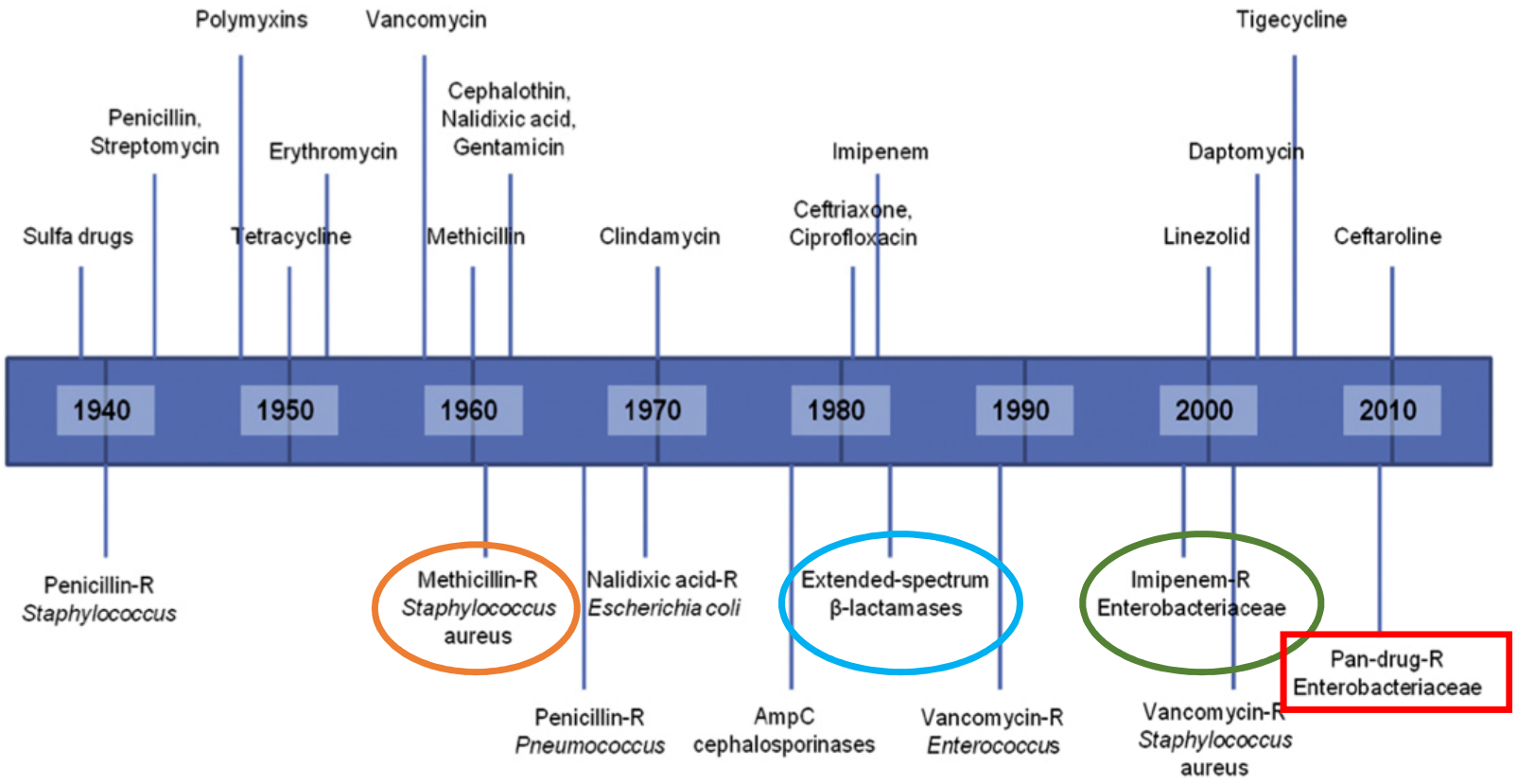
L' antibioticoresistenza è un problema ospedaliero?

Laura Pagani

Università di Pavia

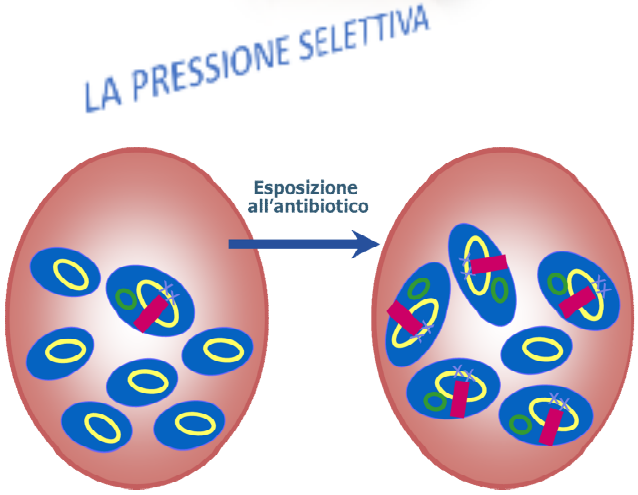

HIGH-LEVEL MEETING ON
ANTIMICROBIAL RESISTANCE
21 SEPTEMBER 2016, UN HEADQUARTERS, NEW YORK
Antibiotic resistance leads to HIGHER medical costs, PROLONGED hospital stays and INCREASED number of deaths, the World Health Organization says.
#AntibioticResistance
bit.ly/amr2016

La Resistenza agli Antibiotici:
una delle più gravi minacce globali alla salute umana nel 21° secolo



Tang S. et al. Advanced Drug Delivery Reviews, 2014. 78:3-13

LA RESISTENZA AGLI ANTIBIOTICI



NATURE REVIEWS | MICROBIOLOGY VOLUME 2 | MARCH 2004 | **251**

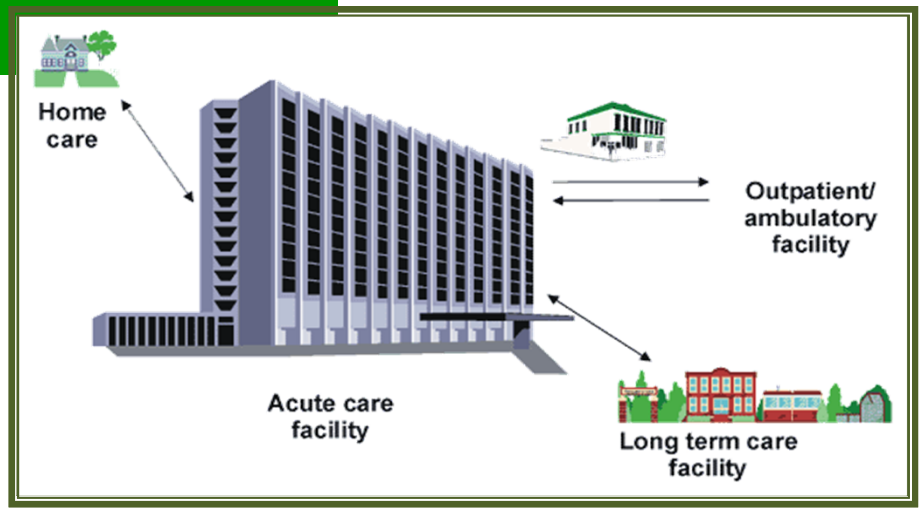
OPINION ANT INFECTIVES

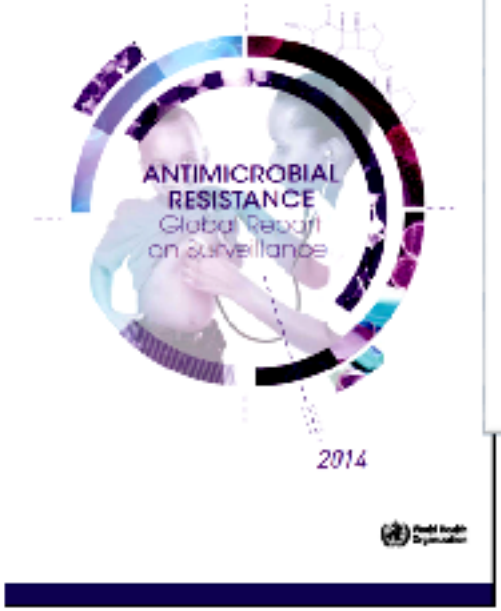
Confronting bacterial resistance in healthcare settings: a crucial role for microbiologists

John E. McGowan Jr and Fred C. Tenover

Over the past decade, antimicrobial resistance has emerged as a major public-health crisis

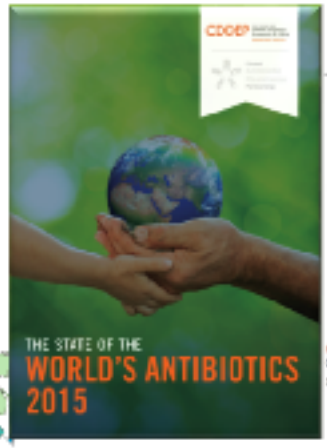
Bacteria that are resistant to antimicrobial agents, which were previously isolated primarily in acute-care hospitals, now cause infection in a wide range of other healthcare settings.

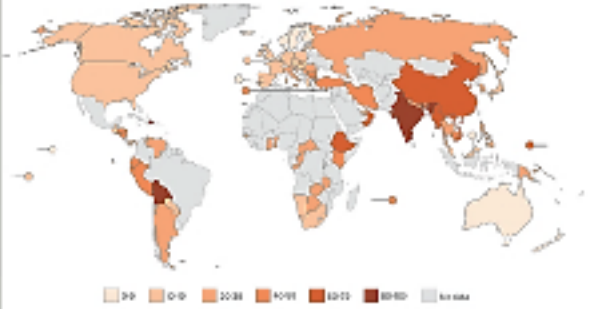


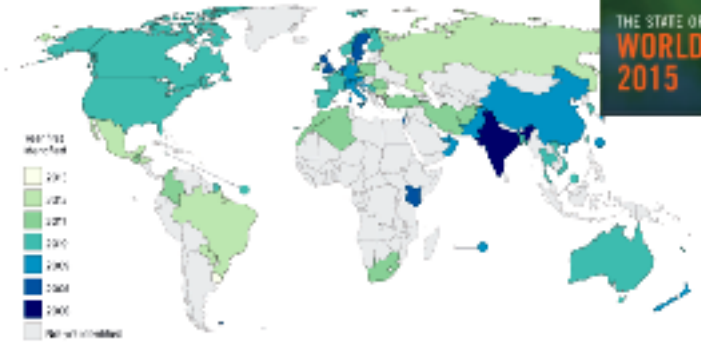


Bacteria commonly causing infections in hospitals and in the community

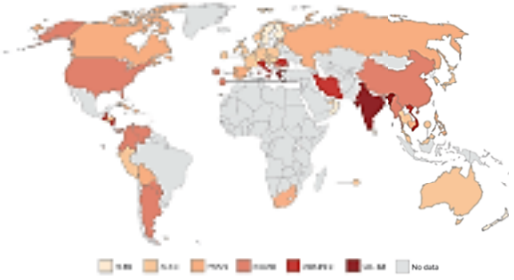
Name of bacterium/ resistance	Examples of typical diseases	No. out of 194 Member States providing data	No. of WHO regions with national reports of 50% resistance or more
Escherichia coli/	Urinary tract infections, blood stream infections		
- vs 3rd gen. cephalosporins		86	5/6
- vs fluoroquinolones		92	5/6
Klebsiella pneumoniae/	Pneumonia, blood stream infections, urinary tract infections		
- vs 3rd gen. cephalosporins		87	6/6
- vs 3rd carbapenems		71	2/6
Staphylococcus aureus/	Wound infections, blood stream infections		
- vs methicillin "MRSA"		85	5/6







Source: Johnson and Woodford 2013 (adapted).



Journal of Global Antimicrobial Resistance xxx (2015) xxx–xxx

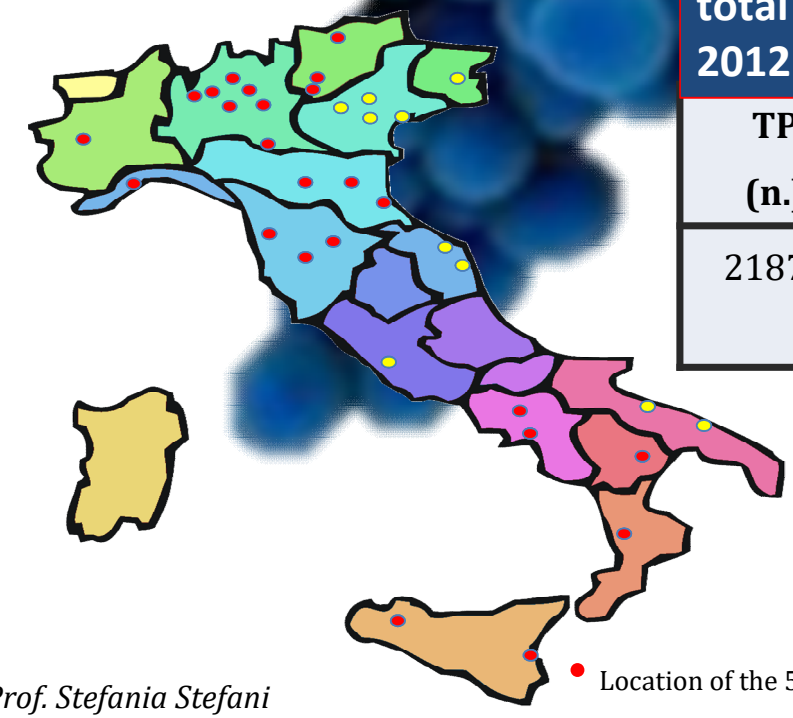
Contents lists available at ScienceDirect

Journal of Global Antimicrobial Resistance

journal homepage: www.elsevier.com/locate/jgar

Epidemiology of *Staphylococcus aureus* in Italy: First nationwide survey, 2012

Floriana Campanile [a,*], Dafne Bongiorno [a], Marianna Perez [a], Gino Mongelli [a], Laura Sessa [a], Sabrina Benvenuto [a], Floriana Gona [b] AMCLI – S. aureus Survey Participants[1], Pietro E. Varaldo [c], Stefania Stefani [a]



● Location of the 52 hospital laboratories participating in the survey

Prevalence of *S. aureus* and MRSA in Italy among total number of pathogens (TP) isolated during 2012

TP (n.)	*S.aureus*/TP (n.-%)	MRSA/TP (n.-%)	MRSA/*S.aureus* (n.-%)
21873	2541/21873 **(11.6%)**	910/21873 **(4.1%)**	910/2541 **(35.8%)**

By courtesy of Prof. Stefania Stefani

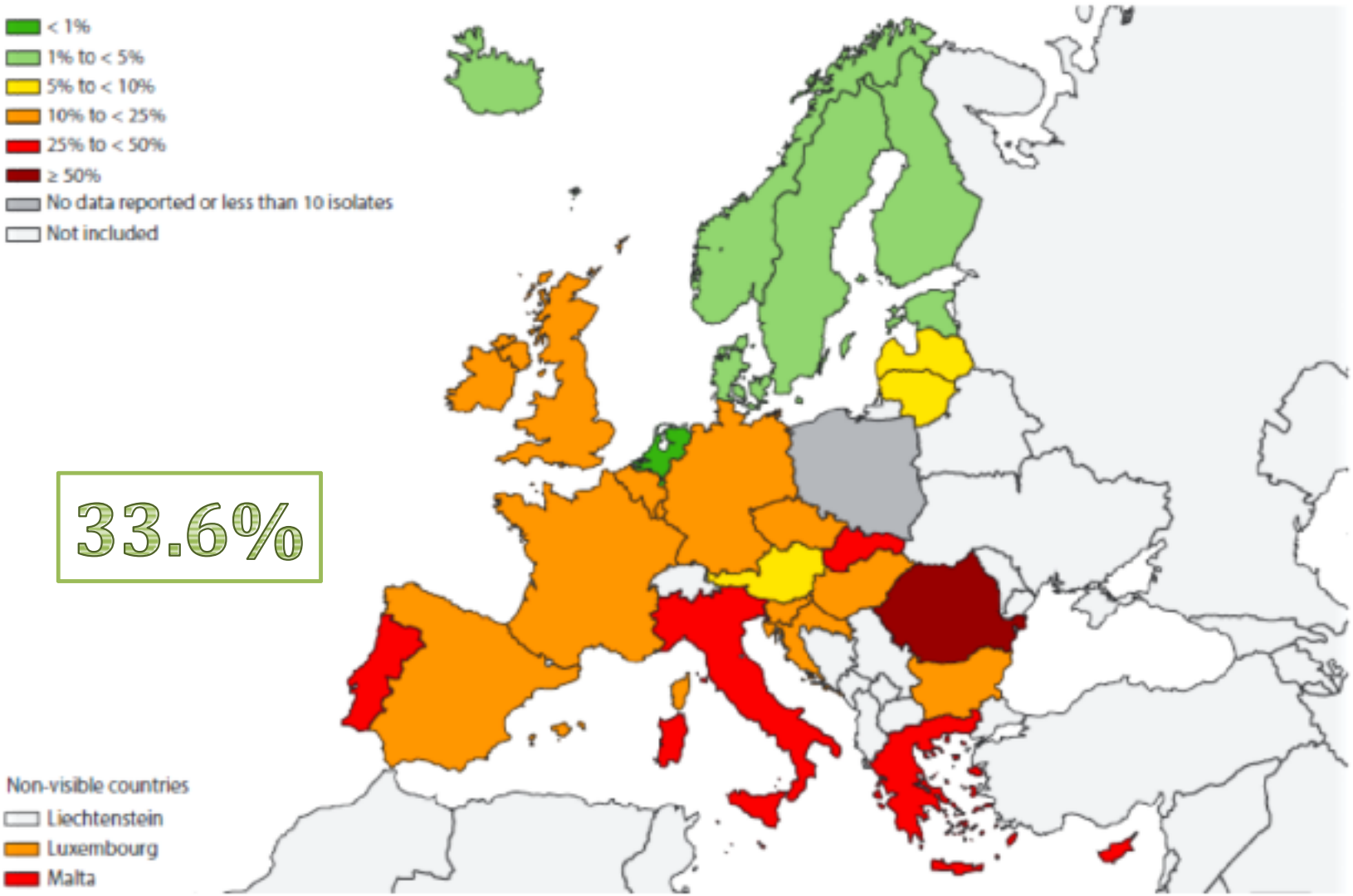
Rates of MRSA and MSSA from BSIs, LRTIs and SSTIs and other sources

Source	*S. aureus* n. (%)	MRSA n. (%)	MSSA n. (%)
BSIs	**465 (18.3)**	**183 (39)**	**282 (61)**
LRTIs	451 (17.7)	184 (41)	267 (59)
SSTIs	**768 (30.2)**	**273 (35.5)**	**495 (64.5)**
other	857 (33.8)	270 (31.5)	587 (68.5)
TOT.	2541	910 (35.8)	1631 (64.2)

BSI (bloodstream infections); LRTI (low-respiratory tract infections); SSTI (skin and soft-tissue infections)

By courtesy of Prof. Stefania Stefani

Staphylococcus aureus. Percentage (%) of invasive isolates with resistance to meticillin (MRSA), by country, EU/EEA countries, 2014



33.6%

Review | Journal of INTERNAL MEDICINE

Click here to view the article Editorial Comment by G. M. Rossolini

doi: 10.1111/joim.12342

Global dissemination of extensively drug-resistant carbapenemase-producing Enterobacteriaceae: clinical perspectives on detection, treatment and infection control

T. Tängdén[1] & C. G. Giske[2]

From the [1]Department of Medical Sciences, Section of Infectious Diseases, Uppsala University, Uppsala; and [2]Department of Clinical Microbiology, Karolinska Institutet – MTC, Karolinska University Hospital, Solna, Stockholm, Sweden

ESβL
MDR
CRE
XDR

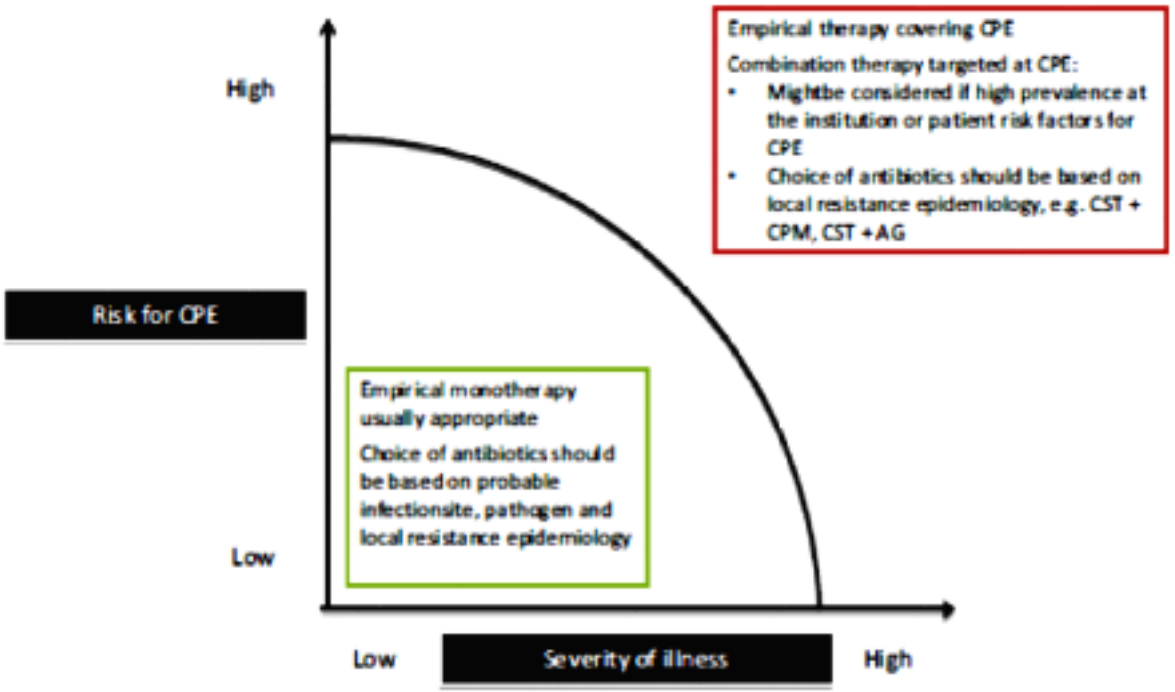


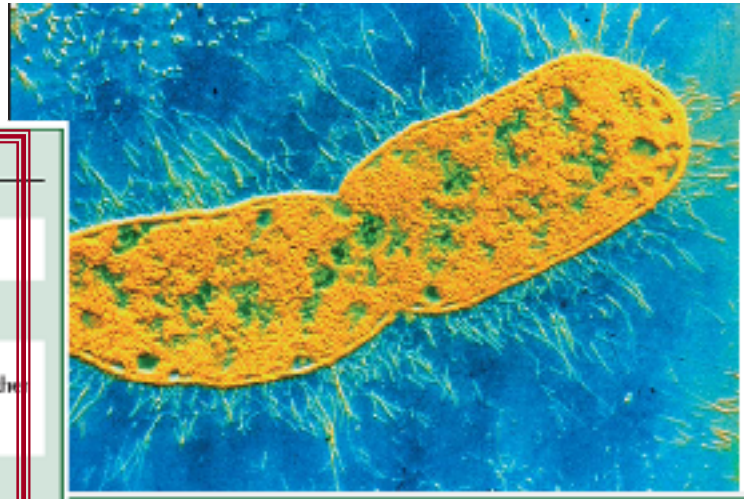
Fig. 4 *Empirical antibiotic therapy covering carbapenemase-producing Enterobacteriaceae (CPE) is justified for severely ill patients at high risk of infection with these bacteria. However, excessive use of broad-spectrum antibiotics should be avoided to prevent further selection of resistance, super-infections and other adverse events. CST, colistin; CPM, carbapenem; AG, aminoglycoside.*

Lancet Infect Dis 2008;
8: 159–66

Review

Extended-spectrum β-lactamase-producing Enterobacteriaceae: an emerging public-health concern

Johann D D Pitout, Kevin B Laupland



	Community onset	Hospital onset
Organism	*Escherichia coli*	*Klebsiella* spp (and others)
Type of ESBL	CTX-M (especially CTX-M15)	SHV (especially SHV2, SHV5) and TEM (especially TEM 26, TEM 51)
Infection	Most often UTIs, but also bacteraemia and gastroenteritis	Respiratory tract, intra-abdominal, and bloodstream infections
Susceptibilities	Resistance to all the penicillins and cephalosporins. High-level resistance to other classes of antibiotics, especially fluoroquinolones and co-trimoxazole	Resistance to all the penicillins and cephalosporins. High-level resistance to other classes of antibiotics, especially fluoroquinolones and co-trimoxazole
Molecular epidemiology	Most isolates often not clonally related, although clusters have been described in Canada, the UK, Italy, and Spain	Most often clonally related
Risk factors	Repeat UTIs and underlying renal pathology; previous antibiotics including cephalosporins and fluoroquinolones; previous hospitalisation; nursing-home residents; older men and women; diabetes mellitus; underlying liver pathology	Longer length of hospital stay; severity of illness (more severe, the higher the risk); longer time in the intensive-care unit; intubations and mechanical ventilation; urinary or arterial catheterisation; previous exposure to antibiotics (especially cephalosporins)

UTI=urinary-tract infection.

Table 2: Characteristics of infections caused by ESBL-producing bacteria

	Country
CTX-M1[3]	Italy
CTX-M2[4]	Israel, Argentina
CTX-M3[5]	Poland
CTX-M9[6]	Spain
CTX-M14[4,7]	Spain, Canada, China
CTX-M15[4]	Worldwide

CMR
July 2015 Volume 28 Number 3

The Role of Epidemic Resistance Plasmids and International High-Risk Clones in the Spread of Multidrug-Resistant *Enterobacteriaceae*

Amy J. Mathers,[a] Gisele Peirano,[b,c] Johann D. D. Pitout[b,c,d]

University of Virginia, Charlottesville, Virginia, USA[a]; Division of Microbiology, Calgary Laboratory Services,[b] and Departments of Pathology and Laboratory Medicine[c] and Microbiology, Immunology and Infectious Diseases,[d] University of Calgary, Calgary, Alberta, Canada; Department of Medical Microbiology, University of Pretoria, Pretoria, South Africa[e]

TABLE 2 Characteristics of *Escherichia coli* ST131 and *Klebsiella pneumoniae* ST258 that define them as high-risk clones

	Description	
Characteristic	*Escherichia coli* ST131	*Klebsiella pneumoniae* ST258
Global distribution	Endemic to all continents except Antarctica	ST258 is endemic to the USA, Israel, Greece, Italy, Poland, and Colombia; ST11 has been reported in China and Brazil; ST512 has been reported in Israel, Italy, and Colombia; ST340 has been reported in Brazil and Greece
Association with various antimicrobial resistance determinants	Various but associated with fluoroquinolone resistance and CTX-M-15 (CTX-M-14 to a lesser extent)	Various but associated with KPC-2 and KPC-3
Ability to colonize and persist in hosts for long periods of time	Rectal colonization for up to 6 mo	Rectal colonization for up to 12 mo
Effective transmission among hosts	Transmission among family members	Successful nosocomial transmission for months after introduction
Enhanced pathogenicity and fitness	Higher aggregate ExPEC-associated virulence scores; high metabolic potential and biofilm production	Unclear
Causes severe and/or recurrent infections	More likely to cause upper UTIs and recurrent UTIs, and the H30-Rx subclone is associated with sepsis	Mortality rates are higher than with non-ST258 *K. pneumoniae* (most likely due to the patient's underlying conditions)

TABLE 3 Laboratory methods for detection of *Escherichia coli* ST131 and *Klebsiella pneumoniae* ST258

	Characteristic(s) of detection of:	
Method	*Escherichia coli* ST131	*Klebsiella pneumoniae* ST258
NGS	High-resolution, accurate, and reproducible; not yet routine	High-resolution, accurate, and reproducible; not yet routine
MLST	Gold standard; expensive and time-consuming; 2 schemes (Achtman and Pasteur)	Gold standard; expensive and time-consuming; Pasteur scheme
PFGE	Used during the late 2000s; poor method since ST131 consists of different pulsotypes	Used during the late 2000s; poor method since ST258 consists of different pulsotypes
Repetitive-sequence-based PCR typing	Standardized fingerprinting kit; rapid and expensive	Standardized fingerprinting kit; rapid and expensive
MLVA	Rapid, cost-effective, and comparable to MLST	Not yet described
PCR	Several techniques; rapid and inexpensive for screening a large no. of isolates	Several techniques; rapid and inexpensive for screening a large no. of isolates; multiplex for clades I and II
MALDI-TOF MS	Rapid and inexperative; not yet routine	Not yet described

J Antimicrob Chemother 2014; **69**: 1785–1791
doi:10.1093/jac/dku079 Advance Access publication 5 May 2014

Journal of Antimicrobial Chemotherapy

Waste water effluent contributes to the dissemination of CTX-M-15 in the natural environment

G. C. A. Amos[1], P. M. Hawkey[2,3], W. H. Gaze[1]†‡ and E. M. Wellington[1]*‡

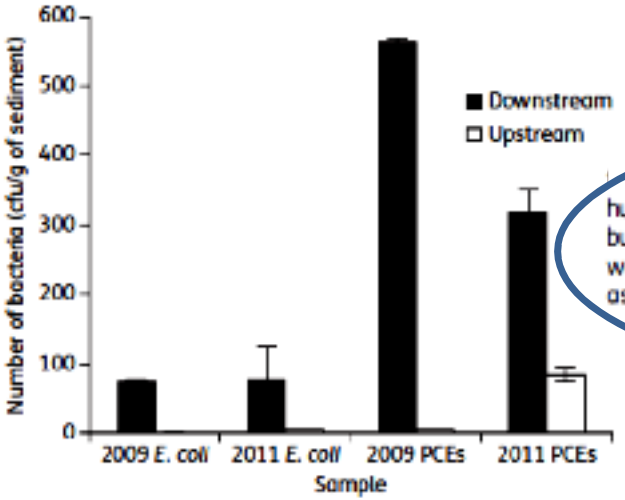


Figure 1. Counts of 3GC-resistant presumptive *E. coli* and PCEs* from samples collected downstream and upstream of a WWTP in 2009 and 2011. Error bars are ± standard errors of biological replicates.

* presumptive coliforms excluding E. coli (PCEs).

Downstream of the WWTP, the human-associated ST3103 and ST38 were codominant in 2009, but neither of these STs was detected in 2011 samples, which were dominated by the well-recognized human disease-associated types ST131 (20%) and ST167 (25%)

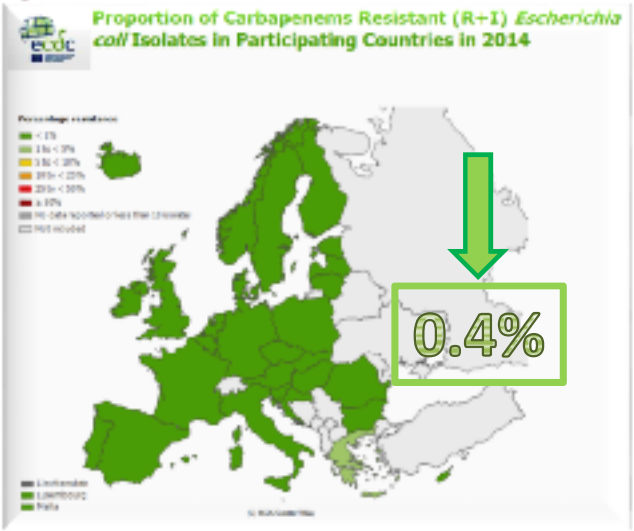
Detection and characterization of β-lactamases in resistant isolates

All *E. coli* were positive for bla_{CTX-M} and bla_{TEM}, but negative for bla_{SHV} (Table 1). Sequencing revealed all bla_{CTX-M}-bearing isolates in 2011 carried $bla_{CTX-M-15}$ and 54.5% of isolates in 2009 carried $bla_{CTX-M-15}$ with the remainder carrying $bla_{CTX-M-1}$.

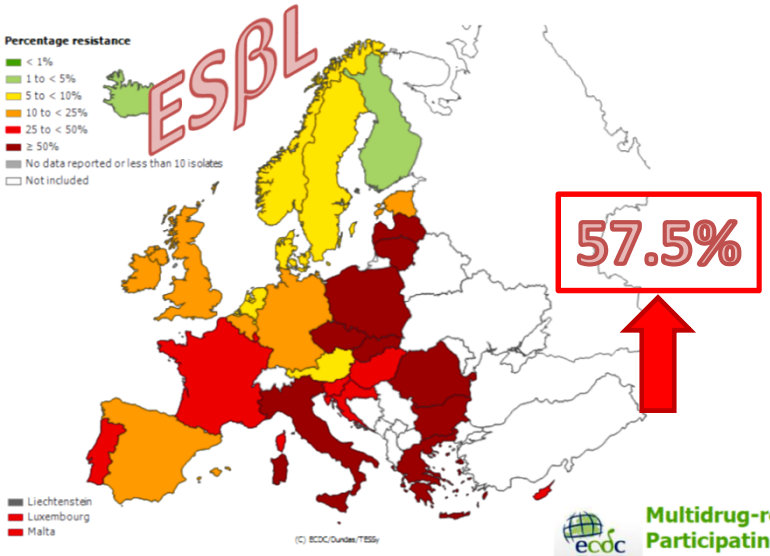
Proportion of Fluoroquinolones Resistant (R+I) *Escherichia coli* Isolates in Participating Countries in 2014

Proportion of 3rd gen. cephalosporins Resistant (R+I) *Escherichia coli* Isolates in Participating Countries in 2014

Proportion of Carbapenems Resistant (R+I) *Escherichia coli* Isolates in Participating Countries in 2014

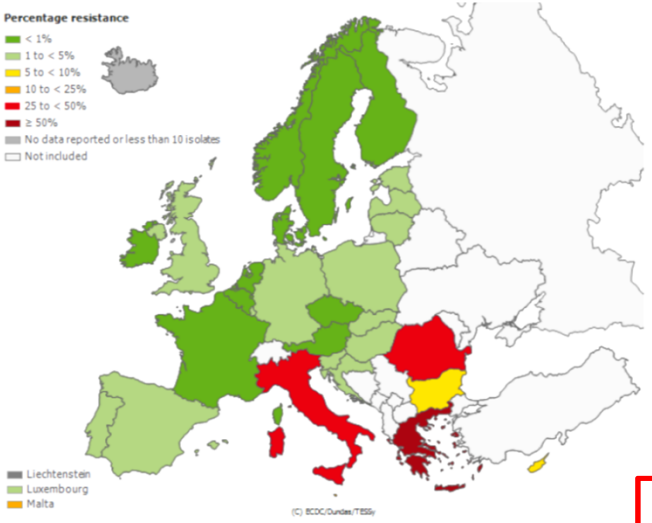


Proportion of 3rd gen. cephalosporins Resistant (R+I) *Klebsiella pneumoniae* Isolates in Participating Countries in 2014



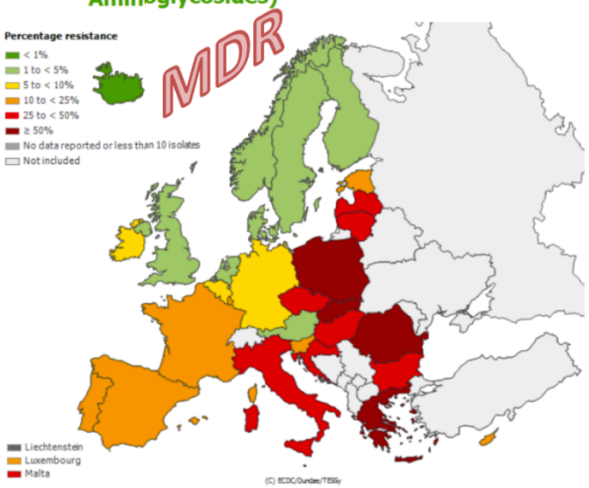
57.5%

Proportion of Carbapenems Resistant (R+I) *Klebsiella pneumoniae* Isolates in Participating Countries in 2014



36.3%

Multidrug-resistant Klebsiella pneumoniae Isolates in Participating Countries in 2014 (Resistant to Third-generation Cephalosporins, Fluoroquinolones and Aminoglycosides)



44.4%

Enterobatteri resistenti ai carbapenemi (CRE)

AMCLI CoSA

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

270 CRE (2%) isolati in 23/25 centri

- 87% *K. pneumoniae*
- 8% *Enterobacter spp.*
- 2% *E. coli*
- 2% *Serratia spp.*
- 1% altri

Species	KPC	VIM	OXA-48	NDM	IMP	Non-carbap.
K. pneumoniae (234)	204	16	3	-	-	11
Enterobacter (21)	-	3	-	-	-	18
E. coli (5)	1	1	-	-	-	3
Serratia (5)	-	-	-	-	-	5
Altri (5)	-	-	-	-	-	5

ESCMID

Final Programme

European Congress of
Clinical Microbiology
and Infectious Diseases

Copenhagen, Denmark
25 – 28 April 2015

ECCMID

25th

www.eccmid.org

O143 **11:54** **Molecular characterization of ESBLs, AmpCs and carbapenemases among Enterobacteriaceae from a recent Italian nationwide survey**

A. Antonelli (Siena, Italy), M. Caltagirone, C. Mauri, J. Nicchi, T. Giani, F. Arena, E. Nucleo, S. Bracco, F. Luzzaro, L. Pagani, G.M. Rossolini*

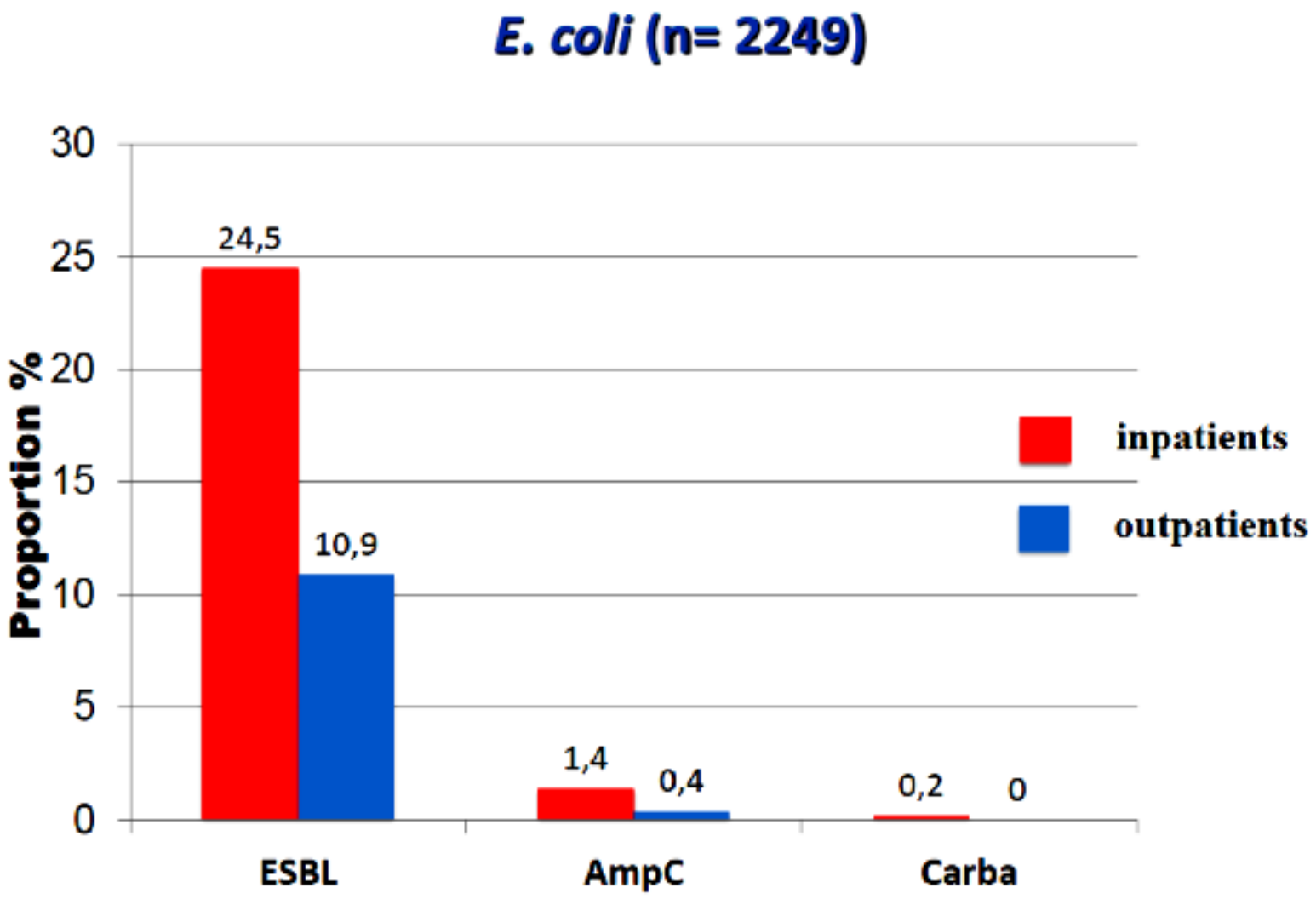
Consecutive, non replicate isolates from infections
1-15 October 2013

AMCLI CoSA

MICs of cefotaxime, and/or ceftriaxone, and/or ceftazidime, and/or cefepime, and/or ertapenem >1mg/l, collected from 14 Italian centers

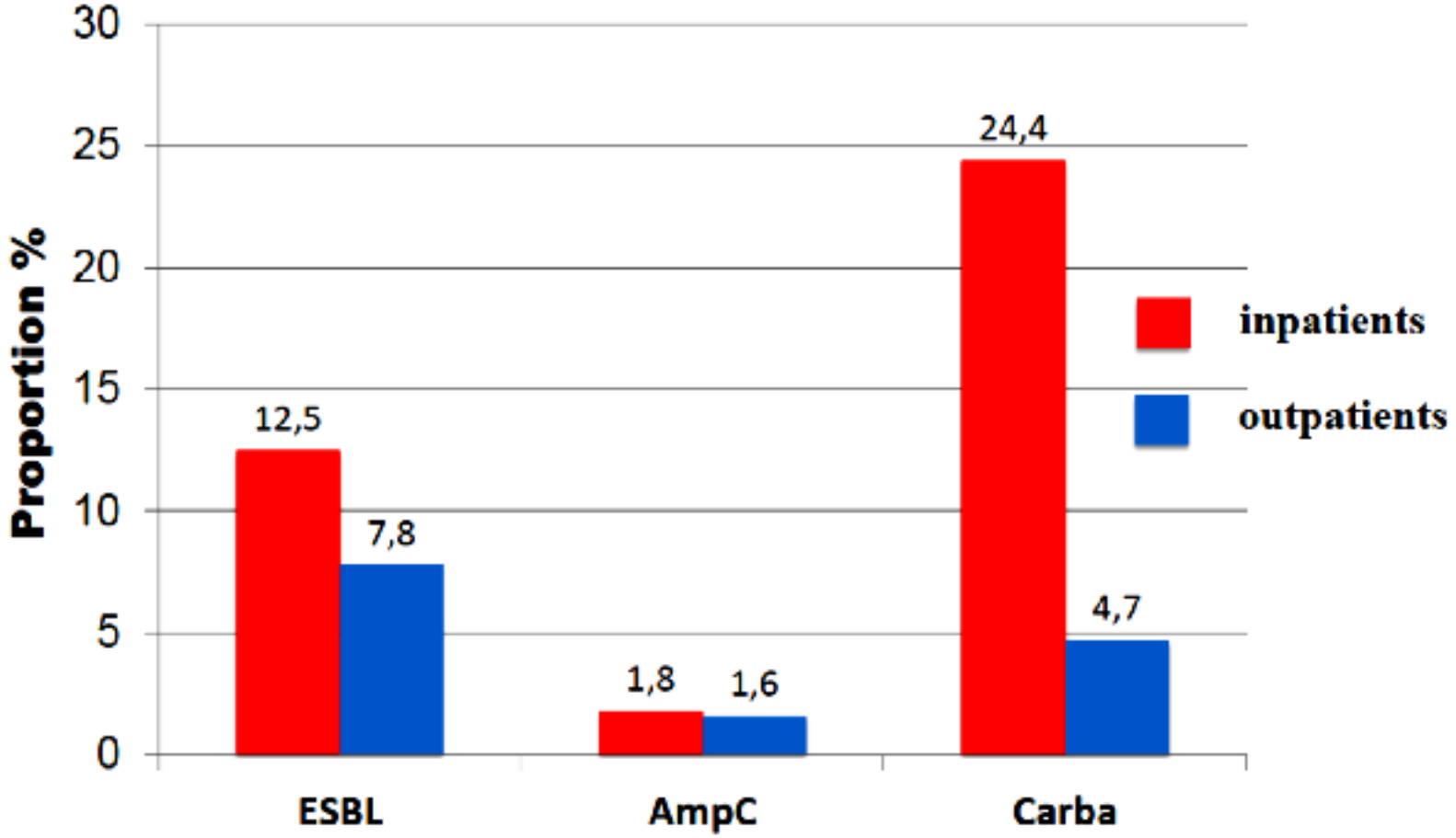
Species	Total isolates	Total Resistant
Escherichia coli	2420	418 (17.3%)
Klebsiella pneumoniae	718	206 (28.7%)
Proteus mirabilis	293	75 (25.6%)
Total	**3431**	**699 (20.4%)**

1-Milano; 2-Lecco; 3-Novara; 4-Sanremo; 5-Bolzano; 6-Udine; 7-Modena Bg; 8-Modena Pc; 9-Firenze; 10-Ancona; 11-Roma;12-San Giovanni Rotondo ;13-Avellino; 14-Cosenza


E. coli (n= 2249)
Proportion %
30
25
20
15
10
5
0
24,5
10,9
1,4
0,4
0,2
0
ESBL
AmpC
Carba
inpatients
outpatients

AMCLI – CoSA

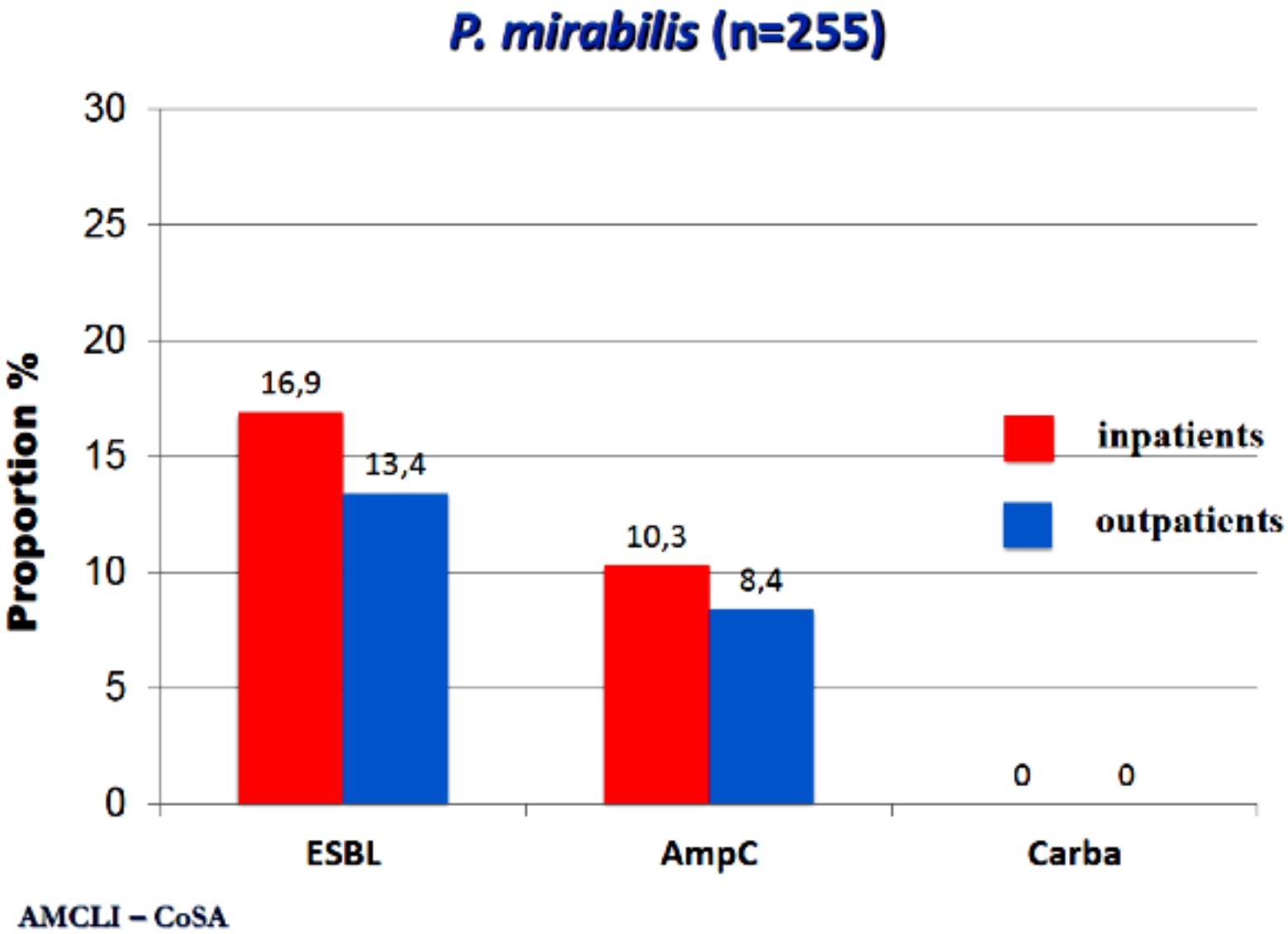
K. pneumoniae (n= 642)



AMCLI – CoSA

Espansione clonale di *K. pneumoniae* produttore di KPC (ST258 & ST512)

In Italia, dal 2009 numerosi episodi epidemici


P. mirabilis (n=255)
Proportion %
30
25
20
15
10
5
0
16,9
13,4
10,3
8,4
0
0
ESBL
AmpC
Carba
inpatients
outpatients

AMCLI – CoSA

- Overall, 20.4 % of *E. coli/ K. pneumoniae/ P. mirabilis* were resistant to 3th and/ or 4th generation cephalosporins and/or ertapenem

- The most common resistance mechanisms found in this Surveillance study are:
  KPC among *K. pneumoniae*,
  CTX-M among *E. coli*, and
  CMY among *P. mirabilis*

- The proportion of resistant isolates among both inpatients and outpatients is increasing

Adv Exp Med Biol - Advances in Microbiology, Infectious Diseases and Public Health
DOI 10.1007/5584_2015_5017

Emergence of *Escherichia coli* Sequence Type 131 (ST131) and ST3948 with KPC-2, KPC-3 and KPC-8 carbapenemases from a Long-Term Care and Rehabilitation Facility (LTCRF) in Northern Italy

Aurora Piazza, Mariasofia Caltagirone, Ibrahim Bitar, Elisabetta Nucleo, Melissa Spalla, Elena Fogato, Roberto D'Angelo, Laura Pagani, and Roberta Migliavacca

J Antimicrob Chemother 2014
doi:10.1093/jac/dku132

Emergence of *Escherichia coli* ST131 sub-clone *H30* producing VIM-1 and KPC-3 carbapenemases, Italy

Marisa Accogli[1], Tommaso Giani[2], Monica Monaco[1], Maria Giufrè[1], Aurora García-Fernández[1], Viola Conte[2], Fortunato D'Ancona[3], Annalisa Pantosti[1], Gian Maria Rossolini[2,4,5] and Marina Cerquetti[1]*

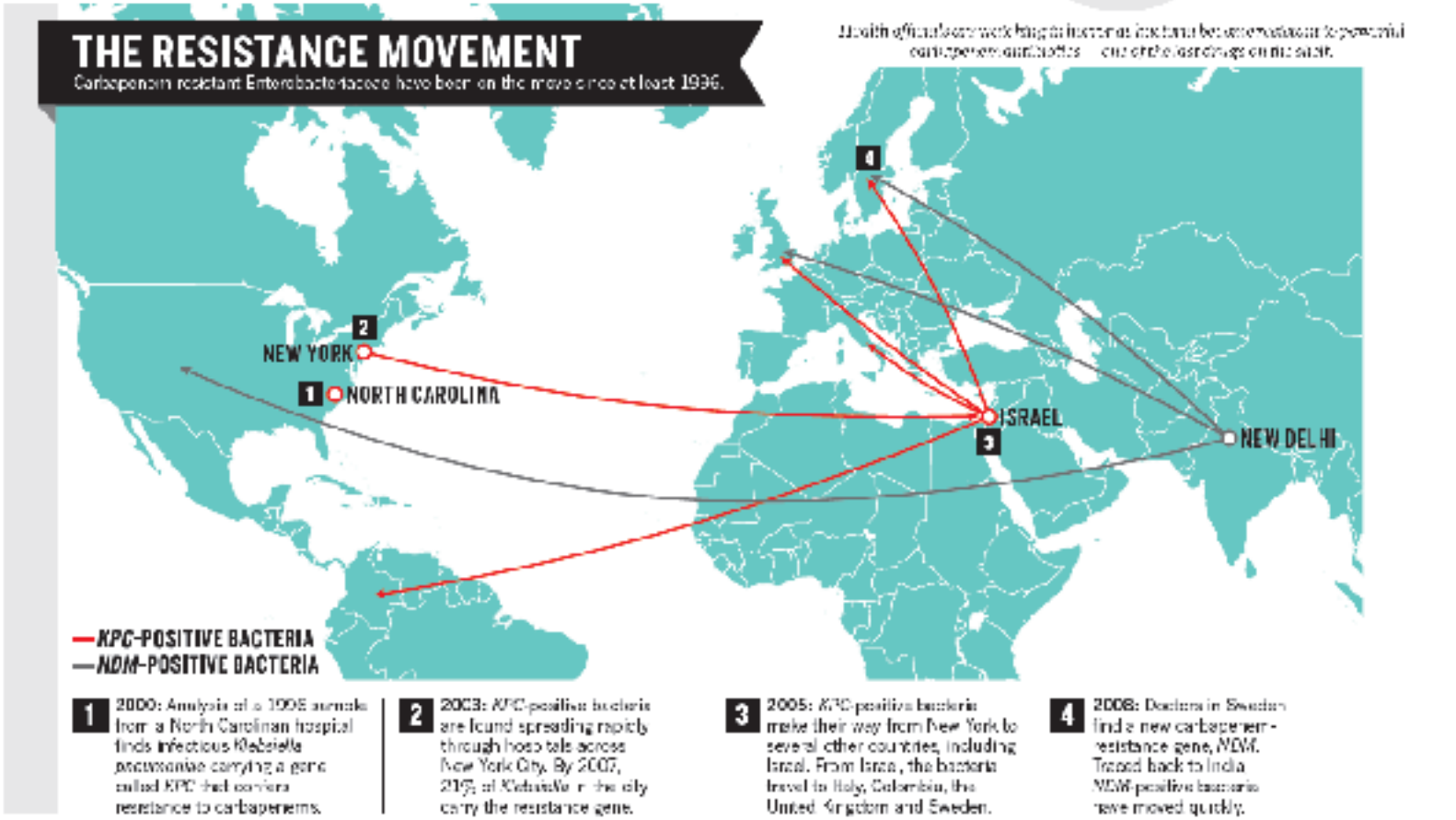
Pazienti ricoverati presso tre strutture di lungodegenza e riabilitazione dell'area milanese afferenti al medesimo Laboratorio di Microbiologia (2011-2013)

Table 1. Characteristics of the 13 *E. coli* isolates considered in the study.

ID	Collection date (yyyy/mm/dd)	MicroScan4 MIC, mg/L (Susceptibility category)			Etest MIC, mg/L (Susceptibility category)			Beta-Lactamase (BL) content		Molecular typing			
		IPM	MER	ETP	IPM	MER	ETP	Carbapenemase	BL	PFGE	MLST	DL	Phylogenetic group
VR	2011-03-04	<=1 (S)	<=1 (S)	1 (I)	0.25 (S)	0.064 (S)	4 (R)	-	CTX-M Gr 1	-			D
ZG	2011-04-08	4 (I)	8 (I)	>1 (R)	1 (S)	>32 (R)	8 (R)	KPC-2	OXA-9	A	131	A	B2
RA	2011-09-30	<=1 (S)	<=1 (S)	>1 (R)	0.75 (S)	0.125 (S)	3 (R)	-	CTX-M Gr 2	-			B2
NE	2012-06-20	8 (I)	8 (I)	>1 (R)	2 (S)	0.5 (S)	1.5 (R)	KPC-2	TEM-1; OXA-9	B	131	A	B2
PA	2012-07-03	<=1 (S)	<=1 (S)	>1 (R)	0.5 (S)	0.5 (S)	1.5 (R)	KPC-2	TEM-1; OXA-9	D			B2
GE	2012-10-02	>8 (R)	8 (I)	>1 (R)	1 (S)	1 (S)	>32 (R)	KPC-3	TEM-1; OXA-9	B2	131	A	B2
SM	2012-10-15	>8 (R)	>8 (R)	>1 (R)	1 (S)	0.38 (S)	4 (R)	KPC-2	TEM-1; OXA-9	B1	131	A	B2
BE	2012-12-03	4 (I)	8 (I)	>1 (R)	0.5 (S)	1 (S)	2 (R)	KPC-3	TEM-1; OXA-9	B3			B2
RMC	2012-12-05	<=1 (S)	<=1 (S)	2 (R)	1 (S)	0.5 (S)	2 (R)	KPC-2	TEM-1; OXA-9	B2	131	A	B2
SS	2013-02-15	<=1 (S)	<=1 (S)	>1 (R)	4 (I)	1.5 (S)	24 (R)	KPC-3	TEM-1; OXA-9	B4			B2
PS	2013-02-15	<=1 (S)	<=1 (S)	>1 (R)	1 (S)	0.25 (S)	1 (I)	KPC-8	TEM-1; OXA-9	D	131	A	B2
DFG	2013-04-05	<=1 (S)	<=1 (S)	>1 (R)	4 (I)	4 (I)	>32 (R)	KPC-2	TEM-1; OXA-9	B5			B2
MD	2013-05-06	32 (R)	32 (R)	32 (R)	2 (S)	1 (S)	>32(R)	KPC-3	TEM-1; OXA-9	C	3948	A	B2

S: susceptible; I: intermediate; R: resistant; IPM: imipenem; MER: meropenem; ETP: ertapenem; PFGE: pulsed-field gel electrophoresis; MLST: multilocus sequence typing; DL: Diversilab

THE LAST RESORT



BY MARYN MCKENNA

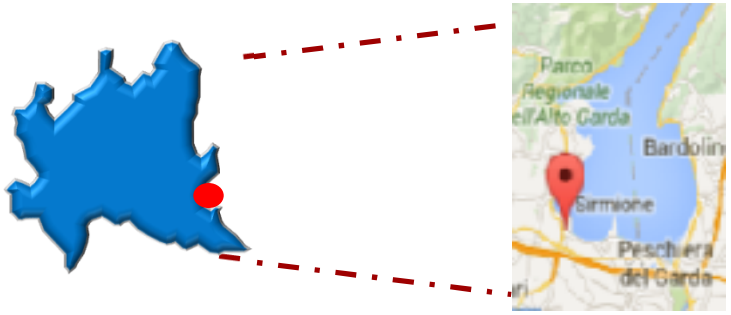
ST405 NDM-5 Producing *Escherichia coli* in Northern Italy: the First Two Clinical Cases

R. Migliavacca, University of Pavia

March & November 2015

3 CARBA R *E. coli* strains from 2 hospitalized patients

→ **Surgical Unit of Desenzano Hospital**



Rectal swab & Wound drainage
60-years-old man

History of vacation in Thailand

Blood
72-years-old oncological woman

Previous hospitalization Borgo Roma Hospital - (hepato biliar surgical ward) Verona (IT)-Rectal colonization by a CARBA R *E. coli*

Conclusions

Hypothesis of a foreign origin of the first two strains

…but the identification of a second strain from a different patient could be related to the presence of an ST405 hot spot area in Italy

➢ 9th of June 2015: NDM *E. coli* intestinal carriage

Presence of *bla*NDM-5 in ST405-D

The *bla*NDM-5 in IncFII

Co-carriage of different R determinants

Long term colonization

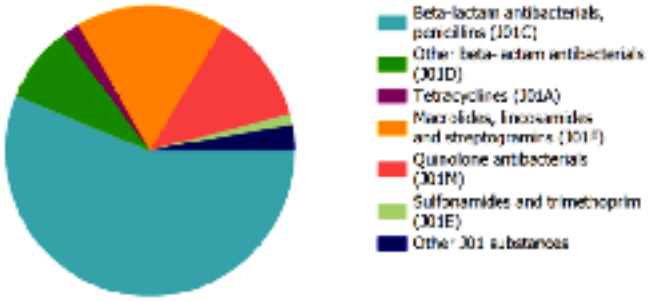
High spreading potential

Prevent the further spread of NDM enzymes within the community

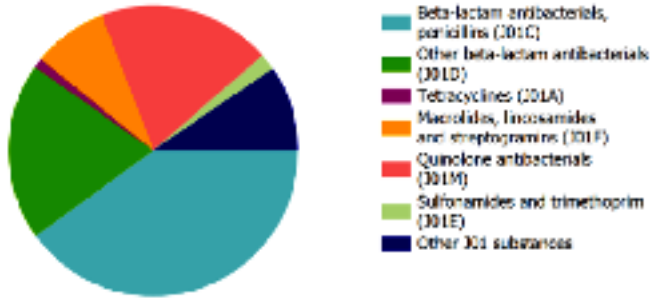
Multidisciplinary action !

Antimicrobial consumption in Italy, 2013

Distribution of the consumption in the community (primary care sector) of ATC group J01



Distribution of the consumption in the hospital sector of ATC group J01



Comments

The total consumption on antiinfectives for systemic use (J) during 2013 registers an upward trend compared to the previous year (+14,1%). In more details the two sectors increase of a + 4.2% for the Ambulatory Care and +69.3% for the Hospital Care respectively. Regarding the AC sector the consumption of antimicrobic (J01) amounts up to 28,6 DDD per 1000 inhabitans die and it increases by +4,4 in comparison with 2012. The largest share in the total consumption of AC during 2013 is concerning the following antimicrobic groups: J01CR (Combinations of penicillins, inclusing beta-lactamase inhibitors, 41%), J01FA (Macrolides, 17%), J01CA (penicillins with extended spectrum, 15%) and J01MA (Fluorquinolones, 12%); concerning the antimycotics: J02AC (Triazole derivates, around 100%), regarding the antimycobacterials: J04AC (Hydrazides) and J04AB (Antibiotics) are both sharing a 39,4% each, and finally relating to the antivirals: J05AB (Nucleoside and nucleotide excl. reverse transcriptase inhibitors, about 95%). 2013 consumption increase versus 2012 is registered within J01XB (Polymyxins, +21%), J02AB (Imidazole derivates, +24%) and among the antivirals for systemic use respectively J05AH (Neuraminicase inhibitors, +33%) and J05AE (Protease inhibitors, +62%). On the other hand the consumption of antimicrobic (J01) within the HC sector amounts up to +4.2 DDD per 1000 inhabitans die and increases by +70.0% in relation to 2012. The largest share in the total consumption of HC during 2013 is regarding the following antimicrobic groups: J01CR (Combinations of penicillins, inclusing beta-lactamase inhibitors, about 20%), J01MA (Fluorquinolones, 10%), J01XB (Polymyxins, 16%); concerning the antimycotics: J02AC (Triazole derivates, around 84%), regarding the antimycobacterial: J04AC (Hydrazides, 62%), and finally relating to the antivirals: J05AF (Nucleoside and nucleotide reverse transcriptase inhibitors, 56%) and J05AR (Antivirals for treatment for HIV infections combinations, 21%). Increases of consumptions versus 2012 are shown within the J01DF (Monobactams, +155%) and J01XB (Polymyxins, >1000%) according to the antimicrobic; among the antimycotics for systemic use J02AB (Imidazole derivates, +500%) and among the antimycobacterials J04AC (Hydrazides, +229%) and J04AK (Other drugs for treatment of tuberculosis, +115%) and finally between the antivirals for systemic use J05AD (Phosphonic acid derivates, +113%) and J05AF (Nucleoside and nucleotide reverse transcriptase inhibitors, +206%).

Outbreak of Colistin-Resistant, Carbapenemase-Producing *Klebsiella pneumoniae*: Are We at the End of the Road?

David van Duin,[a] Yohei Doi[b]

Journal of Clinical Microbiology October 2015 Volume 53 Number 10

Outbreak of KPC-3-producing, and colistin-resistant, *Klebsiella pneumoniae* infections in two Sicilian hospitals

M. L. Mezzatesta[1], F. Gona[1], C. Caio[1], V. Petrolito[1], D. Sciortino[1], A. Sciacca[2], C. Santangelo[3] and S. Stefani[1]
1) Department of Medical Sciences, Section of Microbiology, University of Catania, 2) University Hospital and 3) Vittorio Emanuele Hospital, Catania, Italy

Patients	Date	Hospital	Ward	Specimens	MIC (mg/L) IPM	MEM	DOR	ETP	CEF	CAZ	CTX	TZP	TG	CT	CIP	GM
1	19 August 2010	University	ICU	Abdominal drainage	32	64	64	>128	128	>64	>64	>512	1	16	128	2
2	31 August 2010	University	Surgery	CVC	64	64	64	>128	>128	>64	>64	>512	1	32	128	2
3	10 September 2010	University	ICU	Bloodstream	64	128	64	128	>128	>64	>64	>512	1	16	128	2
4	19 September 2010	University	ICU	Bronchial aspirate	64	64	32	>128	>128	>64	>64	>512	1	32	128	2
5	20 September 2010	University	Internal Medicine	Urine	64	64	64	>128	>128	>64	>64	>512	1	8	256	2
6	23 September 2010	University	Transplant	Sputum	32	64	128	128	128	>64	>64	>512	1	64	128	2
7	26 September 2010	University	Paediatric Haematology	Bloodstream	64	64	256	>128	128	>64	>64	>512	1	32	128	2
8	19 October 2010	VE	Nephrology	Bloodstream	128	512	64	512	512	>512	256	>512	1	8	256	2
3*	20 October 2010	University	ICU	Pharyngeal swab	32	64	64	128	128	>64	>64	>512	1	32	128	2
7*	26 October 2010	University	Paediatric Haematology	Rectal swab	>512	>512	64	>512	256	>512	256	>512	1	8	128	2
4*	27 October 2010	University	ICU	Rectal swab	64	512	64	512	512	>512	256	>512	1	16	128	2

IPM, imipenem; MEM, meropenem; DOR, doripenem; ETP, ertapenem; CEF, cefepime; CAZ, ceftazidime; CTX, cefotaxime; TZP, piperacillin–tazobactam; TG, tigecycline; CT, colistin; CIP, ciprofloxacin; GM, gentamicin; VE, Vittorio Emanuele; CVC, central venous catheter; ICU, intensive-care unit.
*Colonization.

Clin Microbiol Infect 2011; **17:** 1444–1447

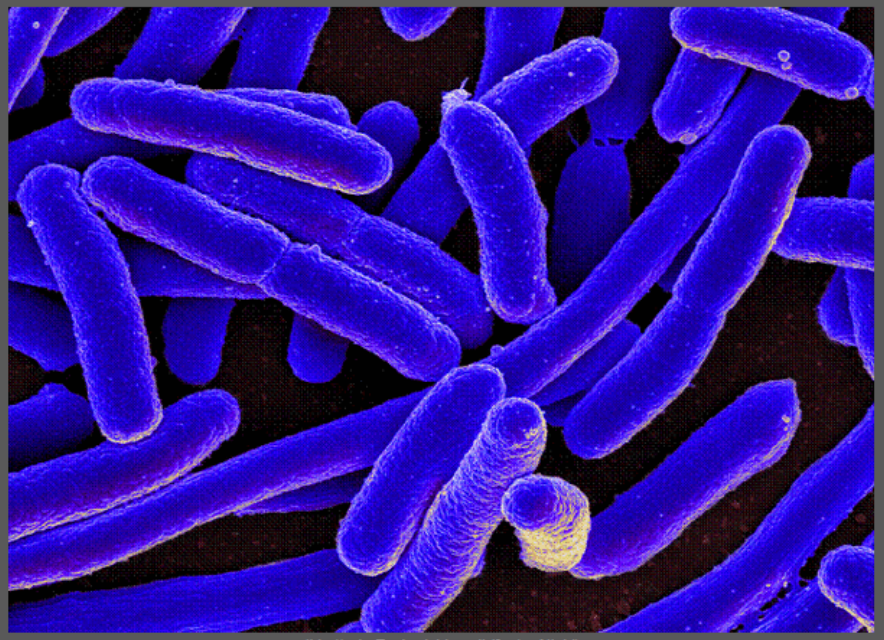
ANSA > Salute e Benessere > Medicina > In Usa scatta allarme super-batterio,colpita donna Pennsylvania

In Usa scatta allarme super-batterio,colpita donna Pennsylvania

Esperti, agente patogeno non rispende ad alcun antibiotico

27 maggio, 20:20

1 di 1

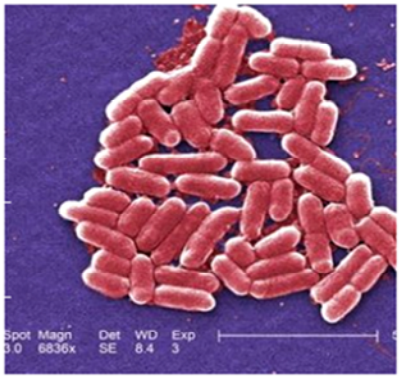


Il batterio Escherichia coli (fonte: Niaid)

Allarme negli Usa, donna colpita da batterio resistente a tutti gli antibiotici

Per la prima volta, alcuni ricercatori hanno trovato una persona portatrice di un batterio con un gene che lo rende resistente persino ai trattamenti più potenti

di VALERIA PINI



Il gene mcr-1 resistente alla colistina è stato trovato per la prima volta nell'The mcr-1 plasmid-borne colistin resistance gene has been found primarily in Escherichia coli

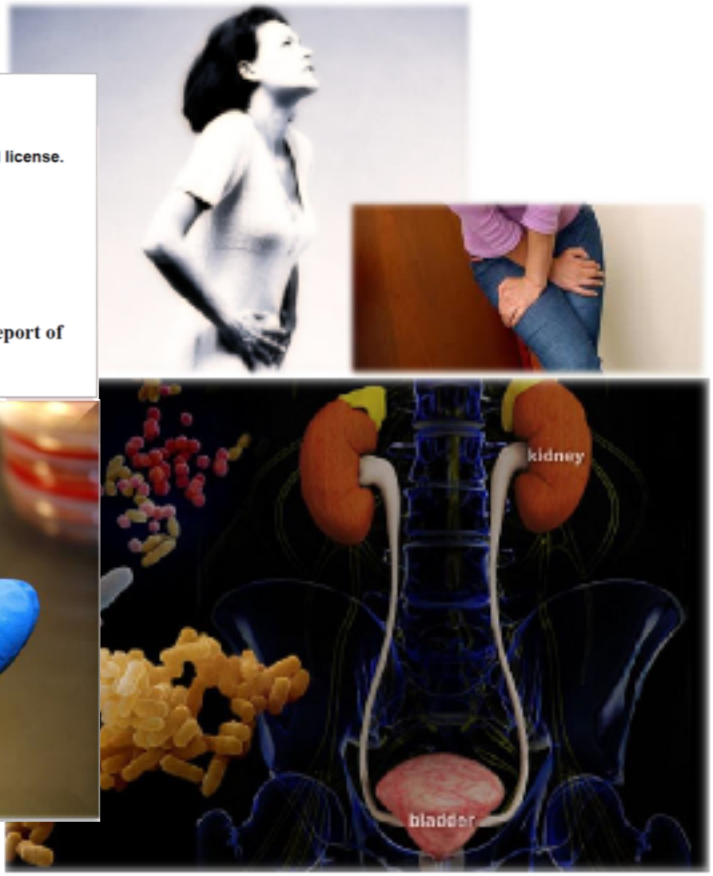
E' ALLARME negli Stati Uniti per un caso di antibioticoresistenza. Per la prima volta negli Usa, è stata trovata una persona portatrice di un batterio con un gene che lo rende resistente persino a uno degli antibiotici più potenti. Secondo quanto emerso da uno studio pubblicato su *Antimicrobial agents and chemotherapy*, rivista dell'*American society for microbiology*, il batterio è stato individuato lo scorso mese nelle urine di una donna della Pennsylvania di 49 anni. Gli esperti del dipartimento della

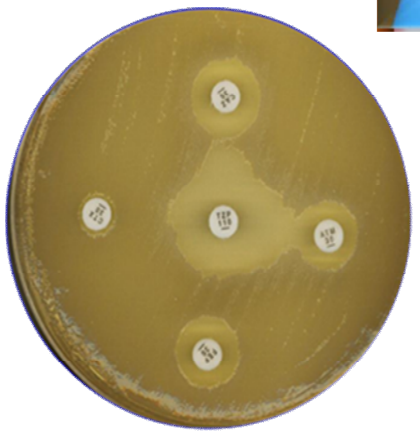
Table 1. Antibiotic resistance profile of MRSN 38863.

Antibiotic	MIC (μg/ml)[1]	
Amikacin	≤8	
Amoxacillin/clavulanate	16/8	
Ampicillin	>16	
Aztreonam	>16	
Cefazolin	>16	
Cefepime	>16	
Ceftazidime	>16	
Ceftriaxone	>32	
Ciprofloxacin	>2	
Colistin	4	
Ertapenem	≤ 0.25	S
Gentamicin	>8	
Imipenem	≤ 0.25	S
Levofloxacin	>4	
Meropenem	≤ 0.25	S
Nitrofurantoin	≤ 16	S
piperacillin-tazobactam	4/4	S
Tetracycline	>8	
Tobramycin	>8	
Trimethoprim/sulfamethoxazole	>2/38	

AAC Accepted Manuscript Posted Online 26 May 2016
Antimicrob. Agents Chemother. doi:10.1128/AAC.01103-16

1 *Escherichia coli* Harboring *mcr-1* and bla_{CTX-M} on a Novel IncF Plasmid: First report of
2 *mcr-1* in the USA





Donna di 49 anni non ospedalizzata
con sintomi di UTI
si presenta all'Ospedale il 26 Aprile 2016

Il gene *mcr-1* viene identificato in *E. coli* in 3 campioni di carne di pollo (Olanda, 2009-2014)

18/11/2015 (Liu et al.) 1° descrizione di COL resistenza plasmide-mediata (gene *mcr-1*) in *E. coli* da animali, cibo e pazienti in Cina

26 Maggio 2016 la segnalazione di *mcr-1* in un isolato di *E. coli* da campione biologico umano negli USA, estende ulteriormente la distribuzione geografica del gene, che è stato riportato in 27 paesi.

Il gene *mcr-1* viene identificato in *E. coli* isolati da 8 pazienti (Lecco-Firenze, 2013-2015)


Antimicrobial Agents and Chemotherapy

LETTER TO THE EDITOR

First Detection of the *mcr-1* Colistin Resistance Gene in *Escherichia coli* in Italy

Antonio Cannatelli,[a] Tommaso Giani,[a] Alberto Antonelli,[a,b] Luigi Principe,[c] Francesco Luzzaro,[c] Gian Maria Rossolini[a,b,d,e]

Department of Medical Biotechnologies, University of Siena, Siena, Italy[a]; Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy[b]; Clinical Microbiology and Virology Unit, Lecco A. Manzoni Hospital, Lecco, Italy[c]; Clinical Microbiology and Virology Unit, Florence Careggi University Hospital, Florence, Italy[d]; Don Carlo Gnocchi Foundation, Florence, Italy[e]

mcr-1 gene detected

Resistenza a colistina mediata da plasmidi: il gene *mcr-1*

Diffusione attraverso i continenti

Identificato in batteri isolati da vari tipi di carne e vegetali

- Pollame
- Maiali

Isolato da batteri in soggetti infetti o colonizzati

- Infezioni varie
- Viaggiatori

Identificato in varie specie microbiche

- *E. coli* e *K. pneumoniae*
- *Salmonella* spp.
- *Shigella* spp.
- *Enterobacter* spp.

Altamente trasferibile e veicolato da plasmidi diversi

Diversità di cloni
Associazione frequente con *bla*$_{CTX\text{-}M\text{-}}$

Skov R.L. *et al. Eurosurveillance.org* 1 march 2016

J Antimicrob Chemother 2016; **71**: 2066–2070
doi:10.1093/jac/dkw274 Advance Access publication 24 June 2016

Journal of Antimicrobial Chemotherapy

Transferable resistance to colistin: a new but old threat

Stefan Schwarz[1]* and Alan P. Johnson[2]

[1]*Institute of Farm Animal Genetics, Friedrich-Loeffler-Institut (FLI), Neustadt-Mariensee, Germany;* [2]*Department of Healthcare-Associated Infection and Antimicrobial Resistance, National Infection Service, Public Health England, London NW9 5EQ, UK*

*Corresponding author. Tel: +49-5034-871-241; Fax: +49-5034-871-143; E-mail: stefan.schwarz@fli.bund.de

In this Leading article, we summarize current knowledge of the occurrence of the first and so far only transferable colistin resistance gene, *mcr-1*. Its location on a conjugative plasmid is likely to have driven its spread into a range of enteric bacteria in humans and animals. Screening studies have identified *mcr-1* in five of the seven continents and retrospective studies in China have identified this gene in *Escherichia coli* originally isolated in the 1980s, while the first European isolate dates back to 2005. Based on the widespread use of colistin in pigs and poultry in several countries and the higher number of *mcr-1*-carrying isolates of animal origin than of human origin, it is tempting to assume that this resistance may have emerged in the animal sector. Whatever its origin, interventions to reduce its further spread will require an integrated global one-health approach, comprising robust antibiotic stewardship to reduce unnecessary colistin use, improved infection prevention, and control and surveillance of colistin usage and resistance in both veterinary and human medicine.

ARTICLE IN PRESS

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journal homepage: www.elsevier.com/locate/ijantimicag

Molecular mechanisms of polymyxin resistance: knowns and unknowns

Sophie Baron, Linda Hadjadj, Jean-Marc Rolain *, Abiola Olumuyiwa Olaitan **

SIM SOCIETÀ ITALIANA DI MICROBIOLOGIA

44°CONGRESSO NAZIONALE DELLA SOCIETÀ ITALIANA DI MICROBIOLOGIA
Pisa, Palazzo dei Congressi - 25 - 28 settembre 2016

P3 Occurrence of ESBLs, KPC and MCR-1 in Gram-negative microorganisms from Oltrepò Pavese environment

M. Caltagirone, E. Nucleo, M. Spalla, R. Brerra, A. Piazza, I. Bitar, F. Novazzi, M. De Cicco, R. Migliavacca, G. Pilla , L. Pagani (Pavia)

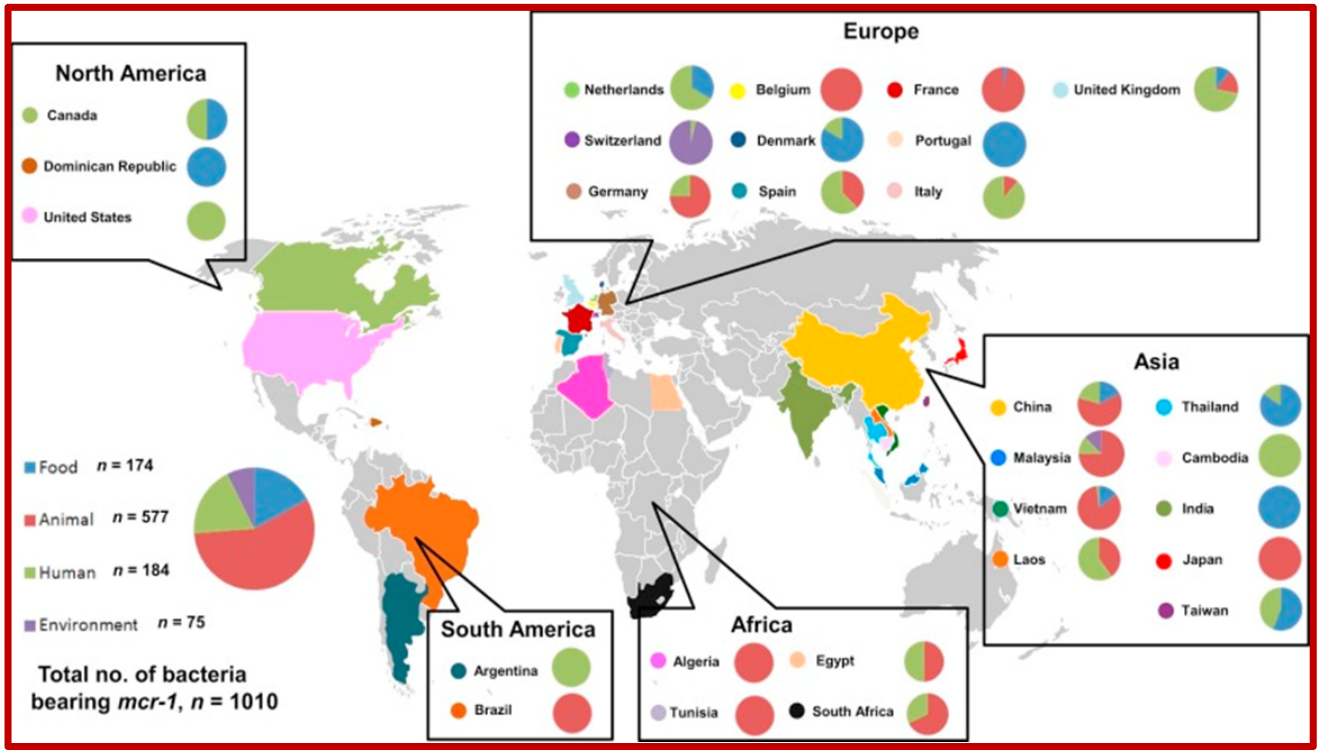


Fig. 2. Global distribution of plasmid-mediated mcr-1 colistin-resistant strains isolated from environments, foods, animals and humans (November 2015 to April 2016).

Resistenza acquisita a colistina in Lombardia: isolati clinici di *Escherichia coli* positivi per *mcr-1*.

Aurora Piazza[1], Carola Mauri[2], Gioconda Brigante[3], Erminia Casari[4], Adriano Anesi[5], Carlo Agrappi[6], Silvia Bracco[7], Federica Novazzi[1], Laura Pagani[1], Roberta Migliavacca[1], Francesco Luzzaro[2].

Il presente studio pilota ha mostrato una prevalenza in Lombardia di *E. coli* con MIC CO >2 mg/L pari allo 0.5%. La diffusione del gene *mcr-1* è risultata essere oltre l'atteso, comprendendo il 55% dei ceppi in *screening*. Di particolare rilievo risultano sia il tipo di campione (100% urina), che la provenienza comunitaria del 70% dei casi di positività.

Busto
Lecco
Legnano
Lodi
Humanitas
Vimercate

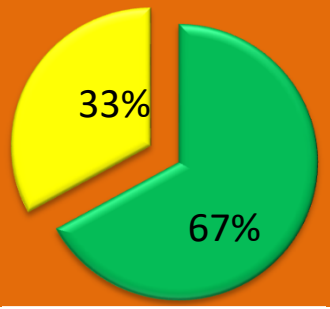
01 Maggio - 31 Agosto 2016

N = 3.902 totale isolati testati per CO

N= 18 isolati con MIC CO >2 mg/L con sistema automatizzato

	MIC (mg/L) mcr-1 pos
Metodo	
Sist. autom.	4 - 16
E-test	3 - 12
BMD	2 - 8

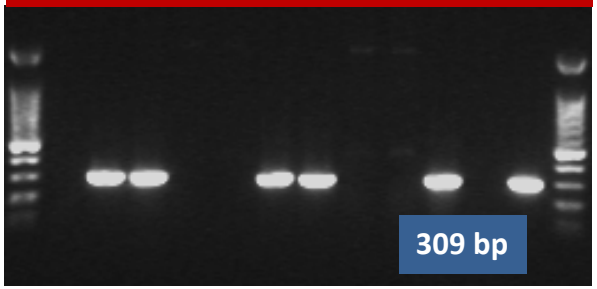
Isolati COL-R: 18 (0,5%) da 4/6 centri



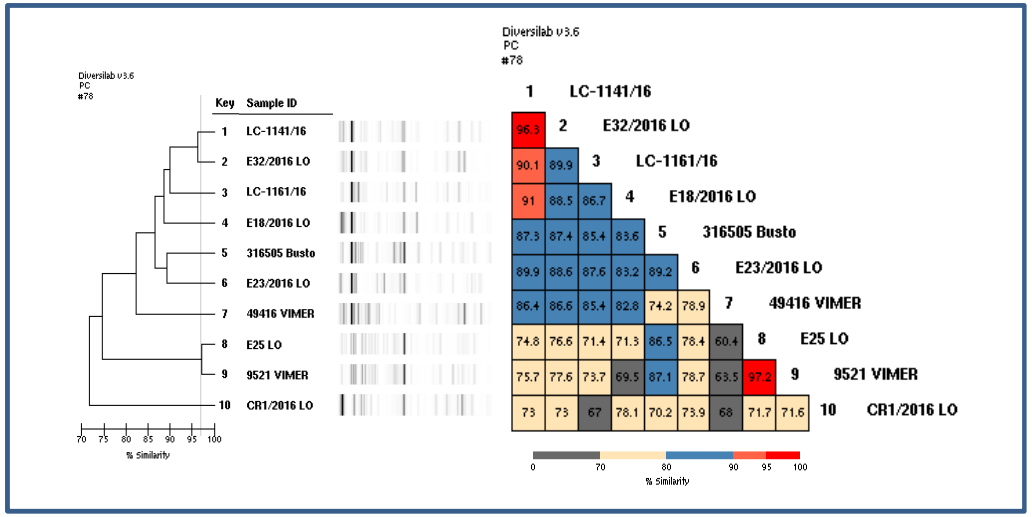
ESTERNI
INTERNI

16/18 urina
2/18 emocoltura

***mcr-1* pos: 55,5% (10/18) dei COL-R**



CLR5-F: 5′-CGGTCAGTCCGTTTGTTC-3′
CLR5-R: 5′-CTTGGTCGGTCTGTAGGG-3



Emergence of the colistin resistance *mcr-1* determinant in commensal *Escherichia coli* from residents of long-term-care facilities in Italy

Maria Giufrè, Monica Monaco, Marisa Accogli, Annalisa Pantosti and Marina Cerquetti* on behalf of the PAMURSA Study Group†

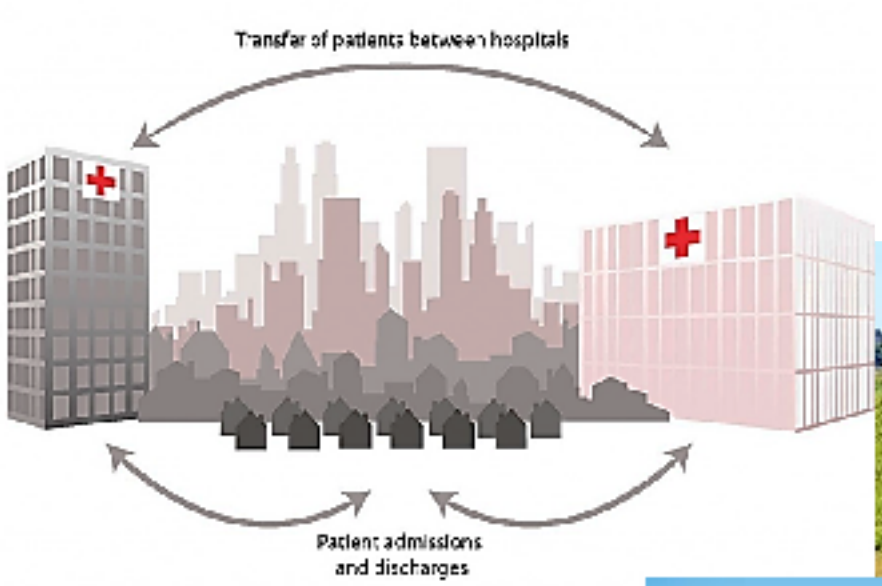
Feb-Mar2015 PP Study 12 LTCFs

Of 303 ESBL-producing *Enterobacteriaceae*, three *E. coli* isolates (3/247, 1.2%) were found to be resistant to colistin (MIC 8 mg/L). The colistin-resistant isolates were obtained from three different residents of the same LTCF.

- **Independent acquisition of different CO-R strains or**
- **Intra-facility spread of the same plasmid carrying the *mcr-1* gene among LTCF residents.**
- **2/3 *E. coli* isolates belonged to CC10 and CC23 in agreement with a probable animal origin of the mcr-1 determinant. Both CC10 and CC23 previously found to be shared between human and avian isolates, indicating that these CCs have a zoonotic potential.**

J Antimicrob Chemother 2016

	Resident 1/isolate EC51	Resident 2/isolate EC61-2	Resident 3/isolate EC62
Resident			
age (years)/gender	95/female	87/female	74/female
length of stay in LTCF	8 years	5 years	3 months
previous hospitalization (last 3 months)	no	yes	no
antimicrobial therapy (within 1 month)	no	no	no
Isolate			
phylogenetic group	D	A	A
ST/CC	ST2165[a]	ST88/CC23	ST10/CC10
ESBL	SHV-12	CTX-M-15	CTX-M-15
MIC of antimicrobial agent (mg/L)			
amikacin	≤4	≤4	≤4
gentamicin	≤1	≤1	≤1
cefotaxime	**≥8**	**≥8**	**≥8**
ceftazidime	**64**	**64**	**32**
cefepime	**16**	**≥64**	**≥64**
ciprofloxacin	1	**≥4**	≤0.06
colistin	**8**	**8**	**8**
imipenem	≤1	≤1	≤1
meropenem	≤0.12	≤0.12	≤0.12
tigecycline	≤0.12	≤0.12	≤0.12


Transfer of patients between hospitals
Patient admissions
and discharges

OPINION

Tackling antibiotic resistance: the environmental framework

Thomas U. Berendonk, Célia M. Manaia, Christophe Merlin, Despo Fatta-Kassinos, Eddie Cytryn, Fiona Walsh, Helmut Bürgmann, Hanning Sørum, Madeleine Norström, Marie-Noelle Pons, Norbert Kreuzinger, Pertti Huovinen, Stefania Stefani, Thomas Schwartz, Vesa Kisand, Fernando Baquero and José Luis Martínez

Abstract | Antibiotic resistance is a threat to human and animal health worldwide, and key measures are required to reduce the risks posed by antibiotic resistance genes that occur in the environment. These measures include the identification of critical points of control, the development of reliable surveillance and risk assessment procedures, and the implementation of technological solutions that can prevent environmental contamination with antibiotic resistant bacteria and genes. In this Opinion article, we discuss the main knowledge gaps, the future research needs and the policy and management options that should be prioritized to tackle antibiotic resistance in the environment.

Box 1 | Bacterial groups and genetic determinants

The following bacterial groups and genetic determinants have been suggested as possible indicators to assess the antibiotic resistance status in environmental settings.

Bacterial groups

- *Escherichia coli*
- *Klebsiella pneumoniae*
- *Aeromonas* spp.
- *Pseudomonas aeruginosa*
- *Enterococcus faecalis*
- *Enterococcus faecium*

Genetic determinants (and the proteins they encode)

- *intI1* (integrase gene of class 1 integrons, a genetic platform for ARG capture)
- *sul1* and *sul2* (sulfonamide-resistant dihydropteroate synthase)
- bla_{TEM} and bla_{SHV} (β-lactamases, frequently identified in Enterobacteriaceae)
- bla_{NDM-1} (New Delhi metallo-β-lactamase)
- bla_{VIM} (carbapenemase, frequent in clinical *Pseudomonas aeruginosa* in certain areas)
- bla_{KPC} (*Klebsiella pneumoniae* carbapenemase)
- *qnrS* (quinolone pentapeptide repeat family)
- *aac-(6')-Ib-cr* (aminoglycoside acetyltransferase)
- *vanA* (vancomycin resistance operon gene)
- *mecA* (penicillin binding protein)
- *ermB* and *ermF* (rRNA adenine N-6-methyltransferase, associated with macrolide resistance)
- *tetM* (ribosomal protection protein, associated with tetracycline resistance)
- *aph* (aminoglycoside phosphotransferase)

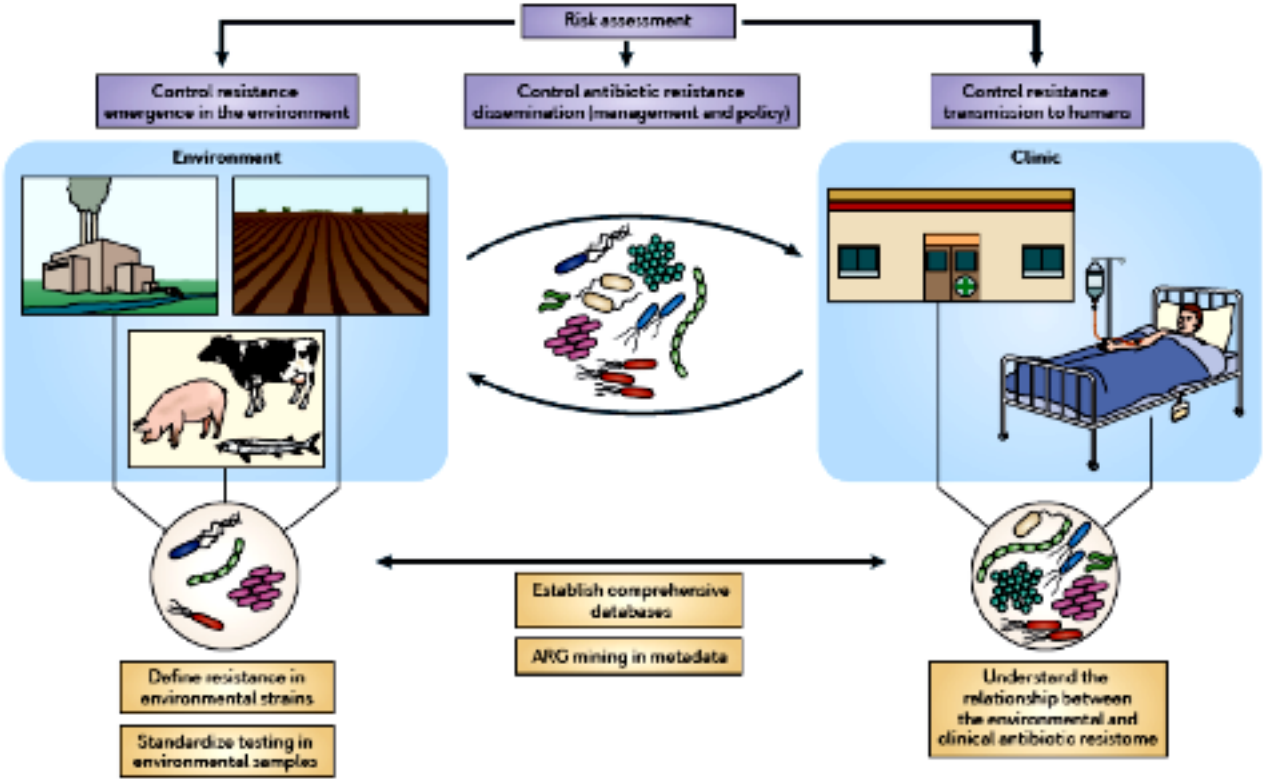
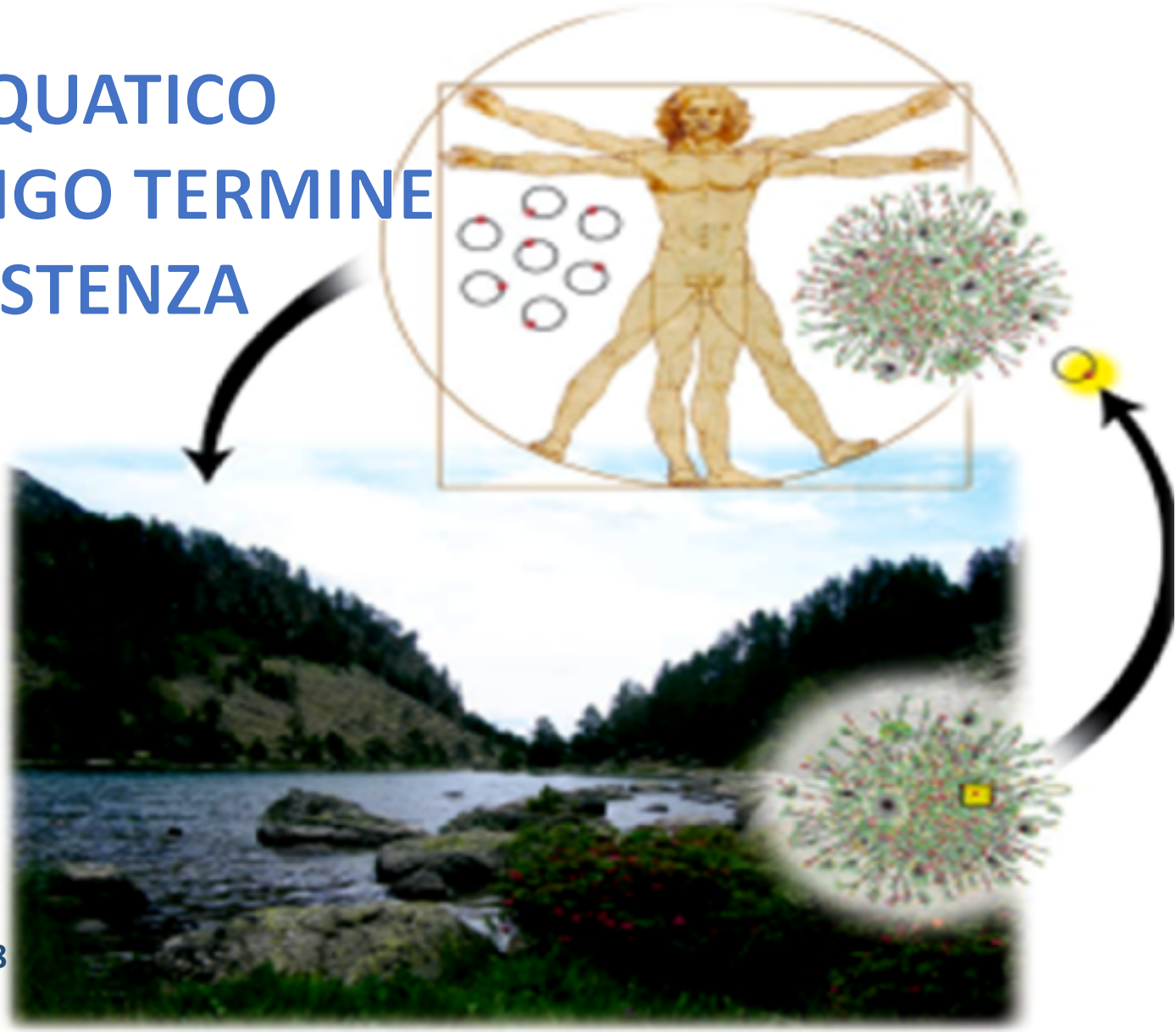


Figure 1 | **Minimizing the spread of antibiotic resistance in the environment.** The figure summarizes the current goals (purple boxes) in trying to minimize the emergence and spread of antibiotic resistance genes (ARGs) and antibiotic resistant bacteria (ARB) in the environment and their transmission into the clinic. The current needs and limitations that must be resolved to achieve these goals are also shown (yellow boxes). To evaluate the spread of antibiotic resistance in the environment, and the risk of transmission to humans, it is necessary to define what constitutes resistance in environmental bacterial strains and to standardize testing in environmental samples. This improvement in the definition and testing of resistance should contribute to the establishment of more comprehensive databases that combine data from both environmental and clinical settings. These databases would contribute to the evaluation of the relationship between the antibiotic resistomes in both settings and facilitate the mining of ARGs in metadata. These strategies would improve the assessment of the risk of dissemination of ARB and ARGs in the environment and their transmission to humans, and they would potentiate the development of control strategies (management and policy) aimed at preventing the dissemination of antibiotic resistance.

L’ AMBIENTE ACQUATICO COME RISERVA A LUNGO TERMINE DI GENI DI RESISTENZA



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Occurrence of ESBLs, KPC and MCR-1 in Gram-negative microorganisms from Oltrepò Pavese environment

P03

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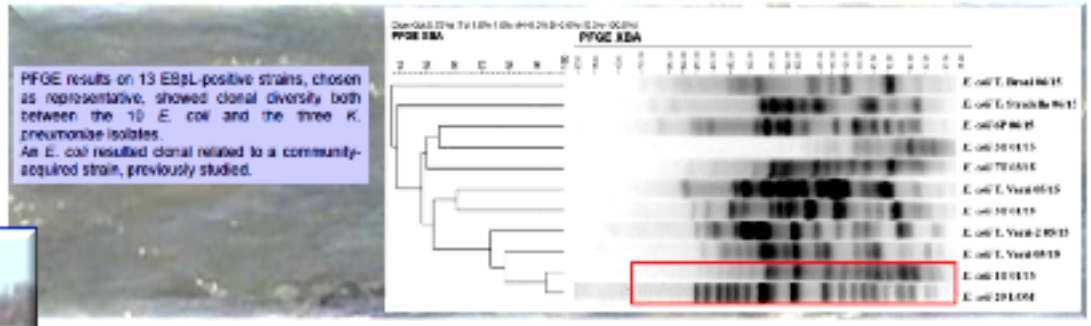

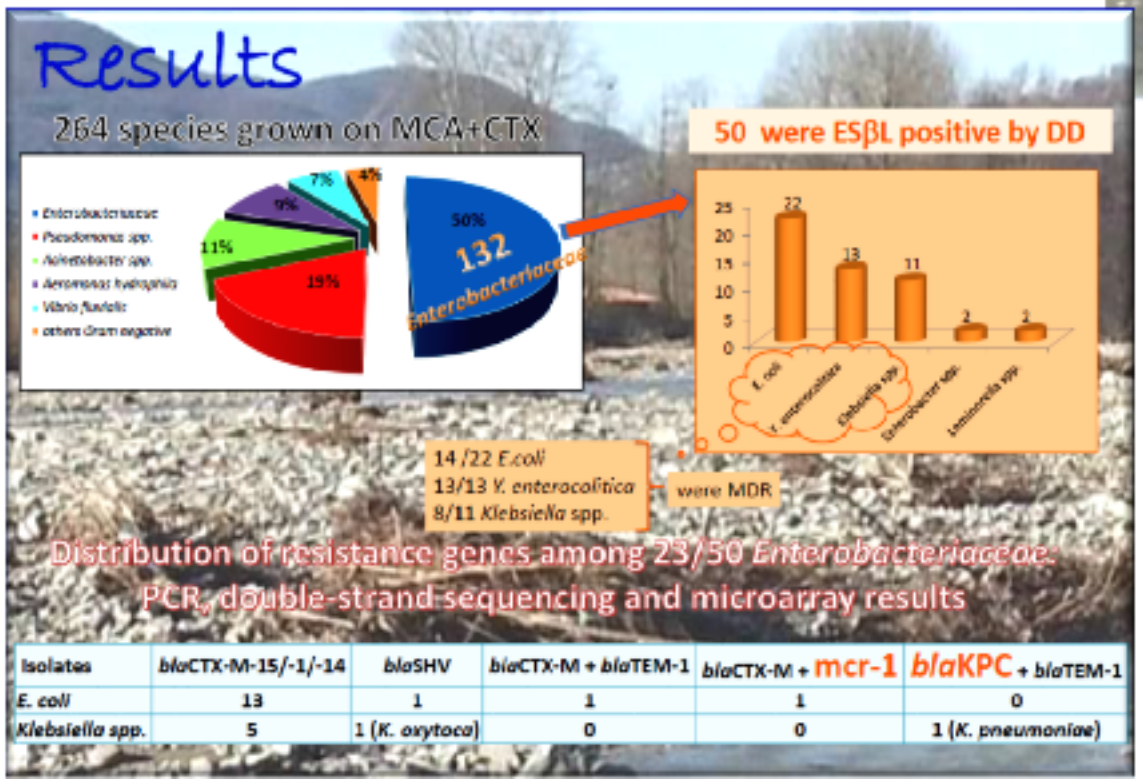

Isolates	*bla*CTX-M-15/-1/-14	*bla*SHV	*bla*CTX-M + *bla*TEM-1	*bla*CTX-M + mcr-1	*bla*KPC + *bla*TEM-1
E. coli	13	1	1	1	0
Klebsiella spp.	5	1 (*K. oxytoca*)	0	0	1 (*K. pneumoniae*)

- Here we report a high occurrence of ESβL-producing *Enterobacteriaceae* from Oltrepò surface waters.
  Due to the extensive use of surface water in the Po valley for both agricultural irrigation and watering animals, the here reported epidemiological data appear particularly worrisome.
- The presence of ESβLs-, carbapenemases- and MCR-1-producing bacteria represents a potential risk to human health and highlights the importance to improve both surveillance and remediation of local surface and ground waters.

Conclusioni

I. La resistenza si è diffusa ampiamente su più fronti. Gli scambi di resistenze possono avvenire in un ospite o nell'ambiente.

II. La diffusione e l'acquisizione dei meccanismi può essere silente e ciò rappresenta una sfida per il controllo delle infezioni, poiché anche pazienti asintomatici possono rappresentare *reservoirs* per la diffusione.

III. Le infezioni sono associate ad aumentata mortalità e costi.

IV. Le opzioni terapeutiche verso microrganismi che sviluppano resistenza sono limitate.

V. È imperativo monitorare l'emergere delle resistenze e controllare il consumo di antibiotici in ambito clinico, ma anche veterinario.

GRAZIE!!!

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Elisabetta Nucleo
Melissa Spalla
Sofia Caltagirone
Aurora Piazza