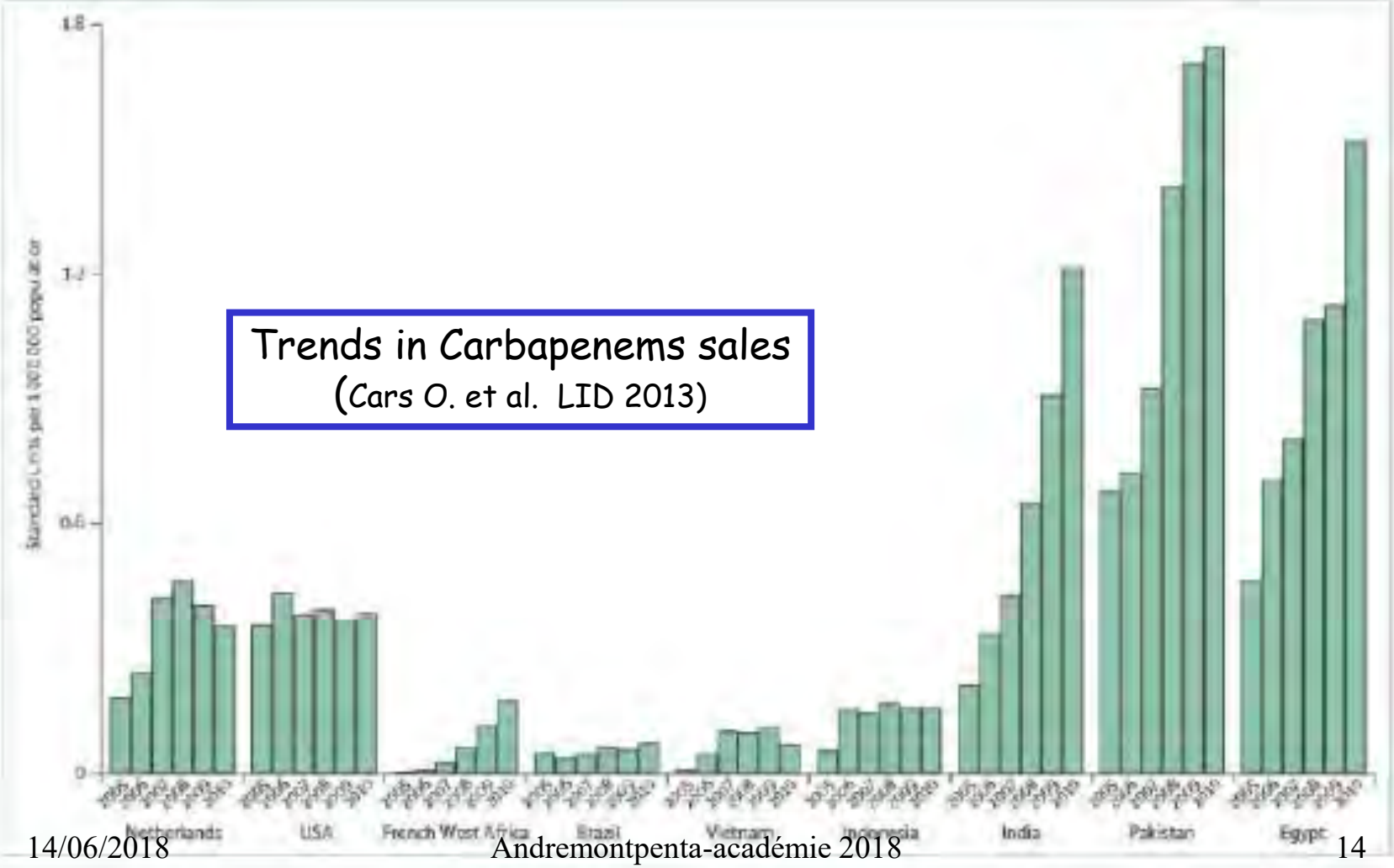
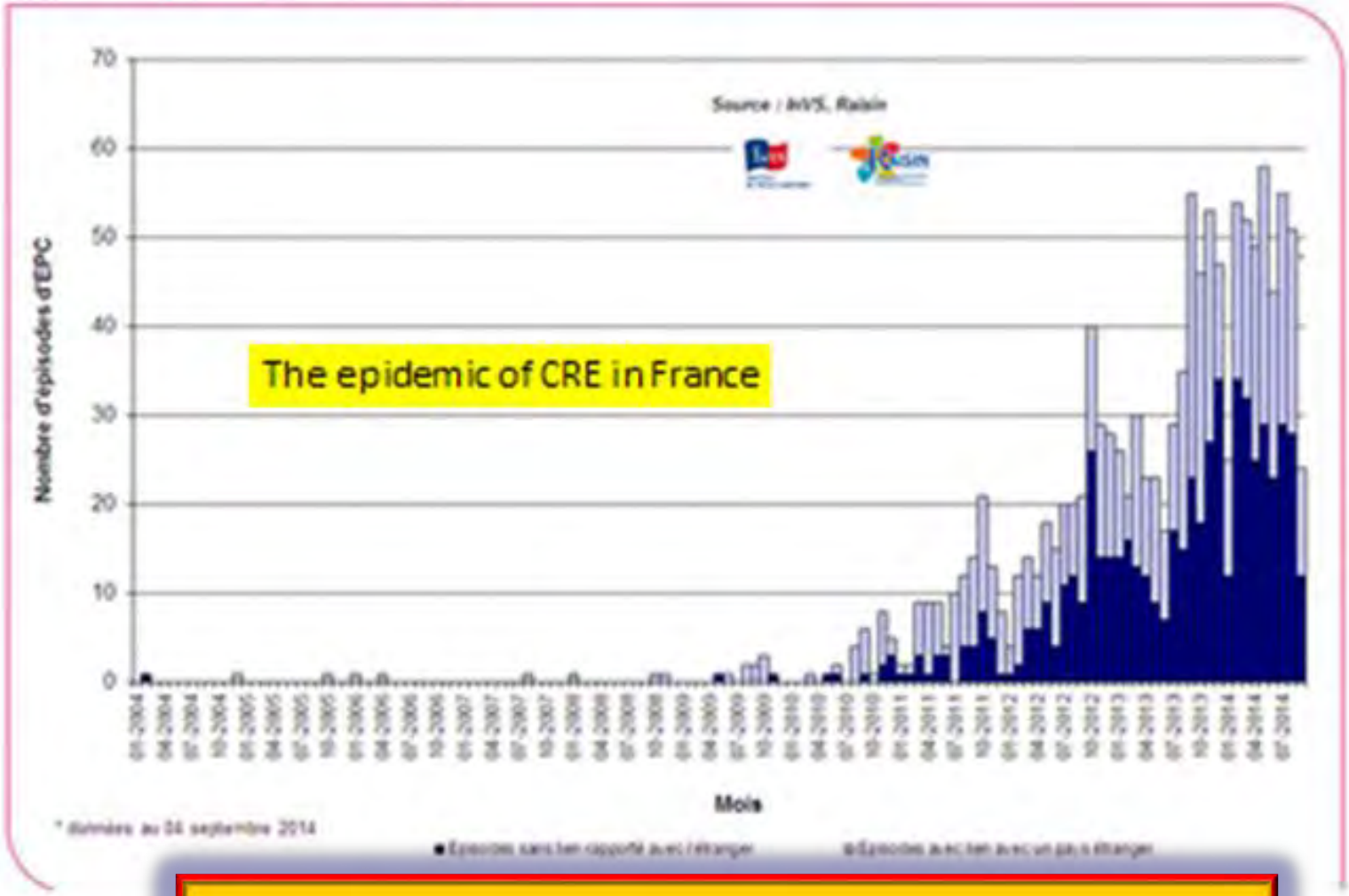


Figure 1 - Nombre d'épisodes impliquant des entérobactéries productrices de carbapénèmases en France signalés à l'InVS entre janvier 2004 et le 04 septembre 2014, selon la mise en évidence ou non d'un lien avec un pays étranger (N=1210).



Last line treatment is now colistin

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

Lancet Infect Dis 2015
Published Online
November 18, 2015

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,

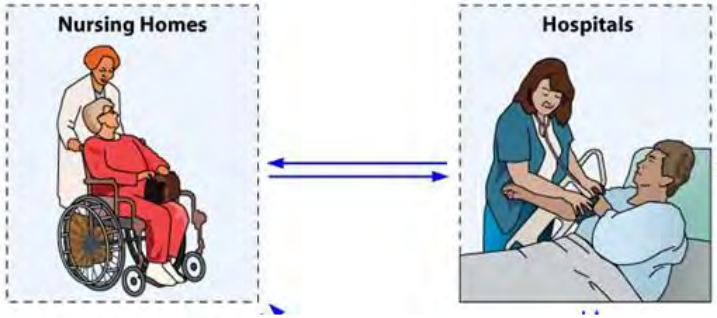
Colistin resistance: a major breach in our last line of defence

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 many Gram-negative bacilli. Colistin resistant and

Liu and colleagues[4] 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 use in agriculture. This will require substantial political

AP Photo

Lancet Infect Dis 2015
Published Online
November 18, 2015



From a medical view of bacterial resistance

ASM Journals
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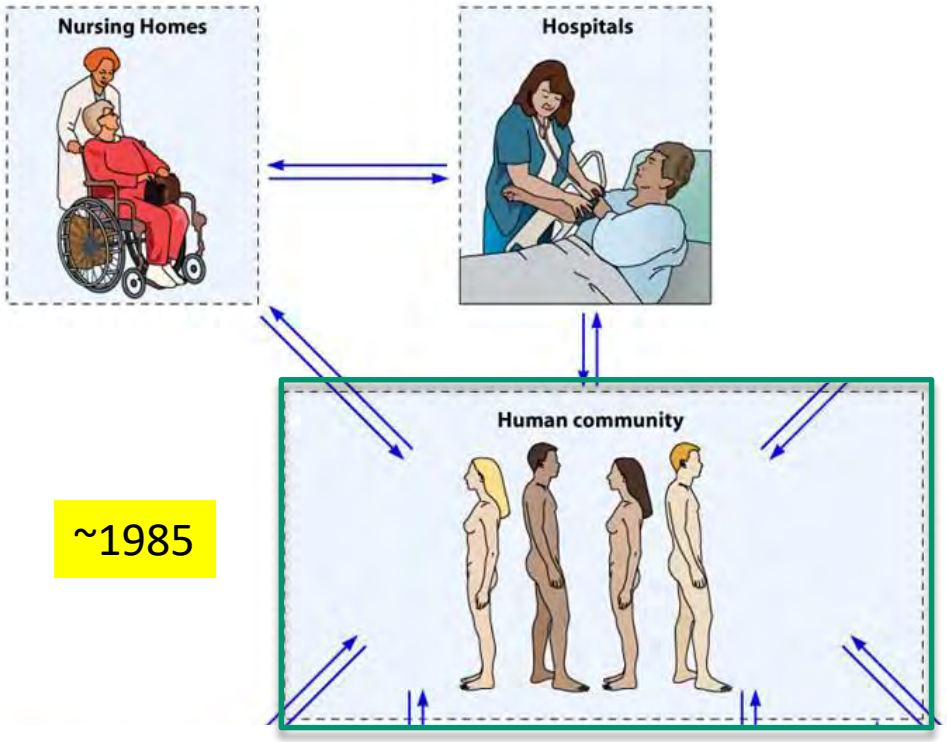
Figure: 02

Woerther et al. CMR 2012



~1985

From a medical view of bacterial resistance

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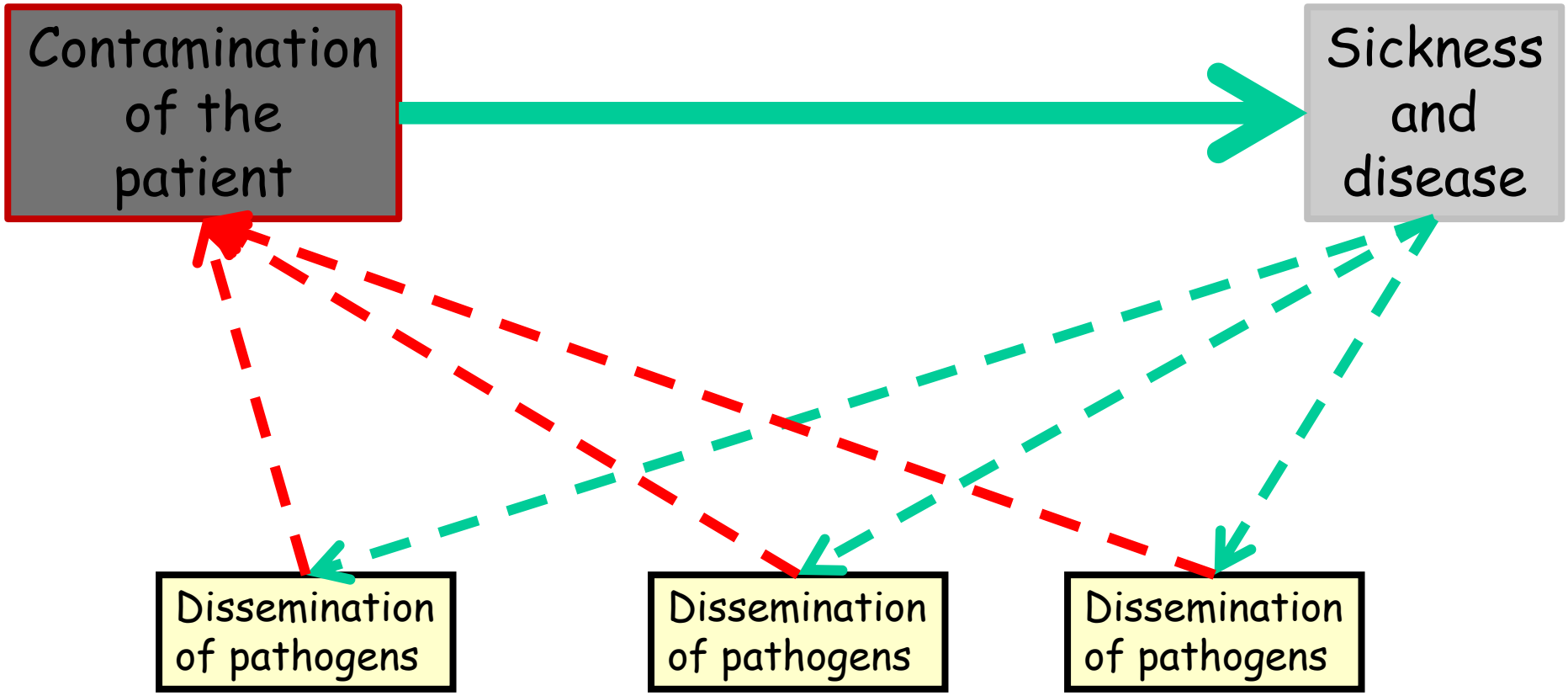
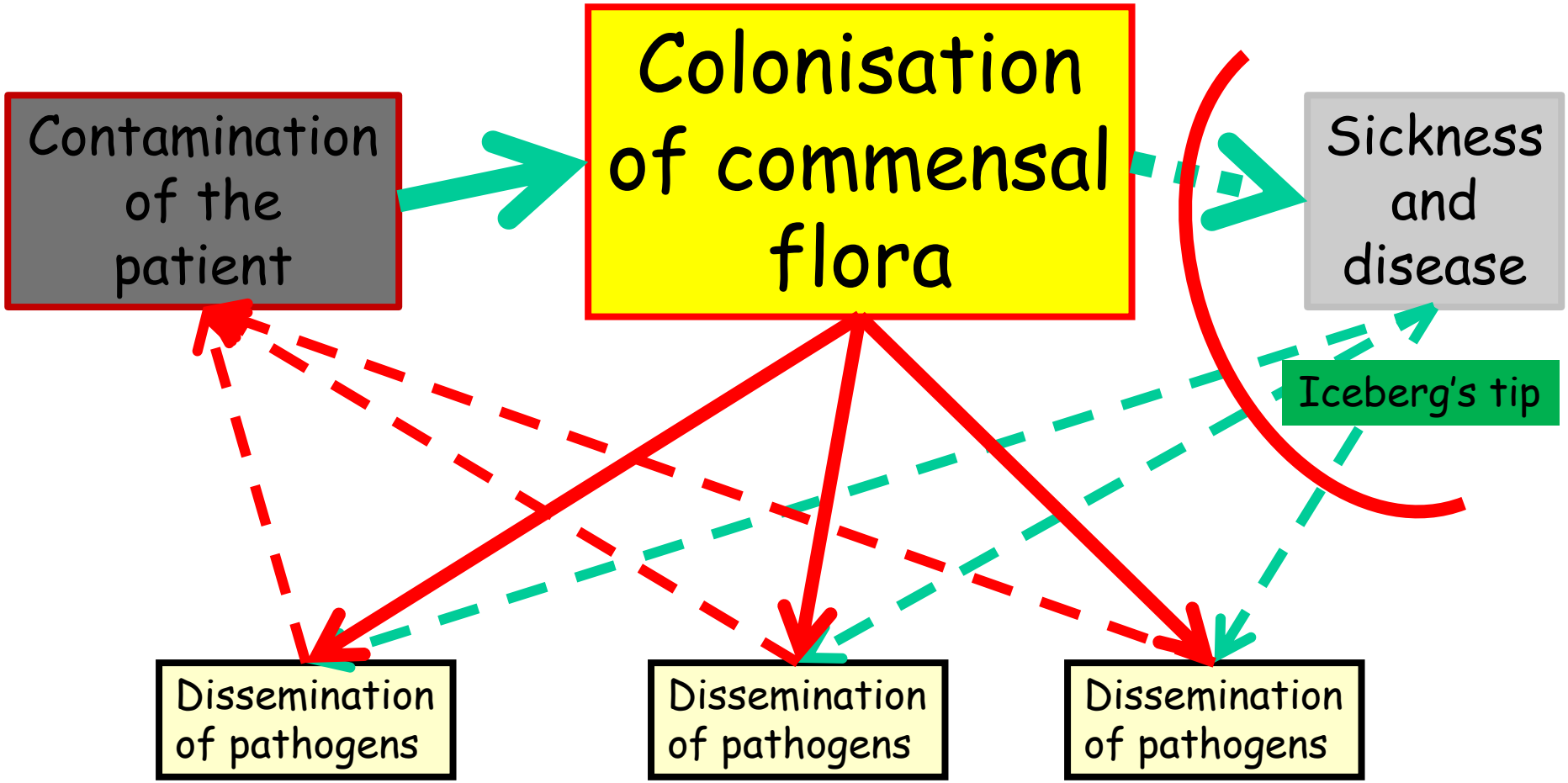
Figure: 02

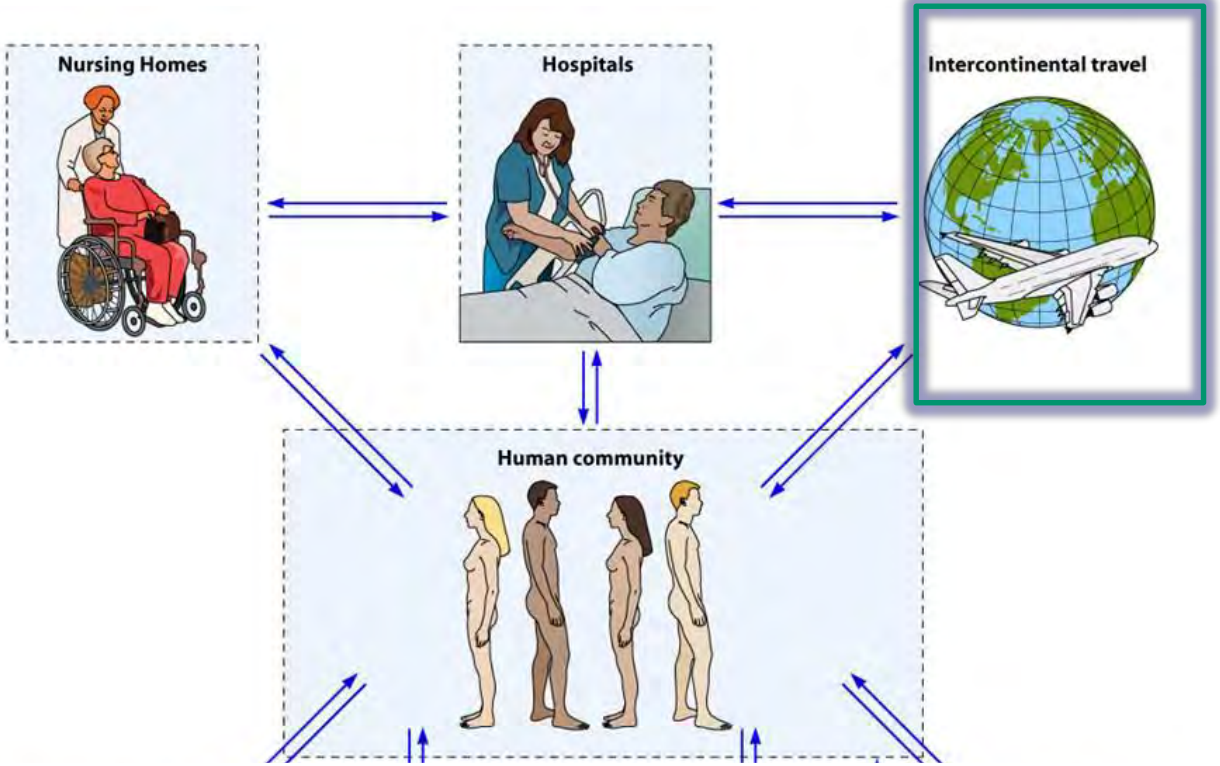
Woerther et al. CMR 2012

« Classical » natural history of bacterial infections



« New » natural history of bacterial infections





~1990

From a medical view of bacterial resistance

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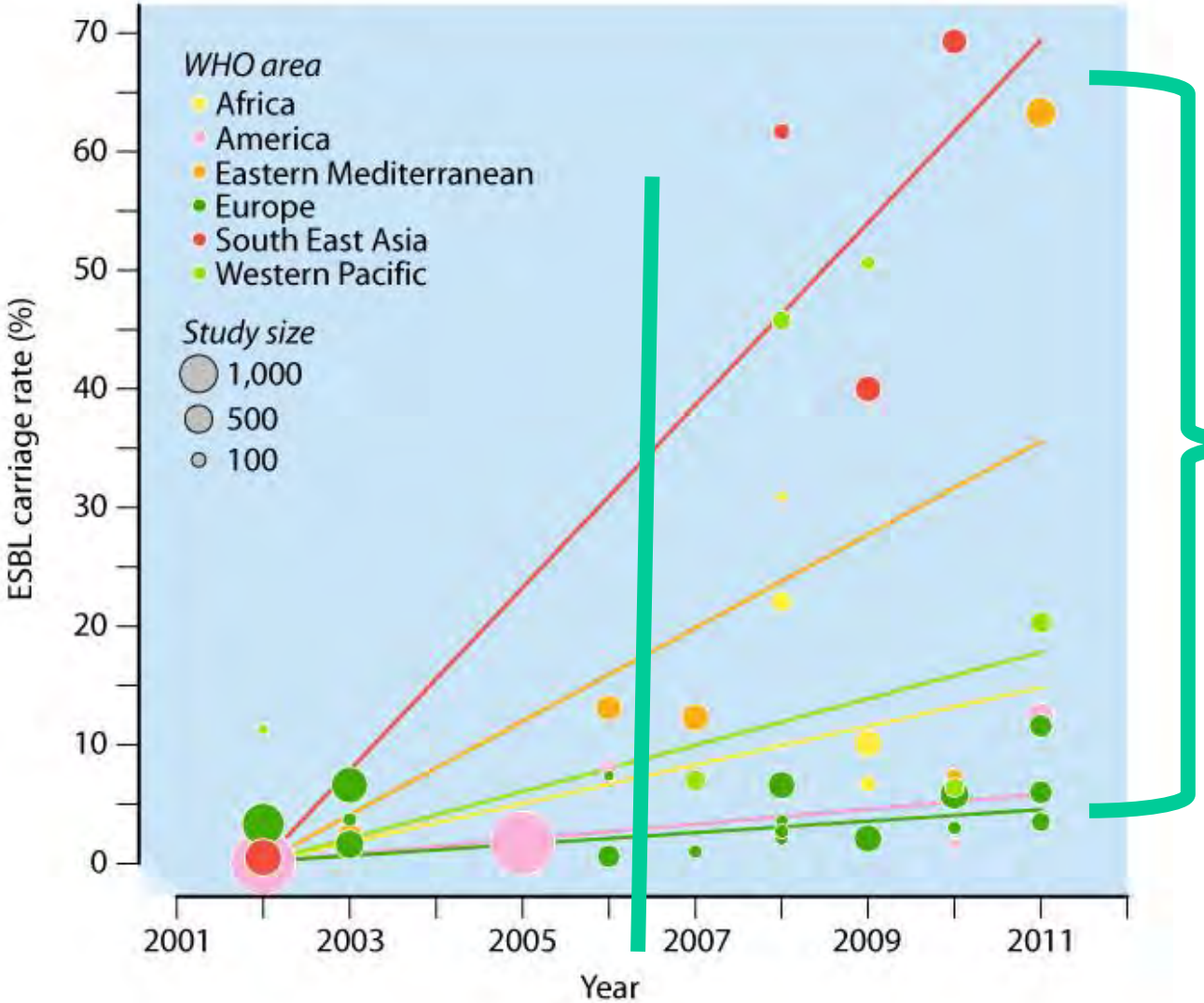

Gap between EU and the « South »

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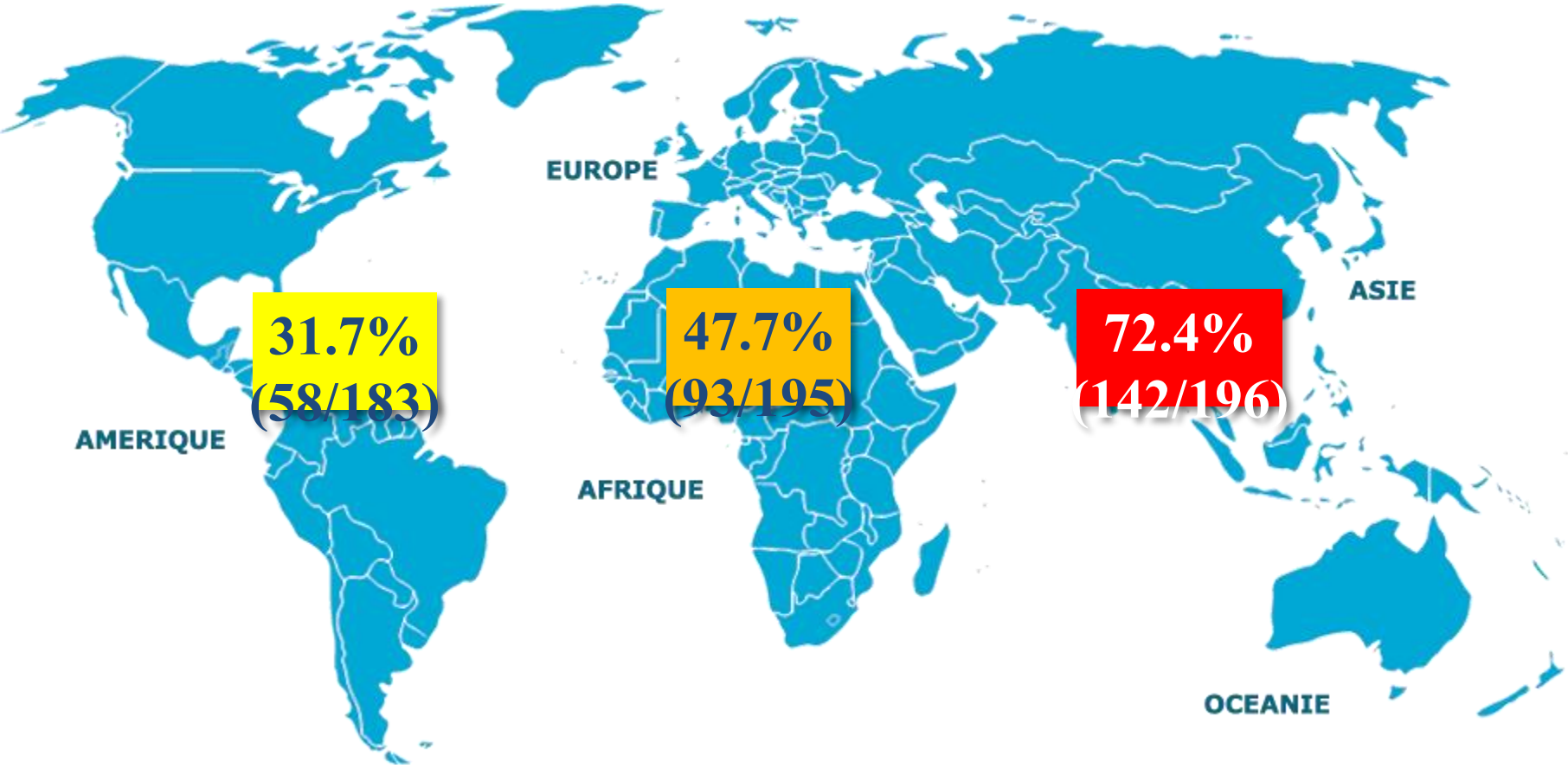
Figure: 01

Evolution of ESBL carriage rates in the community

574 travellers in intertropical zones
Global acquisition rate: 51% (n=293)



Ruppe, et al. CID 2015

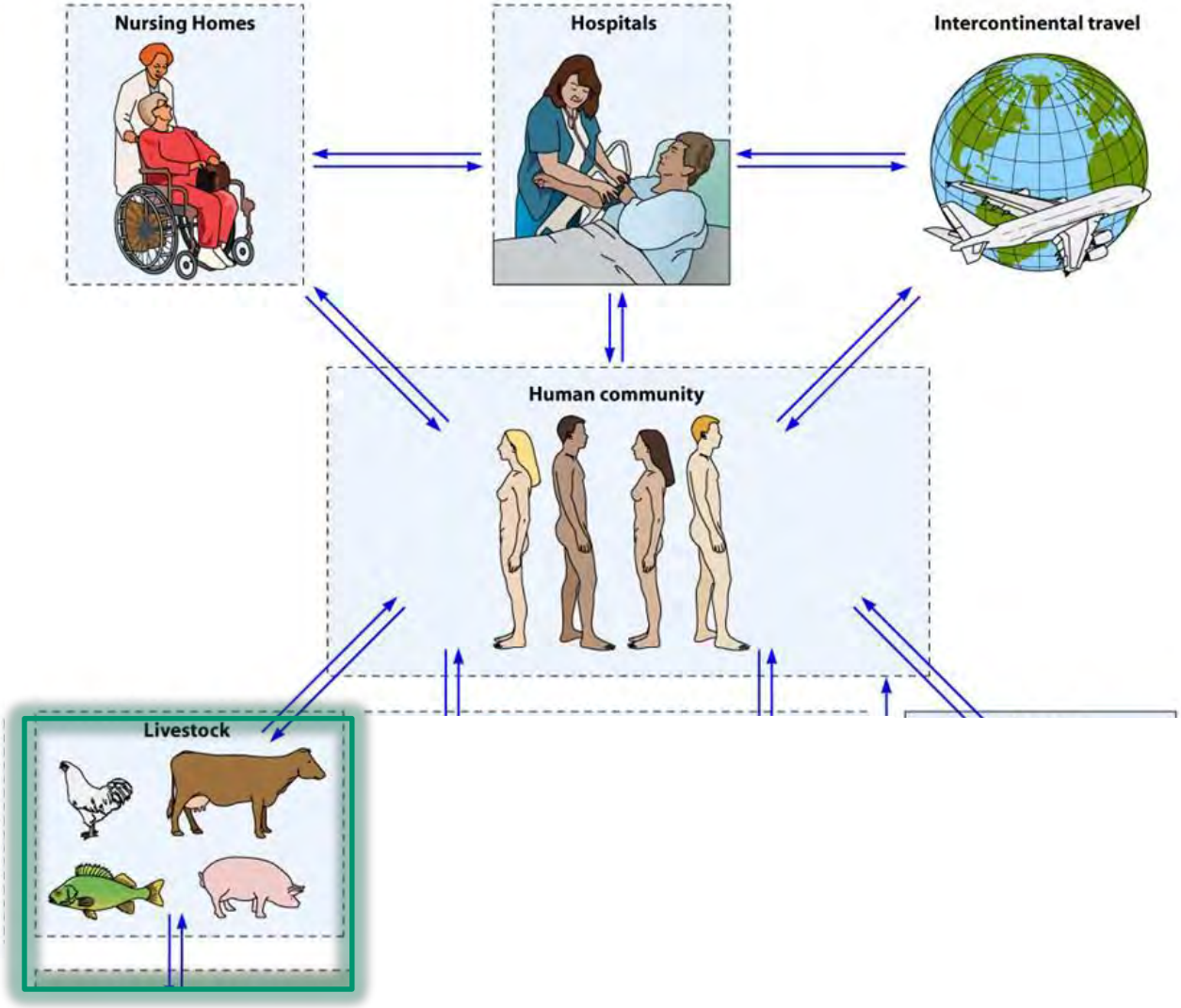


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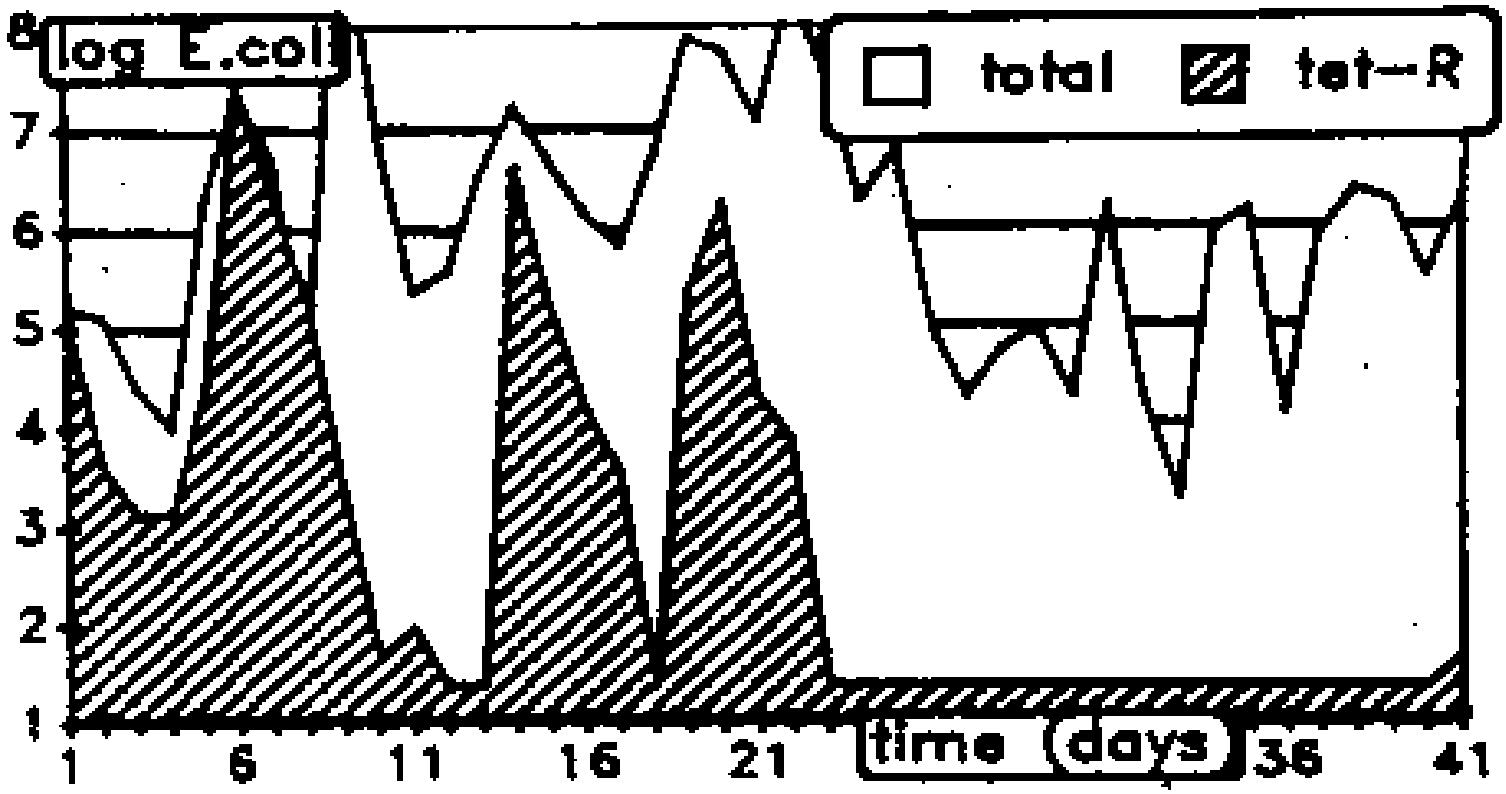
Figure: 02

From a medical view of bacterial resistance

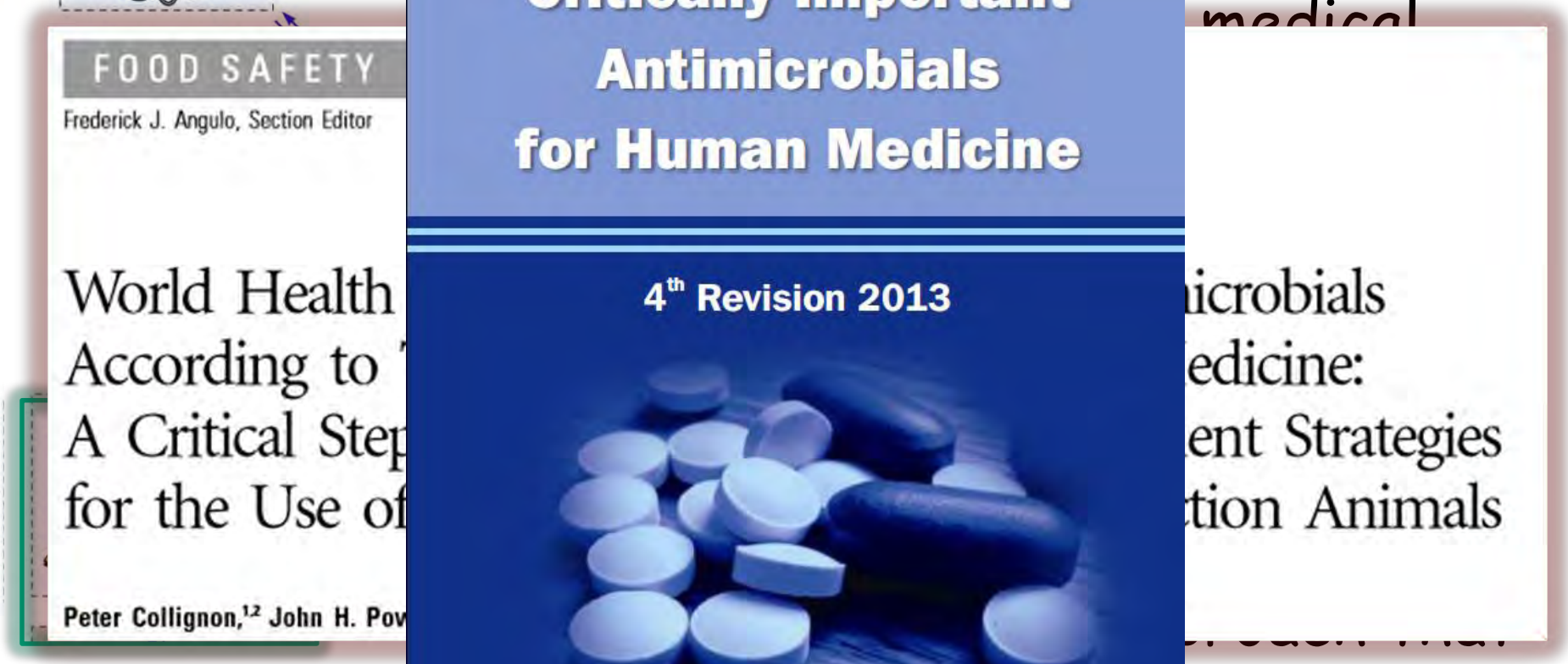
To the « one health » approach that includes the animal world

Influence de l'alimentation stérile (■) ou normale (■) sur la concentration des entérobactéries résistantes dans la flore intestinale de volontaires.



Normale | Sterile

Corpet D. *et al.* Vet. Microbiol. 1993, 35:199



From a
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Figure: 02

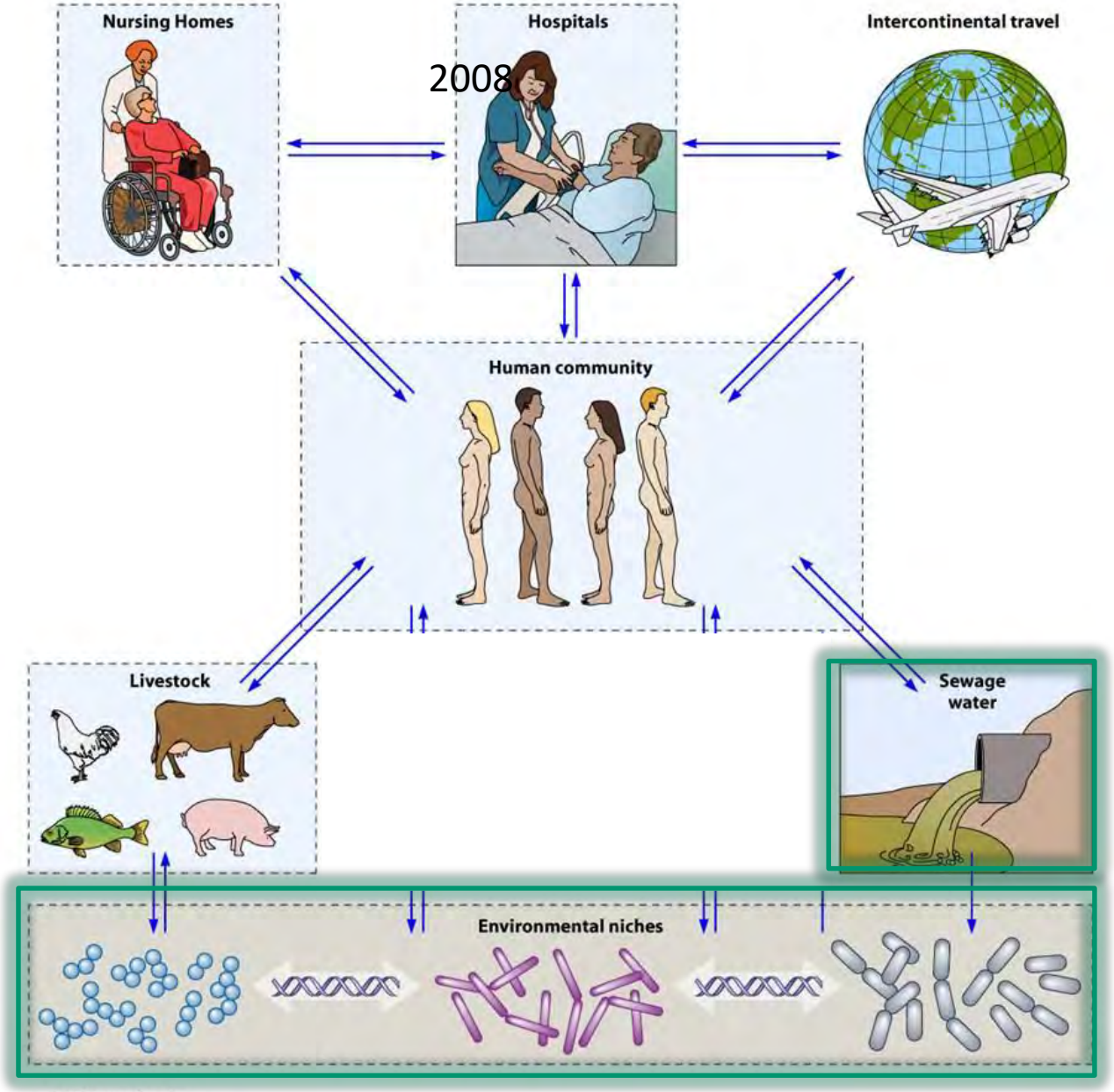

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Figure: 02

From a medical view of bacterial resistance

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

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

Effluent from drug manufactures contains extremely high levels of pharmaceuticals

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

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.

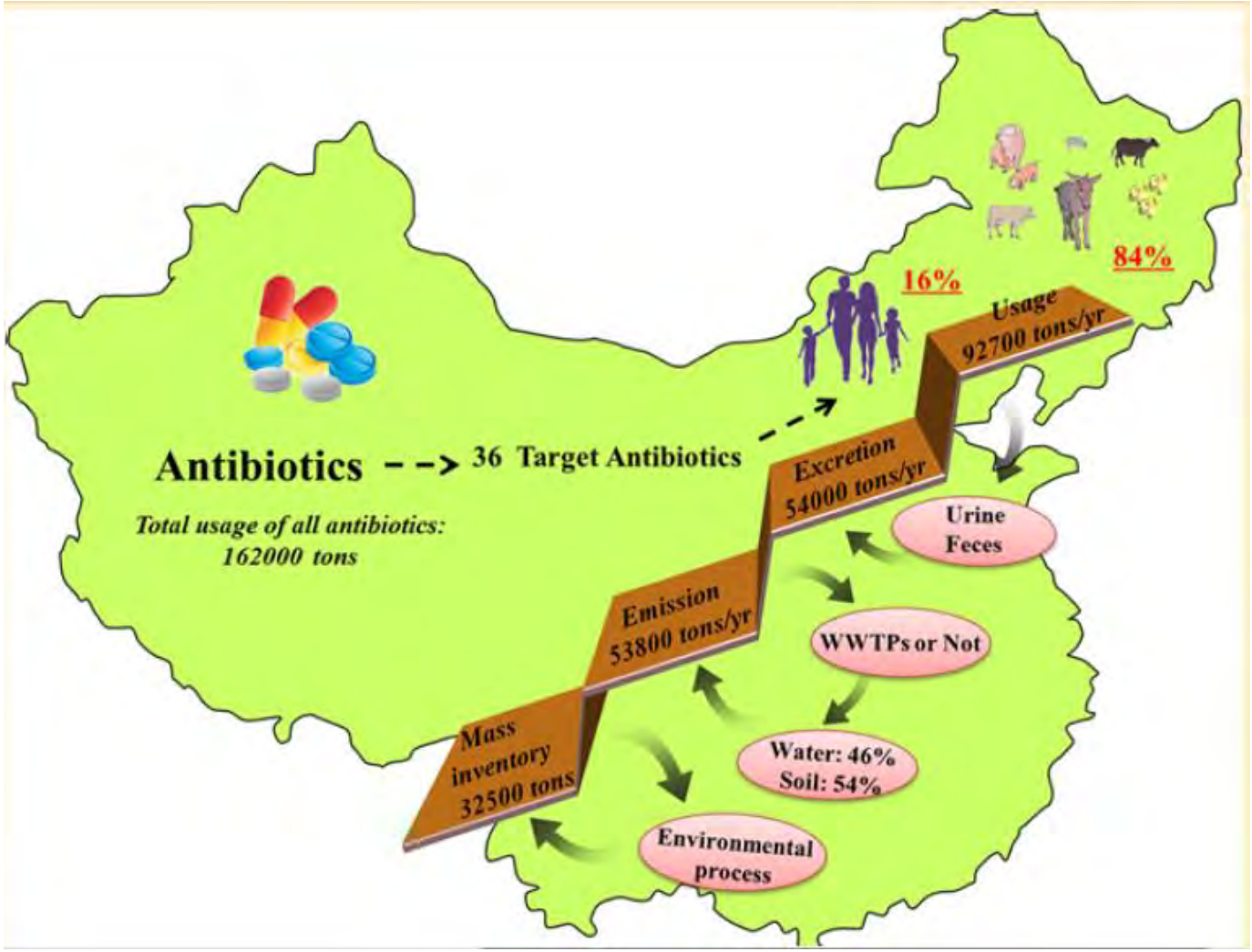
Comprehensive Evaluation of Antibiotics Emission and Fate in the River Basins of China: Source Analysis, Multimedia Modeling, and Linkage to Bacterial Resistance

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

		usage (tons)				
country	year	total	human	animals	DID[a]	ref
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	*b*	251	*b*	20.4	60
Europe	2003	*b*	3440	*b*	20.1	32

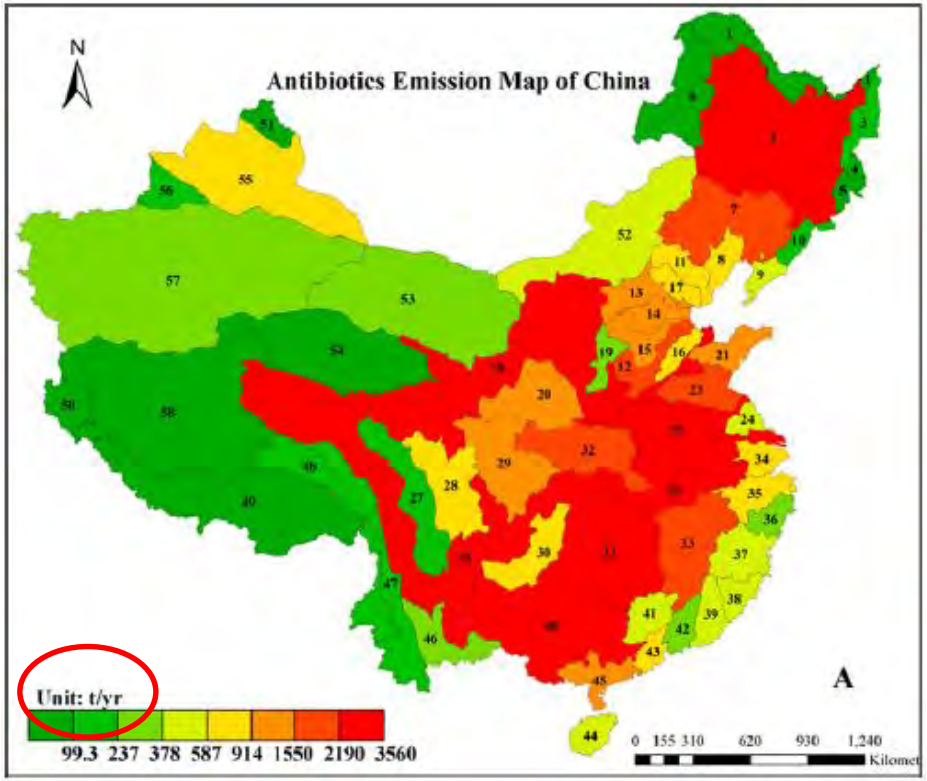
Zhang QQ. Environ. Sci. Tech. 2015

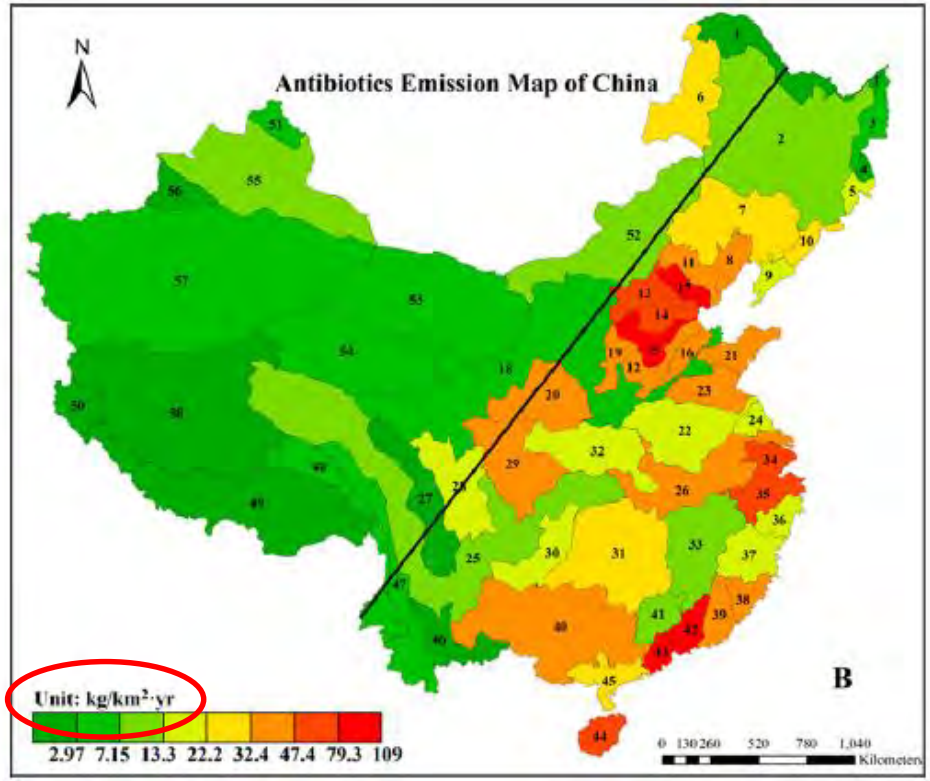
Comprehensive Evaluation of Antibiotics Emission and Fate in the River Basins of China: Source Analysis, Multimedia Modeling, and Linkage to Bacterial Resistance



Zhang QQ. Environ. Sci. Tech. 2015

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

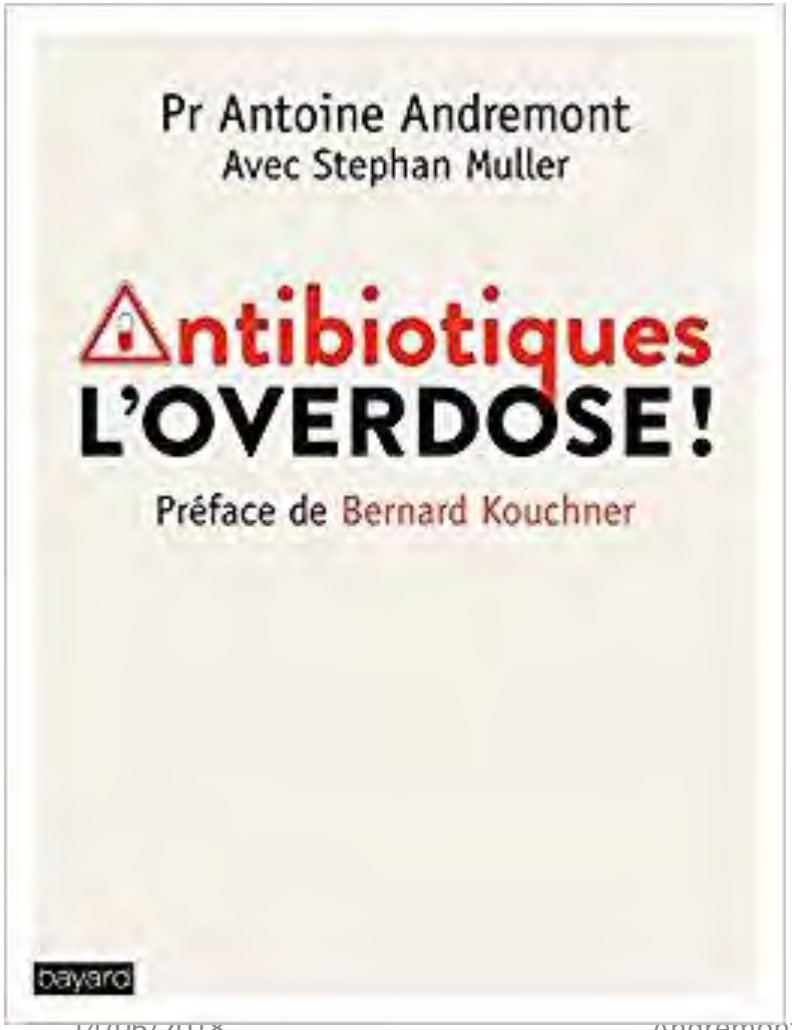




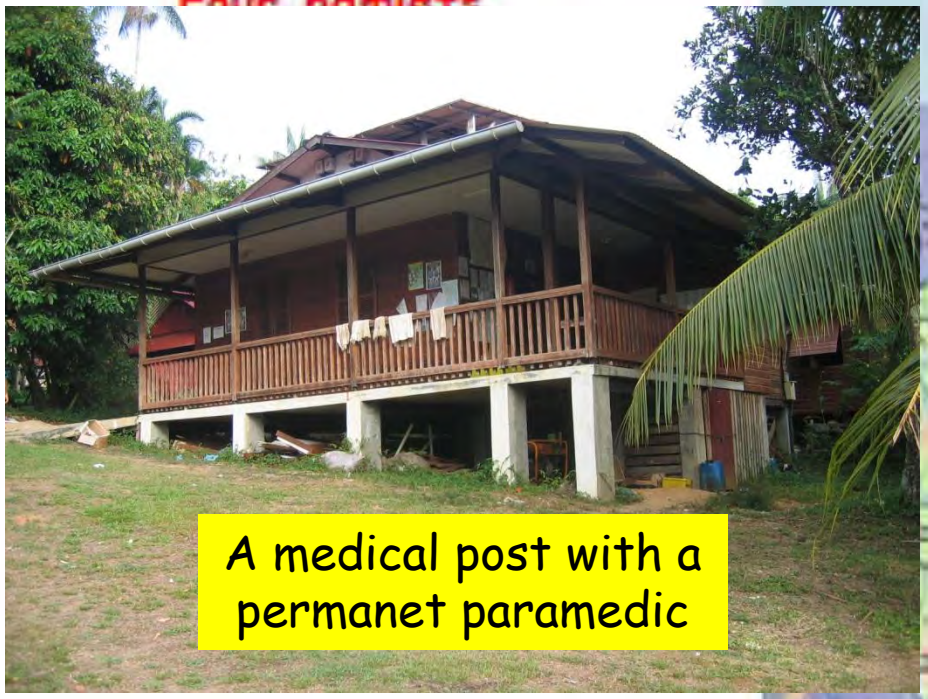
t/Y

Kg/Km^2/Y

D'où le titre :



Diminuer la pression de sélection :
Par de meilleures pratiques
Préserver les écosystèmes



~500 amerindians still living in a traditionnal manner

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

2°15'0.99"N, 52°52'58.99"W

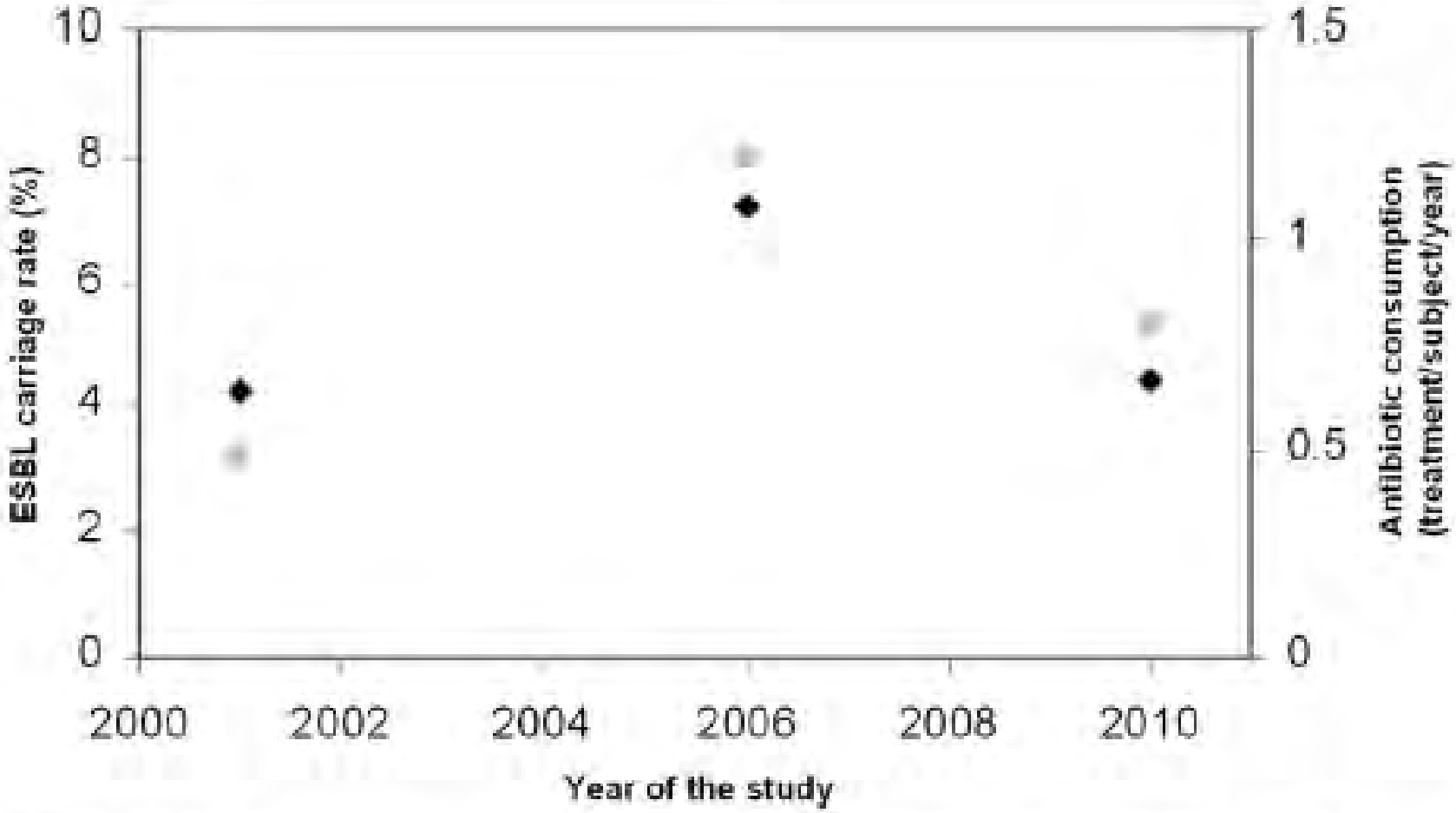


FIG 1 ESBL-E carriage rate in Wayampi volunteers (gray squares) and overall antibiotic exposure of the whole community (black diamonds) in 2001, 2006, and 2010. Linear regression ($y = 8.675x - 1.396$; $R^2 = 0.87$) and Pearson's correlation ($P = 0.24$) were used to evaluate the evolution.

Woerther PL *et al.*, AAC 201


MARAN 2015
Monitoring of Antimicrobial Resistance
and Antibiotic Usage in Animals
in the Netherlands in 2014

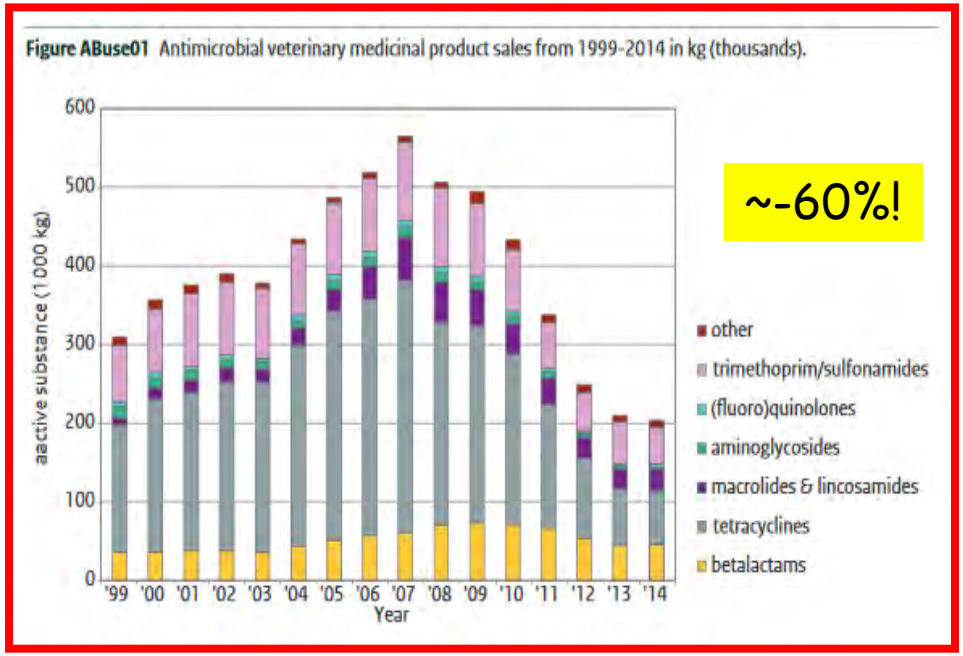


Figure ABuse01 Antimicrobial veterinary medicinal product sales from 1999-2014 in kg (thousands).
~-60%!
aactive substance (1 000 kg)
Year
other
trimethoprim/sulfonamides
(fluoro)quinolones
aminoglycosides
macrolides & lincosamides
tetracyclines
betalactams

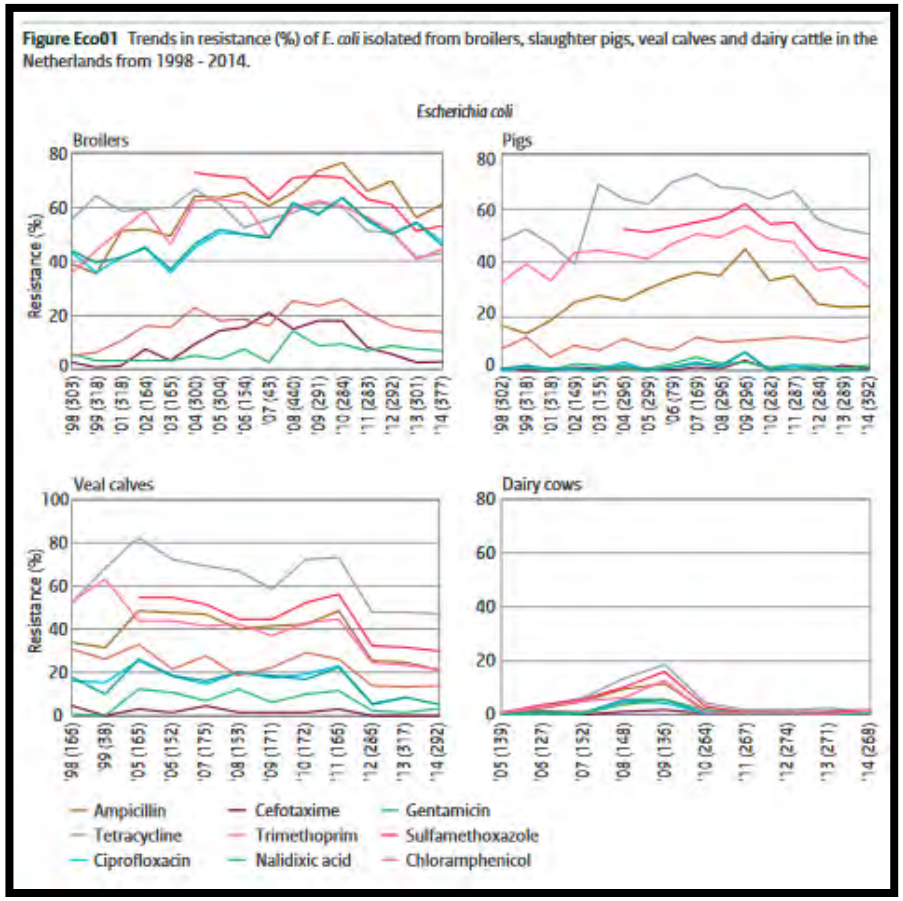
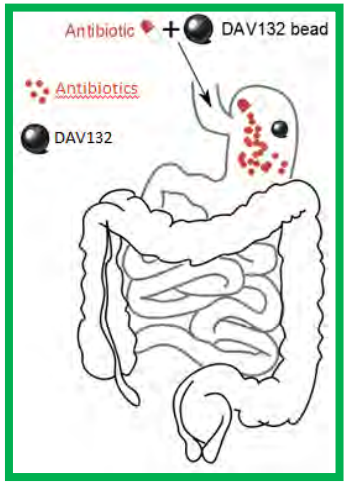
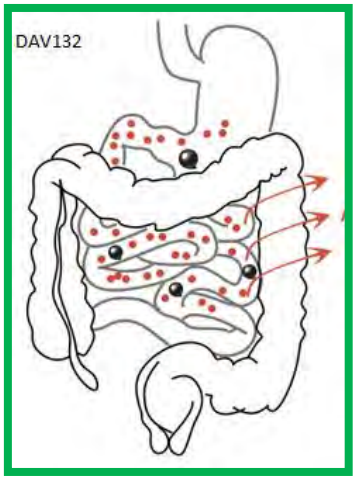
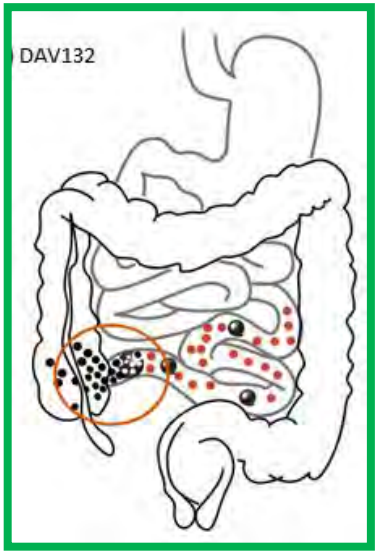


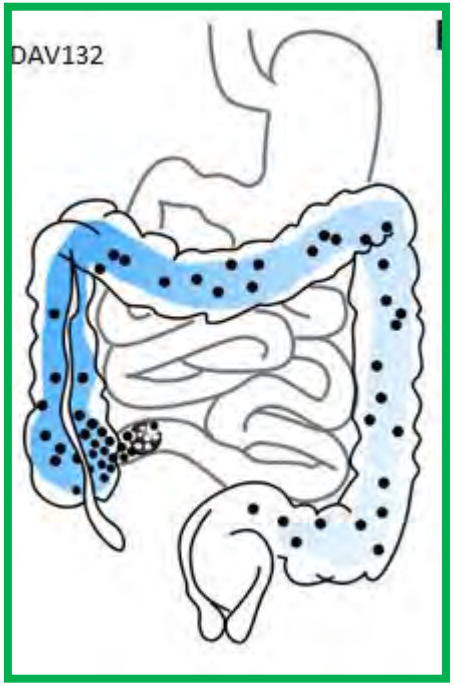
Figure Eco01 Trends in resistance (%) of E. coli isolated from broilers, slaughter pigs, veal calves and dairy cattle in the Netherlands from 1998 - 2014.
Escherichia coli
Broilers
Pigs
Veal calves
Dairy cows
Resistance (%)
Ampicillin
Cefotaxime
Gentamicin
Tetracycline
Trimethoprim
Sulfamethoxazole
Ciprofloxacin
Nalidixic acid
Chloramphenicol

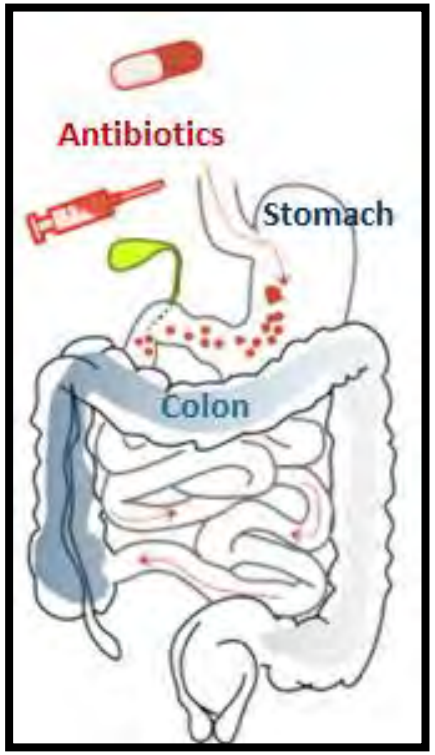
Protéger le microbiote intestinal au cours des traitements











DAV132 reduces fecal moxifloxacin concentrations and the impact on the microbiota while sparing the blood concentrations.

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

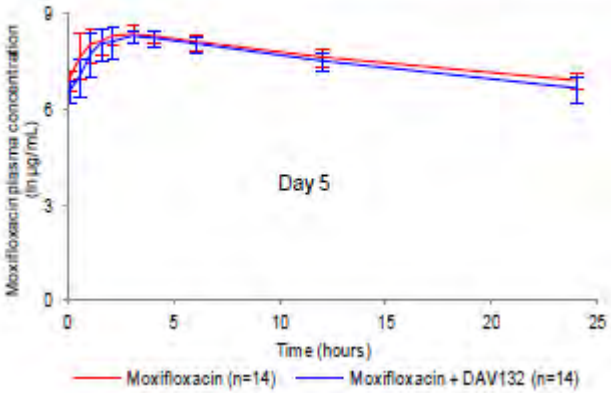


Figure 1: Free MOX fecal concentration (mean ± SD) over D1-D16 (LOQ 40 ng/g; MOX MIC for Enterobacteriaceae 0.5 µg/mL)

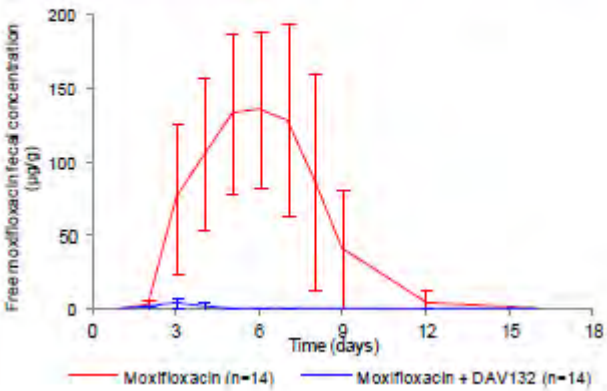
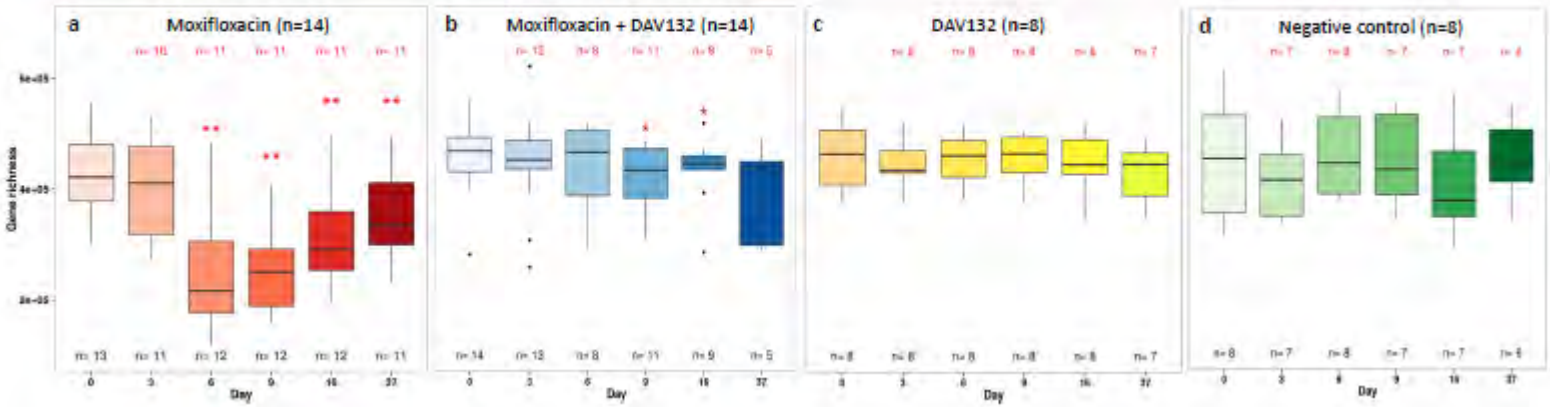


Figure 3: Normalized microbiome gene richness ratio (median, quartiles, 1.5 interquartile range, and outliers) from D1 to D37 in subjects treated with (a) MOX, (b) MOX+DAV132, (c) DAV132, and (d) negative control.



Merci beaucoup pour votre attention.