Global Epidemiology of Carbapenem-Resistant Enterobacteriaceae (CRE)

Mitchell J. Schwaber, MD MSc
Director, National Center for Infection Control
Ministry of Health
State of Israel
November 27, 2012

Mechanisms of carbapenem resistance in Enterobacteriaceae

- A combination of:
  - a β-lactamase that hydrolyzes carbapenems inefficiently

    +
  - a major porin loss

- An efficient carbapenem-hydrolyzing enzyme (carbapenamase)

β -lactamase hydrolyzing carbapenems inefficiently + porin loss

- ESBL or Ambler class C (AmpC) β-lactamase
- Major non-specific porin loss
- The phenotype is often ertapenem resistance and increased MICs of IMI and MER

Epidemiology and clinical consequences

- Sporadic cases arising during carbapenem therapy
- May lead to serious adverse clinical consequences
- May lead to treatment failure, e.g., breakthrough bacteremia
- Strains with limited ability to spread due to metabolic impairment conferred by major porin loss

Courtesy of Yehuda Carmeli

Relative growth rate in experimental *E. coli* strains

fitness cost incurred for major porin loss
(smaller fitness cost incurred for ESBL plasmid carriage)

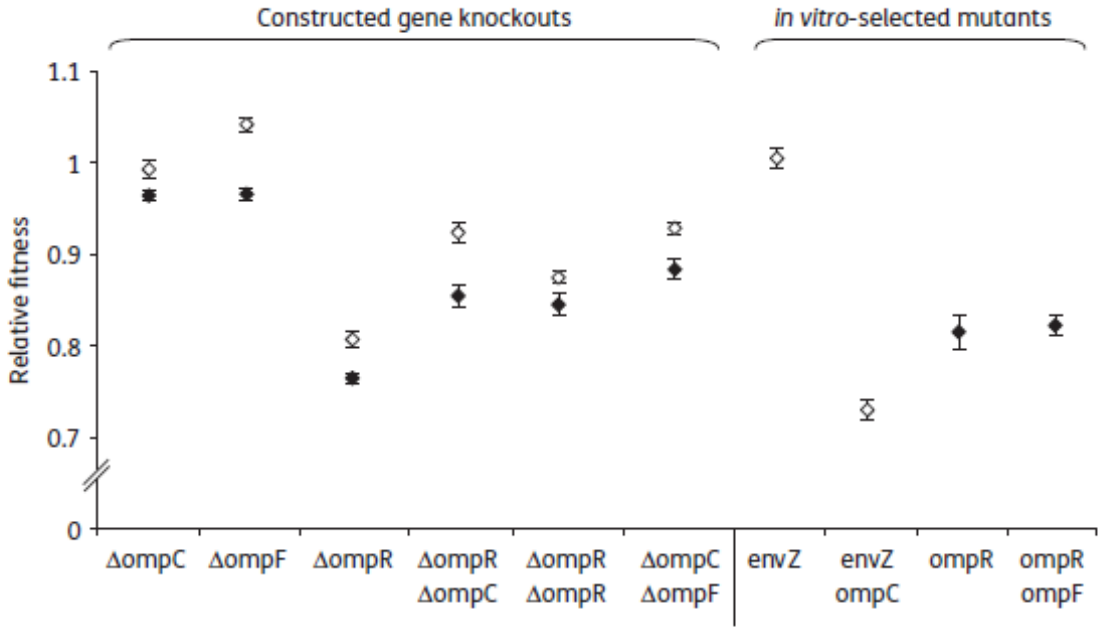
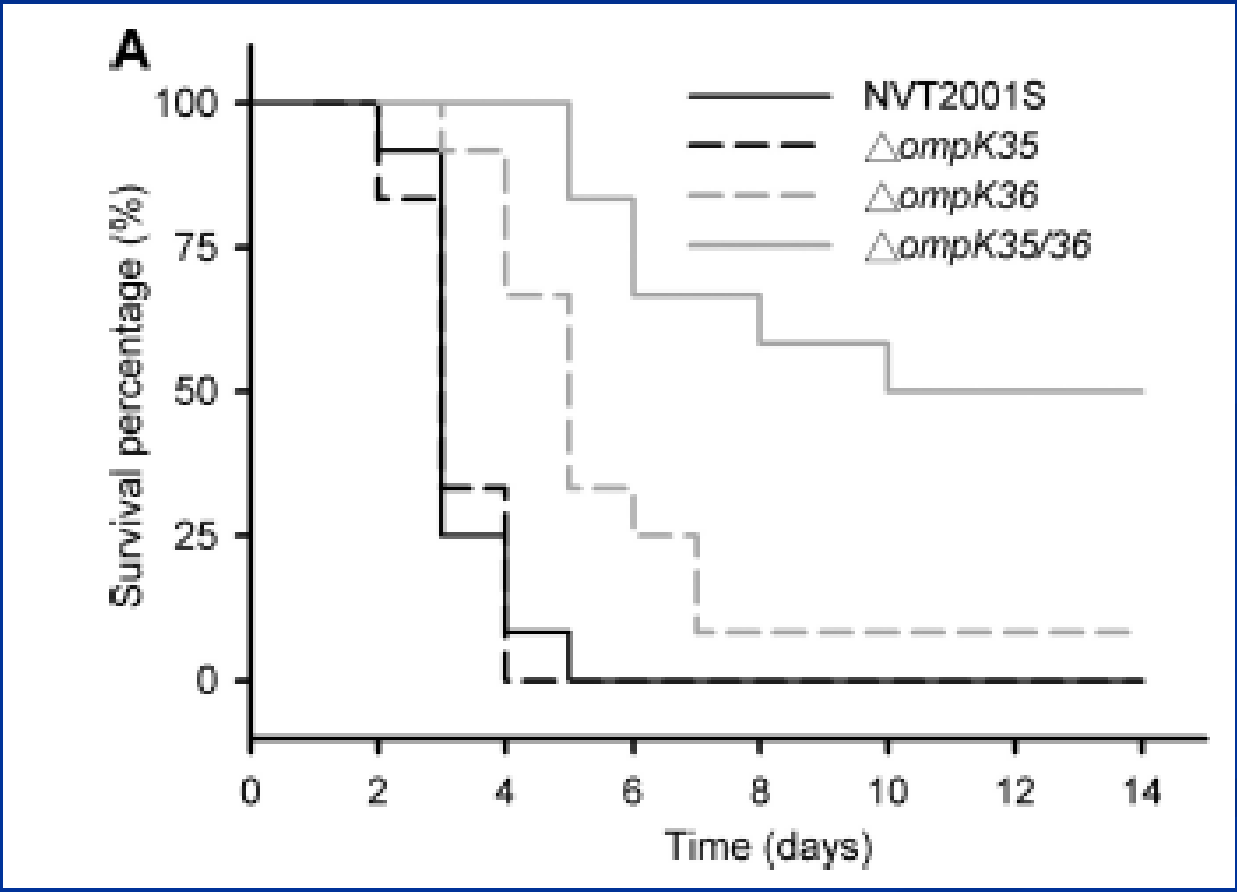


Figure 4. Fitness of constructed and *in vitro*-selected mutants. The growth rate is calculated relative to the wild-type growth rate. Filled symbols show growth rates of mutants with pUUH239.2, while open symbols show mutants without pUUH239.2.

Adler M et al, JAC 2012

Major porin loss OmpK36 and combined OmpK36/35 reduce virulence in *K. pneumoniae* murine peritonitis model



Tsai YK et al, AAC 2011

Spread of non-carbapenemase – producing CRE

- Portugal
  - 4-month period, 2010
  - single hospital
  - 7 clonal CRE strains -
    - CTX-M-15 (ESBL)-producing *K. pneumoniae* ST15 with a new OmpK36 porin variant

Novais A et al, EJCMID 2012

- Italy
  - Clonal outbreak of *K. pneumoniae* ST37 with OmpK35 loss and a new OmpK36 porin variant
  - Carbapenem resistance via combination with various plasmids carrying various ESBLs

Garcia-Fernandez A et al, AAC 2010

Infection control measures recommended for non-carbapenemase-producing CRE

- Likelihood of an outbreak are small
  - Contact precautions
  - Generally no need for contact screening
- If more than one case
  - Re-confirm that it is not a carbapenamase-producing strain
  - Examine clonality; if clonal – enhance IC measures

Carbapenemase-producing Enterobacteriaceae

- First reported from *S. marcescens* in 1982 – SME-1

  (Queenan AM and Bush K, CMR 2007)

- In past 30 years
  - Large variety of carbapenemases identified
  - Belong to 3 β-lactamase classes – A, B, D

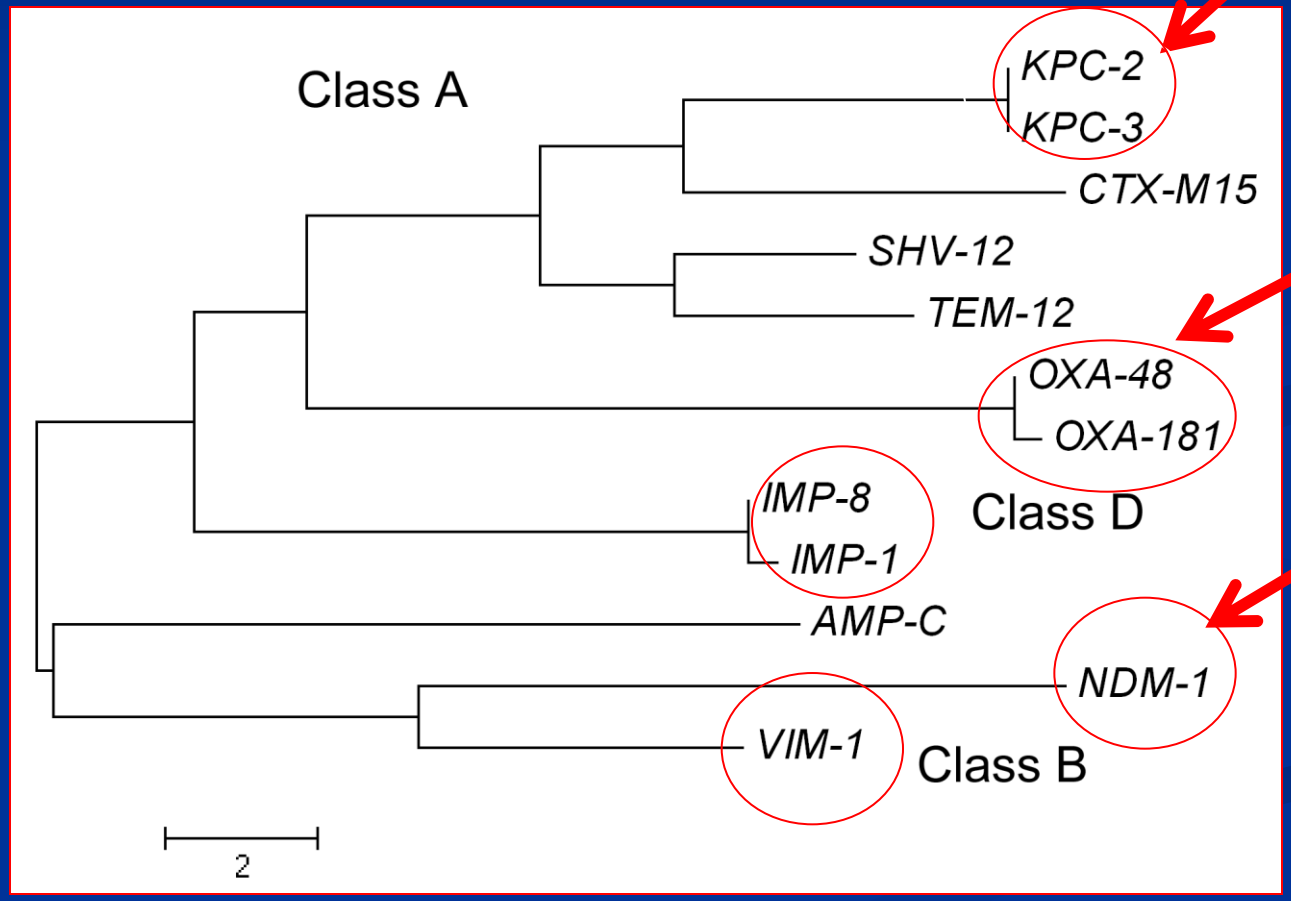
Carbapenemase Genes

- Ambler Class A (serine beta-lactamases): 9 families
  - **KPC**, SME, NMC-A, IMI, PER, GES, SFO, SFC, IBC
- Ambler Class B (metallo-beta-lactamases): 6 families
  - **VIM**, GIM, SIM, **NDM**, **IMP**, SPM
- Ambler Class D: 2 families
  - **OXA**, PSE

Cohen Stuart J et al, IJAA 2010; Nordmann P et al, EID 2011

Classification

- Phylogeny of carbapenemases



Courtesy of Amos Adler

Carbapenemases and the pathogens that produce them

Enterobacteriaceae

Nonfermenters

Table 1
Clinically relevant carbapenemases

Organism	Carbapenemases		
	Class A	Class B (MBLs)	Class D (oxacillins)
Klebsiella pneumoniae	++	+++[a]	++
Escherichia coli	+/−	+/−	+
Proteus mirabilis	+/−	+/−	+
Providencia spp.		+/−	
Klebsiella oxytoca	+/−	+/−	
Serratia marcescens	+/−	+	
Enterobacter spp.	+/−	+	
Citrobacter freundii	+/−	+/−	
Morganella morganii		+/−	
Salmonella enterica	+/−		
Pseudomonas aeruginosa	+	+++	+
Pseudomonas putida	+	+/−	
Acinetobacter baumannii		+	+++
Acinetobacter spp.		+	+

+++, high prevalence (>10%) in certain regions; ++, moderate prevalence (1–10%); +, low prevalence but >1 case; +/−, isolated cases; MBL, metallo-β-lactamase.

[a] Endemic in certain regions: VIM-1/4 in Greece and NDM-1 in India.

Walsh TR, Int J Antimicrob Agents 2010

Carbapenemases – historical perspective

- First successful carbapenemase producers in Enterobacteriaceae:
  - 1996, North Carolina - KPC-2 in *K. pneumoniae*
  - 2001, Greece - VIM-1 in *E. coli* and *K. pneumoniae*
  - 2001, Turkey - OXA-48 in *K. pneumoniae*
  - 2008, Sweden - NDM-1 in *K. pneumoniae*

Courtesy of Amos Adler

Phenotypic characteristics

Gene	Class	Predominant species	Inhibited by	β-lactams to which susceptible	Carbapenem MIC
KPC-2/3	A	*K. pneumoniae*	Boronic acid (partially by clavulanic acid)	-	High MIC_{50}=16
OXA-48	D	Variable	-	3rd gen ceph Aztreonam	Low (Higher w/ESBL & porin changes – Nordmann, EID 2011)
NDM-1*	B	Variable	EDTA/DPA	Aztreonam	High MIC_{50}=16
VIM-1	B	*K. pneumoniae*	EDTA/DPA	Aztreonam	Low MIC_{50}=1

*NDM-1: MHT weak or even negative!

Courtesy of Amos Adler

Dissemination of carbapenemases

- Monoclonal
- Plasmid-borne
- Sub-plasmid elements

The Israeli Carbapenemase Story

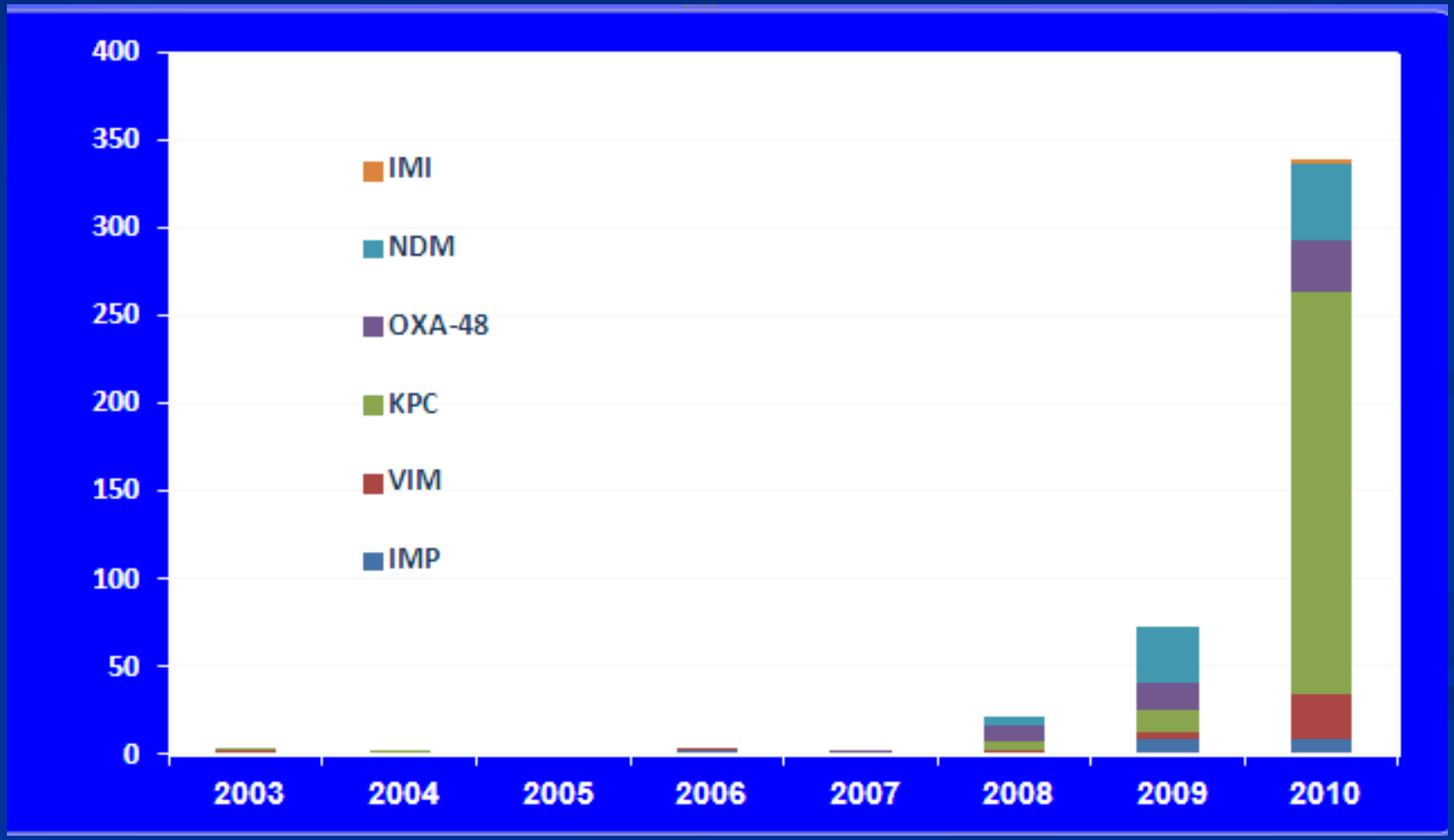
K P C

OXA-48

NDM-1

- KPC: ~17,000
- OXA-48: ~80
- NDM-1: ~30

Great Britain:
Carbapenamase-producing isolates identified at the HPA



http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1294740725984

KPC

First report

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

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]*

KPC

- Found on plasmids
- 12 different KPC genes, most important KPC2, KPC3
- In many cases associated with single genetic element: transposon Tn*4401* (Nordmann P et al, EID 2011)
- Outbreaks caused by *K. pneumoniae,* primarily single MLST type – ST 258
- US
  - First isolate from N. Carolina - 1996
  - Dissemination began early 2000s in northeast; since spread elsewhere
  - By 2007-10% of all isolates of *K. pneumoniae* reported to NHSN – carbapenem resistant (Hidron AI et al, ICHE 2008)
- Large outbreaks in Israel, Colombia, Greece, parts of China
- Sporadic reports throughout Europe, C. and S. America
- Smaller outbreaks involving KPC-producing *E. coli*, *Enterobacter* ; have also been reported in nonfermenters

KPC – affected groups

- Risk factors for infection
  - Antibiotic use
  - ICU stay
  - Reduced functional status (Schwaber MJ et al, AAC 2008)
- Associated with acute-care and long-term care hospitals (Munoz-Price LS et al, ICHE 2010; Ben-David D et al, ICHE 2011)
- No significant community reservoir

KPC-producing CRE treatment options – *a bleak picture*

- Hydrolyze all β-lactams
  - Penicillins
  - Cephalosporins
  - Monobactams
  - Carbapenems
- Multiple associated co-resistances
- Susceptible only to polymyxins (colistin), +/- aminoglycosides (some), +/-tigecycline

(Nordmann P et al, Lancet ID, 2009)

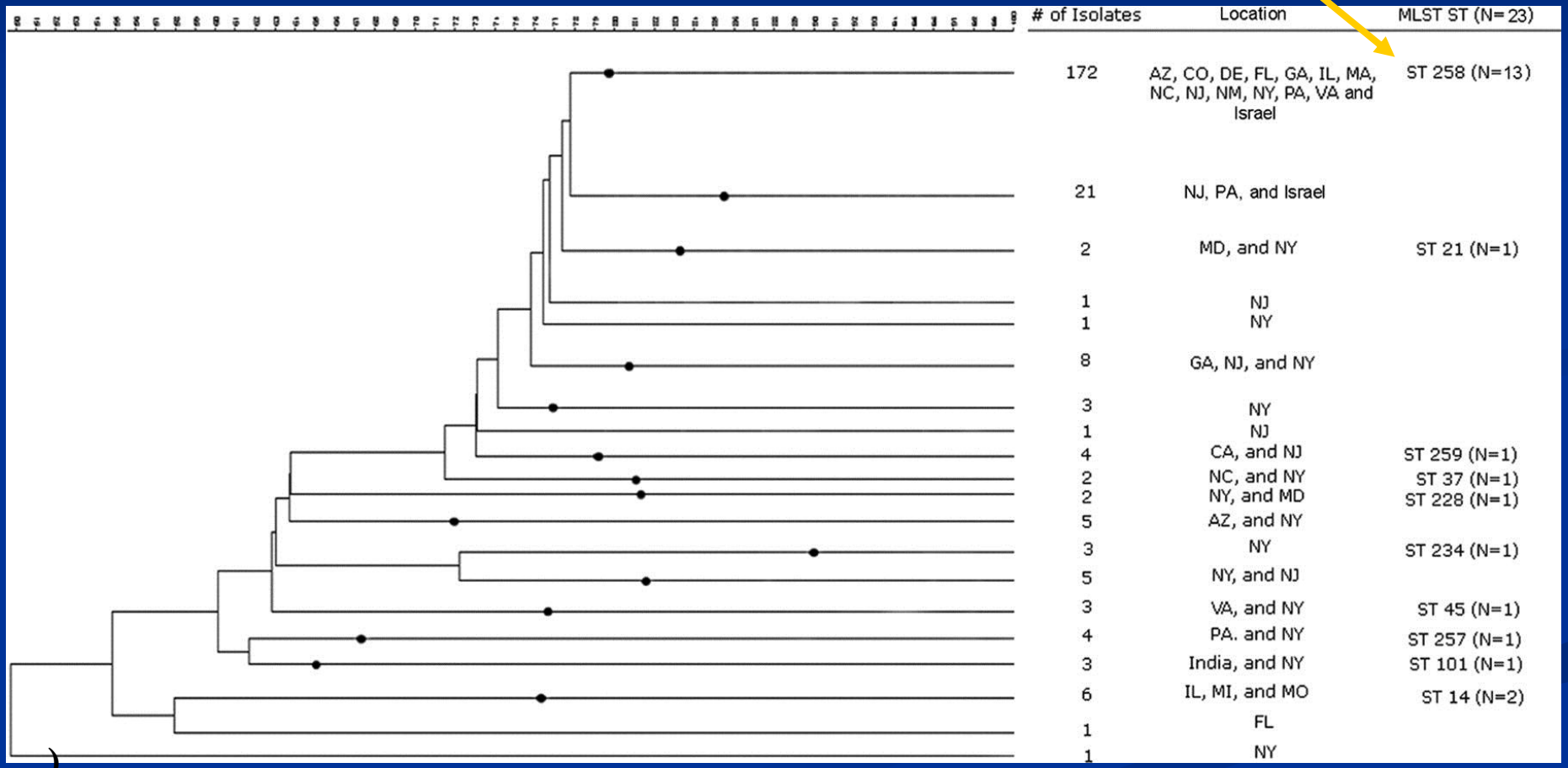
KPC-producing *K. pneumoniae*: a triple threat

- Highly effective at dissemination
- Highly resistant
- High mortality
  - Attributable overall 38%; attributable bacteremia 50%

(Patel G et al ICHE 2008; Schwaber MJ et al AAC 2008; Borer A et al ICHE 2009)

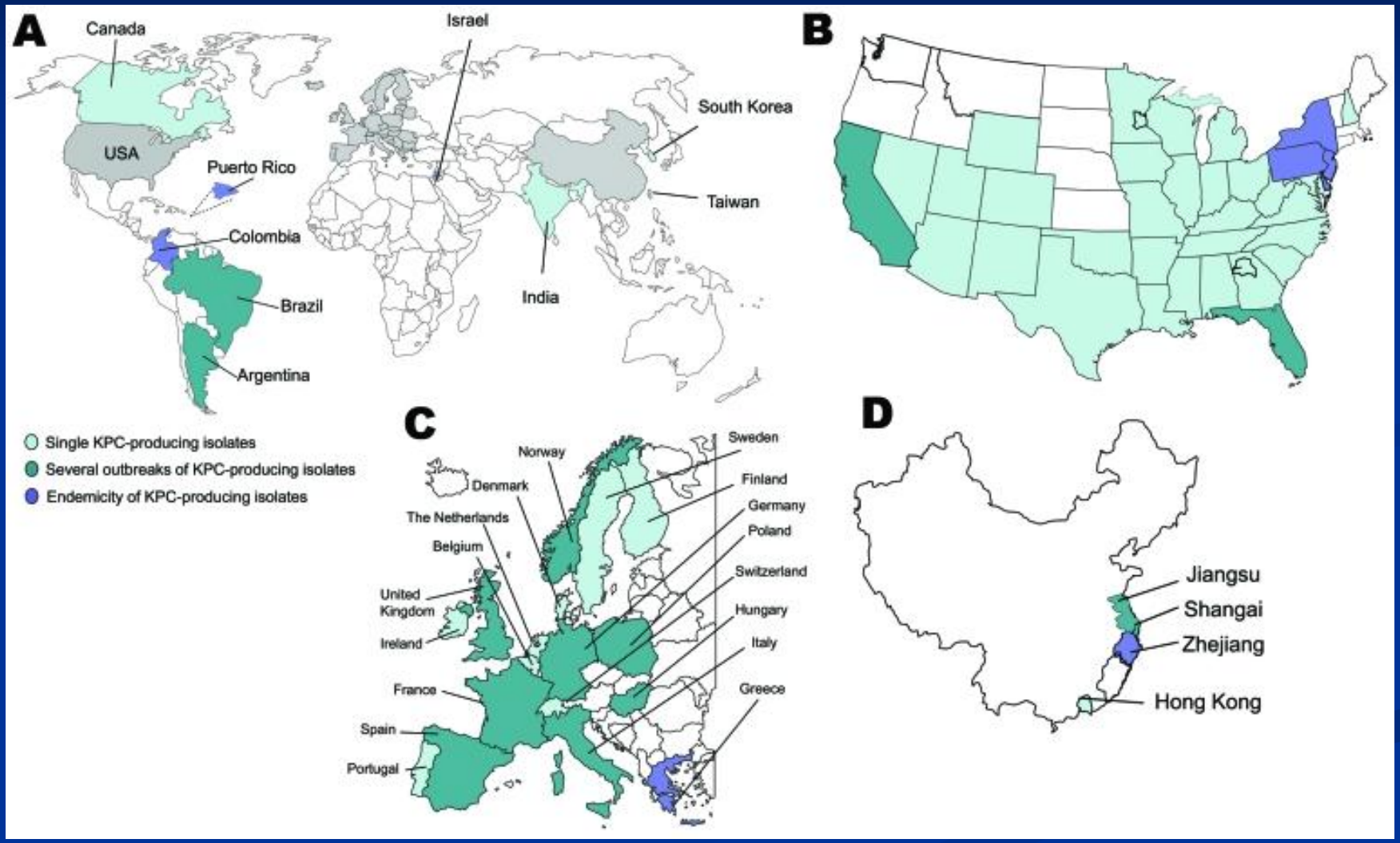
Dendrogram of the CDC's KPC-producing *K. pneumoniae* PFGE database (n = 248)

Predominance of a single clone – ST 258



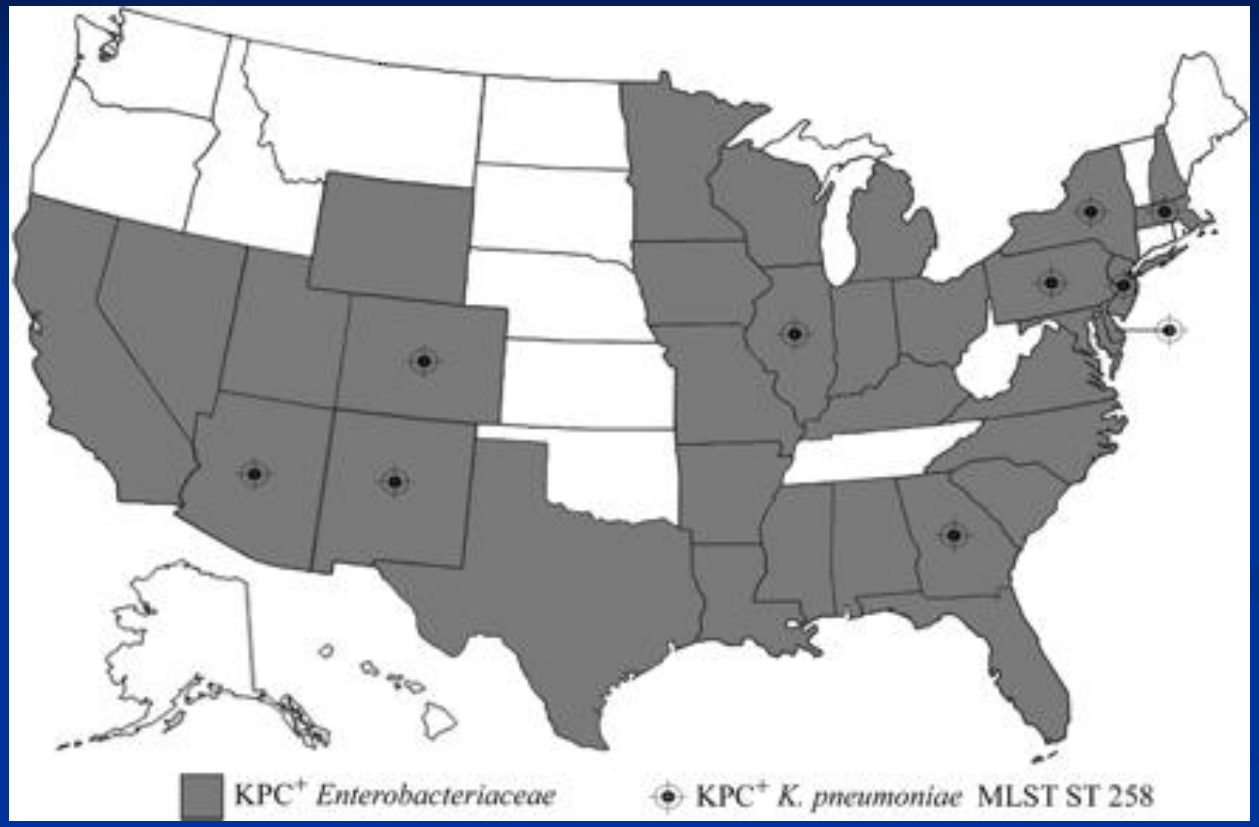
Kitchel B et al, AAC, 2009

Global spread of KPC

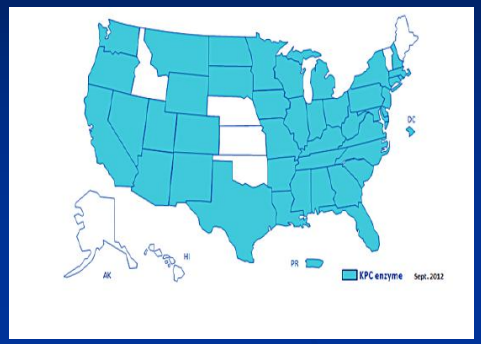


Nordmann P et al, EID 2011

US Spread of ST 258



Kitchel B et al, AAC, 2009



CDC, September 2012

The Israeli picture

KPC first detected in *E. coli*, *Enterobacter* – KPC-2

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Sept. 2006, p. 3098–3101 Vol. 50, No. 9
0066-4804/06/$08.00+0 doi:10.1128/AAC.00438-06

Plasmid-Mediated Imipenem-Hydrolyzing Enzyme KPC-2 among Multiple Carbapenem-Resistant *Escherichia coli* Clones in Israel

Shiri Navon-Venezia,* Inna Chmelnitsky, Azita Leavitt, Mitchell J. Schwaber, David Schwartz, and Yehuda Carmeli

Division of Epidemiology and the Laboratory for Molecular Epidemiology and Antibiotic Research, Tel Aviv Sourasky Medical Center, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

Received 6 April 2006/Returned for modification 14 May 2006/Accepted 12 June 2006

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Apr. 2008, p. 1413–1418 Vol. 52, No. 4
0066-4804/08/$08.00+0 doi:10.1128/AAC.01103-07

Isolation of Imipenem-Resistant *Enterobacter* Species: Emergence of KPC-2 Carbapenemase, Molecular Characterization, Epidemiology, and Outcomes[▽]

Dror Marchaim,* Shiri Navon-Venezia, Mitchell J. Schwaber, and Yehuda Carmeli

Division of Epidemiology, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel

Received 22 August 2007/Returned for modification 31 December 2007/Accepted 16 January 2008

Beginning in 2006 – spread of ST 258 clone of K. pneumoniae – KPC-3

Since then ~17,000 patients infected with CRE; ~90% *K. pneumoniae* ST 258

Arrival in Hong Kong

Int J Antimicrob Agents. 2011 Apr;37(4):386-7. Epub 2011 Feb 12.

Emergence of Klebsiella pneumoniae ST258 with KPC-2 in Hong Kong.

Ho PL, Tse CW, Lai EL, Lo WU, Chow KH.

PMID: 21316928 [PubMed - indexed for MEDLINE]

- Urine sample from 75 y/o woman, frequent visitor to US, prior surgery in NY
- Active surveillance for CRE in Hong Kong introduced after this case
  - Pts with history of hospitalization, surgery or dialysis overseas in past 12 months

Not only ST 258

Journal of Antimicrobial Chemotherapy Advance Access published January 26, 2012

J Antimicrob Chemother
doi:10.1093/jac/dkr552

Journal of Antimicrobial Chemotherapy

A carbapenem-resistant *Klebsiella pneumoniae* epidemic clone in Jerusalem: sequence type 512 carrying a plasmid encoding *aac(6′)-Ib*

Gabriela Warburg[1], Carlos Hidalgo-Grass[1], Sally R. Partridge[2], Marcelo E. Tolmasky[3], Violeta Temper[1], Allon E. Moses[1], Colin Block[1] and Jacob Strahilevitz[1]*

[1]Department of Clinical Microbiology and Infectious Diseases, Hadassah-Hebrew University, Jerusalem, 91120, Israel; [2]Centre for Infectious Diseases and Microbiology, University of Sydney, Westmead Hospital, Sydney, New South Wales 2145, Australia; [3]Center for Applied Biotechnology Studies, Department of Biological Science, College of Natural Sciences and Mathematics, California State University Fullerton, Fullerton, CA 92834-6850, USA

*Corresponding author. Tel: +972-50-894-6353; Fax: +972-2-641-9545; E-mail: jstrahilevitz@hadassah.org.il

J Antimicrob Chemother 2011; **66**: 307–312
doi:10.1093/jac/dkq431 Advance Access publication 3 December 2010

Journal of Antimicrobial Chemotherapy

ST11, the dominant clone of KPC-producing *Klebsiella pneumoniae* in China

Yan Qi[1,2], Zeqing Wei[3], Shujuan Ji[1], Xiaoxing Du[1], Ping Shen[3] and Yunsong Yu[1]*

The natural history of KPC (developed countries)

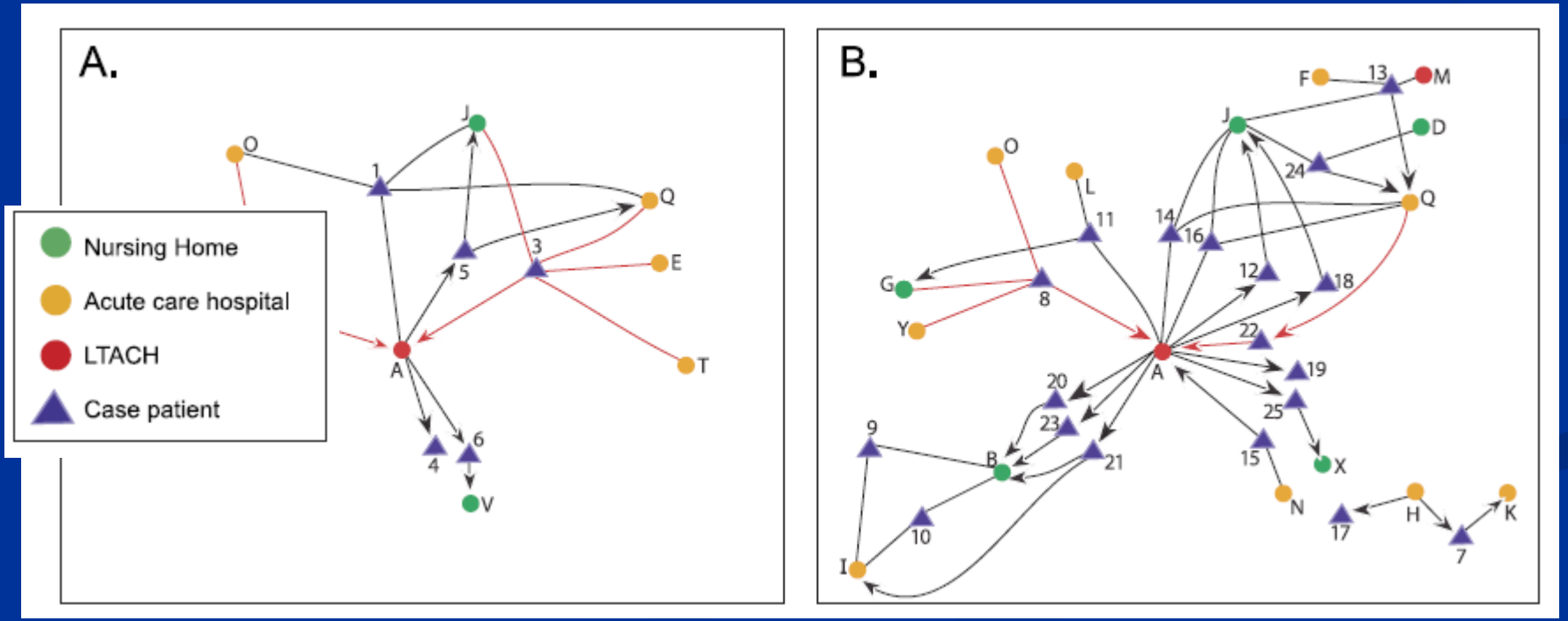
- In healthcare setting: acquisition and GI carriage
- 10-20% in acute care hospital will develop infection (>50% in transplant setting)
- Carriage may extended from few days to years, with ~50% clearance at 3 months
- In-hospital transmission extremely high; average of ~2 new acquisitions per non-isolated patient per hospital stay
- Explosive outbreaks may occur ("super-spreaders?")
- Community spread and intra-familial transmission are extremely rare

Courtesy of Yehuda Carmeli

Regional spread among different types of healthcare facilities

Emergence and Rapid Regional Spread of *Klebsiella pneumoniae* Carbapenemase–Producing *Enterobacteriaceae*

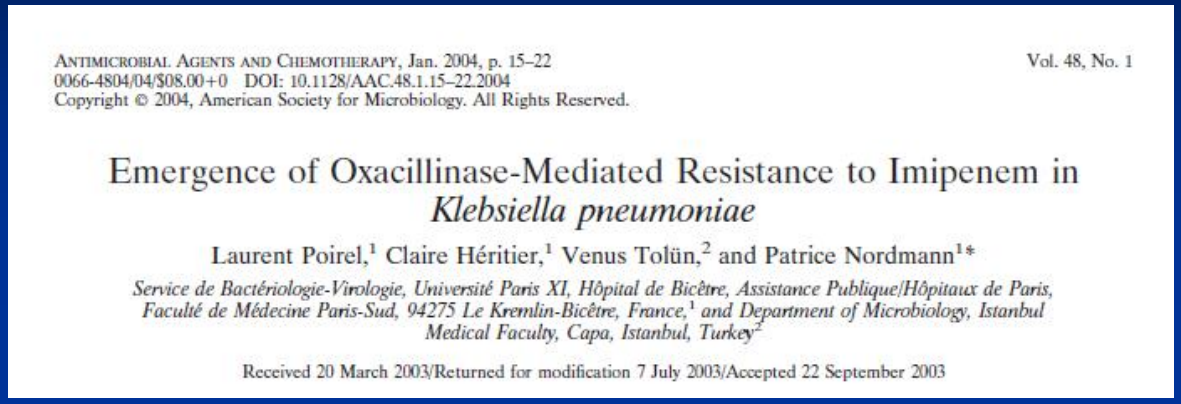
Sarah Y. Won,[1,2] L. Silvia Munoz-Price,[3] Karen Lolans,[4] Bala Hota,[4,5] Robert A. Weinstein,[4,5] and Mary K. Hayden[4] for the Centers for Disease Control and Prevention Epicenter Program



CID 2011

OXA-48

First report in Enterobacteriaceae



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]*

Service de Bactériologie-Virologie, Université Paris XI, Hôpital de Bicêtre, Assistance Publique/Hôpitaux de Paris, Faculté de Médecine Paris-Sud, 94275 Le Kremlin-Bicêtre, France,[1] and Department of Microbiology, Istanbul Medical Faculty, Capa, Istanbul, Turkey[2]

Received 20 March 2003/Returned for modification 7 July 2003/Accepted 22 September 2003

- OXA-48 in Enterobacteriaceae - began in Turkey, spread throughout Mediterranean region – Lebanon, N. Africa, Europe, elsewhere

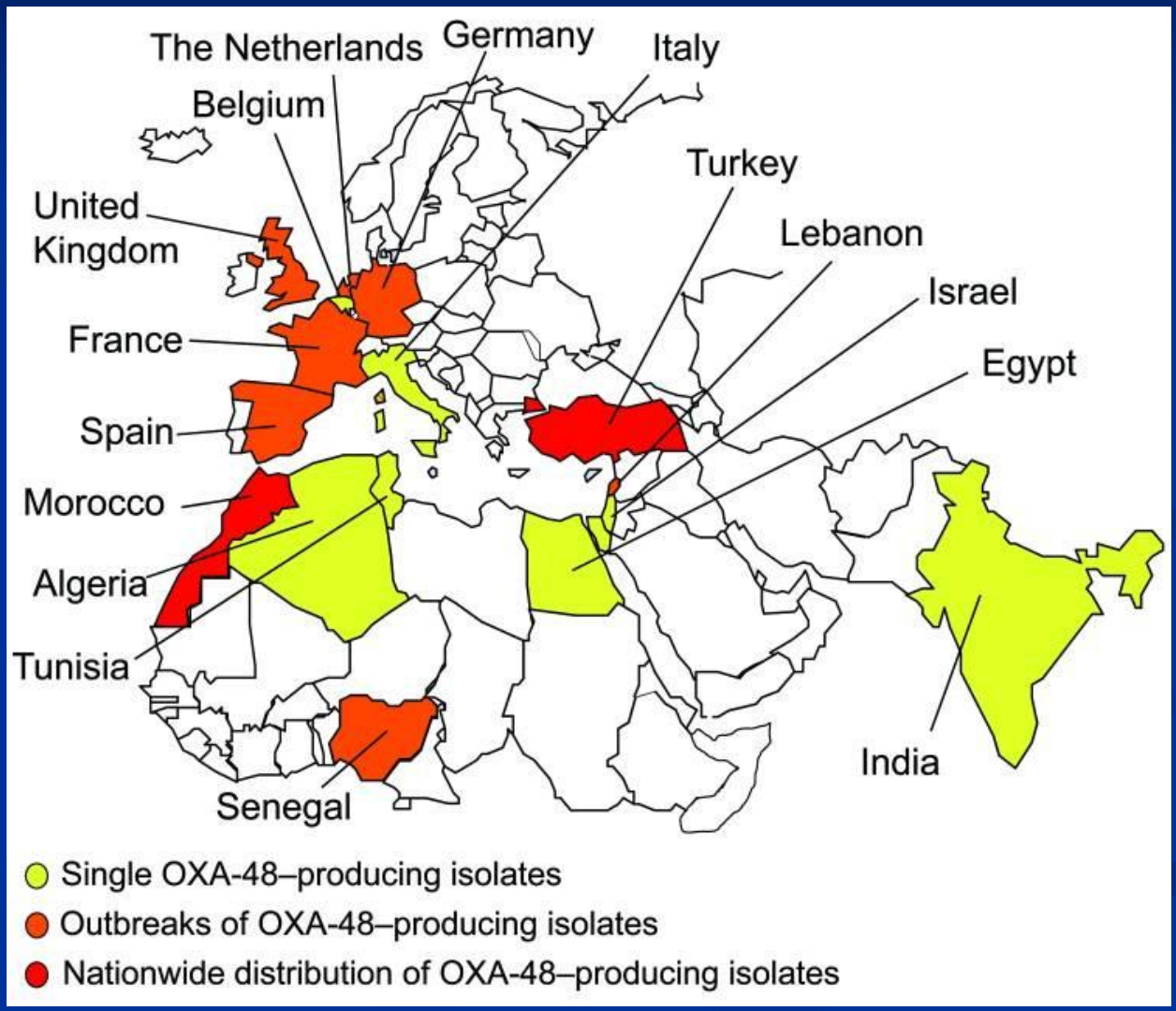
- OXA carbapenemases often seen in *Acinetobacter* – clonal spread

- In Enterobacteriaceae, spread largely via single plasmid; conjugation efficiency ~10,000-fold that of plasmid carrying KPC-3

-Walsh TR IJAA 2010

- Association with medical tourism - Adler A et al, JAC 2011

OXA-48, global picture



Nordmann P et al, EID 2011

OXA-48

- Person-to-person spread documented
  - Rotterdam
    - *K. pneumoniae* ST395 (Poltron et al, CMI 2011)
  - Israel
    - 2012 NICU outbreak – Primarily *K. pneumoniae*
- Attributable mortality – not yet adequately documented

MBLs

VIM, IMP

NDM-1

VIM, IMP

- First acquired MBL:

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Apr. 1995, p. 824–829 Vol. 39, No. 4
0066-4804/95/$04.00+0

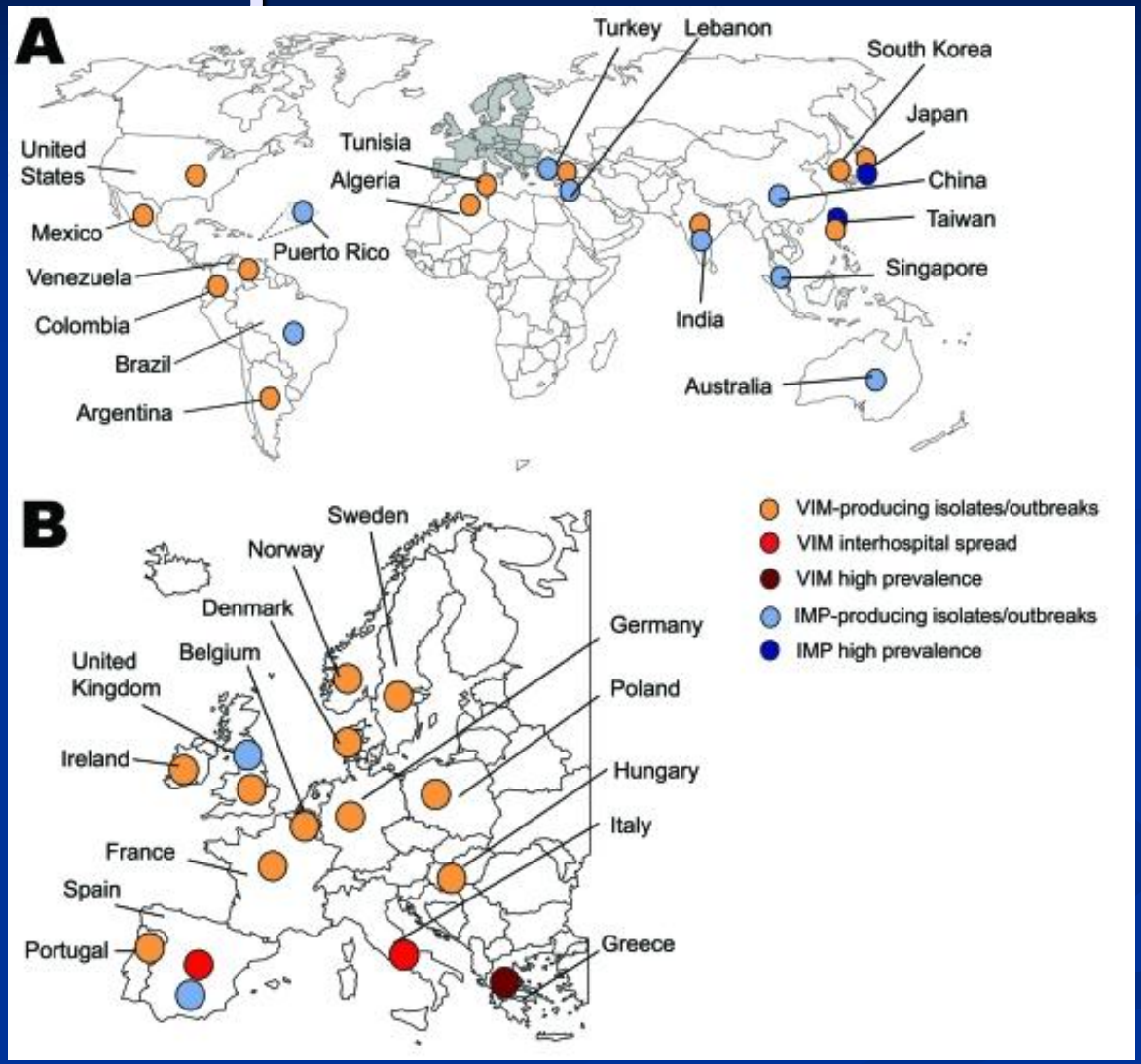
Plasmid-Mediated Dissemination of the Metallo-β-Lactamase Gene *bla*$_{IMP}$ among Clinically Isolated Strains of *Serratia marcescens*

HIDEO ITO,[1,2] YOSHICHIKA ARAKAWA,[1]* SHINJI OHSUKA,[1] ROCHAPORN WACHAROTAYANKUN,† NOBUO KATO,[1] AND MICHIO OHTA[1]

- VIM & IMP
  - Endemic in Greece, Taiwan, Japan
  - Sporadic in many other countries
  - Death rates 18%-67%

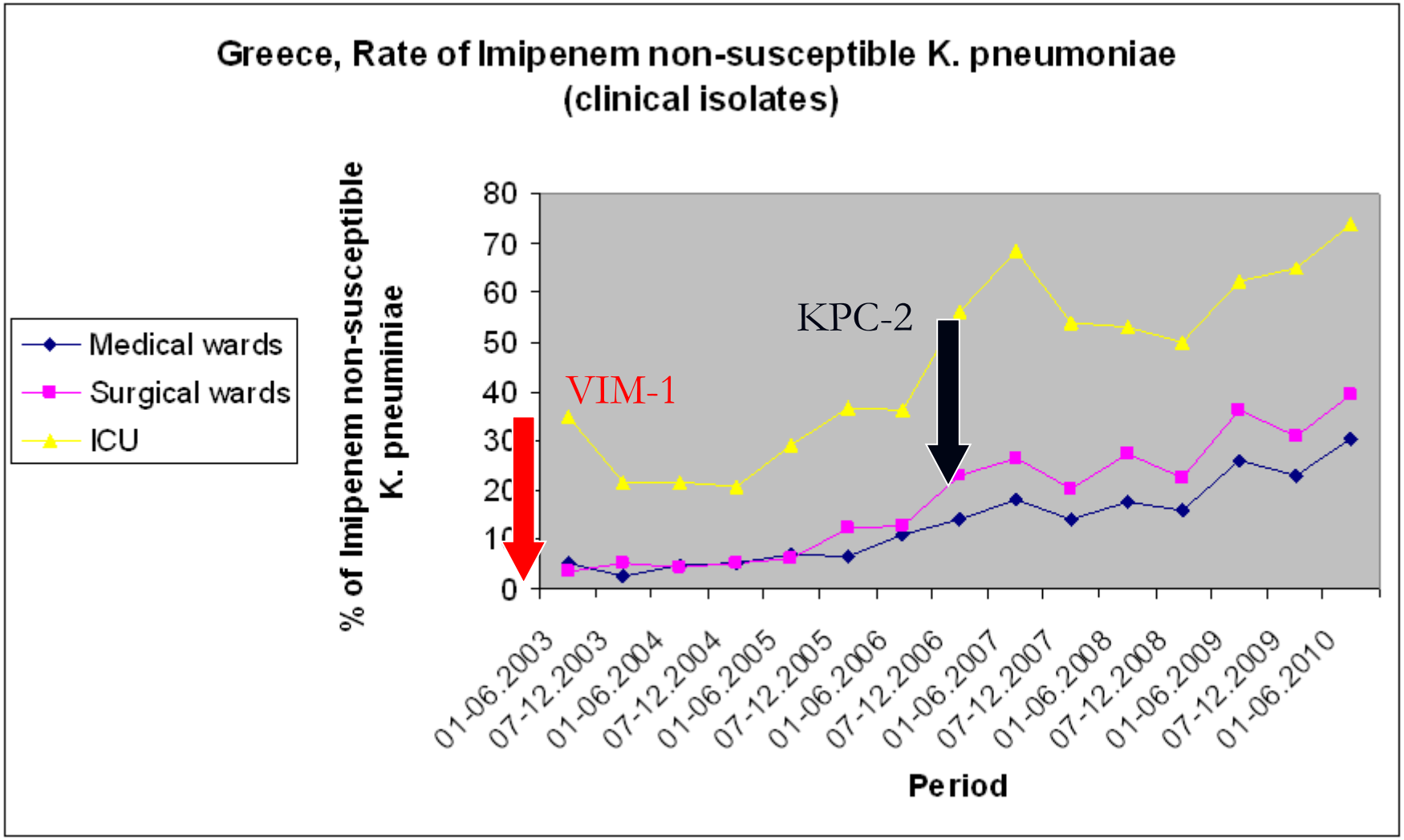
- Nordmann P et al, EID 2011

Global spread of VIM and IMP



Nordmann P et al, EID 2011

Concomitant endemicity of 2 classes of carbapenemases: The Greek experience



Courtesy of Amos Adler

MBLs

NDM-1 new kid on the block

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Dec. 2009, p. 5046–5054 Vol. 53, No. 12
0066-4804/09/$12.00 doi:10.1128/AAC.00774-09

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, Orebro University Hospital, Orebro, Sweden[5]

Received 10 June 2009/Returned for modification 7 August 2009/Accepted 10 September 2009

NDM

- Widespread in India and Pakistan 2005-2010
  - Detected when outbreaks in Europe traced to visitors to India and Pakistan
- Spread very likely by food and water
- Widely disseminated in New Delhi; contaminates tap and sewer water - Walsh TR et al, Lancet ID 2011
  - 30-70% of water sources sampled around New Delhi found contaminated with NDM
  - Estimated >100 million Indians carry NDM
- Medical tourism implicated here too - Kumarasamy KK et al, Lancet ID 2010
  - Extremely high risk of colonization in patients transferred from Indian hospital
- No significant spread in hospitals in developed countries

Courtesy of Yehuda Carmeli

NDM - features of spread

- NDM-1 gene not associated with clonal spread
  - Non-clonally related isolates and species
  - Mostly, but not exclusively, *E. coli* & *K. pneumoniae*
  - Hallmark is environmental spread
- Concern – identified in *E. coli* ST-131
  - Community strain
  - Same ST type mobilizes CTXM-15 ESBL
  - *E. coli* widespread pathogen worldwide; most common cause of pediatric diarrhea in India

Nordmann P et al, EID 2011

NDM also in Hong Kong

2011

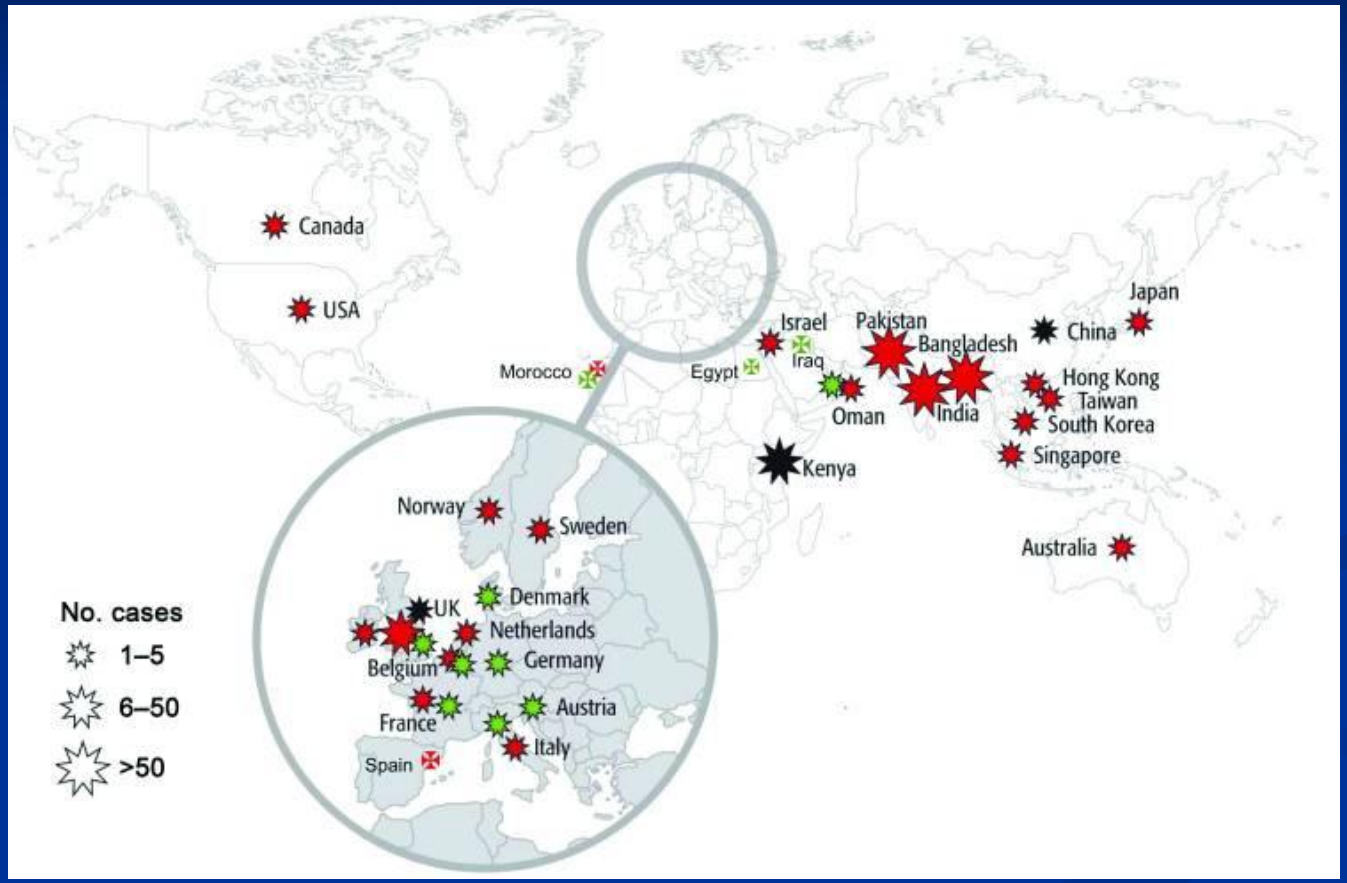
OPEN ACCESS Freely available online

PLoS one

Complete Sequencing of pNDM-HK Encoding NDM-1 Carbapenemase from a Multidrug-Resistant *Escherichia coli* Strain Isolated in Hong Kong

Pak Leung Ho[1,2*], Wai U Lo[1], Man Kiu Yeung[1], Chi Ho Lin[3], Kin Hung Chow[1], Irene Ang[1], Amy Hin Yan Tong[3], Jessie Yun-Juan Bao[3], Si Lok[3], Janice Yee Chi Lo[4]

Global spread of NDM-1



Geographic distribution of New Delhi metallo-β-lactamase-1 producers, July 15, 2011. Star size indicates number of cases reported. Red stars indicate infections traced back to India, Pakistan, or Bangladesh, green stars indicate infections traced back to the Balkan states or the Middle East, and black stars indicate contaminations of unknown origin. (Nordmann P et al, EID 2011)

Concomitant global CRE epidemics?

- 1. Healthcare-associated
  - Carbapenemases of all types, esp KPC
  - Can be curtailed by appropriate surveillance and isolation measures in healthcare facilities
- 2. Community-acquired
  - Primarily NDM, OXA
  - Associated with poor public hygiene, world travel, overuse of antibiotics
  - Difficult to measure due to locations of prominence
  - Difficult to control

Time to sound the alarms??

Journal of Antimicrobial Chemotherapy (2009) **64**, *Suppl. 1*, i29–i36
doi: 10.1093/jac/dkp255

JAC

Has the era of untreatable infections arrived?

David M. Livermore*

Antibiotic Resistance Monitoring and Reference Laboratory, Health Protection Agency Centre for Infections, 61 Colindale Avenue, London NW9 5EQ, UK

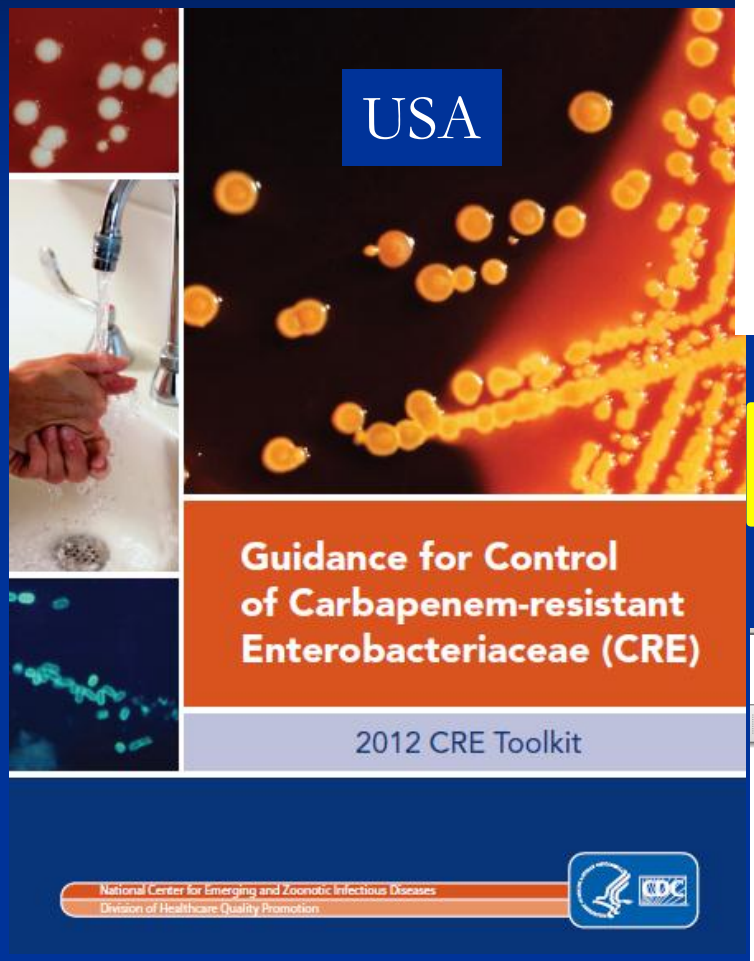
Can we contain KPC spread?

Yes!! - It is confined to the healthcare system

- Required:
  - Early detection of new introduction of colonized patients
  - Rapid response
  - Strict isolation
  - Coordinated regional control involving recruitment of the entire healthcare system

What about other carbapenamases?

- In developed countries community spread is so far limited
  - Importation by tourism is important
- Prevention of spread in healthcare facilities is feasible
  - Requires structured, multifaceted regional action
- In some parts of the world, carbapenamases are spreading extensively in the community
  - Improved water systems, sanitation and hygiene are likely the most important interventions



Advice on Carbapenemase Producers: Recognition, infection control and treatment

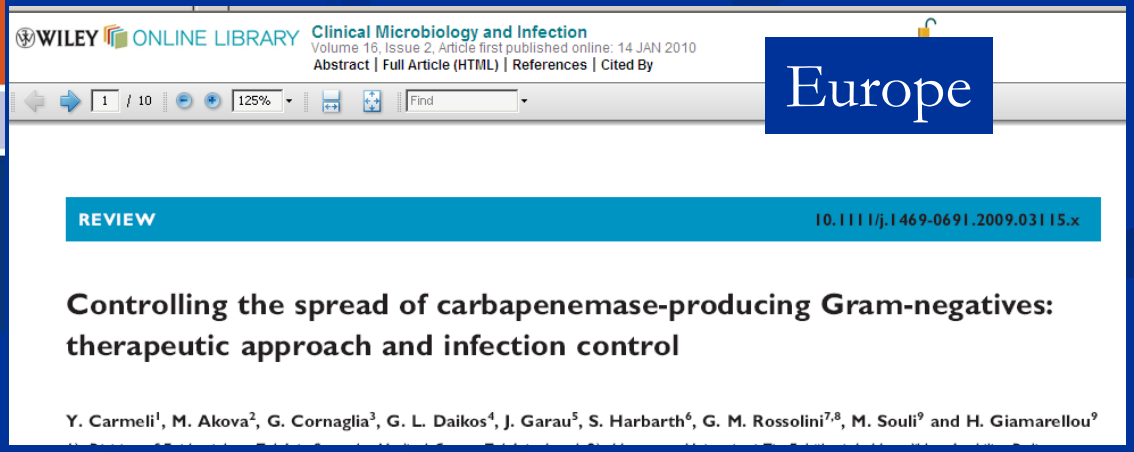
ARHAI
Department of Health
Advisory Committee on Antimicrobial Resistance and Healthcare Associated Infection

UK

Health Protection Agency

Advice on Carbapenemase Producers: Recognition, infection control and treatment

Guidelines for control of spread



Thank you!

非常感谢

תודה רבה!