

# Le malattie infettive del migrante e del viaggiatore

## Movimenti migratori e resistenza agli antibiotici

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di **DIAGNOSTICA  
E SANITÀ PUBBLICA**



**EUROPEAN  
ANTIBIOTIC  
AWARENESS DAY**

18 November 2016

**Promoting prudent antibiotic use**

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# CDC 2013

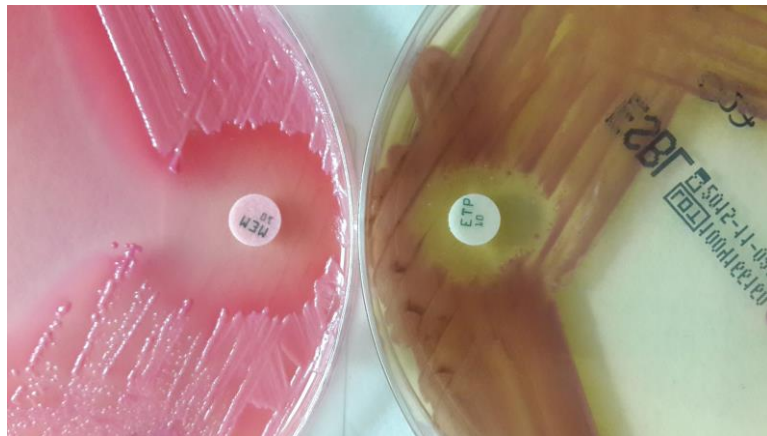
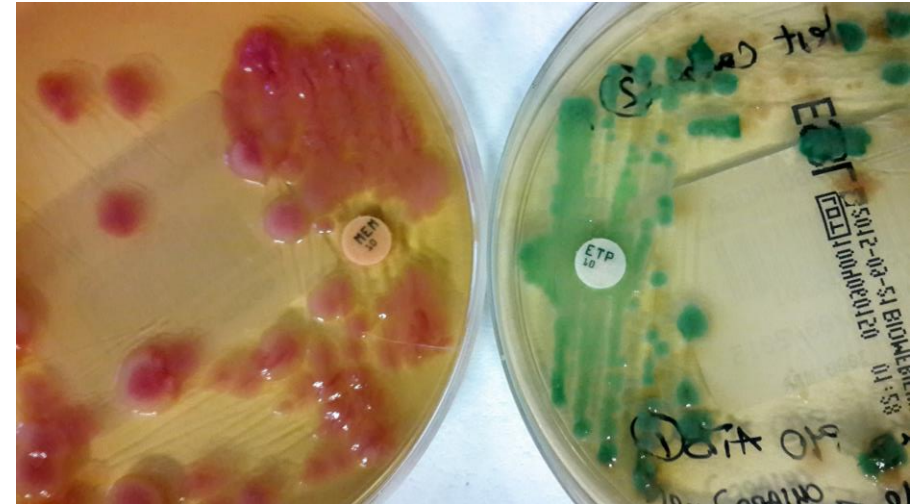
3 microrganismi pongono problemi urgenti di salute pubblica

- **Enterobatteri produttori di carbapenemasi**

- *Neisseria gonorrhoeae* antibiotico resistente
- *C. difficile*

# Enterobatteri produttori di carbapenemasi

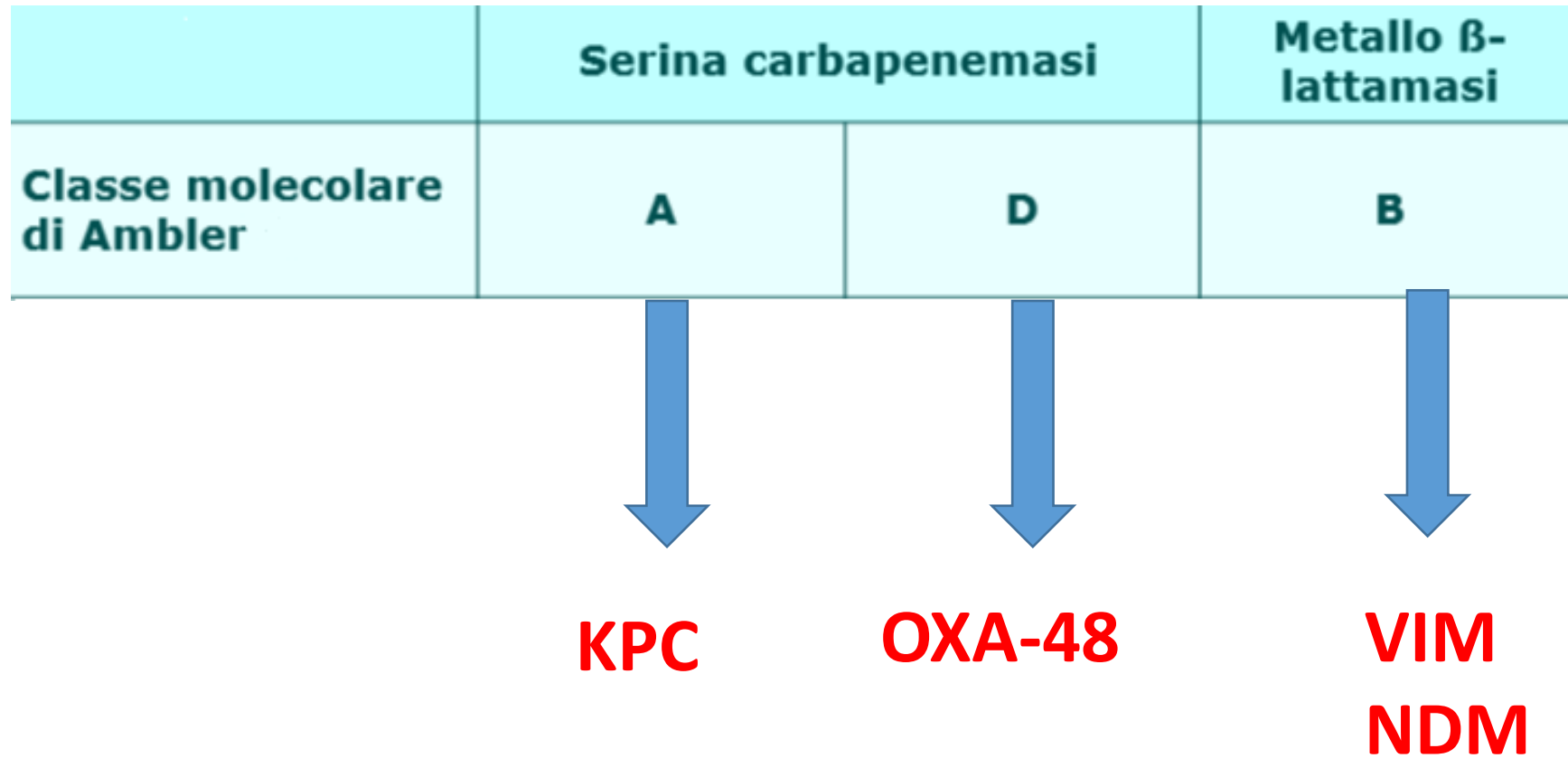
*K. pneumoniae*

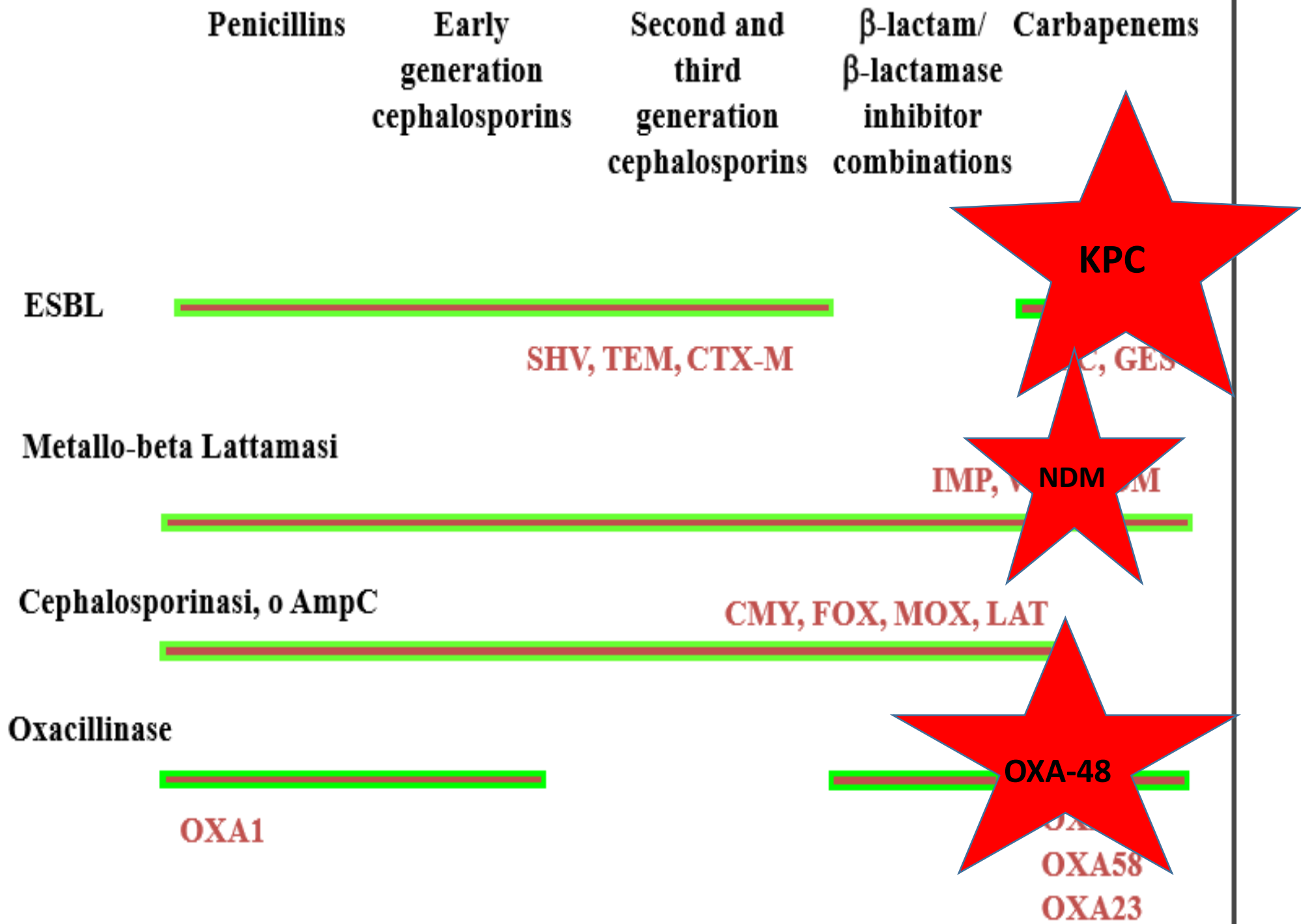


*E. coli*

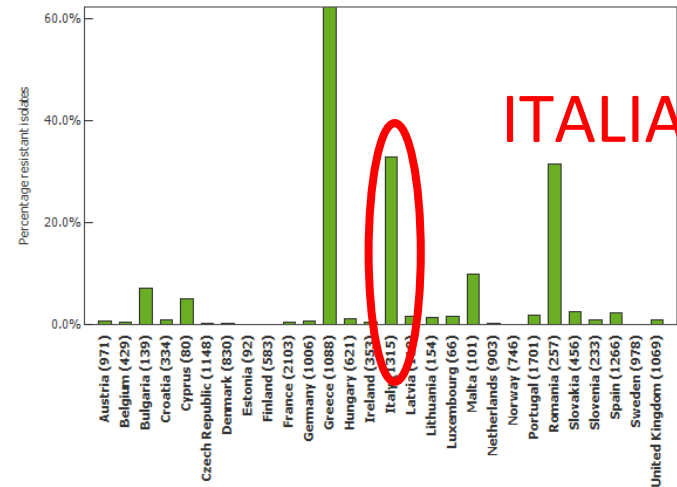
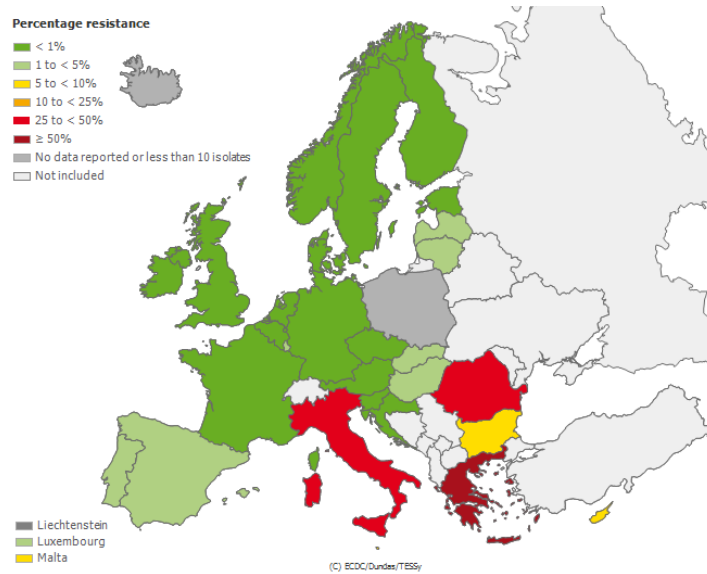
*E. aerogenes*

# Classificazione delle carbapenemasi





# *K. pneumoniae* resistente carbapenemici Dati Ears-net 2014



# Italia: predominanza di KPC

Eurosurveillance, Volume 18, Issue 22, 30 May 2013

Surveillance and outbreak reports

## EPIDEMIC DIFFUSION OF KPC CARBAPENEMASE-PRODUCING KLEBSIELLA PNEUMONIAE IN ITALY: RESULTS OF THE FIRST COUNTRYWIDE SURVEY, 15 MAY TO 30 JUNE 2011

T Giani<sup>1</sup>, B Pini<sup>2</sup>, F Arena<sup>1</sup>, V Conte<sup>1</sup>, S Bracco<sup>2</sup>, R Migliavacca<sup>3</sup>, the AMCLI-CRE Survey Participants<sup>4</sup>, A Pantosti<sup>5</sup>, L Pagani<sup>3</sup>, F Luzzaro<sup>2</sup>, G M Rossolini (gianmaria.rossolini@unisi.it)<sup>1,6,7</sup>

TABLE 2

Mechanisms of resistance in carbapenem-nonsusceptible isolates of *Enterobacteriaceae*, Italy, 15 May–30 June 2011 (n=270)

Species	Isolates	Carbapenemase			Non-carbapenemase Total (%)
		Total (%)	KPC	VIM-1 OXA-48	
<i>Escherichia coli</i>	5	2 (40.0)	1	1	3 (60.0)
<i>Klebsiella pneumoniae</i>	234	223 (95.3)	204	16	11 (4.7)
<i>Klebsiella oxytoca</i>	1	1 (100.0)	0	1	0
<i>Enterobacter cloacae</i>	15	3 (20.0)	0	3	12 (80.0)
Others <sup>a</sup>	15	0	0	0	15 (100.0)
<b>Total</b>	<b>270</b>	<b>229 (84.8)</b>	<b>205</b>	<b>21</b>	<b>41 (15.2)</b>

<sup>a</sup> Including *Enterobacter aerogenes* (n=6), *Serratia marcescens* (n=5), *Proteus mirabilis* (n=1), *Citrobacter freundii* (n=1), and *Hafnia alvei* (n=2).





# KPC la prima volta...

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Apr. 2001, p. 1151–1161  
0066-4804/01/\$04.00+0 DOI: 10.1128/AAC.45.4.1151–1161.2001  
Copyright © 2001, American Society for Microbiology. All Rights Reserved.

Vol. 45, No. 4

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

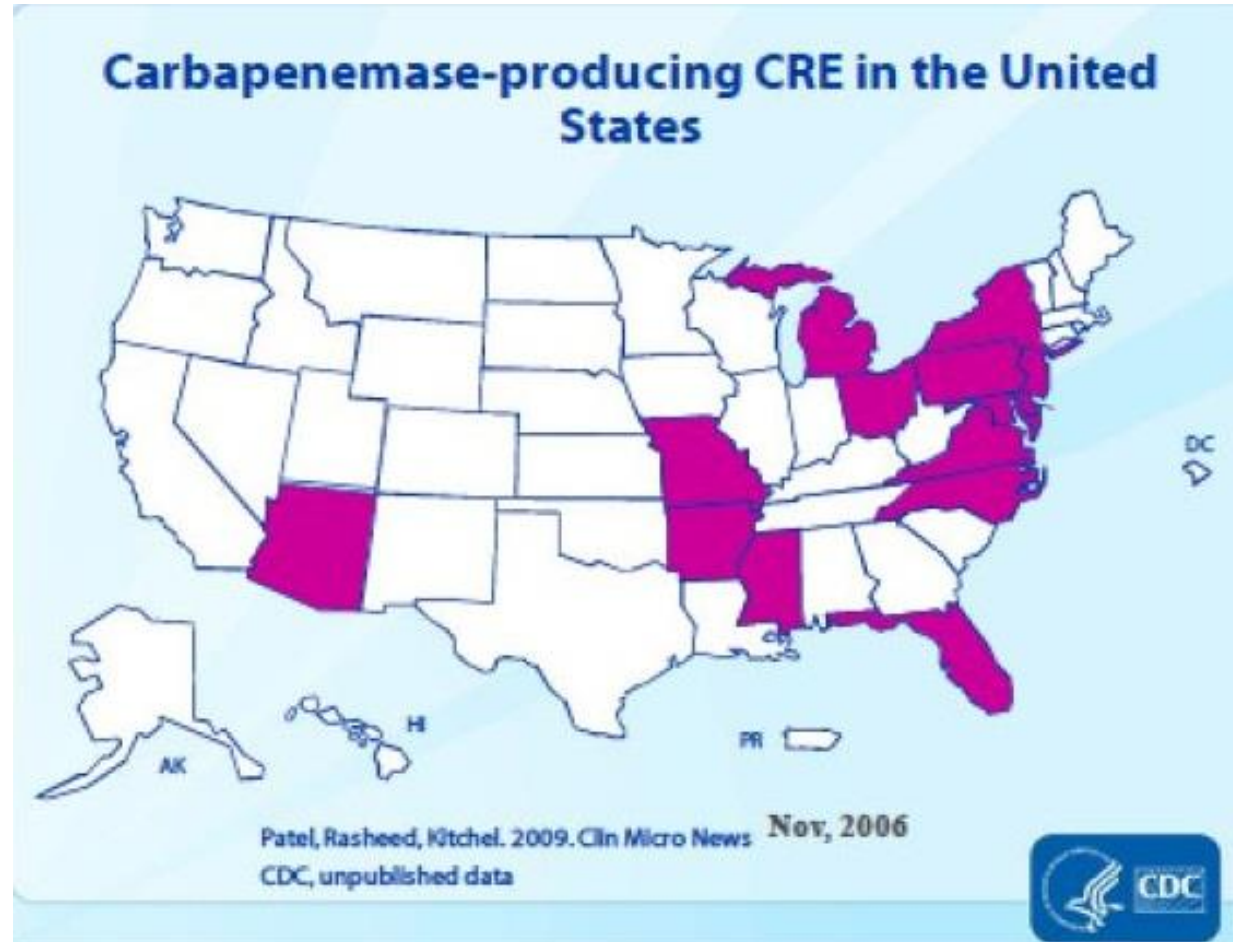
HESNA YIGIT,<sup>1</sup> ANNE MARIE QUEENAN,<sup>2</sup> GREGORY J. ANDERSON,<sup>1</sup>  
ANTONIO DOMENECH-SANCHEZ,<sup>3</sup> JAMES W. BIDDLE,<sup>1</sup> CHRISTINE D. STEWARD,<sup>1</sup>  
SEBASTIAN ALBERTI,<sup>4</sup> KAREN BUSH,<sup>2</sup> AND FRED C. TENOVER<sup>1\*</sup>

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

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

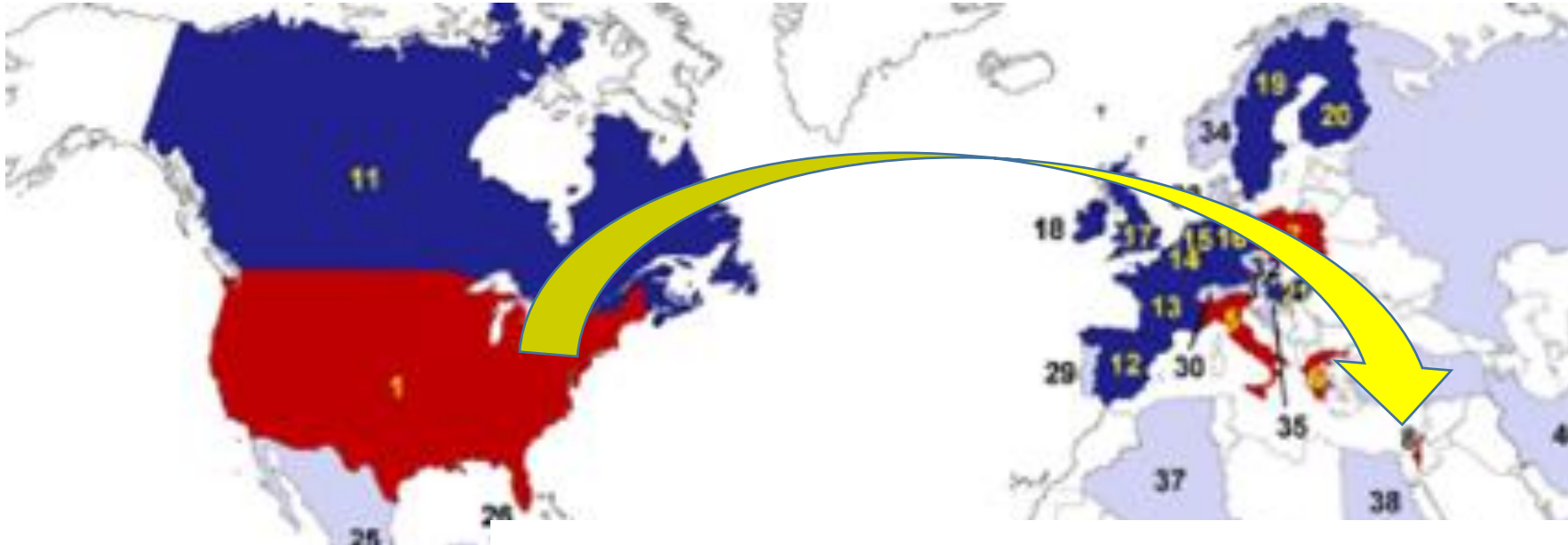
A *Klebsiella pneumoniae* isolate showing moderate to high level imipenem and meropenem resistance was

# KPC agli inizi



Dal 2001 al 2005 rimane negli USA

# KPC: 2006 emerge in Israel



ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Aug. 2007, p. 3026–3029  
0066-4804/07/\$08.00+0 doi:10.1128/AAC.00299-07  
Copyright © 2007, American Society for Microbiology. All Rights Reserved.

Vol. 51, No. 8

## Emergence of KPC-2 and KPC-3 in Carbapenem-Resistant *Klebsiella pneumoniae* Strains in an Israeli Hospital<sup>∇</sup>

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

*Division of Epidemiology and the Laboratory for Molecular Epidemiology and Antibiotic Research,  
Tel Aviv Sourasky Medical Center, Tel Aviv, Israel*

Received 2 March 2007/Returned for modification 6 April 2007/Accepted 4 June 2007

KPC  
2009  
primo caso  
isolato in Italia



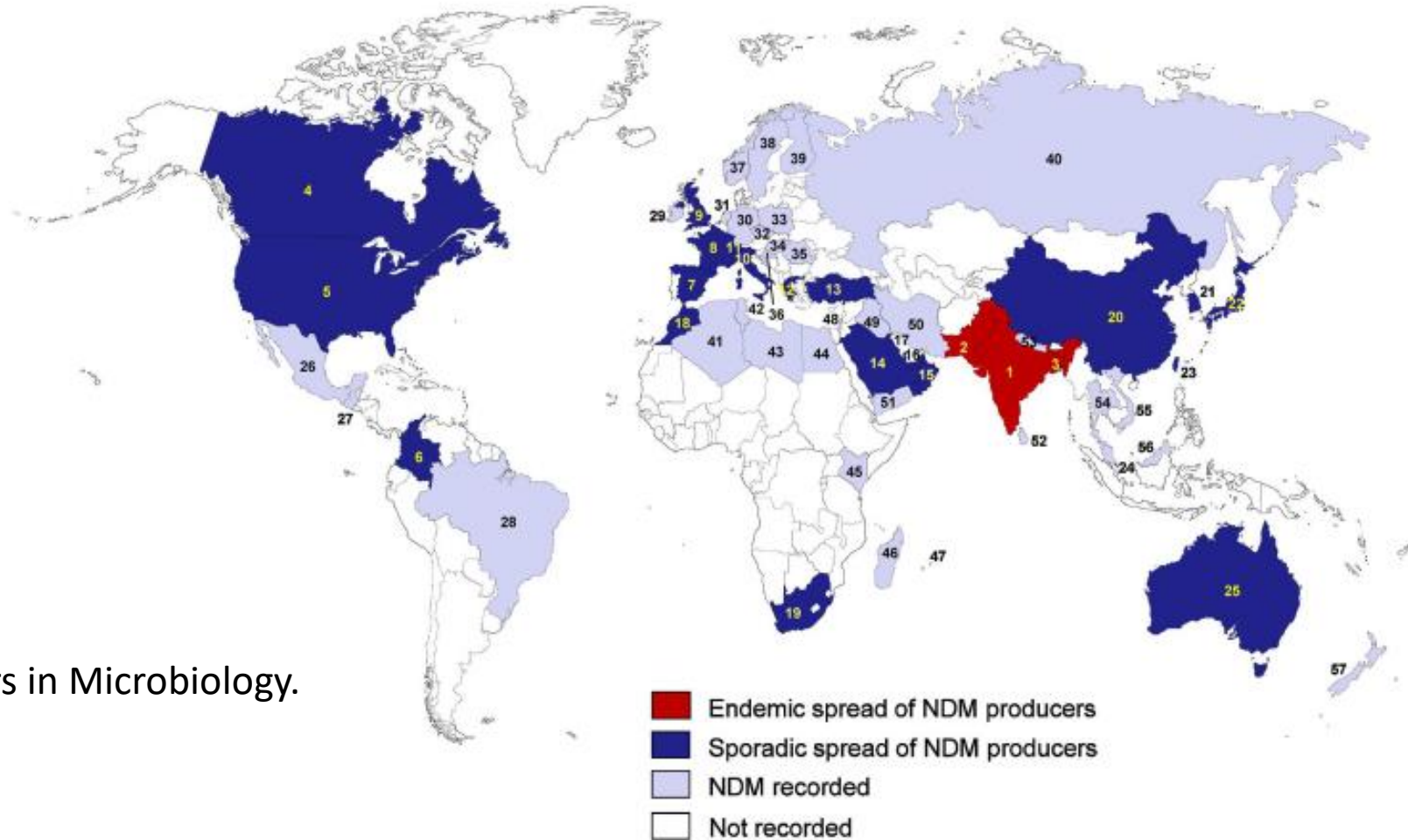
JOURNAL OF CLINICAL MICROBIOLOGY, Nov. 2009, p. 3793–3794  
0095-1137/09/\$12.00 doi:10.1128/JCM.01773-09  
Copyright © 2009, American Society for Microbiology. All Rights Reserved.

Giani T et al

**Emergence in Italy of *Klebsiella pneumoniae* Sequence Type 258  
Producing KPC-3 Carbapenemase<sup>▽</sup>**

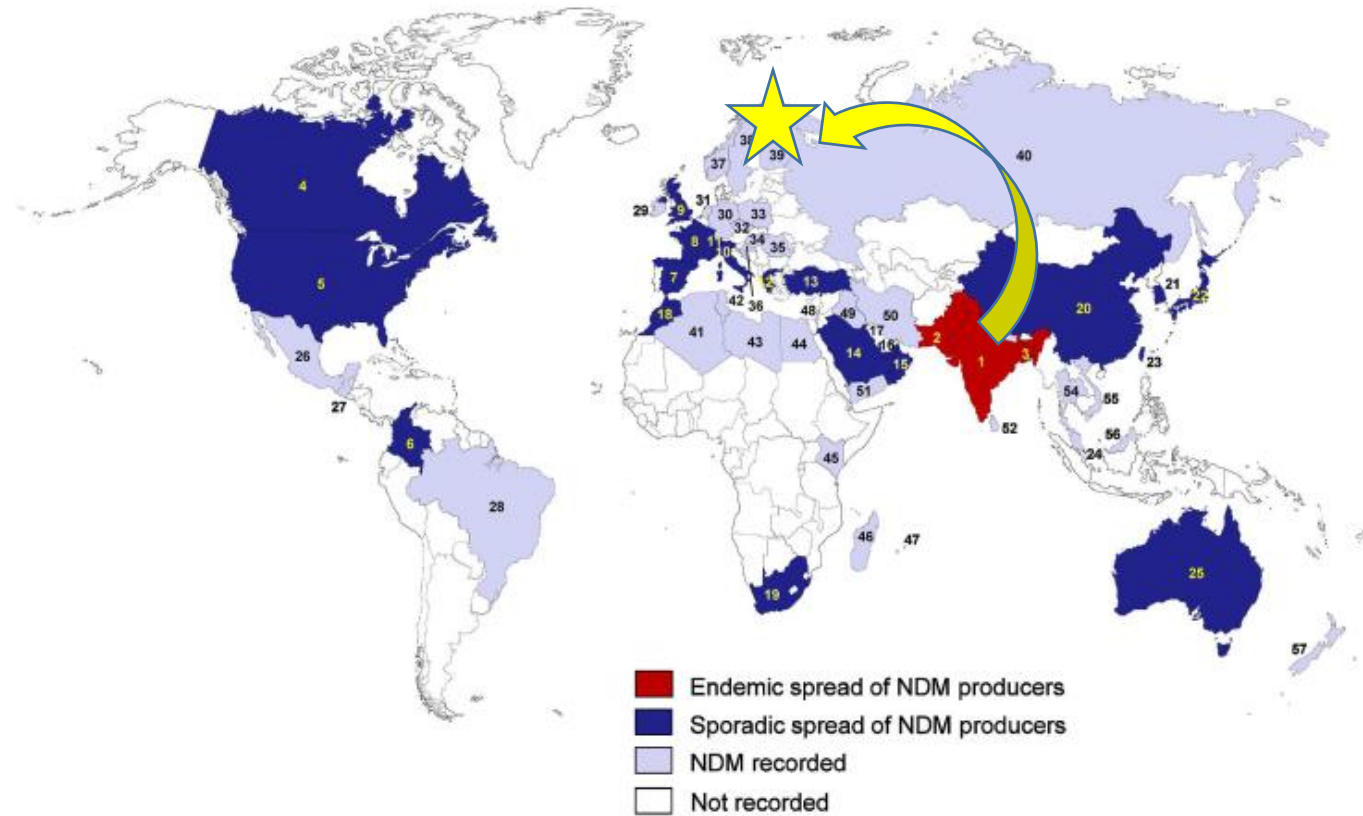


# Epidemiologia di *K. pneumoniae* e *E. coli* produttori di NDM



Ro-Lee et al. Frontiers in Microbiology.  
2016 vol 7 art. 895

NDM  
2008  
primo isolamento  
in Svezia



ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Dec. 2009, p. 5046–5054  
0066-4804/09/\$12.00 doi:10.1128/AAC.00774-09  
Copyright © 2009, American Society for Microbiology. All Rights Reserved.

Vol. 53, No. 12

Characterization of a New Metallo- $\beta$ -Lactamase Gene, *bla*<sub>NDM-1</sub>, and a Novel Erythromycin Esterase Gene Carried on a Unique Genetic Structure in *Klebsiella pneumoniae* Sequence Type 14 from India<sup>∇</sup>

Dongeun Yong,<sup>1,2</sup> Mark A. Toleman,<sup>2</sup> Christian G. Giske,<sup>3</sup> Hyun S. Cho,<sup>4</sup> Kristina Sundman,<sup>5</sup> Kyungwon Lee,<sup>1</sup> and Timothy R. Walsh<sup>2\*</sup>

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



# NDM principale serbatoioio

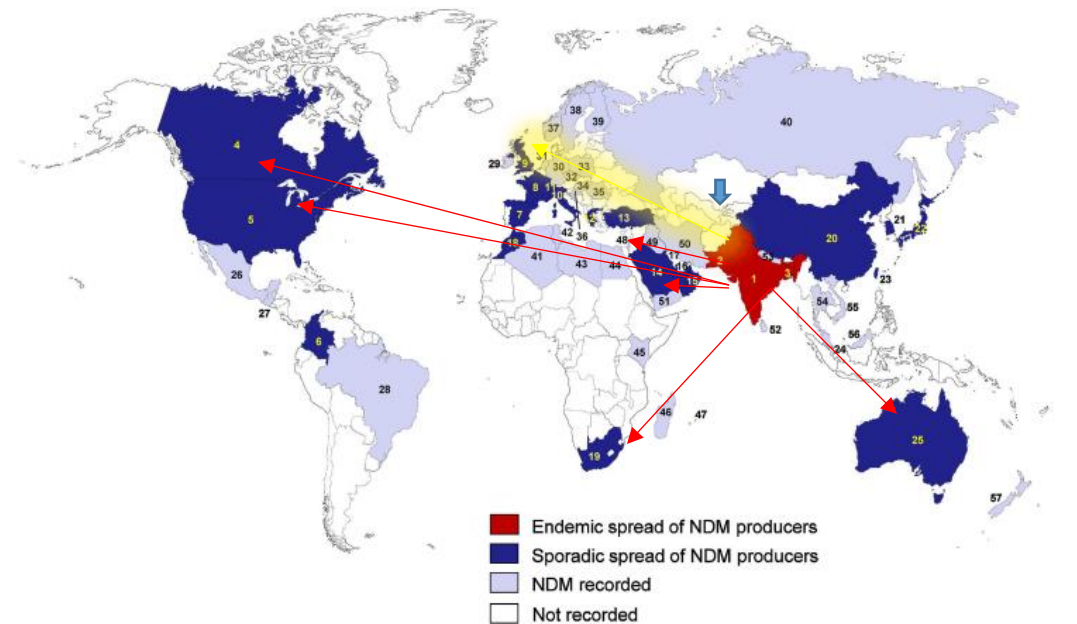
- India, Pakistan, Bangladesh
- Presentano una situazione di endemia
- Presenza di NDM pari al 75.22% (kazi et al, EJCMID 2015)
- Identificata anche nel suolo
- Prevalenza portatori 5-15% (Perry et al JAC 2011)



Kumarasamy et al. Lancet Inf Dis 2010

# NDM: diffusione

- Nel Regno Unito
  - con relazioni strette con il subcontinente indiano
- In tutti i paesi in cui si ha un alto numero di indiani e pakistani
  - Canada
  - USA
  - Paesi del Golfo
  - Arabia Saudita
  - Sud Africa
  - Australia

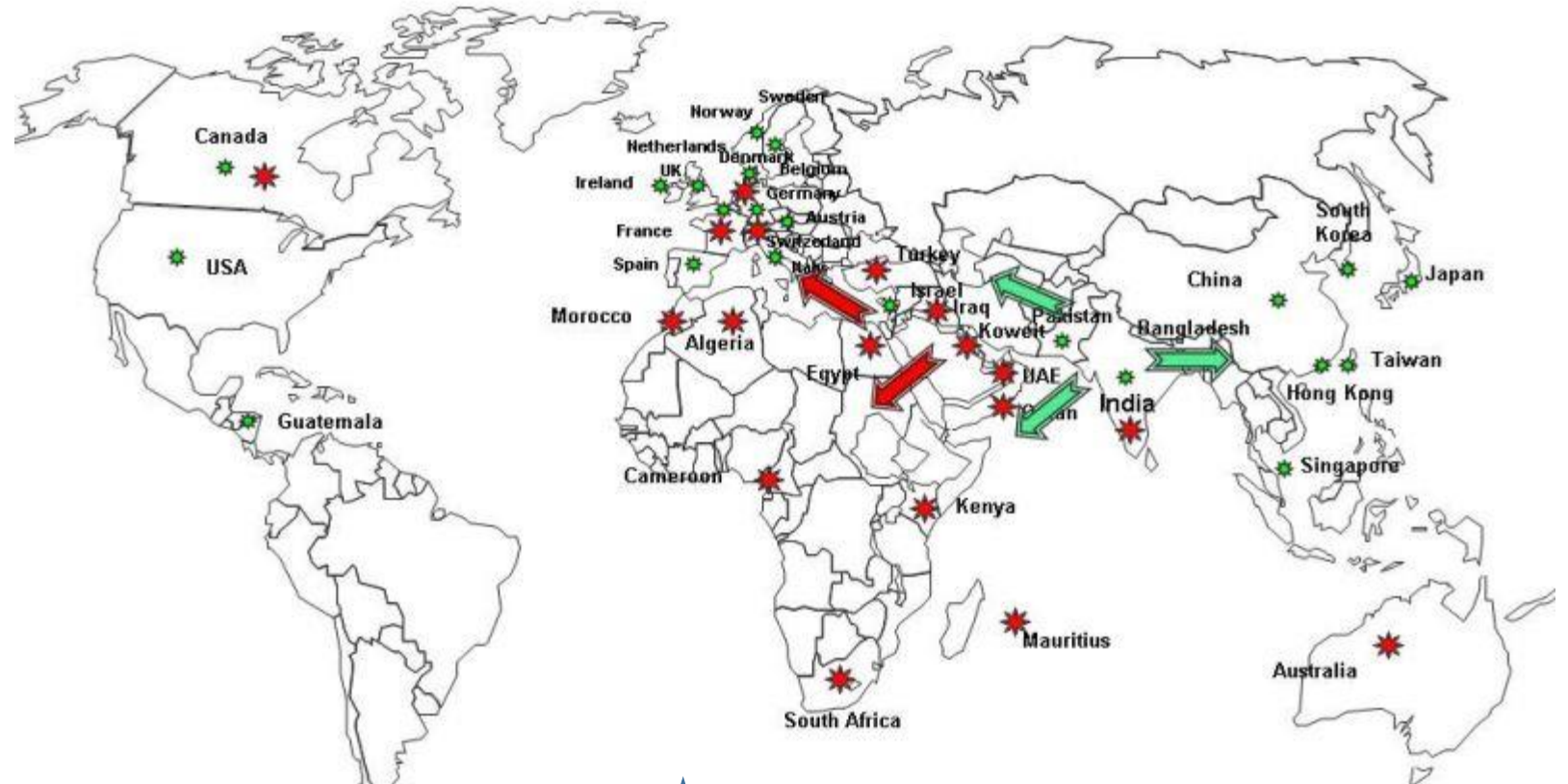




# NDM diffusione dai principali serbatoi (2010-2013)

Ruolo probabile di  
*A. baumannii* nella  
diffusione

Nordmann P e Poirel L 2015

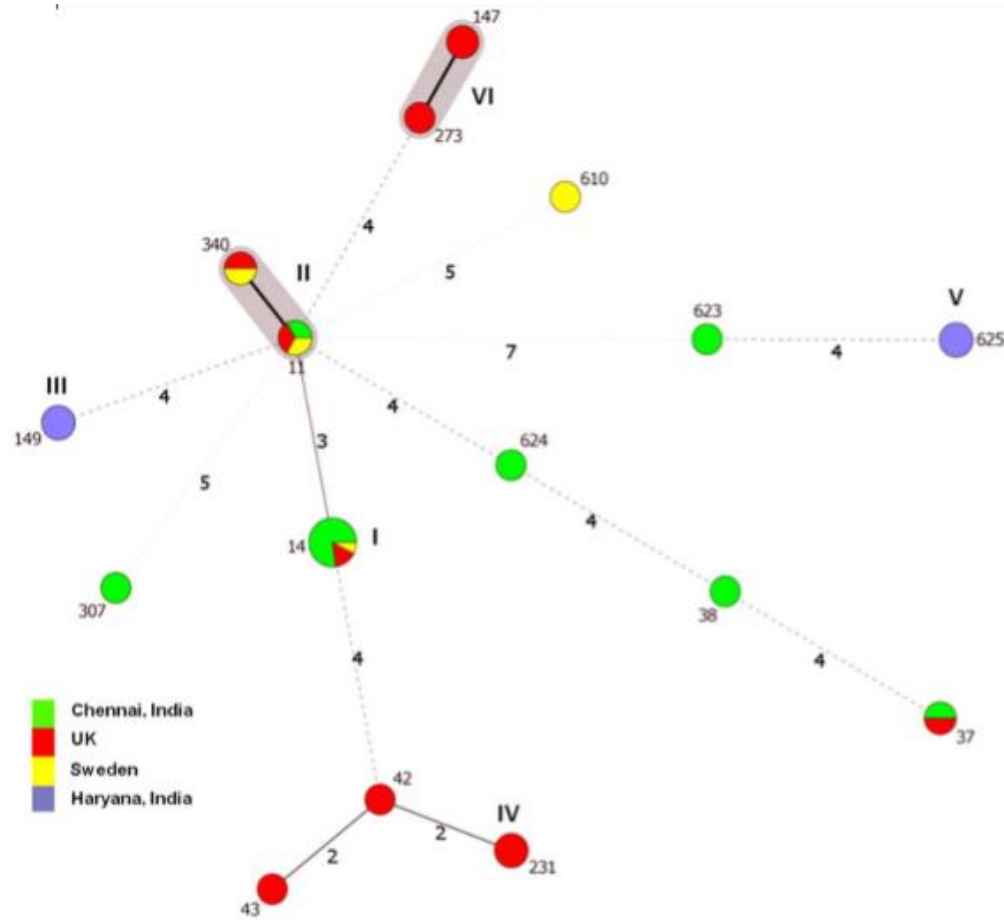


Serbatoio del Sud-Est Asiatico



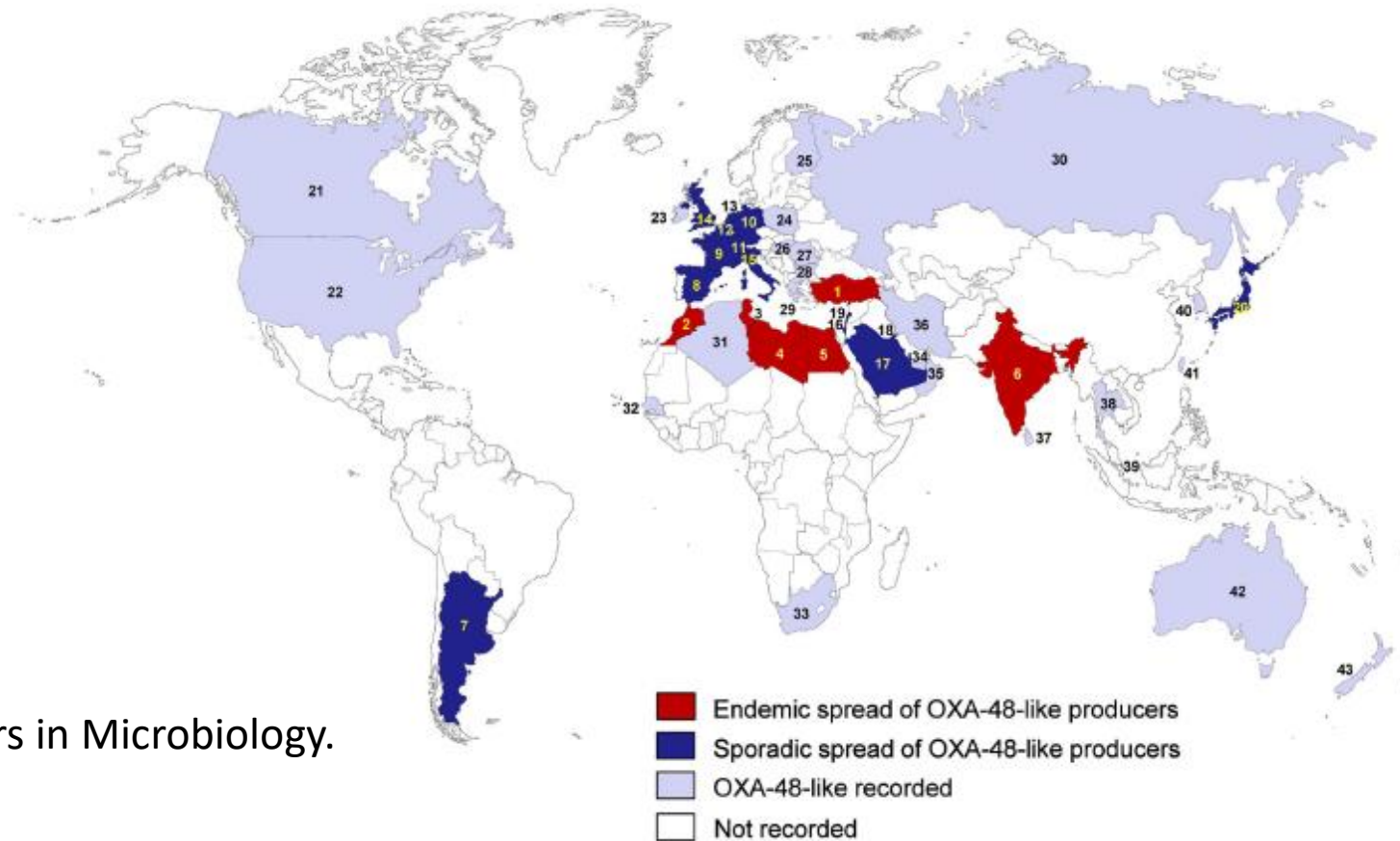
Serbatoio del Medio-Oriente

# NDM-1 epidemia di un gene



VARI CLONI

# Epidemiologia di *K. pneumoniae* e altre enterobatteriaceae produttrici di OXA-48



Ro-Lee et al. *Frontiers in Microbiology*.  
2016 vol 7 art. 895

# OXA-48 il primo isolamento

TURCHIA 2003



ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Jan. 2004, p. 15–22  
0066-4804/04/\$08.00+0 DOI: 10.1128/AAC.48.1.15–22.2004  
Copyright © 2004, American Society for Microbiology. All Rights Reserved

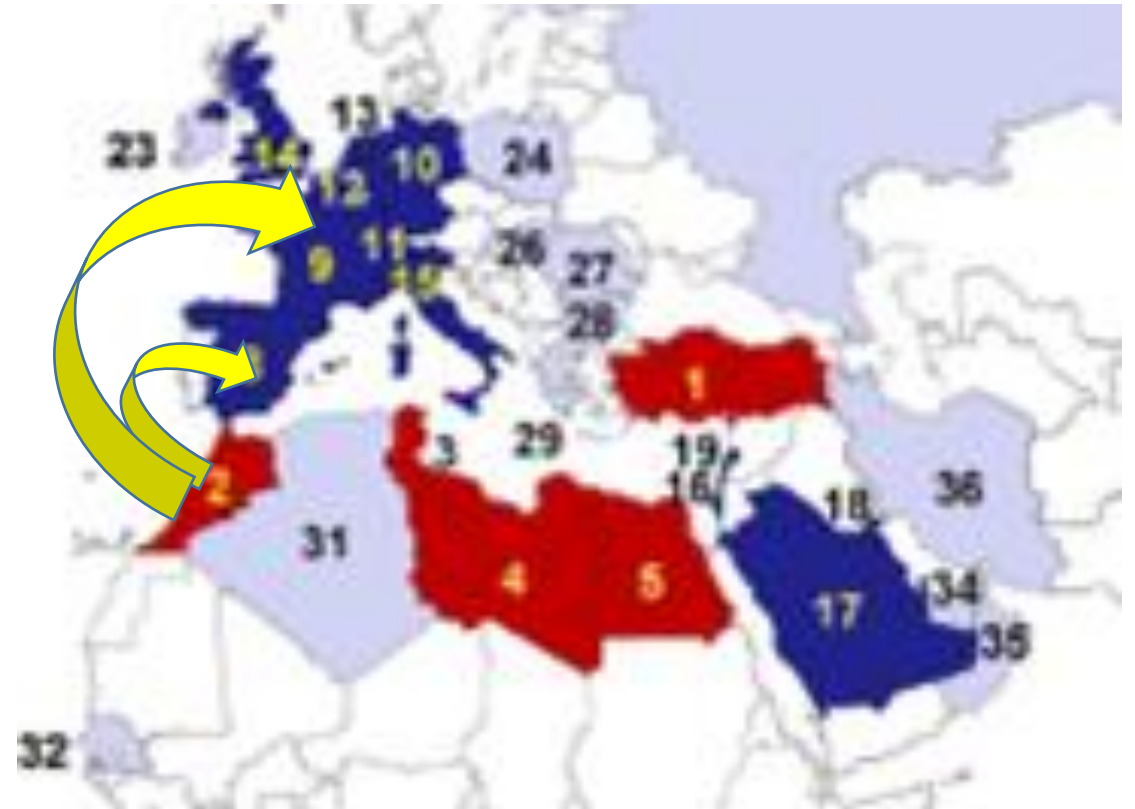
## Emergence of Oxacillinase-Mediated Resistance to Imipenem in *Klebsiella pneumoniae*

Laurent Poirel,<sup>1</sup> Claire Héritier,<sup>1</sup> Venus Tolün,<sup>2</sup> and Patrice Nordmann<sup>1\*</sup>

*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,<sup>1</sup> and Department of Microbiology, Istanbul Medical Faculty, Capa, Istanbul, Turkey<sup>2</sup>*

# OXA-48

- Turchia serbatoio principale
- Paesi Nord-Africani rappresentano un altro serbatoio fondamentale
- Diffusione nei paesi Europei
  - Spagna
  - Francia





# OXA-48

- Diffusione in Israele
  - Turismo medico
  - Pazienti provenienti da Georgia e Giordania

Journal of  
Antimicrobial  
Chemotherapy

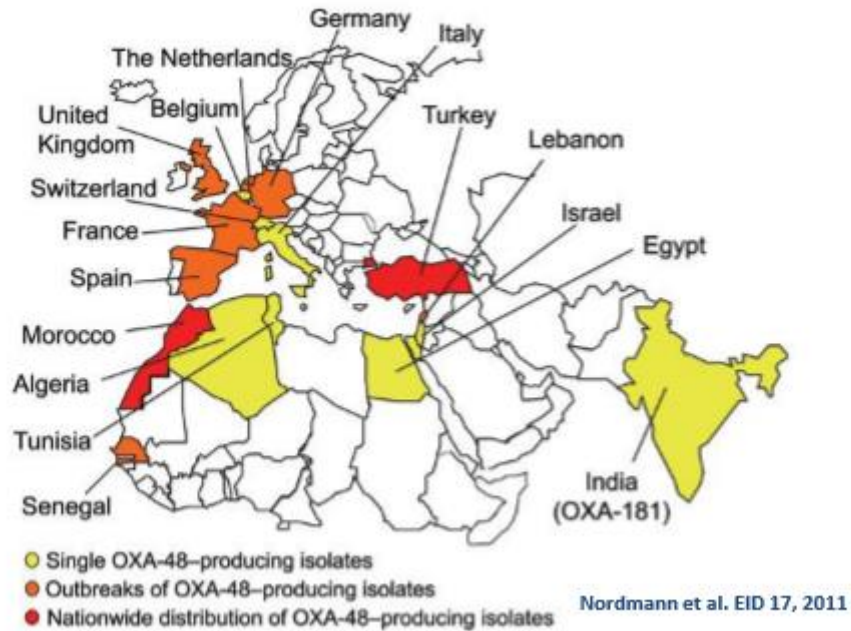
*J Antimicrob Chemother* 2011; **66**: 2763–2766  
doi:10.1093/jac/dkr382 Advance Access publication 19 September 2011

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

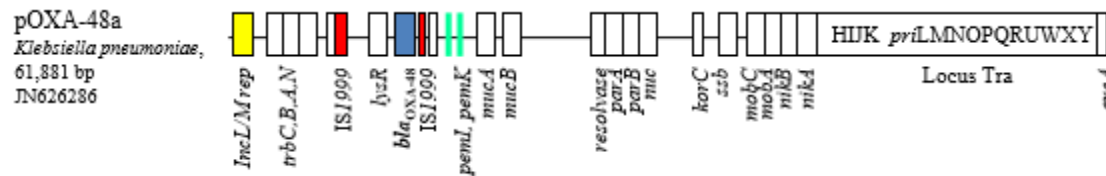
Amos Adler<sup>1\*</sup>, Maya Shklyar<sup>1</sup>, Mitchell J. Schwaber<sup>1</sup>, Shiri Navon-Venezia<sup>1</sup>, Yacoub Dhafer<sup>2</sup>, Rotem Edgar<sup>1</sup>, Ester Solter<sup>1</sup>, Shmuel Benenson<sup>3</sup>, Samira Masarwa<sup>1</sup> and Yehuda Carmeli<sup>1</sup>



# Oxa-48



Successo di un Plasmide  
IncL/M  
Alta trasmissibilità  
Diffuso tra moltissime  
Enterobatteriaceae



# Rischio di epidemie da MDR di ritorno da aeree di endemicità

- Rischio reale
  - per gli stessi portatori
  - In termini di potenziale diffusione di epidemie da MDR
- Fournier et al J Trav Med 2012

# Rischio di epidemie da MDR...

Periodo 2004-2011

Parigi

63 epidemie sostenute da produttori di carbapenemasi

Fournier et al J Trav Med 2012

87% implicavano un'origine al di fuori della Francia

**Table 1** Country, species, and type of carbapenemase in 55 carbapenemase-producing *Enterobacteria* (CPE) events involving patients with a link with a cross-border exchange

Country	Number of events	Number of events by species				Number of events by carbapenemase			
		<i>Klebsiella pneumoniae</i>	<i>Escherichia coli</i>	<i>Citrobacter freundii</i>	<i>Enterobacter cloacae</i>	OXA-48	KPC	VIM	NDM-1
North Africa	22	14*	8*		2*	19	2	1	
Algeria	3	2	1			2		1	
Egypt	4	1	3			3	1		
Morocco	9	5	3*		2*	8	1		
Tunisia	6	6*	1*			6			
Greece	19	16	3			1	14	4	
Italy	2	2					2		
Senegal	2	1			1	2			
Kuwait	2	1	1			2			
Spain	1	1				1			
Turkey	1		1			1			
United States	1			1		1			
Cameroon	1		1						1
India	1		1						1
Israel	1	1					1		
Vietnam	1	1							1
Iraq	1	1							1

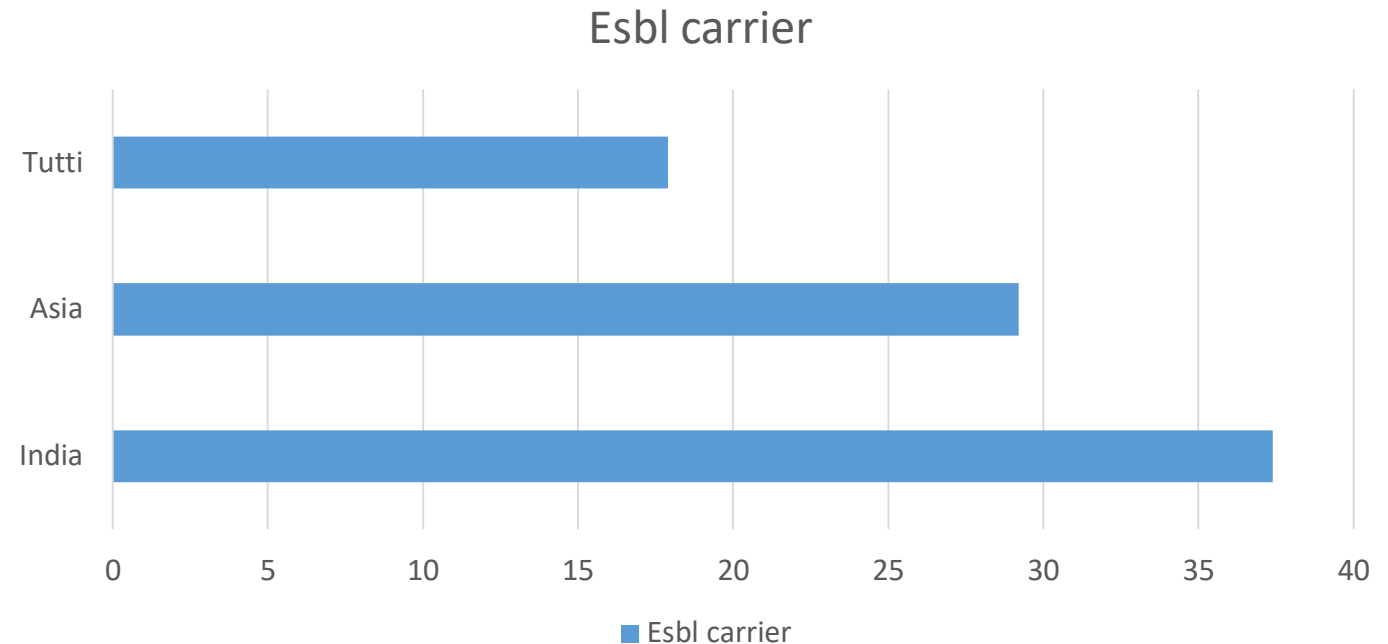
\*Two events involved two species with the same carbapenemase.

# Viaggiatori di ritorno dai paesi in via di sviluppo

- Giocano un ruolo importante
  - Nell'acquisizione di MDR
  - Nella colonizzazione intestinale di MDR
  - Nell'introduzione di questi nei paesi di origine

# Colonizzati da *E. coli* produttori di ESBL

- Studio di Solè et al CMI 2014
- Viaggiatori spagnoli in zone tropicali e subtropicali
- Tasso di colonizzazione al ritorno



# Viaggiatori di ritorno da zone tropicali e subtropicali

Studio di Ruppè et al CID 2015

Più di 500 viaggiatori con screening per MDR

Campioni fecali analizzati per vari mesi

**Table 2. Follow-up of Travelers After Their Return**

Time After Return, mo	Proportion of MRE Carriers Among Carriers at Return (%) <sup>a</sup>				Proportion of MRE Carriers Among All Travelers (%) <sup>a</sup>			
	All	Sub-Saharan Africa	Latin America	Asia	All	Sub-Saharan Africa	Latin America	Asia
0	292/292 (100)	93/93 (100)	57/57 (100)	142/142 (100)	292/574 (50.9)	93/195 (47.7)	57/183 (31.1)	142/196 (72.4)
1	83/245 (33.9)	9/72 (12.5)	10/50 (20)	64/123 (52)	83/527 (15.7)	9/174 (5.2)	10/176 (5.7)	64/177 (36.2)
2	45/236 (19.1)	5/72 (6.9)	5/48 (10.4)	35/116 (30.2)	45/518 (8.7)	5/174 (2.9)	5/174 (2.9)	35/170 (20.6)
3	24/233 (10.3)	3/72 (4.2)	3/47 (6.4)	18/114 (15.8)	24/515 (4.7)	3/174 (1.7)	3/173 (1.7)	18/168 (10.7)
6	11/230 (4.8)	0/72 (0)	3/47 (6.4)	8/111 (7.2)	11/512 (2.1)	0/174 (0)	3/173 (1.7)	8/165 (4.8)
12	5/227 (2.2)	0/72 (0)	1/46 (2.2)	4/109 (3.7)	5/509 (1)	0/174 (0)	1/172 (0.6)	4/163 (2.5)

Abbreviation: MRE, multidrug-resistant Enterobacteriaceae.

<sup>a</sup> Travelers lost to follow-up, those whose stool sample was sent out of time as scheduled, and those who subsequently traveled to tropical regions were excluded at each time point.

# Viaggiatori Filandesi

- Studio di Kantele et al CID 2015
- Screening su 430 viaggiatori
- 21% colonizzati da Enterobatteri produttori di ESBL
- Nel sottogruppo Asiatico
  - Tasso totale di colonizzazione del 23%
  - 47% in quelli che avevano contratto la diarrea del viaggiatori
  - 80% in quelli con diarrea del viaggiatore e trattamento antibiotico



# Conclusioni

Jordi Vila Editoriale J Trav Med 2015

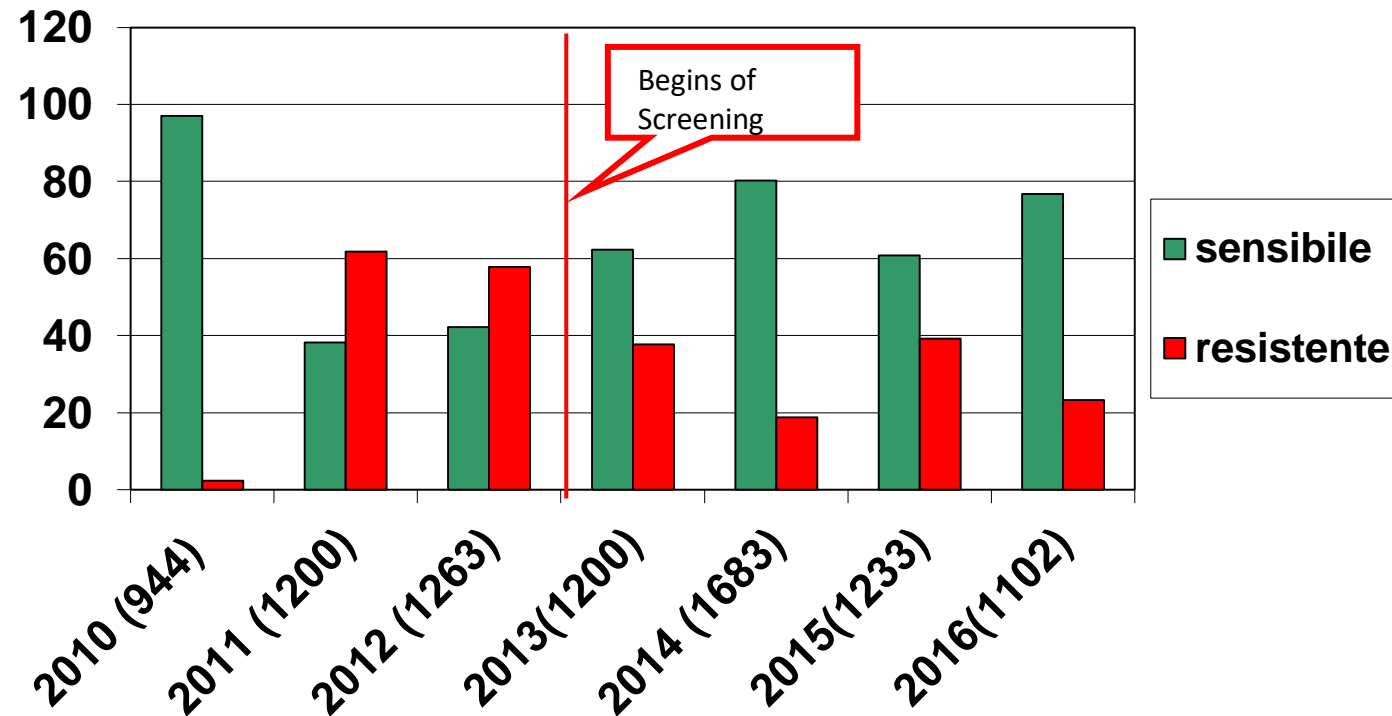
Afferma che i MDR non riconoscono i nostri confini

- Suggestisce di fare lo screening MDR
  - per tutti i pazienti provenienti da aree endemiche
  - per viaggiatori di ritorno da aree endemiche per MDR
    - Considerando il viaggio un fattore di rischio
- Lo screening e l'isolamento dei colonizzati previene la disseminazione

# Utilità dello screening

*K. pneumoniae* resistenti al meropenem Verona  
2010-2016

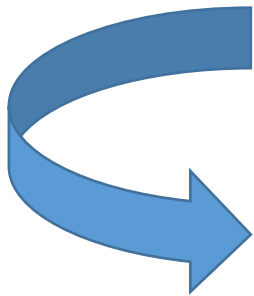
April 15, 2013



# Nuovo allarme

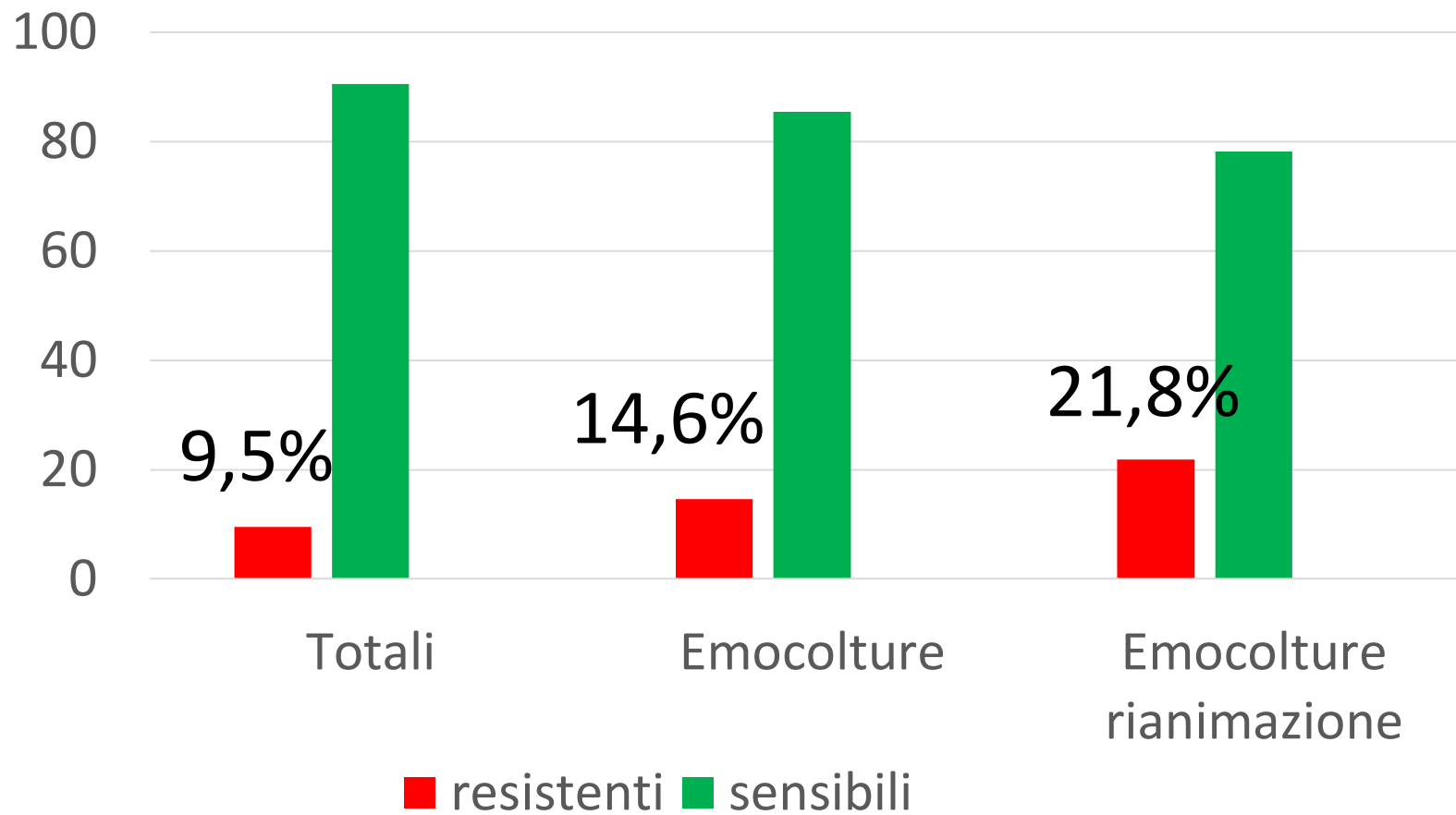
## Resistenza alla colistina

2015 scoperto gene mcr-1  
Resistenza alla colistina mediata da  
plasmide



HGT

# *K. pneumoniae* resistenti alla colistina Verona 2016



GRAZIE PER  
L'ATTENZIONE