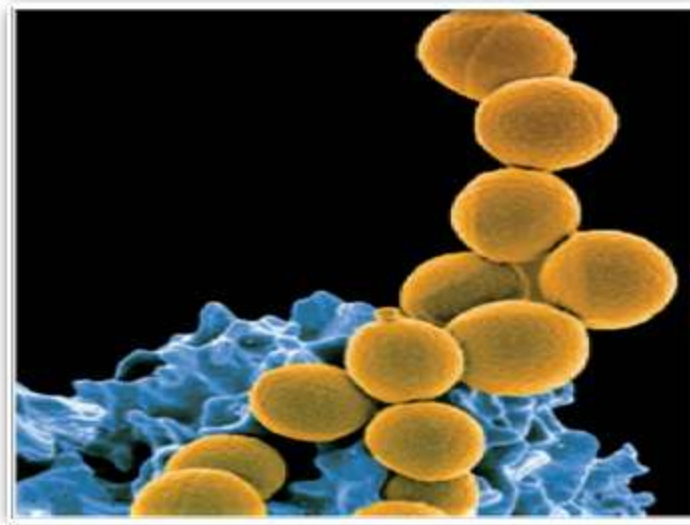


Antimicrobials: a true ONE HEALTH issue: Background from a Medical Perspective

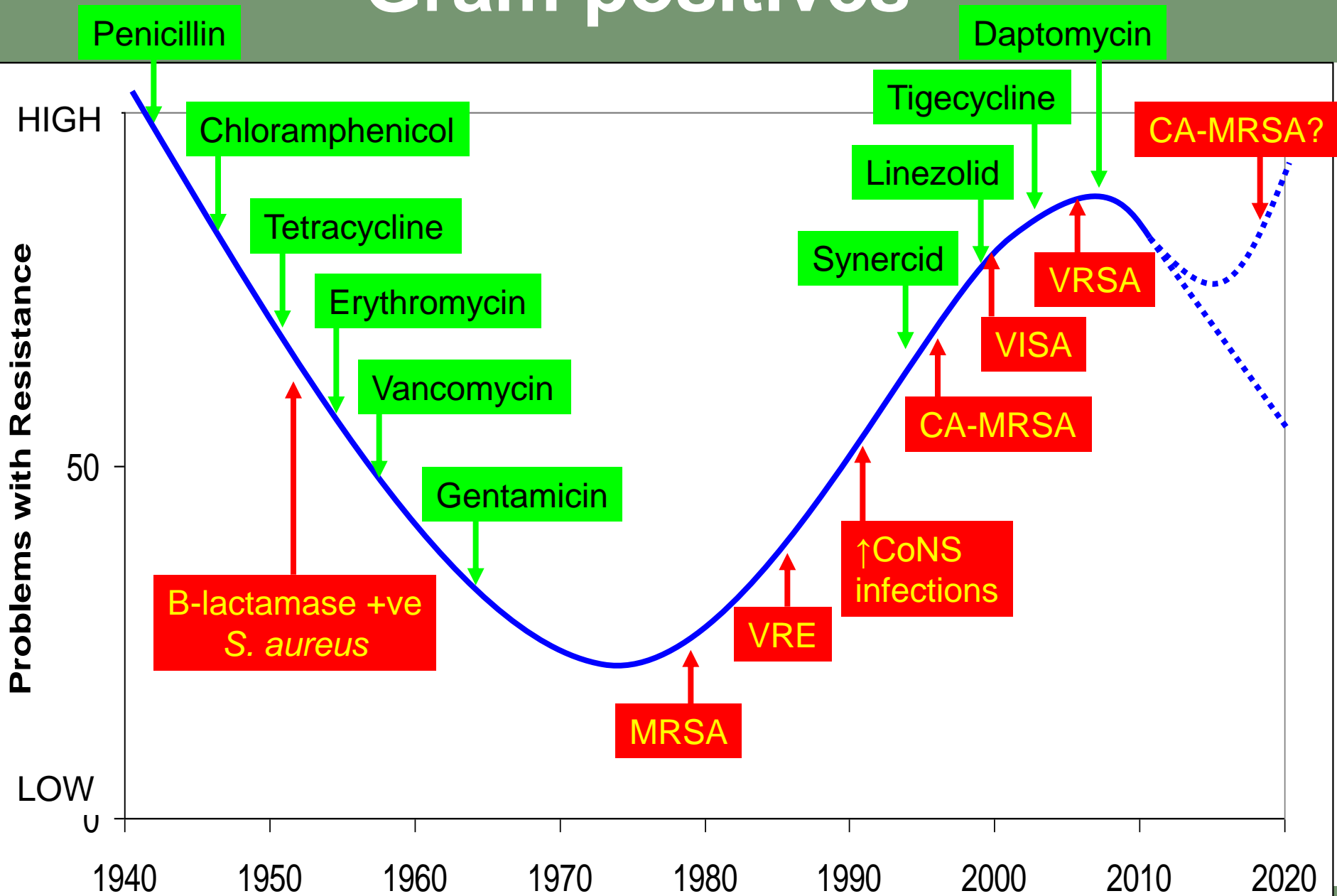
Herman Goossens
Department of Medical Microbiology
Vaccine & Infectious Disease Institute
University of Antwerp, Belgium



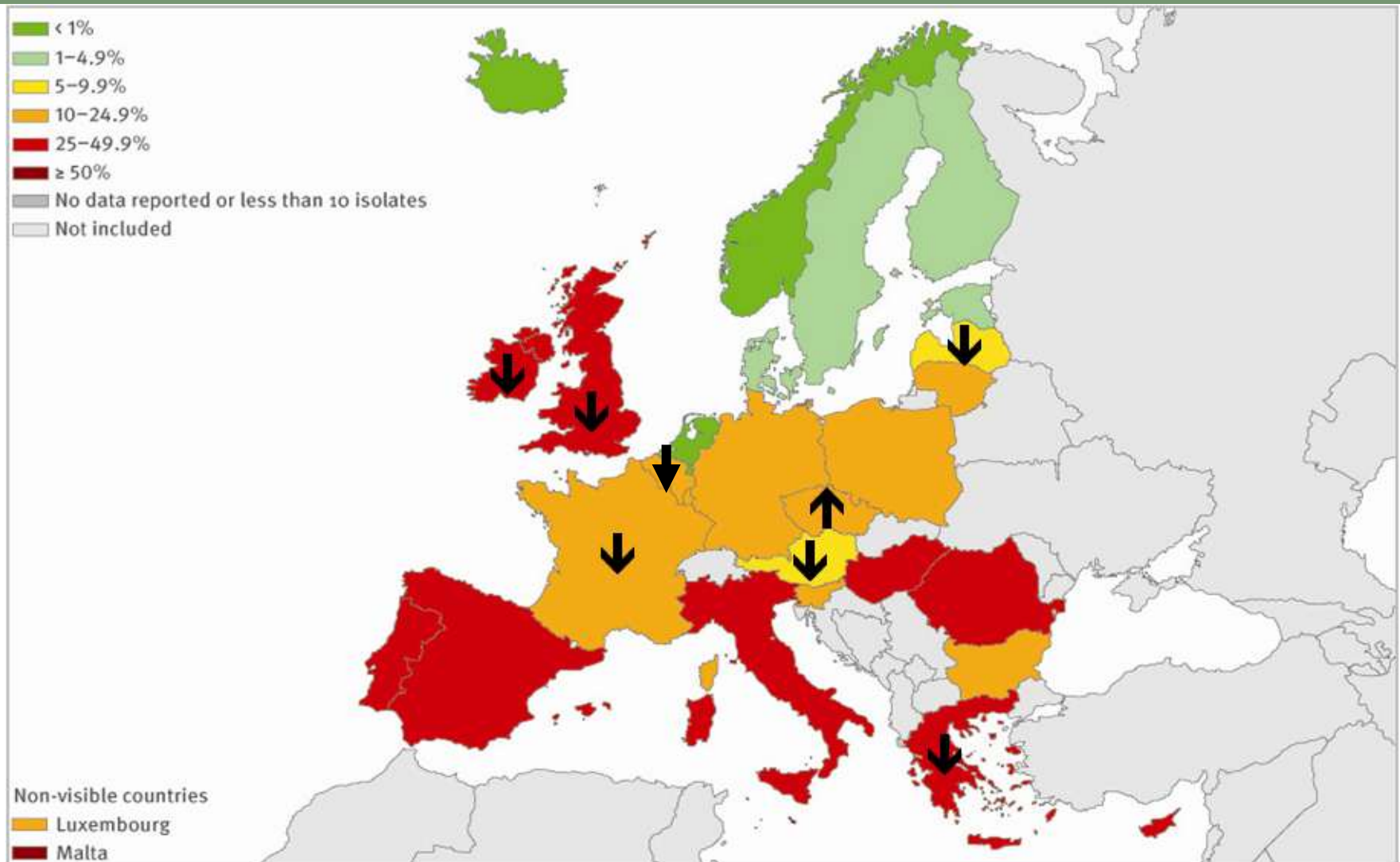
Resistance among the Gram-positives



Gram positives



Staphylococcus aureus : Proportion of Invasive Isolates Resistant to Methicillin (MRSA), 2009

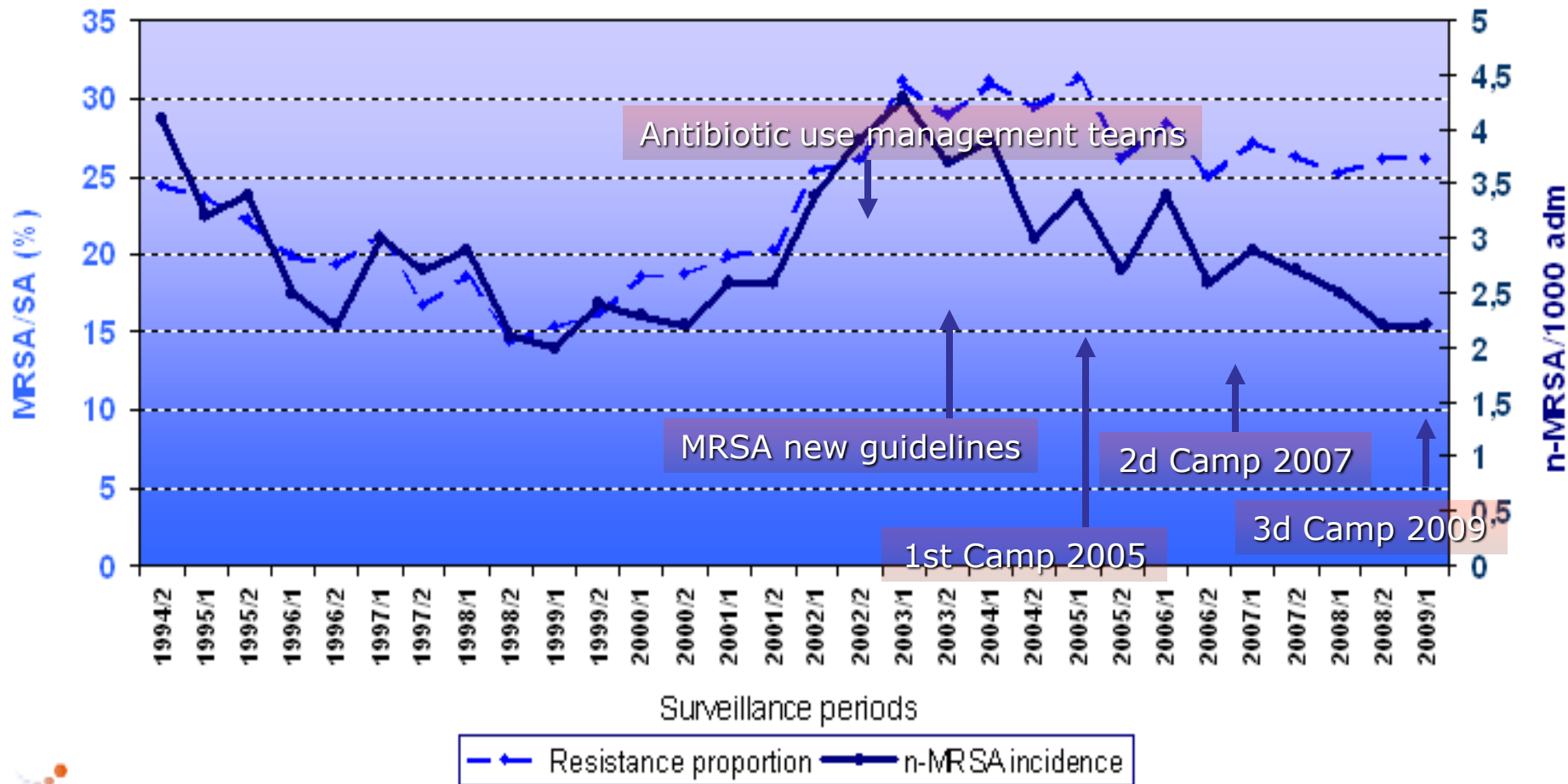


The symbols ↑ and ↓ indicate a significant increasing or decreasing trend for the period 2006-2009, respectively. These trends were calculated on laboratories that consistently reported during 2006-2009.

MRSA in Belgian acute care hospitals: proportion of *S.aureus* clinical isolates and incidence of nosocomial acquisition



1994 - 2009



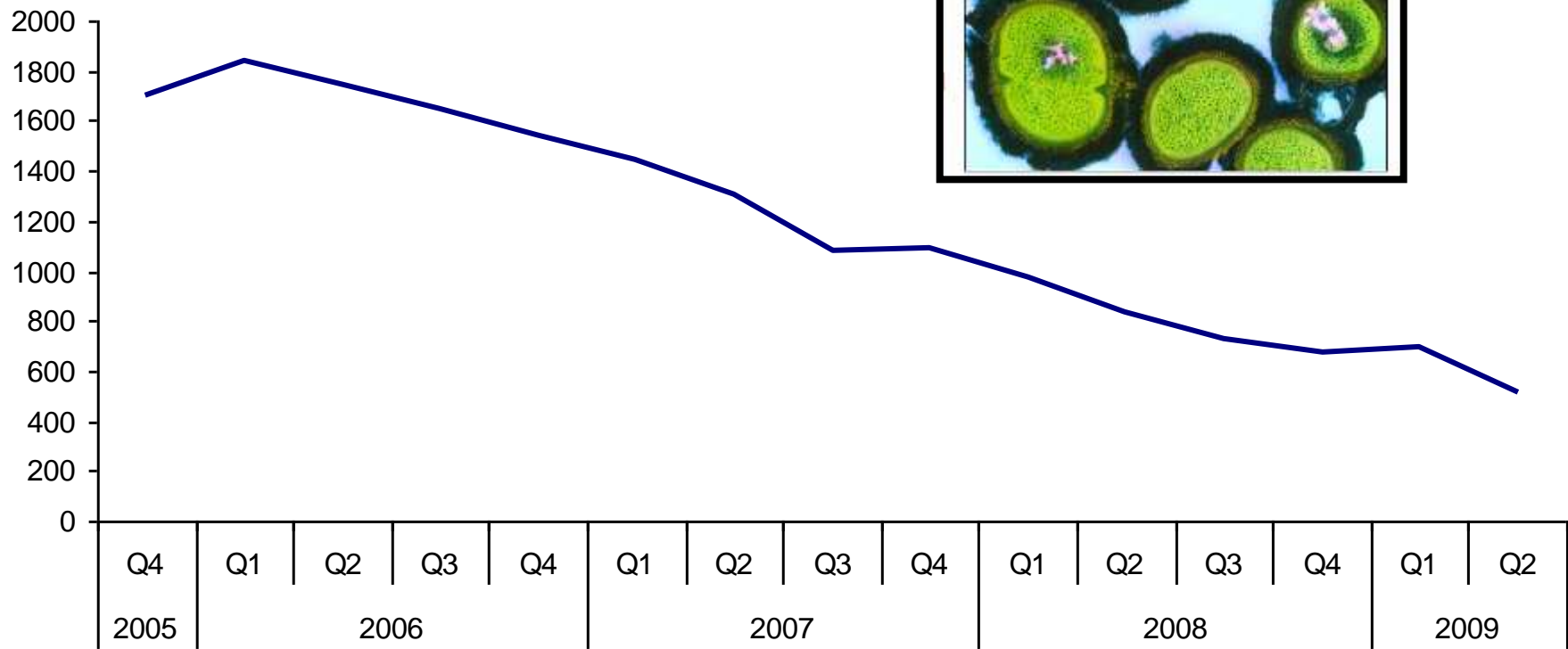
isp
WIV
Source: National surveillance, B. Jans

Mean of rates in cohort of hospitals with min. 5 participations since 1994

Counts of MRSA Bacteraemia Oct 2005 to June 2009

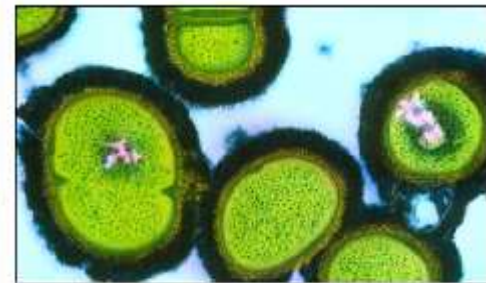


MRSA BSI episodes



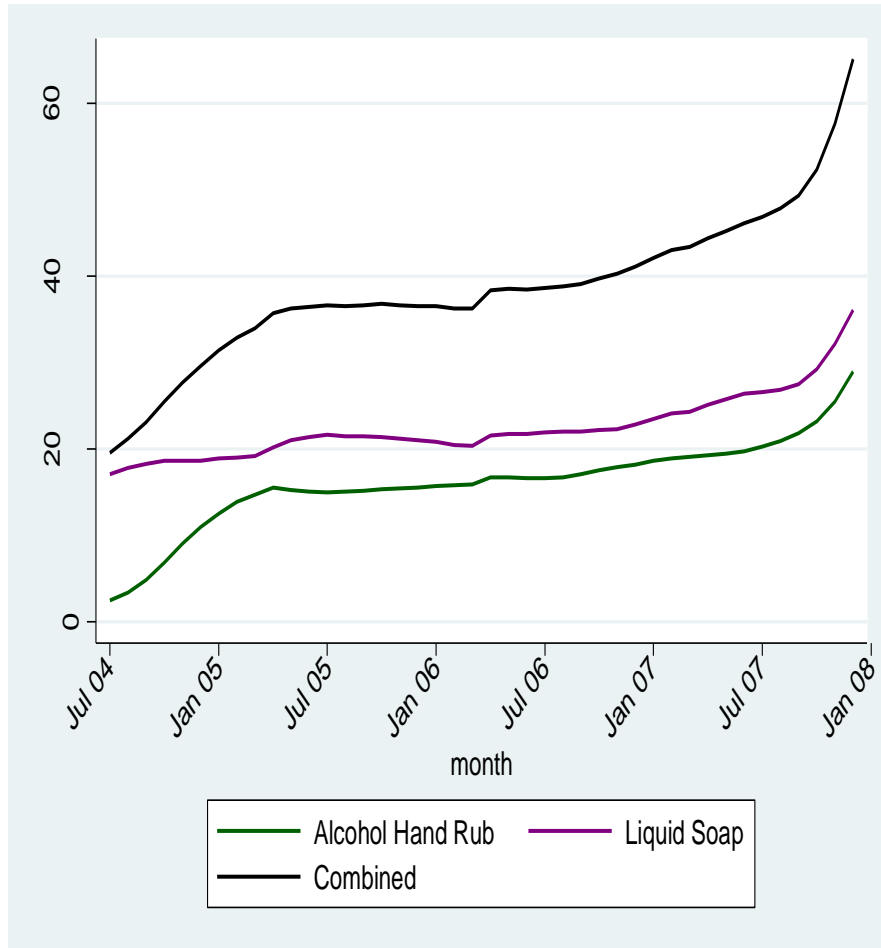
BBC World news

Target to halve MRSA cases is met



A. Pearson and colleagues (HPA, Sept 2009)

Estimated Average Procurement of Alcohol Hand Rub and Liquid Soap in ml/bed-day, 2004-2007 in 148 acute NHS Trusts



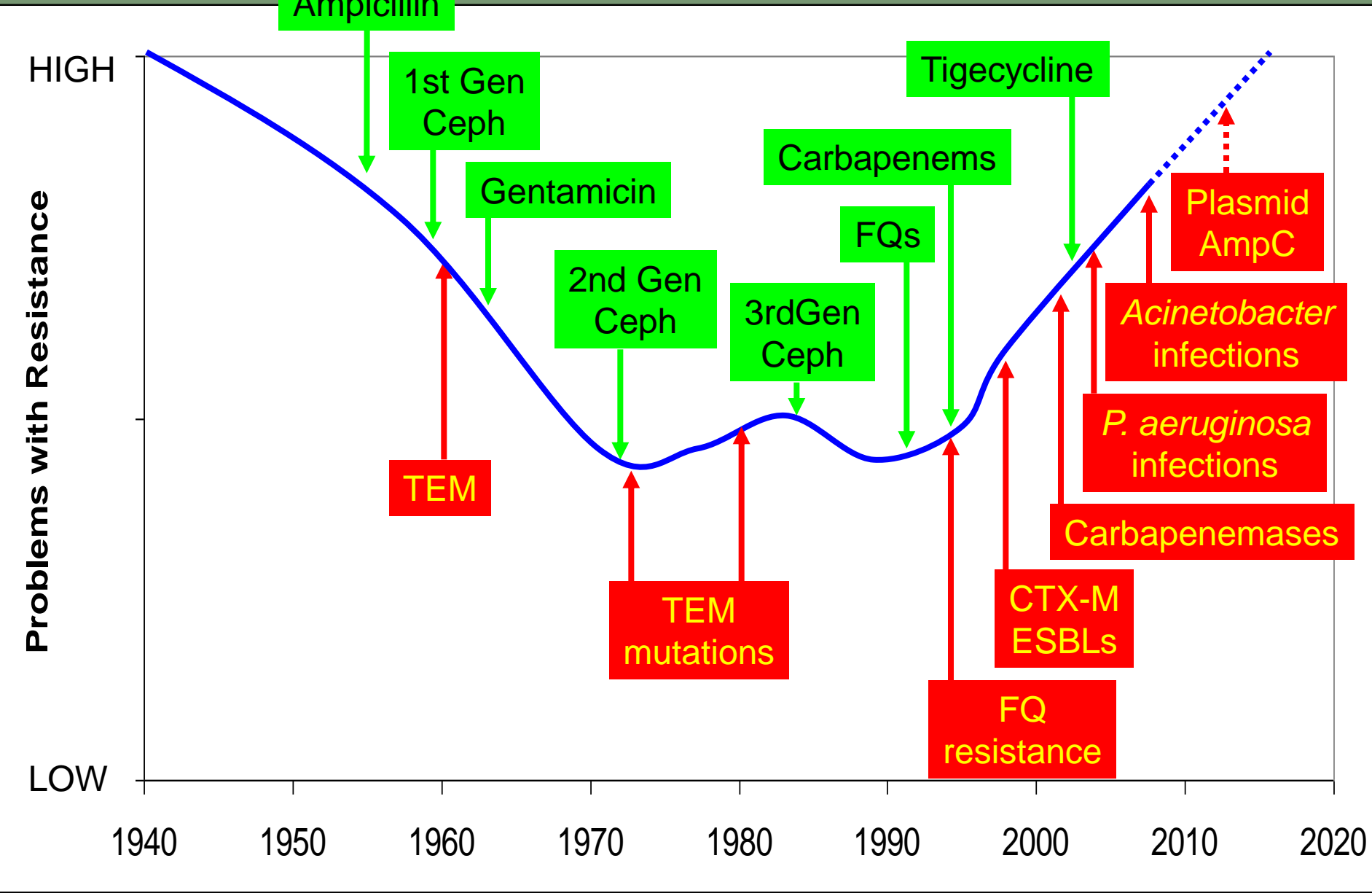
- 3-fold increase in combined use to 60 ml per pt-day
- Analysis shows highly significant association between each ml of AHR used and 1% drop fall in MRSA BSI

Stone S et al. ECCMID
2009 (abstract O140)

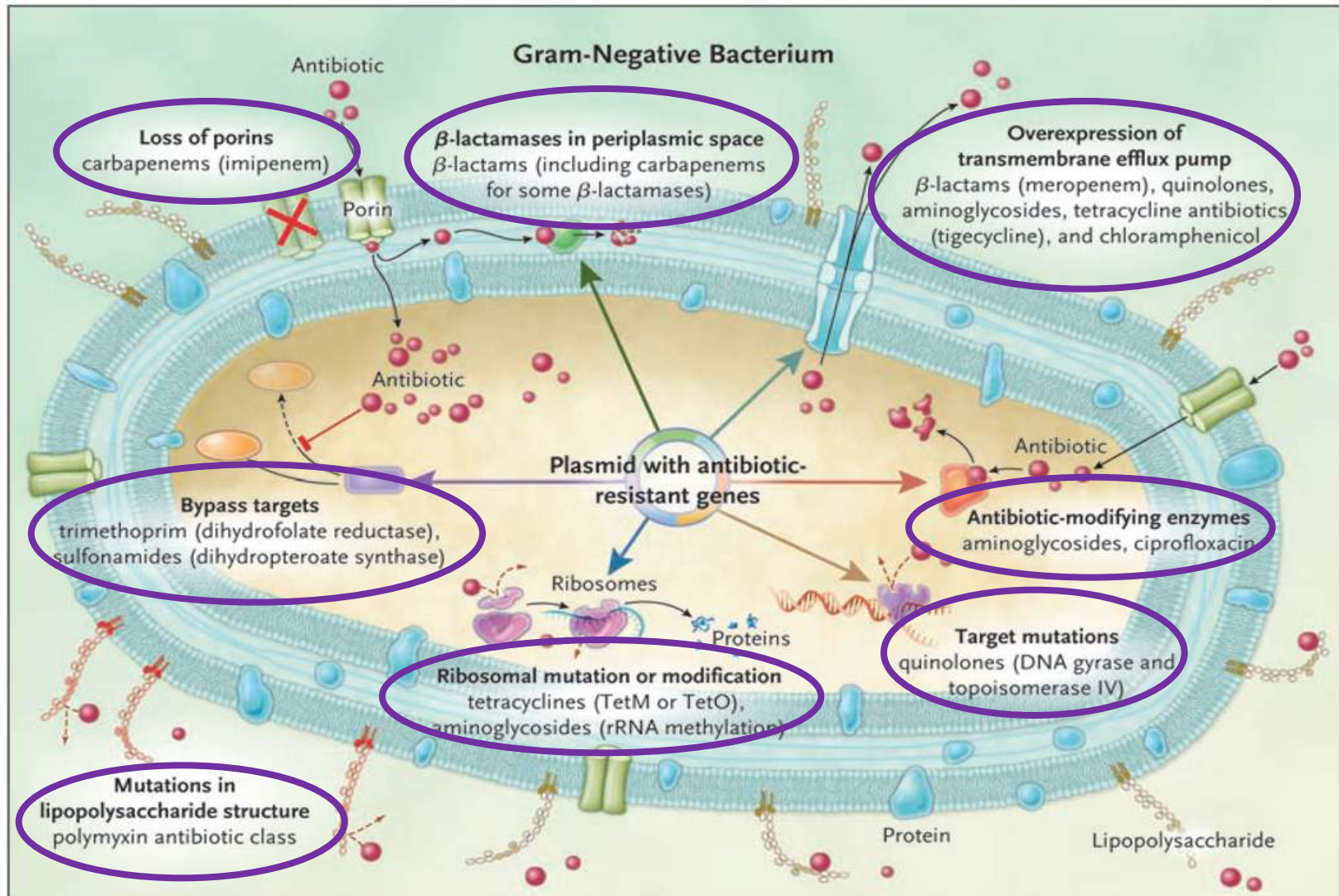
Resistance among the Gram-negatives



The Gram-Negatives ... are Back!



Multiple Mechanisms of Resistance in Gram-Negative Bacteria



Classification of β -Lactamases

Class A

- PC
- SHV-1, TEM-1, 2

- **SHV->1**
- **TEM->2**
- **CTX-M**
- **PER**
- **VEB**

- CARB
- RTG
- CepA

- SME
- IMI
- SME
- NMC
- IND
- **KPC**
- GES
- BIC

Class B

- IMP
- **VIM**
- KHM
- SPM
- GIM
- SIM
- **NDM**
- AIM
- DIM
- BEL

Class C

- AmpC
- CMY
- ACT
- DHA
- ACC
- FOX

Class D

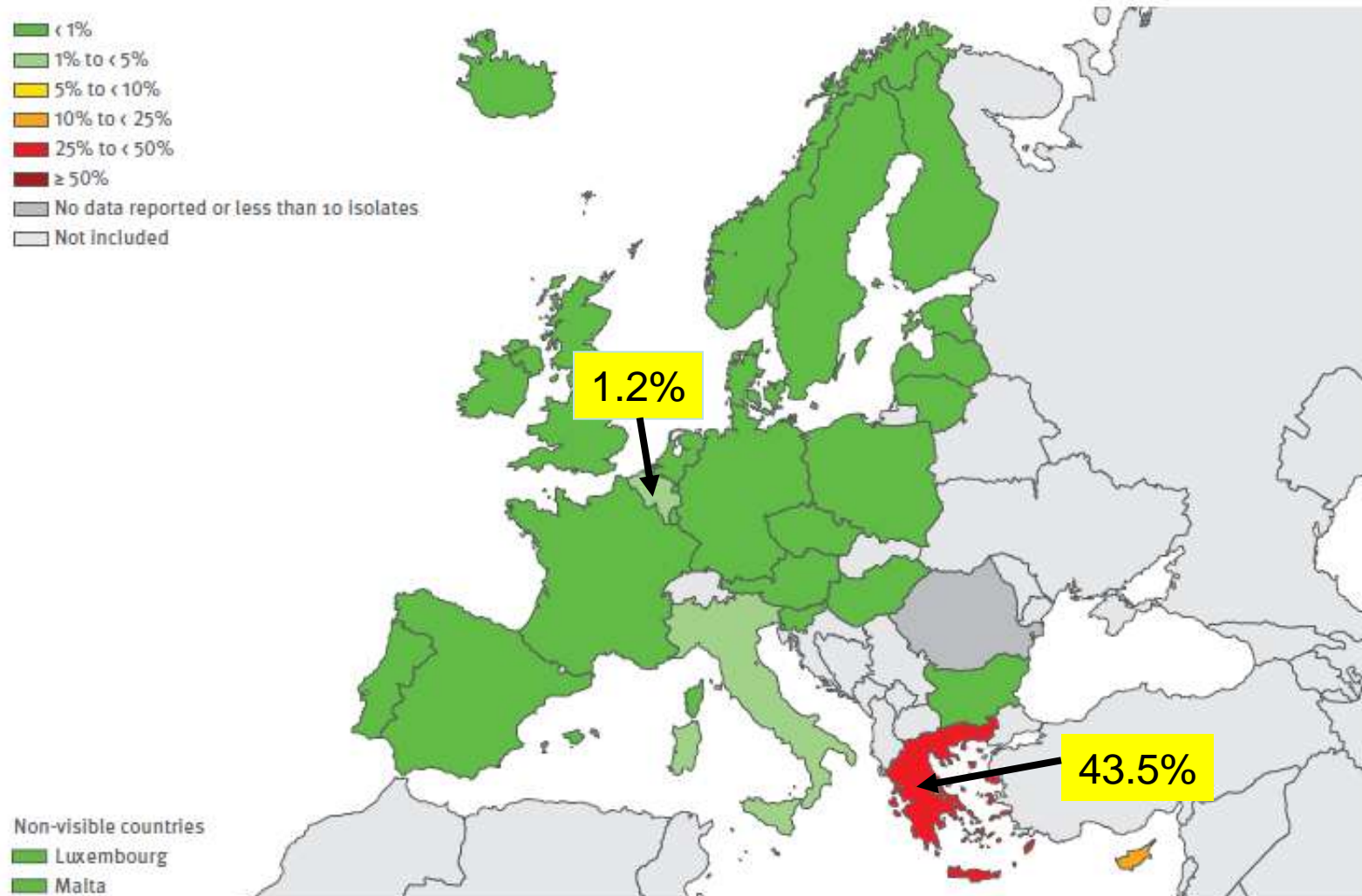
- OXA-1, 10,
- **OXA-11, 15**
- OXA-23/27
- 24/40
- 48, 51/66/69**
- 58, 143**

ESBL

Carbapenemases

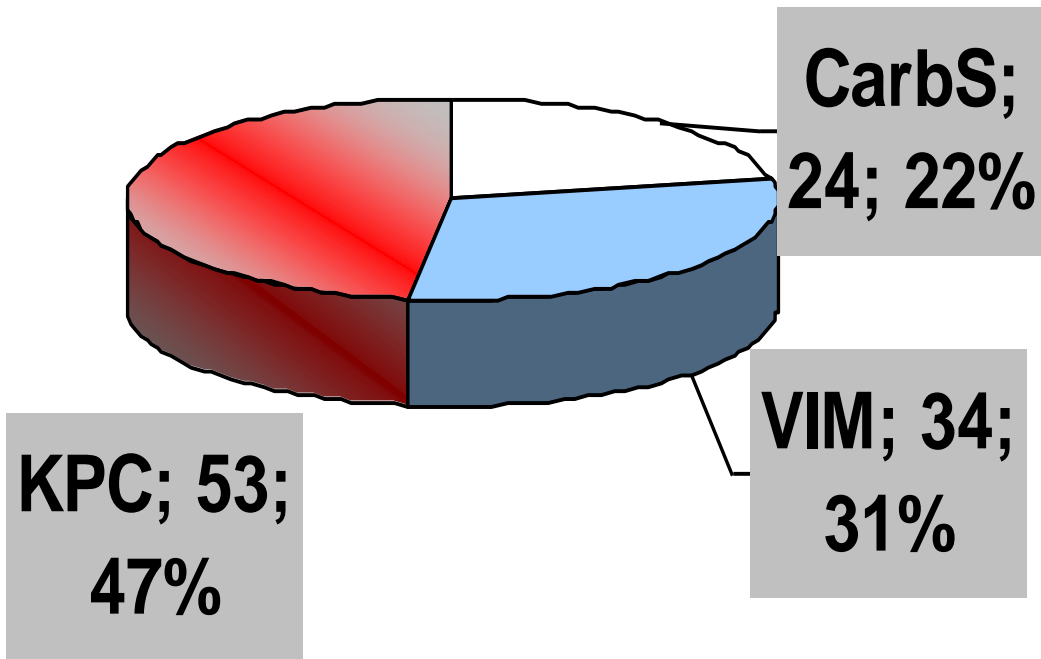
Metallo- β -Lactamases (MBLs)

Resistance to Carbapenems among *K. pneumoniae*, EARS-net 2009



Resistance to Carbapenems among *K. pneumoniae* in Tzaneio General Hospital of Piraeus, Athens, Greece

K. pneumoniae BSI 2008-2010



Treatments of last resort for infections with ESBL and carbapenemase-producing Gram-negatives



Tigecycline

- The first marketed member of glycylycylines
- 9-t-butylglycylamido derivative of minocycline
- Evades common tetracycline efflux pumps and ribosomal protection mechanisms

BUT:

- Bacteriostatic mode of activity
- Many small observational studies
- Not good levels in blood
- Active against Enterobacteriaceae and *Acinetobacter*, but not against *Pseudomonas*
- Variable clinical effectiveness against *Acinetobacter*
- Emergence of resistance during treatment

Colistin

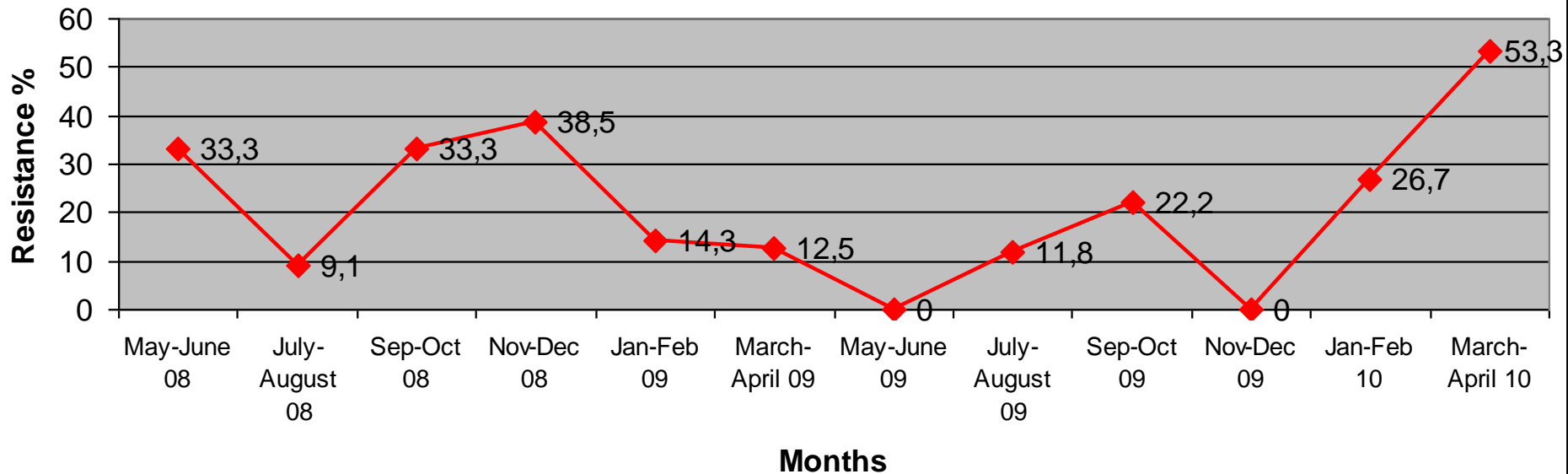
- Old (1950ies) bactericidal drugs, used as a prodrug (Colistin methanesulfonate, CMS)
- About 10 x more active against Gram-negative than Gram-positive bacteria

BUT:

- Inherent resistance: *Burkholderia cepacia*, *Serratia*, *Proteus*, *Bacteroides fragilis* ... and most Gram-negative cocci
- CMS is a very inefficient prodrug (5 – 15% converted to colistin)
- Insufficient plasma concentrations, even at steady state
- Renal toxicity in up to 20% of patients
- Emergence of resistance during treatment

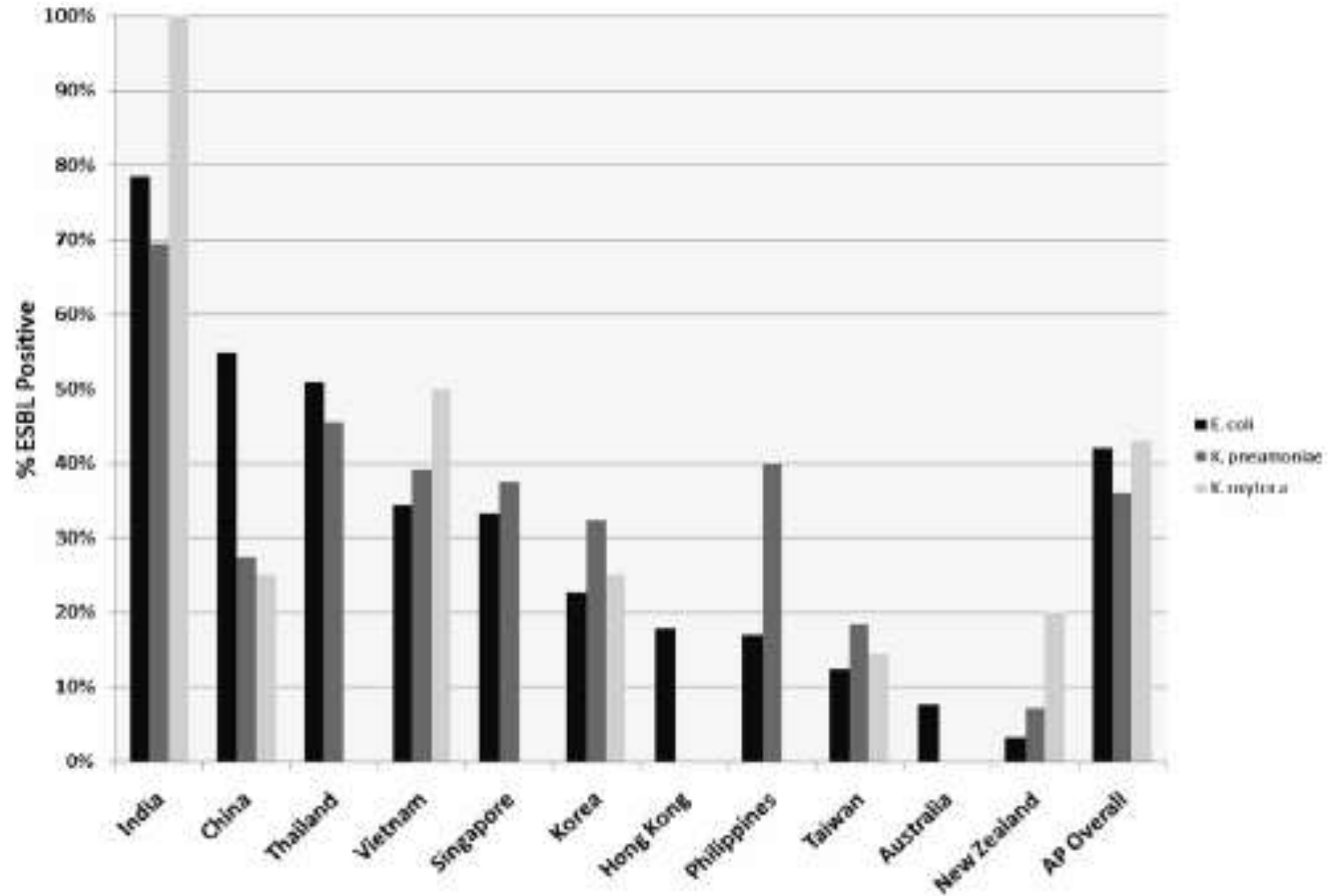
Resistance among KPC-Producing *K. pneumoniae* in Tzaneio General Hospital of Piraeus, Athens, Greece

Colistin Resistance (%) among KPC-KP (2 years), Tzaneio Hosp



Colistin resistance May 08- Oct 10: 27.8 % (41/180)
Non susceptibility to tigecycline: 2.8% (5/180)

Emergence of High Levels ESBL Producing Gram-negative Bacilli in the Asia-Pacific Region



New Delhi Metallo-1: The Mother of all β -Lactamases?

- ***bla*_{NDM-1} (New Delhi Metallo-1):**

- Swedish patient of Indian origin who traveled to New Delhi
- Acquired UTI in India
- New Metallo- β -Lactamase (MBL) gene
- Can hydrolyze all β -lactams except aztreonam
- Located on a 180-kb (*K. pneumoniae*) & 140-kb plasmid (*E. coli*):
 - CMY-4 broadspectrum beta-lactamase
 - Genes inactivating ciprofloxacin, erythromycin, rifampicin, chloramphenicol, and aminoglycosides
 - Efflux pump genes
 - Growth promoters genes that increase transcription
- Potential for fast (global) spread

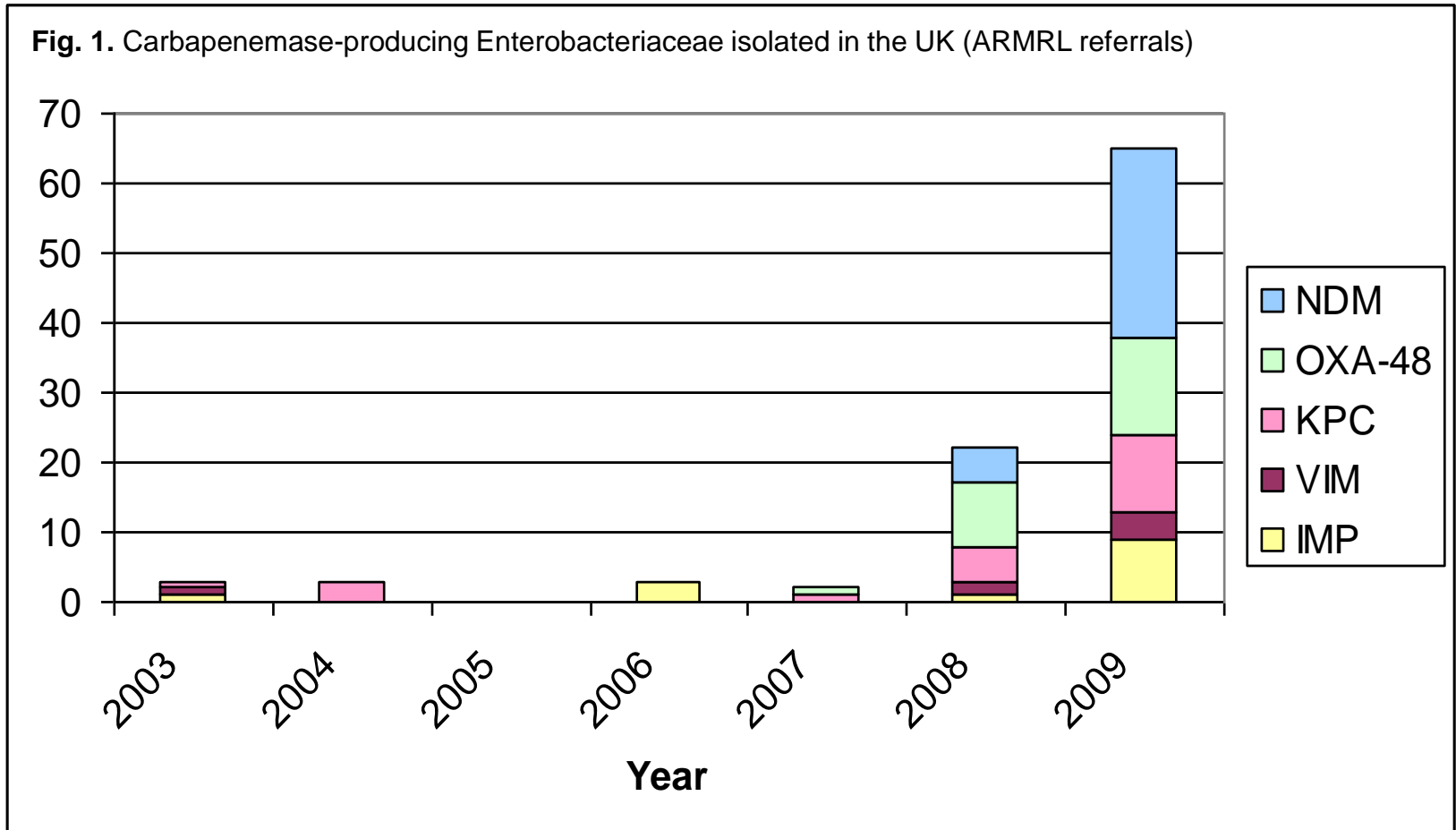
“The rapid dissemination of the *bla*_{NDM-1} carrying plasmids among clinical bacteria would be a nightmare scenario”



NDM-1 among Outpatients

- Objective: to study the prevalence of carbapenemase-producing Enterobacteriaceae in Pakistan
- Stool samples from 200 distinct patients in Rawalpindi, Pakistan
- 64 carbapenemase-positive isolates; only NDM-1 found
- Species:
 - *E. coli*: 30/64 isolates
 - *Enterobacter cloacae*: 21/64 isolates
- Prevalence:
 - Inpatients: 19/70 (27.1%)
 - Outpatients: 18/130 (13.8%)

Carbapenemase-Producing Enterobacteriaceae in the UK



Why Are the Gram-negatives Worse? Because They Have More Sex...



Pandemic Spread of *bla*_{CTX-M-15}-ST131

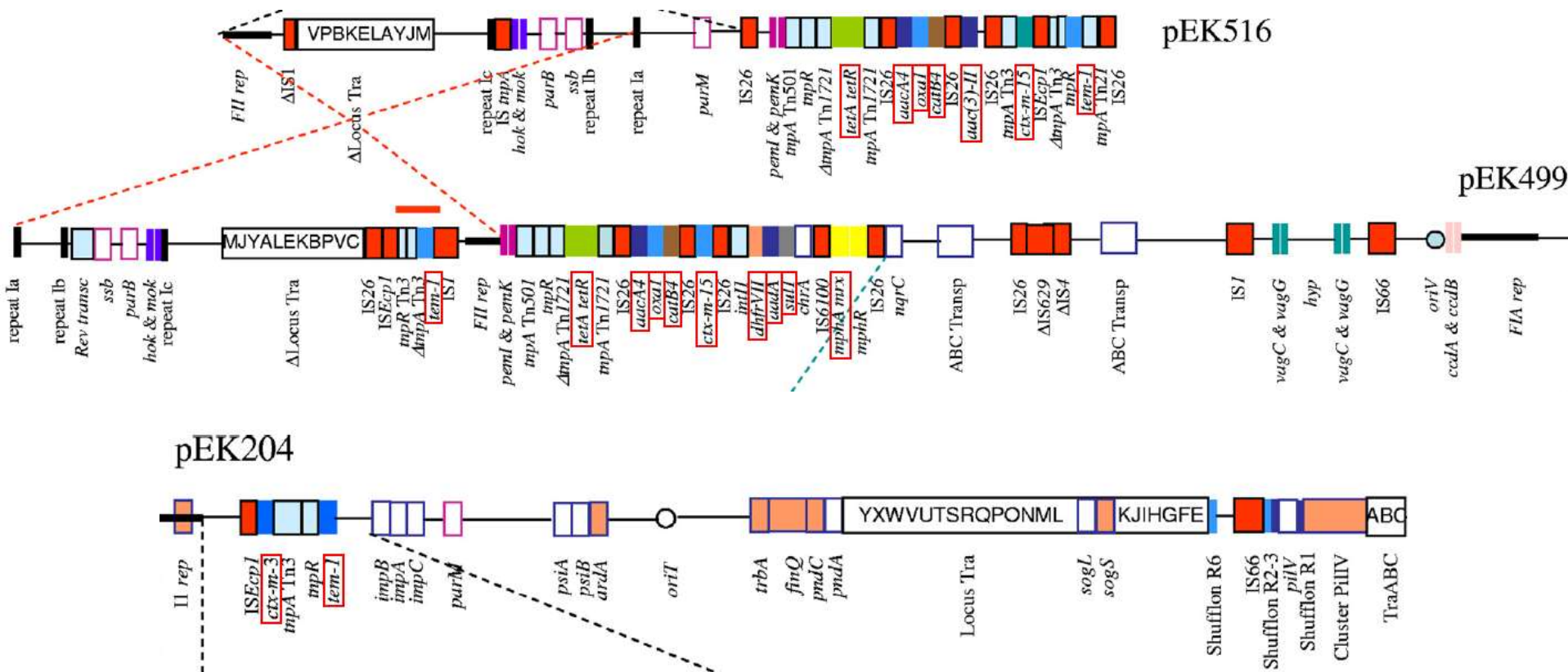
- ***bla*_{CTX-M-15}**
 - Located on multiple **plasmids** belonging to the incompatibility group IncFII
 - *bla*_{CTX-M-15} mostly downstream *ISEcpI*
 - Multidrug co-resistance:
 - *bla*_{OXA-1}
 - *bla*_{TEM-1}
 - *aac6'-Ib-cr* (aminoglycoside acetyltransferase)
 - *tet(A)* (tetracycline efflux protein), ...
- **MLST clone ST131**
 - Disseminated by a widespread, successful **clone**: Serotype O25:H4-MLST profile ST131
 - Causing urinary tract infections
 - O25:H4-ST131 not exclusively associated with *bla*_{CTX-M-15}

Plasmids Belonging to O25:H4-ST131

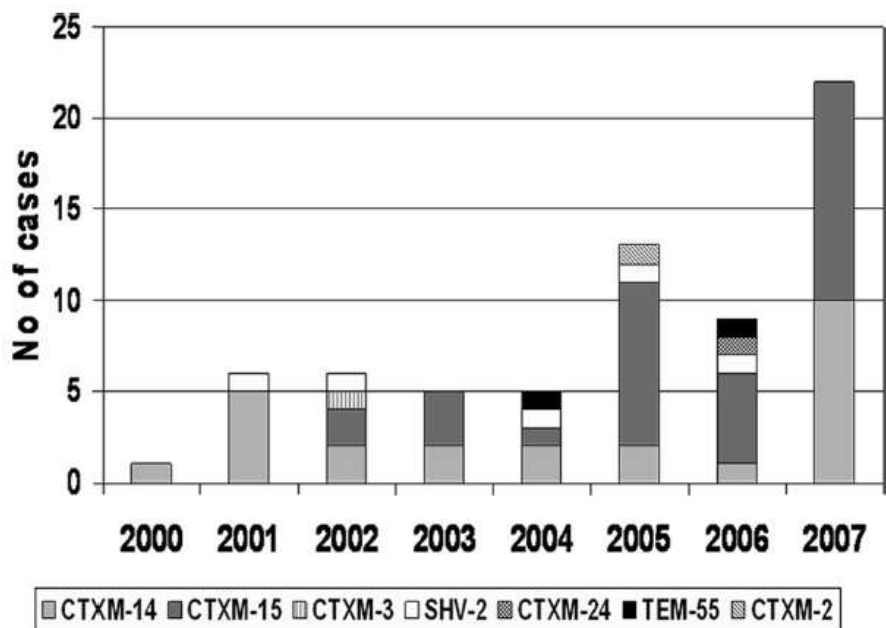
Complete Nucleotide Sequences of Plasmids pEK204, pEK499, and pEK516, Encoding CTX-M Enzymes in Three Major *Escherichia coli* Lineages from the United Kingdom, All Belonging to the International O25:H4-ST131 Clone

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Oct. 2009, p. 4472-4482 Vol. 53, No. 10
0066-4804/09/\$08.00+0 doi:10.1128/AAC.00688-09
Copyright © 2009, American Society for Microbiology. All Rights Reserved.

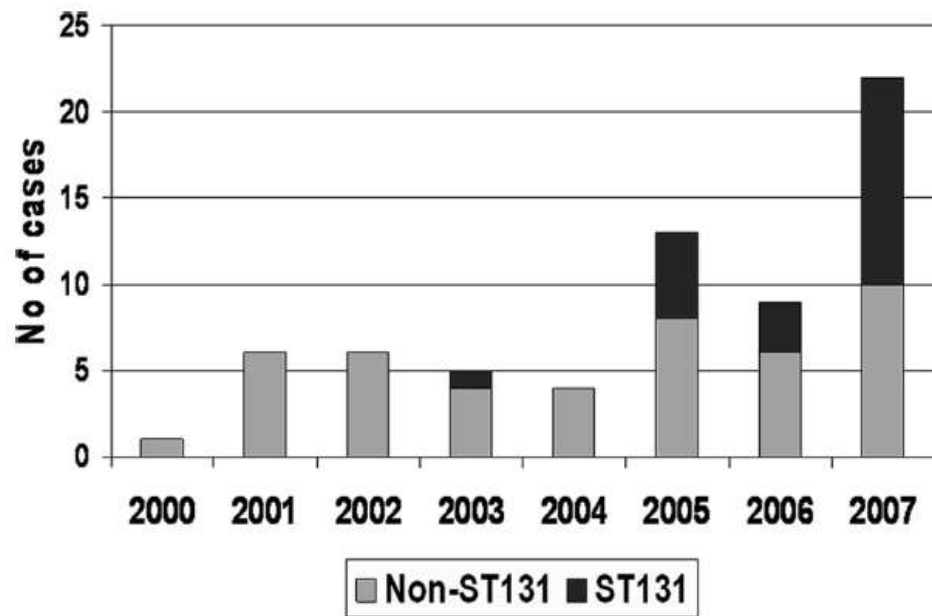
Neil Woodford,^{1*} Alessandra Carattoli,² Edi Karisik,¹ Anthony Underwood,¹
Matthew J. Ellington,¹ and David M. Livermore¹



Spread of MLST Clone ST131 in Canada



Distribution of the different ESBL-producing *Escherichia coli* isolates recovered from blood in the Calgary Health Region from 2000 to 2007



Distribution of *Escherichia coli* MLST clone ST131 isolated from blood in the Calgary Health Region from 2000 to 2007

Molecular Epidemiology of KPC-Producing *Klebsiella pneumoniae* Isolates in the United States: Clonal Expansion of Multilocus Sequence Type 258^v

Brandon Kitchel,^{1*} J. Kamile Rasheed,¹ Jean B. Patel,¹ Arjun Srinivasan,¹ Shiri Navon-Venezia,² Yehuda Carmeli,² Alma Brolund,³ and Christian G. Giske³

Worldwide Diversity of *Klebsiella pneumoniae* That Produces β -Lactamase *bla*_{KPC-2} Gene¹

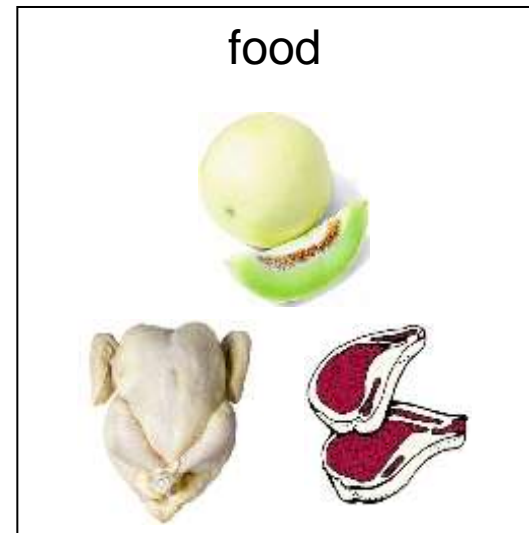
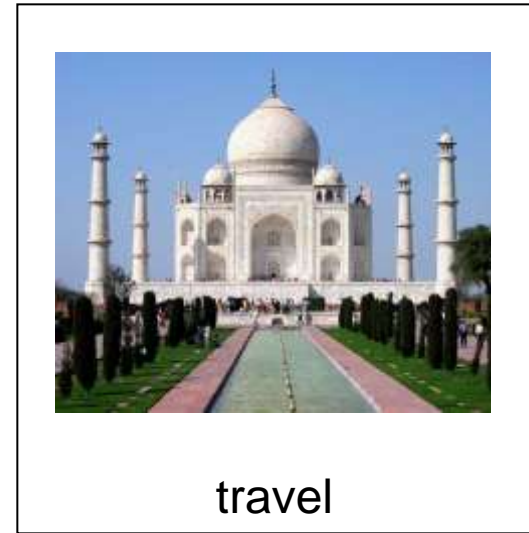
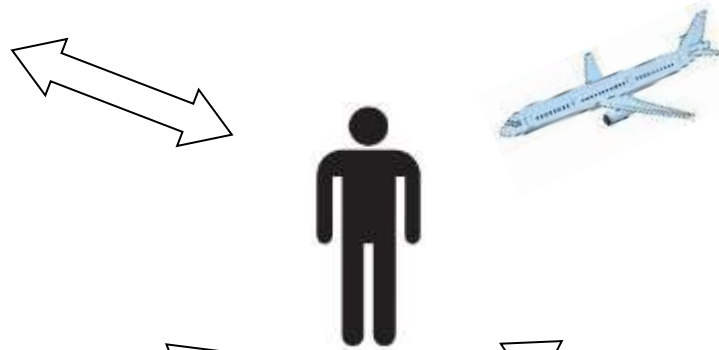
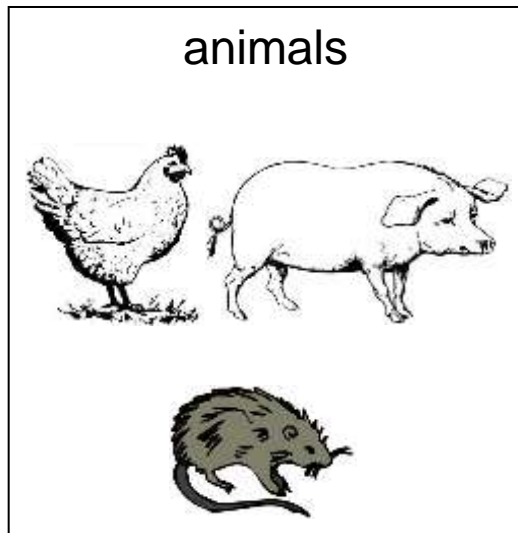
Gaëlle Cuzon Thierry Naas, HaVy Truong, Maria-Virginia Villegas, Karin T. Wisell, Yehuda Carmeli, Ana. C. Gales, Shiri Navon-Venezia, John P. Quinn, and Patrice Nordmann

In Greece: spreading of ESBL and Carbapenemases in same clone

Detection of the new metallo- β -lactamase VIM-19 along with KPC-2, CMY-2 and CTX-M-15 in *Klebsiella pneumoniae*

Spyros Pournaras^{1*}, Aggeliki Poulou^{2,3}, Evangelia Voulgari³, Georgia Vrioni³, Ioulia Kristo¹ and Athanassios Tsakris³

Spread



Intrafamilial Transmission of ESBL-Producing *E. coli* and *S. enterica* among Families of Adopted Children

- High prevalence of multidrug-resistant (MDR) bacteria in developing countries → High risk for carriage and infection
- French study: 24/25 adoptees (Mali) positive for ESBL-producing *Enterobacteriaceae* (E-ESBL)
- Transmission of E-ESBL demonstrated for 5/22 (22%) families in which at least one family member other than the adoptee was found positive for E-ESBL

β-Lactam resistance genes	ESBL-producing <i>Enterobacteriaceae</i>:	
	<i>E. coli</i>, n (%)	<i>Salmonella spp.</i>, n (%)
CTX-M-15	6 (12.2)	-
CTX-M-15/TEM-1	36 (73.5)	-
SHV-12/TEM-1	4 (8.2)	4 (100.0)
SHV-2/TEM1	1 (2.0)	-
Unknown*	2 (4.1)	-
TOTAL	49 (100.0)	4 (100.0)

*: Isolates could not be recultured

International Travel (to India...) is a Risk Factor for Colonization with ESBL

Travel destinations of travelers who were negative for ESBL-producing strains before the trip and rate of fecal colonization with ESBL-producing *E. coli* strains upon return*

Continent or region	No. of travelers	No. (%) of travelers positive for ESBL-producing isolates
Africa	25	1(4)
Asia (India excluded)	31	10 (32)
Central America	6	0 (0)
India	8	7 (88)
Middle East	14	4 (29)
North America	2	0 (0)
South America	1	0 (0)
Southern Europe	16	2 (13)

*: The rate of acquisition of ESBL-producing strains was highest for travelers visiting India ($P < 0,001$)

Dutch patients, retail chicken meat and poultry share the same ESBL genes, plasmids and strains

TABLE 1. Distributions of extended-spectrum beta-lactamase (ESBL) genes in *Escherichia coli* and *Salmonella* spp. isolates from poultry, poultry retail meat samples and from human origin based on array results combined with sequence results

Poultry-associated ESBL genes	Poultry <i>n</i> = 35	Poultry meat samples ^a <i>n</i> = 81	Human ^a <i>n</i> = 409
<i>bla</i> _{CTX-M-1} (%)	49	49	24
<i>bla</i> _{TEM-52} (%)	29	26	6
<i>bla</i> _{SHV-12} (%)	0	16	4
<i>bla</i> _{SHV-2} (%)	11	4	0.4
<i>bla</i> _{CTX-M-2} (%)	9	4	0.2
<i>bla</i> _{TEM-30} (%)	3	1	0
Total (%)	100	100	35

The number of isolates analysed by array among meat and human isolates was 81 and 409, respectively. The number of isolates analysed by sequencing among poultry, meat and human isolates was 35 (100%), 81 (100%) and 208 (51%), respectively.

^aPercentages are extrapolations based on array results and sequence results. For calculation of the percentages see also Fig. 1. For example percentage of *bla*_{CTX-M-1} in human isolates = 0.84 × 0.85 × 0.34 = 24%.

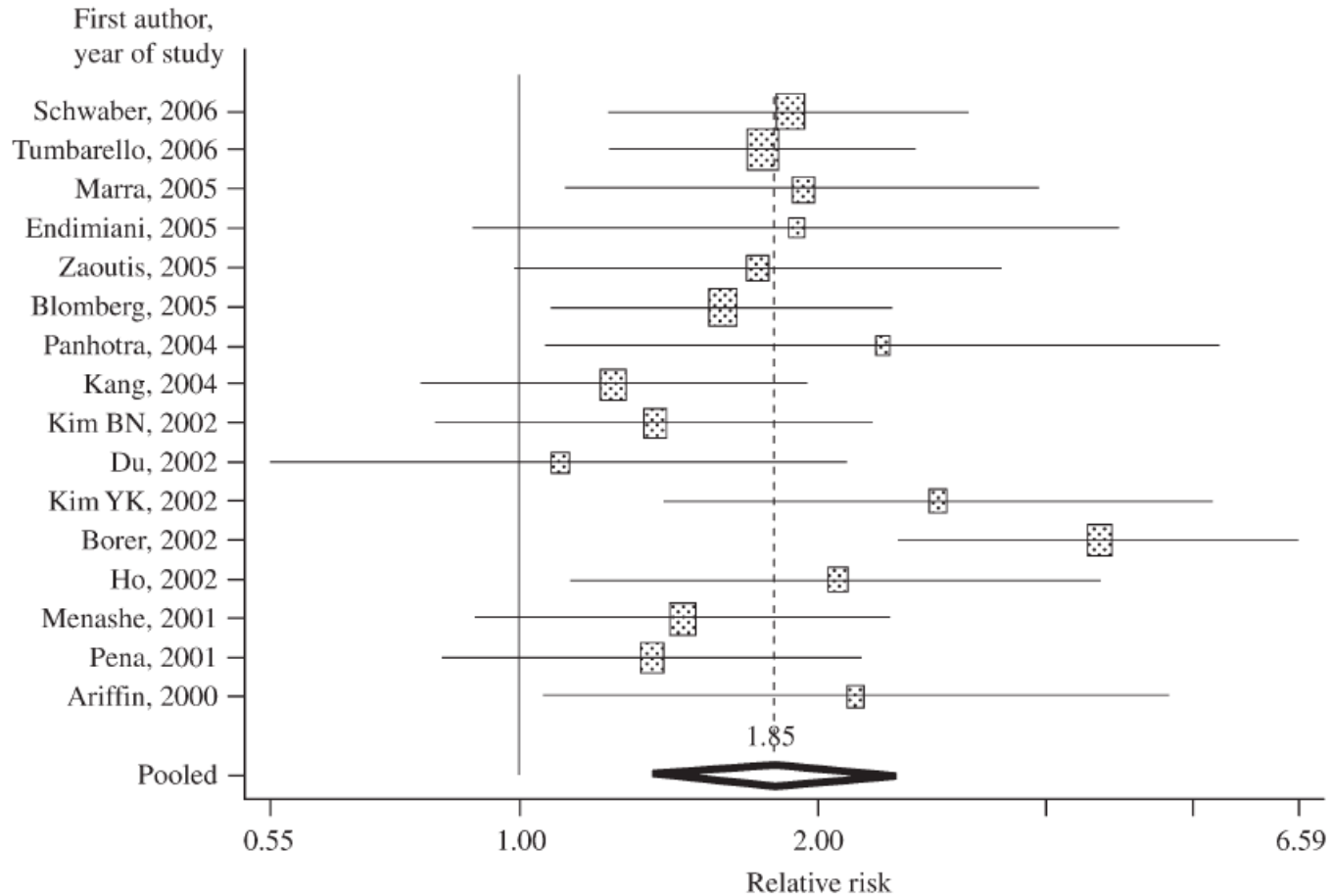
Conclusions

- Resistance due to ESBLs and carbapenemases among Gram-negative bacilli is increasing worldwide
- This emergence is due to the global spread of highly transferable genes and successful clones,
- These genes are on mobile elements with resistance determinants to other classes of antibiotics
- ESBL and carbapenemases genes and strains are found in:
 - Animals
 - Food
 - Healthcare settings and outpatients
- Hence, control of this pandemic spread is challenging and therapeutic options are very limited

Does resistance matter?



Mortality in ESBL vs. non-ESBL Enterobacteriaceae Bacteraemia



What about new antibiotics?



New drugs Under Development

- New beta-lactamase inhibitors
- New beta-lactams
- New aminoglycosides
- Boron based small molecules

New Beta-Lactamase Inhibitor: NXL-104

- Cerexa/Novoxel/AstraZeneca
- Activity against carbapenem resistant Enterobacteriaceae
 - Most KPC producers (not if large amounts of AmpC as well)
 - *Acinetobacter* strains with OXA-48
 - Strains which are carbapenem resistant due to porin loss plus production of an ESBL or AmpC
- In phase 3 development
- BUT: No activity against MBL producers

Neoglycosides: ACHN-490

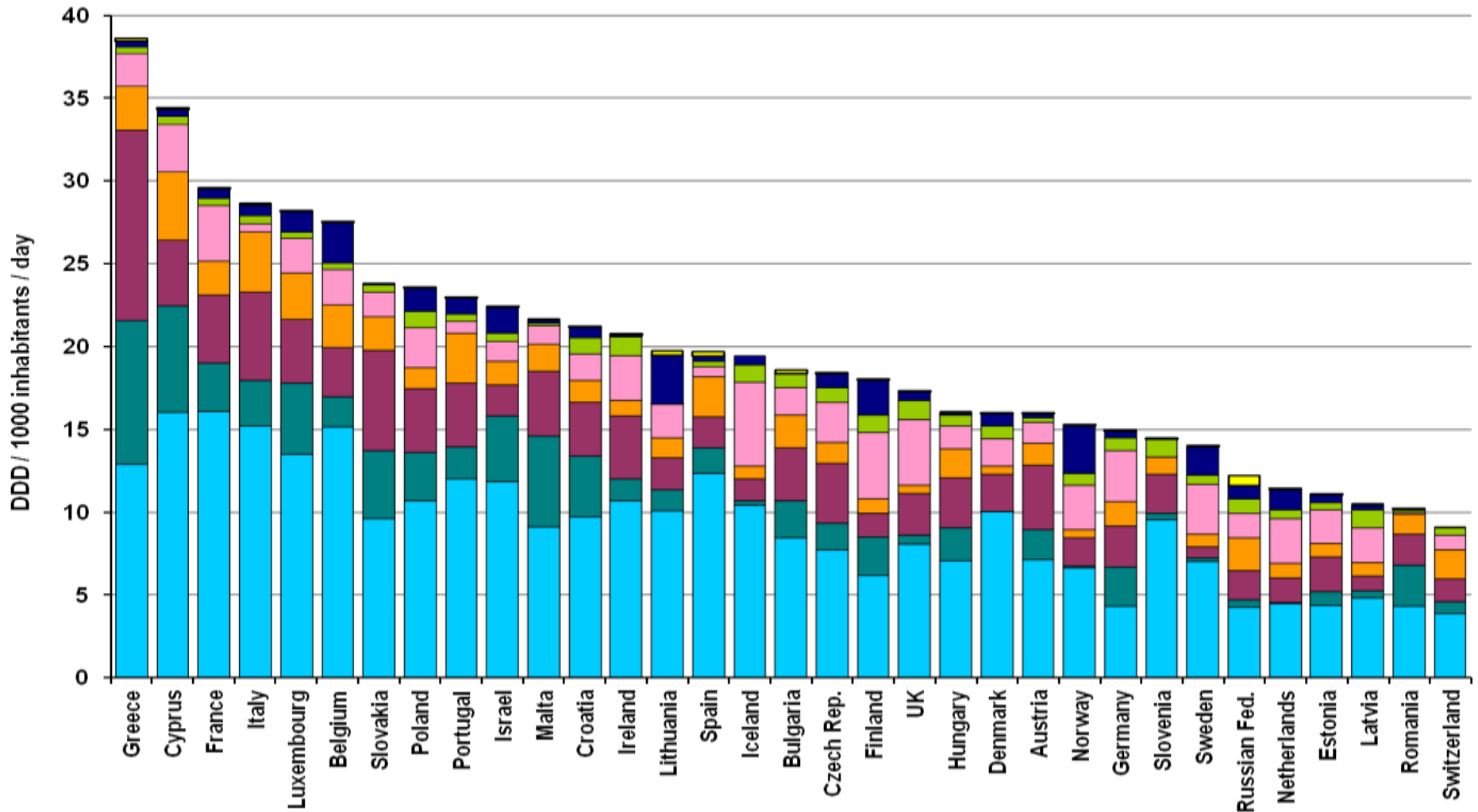
- Targeted against MDR *Enterobacteriaceae*
- In Phase 2 development
- BUT: Producers of 16S ribosomal RNA methylases are typically resistant to ACHN-490
- HENCE: Most MBL producers (including NDM producers) will be resistant to ACHN-490



**"If you cannot
measure it,
you cannot
improve it"**

**Lord Kelvin,
1824-1907**

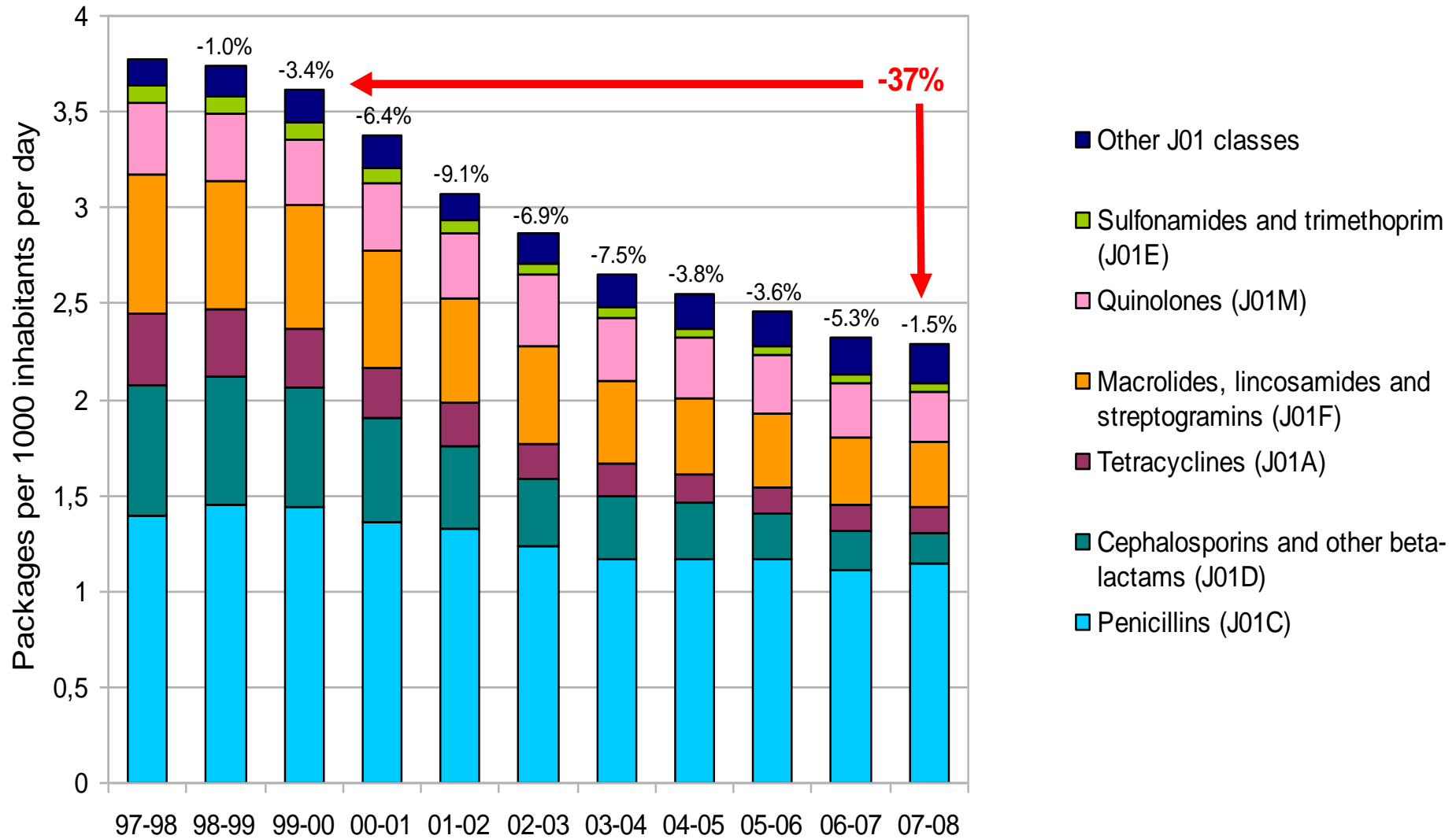
Total Outpatient Antibiotic Use in 33 European Countries in 2009



Belgian National Public Campaigns

- **When:** since November 2000, annually during winter season
- **Organised by:** BAPCOC (Belgian Antibiotic Policy Coordination Committee)
- **Budget:**
 - 400,000 EUR/annual campaign
- **Interventions targeting the public:**
 - Ads on TV, radio and newspaper
 - Information booklets
 - Folders
 - Posters
 - Internet campaigns: www.antibiotics-info.be

Outpatient Antibiotic Use in Belgium in Packages per 1,000 Inhabitants per Day – July – June. 1997 - 2008



Europæisk
antibiotikadag

Et europæisk sundhedsinitiativ



EUROPEAN
ANTIBIOTIC
AWARENESS DAY

A European Health Initiative



Europejski
Dzień Wiedzy o
Antybiotykach

Europejska inicjatywa zdrowotna



Europeiska
Antibiotikadagen

Et folkehelseinitiativ från EU



Európai
Antibiotikum Nap



18 NOVEMBER

Evropski
dan
antibiotikov

Evropska pobuda na področju zdravja



Ziua Europeană
a Informării
despre Antibiotice

O inițiativă europeană în domeniul sănătății



Día Europeo
para el Uso Prudente
de los Antibióticos

Una iniciativa europea para la salud



Journée Européenne
d'Information
sur les Antibiotiques

Une initiative européenne en matière de santé



Jum Ewropew
għall-Għarfien
dwar l-Antibijotiċi

Inizjattiva Ewropea għas-Saħħa



Ευρωπαϊκή
Ημέρα
Αντιβιοτικών

Μια πρωτοβουλία της Ευρωπαϊκής
Ένωσης για την υγεία



EAAD, 2008-2010

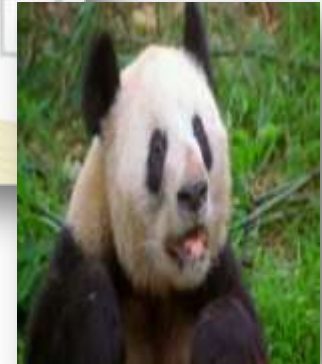
2008

Materials for general public
32 countries participated



2009

- Article in Eurosurveillance
- Materials for primary care prescribers
- Website translated in all EU languages, three TV spots developed
- 34 countries participated



2010

- 36 countries participated
- Materials for hospital prescribers
- Matched Get Smart week in the United States and the campaign in Canada



Earnshaw S, et al. Euro Surveill 2009;14(30)
<http://antibiotic.ecdc.europa.eu>

New Patient Safety Act January 1st 2011

- Antibiotic prescribing indicator: increased adherence to treatment guidelines for infections in outpatient care, and thereby a decrease in antibiotic prescribing.
 - Long term target for **2014: 250 prescriptions/1000 inhabitants** and year
 - Target for 2011: decrease by 10% of the difference between current level and long term target
- The indicator was based on calculations from a diagnosis-prescribing study about respiratory tract infections in primary care
$$\frac{95 \text{ prescriptions/1000 inhabitants}}{0.6 \text{ (primary care)} \times 0.7 \text{ (RTI)}} = 226 \text{ prescriptions/1000 inh.}$$

Regional data Sweden

Distribution of use per ATC3 classes and NUTS3 regions

NUTS	J01A	J01C	J01D	J01E	J01F	J01G	J01M	J01X	J01	QPOP
SE010	3.38	8.07	0.24	0.60	0.67	0.006	0.75	1.92	15.64	Q4
SE021	3.67	6.88	0.23	0.51	0.61	0.003	0.81	1.64	14.34	Q4
SE022	2.49	6.47	0.17	0.56	0.53	0.002	0.64	2.17	13.02	Q2
SE023	2.48	6.39	0.25	0.46	0.59	0.010	0.85	1.40	12.42	Q4
SE024	2.54	6.72	0.16	0.50	0.56	0.009	0.83	2.35	13.66	Q3
SE025	3.02	6.92	0.21	0.48	0.51	0.004	0.83	1.51	13.47	Q2
SE041	3.38	6.86	0.14	0.55	0.81	0.012	0.85	1.73	14.33	Q1
SE044	3.24	7.88	0.25	0.53	0.74	0.005	0.79	2.32	15.75	Q4
SE061	2.45	6.36	0.17	0.55	0.43	0.000	0.84	2.14	12.94	Q3
SE062	2.39	5.57	0.14	0.42	0.47	0.002	0.82	1.89	11.69	Q3
SE063	2.53	5.84	0.18	0.55	0.58	0.004	0.77	1.45	11.91	Q3
SE071	2.65	6.26	0.16	0.57	0.54	0.009	0.77	1.57	12.53	Q2
SE072	1.91	5.89	0.22	0.52	0.40	0.001	0.70	1.71	11.35	Q1
SE081	2.99	4.63	0.26	0.55	0.50	0.004	0.75	1.27	10.96	Q2
SE082	2.31	6.30	0.19	0.57	0.57	0.003	0.81	1.77	12.54	Q2
SE091	2.38	5.64	0.34	0.43	0.57	0.002	0.83	1.61	11.80	Q4
SE092	3.13	6.60	0.26	0.39	0.79	0.001	0.93	2.53	14.62	Q1
SE093	3.18	6.61	0.13	0.54	0.62	0.001	0.84	1.45	13.38	Q1
SE094	2.20	6.62	0.14	0.59	0.54	0.000	0.79	1.80	12.68	Q1
SE0A1	3.24	6.37	0.29	0.49	0.55	0.008	0.89	1.27	13.10	Q3
SE0A2	3.23	6.99	0.34	0.55	0.70	0.008	0.77	1.15	13.75	Q4

WHO Health Day, April 7, 2011

“We have watched too passively as the treasury of drugs that has served us well has been stripped of its value. We urge our colleagues worldwide to take responsibility for the protection of this precious resource. There is no longer time for silence and complacency”.

Carlet J, Collignon P, Goldman D, Goossens H, Gyssens I, Harbarth S, Jarlier V, Levy S, N'Doye B, Pittet D, Richtmann R, Seto W, van der Meer J and Voss A. *Lancet*, 2011; April 7th

