ORDINE PROVINCIALE
DEI MEDICI CHIRURGHI E
DEGLI ODONTOIATRI
DI VENEZIA

FONDAZIONE ARS MEDICA
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DELLA PROVINCIA DI VENEZIA

REGIONE DEL VENETO
ULSS3
SERENISSIMA

UOMINI, ANIMALI E ANTIBIOTICI: UN TRIANGOLO "PERICOLOSO"

GIOVEDÌ 9 MARZO 2017

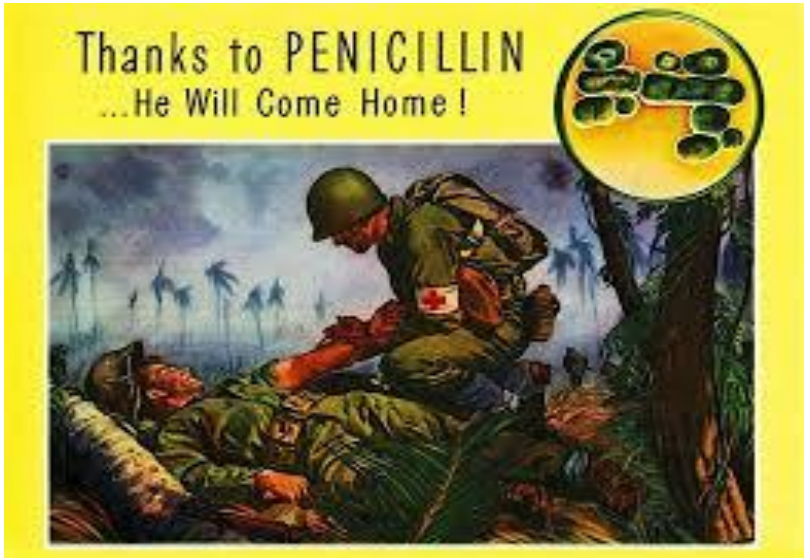
Uomo, batteri e antibiotici: una sfida che dura da 75 anni... Cambia la scena, cambierà anche il finale?

Stefano Grandesso
UOC Laboratorio Analisi Chimico-cliniche e microbiologia
Ospedale dell'Angelo - Mestre

L'inizio della sfida

1929

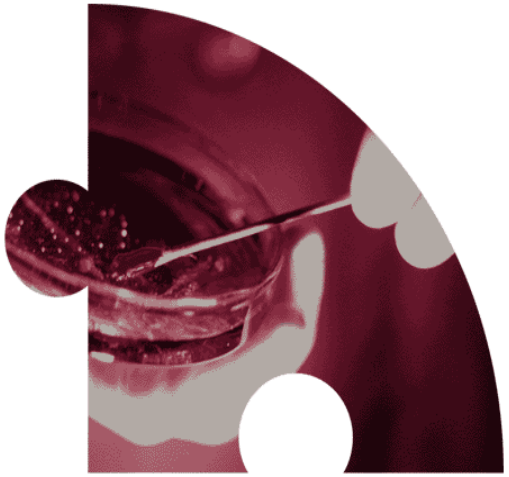
1943



Key Prevention Strategies

- Prevent infection
- Diagnose and treat infection effectively
- Use antimicrobials wisely
- Prevent transmission

Clinicians hold the solution!



Diagnose & Treat Infection Effectively

Step 3: Target the pathogen

Fact:

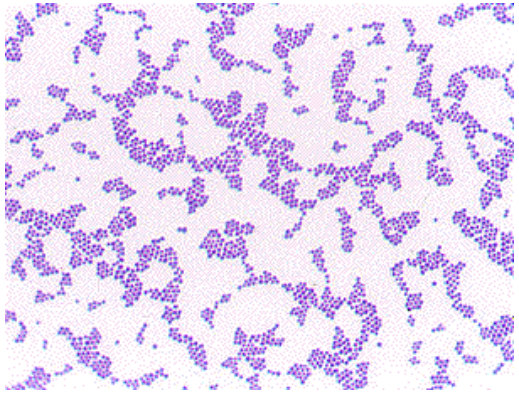
Appropriate antimicrobial therapy (correct regimen, timing, dosage, route, and duration) saves lives.

Use Antimicrobials Wisely

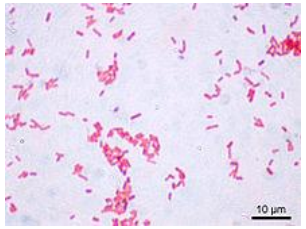
Step 8: Treat infection, not colonization

Fact: A major cause of antimicrobial overuse is “treatment” of colonization.

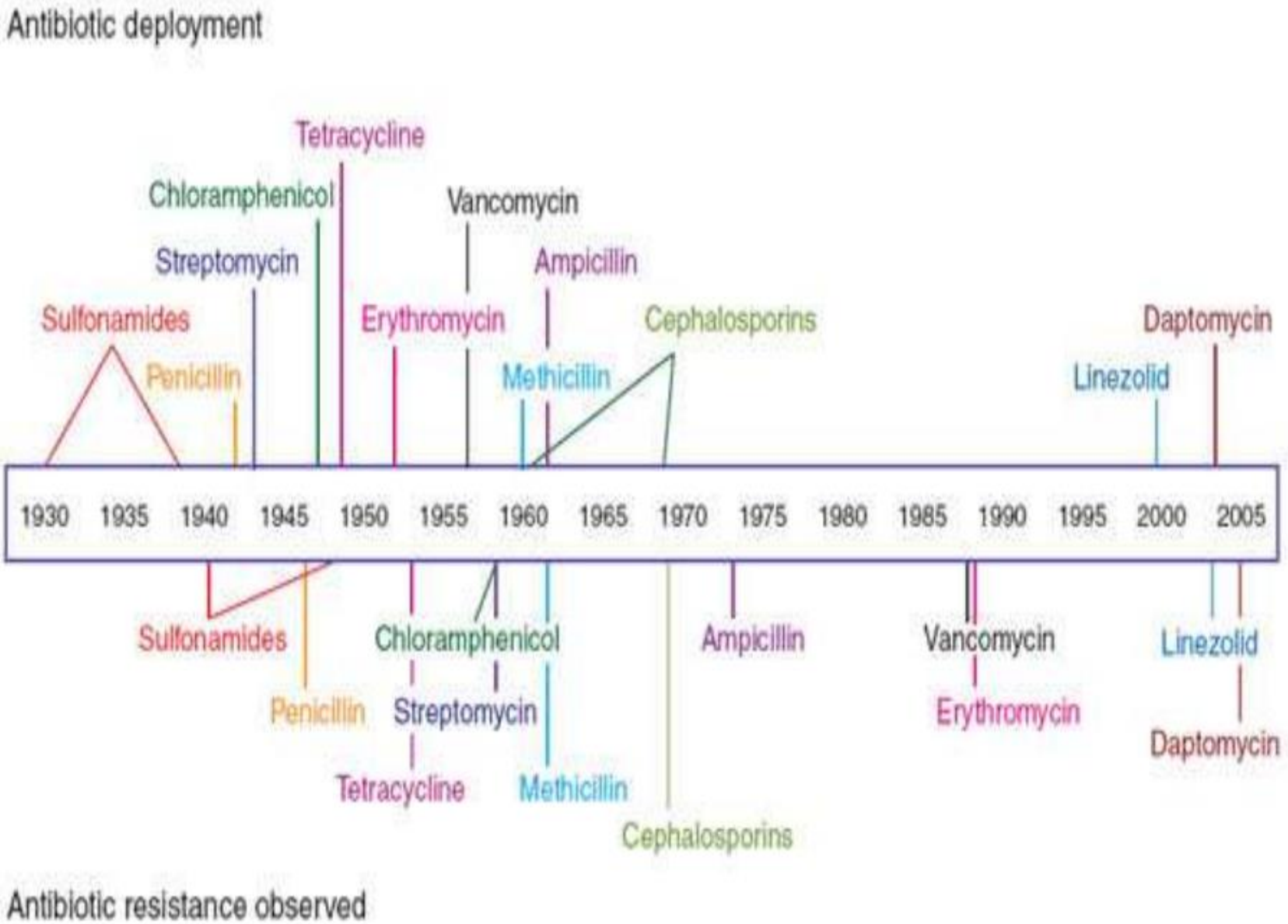
L’inizio della sfida
Primo tempo
I Gram – positivi



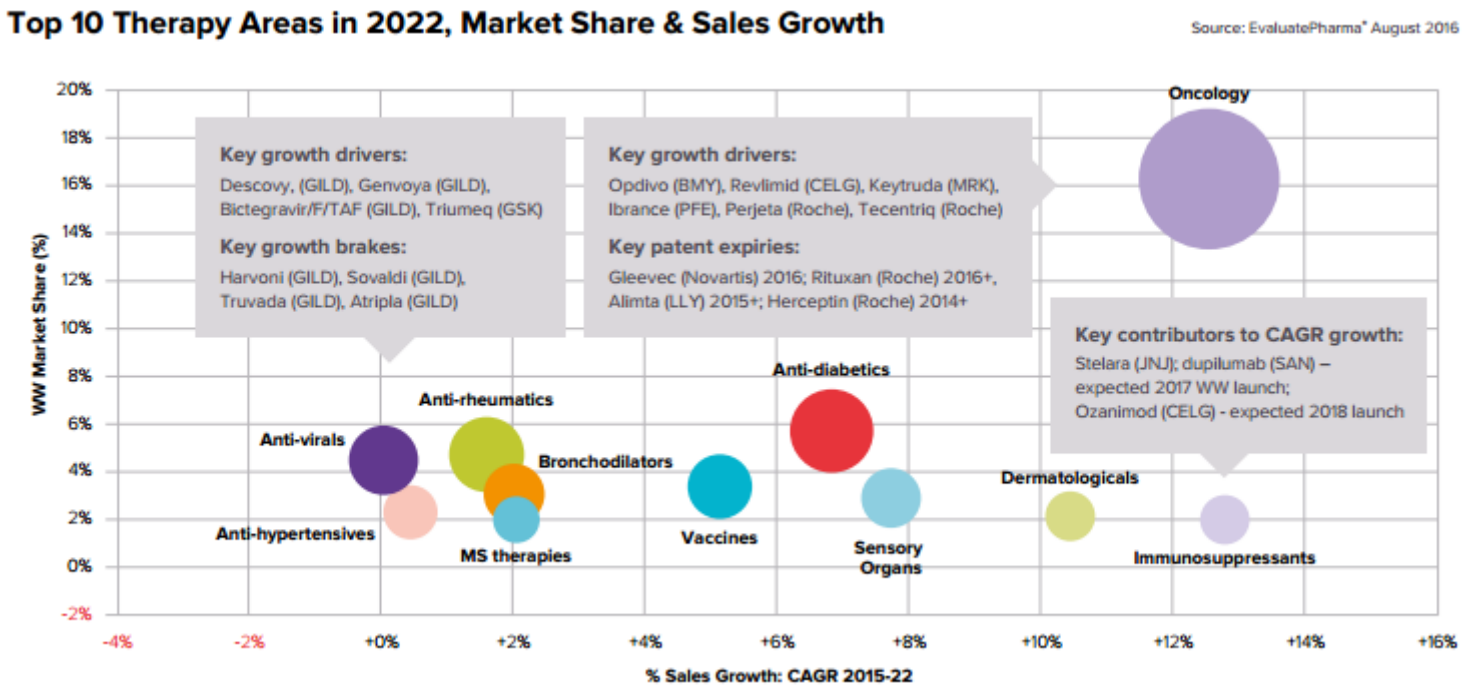
e … i Gram – negativi



Il fenomeno "Resistenza"



E Big Pharma che fa?



Da qui al 2022 … l'industria farmaceutica

Worldwide Prescription Drug & OTC Sales by EvaluatePharma®
Therapy Area (2015 & 2022): Top 15 Categories & Total Market

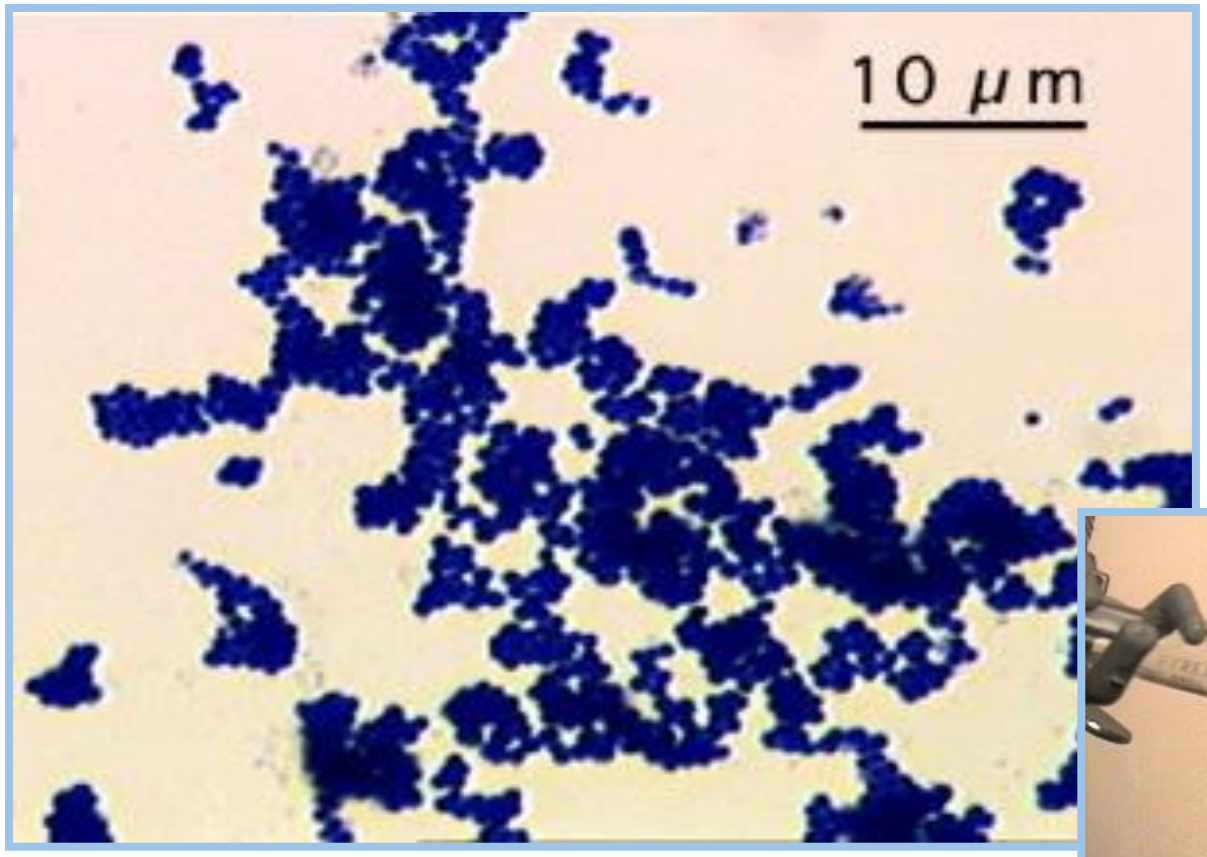
Source: EvaluatePharma® August 2016

Rank	Therapy Area	WW Sales ($bn) 2015	WW Sales ($bn) 2022	CAGR % Growth	WW Market Share 2015	WW Market Share 2022	WW Market Share Chg. (+/-)	Rank Chg. (+/-)
1.	Oncology	83.2	190.0	+12.5%	10.7%	16.3%	+5.6pp	+0
2.	Anti-diabetics	41.7	66.1	+6.8%	5.4%	5.7%	+0.3pp	+2
3.	Anti-rheumatics	48.8	54.5	+1.6%	6.3%	4.7%	-1.6pp	+0
4.	Anti-virals	50.7	50.9	+0.0%	6.5%	4.4%	-2.2pp	-2
5.	Vaccines	27.6	39.0	+5.1%	3.5%	3.4%	-0.2pp	+1
6.	Bronchodilators	30.2	34.7	+2.0%	3.9%	3.0%	-0.9pp	-1
7.	Sensory Organs	19.8	33.3	+7.7%	2.6%	2.9%	+0.3pp	+2
8.	Anti-hypertensives	25.7	26.5	+0.4%	3.3%	2.3%	-1.0pp	-1
9.	Dermatologicals	12.1	24.3	+10.4%	1.6%	2.1%	+0.5pp	+3
10.	MS therapies	20.2	23.2	+2.0%	2.6%	2.0%	-0.6pp	-2

Source: EvaluatePharma® August 2016

Rank	Therapy Area	WW Sales ($bn) 2015	WW Sales ($bn) 2022	CAGR % Growth	WW Market Share 2015	WW Market Share 2022	WW Market Share Chg. (+/-)	Rank Chg. (+/-)
11.	Immunosuppressants	9.5	22.1	+12.8%	1.2%	1.9%	+0.7pp	+6
12.	Anti-coagulants	11.9	20.3	+8.0%	1.5%	1.7%	+0.2pp	+1
13.	Anti-hyperlipidaemics	15.4	18.2	+2.4%	2.0%	1.6%	-0.4pp	-3
14.	Anti-bacterials	12.4	16.9	+4.5%	1.6%	1.4%	-0.2pp	-3
15.	Anti-fibrinolytics	11.1	15.8	+5.2%	1.4%	1.4%	-0.1pp	+0
	Top 15	420	636	+6.1%	54.1%	54.6%	+0.5pp	
	Other	356	529	+5.8%	45.9%	45.4%	-0.5pp	
	Total WW Prescription & OTC Sales	**776**	**1,164**	+6.0%	100.0%	100.0%		
	Total 'Prescription & OTC Sales' includes:							
	WW Generic Sales	**73.1**	**114.8**	+6.7%	9.4%	9.9%	+0.4%	
	OTC Pharmaceuticals	**34.7**	**43.5**	+3.3%	4.5%	3.7%	-0.7%	

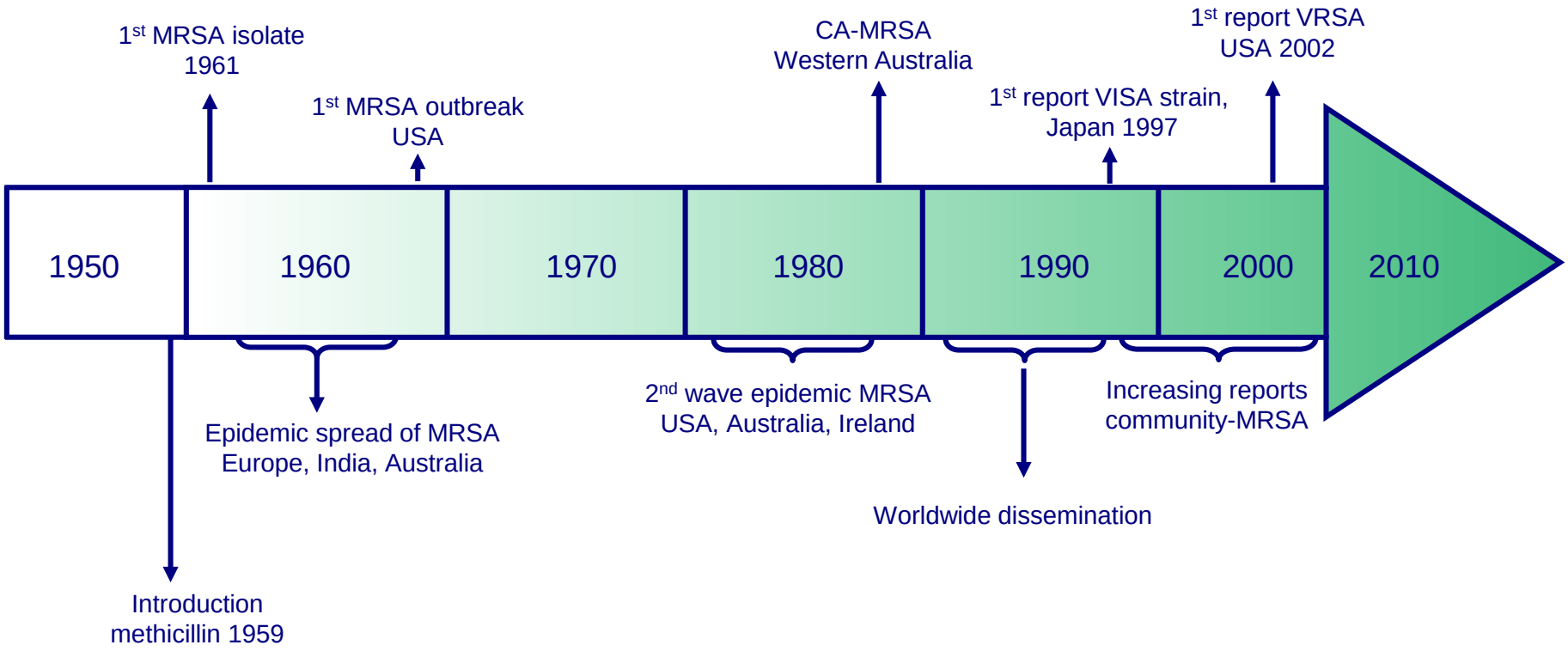
Staphylococcus aureus



MRSA

Staphylococcus aureus meticillino-resistente

The emergence of MRSA



CA-MRSA = community acquired MRSA;
VRSA = vancomycin-resistant *Staphylococcus aureus*;
VSSA = vancomycin-sensitive *S. aureus*.

Adaped from Bartlett JG. The New York Course 2007: Developments in infectious diseases—community-acquired methicillin-resistant *Staphylococcus aureus* infections. Available at: www.medscape.com/viewarticle/562607 (accessed March 2010)

MSSA

OXA = forte attività

VANCO = media attività

MRSA

OXA = non attiva

VANCO = forte attività

S. aureus Oxacillino-Resistente
Incidenza Globale

- USA 7169 (34.2%)
- Canada 1410 (5.7%)
- Brasile 814 (33.7%)
- Argentina 424 (42.7%)
- Francia 718 (21.4%)
- Germania 347 (4.9%)
- Portogallo 318 (54.4%)
- Spagna 352 (19.3%)
- **Italia 297 (50.5%)**
- Giappone 289 (71.6%)
- Hong Kong 172 (73.8%)
- Australia 606 (23.6%)

Progetto Sentry (BMS) 1997-1999
Clin Infect Dis 2001; 32 (Suppl.2): S114

MRSA colonisation increases the risk of subsequent infection

- Nares samples performed at ICU admission (n = 416)
  - 7.2% colonised with MRSA
  - 16.1% colonised with MSSA
- MRSA colonisation was strongly associated with the development of subsequent MRSA infection (aOR, 7.6 [95% CI, 2.48-23.2]; p <0.001)

Staphylococcus aureus colonisation on admission	MRSA infection rates (%)
MRSA (n=30)	**20**
MSSA (n=67)	**0**
No MRSA colonisation (n=386)	**2.6 (*p* < 0.001)**

Patients admitted to ICUs in the Birmingham Veterans Affairs Medical Center, AL, US, Jan–Dec 2005.

Patel M, *et al*. *Infect Control Hosp Epidemiol* 2008; 29:503–9.

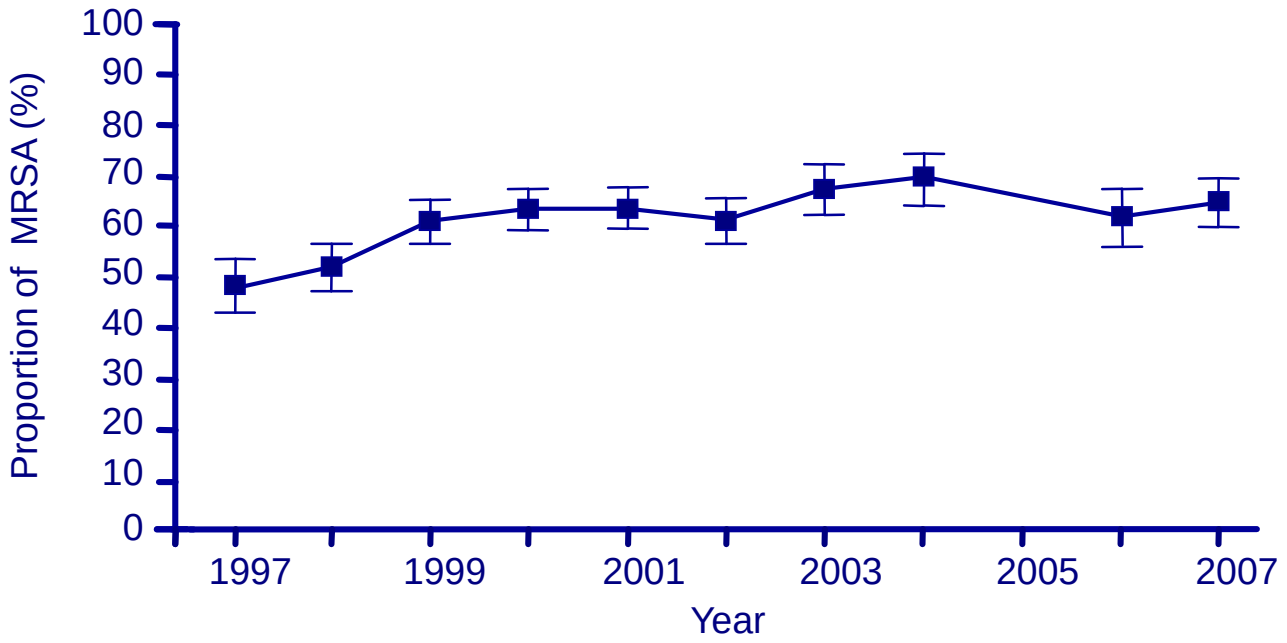
Prevalence and significance of MRSA

- MRSA is currently the most commonly identified antibiotic-resistant pathogen in hospitals in many parts of the world, including
  - Europe
  - The Americas
  - North Africa
  - The Middle- and Far-East
- MRSA infections are associated with:
  - Prolonged hospital stay
  - Higher mortality rates

European Antimicrobial Resistance Surveillance System (EARSS) Report 2008.

MRSA among ICU patients in the USA (1997–2007)

- In a study of central line-associated bacteraemia (CLABSI) in US intensive care units the proportion of MRSA increased from 48% in 1997 to 65% in 2007



Number of ICUs:	491	514	552	544	520	506	498	478	n/a	488	1039

Burton DC, *et al. JAMA* 2009; 301:727–30

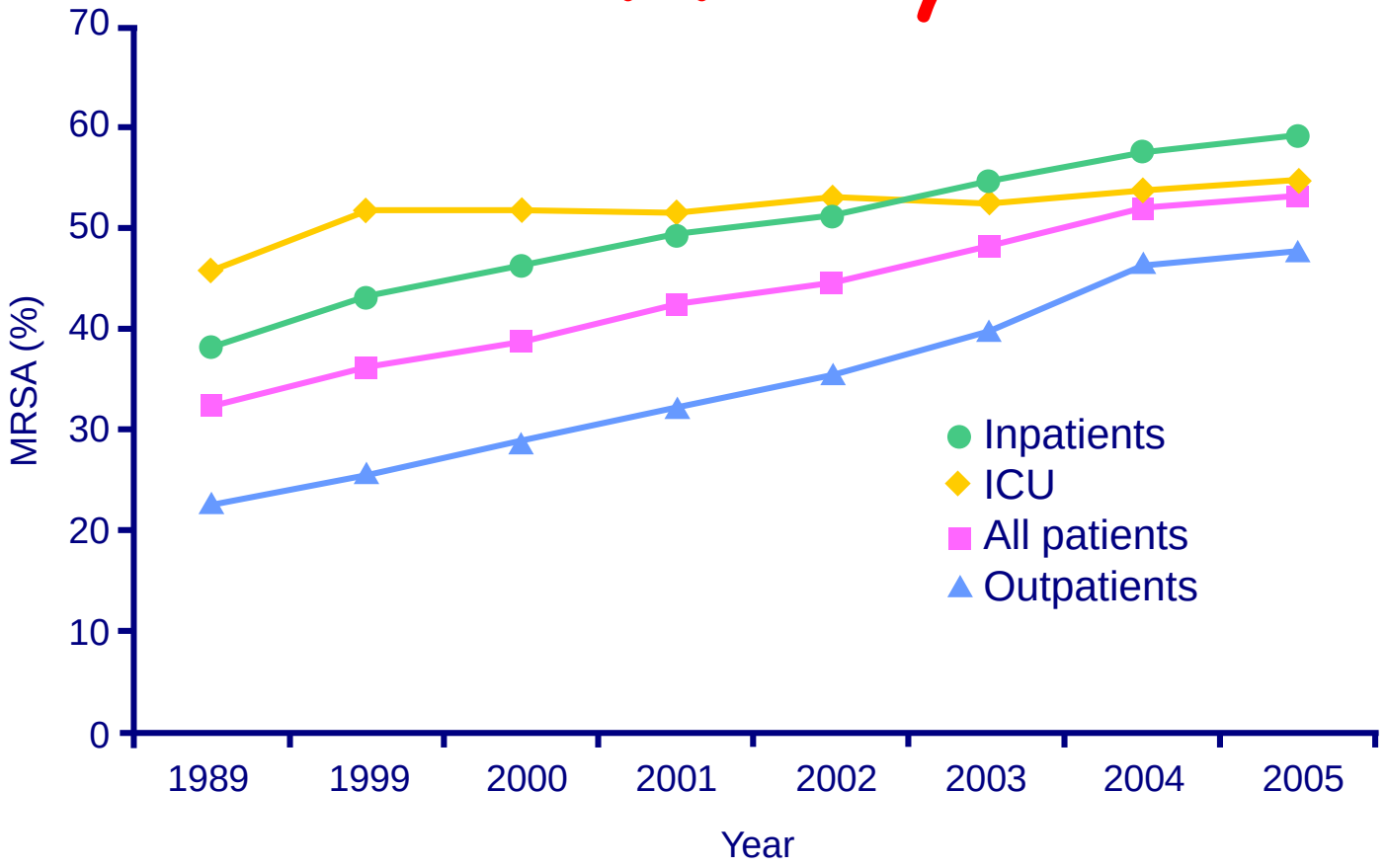
Increased hospital costs for treating bloodstream infections caused by MRSA compared with MSSA

Authors of study	Study dates	Costs assessed	Increase in costs (US $)	Increase in costs (Euros*)
Cosgrove, *et al.*	1997–2000	Hospital charges	7212	5548
McHugh and Riley	1997–1999	Cost per patient day of hospitalisation	3805	2927
Lodise and McKinnon	1999–2001	Adjusted mean cost of hospitalisation	9909	7623
Reed, *et al.*	1996–2001	Mean adjusted initial hospitalisation costs	7273	5595
		Adjusted costs at 12 weeks	8164	6280

*$1.3 = 1.0 Euros.

Cosgrove SE, *et al. Infect Control Hosp Epidemiol* 2006; 42 (Suppl. 2):S82–9; Lodise TP & McKinnon PS. *Diagn Microbiol Infect Dis* 2005; 52:113–22; McHugh CG & Riley LW. *Infect Control Hosp Epidemiol* 2004; 25:425–30; Reed SD, *et al. Infect Control Hosp Epidemiol* 2005; 26:175–83.

MRSA is an important cause of infection in the hospital and in the community



Staphylococcus aureus isolates from 300 clinical laboratories across the USA

Styers D, *et al. Ann Clin Microbiol Antimicrob* 2006, 5:2.

Populations at increased risk of CA-MRSA

- Children < 2 years
- Athletes (mainly contact-sport participants)
- Injection drug users
- Men who have sex with men
- Military personnel
- Inmates of correctional facilities, residential homes or shelters
- Vets, pet owners and pig farmers
- Patients with post-flu-like illness and/or severe pneumonia
- Patients with concurrent skin and soft tissue infection
- History of colonisation or recent infection with CA-MRSA
- History of antibiotic consumption in the previous year, particularly quinolones or macrolides

Nathwani D, *et al. J Antimicrobial Chemother* 2008; 61:976–94.

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Weekly

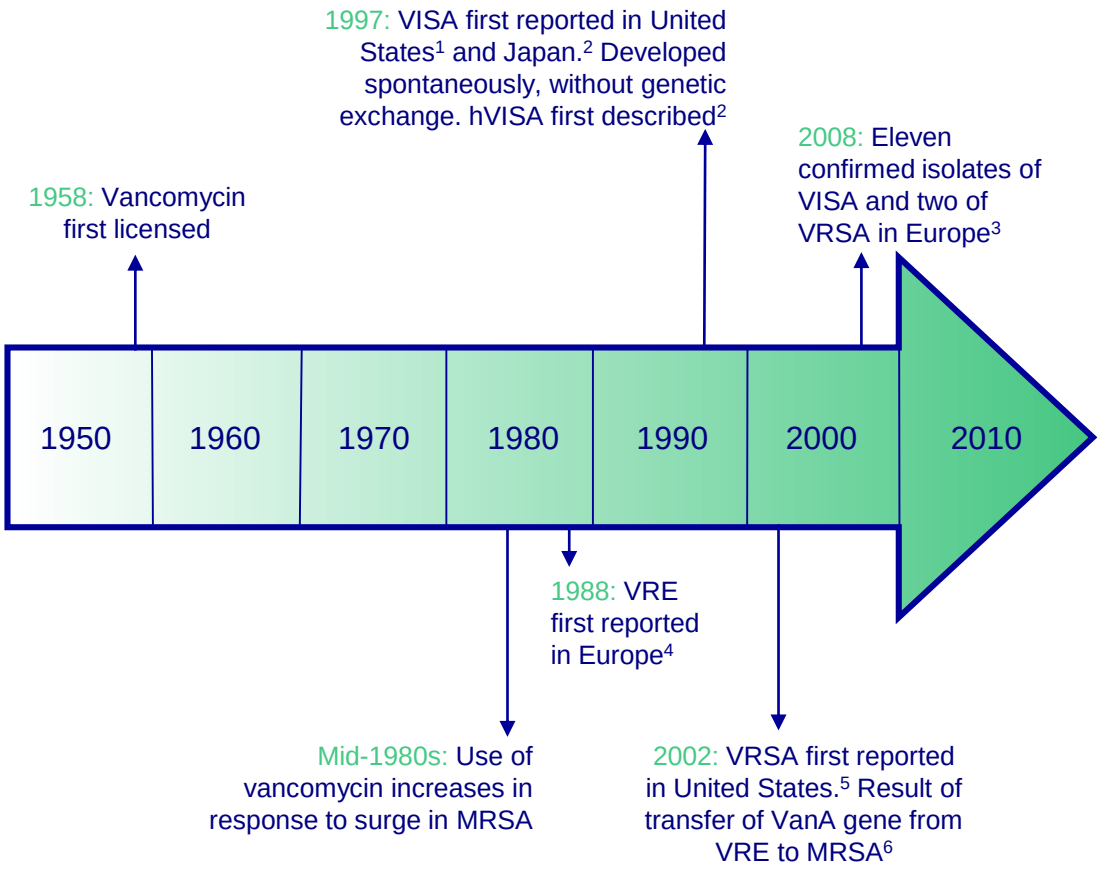
October 11, 2002 / 51(40);902

Public Health Dispatch: Vancomycin-Resistant *Staphylococcus aureus* --- Pennsylvania, 2002

Please note: The text of this report has been corrected and does not correspond to the official electronic PDF version. An erratum has been published; to view the erratum, please click here.

Staphylococcus aureus is one of the most common causes of hospital- and community-acquired infections (*1,2*). Since the recognition of vancomycin-resistant enterococci in 1988, the emergence of vancomycin-resistant *S. aureus* (VRSA) (minimum inhibitory concentration [MIC] ≥32 μg/mL [*3*]) has been anticipated. The transfer of the genetic element containing the *vanA* vancomycin resistance gene from *Enterococcus faecalis* to *S. aureus* was demonstrated in the laboratory in 1992 (*4*); the first clinical infection with VRSA was reported in July 2002 (*5*). This report describes the second documented clinical isolate of VRSA from a patient.

Reduced susceptibility to vancomycin is compromising the utility of first-line agents in MRSA infections



TODAY:

- Outbreaks of VRE encountered in hospitals in various European countries.[3]
- Reports of VISA increasing; VRSA still rare.[3]
- Increasing reports of hVISA.[7]
- Evidence of association between increasing vancomycin MICs and increased risk of treatment failure.[8]
- hVISA bacteraemia is associated with prolonged bacteraemia duration and increased risk of complications.[9]

MRSA = methicillin-resistant *Staphylococcus aureus*; VISA = vancomycin-intermediate *S. aureus*; hVISA = heterogeneous vancomycin-intermediate *S. aureus*; VRE = vancomycin-resistant enterococci ; VRSA = vancomycin-resistant *S. aureus*.

1. CDC. *MMWR* 1997; 46:765–6; 2. Hiramatsu K, *et al. J Antimicrob Chemother* 1997; 40:565–7; 3. EARSS. EARSS Annual Report, 2008; 4. Uttley AH, *et al. Lancet* 1988; 1:57–8; 5. CDC. *MMWR* 2002; 51:565–7; 6. CDC. www.cdc.gov/ncidod/dhqp/ar_visavrsa_labFAQ.html; 7. Bae IG, *et al. J Infect Dis* 2009;200:1355–66; 8. Lodise TP, *et al. Antimicrob Agents Chemother* 2008; 52:3315–20; 10. Maor Y, *et al. J Infect Dis* 2009; 199:619–24.

Table 1. Comparison of community-associated and health care–associated methicillin-resistant *Staphylococcus aureus* (MRSA).

Characteristic	Community-associated MRSA	Health care–associated MRSA
Susceptibility,[a] drug		
Chloramphenicol	Usually susceptible	Frequently resistant
Clindamycin[b]	Usually susceptible	Frequently resistant
Erythromycin	Usually resistant	Usually resistant
Fluoroquinolone	Geographic variability	Usually resistant
TMP-SMZ	Usually susceptible	Usually susceptible
SCC *mec* type	IV	II
Lineage	USA 300, USA 400	USA 100, USA 200
Toxin-producing	More	Fewer
Panton-Valentine leukocidin–producing	Common	Rare
Health care exposure	Less frequent	More frequent

NOTE. SCC, staphylococcal chromosome cassette; TMP-SMZ, trimethoprim-sulfamethoxazole.

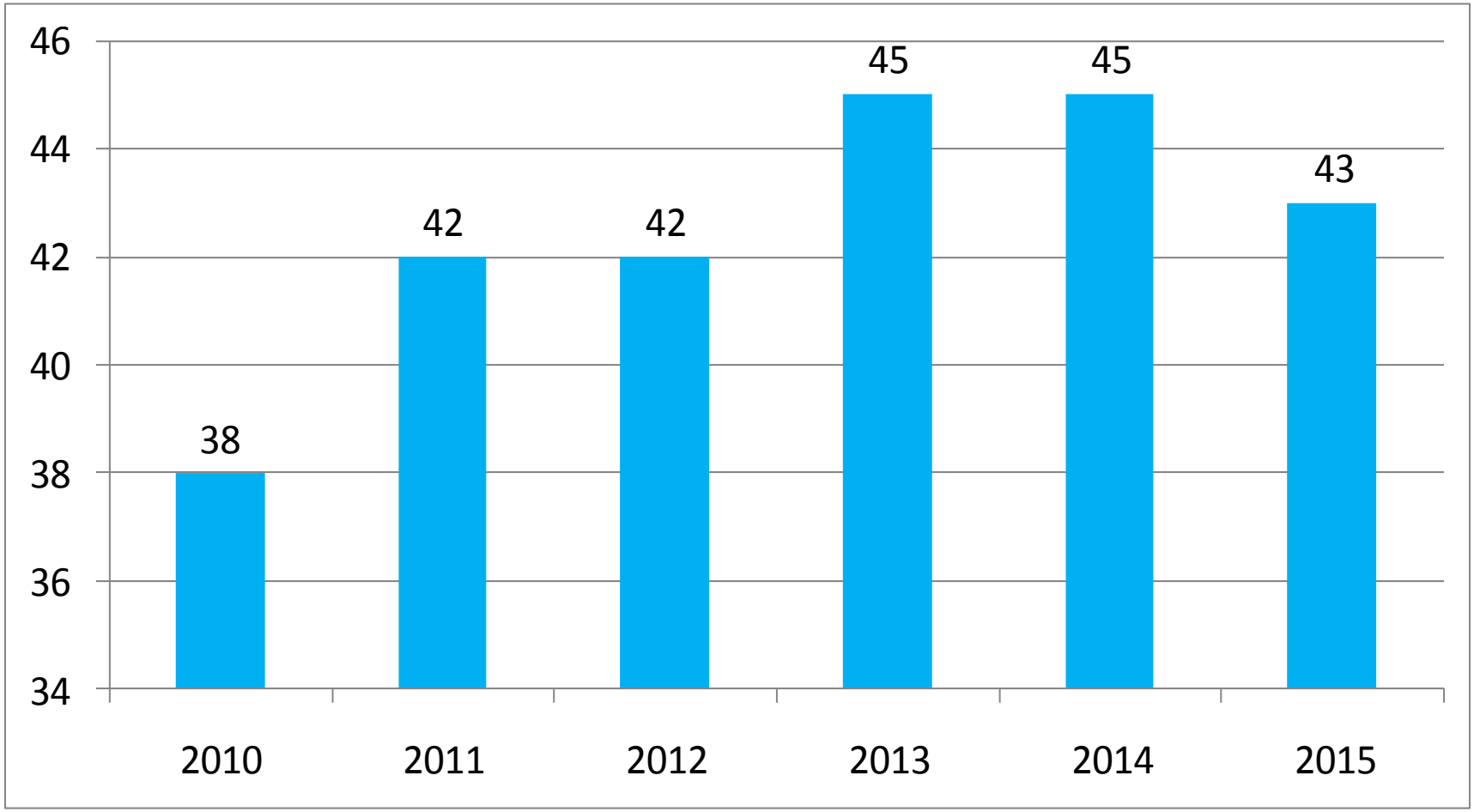
[a] Susceptibility is based on in vitro testing and Clinical and Laboratory Standards Institute break points [2]. A finding of susceptibility does not necessarily make the drug an appropriate treatment choice.

[b] See comment on inducible resistance in the main text.

CID 2005;41:S269-272

MESTRE : % MRSA

Numero di ceppi testati:
2010: 1282
2011: 1462
2012: 1470
2013: 1437
2014: 1931
2015: 2104



	Ceppi Testati	TOT SENSIB	% SENSIB
DAPTOMICINA	7904	7788	98,53
LINEZOLID	7655	7591	99,16
TEICOPLANINA	8652	8444	97,60
TIGECICLINA	7207	7181	99,64
VANCOMICINA	8653	8590	99,27

Staphylococcus aureus e Oxacillino-Resistenza

Impatto clinico rilevante

- **SEMPRE R a tutti i beta lattamici**
  - Penicilline
  - Cefalosporine (ceftarolina …)
  - Carbapenemi
- **FREQUENTE (??) R associata anche ad altre classi di antibiotici**
  - Lincosamidi
  - Macrolidi
  - Fluorochinoloni
- **TALORA R associata anche ad altre classi di antibiotici**
  - Rifampicina
  - Cotrimossazolo
  - Cloramfenicolo
  - Tetracicline
- **POSSIBILI opzioni terapeutiche**
  - Vancomicina (resistente : 2002 - USA)
  - Teicoplanina (resistente : 1990 – USA)
  - Synercid (resistente : 2000 – Taiwan)
  - Linezolid (resistente : 2002 – USA)
  - Tigeciclina (resistente : 2014 – Brasile)
  - Daptomicina (resistente : 2005 – USA)

Vancomicina "MIC creep"

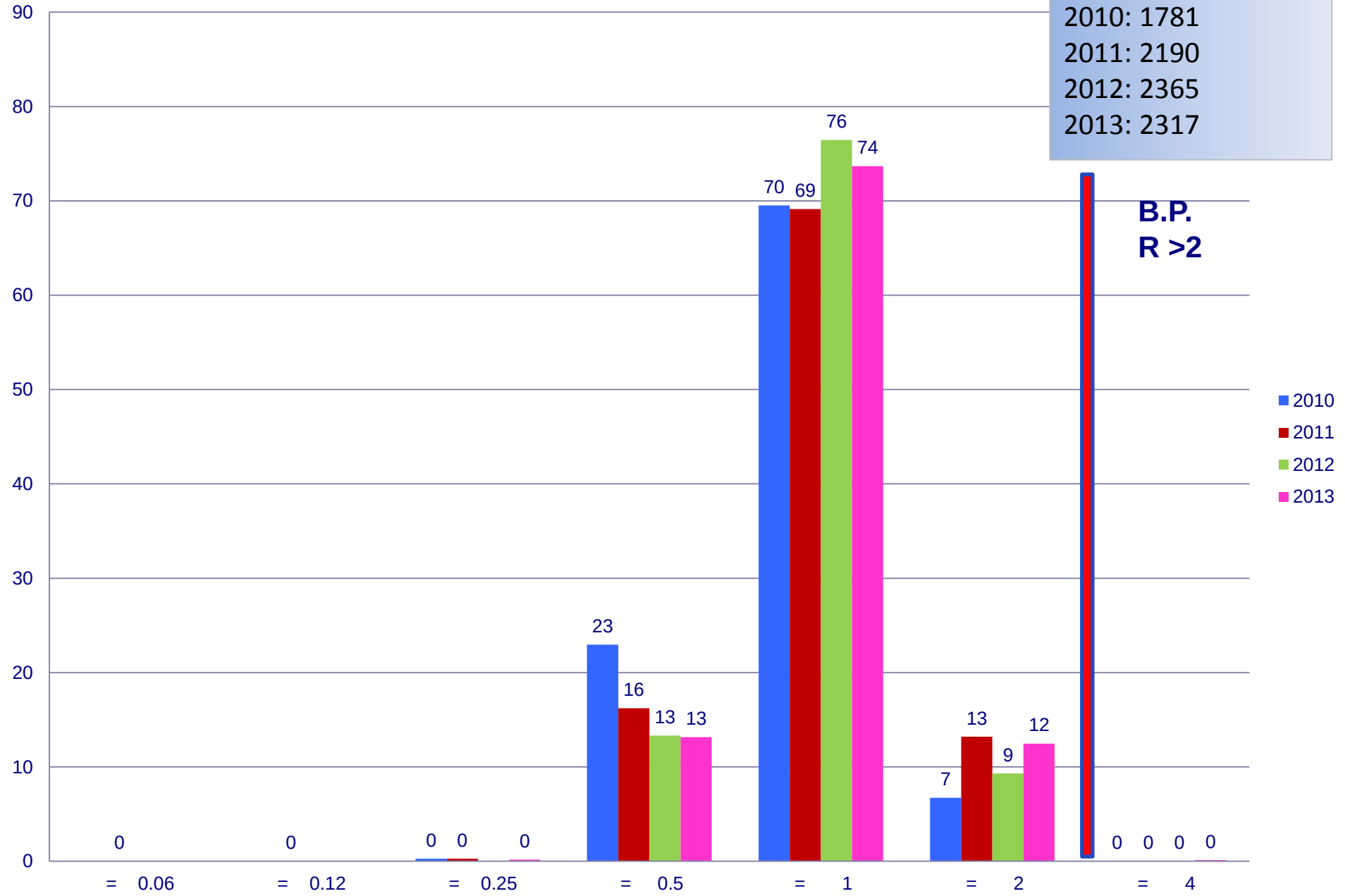
Aumento delle MICs della vancomicina tra i ceppi di *Staphylococcus aureus* sensibili alla vancomicina

- **E' presente in alcune istituzioni (ma non in tutte …)**
- **Ritardata risposta alla terapia antibiotica**
- **Aumentata mortalità**
- **Aumentata percentuale di ricadute**
- **Prolungata ospedalizzazione**
- **Costo di ospedalizzazione totale aumentato**
- **Coinvolge sia gli MRSA che i MSSA**

Dhand A., F1000 Medicine Reports, 2012, 4:4, 1-11

MRSA : % M.I.C. VANCO

Numero ceppi testati:
2010: 1781
2011: 2190
2012: 2365
2013: 2317



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Contents lists available at ScienceDirect

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journal homepage: www.clinicalmicrobiologyandinfection.com

Letter to the Editor

From MIC creep to MIC decline: *Staphylococcus aureus* antibiotic susceptibility evolution over the last 4 years

Table 1
Antibiotic consumption and MIC[a] to vancomycin, daptomycin and linezolid

	2010	2011	2012	2013	2014	p[b]
Total *Staphylococcus aureus* bacteraemia, *n*	32	31	41	42	63	-
DDD/100 patients-day (Total DDD)						
Vancomycin	1.37 (4296)	1.32 (3677)	0.92 (2648)	1.63 (4558)	1.55 (4345)	0.806
Teicoplanin	1.02 (2917)	1.09 (3048)	0.75 (2155)	0.71 (1981)	0.47 (1484)	0.086
Linezolid	4.30 (13 526)	4.04 (11 224)	3.13 (9006)	5.52 (15 443)	5.77 (16 154)	0.462
Daptomycin	0.36 (1129)	0.50 (1386)	0.64 (1849)	1.55 (4342)	2.49 (6970)	0.023
Cloxacillin	0.24 (759)	0.32 (879)	0.53 (1534)	0.87 (2441)	1.36 (3797)	0.015
Quinolones	10.37 (32 593)	11.65 (27 526)	13.08 (37 698)	21.77 (60 862)	21.39 (61 502)	0.029
Antibiotic resistance						
% MRSA	25.0	29.0	29.0	14.0	26.2	0.759
Vancomycin MIC, mean (SD)	2.12 (0.73)	1.62 (0.59)	1.47 (0.46)	1.16 (0.33)	1.16 (0.35)	<0.001
% *S. aureus* vancomycin MIC >1.0 (*n*)	100.0 (31)	66.7 (30)	67.5 (40)	33.3 (39)	50.0 (58)	<0.001
% *S. aureus* vancomycin MIC >1.5 (*n*)	100.0 (31)	53.3 (30)	32.5 (40)	7.7 (39)	6.9 (58)	<0.001
Daptomycin MIC, mean (95% CI)	0.28 (0.18)	0.28 (0.18)	0.42 (0.29)	0.39 (0.32)	0.32 (0.23)	0.906
% *S. aureus* daptomycin MIC >0.25 (*n*)	30.0 (20)	20.0 (5)	60.7 (28)	46.0 (39)	40.0 (60)	0.807
Linezolid						
% *S. aureus* with linezolid MIC >2.0	6.00	0.00	0.00	0.00	1.59	0.309

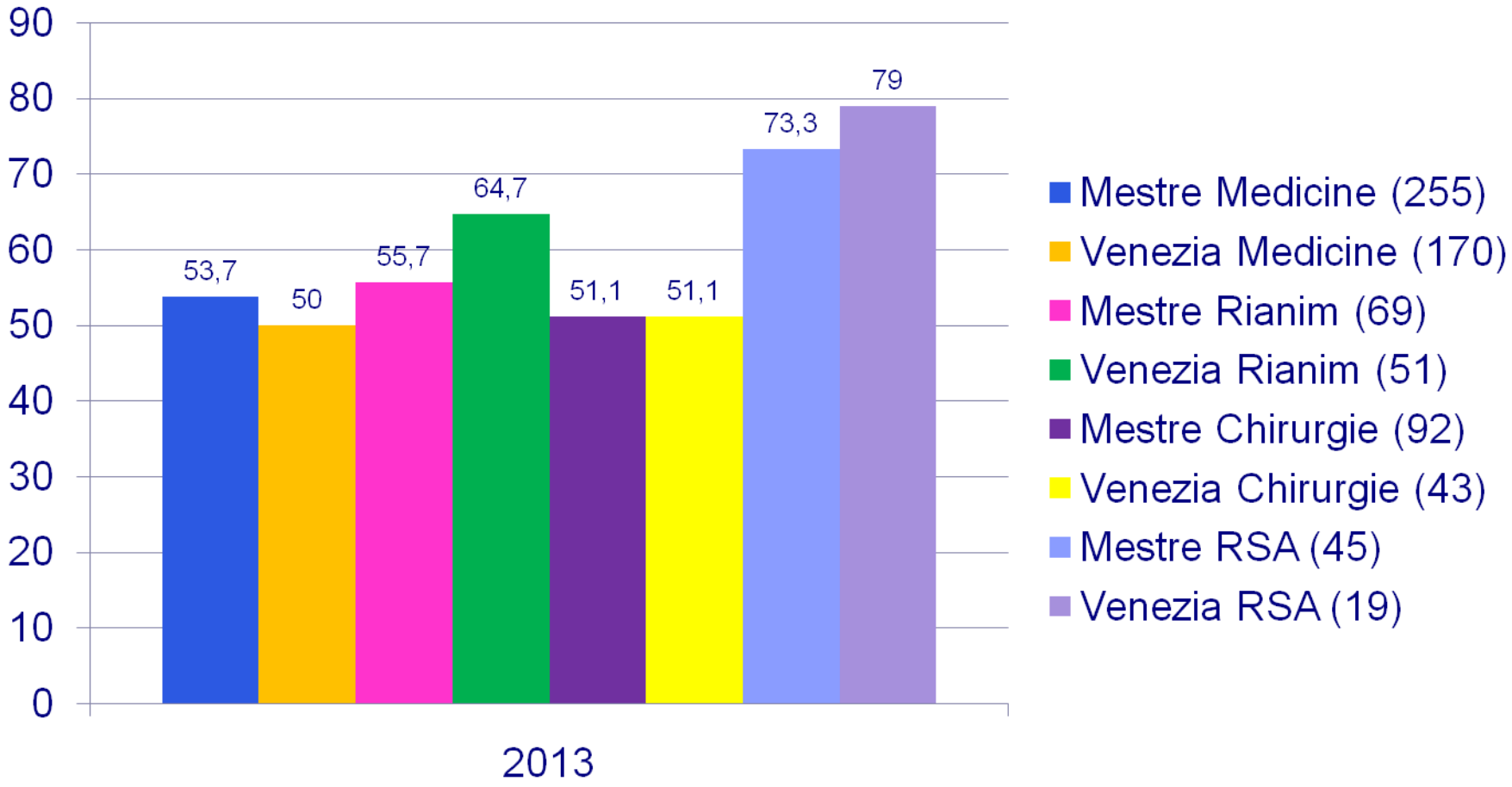
Abbreviations: DDD, Defined Daily Doses; MRSA, methicillin-resistant *S. aureus*.
[a] MIC in mg/L.
[b] p-value for Kendall correlation test.

The main finding of our study is the detection of a progressive reduction in S. aureus vancomycin MIC during the study period.
This study was able to detect a reversal in the recent evolution of S. aureus susceptibility to vancomycin. Although it has not been possible to establish a clear relationship with the antibiotic consumption, we found evidence showing the effect of antimicrobial policy on S. aureus antibiotic susceptibility.

CMI, August 2016, Volume 22, Issue 8, Pages 741–742

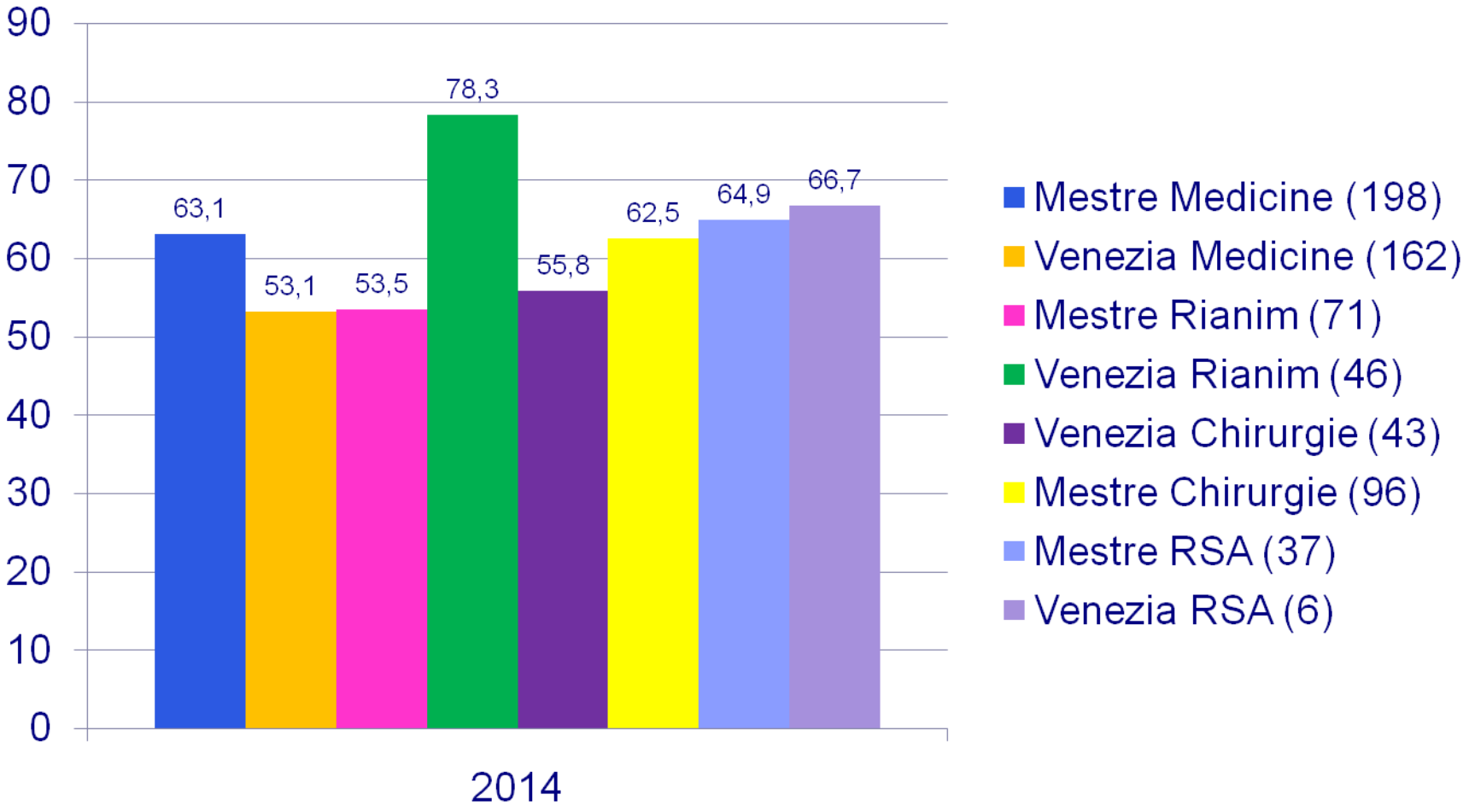
Staph. aureus vs Oxacillina-R

2013



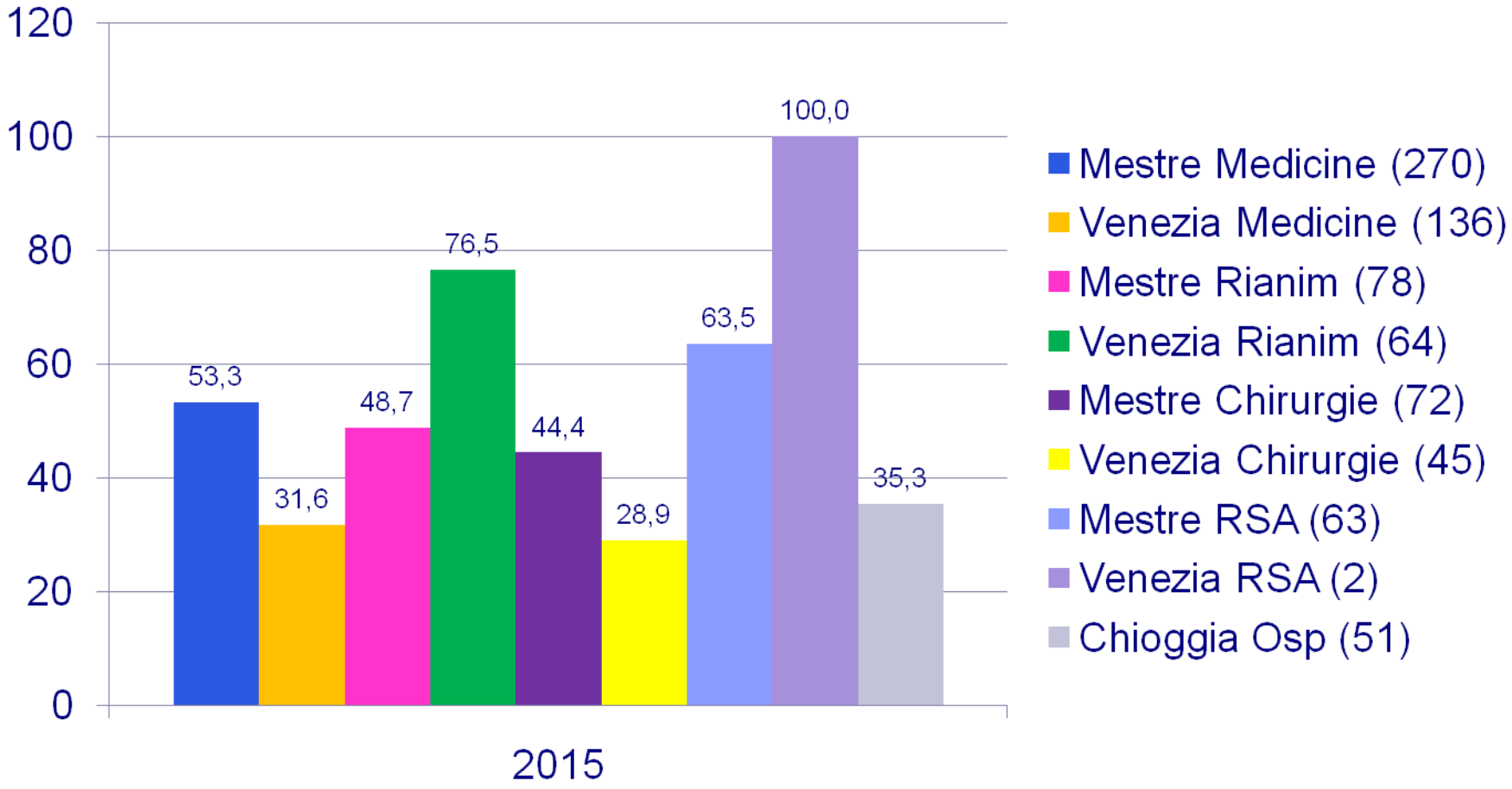
Staph. aureus vs Oxacillina-R

2014

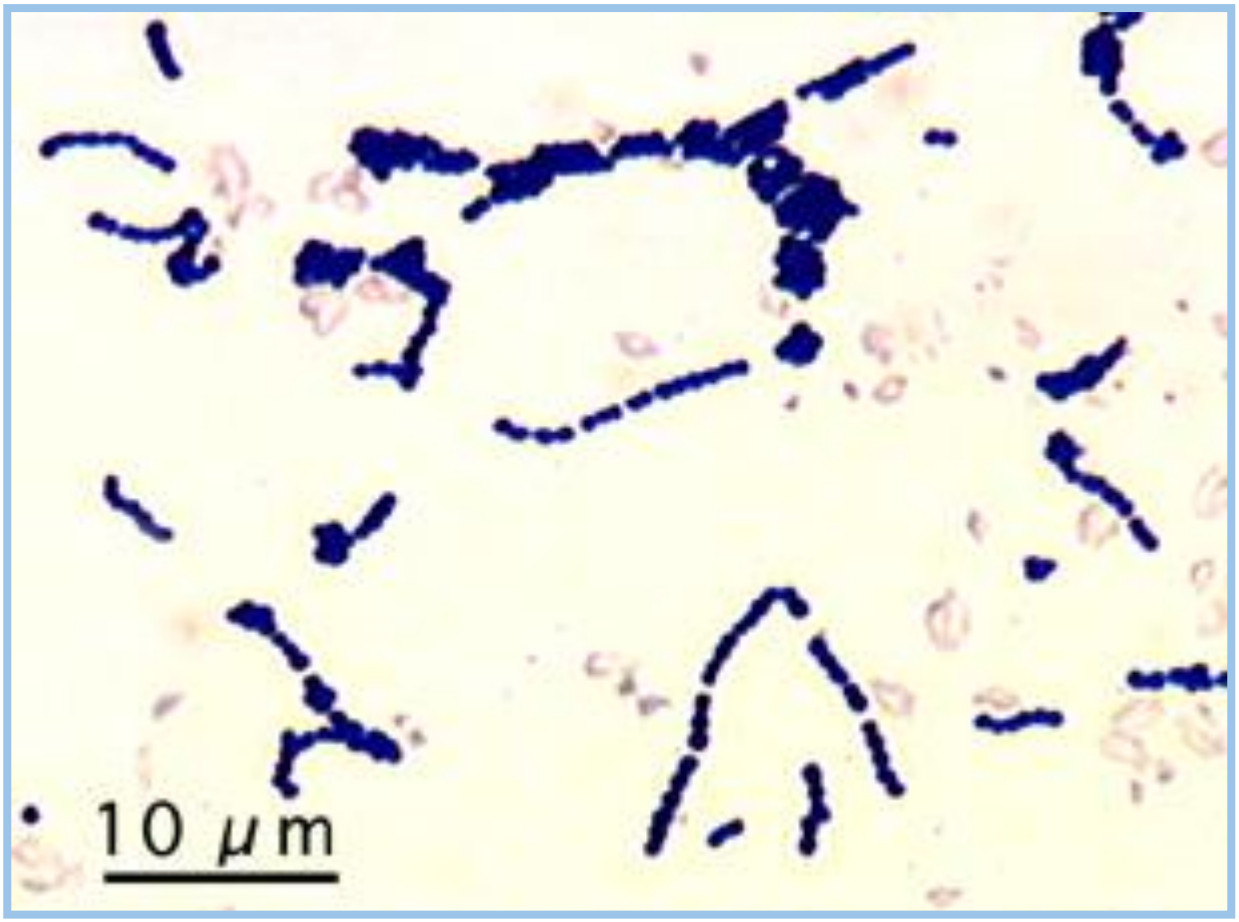


Staph. aureus vs Oxacillina-R

2015



Enterococchi
(molte resistenze intrinseche)



Enterococcus species
Resistenza Intrinseca

- Cefalosporine
- Clindamicina
- Trimetoprim/sulfametossazolo
- Aminoglicosidi (basso livello)
- Quinupristin/dalfopristin (*E. faecalis*)

McManus MC. *Am J Health-Syst Pharm*. 1997;54:1420-1433
Murray BE. *Clin Microbiol Rev*. 1990;3:46-65
Linden PK. Drugs. 2002;62(3):425-41

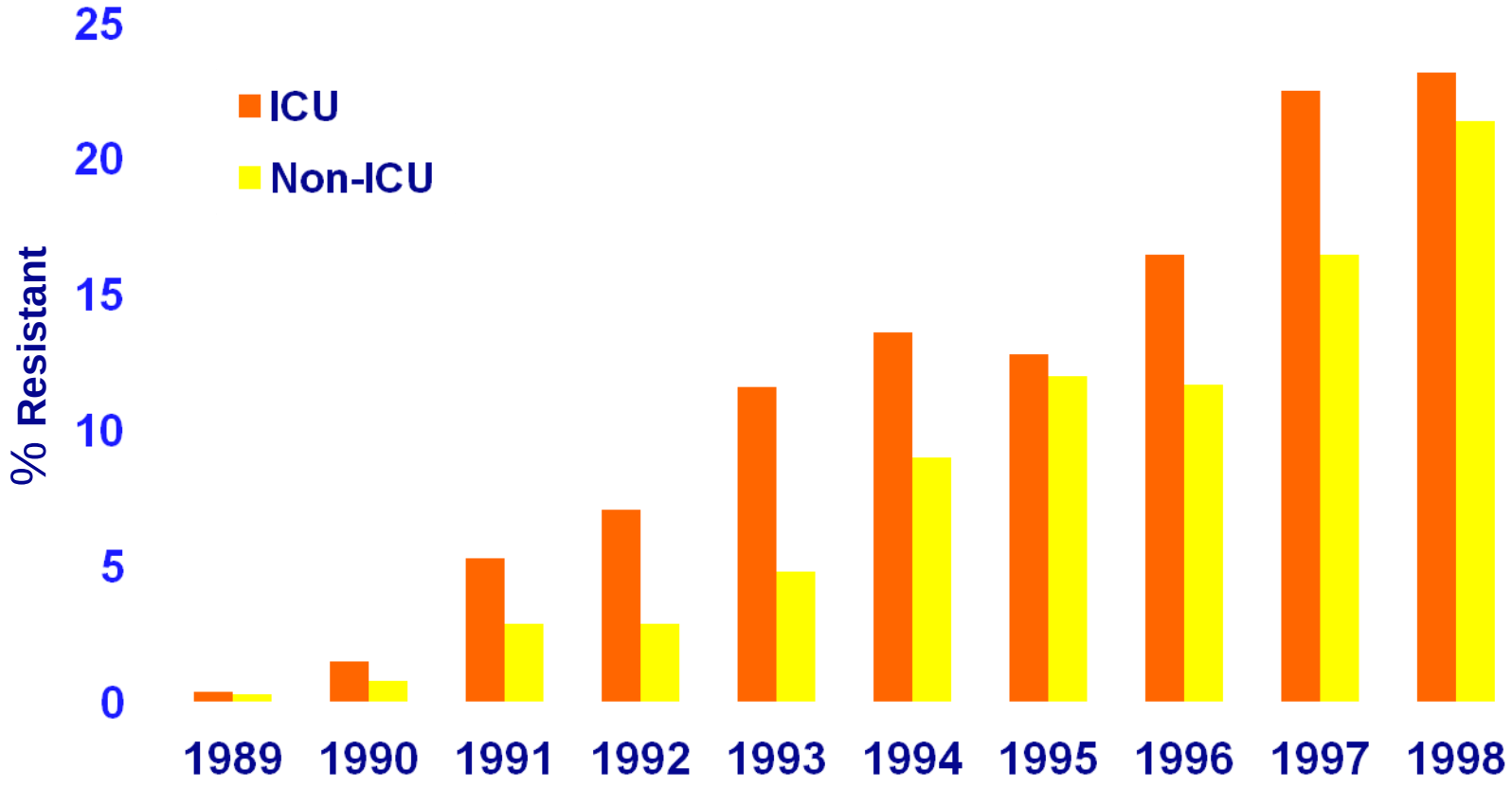
Enterococcus species

Resistenza Acquisita

- Penicillina & Ampicillina
- Aminoglicosidi (alto livello)
- Cloramfenicolo
- Vancomicina
- Teicoplanina
- Quinupristin/dalfopristin
- Linezolid
- Daptomicina

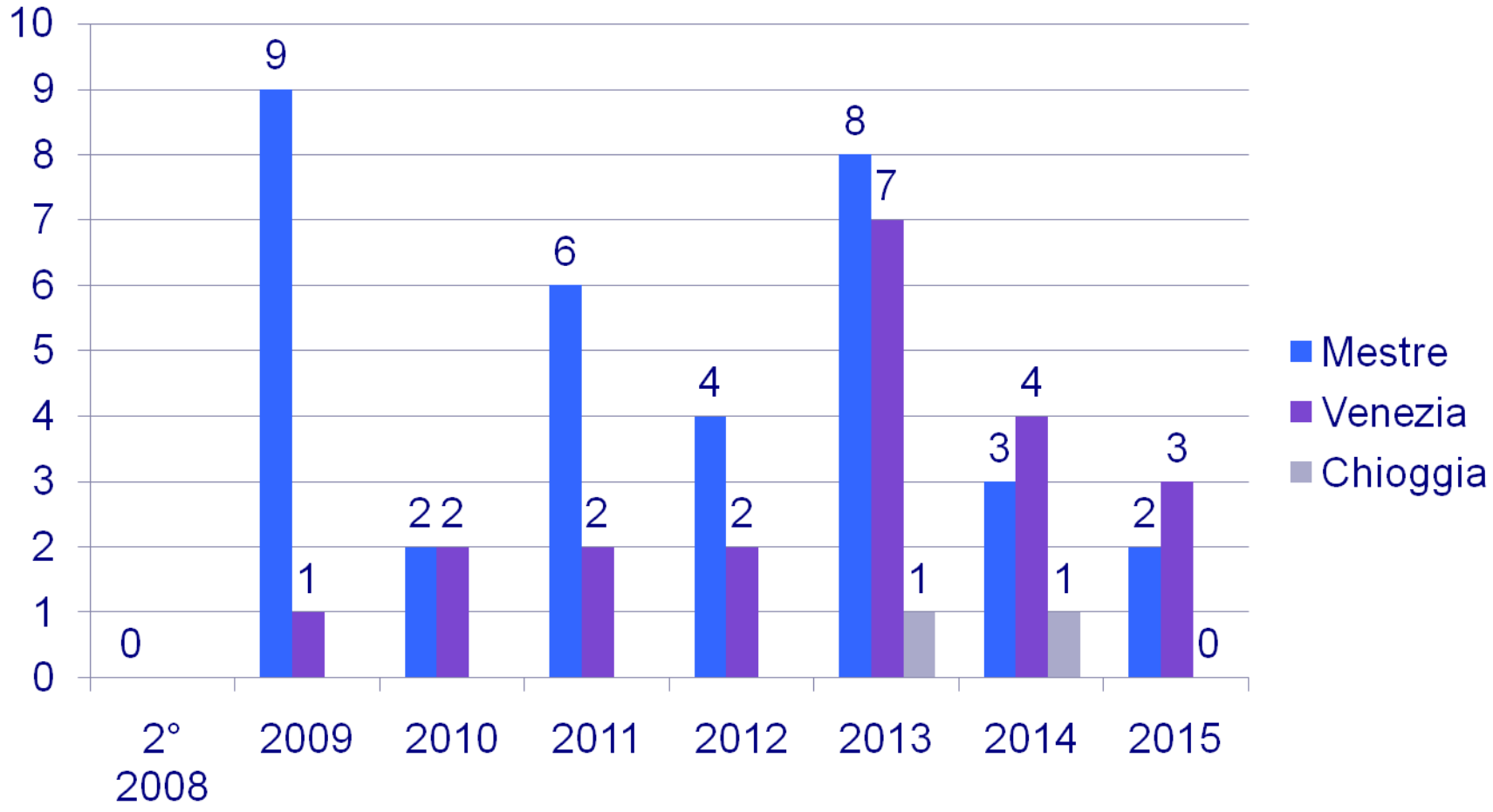
McManus MC. *Am J Health-Syst Pharm*. 1997;54:1420-1433
Murray BE. *Clin Microbiol Rev*. 1990;3:46-65
Herrero IA et al. *N Engl J Med*. 2002;346:867-869
Leclercq R et al. *N Engl J Med*. 1988;319:157-161
Long JK et al. *Mayo Clin Proc.* 2005;80(9):1215-6

Emerging Vancomycin-resistant Enterococcal Infections*



* in U.S. NNIS Hospitals

Enterococcus faecalis
VanA e VanB

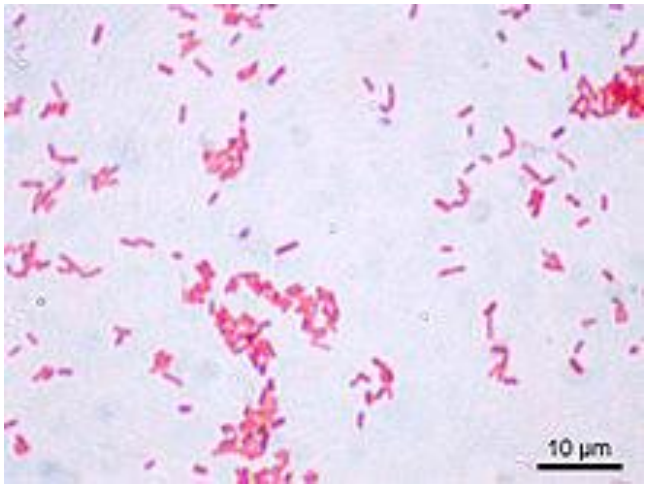


Fine primo quarto

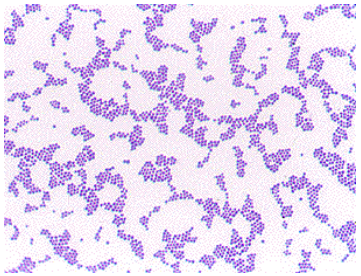
Batteri	**1**
Antibiotici	**1**

Secondo tempo

I Gram – negativi



e … i Gram – positivi



Principali meccanismi di resistenza nei Gram negativi

- impermeabilità della membrana esterna (Gram-neg);
- produzione di ß-lattamasi;
- capacità di pompare il ß-lattamico fuori dalla cellula (***Ps. aeruginosa***)

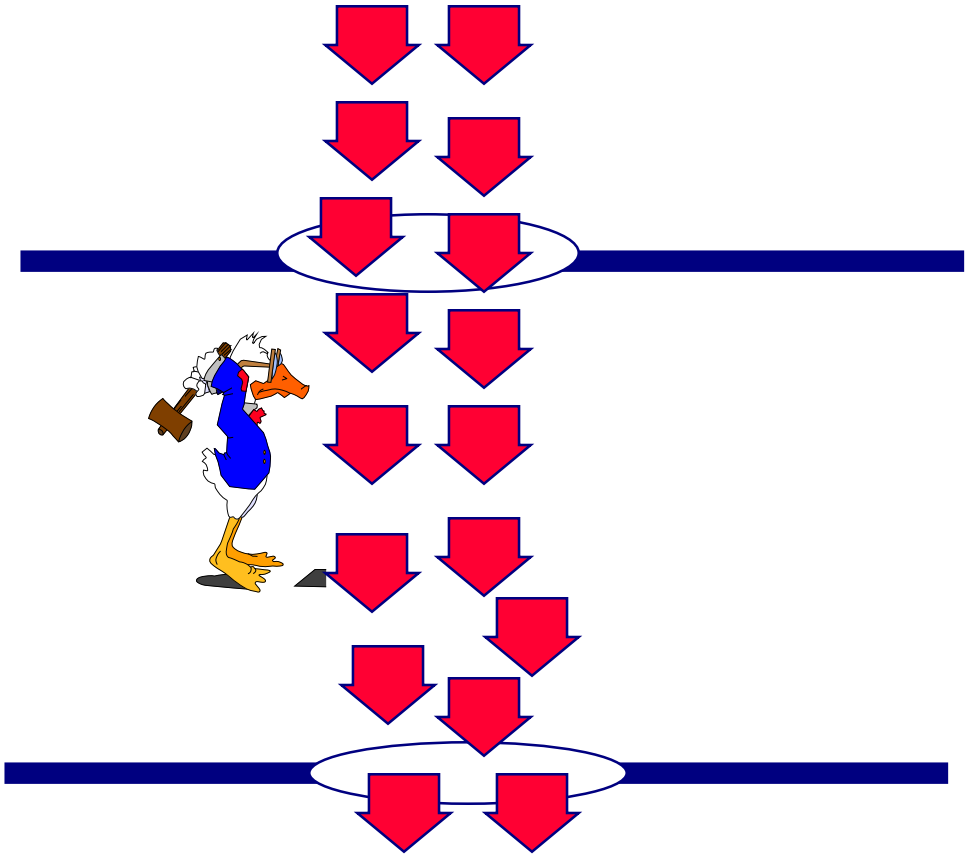
La produzione di ß-lattamasi rappresenta il principale meccanismo di resistenza nei Gram-negativi

ESBL
Batteri produttori di ESBL

- *Klebsiella*
- *Escherichia coli*
- *Enterobacter*
- *Proteus*
- *Salmonella*
- *Citrobacter*
- Altri *(Pseudomonas, Acinetobacter)*

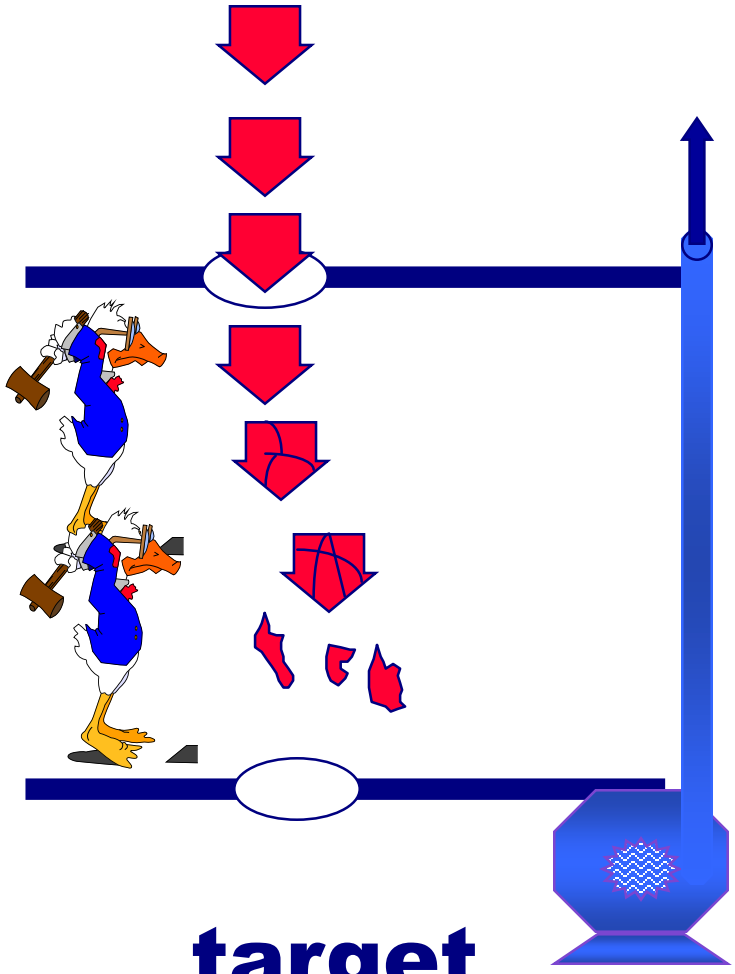
TEM, SHV e CTX-M sono le ESBL maggiormente espresse, piu frequenti in *E. coli* e *K. pneumoniae*

ceppo sensibile



target

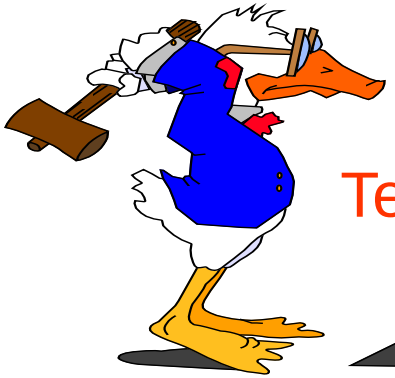
ceppo resistente



target

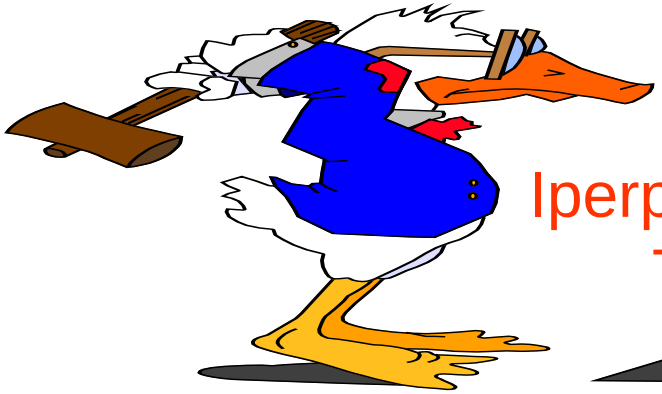
POMPA EFFLUSSO

Betalattamasi nei gram negativi



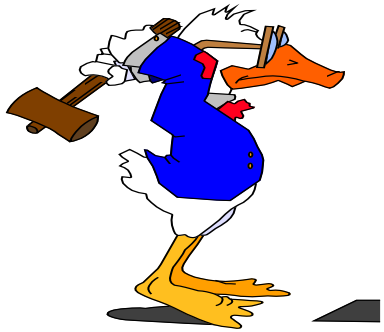
Tem 1 →

Ampicillina R
Amoxi-clav S
Ceftazidime S



Iperproduttore
Tem 1 →

Ampicillina R
Amoxi-clav R
Ceftazidime S



ESBL →

Ampicillina R
Amoxi-clav R
Ceftazidime R
Cefepime S ……R
Imipemen S

Table 1: Intrinsic resistance (R) in Enterobacteriaceae

Enterobacteriaceae are also intrinsically resistant to penicillin G, glycopeptides, fusidic acid, macrolides (with some exceptions[1]), lincosamides, streptogramins, rifampicin, daptomycin and linezolid.

Rule no.	Organisms	Ampicillin	Amoxicilin-clavulanate	Ticarcillin	Piperacillin	Cefazolin	Cefoxitin	Cefamandole	Cefuroxime	Aminoglycosides	Tetracyclines/tigecycline	Polymyxin B/Colistin	Nitrofurantoin
1.1	*Citrobacter koseri*	R		R	R								
1.2	*Citrobacter freundii*	R	R			R	R						
1.3	*Enterobacter cloacae*	R	R			R	R						
1.4	*Enterobacter aerogenes*	R	R			R	R						
1.5	*Escherichia hermannii*	R		R	R								
1.6	*Hafnia alvei*	R	R			R	R						
1.7	*Klebsiella* spp.	R		R	R								
1.8	*Morganella morganii*	R	R			R			R		R	R	R
1.9	*Proteus mirabilis*										R	R	R
1.10	*Proteus vulgaris*	R				R		R	R		R	R	R
1.11	*Proteus penneri*	R				R		R	R		R	R	R
1.12	*Providencia rettgeri*	R	R			R				R[2]		R	R
1.13	*Providencia stuartii*	R	R			R				R[2]		R	R
1.14	*Serratia marcescens*	R	R			R		R	R	Note[3]		R	
1.15	*Yersinia enterocolitica*	R	R	R	R	R	R	R					
1.16	*Yersinia pseudotuberculosis*											R	

[1] Azithromycin is effective in vivo for the treatment of typhoid fever and erythromycin may be used to treat travellers' diarrhoea.

[2] All *Providencia* spp. produce a chromosomal AAC(2')-Ia enzyme. *Providencia* spp. should be considered resistant to all aminoglycosides except amikacin and streptomycin. Some isolates express the enzyme poorly and can appear susceptible to netilmicin *in vitro*, but should be reported as resistant as mutation can result in overproduction of this enzyme.

[3] All *Serratia marcescens* produce a chromosomal AAC(6')-Ic enzyme that may affect moderate the activity of all aminoglycosides except streptomycin and gentamicin.

ESBL

Per ogni antibiotico, dopo l'introduzione nell'uso terapeutico, si sono selezionati ceppi batterici resistenti, in grado di esprimere nuove funzioni di difesa con modalità differenti

ABUSO DI CEFALOSPORINE

- Meticillino Resistenza
- Induzione di ESBL
- Resistenza in pneumococco e enterococco

ABUSO FLUOROCHINOLONI

- Resistenza ai fluorochinoloni
- Diffusione ESBL

ABUSO MACROLIDI

- Resistenza in pneumococco e SβEGA

ESBL

Uso-Abuso Cefalosporine

INFEZIONI DA PATOGENI ESβL

TRATTAMENTO CON CARBAPENEMI

Pseudomonas aeruginosa, Acinetobacter baumannii, Stenotrophomonas maltophilia, Burkholderia cepacia

MDR

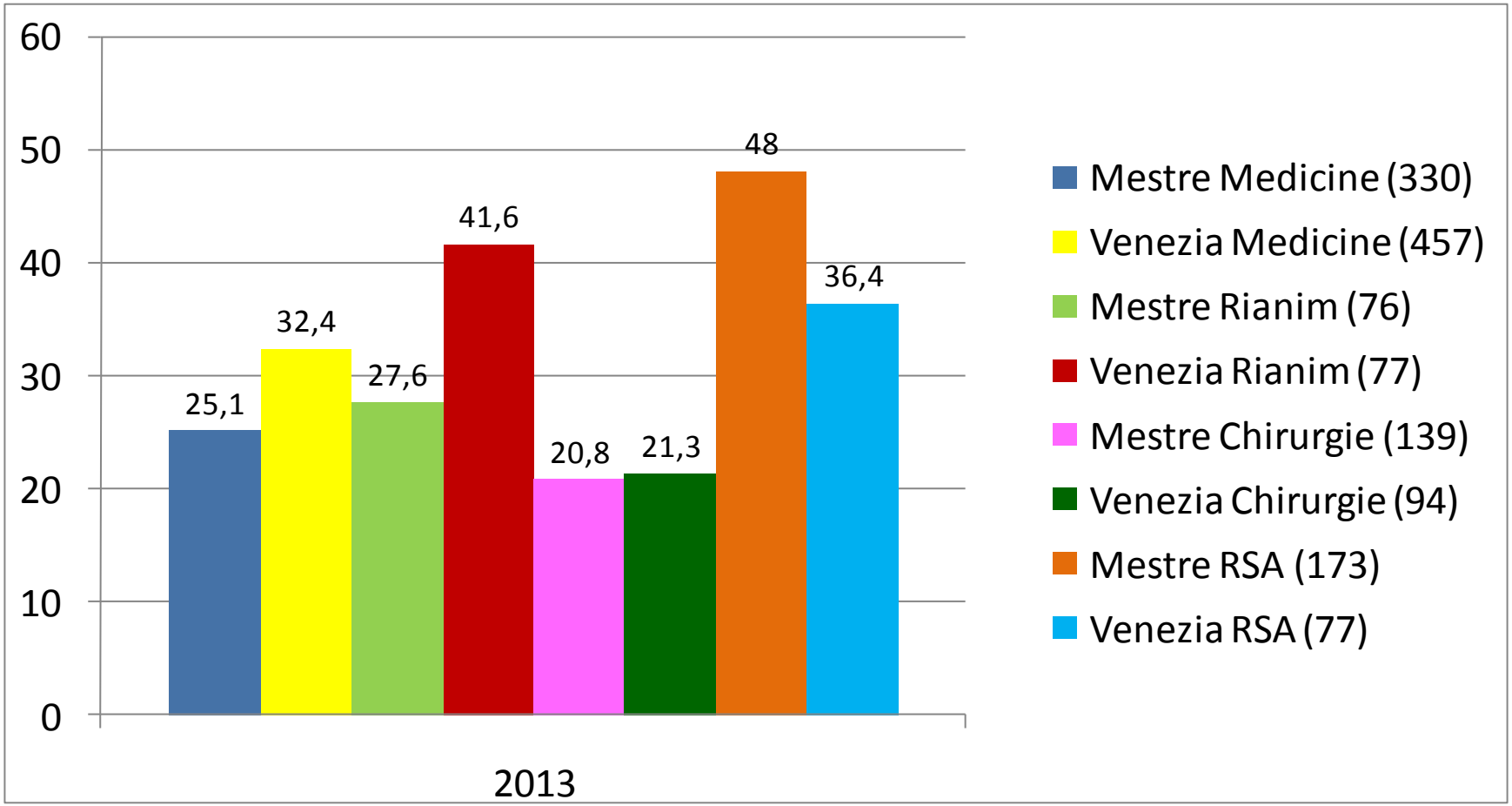
ESBL

Raccomandazioni AMCLI per la refertazione in caso di enterobatteri produttori di ESßL

Ceppo produttore di beta-lattamasi a spettro esteso (ESBL);
ad eccezione dei carbapenemi, la terapia con beta-lattamici (incluse cefalosporine a spettro esteso, aztreonam e combinazioni con inibitori) potrebbe risultare scarsamente efficace o inefficace anche se "in vitro" il ceppo appare sensibile a questi farmaci.
Nel caso in cui si intendano utilizzare tali farmaci si raccomanda preventiva consulenza con un esperto di terapia antibiotica.
I ceppi produttori di ESBL possono causare epidemie intraospedaliere; si raccomanda l'adozione di procedure di "infection control" per limitarne la diffusione.

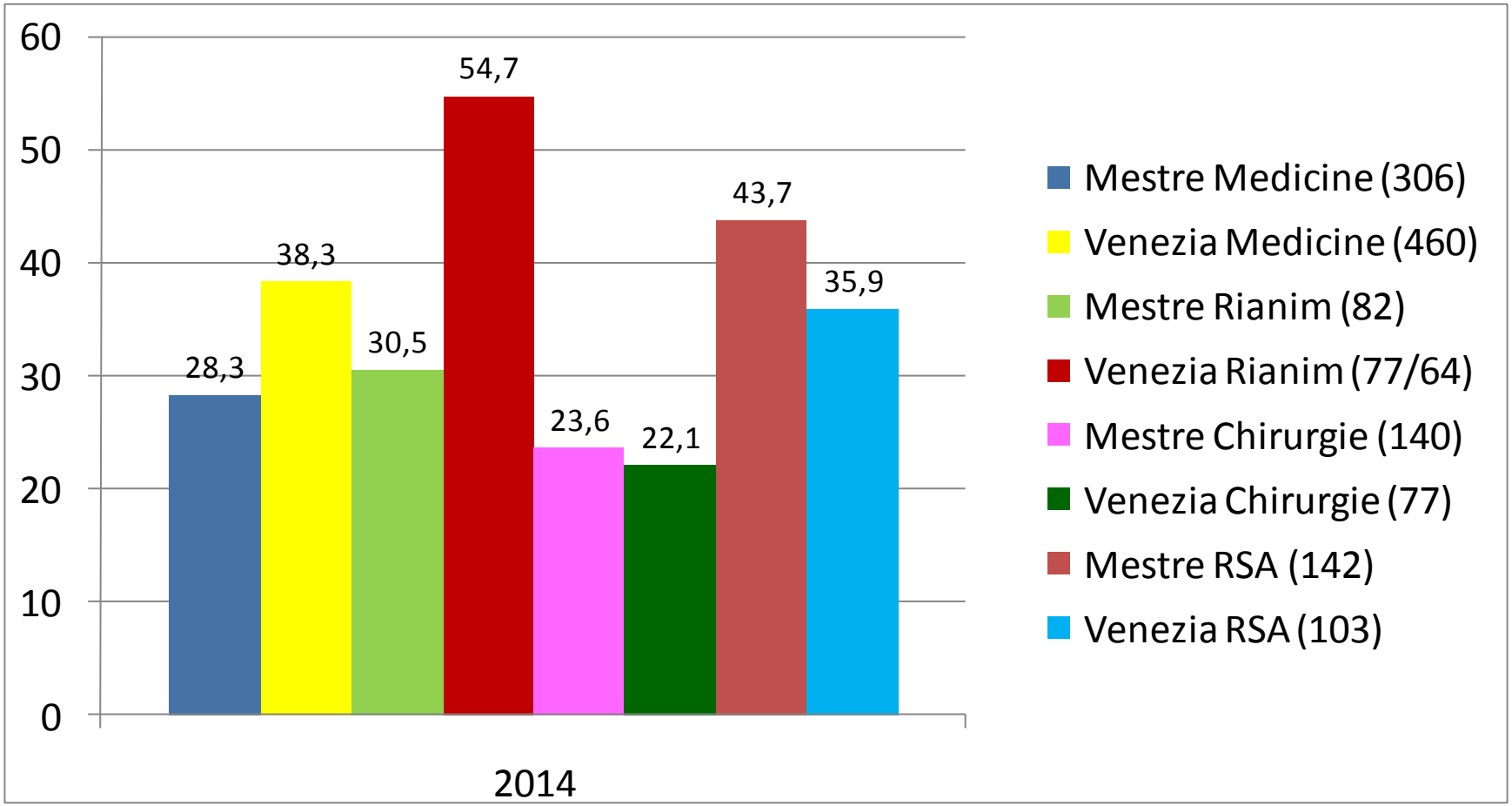
E. coli – ESBL produttore

2013



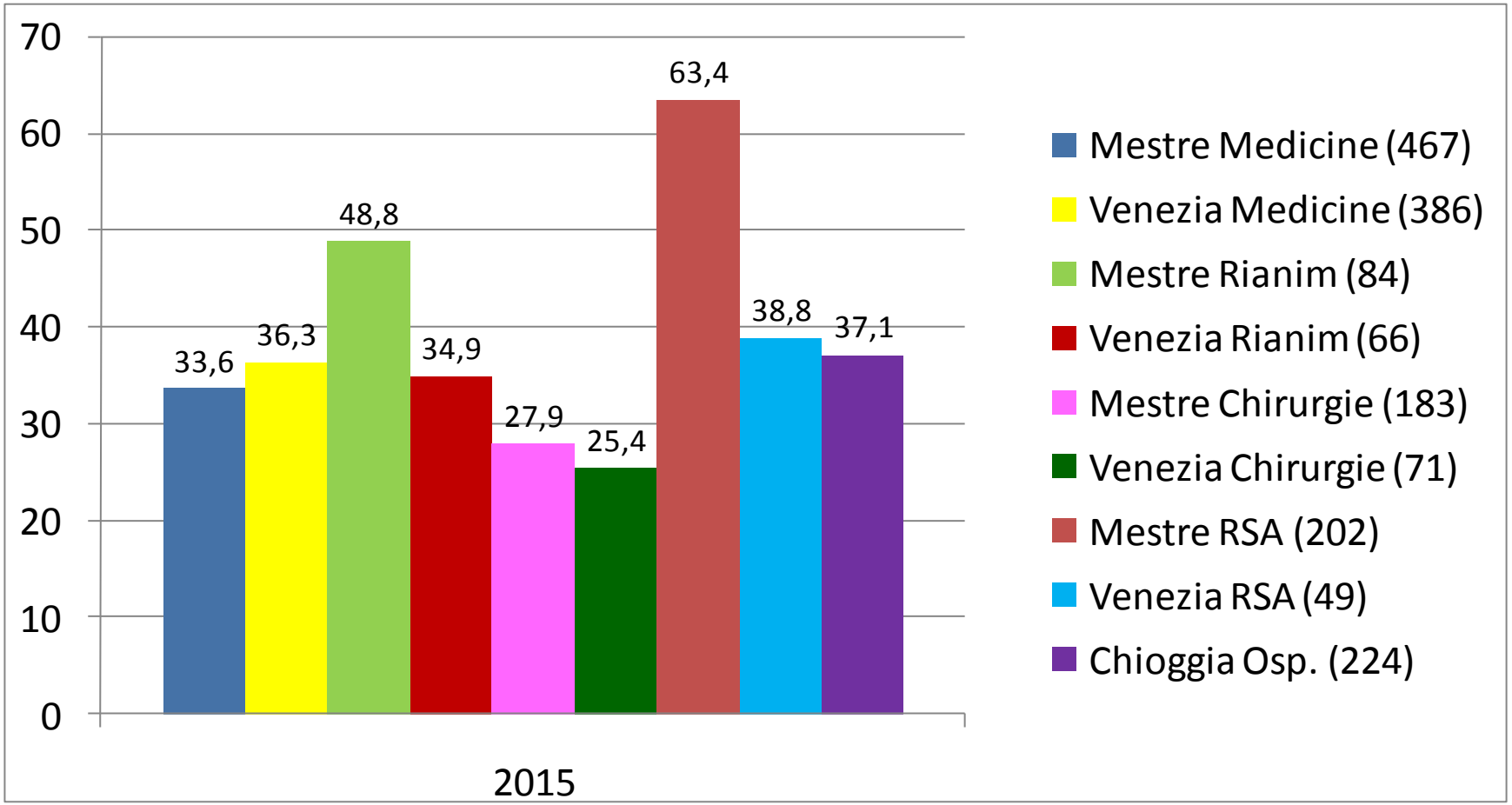
E. coli – ESBL produttore

2014



E. coli – ESBL produttore

2015



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

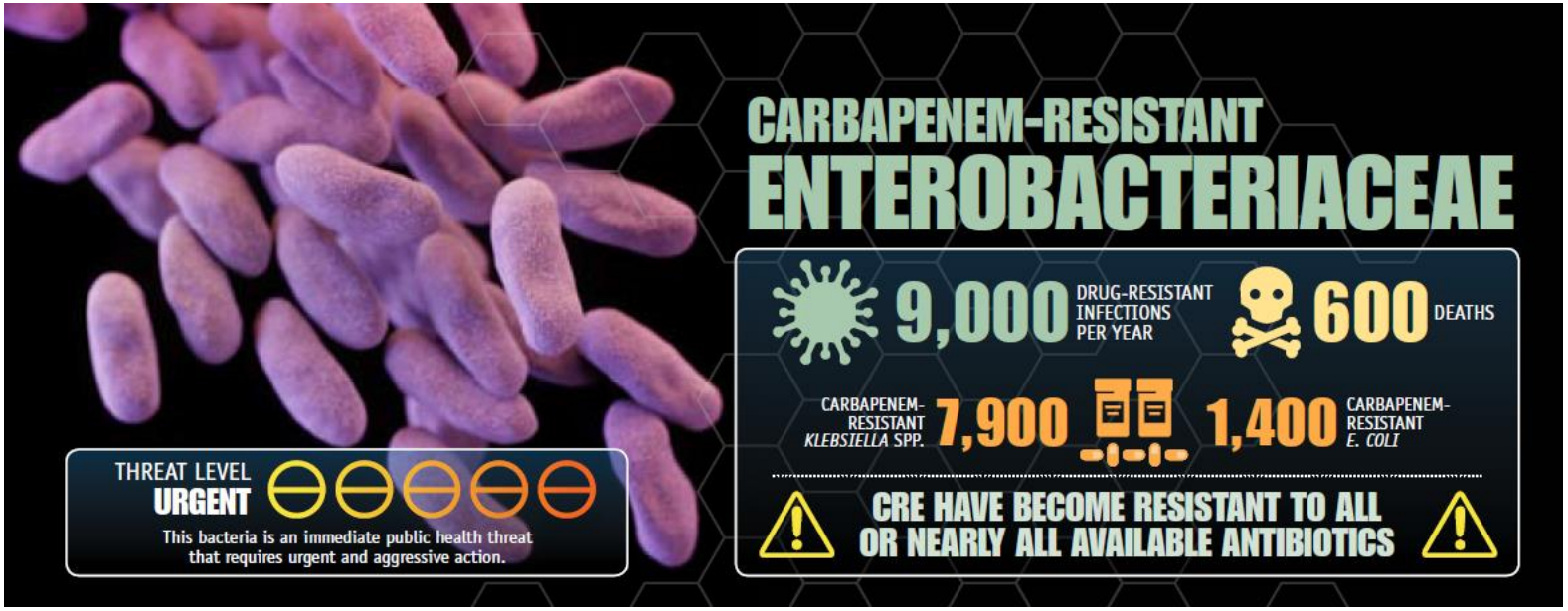
JAC

Has the era of untreatable infections arrived?

David M. Livermore*

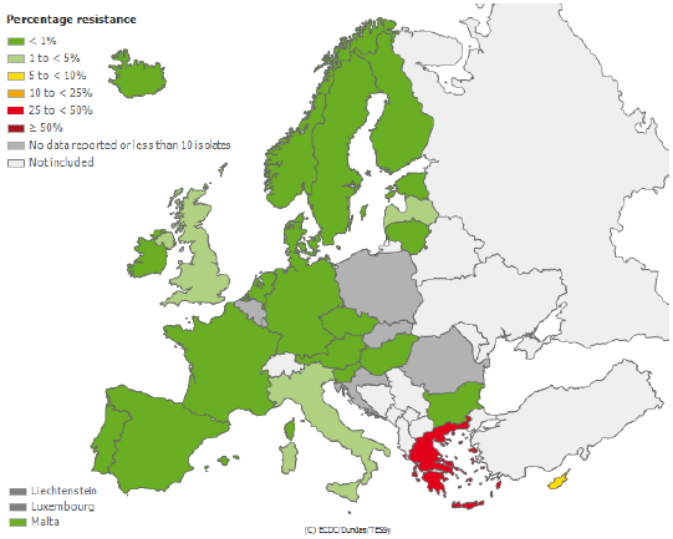
Antibiotic Resistance Monitoring and Reference Laboratory, Health Protection Agency Centre for Infections, 61 Colindale Avenue, London NW9 5EQ, UK

Gram-negatives
Multidrug resistant organisms (MDROs):
quali sono e dove sono (H/T)

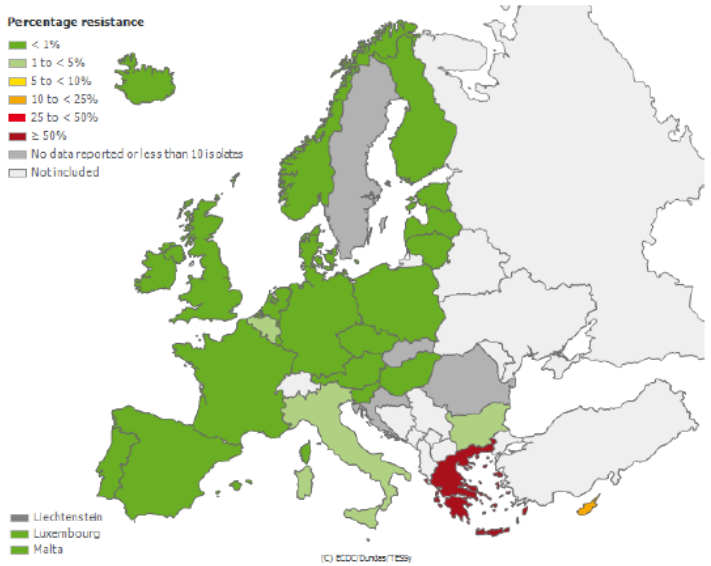

CARBAPENEM-RESISTANT
ENTEROBACTERIACEAE
9,000 DRUG-RESISTANT INFECTIONS PER YEAR
600 DEATHS
CARBAPENEM-RESISTANT *KLEBSIELLA* SPP. 7,900
1,400 CARBAPENEM-RESISTANT *E. COLI*
CRE HAVE BECOME RESISTANT TO ALL OR NEARLY ALL AVAILABLE ANTIBIOTICS
THREAT LEVEL
URGENT
This bacteria is an immediate public health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

Epidemiologia

Proportion of Carbapenems Resistant (R+I) *Klebsiella pneumoniae* Isolates in Participating Countries in 2008

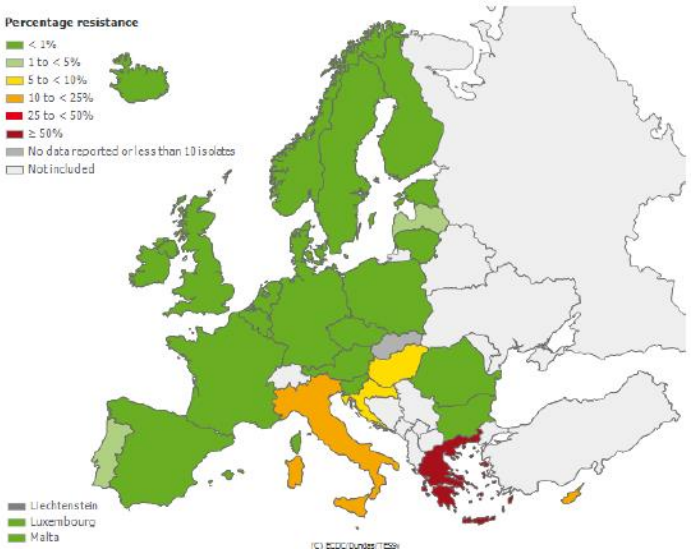


Proportion of Carbapenems Resistant (R+I) *Klebsiella pneumoniae* Isolates in Participating Countries in 2009

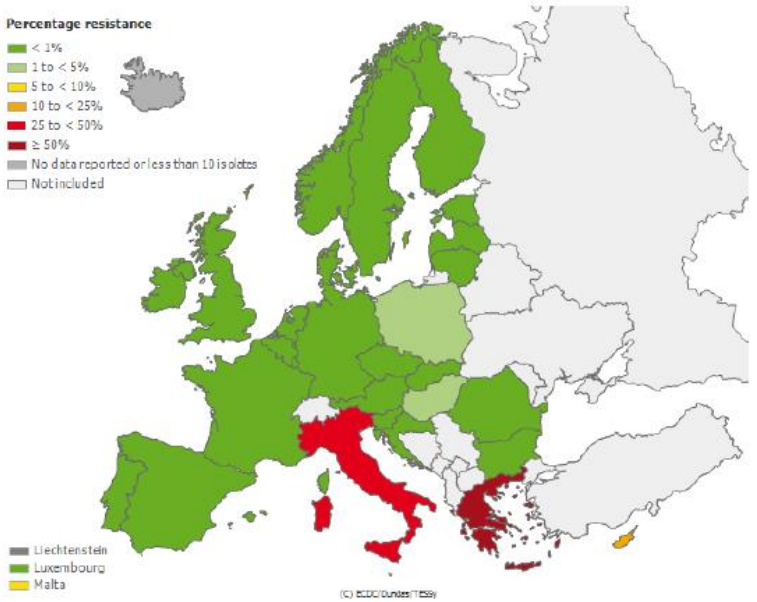


Epidemiologia

Proportion of Carbapenems Resistant (R+I) *Klebsiella pneumoniae* Isolates in Participating Countries in 2010

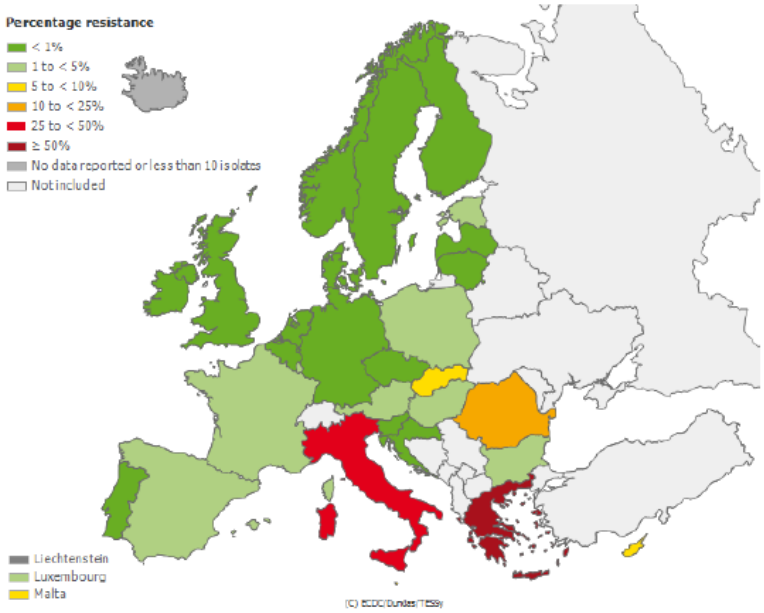


Proportion of Carbapenems Resistant (R+I) *Klebsiella pneumoniae* Isolates in Participating Countries in 2011

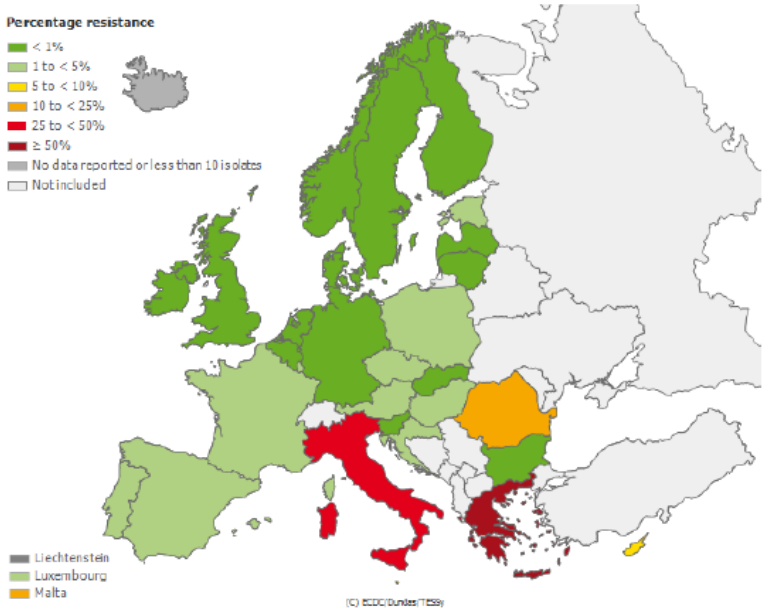


Epidemiologia

Proportion of Carbapenems Resistant (R+I) *Klebsiella pneumoniae* Isolates in Participating Countries in 2012



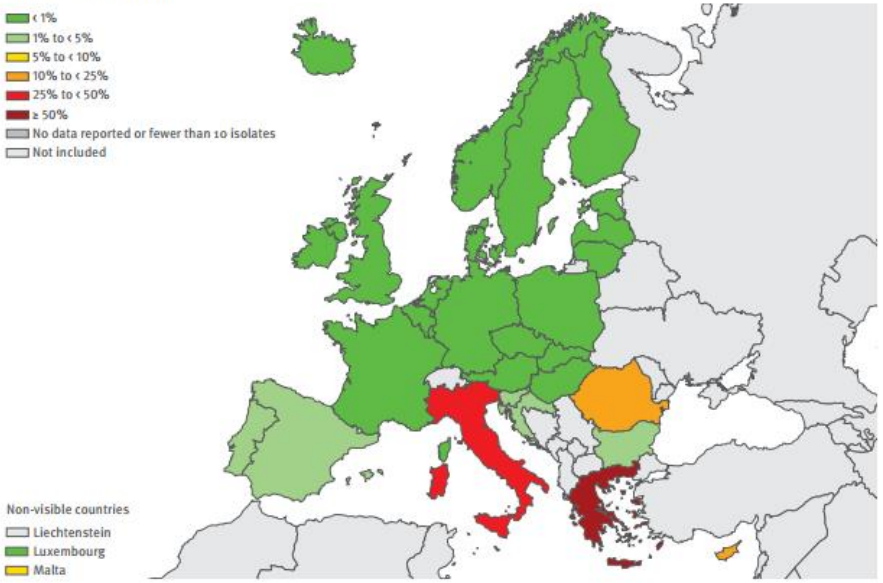
Proportion of Carbapenems Resistant (R+I) *Klebsiella pneumoniae* Isolates in Participating Countries in 2013



Epidemiologia

Figure 3.9. *Klebsiella pneumoniae*. Percentage (%) of invasive isolates with resistance to carbapenems, by country, EU/EEA countries, 2014

Figure 3.9. *Klebsiella pneumoniae*. Percentage (%) of invasive isolates with resistance to carbapenems, by country, EU/EEA countries, 2015



Epidemiologia

Figure 3.7. *Klebsiella pneumoniae*. Percentage (%) of invasive isolates with resistance to third-generation cephalosporins, by country, EU/EEA countries, 2015

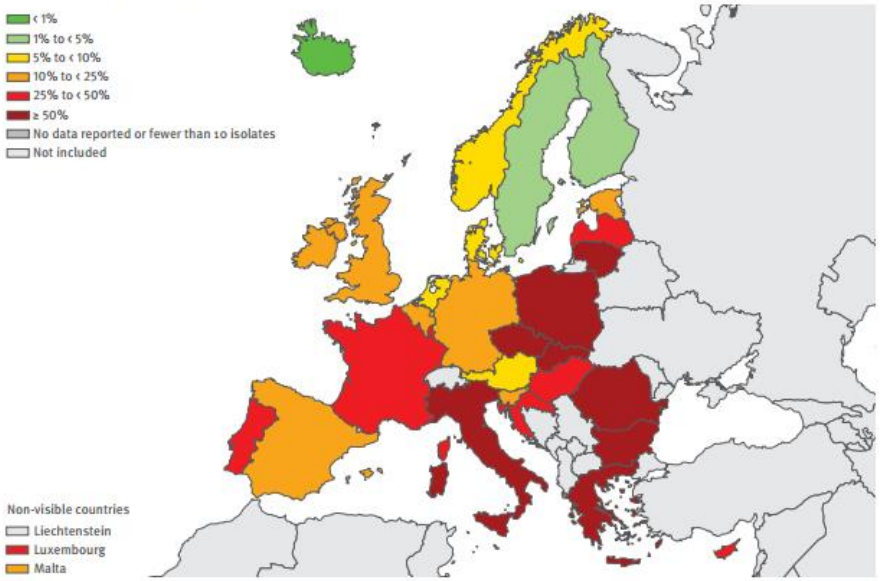
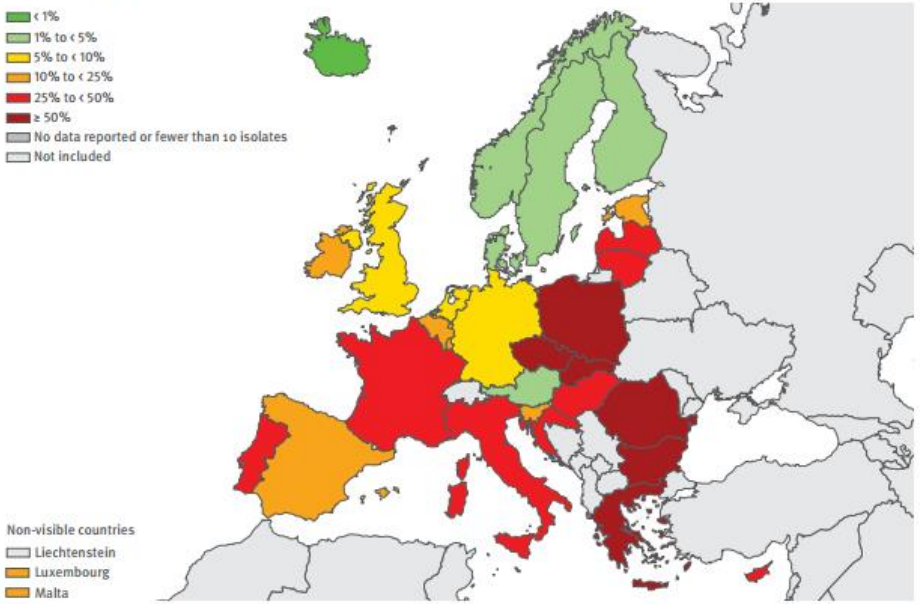


Figure 3.8. *Klebsiella pneumoniae*. Percentage (%) of invasive isolates with resistance to aminoglycosides, by country, EU/EEA countries, 2015



Epidemiologia

Figure 3.6. *Klebsiella pneumoniae*. Percentage (%) of invasive isolates with resistance to fluoroquinolones, by country, EU/EEA countries, 2015

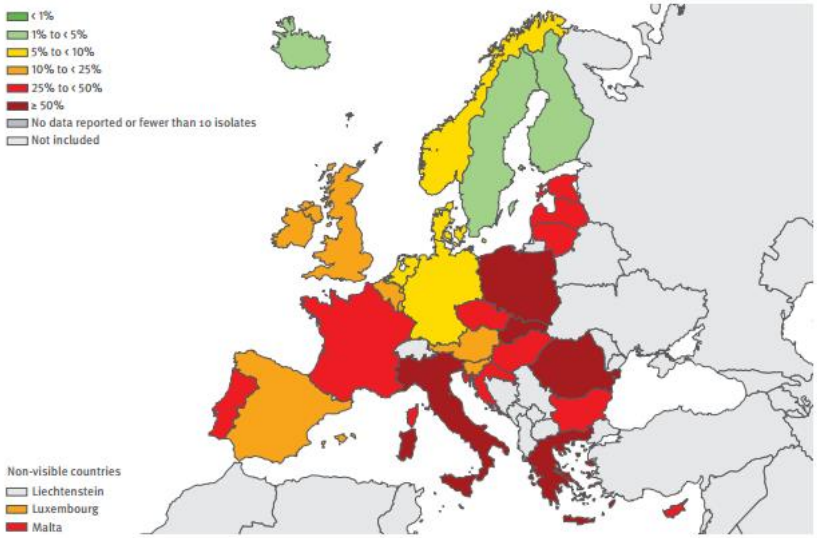
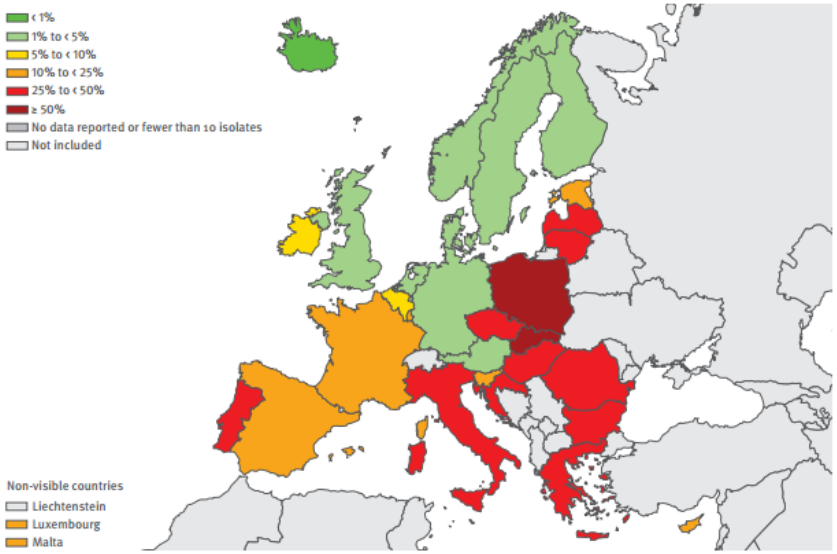


Figure 3.10. *Klebsiella pneumoniae*. Percentage (%) of invasive isolates with combined resistance to fluoroquinolones, third-generation cephalosporins and aminoglycosides, by country, EU/EEA countries, 2015



Negli Stati Uniti …

March 2013

CDC Vitalsigns™

On this Page

4% & 18%

About 4% of US hospitals had at least one patient with a CRE (carbapenem-resistant Enterobacteriaceae) infection during the first half of 2012. About 18% of long-term acute care hospitals* had one.

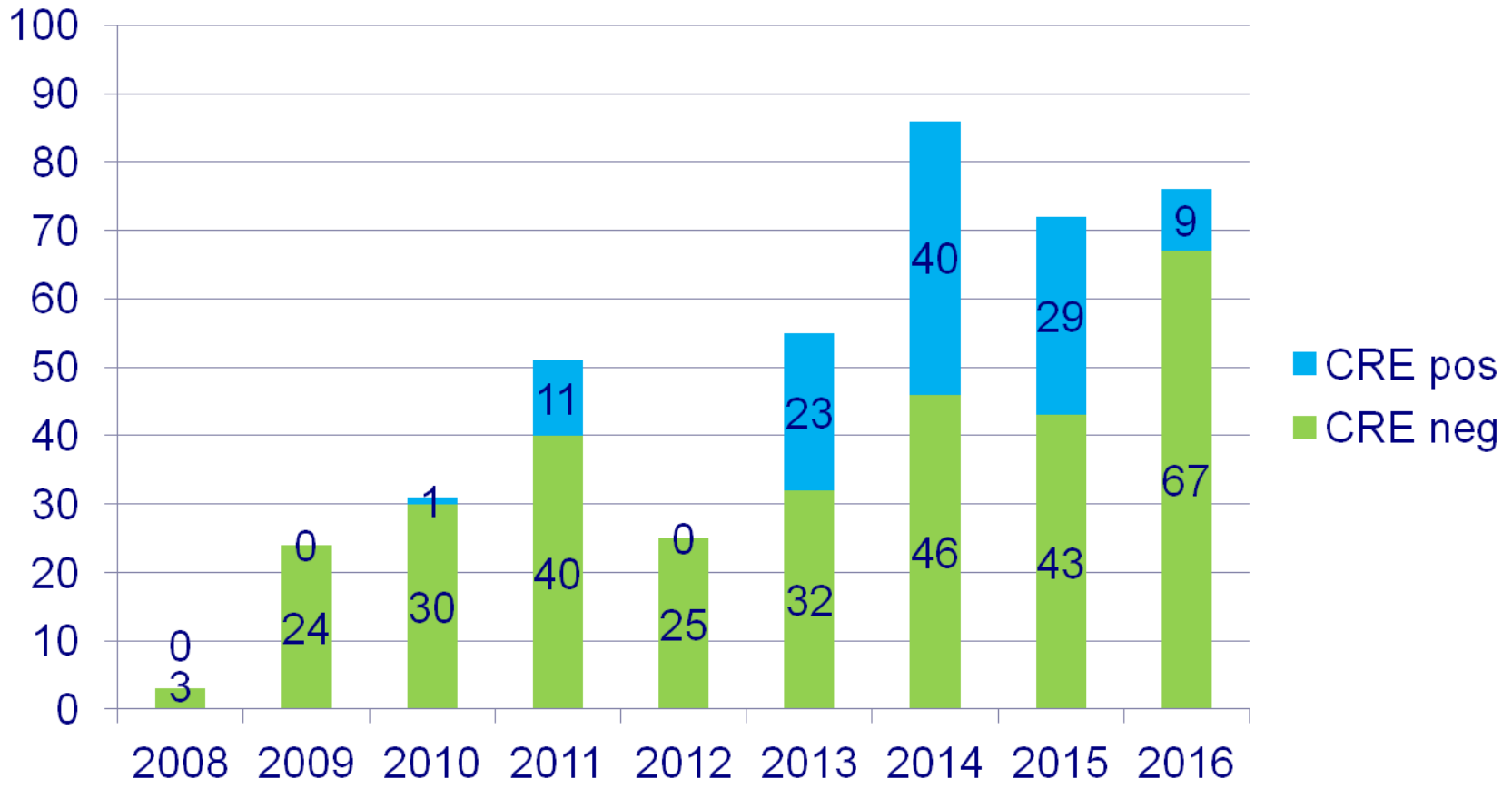
42

One type of CRE infection has been reported in medical facilities in 42 states during the last 10 years.

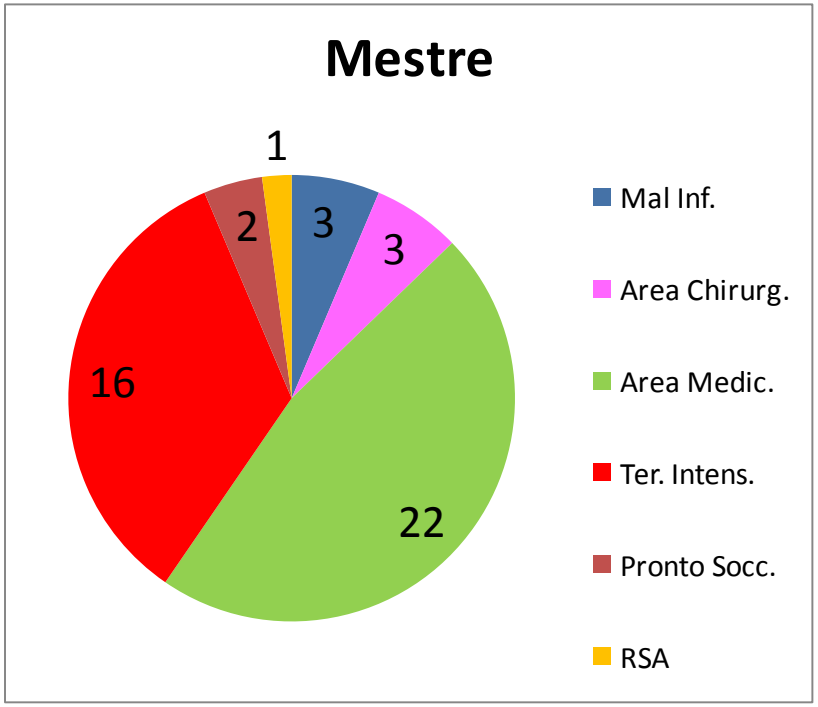
1 in 2

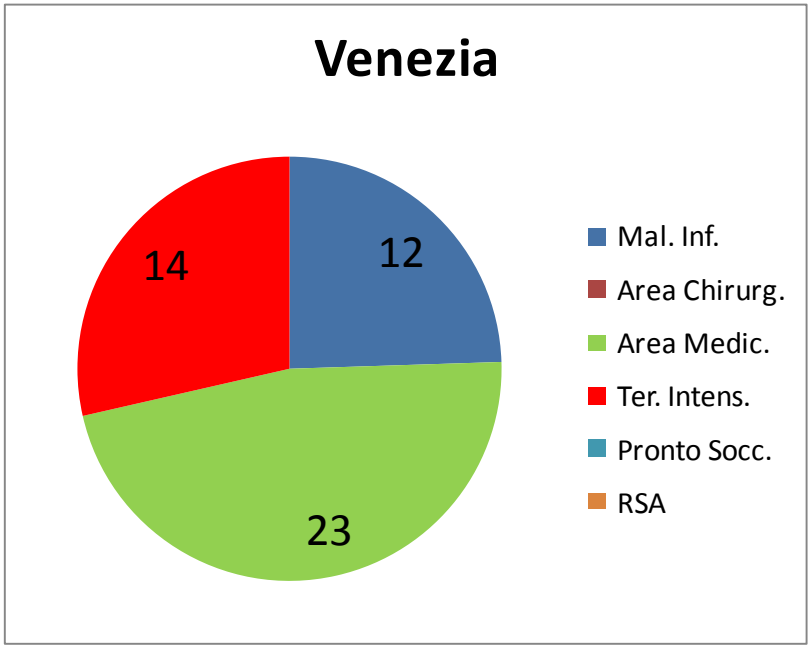
CRE germs kill up to half of patients who get bloodstream infections from them.

Episodi di batteriemia da *K. pneumoniae* ULSS12



Episodi di batteriemia da *K. pneumoniae* CRE per sede





MIC di K. pneumoniae CRE

	0.25	≤0.5	0.5	≤1	1	2	4	>4	8	>8	16	32	64	>64	% I+R
Colistina		27			1				1	29					51
Gentamicina				10		32	17	4							33
Meropenem	1					3	11		8		1	11	23	5	93
Tigeciclina	5		33		19	4	2								10

RAPID COMMUNICATIONS

Colistin resistance superimposed to endemic carbapenem-resistant *Klebsiella pneumoniae*: a rapidly evolving problem in Italy, November 2013 to April 2014

M. Monaco[1,2], T Giani[2,3], M Raffone[1,4], F Arena[3], A Garcia-Fernandez[1], S Pollini[3], Network EuSCAPE-Italy[5], H Grundmann[6], A Pantosti (annalisa.pantosti@iss.it)[1], G M Rossolini[3,7,8]

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3. Department of Medical Biotechnologies, University of Siena, Siena, Italy
4. Federico II University Hospital, Neaples, Italy
5. The network EuSCAPE-Italy participants are listed at the end of this article
6. Department of Medical Microbiology, University of Groningen, University Medical Center Groningen, the Netherlands
7. Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy
8. Clinical Microbiology and Virology Unit, Florence Careggi University Hospital, Florence, Italy

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Monaco M, Giani T, Raffone M, Arena F, Garcia-Fernandez A, Pollini S, Network EuSCAPE-Italy, Grundmann H, Pantosti A, Rossolini GM. Colistin resistance superimposed to endemic carbapenem-resistant Klebsiella pneumoniae: a rapidly evolving problem in Italy, November 2013 to April 2014. Euro Surveill. 2014;19(42):pii=20939. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20939

Article submitted on 08 October 2014 / published on 23 October 2014

Consecutive non-replicate clinical isolates (n=191) of carbapenem non-susceptible Enterobacteriaceae were collected from 21 hospital laboratories across Italy from November 2013 to April 2014 as part of the European Survey on Carbapenemase-producing Enterobacteriaceae (EuSCAPE) project. *Klebsiella pneumoniae* carbapenemase-producing *K. Pneumoniae* (KPC-KP) represented 178 (93%) isolates with 76 (43%) respectively resistant to colistin, a key drug for treating carbapenamase-producing Enterobacteriaceae.

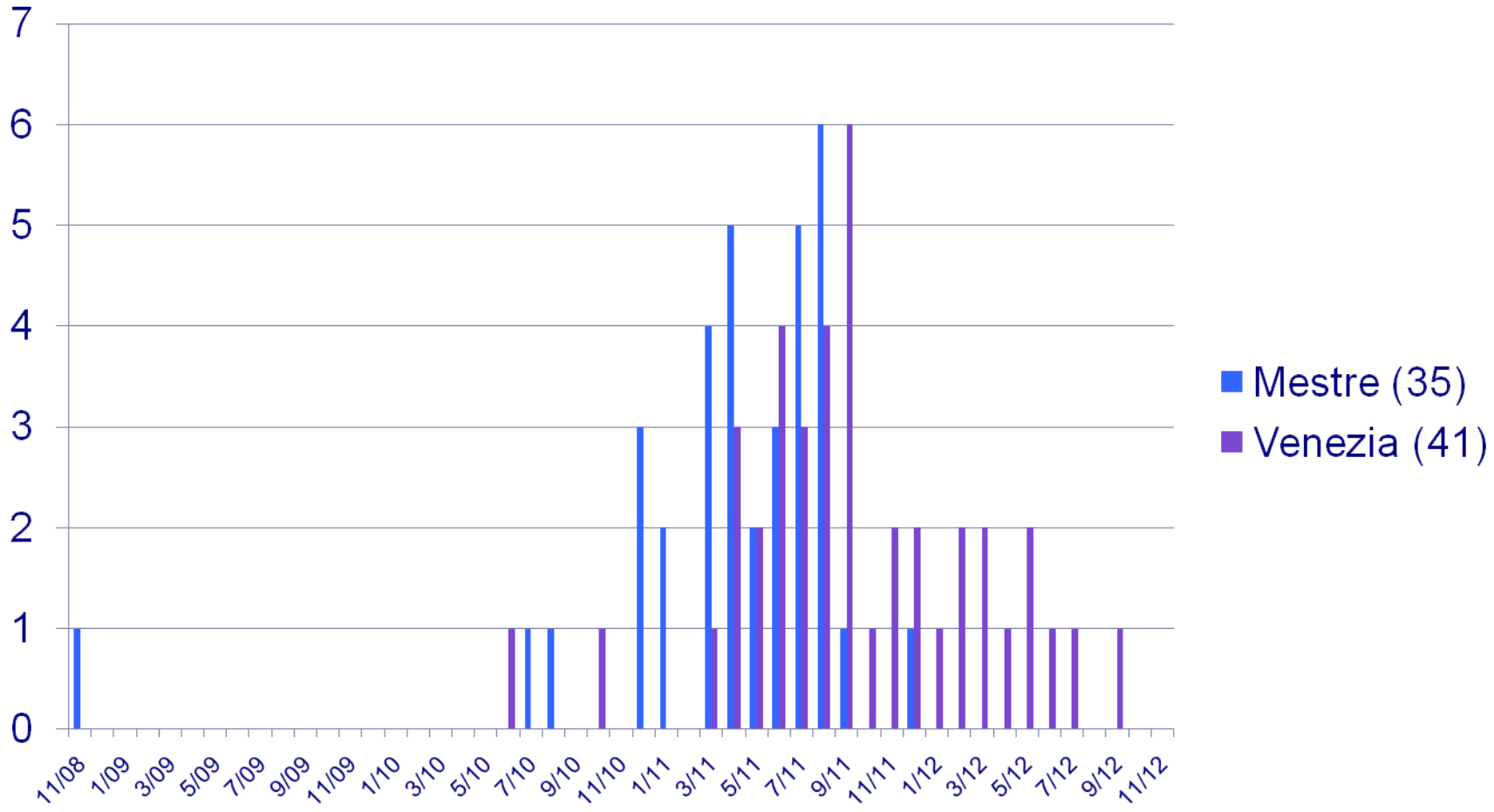
KPC-KP colistin-resistant isolates were detected in all participating laboratories. This underscores a concerning evolution of colistin resistance in a setting of high KPC-KP endemicity.

EuSCAPE: European Survey on Carbapenemase-producing Enterobacteriaceae; KPC: *Klebsiella pneumoniae* carbapenemase; KPC-KP: KPC-producing *K. pneumoniae*.

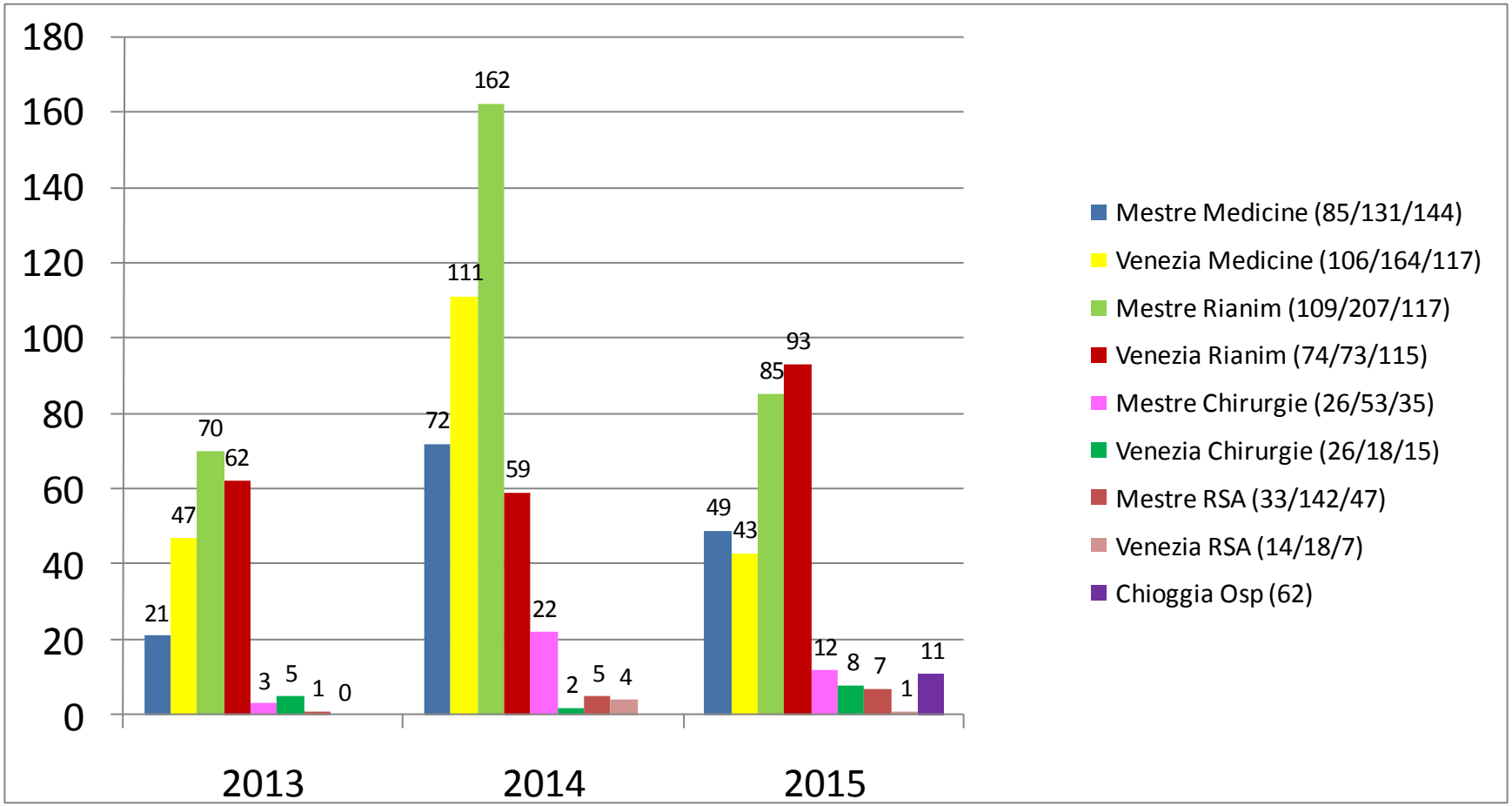
The peripheral laboratories are numbered on the map according to alphabetical order.

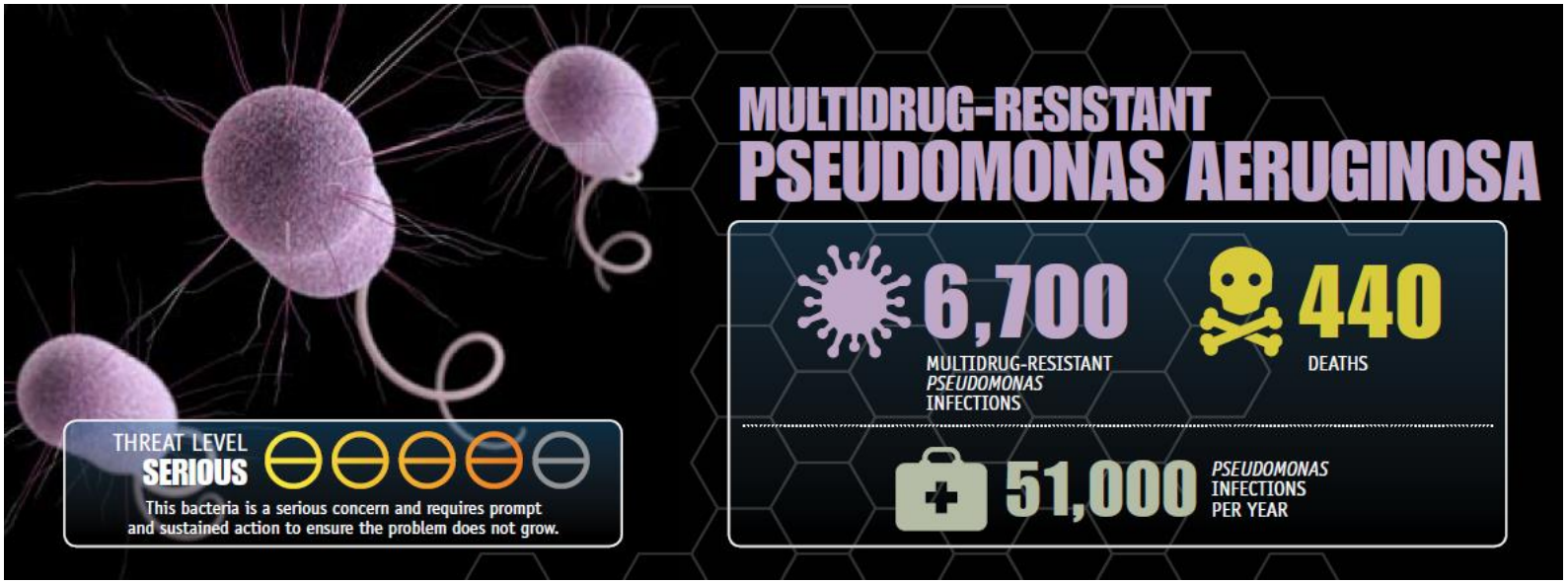
Proportions of colistin-resistant isolates among KPC-KP per peripheral laboratory:. 1, Alessandria: 1/10; 2, Ancona: 8/10; 3, Ferrara: 1/4; 4, Florence: 5/10; 5, Foggia: 4/10; 6, Lecco: 2/9; 7, Milan: 1/10; 8, Modena: 3/7; 9, Neaples: 3/8; 10, Perugia: 5/10; 11, Reggio Calabria: 4/10; 12, Rome: 4/9; 13, Rome: 2/4; 14, Rome: 6/7; 15, San Remo: 4/8; 16, Siena: 6/8; 17, Treviso: 1/7; 18, Turin: 5/9; 19, Udine: 2/8; 20, Venice: 8/10; 21, Vercelli: 1/10.

Klebsiella pneumoniae produttore di carbapenemasi (KPC)

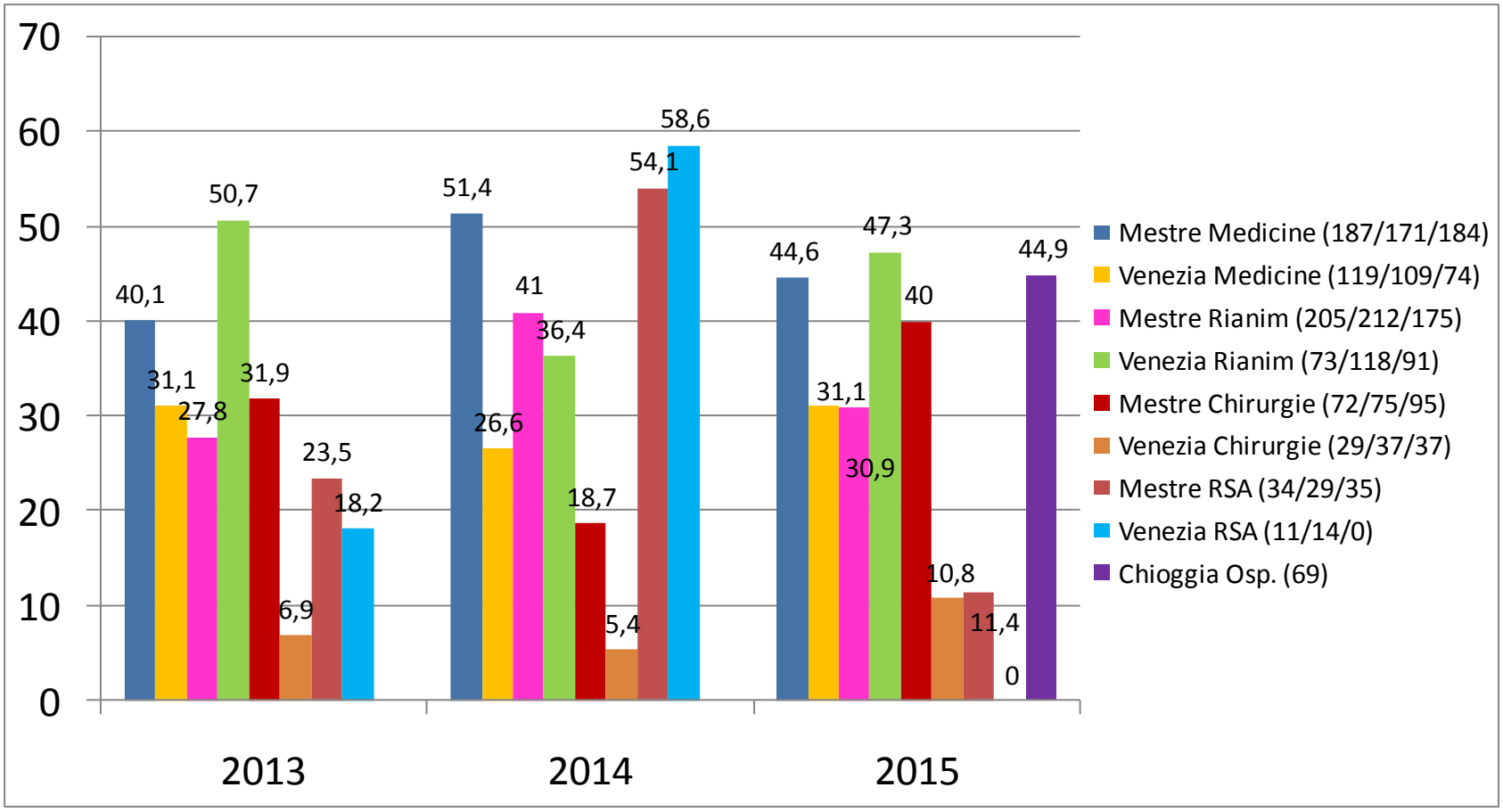


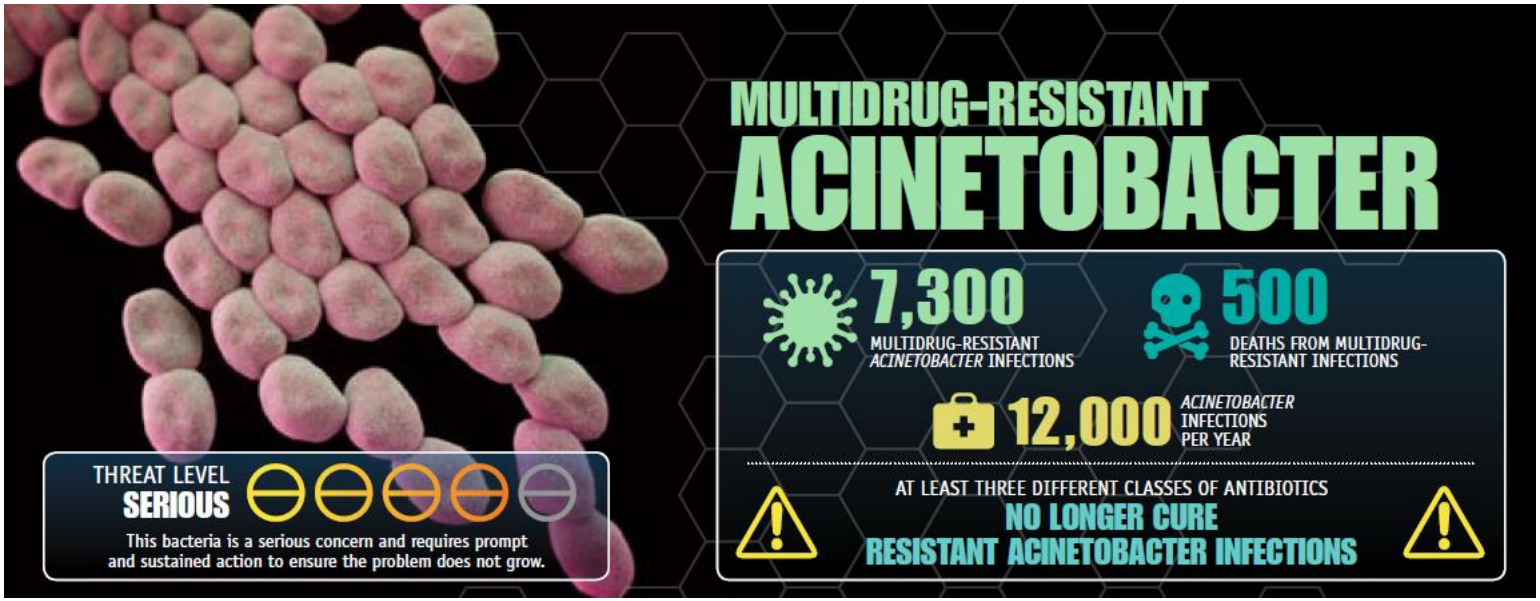
K. pneumoniae KPC
(valore assoluto)




MULTIDRUG-RESISTANT
PSEUDOMONAS AERUGINOSA
6,700
MULTIDRUG-RESISTANT
PSEUDOMONAS
INFECTIONS
440
DEATHS
51,000
PSEUDOMONAS
INFECTIONS
PER YEAR
THREAT LEVEL
SERIOUS
This bacteria is a serious concern and requires prompt
and sustained action to ensure the problem does not grow.

Pseudomonas aeruginosa – Carbapenemi R o I




MULTIDRUG-RESISTANT
ACINETOBACTER
7,300
MULTIDRUG-RESISTANT ACINETOBACTER INFECTIONS
500
DEATHS FROM MULTIDRUG-RESISTANT INFECTIONS
12,000
ACINETOBACTER INFECTIONS PER YEAR
AT LEAST THREE DIFFERENT CLASSES OF ANTIBIOTICS
NO LONGER CURE
RESISTANT ACINETOBACTER INFECTIONS
THREAT LEVEL
SERIOUS
This bacteria is a serious concern and requires prompt and sustained action to ensure the problem does not grow.

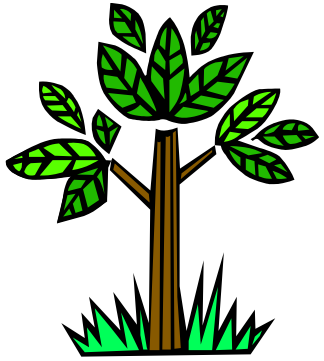
Acinetobacter baumannii

- Coccobacilli Gram negativi, aerobi, non fermentanti
- Ampia diffusione in ambienti naturali
- Rapida insorgenza di resistenza nei confronti della maggioranza degli antibiotici, tra i quali:
  - aminoglicosidi
  - fluorochinoloni
  - carbapenemici

Fagon JY. Am J Med 1993;94:281-8 - Bercault N. Crit Care Med 2001;29:2303-9
Garcia-Garmendia JL. Clin Infect Dis 2001;33:939-46 - Richards MJ. Crit Care Med 1999;27:887-92 - Lortholary O. Clin Infect Dis 1995;20:790-6

Habitat dell'*Acinetobacter*

- *A. baumannii* è ubiquitario in natura
- Isolato da terreno, acqua, animali, esseri umani



Epidemiologia

Figure 3.32. *Acinetobacter* spp. Percentage (%) of invasive isolates with resistance to fluoroquinolones, by country, EU/EEA countries, 2012

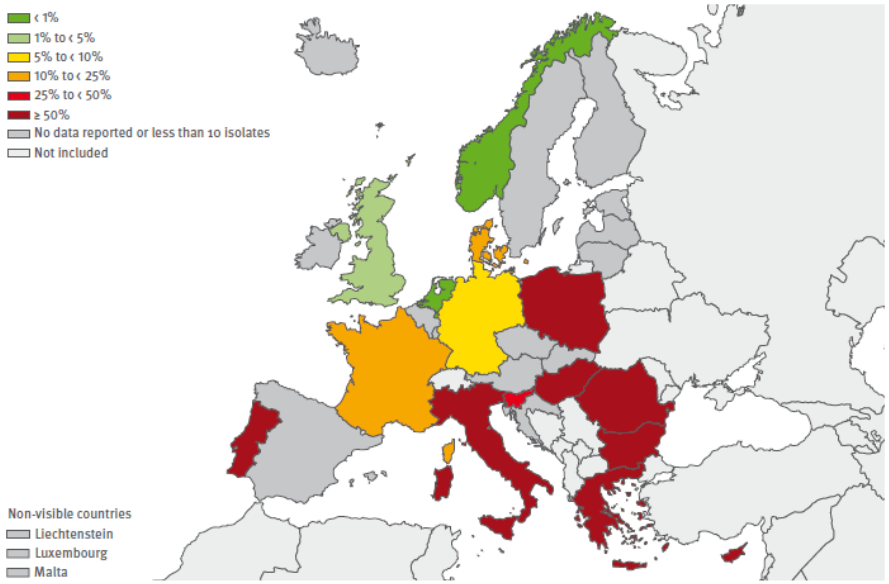
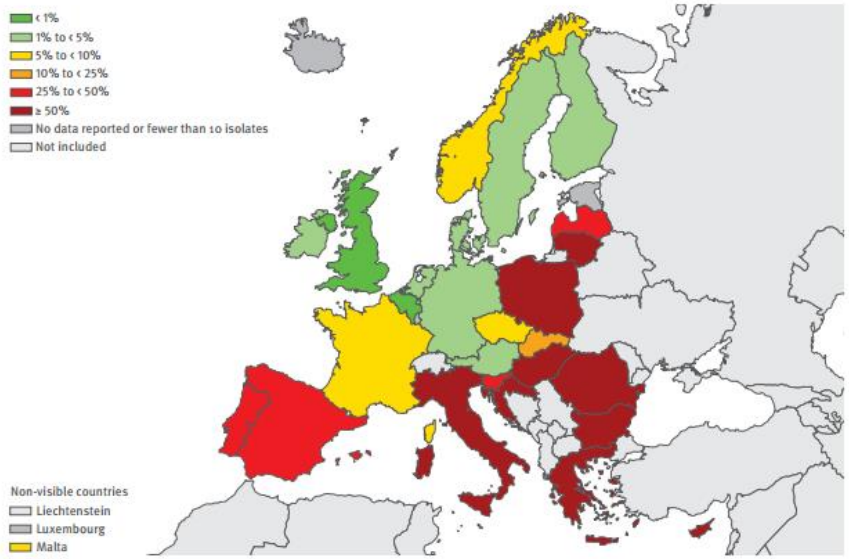


Figure 3.20. *Acinetobacter* spp. Percentage (%) of invasive isolates with combined resistance to fluoroquinolones, aminoglycosides and carbapenems, by country, EU/EEA countries, 2015



Epidemiologia

Figure 3.33. *Acinetobacter* spp. Percentage (%) of invasive isolates with resistance to aminoglycosides, by country, EU/EEA countries, 2012

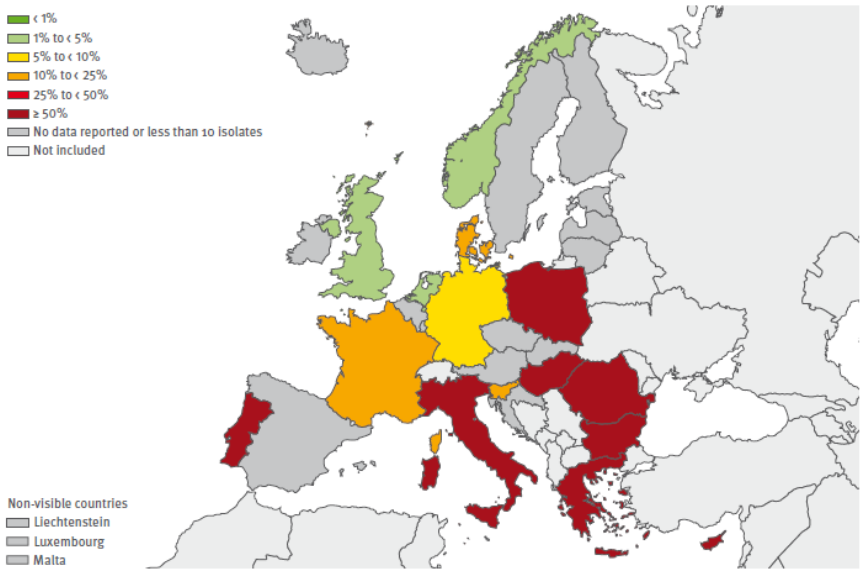
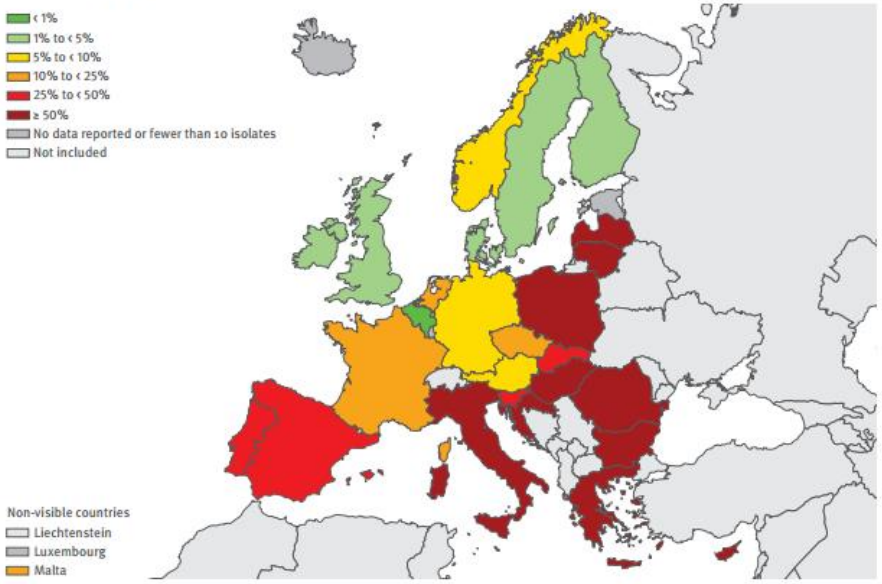


Figure 3.18. *Acinetobacter* spp. Percentage (%) of invasive isolates with resistance to aminoglycosides, by country, EU/EEA countries, 2015



Epidemiologia

Figure 3.34. *Acinetobacter* spp. Percentage (%) of invasive isolates with resistance to carbapenems, by country, EU/EEA countries, 2012

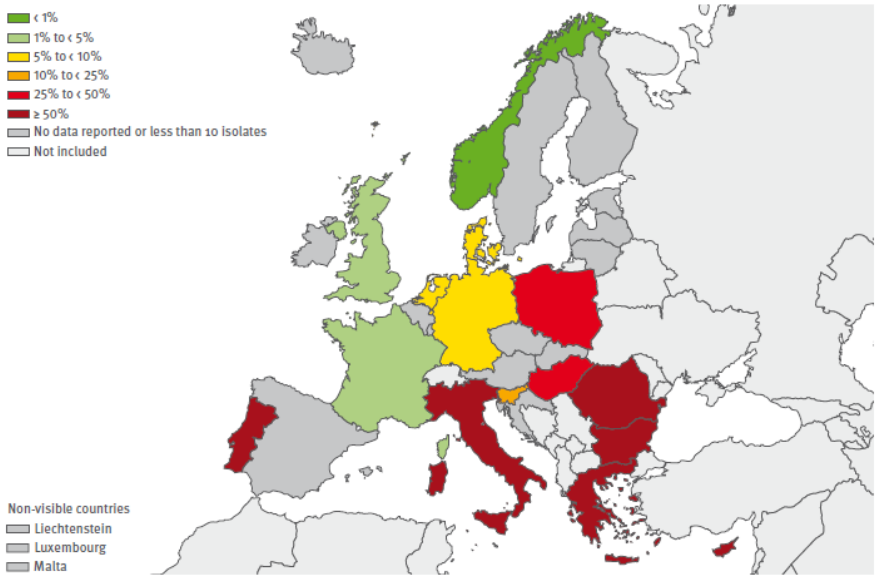
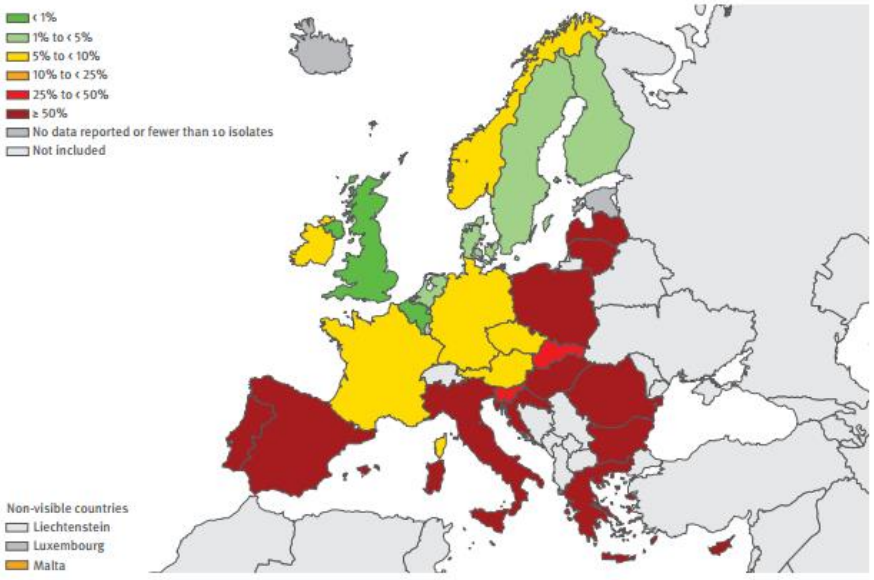


Figure 3.19. *Acinetobacter* spp. Percentage (%) of invasive isolates with resistance to carbapenems, by country, EU/EEA countries, 2015



Epidemiologia

Figure 3.35. *Acinetobacter* spp. Percentage (%) of invasive isolates with combined resistance (resistance to fluoroquinolones, aminoglycosides and carbapenems), by country, EU/EEA countries, 2012

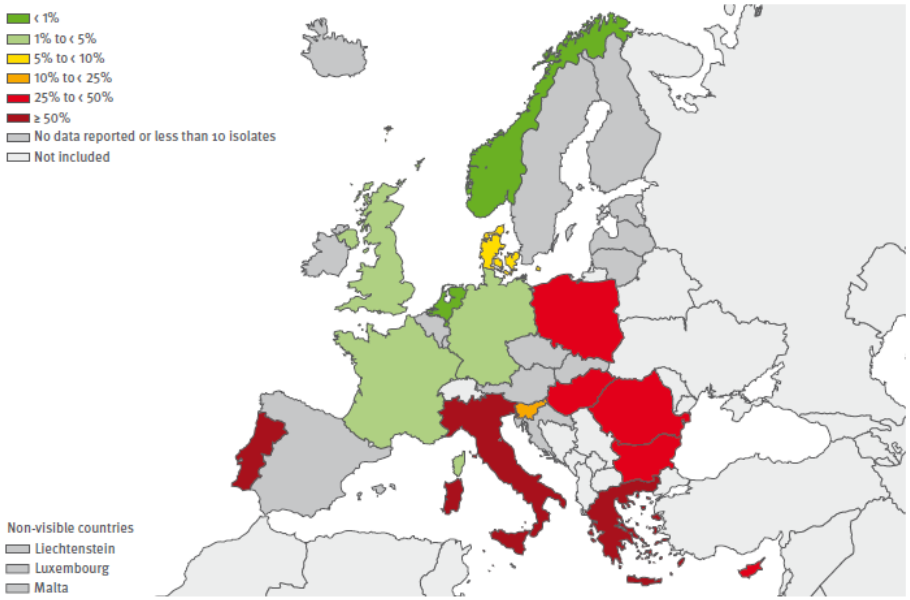
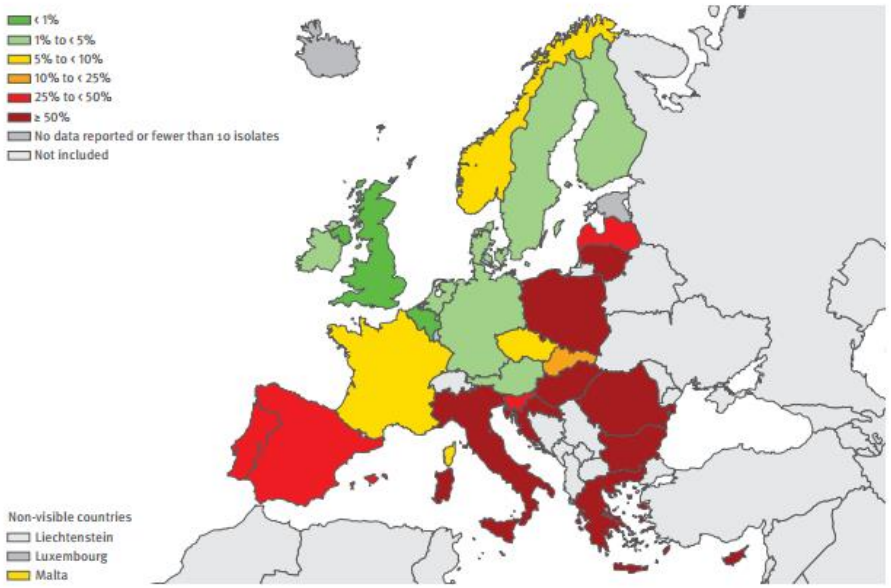
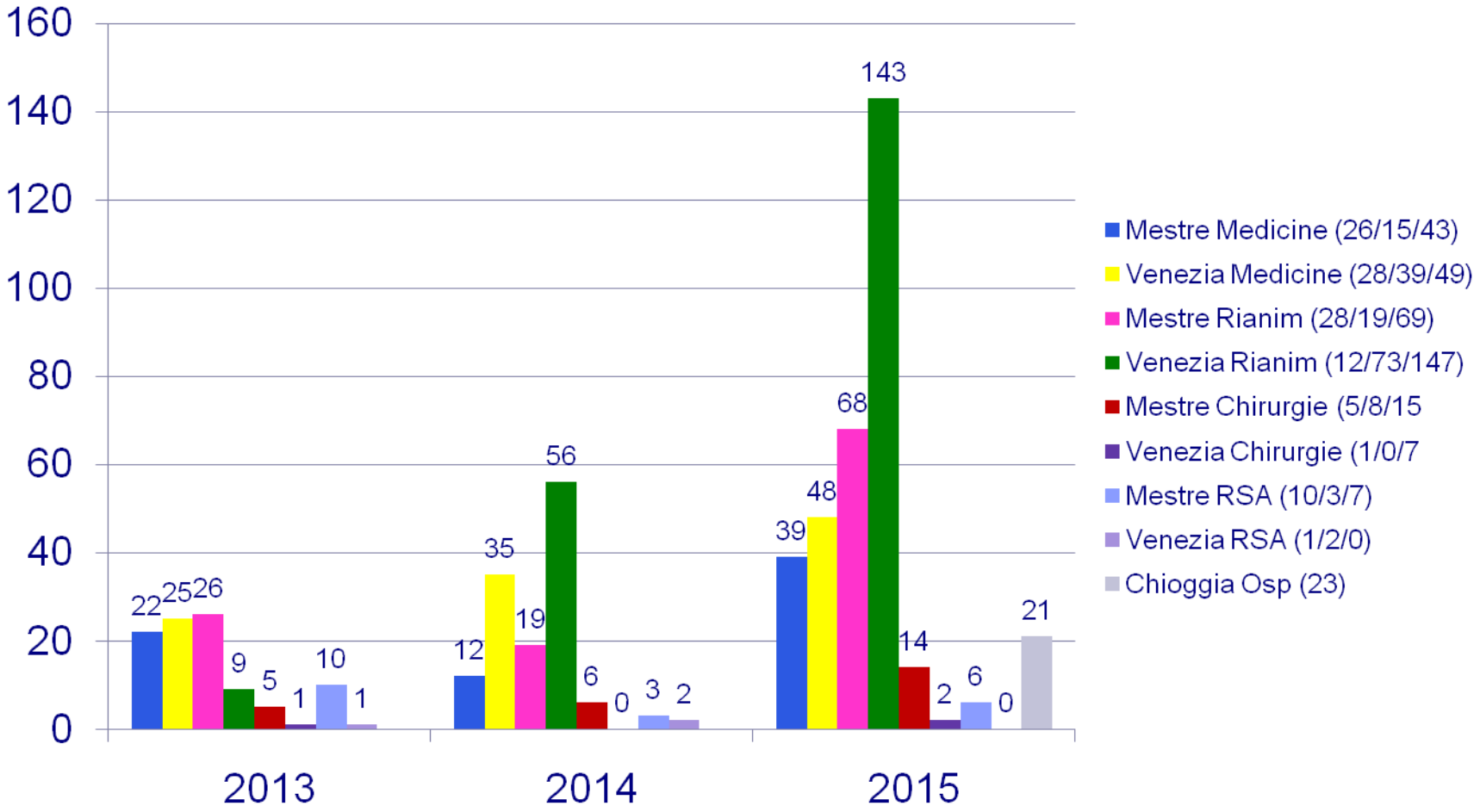


Figure 3.20. *Acinetobacter* spp. Percentage (%) of invasive isolates with combined resistance to fluoroquinolones, aminoglycosides and carbapenems, by country, EU/EEA countries, 2015



Acinetobacter baumannii XDR

(numero assoluto)



JOURNAL OF CLINICAL MICROBIOLOGY, May 2007, p. 1551–1555 Vol. 45, No. 5
0095-1137/07/$08.00+0 doi:10.1128/JCM.02424-06

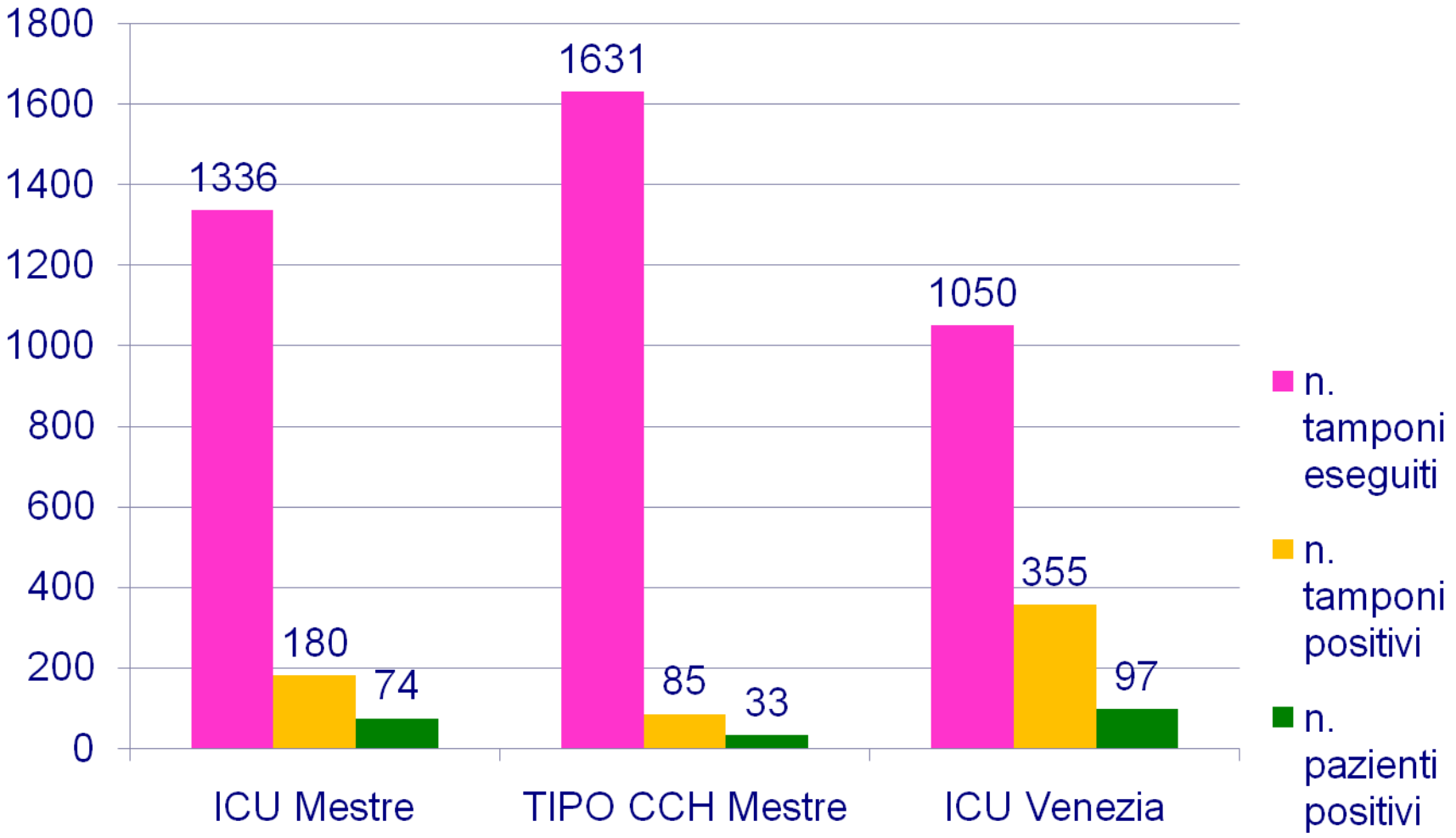
Surveillance Cultures and Duration of Carriage of Multidrug-Resistant *Acinetobacter baumannii*▽

Dror Marchaim,[1]* Shiri Navon-Venezia,[1] David Schwartz,[2] Jalal Tarabeia,[1] Iris Fefer,[1] Mitchell J. Schwaber,[1] and Yehuda Carmeli[1]

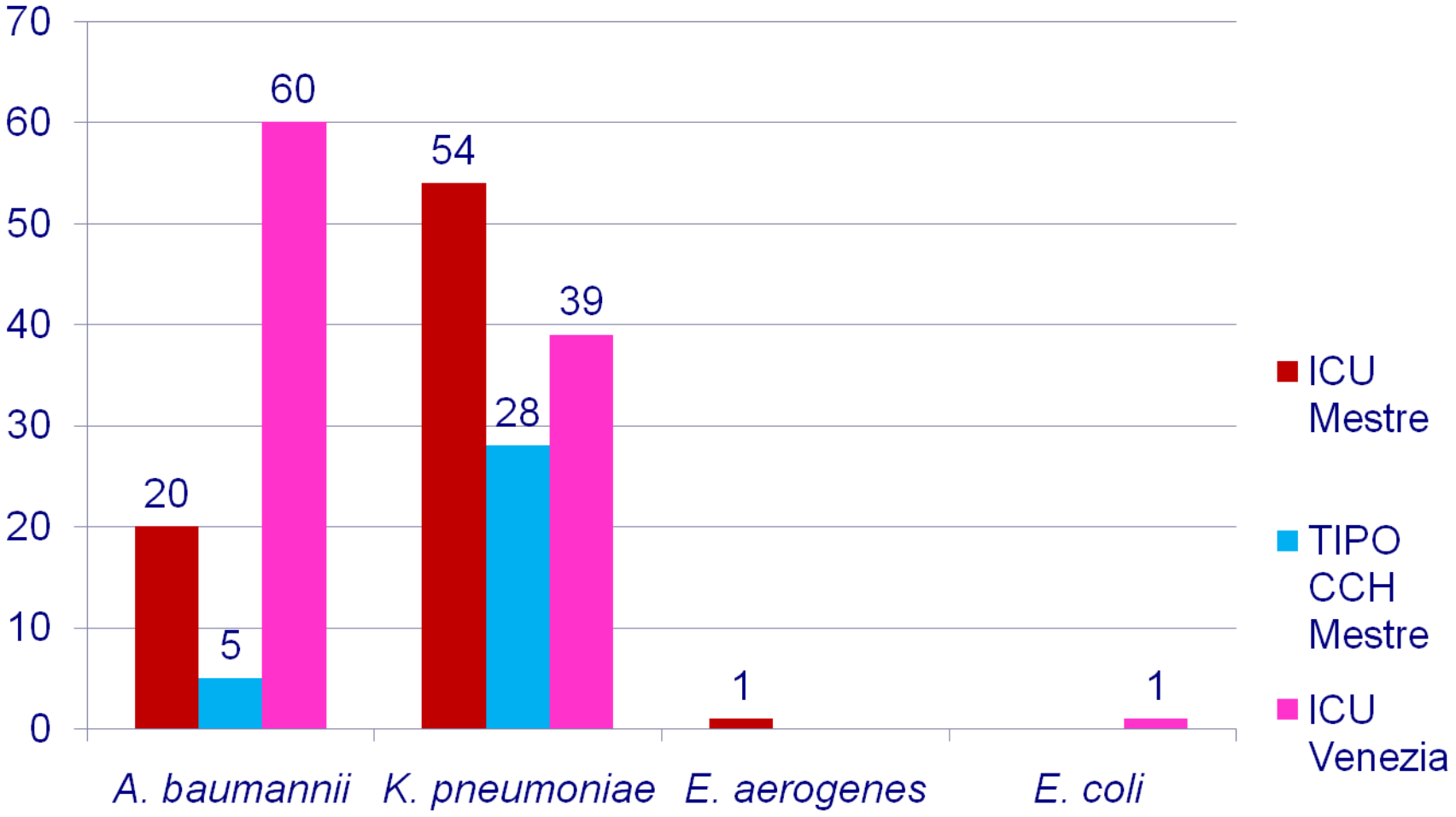
Division of Epidemiology, Tel-Aviv Sourasky Medical Center, 6 Weizmann St., Tel-Aviv 64239, Israel,[1] and Clinical Microbiology Laboratory, Tel-Aviv Sourasky Medical Center, 6 Weizmann St., Tel-Aviv 64239, Israel[2]

Among 30 patients with remote clinical isolation, screening cultures were positive in 5 (17%), with a mean duration of 17.5 months from the last clinical culture. Remote carriers had positive screening cultures from the skin and pharynx but not from nose, rectum, wounds, or endotracheal aspirates.

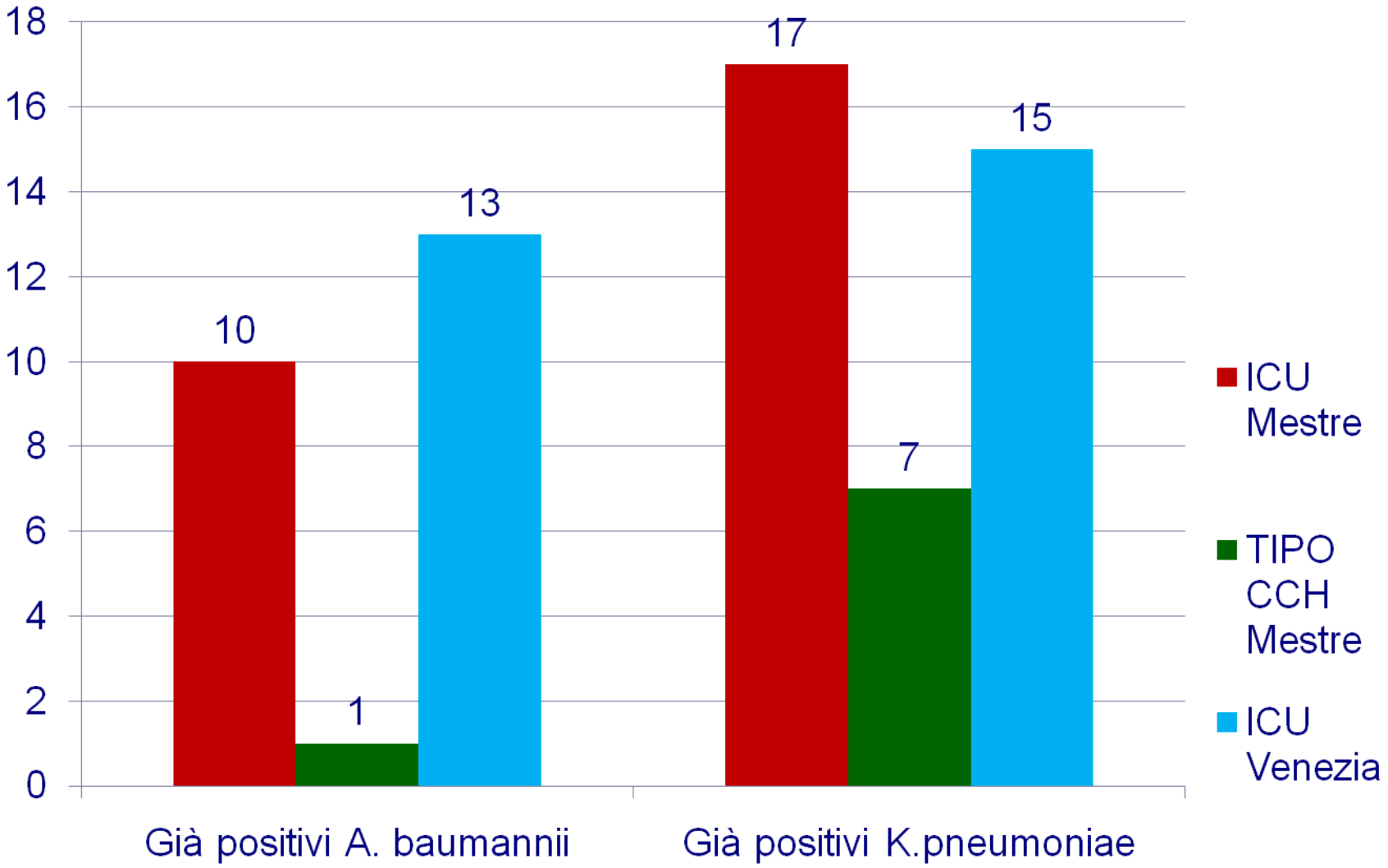
ICU e tamponi rettali di sorveglianza 2014-2015



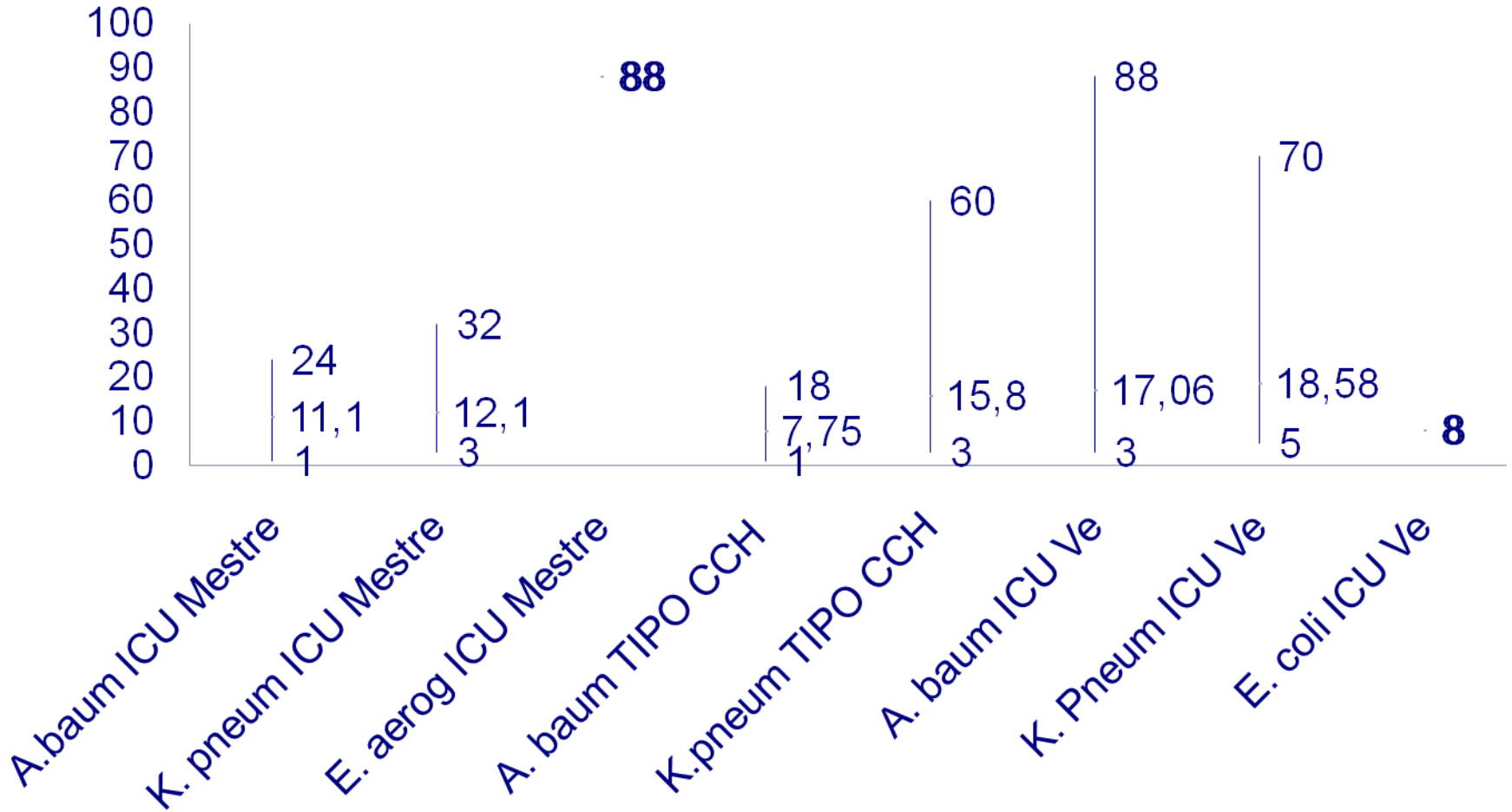
ICU e tamponi rettali di sorveglianza 2014-2015



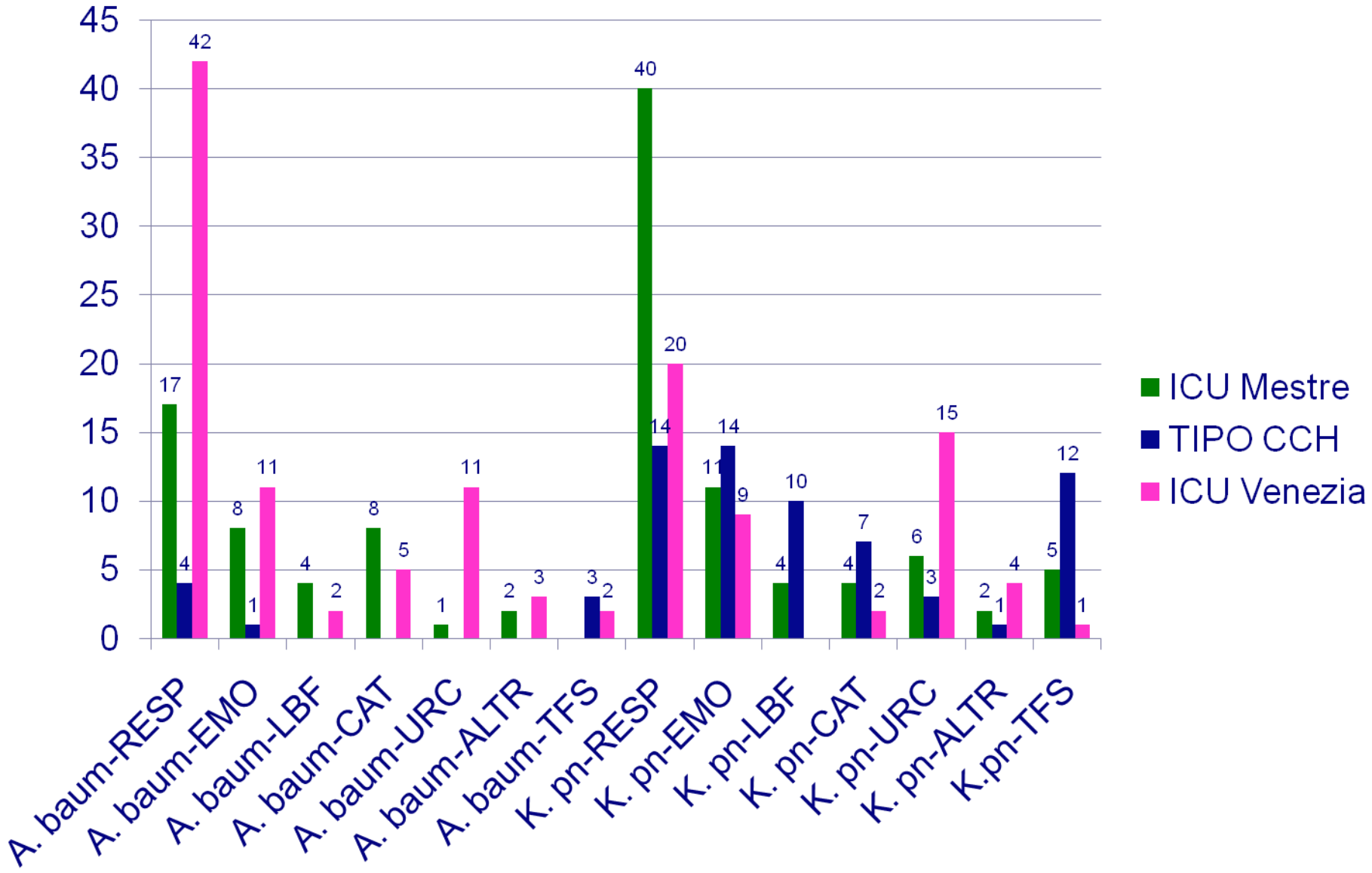
ICU e tamponi rettali di sorveglianza 2014-2015
All'ingresso in ICU …



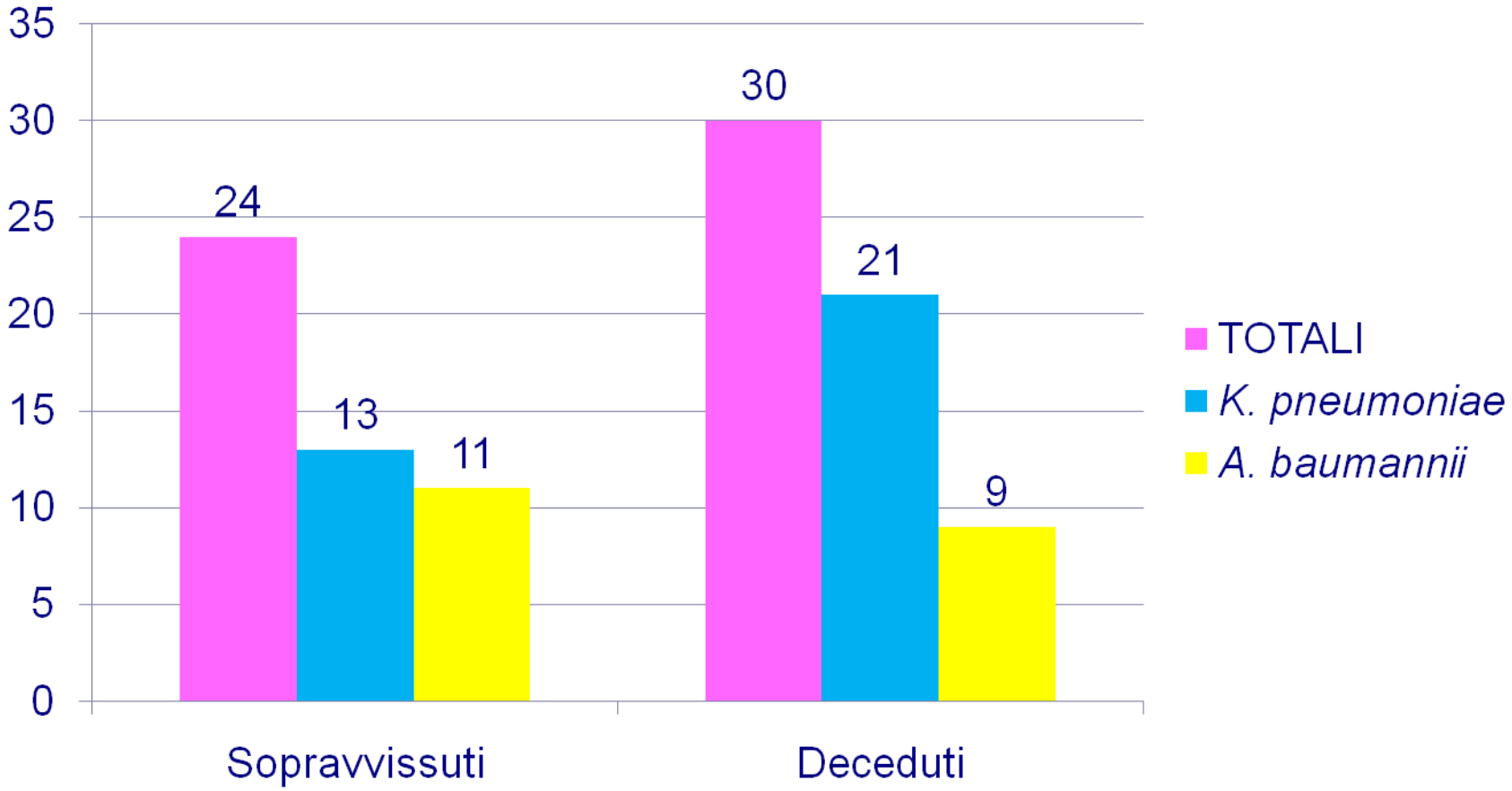
ICU e tamponi rettali di sorveglianza 2014-2015
Tempi di positivizzazione



ICU e tamponi rettali di sorveglianza 2014-2015
Positività in altri tipi di materiali



MORTALITA'


35
30
25
20
15
10
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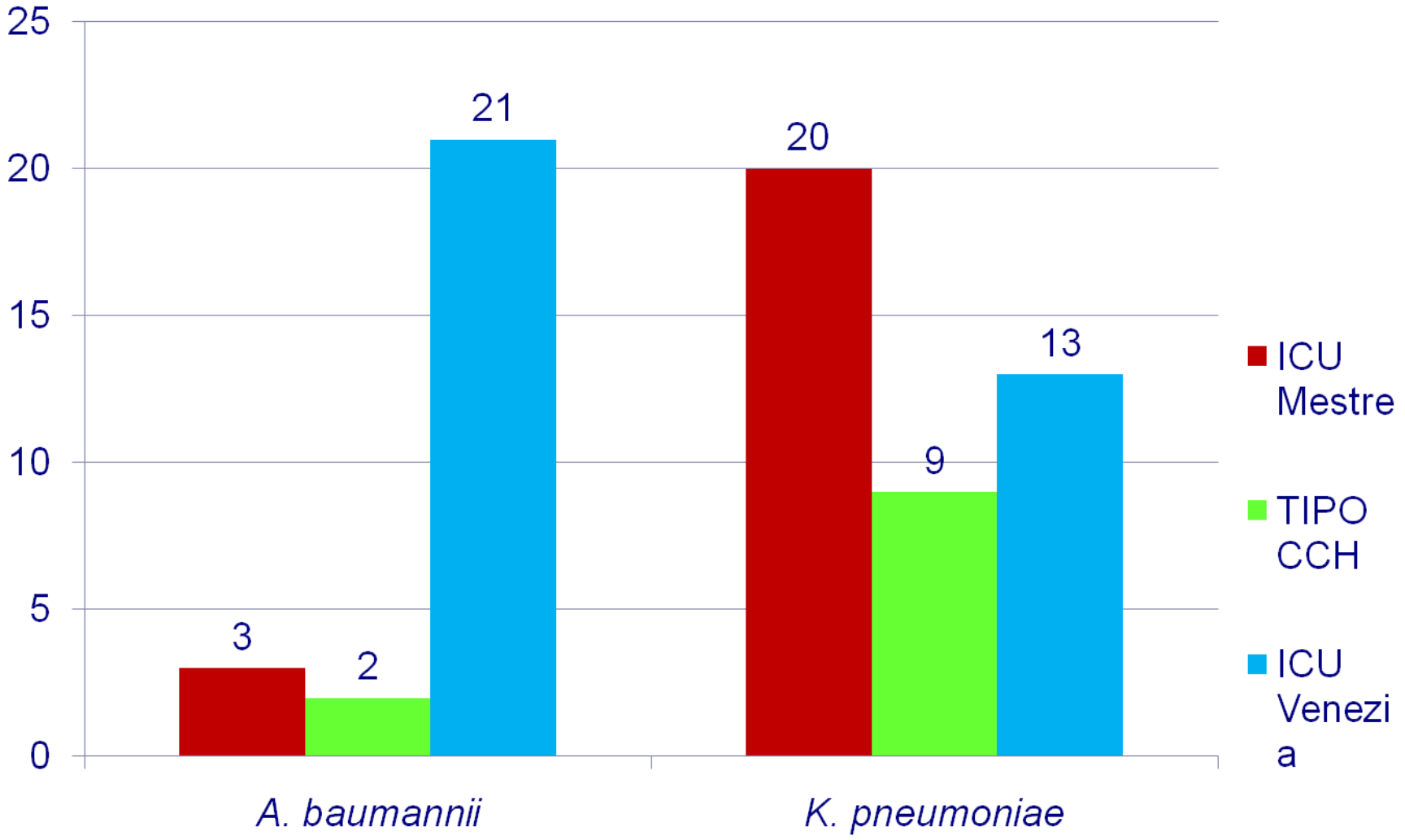
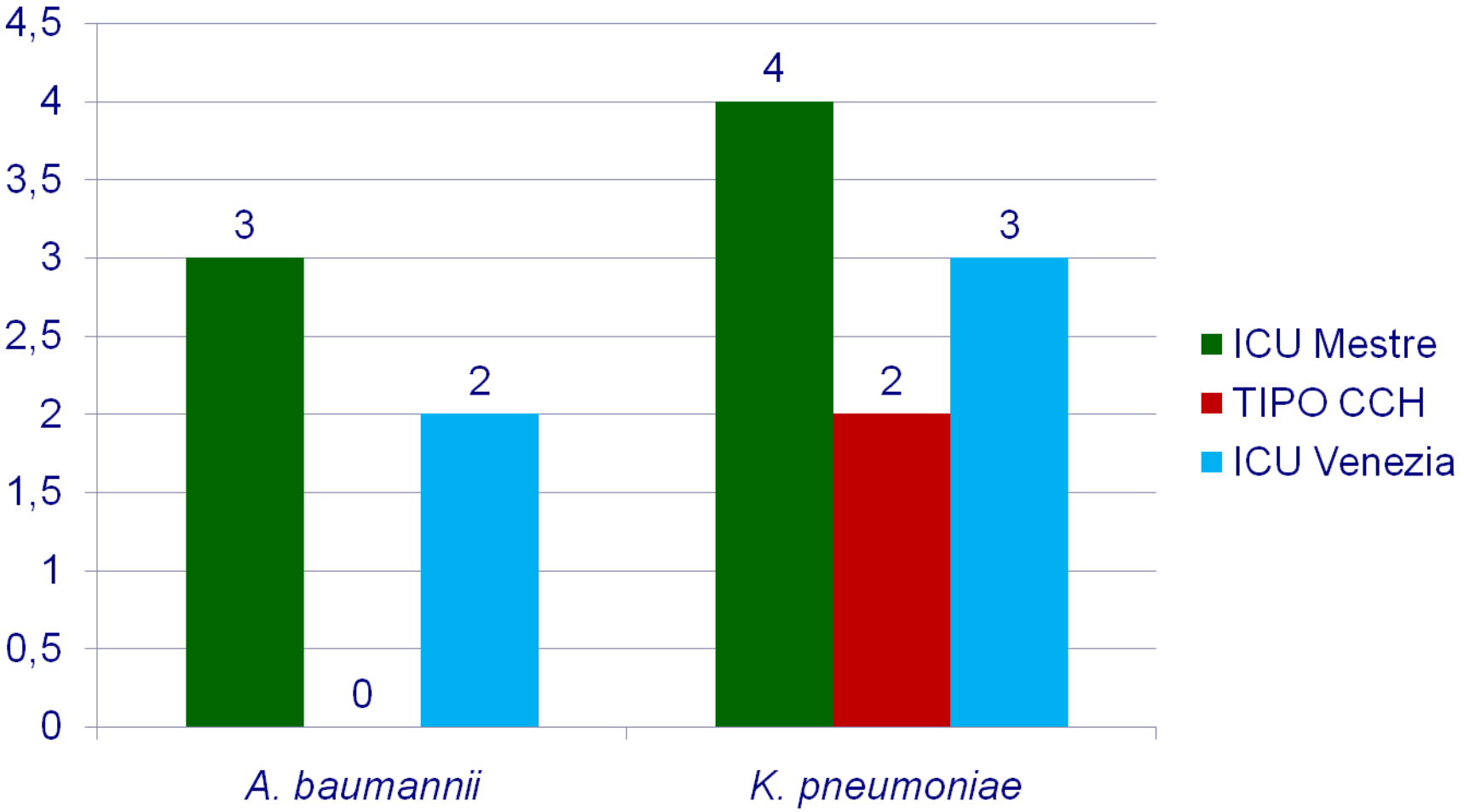
0
24
13
11
30
21
9
Sopravvissuti
Deceduti
TOTALI
K. pneumoniae
A. baumannii

ICU e tamponi rettali di sorveglianza 2014-2015
Negatività in altri tipi di materiali



ICU e tamponi rettali di sorveglianza 2014-2015
Positività pregressa in altre UUOO



Geneva, 25-27 January 2017

World Health Organization

GLOBAL PRIORITY LIST OF ANTIBIOTIC-RESISTANT BACTERIA TO GUIDE RESEARCH, DISCOVERY, AND DEVELOPMENT OF NEW ANTIBIOTICS

Chair: E. Tacconelli (Infectious Diseases, DZIF Center, Tübingen University, Germany) and N. Magrini (WHO, EMP Department)

WHO PRIORITY PATHOGENS LIST FOR R&D OF NEW ANTIBIOTICS

Priority 1: CRITICAL[#]

Acinetobacter baumannii, carbapenem-resistant

Pseudomonas aeruginosa, carbapenem-resistant

Enterobacteriaceae*, carbapenem-resistant, 3rd generation cephalosporin-resistant

Priority 2: HIGH

Enterococcus faecium, vancomycin-resistant

Staphylococcus aureus, methicillin-resistant, vancomycin intermediate and resistant

Helicobacter pylori, clarithromycin-resistant

Campylobacter, fluoroquinolone-resistant

Salmonella *spp.*, fluoroquinolone-resistant

Neisseria gonorrhoeae, 3rd generation cephalosporin-resistant, fluoroquinolone-resistant

Priority 3: MEDIUM

Streptococcus pneumoniae, penicillin-non-susceptible

Haemophilus influenzae, ampicillin-resistant

Shigella *spp.*, fluoroquinolone-resistant

TECHNICAL REPORT

Proposals for EU guidelines on the prudent use of antimicrobials in humans

www.ecdc.europa.eu

Contents

Febbraio 2017

Pan-Resistant New Delhi Metallo-Beta-Lactamase-Producing *Klebsiella pneumoniae* — Washoe County, Nevada, 2016

- On August 25, 2016 in Reno, Nevada, was notified of a patient at an acute care hospital with carbapenem-resistant Enterobacteriaceae (CRE) that was resistant to all available antimicrobial drugs. The specific CRE, *Klebsiella pneumoniae*, was isolated from a wound specimen collected on August 19, 2016. After CRE was identified, the patient was placed in a single room under contact precautions. The patient had a history of recent hospitalization outside the United States. The isolate was sent to CDC for testing to determine the mechanism of antimicrobial resistance, which confirmed the presence of New Delhi metallo-beta-lactamase (NDM).
- The patient was a female in her 70s who arrived in the United States in early August 2016 after an extended visit to India. She was admitted to the acute care hospital on August 18 with a primary diagnosis of systemic inflammatory response syndrome, likely resulting from an infected right hip seroma. The patient developed septic shock and died in early September. During the 2 years preceding this U.S. hospitalization, the patient had multiple hospitalizations in India related to a right femur fracture and subsequent osteomyelitis of the right femur and hip; the most recent hospitalization in India had been in June 2016.
- Antimicrobial susceptibility testing in the United States indicated that the isolate was resistant to 26 antibiotics, including all aminoglycosides and polymyxins tested, and intermediately resistant to tigecycline. Because of a high minimum inhibitory concentration (MIC) to colistin, the isolate was tested at CDC for the *mcr-1* gene, which confers plasma-mediated resistance to colistin; the results were negative. The isolate had a relatively low fosfomycin MIC of 16 *μ*g/mL by ETEST (fosfomycin is approved in the United States only as an oral treatment of uncomplicated cystitis; an intravenous formulation is available in other countries).
- A point prevalence survey, using rectal swab specimens and conducted among patients currently admitted to the same unit as the patient, did not identify additional CRE. Active surveillance for multidrug-resistant bacilli including CRE has been conducted in Washoe County since 2010 and is ongoing; no additional NDM CRE have been identified.
- This report highlights three important issues in the control of CRE. First, isolates that are resistant to all antimicrobials are very uncommon. Among >250 CRE isolate reports collected as part of the Emerging Infections Program, approximately 80% remained susceptible to at least one aminoglycoside and nearly 90% were susceptible to tigecycline . Second, to slow the spread of bacteria with resistance mechanisms of greatest concern (e.g., gene encoding NDM or *mcr-1*) or with pan-resistance to all drug classes, CDC recommends that when these bacteria are identified, facilities ensure that appropriate infection control contact precautions are instituted to prevent transmission and that health care contacts are evaluated for evidence of transmission (*3*). Third, the patient in this report had inpatient health care exposure in India before receiving care in the United States. Health care facilities should obtain a history of health care exposures outside their region upon admission and consider screening for CRE when patients report recent exposure outside the United States or in regions of the United States known to have a higher incidence of CRE.

MMWR, *Weekly* / January 13, 2017 / 66(1);33

Italia maglia nera per antibiotico-resistenza e prevalenza epatite C

ADNKronos Salute | 27 Feb 2017 | 217 Visualizzazioni | 4 Stelle

E la maglia nera per le resistenze agli antibiotici e oltre 280 mila persone colpite da infezioni correlate all'assistenza.
"Le malattie infettive rappresentano un capitolo rilevante in termini di incidenza e mortalità in Italia - afferma Walter Ricciardi, presidente dell'Istituto superiore di sanità - **L'Italia è maglia nera per le resistenze di germi come le klebsielle e altri batteri Gram negativi nei confronti di diversi antibiotici, primi fra tutti i carbapenemi…."**

Ma non solo: **entro il 2050 le infezioni resistenti agli antibiotici potrebbero essere la prima causa di morte al mondo, con un tributo annuo di oltre 10 milioni di vite.** In Italia, la resistenza agli antibiotici si mantiene tra le più elevate in Europa: **nel nostro Paese le infezioni correlate all'assistenza colpiscono ogni anno circa 284.100 pazienti causando non meno di 5 mila decessi.**

"Il Piano nazionale contro la resistenza agli antibiotici, annunciato dal ministro della Salute, va nella giusta direzione - afferma Mario Marazziti, presidente della commissione Affari sociali della Camera - L'aspetto qualificante è la scelta di affrontare in modo integrato tutti gli aspetti dell'antibiotico-resistenza secondo un approccio **'One Health'**, ovvero un **approccio olistico alla salute umana e degli animali**. Fondamentale anche la **disponibilità degli antibiotici di nuova generazione**, che devono essere resi accessibili al paziente nel rispetto dei criteri di una corretta **stewardship**".

Fine secondo quarto
Pausa lunga

Batteri 2

Antibiotici 1

Andiamo al terzo e quarto tempo…

(Lieviti… Clostridium difficile … Parassiti…?)

ORDINE PROVINCIALE
DEI MEDICI CHIRURGHI E
DEGLI ODONTOIATRI
DI VENEZIA

FONDAZIONE ARS MEDICA
VENEZIA

ORDINE DEI MEDICI VETERINARI
DELLA PROVINCIA DI VENEZIA

REGIONE DEL VENETO
ULSS3
SERENISSIMA

UOMINI, ANIMALI E ANTIBIOTICI: UN TRIANGOLO "PERICOLOSO"

GIOVEDÌ 9 MARZO 2017

Grazie per l'attenzione