Могућности концепта примене пробиотика у превенцији резистенције на антибиотике

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ANTIBIOTICI I MORTALITET

1900

- **TBC**
- **pneumonia**
- **dijareja**
- bolesti srca
- bolesti jetre
- povrede
- mozdani udar
- kancer
- bronchitis
- Difterija

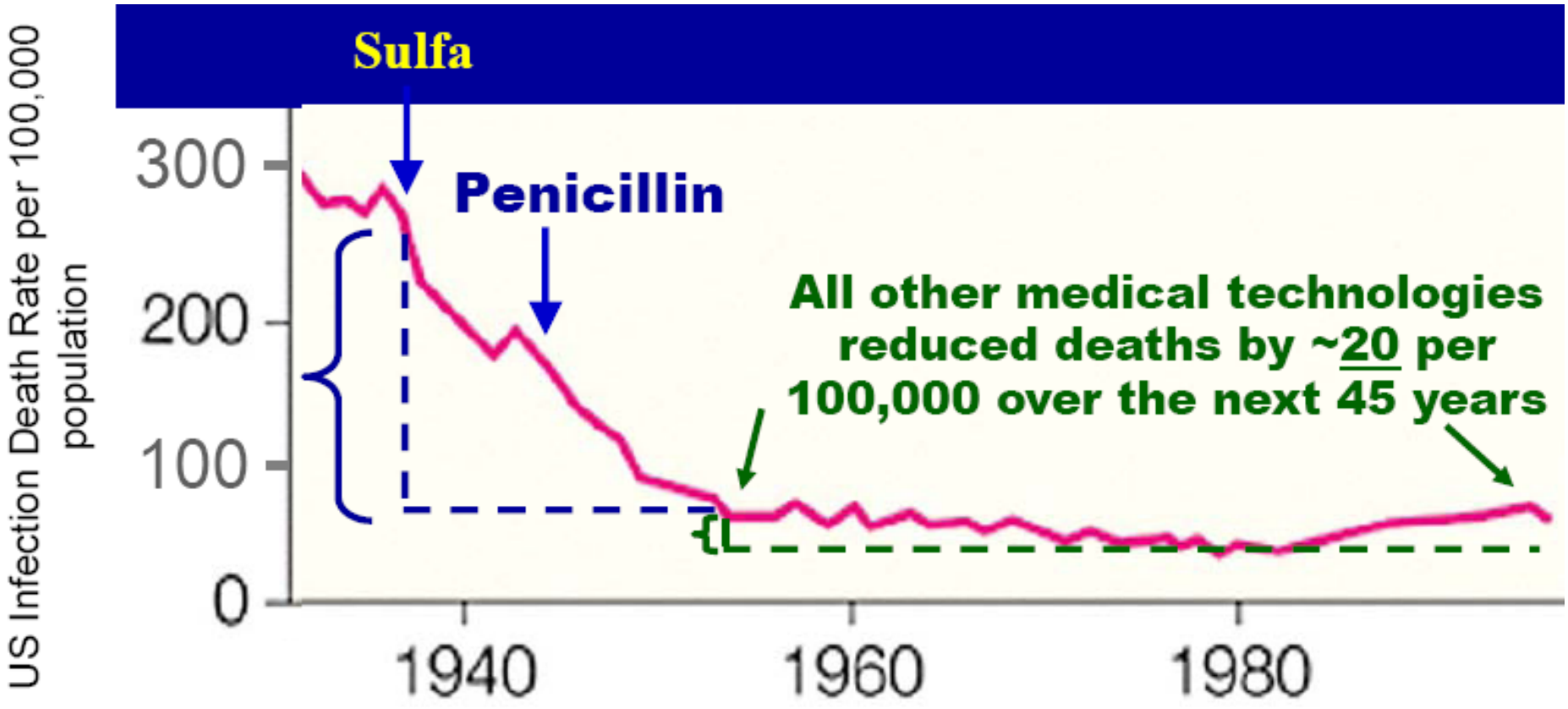
2000

- Bolesti srca
- Kancer
- Mozdani udar
- Hronicne plucne bolesti
- Povrede
- **Pneumonija**
- Dijabetes
- Suicid
- Hronicne bolesti bubrega
- Hronicne bolesti jetre

Prosecna starost 52 god.

Prosecna starost 76 god.

Za 15 godina antibiotici su smanjili smrtnost od infektivnih bolesti za ~220 na 100,000



Armstrong, G. L. et al. JAMA 1999;281:61-66.

Za 15 godina antibiotici su smanjili smrtnost od infektivnih bolesti za ~220 na 100,000

Bacterial Infection	Mortality Rate		
	Pre-Abx	Abx	Difference
CAP	23%	7%	-16%
HAP	60%	30%	-30%
Endocarditis	100%	25%	-75%
Meningitis	>80%	<20%	-60%
Skin infections	11%	<5%	-10%
Acute MI aspirin, streptokinase – 3%			

Armstrong, G. L. et al. JAMA 1999;281:61-66.

Najčešće infekcije u primarnom zdravstvu regiona Niš i upotreba antibiotika

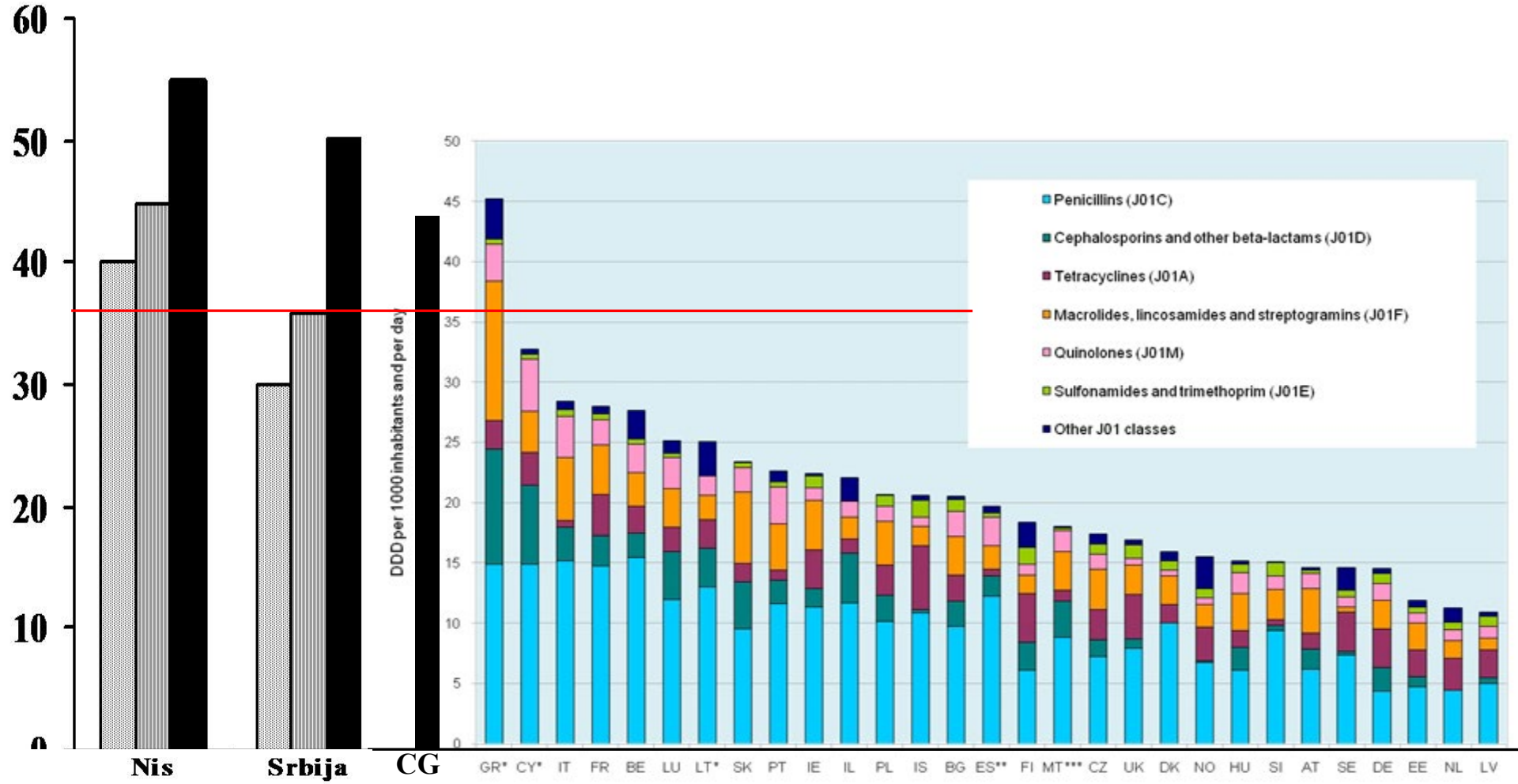
ICD (X revision)	Diagnosis	DID	Number of prescriptions	%	PID
J02	Pharyngitis acuta	11.53	503.470	45.26	3.94
J03	Sinusitis acuta	3.92	182.840	16.44	1.43
J20	Bronchitis acuta	2.36	115.920	10.42	0.91
N30	Cystitis	2.21	116.770	10.52	0.91
N39	Morbitractus urinarii allii	1.28	54.270	4.88	0.42
J03	Tonsilitis acuta	0.71	33.000	2.93	0.25
	Other	2.56	106.000	9.44	0.83
	Total	24.57	1.112.270	100	8.69

ICD – international classification of diseases, DID - defined daily doses per 1000 inhabitants/day
PID – number of packages per 1000 inhabitants/day

R.Velickovic Radovanovic et al Outpatients antibiotic use in primary heathcare of Nis region. Acta fac med naiss 2010
Agencije za lijekove Crne Gore, 2009

UPOTREBA ANTIBIOTIKA

Radmila Veličković-Radovanović et al., ACTA FAC MED NAISS 2010;27(1):27- 32



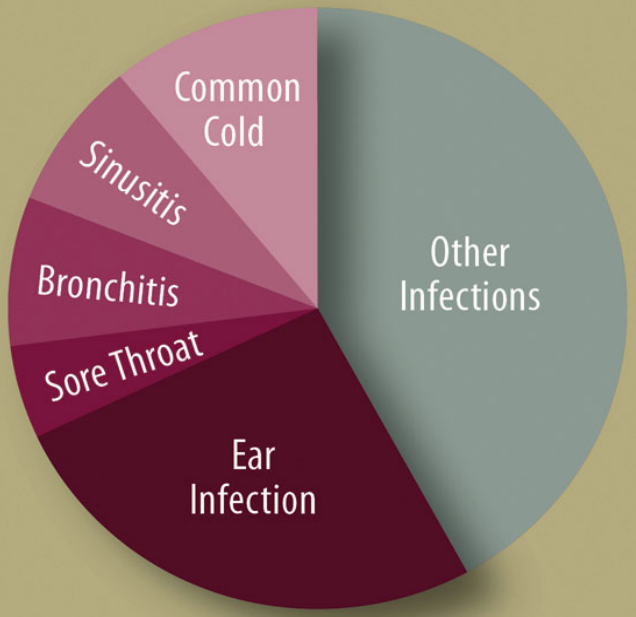
2008.

Good News / Bad News

Antibiotics prescribed for acute respiratory infections in kids younger than 15 years of age

*Comparing 1993–94 to 2007–08

Still account for 58% of all antibiotics prescribed

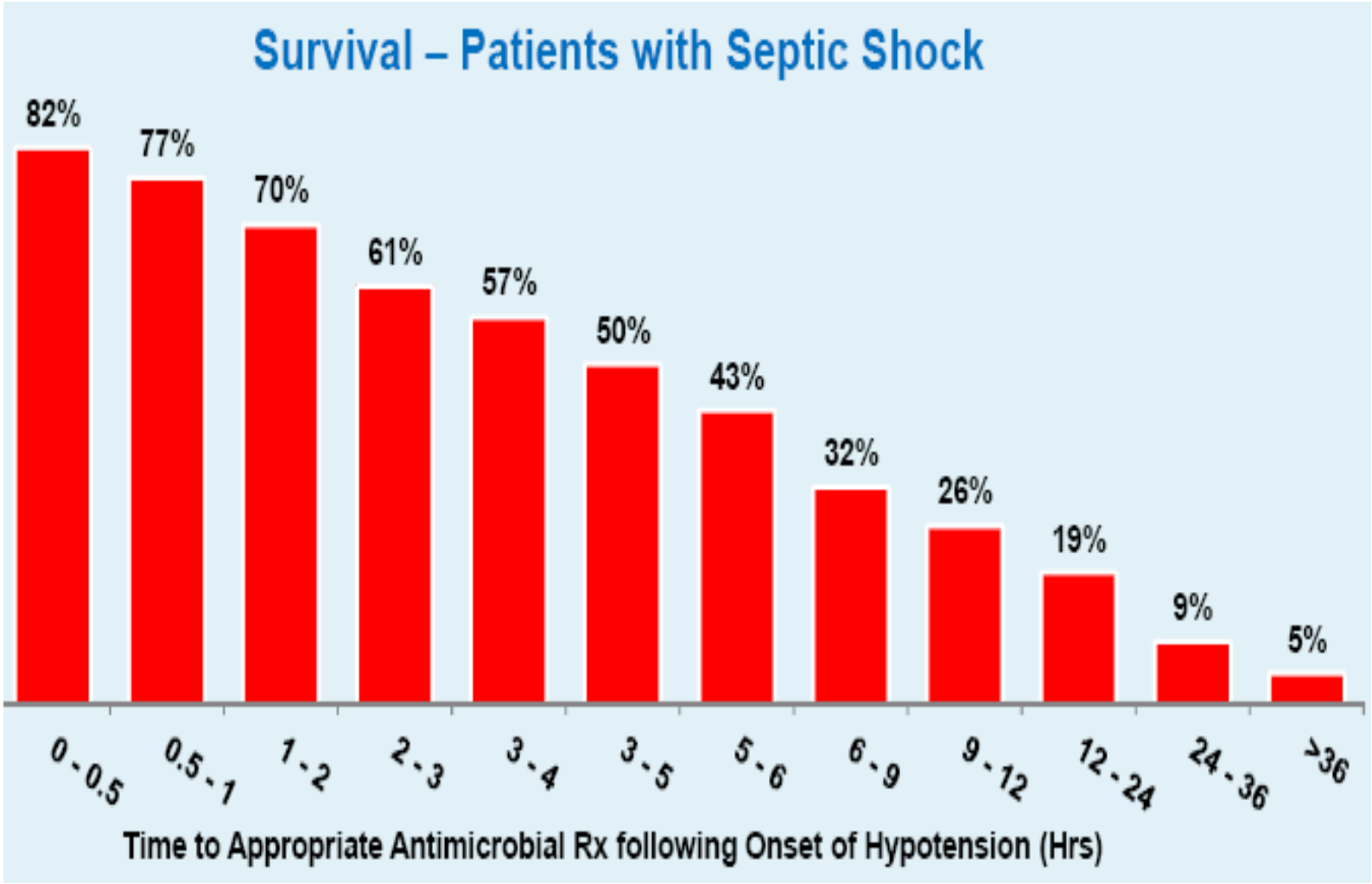


Most of these acute respiratory infections do not require antibiotic treatment; patients may benefit from symptomatic therapy

Source: MMWR. 2011;60:1153-6

CDC - **Morbidity and Mortality Weekly Report (MMWR)**, **2011**

EARLY, APPROPRIATE ANTIBIOTICS THERAPY IS THE KEY FOR SURVIVAL!



Kumar et al.Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Crit Care Med. 2006 Jun;34(6):1589-96.

The effect of the unappropriate therapy in ESBL bacteriemia

Could We Return to the Preantibiotic Era?

128 bacteriemia

- 80 (63%) E. coli
- 28 (22%) K. pneumo
- 20 (16%) P mirbailis

Appropriate therapy

- 54% carbapenems
- 16% other drugs

Mortality (P=0.05)

- 14.9% Appropriate Th
- 35.2% Unappropriate Th

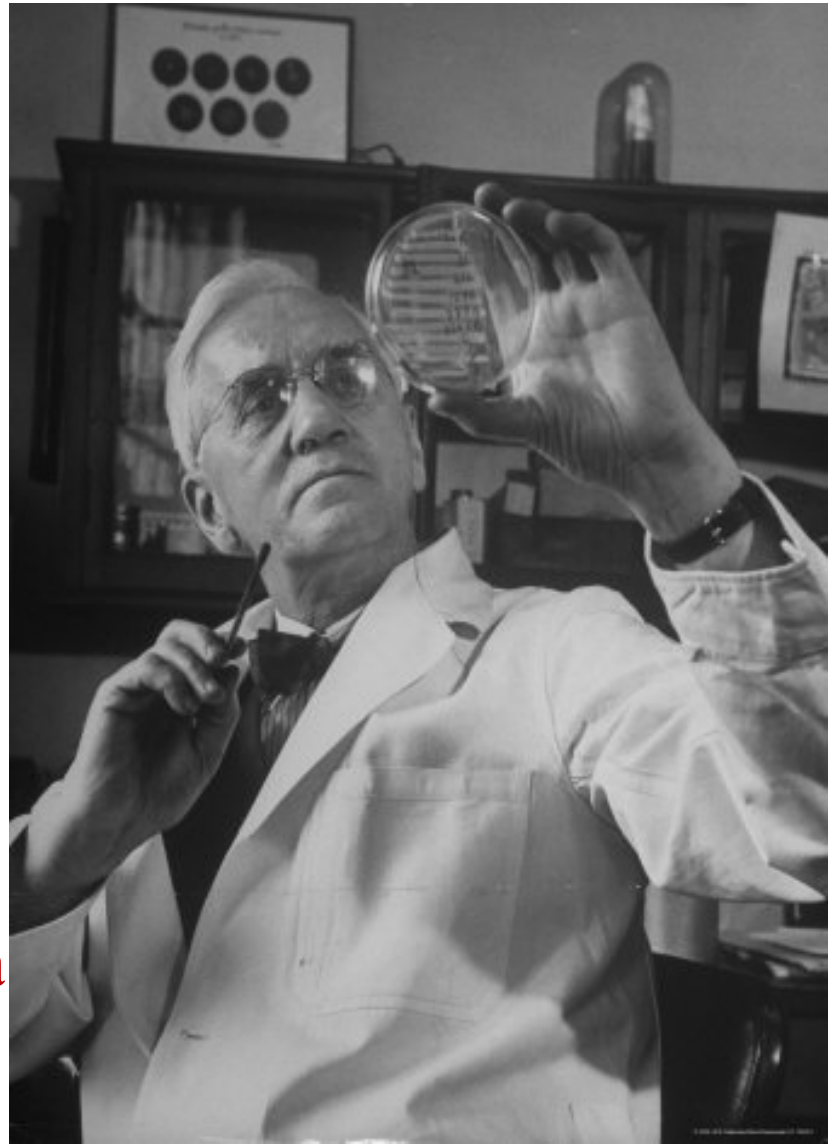
De Rosa et al. 2011; Infection 39:555

REZISTENCIJA

UKOLIKO RAST BAKTERIJA NIJE UGROŽEN NI U PRISUSTVU NAJVEĆE MOGUĆE KONCENTRACIJE LEKA KOJU PACIJENT MOŽE DA PODNESE

REZISTENCIJA

- **1946. (pa i sam Fleminga) na moguću opasnost od rezistentnih bakterija**
- **Eradikacija nije ostvarena zbog razvoja REZISTENCIJE**
- **Razvoj i uvođenje novih antibiotika prati pojavu rezistentnih sojeva**
- **Brzo od primene penicilina javila se rezistencija kod 85% sojeva *Staphylococcus aureus*-a**



Neadekvatna upotreba antibiotika

Loša upotreba vodi ka rezistenciji:

- *Escherichia coli*
- *Staphylococcus aureus*
- *Klebsiella pneumoniae*
- *Acinetobacter*
- *Pseudomonas*
- *Enterobacter* **spp. ESBL**
- **coagulase-negative staphylococci**

Adekvatna inicijalna antibiotska terapija je važna u smanjenju morbiditeta i mortaliteta u bolničkim uslovima

Tenover FC. Am J Infect Control 2006;34 (suppl 1):S3–10.

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Last Updated: Thursday, 24 February, 2005, 11:10 GMT

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NHS superbug death rate doubles

The number of deaths in which the superbug MRSA has been cited as a cause has doubled in four years, official statistics show.

The Office for National Statistics said in 2003 MRSA was mentioned on 955 death certificates - up from 487 in 1999.

Some of the MRSA increase could be down to better reporting

But the figures suggested some of the rise may be down to better reporting of the bug.

Other statistics revealed the number of HIV diagnoses seems to have levelled off after a decade of increases.

However, it was the MRSA figures which have proved most controversial.

Mortality rates were highest among older people with more men than women dying.

MRSA was involved in two out of 1,000 deaths in hospitals and three out of 1,000 deaths in NHS nursing homes,

> **"No other country has seen the super bug infection take over its hospitals in the same way as we have in Britain"**
>
> Michael Howard

Q&A: MRSA

BBC NEWS:VIDEO AND AUDIO
What hospitals are doing to stop the spread of MRSA
VIDEO

BBC iCAN

MRSA infections
What can you do about the hospital 'superbug'?

SEE ALSO:
- Nasty clones causing MRSA problem
  10 Feb 05 | Health
- 'Clean yourself' advice on MRSA
  26 Jan 05 | Health
- NHS targets 'to blame for MRSA'
  15 Jan 05 | Health
- Genetic blueprint of MRSA cracked
  24 Jun 04 | Health
- Q&A: MRSA 'superbugs'
  13 Dec 02 | Health

RELATED INTERNET LINKS:
- Department of Health
- Office for National Statistics

Evolucija rezistencije

- **Lekom uzrokovana selekcija**

u jednoj od 10^7- 10^{12} bakterija dolazi do mutacije koje je čine rezistentnom na primenjeni antibiotik

- **U sredini česte upotrebe antibiotika rezistentni sojevi se brzo šire**

- **Problem predstavljaju *horizontalni transfer gena* i *ukrštena rezistencija***

Program za prevenciju hospitalne rezistencije

Enterobacter	E
Staph aureus	S
Klebsiella (KPC/CRE) →	Clostridium diff.
Acinetobacter	A
Pseudomonas aeruginosa	P
ESBLs	Enterobactriace
Others	

January 1, 2008, [CDPH] Health & Safety Code §1288.8(a)
http://www.dhcs.ca.gov/provgovpart/initiatives/nqi/Documents/SB739.pdf

Boucher HW, Talbot GH, Bradley JS, et al. Bad bugs, no drugs: no SKAPE! An update from the Infectious Diseases Society of America. Clin Infect Dis 2009; 48:1–12.

ESCAPE DANAS, 2020

- *Enterococcus faecium,*
- *Staphylococcus aureus (Stenotrophomonasmaltophilia)*
- *Klebsiella pneumoniae (Clostridioides difficile)*
- *Acinetobacter* spp.
- *Pseudomonas aeruginosa*
- *Enterobacter* spp. (members of *Enterobacterales)*

JEDNOĆELIJSKI RATOVI

taktika bakterijskog pokreta otpora

KAMUFLAŽA

menjaju se PBP receptori na bakterijskim membranama antibiotik ne može da se veže

BARIKADE

promena strukture bakterijske membrane ne propusta antibiotike

RAZORUŽAVANJE

bakterije stvaraju enzime koji razaraju strukturu antibiotika

Beta-laktamaza razgadi 1000 molekula penicilina u sekundi

Rezistencija na antibiotike u bolničkim uslovima

Svetski problem su kliničke i ekonomske posledice

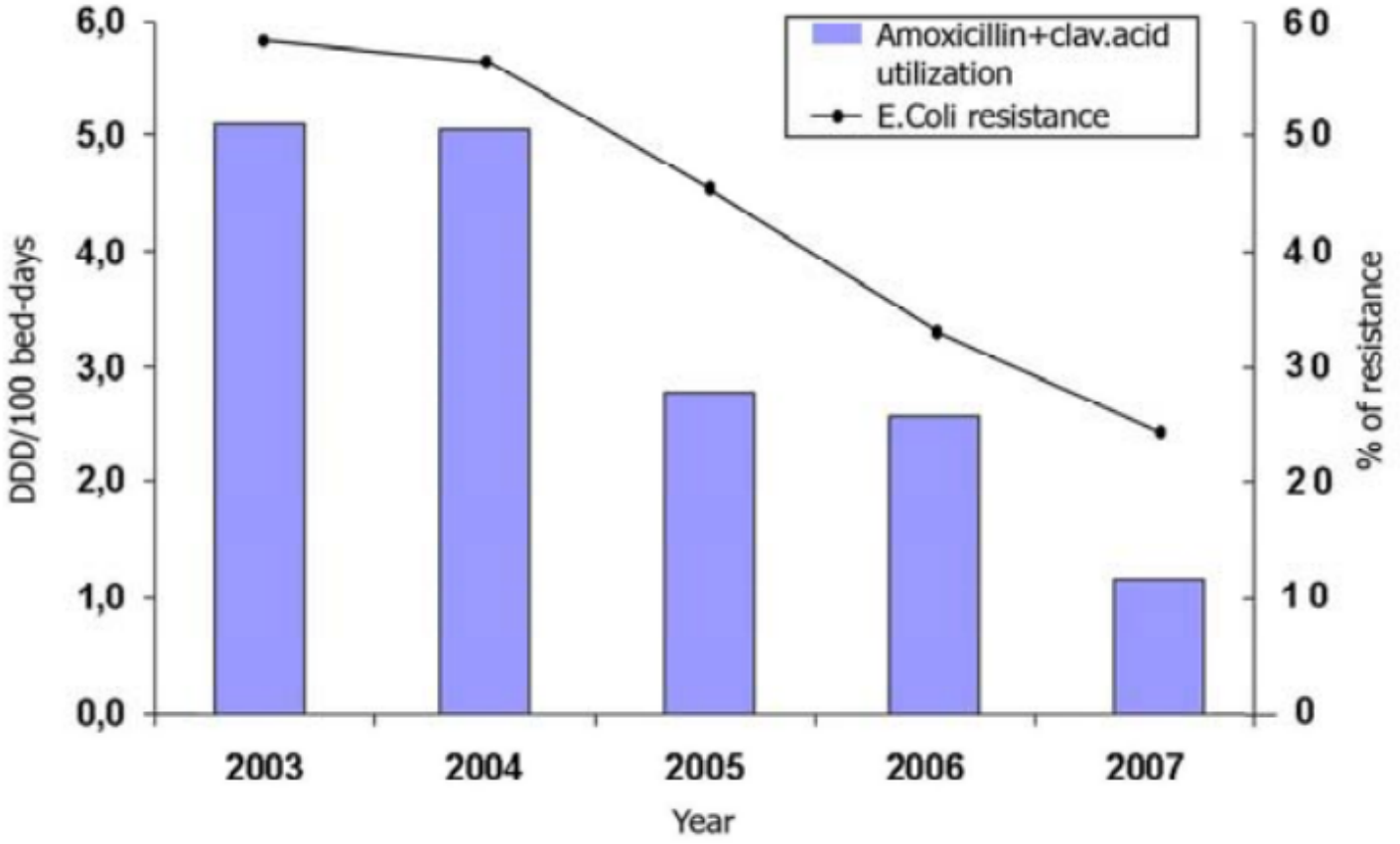
- Povećen morbiditet i mortalitet
- Produžena hospitalizacija
- Povećani troškovi

IDSA predviđa da uskoro neće biti efikasnih antibiotika za ozbiljno bolesne pacijente

IDSA = Infectious Diseases Society of America.

Adapted from Barlow G, Nathwani D. ***Postgrad Med J. 2005;81:680–692; Cunha BA. P&T. 2003;28:524–527; Infectious Diseases Society of America (IDSA).***

Korelacija između potrošnje antibiotika i rezistencije *E. Coli*

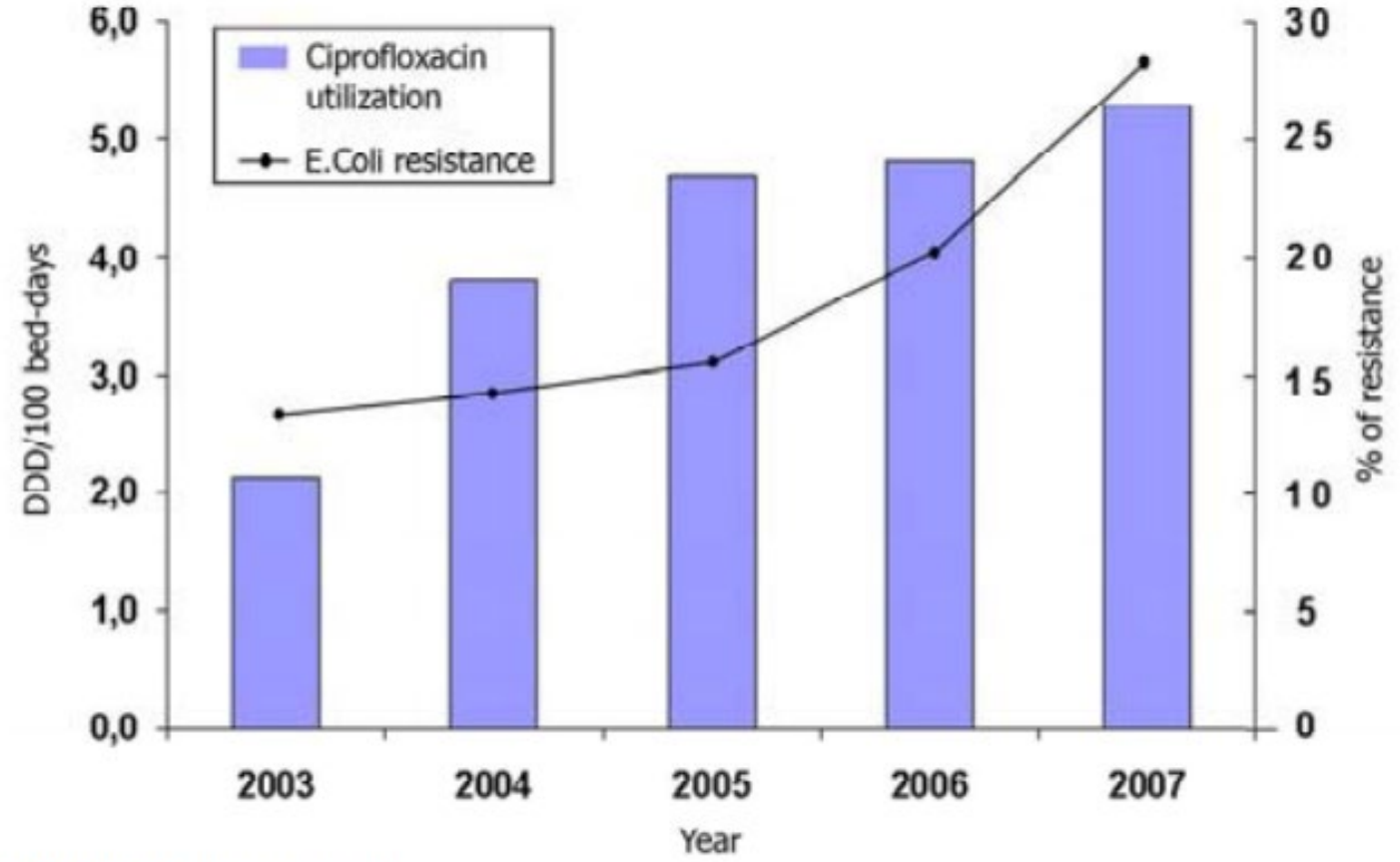


DDD – defined daily doses

Fig. 2 – Correlation between the consumption of amoxicillin+clavulanic acid and the resistance to *E. coli*

Veličković-Radovanović R, et al. Vojnosanit Pregl 2009; 66(4): 307–312.

Korelacija između potrošnje antibiotika i rezistencije *E. Coli*

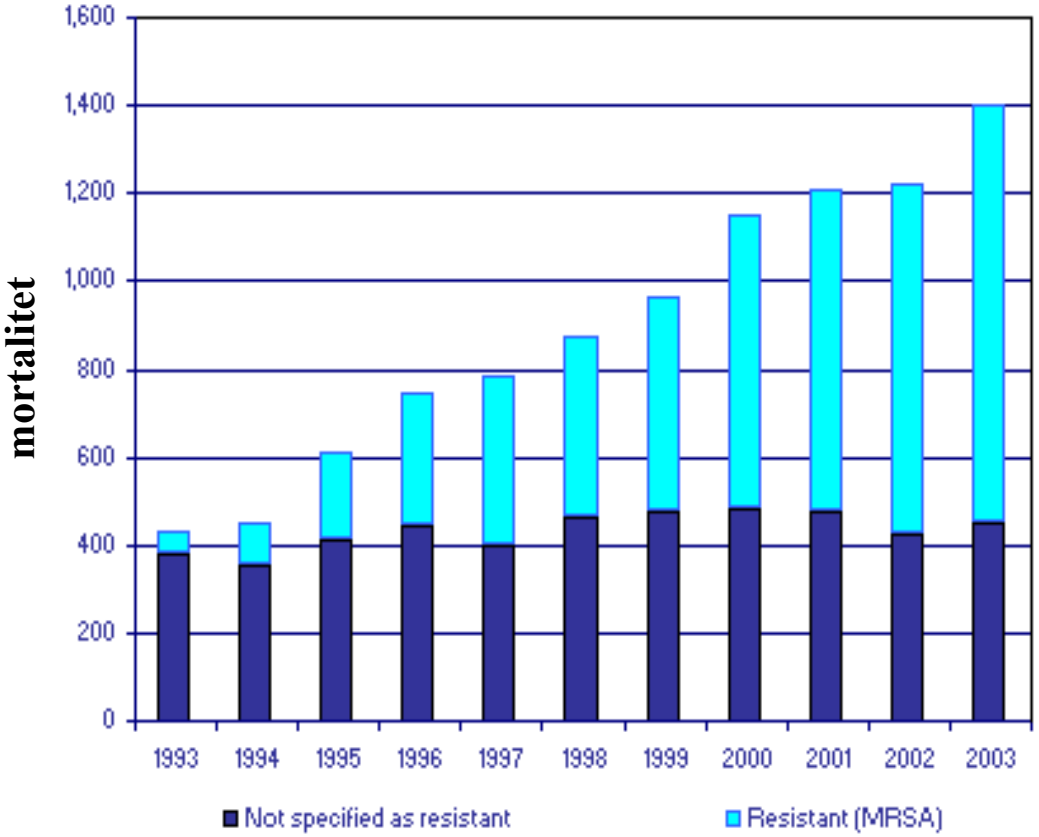


DDD – defined daily doses

Fig. 3 – Correlation between the consumption of ciprofloxacin and the resistance to *E. coli*

Veličković-Radovanović R, et al. Vojnosanit Pregl 2009; 66(4): 307–312.

Meticilin-rezistentni *Staphylococcus aureus* (MRSA) u Velikoj Britaniji



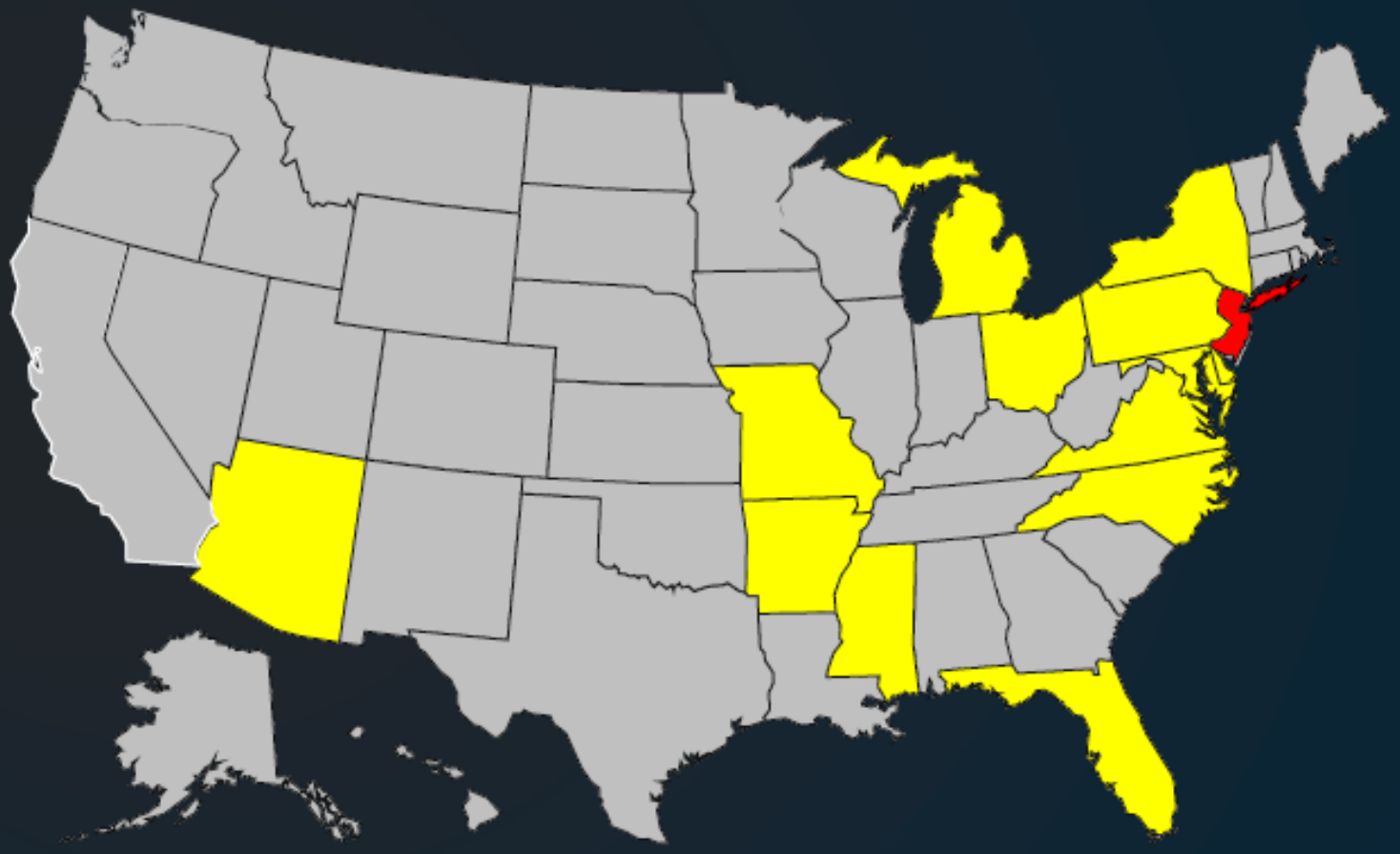
Prvi slučaj rezistencije na penicilin 1947 godine

MRSA je rezistentna i na ampicilin, eritromicin, tetracikline

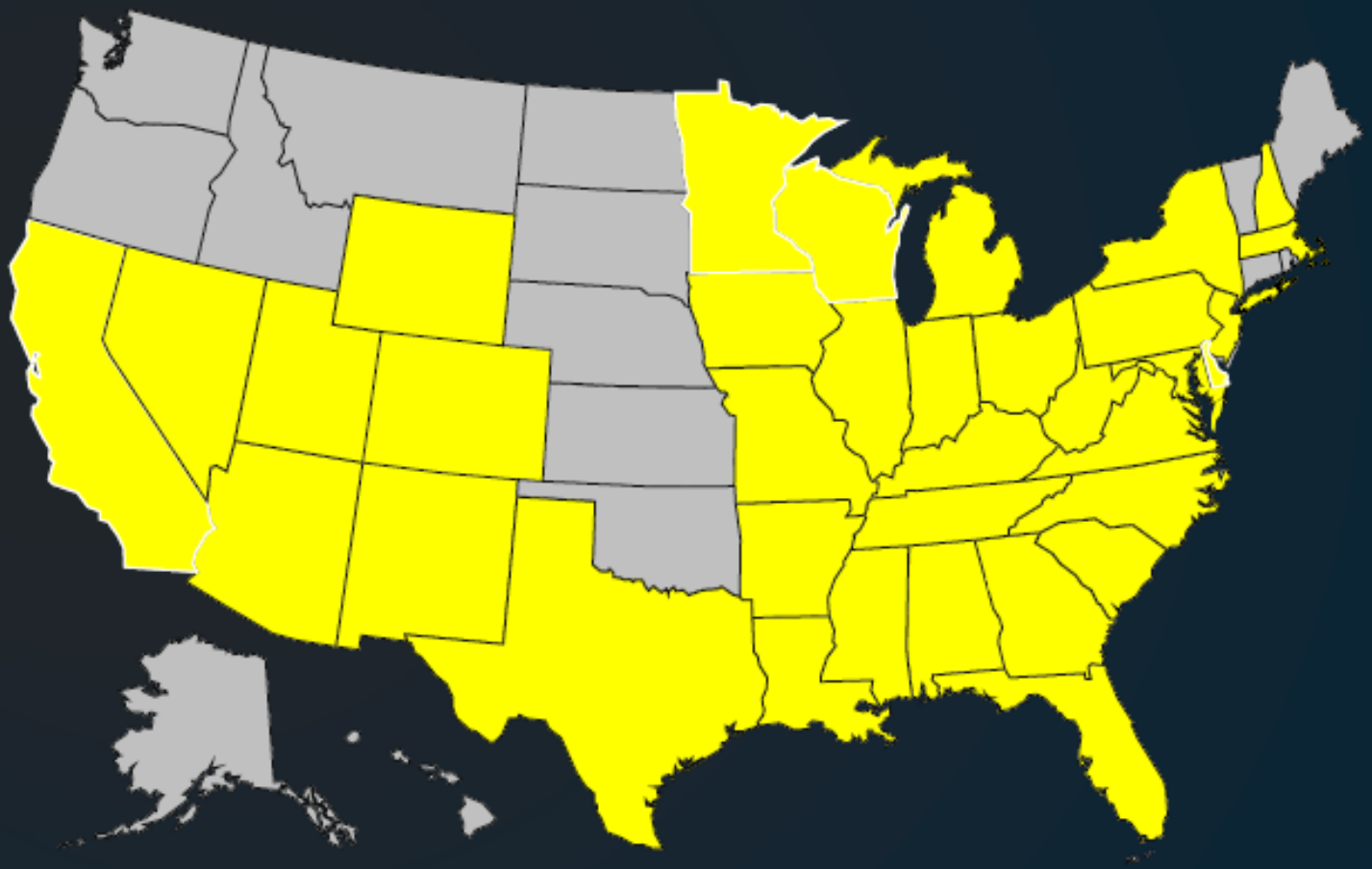
Može se lečiti za sada samo vankomicinom i...

Health Protection Agency, UK

GEOGRAFSKA DISTRIBUCIJA EKSTREMNO REZISTENTNE KLEBSIELE U SAD

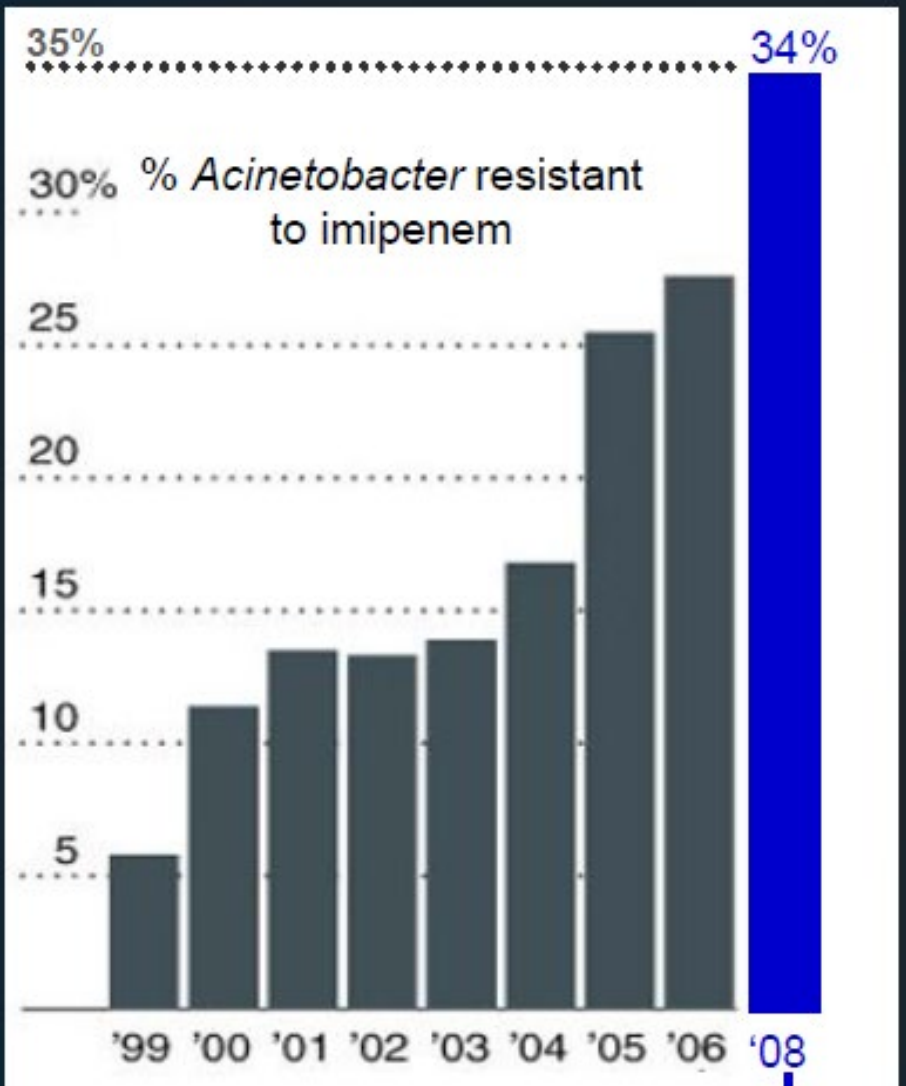


GEOGRAFSKA DISTRIBUCIJA EKSTREMNO REZISTENTNE KLEBSIELE U SAD



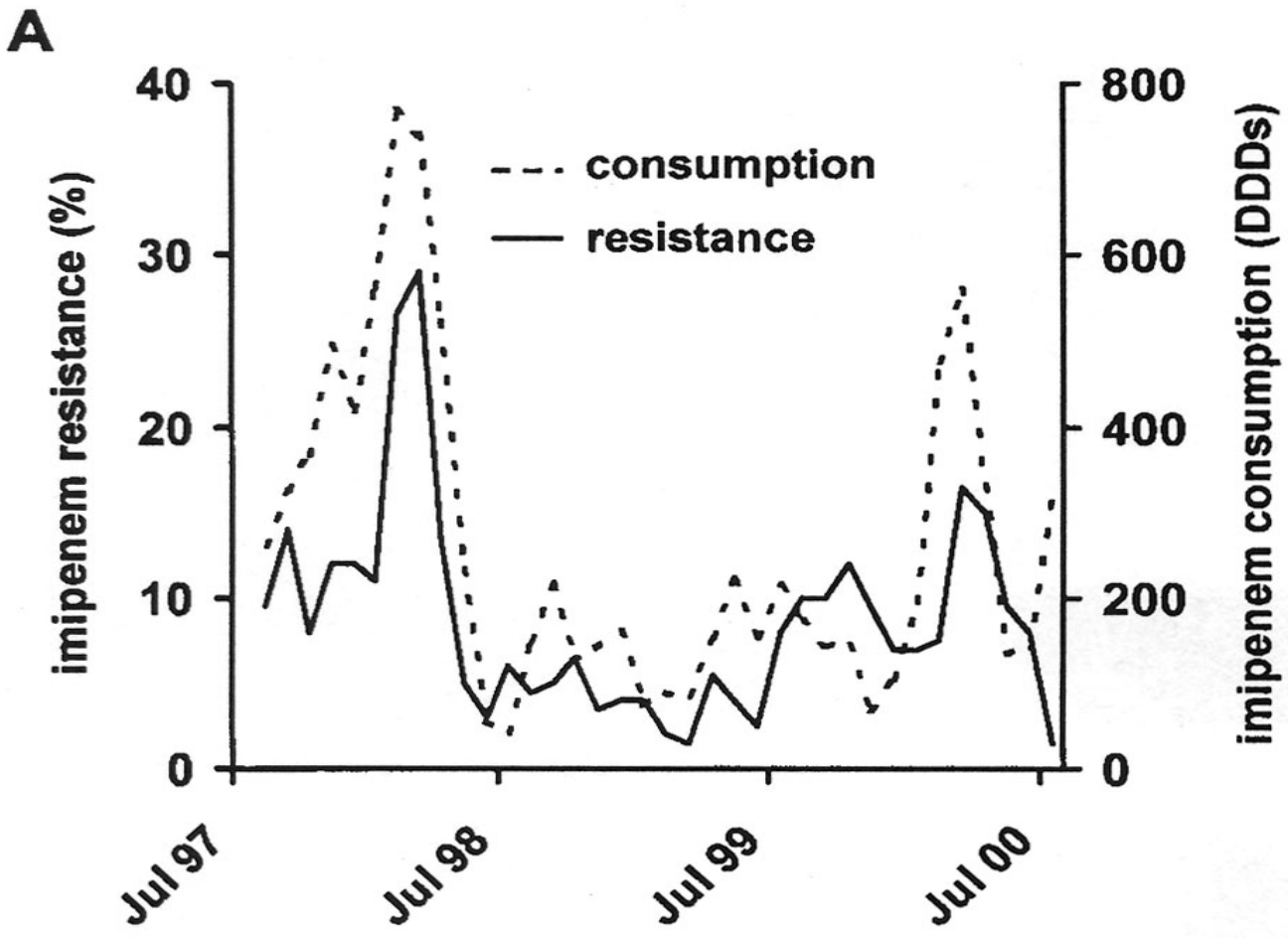
DANAS

ACINETOBAKTER JE EKSTREMNO REZISTENTAN



Kallen et al. (CDC) 2010
Infection Control Hospital
Epi. 31:528-31

Common Cause of Combat Wound Infections in US Soldiers

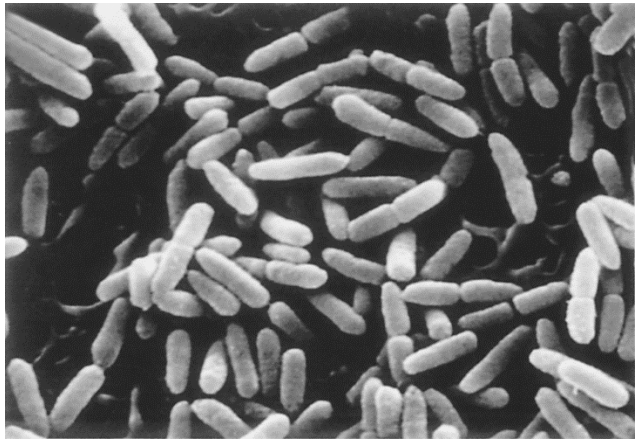


Correlation Between Consumption of Imipenem and Resistance in *P. aeruginosa*

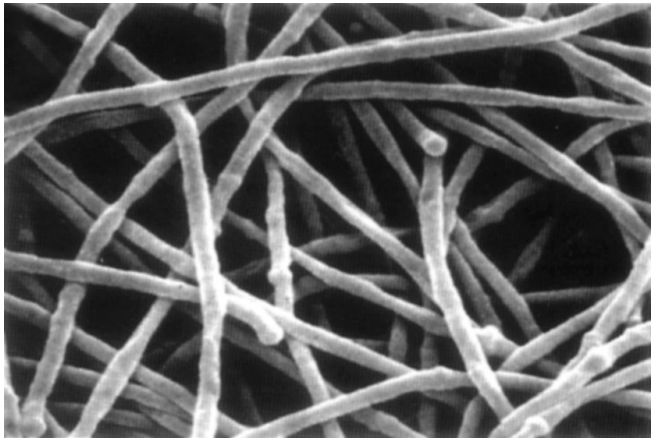
- Lepper PM et all. Antimicrob Agents Chemother 2002;46:2920-25

Beta-laktamski antibiotici modifikuju morfologiju bakterija

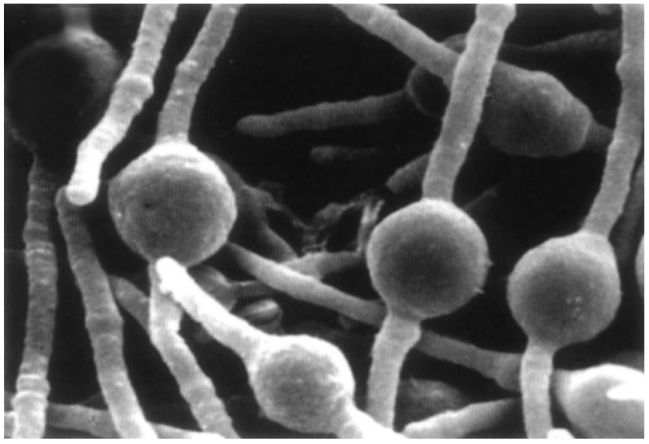
Pseudomonas aeruginosa MB 3286 sojevi:



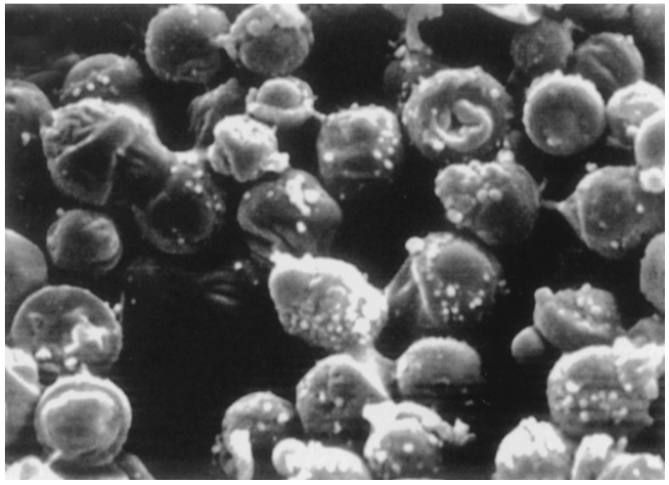
bez antibiotika



Filamenti indukovani ceftazidimom pri 4 μg/ml (2x MIC) (za 7 sati)

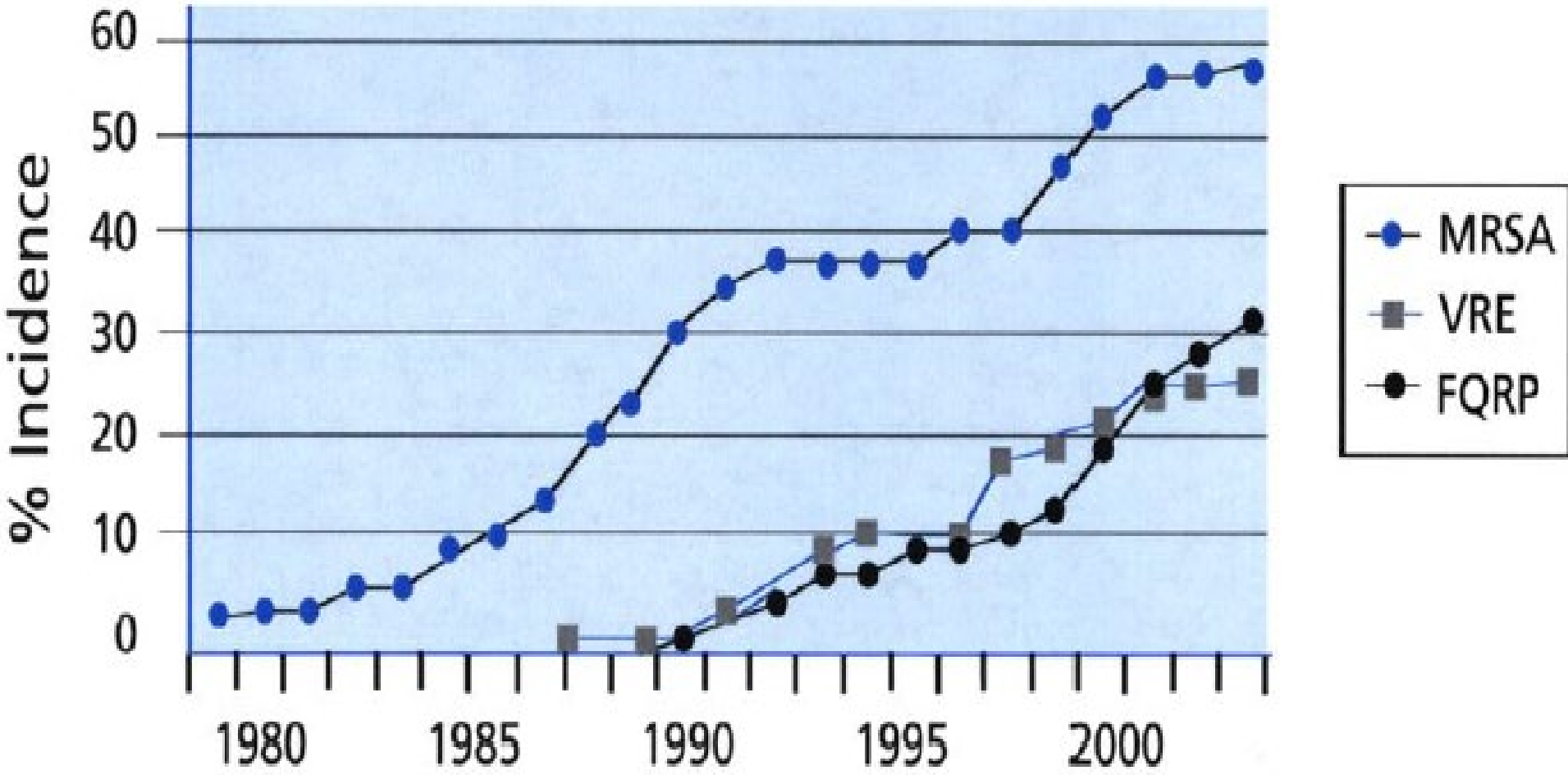


Filamenti koji predstavljaju segmente slične sferoidu indukovani meropenemom pri 2μg/ml (2x MIC) (za 6 sati)



sferoplasti indukovani imipenemom pri 2μg/ml (2x MIC) (za 3 sata)

Adaptirano prema Jackson J.J. and Kropp H



Source: Centers for Disease Control and Prevention

Rezistencija je sve veća pretnja !!!

- **Methicillin-resistant Staphylococcus aureus (MRSA),**
- **Antibiotic-resistant Gram-negative bacteria (GNB),**

  Acinetobacter baumannii,

  Klebsiella pneumoniae and

  Pseudomonas aeruginosa,

  Escherichia coli (E. coli),

  Clostridium difficile (C. diff)

New Delhi metallo-β-lactamase 1 or NDM1 = ESBL

Enterobacter	E
Staph aureus	S
Klebsiella (KPC/CRE) →	Clostridium diff.
Acinetobacter	A
Pseudomonas aeruginosa	P
ESBLs	Enterobactriace
Others	

Table 1. Rates of resistance of bacterial strains in the Surgical Clinic in 2005 and 2008

	Escherichia coli		*Staphylococcus aureus*		*Pseudomonas aeruginosa*		*Enterobacter*		*Acinetobacter*		*Proteus mirabilis*	
Antibiotic	2005	2008	2005	2008	2005	2008	2005	2008	2005	2008	2005	2008
Ampicillin	57·1	57·6	–	–	–	–	–	–	–	–	53·8	51·5
Amoxicillin + Clavulanic acid	22·3	15·2	65·6	73·5	–	–	81·2	79·2	–	–	28·6	20·8
Cefuroxime	16·7	23·9	65·5	69·7	–	–	66·7	86·7	–	–	27·6	21·4
Cefotaxime	–	22·4	66·7	77·6	–	76·2	60·2	62·5	83·3	90·5	30·3	24·2
Ceftriaxone	29·1	36·1	81·8	75·6	87·5	89·9	46·4	53·0	92·9	94·3	26·3	24·3
Imipenem	2·5	1·9	–	7·0	12·5	11·9	8·6	–	11·3	12·7	0	10·5
Meropenem	3·7	3·7	–	1·7	11·8	11·8	0	2·7	7·1	13·2	0	5·3
Gentamicin	30·3	20·1	71·1	57·1	76·0	42·5	57·5	44·6	92·3	88·3	31·4	27·7
Amikacin	17·2	11·9	58·9	39·6	54·3	37·8	47·1	33·4	69·2	58·4	16·7	13·3
Ciprofloxacin	15·4	11·8	45·0	40·6	62·2	42·3	47·3	25·9	73·3	71·2	30·1	28·4
Number of isolates	26	48	35	65	34	59	21	38	15	36	15	27

Journal of
Clinical Pharmacy and Therapeutics

Journal of Clinical Pharmacy and Therapeutics, 2012, 37, 32–36 doi: 10.1111/j.1365-2710.2010.01241.x

Analysis of antibiotic utilization and bacterial resistance changes in a surgical clinic of Clinical Centre, Nis

R. Velickovic-Radovanovic*† MD PhD, J. Petrovic† MD, B. Kocic‡ MD PhD, S. Antic‡ MD and R. Mitic† MD
**Faculty of Medicine, Department of Pharmacy, University of Niš, Niš, †Clinical Centre, Department of Pharmacotherapy, Niš, and ‡Institute for Health Protection, Department of Microbiology, Niš, Serbia*

Sve veća smrtnost !!!

Broj izgubljenih života/ugroženih od strane drug-resistant bakterije uključujući—ESKAPE patogene nije precizno utvrđen;

Važeći podaci kažu: incidenca sve veća a značaj postaje suštinski

- **2005 MRSA infekcije u SAD**

  19,000 smrti; 94,000 infekcija

JAMA. 2007;298:1763-1771

- **CDC reporti: 2 miliona HAIs/90,000 smrti godišnje u SAD**
- **ESKAPE-specific numbers: CDC is collecting**

Boucher HW, Bad Bugs, No Drugs, No ESKAPE CID 2009; 48:1-12

Svake godine se u SAD preko 2 miliona ljudi inficira multirezistentnim bakterijama a 23,000 umre,

Centers for Disease Control and Prevention. The report, "Antibiotic Resistance Threats in the United States, 2013,"

Infekcije koje smatramo noćnim morama!

- carbapenem-resistant Enterobacteriaceae,
- drug-resistant gonorrhea,
- Clostridium difficile, a serious diarrheal infection usually associated with antibiotic use.

C. difficile alone causes about 250,000 hospitalizations and at least 14,000 deaths every year in the United States.

"Get Smart About Antibiotics Week" kampanja koja treba da pokrene borbu protiv rezistencije:

Promoviše primenu protokola

Smanjuje potrebu za propisivanjem antibiotika kod virusnih infekcija kod zdravih i kod dece čiji roditelji to insistiraju

http://www.aware.md

Troškovi rastu, kao i dužina hospitalizacije !!!

Troškovi lečenja/dužina hospitalizacije je rastuća i supstancijalna:

- **Chicago Cook County Hospital Study aproksimirana na SAD**

- $21milijardi troškovi lečenja u celoj SAD (2009)

- 8 miliona dodatnih dana hospitalizacije

- **Poređenje rezistentnih GNB HAIs Vs osetljivih GNB HAIs**

Troškovi lečenja: porast 29.3% ($144 vs. $106)

Dužina hospitalizacije: porast 23.8% (36 vs. 31 dana)

RR Roberts, CID 2009:49, 1175-1184;

PD Maudlin, AAC 2010:54, 109-115

Uticaj visoko i multirezistentne gonoreje !!!

Bez novih antibiotika, CDC predviđa u sledećih sedam godina:

- Porast godišnje~ 600,000 u 2010 to 2.4 mil.u 2017
- to je 5.9 million novih slučajeva

CDC predviđa i porast troškova lečenja:

- 775 novih HIV slučajeva ($180 million)
- 255,000 slučajeva PID kod žena ($585 million)
- 51,000 slučajeva tubalne sterilnosti
- 50,000 slučajeva epididimitisa ($15 million)
- ukupni medicinski troškovi: $780 million

Najveći je porast među:

- Non-Hispanic crnci
- Muški homoseksualci

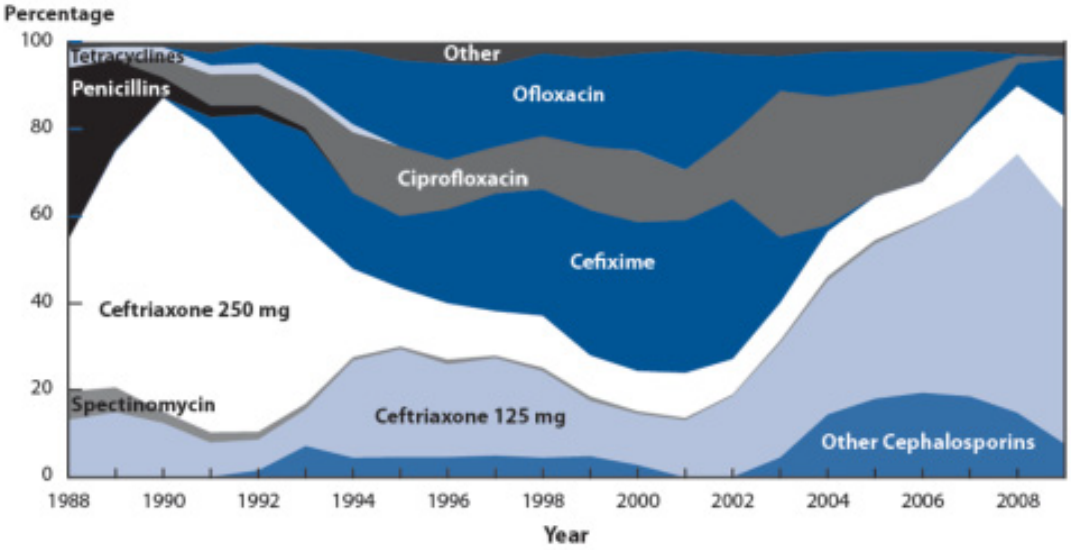
Source: CDC DSTDP, NCHHSTP; 12/19/2011

CDC Centers for Disease Control and Prevention
CDC 24/7: Saving Lives. Protecting People. Saving Money Through Prevention.

2009 Sexually Transmitted Diseases Surveillance

For Questions About STD Data, Contact Us

Figure 32. Gonococcal Isolate Surveillance Project (GISP) —Drugs Used to Treat Gonorrhea Among GISP Participants, 1988–2009



NOTE: For 2009, "Other" includes no therapy (1.5%), azithromycin 2 g (1.7%), and other less frequently used drugs.

THREAT LEVEL
URGENT

This bacteria is an immediate public health threat that requires urgent and aggressive action.

DRUG-RESISTANT NEISSERIA GONORRHOEAE

246,000
DRUG-RESISTANT GONORRHEA INFECTIONS

188,600 RESISTANCE TO TETRACYCLINE

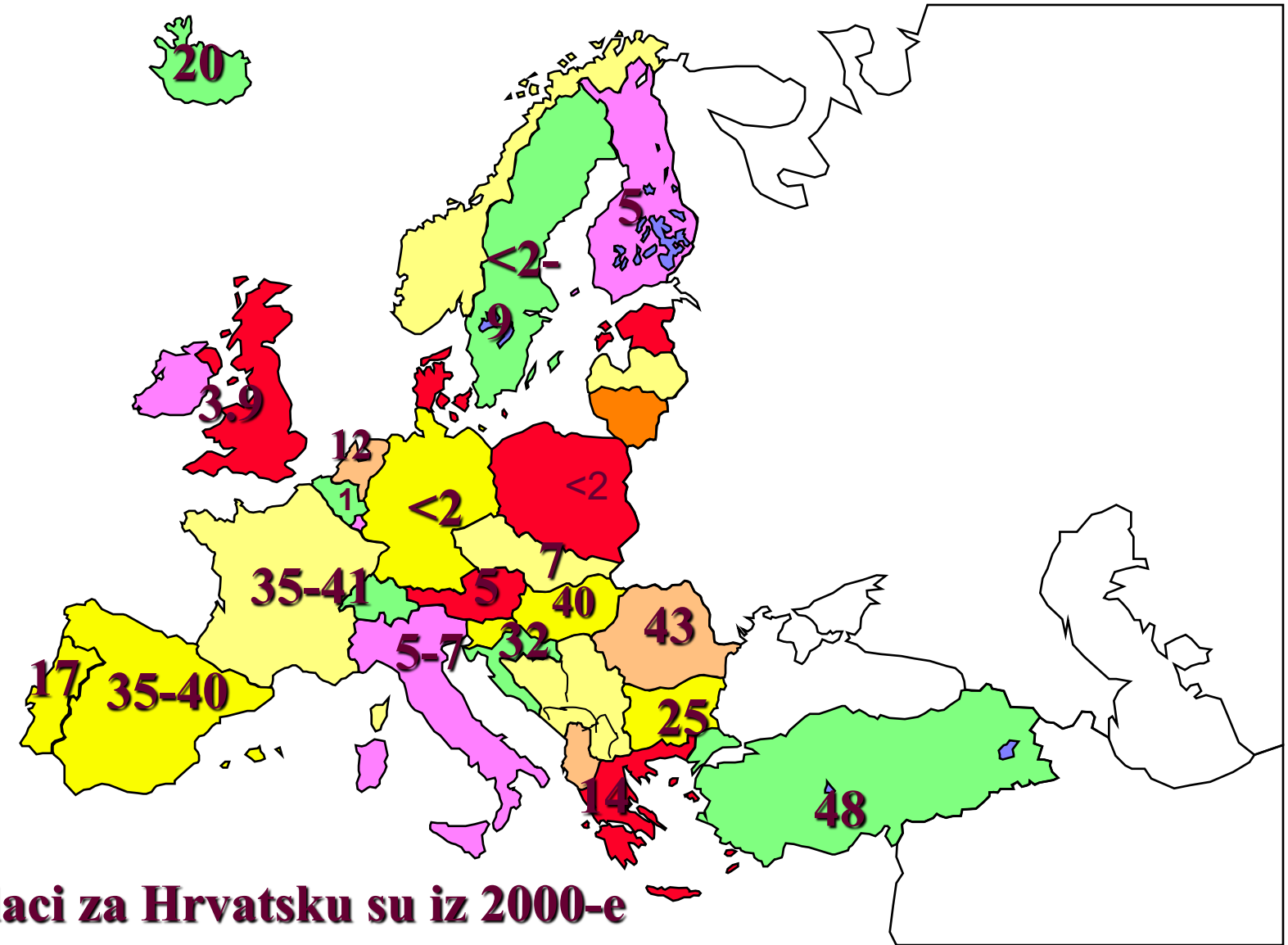
11,480 REDUCED SUSCEPTIBILITY TO CEFIXIME

3,280 REDUCED SUSCEPTIBILITY TO CEFTRIAXONE

2,460 REDUCED SUSCEPTIBILITY TO AZITHROMYCIN

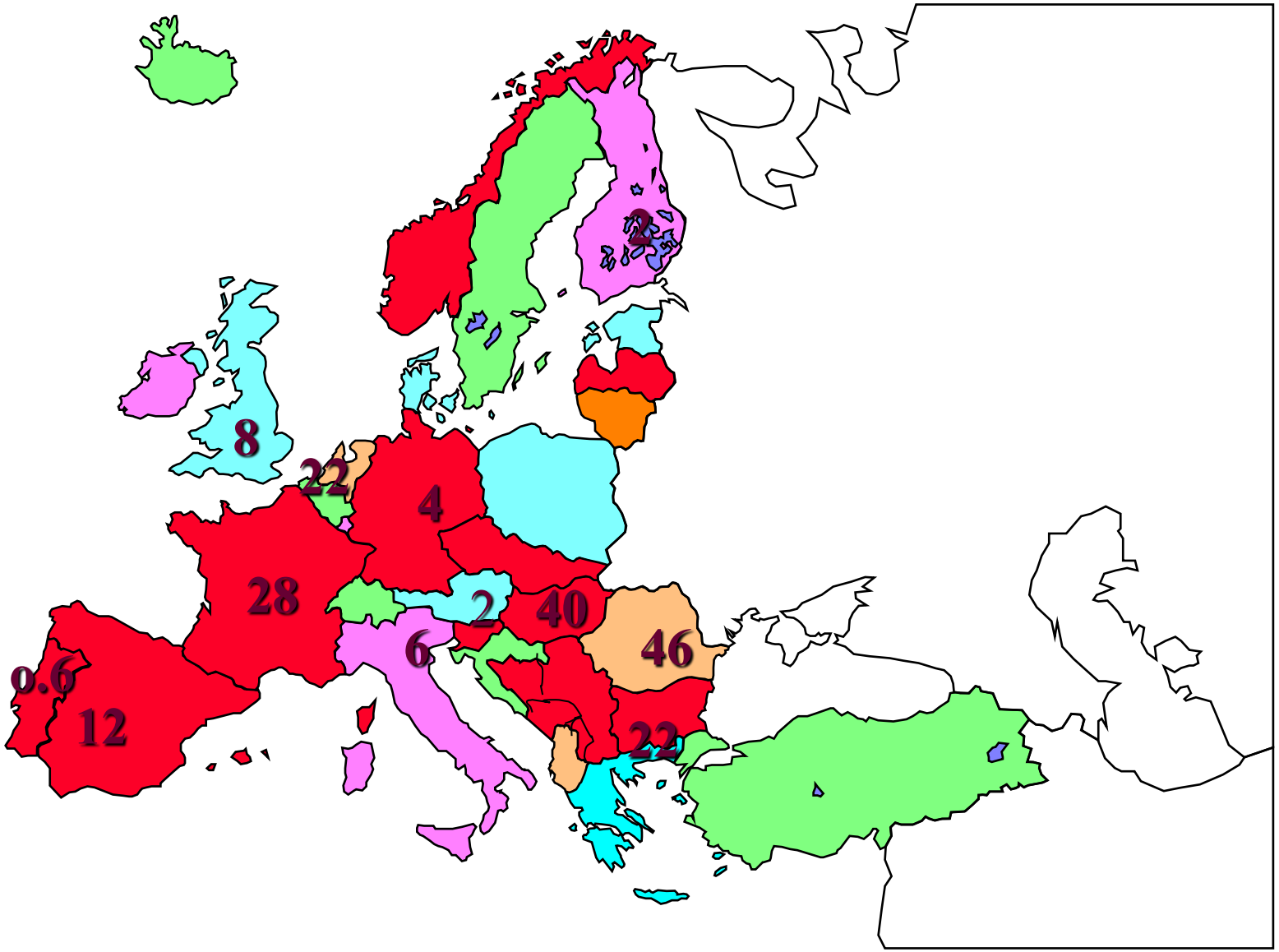
820,000 GONOCOCCAL INFECTIONS PER YEAR

prevalencija rezistencije pneumokoka na penicilin (%)

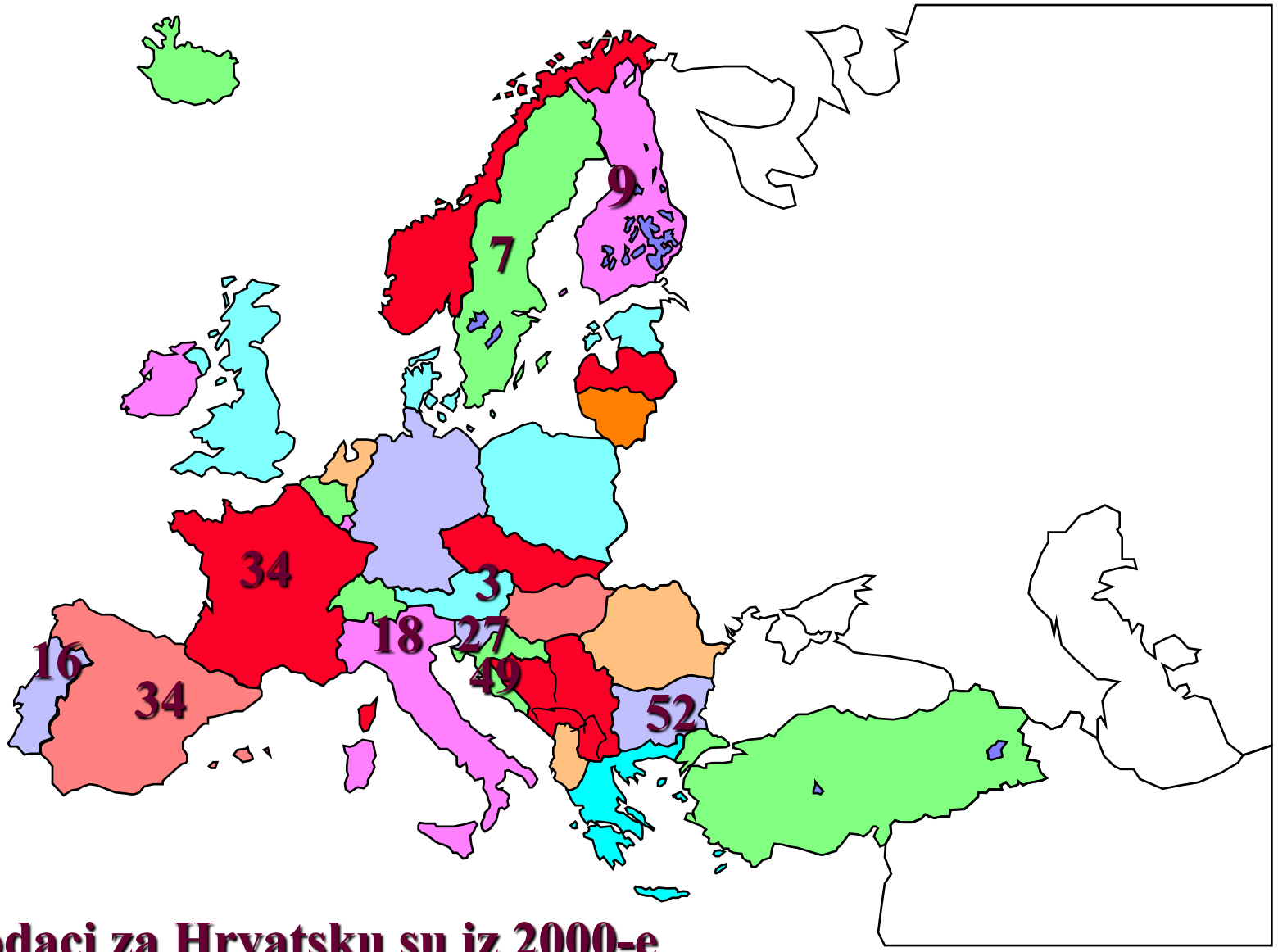


podaci za Hrvatsku su iz 2000-e

prevalencija rezistencije pneumokoka na eritromicin (%)

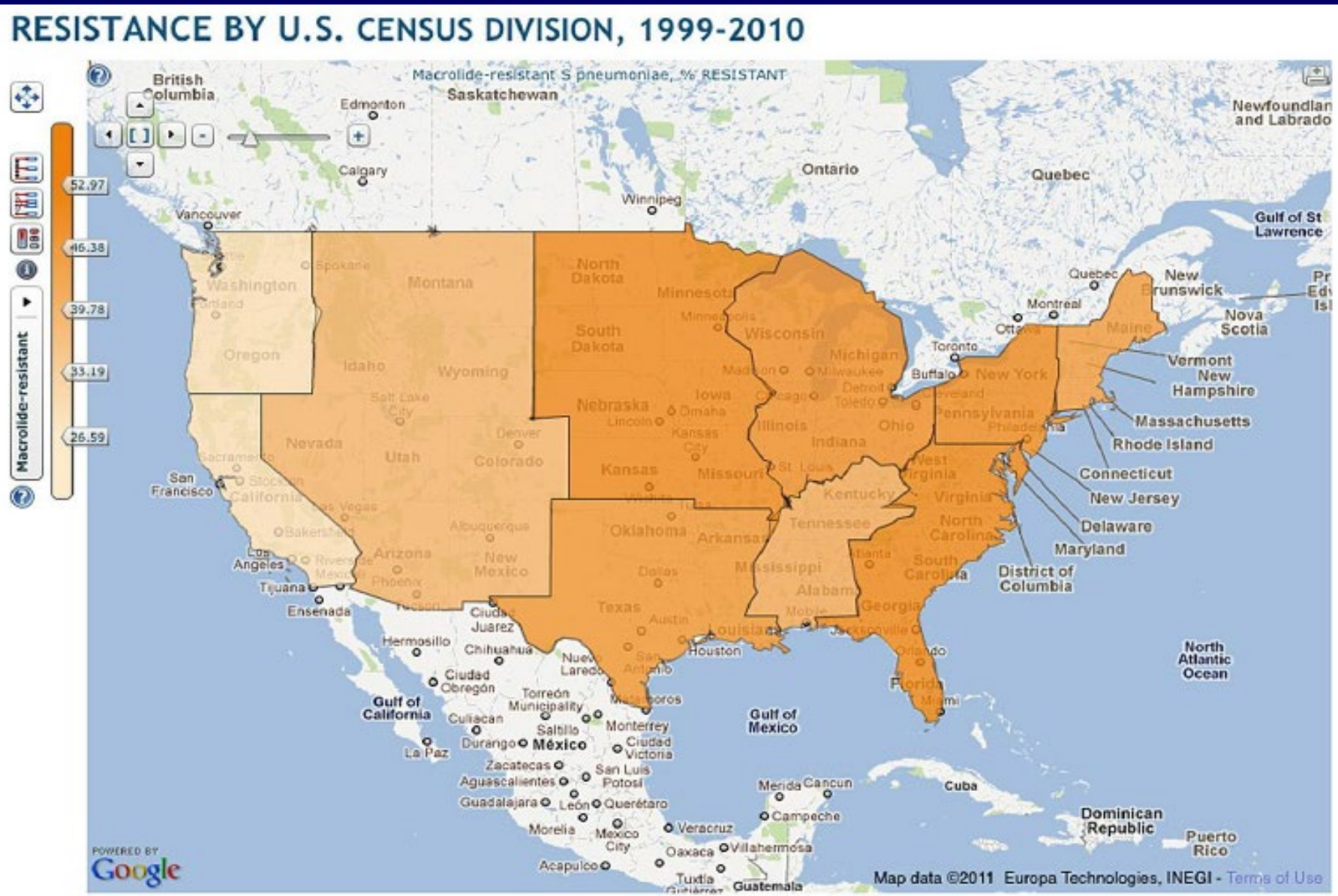


prevalencija rezistencije pneumokoka na kotrimoksazol (%)

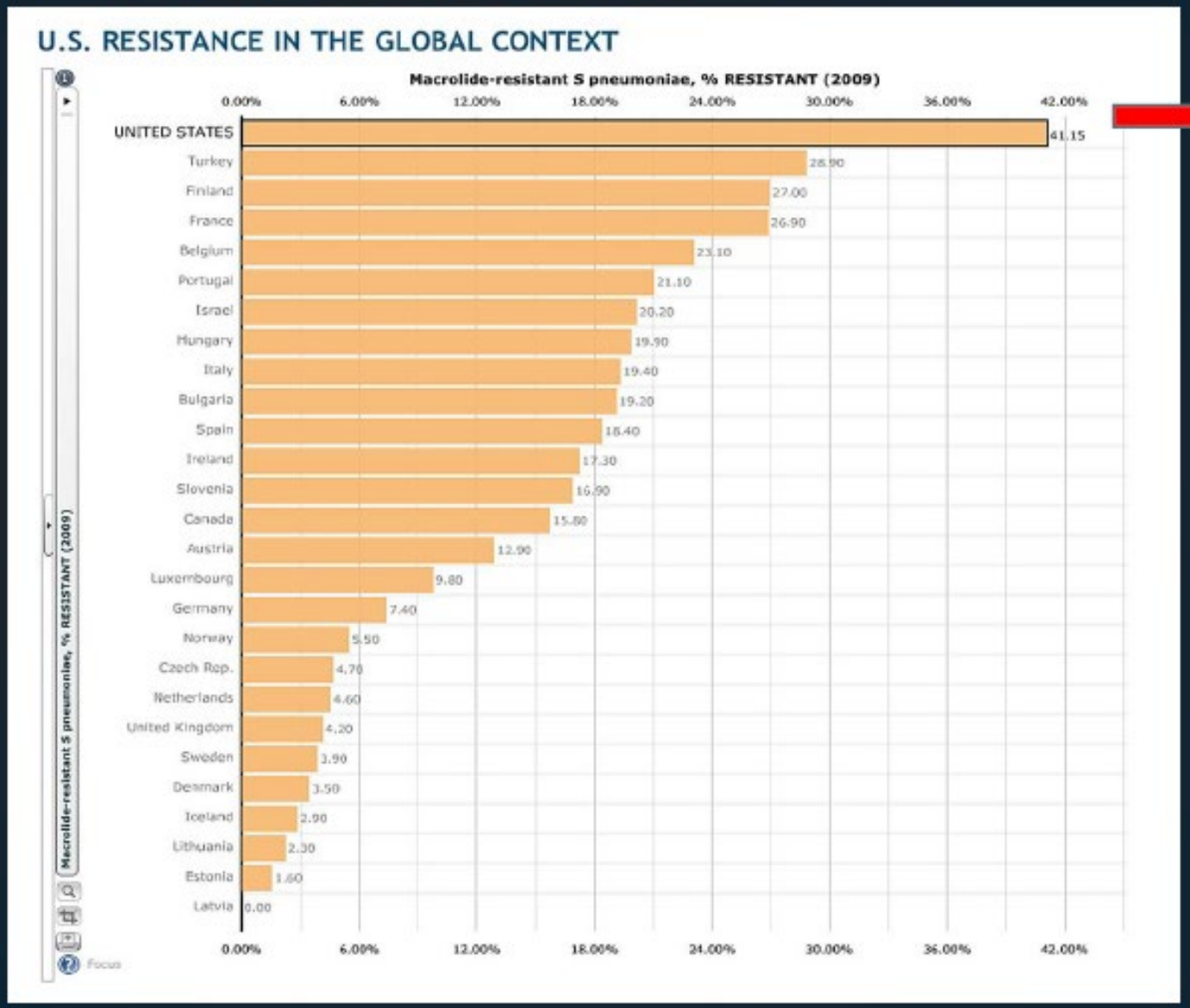


podaci za Hrvatsku su iz 2000-e

REZISTENCIJA PNEUMOKOKA NA MAKROLIDE U SAD

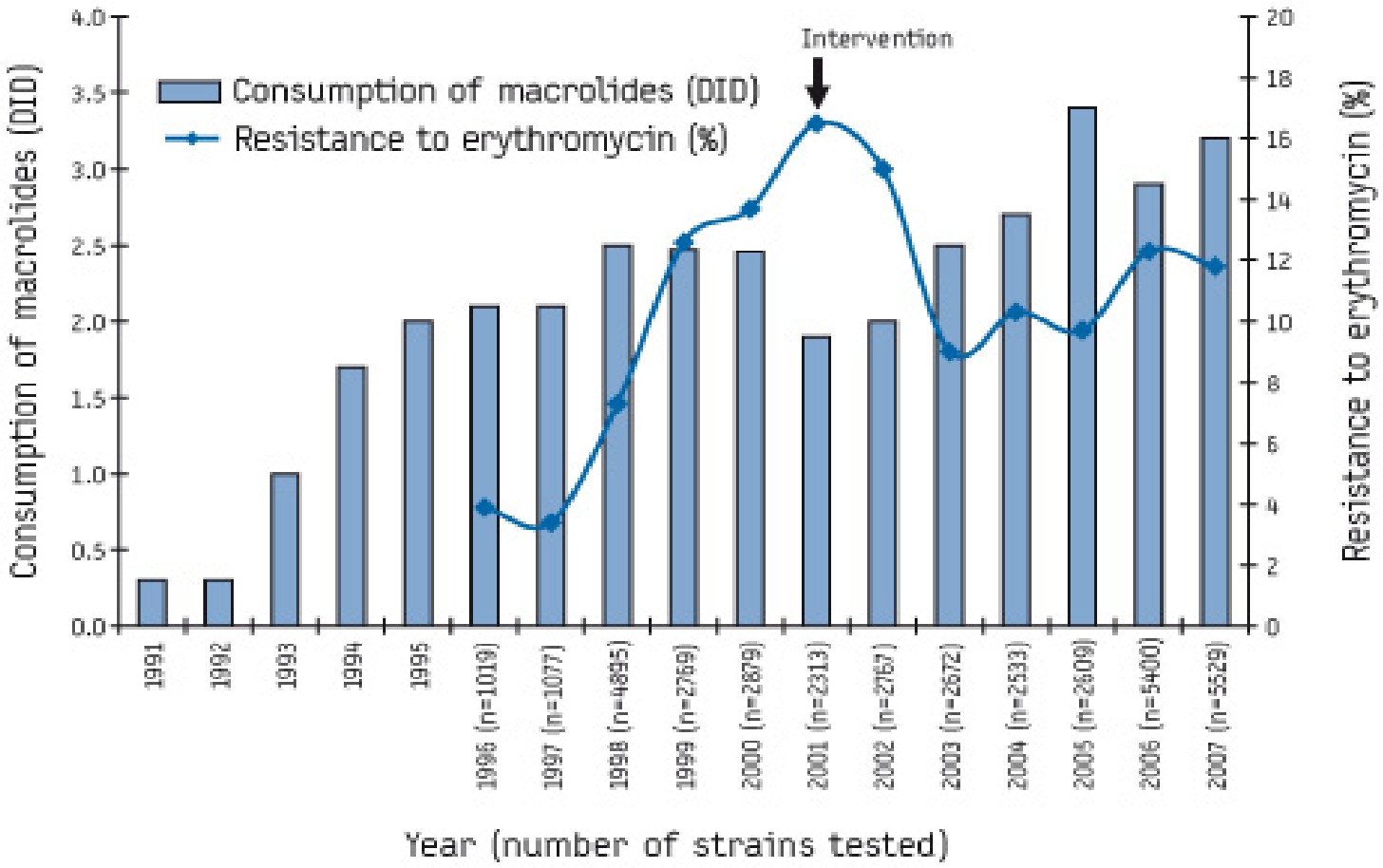


REZISTENCIJA PNEUMOKOKA NA MAKROLIDE U SAD



41%

Total consumption of macrolides in the community and resistance of Streptococcus pyogenes to erythromycin, Czech Republic, 1991-2007

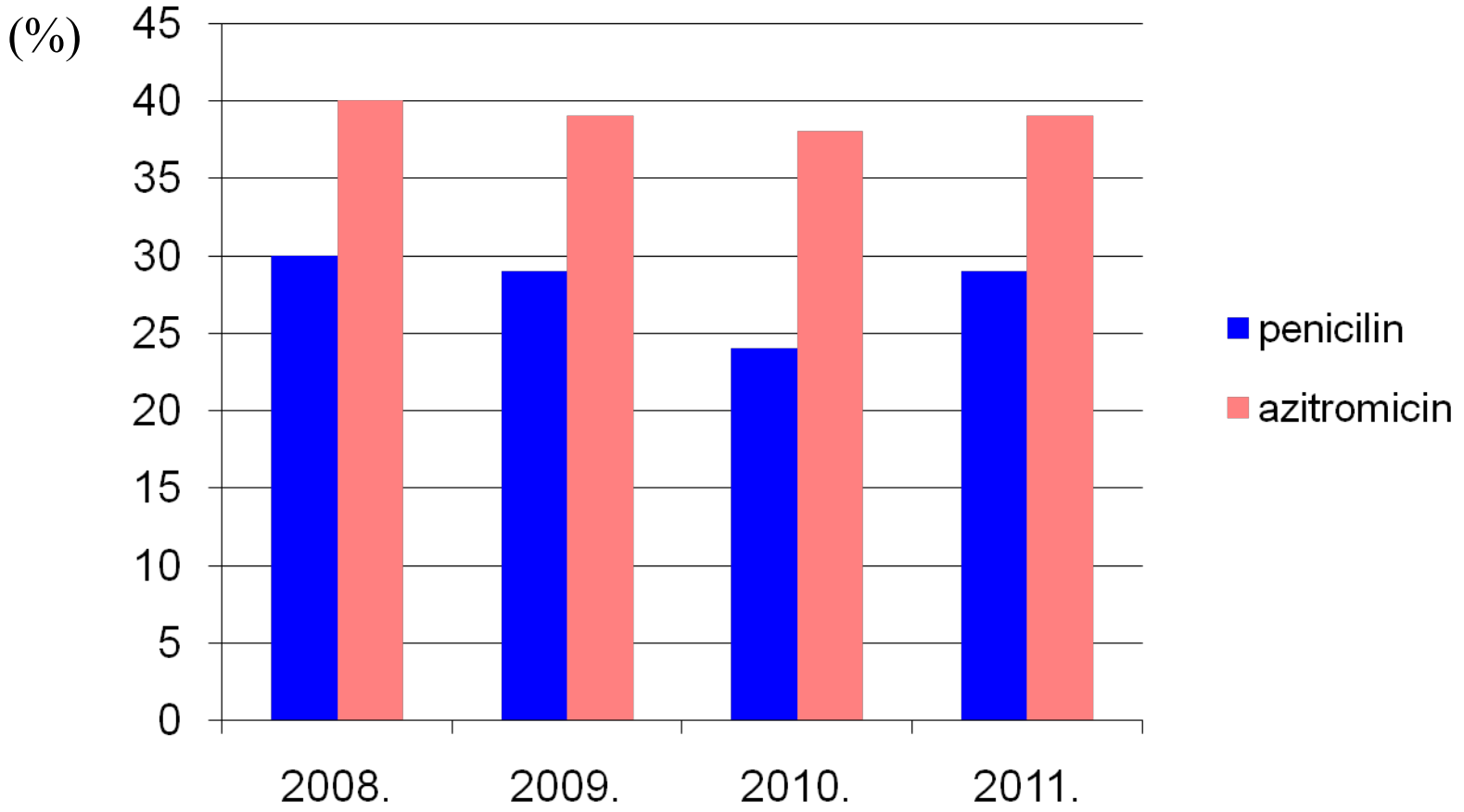


Note: The arrow indicates the beginning of official educational activities in prudent use of antibiotics in paediatric care organised by the Czech Medical Association

Source of data on consumption: 1989-2002 [1], 2003-2006 [3], 2007 - preliminary data.

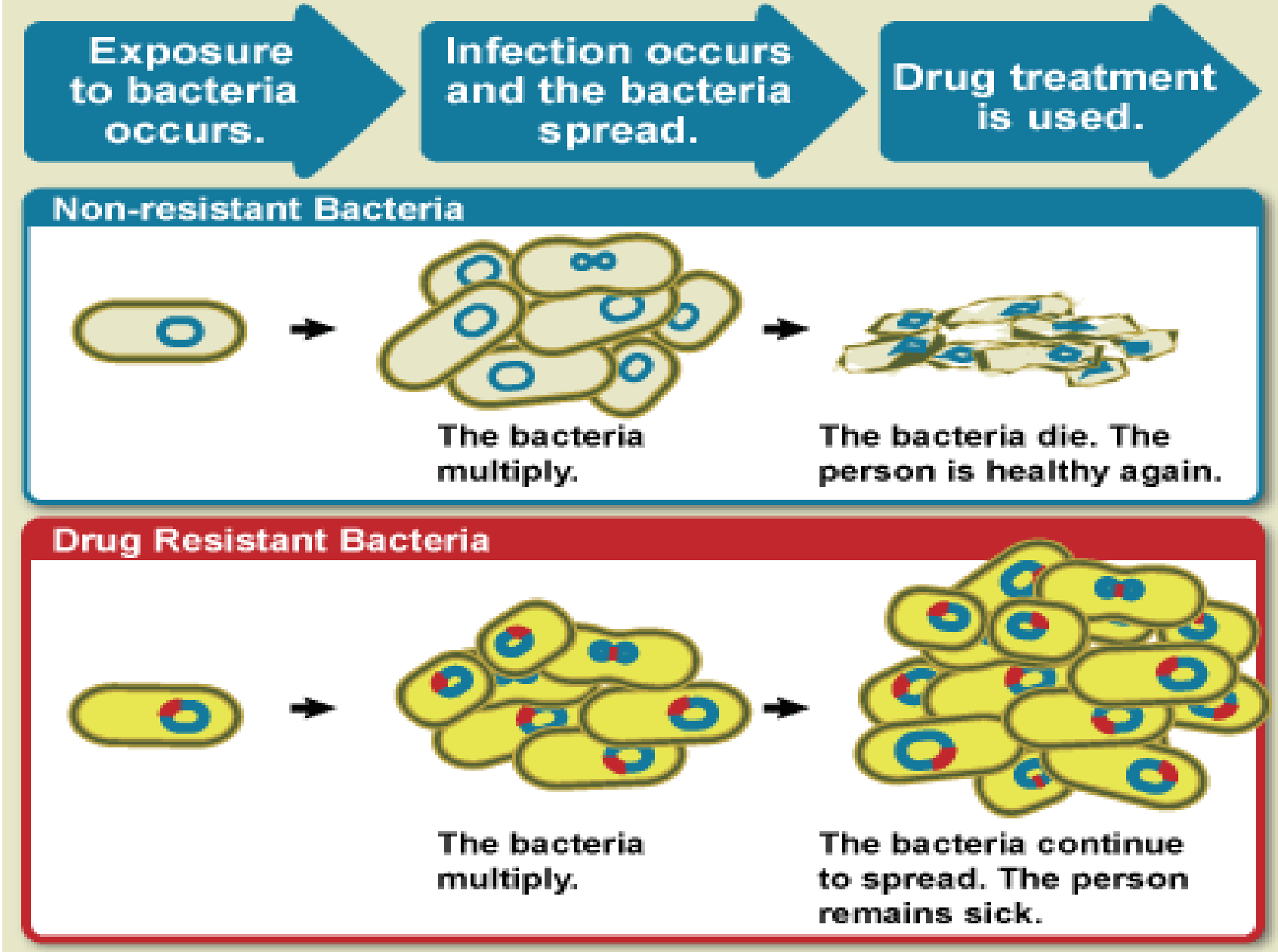
DID - Defined daily doses per 1,000 inhabitants and per day

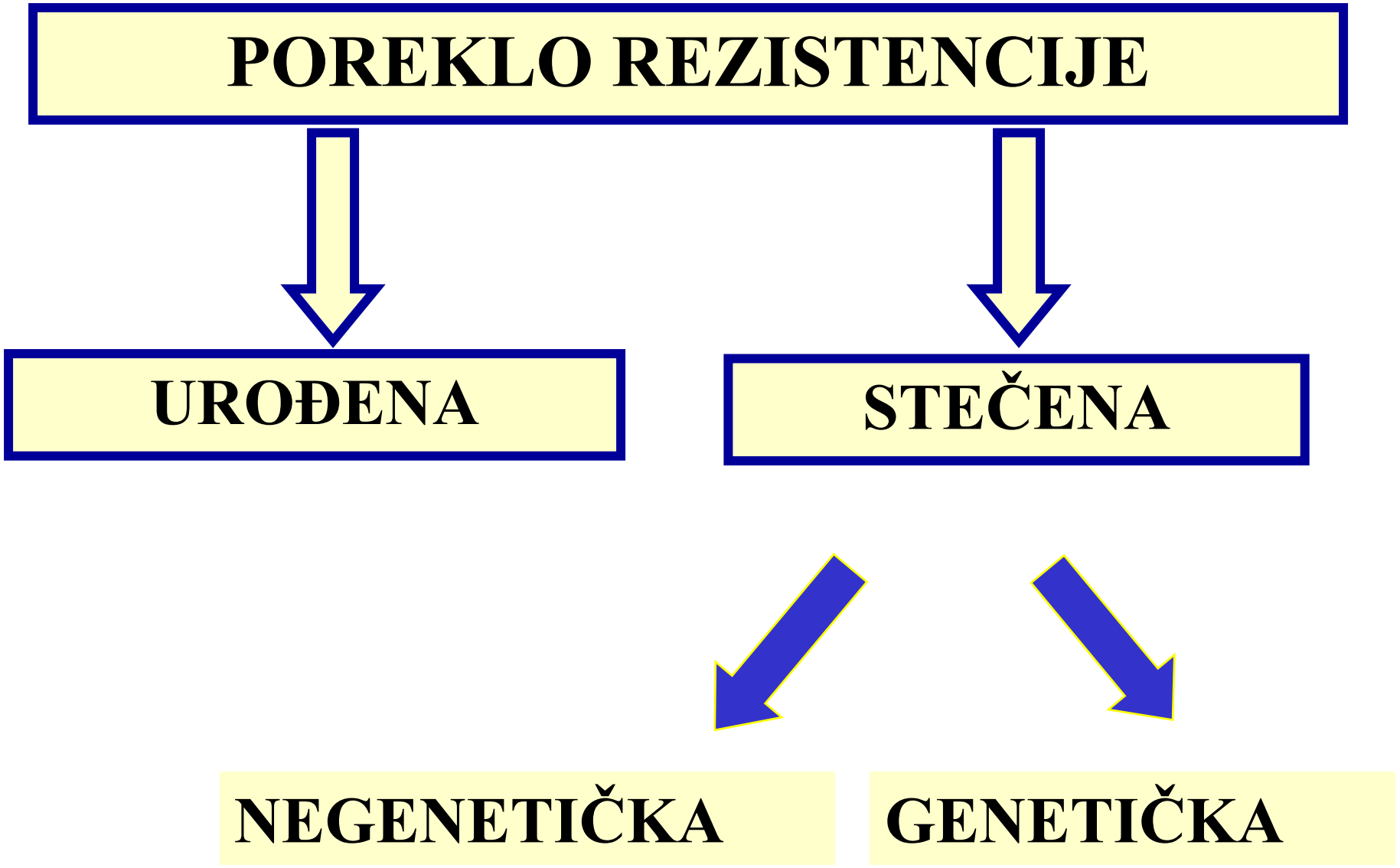
Rezistencija pneumokoka na penicilin i azitromicin u RH



ISKRA. www.iskra.bfm.hr

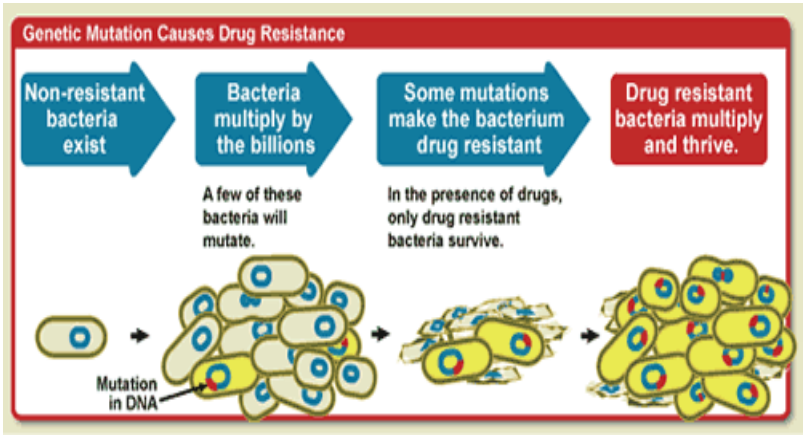
SELEKTIVNI PRITISAK AB



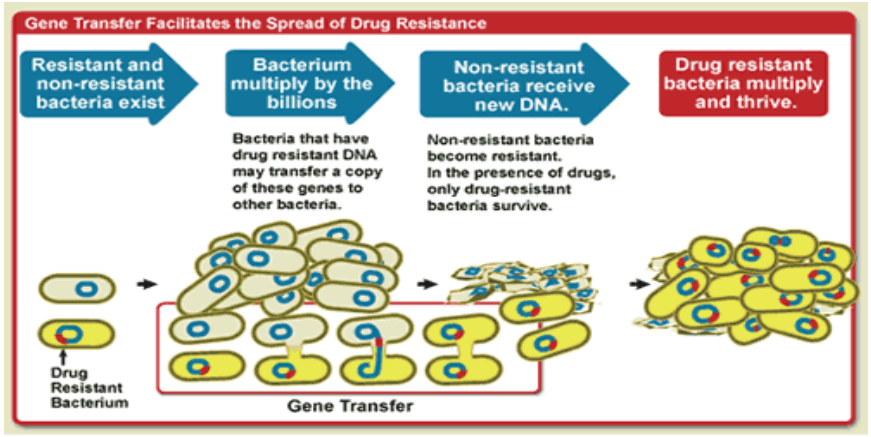

POREKLO REZISTENCIJE
URODJENA
STECENA
NEGENETICKA
GENETICKA

GENETIČKA REZISTENCIJA

HROMOZOMSKA
(spontane mutacije)



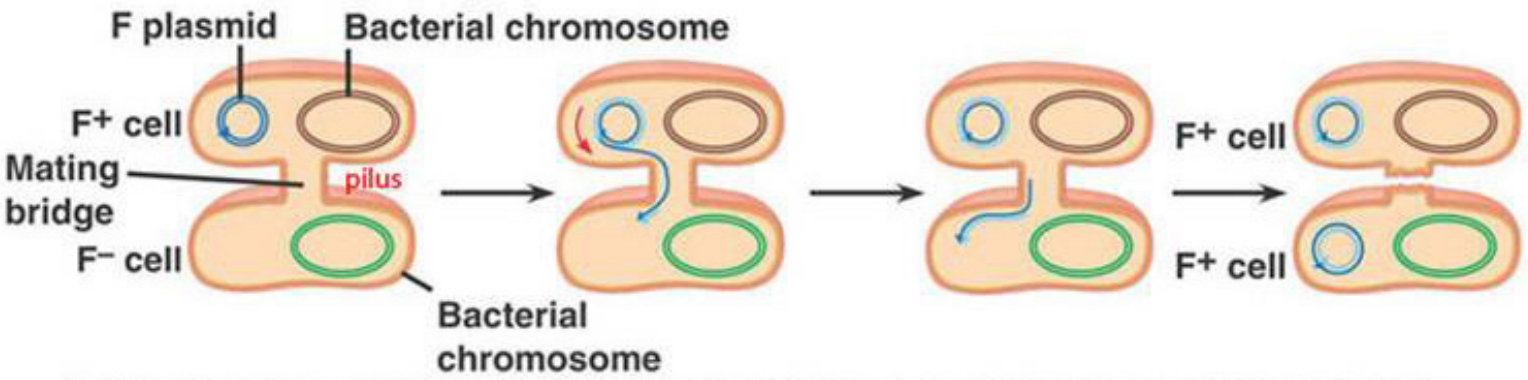
EKSTRAHROMOZOMSKA
(plazmidi, transpozoni)



PLAZMIDI

- **Ekstrahromozomski DNK molekuli koji egzistiraju i replikuju se nezavisno od bakterijskog hromozoma**

- **Lako se prenose sa jednog soja na drugi, sa jedne vrste na drugu vrstu ili čak sa jednog roda na drugi**

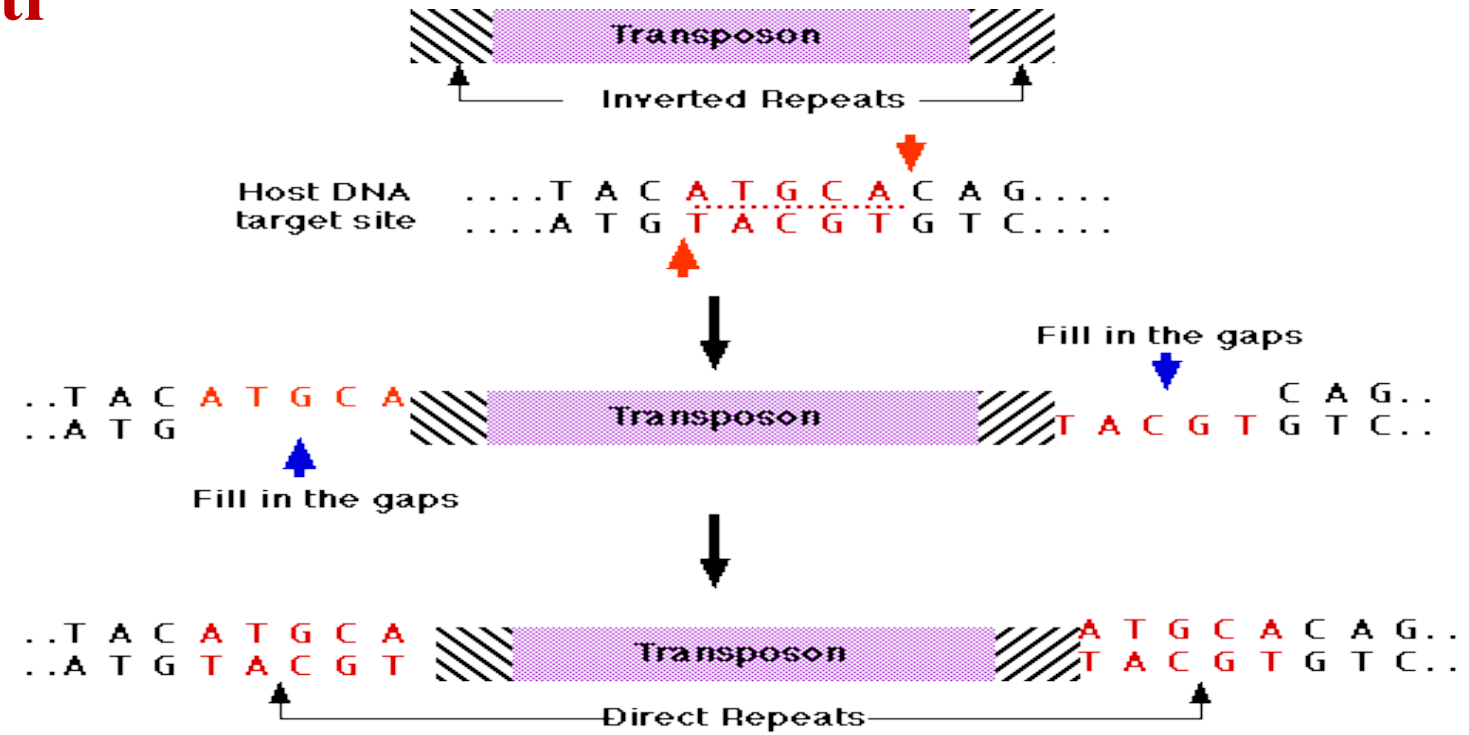


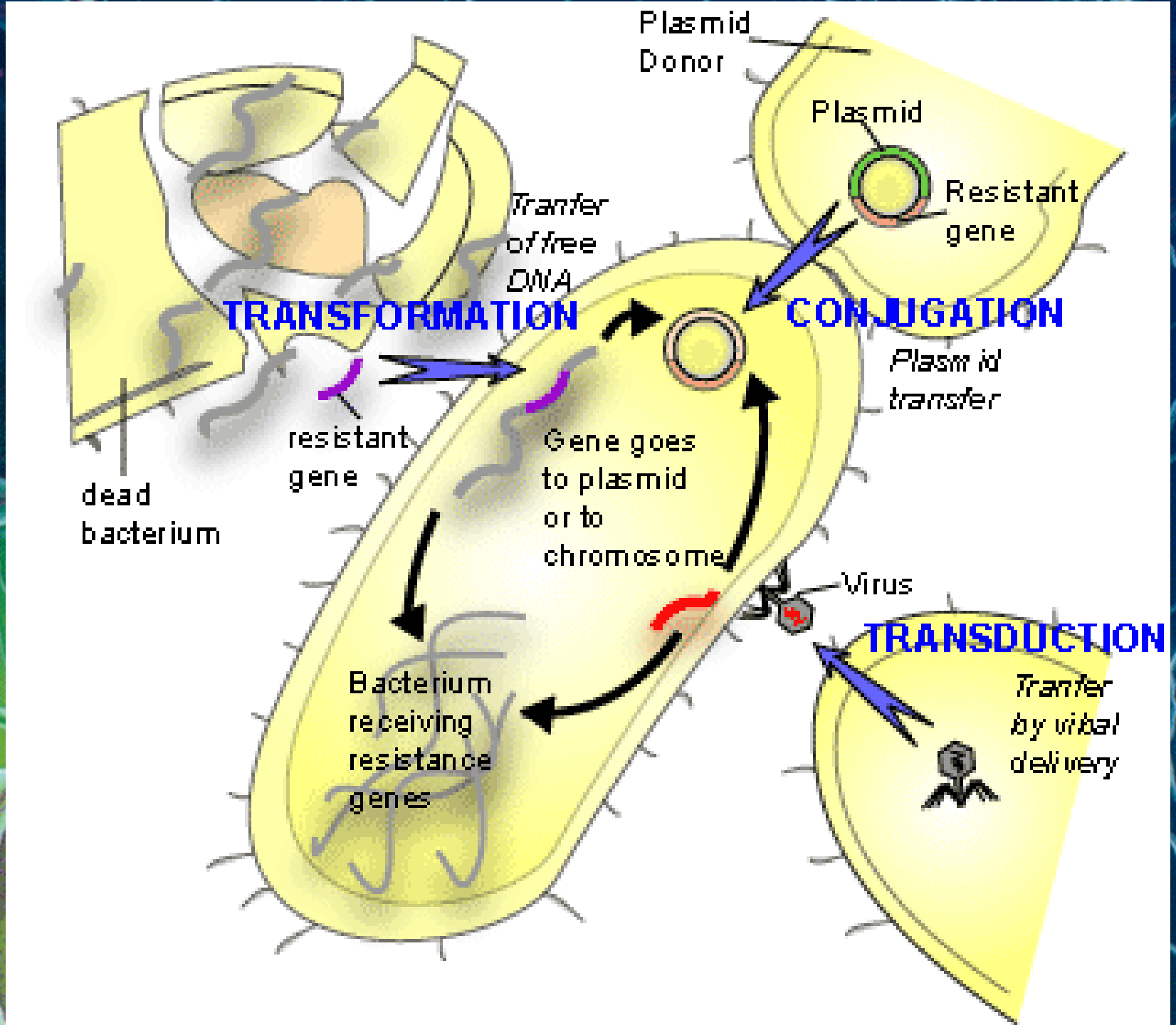
(a) Conjugation and transfer of an F plasmid from an F+ donor to an F− recipient

TRANSPOZONI

- **Segmenti DNK koji se lako prenose sa jednog plazmida na drugi ali i sa plazmida na hromozom i obrnuto**

- **Tokom procesa integracije transpozoni se mogu replikovati**




Plasmid
Donor
Plasmid
Resistant
gene
Tranfer
of free
DNA
TRANSFORMATION
CONJUGATION
Plasmid
transfer
resistant
gene
Gene goes
to plasmid
or to
chromosome
dead
bacterium
Virus
TRANSDUCTION
Tranfer
by viral
delivery
Bacterium
receiving
resistance
genes

PRENOŠENJE GENETSKOG MATERIJALA

TRANSDUKCIJA
prenos pomoću bakteriofaga

KONJUGACIJA
plazmidi
transpozoni

TRANSFORMACIJA
direktno prenošenje DNK među kompatibilnim vrstama

- Ekspresija gena rezistencije
  - **konstitutivna**
  - **inducibilna**
  - **konstitutivno-inducibilna**

MEHANIZMI REZISTENCIJE

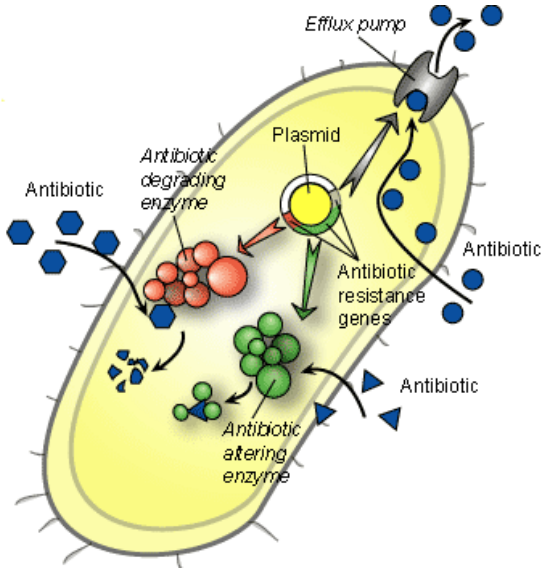
1. ENZIMSKA RAZGRADNJA LEKA

2. IZMENA CILJNOG PROTEINA

3. IZMENA PROPUSTLJIVOSTI BAKTERIJSKOG ZIDA

4. IZMENA STRUKTURE RIBOZOMA

5. IZMENA METABOLIČKOG PUTA



MEHANIZMI REZISTENCIJE

SMANJENA INTRACELULARNA KONCENTRACIJA AB

SMANJENA PERMEABILNOST

IZMENA PORINA

AKTIVNI EFLUKS

INAKTIVACIJA AB

BETA - LAKTAMAZE

ESTERAZE

ACIL TRANSFERAZE

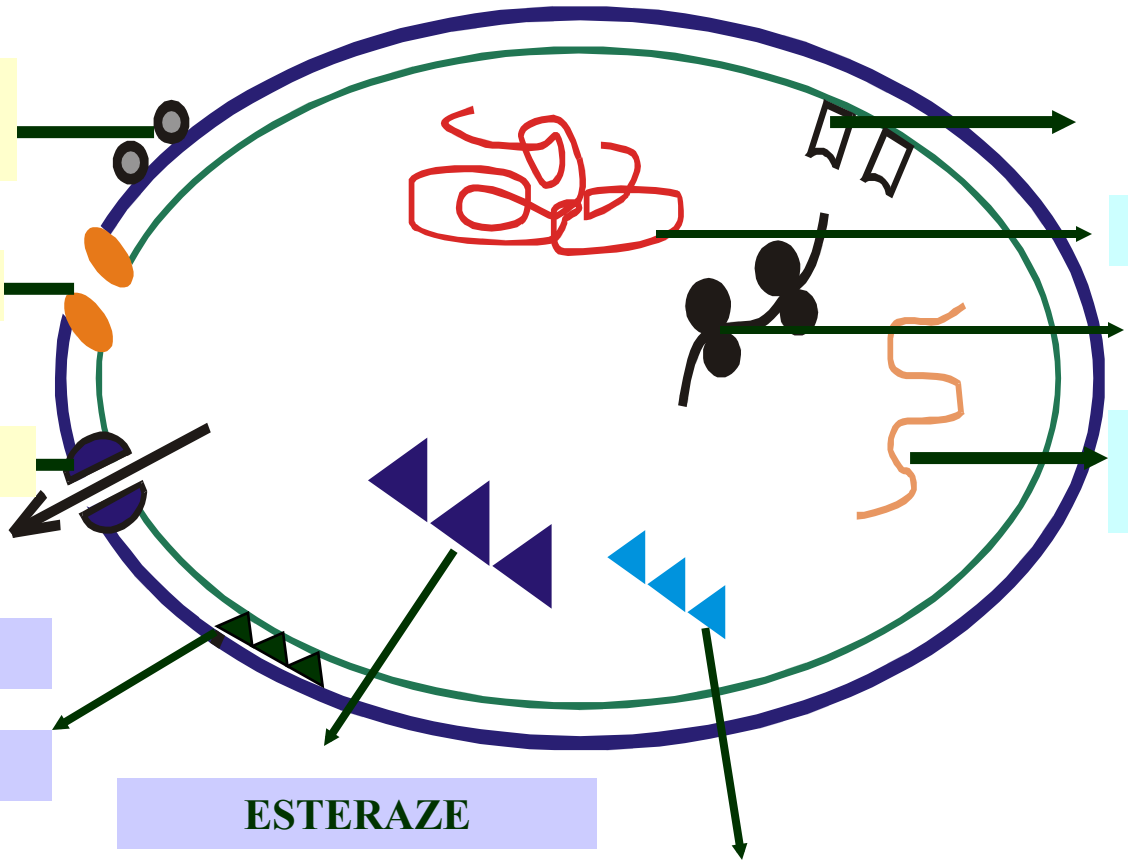
IZMENA CILJNOG PROTEINA

PVP

DNK GIRAZA

RIBOZOMI

RNK POLIMERAZA



Antibiotic Resistance Cycle

Increased Antibiotic Use

Increase in resistant strains

Ineffective empiric therapy
- ➡ Increased morbidity
- ➡ More antibiotics

Increased hospitalization
- ➡ More antibiotics

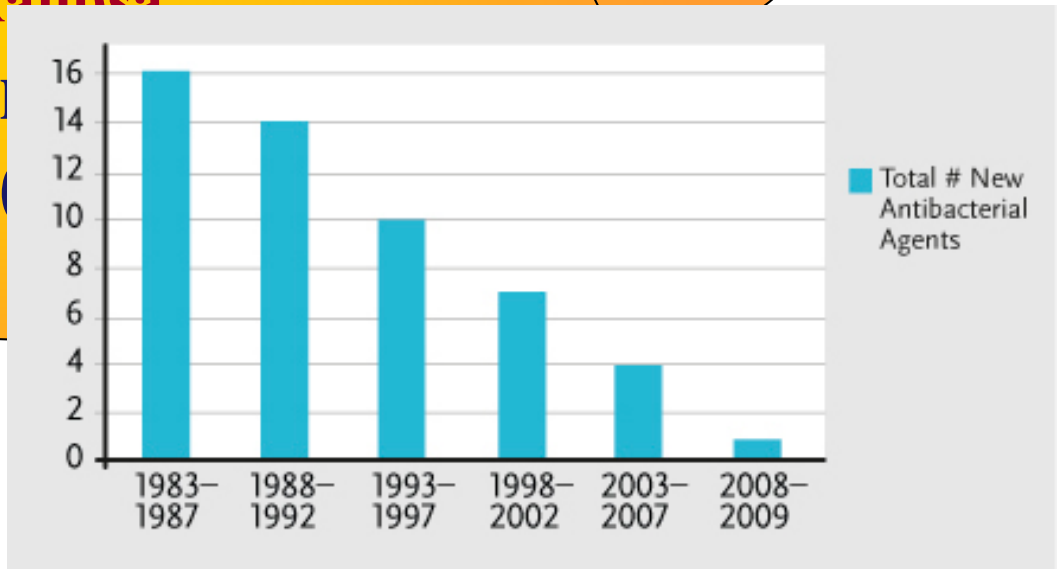
Increased healthcare resource use

Limited treatment alternatives
- ➡ More antibiotics
- ➡ Increased mortality

Bad bugs, No drugs !

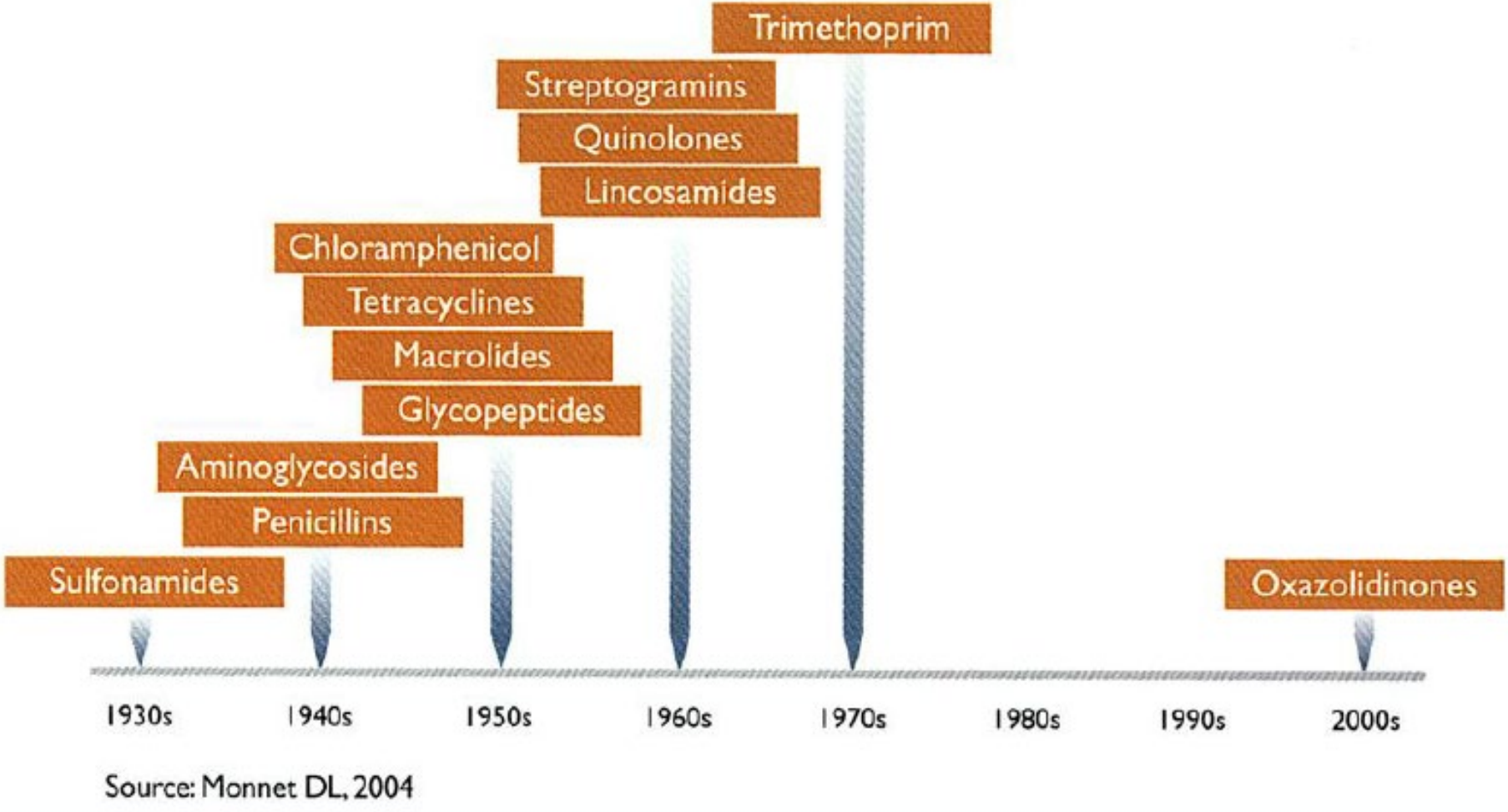
rezistencija na AB sa najmanje NE,
rezistencija prema efikasnim AB,
strah od rezistencije prema svim AB
(postoje sojevi rezistentni i na 10 AB),
neizvestan ishod,
“nova apokalipsa”

Nema novih a
1983-4, 2



Ko pobeđuje u borbi protiv mikroorganizama ?

New Antibacterial Classes???



Source: Monnet DL, 2004

New antibiotics

- daptomycin, lipopeptide, FDA 2003
- linezolid, oxazolidine, FDA 2000
- piperacillin/tazobactam, ureidopenicillin + inh. beta-lact., FDA 1993/2005
- imipenem/cilastatin, carbapenem + inhibitor dipeptidase, FDA 2006
- tigecycline, glycylcyklines, FDA 2005
- ceftarolim, 2010

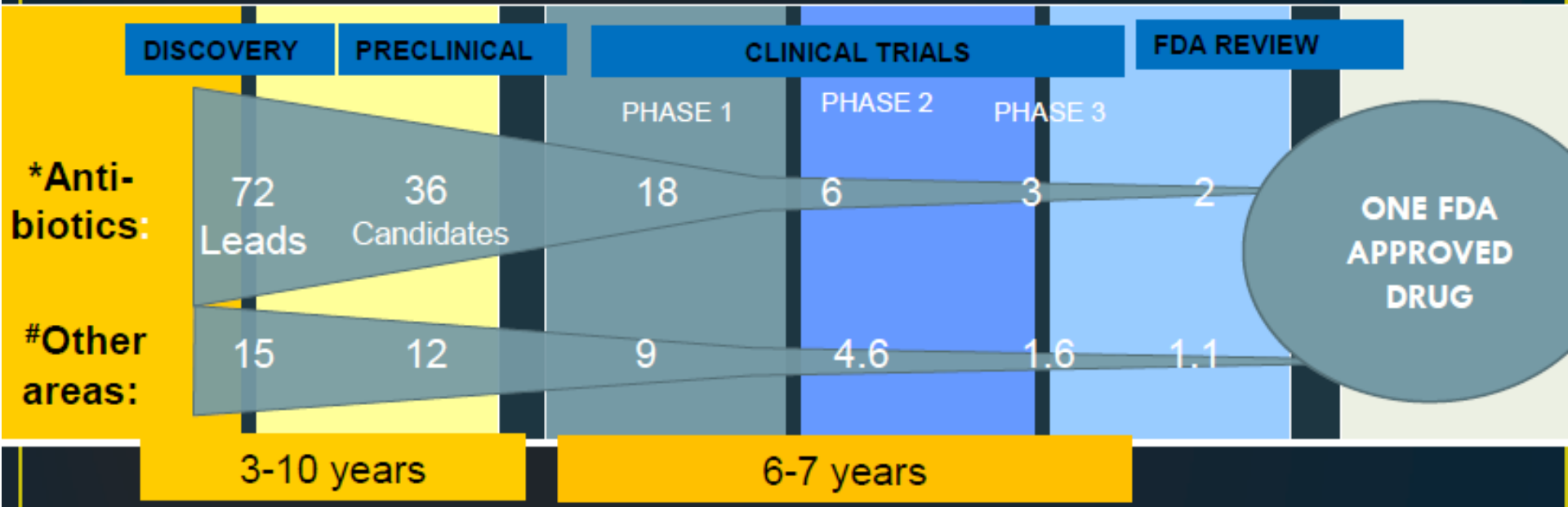
Drug	Class	Target	Mechanism	Route	Potential Class Adverse Events
Linezolid (Approved)	Oxazolidinone	Ribosome A Site	Static	Oral/IV	Marrow Suppression
Quinopristin / dalfopristin (Approved)	Streptogramin	Ribosome	Static	IV	Musculoskeletal Pain, Phlebitis
Approved	Glycopeptide	Cell Wall D-Ala D-Lac	Cidal	IV	Hypersensitivity
Approved	Lipopeptide	Cell Membrane	Cidal	IV	Skeletal Muscle
Approved	Tetracycline	Ribosome	Static	IV	GI Intolerance

Many Disincentives to Antibiotic R&D

Therapy Area	NPV*	Develop-ment ($$)	Develop-ment (years)	Price	Use	Patient pop
Musculo-skeletal	$1150m	$$$$	+++	↑↑↑	Chronic	Large
Neurology	$720m	$$$$	++++	↑↑	Chronic	Large
Oncology	$300m	$$$	++	↑↑↑	Acute/ Chronic	Medium
Anti-bacterials	$100m	$$$	+++	↑	Acute	Small (specialist hospital antibiotics)

David Payne, GSK, September 2011 IDSA/Pew/PhRMA conference
*Projan 2003

Antibiotics have high attrition rates



*Discovery to Phase 2 attrition based on real data for 12 novel mechanism antibiotic candidates at GSK

*Hit to Phase 2 based on novel mechanism AB discovery (GSK) #Based on Paul, et al (2010), Nature Reviews Drug Discovery 9: 203-214. David Payne , GSK, September 2011 IDSA/Pew/PhRMA Meeting

2009 analyses by IDSA & European Centre for Disease Prevention and Control (ECDC)/European Medicines Agency (EMA)

- **samo 15-16 antibiotika u razvoju**
- **samo 8 protiv GNB; koje izazivaju najopasnije po život infekcije**
- **od njih, NI JEDAN NIJE PROTIV bakterija rezistentnih na sve AB**

Boucher et al. Clinical Infectious Diseases 2009; 48:1–12

Dve godine kasnije….2011 IDSA dopuna

- **10 jedinjenja aktivnih protiv GNB, u kliničkim istraživanjima kao IV th**
- **i dalje NI JEDAN NIJE PROTIV bakterija rezistentnih na sve antibiotike**
- **nema studija sa antibioticima protiv GNB koje ugrožavaju život**

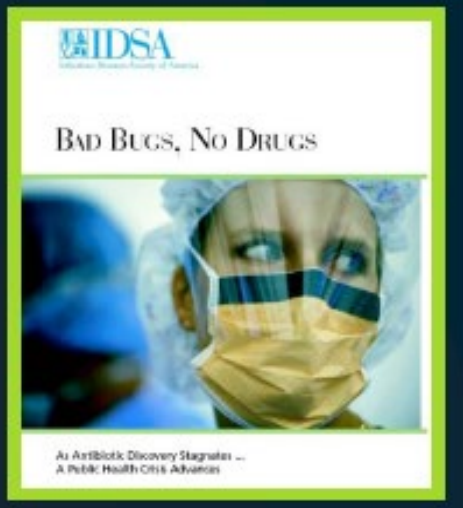
(hospital-associated pneumonia), > 20% pacijenata umire

“Antibiotic resistance is rising for many different pathogens that are threats to health,”

“If we don’t act now, our medicine cabinet will be empty and we won’t have the antibiotics we need to save lives.”

CDC Director Tom Frieden, M.D., M.P.H.

The 10 x '20 Initiative



Bad Bugs Need Drugs

10x'20

Ten new **ANTIBIOTICS** by 2020

Current Status of the 10 x ‘20 Initiative

10
9
8
7
6
5
4
3
2
1

Bad Bugs Need Drugs

10x‘20

Ten new **ANTIBIOTICS** by 2020

ceftaroline fosamil: Forest Laboraties, Inc.
Approved October 29, 2010

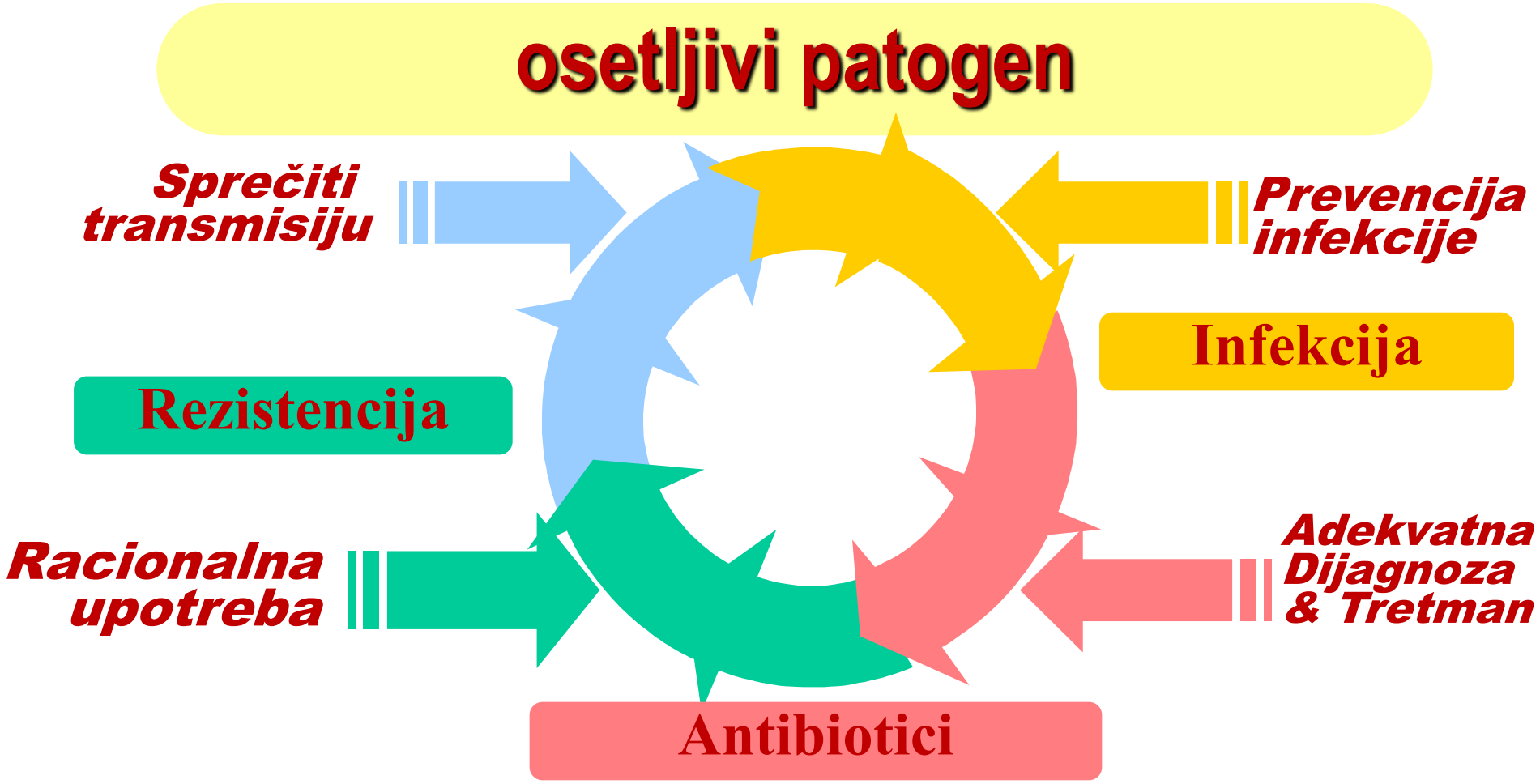
Preporuke za prevenciju i kontrolu rezistencije

- **Ukoliko je moguće primenjivati protokole dekolonizacije u borbi protiv MRO, pre svega MRSA**
- **Pratiti diseminaciju rezistencije na lokalnom i globalnom nivou**
- **Detektovati nove mehanizme rezistencije**
- **Sprovoditi kontinuiranu edukaciju zdravstvenih radnika**

Centar za prevenciju i kontrolu bolesti SAD, decembar 2006. godine

REZISTENCIJA NA ANTIBIOTIKE

strategija za prevenciju



Šta znamo o našoj mikrobioti?

GUT MICROBIOTA WORLDWATCH

Crevna mikrobiota je teža od

1 to 2 Kg

95%

Naših bakterija je u GIT u

Površina creva je veća od 2 teniska terena

400 m²

Bakterije su 10-50x manje nego naše ćelije

bacteria

0,5 - 5 µm

human cell

Bakterija ima 10x više nego naših ćelija

10:1

Naše bakterije mogu da opasaju zemljinu kuglu

2,5 times

The Human Microbiome: Are We More Microbial than Human?

Richard Losick (Harvard): Are We More Microbial than Human?

Are We More Microbial than Human?

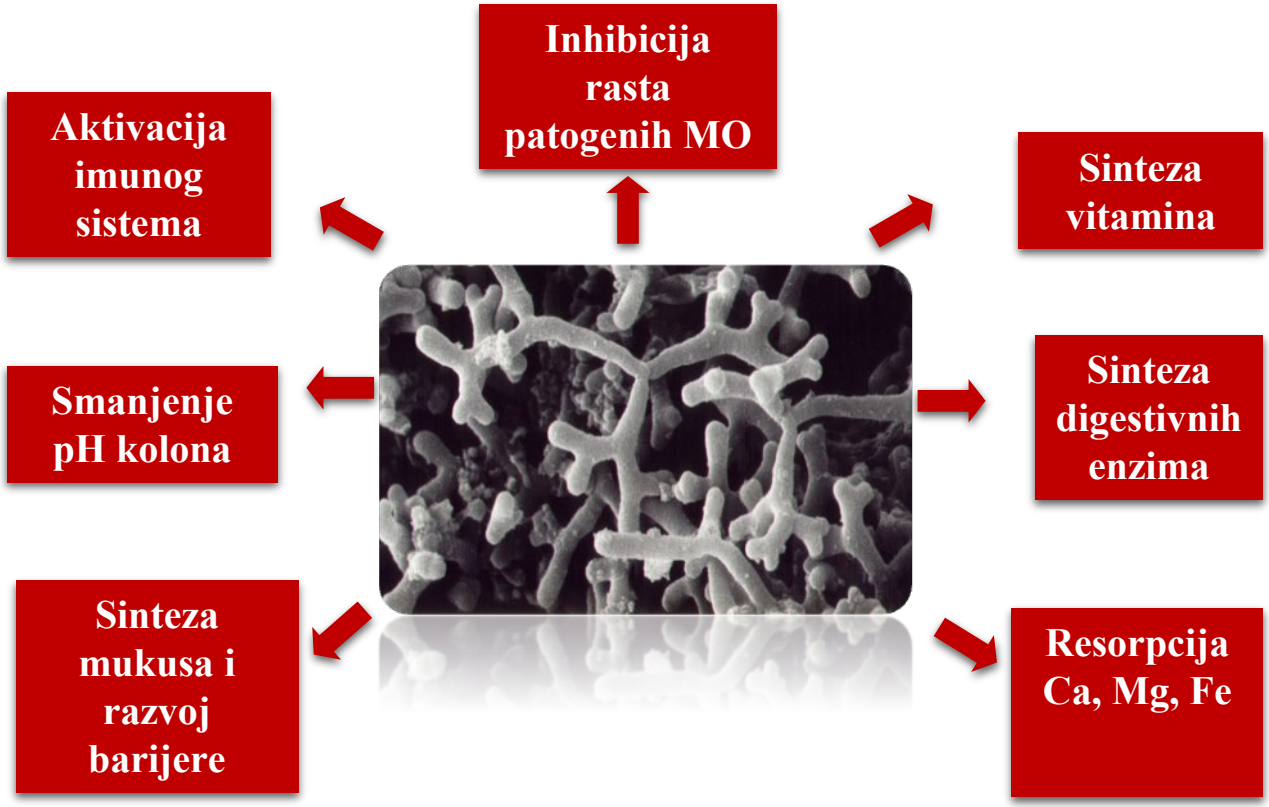
Watch later Share

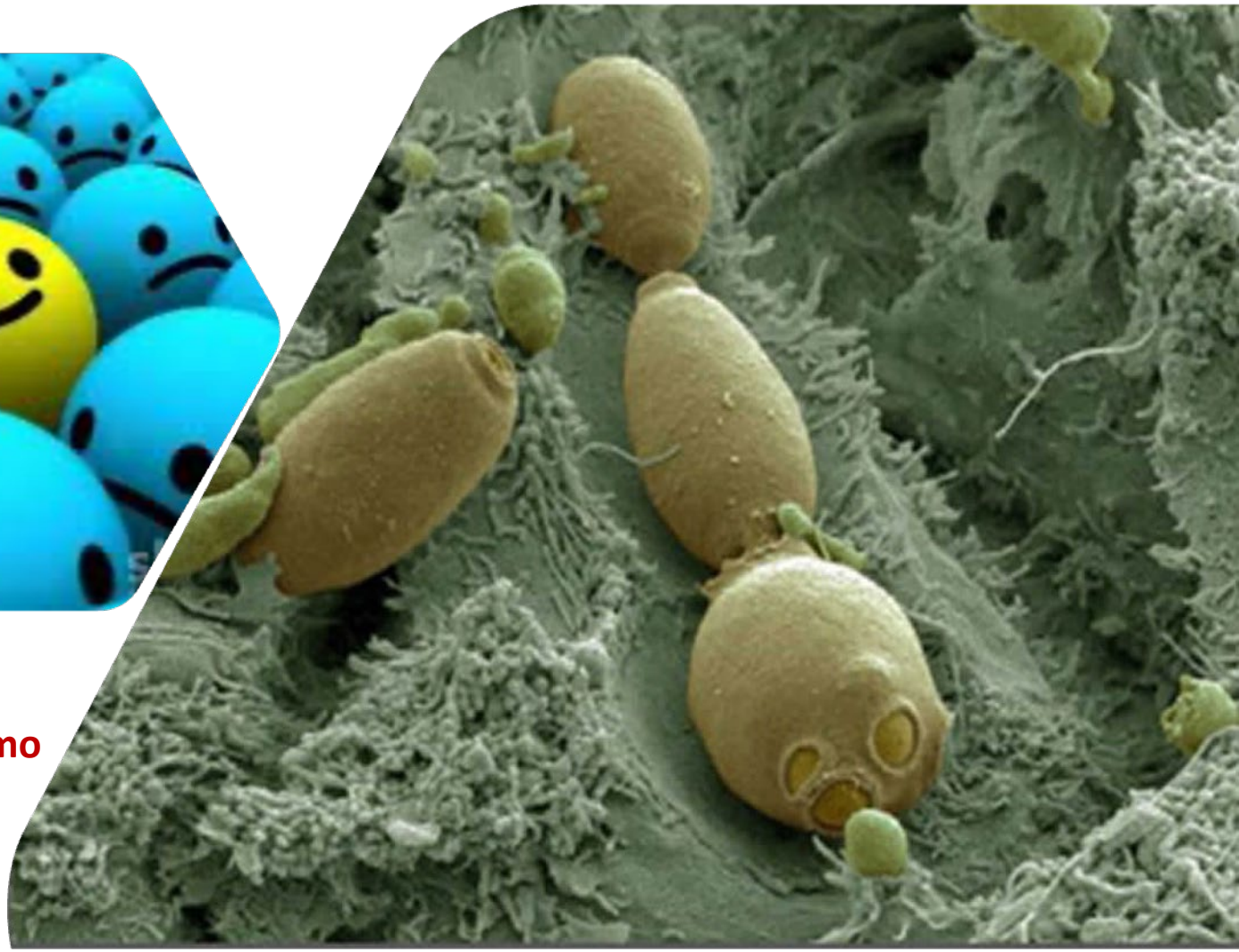
Richard Losick

Harvard University

MORE VIDEOS

Uloga probiotika

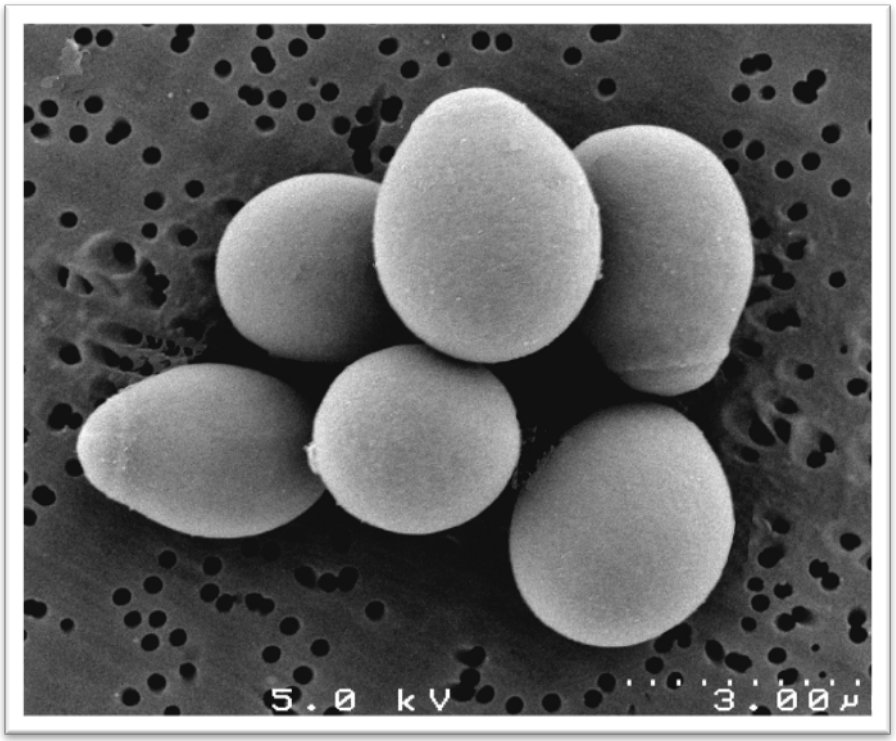


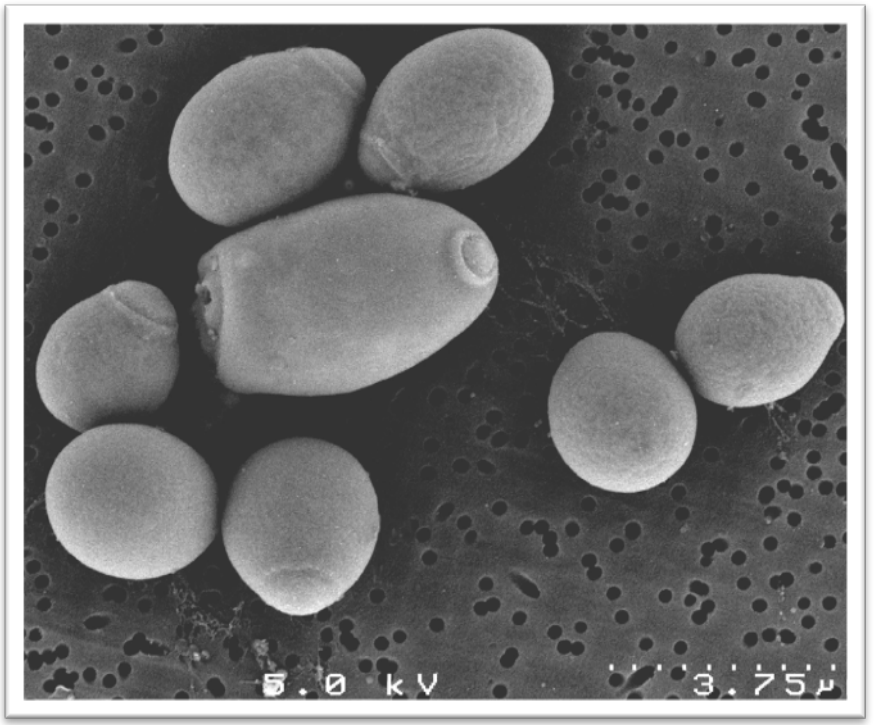


Sve su bakterije ali je samo jedna probiotska gljiva

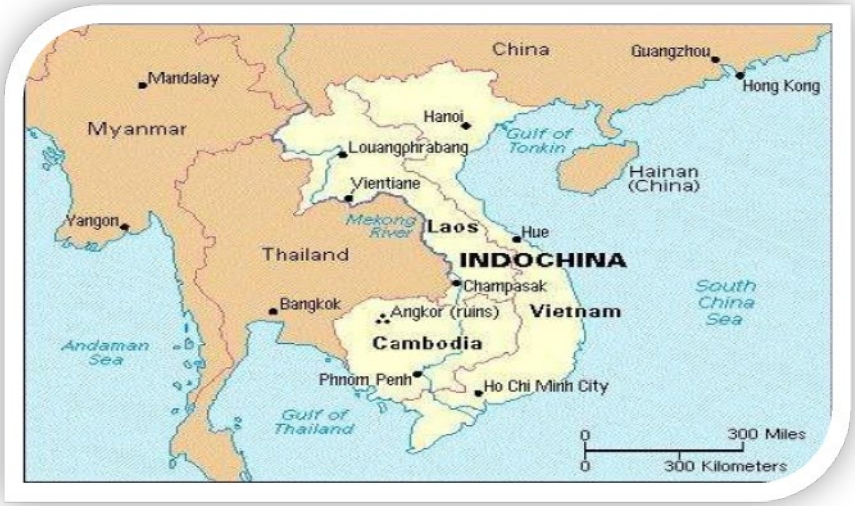
Postoji samo jedna probiotska gljivica

Saccharomyces boulardii





Sve je počelo 1920-tih u Indokini...



1923. ***Henri Boulard****, francuski mikrobiolog, otkrio je da dijareje kod kolere brže prolazi kod seljana koji su žvakali koru azijske trešnje liči i mangostina.*

Saccharomyces boulardii

Moguća terapijska upotreba probiotika

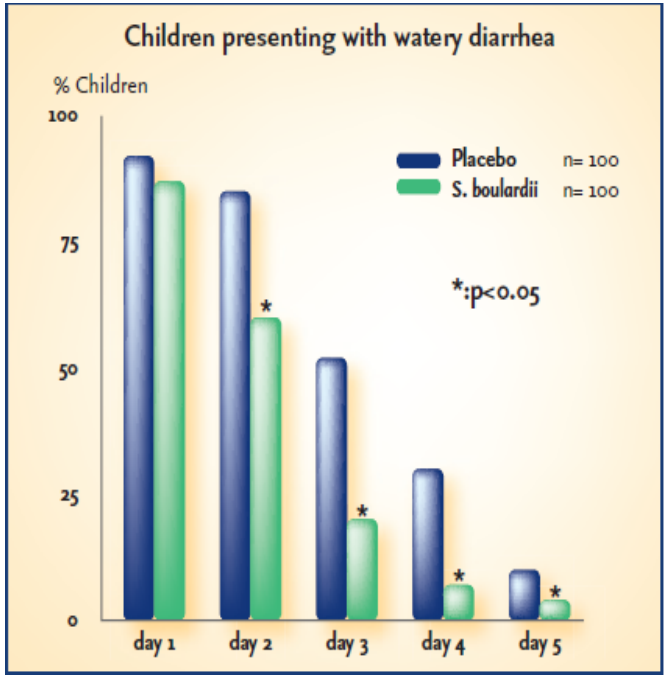
- **Sigurni efekti**
  - Akutni virusni gastroenteritis
  - Antibiotski proliv
  - Helicobacter pylori
  - Putnička dijareja
  - Iritabilni kolon
  - Paučitis
- **Mogući efekti**
  - Hronična opstipacija
  - Cistična fibroza
  - Ulcerozni kolitis
  - NESH
- **Pojedinačni izveštaji**
  - Akutni pankreatitis
  - Kolageni kolitis
  - Kolorektalni karcinom
  - Kronova bolest
  - Dijareja u TPN
  - Intolerancija na laktozu

Saccharomyces boulardi vs. bakterijski probiotici

Karakteristike probiotika	S.boulardii	bakterijski probiotici
veličina ćelije	10 µm	≈ 1 µm
otpornost na nizak pH (gastrični pH = 1,35 – 3,5)	da	ograničeno preživljavanje
otpornost na antibiotike	da	ne svi (zavisno od vrste)
transfer gena odgovornih za rezistenciju na AB	ne (eukariotski mikrorganizam)	da (prokariotski mikroorganizmi)
dospeva u kolon u aktivnom obliku	da	ne svi (zavisno od vrste)
produkcija masnih kiselina kratkog lanca	**da**	**ne svi (zavisno od vrste)**
povećava koncentraciju enzima "četkastog pokrova"	**Da**	**ne svi (zavisno od vrste)**
povećava sekreciju IgA	da	ne svi (zavisno od vrste)
trajna intestinalna kolonizacija	ne	da
pogodan za decu (od 2. meseca)	da	ne svi (zavisno od vrste)

Akutna dijareja

- Bulardi je efikasan u tretmanu akutne dijareje



Kurugol et al. Acta Paediatr. 2005; 94(1): 44-7.

Metodologija:

- Randomizovana, dvostruko slepa, placebo kontrolisana studija.
- 200 dece uzrasta od 3 meseca do 7 godina
- S. boulardi: doza 5 x 10^9 CFU dnevno tokom 5 dana

Patogeni uzročnici:

1. Rotavirusi 41,5%
2. Paraziti 5,5%
3. Shigella 2,5 %
4. Salmonella 2,0%
5. Ostali 48,5%

Akutna dijareja

- Bulardi je efikasan u tretmanu akutne dijareje, 7 dana x 5x 10^9 CFU

Patient characteristics	S. boulardii group (n=128)	Control Subjects (n= 122)	P value
Duration of diarrhea (days)	4.2	5.1	0.001
Mean number of stools reported on day 0	10.8	10.5	NS
Mean number of stools reported on day 3	3.1	4.5	0.01
Mean number of stools reported on day 6	1.5	3.7	0.001

NS= Nonsignificant

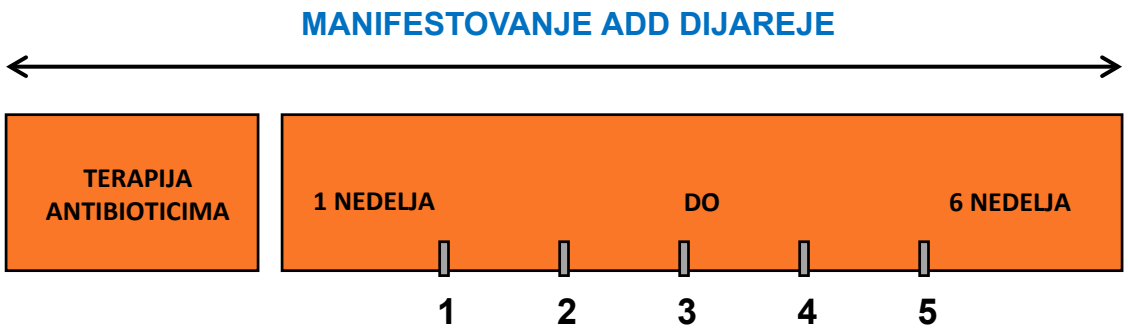
CONCLUSION

S. boulardii has been used as probiotic since last 6 decades, and it has been investigated in several clinical trials worldwide. S. boulardii is significantly effective for the prevention of acute adult diarrhea.

Sholars Journal of Applied Medical Science (SJAMS), 2017, 5 (7D): 2771-2774

EPIDEMIOLOGIJA ANTIBIOTSKIH DIJAREJA

- **ANTIBIOTICI- najčešće korišćeni lekovi**
- **15-25% pacijenata na antibioticima dobije dijareju**
- **15-25%** od njih **ima *C. difficile* kolitis**



*Diarrhées des traitements antibiotiques - *Beaugerie. Rev Prat. 1996; 46(2): 171-6.*

VODEĆI UZROCI SMRTNOSTI

Causes of Death from Gastrointestinal and Liver Diseases

Cause of death	No. of deaths (underlying cause)	No. of deaths (contributing cause)	Crude rate (per 100,000)[b]	ICD-10 code
ıstrointestinal causes of death in the United States, 2009[a]				
Colorectal/anal cancer	52,394	61,233	17.1	C18.0-C21.9
Pancreatic cancer	35,628	37,134	11.6	C25.0-C25.9
Malignant neoplasms of the liver and ntrahepatic bile ducts	19,352	20,923	6.3	C22.0-C22.9
Fibrosis/cirrhosis	15,298	31,017	5.0	K74
Alcoholic liver disease	15,183	20,151	5.0	K70
Esophageal cancer	13,908	15,071	4.5	C15.0-C15.9
Gastric cancer	11,185	12,062	3.7	C16.0-C16.9
Vascular disorders of the intestine	8382	15,694	2.7	K55
Clostridium difficile colitis	7251	11,319	2.4	A04.7
Gastrointestinal hemorrhage, unspecified	7215	26,981	2.4	K92.2
Chronic hepatitis C	6980	16,207	2.3	B18.2
Paralytic ileus and intestinal obstruction	5965	15,494	1.9	K56
Hepatic failure, unspecified	4010	23,795	1.3	K72
Acute pancreatitis	3065	5588	1.0	K85
Ulcers (gastric/duodenal/peptic)	2956	6576	1.0	K25-K28
Diverticular disease	2940	4860	1.0	K57
Malignant neoplasms of the gallbladder	2048	2152	0.7	C23
Cholecystitis	2009	3295	0.7	K81
Perforation of the intestine (nontraumatic)	1996	5241	0.7	K63.1

*GASTROENTEROLOGY 2012;143:1179–1188

No 1.
URGENT THREAT

HAZARD LEVEL
URGENT

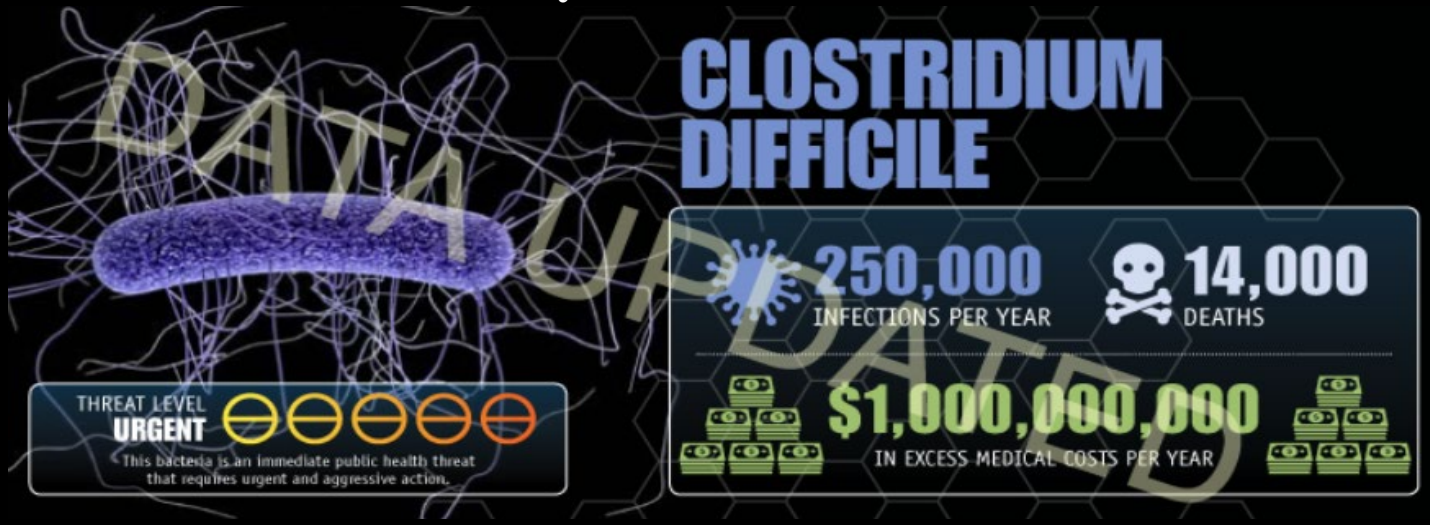
These are high-consequence antibiotic-resistant threats because of significant risks identified across several criteria. These threats may not be currently widespread but have the potential to become so and require urgent public health attention to identify infections and to limit transmission.

Clostridium difficile (C. difficile), Carbapenem-resistant Enterobacteriaceae (CRE), Drug-resistant *Neisseria gonorrhoeae* (cephalosporin resistance)

Update CDC 2015:

500000 / year
15000 deaths
3.8 bilions can be saved/5 y

- Clostridium Difficile (CDIFF)
- Carbapenem-Resistant Enterobacteriaceae (CRE)
- Neisseria gonorrhoeae



2015 CDC study

Clostridium difficile infection (CDI)

Tradicionalne školske činjenice

Clostridium difficile pseudomembranous colitis je posledica primene klindamicina i leči se metronidazolom

C. difficile infection (CDI) udružena sa mnogim drugim antibioticima i često rezistentna na metronidazol


Povezan sa širokom primenom fluorohinolona i cefalosporina
Visok nivo rezistencije na fluorohinolone
“Hipervirulentan”
18-puta više toksina A & B
Binarni toksin: Pojačano vezivanje i ulazak toksina u ćelije

BI/NAP1/027

Tradicionalna lista antibiotika udruženih sa CDAD

MORE FREQUENT	LESS FREQUENT
Cephalosporins (3rd and 4th generation)	Ticarcillin-clavulanate
Ampicillin/Amoxicillin	Metronidazole
Clindamycin	Fluoroquinolones
Other penicillins	Rifampin
Macrolides	5-Fluorouracil
Tetracyclines	Methotrexate
Trimethoprim-Sulfamethoxazole	Cyclophosphamide

ANTIBIOTICI – KOJI SU “NAJGORI”?

RIZIK ZA ANTIBIOTSKI KOLITIS	ANTIBIOTIK
VISOK	KLINDAMICIN, FLUOROHINOLONI, CEFALOSPORINI II i III i IV GENERACIJE
SREDNJI	MAKROLIDI, AMOKSICILIN, AMPICILIN
NIZAK	AMINOGLIKOZIDI, TETRACIKLINI, BAKTRIM,BENZILPENICILIN, PIPERACILIN - TAZABAKTAM

Basetti M, Exp Rev Anti Infect Ther 2012:10:1405-1423

PubMed.gov

antibiotic colitis

Search

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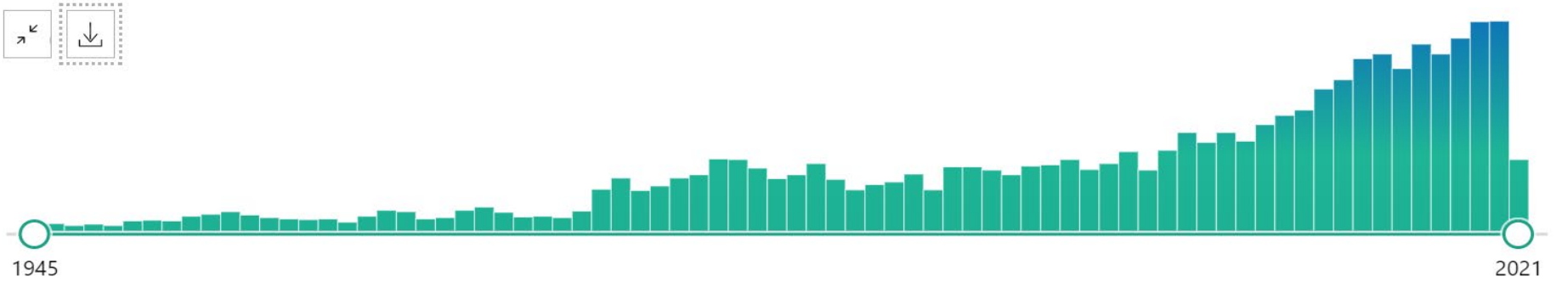
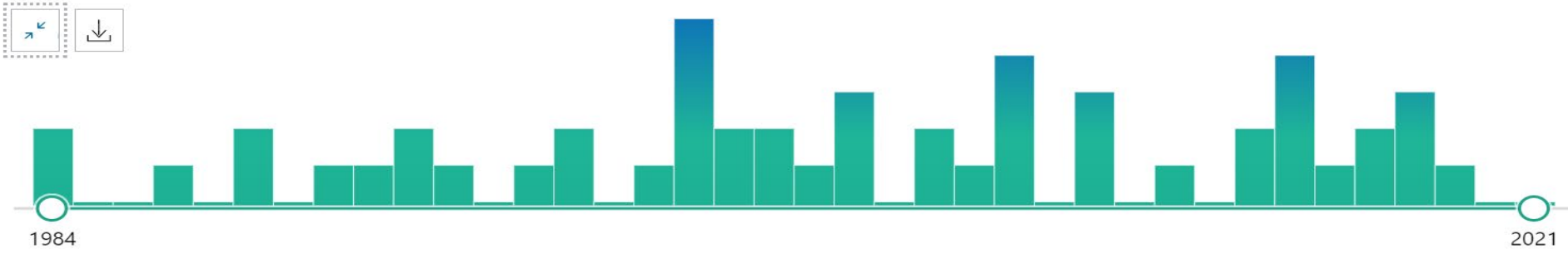
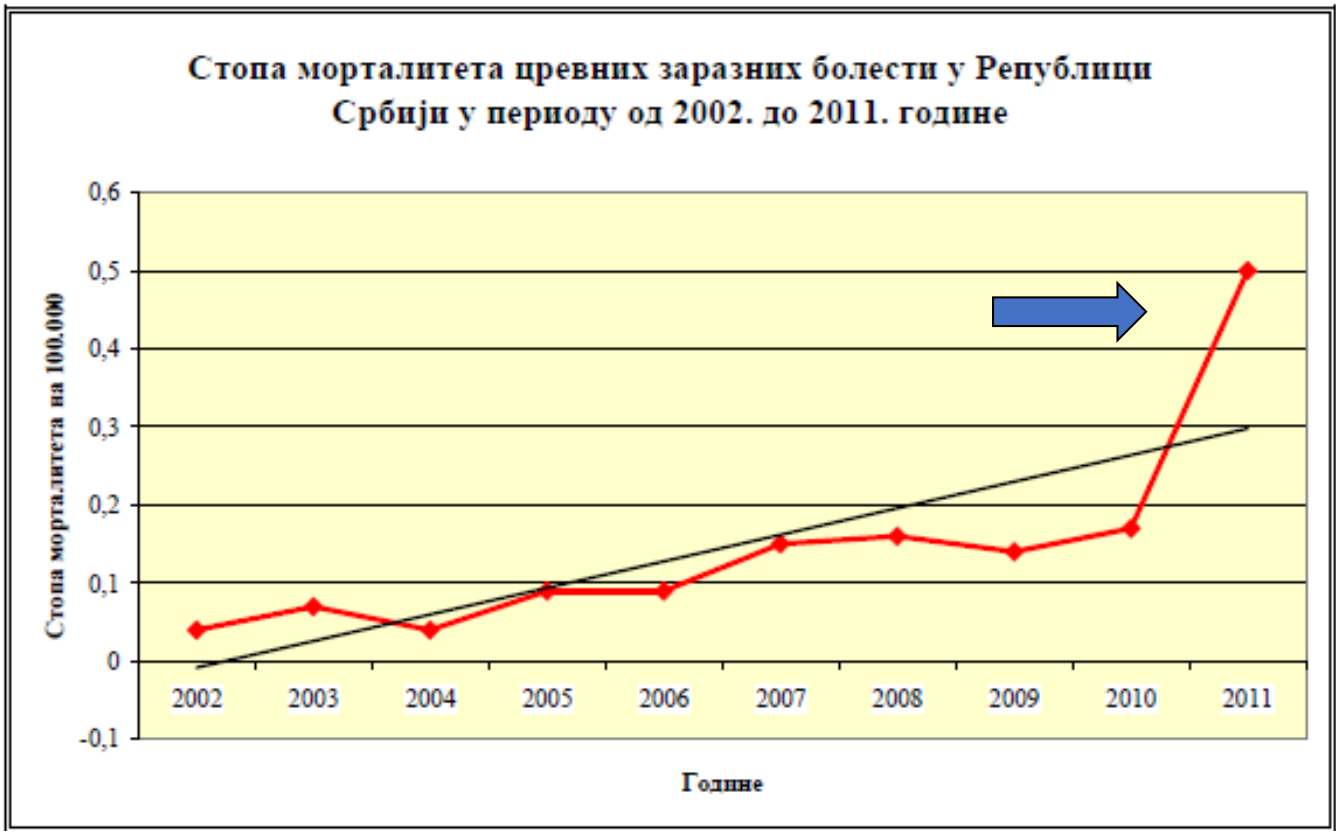
RESULTS BY YEAR 6,242 results



RESULTS BY YEAR 50 results





Najstariji, > 60 g., porast mortaliteta za 35,4% 2011. godine

Vodeći uzroci : septikemija, ***Clostridium difficile***, TBC, Influenza...

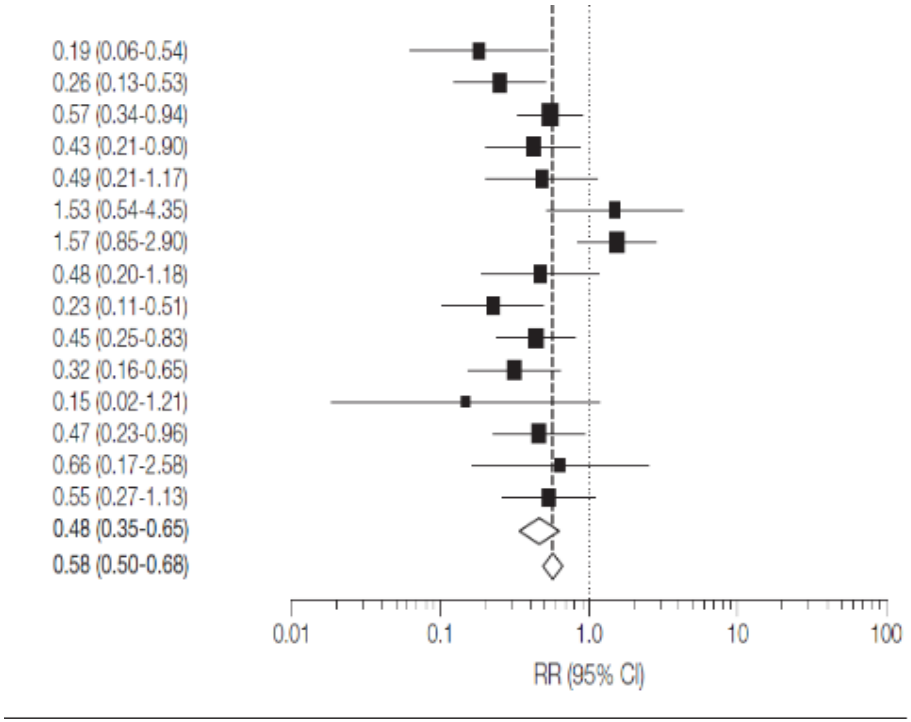
Preuzeto sa sajta IZJZ "M.J. Batut"

PREVENCIJA ANTIBIOTSKOG KOLITISA

META ANALIZA

- **63 RCT**
- **11.800 PACIJENATA**
- **SMANJENJE RELATIVNOG RIZIKA JE**

uz probiotike 62%



JAMA. 2012;307(18):1959-1969

PREPORUKE ZA UPOTREBU PROBIOTIKA 2015. update

TABLE 1. Recommendations for Probiotic Use: Update 2015

Clinical Condition	Effectiveness	Specific Strain of Organism and Strain References	References
Diarrhea			
Infectious childhood—treatment	A	LGG, *Saccharomyces boulardii*, *Lactobacillus reuteri* SD2112	27–30
Prevention of infection	B	*S. boulardii*, LGG	27,28,30
Prevention of AAD	A	*S. boulardii*, LGG, combination of *L. casei* DN114 G01, *L. bulgaricus*, snf *Streptococcus thermophilus*	31–33
Prevention of recurrent CDAD	B/C	*S. boulardii*, LGG, FMT	34–37
Prevention of CDAD	B/C	LGG, *S. boulardii*	34,37
IBD			
Pouchitis			
Preventing and maintaining remission	A	VSL#3	38–40
Induce remission	C	VSL#3	41
Ulcerative colitis			
Inducing remission	B	*Escherichia coli* Nissle, VSL#3	42–44
Maintenance	A	*E. coli* Nissle, VSL#3	43–45
Crohn's	C	*E. coli* Nissle, *S. boulardii*, LGG	46–48
IBS			
	B	*Bifidobacterium infantis* B5624, VSL#3	49–53*
	C	*B. animalis*	54
		L. plantarum 299V	55

Floch M. et al. Recommendations for Probiotic Use—2015 Update. Proceedings and Consensus Opinion. J Clin Gastroenterol 2015;49:S69–S73.

S. boulardii i LGG najviši nivo preporuke 1 za prevenciju AAD – WGO 2017

PEDIATRIC Disorder, action	Probiotic strain, prebiotic, synbiotic	Recommended dose	Evidence level*	Refs.	Comments
	Bacillus mesentericus and *Clostridium butyricum* and *Enterococcus faecalis*	1.1 × 10^7 CFU) & *Clostridium butyricum* (2.0 × 10^7 CFU) and *Enterococcus faecalis* (3.17 × 10^8 CFU)	3	[72,83]	
	Lactobacillus acidophilus, L. paracasei, L. bulgaricus, L. plantarum, Bifidobacterium breve, B. infantis, B. longum, Streptococcus thermophilus (VSL#3)		3	[72,84]	ESPGHAN/ESPID: Insufficient evidence to make a recommendation (only one RCT available and no strain identification))
	Lactobacillus acidophilus & *L. rhamnosus* & *Bifidobacterium longum* & *Saccharomyces boulardii* CNCM I-745		3	[72,85]	
Prevention of antibiotic-associated diarrhea	LGG	1–2 × 10^{10} CFU	1	[86,87]	ESPGHAN Working Group on Probiotics
	Saccharomyces boulardii	250–500 mg	1	[12]	
Prevention of nosocomial diarrhea	LGG	10^{10}–10^{11} CFU, twice daily	1	[12]	Meta-analysis of RCT
	Bifidobacterium bifidum and *Streptococcus thermophilus*		2	[88]	–
Infections in children attending day-care centers	LGG		1	[89–91]	Prevention of AAD in hospitalized patients
	Lactobacillus reuteri DSM 17938	1 × 10^8 CFU/day for 3 months	2	[92,93]	
	Lactobacillus casei DN-114 001 in fermented milk	10^{10} CFU, once daily	2	[94–96]	–
	Lactobacillus casei Shirota in fermented milk	10^{10} CFU, once daily	2	[97]	–

Prof. Hanna Szajewska becomes the scientific leader of the Medical University of Warsaw

Editor: Iwona Kazimierska | Date: August 27, 2020 Source: WUM

Departments: News in Health Manager News

The Medical University of Warsaw has published a ranking of 100 research leaders in 2017-2019, prepared on the basis of criteria developed by the University Research Council.

The summary summarizing the achievements of 2017-2019 includes employees included in the N number at the Medical University of Warsaw (employed at the university as of May 31, 2020).

The first place was taken by prof. Hanna Szajewska, head of the Department of Paediatrics, UCK Medical University of Warsaw (5,958.31 p.); the second prof. Jolanta Małyszko, head of the Department and Clinic of Nephrology, Dialysis and Internal

WE RECOMMEND

- Draft of a new reimbursement list
- I do not regret any day spent in "Polish Mother" ▶
- About control in health care
- Health insurance for everyone

17 RCT sa 3631p

Cilj: incidenca AAD

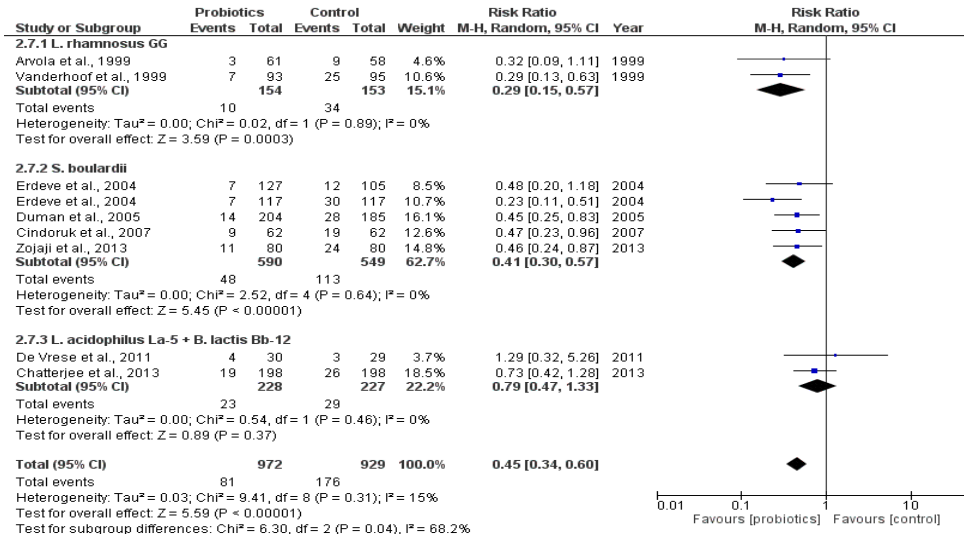
Probiotici značajno smanjuju rizik za AAD

(8,00% vs 17,7%,

RR: 0,49

S.Boulardi 0,41

L.Rhamnosus GG O,29

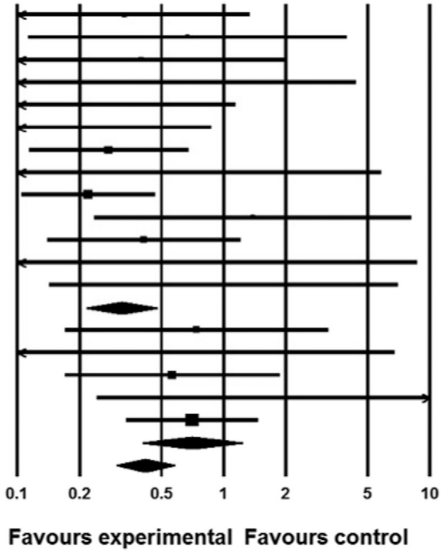


Antibiotics **2017**, *6*, 21; doi:10.3390/antibiotics6040021

Timely Use of Probiotics in Hospitalized Adults Prevents Clostridium difficile Infection: A Systematic Review With Meta-Regression Analysis

Gastroenterology 2017;152:1889–1900

Time to dose	Study name	Events / Total		Relative weight	Risk ratio	p-Value
		probiotics	control			
2.000	Surawicz 1989	3 / 116	5 / 64	8	0.33	0.12
2.000	Thomas 2001	2 / 133	3 / 134	5	0.67	0.66
2.000	Plummer 2004	2 / 69	5 / 69	6	0.40	0.26
2.000	Can 2006	0 / 73	2 / 78	2	0.21	0.32
2.000	Beausoleil 2007	1 / 44	7 / 45	4	0.15	0.07
2.000	Hickson 2007	0 / 57	9 / 56	2	0.05	0.04
2.000	Rafiq 2007	5 / 45	22 / 55	20	0.28	0.00
2.000	Safdar 2008	0 / 23	1 / 17	2	0.25	0.39
2.000	Gao 2010	9 / 171	20 / 84	28	0.22	0.00
2.000	Pozzoni 2012	3 / 106	2 / 98	5	1.39	0.72
2.000	Ouwehand 2014	6 / 304	7 / 146	14	0.41	0.10
2.000	Wong 2014	0 / 76	1 / 82	2	0.36	0.53
2.000	Ehrhardt 2016	2 / 146	2 / 146	4	1.00	1.00
Summary estimate for 2.000					0.32	0.00
3.000	McFarland 1995	3 / 97	4 / 96	14	0.74	0.69
3.000	Wenus 2008	0 / 34	1 / 29	3	0.29	0.44
3.000	Miller 2008a	4 / 95	7 / 94	22	0.57	0.35
3.000	Miller 2008b	2 / 157	0 / 159	3	5.06	0.29
3.000	Allen 2013	12 / 1470	17 / 1471	57	0.71	0.35
Summary estimate for 3.000					0.70	0.22
Overall					0.42	0.00



19RCT – 6261p

Cilj: incidenca CDI

probiotici 1,6% vs

kontrola 3,9%,RR: 0,42

Probiotici značajno efikasniji ako se daju bliže prvoj dozi antibiotika

Smanjenje efikasnosti za svaki dan zakašnjenja

RR: 0,32 vs 0,70 (48h vs72h)

Saccharomyces boulardii
superioran u odnosu na druge probiotike!!!

"Only *S. boulardii* was effective for CDAD"

McFarland LV. Meta-analysis of probiotics for the prevention of Antibiotic Associated Diarrhea (AAD) and the treatment of *Clostridium difficile disease. Am J Gastroenterol. 2006: 101; 1-11.*

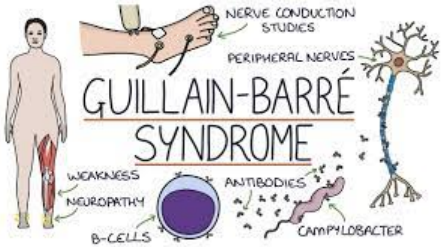
Nekoliko meta analiza i veliki broj randomiziranih studija pokazale su da je *Saccharomyces boulardii* rezistentan na antibiotike, te se preporučuje njegova primena uz svaki antibiotik.[1]

Czerucka D, Piche T, Rampal P. Review article: yeast as probiotics - Saccharomyces boulardii. Aliment Pharmacol Ther. 2007 Sep 15;26(6):767-78.

Putnička dijareja

<u>Najčešće samoograničavajuća bolest, ali i:</u>

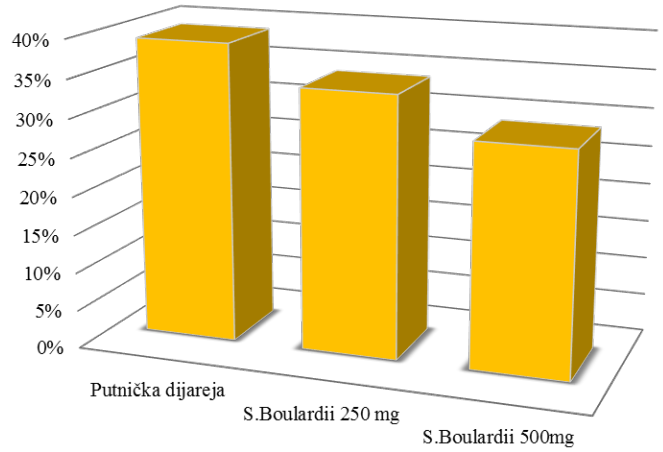
- Postinfektivne manifestacije (komplikacije)- IBS
- Reaktivni artritis
- Polineuritis (Guillain- Barreov sindrom)

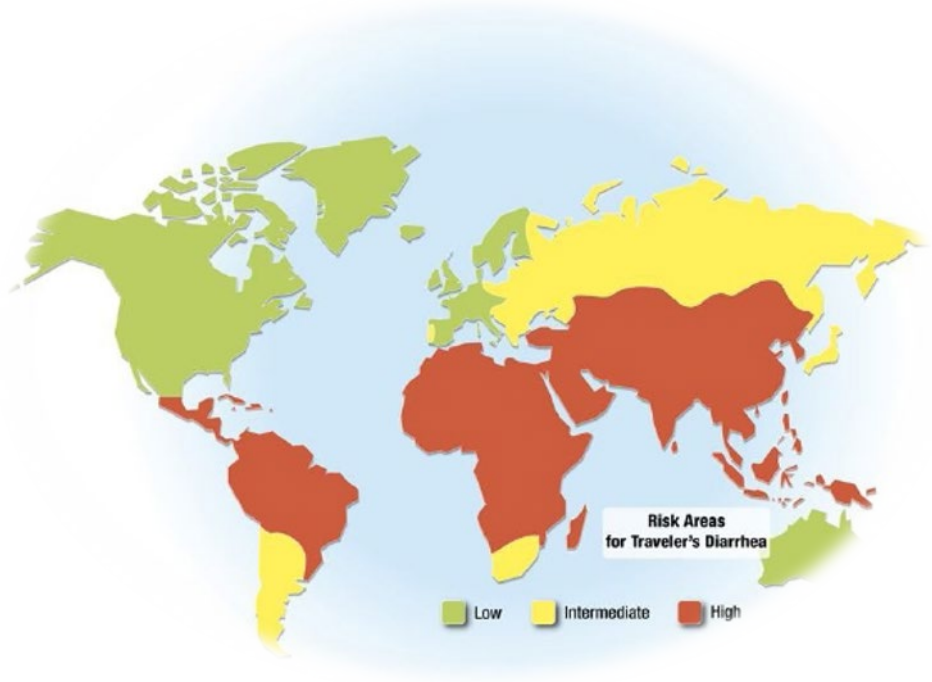


Giddings SL, Stevens AM, Leung DT. Traveler's Diarrhea. Med Clin North Am. 2016 Mar;100(2):317-30. doi: 10.1016/j.mcna.2015.08.017. PMID: 26900116; PMCID: PMC4764790.

Putnička dijareja

Bulardi smanjuje incidencu putničke dijareje

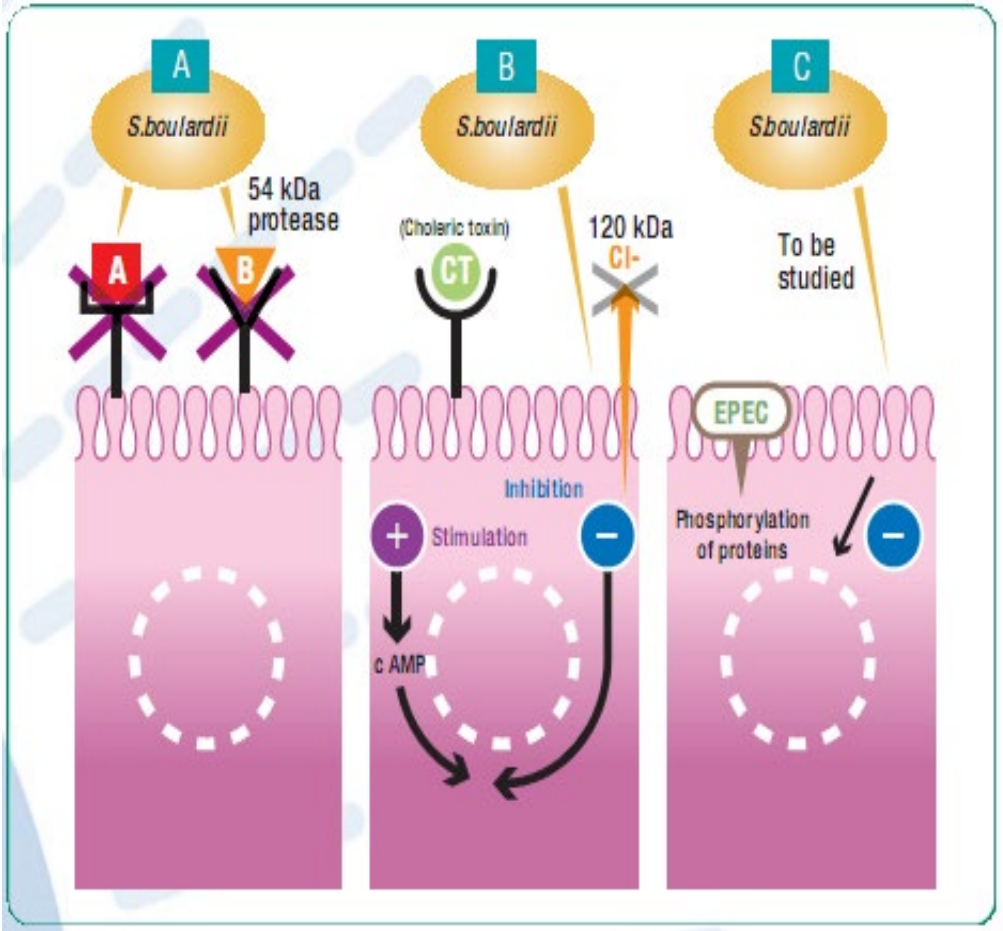




U obe grupe je došlo do statistički značajnog smanjenja dijareje u odnosu na placebo ($p<0.05$)

McFarland LV. Meta-analysis of probiotics for the prevention of traveler's diarrhea. Travel Med Infect Dis. 2007 Mar;5(2):97-105.

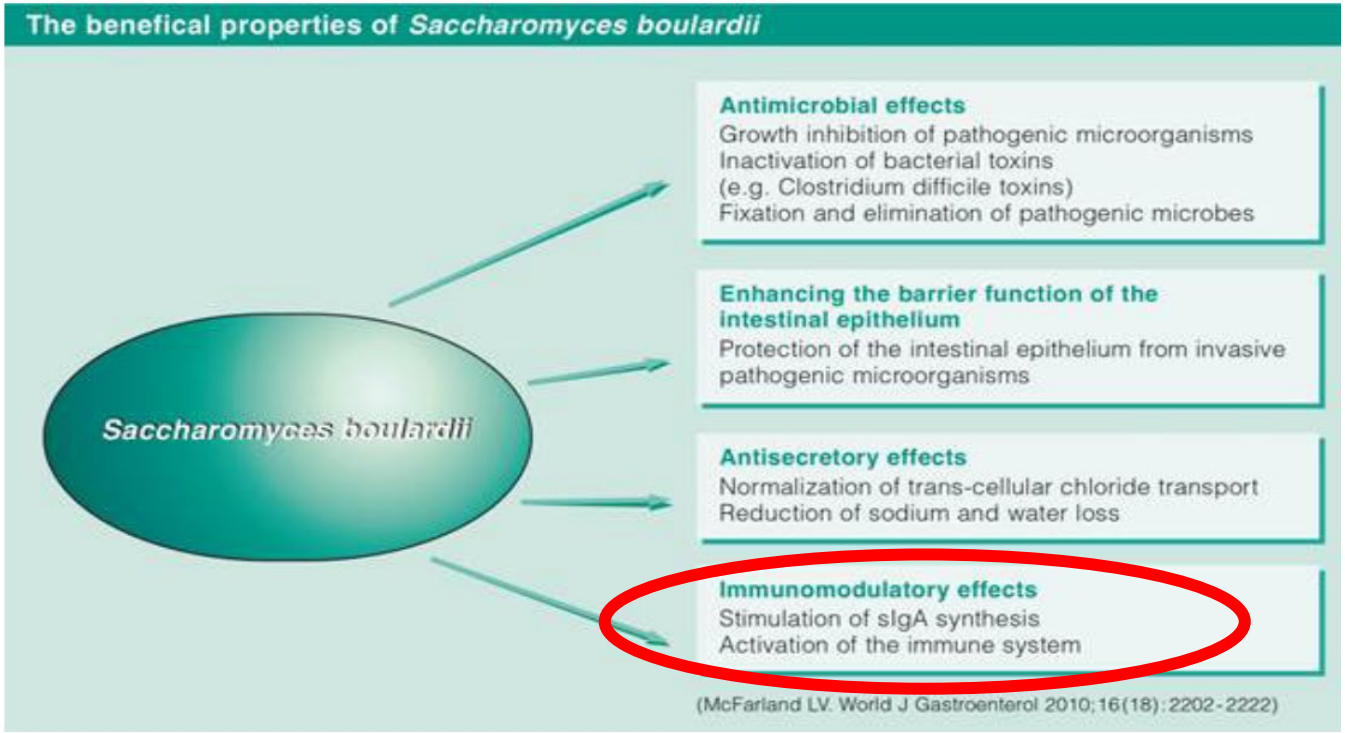
Saccharomyces boulardii mehanizam dejstva



1. Vrši proteolizu toksina A (i receptora) i B *C.difficile,* stimuliše produkciju At na toksin A
2. Zaustavlja sekreciju i gubitak hlorida
3. Zaustavlja fosforilaciju proteina *E.coli* i sprečava vezivanje za crevni epitel
4. Utiče na signalne puteve za inflamaciju (NF-κB i MAP kinaza) u intestinalnim ćelijama
5. Ekspresija PPARγ (glitazonski receptor) – sprečava inflamaciju (IBD, NASH, ateroskleroza...)
6. Sprečava bakterijski "overgrowth"

Pothoulakis C. Anti-inflammatory mechanisms of action of *Saccharomyces boulardii*. Aliment Pharmacol Ther. 2009;30:826-833.

Saccharomyces boulardii



Journal of Fungi

MDPI

J Fungi (Basel). 2020 Jun; 6(2): 78.

PMCID: PMC7344949

Published online 2020 Jun 4. doi: 10.3390/jof6020078

PMID: 32512834

Saccharomyces boulardii: What Makes It Tick as Successful Probiotic?

Pedro Pais,[1,2,†] Vanda Almeida,[1,2,†] Melike Yılmaz,[1,2] and Miguel C. Teixeira[1,2,*]

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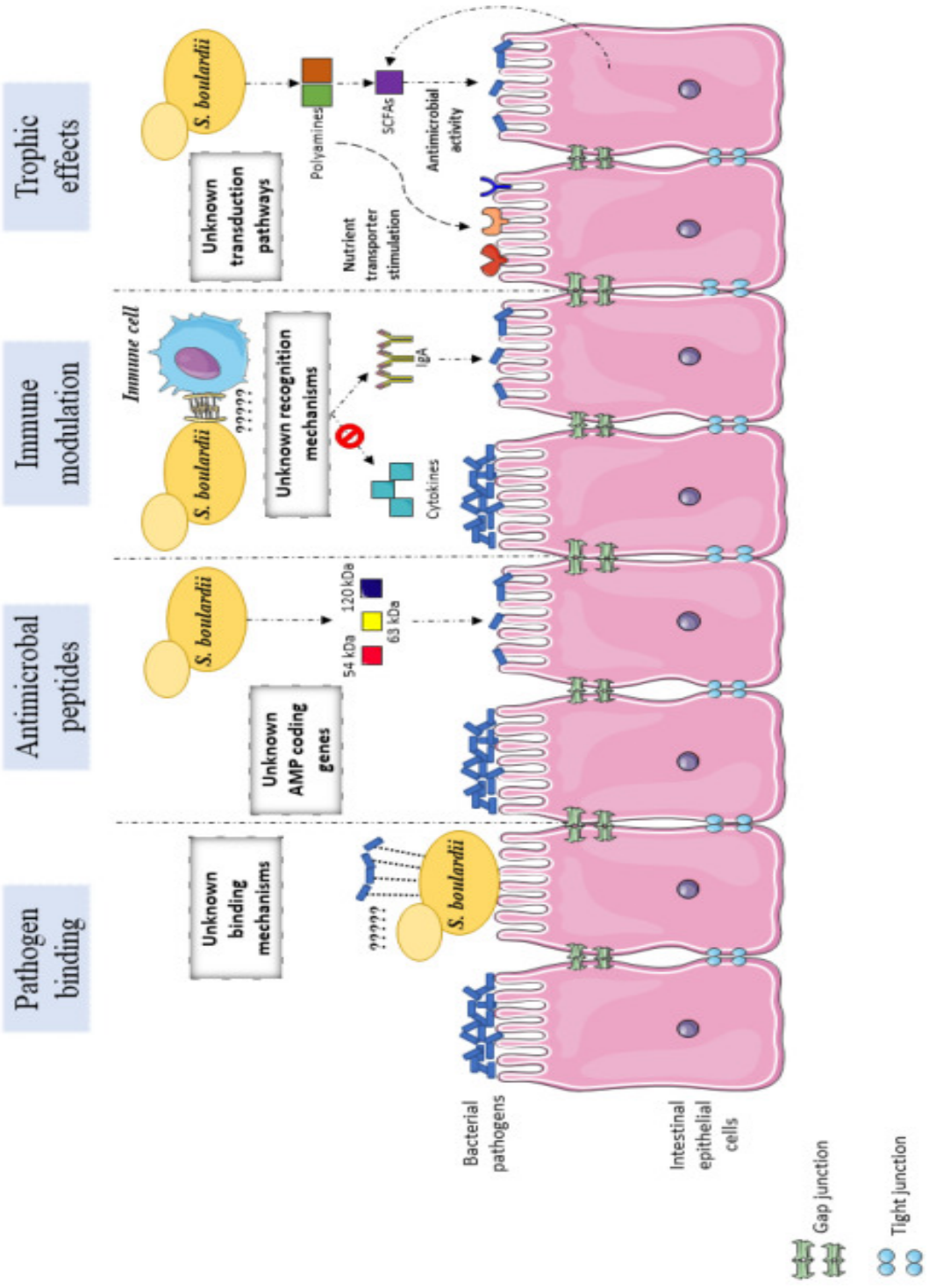
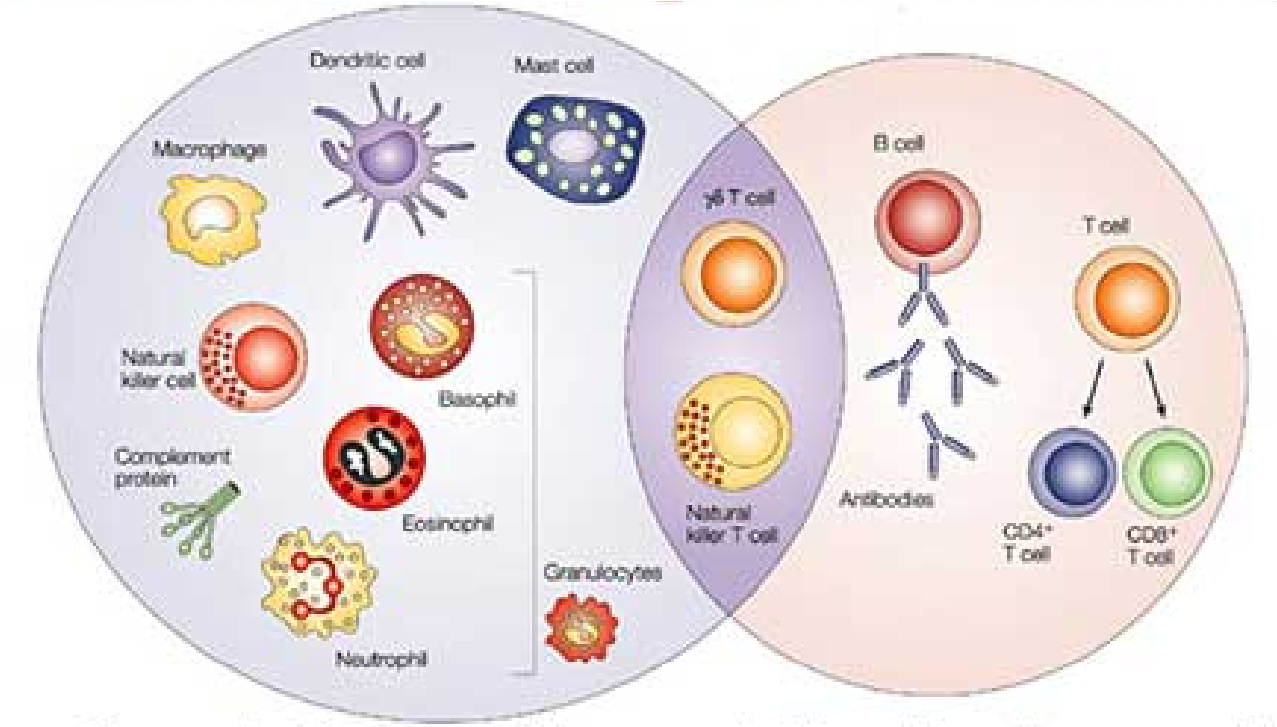
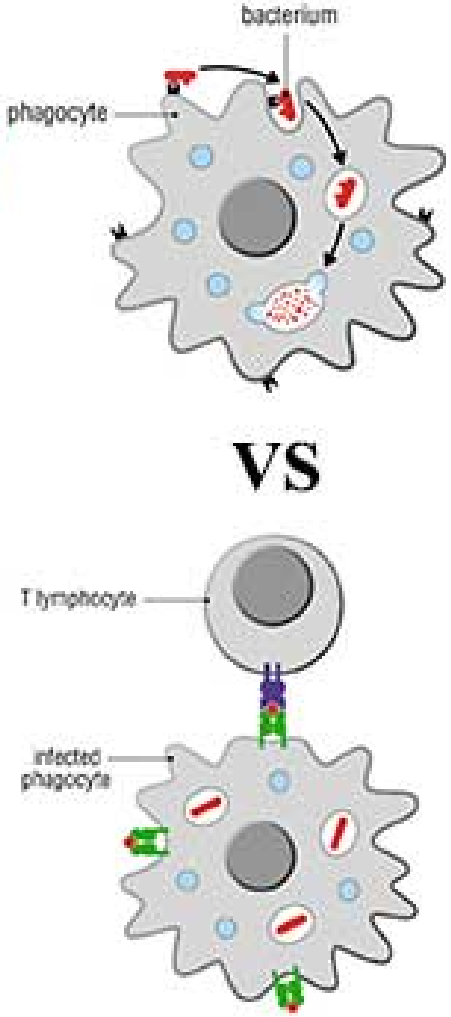


Saccharomyces boulardii

Razlika između

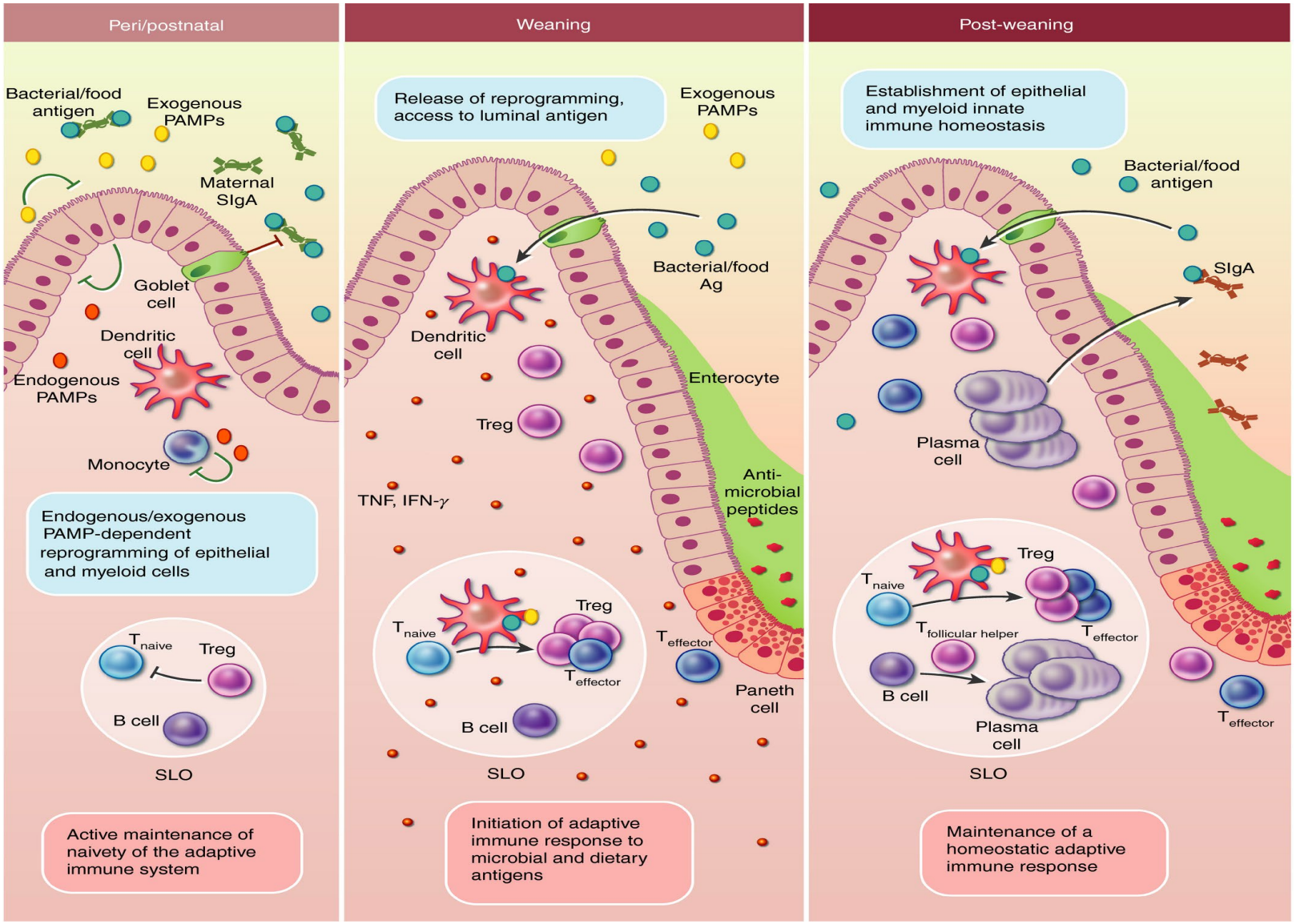
urođenog i stečenog imuniteta





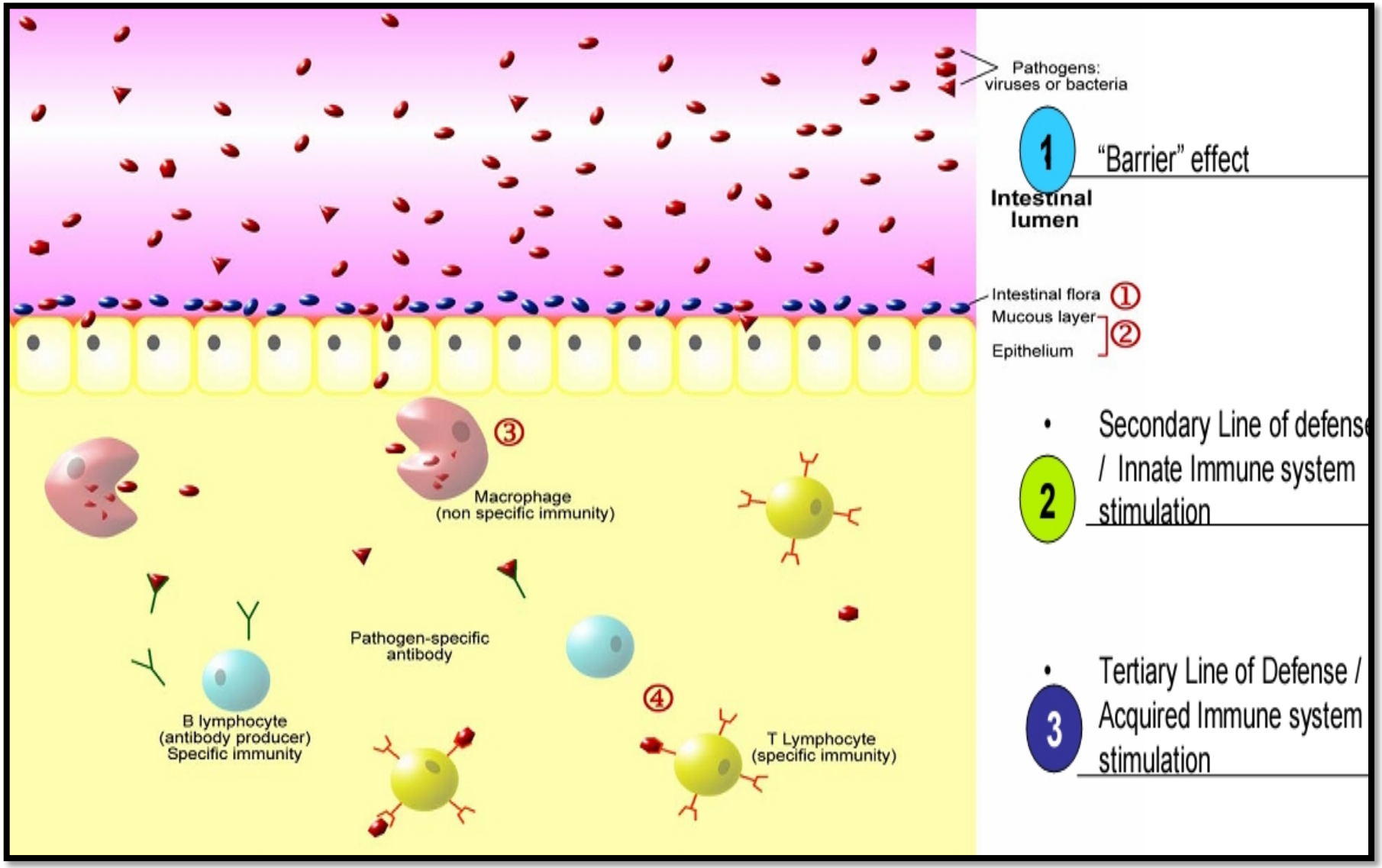
urođeni **stečeni**

‘Layered immunity’ and the ‘neonatal window of opportunity’ – timed succession of non-redundant phases to establish mucosal host–microbial homeostasis after birth

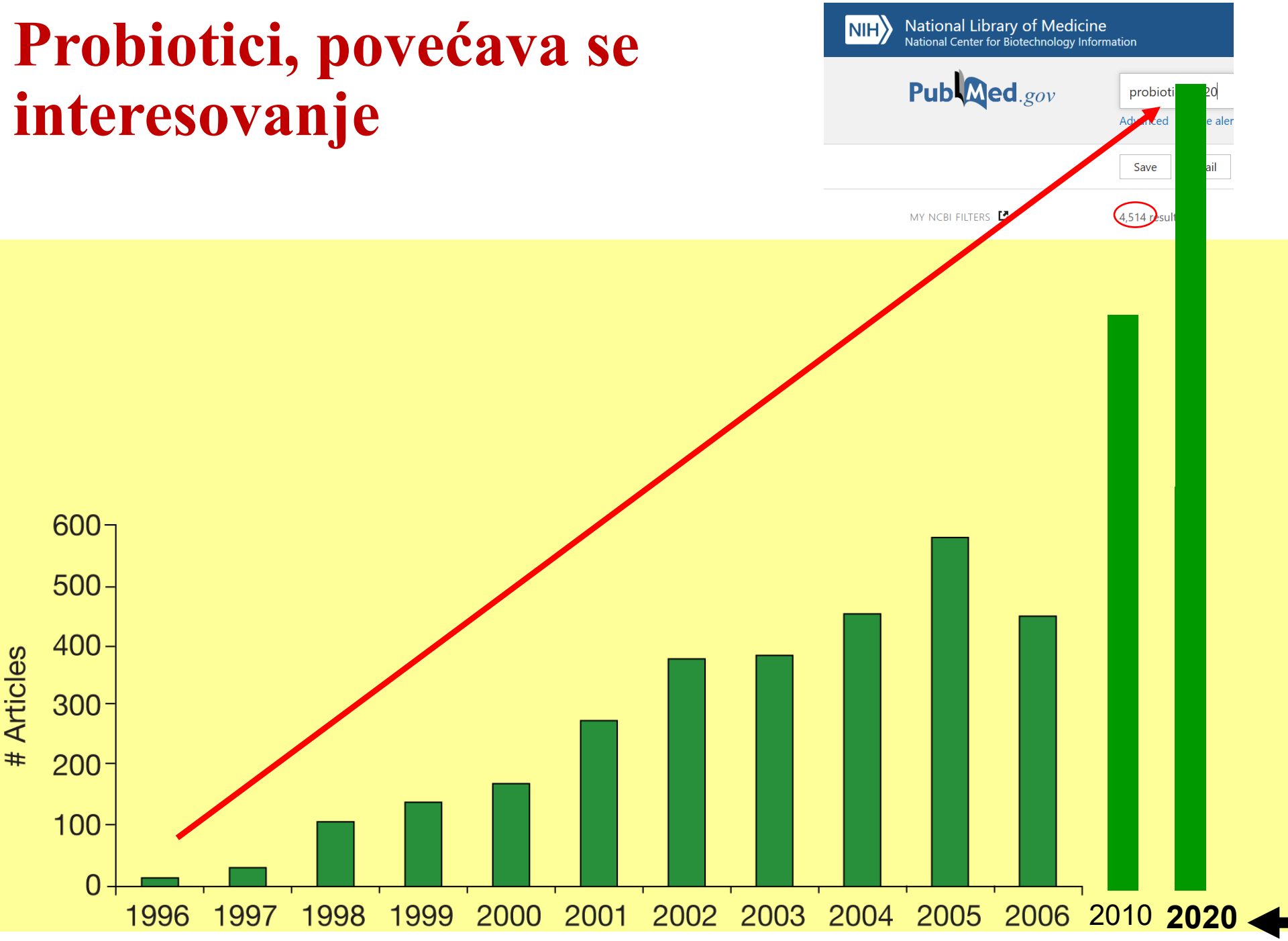


Immunology, Volume: 159, Issue: 1, Pages: 15-25, First published: 27 November 2019, DOI: (10.1111/imm.13149)

Tri nivoa delovanja probiotika



Probiotici, povećava se interesovanje



From Hibbert PL, presented in the First International DIA Conference, October 2006

- 300 do 1000 sojeva,

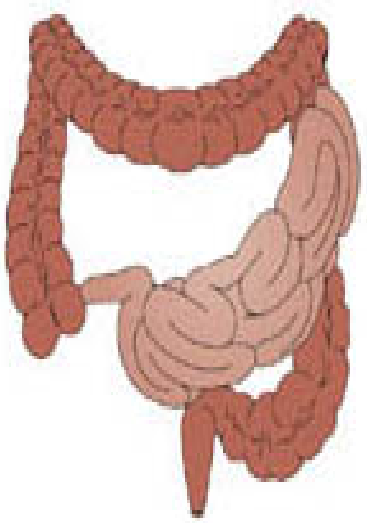
- 99% bakterija pripada 30 do 40 sojeva
- 99% bakterija su anaerobi npr.Bacteroides i Bifidobacteria

- Faecalibacterium prausnitzii kod zdravih najčešća vrsta
- Bakterije čine oko 60% suve mase fecesa

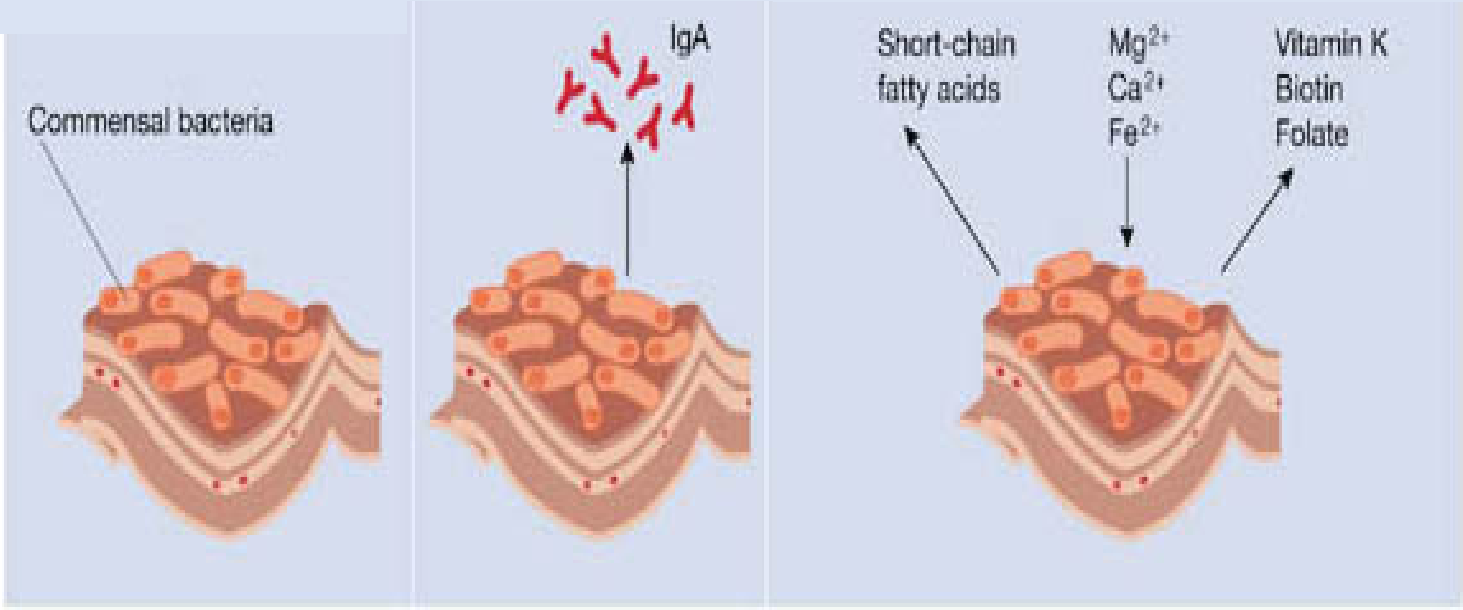
- Svega 4 familije dominiraju u crevu:

  Firmicutes, Bacteroidetes, Actinobacteria, Proteobacteria.

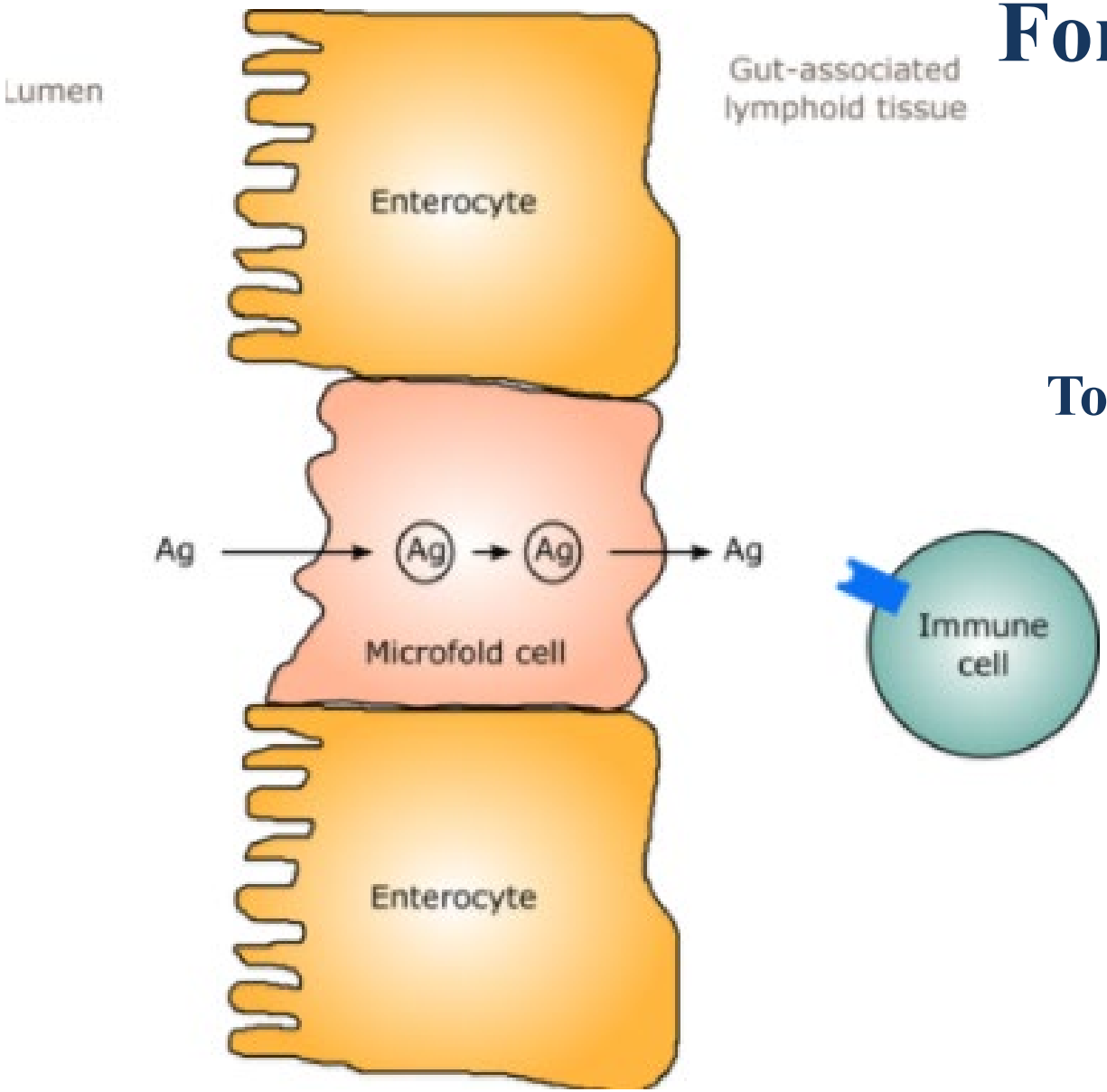
Funkcija mikrobiote, nekada



Protektivna funkcija	Strukturalna funkcija	Metebolička funkcija	
Otklanja patogene Kompeticija za hranu Kompeticija za receptore Stvaranje bakteriocina, mlečne kiseline i dr	Funkcija barijere Indukcija IgA Apikalno približavanje epit. ćelija Razvoj imunog sistema	Kontrola proliferacije epitelnih ćelija Metaboliše kancerogene iz hrane Sinteza vitamina, biotina, folata	Fermentiše nesvarljive sastojke hrane i mukusa poreklom iz endogenog epitela Apsorpcija jona Stvaranje energije



Formiranje GALT



Tolerantan na mikrobiotu
Netolerantan na druge bakterije
Tolerantan na hranu koju dete uzima
Tolerantan na produkte hrane
Tolerantan na metabolite mikrobiote

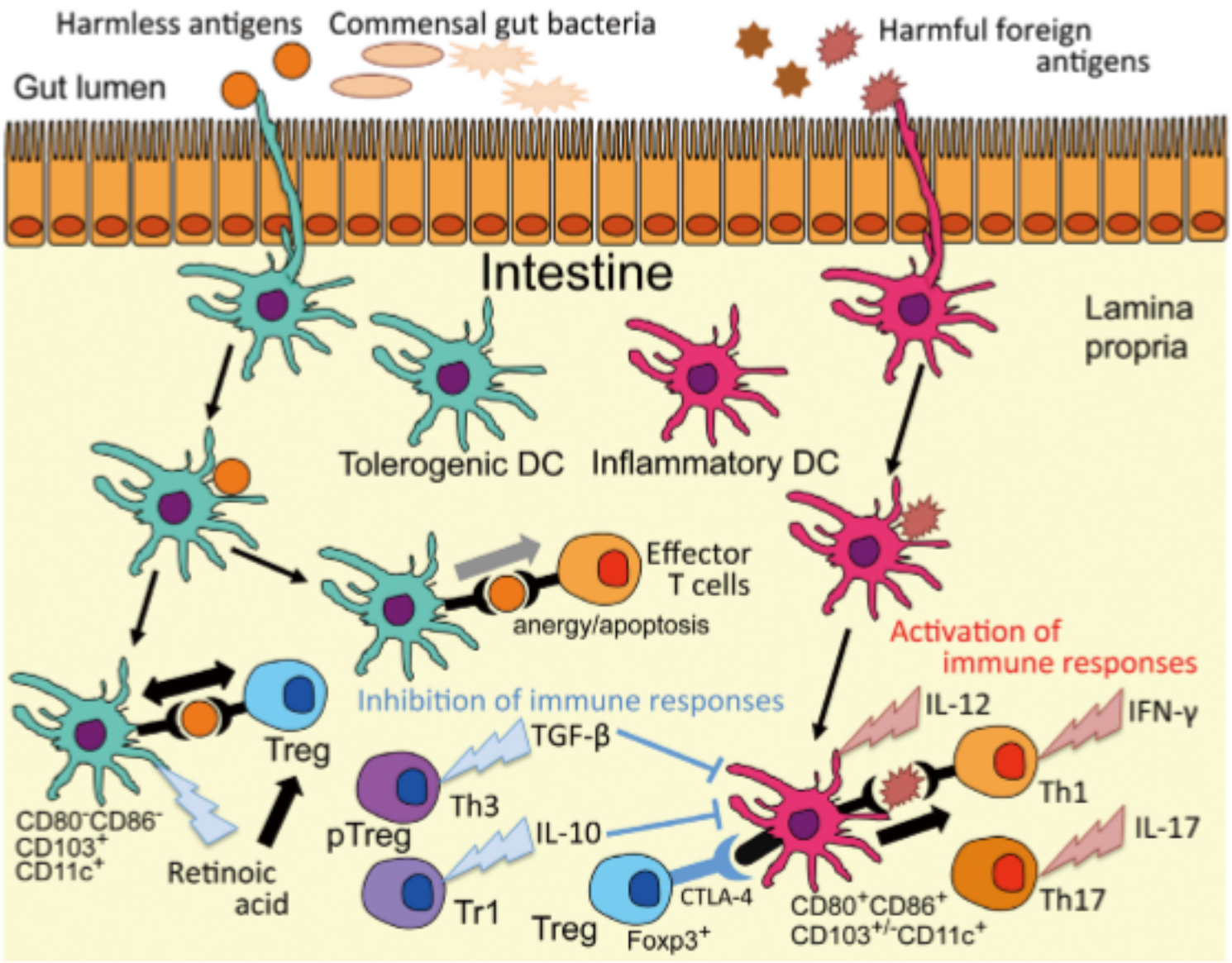


Figure 2. Intestinal immunity and the mechanisms of oral tolerance. Intestinal immunity contains both activating and inhibitory immune responses. Tolerogenic dendritic cells (DCs) and regulatory T cells (Tregs) play critical roles in the induction and maintenance of oral tolerance. CTLA-4, cytotoxic T-lymphocyte-associated protein 4; IFN, interferon; IL, interleukin; pTreg, peripherally inducible Treg; TGF, transforming growth factor.

Yamashita T et al., 2015, Circulation Journal

ENTEROTIP

- Predominanti sastav mikrobiote nevezano od godina, pola težine, ili nacionalne pripadnosti.

- Bacteroides, Prevotella, Ruminococcus.

- Bacteroides više kod onih koji su na proteinskoj ishrani i zasićenim mastima
- Prevotella ćešća kod onih koji koriste ugljene hidrate i proste šećere
- Promenom tipa ishrane menja se enterotip
- Enterotip zavisi i od geografskog područja

Novorođenče ima sterilni GiT,
Mikrobiota se formira oko 2 g.

Ukoliko je dete dojeno
predominira bifidobakterium flora

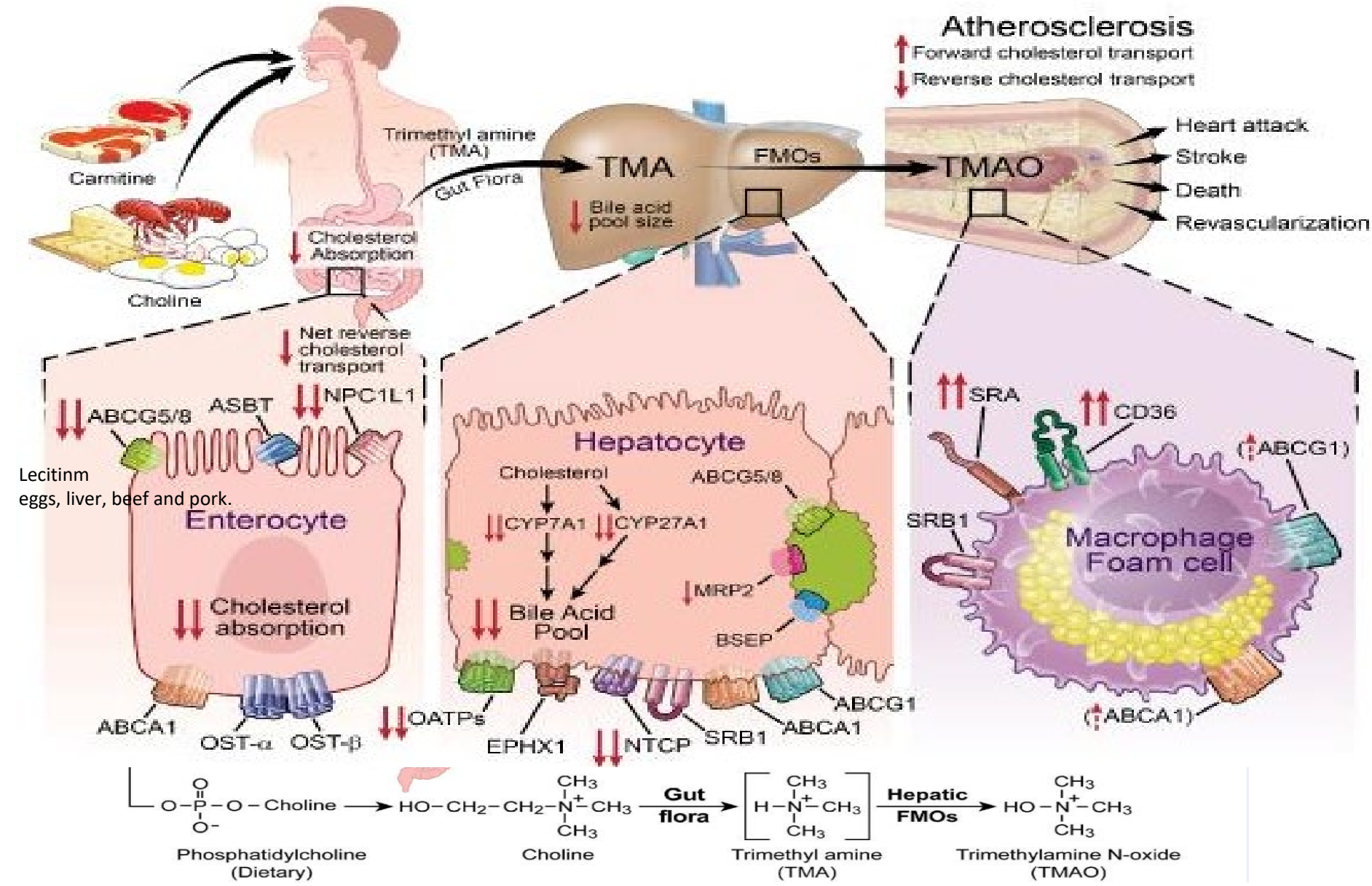
Lactobacilus prirodni porođaj,

kod carskog reza dete dobija bakterije iz okoline od sestara, druge dece

Mikrobiota se razlikuje interindividualno

Kod blizanaca samo 50% istih baktrija

Crevna mikrobiota i metabolizam fosfatidilholina



Koeth, R. A., et al. (2013). Nat. Med. 19, 576–585.
Ferguson, J. F. (2013). Circ. Cardiovasc. Genet. 6, 308–309

frontiers in Public Health

OPINION
published: 08 May 2020
doi: 10.3389/fpubh.2020.00186

Using Probiotics to Flatten the Curve of Coronavirus Disease COVID-2019 Pandemic

David Baud[1], Varvara Dimopoulou Agri[2], Glenn R. Gibson[3], Gregor Reid[4,5] and Eric Giannoni[2]*

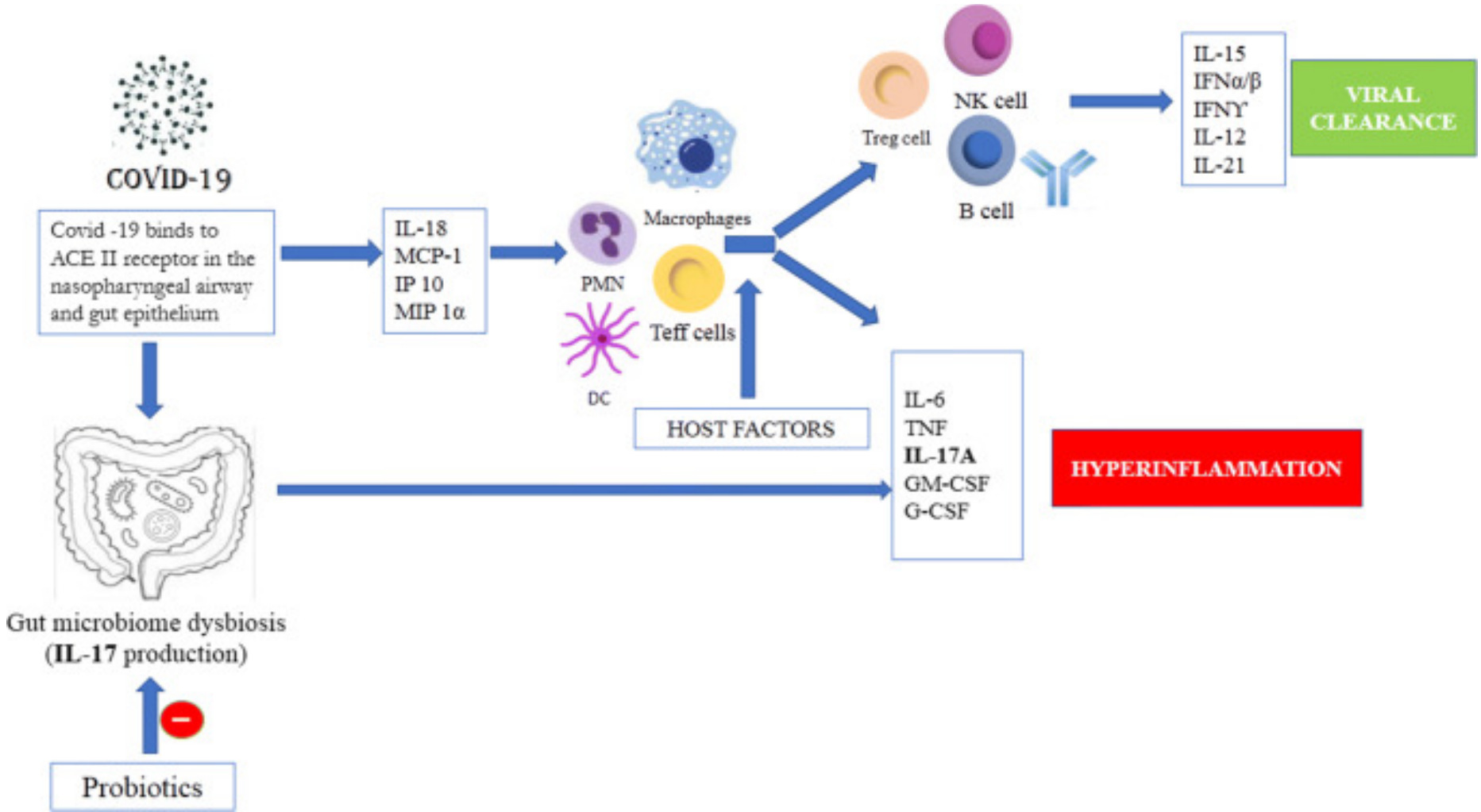
Products	Basis for inclusion	When to administer	References
Lactobacillus casei DN-114 001; DanActive/Actimel Fermented drink, Danone	Reduced incidence and duration of RTIs	Once daily for duration of the pandemic	(12, 13)
Lactobacillus gasseri PA 16/8, *Bifidobacterium longum* SP 07/3, and *B. bifidum* MF 20/5; Tribion harmonis, Merck	Lowering duration and severity of flu-like illness	Once daily for duration of the pandemic	(16)
Lactobacillus rhamnosus GG; Culturelle or other brand names	For digestive health and gut barrier integrity, and prevention of viral RTIs	One capsule daily for duration of the pandemic	(17)
Lactobacillus plantarum DR7; Malaysia	Prevention of upper RTIs, immune modulation	2 g sachet per day for duration of pandemic	(25)
Bifidobacterium breve Yakult, and *Lactobacillus casei* Shirota; available as fermented drinks	Lower incidence of ventilator-associated pneumonia	One of each day for duration of the pandemic	(26)
Bifidobacterium longum BB536; Morinaga, and sold in many formulations	Enhances innate immunity, prevents influenza infection	One each day for duration of the pandemic	(19)
Pediococcus pentosaceus 5-33:3, *Leuconostoc mesenteroides* 32-77:1, *L. paracasei* ssp. *paracasei* 19, *L. plantarum* 2,362 plus inulin, oat bran, pectin, and resistant starch; Medipharm, Sweden	To reduce rate of SIRS, infections, sepsis, days of stay in the intensive care unit, days under mechanical ventilation, and mortality	For COVID-19 patients	(27)
A list of probiotics available in Canada for various health issues; www.probioticchart.ca			
A list of probiotics available in the USA for various health issues; www.usprobioticguide.com			

We must emphasize that none have been tested or proven to have an effect against SARS-CoV2, the virus causing COVID-19, nor are they proven treatments or cures for this condition.

Appl Microbiol Biotechnol. 2020 Aug 19 : 1–16.
doi: 10.1007/s00253-020-10832-4 [Epub ahead of print]
PMCID: PMC7434852
PMID: 32813065

Role of probiotics to combat viral infections with emphasis on COVID-19

Aravind Sundararaman,[1] Mousumi Ray,[1] P. V. Ravindra,[2] and Prakash M. Halami[1]



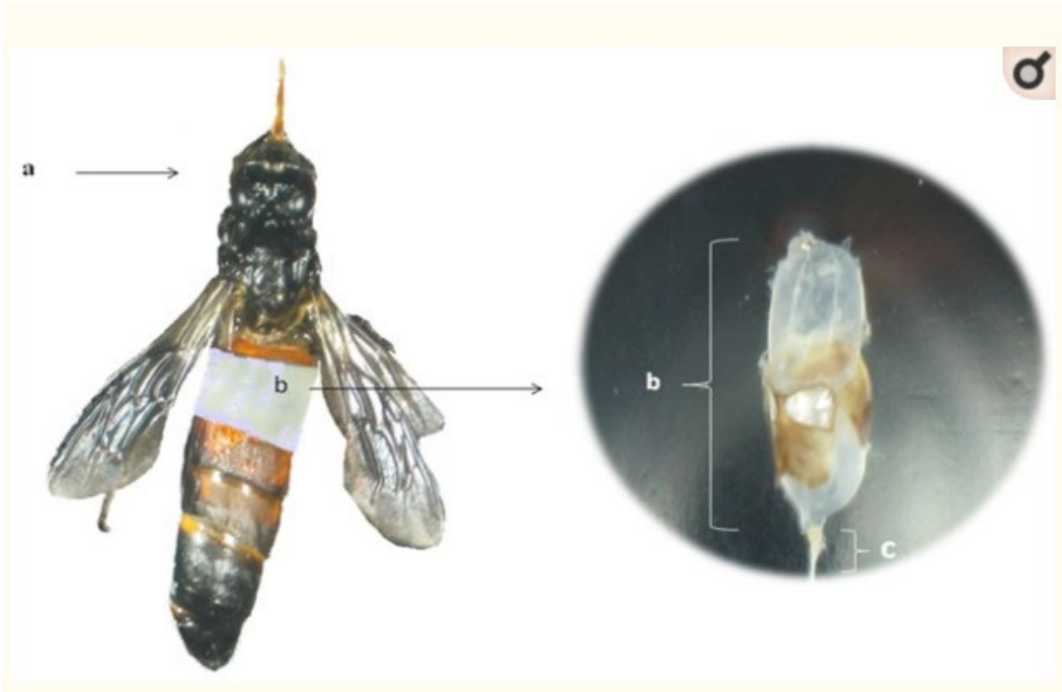
Springer Brazilian Journal of Microbiology

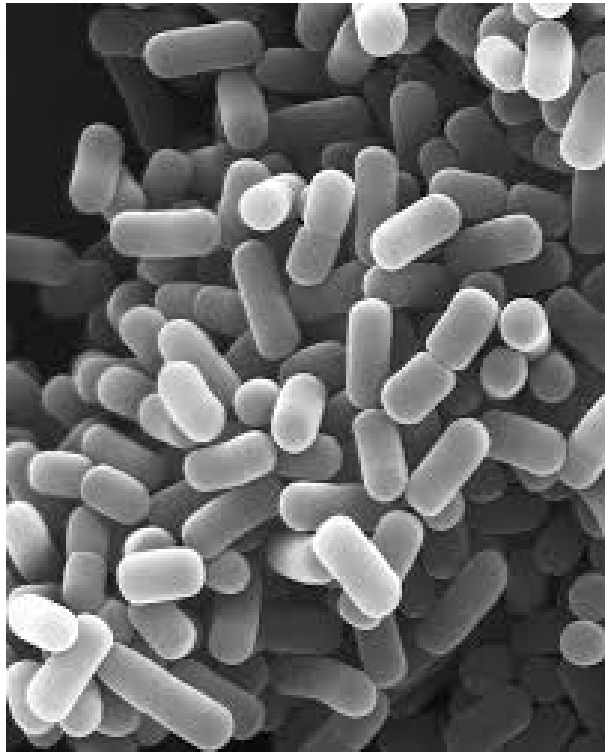
Braz J Microbiol. 2013; 44(3): 717–722.
Published online 2014 Jan 15.

PMCID: PMC3910179
PMID: 24516438

Identification of *Lactobacillus plantarum*, *Lactobacillus pentosus* and *Lactobacillus fermentum* from honey stomach of honeybee

Naser Tajabadi,[1,4] Makhdzir Mardan,[2] Nazamid Saari,[1] Shuhaimi Mustafa,[3] Rasoul Bahreini,[4] and Mohd Yazid Abdul Manap[5]





Lactobacillus plantarum HEAL 9

by PROBI®

Immune concept

- **JAČA** imuni odgovor
- **UBLAŽAVA** simptome prehlade
- **REDUKUJE** broj dana infekcije

- *Smanjuje broj uobičajenih respiratornih infekcija*
- *Sprečava ponovljene epizode prehlade*
- *Smanjuje simptome i trajanje epizoda prehlade*

- Imunomodulacija (anti-inflamatorni efekat)
  - regulacija citokinske produkcije
  - ↑IgA, ↓ IgE
  - ↓ Oksidativni stres

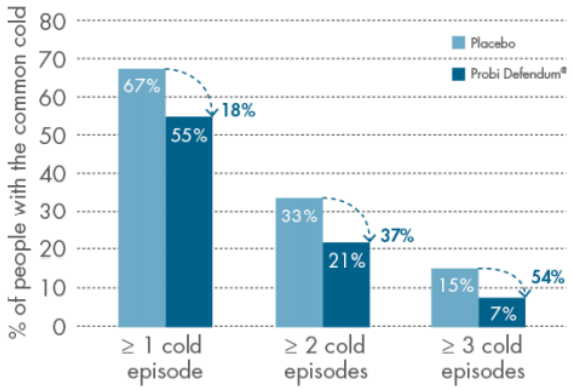
Probi imune concept koji sadrži LpHEAL 9

Berggren *et al.* 2011

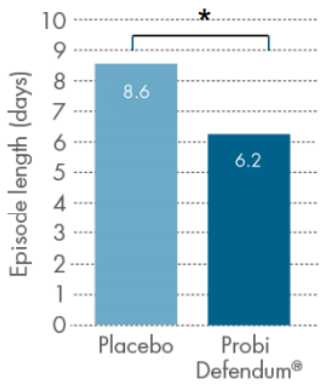
- RCT with 272 participants

Redukcija incidence respiratornih epizoda - prehlada
Redukcija dužine trajanja
Redukcija simptoma

Probi Defendum® reduces the incidence of the common cold



Significant reduction of the episode length



Berggren A, et al. *Eur J Nutr* 2011; 50:203–210

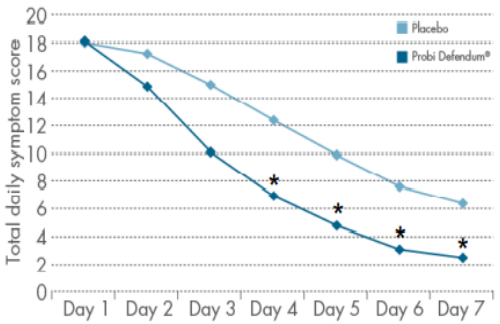
Probi imune concept koji sadrži LpHEAL 9

Busch *et al.* 2013

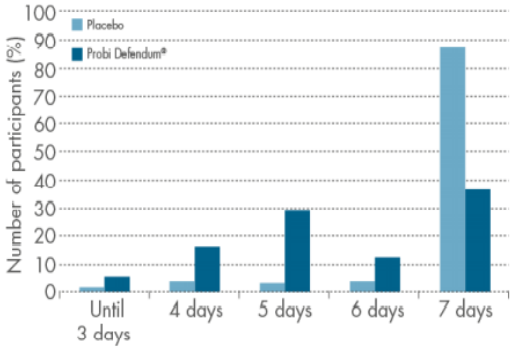
- RCT with 312 participants

Redukcija simptoma – total symptom score redukovan
Redukcija trajanja respiratorne epizode
Poboljšanje većine simptoma RI

Significantly less symptoms per day with Probi Defendum®



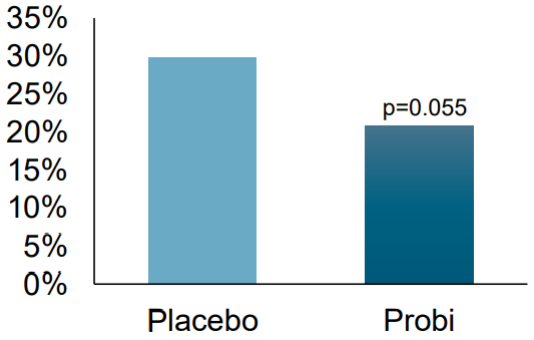
Significantly shorter duration of common cold episodes with Probi Defendum®



All symptoms	Reduction	Significant reduction
Overall condition		
Headache	✓	
Pain in a limb	✓	✓
Throat		
Sore thorat	✓	✓
Difficulties swallowing	✓	✓
Hoarseness	✓	✓
Nose		
Runny nose	✓	✓
Congested nose	✓	✓
Yellow secretion	✓	✓
Bloody secretion	✓	✓
Sneezing	✓	
Bronchial symptoms		
Cough	✓	✓
Yellow secretion	✓	
Other secretion	✓	

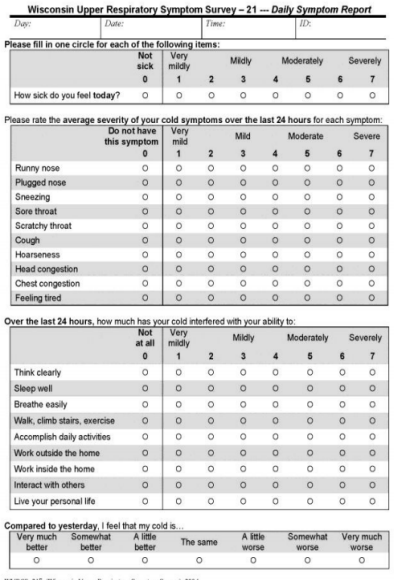
Busch R, et al. *Food and Nutrition Sciences* 2013; 4:13-20

PROBI® *imune concept koji sadrži LpHEAL 9*



Study design: parallel, double blind, randomized, placebo-controlled trial

- Najveće istraživanje koje je sprovedeno
- Skoro 900 učesnika, 18-70 godina sa simptomima prehlade
- Doza: 1mld , 3 meseca praćenje
- Sprovedeno istraživanje na tri sezone prehlade
- Korišćen validirani Upitnik WURSS – 21



Wisconsin Upper Respiratory Symptom Survey – 21 --- *Daily Symptom Report*

Day: | *Date:* | *Time:* | *ID:*

Please fill in one circle for each of the following items:

	Not sick	Very mildly		Mildly		Moderately		Severely
	0	1	2	3	4	5	6	7
How sick do you feel **today?**	○	○	○	○	○	○	○	○

Please rate the **average severity of your cold symptoms over the last 24 hours** for each symptom:

	Do not have this symptom	Very mild		Mild		Moderate		Severe
	0	1	2	3	4	5	6	7
Runny nose	○	○	○	○	○	○	○	○
Plugged nose	○	○	○	○	○	○	○	○
Sneezing	○	○	○	○	○	○	○	○
Sore throat	○	○	○	○	○	○	○	○
Scratchy throat	○	○	○	○	○	○	○	○
Cough	○	○	○	○	○	○	○	○
Hoarseness	○	○	○	○	○	○	○	○
Head congestion	○	○	○	○	○	○	○	○
Chest congestion	○	○	○	○	○	○	○	○
Feeling tired	○	○	○	○	○	○	○	○

Over the last 24 hours, how much has your cold interfered with your ability to:

	Not at all	Very mildly		Mildly		Moderately		Severely
	0	1	2	3	4	5	6	7
Think clearly	○	○	○	○	○	○	○	○
Sleep well	○	○	○	○	○	○	○	○
Breathe easily	○	○	○	○	○	○	○	○
Walk, climb stairs, exercise	○	○	○	○	○	○	○	○
Accomplish daily activities	○	○	○	○	○	○	○	○
Work outside the home	○	○	○	○	○	○	○	○
Work inside the home	○	○	○	○	○	○	○	○
Interact with others	○	○	○	○	○	○	○	○
Live your personal life	○	○	○	○	○	○	○	○

Compared to yesterday, I feel that my cold is...

Very much better	Somewhat better	A little better	The same	A little worse	Somewhat worse	Very much worse
○	○	○	○	○	○	○

ZAKLJUČAK: incidenca ponovljenih respiratornih epizoda u Probi probiotc grupi manja 30% u odnosu na Placebo grupu

Clinical & Experimental Immunology
The Journal of Translational Immunology
British Society for immunology

Clin Exp Immunol. 1999 May; 116(2): 283–290.
doi: 10.1046/j.1365-2249.1999.00891.x

PMCID: PMC1905288
PMID: 10337020

Immunomodulatory effects of *Lactobacillus plantarum* colonizing the intestine of gnotobiotic rats

M V Herías, C Hessle, E Telemo, T Midtvedt,* L Å Hanson, and A E Wold

The results indicate that *L. plantarum* colonization competes with *E. coli* for intestinal colonization and can influence intestinal and systemic immunity.

Asian Journal of Immunology

3(2): 1-15, 2020; Article no.AJI.54889

Immunomodulatory Potentials of Probiotics: A Review

David Chinemerem Nwobodo[1,2*] and Malachy Chigozie Ugwu[2]

[1]Department of Microbiology, Renaissance University, Ugbawka, Enugu State, Nigeria.
[2]Department of Pharmaceutical Microbiology and Biotechnology, Faculty of Pharmaceutical Sciences, Nnamdi Azikiwe University, Awka, Anambra State, Nigeria.

Probiotic bacteria, their cell wall components, and other stimulating molecules have been shown to have significant effects on the functionality of the immune systems through the activation of multiple immune mechanisms.

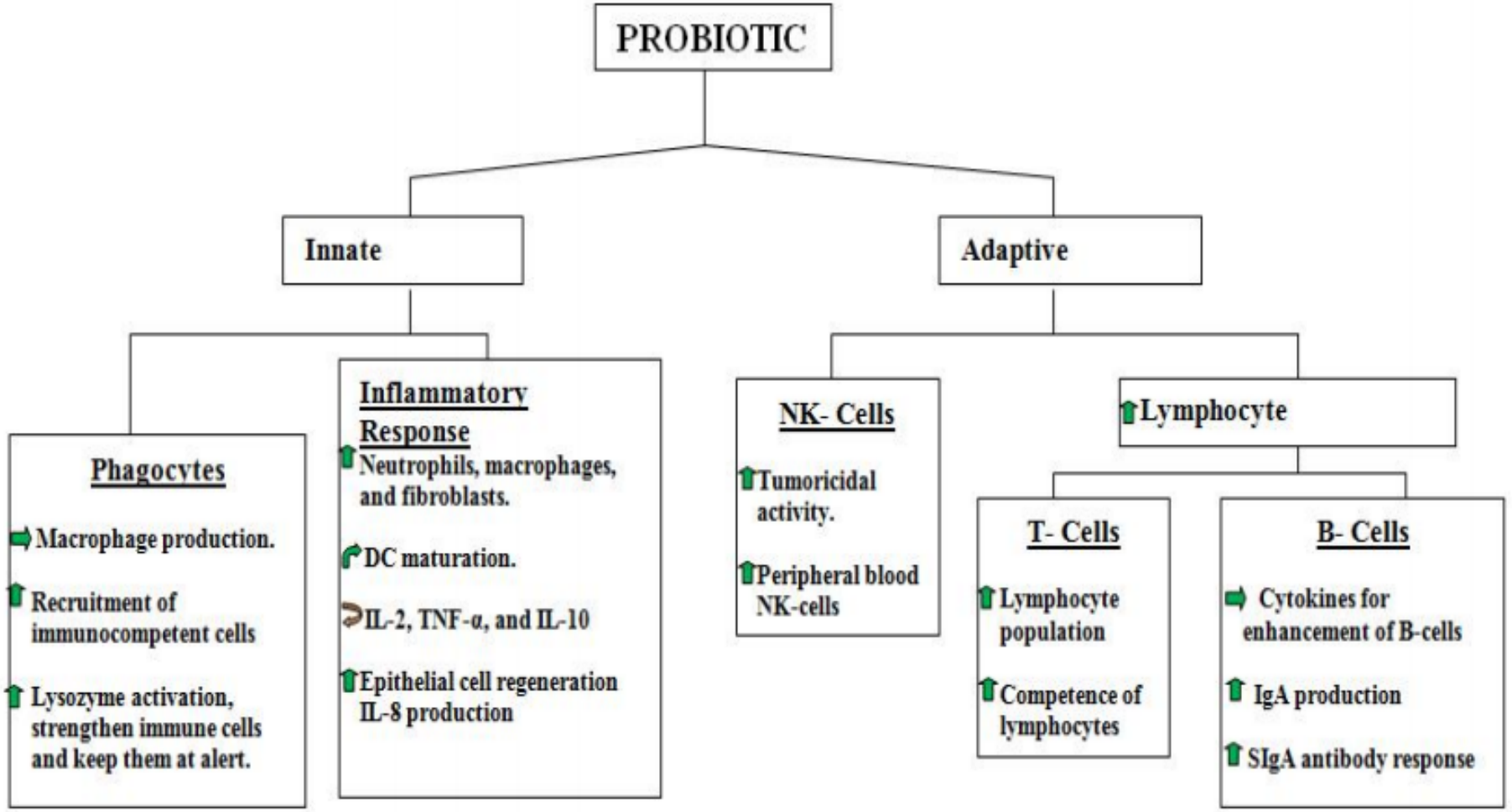


Fig. 1. Mechanisms of immunomodulatory actions of probiotic bacteria

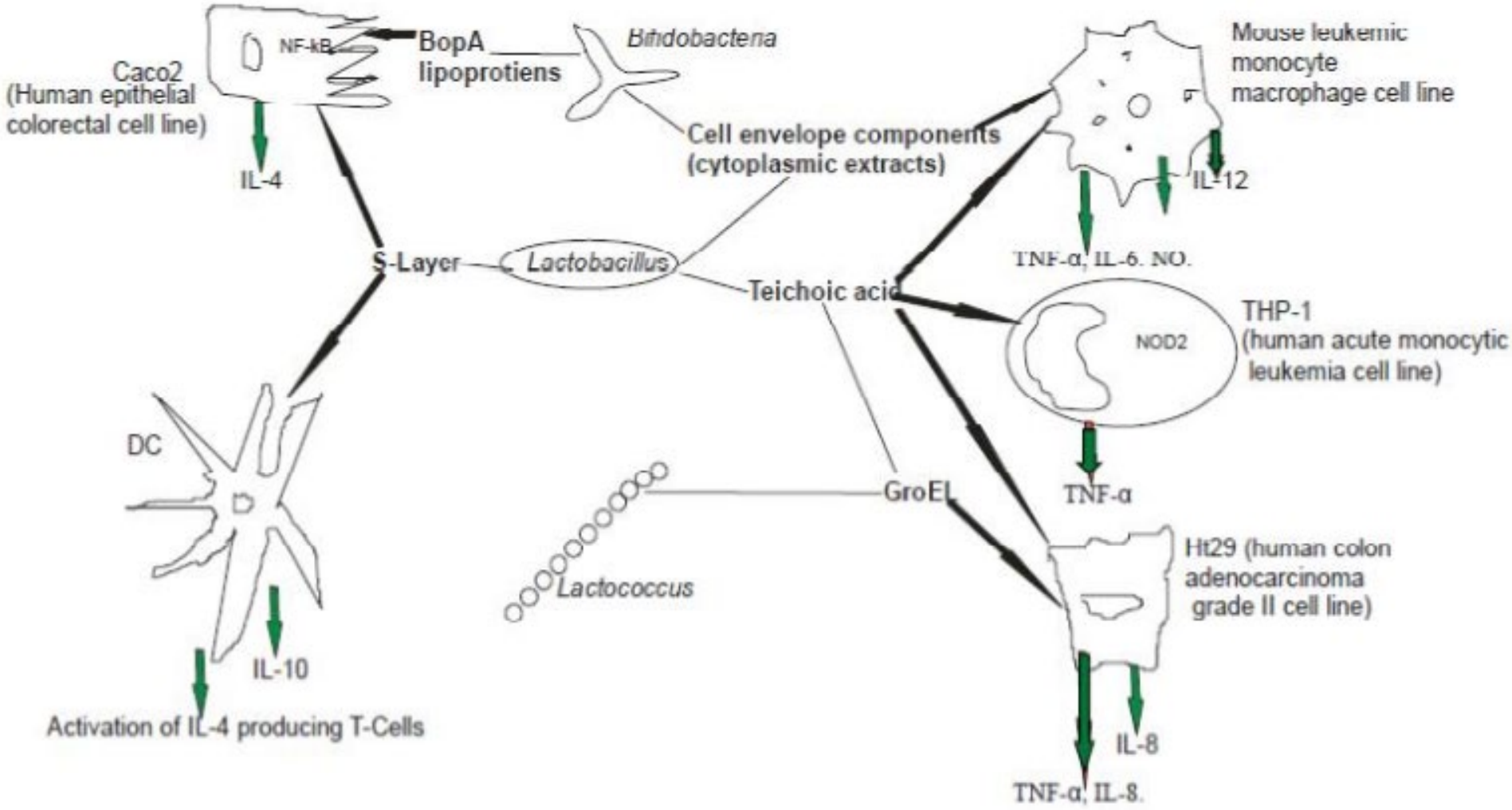
Key ⇧; Increase/ Enhance, ➡; Activate/ Stimulate, ↱; Induce, ↻ ; Release

Table 1. Clinical evidences of immune stimulation by probiotics [47,48]

Lactobacillus plantarum povećava fagocitozu, povećavajući broj neutrofila, makrofaga i fibroblasta (dokazano kod zdravih dobrovoljaca)

Probiotics	Immunological Functions	Subjects
Lactobacillus acidophilus La1, *L. rahmnosus*HN001, *B. bifidum* Bb12, *B. lactis*HN019	Phagocytic activity of blood mononuclear and polymorphonuclear cells	Healthy adults and elderly volunteers
*Lactobacillus casei*Shirota, *B. lactis*HN019	The tumoricidal activity of blood mononuclear cells	Healthy adults and elderly volunteers; patients with colorectal cancer
Lactobacillus brevis Labre, *B. lactis*HN019	Production of interferons by peripheral blood mononuclear cells	Healthy adults and elderly volunteers
Lactobacillus plantarum	Increased neutrophils, macrophages, and fibroblast	Adult volunteers
Lactobacillus rhamnosus GG	Anti-rotavirus antibody responses	Children with rotavirus
*L. rahmnosus*GG	Antibody responses following vaccination	Adult volunteers
Bacillus subtilis CU1	Increased the levels of secretory IgA in stools and saliva, high serum IFN-gamma	Elderly during common infectious disease

Gill HS, Cross MC. Probiotics and immune function. In: Calder PC, Field CJ, Gill HS, edition. Nutrition and immune function. CABI Publishing, Wallingford, UK; 2002.
Nasrabadi MH, Aboutalebi H, Ebrahimi MT, Zahedi F. The healing effect of L. plantarum isolated from Iranian traditional cheese on gastric ulcer in rats. African Journal of Pharmacy and Pharmacology. 2011;5(12):1446-1451.



Molekuli ili delovi probiotskih bakterija mogu da modulišu imuninet epitelnih ćelija i domaćina

Nwobodo and Ugwu; AJI, 3(2): 1-15, 2020; Article no.AJI.54889

Asian Journal of Immunology

3(2): 1-15, 2020; Article no.AJI.54889

Immunomodulatory Potentials of Probiotics: A Review

David Chinemerem Nwobodo[1,2*] and Malachy Chigozie Ugwu[2]

[1]Department of Microbiology, Renaissance University, Ugbawka, Enugu State, Nigeria.
[2]Department of Pharmaceutical Microbiology and Biotechnology, Faculty of Pharmaceutical Sciences, Nnamdi Azikiwe University, Awka, Anambra State, Nigeria.

Table 2. Immunomodulatory molecules of probiotic microorganisms

Probiotics	Molecules	Effects
Lactobacillus casei *Lactobacillus plantarum*	Peptidoglycan	General immune stimulation [33,48]
Lactobacillus casei *Lactobacillus fermentum*	Lipoteichoic acid	Increased levels of TNF-α in mouse macrophage cell [45].
Bifidobacteriumlongum	DNA	Increased cytokine IL-10 [45].
Lactobacillusacidophilus	Surface layer	Activation of IL-4 producing T-cells [66].
*B. bifidum*MIMBb75	BOpA protein	Induce production of IL-8 by colorectal cell line [67,68].
*Escherichia coli*Nissle 1917	Flagellin	Induce production of IL-8 by colorectal cell line [68].
S. thermophiles *L. plantarum*	Cell wall-associated polysaccharide (CAPs)	General immune stimulation [33,48].

Review Article

Annals of Nutrition & Metabolism

Ann Nutr Metab 2019;74:115–124
DOI: 10.1159/000496426

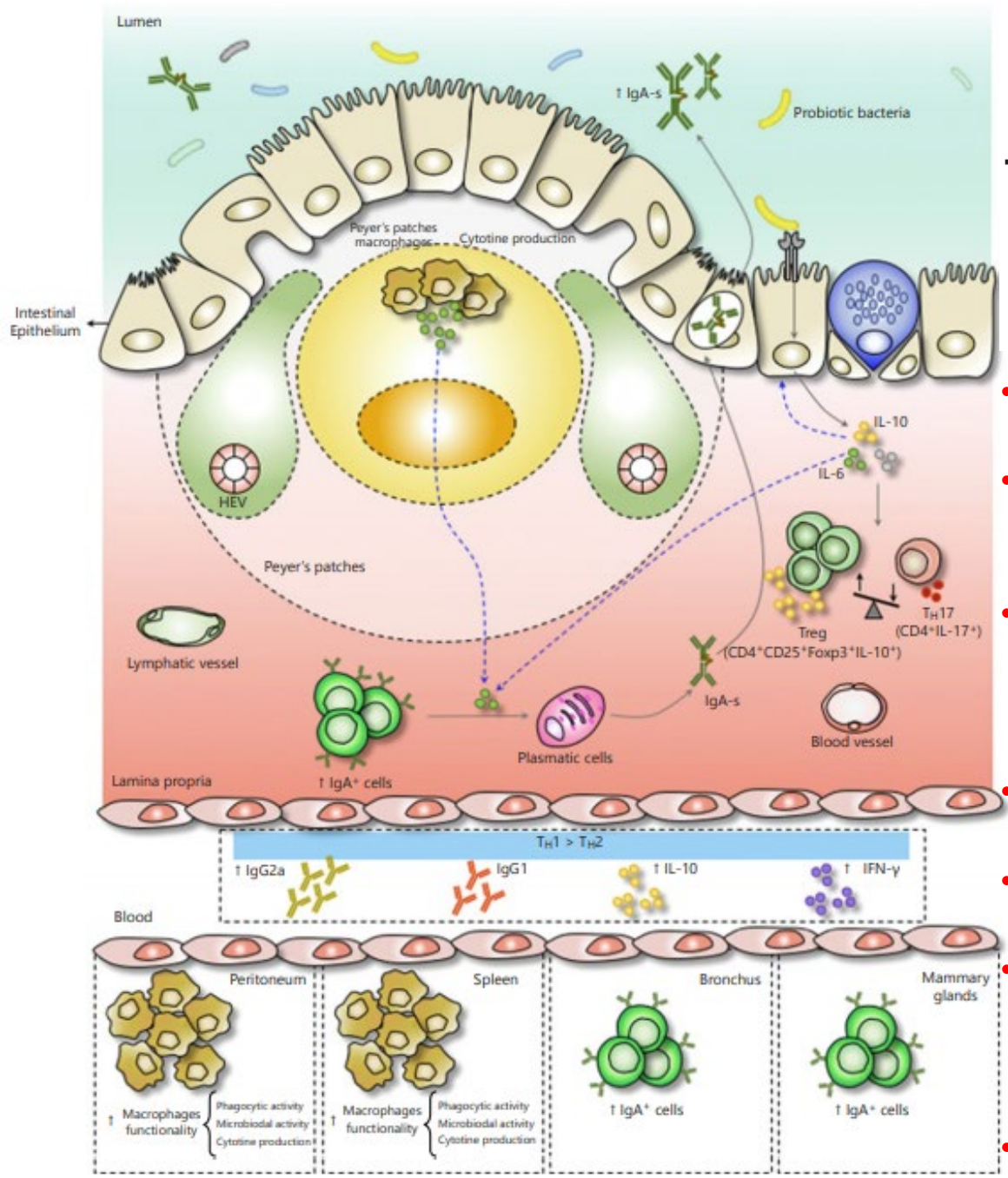
Received: January 5, 2018
Accepted: December 21, 2018
Published online: January 23, 2019

Beneficial Effects of Probiotic Consumption on the Immune System

Carolina Maldonado Galdeano[a, b] Silvia Inés Cazorla[a, b]
José María Lemme Dumit[a, b] Eva Vélez[a, b] Gabriela Perdigón[a, b]

Osnovna poruka:

Probiotske bakterije, supstancije iz njihovog zida, ili mleko fermentisano probioticima ima značajan uticaj na funkciju mukoznog i sistemskog imuniteta a preko aktivacije različitih imunih mehanizama



Review Article

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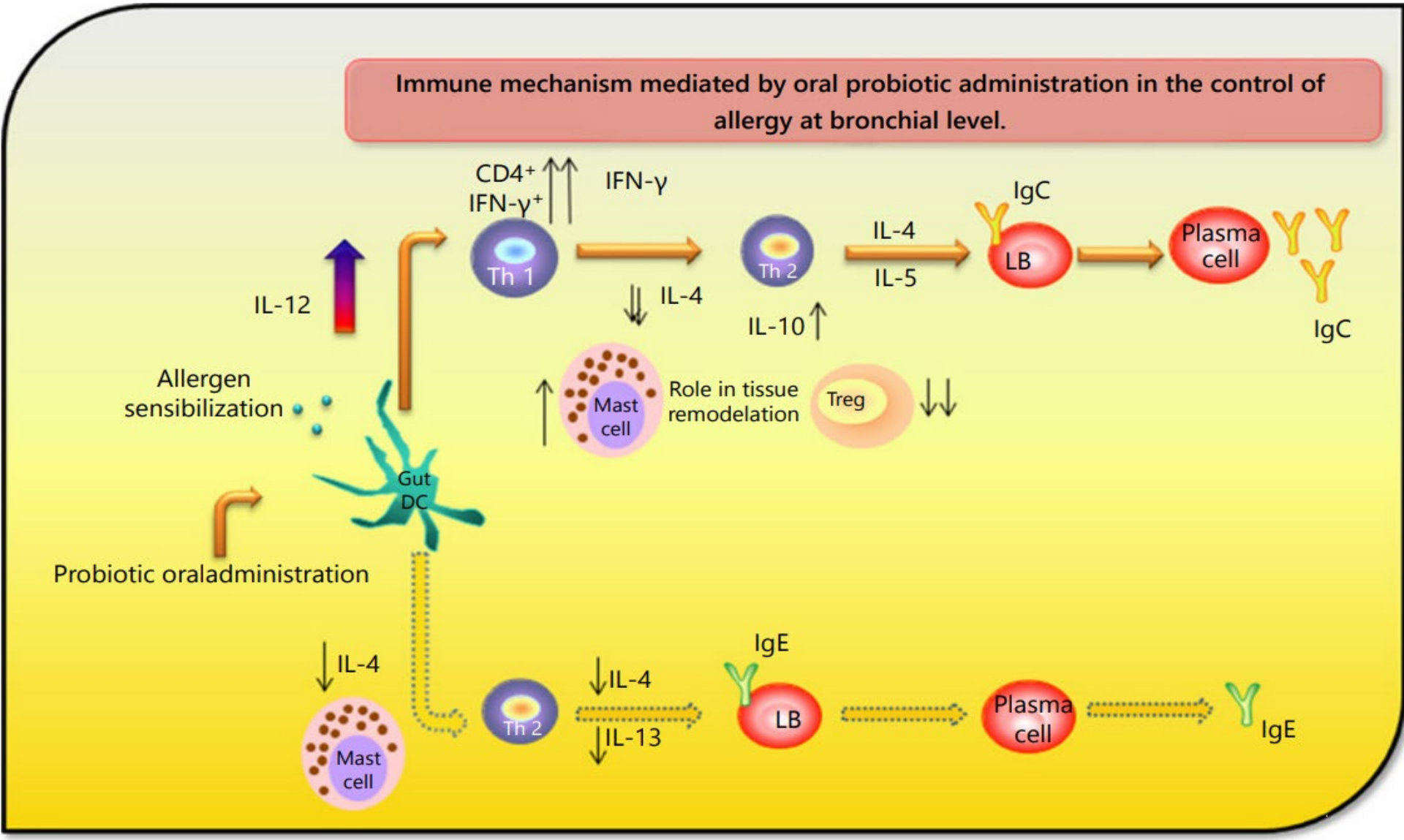
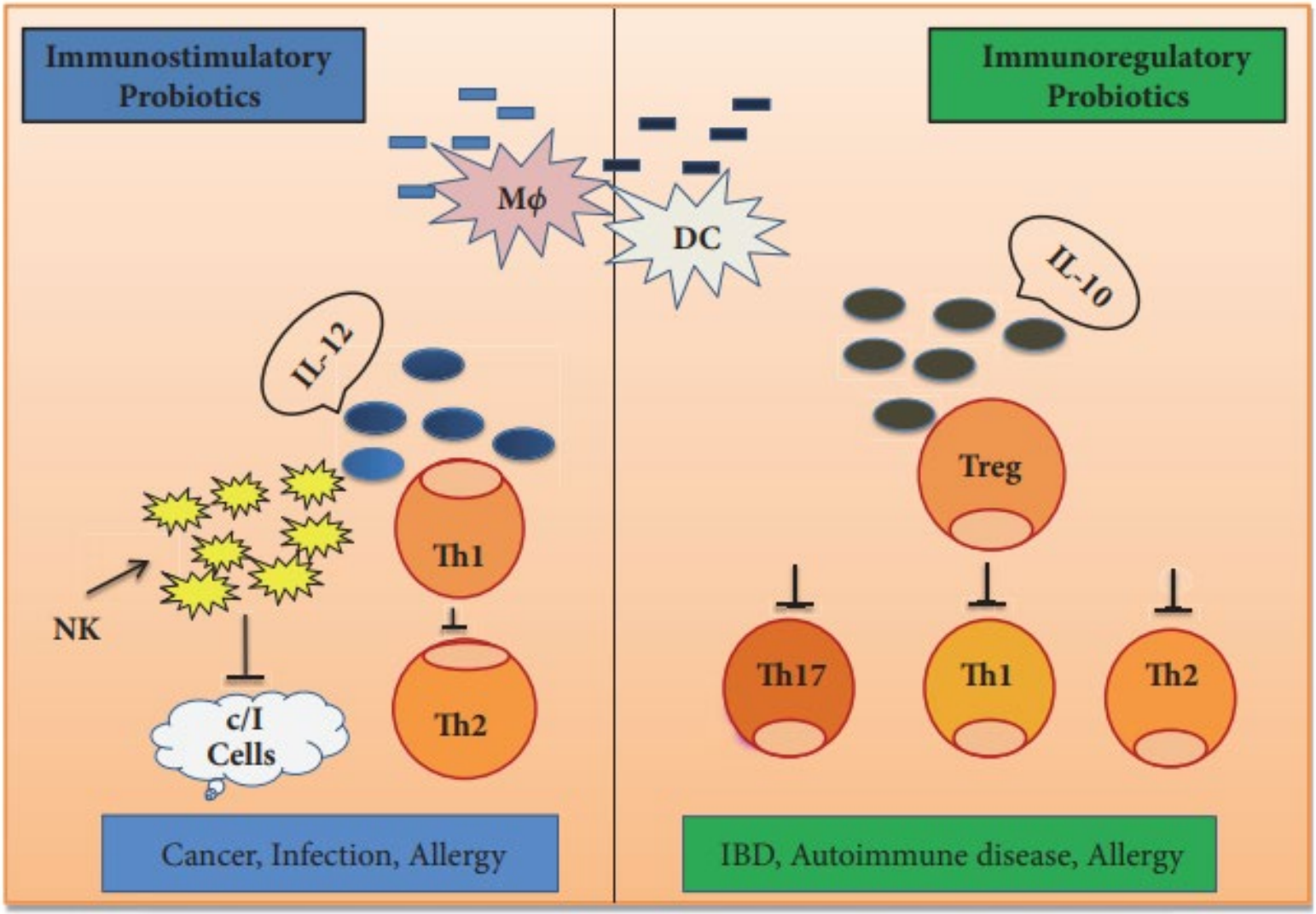
Beneficial Effects of Probiotic Consumption on the Immune System

Carolina Maldonado Galdeano[a, b] Silvia Inés Cazorla[a, b]
José María Lemme Dumit[a, b] Eva Vélez[a, b] Gabriela Perdigón[a, b]

- **Probiotici se vezuju za receptore na IEC.**
- **IECs oslobađaju citokine i hemokine koji aktiviraju B ćelije da stvaraju u lamina propria IgA.**
- **U isto vreme, citokini stimulisani probioticima aktiviraju Treg cells (Foxp3+) koji održavaju imunu homeostazu mukoze.**
- **Makrofazi iz PPs stimulisani probioticima oslobađaju citokine.**
- **Oni održavaju hiporeaktivnost ka komensalima.**
- **Posle stimulacije,udaljeni makrofagi (peritoneum, slezina), pojačavaju fagocitozu, lučenje citokiina i homeostazu urođenog imuniteta**
- **Probiotici održavaju Th1 imuni**



- **Oralni probiotici aktiviraju DCs na nivou creva, sa oslobađanjem IL-12 koji stečeni imunitet održava na Th1 profilu u bronhima.**
- **Povećanje ekspresije CD4 IFN-γ u Th1 ćelijama dovodi do povećanja IgG stvaranja umesto IgE. Treg ćelije se ne povećavaju, tako da se regulatorni efekat izazvan probioticima izgleda održava preko IL-10, izTh1 i Th2 ćelija.**
- **Povećava se broj mast ćelija koji održavaju reparaciju tkivnog oštećenja,**
- **Th2 odgovor je bio smanjen sa smanjenom IL-4, IL-13, i IgE produkcijom.**



Hindawi
BioMed Research International
Volume 2018, Article ID 8063647, 10 pages
https://doi.org/10.1155/2018/8063647

Review Article

Immunomodulatory Effects of Probiotics on Cytokine Profiles

Md. Abul Kalam Azad,[1,2] **Manobendro Sarker**,[3,4,5] **and Dan Wan**[1,6]

Elseviers et al. BMC Infectious Diseases (2015) 15:129
DOI 10.1186/s12879-015-0869-0

BMC Infectious Diseases

RESEARCH ARTICLE Open Access

Prevalence and management of antibiotic associated diarrhea in general hospitals

Monique M Elseviers[1*], Yoleen Van Camp[1], Sander Nayaert[1], Khyra Duré[1], Lieven Annemans[2], Ann Tanghe[3] and Sebastian Vermeersch[3]

Abstract

Background: Antibiotic-associated diarrhea (AAD) is a common adverse effect of antibiotic (AB) treatment. This study aimed to measure the overall prevalence of AAD (including mild to moderate diarrhea) in hospitalized AB treated patients, to investigate associated risk factors and to document AAD associated diagnostic investigations, contamination control and treatment.

Methods: During 8 observation days (with time delay of 10–14 days between each observation day), all adult patients hospitalized at an internal medicine ward of 4 Belgian participating hospitals were screened for AB use. Patients receiving AB on the observation day were included in the study and screened for signs and symptoms of AAD using a period prevalence methodology. Clinical data were collected for all AB users and AAD related investigations and treatment were collected for the entire duration of AAD. Additionally, nurses noted daily the frequency of all extra care associated to the treatment of the diarrhea.

Results: A total of 2543 hospitalized patients were screened of which 743 were treated with AB (29.2%). Included AB users had a mean age of 68 yr (range 16–99) and 52% were male. Penicillins were mostly used (63%) and 19% received more than one AB. AAD was observed in 9.6% of AB users including 4 with confirmed *Clostridium difficile* infection. AAD started between 1 and 16 days after AB start (median 5) and had a duration of 2 to 41 days (median 4). AAD was significantly associated with higher age and the use of double AB and proton pump inhibitors. AAD patients had extra laboratory investigations (79%), received extra pharmacological treatment (42%) and 10 of them were isolated (14%). AAD related extra nursing time amounted to 51 minutes per day for the treatment of diarrhea.

Conclusions: In this observational study, with one third of hospitalized patients receiving AB, an AAD period prevalence of 9.6% in AB users was found. AAD caused extra investigations and treatment and an estimated extra nursing care of almost one hour per day. Preventive action are highly recommended to reduce the prevalence of AAD and associated health care costs.

Keywords: Antibiotic use (AB), Antibiotic associated diarrhea (AAD), *Clostridium difficile* infection, AB use point prevalence, AAD prevalence, Contamination control, AAD related nursing care

nature microbiology

ARTICLES

https://doi.org/10.1038/s41564-021-00920-0

NATURE MICROBIOLOGY | VOL 6 | AUGUST 2021 | 1043–1054 | www.nature.com/naturemicrobiology

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OPEN

Probiotics impact the antibiotic resistance gene reservoir along the human GI tract in a person-specific and antibiotic-dependent manner

Emmanuel Montassier[1,2,3,9] ✉, Rafael Valdés-Mas[4,9], Eric Batard[1,2], Niv Zmora[4,5,6], Mally Dori-Bachash[4], Jotham Suez[4,8,10] ✉ and Eran Elinav[4,7,10] ✉

Antimicrobial resistance poses a substantial threat to human health. The gut microbiome is considered a reservoir for potential spread of resistance genes from commensals to pathogens, termed the gut resistome. The impact of probiotics, commonly consumed by many in health or in conjunction with the administration of antibiotics, on the gut resistome is elusive. Reanalysis of gut metagenomes from healthy antibiotics-naïve humans supplemented with an 11-probiotic-strain preparation, allowing direct assessment of the gut resistome in situ along the gastrointestinal (GI) tract, demonstrated that probiotics reduce the number of antibiotic resistance genes exclusively in the gut of colonization-permissive individuals. In mice and in a separate cohort of humans, a course of antibiotics resulted in expansion of the lower GI tract resistome, which was mitigated by autologous faecal microbiome transplantation or during spontaneous recovery. In contrast, probiotics further exacerbated resistome expansion in the GI mucosa by supporting the bloom of strains carrying vancomycin resistance genes but not resistance genes encoded by the probiotic strains. Importantly, the aforementioned effects were not reflected in stool samples, highlighting the importance of direct sampling to analyse the effect of probiotics and antibiotics on the gut resistome. Analysing antibiotic resistance gene content in additional published clinical trials with probiotics further highlighted the importance of person-specific metagenomics-based profiling of the gut resistome using direct sampling. Collectively, these findings suggest opposing person-specific and antibiotic-dependent effects of probiotics on the resistome, whose contribution to the spread of antimicrobial resistance genes along the human GI tract merit further studies.

MICROBIAL DRUG RESISTANCE
Volume 25, Number 6, 2019

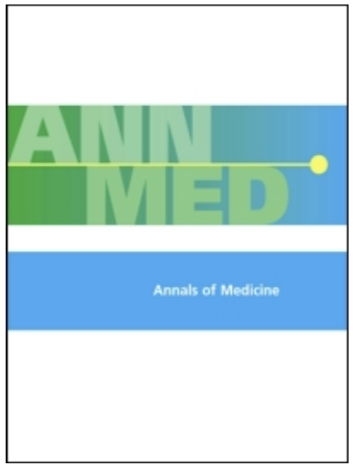
DOI: 10.1089/mdr.2018.0319

Multidrug-Resistant Bacteria and Alternative Methods to Control Them: An Overview

Roberto Vivas,[1] Ana Andréa Teixeira Barbosa,[1] Silvio Santana Dolabela,[1] and Sona Jain[1,2]

Antibiotic resistance is one of the greatest challenges in the health system nowadays, representing a serious problem for public health. Initially, antibiotic-resistant strains were restricted to the hospital environment, but now they can be found everywhere. Globalization, excessive use of antibiotics in animal husbandry and aquaculture, use of multiple broad-spectrum agents, and lack of good antimicrobial stewardship can be listed as the factors most responsible for the spread of antibiotic resistance. The increase in the prevalence of antibiotic-resistant pathogens implies having fewer antimicrobial agents to treat infections. The estimate is that by 2050, there will be no effective antibiotic available, if no new drug is developed or discovered. This raises the need to search for alternative methods of controlling antibiotic-resistant pathogens. Considering this problem, the objective of this review is to outline the most frequent antibiotic-resistant bacteria and describe the advantageous and limitations of alternative methods that have been proposed to control them.

Keywords: MRSA, VRE, antibiotic resistance, alternative therapies, bacteriocins, phage therapy



Annals of Medicine

ISSN: 0785-3890 (Print) 1365-2060 (Online) Journal homepage: https://www.tandfonline.com/loi/iann20

Probiotic approach to prevent antibiotic resistance

Arthur C. Ouwehand, Sofia Forssten, Ashley A. Hibberd, Anna Lyra & Buffy Stahl

To cite this article: Arthur C. Ouwehand, Sofia Forssten, Ashley A. Hibberd, Anna Lyra & Buffy Stahl (2016) Probiotic approach to prevent antibiotic resistance, Annals of Medicine, 48:4, 246-255, DOI: 10.3109/07853890.2016.1161232

To link to this article: https://doi.org/10.3109/07853890.2016.1161232

Published online: 26 Mar 2016.