

Carbapenem-Resistant Enterobacteriaceae Spread and Healthcare Infection Impact: *Is there any Light at the End of the Tunnel?*

Global Impact



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November 20, 2014



JAMA, December 24, 2008

COMMENTARIES

Carbapenem-Resistant Enterobacteriaceae A Potential Threat

Mitchell J. Schwaber, MD, MSc

Yehuda Carmeli, MD, MPH

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JAMA 2008; 300:2911-3

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Carbapenem-Resistant Enterobacteriaceae Apocalypse Now

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Carbapenem-Resistant Enterobacteriaceae ~~Apocalypse Now~~

Reviewer #2 (Remarks to the Author):

"I appreciate the authors' passion about this subject and agree with the major thrust of the commentary, but 'Apocalypse now'...is over-the-top."

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Carbapenem-Resistant Enterobacteriaceae A ~~Looming~~ Threat

Editorial office:

*“we prefer ‘Potential’ - rather than ‘looming’ –
...a more circumspect term here is more appropriate...”*

JAMA, December 24, 2008

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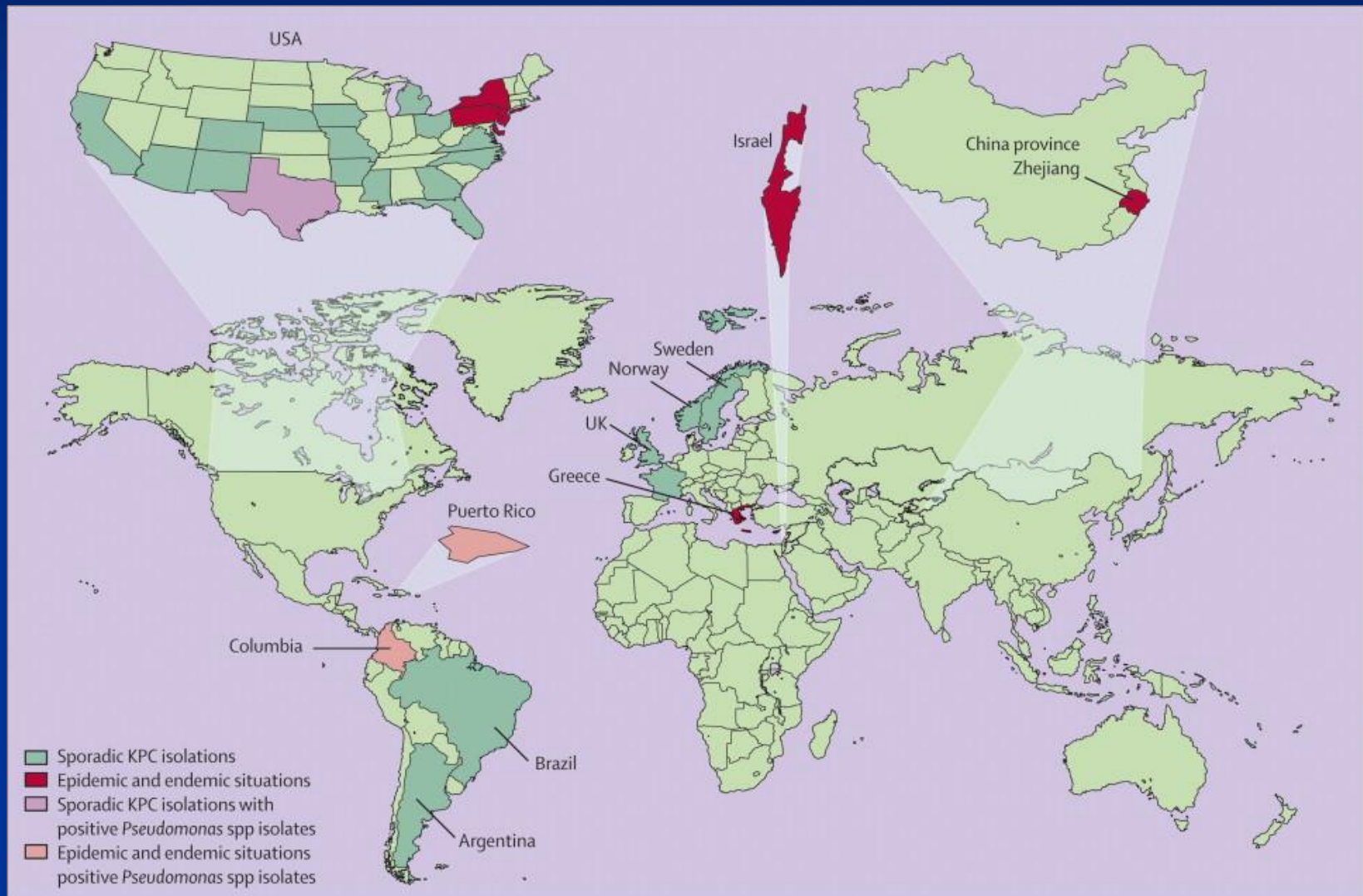
tant among these are carbapenemases, primarily the serine β -lactamase KPC and the metallo- β -lactamase VIM.³ The genes coding for these enzymes are carried by plasmids that

The spread of CRE has potentially devastating consequences for global public health and should be addressed with urgency by the international medical community and policy makers.

Appropriate measures to confront the emergence of CRE, if instituted immediately, will be important to help prevent what may otherwise be globally significant morbidity and mortality from these bacterial pathogens.

Carbapenemase-producing Enterobacteriaceae, 2009

Nordmann P et al, *Lancet Infect Dis* 2009; 9:228-36.



Carbapenemase-producing Enterobacteriaceae, 2013

Munoz-Price LS et al, *Lancet Infect Dis* 2013; 13:785-96

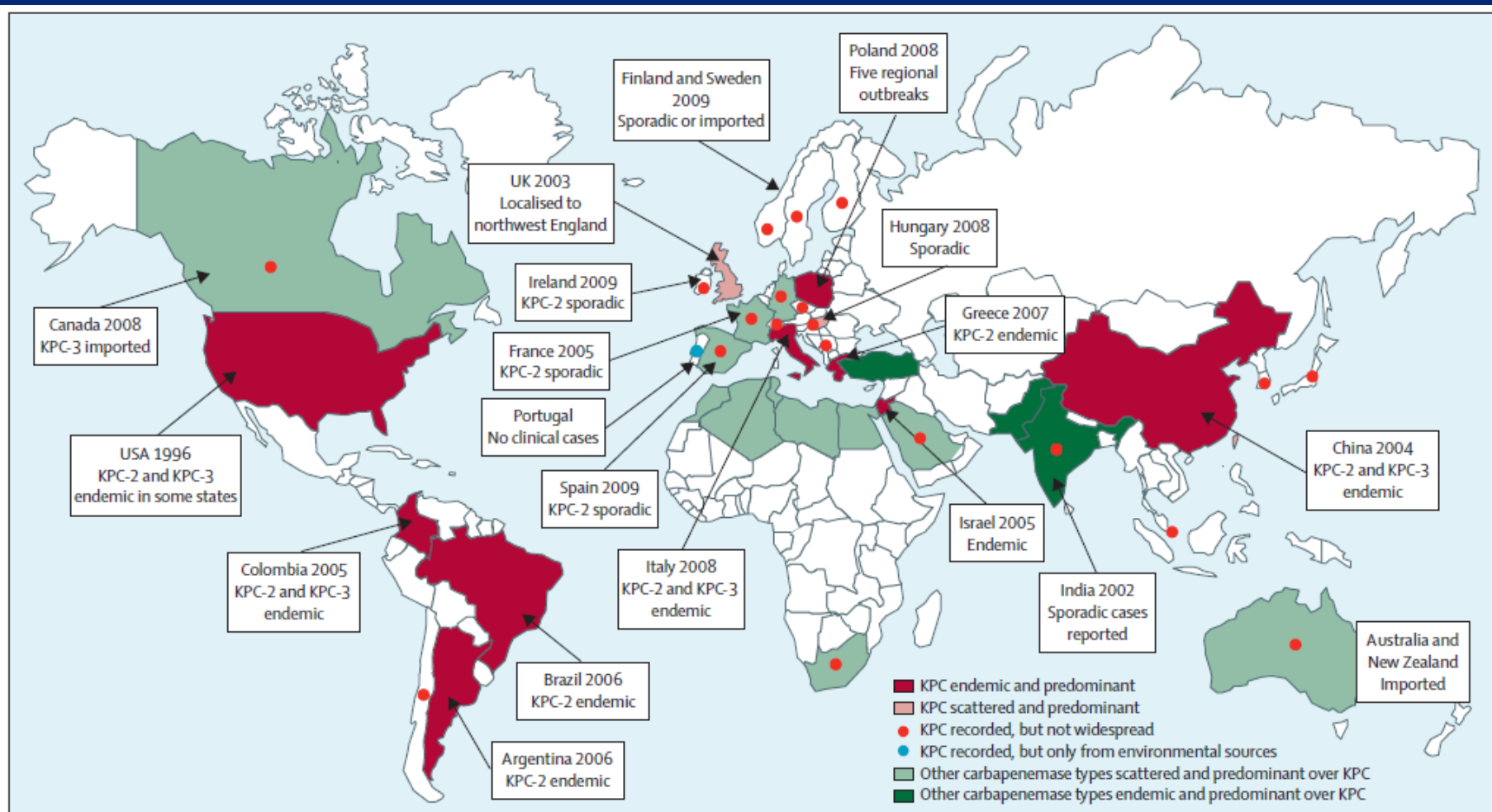


Figure: Epidemiological features of producers of *Klebsiella pneumoniae* carbapenemases by country of origin
Other carbapenemase types include VIM, OXA-48, or NDM. KPC=*Klebsiella pneumoniae* carbapenemase.

ANTIBIOTIC RESISTANCE THREATS in the United States, 2013



U.S. Department of
Health and Human Services
Centers for Disease
Control and Prevention



THREAT LEVEL
URGENT



These bacteria are immediate public health threats that require urgent and aggressive action.

MICROORGANISMS WITH A THREAT LEVEL OF URGENT

Clostridium difficile

Carbapenem-resistant **Enterobacteriaceae**

Drug-resistant *Neisseria gonorrhoeae*

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**

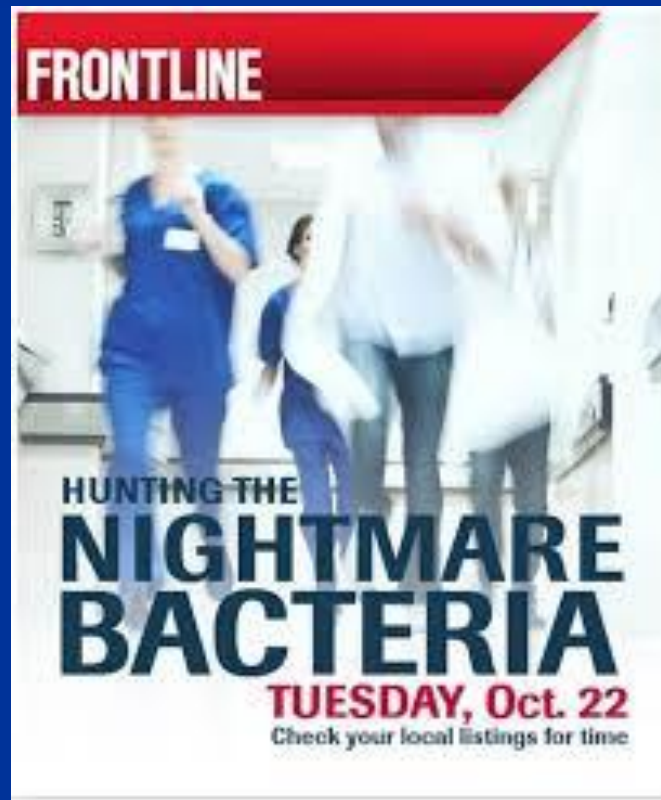


Press Release

For Immediate Release: March 5, 2013

CDC: Action needed now to halt spread of deadly bacteria

*“CRE are **nightmare bacteria**. Our strongest antibiotics don’t work and patients are left with potentially untreatable infections,”* said CDC Director Tom Frieden, M.D., M.P.H.



Why are these pathogens so threatening

- 1. Degree of resistance
- 2. Efficiency of spread
- 3. Virulence of Enterobacteriaceae

Two broad categories of CRE

■ Non-carbapenemase producing

- Mechanism of carbapenem resistance: ESBL + porin loss
- Can cause severe infection, *but* -
- Limited ability to cause outbreaks due to metabolic impairment conferred by major porin loss

■ Carbapenemase producing

- Associated with widespread outbreak potential
- Mechanisms of spread
 - Monoclonal
 - Plasmid-borne
 - Sub-plasmid elements

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Carbapenemase-producing Enterobacteriaceae

- First reported from *S. marcescens* in 1982 – SME-1
(Queenan AM and Bush K, Clin Microbiol Rev 2007;20:440-58)
- In past 30+ years
 - Large variety of carbapenemases identified
 - Belong to 3 β -lactamase classes – A, B, D

Carbapenemase Genes

- Ambler Class A
 - KPC, SME, NMC-A, IMI, PER, GES, SFO, SFC, IBC
- Ambler Class B (metallo- β -lactamases)
 - VIM, GIM, SIM, NDM, IMP, SPM
- Ambler Class D
 - OXA

Cohen Stuart J et al, Int J Antimicrob Agents 2010; 36:205-10
Nordmann P et al, Emerg Infect Dis 2011; 17:1791-8

The Israeli Carbapenemase Story

K P C

NDM

OXA-48

VIM

- KPC: >20,000
- NDM: 250
- OXA-48: ~200
- VIM: ~30

Carbapenemase-producing Enterobacteriaceae, 2013

Munoz-Price et al, *Lancet Infect Dis* 2013; 13:785-96

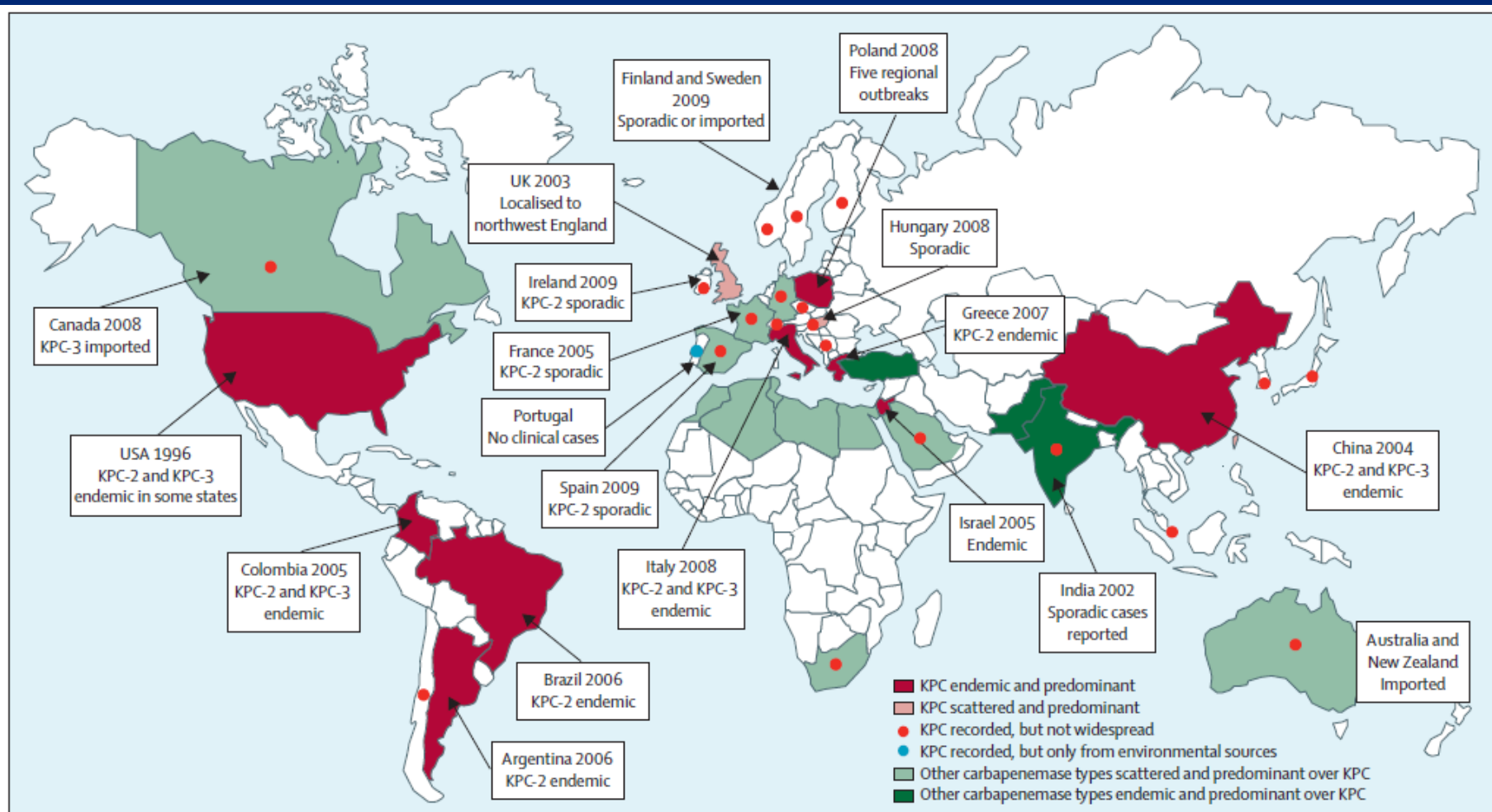


Figure: Epidemiological features of producers of *Klebsiella pneumoniae* carbapenemases by country of origin
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Varying epidemiology of spread

■ Healthcare associated

- Prototype – *K. pneumoniae* ST258
- Involvement of different types of healthcare institutions

■ Environmentally associated

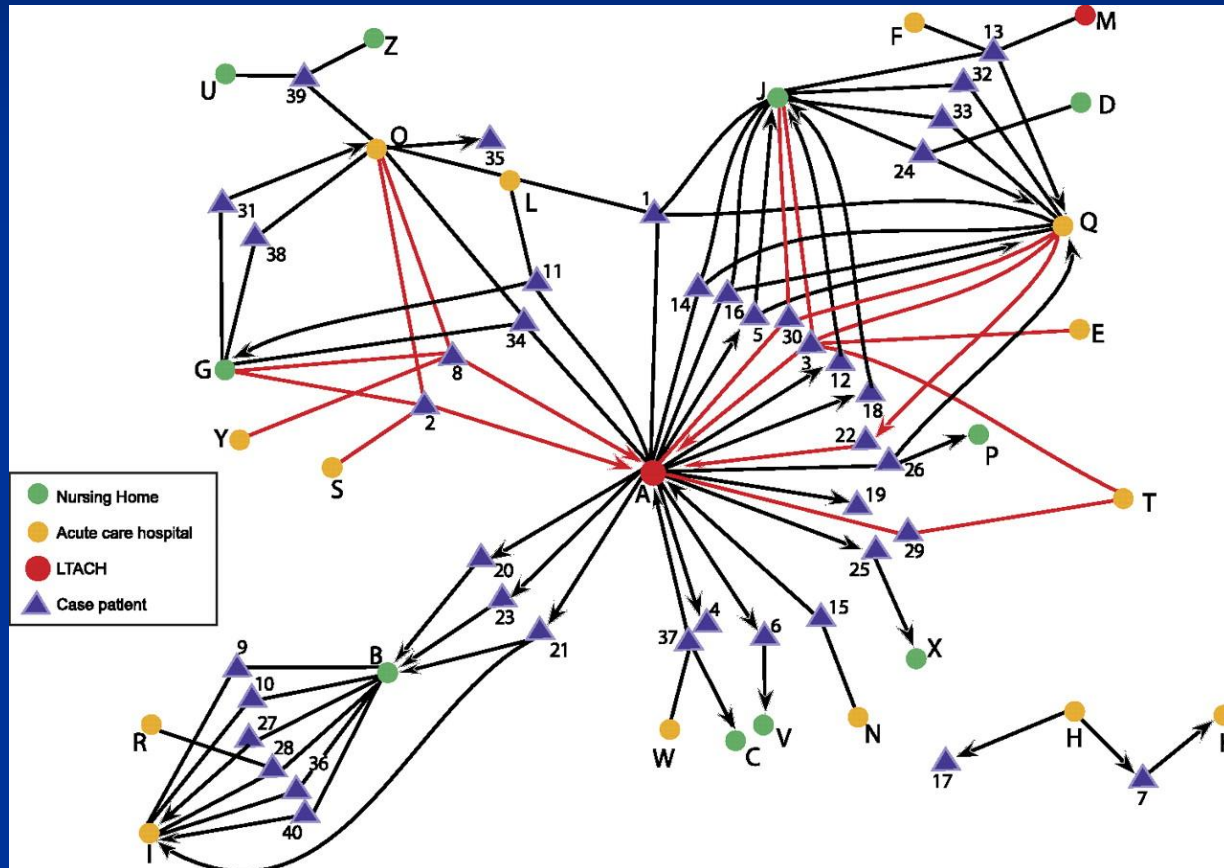
- Detection of NDM producers in water and sewage samples in New Delhi (Walsh TR et al, Lancet ID 2011; 11:355-62)
- Detection of KPC producers in river samples in Brazil (Oliveira S et al, JAC 2014; doi:10.1093/jac/dkt431, Advance Access publication 24 October 2013)
- Potential for extensive environmental dissemination, including drinking water, resulting in human carriage

■ Combined characteristics of spread

- Outbreaks of community-origin CRE in hospitals

Healthcare-associated – Involvement of different types of facilities

Exposure network graph demonstrating the relationships of cases to long-term acute care hospitals (LTACHs), acute care hospitals, and nursing homes during the entire 12-month study period.



Won S Y et al. Clin Infect Dis 2011; 53:532-540

An additional challenge: Medical “tourism”

J Antimicrob Chemother 2011; **66**: 2763–2766
doi:10.1093/jac/dkr382 Advance Access publication 19 September 2011

**Journal of
Antimicrobial
Chemotherapy**

Introduction of OXA-48-producing Enterobacteriaceae to Israeli hospitals by medical tourism

Amos Adler^{1*}, Maya Shklyar¹, Mitchell J. Schwaber¹, Shiri Navon-Venezia¹, Yacoub Dhaher², Rotem Edgar¹, Ester Solter¹, Shmuel Benenson³, Samira Masarwa¹ and Yehuda Carmeli¹

The New York Times

Middle East

WORLD U.S. N.Y. / REGION BUSINESS TECHNOLOGY SCIENCE HEALTH SPORTS OPINION
AFRICA AMERICAS ASIA PACIFIC EUROPE MIDDLE EAST



Across Forbidden Border, Doctors in Israel Quietly Tend to Syria's Wounded



CRE isolates isolated from Syrian wounded hospitalized in Israel

CRE isolates and carbapenemases identified among Syrian patients hospitalized in Israel						
	NDM	OXA-48	KPC	Non-carbapenemase producer	Not available for PCR	Total
<i>K.pneumoniae</i>	9	8	0	2	2	21
<i>E. coli</i>	4	6	0	1	0	11
<i>Enterobacter cloacae</i>	2	0	0	2	0	4
<i>Providencia rettgeri</i>	2	0	0	0	0	2
<i>Citrobacter braakii</i>	1	0	0	0	0	1
Total	18	14	0	5	2	39

NDM – also traveling the world, aided by medical tourism

Lancet Infect Dis 2010; 10: 597-602

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

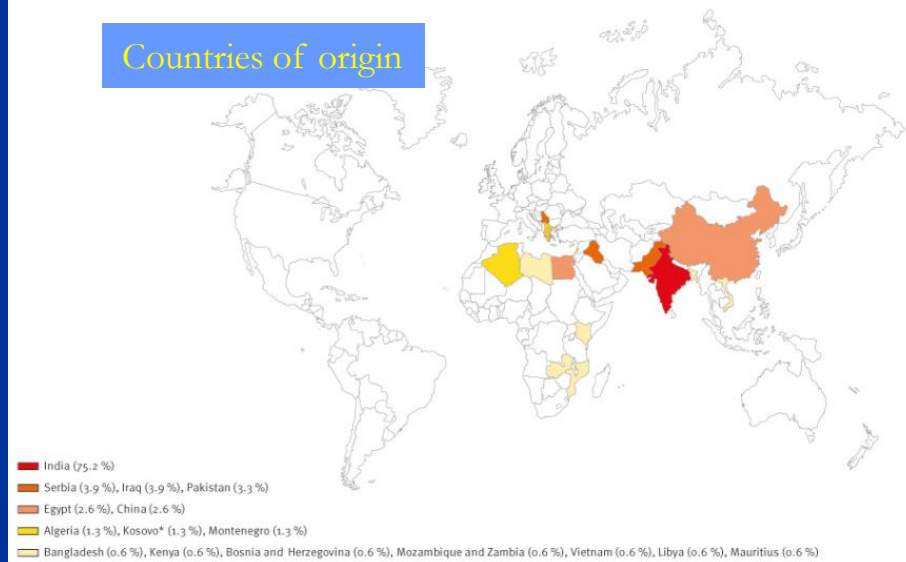
Karthikeyan K Kumarasamy, Mark A Toleman, Timothy R Walsh, Jay Bagaria, Fafhana Butt, Ravikumar Balakrishnan, Uma Chaudhary, Michel Doumith, Christian G Giske, Seema Irfan, Padma Krishnan, Anil V Kumar, Sunil Maharjan, Shazad Mushtaq, Tabassum Noorie, David L Paterson, Andrew Pearson, Claire Perry, Rachel 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

Many of the UK NDM-1 positive patients had travelled to India or Pakistan within the past year, or had links with these countries.

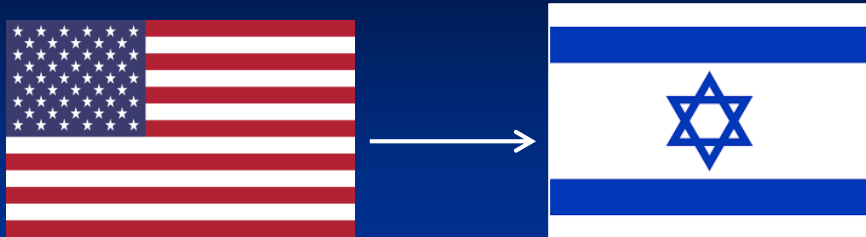
Several of the UK source patients had undergone elective, including cosmetic, surgery while visiting India or Pakistan. India also provides cosmetic surgery for other Europeans and Americans, and *bla*NDM-1 will likely spread worldwide.

B. Putative countries of origin for imported published isolates carrying the *bla*_{NDM-1} gene

Countries of origin



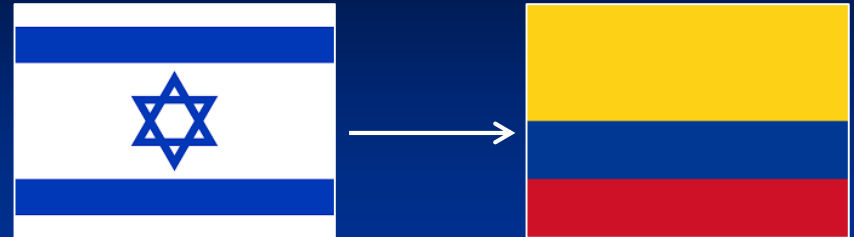
Sometimes we import...



Navon-Venezia S et al, Antimicrob Agents Chemother 2009; 53: 818-20

First report on a hyperepidemic clone of KPC-3-producing *Klebsiella pneumoniae* in Israel genetically related to a strain causing outbreaks in the United States

...and sometimes we export

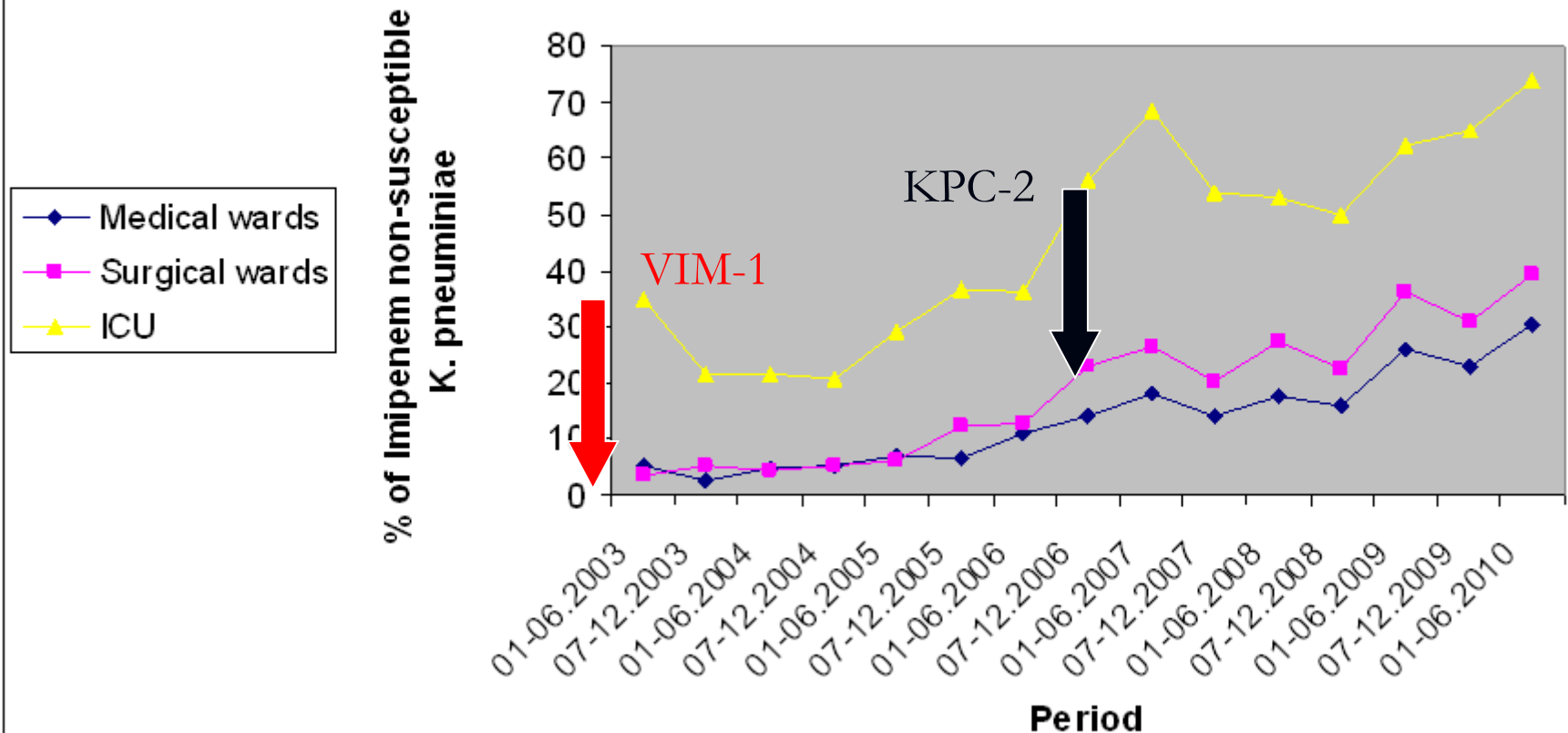


Lopez JA et al, Clin Microbiol Infect 2011; 17:52-6

Intercontinental spread from Israel to Colombia of a KPC-3-producing *Klebsiella pneumoniae* strain

Concomitant endemicity of 2 classes of carbapenemases: The Greek experience

Greece, Rate of Imipenem non-susceptible *K. pneumoniae* (clinical isolates)



So, after all this gloom, is there a
light at the end of the tunnel?



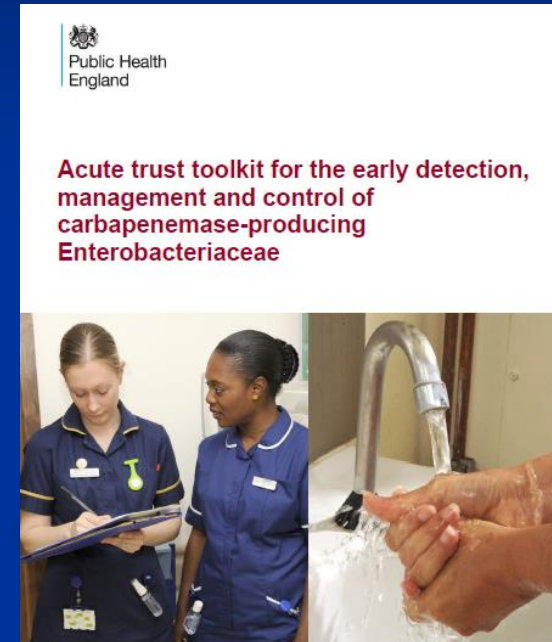
So, after all this gloom, is there a
light at the end of the tunnel?



Answer: Yes, but the tunnel is long
and we still have a long way to go

What can be done?

- Since treatment options are so limited, main focus in CRE control is containment of spread



Comparison of containment guidelines

Temkin E et al, Ann NY Acad Sci 2014; 1323:22-42

Intervention	Israel	US	Europe
Hand hygiene	++	++	-
Active surveillance			
On admission	++ (risk groups)	+	++ (risk groups)
During hospitalization	++ (risk groups)	++ (risk groups) + (routine in risk units)	++ (risk groups)
Patient cohorting	++ (most settings)	++	
Staff cohorting	++ (acute care)	++	++
Dedicated equipment	++	-	-
Contact precautions	++	++ (acute care)	++
Mandatory reporting	++	+	++
Chlorhexidine baths	-	+	-
Minimize use of invasive devices	-	++	-
Selective gut decontamination	-	-	--
Antibiotic stewardship	-	++	-

Do the guidelines work?

Do the guidelines work?

Yes, *if* implemented correctly and consistently

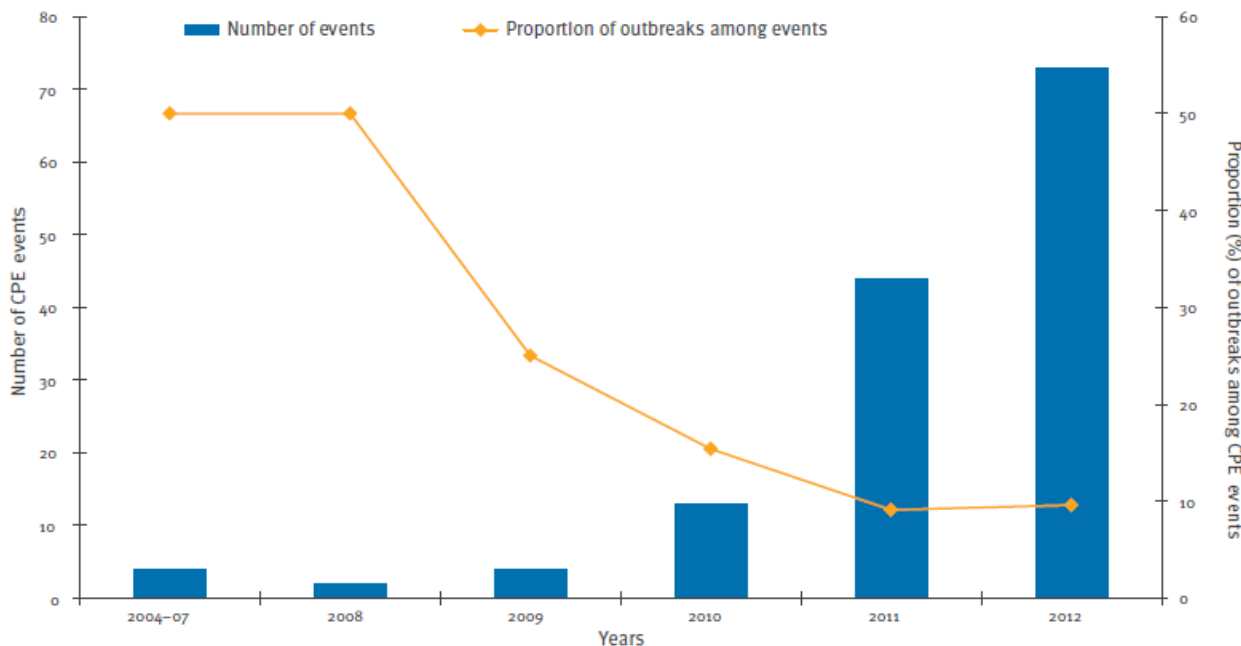
France - CRE intervention

Long-term control of carbapenemase-producing Enterobacteriaceae at the scale of a large French multihospital institution: a nine-year experience, France, 2004 to 2012

S Fournier (sandra.fournier@sap.aphp.fr)¹, C Montell¹, M Lepointeur¹, C Richard², C Brun-Buisson³, V Jarlier⁴, AP-HP Outbreaks Control Group⁵

FIGURE

Number of carbapenemase-producing Enterobacteriaceae (CPE) events (n=140) and proportion of outbreaks among these events at Assistance Publique-Hôpitaux de Paris, France, 2004–2012



A CPE event was defined as one index case (respectively defined as infected or colonised with CPE), followed or not by secondary case(s).

Measures employed
Barrier precautions
Dedicated staff
Screening

Euro Surveill.
2014;19:pii=20802

■ Israel – CRE intervention (ongoing since 2007)

■ Bundle including:

- Mandatory isolation and reporting guidelines
- Cohorting of carriers and staff
- Ongoing active surveillance
- Central oversight and regulation

■ Results

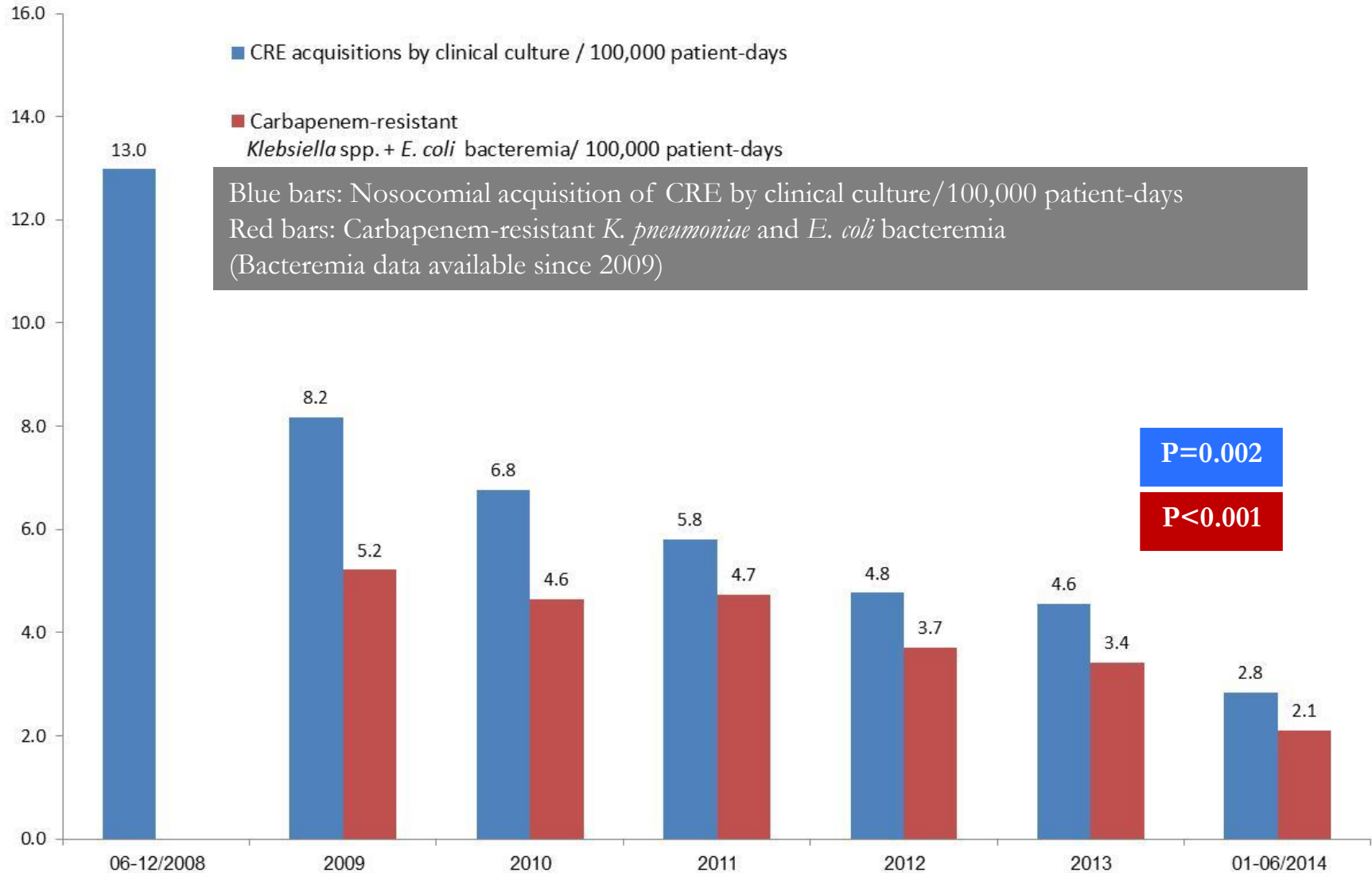
- Decrease in incidence of acquisition per clinical culture from 55-2.8 cases/100,000 pt-days
- Decrease in morbidity and mortality as evidenced by significant drop in CRE bacteremia

Schwaber MJ and Carmeli Y, Clin Infect Dis 2014; 58:697-703

- Downward trends continue

Measures of success

III: Reduction in morbidity



Control of community spread

- In developed countries community spread is so far limited
 - Importation by tourism is important
- 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

What is required

- Being aware of the scope of the problem
 - Endemic setting – containment of transmission at regional level
 - Sporadic – aggressive local interventions to prevent spread
 - Absent – detection and control measures in place *prior to arrival* of first case
- Bringing to bear adequate resources
 - Healthcare infrastructure
 - Infection control and microbiology personnel
 - Hospital staffing
 - Surveillance (requires epidemiologic and microbiologic resources)
 - Sanitation and hygiene
- Central regulation and oversight – national/regional

Involve the public and the political leadership!

Thank you!



Igreja do Santo Sepulcro, em Jerusalém