

*Screening-ului bacteriilor producatoare
de carbapenemase- PROGRAMUL PILOT
sau ce ne demonstreaza epidemiologia
moleculara*

Dr Dorina Timofte
Institute of Infection and Global Health
University of Liverpool



Outline:

- *Rezistenta la carbapeneme- De ce ar trebui sa ne îngrijoreze?*
- *Screening-ului bacteriilor producatoare de carbapenemase-PROGRAMUL PILOT*
- *Epidemiologie moleculara-evidenta*
- *Rezultate*

WHO warns against 'post-antibiotic' era

Agency recommends global system to monitor spread of resistant microorganisms

Sara Reardon

30 April 2014

[Rights & Permissions](#)



Analysis: Antibiotic apocalypse

By James Gallagher
Health editor, BBC News website

© 19 November 2015 | [Health](#)

Share



Some bacteria are becoming resistant to our best drugs

NEWS

[Home](#) | [UK](#) | [World](#) | [Business](#) | [Politics](#) | [Tech](#) | [Science](#) | **Health** | [Education](#) | [Entertainment](#)[Health](#)

Antibiotics resistance 'as big a risk as terrorism' - medical chief

By Fergus Walsh
Medical correspondent

© 11 March 2013 | [Health](#) |



DAME SALLY DAVIES
The Risks to Society of
Unrestricted Antibiotic Use
Chief Medical officer, UK

A portrait of Dame Sally Davies, Chief Medical Officer for the UK, speaking at a podium. She is wearing glasses and a blue jacket over a dark turtleneck. The text overlay identifies her and provides information about the risks of antibiotic use.

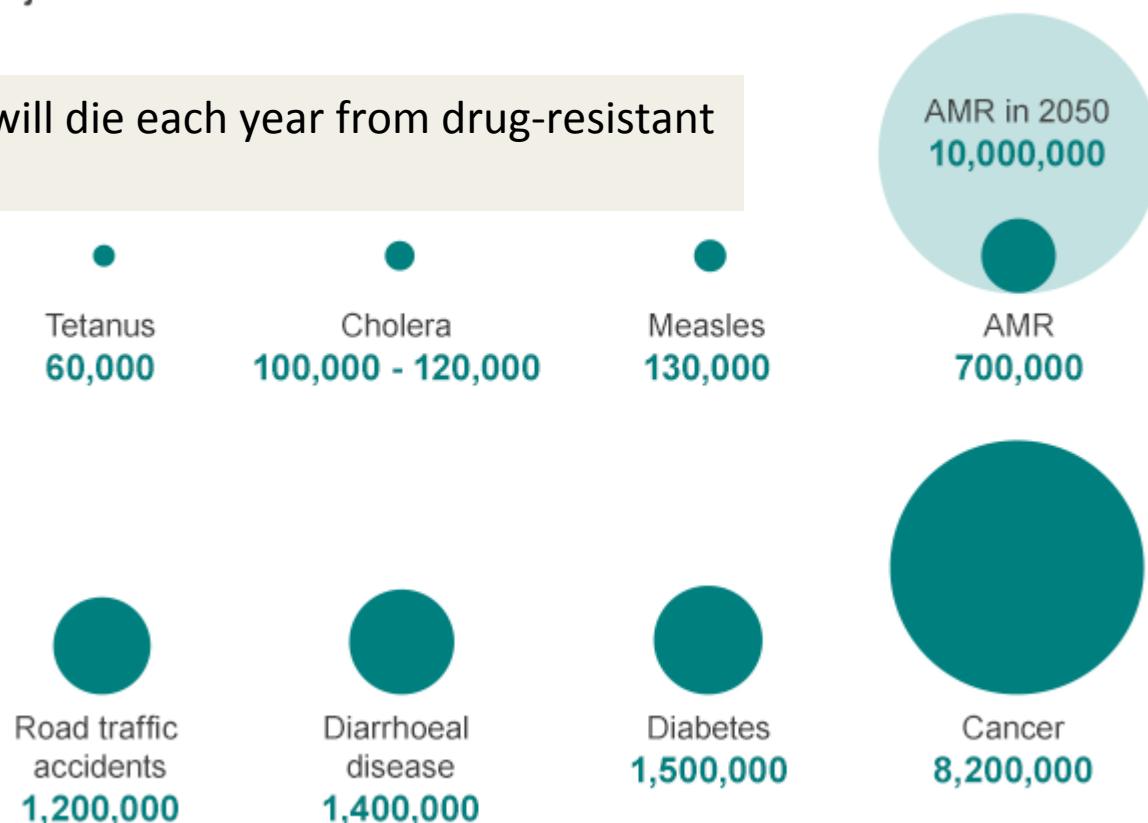


Review on Antimicrobial Resistance

Tackling drug-resistant infections globally

Deaths attributable to antimicrobial resistance every year compared to other major causes of death

10 million more people will die each year from drug-resistant infections by 2050



Source: Review on Antimicrobial Resistance 2014

Carbapenem resistance in *Enterobacteriaceae*: here is the storm!

Patrice Nordmann, Laurent Dortet and Laurent Poirel

Service de Bactériologie-Virologie, INSERM U914 'Emerging Resistance to Antibiotics', Hôpital de Bicêtre, Assistance Publique/Hôpitaux de Paris, Faculté de Médecine Paris Sud, K.-Bicêtre, 78 rue du Général Leclerc, 94275 Le Kremlin-Bicêtre Cedex, France

Magiorakos *et al.* *Antimicrobial Resistance and Infection Control* 2013, 2:6
<http://www.aricjournal.com/content/2/1/6>



LETTER TO THE EDITOR

Open Access

The rise of carbapenem resistance in Europe: just the tip of the iceberg?

Anna-Pelagia Magiorakos^{1*}, Carl Suetens¹, Dominique L Monnet¹, Carlo Gagliotti², Ole E Heuer¹ and EARS-Net Coordination Group and EARS-Net participants

Analysis:

By James Gallagher
Health editor, BBC News

© 19 November 2015 | He

Year Positive isolates (%)/number of isolates

Escherichia coli

Pigs at slaughter	All	166 (20.6%)/804
Pigs at slaughter	2012	31 (14.4%)/216
Pigs at slaughter	2013	68 (25.4%)/268
Pigs at slaughter	2014	67 (20.9%)/320
Retail meat	All	78 (14.9%)/523
Chicken	2011	10 (4.9%)/206
Pork	2011	3 (6.3%)/48
Chicken	2013	4 (25.0%)/16
Pork	2013	11 (22.9%)/48
Chicken	2014	21 (28.0%)/75
Pork	2014	29 (22.3%)/130
Inpatient	2014	13 (1.4%)/902

Klebsiella pneumoniae

Inpatient	2014	2 (0.7%)/420
-----------	------	--------------

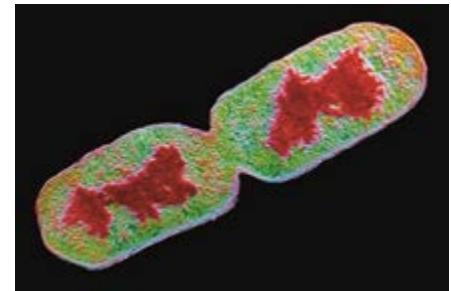


Animal
Mediated
Mechanism
Cell
Spectrum
Thus
Species
Rare
Coli
Enterobacteriaceae
Resistance
Polymyxin
Modification
Research
Food
Cell
Plasmid
MCR-1
Activity
Isolated

mcr-1 in Romania

Izolate clinice umane:

- 145 tulpini de Enterobacteriaceae (75% cu rezistenta la colistin)- isolate clinice provenite din Iasi, Cluj, Tg. Mures si Timisoara;
- Nr de tulpini positive pentru mcr-1: **0**



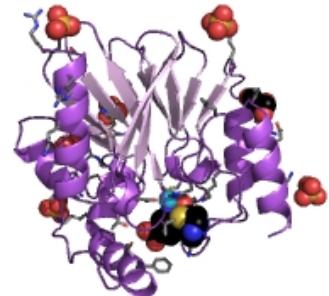
Tulpini de *E. coli* izolate de la pui (3 abatoare din Moldova):

- Tulpini positive **12/92 (13%) tulpini pozitive**



Carbapenemasele- De ce sa ne ingrijoreze?

- Enzime care **distrug antibioticele β-lactamice**, inclusiv carbapenemele
- Sunt amplasate pe **elemente genetice mobile** (plasmide, integroni)
- Genele care le codifica sunt frecvent asociate cu alte gene de rezistenta: → **PDR Pan-Drug-Resistance**
- Extrem de dificil de tratat
- Asociate cu o rata crescuta **de morbiditate si mortalitate** la pacientii infectati cu aceste organisme



Mecanismul rezistentei la carbapeneme

Classification	Enzyme	Most Common Bacteria
Class A	KPC, SME, IMI, NMC, GES	Enterobacteriaceae (rare reports in <i>P. aeruginosa</i>)
Class B (metallo-β-lactamse)	IMP, VIM, GIM, SPM, NDM	<i>P. aeruginosa</i> Enterobacteriaceae <i>Acinetobacter</i> spp.
Class D	OXA	<i>Acinetobacter</i> spp.

“The BIG FIVE”

Spectrul de rezistență al unui izolat de *K. pneumoniae*-producător de KPC

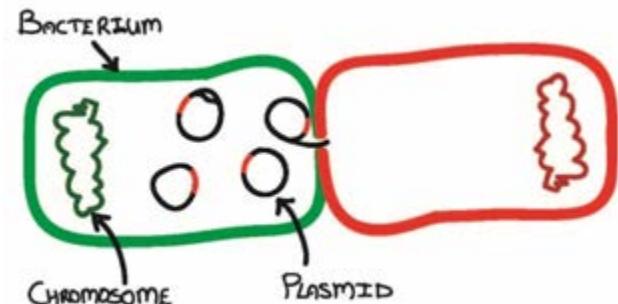
Antimicrobial	Interpretation	Antimicrobial	Interpretation
Amikacin	I	Chloramphenicol	R
Amox/clav	R	Ciprofloxacin	R
Ampicillin	R	Ertapenem	R
Aztreonam	R	Gentamicin	R
Cefazolin	R	Imipenem	R
Cefpodoxime	R	Meropenem	R
Cefotaxime	R	Piperacillin/Tazo	R
Cetotetan	R	Tobramycin	R
Cefoxitin	R	Trimeth/Sulfa	R
Ceftazidime	R	Polymyxin B	MIC >4mg/ml
Ceftriaxone	R	Colistin	MIC >4mg/ml
Cefepime	R	Tigecycline	S

R = Resistance/NOT effective

S= Sensitive/Effective

Cum se raspandesc

- “*successful clonal lineages*”- care sunt selectionate in spitale unde utilizarea antibioticelor este crescuta si apar oportunitati de transmitere intre pacienti;
 - *Klebsiella pneumoniae* sequence type (ST) 258 purtatoare de *K. pneumoniae* carbapenemases (KPC) a cauzat epidemii de proportii nationale si internationale
- Gene *asociate cu anumite plasmide* care se transmit usor- (IncFII)



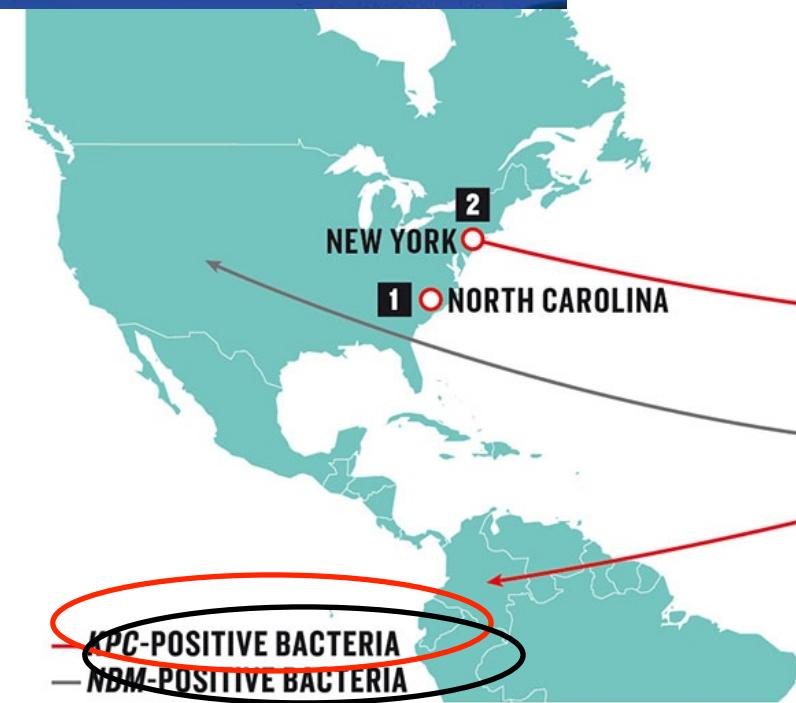
KPC-producing CRE in the United States, 2006



Carbapenemase-producing CRE in the United States, 2013



3





Medical Tourism

India has cemented its place in the world healthcare scenario. This could be attributed to several reasons; highly skilled and trained medical professionals, rapidly developing healthcare standards (that now match western standards), strong focus on research and low cost, to name a few.

500,000

Medical tourists visited India in 2010

60,000

Doctors graduate from Indian medical colleges annually



\$18 billion

Expected size of the wellness

Search for

in All Fields



GO

Adv

Home | Journals | Content Collections | Multimedia | Conferences | Information for | Su

The Lancet Infectious Diseases, Volume 11, Issue 5, Pages 355 - 362, May 2011
doi:10.1016/S1473-3099(11)70059-7  Cite or Link Using DOI

< Previous Article | Next Article

This article can be found in the following collections: [Public Health](#); [Gastroenterology \(Gastrointestinal infections\)](#); [Infectious Diseases \(Anti-infective therapy\)](#), [Gastrointestinal infections](#), [Healthcare-associated infections](#)
Published Online: 07 April 2011

Copyright © 2011 Elsevier Ltd All rights reserved.

Dissemination of NDM-1 positive bacteria in the New Delhi environment and its implications for human health: an environmental point prevalence study

Prof [Timothy R Walsh](#) PhD   , [Janis Weeks](#) BSc , [David M Livermore](#) PhD , [Mark A Toleman](#) PhD 

Summary

Background

Not all patients infected with NDM-1-positive bacteria have a history of hospital admission in India, and extended-spectrum β-lactamases are known to be circulating in the Indian community. We therefore measured the prevalence of the NDM-1 gene in drinking water and seepage samples in New Delhi.

patients in the UK.

'Most not all, had previously travelled to the Indian hospital treatment there.'

THE RISKS FROM MEDICAL TOURISM

Abstract ▾

Send to: ▾

J Antimicrob Chemother. 2015 Apr;70(4):1016-20. doi: 10.1093/jac/dku527. Epub 2015 Jan 27.

Snapshot on carbapenemase-producing *Pseudomonas aeruginosa* and *Acinetobacter baumannii* in Bucharest hospitals reveals unusual clones and novel genetic surroundings for blaOXA-23.

Gheorghe I¹, Novais Å², Grosso F², Rodrigues C², Chifiriuc MC¹, Lazar V¹, Peixe L³.

⊕ Author information

Abstract

OBJECTIVES: The present study was designed to provide a snapshot on carbapenemase-producing *Pseudomonas aeruginosa* (n=11) and *Acinetobacter baumannii* (n=7) isolates in hospitalized patients (November 2011, January–March 2012) from two main hospitals in Bucharest, south Romania.

METHODS: Clonality among isolates was established by PFGE, MLST and Fourier transform infrared spectroscopy. Carbapenemases were screened by the Blue-Carba test, PCR and sequencing. Transferability of blaOXA-23 was tested by conjugation and plasmid typing (number, size and identity) was assessed by S1-PFGE, replicon typing, hybridization and PCR mapping.

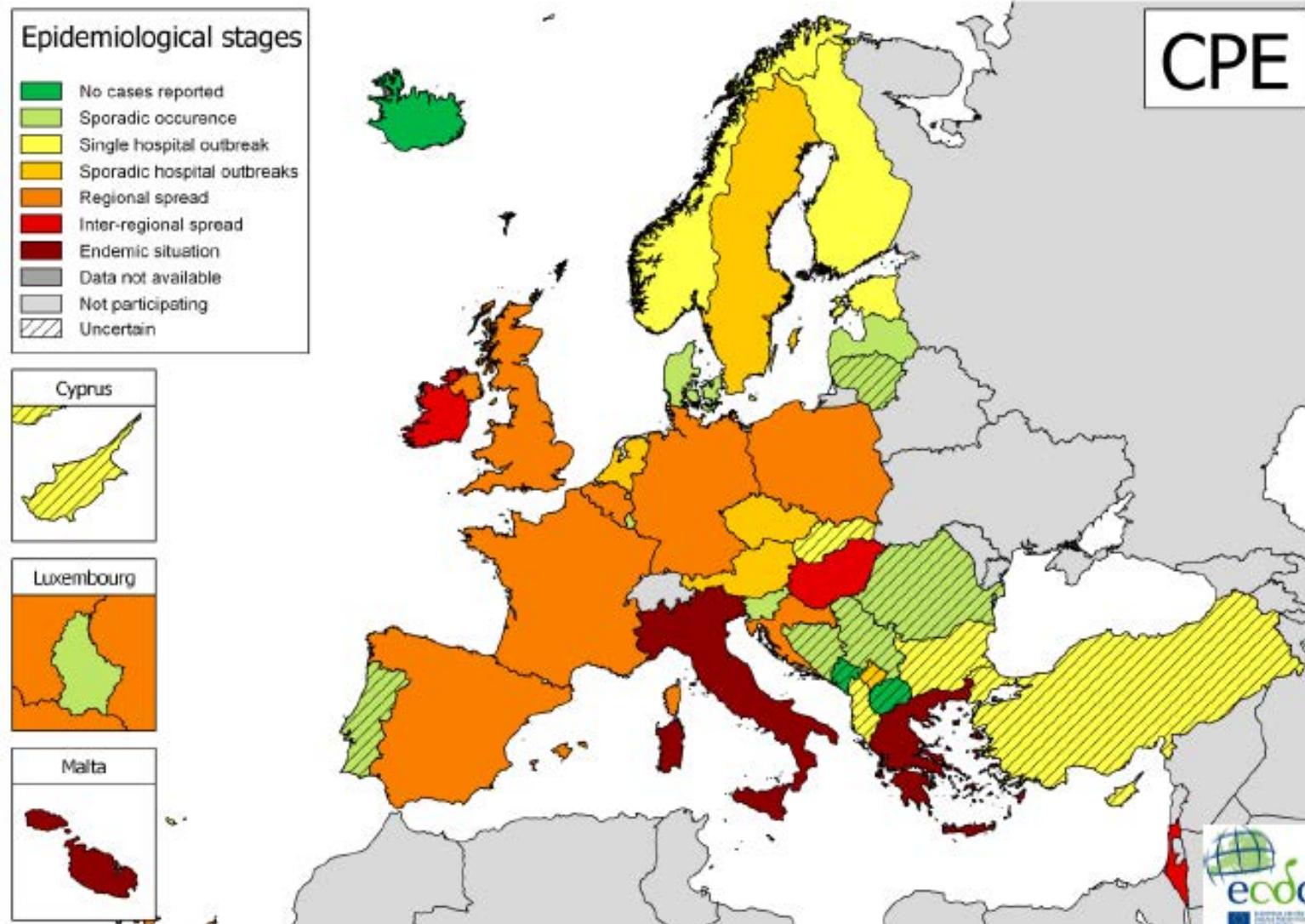
RESULTS: All *P. aeruginosa* isolates carried chromosomally located blaVIM-2, associated with a common class 1 integron (aacA7-blaVIM-2) or an atypical configuration (aacA7-blaVIM-2-dfrB5-tniC). These isolates belonged to unusual lineages; mostly ST233 disseminated in one hospital unit, with ST364 and ST1074 also being detected. *A. baumannii* isolates carried blaOXA-23 in Tn2008, which was found truncating a TnaphA6 transposon located in a common 60 kb GR6 (aci6) pABKp1-like conjugative plasmid in highly related CC92 clones (ST437, ST764 and ST765), where CC stands for clonal complex.

CONCLUSIONS: Our results show the spread of VIM-2-producing *P. aeruginosa* and OXA-23-producing *A. baumannii* clinical isolates in two hospitals from Bucharest and highlight a peculiar population structure in this Eastern European country. Also, we demonstrate the dissemination of a common and conjugative aci6 pABKp1-like plasmid scaffold in different *A. baumannii* clones and we report the first known identification of Tnaph6-carrying pACICU2-like plasmids in Europe.

© The Author 2015. Published by Oxford University Press on behalf of the British Society for Antimicrobial Chemotherapy. All rights reserved. For Permissions, please e-mail: journals.permissions@oup.com.

European survey on carbapenemase-producing Enterobacteriaceae (EuSCAPE)

Figure 1. Occurrence of carbapenemase-producing *Enterobacteriaceae* (CPE) (all types of isolates) based on self-assessment by national experts, EuSCAPE project, 38 European countries, March 2013



Carbapenemase-producing *Enterobacteriaceae* in Europe: a survey among national experts from 39 countries, February 2013

TABLE 3

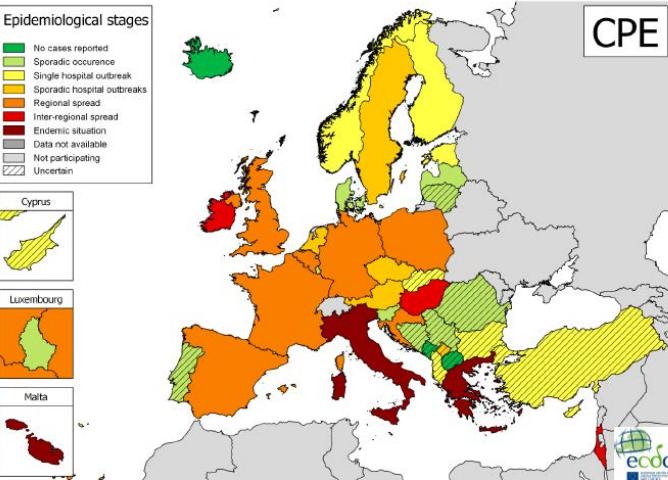
National management of carbapenemase-producing *Enterobacteriaceae* (CPE) in 39 European countries, 2013*

C Glasner¹, I
M Gniadkow
N Woodford
the Europea

1. Department of Microbiology, Academic Medical Center, Amsterdam, The Netherlands
2. European Reference Laboratory for Enteric Pathogens, Institut Pasteur, Paris, France
3. Department of Microbiology, University of Antwerp, Belgium
4. Service de Microbiologie, IRCCyN, Nantes, France
5. United Kingdom Reference Laboratory for Enteric Pathogens, London, United Kingdom
6. Division of Microbiology, National Institute for Public Health and the Environment, Bilthoven, The Netherlands
7. Clinical Microbiology, University College Dublin, Dublin, Ireland
8. Sweden, National Institute of Public Health, Solna, Sweden
9. National Institute of Public Health, Ljubljana, Slovenia
10. Department of Microbiology, University of Ljubljana, Ljubljana, Slovenia
11. Norway, National Institute of Public Health, Oslo, Norway
12. Sector of Microbiology, King's College London, London, United Kingdom
13. INSEAD de Marne-la-Vallée, Paris, France
14. Medical Faculty, University of Regensburg, Regensburg, Germany
15. Department of Microbiology, University of Macedonia, Thessaloniki, Greece
16. Institute of Hygiene, University of Berlin, Berlin, Germany
17. Department of Microbiology, Marmara University, Istanbul, Turkey

Country	National system for surveillance	Officially nominated national reference laboratory	National recommendation or guideline for submitting isolates to national expert or reference laboratories	Agreed criteria or a policy for submitting isolates to national expert or reference laboratories ^a	National recommendation or obligation for reporting (notification) to health authorities	National recommendation or guideline on infection control measures
Montenegro						
Norway	•	•	•	•	• ^b	•
Poland	•	•	•	•	• ^b	•
Portugal	•	•	•	•	• ^b	•
Romania	• ^c	•				
Serbia	•	•				
Slovakia	•	•			• ^b	
Slovenia			•	•		•
Spain	•	•	•	•	• ^b	
Sweden	•	•	•	•	• ^b	•
Switzerland	•			•		
The Former Yugoslav Republic of Macedonia	•	•			• ^b	
The Netherlands	•		•	•	• ^b	•
Turkey	• ^c	• ^c	•	•	• ^b	•

Figure 1. Occurrence of carbapenemase-producing *Enterobacteriaceae* (CPE) (all types of isolates) based on self-assessment by national experts, EuSCAPE project, 38 European countries, March 2013



Proiect pilot: Implementarea screening-ului pentru identificarea pacientilor colonizati cu bacterii Gram-negative producatoare de carbapenemase

Scop:

- determinarea prevalentei rezistentei la carbapeneme in spitalele participante
- Identificarea la internare a pacientilor cu colonizare intestinala

Motivatie:

- Lipsa studiilor care sa determine nivelul de colonizare intestinala cu bacterii GN producatoare de carbapenemase
- Colonizarea este o conditie pentru dezvoltarea infectiei
- Identificarea precoce a purtatorilor permite implementarea masurilor de control



Sursa: www.atcc.org

Implementarea screening-ului pentru CPOs: Studiu pilot

- În perioada Dec 2014-Mai 2015 în trei spitale din Tg. Mures (H1 și H2) și unul din Iasi (H3)
- Stabilirea de comun acord a protocolelor de lucru și selectarea secțiilor participante;
- S-au prelevat probe (tampon rectal/materii fecale) la pacienți **în primele 48 ore de la internare** ;
- Pacienți internați în secțiile selecționate:
Pediatrie, Gastroenterologie,
Nefrologie, Boli infectioase, ATI,
Pneumoftiziologie , Chirurgie



Selectarea pacientilor:

Grupe cu factori de risc:

- pacienți cu spitalizări anterioare:
 - în țara în ultimul an
 - sau în străinătate în ultimii doi ani;
- pacienți tratați anterior cu antibiotic din grupa carbapenemelor;
- Sau confirmati anterior cu o infectie cu o bacterie cu rezistență la carbapeneme;



Implementarea screening-ului pentru CPOs: Studiu pilot

- Pacienti cu izolatele clinice cu rezistenta la CARB au fost de asemenea inclusi;
- Carbapenem-resistant organisms (CROs) – Enterobacteriaceae si non-fermenters (*Acinetobacter* spp, *Pseudomonas* spp)
- In total, **820 probe** (fecale, izolate clinice sau probe de mediu);



Testarile moleculare

- PCR screening pentru:
 - extended spectrum beta-lactamases (ESBL) including *bla*_{CTX-M, SHV, TEM, OXA}
 - carbapenem-resistance genes (*bla*_{NDM}, *bla*_{KPC}, *bla*_{OXA-48}, *bla*_{IMP}, *bla*_{VIM}, *bla*_{SPM})
 - Carbapenem hydrolysing class D beta-lactamases (CHDL) corresponding to OXA-23, OXA-24/40, OXA-58 and OXA-148 groups
 - OXA-51/69 type of *A. baumannii*
- *Studii de conjugare*, pentru demonstrarea transmiterii rezistentei
- *Plasmid typing*-Identificarea plasmidelor purtatoare ale genelor de rezistență
- *SECVENTIRE* pentru confirmarea genelor

[HOME](#)[ARCHIVES](#)[ABOUT US](#)[EDITORIAL POLICY](#)[FOR AUTHORS](#)[FOR REVIEWERS](#)[LINKS](#)

15-

Search

[!\[\]\(51e24a718c479f61046a6569471331fa_img.jpg\) Submit article](#)[!\[\]\(821acc15c470127e6ad8ef362d2c5a7f_img.jpg\) RSS Feed](#)[!\[\]\(eba903ee4dc5f81044c5c13ca9966076_img.jpg\) Follow us on Twitter](#)[!\[\]\(5fbc60decb3ef3e18ac6af3c11358089_img.jpg\) Subscribe](#)[!\[\]\(212a2318a401861c7559cff43c43bd71_img.jpg\) Unsubscribe](#)[!\[\]\(912eb35f342458fc87c7c1d0cfd433ba_img.jpg\) Contact](#)[!\[\]\(9f2eb39b5cb6ca001ddfe685f3184b1d_img.jpg\) Sitemap](#)

Announcements

[Home](#) ▶ [Eurosurveillance Edition 2016: Volume 21/ Issue 25](#) ▶ Article 2[◀ Back to Table of Contents](#)[◀ Previous](#)[!\[\]\(1f90c95fe6d3ba43da0a9f07bb3fa77a_img.jpg\) Tweet](#) [Next ▶](#)

Eurosurveillance, Volume 21, Issue 25, 23 June 2016

Surveillance and outbreak report

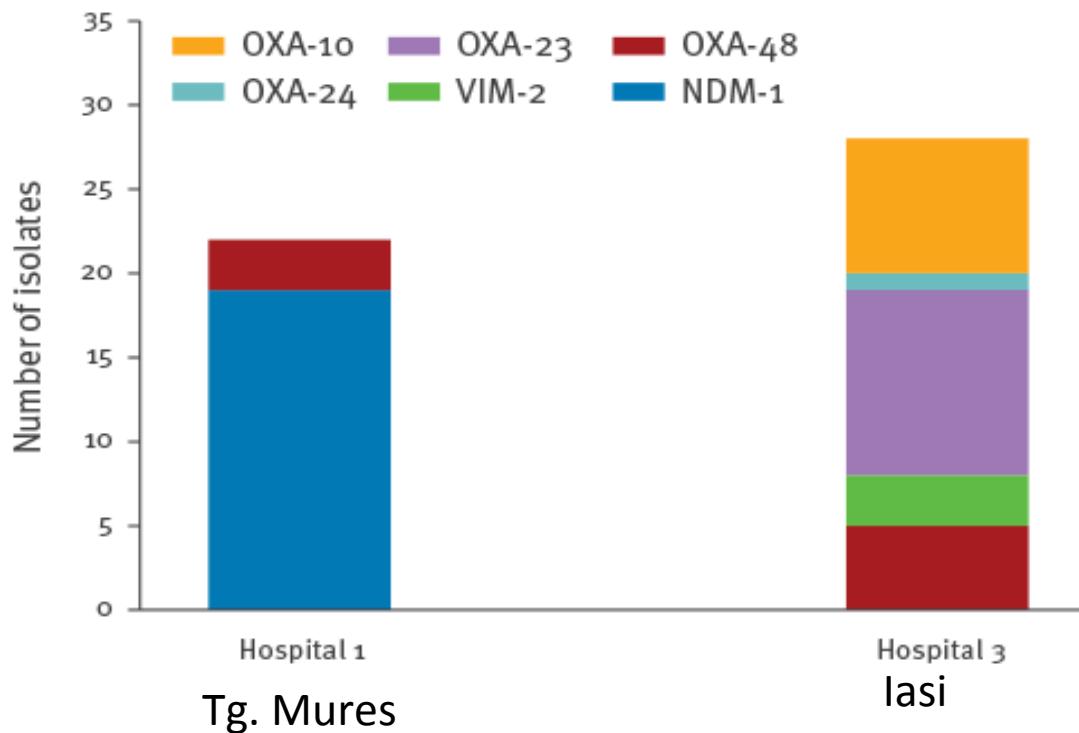
ACTIVE SURVEILLANCE SCHEME IN THREE ROMANIAN HOSPITALS REVEALS A HIGH PREVALENCE AND VARIETY OF CARBAPENAMASE-PRODUCING GRAM-NEGATIVE BACTERIA: A PILOT STUDY, DECEMBER 2014 TO MAY 2015

D Timofte ^{1 2 3 4}, CV Panzaru ^{4 5 7}, IE Maciuca ^{1 4}, M Dan ⁷, AD Mare ⁶, A Man ⁸, F Toma ⁶

[+ Author affiliations](#)

PREVALENȚA REZISTENȚEI LA CARBAPENEME

- Tg. Mures: 5.11% (H1), 11.4% (H2)
- Iasi: 20.3% (H3)



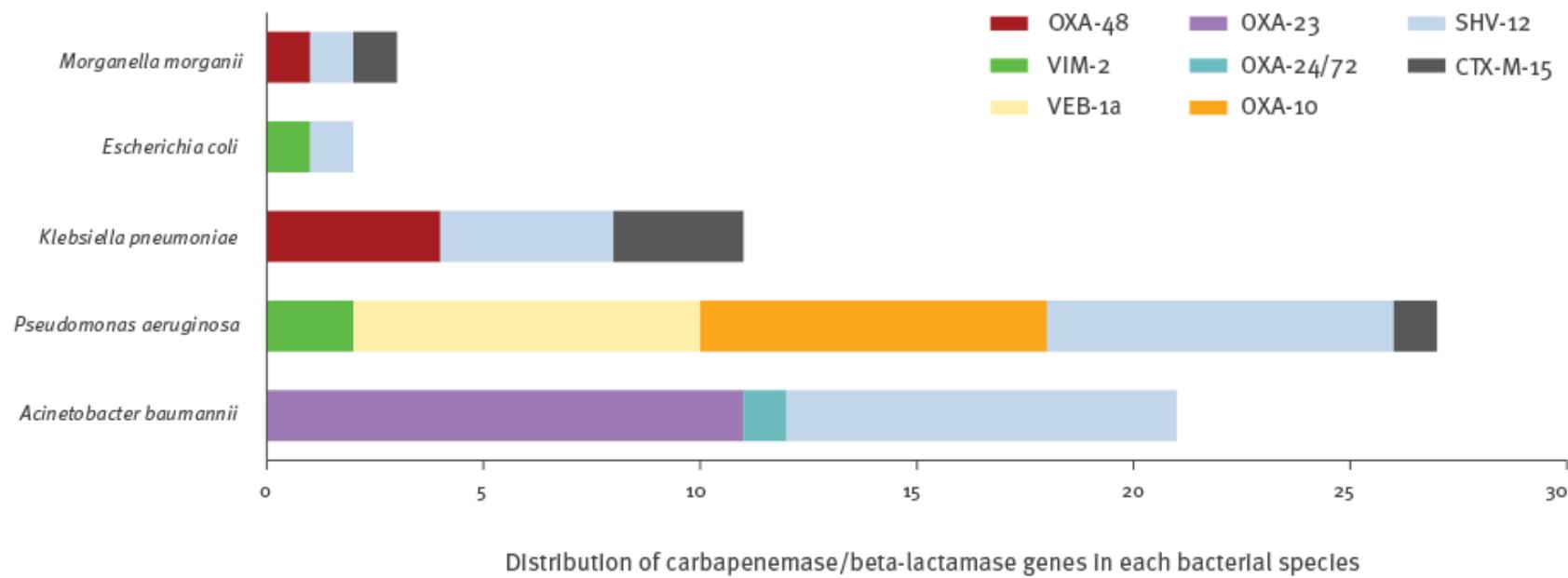
Genes associated with carbapenem resistance (here including *bla*_{OXA-10}) identified in two hospitals, north-central (Hospital 1, 22 isolates) and north-east Romania (Hospital 3, 28 isolates), December 2014–May 2015

Surveillance and outbreak report

ACTIVE SURVEILLANCE SCHEME IN THREE ROMANIAN HOSPITALS REVEALS A HIGH PREVALENCE AND VARIETY OF CARBAPENAMASE-PRODUCING GRAM-NEGATIVE BACTERIA: A PILOT STUDY, DECEMBER 2014 TO MAY 2015

D Timofte ^{1 2 3 4}, CV Panzaru ^{4 5 7}, IE Maciuca ^{1 4}, M Dan ⁷, AD Mare ⁶, A Man ⁶, F Toma ⁶

+ Author affiliations



Carbapenemase-producing Gram-negative bacterial species (n = 5) and distribution of carbapenemase- and beta-lactamase genes (n = 8) identified in each bacterial species in Hospital 3 (28 isolates), north-east Romania, December 2014–May 2015

Portaj intestinal cu bacterii producatoare de carbapenemase

Spitalul H1 din Targu Mures

OXA-48 *Klebsiella* spp

- Probe fecale- 3 izolate

NDM-1 *Serratia* and *Klebsiella* spp

- Probe clinice- 7 izolate
- Probe fecale- 9 izolate
- Probe mediu- 3 izolate

Spitalul H3 din Iasi

OXA-10 *Pseudomonas* spp

- 2 izolate probe clinice
- 6 izolate probe fecale

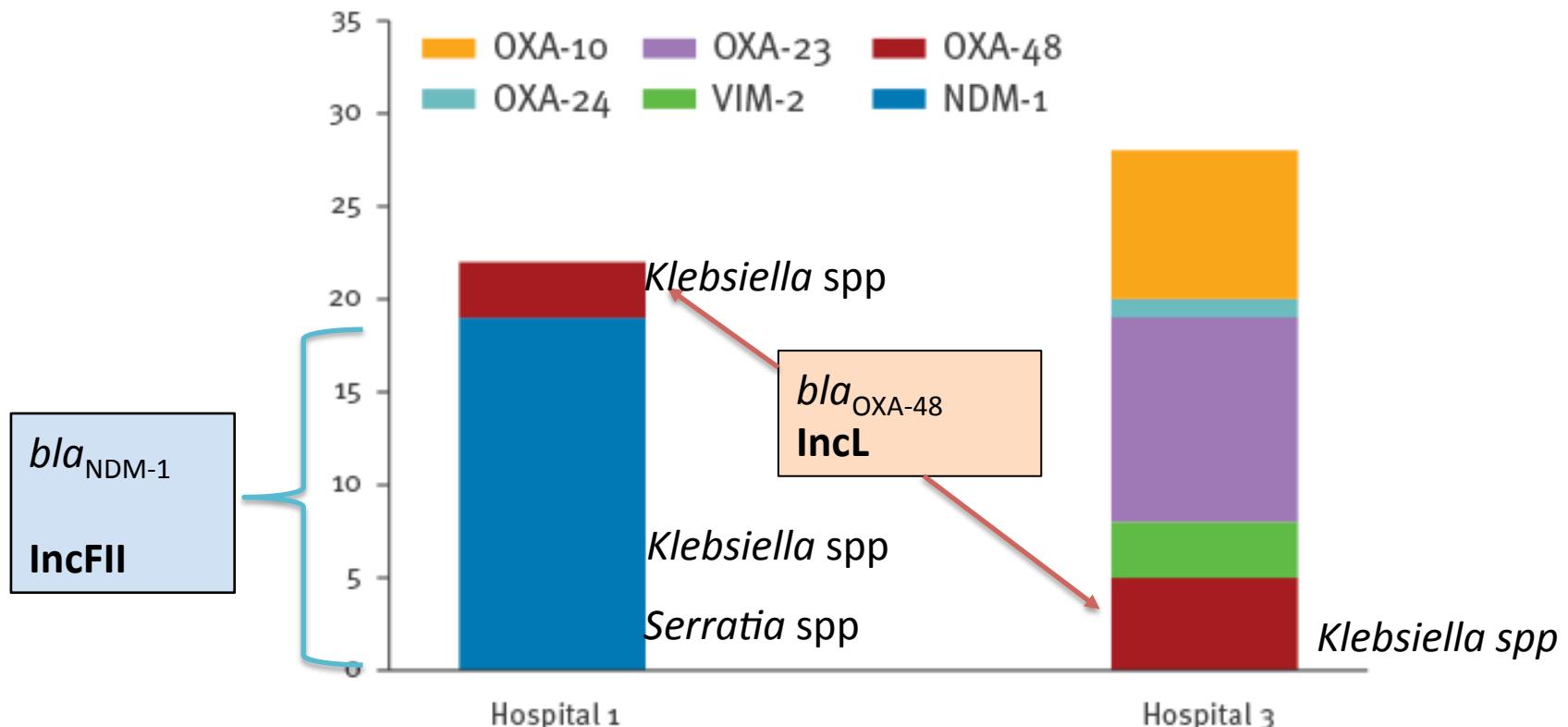
OXA-23 *Acinetobacter* spp

- 9 izolate probe clinice
- 3 izolate probe fecale

In total 50 CP-GNB au fost identificate:

- 27 au fost din probe clinice
- 23 au fost obtinute din materii fecale/tampon rectal

Suportul genetic- caracterizarea plasmidelor



Genes associated with carbapenem resistance (here including bla_{OXA-10}) identified in two hospitals, north-central (Hospital 1, 22 isolates) and north-east Romania (Hospital 3, 28 isolates), December 2014–May 2015

“Plasmids without frontiers”

Other plasmids associated with NDM-1: IncM, IncN, IncN2, IncR, IncF



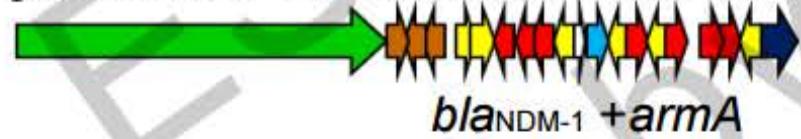
NDM-positive plasmids, IncM, IncN1,2, IncR, IncF groups . A. Carattoli 2016, unpublished

Escherichia coli
Klebsiella pneumoniae
Citrobacter freundii
Enterobacter cloacae
Enterobacter hormaechei

pNDM-HK IncM *Escherichia coli*, Honk-Kong, IncL/M 88,803 bp, HQ451074



pNDM-GUE, IncF *Escherichiacoli*, France, IncFII, 65245 bp , JQ364967



pNDM-1 IncN2 *Escherichiacoli*, Australia, 35947 bp , JF785549

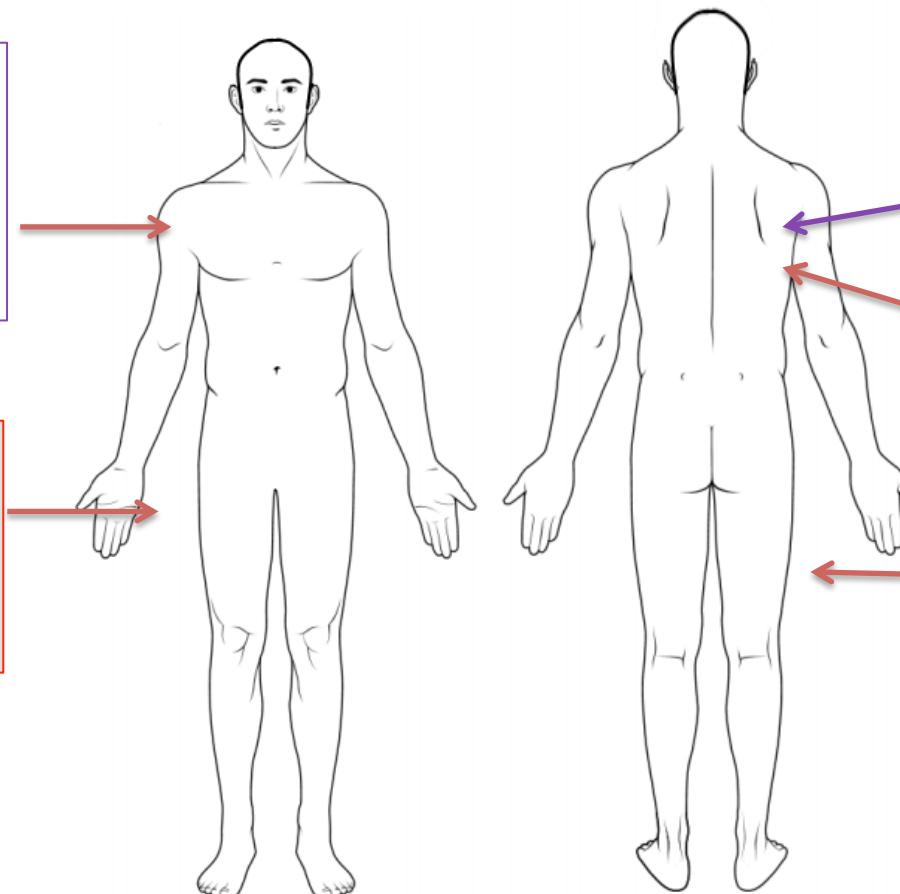


Pacienti colonizati/infectati cu multiple bacterii producatoare de carbapenemase

Infectii (pneumonie sau bacteriemie) cu

A. baumannii OXA-23-producing infections

Colonizare intestinala cu OXA-23-producing *A. baumannii*



Pacient 1 si 2

Pacient 3

Factori de risc identificati:

Pacienti identificati **pozitivi pentru portaj intestinal** cu OXA-23 *A. baumanii*, OXA-48 *K. pneumoniae*, OXA-10 *P. aeruginosa*:

- doi pacienti au avut multiple spitalizari in anul premergator (diverse spitale);
- Sase pacienti au fost admisi in acelasi spital in anul anterior;
- Toti au fost tratati cu imipenem;

Importanta identificarii pacientilor care au un risc ridicat de colonizare intestinala



Concluzii



Scopul proiectului:

- **Evidenta stiintifica** care demonstreaza nivelul raspandirii carbapenemaselor in spitalele investigate
- **Conscientizarea riscului** de raspandire silentioasa a acestora in absenta unui program coordonat de detectie si raportare

Initierea unui raport inaintat Comisiei consultative de epidemiologie a Ministerului Sanatatii

- Necesitatea introducerii unui sistem national de supraveghere a infectiilor cu CPOs;
- Formarea unui **grup de lucru** care sa initieze elaborarea unui ghid pentru **“Depistarea precoce, managementul si controlul Infectiilor cu bacterii Gram-negative producatoare de carbapenemase”**

Va multumesc!

