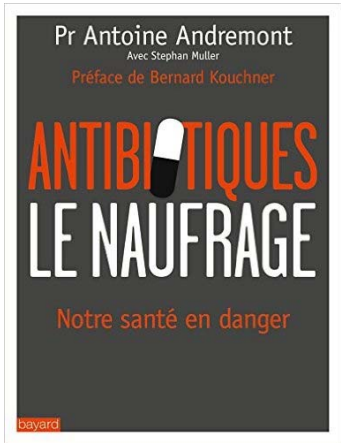
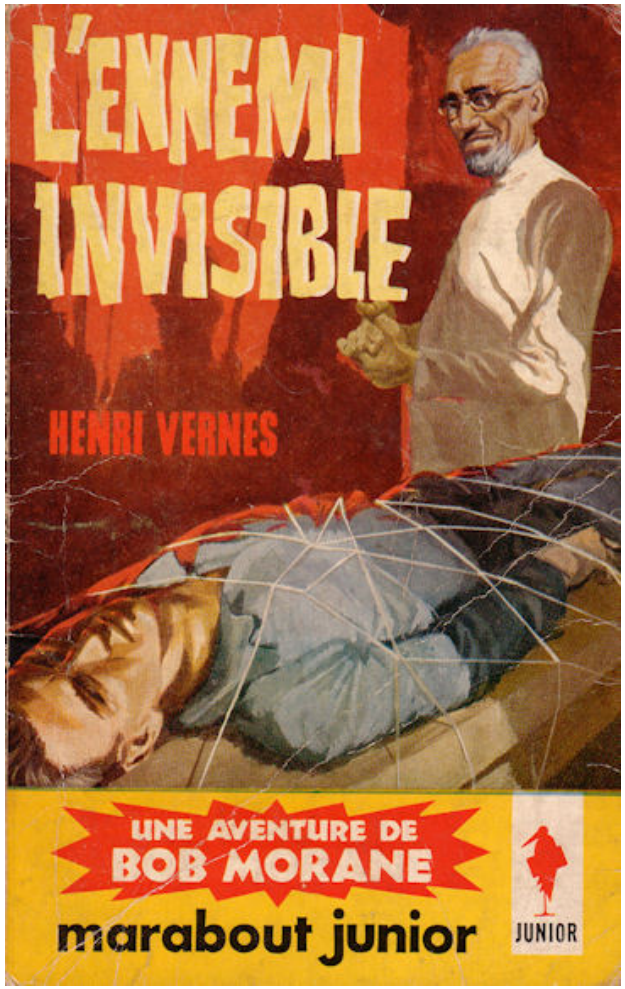
Comprendre la montée des résistances bactériennes et les remèdes proposés pour y remédier!



Antoine Andremont

Faculté de médecine Paris Diderot

LI: DaVolterra (LIR)



- Tout le monde la craint, mais bien peu la voit…
- La mortalité due à la résistance est « encore » très faible, du moins ici…

March 11, 2013, G8 Submit UK

The INDEPENDENT

NEWS | VOICES | SPORT | TECH | LIFE | PROPERTY | ARTS & ENTS | TRAVEL | MONEY | IND

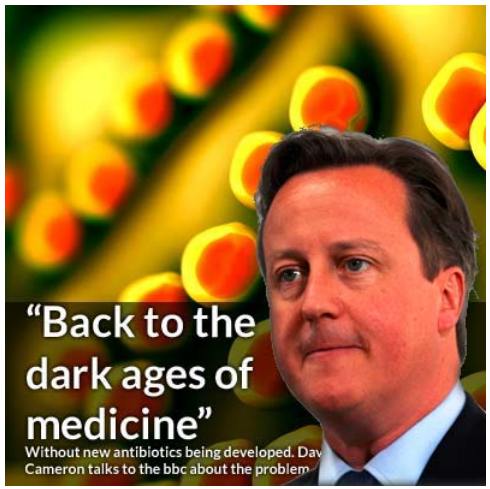
UK | World | Business | People | Science | Environment | Media | Technology | Education | Obituaries | Diary

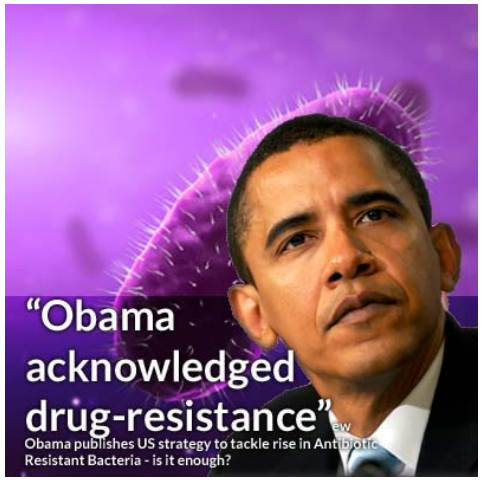
News > Science

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

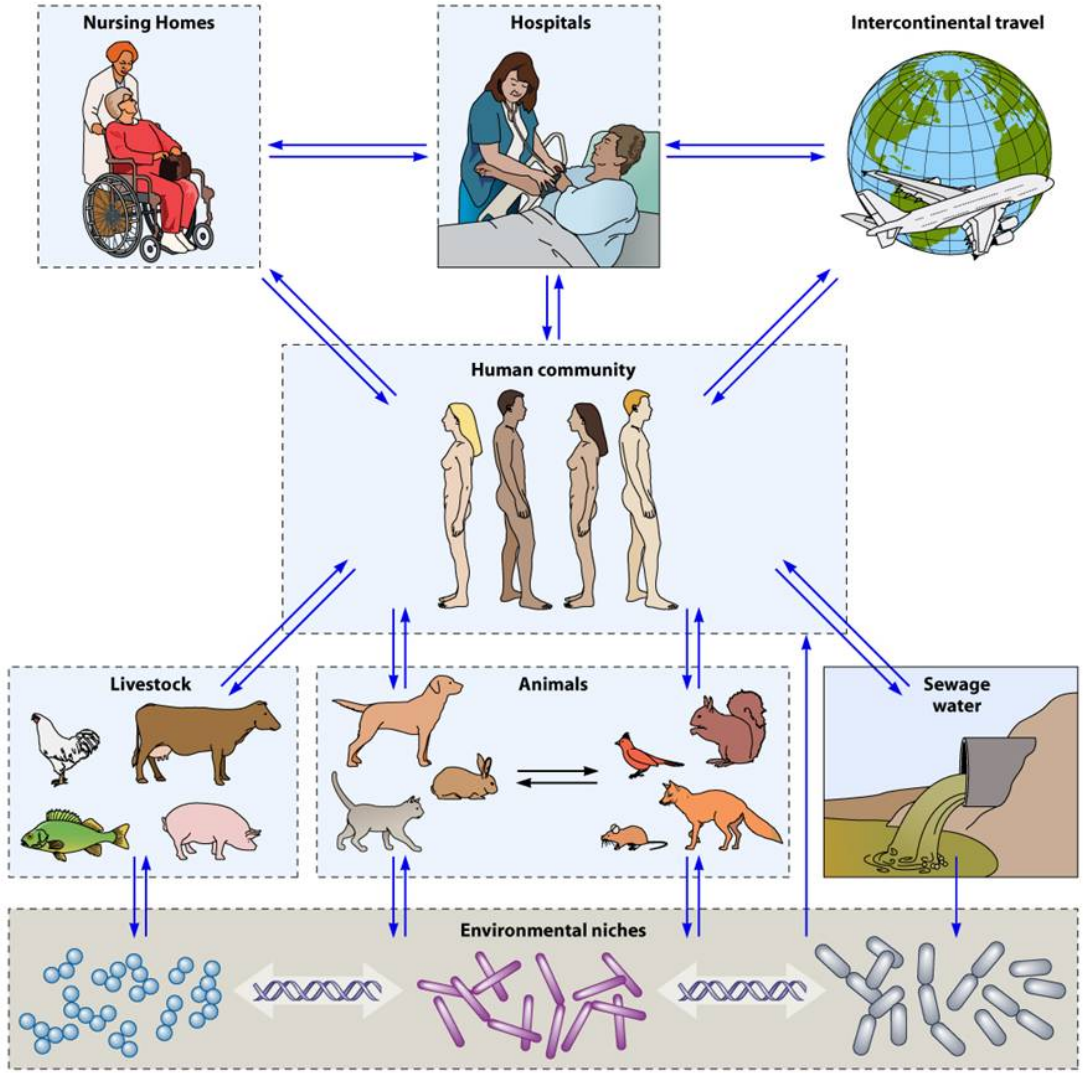
Transatlantic Taskforce on Antimicrobial Resistance (TATFAR)

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:



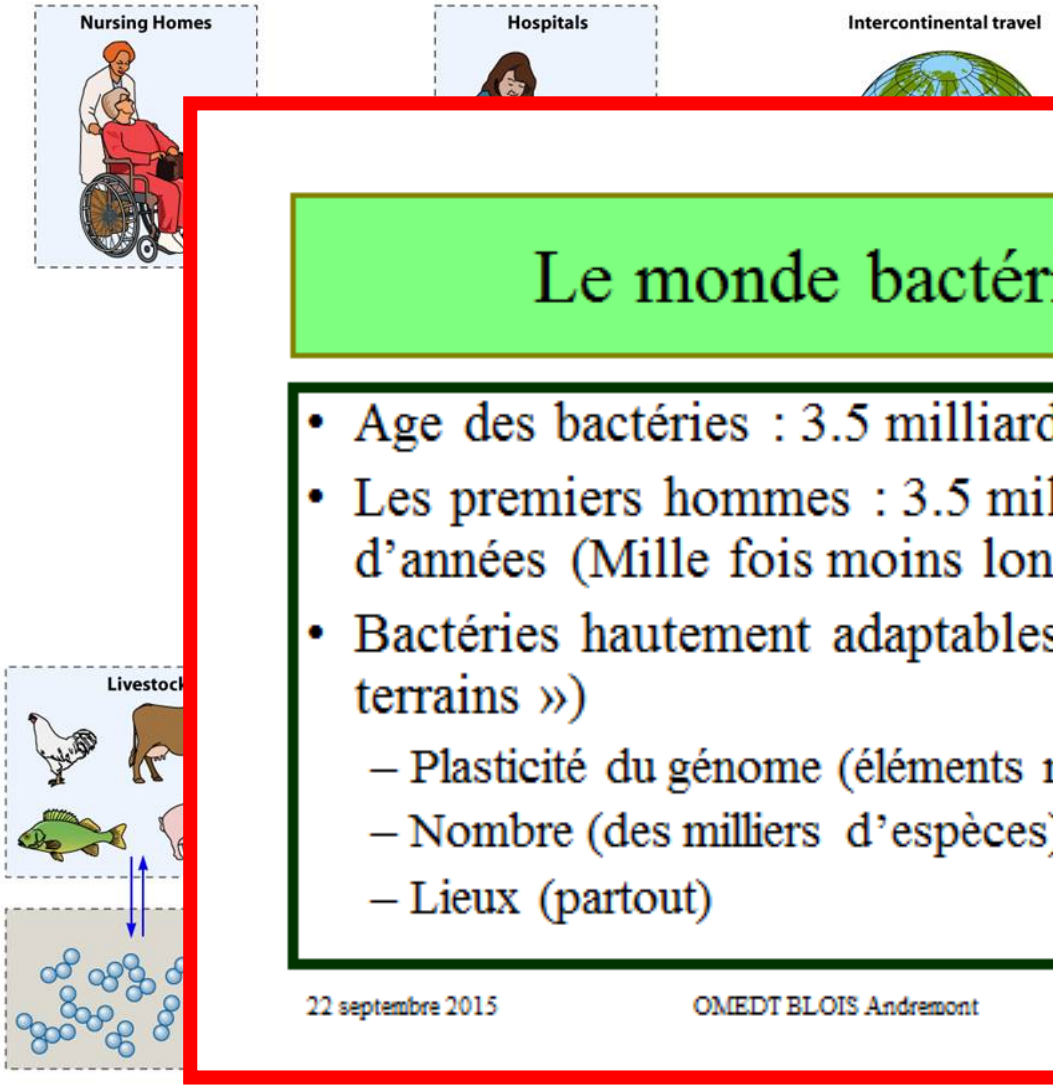


Demain 23 Septembre, peut-être, Marisol Touraine ?



From a medical view of bacterial resistance

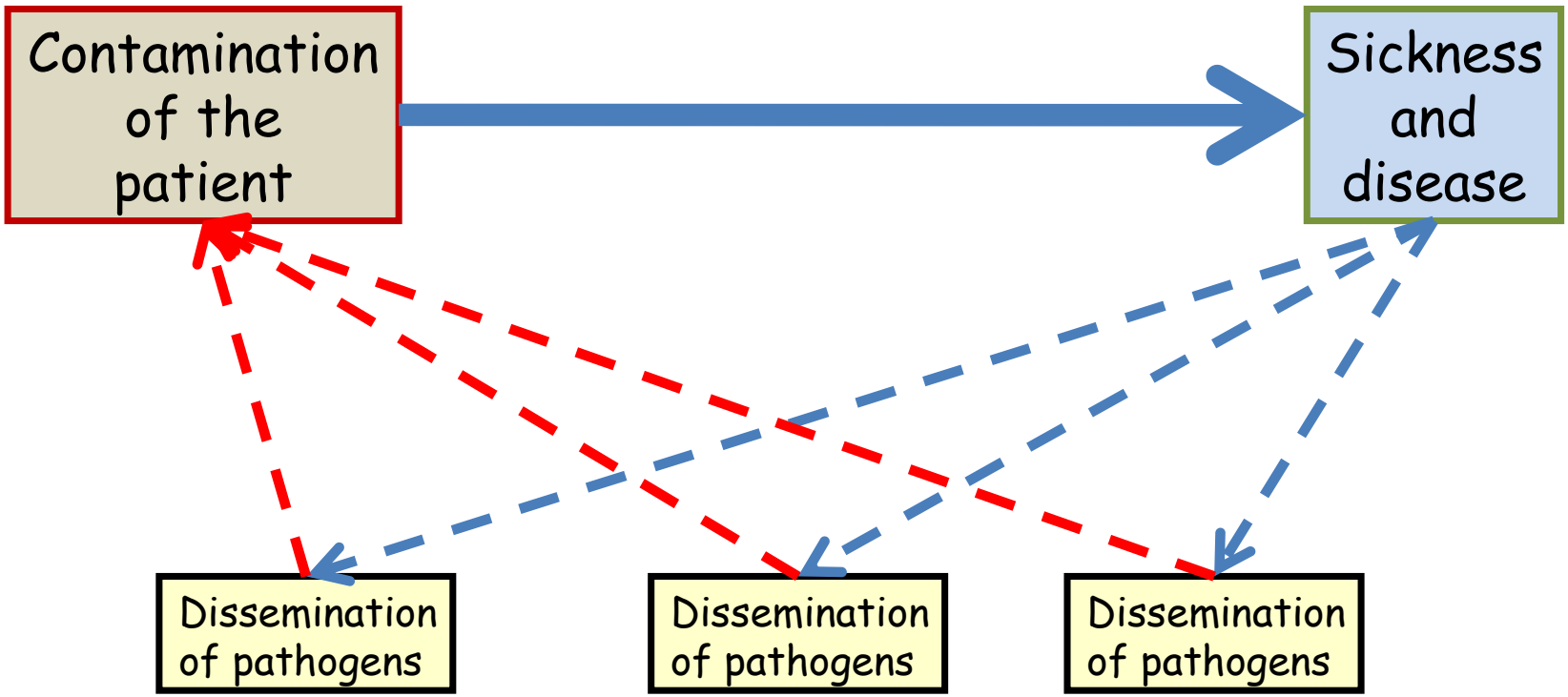
To a more global and environmental view



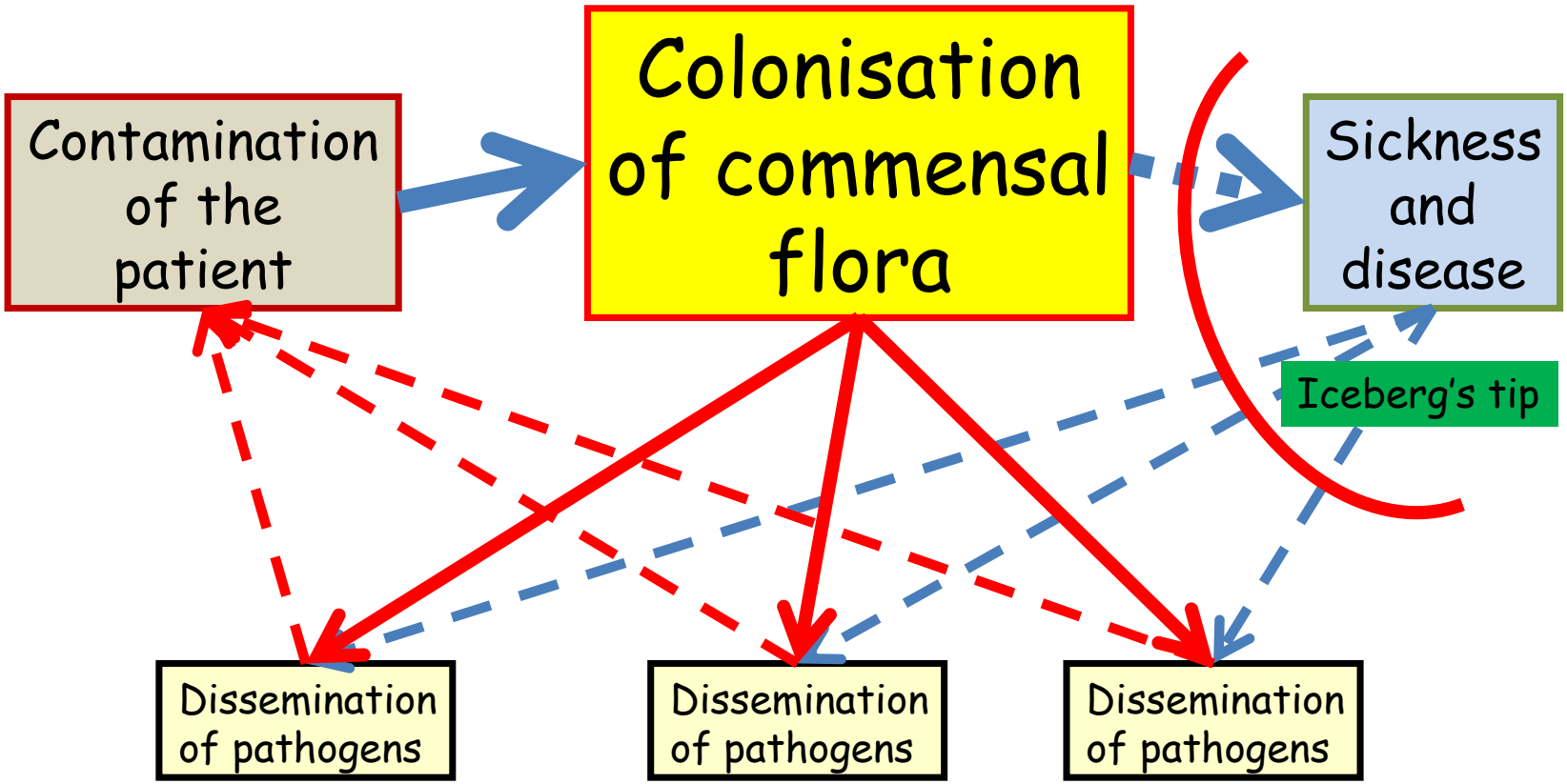
Le monde bactérien

- Age des bactéries : 3.5 milliards d'années
- Les premiers hommes : 3.5 millions d'années (Mille fois moins longtemps)
- Bactéries hautement adaptables (« tous terrains »)
  - Plasticité du génome (éléments mobiles)
  - Nombre (des milliers d'espèces)
  - Lieux (partout)

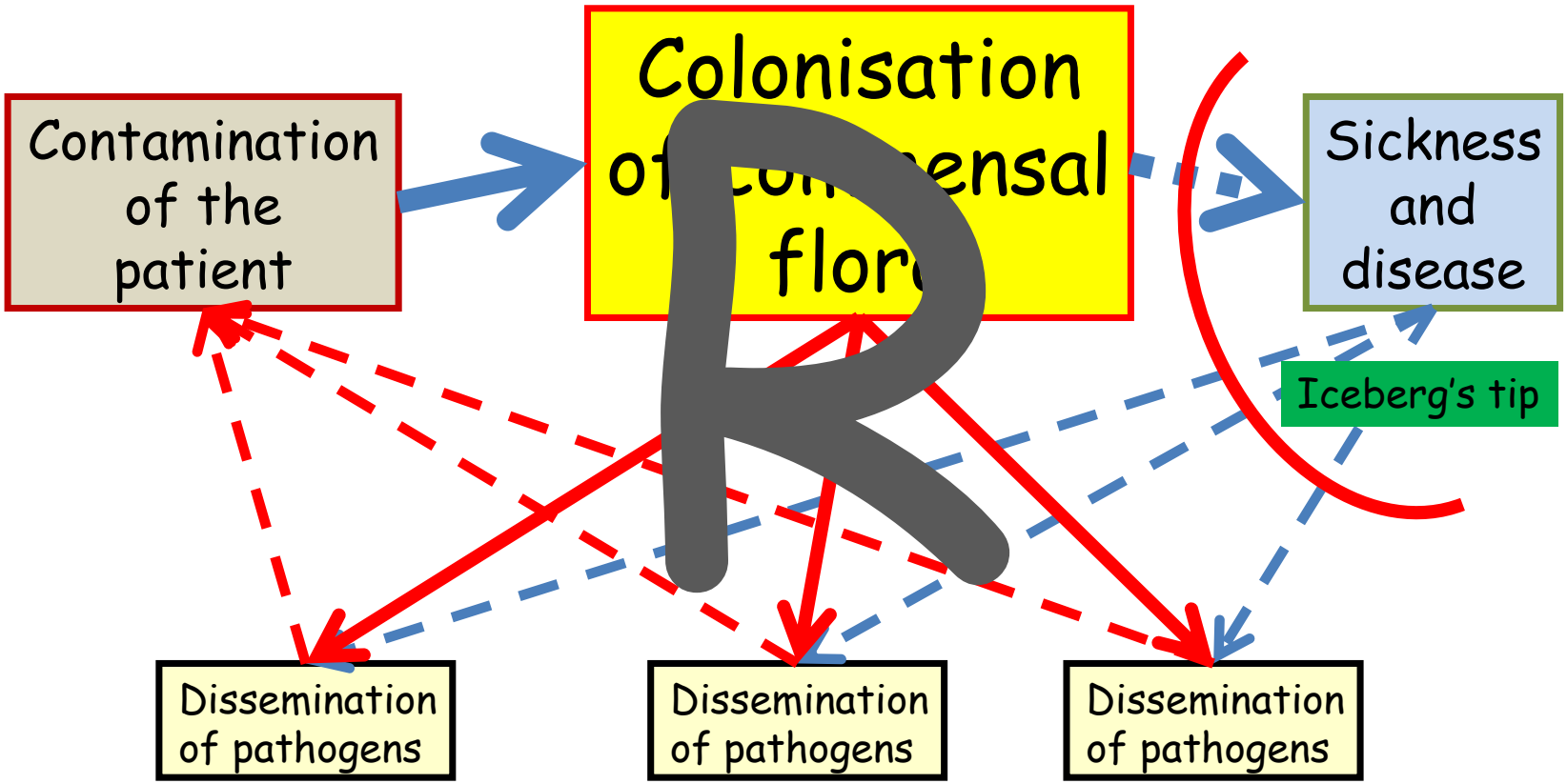
« Classical » natural history of bacterial infections



« New » natural history of bacterial infections

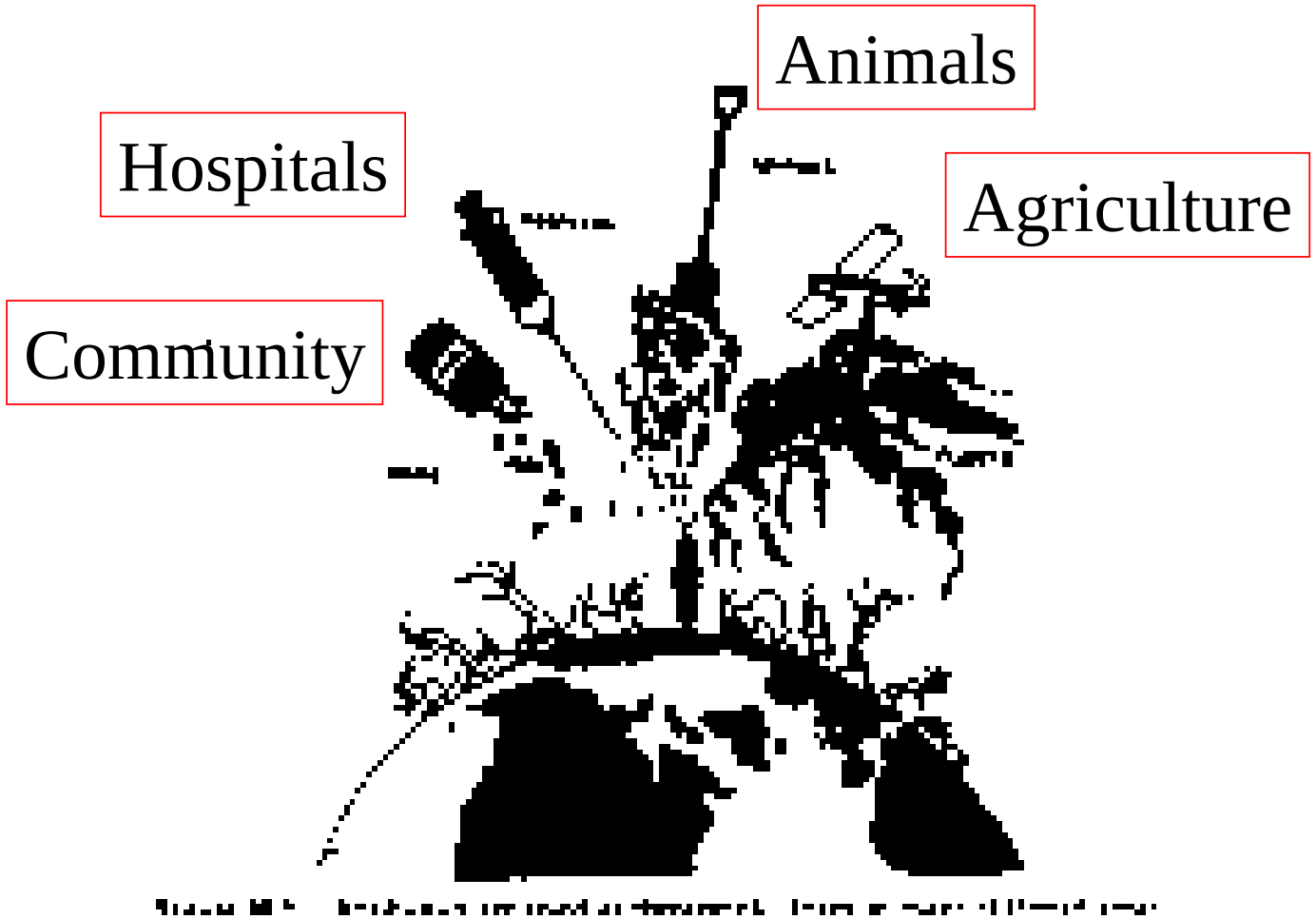


« New » natural history of bacterial infections



Human or animal populations and the environment

Global use of antibiotics



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

Une « crise » des antibiotiques

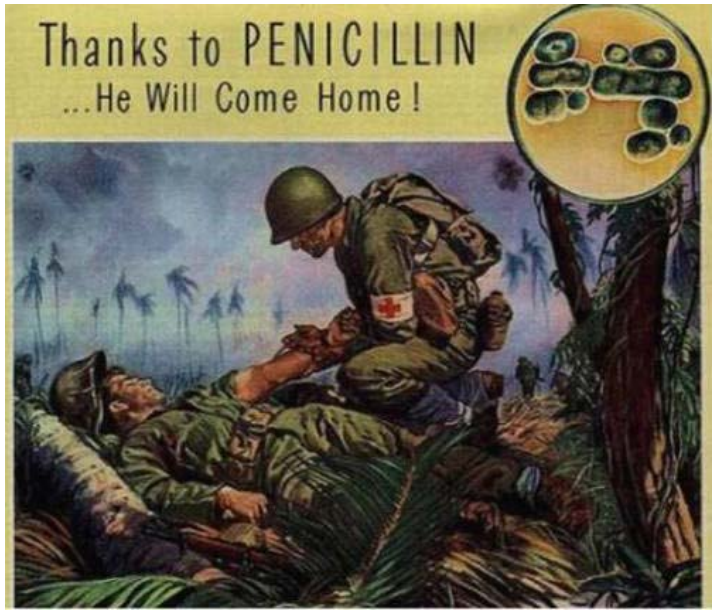
- Des médicaments miracles :
  - Fait reculer les maladies bactériennes :
    - très graves comme la tuberculose dont la diagnostic n'est plus « catastrophique »
    - D'autres très fréquentes, comme les infections urinaires, dont le traitement est « confortable »
  - Permis de remarquables progrès médicaux
    - Greffes
    - Chiothérapies
    - Réanimation
- Mais dont l'efficacité aujourd'hui s'épuise…

Cette histoire singulière a trois « saisons »

1. Un début aussi « foudroyant » pour les bactéries, que « miraculeux » pour les patients.
2. Une épopée thérapeutique, industrielle et financière qui accompagne les « trente glorieuses ».
3. Un retournement inattendu depuis 1990, transformant les « antibios » en ressource limitée, mettant réellement notre santé « en danger ».

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

Prof. Alexander Fleming



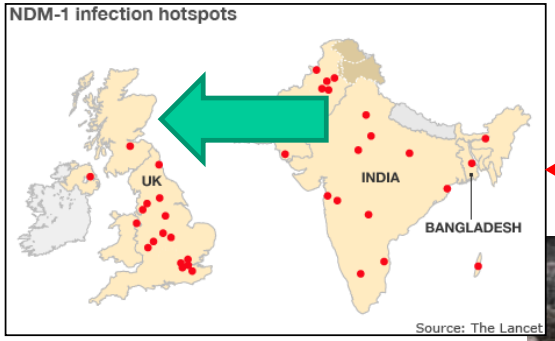
In 1945 interview with (The New York Times)

"Misuse of penicillin could lead to the propagation of mutant forms of bacteria that would resist the new miracle drug"


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
We can fall anytime !

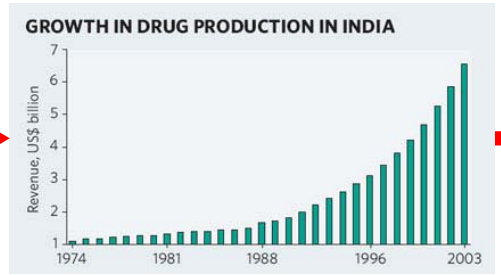
…qui se joue entre le « Nord » et le « Sud »

- Une découverte au Nord rapidement transposée au Sud dans un monde encore très « colonialiste »
- Une « nouvelle » crainte d'invasion du Nord par les bactéries résistantes du Sud.


NDM-1 infection hotspots
UK
INDIA
BANGLADESH
Source: The Lancet

?

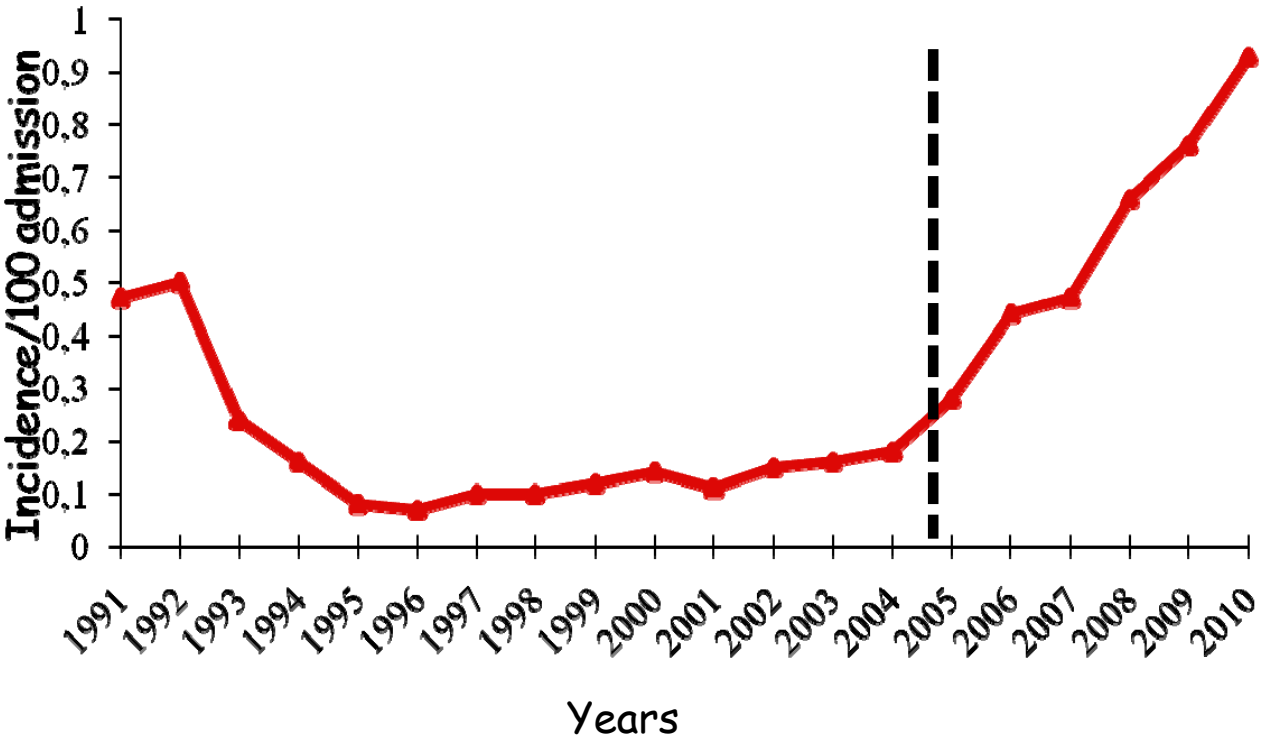

The Game of
BRITISH EMPIRE
OR
TRADING WITH THE COLONIES
BRITISH MANUFACTURE
MADE IN ENGLAND


GROWTH IN DRUG PRODUCTION IN INDIA
Revenue, US$ billion
7
6
5
4
3
2
1
1974
1981
1988
1996
2003

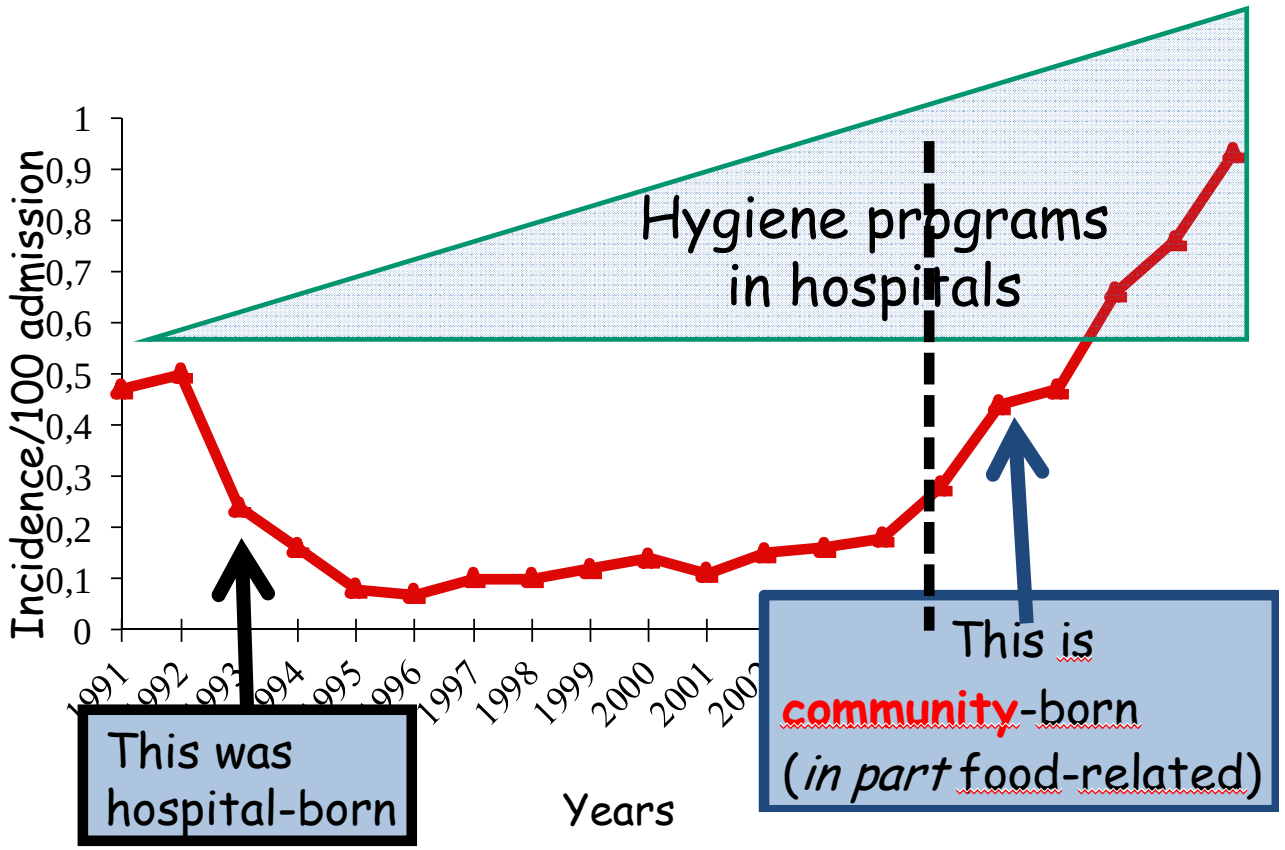
L'exemple de *E. coli*

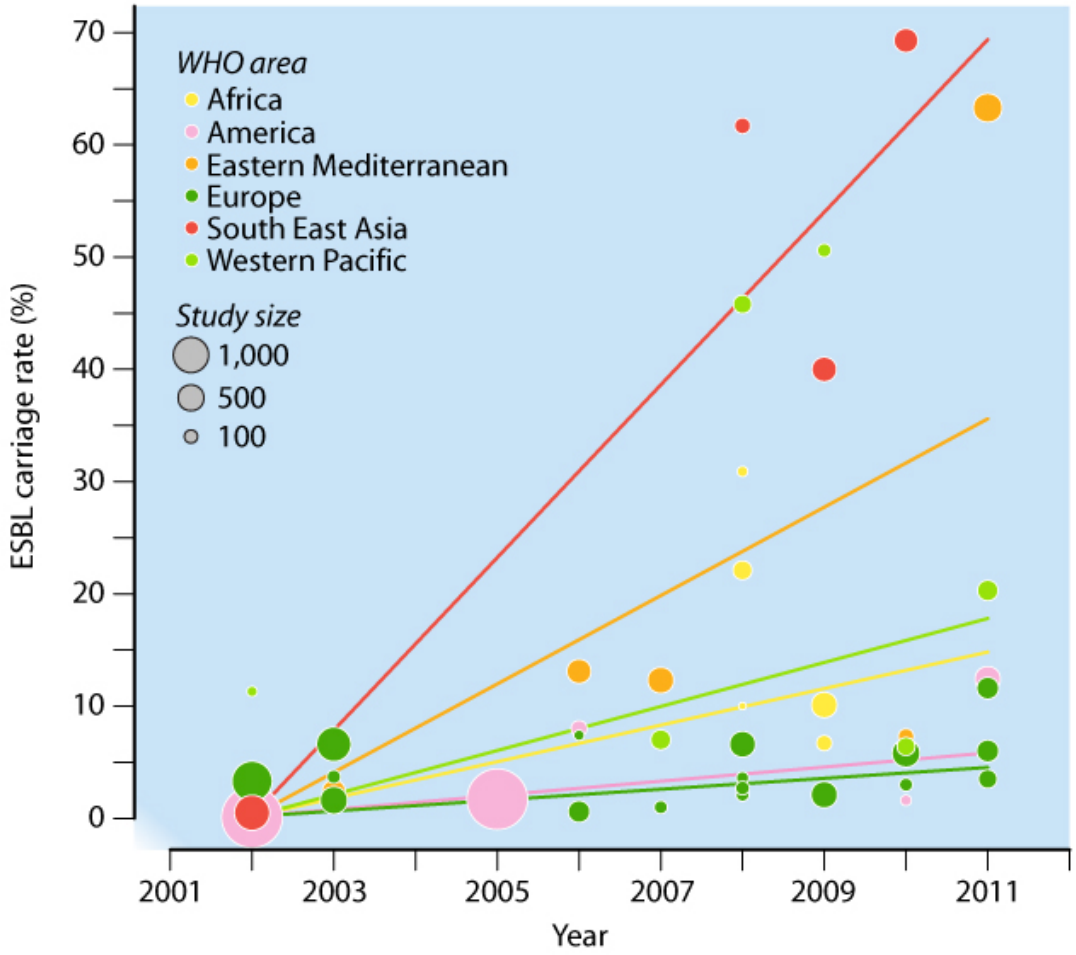
- Bactéries intestinales « normales »
- Mais aussi causes d'infections urinaires (cystites) très fréquentes qui peuvent se compliquer de septicémies
- Le « confort antibiotique » en a fait oublier la gravité potentielle
- Mais la résistance aux antibiotiques puissants (cephalosporines, fluoroquinolones) change la donne…

ESBL burden of diseases
Paris (France) Bichat university hospital



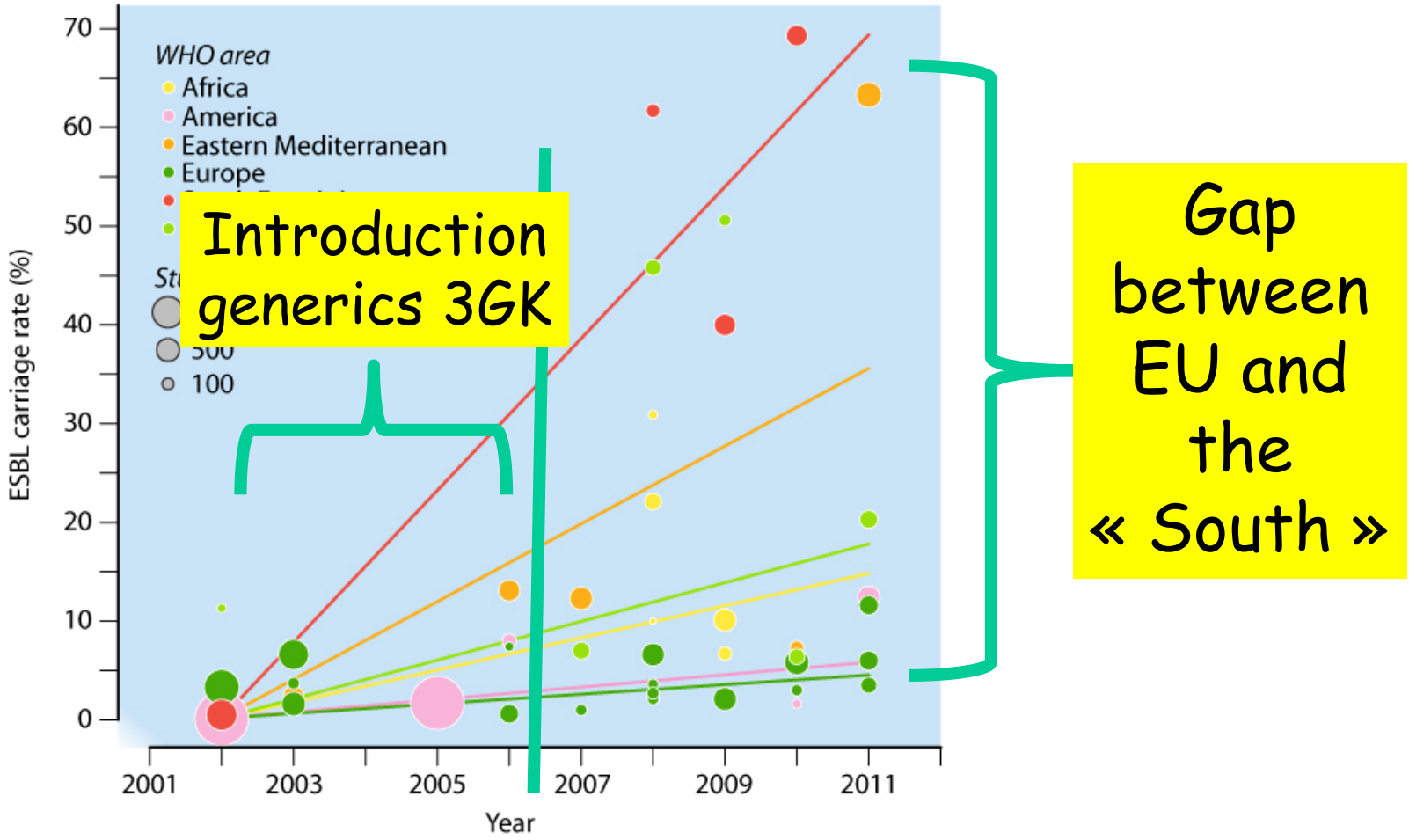
BLSEburden of diseases
Paris (France) Bichat university hospital





ScEYEnce Studios
ASM Journals
CMR00023-13
Dr. Woerther
Figure: 01

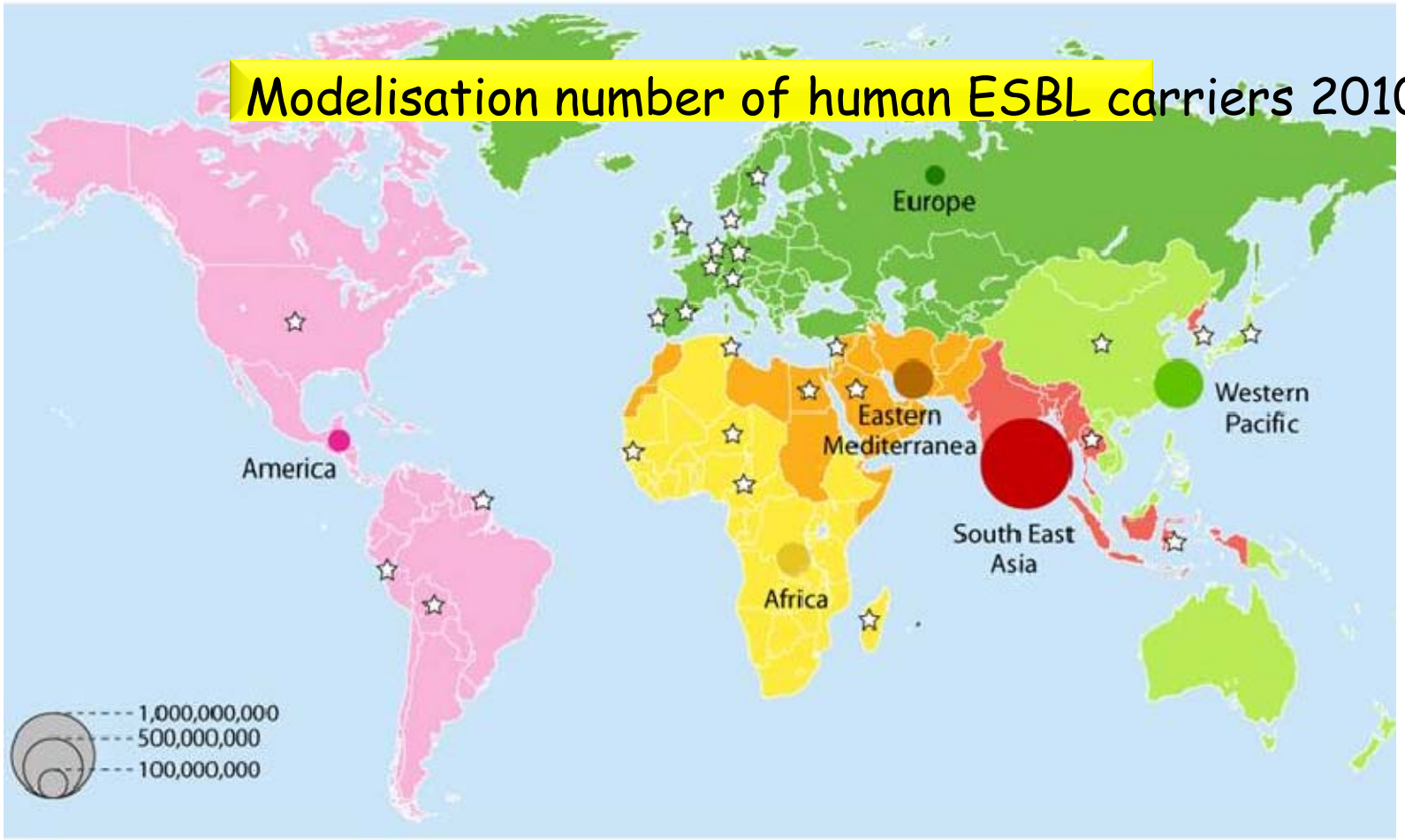
Evolution of ESBL carriage rates in the community worldwide



ScEYEnce Studios
ASM Journals
CMR00023-13
Dr. Woerther
Figure: 01

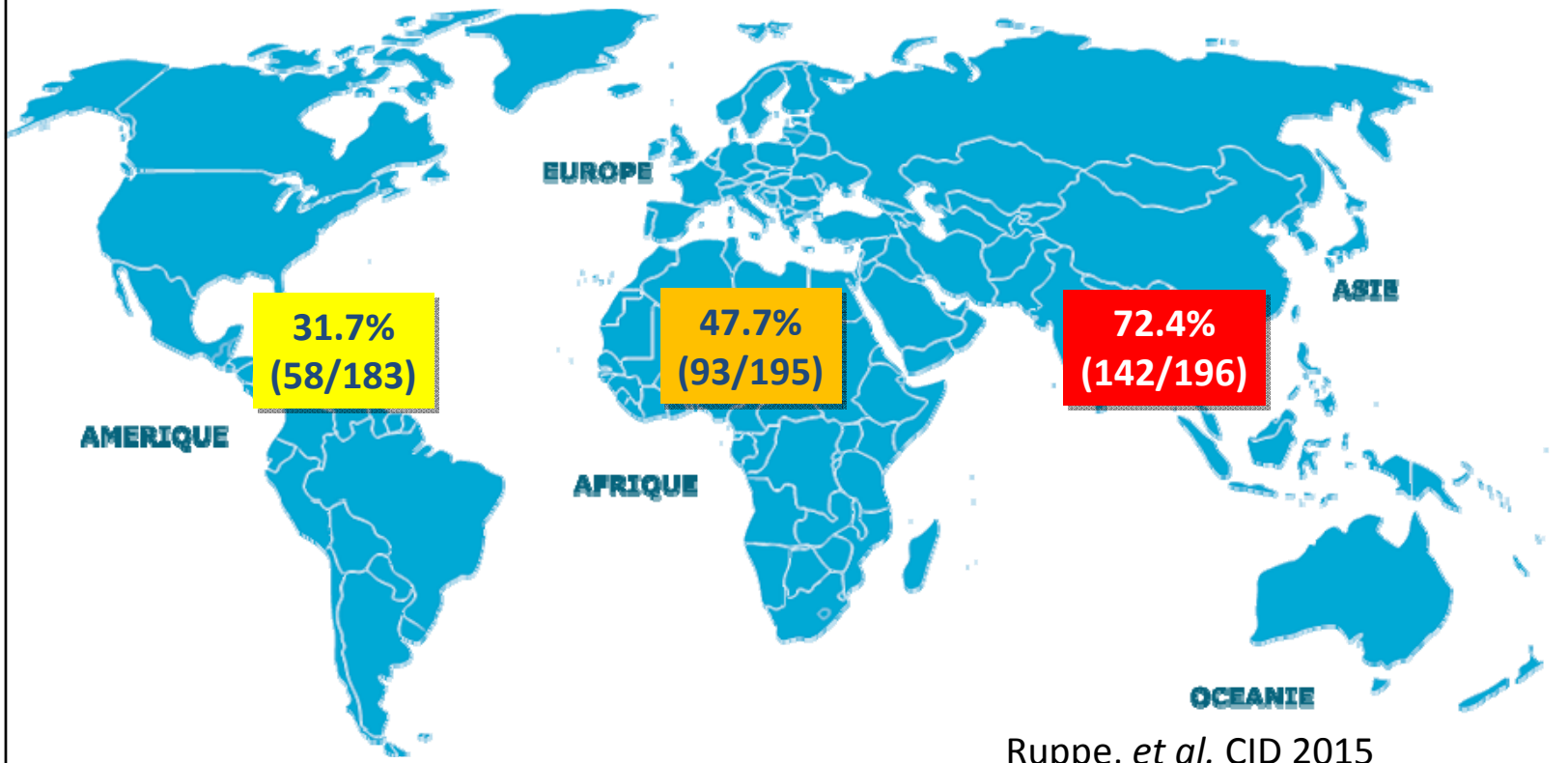
Evolution of ESBL carriage rates in the community

Modelisation number of human ESBL carriers 2010



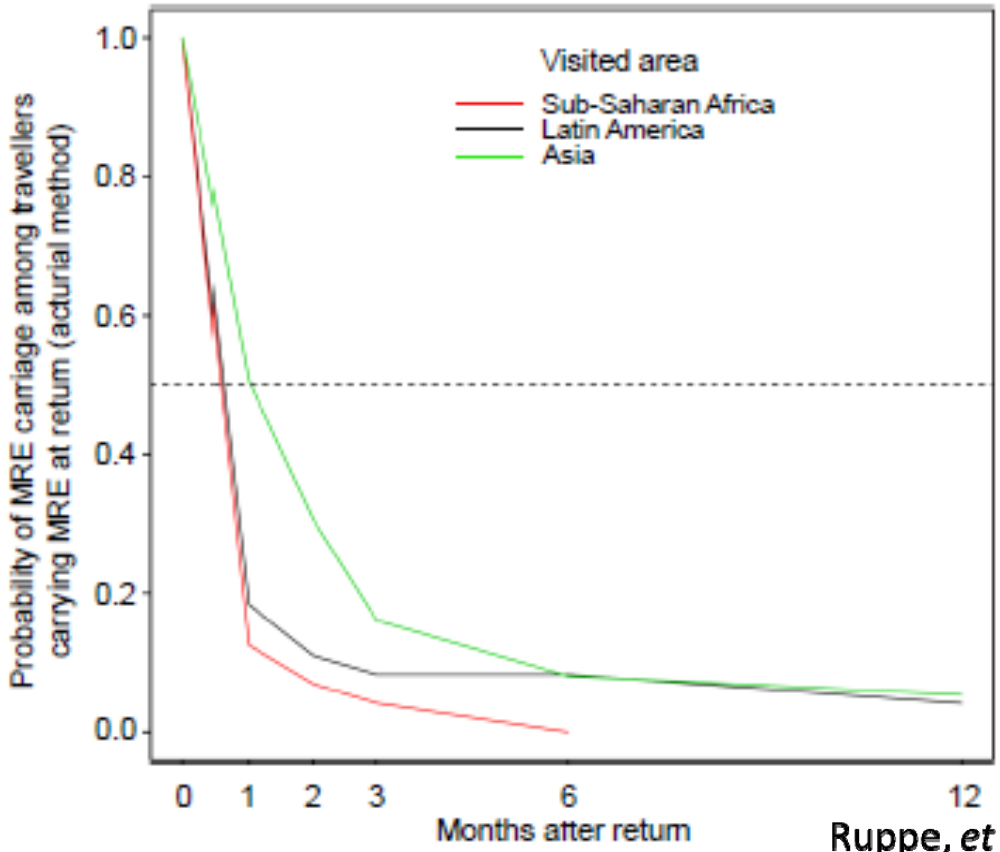
cEYEnce Studios
SM Journals
MR00023-13
r. Woerther
igure: 03

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



Ruppe, *et al.* CID 2015

Rate of clearence of ESBL in returning travellers



Ruppe, *et al.* CID 2015

World Health Organization

ia centre | Publications | Countries | Programmes | About WHO

Drug resistance

Ministerial Conference on Antibiotic Resistance

Joining Forces for Future Health

Date: 25-26 June 2014
Place: The Hague, The Netherlands

Speech Daphne Deckers on AMR conference

News item | 26-06-2014

The Dutch tv-host, writer and former topmodel Daphne Deckers gave an impressive speach about her own experience with antimicrobial resistance, yesterday at the ministerial conference about this topic in The Hague. You can find the full speech here.

Que s’est-il passé au tournant du millénaire ?

A schematic view of antibiotic/resistance evolution

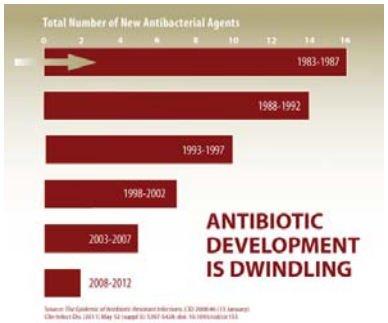
As patents get old, generics invade the markets

Towards pan-resistance?

New antibiotics

Resistance

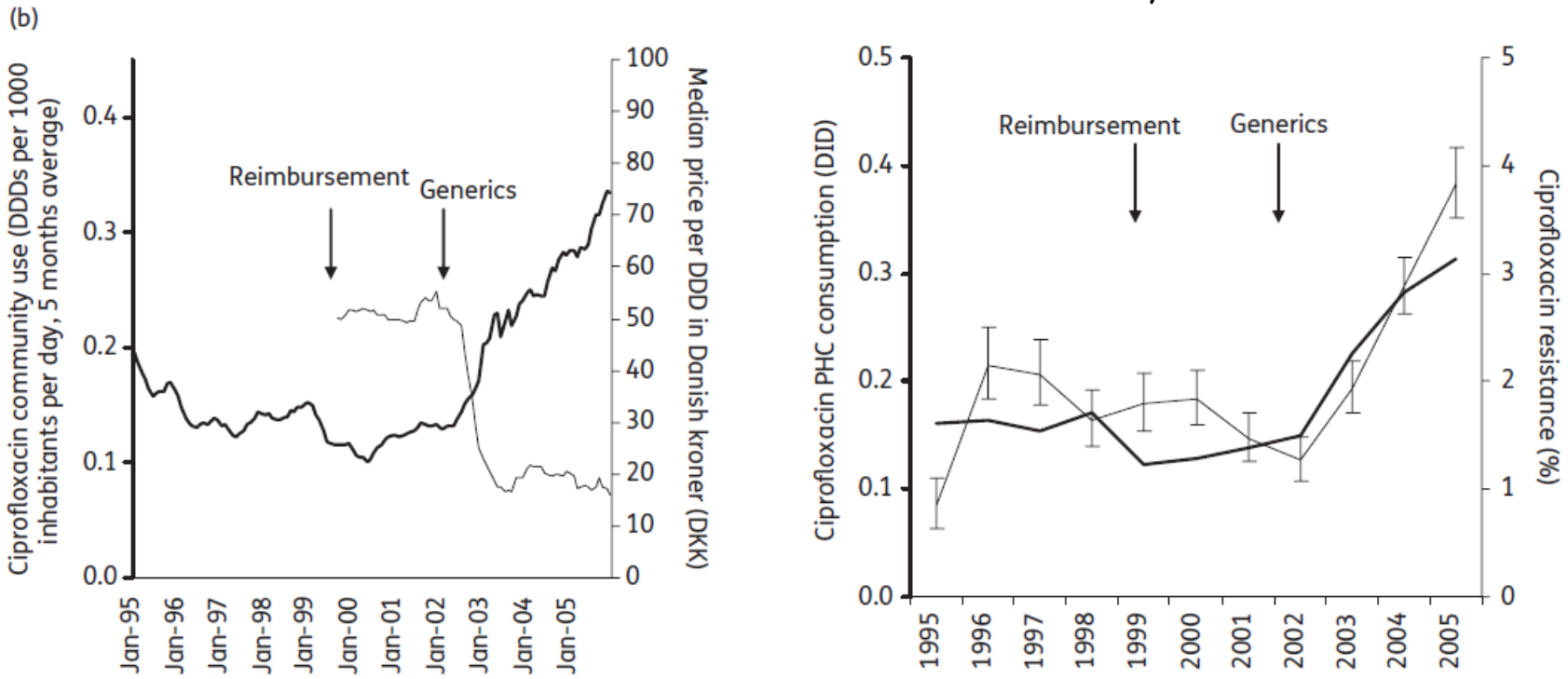
Towards innovation?



1950 1975 2000

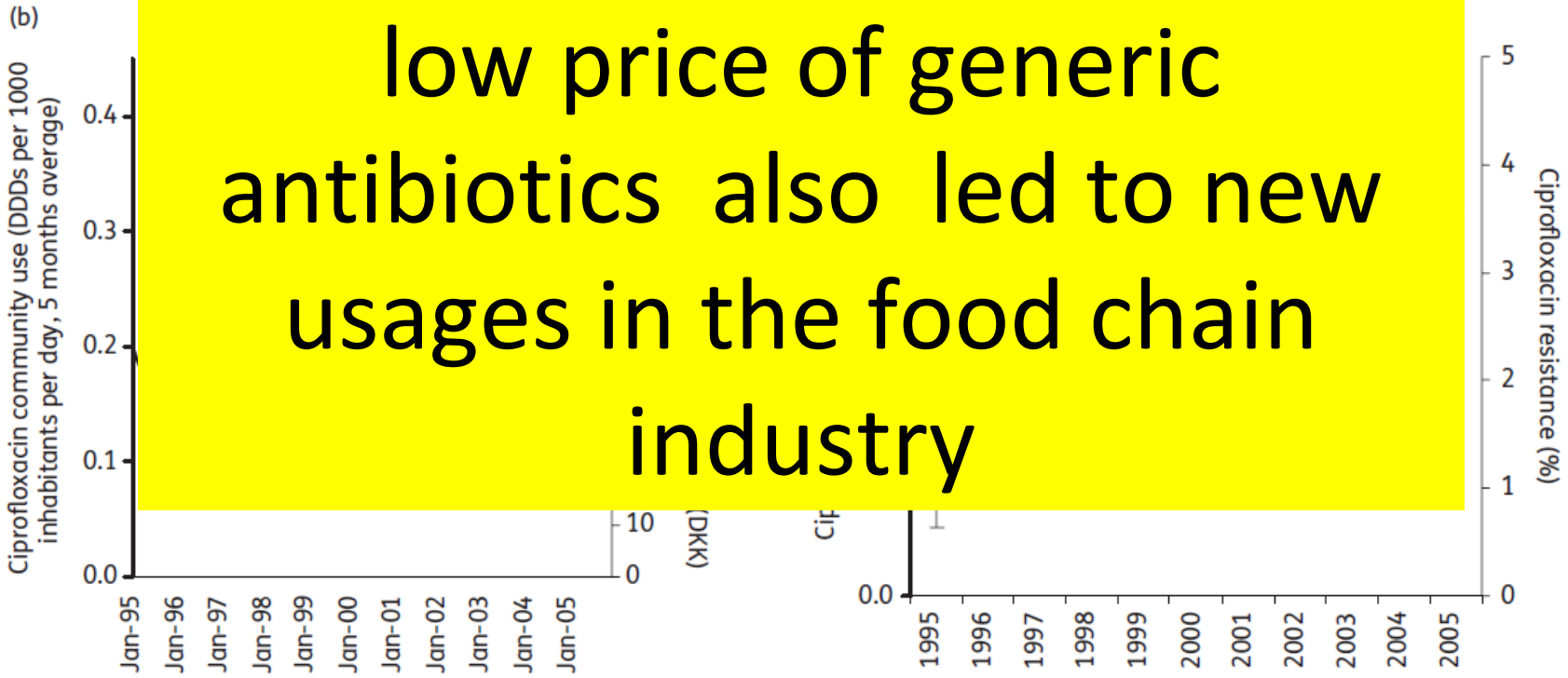
The « catastrophic » impact of antibiotic generics on resistance has been well demonstrated for ciprofloxacin in Denmark.

Jensen US, *et al.* JAC 2010



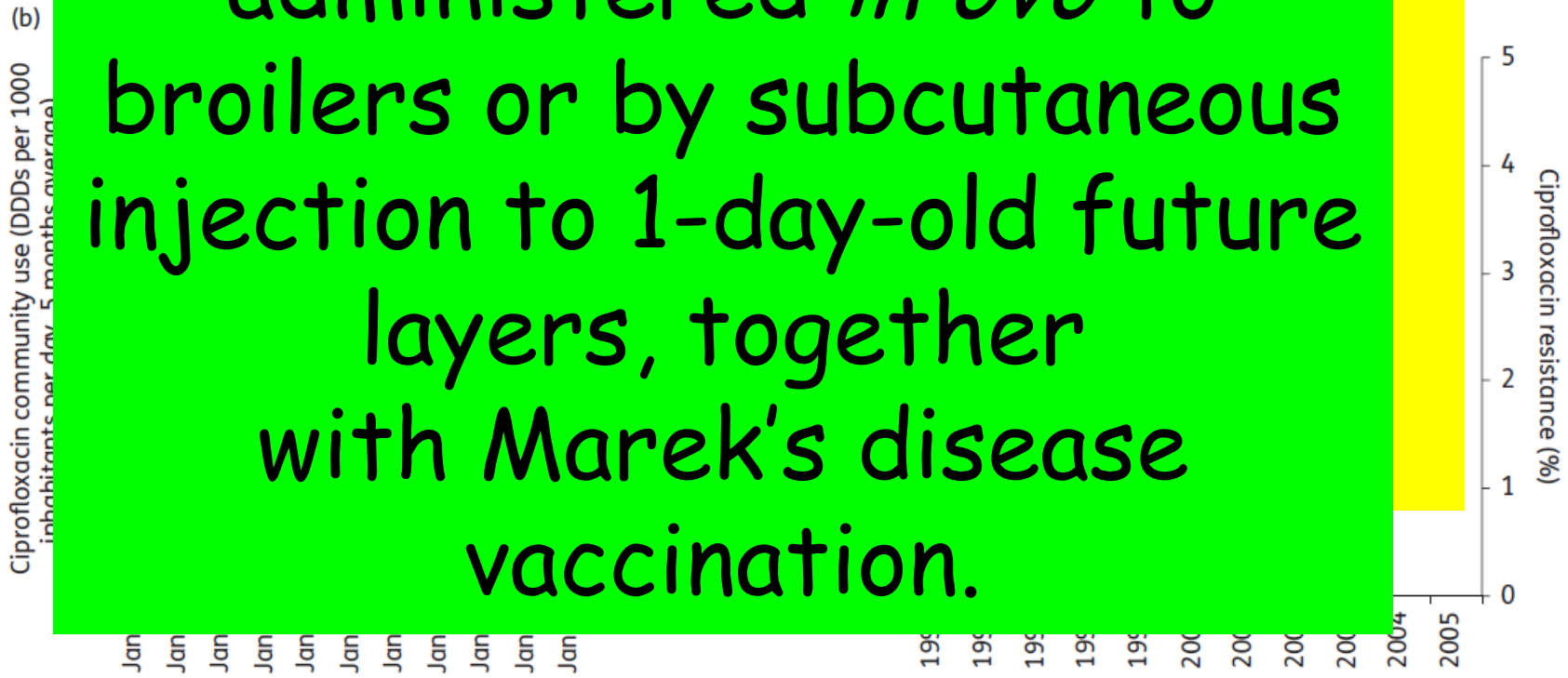
The « catastrophic » impact of antibiotic generics on resistance has been well demonstrated for ciprofloxacin in Denmark

It is most probable that the low price of generic antibiotics also led to new usages in the food chain industry



The « catastrophic » impact of antibiotic generics on resistance has been well

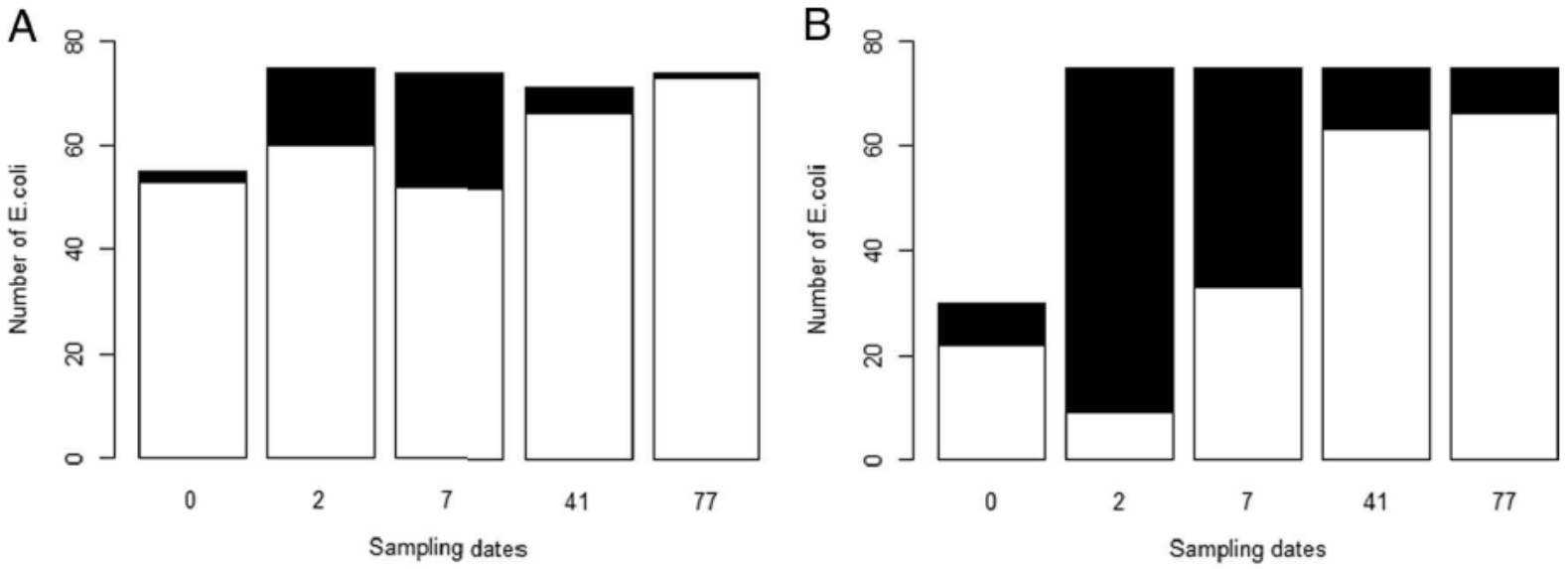
C3G are automatically administered *in ovo* to broilers or by subcutaneous injection to 1-day-old future layers, together with Marek's disease vaccination.



Impact of Third-Generation-Cephalosporin Administration in Hatcheries on Fecal Escherichia coli Antimicrobial Resistance in Broilers and Layers

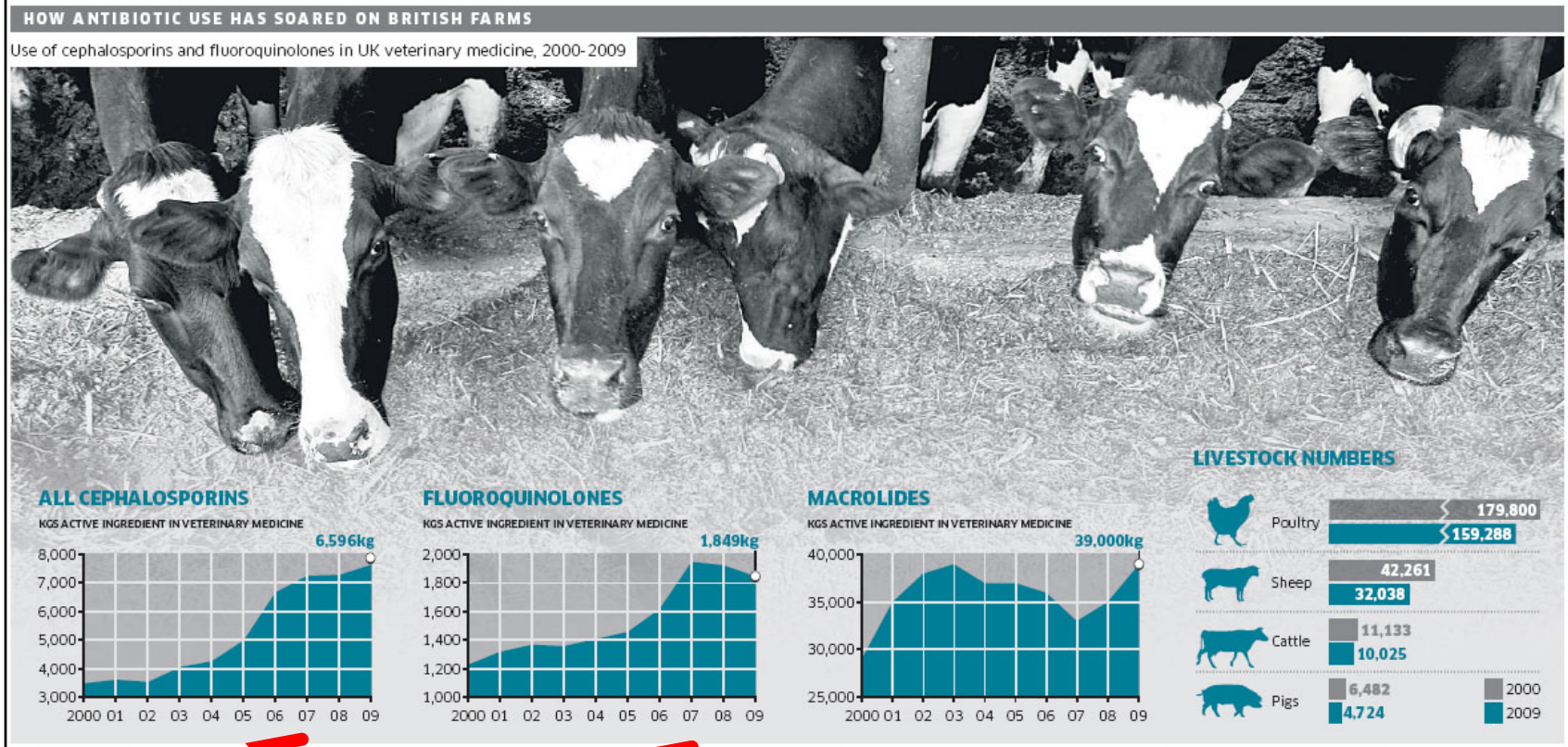
Without

With



Baron S. *et al. AAC 2014*

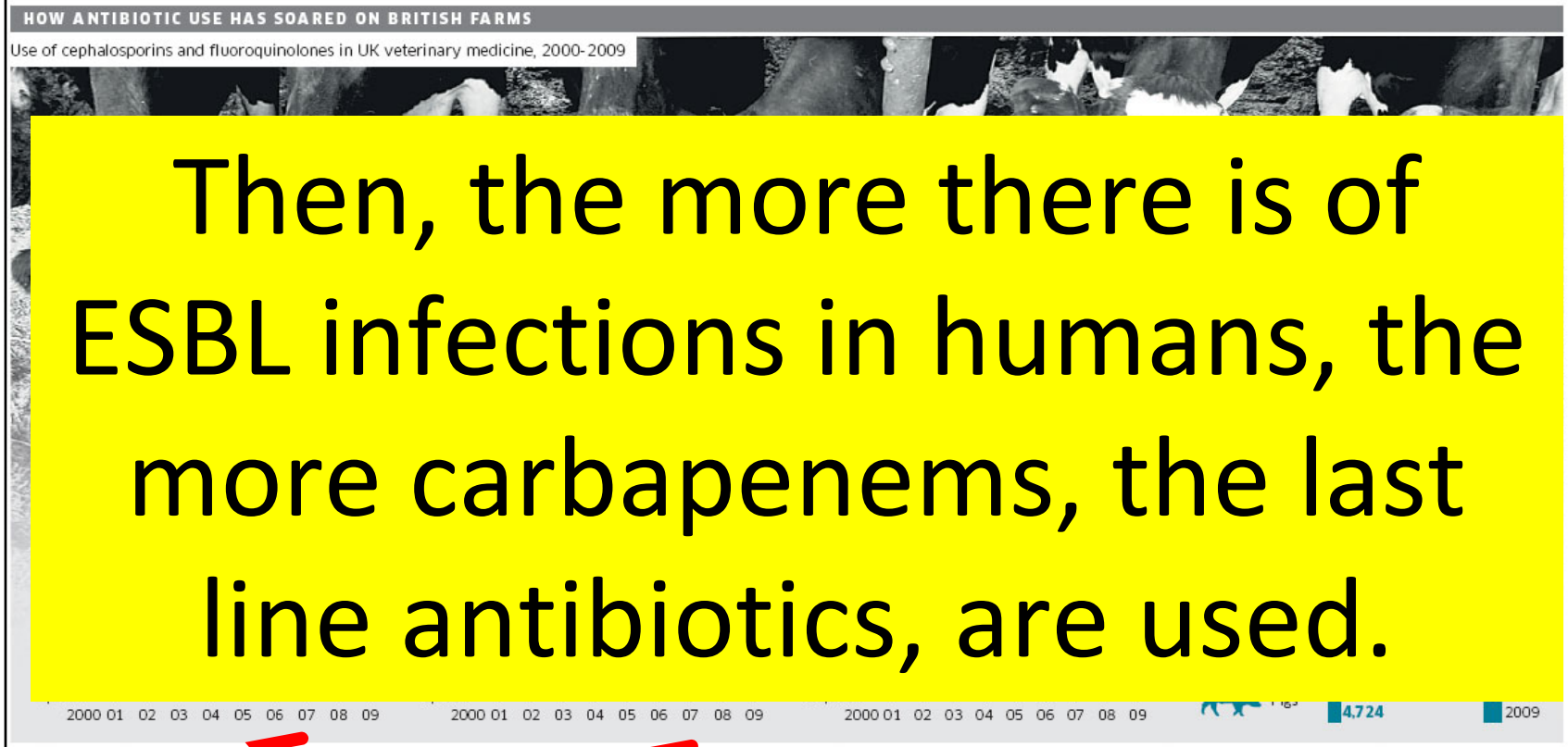
La dynamique de la consommation animale : UK



THE INDEPENDENT

June 17, 2011

La dynamique de la consommation animale : UK



Then, the more there is of ESBL infections in humans, the more carbapenems, the last line antibiotics, are used.

THE INDEPENDENT

June 17, 2011

Downloaded Sep 17, 2015

ResistanceMap BETA

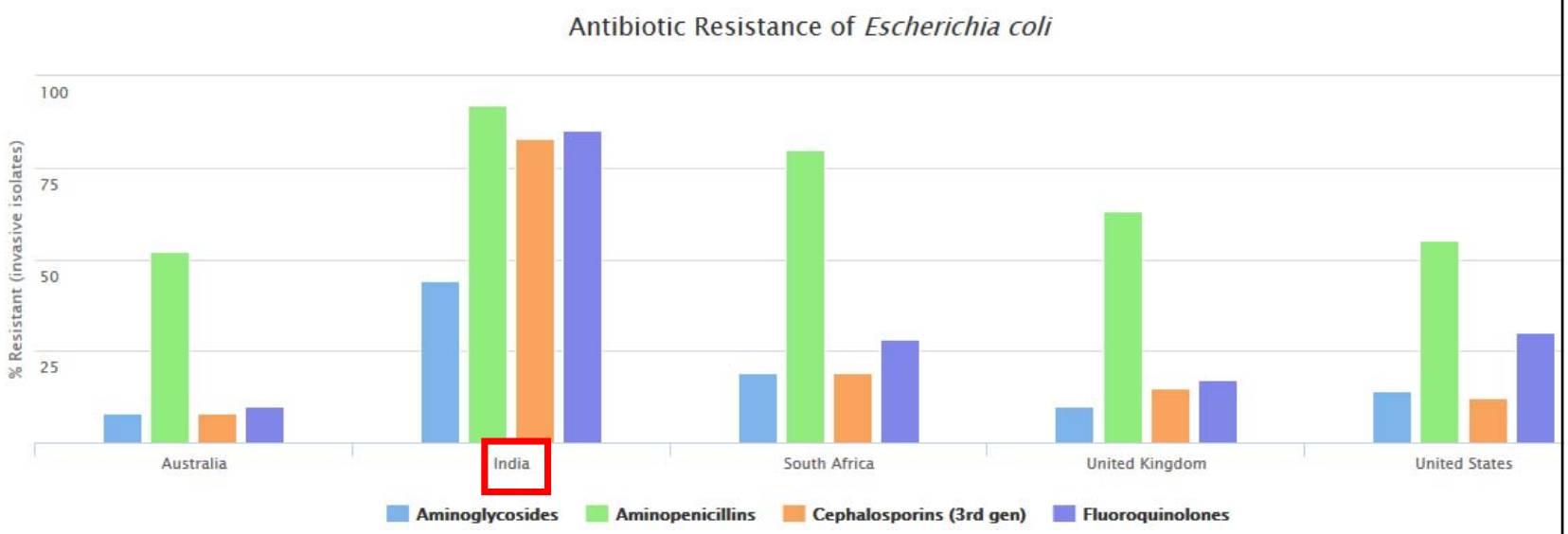
CDDEP THE CENTER FOR Disease Dynamics, Economics & Policy WASHINGTON DC • NEW DELHI

Antibiotic Resistance | Antibiotic Use | Countries | Drug Resistance Index | About | News and Research

Antibiotic Resistance

Map | Trend | Chart

Clinical isolates~infections)



Antibiotic resistance—the need for global solutions

Lancet Infect Dis 2013; 13: 1057–98

Ramanan Laxminarayan, Adriano Duse, Chand Wattal, Anita K M Zaidi, Heiman F L Wertheim, Nithima Sumpradit, Erika Vlieghe, Gabriel Levy Hara, Ian M Gould, Herman Goossens, Christina Greko, Anthony D So, Maryam Bigdeli, Göran Tomson, Will Woodhouse, Eva Ombaka, Arturo Quizhpe Peralta, Farah Naz Qamar, Fatima Mir, Sam Kariuki, Zulfiqar A Bhutta, Anthony Coates, Richard Bergstrom, Gerard D Wright, Eric D Brown, Otto Cars

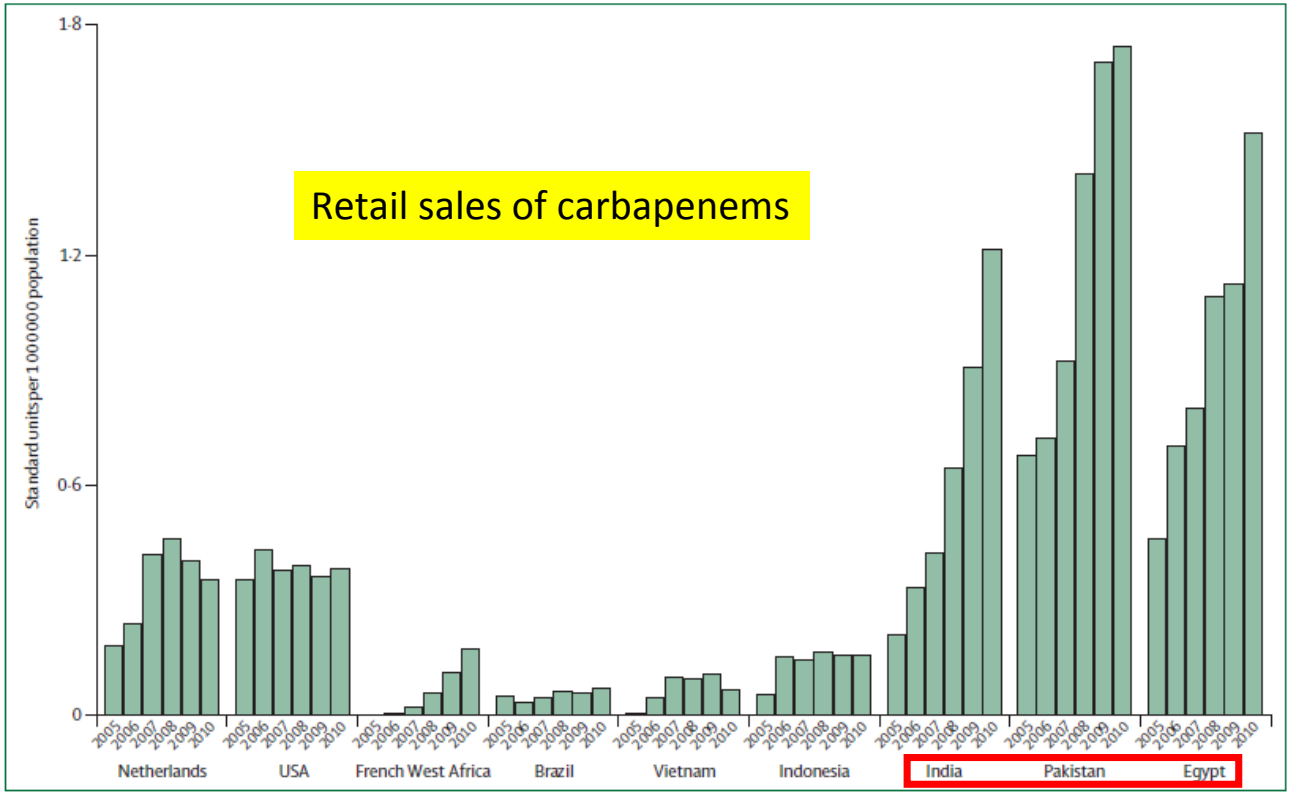


Figure 1: **Trends in retail sales of carbapenem antibiotics for Gram-negative bacteria**
Based on data obtained from IMS Health's MIDAS™ database. *An IMS grouping of Benin, Burkina Faso, Cameroon, Congo (Brazzaville), Gabon, Guinea, Ivory Coast, Mali, Senegal, and Togo.

Emergence of a new antibiotic resistance mechanism in India, Pakistan, and the UK: a molecular, biological, and epidemiological study

Lancet Infect Dis 2010; 10: 597–602

Karthikeyan K Kumarasamy, Mark A Toleman, Timothy R Walsh, Jay Bagaria, Fafhana Butt, Ravikumar Balakrishnan, Uma Chaudhary, Michel Doumith, Christian G Giske, Seema Irfan, Padma Krishnan, Anil V Kumar, Sunil Maharjan, Shazad Mushtaq, Tabassum Noorie, David L Paterson, Andrew Pearson, Claire Perry, Rachel Pike, Bhargavi Rao, Ujjwayini Ray, Jayanta B Sarma, Madhu Sharma, Elizabeth Sheridan, Mandayam A Thirunarayan, Jane Turton, Supriya Upadhyay, Marina Warner, William Welfare, David M Livermore, Neil Woodford

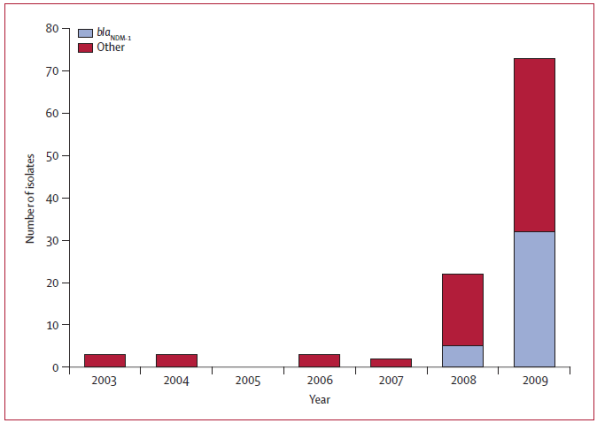


Figure 1: Numbers of carbapenemase-producing Enterobacteriaceae referred from UK laboratories to the UK Health Protection Agency's national reference laboratory from 2003 to 2009
The predominant gene is bla_{NDM-1}, which was first identified in 2008. The other group includes diverse producers of KPC, OXA-48, IMP, and VIM enzymes.

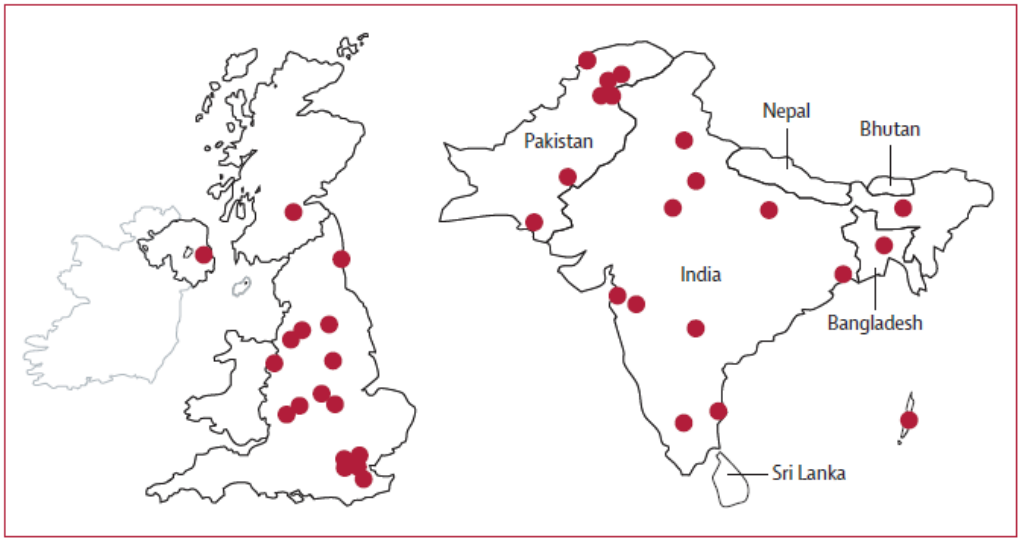


***Figure 5*: Distribution of NDM-1-producing Enterobacteriaceae strains in Bangladesh, Indian, Pakistan, and the UK**

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

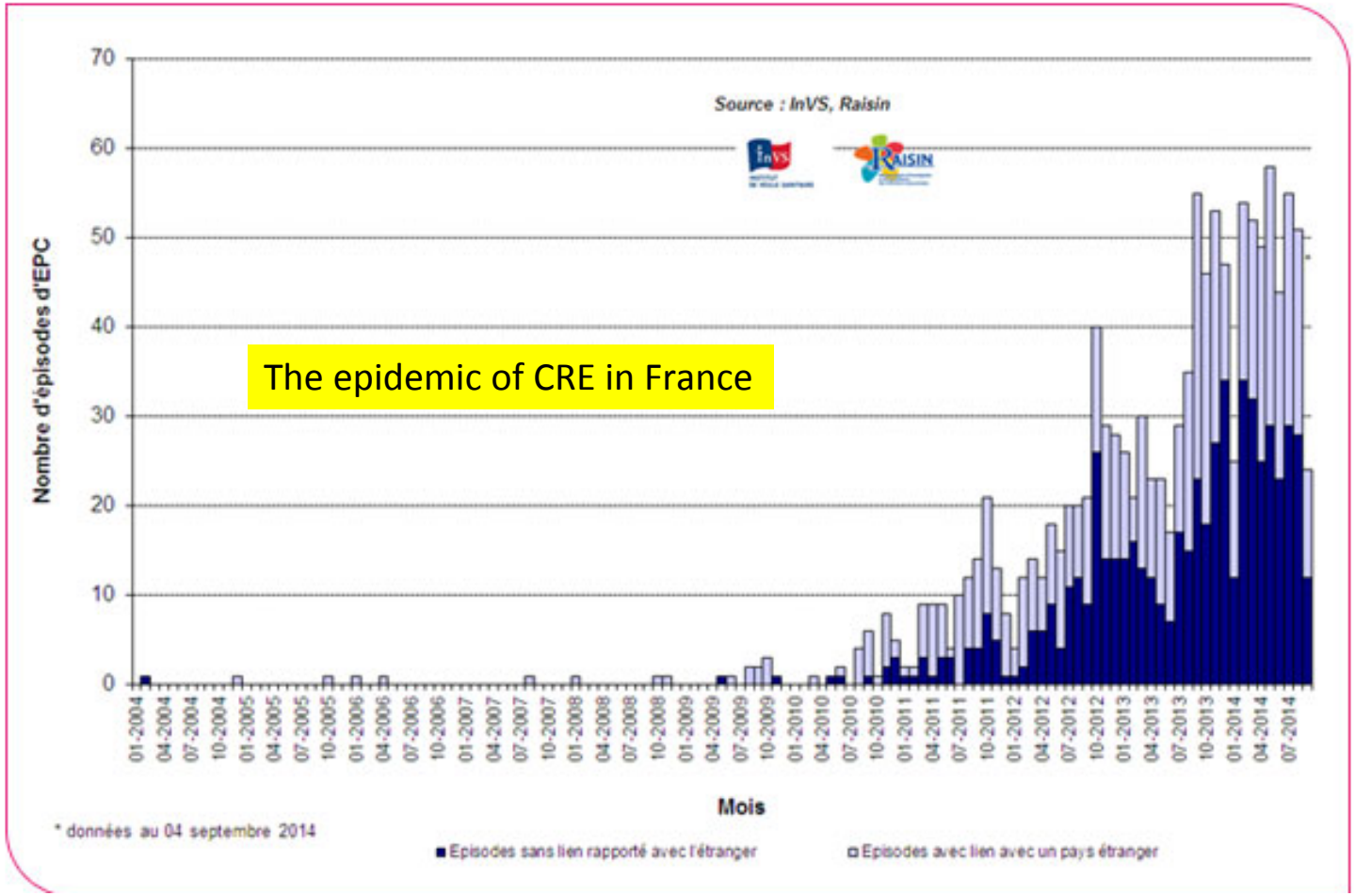
Lancet Infect Dis 2011;
11: 355–62

Figure 1: Map of NDM-1-positive samples from New Delhi centre and surrounding areas

The dissemination of NDM-1

Rogers BA *et al.* CID 2011

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).



The question is more complex than we thought…

PLOS | ONE

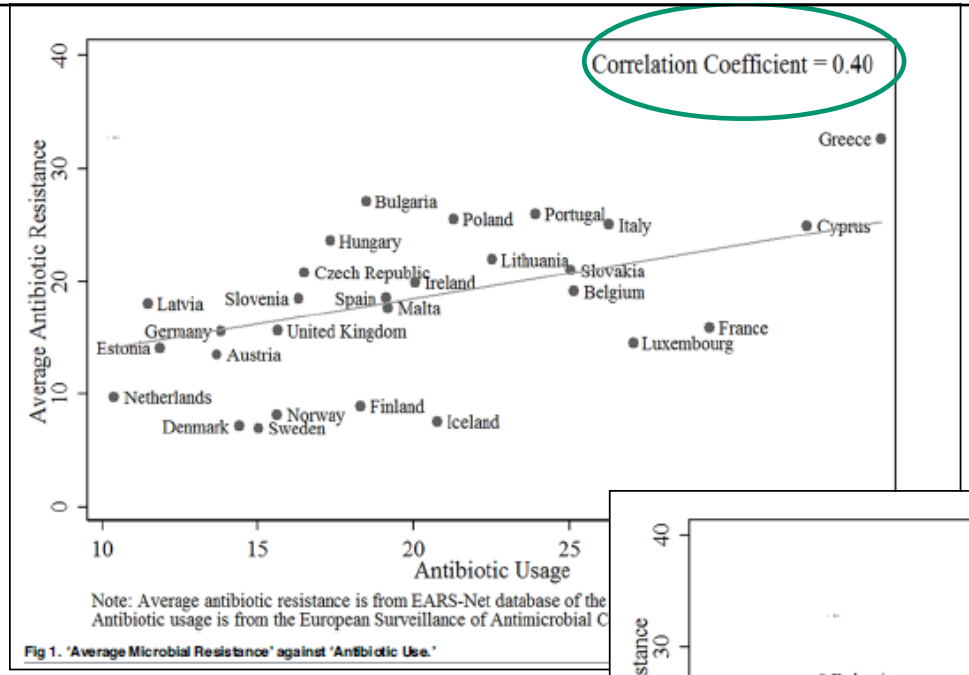
RESEARCH ARTICLE

Antimicrobial Resistance: The Major Contribution of Poor Governance and Corruption to This Growing Problem

Peter Collignon[1,2]*, Prema-chandra Athukorala[3,4], Sanjaya Senanayake[5,6], Fahad Khan[3]

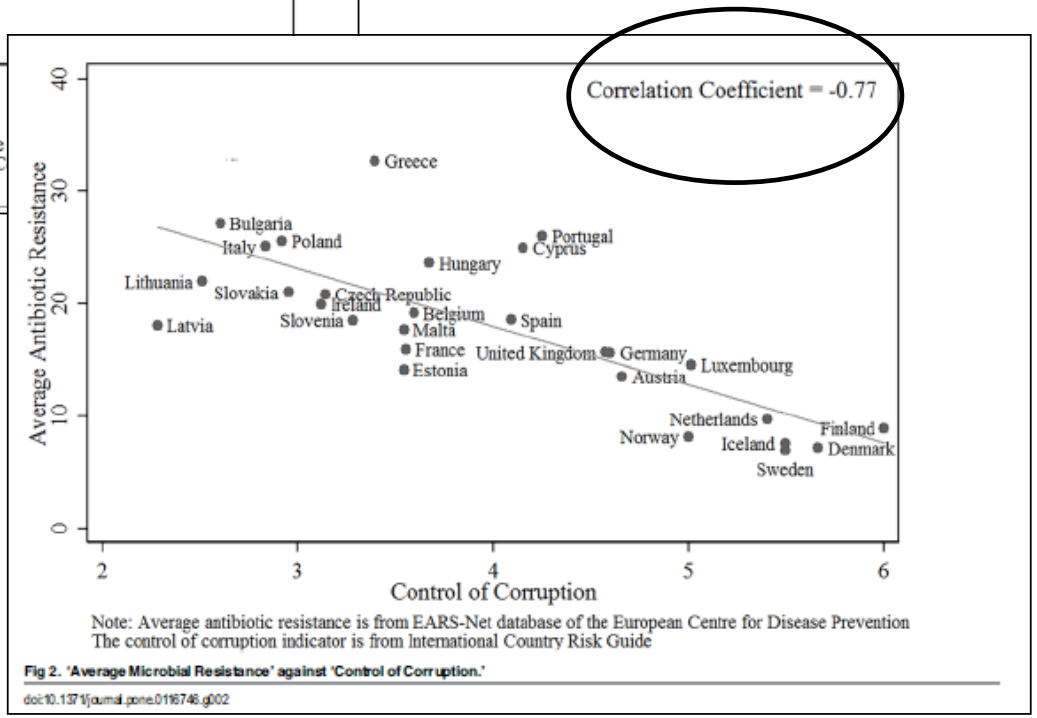
1 ACT Pathology, Canberra Hospital, Australian National University, Garran, Australia, 2 Canberra Clinical School, Australian National University, Garran, Australia, 3 Arndt-Corden Department of Economics, Australian National University, Acton, Australia, 4 School of Environment and Development, University of Manchester, Manchester, England, 5 Australian National University, Garran, Australia, 6 Canberra Hospital, Garran, Australia

* peter.collignon@act.gov.au



Note: Average antibiotic resistance is from EARS-Net database of the
Antibiotic usage is from the European Surveillance of Antimicrobial C

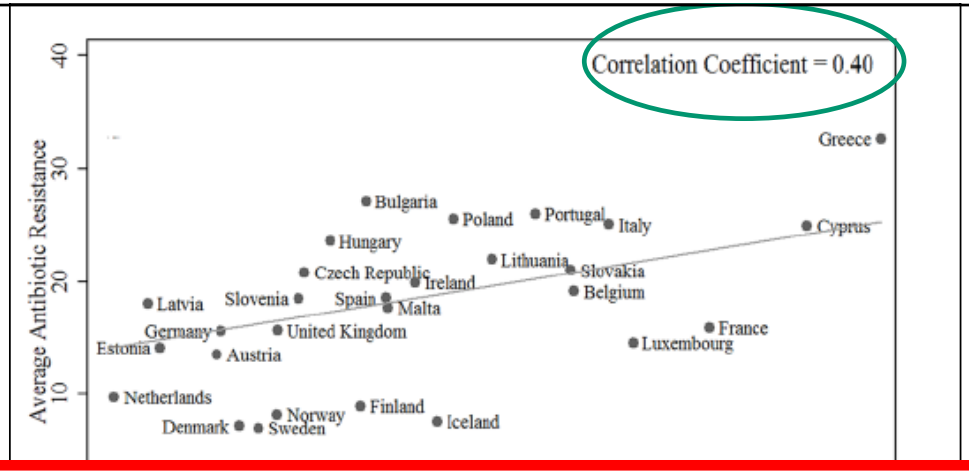
Fig 1. 'Average Microbial Resistance' against 'Antibiotic Use.'



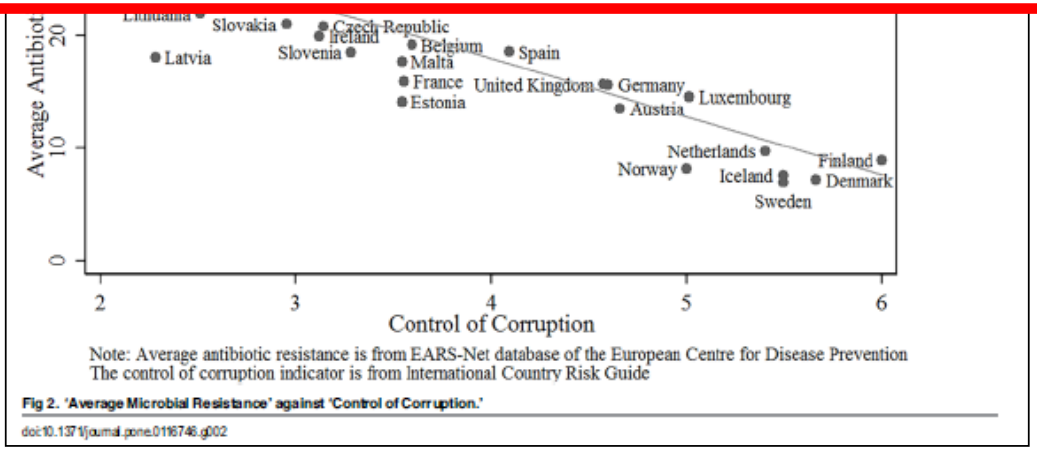
Note: Average antibiotic resistance is from EARS-Net database of the European Centre for Disease Prevention
The control of corruption indicator is from International Country Risk Guide

Fig 2. 'Average Microbial Resistance' against 'Control of Corruption.'

doi:10.1371/journal.pone.0116748.g002



Only 28% of the total variation in antibiotic resistance among countries is attributable to variation in antibiotic usage. If time effects are included the explanatory power increases to 33%. However when the control of corruption indicator is included as an additional variable, 63% of the total variation in antibiotic resistance is now explained by the regression.



Note: Average antibiotic resistance is from EARS-Net database of the European Centre for Disease Prevention
The control of corruption indicator is from International Country Risk Guide

Fig 2. 'Average Microbial Resistance' against 'Control of Corruption.'

doi:10.1371/journal.pone.0116748.g002

What can we do to reduce resistance ?

1. Reduce antibiotic usage
2. Modify antibiotic usage
3. Decrease antibiotic concentrations in the colon during treatments
4. Use of Fecal transplant or « new » probiotics

Four hamlets

Spread over 6 km

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

2°15'0.99"N, 52°52'58.99"W

A medical post with a permanet paramedic

~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

All medical care and drug delivery carefully recorded

- Troi
  - –
  - – Restricted area

2°15'0.99"N, 52°52'58.99"W

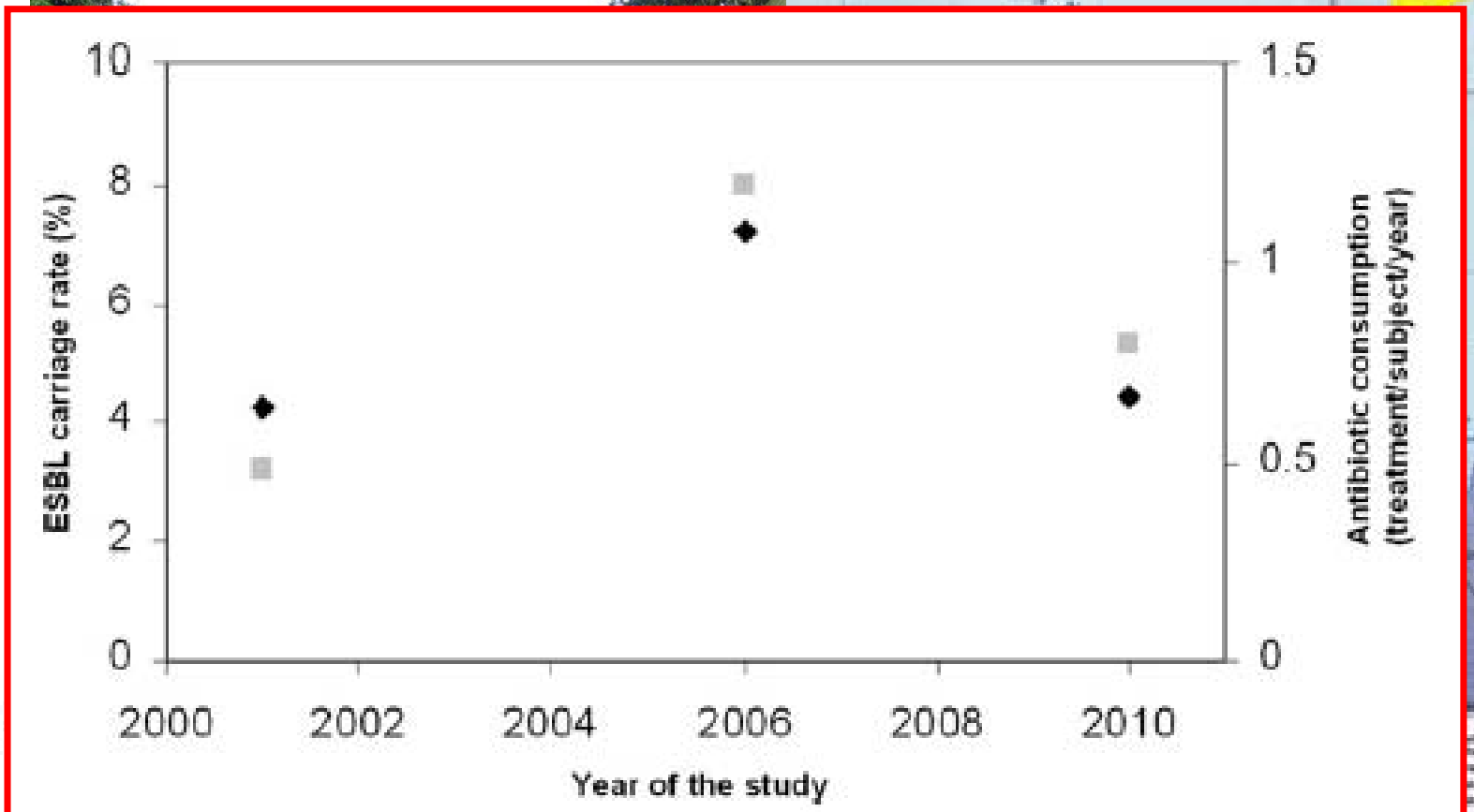


FIG 1 ESBL-E carriage rate in Wayampi volunteers (gray squares) and overall antibiotic exposure of the whole community (black diamonds) in 2001, 2006, and 2010. Linear regression ($y = 8.675x - 1.396$; $R^2 = 0.87$) and Pearson's correlation ($P = 0.24$) were used to evaluate the evolution.

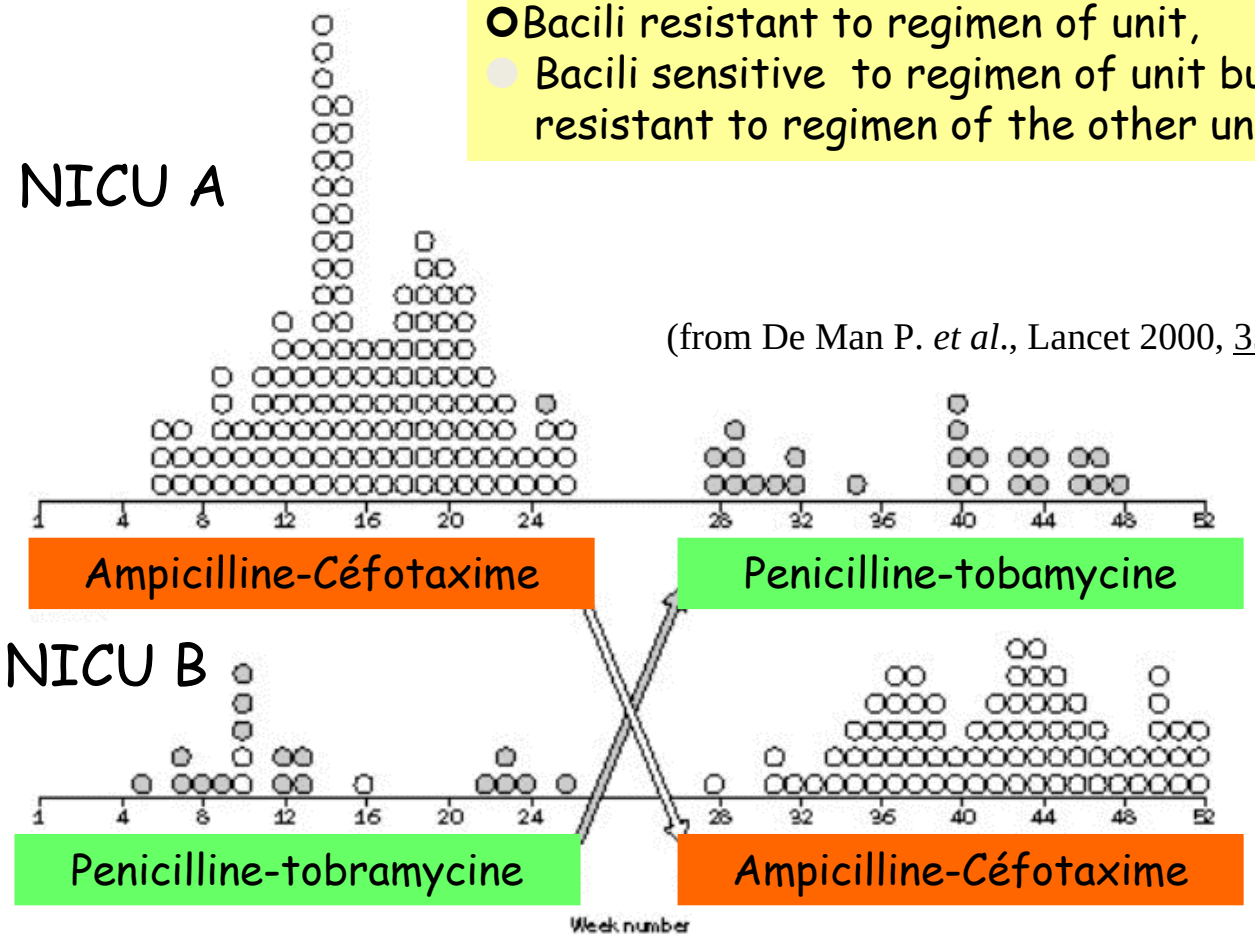
Woerther PL *et al.*, AAC 2013

How can we do that ?

1. Reduce antibiotic usage
2. Modify antibiotic usage
3. Decrease antibiotic concentrations in the colon during treatments
4. Use of Fecal transplant or « new » probiotics

Antibiothérapie empirique et colonisation intestinale chez des nouveaux-nés de réanimation

- Bacili resistant to regimen of unit,
- Bacili sensitive to regimen of unit but resistant to regimen of the other unit



(from De Man P. *et al.*, Lancet 2000, 355 : 973)

Sympo BMS Mai 2000

For vets : Modify the doses for metaphylaxia

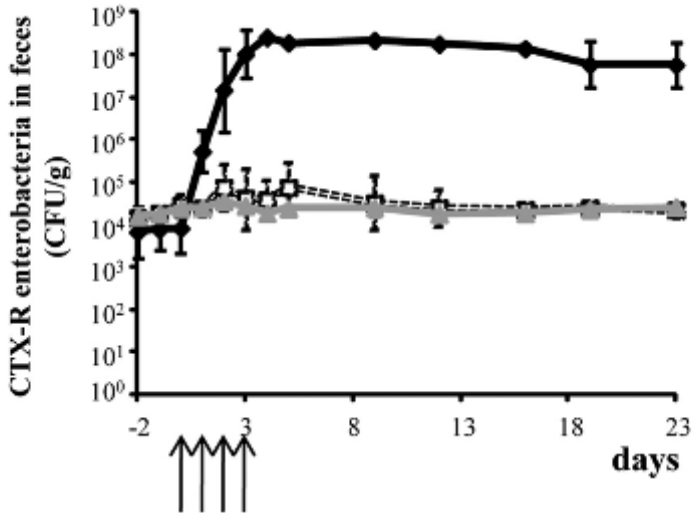


FIG 2 Impact of the different cefquinome dosage regimens on cefotaxime-resistant *Enterobacteriaceae* in the fecal flora of rats before, during, and after treatment. ◆, Patent-phase-adjusted dose (50 mg/kg of body weight); □, prepatent-phase-adjusted dose (5 mg/kg); ▲, control untreated group. Data are means ± standard deviations (SDs). The arrows indicate the days of antibiotic administration.

Animals without symptoms have low inocula at most

✓Thus small doses are enough for treatment

✓This strongly devrease the impact on the microbiota

Vasseur *et al.* AAC 2014

How can we do that ?

1. Reduce antibiotic usage
2. Modify antibiotic usage
3. Decrease antibiotic concentrations in the colon during treatments
4. Use of Fecal transplant or « new » probiotics

The idea goes far back in the 80s

THE JOURNAL OF INFECTIOUS DISEASES • VOL. 160, NO. 2 • AUGUST 1989
© 1989 by The University of Chicago. All rights reserved. 0022-1899/89/6002-0013$01.00

Use of β-Lactamase-Producing Anaerobes to Prevent Ceftriaxone from Degrading Intestinal Resistance to Colonization

Florence Léonard, Antoine Andremont, Bernard Leclerq, Roger Labia, and Cyrille Tancrède

From the Laboratoire d'Ecologie Microbienne, Service de Réanimation Médico-Chirurgicale, Institut Gustave-Roussy, Villejuif, and Centre National de la Recherche Scientifique, Paris, France

PCT ORGANISATION MONDIALE DE LA PROPRIETE INTELLECTUELLE
Bureau international

DEMANDE INTERNATIONALE PUBLIEE EN VERTU DU TRAITE DE COOPERATION EN MATIERE DE BREVETS (PCT)

(51) Classification internationale des brevets[4] : A61K 35/74 — A1

(11) Numéro de publication internationale: **WO 88/ 07865**

(43) Date de publication internationale: 20 octobre 1988 (20.10.88)

(21) Numéro de la demande internationale: PCT/FR88/00172

(22) Date de dépôt international: 8 avril 1988 (08.04.88)

(31) Numéro de la demande prioritaire: 87/05110

(32) Date de priorité: 10 avril 1987 (10.04.87)

(33) Pays de priorité: FR

(71) Déposant *(pour tous les Etats désignés sauf US)*: INSTITUT GUSTAVE ROUSSY [FR/FR]; Rue Camille-Desmoulins, F-94805 Villejuif Cédex (FR).

(72) Inventeurs; et
(75) Inventeurs/Déposants *(US seulement)* : TANCREDE, Cyrille [FR/FR]; 15, avenue Joffre, F-92420 Vaucresson (FR). ANDREMONT, Antoine [FR/FR]; 252, rue de Vaugirard, F-75015 Paris (FR). LABIA, Roger [FR/FR]; 1, rue Falret, F-92170 Vanves (FR). LEONARD, Florence [FR/CH]; Chemin des Ormeaux, CH-1066 Epalinges (CH).

(74) Mandataire: LACHASSAGNE, Jacques; B.P. 07, F-78430 Louveciennes (FR).

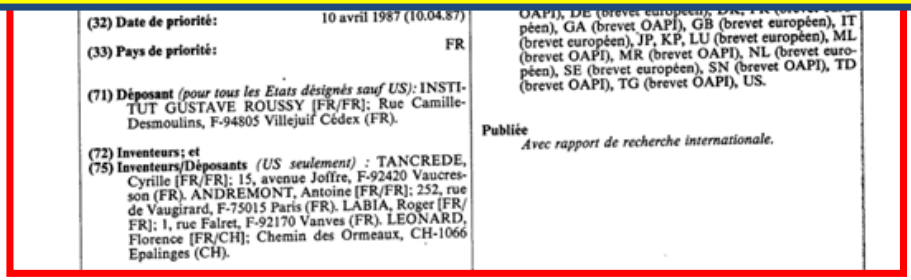
(81) Etats désignés: AT (brevet européen), AU, BE (brevet européen), BJ (brevet OAPI), CF (brevet OAPI), CG (brevet OAPI), CH (brevet européen), CM (brevet OAPI), DE (brevet européen), DK, FR (brevet européen), GA (brevet OAPI), GB (brevet européen), IT (brevet européen), JP, KP, LU (brevet européen), ML (brevet OAPI), MR (brevet OAPI), NL (brevet européen), SE (brevet européen), SN (brevet OAPI), TD (brevet OAPI), TG (brevet OAPI), US.

Publiée
Avec rapport de recherche internationale.

The idea goes far back in the 80s

Envoyer « vectoriser » dans le colon un produit qui :

- ✓détruise les résidus antiotiques et préserve la flore
- ✓sans affecter l'efficacité des traitements



(32) Date de priorité: 10 avril 1987 (10.04.87)

(33) Pays de priorité: FR

(71) Déposant *(pour tous les Etats désignés sauf US)*: INSTITUT GUSTAVE ROUSSY [FR/FR]; Rue Camille-Desmoulins, F-94805 Villejuif Cédex (FR).

(72) Inventeurs; et
(75) Inventeurs/Déposants *(US seulement)* : TANCREDE, Cyrille [FR/FR]; 15, avenue Joffre, F-92420 Vaucresson (FR). ANDREMONT, Antoine [FR/FR]; 252, rue de Vaugirard, F-75015 Paris (FR). LABIA, Roger [FR/FR]; 1, rue Falret, F-92170 Vanves (FR). LEONARD, Florence [FR/CH]; Chemin des Ormeaux, CH-1066 Epalinges (CH).

OAPI), DE (brevet européen), DK, FR (brevet européen), GA (brevet OAPI), GB (brevet européen), IT (brevet européen), JP, KP, LU (brevet européen), ML (brevet OAPI), MR (brevet OAPI), NL (brevet européen), SE (brevet européen), SN (brevet OAPI), TD (brevet OAPI), TG (brevet OAPI), US.

Publiée
Avec rapport de recherche internationale.

Three (?) companies are reviving the concept

1. IPSAT which failed to go to the market with a penicillinase
2. SyntheticBiologics which communicates on the use of a cephalosporinase
3. DaVolterra which develops a broader approach using adsorbents to inactivate a large range of antibiotics

How can we do that ?

1. Reduce antibiotic usage
2. Modify antibiotic usage
3. Decrease antibiotic concentrations in the colon during treatments
4. Use of Fecal transplant or « new » probiotics

E. coli (Mutaflor) probiotic and MDR colonisation in eldery nursing home pts

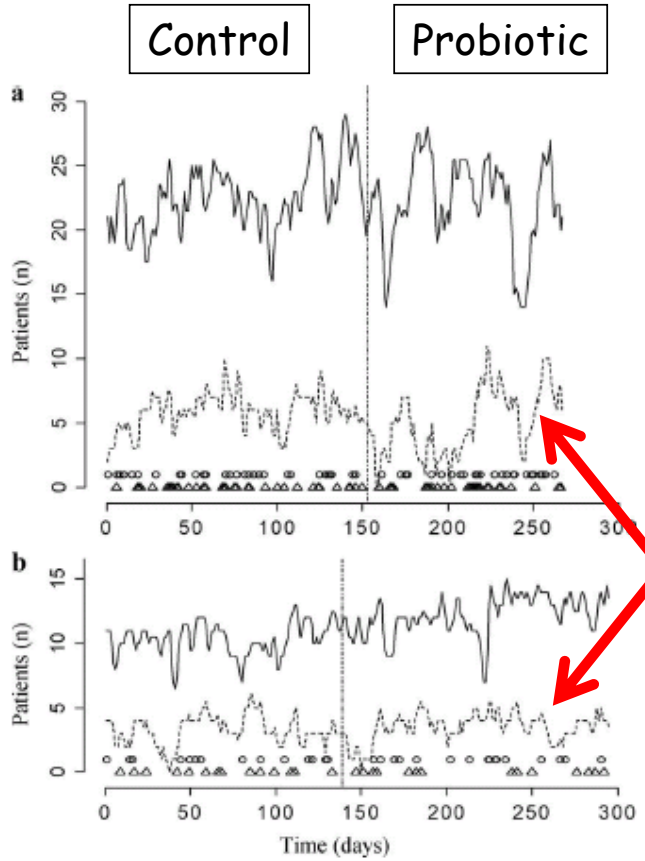
Site of colonisation	% positive after 5 wks Rx	
	Placebo N=36	Probiotic N=33
Feces	58	77
Urine	77	75

Tannock, GW *et al.* JMM 2011

Effect of probiotic on VRE colonisation in patients.

Gastro nephro

Geriatry



Multispecies probiotic
Bifidus 4, *Lactobacillus* 5, *Enterococcus* 1

VRE colonisation

De Regt MJA, *et al. AAC* 2010

Donor feces infusion for eradication of Extended Spectrum beta-Lactamase producing *Escherichia coli* in a patient with end stage renal disease

Singhj R. *et al.* CMI 2014

- ✓ Man 60y, HTA, end-stage renal diseases, Two allotransplantation (2000-3)
- ✓ 2006-12 X epidodes aof pyelonephritis ESBL E;. Coli
- ✓ 2012 Graft failure, Perotoneal dyalisis

- ✓ Fecal transplantation in 2013 (protocole FECAL trial). No previous antibiotic
- ✓ One single duodenal infusion
- ✓ Restal culture negative for ESBL from Week 2
- ✓ Follow-up 12 weeks. No symptom of infection.

- ✓ 64 pts in 4 EU centers
- ✓ ESBL or CPE infections resolved but persistent carriage
- ✓ Decontamination plus FT vs No treatment
- ✓ End point : Lack of carriage 35-48 days after randomisation
- ✓ Starting T3-2015

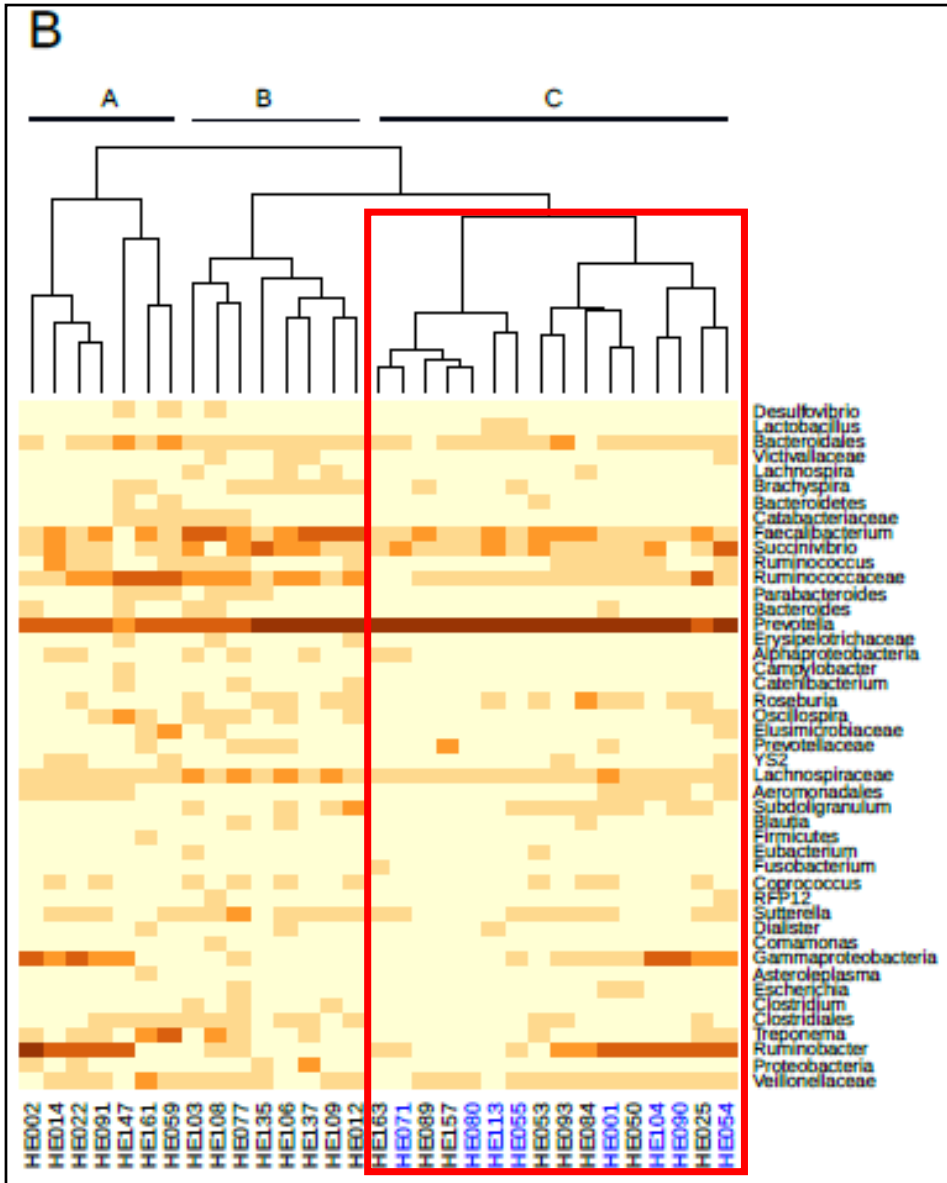
A new type of probiotics coming from the amerindians ?

A collaboration with Andres Moya from Valencia (Spain)

Comparison of the « active » microbiota of 8 ESBL (CTX-M carriers to 24 non carriers controls

- South of French Guiana
- Restricted area

2°15'0.99"N, 52°52'58.99"W

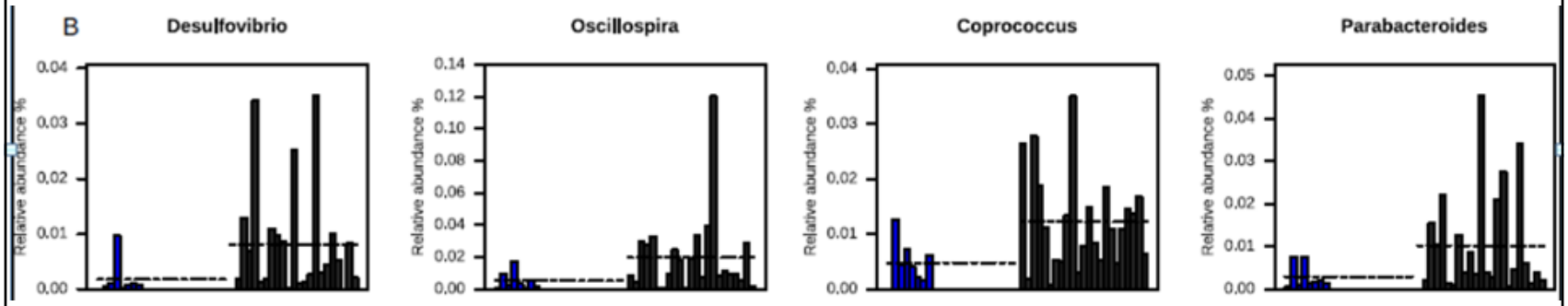


Heat maps and clustering based on taxon composition and abundance (Bray-Curtis distance) in the active microbiota (16S rRNA).

ESBL carriers blue
Non-carriers black.

Gonsalves *et al.* Accepted

Relative abundance of the bacterial biomarkers. (B) non-carriers' biomarkers in active microbiota. Dashed line represents mean value.



Gonsalves *et al.* Accepted

Pour résumer

- ✓Jusqu'à présent nous avons eu une approche trop exclusivement médicale de l'antibiorésistance
- ✓Nous devaons prendre en compte la compléxité mondiale et environnementale du phénomène
- ✓Le contrôle sera long et coûteux, c'est certain!

« The question »
a painting from Alam-Tadena (1836-1912)

Merci beaucoup pour votre attention.