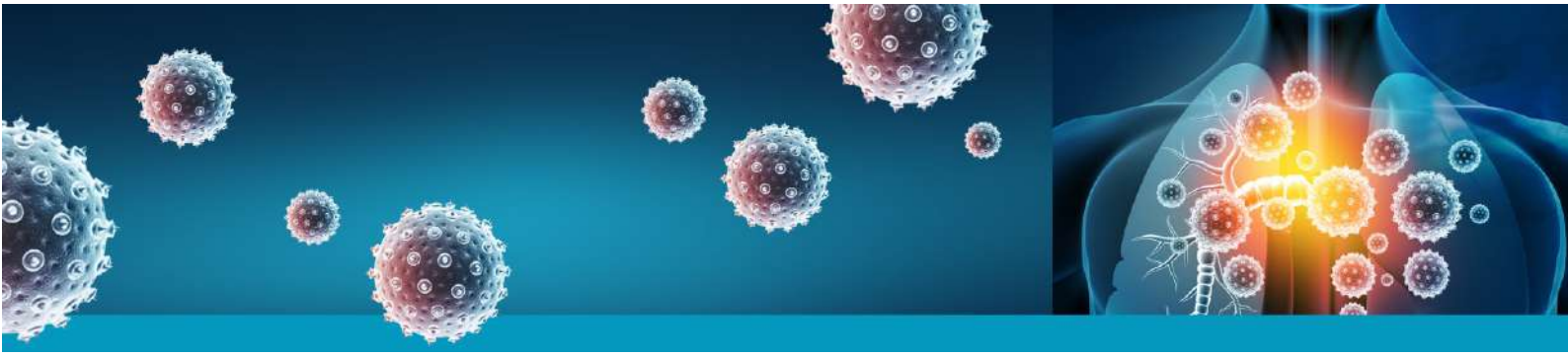


SUVREMENE SPOZNAJE O EPIDEMIOLOGIJI, KLINIČKOJ SLICI, LABORATORIJSKOJ DIJAGNOSTICI, TERAPIJI I PREVENCIJI RESPIRATORNIH INFEKCIJA

VODITELJI:

Izv. prof. dr. sc. prim. Rok Čivljak
Prof. dr. sc. prim. Sunčanica Ljubin Sternak
Prim. dr. Tatjana Nemeth Blažić
Dr. Dragan Soldo
Izv. prof. dr. sc. prim. Mario Sviben
Doc. dr. sc. Irena Tabain
Prof. dr. sc. prim. Jasmina Vraneš

Zagreb, 15. svibanj 2023.

KNJIGA SAŽETAKA

Poštovane kolegice, poštovane kolege

respiratorne infekcije značajan su javno zdravstveni problem. Smatra se da su upravo one glavni razlog zbog čega se pacijenti javljaju svojem liječniku ili ljekarniku. Zbog lakog načina širenja u globaliziranom svijetu, upravo respiratorne infekcije najlakše dovode do javno zdravstvene krize sa svim neželjenim posljedicama jedne pandemije što se imalo za priliku vidjeti u kontekstu pandemijske krize uzrokovane ovaj put s infekcijom SARS CoV-2 virusom.

Iako su virusi glavni uzročnici respiratornih infekcija brojni drugi bakterijski organizmi, ali i gljive i paraziti mogu uzrokovati infekcije gornjih ili donjih dišnih puteva.

Ovim multidisciplinarnim skupom u organizaciji najrelevantnijih stručnih društava Hrvatskog liječničkog zbora u oblasti respiratornih infekcija željeli bismo Vam prezentirati novosti u epidemiologiji kao i praćenju najznačajnijih respiratornih infekcija; osobitosti kliničkih slika pojedinih infekcija; novosti u laboratorijskoj dijagnostici te mogućnosti liječenja i prevencije s osobitim osvrtom na antimikrobnu otpornost i nova cjepiva.

Na skupu sudjeluju stručnjaci raznih specijalnosti s obzirom da i pristup ovim infekcijama treba biti multidisciplinaran.

Skup je namijenjen kolegicama i kolegama koji se u svojem radu susreću s ovom problematikom – liječnicima specijalistima i specijalizantima obiteljske medicine, infektolozima, mikrobiolozima, epidemiolozima, pedijatrima, pulmolozima, liječnicima koji se bave školskom medicinom, no i svim ostalima koje interesira ovo područje.

Voditelji

7 15-8 00	Registracija polaznika
8 00-8 15	Otvaranje simpozija
8 15-8 30	Prim.dr.Goranka Petrović Epidemiologija respiratornih infekcija u zemlji i svijetu
8-30-8 45	Dr.Dragan Soldo Respiratorne infekcije u ordinaciji liječnika obiteljske medicine
8 45-9 00	Izv.prof.dr.sc. prim.Rok Čivljak Klinički aspekti i liječenje respiratornih infekcija u odrasloj dobi
9 00-9 15	Prim.dr.sc. Srđan Roglić Klinički aspekti i liječenje respiratornih infekcija u dječjoj dobi
9 15-9 30	Dr. Eva Huljev Atipične pneumonije
9 30-9 45	Doc.dr.sc. Vladimir Krajinović Bolničke pneumonije
9 45-10 00	Mini simpozij Astra Zeneca - Prim.dr.sc. Srđan Roglić Primjena protutijela u profilaksi respiratornih infekcija
10 00-10 30	Pauza
10 30-10 45	Doc.dr.sc.prim.Lana Kovač Bilić Klinički aspekti i liječenje upala srednjeg uha
10 45-11 00	Mini simpozij Oktal Pharma - Dr.sc. Andro Košec Otikon mini-novo terapijsko rješenje kod uhobolje
11 00-11 15	Izv.prof.dr.sc. Tomislav Meštrović Uzimanje uzoraka, obrada i mikrobiološka dijagnostika respiratornih infekcija
11 15-11 30	Prof.dr.sc. prim. Jasmina Vraneš Novi trendovi i dijagnostičke strategije u otkrivanju SARS Cov -2 infekcije
11 30-11 45	Mini simpozij Inel-medicinska tehnika d.o.o. i QIAGEN – Eric Jan Cools Two quick and easy to use molecular solutions for respiratory testing
11 45-12 00	Prof.dr.sc. prim.Sunčanica Ljubin Sternak Infekcija uzrokovana rinovirusom -prolazna neugodnost ili teška bolest?
12 00-12 15	Mini simpozij Biosistemi d.o.o. – Dr.sc.Branka Jeličić Omogućavanje ranog otkrivanja: naši proizvodi za proučavanje respiratornih infekcija
12 15-12 30	Doc.dr.sc. Irena Tabain Utjecaj COVID-19 pandemije na uobičajene sezonske cikluse respiratornih virusa od posebnog značaja

12 30-13 30	Pauza
13 30-13 45	Dr.Ana Čičmak Gljive uzročnici respiratornih infekcija
13 45-14 00	Mini simpozij Diahem – Katarzyna Malesa Platelia Aspergillus Ag Assay – a unique tool for screening, monitoring and diagnosing invasive aspergilosis in high risk patients
14 00-14 15	Prim.dr.sc.Iva Butić Laboratorijska dijagnostika pneumokoka, moraksele i hemofilusa
14 15 -14 30	Dr.Irina Pristaš Laboratorijska dijagnostika streptokoka i bordetele
14 30- 14 45	Mini simpozij A&B -Prof.dr.sc. Ivana Ćirković Primena MALDI -TOF MS u mikrobiološkoj dijagnostici respiratornih infekcija
14 45-15 00	Mr.sc.dr. Selma Bošnjak Mikrobiološka dijagnostika legioneloza
15 00-15 30	Pauza
15 30-15 45	Doc.dr.sc.Mateja Janković Makek Klinički aspekti i liječenje tuberkuloze
15 45-16 00	Doc.dr.sc.Ljiljana Žmak Noviteti u dijagnostici tuberkuloznih infekcija
16 00-16 15	Izv.prof.dr.sc.prim. Mario Sviben Parazitarne infekcije dišnog sustava
16 15-16 30	Prof.dr.sc. Arjana Tambić Andrašević Antimikrobna rezistencija i terapijske mogućnosti za liječenje bakterijskih respiratornih patogena
16 30-16 45	Doc.dr.sc.prim.Bernard Kaić; Prim.dr. Tatjana Nemeth Blažić Prevencija respiratornih infekcija cijepljenjem
16 45-17 30	Rasprava. Zaključci

Epidemiologija respiratornih infekcija

u zemlji i svijetu

Goranka Petrović
Hrvatski zavod za javno zdravstvo

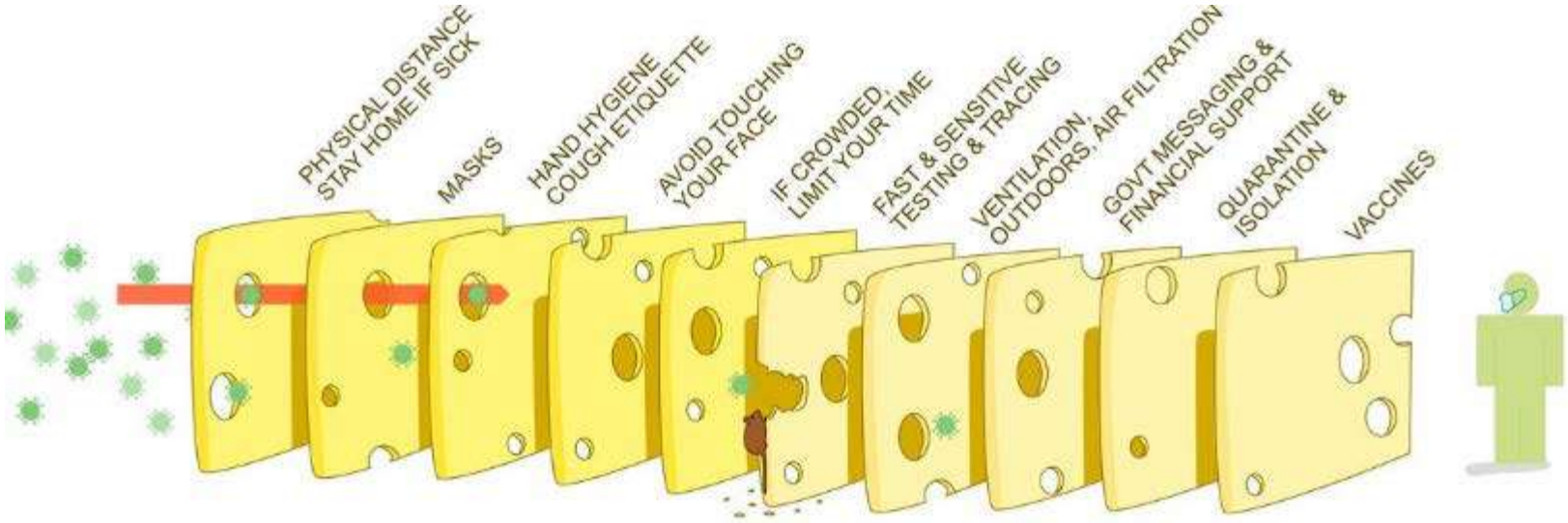
Suvremene spoznaje o epidemiologiji, kliničkoj slici, laboratorijskoj dijagnostici, terapiji i prevenciji respiratornih infekcija
Zagreb, 15.svibnja 2023.

Respiratorne infekcije

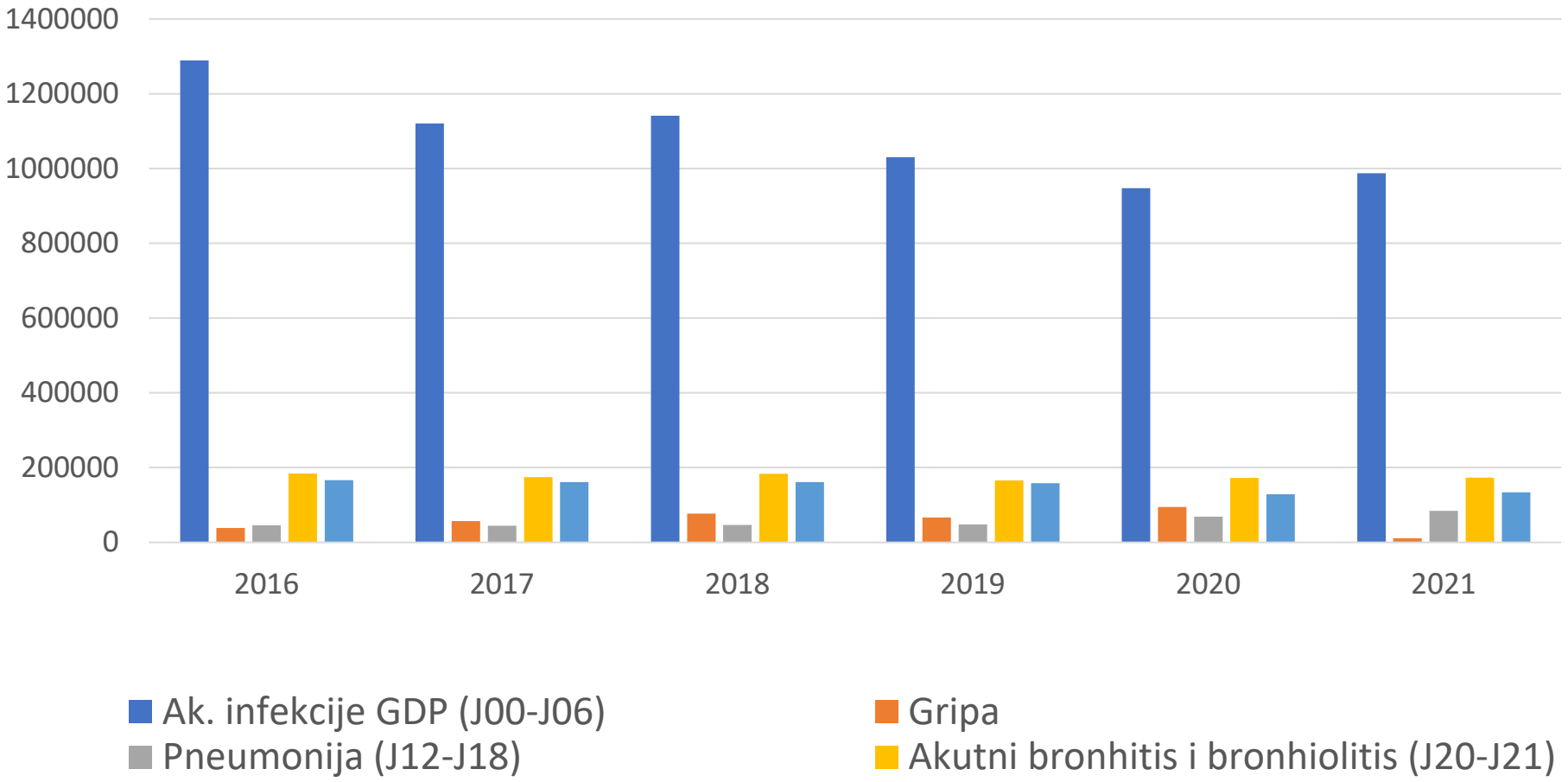
- brojni uzročnici (virusi, bakterije, gljivice)
- više uzorčnika ista kl.slika i obratno
- sezonski karakter
- rizični faktori (dob, komorbiditeti, SES)
- kapljični put -> brzo širenje, epidemije, mutacije
- pandemijski potencijal nekih uzročnika
- utjecaj COVID-19 pandemije na respiratorne patogene (ekologija, epidemiologija, imunost ljudi)

Respiratorne infekcije

- opterećenje zdravstvenog sustava
- opterećenje zajednice (bolovanja, dostupnost usluga i dr.)
- slojeviti pristup u prevenciji

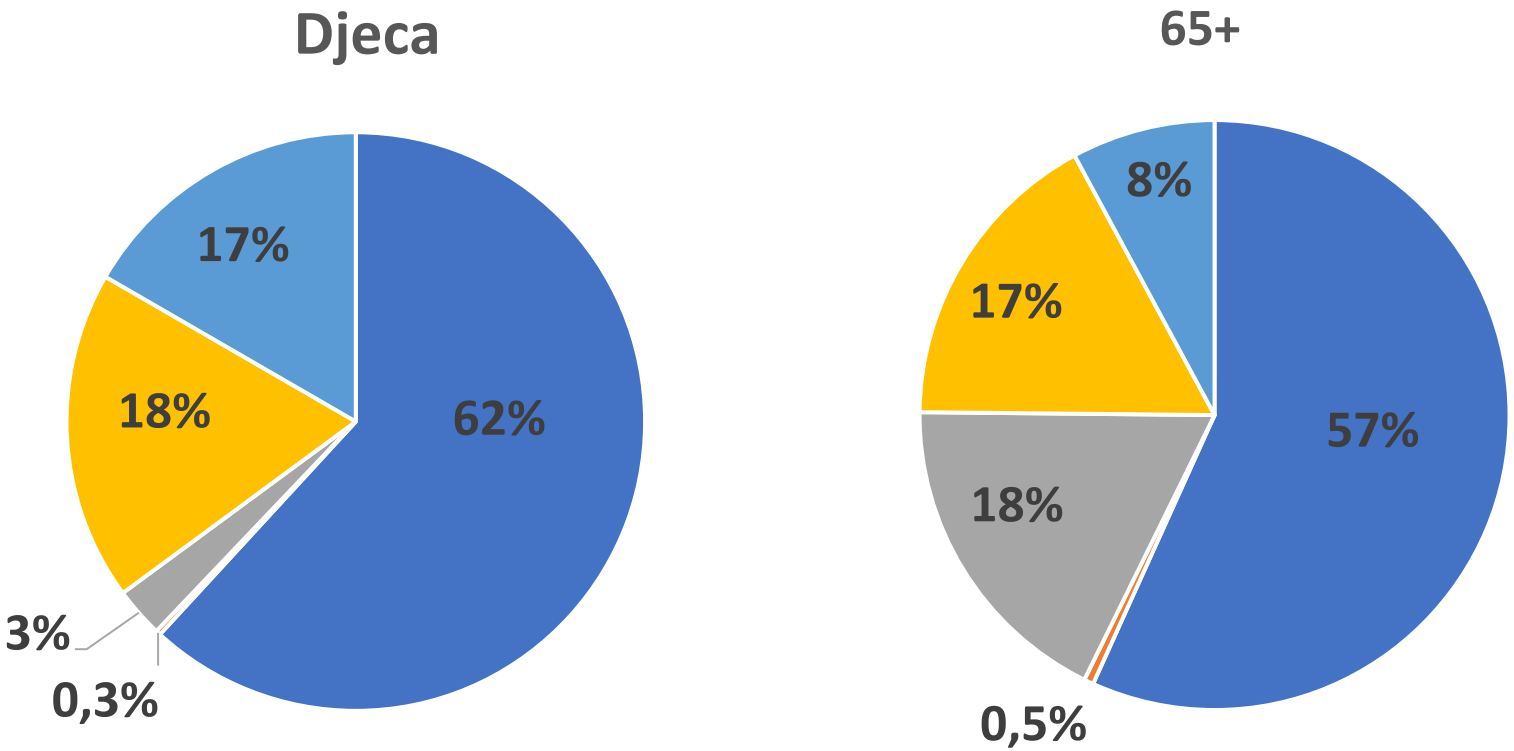


Posjete u PZZ zbog respiratornih infekcija u Hrvatskoj, 2016-2021.

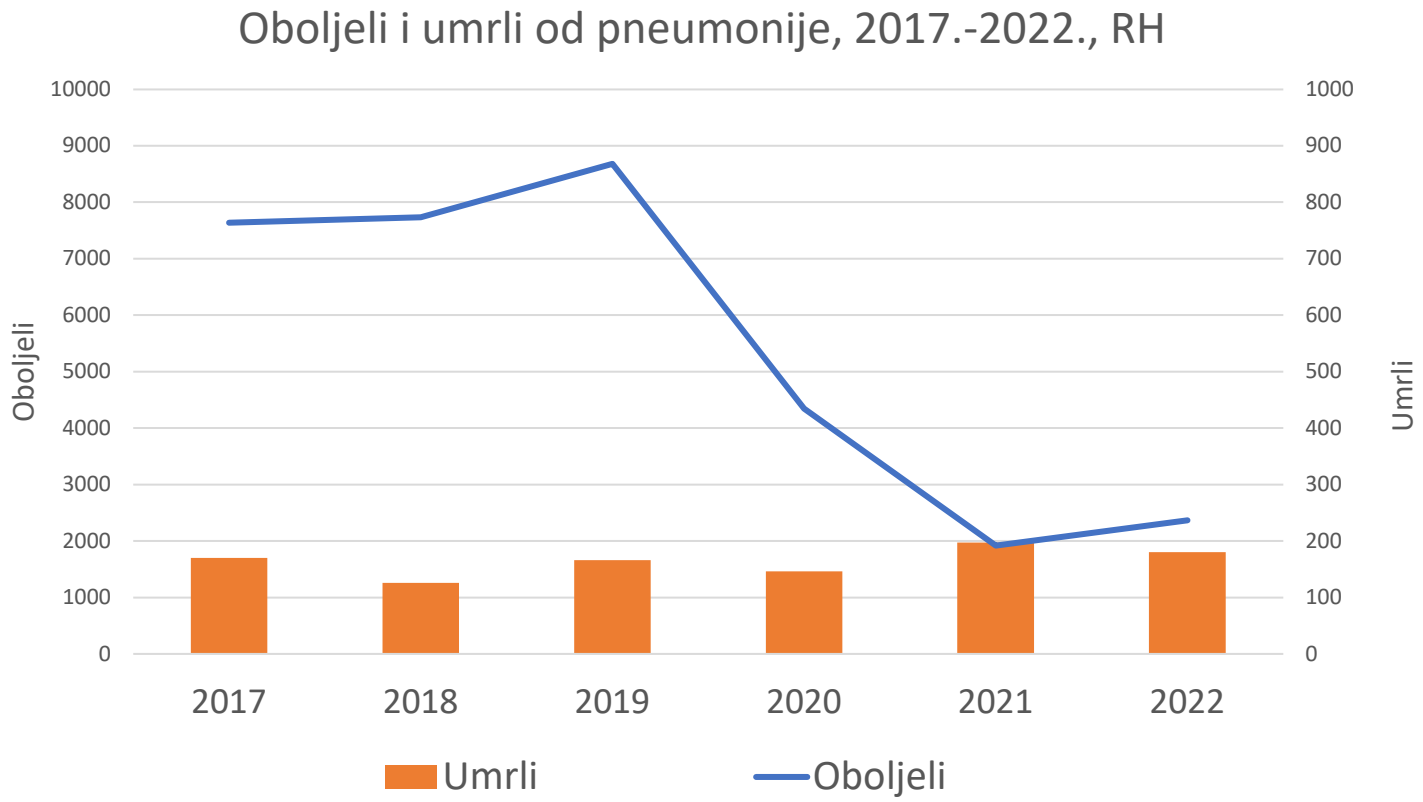


Hrvatski zdravstveno-statistički ljetopis za 2021., HZJZ

Respiratorne infekcije, posjete PZZ, 2021.



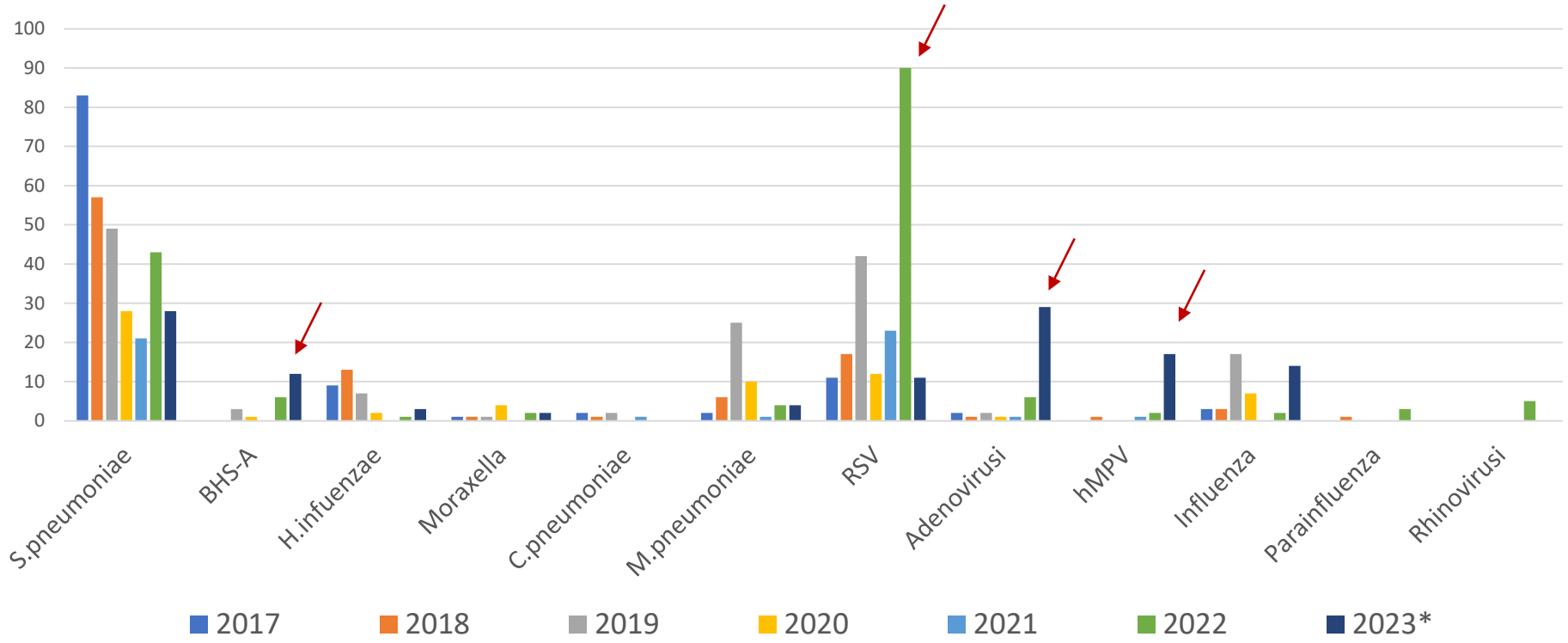
Hrvatski zdravstveno-statistički ljetopis za 2021., HZJZ



Prosjek	Oboljeli	Umrli
2017_19	8018	154
2020_22	2877	174

Izvor: Registar zaraznih bolesti, HZJZ

Odabrani uzročnici u prijavama pneumonija, RH, 2017. -2023.*



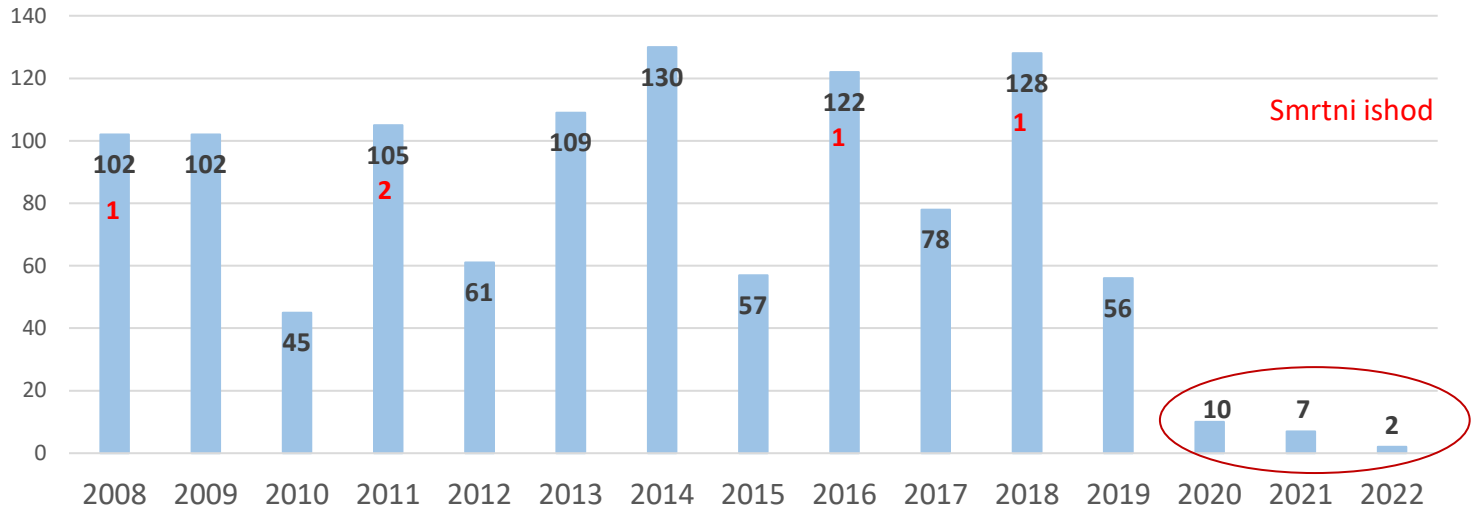
*prijave zaključno sa danom 28.4.2023.

Koinfekcije

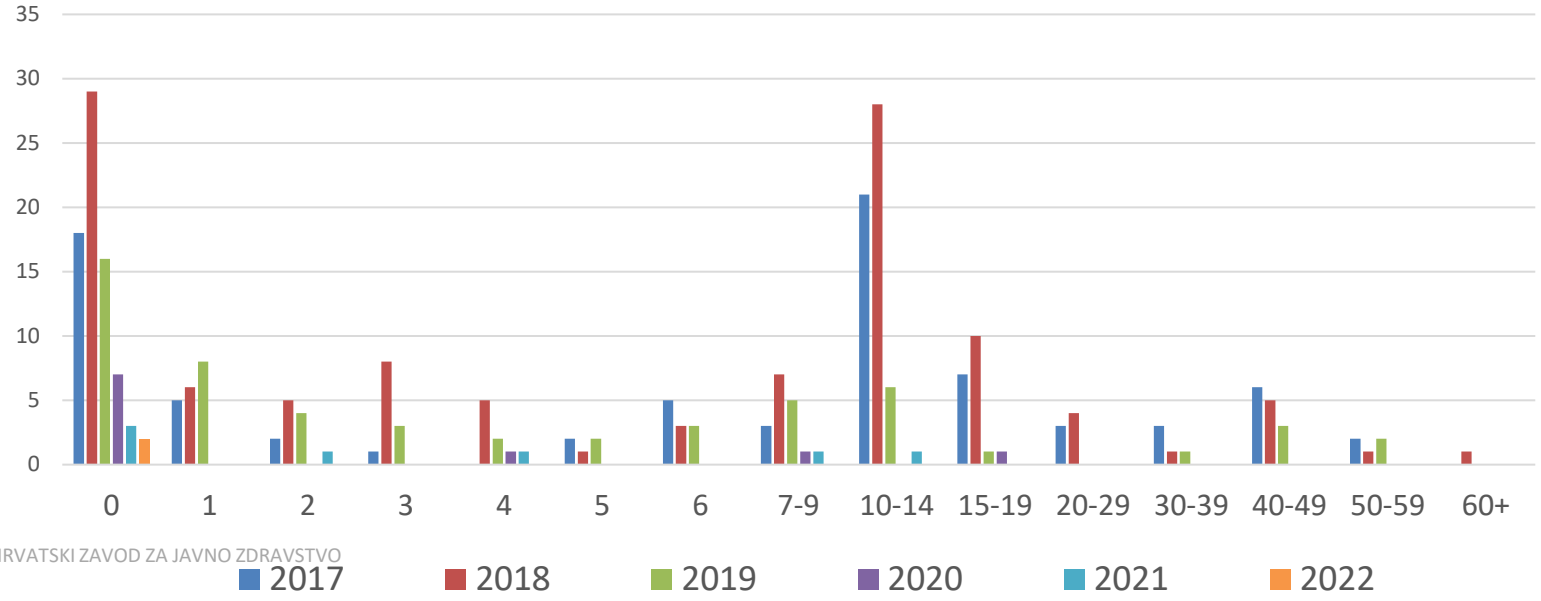
2022. Moraxella i S.pneumoniae(1)

2023.BHS-A i AdV (1); BHS-A i RSV (1), AdV i RhV (1), H.influenzae i Moraxella (2)

Hripavac u RH, 2008.- 2022.

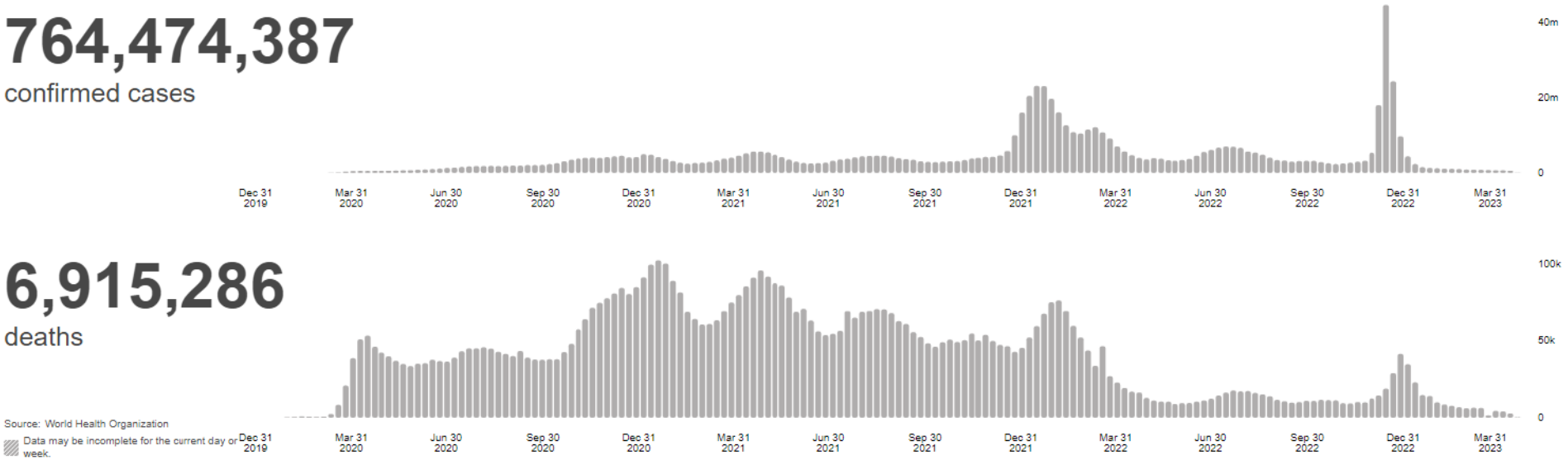


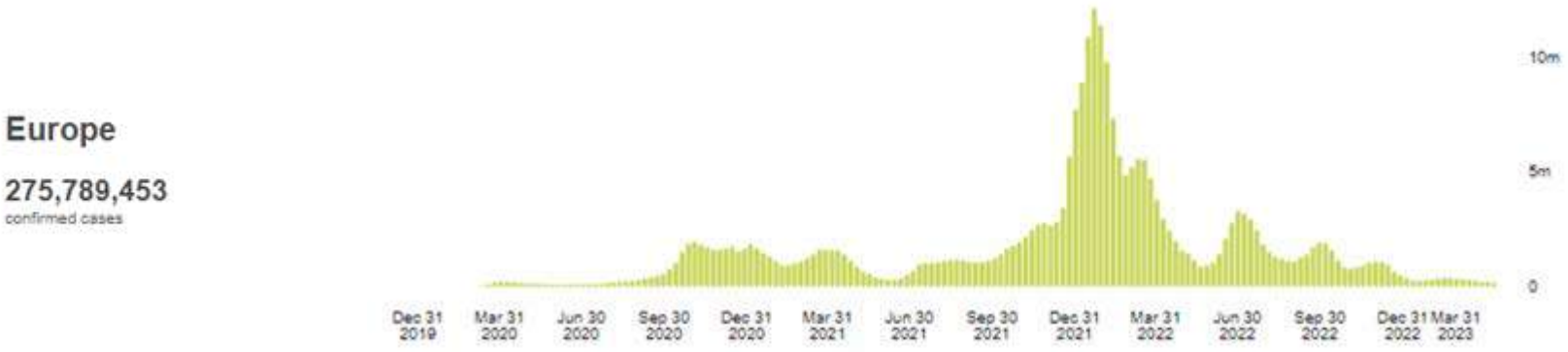
Oboljeli od hripavca prema dobi u RH



Izvor: Hrvatski zavod za javno zdravstvo

COVID-19 u svijetu



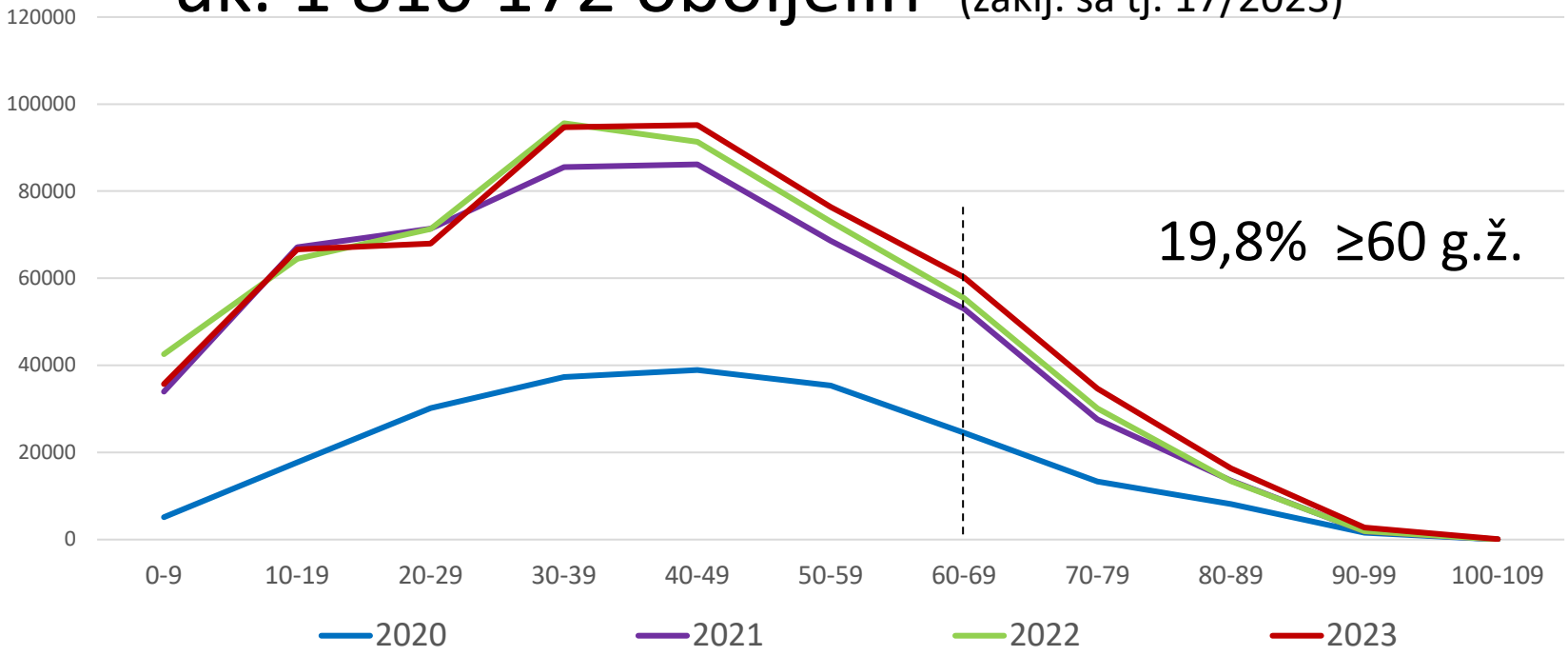


Podaci zaključno sa 26.4.2023.

WHO Coronavirus (COVID-19) Dashboard

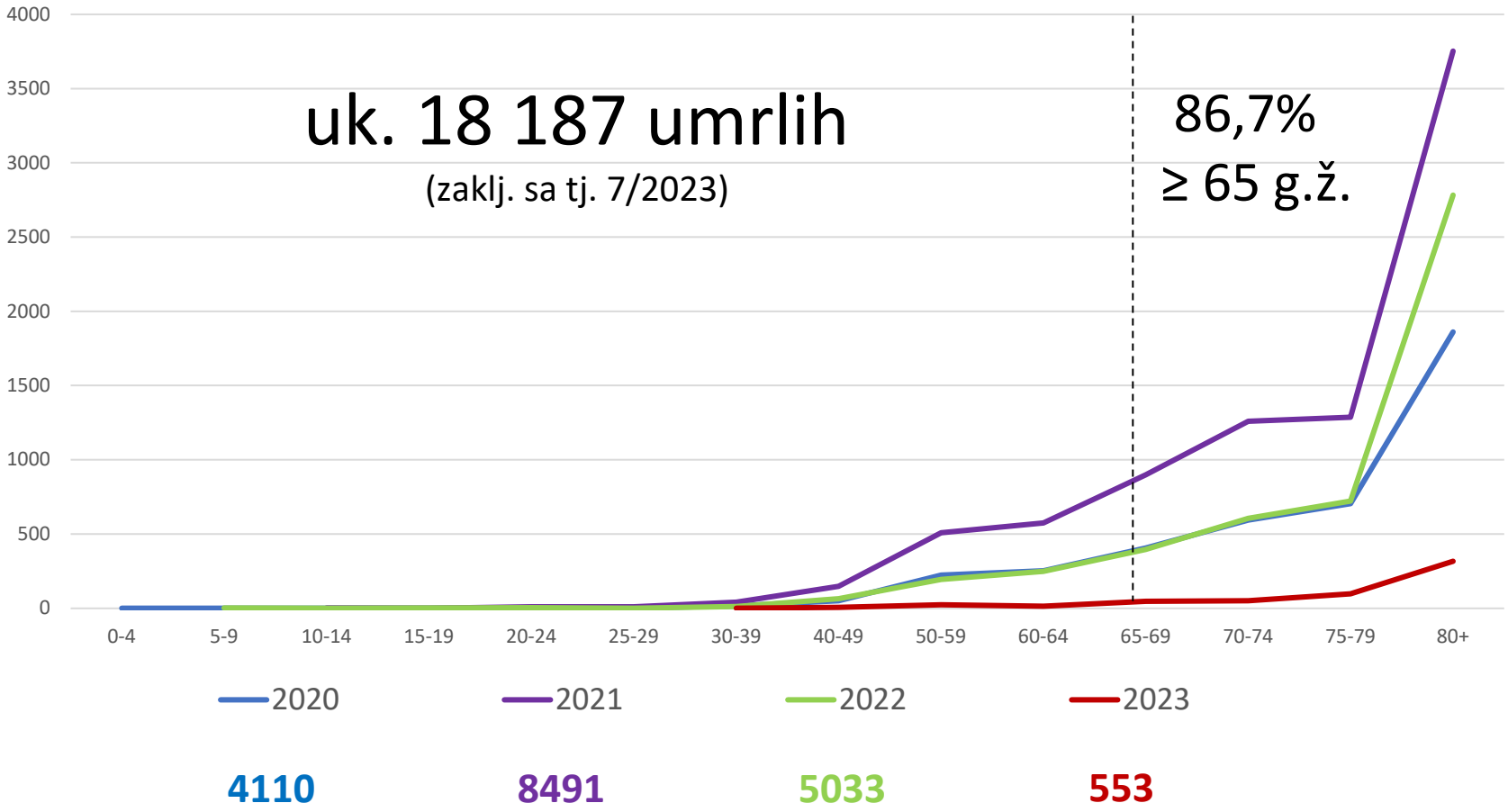
COVID-19 u RH

uk. 1 810 172 oboljelih (zaklj. sa tj. 17/2023)

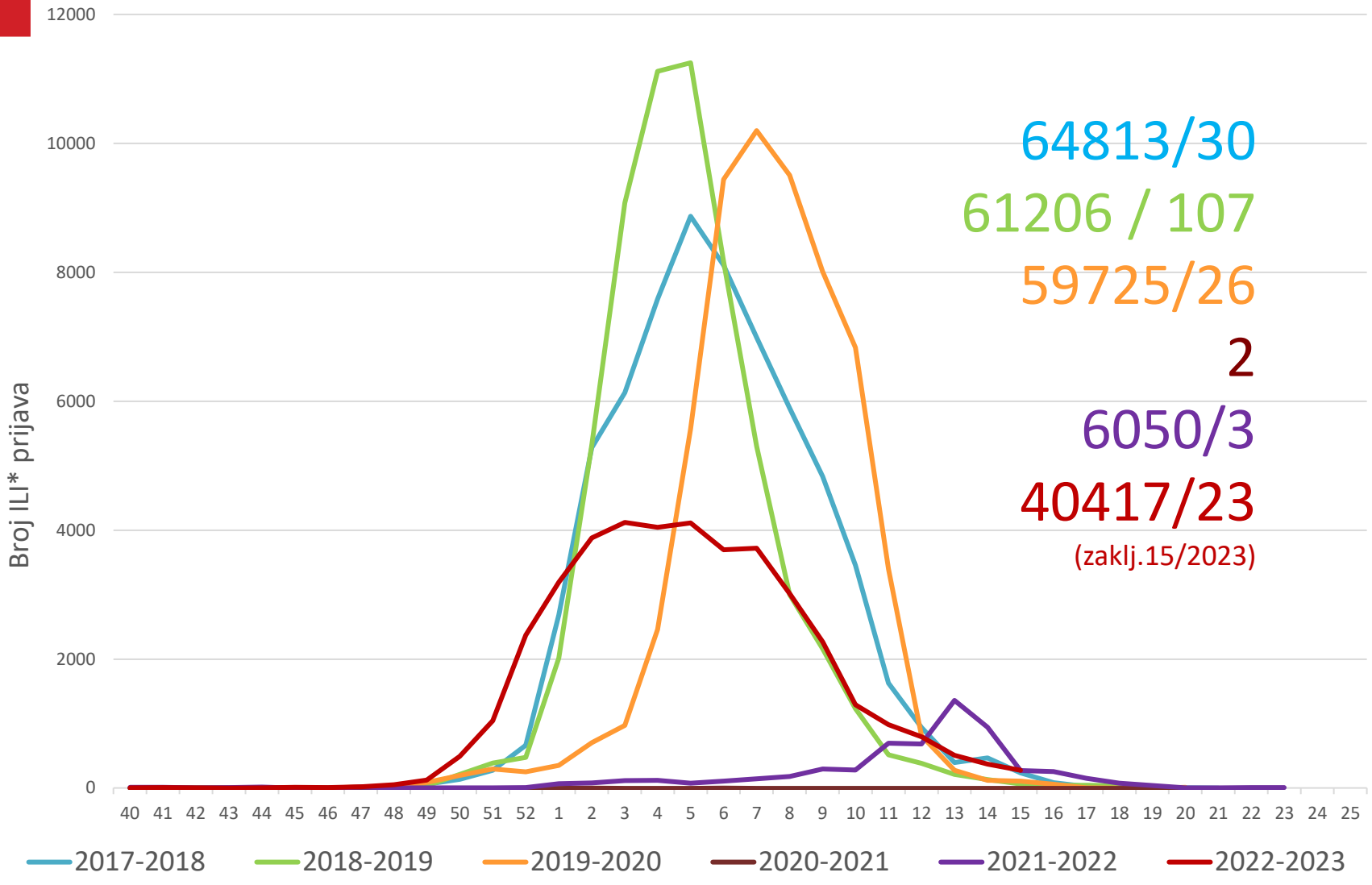


Originalni Wuhan soj D614G	Alfa varijanta Delta varijanta	Omicron (podvarijante)	
212 089	**508 572**	**539 098**	**550 413**

COVID-19 u RH

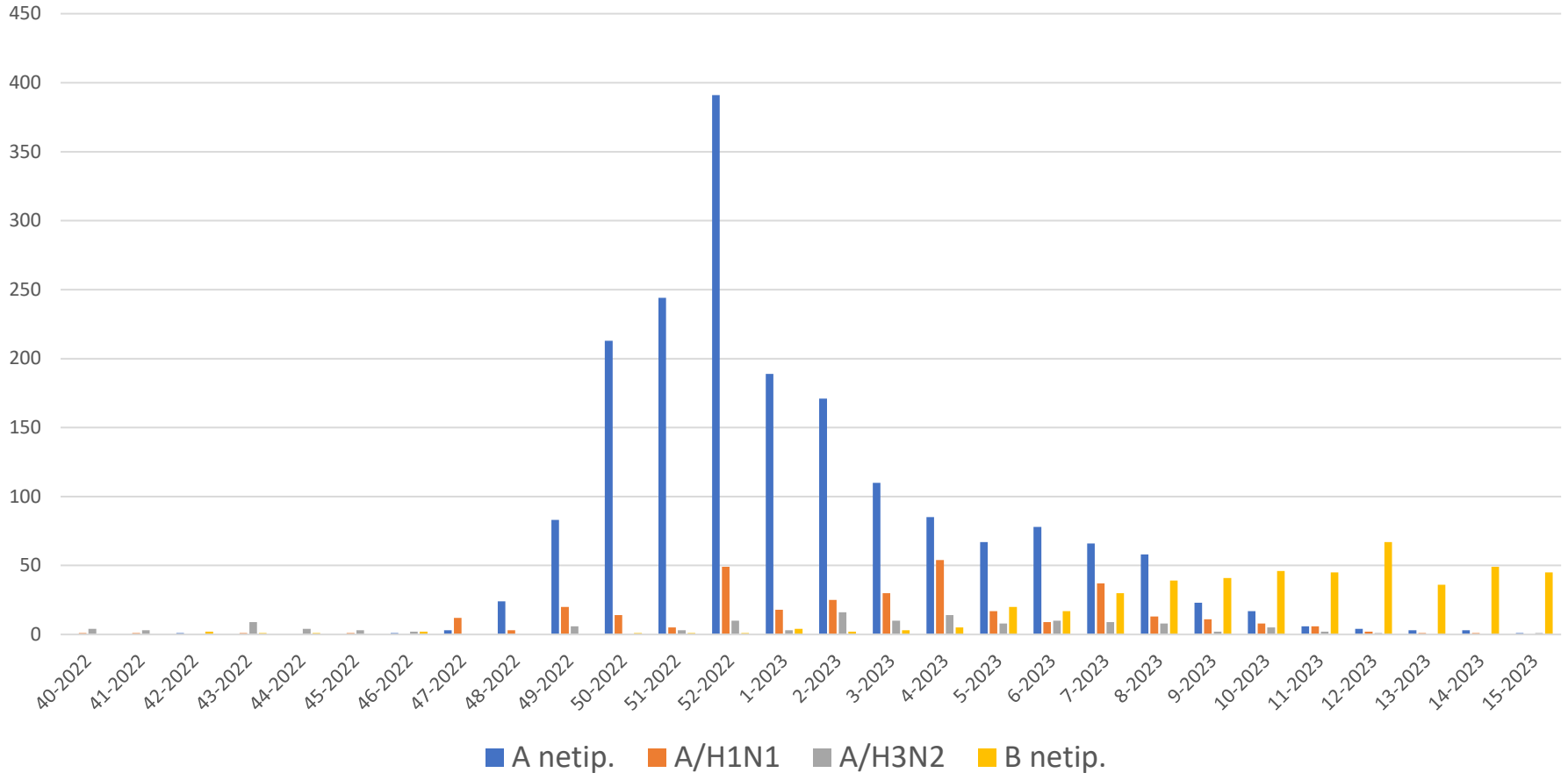

uk. 18 187 umrlih
(zaklj. sa tj. 7/2023)
86,7%
≥ 65 g.ž.
4000
3500
3000
2500
2000
1500
1000
500
0
0-4
5-9
10-14
15-19
20-24
25-29
30-39
40-49
50-59
60-64
65-69
70-74
75-79
80+
2020
2021
2022
2023
4110
8491
5033
553

Gripa u RH



*Influenza-Like Illness

Cirkulirajući virusi influenze tijekom sezone 2022./2023. u RH



Izvor: Služba za mikrobiologiju, HZJZ

European Centre for Disease Prevention and Control
An agency of the European Union

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< Media centre

Increase in Invasive Group A streptococcal infections among children in Europe, including fatalities

Press release

12 Dec 2022

World Health Organization | Europe

Health topics | Our work | Newsroom | Data | Emergencies

Home / News / Increase in invasive Group A streptococcal infections among children in Europe, including fatalities

Increase in invasive Group A streptococcal infections among children in Europe, including fatalities

12 December 2022 | News release | Reading time: 2 min (639 words)

CDC Centers for Disease Control and Prevention
CDC 24/7: Saving Lives, Protecting People™

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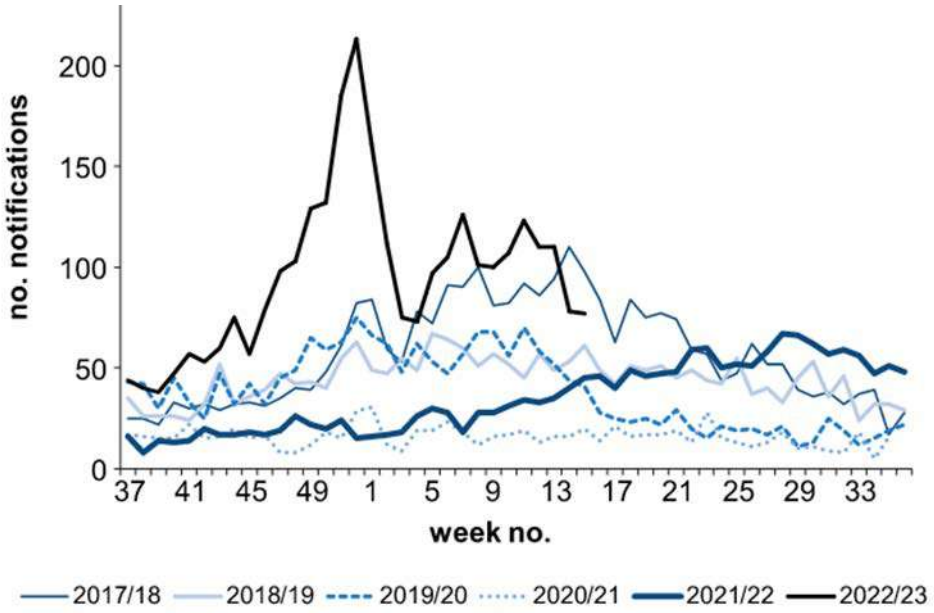
Group A Streptococcal (GAS) Disease

Increase in Invasive Group A Strep Infections, 2022–2023

CDC is looking into an increase in invasive group A strep (iGAS) infections among children in the United States. iGAS infections include necrotizing fasciitis and streptococcal toxic shock syndrome.

UK Health Security Agency

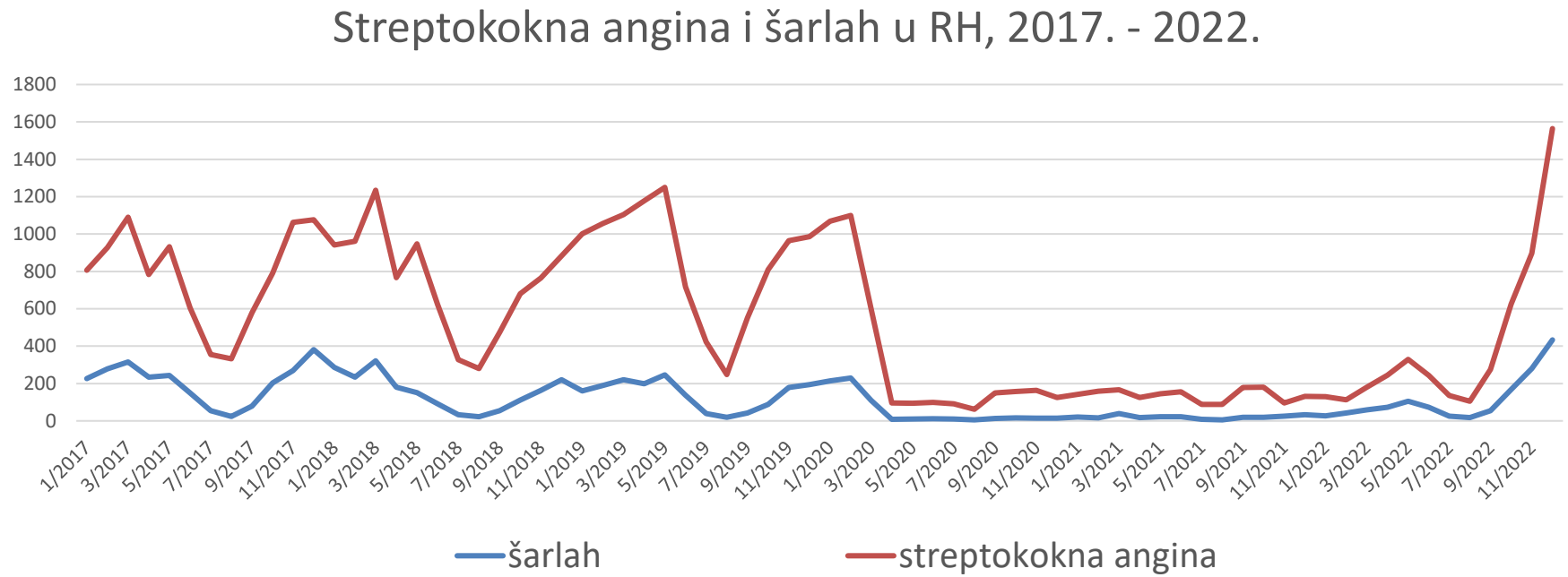
Weekly laboratory notifications of invasive GAS, England, by season, 2017 to 2018 onwards (weeks 37 to 15)



Investigations are continuing following reports of an increase in lower respiratory tract GAS infections, particularly empyema, in children during November and December 2022 (1). The current emm types have been circulating for many years. While a newer strain of emm1 (M1UK) was documented as having emerged and expanded in the last decade, its role (if any) in driving the current high levels of iGAS in children remains uncertain. Detailed genomic and biological investigations are under way to investigate any differences in the pathogen being seen this season.

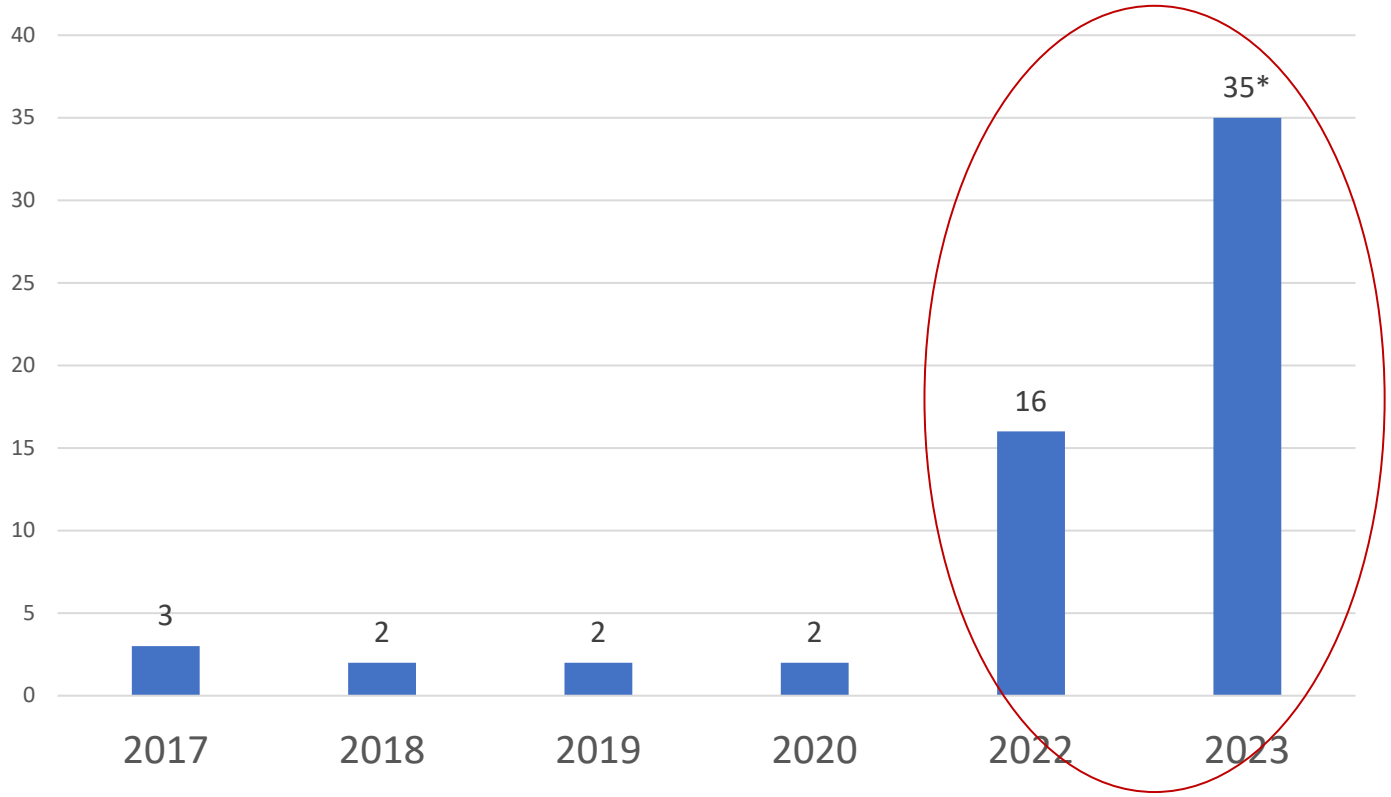
The elevated iGAS levels in children compared to the period when pandemic control measures were in place is likely to be a consequence of the heightened scarlet fever activity given the crossover of strains associated in both presentations (2, 3). Reduced exposure to GAS infections during the pandemic is also likely to have led to increased susceptibility to these infections in children, in view of the very low levels seen during the pandemic. Prompt treatment of scarlet fever with antibiotics is recommended to reduce risk of possible complications and limit onward transmission.

BHS -A streptokokne infekcije u RH



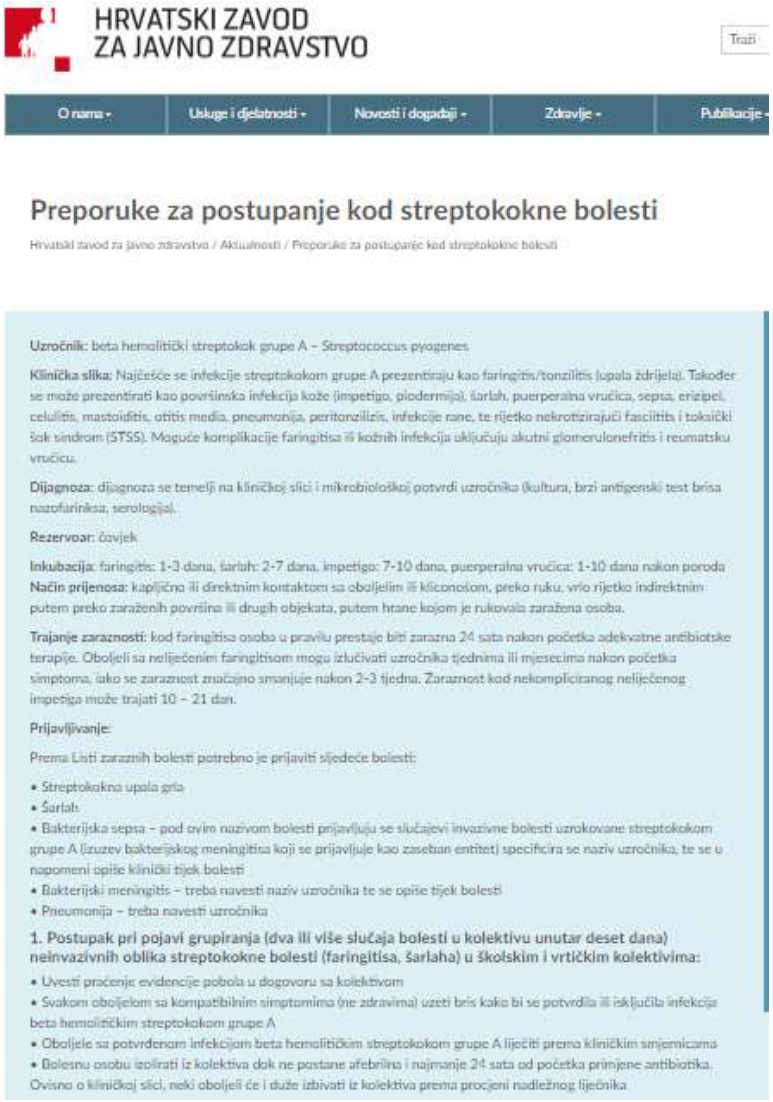
Prosinac (%)	BHS angina	šarlah
2017	11.5	15.5
2018	9.9	11.8
2019	9.6	11.4
2020	3.3	2.3
2021	8.0	13.5
2022	32.3	31.9

Invazivna BHS-A infekcija u RH



*zaključno sa tj. 15/2023

Invazivna BHS-A infekcija u RH, 2022./2023.



HRVATSKI ZAVOD ZA JAVNO ZDRAVSTVO

Traži

O nama | Usluge i djelatnosti | Novosti i događaji | Zdravlje | Publikacije

Preporuke za postupanje kod streptokokne bolesti

Hrvatski zavod za javno zdravstvo / Aktualnosti / Preporuke za postupanje kod streptokokne bolesti

Uzročnik: beta hemolitički streptokok grupe A – Streptococcus pyogenes

Klinička slika: Najčešće se infekcije streptokokom grupe A prezentiraju kao faringitis/tonzilitis (upala ždrijela). Također se može prezentirati kao površinska infekcija kože (impetigo, piodermija), šarlah, puerperalna vrućica, sepsa, erizipel, celulitis, mastoiditis, otitis media, pneumonija, peritonzilitis, infekcije rane, te rijetko nekrotizirajući fasciitis i toksički šok sindrom (STSS). Moguće komplikacije faringitisa ili kožnih infekcija uključuju akutni glomerulonefritis i reumatsku vrućicu.

Dijagnoza: dijagnoza se temelji na kliničkoj slici i mikrobiološkoj potvrdi uzročnika (kultura, brzi antigenski test brisa nazofarinksa, serologija).

Rezervoar: čovjek

Inkubacija: faringitis: 1-3 dana, šarlah: 2-7 dana, impetigo: 7-10 dana, puerperalna vrućica: 1-10 dana nakon poroda
Način prijenosa: kapljično ili direktnim kontaktom sa oboljelim ili kliconošom, preko ruku, vrlo rijetko indirektnim putem preko zaraženih površina ili drugih objekata, putem hrane kojom je rukovala zaražena osoba.

Trajanje zaraznosti: kod faringitisa osoba u pravilu prestaje biti zarazna 24 sata nakon početka adekvatne antibiotske terapije. Oboljeli sa neliječenim faringitisom mogu izlučivati uzročnika tjednima ili mjesecima nakon početka simptoma, iako se zaraznost značajno smanjuje nakon 2-3 tjedna. Zaraznost kod nekompliciranog neliječenog impetiga može trajati 10 – 21 dan.

Prijavljivanje:

Prema Listi zaraznih bolesti potrebno je prijaviti sljedeće bolesti:

- Streptokokna upala grla
- Šarlah
- Bakterijska sepsa – pod ovim nazivom bolesti prijavljuju se slučajevi invazivne bolesti uzrokovane streptokokom grupe A (izuzev bakterijskog meningitisa koji se prijavljuje kao zaseban entitet) specificira se naziv uzročnika, te se u napomeni opiše klinički tijek bolesti
- Bakterijski meningitis – treba navesti naziv uzročnika te se opiše tijek bolesti
- Pneumonija – treba navesti uzročnika

1. Postupak pri pojavi grupiranja (dva ili više slučaja bolesti u kolektivu unutar deset dana) neinvazivnih oblika streptokokne bolesti (faringitisa, šarlaha) u školskim i vrtićkim kolektivima:

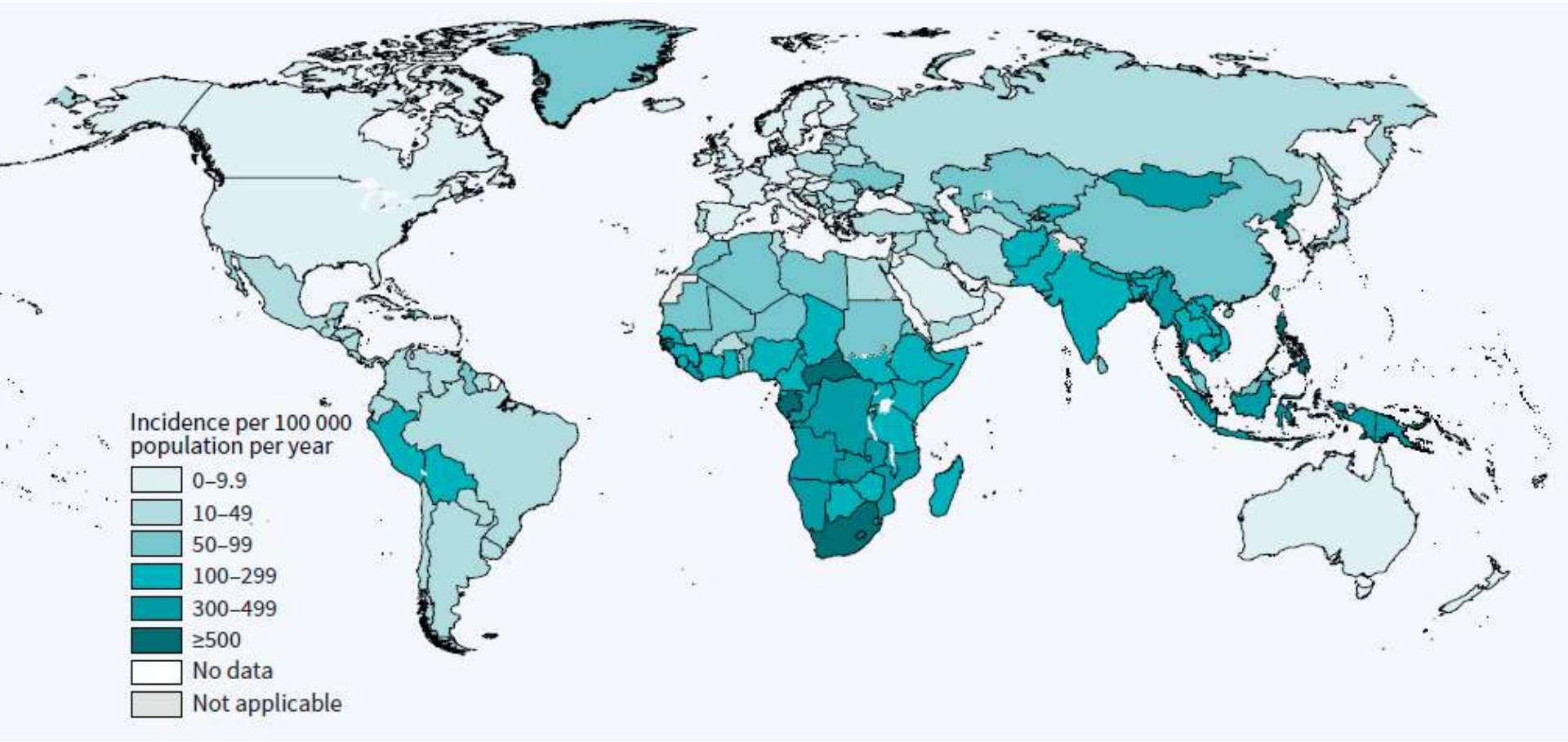
- Uvesti praćenje evidencije pobola u dogovoru sa kolektivom
- Svakom oboljelom sa kompatibilnim simptomima (ne zdravima) uzeti bris kako bi se potvrdila ili isključila infekcija beta hemolitičkim streptokokom grupe A
- Oboljele sa potvrđenom infekcijom beta hemolitičkim streptokokom grupe A liječiti prema kliničkim smjernicama
- Bolesnu osobu izolirati iz kolektiva dok ne postane afebrilna i najmanje 24 sata od početka primjene antibiotika. Ovisno o kliničkoj slici, neki oboljeli će i duže izbivati iz kolektiva prema procjeni nadležnog liječnika

Dob	Oboljeli	Umrli
1_5	15	1
6_14	3	
15_19	0	
20_39	11	2
40_59	12	3
60+	10	4
ukupno	51	10

Tuberkuloza u svijetu u 2021.

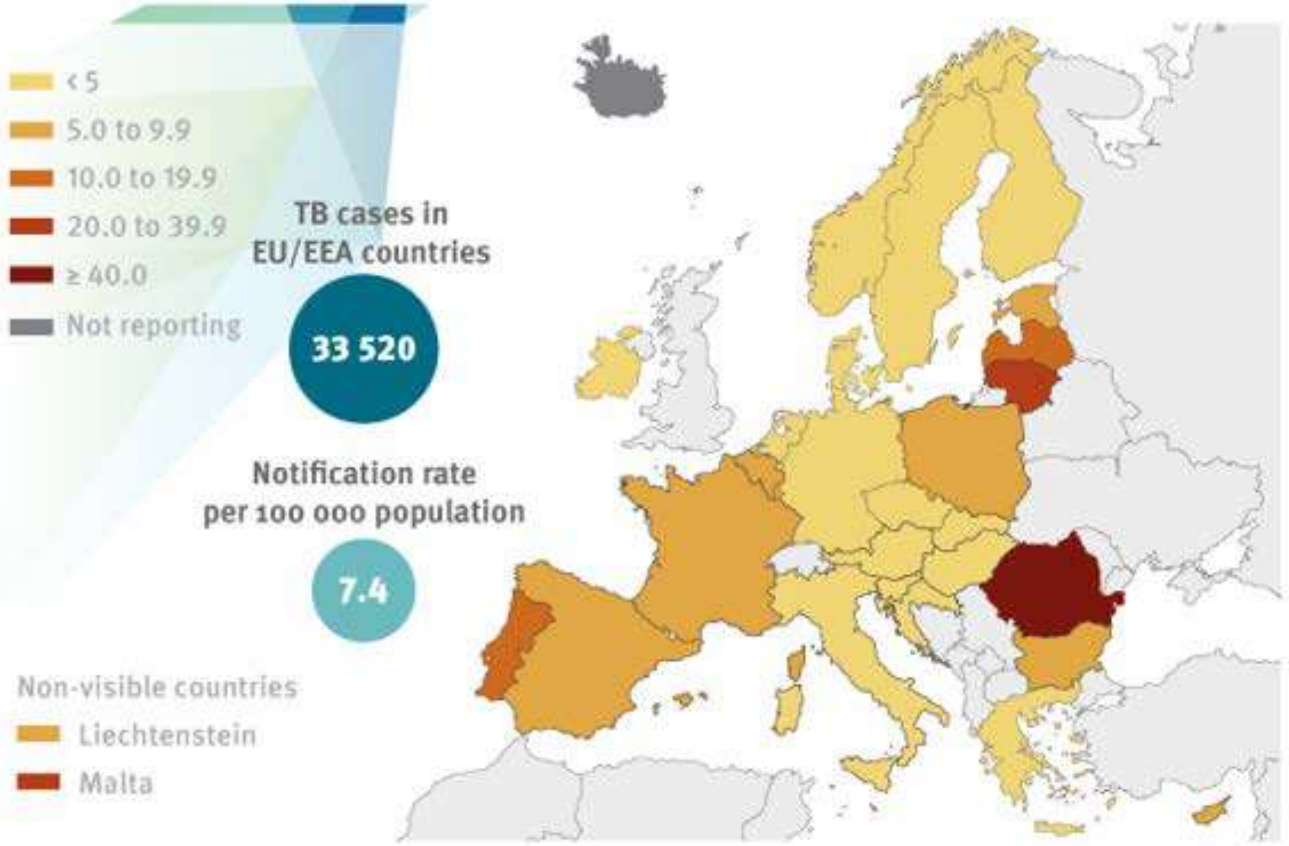
- **10,6 mil. novooboljelih** (+**4,5%** 2020.)
- **450 000** sluč. RR/MDR TBC (+**3,1%** 2020.)
  - 3.6% novooboljelih od TBC
  - 18% već prethodno liječenih od TBC
- **1,6 mil. umrlih** u 2021. (1,5mil.2020; 1,4mil.2019)
  - 1.4 mil. HIV-negativni
  - 187 000 HIV-pozitivni

Tuberkuloza u svijetu u 2021.



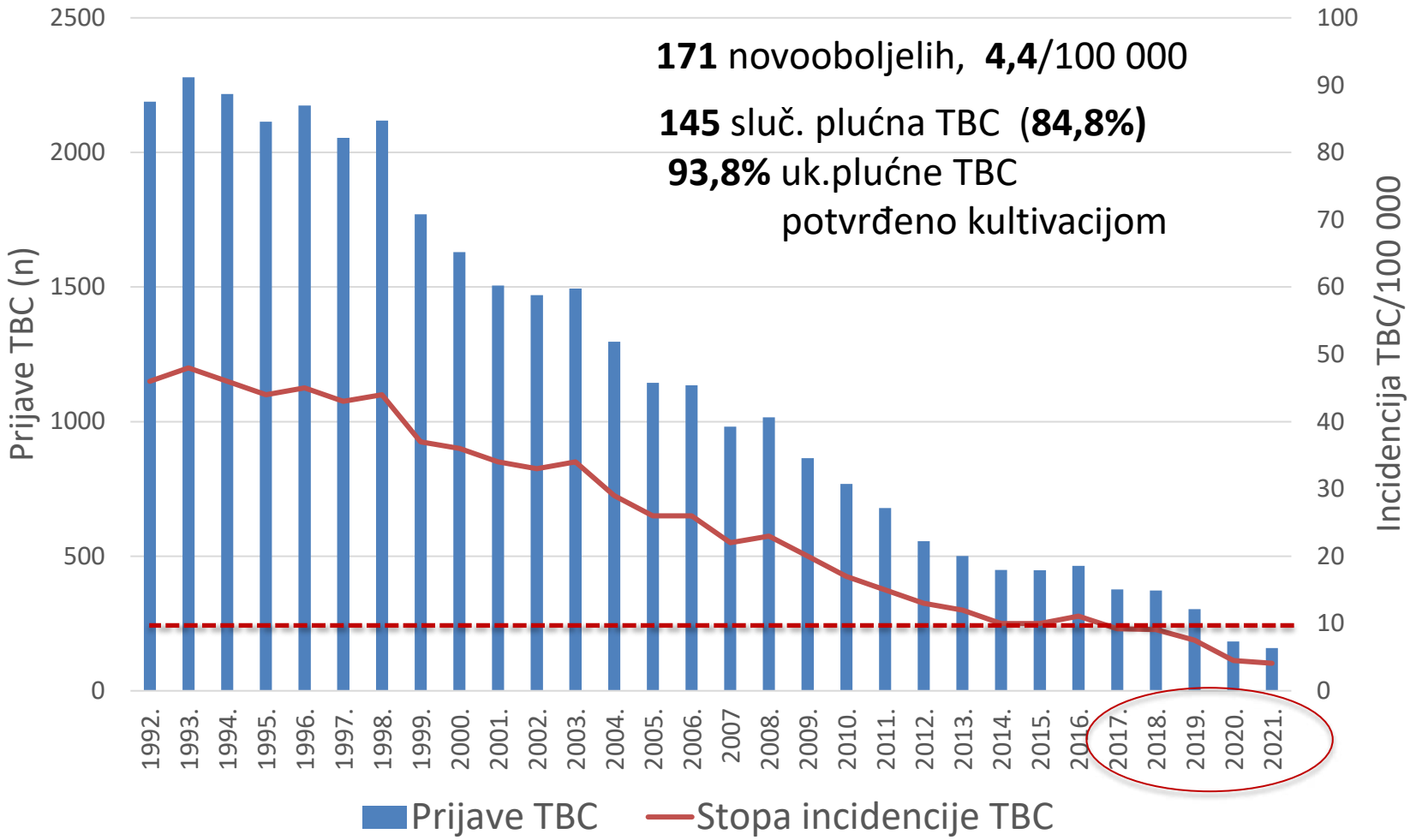
Izvor: Global tuberculosis report 2022, WHO

Cases per 100 000 population in the EU/EEA, 2021



Source: ECDC/WHO (2023) 2023 Report – 2021 data.
ecdc.europa.eu/en/tuberculosis

Tuberkuloza u RH, 1992. – 2021.

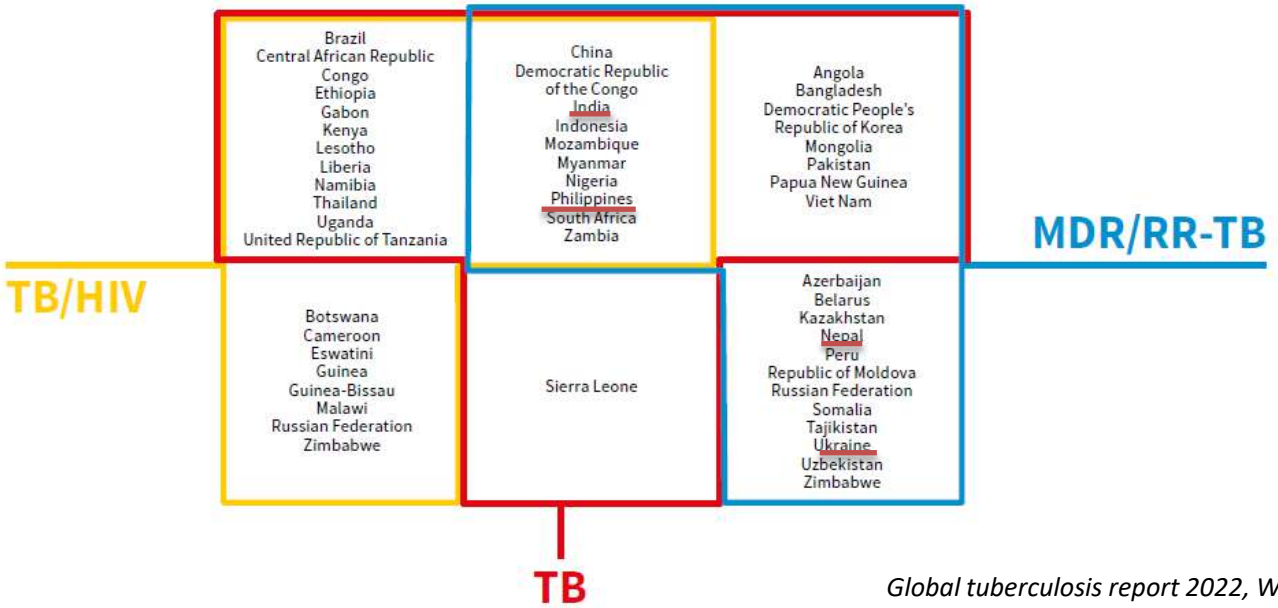


Izazovi u nadzoru TBC

- Migracije

  -> prisilne (ratni konflikti i sl) – Ukrajina

  -> ekonomske - uvoz radne snage; države sa visokom incidencijom TBC (Filipini, Indija,Nepal i dr).

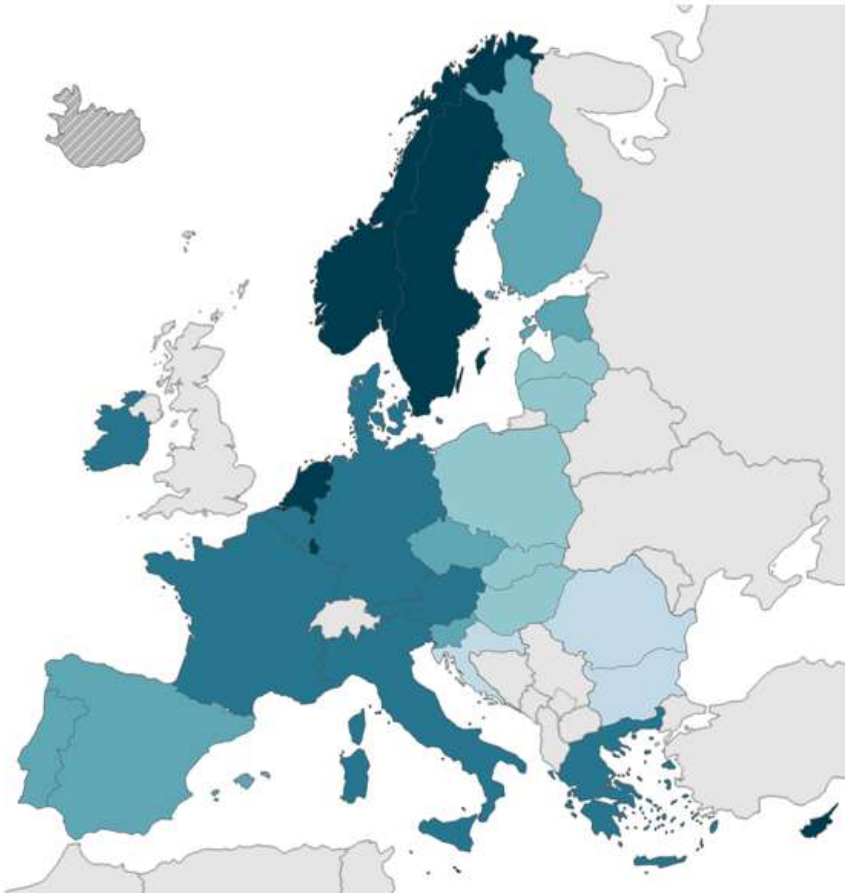


Global tuberculosis report 2022, WHO

TB in persons of foreign origin*, EU/EEA†, 2021

11 334 TB cases of foreign origin*

33.8% of all TB cases (range 0.0–98.1%)



Notified in persons originating from other countries than the reporting country.
Iceland did not report data for 2021.

Source: ECDC/WHO (2023). Tuberculosis surveillance and monitoring in Europe 2023–2021 data

Zaključak

- izrazita raznolikost respiratornih patogena
- opterećenje zdravstvenog sustava i zajednice
- problem antimikrobne rezistencije
- realna globalna javnozdravstvena prijetnja
- kontinuirani nadzor nad respiratornim infekcijama (epidemiološki, laboratorijski)

HRVATSKO DRUŠTVO OBITELJSKIH DOKTORA

RESPIRATORNE INFEKCIJE U ORDINACIJI LIJEČNIKA OBITELJSKE MEDICINE

Dragan Soldo, dr.med.

Zagreb 15.05.2023.

REALNOST U PRAKSI?

Doktore, vani čeka pacijent za BAT…

Na drugoj liniji je kontrolor HZZO, javite se!

Koliki Vam je šećer? Koliko dugo? Zašto niste podigli terapiju?

Cezih opet ne radi…

Kad ćete cijepiti moju MAMU…

Doktore, zašto se ne javljate na telefon

Dobar dan, stigao je nalaz. Pozitivni ste! Kakvi su sad simptomi, s kim živite, koji je bio 1. dan bolesti…

Možete me **naručiti** na testiranje pročitala sam na internetu da to radi **izabrani liječnik**…

Ja sam SAMO nazvao/došao da mi isprintate nalaz

Trebate potvrdu za granicu

Doktore zovem vas samo da kažem da sam vam poslao mail …

PROBLEMI U ZBRINJAVANJE RESPIRATORNIH INFEKCIJA U PRAKSI

- Nemamo izvršitelja
- Postojeći timovi su preopterećeni
- Nedostupna dijagnostika na razini PZZ-a
- Za mlade liječnike je to preveliki zalogaj
- Progresivno raste administracija (mailovi, naručivanje, centralni repozitorij, administracija oko cijepljenja, nove potvrde – maske, rad od kuće, online nastava, prelazak granice, pelene, iznajmljivanje apartmana……)

PROBLEM IZVRŠITELJA?

- 300 timova nedostaje u sustavu
- 2179 nositelj tima (1094 specijalista, preko 100 TBN)
- 285 specijalizanata – imaju ordinacije
- 787 liječnika 60+ (183 65+)
- 300 – 400 mladih liječnika s Fakulteta u sustavu

KAKO NAS VIDE U ZAPADNOJ EUROPI

ŠTO JE DOBRA KLINIČKA PRAKSA U OBITELJSKOJ MEDICINI

- Anamneza i klinički pregled
- Vrijeme kao dijagnostičko i terapijsko pomagalo
- POCT
- Provođenje adekvatne simptomatske terapije
- Dostupnost brze dijagnostičke obrade za respiratorne infekcije koje treba medikamentozno liječiti (influenza, covid 19, pneumonija, angina)

ŠTO SU IZAZOVI KOJE JE DONIJELA PANDEMIJA

- Pregled nije moguć zbog korištenja OZO
- Eksplozija zloporabe azitromicina u liječenju ARI
- Poteškoće vezane uz expresnu dostupnost
- Eksplozija akutnih respiratornih infekcija nakon ukidanja mjera
- Dugovi prošlosti u zbrinjavanju kroničnih bolesnika

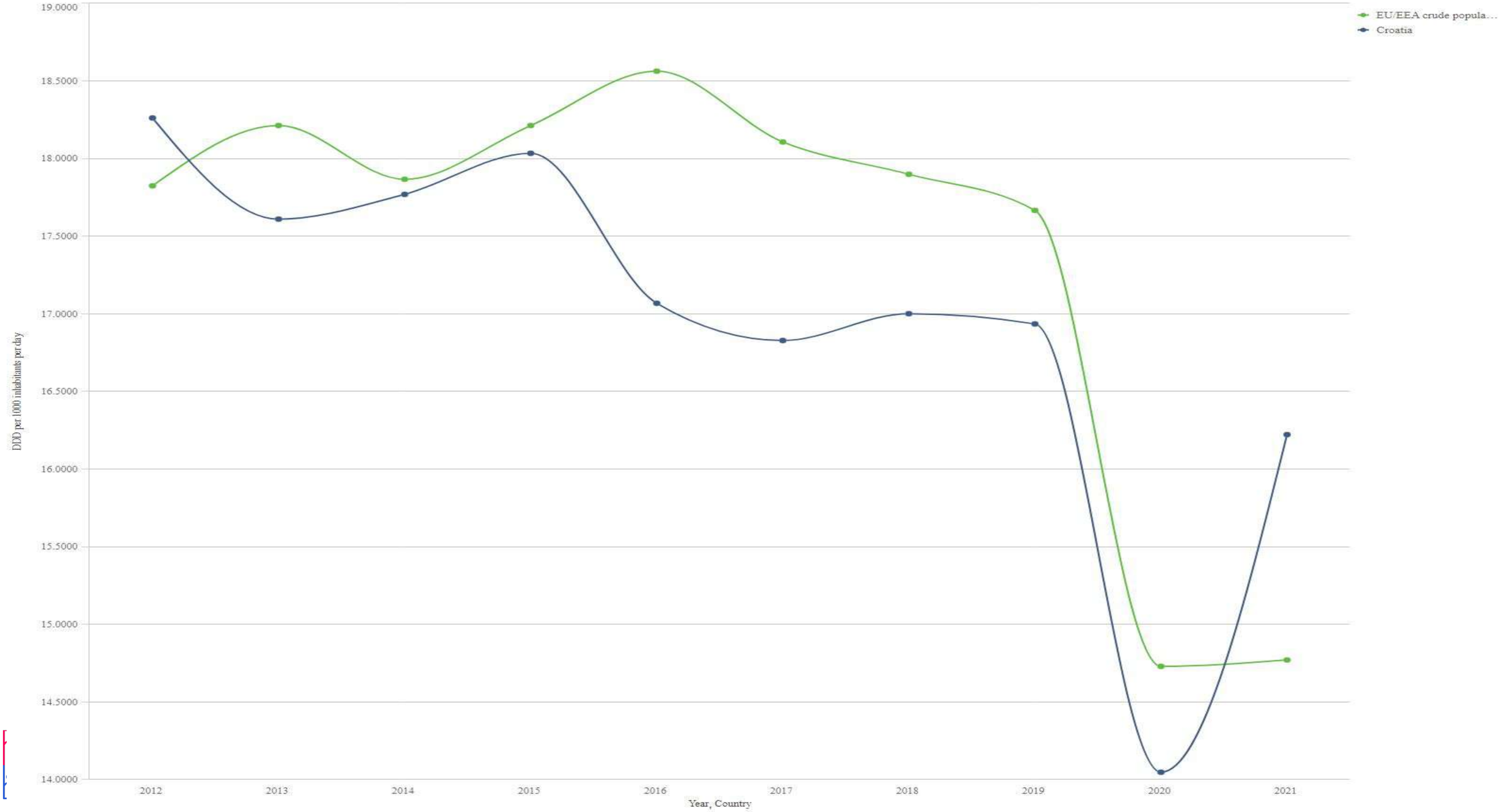
IMAMO LI SMJERNICE?

- Smjernice za liječenje grlobolje
- Smjernice za liječenje sinusitisa
- Smjernice za antibotičko liječenje najčešćih infektivnih bolesti u obiteljskoj medicini
- Smjernice za liječenje vanbolničkih pneumonija
- Smjernice za liječenje oboljelih od Covid-19 infekcije

KOLIKO IH PRATIMO?

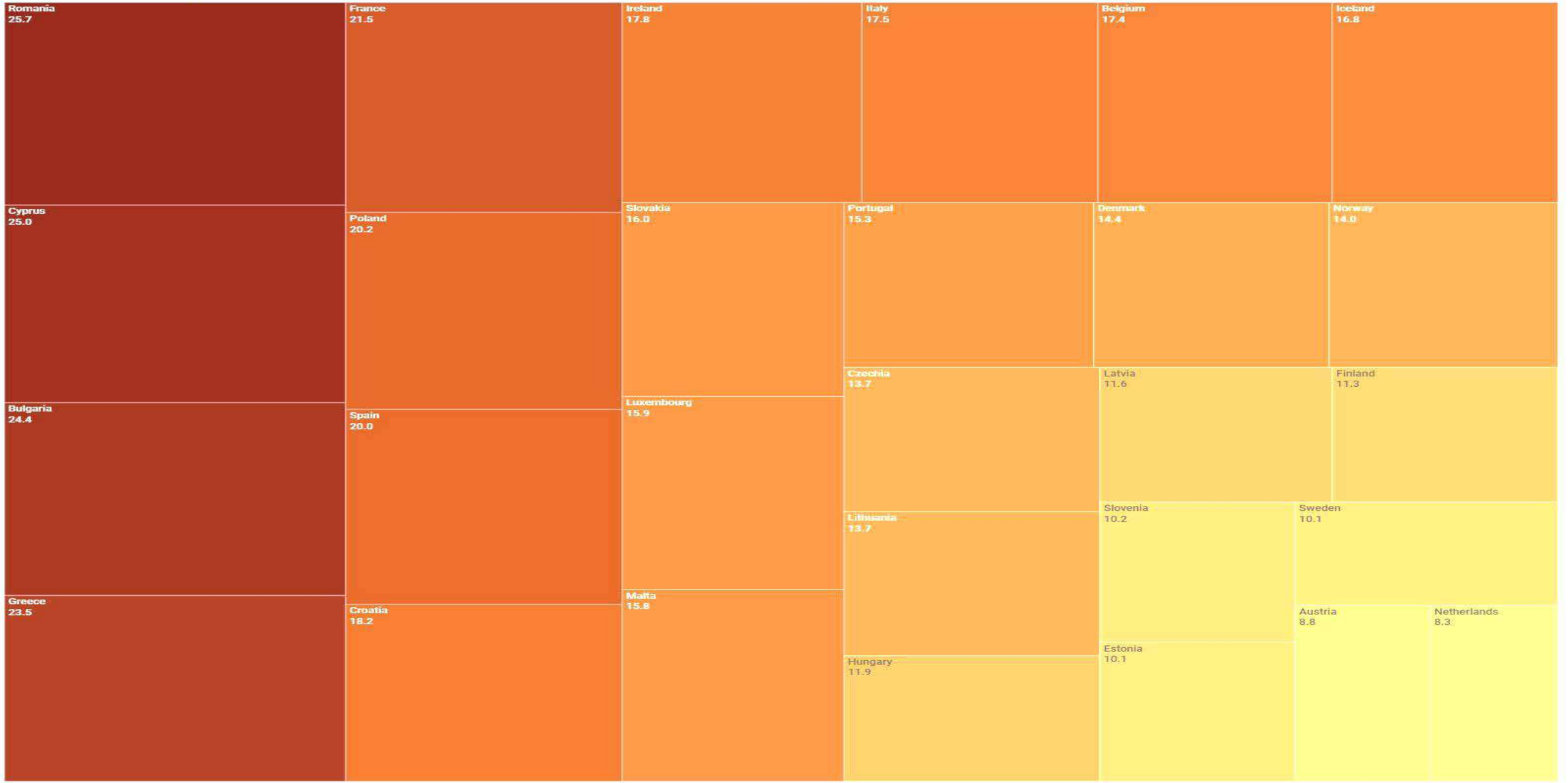
- Potrošnja antibiotika je jedan od indikatora kvalitete
- Nemamo stručnu kontrolu
- Nemamo algoritme za pomoć pri odlučivanju
- Ali……

Trend of the consumption of ATC group J01 in the community (primary care) sector (expressed as DDD per 1000 inhabitants per day)
Croatia, 2012-2021



Antibacterials for systemic use (ATC group J01), EU/EEA countries, 2021

DDD / 1000 inhabitants / day

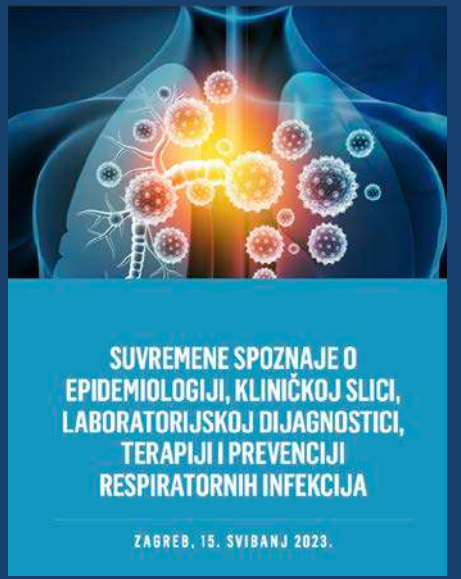


PORUKA ZA DOMA

- Vrijeme je ključno dijagnostičko i terapijsko pomagalo u zbrinjavanju akutnih respiratornih infekcija u OM
- Imamo jako puno prostora za napredak
- Nemamo vremena, ali srećom nam ni ne treba puno – uz problem izvršitelja
- Za bolje ishode liječenja trebamo dostupniju dijagnostiku na razini PZZ-a

Klinički aspekti i liječenje respiratornih infekcija u odraslih

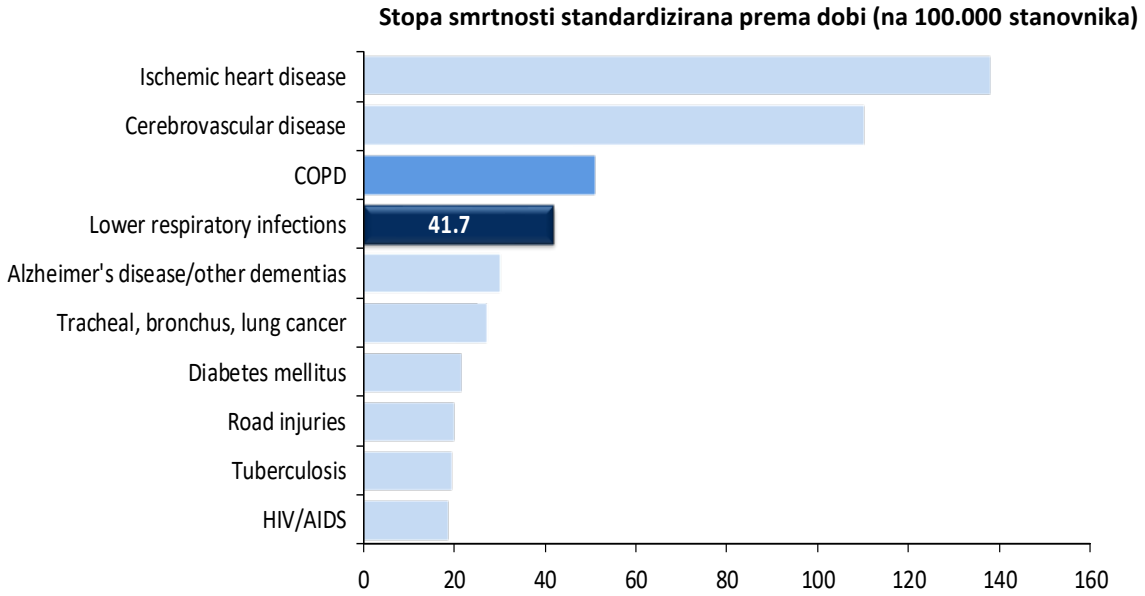
Izv. prof. dr. sc. Rok Čivljak
Medicinski fakultet Sveučilišta u Zagrebu
Klinika za infektivne bolesti "Dr. Fran Mihaljević"



Sadržaj

Infekcije donjeg dišnog sustava: među vodećim uzrocima smrti u svijetu

Deset vodećih uzroka smrti, 2013.



AIDS, acquired immunodeficiency syndrome; COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency virus.

1. Naghavi M, et al. Lancet. 2015;385:117–71.

Podjela akutnih respiratornih infekcija (ARI)

- **Infektivne bolesti gornjeg DS**
  - prehlada
  - febrilni respiratorni katar
  - faringitis
  - laringitis
  - otitis media
  - sinusitis
- **Infektivne bolesti donjeg DS**
  - bronhitis (AB, AE-KOPB)
  - bronhiolitis
  - pneumonija
- **Infektivne bolesti DS u širem smislu**
  - šarlah
  - hripavac
  - ospice
  - vodene kozice
  - gripa
  - COVID-19…

Najčešći uzročnici ARI

- **Virusi**
  - Influenca virusi
  - Parainfluenca virusi
  - Rinovirusi
  - Koronavirusi (SARS-CoV-2)
  - Adenovirusi
  - Respiratorni sincicijski virus (RSV)
  - Humani metapneumovirus (hMPV)
  - Enterovirusi
  - Reovirusi

- **Bakterije**
  - *Streptococcus pneumoniae*
  - *Haemophilus influenzae*
  - *Staphylococcus aureus*
  - *Moraxella catarrhalis*
  - *Streptococcus pyogenes*
  - *Klebsiella pneumoniae*
  - *Pseudomonas aeruginosa*
  - *Legionella pneumophila*
  - *Mycoplasma pneumoniae*
  - *Chlamydophila pneumoniae*
  - *Coxiella burnettii*

Received: 27 December 2018 | Revised: 25 January 2019 | Accepted: 18 February 2019
DOI: 10.1002/jmv.25437

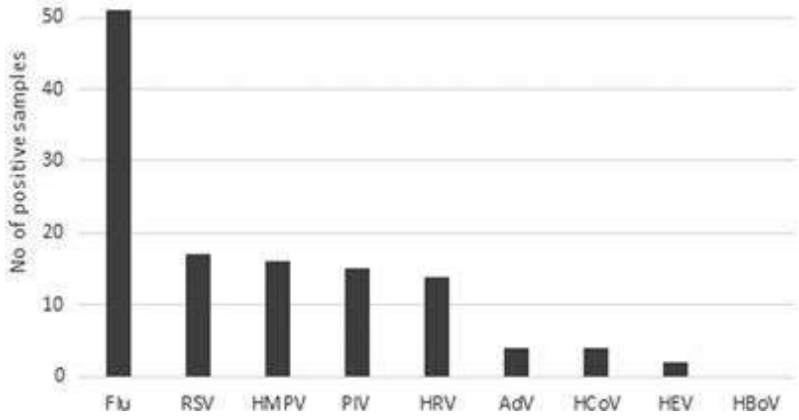
RESEARCH ARTICLE

WILEY JOURNAL OF MEDICAL VIROLOGY

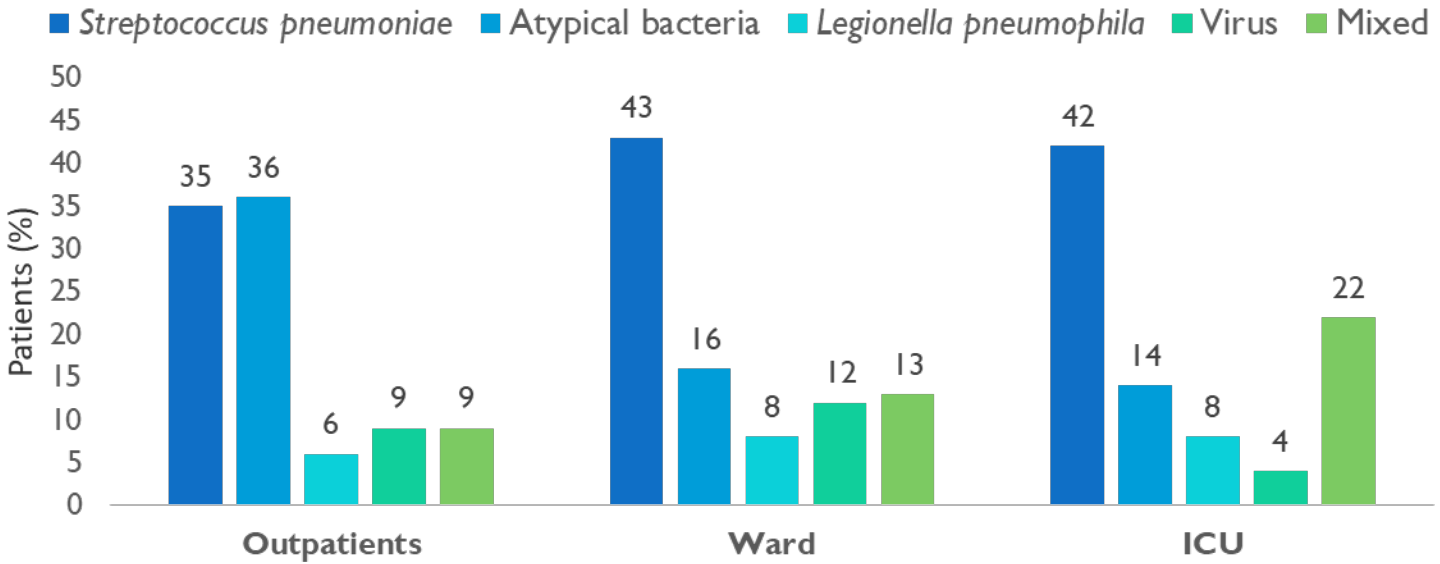
Viral pathogens associated with acute respiratory illness in hospitalized adults and elderly from Zagreb, Croatia, 2016 to 2018

Rok Civljak[1] | Tatjana Tot[2] | Ann R. Falsey[3] | Eva Huljev[1] | Jasmina Vranes[4,5] | Suncanica Ljubin-Sternak[4,5]

- **Influenca virus** **41.5%**
- RSV 13.8%
- hMPV 13.0%
- PIV 12.2%
- Rinovirusi 11.4%
- Adenovirusi 3.3%
- Koronavirusi 3.3%
- Enterovirusi 1.6%



Etiologija CAP ovisno o težini bolesti/mjestu liječenja



Mixed: Bacteria + **virus**: 29% out of 208 mixed infections

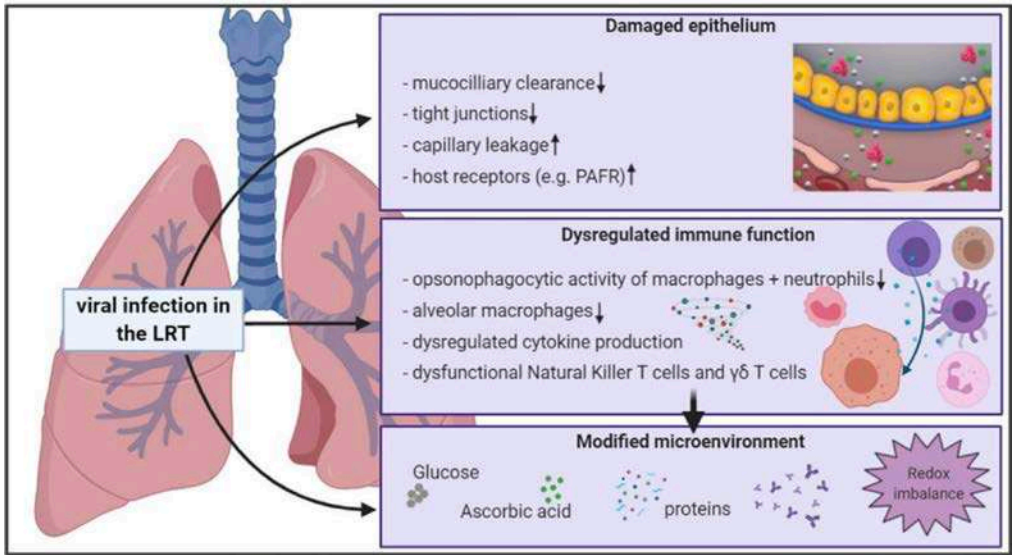
Atypical + **virus**: 6%

Atypical bacteria include the value for *Legionella pneumophila*

Cillóniz C, *et al. Thorax*. 2011;66(4):340–6.

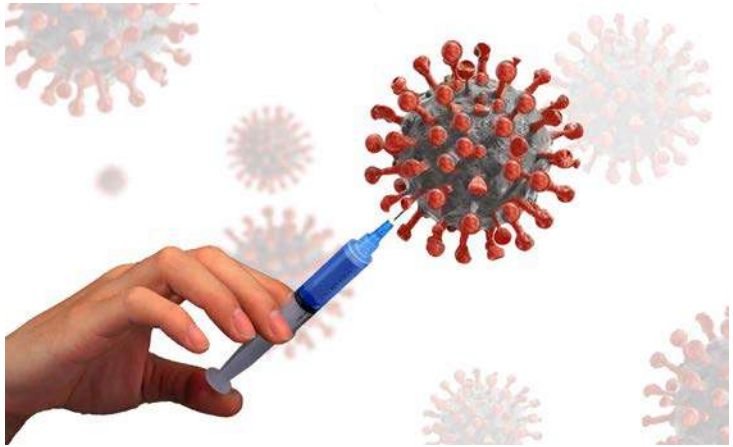
Promjene dišnog sustava zbog infekcije virusom gripe

Povećani rizik sekundarne bakterijske infekcije tijekom infekcije virusom gripe djelomično je posljedica učinka gripe na odgovor dišnog sustava domaćina, što uključuje **oštećenje zaštitne funkcije epitelne barijere**, **urođenog i stečenog imunosnog odgovora** te **promjenu mikrookoliša u dišnom sustavu**.



Partly adopted from Sender et al., 2020. *Created with BioRender.com*.
Sender V, et al. Front Cell Infect Microbiol. 2021.

Pozitivni učinci pandemije COVID-19



1 **Bolja procijepljenost protiv gripe**

- manji broj ljudi obolio od gripe

2 **Preventivne mjere protiv COVID-19**

- češće nošenje maski
- bolja higijena ruku
- distanciranje
- manja okupljanja

Stvarni učinak gripe je nedovoljno prepoznat

Kako se najčešće percipira gripa

Gripa je jednostavna respiratorna bolest koja prolazi unutar tjedan dana

Vrućica, glavobolja,
Bolovi u mišićima, Kašalj

Stvarni učinak gripe

Cijela santa leda predstavlja = stvarni medicinski, ekonomski i društveni teret gripe te njezinih komplikacija i posljedica

Srčani udar
Moždani udar
Pneumonija
Pogoršanje osnovne kronične bolesti
Dijabetes, astma, KOPB...
Smrt

1. https://www.cdc.gov/flu/about/burden/index.html accessed in October 2022,
2. https://www.ecdc.europa.eu/en/seasonal-influenza/facts/factsheet accessed in October 2022

Čimbenici rizika za nastanak komplikacija gripe

- djeca u dobi < 5 godina (osobito **< 2 godine**)
- odrasli u dobi ≥ **65 godina**
- **kronične bolesti i stanja**:
  - astma, KOPB, cistična fibroza
  - kardiovaskularne bolesti (osim hipertenzije)
  - kronične bubrežne, jetrene, neurološke bolesti
  - hematološke, endokrine i metaboličke bolesti
- **imunosupresija** (urođena, iatrogena, HIV)
- **trudnoća**
- djeca i adolescenti na **terapiji acetilsalicilnom kiselinom**
- **štićenici domova**

*Center for Disease Control and Prevention: People at high risk for flu complications

Retrospektivno istraživanje odraslih hospitaliziranih s gripom u Klinici za infektivne bolesti „Dr. Fran Mihaljević“ u Zagrebu (2017./2018. – 2021./2022.)

- ukupno hospitalizirano **993 bolesnika**
- muškaraca 531 (**53,5** %)
- medijan dobi **65 godina** (raspon 18–97)
- gripa je etiološki dokazana kod 680 (**68,5** %) bolesnika
- umrlo ukupno 33 (**3,3** %) hospitaliziranih bolesnika
  - onih s pneumonijom 30 (**4,4** %)
  - onih liječenih u JIL-u 23 (**22,6** %)
  - onih mehanički ventiliranih 19 (**31,7** %)

Perović Mihanović M i sur. CROCMID 2022.

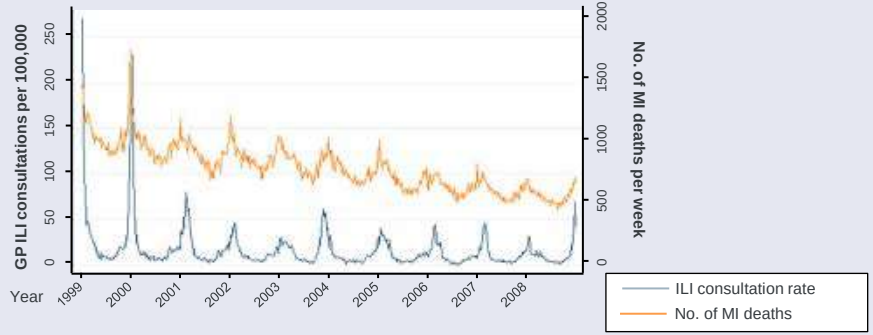
Usporedba epidemioloških obilježja u bolesnika sa i bez pneumonije

Obilježje	Svi bolesnici s gripom (N = 993)	Bolesnici bez pneumonije (N = 303)	Bolesnici s pneumonijom (N = 690)	OR (95% CI)	*p*
Ima komorbiditet	947 (95.4%)	279 (92.1%)	668 (**96.8%**)	2.61 (1.38-4.97)	**0.002**
• ≥ 2 komorbiditeta	811 (81.7%)	231 (76.2%)	580 (**84.1%**)	1.64 (1.16-2.32)	**0.004**
Trajanje bolesti do prijema	4 (0-20)	3 (0-15)	**4** (0-20)	/	**< 0.001**
Prijem u JIL	102 (10.3%)	12 (4.0%)	90 (**13.0%**)	3.63 (1.94-7.41)	**< 0.001**
C-reaktivni protein	83.2 (0.3-518.6)	**44.7** (0.3-322.2)	**108.5** (0.8-518.6)	/	**< 0.001**
Kardijalna dekompenzacija	122 (12.3%)	24 (7.9%)	98 (**14.3%**)	1.93 (1.20-3.23)	**0.005**
Akutna bubrežna insuf.	108 (10.9%)	19 (6.3%)	89 (**12.9%**)	2.25 (1.33-3.99)	**0.001**
Bolnička infekcija	97 (9.8%)	17 (5.6%)	80 (**11.6%**)	1.94 (1.12-3.56)	**0.013**
Oseltamivir + antibiotik	661 (66.6%)	153 (**50.5%**)	508 (**73.8%**)	2.73 (2.04-3.66)	**< 0.001**
Primio antibiotik	785 (79.1%)	182 (**60.7%**)	603 (**91.4%**)	4.56 (3.27-6.29)	**< 0.001**
Smrtni ishod	33 (3.3%)	3 (**1.0%**)	30 (**4.4%**)	4.54 (1.40-23.43)	**0.006**

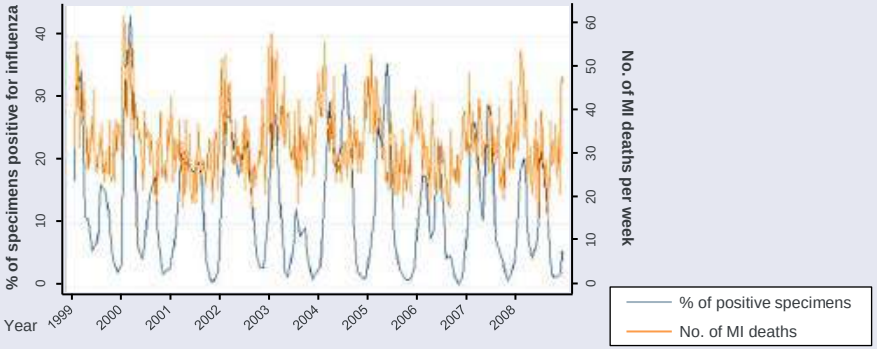
Perović Mihanović M i sur. CROCMID 2022.

Gripa kao okidač za infarkt miokarda i kardiovaskularnu smrt

England and Wales



Hong Kong



- Studije ukazuju na povećanu smrtnost od kardiovaskularnih bolesti i veću incidenciju infarkta miokarda u vrijeme cirkulacije gripe[1]
  - Sveukupno do **5.6%** smrti od infarkta miokarda u Hong Kongu i **3.4%** u Engleskoj i Walesu se povezuje s gripom[4]*
- Opservacijske i intervencijske studije također ukazuju na ovu povezanost[1,2]
  - Gripa je povezana s **2x** većim rizikom infarkta miokarda[2,3]
- Dokazi možda još uvijek nisu dovoljni za potvrdu povezanosti, ali dosadašnji podaci su uvjerljivi[5]

* Nisu laboratorijski potvrđeni

Tjedna cirkulacija gripe i broj smrti povezanih s infarktom miokarda (MI). ILI: influenza-like illness

1.Warren-Gash, Lancet ID, 2009. 2.Kwok, Int J Clin Pract, 2015. 3.Barnes, Heart, 2015. 4.Warren-Gash, JID, 2012. 5.Finelli, JID, 2011

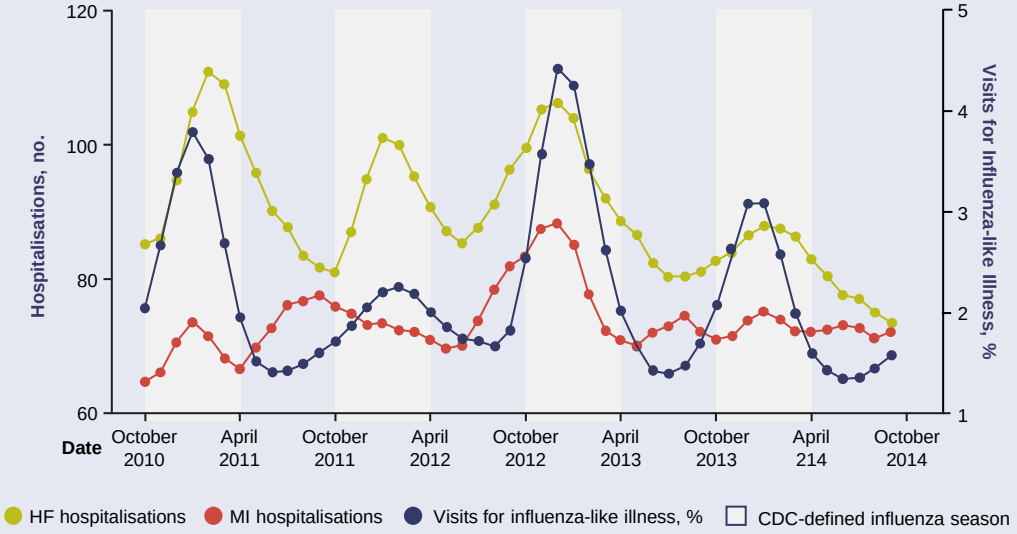
Povezanost između aktivnosti gripe (ILI) i hospitalizacija zbog zatajenja srca u SAD-u

Aktivnost gripe (posjete liječniku zbog ILI) u 4 zajednice u SAD* je uspoređena sa stopama hospitalizacije zbog zatajenja srca i infarkta miokarda u uzorku >451,000 osoba (listopad 2010. do rujan 2014.)

- U prosjeku, **5%** povećanje mjesečne aktivnosti gripe (ILI) je bilo povezano s **24%** povećanjem stope hospitalizacija zbog zatajenja srca unutar istog mjeseca
- Infarkt miokarda je bio pozitivno, ali ne statistički značajno povezan s aktivnosti gripe (ILI)

"Aktivnost gripe bila je vremenski povezana s povećanjem hospitalizacija zbog srčanog zatajenja tijekom četiri sezone gripe. Ti podaci upućuju na to da gripa može doprinijeti riziku hospitalizacije zbog zatajenja srca u općoj populaciji."

Prosječna aktivnost gripe (ILI) i broj hospitalizacija između listopada 2010. i rujna 2014.



*Minnesota, Maryland, North Carolina, Mississippi

CVD, cardiovascular disease; HF, heart failure; ILI, influenza-like illness; MI myocardial infarction

1. Kytömaa C, *et al. JAMA Cardiol*. 2019;4(4):363–9

Akutni infarkt miokarda i moždani udar povezani s laboratorijski potvrđenim respiratornim infekcijama u Škotskoj (2004.–2014.)

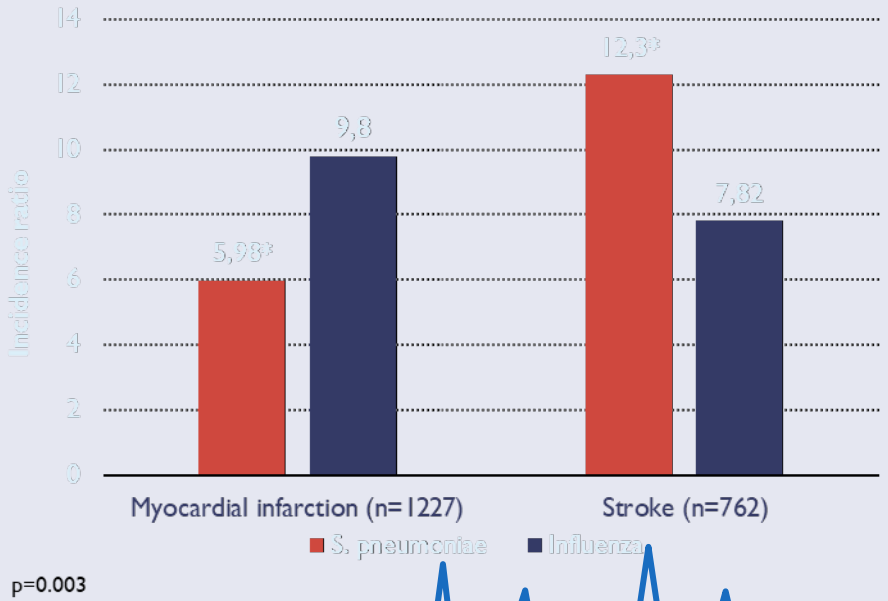
- Nacionalni podatci nadzora infekcija povezani sa Škotskim podacima o smrtnosti
- 1989 odraslih 40+ s laboratorijski potvrđenom respiratornom infekcijom (median 66 godina starosti)

10x ↑ rizik prvog MI[3]

8x ↑ rizik prvog moždanog udara

> **„Zabilježeni utjecaj virusa gripe kao kardiovaskularnog okidača ističe potrebu za odgovarajućom prevencijom gripe."**

Povećane stope rizika incidencije MI i moždanog udara, mjereno 1–3 dana nakon gripe, 9,8 (95% CI 2.47–14.4) i 7.82 (95% CI 2.37–40.5)



MI, myocardial infarction; *S. pneumoniae*, Streptococcus pneumoniae

1. Warren-Gash C, et al. Eur Respir J. 2018;51(3):1701794

Osobe s dijabetesom imaju ozbiljnije ishode nakon infekcije virusom influence

Infekcija virusom influence kod osoba s dijabetesom povećava:

3-6x rizik **hospitalizacije**[1,4*]

4x rizik **prijema u JIL** poslije hospitalizacije[*]

4x rizik **smrti od pneumonije**[2*]

6x rizik **smrti**[4*]

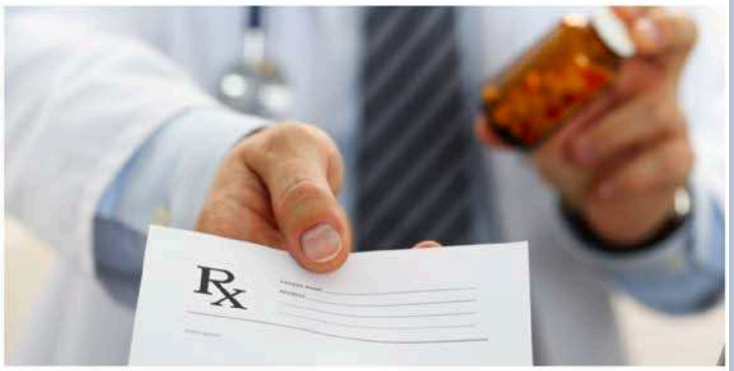
***u odnosu na osobe bez dijabetesa**

.**1.** Allard R, *et al. Diabetes Care.* 2010; 33:1491–3. ***2*** Valdez R, *et al. Am J Public Health.* 1999; 89: 1715–21. **3.** Bouter KP, Diabetes Res Clin Pract 1991;12:61-8. **4.** https://www.gov.uk/government/publications/influenza-the-green-book-chapter-19 (p4)accessed date October 2022

What You Should Know About Flu Antiviral Drugs

Español | Other Languages | Print

On December 14, 2022, CDC released a Health Alert Network (HAN) to pro
treatment of flu.



https://www.cdc.gov/flu/treatment/whatyoushould.htm

Following is a list of all the health and age factors that are known to increase a person's risk of getting serious complications from flu:

- Asthma
- Neurologic and neurodevelopment conditions
- Blood disorders (such as sickle cell disease)
- Chronic lung disease (such as chronic obstructive pulmonary disease [COPD] and cystic fibrosis)
- Endocrine disorders (such as diabetes mellitus)
- Heart disease (such as congenital heart disease, congestive heart failure and coronary artery disease)
- Kidney disorders
- Liver disorders
- Metabolic disorders (such as inherited metabolic disorders and mitochondrial disorders)
- People who are obese with a body mass index [BMI] of 40 or higher
- People younger than 19 years of age on long-term aspirin- or salicylate-containing medications.
- People with a weakened immune system due to disease (such as people with HIV or AIDS, or some cancers such as leukemia) or medications (such as those receiving chemotherapy or radiation treatment for cancer, or persons with chronic conditions requiring chronic corticosteroids or other drugs that suppress the immune system)

Other people at higher risk from flu:

- Adults 65 years and older
- Children younger than 2 years old[1]
- Pregnant women and women up to 2 weeks after the end of pregnancy
- People from certain racial and ethnic minority groups, including non-Hispanic Black, Hispanic or Latino, and American Indian or Alaska Native persons
- People who live in nursing homes and other long-term care facilities

[1] Although all children younger than 5 years old are considered at higher risk for serious flu complications, the highest risk is for those younger than 2 years old, with the highest hospitalization and death rates among infants younger than 6 months old.

Antivirusno liječenje gripe

Lijek	Indikacije	Preporučen za	Doza (odrasli)	Trajanje
Oseltamivir (oralni)	Liječenje	Sve dobne skupine	2x75 mg	**5 dana**
	Profilaksa	≥ 3 mjeseca	1x75 mg	**7 dana**
Zanamivir (inhalacijski)	Liječenje	≥ 7 godina	2x10 mg (2 inhalacije)	**5 dana**
	Profilaksa	≥ 5 godina	1x10 mg	**7 dana**
Peramivir (intravenski)	Liječenje	≥ 2 godine	1x600 mg	**1 dan**
	Profilaksa	Ne preporuča se		
Baloxavir (oralni)	Liječenje	≥ 12 godina	1x40-80 mg	**1 dan**
	Profilaksa	Ne preporuča se		

CDC. Approved by FDA, 2022/2023.

Therapeutic Management of Nonhospitalized Adults With COVID-19

Last Updated: April 20, 2023

Patient Disposition	Panel's Recommendations
All Patients	• Symptom management should be initiated for all patients (AIII). • The Panel **recommends against** the use of **dexamethasone**[a] or other systemic corticosteroids in the absence of another indication (AIIb).
Patients Who Are at High Risk of Progressing to Severe COVID-19[b]	*Preferred therapies. Listed in order of preference:* • **Ritonavir-boosted nirmatrelvir (Paxlovid)**[c,d] (AIIa) • **Remdesivir**[d,e] (BIIa) *Alternative therapy. For use when the preferred therapies are not available, feasible to use, or clinically appropriate:* • **Molnupiravir**[d,f,g] (CIIa)

Each recommendation in the Guidelines receives a rating for the strength of the recommendation (A, B, or C) and a rating for the evidence that supports it (I, IIa, IIb, or III). See Guidelines Development for more information.

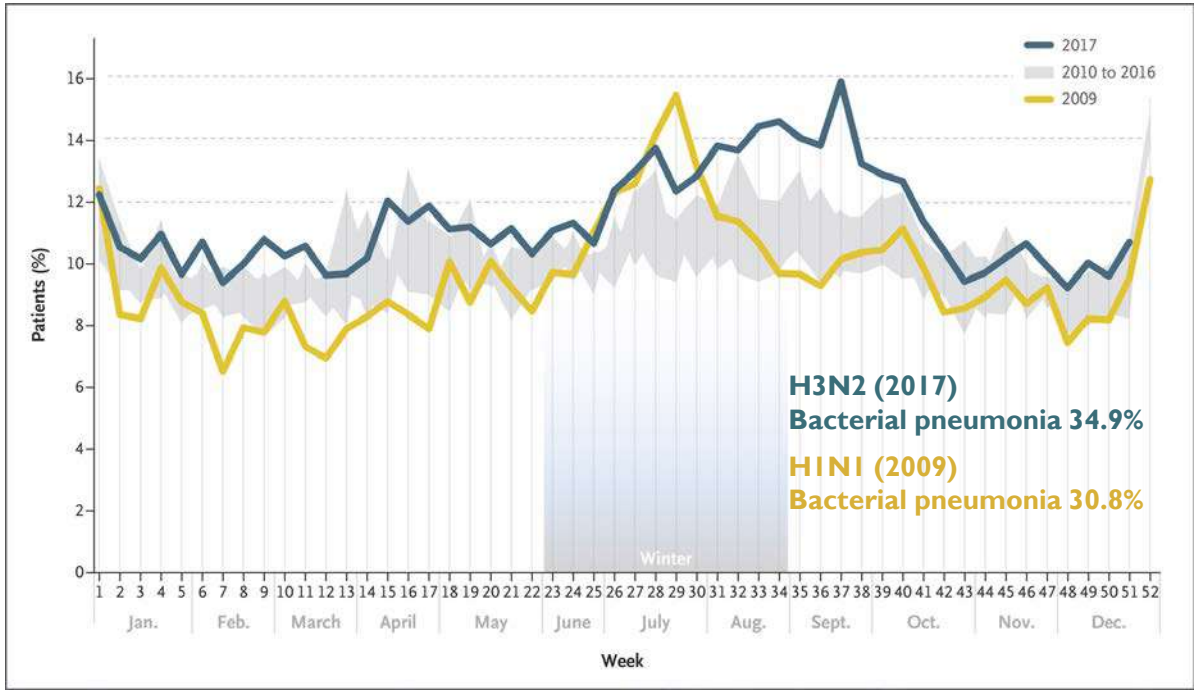
[a] There is currently a lack of safety and efficacy data on the use of dexamethasone in outpatients with COVID-19. Using systemic glucocorticoids in outpatients with COVID-19 may cause harm.

[b] For a list of risk factors, see the CDC webpage Underlying Medical Conditions Associated With Higher Risk for Severe COVID-19. When deciding whether to prescribe antiviral treatment to a patient who has been vaccinated, clinicians should be aware of the conditions associated with a high risk of disease progression. These conditions include older age, a prolonged amount of time since the most recent vaccine dose (e.g., >6 months), and a decreased likelihood of an adequate immune response to vaccination due to a moderate to severe immunocompromising condition or the receipt of immunosuppressive medications. The number and severity of risk factors also affects the level of risk.

Therapeutic Management of Adults Hospitalized for COVID-19

Disease Severity	Recommendations for Antiviral or Immunomodulator Therapy		Recommendations for Anticoagulant Therapy
	Clinical Scenario	Recommendation	
Hospitalized for Reasons Other Than COVID-19	Patients with mild to moderate COVID-19 who are at high risk of progressing to severe COVID-19[a,b]	See Therapeutic Management of Nonhospitalized Adults With COVID-19.	For patients without an indication for therapeutic anticoagulation: • **Prophylactic dose of heparin**, unless contraindicated (**AI**); (**BIII**) for pregnant patients
Hospitalized but Does Not Require Oxygen Supplementation	All patients	The Panel **recommends against** the use of **dexamethasone** (**AIIa**) or other systemic corticosteroids (**AIII**) for the treatment of COVID-19.[c]	
	Patients who are at high risk of progressing to severe COVID-19[a,b]	**Remdesivir**[d] (**BIII**)	
Hospitalized and Requires Conventional Oxygen[e]	Patients who require minimal conventional oxygen	**Remdesivir**[d,f] (**BIIa**)	For nonpregnant patients with D-dimer levels above the ULN who do not have an increased bleeding risk: • **Therapeutic dose of heparin**[h] (**CIIa**) For other patients: • **Prophylactic dose of heparin**, unless contraindicated (**AI**); (**BIII**) for pregnant patients
	Most patients	Use **dexamethasone plus remdesivir**[f] (**BIIa**). If remdesivir cannot be obtained, use **dexamethasone** (**BI**).	
	Patients who are receiving dexamethasone and who have rapidly increasing oxygen needs and systemic inflammation	Add **PO baricitinib**[g] (**BIIa**) or **IV tocilizumab**[g] (**BIIa**) to 1 of the options above.	
Hospitalized and Requires HFNC Oxygen or NIV	All patients	**Dexamethasone** should be administered to all patients (**AI**). If the patient has not already received a second immunomodulator, promptly add 1 of the following (listed in order of preference): • **PO baricitinib**[g,i] (**AI**) • **IV tocilizumab**[g,i] (**BIIa**) Add **remdesivir** to 1 of the options above in certain patients (**CIIa**).[j]	For patients without an indication for therapeutic anticoagulation: • **Prophylactic dose of heparin**, unless contraindicated (**AI**); (**BIII**) for pregnant patients For patients who are started on a therapeutic dose of heparin in a non-ICU setting and then transferred to the ICU, the Panel recommends switching to a **prophylactic dose of heparin**, unless there is another indication for therapeutic anticoagulation (**BIII**).
Hospitalized and Requires MV or ECMO	All patients	**Dexamethasone** should be administered to all patients (**AI**). If the patient has not already received a second immunomodulator, promptly add 1 of the following (listed in alphabetical order): • **PO baricitinib**[g,i] (**AI**) • **IV tocilizumab**[g,i] (**BIIa**)	

Udio bolesnika zaprimljenih u JIL s bakterijskom pneumonijom, virusnim pneumonitisom i sepsom
(Australija i Novi Zeland, 2009. – 2017.)



Burrell A et al. NEJM. 2018.

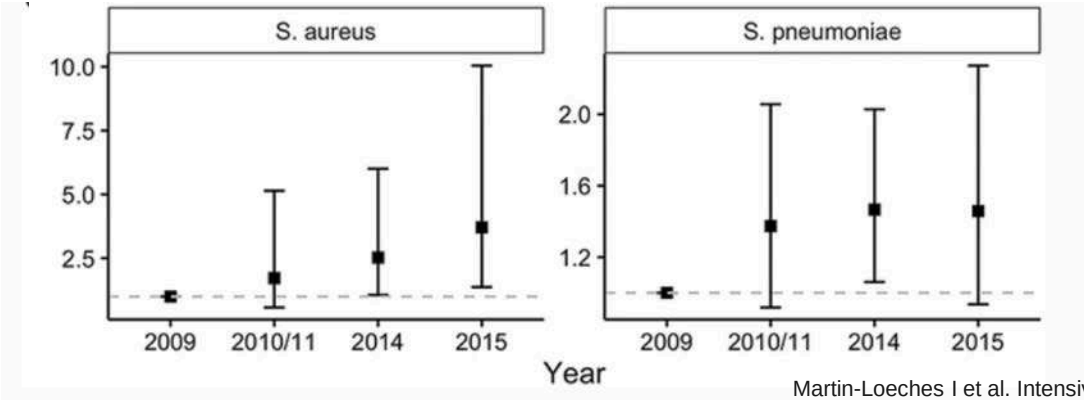
ORIGINAL

Increased incidence of co-infection in critically ill patients with influenza

Ignacio Martin-Loeches[1,2*], Marcus J Schultz[3], Jean-Louis Vincent[4], Francisco Alvarez-Lerma[5], Lieuwe D. Bos[3], Jordi Solé-Violán[6], Antoni Torres[7] and Alejandro Rodriguez[8,9]

Porast incidencije koinfekcija u bolesnika s gripom zaprimljenih u JIL:

Od 2901 bolesnika njih 482 (16,6%) je imalo koinfekciju



Martin-Loeches I et al. Intensive Care Med. 2017.

Čimbenici rizika za *Staph. aureus*

* Intravenski ovisnici[1]
* Kronična renalna insuficijencija, osobito dijaliza[1]
* Inzulin-ovisna šećerna bolest[1]
* Klinička slika koja sugerira prisutnost PVL*-producirajućeg *Staph. aureus* (npr. leukopenija, nekroza, kavitacija, apsces kože)[2]
* **Koinfekcija virusom influence[3]**

[1]https://www.cdc.gov/hai/organisms/staph.html
[2]Nathwani D, et al. J Antimicrob Chemother. 2008.
[3]Jia L, et al. Front Immunol. 2019.

PVL* (engl. panton-valentine leukocidin) - panton-valentine leukocidin čimbenik virulencije

Koinfekcija utječe na prezentaciju i prognozu teškog CAP

Varijabla	Virusna (n=53)	Bakterijska koinfekcija (n=45)
Dob	64	63
Spol, muški %	71.7	73.3
PSI*score IV-V %	62.3	80
ARDS** %	24.5	48.9
MV*** %	41.5	80
Šok %	5.7	24.4
Komplikacije %	28.3	68.9
Smrtni ishod (u bolnici) %	11.3	28.9

PSI* index težine pneumonije, ARDS** akutni respiratorni distresni sindrom, MV*** mehanička ventilacija

Voiriot G et al. Crit Care. 2016.

Bakterijemijska pneumonija

Multivarijatna analiza pokazala da smrtnost bolesnika značajno povećavaju…

- Hipotermija
- Respiracijska insuficijencija
- Poremećaj svijesti
- Trahealna intubacija
- *S. aureus*
- Septički šok
- Neadekvatna empirijska terapija
- Dob

Characteristics of 319 episodes of bacteraemia pneumonia in 295 patients

Characteristic	All (n=319)	CABP (n=211)	NBP (n=108)	P value
Age in years	68 (0.003–100)	70 (0.003–100)	66 (0.003–98)	0.1
Male:female ratio	1.5	1.6	1.5	NS
Nursing home residents (%)	18	22	10	0.01
Fever (°C)[a]	38.7 (35.1–42)	38.7 (35.1–40.5)	38.8 (36–42)	NS
Systolic BP (mmHg)	120 (60–200)	115 (60–200)	130 (60–200)	0.005
Leucocyte count	13.2 (0.1–69.8)	13.7 (0.1–59.6)	12.6 (0.2–69.8)	NS
BUN (mg/dl)	23.5 (1–140)	23 (1–125)	24 (4–140)	NS
Creatinine (mg/dl)	1.1 (0.1–10.2)	1.1 (0.1–10.2)	1.1 (0.2–10)	NS
Albumin (g/dl)	3.1 (1.8–6.3)	3.3 (1.8–6.3)	2.9 (1.8–4.1)	0.0002
Functional capacity (%)[b]				
0	9.3	12.8	2.5	
1	8.9	10.3	6.2	
				0.03
2	21.5	21.2	22.2	
3	60.3	55.8	69.1	
Complications				
ARF (%)	8.7	11.1	4.3	0.03
Respiratory failure (%)	24.1	24.2	24.0	NS
DIC (%)	1.1	1.7	0.0	NS
Appropriate antibiotic treatment (%)	65.8	77.3	43.5	0.0001
Hospital stay (days)	7 (1–111)	6 (1–56)	14 (1–111)	0.0001
Mortality (%)	33.9	31	40	0.1

ARF, acute renal failure; BP, blood pressure; BUN, blood urea-nitrogen; CABP, community-acquired bacteraemic pneumonia; DIC, disseminated intravascular coagulopathy; NBP, nosocomial bacteraemic pneumonia; NS, not significant.

Bishara J, et al. Eur J Clin Microbiol Infect Dis. 2000;19(12):926–31.

Contents lists available at ScienceDirect
International Journal of Infectious Diseases
journal homepage: www.elsevier.com/locate/ijid

Bacterial co-infection at hospital admission in patients with COVID-19

Estela Moreno-García [1,#], Pedro Puerta-Alcalde [1,#,*], Laura Letona [1,#], Fernanda Meira [1], Gerard Dueñas [1], Mariana Chumbita [1], Nicole Garcia-Pouton [1], Patricia Monzó [1], Carlos Lopera [1], Laia Serra [1], Celia Cardozo [1], Marta Hernandez-Meneses [1], Verónica Rico [1], Marta Bodro [1], Laura Morata [1], Mariana Fernandez-Pittol [2], Ignacio Grafia [1], Pedro Castro [3], Josep Mensa [1], José Antonio Martínez [1], Gemma Sanjuan [1], Mª Angeles Marcos [2], Alex Soriano [1], Carolina Garcia-Vidal [1,*], COVID-19-researcher group

Bakterijska koinfekcija pri prijemu u bolesnika s COVID-19 zabilježena je u 9.1% slučajeva

Epidemiology of bacterial co-infections at COVID-19 admission.

	n=102 (%)
Respiratory co-infection diagnosed by pneumococcal urinary antigen	79
Respiratory co-infection diagnosed by sputum culture	15[a]
S. pneumoniae	4[b]
P. aeruginosa	2
S. aureus	5
K. pneumoniae	1
H. influenzae	6

Bacteremia	8
E. coli	3
S. aureus	3
P. aeruginosa	1
H. influenzae	1

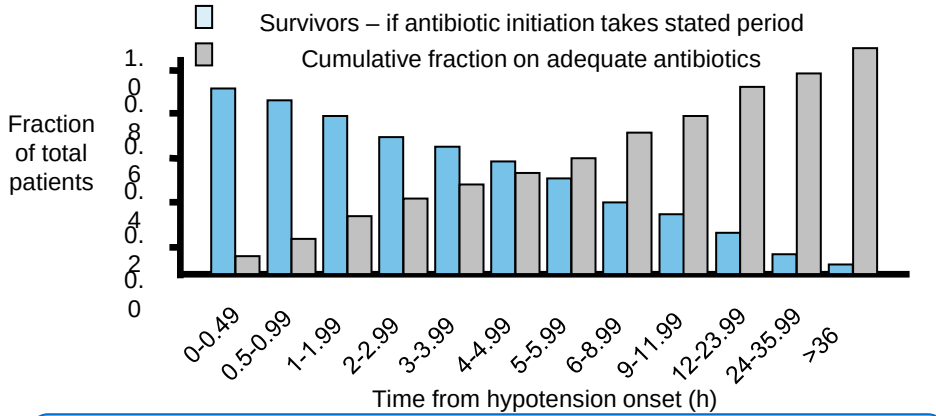
Neovisni čimbenici rizika povezani s bakterijskom koinfekcijom:

- **Sat O_2 < 94%**
  (OR 2.47, CI 1.57–3.86)
- **Ferritin < 338 ng/mL**
  (OR 2.63, CI 1.69–4.07)
- **PCT > 0.2 ng/mL**
  (OR 1.74, CI 1.11–2.72)

Moreno-García E, et al. Int J Infect Dis. 2022.

Odgovarajuća terapija u septičnih bolesnika je važna

Smrtnost se povećava sa svakim satom odgode terapije



Odgovarajuća antimikrobna terapija mora se započeti unutar 1 sata od dokumentirane hipotenzije

Kumar A, et al. Crit Care Med 2006;34(6):1589–96.

Empirijsko ambulantno liječenje CAP*

Bez čimbenika rizika i komorbiditeta	**I**	**II**	**III**
	Amoksicilin	Doksiciklin	Makrolid

Uz komorbiditete	**I**	**+ II**	**III**
	Koamoksiklav ili cefalosporin	+ Makrolid ili doksiciklin	Respiratorni kinolon

Čimbenici rizika za MRSA/*Pseudomonas*

- prethodni izolat MRSA/*Pseudomonas* iz RS
- nedavna hospitalizacija
- parenteralno antimikrobno liječenje (<90 dana)

Komorbiditeti

- kronične bolesti srca, pluća, jetre, bubrega
- dijabetes
- alkoholizam
- neoplazme
- asplenija

***CAP – *Community-acquired pneumonia* (pneumonija iz opće populacije)**

ATS/IDSA guidelines 2019

Empirijsko bolničko liječenje CAP*

	I	II
Standardno liječenje	• Ampicilin-sulbaktam 4x1,5-3g • Cefotaksim 3x1-2g • Ceftriakson 1x1-2g • Ceftarolin 2x600mg	• Azitromicin 1x500mg • Klaritromicin 2x500mg • Levofloksacin 1x750mg • Moksifloksacin 1x400mg
Prethodni izolat MRSA/ Čimbenik rizika za MRSA	• Vankomicin 15mg/kg/12 h	• Linezolid 2x600mg • Ceftarolin 2x600mg
Prethodni izolat *Pseudomonas* / Čimbenik rizika za *Pseudomonas*	• Piperacillin-tazobactam 4x4,5g • Cefepim 3x2 g • Ceftazidim 3x2 g	• Imipenem 4x500mg • Meropenem 3x1g • Aztreonam 3x2g

***CAP – *Community-acquired pneumonia* (pneumonija iz opće populacije)**

ATS/IDSA guidelines 2019

Internal and Emergency Medicine
October 2016, Volume 11, Issue 7, pp 929–940 | Cite as

Adherence to guidelines for hospitalized community-acquired pneumonia over time and its impact on health outcomes and mortality

Authors Authors and affiliations

Elisa Costantini, Elias Allara, Filippo Patrucco, Fabrizio Faggiano, Fozia Hamid, Piero Emilio Balbo

Abstract

We aimed to evaluate the compliance with guidelines over time, and to assess its impact on all-cause mortality and clinical outcomes. We retrospectively compared two cohorts of patients admitted to the hospital, throughout 2005, just after the implementation of a local clinical pathway based on CAP international guidelines, and 7 years later over 2012. We included all patients with a diagnosis of pneumonia and/or related complications. 564 patients were included.

The Pneumonia Severity Index calculation was better documented in 2012 (25.23 %) compared to 2005 (17.70 %; p = 0.032), but **compliance with guideline empirical antibiotic therapy was lower in 2012** (56.70 %) than in 2005 (68.75 %; p = 0.004). Performance of guideline recommended **urinary antigen tests** was higher in 2012, and **associated with 57.3 % lower odds of in-hospital mortality** (95 % CI 15.0–78.5 %) **and with 65.9 % lower odds of 30-day mortality** (95 % CI 31.5–83.0 %). **Compliance with empirical antibiotic therapy was associated with 2.9 days lower mean length of hospital stay** (95 % CI −4.2 to −1.6 days) and **with 2.0 days lower mean duration of antibiotic therapy** (95 % CI −3.3 to −0.7 days).

Compliance with guidelines changed over time, with some effects on mortality and with an apparent reduction in the length of hospital stay and the duration of antibiotic therapy. Specific clinical training and hospital control policies could achieve greater compliance with guidelines, and thus reduce a burden on hospital services.

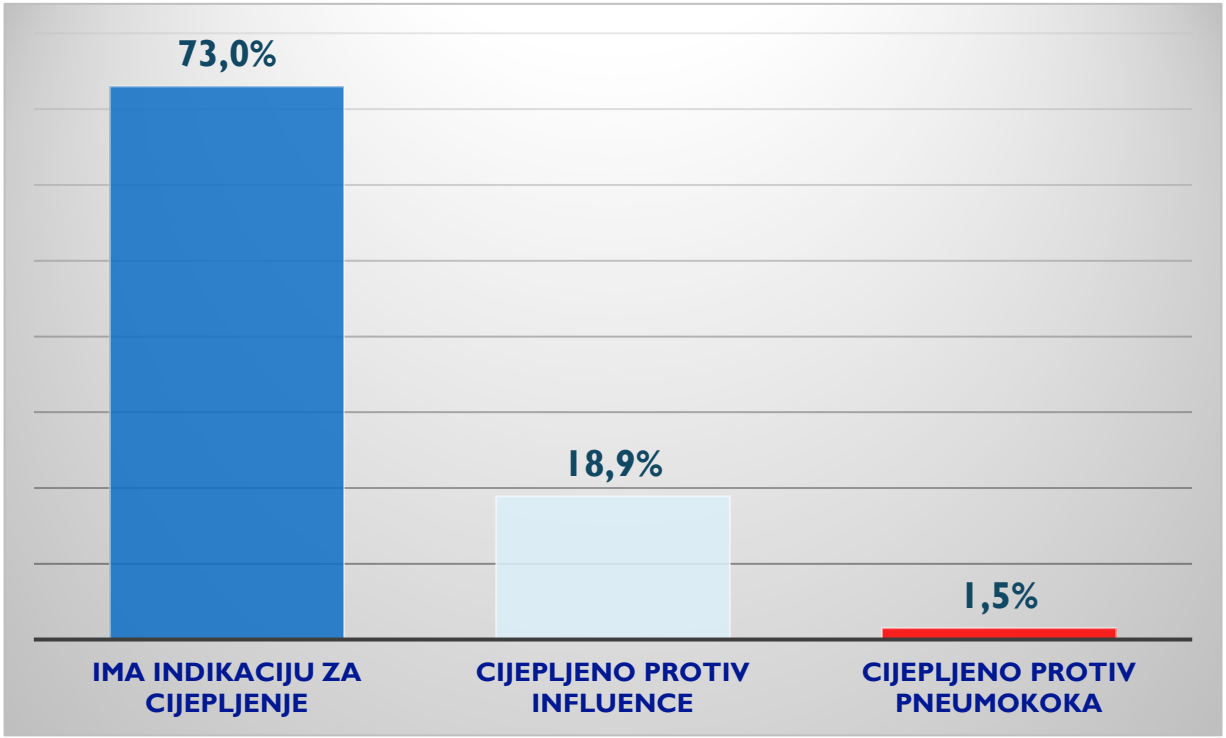
Guideline-concordant antibiotic use and survival among patients with community-acquired pneumonia admitted to the intensive care unit

Abstract | References

RESULTS:
The median age was 71 years (interquartile range, 60-79 years). Sixty-two of 129 patients (48%) were male. Comorbidities included liver dysfunction (5%), heart failure (48%), renal dysfunction (30%), cerebrovascular disease (16%), and cancer (11%). The median PSI score was 119 (98-142), and overall mortality was 19%. Fifty-three patients (41%) received guideline-endorsed therapies. **Guideline-discordant therapy was associated with an increase in inpatient mortality** (25% vs 11%; odds ratio = 2.99 [95% CI, 1.08-9.54]). Receipt of guideline-concordant antibiotics was not associated with reductions in time to clinical stability, time to oral antibiotics, or length of hospital stay when patients who died were excluded from the analysis.
CONCLUSION:
Guideline-concordant empiric antibiotic therapy was associated with improved survival among these patients with CAP who were admitted to 5 ICUs.

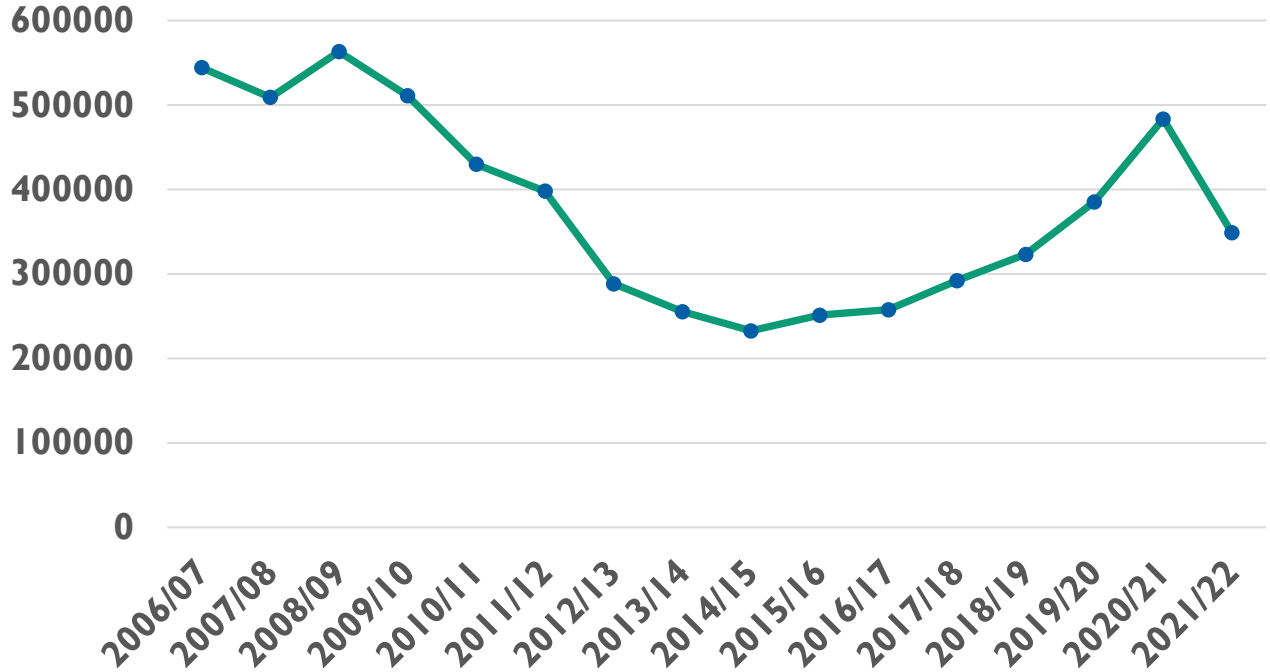
Frei CR, et al. Clin Ther. 2010;32:293-9.

Procijepljenost protiv gripe i pneumokoka u bolesnika hospitaliziranih s gripom (BFM 2017./2018. – 2021./2022.)

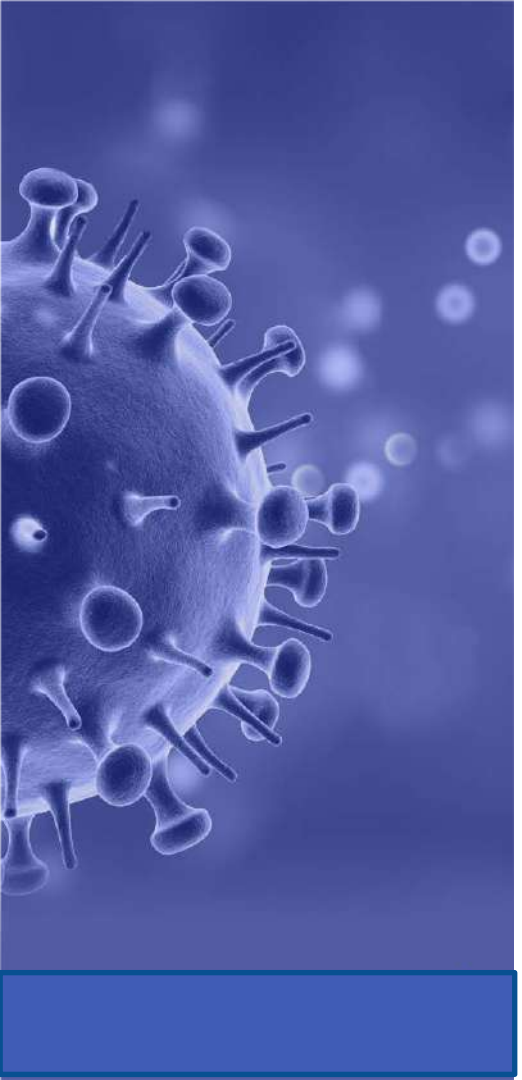


Perović Mihanović M i sur. CROCMID 2022.

Potrošnja cjepiva protiv gripe u Hrvatskoj (2006.–2022.)



HZJZ: https://www.hzjz.hr/cat/periodicne-publikacije/



Cijepljenje protiv gripe je povezano s manjom stopom hospitalizacija zbog kardiovaskularnih događaja u bolesnika s dijabetesom tip 2[1]

Retrospektivna kohortna analiza učinkovitosti cijepljenja protiv gripe u bolesnika s dijabetesom tip 2 u Engleskoj tijekom sedmogodišnjeg razdoblja (N = 124,503).

22% ↓
hospitalizacija zbog
srčanog zatajenja
(IRR 0.78, 95% CI 0.65–0.92)*[1]

30% ↓
hospitalizacija zbog
moždanog udara
(IRR 0.70, 95% CI 0.53–0.91)*[1]

19% ↓
hospitalizacija zbog
akutnog infarkta miokarda
(IRR 0.81, 95% CI 0.62–1.04)*[1]

†Retrospective cohort analysis of the effectiveness of influenza vaccination in people with T2DM in England over a 7 year period (N=124,503).[1] *vs unvaccinated people with diabetes.

CI, confidence interval; **CV**, cardiovascular; **CVD**, cardiovascular disease; **HR**, hazard ratio; **IRR**, incidence rate ratio; **MI**, myocardial infarction; **T2DM**, type 2 diabetes mellitus.

1. Vamos EP, *et al. Can Med Assoc J*. 2016; 188: E342–51.

Cijepljenje protiv gripe u Hrvatskoj

- HZJZ je i ove godine naručio **četverovalentno inaktivirano cjepivo** protiv sezonske gripe koje je besplatno za osobe s povećanim rizikom
- Cijepljenje protiv gripe **počelo je 17. listopada 2022.** kod liječnika obiteljske medicine i izabranih pedijatara te u Zavodima za javno zdravstvo i punktovima za cijepljenje protiv COVID-a
- Cjepivo protiv COVID-a i cjepivo protiv gripe **mogu se primiti istovremeno**
- Osobe koje nemaju pravo na besplatno cijepljenje mogu se cijepiti ako osobno **nabave/kupe cjepivo na temelju liječničkog recepta**
- **Hrvatska ljekarnička komora** uskoro će obavijestiti građanstvo o mogućnostima cijepljenja u ljekarnama
  - prema Zakonu o lijekovima i Pravilniku o propisivanju i izdavanju lijekova na recept, ljekarnici cjepiva mogu izdati samo na liječnički recept kojega liječnik propisuje na ime pacijenta (čuvati i prenositi cjepivo na temperaturi hladnjaka)

HZJZ: https://www.hzjz.hr

Zaključci

01 Akutne respiratorne infekcije (ARI)

Najčešće infektivne bolesti u općoj populaciji
Virusi (influenca, SARS-CoV-2) imaju vodeću ulogu
Pneumokok ostaje dominantni bakterijski patogen
"Novi" virusi - sve značajniji patogeni (RSV, bokavirus…)

02 Klinička prezentacija

Dobra klinička procjena i brza etiološka dijagnoza

03 Liječenje ARI

Simptomatska terapija nije jedini oblik liječenja

04 Mogućnosti prevencije

Cijepljenje nije indicirano samo rizičnim skupinama

KLINIČKI ASPEKTI I LIJEČENJE RESPIRATORNIH INFEKCIJA U DJEČJOJ DOBI

Prim.dr. sc. Srđan Roglić, dr. med.

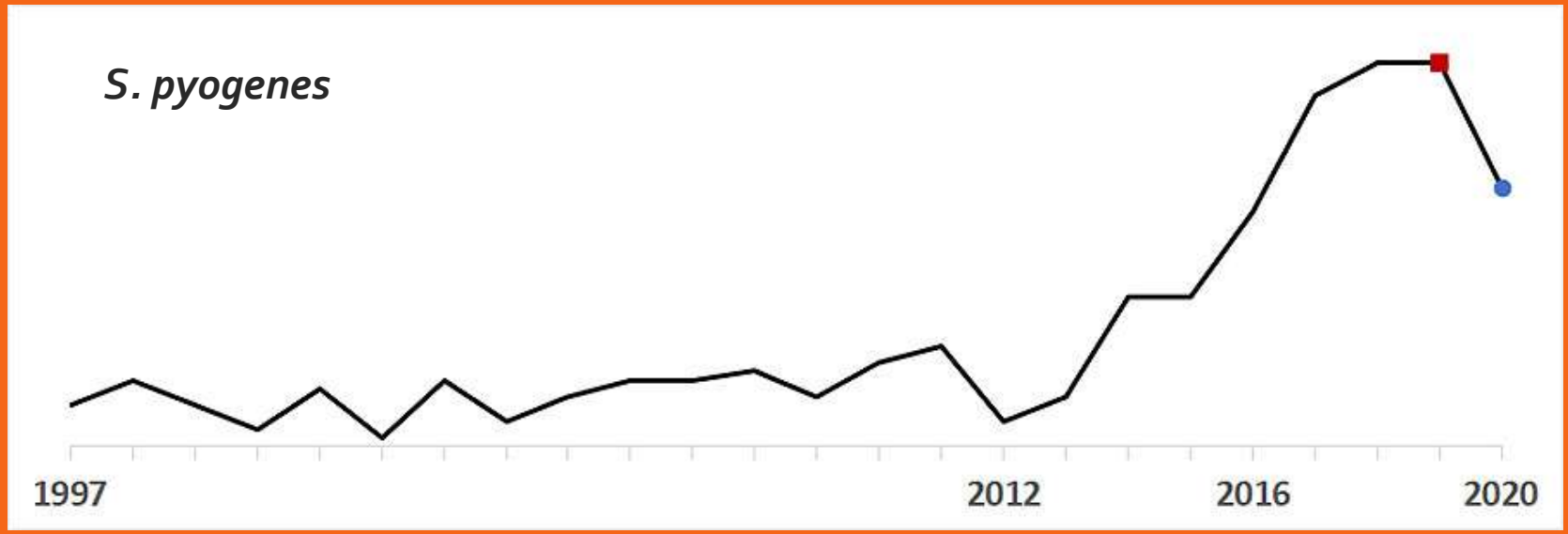
Zavod za infektivne bolesti djece

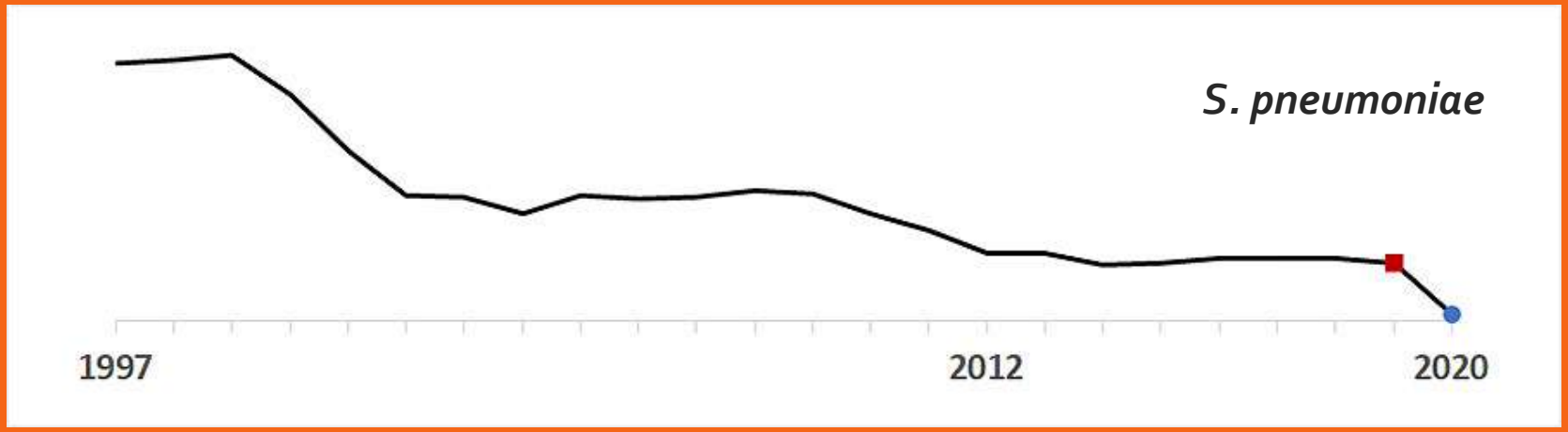
Klinika za infektivne bolesti

"Dr Fran Mihaljević"

Medicinski fakultet

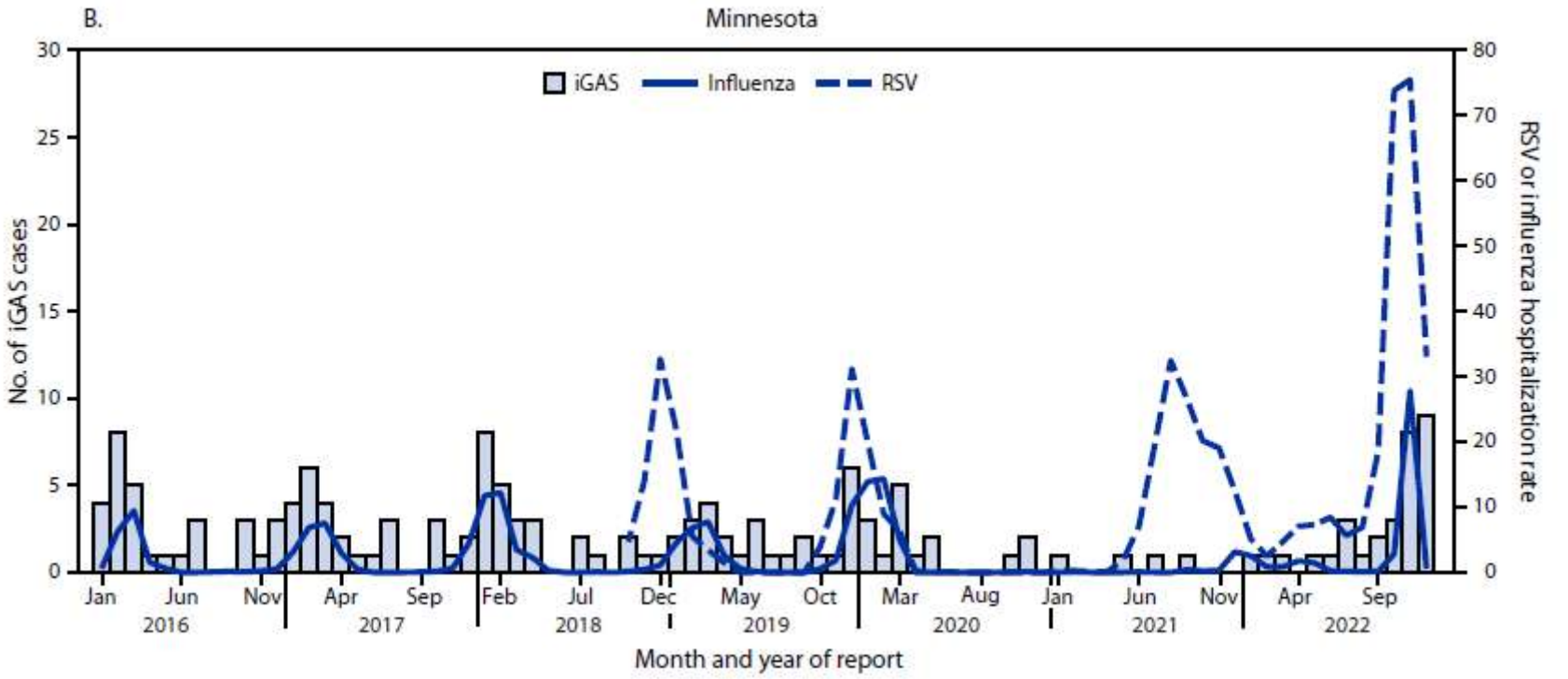
Sveučilišta u Zagrebu





Izvor: https://www.cdc.gov/abcs/reports-findings/data-2020.html

FIGURE. Cases of invasive group A *Streptococcus* infections* and hospitalization rates† for influenza§ and respiratory syncytial virus¶ among children and adolescents aged <18 years — Colorado and Minnesota, January 2016–December 2022**



Abbreviations: iGAS = invasive group A *Streptococcus* infection; RSV = respiratory syncytial virus.

* iGAS infections were identified through each state's Emerging Infections Program Active Bacterial Core surveillance systems. Cases in Colorado are from the Denver metropolitan area; cases in Minnesota throughout the state are reportable to the Minnesota Department of Health.

† Hospitalizations per 100,000 population.

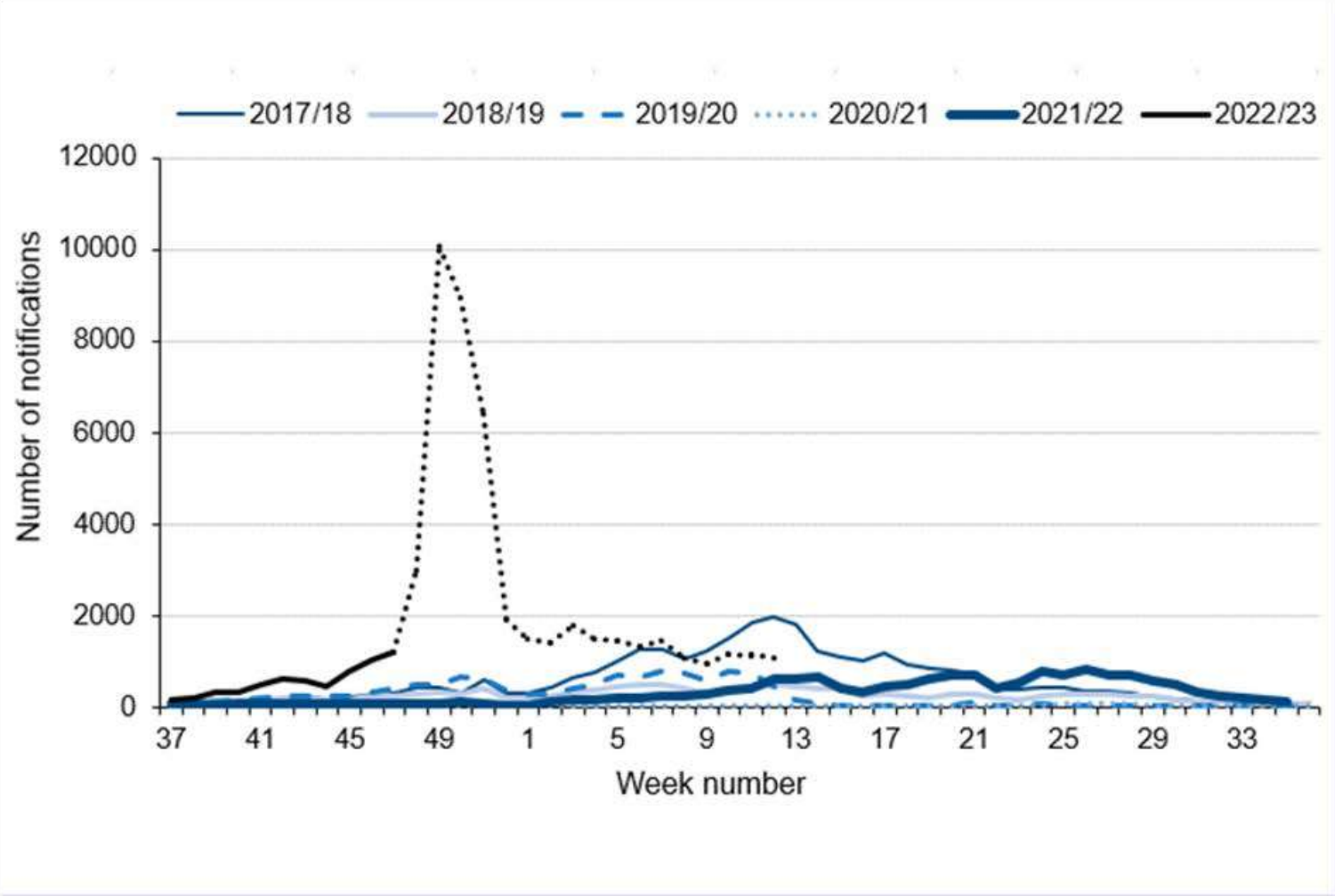
§ Colorado influenza hospitalizations are reported from the Denver metropolitan area, and rates in children and adolescents aged <18 years were calculated using age-specific and geographically defined population data obtained from the Colorado Department of Local Affairs, Demography Office. Influenza hospitalizations in Minnesota throughout the state are reportable to the Minnesota Department of Health; Minnesota influenza hospitalization rates in children and adolescents aged <18 years were calculated using age-specific and statewide population data obtained from CDC WONDER.

¶ RSV hospitalizations in Colorado were from the Denver metropolitan area; RSV hospitalization rates in children and adolescents aged <18 years were calculated using age-specific and Denver metropolitan population data obtained from the Colorado Department of Local Affairs, Demography Office. Colorado RSV hospitalization data are available during July 2019–December 2022. Minnesota RSV hospitalization rates are from the seven-county Twin Cities metropolitan area; rates in children and adolescents aged <18 years were calculated using age-specific and seven-county metropolitan population data obtained from CDC WONDER. Minnesota RSV hospitalization data were available during October 2018–December 2022.

** COVID-19 cases were not included because of the short period for which data were available and the variations in testing practices and surveillance catchment areas that limit the comparability of data.

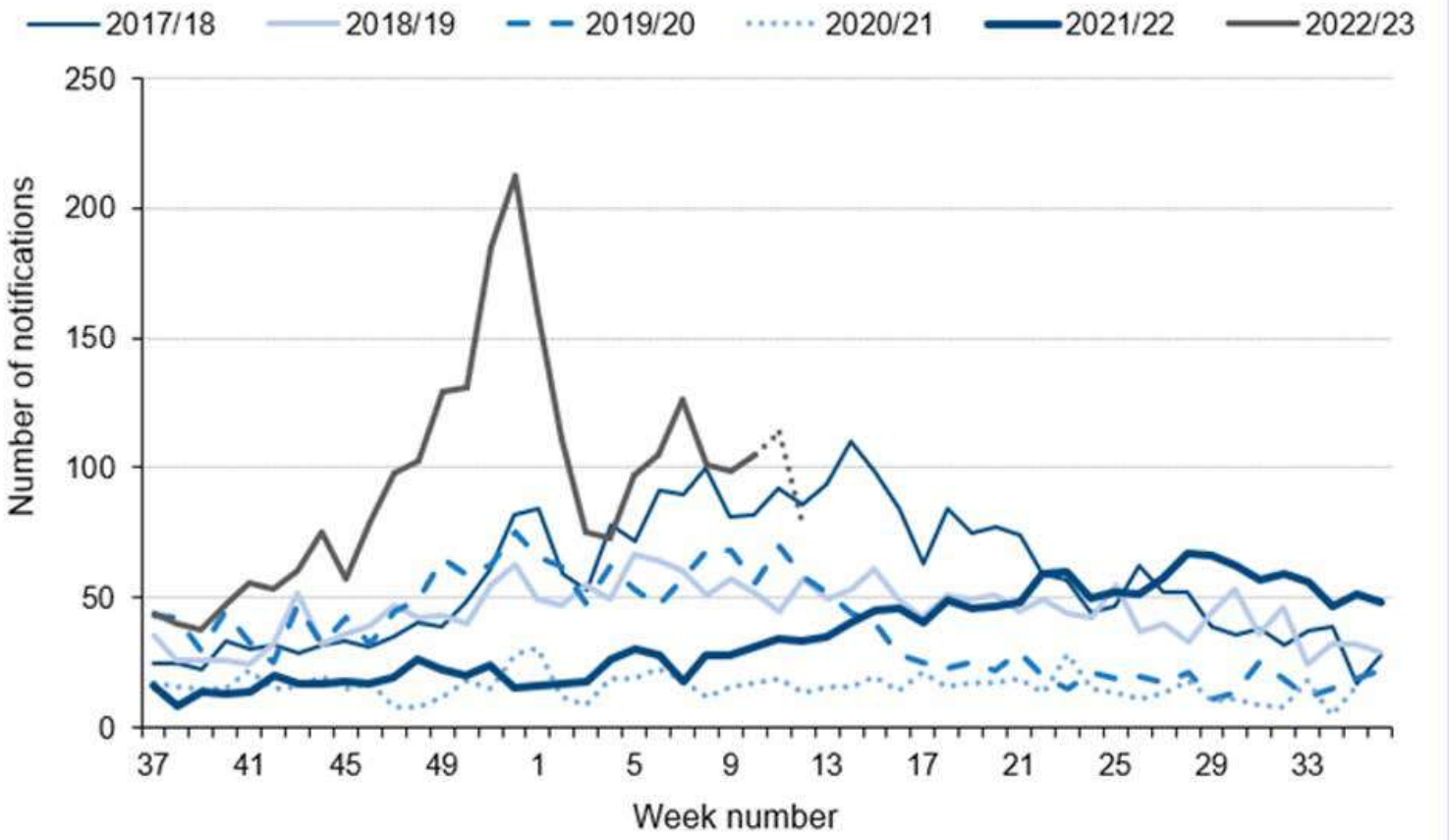
Barnes M. i sur. MMWR Morb Mortal Wkly Rep. 2023;72(10):265-267.

UK, ŠARLAH



https://www.gov.uk/government/publications/group-a-streptococcal-infections-activity-during-the-2022-to-2023-season/group-a-streptococcal-infections-12th-update-on-seasonal-activity-in-england

UK, IGAS



https://www.gov.uk/government/publications/group-a-streptococcal-infections-activity-during-the-2022-to-2023-season/group-a-streptococcal-infections-12th-update-on-seasonal-activity-in-england

Clinical Microbiology and Infection
Available online 15 March 2023
In Press, Journal Pre-proof What's this?

Original Article

The ongoing Streptococcus pyogenes (Group A Streptococcus) outbreak in London, United Kingdom in December 2022: a molecular epidemiology study

Adela Alcolea-Medina [1 2 #], Luke B Snell [1 3 #], Christopher Alder [3], Themoula Charalampous [1], Tom G S Williams [3], Synnovis Microbiology Laboratory Group [2 †], Mark Tan [3], Noor Al-Yaakoubi [3], Gul Humayun [3], William Newsholme [4], Simon Goldenberg [4], Gaia Nebbia [3], Stuart J D Neil [1], Rahul Batra [3], Jonathan D Edgeworth [1 3]

56 tipiziranih	DJECA		ODRASLI	
	invazivne	ostale	invazivne	ostale
*emm*12	2	24	2	5
*emm*1*	5	3	0	1
ostali	0	7	1	6

***emm1**$_{UK}$*
7/9 (78%)
4/5 (80%)

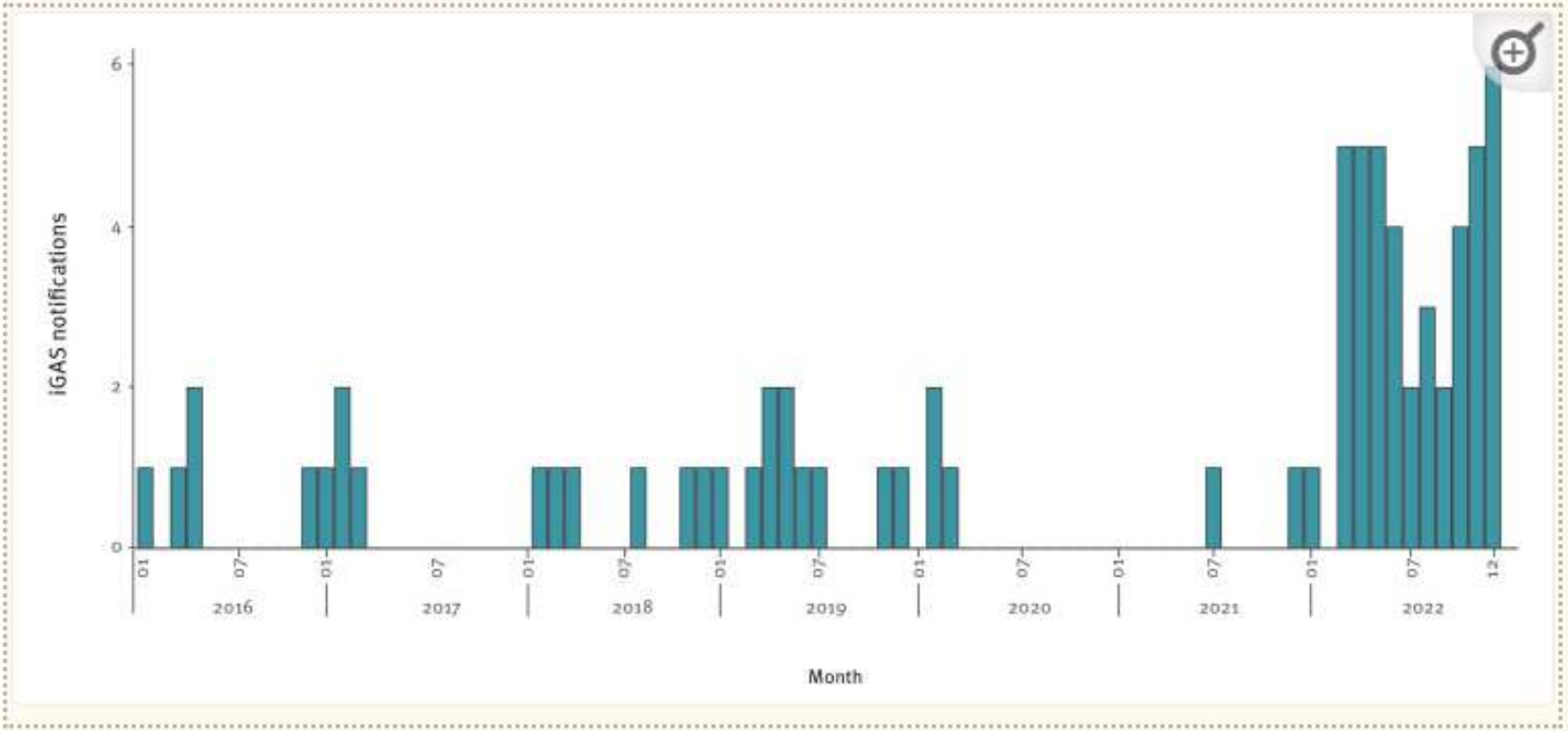


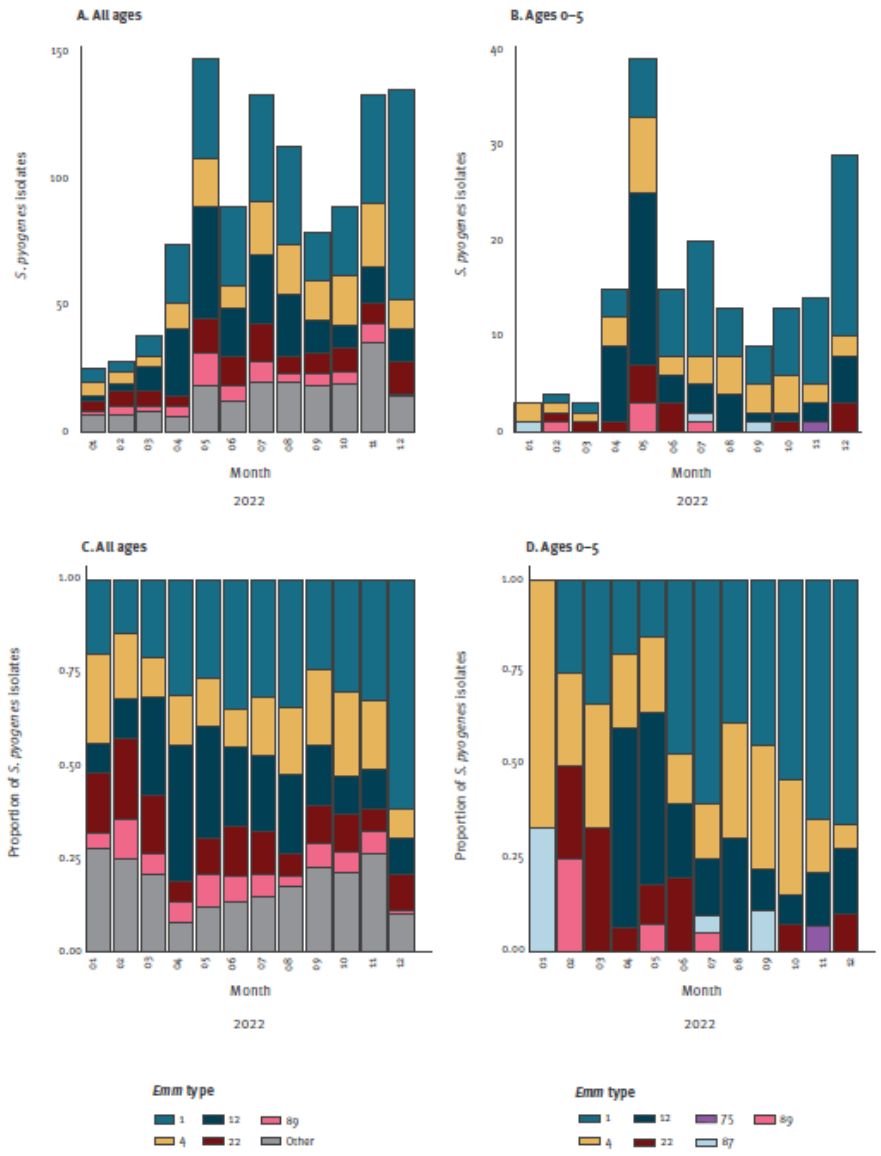
Figure 2

Notifications of culture-confirmed invasive group A streptococcal infections (streptococcal toxic shock syndrome or necrotising fasciitis) among children aged 0–5 years, by month of disease onset, the Netherlands, 1 January 2016–31 December 2022 (n = 72)

de Gier B i sur. Euro Surveill. 2023;28(1):2200941.

FIGURE 3

(A) Number and (C) proportion of *emm* types among all *Streptococcus pyogenes* isolates (n = 1,083) and (B) number and (D) proportion among *S. pyogenes* isolates from children aged 0–5 years (n = 177), by month of isolate submission to NRLBM, the Netherlands, 1 January–31 December 2022



NRLBM: Dutch National Reference Laboratory for Bacterial Meningitis.

Increase is not attributable to a specific *emm* type.

ANGINA, RINOFARINGITIS

Cochrane Library

Cochrane Database of Systematic Reviews

Different antibiotic treatments for group A streptococcal pharyngitis (Review)

van Driel ML, De Sutter AIM, Thorning S, Christiaens T

Key results

Antibiotic effects were similar, and all antibiotics caused side effects (such as nausea and vomiting, rash), but there was no strong evidence to show meaningful differences between antibiotics. Studies did not report on long-term complications, therefore it was unclear if any class of antibiotics was better in preventing serious but rare complications.

All studies were performed in high-income countries with a low risk of streptococcal complications, so there is a need for trials in low-income countries and Aboriginal communities, where the risk of complications remains high. Our review supports the use of penicillin as a first-choice antibiotic in people with throat infections caused by GABHS.

PNEUMONIJA IZ OPĆE POPULACIJE

ETIOLOGIJA	PREPORUČENA TERAPIJA
bakterijska	**amoksicilin** 90 mg/kg/dan u 2 doze (do 4 g/dan) alternativa: **ko-amoksiklav** 90 mg/kg/dan amoksicilina u 2 doze preosjetljivost na penicilin: **cefpodoksim** 8 mg/kg/dan u 2 doze (do 400 mg/dan) anafilaksija na penicilin: **doksiciklin*** 4 mg/kg/dan u 2 doze (do 200 mg/dan) **levofloksacin** 16-20 mg/kg/dan u 2 doze (6 mj.-5 g.) (do 750 mg/dan), odnosno 8-10 mg/kg jednom dnevno (stariji od 5 g.) (do 750 mg)
atipična	**azitromicin** 10 mg/kg jednom dnevno (do 500 mg) **klaritromicin** 15 mg/kg/dan u 2 doze (do 1 g/dan) **doksiciklin*** 4 mg/kg/dan u 2 doze (do 200 mg/dan)
aspiracijska	**ko-amoksiklav** 90 mg/kg/dan amoksicilina u 2 doze

Pavlov i sur. Liječ Vjesn 2021;143:349–366

PNEUMONIJA IZ OPĆE POPULACIJE

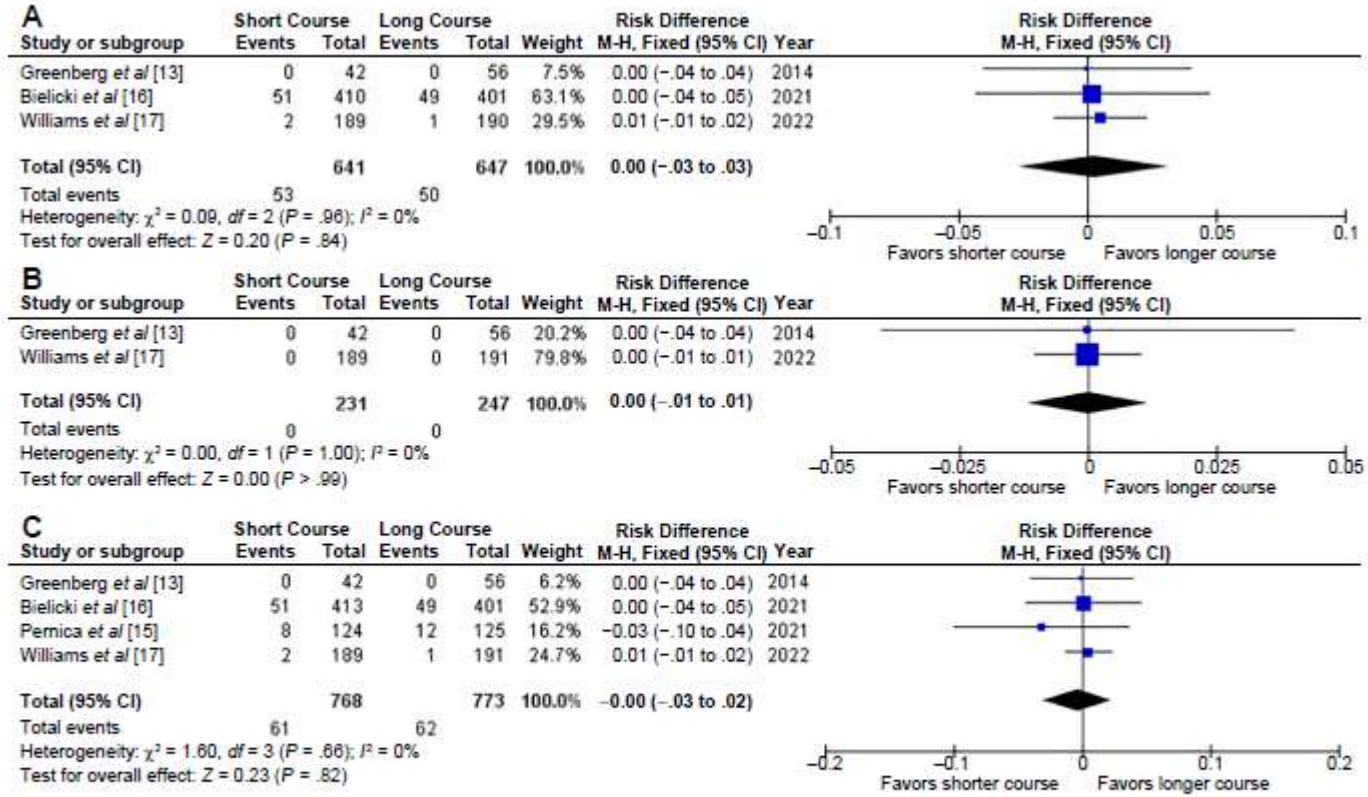


Figure 1. Need for antibiotic retreatment (*A*), need for hospitalization (*B*), and treatment failure (*C*) (includes need for antibiotic retreatment of need for hospitalization) within 1 month after randomization [13, 15–17]. Abbreviations: CI, confidence interval; *df*, degrees of freedom; I^2, inconsistency index; M-H, Mantel–Haenszel test.

Kuitunen I i sur. Clin Infect Dis. 2023 Feb 8;76(3):e1123-e1128.

PNEUMONIJA IZ OPĆE POPULACIJE

Short-Course vs Long-Course Antibiotic Therapy for Children With Nonsevere Community-Acquired Pneumonia

A Systematic Review and Meta-analysis

Qinyuan Li, MD[1,2,3,4]; Qi Zhou, PhD[5]; Ivan D. Florez, MD, MSc, PhD[6,7,8]; et al

» Author Affiliations

JAMA Pediatr. 2022;176(12):1199-1207. doi:10.1001/jamapediatrics.2022.4123

- A 3-day course of antibiotic treatment was noninferior to a 5-day course for the outcome of treatment failure (risk ratio, 1.01; 95% CI, 0.91-1.12; I2 = 0%), and a 5-day course was noninferior to a 10-day course (risk ratio, 0.87; 95% CI, 0.50-1.53; I2 = 0%).
- A shorter course of antibiotics was noninferior to a longer course in children aged 2 to 59 months with nonsevere CAP

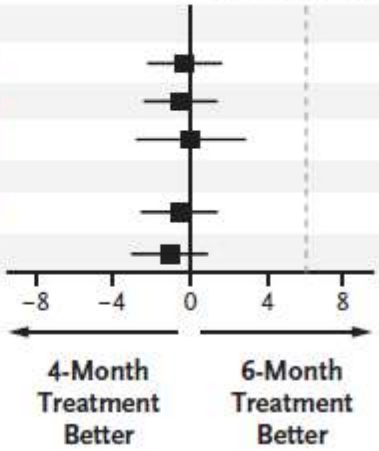
The NEW ENGLAND JOURNAL of MEDICINE

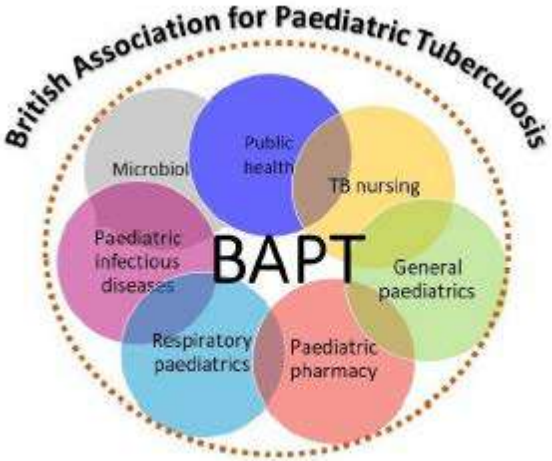
ESTABLISHED IN 1812 MARCH 10, 2022 VOL. 386 NO. 10

Shorter Treatment for Nonsevere Tuberculosis in African and Indian Children

A. Turkova, G.H. Wills, E. Wobudeya, C. Chabala, M. Palmer, A. Kinikar, S. Hissar, L. Choo, P. Musoke, V. Mulenga, V. Mave, B. Joseph, K. LeBeau, M.J. Thomason, R.B. Mboizi, M. Kapasa, M.M. van der Zalm, P. Raichur, P.K. Bhavani, H. McIlleron, A.-M. Demers, R. Aarnoutse, J. Love-Koh, J.A. Seddon, S.B. Welch, S.M. Graham, A.C. Hesseling, D.M. Gibb, and A.M. Crook, for the SHINE Trial Team*

	No. of Patients	4-Month Treatment	6-Month Treatment	Risk Difference (95% CI)
		no. of participants with event/total no. (%)		*percentage points*
Primary outcome				
Modified intention-to-treat population	1145	16/572 (3)	18/573 (3)	−0.3 (−2.3 to 1.6)
Per-protocol population	1121	14/563 (2)	17/558 (3)	−0.6 (−2.5 to 1.4)
Intention-to-treat population	1204	44/602 (7)	44/602 (7)	0 (−2.9 to 2.9)
Key secondary outcome				
Modified intention-to-treat population	910	10/450 (2)	13/460 (3)	−0.6 (−2.6 to 1.4)
Per-protocol population	895	8/445 (2)	13/450 (3)	−1.1 (−3.1 to 0.9)





Clinical Guidance

Care of children and young people exposed to or infected with tuberculosis

- Short TB treatment regimen
  - 2X4+2X2
  - Non-severe TB
    - Periferni limfni čvor
    - Medijastinalni limfni čvor bez opstrukcije dišnog puta
    - Nekomplicirani pleuralni izljev
    - Plućna (sputum negativan, bez kavitacija, jedan režanj)
    - Nije milijarna
  - Kontrolna obrada prije prekida terapije

ATIPIČNE PNEUMONIJE

EVA HULJEV, DR.MED.

IVANA JAPIRKO, DR.MED.

KLINIKA ZA INFEKTIVNE BOLESTI „DR. FRAN MIHALJEVIĆ”

KLINIČKO RAZVRSTAVANJE PNEUMONIJA

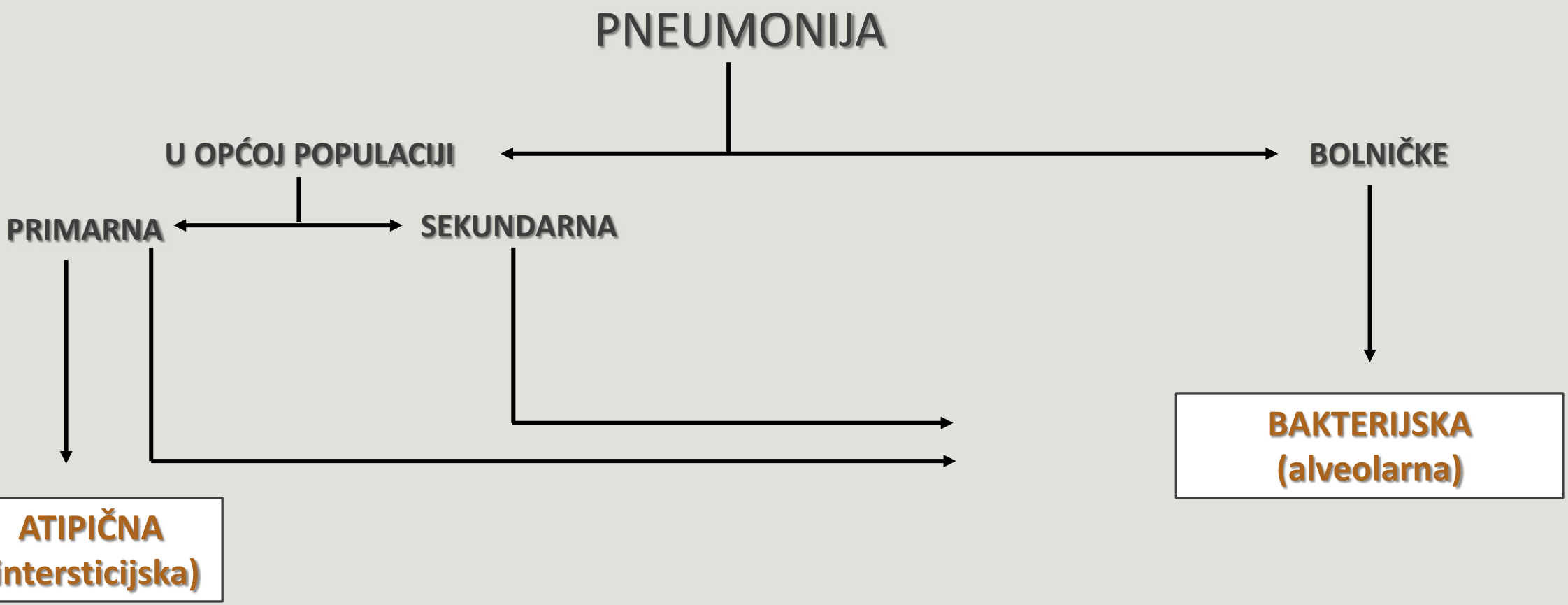
pneumonija = akutna upala plućnoga parenhima uzrokovana brojnim i raznovrsnim mikroorganizmima

Klinička prezentacija

- ✓febrilitet
- ✓kašalj
- ✓zaduha
- ✓probadanje u prsima

simptomi i znakovi akutne upale donjeg dišnoga sustava

KLINIČKO RAZVRSTAVANJE PNEUMONIJA



UZORČNICI ATIPIČNIH PNEUMONIJA

- ✓ respiratorni virusi
- ✓ *M. pneumoniae*
- ✓ *C. pneumoniae*
- ✓ *L. pneumophila*
- ✓ *C. burnetii*
- ✓ *C. psittaci*

PATOGENEZA

inhalacija mikroorganizama

↓

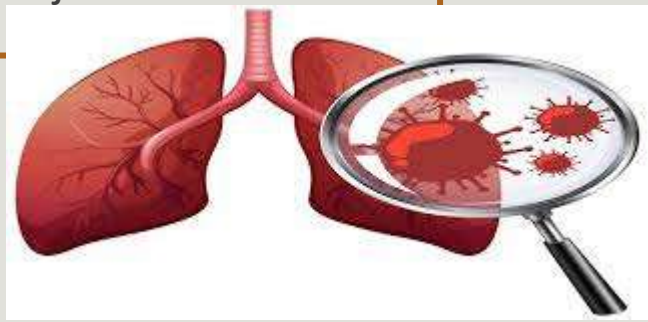
retikuloendotelni sustav

↓

plućni parenhim

↓

intersticijska pneumonija



KLINIČKA SLIKA ATIPIČNIH PNEUMONIJA

- ✓ postupan razvoj kliničkim simptoma
- ✓ temperatura visokih vrijednosti (rijetko praćena tresavicom)
- ✓ kliničkom slikom dominiraju opći simptomi: mialgije, artalgije, glavobolja, mučnina, povraćanje
- ✓ rijetka pojava bolova u prsima, zaduhe i pleuralnog izljeva
- ✓ suh i nadražajan kašalj (pojavljuje se tek nakon 4 do 5 dana)
- ✓ auskultacijski nalaz: u početku bolesti normalan

DIJAGNOSTIČKI POSTUPCI

laboratorijski nalazi	radiološka dijagnostika	mikrobiološka dijagnostika
✓leukociti: normalan broj ✓neutrofilija: rijetko ✓CRP: povišen, ali umjereno ✓aminotransferaze: nerijetko povišene	✓nježni, mrežoliki ili mrljasti, neoštro ograničen infiltrat segemntalnog ili lobarnog opsega ✓nerazmjer auskultacijskog nalaza i RTG nalaza	✓dokazivanje antigena (*L. pneumophila* u mokraći) ✓PCR: mikobakterije, klamidije, respiratorni virusi ✓serološka dijagnostika

Mycoplasma pneumoanie

- ✓najmanji prokarioti koji se razmnožavaju samostalno
- ✓koloniziraju sluznice usta i dišnoga sustava

EPIDEMIOLOGIJA

- ✓prenosi se kapljicama respiratornoga sekreta
- ✓uzrokuje različite respiratorne infekcije (javljaju se tijekom cijele godine)
- ✓klinički izražene infekcije najučestalije su u starije djece i u mlađih odraslih
- ✓većina infekcija prolazi asimptomatski ili uz vrlo blage respiratorne simptome
- ✓**pneumonija** je najvažnija bolest koju uzrokuju mikoplazme
- ✓u dobnoj skupini 5-20 godina uzrokuje 30-60% svih pneumomija

Legionella pneumophila

✓aerobna, gram-negativna unutarstanična bakterija

EPIDEMIOLOGIJA

✓ubikvitarni mikroorganizmi, rasprostranjeni posvuda (održavaju se i razmnožavaju u vodi i vlažnom tlu)

✓koloniziraju različite vodoopskrbne sustave koje je izgradio čovjek (vodovodi, rezervoari, tornjevi, uređaji za zagrijavanje, hlađenje i isparivanje vode)

✓za legionarsku bolest je karakteristično sezonstvo: kolovoz i rujan

✓prenosi se inhalacijom kontaminiranog aerosola, nema prijenosa s čovjeka na čovjeka

✓uzrokuje 2-15% pneumonija

Coxiella burnetii

- ✓ obligatni je unutarstanični parazit
- ✓ vrlo je otporna, može dugo preživljavati i izvan žive stanice (poprima odlike spora)

EPIDEMIOLOGIJA

- ✓ Q-groznica je klasična zoonoza: bolest divljih i gotovo svih domaćih životinja (održava i prenosi se preko krpelja)
- ✓ najvažniji rezervoar bolesti za čovjeka su ovce i koze (inaparentna, kronična infekcija)
- ✓ rikecije u vanjsku sredinu dospijevaju izlučevinama, osobito preko plodove vode i u posteljici
- ✓ čovjek se zarazi udisanjem inficiranog aerosola
- ✓ endemska i profesionalna bolest

Chlamydophila psittaci

- ✓gram-negativne unutarstanične bakterije
- ✓dva morfološki i funkcionalno različita oblika: zarazno **elementarno** i reproduktivno **retikularno** tjelešce

EPIDEMIOLOGIJA

- ✓klasična zoonoza; bolest ptica (inaparentna, subklinička, kronična infekcija)
- ✓najčešći izvor zaraze jesu papige i golubovi
- ✓čovjek se zarazi inhalacijom uzročnika nakon izloženosti sasušenom fecesu i respiratornim sekretima zaraženih ptica
- ✓profesionalna bolest
- ✓moguć je i interhumani prijenos

Chlamydophila pneumoniae

- ✓gram-negativne unutarstanične bakterije
- ✓dva morfološki i funkcionalno različita oblika: zarazno **elementarno** i reproduktivno **retikularno** tjelešce

EPIDEMIOLOGIJA

- ✓patogena samo za čovjeka
- ✓izvor infekcije su bolesnici, ali i asimptomatske kliconoše
- ✓prenosi se kapljicama respiratornog sekreta
- ✓obolijevaju odrasle osobe
- ✓opisuje se kao uzročnik pneumonija iz opće populacije 0-40% (ovisi o dijagnostici)

BOLNIČKE PNEUMONIJE

doc. dr. sc. Vladimir Krajinović, dr. med.
Zavod za intenzivnu medicinu i neuroinfektologiju
Klinika za infektivne bolesti, Zagreb

15.5.2023.

BOLNIČKE (NOZOKOMIJALNE) **INFEKCIJE**

- Iako su samo oko 10% bolničkih kreveta oni u JIL, više od 20% svih bolničkih infekcija pacijenti akviriraju u JIL *

- Najčešće i klinički najvažnije infekcije akvirirane u JIL su one povezane s „cijevima” (kateterima, tubusima, kanilama...) koje su bolesnicima često neophodni
  - sepsa povezane s intravaskularnim kateterima (engl. CRBSI)
  - pneumonija povezana s liječenjem respiratorom (engl. VAP)
  - infekcije mokraćnog sustava povezane s urinarnim kateterom (engl. CAUTI)

* Fridkin SK. Infect Dis Clin North Am. 1997.
** Uptodate, 2023.

BOLNIČKE (NOZOKOMIJALNE) PNEUMONIJE

Pojmovi i definicije*

- **Bolnička pneumonija** *(Hospital-acquired (nosocomial) pneumonia (HAP))*
  - Pneumonija stečena ≥48 sati nakon bolničkog prijema; uključuje HAP i VAP

- **Pneumonija povezana s respiratorom** (*Ventilator-associated pneumonia (VAP*))
  - Pneumonija stečena ≥48 sati nakon endotrahealne intubacije

- Pneumonija povezana sa zdravstvenom skrbi *(Health care-associated pneumonia (HCAP))***
  - Mali rizik za većinu bolesnika u takvim ustanovama, niska incidencija, maknute iz smjernica 2016

* Kalil AC, et al. Clin Infect Dis. 2016.
**Torres A et al, Eur Respir J. 2017;50(3)

BOLNIČKE PNEUMONIJE
EPIDEMIOLOGIJA

- Iako se najviše bolničkih pneumonija pojavljuje u neventiliranih bolesnika (NCV-HAP), najviši rizik akviriranja upale pluća je u intubiranih bolesnika na mehaničkoj ventilaciji
  - 10x veći rizik HAP-a*
- Smrtnost za VAP i NV-HAP je slična (od 15 do 30%)
- VAP i NV-HAP produljuju trajanje hospitalizacije i troškove liječenja**
- VAP produljuje trajanje mehaničke ventilacije 7.6 do 11.5 dana, a hospitalizaciju čak 11.5 do 13.1 dan u usporedbi sa sličnim bolesnicima bez VAP-a

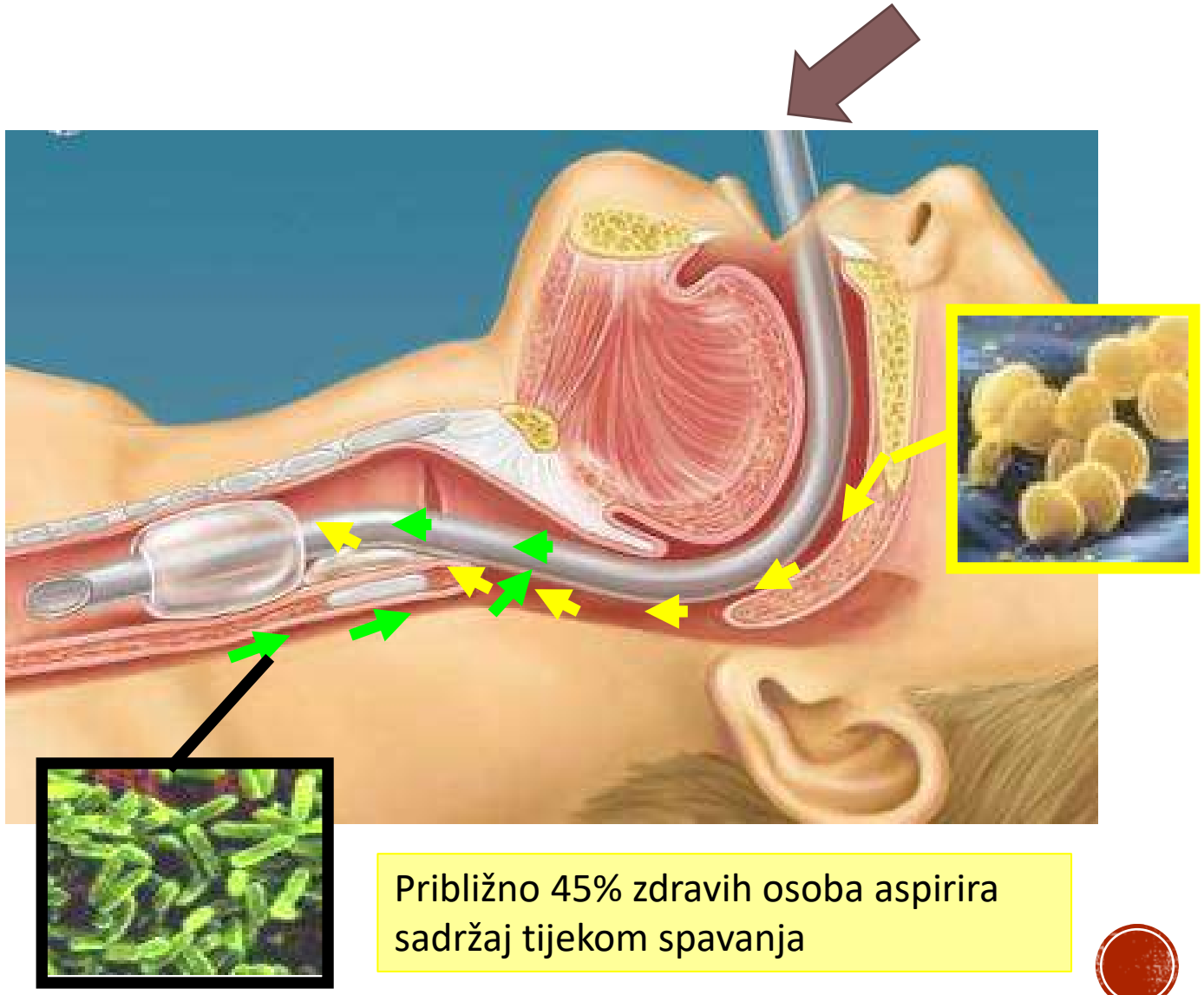
*Walter J, et al. Euro Surveill. 2018;23(32)
**Kalil AC, et al. Clin Infect Dis. 2016.

BOLNIČKE PNEUMONIJE
PATOGENEZA

1. Mikroaspiracija bakterija koje su kolonizirale orofaringealni trakt

2. Direktni kontakt s izvorima infekcije iz okoline npr. respiratorni uređaji

3. (kontaminirane) ruke bolničkog osoblja



Približno 45% zdravih osoba aspirira sadržaj tijekom spavanja

Garrouste-Orgeas M. Am J Respir Crit Care Med. 1997;156(5):1647.

BOLNIČKE PNEUMONIJE

MDR FAKTORI RIZIKA

Dva najvažnija*:

1. Dugotrajna hospitalizacija
2. Nedavna izloženost primjeni antibiotika

*Kalil AC, et al. Clin Infect Dis. 2016.

Ventilator-associated pneumonia: Risk factors for multidrug-resistance in adults

Risk factors for MDR pathogens:
▪ IV antibiotic use within the previous 90 days
▪ Septic shock at the time of VAP
▪ ARDS preceding VAP
▪ ≥5 days of hospitalization prior to the occurrence of VAP
▪ Acute renal replacement therapy prior to VAP onset
Risk factors for MDR *Pseudomonas* and other gram-negative bacilli:
▪ Treatment in an ICU in which >10 percent of gram-negative isolates are resistant to an agent being considered for monotherapy
▪ Treatment in an ICU in which local antimicrobial susceptibility rates are not known
▪ Colonization with OR prior isolation of MDR *Pseudomonas* or other gram-negative bacilli
Risk factors for MRSA:
▪ Treatment in a unit in which >10 to 20 percent of *Staphylococcus aureus* isolates are methicillin resistant
▪ Treatment in a unit in which the prevalence of MRSA is not known
▪ Colonization with OR prior isolation of MRSA

MDR: multidrug resistant; IV: intravenous; VAP: ventilator-associated pneumonia; ARDS: acute respiratory distress syndrome; ICU: intensive care unit; MRSA: methicillin-resistant *S. aureus*.

Adapted from: Kalil AC, Metersky ML, Klompas M, et al. Management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 clinical practice guidelines by the Infectious Diseases Society of America and the American Thoracic Society. Clin Infect Dis 2016; 63:e61.

UpToDate®

BOLNIČKE PNEUMONIJE
MIKROBIOLOGIJA

- Najčešći uzročnici:
  - *Staphylococcus aureus* (uključujući MRSA) i
  - *Pseudomonas aeruginosa*
- Drugi česti:
  - aerobni gram-negativni bacilli (npr. Escherichia coli, Klebsiella pneumoniae, Enterobacter spp, **Acinetobacter spp**) and gram-positive cocci (eg, Streptococcus spp)*
- Sve je više dokaza o virusima kao uzročnicima HAP u općim i kirurškim JIL te virusima i gljivama u imunokompromitiranih bolesnika**
- Pateogeni koji uzrokuju NV-HAP uglavnom su isti kao i oni koji uzrokuju VAP

*Weiner LM, et al. Infect Control Hosp Epidemiol. 2016.
** Shorr AF, et al. Respir Med. 2017.

BOLNIČKE PNEUMONIJE
KLINIČKA PREZENTACIJA

Postupni ili nagli početak 48 sati nakon intubacije:*

- Simptomi – dispneja (rijetko, jer su bolesnici na respiratoru i ne govore)
- Znakovi – vrućica, tahipneja, pojačana količina sekrecije ili gnojna sekrecija, hemoptiza, hropci, krepitacije, oslabljeno disanje, bronhospazam
- Parametri respiratora – reduciran „tidal" volumen, povećani tlak u dišnim putevima
- Laboratorijski nalazi – pogoršanje hipoksemije, leukocitoza
- Imaging – novi ili progresija infiltrata na RTG-u ili CT-u pluća

*Meduri GU. Clin Chest Med. 1995;16(1):61.

BOLNIČKE PNEUMONIJE
DIJAGNOZA

- Sigurna klinička dijagnoza nije jednostavna
- Novonastali infiltrat na RTG pluća plus klinički dokaz infektivnog uzroka infiltrata
  - novonastali febrilitet
  - gnojni sputum
  - leukocitoza i
  - Pad oksigenacije

Ni jedan pojedini znak ili simptom kao ni njihova kombinacija nije visoko osjetljiv niti specifičan za dijagnozu

Kulture sekreta iz pluća (sputum, endotrahealni aspirati, bronhoalveolarni lavat) često su lažno pozitivni ili lažno negativni

*Kalil AC, et al. Clin Infect Dis. 2016.

BOLNIČKE PNEUMONIJE

UZIMANJE UZORAKA I EMPIRIJSKA TERAPIJA

- Uzeti uzorke iz donjih dišnih putova i hemokulture prije započinjanja antimikrobne terapije ili promjene terapije (ako je pacijent već na terapiji)
- Nakon uzimanja uzorka daje se odmah empirijski ATB
- Po uvidu u nalaz deeskalacija terapije

Torres A, et al. Am J Respir Crit Care Med. 1994.
Chastre J, et al. Am J Respir Crit Care Med. 1995.

BOLNIČKE PNEUMONIJE
TIP RESPIRATORNOG UZORKA

- Nema konsenzusa o načinu uzimanja uzoraka (invazivno ili neinvazivno) niti o kulturi uzorka (kvantitativno ili nekvantitativno
  - Niti jedan pristup nije pokazao superiornost u ishodu (smrtnost ili trajanje hospitalizacije)
- Ipak, većina smatra da su invazivne metode uzimanja uzorka (eg, mini-brochoalveolarna lavaža [BAL], bronhoskopski BAL, il *protected specimen brush* [PSB]) s kvantitativnom kulturom bolja opcija
  - osjetljivija
  - pruža mogućnost ciljanog liječenja ATB užeg spektra (promovirajući antimicrobial stewardship)
- Neinvazivne uzimanje uzorka (aspirat trahealnog sekreta i semikvantitativna kultura je vrlo dobra alternativa
  - Iako neinvazivan, veća je vjerojatnost neadekvatne primjene antibiotika

BOLNIČKE PNEUMONIJE
ANTIMIKROBNO LIJEČENJE

- **Empirijsko liječenje**
  - Lokalna distribucija patogena
  - Njihova antimikrobna osjetljivost (uvijek antibiogram)
- **Izbor antibiotika***
  - Baziran na faktorima rizika za MDR patogen
    - Recentna primjena antibiotika
    - Komorbiditeti
    - Podatci o prethodnoj kolonizaciji uzročnikom
- **Dodatan oprez**
  - Nuspojave ATB
  - Interakcije
  - Troškovi
  - Kliničko iskustvo s lijekom

* Uptodate, 2023.

BOLNIČKE PNEUMONIJE

PREVENCIJA

Tzv „bundle of care”

- Pranje ruku
- Izbjeći intubaciju (kad je moguće)
- Minimalna sedacija
- Pridržavanje protokola za skidanje s respiratora
- Provođenje fizikalne terapije
- Redovita sestrinska njega
- Elevacija uzglavlja kreveta
- Promjena cijevi respiratora kad su zaprljane sekretom

Klompas M, et al. Infect Control Hosp Epidemiol. 2022;43(6):687.

Klinički aspekti i liječenje upala srednjeg uha

Doc. dr. sc. Lana Kovač Bilić, prim. dr. med.
specijalist otorinolaringolog
audiolog i fonijatar

orl
Klinika za bolesti uha, nosa i grla i kirurgiju glave i vrata

KBC ZAGREB

AKUTNA UPALA SREDNJEG UHA

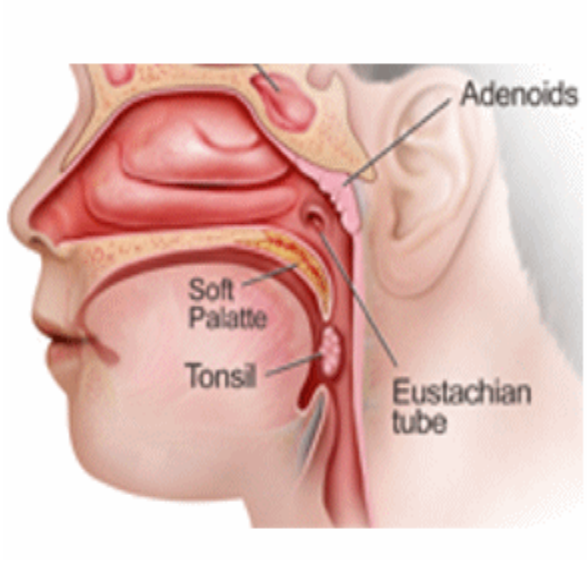
Najčešća infekcija kod male djece od 6 do 18 mjeseci s vrhom incidencije oko 9 mjeseci a sve rjeđe iza 3 godine života (oko 80% djece ima upalu uha prije 3 godine).

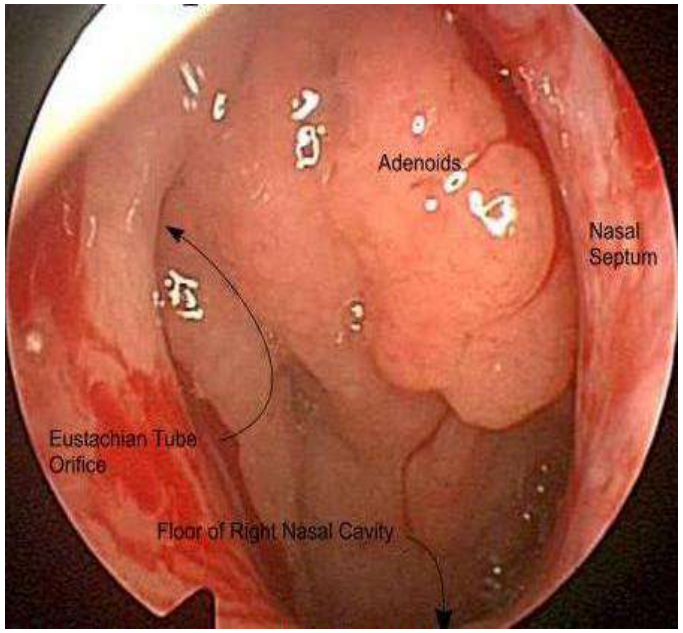
- Najveći broj akutnih upala uha prolazi bez antibiotika, a liječenje je bazirano na adekvatnoj analgeziji i rješavanju opstrukcije nosa i nosnog ždrijela.

- Dijagnostika upala uha je jednostavna a problem postoji kad i koliko dugo davati antibiotsku terapiju.

- U liječenju postoje nacionalne i internacionalne smjernice koje se moraju obnavljati barem svakih 10 godina te prilagođavati mikrobiološkoj evoluciji i stvaranju rezistencije na pojedine antibiotike

- Eustahijeva tuba je kraća, horizontalnije postavljena
- Uvećane adenoidne vegetacije
- Nije u potpunosti razvijen imunološki sustav





FAKTORI RIZIKA AKUTNE UPALE SREDNJEG UHA

Uvećane adenoidne vegetacije
Kronični serozni otitis (COME)
Kolektiv (jaslice, vrtić, škola)
Nedostatak željeza (čak i bez anemije)
Kratko vrijeme dojenja, dugotrajno hranjenje na bočicu, lizalice
Pasivno pušenje
Laringofaringealni refluks (LPR)
Alergija, atopija
Obiteljska anamneza recidivirajućih upala uha
Imunološki deficit (imunoglobulini, splenektomija, AIDS, imunosupresivna terapija)
Rascjep tvrdog i mekog nepca
Trisomija 21
Kartagenerov sindrom, mukoviscidoze

Bakterije	Učestalost	Rezistencija
Haemophilus influenzae	30-40%	15% stvara betalaktamazu 8% smanjene osjetljivosti na amoksicilin
Streptococcus pneumoniae	25-40%	42% smanjene osjetljivosti na penicilin 4% rezistencije
Moraxella catarrhalis	5-10%	
Streptococcus pyogenes	< 5%	
Staphylococcus aureus	< 5%	
Corynebacterium	< 5%	
Pseudomonas aerginosa	< 5%	
Enterobacteriaceae	< 5%	

FAKTORI RIZIKA REZISTENCIJE **Streptococcus pneumoniae**
Učestali boravak u kolektivu
Djeca manja od 2 godine
Nedavna hospitalizacija
Nedavno liječenje antibiotikom (< 30 dana)
Učestale akutne upale srednjeg uha

CIJEPLJENJE

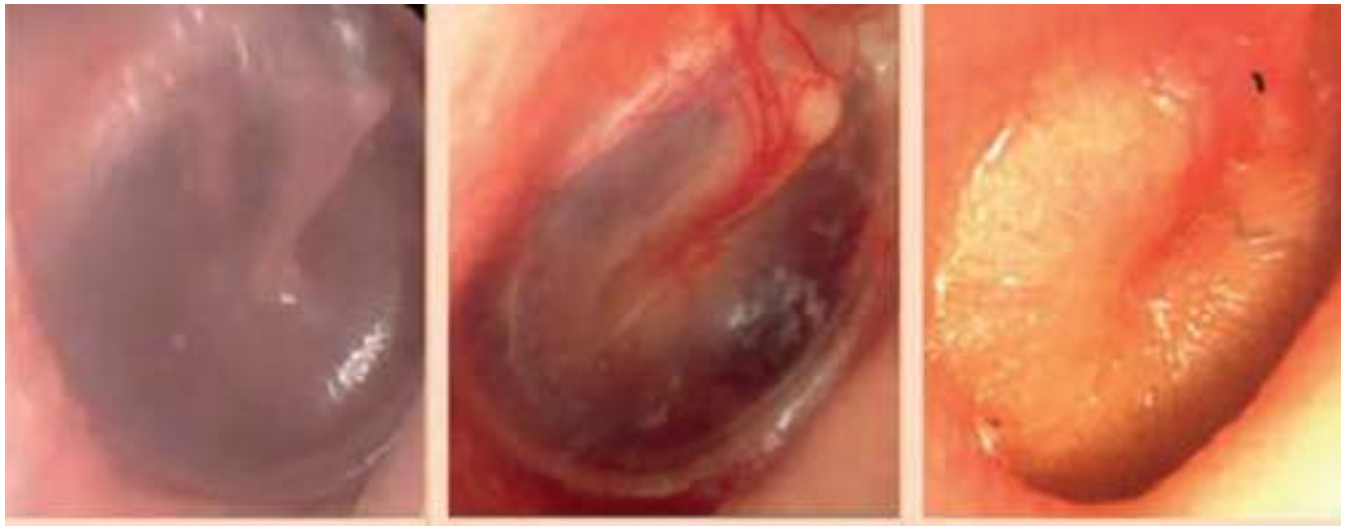
- **Prevenar7** – značajan porast *S. pneumoniae i*
  i netipiziranih sojeva *H.influenzae*
  (Kanada - smanjenje infekcije 13%-19%)
- **Prenevar 13 i Pneumo23** – smanjenje *S. pneumoniae* nema podataka da li se povećava apsolutni broj ili samo postotak slučajeva infekcije s *H.influenzae i M. catarrhalis*
- ***Tamir et al.*** *Smanjenje epizoda OMA u male djece (< 2god) od 2011. godine i simptomi znatno manje izraženi*
- ***Ben-Shimol et al.*** *Smanjenje serotipova S. pneumoniae pokrivenih Prevenar13 od 85%*

DIJAGNOSTIKA AKUTNE UPALE SREDNJEG UHA

OPĆI I FUNKCIONALNI ZNAKOVI AKUTNE UPALE UHA
Temperatura (> 38,5℃ u 50% slučajeva Streptococcus pneumoniae)
Pospanost, poremećaj sna
Gubitak apetita, povraćanje, proljev
Uznemirenost, plač
Nosna sekrecija, kašalj
Bol u uhu

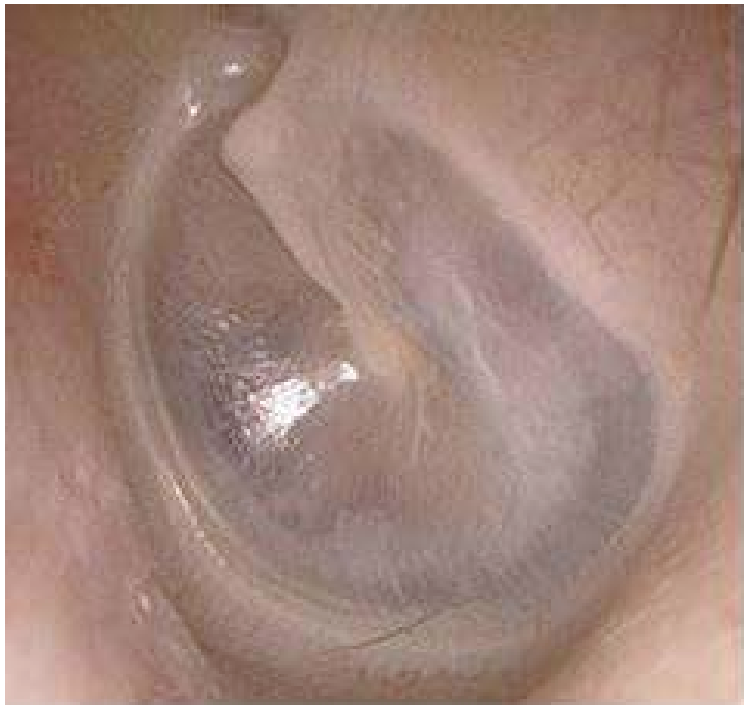
OTOSKOPSKI NALAZ

Normalan bubnjić | Kongestivni otitis | Gnojni otitis

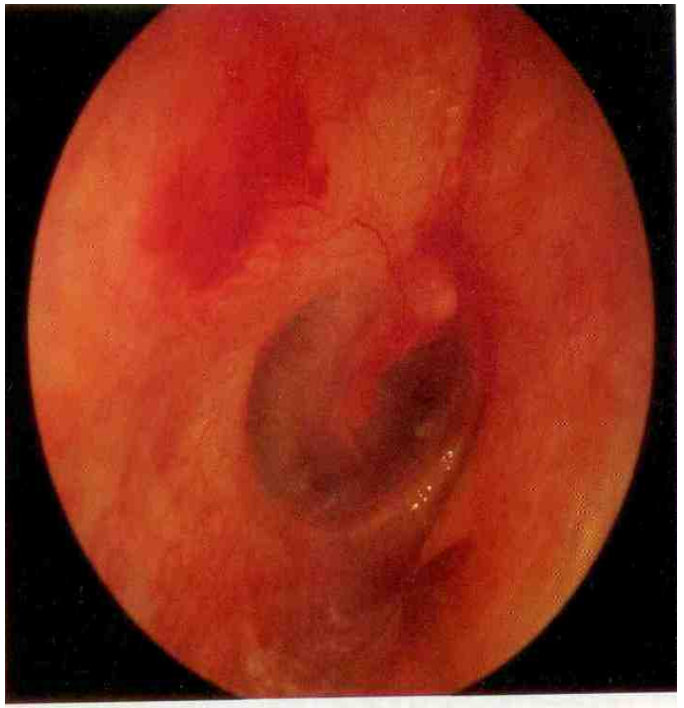


PROZIRNOST	PROZIRNOST	KONGESTIJA	RETROTIMPANALNI GNOJ
TROKUTASTI ODSJAJ	+	-	-
IZBOČENOST BUBNJIĆA	-	-	+
VIDLJIVOST MANUBRIUMA	+	+	-

KONGESTIVNA ILI KATARALNA UPALA SREDNJEG UHA



Normalan bubnjić

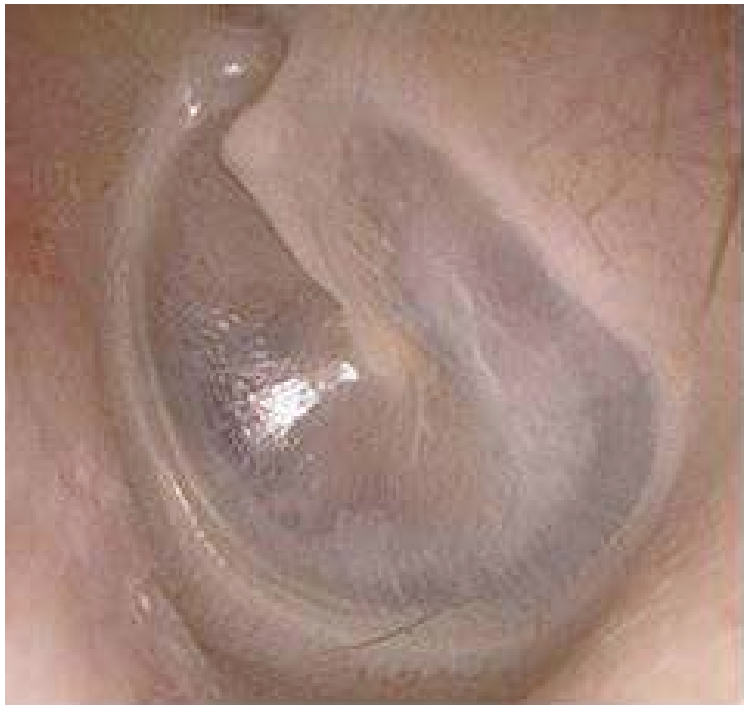


Kongestivna ili kataralna akutna upala

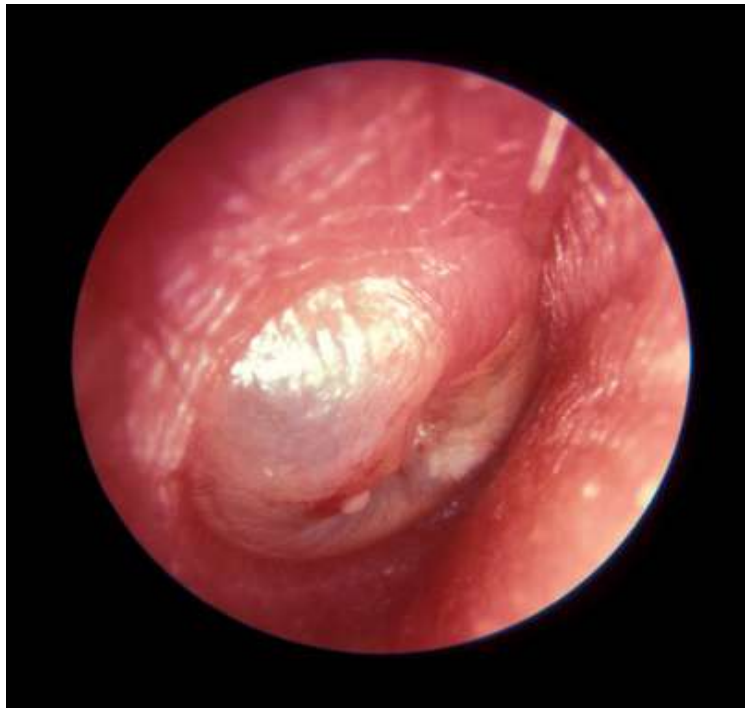
KONGESTIVNA ILI KATARALNA UPALA SREDNJEG UHA

- Hiperemija bubnjića
- Nema retrotimpanalnog sekreta
- Virusna etiologija (RSV, influenza, parainfluenza, adenovirus)
- U 60-70% slučajeva dolazi do bakterijske superinfekcije
- Otežan pregled zbog plača i napinjanja djeteta – lažno pozitivni nalaz

GNOJNA ILI PURULENTNA UPALA SREDNJEG UHA



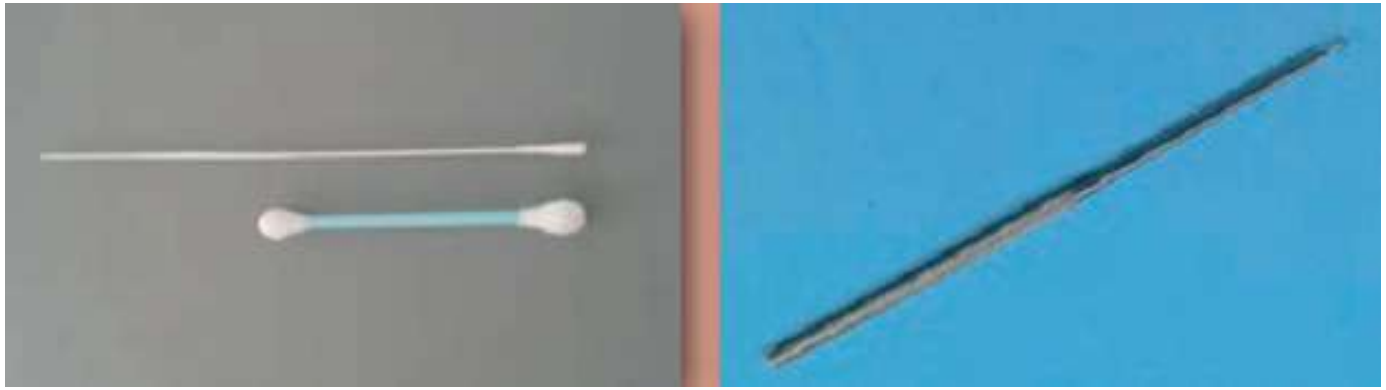
Normalan bubnjić



Gnojna ili purulentna akutna upala uha

GNOJNA ILI PURULENTNA UPALA SREDNJEG UHA

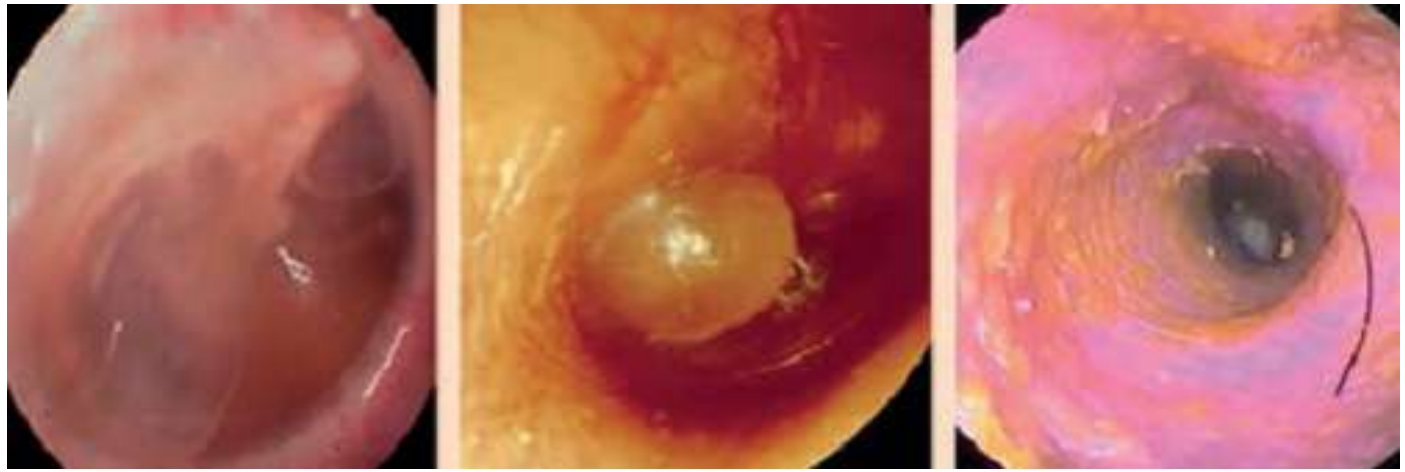
- Bubnjić izbočen, purulentni sekret ukoliko postoji perforacija
- Potrebno vizualizirati najmanje ¾ bubnjića za postavljanje dijagnoze
- Ukoliko je potrebno koristiti aspirator, vatene štapiće ili metalne omče



DIFERENCIJALNA DIJAGNOZA AKUTNE UPALE SREDNJEG UHA

OTOSKOPSKI NALAZ

Serozni otitis | Bulozni otitis | Otitis externa



Bolnost	**-**	**++**	**++**
Temperatura	-	-/+	-/+
Sekrecija iz uha	-	-/+ ako perforira mjehurić	+
Prozirnost	Mat/ jantar, sekret	Kongestija	Slaba vidljivost bubnjića
Trokutasti odsjaj	+	-/+	Slaba vidljivost bubnjića
Izbočenost bubnjića	-	+ (mjehurić na bubnjiću)	Slaba vidljivost bubnjića
Vidljivost manubriuma	+	+	Slaba vidljivost bubnjića

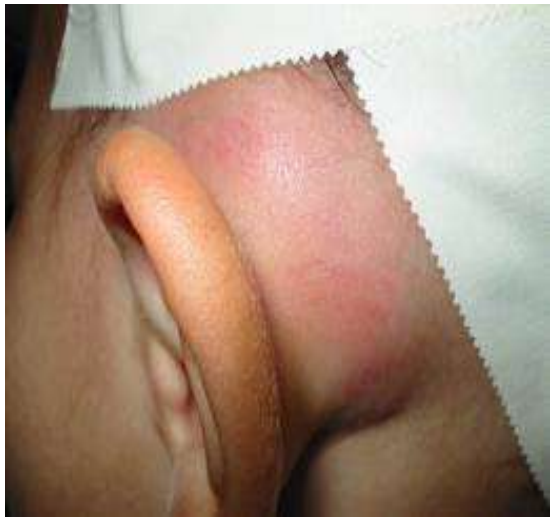
KOMPLIKACIJE AKUTNE UPALE SREDNJEG UHA

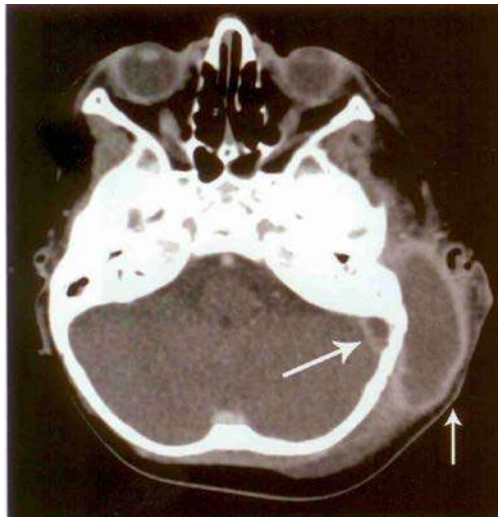
INTRAKRANIJALNE

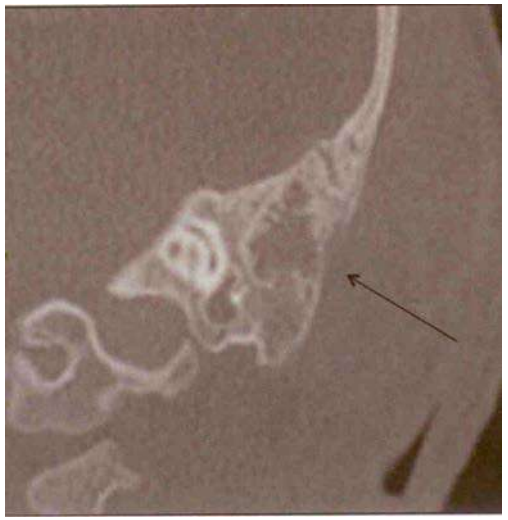
- **Meningitis**
- Subduralni apsces
- Epidurani apsces
- Apsces mozga
- Tromboza sigmoidnog sinusa

EKSTRAKRANIJALNE

- Akutni mastoiditis
- **Subperiostalni apsces**
- Pareza ličnog živca
- Gradenigov sindrom
- Labirintitis







LIJEČENJE AKUTNE UPALE SREDNJEG UHA

- **Analgetici/antipiretici**

  od 2016. godine u smjernicama se preferira kombinacija ibuprofena i paracetamola

  Tramadol u kapima od 3 godine života

- **Kapi za uho**

  Ciloxan® – jedine netoksične kapi – mogu na otvoren bubnjić

  Ciloxadex® – nema ih u RH

  Auridol® - jedine lidokainske kapi

- **Rinofaringealna higijena**

  učenje ispuhivanja nosa

  ispiranje izotoničnom i hipertoničnom otopinom

  vazokonstriktor (od 2 godine života, efedrin zabranjen!!)

- **Antibiotik**

Antibiotik treba odmah primijeniti:

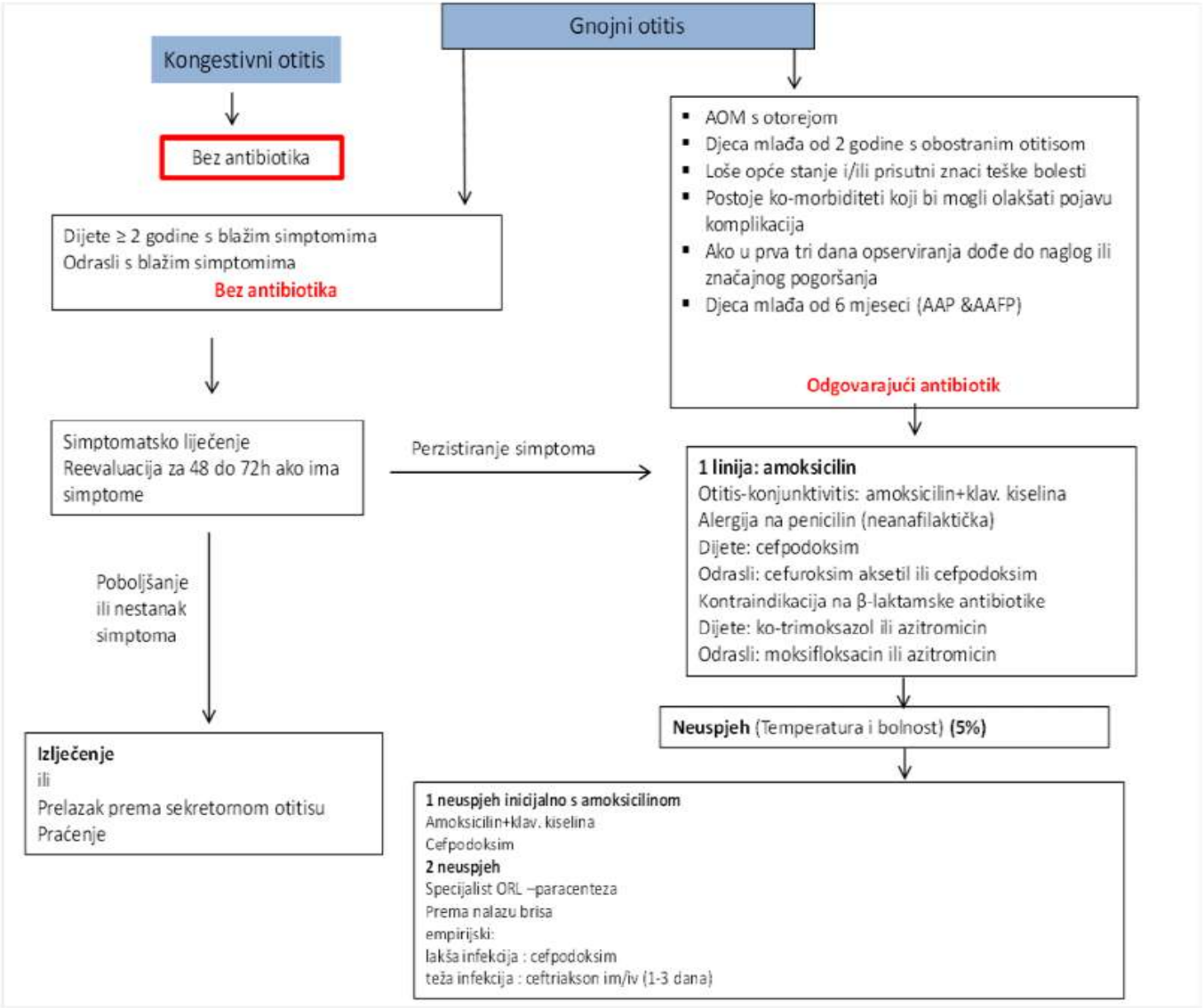
1. Kod AOM s otorejom (perforacijom bubnjića)
2. Kod djece mlađe od 2 godine s obostranim otitisom
3. Ako je opće stanje jako loše i/ili su prisutni znaci teške bolesti
4. Ako postoje ko-morbiditeti koji bi mogli olakšati pojavu komplikacija
5. Ako treći dan ne dolazi do spontanog poboljšanja
6. Ako u prva tri dana opservacije dolazi do naglog ili značajnog pogoršanja

** American Academy of Pediatrics i American Academy of Family Physicians dodatno preporučuju primjenu antibiotika kod djece mlađe od 6 mjeseci*

Smjernice za akutnu upalu srednjeg uha za djecu i odrasle: ambulantno i bolničko liječenje (HDORL, 2020.)

Lana Kovač Bilić, Robert Trotić, Arijana Tambić Andrašević, Krsto Dawidowsky, Darija Birtić, Marko Velepič, Željka Roje, Hrvoje Tiljak, Sanja Dorner

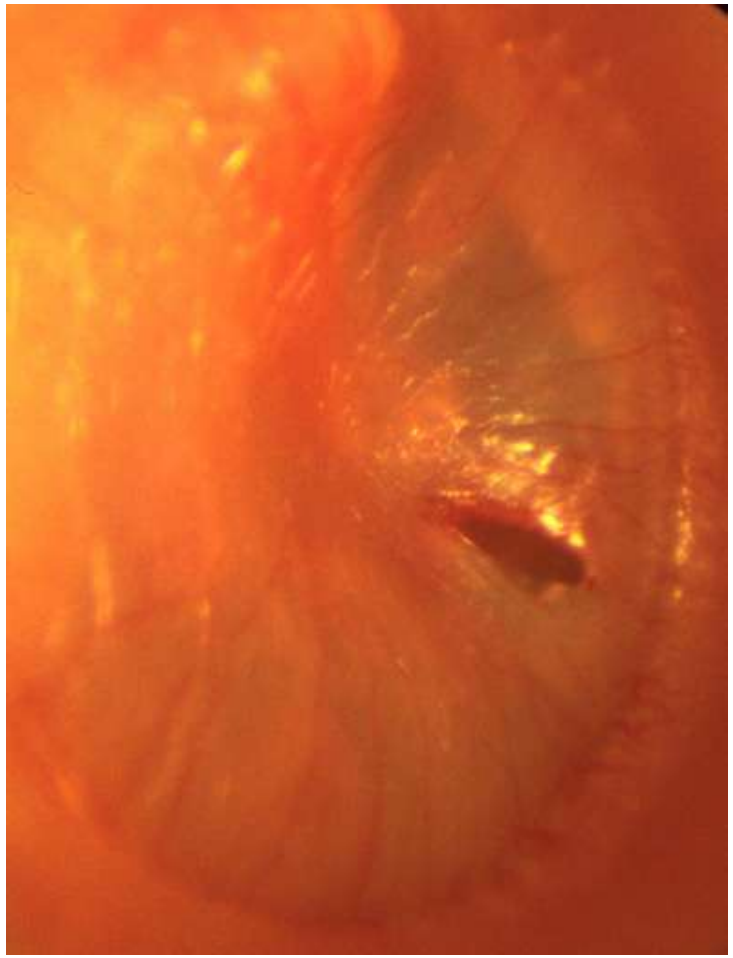
https://hrcak.srce.hr/file/354995



POTREBA ZA ORL PREGLEDOM

- Dijete < 2 godine bez mogućnosti vizualizacije bubnjića
- Potreba za paracentezom
- Kronična upala; sekretorni otitis koji traje > 3 mjeseca

PARACENTEZA



- **Nedonošče**
- Dijete ≤ 3 mjeseca
- Izrazita bolnost sa izbočenim bubnjićem
- Rezistencija nakon drugog antibiotika
- Rezistencija nakon prvog antibiotika koji nije amoksicilin
- **Komplikacija otitisa; mastoiditis, meningitis**
- **Imunološki deficit**

KRONIČNA UPALA SREDNJEG UHA

MEE (Middle Ear Effusion)

AOM
(Acute Otitis Media)

- akutna upala, izljev u srednje uho, simptomi upale i bolovi
- akutni miringitis
- akutna upala sa kongestijom

COME
(Chronic Otitis Media with Effusion)

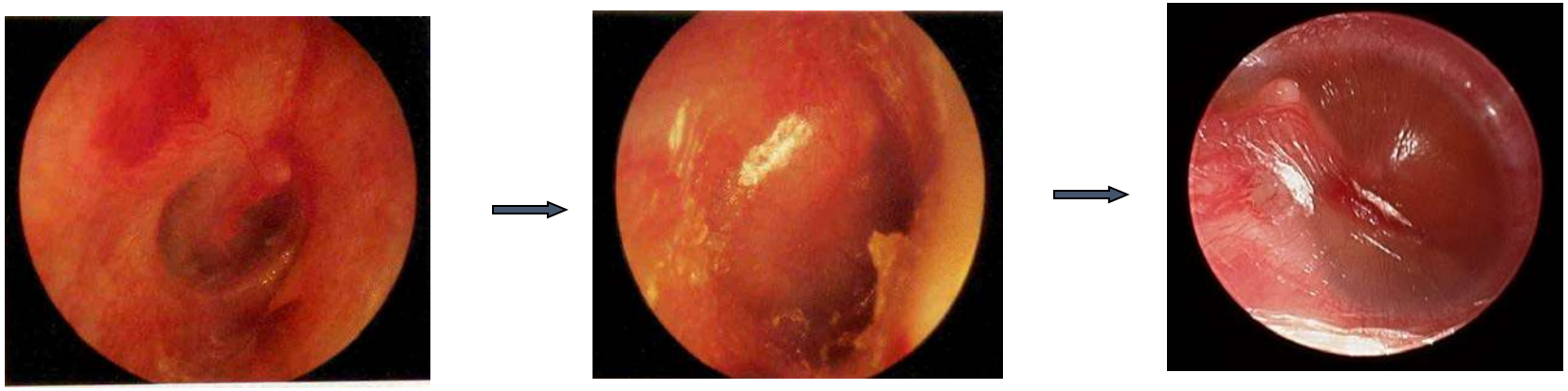
- izljev u srednje uho bez simptoma upale, zatvoren bubnjić, metaplazija epitela sluznice srednjeg uha

Trajanje MEE (Bluestone)

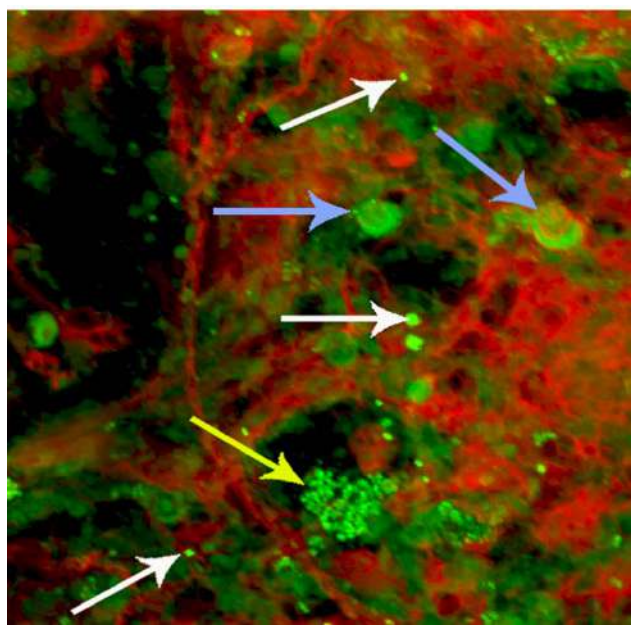
- akutno – do 3 tjedna
- subakutno – od 3 tjedna do 2 mjeseca
- kronično – dulje od 3 mjeseca

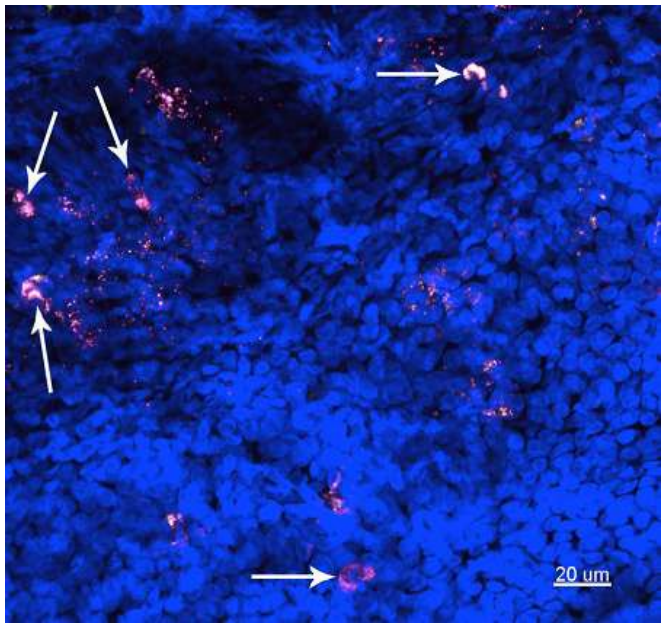
SEKRETORNI OTITIS (COME, Glue ear)

- Prevalencija SO je 25-40% kod djece od 1-5 godina
- SO je direktna posljedica upale i lokalnog imunološkog odgovora
- upala aktivirana imunološkom reakcijom na patogen manje izražena bez akutnih upalnih znakova sa retrotimpaničnim izljevom

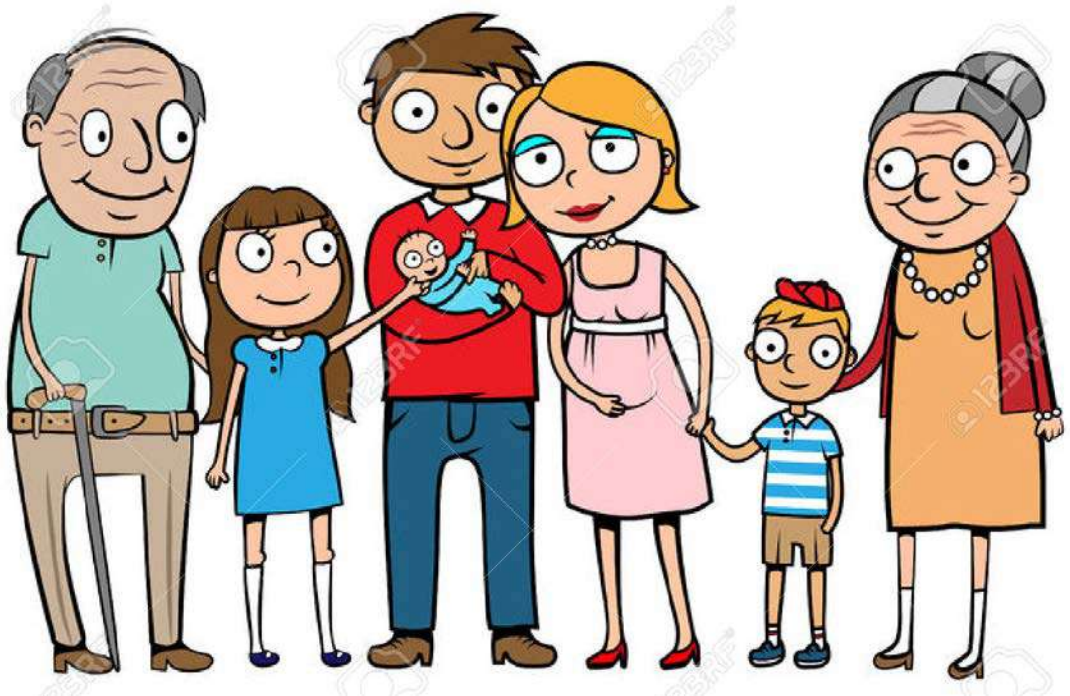


- **proteini** (glikoproteini, gamaglobulini, kolagenaze, metalproteinaze), **upalne stanice** (polinukleari, limfociti) i **medijatori upale**
- najčešće sterilan, kultura bakterija negativna u 75% slučajeva - PCR bakterijski genom 94% - **biofilm**
- **perzistiranje intracelularne bakterijske infekcije!! (Thornton 2010)**





- **predispozicije** - promjene u mukocilijarnom transportu, metaplazija u sekretorni epitel, promjene u transepitelijalnom transportu, pojačana izmjena plinova
- **obiteljska predispozicija** – 2,6 x, geni regulatori upala



DIJAGNOSTIKA SEKRETORNOG OTITISA

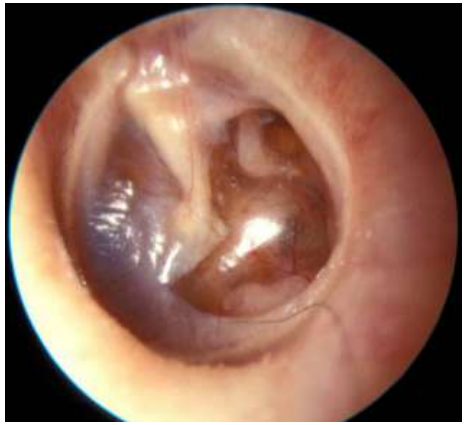
- Anamneza

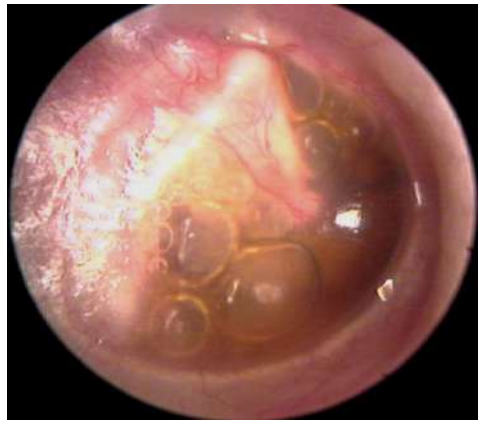
  slabiji sluh primjećuje okolina, zaostajanje u razvoju govora, problemi u školi, problemi ponašanja, problemi sna
- Otoskopija – endoskop, mikroskop

  stanjen bubnjić, posterosuperiorna retrakcija
- Ostali ORL status

  submukozni rascjep, morfološki aspekt (sindrom)

  alergija, fiberskopija epifarinksa





https://hrcak.srce.hr/file/355209

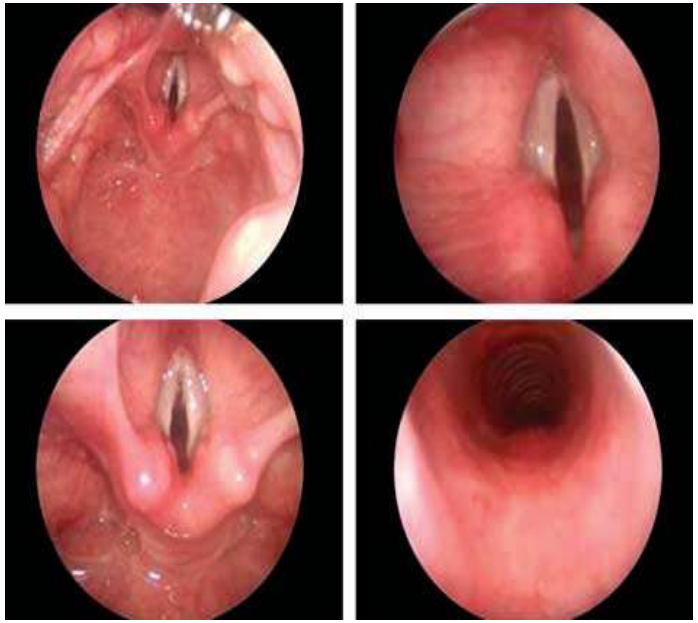
Dijagnostika SO temelji se na postojanju retrotimpaničkog izljeva u trajanju **duže od 3 mjeseca**.

Dijagnoza se postavlja **otoskopijom i timpanometrijom**, samo otoskopijom kod evidentnih nalaza, te pneumatskom otoskopijom.

Audiometrija, barem u slobodnom polju, preporuča se kod djece s SO, a koja imaju zaostajanje u govoru, probleme u školi, probleme s ravnotežom.

Preporuča se **ABR ili ASSR** nakon postavljanja cjevčica ukoliko se ne može učiniti audiometrija ili su nalazi audiometrije u slobodnom polju izuzetno loši

- Dijagnostika LPR opravdana je samo ako kod teških oblika SO postoje evidentni simptomi LPR kod djece starije od 7 godina ili ako su prisutni recidivirajući laringitisi ili rinosinuitisi.

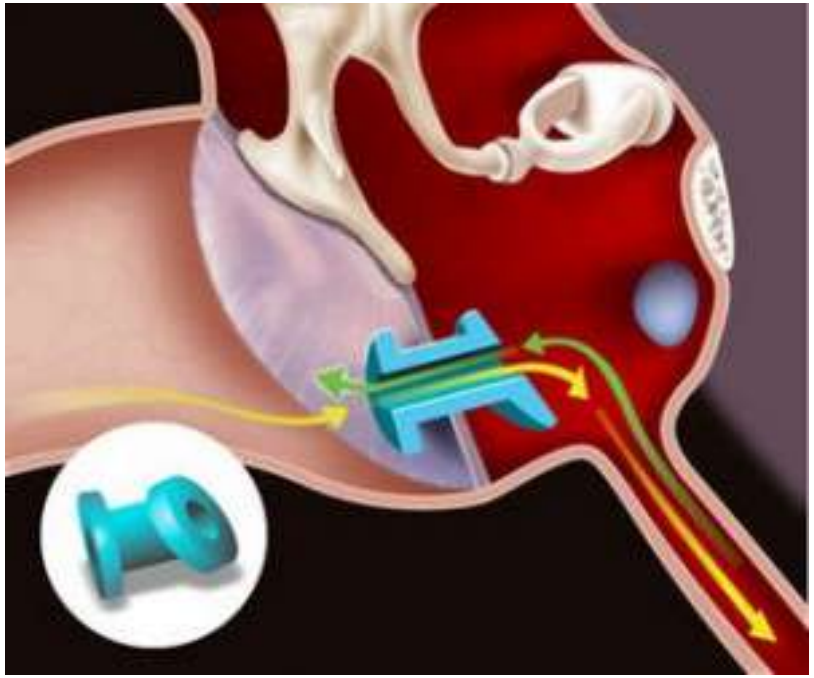


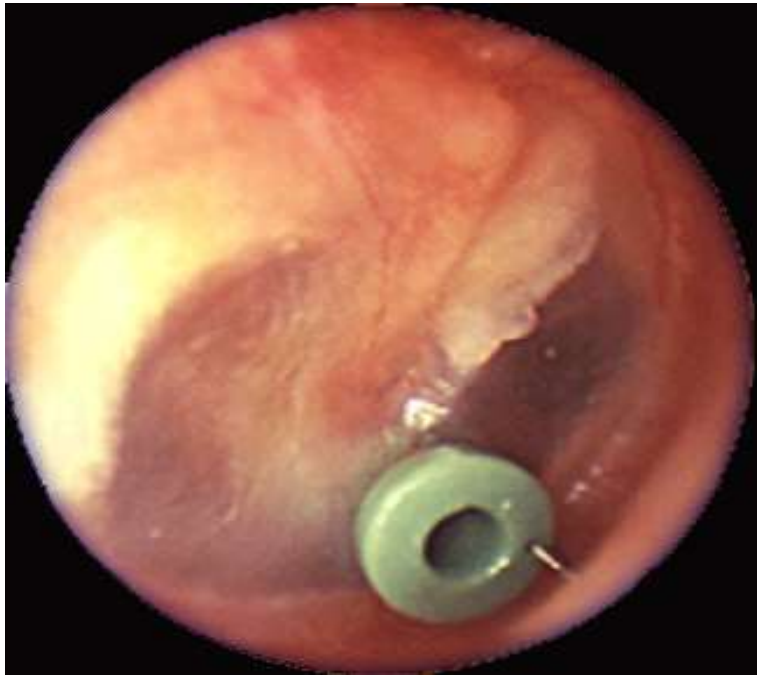
- Logopedska obrada preporuča se samo nakon liječenja SO kod djece sa preoperativnom sumnjom na zaostajanje u razvoju govora i zaostajanje u čitanju.

- Alergološka obrada opravdana je samo ukoliko je SO povezan sa astmom i/ili kroničnim rinitisom.

- Radiološka obrada nije potrebna u dijagnostici i liječenju nekompliciranih oblika SO

VENTILACIJSKE CJEVČICE



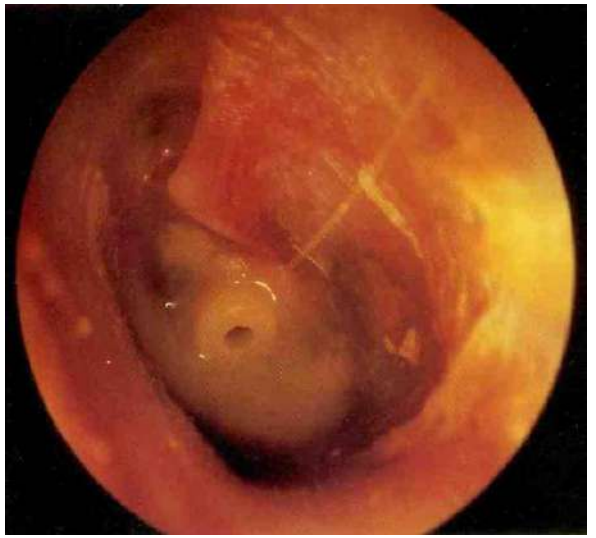


VENTILACIJSKE CJEVČICE

Transtimpaničke ventilacijske cjevčice normaliziraju sluh ako su na mjestu i uredno prohodne.

Transtimpaničke ventilacijske cjevčice smanjuju učestalost akutne upale srednjeg uha kod djece mlađe od 3 godine.

Sekrecija iz uha nakon postavljanja ventilacijskih cjevčica liječi se lokalno antibiotskim kapima.

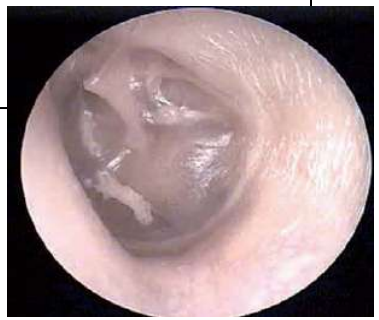


VENTILACIJSKE CJEVČICE

- Transtimpaničke ventilacijske cjevčice imaju preventivnu ulogu u nastanku kronične upale uha sa kolesteatomom.

- Miringoskleroza (10%) i lokalizirana atrofija bubnjića (14%) su češće nakon postavljanja cjevčica. Miringoskleroza je strukturna promjena bubnjića i ne utječe na situaciju u srednjem uhu a lokalizirana atrofija bubnjića samo izuzetno rijetko može dovesti do retrakcijskog džepa i/ili kolestetoma.

- Jatrogene komplikacije postavljanja ventilacijskih cjevčica vrlo često su povezane sa napredovanjem osnovne bolesti što se mora jasno objasniti roditeljima preoperativno



- SO samo ukoliko postoji retrotimpanički izljev duže od 3 mjeseca

- Lijekovi mogu kratkotrajno smanjiti simptome ali nemaju učinka na duže vrijeme (> 2 mjeseca)
  Smanjuju simptome dok ili ne dođe do spontanog izlječenja ili kirurškog djelovanja

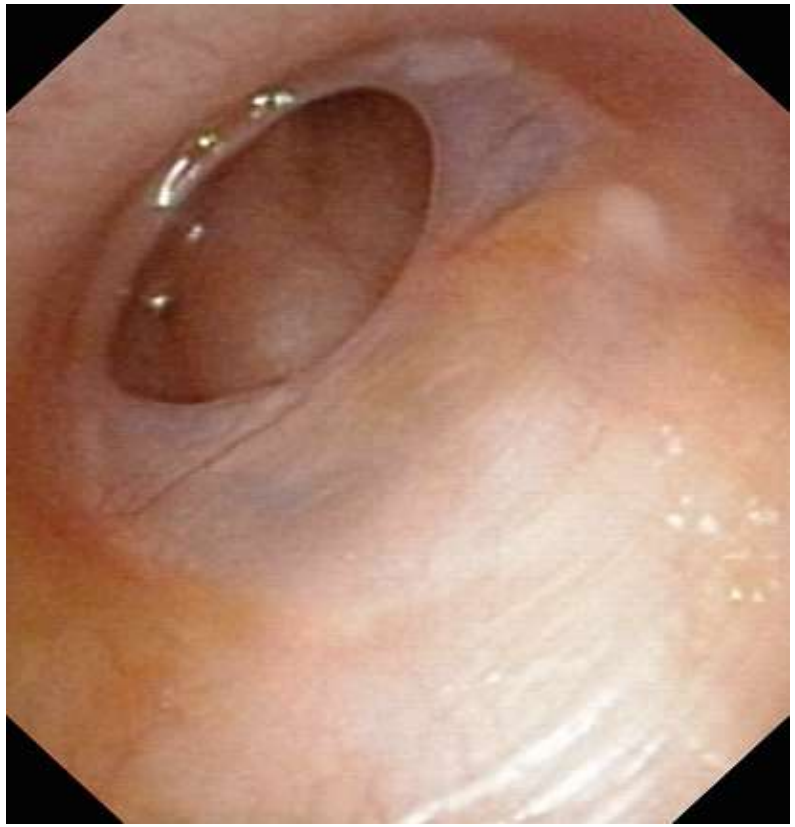
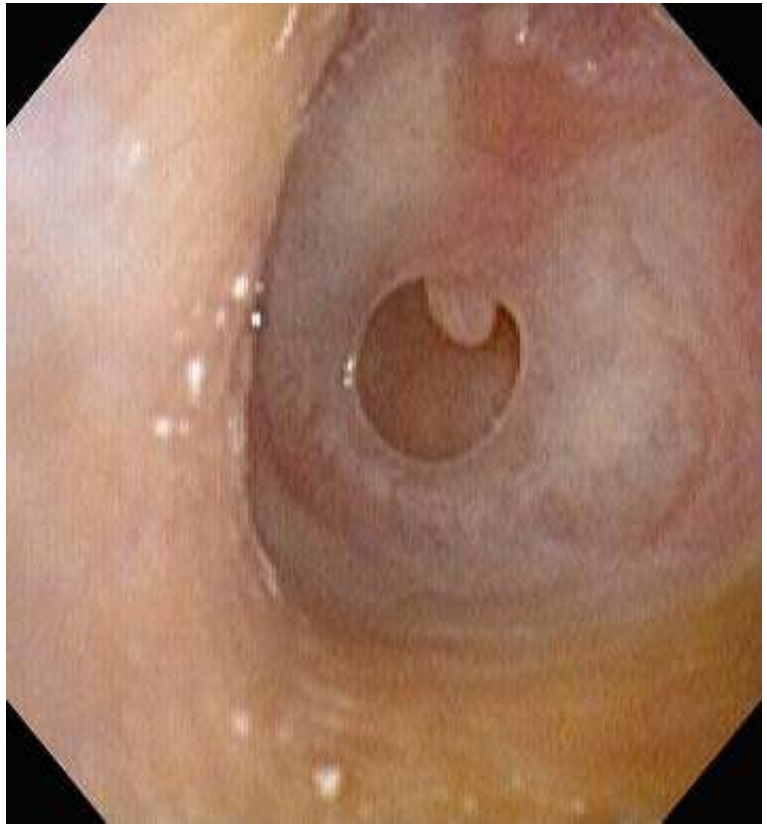
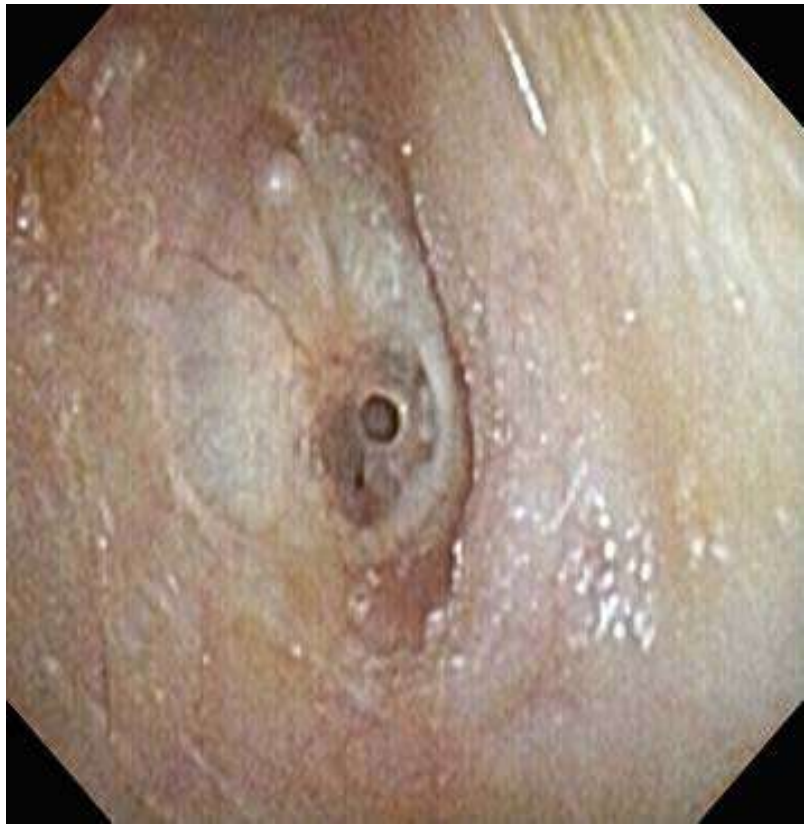
- Ventilacijske cjevčice
  Provodna ili mješovita nagluhost > 30 dB na boljem uhu
  Posteriorna mezotimpanička retrakcija s SO
  Recidivirajuće akutne upale uha kod djece mlađe od 3 godine(3 epizode u 6mj, 4 u godinu dana)

- Adenoidektomija uz ventilacijske cjevčice
  Kod djece starije od 4 godine ukoliko su adenoidne vegetacije dokazane fiberskopijom ili tijekom ugradnje cjevčica
  Kod simptomatske opstruktivne adenoidne hipertrofije kod djece mlađe od 4 godine

- Poseban oprez kod djece s kraniofacijalnim malformacijama (rascjepi, trisomija 21, ..) – praćenje svakih 6 mjeseci do 6 godina i dalje jednom godišnje.

- SO kod djece starije od 7 godina – LPR, alergije, ..

KRONIČNA UPALA SREDNJEG UHA S PERFORACIJOM BUBNJIĆA

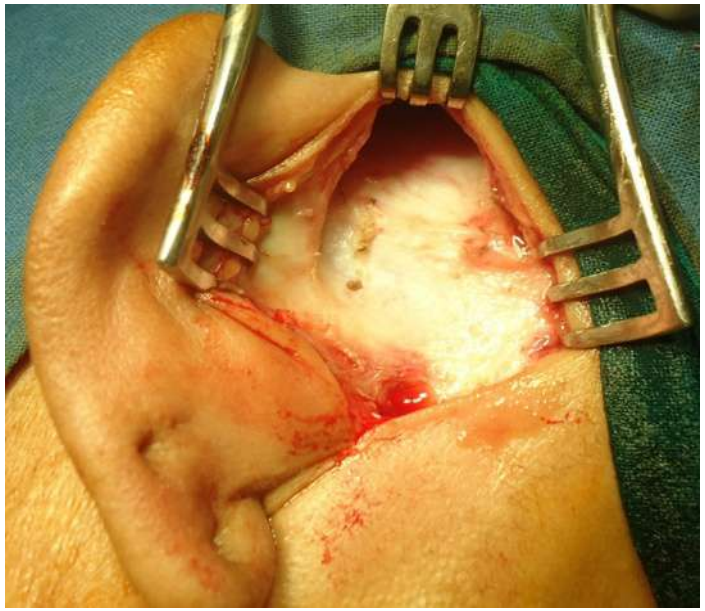
ETIOLOGIJA

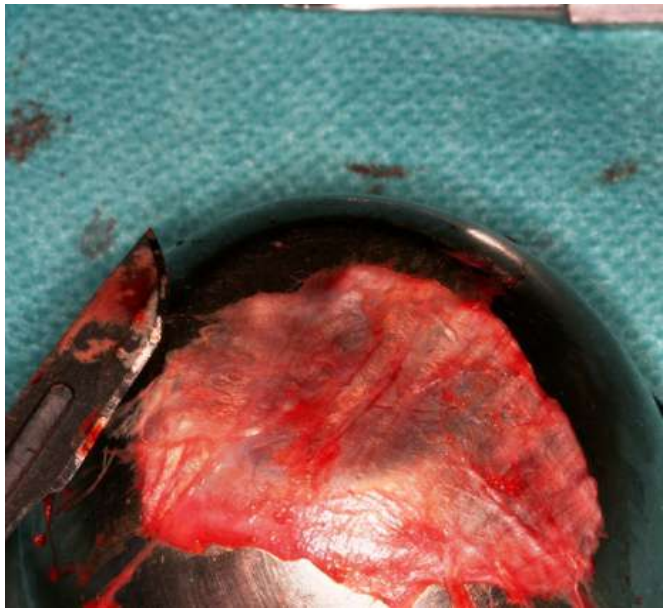
- *P. aeruginosa, S. aureus*

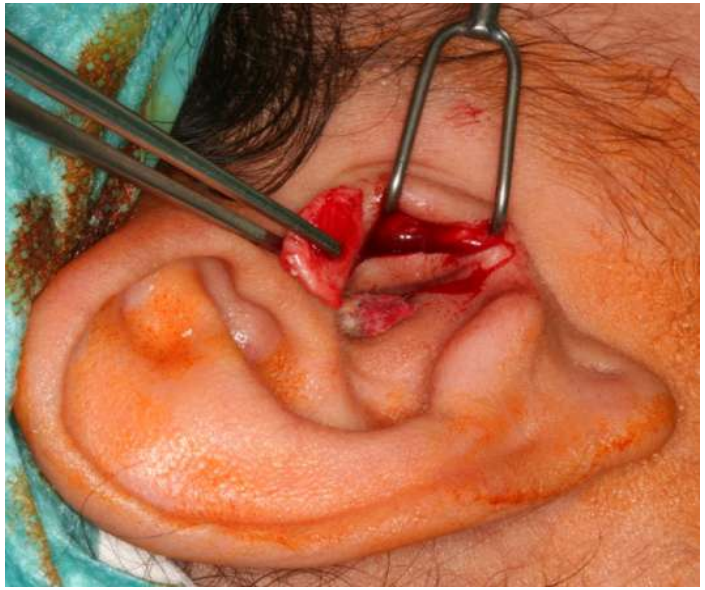
- Sekrecija - peroralni antibiotik – ciprofloksacin
  - antibiotske kapi (Ciloxan)

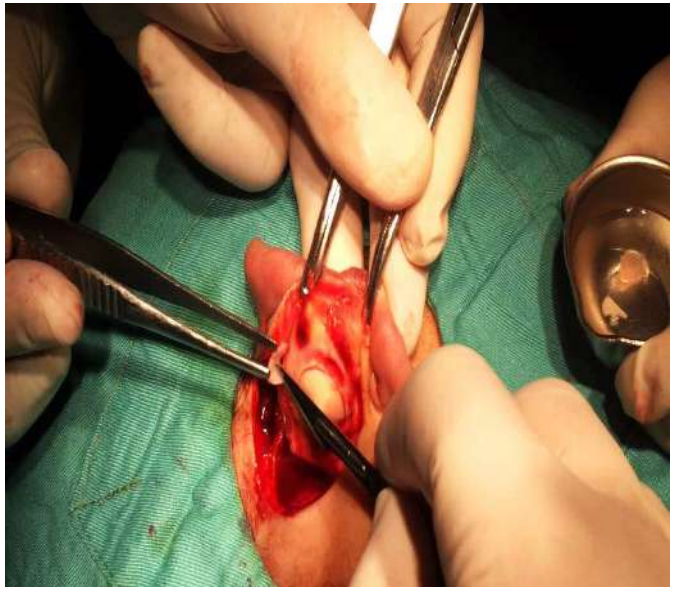
- Kirurgija srednjeg uha – zatvaranje defekta bubnjića

- **Pristupi na uho**
  - Transkanalni ili transmeatalni
  - Endauralni
  - Retroaurikularni
- **Materijal**
  - Fascija temporalnog mišića
  - Perihondrij tragusa
  - Hrskavica tragusa i konhe

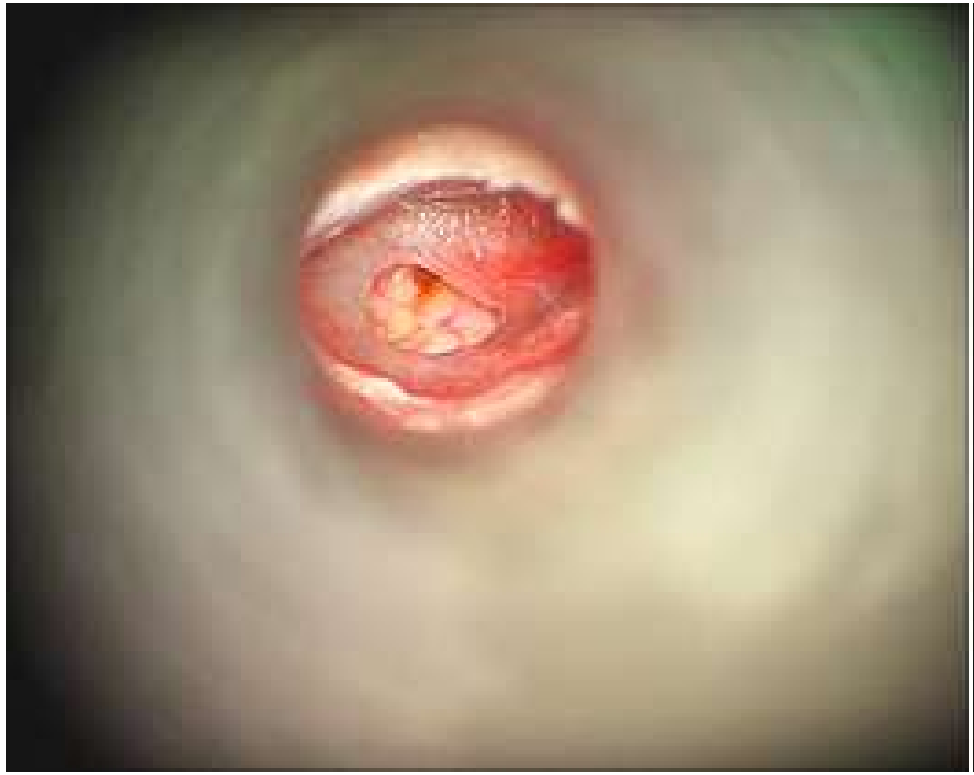


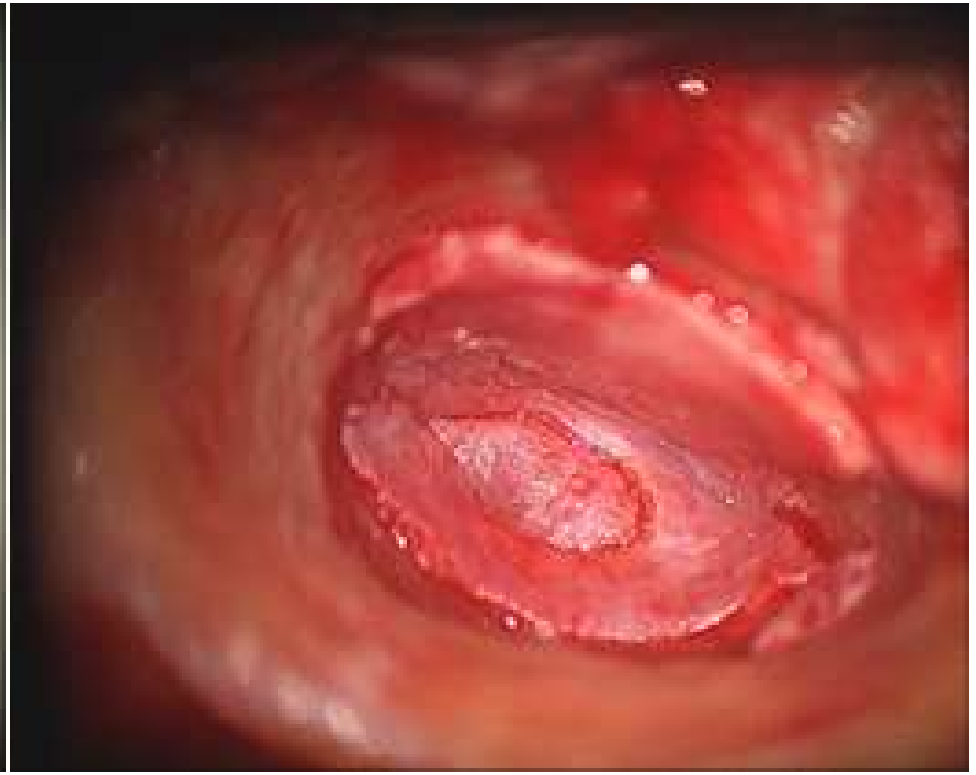






TIMPANOPLASTIKA





RETRAKCIJSKI DŽEP

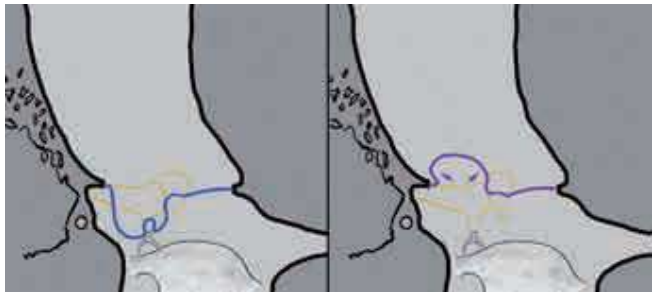
- retrakcijski džep ima kliničku važnost u nastanku kolesteatoma stoga je rana i točna dijagnoza te adekvatno liječenje ključno u prevenciji nastanka kolesteatoma srednjeg uha
- **dio bubnjića ili cijeli bubnjić se zbog atrofije središnjeg, fibroznog sloja uvlači prema medijalnom djelu bubnjišta**

RIZICI NASTANKA RETRAKCIJSKOG DŽEPA

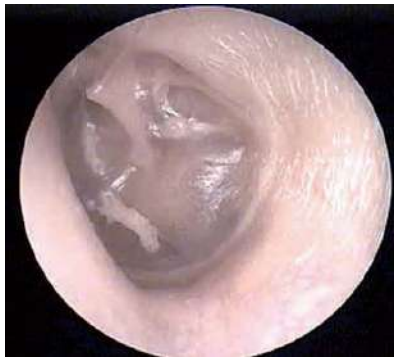
- česte upale uha
- rano pojavljivanje prve upale uha
- serozni otitis koji se javlja u dobi starijoj od 7 godina
- obiteljska anamneza seroznih otitisa

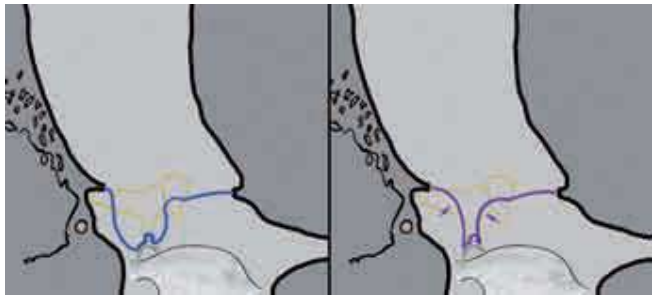
- alergijski rinitis, rascjep nepca, trisomija 21, kraniofacijalne malformacije

PODJELA RETRAKCIJSKOG DŽEPA

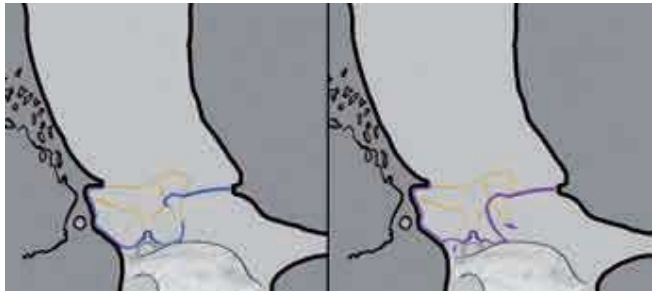


Tip I
kontrolirajući, nefiksiran

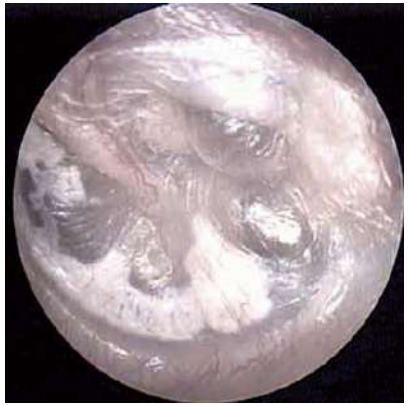




Tip II
kontrolirajući, fiksiran



Tip III
nekontrolirajući, fiksiran



RAZVOJ RETRAKCIJSKOG DŽEPA

1. Stabilan retrakcijski džep

- nije marginalan
- zdrava koža
- nema fiksacije
- nema simptoma

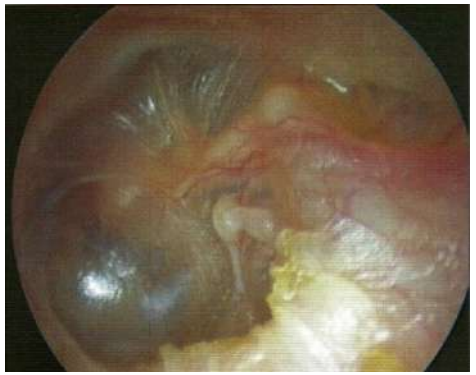
2. Potencijalno nestabilan retrakcijski džep

- pars flaccida, posterosuperorni dio
- adheriran uz koščice
- minimalni simptomi (do 20 dB)

3. Opasan retrakcijski džep ("prekolesteatom")

- izloženost kože
- diskeratoza ("vulkanska erupcija")
- erozija koščica
- gnojna sekrecija

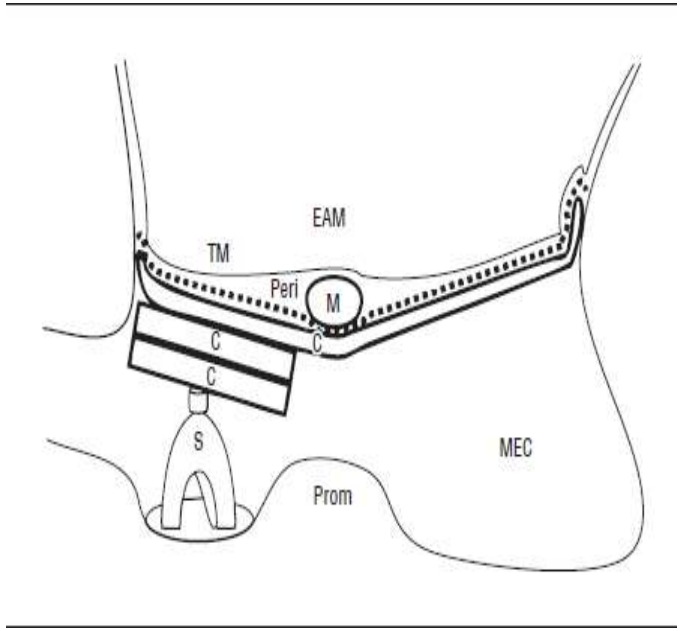
4. Kolesteatom

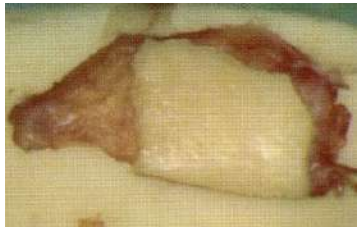


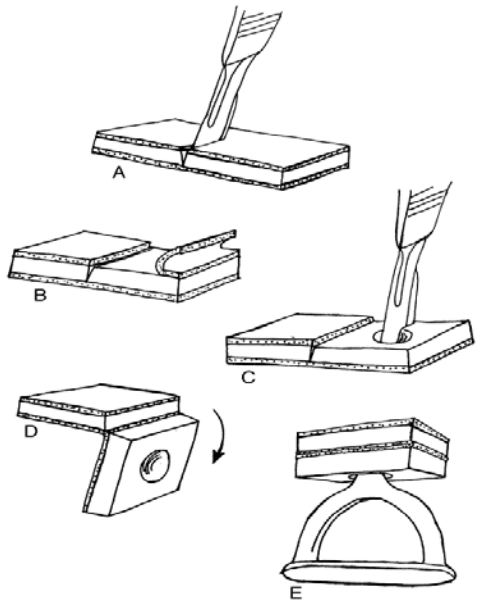
LIJEČENJE RETRAKCIJSKOG DŽEPA

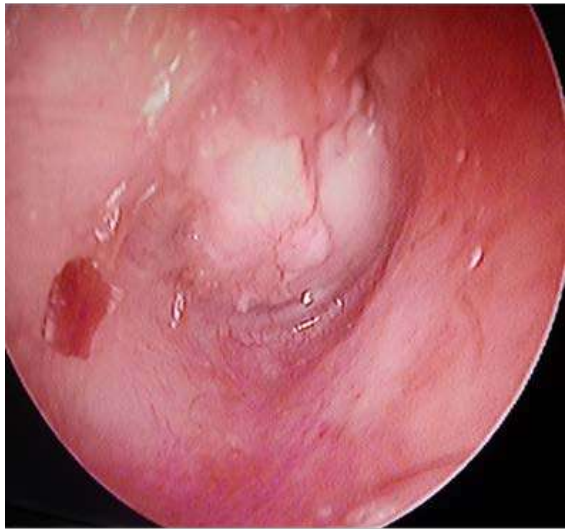
- odluka o kirurškom liječenju povezana je s tim da simptomi u ranom stadiju kao i u uznapredovalom stadiju bolesti mogu biti minimalni
- kirurgija u uznapredovalom stadiju bolesti sa provodnom nagluhošću
- **“preventivna timpanoplastika”**
- ukoliko postoji serozni otitis obavezna ventilacijska cjevčica
- tehnika “plato dvostrukom hrskavicom” (double cartilage plate)

LIJEČENJE RETRAKCIJSKOG DŽEPA



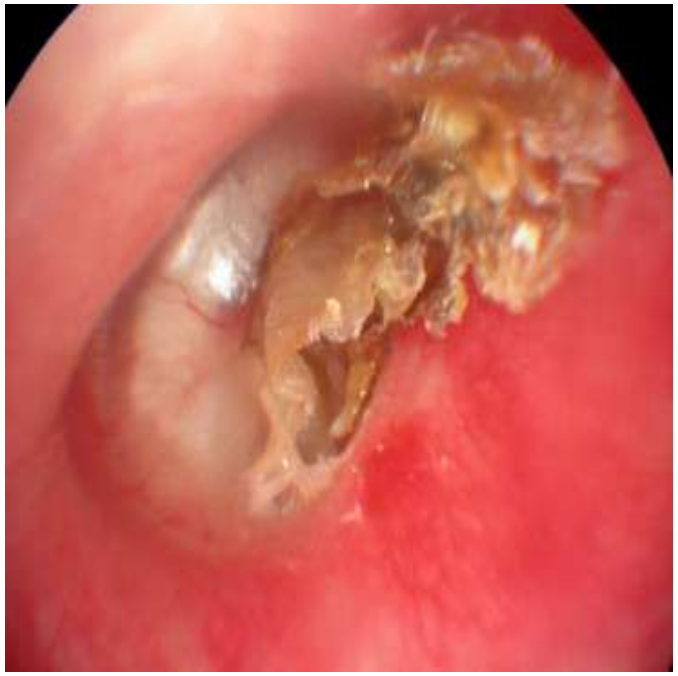


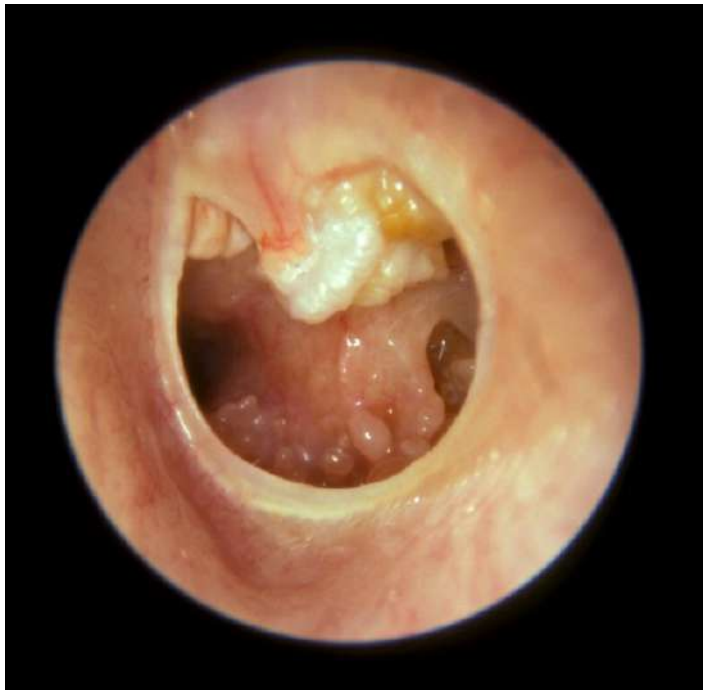


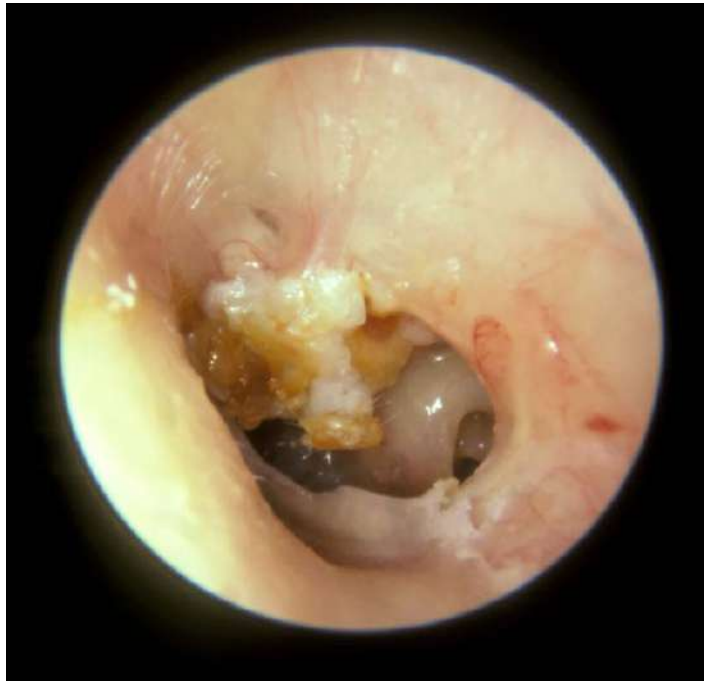


KOLESTEATOM

P. aeruginosa, S. aureus

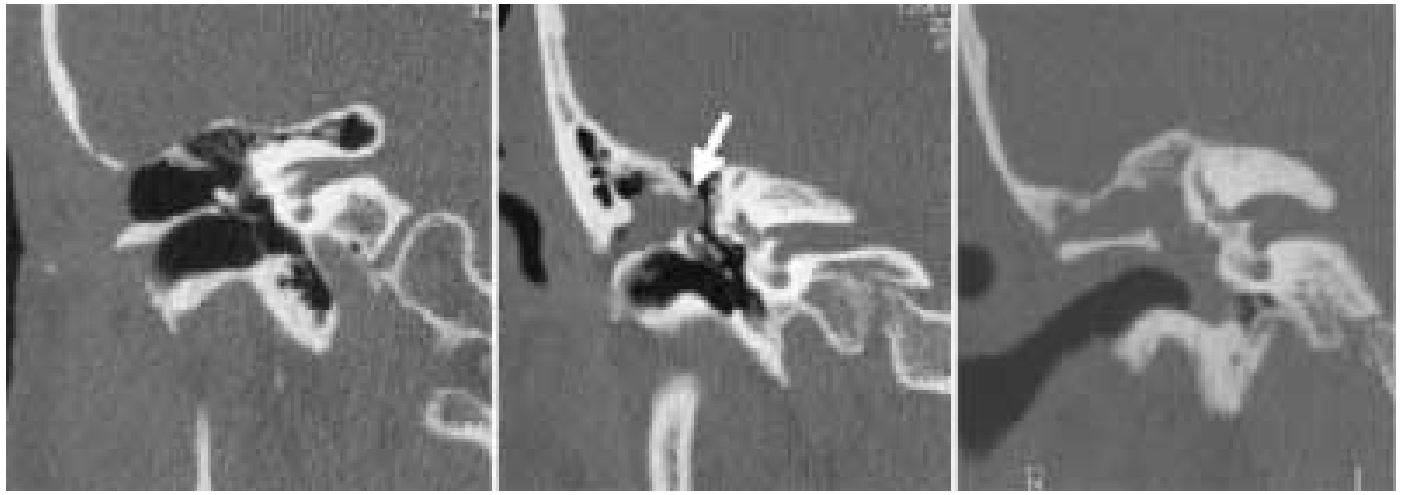






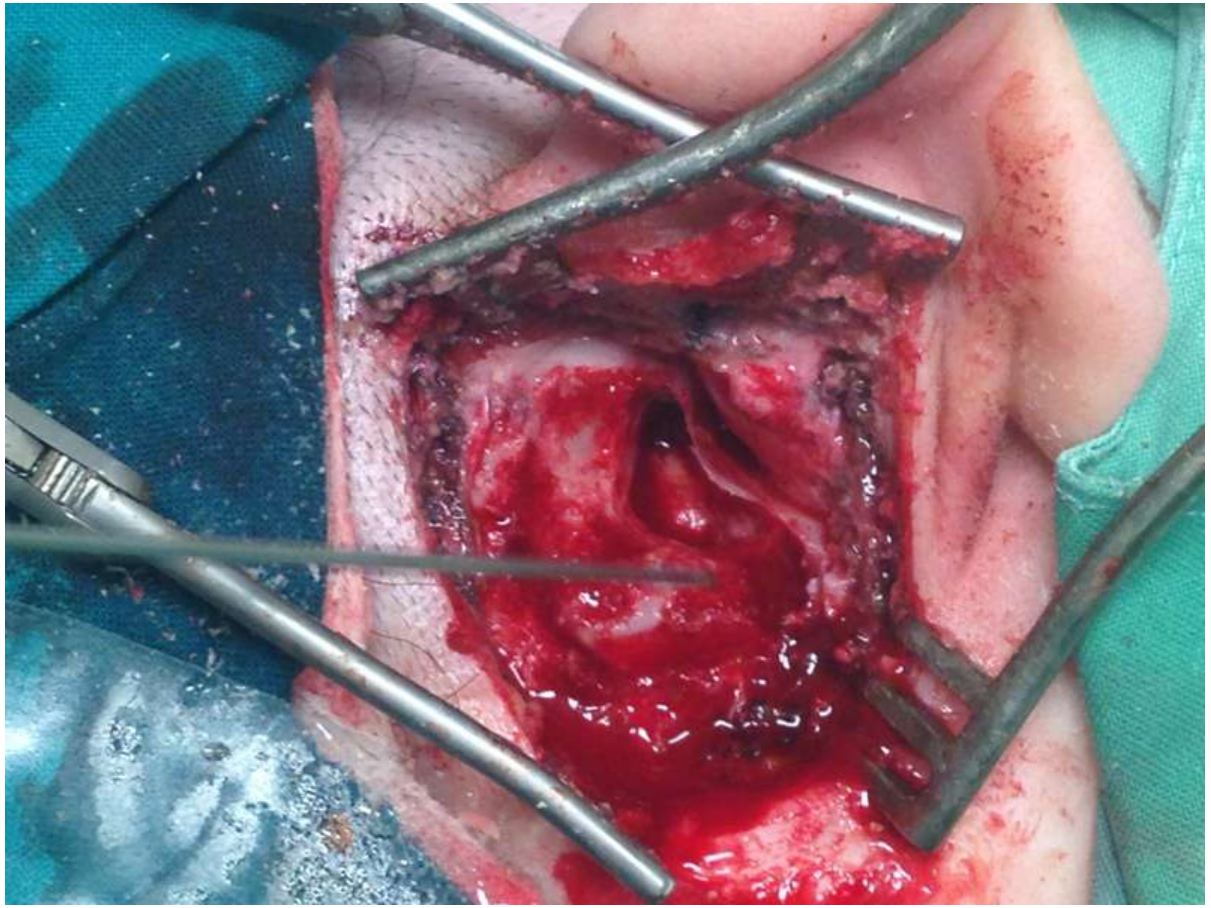
LIJEČENJE KOLESTEATOMA

- Sekrecija - peroralni antibiotik – ciprofloksacin
  - antibiotske kapi (Ciloxan)
- Kirurgija srednjeg uha – odstranjenje kolesteatoma i rekonstrukcija lanca slušnih koščica
- Radiološka obrada – CT indicirana kod djece i sumnje na kolesteatom



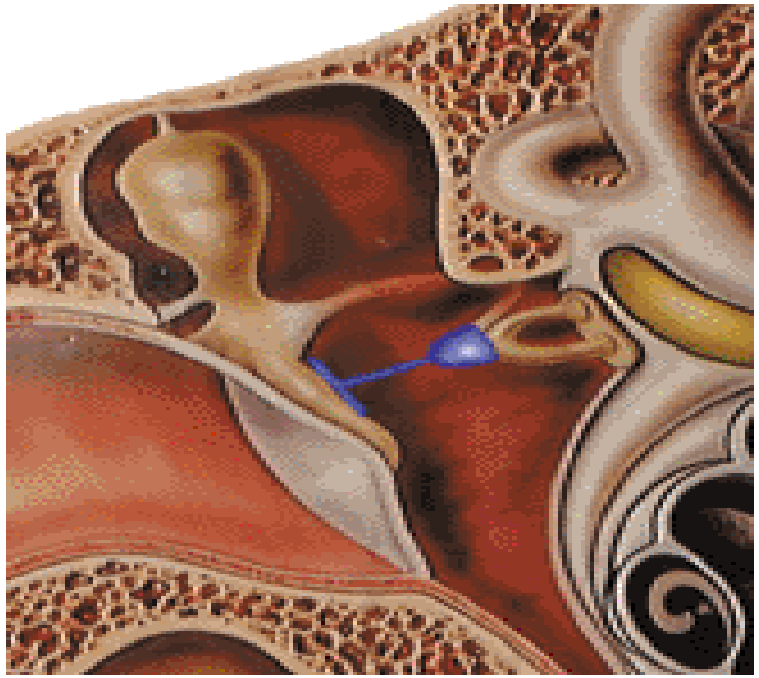
LIJEČENJE KOLESTEATOMA

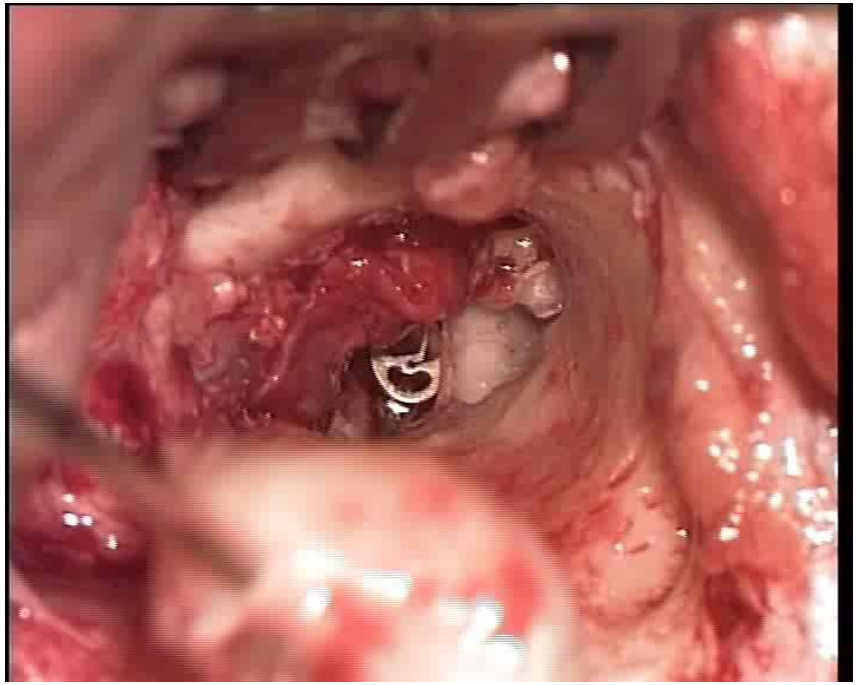
Mastoidektomija s odstranjenjem kolestetoma



LIJEČENJE KOLESTEATOMA

Rekonstrukcija lanca slušnih koščica uz ostatni stapes

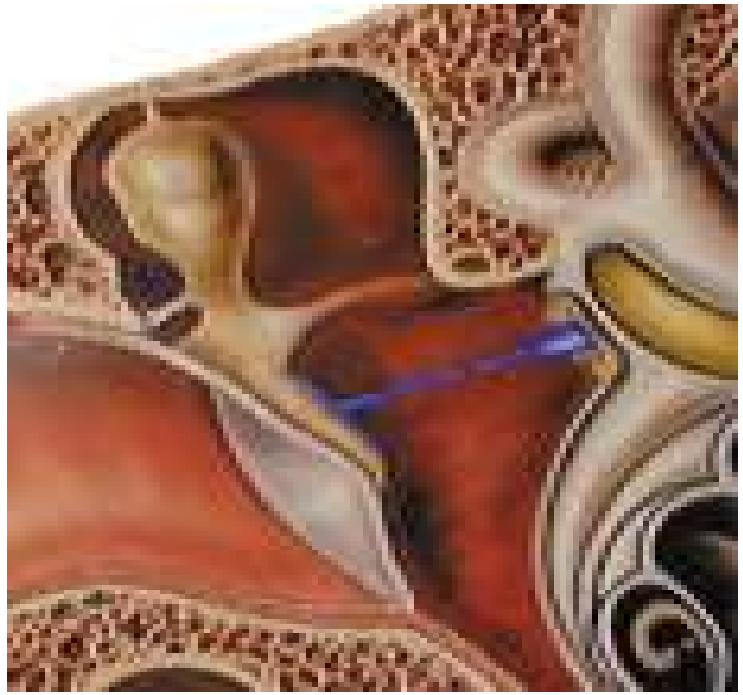


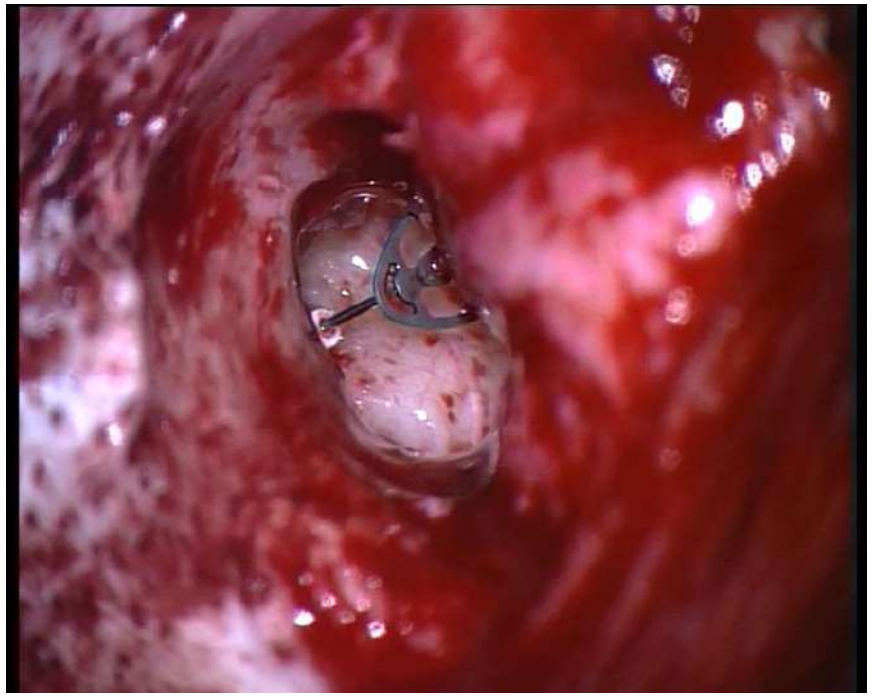


PORP – Partial ossicular replacement prosthesis

LIJEČENJE KOLESTEATOMA

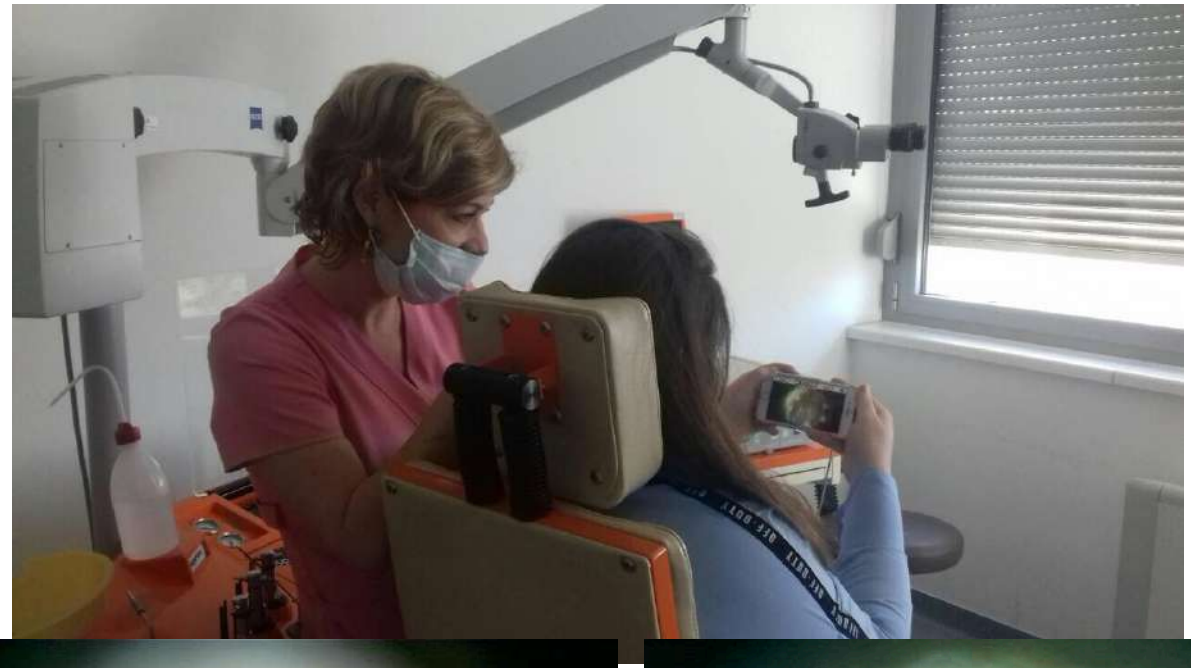
Rekonstrukcija lanca slušnih koščica bez stapesa

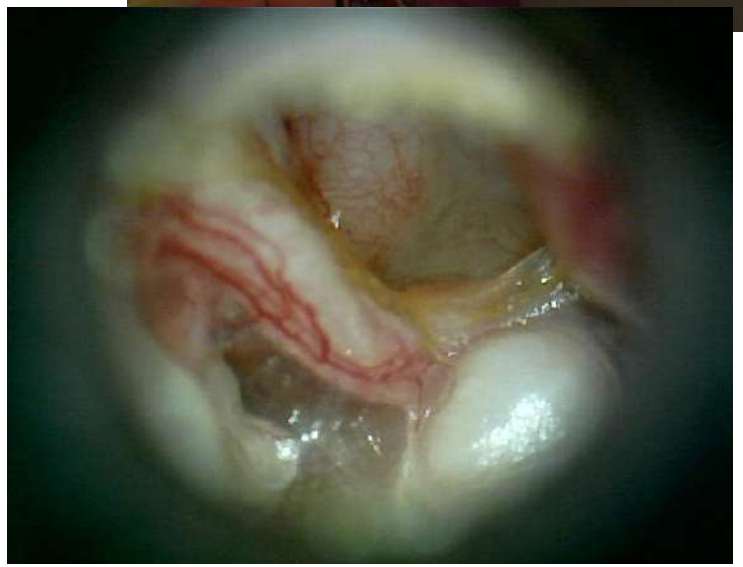


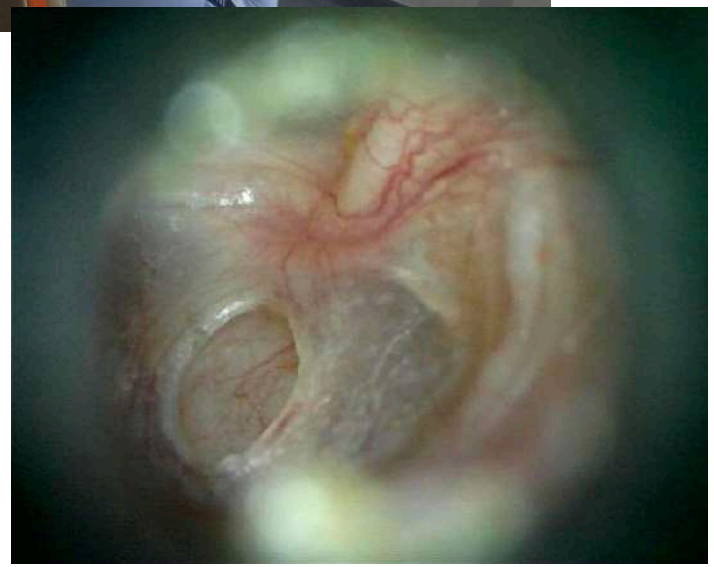


TORP – Total ossicular replacement prosthesis

NOVOSTI U OTOLOŠKOJ DIJAGNOSTICI







The art of medicine consists in amusing the patient while nature cures the disease.
Voltaire

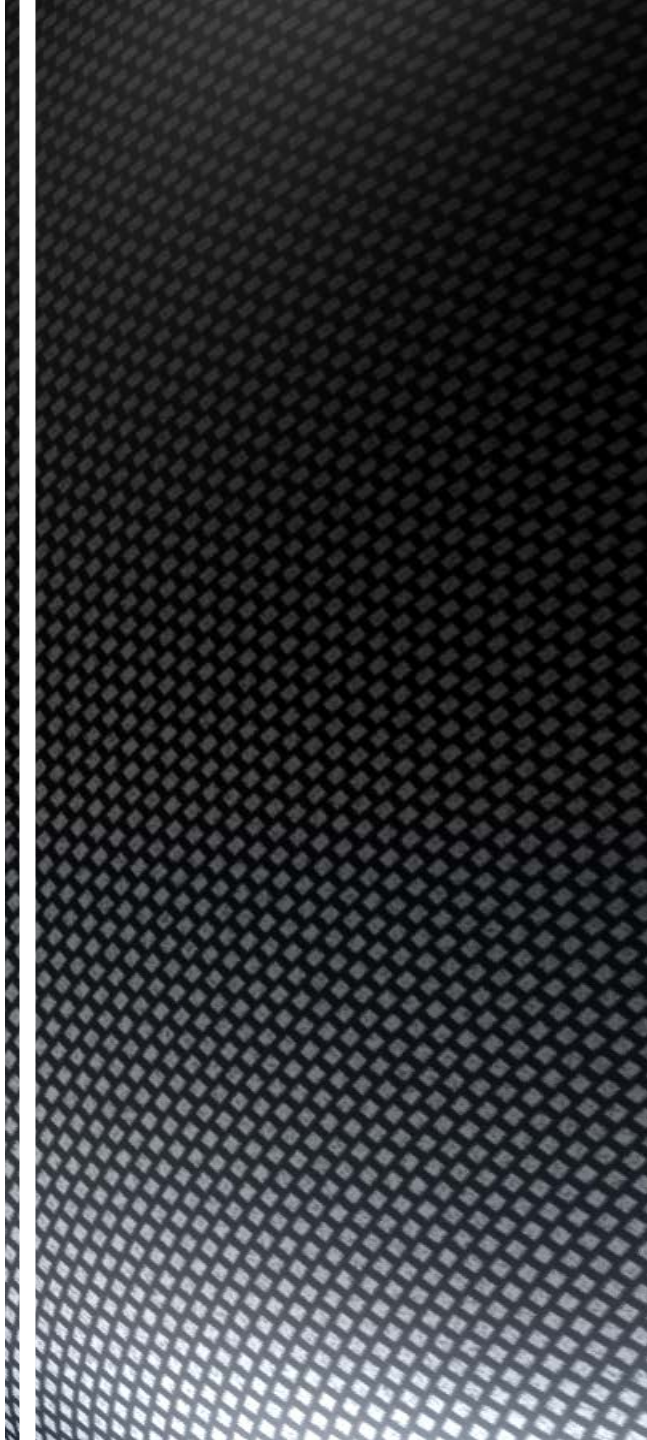
SUVREMENE SPOZNAJE O EPIDEMIOLOGIJI, KLINIČKOJ SLICI, LABORATORIJSKOJ DIJAGNOSTICI, TERAPIJI I PREVENCIJI RESPIRATORNIH INFEKCIJA

Zagreb, 15. svibanj 2023.

Stručni simpozij

Uzimanje uzoraka, obrada i mikrobiološka dijagnostika respiratornih infekcija

Izv. prof. dr. sc. TOMISLAV MEŠTROVIĆ, dr. med.



Važnost pravilnog uzorkovanja

- **Pravilno uzorkovanje** put prema rezultatima mikrobiološke obrade koji su točni, brzi i klinički relevantni

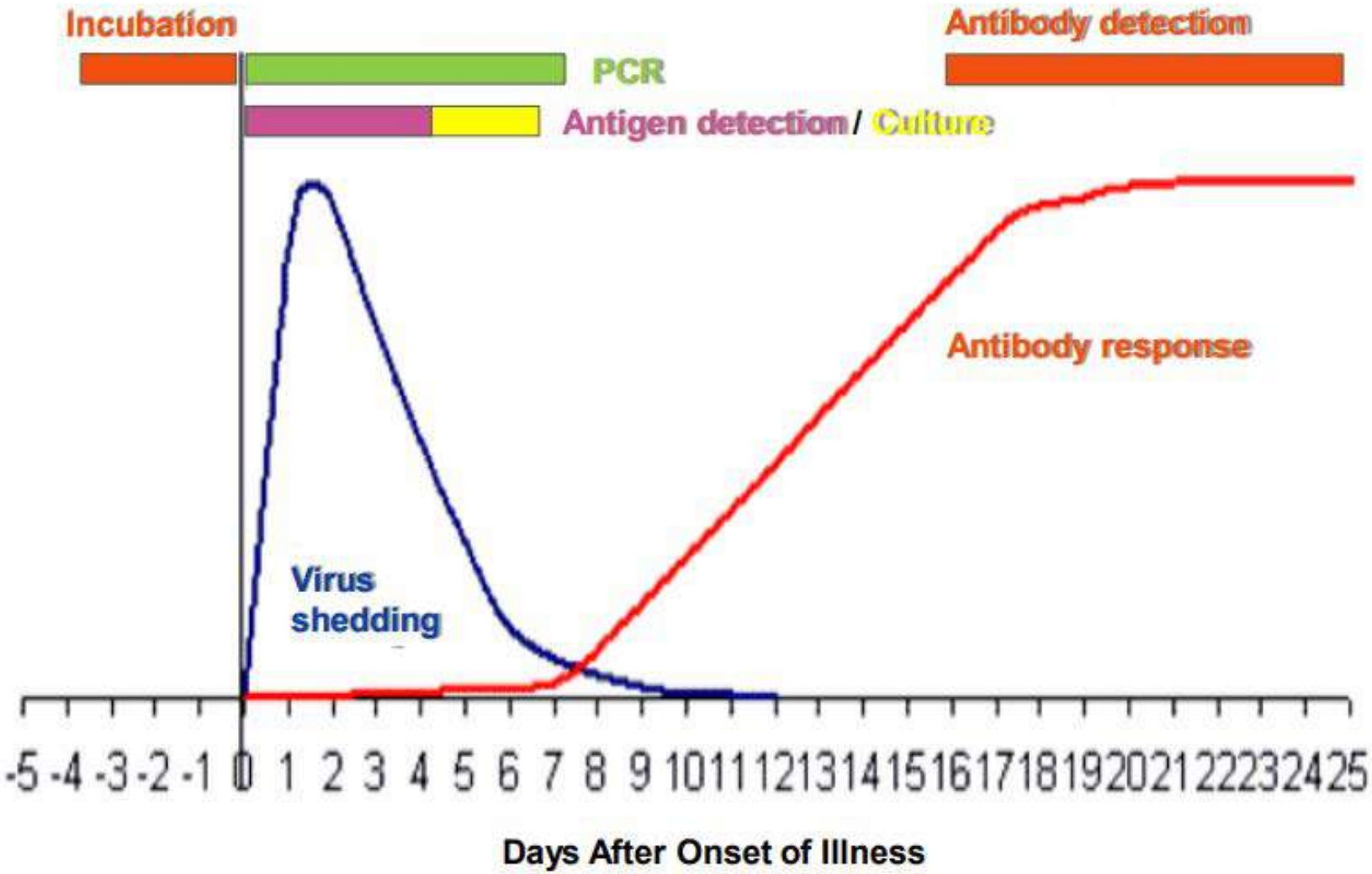
- **Zdravstveni kriterij** – više od polovice lažno negativnih nalaza uzrokovano pogreškama pri uzorkovanju

- **Ekonomski kriterij** – pravilno uzorkovanje maksimizira odnos troškova i djelotvornosti (*cost-effectiveness*)

Opći principi uzorkovanja i dijagnostičke obrade

- Uzorkovanje uvelike ovisi o potencijalnom **uzročniku** kojeg želimo dokazati **i testu** koji će se koristiti
- Uzorak se nerijetko mora uzeti **što prije u tijeku bolesti**
- Kod uzimanja uzoraka valja koristiti **mjere osobne zaštite**
- **Brza i adekvatna** dostava uzoraka radi laboratorijske obrade
- **Individualna interpretacija** rezultata za svakog uzročnika

Kada uzeti uzorak?



Koji uzorak uzeti (smjernice CDC-ja)

CENTERS FOR DISEASE CONTROL AND PREVENTION

LISTS OF RECOMMENDED CLINICAL SPECIMENS TO COLLECT FROM OUTPATIENTS, INPATIENTS, AND FATAL CASES IN THE SETTING OF AN UNEXPLAINED RESPIRATORY DISEASE

The specimens are listed in order of priority; those listed first are those most useful for testing for the greatest number of different pathogens with a single clinical specimen.

OUTPATIENTS

Upper Respiratory
- Nasopharyngeal (NP) and oropharyngeal (OP)
- Nasopharyngeal wash/aspirate

Lower Respiratory
- Sputum

Blood
- Serum: Acute (at onset) and convalescent (3-6 weeks post onset)
- Blood (plasma)

Urine

Stool

INPATIENTS

Lower Respiratory
- Bronchoalveolar lavage, tracheal aspirate, pleural fluid
- Sputum

Upper Respiratory
- Nasopharyngeal (NP) and oropharyngeal (OP) swabs
- Nasopharyngeal wash/aspirate

Blood
- Serum: Acute (at onset) and convalescent (3-6 weeks post onset)
- Whole blood (plasma)

Tissue (e.g., lung)

Urine

Stool

FATAL CASES

All available premortem specimens

Tissue
- Fixed tissue from all major organs (e.g., lung, heart, spleen, liver, brain, kidney, adrenals)
- Non-fixed tissue from lung and upper airways (e.g., trachea, bronchus)

Lower Respiratory
- Bronchoalveolar lavage, tracheal aspirate, pleural fluid
- Sputum

Blood
- Serum
- Blood (plasma)

Deep lung swab for bacterial culture

DEPARTMENT OF HEALTH & HUMAN SERVICES • USA

Održavanje i transport uzoraka

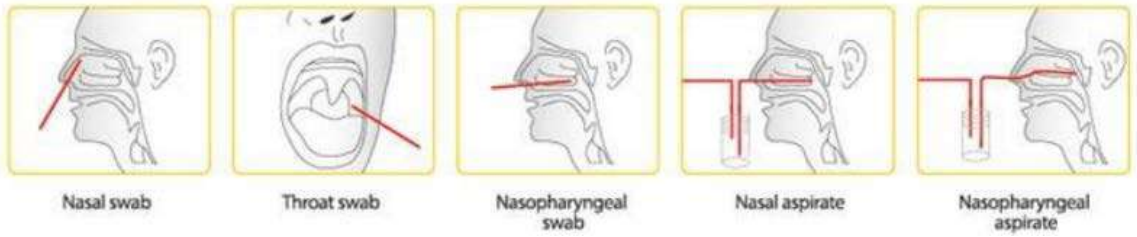
- Spremnike s uzorcima **adekvatno označiti:** ime i prezime pacijenta, identifikacijski broj, vrsta uzorka, datum i vrijeme

- Spremnici nepropusni i u plastičnim vrećicama sa zasebnim odjeljkom za eventualnu dokumentaciju pacijenta

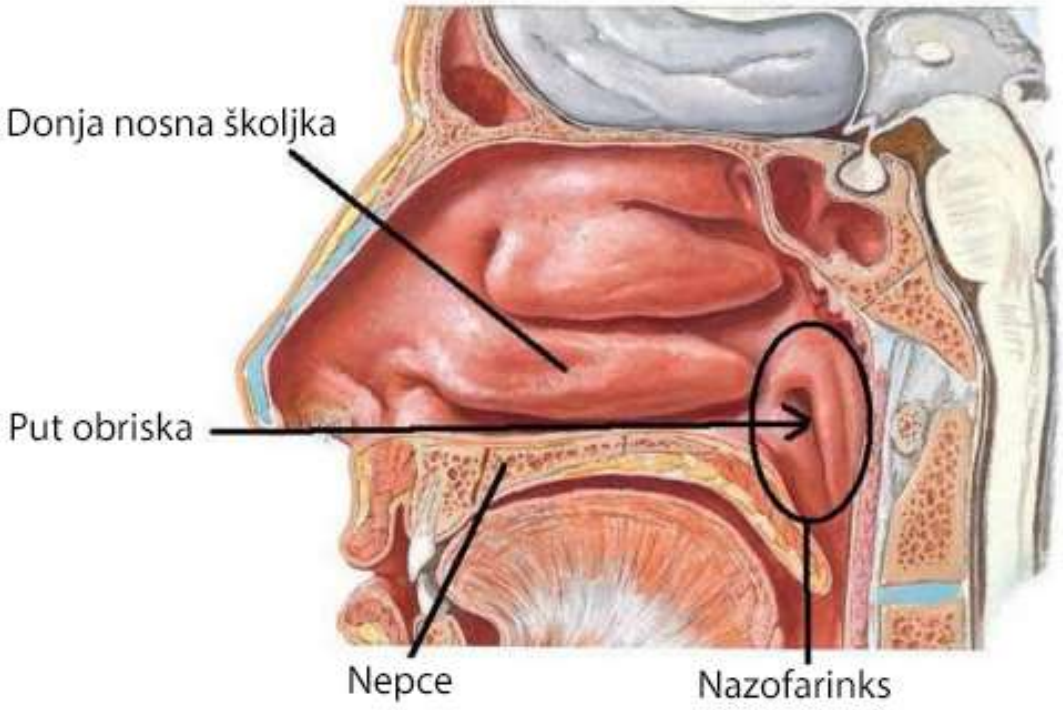
- **Održavanje optimalnih uvjeta** pohrane (izbjegavanje ekstremnih temperatura) za vrijeme prijenosa uzoraka

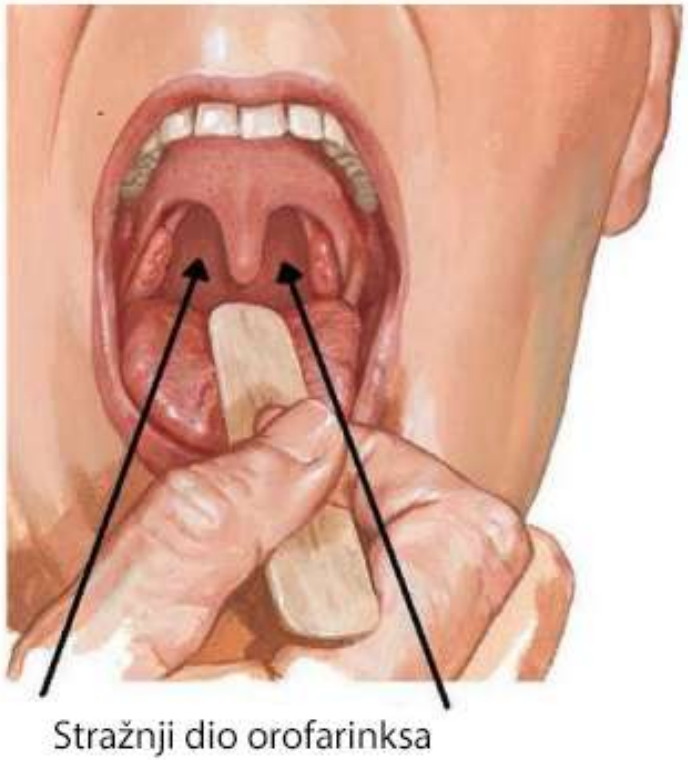
Gornji dišni sustav

- Uzorci iz gornjeg dišnog sustava:
  - **BRIS ŽDRIJELA –** BHS-A
  - **BRIS NAZOFARINKSA –** pertusis, difterija, BHS-A, *N. meningitidis*, virusi
  - **NAZOFARINGEALNI ISPIRAK/ASPIRAT –** virusi
  - **BRIS NOSA –** kliconoštvo (MSSA, MRSA), virusi
  - **BRIS USNE ŠUPLJINE –** gljive, BHS-A, *S. aureus*, virusi
  - **BRIS UHA –** *P. aeruginosa*, *S. aureus*, *V. alginolyticus*, gljive
  - **ASPIRAT SINUSA –** bakterije, virusi, gljive, polimikrobne infekcije

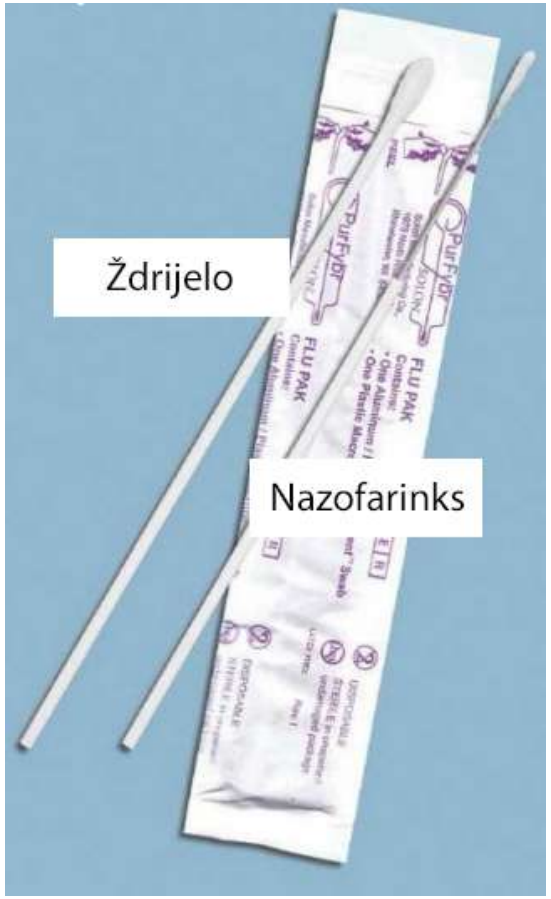


Bris ždrijela i nazofarinksa





Bris ždrijela i nazofarinksa



- U svrhu pravilnog prikupljanja uzorka potrebno je koristiti brisni štapić od **najlona (Dacron), poliestera ili celuloznih vlakana**

- **NE KORISTITI** brisne štapiće od pamuka ili kalcijeva alginata, ili one s drvenim štapićem jer mogu biti inhibitorni za PCR

Transport obrisaka iz gornjeg dišnog sustava

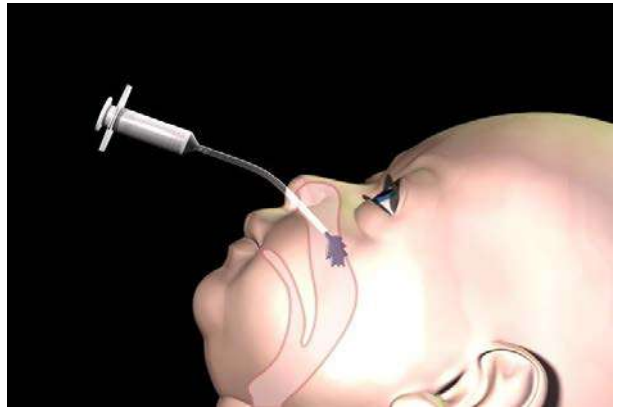
- Bris je potrebno transportirati na jedan od sljedećih načina:
  - bez transportnog medija na sobnoj temperaturi do 2 sata od uzimanja uzorka
  - u transportnom mediju (Stuart, Amies) do 24 sata na sobnoj temperaturi od uzimanja uzorka
  - ako nema transportnog medija, prihvatljiva opcija je uzorak pohraniti i transportirati na +4°C, do 24 sata od uzimanja uzorka

Transport obrisaka iz gornjeg dišnog sustava

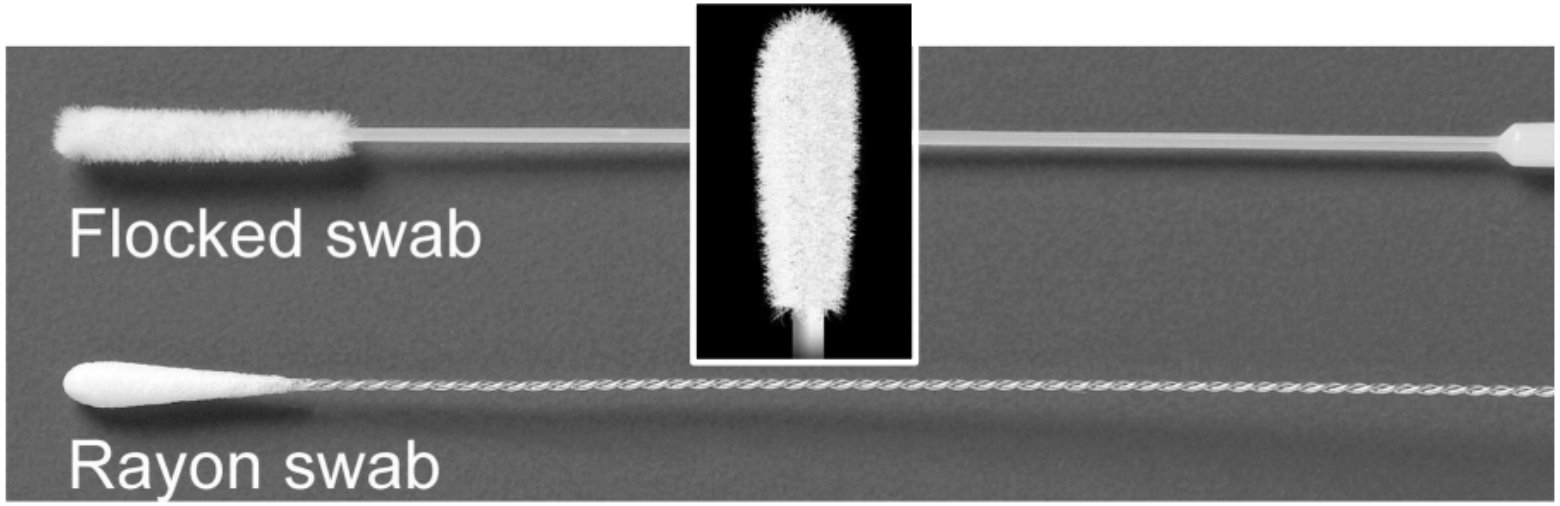
- **Virusni transportni medij (VTM)** ili slična otopina za stabilizaciju virusa
- Najčešće **Hanksova ili Eaglova otopina** uz dodatak fetalnog goveđeg seruma / serumskog albumina te antibiotika
- Mogu se pripremiti lokalno, ali postoje komercijalno pripravljeni **univerzalni transportni mediji**

Nazofaringealni ispirak

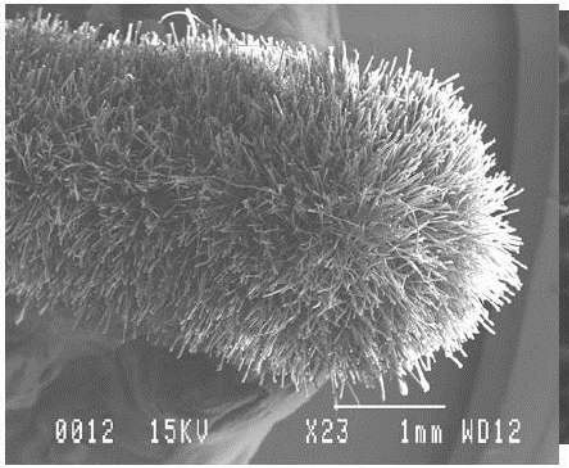
- Uzorak koji se primarno koristi za **izolaciju virusa** → važno brzo dostaviti u laboratorij
- U položaju **hiperekstendirane glave** instilirati oko 5 mililitara sterilne fiziološke otopine u svaku nosnicu
- Zatim nagnuti glavu prema naprijed i sakupiti tekućinu u sterilni kontejner ili aspirirati špricom



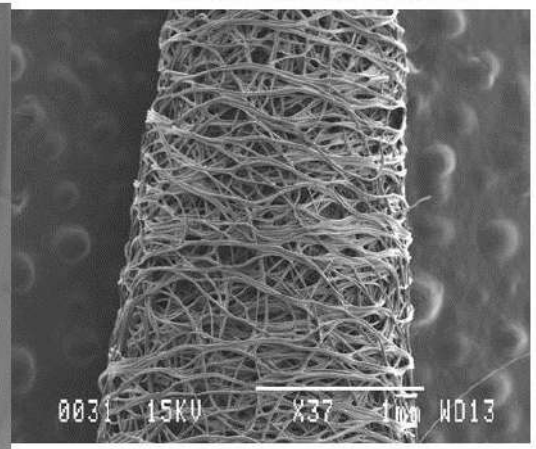
Patentirani četkasti bris (flocked swab)

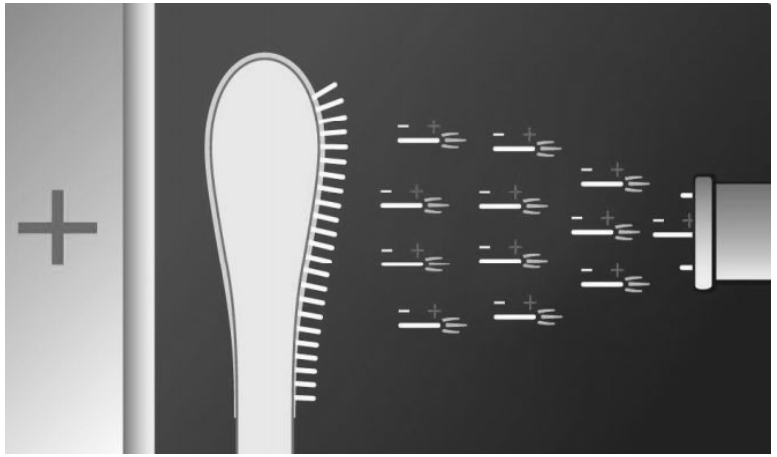


New flocked swab under electron microscope



Traditional swab under EM





Patentirani četkasti bris (flocked swab)

ELSEVIER

Journal of Virological Methods

Volume 185, Issue 1, October 2012, Pages 89-93

Comparison of nasopharyngeal flocked swabs and nasopharyngeal wash collection methods for respiratory virus detection in hospitalized children using real-time polymerase chain reaction

Carolynn DeByle [a], Lisa Bulkow [a], Karen Miernyk [a, b], Lori Chikoyak [c], Kimberlee Boyd Hummel [a], Thomas Hennessy [a], Rosalyn Singleton [a, b]

APMIS JOURNAL OF PATHOLOGY, MICROBIOLOGY AND IMMUNOLOGY

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Original Article

Comparison of nasopharyngeal aspirate with flocked swab for PCR-detection of respiratory viruses in children

Hege Smith Tunsjø, Are Stuitz Berg, Christopher Steven Inchley, Irmelin Kittelsen Røberg, Truls Michael Leegaard

View issue TOC
Volume 123, Issue 6
June 2015
Pages 473–477

Pediatr Crit Care Med. 2016 Apr;17(4):279-86. doi: 10.1097/PCC.0000000000000661.

Optimizing Virus Identification in Critically Ill Children Suspected of Having an Acute Severe Viral Infection.

Randolph AG[1], Agan AA, Flanagan RF, Meece JK, Fitzgerald JC, Loftis LL, Truemper EJ, Li S, Ferdinands JM; Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) PICFlu Study Group.

⊕ Collaborators (73)

Usporedba obrisaka i ispiraka nazofarinksa

pathogens

Open Access | Systematic Review

Nasopharyngeal Swabs vs. Nasal Aspirates for Respiratory Virus Detection: A Systematic Review

by Matthew F. Flynn [1,2,*], Martin Kelly [2] and James S. G. Dooley [1]

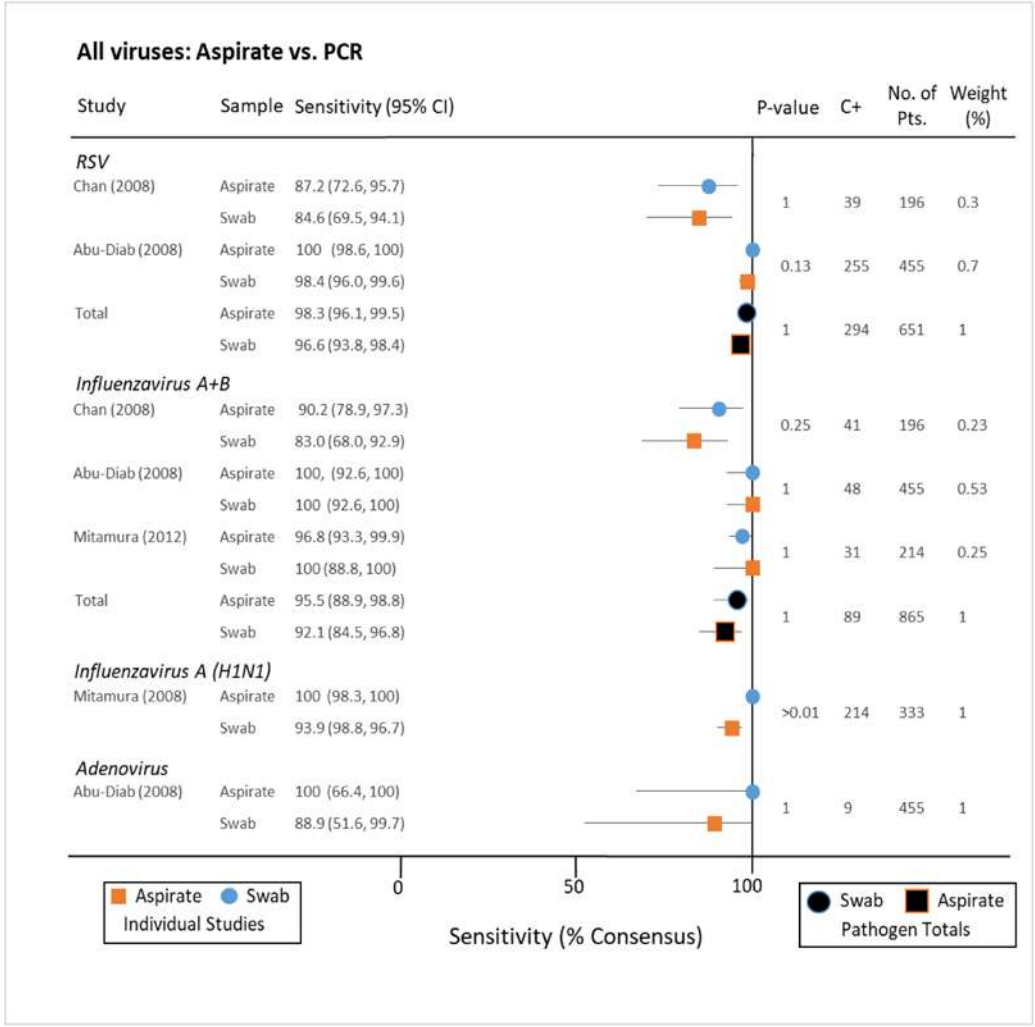
[1] School of Biomedical Sciences, Ulster University, Cromore Road, Coleraine BT52 1SA, UK

[2] Altnagelvin Area Hospital, Glenshane Road, Londonderry BT47 6SB, UK

* Author to whom correspondence should be addressed.

Pathogens **2021**, *10*(11), 1515; **https://doi.org/10.3390/pathogens10111515**

Author	Year	Patients	Wash/Aspirate	Population	Lab Technique	Swab
DeByle [33]	2012	314	aspirate-wash	infants	RT-PCR	flocked
Chan [35]	2008	196	aspirate	Infants, children	DIF and RT-PCR	unknown
Suave [41]	2012	89	wash	Infants, children	DIF	flocked
Munywoki [34]	2011	299	aspirate-wash	Infants, children	RT-PCR	flocked
Abu-Diab [39]	2008	455	aspirate	Infants, children	DIF	flocked
Agoritsas [40]	2006	122	wash	Infants, children	DIF and viral culture	foam
Tunsjo [37]	2015	81	aspirate	infants	RT-PCR	flocked
Nunes [42]	2016	484	aspirate-wash	infants	RT-PCR	flocked
Li [35]	2013	103	aspirate-wash	adults	RT-PCR	flocked
Abdullahi [44]	2007	62	aspirate-wash	infants	culture	rayon tipped
Winokur [43]	2013	15	wash	adults	DIF	flocked
Gritzfeld [24]	2011	24	wash	adults	culture and RT-PCR	rayon tipped
Mitamura [38]	2012	330	aspirate	children, adults	DIF	unknown



Optimalno uzorkovanje za dokaz respiratornih virusa

BMJ Global Health

BMJ Glob Health. 2020 Nov;5(11):e003053. doi: 10.1136/bmjgh-2020-003053.

Original research

Comparison of detection rate of 16 sampling methods for respiratory viruses: a Bayesian network meta-analysis of clinical data and systematic review

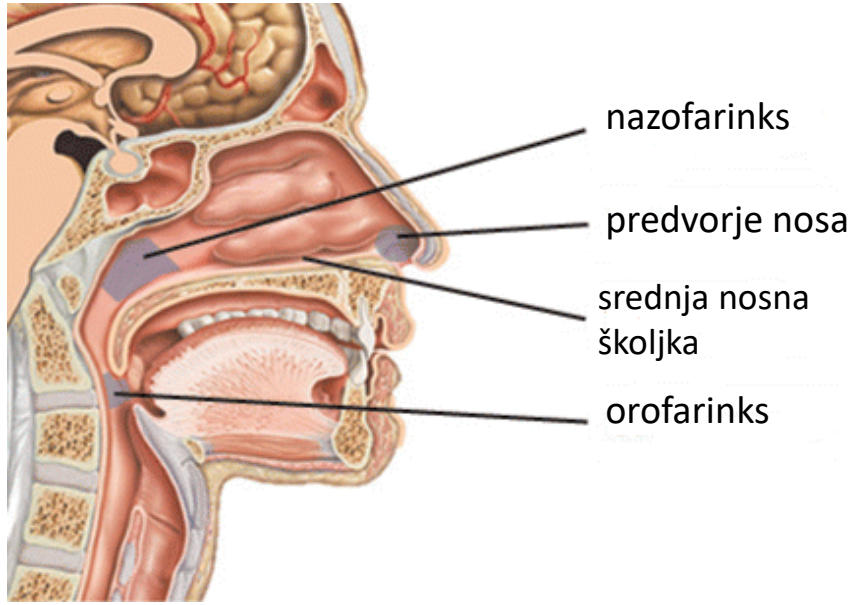
Nianzong Hou [1], Kai Wang [2], Haiyang Zhang [1], Mingjian Bai [3], Hao Chen [4], Weidong Song [5], Fusen Jia [1], Yi Zhang [1], Shiliang Han [1], Bing Xie [1]

Correspondence to Professor Bing Xie; xiebingshouzuwaike@163.com; Dr Kai Wang; wangkaiicu@163.com; Dr Nianzong Hou;

PDF

PDF + Supplementary Material

XML



Mid-turbinate swab – optimalan izbor zbog stope pozitiviteta, cijene i komoditeta?

Donji dišni sustav

- **Primarno nesterilni uzorci iz donjeg dišnog sustava:**
  - Ekspektorirani iskašljaj (sputum)
  - Inducirani iskašljaj (sputum)
  - Endotrahealni aspirat (ETA)
  - Bronhoalveolarni lavat (BAL)
  - Ispirak bronha
- **Primarno sterilni uzorci iz donjeg dišnog sustava:**
  - Aspirat pluća
  - Transtrahealni aspirat
  - Bioptat pluća
  - Pleuralna tekućina

Donji dišni sustav – transport i pohrana

- **Primarno nesterilni uzorci (sputum, ETA, BAL)**
  - transportirati i obraditi što je prije moguće
  - u sterilnoj posudi s navojem od 15 ml na sobnoj temperaturi do 2 sata, ili na + 4 °C do 24 sata od uzimanja

- **Primarno sterilni uzorci:**
  - dostaviti u laboratorij što prije moguće u sterilnoj posudici s navojem
  - do 24 sata uzorak može stajati na sobnoj temperaturi, po mogućnosti u anaerobnom transportnom mediju
  - bioptat staviti u nekoliko kapi sterilne fiziološke otopine kako bi se zadržala vlažnost tkiva

Sputum kao najčešći uzorak

- Jedina **neinvazivna metoda uzorkovanja** za donji dišni sustav
- **Ekspektorirani sputum** – nakon buđenja, duboki udah i iskašljaj u sterilnu posudu s navojem, količina ≥ 2 ml
- **Inducirani sputum** – ako se pacijent ne može sponatno iskašljati, inhalacija sa zagrijanom fiziološkom otopinom ili hipertoničnom otopinom (3-15%) soli

Određivanje adekvatnosti

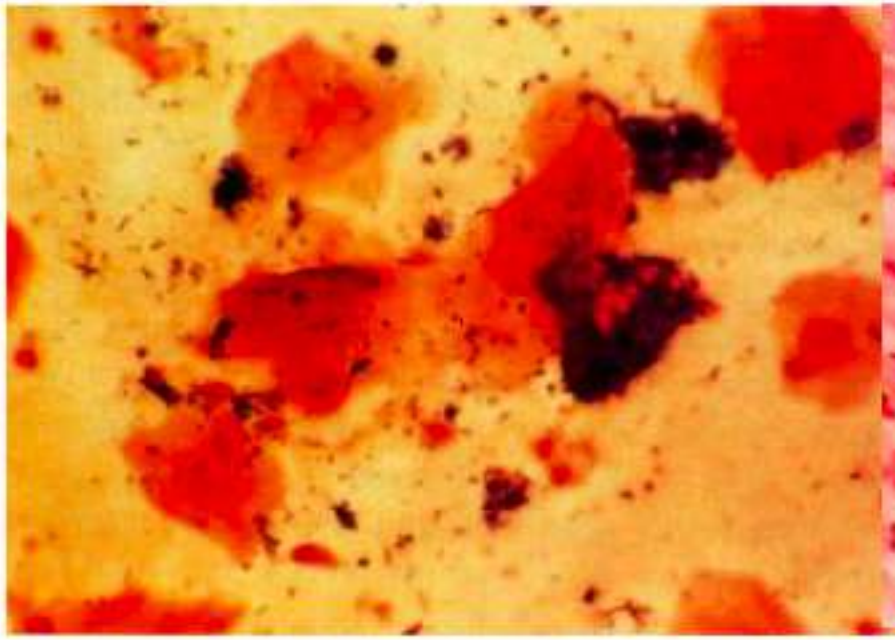
- **Mukoidni uzorak:** sterilnom ezom odabrati gnojan/krvav dio uzorka, razmazati po predmetnom stakalcu i obojati po Gramu
- **Nemukoidni (tekući) uzorak:** kap sedimenta prethodno centrifugiranog uzorka staviti na stakalce i obojati po Gramu
- Mikroskopirati pod **povećanjem 10 x 10**
- U nalazu je potrebno izvijestiti o broju epitelnih stanica, polimorfonuklearnih neutrofila te označiti količinu i vrstu viđenih mikroorganizama

Određivanje adekvatnosti

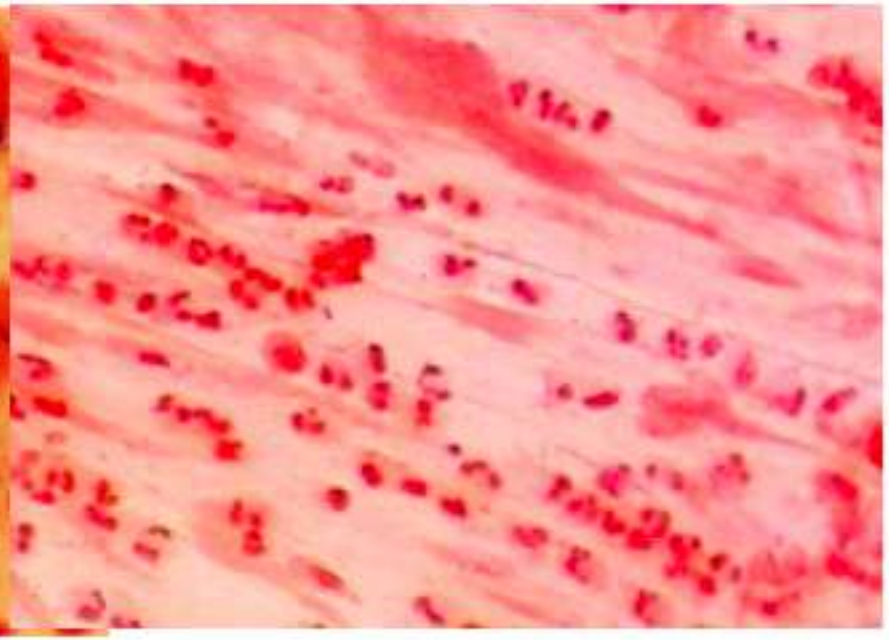
- Većina autora gleda broj epitelnih stanica (ES) i/ili polimorfonuklearnih neutrofila (PMN) po vidnom polju
- **Adekvatan uzorak: <10 ES i >25 PMN u jednom vidnom polju**
- Važno uzeti u obzir: neutropenija kod imunosuprimiranih bolesnika

Određivanje adekvatnosti

Neadekvatno



Adekvatno



Određivanje adekvatnosti

- Nekim autorima je kriterij za odbacivanje uzoraka **omjer neutrofila i epitelnih stanica**
- Adekvatan uzorak ima omjer **PMN:ES > 2:1**
- Prednost korištenja omjera PMN/ES – mogućnost kompenzacije neravnomjerne distribucije stanica prilikom izrade preparata
- **Minimalni kriterij za neadekvatnost uzorka:** broj >10 ES po vidnom polju (10 x 10)

Kvantitativno nasađivanje (ETA, bronhoskopija)

- Uzorci kontaminirani mikrobiotom usne šupljine nasađuju se kvantitativno → **razlučivanje kontaminacije i infekcije**
- **Ne centrifugiraju se** prije nasađivanja
- Nasađivanje kalibriranom ezom (10 µl) ili nasađivanje 20-erostrukog razrjeđenja uzorka

Kvantitativno nasađivanje (ETA, bronhoskopija)

Broj kolonija	CFU/ml uzorka	značajnost		
		PSB	BAL	ETA
<10 kolonija na ploči	10^2	-	-	-
10-99 kolonija	10^3	+	-	-
100-999 kolonija	10^4	+	+	-
>1000 kolonija	10^5	+	+	+

- **Interpretacija broja poraslih kolonija na ploči pri nasađivanju kalibriranom ezom (10 µl)**
- **Izvor:** Pristaš I, Abram M, Bubonja Šonje M, Tićac B, Vučković D, Tambić Andrašević A. Bakteriološka dijagnostika infekcija dišnog sustava: smjernice za mikrobiološku dijagnostiku Hrvatskog društva za kliničku mikrobiologiju Hrvatskog liječničkog zbora. Zagreb: Hrvatsko društvo za kliničku mikrobiologiju; 2015.

Kvantitativno nasađivanje (ETA, bronhoskopija)

Broj kolonija	CFU/ml uzorka	značajnost		
		PSB	BAL	ETA
3 – 24 kolonije na ploči	10^3	+	-	+
24 - 249 kolonija	10^4	+	+	-
≥250 kolonija	$\geq 10^5$	+	+	+

- **Interpretacija broja kolonija pri nasađivanju pri nasađivanju 20-rostrukog razrjeđenja uzorka**
- **Izvor:** Pristaš I, Abram M, Bubonja Šonje M, Tićac B, Vučković D, Tambić Andrašević A. Bakteriološka dijagnostika infekcija dišnog sustava: smjernice za mikrobiološku dijagnostiku Hrvatskog društva za kliničku mikrobiologiju Hrvatskog liječničkog zbora. Zagreb: Hrvatsko društvo za kliničku mikrobiologiju; 2015.

Uzorak za serološku obradu

- Najkorisniji je **parni serum**
- **Prvi ili akutni serum:** unutar sedam dana od pojave simptoma
- **Drugi ili rekonvalescentni serum:** dva tjedna (ili više) nakon akutnog uzorka

Slina kao uzorak?

› Emerg Microbes Infect. 2017 Jun 7;6(6):e49. doi: 10.1038/emi.2017.35.

Additional molecular testing of saliva specimens improves the detection of respiratory viruses

Kelvin Kw To [1 2 3 4 5], Lu Lu [4], Cyril Cy Yip [5], Rosana Ws Poon [5], Ami My Fung [5], Andrew Cheng [5], Daniel Hk Lui [6], Deborah Ty Ho [4], Ivan Fn Hung [1 2 7], Kwok-Hung Chan [1 2 3 4], Kwok-Yung Yuen [1 2 3 4 5]

Emerging Microbes & Infections

› Ann Lab Med. 2023 Sep 1;43(5):434-442. doi: 10.3343/alm.2023.43.5.434. Epub 2023 Apr 21.

ANNALS OF LABORATORY MEDICINE

Comparison of Nasal Swabs, Nasopharyngeal Swabs, and Saliva Samples for the Detection of SARS-CoV-2 and other Respiratory Virus Infections

Eun Ju Jung [1], Su Kyung Lee [2], Seon Hee Shin [3], Jin Soo Kim [3], Heungjeong Woo [1], Eun-Jung Cho [2], Jungwon Hyun [2], Jae-Seok Kim [4], Hyun Soo Kim [2]

Samouzorkovanje za epidemiološki nadzor

EUROPEAN RESPIRATORY *journal*
FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Head-to-head comparison of SARS-CoV-2 antigen-detecting rapid test with self-collected nasal swab *versus* professional-collected nasopharyngeal swab

Andreas K. Lindner, Olga Nikolai, Franka Kausch, Mia Wintel, Franziska Hommes, Maximilian Gertler, Lisa J. Krüger, Mary Gaeddert, Frank Tobian, Federica Lainati, Lisa Köppel, Joachim Seybold, Victor M. Corman, Christian Drosten, Jörg Hofmann, Jilian A. Sacks, Frank P. Mockenhaupt, Claudia M. Denkinger

European Respiratory Journal 2021 57: 2003961; **DOI:** 10.1183/13993003.03961-2020

APMIS JOURNAL OF PATHOLOGY, MICROBIOLOGY AND IMMUNOLOGY

Original Article | Open Access

Diagnostic performance of patient self-collected oral swab (tongue and cheek) in comparison with healthcare worker-collected nasopharyngeal swab for severe acute respiratory syndrome coronavirus-2 detection

Arati Mane, Shilpa Jain, Ankita Jain, Vijay Nema, Swarali Kurle, Vandana Saxena, Michael Pereira, Atul Sirsat, Gaurav Pathak, Vikalp Bhoi, Shailaja Bhavsar, Samiran Panda

First published: 04 August 2022 | https://doi.org/10.1111/apm.13266

Eurosurveillance

Research articles

Self-sampling for community respiratory illness: a new tool for national virological surveillance

A J Elliot[1], A Bermingham[2], A Charlett[2], A Lackenby[2], J Ellis[2], C Sadler[2], P Sebastianpillai[2], C Powers[2], D Foord[3], E Povey[3], B Evans[2], H Durnall[4], D M Fleming[4], D Brown[2], G E Smith[1], M Zambon[2]

Eurosurveillance

Research articles

Self-sampling for analysis of respiratory viruses in a large-scale epidemiological study in Sweden

A Plymoth[1], M Rotzén-Östlund[2,3], B Zweygberg-Wirgart[2,3], C G Sundin[4], A Ploner[1], O Nyrén[1], A Linde[5]

Od dijagnostike do nalaza

- Identifikacija se izvodi u skladu s laboratorijskim postupcima za identifikaciju mikroorganizama
- Kad je moguće, **testiranje osjetljivosti na antimikrobne** lijekove prema smjernicama Odbora za praćenje rezistencije *Akademije medicinskih znanosti Hrvatske* (AMZH) i smjernicama EUCAST-a (*European Committee on Antimicrobial Susceptibility Testing*)
- Izdavanje nalaza: **pozitivan vs. negativan nalaz!**

Zaključak

- Za pravilno uzorkovanje ključna **suradnja** liječnika (i drugog medicinskog osoblja) **s mikrobiološkim laboratorijem**
- Slijediti upute/smjernice o **pravilnom odabiru, uzimanju i transportu** uzoraka za dijagnostiku respiratornih bolesti
- Procjena adekvatnosti uzoraka prije mikrobiološke obrade
- **Samouzorkovanje** → novi način provođenja epidemiološkog nadzora (surveillance)

Hvala na pažnji!

Suvremene spoznaje o epidemiologiji, kliničkoj slici, laboratorijskoj dijagnostici, terapiji i prevenciji respiratornih infekcija, Zagreb, 15. svibanj 2023.

Novi trendovi i dijagnostičke strategije u otkrivanju SARS-CoV-2 infekcije

Prof. dr. sc. prim. Jasmina Vraneš, dr. med.

Medicinski fakultet Sveučilišta u Zagrebu

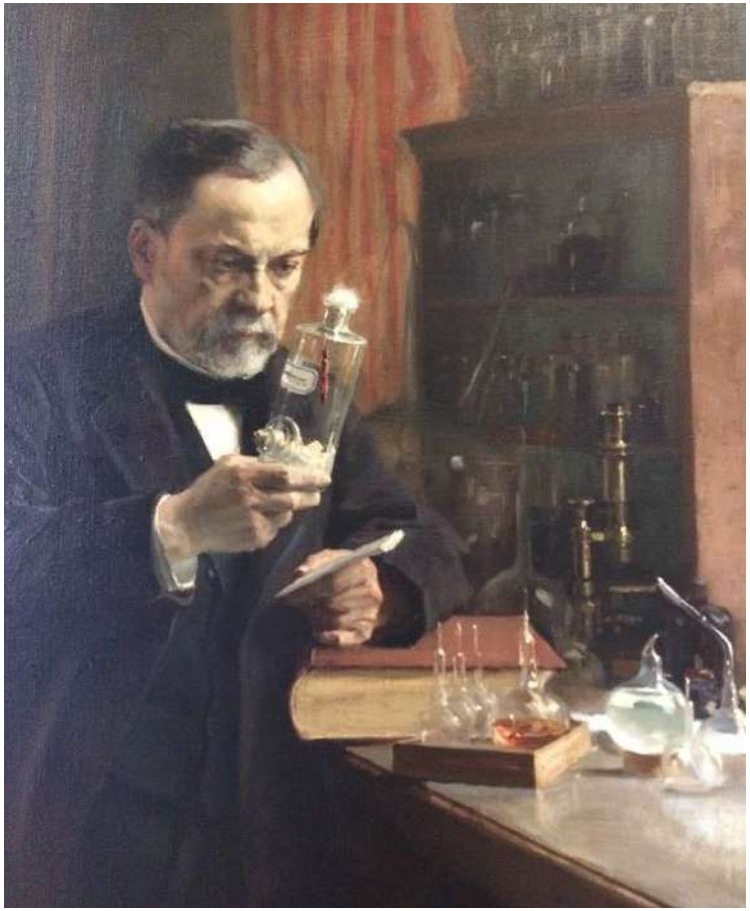
& Nastavni zavod za javno zdravstvo „Dr. Andrija Štampar”

jasmina.vranes@stampar.hr

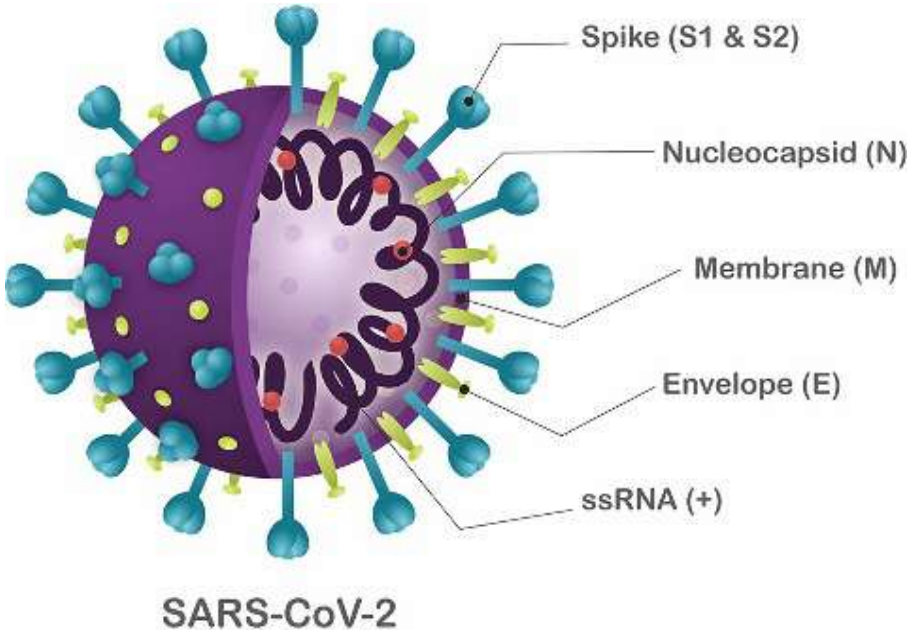
Molekularna mikrobiologija

- Kulturomika obilježila 19. i 20. stoljeće

- Danas nove mogućnosti: genomika, transkriptomika, proteomika, metabolomika...



COVID-19: mikrobiološka dijagnostika



SARS-CoV-2

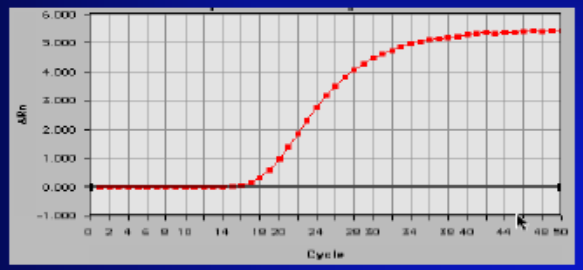
- RT-qPCR
- Druge amplifikacijske metode
- Brzi testovi
- Sekvenciranje
- Serologija

Real-time PCR

Real-time PCR is kinetic

- Detection of "amplification-associated fluorescence" at each cycle during PCR
- No gel-based analysis at the end of the PCR reaction
- Computer based analysis of the cycle-fluorescence time course

Increasing fluorescence



Linear plot

} Log-view augments this part

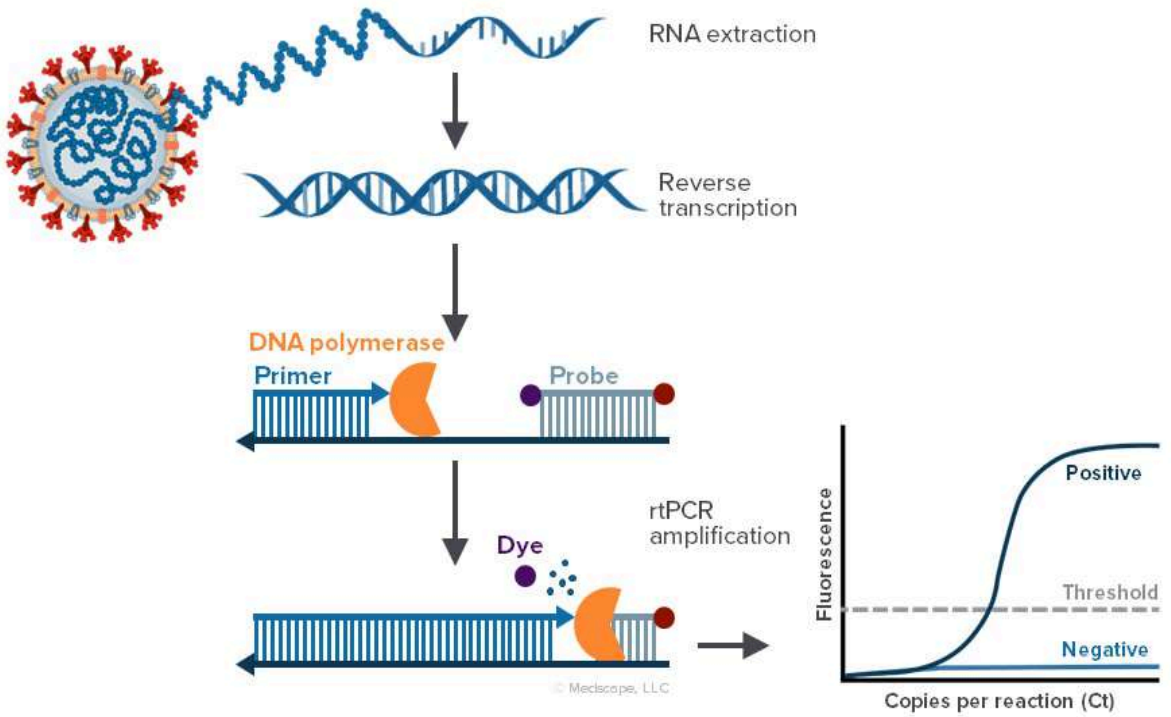
PCR cycle

Nigel Walker, NIEHS (www)

Ct (*cycle threshold*) vrijednost RT-PCR testa:

Broj PCR ciklusa neophodnih da bi se targetirana sekvenca amplificirala do detektabilne razine

rtPCR and SARS-CoV-2 Cycle Threshold Value

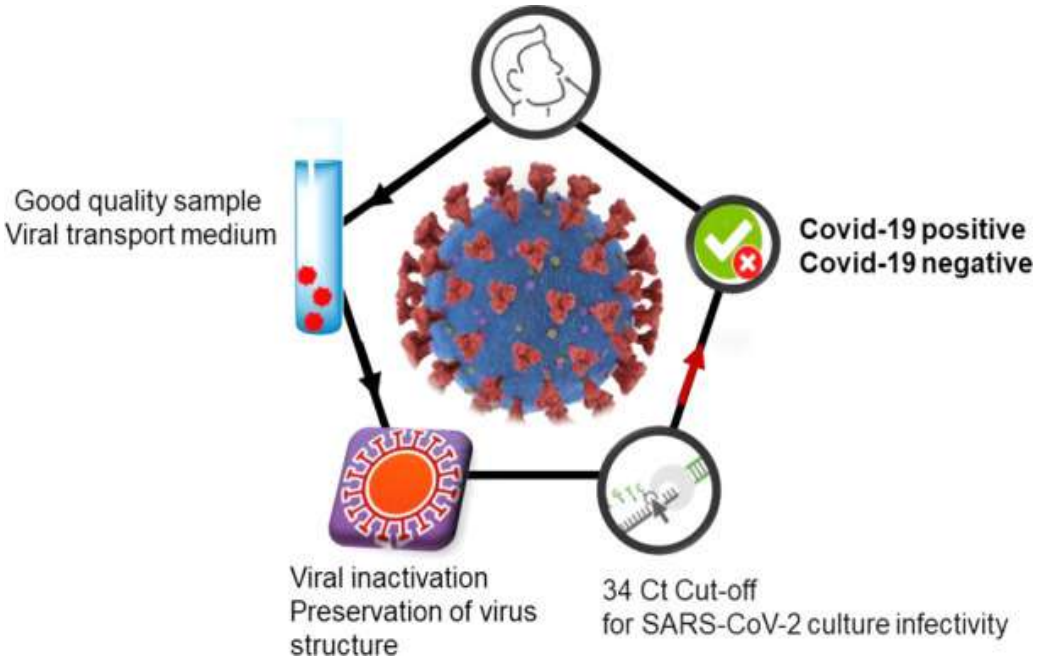


- Ct value is oftentimes associated with real-time PCR (rtPCR) or fluorescence-based PCR

Public Health England. Understanding cycle threshold (Ct) in SARS-CoV-2 RT-PCR: a guide for health protection terms. 2020.

Brojni čimbenici utječu na Ct vrijednost: ciljni geni, metoda detekcije, ekstrakcija RNA da ili ne, učinkovitost amplifikacije, vrsta PCR uređaja……

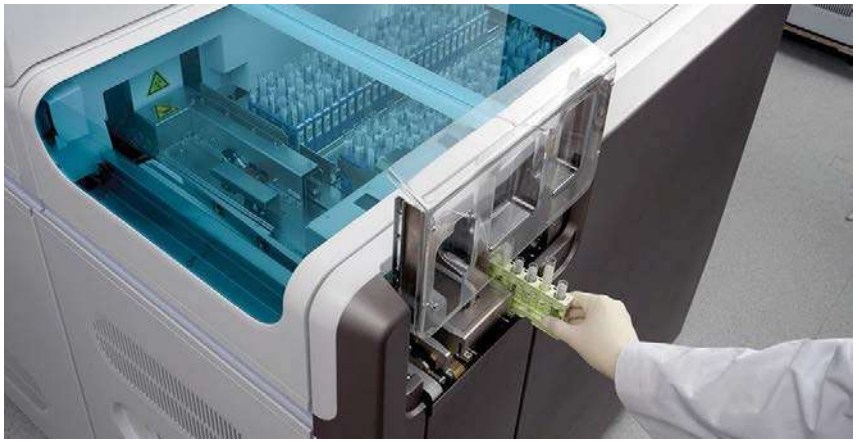
Kako **uzorkovanje** utječe na Ct vrijednost PCR testa?



Danas su dostupni u potpunosti automatizirani visoko-protočni qPCR uređaji (1.300 uzoraka /dan!)

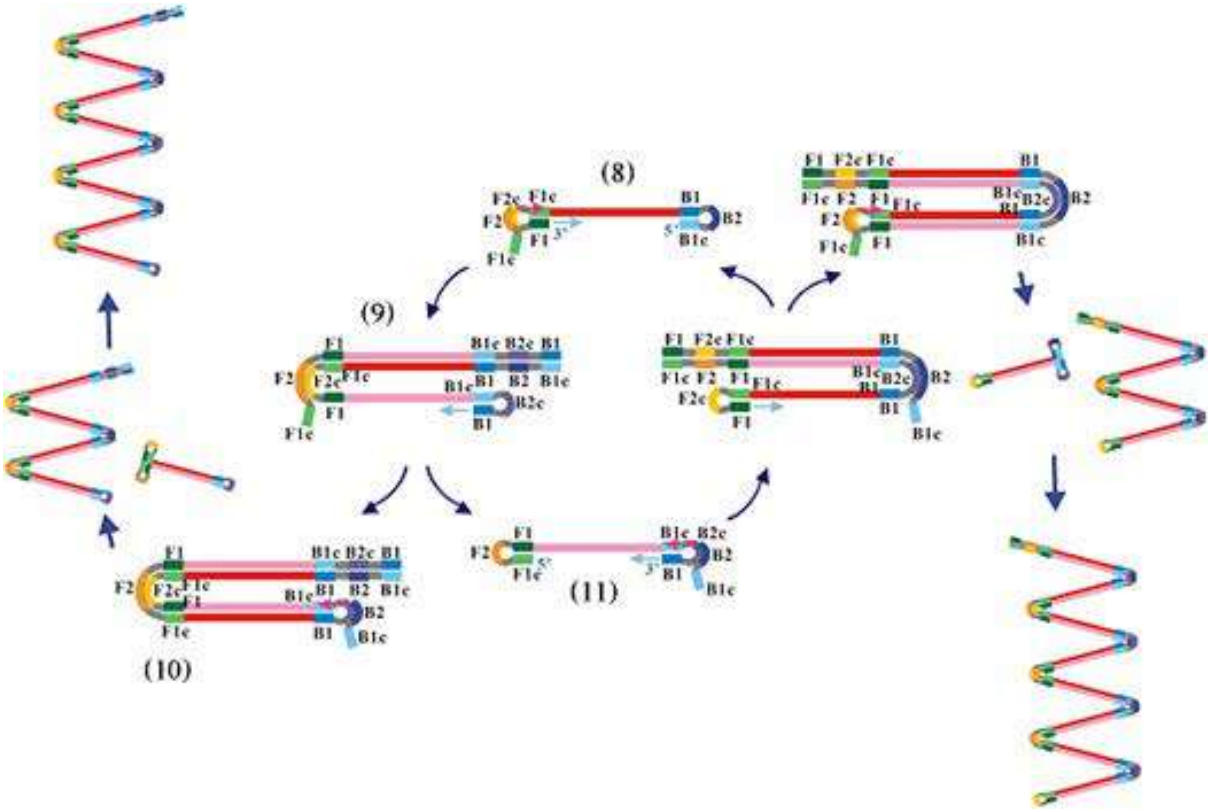
COBAS® 6800/8800

Multiplex RT-qPCR



Druge amplifikacijske metode: RT LAMP, etc.

(**L**oop-mediated isothermal **AMP**lification)



http://loopamp.eiken.co.jp/e/lamp/anim.html

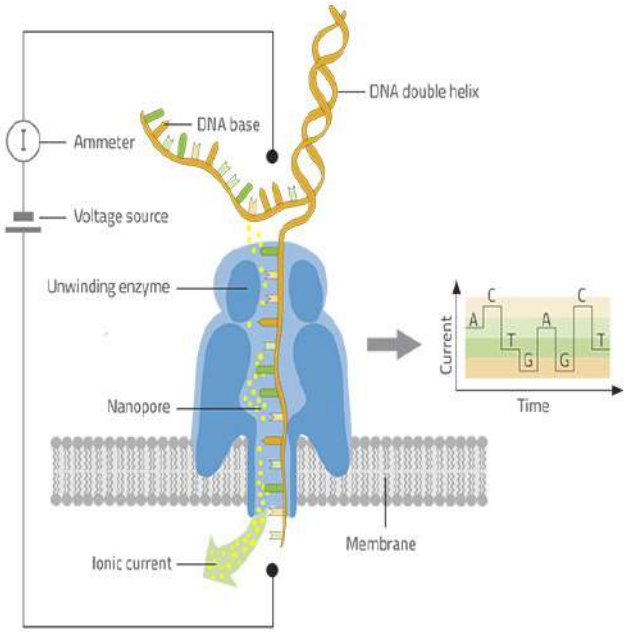
Point-of-care testiranje (POCT)

- WHO ASSURED kriteriji za brze testove:
  - A=*affordable*
  - S=*sensitive*
  - S=*specific*
  - U=*user friendly* (simple to perform in a few steps with minimal training)
  - R=*robust and rapid* (results available in less than 30 minutes)
  - E=*equipment free*
  - D= *deliverable to those who need the test*

DNA-based POCT

Brzi antigenski testovi

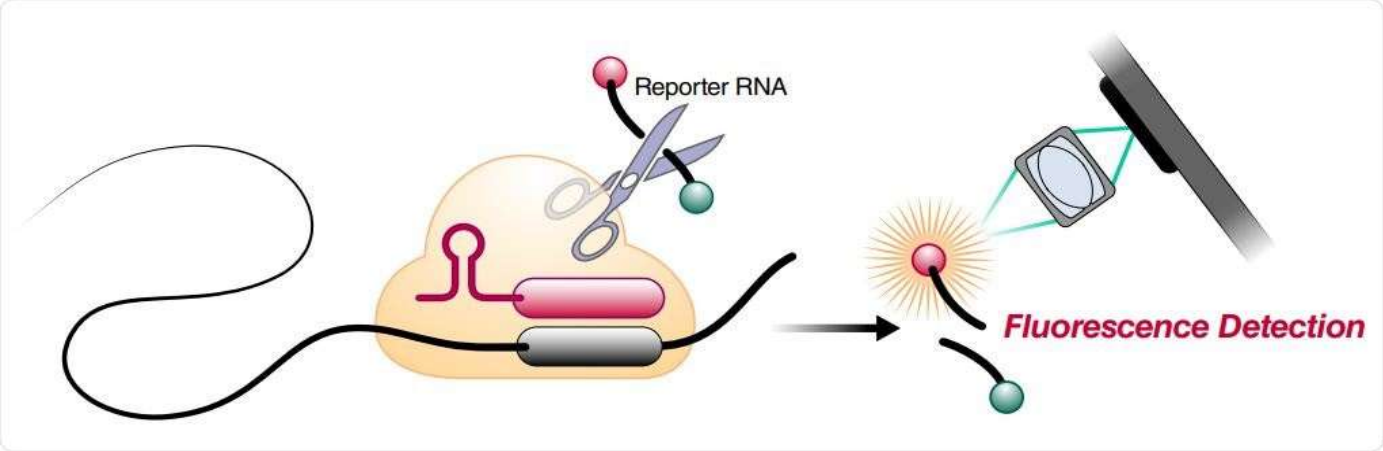
Sekvenciranje –WGS danas POCT!



Simplified point-of-care full SARS-CoV-2 genome sequencing using nanopore technology. Image Credit: vchal / Shutterstock

CRISPR-Cas13

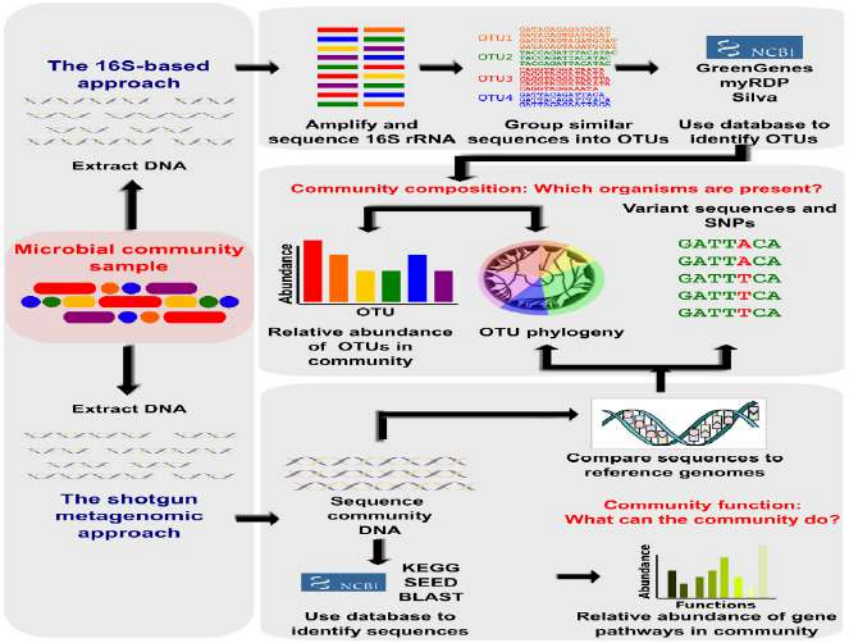
Clustered Regulary Interspaced Short Palindromic Repeats



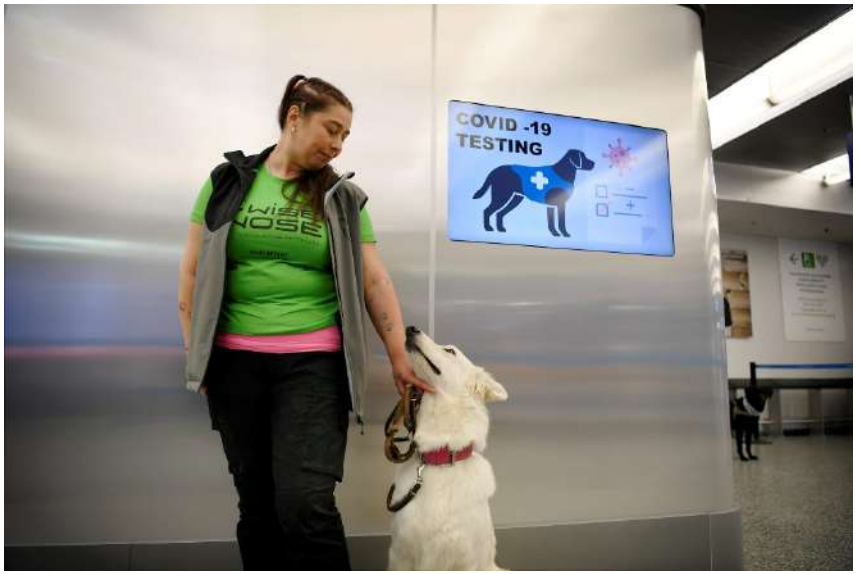
Meštrović T. Rapid detection of SARS-CoV-2 with portable CRISPR-based mobile phone diagnostic test. News, Oct 4, 2020.

Genomika, metagenomika i metabolomika

(Morgen & Huttenhover. Determining the population diversity based on 16s rRNA. PLOS Computational Biology 2012;8)



Aerodrom u Helsinkiju



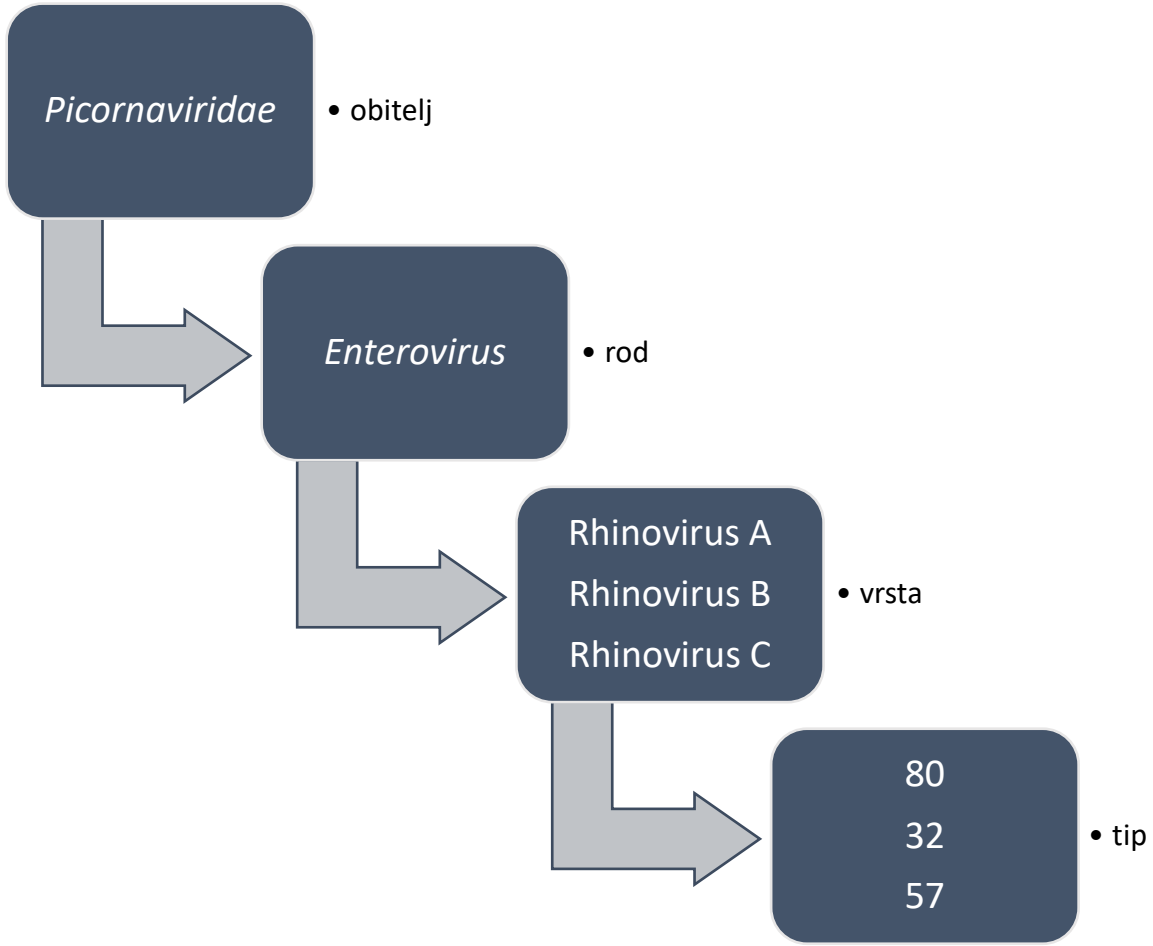
Suradnici u dijagnostici SARS-CoV-2 infekcije (NZJZ AŠ):
prof. dr. sc. S. Ljubin Sternak, dr. J. Knežević, dr. S. Šuto, prim. mr. sc. T. Marijan, mr. sc. V. Tičić, dr. M. Anušić, dr. N. Pražić, ing. M. Kvaternik Celjak, ing. S. Česić, ing. A. Haramustek, ing. Ž. Begić, ing. K. Stepušin Seferović, ing. T. De Zan, ing. V. Ptiček, Z A Stipčić, i drugi

Infekcija uzrokovana rinovirusom- prolazna neugodnost ili teška bolest?

Prof.dr.sc. Sunčanica Ljubin Sternak, prim.dr.med.

Rinovirusi - otkriće i klasifikacija

- 1956 izolirani na staničnoj kulturi bubrega majmuna
  - prvotno prepoznato oko 100 serotpiova koji pripadaju vrsti A i B
- 2006 otkrivena nova grupa rinovirusa (grupa C) molekularnim tehnikama
  - danas oko 170 genotipova (tipova)
  - pripadaju istoj vrsti ako je sličnost dobivena sekvenciranjem >70%
  - isti tip ako je sličnost 87-90% ovisno o dijelu genoma koji se sekvencira
- Različiti st. Receptori* za vrste
  - RV-A ➡ ICAM-1 i LDL-R
  - RV-B ➡ ICAM-1
  - RV-C ➡ CDHR3



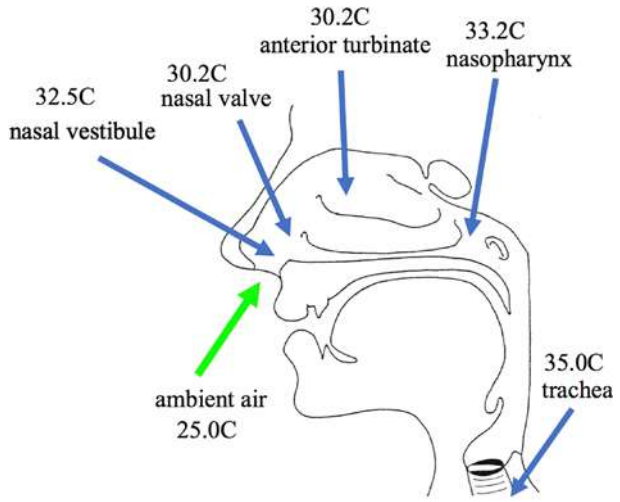
*ICAM – intercelluler adhesion molecule; LDL-R – low density lipoprotein receptor; CDHR3 – cadherin related family member 3

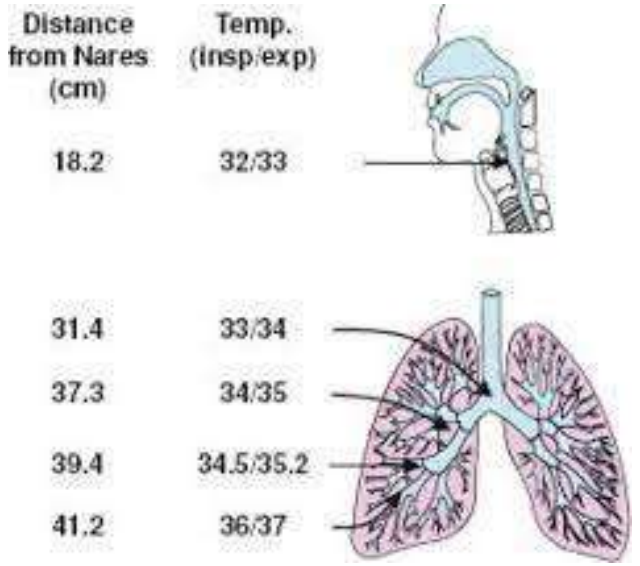
Rinovirusi – klinička slika

- U 2019 zabilježeno je 17,2 bilijuna slučajeva infekcija gornjeg dišnog sustava (URTI) na globalnoj razini; prosječno djeca godišnje imaju 8-12 URTI, a odrasli 2-3 URTI
- Rinovirusi su najčešći uzročnici prehlade
  - Djeca – dvije rinovirusne infekcije na godinu
  - Odrasli – jedna infekcija godišnje (Izvor: CDC, National Center for Immunization and Respiratory Diseases)

Uzrokuju li rinovirusi samo infekcije gornjeg dišnog sustava?

- Većina RV se najučinkovitije replicira u staničnoj kulturi pri 33-35°C, pa se pretpostavljalo da će više temperature u donjim dišnim putevima (LRT) onemogućiti umnažanje virusa i razvoj LRTI
- Izravna mjerenja u donjim dišnim putovima pokazala su da temperatura od 33–35 °C u velikim i srednjim dišnim putovima predstavlja idealnu temperaturu za replikaciju RV.
- Temperatura malih dišnih putova približava se središnjoj temperaturi od 37°C. Ipak, pokazalo se da in vitro epitelne stanice donjih dišnih putova podupiru replikaciju RV mnogo bolje nego stanice dobivene iz gornjih dišnih putova
- Nova istraživanja pokazala su da se optimalna temperatura značjno razlikjuje između RV tipova te da se neki učinkovito repliciraju pri 37°C





Prevalencija rinovirusa u djece s bronhiolitisom i pneumonijom – meta-analize

Authors	Publication Year	Population Examined	Final number of included studies	Sample size	Rhinovirus prevalence
Kenmoe et al.	2020	Children < 2 years with bronchiolitis	51	79,803	19.29% * (95% CI 16.67-22.04%) *
Pratt et al.	2022	Children with community-acquired pneumonia	186	152,209	22.1% (95% CI 19.5-24.7%)

Izvor: Ljubin-Sternak S and Meštrović T. Rhinovirus—A True Respiratory Threat or a Common Inconvenience of Childhood? Viruses 2023

RV je drugi uzročnik po učestalosti bronhiolitisa i pneumonija u djece nakon RSV-a

Rinovirusi – naša iskustva

RESEARCH ARTICLE

WILEY JOURNAL OF MEDICAL VIROLOGY

Viral pathogens associated with acute respiratory illness in hospitalized adults and elderly from Zagreb, Croatia, 2016 to 2018

Rok Civljak[1] | Tatjana Tot[2] | Ann R. Falsey[3] | Eva Huljev[1] | Jasmina Vranes[4,5] | Suncanica Ljubin-Sternak[4,5]

[1]Department of Respiratory Tract Infections, Dr Fran Mihaljevic University Hospital for Infectious Diseases, University of Zagreb School of Medicine, Zagreb, Croatia

[2]Department of Microbiology, General Hospital Karlovac, Karlovac, Croatia

[3]Department of Medicine, Rochester General Hospital and University of Rochester School of Medicine and Dentistry, Rochester, New York

[4]Department of Clinical Microbiology, Dr Andrija Stampar Teaching Institute of Public Health, Zagreb, Croatia

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Funding information
Hrvatska Zaklada za Znanost, Grant/Award Number: IP-2016-06-7556

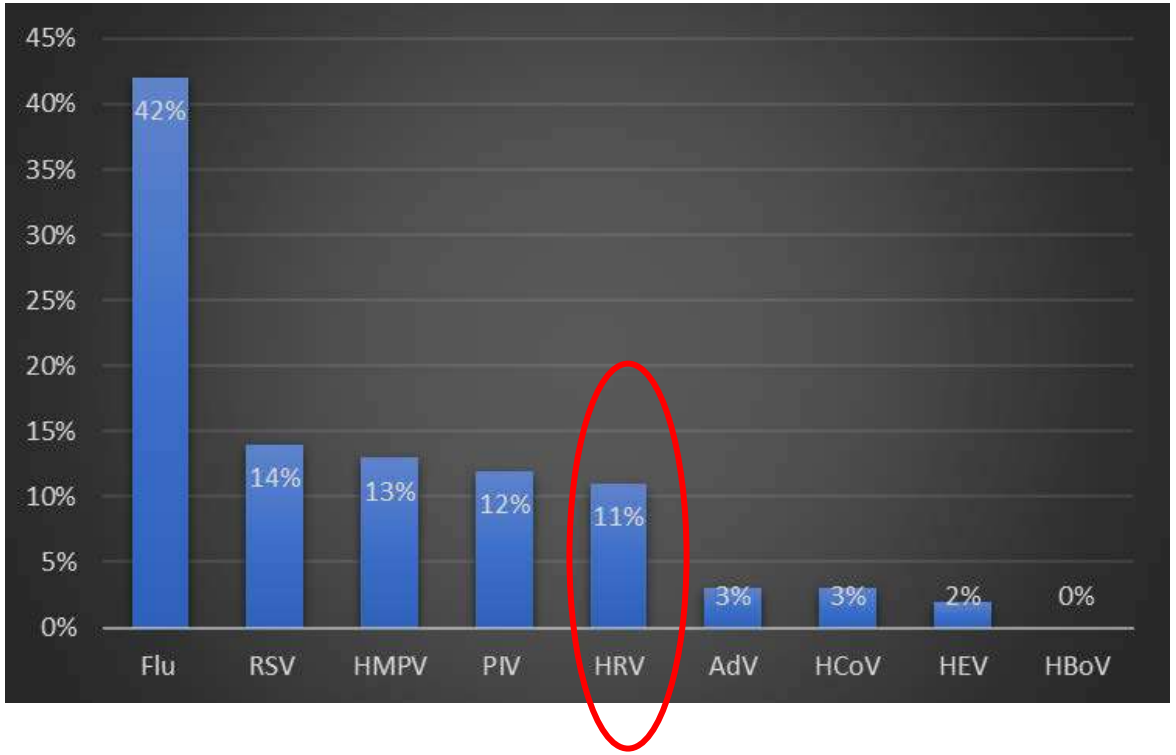
Abstract

Aims: To investigate the viral etiology of acute respiratory infection (ARI) in hospitalized adults and elderly patients in Croatia, compare the prevalence of detected viruses, and to determine clinical characteristics and seasonal occurrence of investigated infections.

Methods: From January 2016 to June 2018, a total of 182 adult patients presented with symptoms of ARI and admitted to the hospital were tested for 15 respiratory viruses by multiplex reverse-transcription polymerase chain reaction. Clinical data were collected by retrospective analysis of the patient's chart.

Results: A virus was identified in 106 (58.5%) of the patients. The most commonly detected virus was influenza virus (41.5%), followed by respiratory syncytial virus (13.8%), human metapneumovirus (13.0%), parainfluenza viruses (12.2%), rhinoviruses (11.4%), adenovirus and coronaviruses with equal frequencies (3.3%), and enterovirus (1.6%). The serum level of C-reactive protein and white blood cell count were significantly lower in patients with respiratory viruses identified when compared with those in whom no virus was detected ($P < 0.001$ and $P = 0.007$, respectively). There were no differences in clinical symptoms according to the type of the detected virus, except for more frequent illness exposure recall for influenza infection ($P = 0.010$). Influenza, parainfluenza, and pneumoviruses were detected mostly in winter months, while rhinoviruses in autumn and spring.

Conclusions: In addition to influenza, pneumoviruses, rhinoviruses, and parainfluenza viruses play an important role in etiology of ARIs in adults. Fast and accurate laboratory diagnosis for respiratory viruses in routine practice is needed for clinicians optimally manage patients with ARI and potentially avoid the unnecessary use of antimicrobial drugs.



Rinovirusi – naša iskustva

frontiers in Microbiology

ORIGINAL RESEARCH
published: 03 December 2019
doi: 10.3389/fmicb.2019.02737

The Emerging Role of Rhinoviruses in Lower Respiratory Tract Infections in Children – Clinical and Molecular Epidemiological Study From Croatia, 2017–2019

Sunčanica Ljubin-Sternak[1,2], Tomislav Meštrović[3,4], Irena Ivković-Jureković[5,6], Branko Kolarić[7,8], Anamarija Slović[9], Dubravko Forčić[6], Tatjana Tot[10], Maja Mijač[1,2] and Jasmina Vranoš[1,2]*

[1] Molecular Microbiology Department, Dr. Andrija Štampar Teaching Institute of Public Health, Zagreb, Croatia, [2] Medical Microbiology Department, School of Medicine, University of Zagreb, Zagreb, Croatia, [3] Clinical Microbiology and Parasitology Unit, Polyclinic "Dr. Zora Profozić", Zagreb, Croatia, [4] University Centre Varaždin, University North, Varaždin, Croatia, [5] Department of Pulmonology, Allergy, Immunology and Rheumatology, Children's Hospital Zagreb, Zagreb, Croatia, [6] Faculty for Dental Medicine and Healthcare/School of Medicine, Josip Juraj Strossmayer University of Osijek, Osijek, Croatia, [7] Department of Epidemiology, Dr. Andrija Štampar Teaching Institute of Public Health, Zagreb, Croatia, [8] Faculty of Medicine, University of Rijeka, Rijeka, Croatia, [9] Center of Excellence for Virus Immunology and Vaccines, Center for Research and Knowledge Transfer in Biotechnology, University of Zagreb, Zagreb, Croatia, [10] Department of Microbiology, General Hospital Karlovac, Karlovac, Croatia

OPEN ACCESS

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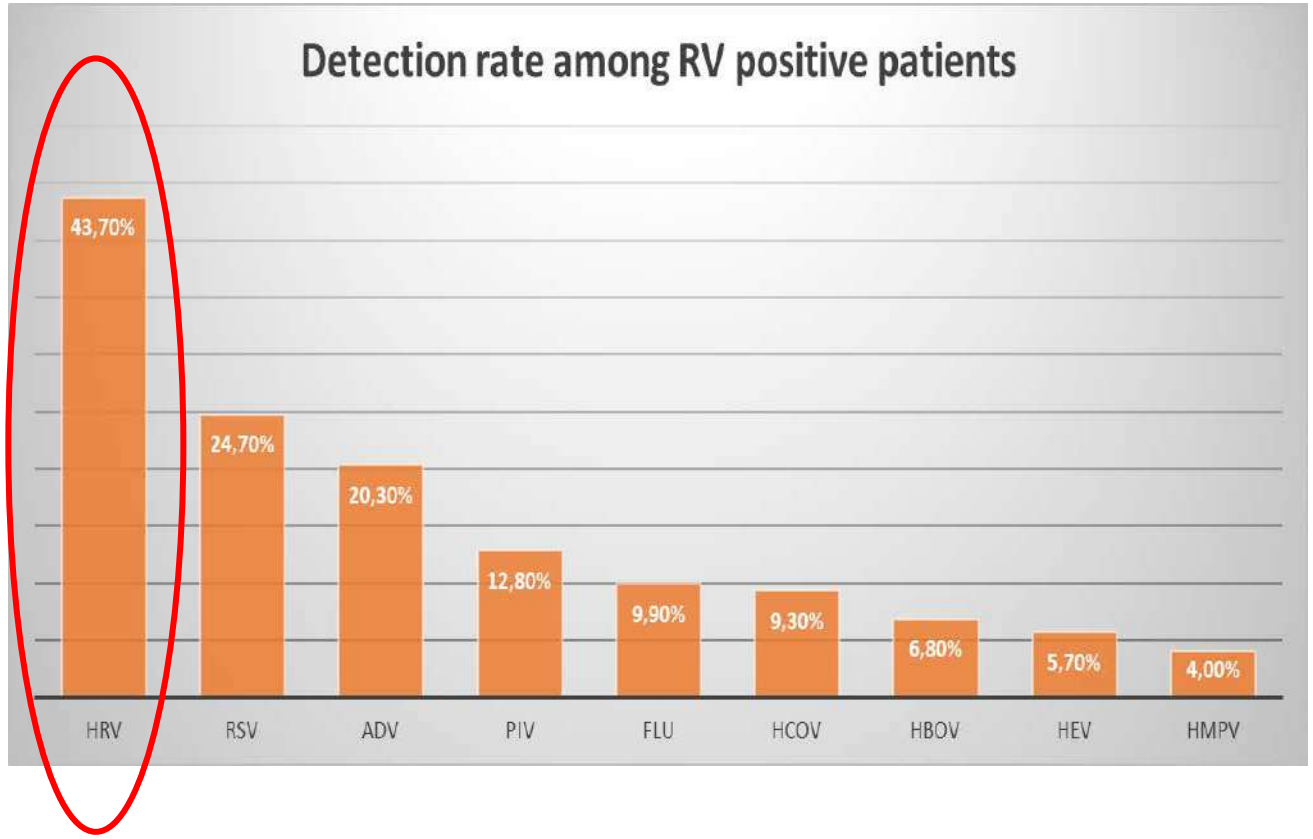
Specialty section:
This article was submitted to Virology, a section of the journal Frontiers in Microbiology

Received: 18 September 2019
Accepted: 11 November 2019
Published: 03 December 2019

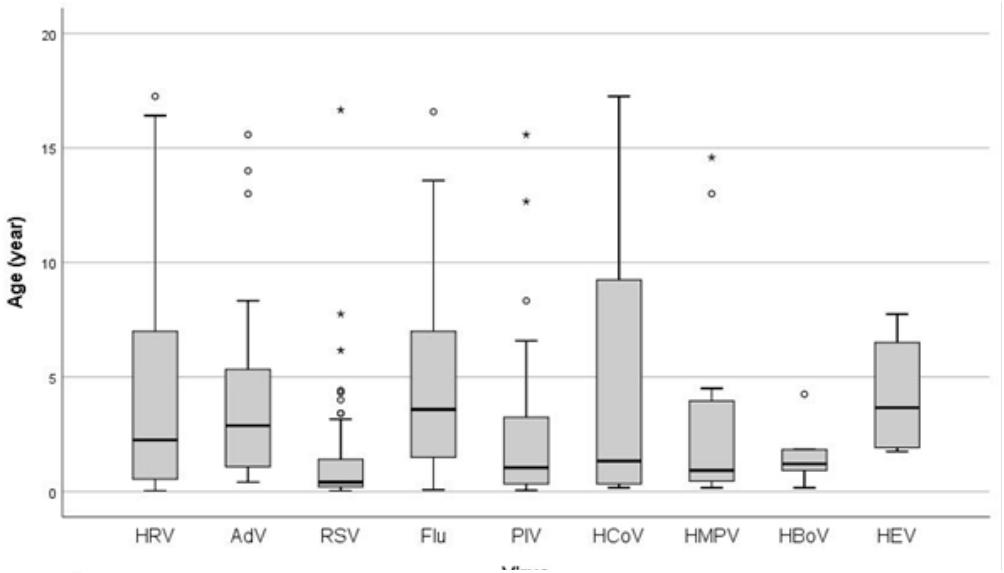
Citation:
Ljubin-Sternak S, Meštrović T, Ivković-Jureković I, Kolarić B, Slović A, Forčić D, Tot T, Mijač M and Vranoš J (2019) The Emerging Role of Rhinoviruses in Lower Respiratory Tract Infections in Children – Clinical and Molecular Epidemiological Study From Croatia, 2017–2019. Front. Microbiol. 10:2737. doi: 10.3389/fmicb.2019.02737

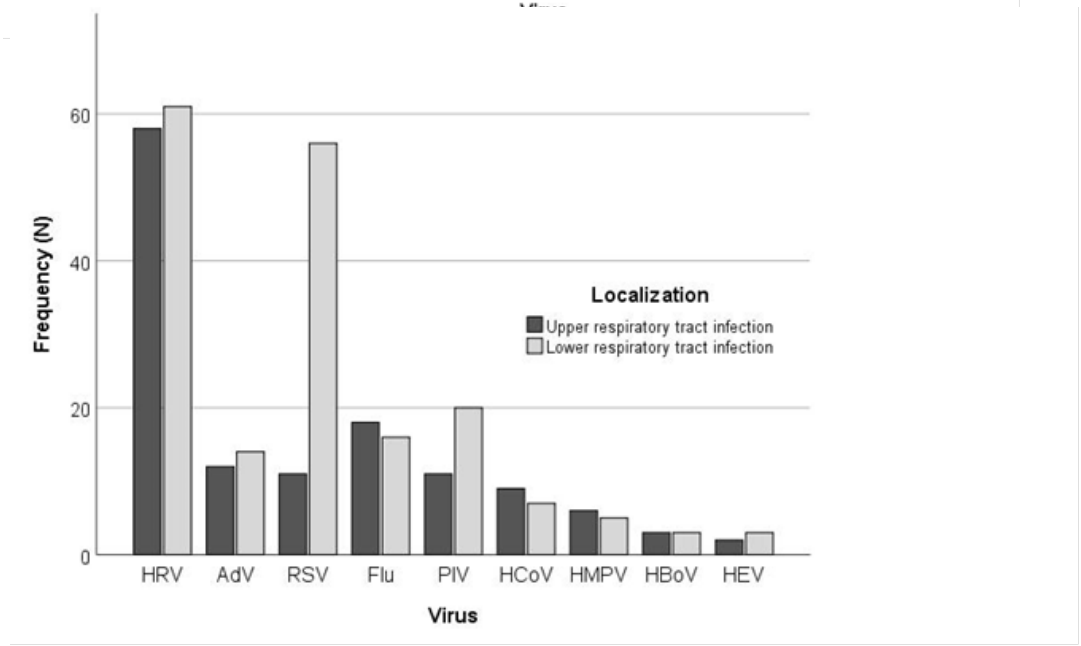
Rhinoviruses (RVs) are increasingly implicated not only in mild upper respiratory tract infections, but also in more severe lower respiratory tract infections; however, little is known about species diversity and viral epidemiology of RVs among the infected children. Therefore, we investigated the rhinovirus (RV) infection prevalence over a 2-year period, compared it with prevalence patterns of other common respiratory viruses, and explored clinical and molecular epidemiology of RV infections among 590 children hospitalized with acute respiratory infection in north-western and central parts of Croatia. For respiratory virus detection, nasopharyngeal and pharyngeal flocked swabs were taken from each patient and subsequently analyzed with multiplex RT-PCR. To determine the RV species in a subset of positive children, 5′UTR in RV-positive samples has been sequenced. Nucleotide sequences of referent RV strains were retrieved by searching the database with Basic Local Alignment Tool, and used to construct alignments and phylogenetic trees using MAFFT multiple sequence alignment tool and the maximum likelihood method, respectively. In our study population RV was the most frequently detected virus, diagnosed in 197 patients (33.4%), of which 60.4% was detected as a monoinfection. Median age of RV-infected children was 2.25 years, and more than half of children infected with RV (55.8%) presented with lower respiratory tract infections. Most RV cases were detected from September to December, and all three species co-circulated during the analyzed period (2017–2019). Sequence analysis based on 5′UTR region yielded 69 distinct strains; the most prevalent was RV-C (47.4%) followed by RV-A (44.7%) and RV-B (7.9%). Most of RV-A sequences formed



Rinovirusi – naša iskustva

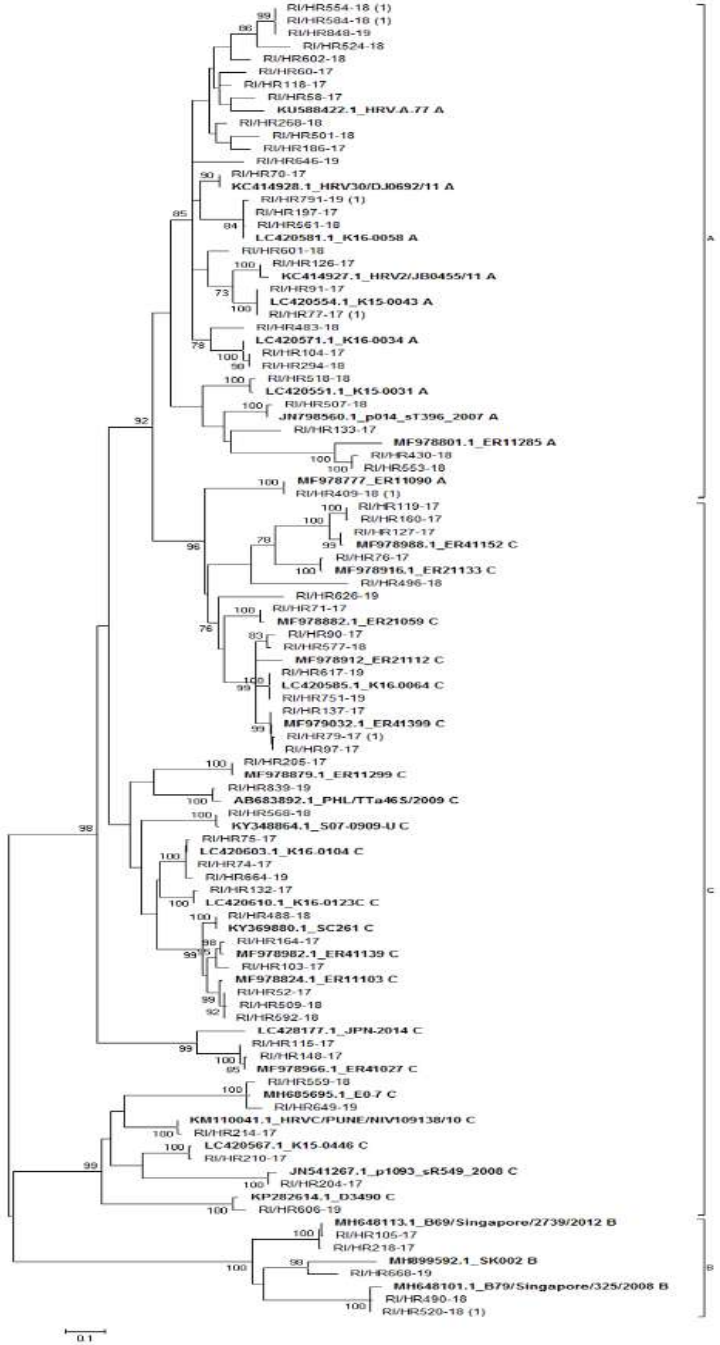
- Medijan dobi za djecu s HRV (2.25) je viši nego u djece inficirane s RSV (0.41), PIVs (1.04), HCoV (1.33), HMPV (0.92), i HBoV (1.21), ali niži nego u djece inficirane s Flu (3.58), AdV (2.88), i HEV (3.66)
- Više od polovice djece inficirane s HRV imalo je infekciju donjeg dišnog sustava (LRTI 110; 55.8% vs. URTI 87; 44.2%; P=0.336)





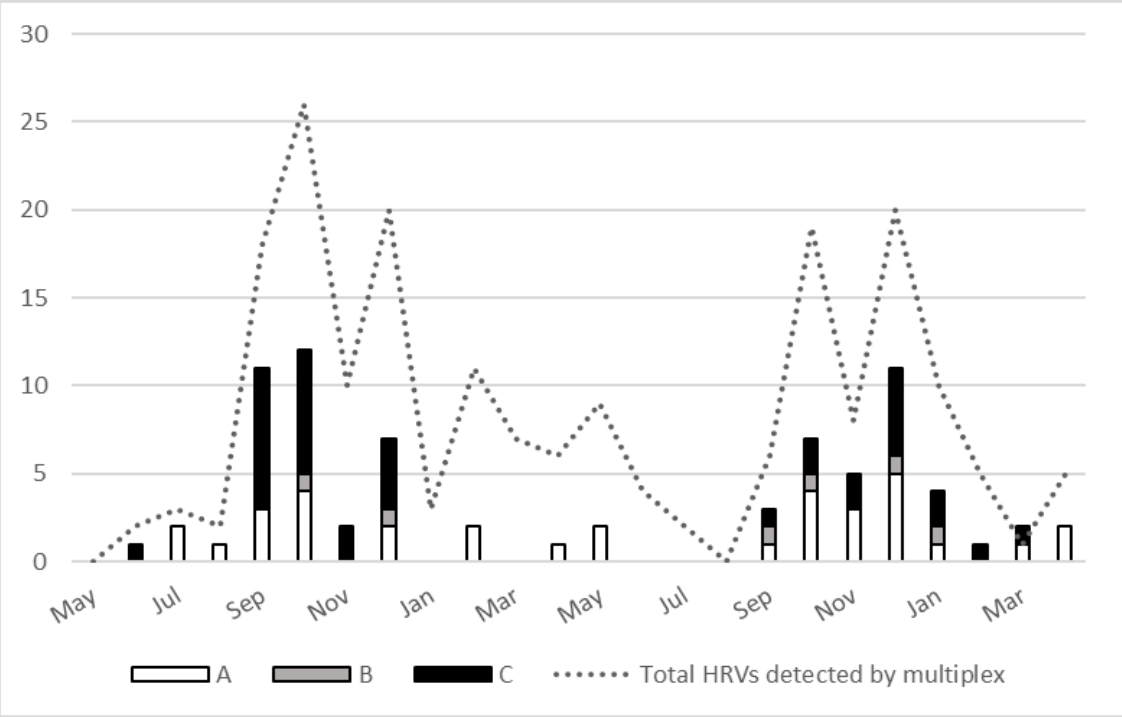
Rinovirusi – naša iskustva

- Od ukupno 197 HRV-pozitivnih uzoraka, sekvencirano je 76 (39%)
- Ampilfikacija, sekvenciranje i analiza 395 bp 5’ UTR regije
- Najčešći su bili HRV-C (47.4%) zatim HRV-A (44.7%) i HRV-B (7.9%)
- Nije bilo značajne razlike u simptomima i kliničkoj prezentaciji s obzirom na vrstu!

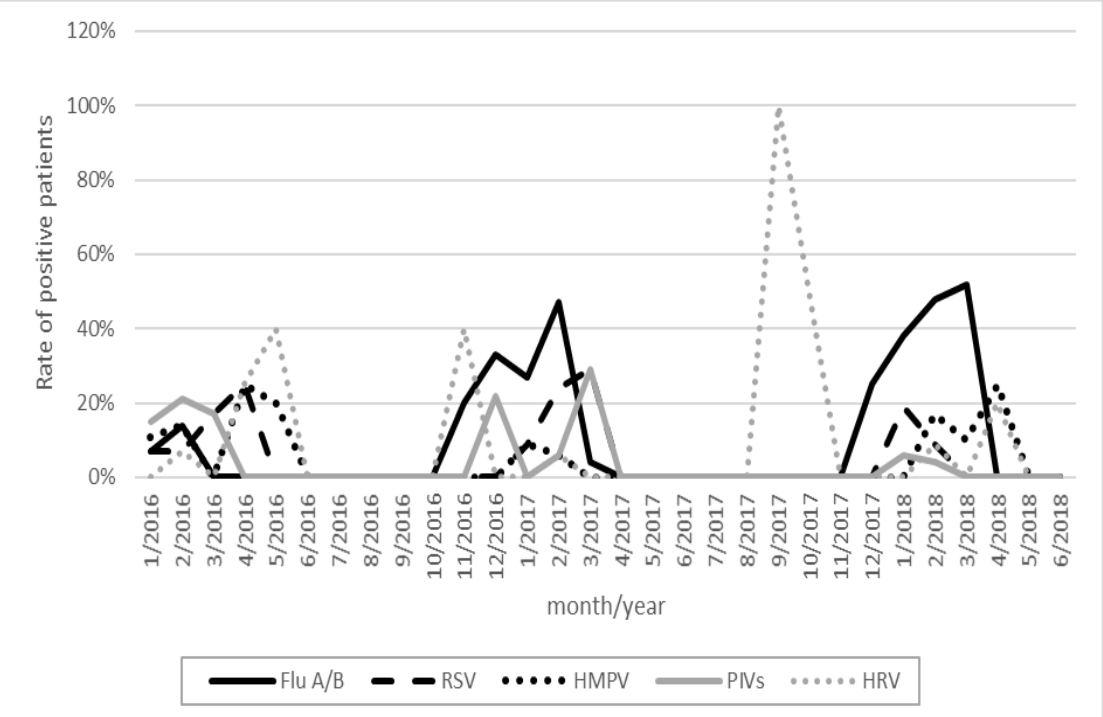


Rinovirusi – naša iskustva

Većina slučajeva je detektirana od rujna do siječnja, sve tri vrste su cirkulirale tiejkom analiziranog perioda (2016-2018)

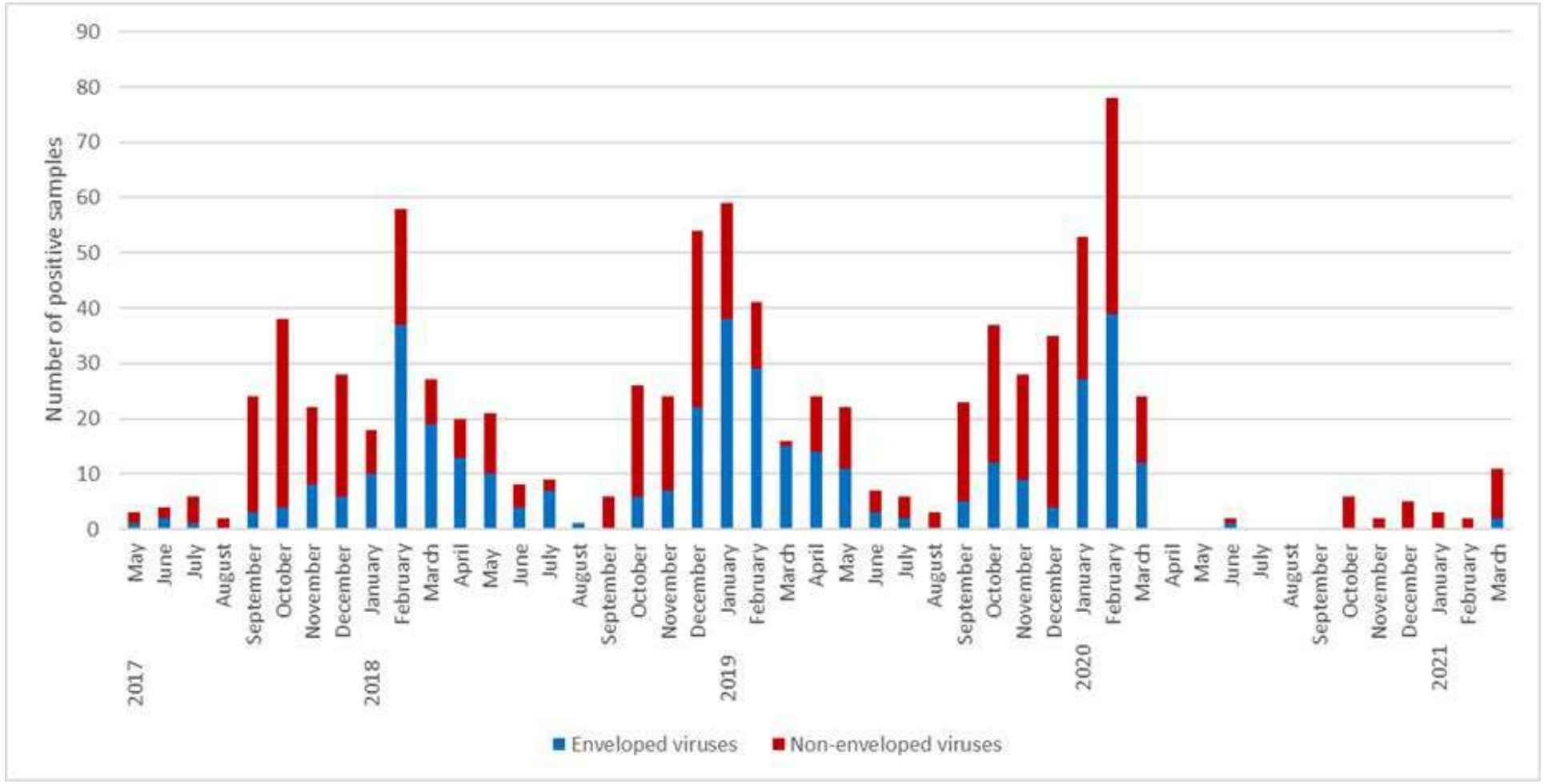


S. Ljubin-Sternak et al. Front in Microbiol. 2019

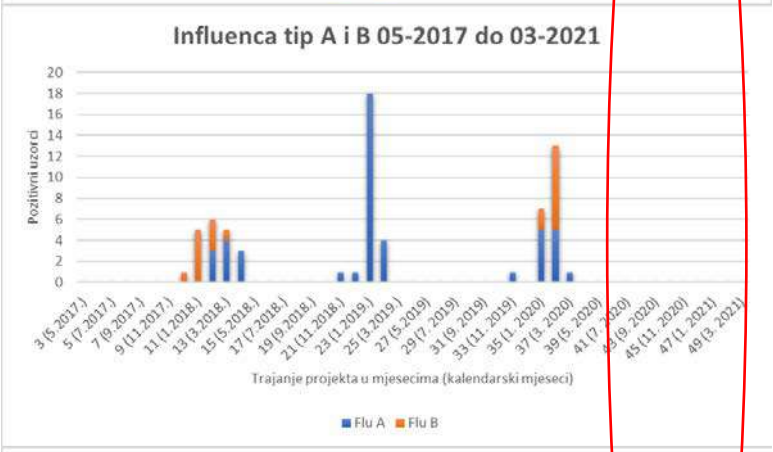


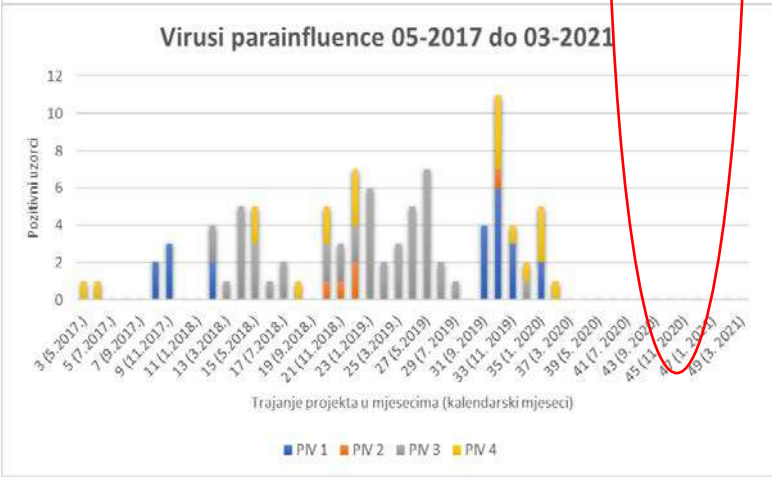
Čivljak et al; J Med Virol. 2019

Naša iskustva – sezonstvo respiratornih virusa 2017-2021




Respiratorni sincicijski i metapneumovirus 05-2017 do 03-2021
Pozitivni uzorci
Trajanje projekta u mjesecima (kalendarski mjeseci)
RSV
HMPV


Influenca tip A i B 05-2017 do 03-2021
Pozitivni uzorci
Trajanje projekta u mjesecima (kalendarski mjeseci)
Flu A
Flu B

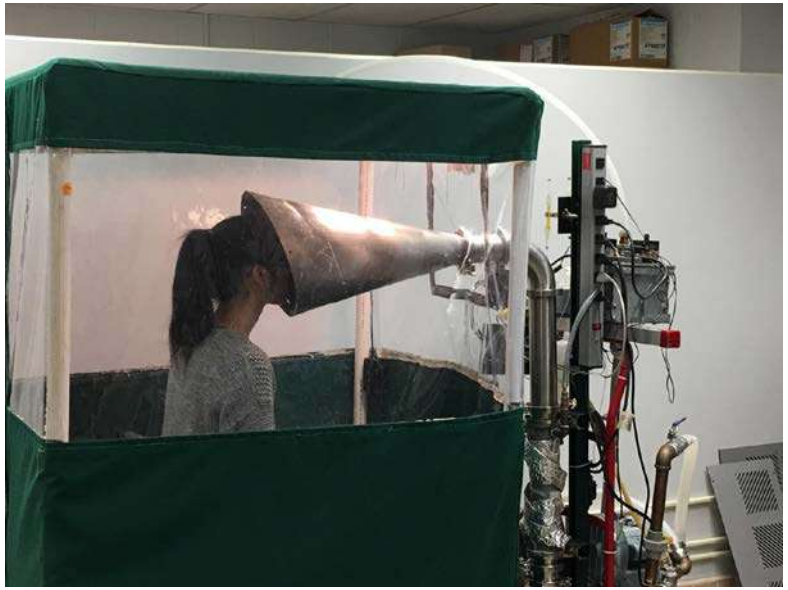

Virusi parainfluence 05-2017 do 03-2021
Pozitivni uzorci
Trajanje projekta u mjesecima (kalendarski mjeseci)
PIV 1
PIV 2
PIV 3
PIV 4

≠


Rinovirusi 05-2017 do 03-2021
Pozitivni uzorci
Trajanje projekta u mjesecima (kalendarski mjeseci)

Sprječavaju li kirurške maske širenje rinovirusa?

Leung N et al. Respiratory virus shedding in exhaled breath and efficacy of face masks, **Nature medicine** 2020



Virus shedding by participants was measured using the Gesundheit II machine developed by the University of Maryalnd's Dr. Don Milton

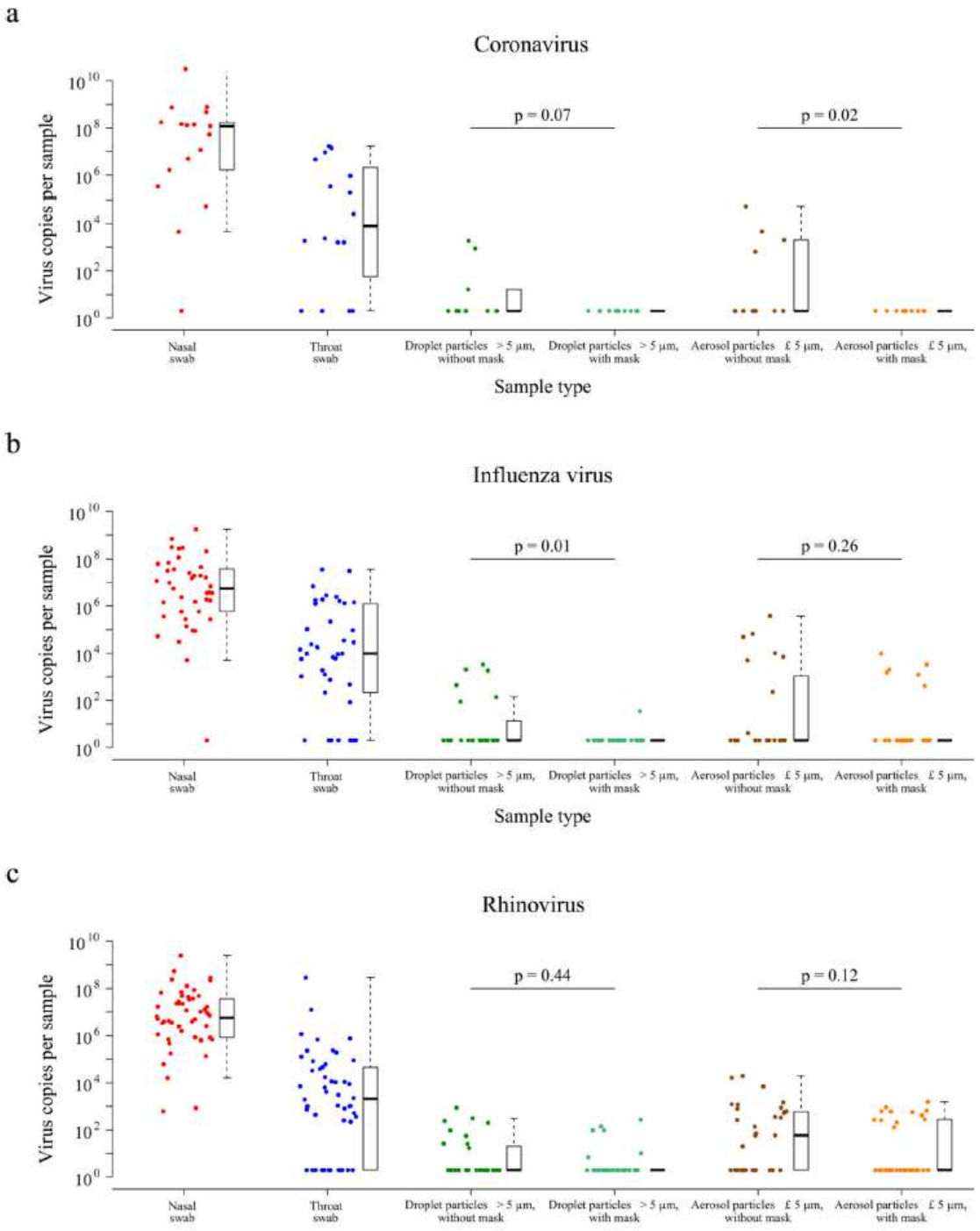


Figure 1. Efficacy of surgical face masks in reducing respiratory virus shedding in respiratory droplets and aerosols of symptomatic individuals with (a) coronavirus, (b) influenza virus or (c) rhinovirus infection.

The figure showed the virus copies per sample collected in nasal swab (red), throat swab (blue), respiratory droplets collected for 30 minutes while not wearing (dark green) or wearing (light green) a surgical face mask, and aerosols collected for 30 minutes while not wearing (brown) or wearing (orange) a face mask, collected from individuals with acute respiratory symptoms who were RT-PCR positive for coronavirus, influenza virus and rhinovirus in any samples. P-values for mask intervention as predictor of $\log_{10}$virus copies

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Omogućavanje ranog otkrivanja: Naši proizvodi za proučavanje respiratornih infekcija

Dr.sc. Branka Jeličić, ***Voditeljica servisne i tehničke podrške***

Tailored respiratory diagnostic solutions

Enabling clinical laboratories to identify multiple respiratory pathogens in the same sample

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About Biosistemi d.o.o.

With more than 30 years in business as a stable and growing company in service of science and diagnostics, activities of Biosistemi d.o.o. are based on knowledge, experience and focus of the sales team, application and service support, and professional logistics.

Professionalism, partnership, teamwork, integrity, and open communication are our basic principles of cooperation with customers, dealers and within Biosistemi.

MISSION

Our purpose is to use our knowledge and expertise in creating tailor-made workflows in partnership with the customer and provide reliable quality support to accelerate research, encourage innovation and improve outcomes in diagnostic area.

VISION

We have dedicated ourselves to becoming a partner of choice that contributes to improving lives by making future a reality.

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In partnership with leading brands in the field of molecular biology and pathogen research, as well as prominent diagnostic brands with extensive portfolio of respiratory pathogen detection solutions for every laboratory.

ThermoFisher SCIENTIFIC

Sacace BIOTECNOLOGIES

Clonit

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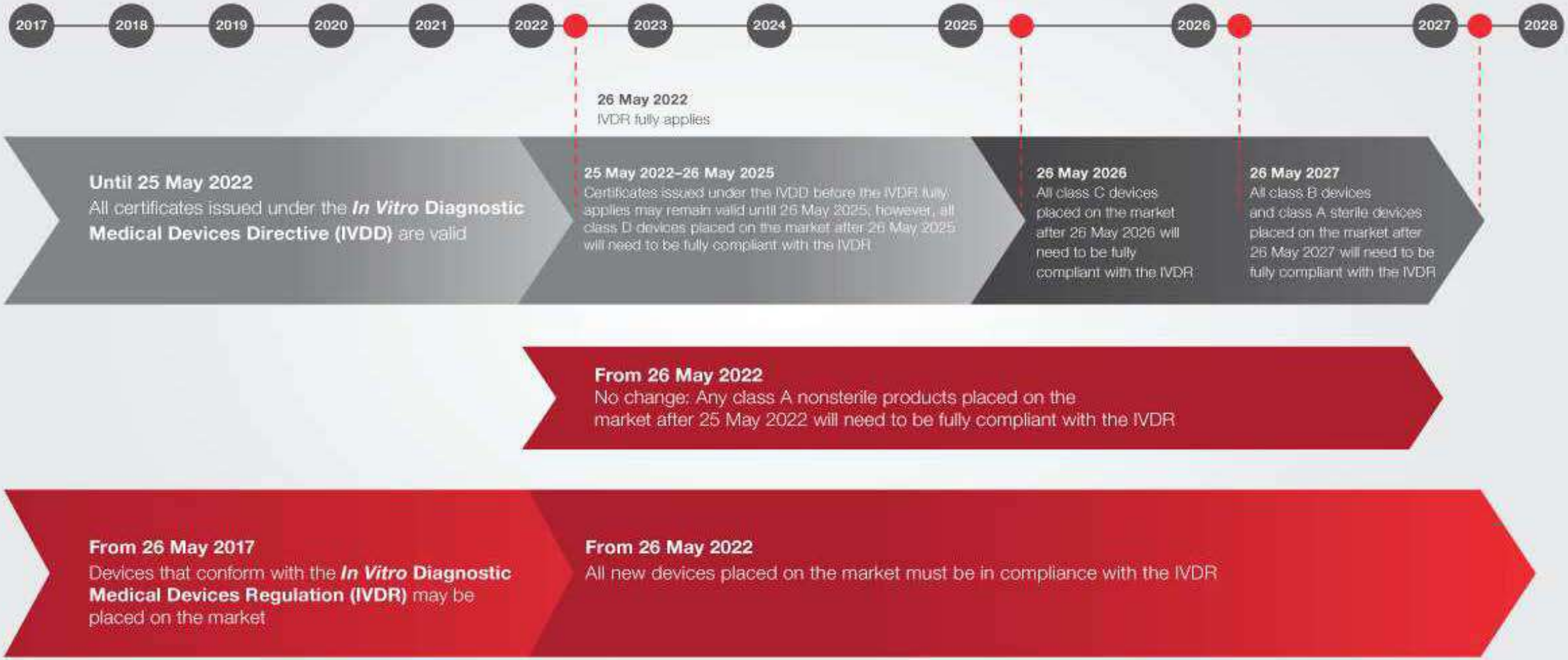
IVDR transition timelines



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We present you our complete workflow adjustable for laboratory throughput, experience and ease-of-use

Flow Cytometry

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Extraction Kits Reagents (To Use With SaMag™ System)

PRODUCT	CAT.	TYPE	COMPOSITION	DESCRIPTION
SaMag™ Viral Nucleic Acid Extraction Kit	SM003	CEIVD	1 kit (48 extractions) including all plastic disposables	For extraction of viral nucleic acids from plasma, serum or cell-free body fluids
SaMag™ Bacterial DNA Extraction Kit	SM006	CEIVD	1 kit (48 extractions) including all plastic disposables	For extraction of genomic DNA from both Gram-positive and Gram-negative bacteria from a variety of matrixes
SaMag™ STD DNA Extraction Kit	SM007	CEIVD	1 kit (48 extractions) including all plastic disposables	For extraction of STD DNA (for ex. Chlamydia trachomatis, Neisseria gonorroeae, Human Papilloma Virus...etc.) from swabs, urine, seminal liquid
SaMag™ TB DNA Extraction Kit	SM008	CEIVD	1 kit (48 extractions) including all plastic disposables	For extraction of Mycobacterium tuberculosis DNA from clinical specimen or culture
SaMag™ Tissue DNA Extraction Kit	SM004	CEIVD	1 kit (48 extractions) including all plastic disposables	For extraction of genomic DNA from a variety of tissues
SaMag™ Blood DNA Extraction Kit	SM001	CEIVD	1 kit (48 extractions) including all plastic disposables	For extraction of genomic DNA from whole blood, peripheral blood mononuclear cells or buffy coat
SaMag™ FFPE DNA Extraction Kit	SM009	CEIVD	1 kit (48 extractions) including all plastic disposables	For extraction of genomic DNA from FFPE samples

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Image	Name	Sample Type
	MagMAX Viral/Pathogen Nucleic Acid Isolation Kit	Blood Buccal swab Cell Cultures Plasma serum Feces Saliva Other swabs
	MagMAX Viral/Pathogen II (MVP II) Nucleic Acid Isolation Kit	Blood Buccal swab Cell Cultures Plasma serum Feces Saliva Other swabs
	MagMAX Viral/Pathogen Ultra Nucleic Acid Isolation Kit	Blood Buccal swab Cell Cultures Plasma serum Feces Saliva Other swabs
	MagMAX Pathogen RNA/DNA Kit	Blood Buccal swab Cell Cultures Plasma serum Feces Saliva

KingFisher Automated Purification Instruments

Each benchtop KingFisher purification instrument is designed for processing at different throughput levels, volume
run. Decide which automated purification system is right for your laboratory research or testing.

KingFisher instrument			
			
	Duo Prime	Flex	Apex

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ThermoFisher SCIENTIFIC

Validated workflow
Its full workflow, from sample preparation to software-generated result in just 3 hours, makes it easy to implement

Single tube
Detecting 5 viruses and an endogenous internal control, all in a single well, makes it easy to perform routine patient testing

Affordable price
Easily adopt this panel and never overpay for the targets you need

PCR performance
High sensitivity for the vast majority of strains gives you confidence in results

Controls included
Included RNase P and positive controls offer reliable runs, time after time

Flexible throughput
Scalable to fit your needs, allowing you to test from 1 to 94 samples, as needed

A51334	TAQPATH COVID-19 RNASE P COMBO 1000 RXNS
A51334RR	TAQPATH COVID-19 RNASE P COMBO EACH
A48067	TAQPATH COVID-19 CE-IVD KIT EACH
A49867RR	TAQPATH COVID-FLU-RSV ASY KIT EACH
A47814	TAQPATH RTPCR COVID-19-1000RXN EACH
A49538	TAQPATH COVID-FLU ASY KIT EACH
A51330	TQPATH COV-19 MS2 COMBO KT 2.0 1000 RXNS
A49956	TQPTH COVID FLU RSV ASSAY KIT EACH
A49958	TQPTH COVID FLU RSV DIL BUFFER EACH

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V439-48FRT	ARVI Plus Real-TM
V57-100FRT	ARVI Screen Real-TM
R-V33-FRT	Avian A Screening & Avian H5N1 Typing FRT
B84-100FRT	Bordetella pertussis/B.parapertussis/B.bronchiseptica Real-TM
V54-50FRT	Influenza A H1N1 & H3N2 Real-TM
V47-50FRT	Influenza A H5 H7 H9 Typing FRT
V36-100FRT	Influenza A, B Real-TM
B50-50FRT	Legionella pneumophila Real-TM
V65-50FRT	MERS-SARS CoV Real-TM
H3611-50FRT	MTB MDR Real-TM
B15-50FRT	MTB Real-TM
B41-50FRT	Mycobacterium tuberculosis Diff Real-TM
B42-4-50FRT	Mycoplasma pneumoniae / Chl. pneumoniae Real-TM
B42-4-100FRT	Mycoplasma pneumoniae / Chl. pneumoniae Real-TM
B76-50FRT	Pseudomonas aeruginosa Quant Real-TM
V435-100FRT	SARS-CoV-2 Real-TM
V448-100FRT	SARS-CoV-2/Hrsv/Influenza A/B Real-TM
V440-100FRT	SARS-CoV-2/Influenza A/B Real-TM
V55-50FRT	Swine Influenza Virus H1 Real-TM

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Sacace
BIOTECNOLOGIES

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EBR019032	M. tuberculosis Complex
EBR012032	Mycoplasma pneumoniae
EBR008032	Adenovirus
EBR011032	Legionella spp.
EBR007032	Legionella pneumophila
EBR010032	Mycobacterium avium Complex
RT-25HT	Covid 19 HT Screen (N1,N2)
RT-25HT501	Covid 19 HT Screen 501 (N1,N2, S gene)
RT-26	Flu A/Flu B/ SARS-CoV-2
RT-27	Covid Variant Catcher
RT-27v2	Covid Ultra Variant Catcher

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	QuantStudio 5 Real-Time PCR System	QuantStudio 7 Flex Real-Time PCR System	QuantStudio 7 Pro Real-Time PCR System	QuantStudio 12K Flex Real-Time PCR System
Format	TaqMan array plates	TaqMan array plates, TaqMan array cards	TaqMan array plates, TaqMan array cards	TaqMan array plates, TaqMan array cards, OpenArray plates
Throughput	Low to medium	Medium to high	Medium to high	Very high
Run time	96-well block: <30 min 384-well block: <35 min	96-well block (fast): 30 min 384-well block: 35 min	96-well block: 30 min 384-well block: 35 min	• 96-well block: 30 min • 384-well block: 35 min • Gene expression: 2 hr • Genotyping: 4 hr
Automation	No	Yes	Yes	Yes

CE IVD

CE IVD

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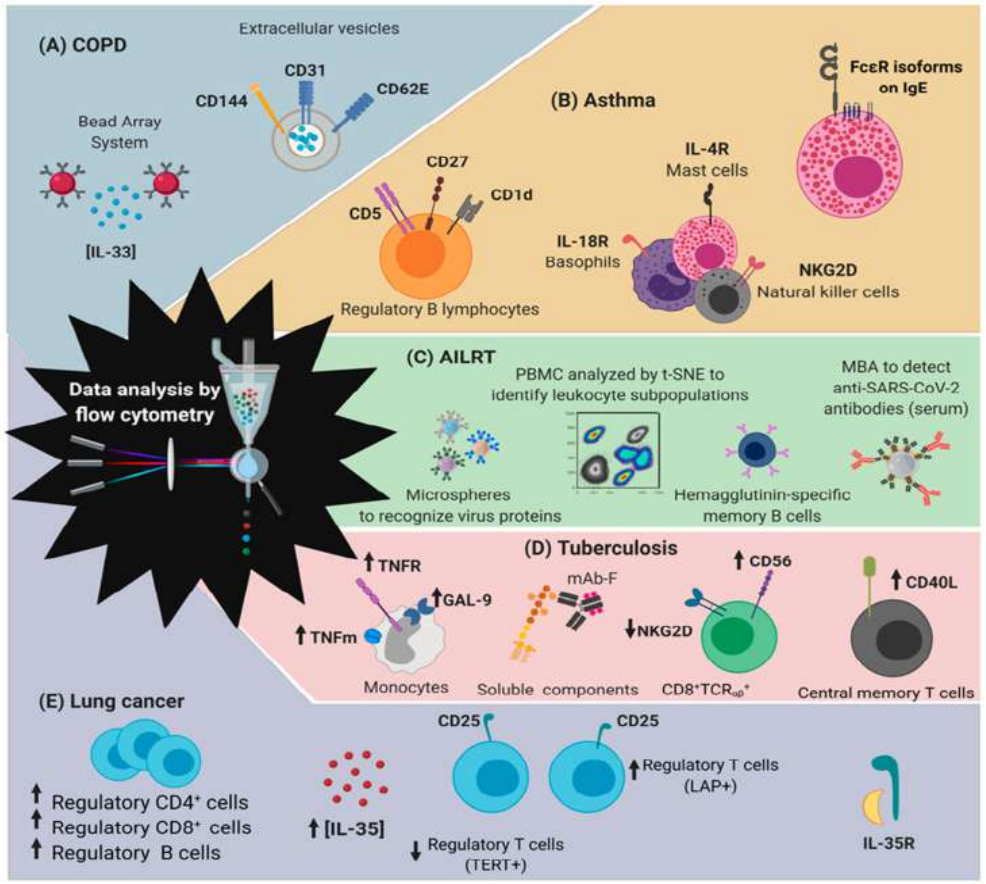
Flow Cytometry

Flow Cytometry: From Experimental Design to Its Application in the Diagnosis and Monitoring of Respiratory Diseases



Flores-Gonzalez J, Cancino-Díaz JC, Chavez-Galan L. Flow Cytometry: From Experimental Design to Its Application in the Diagnosis and Monitoring of Respiratory Diseases. Int J Mol Sci. 2020 Nov 22;21(22):8830. doi: 10.3390/ijms21228830. PMID: 33266385; PMCID: PMC7700151.

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Infectious disease testing

Real-time PCR research for molecular detection of infectious disease pathogens

Respiratory tract testing solutions

Targeted panels

Targets: 2 to 9

Example: *Chlamydia pneumoniae, Moraxella catarrhalis, Klebsiella pneumoniae*

Syndromic panels

Targets: 10 to 30

Example: Viral and bacterial targets

Antibiotic resistance (ABR) testing solutions

Common ABR markers of interest			
aac(6')-Ib-cr	*blaOXA*	*femA*	*qnrA*
blaACC	*blaPER-1*	*mcr1*	*qnrB*
blaACT	*blaSHV*	*mcr2*	*qnrS*
blaCMY	*blaTEM*	*mcr3*	*sul1*
blaCTX-M	*blaVEB*	*mecA*	*sul2*
blaDHA	*blaVIM*	*mecC*	*tetA*
blaFOX	*cfr*	*metA*	*tetB*
blaGES	*dfrA1*	*nimB*	*tetM*
blaIMP	*dfrA5*	*nimD*	*tetS*
blaKPC	*ermA*	*nimE*	*vanA*
blaMOX	*ermB*	*nimH*	*vanB*
blaNDM	*ermC*	*nimJ*	*vanZ*

Maximize return on investment

We offer a variety of PCR platforms with different capacities to allow you to expand and adapt your menu as testing needs change.

Scalable and efficient

Our selection of formats for real-time PCR assays will enable you to process tens to hundreds of samples per day on a single instrument.

Detect all relevant pathogens

Interrogate carefully curated content with our predesigned microbial panels, or customize your own panel if you are interested in specific targets.

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Infectious disease testing

Real-time PCR research for molecular detection of infectious disease pathogens

Respiratory tract targets				
Adenovirus	*Coronavirus OC43*	*Human metapneumovirus (hMPV)*	*Moraxella catarrhalis*	*Respiratory syncytial virus A (RSV A)*
Bocavirus	*Coxiella burnetii**	*Influenza A (pan)*	*Mumps virus*	*Respiratory syncytial virus B (RSV B)*
Bordetella (pan)	*Enterovirus (pan)*	*Influenza A/H1-2009*	*Mycoplasma pneumoniae*	*Rhinovirus*
*Bordetella holmesii**	*Enterovirus D68*	*Influenza A/H3*	*Parainfluenza virus 1*	*SARS-CoV (SARS)*
Bordetella pertussis	*Haemophilus influenzae*	*Influenza B*	*Parainfluenza virus 2*	*SARS-CoV-2*
Chlamydia pneumoniae	*Herpesvirus 6 (HHV6)*	*Klebsiella pneumoniae complex*	*Parainfluenza virus 3*	*Staphylococcus aureus*
Coronavirus 229E	*HHV3 (varicella zoster virus)*	*Legionella pneumophila*	*Parainfluenza virus 4*	*Streptococcus pneumoniae*
Coronavirus HKU1	*HHV4 (Epstein-Barr virus)*	*Measles virus*	*Parechovirus*	
Coronavirus NL63	*HHV5 (cytomegalovirus)*	*MERS-CoV*	*Pneumocystis jirovecii*	

* Only available on the Applied Biosystems™ TaqMan™ Array Respiratory Tract Microbiota Comprehensive Card.

Target color code: Bacterium | Fungus | Virus

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Obratite nam se s povjerenjem!

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Trnjanska cesta 73, 10 000 Zagreb, Croatia

tel: + 385 1 3460 838; **fax:** + 385 1 3460 840

e-mail: biosistemi@biosistemi.hr

website: www.biosistemigrupa.com

@biosistemigrupa

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Utjecaj COVID-19 pandemije na uobičajene sezonske cikluse respiratornih virusa od posebnog značaja

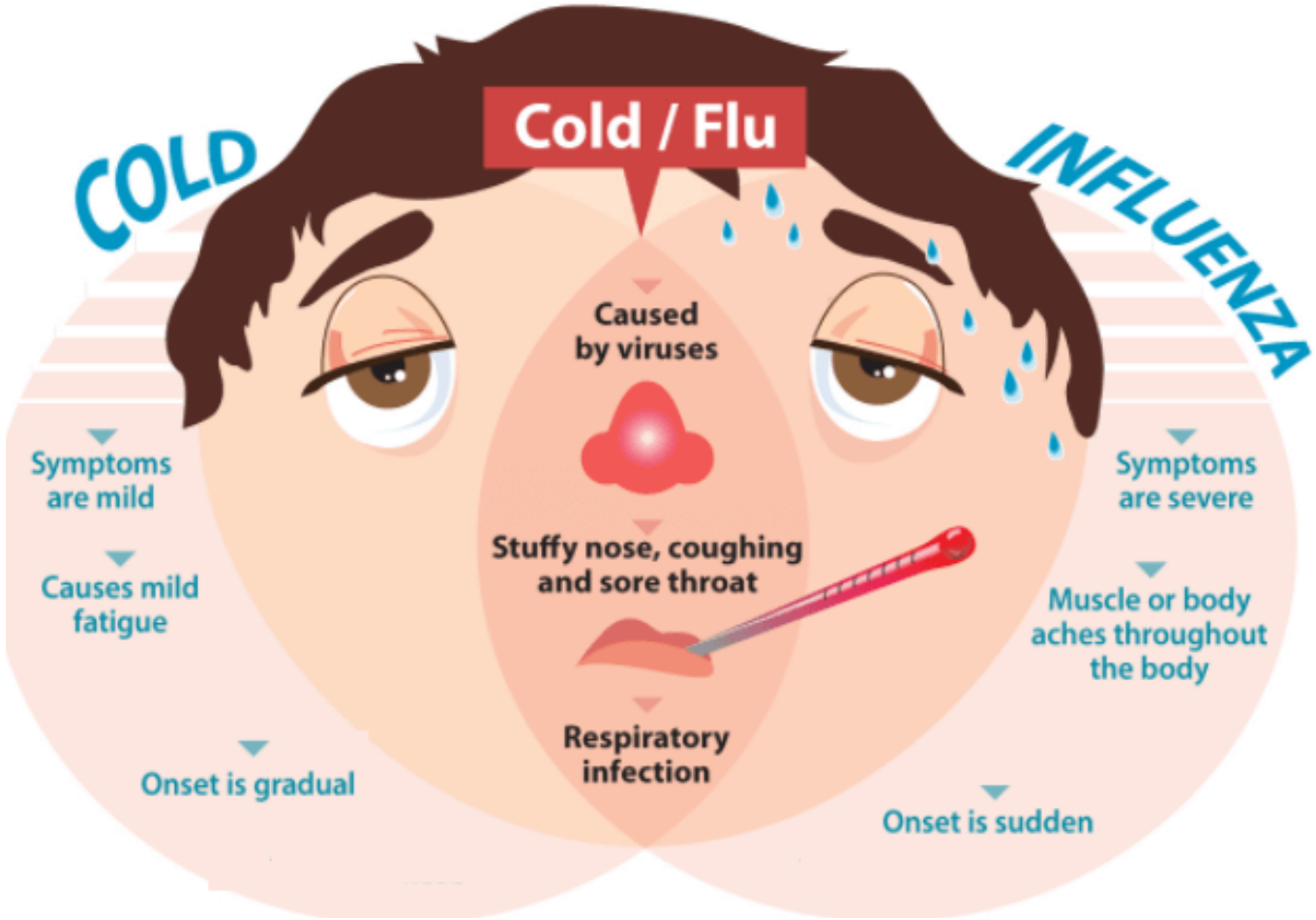
Irena Tabain, Ivana Ferenčak, Željka Hruškar, Anita Jurić, Josipa Kuzle, Dragan Jurić,
Maja Bogdanić, Tatjana Vilibić-Čavlek, Goranka Petrović

Hrvatski zavod za javno zdravstvo

RC MiZ za virološku dijagnostiku infekcija dišnog i probavnog sustava

Suvremene spoznaje o epidemiologiji, kliničkoj slici, laboratorijskoj dijagnostici, terapiji i prevenciji respiratornih infekcija

Zagreb, 15. svibnja 2023. godine


Cold / Flu
COLD
INFLUENZA
Caused by viruses
Symptoms are mild
Causes mild fatigue
Onset is gradual
Stuffy nose, coughing and sore throat
Respiratory infection
Symptoms are severe
Muscle or body aches throughout the body
Onset is sudden

Dvogodišnji ciklus RSV epidemija

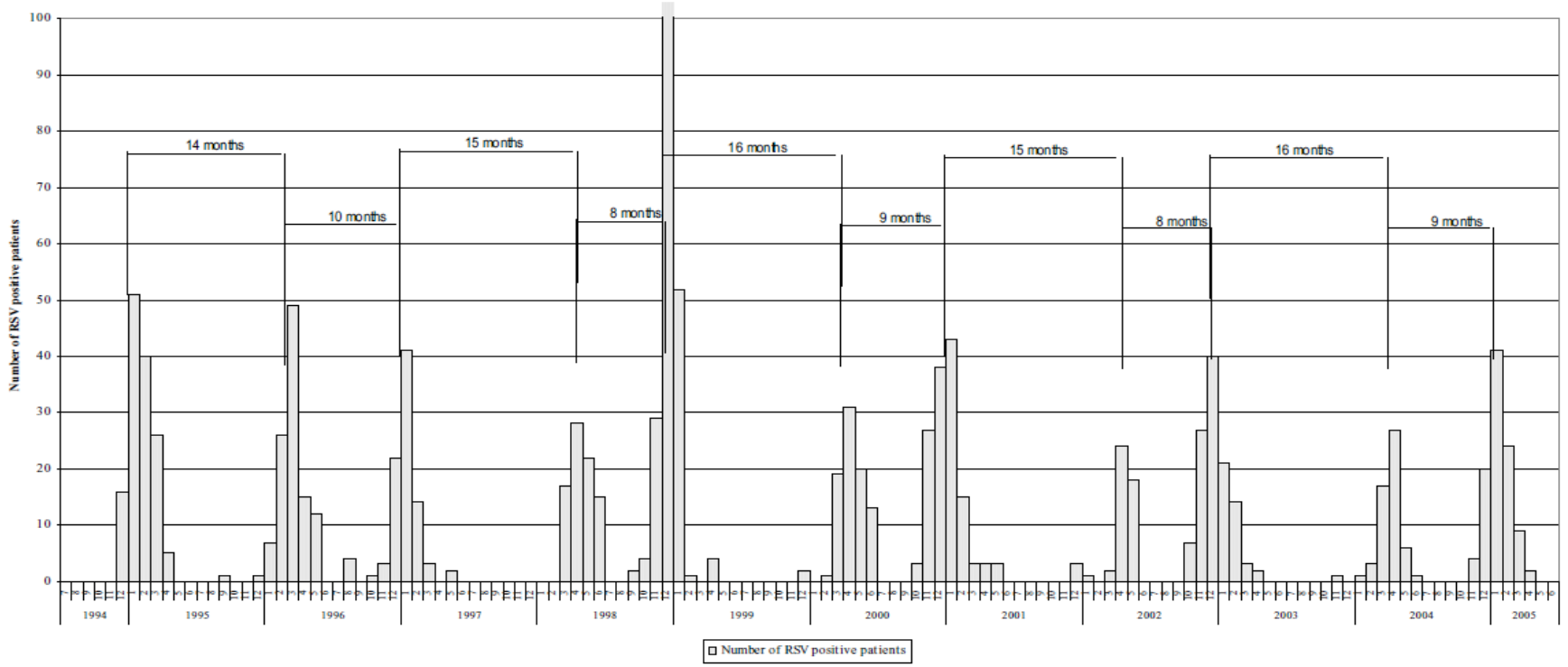
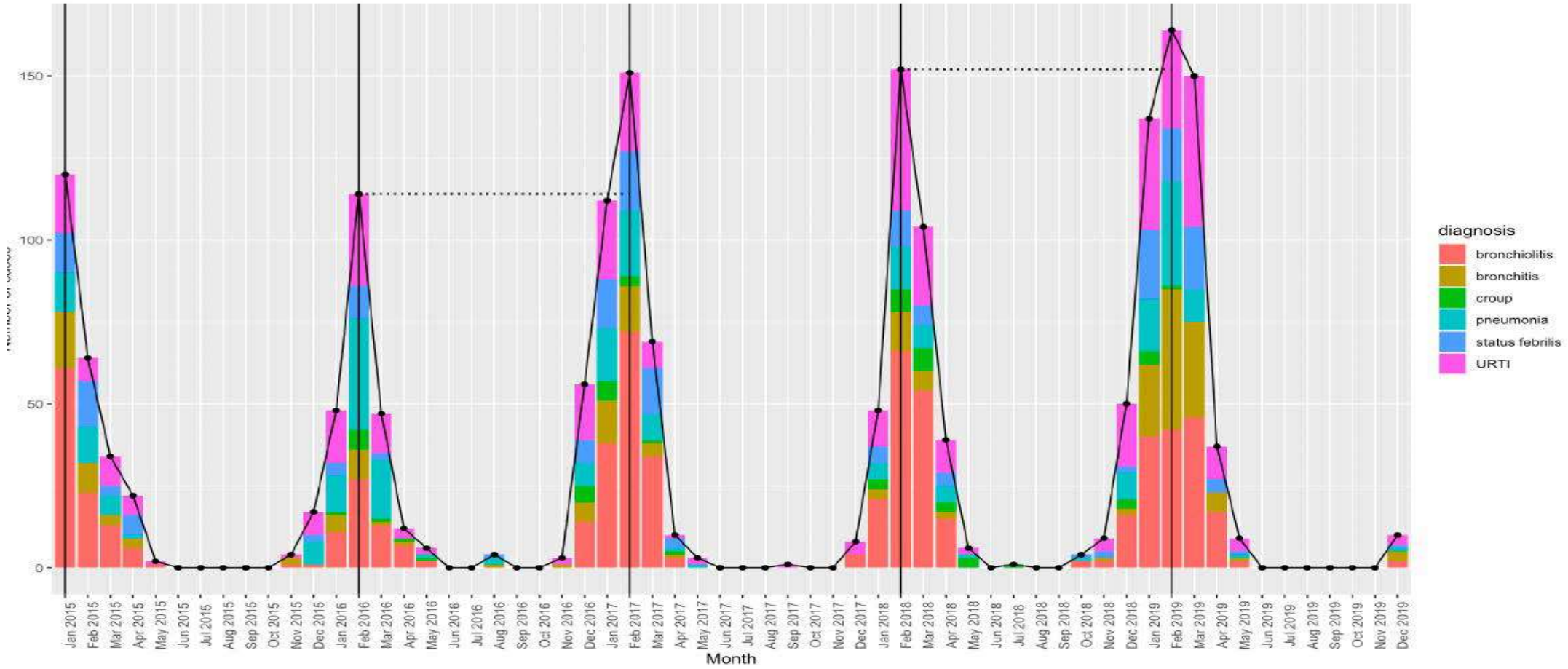


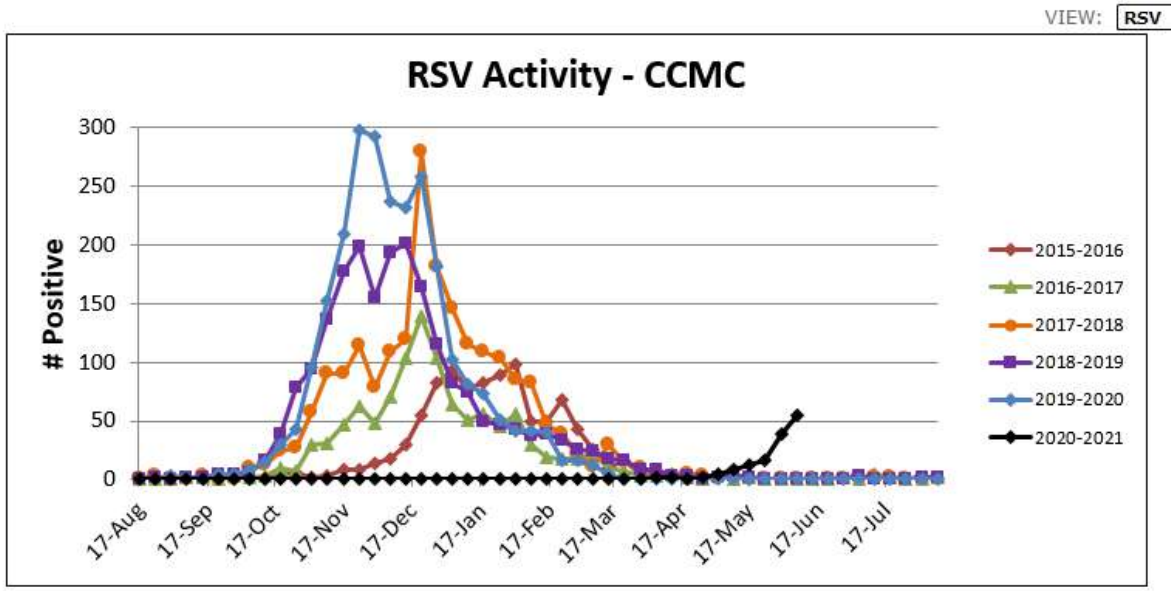
Figure 1
Seasonal occurrence of respiratory syncytial virus infections (number of cases) in Croatia (1994–2005).

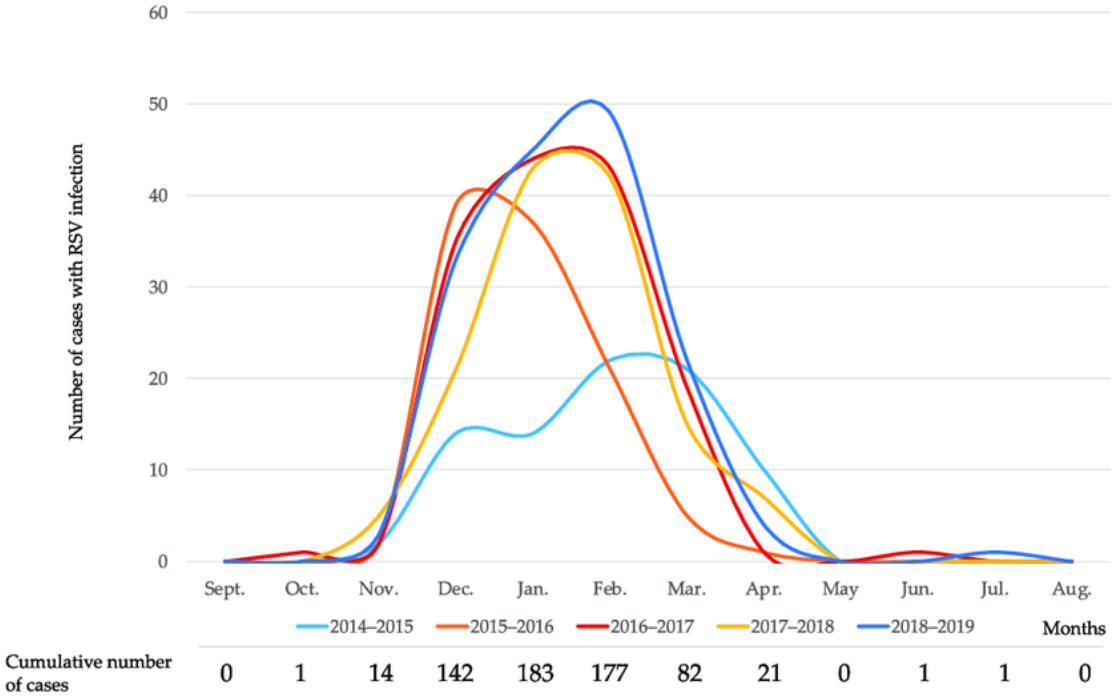
- Nakon velike RSV epidemije, slijedi mala RSV epidemija nakon 14-16 mjeseci i opet 8-10 mjeseci velika RSV epidemija

RSV potvrđeni slučajevi 2015-2019



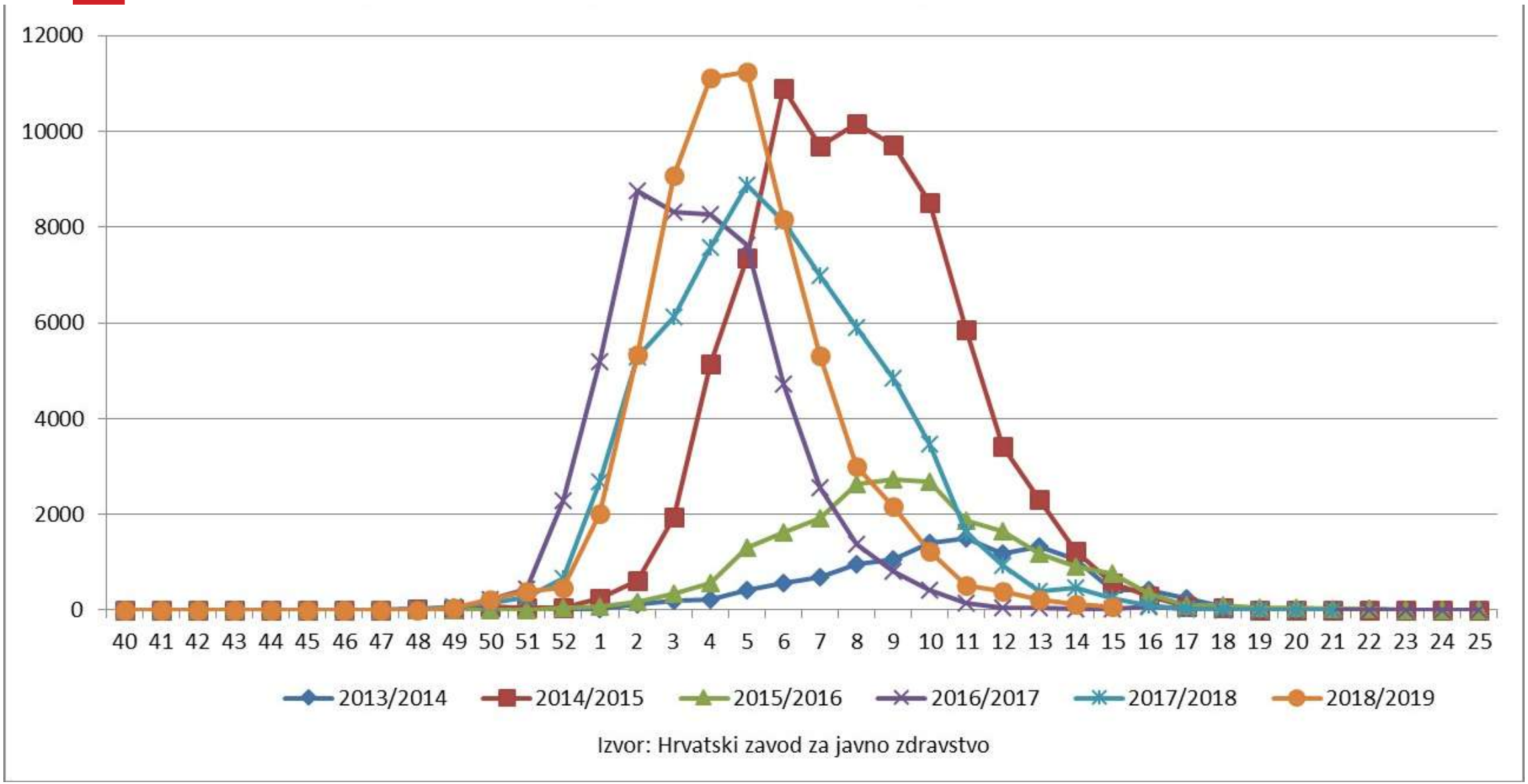
RSV epidemije-iskustva u EU



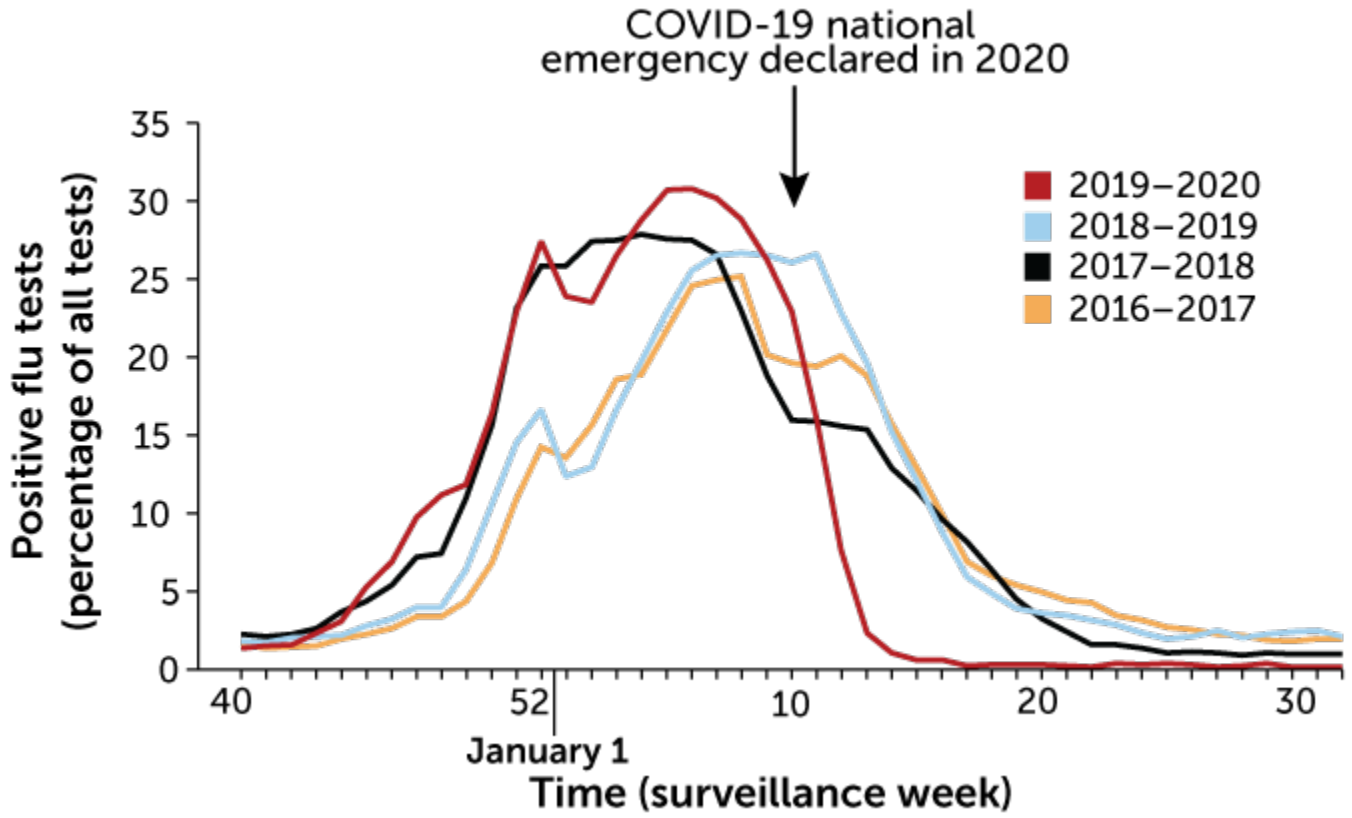


Cumulative number of cases	0	1	14	142	183	177	82	21	0	1	1	0

Influenca 2012-2019 u RH

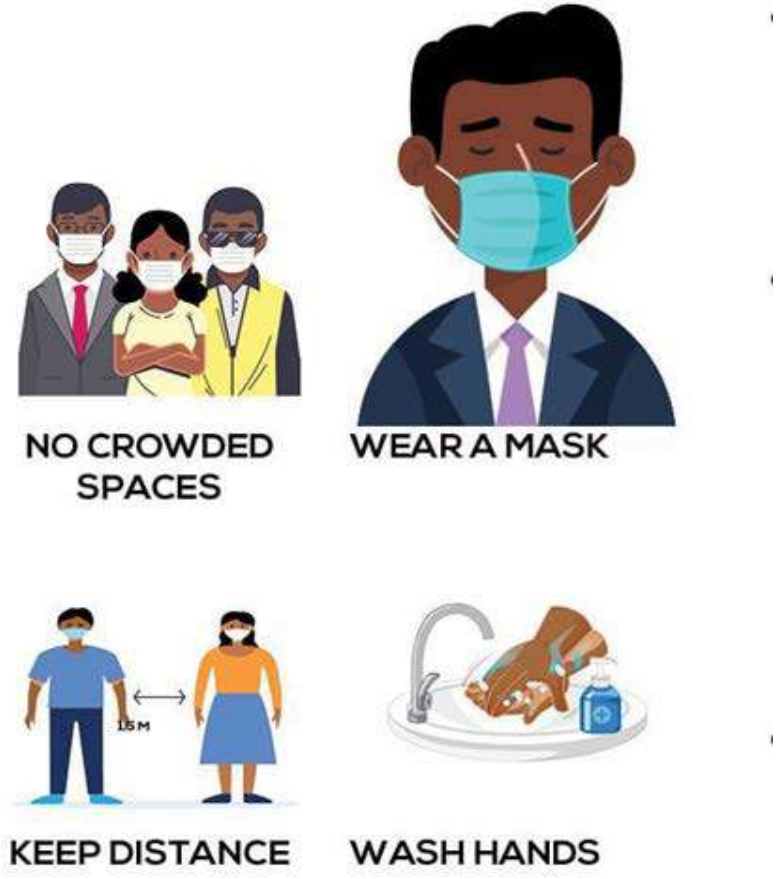


Influenca sezone u EU

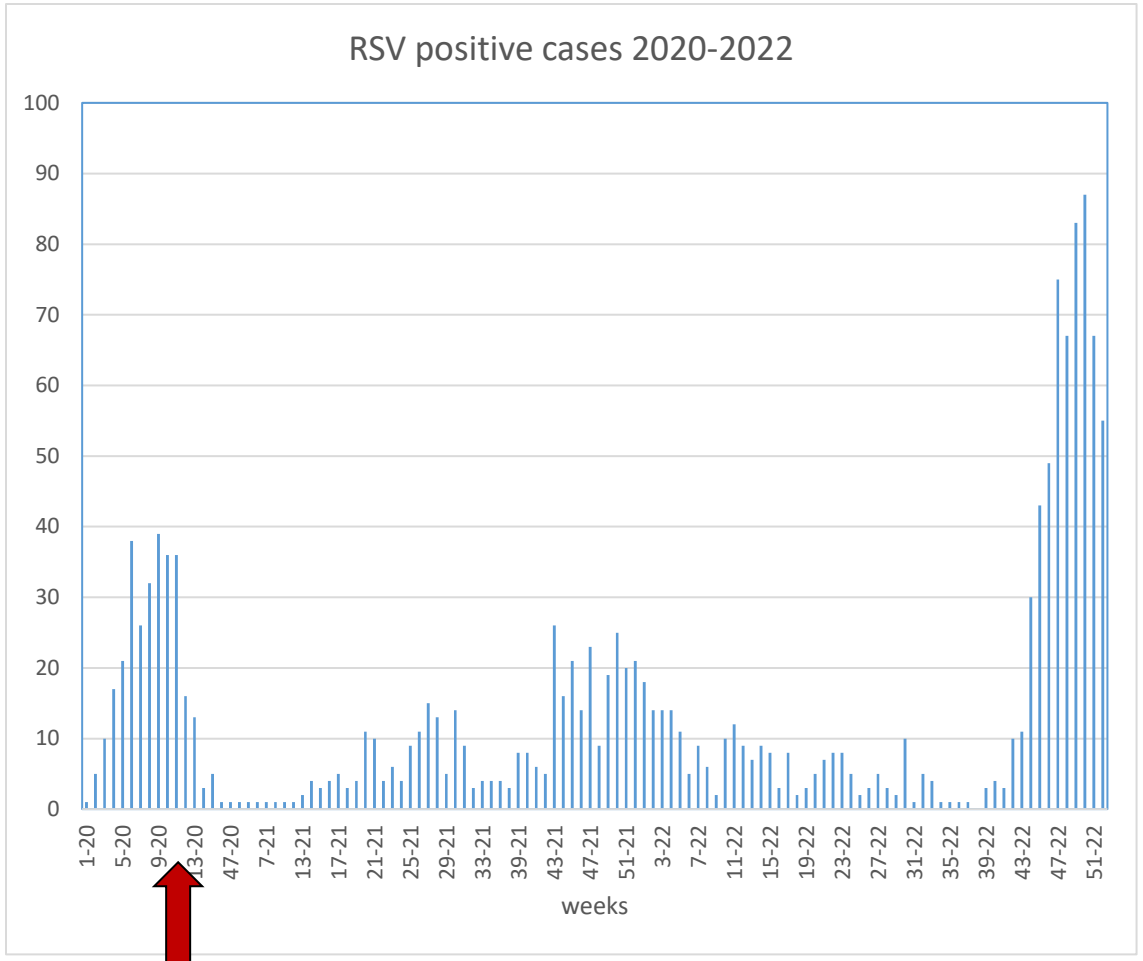


Covid-19 pandemija

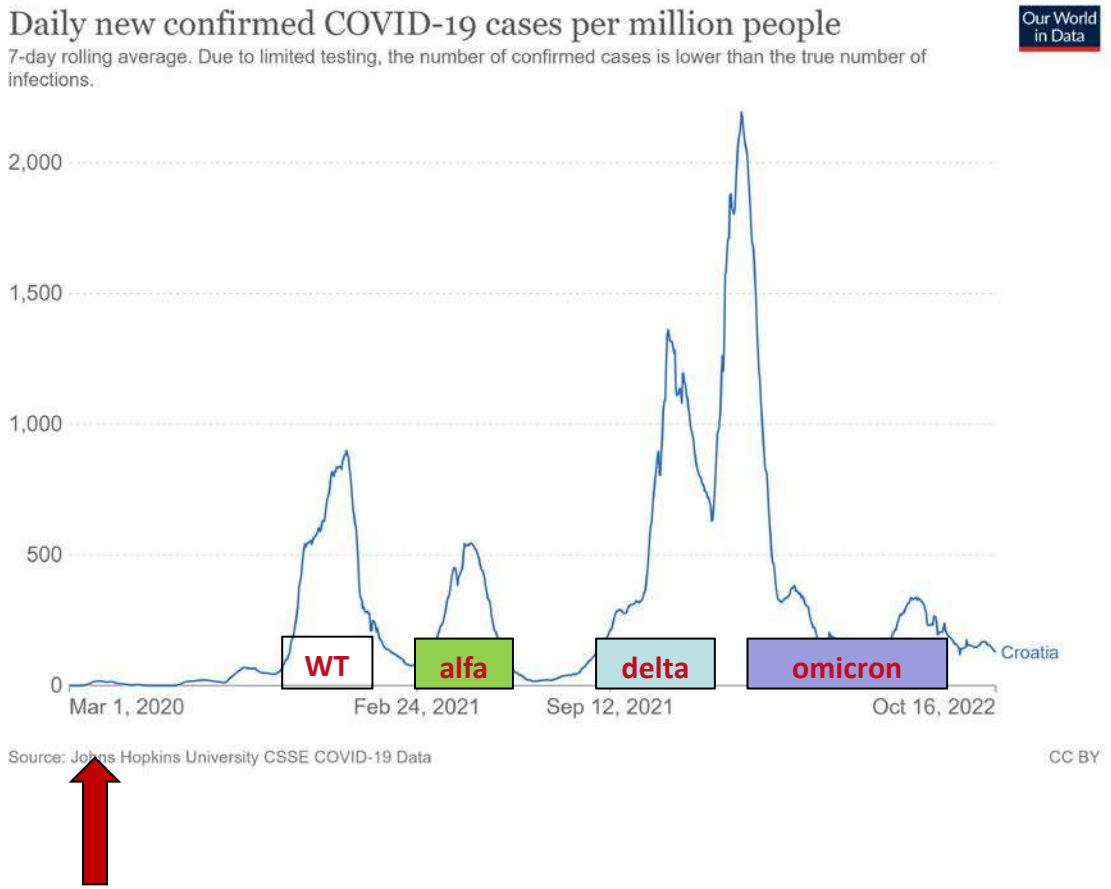
- Primjena ne-farmakoloških mjera
- Kontrola širenja SARS-CoV-2
- Utjecaj na ostale viruse: influenca i RSV
- sezone mogu izvan uobičajenih okvira i s povećanim brojem oboljelih



RSV potvrđeni slučajevi 2020-2022

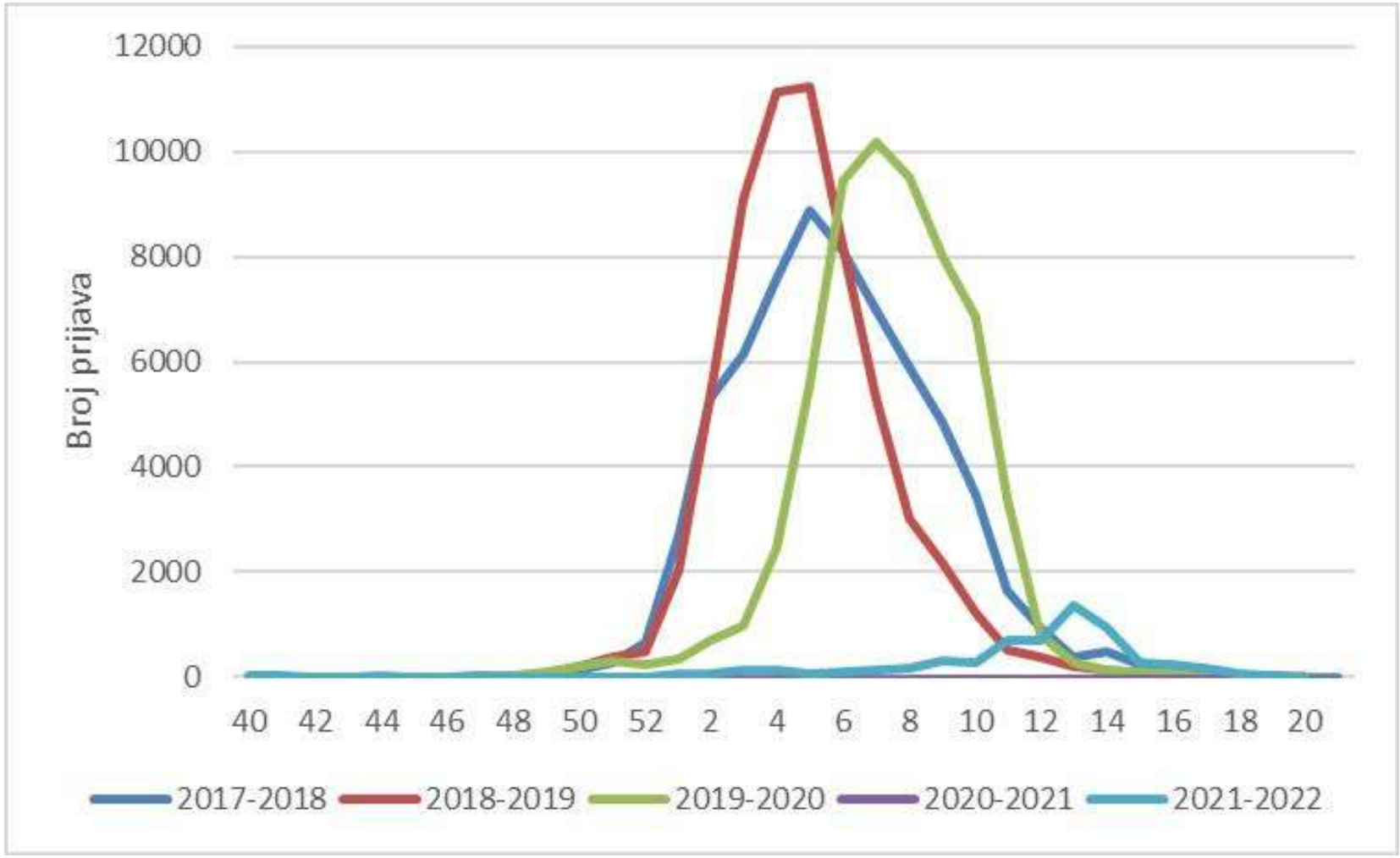


Week 12 COVID-19 restrictions

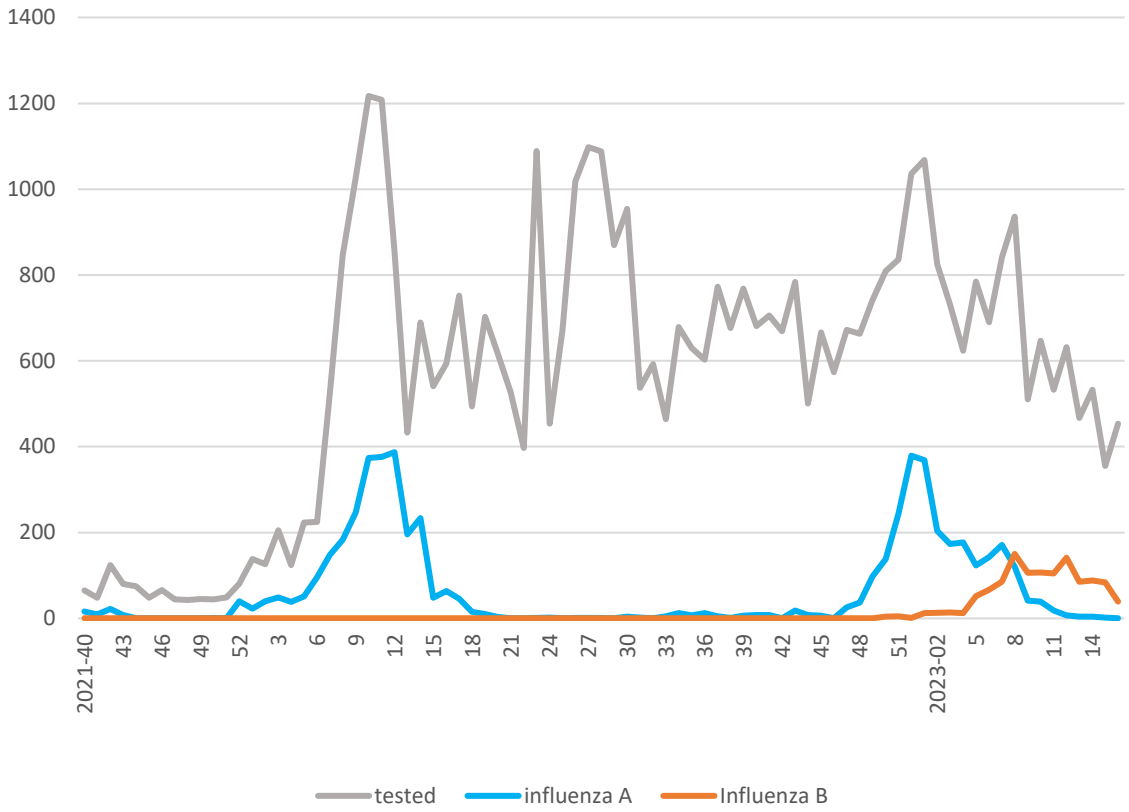


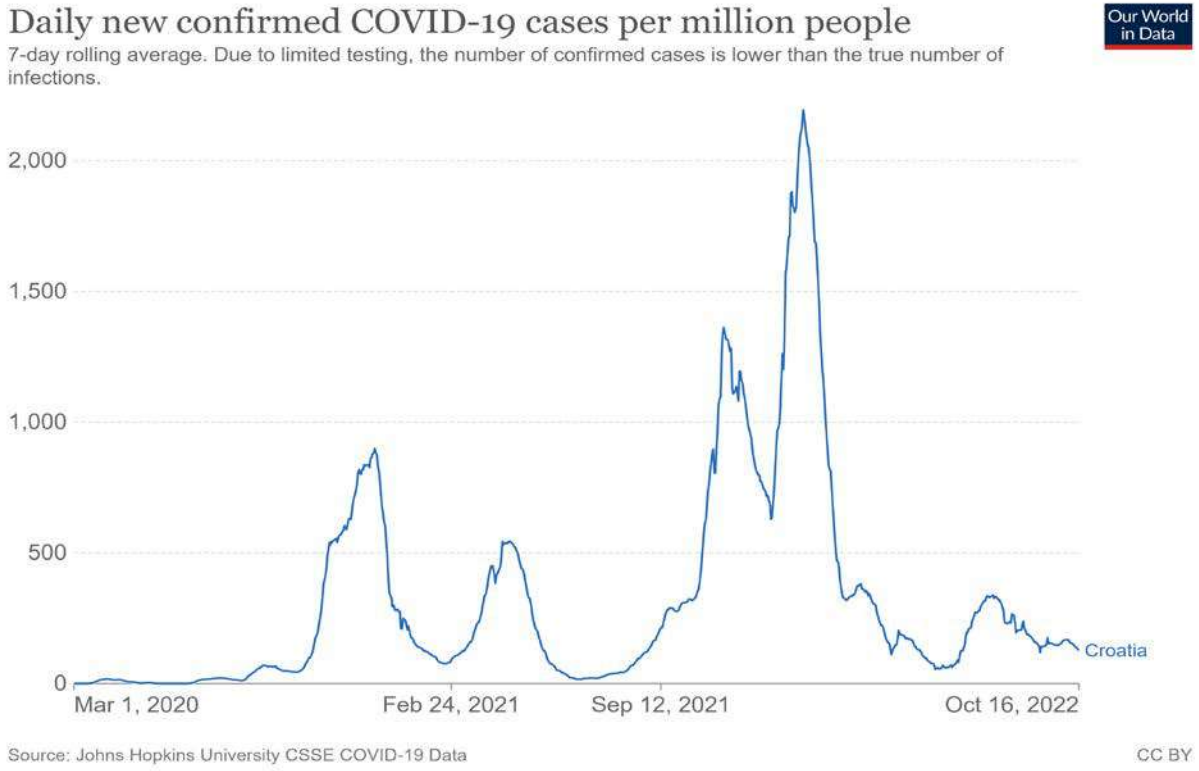
Week 12 COVID-19 restrictions

Influenca 2017-2022



Influenca 2021-2023





Zaključci

- Tijekom pandemije uočena je promjena u dinamici detekcije RSV i influence.
- Preporuča se uspostava cjelogodišnjeg praćenja aktivnosti SARS-CoV-2, RSV i influenca virusa kako bismo im odredili obrasce pojavljivanja.
- važno u svrhu uspostave odgovarajućih i pravovremenih javno-zdravstvenih preventivnih mjera

Mikoze respiratornog sustava

Ana Čičmak
HZJZ
Odjel za mikološku dijagnostiku
15.5.2023.

Gljivične infekcije KOPB bolesnika

- KOPB- kronična nespecifična inflamatorna bolest sa opstrukcijom dišnih puteva, destrukcijom alveola, poremećajem funkcije cilijarnog epitela, fagocitnog sustava i NK aktivnosti
- 4. mjesto uzroka morbiditeta/mortaliteta sa kontinuiranim porastom incidencije u svijetu
- najčešća kronična bolest u kritičnih bolesnika, 22%
- Liječenje KOPB-a dugotrajno i visokim dozama kortikosteroida, širokospektralnim antibioticima i imunosupresivima je značajan rizični faktor kolonizacije i infekcije gljivama

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Shahi i sur.:Aspergillus colonization in patients with chronic obstructive pulmonary disease, 2015.

Aspergillus infection in chronic obstructive pulmonary diseases; Liang Guo i sur.,2022.

Gljivične infekcije KOPB bolesnika

- Aspergiloza pluća: senzibilizacija, kronična plućna aspergiloza (KPA), invazivna plućna aspergiloza (IPA)
- KOPB 3. i 4. stupnja je najznačajniji predisponirajući čimbenik kolonizacije/infekcije Aspergilusom kod bolesnika na intenzivnoj njezi
- 1,63% KOPB bolesnika ima koloniziran donji respiratorni trakt (DRT) Aspergilusom, a 22,1% njih ima vjerojatnu IPA

Shahi i sur.:Aspergillus colonization in patients with chronic obstructive pulmonary disease, 2015.

Gljivične infekcije KOPB bolesnika

- Nedostatak specifične kliničke slike i uniformnih dijagnostičkih kriterija
- Definicija kolonizacije: ≥1 pozitivna kultura/3 uzastopna mjeseca
- Uzorci: sputum, BAL, aspirat traheje
- Prevalencija kolonizacije Aspergilusom 24,6% ; 44% *A. fumigatus*, 31% *A. flavus*, 6,2% *A. niger*, 6,2% *A. terreus*, 6,2% *A. orezea*, 6,2% *A. tubingensis*
- Izolacija *P. aeruginosa* u egzacerbirajućem KOPB-u visoko je povezana sa izolacijom *Aspergillus* vrste)

Shahi i sur.:Aspergillus colonization in patients with chronic obstructive pulmonary disease, 2015.

Linrui Xu i sur.: A Higher Rate of Pulmonary Fungal Infection in Chronic Obstructive Pulmonary Disease Patients with Influenza in a Large Tertiary Hospital, 2019.

Gljivične infekcije KOPB bolesnika

Dijagnostičke metoda dokazivanja PA

- Kultivacija uzorka DRT/48-72h, niske osjetljivosti;

  < 30 % kod IPA, kronične nekrotizirajuće PA (KNPA), kronične kavitarne PA (KKPA), alergijska bronhopulmonarna aspergiloza (ABPA)

  < 10% kod aspergilusnih nodula
- Mikroskopija; <10% pozitivnih nalaza
- BAL- GM test; 80-90% O i S za sve oblike IPA, 75% za KPA (lažno + tijekom terapije PIP/TZP i AMC
- Serum-GM test; 20-80% za IPA, 20-30% za KNPA, 10-65% KPA

Gljivične infekcije KOPB bolesnika

- IgG detekcija temeljna u dijagnostici KPA (O 70-90%), nije prikladno za IPA-KOPB tijekom terapije kortikosteroidima i imunološkog poremećaja same bolesti
- PCR krv/serum visoka O i S, na test ne utječe primijenjena terapija, ne razlikuje kolonizaciju od infekcije, otežano zbog debljine staničnog zida
- mNGS: rana dijagnostika specifičnih patogena, ne razlikuje kolonizaciju od infekcije otežano zbog debljine staničnog zida, ne preporuča se kao monodijagnostika
- Biopsija pluća; invazija hifa u plućno tkivo je dijagnostički kriterij PA
- Preporuka dijagnostike KOPB bolesnika s visokim rizikom za IPA: kombinacija višestrukih testova

Karakteristike IPA- KOPB i IPA hematoloških bolesnika

karakteristike	**IPA- KOPB**	**IPA hematoloških bolesnika**
Klinička slika	Pneumonija otporna na antibiotsko liječenje Pogoršanje dispneje	Visoka temperatura Bol u prsima Kašalj Hemoptiza
Radiološki nalaz	Nespecifične konsolidacije i noduli	Klinasta konsolidacija Noduli „Halo” znak „zračni polumjesec”

Liang Guo i sur.: Aspergillus infection in chronic obstructive pulmonary diseases, 2022.

Dijagnostika i terapija IPA KOPB bolesnika

Dokazana IPA	**Vjerojatna IPA**	**Moguća IPA**
Pozitivan histopatološki nalaz	Postoje faktori rizika domaćina: 3. i 4. stupanj KOPB, kortikosteroidna terapija, Klinički kriterij; dispneja koja traje uz antibiotsku terapiju, nove abnormalnosti u radiološkim prikazima tijekom zadnja 3 mjeseca Mikrobiološki kriterij: izolacija Aspergilusa u kulturi, pozitivna mikroskopija, detekcija IgG i/ili 2 uzastopna pozitivna GM u serumu	Kombinacija faktora rizika od strane domaćina + klinički kriterij Bez etiološkog dokaza
antifungalna profilaksa se ne primjenjuje Uvođenje AF th dokazanih i vjerojatnih IPA, te moguće IPA sa progresijom simptoma i radioloških nalaza: 1. vorikonazol 2. AMB lip 3. drugi azoli /POSA, ESA		

Mikoze nosa i paranazalnih sinusa

- 13% opće populacije boluje od rinosinusitisa
- Stalna izloženost sluznice mikroorganizmima iz zraka
- Faktori rizika domaćina: anatomska nepravilnost, oštećenje sluznice, nosna polipoza, imunogenetika, tip I preosjetljivosti
- Kolonizacija bakterijama *P. aeruginosa i S. aureus* rizična je podloga kolonizaciji/infekciji gljivama *Aspergillus* spp., tamne plijesni: *Alternaria*, *Cladosporium*, vrste Reda *Mucorales*

George R. Thompson III, MD,Thomas F. Patterson,MD:Fungal disease of the nose and paranasal sinuses,2012.

Klinički oblici, dijagnostika i terapija fungalnog rinosinusitisa (FRS)

Neinvazivni	**Invazivni**
Kolonizacija saprofitnim plijensima	Kronični invazivni fungalni sinusitis
Mycetoma	Granulomatozni invazivni fungalni sinusitis
AFRS	Akutni fulminantni invazivni fungalni sinusitis

Dijagnostika i terapija ovisi o tipu FRS: radiološke metode, niska osjetljivost mikrobiološke kultivacije
Liječenje: kirurški, embolizacija, kortikosteroidi, imunoterapija, AFT bez značajnog učinka

George R. Thompson III, MD,Thomas F. Patterson,MD:Fungal disease of the nose and paranasal sinuses, 2012.

Laboratorijska dijagnostika pneumokoka, hemofilusa i moraksele

Iva Butić

Klinika za infektivne bolesti „Dr. Fran Mihaljević”

Suvremene spoznaje o epidemiologiji, kliničkoj slici, laboratorijskoj dijagnostici, terapiji i prevenciji respiratornih infekcija, Zagreb, 15. svibnja 2023.

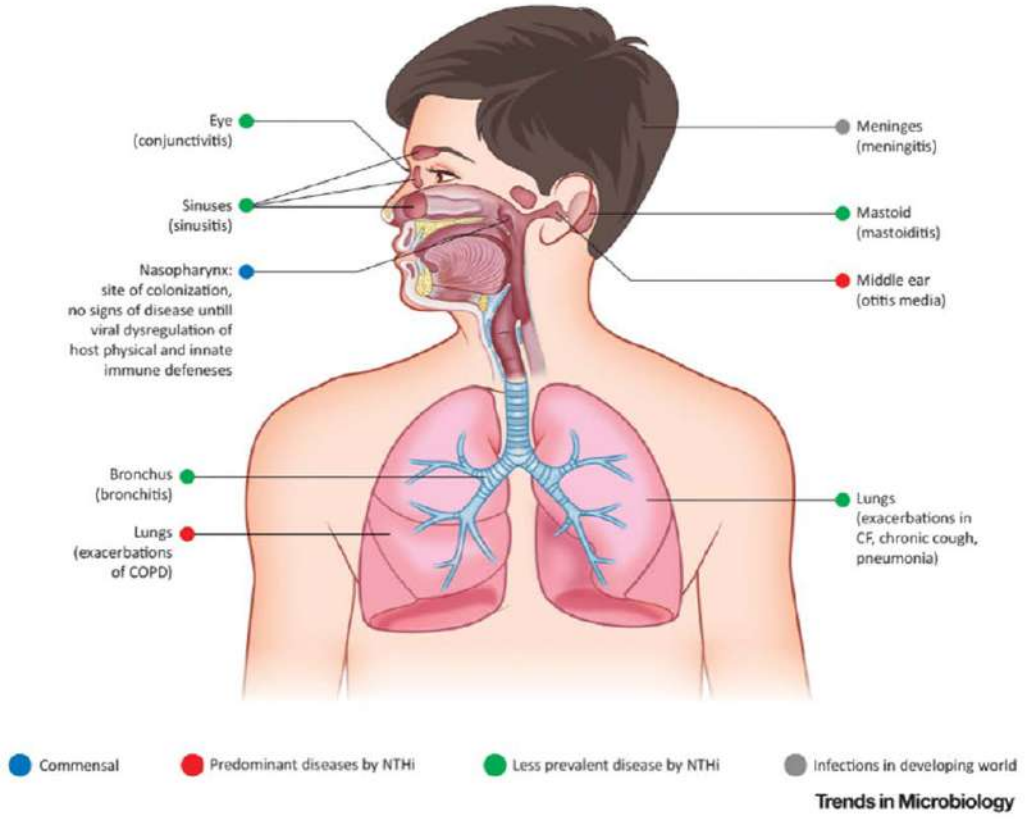
Streptococcus pneumoniae

- Jedan od najznačajnijih humanih patogena
- Visok morbiditet, visok mortalitet
- Nazofaringealno kliconoštvo: 5-10% zdravi odrasli, 20-40% zdrava djeca (cca.85% u zimskim mjesecima)
- Kapljični put prijenosa
- Upala pluća – najčešća klinička manifestacija
- Polisaharidna kapsula:
  - ✓ najznačajniji faktor virulencije
  - ✓ određuje serotip (>100 različitih serotipova *S.pneumoniae*)
  - ✓ zastupljena u pneumokoknim cjepivima

Atkinson W, et al, eds. Epidemiology and Prevention of Vaccine-Preventable Diseases.
http://www.cdc.gov/vaccines/pubs/pinkbook/downloads/pneumo.pdf. Accessed March 2015.
World Health Organization. Available from: http://www.who.int/immunization/diseases/pneumococcal/en/Accessed March 2015.
Linares J, et al. Clin Microbiol Infect 2010.
Kim SH, et al. Antimicrob Agents Chemother 2012.

Haemophilus influenzae

- Mikrobiota suznice gornjeg dišnog sustava (nazofarinks)
- Polisaharidna kapsula - šest različitih serotipova A – F
- 95% invazivnih infekcija uzrokuje *H. influenzae* tip B
- Cjepivo uključuje samo *H. influenzae* tip B

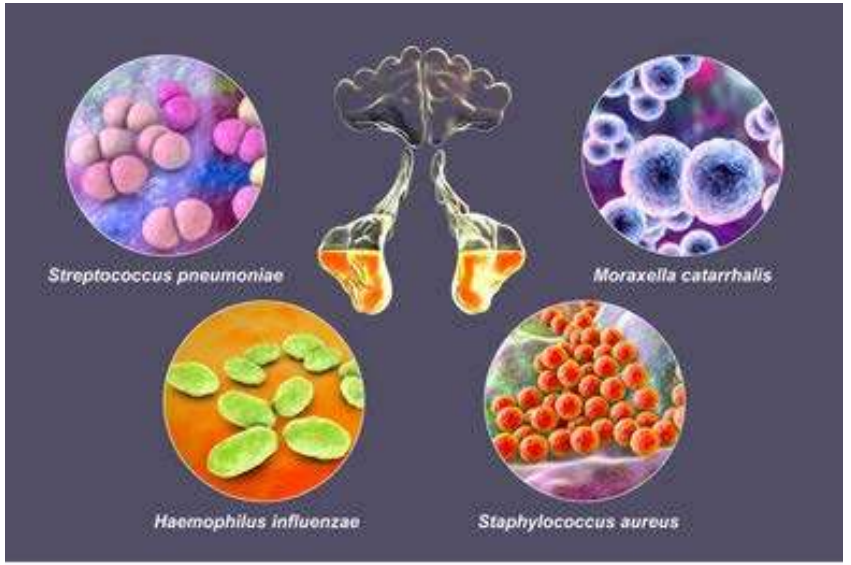


Moraxella catarrhalis

- Mikrobiota suznice gornjeg dišnog sustava (nazofarinks)

- Znajačaj oportunistički patogen (imunodeficijencija, starija životna dob, neutropenija...)

- Najčešće uzrokuje:
  - upalu srednjeg uha (3. najčešći uzročnik)
  - sinusitis
  - upalu pluća
  - meningitis
  - bakterijemija
  - konjuktivitis



Mikrobiološka dijagnostika infekcija uzrokovanih pneumokokom, hemofilusom i morakselom

- Infekcije **gornjih** dišnih puteva
  - Upala srednjeg uha (*S. pneumoniae, H. influenzae, M. catarrhalis*)
  - Upala sinusa (*S. pneumoniae, H. influenzae, M. catarrhalis*)
- Infekcije **donjih** dišnih puteva
  - Upala pluća
- Sepsa

Tablica 1. Adekvatni uzorci za dijagnostiku bakterijskih i gljivičnih infekcija gornjeg dišnog sustava (1)

UZORAK	TRAŽENI PATOGEN	BOLEST ILI STANJE
Bris usne šupljine, jezika	*Candida albicans*	Oralna kandidijaza
	BHS-A, Staphylococcus aureus	Ulkus usne šupljine, parotitis
Bris	*Staphylococcus aureus** *S. aureus* (MRSA)*	Kliconoštvo
	*Klebsiella ozaenae**	Ozena
	*Klebsiella rhinoscleromatis**	Rinoskleroma
Bris	BHS-A	Streptokokni faringitis
	*Corynebacterium diphtheriae**	Difterija
	*Neisseria gonorrhoeae**	Gonokokni faringitis
	*Neisseria meningitidis**	Meningokokno kliconoštvo
	*Borrelia vincentii (spirohete)** + anaerobi (fuziformni štapići)*	Vincentova angina
B	*Bordetella pertussis**	Pertusis (hripavac)
	BHS-A	Streptokokni faringitis
	*Neisseria meningitidis**	Meningokokno kliconoštvo
	*Corynebacterium diphtheriae**	Difterija
Bris uha (zvukovoda)	*Pseudomonas aeruginosa*	Otitis externa (upala zvukovoda)
	S. aureus	
	BHS-A	
	Rjeđi uzročnik: *Vibrio alginolyticus*	
	Aspergillus spp. i *C. albicans*	Kronični otitits externa

UZORAK	TRAŽENI PATOGEN	BOLEST ILI STANJE
Tekućina dobivena timpanocentezom, tekućina nakon perforacije bubnjića uzeta brisom	*S. pneumoniae* *H. influenzae* *M. catarrhalis* Rjeđi uzročnici: *S. aureus,* BHS-A, enterobakterije, *Alloiococcus otitidis,* čista kultura bilo kojeg mikroorganizma**	Akutni otitis media (akutna upala srednjeg uha)
	Pseudomonadaceae, *S. aureus*/MRSA, anaerobi, čista kultura bilo kojeg mikroorganizma**	Kronični otitis media (kronična upala srednjeg uha)
Punktat sinusa	*S. pneumoniae, H. influenzae, M. catarrhalis,* *S. aureus,* viridans streptokoki, BHS-A anaerobi, čista kultura bilo kojeg mikroorganizma**	Sinusitis
Bris oka (konjunktiva)	*Haemophilus influenzae, Streptococcus pneumoniae, S. aureus, N. gonorrhoeae**, *Moraxella* spp., BHS-A, *Chlamydia trachomatis****	Konjunktivitis
Hemokultura	*Fusobacterium necrophorum*	Lemierrova bolest

* Indikacija za pretragu u dogovoru s kliničarem ili uz posebnu naznaku na uputnici
** Kliničku značajnost potrebno je prokomentirati s kliničarem;
*** Molekularna dijagnostika / detekcija antigena / izolacija na kulturi stanica

Pristaš I, Abram M, Bubonja Šonje M, Tićac B, Vučković D, Tambić Andrašević A. Bakteriološka dijagnostika infekcija dišnog sustava: smjernice za mikrobiološku dijagnostiku Hrvatskog društva za kliničku mikrobiologiju Hrvatskog liječničkog zbora. Zagreb: Hrvatsko društvo za kliničku mikrobiologiju; 2015.

SMJERNICE ZA LIJEČENJE PNEUMONIJA IZ OPĆE POPULACIJE U ODRASLIH

GUIDELINES FOR THE MANAGEMENT OF COMMUNITY-ACQUIRED PNEUMONIA IN ADULTS

ILIJA KUZMAN, NEVEN RAKUŠIĆ, ROK ČIVLJAK, IVAN PULJIZ, MARKO KUTLEŠA, ANTEA TOPIĆ, IVICA MAŽURANIĆ, ANĐELKO KORUŠIĆ, ZLATA OŽVAČIĆ ADŽIĆ, BRUNO BARŠIĆ, MIROSLAV SAMARŽIJA, DRAGAN SOLDO[1,2]

Tablica 9. Zastupljenost uzročnika pneumonije prema težini bolesti i mjestu liječenja

Table 9. *Frequency of pathogens of pneumonia according to severity of the disease and site of treatment*

Ambulantno liječenje Outpatient treatment	Hospitalizirani bolesnici Ward hospitalization	Hospitalizirani u JIL-u ICU hospitalization
S. pneumoniae	*S. pneumoniae*	*S. pneumoniae*
M. pneumoniae	*M. pneumoniae*	*L. pneumophila*
C. pneumoniae	*C. pneumoniae*	Gram-negativne enterobakterije / Gram-negative enterobacteria
H. influenzae	*L. pneumophila*	*S. aureus*
Respiratorni virusi / Respiratory viruses	*H. influenzae*	*H. influenzae*
C. burnetii	*C. burnetii*	Anaerobne bakterije / Anaerobes

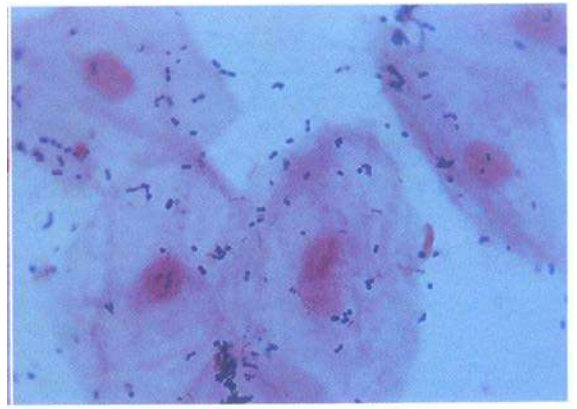
I. Kuzman i sur. Smjernice za liječenje pneumonija u odraslih Liječ Vjesn 2017; godište 139

Community-acquired pneumonia: Initial evaluation and site of care based on severity assessment in adults

	Severity score*	Site of care	Microbiologic evaluation
Mild	PSI: I or II or CURB-65: 0¶	Ambulatory care	▪ COVID-19 testing during the pandemic ▪ Influenza testing (when incidence is high and results would change management)Δ ▪ Otherwise, testing is usually not needed
Moderate	PSI: III or IV or CURB-65: 1¶ to 2	General medical ward	▪ Blood cultures ▪ Sputum Gram stain and culture ▪ Urine streptococcal antigen ▪ *Legionella* testing◇ ▪ Respiratory viral panel during respiratory virus season§ ▪ COVID-19 testing¥ ▪ HIV screening‡
Severe	PSI: IV or V or CURB-65: ≥3 and/or Fulfillment of ATS/IDSA criteria for ICU admission†	ICU	▪ Blood cultures ▪ Sputum Gram stain and culture ▪ Urine streptococcal antigen test ▪ *Legionella* testing◇ ▪ Respiratory viral panel§ ▪ Bronchoscopy specimens for Gram stain, fungal stain, aerobic, fungal culture, and molecular testing (when feasible)** ▪ COVID-19 testing¥ ▪ HIV screening‡

Mikrobiološka dijagnostika sputuma

- Ekspektorirani sputum (najbolje prvi jutarnji)
- Inducirani sputum (*M.tuberculosis*)
- **Gram preparat – kvaliteta uzorka i interpretacija nalaza!**
- Kvaliteta uzorka: broja ES i/ili PMN po vidnom polju (10x10 povećanje)
- Neadekvatan uzorak : minimalni kriterij broj ES>10 po vidnom polju
- Adekvatan uzorak:
  - >25 PMN u jednom vidnom polju ili
  - omjer PMN:ES >2:1.
- Veliki broj ES - kontaminacija orofaringealnim sekretom
- Fagocitirani mikroorganizmi u PMN u gram preparatu – znak infekcije!
- Kod imunosuprimiranih osoba, moguća neutropeniju može utjecati i na broj PMN u uzorku iz respiratornog trakta.



Question 1: In Adults with CAP, Should Gram Stain and Culture of Lower Respiratory Secretions Be Obtained at the Time of Diagnosis?

Recommendation

We recommend not obtaining sputum Gram stain and culture routinely in adults with CAP managed in the outpatient setting (strong recommendation, very low quality of evidence).

We recommend obtaining pretreatment Gram stain and culture of respiratory secretions in adults with CAP managed in the hospital setting who:

1. are classified as severe CAP (*see* Table 1), especially if they are intubated (strong recommendation, very low quality of evidence); or

2.

   a. are being empirically treated for MRSA or *P. aeruginosa* (strong recommendation, very low quality of evidence); or

   b. were previously infected with MRSA or *P. aeruginosa*, especially those with prior respiratory tract infection (conditional recommendation, very low quality of evidence); or

   c. were hospitalized and received parenteral antibiotics, whether during the hospitalization event or not, in the last 90 days (conditional recommendation, very low quality of evidence).

Metlay J et al. Diagnosis and Treatment of Adults with Community-acquired Pneumonia. An Official Clinical Practice Guideline of the American Thoracic Society and Infectious Diseases Society of America. Am J Respir Crit Care Med. 2019 Oct 1;200(7):e45-e67

Question 2: In Adults with CAP, Should Blood Cultures Be Obtained at the Time of Diagnosis?
Recommendation

We recommend not obtaining blood cultures in adults with CAP managed in the outpatient setting (strong recommendation, very low quality of evidence).

We suggest not routinely obtaining blood cultures in adults with CAP managed in the hospital setting (conditional recommendation, very low quality of evidence).

We recommend obtaining pretreatment blood cultures in adults with CAP managed in the hospital setting who:

1. are classified as severe CAP (*see* Table 1) (strong recommendation, very low quality of evidence); or
2.
   a. are being empirically treated for MRSA or *P. aeruginosa* (strong recommendation, very low quality of evidence); or
   b. were previously infected with MRSA or *P. aeruginosa*, especially those with prior respiratory tract infection (conditional recommendation, very low quality of evidence); or
   c. were hospitalized and received parenteral antibiotics, whether during the hospitalization event or not, in the last 90 days (conditional recommendation, very low quality of evidence).

Metlay J et al. Diagnosis and Treatment of Adults with Community-acquired Pneumonia. An Official Clinical Practice Guideline of the American Thoracic Society and Infectious Diseases Society of America. Am J Respir Crit Care Med. 2019 Oct 1;200(7):e45-e67

Question 3: In Adults with CAP, Should *Legionella* and Pneumococcal Urinary Antigen Testing Be Performed at the Time of Diagnosis?

Recommendation

We suggest not routinely testing urine for pneumococcal antigen in adults with CAP (conditional recommendation, low quality of evidence), except in adults with severe CAP (conditional recommendation, low quality of evidence).

We suggest not routinely testing urine for *Legionella* antigen in adults with CAP (conditional recommendation, low quality of evidence), except

1. in cases where indicated by epidemiological factors, such as association with a *Legionella* outbreak or recent travel (conditional recommendation, low quality of evidence); or

2. in adults with severe CAP (*see* Table 1) (conditional recommendation, low quality of evidence).

We suggest testing for *Legionella* urinary antigen and collecting lower respiratory tract secretions for *Legionella* culture on selective media or *Legionella* nucleic acid amplification testing in adults with severe CAP (conditional recommendation, low quality of evidence).

Metlay J et al. Diagnosis and Treatment of Adults with Community-acquired Pneumonia. An Official Clinical Practice Guideline of the American Thoracic Society and Infectious Diseases Society of America. Am J Respir Crit Care Med. 2019 Oct 1;200(7):e45-e67

Uzorci za mikrobiološku dijagnostiku infekcija donjeg dišnog sustava

- **Endotrahealni aspirat (ETA)**
  - Kontaminacija uzorka je moguća, jer se sekret iz usne šupljine može cijediti uz endotrahealni tubus.
  - Uzorkovati **samo** kod bolesnika koji ima klinički suspektnu pneumoniju
  - traheostoma kolonizira 24 h nakon insercije te je kliničku značajnost izoliranih mikroorganizama teško interpretirati!

- **Bronhoalveolarni lavat (BAT)**
  - segment pluća ispire se sterilnom FO nakon uvođenja fleksibilnog bronhoskopa
  - moguća je kontaminacija mikrobiotom usne šupljine
  - uzorak je iz distalnih bronhiola i alveola, ciljano iz područja zahvaćenog infekcijom

- **Aspiracija četkicom (protected specimen brush, PSB)**
  - prikupljanje staničnih materijala (najbolji uzorak za virusološku i citološku analizu)

Izdavanje nalaza

- *S. pneumoniae* - izdati i obraditi u bilo kojem broju!
- *H.influenzae* - izdati i obraditi u bilo kojem broju!
- *M.catarrhalis* - obraditi i izdati ako:
  - ≥104 CFU/ml za BAL i
  - ≥105 CFU/ml za ETA, čak ako i ne dominiraju u kulturi

Pristaš I, Abram M, Bubonja Šonje M, Tićac B, Vučković D, Tambić Andrašević A. Bakteriološka dijagnostika infekcija dišnog sustava: smjernice za mikrobiološku dijagnostiku Hrvatskog društva za kliničku mikrobiologiju Hrvatskog liječničkog zbora. Zagreb: Hrvatsko društvo za kliničku mikrobiologiju; 2015.

Intensive Care Med
https://doi.org/10.1007/s00134-023-07033-8

GUIDELINES

ERS/ESICM/ESCMID/ALAT guidelines for the management of severe community-acquired pneumonia

Question 1: In patients with sCAP, should rapid microbiological techniques be added to current testing of blood and respiratory tract samples?

Go to:

Recommendations
If the technology is available, we **suggest** sending a lower respiratory tract sample (either sputum or endotracheal aspirates) for multiplex PCR testing (virus and/or bacterial detection) whenever non-standard sCAP antibiotics are prescribed or considered.
Conditional recommendation, very low quality of evidence.

ERS/ESICM/ESCMID/ALAT guidelines for the management of severe community-acquired pneumonia. Intensive Care Med. 2023 Apr 4:1–18.

Laboratorijska dijagnostika streptokoka i bordetele

Irina Pristaš, dr.med.

Klinika za infektivne bolesti

Suvremene spoznaje o epidemiologiji, kliničkoj slici, laboratorijskoj dijagnostici, terapiji i prevenciji respiratornih infekcija; Zagreb, 15.svibanj 2023.

Streptokoki

- Standardne fenotipske metode više nisu dovoljne u identifikaciji ovih mikroorganizama radi kontinuiranih promjena u taksonomiji
  - Klinički i/ili epidemiološki značajno – potrebna dodatna identifikacija

- Rod *Streptococcus*
  - komenzali
  - patogeni
  - > 100 vrsta

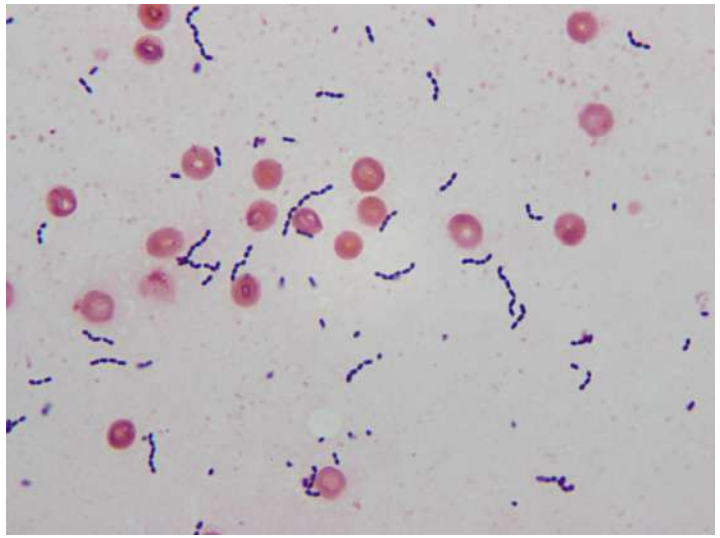
- Rod *Enterococcus*
  - *E.faecalis*
  - *E.faecium*
  - > 50 vrsta

Identifikacija streptokoka

- osnovna:
  - Izgled kolonija, gram bojanje, hemoliza na KA, Lancefieldove grupe
- Daljnja ID:
  - komercijalni testovi
- Krajnja ID:
  - MALDI-TOF MS
  - NAAT

Identifikacija streptokoka

- mikroskopski preparat:
  - Gram-pozitivni koki u paru i lančićima
- rast na krvnom agaru:
  - različit stupanj hemolize – pomoć u ranoj dijagnostici
- serogrupiranje – Lancefield grupe – 20 serotipova (A-V, isključujući I i J)-latex aglutinacija



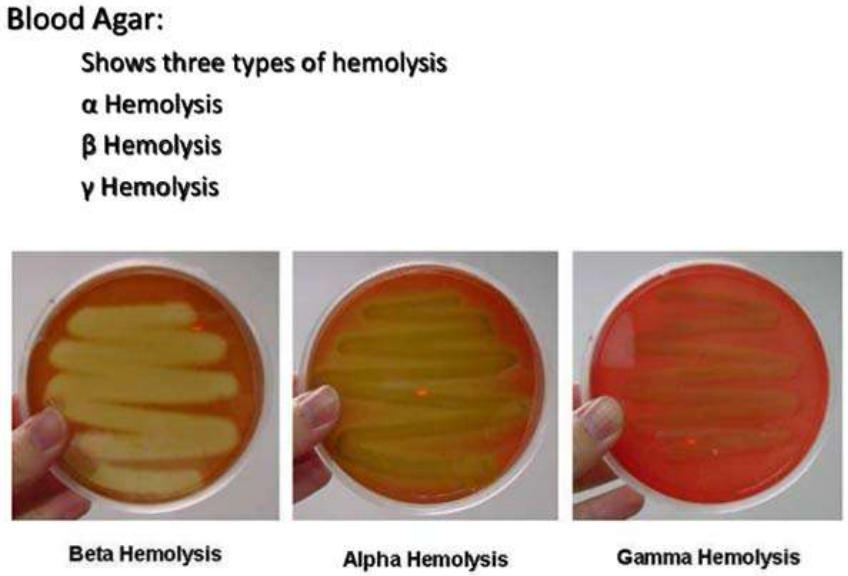


Table:1 Lancefield group and species(1,6)

Species	Lancefield group
Streptococcus pyogenes	A
Streptococcus agalactiae	B
Streptococcus canis	G
Streptococcus dysgalactiae subspecies dysgalactiae	C
Streptococcus dysgalactiae subspecies equisimilis	C, G, A and L
Streptococcus equi subsp. zooepidemicus	C
Streptococcus equi subsp. equi	C
Streptococcus anginosus group	A, C, F and G
	or ungroupable
Streptococcus bovis group	D
Streptococcus suis	R, S and T or ungroupable
Enterococcus species	D

- korisno u identifikaciji, koristiti uz ostale testove za točnu ID

UK Standards for Microbiology Investigations | Issued by the Standards Unit, Public Health England

Komercijalni ID sistemi

- Nepouzdani rezultati u identifikaciji α – hemolitičkih streptokoka
- Loša diskriminacija između *S.pneumoniae* i *S.mitis* grupe (genetski vrlo slični) – *S.mitis/oralis* mogu biti pogrešno identificirani kao *S.pneumoniae*
- *S.porcinus* (patogen u svinja) –križno reagira sa grupom B streptokoka
- RADT – brzi Ag test za BHS-A

Matrix Assisted Laser Desorption Ionisation Time-of-Flight Mass Spectrometry (MALDI-TOF)

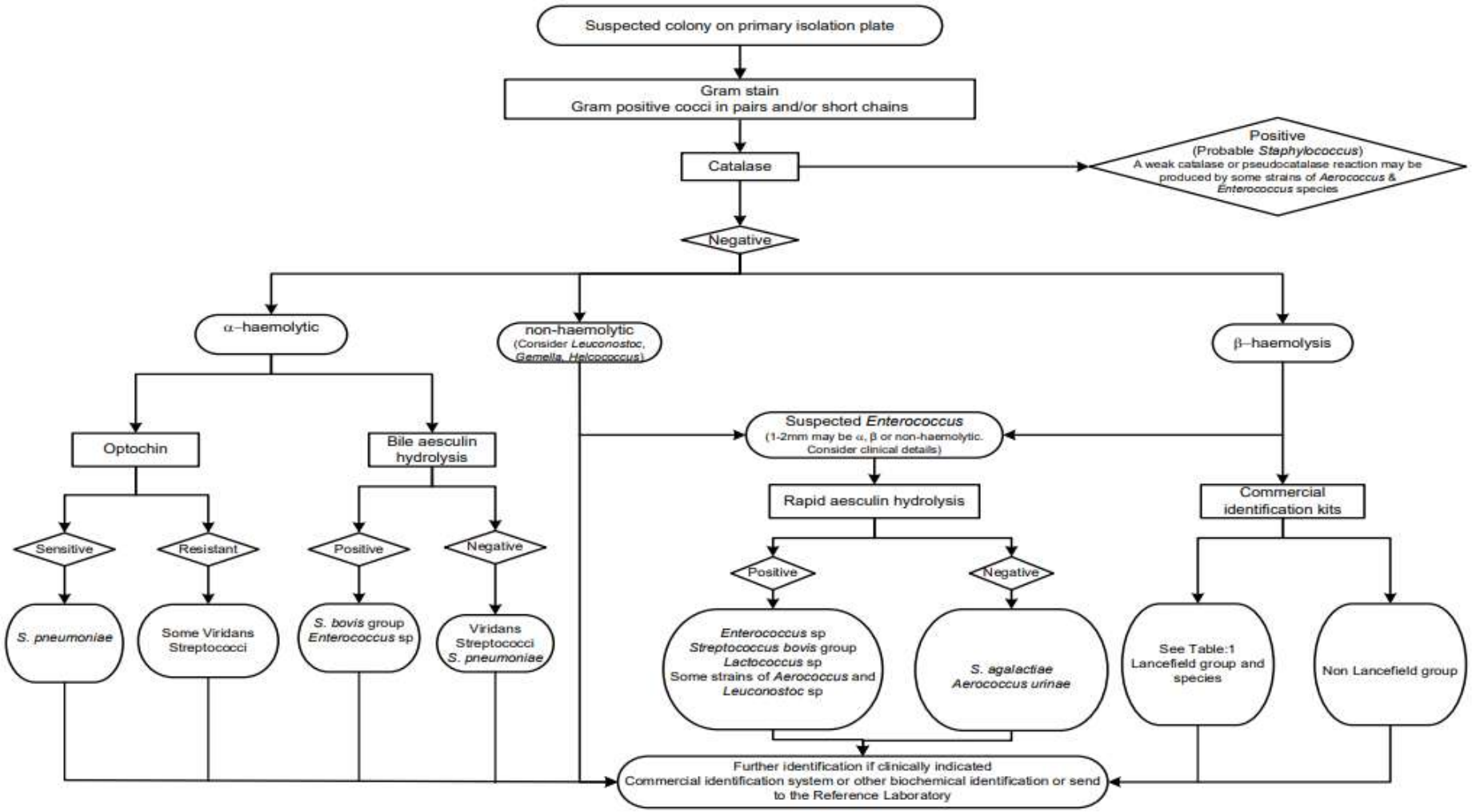
- ograničenja u ID:
  - ne može razlikovati *S.pneumoniae* od ostalih *S.mitis* grupe
    - upotrebom testa topivosti u žuči sa MALDI – točnija def *S.pneumoniae*

Molekularni testovi NAAT

- NAAT za detekciju BHS-B
- identifikacija i rezistencija na glikopeptide u enterokoka

Appendix 1: Identification of *Streptococcus* species, *Enterococcus* species and morphologically similar organisms

An accessible text description of this flowchart is provided with this document.



The flowchart is for guidance only and for the identification of species in cases where confirmation by an alternative technique is required or automated methods are not available.

1. Some *S. pneumoniae* may be resistant to optochin: if there is a clinical suspicion of pneumococcal infection, confirm by performing bile solubility test.
2. Occasional strains of *S. oralis*, *S. mitis* and *S. pseudopneumoniae* may be optochin sensitive:
   S. pseudopneumoniae optochin resistant when incubated in increased CO_2
3. Some strains of *Aerococcus* and *Leuconostoc* species can hydrolyse aesculin

Bordetele

- 16 vrsta u rodu Bordetella
  - klasične bordetele – *B.pertussis, B.parapertussis, B.bronchiseptica*
  - non-klasične – *B.hinzii, holmesii, trematum, avium, petrii, broncialis, flabilis, sputigena*
    - *B.ansorpii*

Identifikacija

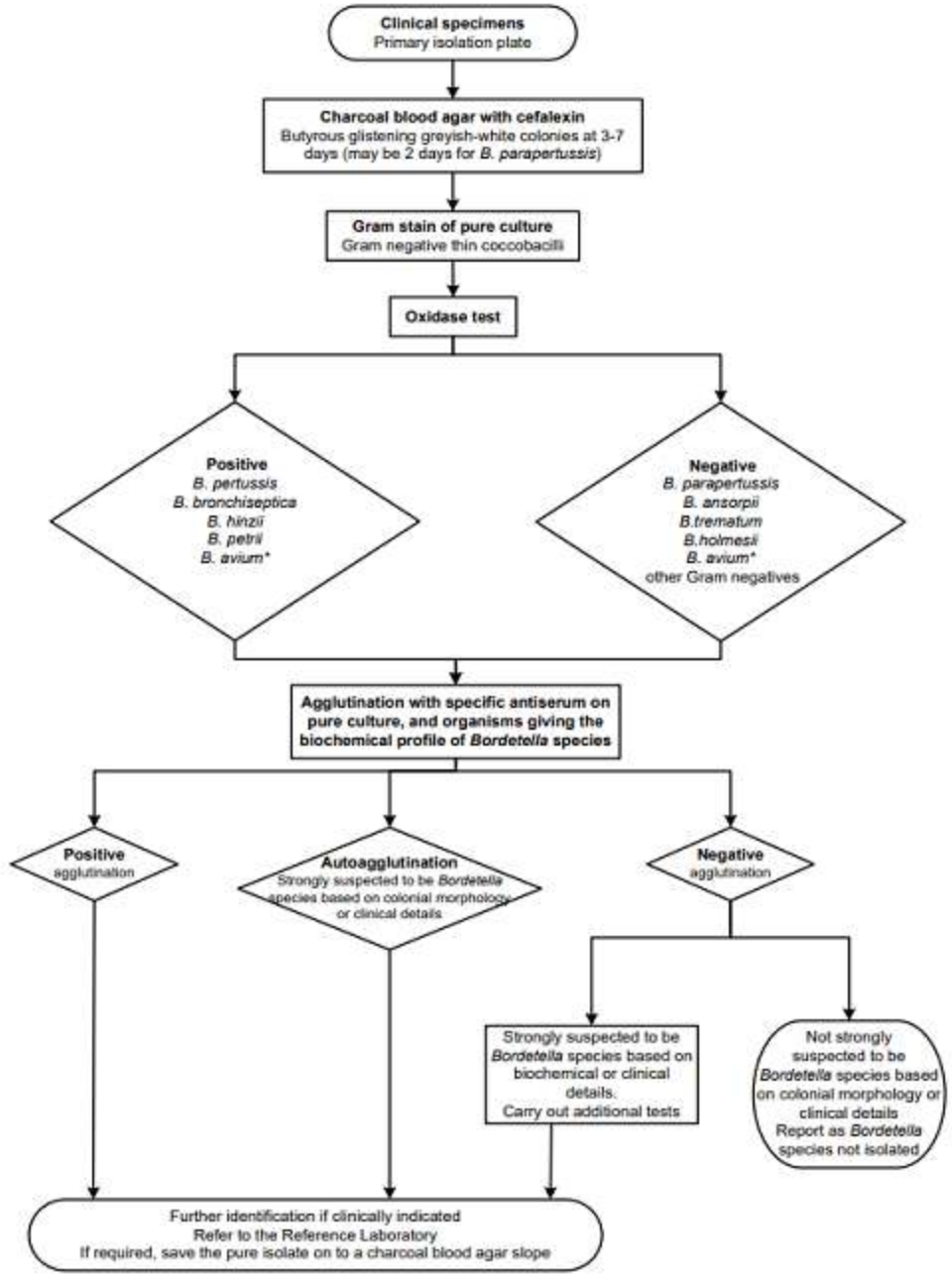
- kolonije koje rastu na selektivnim medijima preliminarno se identificiraju:
  - izgled kolonija
  - gram bojanje
  - aglutinacija polivalentnim serumima
  - kultivacija i dalje ima značajnu ulogu u dijagnostici, ponajviše zbog testiranja osjetljivosti

- Potpuna identifikacija:
  - molekularne metode
  - MALDI-TOF MS

Identifikacija

- MLVA (Multiple-locus Variable–Number Tandem Repeat Analysis)
- WGS
- 16S rRNA sekvenciranje

4 Identification of *Bordetella* species

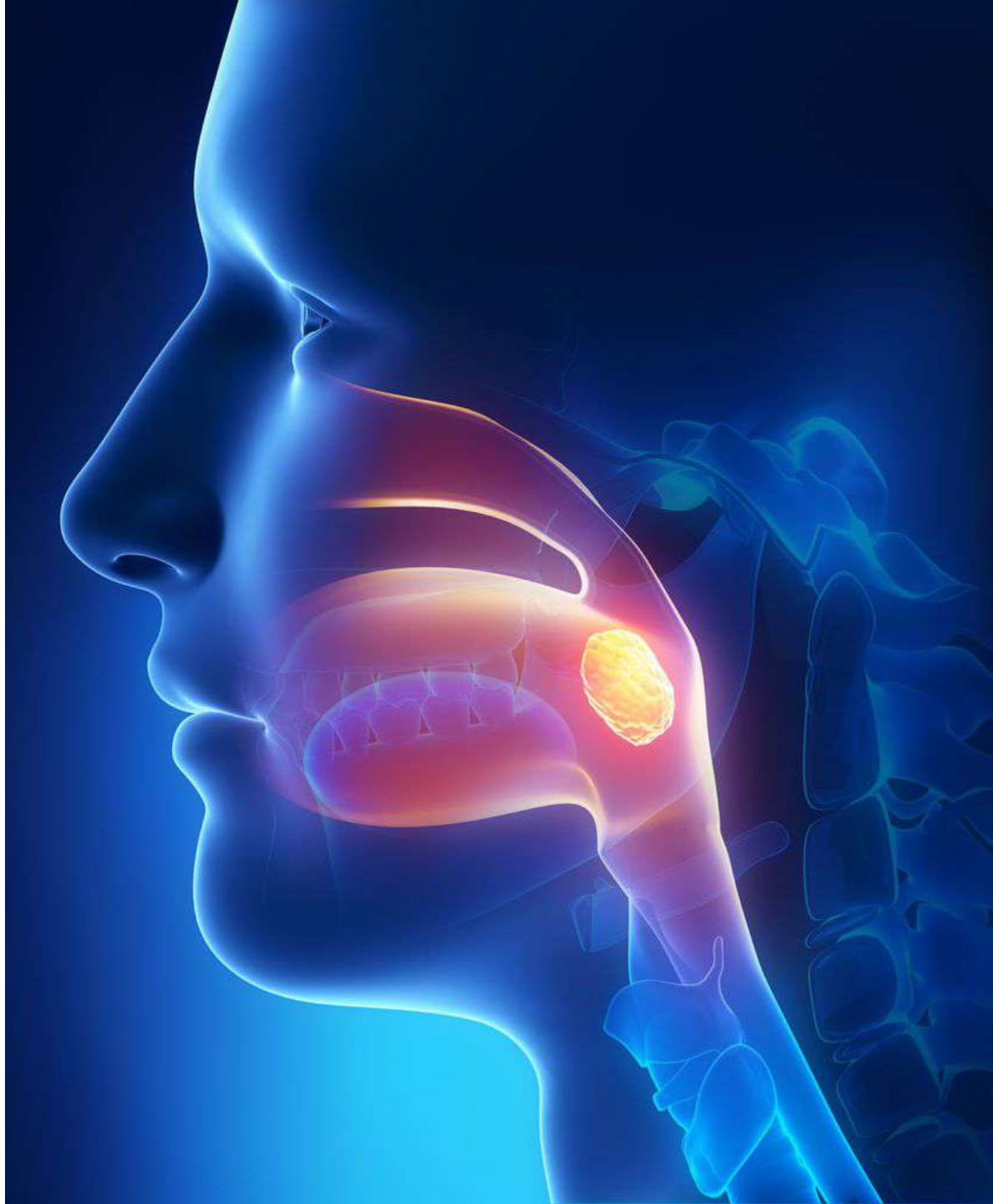


УНИВЕРЗИТЕТ У БЕОГРАДУ
МЕДИЦИНСКИ ФАКУЛТЕТ

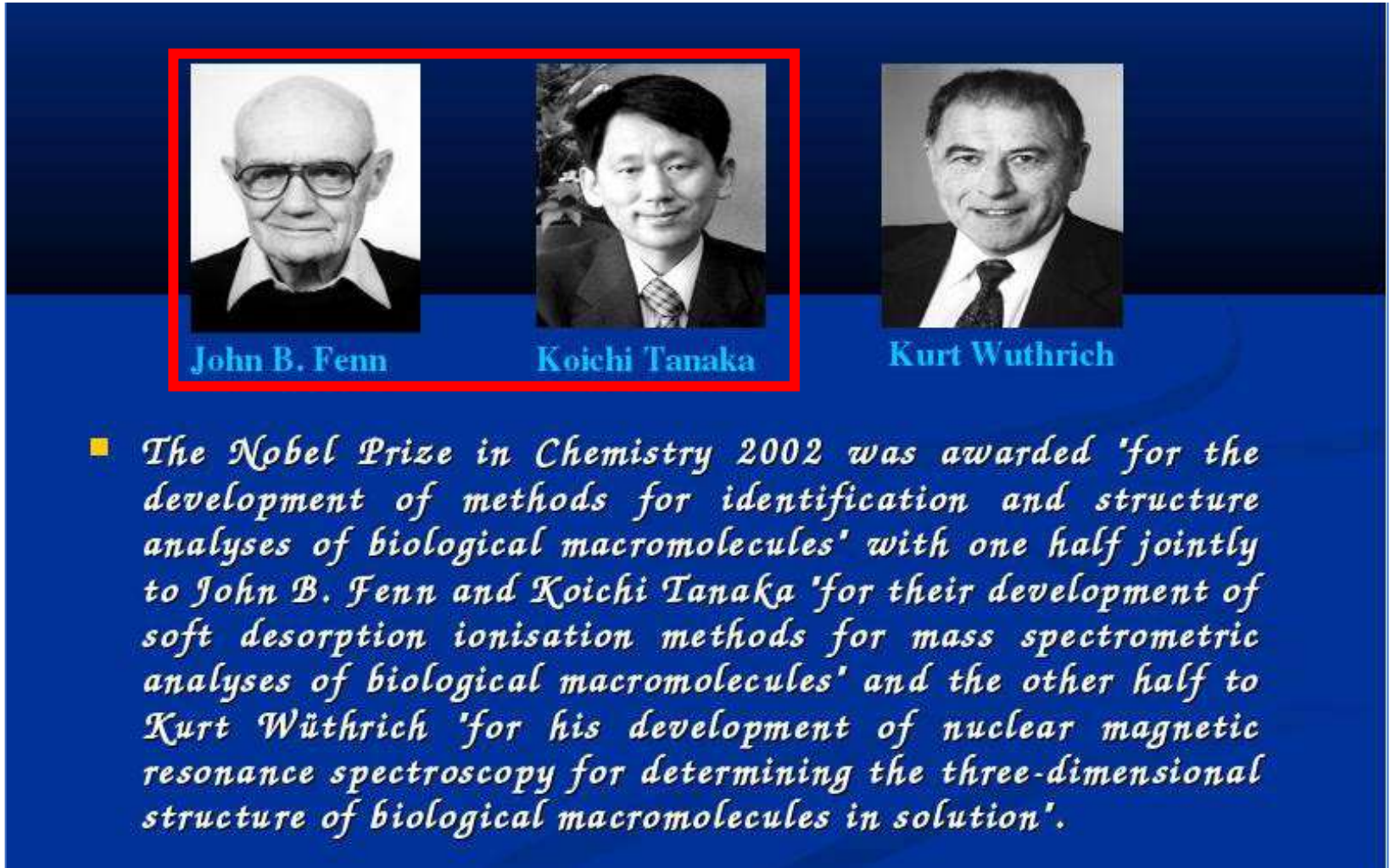
Srpsko udruženje za kliničku mikrobiologiju
SUKM

Primena MALDI-TOF MS u mikrobiološkoj dijagnostici respiratornih infekcija

Prof. dr Ivana Ćirković
Institut za mikrobiologiju i imunologiju
Univerzitet u Beogradu – Medicinski fakultet



Masena spektrometrija (MS) je analitička tehnika u kojoj se uzorci jonizuju u naelektrisane molekule, i uz pomoć analizatora može se meriti odnos njihove mase i naelektrisanja (m/z).
U **MALDI-TOF MS**, **izvor jona** je matriksom potpomognuta laserska desorpcija/jonizacija (Matrix-assisted laser desorption/ionization, **MALDI**), a **analizator** mase je analizator vremena leta (Time of Flight, **TOF**) – omogućen je screening proteina mikroorganizama.



Različite vrste/rodovi – razlike u ”peak patterns”

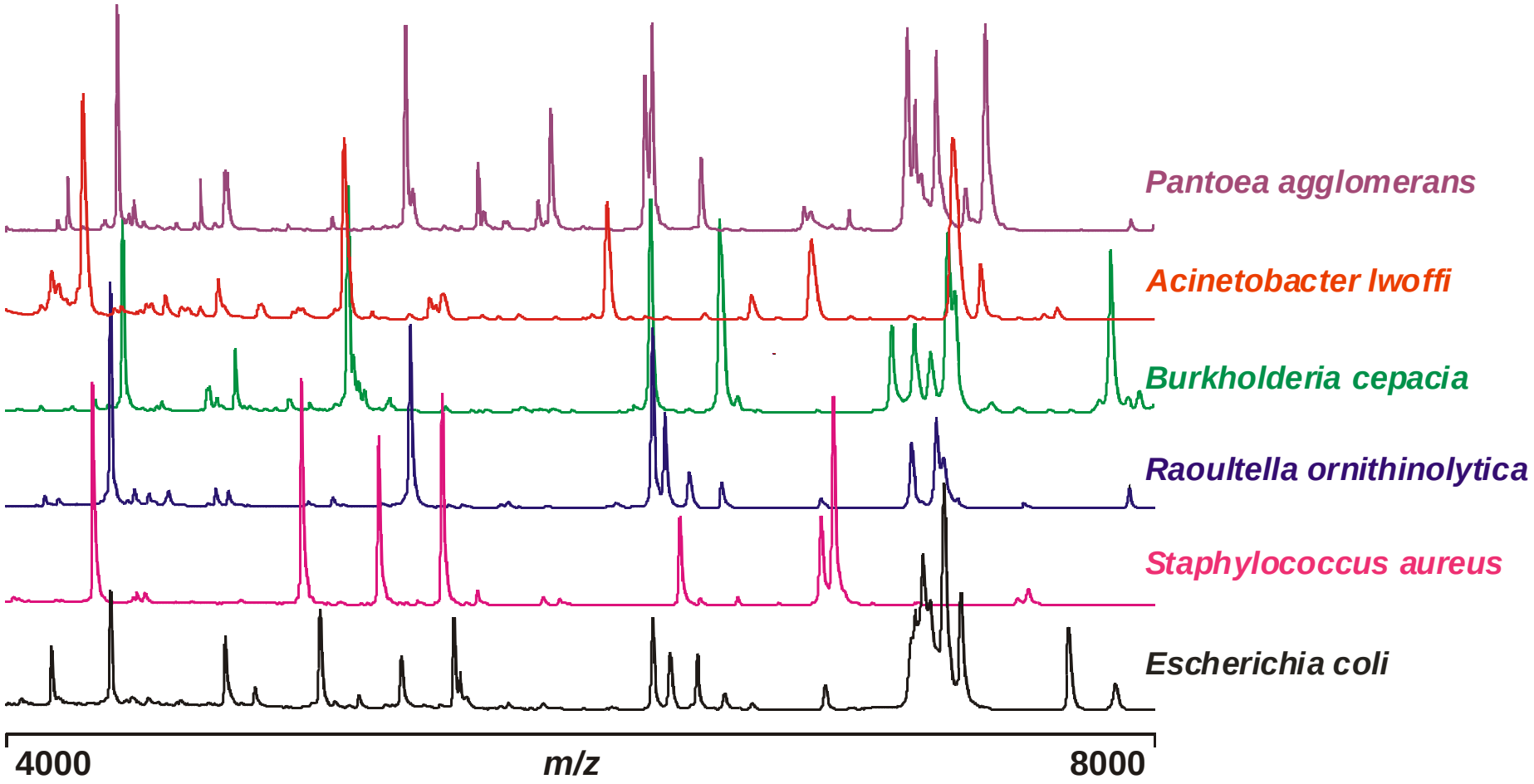


TABLE 1 | Microbial detection methods used in clinical microbiology.

Detection method	Advantages	Disadvantages
Conventional; culture on microbiological media and identification by biochemical tests	• Sensitive • Inexpensive	• Lengthy and time consuming process • Might require 24–48 h
Immunological-based methods	• Faster than conventional methods • Can detect both contaminating organisms and their toxins	• Not as specific, sensitive, and rapid as nucleic-acid based detection methods • Require large amounts of antigen • Developed for only a small number of microorganisms
Florescent *in situ* hybridization (FISH)	• Rapid detection and identification directly from slide smears • Fast and ease-of use of conventional staining methods combined with specificity of molecular methods	• Test limited by the availability of specific antigens for detection
Molecular based methods (i) Real-time PCR (ii) Multiplex-PCR	• Culturing of the sample is not required • Specific, sensitive, rapid, and accurate • Closed-tube system reduces the risk of contamination • Can detect many pathogens simultaneously	• A highly precise thermal cycler is needed • Trained laboratory personnel required for performing the test
DNA sequencing	• 16S rDNA and 18S rDNA sequencing are the gold standards • Can identify fastidious and uncultivable microorganisms	• Trained laboratory personnel and powerful interpretation softwares are required • Expensive • Not suitable for routine clinical use
Microarrays	• Large scale screening system for simultaneous diagnosis and detection of many pathogens	• Expensive • Trained laboratory personnel required
Loop-mediated isothermal amplification (LAMP) assay	• Can generate large copies of DNA in less than an hour • Easy to use • No sophisticated equipment is required	• Developed for only a small number of microorganisms as yet
Metagenomic assay	• Useful for random detection of pathogens	• Data acquisition and data analysis is time consuming • Trained laboratory personnel required
MALDI-TOF MS	• Fast • Accurate • Less expensive than molecular and immunological-based detection methods • Trained laboratory personnel not required	• High initial cost of the MALDI-TOF equipment

Singhal N et al. 2015 Front Microbiolol.

TABLE 1 | Microbial detection methods used in clinical microbiology.

Detection method	Advantages
MALDI-TOF MS	

Identification performance of the VITEK® MS PRIME MALDI-TOF system

D. JACOB[1], M. WANHAM[2], S. BLAMEY[3], E. MILLER[4], C. CANTRELL[4], P-J. COTTE-PATTAT[1], R. BIRCH[3], S. ELIZABETH[3], T. TROST[3], V. GIRARD[1]
[1]BIOMÉRIEUX, LA BALME-LES-GROTTES, FRANCE, [2]CADUCEUM, LYON, FRANCE, [3]BIOMÉRIEUX, INC., HAZELWOOD, MO, [4]BIOMÉRIEUX, INC. DURHAM, NC,

BIOMÉRIEUX

ECCMID 2021 – 9-12 July 2021

INTRODUCTION

The development of matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF MS) has revolutionized the routine identification of microorganisms in clinical microbiology laboratories and has been beneficial in decreasing time to identification of causative organisms compared to traditional methods.

VITEK MS PRIME is a new MALDI-TOF MS microbial identification system. This work presents biological performance of VITEK MS PRIME over a broad range of species as well as clinical trials showing consistent performance between different strains of the same species.

The performance study covers all claimed microorganisms on VITEK MS system while the clinical trials focus on a subset of representative microorganisms in a clinical setting.

METHODS

A broad performance study was conducted on 477[a] species (one strain per species): 135 Gram-positive bacteria, 211 Gram-negative bacteria, 36 yeasts, 52 moulds, 30 mycobacteria and 13 *Nocardia*. Clinical trials were performed on a set of 100 species (five strains per species) of the most common and/or clinically relevant species/group/complex from Gram-positive (29) and Gram-negative (32) bacteria, yeasts (17) and moulds (10), mycobacteria (8) and *Nocardia* (4). Biological performance was determined by comparing VITEK MS PRIME identification using knowledge base V3.2.0 to a reference identification.

	Performance study		Clinical trials	
	species	strains	species	strains
Gram-positive bacteria	135	135	29	145
Gram-negative bacteria	211	211	32	160
Moulds	52	52	10	50
Yeasts	36	36	17	85
Mycobacteria	30	30	8	40
Nocardia	13	13	4	20
Total	477	477	100	500

Table 1. Species and strains distribution for performance study and clinical trials

Each strain have been previously well-characterized and no additional reference testing was required.
For clinical trials, five unique clinical isolates for each of the 100 species were tested as far as possible.

PERFORMANCE STUDY RESULTS

The global biological performance is calculated from 1458 samples. The study covers 400 displayed labels and 477 species, for a total of 486 unique tests (9 mycobacteria species were tested both on solid and liquid media).

Microorganism	Overall Correct ID		No ID		Wrong Identification		Total
	N	%	N	%	N	%	N
Gram-positive bacteria	401	**99.0**	4	0.99	0	0	405
Gram-negative bacteria	620	**98.0**	10	1.58	3	0.47	633
Yeasts	108	**100.00**	0	0	0	0	108
Moulds	152	**97.4**	4	2.56	0	0	156
Mycobacteria	115	**98.3**	2	1.7	0	0	117
Nocardia	39	**100.00**	0	0	0	0	39
Total	1435	**98.42**	20	1.37	3	0.21	1458

Table 2. Identification results of performance study after repeat testing

A global correct identification rate of 98.4% (1435/1458) was obtained, with 0.2% (3/1458) discordant ID and 1.4% (20/1458) no ID. In more detail, identification performance was 99.0% (401/405) for Gram-positive, 98.0% (620/633) for Gram-negative, 100.0% (108/108) for yeasts, 97.4% (152/156) for moulds, 98.3% (115/117) for mycobacteria and 100.0% (39/39) for *Nocardia*.

Klebsiella variicola wrongly identified to *Klebsiella pneumoniae* was the sole misidentification in this study.

CLINICAL TRIALS RESULTS

Clinical strains for all isolates tested showed a global agreement rate of 98.4% (492/500). The agreement rate within each organism group is above 95.3%.

In detail, Gram-positive bacteria at 99.3% (144/145), Gram-negative bacteria at 98.8% (158/160), yeast at 95.3% (81/85), moulds at 98.0% (49/50), mycobacteria at 100.0% (40/40) and *Nocardia* at 100.0% (20/20) proper identification.
An error rate of 0.4% (2/500) was obtained overall, and the combined no identification rate was at 1.2% (6/500).

Microorganism	Overall Correct ID		No ID		Wrong Identification		Total
	N	%	N	%	N	%	N
Gram-positive bacteria	144	**99.3**	0	0.0	1	0.7	145
Gram-negative bacteria	158	**98.8**	2	1.3	0	0.0	160
Yeasts	81	**95.3**	4	4.7	0	0.0	85
Moulds	49	**98.0**	0	0.0	1	2.0	50
Mycobacteria	40	**100.0**	0	0.0	0	0.0	40
Nocardia	20	**100.0**	0	0.0	0	0.0	20
Total	492	**98.4**	6	1.2	2	0.4	500

Table 3. Identification results of clinical trials after repeat testing

Only two misidentifications were observed, with one strain of *Trichophyton rubrum* wrongly identified as *Trichophyton violaceum* and one strain of *Listeria monocytogenes* wrongly identified as *Listeria innocua*, although they were correctly identified at genus level.

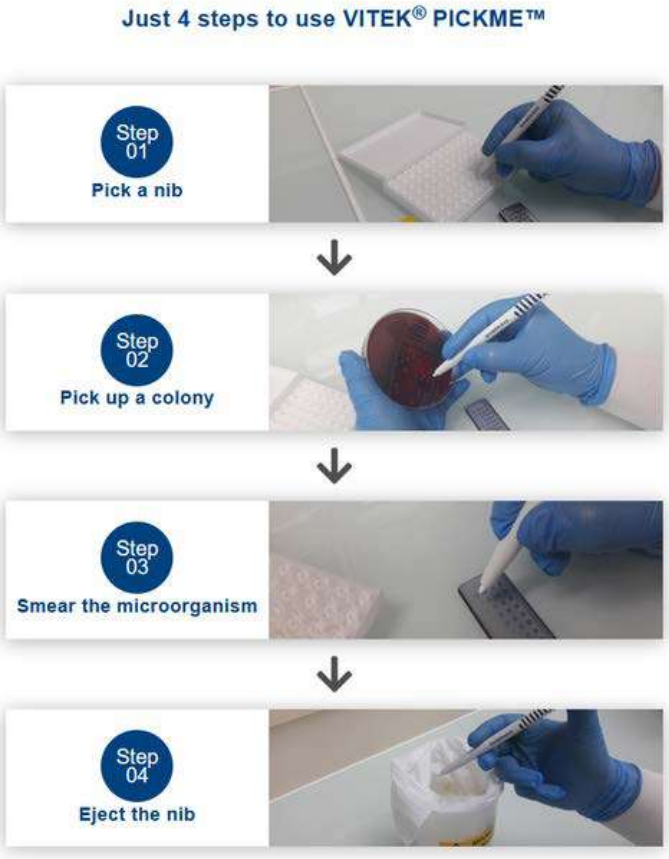
CONCLUSIONS

These studies showed that the new VITEK MS PRIME system provides reliable identification on a diverse panel of species and microorganisms, with a correct identification rate of 98.4% in both performance study and clinical trials. This performance combined to new features improving workflow efficiency will allow rapid and accurate identifications and help drive informed clinical decisions to optimize patient outcomes.

Footnotes
[a]Two strains were not able to be tested

TABLE 1 | Microbial detection methods used in clinical microbiology.

Detection method	Advantages
MALDI-TOF MS	• Fast • Accurate • Less expensive than molecular and immunological-based detection methods • Trained laboratory personnel not required



Faringitis

BAKTERIJE

- ✓ ***Streptococcus pyogenes*** (engl. *Group A Streptococcus*, GAS)
- ✓ **grupe C i G streptokoka**
- ✓ ***Arcanobacterium haemolyticum***

Retki : *Corynebacterium diphtheriae*, *Corynebacterium ulcerans, Neisseria gonorrhoeae, Francisella tularensis, Yersinia enterocolitica, Chlamydia pneumoniae* i *Mycoplasma pneumoniae*

GLJIVE

Bris nazofarinksa

- ✓ **pertusis** – *Bordetella pertussis* i bolesti nalik pertusisu - *Bordetella parapertussis, Bordetella holmesii, Bordetella bronchiseptica, Bordetella hinzii*
- ✓ **difterija** – *Corynebacterium diphtheriae*
- ✓ **streptokokni faringitis kod dece** – *Streptococcus pyogenes*
- ✓ **meningokokno kliconoštvo** – *Neisseria meningitidis*

Uzročnici akutnog otitis media

BAKTERIJE

Streptococcus pneumoniae

Haemophilus influenzae

Moraxella catarrhalis

ređe

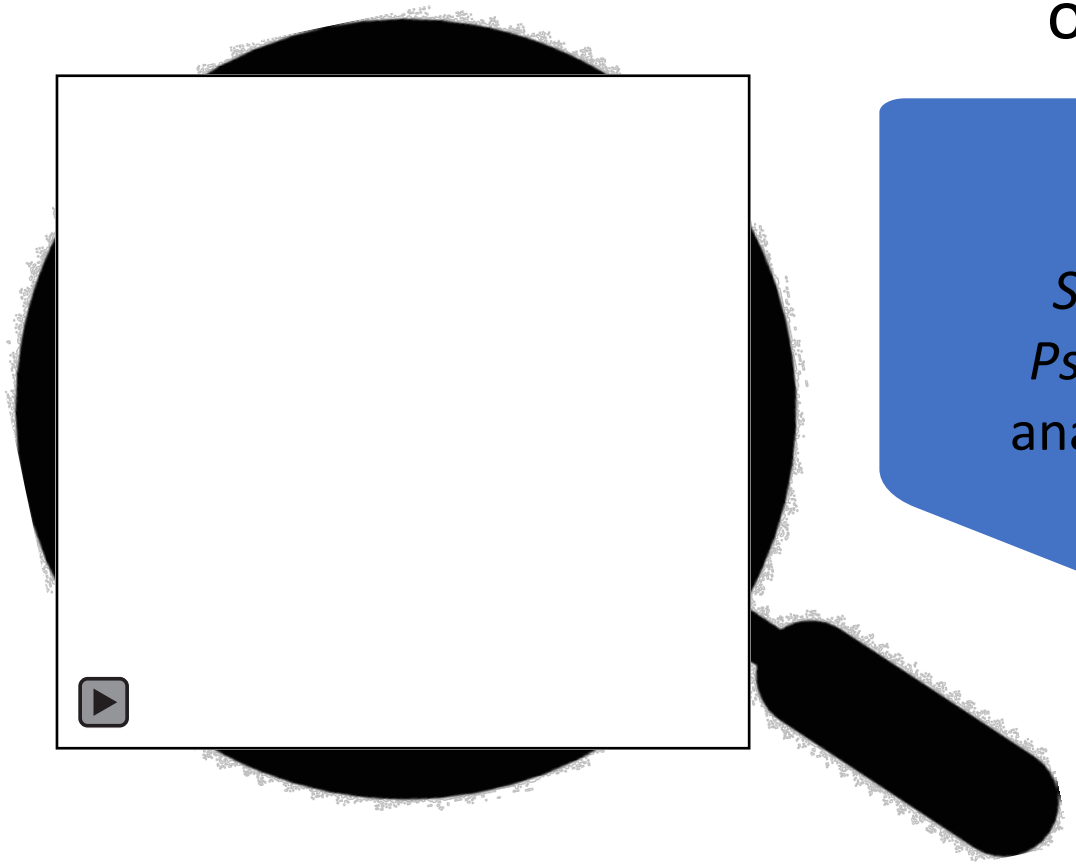
Streptococcus pyogenes

Staphylococcus aureus

Alloiococcus otitidis

Turicella otitidis

Pseudomonas aeruginosa



Uzročnici hroničnog otitis media

BAKTERIJE

S. aureus/MRSA,

Pseudomonas spp.

anaerobne bakterije

VITEK MS can differentiate between closely related species

S. mitis/oralis from *S. pneumoniae*

Rapid laboratory diagnosis for respiratory infectious diseases by using MALDI-TOF mass spectrometry

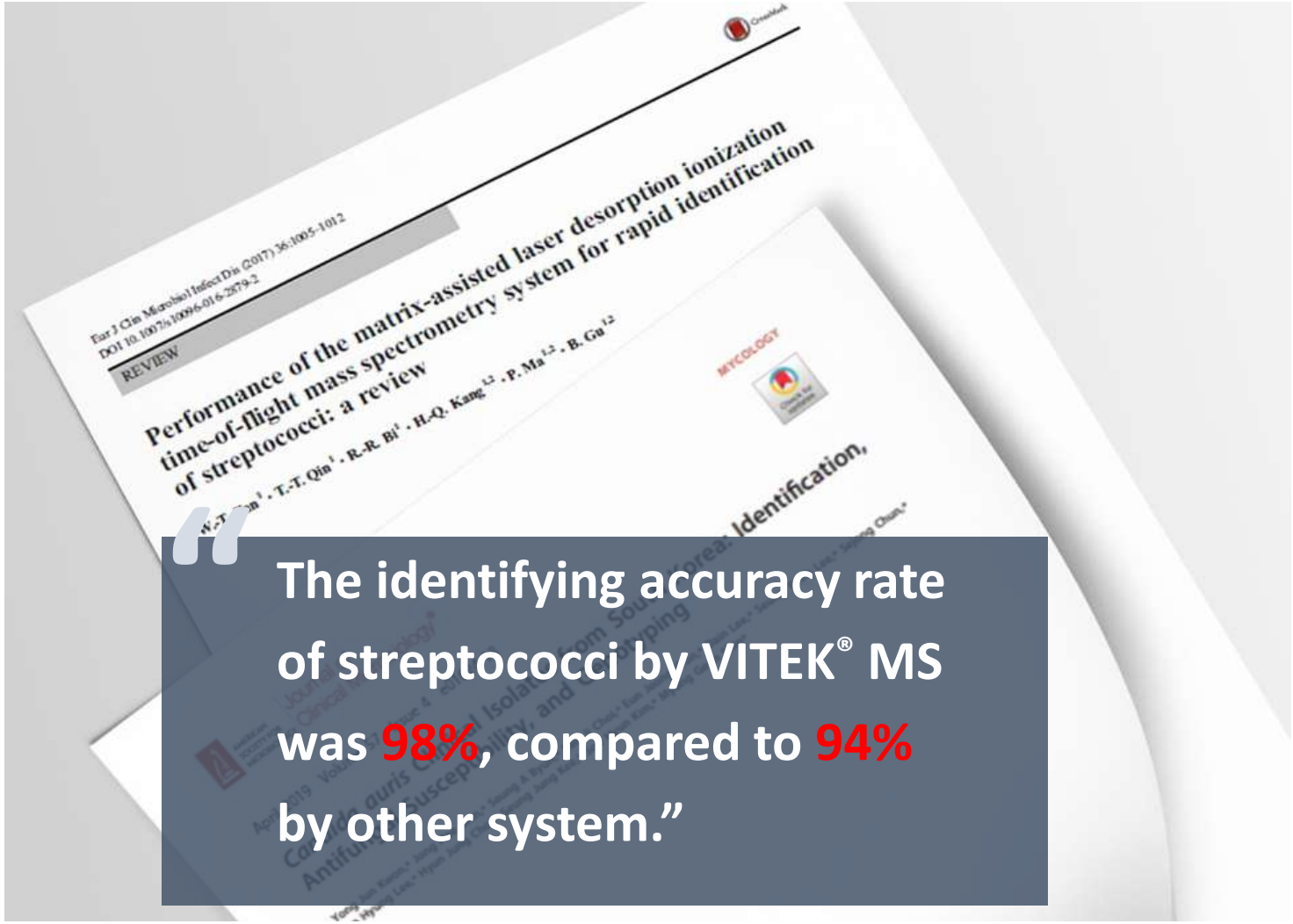
Yun F. (Wayne) Wang[1], Jianfeng Fu[2]

J Thorac Dis 2014;6(5):507-511

Here we only list a few studies to prove the concept. The *Streptococcus mitis* group is a set of closely related species in which conventional identification methods cannot reliably make differentiation analysis. The most important pathogen within the *S. mitis* group, *S. pneumonia*, is conventionally distinguished from the others on the basis of its susceptibility to optochin or its solubility in bile (5). In a recent study, the Vitek MS v2.0 System (MALDI-TOF-MS technology) accurately distinguished *Streptococcus pneumonia* from nonpneumococcal *S. mitis* group species. Only 1 of 116 nonpneumococcal isolates (<1%) was misidentified as *S. pneumoniae*. None of 95 pneumococcal isolates was misidentified. In this case, MALDI-TOF-MS provides a rapid, simple means of discriminating among these challenging organisms (6).

VITEK MS can differentiate between closely related species

S. mitis/oralis from *S. pneumoniae*



Fan et al. 2017. Performance of the matrix-assisted laser desorption ionization time-of-flight mass spectrometry system for rapid identification of streptococci: a review.

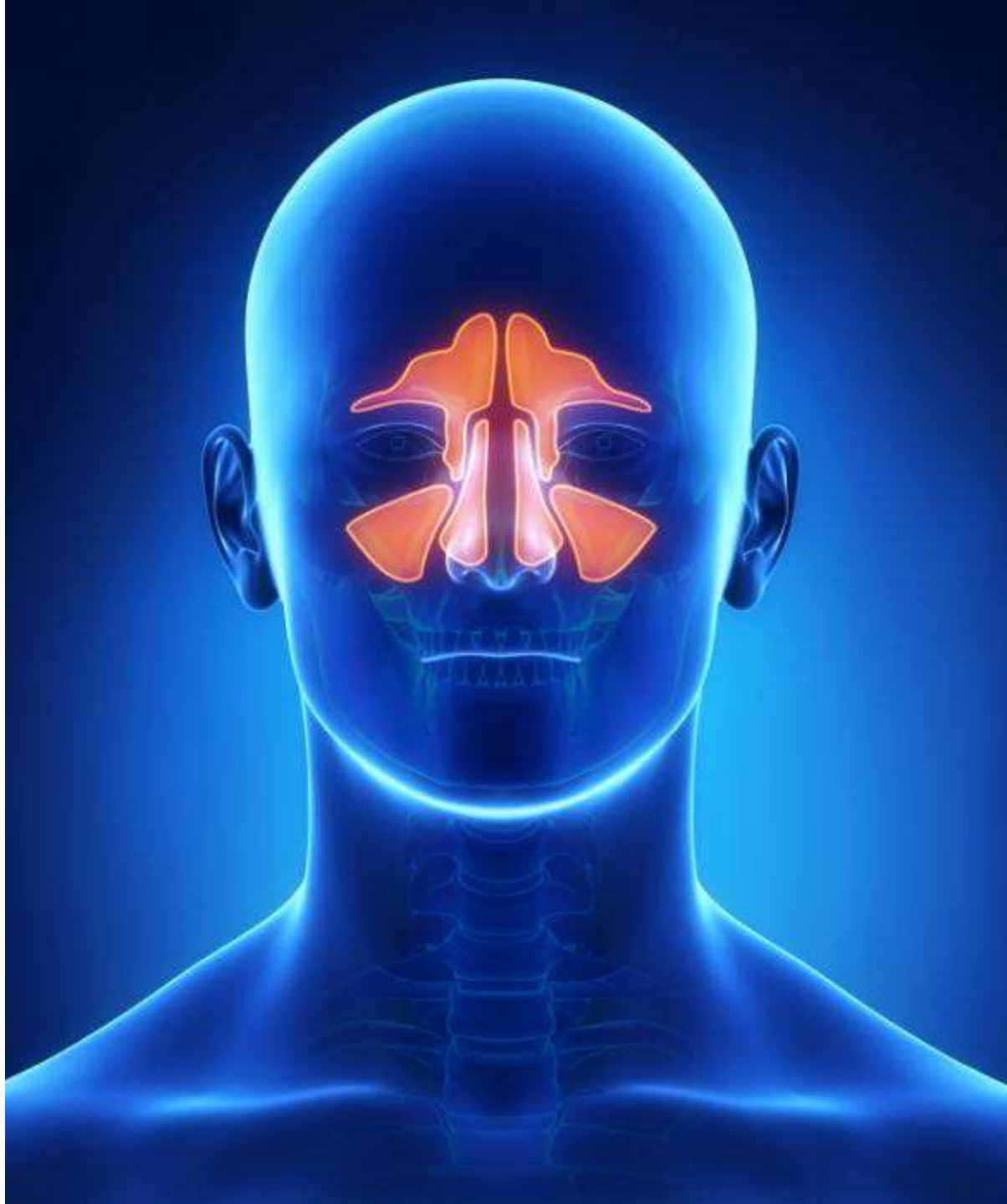
Akutni sinuzitis

- ✓ *Streptococcus pneumoniae*, *Haemophilus influenzae* i *Moraxella catarrhalis*

- ✓ ređi *Staphylococcus aureus*, *Streptococcus pyogenes* i streptokoke anginosus grupe: *Streptococcus anginosus, Streptococcus constellatus* i *Streptococcus intermedius*
- ✓ gljive

Hronični sinuzitis

- ✓ *Streptococcus pneumoniae*, *Haemophilus influenzae* i *Moraxella catarrhalis*, *Staphylococcus aureus*, *Streptococcus pyogenes*, *Pseudomonas aeruginosa*, *Enterobacterales* i anaerobne bakterije; gljive.



HZJZ

MIKROBIOLOŠKA DIJAGNOSTIKA LEGIONELA

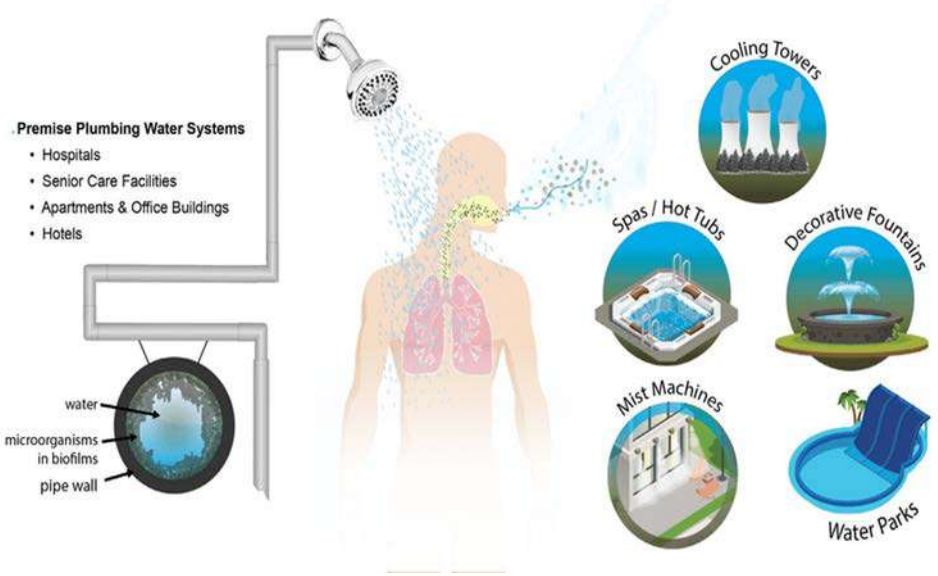
Selma Bošnjak

Hrvatski zavod za javno zdravstvo, Zagreb

HZJZ

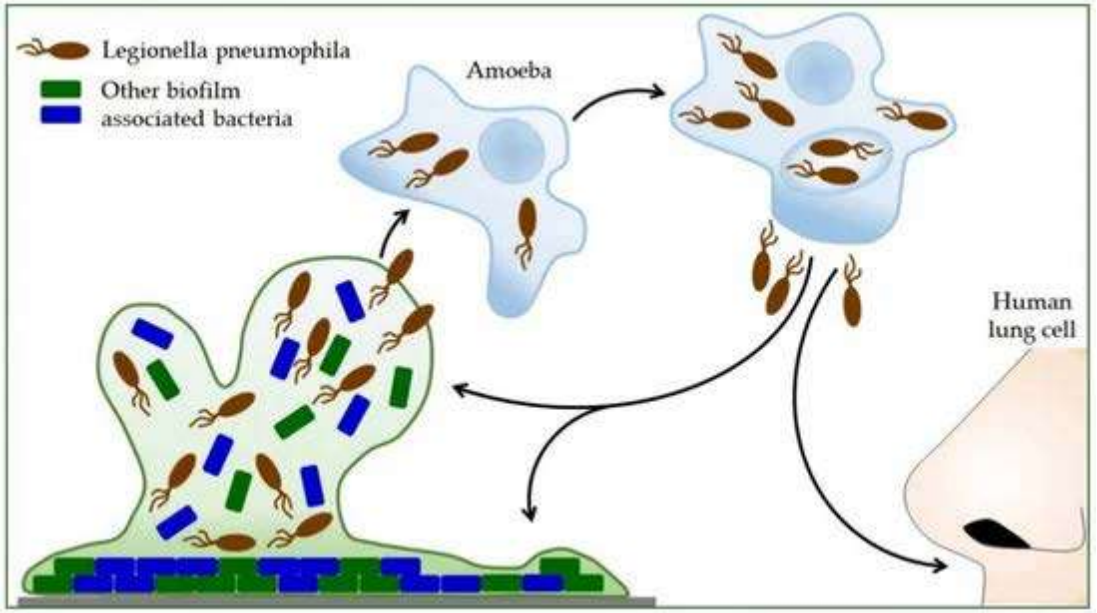
Javnozdravstveni značaj

- *Legionarska bolest (LD) čini otprilike 2-15% svih slučajeva vanbolnički stečene pneumonije (CAP) koja zahtijeva hospitalizaciju u Europi i Sjevernoj Americi.*
- *L. pneumophila najčešći uzročnik može uzrokovati sporadičnu i epidemijsku CAP, kao i bolničku pneumoniju (HAP), kako kod zdravih tako i kod imunokompromitiranih osoba.*
- *Legioneloze također predstavljaju infekcije respiratornog trakta povezane s putovanjem, boravkom u hotelima, SPA centrima, Welness centrima.*
- *Kategoriziraju se kao infekcije stečene :*
  1. *u zajednici*
  2. *u bolnici*
  3. *na putovanju.*



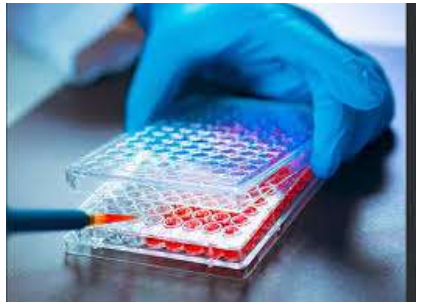
Značajke legionela

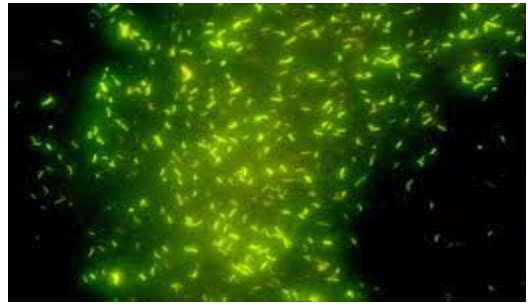
- *Gram-negativni, aerobni bacili koji ne stvaraju spore, nemaju kapsule, pozitivni katalaza i oksidaza.*
- *Raspon temperature rasta je od 25°C -50°C* ***(optimalna35°C).***
- *Legionele mogu preživjeti i rasti kao paraziti unutar slobodnoživućih protozoa najčešće su to Acanthamoeba i Hartmannella*
- *Biofilm*
- *Neke bakterijske vrste stimuliraju postojanost L. pneumophila u biofilmu(Klebsiella pneumoniae, Flavobacterium sp., Pseudomonas putida, Pseudomonas fluorescens, Pseudomonas aeruginosa)*
- *Kao izvor energije koriste aminokiseline, a ne ugljikohidrate*



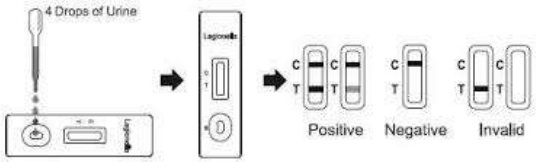
HZJZ

Serologija(ELISA,IFA,DFA)



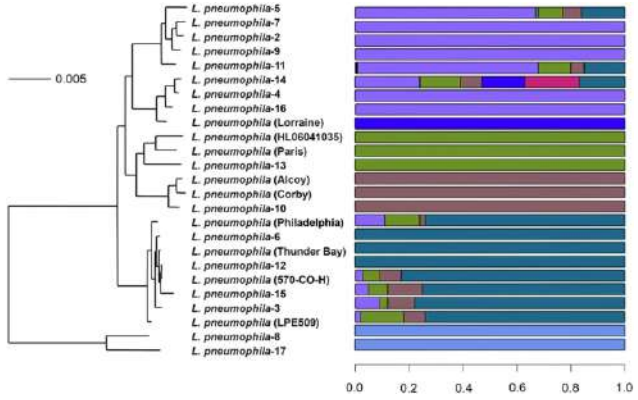


UAT- LEGIONELLA PNEUMOPHILA SG 1



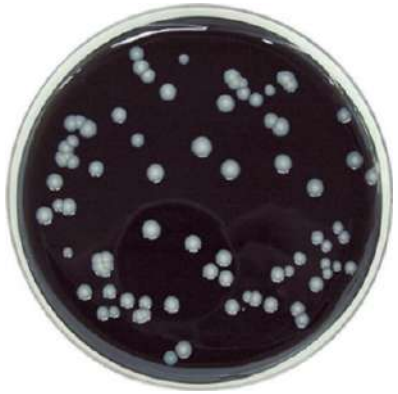
RT PCR/mip gene –LP
16s rRNA

WGS



Kultivacija na BCYE
-Inkubacija 35-37C 10 dana, aerobno u prisustvu vlage

- *Makroskopski i mikroskopski pregled sumnjivih kolonija /2 dan*
- *Identifikacija sumnjivih kolonija MALDI TOF MS*
- *Serotipizacija (latex aglutinacija)*



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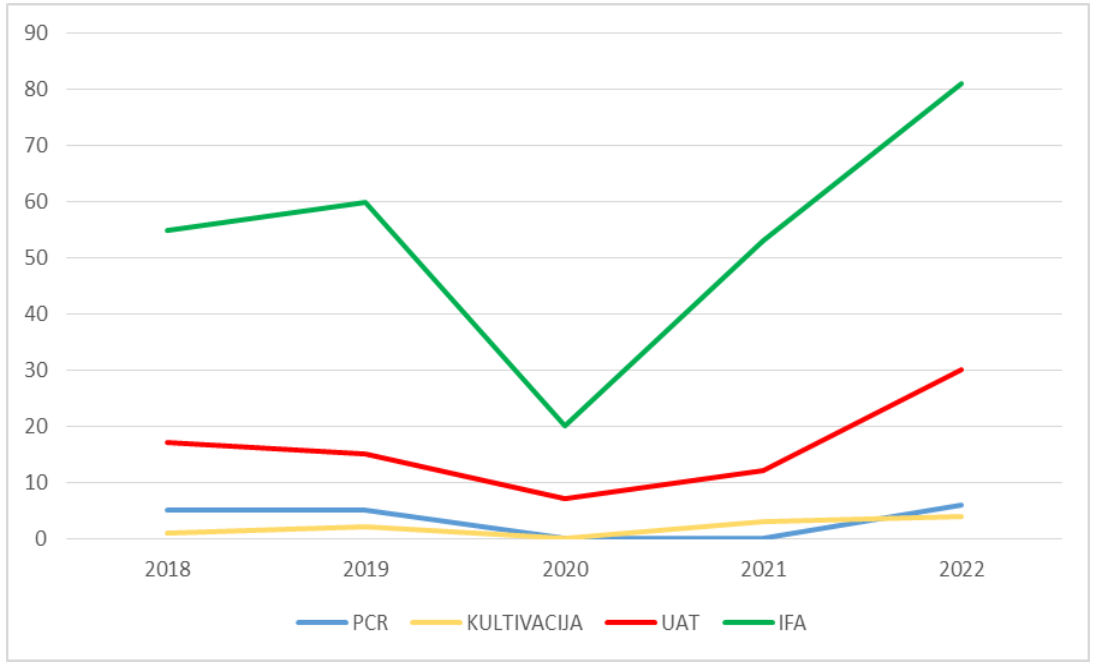
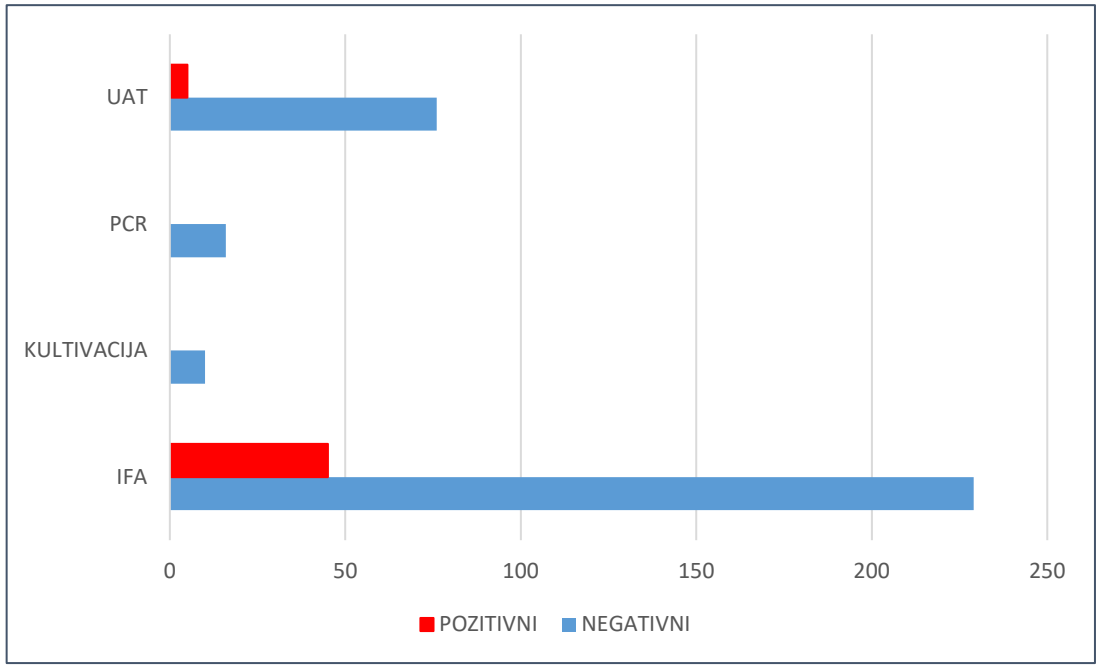


Broj pacijenata s pneumonijom testiranih UAT, kultivacijom, Legionella pneumophila PCR i Legionella pneumophila IFA, 2018-2022.

Odjel za bakteriologiju HZJZ



Broj pozitivnih uzoraka po metodama, 2018-2022

Odjel za bakteriologiju HZJZ

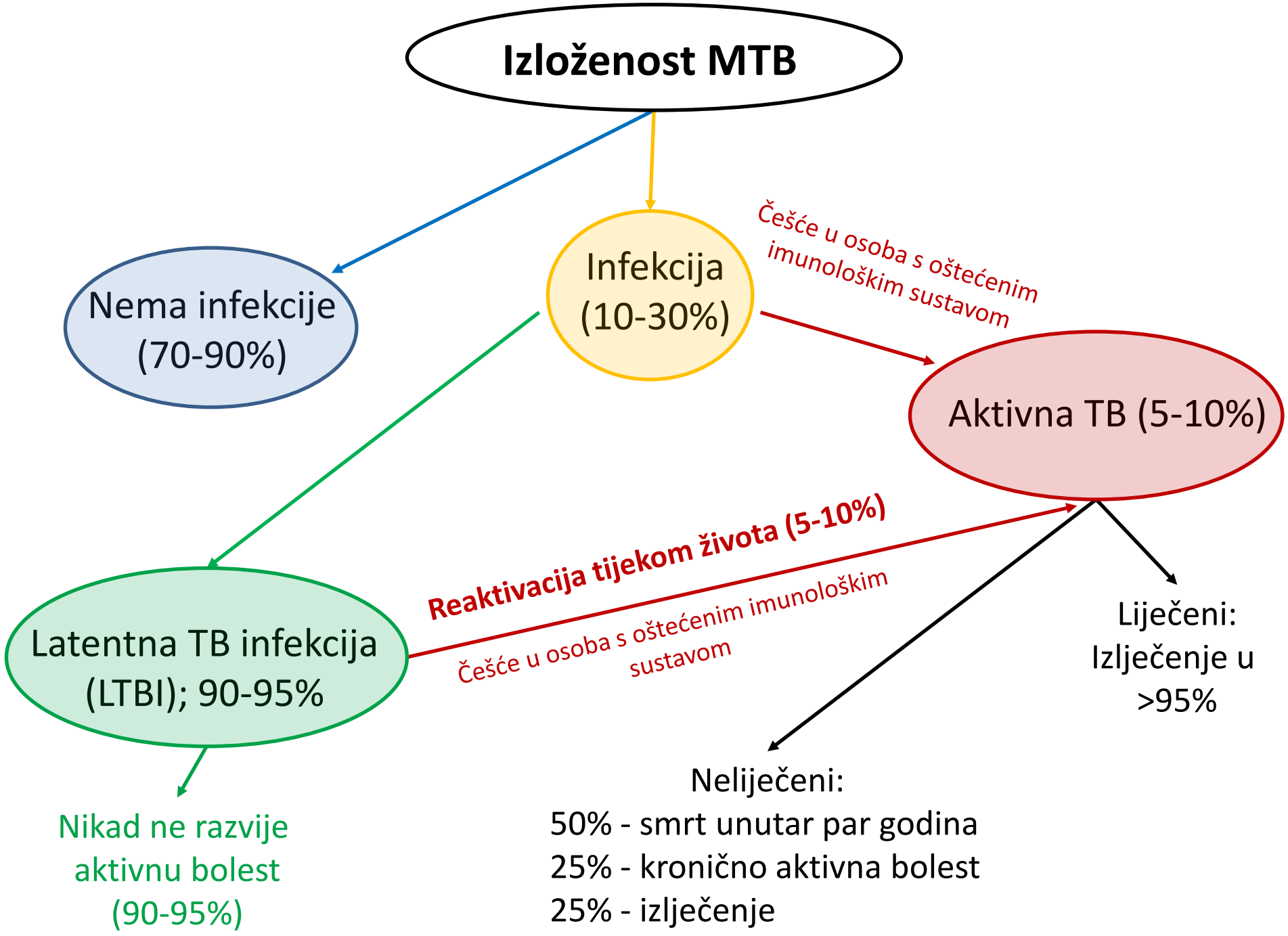
Legioneloze i dalje predstavljaju važan uzrok morbiditeta i potencijalno mortaliteta koji se može spriječiti pravovremenom dijagnostikom.

- *Nadzor nad LD-om na europskoj razini započeo je 1986. godine, a od 2010. godine provodi ga Europska mreža za nadzor legionarske bolesti (ELDSNet), nasljednica EWGLI-ja (Europska radna skupina za infekcije legionelom), a koordinira Europska Centar za prevenciju i kontrolu bolesti (ECDC).*
- *S ciljem jačanja nadzora i kapaciteta za istraživanje izbijanja bolesti u zemljama Europe, ECDC je započeo godišnju shema EQA na kliničkim uzorcima i uzorcima iz okoliša Legionella spp. u 2019.*

	November 2021 distribution			April 2022 distribution		
Country	Clinical EQA samples – 5159	Environmental EQA samples – 5160	Number of participating laboratories per country	Clinical EQA samples – 5370	Environmental EQA samples – 5371	Number of participating laboratories per country
Austria	Yes	-	1	Yes	-	1
Belgium	Yes	Not examined	1	Not examined	Not examined	0
Bulgaria	Yes	Yes	2	Yes	Yes	2
Croatia	Yes	Yes	2	Yes	Yes	2
Cyprus	Yes	-	1	Yes	Yes	2
Czechia	Yes	Yes	2	Yes	Yes	2
Denmark	Yes	Yes	2	-	-	0
Estonia	Yes	Yes	2	Yes	Yes	2
Finland	Yes	Yes	2	Yes	Yes	2
France	Yes	Yes	2	Yes	Yes	2
Germany	Yes	Yes	2	Not examined	Not examined	1
Greece	Yes	Yes	2	Yes	Yes	2
Hungary	Yes	Yes	2	-	-	0
Iceland	Yes	Not examined	1	Yes	Yes	2
Ireland	Yes	Yes	2	Yes	Yes	2
Italy	Yes	Yes	2	Yes	Yes	2
Latvia	Yes	Yes	2	Yes	Yes	2
Lithuania	Yes	-	1	Yes	-	1
Malta	Yes	-	1	Not examined	-	0
Netherlands	Yes	Yes	2	Yes	Yes	2
Norway	Yes	Yes	2	Yes	Yes	2
Poland	-	Yes	1	Yes	Yes	2
Portugal	Yes	Yes	2	Yes	Yes	2
Romania	Not examined	Not examined	0	Yes	Yes	2
Slovak Republic	Yes	Yes	2	Yes	Yes	2
Slovenia	Yes	Yes	2	Yes	Yes	2
Spain	Yes	-	1	Yes	-	1
Sweden	Yes	Yes	2	Yes	Yes	2

Klinički aspekti i novosti u liječenju tuberkuloze

Doc. dr. sc. Mateja Janković Makek
KPB Jordanovac, KBC Zagreb, MF Zagreb


Izloženost MTB
Nema infekcije (70-90%)
Infekcija (10-30%)
Češće u osoba s oštećenim imunološkim sustavom
Aktivna TB (5-10%)
Reaktivacija tijekom života (5-10%)
Češće u osoba s oštećenim imunološkim sustavom
Latentna TB infekcija (LTBI); 90-95%
Liječeni: Izlječenje u >95%
Neliječeni:
50% - smrt unutar par godina
25% - kronično aktivna bolest
25% - izlječenje
Nikad ne razvije aktivnu bolest (90-95%)

Aktivna tuberkuloza

progresivna primarna infekcija (5 – 10%) - češće u određenih skupina bolesnika (npr. HIV i djeca <5 god)

temperatura (cca 14 do 21 dan); rjeđe pleuritička bol s ili bez popratnog izljeva; katkad retrosternalna bol (uslijed uvečanih limfnih čvorova)

reaktivacija primarne infekcije (90-95%)

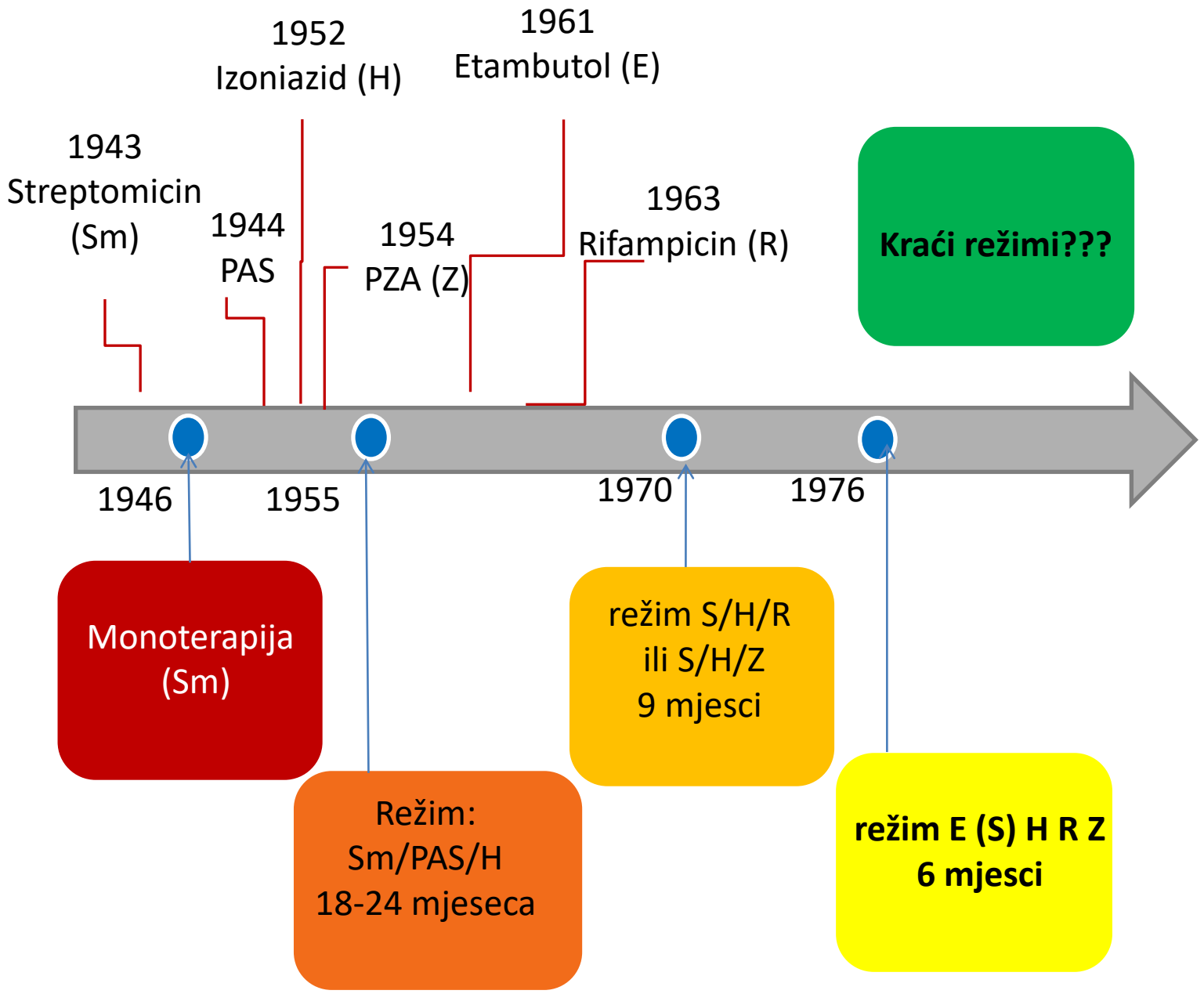
Simptomi (kašalj, gubitak na težini, malaksalost, vrućica i/ili noćno znojenje, bol u prsima, dispneja, hemoptize) tipično nastaju polagano i prisutni su tjednima/mjesecima prije dijagnoze

Principi ATL terapije:

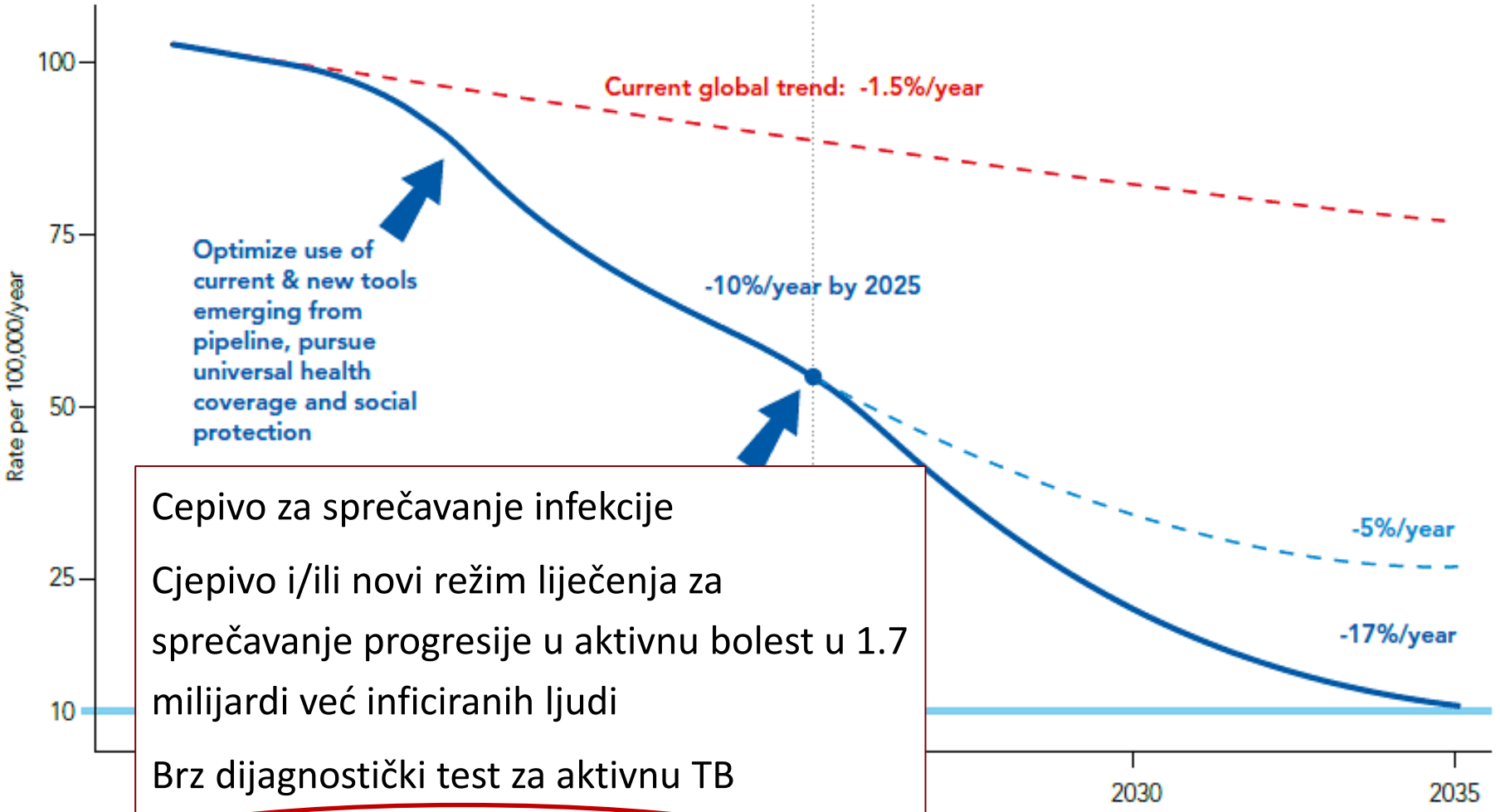
Kombinacija lijekova → **Prevencija rezistencije**

Trajanje terapije → **Prevencija relapsa**

Liječenje osjetljive tuberkuloze



WHO strategija elimininacije tuberkuloze



Cepivo za sprečavanje infekcije

Cjepivo i/ili novi režim liječenja za sprečavanje progresije u aktivnu bolest u 1.7 milijardi već inficiranih ljudi

Brz dijagnostički test za aktivnu TB

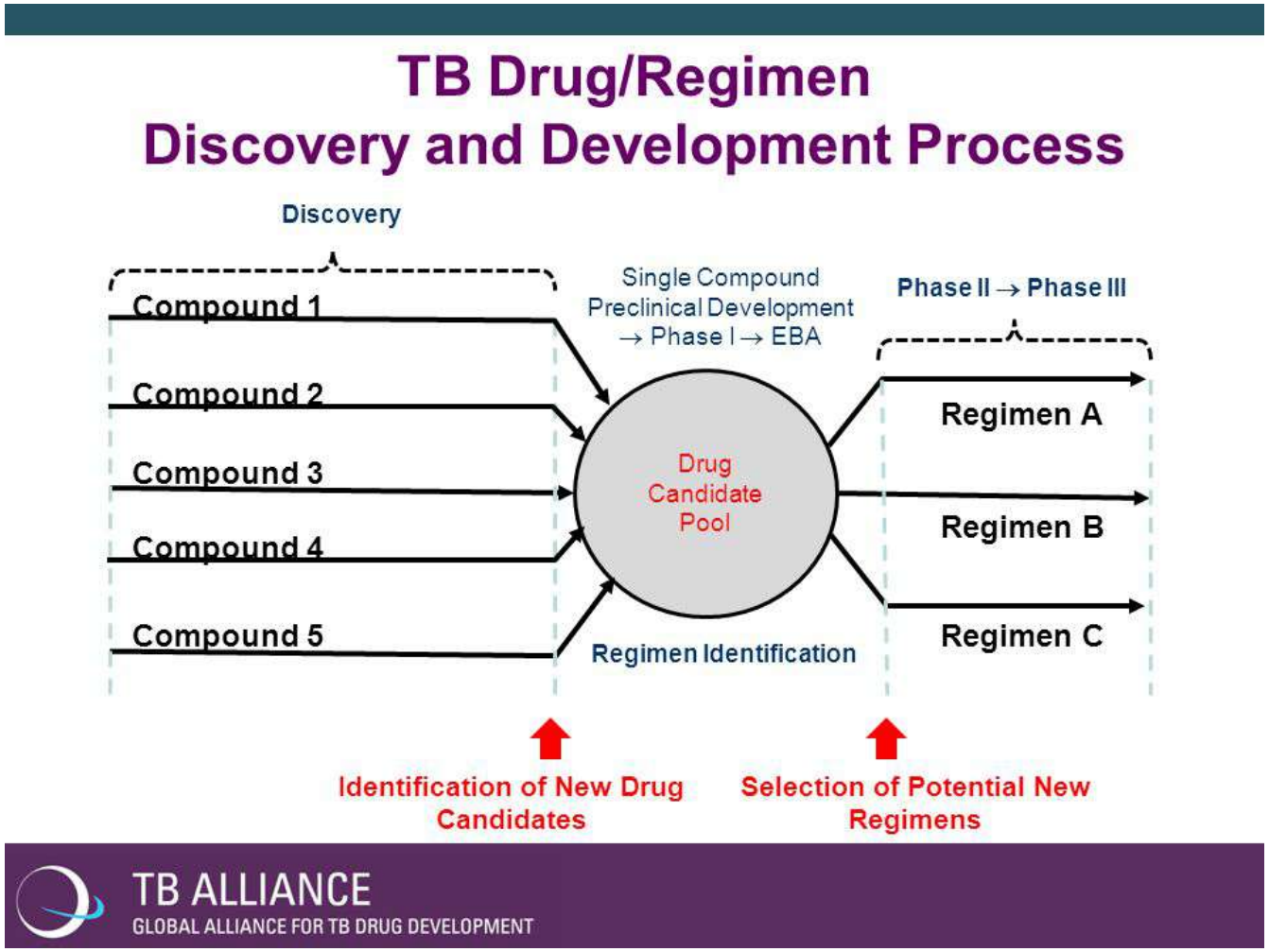
Jednostavniji i kraći režimi za liječenje aktivne TB

Osjetljiva TB - kraći režimi bazirani na florokinolonima: studije faze III

- REMox-TB consortium (2 MHRZ/2 MHR ili 2 MERZ/2 MR vs. 2 EHRZ/4 RH)
- OFLOTUB consortium (2 GHRZ/2 GRH versus 2 EHRZ/4 HR)
- Brža negativizacija ali i viša stopa relapsa bolesti po provedenom liječenju
- Potrebni su biomarkeri koji bi predvidjeli dugoročne rezultate liječenja (tko će dobiti relaps a tko ne)

N Engl J Med. 2014 Oct 23;371(17):1577-87. doi: 10.1056/NEJMoa1407426.

Perspektiva: novi lijekovi, novi režimi, „kombinirana” istraživanja faze 2 i 3



Cilj novih terapijskih režima: skraćenje trajanja liječenja na 4 mjeseca ili manje

Four-Month Rifapentine Regimens with or without Moxifloxacin for Tuberculosis

Susan E. Dorman, M.D., Payam Nahid, M.D., M.P.H., Ekaterina V. Kurbatova, M.D., Ph.D., M.P.H., Patrick P.J. Phillips, Ph.D., Kia Bryant, M.P.H., Kelly E. Dooley, M.D., Ph.D., Melissa Engle, C.R.T., C.C.R.C., Stefan V. Goldberg, M.D., Ha T.T. Phan, Dr.P.H., M.D., James Hakim, M.D., John L. Johnson, M.D., Madeleine Lourens, M.B., Ch.B., Ph.D., et al., for the AIDS Clinical Trials Group and the Tuberculosis Trials Consortium

Article Figures/Media Metrics

42 References 85 Citing Articles Letters

May 6, 2021
N Engl J Med 2021; 384:1705-1718
DOI: 10.1056/NEJMoa2033400
Chinese Translation 中文翻译

WHO:

Treatment of drug-susceptible TB using 4-month regimens

Recommendation 6.

People aged 12 years or older with drug-susceptible pulmonary TB, may receive a 4-month regimen of isoniazid, rifapentine, moxifloxacin and pyrazinamide[8] (conditional recommendation, moderate certainty of evidence) – new recommendation.

CDC Releases Interim Guidance on a Four-month TB Treatment Regimen

February 24, 2022

Dear Colleagues,

Today, the U.S. Centers for Disease Control and Prevention (CDC) released new interim guidance for a 4-month treatment regimen to treat drug-susceptible TB disease that is as effective as the standard 6-month regimen for TB treatment. The new 4-month rifapentine-moxifloxacin regimen is a daily treatment option for people 12 years of age and older with drug-susceptible pulmonary TB disease in the United States.

Shorter treatment regimens for TB disease can be more convenient and help patients finish treatment faster. The 4-month rifapentine-moxifloxacin regimen has an intensive phase of 8 weeks of daily treatment with rifapentine, isoniazid, pyrazinamide, and moxifloxacin followed by a continuation phase of 9 weeks of daily treatment with rifapentine, isoniazid, and moxifloxacin (a total of 17 weeks for treatment).

Ali,....

EUROPEAN RESPIRATORY *journal*
FLAGSHIP SCIENTIFIC JOURNAL OF ERS

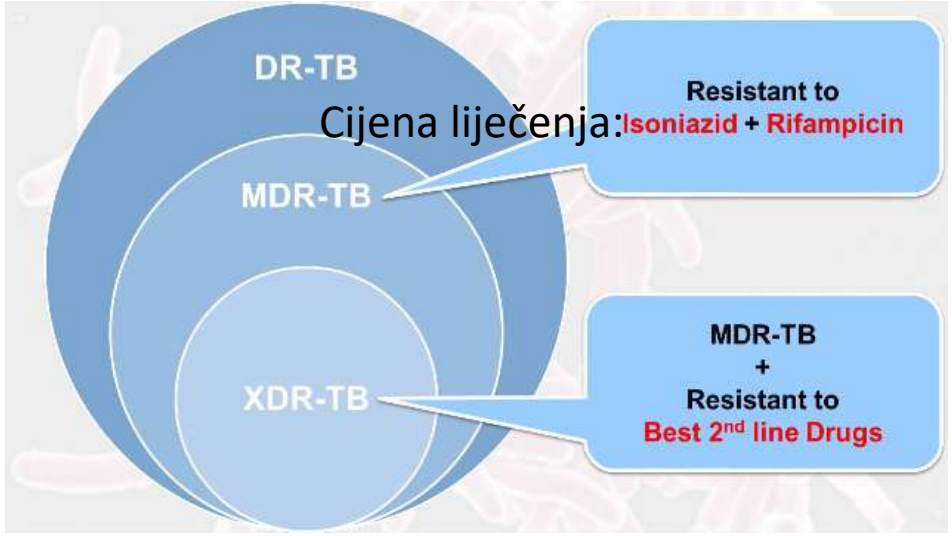
Rifapentine access in Europe: growing concerns over key tuberculosis treatment component

Lorenzo Guglielmetti, Gunar Günther, Claude Leu, Daniela Cirillo, Raquel Duarte, Alberto L. Garcia-Basteiro, Delia Goletti, Mateja Jankovic, Liga Kuksa, Florian P. Maurer, Frédéric Méchaï, Simon Tiberi, Frank van Leth, Nicolas Veziris, Christoph Lange on behalf of the Study Group on Mycobacteria of the European Society of Microbiology and Infectious Diseases (ESGMYC), European Society of Mycobacteriology (ESM), European Respiratory Society (ERS) and, the Tuberculosis Network European Trials group (TBnet)

European Respiratory Journal 2022 59: 2200388; **DOI:** 10.1183/13993003.00388-2022

Rezistentna tuberkuloza

- primarna rezistencija – osoba izložena/zaražena rezistentnom mikroorganizmu
- sekundarna rezistencija – nastaje za vrijeme TB terapije (neadekvatan terapijski režim; loša adherencije bolesnika; drugi razlozi poput malapsorpcije lijekova ili neadekvatne koncentracije lijeka zbog interakcije s drugim lijekovima)



Cijena liječenja:

ishod liječenja (dugotrajno, komplicirano) - ovisi o razmjeru rezistencije

	Euro (mean)	Min	Max
Osjetljiva TB	334	41	1299
MDR TB	23272	2112	77354
XDR TB	90657	65031	124887

Gunther G et al. ERJ 2015

Rezistentna TB – revolucionarno skraćenje trajanja liječenja

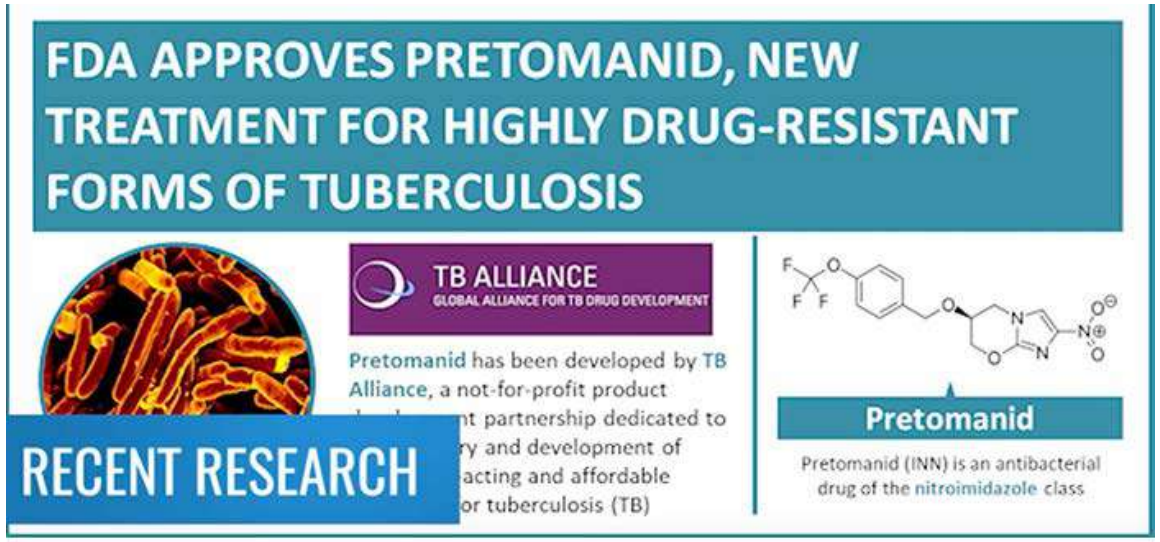
ORIGINAL ARTICLE

A 24-Week, All-Oral Regimen for Rifampin-Resistant Tuberculosis

Bern-Thomas Nyang'wa, M.B., B.S., Catherine Berry, B.Med., Emil Kazounis, M.Med.Sci., Ilaria Motta, Ph.D., Nargiza Parpieva, Sc.D., Zinaida Tigay, M.D., Varvara Solodovnikova, M.D., Irina Liverko, Sc.D., Ronelle Moodliar, M.B., B.S., Matthew Dodd, M.Sc., Nosipho Ngubane, M.B., B.Ch., Mohammed Rassool, M.B., B.Ch., et al., for the TB-PRACTECAL Study Collaborators*

Article Figures/Media Metrics

December 22, 2022
N Engl J Med 2022; 387:2331-2343



WHO:

Section 1. The 6-month bedaquiline, pretomanid, linezolid and moxifloxacin (BPaLM) regimen for MDR/RR-TB (NEW)

1.1 Recommendation

NEW RECOMMENDATION

No.	Recommendation
1.1	WHO suggests the use of a 6-month treatment regimen composed of bedaquiline, pretomanid, linezolid (600 mg) and moxifloxacin (BPaLM) rather than the 9-month or longer (18-month) regimens in MDR/RR-TB patients. *(Conditional recommendation, very low certainty of evidence)*

2022 Global New TB Drug Pipeline[1] Updated 11/3/2022

Discovery | Preclinical Development | Clinical Development

Lead optimization → Early stage development → GMP/GLP toxicity → Phase 1 → Phase 2 → Phase 3 → Regulatory Market Approvals

Indazole sulfonamides
Diarylthiazoles
DprE1 inhibitors
Direct InhA inhibitors
Mtb energy metabolism
Gyrase inhibitors
Arylsulfonamides
Inhibitors of MmpL3, Translocase-1, ClpC1, PKS13,F-ATP synthase
Oxazolidinones
DnaE1/Nargenicin analogs

TBD-09, TBD-10 (MK-7762, -3854)
MPL-447*
JSF-3285*
CPZEN-45*
NTB-3119*
MBX-4888A (1810)*
FNDR-10045*, FNDR-20364*

GSK-839*
OTB-658

BVL-GSK098*
GSK-286*
TBAJ-876
TBAJ-587
TBI-223
Macozinone* (PBTZ-169)

Sanfetrinem
Delpazolid
Sutezolid
Sudapyridine (WX-081)
BTZ-043*
TBA-7371*
OPC-167832*
GSK-656* (070)
Telacebec*
SPR 720*
SQ-109*

Results Reported / Expected in 2022/23

TB Practecal
ZeNix
Simplici TB (4-month regimen)
Truncate TB (2-month regimens)
STREAM 2

Bedaquiline*
Delamanid*
Pretomanid*

*New chemical class. Known chemical classes for any indication are color coded: rifamycin, oxazolidinone, nitroimidazole, diarylquinoline, benzothiazinone, imidazopyridine amide, beta-lactam. [1]New Molecular Entities not yet approved, being developed for TB or conditionally approved for TB. Showing most advanced stage reported for each. Details for projects listed can be found at http://www.newtbdrugs.org/pipeline/clinical

Pyrifazimine (TBI-166)

Ongoing projects without a lead compound identified: http://www.newtbdrugs.org/pipeline/discovery

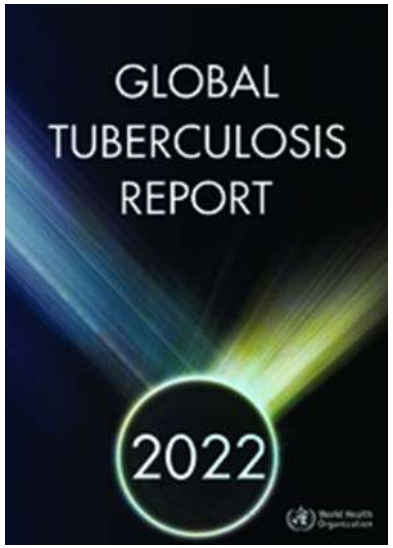
Underline = updates since May 2022

WORKING GROUP ON NEW TB DRUGS
www.newtbdrugs.org

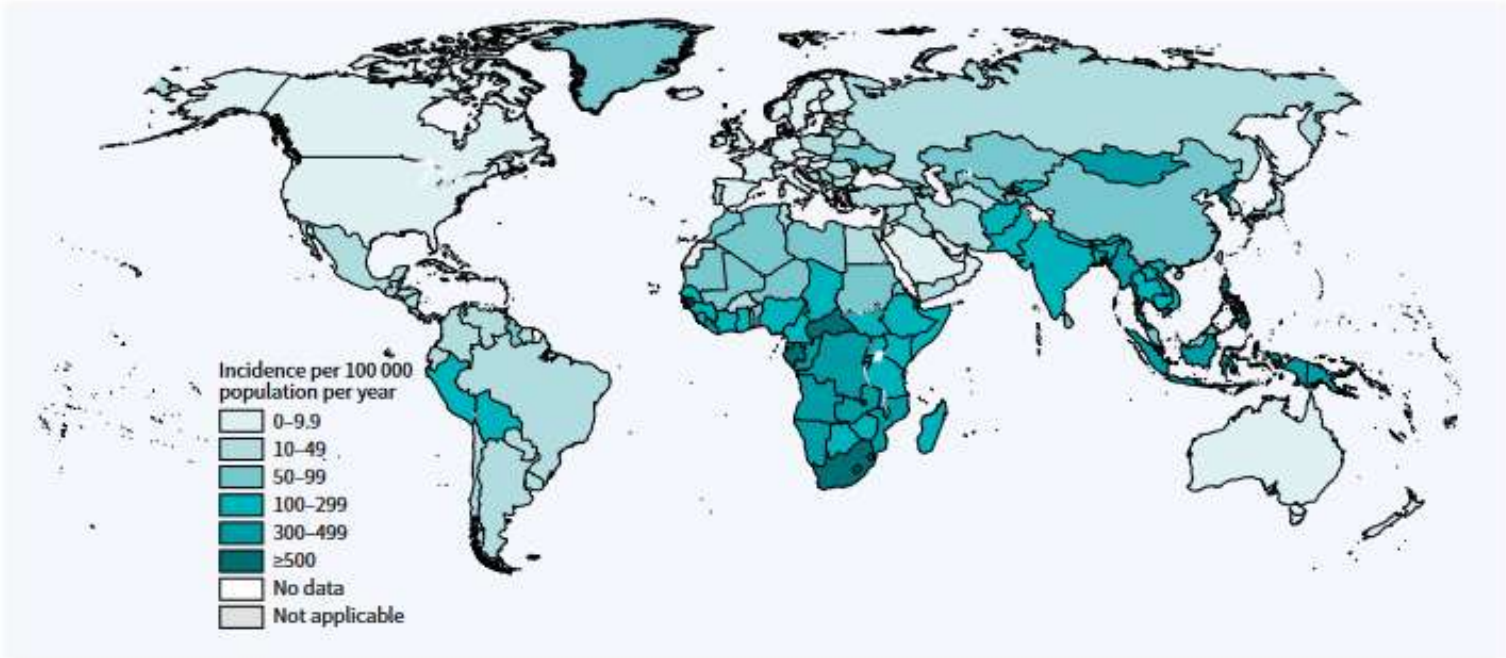
Updated: November 2022

Noviteti u dijagnostici tuberkuloze

Doc. dr. sc. Ljiljana Žmak, prim. dr. med.
Hrvatski zavod za javno zdravstvo
Medicinski fakultet Sveučilišta u Zagrebu

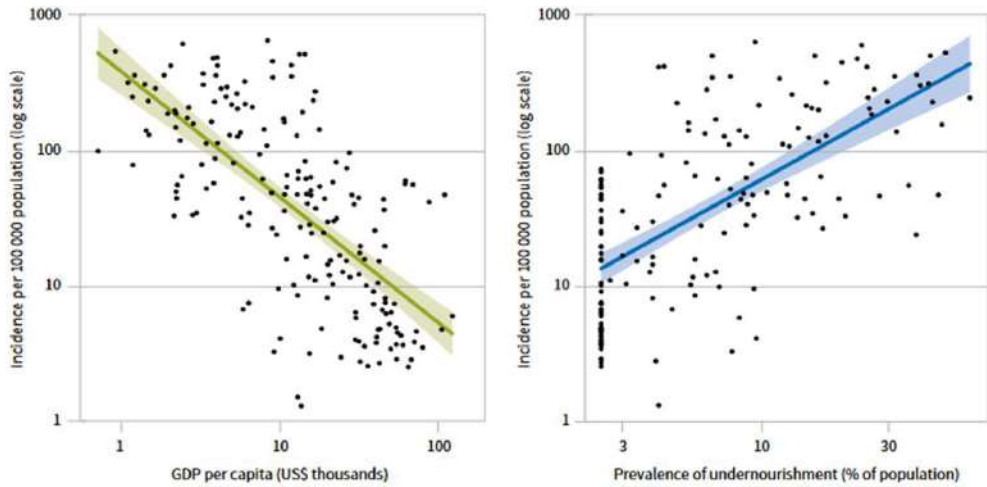


Estimated TB incidence rates, 2021



- u 2021., 1.6 milijuna smrti
- ok 10,6 milijuna oboljelih
- u 2021. 47 zemalja je imalo incidenciju ispod 10/100 000

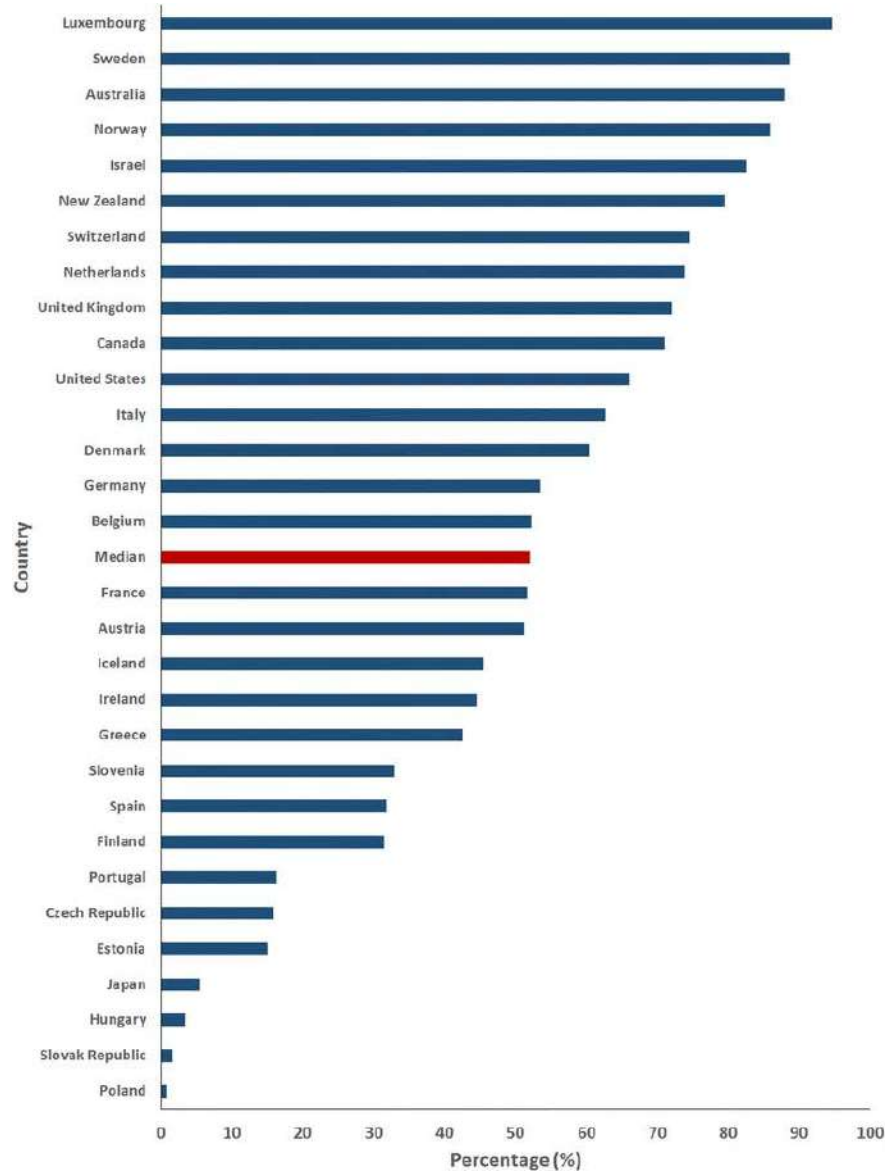
The relationship between GDP per capita and the prevalence of undernourishment, and TB incidence per 100 000 population, 2021[a]



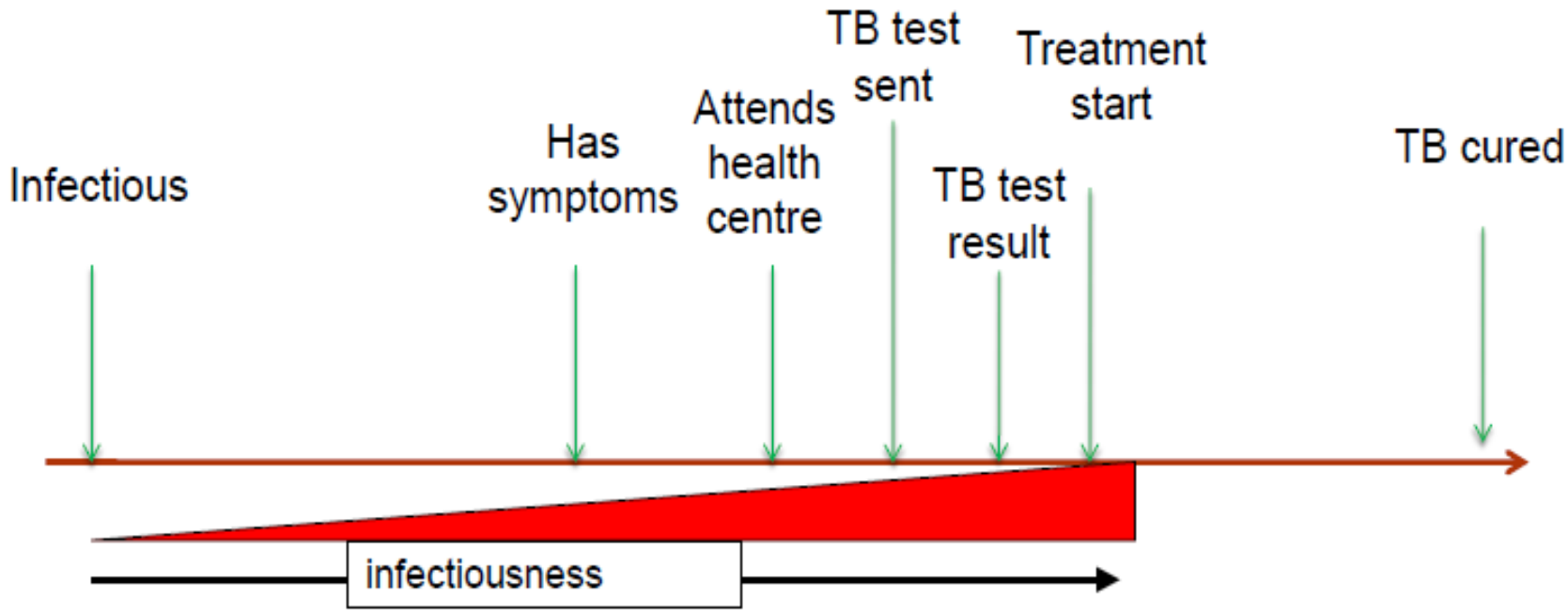
HZJZ

SVEUČILIŠTE U ZAGREBU MEDICINSKI FAKULTET

Postotak tuberkuloza kod osoba rođenih u inozemstvu za odabrane zemlje OECD-a s visokim dohotkom



Pareek, M., Greenaway, C., Noori, T. et al. The impact of migration on tuberculosis epidemiology and control in high-income countries: a review. BMC Med 14, 48 (2016). https://doi.org/10.1186/s12916-016-0595-5



(A Grant. AIDS2012)

IZAZOVI U DIJAGNOSTICI I PREVENCIJI TUBERKULOZE

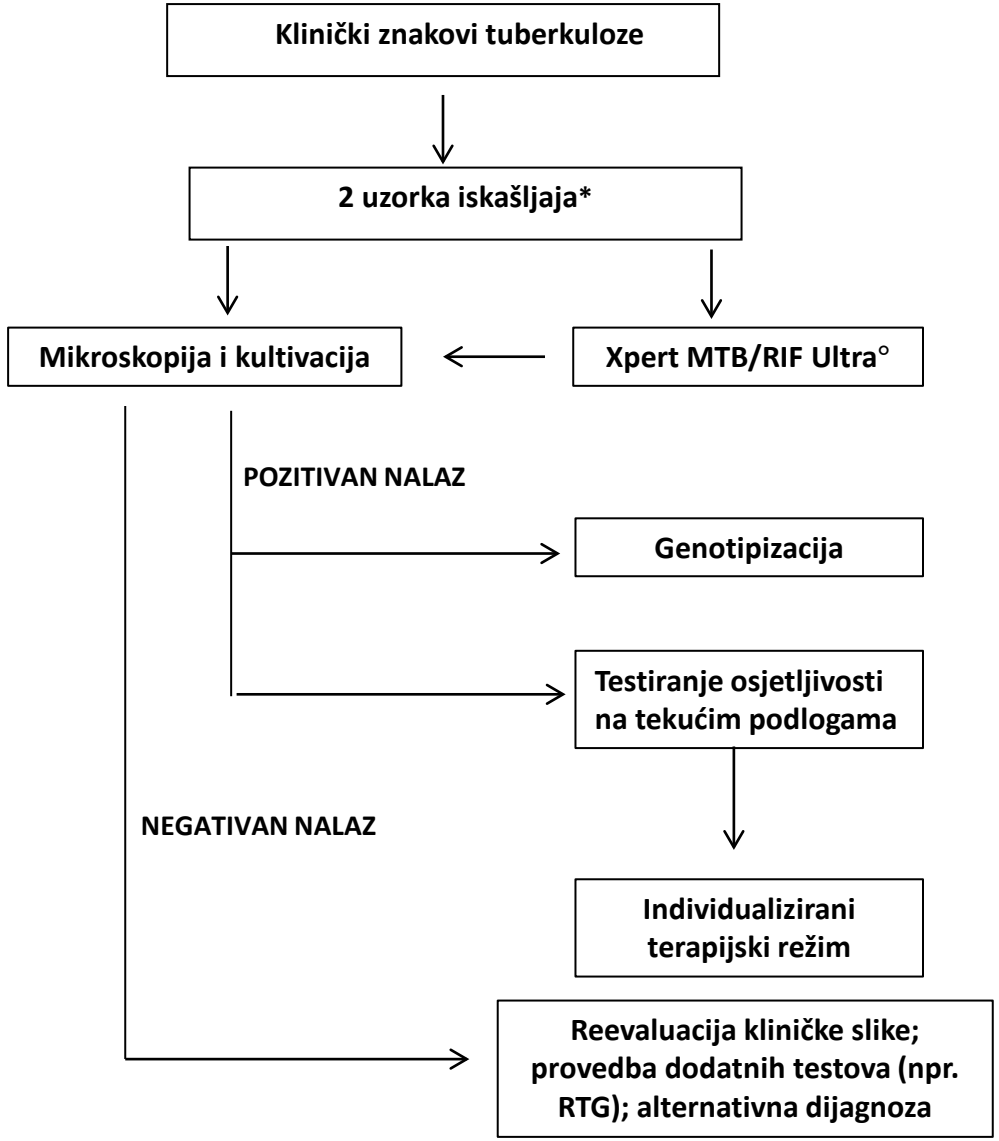
1. ŠTO RANIJE OTKRITI BOLESNIKA TE ZAPOČETI ADEKVATNU TERAPIJU
2. ODREDITI KOD KOJIH JE KONTAKATA DOŠLO DO INFEKCIJE
3. OTKRITI LANAC ZARAZE U POPULACIJI

Prvi korak u kontroli širenja tuberkuloze je pravovremena dijagnoza

Glavne karike u laboratorijskoj dijagnostici aktivne tuberkuloze:

1. Mikroskopija
2. Kultivacija
3. Brza PCR dijagnostika
4. Testiranje osjetljivosti na antituberkulotike
5. Detekcija biomarkera
6. Genotipizacija

KVALITETAN UZORAK



*ako Xpert test nije dostupan poslati oba uzorka na klasičnu dijagnostiku
° Mogu se koristiti i drugi molekularni testovi podržani od strane SZO

PROGRAMSKE SMJERNICE ZA SUZBIJANJE I SPRJEČAVANJE TUBERKULOZE

(siječanj 2020.)

HZJZ

SVEUČILIŠTE U ZAGREBU MEDICINSKI FAKULTET

DAVANJE UZORAKA ZA DIJAGNOSTIKU

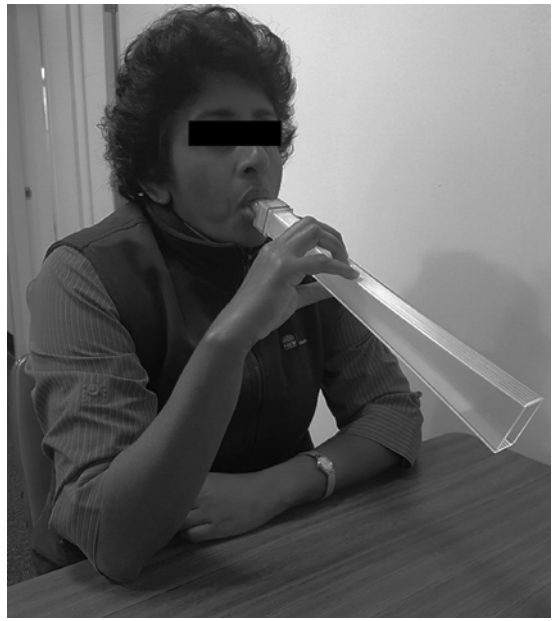
- **2 uzorka sputuma: Glavni izazovi: 1. Nemogućnost davanja sputuma**
  2. Kontaminacija uzorka

1. Nemogućnost davanja sputuma

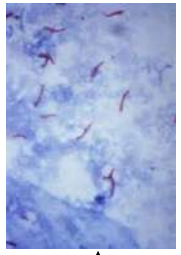
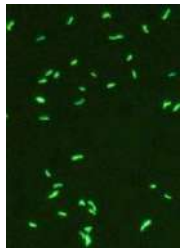
- 10% osoba s TB ne producira sputum
- kontrolni sputumi tijekom terapije
- rezonantna frekvencija olakšava odvajanje mukusa te iskašljavanje

2. Kontaminacija uzorka

- OMNIgene® SPUTUM (DNA Genotek Inc., Canada) reagens koji se dodaje u sputum u svrhu dekontaminacije -8 dana bez hlađenja



MIKROSKOPIJA

1882 — 1890 — 1957 — 2006 — 2015

- slaba osjetljivost (visoka cijena fluorescentnih mikroskopa)
- veliki izazov u djece
- ne razlikuje NTM

KULTIVACIJA

1930 — 1977 — 1995 — 2005




- opremljenost laboratorija
- visoka cijena
- dužina trajanja (ne razlikuje C, NTM od TBC)

BRZA PCR DIJAGNOSTIKA

GeneXpert Ultra test

- Osjetljivost oko 90%
- Niža osjetljivost kod M- uzoraka

IZAZOVI: Visoka cijena
samo 3,5% uzoraka pozitivno

Technologies endorsed by WHO

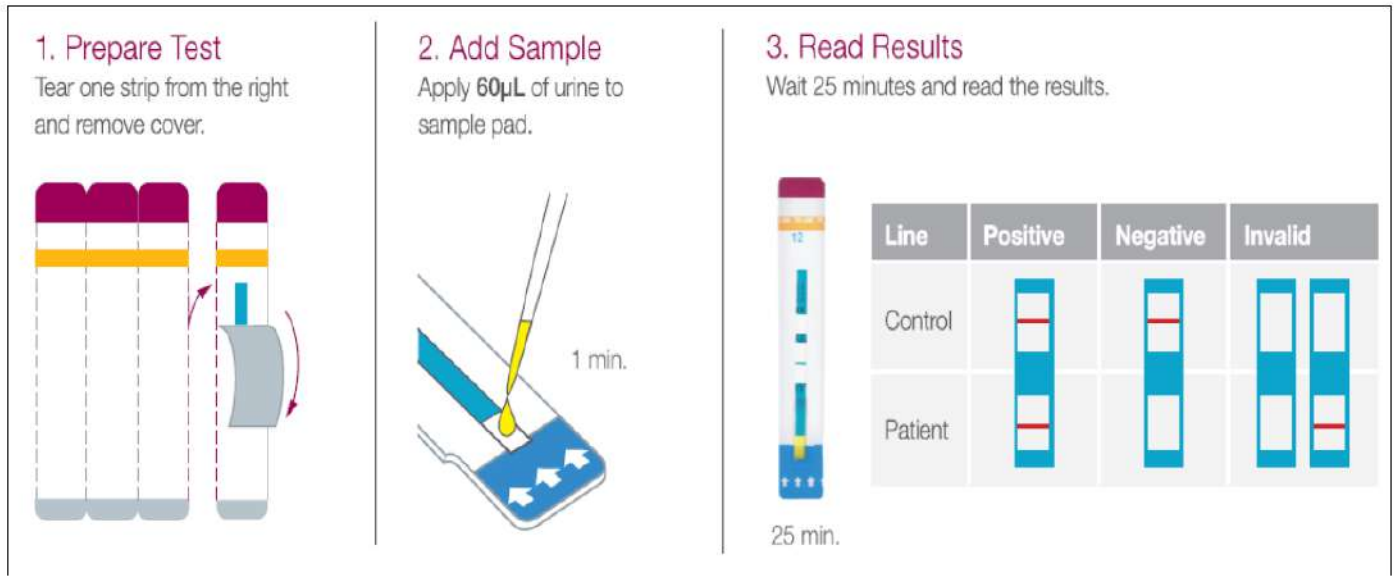
Molecular detection of TB disease and/or drug resistance

- Xpert MTB/RIF, MTB/RIF Ultra and MTB/XDR, Cepheid, USA
- GenoType® MTBDRplus, Hain Lifescience/Bruker, Germany
- Genoscholar® NTM+MDRTB II; Nipro, Japan
- GenoType® MTBDRsl, Hain Lifescience/Bruker, Germany
- TB LAMP, Eiken, Japan
- Truenat MTB, MTB Plus and MTB-RIF Dx assays, Molbio Diagnostics, India
- FluoroType MTB and MTBDR assays Hain Lifescience, Germany
- Abbott RealTime MTB and MTB RIF/INH on m2000sp and m2000rt systems, Abbott, USA
- BD Max MDR-TB, Becton Dickinson, USA
- Roche cobas® MTB and MTB-RIF/INH on Cobas 6800/880 systems, Roche Diagnostics, Switzerland
- Genoscholar PZA TB II, Nipro, Japan

Rujan 2022.

BRZA DETEKCIJA ANTIGENA (POC)

Prva preporuka WHO za korištenja brzog POC testa u HIV+ bolesnika sa sumnjom na aktivnu TB



- jednostavan i jeftin (20 kuna)
- dokazu lipoarabinomanan (LAM) antigena izravno u uzorcima urina
- urin je poželjan uzorak za POC testove (lako se dobiva, nema stvaranja aerosola)
- za HIV+ < 100 CD4 T-limfocita ili su teškog općeg stanja

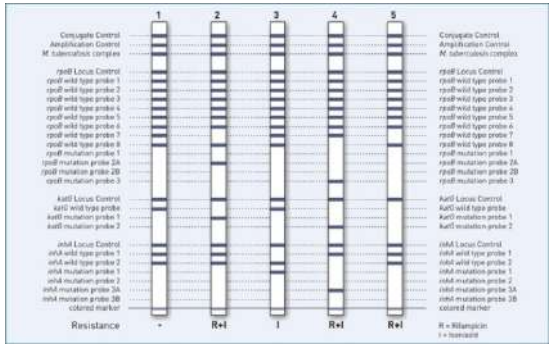
- Aeonose-dostupan na tržištu od kraja 2015. godine
- osjetljivost 76%
- 10 min

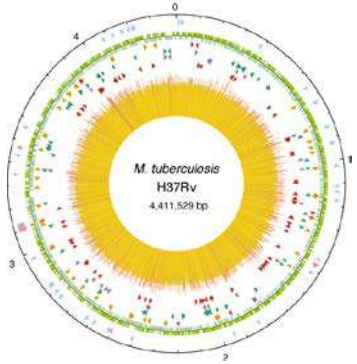
HZJZ

SVEUČILIŠTE U ZAGREBU MEDICINSKI FAKULTET

TESTIRANJE OSJETLJIVOSTI NA ANTITUBERKULOTIKE

Hain MTBDRplus, MTBDRsl, INNO-LIPA





1963 — 1993 — 1995 — 2013

TESTIRANJE OSJETLJIVOSTI NA ANTITUBERKULOTIKE

- u pojedinim državama EU fenotipski test osjetljivosti se prestao raditi (Engleska, Nizozemska…)
- fenotipsko testiranje samo kod rezistentnih sojeva
- radi se samo WGS

PREDNOSTI:

1. Brzina
2. Cijena
3. Identifikacija i genotipizacija

NEDOSTACI:

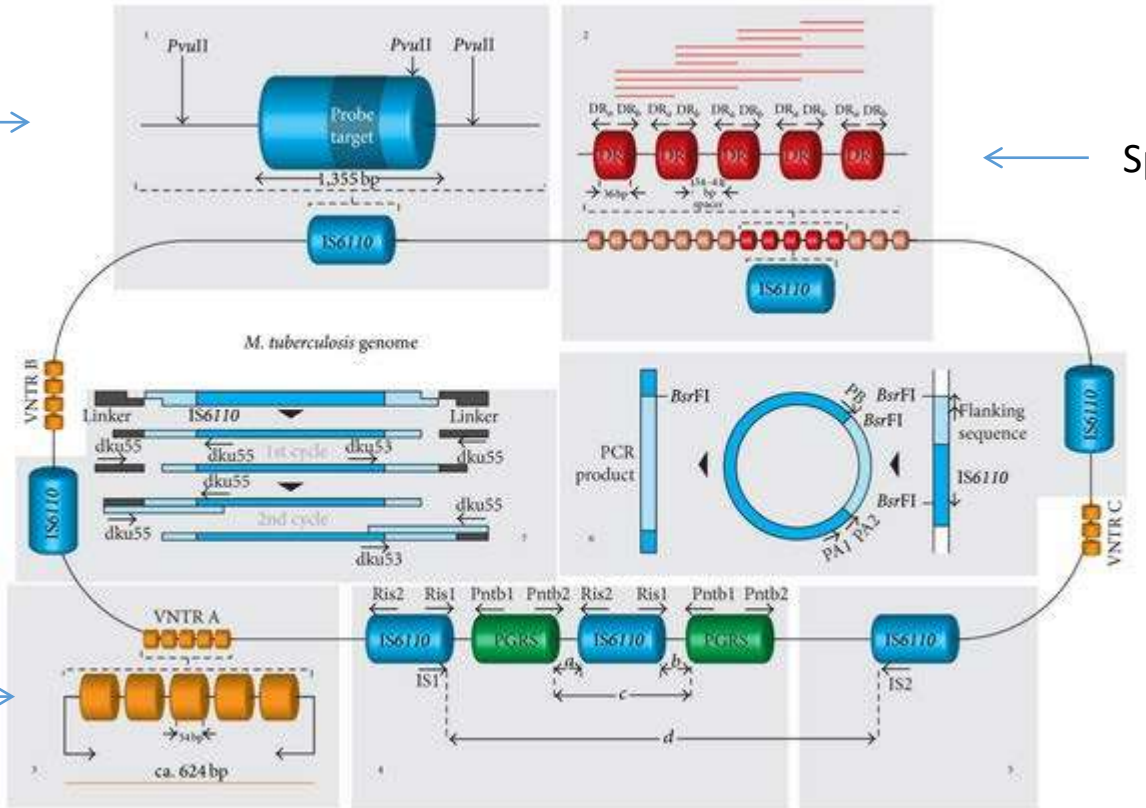
1. Nemogućnost testiranja direktno iz uzorka
2. Mapiranje svih mutacija
3. Biostatistička analiza

MOLEKULARNA GENOTIPIZACIJA

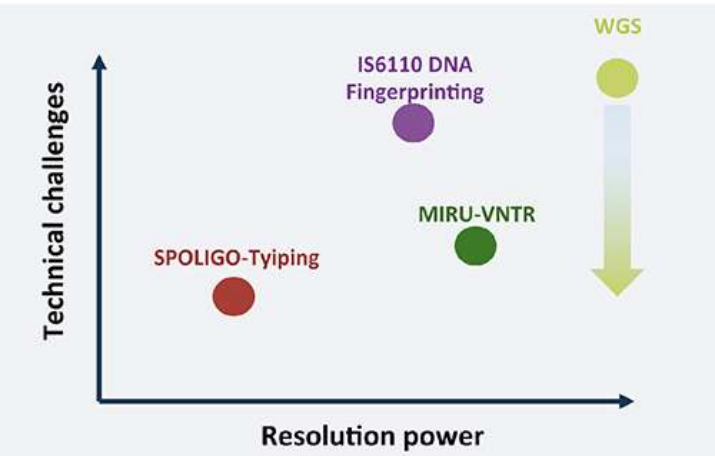
- razni polimorfizmi u genomu koriste se kao genetički markeri
- opisane razlike koriste se za tipiziranje sojeva i proučavanje evolucijskih odnosa između njih

IS6110-RFLP →

← Spoligotyping



MIRU-VNTR →



HZJZ

SVEUČILIŠTE U ZAGREBU MEDICINSKI FAKULTET

MOLEKULARNA GENOTIPIZACIJA

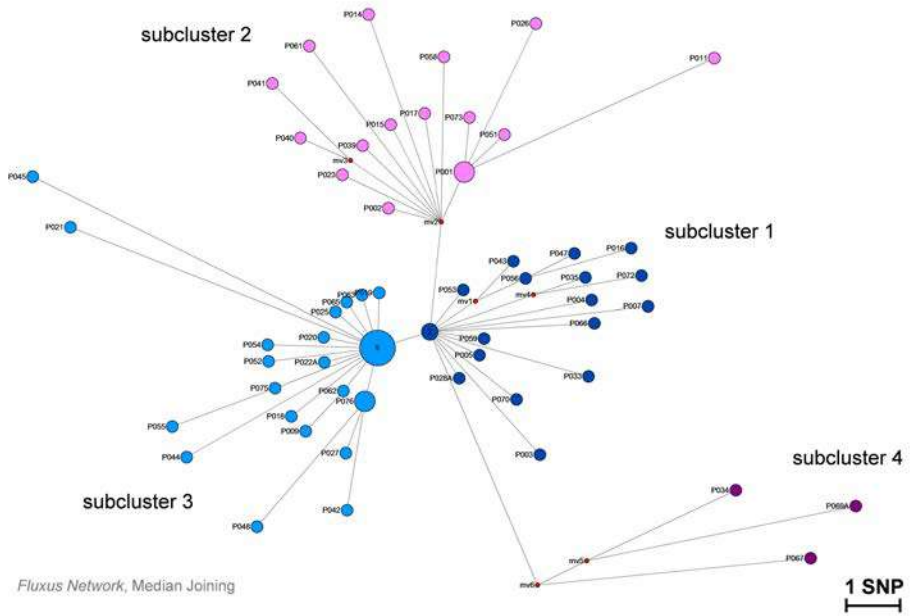
Isti ili različiti….jel to dovoljno?

- razumijevanje prijenosa M. tuberculosis neophodno je prilikom vođenja učinkovitih strategija kontrole TB
- tradicionalno tipiziranje nema dovoljnu diskriminatornu moć
- trenutnom MIRU VNTR metodom možemo sa sigurnošću isključiti ili potencijalno povezati bolesnike
- metoda se bazira na analizi malog dijela genoma

Prava kompleksnost dinamike prijenosa ne može se utvrditi samo analizom malog dijela genoma

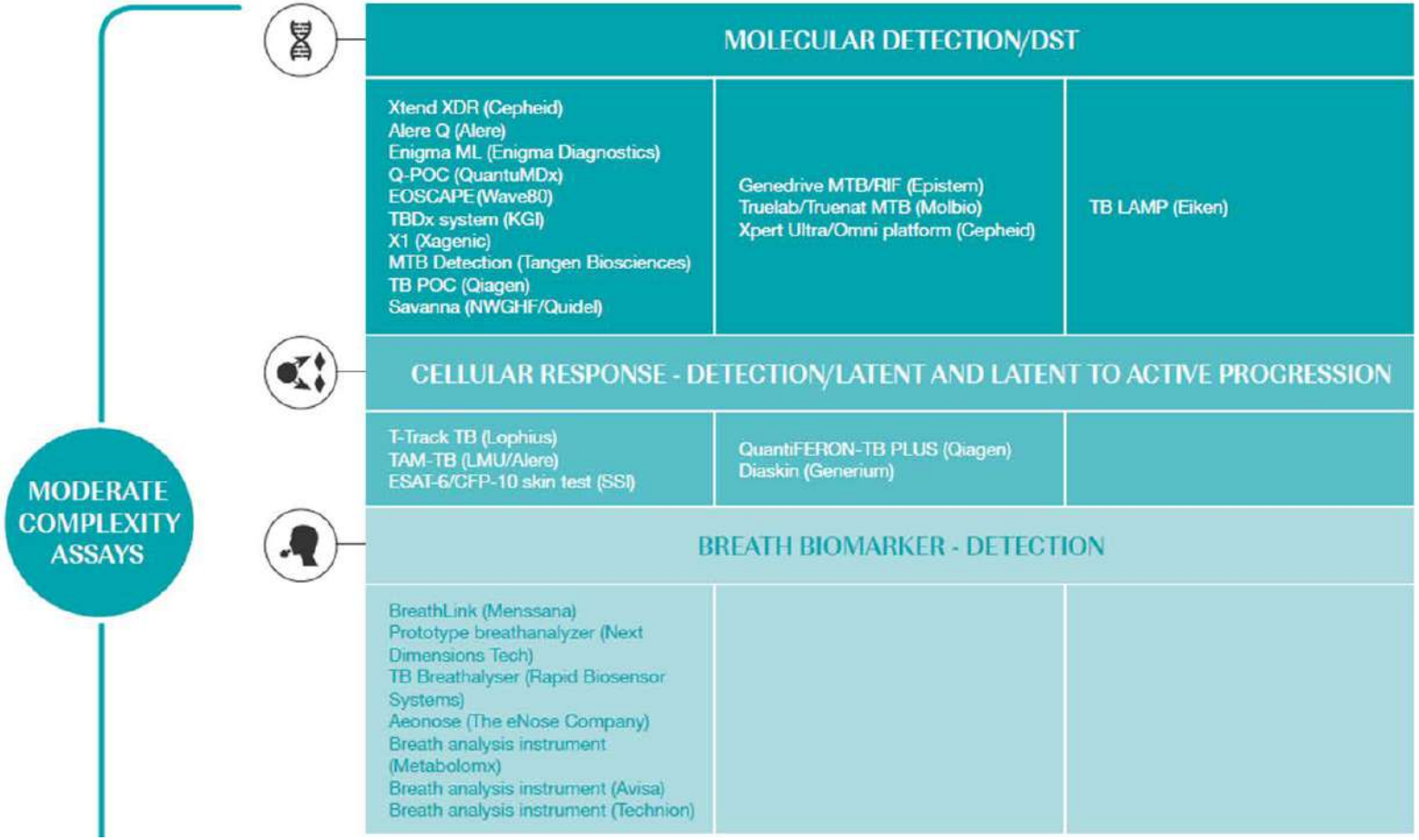
MOLEKULARNA GENOTIPIZACIJA-WGS

-molekularna genotipizacija
-identifikacija
-detekcija mutacija koje dovode do rezistencije na antituberkulotike
-2018. zadnja godina slanja QC za MIRU-VNTR



NAGLASAK ISTRAŽIVANJA NA…

1. POC test
2. Test koji će otkriti vjerojatnost progresije latentne infekcije u akutnu TB
3. FIND trenutno evaluira automatizirani WGS sistem…od obradu uzoraka do bioinformatičke analize



DETEKCIJA VOLATILNIH BIOMARKERA

Brojna istraživanja sa afričkim gigantskim štakorima

Weetjens et al. IJTLD 2009

IMAGE

African Giant Pouched Rat

The African Giant Pouched Rat (Cricetomys gambianus). This incredible rodent has been trained to smell tuberculosis and land mines in certain areas of Africa.

PHOTOGRAPH BY JOEL SARTORE AND NATIONAL GEOGRAPHIC PHOTO ARK

Parazitarne infekcije dišnog sustava

Izv.prof.dr.sc. Mario Sviben,prim.dr.med.
Hrvatski zavod za javno zdravstvo i Medicinski fakultet Sveučilišta u Zagrebu

- Parazitarne infekcije – velik uzročnik morbiditeta i mortaliteta širom svijeta
- Respiratorni sustav (RS) može biti inficiran brojnim parazitarnim organizmima
- Endemski prisutne parazitoze; parazitoze tropskih krajeva – putovanja, rad, imigracija
- Najčešće zahvaćena pluća
- Ulazak?
- Migracija parazita tijekom životnog ciklusa
- Emolizacijsko širenje ili direktna invazija
- Zahvaćanje RS tijekom generalizirane parazitoze
- Diferencijalna dijagnostika pacijenata s lezijama u plućima pogotovo kod obrade sumnje na tuberkulozu ili na malignitet

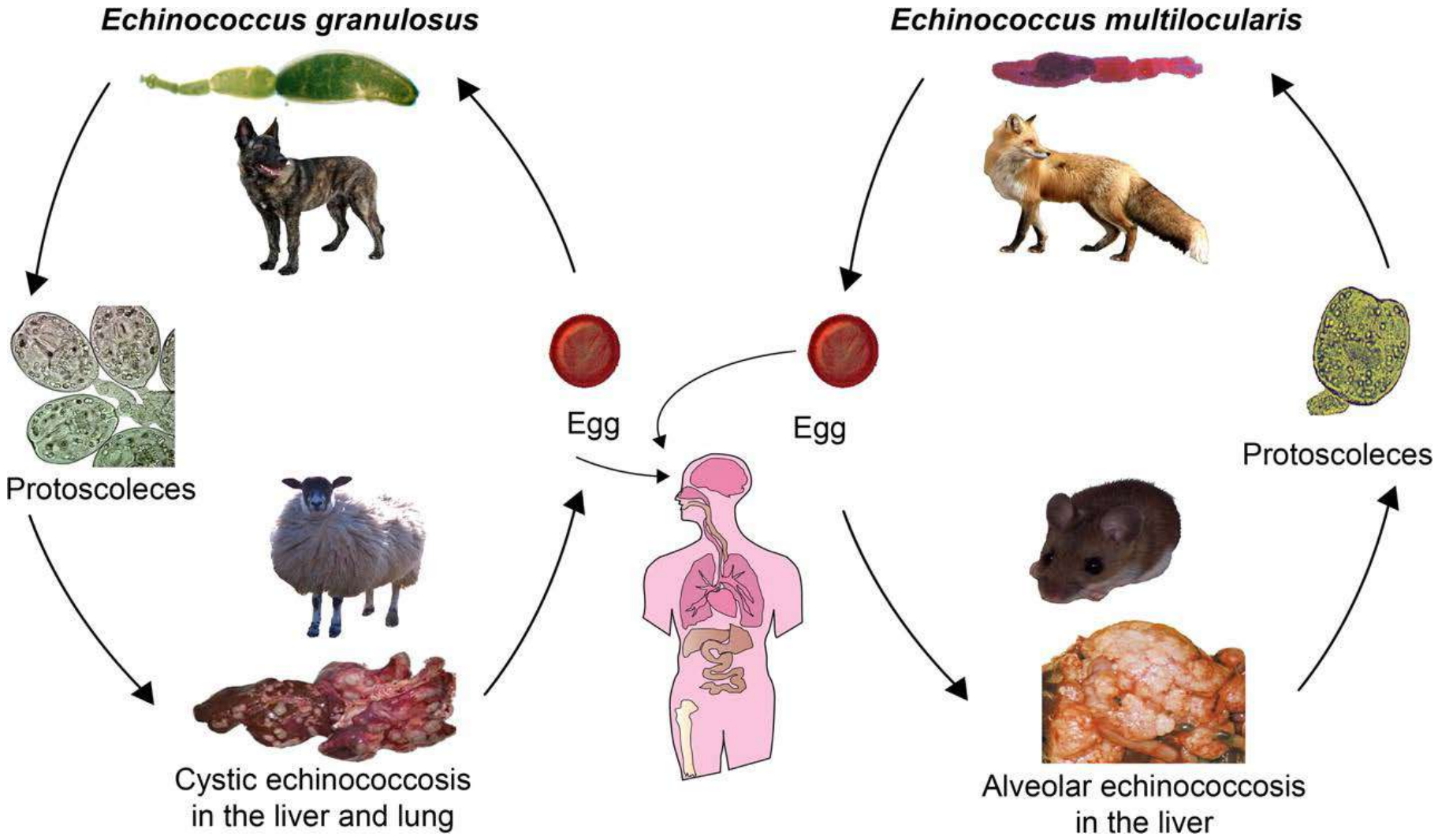
- Echinococcus
- Paragonimus
- Schistosoma
- Ascaris
- Ancylostoma
- Dirofilaria
- Tropska pulmonalna eozinofilija
- Toxocara
- Entamoeba histolytica
- Plasmodium falciparum …

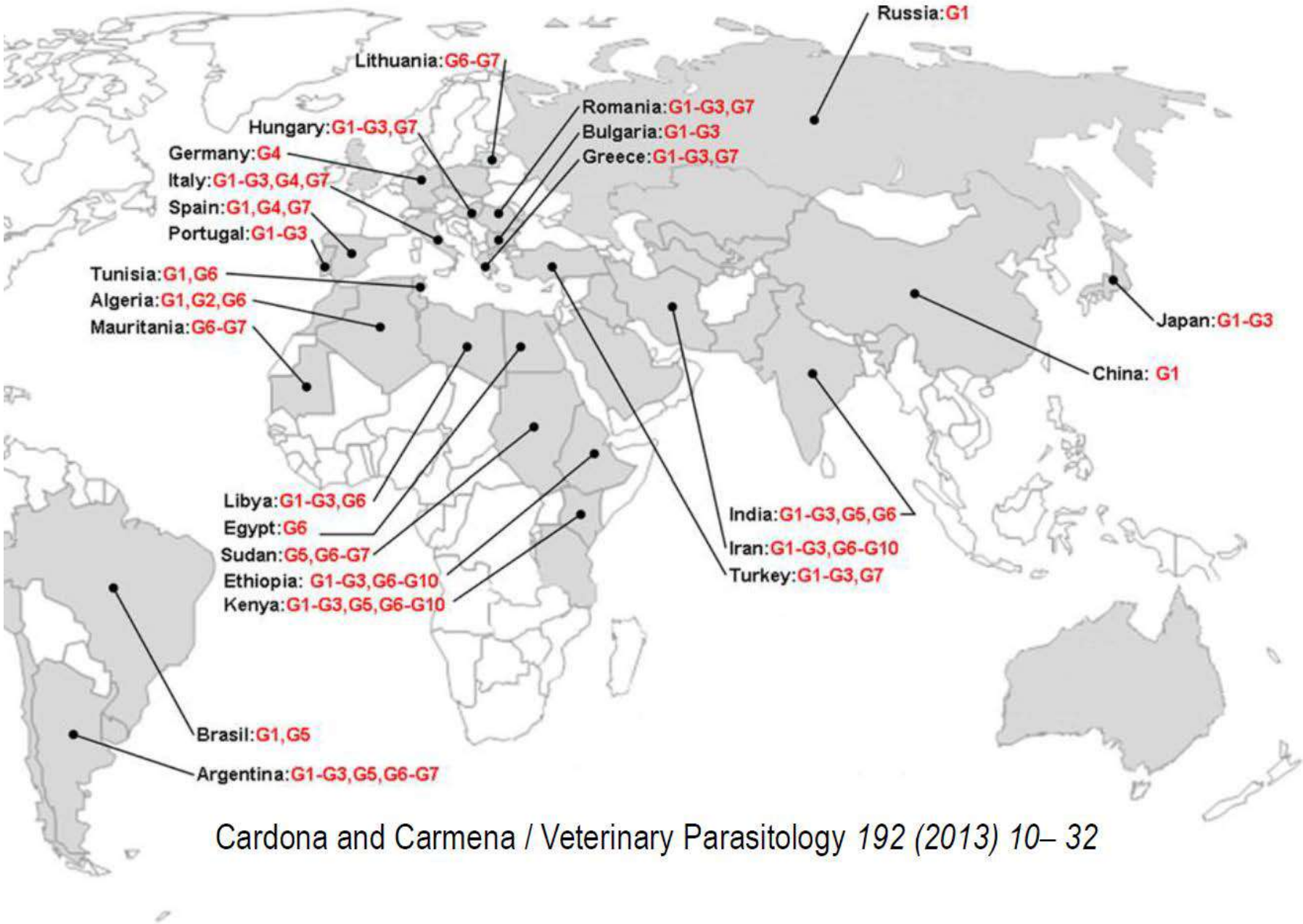
Echinococcus

- *E. granulosus*
- *E. multilocularis*
- Najmanje 10 genotipova
- G1 najznačajniji – ovčji tip

***Echinococcus* species, strains and genotypes**

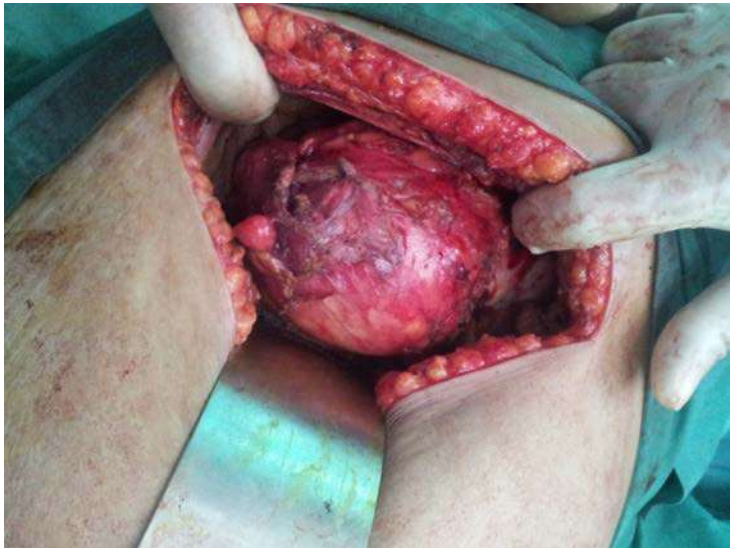
Species	Strain/genotype	Known intermediate hosts	Infective to humans	Disease in humans	Known definitive hosts
Echinococcus granulosus	Sheep/G1	Sheep (cattle, pigs, camels, goats, macropods)	Yes	Cystic (Unilocular)	Dog, fox, dingo, jackal and hyena
	Tasmanian sheep/G2	Sheep (cattle?)	Yes	Cystic (Unilocular)	Dog, fox
	Buffalo/G3	Buffalo (cattle?)	?	?	Dog, fox?
	Camel/G6	Camels (sheep)	Yes	Cystic (Unilocular)	Dog
	Pig/G7	Pigs	Yes	Cystic (Unilocular)	Dog
	Cervid/G8 and G10	Cervids	Yes	Cystic (Unilocular)	Wolf, dog
	?/G9		Yes	Cystic (Unilocular)	
	Lion/?	Zebra, wildebeest, warthog, bushpig, buffalo, various Antelope, giraffe? Hippopotamus?	?	?	Lion
Echinococcus equines	Horse/G4	Horses and other equines	No	-	Dog
Echinococcus ortleppi	Cattle/G5	Cattle	Yes	Cystic (Unilocular)	Dog
Echinococcus multilocularis	Some isolate variation (see text)	Rodents, domestic and wild pig, dog, monkey, (hors?)	Yes	Alveolar (multivesicular)	Fox, dog, cat, wolf, racoon-dog, coyote
Echinococcus shiquicus	?	Lagomorphs (pika)	?	?	Tibetan fox
Echinococcus vogeli	None reported	Rodents	Yes	Polycystic	Bush dog
Echinococcus oligarthrus	None reported	Rodents	Yes	Polycystic	Wild felids


Echinococcus granulosus
Echinococcus multilocularis
Egg
Egg
Protoscoleces
Protoscoleces
Cystic echinococcosis
in the liver and lung
Alveolar echinococcosis
in the liver



Cardona and Carmena / Veterinary Parasitology *192 (2013) 10– 32*

Echinococcus



- Klinička slika
- Cistična ehinokokoza (CE)
- Pluća zahvaćena kod 25% pacijenata
- Inkubacija 2-15 godina
- Mortalitet 2-4 % (kod kirurških slučajeva)
- Klinička slika: intaktna ili puknuta cista
- Intaktne ciste: slučajan radiološki nalaz;ponekad simptomi kompresije - kašalj, dispneja, bolovi u prsima
- Puknuta cista: anafilaktični šok, simptomi slični astmi, sepsa, pneumonija, pneumotoraks, pleuralni izljev

Echinococcus

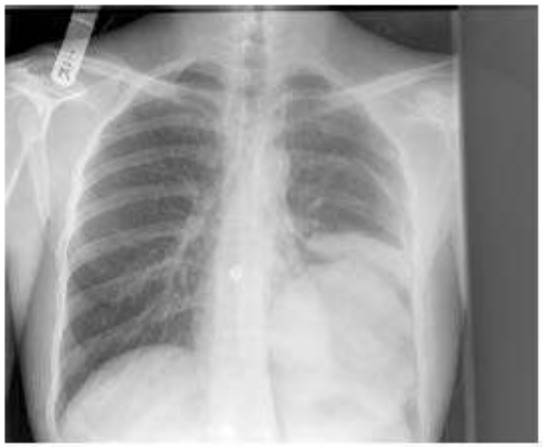


Figure 1 Chest x-ray showing a hydatid cyst in the left lower lobe with a collapsed hydatid cyst exhibiting the 'lily pad' sign lying above it.

- Dijagnostika
- Radiološka –slike
- Laboratorijska: ELISA, western blot test, PCR
- Terapija: ponekad spontana rezolucija,kirurška - poštedna

  Medikamentozno liječenje benzimidazolima – rezidualno, postkirurško, inoperabilne lezije

  Antihelmintici slabe stijenku ciste i povećavaju mogućnost rupture – ne koristiti prije operacije

  PAIR – puncture, aspiration, injection and reaspiration – WHO kontraindicirana u slučajevima plućnih lezija

Human Alveolar Echinococcosis, Croatia

Davorka Dušek, Adriana Vince, Ivan Kurelac, Neven Papić, Klaudija Višković, Peter Deplazes, Relja Beck

Author affiliations: University Hospital for Infectious Diseases, Zagreb, Croatia (D. Dušek, A. Vince, I. Kurelac, N. Papić, K. Višković); University of Zagreb School of Medicine, Zagreb (D. Dušek, A. Vince, N. Papić); University of Zurich, Zurich, Switzerland (P. Deplazes); Croatian Veterinary Institute, Zagreb (R. Beck)

DOI: https://doi.org/10.3201/eid2602.181826

Alveolar echinococcosis is a parasitic disease caused by the tapeworm larval stage of *Echinococcus multilocularis*. This zoonotic disease has not been known to occur in Croatia. We report a confirmed case of human alveolar echinococcosis in a patient in Croatia who had never visited a known *E. multilocularis*–endemic area.

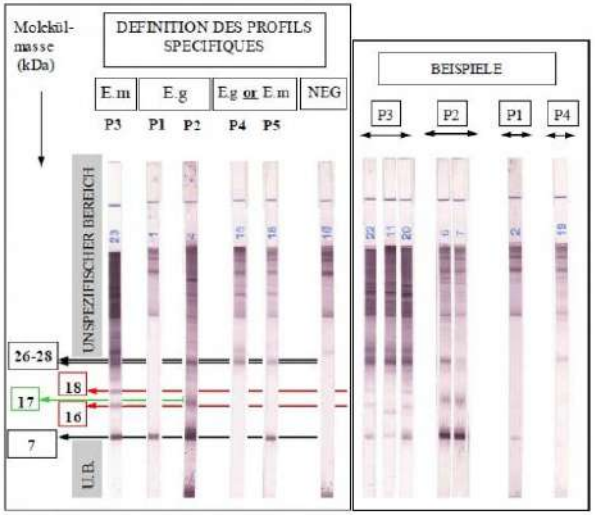
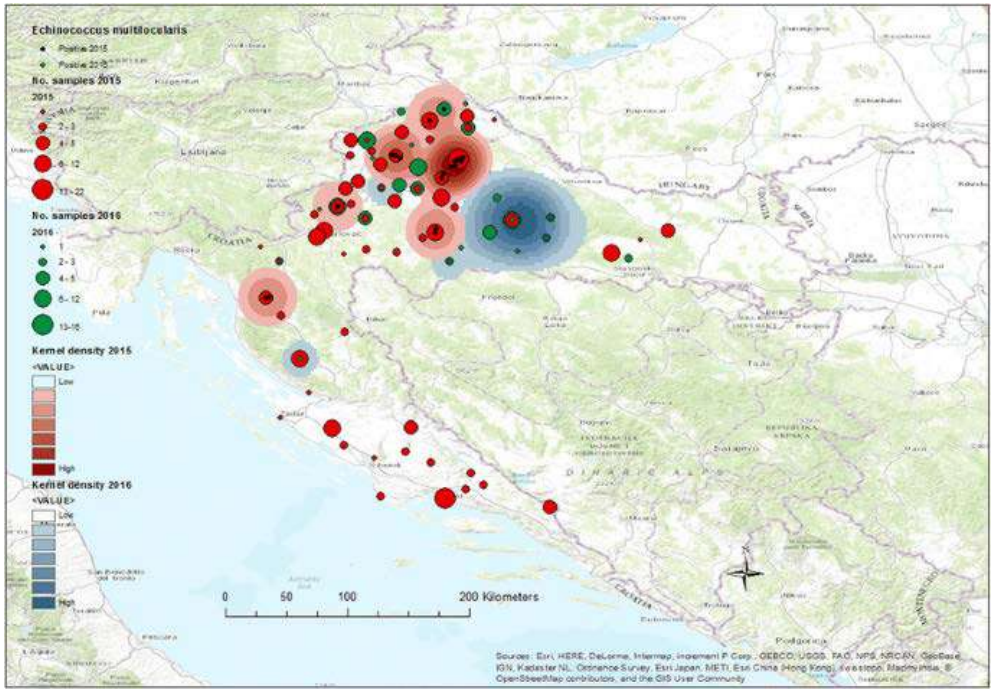
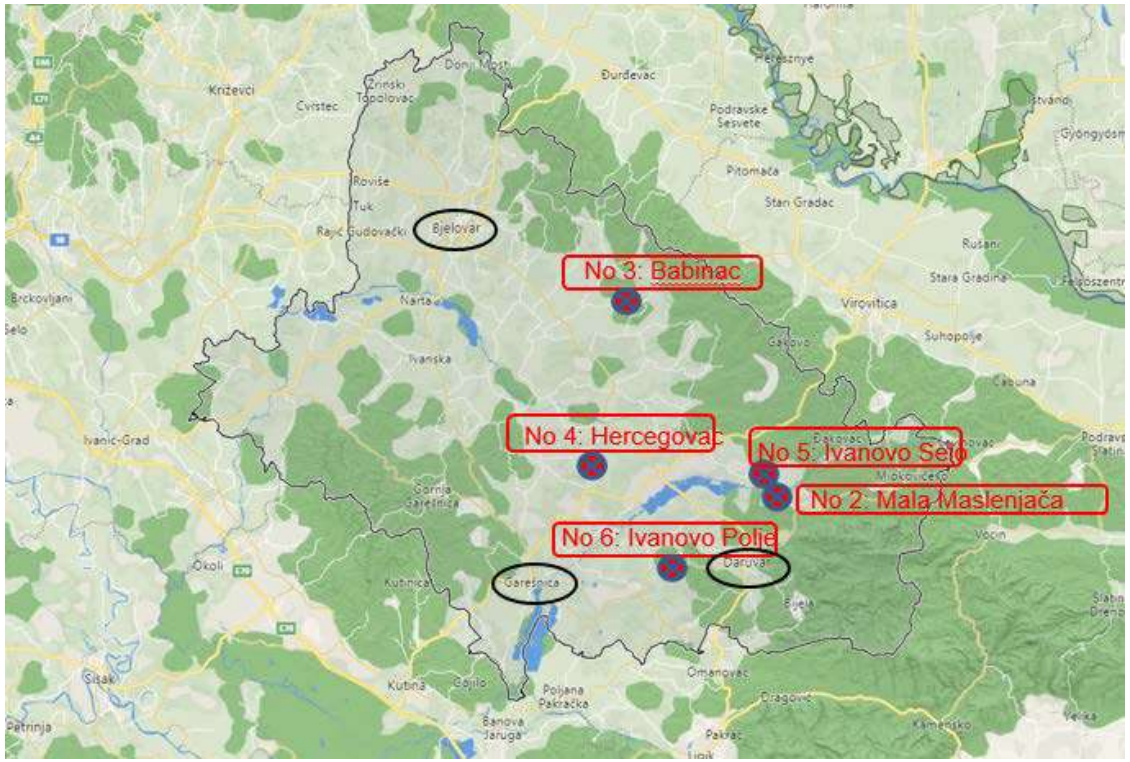


Abb. 1: Beispiele positiver und negativer Ergebnisse



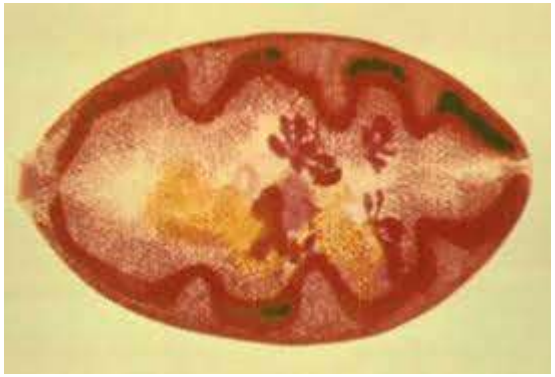
Beck R, Mihaljević Ž, Brezak R i sur. First detection of. E. multilocularis in Croatia. Parasitology Research 2018;117:617-621.

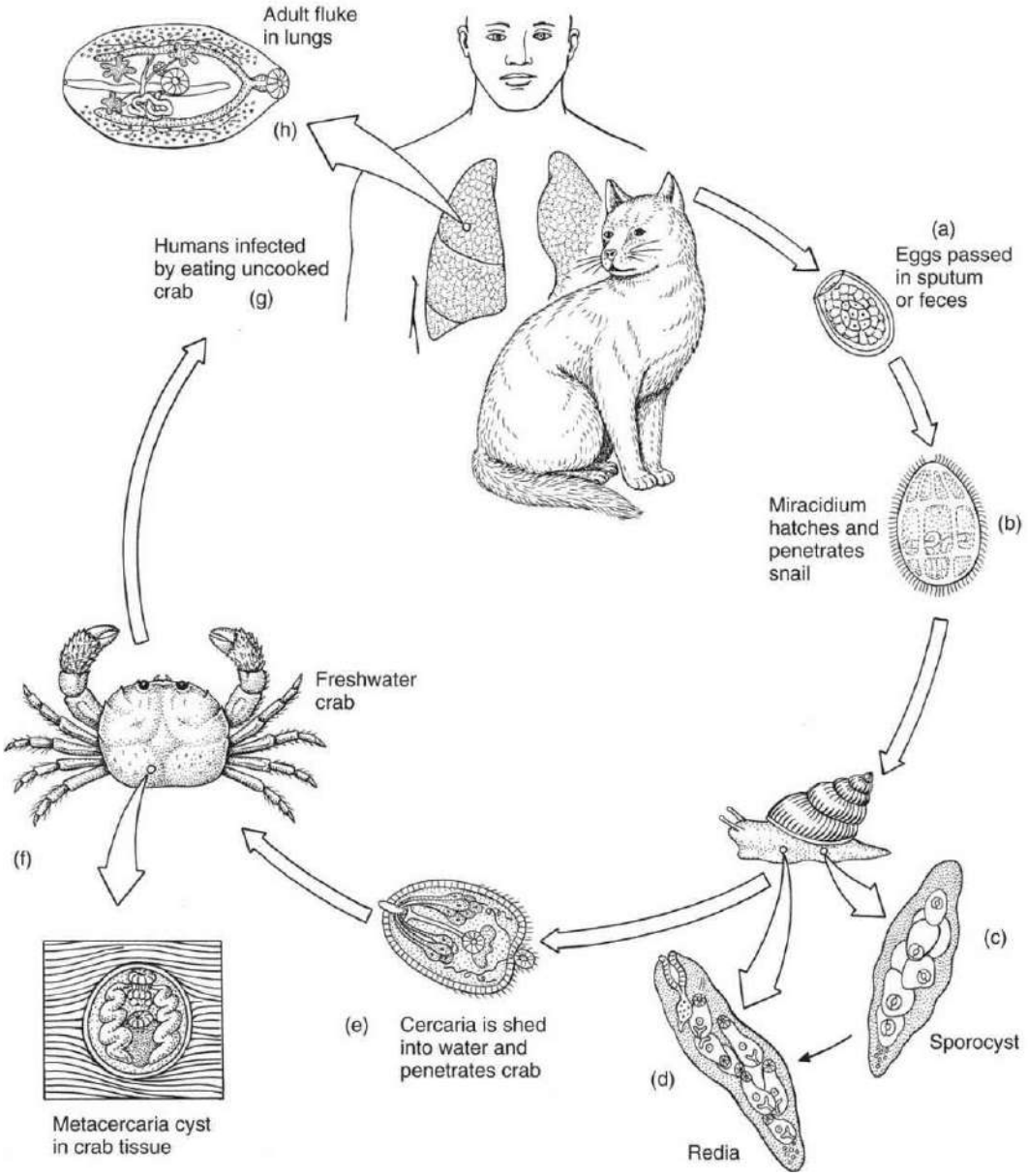
Distributon of human cases in Bjelovarsko – Bilogorska County



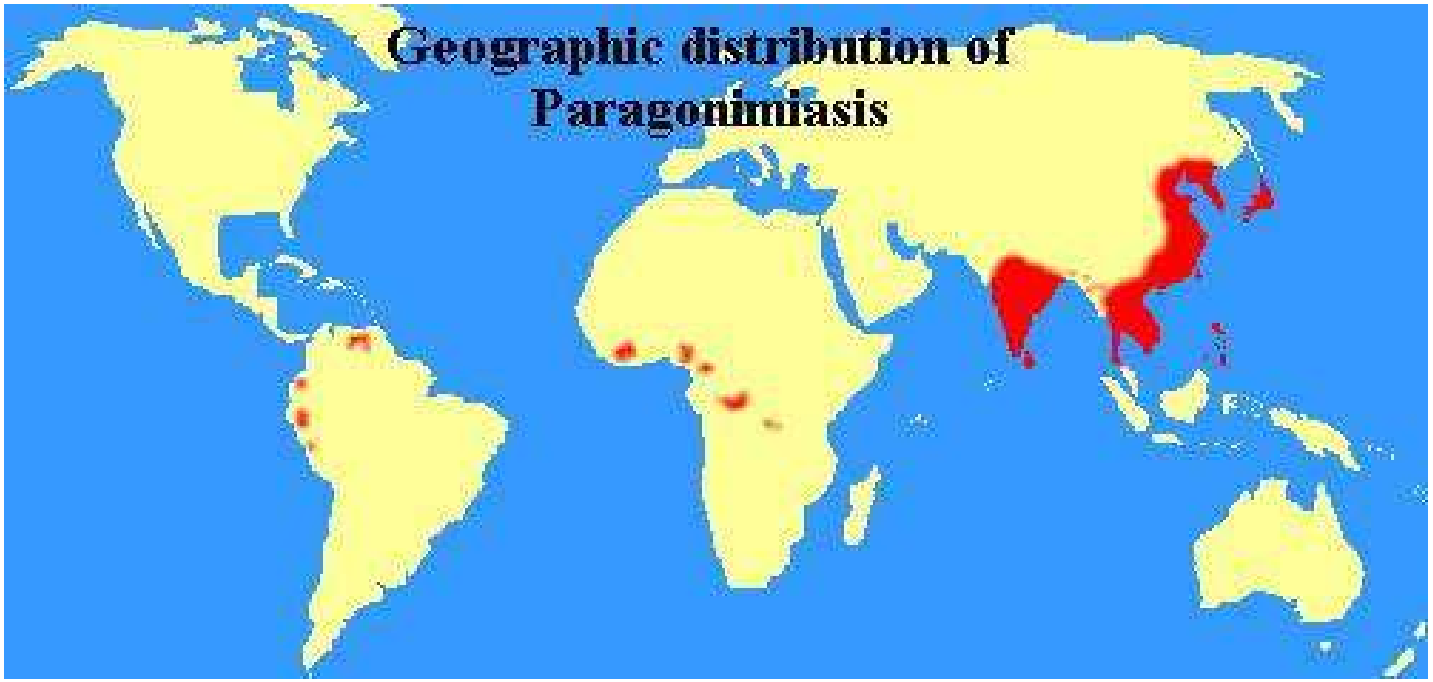
Paragonimus

- 10 ak vrsta proširenih u Aziji, Africi i Amerikama
- *P. westermani* najučestaliji
- Adultni oblici metilja žive u plućima gdje uzrokuju formiranje enkapsulirane ciste
- 24 mil. oboljelih




Adult fluke
in lungs
(h)
Humans infected
by eating uncooked
crab (g)
(a)
Eggs passed
in sputum
or feces
Miracidium
hatches and
penetrates
snail
(b)
Freshwater
crab
(f)
(c)
Sporocyst
(d)
Redia
(e) Cercaria is shed
into water and
penetrates crab
Metacercaria cyst
in crab tissue

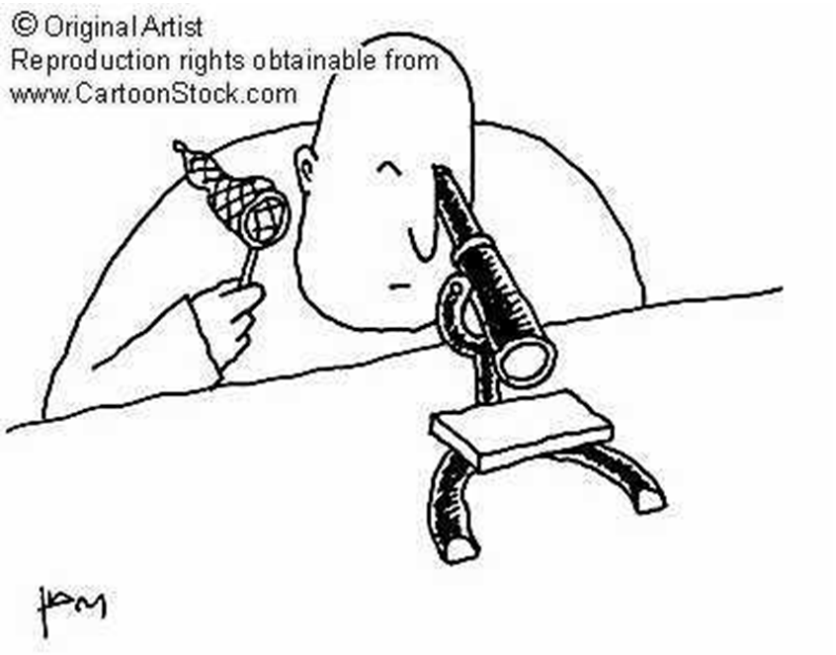
Paragonimus



Paragonimus

- Klinička slika
- Febrilitet, bolovi u prsima, dispneja, kroničan kašalj s hemoptizom
- Eozinofilija
- Nalazi: radiološki pleuralne i parenhimalne lezije – pleuralni izljev, pneumotoraks, empijem, zadebljanje pleure, nodularne promjene u plućima
- D.D.-karcinom bronha, tuberkuloza, mezoteliom, metastatski tumor

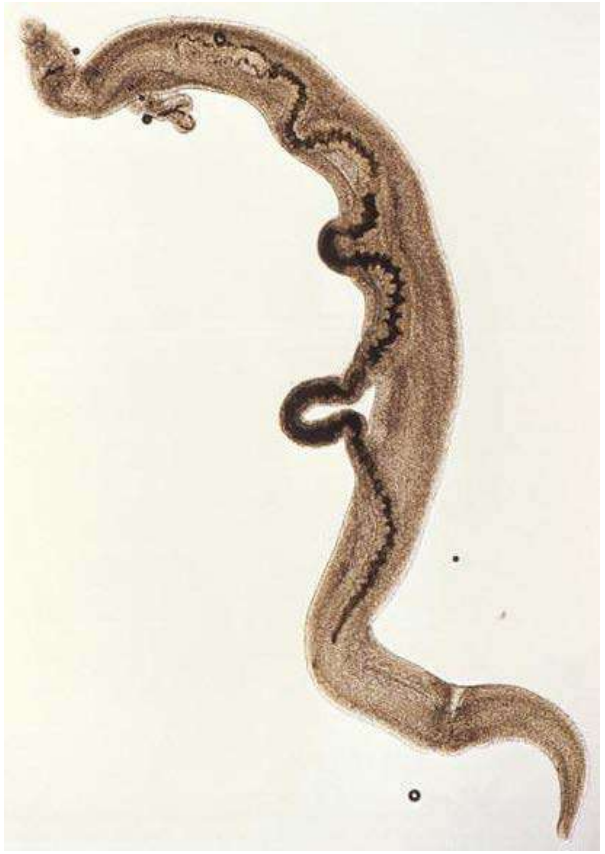
Paragonimus



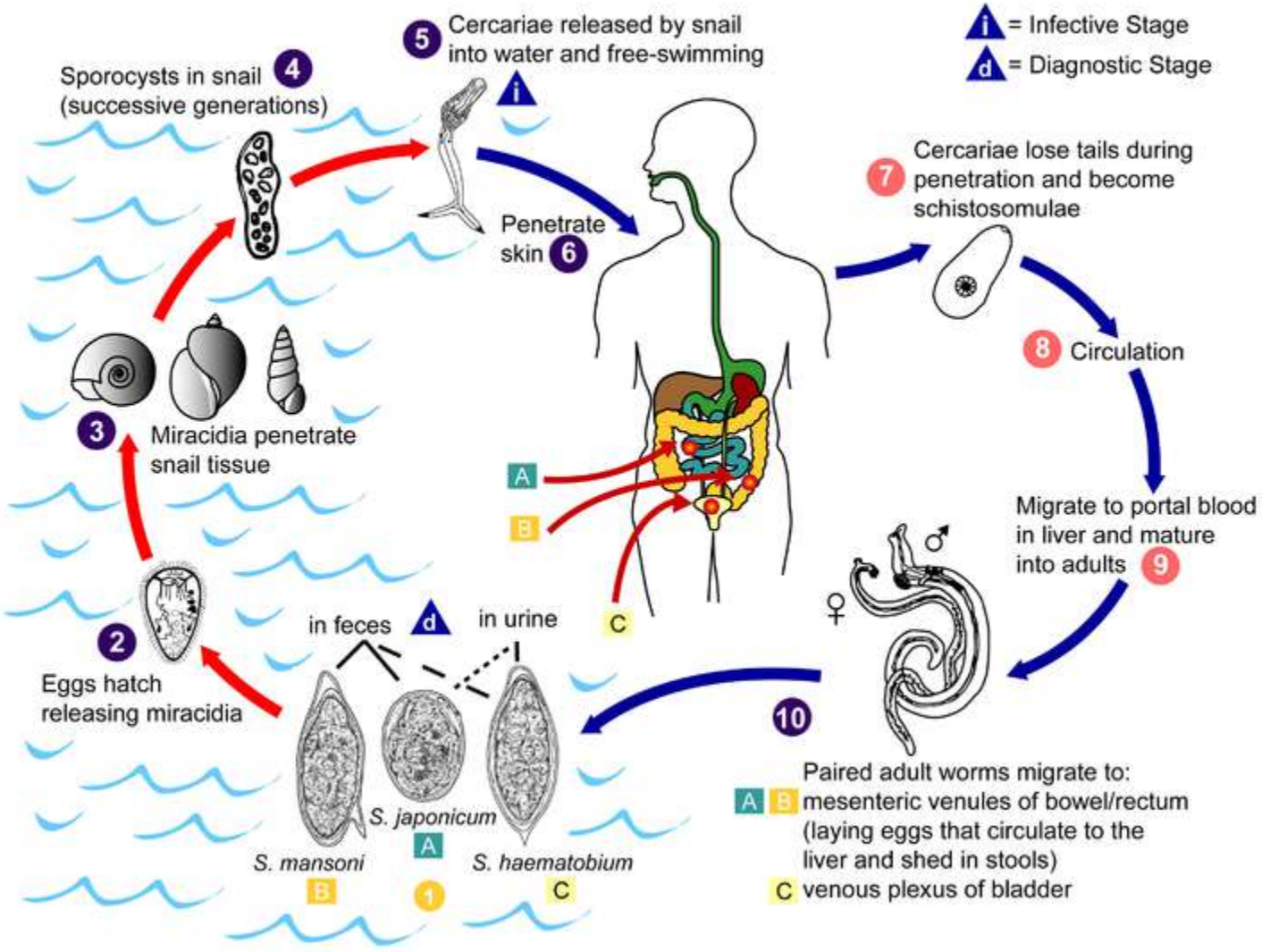
- Dijagnostika: Nalaz jaja u stolici, sputumu, BALu;serologija – referentni laboratoriji
- Terapija: prazikvantel
- Profilaksa: termička obrada rakova, higijena u kuhinji

Schistosoma

- Najznačajnije i najčešće vrste:
- *S. mansoni, S. haematobium* – subsaharska Afrika, Južna Amerika
- *S. japonicum* deleki istok Azije



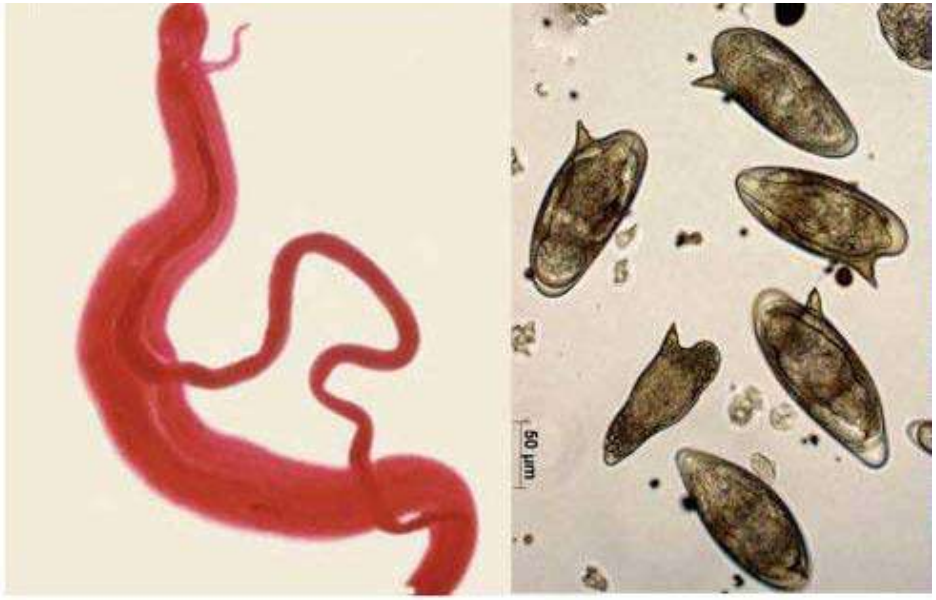
Schistosomiasis



Schistosoma

- Klinička slika
- Akutna bolest – Katayama groznica – u neimunih domaćina-4-6 tjedana nakon infekcije
- Wheezing, suhi kašalj, temperatura, mijalgije, glavobolja, hepatosplenomegalija, eozinofilija
- Kronična bolest – periportalna fibroza, portalna hipertenzija, plućа-ektopična migracija jaja u pulmonarnu vaskulaturu-granulomatozna upala-fibroza pluća, pulmonalna hipertenzija, cor pulmonale

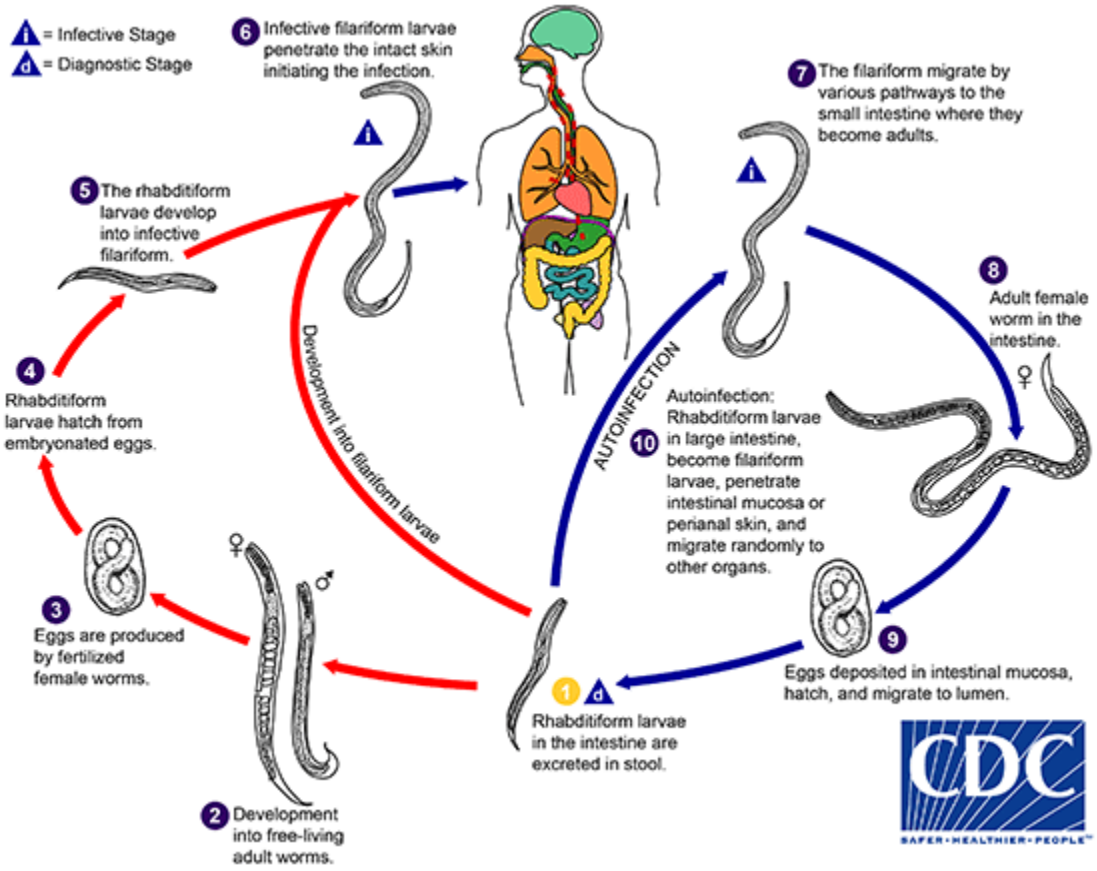
Schistosoma



- Radiološki – male nodularne lezije u plućima u akutnoj infekciji, intersticijske i granulomatozne promjene u kroničnoj bolesti
- D.D.- tuberkuloza, sarkoidoza, metastatska bolest
- Laboratorij – nalaz jaja u stolici i/ili urinu-terminalni urin
- Serologija, nije korisna u praćenju bolesti
- Th. praziquantel

Strongyloides

Strongyloides



Strongyloides

- Akutni stadij, kronični stadij
- Simptomi: febrilitet, kašalj, dispneja, wheezing, hemoptiza
- Pacijenti sa oslabljenom staničnom imunošću – preplavljujuća generalizirana infekcija
- Mortalitet 26-50 % - serološko testiranje pacijenata prije medicinskih, imunosupresijskih zahvata

Journal of Helminthology

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Seroprevalence and microscopy detection rates of strongyloidiasis in Croatian patients with eosinophilia

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Short Communication

*These authors contributed equally to this work.

Cite this article: Sviben M, Meštrović T, Topić MB, Sternak SL, Dida GO (2023). Seroprevalence and microscopy detection rates of strongyloidiasis in Croatian patients with eosinophilia. *Journal of Helminthology* **97**, e10, 1–5. https://doi.org/10.1017/S0022149X22000888

Received: 28 April 2022
Revised: 26 August 2022
Accepted: 15 December 2022

Keywords:
Strongyloides stercoralis; strongyloidiasis; seroprevalence; microscopy; eosinophilia; epidemiology; parasitic diseases; Croatia

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T. Meštrović,
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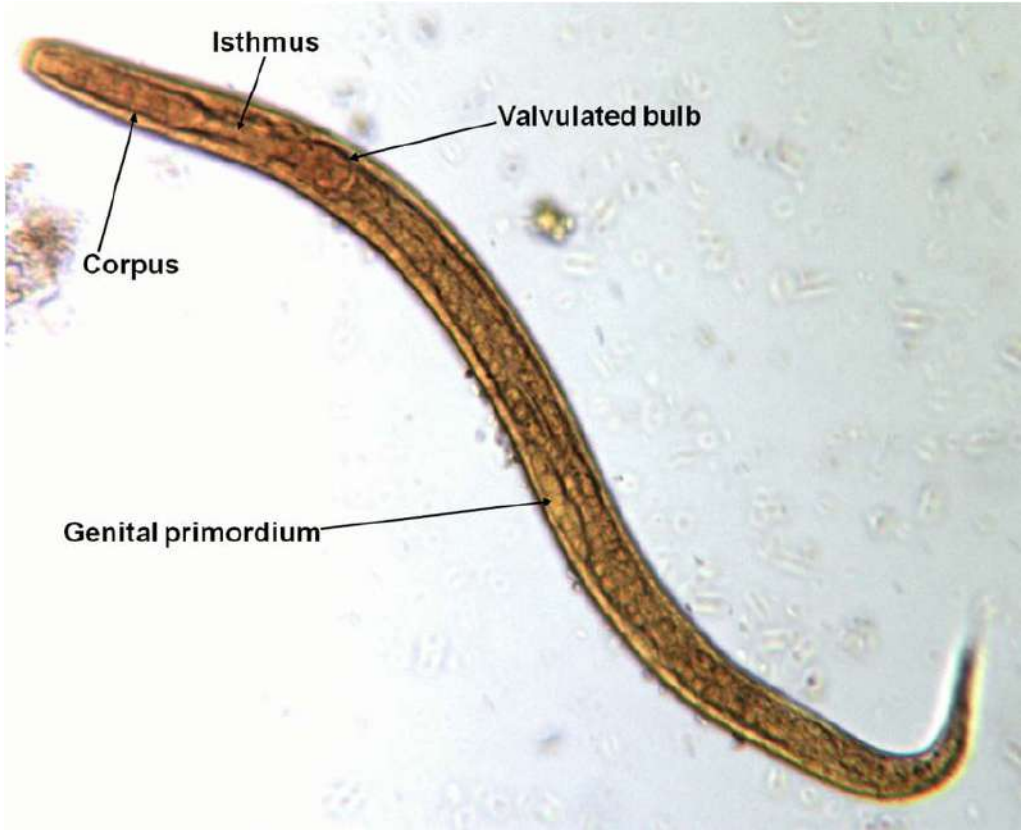
Abstract

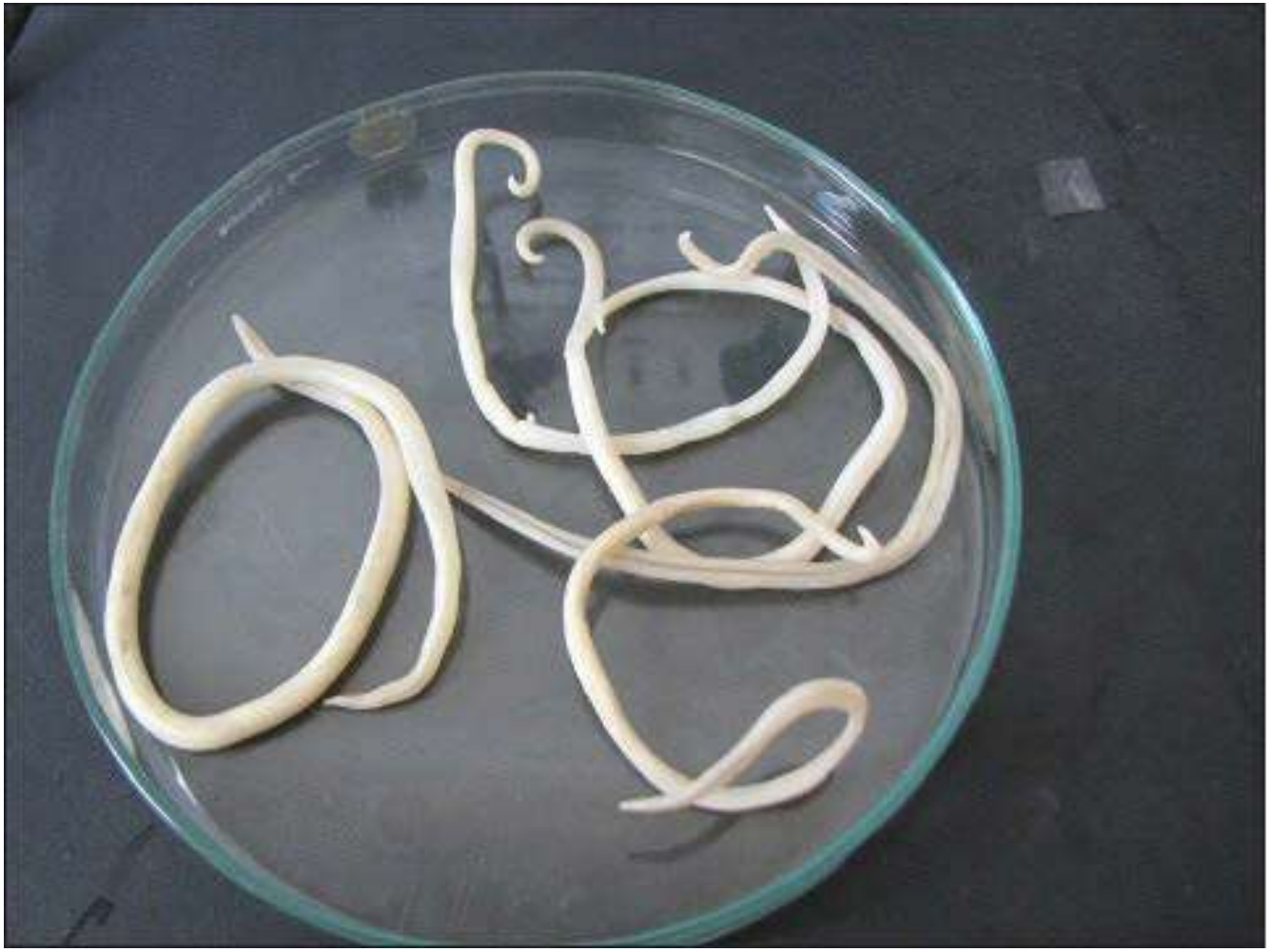
Infection with the parasitic nematode *Strongyloides stercoralis* is characteristic for tropical and subtropical regions of the world, but autochthonous cases have been reported in European countries as well. Here we present the first nation-wide survey of *S. stercoralis* seroprevalence in Croatian individuals presenting with eosinophilia, and evaluate the fraction of positive microscopy rates in stool specimens of seropositive individuals. In our sample of 1407 patients tested between 2018 and 2021, the overall prevalence of strongyloidiasis was 9.31%, with significantly higher rates in those older than 60 years of age ($P = 0.005$). Of those, one-quarter (25.95%) were also positive following microscopy examination of faeces after using the merthiolate–iodine–formaldehyde concentration method. Our findings reinforce the notion of endemic strongyloidiasis transmission in Croatia, particularly in older individuals, and highlight the need to consider the presence of *S. stercoralis* in patients with eosinophilia.

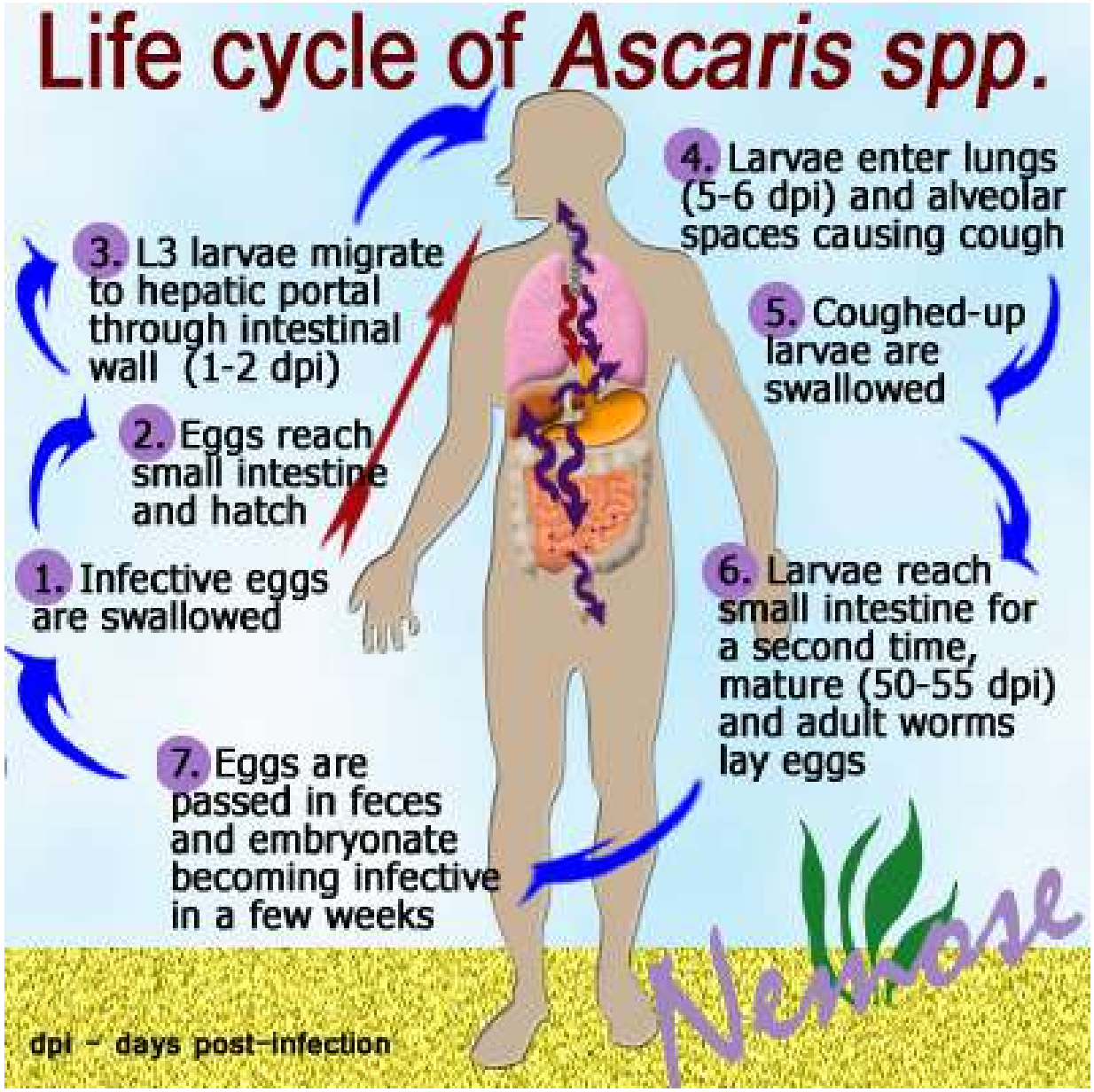
Strongyloides



- Radiološki – mrljasti alveolarni infiltrati, difuzni intersticijski infiltrati, pleuralni izljev
- Laboratorijska dijagnostika – nalaz ličinki, serologija
- Terapija: tiabendazol ili ivermektin

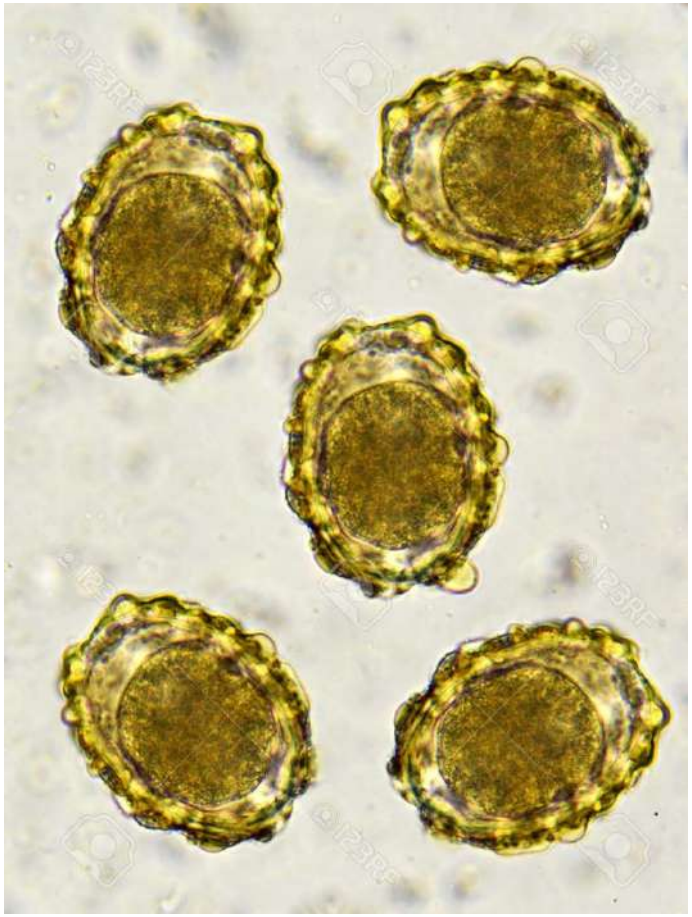
Ascaris lumbricoides



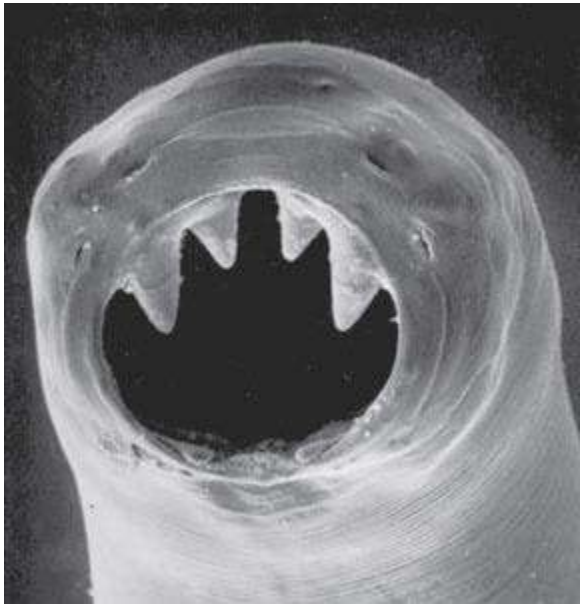

Life cycle of Ascaris spp.
1. Infective eggs are swallowed
2. Eggs reach small intestine and hatch
3. L3 larvae migrate to hepatic portal through intestinal wall (1-2 dpi)
4. Larvae enter lungs (5-6 dpi) and alveolar spaces causing cough
5. Coughed-up larvae are swallowed
6. Larvae reach small intestine for a second time, mature (50-55 dpi) and adult worms lay eggs
7. Eggs are passed in feces and embryonate becoming infective in a few weeks
dpi = days post-infection

Ascaris lumbricoides

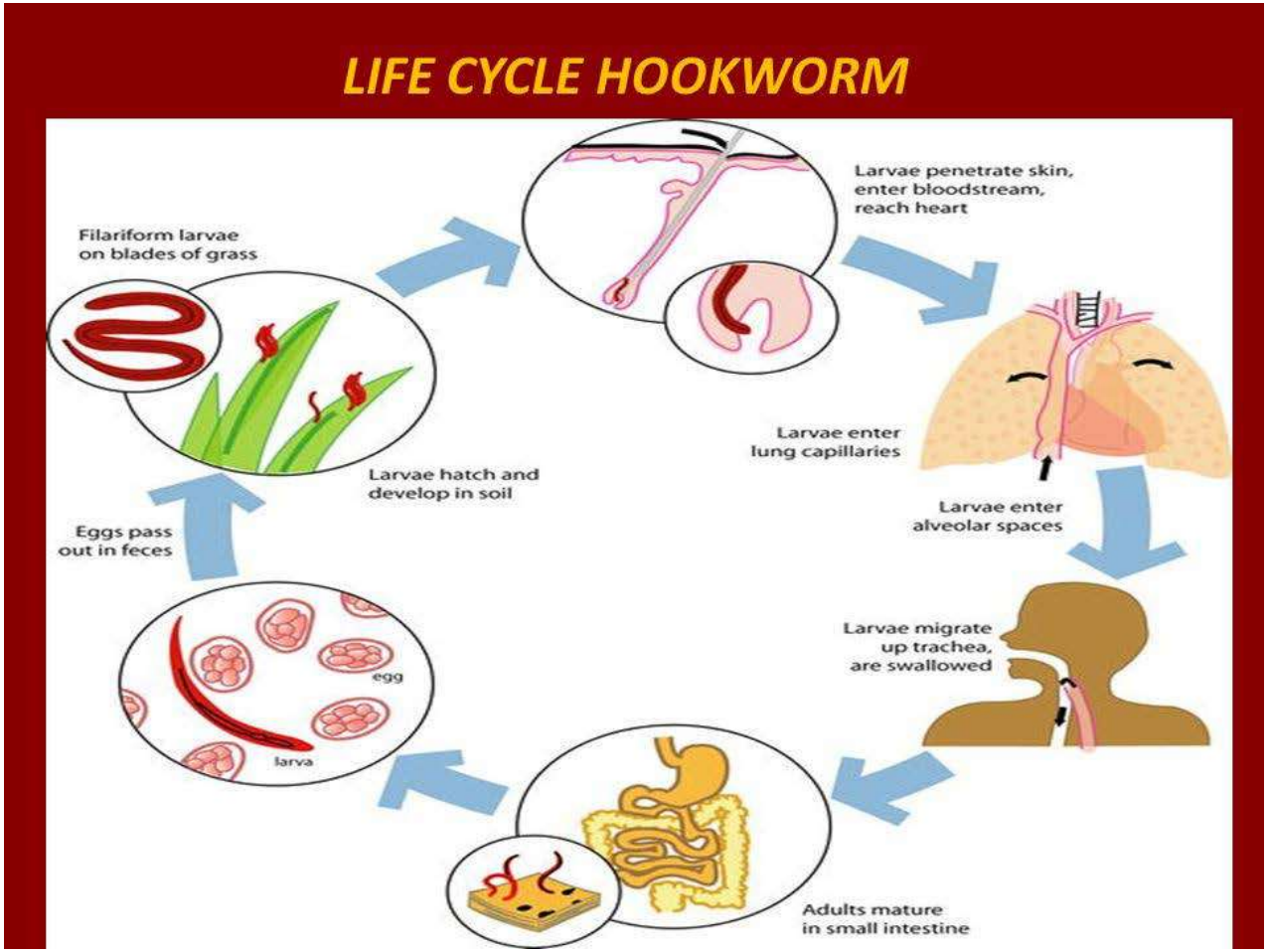
- Klinička slika
- Migracija ličinki kroz pluća – ezinofilna pneumonija (Loffler sy.) – kašalj, wheezing, hemoptiza, dispneja
- Rtg – mrljasti infiltrati u plućima
- Dijagnostika: nalaz jaja u stolici, serologija
- Terapija: benzimidazoli



Ancylostoma, Necator



Ancylostoma, Necator



Ancylostoma, Necator

- Loeffler sy.
- Dg. teška tijekom pulmonalne faze bolesti
- Nalaz ličinki u sputumu, stolici, koprokultura
- Th. benzimidazoli

Coll. Antropol. **37** (2013) 3: 995–997
Short communication

Dirofilaria Repens as a Cause of Subconjunctival Infection in a 77-Years Old Female Patient from Croatia – A Case Report

Mario Sviben[1], Tomislav Meštrović[2], Khalil Nemer[3], Katarina Palko Bartulović[3], Robert Škara[3] and Gordana Mlinarić Galinović[1]

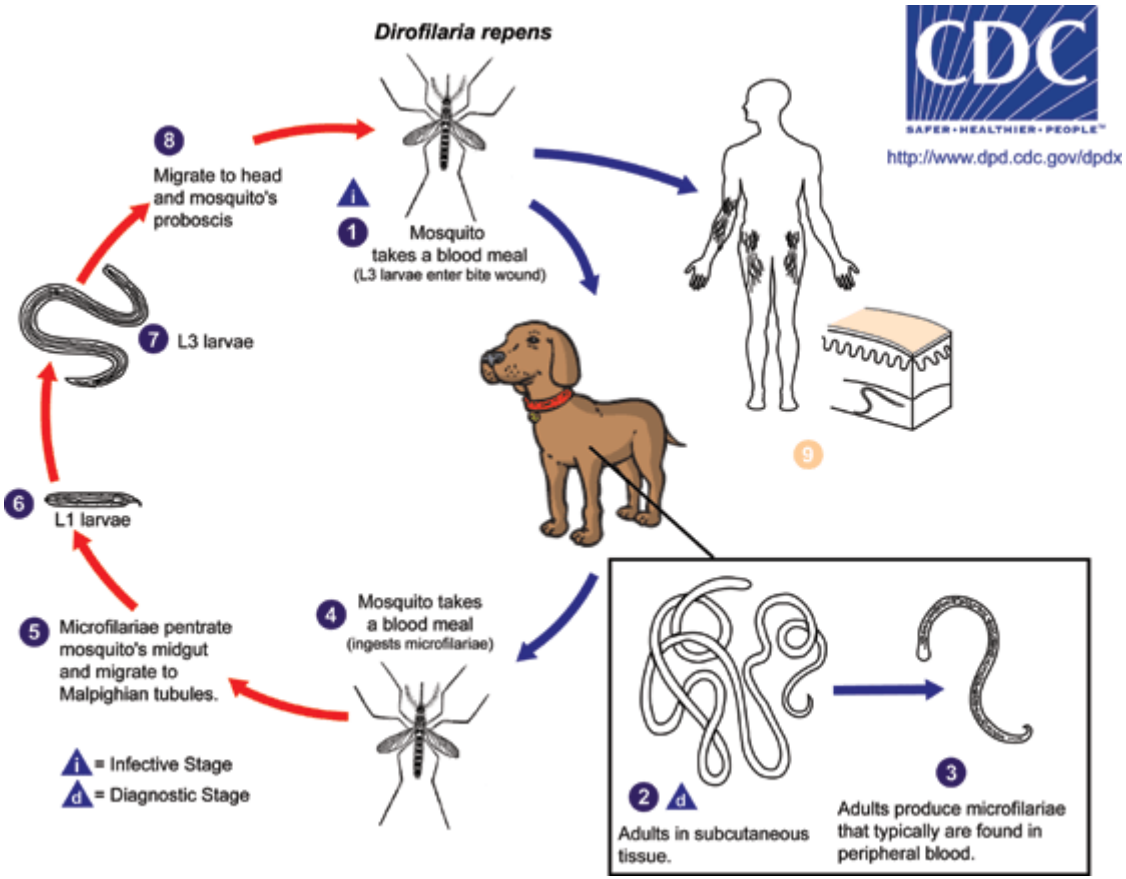
[1] Microbiology Service, Croatian National Institute of Public Health, Zagreb, Croatia
[2] Clinical Microbiology and Parasitology Laboratory, Polyclinic »Dr. Zora Profozić«, Zagreb, Croatia
[3] General Hospital »dr. Ivo Pedišić«, Sisak, Croatia

ABSTRACT

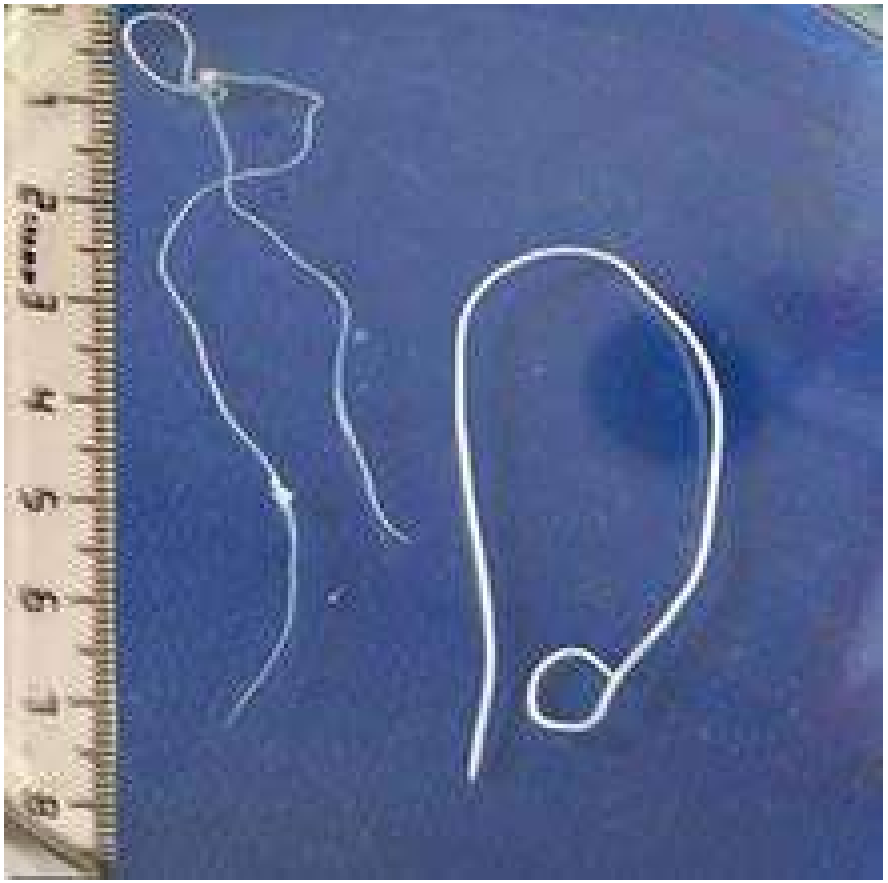
The zoonotic parasites of the genus Dirofilaria are on the increase as an accidental finding or as a cause of disease in humans worldwide. Human dirofilariasis usually manifests as either subcutaneous infiltrates or lung parenchymal disease, in many cases asymptomatically. We report the case of a 77-year old female patient presenting with irritation and pain in her left eye. Ophthalmologic examination of the temporal part of her left eye revealed motile and threadlike organism, which was surgically extracted and morphologically identified as Dirofilaria. Further molecular diagnostics with polymerase chain reaction (PCR) confirmed that the isolated organism is Dirofilaria repens. Due to already recognized autochthonous occurrence of human dirofilariasis in Croatia, human dirofilariasis must be included in the differential diagnosis of patients presenting with subcutaneous nodules, eye affection and other potential manifestations of this disease.

Key words: *dirofilariasis, nematode, subconjunctival infection, ophthalmology, parasitology*

Dirofilaria



Dirofilaria



- Nezreli crv – pulmonalne arterije – vaskulitis
- Solitarni pulmonalni nodul periferno u plućima – d.d.karcinom pluća
- Dg. biopsija
- Th. kirurška

Toxocara

Journal of Helminthology (2009) **83**, 369–371
doi:10.1017/S0022149X09381213

Seroprevalence of *Toxocara canis* infection among asymptomatic children with eosinophilia in Croatia

M. Sviben*, T.V. Čavlek, E.M. Missoni and G.M. Galinović

Croatian National Institute of Public Health, Microbiology Service, Rockefellerova 7, 10000 Zagreb, Croatia

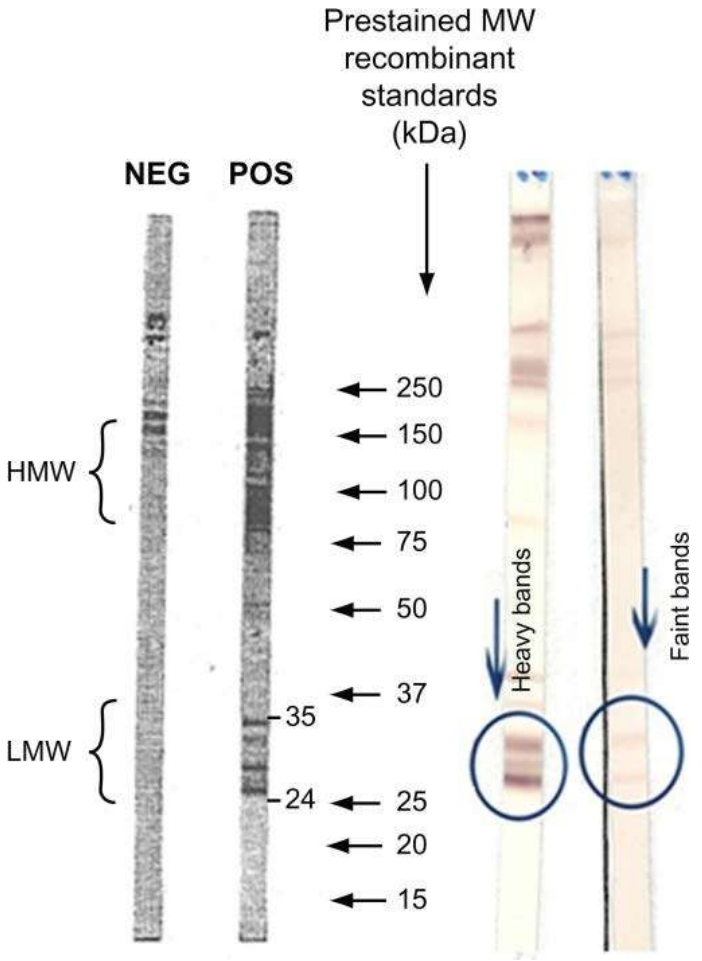
(Accepted 7 February 2009; First Published Online 22 May 2009)

Abstract

A total of 142 serum specimens from Croatian children aged 3–18 years, with peripheral eosinophilia and without any clinical symptoms, were tested for the presence of *Toxocara canis* IgG antibodies using an enzyme-linked immunosorbent assay (ELISA) and Western blot method. The overall *T. canis* seropositivity rate in the samples tested was 31%. There was no statistical difference in the seroprevalence rate between boys (32.1%) and girls (29.7%, $\chi^2 = 0.092, P = 0.761$). The *T. canis* seropositivity varied significantly between age groups both in boys (Fisher's test $P < 0.001$) and girls (Fisher's test $P = 0.007$). The highest seroprevalence rate was found in boys aged 11–14 (42.9%) and girls aged 7–10 (44.2%). Our results showed a high seroprevalence rate of *T. canis* infection among children with eosinophilia. It is important that testing for toxocariasis should be included in a differential diagnosis of eosinophilia, especially in children.

Toxocara

- *T. canis* i *T. cati*
- Migracija po tijelu-jetra, CNS, oko, pluća
- Tri kliničke forme: visceralna, okularna, subklinička
- Respiratorni simptomi: wheezing, kašalj, dispneja, pulmonalni infiltrati i pleuralni izljev na rentgenu

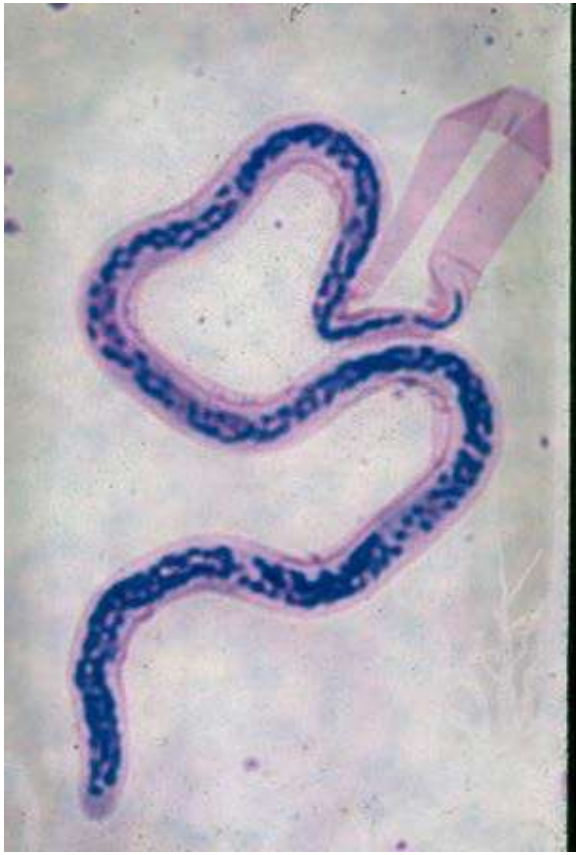


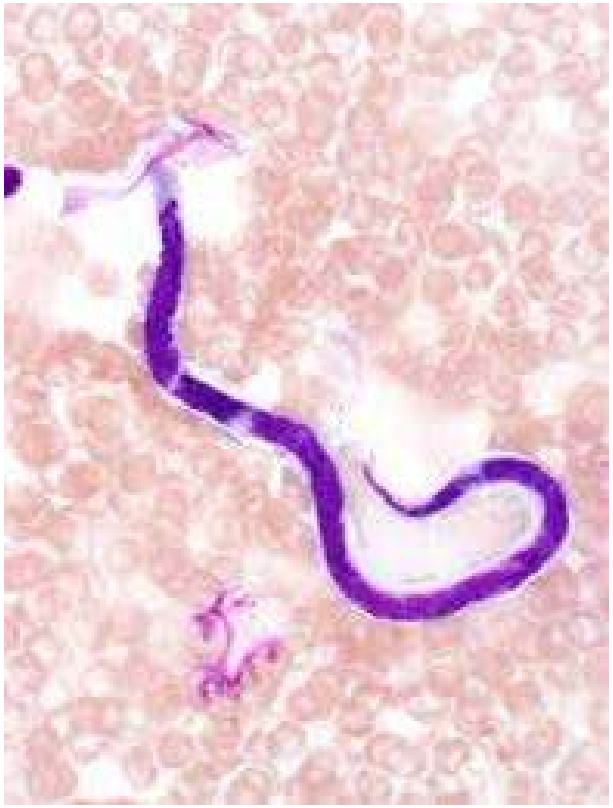
- Eozinofilija
- Dijagnostika:

  EIA i western blot test

Western blot-specific IgG anti-Toxocara canis.
Low molecular weight zone is Toxocara

Tropska pulmonalna eozinofilija





Tropska pulmonalna eozinofilija

Tropska pulmonalna eozinofilija

- Uzrokovana limfatičkim mikrofilarijama roda Wuchereria i Brugia
- Prijenosnik komarac
- Protutjelima opsonizirane mikrofilarije bivaju zarobljene u plućima
- Ks: imunološki uzrokovana bolest: paroksizmalni kašalj, zaduha, wheezing, povišena temperatura, slabost
- Rtg. Retikulonodularni crtež
- Funkcionalni testovi pluća: obstruktivni defekt
- Dg. Krvni razmaz i gusta kap
- Th: DEC, nužna radi spječavanja pulmonalne fibroze

Am. J. Trop. Med. Hyg., 78(1), 2008, pp. 17–19

Neonatal Respiratory Tract Involvement by *Trichomonas vaginalis*: A Case Report and Review of the Literature

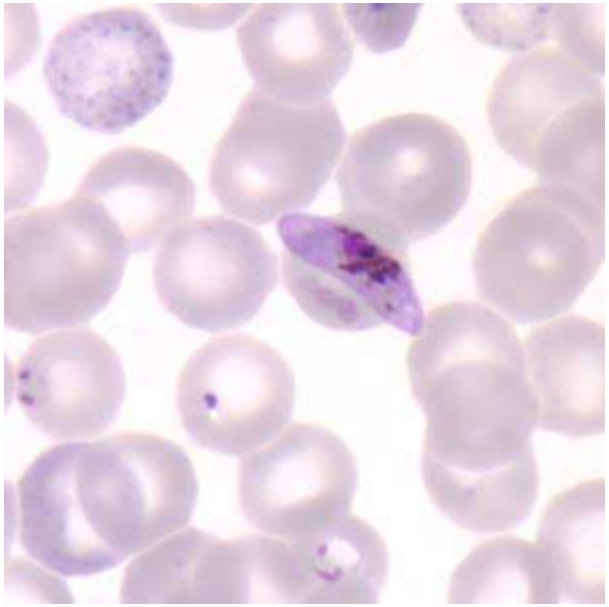
J. Elliot Carter* and Kenneth C. Whithaus

University of South Alabama Department of Pathology, Mobile, Alabama

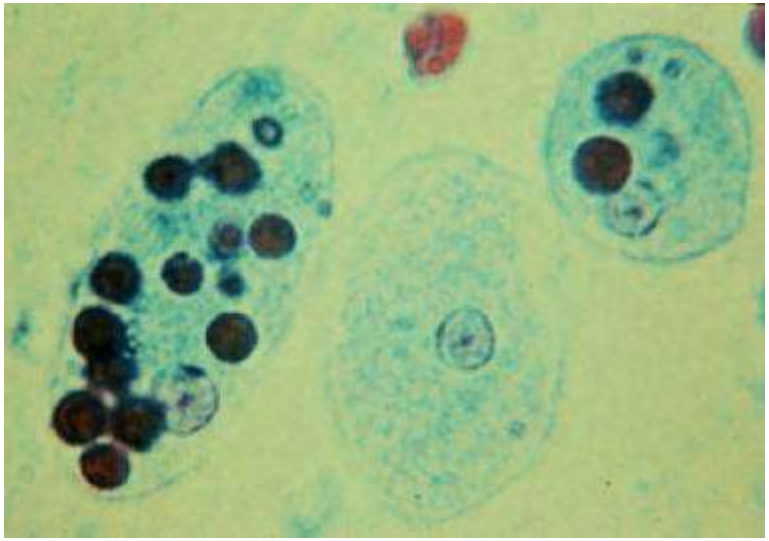
Abstract. Only occasional cases of *Trichomonas* spp. infection have been reported in neonates, and these usually represent vaginal infections with *Trichomonas vaginalis* acquired during passage down the birth canal. We report the case of a 2-week-old girl who was brought by her mother to the Children's Emergency Clinic at our institution for symptoms of lethargy and poor appetite. The neonate was subsequently diagnosed with herpetic encephalitis and developed increasing respiratory difficulty, requiring intubation. Routine viral culture of a nasopharyngeal wash showed no viral organisms, but trichomonads were abundant microscopically on the viral culture medium. Molecular studies identified the organism as *T. vaginalis*. The significance of this organism as a neonatal respiratory pathogen and its contribution to neonatal respiratory distress are discussed.

Malarija

- Mortalitet 500 000 ljudi
- Pulmonalne manifestacije od kašlja do nekardiogenog plućnog edema do ARDS
- Epidemiološka anamneza!!!
- Cjepivo
- Trojna artemisininska terapija



Entamoeba histolytica



- Pulmonarna emebijaza – uglaznom ekstenzijom iz abscesa jetre no i hematogenim putem
- Febrilitet, kašalj, iskašljavanje gnoja
- Nalaz trofozoita u iskašljanom sadržaju, nalaz cisti u stolici, pozitivna serologija
- Th: kirurška, medikamentozna

Format: Abstract Send to

BMJ Case Rep. 2017 Aug 23;2017. pii: bcr-2017-221252. doi: 10.1136/bcr-2017-221252.

A rare case of pulmonary toxoplasmosis in a patient with undifferentiated inflammatory arthritis on chronic methotrexate and corticosteroid therapy.

Abdulkareem A[1], D'Souza RS[2], Patel N[3], Donato AA[1].

Author information

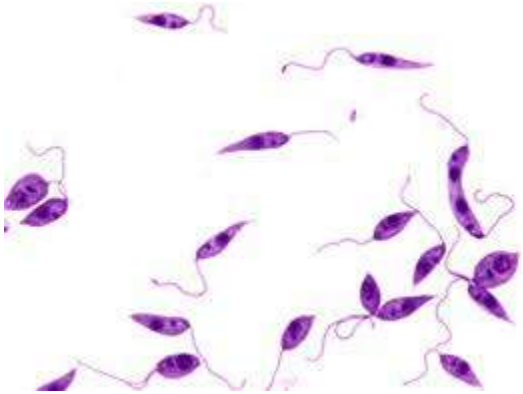
Abstract

Pulmonary toxoplasmosis is a serious pulmonary condition caused by the protozoan *Toxoplasma gondii* It typically affects immunocompromised patients presenting acutely with cough, fever, myalgias, arthralgias and lymphadenopathy, and chronically with persistent cough and dyspnoea. Because of its protean features, it can mimic many more common lung conditions in the immunocompromised patient, including atypical pneumonia, *Pneumocystis* pneumonia and interstitial lung disease. In this article, we present the case of a 55-year-old woman who presented to our hospital with persistent dyspnoea and cough, initially suspected to have an arthritis-related interstitial lung disease. She received a final diagnosis of pulmonary toxoplasmosis after lung biopsy demonstrated *Toxoplasma* cysts, later confirmed by serology. Treatment with trimethoprim-sulfamethoxazole resulted in significant improvement of her respiratory symptoms after 3 months.

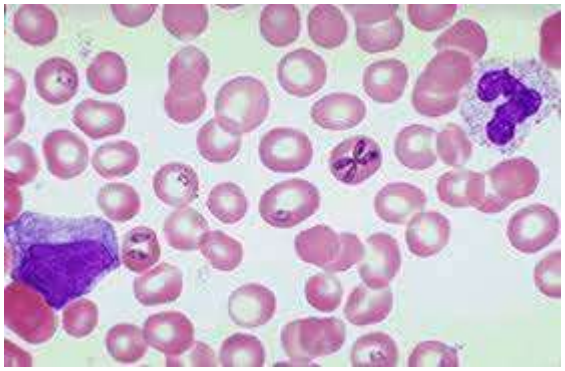
KEYWORDS: drugs: infectious diseases; drugs:musculoskeletal and joint diseases; infections; respiratory system; rheumatoid arthritis

PMID: 28835429 DOI: 10.1136/bcr-2017-221252

Leishmania

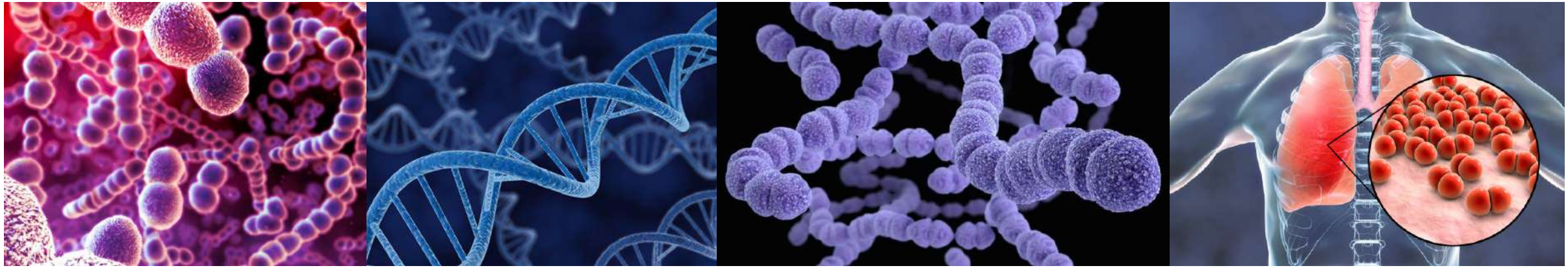


Babesia



Zaključak:

- Većina parazita koji inficiraju RS su endemski u tropskim i subtropskim krajevima
- Putovanja, imigracija, promjena klime, ljudsko ponašanje – pojavnost i u endemskim krajevima
- Većina pulmonalnih parazitarnih infekcija klinički asimptomatska ili blago simptomatska, klinička slika nespecifična
- Epidemiološka anamneza bitna u postavljanju dijagnoze
- Novi dijagnostički testovi, adekvatna terapija



Antimikrobna rezistencija i terapijske mogućnosti za liječenje bakterijskih respiratornih patogena

Izv.prof.dr.sc. Arjana Tambić Andrašević, dr.med., FESCMID

Klinika za infektivne bolesti “Dr. Fran Mihaljević”

Grlobolja

Algoritamski prema prijedlogu ISKRA smjernica [Ref.1]

ISKRA

—Samo **5% do 15%** akutnih grlobolja uzrokuje **beta-hemolitički streptokok grupe A (BHS-A)** i podložno je terapiji antibiotikom; velik dio grlobolja se javlja u tijeku virusnih infekcija gornjih dišnih puteva i predstavlja čestu indikaciju za nepotrebnu primjenu antibiotika.
—Bakterijsku etiologiju se može djelomično razlikovati od virusne uporabom **Centorovih kriterija** (temperatura > 38°C, eksudat na tonzilama, povećani i bolni prednji cervikalni limfni čvorovi, odsutnost kašlja i kataralnih simptoma) koji su sigurniji u isključivanju negoli potvrđivanju bakterijske etiologije (i uz 4 boda po Centoru vjerojatnost da se radi o streptokoknoj infekciji je samo 40%-60%).

Zbroj bodova po Centoru	Vjerojatnost streptokokne etiologije	Etiološka dijagnostika BRZI antigen test u ordinaciji ili bris na kulturu	Antimikrobna terapija
0-1	<20%	Ne	Ne
2-3		Da	Nakon nalaza brisa*
4	40-60%	Da	Nakon nalaza brisa*

* Kod teže kliničke slike antibiotska terapija se može početi i prije dokazanog BHS-A u kulturi, a nakon pripadnog nalaza revidirati potreba za nastavkom terapije

Antibiotike treba primijeniti u slučaju akutne grlobolje bez obzira na Centorove kriterije u slučajevima: **vrlo teškog općeg stanja, sumnje na peritonzilarni infiltrat ili apsces, reumatske vrućice u osobnoj ili obiteljskoj anamnezi**

Terapija

—U većini slučajeva akutne grlobolje dovoljno je simptomatsko liječenje i odmaranje
—Simptomatska terapija: Prvi lijek izbora je **analgoantipiretik paracetamol**
—Antimikrobna terapija:

Prvi izbor antibiotika

Djeca	Odrasli
penicilin V 40 000 - 80 000 i.j./kg (25 - 50 mg/kg) podijeljeno u 3 doze / 10 dana ili jednokratno: benzatin penicilin G (Extencillin) 600 000 i.j. im. <= 27 kg* benzatin penicilin G (Extencillin) 1 200 000 i.j. im. > 27 kg*	penicilin V 1 500 000 i.j. svakih 8 sati / 10 dana ili jednokratno: benzatin penicilin G (Extencillin) 1 200 000 i.j.*

*i drugi pripravci depo preparata benzilpenicilina u odgovarajućim dozama

Za alternativu kod preosjetljivosti na penicilin vidi Ref.1.

Bitne napomene

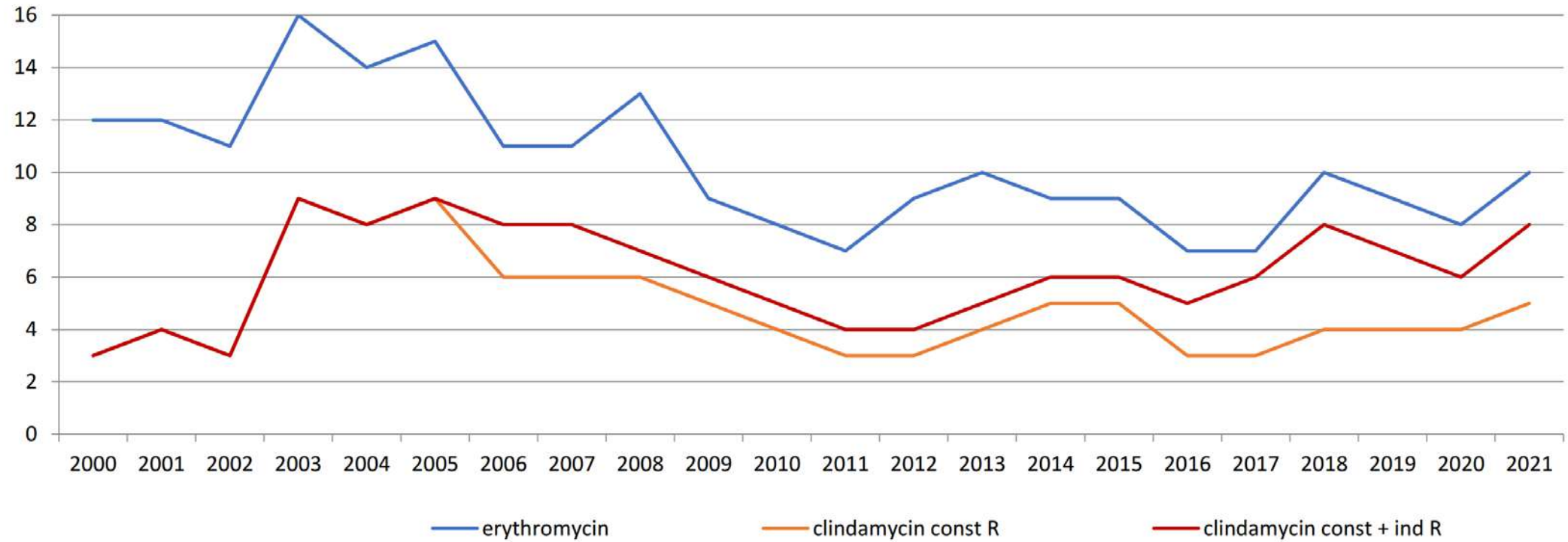
—Dijagnoza grlobolje ne podrazumijeva automatsku primjenu antibiotika
Grlobolja se najčešće javlja u tijeku virusne infekcije te je najčešće simptomatska terapija dovoljna.
—Kod teškog općeg stanja pacijenta treba dati antibiotik bez obzira na bakteriološki nalaz
Osjetljivost propisno uzetog brisa grla je 90-95% i ovisi o načinu na koji je uzet, na koji je transportiran te je li pacijent prije učinjenog brisa ždrijela uzimao antibiotike.
—Antibiotike ne treba primjenjivati kod blagih kliničkih slika grlobolje samo zbog bojazni da neprepoznata streptokokna infekcija može dovesti do razvoja poststreptokoknih sekvela ili teških kliničkih slika
Tradicionalno se smatralo da je glavni razlog liječenja grlobolje antibioticima sprječavanje razvoja reumatske groznice i poststreptokoknog glomerulonefritisa. Od 1950-tih godina u razvijenim zemljama, pa i Hrvatskoj, je došlo do pada incidencije reumatske groznice najviše zbog povećanja standarda života, te sprječavanje mogućih, vrlo rijetkih, sekvela ne treba biti motivacija za primjenu antibiotika.
—Asimptomatske kliconoše BHS-A u pravilu ne treba ni tražiti, niti liječiti
Neke osobe i nakon završene odgovarajuće antistreptokokne terapije ostaju kliconoše streptokoka. Kliconoštvo treba tražiti i eradicirati samo kod pacijenata koji u anamnezi imaju reumatsku groznicu, kod opetovanih streptokoknih infekcija unutar obitelji te situacije epidemije reumatske groznice ili streptokoknog glomerulonefritisa.
—Rutinsko testiranje antistreptolizinskog titra (ASO titar) u svrhu dijagnosticiranja streptokokne grlobolje se ne preporučuje.
Pojedinačni titar ASO nije dovoljno osjetljiv niti specifičan u dijagnosticiranju streptokokne grlobolje.
—Virusne infekcije grla su česte u djece i nisu indikacija za tonzilektomiju

Ref.1. Tambić Andrasević A, Baudoin T, Vukelić D, Matanović BM, Bejuk D, Puzevski D, Abram M, Tešović G, Grgurev Z, Tomac G, Pristas I. Iskra guidelines on sore throat: diagnostic and therapeutic approach - Croatian national guidelines. Lijec Vjesn 2009;131(7-8):.

Akademija medicinskih znanosti Hrvatske, Kolegij za javno zdravstvo, Odbor za praćenje rezistencije bakterija na antibiotike u RH
Croatian Academy of Medical Sciences, Public Health Collegium, Croatian Committee for Antibiotic Resistance Surveillance

Beta-hemolitički streptokok grupe A / *Group A streptococcus*

rezistencija na antibiotike u RH / *antibiotic resistance in Croatia*, 2000. - 2021.



Clindamycin const R = konstitutivna rezistancija na klindamicin / *constitutive clindamycin resistance*
Clindamycin const + ind R = ukupna (konstitutivna + inducibilna) rezistancija na klindamicin / *total (constitutive + inducible) clindamycin resistance*

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Guideline

Otitis media (acute): antimicrobial prescribing

September 2017

Background

- Acute otitis media is a self-limiting infection of the middle ear mainly affecting children.
- It can be caused by viruses and bacteria, and both are often present at the same time.
- Symptoms last for about 3 days, but can last for up to 7 or 8 – most children get better within 3 days without antibiotics.
- Antibiotics do not improve pain at 24 hours, and at later time points the number of children improving with antibiotics is similar to the number with adverse effects, such as diarrhoea.
- Antibiotics make little difference to the rates of common complications, such as hearing loss (which is usually temporary), perforated eardrum and recurring infection.
- Complications such as mastoiditis are rare, and the number needed to treat with antibiotics to prevent 1 child from developing mastoiditis is 4831.
- Acute otitis media is uncommon in adults – the recommendations in this guideline are based on the evidence identified, which was for children and young people.

Children and young people with symptoms or signs of acute otitis media with otorrhoea (discharge following ear drum perforation) or children under 2 years with acute otitis media in both ears

- Consider a back-up antibiotic prescription or an immediate antibiotic prescription (see the recommendations on choice of antibiotic) in line with the NICE guideline on respiratory tract infections (self-limiting): prescribing antibiotics.

Children and young people who are systemically very unwell, have symptoms and signs of a more serious illness or condition, or are at high-risk of serious complications because of pre-existing comorbidity

Children and young people under 18 years

Antibiotic[1]	Dosage and course length[2,3]
First choice	
Amoxicillin	1 to 11 months, 125 mg three times a day for 7 days 1 to 4 years, 250 mg three times a day for 7 days 5 to 11 years, 500 mg three times a day for 7 days 12 to 17 years, 500 mg three times a day for 7 days
Alternative first choices for penicillin allergy or intolerance	
Clarithromycin	Under 8 kg, 7.5 mg/kg twice a day for 7 days 8 to 11 kg, 62.5 mg twice a day for 7 days 12 to 19 kg, 125 mg twice a day for 7 days 20 to 29 kg, 187.5 mg twice a day for 7 days 30 to 40 kg, 250 mg twice a day for 7 days 12 to 17 years, 250 mg twice a day or 500 mg twice a day for 7 days
Erythromycin (in pregnancy)	8 to 17 years[4], 250 to 500 mg four times a day for 7 days or 500 to 1000 mg twice a day for 7 days
Second choice (worsening symptoms on first choice taken for at least 2 to 3 days)	
Co-amoxiclav	1 to 11 months, 0.25 ml/kg of 125/31 suspension three times a day for 7 days 1 to 5 years, 5 ml of 125/31 suspension three times a day or 0.25 ml/kg of 125/31 suspension three times a day for 7 days 6 to 11 years, 5 ml of 250/62 suspension three times a day or 0.15 ml/kg of 250/62 suspension three times a day for 7 days 12 to 17 years, 250/125 mg three times a day or 500/125 mg three times a day for 7 days
Alternative second choice for penicillin allergy or intolerance, or worsening symptoms on second choice taken for at least 2 to 3 days	
Consult local microbiologist	

Sinusitis (acute): antimicrobial prescribing

NICE National Institute for Health and Care Excellence

Choice of antibiotic: adults aged 18 years and over

Antibiotic[1]	Dosage and course length
First choice	
Penicillin V	500 mg four times a day for 5 days
Alternative first choices for penicillin allergy or intolerance	
Doxycycline	200 mg on first day, then 100 mg once a day for 5 days
Clarithromycin	500 mg twice a day for 5 days
Erythromycin (in pregnancy)	250 to 500 mg four times a day or 500 to 1000 mg twice a day for 5 days
Second choice (worsening symptoms on first choice taken for at least 2 to 3 days)	
Co-amoxiclav	500/125 mg three times a day for 5 days
Alternative second choice for penicillin allergy or intolerance, or worsening symptoms on second choice taken for at least 2 to 3 days	
Consult local microbiologist	
[1]See BNF for appropriate use and dosing in specific populations, for example, hepatic impairment, renal impairment, pregnancy and breast-feeding.	

Choice of antibiotic: children and young people under 18 years

Antibiotic[1]	Dosage and course length
First choice	
Penicillin V	1 to 11 months, 62.5 mg four times a day for 5 days 1 to 5 years, 125 mg four times a day for 5 days 6 to 11 years, 250 mg four times a day for 5 days 12 to 17 years, 500 mg four times a day for 5 days
Alternative first choice for penicillin allergy or intolerance	
Clarithromycin	Under 8 kg, 7.5 mg/kg twice a day for 5 days 8 to 11 kg, 62.5 mg twice a day for 5 days 12 to 19 kg, 125 mg twice a day for 5 days 20 to 29 kg, 187.5 mg twice a day for 5 days 30 to 40 kg, 250 mg twice a day for 5 days 12 to 17 years, 250 mg twice a day or 500 mg twice a day for 5 days[2]
Doxycycline[3]	12 to 17 years, 200 mg on first day, then 100 mg once a day for 5 days
Second choice (worsening symptoms on first choice taken for at least 2 to 3 days)	
Co-amoxiclav	1 to 11 months, 0.25 ml/kg of 125/31 suspension three times a day for 5 days 1 to 5 years, 5 ml of 125/31 suspension three times a day or 0.25 ml/kg of 125/31 suspension three times a day for 5 days 6 to 11 years, 5 ml of 250/62 suspension three times a day or 0.15 ml/kg of 250/62 suspension three times a day for 5 days 12 to 17 years, 250/125 mg three times a day or 500/125 mg three times a day for 5 days[2]
Alternative second choice for penicillin allergy or intolerance, or worsening symptoms on second choice taken for at least 2 to 3 days	
Consult local microbiologist	
[1]See BNF for children for appropriate use and dosing in specific populations, for example hepatic impairment, renal impairment. [2]The age bands apply to children of average size and, in practice, the prescriber will use the age bands in conjunction with other factors such as the severity of the condition being treated and the child's size in relation to the average size of children of the same age. [3]Doxycycline is contraindicated in children under the age of 12 years	

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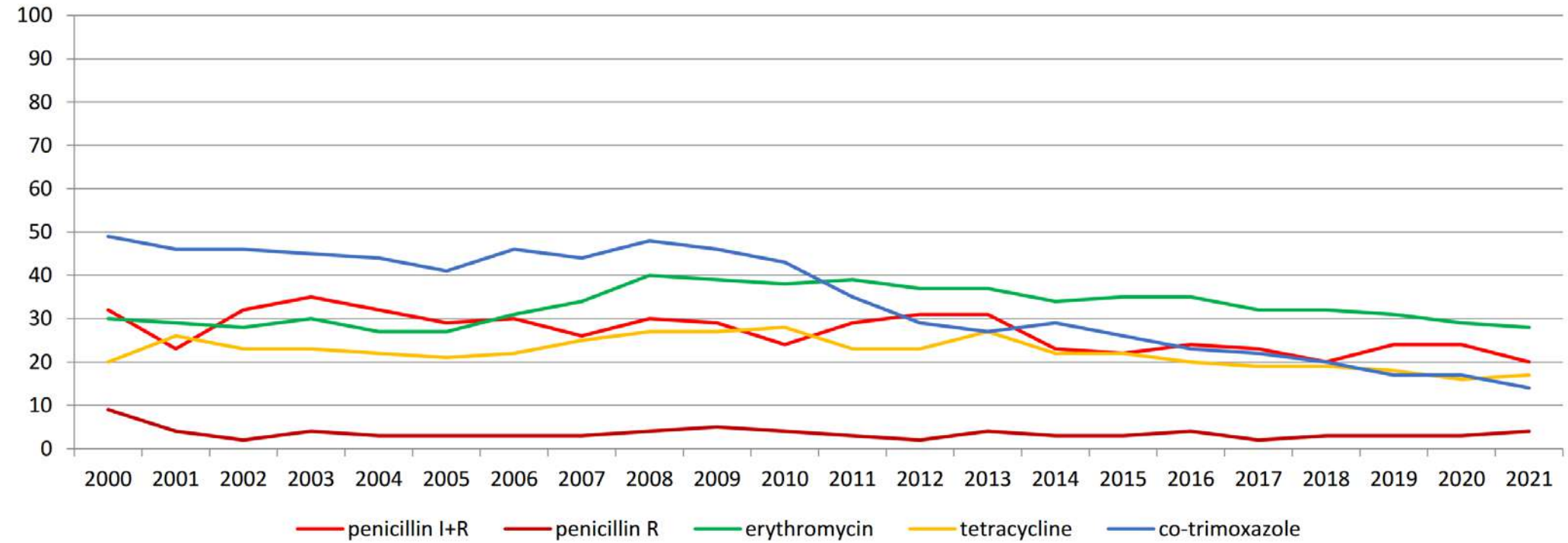
Croatian Academy of Medical Sciences, Public Health Collegium, Committee for Antibiotic Resistance Surveillance

Streptococcus pneumoniae

rezistencija na antibiotike u RH / *resistance to antibiotics in Croatia*, 2000. - 2021.



R = visoka rezistencija / *high level resistance*
I = osjetljivost uz povećanu izloženost / *susceptible, increased exposure*

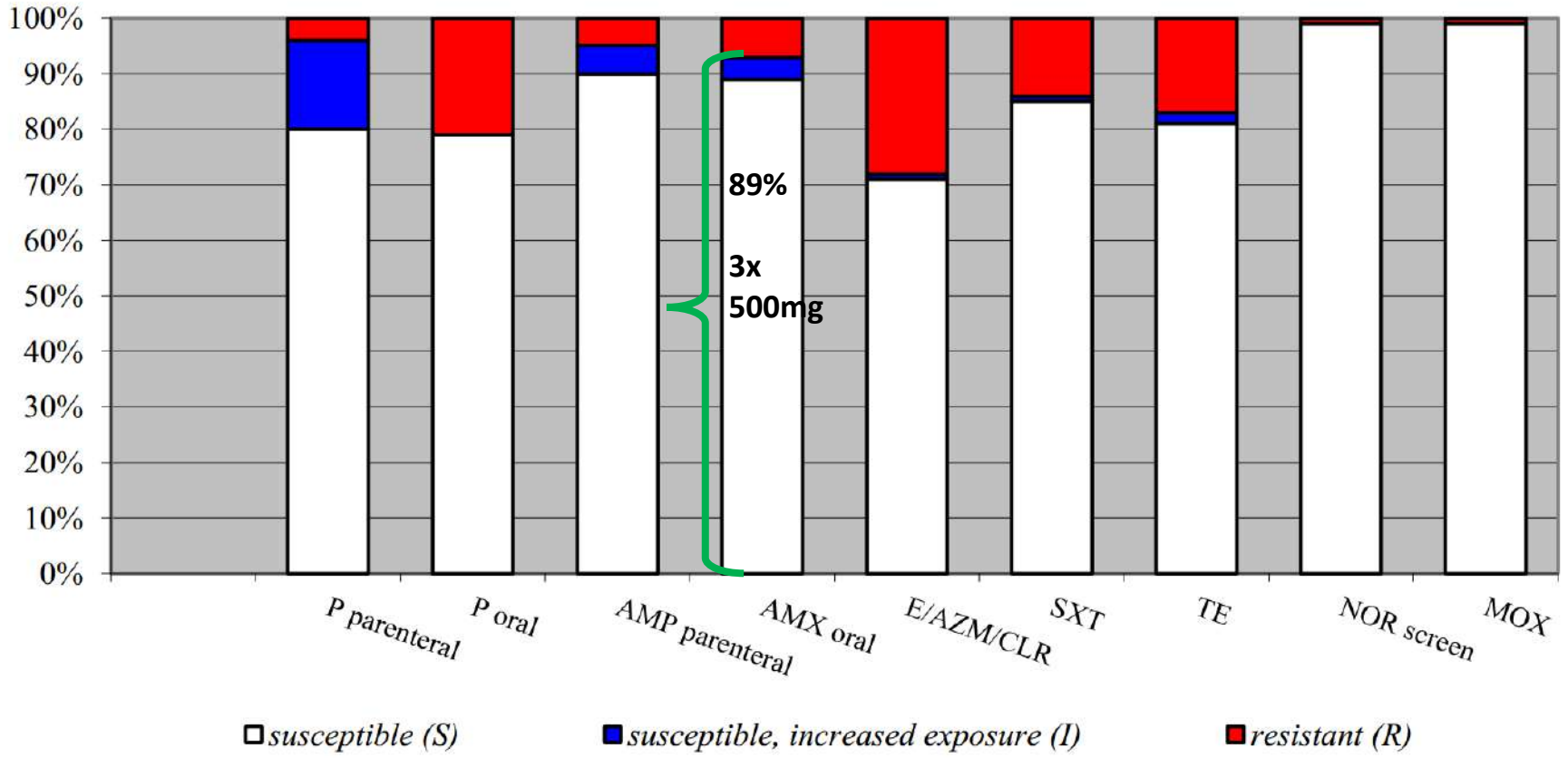
***S.pneumoniae*:** susceptibility to penicillin and ampicillin

Croatia, 2021

AMX (I) + (S)

93%

3 x 1g p.o.



Akutna upala srednjeg uha

Adaptirano prema NICE smjernicama [Ref.1.]

—Akutni *otitis media* (AOM) je samoograničavajuća infekcija srednjeg uha, koja se najčešće javlja u djece te se ovi naputci odnose na djecu i adolescente
—AOM uzrokuju virusi, bakterije, a često istovremeno mogu biti prisutni i virusi i bakterije
—Simptomi najčešće traju 3 dana (mogu i do tjedan dana) i prolaze spontano bez uporabe antibiotika
—Uporaba antibiotika ima slab učinak na pojavu komplikacija ili ponavljajućih infekcija

Kada primijeniti antibiotik odmah:

—Kod AOM s otorejom (perforacijom bubnjića)
—Kod djece mlađe od 2 godine s obostranim otitisom
—Ako je opće stanje jako loše i/ili prisutni znaci teške bolesti
—Ako postoje ko-morbiditeti koji bi mogli olakšati pojavu komplikacija

Kada primijeniti antibiotik nakon promatranja:

—Ako treći dan ne dolazi do spontanog poboljšanja
—Ako u prva tri dana promatranja dođe do nagloг ili značajnog pogoršanja

Kada uputiti u bolnicu:

Ako je AOM povezan sa: teškom sistemnom infekcijom, akutnim komplikacijama (mastoiditisom, meningitisom i drugim infekcijama središnjeg živčanog sustava)

Ref1. Otitis media (acute): antimicrobial prescribing. NICE guideline Published: 28 March 2018 www.nice.org.uk/guidance/ng91
Ref2. Tambić Andrašević A, Tambić T. Rezistencija bakterijskih izolata u 2018. godini. U: Tambić Andrašević A, Tambić T, ur. Osjetljivost i rezistencija bakterija na antibiotike u Republici Hrvatskoj u 2018.g. Zagreb: Akademija medicinskih znanosti Hrvatske, 2020:13-120.
Ref.3. The European committee on Antimicrobial Susceptibility Testing. Breakpoint tables. Version 10.0., 2020. http://www.eucast.org
Ref.4. AAP Clinical Practice Guideline: The Diagnosis and Management of Acute Otitis Media Pediatrics. 2019;131(3):1401-1485.
Ref.5. Kovač Bilić L, Tronić R, Tambić Andrašević A, et al. Smjernice za akutnu upalu srednjeg uha za djecu i odrasle: ambulantno i bolničko liječenje. Med Jad 2020;50(3):199-205.

Prvi izbor antibiotika

Amoksicilin 250 mg/5 mL 3xdnevno (ukupna dnevna doza 40-60 mg/kg)* kroz 5 do 7 dana***

kg**	mL		kg**	mL		kg**	mL	
	40 mg/kg	60 mg/kg		40 mg/kg	60 mg/kg		40 mg/kg	60 mg/kg
5	1.3	2	17	4.5	6.8	29	7.7	11.6
6	1.6	2.4	18	4.8	7.2	30	8	12
7	1.8	2.8	19	5	7.6	31	8.3	12.4
8	2.1	3.2	20	5.3	8	32	8.5	12.8
9	2.4	3.6	21	5.6	8.4	33	8.8	13.2
10	2.7	4	22	5.8	8.8	34	9.0	13.6
11	2.9	4.4	23	6.1	9.2	35	9.3	14
12	3.2	4.8	24	6.4	9.6	36	9.6	14.4
13	3.5	5.2	25	6.6	10	37	9.9	14.8
14	3.7	5.6	26	6.9	10.4	38	10.1	15.2
15	4	6	27	7.2	10.8	39	10.4	15.6
16	4.3	6.4	28	7.5	11.2	40	10.7	16

Ako nakon 2 do 3 dana primjene amoksicilina nema poboljšanja

Amoksicilin + klavulanska kiselina*

60 mg/kg tjelesne težine amoksicilinske komponente
podijeljeno u tri doze dnevno kroz 7 dana

*Prema podacima iz 2019.g. u Hrvatskoj doziranje amokscilina od 40 mg/kg podijeljeno u tri doze dnevno pokriva 87%, a doziranje od 60 mg/kg podijeljeno u tri doze dnevno 93% pneumokoka (Ref.2., Ref.3.) – ISKRA predlaže više doziranje

**U izvornim NICE smjernicama djeca su grupirana po dobi kojoj odgovaraju određene lako mjerljive doze. Kako je u Hrvatskoj uobičajeno doziranje prema tjelesnoj težini, pojedinačne doze sirupa (u mL) su prilagođene kg tjelesne težine

***Hrvatski stručnjaci predlažu terapiju od 10 dana kod teže bolesne djece i djece ≤ 2 godine. (Ref.4. i Ref.5.)

Iako nije spomenuto u NICE smjernicama, hrvatski stručnjaci smatraju da se amoksicilin može primjenjivati u dozi od 80 do 90 mg amoksicilina/kg tjelesne težine podijeljeno u dvije doze dnevno (Ref.4.)

Za alternativu kod preosjetljivosti na penicilin vidi Ref.1., Ref.4., Ref.5.

Prvi izbor antibiotika

Amoksicilin 250 mg/5 mL 3xdnevno (ukupna dnevna doza 40-60 mg/kg)* kroz 5 do 7 dana***

kg**	mL		kg**	mL		kg**	mL	
	40 mg/kg	60 mg/kg		40 mg/kg	60 mg/kg		40 mg/kg	60 mg/kg
5	1.3	2	17	4.5	6.8	29	7.7	11.6
6	1.6	2.4	18	4.8	7.2	30	8	12
7	1.8	2.8	19	5	7.6	31	8.3	12.4
8	2.1	3.2	20	5.3	8	32	8.5	12.8
9	2.4	3.6	21	5.6	8.4	33	8.8	13.2
10	2.7	4	22	5.8	8.8	34	9.0	13.6
11	2.9	4.4	23	6.1	9.2	35	9.3	14
12	3.2	4.8	24	6.4	9.6	36	9.6	14.4
13	3.5	5.2	25	6.6	10	37	9.9	14.8
14	3.7	5.6	26	6.9	10.4	38	10.1	15.2
15	4	6	27	7.2	10.8	39	10.4	15.6
16	4.3	6.4	28	7.5	11.2	40	10.7	16

Ako nakon 2 do 3 dana primjene amoksicilina nema poboljšanja

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**U izvornim NICE smjernicama djeca su grupirana po dobi kojoj odgovaraju određene lako mjerljive doze. Kako je u Hrvatskoj uobičajeno doziranje prema tjelesnoj težini, pojedinačne doze sirupa (u mL) su prilagođene kg tjelesne težine

***Hrvatski stručnjaci predlažu terapiju od 10 dana kod teže bolesne djece i djece ≤ 2 godine. (Ref.4. i Ref.5.)

Akutni sinuitis

Adaptirano prema NICE smjernicama (Ref.1)

—Akutni sinuitis (rhinosinuitis) se obično razvija nakon prehlade, najčešće ga uzrokuju virusi, traje oko 2 do 3 tjedna i većina ljudi ozdravi bez antibiotika uz primjenu antipiretika po potrebi i upute da se pacijent javi ako dođe do naglog ili značajnog pogoršanja
—Samo otprilike 2% sinuitisa uzrokuju bakterije te se ponekad u liječenju primjenjuju antibiotici

Kada primijeniti antibiotik odmah:

—Ako je opće stanje jako loše i/ili prisutni znaci teške bolesti
—Ako postoje ko-morbiditeti koji bi mogli olakšati pojavu komplikacija

Kada primijeniti antibiotik tijekom promatranja:

—Ako nakon 10 dana ne dolazi do spontanog poboljšanja, ponovno razmotriti potrebu davanja antibiotika ili izdati recept za antibiotik uz odgodu primjene te preporuku čekanja spontanog poboljšanja u narednih 7 dana
—Ako tijekom promatranja dođe do naglog ili značajnog pogoršanja primijeniti antibiotik

Kada uputiti u bolnicu:

Ako je sinuitis povezan sa: teškom sistemnom infekcijom, intraorbitalnim ili periorbitalnim komplikacijama, znacima i simptomima meningitisa, teškom frontalnom glavoboljom ili neurološkim ispadima.

Prvi izbor antibiotika

Djeca: Amoksicilin 250 mg/5 mL 3xdnevno (ukupna dnevna doza 40-60 mg/kg)* kroz 5 dana

kg**	mL		kg**	mL		kg**	mL	
	40 mg/kg	60 mg/kg		40 mg/kg	60 mg/kg		40 mg/kg	60 mg/kg
5	1.3	2	17	4.5	6.8	29	7.7	11.6
6	1.6	2.4	18	4.8	7.2	30	8	12
7	1.8	2.8	19	5	7.6	31	8.3	12.4
8	2.1	3.2	20	5.3	8	32	8.5	12.8
9	2.4	3.6	21	5.6	8.4	33	8.8	13.2
10	2.7	4	22	5.8	8.8	34	9.0	13.6
11	2.9	4.4	23	6.1	9.2	35	9.3	14
12	3.2	4.8	24	6.4	9.6	36	9.6	14.4
13	3.5	5.2	25	6.6	10	37	9.9	14.8
14	3.7	5.6	26	6.9	10.4	38	10.1	15.2
15	4	6	27	7.2	10.8	39	10.4	15.6
16	4.3	6.4	28	7.5	11.2	40	10.7	16

Odrasli: Amoksicilin 3x500 mg ili 3x1000 mg* kroz 5 dana

Antibiotik izbora ako je opće stanje jako loše, prisutni znaci teške bolesti te ako postoje ko-morbiditeti koji bi mogli olakšati pojavu komplikacija ili drugi izbor ako nakon 2 do 3 dana liječenja prvim antibiotikom ne dođe do poboljšanja

Amoksicilin + klavulanska kiselina*

Djeca: Doze amoksicilinske komponente kao iznad kroz 5 dana

Odrasli: 2-3×875/125 mg dnevno kroz 5 dana

*U izvornim NICE smjernicama prvi lijek izbora je penicilin V, no za Hrvatsku ISKRA preporučuje amoksicilin zbog bolje djelotvornosti na pneumokoke smanjene osjetljivosti na penicilin. Doziranje amoksicilina od 40 mg/kg podijeljeno u tri doze za djecu ili 3x500 mg za odrasle dnevno djeluje na izolate pneumokoka koji su osjetljivi (S) na amoksicilin uz standardno doziranje (u Hrvatskoj u 2019.g. 61% izolata), a doziranje od 60 mg/kg podijeljeno u tri doze dnevno za djecu ili 3x1000 mg za odrasle djeluje i na izolate koji su osjetljivi na amoksicilin uz povećanu izloženost/doziranje (I) (u Hrvatskoj u 2019.g. je takvim doziranjem pokriveno 89% pneumokoka i većina izolata haemofilusa) (Ref.2, 3.)

**U izvornim NICE smjernicama djeca su grupirana po dobi kojoj odgovaraju određene jako injektivne doze. Kako je u Hrvatskoj uobičajeno doziranje prema tjelesnoj težini, pojedinačne doze sirupa (u mL) su prilagođene kg tjelesne težine

Iako nije spomenuto u NICE smjernicama, hrvatski stručnjaci smatraju da se amoksicilin za djecu može primjenjivati u dozi od 80 - 90 mg amoksicilina/kg tjelesne težine podijeljeno u dvije doze dnevno (Ref.4).

Za alternativu kod preosjetljivosti na penicilin vidi Ref.1.

Ref.1. Sinusitis (acute): antimicrobial prescribing. NICE guideline Published: October 2017 www.nice.org.uk/guidance/ng79
Ref.2. Tambić Andrašević A, Tambić T. Rezistencija bakterijskih izolata u 2019. godini. U: Tambić Andrašević A, Tambić T, ur. Osjetljivost i rezistencija bakterija na antibiotike u Republici Hrvatskoj u 2019.g. Zagreb: Akademija medicinskih znanosti Hrvatske, 2020:13-120.
Ref.3. The European Committee on Antimicrobial Susceptibility Testing. Breakpoint tables. Version 10.0., 2020. http://www.eucast.org
Ref.4. AAP Clinical Practice Guideline: The Diagnosis and Management of Acute Otitis Media Pediatrics. 2013;131(3):1451–1465.

Prvi izbor antibiotika

Djeca: Amoksicilin 250 mg/5 mL 3xdnevno (ukupna dnevna doza 40-60 mg/kg)* kroz 5 dana

kg**	mL		kg**	mL		kg**	mL	
	40 mg/kg	60 mg/kg		40 mg/kg	60 mg/kg		40 mg/kg	60 mg/kg
5	1.3	2	17	4.5	6.8	29	7.7	11.6
6	1.6	2.4	18	4.8	7.2	30	8	12
7	1.8	2.8	19	5	7.6	31	8.3	12.4
8	2.1	3.2	20	5.3	8	32	8.5	12.8
9	2.4	3.6	21	5.6	8.4	33	8.8	13.2
10	2.7	4	22	5.8	8.8	34	9.0	13.6
11	2.9	4.4	23	6.1	9.2	35	9.3	14
12	3.2	4.8	24	6.4	9.6	36	9.6	14.4
13	3.5	5.2	25	6.6	10	37	9.9	14.8
14	3.7	5.6	26	6.9	10.4	38	10.1	15.2
15	4	6	27	7.2	10.8	39	10.4	15.6
16	4.3	6.4	28	7.5	11.2	40	10.7	16

Odrasli: Amoksicilin 3x500 mg ili 3x1000 mg* kroz 5 dana

Antibiotik izbora ako je opće stanje jako loše, prisutni znaci teške bolesti te ako postoje ko-morbiditeti koji bi mogli olakšati pojavu komplikacija ili drugi izbor ako nakon 2 do 3 dana liječenja prvim antibiotikom ne dođe do poboljšanja

Amoksicilin + klavulanska kiselina*

Djeca: Doze amoksicilinske komponente kao iznad kroz 5 dana

Odrasli: 2-3×875/125 mg dnevno kroz 5 dana

*U izvornim NICE smjernicama prvi lijek izbora je penicilin V, no za Hrvatsku ISKRA preporučuje amoksicilin zbog bolje djelotvornosti na pneumokoke smanjene osjetljivosti na penicilin. Doziranje amoksicilina od 40 mg/kg podijeljeno u tri doze za djecu ili 3x500 mg za odrasle dnevno djeluje

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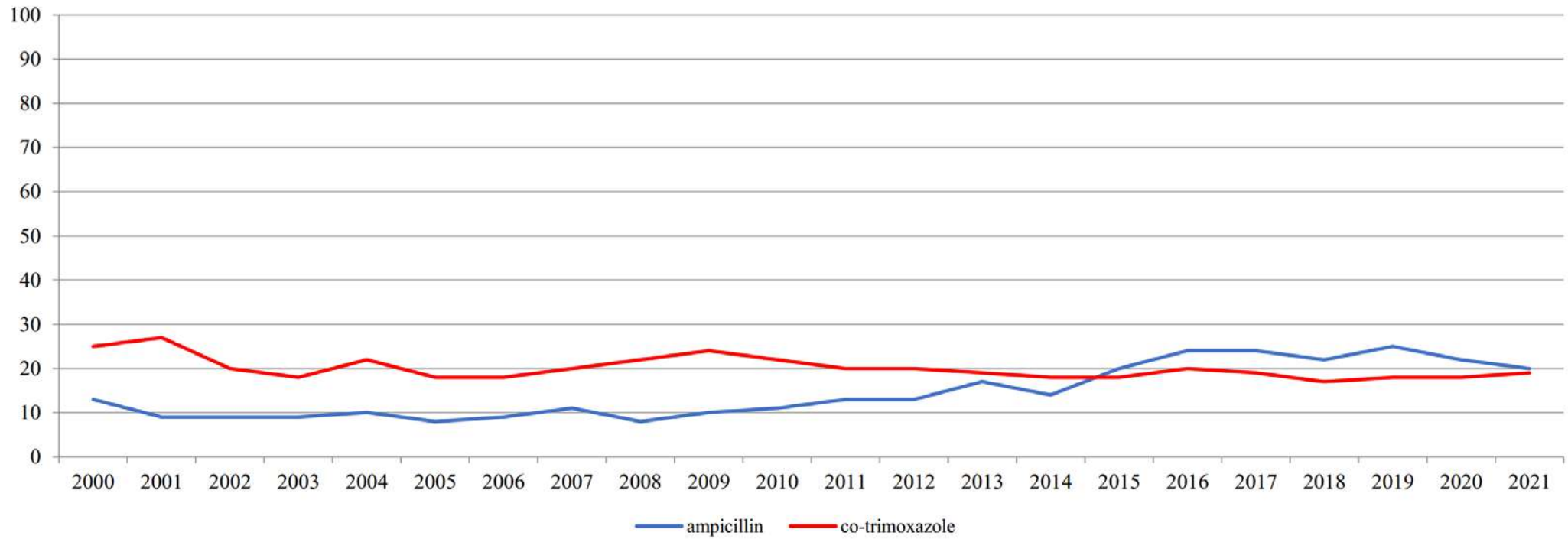
Croatian Academy of Medical Sciences, Public Health Collegium, Croatian Committee for Antibiotic Resistance Surveillance

Haemophilus influenzae

rezistencija na antibiotike u RH / *resistance to antibiotics in Croatia*, 2000. - 2021.



Prevencija respiratornih infekcija cijepljenjem

Doc. prim. dr. sc. Bernard Kaić[1], prim. Tatjana Nemeth Blažić[1]

1 Hrvatski zavod za javno zdravstvo, Zagreb, Hrvatska

U skupinu respiratornih infekcija ubraja se velik broj raznih bolesti koje zahvaćaju gornji i/ili donji dišni sustav, a s obzirom na velik broj oboljelih ili teške oblike bolesti koje neke od njih mogu uzrokovati, imaju velik javnozdravstveni značaj. Protiv nekih od tih zaraznih bolesti postoji cijepljenje kao primarna prevencija i zaštita od nastanka infekcije ili od teških oblika bolesti i smrti. To su između ostaloga, cijepljenje protiv difterije, hripavca, gripe, pneumokoka, COVID-19.

Sve je veći broj dostupnih cjepiva protiv respiratornih infekcija i različitih dizajna u proizvodnji cjepiva protiv određenog uzročnika.

Primjerice samo protiv gripe na tržištu su živa atenuirana cjepiva, cjepiva od cijelih mrtvih virusa, podjedinična, fragmentirana, adjuvantirana, rekombinantna i cjepiva s visokom dozom antigena. Zadnjih godina najaktualnije cjepivo, ono protiv bolesti COVID-19 također na tržištu se nalazi u raznim oblicima: mRNA cjepivo, adenovirusno vektorsko, rekombinantno proteinsko adjuvantirano i neadjuvantirano, mrtvi virusi, a proizvedena su na temelju originalnog wuhanskog soja, različitih podvarijanti omikrona i beta varijante. Često je teško odrediti kojem od dostupnih cjepiva dati prednost pri primjeni, a ponajviše zato što nedostaju solidni dokazi iz kliničkih i epidemioloških ispitivanjima na kojima bi se temeljila preporuka.

Održavanje ovog simpozija pomogli su:

A&B
Alkaloid
Altamedics
Astra zeneca
Becton Dickinson Croatia
Belupo
Biogen
Biomax
Biosistemi grupa
Biospectra
DiaHem
Inel -medicinska tehnika
JANAF
Kefo
Kemolab
Labena
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Oktal pharma
Pfizer Croatia
Roche
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Xellia

Zahvaljujemo!


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LIFE DISCOVERED. LIFE DIAGNOSED.

- C. difficile
- GBS DS
- GBS LB
- SARS-CoV-2
- Strep A
- Carba C

Fleksibilna molekularna platforma sposobna za pojedinačno i/ili višestruko testiranje. Analizator malih dimenzija, koji unaprijeđuje standardizaciju testiranja u vašem zdravstvenom sustavu.

- HpSA®
- Campy

Fluorescentno imunološka platforma, usmjerena na gastrointestinalno testiranje. Analizator malih dimenzija koji, poboljšava bolničku operativnu učinkovitost.

Uređaj koji dokazano pruža zaštitu od koronavirusa koji uzrokuje COVID-19.

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