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ESCMID EUROPEAN SOCIETY OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES

Why are some carbapenemases successful?

SaludMadrid

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Why are some carbapenemases successful?

- What have we learned from **ESBLs**, particularly from **CTX-Ms**?

  - Emergence of specific ESBLs in different and distant parts of the world and latter spread and dominance of other ESBLs

    - 1989-2000

FEC-1	Japan	CTX-M-9	Spain
CTX-M-1	Germany	CTX-M14	Korea
CTX-M-2	Argentina	CTX-M-15	India
Toho-1	Japan	CTX-M-8	Brazil
CTX-M-3	Poland	CTX-M-25	Canada

    - 2000 - … Globalization of specific β-lactamases (CTX-M-15, …)

  Cantón, Gonzalez-Alba, Galán. Frontiers Microbiol 2012; 3:1-19

  - Different evolutionary trajectories following different selective forces also affecting the spectrum of different CTX-Ms

    - from cefotaximases to cetaximases/ceftazidimases

  Novais et al. Antimicrob Agents Chemother 200852;2377-82
  Novais et al. PlosPathogen 2010; 6, e1000735

Why are some carbapenemases successful?

- What did we learn with **ESBLs** and particularly with **CTX-Ms**?

  - different genetic environments of *bla*$_{CTX-M}$ genes participating in the mobilization, spread and maintenance of these genes

    - ISEcp1, ISCR1, IS10, IS26, …

    Lartige et al. FEMS Microbiol Lett 2004;234:201-7

  - "epidemic resistance plasmids" from different incompatibility groups harbouring different resistance/virulence traits

    - IncFII, IcN, IncI1, InnL/M , IncK, IncHI2 …
    - *qnr, aac(6')Ib-cr, …*

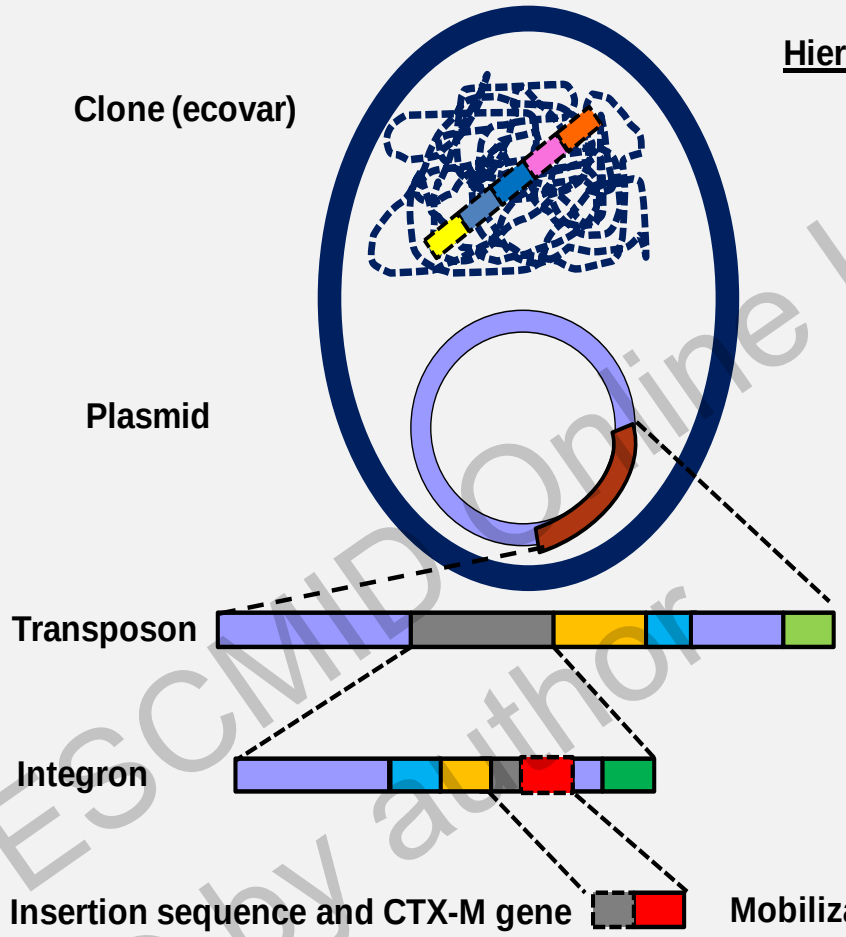
    Caratoli A. AAC 2009; 53:2227-38, Cantón et al. Frontiers Microbiol 2012; 3:1-19

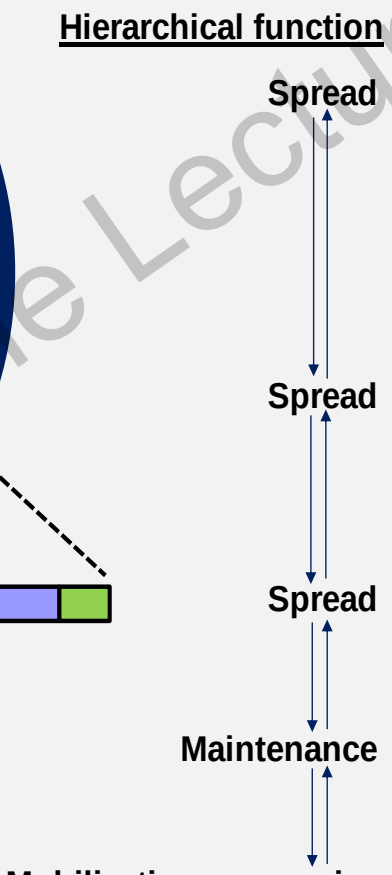
  - dispersion of multi-drug resistant and virulent **high-risk clones**

    - *E. coli* (ST38, ST131, ST405 …), *K. pneumoniae* (ST11, ST15, …)

    Cantón et al. Frontiers Microbiol 2012; 3:1-19

Hierarchical complexity of *bla*$_{CTX-M}$ genes within genetic structures and bacterial clones





B2 O:25:H4ST131

E. coli

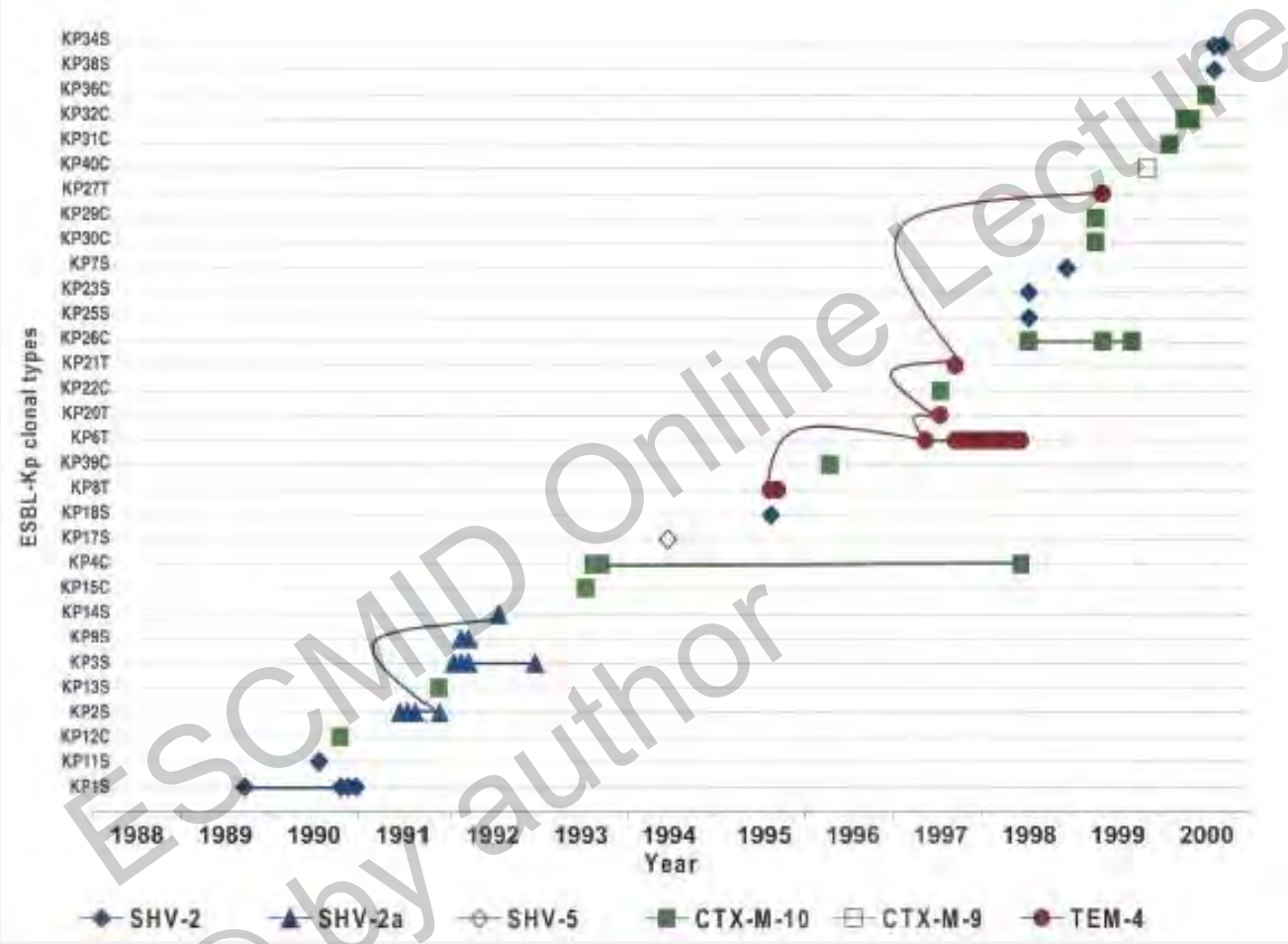
High-risk clones

Cantón et al. Front Microbiol 2012; 3:110

From clones to high risk clones (HiRiCs)

ESBL producing *K. pneumoniae*

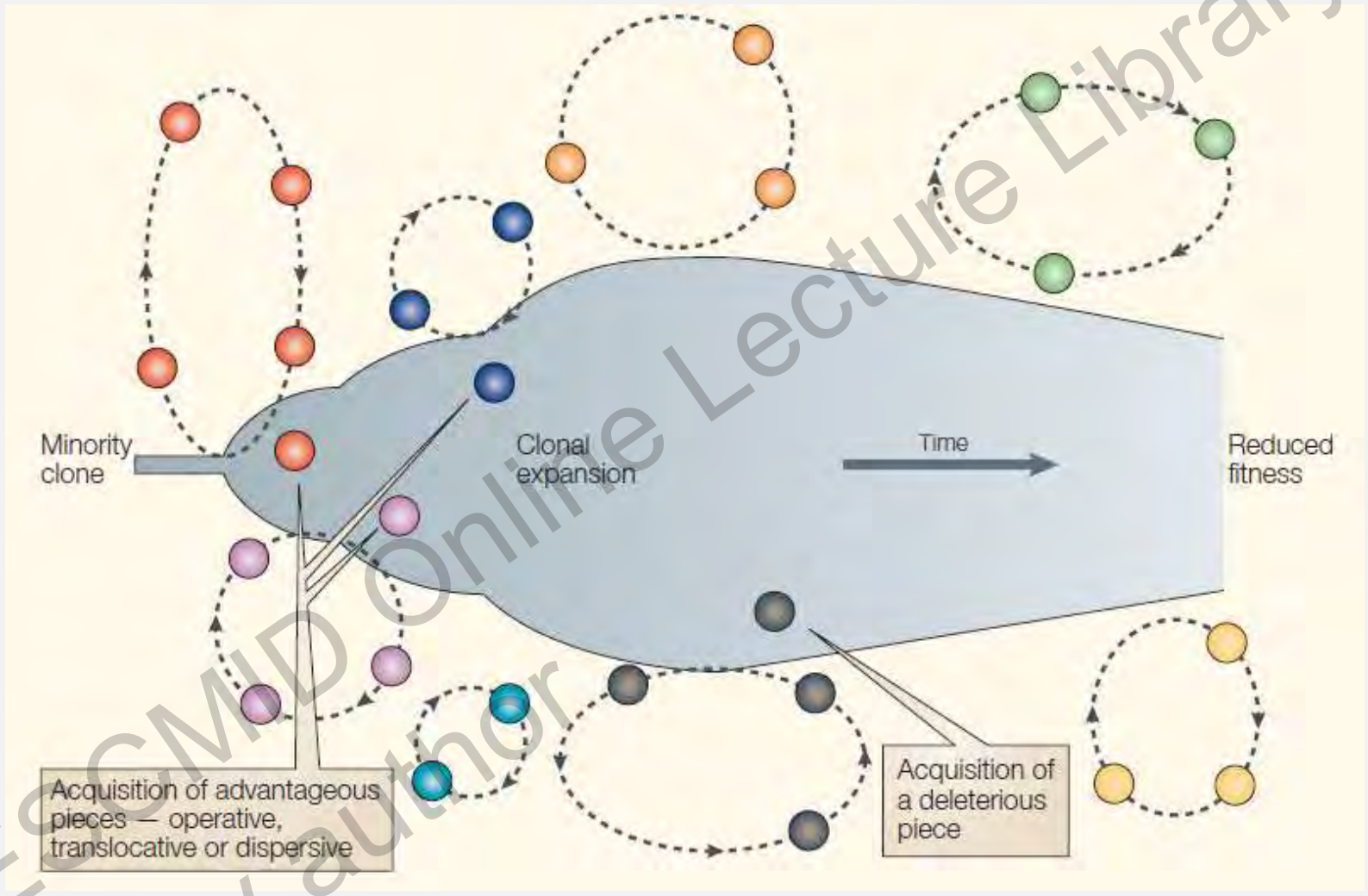
Hospital Ramón y Cajal (Madrid, Spain 1989 to 2000)



- Ephemeral clones
- Persistent clones

Coque, Oliver, Pérez-Díaz, Baquero, Cantón.
Antimicrob Agents Chemother 2002; 46: 500-10

From clones to high risk clones (HiRiCs)



Baquero F. Nat Rev Microbiol 2004; 2:510-8

Baquero, Coque, Cantón. ASM News 2003; 69: 547-51
Cantón, Coque, Baquero. Curr Opin Infect Dis 2003; 16:315-25
Cantón, Ruiz-Garbajosa Curr Opin Pharmacol 2011; 11:477-85

High risk clones (HiRiCs)

- Bacterial **clones associated** with

  - **antimicrobial resistance mechanism** of critical clinical importance
  - ability to efficiently **colonize** human hosts during **long periods** of time
  - ability to **be transmitted with high efficiency** among patients
  - ability to produce **severe or invasive infections**

TROCAR FP7 Health EU project

- Major role in the **spread of resis**tance

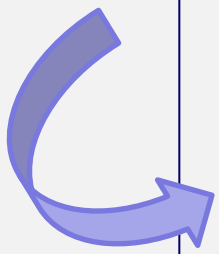
- Risk lying in their

  - tenacity and flexible ability to accumulate and exchange resistance and virulence genes

Willems et al. FEMS Microbiol Rev 2011; 35:872-900
Woodford et al. FEMS Microbiol Rev 2011; 35:736-55
Baquero & Coque. FEMS Microbiol Rev 2011 35:705

Why are some carbapenemases successful?

- **Do we have similar situation with carbapenemase producers than with ESBL producers?**



- complex group of enzymes
- chronological emergence in different geographic areas
- different population structure and dispersion models
  - dispersion and predominance of high-risk clones
  - polyclonal situation
- insertion of *bla*$_{carba}$ genes in well adapted plasmid
- variable virulence traits (even with less virulence)
- different susceptibility profile (multirresistance phenotype)

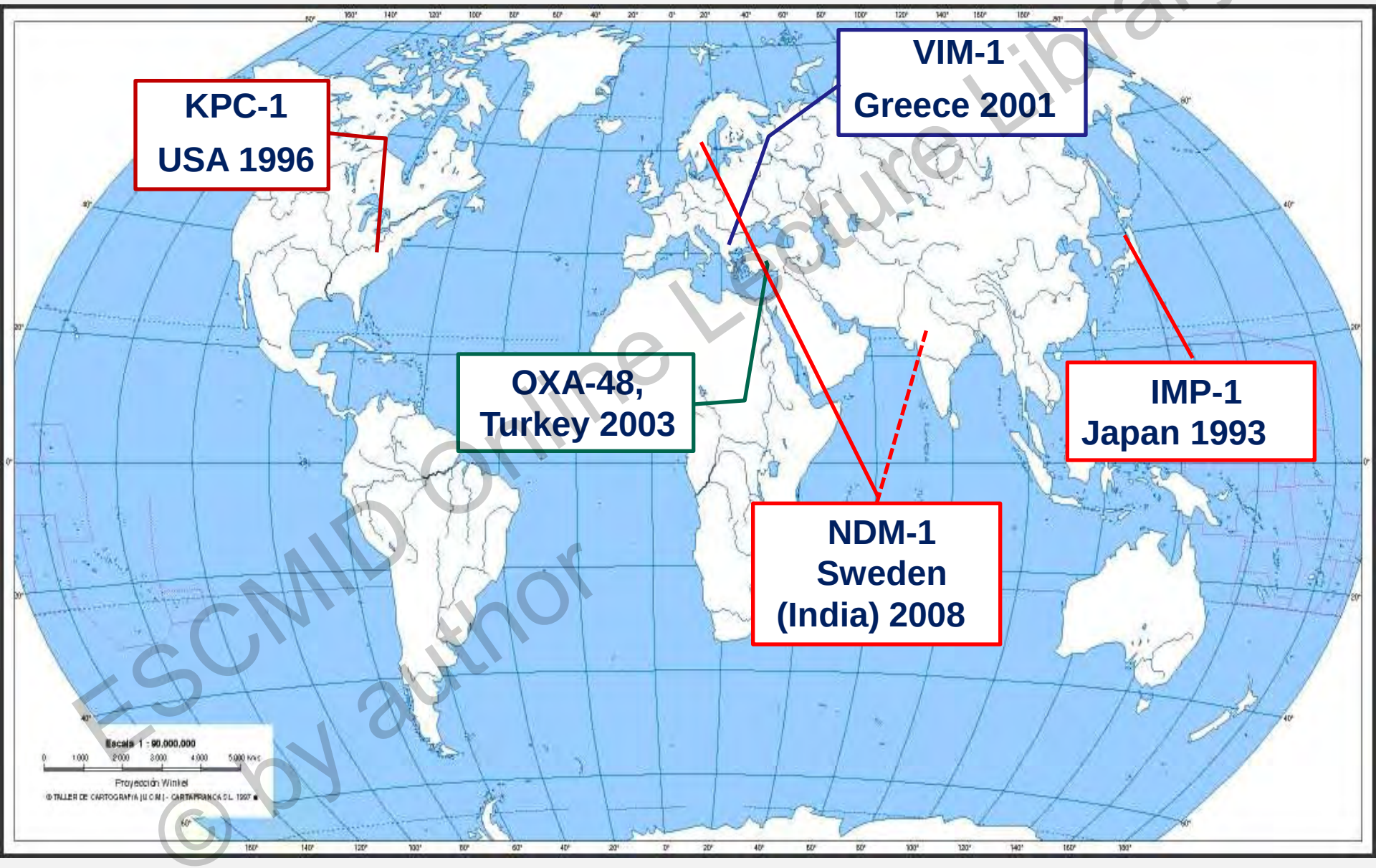
Carbapenemases

Molecular class[1] (Functional Group[2])	Enzymes	Inhibited by		ATM	Organisms	Gene	Relevance
		CLA	EDTA				
A (2f)	Sme-1 to -3, IMI-1 to -3, NmcA, SFC-1	±	-	R	*S. marcescens* *E. cloacae*	Ch	±
	KPC-2 to -15	±	-	R	*Enterobacteriaceae* *P. aeruginosa* *A. baumannii*	Pl	+++ +
	GES-1 to 23	+	-	S/R	*Enterobacteriaceae* *P. aeruginosa* *A. baumannii*	Pl	+
B (3)	IMP-1 to -45, VIM-1 to -39, NDM-1 to -10, SPM-1, SIM, GIM, IND-1 to -15, AIM, DIM, KHM, ...	-	+	S	*Enterobacteriaceae* *P. aeruginosa* other GNNFB	Pl/Ch	± / +++
D (2df)[3]	OXA-23 group (-23,-27 -49) OXA-24 group (-24,-25,-26,-40,-72) OXA-40 group (-40, -143) OXA-58 OXA-48 group (-48,-162,-163,-181, -204,-232)	±	-[4]	S	*A. baumannii* *P. aeruginosa* *Enterobacteriaceae*	Pl/Ch	++

1: Ambler classification. 2: Bush, Jacoby & Medeiros classification; 3: only class D carbapenemases representative of different groups have been included;
4: some OXA enzymes may be slightly inhibited by EDTA. CLA: clavulanate; EDTA: ethylenediaminetetraacetic ac; ATM: aztreonam; Ch: Chromosomal; Pl: plasmid

Updated from Cantón et al. Clin Microbiol Infect 2012; 18:413-31

Emergence of successful carbapenemases in Enterobacteriaceae



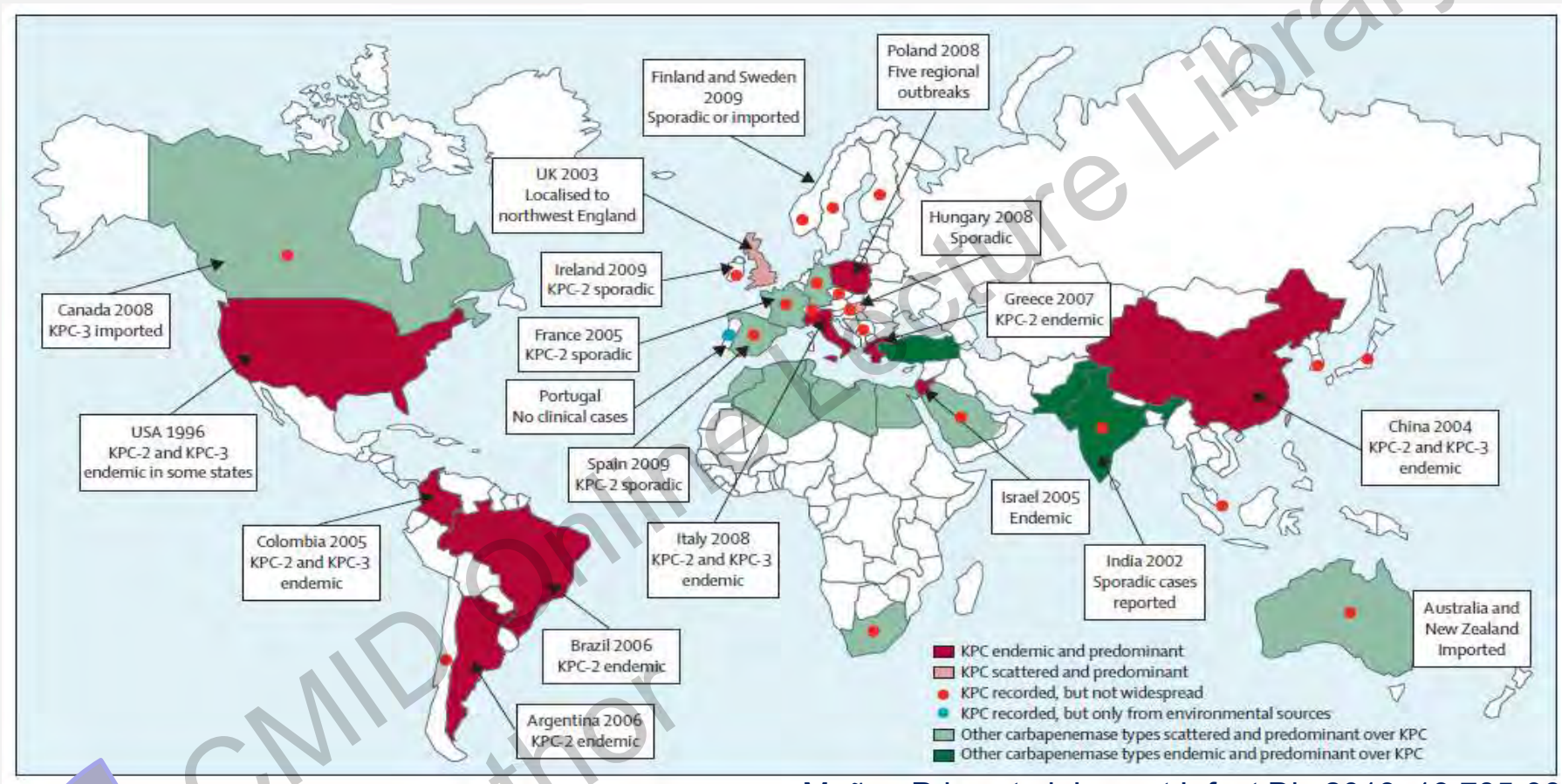
Carbapenemases: population structure

- Emergence and dispersion of specific clones associated with
  - specific carbapenemases (***clonal spread***)
    ST258 *K. pneumoniae* and KPC-2
  - different carbapenemases (***polyclonal spread***)
    ST15 *K. pneumoniae* and OXA-48 and VIM-1
    ST14 *K. pneumoniae* and NDM-1, KPC and ST14
    ST131 *E. coli* and KPC-2, VIM-1 and NDM-1
    ST101 *E. coli* and KPC-2 and NDM-1
- Acquisition of (new) carbapenemases in pre-existing carbapenemase clones
  clones coproducing different carbapenemases

Also expressing ESBLs and other resistance mechanisms

Acquisition witin the clonal local pool?

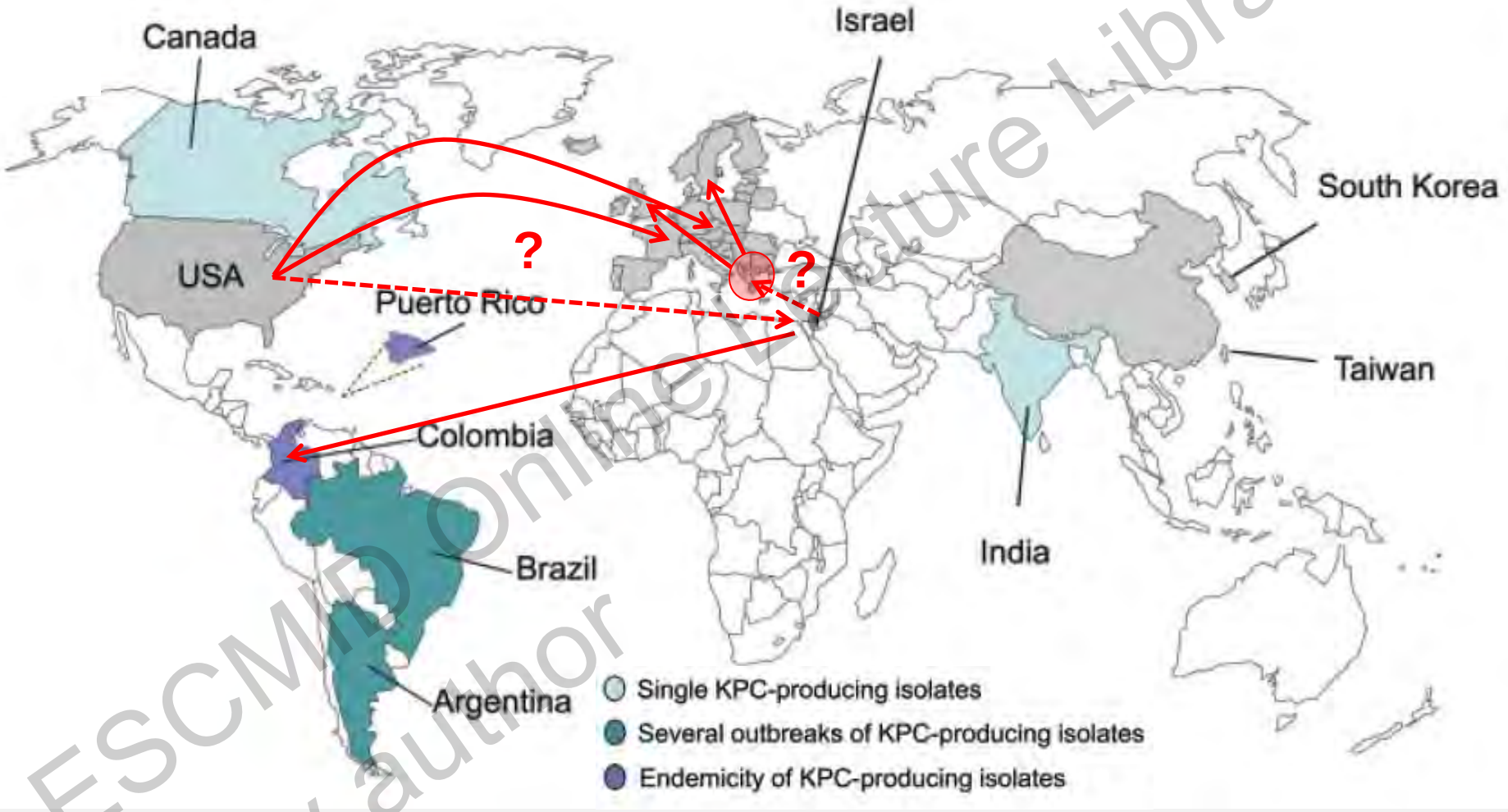
World wide dissemination of KPC-Enterobacteriaceae



Muñoz-Price et al. Lancet Infect Dis 2013; 13:785-96

- Few *K. pneumoniae* clones associated with bla_{KPC} dissemination:
  - high-risk clones (ST258)
  - clones belonging to the same clonal complex of ST258 (ST11, 14,…)
  - minor clones (singletone clones) based in local epidemiology

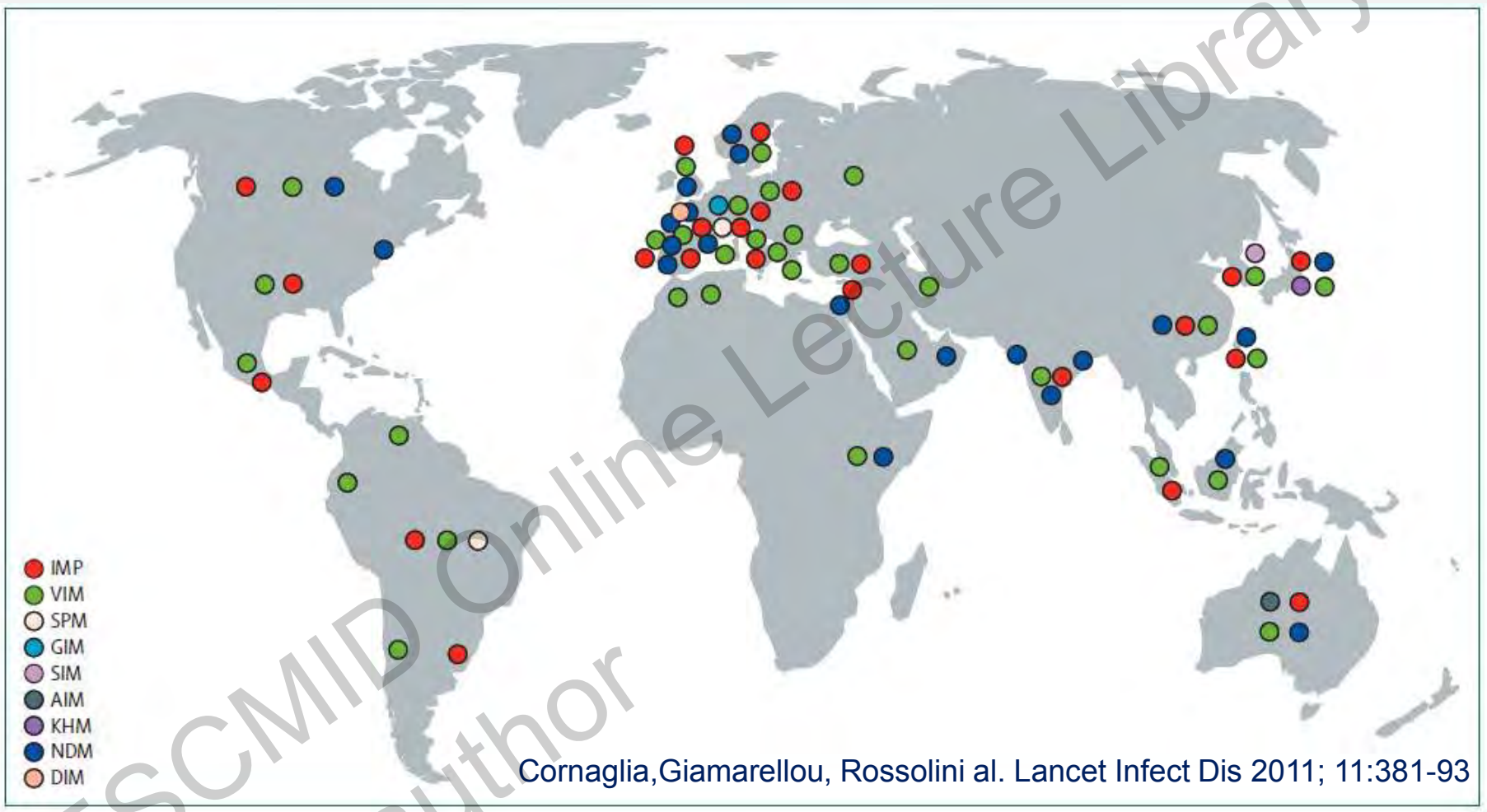
Dispersion of KPC-*K. pneumoniae* high-risk clone ST258



- Cross border dissemination (*K. pneumoniae* ST258) from endemic areas

Magiorakos et al.. ECDC. 2011; Nordmann et al. EID 2011; 17:1791-8;
Cantón et al. CMI 2012; 18:413-31; Muñoz-Price et al. LID 2013; 13:785-96

World wide dissemination of MBL-Enterobacteriaceae

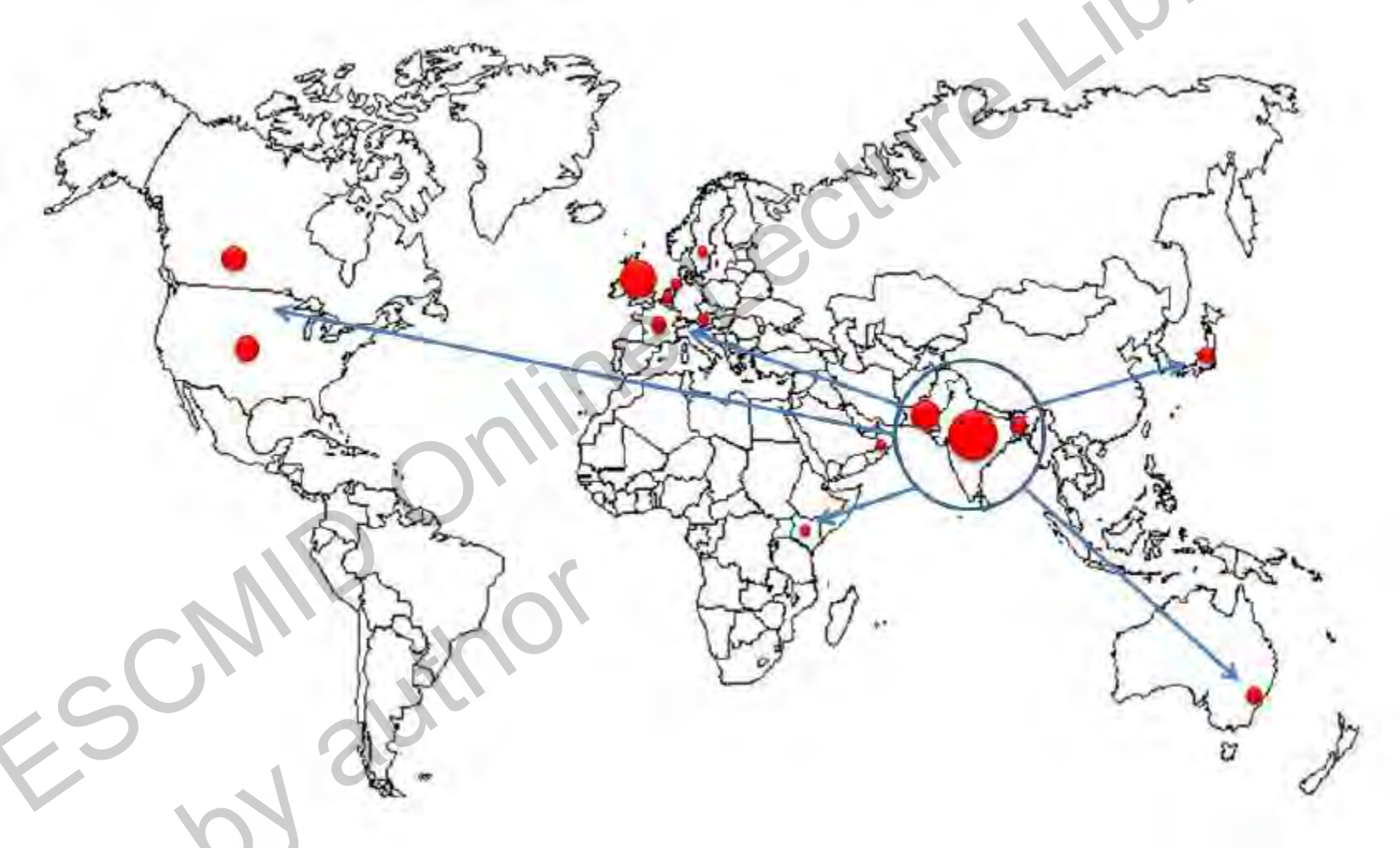


Cornaglia,Giamarellou, Rossolini al. Lancet Infect Dis 2011; 11:381-93

- In different Enterobacteriaceae, including *E. coli*, *K. pneumoniae*, *Enterobacter* spp., (also in *P. aeruginosa* and *A. baumannii*)
  - high-risk clones (ST11, …) and polyclonal situation

Dissemination of NDM-Enterobacteriaceae

NDM-1

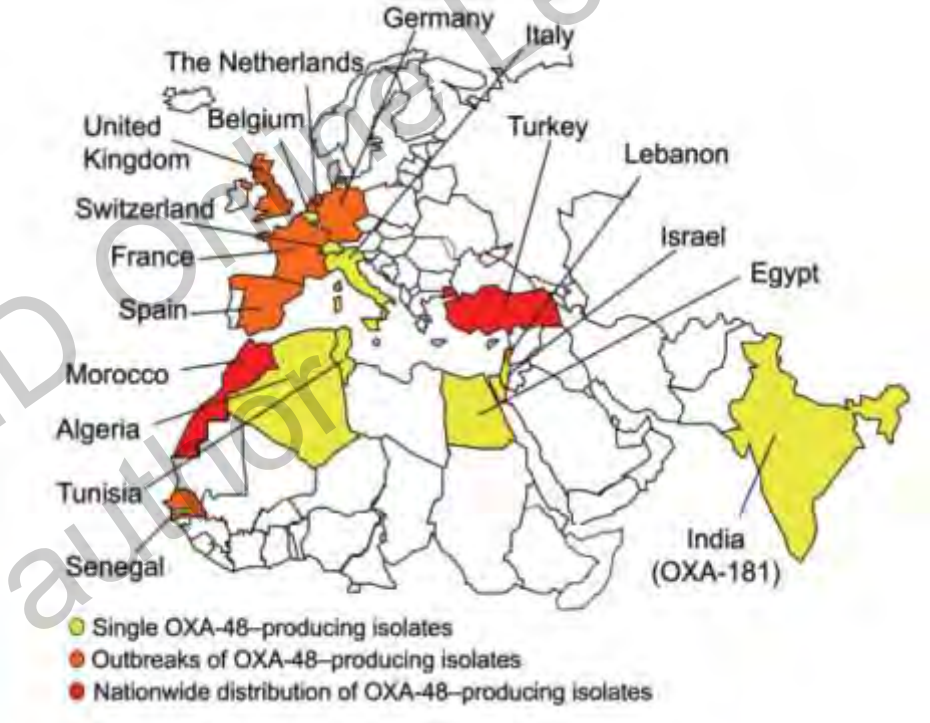


Rolain et al. Clin Microbiol Infect 2010;16:1699-701
Struelens et al. Eurosurveillance 2010; 15 18 nov

Carbapenemase producing Enterobacteriaceae

OXA-48

- First identified in *K. pneumoniae* in Istanbul (Turkey) in 2003
- Extensively reported as a source of *K. pneumoniae* nosocomial outbreaks
- Well disseminated in the Mediterranean area and in western EU countries (*cross-border dissemination*)



Nordmann et al. Emerging Infect Dis 2011; 17:1791-8; Cantón et al. Clin Microbiol Infect 2012; 18:413-31

OXA-48 and Enterobacteriaceae clones

- **Polyclonal structure**
  - different clones in different Enterobacteriaceae species, including high-risk clones and non-widespread clones

Poirel et al. J Antimicrob Chemother 2012;67:1597-606
Potron et al. Euro Surveill 2013; 18(31) doi:pii: 20549

- Dispersion of **specific clones**: ST395, ST101 *K. pneumoniae*
  - hospital outbreaks in different countries
  - spread in the community

Potron et al. Clin Microbiol Infect 2011; 17:E24-6
Pitart et al. Antimicrob Agenst Chemother 2011; 55: 4398-401

- Emergence **in widespread clones *E. coli*** O25b:H4 ST131
  - Ireland, UK
  - absence of other β-lactamases (ESBLs, OXA, …)

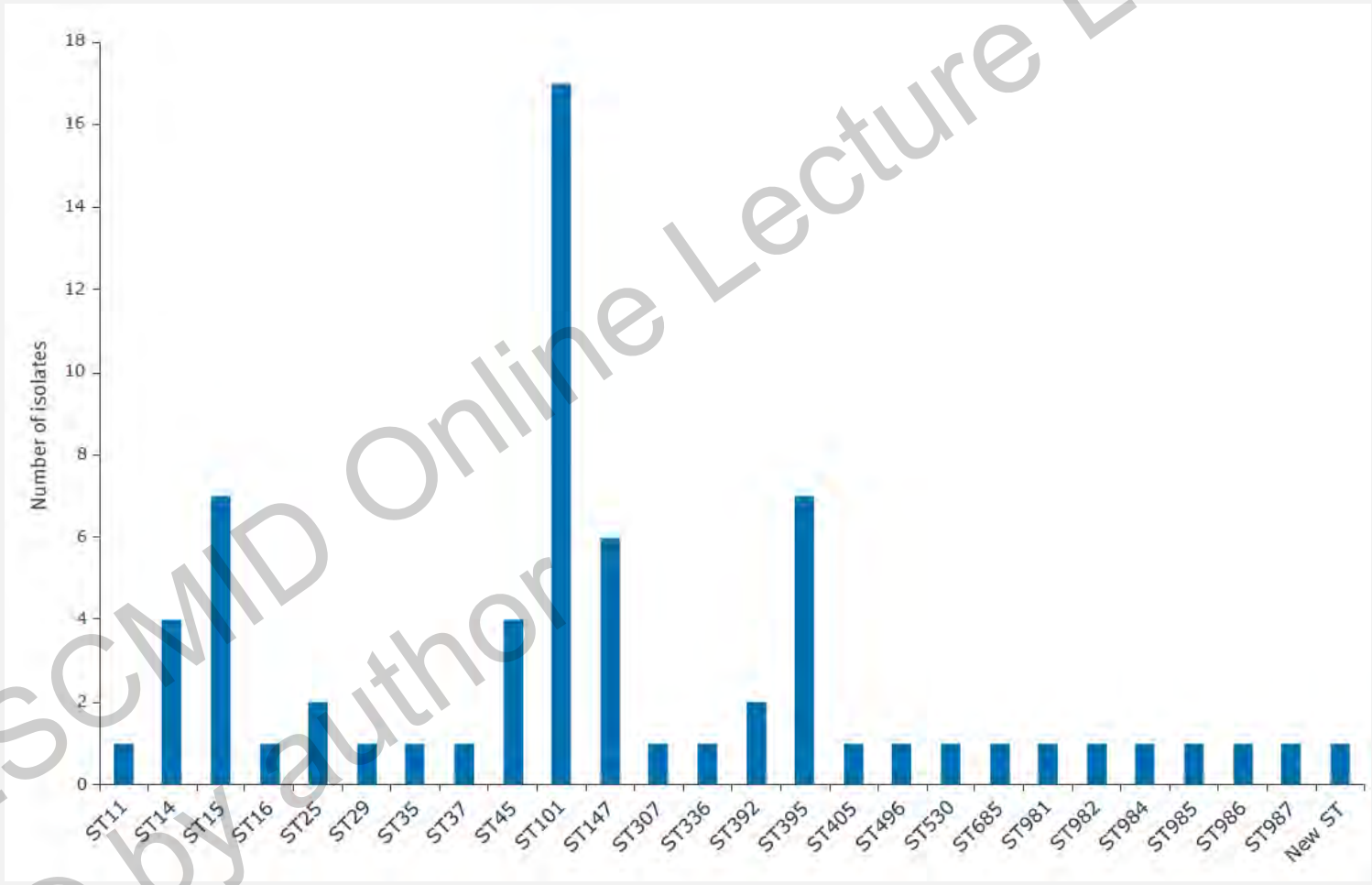
Morris et al. Antimicrob Agents Chemither 2012; 56:4030-1
Dimou et al. J Antimicrob Chemothr 2012; 67:1660-5

- **Cross border dissemination** from endemic areas

Cantón et al. Clin Microbiol Infect 2012; 18:413-31

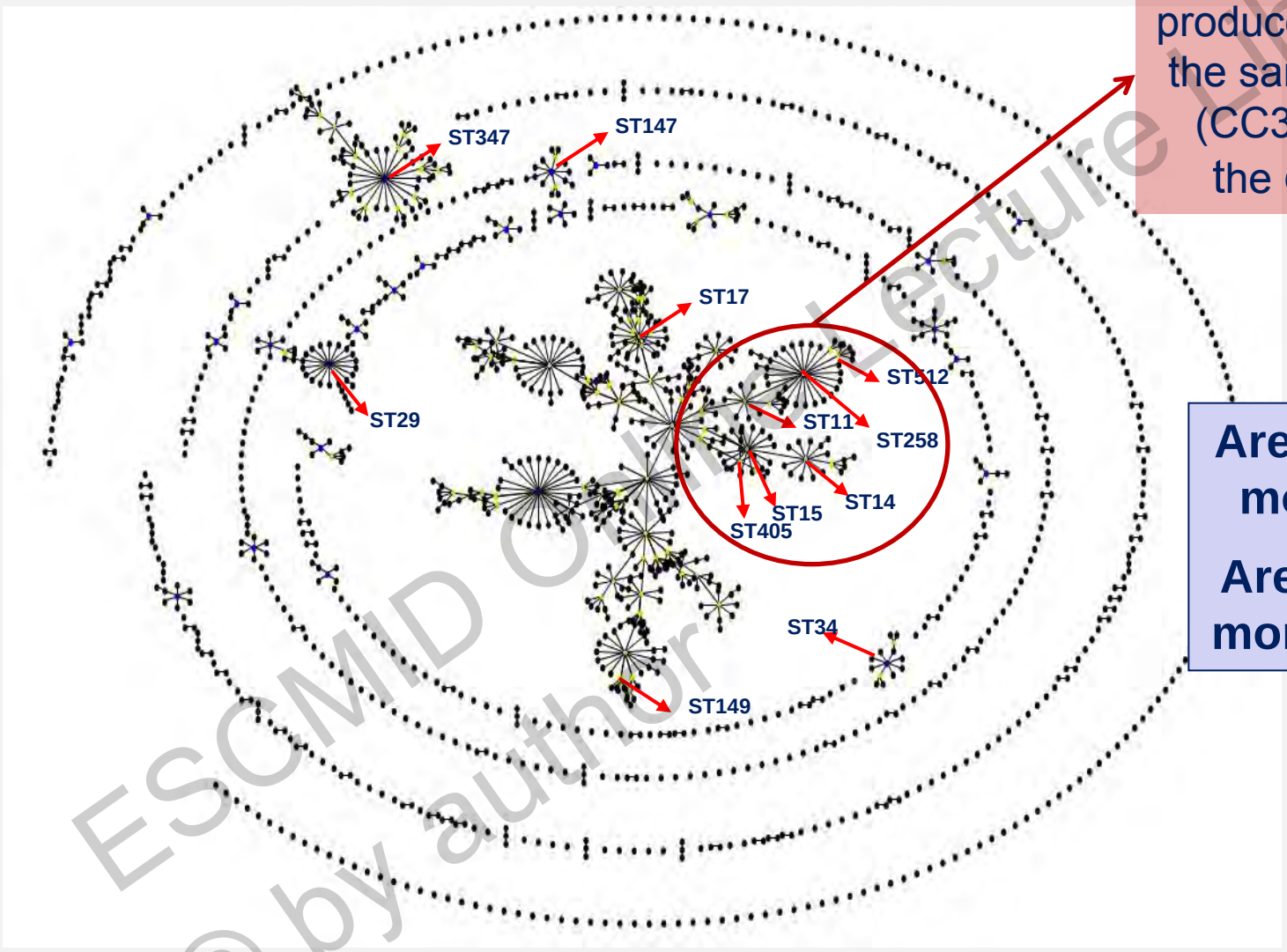
OXA-48 and Enterobacteriaceae clones

- Polyclonal struture with over-representation of specific clones



Potron et al. Euro Surveill 2013; 18(31). pii: 20549

Klebsiella pneumoniae population snapshot



Most carbapenemase producers are clustered in the same clonal complex (CC37) irrespective of the carbapenamase

Are these clones more virulent?

Are these clones more persistent?

http://www.pasteur.fr/recherche/genopole/PF8/mlst/ (last accessed May 8th , 2014)

Carbapenemase producing *K. pneumoniae*

Are these clones producing carapenemases more virulent?

- Most studies has been performed with KPC-producers
  - No specific virulence factors associated with these clones
  - Low impact of carbapenemase expression on virulence [1,2]

- In general, low virulence of KPC-isolates in
  - mouse lethality model due to the absence of known virulence factors (K1, K2, and K5 capsular polysaccharides, *rmpA* aerobactin)[3]
  - nematode (*Caenorhabditis elegans*) killing assay due to the absence of siderophores genes[4]

- Higher virulence of ST258 and its single (ST11) and double (ST277) locus variants than non-ST258 clones (ST377, ST378)[4]

[1]Nordmann et al. LID 2009; 9:228-36; [2]Siu et al. MDR 2012; 18:380-4
[3]Siu et al. MDR 2012; 380-[4]Lavigne et al. Plos One 2013; 8:e67847

Carbapenemase producing *K. pneumoniae*

Are these clones producing cabapenemases more virulent?

- Lower mortality of KPC-(+) vs KPC-(-) blood isolates in the *Galleria mellonella* insect model but discrepant with clinical results[1]

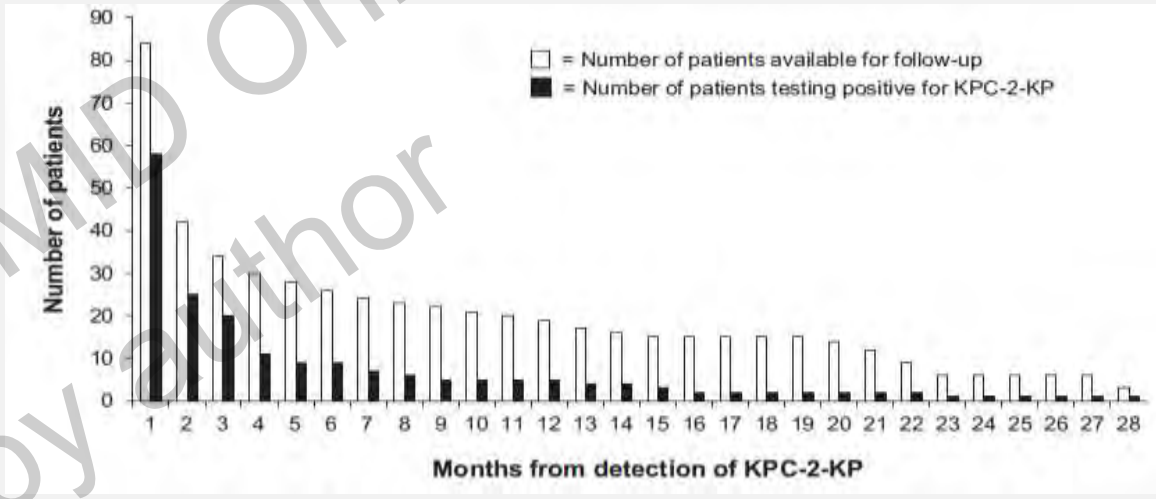
- High susceptibility of a *bla*$_{KPC-2}$ InCFIIk-ST258 strain circulating in Greece to serum killing and rapidly phagocytosed[2]
- ST258 strains carrying *bla*$_{KPC-3}$ are less virulent than those with *bla*$_{KPC-2}$[3]

[1]MaLaughlin et al. BMC Infec Dis 2014; 14:31; [2]Tzouvelekis et al. AAC 2013 57:5144-46;
[3]Diago-Navarro et al. JID 2014; Mar 14 [Epub ahead of print]

Carbapenemase producing *K. pneumoniae*

Are these clones producing carbapenemases more persistent?

- Only 10% of KPC-ST258 colonized patients develops infections[1,2]
- Risk factor of infection: previous colonization[3]
- Prolonged in patient from LTCF[4]
- The majority of patient might spontaneously decolonized within 6 moths after hospital discharge[5]

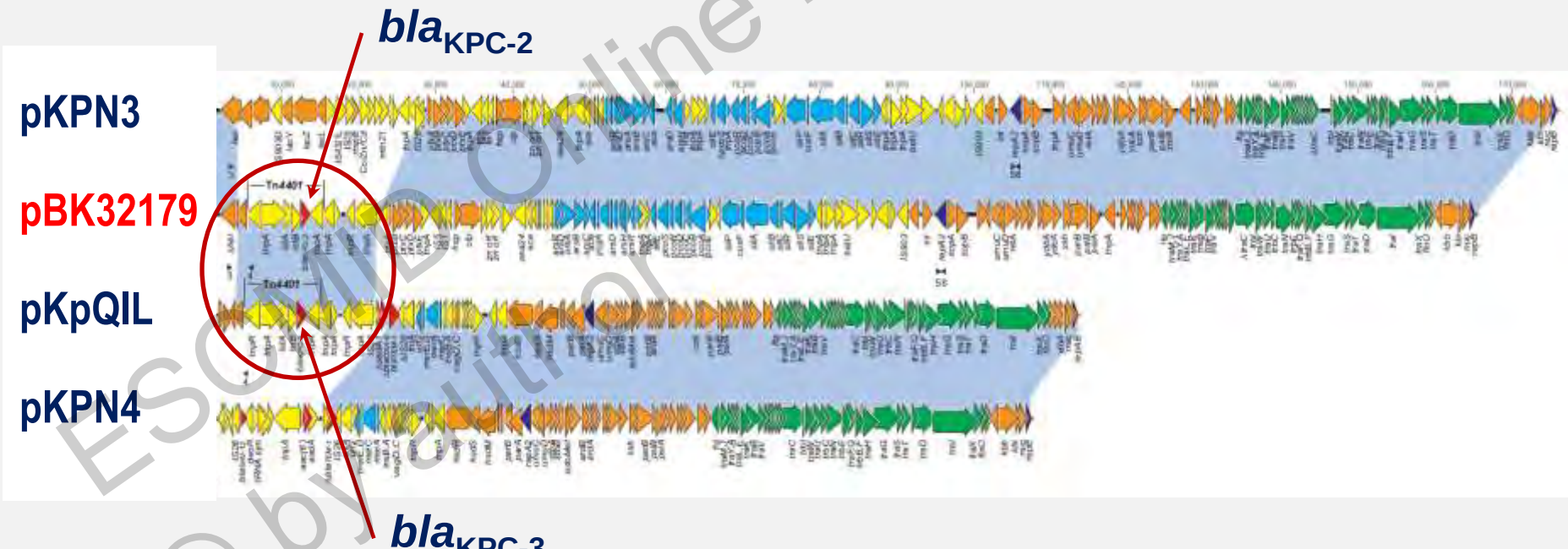


[1]Borer et al. AJIC 2012; 40:421-5; [2]Schechner et al. CMI 2013; 19:451-6; [3]Gasink et al ICHE 2009; 30: 1180-5; [4]Feldman et al. Clin Microbiol Infect 2012; 19:E190-6; [5]Lübbert et al. Am J Infect Control 2014; 42:376-80

bla$_{KPC}$ genes and plasmids

Are these traits associated with plasmids?

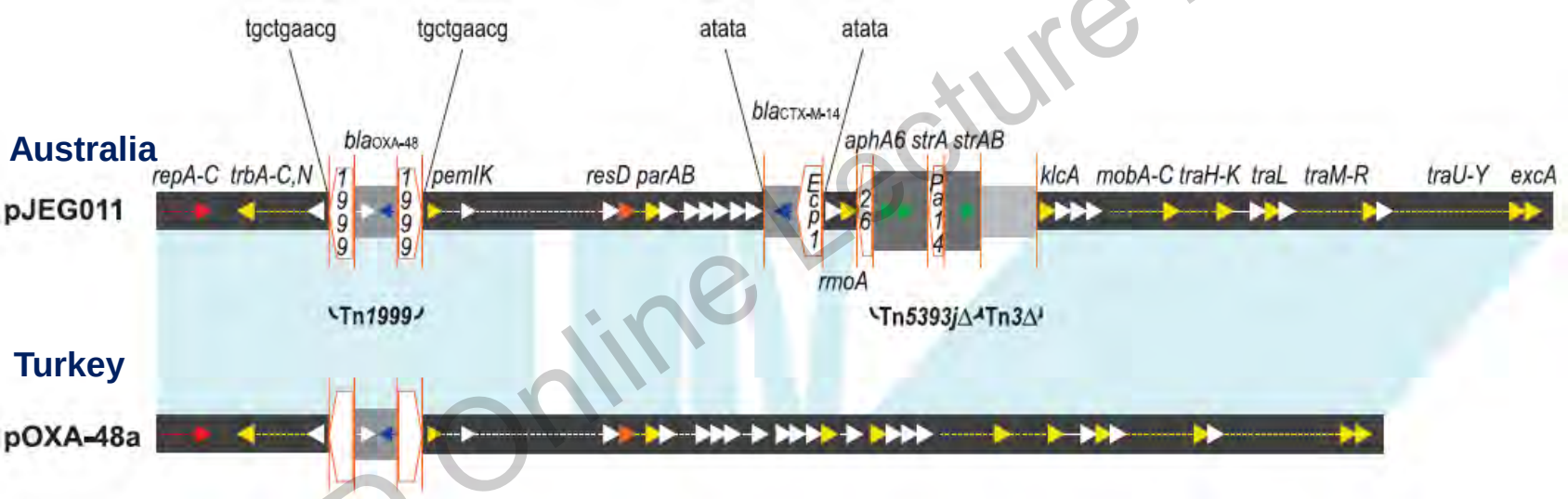
- *bla*$_{KPC}$ in highly transferable plasmids of different sizes
  - mostly common scaffolds and derived well-known plasmids from *K. pneumoniae* (KPN3 and KPN4)
  - different incompatibility groups (FII, L/M, N, A/C, R, X, ColE1, I2, …)



Leavitt et al. A AC 2010; 54:4493-6; García-Fernández et al. AAC 2012;56:2143-5
Cheng et at. AAC 2013;1542-5; Cheng et al. AAC 2013; 29 July

bla$_{OXA-48}$ gene and plasmids

- Dissemination mainly associated with **IncL/M** plasmids (Turkey, Libano, Australia, Spain, Belgium, …) but also with IncA/C and IncF



Poirel et al. AAC 2012; 56.559-62; Espedido Plos One 2013; 8:e59920

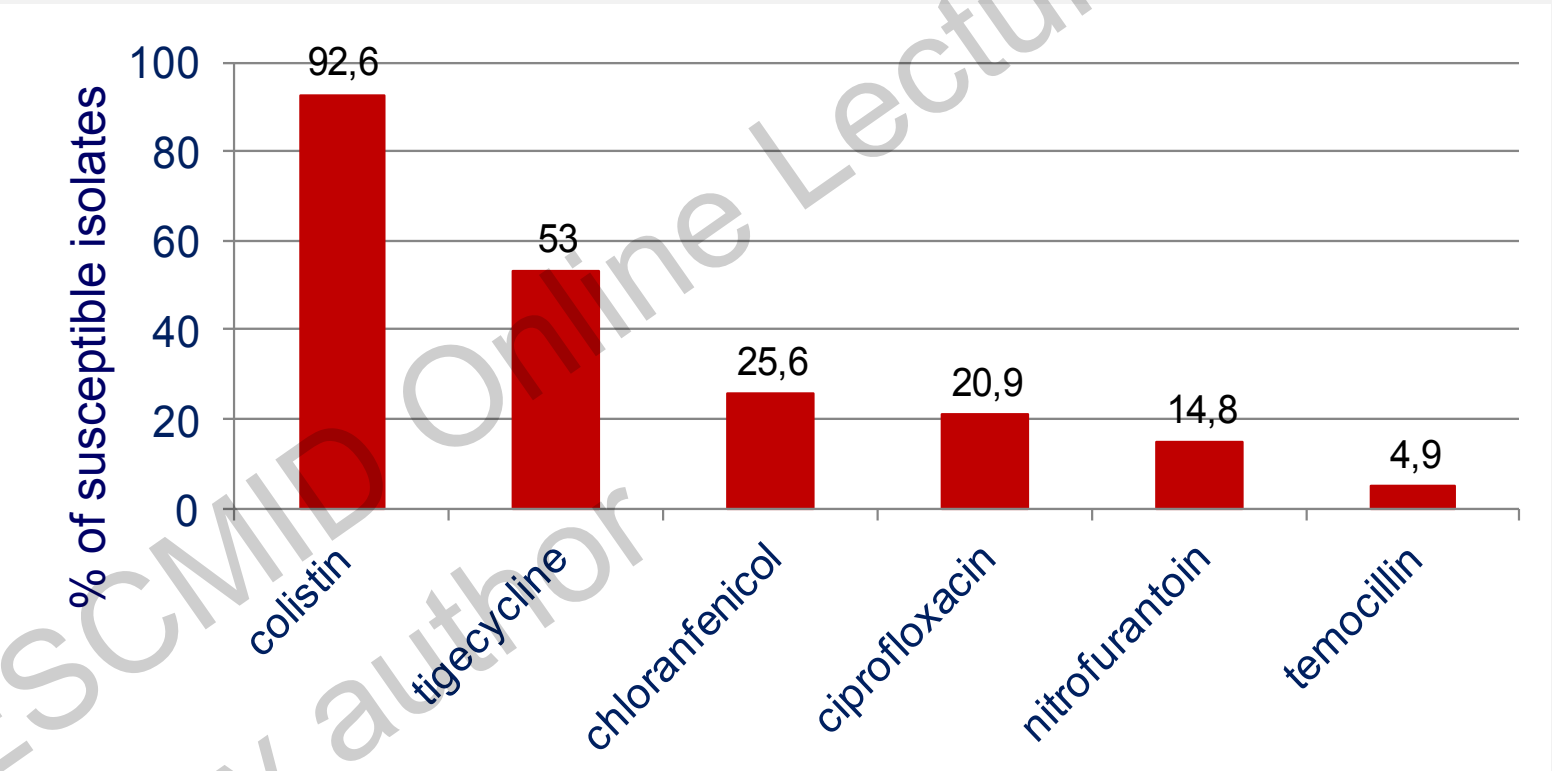
- the *bla*$_{OXA-48}$ gene within in a composite transposon, Tn1999, inserted into the *tir* gene, encoding a transfer inhibition protein
  - increased transfer frequency

Potron et al. Antimicrob Agents Chemother 2014; 58:467-71

Carbapenemase producing isolates

Co-resistance

- Antibiotic susceptibility of carbapenemase producing isolates (n=81)



Livermore et al. Int J Antimicrob Agents 2011;37:415-9

Why are some carbapenemases successful?

Conclussions

- Resemblance with ESBL producers (emergence/dissemination)
- Dispersion associated with clonal (high-risk clones) and polyclonal situations
- Associated carbapenemase producing high-risk clones are
  - less virulent than susceptible isolates
  - high capacity to colonize and persist over time
- Presence of *bla*$_{\text{carbapenemase}}$ genes in ancient well adapted plasmids with highly transferable activity
- Co-resistance might play a role on selection and persistence

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FIS 040162; REIPI C03/14, CIBER-ESP

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SAF 2003-09285

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SEVENTH FRAMEWORK PROGRAMME

trocar TRANSLATIONAL RESEARCH ON COMBATING ANTIMICROBIAL RESISTANCE

R-GNOSIS RESISTANCE IN GRAM-NEGATIVE ORGANISMS: STUDYING INTERVENTION STRATEGIES

24th ECCMID Barcelona, Spain 10 – 13 May 2014
ESCMID EUROPEAN SOCIETY OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES

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