# Carbapenemases: pessimisme ET optimisme

UNIVERSITÉ DE FRIBOURG
UNIVERSITÄT FREIBURG

Emerging Antibiotic Resistance Unit

Instituts thématiques Inserm
Institut national de la santé et de la recherche médicale

Paris

Centre hospitalier universitaire vaudois

NARA
Nationales Referenzlaboratorium zur Früherkennung neuer Antibiotikaresistenzen und Resistenzmechanismen

**Prof. Patrice Nordmann**

# Emergence of carbapenemases in *Enterobacteriaceae*

**NmcA**
*Enterobacter cloacae*

**1994**
**FRANCE**
Naas, Nordmann
PNAS 1994: 91: 7693-7697

**IMP-1**
*Serratia marcescens*

**1994**
**JAPAN**
Osano, Arakawa, Wacharotayankun, Ohta, Horii, Ito, Yoshimura, Kato
AAC 1994 : 38: 71-78

**KPC**
*Klebsiella pneumoniae*

**2001**
**USA**
Yigit, Queenan, Anderson, Domenech-Sanchez, Biddle, Steward, Alberti, Bush, Tenover
AAC 2001 : 45: 1151-1161

**OXA-48**
*Klebsiella pneumoniae*

**2004**
**FRANCE (TURKEY)**
Poirel, Heritier, Tolün, Nordmann
AAC 2004 : 48: 15-22

**NDM-1**
*Klebsiella pneumoniae*

**2009**
**SWEDEN (INDIA)**
Yong, Toleman, Giske, Cho, Sundman, Lee, Walsh
AAC 2009 : 53: 5046-5054

# KPCs; Klebsiella Pneumoniae Carbapenemase

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Apr. 2001, p. 1151–1161
0066-4804/01/$04.00+0 DOI: 10.1128/AAC.45.4.1151–1161.2001
Vol. 45, No. 4

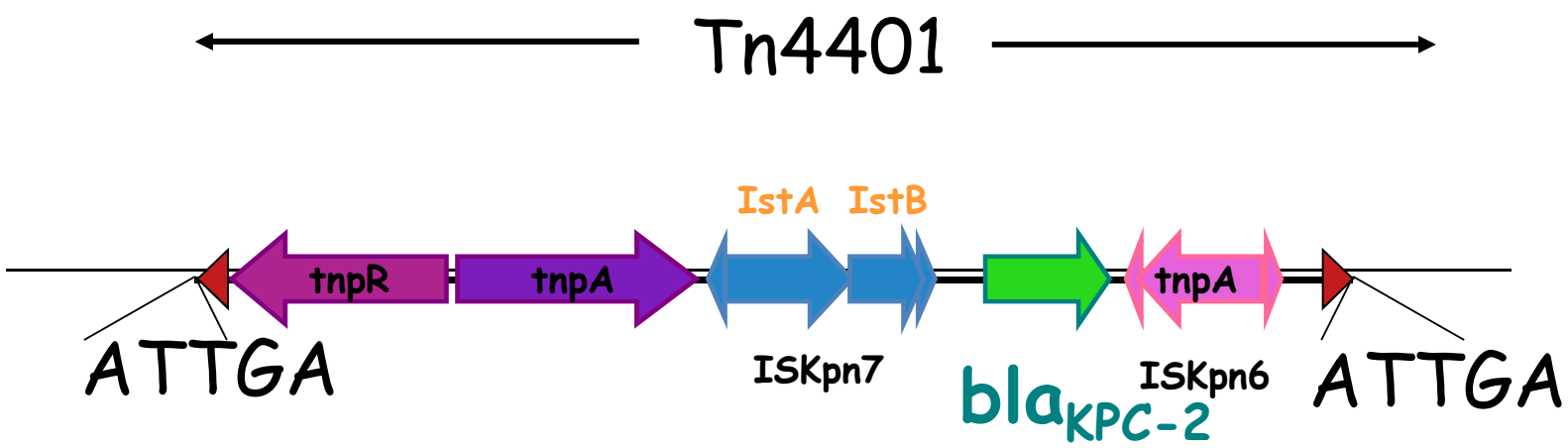

## Novel Carbapenem-Hydrolyzing β-Lactamase, KPC-1, from a Carbapenem-Resistant Strain of *Klebsiella pneumoniae*

HESNA YIGIT,[1] ANNE MARIE QUEENAN,[2] GREGORY J. ANDERSON,[1] ANTONIO DOMENECH-SANCHEZ,[3] JAMES W. BIDDLE,[1] CHRISTINE D. STEWARD,[1] SEBASTIAN ALBERTI,[4] KAREN BUSH,[2] AND FRED C. TENOVER[1]*

*Hospital Infections Program, National Center for Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia 30333[1]; The R. W. Johnson Pharmaceutical Research Institute, Raritan, New Jersey 08869[2]; and Unidad de Investigacion, Hospital Son Dureta, Andrea Doria, Palma de Mallorca, 07014,[4] and Area de Microbiologia, Universidad de las Islas Baleares, Cra. Valldemosa, Palma de Mallorca, 07071,[3] Spain*

Received 19 September 2000/Returned for modification 21 November 2000/Accepted 23 January 2001


# The *bla*$_{KPC}$-borne transposon



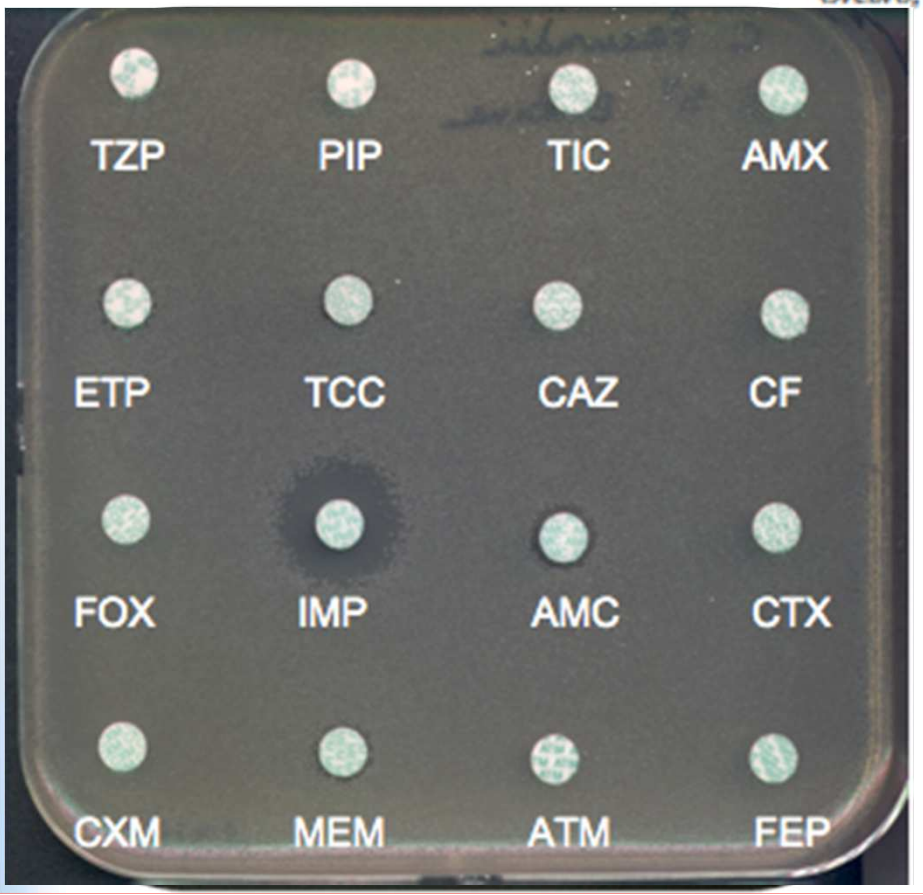

***K. pneumoniae***

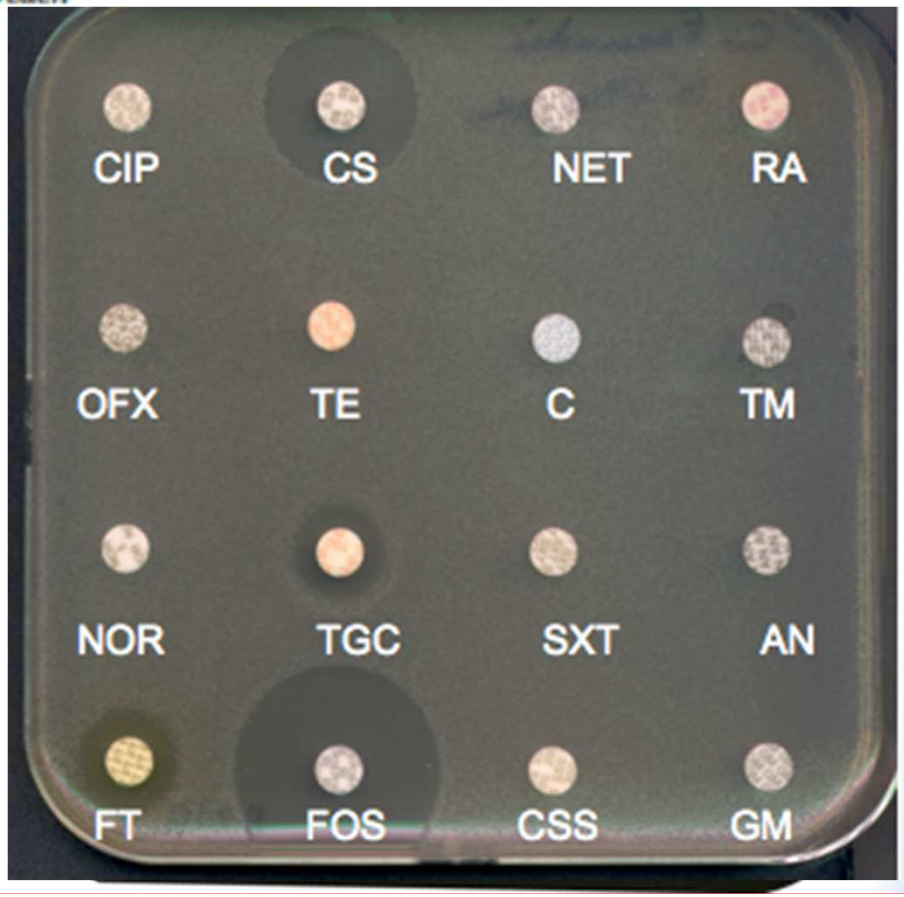
AAC,2009; 53 5046-5054

# Characterization of a New Metallo-β-Lactamase Gene, *bla*$_{NDM-1}$, and a Novel Erythromycin Esterase Gene Carried on a Unique Genetic Structure in *Klebsiella pneumoniae* Sequence Type 14 from India[▽]

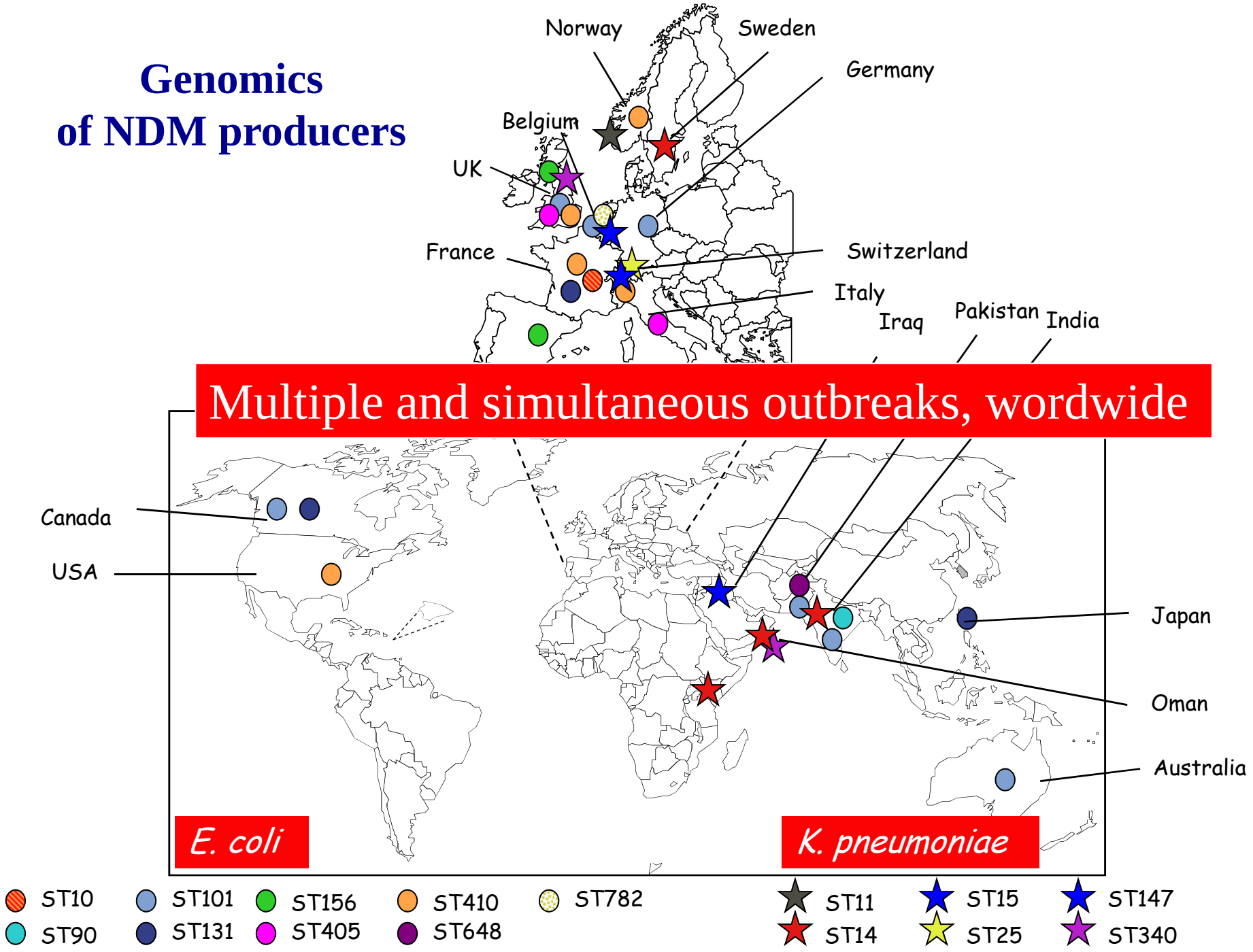
Dongeun Yong,[1,2] Mark A. Toleman,[2] Christian G. Giske,[3] Hyun S. Cho,[4] Kristina Sundman,[5] Kyungwon Lee,[1] and Timothy R. Walsh[2]*

*Yonsei University College of Medicine, Research Institute of Antimicrobial Resistance, Seoul, Republic of Korea[1]; Department of Medical Microbiology, Cardiff University, Cardiff, United Kingdom[2]; Clinical Microbiology, MTC—Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden[3]; Yonsei University College of Life Science and Biotechnology, Seoul, Republic of Korea[4]; and Department of Clinical Microbiology, Örebro University Hospital, Örebro, Sweden[5]*

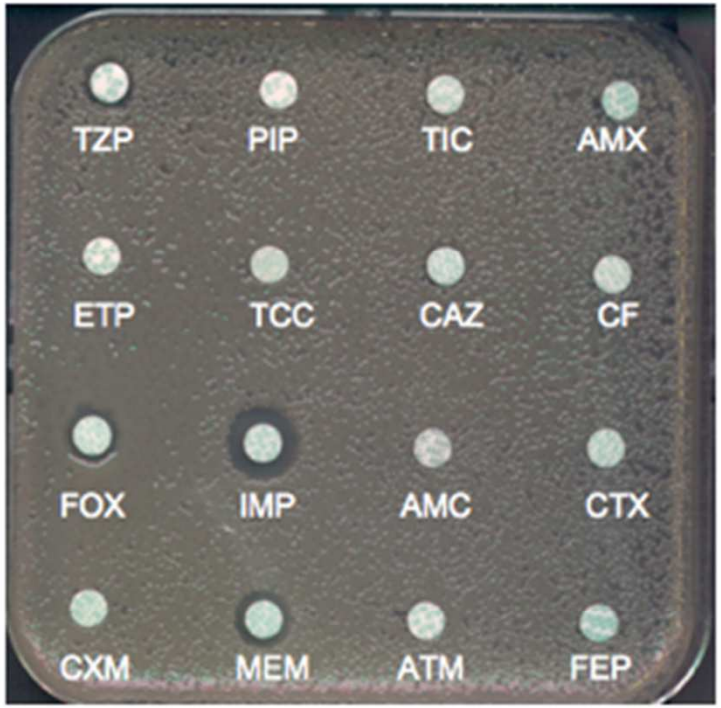


# Genomics of NDM producers



# OXA-48 + CTX-M-15



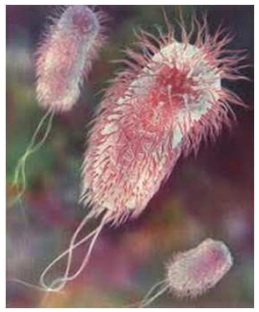
ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Jan. 2004, p. 15–22 Vol. 48, No. 1
0066-4804/04/$08.00+0 DOI: 10.1128/AAC.48.1.15–22.2004


## Emergence of Oxacillinase-Mediated Resistance to Imipenem in *Klebsiella pneumoniae*

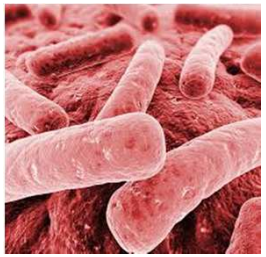
Laurent Poirel,[1] Claire Héritier,[1] Venus Tolün,[2] and Patrice Nordmann[1]*

# High frequency transfer of the OXA-48 gene

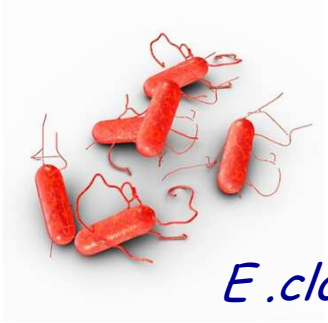
OXA-48



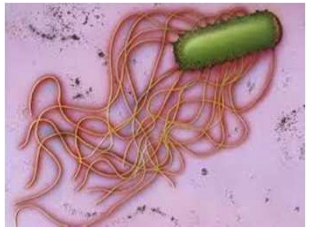
*E .coli*



*K. pneumoniae*



*E .cloacae*



*P. mirabilis*

AAC
Journals.ASM.org

Derepressed Transfer Properties Leading to the Efficient Spread of the Plasmid Encoding Carbapenemase OXA-48

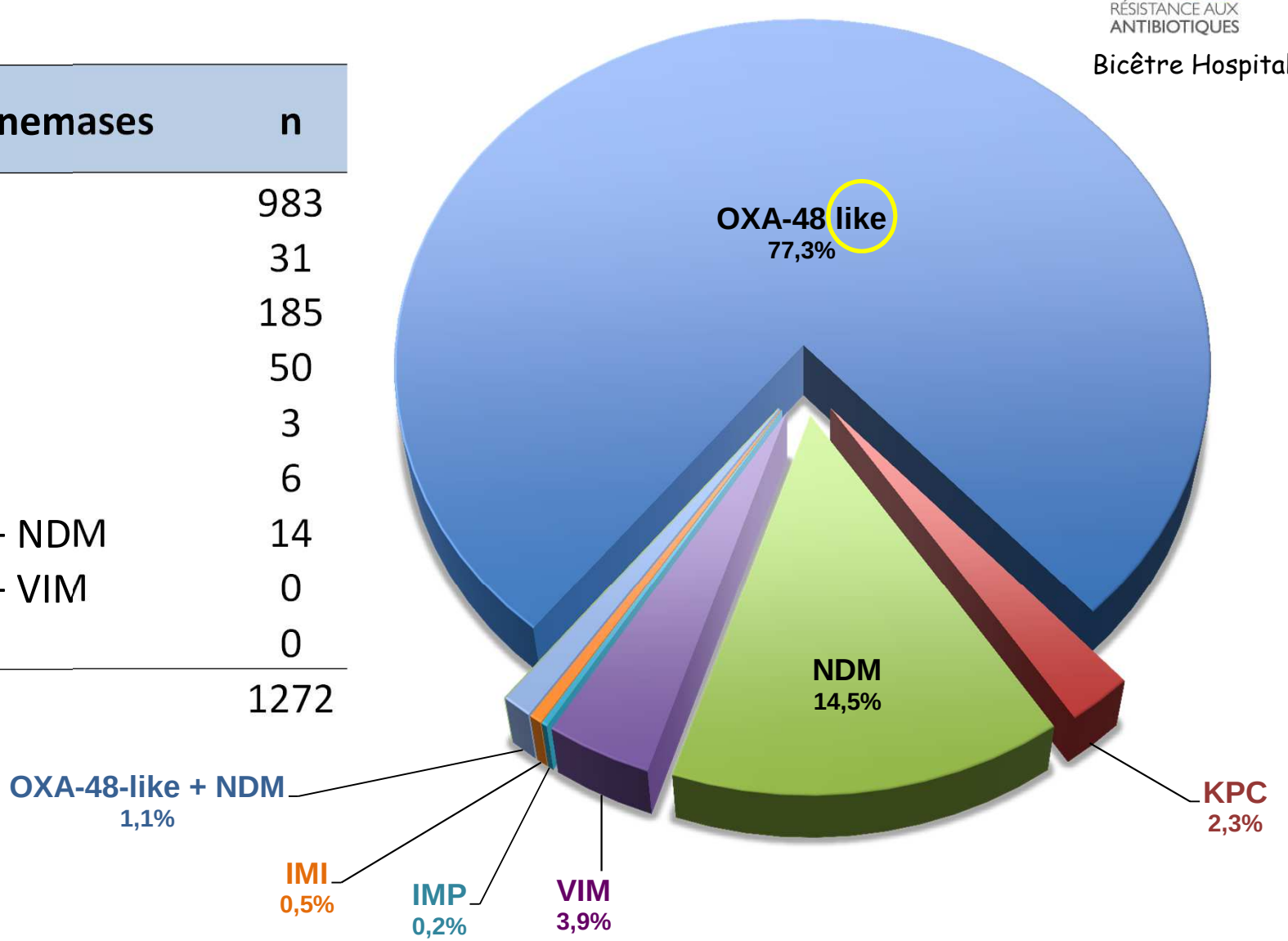
Anaïs Potron,[a] Laurent Poirel,[a,b] Patrice Nordmann[a,b]


KPC
OXA-48
NDM

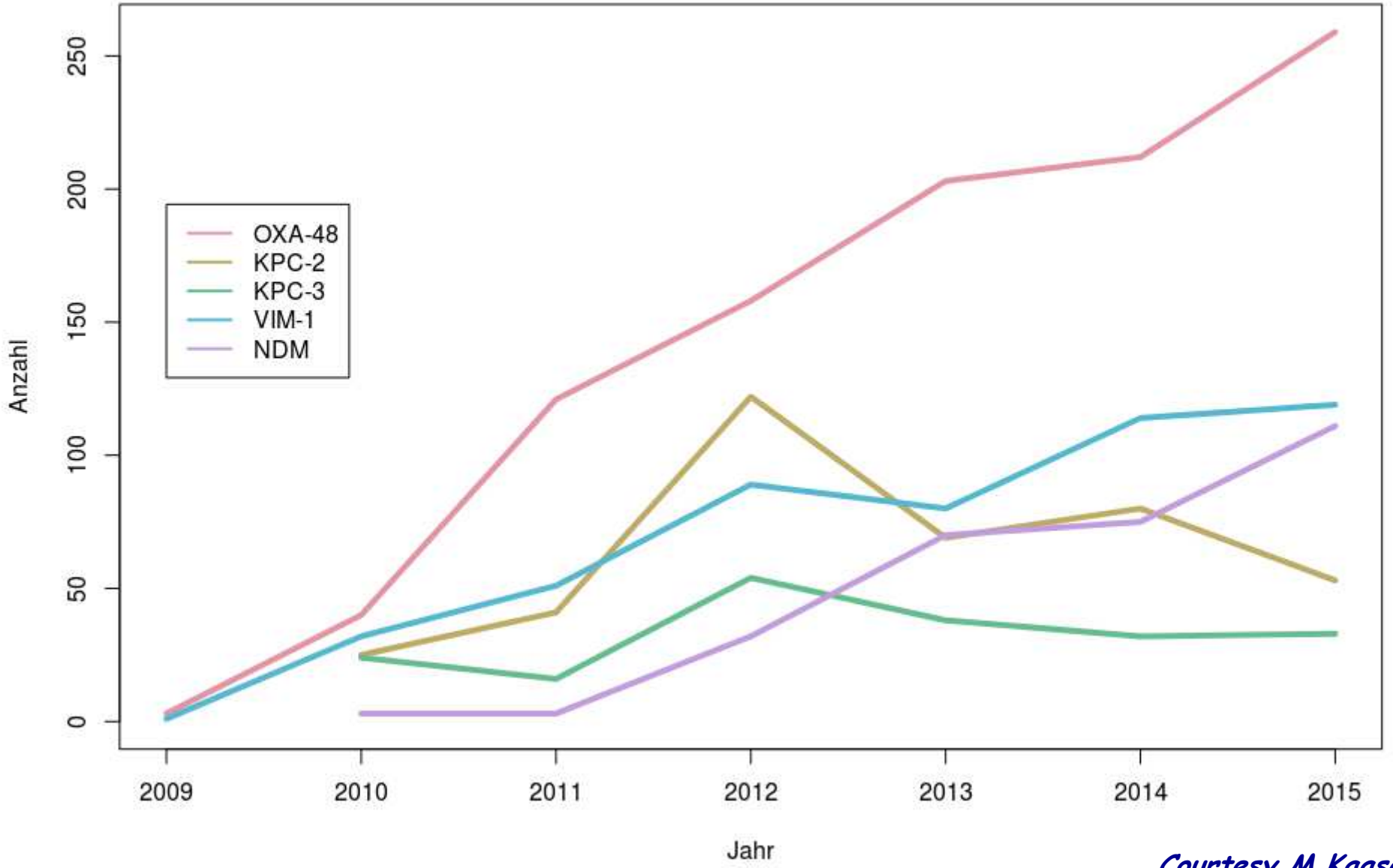
# Distribution CPE per type of carbapenemase in France 2015

CNR RÉSISTANCE AUX ANTIBIOTIQUES
Bicêtre Hospital

| Carbapenemases | n |
|---|---|
| OXA-48 like | 983 |
| KPC | 31 |
| NDM | 185 |
| VIM | 50 |
| IMP | 3 |
| IMI | 6 |
| OXA-48-like + NDM | 14 |
| OXA-48-like + VIM | 0 |
| NDM + VIM | 0 |
| total | 1272 |

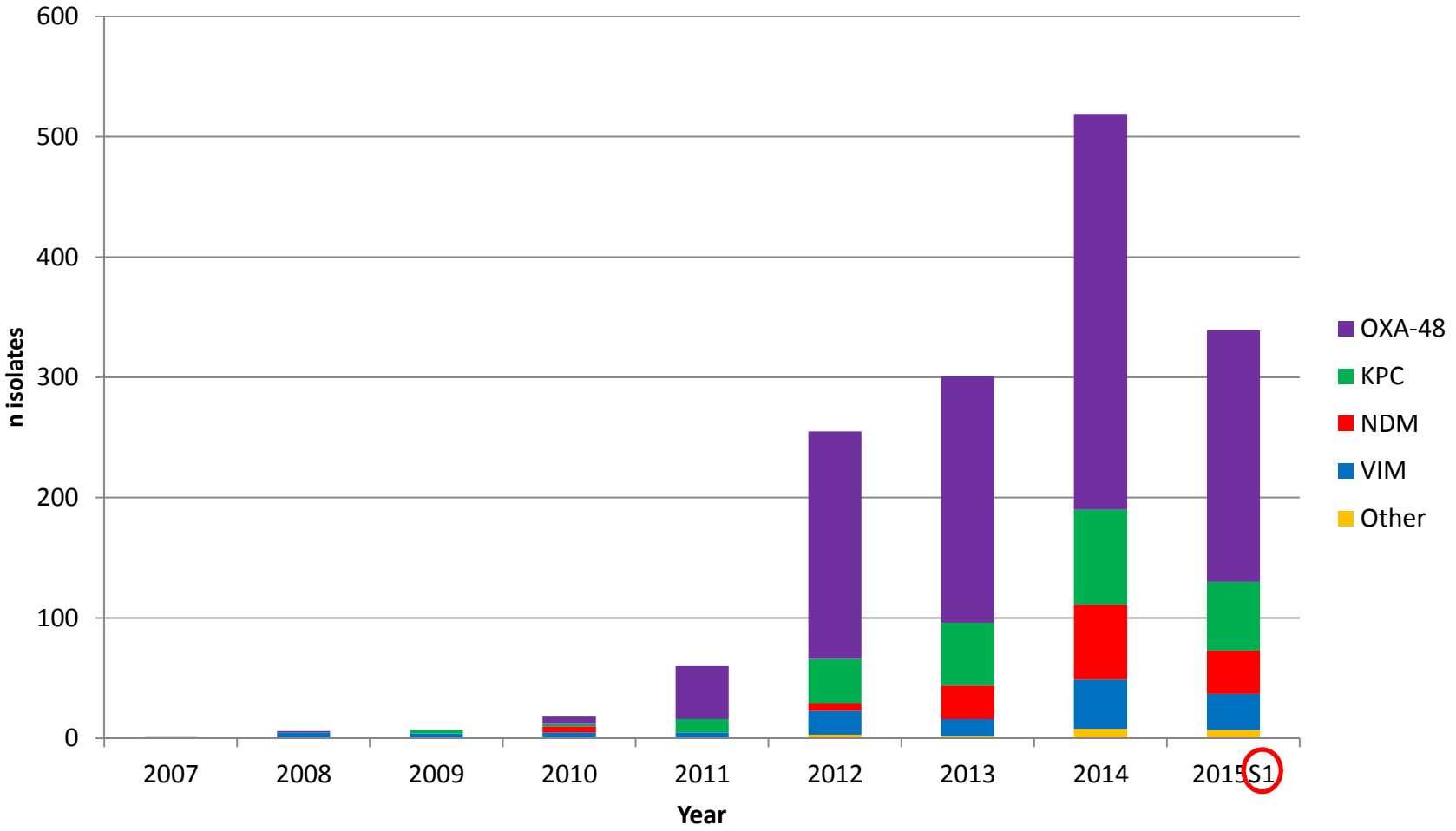


## Carbapenemasen bei Enterobacteriaceae ohne Screening




*Courtesy M.Kaase*

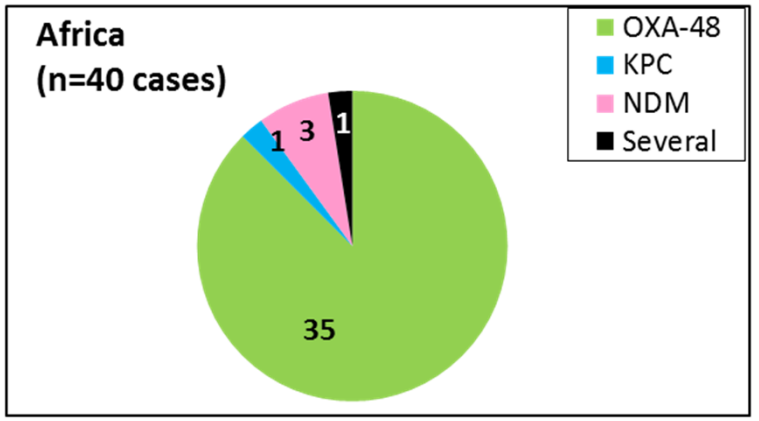
# Evolution of CPE isolates confirmed at the National Reference Centre, Belgium, January 2007 - June 2015 (n=1502)

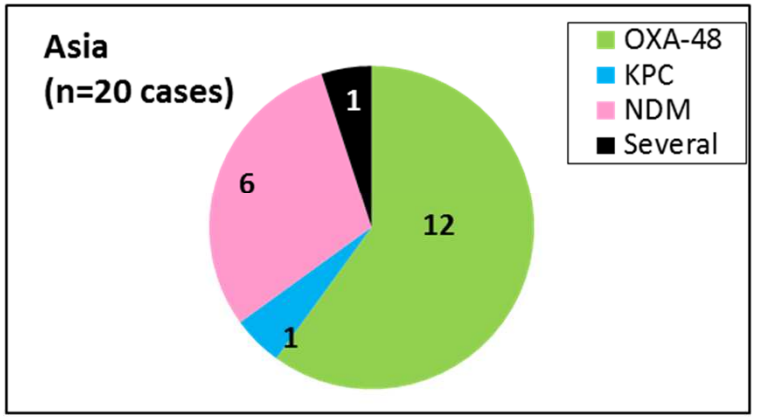


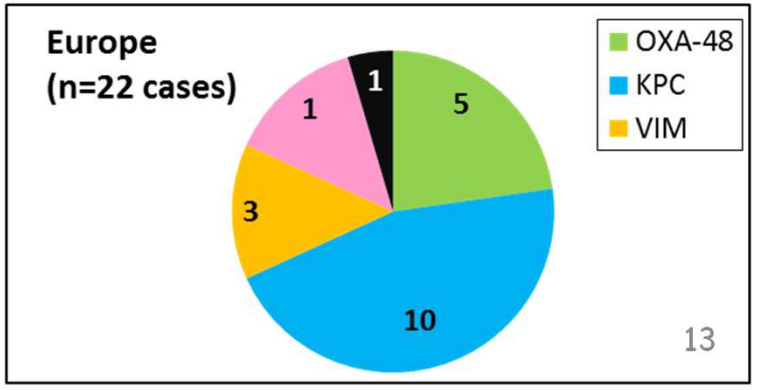

*Courtesy Y.Glupczynski and S.Malhotra*

# Travel-related CPE cases:
## 1/1/2012 – 30/6/2014 (n= 85 patients)

| Countries | Cases | OXA-48 | KPC | VIM | NDM | Several |
|---|---|---|---|---|---|---|
| *African Continent* | 40 | 35 | 1 | | 3 | 1 |
| *Morocco* | 20 | 19 | 1 | | | |
| *Egypt* | 6 | 3 | | | 2 | 1 |
| *Tunisia* | 7 | 7 | | | | |
| *Senegal* | 1 | 1 | | | | |
| *Algeria* | 2 | 2 | | | | |
| *Libya and Tunisia* | 1 | 1 | | | | |
| *Guinea* | 1 | | | | 1 | |
| *African country (n.s.)* | 2 | 2 | | | | |
| *Asian continent* | 20 | 12 | 1 | | 6 | 1 |
| *India* | 5 | | | | 4 | 1 |
| *Pakistan* | 2 | 1 | | | 1 | |
| *Thailand* | 1 | 1 | | | | |
| *Vietnam* | 1 | | | | 1 | |
| *Iran* | 1 | 1 | | | | |
| *Turkey (Eurasia)* | 10 | 9 | 1 | | | |
| *European continent* | 22 | 5 | 10 | 3 | 3 | 1 |
| *Greece* | 12 | 3 | 6 | 1 | 2 | |
| *Italy* | 4 | | 4 | | | |
| *Romania* | 2 | 1 | | 1 | | |
| *France* | 1 | 1 | | | | |
| *Serbie* | 1 | | | | 1 | |
| *Spain* | 1 | | | 1 | | |
| *Albania* | 1 | | | | | 1 |
| *Country unknown* | 3 | 3 | | | | |
| *TOTAL* | 85 | 55 | 12 | 3 | 12 | 3 |

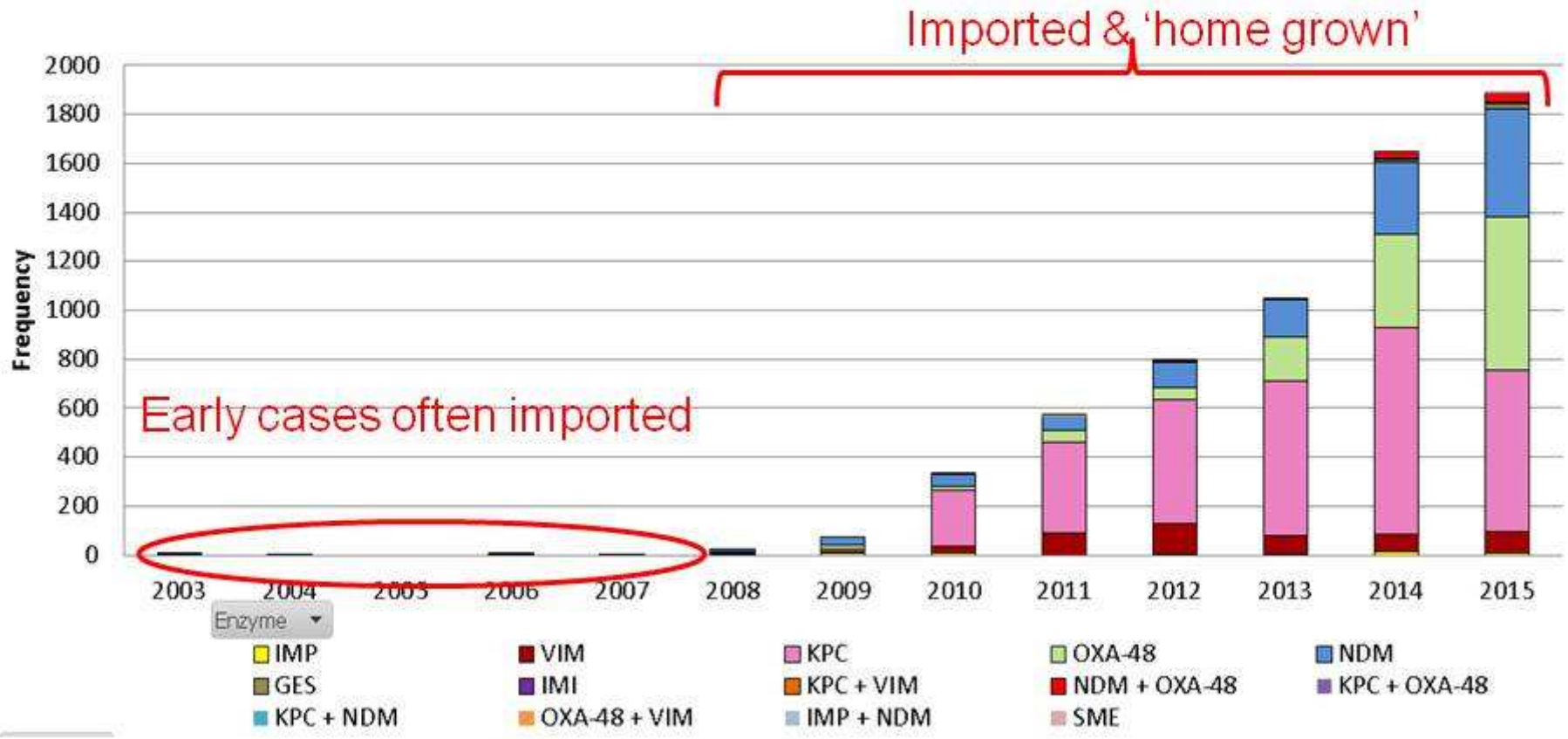


Public Health England

# CPE in the UK, 2000-2015

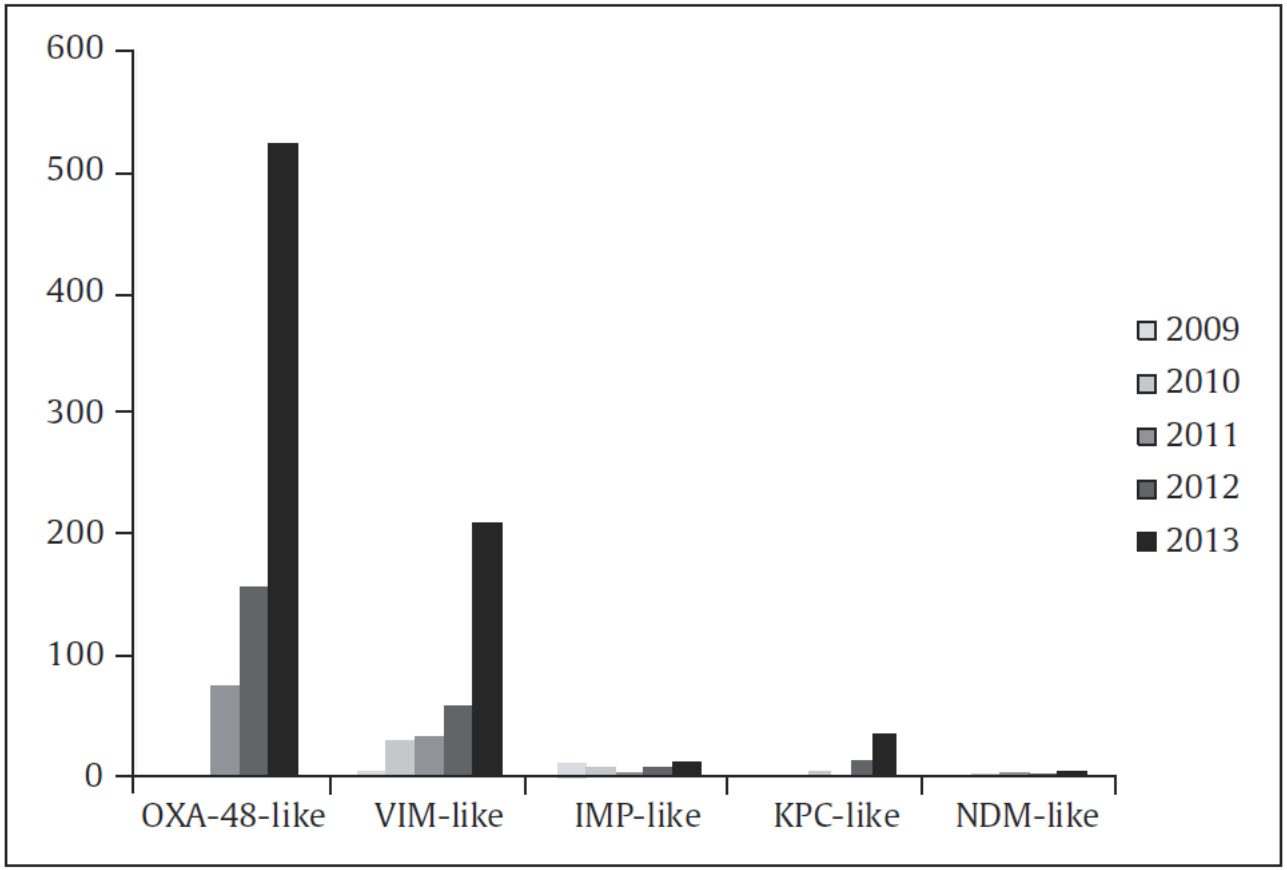



*Klebsiella* spp. 69%; *E. coli* 18%, *Enterobacter* spp., 9%; others 4%

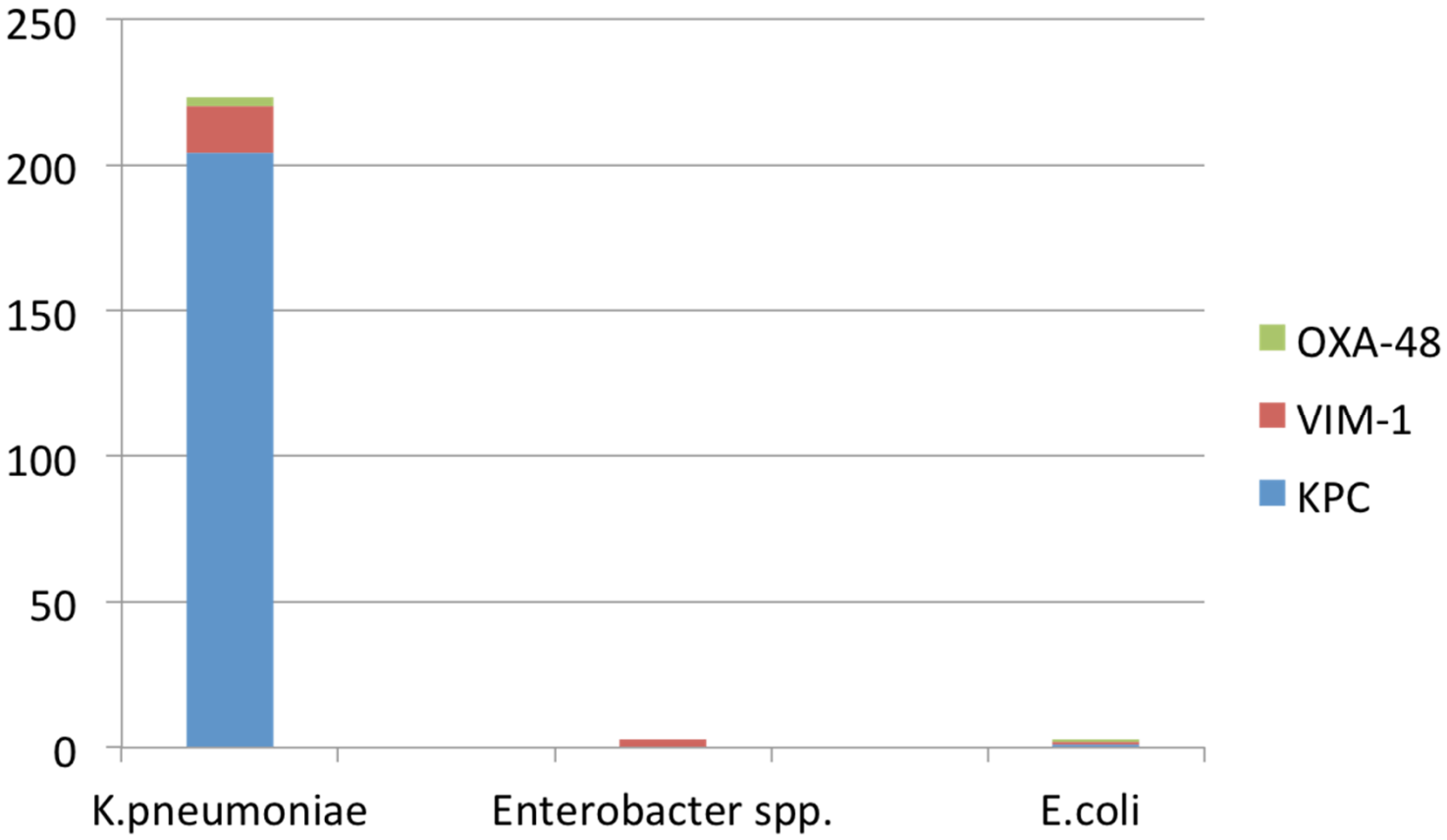
AMRHAI, Unpublished data

# CPE received at the Spanish reference laboratory



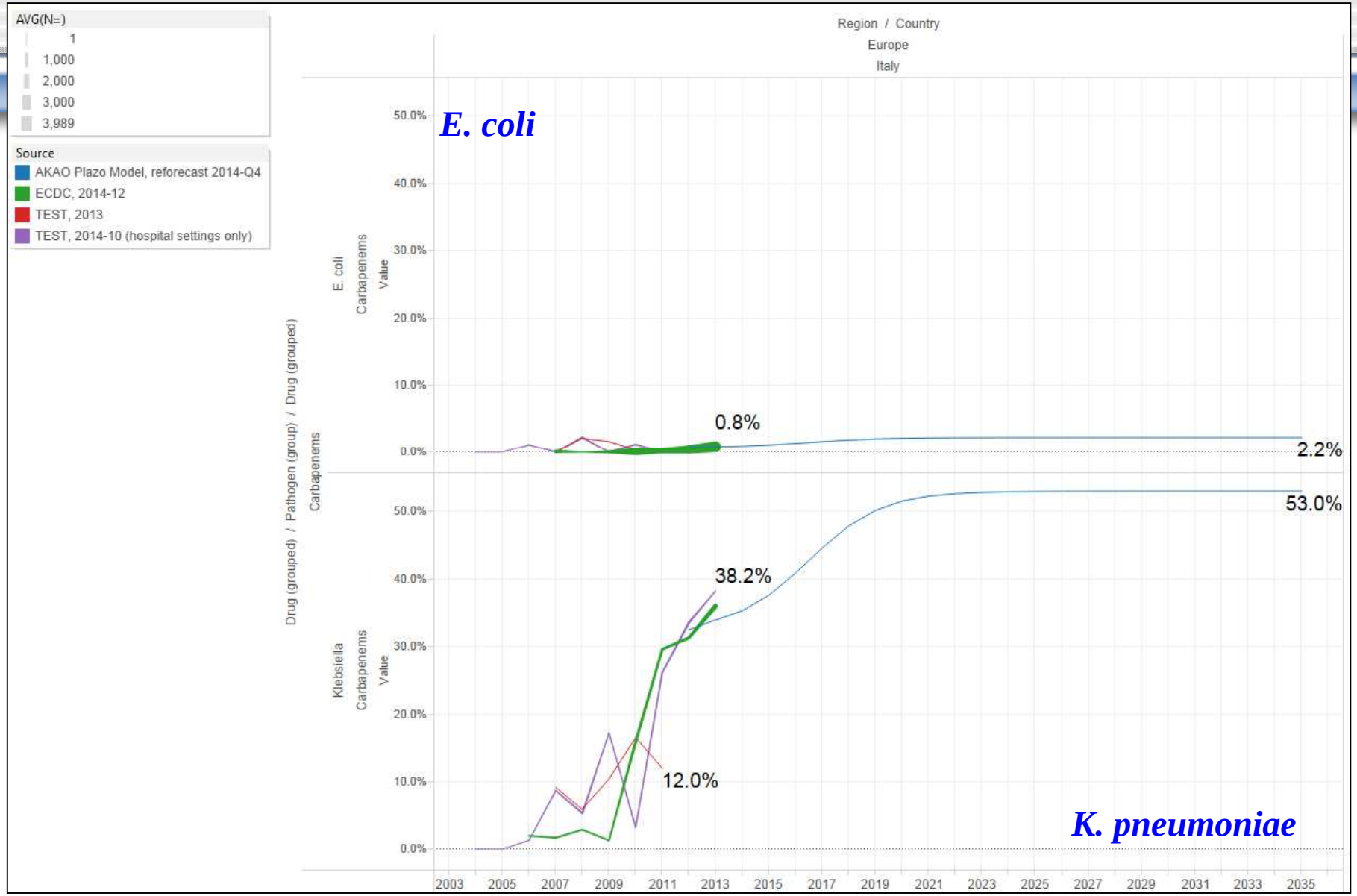

*Oteo et al., 2015*

# CPE in Italy, 2011



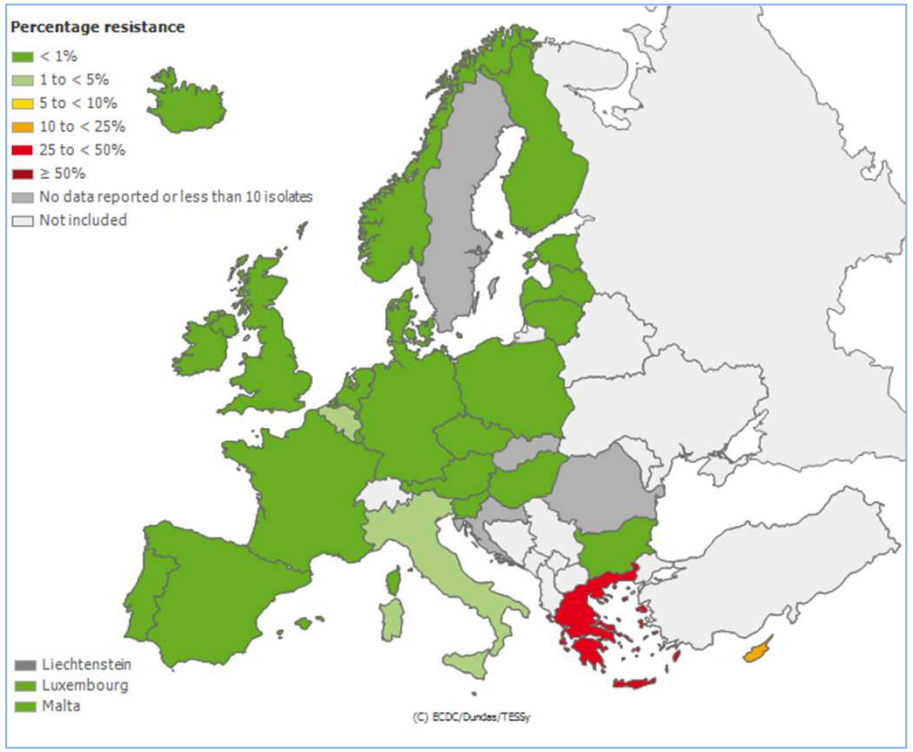

*Giani et al, 2013*

# Italy

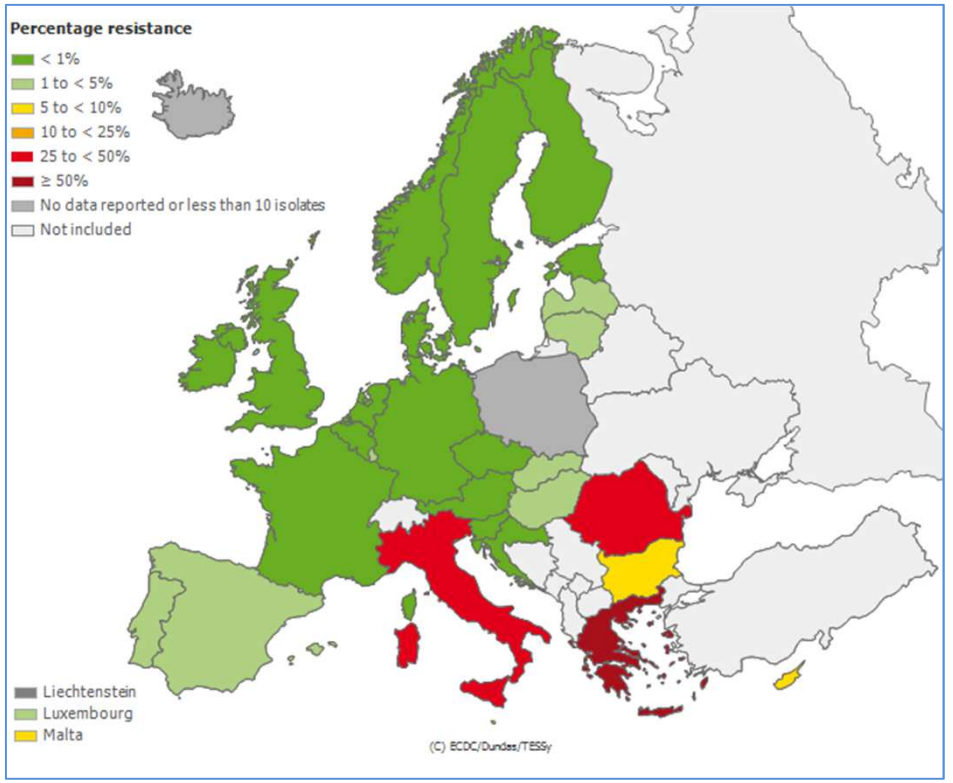

AVG(N=)
1
1,000
2,000
3,000
3,989
Source
AKAO Plazo Model, reforecast 2014-Q4
ECDC, 2014-12
TEST, 2013
TEST, 2014-10 (hospital settings only)
Region / Country
Europe
Italy
E. coli
Carbapenems
Value
Drug (grouped) / Pathogen (group) / Drug (grouped)
Carbapenems
0.8%
2.2%
Klebsiella
Carbapenems
Value
38.2%
53.0%
12.0%
K. pneumoniae
50.0%
40.0%
30.0%
20.0%
10.0%
0.0%
2003
2005
2007
2009
2011
2013
2015
2017
2019
2021
2023
2025
2027
2029
2031
2033
2035

# Carbapenem-resistant *K. pneumoniae*

2009

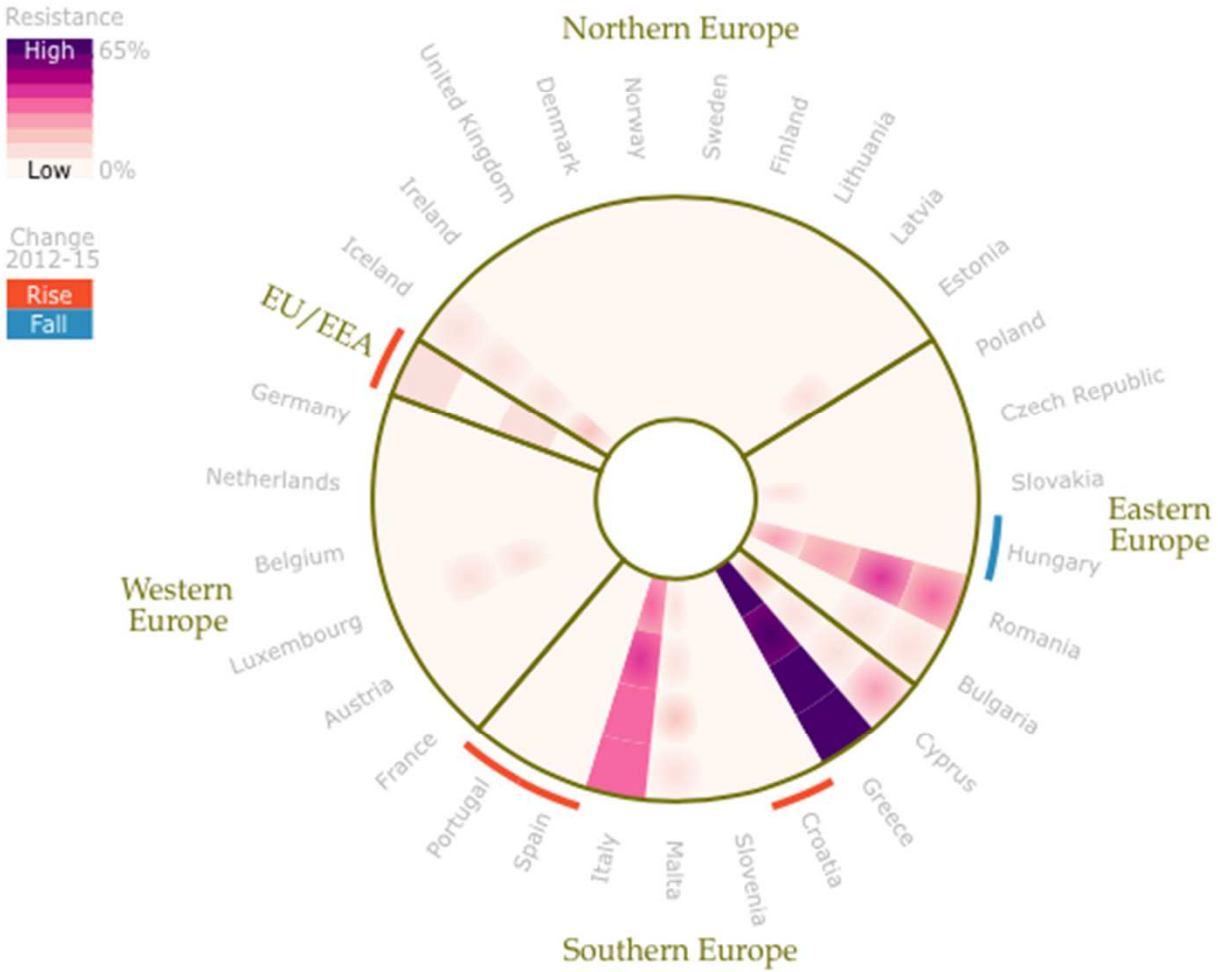



2014



# *Klebsiella pneumoniae*

Percentage of invasive isolates with resistance to carbapenem antibiotics

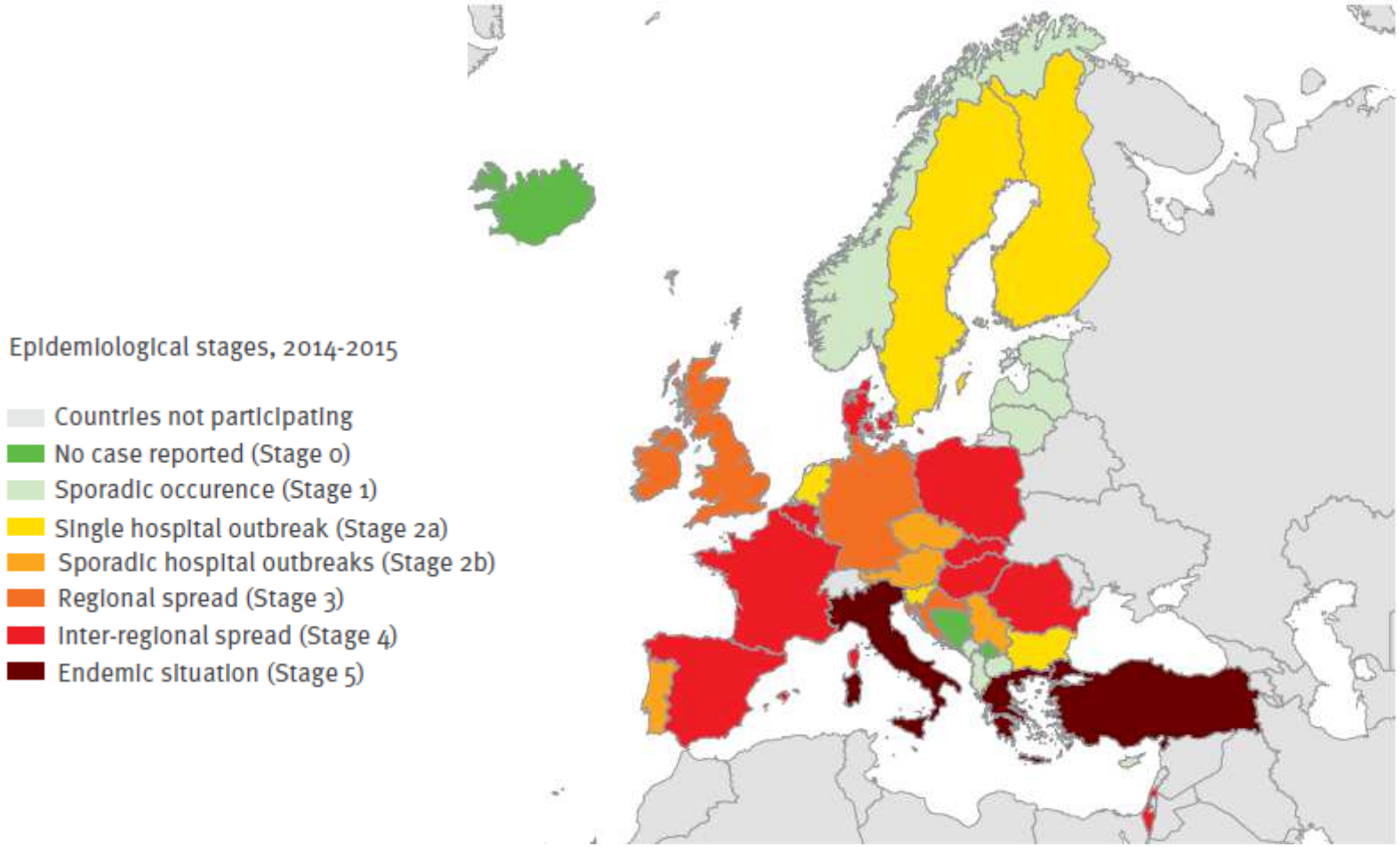



*Klebsiella pneumoniae*, sometimes called Kleb, is a common cause of urinary tract, respiratory tract and bloodstream infections. It can spread rapidly between patients in healthcare settings and is a frequent cause of hospital outbreaks.

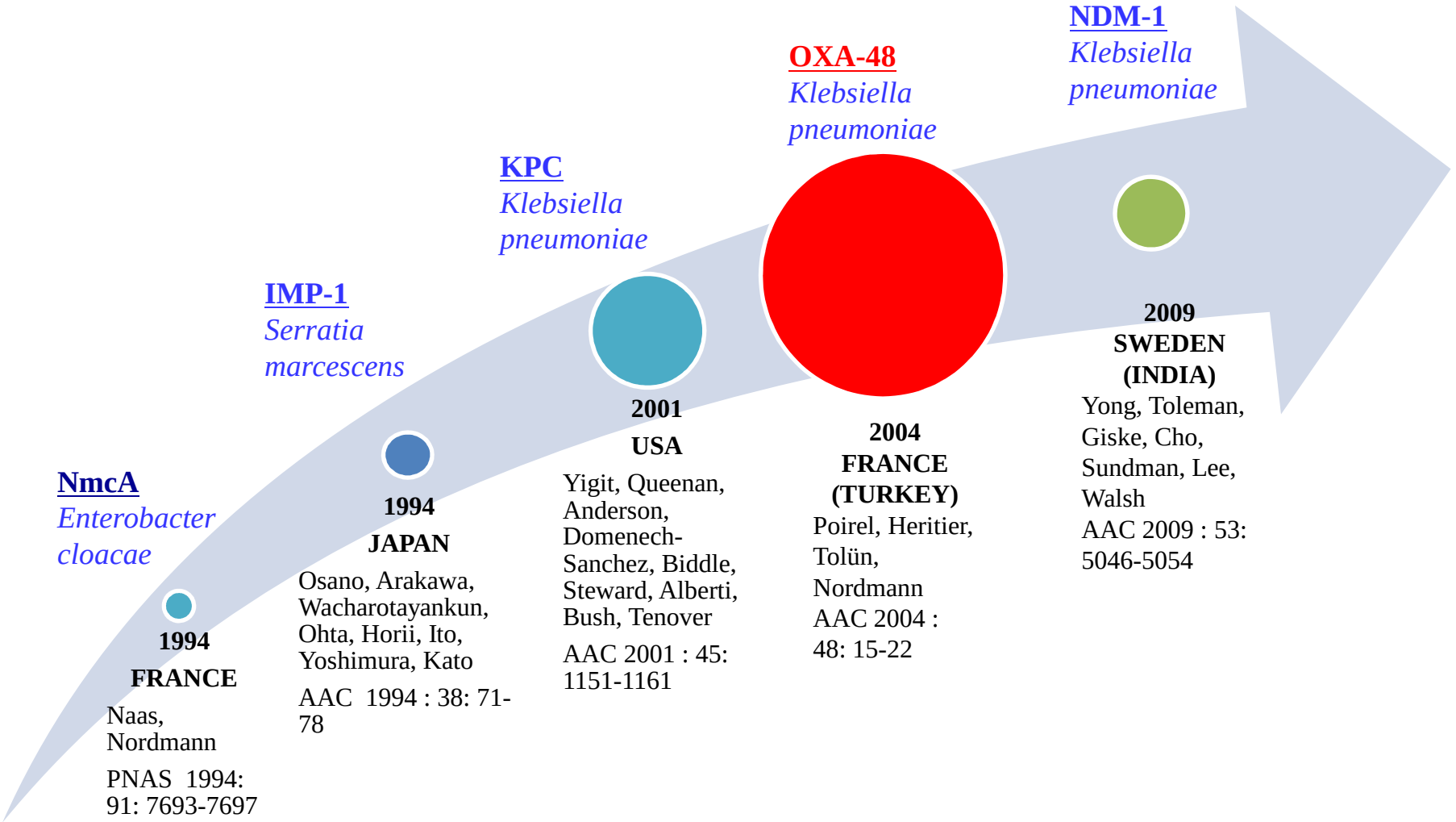
Antibiotic resistance in Kleb is a public health concern of increasing importance in Europe. Combined resistance to multiple antibiotic groups is common. Although carbapenem resistance percentages (shown) remained at low levels for most countries in 2015, resistance to carbapenems at the EU/EEA level has increased significantly over the last four years. The vast majority of the carbapenem-resistant samples had additional resistance to other antibiotic groups. Very few options are left for patients infected with multidrug-resistant Kleb with additional resistance to carbapenems.

# Carbapenemase-producing *Enterobacteriaceae* in Europe: assessment by national experts from 38 countries, May 2015

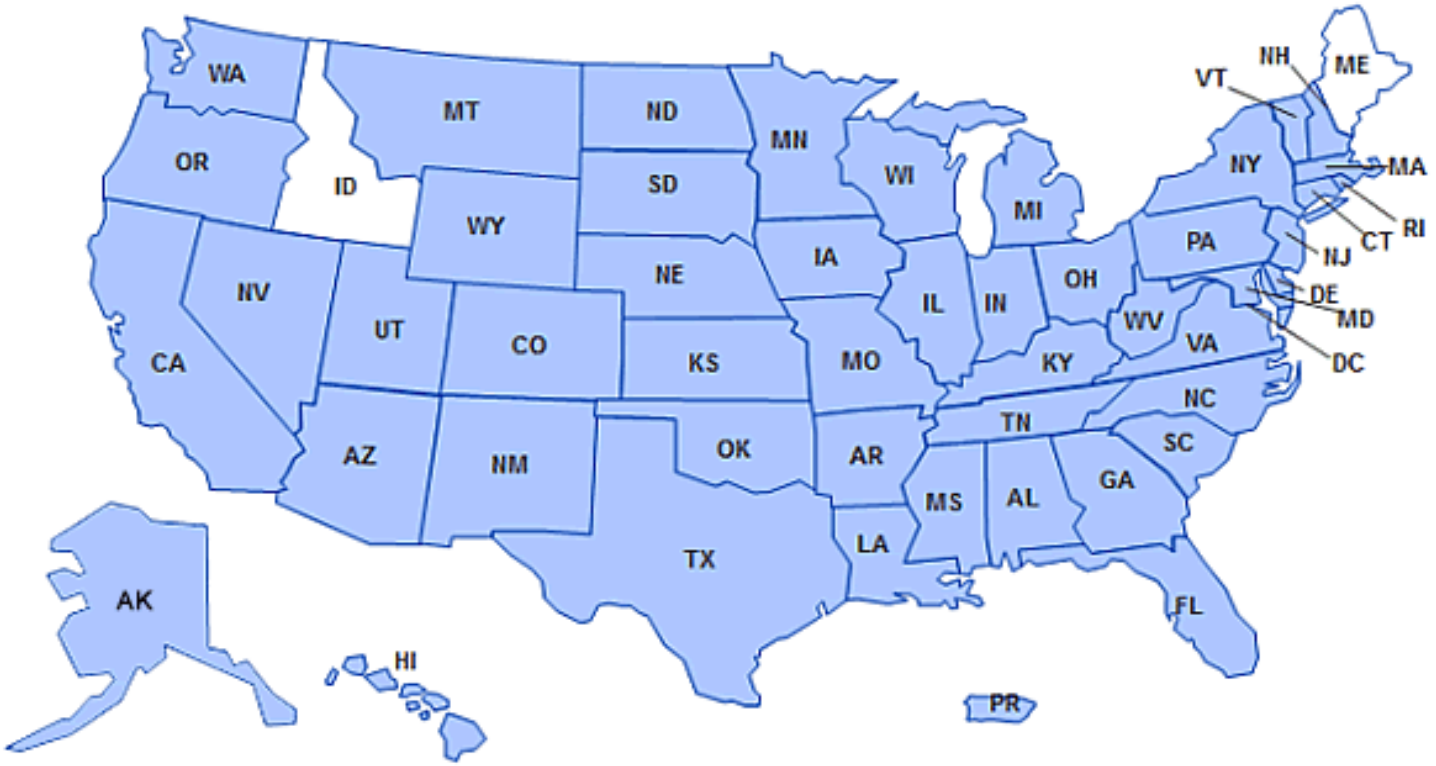
*Eurosurveillance*



# Emergence of carbapenemases in *Enterobacteriaceae*, 2017, Europe



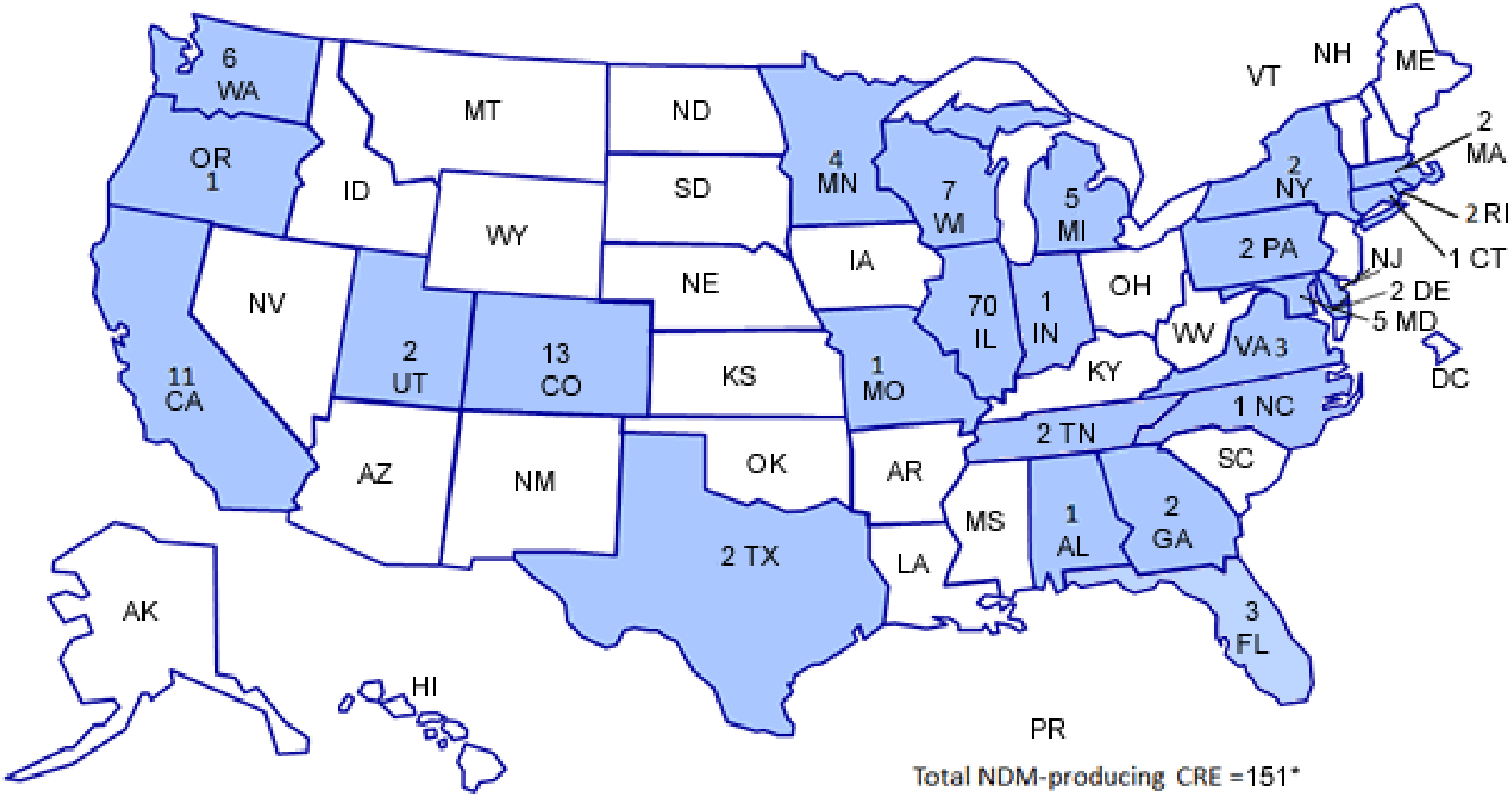
# KPCs in the USA




This map was last updated on February 2015

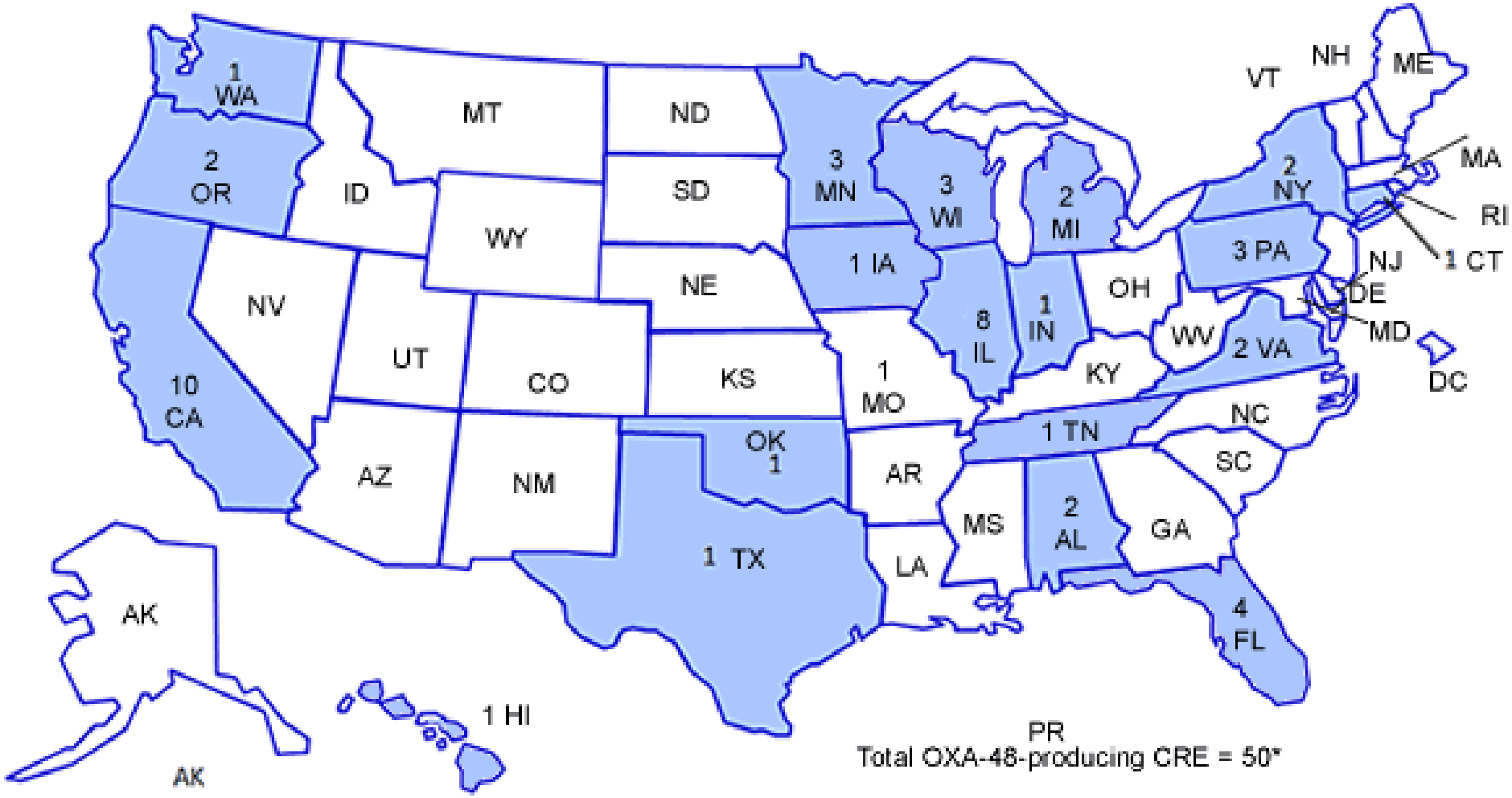
**17% of ESBLs have KPC**

# NDMs in the USA



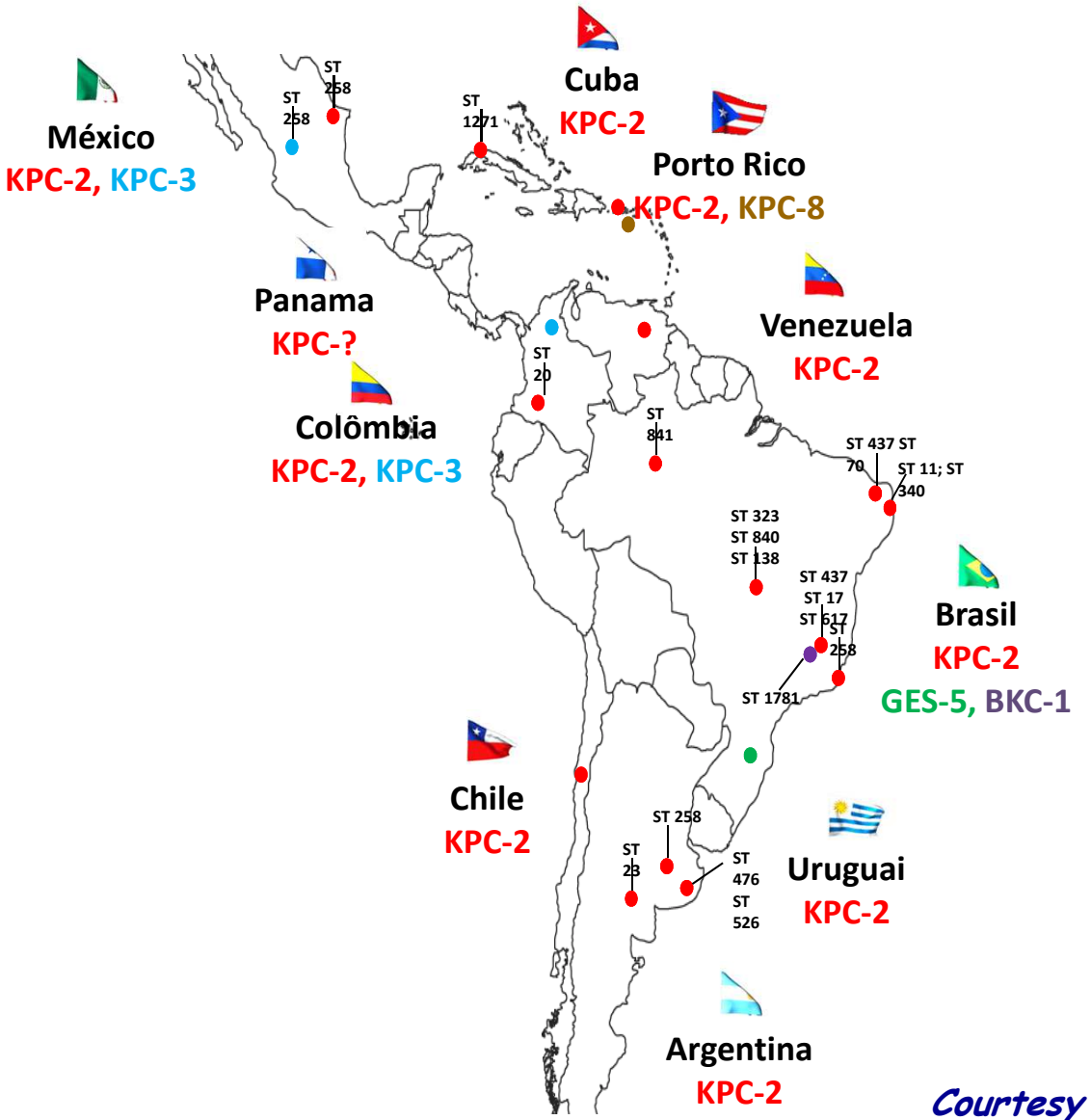

This map was last updated on January, 2016

# OXA-48s in the USA




This map was last updated on January, 2016

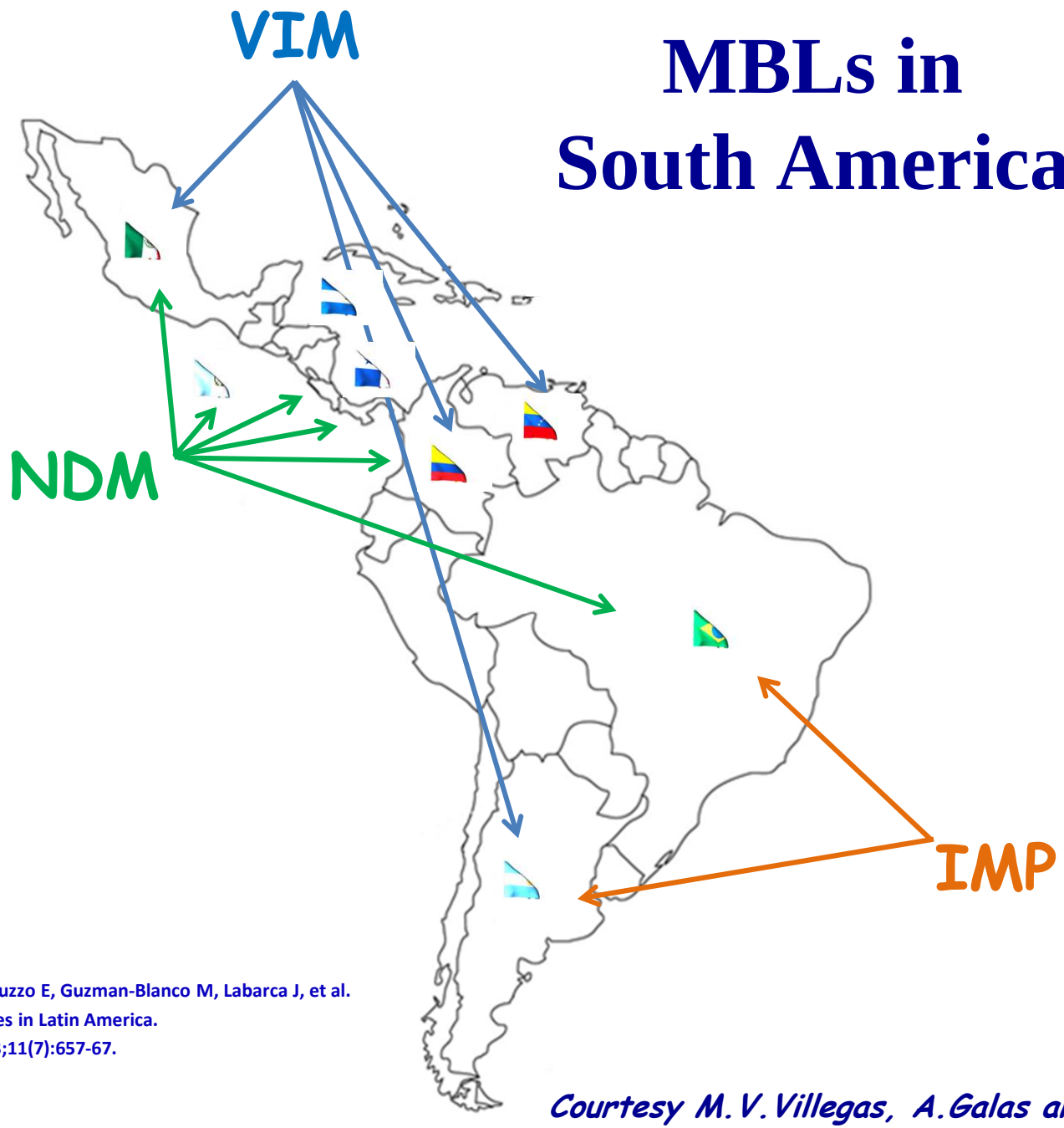
# *K. pneumoniae* producing KPCs in South-America




*Courtesy A.Galas and S.Vega*

http://www.paho.org/hq/index.php?option=com_docman&task=doc_view&gid=24471

# MBLs in South America




Maya JJ, Ruiz SJ, Blanco VM, Gotuzzo E, Guzman-Blanco M, Labarca J, et al.
Current status of carbapenemases in Latin America.
Expert Rev Anti Infect Ther. 2013;11(7):657-67.

*Courtesy M.V.Villegas, A.Galas and S.Vega*

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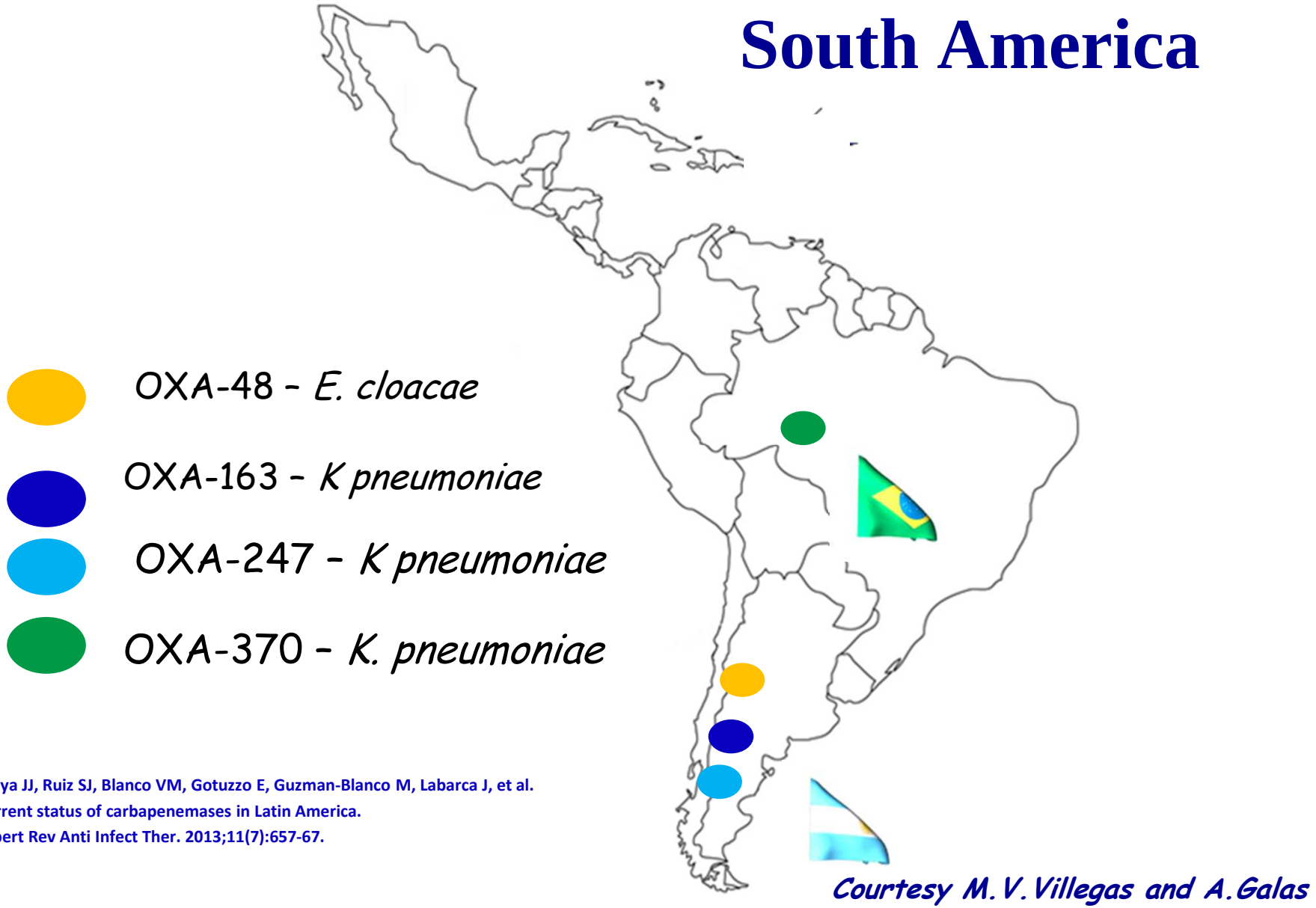
# OXAs in South America




Maya JJ, Ruiz SJ, Blanco VM, Gotuzzo E, Guzman-Blanco M, Labarca J, et al.
Current status of carbapenemases in Latin America.
Expert Rev Anti Infect Ther. 2013;11(7):657-67.

*Courtesy M.V.Villegas and A.Galas*

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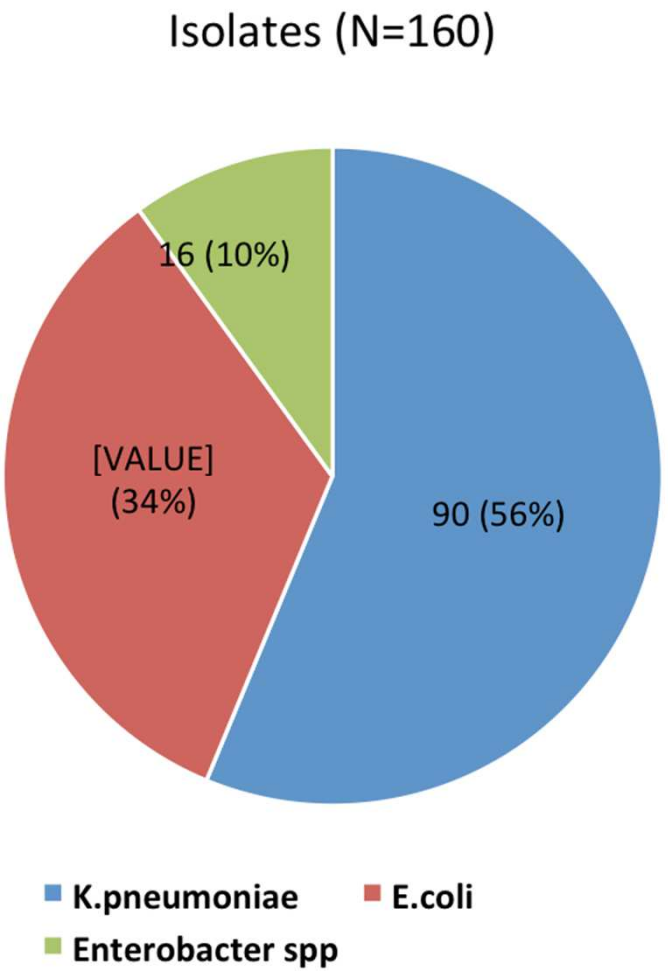
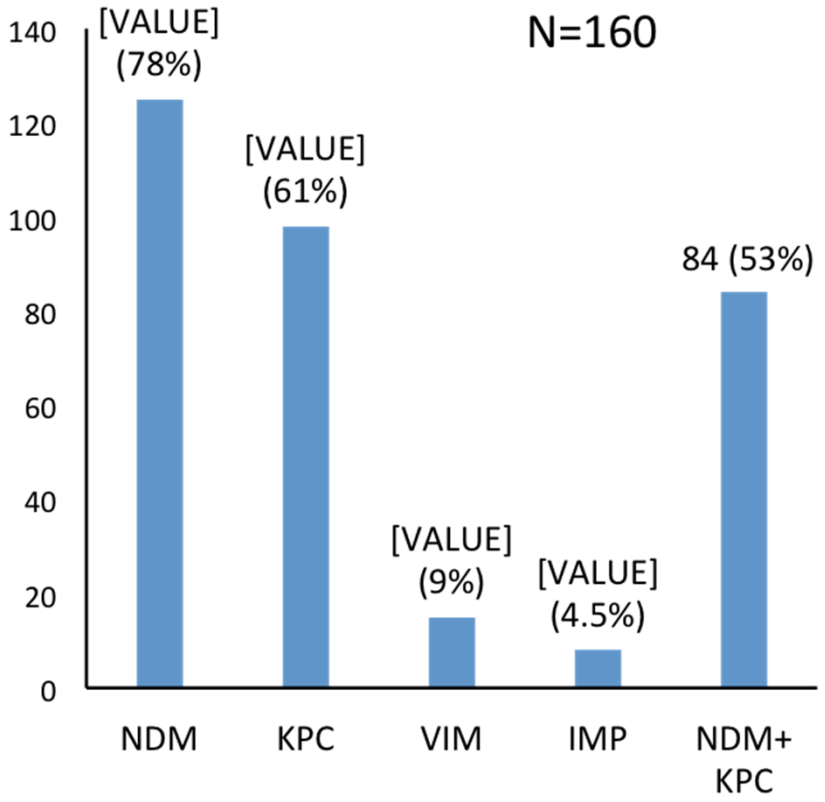
# INDIA

## Kasturba Hospital, Manipal, Karnataka,

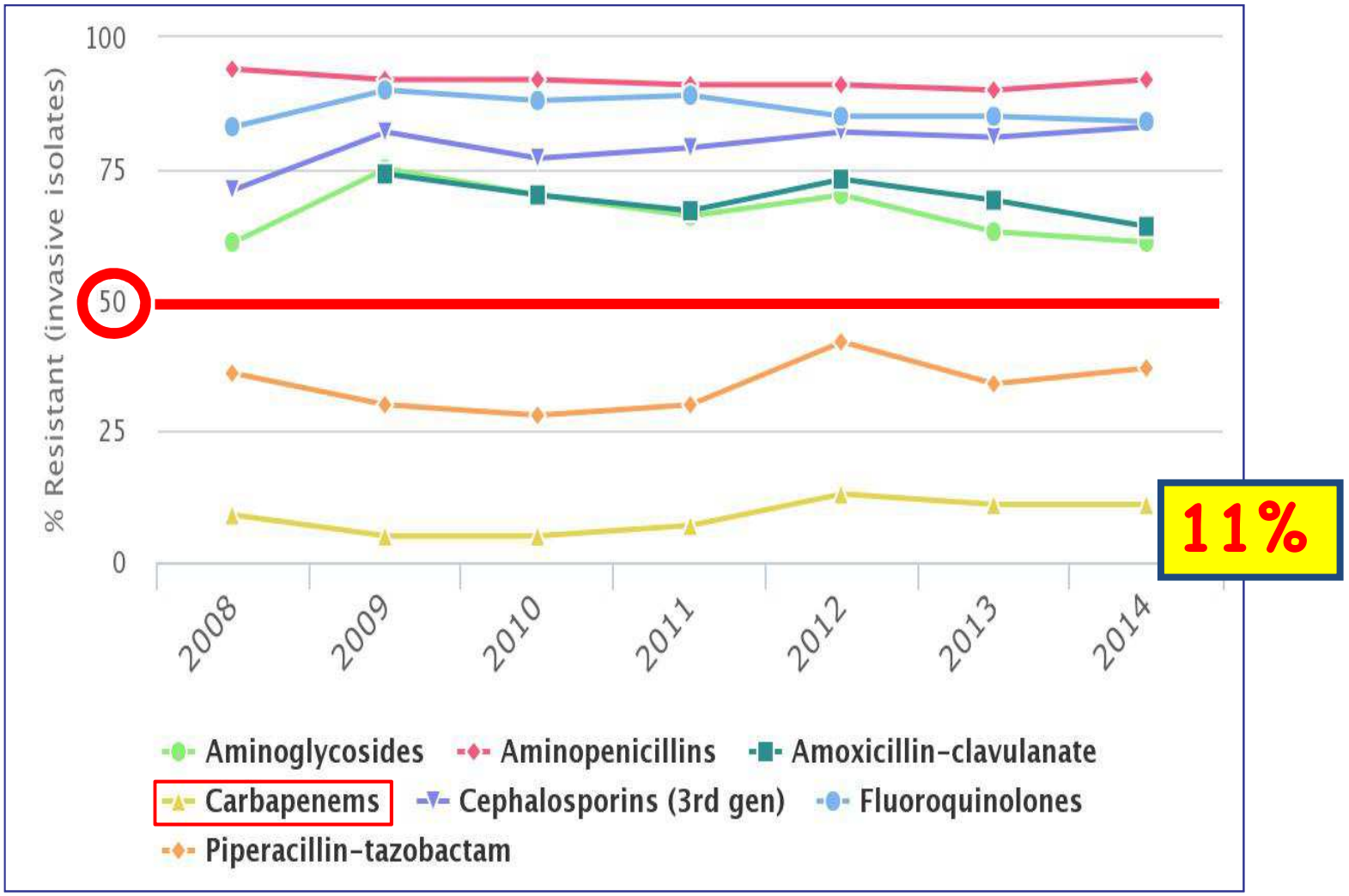
**June 2015 –December 2015**



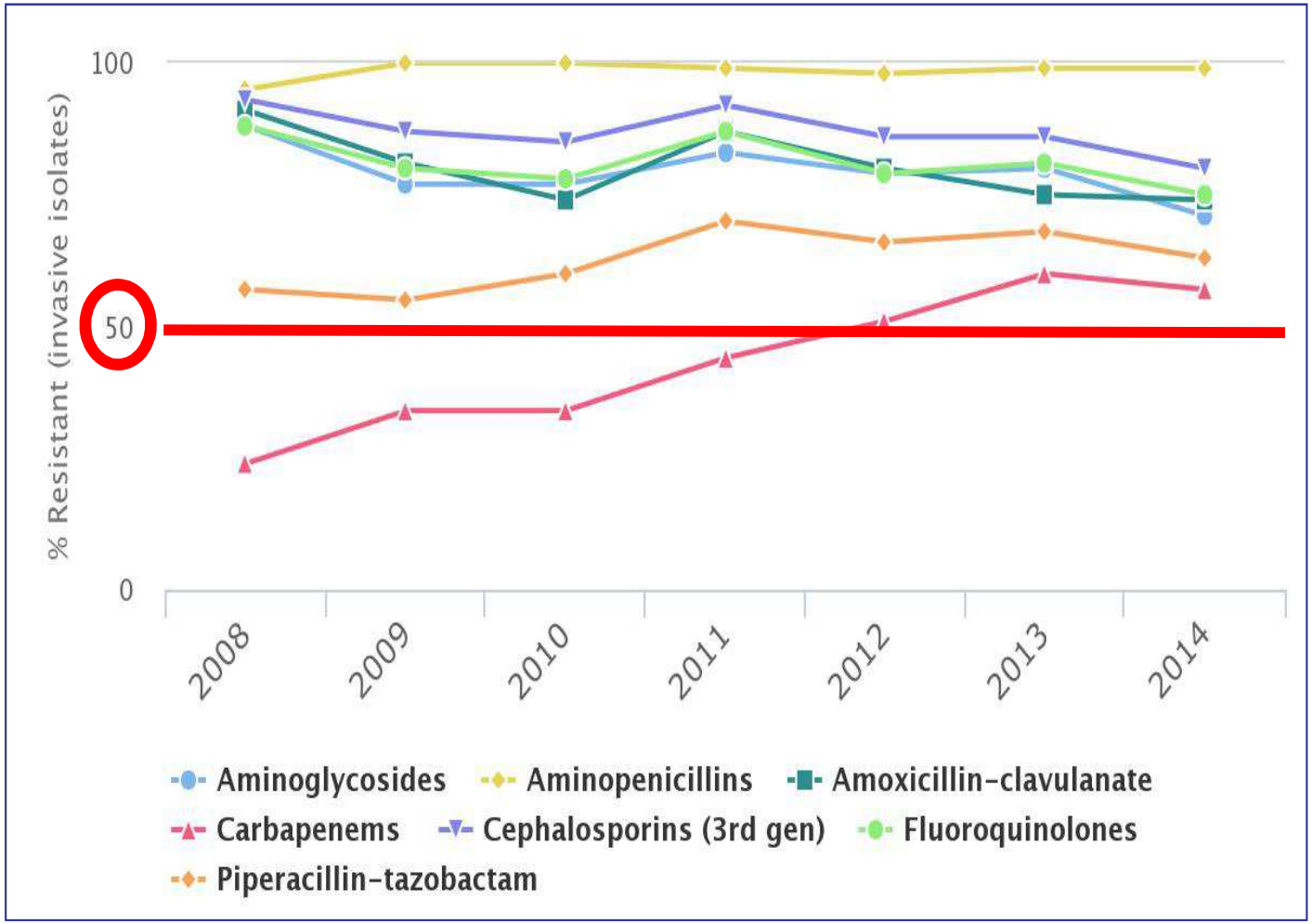

*Courtesy S.Malhotra*

# Antibiotic resistance of *Escherichia coli* in India




Center for Diseases Dynamics, Economics & Policy (cddep.org)

# Antibiotic resistance of *Klebsiella pneumoniae* in India



# India, the reasons of the success

Hygiena

Diarrhea

Population; overcrowded

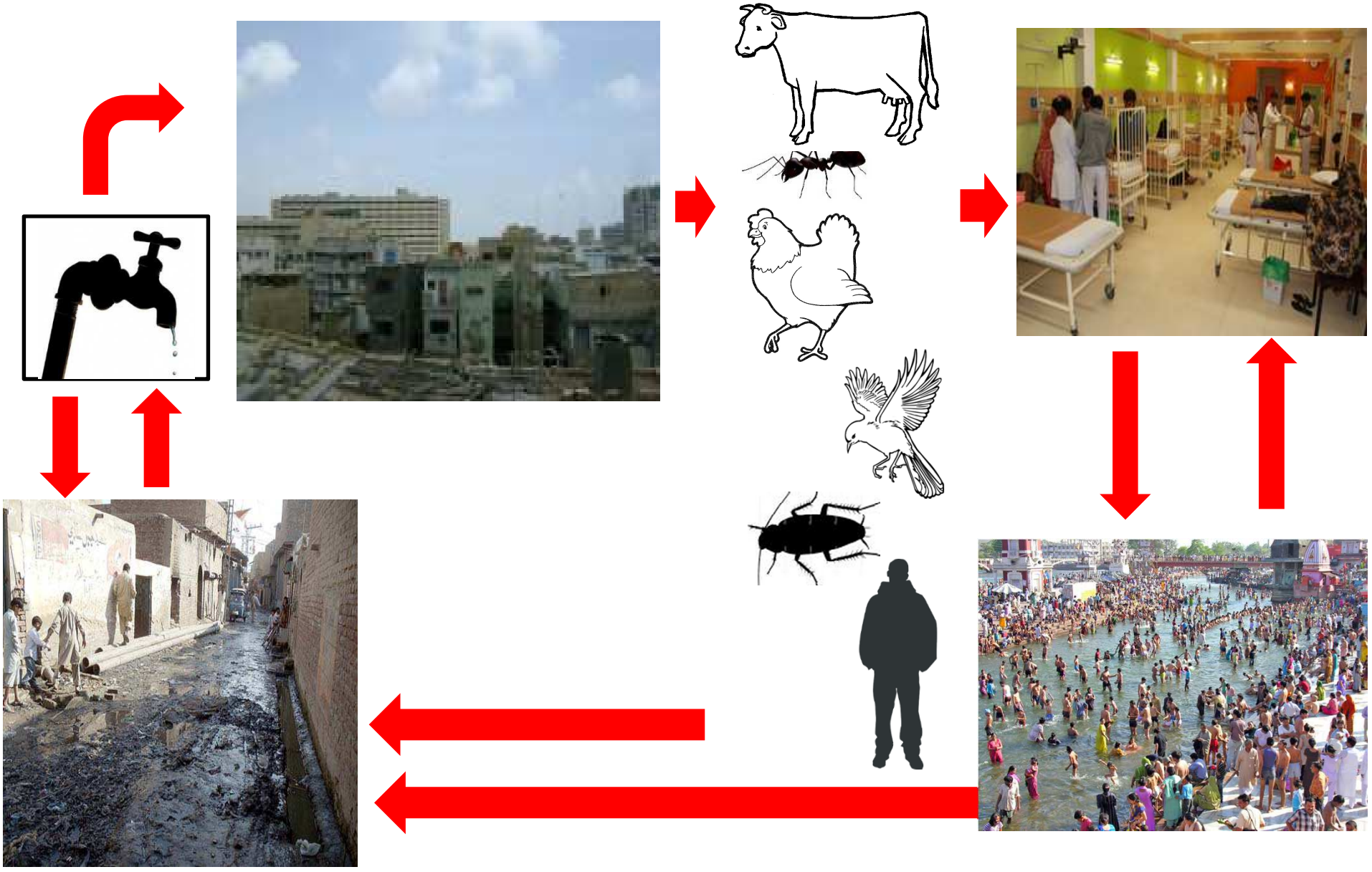
Antibiotics; misuse and overuse, over-the-counter sale

Spread of NDM-1 producers in *E. coli*, *K. pneumoniae*...

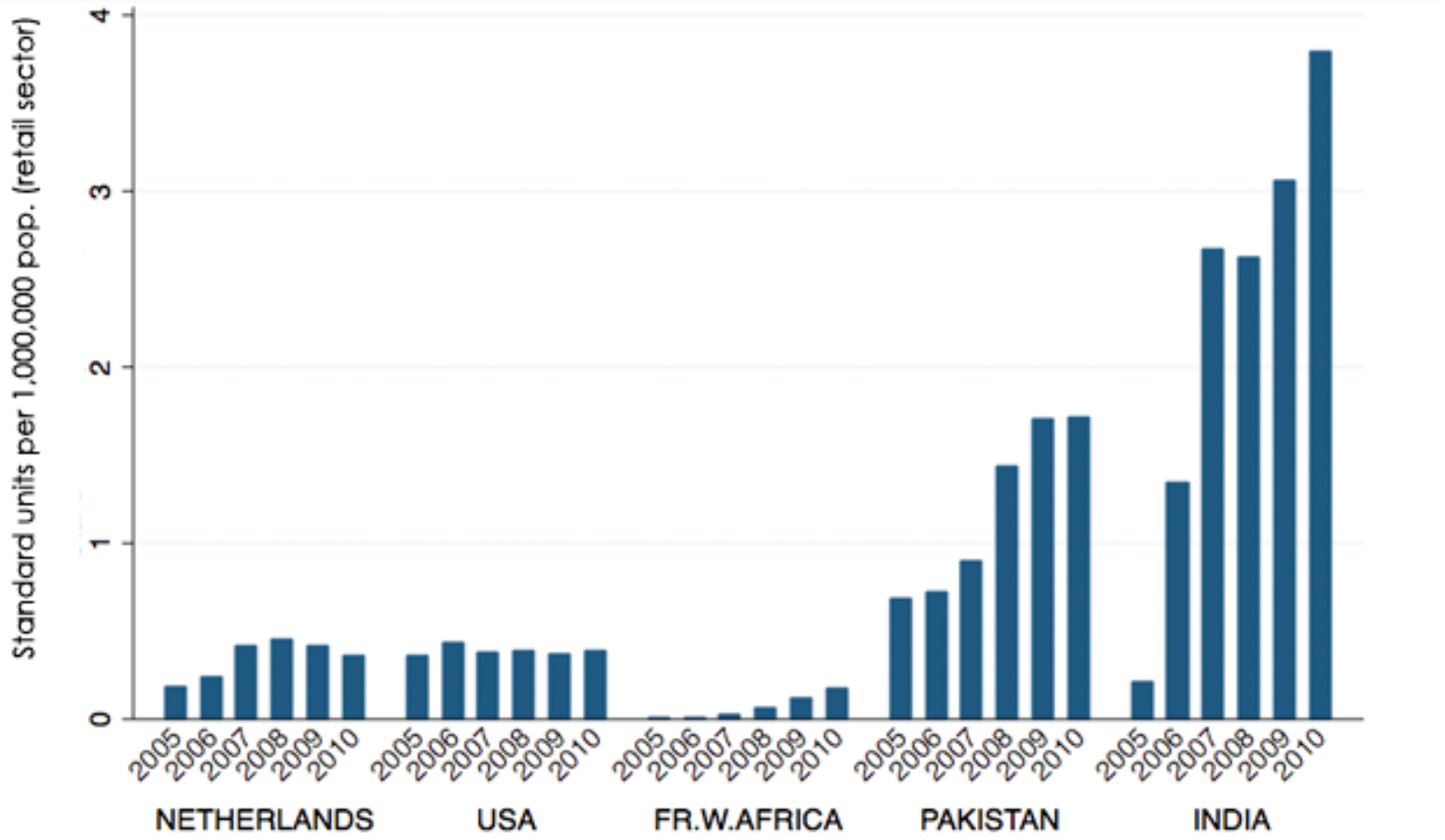
Subtropical continent

*...and then higher mortality rate and length of hospitalization, overuse of broad-spectrum of antibiotics....*

# Compartmentalization of sectors is not valid anymore



# Retail sales of carbapenem antibiotics to treat Gram-negative bacteria are increasing rapidly in India and Pakistan

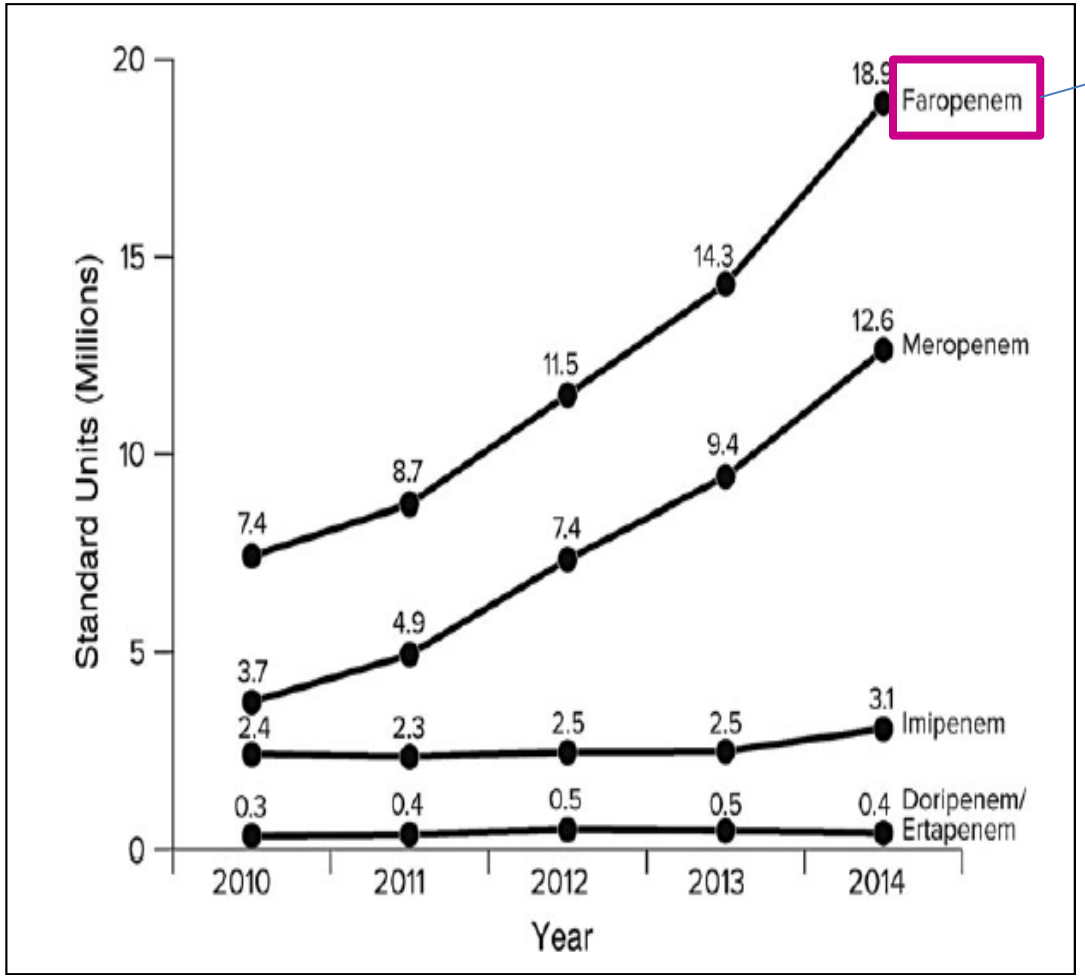







CDDEP
THE CENTER FOR
Disease Dynamics, Economics & Policy
WASHINGTON DC • NEW DELHI

# Carbapenem consumption in India

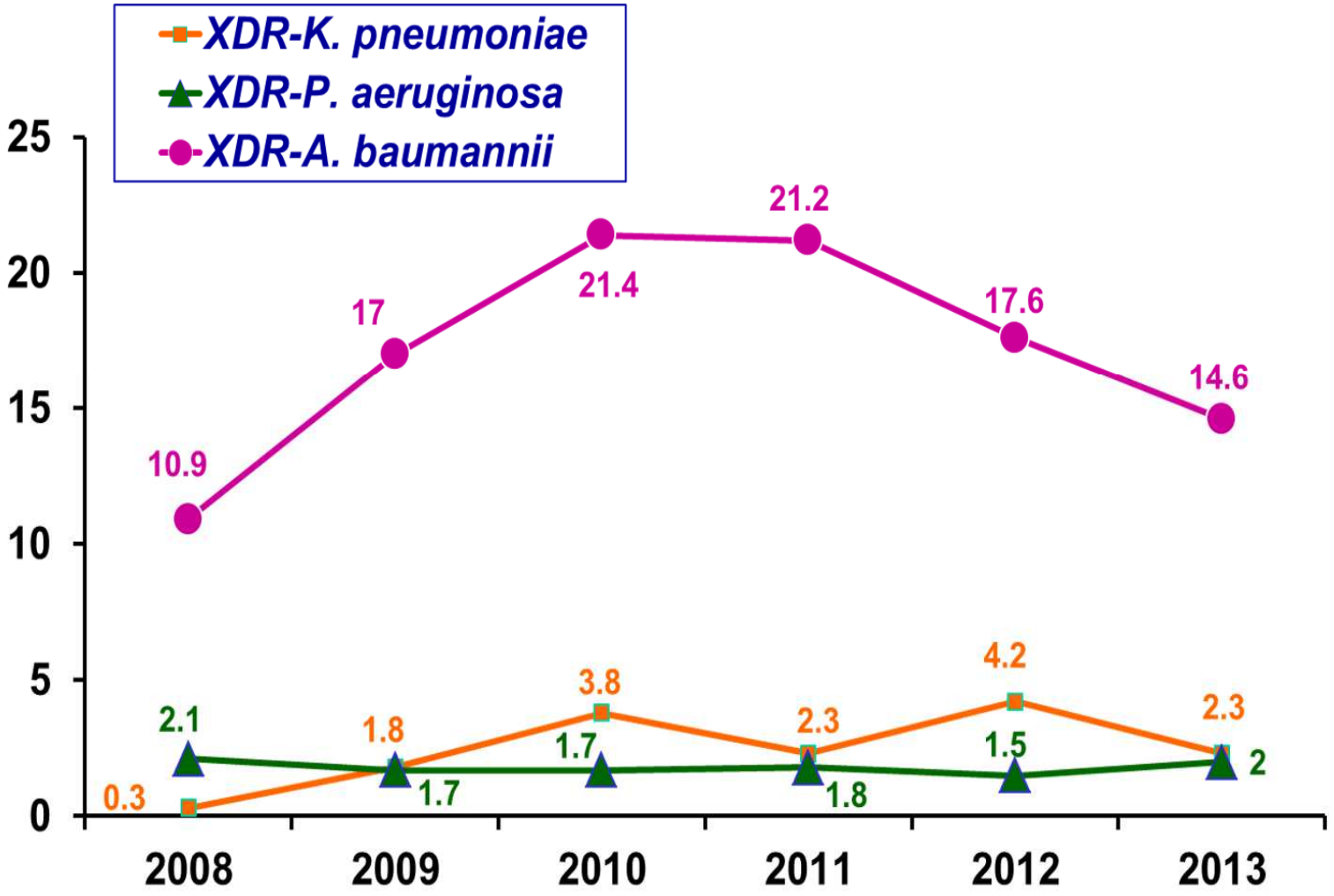



Oral carbapenem !!

Gandra S et al. Clin Infect Dis. 2016;62:1050-2.

# Trend on XDR Gram-Negative Bacilli

## China, CHINET 2013




汪复等.中国感染与化疗杂志 2014;14:369-78.

# Characterization of carbapenem-resistant *Enterobacteriaceae* in China: a nationwide retrospective 9-years surveillance study

Qiwen Yang[1], Huanli Duan[1], Hui Zhang[1], Hui Wang[2], Meng Xiao[1], Yingchun Xu[1], Minjun Chen[1].
1. Department of laboratory medicine, Peking Union Medical College Hospital, Beijing, China. 100730.
2. Department of laboratory medicine, Peking University, People's Hospital, Beijing, China. 100044.

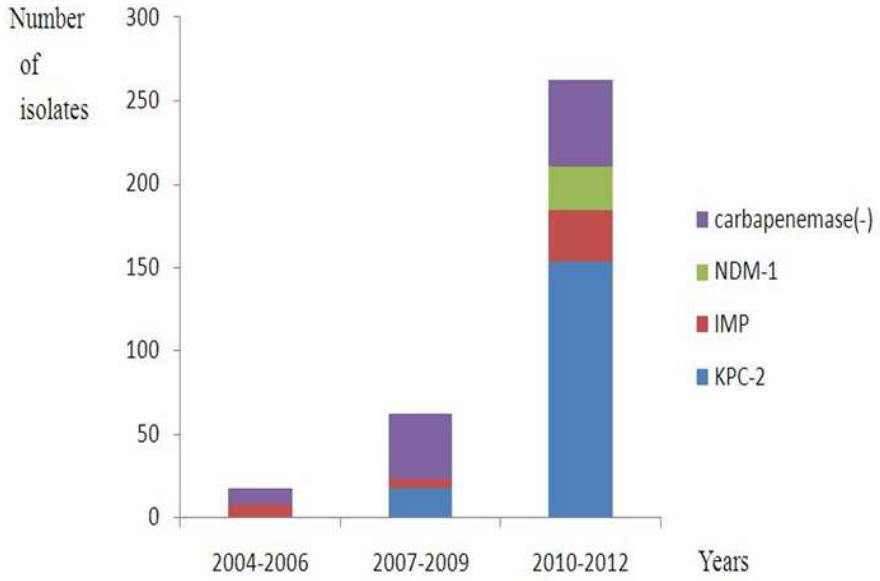


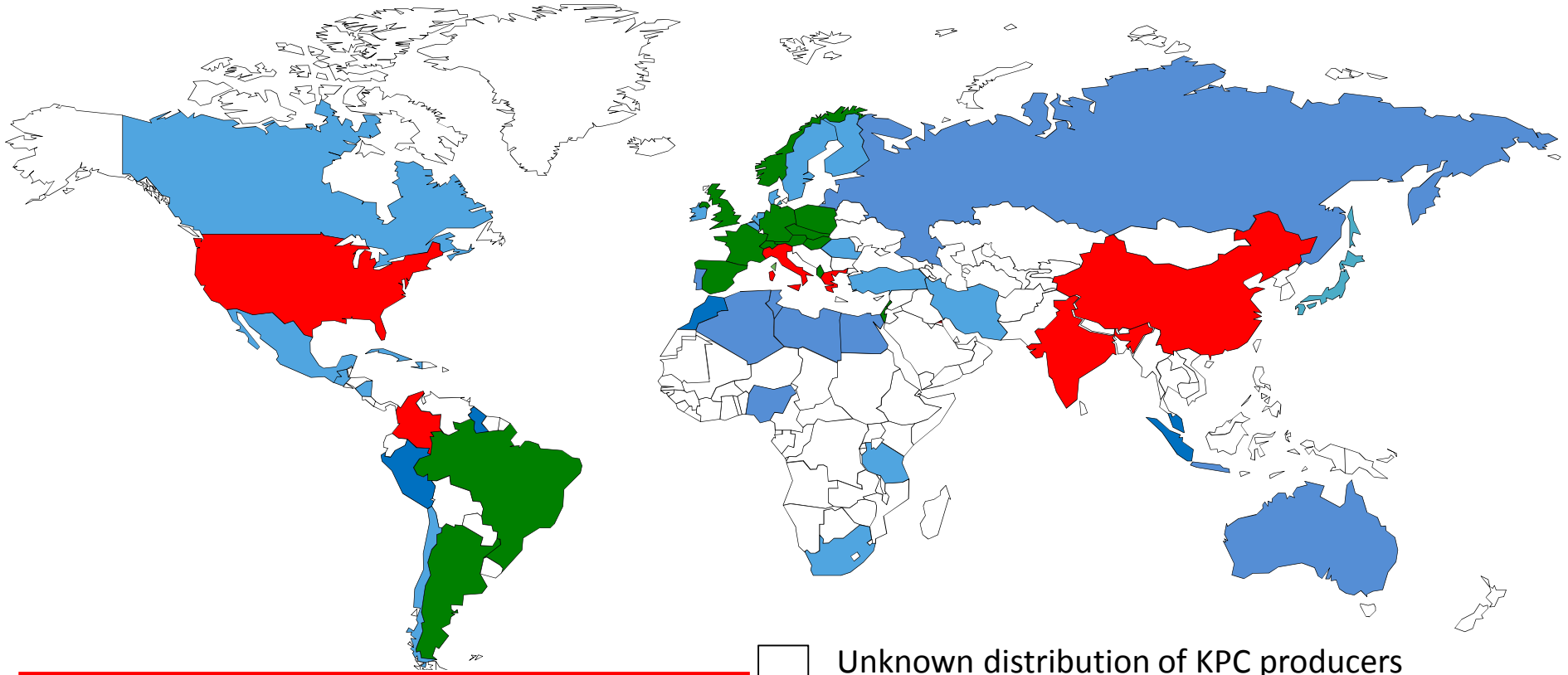

FIG 1. Number of CREs with different resistance mechanisms during 2004-2012.

## Conclusions

1. Carbapenem-resistant *Enterobacteriaceae* is a big problem in China, especially in recent years.
2. Carbapenemase production is the major mechanism of CRE, which accounted for 70% of total CREs. KPC-2 is the predominant carbapenemase and KPC-2-producing CREs showed high prevalence in east China and Beijing. Carbapenemase genes were located in different plasmids which accelerate their spread.
3. Nearly one-third CREs lacked their porins, rather than producing carbapenemases. Most of them lacked both major porins, which lead to high level resistance to carbapenems.


Xinjiang
Heilongjiang
Jilin
Inner Mongolia
Liaoning
Beijing
Tianjin
Qinghai
Ningxia
Shanxi
Hebei
Shandong
Gansu
Tibet
Shaanxi
Henan
Anhui
Jiangsu
Shanghai
Sichuang
Chongqing
Hubei
Zhejiang
Hunan
Jiangxi
Guizhou
Fujian
Yunnan
Guangxi
Guangdong
Hainan
Carbapenemases
KPC
NDM
KPC+NDM
IMP
Others

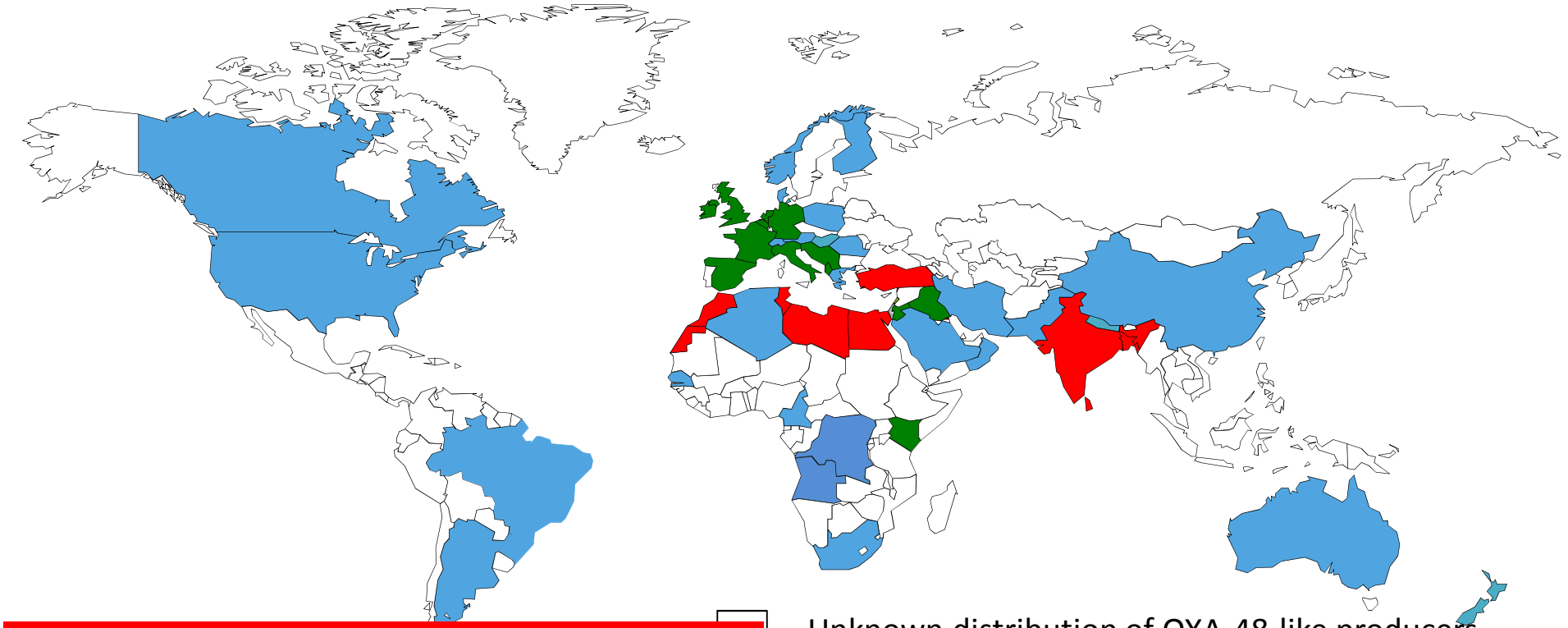
# KPC producers- *Enterobacteriaceae*, 2017



Unknown distribution of KPC producers
Sporadic spread of KPC producers
Outbreaks due to KPC producers
Endemicity of KPC producers

Key points:
-High level resistance to carbapenems
-Still mostly in *K. pneumoniae, rarely in E. coli*
- Several South American countries
Italy and Greece are now endemic countries

# OXA-48-like producers- *Enterobacteriaceae*, 2017

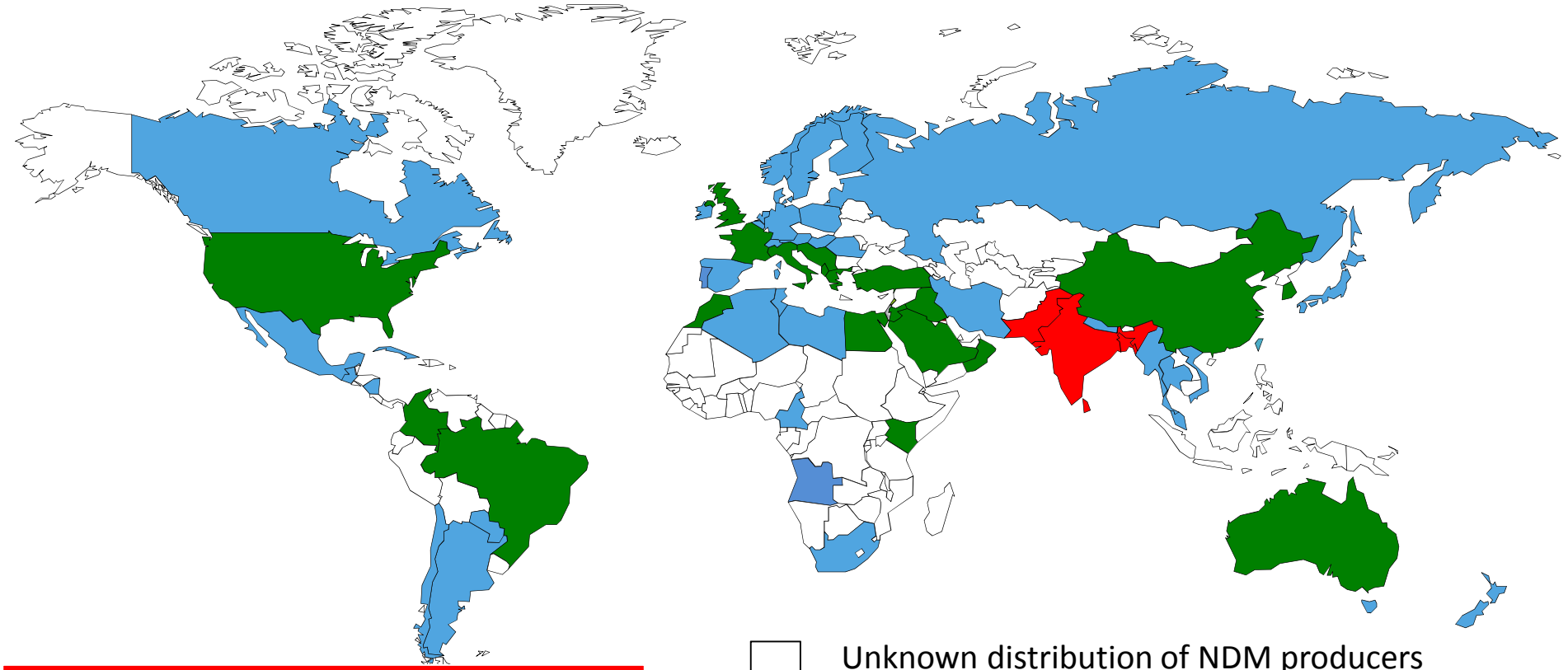


Unknown distribution of OXA-48-like producers
Sporadic spread of OXA-48-like producers
Outbreaks due to OXA-48-like producers
Endemicity of OXA-48-like producers

Key
- - Variable resistance levels to carbapenems
- Main known reservoirs; North Africa, Middle East, Turkey and India
- Community aquisition and easy transfer (++)
- *K. pneumoniae, E.cloacae, E.coli (++)*

*Nordmann & Poirel, 2014 Clin Microb Infect,*

# NDM producers- *Enterobacteriaceae*, 2017



Unknown distribution of NDM producers
Sporadic spread of NDM producers
Outbreaks due to NDM producers
Endemicity of NDM producers

Key points:
- Variable resistance levels to carbapenems
-*K. pneumoniae, E. coli, E.cloacae…*
-Secondary reservoirs; Balkans
and the Middle East

# Three irreversible resistance waves towards pandrug resistance in *Enterobacteriaceae*

2017

1960's-70's

Penicillinases

60-70%

1990's-2000's

ESBLs

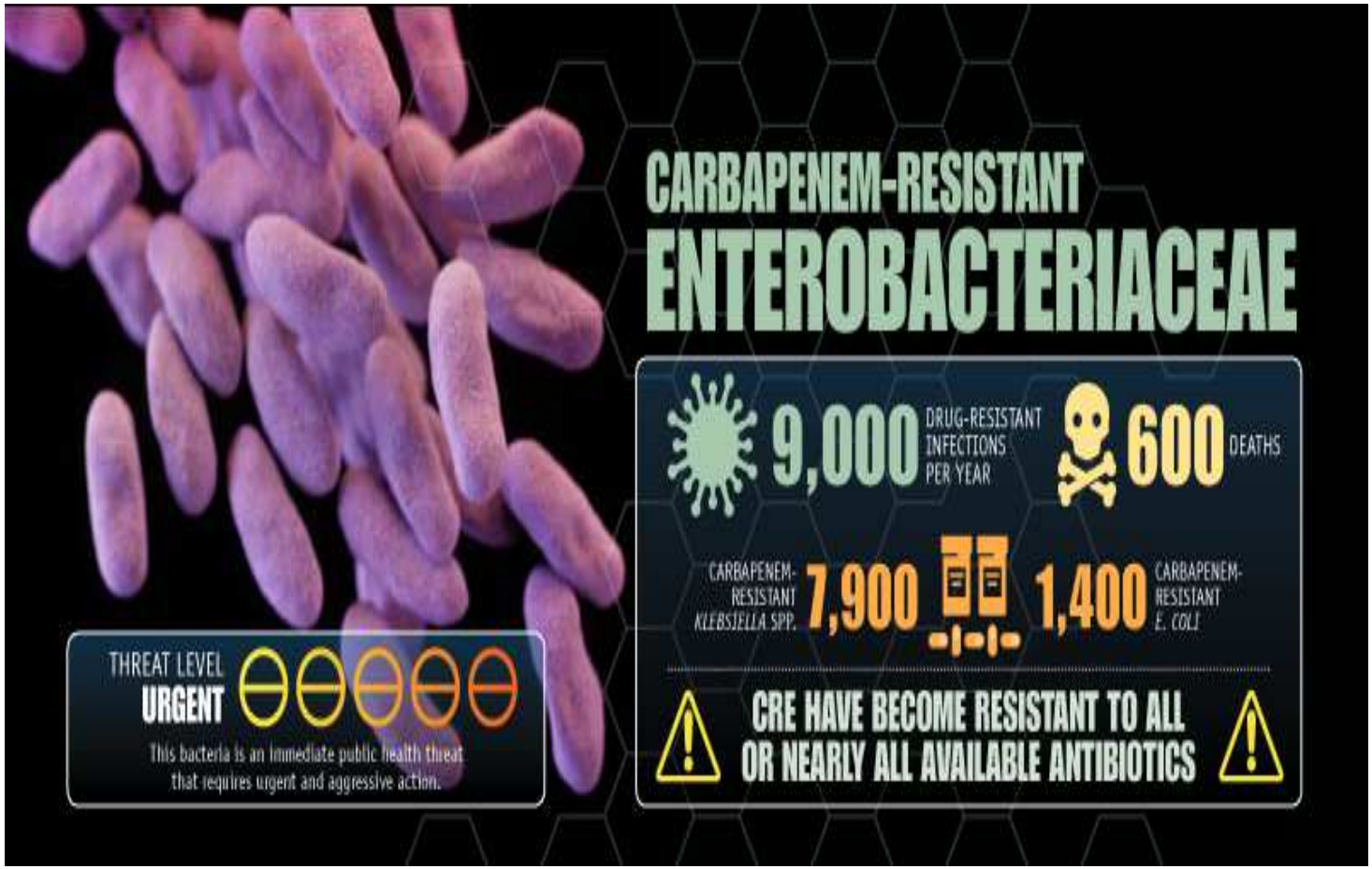
10-80%

2010....

Carbapenemases

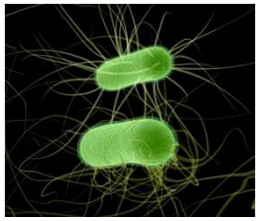
0.01-30 ?%

# CDC- USA, 2015

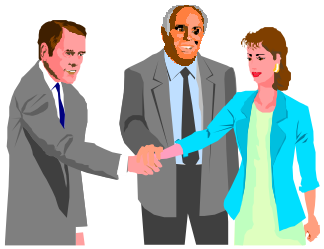

CARBAPENEM-RESISTANT
ENTEROBACTERIACEAE
9,000 DRUG-RESISTANT INFECTIONS PER YEAR
600 DEATHS
CARBAPENEM-RESISTANT KLEBSIELLA SPP. 7,900
1,400 CARBAPENEM-RESISTANT E. COLI
CRE HAVE BECOME RESISTANT TO ALL OR NEARLY ALL AVAILABLE ANTIBIOTICS
THREAT LEVEL
URGENT
This bacteria is an immediate public health threat that requires urgent and aggressive action.

# Carbapenemase producers are spreading now in the community; NDM and OXA-48-like producers

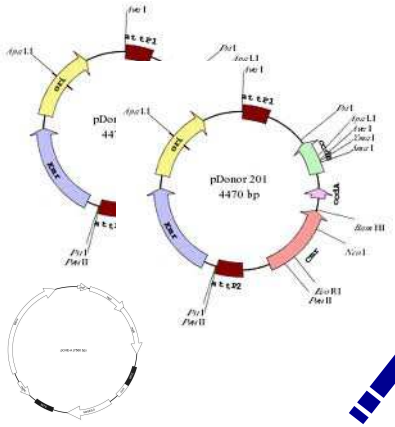
# Plasticity of the carbapenemase genes; from the environment to colonized, infected and hospitalized patients

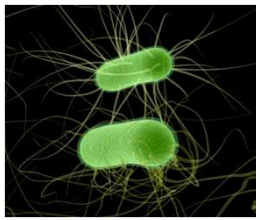


*E. coli* (OXA-48-like, NDM )



*K. pneumoniae*(OXA-48-like, NDM )



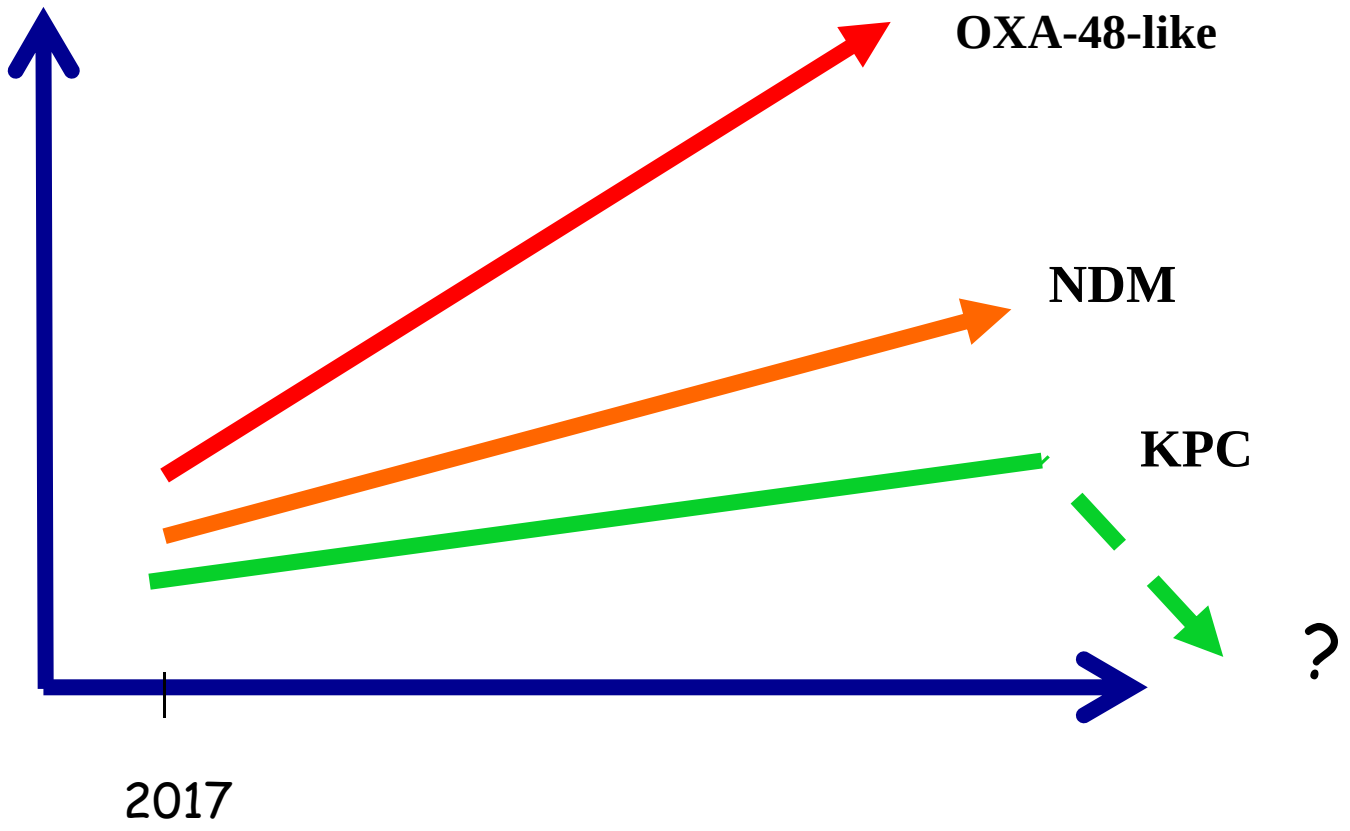


*E. coli* (OXA-48-like, NDM )


Three major determinants foster the unrelenting spread of carbapenemases:
Mobile genes
Successful clones
Travellers

# 842 millions airplane tickets -2013


# Future spread of carbapenemase in *Enterobacteriaceae*




OXA-48: *E. coli* ++, community-acquired, highly transferable plasmid
NDM: *Enterobacteriaceae*, community- and hospital-acquired
KPC; *K. pneumoniae*, hospital-acquired

# Our future ?

**Multidrug-resistant bacteria**

# Our future ?

**Multidrug-resistant bacteria**

**AND novel powerful antibiotics**

| | Ceftazidime-avibactam | Ceftolozane-tazobactam |
|---|---|---|
| **Forces** | **Activité sur :**<br>• **BLSE +++**<br>• **AmpC (hyperproduction des EB)**<br>• **Carbapénèmases (KPC, OXA 48)**<br>• *P. aeruginosa* cefta R et imipénème R | **Activité sur :**<br>• BLSE (*E.coli* +++, *Kp* ±) ...<br>• *P. aeruginosa* - R cefta et imipénème |
| **Faiblesses** | **Pas d'activité sur :**<br>• Anaérobies<br>• **Metallo-carbapénèmases**<br>• Oxacillinases d'*Acinetobacter*<br>• **CG+ ??? = 0** | **Pas d'activité sur :**<br>• La plupart de anaérobies *(B. fragilis+)*<br>• Entérocoques<br>• Staphylocoques<br>• **Carbapénèmases**<br>• AmpC hyperproduction des EB<br>• Oxacillinases d'*Acinetobacter* |

Courtesy, JP Bedos

# Novel β-lactams/inhibitor

| | ESBL | Amp C | Carbapenemases | | | *Pseudomonas spp* | *Acinetobacter* | Phase |
|---|---|---|---|---|---|---|---|---|
| | | | KPC | Oxa-48 like | **MBL** | | | |
| Ceftaroline/avibactam | ++ | ++ | + | - | - | - | - | |
| **Aztréonam/avibactam** | ++ | ++ | ++ | + | ++ | + | - | 2 |
| Imip/relebactam (MK 7655) | ++ | ++ | ++ | - | - | + | - | 3 |
| Mero/vaborbactam (RPX 7009) | ++ | ++ | ++ | - | - | +/- | - | 3 |
| Cefépime/zidebactam (WCK 5222) | ++ | ++ | ++ | ++ | ++ | ++ | - | 2 |
| **Céfidérocol** (**S** 649266) (sidérophore cephalosporin AB) | ++ | ++ | ++ | ++ | ++ | ++ | + | 3 |

Courtesy, JP Bedos

**…..and others such as plazomicin**

# WHO's 'priority pathogens' list highlights urgent need for new drugs

***Feb 27, 2017***

**Priority 1: Critical**

**• *Enterobacteriaceae*, carbapenem-resistant, ESBL producers**

•*Acinetobacter baumannii*, carbapenem-resistant.

•*Pseudomonas aeruginosa*, carbapenem-resistant.

**Priority 2: High**

• *Enterococcus faecium*, vancomycin-resistant.

• *Staphylococcus aureus*, methicillin-resistant, vancomycin-intermediate and resistant.

• *Helicobacter pylori*, clarithromycin-resistant.

• Campylobacter spp., fluoroquinolone-resistant.

• *Salmonella*, fluoroquinolone-resistant.

• *Neisseria gonorrhoeae*, cephalosporin-resistant, fluoroquinolone-resistant.

**Priority 3: Medium**

• *Streptococcus pneumoniae*, penicillin-non-susceptible.

• *Haemophilus influenzae*, ampicillin-resistant.

• *Shigella* spp., fluoroquinolone-resistant.