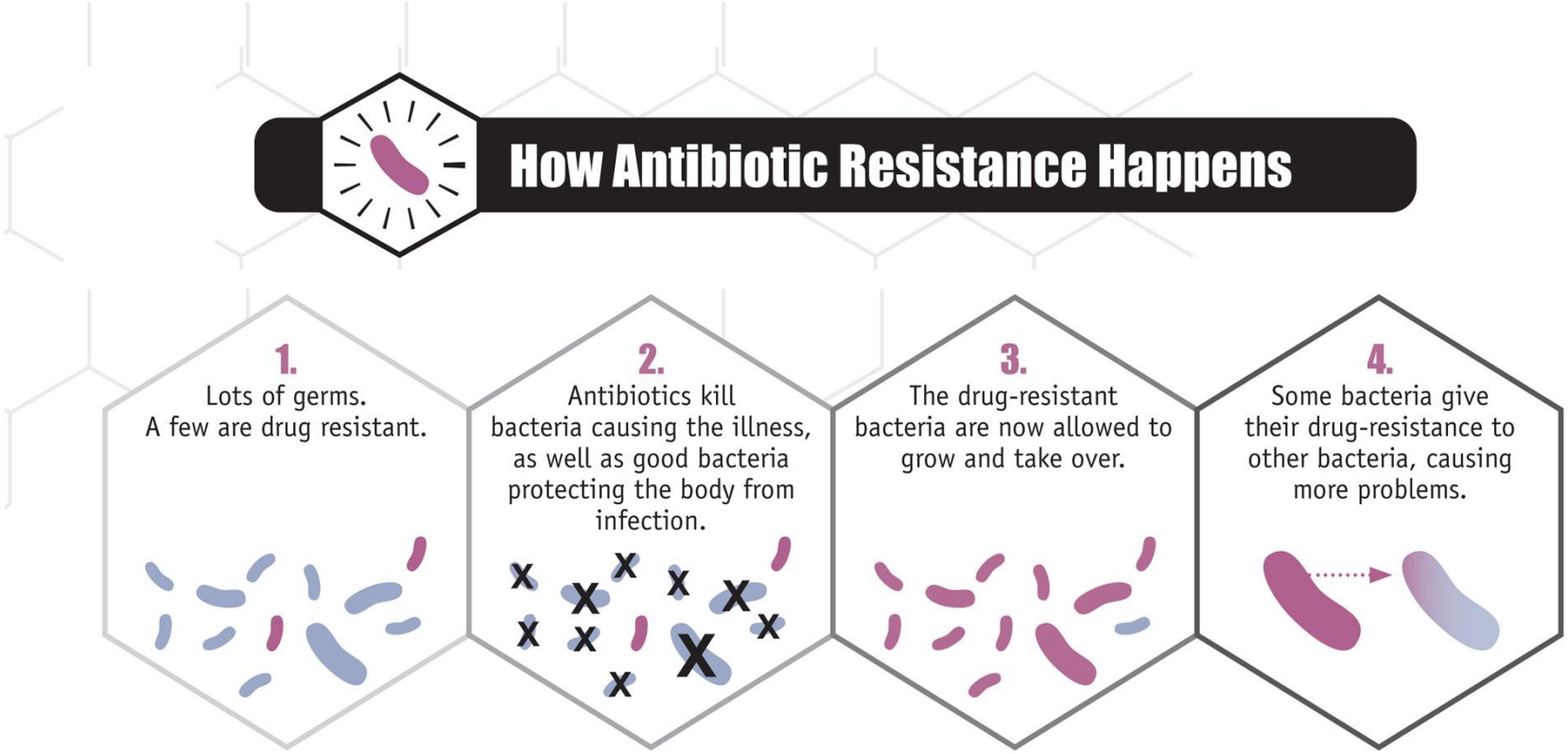
UNIVERZITET U BEOGRADU
MEDICINSKI FAKULTET

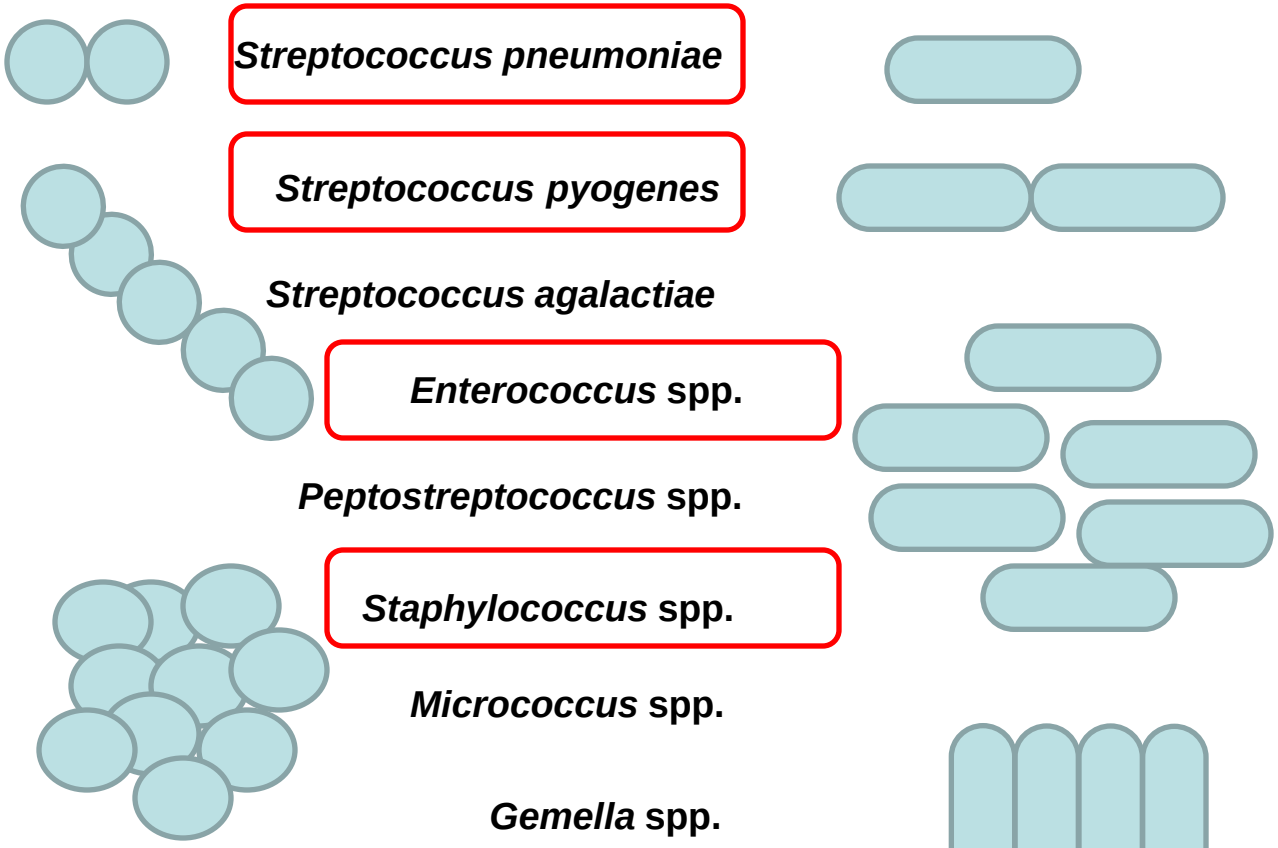
Problem rezistencije kod Gram pozitivnih bakterija na antibakterijske lekove

doc. dr Ivana Ćirković
Institut za mikrobiologiju i imunologiju
Medicinski fakultet u Beogradu

Rezistencija bakterija na antibiotike



Rezistencija Gram pozitivnih bakterija na antibiotike



Streptococcus pneumoniae

Streptococcus pyogenes

Streptococcus agalactiae

Enterococcus spp.

Peptostreptococcus spp.

Staphylococcus spp.

Micrococcus spp.

Gemella spp.

Mycobacterium tuberculosis

Clostridium spp.

Mycobacterium leprae

Listeria monocytogenes

Bacillus spp.

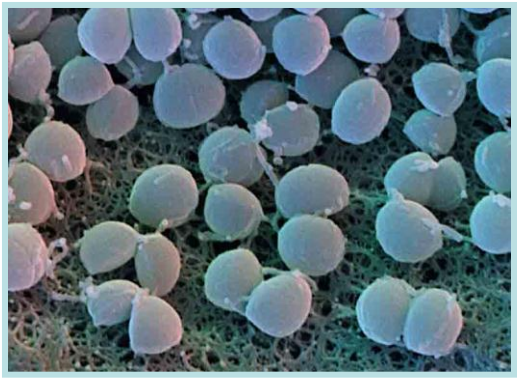
Lactobacillus spp.

Erysipelothrix rhusiopathiae

Corynebacterium diphtheriae

Proprionibacterium spp.

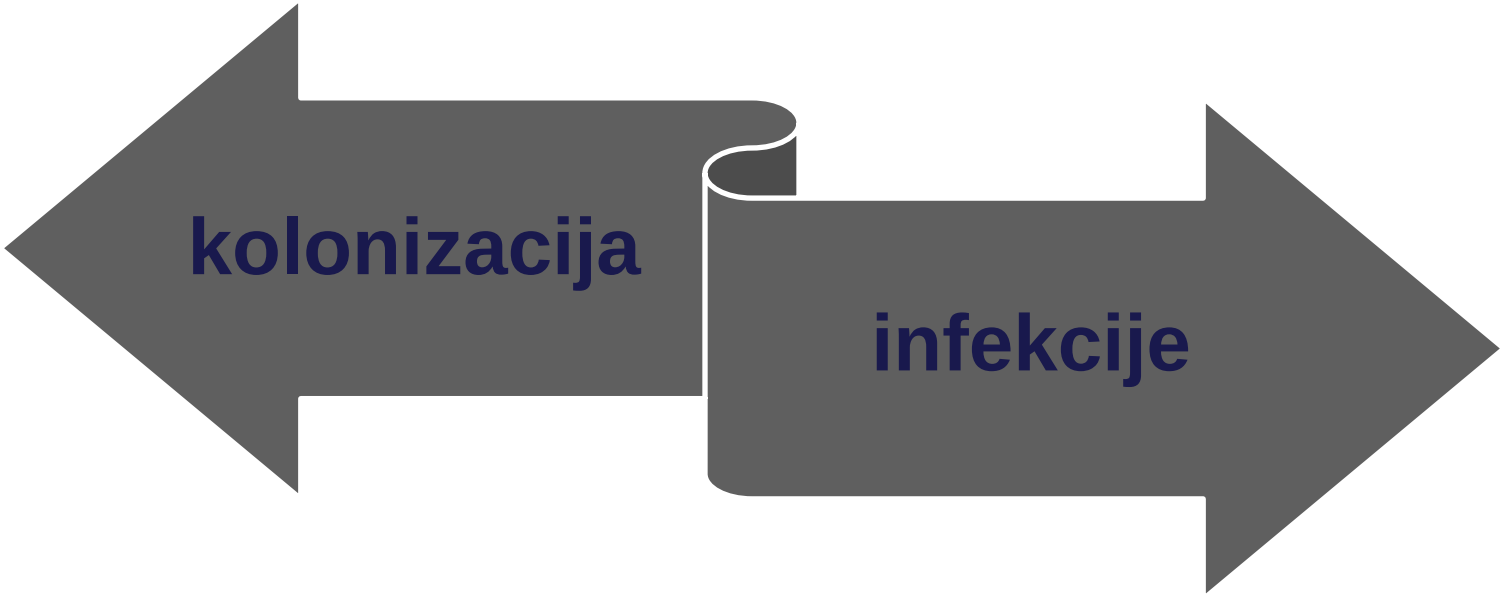
Staphylococcus spp.



- 49 vrsta i 24 podvrste
- Podela stafilokoka:
  - koagulaza pozitivne (8 vrsta) – *Staphylococcus aureus*
  - koagulaza negativne (41 vrsta) – *S. epidermidis*, …
    S. stepanovicii

Staphylococcus aureus

uslovno patogena bakterija



Staphylococcus aureus

kolonizacija

- **Človek**

  - koža (poglavina, pazušna jama, spoljašnje genitalije)
  - sluznica (nos, farings, kolon, vagina...)

20% ljudi – rezidentna flora nosa

60% ljudi – tranzitorna flora nosa

20% ljudi – nema *S. aureus* u nosu

Staphylococcus aureus

kolonizacija

- Životinje – konji, psi, mačke, goveda... - kolonizacija i infekcije
- U zemlji, vazduhu, prašini
- Razne površine (bolnička, vanbolnička sredina)

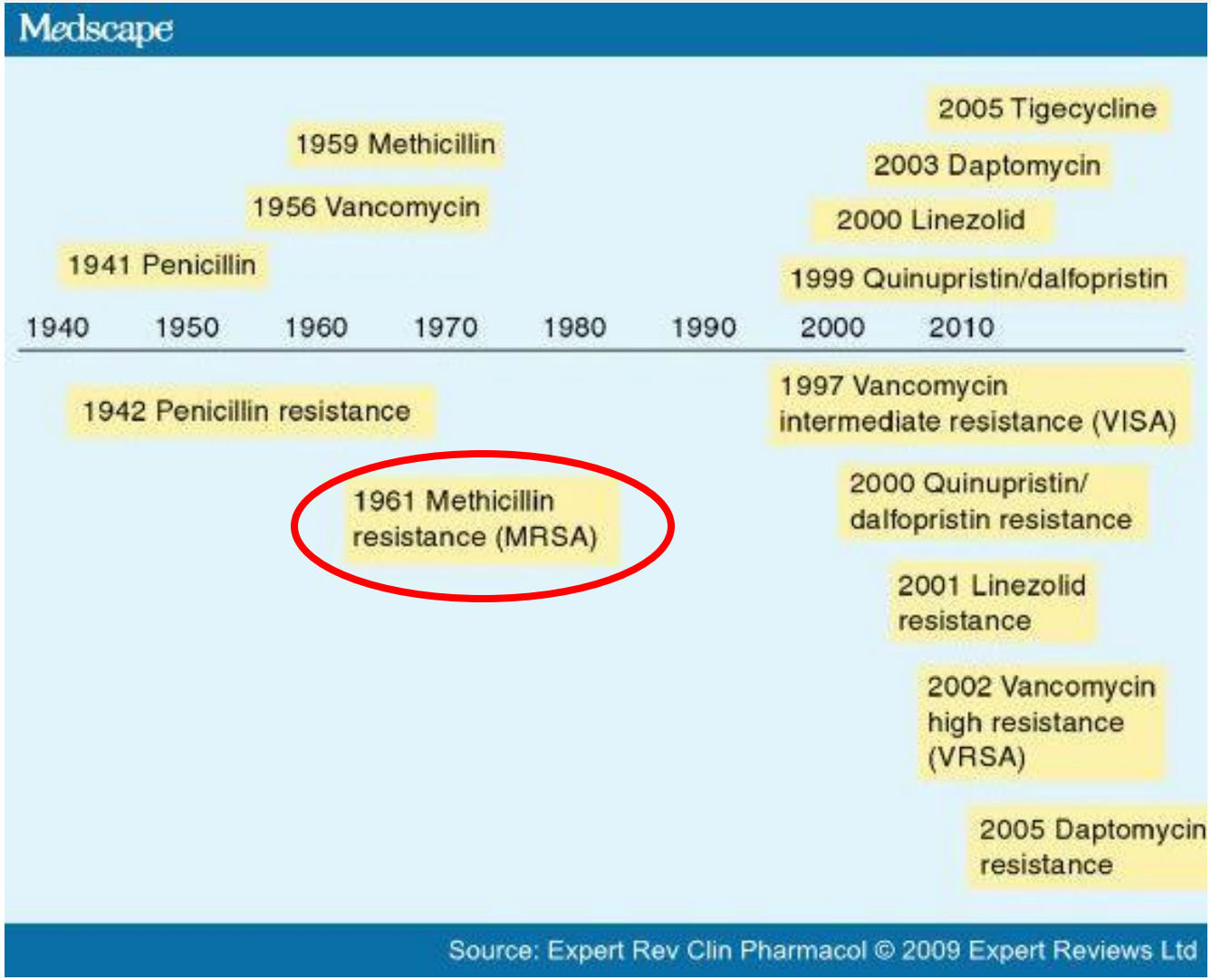
*otporna bakterija na brojne faktore spoljašnje sredine (može da preživi mesecima na neživim predmetima)

Staphylococcus aureus

Infekcije:

- piogena oboljenja
  - lokalne infekcije kože i mekih tkiva (eng. skin and soft tissue infections, SSTI)
  - invazivne infekcije (bakterijemija, sepsa, pneumonija, osteomijelitis, endokarditis, meningitis, ...)
- toksemična oboljenja
  - stafilokokno trovanje hranom
  - sindrom oparene kože
  - stafilokokni toksični šok sindrom

Staphylococcus aureus – rezistencija na antibiotike

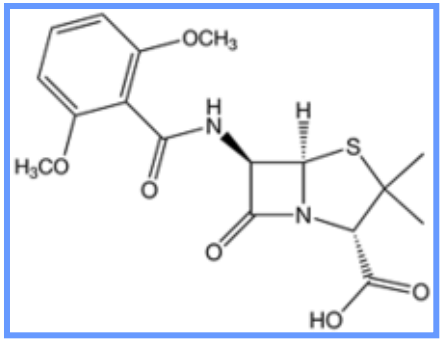


Meticilin-rezistentni *Staphylococcus aureus* (MRSA)

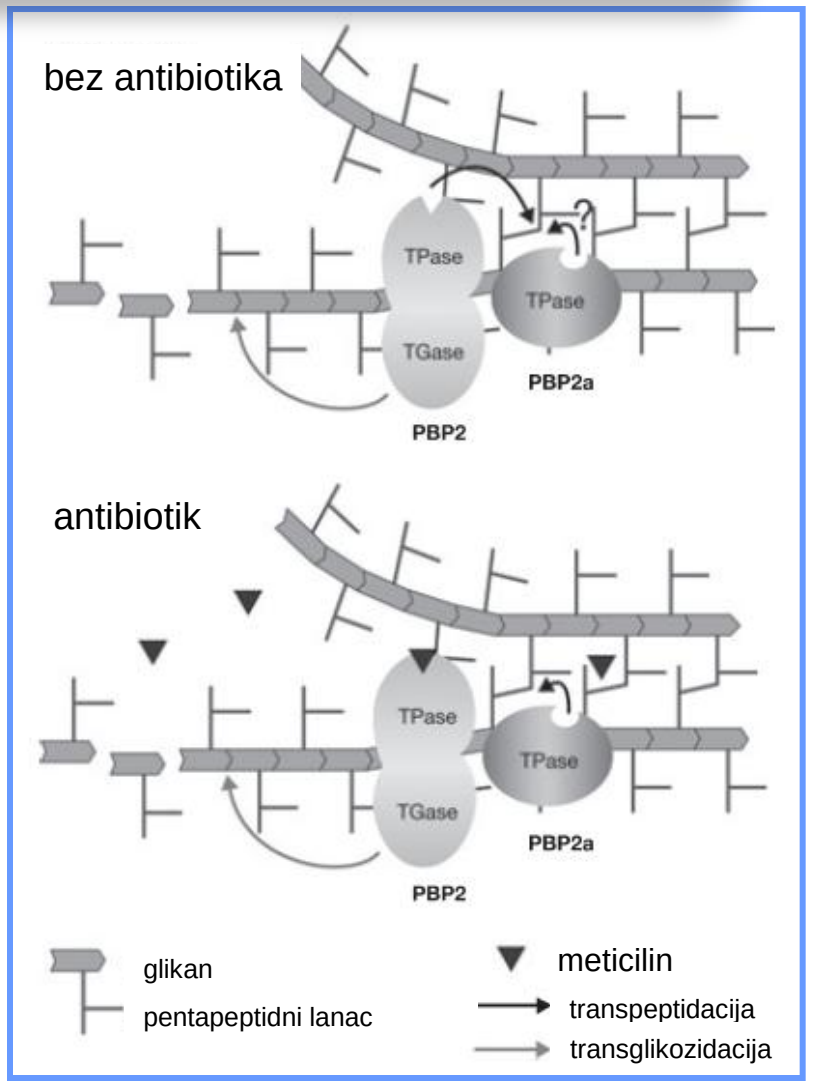
- *mec*A gen - PBP2a
- *mec*C gen – PBP2c

↓

rezistencija na sve β-laktame



meticilin



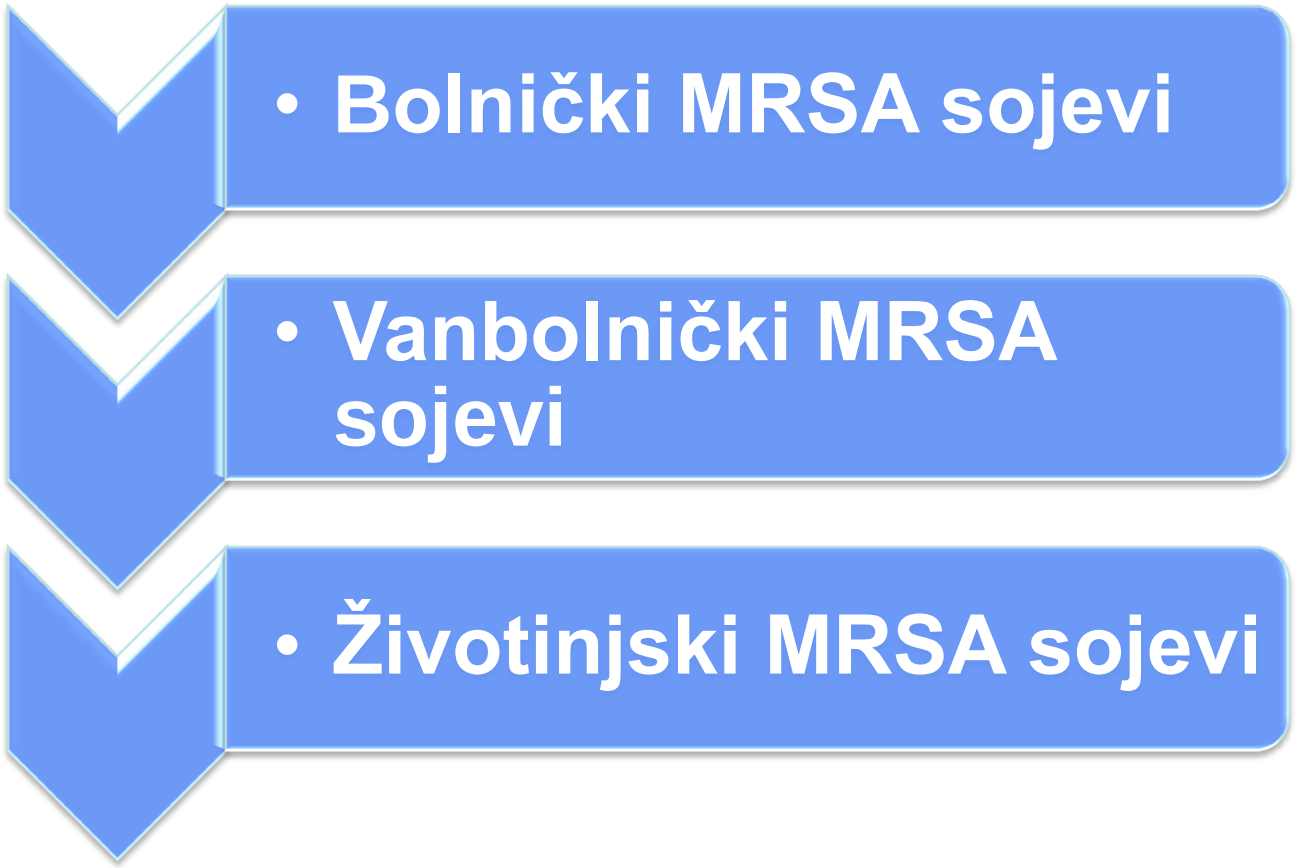
Meticilin-rezistentni *Staphylococcus aureus* (MRSA)

MRSA
(*mecA* ili *mecC*)

=

1. **Penicilini**
2. **Cefalosporini**
3. **Karbapenemi**
4. **Beta-laktami + inhibitori beta-laktamaza**

BETA-LAKTAMI – 70 % propisanih antibiotika


• Bolnički MRSA sojevi
• Vanbolnički MRSA sojevi
• Životinjski MRSA sojevi

Bolnički *versus* vanbolnički MRSA sojevi

Bolnički MRSA sojevi

- multirezistentni
- stariji, imunokompromitovani pacijenti
- infekcije rana, invazivne infekcije
- rezervoar: pacijenti, medicinsko osoblje, bolničko okruženje

Vanbolnički MRSA sojevi

- osetljivi na antibiotike
- mladi pacijenti koji nisu imali prethodni kontakt sa zdravstvenim ustanovama
- infekcije kože i mekih tkiva
- rezervoar: sportisti, učenici, vojnici, I.V. narkomani, zatvorenici, okruženje (novčanice, telefoni, kompjuterska tastatura, ...)

Životinjski MRSA sojevi

Značaj MRSA

✓medicinski

- značajan uzročnik intrahospitalnih infekcija:

e.g. 50% infekcija na odeljenjima intenzivne nege
40% infekcija na drugim odeljenjima

- smrtnost u Americi veća od AIDS (CDC, 2005.)

✓ekonomski

- poskupljuje lečenje (3.000 - 30.000 $ po pacijentu)

Faktori rizika za MRSA infekcije

- ✓ MRSA kliconoštvo
- ✓ Dijabetes
- ✓ Imunodeficijencija
- ✓ Starost
- ✓ Neracionalna upotreba antibiotika
- ✓Pacijenti na dijalizi
- ✓Intravenski narkomani
- ✓....

✓direktan, nezavisni faktor rizika za MRSA infekciju
✓kolonizovani pacijent ima 10 puta veći rizik od MRSA infekcija

Journal of Antimicrobial Chemotherapy (2008) **61**, 26–38
doi:10.1093/jac/dkm416
Advance Access publication 6 November 2007

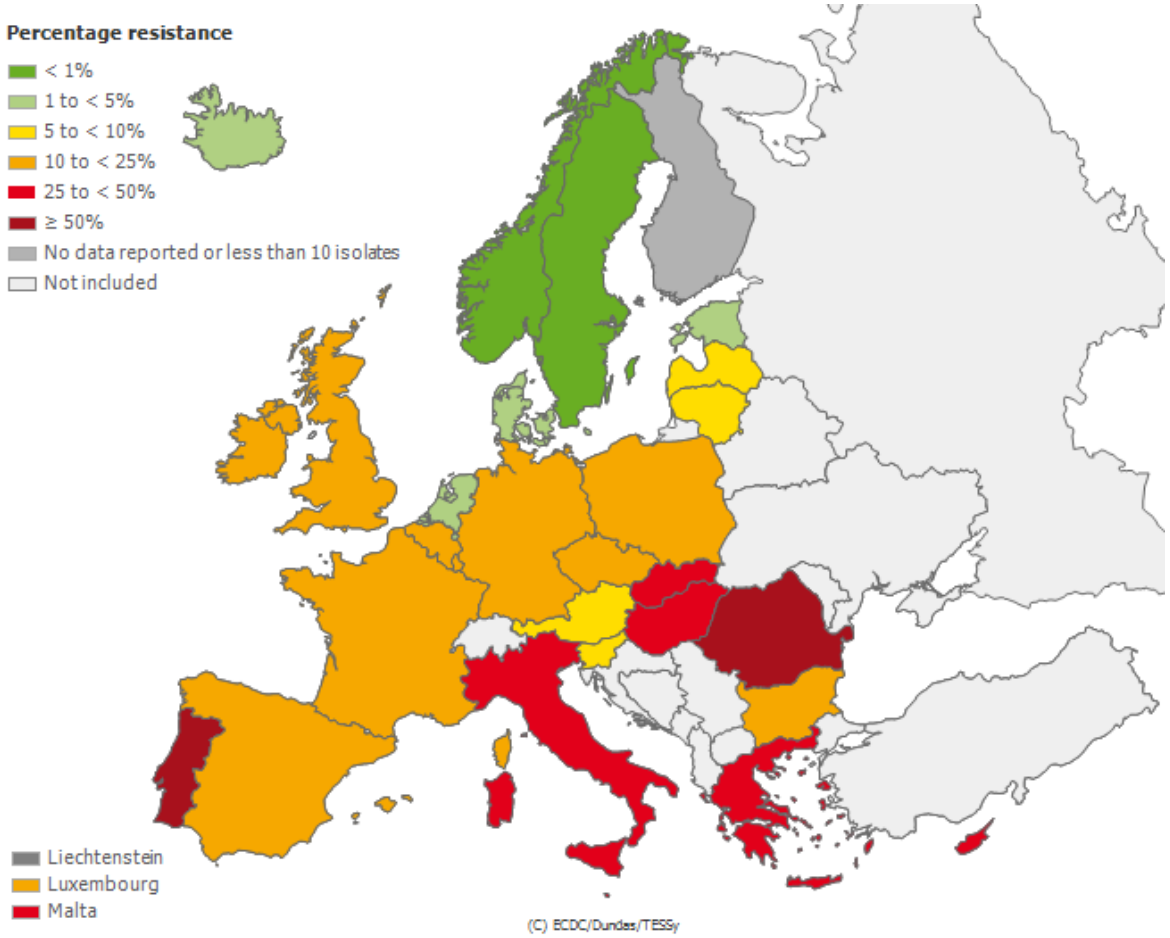
JAC

Does antibiotic exposure increase the risk of methicillin-resistant *Staphylococcus aureus* (MRSA) isolation? A systematic review and meta-analysis

Evelina Tacconelli*, Giulia De Angelis, Maria A. Cataldo, Emanuela Pozzi and Roberto Cauda

Results: Seventy-six studies, including a total of 24 230 patients, met the inclusion criteria. Antibiotic exposure was determined in the 126 ± 184 (mean ± SD) days preceding MRSA isolation. The risk of acquiring MRSA was increased by 1.8-fold [95% confidence interval (CI), 1.7–1.9; $P < 0.001$] in patients who had taken antibiotics. The RR for single classes of antibiotics was 3 (95% CI, 2.5–3.5) for quinolones, 2.9 (95% CI, 2.4–3.5) for glycopeptides, 2.2 (95% CI, 1.7–2.9) for cephalosporins and 1.9 (95% CI, 1.7–2.2) for other β-lactams. Significant heterogeneity was detected among studies. A regression analysis revealed that the heterogeneity was linked to the length of time in which antibiotic exposure was detected before MRSA isolation (more or less than 180 days).

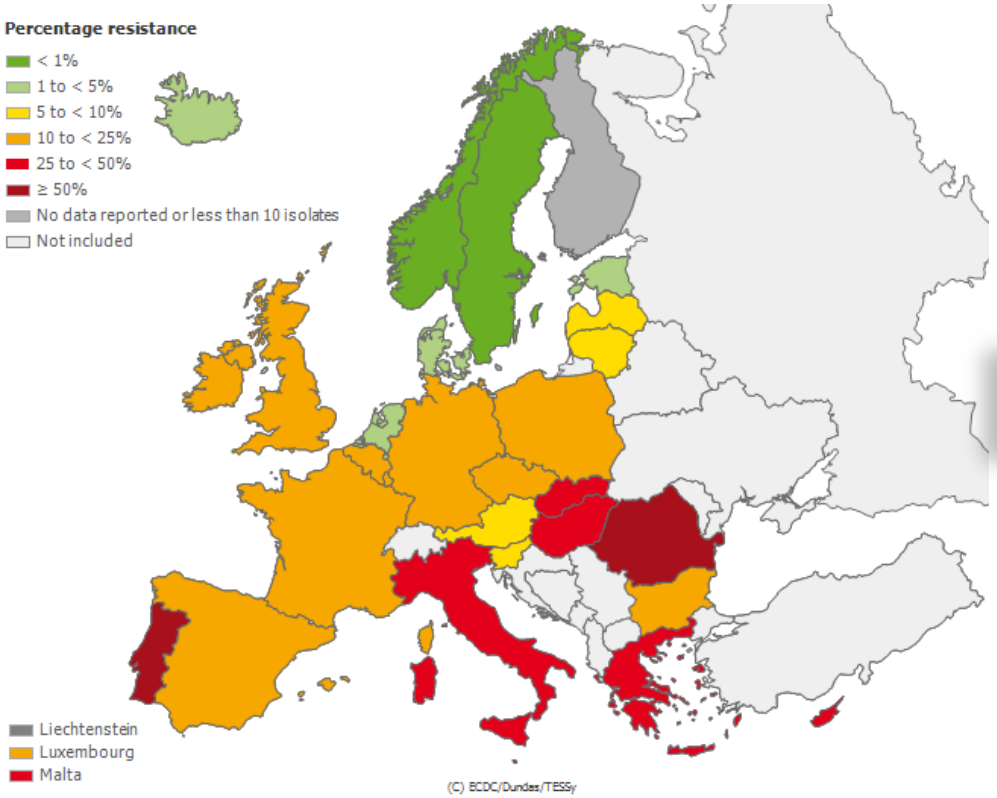
Učestalost izolovanja invazivne MRSA, EU 2012.



MRSA u EU - 5 zemalja 25-50%, 2 zemlje >50%

Učestalost izolovanja invazivne MRSA u Srbiji, 2013.

EARS-Net 2012. godina



MRSA u Srbiji - 2013. godina

42,8%

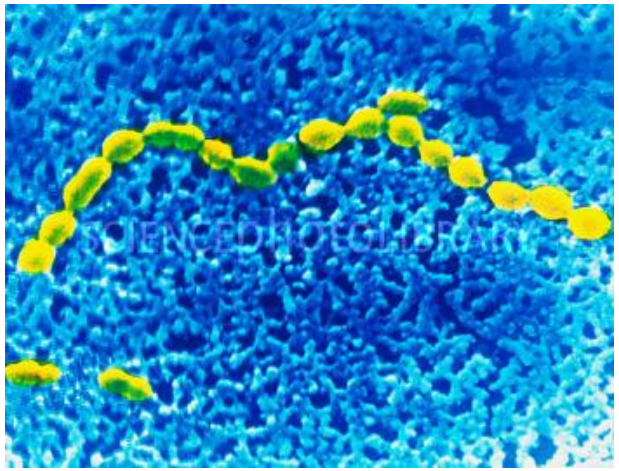
Rezistencija *S. aureus* na glikopeptidne antibiotike

Antibiotik	Godina uvođenja u kliničku upotrebu	Godina izolacije rezistentnih sojeva	Vreme do pojave rezistencije (godine)
Penicilin	1941.	1942.	1
Meticilin	1959.	1961.	2
Vankomicin	1958*, 1985	1996. (**VISA**) 2002. (**VRSA**)	38 44
Linezolid	2000.	2001.	1
Daptomicin	2003.	2005.	2

VISA – vankomicin intermedijarno osetljiv *S. aureus*
VRSA – vankomicin rezistentan *S. aureus*

Retko se izoluju u Evropi, ali predstavljaju pretnju u budućnosti !

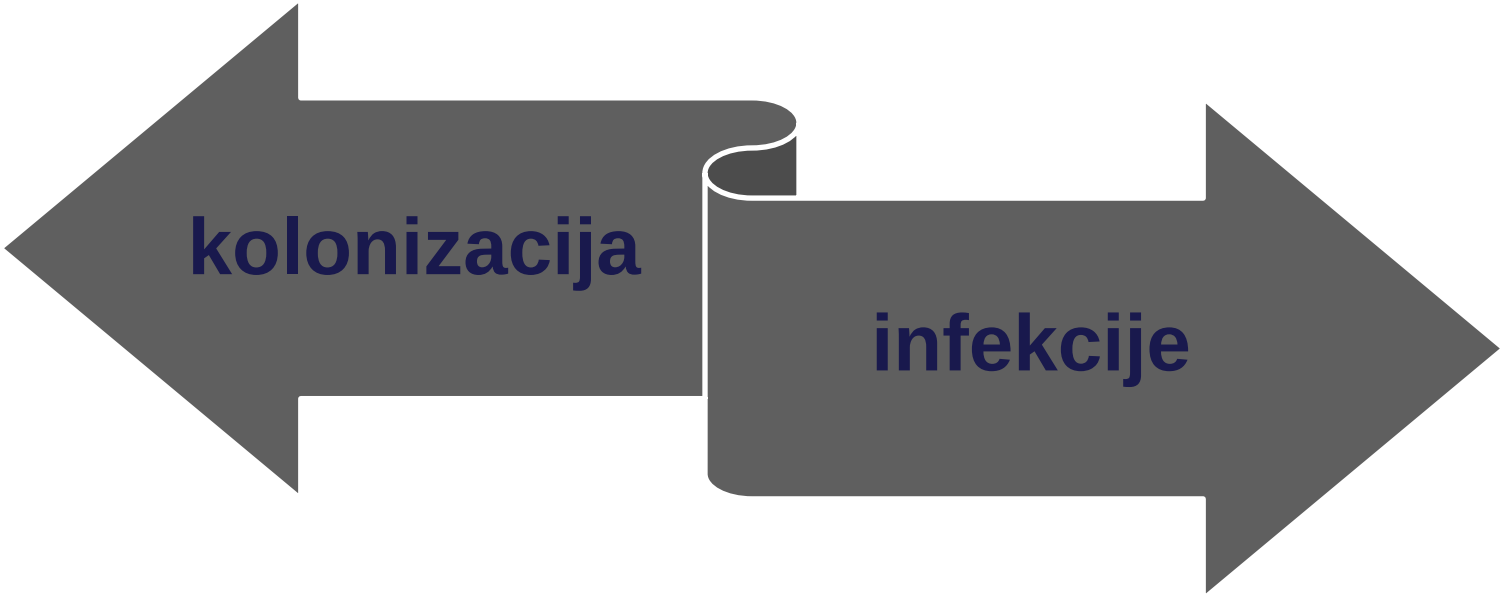
Enterococcus spp.



- 44 vrste
- najznačajnije vrste:
  - *E. faecalis* - 80-90%
  - *E. faecium* - 10-15%
  - ... - ≤ 5%

Enterococcus spp.

uslovno patogena bakterija



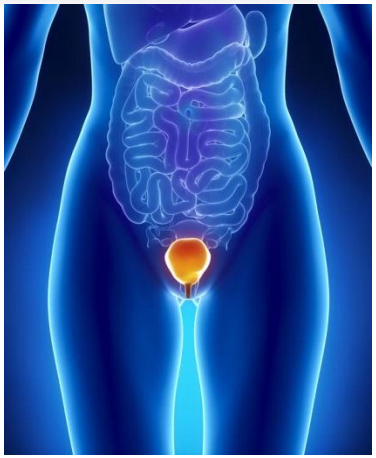
Enterococcus spp.

- kolonizacija

E. faecium u debelom crevu

  - **Čovek**
    - digestivni trakt (debelo crevo)
    - orofarings, vagina, koža, ...
  - **Životinje** (digestivni trakt)
  - **U zemlji, vazduhu, prašini**
  - **Razne površine** (bolnička, vanbolnička sredina)

Enterococcus spp.



Infekcije:

- vanbolnička sredina
  - urinarne infekcije
- bolnička sredina
  - urinarne infekcije (kateteri)
  - infekcije rana
  - endokarditis
  - intraabdominalne infekcije
  - bakterijemija/sepsa
  - meningitis
  - osteomijelitis
  - ...

Enterococcus spp. – rezistencija na antibiotike

NAJREZISTENTNIJA GRAM POZITIVNA BAKTERIJA:

a) urođena rezistencija

cefalosporini
aminoglikozidi (nizak nivo)
sulfonamidi
makrolidi
linkozamidi

b) stečena rezistencija

penicilini
aminoglikozidi (visok nivo)
glikopeptidi
fluorohinoloni

Enterococcus spp. – rezistencija na glikopeptidne antibiotike

krajem 1980. god.-Vankomicin rezistentan *Enterococcus* (VRE)

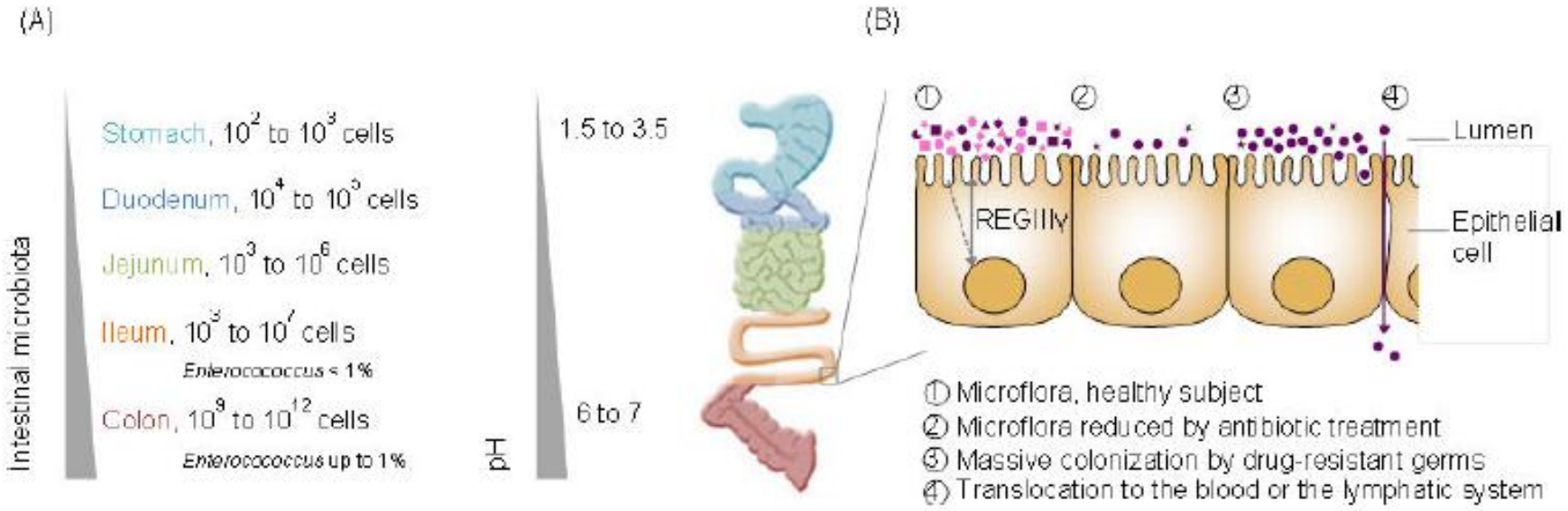
TABLE 1

Vancomycin resistance in enterococci. See cited reviews for details [96;97]

	Acquired resistance						Intrinsic resistance
phenotype	**VanA**	**VanB**	**VanD**	**VanE**	**VanG**	**VanL**	**VanC**
ligase gene	*vanA*	*vanB*[2]	*vanD*[2]	*vanE*	*vanG*[2]	*vanL*	*vanC*
MIC $_{vancomycin}$ in mg/L	16 - 1000	4 - 32 (-1000)	64 - 128	8 - 32	16	8	2 - 32
MIC $_{teicoplanin}$ in mg/L	(4-) 16 - 512	0,5 - 1	4 - 64	0,5	0,5	S	0,5 - 1
expression	inducible	inducible	constitutive	inducible	inducible	inducible	constitutive/ inducible
localisation	plasmid/ chromosome	plasmid/ chromosome	chromosome	chromosome	chromosome	chromosome?	chromosome
transferable by conjugation	+/-	+/-	-	-	+	-	-
distribution among enterococcal species	*E. faecium* *E. faecalis* *E. durans* *E. hirae* *E. gallinarum*[1] *E. casseliflavus*[1] *E. raffinosus* *E. avium* *E. mundtii*	*E. faecium* *E. faecalis* *E. durans* *E. gallinarum*[1]	*E. faecium* *E. faecalis* *E. raffinosus*	*E. faecalis*	*E. faecalis*	*E. faecalis*	*E. gallinarum: vanC1* *E. casseliflavus: vanC2/3*

[1] acquisition of *vanA* or *vanB* cluster in addition to *vanC1* or *vanC2/3* genes – rare event
[2] subtypes exist (*vanB*1-3, *vanD*1-5, *vanG*1-2); S, susceptible to teicoplanin (no value given in the corresponding paper)

Vankomicin rezistentni *Enterococcus* (VRE)

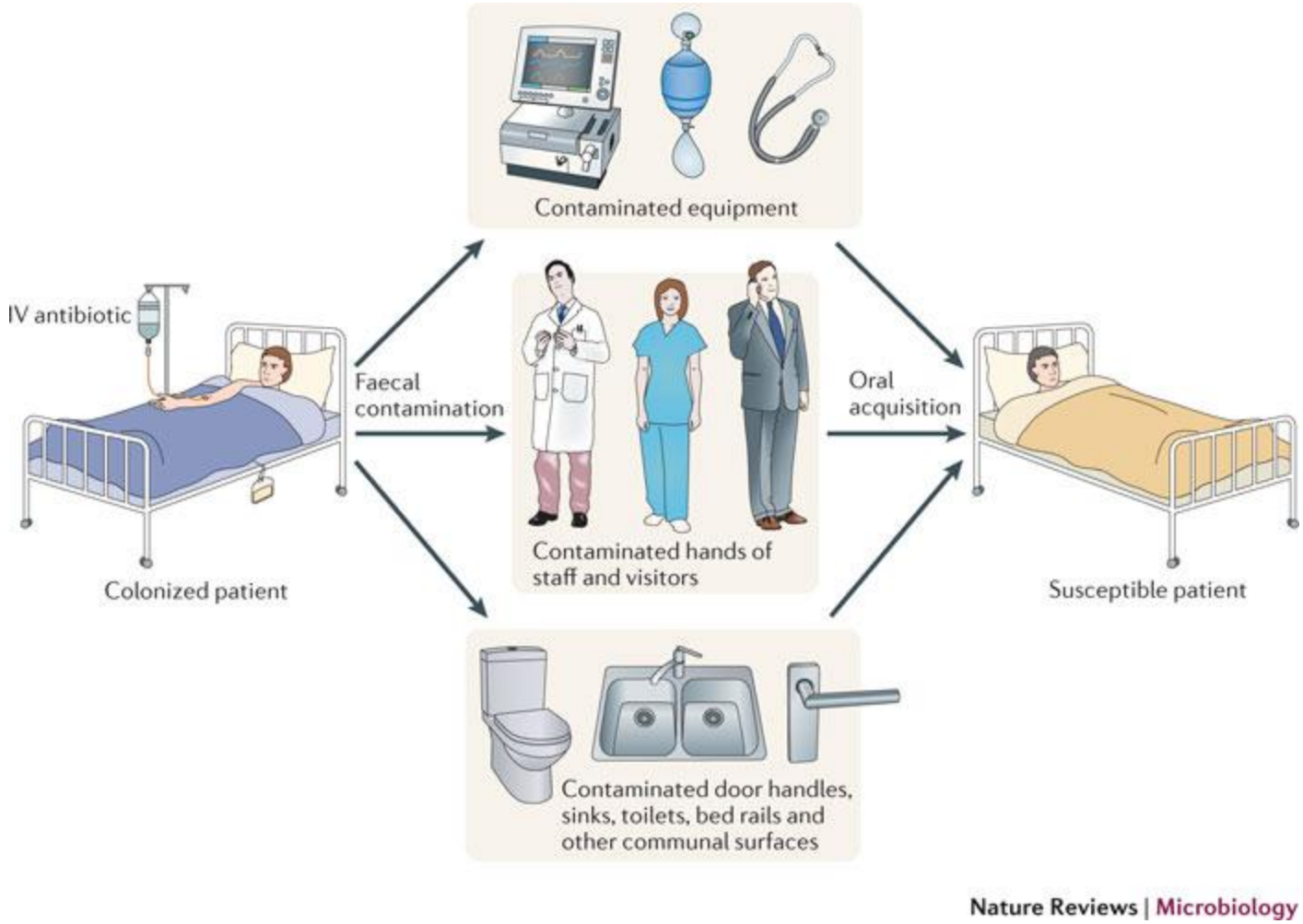


Neracionalna upotreba antibiotika = poremećaj sastava fiziološke flore
+ selekcija rezistentnih patogena

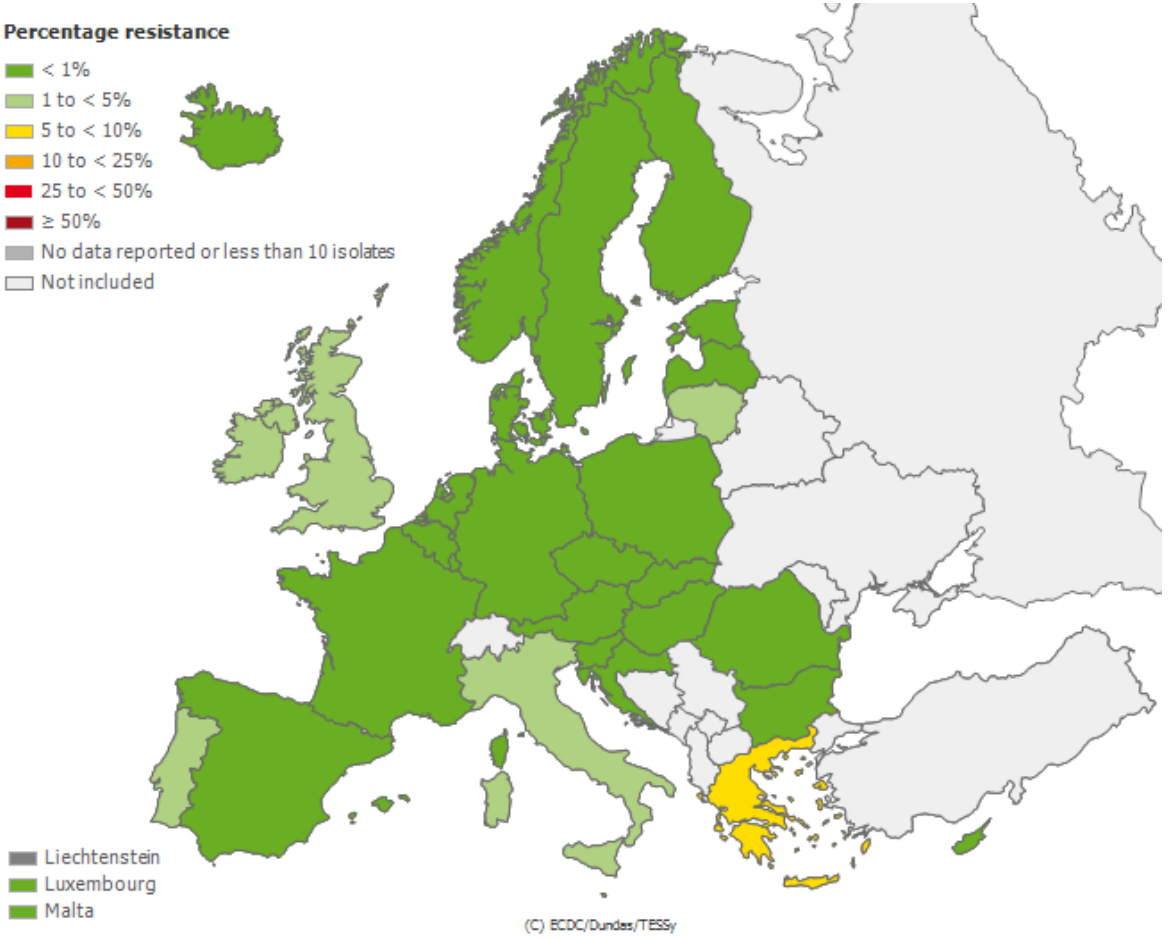
↓

diseminacija po organizmu

Vankomicin rezistentni *Enterococcus* (VRE)



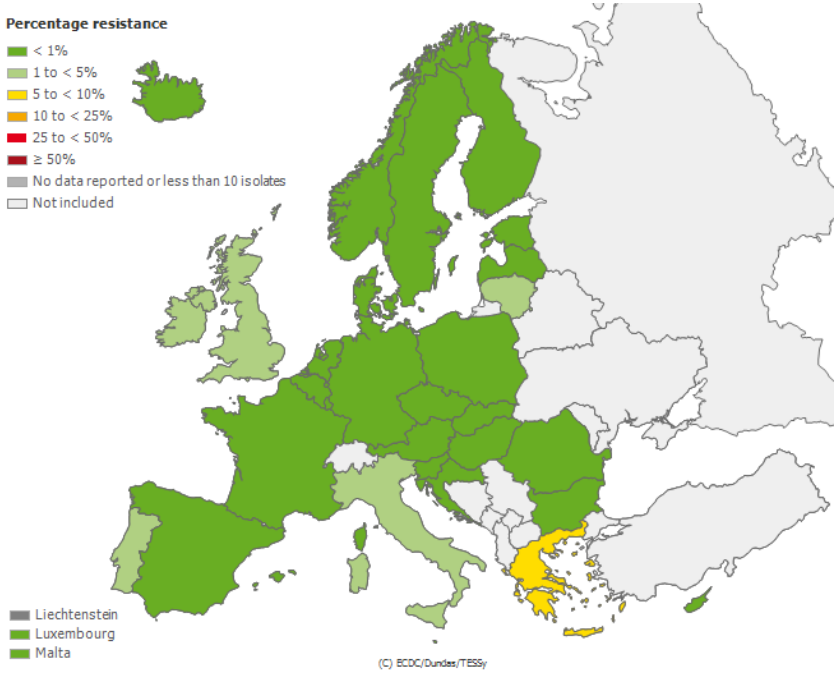
Invazivni VR *Enterococcus faecalis*, EU 2012.



VR *Enterococcus faecalis* u EU - 1 zemlja 5-10%

Invazivni VR *Enterococcus faecalis* u Srbiji, 2013.

EARS-Net 2012. godina

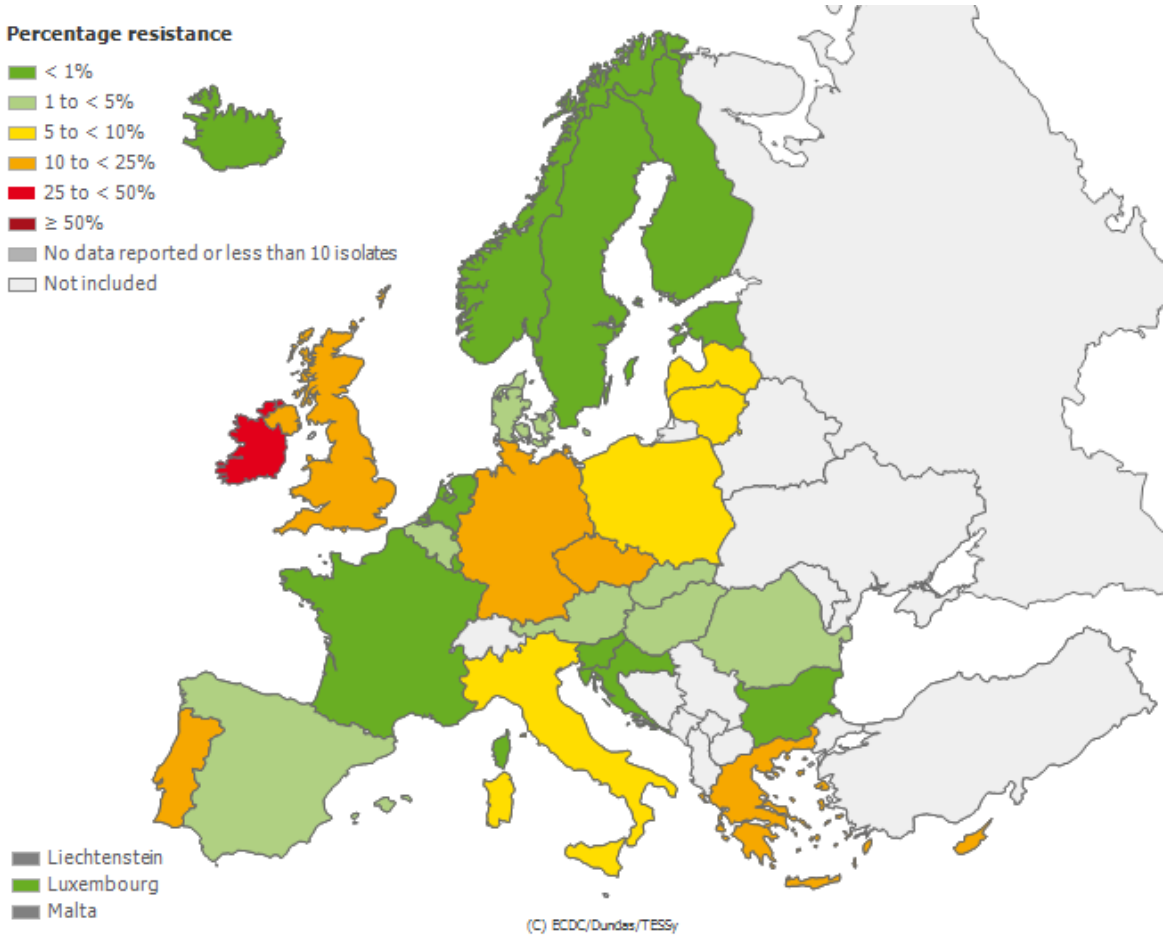


Grčka – 7%

u Srbiji - 2013. godina

7,3%

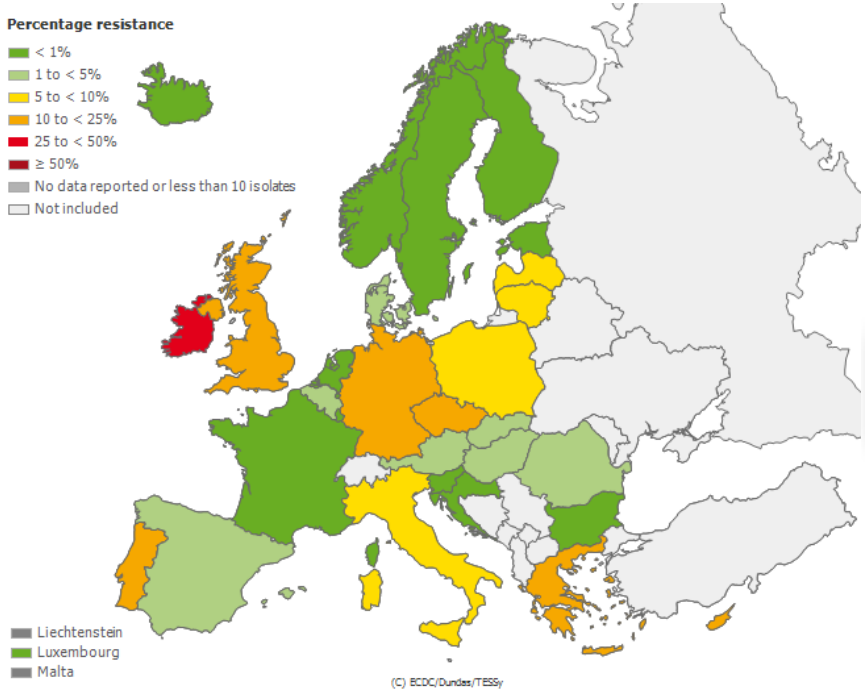
Invazivni *Enterococcus faecium*, EU 2012.



VR *Enterococcus faecium* u EU - 6 zemalja 10-25% i 1 zemlja 25-50%

Invazivni VR *Enterococcus faecium* u Srbiji, 2013.

EARS-Net 2012. godina



Irska – 44%

u Srbiji - 2013. godina

74,3%

ORIGINAL ARTICLE 10.1111/j.1469-0691.2008.02026.x

The dynamic relationship between antibiotic use and the incidence of vancomycin-resistant *Enterococcus*: time-series modelling of 7-year surveillance data in a tertiary-care hospital

E. I. Kritsotakis, A. Christidou, M. Roumbelaki, Y. Tselentis and A. Gikas

Laboratory of Clinical Bacteriology, Parasitology, Zoonoses and Geographical Medicine, University
Hc

ABSTRACT

The role of antibiotics in the epidemiology of vancomycin-resistant *Enterococcus* (VRE) has been studied extensively, but controversies remain as to which, and to what extent, antibiotics facilitate the emergence and dissemination of VRE in hospitals. Aggregate data on the use of several antibiotic classes in terms of defined daily doses (DDD) per 100 patient-days (PD), and VRE incidence rates in terms of clinical isolates per 1000 PD, were evaluated during a 7-year period at a tertiary-care hospital. Time-series analysis (autoregressive integrated moving average (ARIMA) and transfer function models) was used to quantify the temporal effect of antibiotic use on VRE incidence and estimate effect-delays. The incidence rate of VRE observed in a specific bimester was found to be a function of its value during the preceding bimester and of prior changes in the volume of use of four antibiotic classes. In particular, an increase of one DDD/100 PD in the use of glycopeptides, fluoroquinolones, extended-spectrum cephalosporins and β-lactam–β-lactamase inhibitor combinations resulted, independently, in average changes of +0.024, +0.015, + 0.020 and −0.010 isolates per 1000 PD in the incidence of VRE, with average delays of 2, 4, 2 and 6 months, respectively, which explained 56% of the observed variation in VRE rates over time. Efforts to reduce VRE cross-transmission should be supplemented by targeted antibiotic control policies. The use of glycopeptides, broad-spectrum cephalosporins and fluoroquinolones in high amounts should be the targets of such policies. Penicillin–β-lactamase inhibitor combinations might be suitable substitutes for extended-spectrum cephalosporins.

Streptococcus pneumoniae

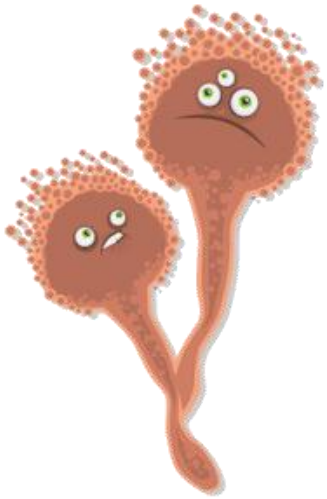
- striktno patogena bakterija
- humani patogen

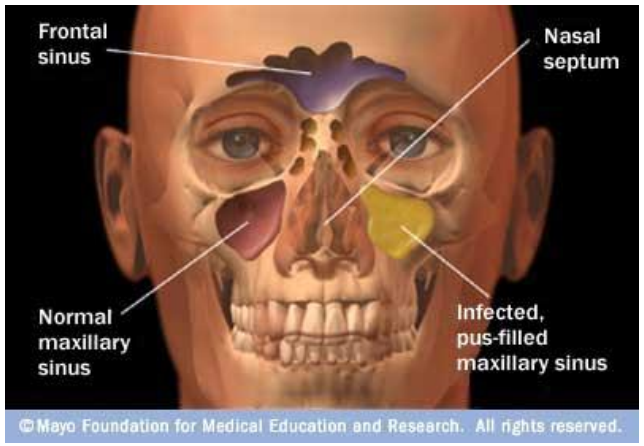
Nazofaringealno kliconoštvo kod odraslih i dece (čak do 40%)

Streptococcus pneumoniae

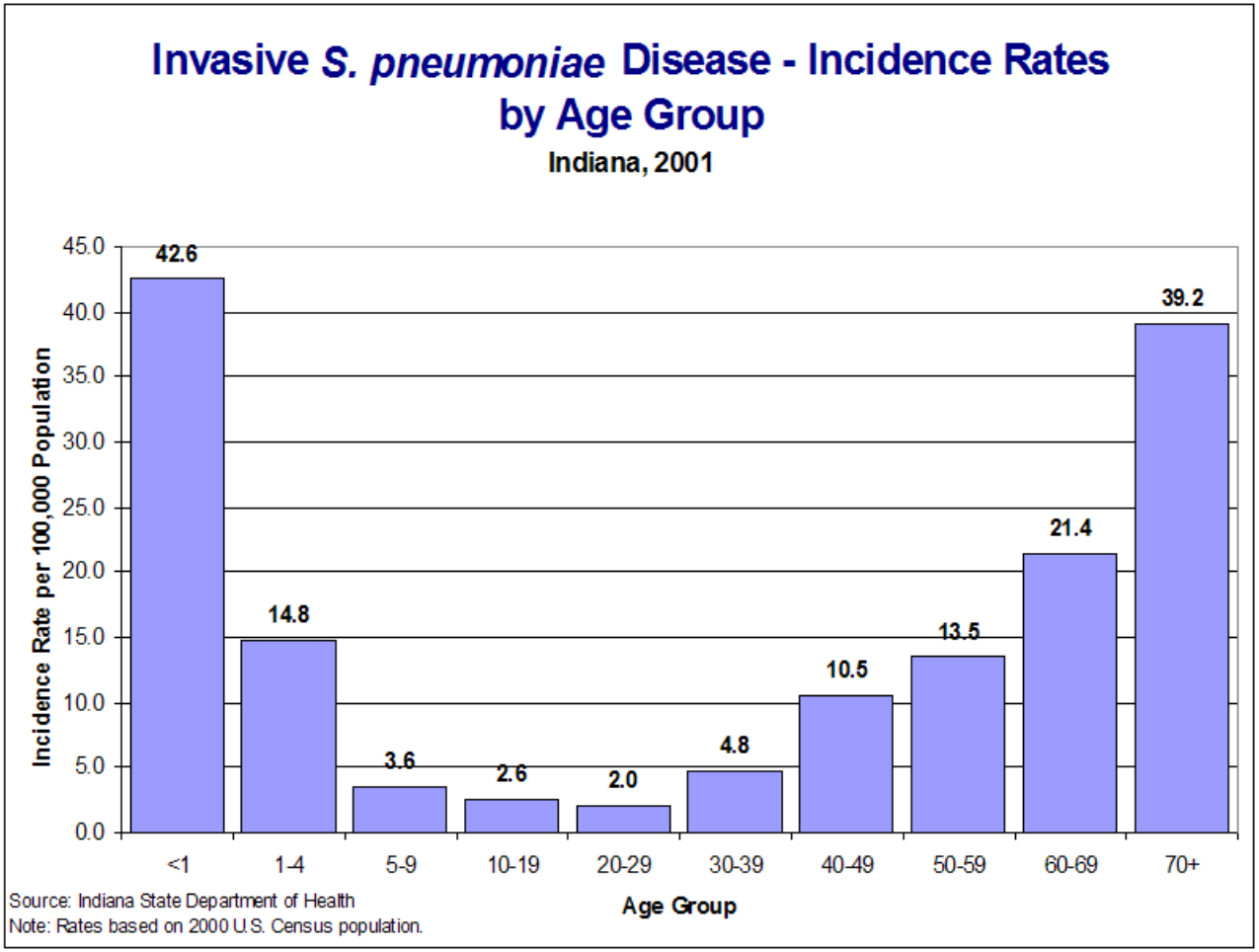
Oboljenja:

- otitis media
- sinuzitis
- pneumonija
- sepsa
- meningitis





Streptococcus pneumoniae



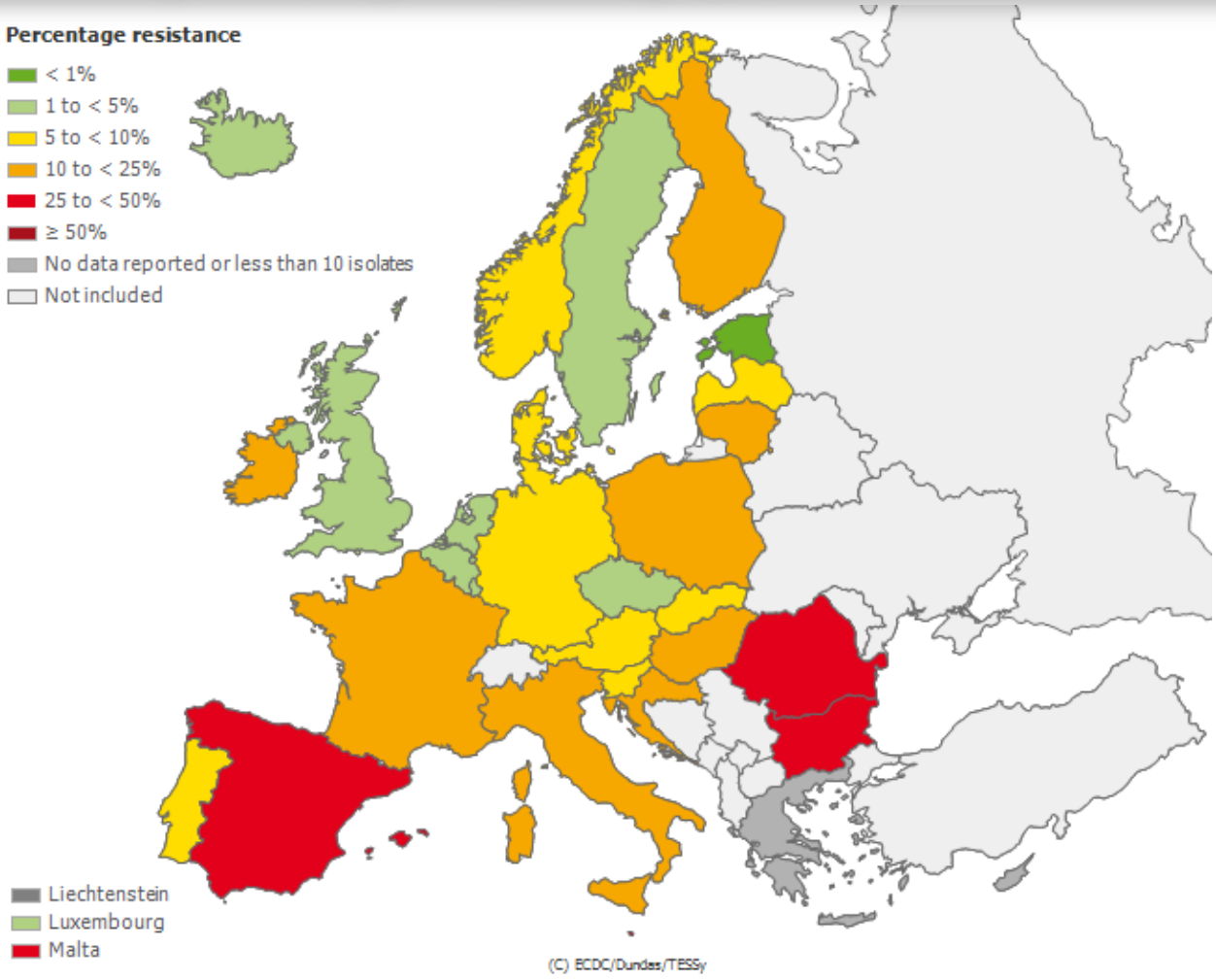
Penicilin neosetljiv *S. pneumoniae* (PNSP)

- Registrovani prvi put početkom 1990.- ih
  - penicilin-intermedijarno osetljivi *S. pneumoniae* (PISP)
  - penicilin-rezistentan *S. pneumoniae* (PRSP)

Mehanizam rezistencije:
Izmena penicilin-vezujućih proteina (PBP)

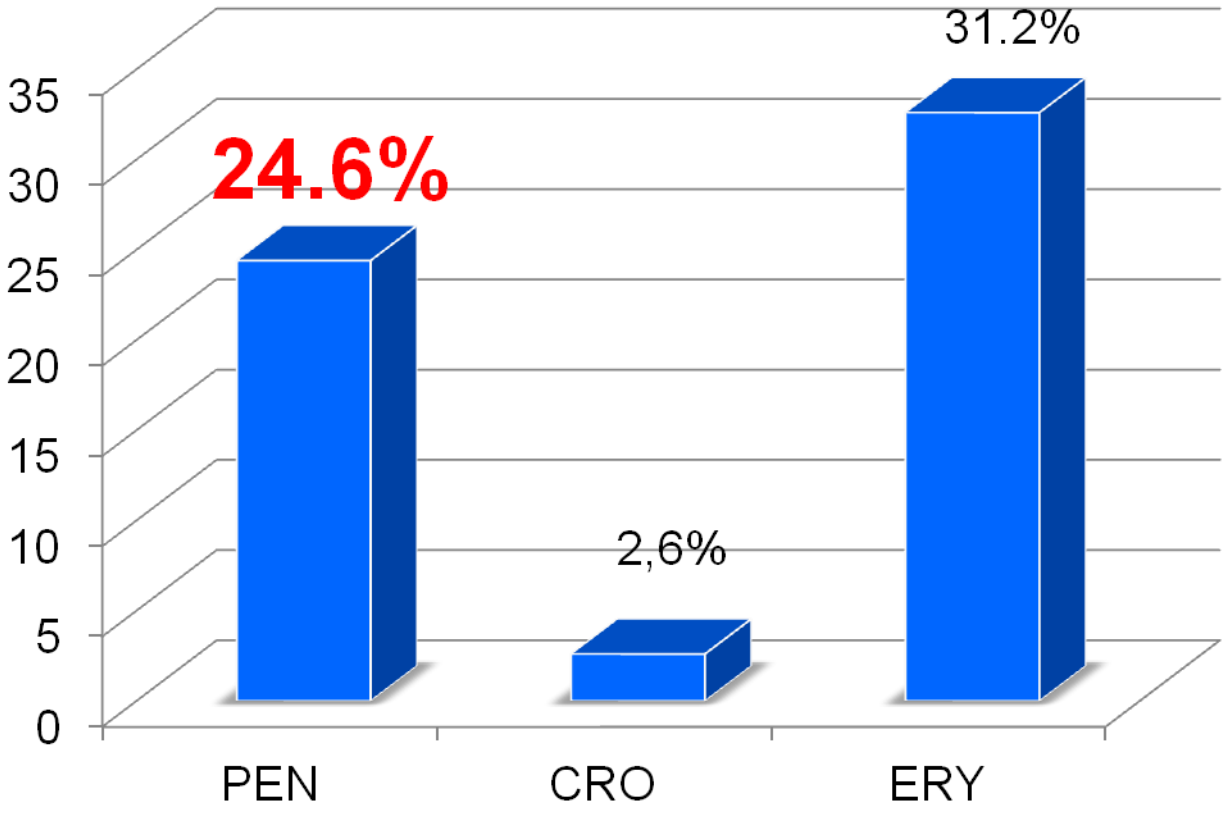
Značaj tipa neosetljivosti:
Neinvazivne infekcije + pneumonije izazvane PISP mogu se uspešno lečiti penicilinima

Invazivni penicilin neosetljiv *S. pneumoniae* (PNSP) u Evropi, 2012.



<1 u jednoj zemlji, 1–5% u sedam zemalja,5–10% u sedam zemalja, 10–25% u devet zemalja i 25–50% u četiri zemlje

Invazivni penicilin neosetljiv *S. pneumoniae* (PNSP) u Srbiji, 2013.



PEN	**Penicillin**
CRO	**Cefriakson**
ERY	**Eritromicin**

Broj izolata: 47

S. pneumoniae

•najznačajniji uzročnik bakterijskih vanbolničkih pneumonija
•značajan uzročnik invazivnih infekcija

Terapija u zemljama sa visokom stopom PNSP:
1. makrolidi
2. fluorohinoloni
(levofloksacin, moksifloksacin)

SELEKTIVNI PRITISAK

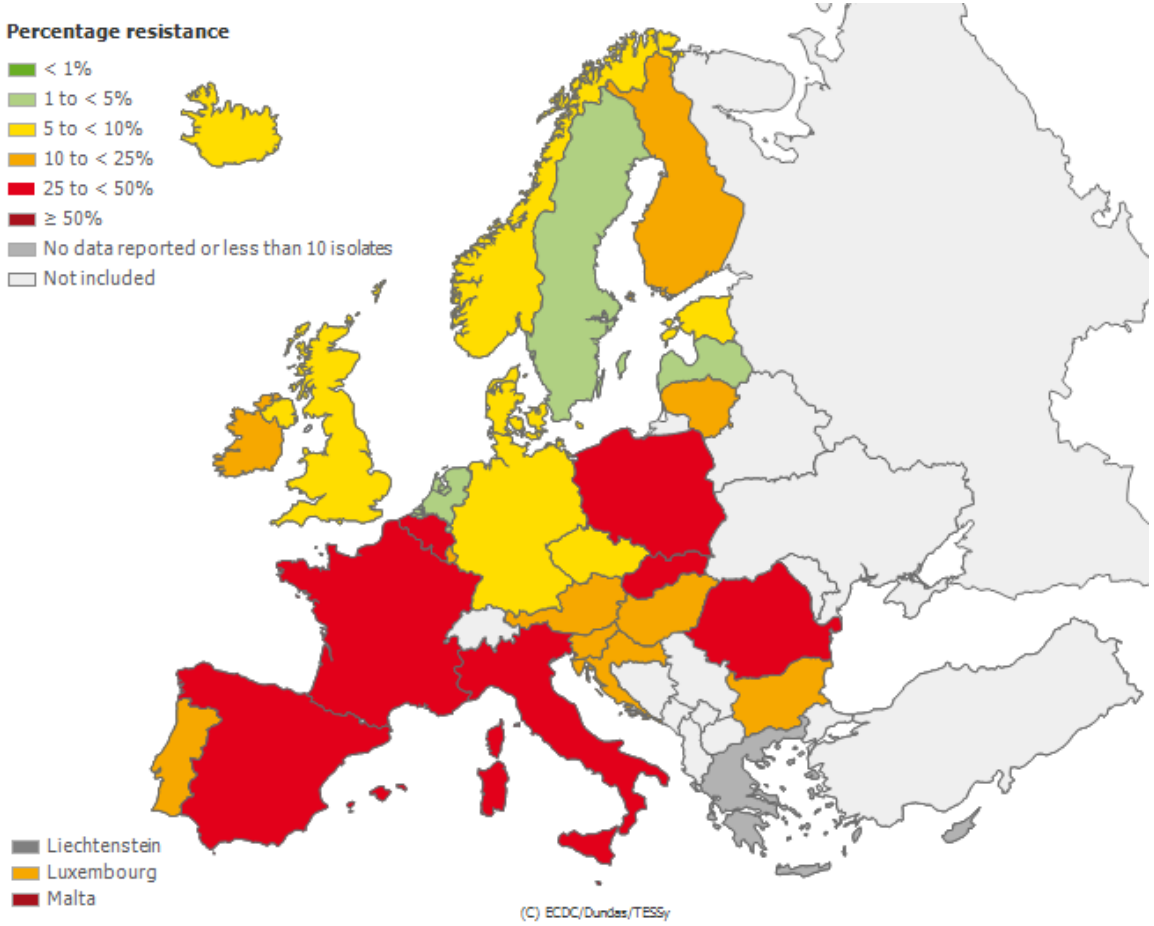
S. pneumoniae rezistencija na MLS

Makrolidi, linkozamidi, streptogramini (MLS)

Stečena rezistencija:

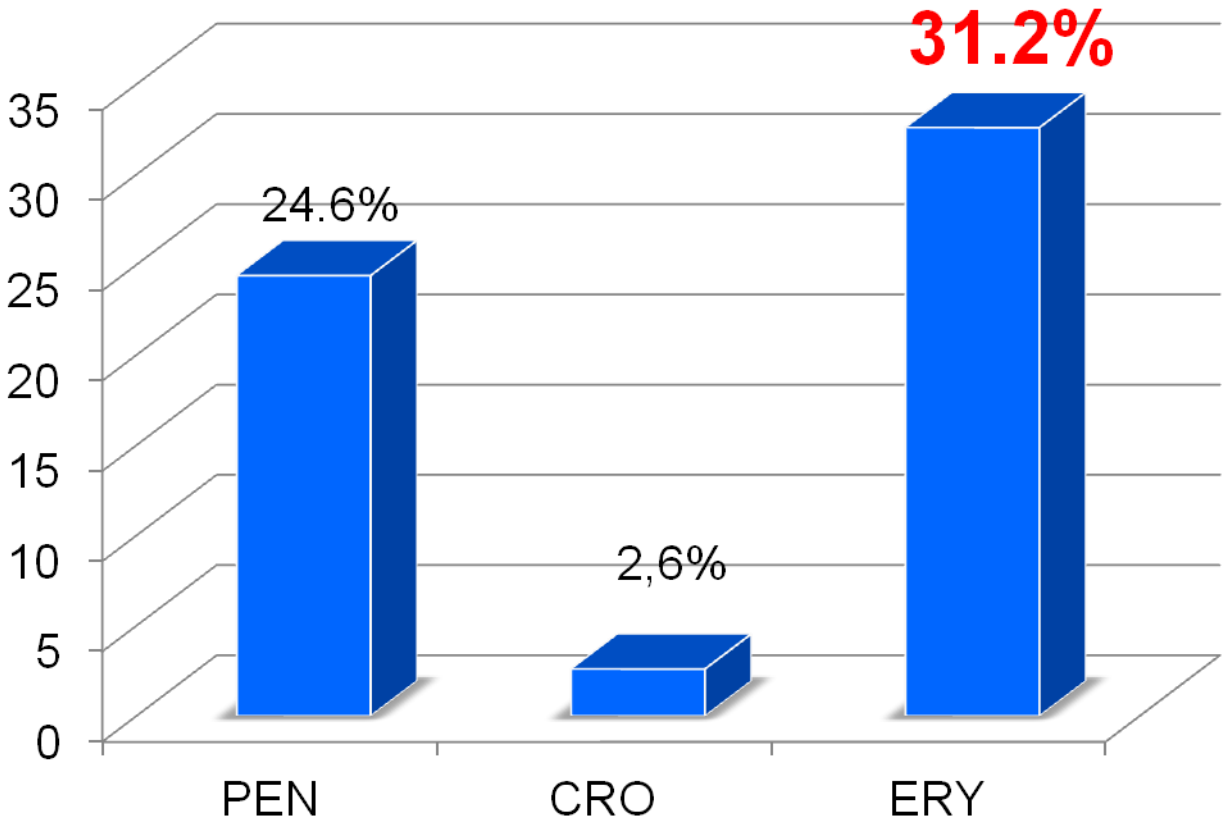
1. ***erm*** (erithromicin ribozomni methilacioni) **gen**
2. ***mef*** (makrolidi efluks sistem) **gen**

MLS rezistencija kod *S. pneumoniae* u Evropi, 2012.



<1 u tri zemlje, 1–5% u sedam zemalja,5–10% u sedam zemalja, 10–25% u osam zemalja i 25–50% u deset zemalja.

MLS rezistencija kod *S. pneumoniae* u Srbiji, 2013.



PEN	**Penicillin**
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Broj izolata: 47

S. pneumoniae
dvostruka (unakrsna) rezistencija

kod sojeva *S. pneumoniae* nađenih kod dece!

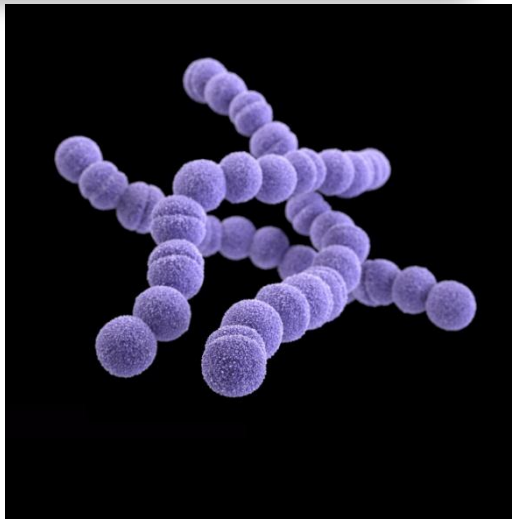
beta-laktami + makrolidi

Povećanje upotrebe jedne grupe antibiotika dovodi i do povećanja rezistencije i na drugu grupu antibiotika

↑ **MAKROLIDI =** ↑ **rezistencije na beta-laktame i makrolide**

Streptococcus pyogenes
BHS grupa A

- striktno patogena bakterija
- humani patogen



Orofaringealno kliconoštvo kod odraslih i dece (do 15%)

Streptococcus pyogenes
BHS grupa A

1. piogena oboljenja (tonzilofaringitis, infekcije kože i mekih tkiva, invazivne infekcije...)
2. toksemična oboljenja (šarlah, TŠS)
3. poststreptokokne nesupurativne sekvele (reumatska groznica, akutni glomerulonefritis)

S. pyogenes

do sada nije registrovana rezistencija na peniciline

alternativna terapija – makrolidi!

S. pyogenes
rezistencija na MLS

Makrolidi, linkozamidi, streptogramini (MLS)

Stečena rezistencija:

1. ***erm*** (erithromicin ribozomni methilacioni) **gen**
2. ***mef*** (makrolidi efluks sistem) **gen**

S. pyogenes
rezistencija na MLS u Evropi

TABLE

Invasive group A streptococcal infection surveillance in Europe, 1990 onwards

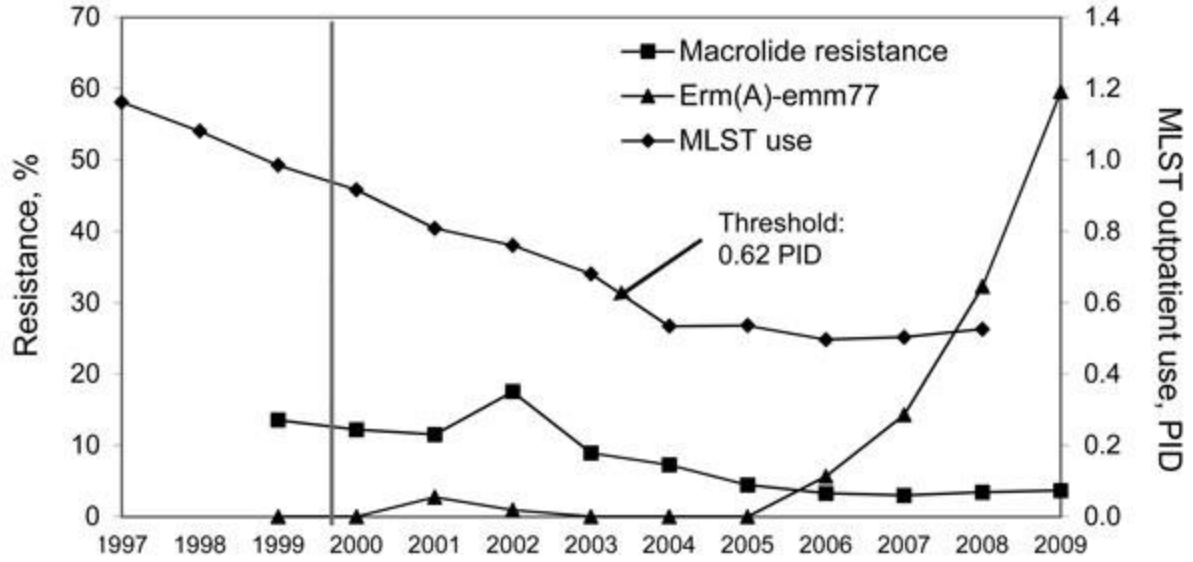
Country	Surveillance methods				Latest estimates		References
	Surveillance period*	Coverage	Surveillance method/s	Clinical information available	Incidence per 100 000 (year)	Macrolide resistance (year)	
Belgium	1994-	National	Microbiology laboratory reports	No	1.0 (2003)	na	[34;67]
	1994-	National	Isolates submitted to reference laboratory	No	na	8.9% (1997)	
Czech Republic	1994-98	National	Isolates submitted to reference laboratory	Yes	0.40 (1994-98	na	[56]
Denmark	1969-	National	Isolates submitted to reference laboratory	Yes	3.30 (1998)	1.8% (2003)	[32;68]
Finland	1988-96	National	Isolates submitted to reference laboratory	No	na	4.5% (1996)†	[27;69]
	1995-	National	Microbiology laboratory notifications + isolates submitted to reference laboratory	No	2.27 (2003)†	na	
France	1998-	National	Isolates submitted to reference laboratory (invasive & non invasive GAS)	Yes	na	23% (2002)†	[40] [33;70;71]
	1987-	National	Microbiology laboratory reports	No	1.7 (2002)†	na	
Hungary	1975-	National	Microbiology laboratory reports (invasive & non invasive GAS)	No	1.3 (2002)†	na	[72]
Iceland	1975-	National	Microbiology laboratory reports	No	3.8 (1996-02	na	[36]
Israel	1980-	Regional	Clinical & microbiology laboratory reports	Yes	4.8 (1990-94	2.2% (1987-94)	[61]
Italy	1993-	National	Microbiology laboratory reports (invasive & non invasive GAS)	Yes	0.06 (1994-96	32% (1994-96)	[39]
Netherlands	1992-03	National	Isolates submitted to reference laboratory	Yes	3.1 (2002)	na	[17]
Norway	1975-	National	Notification through laboratory	Yes	3.3 (2002)	na	[30]
Portugal	1998-99	Sentinel sites	Isolates submitted to reference laboratory	No	na	11% (1998-99)	[42]
Russia	2000-01	Sentinel sites	Isolates submitted to reference laboratory (invasive & non invasive GAS)	Yes	na	11% (2000-01)	[41]
Sweden	1989-	National	Microbiology laboratory reports + isolates submitted to reference laboratory	Yes	2.9 (2000)	na	[28;29;55]
United Kingdom	1975-	England, Wales, Northern Ireland	Microbiology laboratory reports	No	3.5 (2003)†	4% (2003)	[24;25;73] [54]
	1988-	Scotland	Microbiology laboratory reports	No	3.6 (2002)†	na	
	1980-	National	Isolates submitted to reference laboratory	Yes	na	5% (1994-97)	

* The dash indicates still ongoing
† Blood ± CSF only
na= not available/applicable

MLS rezistencija kod *S. pyogenes* u Srbiji

18,6%

Antimicrobial Drug Use and Macrolide-Resistant *Streptococcus pyogenes*, Belgium



Zaključak

Rezistencija Gram pozitivnih bakterija na antibakterijske lekove je globalni problem!

U Evropi, Srbija spada u red zemalja sa najvišom stopom rezistencija Gram pozitivnih bakterija na antibakterijske lekove!

Hvala na pažnji!