Epidemiologia dei Gram negativi multiresistenti

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www.ilgirodelmondo.it

Outline

- I percorsi dell'antibioticoresistenza
- Epidemiologia globale
- I dati in Europa
- I dati locali

Storia della Multiresistenza nei Gram-Negativi

Inizio uso massiccio di antibiotici β-lattamici

β-lattamasi semplici (penicillinasi)

Anni '80

ESBL (Extended-Spectrum β-Lactamases) (1983 Germania/Francia)

Segnalazioni iniziali da *Klebsiella pneumoniae* e *E. coli*

Anni '90

Carbapenemasi

KPC in USA, 1996-97

VIM (Verona 1996), IMP, SPB, GBL metallo-β-lattamasi in *P.aeruginosa* e Eb

Anni 2000

Aumento delle infezioni da ceppi MDR e PDR

P.aeruginosa e A.baumannii con multiresistenza estrema

colistine-resistenza

NDM India 2009

Anni 2010-2020

Globalizzazione della resistenza

Pandemia di carbapenemasi

Diffusione rapida di NDM, OXA

combinazioni antibiotiche e nuovi farmaci

Oggi

Sfida clinica globale

Resistenza a quasi tutte le classi di antibiotici

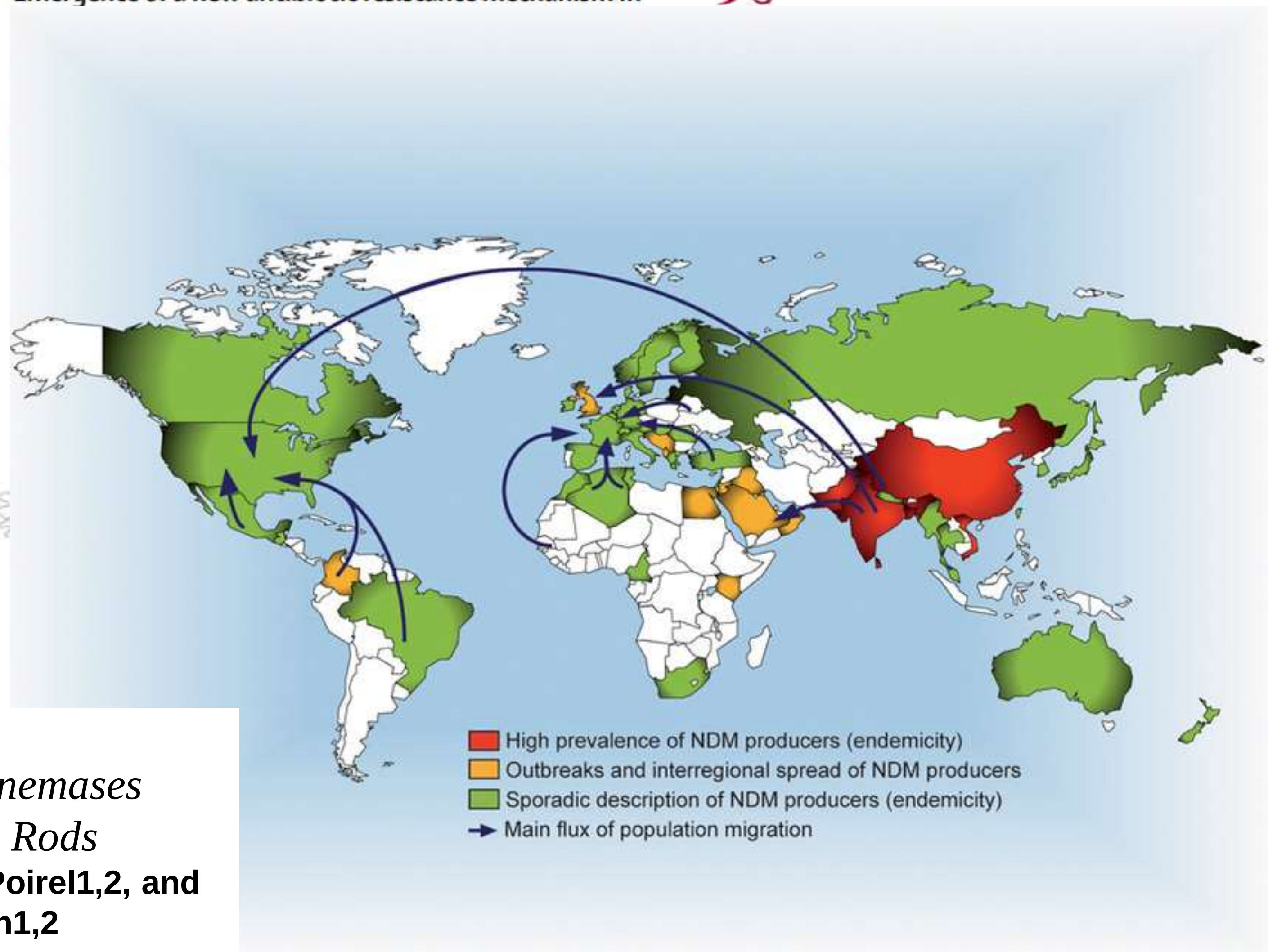
Necessità di sorveglianza attiva, stewardship antibiotica e ricerca di nuovi farmaci

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Dec. 2009, p. 5046–5054 Vol. 53, No. 12
0066-4804/09/$12.00 doi:10.1128/AAC.00774-09

Characterization of a New Metallo-β-Lactamase Gene, bla_{NDM-1}, and a Novel Erythromycin Esterase Gene Carried on a Unique Genetic Structure in *Klebsiella pneumoniae* Sequence Type 14 from India[▽]

Dongeun Yong,[1,2] Mark A. Toleman,
Kyungwon

Emergence of a new antibiotic resistance mechanism in



Chapter 48

NDM-Type Carbapenemases in Gram-Negative Rods

Laurent Dortet1, Laurent Poirel1,2, and Patrice Nordmann1,2

Flussi turistici in Italia

58,3 million
international travellers to Italy in 2017*

11,361,460
Italian travellers to abroad in 2016**

*Source: World Tourism Organization (UNWTO) Turism Highlights 2018
** Source: "Viaggi e vacanze all'Estero e in Italia" ISTAT 2017.

Among International Italian travelers:
57% to UE-Europe
20% to non-UE-Europe,
22% to non European countries

L'Italia è la 5° nazione per ricezione di turisti

Between 30% and 40% of travellers adquire a AMR in international travellers

BMC Part of Springer Nature

Antimicrobial Resistance & Infection Control

Acquisition of multidrug-resistant Enterobacterales during international travel: a systematic review of clinical and microbiological characteristics and meta-analyses of risk factors

Between 21% and 51% of healthy travelers acquire multidrug-resistant Enterobacteriaceae when traveling abroad, depending on the region visited. The highest rates were observed in trips to South Asia, with a median of 71%.

Open Forum Infectious Diseases

BRIEF REPORT

Acquisition and Long-term Carriage of Multidrug-Resistant Organisms in US International Travelers

Colin J. Worby, Ashlee M. Earl, Sarah E. Turbett, Margaret Becker

Screening of stool from 608 US international travelers and identified an acquisition rate of 38% (gram-negative bacteria producing extended-spectrum beta-lactamases, *mcr*-mediated colistin-resistant Enterobacterales, and carbapenemase-producing carbapenem-resistant Enterobacterales) following travel.

www.thelancet.com/microbe Vol 2 April 2021

Dynamics of intestinal multidrug-resistant bacteria colonisation contracted by visitors to a high-endemic setting: a prospective, daily, real-time sampling study

A study that collected daily stool samples from 20 European visitors to Laos over a three-week period found that 74% of the samples contained gram-negative bacteria producing extended-spectrum beta-lactamases.

The NEW ENGLAND JOURNAL of MEDICINE

Acquisition of Antibiotic-Resistant Bacteria by U.S. International Travelers

Stool samples from 412 U.S. travelers before and after international travel.
No travelers had CP-CRE or MCRE in the stool before travel.Identified 1% who acquired carbapenemase-producing carbapenem-resistant Enterobacterales and 5% who acquired *mcr*-mediated colistin-resistant Enterobacterales (*Peru)

Which AMR?

Table S5. Number of studies and isolates for species that were documented in the analyzed studies.

#	Species	Number of documenting travelling AMR	
		studies	isolates
01	Acinetobacter spp.*	21	187
02	Aeromonas spp.*	3	108
03	Brucella melitensis	1	14
04	Burkholderia pseudomallei	5	5
05	Campylobacter spp.*	19	3281
06	Citrobacter spp.*	3	3
07	Comamonas spp.	1	1
08	Corynebacterium diphtheriae	2	2
09	Enterobacter spp.*	9	49
10	Enterococcus spp.*	8	40
11	Escherichia coli*	59	5461
12	Klebsiella spp.*	28	207
13	Lactococcus garvieae	1	1
14	Morganella morganii*	1	1
15	Mycobacterium spp.	5	91
16	Neisseria gonorrhoeae	3	120
17	Plesiomonas spp.*	2	39
18	Proteus spp.*	7	14
19	Providencia spp.*	2	2
20	Pseudomonas spp. *	12	44
21	Raoultella ornithinolytica*	1	1
22	Salmonella spp.*	63	6032
23	Shigella spp.*	29	6931
24	Staphylococcus aureus	35	2162
25	Streptococcus pyogenes	1	1
26	Vibrio spp.*	3	5
27	enteric bacteria (not specified) *	29	5200
28	Other organisms (not specified)	3	58
	Total		30060

*, enteric bacteria.

Tropical Medicine and Infectious Disease

Trop. Med. Infect. Dis. **2021**, *6*, 11.

MDPI

Review

Travel-Related Antimicrobial Resistance: A Systematic Review

Hamid Bokhary [1,2,3,4,*], Krisna N. A. Pangesti [1,4], Harunor Rashid [3,5], Moataz Abd El Ghany [3,4,6,†] and Grant A. Hill-Cawthorne [1,†]

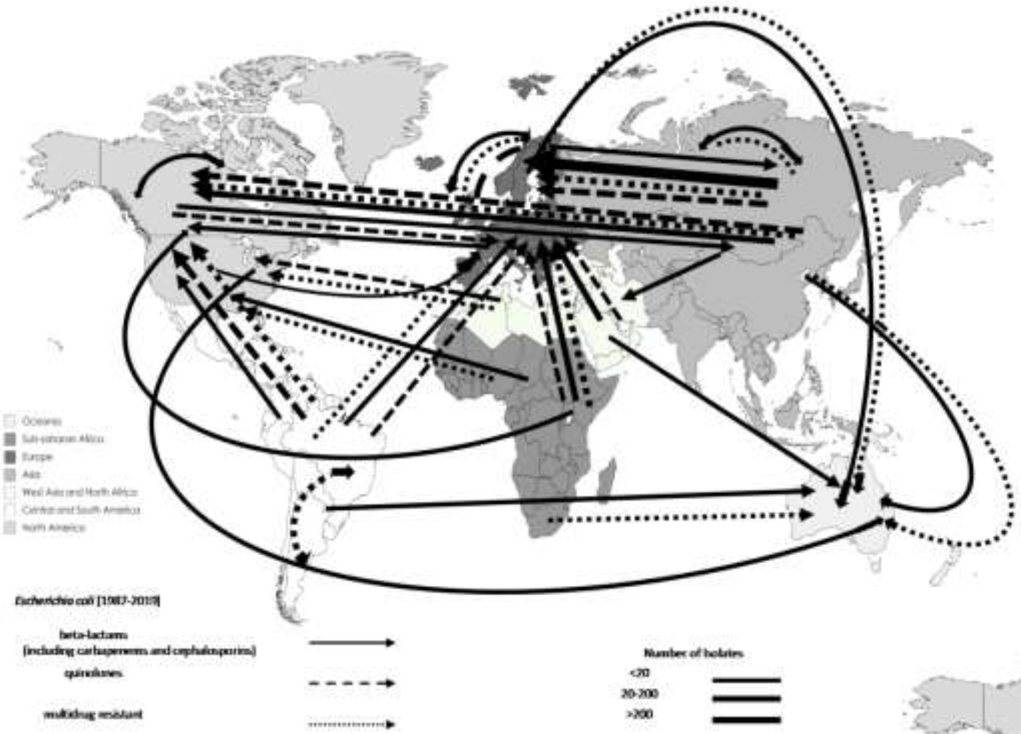
- 236 studies
- 30.060 drug resistant isolates

- Resistant Enterobacteriaceae (65%)
  - Salmonella spp. 23%
  - Shigella spp. 21%
  - E. coli 18%
  - Campylobacter spp. 11%

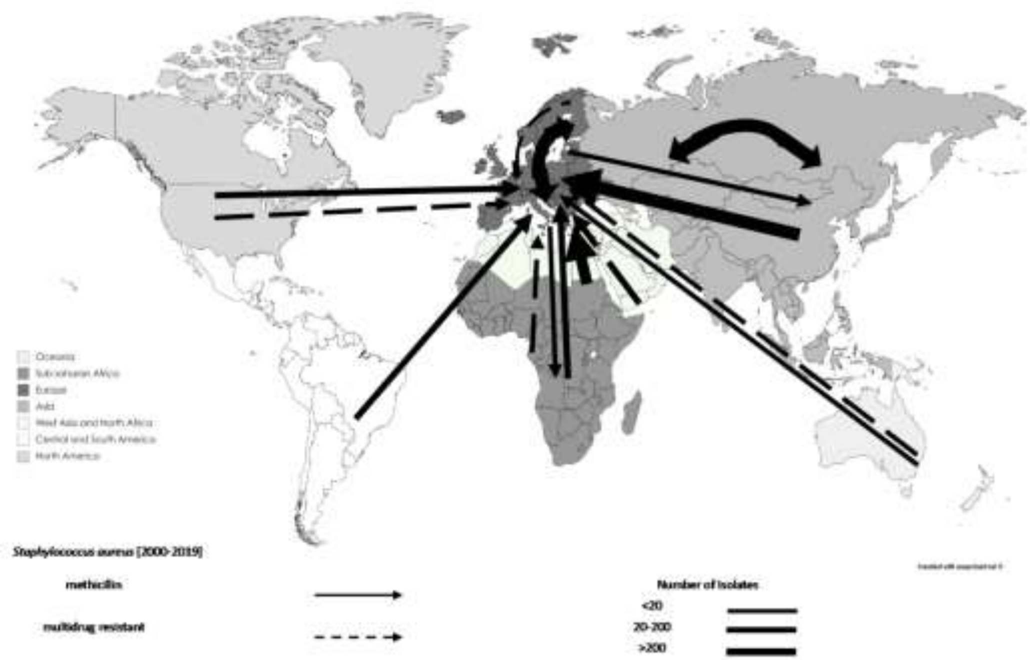
  S. aureus 9%

- Predominant resistance was observed against
  - beta-lactams (35%)
  - quinolones (31%).

- From 139 (Asia)→ to 34 countries


Oceania
Sub-saharan Africa
Europe
Asia
West Asia and North Africa
Central and South America
North America
Escherichia coli [1987-2019]
beta-lactams
(including carbapenems and cephalosporins)
quinolones
multidrug resistant
Number of isolates
<20
20-200
>200

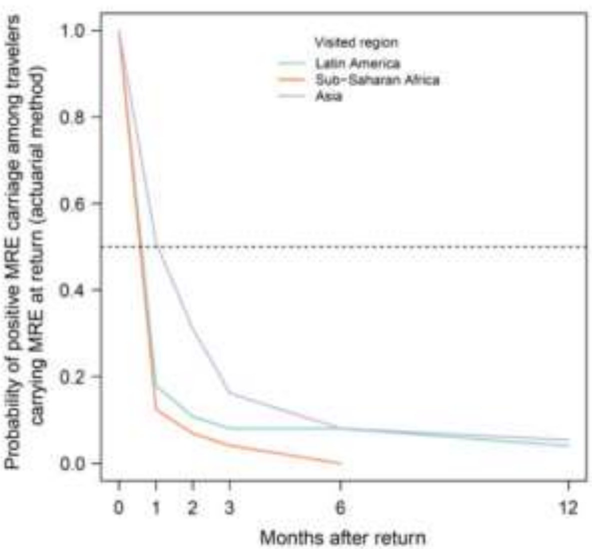
E.coli


Oceania
Sub-saharan Africa
Europe
Asia
West Asia and North Africa
Central and South America
North America
Staphylococcus aureus [2000-2019]
methicillin
multidrug resistant
Number of isolates
<20
20-200
>200

MRSA

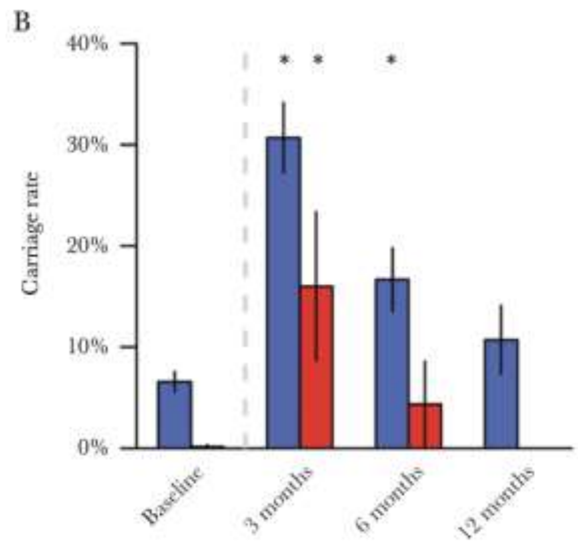
High Rate of Acquisition but Short Duration of Carriage of Multidrug-Resistant Enterobacteriaceae After Travel to the Tropics

Etienne Ruppé,[1,2,3] Laurence Armand-Lefèvre,[1,2,3] Candice Estellat,[4,5,6,a] Paul-Henri Consigny,[7,a] Assiya El Mniai,[1]



Acquisition and Long-term Carriage of Multidrug-Resistant Organisms in US International Travelers

Colin J. Worby,[1] Ashlee M. Earl,[1] Sarah E. Turbett,[2,3,4] Margaret Becker,[4] Sowmya R. Rao,[5,6] Elizabeth Oliver,[2] Allison Taylor Walker,[7] Maroya Walters,[8] Paul Kelly,[9] Daniel T. Leung,[10] Mark Knouse,[11] Stefan H. F. Hagmann,[12] Edward T. Ryan,[2,3,13] and Regina C. LaRocque[2,3]



Tropical Medicine and Infectious Disease

MDPI

Review

Risk of Colonization with Multidrug-Resistant Gram-Negative Bacteria Among Travellers and Migrants: A Narrative Review

Diogo Mendes Pedro [1,2,3,4,*], Daniela Santos [1], Maria Meneses [1], Fátima Gonçalves [2],

Table 1. Risk factors for MDR Gram-negative colonization in travellers and migrants.

Risk Factor	Reference
Travel to a low- or middle-income tropical or subtropical countries	Kajova et al. (2021) [2], Arcilla et al. (2017) [3], Tham et al. (2010) [4], Seijas-Pereda et al. (2024) [40], Meurs et al. (2020) [62], Voor In'T Holt et al. (2020) [63], Lübbert et al. (2015) [64], Schaumburg et al. (2019) [65], Ruppé et al. (2018) [66]
Travel to Asia—especially the Indian subcontinent	Tham et al. (2010) [4], Seijas-Pereda et al. (2024) [40], Meurs et al. (2020) [62], Voor In'T Holt et al. (2020) [63], Ruppé et al. (2018) [66]
Traveller's diarrhoea	Östholm-Balkhed et al. (2013) [23], Kantele et al. (2015) [67], Muzembo et al. (2022) [68]
Chronic intestinal disease	Arcilla et al. (2017) [3]
Duration of stay	Kuenzli et al. (2014) [69], Vading et al. (2016) [70]
Visiting friends and family	Meurs et al. (2020) [62], Hassing et al. (2015) [71], Worby et al. (2023) [72]
Staying at a hotel	Meurs et al. [62], von Wintersdorff et al. (2014) [73]
Consuming street food, local ice creams, or local pastries	Arcilla et al. (2017) [3], Kuenzli et al. (2014) [69]
Age	Östholm-Balkhed et al. (2013) [23], Miranda et al. (2016) [24], Lääveri et al. (2018) [74], Kantele et al. (2015) [67]
Antibiotic use	Kajova et al. [2], Dethlefsen et al. (2008) [75], Kantele et al. (2015) [67]
Contact with animals	Ahmed et al. (2007) [76], Shnaiderman-Torban et al. (2019) [77], Zhu et al. (2021) [78]
Use of a healthcare facility abroad	Kajova et al. [2], Vading et al. (2016) [70]
Trip to mass gatherings	Memish et al. (2019) [79], Smith-Palmer et al. (2016) [80], Jacobsson et al. (2018) [81], Al-Tawfiq et al. (2015) [16], Leangapichart et al. (2017) [82], Pao et al. (2024) [83], Jani et al. (2018) [84], Ahammad et al. (2014) [85]

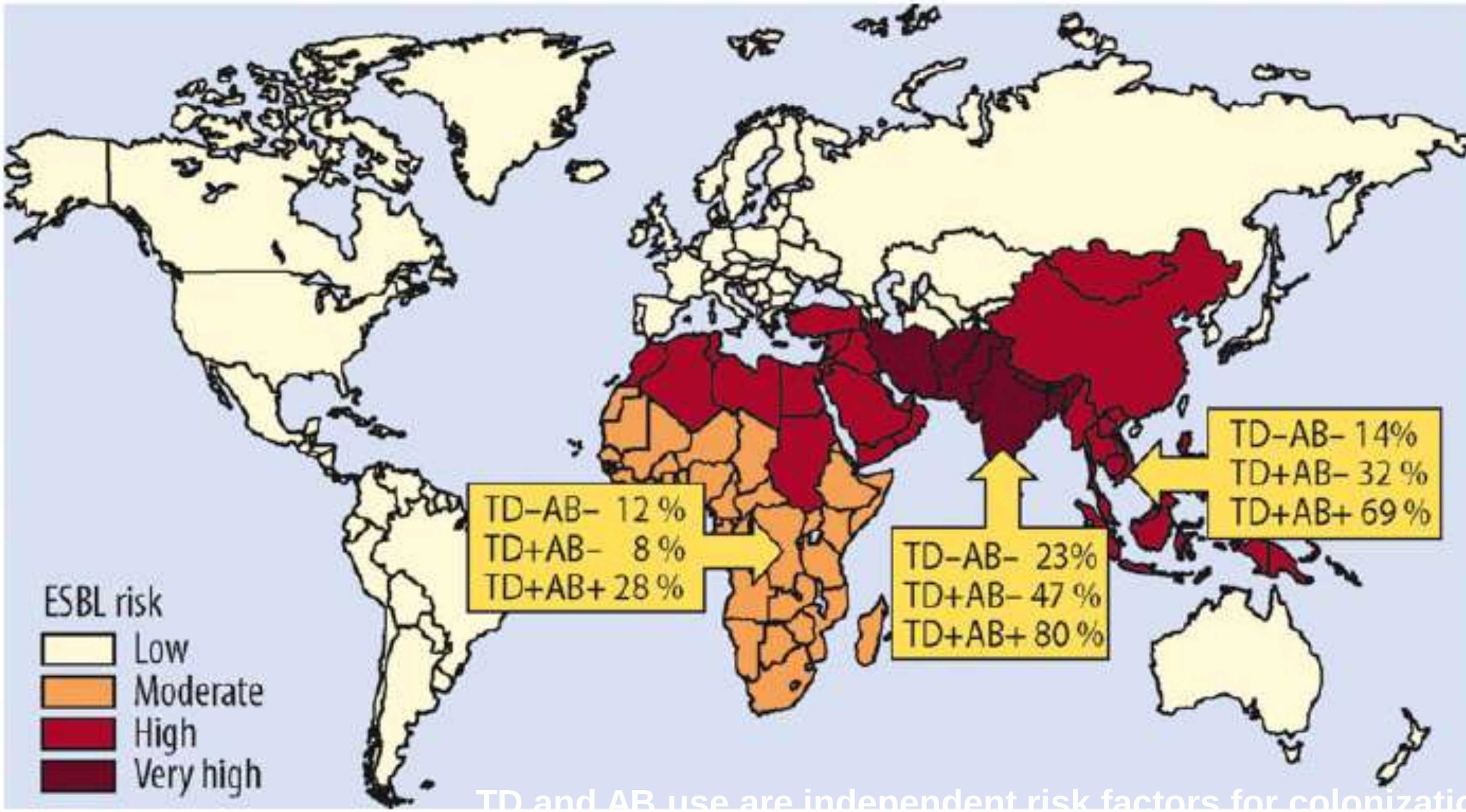
Clinical Infectious Diseases Advance Access published January 21, 2015

MAJOR ARTICLE

Previaggio: 4/434 (1%) ESBL+
Postviaggio 90/430 (21%) ESBL +

Antimicrobials Increase Travelers' Risk of Colonization by Extended-Spectrum Betalactamase-Producing *Enterobacteriaceae*

Anu Kantele,[1,2,3,4] Tinja Lääveri,[1,2] Sointu Mero,[3] Katri Vilkman,[2,3] Sari H. Pakkanen,[3] Jukka Ollgren,[5] Jenni Antikainen,[3] and Juha Kirveskari[5]
[1]Department of Clinical Medicine, University of Helsinki, [2]Division of Infectious Diseases, Department of Medicine, Helsinki University Hospital, and



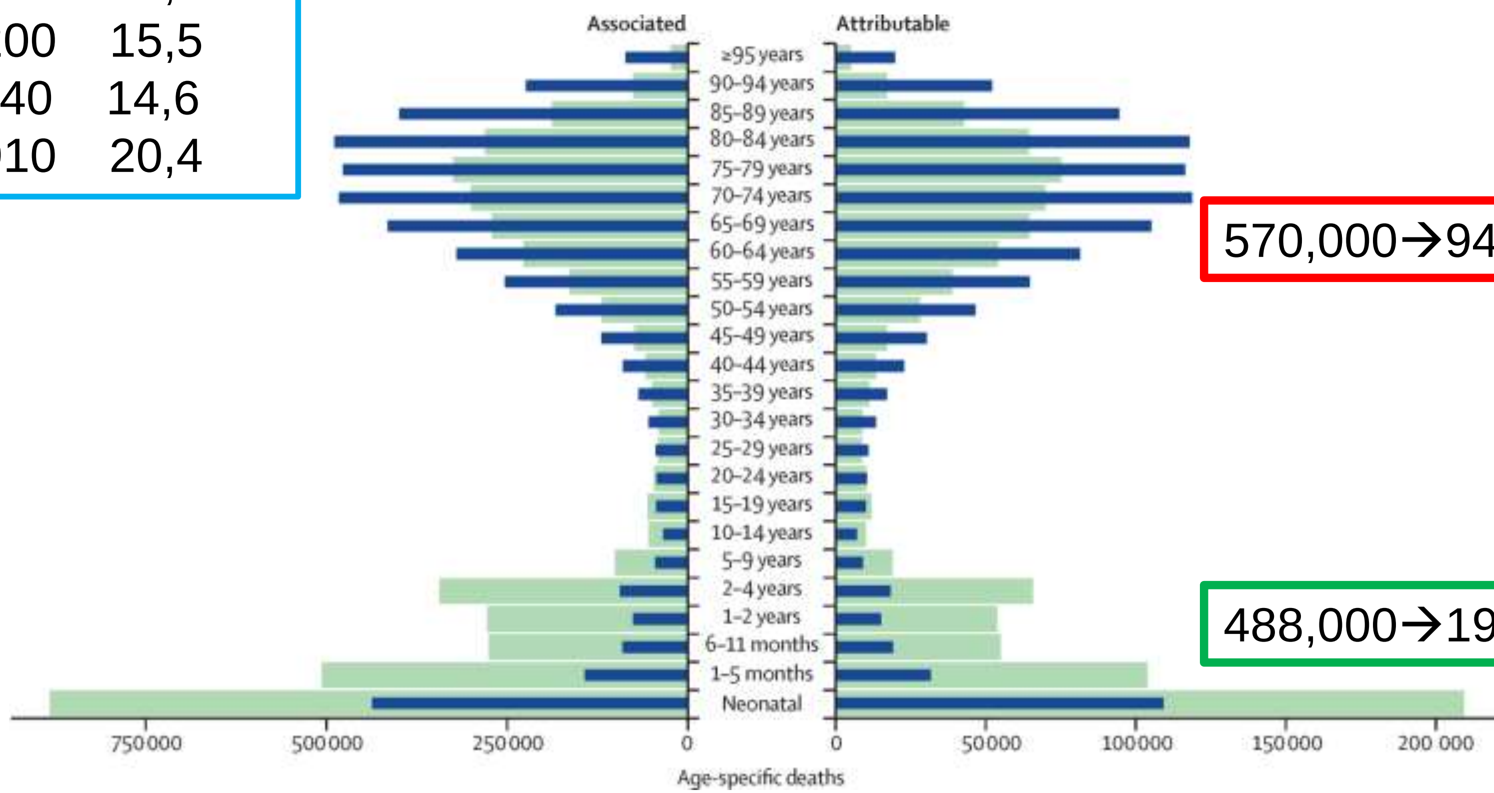
TD and AB use are independent risk factors for colonizatio

Global burden of bacterial antimicrobial resistance 1990–2021: a systematic analysis with forecasts to 2050

*GBD 2021 Antimicrobial Resistance Collaborators**

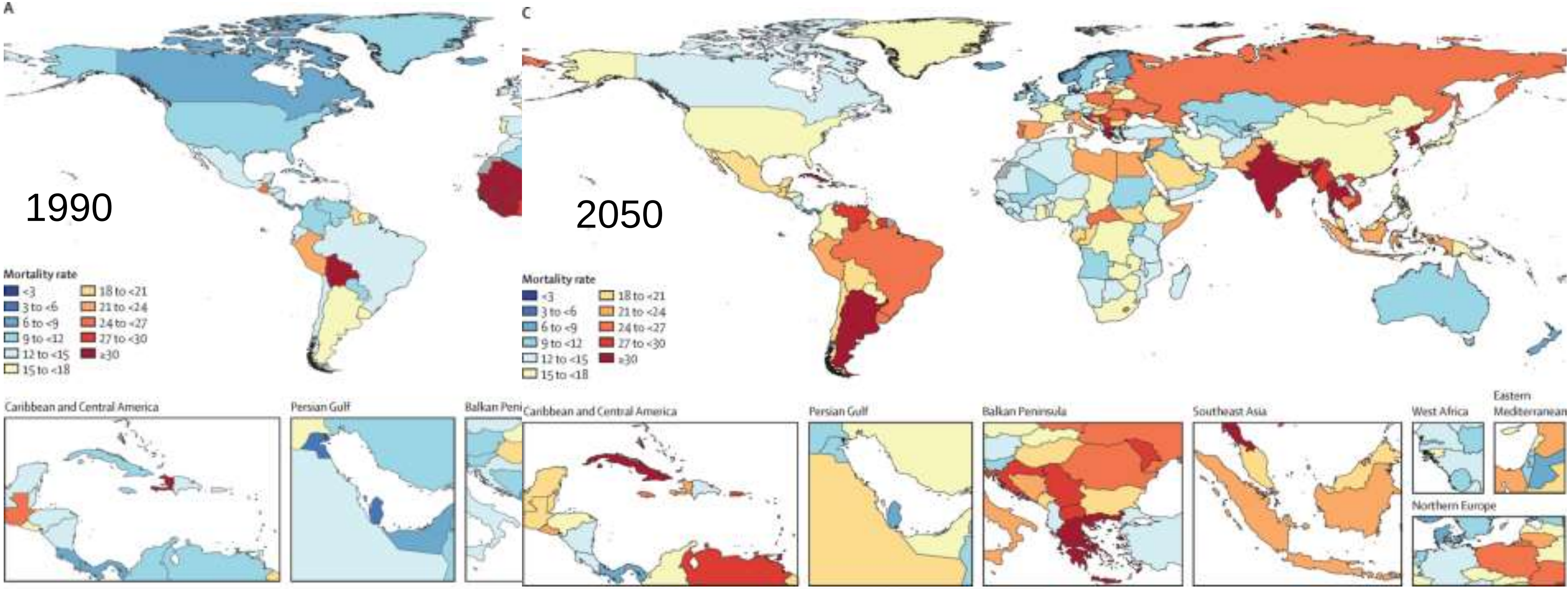
Global

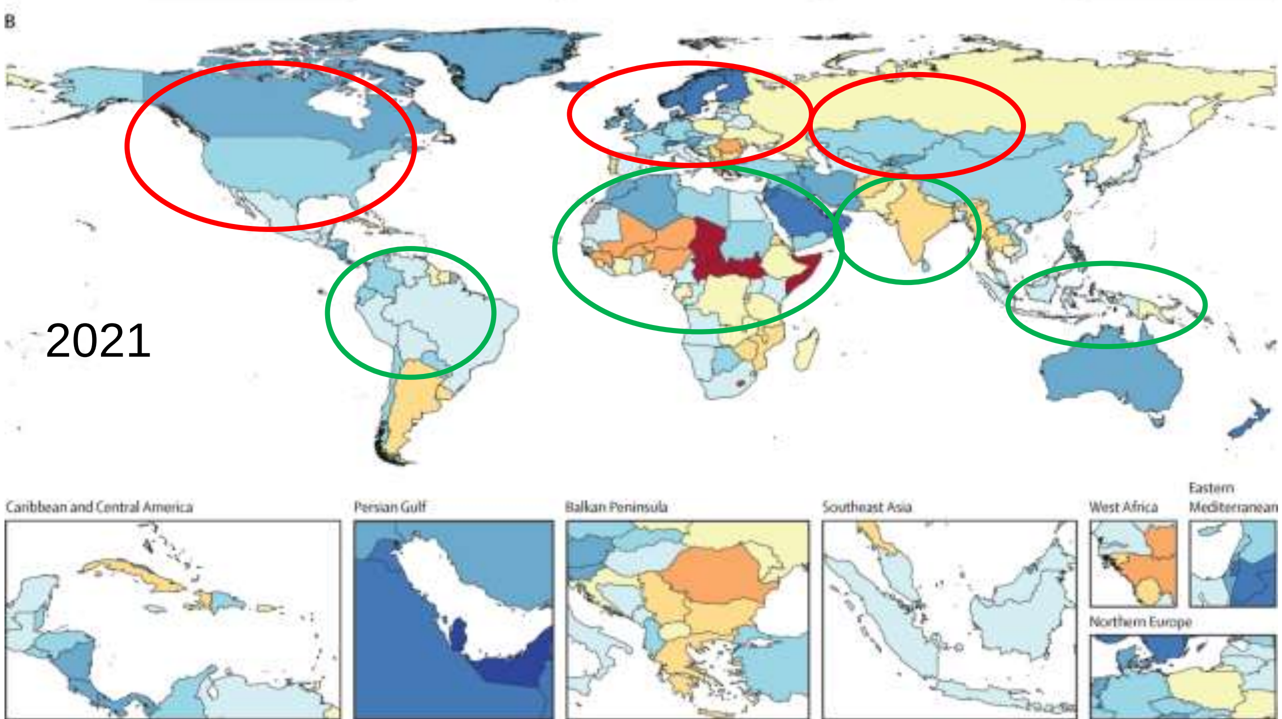
	attr. deaths x1000	attr. death rate $/10^5$
1990	1060	19,8
2019	1200	15,5
2021	1140	14,6
2050	1910	20,4



570,000→948,000

488,000→193,000





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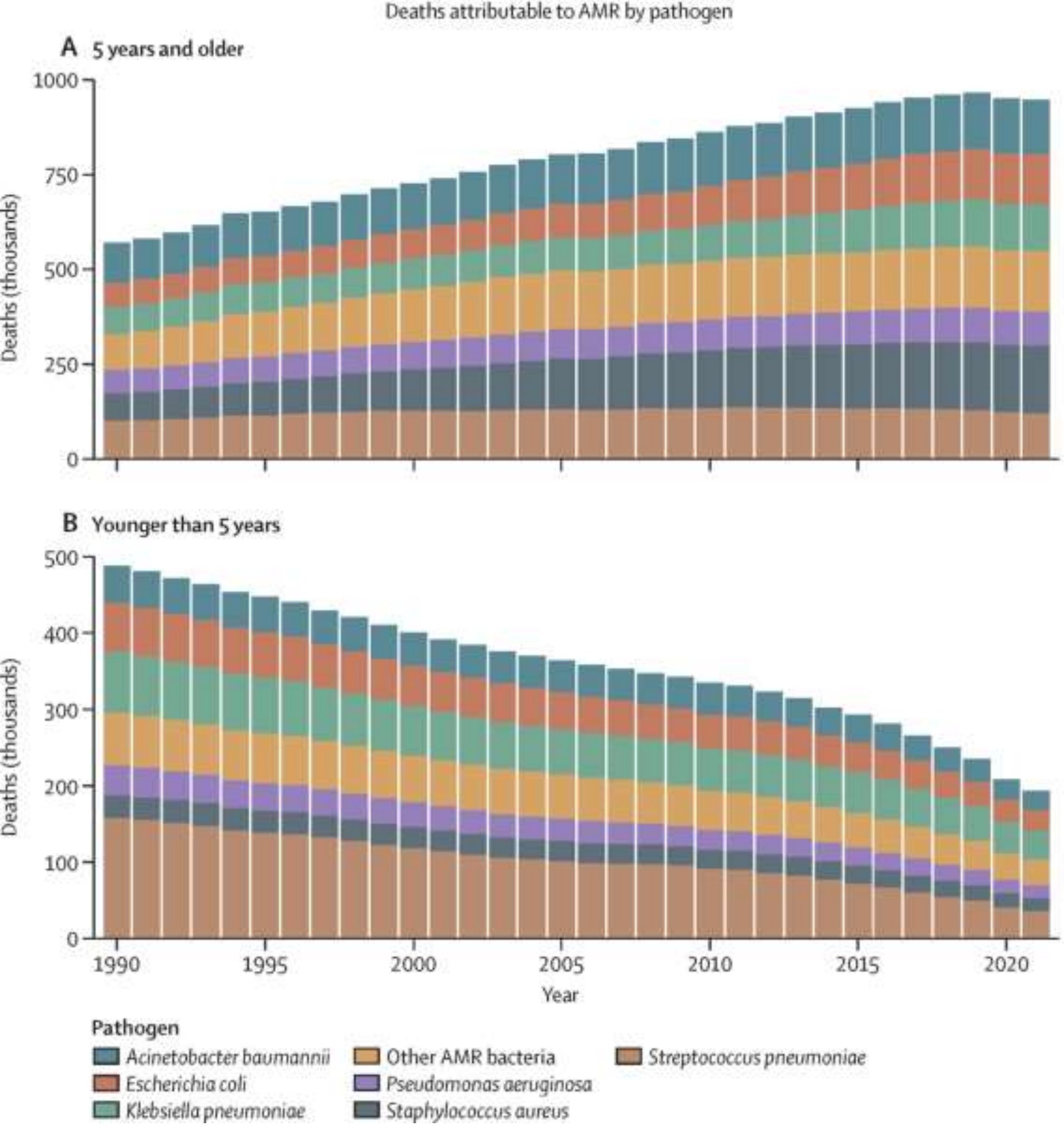


Pathogen share of AMR-attributable deaths

C

	1990	1995	2000	2005	2010	2015	2019	2021
Acinetobacter baumannii	18·6%	17·9%	16·8%	16·4%	16·6%	15·9%	15·4%	15·2%
Escherichia coli	11·1%	10·8%	10·6%	11·0%	11·9%	13·1%	13·7%	14·0%
Klebsiella pneumoniae	12·4%	11·6%	10·9%	10·6%	10·8%	12·0%	12·8%	12·7%
Pseudomonas aeruginosa	10·7%	10·3%	10·0%	9·8%	9·4%	9·4%	9·6%	9·4%
Staphylococcus aureus	12·8%	13·7%	15·1%	16·7%	17·6%	18·3%	18·4%	18·8%
Streptococcus pneumoniae	17·5%	17·4%	17·4%	16·2%	15·5%	14·3%	13·3%	12·6%
Other AMR bacteria	16·8%	18·4%	19·3%	19·3%	18·1%	17·0%	16·8%	17·1%

D

	1990	1995	2000	2005	2010	2015	2019	2021
Acinetobacter baumannii	10·1%	10·5%	10·8%	11·5%	12·3%	12·4%	12·6%	13·0%
Escherichia coli	13·1%	13·2%	13·1%	13·2%	13·2%	13·4%	13·7%	14·3%
Klebsiella pneumoniae	16·1%	16·0%	16·1%	16·2%	16·3%	18·0%	19·2%	19·4%
Pseudomonas aeruginosa	8·1%	8·1%	8·2%	8·1%	7·8%	8·2%	8·6%	8·6%
Staphylococcus aureus	6·2%	6·6%	6·9%	7·3%	7·5%	8·0%	8·7%	9·1%
Streptococcus pneumoniae	32·3%	30·8%	29·4%	27·7%	27·2%	24·4%	20·8%	18·2%
Other AMR bacteria	14·2%	14·7%	15·4%	16·0%	15·7%	15·6%	16·4%	17·5%

Year

Sorveglianza AR-ISS/EARS-Net

- *Staphylococcus aureus*
- *Streptococcus pneumoniae*
- *Enterococcus faecalis*
- *Enterococcus faecium*
- *Escherichia coli*
- *Klebsiella pneumoniae*
- *Pseudomonas aeruginosa*
- *Acinetobacter species*

9 laboratori piemontesi (copertura del 37% della regione)
Raccolta annuale dati di sensibilità degli isolati da sangue e liquor (dal 2023 anche urine)
Dal 2023 TUTTI gli ospedali ASL CdT (SGB-OMV-OAS-MART)

https://www.epicentro.iss.it/antibiotico-resistenza/ar-iss

Escherichia coli Fluorochinoloni R

Europa
2020: 25.1%
2021: 2
2022: 2
2023: 2

Itali
2020: 37
2021: 32
2022: 31
2023: 3

ASL CdT
Invasivi
2020: 31.9%
2021: 30.0%
2022: 34.1%
2023: 32.5%
2024: 34.3%

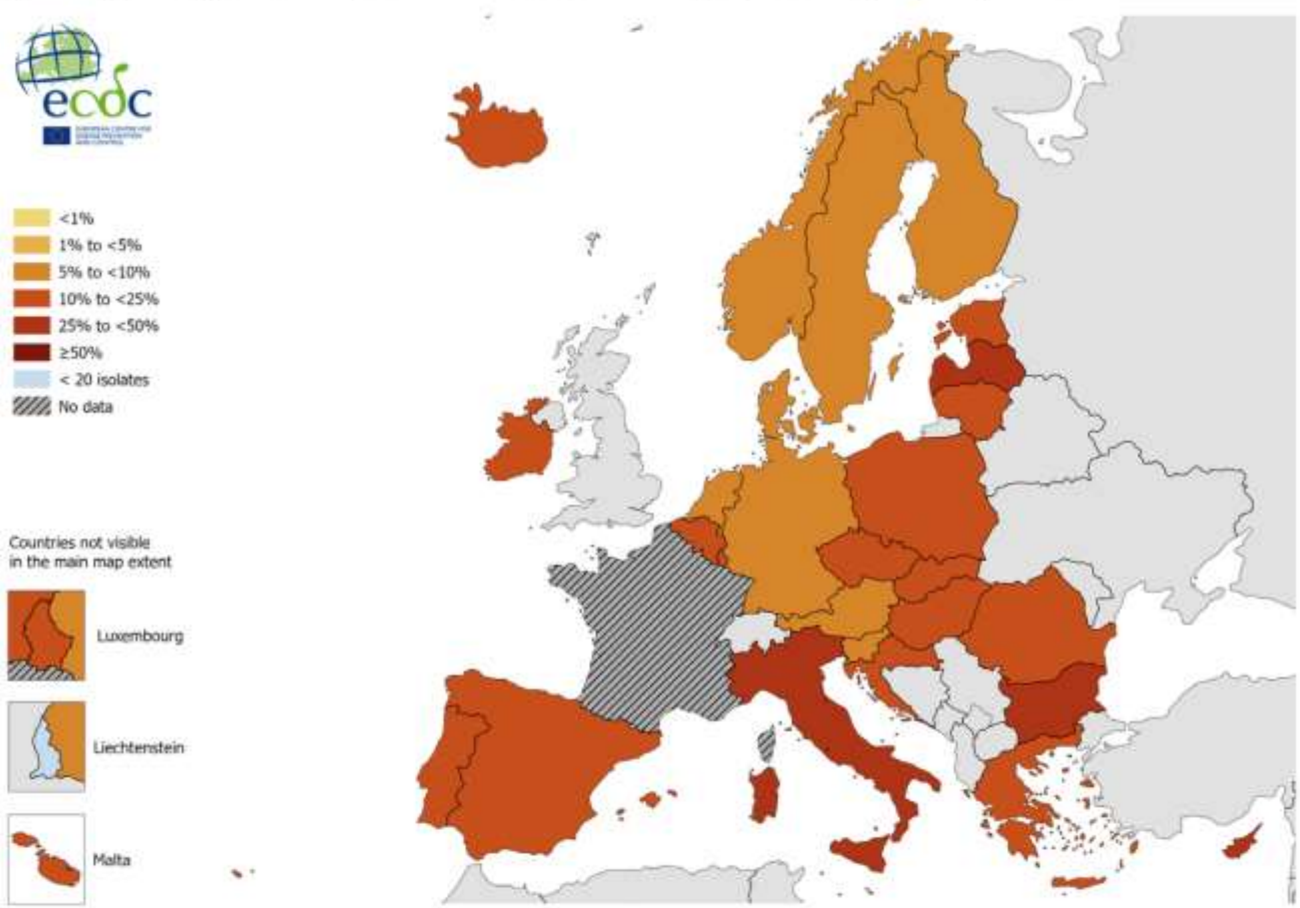
Escherichia coli Cefalosporine 3^ R

Europa
2020: 15.8%
2021: 14.9%
2022: 15.4%
2023: 16.2%

Italia
2020: 26.4%
2021: 23.8%
2022: 24.2%
2023: 26.3%

ASL CdT Invasivi
2020: 17.4%
2021: 18.3%
2022: 25.1%
2023: 31.1%
2024: 29.0%

Figure 2. *Escherichia coli*. **Percentage of invasive isolates resistant to third-generation cephalosporins (cefotaxime/ceftriaxone/ceftazidime), by country, EU/EEA, 2023**



Administrative boundaries: © EuroGeographics. The boundaries and names shown on this map do not imply official endorsement or acceptance by the European Union. Map produced by ECDC on 13 September 2024

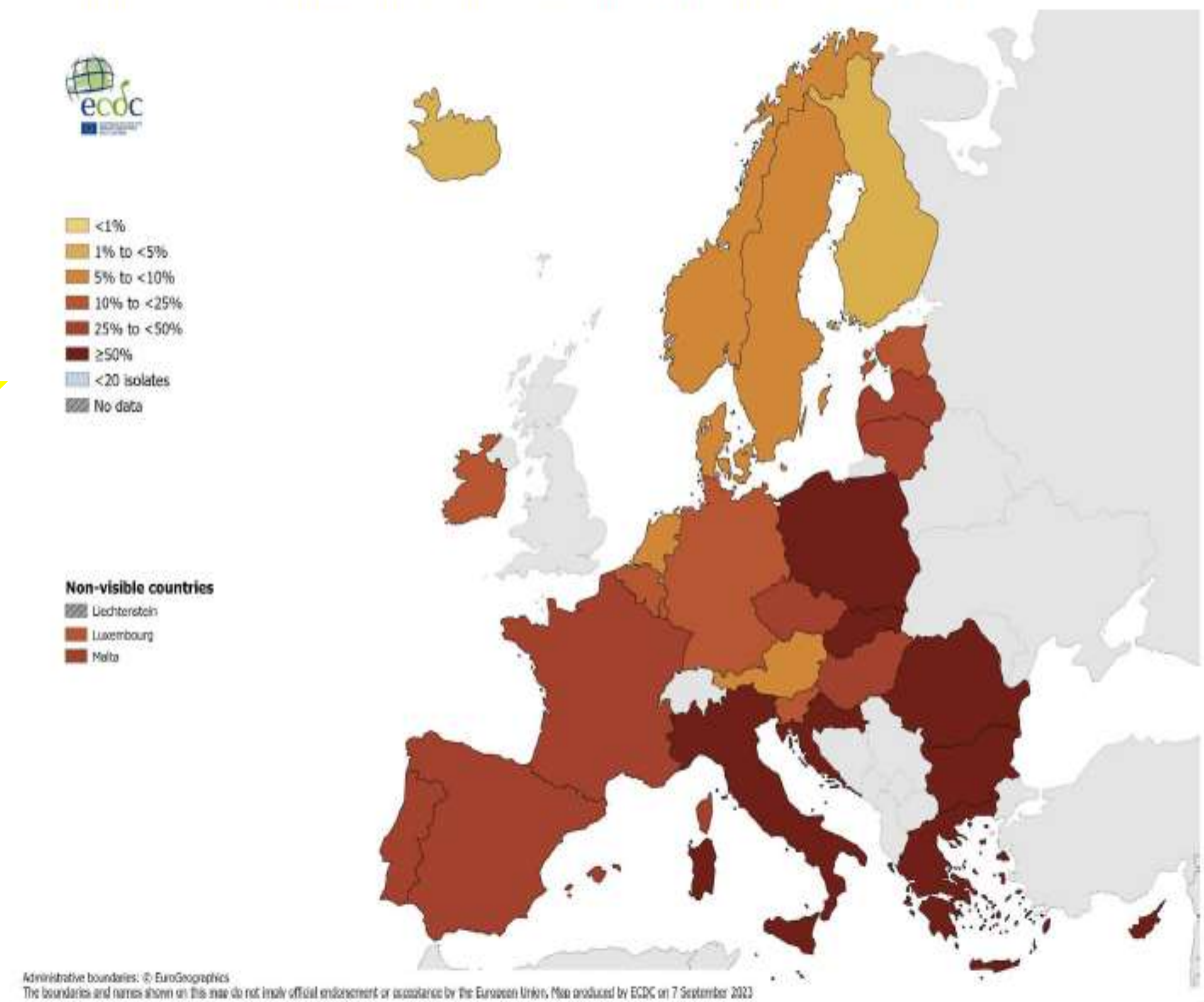
Klebsiella pneumoniae Cefalosporine 3^ R

Europa
2020: 35.0%
2021: 35.9%
2022: 34.1%
2023: 34.8%

Italia
2020: 54.3%
2021: 53.3%
2022: 53.3%
2023: 52.1%

ASL CdT Invasivi
2020: 40.9%
2021: 38.4%
2022: 43.2%
2023: 53.4%
2024: 31.7%

Figure 4. *Klebsiella pneumoniae*. Percentage of invasive isolates resistant to third-generation cephalosporins (cefotaxime/ceftriaxone/ceftazidime), by country, EU/EEA, 2022



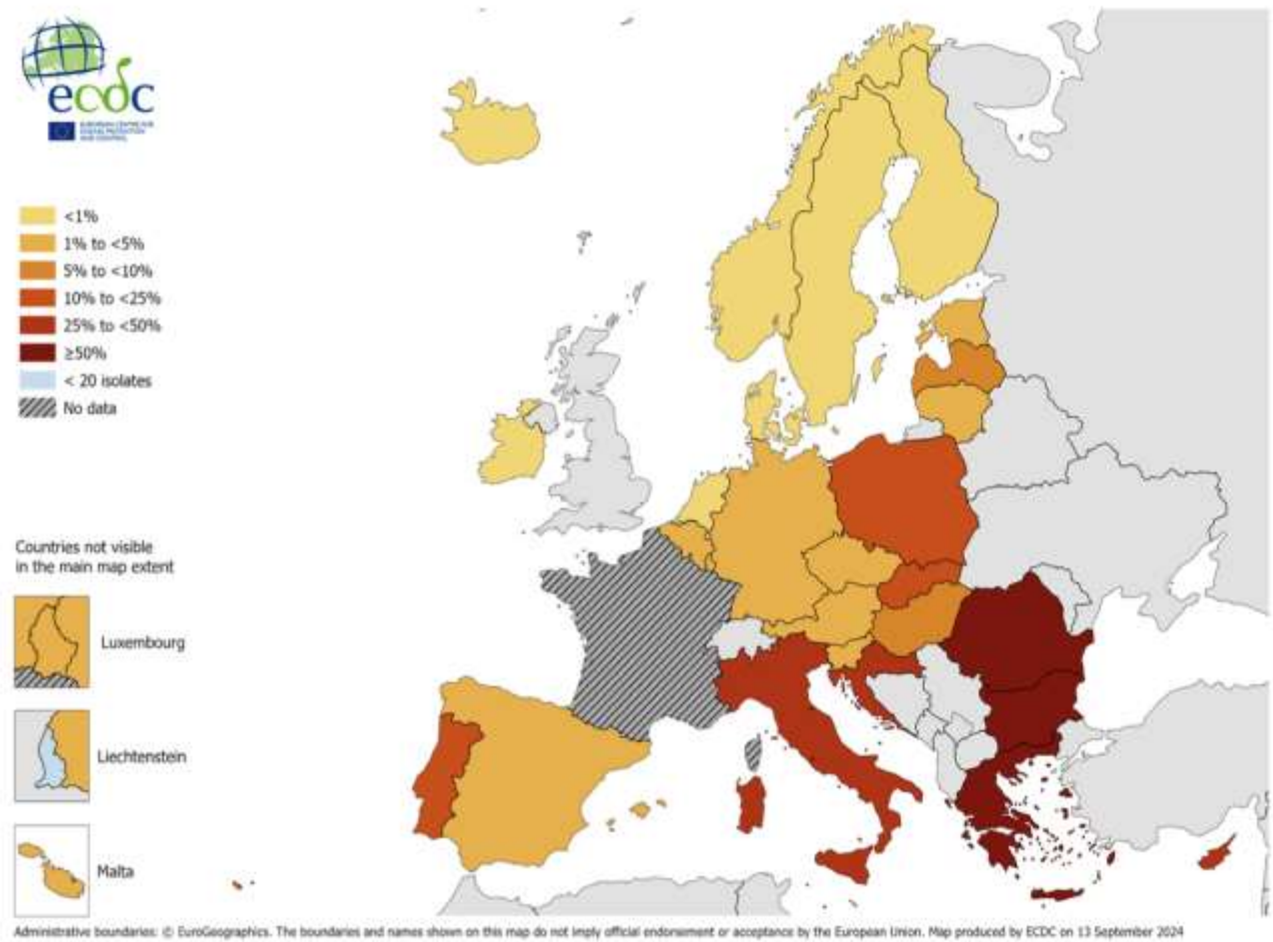
Klebsiella pneumoniae Carbapenemi R

Europa
2020: 11.6%
2021: 13.6%
2022: 12.7%
2023: 13.3%

Italia
2020: 29.5%
2021: 26.7%
2022: 24.9%
2023: 25.4%

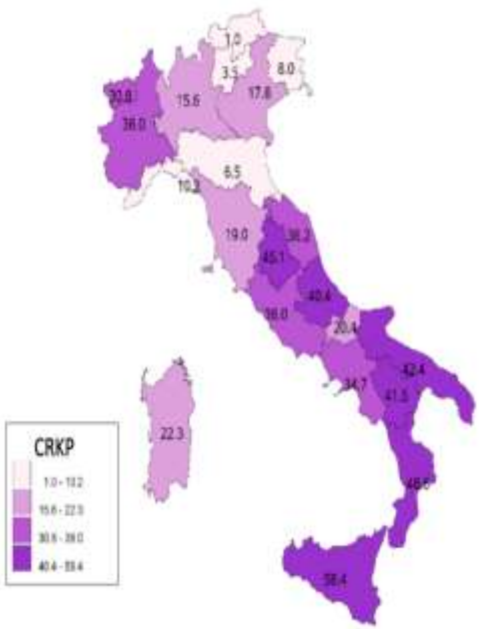
ASL CdT
Invasivi
2020: 19.2
2021: 15.3%
2022: 14.4%
2023: 36.4%
2024: 27,3%

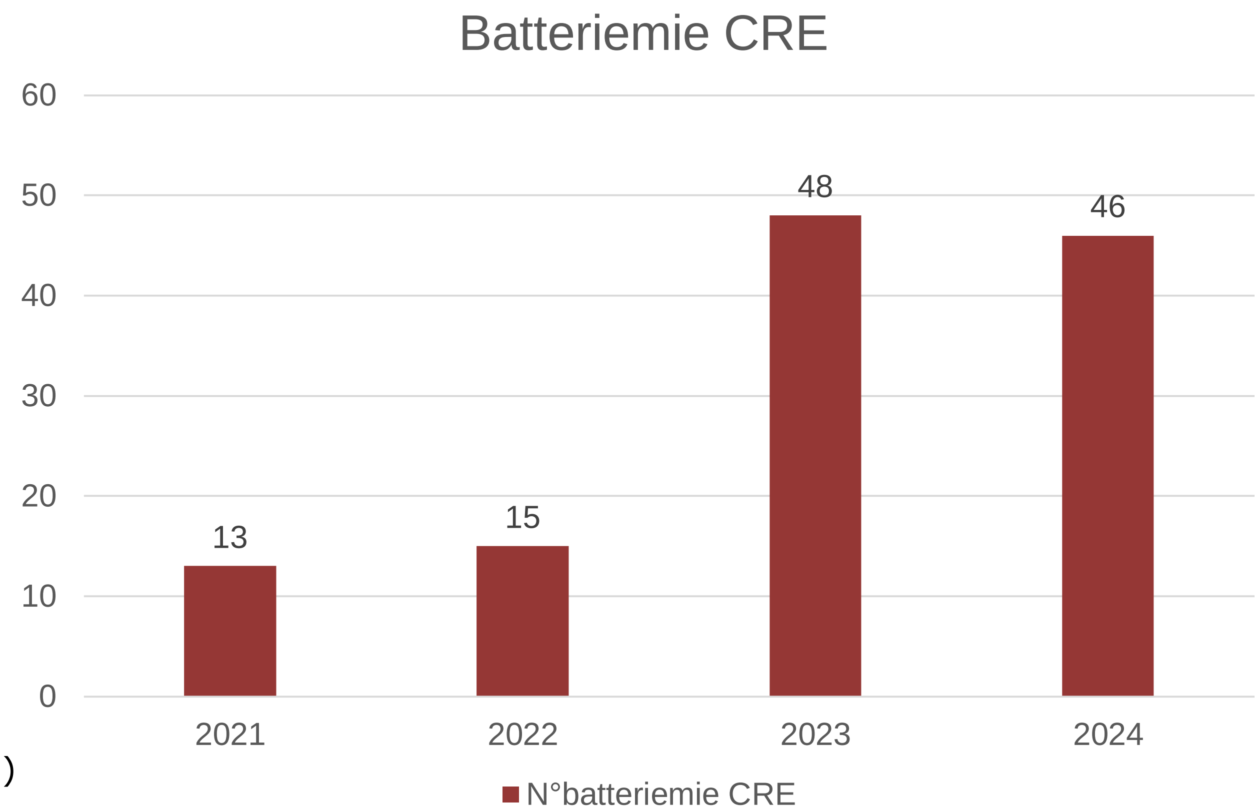
Figure 5. ***Klebsiella pneumoniae*****. Percentage of invasive isolates resistant to carbapenems (imipenem/meropenem), by country, EU/EEA, 2023**



«There was an increase in the number of reported invasive K. pneumoniae isolates»

BATTERIEMIE DA BATTERI RESISTENTI AI CARBAPENEMI

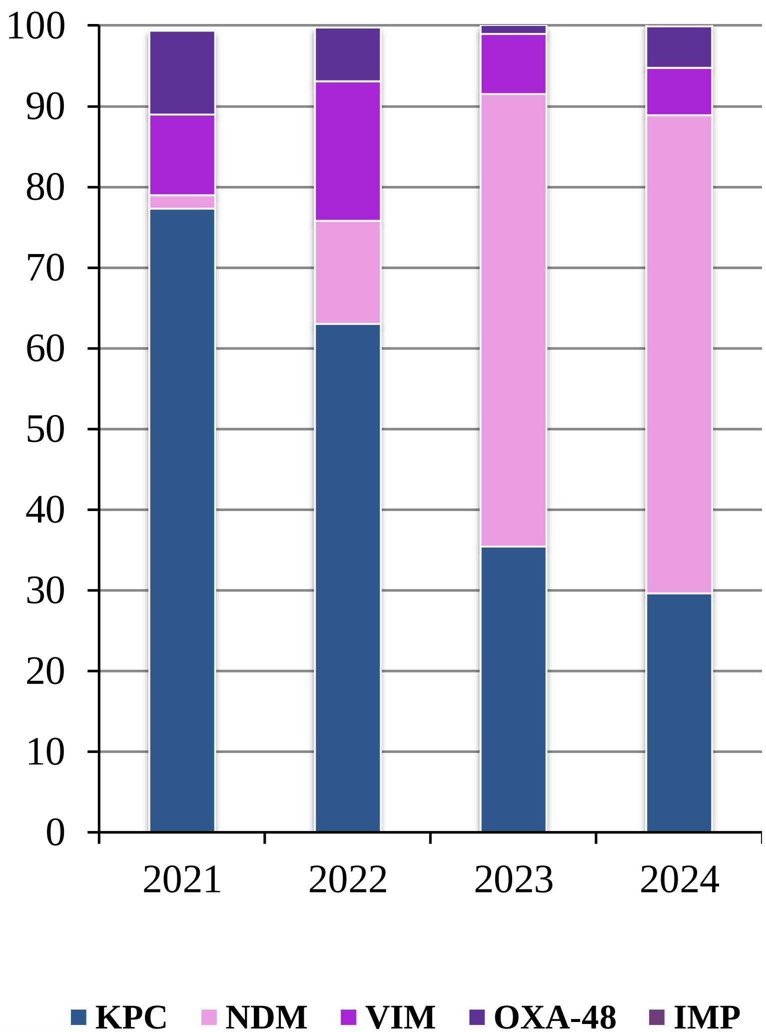




AR-ISS- 2023 report batteriemie da CRE:
25.4% (83% KPC, 7% NDM)

Microrganismi CRE (>95% Kp):
altri microrganismi: E.coli – ENC, AcB e PA

Screening carbapenemasi su TR-Meccanismi di resistenza ASL CdT



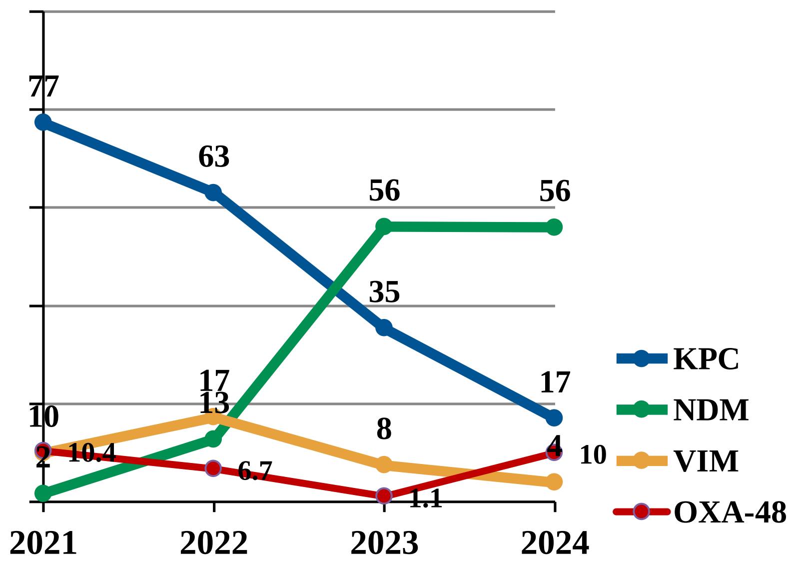
Geni di resistenza su TR ASL CdT

2024	POS	%POS
TOT	552	**6,6%**
KPC	121	19,5%
NDM	**337**	**54,2%**
VIM	26	4,2%
OXA-48	57	9,2%
Altri (Pseudo,ACB, STEMA)	81	13%

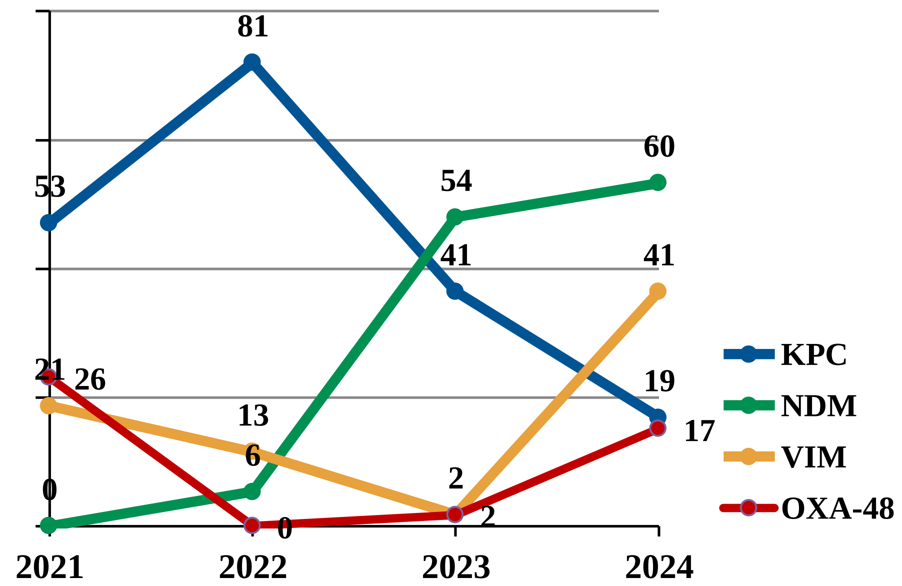
Totale TR: 8396

CRE - Geni di Resistenza

Tamponi Rettali



Emocolture



Pseudomonas aeruginosa

- Resistenza intrinseca
- Resistenza acquisita
- Multidrug-resistant (**MDR**) R almeno 1 agente in almeno 3 classi.
- Extensively drug-resistant (**XDR**) R almeno 1 agente in tutte meno 2 cl.
- Pandrug-resistant (**PDR**) R a tutti gli antibiotici testati
- Difficult to treat (**DTR**) I o R a tutti i carbapenemi, beta-lattamici, e fq

- Ventilator-associated pneumonia – 15.4 % da P.a.
- Central line-associated blood stream infection – 14.2 (ICUs) 11.9 (hosp)
- Catheter-associated UTI– 8,7% (ICUs) 10,6% (hosp)
- Surgical site infection – 3.9%

- Meccanismi di resistenza
- β-lattamasi (AmpC, MBL) β-lattamici, carbapenemi
- Efflusso (Mex pumps) FQ, AG, β-lattamici
- Porine mutate (OprD) Imipenem, carbapenemi
- Mutazioni del target (gyrA) FQ
- Enzimi inattivanti Aminoglicosidi
- Biofilm Tutti (barriera fisica)

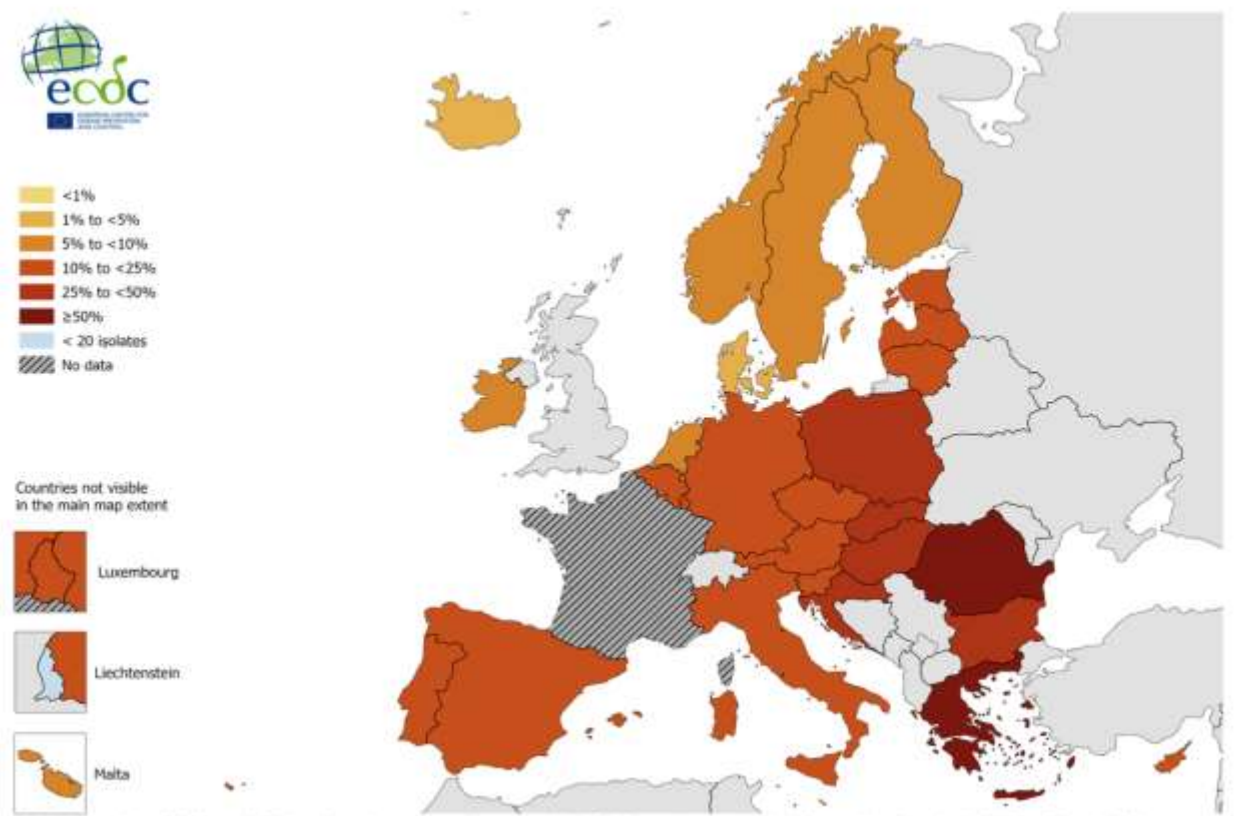
Pseudomonas aeruginosa Carbapenemi R (MDRO)

Europa
2020: 17.9%
2021: 18.1%
2022: 20.0%
2023:18.6

Italia
2020: 15.9%
2021: 16.4%
2022: 16.5%
2023: 17.1%

ASL CdT Invasivi
2020: 15.3%
2021: 7.4%
2022: 0%
2023: 2.7%
2024: 6.9 %

Figure 6. *Pseudomonas aeruginosa*. **Percentage of invasive isolates with resistance to carbapenems (imipenem/meropenem), by country, EU/EEA, 2023**



Acinetobacter baumannii

- Ambiente tropicale
- Guerre e disastri naturali
- Ambiente ospedaliero (TI, manovre invasive, patologie associate)

- Tipico andamento epidemico

- Ventilator-associated pneumonia isolates – 12.8 % dei G-
- Central line-associated bloodstream infection isolates – 8.8
- Catheter-associated urinary tract infection isolates – 1.3
- Surgical site infection isolates – 1.3

- Meccanismi di resistenza:
- Oxa type
- MBL (rare ma emergenti)
- AMP-C

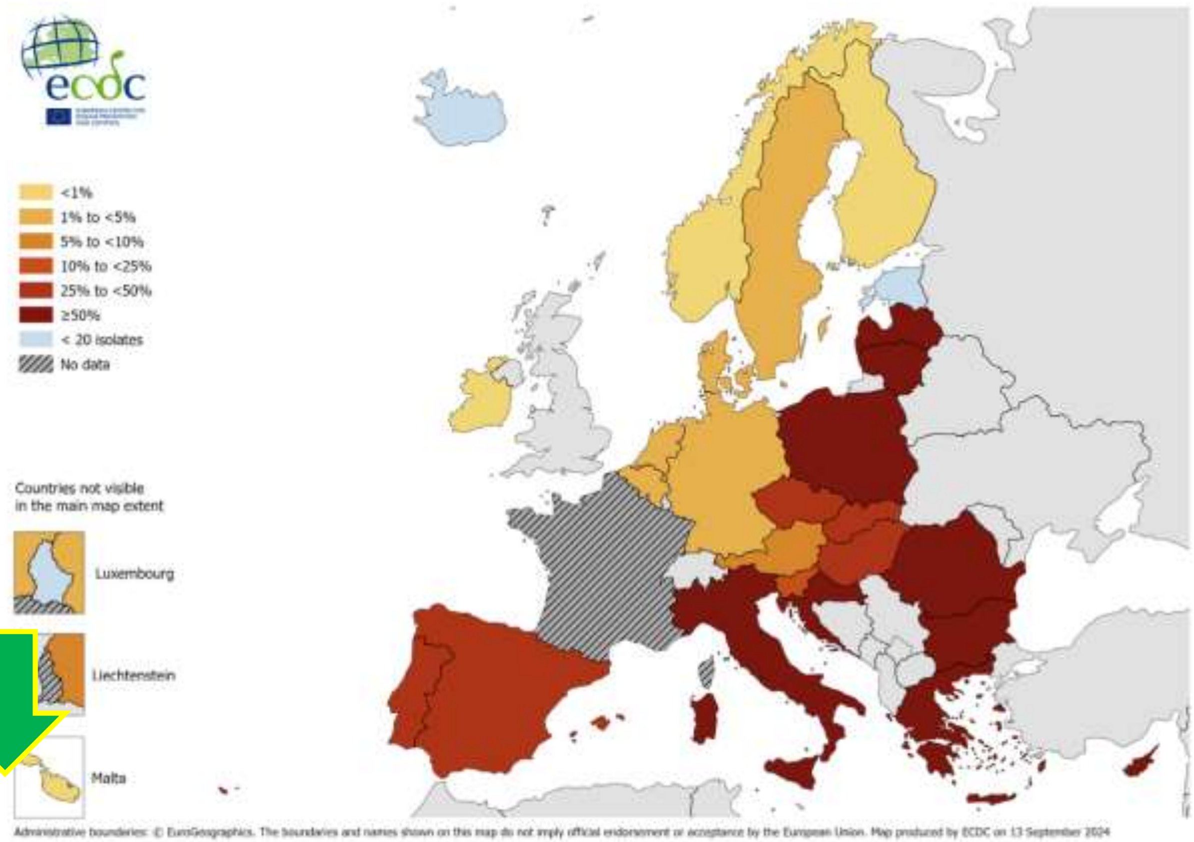
Acinetobacter baumannii Carbapenemi R (MDRO)

Europa
2020: 37.9%
2021: 39.9%
2022: 36.3%
2023: 40%

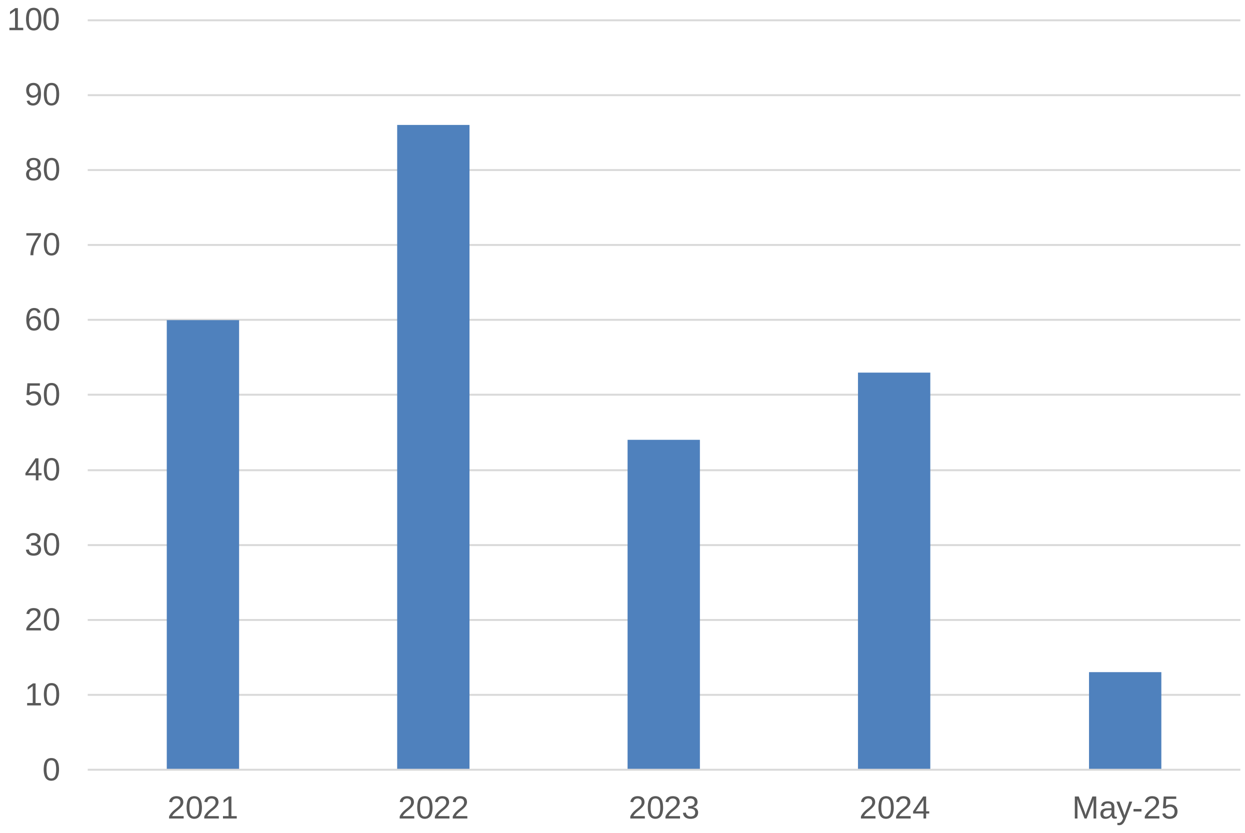
Italia
2020: 80.8%
2021: 86.9%
2022: 88.5%
2023: 76 %

ASL CdT Invasivi
2020: 80%
2021: 0%
2022: 100%
2023: 75%
2024: 22%

Figure 7. *Acinetobacter* **species. Percentage of invasive isolates with resistance to carbapenems (imipenem/meropenem), by country, EU/EEA, 2023**

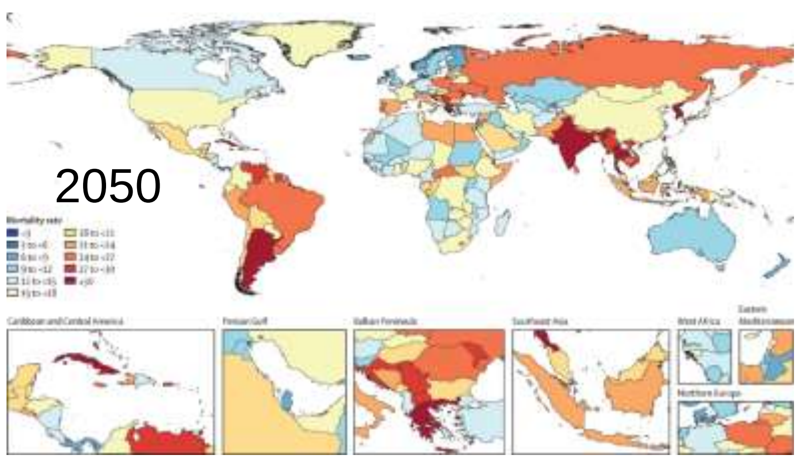


Acinetobacter baumannii MDR - ASL Città di Torino

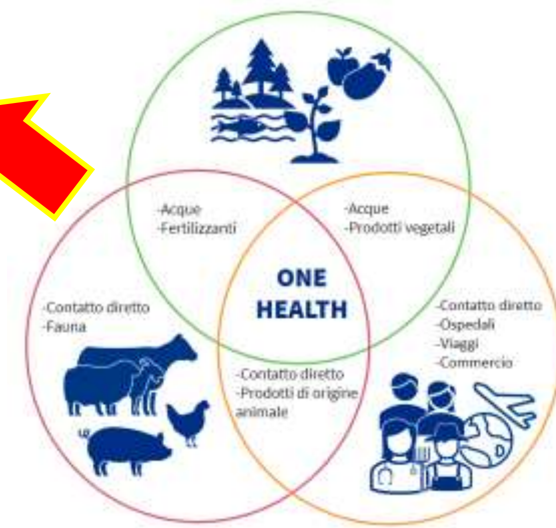


INFECTION
CONTROL

Antibiotic stewardship
Enhancing infection prevention and control
Controlling the source of infection
Prescribing antibiotics when they are truly needed
Prescribing appropriate antibiotic(s) with adequate dosages
Using the shortest duration of antibiotics based on evidence
Reassessing treatment when culture results are available
Supporting surveillance of AMR and HAIs and monitoring of antibiotic consumption
Educating staff
Supporting an interdisciplinary approach



2050



-Acque
-Fertilizzanti
-Acque
-Prodotti vegetali
ONE HEALTH
-Contatto diretto
-Fauna
-Contatto diretto
-Ospedali
-Viaggi
-Commercio
-Contatto diretto
-Prodotti di origine animale