Pomen protimikrobnih zdravil in skrbi za njihovo ustrezno predpisovanje

Bojana Beović
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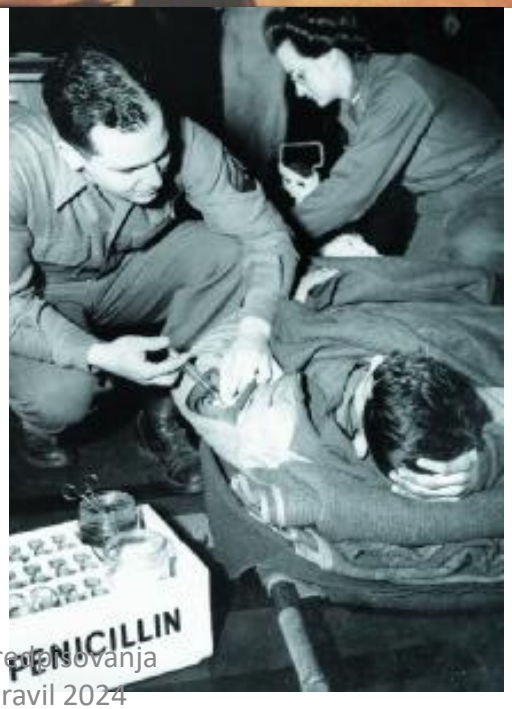
UKC Ljubljana


Penicillin
THE NEW LIFE-SAVING DRUG
Saves Soldiers' Lives!
Men who might have died will live...if YOU
Give this job Everything You've got!


PENICILLIN

Pomen antibiotičnega zdravljenja

- **Smrtnost pljučnice po gripi zmanjšana s 30 na 10%** (predvidena resnost gripe leta 1918 flu v današnjih razmerah, Chen YW, et al. PlosOne 2012; 7: e29219.)

- **Zmanjšanje smrtnosti bakterijskega meningitisa z 80% na 20%** (1935 - 1957, Wilson FM, Lerner AM, NEJM 1964; 271: 1235-8.)

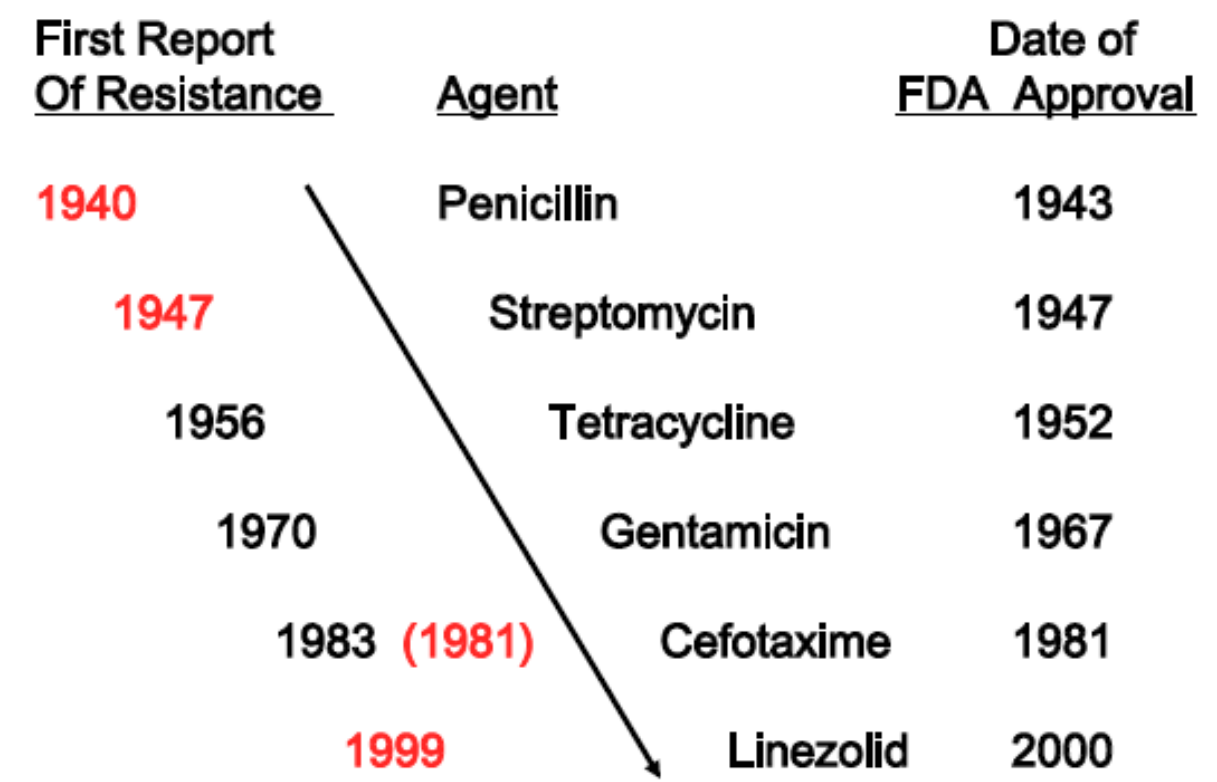
- **Zmanjšanje pogostnosti okužb kirurške rane pri kolorektalni kirurgiji z 20 na 10%**

Talbot TR, Kaiser AB. Postoperative infections and antimicrobial prophylaxis. V: Mandell GL, Bennett JE, Dolin R. Mandel, Douglas, and Bennett's principles and practice of infectious diseases. Philadelphia: Elsevier Churchill Livingstone; 2005. p 3533-47.

- Veliki kirurški posegi
- Transplantacije organov
- Obravnava na oddelkih za intenzivno zdravljenje
- Nevtropenični bolniki
- Drugi imunsko oslabeli bolniki
- Okužbe pri kroničnih bolnikih
- Okužbe pri starostnikih

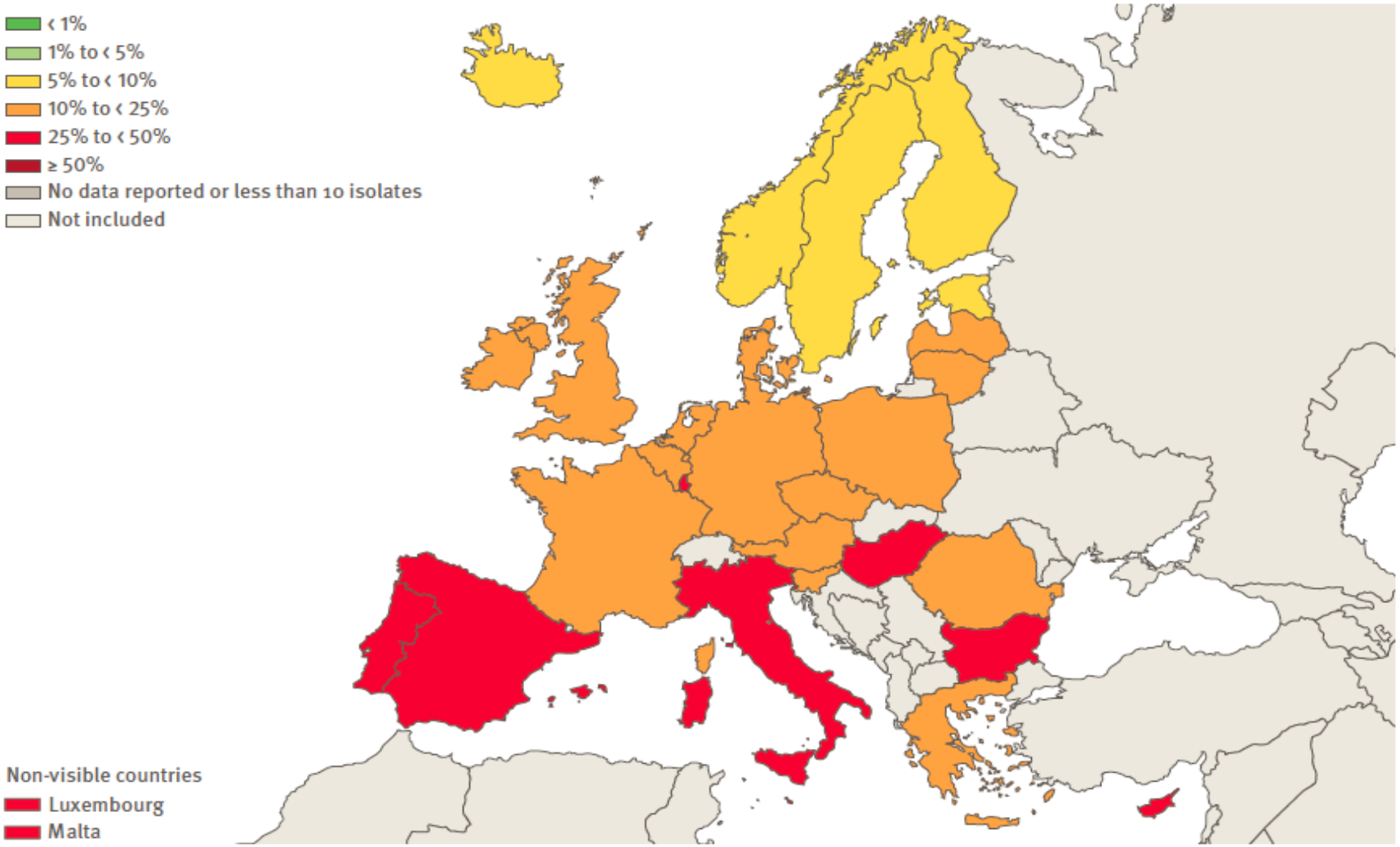
SMRTNO NEVARNO

Razvoj odpornosti proti antibiotikom



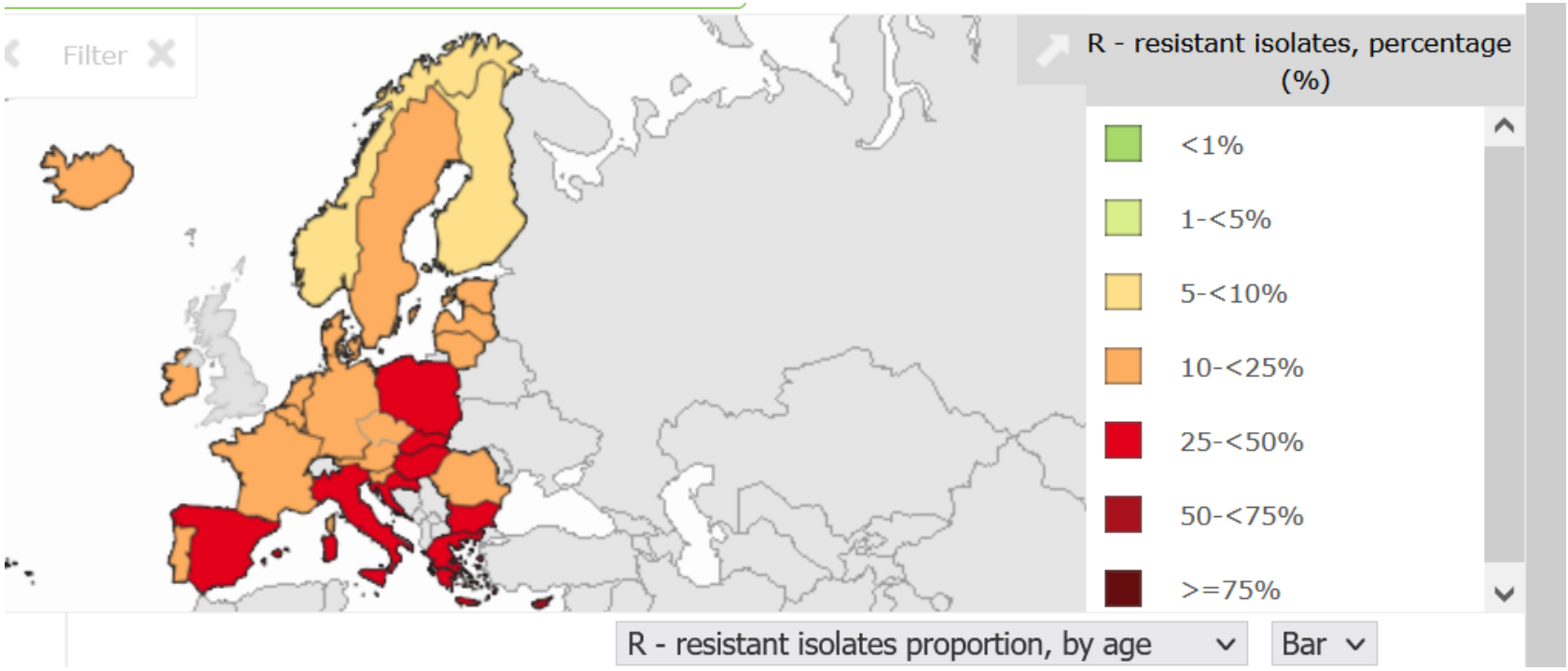
Bush K, Page MGP. J Pharmacokinet Pharmacodyn, objavljeno na spletu 4. februarja 2017

Figure 5.15: ***Escherichia coli*: proportion of invasive isolates with resistance to fluoroquinolones in 2009**



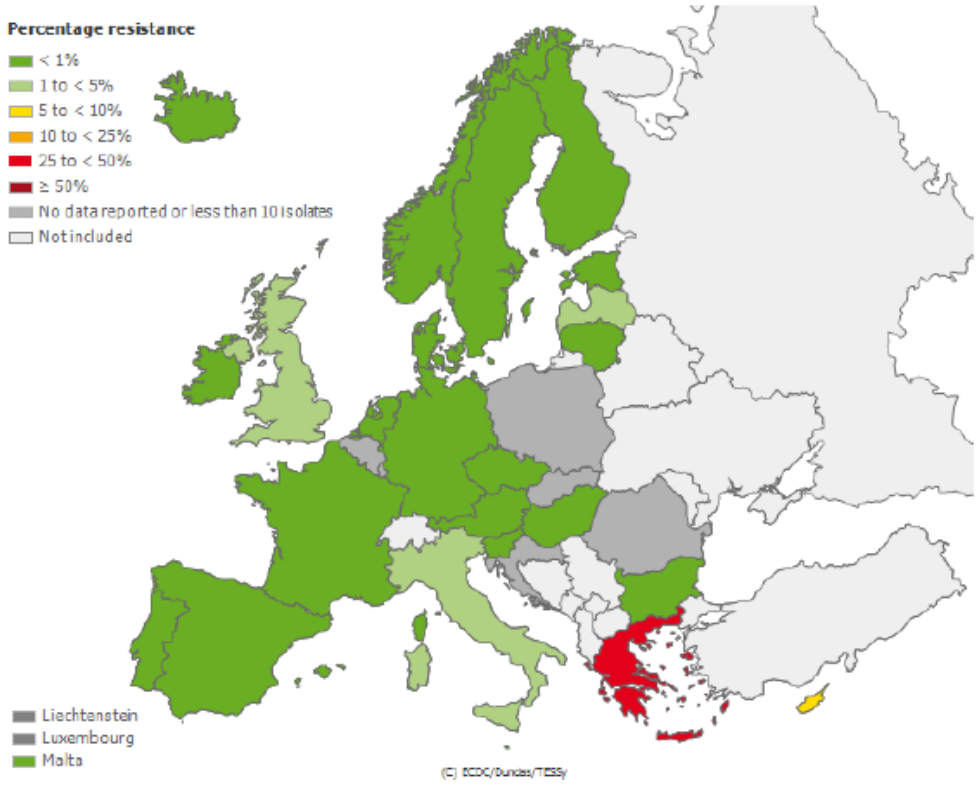
https://ecdc.europa.eu/en/publications-data/antimicrobial-resistance-surveillance-europe-2009

E. coli, odpornost proti fluorokinolonom 2021



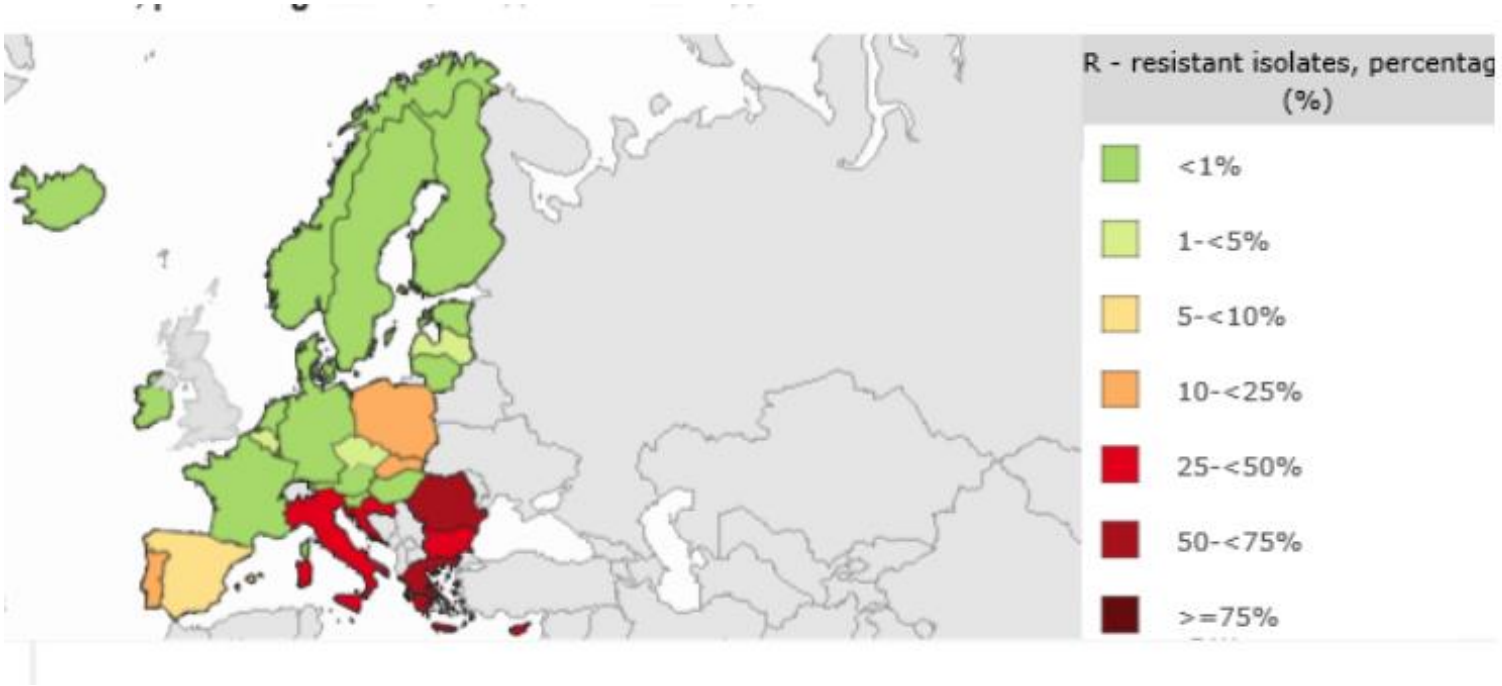
https://ecdc.europa.eu/en/publications-data/surveillance-antimicrobial-resistance-europe-2017

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



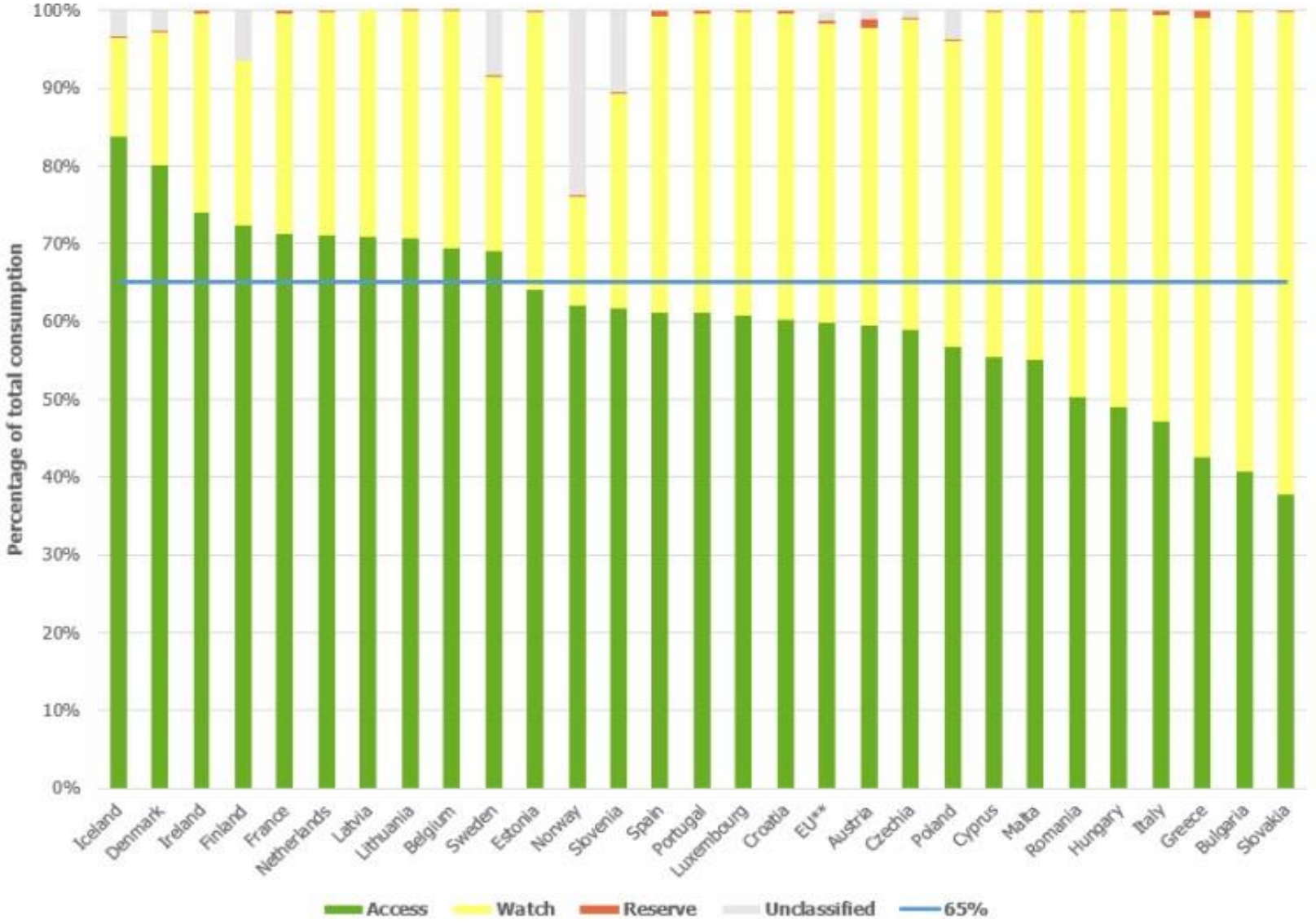
This report has been generated from data submitted to TESSy, The European Surveillance System on 2015-04-17. Page: 1 of 1. The report reflects the state of submissions in TESSy as of 2015-04-17 at 16:00

Odpornost proti karbapenemom, Klebsiella pneumoniae 2021



Antimicrobial consumption in the EU/EEA (ESAC-NET) - AER for 2022 (europa.eu)

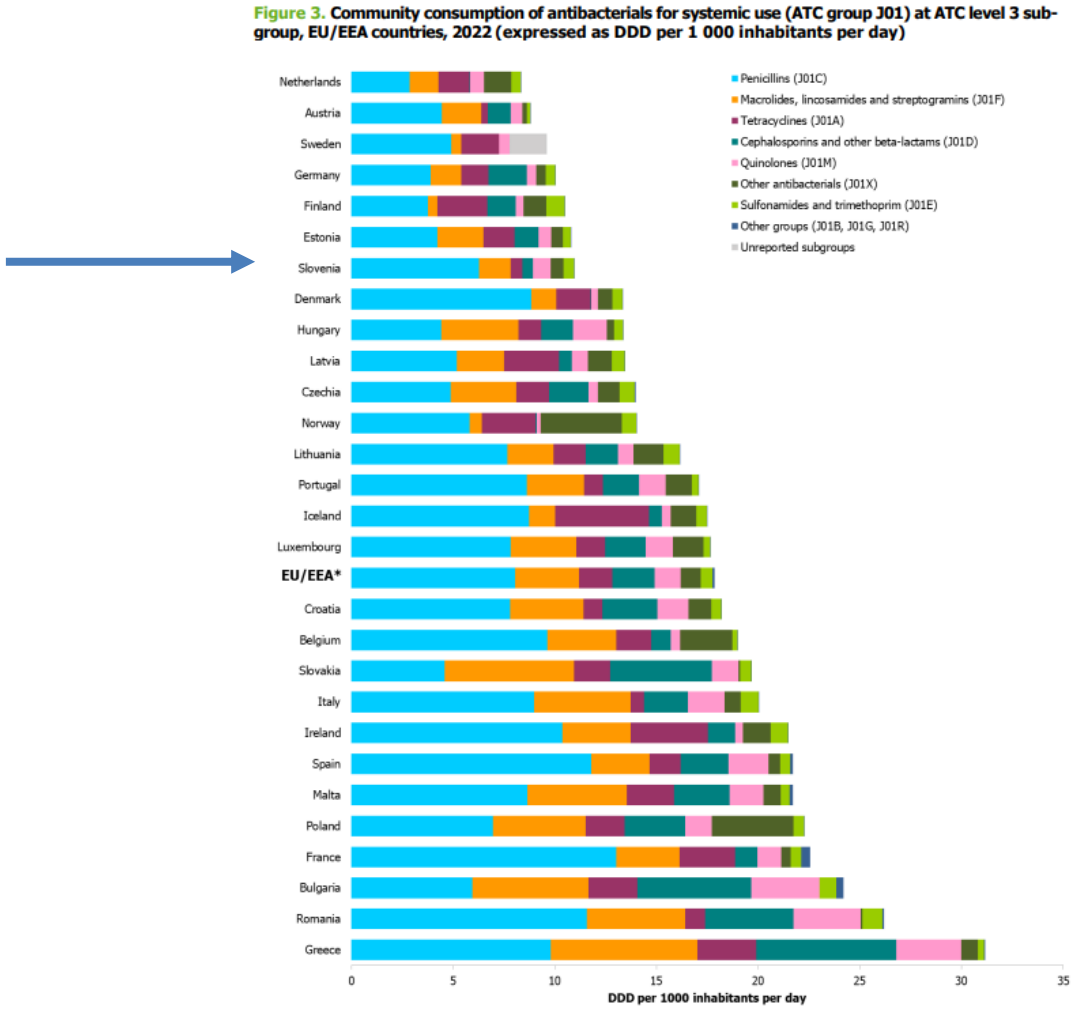
Figure 1. Total consumption of antibacterials* according to WHO AWaRe classification, percentage by class EU/EEA countries, 2022



https://www.ecdc.europa.eu/en/antimicrobial-consumption/database/rates-country

Ambulantna poraba v EU

(DDD/1000 preb/dan)



Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modelling analysis

*Alessandro Cassini, Liselotte Diaz Högberg, Diamantis Plachouras, Annalisa Quattrocchi, Ana Hoxha, Gunnar Skov Simonsen, Mélanie Colomb-Cotinat, Mirjam E Kretzschmar, Brecht Devleesschauwer, Michele Cecchini, Driss Ait Ouakrim, Tiago Cravo Oliveira, Marc J Struelens, Carl Suetens, Dominique L Monnet, and the Burden of AMR Collaborative Group**

- *33 110 (28 480–38 430) attributable deaths*

(25,100 in 2007 = + 32%!!!)

- *170 (150–192) DALYs* per 100 000 population*

*DALY, disability-adjusted life-years

Lancet ID 2018. Published Online November 5, 2018 http://dx.doi.org/10.1016/S1473-3099(18)30605-4
ECDC, EMEA. EMEA doc. ref. EMEA/576176/2009, Stockholm, September 2009

Table 2. Total number of blood isolates of the selected antibiotic-resistant bacteria as reported to EARS-Net, and estimated number of bloodstream infections, number of infections, number of attributable deaths and number of disability-adjusted life years (DALYs), EU/EEA, 2016-2020

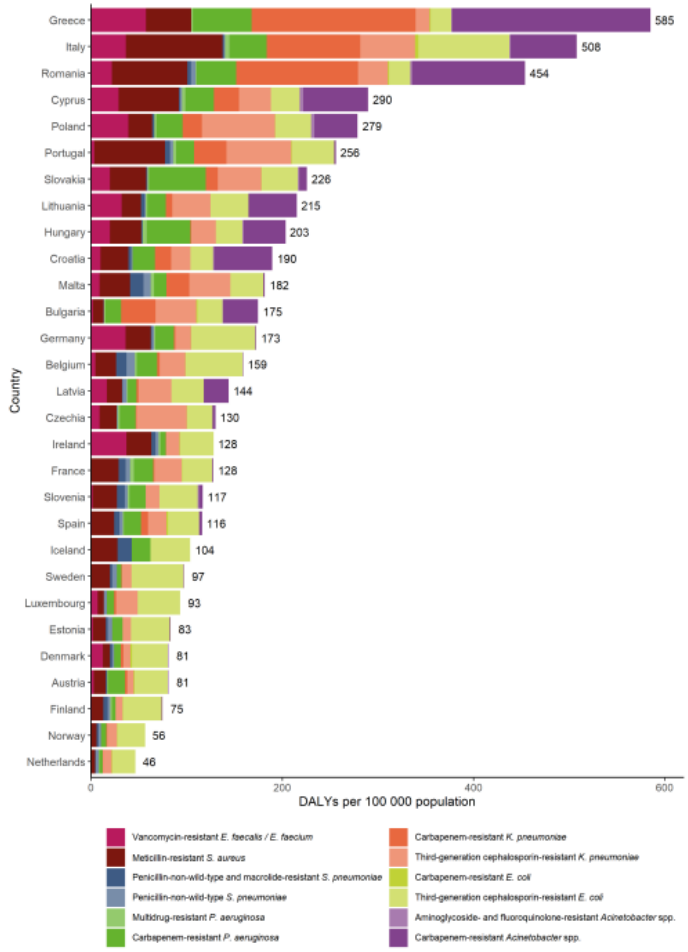
	2016	2017	2018	2019	2020
Number of blood isolates as reported to EARS-Net*	39 729	44 306	53 557	54 450	51 798
Estimated number of bloodstream infections after correction for population coverage	107 404	109 556	127 896	134 277	122 070
Estimated median number of infections, all types (95% UI)	685 433 (589 451 - 792 873)	701 816 (603 052 - 811 925)	822 075 (706 070 - 951 816)	865 767 (742 802 - 1 003 591)	801 517 (684 955 - 932 213)
Estimated median number of attributable deaths (95% UI)	30 730 (26 935 - 34 836)	31 178 (27 388 - 35 296)	36 605 (32 227 - 41 352)	38 710 (34 053 - 43 748)	35 813 (31 395 - 40 584)
Estimated median number of DALYs (95% UI)	909 488 (813 858 – 1 013 060)	918 117 (820 200 – 1 024 443)	1 046 858 (940 859 – 1 161 268)	1 101 288 (988 703 – 1 222 498)	1 014 799 (908 022 – 1 129 999)

European Centre for Disease Prevention and Control. Assessing the health burden of infections with antibiotic-resistant bacteria in the EU/EEA, 2016-2020. Stockholm: ECDC; 2022.

Assessing the health burden of infections with antibiotic resistant bacteria in the EU/EEA, 2016-2020,
ECDC technical report, 2022

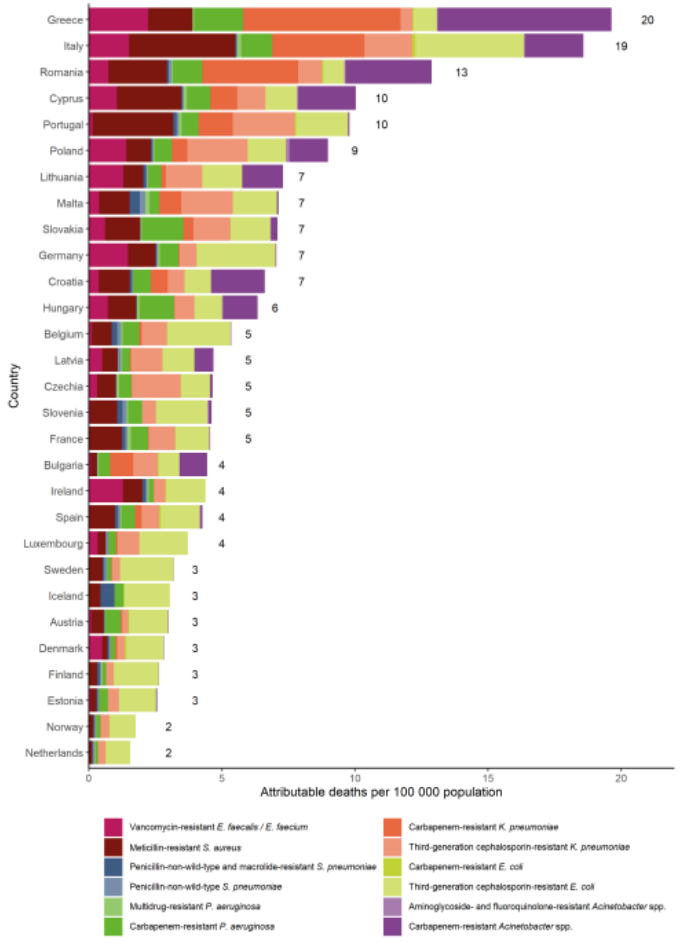
Burden of AMR in EU/EEA, 2020

Figure 4. Estimations of the burden of infections with antibiotic-resistant bacteria presented as disability-adjusted life years (DALYs) per 100 000 population by country*, EU/EEA, 2020



**For Sweden, data reported to EARS-Net for 2016-2020 could not be checked for possible duplicate cases reported from the same patient.*

Figure 5. Estimations of the burden of infections with antibiotic-resistant bacteria presented as attributable deaths per 100 000 population by country*, EU/EEA, 2020



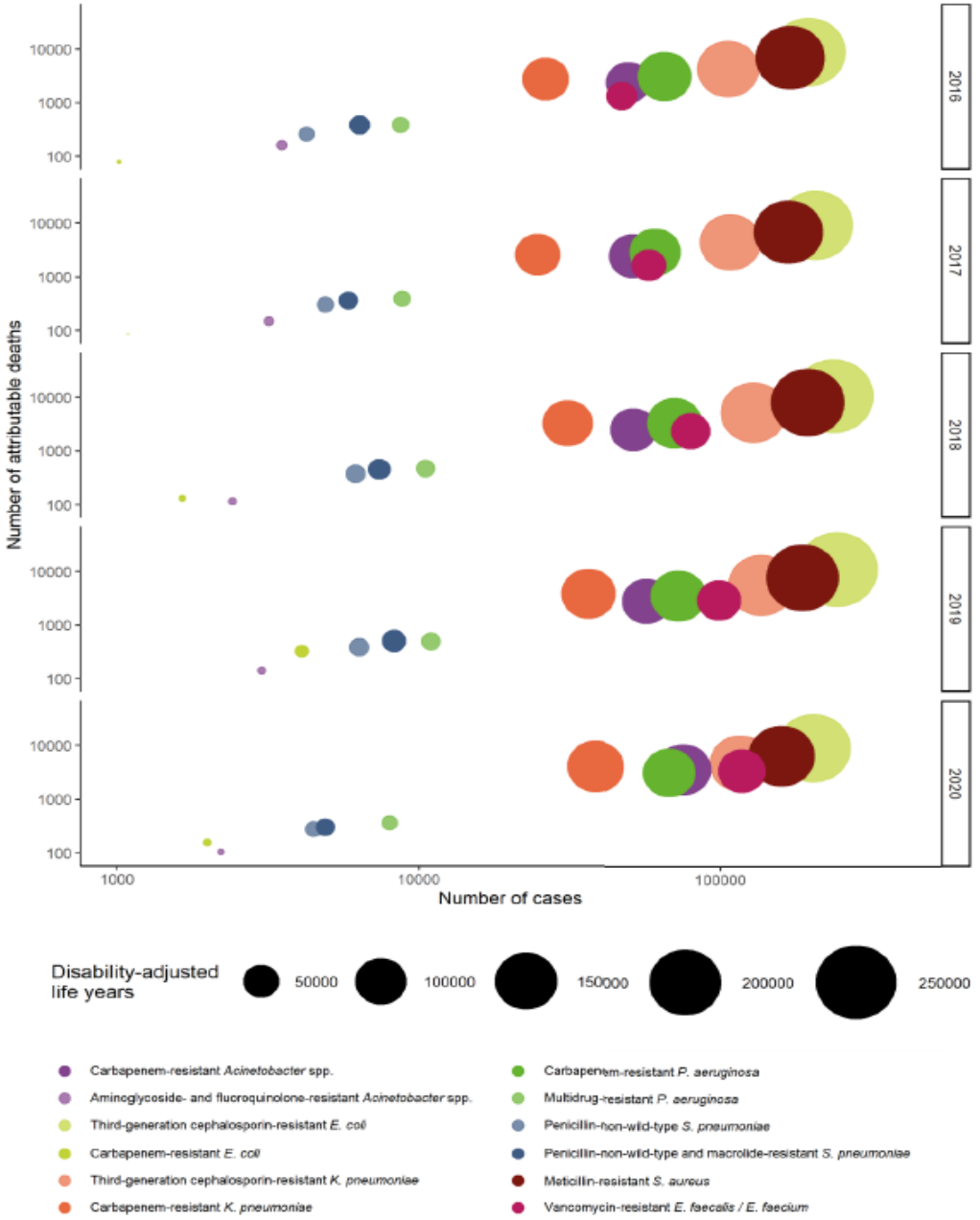
**For Sweden, data reported to EARS-Net for 2016-2020 could not be checked for possible duplicate cases reported from the same patient.*

Most common:

1. ***E. coli*** **R to cef3g**
2. **MRSA**
3. ***K. pneumoniae*****, R to cef3g**

Assessing the health burden of infections with antibiotic resistant bacteria in the EU/EEA, 2016-2020, *ECDC technical report, 2022*

Figure 1. Estimated number of cases, deaths and disability-adjusted life years for the selected antibiotic-resistant bacteria, EU/EEA, 2016-2020 (logarithmic x- and y-scale)



Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis

Lancet 2022; 399: 629–55

*Antimicrobial Resistance Collaborators**

1,27 milijona smrti, pripisljivih mikrobni odpornosti

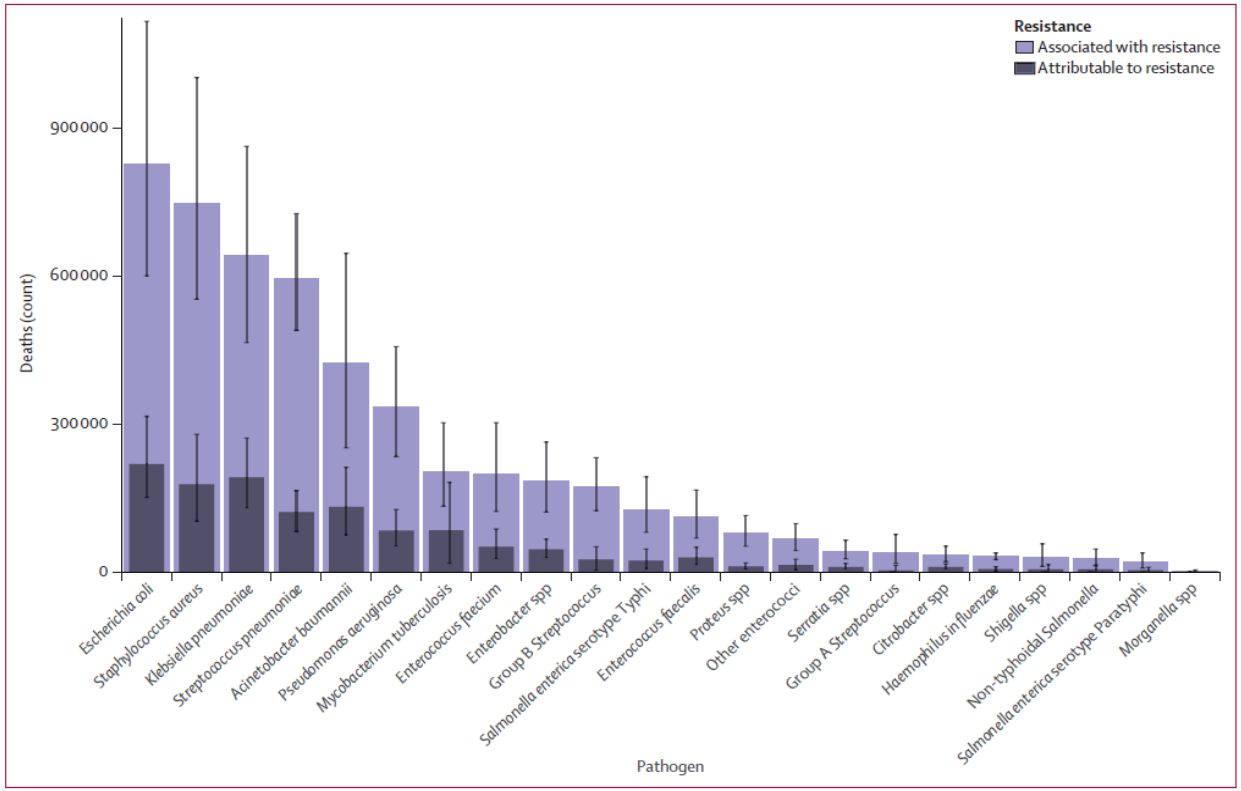
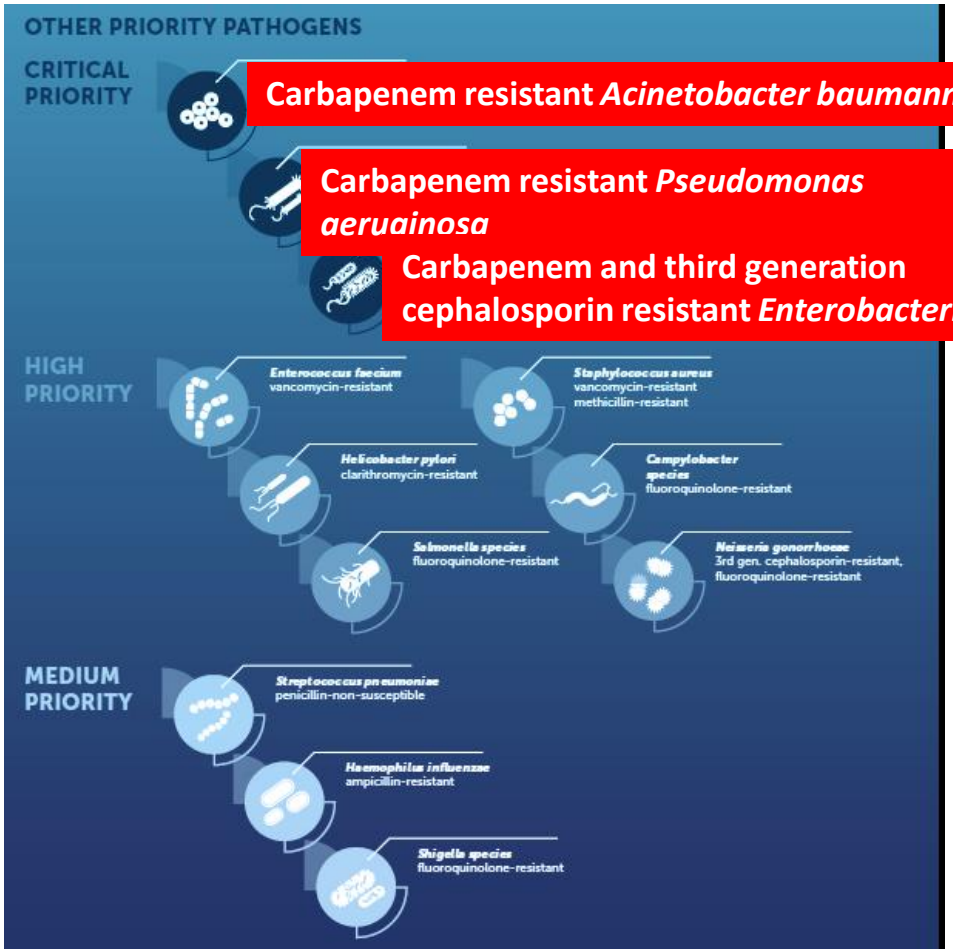


Figure 4: **Global deaths (counts) attributable to and associated with bacterial antimicrobial resistance by pathogen, 2019**
Estimates were aggregated across drugs, accounting for the co-occurrence of resistance to multiple drugs. Error bars show 95% uncertainty intervals.



WHO priority pathogens

(except *M tuberculosis*)

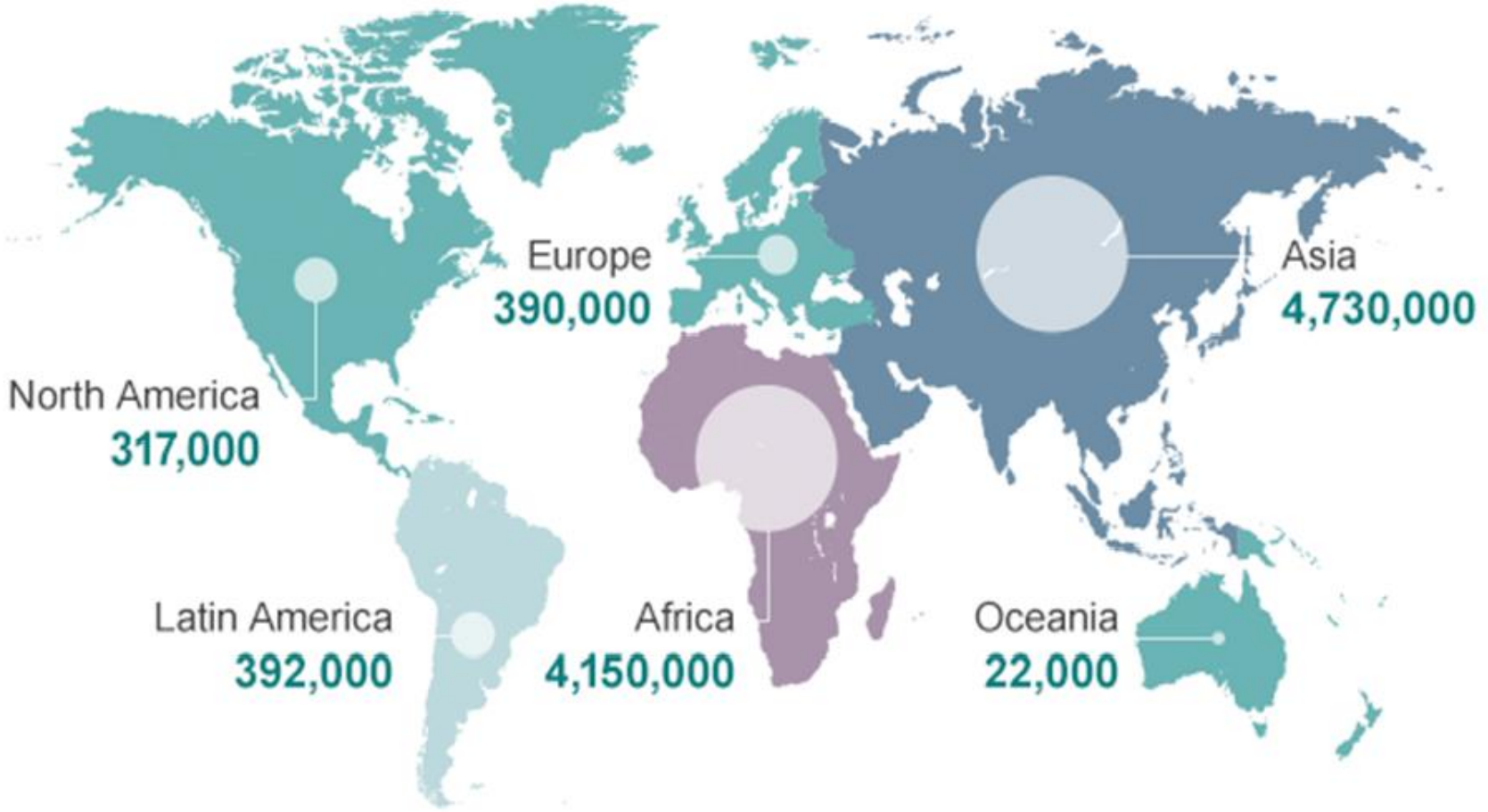
Attributable deaths globally 2019

Carbapenem-R *Acinetobacter baumannii*: 57,700
Carbapenem-R *Pseudomonas aeruginosa*: 38,100
Carbapenem-R *Enterobacteriaceae*: 105,250
Third generation cephalosporin-R *Enterobacteriaceae*: 117,838

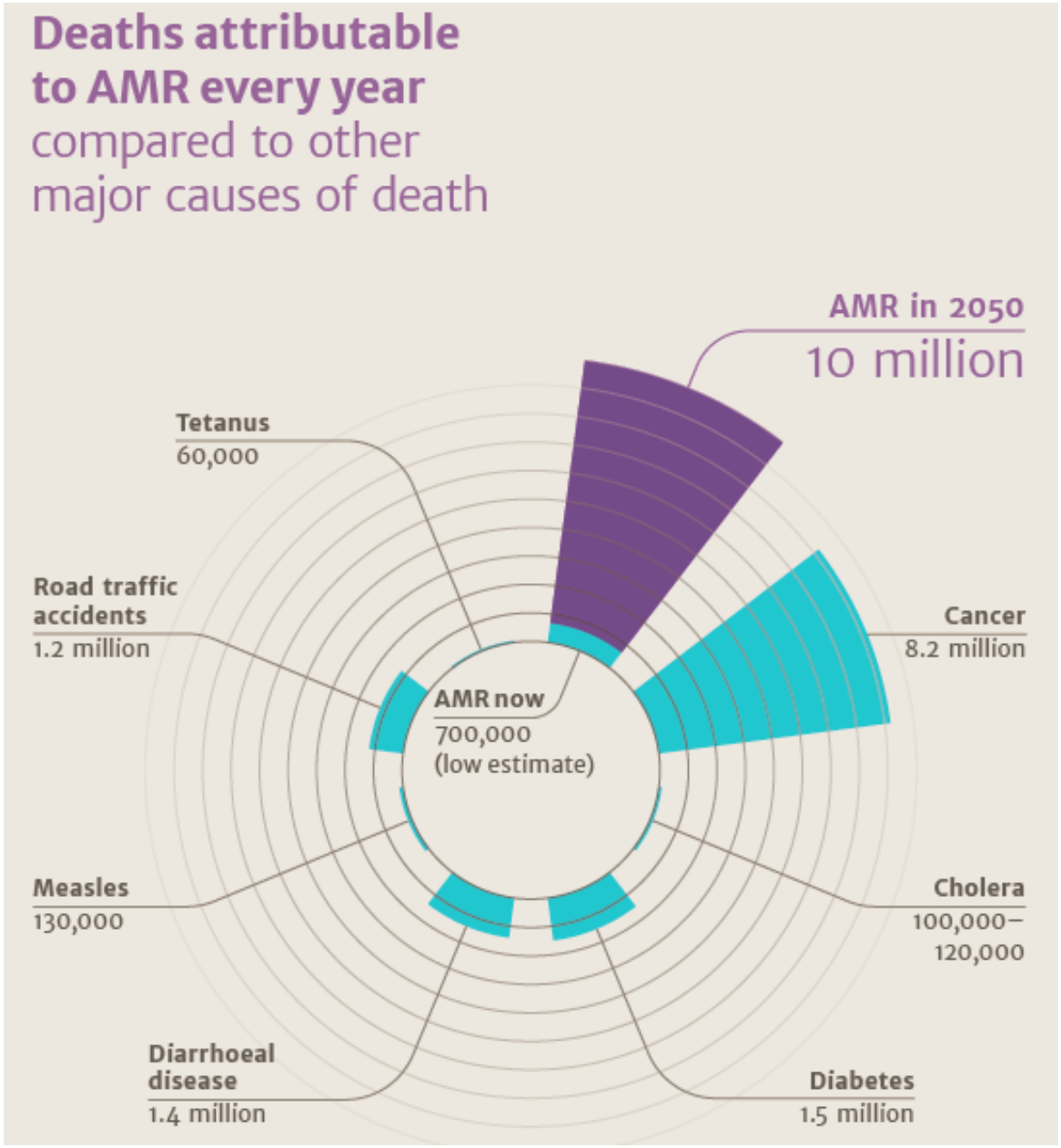
1.27 million (95% UI 0.911–1.71) deaths attributable to bacterial AMR!
COVID-19 pandemic: 6.961.014 deaths up to October 13, 2023

https://www.who.int/publications/i/item/9789240021303, Lancet 2022; 399: 629–55

Letno število smrti zaradi protimikrobne odpornosti leta 2050

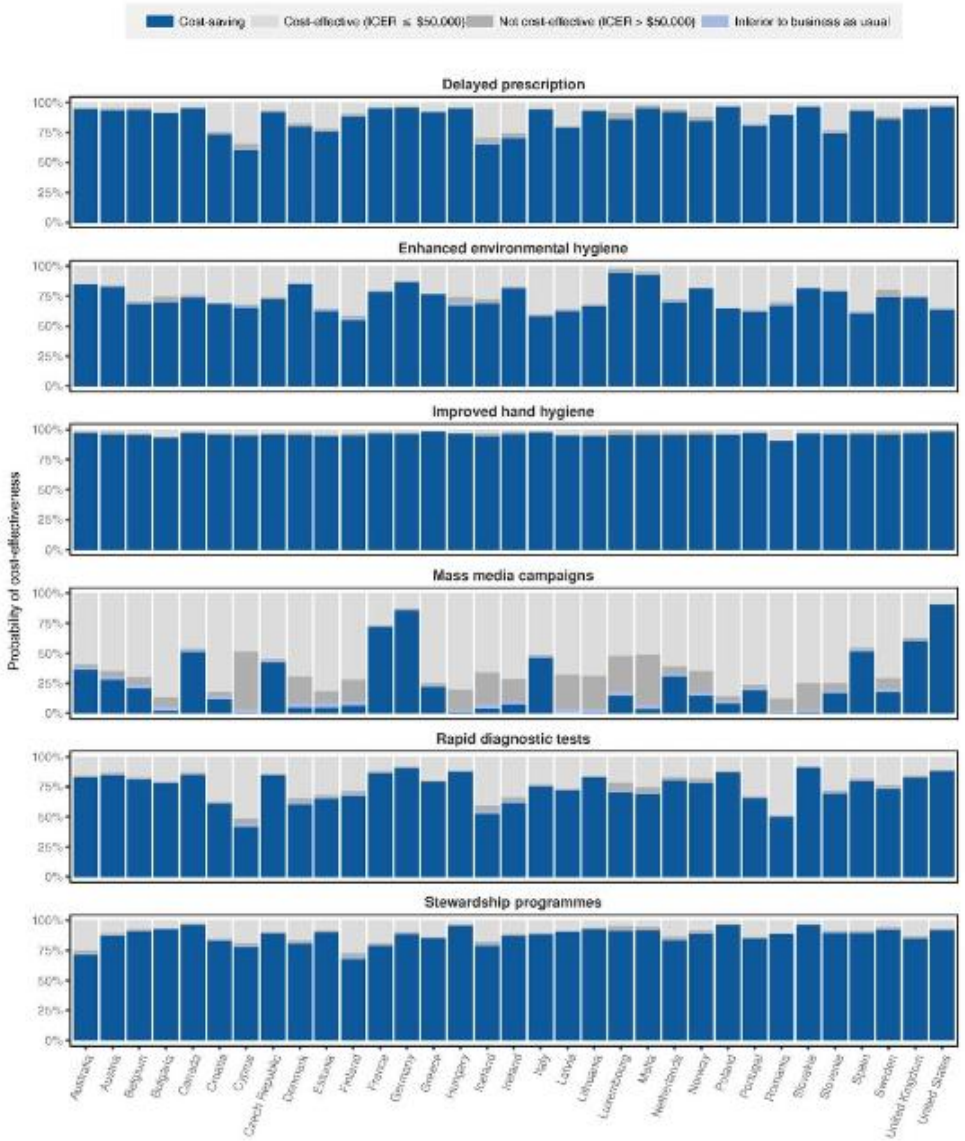


O'Neill J. Review on Antimicrobial Resistance. Tackling drug-resistant infections globally: An overview of our work. 2016 (supported by Wellcome Trust and UK governement)



O'Neill J. 'Review on Antimicrobial Resistance. Tackling drug-resistant infections globally: An overview of our work. 2016'

(supported by Wellcome Trust and UK governement)



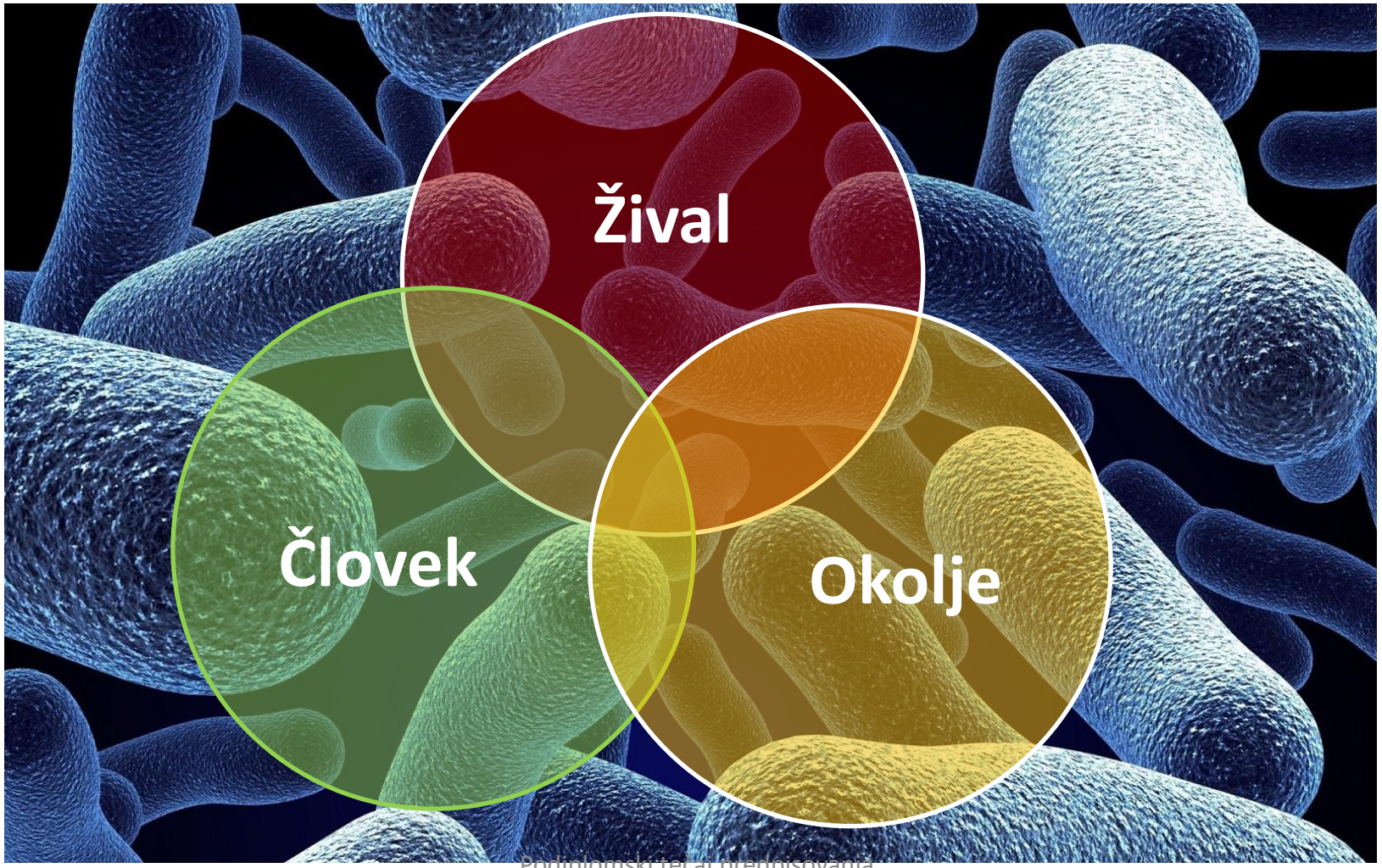
NRA zmanjšuje stroške zdravljenja skoraj tako učinkovito kot higiena rok!

OECD (2018). Stemming the superbug tide: Just a few dollars more. OECD Publishing, Paris. Available ahttps://read.oecd-ilibrary.org/social-issues-migration-health/stemming-the-superbug-tide_9789264307599-en#page3t

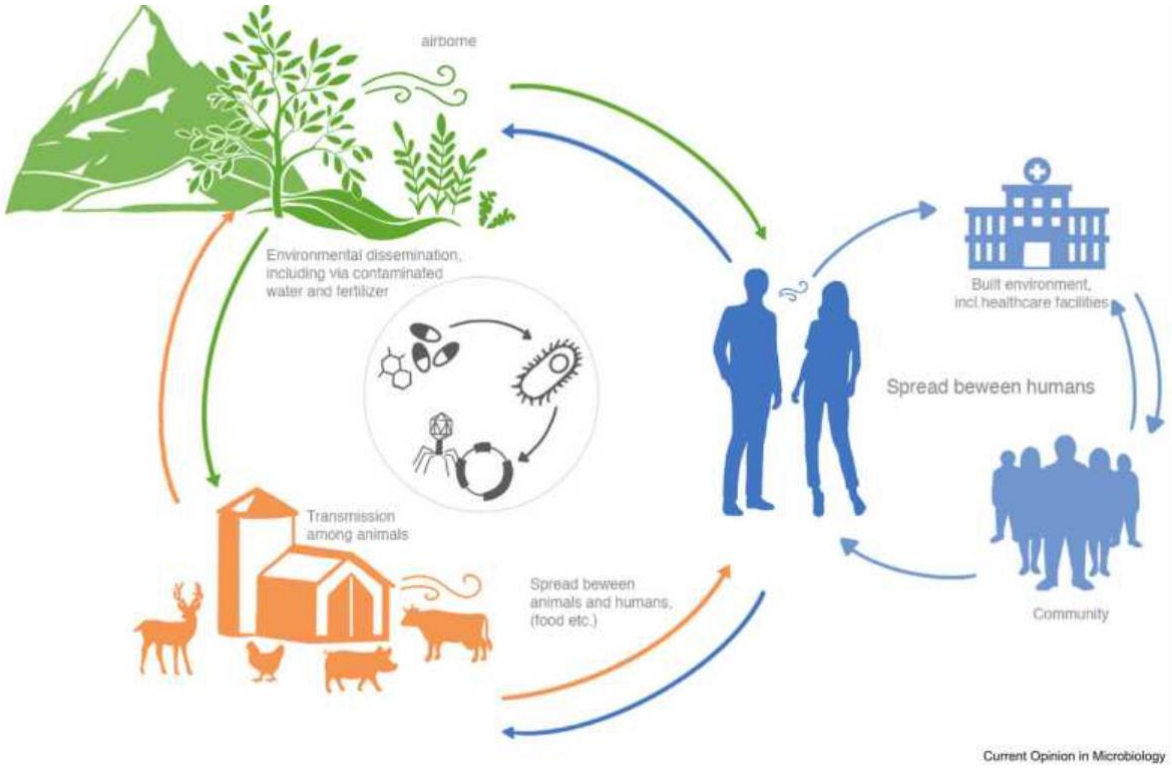
Bakterije so naše najbližje okolje

1. Savage D. *Annu Rev Microbiol* 1977;31:107–33. 2. Big think. Humans: 10% Human and 90% Bacterial. Available at: http://bigthink.com/amped/humans-10-human-and-90-bacterial. Accessed September 2016; 3. Behance. 10% human 90% bacteria. Available at: https://www.behance.net/gallery/4292835/10-Human-90-Bacteria. Accessed September 2016.

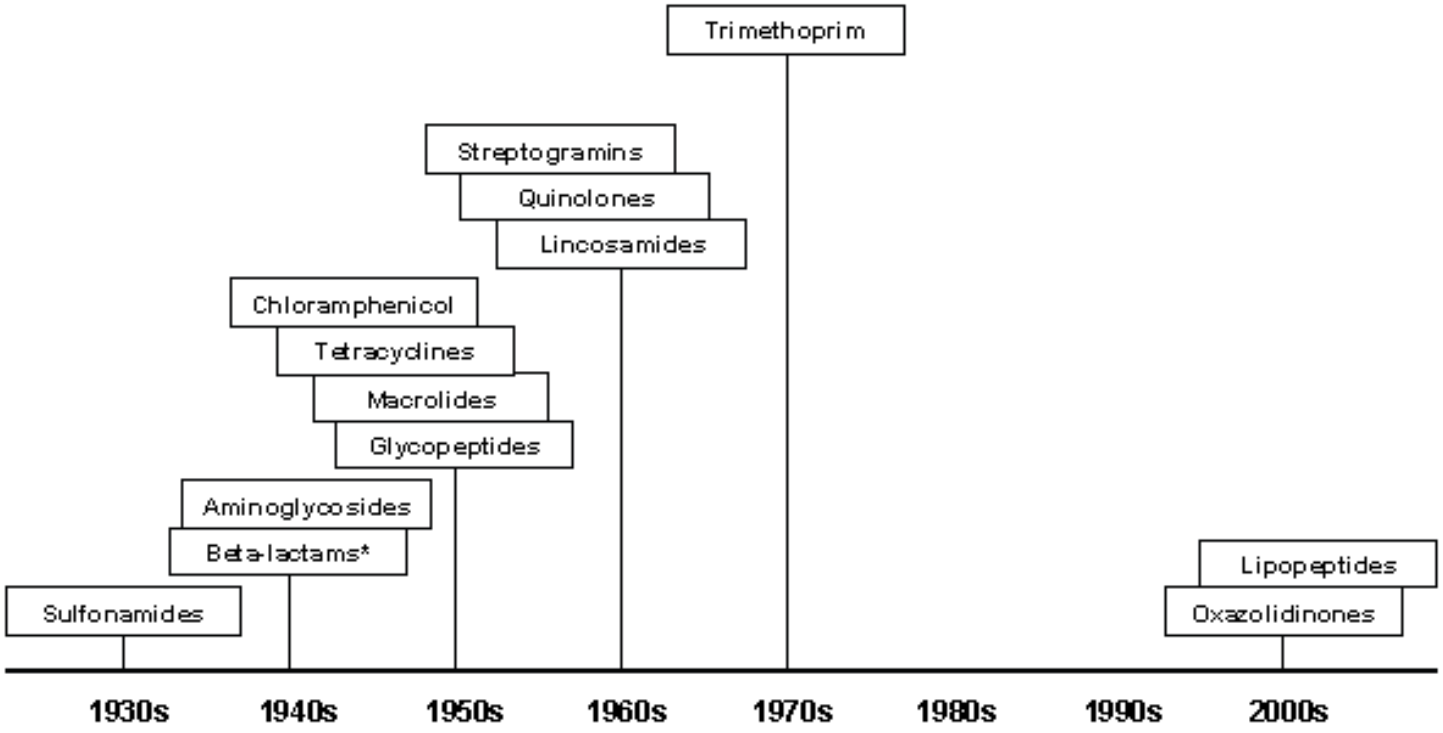
Načelo „Enega zdravja“ (One Health)



Povezanost sveta človeka, živali, rastlin in okolja



New Classes of Antibiotics on the Market



EMEA & ECDC. The Bacterial Challenge: Time to React. www.ecdc.europa.eu

Kakšen je razvoj novih antibiotikov?

Antibiotiki, ki delujejo proti po Gramu negativnim odpornim bakterijam v zadnjih fazah razvoja ali so bili odobreni nedavno:

16 novih molekul

2 z novim mehanizmom delovanja:
(murepavadin)
cefiderokol

- Talbot GH, et al. Clin Infect Dis. 2019 Feb 1. doi: 10.1093/cid/ciz089.

The antibiotic pipeline 2022

- 27 molekul, aktivnih proti patogenom, ki so prioriteta za Svetovno zdravstveno organizacijo
- Analiza teh 27 molekul:
- 6 je inovativnih
- **Med inovativnimi samo dve molekuli, ki delujeta proti kritičnim večkratno odpornim Gramu negativnim bakterijam** (i.e. CRAB, CRPA, CRE)

2021 Antibacterial agents in clinical and preclinical development: an overview and analysis. Geneva: World Health Organization; 2022. Licence: CC BY-NC-SA 3.0 IGO.

Kaj še lahko storimo?

- cepiva, monoklonska ali poliklonska protitelesa
- bakteriofagi
- hemoperfuzijska sredstva
- zaviralci „quorum sensing“
- zaviralci citotoksinov
- neimunska toleranca za bolezen
- vpliv na mikrobiom (probiotiki)
- .....

Opal SM. Critical Care (2016) 20:397. DOI 10.1186/s13054-016-1549-1

Protimikrobna odpornost je ena od ekoloških katastrof, ki jih je povzročil človek!

Antibiotic resistance: another man-made environmental catastrophe that our politicians refuse to talk about. Available at: http://www.conservativehome.com/the-deep-end/2015/05/antibiotic-resistance-another-man-made-environmental-catastrophe-that-our-politicians-refuse-talk-about.html. [Accessed September 2016]., http://www.telesurtv.net/english/multimedia/Biggest-Ecological-Disaster-in-Brazils-History-20151124-0012.html, http://www.telesurtv.net/english/multimedia/Biggest-Ecological-Disaster-in-Brazils-History-20151124-0012.html, http://www.stormchaser.ca/Environmental_Disasters/Aral%20Sea/Aral_Sea.html, http://www.thehindu.com/todays-paper/tp-national/bhopal-toxic-waste-to-be-sent-to-germany/article3507271.ece

Kaj lahko storimo?

Primer: 53 letna pacientka s plazmocitomom, ugotovljenim pred 2,5 leti

Področje velike protimikrobne odpornosti JV Evropa, Azija

- Uspešna avtologna PKMC pred 8 meseci
- Pljučnica, pnevmokoki v sputumu, pnevmokokni antigen poz v urinu, zdravnik se vseeno odloči za TMP-SMX, meropenem, moksifloksacin, ganciklovir, liposomalni amphotericin.
- **Dan 3:** boljša, na oralnem moksifloksacin plus TMP-SMX.
- **Dan 10**, bolnica afebrilna, a postane tahipnoična
- Kontrolni HRCT, eden narejen že ob sprejemu, pokaže isto sliko in še dodatno konsolidacijo v desnem srednjem režnju
- Radiolog je mnenja, da gre za pričakovano evolucijo pnevmokokne pljučnice

S prijaznostjo prof Hakana Hanbergerja, Univerza Linkoping, Švedska

Interaktivno vprašanje

Primer: 53 letna pacientka s plazmocitomom, ugotovljenim pred 2,5 leti

Področje velike protimikrobne odpornosti JV Evropa, Azija

Kateri antibiotik boste izbrali?

1. **Nadaljujete moksifloksacin**
2. **HAP: piperacillin-tazobaktam**
3. **HAP: meropenem**
4. **HAP: meropenem + kolistin**
5. **HAP: meropenem + kolistin + vankomicin**

Primer: 53 letna pacientka s plazmocitomom, ugotovljenim pred 2,5 leti

Področje velike protimikrobne odpornosti JV Evropa, Azija

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4. **HAP: meropenem + kolistin**
5. **HAP: meropenem + kolistin + vankomicin**

Slovenija: *Pseudomonas aeruginosa*: 17,4% R proti karbapenemom, R proti pip/tazo 13,0%
K. pneumoniae: 23,7% ESBL, 0,0 CRE

Grčija: P. aeruginosa 49,3% R proti karbapenemom, R proti pip/tazo 29,6%
K. pneumoniae ESBL 69,2%, CRE 64,7% (EARS-NET)

European Centre for Disease Prevention and Control. Antimicrobial resistance surveillance in Europe 2015. Annual Report of the European Antimicrobial Resistance Surveillance Network (EARS-Net). Stockholm: ECDC; 2018.

S prijaznostjo prof Hakana Hanbergerja, Univerza Linkoping, Švedska

Primer: 53 letna pacientka s plazmocitomom, ugotovljenim pred 2,5 leti
Področje velike protimikrobne odpornosti JV Evropa, Azija

- **Dan 13**: ponovno vročina (39C) bolnica postane hipoksična, še vedno na moksifloksacinu.
- Odvzete hemokulture, BAL, zamenjan CVK

S prijaznostjo prof Hakana Hanbergerja, Univerza Linkoping, Švedska

Dan 13: Pip-tazo dodan.
Dan 14 in 15; BAL in hemokulture: ***P. aeruginosa,*** občutljiv samo za kolistin, dodan kolistin

MIC(µg/ml)	IMIP	P/T	CAZ	AMK	CIP	COL
Ps.aeruginosa **MBL pharyngeal culture one day before intubation**	>8	>64/4	>16	>32	>2	0.75
Ps. aeruginosa **MBL(+) in BAL**	>8	>64/4	>16	>32	>2	0.75
Ps. aeruginosa **MBL(+) in blood**	>8	>64/4	>16	>32	>2	0.75

Dan 16: bolnica umre v septičnem šoku

Primer: 53 letna pacientka s plazmocitomom, ugotovljenim pred 2,5 leti

Področje majhne protimikrobne odpornosti: Skandinavija

- Uspešna avtologna PKMC pred 8 meseci
- Pljučnica, pnevmokoki v sputumu, pnevmokokni antigen poz v urinu
- Stabilna, saturacija 95%, RR 120/80, FP 84/min, T 38,6, FD 22/min

S prijaznostjo prof Hakana Hanbergerja, Univerza Linkoping, Švedska

Interaktivno vprašanje

Primer: 53 letna pacientka s plazmocitomom, ugotovljenim pred 2,5 leti

Področje majhne protimikrobne odpornosti: Skandinavija

Kateri antibiotik izberejo?

1. penicilin G 3gx4
2. cefotaksim + eritromicin
3. penicilin G + moksifloksacin
4. ne vem

S prijaznostjo prof Hakana Hanbergerja, Univerza Linkoping, Švedska

Primer: 53 letna pacientka s plazmocitomom, ugotovljenim pred 2,5 leti

Področje majhne protimikrobne odpornosti: Skandinavija

- **Dan 3**; izboljšanje, preklop pa amoksicilin p.o.
- **Dan 10**, bolnica afebrilna, a postane tahipnoična

- Kontrolni HRCT, eden narejen že ob sprejemu, pokaže isto sliko in še dodatno konsolidacijo v desnem srednjem režnju

- Radiolog je mnenja, da gre za pričakovano evolucijo pnevmokokne pljučnice

S prijaznostjo prof Hakana Hanbergerja, Univerza Linkoping, Švedska

Interaktivno vprašanje:

Primer: 53 letna pacientka s plazmocitomom, ugotovljenim pred 2,5 leti

Področje majhne protimikrobne odpornosti: Skandinavija

Kateri antibiotik izberejo?

1. HAP: Piperacilin-tazobaktam
2. HAP: meropenem
3. HAP: meropenem + kolistin
4. HAP: meropenem + kolistin + vancomycin
5. HAP: Pip-tazo + kolistin
6. HAP: Pip-tazo + kolistin + vankomicin

European Centre for Disease Prevention and Control. Antimicrobial resistance surveillance in Europe 2015. Annual Report of the European Antimicrobial Resistance Surveillance Network (EARS-Net). Stockholm: ECDC; 2017.

S prijaznostjo prof Hakana Hanbergerja, Univerza Linkoping, Švedska

Primer: 53 letna pacientka s plazmocitomom, ugotovljenim pred 2,5 leti

Področje majhne protimikrobne odpornosti: Skandinavija

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2. HAP: meropenem
3. HAP: meropenem + kolistin
4. HAP: meropenem + kolistin + vancomycin
5. HAP: Pip-tazo + kolistin
6. HAP: Pip-tazo + kolistin + vankomicin

Švedska: *P.aeruginosa*, odporen proti karbapenemom: 9,0%, pip/tazo 6,3%
K. pneumoniae ESBL 5,6% (EARS-net)

European Centre for Disease Prevention and Control. Antimicrobial resistance surveillance in Europe 2015. Annual Report of the European Antimicrobial Resistance Surveillance Network (EARS-Net). Stockholm: ECDC; 2018.

S prijaznostjo prof Hakana Hanbergerja, Univerza Linkoping, Švedska

Kje bi želeli imeti hospitalizirano svojo mamo?