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CROATIAN ACADEMY OF MEDICAL SCIENCES
PUBLIC HEALTH COLLEGIUM
COMMITTEE FOR ANTIBIOTIC RESISTANCE SURVEILLANCE IN CROATIA

KLINIKA ZA INFEKTIVNE BOLESTI "DR. F. MIHALJEVIĆ"
REFERENTNI CENTAR ZA PRAĆENJE REZISTENCIJE BAKTERIJA NA ANTIBIOTIKE MINISTARSTVA ZDRAVSTVA
UNIVERSITY HOSPITAL FOR INFECTIOUS DISEASES "DR. F. MIHALJEVIĆ"
REFERENCE CENTER FOR ANTIBIOTIC RESISTANCE SURVEILLANCE
CROATIAN MINISTRY OF HEALTH

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AUTORI / *AUTHORS*

Prof. prim. dr. sc. Arjana Tambić Andrašević, dr. med., FESCMID
Dr. sc. Ljiljana Žmak, dr. med.
Dr. sc. Mihaela Obrovac, dr. med.
Prim. Marina Payerl Pal, dr. med.
Damjan Debelec, prvostupnik medicinsko laboratorijske dijagnostike
Prof. prim. dr. sc. Suzana Bukovski, dr. med.
Prim. dr. sc. Blaženka Hunjak, dr. med.
Izv.prof.Andrea Babić-Erceg, dr.med.
Tatjana Unukić, prvostupnik medicinsko laboratorijske dijagnostike
Dr.sc. Sanja Pleško, dr. med.
Zoran Herljević, dr. med
Violeta Rezo Vranješ, dr. med.
Prof. dr. sc. Ivana Mareković, dr. med.
Marko Siroglavić, dr. med.
Iva Butić, dr. med.
Silvija Šoprek, dr. med.
Irina Pristaš, dr. med.
Sandra Lucić, mag. MLD
Irena Groš, mag. MLD

UREDNICI / *EDITORS*

Prof. prim. dr. sc. Arjana Tambić Andrašević, dr. med., FESCMID
Prim. dr. sc. Tera Tambić, dr. med.

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Jasminka Blaha

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Članovi Odbora za praćenje rezistencije bakterija na antibiotike
Members of the Croatian committee for antibiotic resistance surveillance

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PREDGOVOR:

I godinu 2021. je još uvijek značajno obilježila pandemija SARS-CoV-2, no fokus interesa se dominantno usmjerio na uvođenje i provođenje cijepljenja protiv COVID-19, pojavile su se varijante virusa manjeg patogenog potencijala te su i mjere izolacije pacijenata popustile i omogućile veću aktivnost bolnica u smislu liječenja pacijenata s drugim dijagnozama. Sukladno tome, povećao se i broj bakterioloških pretraga te brojevi izolata obrađeni u ovom izvješću za većinu bakterijskih vrsta rastu u odnosu na prethodnu godinu i dosežu brojke prijašnjih predpandemijskih godina. Multiplo rezistentni bolnički patogeni porasli su, nažalost, tijekom pandemije i brojem i stopom rezistencije što najbolje ukazuje koliko su u sprječavanju širenja rezistencije važne standardne mjere predostrožnosti, koje su tijekom pandemije često bile zanemarivane zbog pretjerane uporabe zaštitnih sredstava u sklopu kontaktne izolacije pacijenata s COVID-19. Utjecaj virusne pandemije na bakterijsku rezistenciju na antibiotike jasno ukazuje koliko su razni sektori u zdravstvu usko povezani i kako se problemu širenja rezistencije treba pristupati zajednički na različitim razinama, što se već dugi niz godina i čini, ne samo u okviru humane medicine, već i u okviru jedinstvenog zdravstva (engl. „One health“), što podrazumijeva kontrolu potrošnje antibiotika i širenja rezistencije i u veterinarskom sektoru i sektoru okoliša. U Hrvatskoj, ove sektore i razne struke unutar tih sektora povezuje Interdisciplinarna sekcija za kontrolu rezistencije na antibiotike (ISKRA), a podatci o rezistenciji izneseni u ovoj publikaciji rezultat su aktivnosti predviđenih Nacionalnim programom za kontrolu otpornosti bakterija na antibiotike. Dok se programi praćenja rezistencije i praćenja potrošnje antibiotika uspješno provode već dugi niz godina, intervencije potaknute ovakvim podacima su još uvijek manjkave. Podaci o rezistenciji se na nacionalnoj razini koriste za prilagodbu međunarodnih smjernica za liječenje izvanbolničkih infekcija, često su prezentirani na stručnim skupovima, no nedostaje rasprava o rezistenciji i posljedične intervencije na razini odjela i zdravstvenih ustanova. Iako su u mnogim sredinama elementi programa upravljanja antimikrobnom terapijom već dugo u praksi, formalno uvođenje timova za upravljanje antimikrobnom terapijom značajno bi unaprijedilo borbu protiv rezistencije na lokalnoj razini. Tijekom obje pandemijske godine tradicionalni stručni skup povodom obilježavanja Europskog dana i Svjetskog tjedna svjesnosti o antimikrobnim lijekovima u studenom uspio se organizirati kao webinar pri čemu je virtualno okupljanje donijelo i neke prednosti poput bolje iskoristivosti radnog vremena i veće mogućnosti interaktivnog sudjelovanja. U 2021.g. održan je virtualno i jubilarni X. hrvatski simpozij o rezistenciji bakterija na antibiotike, koji se održava svake tri godine već tri desetljeća. I ove godine, simpozij je privukao brojne kolege iz Hrvatske i inozemstva koji su rekapitulirali značajne događaje u području rezistencije bolničkih i izvanbolničkih patogena, veterinarskih i okolišnih izolata, a nezaobilazna tema je bilo upravljanje antimikrobnom terapijom o čemu su svoja iskustva s nama podijelili pozvani stručnjaci iz inozemstva te naši stručnjaci koje rade u inozemstvu.

Svima koji su sudjelovali u prikupljanju podataka, analizi rezultata i nastanku ove publikacije iskreno zahvaljujem na velikom uloženom trudu i nadam se da će ovi podatci biti uspješno korišteni u svrhu racionalizacije uporabe antibiotika i kontrole širenja rezistencije.

Arjana Tambić Andrašević
Predsjednica Odbora za praćenje rezistencije bakterija na antibiotike u RH

PREFACE

The year 2021 was also marked by the SARS-CoV-2 pandemic but the major interest was focused on COVID-19 vaccination, new virus variants with apparently lower pathogenic potential emerged, and this led to the relaxation of isolation restrictions and the increase in hospital activities related to treatment of other diseases. Consequently, the number of bacteriological testing increased which is reflected in the higher numbers of isolates for majority of species included in this report, approaching figures similar to the prepandemic era. Unfortunately, the absolute numbers and the rates of multiply resistant nosocomial pathogens increased during the pandemic which clearly indicates how important standard precautions are in preventing the spread of resistance, which was to some extent neglected due to the overuse of personal protective equipment used for COVID-19 related contact precautions. The impact of the viral pandemic on bacterial resistance to antibiotics clearly shows how closely related the various sectors in healthcare are and how the problem of antimicrobial resistance should be approached jointly at different levels. Such an approach is being practiced for many years, not only within the human medicine sector, but also within the "One health" framework, which implies good collaboration on antibiotic consumption and antibiotic resistance control among the human, veterinary and environmental sectors. In Croatia, these sectors and various professions within these sectors are linked by the Interdisciplinary Section for the Control of Antibiotic Resistance (ISKRA), and the data on resistance presented in this publication are the result of activities foreseen by the National program for the antibiotic resistance control. While antibiotic resistance and antibiotic consumption surveillance programs have been successfully implemented for many years, data-driven interventions are still insufficient. Data on resistance are used at the national level to adapt international guidelines for the treatment of community-acquired infections, they are often presented at expert meetings, but there is a lack of discussion on resistance and consequent interventions at the level of hospital wards and healthcare institutions. Although elements of antimicrobial stewardship programs have long been in practice in many healthcare settings, the formal introduction of antimicrobial stewardship teams would significantly advance the fight against resistance at the local level. During both pandemic years, the traditional symposium marking The European Antimicrobial Awareness Day and the World Antimicrobial Awareness Week in November managed to be organized as a webinar, whereby the virtual gathering also brought some advantages such as a better use of working time and a greater opportunity for interactive participation. In 2021 the jubilee 10th Croatian Symposium on Antibiotic Resistance, which has been held every three years for three decades, was also held virtually. This year too, the symposium attracted numerous colleagues from Croatia and abroad who recapitulated significant events in the field of resistance in hospital and community acquired pathogens, veterinary and environmental isolates, and the inevitable topic was the antimicrobial stewardship. Invited international speakers and our experts who work abroad shared with us their experience and practical aspects of antimicrobial stewardship in their institutions.

I sincerely thank everyone who participated in the collection of data, analysis of the results and creation of this publication for their great effort, and I hope that these data will be successfully used to rationalize the use of antibiotics and control the spread of resistance.

Arjana Tambić Andrašević
President of the Croatian Committee for Antibiotic Resistance Surveillance

PRAĆENJE REZISTENCIJE NA ANTIBIOTIKE U HRVATSKOJ

- Praćenje rezistencije na antibiotike na nacionalnoj razini je u Hrvatskoj započelo 1996. g. osnivanjem **Odbora za praćenje rezistencije bakterija na antibiotike** pri Akademiji medicinskih znanosti Hrvatske. Odbor je u početku prikupljao podatke iz 17 centara odabranih da geografski predstavljaju pouzdan uzorak za Hrvatsku, no s vremenom su se Odboru priključili gotovo svi mikrobiološki laboratoriji u zemlji tako da podaci pokrivaju više od 90% hrvatske populacije. Sudjelovanje u radu Odbora je započeto na dobrovoljnoj bazi, no nakon pristupanja Europskoj uniji sudjelovanje u nacionalnom praćenju rezistencije postaje i obveza. Standardizacija rada mikrobioloških laboratorija prepoznata je kao prioritet od samog početka rada Odbora te su kao obavezni standardi unutar hrvatske mreže praćenja prihvaćeni američki Clinical and Laboratory Standards Institute (CSLI) standardi do 2010.g., a od 2011.g. svi su hrvatski laboratoriji usvojili standarde europskog odbora The European Committee on Antimicrobial Susceptibility Testing (EUCAST).
- **The European Committee on Antimicrobial Susceptibility Testing (EUCAST)** je odbor osnovan unutar Europskog društva kliničke mikrobiologije i infektologije (The European Society of Clinical Microbiology and Infectious Diseases, ESCMID) sa ciljem harmonizacije metodologije testiranja osjetljivosti na antibiotike među europskim zemljama, no EUCAST standardi su sve više prihvaćeni i na drugim kontinentima. Kada je EUCAST 2010.g. donijeo jedinstvene europske standarde za disk difuzijsku metodu, hrvatski laboratoriji su, zahvaljujući dobro uhodanoj mreži Odbora za praćenje rezistencije, lako usvojili nove europske standarde i sinhronizirano ih počeli primjenjivati od 2011.g. Kako bi se osiguralo redovito ažuriranje EUCAST standarada u svim hrvatskim laboratorijima, unutar Odbora osnovano je 2011.g. **Povjerenstvo za metodologiju određivanja osjetljivosti na antibiotike („National Antibiotic Committee, NAC“)**.
- Europski projekt za praćenje rezistencije u invazivnih izolata, **The European Antimicrobial Resistance Surveillance System (EARSS)** započeo je 1998.g., a članovi Odbora su se spremno uključili u ovaj projekt na samom početku njegovog rada. EARSS je 2010.g. prerastao u kontinuirani program Europskog centra za prevenciju i kontrolu bolesti (European Center for Diseases Prevention and Control, ECDC) **The European Antimicrobial Resistance Surveillance Network (EARS-Net)** u kojem Hrvatska, od pristupanja Europskoj uniji (EU) 2013.g., ima i obvezu sudjelovati.
- Europski projekt za praćenje potrošnje antibiotika, **The European Surveillance of Antimicrobial Consumption (ESAC)** započeo je 2001.g. i pristupanje ovom projektu od samog njegovog osnutka, potaknulo je Odbor za praćenje rezistencije da uz prikupljanje podataka o rezistenciji započne i s prikupljanjem podataka o potrošnji antibiotika sukladno međunarodno priznatim ESAC standardima. Ovaj projekt je 2011.g. prerastao u kontinuirani program ECDC-a **The European Surveillance of Antimicrobial Consumption Network (ESAC-Net)** u kojem Hrvatska od 2013.g., kao zemlja članica EU, ima i obvezu sudjelovati.
- U okviru Odbora osnovana je 2003.g. i hrvatska podružnica internacionalne organizacije The Alliance for the Prudent Use of Antibiotics, **The APUA Croatia Chapter**. Glavna inicijativa unutar podružnice je bilo uvođenje pilot projekta praćenja potrošnje antibiotika u bolnicama što je preraslo u sustavno praćenje na nacionalnoj razini.
- Od ranih 2000-tih Svjetska zdravstvena organizacija ističe da problem rezistencije nadilazi pitanje struke i potiče uključivanje vlada u rješavanje tog problema na nacionalnoj i međunarodnoj razini. Ministarstvo zdravstva (MZ) RH je od samog početka rada Odbora imalo svog predstavnika u Odboru, a suradnja s MZ je produbljena 2003.g. osnivanjem **Referentnog centra MZ za praćenje rezistencije na antibiotike pri Klinici za infektivne bolesti „Dr. Fran Mihaljević“**, koji je preuzeo tehničku podršku praćenju rezistencije.

- Podaci o rezistenciji i potrošnji antibiotika u Hrvatskoj dobili su svoj pravi smisao kad je 2006.g., u skladu s preporukama Europske unije, osnovano interdisciplinarno tijelo pri MZ, **Interdisciplinarna sekcija za kontrolu rezistencije na antibiotike (ISKRA)**. Ovo tijelo koordinira sve aktivnosti na području kontrole rezistencije na antibiotike u području humane medicine, veterine i poljoprivrede. Uz praćenje rezistencije i potrošnje antibiotika, u bitne nacionalne aktivnosti ubraja se i edukacija o racionalnoj primjeni antibiotika koja je nužna za one koji antibiotike propisuju, izdaju i konzumiraju. U tu svrhu podaci o rezistenciji i potrošnji antibiotika se koriste za razvijanje smjernica o uporabi antibiotika te u javnim kampanjama za podizanje svijesti o antibioticima.
- Europska unija je započela javnu kampanju za podizanjem svijesti o antibioticima 2008.g. kada je 18. studenoga proglašen Europskim danom svjesnosti o antibioticima, **The European Antibiotic Awareness Day (EAAD)**. Od 2015.g. Svjetska zdravstvena organizacija cijeli taj tjedan označava kao Svjetski tjedan svjesnosti o antibioticima, **The World Antibiotic Awareness Week (WAAW)**. I u Hrvatskoj je javna kampanja započela 2008.g. i od tada se svake godine u zimskoj sezoni provode razne aktivnosti, najviše koncentrirane oko EAAD / WAAW. U 2020.g. ime WAAW je promijenjeno u **the World Antimicrobial Awareness Week (WAAW)**.
- Edukacija zdravstvenih djelatnika se odvija kroz dodiplomske i poslijediplomske programe nastave, tečajeve i druge stručno znanstvene skupove. Odbor za praćenje rezistencije u suorganizaciji s mnogim drugim institucijama redovito organizira sljedeće skupove:
    - Hrvatski simpozij o rezistenciji bakterija na antibiotike, svake tri godine od 1994.g.
    - Tečaj o testiranju osjetljivosti na antibiotike, svake tri godine od 1999.g.
    - Simpozij povodom Europskog dana / Svjetskog tjedna svjesnosti o antibioticima, svake godine od 2008.g.

ANTIBIOTIC RESISTANCE SURVEILLANCE IN CROATIA

- Antibiotic resistance surveillance at the national level was initiated in Croatia in 1996 when the **Croatian Committee for Antibiotic Resistance Surveillance** was established at the Croatian Academy of Medical Sciences. The Committee initially collected data from 17 centers selected to geographically represent a reliable sample for Croatia, but over time, nearly all microbiological laboratories in the country joined the Committee so that the data cover more than 90% of the Croatian population. Participation in the work of the Committee was initially on a voluntary basis, but after joining the European Union, participation in the national antibiotic resistance surveillance program became an obligation. The standardization of the work in microbiological laboratories has been recognized as a priority since the very beginning of the surveillance network and the American Clinical and Laboratory Standards Institute (CSLI) standards have been made a requirement for all laboratories in the surveillance network by 2010, and since 2011 they were replaced by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) standards.
- **The European Committee on Antimicrobial Susceptibility Testing (EUCAST)** is the European Society of Clinical Microbiology and Infectious Diseases, ESCMID committee founded with the aim of harmonizing antibiotic susceptibility testing methodology among the European countries but with time EUCAST standards became increasingly in use on other continents as well. When EUCAST developed unique European standards for the disk diffusion method in 2010, thanks to the well established surveillance network, all the Croatian laboratories switched to EUCAST simultaneously in 2011. To enable regular updating and implementation of EUCAST standards, the National Antibiotic Committee (NAC) was founded in 2011 within the Croatian Committee for Antibiotic Resistance Surveillance.
- **The European Antimicrobial Resistance Surveillance System (EARSS)** started in 1998 and the members of the Croatian Committee for Antibiotic Resistance Surveillance readily joined the project from the very beginning of its activities. In 2010 EARRS was transferred to the continuous program of The European Center for Diseases Prevention and Control (ECDC) **The European Antimicrobial Resistance Surveillance Network (EARS-Net)** in which Croatia is allowed and obliged to take part since joining European Union in 2013.
- **The European Surveillance of Antimicrobial Consumption (ESAC)** started in 2001 and being a participant in the project from the very beginning the Croatian Committee for Antibiotic Resistance Surveillance decided to start collecting antibiotic consumption data using international ESAC standards. In 2011 ESAC was transferred to the continuous ECDC program **The European Surveillance of Antimicrobial Consumption Network (ESAC-Net)** in which Croatia is allowed and obliged to take part since joining European union in 2013.
- **The Alliance for the Prudent Use of Antibiotics (APUA) Croatia Chapter** was founded in 2003 within the Croatian Committee for Antibiotic Resistance Surveillance. The main APUA initiative was introducing a pilot project on antibiotic use in hospitals which evolved into a continuous national program.
- Since the early 2000s the World Health Organization emphasizes that the problem of resistance goes beyond the profession and encourages the involvement of governments in solving this problem at national and international levels. The Ministry of Health (MoH) of the Republic of Croatia has had its representative at the Croatian Committee for Antibiotic Resistance Surveillance since its founding, and the collaboration with the MoH became even stronger in 2003 when a **MoH Reference Center for Antibiotic Resistance Surveillance** was founded at the University Hospital for Infectious Diseases "Dr. Fran Mihaljević ", with a task to provide technical support for antibiotic resistance surveillance.

- In 2006 Croatian resistance and antibiotic consumption data have been given a true meaning when, in line with the EU recommendations, an intersectoral coordination mechanism, the **Interdisciplinary Section for Antibiotic Resistance Control (ISKRA)** was set up at the MoH.
- This body coordinates all activities related to the antibiotic resistance control in the field of human medicine, veterinary medicine and agriculture. In addition to monitoring antibiotic resistance and consumption, essential activities include education on the rational use of antibiotics for those who prescribe, dispense and consume antibiotics. For this purpose, antibiotic resistance and consumption data are used to develop guidelines on antibiotic use and to educate citizens during public antibiotic awareness campaigns.
- European union started the antibiotic awareness public campaign in 2008 when **the European Antibiotic Awareness Day (EAAD)** was proclaimed on 18th November. In 2015 this week was proclaimed **the World Antibiotic Awareness Week (WAAW)** by the World Health Organization. In Croatia, a public campaign also started in 2008 and since then, every year in the winter season, various public campaign activities take part, mostly concentrated around EAAD / WAAW. In 2020 the WAAW name was changed into **the World Antimicrobial Awareness Week (WAAW).**
- Education of health professionals takes place through undergraduate and postgraduate teaching programs, courses and other professional scientific conferences. The Croatian Committee for Antibiotic Resistance Surveillance in collaboration with many other institutions regularly organizes the following meetings:
    - Croatian Symposium on Antibiotic Resistance, organized every three years since 1994
    - Course on Antibiotic Ssusceptibility Testing, organized every three years since 1999
    - European Antibiotic Awareness Day / World Antibiotic Awareness Week Symposium, organized every year since 2008

REZISTENCIJA BAKTERIJSKIH IZOLATA U 2021. GODINI

ANTIBIOTIC RESISTANCE IN 2021

Arjana Tambić Andrašević
Sandra Lucić

Klinika za infektivne bolesti "Dr. Fran Mihaljević"
University Hospital for Infectious Diseases "Dr. Fran Mihaljević"

UVOD

Od početka praćenja svi laboratoriji koji sudjeluju u nacionalnom praćenju rezistencije obavezni su pridržavati se opisane metodologije prijavljivanja, primjenjivati iste standarde u testiranju osjetljivosti i sudjelovati u vanjskoj kontroli kvalitete. Prelaskom europskog projekta European Antimicrobial Resistance Surveillance System (EARSS) u EARS-Net program Europskog centra za prevenciju i kontrolu bolesti, praćenje rezistencije na nacionalnoj razini postalo je obavezno u svim zemljama članicama Europske unije pa tako, od ulaska u Europsku uniju, i u Hrvatskoj. Povjerenstvo za metodologiju određivanja osjetljivosti na antibiotike (nacionalno povjerenstvo za antibiotike, engl. „national antibiotic committee", NAC) je tijelo pri Odboru za praćenje rezistencije koje prati novosti u standardima European Committee on Antimicrobial Susceptibility Testing (EUCAST) i na zimskom sastanku Odbora donosi preporuke o standardima važećim za narednu godinu. Zahvaljujući redovitim sastancima Odbora i djelovanju nacionalnog povjerenstva za antibiotike postignut je visok stupanj standardizacije u međulaboratorijskom testiranju, a rezultati vanjske kontrole rada laboratorija ukazuju na visoku pouzdanost prijavljenih rezultata. Iako se u ovom poglavlju prikazuju agregirani nacionalni podaci, oni zapravo predstavljaju skup podataka koji se na lokalnoj razini obrađuju po izolatu uz veliku pažnju da se uključi samo jedan izolat po pacijentu te da se u razdoblju ispitivanja svi izolati testiraju na sve zadane antibiotike. Manjak ovakve organizacije praćenja je da na nacionalnoj razini, nije moguće analizirati podatke prema demografskim osobinama pacijenata, ali uključivanje velikog broja izolata iz različitih uzoraka omogućuje dosljedno praćenje stopa rezistencije i pravodobno otkrivanje sojeva s rijetkim mehanizmima rezistencije.

INTRODUCTION

From the very beginning of the surveillance program all laboratories that participate in the antibiotic resistance surveillance network are obliged to adhere to the specified surveillance methodology, comply with the same sensitivity testing standards and take part in the external quality assurance scheme (EQAS). Following transition of the European Antimicrobial Resistance Surveillance System (EARSS) project into the EARS-Net program of the European Center for Disease Prevention and Control (ECDC) antimicrobial resistance (AMR) surveillance at the national level became obligatory for all European Union Member States including Croatia. Croatian national antibiotic committee (NAC) for susceptibility testing methodology is a subcommittee of the Committee for antibiotic resistance surveillance and it closely follows developments within the European Committee on Antimicrobial Susceptibility Testing (EUCAST) and updates national susceptibility testing standards accordingly every year at the Committee winter meeting. Due to the regular Committee meetings and NAC activity a high level of interlaboratory standardization is achieved and the EQAS results demonstrate high reproducibility of delivered resistance data. Although this chapter reports aggregated national resistance data, these data represent a compilation of isolate based data analysed at the level of a local laboratory and great attention is given to exclude copy isolates and to test all isolates to all the antibiotics of the well defined panel throughout the surveillance period. The pittfal of this surveillance sheme is that patient demographic data are not available at the national level but analysis of a large number of clinical isolates enables consistent monitoring of trends in resistance and timely notification of isolates with novel resistance mechanisms.

MATERIJALI I METODE

Globalno praćenje rezistencije

U praćenje su uključeni svi izolati dogovorenih bakterijskih vrsta izolirani iz kliničkih materijala u razdoblju od 1.10. do 31.12.2021.g. Rezultati za izolate streptokoka grupe A, salmonela, šigela i anaerobnih bakterija prikupljaju se, zbog malog broja izolata, tijekom cijele godine, od 1.1. do 31.12.2021. Podatke za 2021.g. podnijelo je 39 centara (popis u legendi za tablice), što obuhvaća >90% populacije u Hrvatskoj.

Osnovna načela metodologije praćenja rezistencije, kojih se pridržavaju svi koji u praćenju sudjeluju, uključuju:

a. u ispitivanom razdoblju svi izolati određene bakterijske vrste testiraju se na sve antibiotike predviđene za tu vrstu. Od 2010.g. na snazi je dogovor da iznimka za ovo pravilo bude testiranje osjetljivosti *P. aeruginosa* i *A. baumannii* na kolistin. Zbog skupoće testiranja, a rijetke rezistencije, preporuča se da se kolistin testira samo kod izolata rezistentnih na karbapeneme.

b. antibiotici predviđeni za određenu vrstu navedeni su u formularima za praćenje rezistencije za tekuću godinu

c. u ispitivanom razdoblju s dogovorenom paletom antibiotika testiraju se svi izolati iz kliničkih materijala ili barem prvih 100 uzastopnih izolata

d. iz podataka se isključuju duplikatni sojevi, definirani kao izolati iste bakterijske vrste, izolirani u istog pacijenta, u bilo kojem uzorku, u razdoblju od 30 dana.

Laboratoriji svoje podatke elektronski šalju na obradu u Referentni centar za praćenje rezistencije, Klinika za infektivne bolesti "Dr. F. Mihaljević". Na svakom formularu su označeni neuobičajeni fenotipovi na koje treba obratiti pažnju i koje treba poslati na retestiranje u Referentni centar. Takvi izolati od posebnog interesa uključuju:

1. pneumokoke rezistentne na norfloksacin
2. stafilokoke rezistentne na vankomicin i / ili linezolid
3. enterokoke rezistentne na linezolid
4. enterobakterije rezistentne ili osjetljive uz pojačanu izloženost na bilo koji od karbapenema (ertapenem, meropenem, imipenem)

Tijekom 2021.g. korišteni su za testiranje i interpretaciju nalaza standardi europskog odbora, European Committee on Antimicrobial Susceptibility Testing (EUCAST) (Clinical Breakpoint Tables v. 11.0). U testiranju osjetljivosti na antibiotike većina laboratorija koristi disk difuzijsku metodu, a određivanje minimalnih inhibitornih koncentracija (MIK) se koristi za određivanje osjetljivosti anaerobnih bakterija, osjetljivosti na penicilin i ampicilin kod pneumokoka smanjene osjetljivosti na penicilin, osjetljivosti stafilokoka na glikopeptide te pseudomonasa i acinetobaktera na kolistin. Svake godine, na sastanku Odbora u prosincu komentiraju se i usvajaju promjene u EUCAST standardima za nadolazeću godinu. Već u 2019.g. su svi članovi Odbora trebali usvojiti novu interpretaciju S, I i R kategorija, što predstavlja najznačajniju izmjenu EUCAST standarda posljednjih godina. Od 2019.g. kategorija S znači "osjetljiv uz standardno doziranje", kategorija I "osjetljiv uz povećanu izloženost" te kategorija R "rezistentan". U 2021.g. EUCAST standardi su za neke kombinacije mikroorganizama i antibiotika uveli odvojenu interpretaciju za slučaj infekcije središnjeg živčanog sustava i slučaj ostalih infekcija. Dogovorno, za potrebe praćenja koristit će se interpretacija za "ostale (ne-meningitis) infekcije". U 2021.g. uvedeno je praćenje osjetljivosti enterokoka na linezolid, stafilokoka na tetraciklin i šigela na azitromicin.

Minimalne inhibitorne koncentracije se određuju korištenjem gradijent testova (Etest, bioMérieux; MIC Test Strip, Liofilchem). Za određivanje MIK kolistina od 2017.g.

usvojen je naputak EUCAST-a da se koristi mikrodilucija u bujonu (MICRONAUT MIC-Strip, Merlin Diagnostika; MIKROLATEST MIC, Erba Lachema). U skladu s upozorenjem EUCAST-a da je korištenje gradient strip testova nepouzdano u određivanju osjetljivosti pneumokoka na penicilin, posebno u izolata s rasponom MIK vrijednosti 0.5 – 2.0 mg/L, Odbor je preporučio testiranje osjetljivosti pneumokoka na penicilin metodom mikrodilucije u bujonu, no za sada uporaba mikrodilucije u bujonu nije obavezni uvjet za prijavljivanje vrijednosti MIK penicilina za potrebe praćenja rezistencije.

Vrste bakterija i ispitani antibiotici navedeni su u tablicama u daljnjem tekstu.

Ciljane studije

Podaci o osjetljivosti *M. tuberculosis* su obrađivani u nacionalnom laboratoriju za tuberkulozu, Hrvatskog zavoda za javno zdravstvo. Rezistencija *M. tuberculosis* je opisana u posebnom poglavlju ove publikacije.

Od 2016.g. su u praćenje rezistencije uključeni i klinički izolati gonokoka. Rezultati praćenja su analizirani na Odjelu za bakteriologiju Hrvatskog zavoda za javno zdravstvo i opisani su u zasebnom poglavlju ove publikacije.

U sklopu European Antimicrobial Resistance Surveillance System (EARSS) projekta, a potom EARS-Net programa Odbor posebno obrađuje rezistenciju u invazivnih izolata (iz krvi i likvora) bakterijskih vrsta *S. pneumoniae, S. aureus, E. faecalis, E. faecium, E. coli, K. pneumoniae, P. aeruginosa* i *Acinetobacter baumannii*. Za ove izolate referentni centar (RC) za praćenje rezistencije prikuplja i obrađuje demografske podatke pacijenata, a u svrhu detaljnije analize izolati se šalju u Zavod za kliničku mikrobiologiju Klinike za infektivne bolesti "Dr. F. Mihaljević". RC za praćenje rezistencije šalje podatke o invazivnim izolatima u The European Surveillance System (Tessy) Europskog centra za kontrolu bolesti (engl. "European Center for Disease Control", ECDC). Podaci o invazivnim izolatima od početka praćenja do 2021.g. prikazani su u zasebnom poglavlju ove publikacije.

Od 2001.g., uključivanjem u europski projekt European Surveillance of Antimicrobial Consumption (ESAC), a potom i ESAC-Net, Hrvatska prati potrošnju antibiotika izraženu u definiranim dnevnim dozama na 1000 stanovnika dnevno (DDD/TID). Podaci o bolničkoj i izvanbolničkoj potrošnji antimikrobnih lijekova se također šalju u Tessy sustav ECDC-a. Podaci o potrošnji antibiotika u Hrvatskoj u 2021.g. su objavljeni kao posebno poglavlje ove publikacije, a uključuju i detaljniju analizu bolničke potrošnje antibiotika koja se detaljnije počela pratiti od 2006.g. u sklopu APUA Croatia inicijative i u skladu s naputcima ISKRA-e.

U posebnom poglavlju prikazan je osvrt na sojeve poslane na retestiranje u Referentni centar za praćenje rezistencije. Iz ovog poglavlja bolje se može uočiti problem multiplorezistentnih bakterija u Hrvatskoj s obzirom da se rijetki izolati s novim mehanizmima rezistencije često ne prikazuju kao značajan postotak u velikom broju izolata obrađenih u masovnom praćenju.

Od 2019.g. posebno se prati osjetljivost na antifugike u invazivnih izolata kandida. Svi invazivni izolati se šalju u Zavod za kliničku i molekularnu mikrobiologiju Kliničkog bolničkog centra Zagreb, gdje se retestira osjetljivost izolata i obrađuju podaci koji su prikazani u posebnom poglavlju ove publikacije.

MATERIALS AND METHODS

Global surveillance

Global antibiotic resistance surveillance includes all clinical isolates of designated bacterial species isolated from 1 October till 31 December, 2021. Data on group A streptococci, salmonellae, shigellae and anaerobic bacteria are collected throughout the year, from 1 January to 31 December, 2021 due to the small number of isolates. In 2021 thirty-nine centres took part in antibiotic resistance surveillance (names of the centres are listed in the legend to the tables) which makes a catchment population of >90%.

Basic principles of resistance surveillance methodology, obligatory for all the participants, include the following:

a. during the study period all isolates of a given species are to be tested against all the designated antibiotics. Since 2010 the exception from this rule is applied for *P. aeruginosa, A.baumannii* and colistin. Because of the high cost for colistin testing and low incidence of resistance it was decided that colistin should be tested only in pseudomonas and acinetobacter isolates that are resistant to carbapenems.

b. all antibiotics that are to be tested in a particular bacterial species are listed on the antibiotic resistance surveillance form for the current year

c. during the study period a designated set of antibiotics is to be tested against all or at least the first 100 consecutive clinical isolates of each species

d. copy isolates are defined as isolates of the same species collected from the same patient within a 30 day period and they are excluded from the data

Laboratories send their data for analysis to the Croatian Reference Centre for Antibiotic Resistance Surveillance, University Hospital for Infectious Diseases "Dr. F. Mihaljević". Unusual and alert phenotypes are indicated on every collection form and they are to be referred to the Reference center. The alert microorganisms include the following:

1. pneumococci resistant to norfloxacin
2. staphylococci resistant to vancomycin and / or linezolid
3. enterococci resistant to linezolid
4. enterobacterales resistant or susceptible increased exposure to any carbapenem (ertapenem, meropenem, imipenem)

In 2021 all laboratories used the European Committee on Antimicrobial Susceptibility Testing (EUCAST) standards for susceptibility testing (Clinical Breakpoint Tables v. 11.0). Disk diffusion method is the most widely used susceptibility testing method in Croatian laboratories and minimal inhibitory concentration (MIC) testing is used for testing susceptibility in anaerobic bacteria and for detection of penicillin and ampicillin resistance in penicillin non-wild type pneumococci, glycopeptide resistance in staphylococci and colistin resistance in pseudomonas and acinetobacter. Every year at the Croatian Committee for Antibiotic Resistance Surveillance meeting in December the EUCAST updates for the coming year are discussed and adopted. Since 2019 all Committee members are using the new interpretation of the S, I and R categories, which is the most significant change in EUCAST standards in recent years. From 2019 category "S" means "susceptible, standard dosing", category "I" "susceptible, increased exposure" and category "R" "resistant". In 2021 for some drug bug combinations EUCAST introduced separate interpretation for meningitis and other infections. For surveillance purpose it was agreed that interpretation for other (non-meningitis) infections will be applied. In 2021 susceptibility of enterococci to linezolid, staphylococci to tetracycline and shigellae to azithromycin was included in surveillance.

Minimal inhibitory concentrations are determined by gradient tests (Etest, bioMérieux; MIC Test Strip, Liofilchem). In 2017 the EUCAST recommendation to use microbroth

dilution for testing colistin MIC (MICRONAUT MIC-Strip, Merlin Diagnostika; MIKROLATEST MIC, Erba Lachema) was adopted. In line with the EUCAST warning that the use of gradient strip tests is unreliable in determining the susceptibility of pneumococci to penicillin, especially in isolates with a MIC range of 0.5 - 2.0 mg / L, the Committee recommended penicillin susceptibility testing in pneumococci to be done by broth microdilution method, but as for now, the use of broth microdilution is not mandatory for reporting the penicillin MIC values for surveillance purpose.

Bacterial species and antibiotics tested are listed in tables.

Focused studies

Data on *M. tuberculosis* were processed in the National Laboratory for Tuberculosis at the Croatian Public Health Institute. Resistance in *Mycobacterium tuberculosis* is described in a separate chapter of this publication.

Gonococci are included in antibiotic resistance surveillance since 2016. Data are analyzed at the Department of Bacteriology of the Croatian Public Health Institute and are described in a separate chapter of this publication.

Data on invasive isolates (isolates from blood and cerebrospinal fluid) of *S. pneumoniae, S. aureus, E. faecalis, E. faecium, E. coli, K. pneumoniae, P. aeruginosa* and *Acinetobacter baumannii* were first collected within the European Antimicrobial Resistance Surveillance System (EARSS) project and afterwards within the EARS-Net program. For these isolates Reference center (RC) for resistance surveillance collects and analyses patient demographic data and for the purpose of more detailed analysis isolates are regularly sent to the Department of Clinical Microbiology, University Hospital for Infectious Diseases "Dr. F. Mihaljević". RC for resistance surveillance is obliged to send Croatian resistance data to The European Surveillance System (Tessy), a global European Center for Disease Control (ECDC) surveillance network. Data on invasive isolates from the beginning of surveillance until 2021 are presented in a separate chapter of this publication.

Croatia started to analyse antibiotic consumption data expressed as defined daily doses per thousand inhabitants daily (DDD/TID) in 2001 after joining first the European Surveillance of Antimicrobial Consumption (ESAC) project and afterwards the ESAC-Net program. Data on hospital and ambulatory antibiotic consumption are regularly sent to ECDC Tessy. Antibiotic consumption data for 2021 are presented in a separate chapter of this publication and they also include a more detailed analysis of antibiotic consumption in hospitals which was initiated by the APUA Croatia Chapter in 2006 and is in line with ISKRA requirements.

A special chapter deals with the isolates sent for retesting to the Reference Center for Antibiotic Resistance Surveillance. This detailed report provides a better insight in the spread of multiply resistant bacteria in Croatia as the presence of some strains with novel resistance mechanisms may still not be seen as a significant increase in resistance rates.

In 2019 surveillance on susceptibility of invasive candida isolates to antifungals was started. All invasive isolates are sent to the Department of Clinical and Molecular Microbiology of the Clinical Hospital Center Zagreb for retesting and data analysis. Results are presented in a special chapter of this publication.

REZULTATI

U praćenju rezistencije u 2021.g. sudjelovalo je 39 centara u Hrvatskoj. Prosječni rezultati za Hrvatsku i rezultati za pojedinačne centre prikazani su u tablicama i grafovima u daljnjem tekstu. Rezultati laboratorija koji su prijavili manje od 30 izolata pojedine bakterijske vrste smatraju se nepouzdanim podacima za taj centar, ali su uvršteni u tablice i uključeni su u zbirne rezultate za RH. Podaci o izolatima malo vjerojatnog fenotipa, koji nisu potvrđeni u RC za praćenje rezistencije, označeni su zvjezdicom kao nepotvrđeni i ne smatraju se važećima.

Zbog malog broja izolata u ispitivanom razdoblju neki centri su ispitivanje proširili na cijelu godinu, a neki su zbog različitih razloga odstupali od predviđenog razdoblja praćenja. Odstupanja od predviđenog razdoblja praćenja uključuju:

- ČK ZZJZ je za *A. baumannii* prikazao rezultate za cijelu godinu
- GS ZZJZ je za sve vrste prikazao rezultate za cijelu godinu
- IG ZZJZ je za *E. faecium* prikazao rezultate za cijelu godinu
- KA OB je za *S. aureus*/MSSA, *S. aureus*/MRSA i *H. influenzae* prikazao rezultate za cijelu godinu
- KA ZZJZ je za *S. pneumoniae, E. faecium* i *H. influenzae* prikazao rezultate za cijelu godinu
- PU ZZJZ je za *H. influenzae* prikazao rezultate za cijelu godinu
- SB NZZJZ je za *S. pneumoniae* i *H. influenzae* prikazao rezultate za cijelu godinu
- VK ZZJZ je za *S. pneumoniae, S. aureus*/MSSA, *S. aureus*/MRSA, *E. faecium, H. influenzae i A. baumannii* prikazao rezultate za cijelu godinu (izolati iz OŽB Vinkovci)
- VŽ ZZJZ je za *P. aeruginosa* prikazao rezultate za cijelu godinu
- ZG HZJZ je za BHS-A prikazao rezultate za razdoblje od 1.10 do 31.12.2021.
- ZG KBC je za *S. pneumoniae, S. aureus/*MSSA, *S. aureus*/MRSA i *H,.influenzae* prikazao rezultate za razdoblje od 4.10. do 3.1.2021., za *E. faecalis, K. pneumoniae* i *P. aeruginosa* za razdoblje od 4.10 do 13.10.2021., za *E. faecium* i *A. baumannii* za razdoblje od 4.10. do 22.11.2021., za *E. coli* za razdoblje od 4.10. do 12.10.2021, za *P. mirabilis* za razdoblje od 4.10. – 1.11.2021., *Enterobacter* spp., *Klebsiella aerogenes, Serratia* spp. i *Citrobacter* spp. za razdoblje od 4.10. do 20.10.2021.
- ZG KBM je za *H.influenzae* prikazao rezultate za cijelu godinu
- ZG NZZJZ je za *S. pneumoniae, S. aureus/*MSSA, *S. aureus*/MRSA i *H,.influenzae* prikazao rezultate za cijelu godinu, *E. faecalis* za razdoblje od 6.10. do 3.11.2021., *E. coli*, *P. mirabilis*, *K. pneumoniae*, *Enterobacter* spp., *Klebsiella aerogenes*, *Serratia* spp., *Citrobacter* spp. od 15.11. do 30.11.2021., *E. faecium*, *P. aeruginosa*. i *A. baumannii* prikazao rezultate za razdoblje od 4.10. do 30.11.2021.

Četiri laboratorija su prijavila izolaciju šigela: ČK ZZJZ *Sh. flexnerii* (1); RI NZZJZ *Sh. flexnerii* (1), *Sh. sonnei* (3); ZG KBCSM *Sh. sonnei* (1); ZG KIB *Sh. flexnerii* (1), *Sh. sonnei* (9). Ukupno je tijekom 2021.g. izolirano 16 šigela.

U 2021.g. ukupno je obrađeno 1 237 anaerobnih bakterija, 622 gram-pozitivnih i 615 gram-negativnih iz 24 centra: ČK ZZJZ gram-pozitivni anaerobi (27), gram-negativni anaerobi (30); DU ZZJZ gram-pozitivni anaerobi (3), gram-negativni anaerobi (1); KA OB gram-pozitivni anaerobi (24), gram-negativni anaerobi (28); KA ZZJZ gram-pozitivni anaerobi (3), gram-negativni anaerobi (3); KT MAGD. gram-pozitivni anaerobi (2), gram-negativni anaerobi (1); OG OB gram-pozitivni anaerobi (5), gram-negativni anaerobi (8); OS KBC gram-pozitivni anaerobi (7), gram-negativni anaerobi (120); PK OŽB gram-pozitivni anaerobi (1), gram-negativni anaerobi (1); PU ZZJZ gram-pozitivni anaerobi (3), gram-negativni anaerobi (8); RI KBC gram-pozitivni anaerobi (23), gram-negativni anaerobi (56); SB ZZJZ gram-pozitivni anaerobi (12), gram-negativni anaerobi (13); SK ZZJZ gram-pozitivni anaerobi (4), gram-negativni anaerobi (7); ST KBC gram-pozitivni anaerobi (177), gram-negativni anaerobi (57); ŠI ZZJZ gram-pozitivni anaerobi (21), gram-negativni anaerobi (28); VK ZZJZ gram-pozitivni anaerobi (2), gram-negativni anaerobi (8); VT ZZJZ gram-negativni anaerobi (1); VŽ ZZJZ gram pozitivni anaerobi (90), gram-negativni anaerobi (60); ZD ZZJZ gram-pozitivni anaerobi (13), gram-negativni anaerobi (17); ZG KBCSM gram-pozitivni anaerobi (50), gram-negativni anaerobi (18); ZG KBD gram-pozitivni anaerobi (20), gram-negativni anaerobi (16); ZG KBM gram-pozitivni anaerobi (22), gram-negativni anaerobi (50); ZG KBSD gram-pozitivni anaerobi (75), gram-negativni anaerobi (51); ZG KDB gram-pozitivni anaerobi (30), gram-negativni anaerobi (27); ZG KIB gram-pozitivni anaerobi (5), gram-negativni anaerobi (4); ZG KZT gram-pozitivni anaerobi (3), gram-negativni anaerobi (2).

RESULTS

Thirty-nine centers took part in antibiotic resistance surveillance in Croatia in 2021. Average data for Croatia and results for individual laboratories are presented in tables and figures further in the text. Results of the laboratories that reported less than 30 isolates of a single bacterial species were included in tables as to add to the total number for Croatia, but were flagged as not reliable resistance rate data for that individual centre. Where isolates of less probable phenotype were reported without being sent to a central laboratory for retesting, data were flagged as not retested centrally and these data are not considered to be reliable.

Due to low numbers of isolates in the surveillance period some centers expanded surveillance to the whole year and some centers reported different surveillance periods for various reasons. Deviations from official surveillance periods were reported as follows:

- ČK ZZJZ reported data for *A. baumannii* for the whole year
- GS ZZJZ reported data for all species for the whole year
- IG ZZJZ reported data for *E. faecium* for the whole year
- KA OB reported data for *S. aureus*/MSSA, *S. aureus*/MRSA and *H. influenzae* for the whole year
- KA ZZJZ reported data for *S. pneumoniae, E. faecium* and *H. influenzae* for the whole year
- PU ZZJZ reported data for *H. influenzae* for the whole year
- SB NZZJZ reported data for *S. pneumoniae* and *H. influenzae* for the whole year
- VK ZZJZ reported data for *S. pneumoniae, S. aureus*/MSSA, *S. aureus*/MRSA, *E. faecium, H. influenzae* and *A. baumannii* for the whole year (isolates from OB Vinkovci)
- VŽ ZZJZ reported data for *P. aeruginosa* for the whole year
- ZG HZJZ reported data for BHS-A for the period 1.10. – 31.12.2021.
- ZG KBC reported data for *S. pneumoniae, S. aureus/*MSSA, *S. aureus*/MRSA and *H. influenzae* for the period 4.10. – 3.1.2021., *E. faecalis, K. pneumoniae* and *P. aeruginosa* for the period 4.10. – 13.10.2021., *E. faecium, and A. baumannii* for the period 4.10. – 22.11.2021., *E. coli* for the period 4.10. – 12.10.2021., *P. mirabilis* for the period 4.10. – 1.11.2021., *Enterobacter* spp., *Klebsiella aerogenes, Serratia* spp. and *Citrobacter* spp.for the period 4.10. – 20.10.2021.
- ZG KBM reported data for *H. influenzae* for the whole year
- ZG NZZJZ reported data for *S. pneumoniae, S. aureus/*MSSA, *S. aureus*/MRSA and *H. influenzae* for the whole year, *E. faecalis* for the period 6.10. – 3.11.2021., *E. coli, P. mirabilis, K. pneumoniae, Enterobacter* spp., *Klebsiella aerogenes, Serratia* spp. and *Citrobacter* spp. for the for the period 15.11. – 30.11.2021., *E. faecium, P. aeruginosa.* and *A. baumannii* for the period 4.10. – 30.11.2021.

Four laboratories reported shigella isolates: ČK ZZJZ *Sh. flexnerii* (1); RI NZZJZ *Sh. flexnerii* (1), *Sh. sonnei* (3); ZG KBCSM *Sh. sonnei* (1); ZG KIB *Sh. flexnerii* (1), *Sh. sonnei* (9). Altogether 16 shigella isolates were reported in 2021.

In 2021 altogether 1 237 anaerobic bacteria were isolated, 622 gram-positives and 615 gram-negatives. They were isolated in 24 centers: ČK ZZJZ gram-positive anaerobes (27), gram-negative anaerobes (30); DU ZZJZ gram-positive anaerobes (3), gram-negative anaerobes (1); KA OB gram-positive anaerobes (24), gram-negative anaerobes (28); KA ZZJZ gram-positive anaerobes (3), gram-negative anaerobes (3); KT MAGD gram-positive anaerobes (2), gram-negative anaerobes (1); OG OB gram-positive anaerobes (5), gram-negative anaerobes (8); OS KBC gram-positive anaerobes (7), gram-negative anaerobes (120); PK OŽB gram-positive anaerobes (1), gram-negative anaerobes (1); PU ZZJZ gram-positive anaerobes (3), gram-negative anaerobes (8); RI KBC gram-positive anaerobes (23), gram-negative anaerobes (56); SB ZZJZ gram-positive anaerobes (12), gram-negative anaerobes (13); SK ZZJZ gram-positive anaerobes (4), gram-negative anaerobes (7); ST KBC gram-positive anaerobes (177), gram-negative anaerobes (57); ŠI ZZJZ gram-positive anaerobes (21), gram-negative anaerobes (28); VK ZZJZ gram-positive anaerobes (2), gram-negative anaerobes (8); VT ZZJZ gram-negative anaerobes (1); VŽ ZZJZ gram-positive anaerobes (90), gram-negative anaerobes (60); ZD ZZJZ gram-positive anaerobes (13), gram-negative anaerobes (17); ZG KBCSM gram-positive anaerobes (50), gram-negative anaerobes (18); ZG KBD gram-positive anaerobes (20), gram-negative anaerobes (16); ZG KBM gram-positive anaerobes (22), gram-negative anaerobes (50); ZG KBSD gram-positive anaerobes (75), gram-negative anaerobes (51); ZG KDB gram-positive anaerobes (30), gram-negative anaerobes (27); ZG KIB gram-positive anaerobes (5), gram-negative anaerobes (4); ZG KZT gram-positive anaerobes (3), gram-negative anaerobes (2).

DISKUSIJA

U tijeku epidemije SARS-CoV-2 virusa u 2020.g. je bio zabilježen značajno manji broj respiratornih patogena, što se objašnjavalo općenito manjom učestalošću respiratornih infekcija zbog primjene protuepidemijskih mjera. Tijekom 2021.g. protuepidemijske mjere, pogotovo izbjegavanje pohađanja kolektiva su bile znatno blaže, socijalni kontakti su bili značajno veći što je očekivano dovelo do porasta registriranih izolata pneumokoka i hemofilusa, iako ne još do razina registriranih u predepidemijsko doba. S obzirom da pneumokoki i hemofilusi dominantno potječu iz briseva nazofarinksa koji se još uvijek neprimjereno uzimaju za dijagnostiku infekcija gornjih dišnih puteva, nadamo se da je broj izolata manji i zbog manjeg uzimanja ovih uzoraka. U 2021.g. registriran je, međutim, broj izolata streptokoka grupe A još niži negoli u 2020.g.

Rezistencija na penicilin u beta-hemolitičkog streptokoka grupe A (BHS-A) još nije opisana te je ovaj antibiotik prvi lijek izbora u liječenju streptokoknih infekcija. Makrolidi su alternativa penicilinu u liječenju grlobolje kod osoba preosjetljivih na penicilin. Rezistencija BHS-A na makrolide u 2021.g. (10%) je podjednaka stopama uočenim zadnjih godina (8% u 2020.g., 9% u 2019.g., 10% u 2018.g., 7% u 2017.g. i 2016.g., 9% u 2015.g. i 2014.g, 10% u 2013.g., 9% u 2012. g., 7% u 2011.g., 8% u 2010.g., 9% u 2009.g., 13% u 2008.g.). Rezistencija na klindamicin je također slična kao prošlih godina (konstitutivna 5% u 2021.g., 4% u 2020.g., inducibilna 3% u 2021.g. i 2020.g.). Prema EUCAST standardima izolati s inducibilnom rezistencijom su se do 2014.g. izdavali kao osjetljivi na klindamicin uz upozorenje da se izbjegava dugotrajnija terapija teških infekcija klindamicinom, a od 2014.g. se takvi izolati interpretiraju kao rezistentni na klindamicin uz opasku da se klindamicin još uvijek može primijeniti u kratkotrajnom liječenju ili u liječenju blažih infekcija kože i mekih tkiva. Klindamicin se preporuča i u kombiniranoj terapiji s penicilinom kod teških nekrotizirajućih infekcija s obzirom da djeluje brže od beta-laktama i sprječava sintezu toksina. Utjecaj inducibilne rezistencije na učinak u kombiniranoj terapiji nije posebno proučen no s obzirom na akutnu fazu širenja nekroze u takvim slučajevima vjerojatno je uputno u početku terapije uključiti klindamicin čak i kod infekcija uzrokovanih streptokokom s inducibilnom rezistencijom na klindamicin.

Pneumokoki, *Haemophilus influenzae* i *Moraxella catarrhalis* se smatraju respiratornim patogenima, no često se nalaze i kao dio fiziološke mikrobiote gornjih dišnih puteva u zdravih ljudi ili tijekom virusne infekcije gornjih dišnih puteva. Izolati pneumokoka i hemofilusa opisani u ovom poglavlju potječu pretežno iz briseva nazofarinksa koji pokazuju nisku specifičnost i osjetljivost i ne preporučuju se kao uzorci za dijagnosticiranje etiologije infekcija gornjih dišnih puteva, no mogu poslužiti za epidemiološko istraživanje osjetljivosti ovih bakterijskih vrsta na antibiotike. Neinvazivni pneumokoki često pokazuju veće stope rezistencije negoli invazivni izolati. Rezistencija invazivnih pneumokoka opisana je u poglavlju o invazivnim izolatima i mjerodavnija je kao putokaz za primjenu antimikrobne terapije. Praćenje stopa rezistencije ukupnih pneumokoka omogućuje, međutim, uočavanje bitnih trendova u širenju rezistencije. U Hrvatskoj je rezistencija pneumokoka na penicilin za sada još uvijek niska (4% u 2021.g., 3% u 2020.g., 2019.g. i 2018.g., 2% u 2017.g.) i parenteralni penicilin je još uvijek lijek izbora u liječenju pneumokoknih pneumonija. Empirijsko liječenje pneumonije treba, međutim, započeti višim dozama penicilina kako bi se učinkovito djelovalo na pneumokoke koji pokazuju osjetljivost samo uz povećanu izloženost penicilinu. Do 2019.g. takvi izolati su se nazivali intermedijarnima, no od 2019.g. EUCAST je pojam intermedijarne osjetljivosti zamijenio pojmom osjetljivosti uz povećanu izloženost, sugerirajući da su i takvi izolati podložni liječenju ispitivanim antibiotikom, samo uz povećano izlaganje, što se u slučaju parenteralnog penicilina lako postiže povećanjem doze. Udio pneumokoka osjetljivih na penicilin uz povećanu izloženost u 2021.g. iznosi

16% i u razini je stopa zadnjih godina (21% u 2020.g. i 2019.g., 17% u 2018.g., 21% u 2017.g.). Infekcije uzrokovane pneumokokima koji zahtjevaju povećanu izloženost penicilinu nisu dostupne liječenju oralnim penicilinom, a u slučaju da zahvaćaju središnji živčani sustav (SŽS) ni parenteralnim penicilinom. Otpornost pneumokoka na penicilin u slučaju infekcije SŽS ili liječenja drugih infekcija oralnim pripravkom u 2021.g. iznosi između 20% i 21%. Pneumonije uzrokovane izolatima koji zahtjevaju povećanu izloženost penicilinu se mogu liječiti parenteralnim penicilinom u dozama prilagođenima visini minimalnih inhibitornih koncentracija (MIK) uzročnika. Prema rasponu MIK-ova penicilina registriranih u 2021.g., 96% svih pneumokoka ima MIK penicilina ≤2.0 mg/L i reagirat će na dozu od 6x2.4g (6x4MIU), 94% pneumokoka ima MIK penicilina ≤1.0 mg/L i reagirat će na dozu od 4x2.4g (4x4MIU) ili 6x1.2g (6x2MIU), a 91% pneumokoka ima MIK penicilina ≤0.5 mg/L i reagirat će na dozu od 4x1.2g (4x2MIU). Ove stope su podjednake prošlogodišnjima. Zbog povoljnijih farmakodinamskih osobina i dobre djelotvornosti na pneumokoke i hemofiluse, amoksicilin/ampicilin se češće od penicilina upotrebljava kao prva linija u liječenju upale uha, sinusitisa i pneumonija. U 2021.g. je bilo 90% osjetljivih pneumokoka koji su dostupni liječenju standardnom dozom amoksicilina od 3x500mg, što je podjednako prijašnjim stopama (87% u 2020.g. i 2019.g., 90% u 2018.g.). Povećanim doziranjem oralnog amoksicilina od 3x750mg ili 3x1000mg (pripravak dostupan na tržištu) može se obuhvatiti 93% pneumokoka (92% u 2020.g., 93% u 2019.g., 94% u 2018.g.), a parenteralnom primjenom ampicilina 98% izolata (97% u 2020.g., 2019.g. i 2018.g.) te je ampicilin / amoksicilin prihvatljiva opcija i za oralnu i za parenteralnu empirijsku terapiju respiratornih bakterijskih infekcija. U 2019.g. je EUCAST po prvi puta uveo standard za testiranje osjetljivosti na ampicilin i amoksicilin disk difuzijom. U 2021..g. četiri laboratorija nisu udovoljila zahtjevu da se od 2019.g. osjetljivost na ampicilin / amoksicilin testira istovremeno i disk difuzijom i određivanjem MIK-a, te se zbirni podaci na nacionalnoj razini ponešto, ali ne značajno, razlikuju za set izolata testiranih disk difuzijom i set izolata testiranih određivanjem MIK-ova. U ovoj diskusiji koriste se podaci dobiveni određivanjem MIK-ova kako bi se održala sljedivost s podacima prethodnih godina. Rezistencija pneumokoka na makrolide (28%), ko-trimoksazol (14%) i tetraciklin (17%) je slična prošlogodišnjim stopama (29%, 17% i 16%). Dugoročno gledajući rezistencija na ko-trimoksazol pokazuje trend pada (43% u 2010.g., 35% u 2011.g., 29% u 2012.g., 27% u 2013.g., 29% u 2014.g., 26% u 2015.g., 23% u 2016.g., 22% u 2017.g., 20% u 2018.g., 17% u 2019.g. i 2020.g., 14% u 2021.g.). U 2019.g. EUCAST je izmijenio standard očitavanja zone inhibicije za ko-trimoksazol što omogućuje da se manja zona interpretira kao S kategorija, no ne čini se da je to utjecalo na stope rezistencije na ko-trimoksazol s obzirom da je trend pada rezistencije uočen davno prije uvođenja promjene u interpretaciji. Otpornost pneumokoka na respiratorne kinolone je još uvijek niska (1%).

Otpornost *H.influenzae* na amoksicilin se u 2021.g. vratila na 20% (14% u 2014.g., 20% u 2015.g., 24% u 2016. i 2017.g., 22% u 2018.g., 25% u 2019.g. te 22% u 2020.g.). Prelaskom na EUCAST standarde detektiramo više izolata s graničnom rezistencijom na ampicilin, uzrokovanom promjenom ciljnih PBP molekula, što ponekad dovodi, možda, i do precjenjivanja rezistencije. Prema EUCAST standardima i za osjetljive hemofiluse potrebne su više doze amoksicilina (3x750mg tj. 3x1000mg). Iz tog razloga parenteralni amoksicilin/ampicilin sa ili bez inhibitora ima kategorije „S“ i „R“, dok njihovi oralni pripravci mogu imati samo kategorije „I“ i „R“. Rezistencija na ko-trimoksazol (19%) je slična stopama rezistencije prethodnih godina, a rezistencija na ceftriakson nije uočena.

Staphylococcus aureus je glavni uzročnik infekcija kože i mekih tkiva i kao takav ujedno i najčešći uzročnik kirurških infekcija. Rezistencija na penicillin se proširila još 1940-tih godina i danas su još samo rijetki izolati osjetljivi na penicilin. Osim uobičajene rezistencije na penicilin te umjerenih stopa rezistencije na makrolide (17%) i klindamicin (14%) meticilin senzitivni *Staphylococcus aureus* (MSSA) sojevi ne pokazuju značajnije stope rezistencije na druge antistafilokokne antibiotike. Od 2021.g. se uvelo testiranje

osjetljivosti stafilokoka na tetraciklin i rezistencija na tetraciklin kod MSSA iznosi 4%. Stečena rezistencija na kinolone kod MSSA je manja od 10% no i kod osjetljivih izolata, samo se od moksifloksacina može očekivati osjetljivost uz standardno doziranje, dok ciprofloksacin i levofloksacin djeluju samo ako se primjenjuju u višoj dozi. Meticilin rezistentni *Staphylococcus aureus* (MRSA) sojevi su rezistentni na sve beta-laktamske antibiotike (osim novijih cefalosporina, ceftarolina i ceftobiprola), a često pokazuju križnu rezistenciju i na druge klase antibiotika. Nakon 2008.g. uočen je trend pada udjela MRSA sojeva i najniže stope (12%) su zabilježene 2013. i 2014.g., no od 2015.g. stopa MRSA opet počinje rasti, a nagli skok je, nažalost, zabilježen 2020.g. i još više u 2021.g. (25% u 2007. g., 26% u 2008. g., 21% u 2009. g., 16% u 2010. g., 14% u 2011. g., 13% u 2012. g., 12% u 2013.g. i 2014.g., 14% u 2015.g., 16% u 2016.g., 15% u 2017.g., 16% u 2018.g. i 2019.g., 21% u 2020.g., 27% u 2021.g.). I ukupan broj MRSA izolata je znatno porastao u odnosu na prethodne godine (1238 u 2021.g., 699 u 2020.g., 784 u 2019.g.). Udio MRSA sojeva s inducibilnom rezistencijom na klindamicin (29%) je podjednak prošlogodišnjim vrijednostima (16% u 2014.g., 21% u 2015.g., 28% u 2016.g., 32% u 2017.g., 26% u 2018.g., 29% u 2019.g., 28% u 2020.g.). Rezistencija MRSA na gentamicin (13%) je identična prošlogodišnjoj stopi i potvrđuje trend pada rezistencije (91% u 2006.g., 81% u 2009.g., 77% u 2010.g., 69% u 2011.g., 64% u 2012.g., 59% u 2013.g., 43% u 2014.g., 38% u 2015.g., 32% u 2016.g., 23% u 2017.g., 18% u 2018.g. i 2019.g., 13% u 2020.g.). Rezistencija na linezolid i vankomicin nije uočena. Udio izolata s MIK-om vankomicina od 2.0 mg/L je iznosio 10% u 2021.g., 5% u 2020.g., 14% u 2019.g., 10% u 2018.g., 9% u 2017.g., 8% u 2016.g., 7% u 2015.g., 16% u 2014.g., 20% u 2013.g. Rezistencija MRSA na ceftarolin je 5%, a još 9% izolata treba liječiti višim dozama. U slučaju pneumonije, na ceftarolin je rezistentno 14% izolata. Stopa rezistencije na ko-trimoksazol je identična prošlogodišnjoj (5%), a rezistencija na tetraciklin, čije praćenje je uvedeno 2021.g., iznosi 10% i ne razlikuje se značajno od stopa rezistencije kod MSSA.

Enterokoki su prirodno rezistentni na mnoge grupe antibiotika, a gotovo svi izolati *Enterococcus faecium* pokazuju rezistenciju na ampicilin. Svi enterokoki pokazuju urođenu rezistenciju niskog stupnja na aminoglikozide, ali se aminoglikozidi kod divljih tipova enterokoka još uvijek mogu upotrebljavati u terapiji kombiniranoj s ampicilinom ili glikopeptidima u svrhu postizanja sinergističkog učinka. Kod sojeva visoko rezistentnih na aminoglikozide, ovi se antibiotici ne mogu upotrebljavati niti u kombiniranoj terapiji. Udio sojeva s visokom rezistencijom na aminoglikozide iznosi 24% za *E. faecalis* i 36% za *E .faecium*, što je identično odnosno slično kao i prethodne godine. Rezistencija na vankomicin je još uvijek rijetka u *E. faecalis* (1%), dok rezistencija na vankomicin u *E. faecium* pokazuje veliki skok i potvrđuje trend porasta uočen posljednjih godina (1% u 2012.g., 5% u 2013.g., 7% u 2014.g., 15% u 2015.g., 17% u 2016.g., 16% u 2017.g., 18% u 2018.g., 32% u 2019.g., 27% u 2020., 45% u 2021.g.). Porast rezistencije na vankomicin uočava se od 2015.g., kad se vankomicin rezistentni *E. faecium* (VRE) izolati počinju s većom učestalošću javljati u raznim regijama Hrvatske, a ne samo u zagrebačkim bolnicama kao što je to bilo u početku. U 2021.g., uz porast stope rezistencije na vankomicin uočen je i porast ukupnog broja *E.faecium* u odnosu na prethodnu godinu, ali i na predepidemijsko razdoblje. U 2014.g. EUCAST je uveo testiranje osjetljivosti enterokoka na kinolone, s tim da se disk difuzijom testira osjetljivost na norfloksacin kao indikator osjetljivosti na ciprofloksacin i levofloksacin. Kinoloni su namijenjeni liječenju enterokoknih infekcija, samo ako se radi o nekompliciranim infekcijama mokraćnog sustava. Rezistencija na kinolone u *E. faecalis* (23%) i *E. faecium* (87%) podjednaka je stopama prethodnih godina (22% i 75% u 2017.g., 22% i 84% u 2018.g., 22% i 85% u 2019.g., 23% i 81% u 2020.g.). Za nekomplicirane uroinfekcije koje urokuje *E. faecalis* može se koristiti i nitrofurantoin na koji ovaj uzročnik pokazuje nisku rezistenciju (1%).

Escherichia coli je najčešći uzročnik infekcija mokraćnog sustava (IMS), a ostale enterobakterije češće uzrokuju kompliciranе IMS ili infekcije raznih sustava povezane s bolničkom skrbi. S obzirom da su enterobakterije dio fiziološke mikrobiote često su izložene primjeni antibiotika, a širenje jednom nastalih mutanti teško je uočiti i kontrolirati. Broj prijavljenih izolata *E.coli* je u pandemijskoj 2020.g. bio znatno niži od uobičajenog, no u 2021.g. broj prijavljenih izolata je sličan predepidemijskom razdoblju, što govori u prilog povratu dijagnostičke aktivnosti za bakterijske infekcije, koja je bila reducirana u početku covid epidemije. Od početka praćenja *E. coli* pokazuje visoku rezistenciju na ampicilin, koja i u 2021.g. iznosi 48%, slično kao i prethodnih godina. Amoksicilin s dodatkom klavulanske kiseline, međutim, pokazuje dobru djelotvornost jer klavulanska kiselina uspješno blokira beta-laktamaze širokog spektra i većinu beta-laktamaza proširenog spektra (engl. "extended spectrum beta-lactamases, ESBL"). Kombinacija s klavulanskom kiselinom, međutim, ograničava primjenu amoksicilina u visokim dozama, kakve su često potrebne kod ozbiljnih sistemnih infekcija. U 2014.g. EUCAST je po prvi puta razdvojio interpretaciju osjetljivosti na amoksicilin s klavulanskom kiselinom ovisno o tome radi li se o nekompliciranoj IMS ili drugim oblicima infekcije. Nakon te podjele, stope rezistencije su ostale podjednake odnosno pokazuju blagi trend porasta, ako se interpretiraju za primjenu kod nekompliciranih IMS (7% u 2013.g. i 2014.g., 9% u 2015.g., 10% u 2016.g., 2017.g., 2018.g. i 2019.g., 11% u 2020.g., 12% u 2021.g.) no znatno su se povisile nakon promjene standarda uz lagani trend porasta u sljedećim godinama, ako se interpretiraju za primjenu kod ostalih infekcija (16% u 2014. i 2015.g., 15% u 2016.g., 2017.g. i 2018.g., 16% u 2019.g., 19% u 2020.g., 22% u 2021.g.). Od 2020.g. u EUCAST standardima za enterobakterije se uvodi posebna interpretacja osjetljivosti na parenteralni i oralni cefuroksim s tim da za oralnu primjenu postoje kategorije „S" i „R" ali se preporuča samo za nekompliciranе uroinfekcije, dok se parenteralni cefuroksim može primjenjivati i za sistemne infekcije ali samo u višoj dozi te za parenteralni cefuroksim postoje samo kategorije „I" i „R". Rezistencija na oralni cefuroksim je slična prošlogodišnjoj (10% u 2021.g., 11% u 2020.g.), a na parenteralni cefuroksim je identična prošlogodišnjoj (10%). Rezistencija na cefalosporine treće generacije (8% do 11%) je slična prošlogodišnjim stopama (7% do 9%). Novi pripravci cefalosporina s inhibitorima beta-laktamaza, ceftazidim / avibaktam i ceftalozan / tazobaktam pokazuju visoku učinkovitost na ESBL sojeve te rezistencija *E.coli* na ove antibiotike iznosi <1% i 1% što je istovjetno učinku karbapenema (<1% rezistentnih izolata) i nešto bolje od učinka piperacilin / tazobaktama (4% rezistentnih izolata). Rezistencija na ciprofloksacin je 2017.g. dosegla 20%, ali od tada stagnira i ovogodišnja stopa se ne razlikuje bitno od prošlogodišnjih stopa (14% u 2012. i 2013.g., 17% u 2014.g., 18% u 2015.g., 19% u 2016.g., 20% u 2017.g. i 2018.g., 19% u 2019.g., 18% u 2020.g., 19% u 2021.g.). Stope rezistencije na ko-trimoksazol (26%), gentamicin (9%), amikacin (1%), nitrofurantoin (3%), fosfomicin (1%) i nitroksolin (1%) su jednake prošlogodišnjim stopama.

Proteus mirabilis još uvijek izaziva pretežno izvanbolničke infekcije i prirodno bi trebao biti bakterijska vrsta dobro osjetljiva na sve beta-laktamske antibiotike usmjerene na gram-negativne bakterije. Nažalost, rezistencija na beta-laktamske antibiotike je već dosegla visoke stope i u 2021.g. iznosi za ampicilin 46%, za ko-amoksiklav 22%, za piperacilin/tazobaktam 4%, za cefalosporine 3. i 4. generacije od 8% za cefepim do 19% za cefiksim, što je slično prošlogodišnjim stopama. Rezistencija je jednaka ili nešto niža negoli prošle godine za nove cefalosporine u kombinaciji s inhibitorima beta-laktamaza, ceftazidim / avibaktam (1% u 2018.g., 2019.g., 2020.g. i 2021.g.), ceftalozan / tazobaktam (10% u 2018.g., 9% u 2019.g., 8% u 2020.g., 7% u 2021.g.). Stope rezistencije na ciprofloksacin (26%), gentamicin (21%), amikacin (12%) i ko-trimoksazol (40%) su također slične ili jednake prošlogodišnjima. Zbog svoje urođene otpornosti na kolistin, tigeciklin te niže osjetljivosti na imipenem *Proteus mirabilis* i drugi *Proteus* spp. bi u budućnosti mogli predstavljati sve veći problem, naročito kod uroloških bolesnika i infekcija povezanih s bolničkom skrbi.

Klepsijele i enterobakteri često uzrokuju infekcije povezane s bolničkom skrbi te već dugi niz godina pokazuju visoke stope rezistencije. *Klebsiella pneumoniae* je prirodno rezistentna na ampicilin no rezistencija na ostale beta-laktame je stečena uslijed dugotrajnog izlagnja antibioticima. Stope rezistencije na cefalosporine treće i četvrte generacije (41% za cefepim i ceftazidim do 43% za cefiksim) su slične prošlogodišnjima te i dalje više negoli u predepidemijskoj godini (35% do 38% u 2019.g.). I rezistencija na ko-amoksiklav i ceftolozan / tazobaktam je ostala visoka, slična prošlogodišnjim stopama (ko-amoksiklav 38% u 2018.g. i 2019.g., 45% u 2020.g., 43% u 2021.g.; ceftolozan / tazobaktam 20% u 2018.g. i 2019.g., 25% u 2020.g. i 2021.g.), a rezistencija na piperacilin / tazobaktam je u daljnjem porastu (19% u 2018.g., 21% u 2019.g., 27% u 2020.g., 31% u 2021.g.). Ceftazidim / avibaktam i dalje pokazuje vrlo nisku rezistenciju (2% u 2018.g., 2019.g., 2020.g., 1% u 2021.g.) te sa svojom djelotvornošću na sojeve koji proizvode ESBL i AmpC betalaktamaze, ali i velik dio karbapenemaza (KPC, OXA-48), najučinkovitiji beta-laktam kod klepsijela. Nakon što je broj klepsijela rezistentnih na karbapeneme po prvi puta u 2014.g. dosegao razinu vidljivu kao postotak rezistencije na imipenem i meropenem (1%), te su stope u 2019.g. narasle na 5% i 6%, a u pandemijskoj 2020.g. na 7% i 16% uz dodatno 8% i 2% izolata osjetljivo uz povećanu izloženost („I" kategorija). Te razine su ostale slične i u 2021.g. (8% i 14% rezistentnih te 4 i 2% osjetljivih uz povećanu izloženost), ali je ukupan broj izoliranih klebsijela veći negoli prethodne godine (5864 izolata u 2019.g., 4244 izolata u 2020.g., 5601 izolata u 2021.g.), što ukazuje da se širenje na karbapeneme rezistentnih klepsijela nastavilo. Rezistencija na ciprofloksacin (41%), gentamicin (31%), amikacin (6%) i ko-trimoksazol (39%) pokazuje stope slične prošlogodišnjima.

Enterobakteri, citrobakteri i seracije čine grupu enterobakterija koje prirodno posjeduju inducibilne cefalosporinaze i s izuzetkom *Citrobacter koseri* pokazuju rezistenciju ne samo na ampicilin već i na ko-amoksiklav i cefalosporine prve generacije. Od 2019.g. *Enterobacter aerogenes* je preimenovan u *Klebsiella aerogenes* no ta vrsta se i nadalje analizira unutar ove grupe enterobakterija. Cefuroksim samo marginalno djeluje na ove enterobakterije i prema EUCAST standardima ne postoji klinička interpretacija osjetljivosti na cefuroksim za ovu grupu bakterija. Divlji sojevi su osjetljivi na treću generaciju cefalosporina, no u tijeku terapije cefalosporinima može doći do probira derepresiranih mutanti koji stabilno hiperproduciraju AmpC cefalosporinaze i time uvjetuju rezistenciju i na cefalosporine treće generacije. Udio derepresiranih mutanti rezistentnih na cefalosporine treće i četvrte generacije (10% za cefepim do 28% za cefiksim) je u okvirima stopa registriranih prošlih godina (16% do 32% u 2017.g., 10% do 25% u 2018.g., 12% do 26% u 2019.g., 12% do 28% u 2020.g.), a i rezistencija na karbapeneme, koja je postala vidljiva 2013.g. (1%), ostala je gotovo jednaka (1% rezistentnih i 1% osjetljivih uz povećano izlaganje za imipenem i 1% rezistentnih za meropenem, 6% rezistentnih za ertapenem) i u 2021.g. Od ceftalozan / tazobaktama se prvenstveno očekuje prednost u liječenju infekcija koje uzrokuju pseudomonasi i enterobakterije koje proizvode ESBL kojih je više među *K.pneumoniae* i *E.coli* izolatima negoli među enterobakterima i stopa rezistencije u enterobaktera (11% u 2018.g. i 2019..g., 8% u 2020.g. i 2021.g.) je slična stopama rezistencije na cefepim (10% u 2018.g., 12% u 2019.g. i 2020.g., 10% u 2021.g.) i piperacilin / tazobaktam (9% u 2018.g., 10% u 2019.g. i 2020.g., 13% u 2021.g.). Stope rezistencije na ciprofloksacin (10%), gentamicin (8%), amikacin (1%) i ko-trimoksazol (11%) su slične prošlogodišnjima.

Multiplorezistentni *Pseudomonas aeruginosa*, poglavito sojevi rezistentni na karbapeneme, već dugi niz godina predstavljaju jedan od najvećih problema rezistencije u Hrvatskoj. Rezistencija na imipenem i meropenem je u 2020.g. značajno porasla, no nije nastavila rasti u 2021.g. (17% u 2018.g., 18% u 2019.g., 23% i 22% u 2020.g., 20% i 21% u 2021.g.). Ni rezistencija na nove cefalsosporine s inhibitorom, ceftazidim / avibaktam tazobaktam (4% u 2018.g., 6% u 2019.g., 7% u 2020.g., 6% u 2021.g.) i

ceftalozan / tazobaktam (4% u 2018.g., 6% u 2019.g., 7% u 2020.g., 5% u 2021.g.) se ne povećava. Rezistencija na piperacilin / tazobaktam (10% u 2019.g., 12% u 2020.g., 9% u 2021.g.), ceftazidim (16% u 2019.g., 21% u 2020.g., 15% u 2021.g.) i cefepim (13% u 2019.g., 16% u 2020.g., 13% u 2021.g.) je nakon porasta u 2020.g. ponovno došla na stope slične onima u predepidemijskom razdoblju. Rezistencija na ciprofloksacin (20%) i amikacin (6%) je nešto niža negoli prethodne godine. Od 2020.g. EUCAST standardi ne predviđaju testiranje *P. aeruginosa* na gentamicin jer smatraju da ovaj antibiotik nije djelotvoran za pseudomonasne infekcije. Za aminoglikozide se općenito preporuča da se za infekcije izvan urotrakta koriste samo u kombinaciji s drugim antibioticima. Opće je poznato da se za liječenje pseudomonasnih infekcija koriste više doze antibiotika što je od 2020.g. jasno iskazano u EUCAST standardima kao nepostojanje „S" kategorije (osjetljiv uz standardno doziranje) kod pseudomonasa za mnoge antibiotike (ceftazidim, cefepim, piperacilin/tazobaktam, imipenem, ciprofloksacin). Za testiranje osjetljivosti na kolistin potrebno je učiniti test mikrodilucije u bujonu, što je bitno zahtjevnije i skuplje od testiranja disk difuzijom te se u ovom slučaju odstupa od pravila da se u razdoblju praćenja rezistencije svi izolati testiraju na sve antibiotike i na kolistin se testiraju samo multiplo, poglavito na karbapeneme rezistentni sojevi. Podatak o rezistenciji na kolistin kod *P.aeruginosa* se, stoga, ne može uspoređivati sa stopama rezistencije na druge antibiotike, ali omogućuje praćenje kolistinske rezistencije u subpopulaciji multiplorezistentnih pseudomonasa. U 2021.g. ta je stopa značajno viša negoli prethodnih godina (3% u 2019.g. i 2020.g., 8% u 2021.g.).

Rezistencija na karbapeneme kod *Acinetobacter baumannii* se u Hrvatskoj naglo proširila od 2008.g. i u 2020.g. su se zadržale visoke stope rezistencije na imipenem i meropenem (94%), podjednake prošlogodišnjima. Prema EUCAST standardima ne postoje jasni dokazi o učinkovitosti ampicilin/sulbaktama na acinetobaktere, no kako je to jedan od rijetkih antibiotika koji još pokazuju djelotvornost *in vitro*, ovaj antibiotik se u Hrvatskoj testira i interpretira prema američkim standardima. Rezistencija i osjetljivost uz povećanu izloženost za ampicilin/sulbaktam se zadržala na visokim vrijednostima (40% i 16% u 2018.g., 34% i 20% u 2019.g., 31% i 18% u 2020.g., 32% i 23% u 2021.g.). Nažalost, povečanje broja izolata *A. baumannii* uočeno u pandemijskoj 2020.g., nastavilo se i u 2021.g. (1740 izolata u 2019.g., 2087 izolata u 2020.g., 2582 izolata u 2021.g.), što je najuočljiviji pokazatelj manjkavosti u primjeni standardnih mjera i mjera kontaktne izolacije za multiplorezistentne bakterije u tijeku epidemije COVID-19. Kao i kod pseudomonasa, kolistin se testira samo kod na karbapeneme rezistentnih izolata, no kako već nekoliko godina takvi izolati čine >90% ukupnih acinetobaktera, može se smatrati da se kolistin testira na skoro svim izolatima i stope kolistinske rezistencije se mogu uspoređivati sa stopama za ostale antibiotike. Stope rezistencije acinetobaktera na kolistin su još uvijek niske (2% u 2020.g., 1% u 2021.g.)

Rezistencija salmonela na ampicilin je 2014.g. prešla 10% (14% u 2014.g., 16% u 2015.g., 14% u 2016.g., 13% u 2017.g., 15% u 2018.g., 16% u 2019.g., 19% u 2020.g. i 2021.g.). ESBL sojevi su i dalje rijetki među salmonelama i u 2020.g. rezistencija na ceftazidim i ceftriakson je iznosila 3% i 2%. Rezistencija na ko-amoksiklav (8%), ko-trimoksazol (4%) i ciprofloksacin (4%) je slična prošlogodišnjim stopama. Do 2013.g. osjetljivost salmonela na ciprofloksacin na razini Hrvatske je bila 100%, a rezistencija na nalidiksičnu kiselinu, koja je bolji pokazatelj niske razine rezistencije na kinolne je bila do 2%. Od 2014.g. EUCAST je uveo preciznije testiranje osjetljivosti na kinolone (ciprofloksacin) preko pefloksacinskog diska što je vjerojatno utjecalo na registriranje stopa rezistencije na ciprofloksacin od 2% u 2014.g., no i od tada rezistencija na ciprofloksacin ima tenddenciju blagog porasta (4% u 2015.g., 3% u 2016.g., 4% u 2017.g., 2018.g. i 2019.g., 5% u 2020.g., 4% u 2021.g.).

Osjetljivost u *Campylobacter coli* i *Campylobacter jejuni* se prati od 2013.g. Trend porasta rezistencije na ciprofloksacin se u 2019.g. zaustavio, ali je rezistencija još uvijek

visoka (u 2015.g. 52% i 50%, u 2016.g. 60% obje vrste u 2017.g. 69% i 66%, u 2018.g. 78% i 76%, u 2019.g. 71% i 75%, u 2020.g. 74% i 71%, 77% obje vrste u 2021.g.). Rezistencija na eritromicin (1% za obje vrste) je i dalje niska, a trend porasta rezistencije na tetraciklin se zaustavio u 2020.g., a u 2021.g. su čak registrirane nešto niže stope (35% i 30% u 2017.g., 41% i 36% u 2018.g., 46% i 42% u 2019.g., 35% i 41% u 2020.g., 33% i 28% u 2021.g.).

Četiri laboratorija je prijavilo izolaciju šigela: ČK ZZJZ *Sh. flexneri* (1); RI NZZJZ *Sh. flexneri* (1), *Sh. sonnei* (3); ZG KBCSM *Sh. flexneri* (1) i ZG KIB *Sh. flexneri* (1), *Sh. sonnei* (9). Ukupno je tijekom 2021.g. izolirano 16 šigela.

Među gram-negativnim anaerobima rezistencija je visoka na penicilin (80%) i klindamicin (33%), a kod gram-pozitivnih anaeroba rezistencija je visoka na metronidazol (59%) te klindamicin (15%). Rezistencija na ko-amoksiklav, piperacilin/tazobaktam i ertapenem je niska (≤10%).

DISCUSSION

During the SARS-CoV-2 virus epidemic in 2020 a significantly lower number of respiratory pathogens was recorded, which can be explained by the generally lower incidence of community-acquired upper respiratory tract infections due to the application of anti-epidemic measures. During 2021 anti-epidemic measures, especially the avoidance of attending collectives, were significantly milder, social contacts became more common, which, as expected, led to an increase in registered isolates of pneumococcus and hemophilus, although not yet to the level registered in the pre-epidemic era. Given that pneumococci and hemophilus predominantly originate from nasopharyngeal swabs, which are still inappropriately taken for the diagnosis of upper respiratory tract infections, we hope that the reduction of isolates is at least partly also due to the reduction in collecting these samples. In 2021, the number of group A streptococci isolates, however, was even lower than in 2020.

Resistance to penicillin in Group A streptococcus (GAS) has not yet been described and penicillin is a drug of first choice in treating streptococcal infections. Macrolides are alternative therapy for sore throat in patients with hypersensitivity to penicillin. Resistance of GAS to macrolides in 2021 (10%) is similar to the rates observed in recent years (8% in 2020, 9% in 2019, 10% in 2018, 7% in 2017 and 2016, 9% in 2015 and 2014, 10% in 2013, 9% in 2012, 7% in 2011, 8% in 2010, 9% in 2009, 13% in 2008). Resistance to clindamycin is also similar as in previous years (constitutive 5% in 2021, 4% in 2020, inducible 3% in 2021 and 2020). Until 2014 the EUCAST standards recommended to report isolates with inducible clindamycin resistance as susceptible to clindamycin with a warning to avoid prolonged therapy but since 2014 these isolates are reported as resistant to clindamycin with a note that clindamycin may still be used for short-term therapy or less severe skin and soft tissue infections. Clindamycin is recommended for use in combination with penicillin for treating severe necrotizing infections as it blocks toxin synthesis and has a more rapid antibacterial effect than beta-lactams. The clinical importance of inducible clindamycin resistance in combination treatment of severe streptococcal infections is not well studied but considering the rapid spread of such infections it is probably wise to add clindamycin to initial treatment even for infections caused by GAS with inducible clindamycin resistance.

Pneumococci, *Haemophilus influenzae* and *Moraxella catarrhalis* are classified as respiratory pathogens but are frequently found as part of the normal microbiota of the upper respiratory tract in healthy individuals or during a viral upper respiratory tract infection. Most of the pneumococcal and haemophilus isolates reported in this chapter originate from nasopharyngeal swabs and aspirates, samples that are not adequate for the diagnostics of bacterial upper respiratory infections, but can be used for surveillance studies to estimate antimicrobial resistance rates in these pathogens. Non-invasive pneumococci often have higher resistance rates than invasive isolates. Resistance in invasive isolates is described in a separate chapter of this publication and is more relevant for choosing adequate empirical antibiotic therapy. Resistance rates in all site isolates are, however, important for epidemiological surveillance and can indicate trends in antibiotic resistance. In Croatia, penicillin resistance in pneumococci is still low (4% in 2021, 3% in 2020., 2019, and 2018, 2% in 2017) and parenteral penicillin is still a drug of first choice for treating pneumococcal pneumonia. Empirical therapy of pneumonia should, however, include higher penicillin dosing to achieve efficacy against pneumococci susceptible only with increased exposure. Until 2019 such isolates were categorised as intermediate but in 2019 EUCAST changed the term intermediate into susceptible, increased exposure, suggesting that these isolates are still treatable with the tested antibiotic but exposure to the drug should be increased. In case of pneumococci and penicillin this could be easily achieved by increasing the penicillin dosing. The rate of penicillin susceptible, increased exposure pneumococcal isolates in 2021 was 16% which

is similar to the rates recorded in previous years (21% in 2020 and 2019, 17% in 2018, 21% in 2017). Infections caused by penicillin susceptible, increased exposure pneumococci cannot be treated with oral penicillin and in case they involve central nervous system (CNS) they cannot be treated with parenteral penicillin either. Resistance to penicillin in case of CNS infections or other infections if treated with oral penicillin is, therefore, 20 - 21% in 2021. However, pneumonia caused by such pneumococci can still be treated with parenteral penicillin if dosing is adjusted to the minimal inhibitory concentration (MIC) of the isolate. According to the MIC range of pneumococci isolated in 2021, 96% of pneumococci have penicillin MIC ≤2.0 mg/L and will be covered by 6x2.4g (6x4MIU) dosing, 94% have penicillin MIC ≤1.0 mg/L and will be covered by 4x2.4g (4x4MIU) or 6x1.2g (6x2MIU) dosing and 91% have penicillin MIC ≤0.5 mg/L and will be covered by 4x1.2g (4x2MIU) dosing. These values are similar to the last year rates. Due to the better pharmacodynamic characteristics and good activity against pneumococci and haemophilus amoxicillin / ampicillin is used as a first line treatment of acute otitis media, sinusitis and pneumonia more frequently than penicillin. In 2021, 90% of pneumococci were treatable with standard oral amoxicillin dosing of 3x500mg which is similar to the previous rates (87% in 2020 and 2019, 90% in 2018). Increased dose of 3x750mg or 3x1000mg (formulation available at the market) covers 93% of pneumococci (92% in 2020, 93% in 2019, 94% in 2018) and parenteral ampicillin covers 98% (97% in 2020, 2019 and 2018) of pneumococci. Oral and parenteral ampicillin / amoxicillin are thus suitable first line antibiotics for empirical therapy of respiratory tract infections. In 2019 EUCAST introduced standards for disk diffusion amoxicillin / ampicillin testing. In 2021 four laboratories did not comply with the request to test all isolates with both methods, disk diffusion and minimal inhibitory concentration (MIC) detection simultaneously. Summary results at the national level show some but not substantial difference for sets of isolates tested with one or the other method. As in previous years MIC rates are used in this discussion to enable comparison with historical data. Pneumococcal resistance rates to macrolides (28%), co-trimoxazole (14%) and tetracycline (17%) are similar to the last year rates (29%, 17% and 16%). Resistance to co-trimoxazole is showing decreasing trend (43% in 2010, 35% in 2011, 29% in 2012, 27% in 2013, 29% in 2014, 26% in 2015, 23% in 2016, 22% in 2017, 20% in 2018, 17% in 2019 and 2020, 14% in 2021). Since 2019 the change in EUCAST standards allows smaller inhibition zone for co-trimoxazole to be interpreted as S but it does not seem that this influenced susceptibility rates as the decreasing trend in co-trimoxazole resistance was recorded long before this change was introduced. Resistance of pneumococci to respiratory quinolones is still low (<1%).

In 2021 ampicillin resistance in *H.influenzae* returned to 20% (14% in 2014, 20% in 2015, 24% in 2016 and 2017, 22% in 2018, 25% in 2019, 22% in 2020). When switching to EUCAST standards we started to detect more isolates with borderline resistance mediated by modification of the target PBP molecules, which possibly leads to a slight overestimation of clinical resistance. EUCAST standards imply that even susceptible isolates need to be treated with higher doses of oral amoxicillin (3x750mg or 3x1000mg). For this reason, parenteral amoxicillin / ampicillin with or without inhibitors has categories "S" and "R", while their oral preparations can only have categories "I" and "R". Resistance to co-trimoxazole (19%) is similar to resistance rates in previous years, and resistance to ceftriaxone has not been observed.

Staphylococcus aureus is the main cause of skin and soft tissue infections and as such is also the most common cause of surgical infections. Penicillin resistance spread back in the 1940s and today only a few penicillin-susceptible isolates remain. Apart from the common resistance to penicillin and moderate rates of resistance to macrolides (17%) and clindamycin (14%), methicillin-susceptible *Staphylococcus aureus* (MSSA) strains show no significant rates of resistance to other antistaphylococcal antibiotics. Since 2021 susceptibility testing to tetracycline was introduced and resistance in MSSA was found to

be 4%. Acquired resistance to quinolones in MSSA is less than 10%, but even in in susceptible isolates only moxifloxacin is expected to be effective with standard dosing while ciprofloxacin and levofloxacin work only if used at a higher dose. Methicillin-resistant *Staphylococcus aureus* (MRSA) strains are resistant to all beta-lactam antibiotics (except newer cephalosporins, ceftaroline, and ceftobiprole), and often show cross-resistance to other classes of antibiotics. After 2008 a decreasing trend in MRSA rates was observed and the lowest rates (12%) were recorded in 2013 and 2014, but since 2015 the MRSA rate is starting to rise again, and a sudden increase was unfortunately recorded in 2020 and again in 2021 (25% in 2007, 26% in 2008, 21% in 2009, 16% in 2010, 14% in 2011, 13% in 2012, 12 % in 2013 and 2014, 14% in 2015, 16% in 2016, 15% in 2017, 16% in 2018 and 2019, 21 % in 2020, 27% in 2021). In addition, the total number of MRSA isolates has also raised (1238 in 2021, 699 in 2020, 784 in 2019). The proportion of MRSA strains with inducible resistance to clindamycin (29%) is similar to last year's values (16% in 2014, 21% in 2015, 28% in 2016, 32% in 2017, 26 % in 2018, 29% in 2019, 28% in 2020). MRSA resistance to gentamicin (13%) is the same as last year and still in line with the decreasing trend (91% in 2006, 81% in 2009, 77% in 2010, 69% in 2011, 64% in 2012, 59% in 2013, 43% in 2014, 38% in 2015, 32% in 2016, 23% in 2017, 18% in 2018 and 2019, 13% in 2020 and 2021). Resistance to linezolid and vancomycin was not observed. The share of isolates with MIC of 2.0 mg / L was 10% in 2021, 5% in 2020, 14% in 2019, 10% in 2018, 9% in 2017, 8% in 2016. g., 7% in 2015, 16% in 2014, 20% in 2013. MRSA resistance to ceftaroline is 5%, and another 9% of isolates should be treated with higher doses. In case of pneumonia, 14% of isolates are considered ceftaroline resistant. Resistance to co-trimoxazole is the same as last year (5%), and resistance to tetracycline which was introduced in 2021 is 10% and not very different from the rates seen in MSSA.

Enterococci are naturally resistant to many antibiotic classes, and almost all isolates of *Enterococcus faecium* show resistance to ampicillin. All enterococci show innate low-grade resistance to aminoglycosides, but aminoglycosides in wild-type enterococci can still be used in therapy combined with ampicillin or glycopeptides to achieve a synergistic effect. In strains highly resistant to aminoglycosides, these antibiotics cannot be used even in combination therapy. The proportion of strains with high level resistance to aminoglycosides is 24% for *E.faecalis* and 36% for *E.faecium*. Vancomycin resistance is still rare in *E. faecalis* (1%), while vancomycin resistance in *E. faecium* shows a sudden raise in line with the increasing trend observed in recent years (1% in 2012, 5% in 2013, 7 % in 2014, 15% in 2015, 17% in 2016, 16% in 2017, 18% in 2018, 32% in 2019, 27% in 2020, 45% in 2021). An increase in vancomycin resistance has been observed since 2015, when vancomycin-resistant *E. faecium* (VRE) isolates began to occur with greater frequency in various regions of Croatia, and not only in Zagreb hospitals as it was in the beginning. In 2021 along with the raise in resistance rates, the raise in total numbers of *E.faecium* was observed. In 2014 EUCAST has introduced susceptibility testing of enterococci to quinolones using norfloxacin as an indicator of susceptibility to ciprofloxacin and levofloxacin. Quinolones are intended to treat enterococcal infections only in case of uncomplicated urinary tract infections. Resistance to quinolones in *E. faecalis* (23%) and *E. faecium* (87%) is similar to the rates of previous years (22% and 75% in 2017, 22% and 84% in 2018, 22% and 85% in 2019, 23% and 87% in 2020). For uncomplicated urinary tract infections caused by *E. faecalis*, nitrofurantoin can also be used and resistance to this antibiotic is still low (1%).

Escherichia coli is the most common pathogen causing urinary tract infections (UTI) and other enterobacteriaceae are more common in complicated UTI or health care associated infections affecting different organ systems. As part of human microbiota enterobacteriaceae are frequently exposed to antibiotics and once the resistant mutants emerge they are difficult to spot and control. The number of reported *E.coli* isolates in the pandemic 2020 was significantly lower than usual, but in 2021 the number of reported

isolates is similar to the pre-epidemic period, which indicates that diagnostics for bacterial infections has recovered after being reduced at the beginning of the covid epidemic. Since the early days of surveillance, *E. coli* has shown high resistance to ampicillin, which in 2021 is 48%, similar to previous years. Amoxicillin with the addition of clavulanic acid, however, shows good efficacy because clavulanic acid successfully blocks broad-spectrum beta-lactamases and most extended-spectrum beta-lactamases ("extended spectrum beta-lactamases, ESBL"). The combination with clavulanic acid, however, limits the use of amoxicillin in high doses, which are often needed in serious systemic infections. In 2014 for the first time, EUCAST introduced different interpretation of amoxicillin/clavulanic acid susceptibility for uncomplicated UTI and for other infections. After this differentiation, resistance rates did not change significantly if interpretation for uncomplicated UTI is applied (7% in 2013 and 2014, 9% in 2015, 10% in 2016). g., 2017, 2018 and 2019, 11% in 2020, 12% in 2021) but they increased significantly after the change of standards with a slightly increasing trend in the following years, if interpretation for other infections is applied (16% in 2014 and 2015, 15% in 2016, 2017 and 2018, 16% in 2019, 19% in 2020, 22% in 2021). From 2020 EUCAST standards for enterobacteria introduce a separate interpretation of susceptibility to parenteral and oral cefuroxime, with categories "S" and "R" being applicable for oral cefuroxime which is recommended for use in uncomplicated urinary tract infections only, while parenteral cefuroxime can be used for systemic infections but only at a higher dose and therefore for parenteral cefuroxime there are only categories "I" and "R". Resistance to oral cefuroxime is similar to last year (10% in 2021, 11% in 2020), and to parenteral cefuroxime is identical to last year (10%). Resistance to third-generation cephalosporins (8% to 11%) is similar to last year's rates (7% to 9%). New cephalosporins with beta-lactamase inhibitors, ceftazidime / avibactam and ceftalozane / tazobactam show high efficiency against ESBL strains and the resistance of *E.coli* to these antibiotics is <1% and 1%, which is identical to the efficacy of carbapenems (<1% of resistant isolates) and slightly better than the efficacy of piperacillin / tazobactam (4% of resistant isolates). Resistance to ciprofloxacin is 2017 reached 20%, but since then it has stagnated and this year's rate does not differ significantly from last year's rate (14% in 2012 and 2013, 17% in 2014, 18% in 2015, 19% in 2016, 20% in 2017 and 2018, 19% in 2019, 18% in 2020, 19% in 2021). Resistance rates to co-trimoxazole (26%), gentamicin (9%), amikacin (1%), nitrofurantoin (3%), fosfomycin (1%) and nitroxoline (1%) are the same as last year's rates.

Proteus mirabilis still causes predominantly community-acquired infections and should naturally be a bacterial species well-susceptible to all beta-lactam antibiotics directed at gram-negative bacteria. Unfortunately, resistance to beta-lactam antibiotics has already reached high rates and in 2021 resistance is 46% for ampicillin, 22% for co-amoxiclav, 4% for piperacillin/tazobactam, 8% (cefepime) to 19% (cefixime) for the 3rd and 4th generation cephalosporins, which is similar to last year's rates. Resistance is the same or slightly lower than last year for new cephalosporins combinations with beta-lactamase inhibitors, ceftazidime / avibactam (1% in 2018, 2019, 2020 and 2021), ceftalozane / tazobactam (10% in 2018, 9% in 2019, 8% in 2020, 7% in 2021). Rates of resistance to ciprofloxacin (26%), gentamicin (21%), amikacin (12%) and co-trimoxazole (40%) are also similar or equal to last year. Due to their innate resistance to colistin, tigecycline and lower susceptibility to imipenem, *Proteus mirabilis* and other *Proteus* spp. could represent an increasing problem in the future, especially in urological patients and infections associated with hospital care.

Klebsiella spp. and *Enterobacter* spp. usually cause healthcare associated infections and for many years demonstrate high rates of resistance. *K.pneumoniae* has innate resistance to ampicillin but resistance to other beta-lactams is acquired due to high antibiotic exposure. Third- and fourth-generation cephalosporin resistance rates (41% for cefepime and ceftazidime to 43% for cefixime) are similar to last year (41% for cefepime to 43%

for cefixime) and still higher than in the pre-epidemic year (35% to 38% in 2019). Also, resistance to co-amoxiclav and ceftolozane / tazobactam remained high, similar to last year's rates (co-amoxiclav 38% in 2018 and 2019, 45% in 2020, 43% in 2021; ceftolozane / tazobactam 20% in 2018 and 2019, 25% in 2020 and 2021), and resistance to piperacillin / tazobactam has raised (19% in 2018, 21 % in 2019, 27% in 2020, 31% in 2021). Ceftazidime / avibactam still shows very low resistance (2% in 2018, 2019, 2020, 1% in 2021) and with its effectiveness against strains producing ESBL, AmpC beta-lactamase and a large number of carbapenemases (KPC, OXA-48), it remains the most effective beta-lactam for treatment of klebsiella infections. The number of carbapenem-resistant *K.pneumoniae* isolates reached the level visible as a percentage of resistance to imipenem and meropenem (1%) for the first time in 2014, the rates in 2019 increased to 5% and 6% and in 2020 there was a sudden increase in carbapenem resistance and rates reached 7% and 16% with an additional 8% and 2% isolates being susceptible at increased exposure ("I" category). These rates remained similar in 2021 (8% and 14% resistant and 4% and 2% susceptible with increased exposure), but the total number of *Klebsiella* isolates is higher than the previous year (5864 isolates in 2019, 4244 isolates in 2020, 5601 isolates in 2021), indicating that the spread of carbapenem-resistant klebsiellas continued. Resistance to ciprofloxacin (41%), gentamicin (31%), amikacin (6%) and co-trimoxazole (39%) shows rates similar to last year.

Enterobacter spp., *Citrobacter* spp. and *Searratia* spp. form a group of enterobacteriaceae which poses innate inducible cephalosorinases and with the exception of *Citrobacter koseri* demonstrate resistance not only to ampicillin but to co-amoxiclav and 1st generation cephalosporins as well. In 2019 *Enterobacter aerogenes* was renamed into *Klebsiella aerogenes* and this species continues to be discussed here within this group of Enterobacterales. Cefuroxime is marginally active against these bacteria and EUCAST standards do not include cefuroxime interpretation for this group of enterobacteria. Wild type isolates are susceptible to the 3rd generation cephalosporins but resistant derepressed mutants that hyperproduce AmpC cephalosporinases often emerge during therapy with these agents. The proportion of derepressed mutants resistant to third- and fourth-generation cephalosporins (10% for cefepime to 28% for cefixime) is within the limits of the rates registered in previous years (16% to 32% in 2017, 10% to 25% in 2018, 12% to 26% in 2019, 12% to 28% in 2020), and resistance to carbapenems, which became visible in 2013 (1%), remained almost the same in 2021 (1% resistant and 1% susceptible with increased exposure to imipenem and 1% resistant to meropenem, 6% resistant to ertapenem). Ceftalozan / tazobactam is primarily expected to be an advantage in the treatment of infections caused by pseudomonas and ESBL-producing enterobacteria, which are more common among *K.pneumoniae* and *E.coli* isolates than among Enterobacter group, and the ceftolozane / tazobactam resistance rate in Enterobacter group (11% in 2018 and 2019, 8% in 2020 and 2021) is similar to the rate of resistance to cefepime (10% in 2018, 12% in 2019 and 2020, 10% in 2021) and piperacillin / tazobactam (9% in 2018, 10% in 2019 and 2020, 13% in 2021). Resistance rates to ciprofloxacin (10%), gentamicin (8%), amikacin (1%) and co-trimoxazole (11%) are similar to last year.

Multiply resistant *Pseudomonas aeruginosa*, especially carbapenem resistant isolates, have been one of the biggest resistance problems in Croatia for many years. Resistance to imipenem and meropenem increased significantly in 2020 but did not continue to raise in 2021 (17% in 2018, 18% in 2019, 23% and 22% in 2020, 20% and 21% in 2021). Resistance to the new cephalosporins with an inhibitor, ceftazidime / avibactam (4% in 2018, 6% in 2019, 7% in 2020, 6% in 2021) and ceftalozane / tazobactam (4% in 2018, 6% in 2019, 7% in 2020, 5% in 2021) also did not increase further. Resistance to piperacillin / tazobactam (10% in 2019, 12% in 2020, 9% in 2021), ceftazidime (16% in 2019, 21% in 2020, 15 % in 2021) and cefepime (13% in 2019, 16% in 2020, 13% in 2021), after the increase in 2020, came back to rates similar to those in the pre-epidemic

period. Resistance to ciprofloxacin (20%) and amikacin (6%) is slightly lower than the previous year. From 2020 EUCAST standards do not include testing of *P. aeruginosa* for gentamicin because this antibiotic is not effective for pseudomonas infections. For aminoglycosides, it is generally recommended that they should be used only in combination with other antibiotics for infections outside the urinary tract. It is common knowledge that higher doses of antibiotics are used to treat pseudomonas infections, and since 2020 this is clearly stated in EUCAST standards as for pseudomonas there is no "S" category (susceptible to standard dosage) for many antibiotics (ceftazidime, cefepime, piperacillin / tazobactam, imipenem, ciprofloxacin). Colistin susceptibility testing requires the use of a broth microdilution test, which is significantly more demanding and expensive than disk diffusion testing, and therefore the rule to test all isolates with all antibiotics under surveillance in this case is modified and only multiply, in particular carbapenem resistant isolates are tested with colistin. Therefore, the data on resistance to colistin in *P.aeruginosa* cannot be compared with the rates of resistance to other antibiotics, but these data still enable the monitoring of colistin resistance in the subpopulation of multiresistant pseudomonas isolates. In 2021 this rate is significantly higher than in previous years (3% in 2019 and 2020, 8% in 2021).

Carbapenem resistance in *A. baumannii* has rapidly spread throughout Croatia since 2008 and in 2021 resistance rates to imipenem and meropenem (94%) are still extremely high and similar to the last year results. According to the EUCAST guidelines there is no sufficient evidence that acinetobacter is a good target for ampicillin/sulbactam. However, this is one of the rare antibiotics that still demonstrate *in vitro* activity against acinetobacter in Croatia, so in Croatia American standards are used to test and interpret susceptibility of acinetobacter to ampicillin / sulbactam. Resistance and susceptibility with increased exposure are still high for ampicillin / sulbactam (40% and 16% in 2018, 34% and 20% in 2019, 31% and 18% in 2020, 32% and 23% in 2021). Unfortunately, the increase in the number of A. baumannii isolates observed in the pandemic 2020 continued in 2021 (1740 isolates in 2019, 2087 isolates in 2020, 2582 isolates in 2021), which is the most noticeable indicator of the neglect to comply with standard and contact isolation precautions for multidrug-resistant bacteria during the COVID-19 epidemic. As with pseudomonas, colistin is tested only on carbapenem-resistant isolates, but since for several years such isolates constitute >90% of the total acinetobacter isolates, it can be considered that colistin is tested on almost all isolates and the rates of colistin resistance can be compared with the rates for other antibiotics. Acinetobacter resistance rates to colistin are still low (2% in 2020, 1% in 2021).

Ampicillin resistance in salmonellae exceeded 10% in 2014 (14% in 2014, 16% in 2015, 14% in 2016, 13% in 2017, 15% in 2018, 16% in 2019, 19% in 2020 and 2021). ESBL isolates are still rare among salmonellae and in 2020 resistance to ceftazidime and ceftriaxone was 3% and 2%. Resistance to co-amoxiclav (8%), co-trimoxazole (4%) and ciprofloxacin (4%) is similar to last year's rates. Until 2013 the susceptibility of salmonella to ciprofloxacin at the national level was 100%, and the resistance to nalidixic acid, which was considered to be a better indicator of a low level of resistance to quinolones, was up to 2%. Since 2014 EUCAST introduced the use of pefloxacin disk as a better indicator of susceptibility to the quinolones (ciprofloxacin) which probably influenced the recording of a ciprofloxacin resistance rate of 2% in 2014, but the increasing trend was also recorded in the years that followed (4% 2015, 3% in 2016, 4% in 2017, 2018 and 2019, 5% in 2020, 4% in 2021).

Susceptibility rates in *Campylobacter coli* and *Campylobacter jejuni* were first reported in 2013. Increasing trend of resistance to ciprofloxacin has stopped in 2019 but resistance rates are still high (52% and 50% in 2015, 60% for both species in 2016, 69% and 66% in 2017, 78% and 76% in 2018, 71% and 75% in 2019, 74% and 71% in 2020, 77% for both species in 2021). Resistance to erythromycin (1% for both species) is still low and

the increasing trend in tetracycline resistance seems to be stopped in 2020 and the rate even slightly decreased in 2021 (35% and 30% in 2017, 41% and 36% in 2018, 46% and 42% in 2019, 35% and 41% in 2020, 33% and 28% in 2021).

Four laboratories reported shigella isolates: ČK ZZJZ *Sh. flexneri* (1); RI NZZJZ *Sh. flexneri* (1), *Sh. sonnei* (3); ZG KBCSM *Sh. flexneri* (1) and ZG KIB *Sh. flexneri* (1), *Sh. sonnei* (9). Altogether 16 shigella isolates were reported in 2021.

Among gram-negative anaerobes resistance is high to penicillin (80%) and clindamycin (33%), and in gram-positive anaerobes high resistance is recorded for metronidazole (59%) and for clindamycin (15%). Resistance to co-amoxiclav, piperacillin/tazobactam and ertapenem is low (≤10%).

LEGENDA ZA TABLICE / *LEGEND TO TABLES* :

Šifra / *code*	**USTANOVE** / *CENTERS*
BJ ZZJZ	ZZJZ Bjelovarsko-bilogorske županije, Bjelovar
ČK ZZJZ	ZZJZ Međimurske županije, Čakovec
DU ZZJZ	ZZJZ Dubrovačko-neretvanske županije, Dubrovnik
GS ZZJZ	ZZJZ Ličko-senjske županije, Gospić
IG ZZJZ	ZZJZ Zagrebačke županije, Ivanić Grad
KA OB	Opća bolinica Karlovac, Karlovačka županija
KA ZZJZ	ZZJZ Karlovačke županije, Karlovac
KC ZZJZ	ZZJZ Koprivničko-križevačke županije, Koprivnica
KR ZZJZ*	ZZJZ Krapinsko-zagorske županije , Krapina
KT MAGD.	Klinika za kardiovaskularne bolesti «Magdalena», Krapinske Toplice
OG OB	Opća bolnica Ogulin, Karlovačka županija
OS KBC	Klinički bolnički centar «Osijek», Osijek
OS NZZJZ	Nastavni ZZJZ Osječko-baranjske županije, Osijek
PK OŽB	Opća županijska bolnica, Pakrac i bolnica hrvatskih veterana
PU NZZJZ	Nastavni ZZJZ Istarske županije, Pula
PŽ OŽB	Opća županijska bolnica Požega, Požeško-slavonska županija
PŽ ZZJZ	ZZJZ Požeško-slavonske županije, Požega
RI KBC	Klinički bolnički centar Rijeka, Rijeka
RI NZZJZ	Nastavni ZZJZ Primorsko-goranske županije, Rijeka
SB NZZJZ	Nastavni ZZJZ Brodsko-posavske županije, Slavonski Brod
SK ZZJZ	ZZJZ Sisačko-moslavačke županije, Sisak
ST KBC	Klinički bolnički centar Split, Split
ST NZZJZ	Nastavni ZZJZ Splitsko-dalmatinske županije, Split
ŠI ZZJZ	ZZJZ Šibensko-kninske županije, Šibenik
VK ZZJZ	ZZJZ Vukovarsko-srijemske županije, Vinkovci
VT ZZJZ	ZZJZ «Sveti Rok», Virovitičko-podravske županije, Virovitica
VŽ ZZJZ**	ZZJZ Varaždinske županije, Varaždin
ZD ZZJZ	ZZJZ Zadarska županije, Zadar
ZG KBC***	Klinički bolnički centar «Zagreb», Zagreb
ZG KBD	Klinička bolnica «Dubrava», Zagreb
ZG KBM******	Klinička bolnica «Merkur», Zagreb
ZG KBCSM*******	Klinički bolnički centar «Sestre milosrdnice», Zagreb
ZG KZT	Klinika za traumatologiju, Zagreb
ZG KIB	Klinika za infektivne bolesti «Dr. F. Mihaljević», Zagreb
ZG LAB PLUS	Poliklinika LabPlus, Zagreb
ZG NZZJZ	Nastavni ZZJZ grada Zagreba, Zagreb
ZG HZJZ	Hrvatski zavod za javno zdravstvo, Zagreb
ZG KDB	Klinika za dječje bolesti Zagreb, Zagreb
ZG KBSD	Klinička bolnica «Sveti Duh», Zagreb

* uključuje podatke i za: Opću bolnicu Zabok

** uključuje podatke i za: Bolnicu za plućne bolesti i TBC, Klenovnik

*** uključuje podatke i za: Kliniku za plućne bolesti "Jordanovac", Zagreb

**** uključuje podatke i za: Sveučilišnu Kliniku za dijabetes, endokrinologiju i bolesti metabolizma "Vuk Vrhovac", Zagreb

***** uključuje podatke i za: Institut za tumore, Zagreb

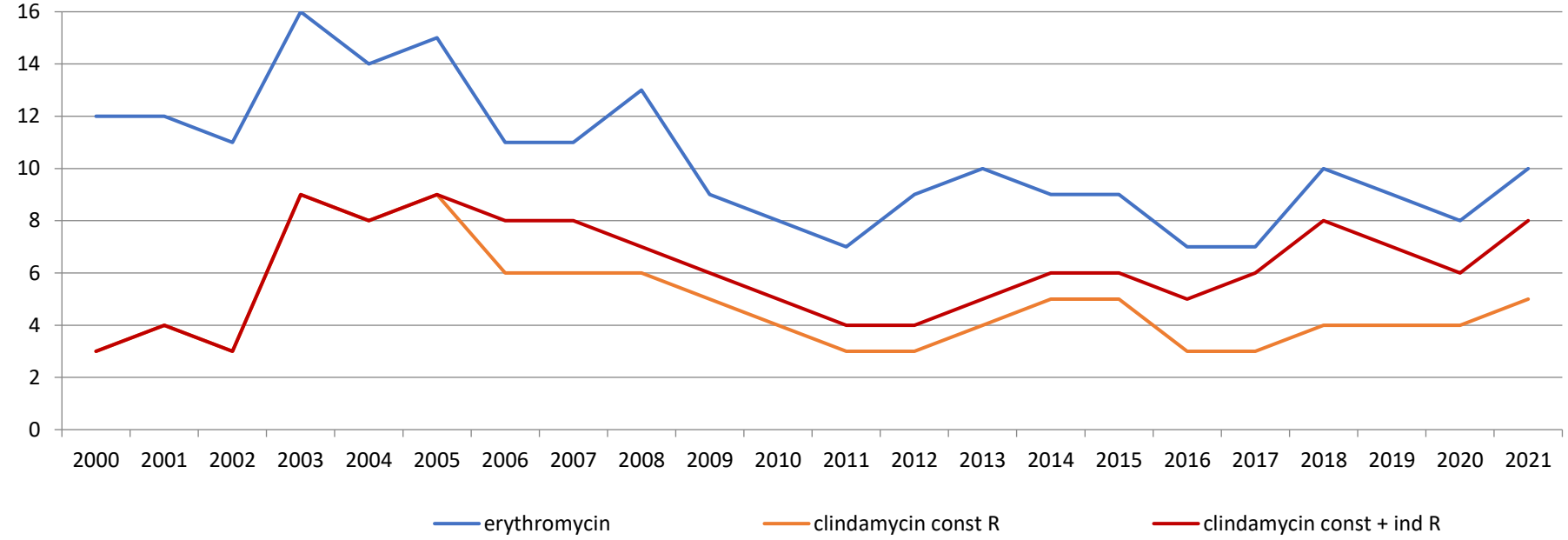
ANTIBIOTICI / *ANTIBIOTICS*:

P $_{\textbf{parenteral}}$	*penicillin parenteral*
P $_{\textbf{oral}}$	*penicillin oral*
AMP	*ampicillin*
AMP $_{\textbf{parenteral}}$	*ampicillin parenteral*
AMX $_{\textbf{oral}}$	*amoxicillin oral*
AMC	*amoxicillin + clavulanic acid*
AMC $_{\textbf{u}}$	*amoxicillin + clavulanic acid* $_{\textbf{uncomplicated urinary tract infection}}$
SAM	*ampicillin + sulbactam*
FOX	*cefoxitin*
CN	*cefalexin (I. gen. cephalosporins)*
CXM	*cefuroxime (II. gen. cephalosporins)*
CXM $_{\textbf{parenteral}}$	*cefuroxime parenteral*
CXM $_{\textbf{oral}}$	*cefuroxime oral*
CAZ	*ceftazidime (III. gen. cephalosporins)*
CRO	*ceftriaxone (III. gen. cephalosporins)*
CTB	*ceftibuten (III. gen. cephalosporins)*
CFM	*cefixime (III. gen. cephalosporins)*
CFEP	*cefepime (IV. gen. cephalosporins)*
CZA	*ceftazidime/avibactam*
C/T	*ceftolozane/tazobactam*
CPT	*ceftaroline*
PTZ	*piperacillin/tazobactam*
ERT	*ertapenem*
IMP	*imipenem*
MER	*meropenem*
E	*erythromycin*
AZM	*azithromycin*
CLR	*clarythromycin*
CC	*clindamycin*
TE	*tetracycline*
SXT	*co-trimoxazole*
NF	*nitrofurantoin*
VA	*vancomycin*
RIF	*rifampicin*
CIP	*ciprofloxacin*
NOR	*norfloxacin*
NOR $_{\textbf{screen}}$	*norfloxacin* -indikator rezistencije na kinolone */quinolone resistance indicator*
GM	*gentamicin*
GM30	*gentamicin "high level resistance"*
NT	*netilmicin*
AN	*amikacin*
MUP	*mupirocin*
MTZ	*metronidazole*
MOX	*moxifloxacin*
LZD	*linezolid*
NA	*nalidixic acid*
COL	*colistin*
TGC	*tigecycline*
FOT	*fosfomycin*
NIB	*nitroxolin*

UK = ukupan broj izolata / *total number of isolates*
No = broj izolata / *number of isolates*
I% = % osjetljivi uz povećanu izloženost / % *susceptible, increased exposure*
R% = % rezistentni / % *resistant*

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*

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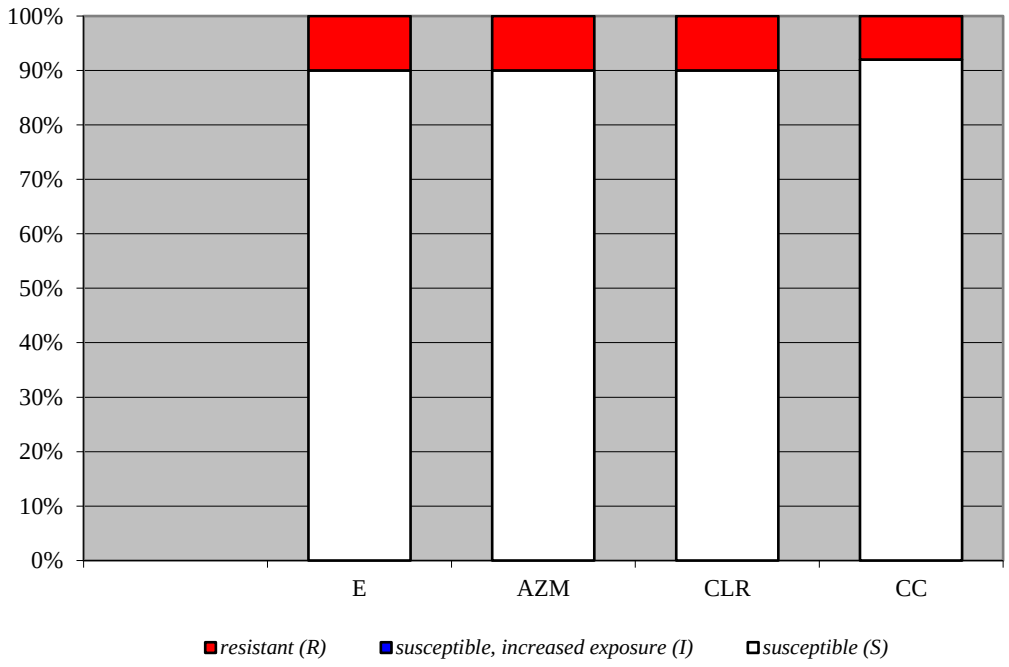
Beta-hemolitički streptokok grupe A / *Group A streptococcus*

rezistencija na antibiotike u razdoblju od 1.01.- 31.12.2021., zbirni prikaz izolata iz 39 centara u RH /
antibiotic resistance for the period 1.01. - 31.12.2021, summary results for the isolates from 39 centers in Croatia

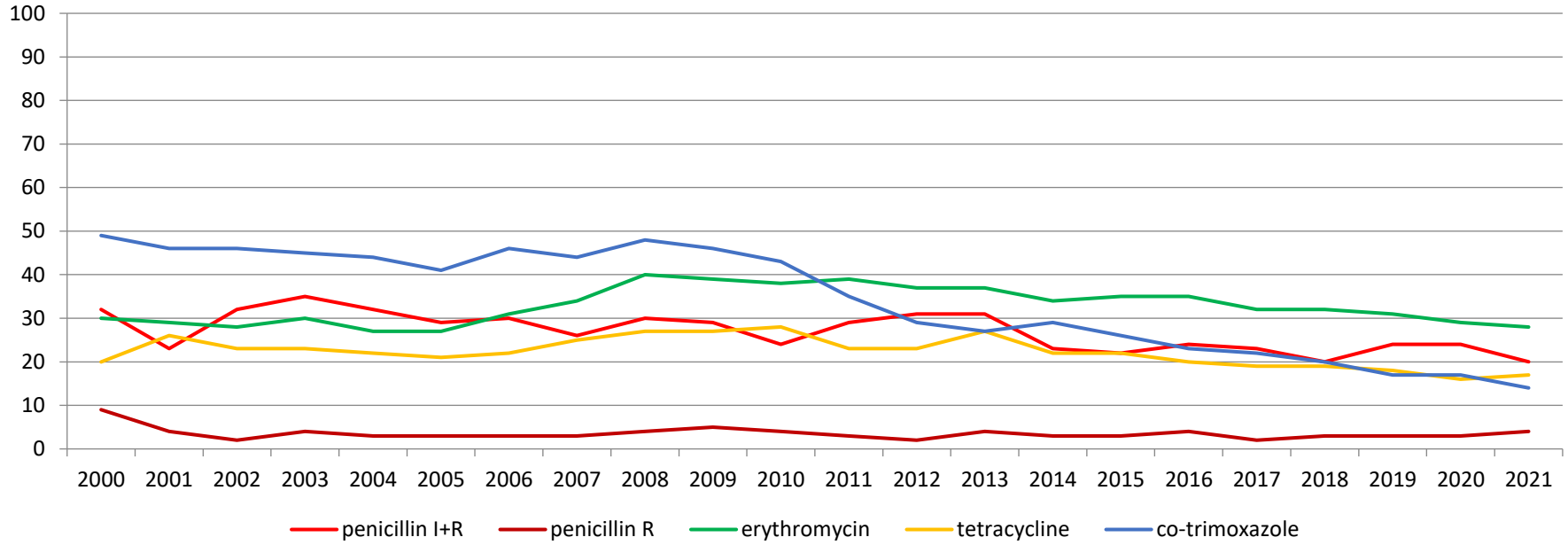
ANTIBIOTIK / *ANTIBIOTIC*	**Broj izolata** / *No. of isolates*	**% rezistentnih (R) (% osjetljivih uz povećanu izloženost (I)) izolata** / *% of resistant (R) (% of susceptible, increased exposure (I)) isolates*	**Raspon lokalnih rezultata*** / *Range of local results**
Erythromycin	2 570	10 (0)	0 (0) - 21 (0)
Azithromycin	2 570	10 (0)	0 (0) - 21 (0)
Clarythromycin	2 570	10 (0)	0 (0) - 21 (0)
Clindamycin	2 568	8 (0)	0 (0) - 18 (0)
constitutive		5	0 - 12
inducible		3	0 - 6

*rezultati centara s malim brojem izolata (<30) nisu uzeti u obzir /
results from the centers with small number of isolates (<30) were not taken into consideration



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*

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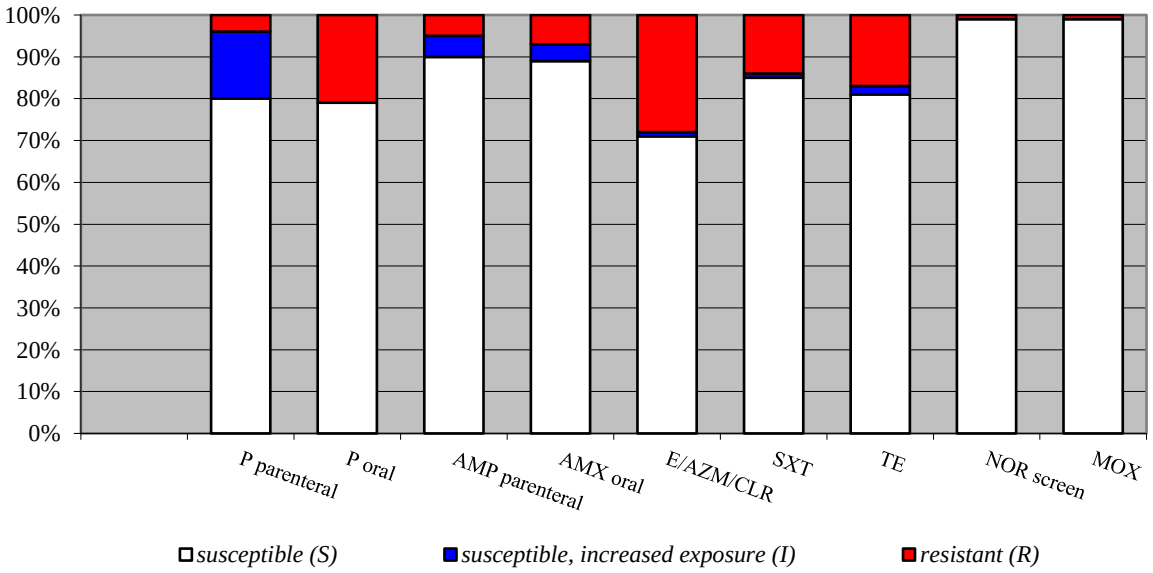
Streptococcus pneumoniae

rezistencija na antibiotike u razdoblju od 1.10.- 31.12.2021.,
zbirni prikaz izolata iz 39 centara u RH /
antibiotic resistance for the period 1.10. - 31.12.2021,
summary results for the isolates from 39 centers in Croatia

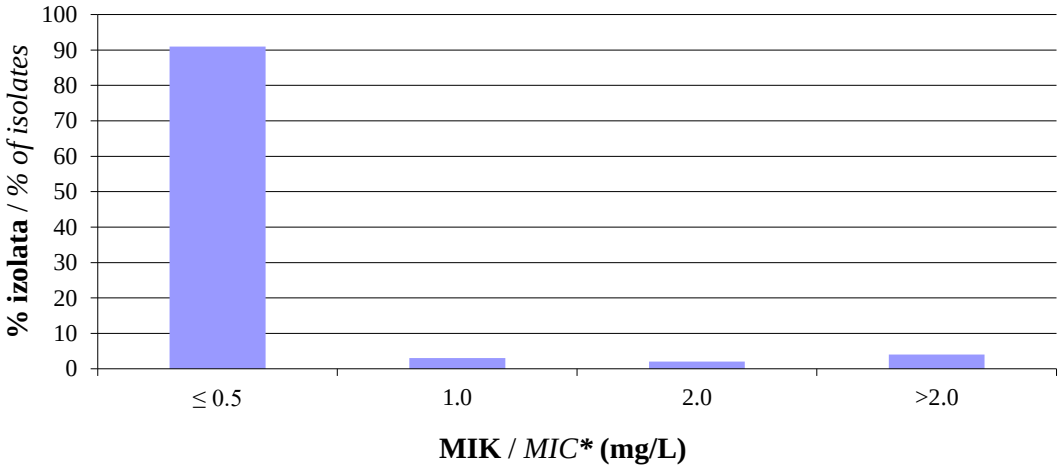
ANTIBIOTIK / *ANTIBIOTIC*	**Broj izolata** / *No. of isolates*	**% rezistentnih (R) (% osjetljivih uz povećanu izloženost (I)) izolata** / *% of resistant (R) (% of susceptible, increased exposure (I)) isolates*	**Raspon lokalnih rezultata*** / *Range of local results**
Penicillin $_{\text{parenteral}}$	1 135	4 (16)	0 (0) - 8 (4)
Penicilin $_{\text{oral}}$	1 135	21 (0)	4 (0) - 53 (0)
Ampicillin $_{\text{parenteral}}$	1 133	5 (5)	0 (0) - 21 (2)
Amoxicillin $_{\text{oral}}$	1 117	7 (4)	0 (0) - 22 (0)
Erythromycin/Azithromycin/ Clarythromycin	1 140	28 (1)	0 (0) - 49 (12)
Co-trimoxazole	1 139	14 (1)	0 (0) - 49 (12)
Tetracycline	1 010	17 (2)	0 (0) - 30(0)
Norfloxacin $_{\text{screen}}$	1 106	1 (0)	0 (0) - 13 (0)
Moxifloxacin	1 102	1 (0)	0 (0) - 4 (0)

* rezultati centara s malim brojem izolata (<30) nisu uzeti u obzir /
results from the centers with small number of isolates (<30) were not taken into consideration



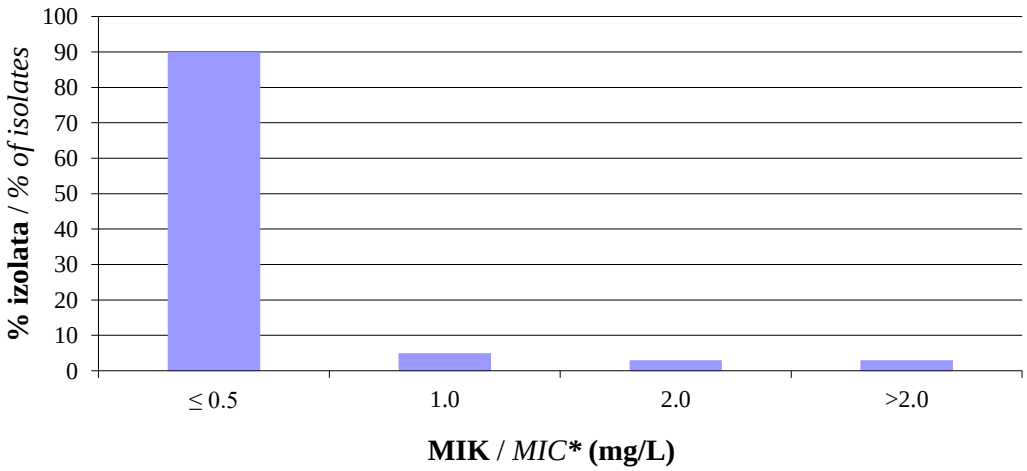
Streptococcus pneumoniae

Distribucija MIK-ova penicilina, (1 116 *S. pneumoniae* izolata) /
Penicillin MIC distribution, (1 116 S. pneumoniae isolates), 1.10. – 31.12.2021.



*MIK = minimalna inhibitorna koncentracija / *MIC = minimal inhibitory concentration*

Distribucija MIK-ova ampicilina, (1 022 *S. pneumoniae* izolata) /
Ampicillin MIC distribution, (1 022 S. pneumoniae isolates), 1.10. – 31.12.2021.



*MIK = minimalna inhibitorna koncentracija / *MIC = minimal inhibitory concentration*

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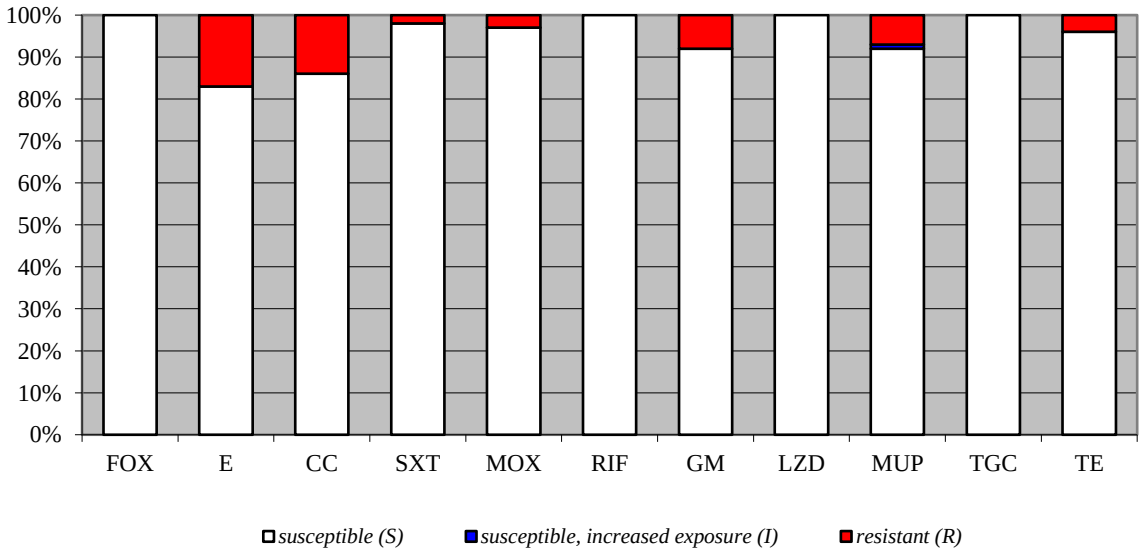
Staphylococcus aureus / MSSA

rezistencija na antibiotike u razdoblju od 1.10.- 31.12.2021.,
zbirni prikaz izolata iz 39 centara u RH /
antibiotic resistance for the period 1.10. - 31.12.2021,
summary results for the isolates from 39 centers in Croatia

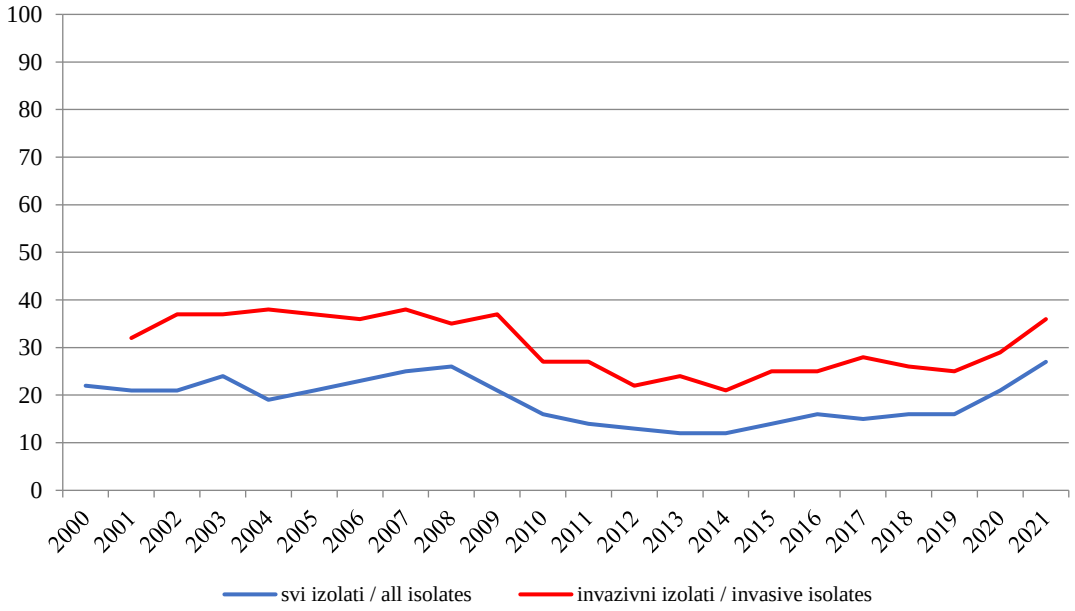
ANTIBIOTIK / *ANTIBIOTIC*	**Broj izolata** / *No. of isolates*	**% rezistentnih (R) (% osjetljivih uz povećanu izloženost (I)) izolata** / *% of resistant (R) (% of susceptible, increased exposure (I)) isolates*	**Raspon lokalnih rezultata*** / *Range of local results**
Cefoxitin/ Methicillin	3 347	0 (0)	0 (0) - 0 (0)
Erythromycin	3 303	17 (0)	4 (0) - 28 (0)
Clindamycin	3 303	14 (0)	5 (0) – 28 (8)
constitutive		8	0 - 25
inducible		6	0 - 23
Co-trimoxazole	3 305	2 (0)	0 (0) – 9 (0)
Moxifloxacin	3 122	3 (0)	0 (0) - 10 (0)
Rifampicin	3 168	0 (0)	0 (0) - 7 (0)
Gentamicin	3 299	8 (0)	0 (0) - 45 (0)
Linezolid	3 155	0 (0)	0 (0) - 0 (0)
Mupirocin	3 190	7 (1)	0 (0) - 25 (0)
Tigecycline	2 980	0 (0)	0 (0) – 6 (0)
Tetracycline	2 756	4 (0)	0 (0) - 14 (0)

*rezultati centara s malim brojem izolata (<30) nisu uzeti u obzir / *results from the centers with small number of isolates (<30) were not taken into consideration*

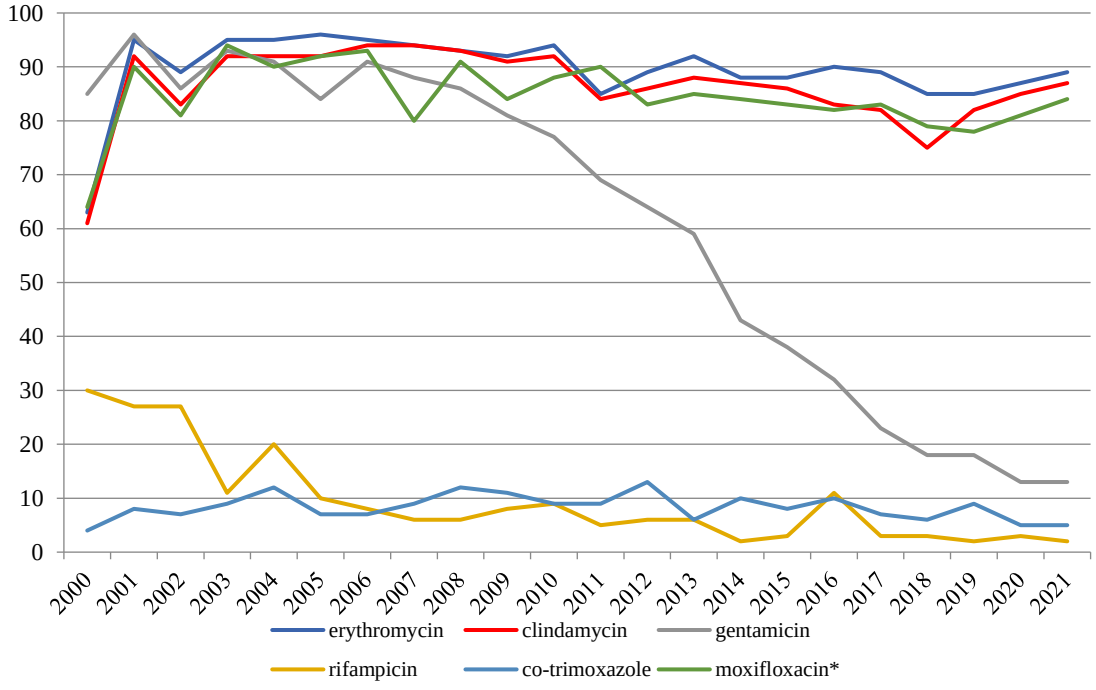


Staphylococcus aureus / MRSA

Methicillin resistant *Staphylococcus aureus* (MRSA) – stope / *rates*, 2000. - 2021.



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



* do 2019. godine testiran ciprofloxacin / ciprofloxacin tested by 2019

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Staphylococcus aureus / MRSA

rezistencija na antibiotike u razdoblju od 1.10. - 31.12.2021.,
zbirni prikaz izolata iz 39 centara u RH /
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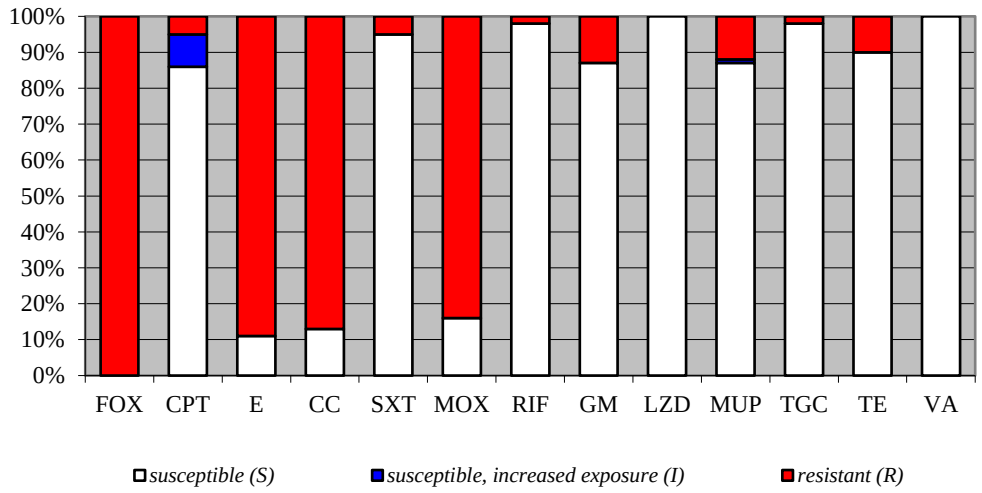
ANTIBIOTIK / *ANTIBIOTIC*	**Broj izolata** / *No. of isolates*	**% rezistentnih (R) (% osjetljivih uz povećanu izloženost (I)) izolata** / *% of resistant (R) (% of susceptible, increased exposure (I)) isolates*	**Raspon lokalnih rezultata*** / *Range of local results**
Cefoxitin/ Methicillin	1 238	100 (0)	100 (0) - 100 (0)
Ceftaroline	1 022	5 (9)	0 (0) - 13 (1)
Erythromycin	1 225	89 (0)	73 (0) - 96 (0)
Clindamycin	1 226	87 (0)	87 (0) - 96 (0)
constitutive		57	6 - 88
inducible		29	0 - 89
Co-trimoxazole	1 228	5 (0)	0 (0) - 6 (0)
Moxifloxacin	1 176	84 (0)	60 (0) - 97 (0)
Rifampicin	1 189	2 (0)	0 (0) - 7 (0)
Gentamicin	1 226	13 (0)	0 (0) - 36 (0)
Linezolid	1 194	0 (0)	0 (0) - 0 (0)
Mupirocin	1 181	12 (1)	3 (0) - 64 (0)
Tigecycline	1 143	2 (0)	0 (0) - 9 (0)
Tetracycline	1 067	10 (0)	3 (0) - 25 (0)
Vankomicin	1 044	0 (0)	0 (0) - 0 (0)

*rezultati centara s malim brojem izolata (<30) nisu uzeti u obzir /
results from the centers with small number of isolates (<30) were not taken into consideration



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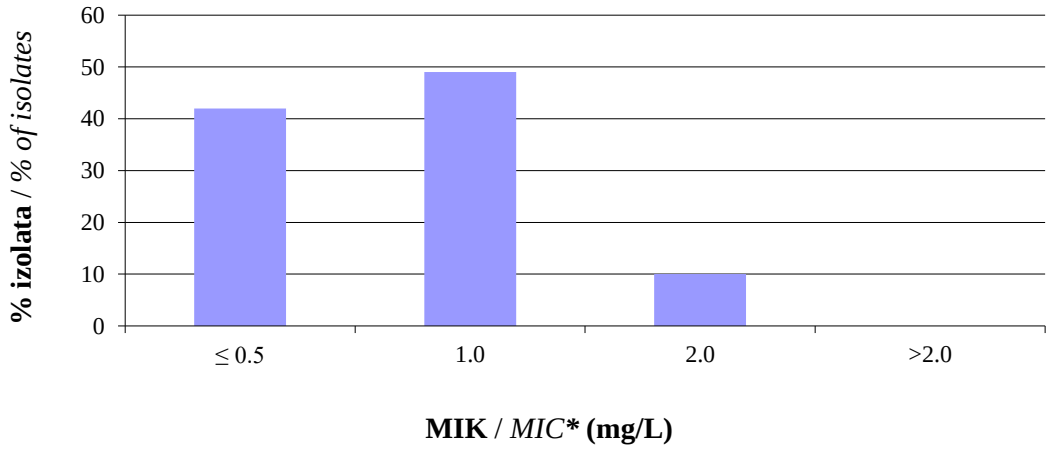
Staphylococcus aureus / MRSA

Distribucija MIK-ova vankomicina, (1135 MRSA izolata) /
Vancomycin MIC distribution, (1135 MRSA isolates), 1.10. – 31.12.2021.



*MIK = minimalna inhibitorna koncentracija / *MIC = minimal inhibitory concentration*

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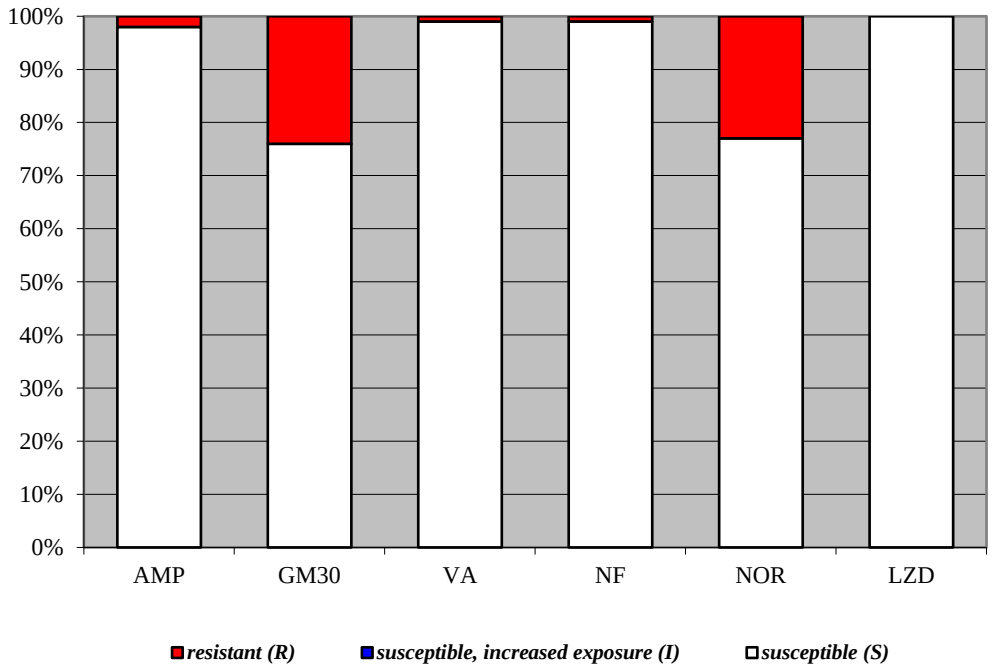
Enterococcus faecalis

rezistencija na antibiotike u razdoblju od 1.10. - 31.12.2021.,
zbirni prikaz izolata iz 39centara u RH /
antibiotic resistance for the period 1.10. - 31.12.2021,
summary results for the isolates from 39 centers in Croatia

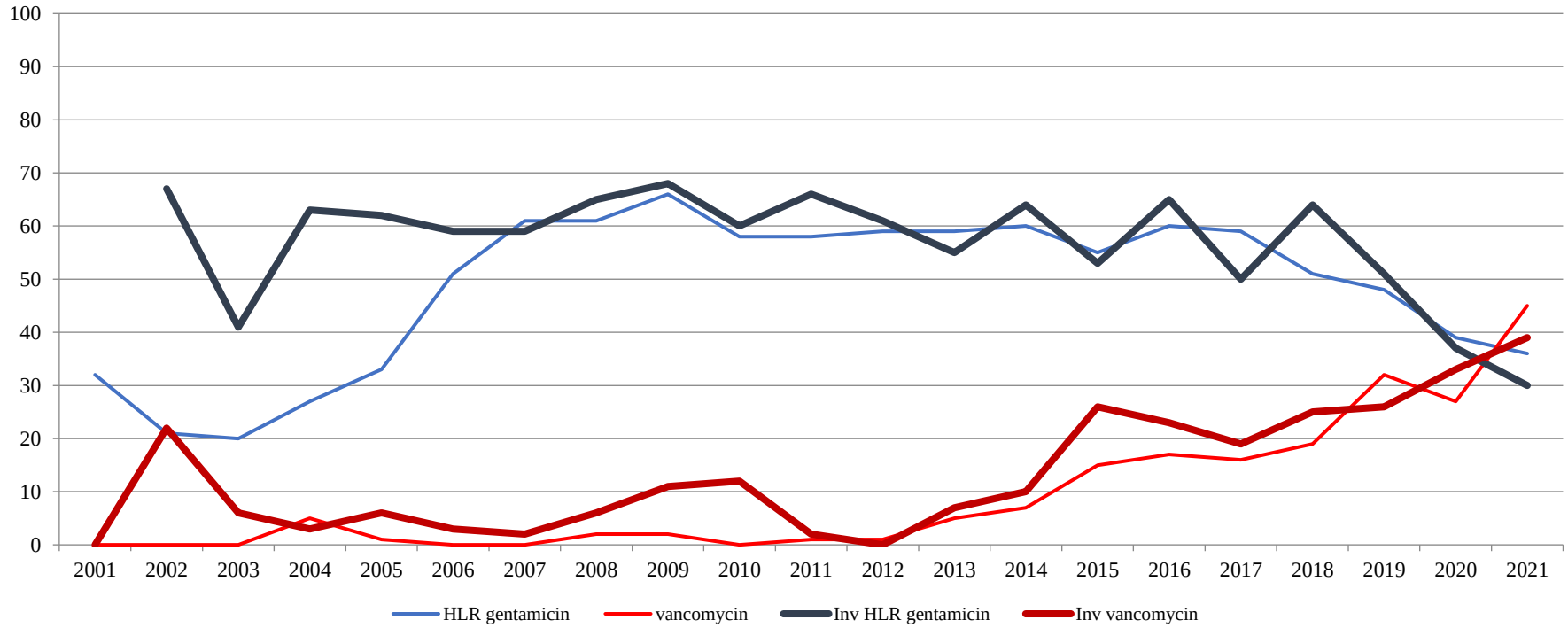
ANTIBIOTIK / *ANTIBIOTIC*	**Broj izolata** / *No. of isolates*	**% rezistentnih (R) (% osjetljivih uz povećanu izloženost (I)) izolata** / *% of resistant (R) (% of susceptible, increased exposure (I)) isolates*	**Raspon lokalnih rezultata*** / *Range of local results**
Ampicillin	5 419	2 (0)	0 (0) - 36 (0)
Gentamicin	5 357	24 (0)	2 (0) - 47 (0)
Vancomycin	5 421	1 (0)	0 (0) - 6 (0)
Nitrofurantoin	5 331	1 (0)	0 (0) - 20 (0)
Norfloxacin $_{\text{screem}}$	5 286	23 (0)	0 (0) - 85 (0)
Linezolid	4 967	0 (0)	0 (0) -2 (0)

*rezultati centara s malim brojem izolata (<30) nisu uzeti u obzir /
results from the centers with small number of isolates (<30) were not taken into consideration



Enterococcus faecium

rezistencija na antibiotike u RH / *resistance to antibiotics in Croatia,* 2001. - 2021.



HLR gentamicin = visoka rezistencija na gentamicin / *high level gentamicin resistance*; Inv = invazivni izolati / *invasive isolates*

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Enterococcus faecium

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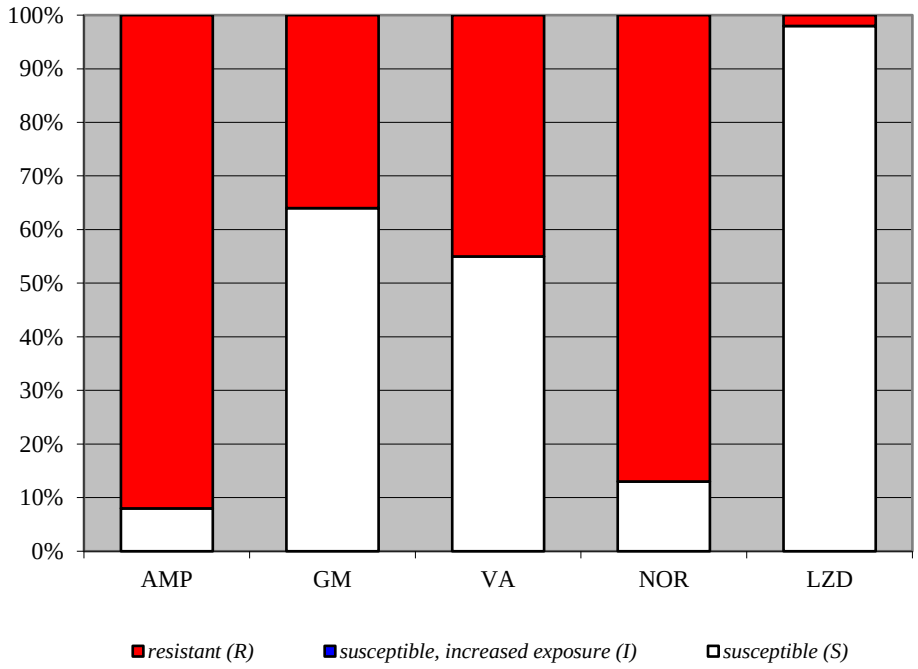
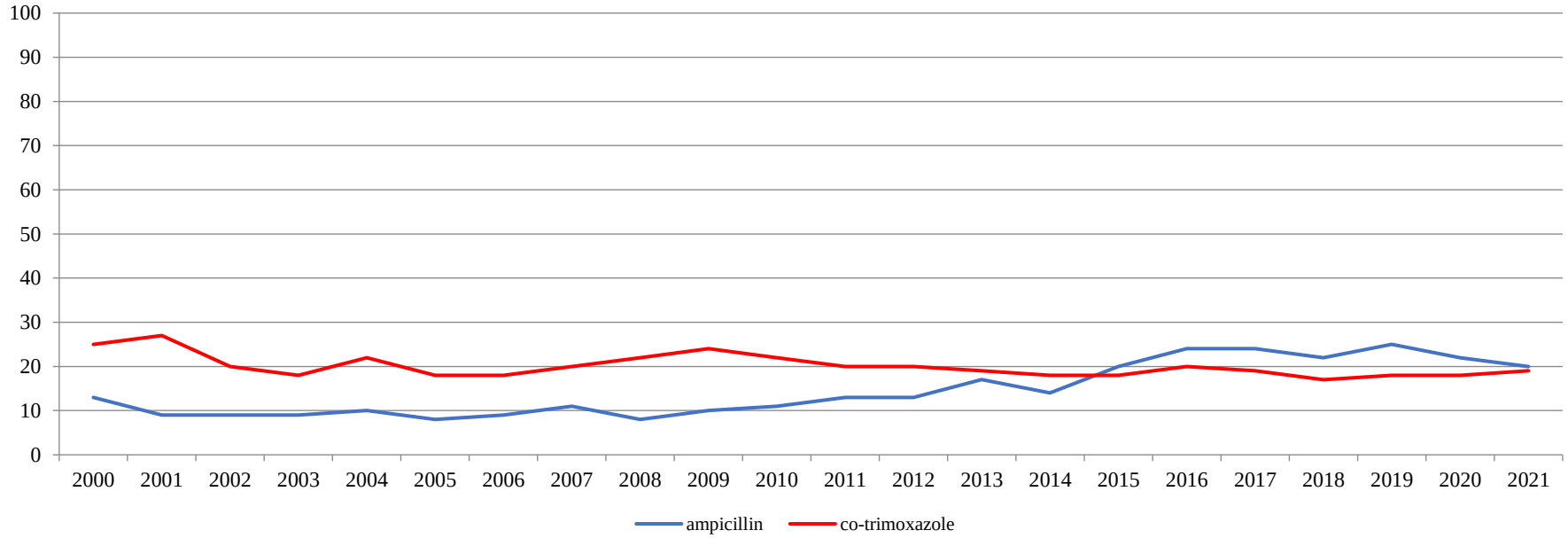
Ampicillin	1 242	92 (0)	36 (0) - 100 (0)
Gentamicin	1 142	36 (0)	7 (0) - 66 (0)
Vancomycin	1 270	45 (0)	0 (0) - 87 (0)
Norfloxacin	1 134	87 (0)	23 (0) - 97 (0)
Linezolid	1 230	2 (0)	0 (0) – 3 (0)

*rezultati centara s malim brojem izolata (<30) nisu uzeti u obzir /
results from the centers with small number of isolates (<30) were not taken into consideration



Haemophilus influenzae

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



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Haemophilus influenzae

rezistencija na antibiotike u razdoblju od 1.10. - 31.12.2021.,
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ANTIBIOTIK / *ANTIBIOTIC*	**Broj izolata** / *No. of isolates*	**% rezistentnih (R) (% osjetljivih uz povećanu izloženost (I)) izolata** / *% of resistant (R) (% of susceptible, increased exposure (I)) isolates*	**Raspon lokalnih rezultata*** / *Range of local results**
Ampicillin parenteral	942	20 (0)	0 (0) - 63 (0)
Amoxicillin oral	942	20 (80)	0 (100) – 63 (37)
Amoxicillin + clav. acid parenteral	932	4 (0)	0 (0) - 17 (0)
Amoxicillin + clav. acid oral	932	4 (96)	0 (100) – 17 (83)
Cefuroxime parenteral	890	8 (5)	0 (0) - 26 (3)
Cefuroxime oral	938	8 (92)	0 (100) - 22 (78)
Ceftriaxone	850	0 (0)	0 (0) - 8 (0)
Co-trimoxazole	941	19 (3)	0 (0) - 35 (6)

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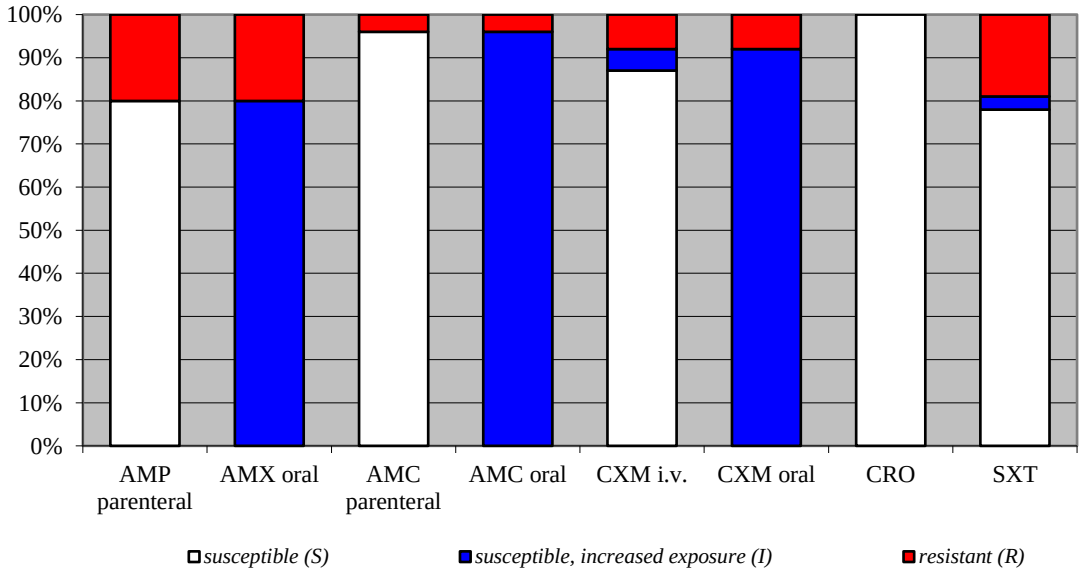
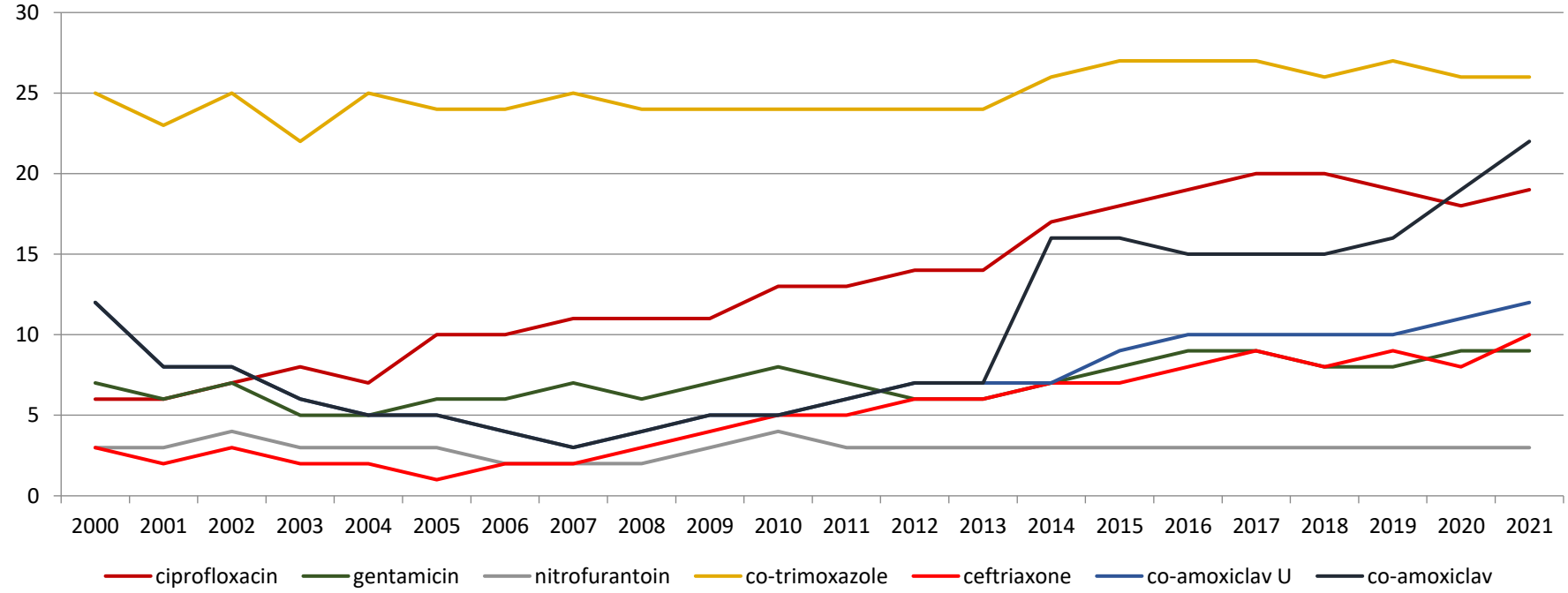


Escherichia coli

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



co-amoxiclav U = za nekompliciranе urinarne infekcije / for uncomplicated urinary tract infections

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Escherichia coli

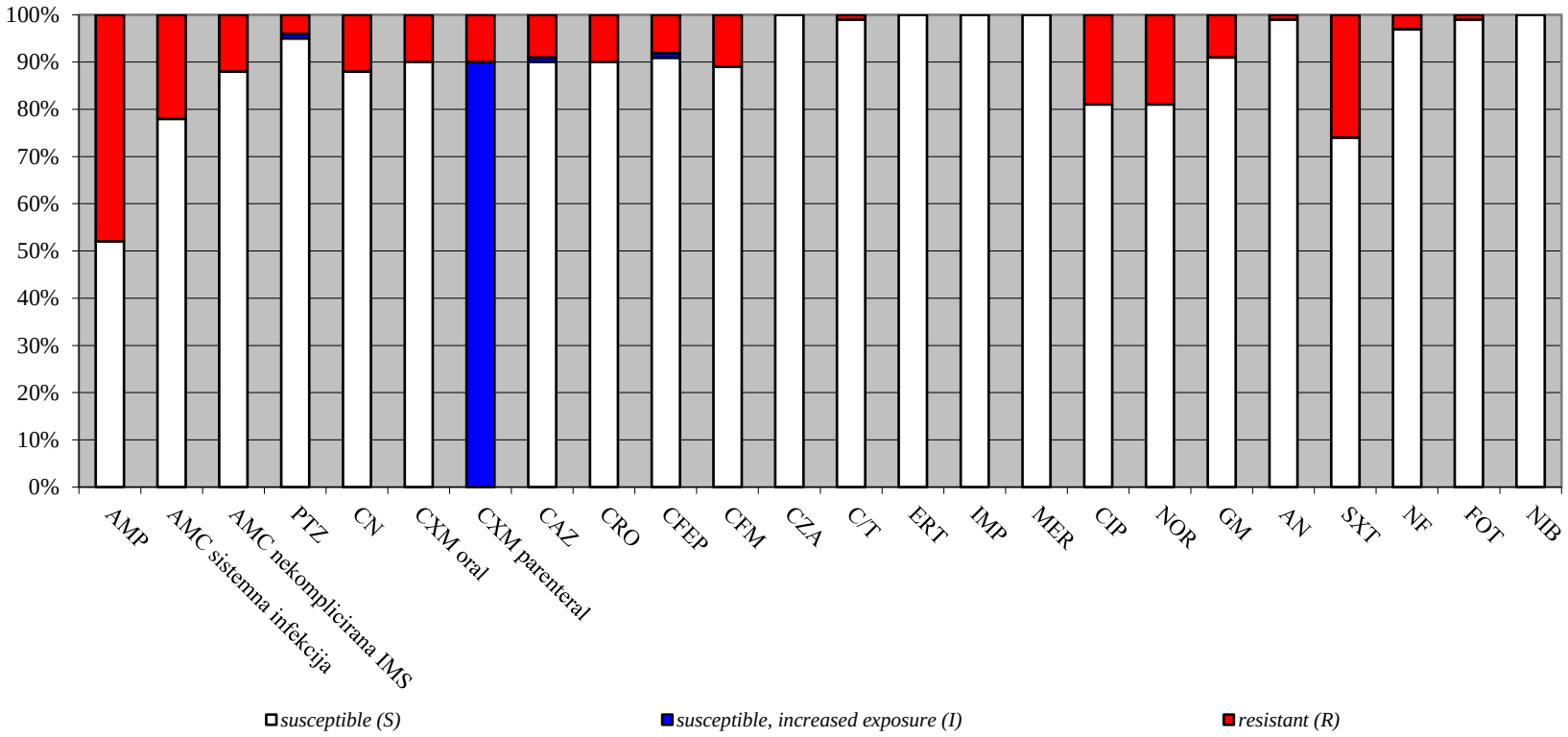
rezistencija na antibiotike u razdoblju od 1.10. - 31.12.2021.,
zbirni prikaz izolata iz 39 centara u RH /
antibiotic resistance for the period 1.10. - 31.12.2021,
summary results for the isolates from 39 centers in Croatia

ANTIBIOTIK / *ANTIBIOTIC*	**Broj izolata** / *No. of isolates*	**% rezistentnih (R) (% osjetljivih uz povećanu izloženost (I)) izolata** / *% of resistant (R) (% of susceptible, increased exposure (I)) isolates*	**Raspon lokalnih rezultata*** / *Range of local results**
Ampicillin	18 825	48 (0)	36 (0) - 54 (0)
Amoxicillin + clav. acid sistemna infekcija	18 306	22 (0)	7 (0) - 55 (0)
Amoxicillin + clav. acid nekomplicirana IMS	18 717	12 (0)	4 (0) - 21 (0)
Piperacillin + tazobactam	17 912	4 (1)	0 (0) - 13 (0)
Cephalexin	18 160	12 (0)	6 (0) - 22 (0)
Cefuroxime oral	18 773	10 (0)	4 (0) - 20 (0)
Cefuroxime parenteral	18 346	10 (90)	0 (100) – 20 (86)
Ceftazidime	18 457	9 (1)	0 (0) - 22 (5)
Ceftriaxone	18 461	10 (0)	0 (0) - 27 (4)
Cefepime	17 921	8 (1)	0 (0) – 20 (1)
Cefixime	18 482	11 (0)	4 (0) – 36 (0)
Ceftazidime + avibactam	16 483	0 (0)	0 (0) – 3 (0)
Ceftolozane + tazobactam	16 407	1 (0)	0 (0) – 4 (0)
Ertapenem	17 919	0 (0)	0 (0) - 1 (0)
Imipenem	17 915	0 (0)	0 (0) - 0 (1)
Meropenem	17 918	0 (0)	0 (0) - 1 (0)
Ciprofloxacin	18 444	19 (0)	9 (0) - 39 (0)
Norfloxacin	18 732	19 (0)	0 (0) - 39 (0)
Gentamicin	18 811	9 (0)	3 (0) - 16 (0)
Amikacin	18 385	1 (0)	0 (0) - 8 (0)
Co-trimoxazole	18 809	26 (0)	10 (0) - 34 (0)
Nitrofurantoin	18 662	3 (0)	0 (0) - 20 (0)
Fosfomycin oral	18 288	1 (0)	0 (0) - 9 (0)
Nitroxolin	15 462	0 (0)	0 (0) - 3 (0)

*rezultati centara s malim brojem izolata (<30) nisu uzeti u obzir /
results from the centers with small number of isolates (<30) were not taken

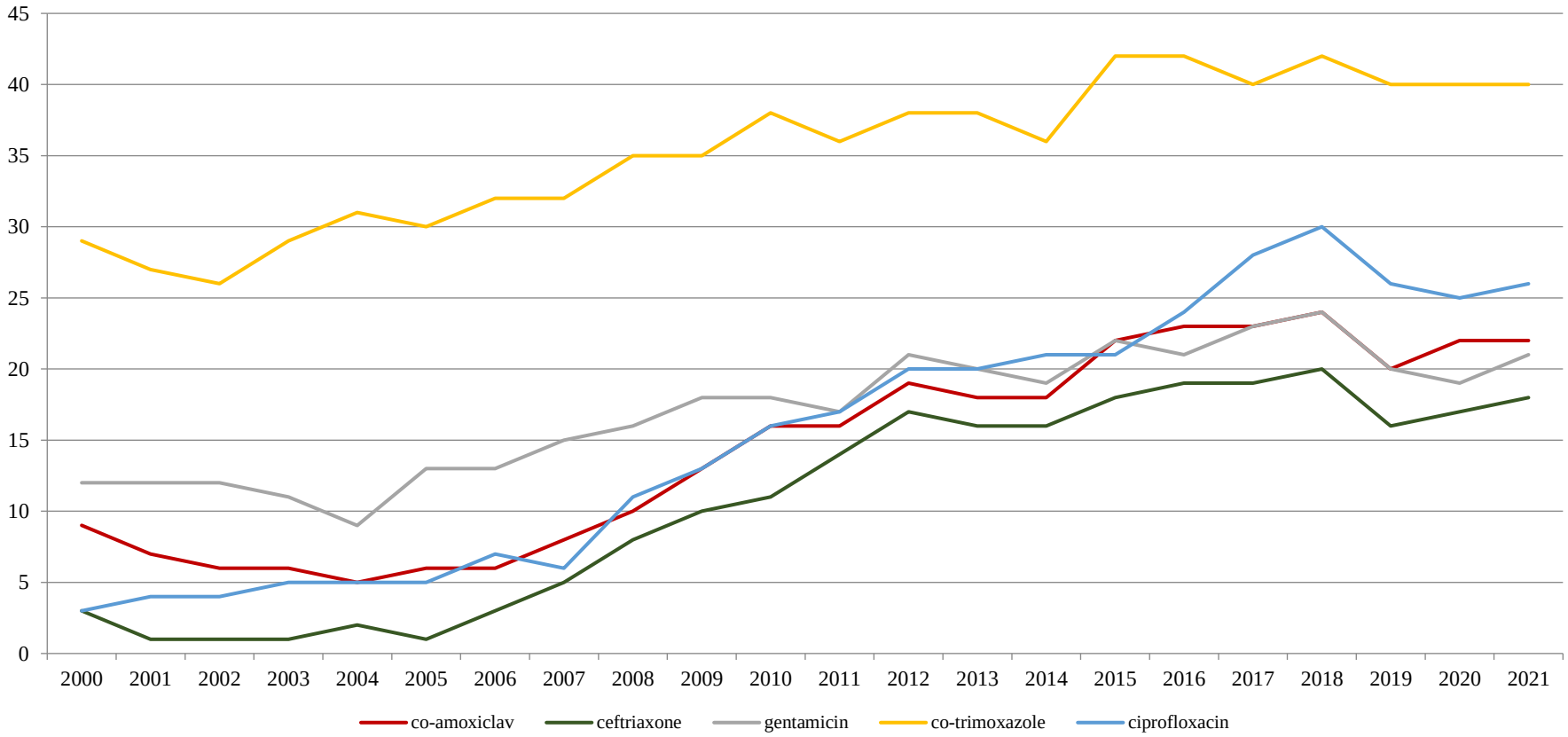
Escherichia coli

osjetljivost na antibiotike u RH / *sensitivity to antibiotics in Croatia*, 1.10. – 31.12.2021



Proteus mirabilis

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



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Croatian Committee for Antibiotic Resistance Surveillance

Proteus mirabilis

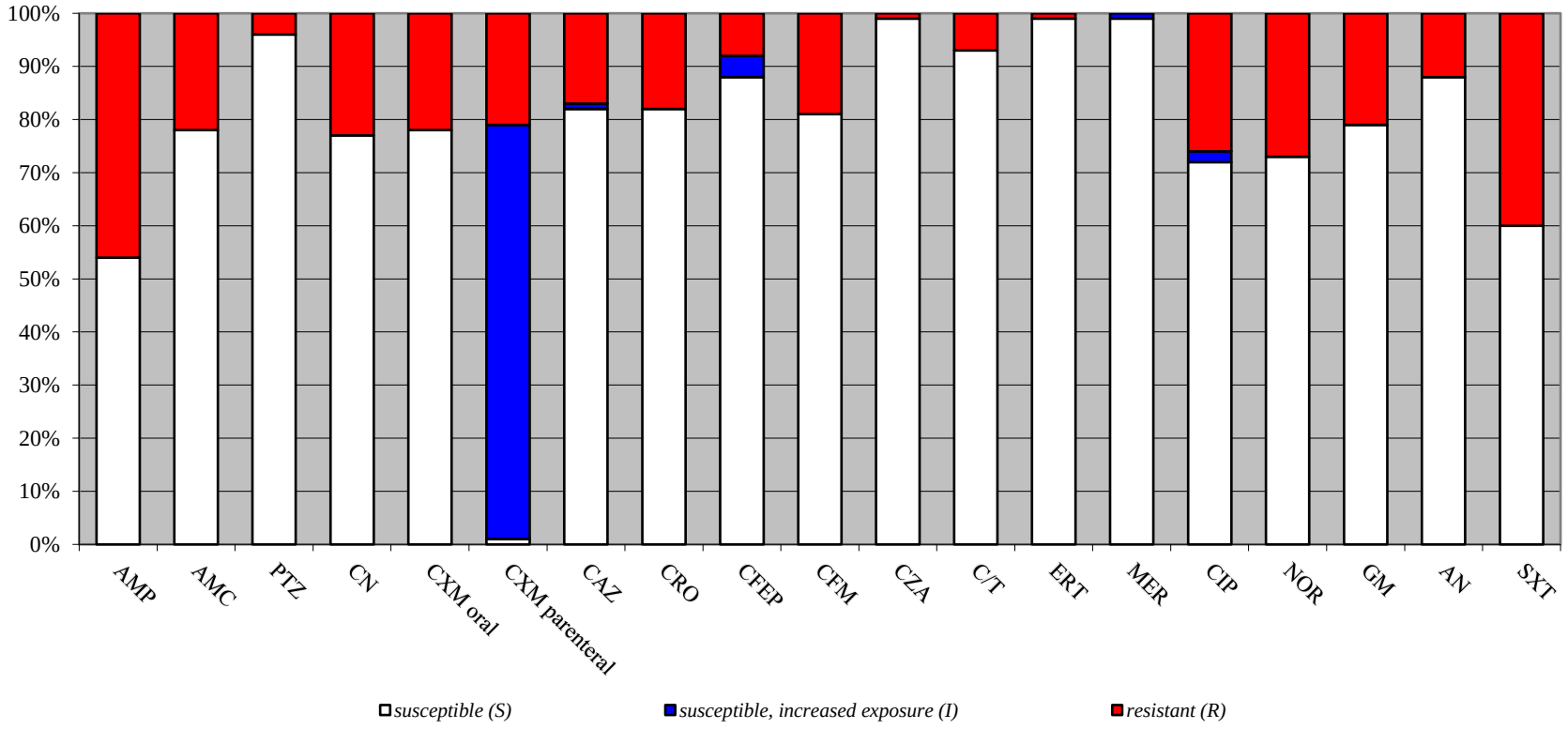
rezistencija na antibiotike u razdoblju od 1.10. - 31.12.2021., zbirni prikaz izolata iz 39 centara u RH /
antibiotic resistance for the period 1.10. - 31.12.2021, summary results for the *isolates from 39 centers in Croatia*

ANTIBIOTIK / *ANTIBIOTIC*	**Broj izolata** / *No. of isolates*	**% rezistentnih (R) (% osjetljivih uz povećanu izloženost (I)) izolata** / *% of resistant (R) (% of susceptible, increased exposure (I)) isolates*	**Raspon lokalnih rezultata*** / *Range of local results**
Ampicillin	3 773	46 (0)	17 (0) - 73 (0)
Amoxicillin + clav. acid	3 789	22 (0)	3 (0) - 61 (0)
Piperacillin + tazobactam	3 639	4 (0)	0 (0) - 28 (0)
Cephalexin	3 622	23 (0)	7 (0) - 59 (0)
Cefuroxime $_{\text{oral}}$	3 750	22 (0)	5 (0) - 59 (0)
Cefuroxime $_{\text{parenteral}}$	3 750	21 (78)	0 (0) – 59 (41)
Ceftazidime	3 706	17 (1)	0 (0) - 57 (0)
Ceftriaxone	3 708	18 (0)	2 (0) – 58 (0)
Cefepime	3 637	8 (4)	1 (0) - 25 (2)
Cefixime	3 649	19 (0)	3 (0) - 58 (0)
Ceftazidime + avibactam	3 377	1 (0)	0 (0) – 7 (0)
Ceftolozane + tazobactam	3 311	7 (0)	0 (0) – 32 (0)
Ertapenem	3 690	1 (0)	0 (0) – 3 (0)
Meropenem	3 673	0 (1)	0 (0) – 3 (0)
Ciprofloxacin	3 676	26 (2)	5 (37) – 68 (0)
Norfloxacin	3 649	27 (0)	6 (0) – 68 (0)
Gentamicin	3 769	21 (0)	6 (0) – 56 (0)
Amikacin	3 665	12 (0)	1 (0) – 51 (0)
Co-trimoxazole	3 730	40 (0)	17 (0) – 66 (0)

*rezultati centara s malim brojem izolata (<30) nisu uzeti u obzir /
results from the centers with small number of isolates (<30) were not taken into consideration

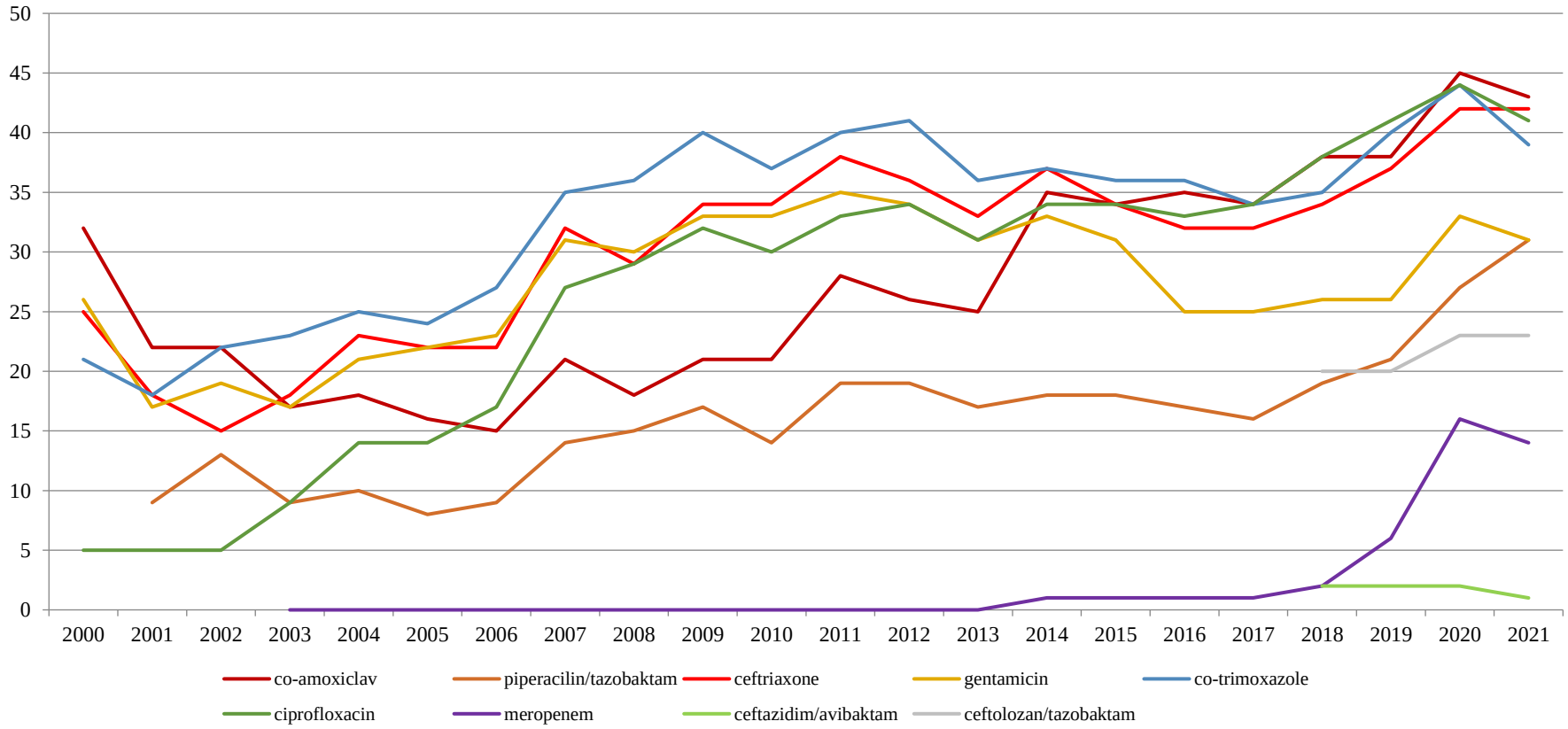
Proteus mirabilis

osjetljivost na antibiotike u RH / *sensitivity to antibiotics in Croatia*, 1.10. – 31.12.2021.



Klebsiella pneumoniae

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



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Klebsiella pneumoniae

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ANTIBIOTIK / *ANTIBIOTIC*	**Broj izolata** / *No. of isolates*	**% rezistentnih (R) (% osjetljivih uz povećanu izloženost (I)) izolata** / *% of resistant (R) (% of susceptible, increased exposure (I)) isolates*	**Raspon lokalnih rezultata*** / *Range of local results**
Ampicillin	5 601	100 (0)	100 (0) - 100 (0)
Amoxicillin + clav. acid	5 628	43 (0)	11 (0) - 61 (0)
Piperacillin + tazobactam	5 356	31 (1)	8 (0) - 59 (0)
Cephalexin	5 373	45 (0)	16 (0) - 64 (0)
Cefuroxime $_{\text{oral}}$	5 564	44 (0)	16 (0) - 63 (0)
Cefuroxime $_{\text{parenteral}}$	5 564	44 (56)	18 (82) – 63 (37)
Ceftazidime	5 552	41 (1)	9 (0) - 62 (2)
Ceftriaxone	5 556	42 (0)	16 (0) - 72 (2)
Cefepime	5 354	41 (1)	13 (0) - 62 (2)
Cefixime	5 365	43 (0)	14 (0) - 73 (0)
Ceftazidime + avibactam	5 022	1 (0)	0 (0) – 8 (0)
Ceftolozane + tazobactam	4 972	23 (0)	0 (0) – 48 (0)
Ertapenem	5 380	21 (0)	0 (0) – 56 (0)
Imipenem	5 356	8 (4)	0 (0) – 24 (3)
Meropenem	5 359	14 (2)	0 (0) - 39 (1)
Ciprofloxacin	5 433	41 (1)	14 (0) - 61 (1)
Norfloxacin	5 358	41 (0)	14 (0) - 61 (0)
Gentamicin	5 602	31 (0)	11 (0) - 52 (0)
Amikacin	5 518	6 (0)	0 (0) – 22 (0)
Co-trimoxazole	5 517	39 (1)	24 (0) - 56 (1)

*rezultati centara s malim brojem izolata (<30) nisu uzeti u obzir /
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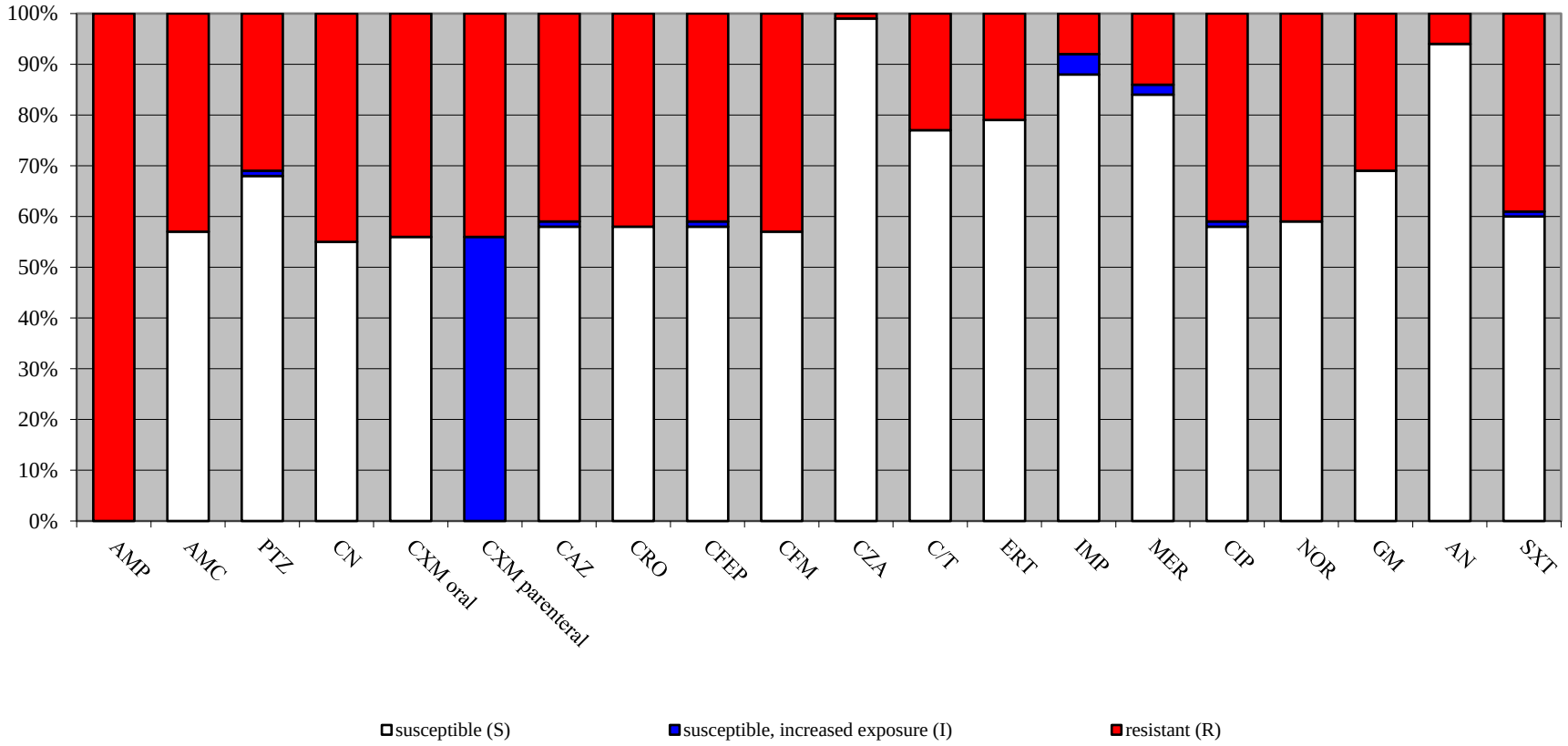
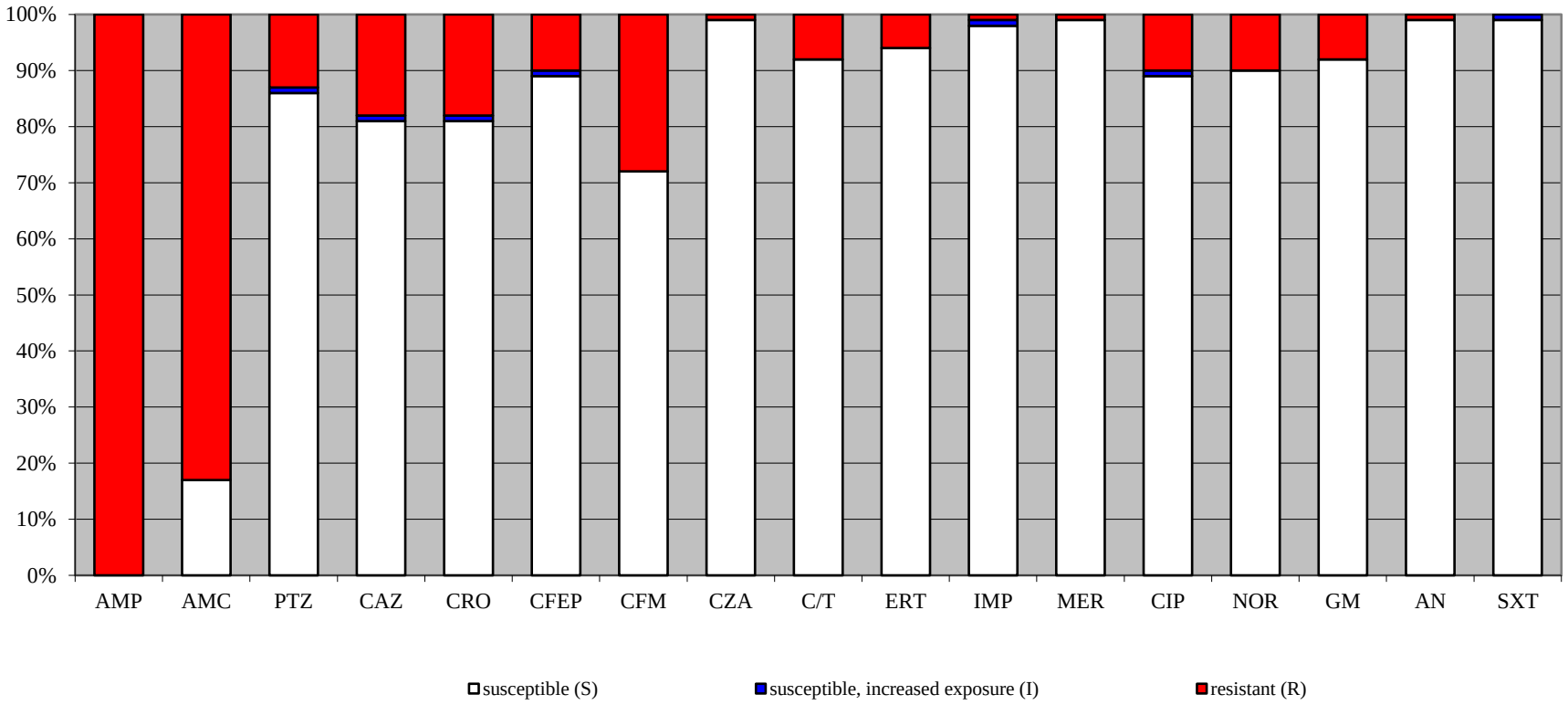
Klebsiella pneumoniae

osjetljivost na antibiotike u RH / *sensitivity to antibiotics in Croatia*, 1.10. – 31.12.2021.



Enterobacter spp., *Klebsiella aerogenes, Serratia* spp., *Citrobacter* spp.

osjetljivost na antibiotike u RH / *sensitivity to antibiotics in Croatia,* 1.10. – 31.12.2021.



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Enterobacter spp., *Klebsiella aerogenes, Serratia* spp., *Citrobacter* spp.

rezistencija na antibiotike u razdoblju od 1.10. - 31.12.202.,
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ANTIBIOTIK / *ANTIBIOTIC*	**Broj izolata** / *No. of isolates*	**% rezistentnih (R) (% osjetljivih uz povećanu izloženost (I)) izolata** / *% of resistant (R) (% of susceptible, increased exposure (I)) isolates*	**Raspon lokalnih rezultata*** / *Range of local results**
Ampicillin	3 428	100 (0)	100 (0) - 100 (0)
Amoxicillin + clav. acid	3 487	83 (0)	35 (0) - 100 (0)
Piperacillin + tazobactam	3 325	13 (1)	1 (0) - 44 (0)
Ceftazidime	3 439	18 (1)	5 (0) - 53 (0)
Ceftriaxone	3 447	18 (1)	4 (0) - 53 (0)
Cefepime	3 325	10 (1)	2 (0) - 48 (0)
Cefixime	3 256	28 (0)	9 (0) – 80 (0)
Ceftazidime + avibactam	3 103	1 (0)	0 (0) – 5 (0)
Ceftolozane + tazobactam	3 066	0 (0)	0 (0) – 19 (0)
Ertapenem	3 382	6 (0)	0 (0) – 25 (0)
Imipenem	3 334	1 (1)	0 (0) - 8 (3)
Meropenem	3 337	1 (0)	0 (0) - 6 (3)
Ciprofloxacin	3 332	10 (1)	0 (4) - 19 (0)
Norfloxacin	3 233	10 (0)	3 (0) - 23 (0)
Gentamicin	3 416	8 (0)	0 (0) - 28 (0)
Amikacin	3 365	1 (0)	0 (0) - 4 (0)
Co-trimoxazole	3 335	11 (0)	0 (3) - 35 (0)

*rezultati centara s malim brojem izolata (<30) nisu uzeti u obzir /
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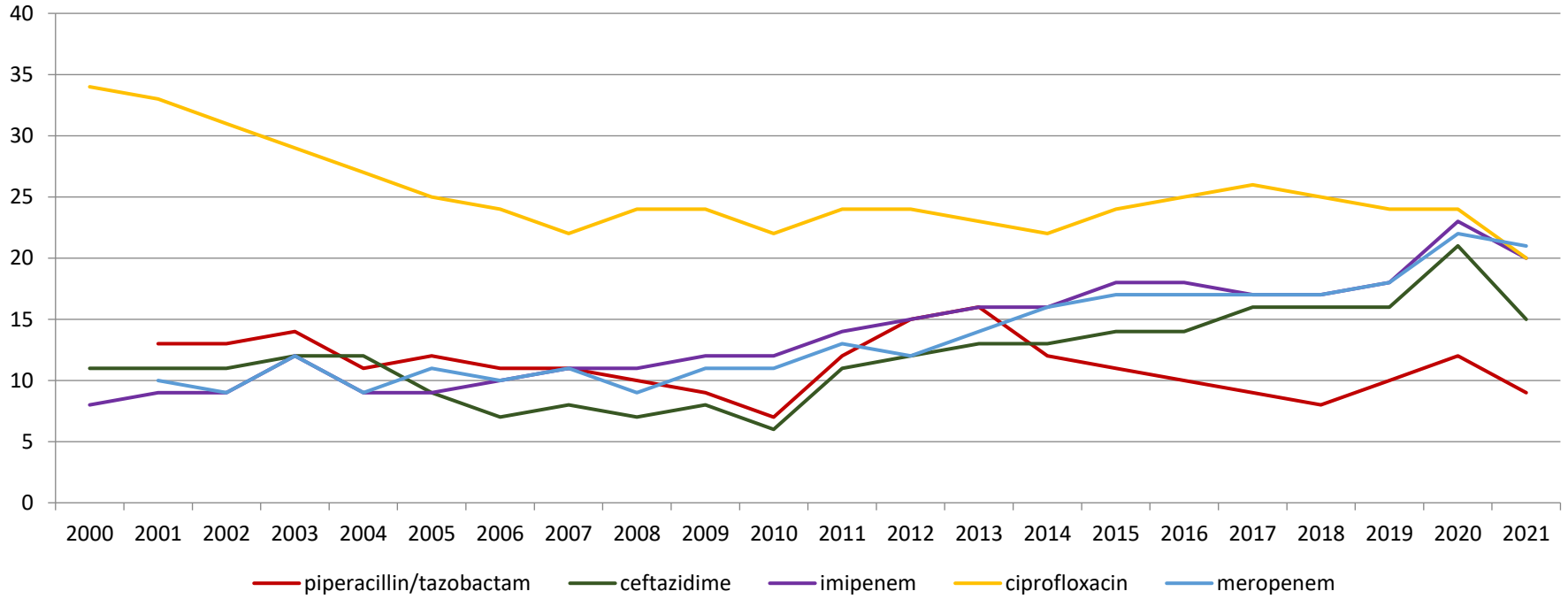
Pseudomonas aeruginosa

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



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Pseudomonas aeruginosa

rezistencija na antibiotike u razdoblju od 1.10. - 31.12.2021.,
zbirni prikaz izolata iz 39 centara u RH /
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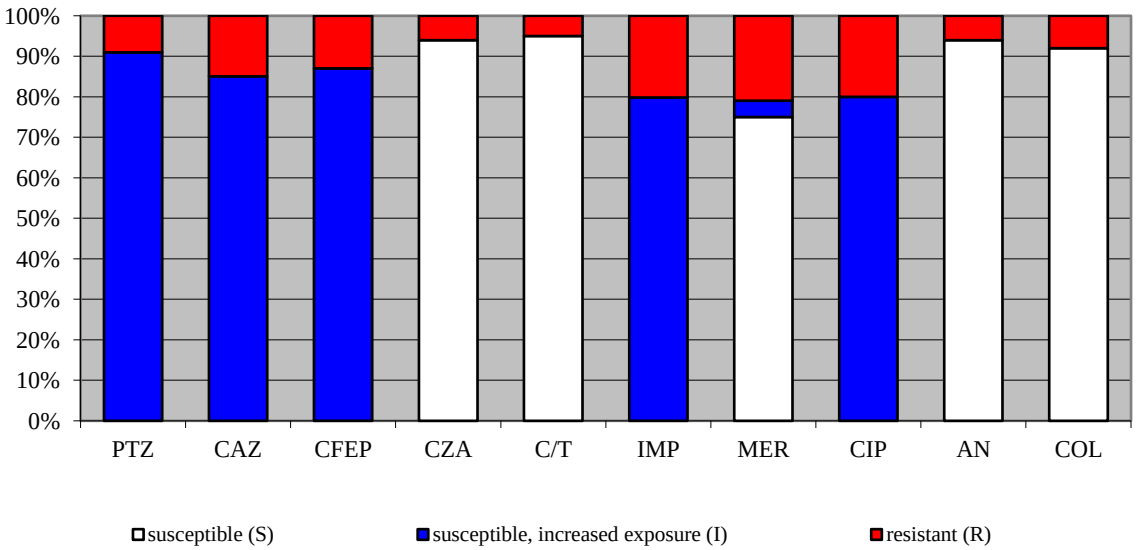
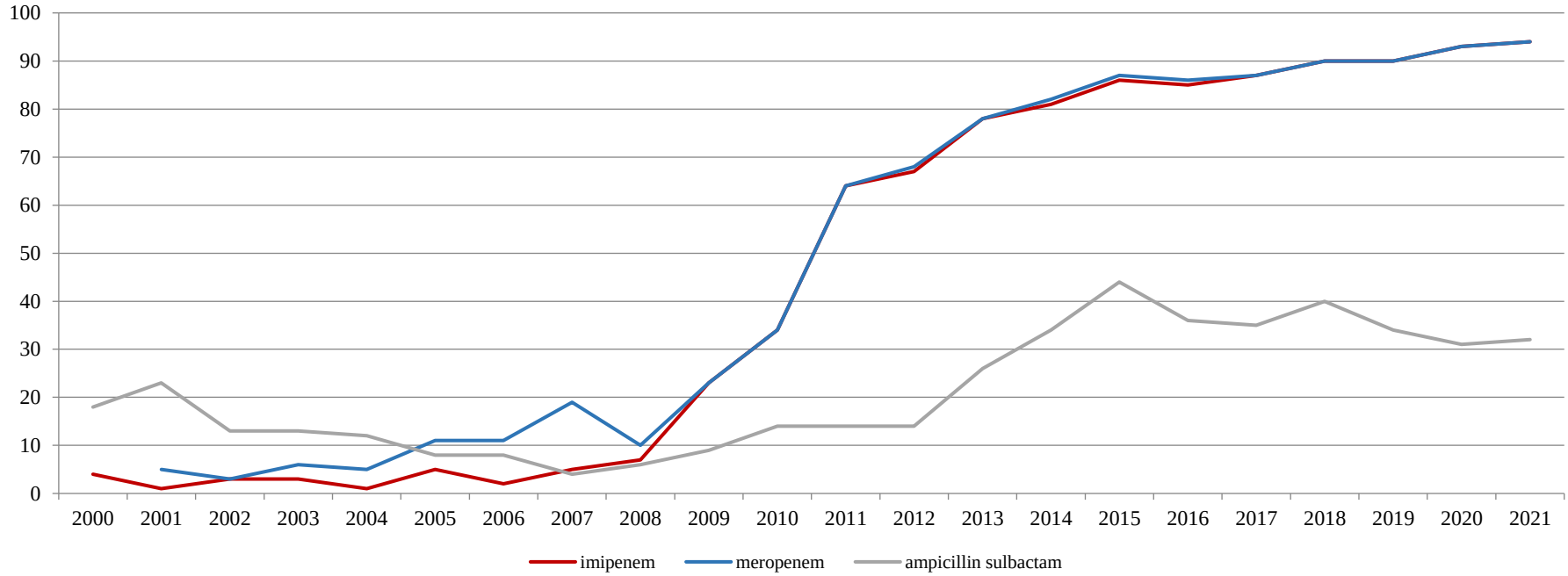
ANTIBIOTIK / *ANTIBIOTIC*	**Broj izolata** / *No. of isolates*	**% rezistentnih (R) (% osjetljivih uz povećanu izloženost (I)) izolata** / *% of resistant (R) (% of susceptible, increased exposure (I)) isolates*	**Raspon lokalnih rezultata*** / *Range of local results**
Piperacilin + tazobaktam	3 744	9 (91)	0 (100) - 33 (67)
Ceftazidim	3 744	15 (85)	0 (100) - 41 (59)
Cefepim	3 752	13 (87)	2 (98) - 30 (70)
Ceftazidime + avibactam	3 461	6 (0)	0 (0) – 19 (0)
Ceftolozane + tazobactam	3 447	5 (0)	0 (0) – 15 (0)
Imipenem	3 748	20 (79)	0 (0) - 100 (0)
Meropenem	3 742	21 (4)	2 (5) - 100 (0)
Ciprofloxacin	3 754	20 (80)	8 (92) - 46 (54)
Amikacin	3 727	6 (0)	1 (0) - 17 (0)
Colistin	834	8 (0)	0 (0) - 23 (0)

*rezultati centara s malim brojem izolata (<30) nisu uzeti u obzir /
results from the centers with small number of isolates (<30) were not taken into consideration



Acinetobacter baumannii

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



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Acinetobacter baumannii

rezistencija na antibiotike u razdoblju od 1.10. - 31.12.2021.,
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Ampicillin + sulbactam	2 582	32 (23)	1 (99) - 98 (0)
Meropenem	2 620	94 (0)	81 (0) - 100 (0)
Imipenem	2 617	94 (0)	81 (0) - 100 (0)
Ciprofloxacin	2 608	96 (4)	93 (7) - 100 (0)
Gentamicin	2 608	93 (0)	78 (0) - 100 (0)
Amikacin	2 607	90 (0)	23 (0) - 100 (0)
Co-trimaxazole	2 498	59 (6)	15 (5) - 94 (2)
Colistin	2 202	1 (0)	0 (0) - 5 (0)

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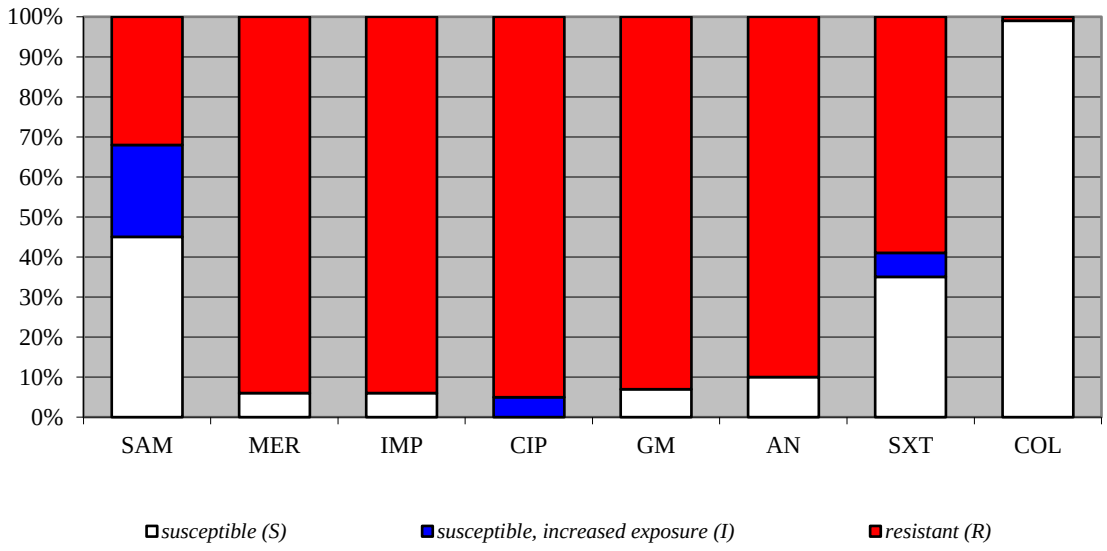

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Salmonella spp.

rezistencija na antibiotike u razdoblju od 01.01. - 31.12.2021.,
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summary results for the isolates from 39 centers in Croatia

ANTIBIOTIK / *ANTIBIOTIC*	**Broj izolata** / *No. of isolates*	**% rezistentnih (R) (% osjetljivih uz povećanu izloženost (I)) izolata** / *% of resistant (R) (% of susceptible, increased exposure (I)) isolates*	**Raspon lokalnih rezultata*** / *Range of local results**
Ampicillin	1 278	19 (0)	0 (0) - 43 (0)
Amoxicillin + clav. acid	1 277	8 (0)	0 (0) - 15 (0)
Ceftazidim	1 277	3 (1)	0 (0) - 14 (2)
Ceftriaxone	1 277	2 (0)	0 (0) - 10 (1)
Ciprofloxacin	1 274	4 (0)	0 (0) - 11 (0)
Co-trimoxazole	1 273	4 (0)	0 (0) - 10 (0)

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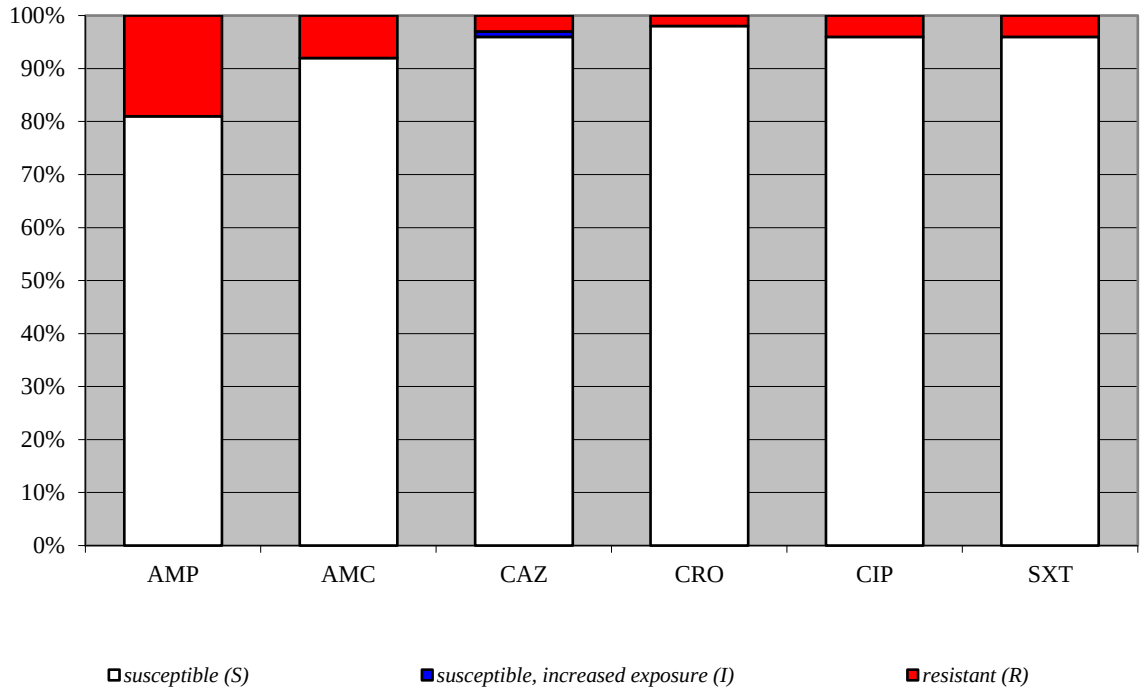

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Campylobacter jejuni

rezistencija na antibiotike u razdoblju od 1.01.- 31.12.2021.,
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Ciprofloxacin	2 651	77 (23)	50 (0) - 96 (0)
Erythromicin	2 651	1 (0)	0 (0) - 4 (0)
Tetracycline	2 647	28 (0)	17 (0) - 51 (0)

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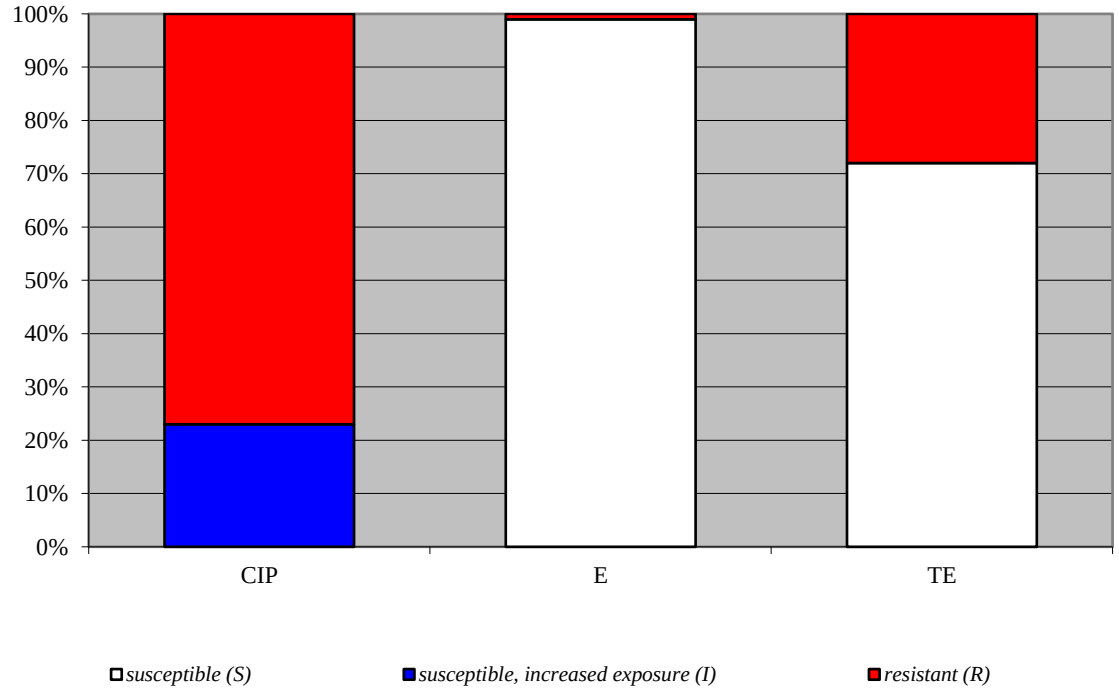

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Campylobacter coli

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ANTIBIOTIK / ANTIBIOTIC	**Broj izolata** / No. of isolates	**% rezistentnih (R) (% osjetljivih uz povećanu izloženost (I)) izolata** / *% of resistant (R) (% of susceptible, increased exposure (I)) isolates*	**Raspon lokalnih rezultata*** / Range of local results*
Ciprofloxacin	581	77 (23)	53 (0) - 89 (11)
Erythromicin	581	1 (0)	0 (0) - 3 (0)
Tetracycline	581	33 (0)	11 (0) - 35 (0)

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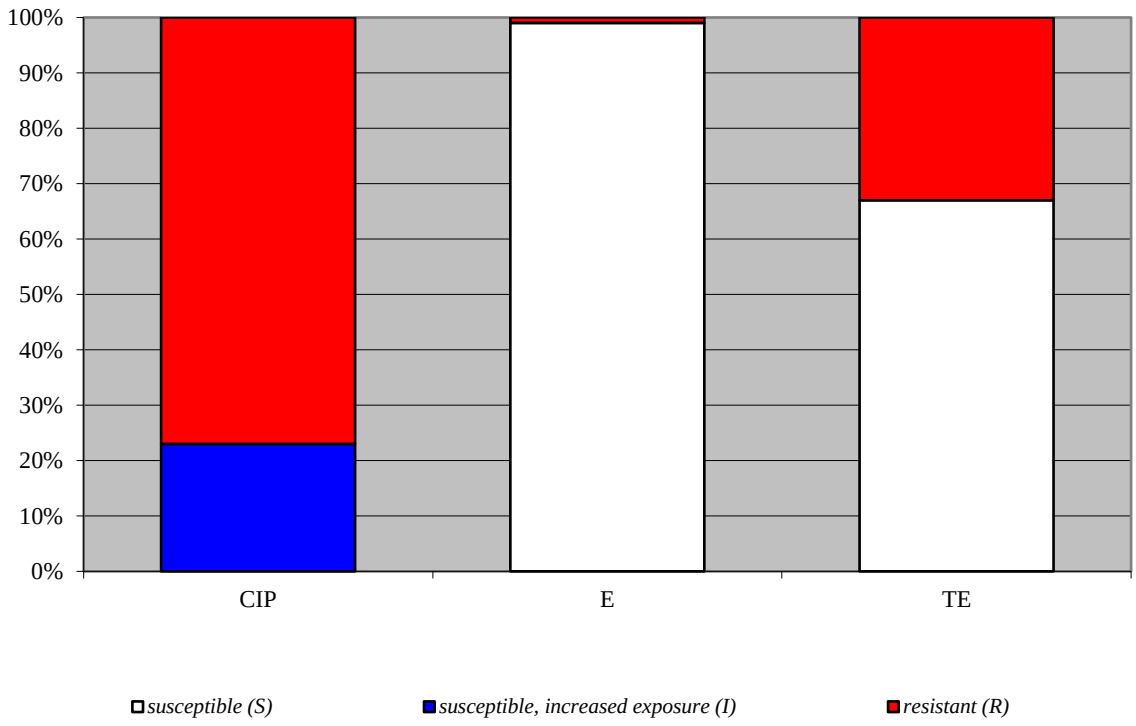

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***Shigella* spp.** – rezistencija na antibiotike u RH / *antibiotic resistance in Croatia*, 01.01. – 31.12.2021.

***Shigella* spp.**	**AMP**			**AMC**			**CAZ**			**CRO**			**CIP**			**SXT**		
	No	I %	**R %**	No	I %	**R %**	No	I %	**R %**	No	I %	**R %**	No	I %	**R %**	No	I %	**R %**
Shigella sonnei*	13	0	**100**	13	0	**31**	13	0	**85**	13	0	**85**	13	0	**92**	13	0	**92**
Shigella flexneri*	3	0	**67**	3	0	**33**	3	0	**0**	3	0	**0**	3	0	**0**	3	0	**67**
UKUPNO / *TOTAL**	16	0	**94**	16	0	**31**	16	0	**69**	16	0	**69**	16	0	**75**	16	0	**86**

*podatak o postotku rezistencije nepouzdan zbog premalo izolata / *resistance rate data unreliable due to small number of isolates*

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Anaerobne bakterije / *Anaerobes*

rezistencija na antibiotike u RH / *antibiotic resistance in Croatia*, 01.01. – 31.12.2021.

Anaerobne bakterije / *Anaerobes*	**P**			**AMC**			**PTZ**			**ERT**			**MTZ**			**CC**		
	No	I %	**R %**	No	I %	**R %**	No	I %	**R %**	No	I %	**R %**	No	I %	**R %**	No	I %	**R %**
Gram pozitivni anaerobi osim *C.difficile* / *Gram-positive anaerobes except C. difficile*	621	2	**8**	622	0	**1**	499	1	**1**	609	0	**2**	620	0	**59**	622	0	**15**
Gram negativni anaerobi /*Gram-negative Anaerobes*	613	0	**80**	615	3	**10**	496	4	**8**	605	0	**4**	615	0	**15**	614	0	**33**
UKUPNO / *TOTAL*	1234	1	**44**	1237	1	**6**	995	2	**4**	1214	0	**3**	1235	0	**37**	1236	0	**24**

OSJETLJIVOST *M. TUBERCULOSIS* U HRVATSKOJ U 2021. GODINI

SENSITIVITY OF M. TUBERCULOSIS IN CROATIA, 2021

Ljiljana Žmak
Mihaela Obrovac

Hrvatski zavod za javno zdravstvo
Služba za mikrobiologiju
Odjel za tuberkulozu
Croatian Institute of Public Health
Microbiology Service
Department for Tuberculosis

HRVATSKI ZAVOD ZA JAVNO ZDRAVSTVO
Croatian Institute of Public Health
Rockefellerova 7, 10 000 Zagreb
Služba za mikrobiologiju
Odjel za tuberkulozu
Microbiology Service
Department for Tuberculosis

Doc dr. sc. Ljiljana Žmak
Dr. sc. Mihaela Obrovac
e-mail: ljiljana.zmak@hzjz.hr
Tel.: 01/48 63 360

Mikobakterije izolirane u Hrvatskoj u 2021. godini

Podaci Registra za tuberkulozu Službe za epidemiologiju Hrvatskog zavoda za javno zdravstvo ukazuju na pad broja oboljelih od tuberkuloze (TBC). Međutim, treba uzeti u obzir da je 2021. godina bila pandemijska godina. Premda se epidemiološki podaci još obrađuju, do sada je u prošloj godini prijavljeno 158 novooboljelih, što daje stopu učestalosti od 3,9/100.000, dok je u 2020. godini stopa učestalosti iznosila 4,6/100.000 stanovnika.

Za analizu podataka o bakteriološkoj dijagnostici TBC u Hrvatskoj u 2021. godini koristio se „Upitnik o radu TBC laboratorija u 2021. godini". U prošloj godini, radi iznimne situacije uzrokovane COVID-19 pandemijom, dijagnostika tuberkuloze provodila se u 13 laboratorija organiziranih na tri razine. Ukupno je pregledano 21.090 kliničkih uzoraka na TBC što je slično broju uzoraka iz također pandemijske 2020. godine. Iako je preporučeni minimalni godišnji broj uzoraka za obradu na mikobakterije 2000, samo je tri laboratorija u 2021. obradilo je više od 2000 uzoraka. Nadalje, svi laboratoriji iz naše mreže još uvijek ne koriste tekuće podloge za sve uzorke nego samo za paucibacilarne ili izvanplućne uzorke. U 3,8% uzoraka kultivacijom je otkriven *M. tuberculosis*, a raspon pozitivnih kultura među laboratorijima se kretao od 0,9 do 20,0%. Ukupno je izolirano 1.009 sojeva mikobakterija (Tablica 1).

Tijekom 2021. godine genotipizirano je 151 izolata *M. tuberculosis* iz cijele Hrvatske. U skladu s očekivanim, *M. tuberculosis* je najčešće izoliran iz plućnih uzoraka, a među a među 9 (6,0%) izvanplućnih bakteriološki dokazanih slučajeva TBC najčešća je bila TBC pleure (N=4), TBC središnjeg živčanog sustava (N=2), limfoglandularna TBC (N=1), te TBC rane (N=1) i tkiva (N=1). Tijekom 2021. godine iz humanih kliničkih materijala nije izoliran *M. bovis*, dok je *M. bovis* – BCG soj izoliran kod jednog pacijenta.
Među 1.009 izoliranih sojeva mikobakterija, *M. tuberculosis* i dalje dominira s 799 (79,2%) izolata. Udio netuberkuloznih mikobakterija (NTM) među izoliranim mikobakterijama na razini je brojeva u 2020. godini, te je iznosio 20,7%. Osobe s izolatima NTM se bilježe od 1982. godine, a kod višekratnih izolacija se utvrđuju mikrobiološki kriteriji za mikobakterioze i popunjava obrazac za NTM. U 2021. godini od uvjetno patogenih sporastućih mikobakterija najviše je izoliran *M. xenopi* (47 izolata), *M. avium* (37 izolata) te *M. intracellulare* (28 izolata) (Tablica 2.). Od brzorastućih mikobakterija najveći broj izolata odnosio se na *M. fortuitum* (22 izolata), a slijede ga *M. chelonae* sa 15 izolata i *M. abscessus* sa tri izolata. *M. gordonae* kao saprofitna mikobakterija je identificiran u 16,7% izolata NTM. Najčešće se radi o kontaminaciji uzoraka, slučajnim nalazima i prolaznim kolonizacijama. U 2021. godini je otkriveno 51 osoba sa zadovoljenim mikrobiološkim kriterijima za dijagnozu mikobakterioze (dva i više izolata, ili izolat iz asp. bronha). Kod 17 bolesnika izoliran je *M. xenopi*, a slijede ga *M. avium* koji je izoliran kod 12 bolesnika te *M. intracellulare* kod sedam i *M. gordonae* kod osam bolesnika.

Nastavljen je izrazito povoljan trend broja rezistentnih sojeva *M. tuberculosis*. Od 799 testiranih sojeva samo je 13 (1,6%) bilo rezistentno na prvu liniju antituberkulotika, a otkriveni su kod pet bolesnika s rezistentnom tuberkulozom (Tablica 3.). Među bolesnicima s rezistentnim oblikom

tuberkuloze, njih četiri (80,0%) je imalo monorezistenciju na izonijazid, a jedan na streptomicin, dok ostali vidovi rezistencije nisu nađeni.

Mycobacteria isolated in Croatia in 2021

Data from the Tuberculosis Registry of the Epidemiology Service of the Croatian Institute of Public Health indicate a small decline in the number of tuberculosis patients (TB). However, it should be taken into account that the whole of 2021 was also a pandemic year. Although epidemiological data are still being processed, 158 new cases have been reported so far in the last year, which gives an incidence rate of 3.9 / 100,000, while in 2020 the incidence rate was 4.6 / 100,000 inhabitants.

To analyze data on TB bacteriological diagnostics, the "Questionnaire on the work of TB laboratories in 2021" was used. Last year, due to the exceptional situation caused by the COVID-19 pandemic, the diagnosis of tuberculosis was carried out in 13 laboratories organized at three levels. A total of 21,090 clinical samples were examined for TB, which is similar to the numberof samples in 2020. Although the recommended minimum annual number of samples to be processed for mycobacteria is 2000, only three laboratories in 2021 processed more than 2000 samples. Furthermore, not all laboratories in our network use liquid media for all samples but only for paucibacillary or extrapulmonary samples. In 3.8% of samples, *M. tuberculosis* was detected by cultivation, and the range of positive cultures among laboratories ranged from 0.9 to 20.0%. A total of 1,009 strains of mycobacteria were isolated (Table 1).

During 2021, 151 isolates of *M. tuberculosis* were genotyped. As expected, *M. tuberculosis* was most often isolated from lung samples, and among 9 (6.0%) extrapulmonary bacteriologically confirmed cases of TB, the most common was pleural TB (N=4) and TB of the central nervous system (N=2), followed by lymphoglandular TB (N =1), pleural TB (N=1) wound TB (N=1) and tissue TB (N=1).
During 2021, *M. bovis* was not isolated from human clinical samples, while *M. bovis* - BCG strain was isolated in one patient.

Among 1,009 isolated strains of mycobacteria, *M. tuberculosis* still dominates with 799 (79.2%) isolates. The number of non-tuberculous mycobacteria (NTM) among isolated mycobacteria was similar to the number in 2020, accounting for 20.7% of all isolates. Patients with NTM isolates are systematically documented since 1982, and in case of multiple isolates, microbiological criteria for mycobacteriosis are established and a questionnaire for NTM is used. Among conditionally pathogenous slow growing NTM in 2021 prevailed isolates of *M. xenopi* (47 isolates), *M. avium* (37 isolates) and *M. intracellulare* (28 isolates) (Table 2). In the rapidly growing group the most commonly isolated species were *M. fortuitum* (22 isolates), followed by *M. chelonae* with 15 isolates and *M. abscessus* with three isolates. *M. gordonae* as a saprophytic mycobacterium was identified in 16.7% of NTM isolates. In most cases, the isolation was the result of specimen contamination, accidental finding and transient colonization. In 2021, a total of 51 cases fulfilled the microbiological criteria for mycobacteriosis (two or more isolates). *M. xenopi* was isolated in 17 patients, followed by *M. avium* in 12 patients and *M. intracellulare* in seven patients and *M. gordonae* in eight patients.

The number of resistant *M. tuberculosis* strains and, by extension, number of resistant TB cases has demonstrated a continuous favorable trend. Of the 799 strains tested, only 13 (1.6%) were resistant to first line antituberculotics, and were detected in five patients with resistant tuberculosis (Table 3). Among patients with the resistant form of tuberculosis, four (80.0%) had monoresistance to isoniazid, while one had monoresistance to streptomycin. No other forms of resistance were detected.

Tablica / *Table* **1.**
Mikobakterije izolirane u Hrvatskoj, 2011. – 2021. /
Mycobacteria strains isolated in Croatia, 2011-2021

Godina	Ukupno mikobakterija	*M. tuberculosis*		*M. bovis*		Netuberkulozne mikobakterije	
		Broj	%	*M. bovis*	BCG soj	Broj	Broj
2011.	2351	2000	85,0	-	**2011.**	2351	2000
2012.	2108	1807	85,7	1	**2012.**	2108	1807
2013.	2153	1748	81,2	-	**2013.**	2153	1748
2014.	1969	1541	78,3	-	**2014.**	1969	1541
2015.	1880	1505	80,1	-	**2015.**	1880	1505
2016.	2021	1587	78,5	-	**2016.**	2021	1587
2017.	1596	1246	78,1	-	**2017.**	1596	1246
2018.	1689	1387	82,1	-	**2018.**	1689	1387
2019.	1751	1281	73,2	4	**2019.**	1751	1281
2020.	1081	855	79,1	-	**2020.**	1081	855
2021.	1009	799	79,2	-	**2021.**	1009	799

Tablica / *Table* **2.**
Netuberkulozne mikobakterije (NTM) izolirane u Hrvatskoj u 2021. /
Nontuberculous mycobacteria (NTM) isolated in Croatia in 2021

	Vrsta	**Broj**	**%**
Uvjetno patogene mikobakterije	M. xenopi	47	22,5
	M. avium	37	17,7
	M. intracellulare	28	13,4
	M. intermedium	1	0,5
	M. heckeshornense	1	0,5
	M. genavense	1	0,5
	M. fortuitum	22	10,5
	M. chelonae	15	7,2
	M. abscessus	3	1,4
	M. mucogenicum	4	1,9
Saprofitne mikobakterije	*M. gordonae*	35	16,7
	Mycobacterium sp.	15	7,2
Ukupno		**209**	**100**

Tablica / *Table* **3.**

Bolesnici s rezistentnom tuberkulozom u Hrvatskoj, 2020. /
Resistant tuberculosis in Croatia, 2020

	Broj / *Number*	**%**
Ukupno bolesnika / *Patients total*	**9**	**100**
Monorezistencija / *Monoresistance*		
S	3	33,3
H	3	33,3
Z	2	22,2
Multirezistencija / Multiresistance		
HRSEZ, Km	1	11,1

Legenda - *Key*: **R -** rifampicin **S** – streptomicin **H** – izoniazid **Z** - pirazinamid **E** - etambutol Km - kanamicin

POGLAVLJE / CHAPTER 3.

OSJETLJIVOST GONOKOKA U HRVATSKOJ U 2021

Blaženka Hunjak
Tatjana Unukić
Andrea Babić-Erceg

Hrvatski zavod za javno zdravstvo,
Rockefellerova 2, 10000 Zagreb, Hrvatska
Služba za mikrobiologiju,
Croatian Institute of Public Health,
Rockefeller str. 2, 10000 Zagreb, Croatia
Division for Microbiology,

Hrvatski zavod za javno zdravstvo,
Rockefellerova 2, 10000 Zagreb, Hrvatska
Služba za mikrobiologiju

Dr.sc.B. Hunjak, prim.dr.med.
Izv.prof.Andrea Babić-Erceg, dr.med.
Tatjana Unukić, prvostupnik medicinsko laboratorijske dijagnostike

Antimikrobna rezistencija u gonokoka izoliranih Hrvatskoj u 2021. godini

Godine 2021. koja je također obilježena COVID-19 pandemijom, bili smo nešto uspješniji u sakupljanju izolata Neisseria gonorrhoeae (NG) na razini RH, iako nam je cilj dosegnuti rezultate iz 2019. god. kada smo sakupili više od 70 NG izolata iz cijele RH. Međutim, jasno nam je da ne samo djelatnici HZJZ-a, nego i ostalih ustanova su još uvijek uvelike uključeni u dijagnostiku korone. Prošle godine smo u ovoj publikaciji opisali izviješća recentne literature iz ovog područja, jer je NG vrlo dobar model praćenja napredovanja rezistencije i razvitka višestruko otpornih bakterija. U svjetlu razvoja rezistencije u NG kao modela razvoja antimikrobne rezistencije (AMR) prikazujemo još par zanimljivih slučajeva iz inozemstva i neke rezultate Projekta Euro – GASP , koji prati rezistenciju i učestalost NG, zajedno s epidemiološkim podacima.

Francuski nacionalni referentni centar za bakterijske SPI izvještava o novom slučaju urogenitalne infekcije sa NG rezistentne na više lijekova s rezistencijom na ceftriakson kod heteroseksualnog para u jugoistočnoj Francuskoj, sa kliničkom slikom vaginitisa kod žene i uretritisa kod muškaraca. Anamneza pacijentice otkrila je da je izolat N. gonorrhoeae F92 vjerojatno prenio suprug pacijentice koji je imao uretritis po povratku iz Vijetnama i Švicarske. Prva epizoda dijagnosticirana je samo PCR-om na vaginalnom brisu bez kulture za bolesnicu koja je liječena jednokratnom dozom ceftriaksona od 1 g. Učinkovitost liječenja kontrolirana je testom izlječenja koji je bio negativan. Pacijent je liječen izvan Francuske. Kultura na vaginalnom brisu za pacijenticu bila je pozitivna nakon druge epizode.

Izolat F92 N. gonorrhoeae pokazao je otpornost na ceftriakson (MIC 0,5 mg/L), cefiksim (MIC 2 mg/L), tetraciklin (MIC 4 mg/L) i ciprofloksacin (MIC > 32 mg/L). Izolat je ostao osjetljiv na spektinomicin (MIC 16 mg/L) i na azitromicin (MIC 0,5 mg/L). Također je imao MIC gentamicina (MIC 8 mg/L). Bolesnica je izliječena jednokratnom dozom azitromicina od 2 g.

Sekvenciranje cijelog genoma izolata N. gonorrhoeae F92 identificiralo je MLST1901, novi NG-MAST (porB 2553, tbpB 2459) i sličan NG-STAR233. Otpornost na cefalosporine proširenog spektra dala je mozaički alel sličan penA-60.001, koji kodira mozaični protein koji veže penicilin 2. Čini se da se izolat F92 razlikuje od uspješnog klona FC428, dva izolata F90 i F91 pronađena u Francuskoj u 2017. i 2019. i imao je nisku genetsku bliskost s izolatom N. gonorrhoeae F89.Drugi zanimljiv slučaj također svjedoči o razvitku višestruke otpornosti izolata gonokoka. Slučaj XDR NG identificiran je kod stanovnika UK-a koji je dobio infekciju na Tajlandu. Pacijent je razvio uretralne simptome u Tajlandu i ondje je liječen oralnim cefiksimom i azitromicinom. Njegovi su simptomi perzistirali, a po povratku u UK nastavljena je obrada. Kulture su bile pozitivne i iz uretralnih i iz faringealnih briseva. Oba su izolata bila rezistentna na ceftriakson (MIC 0,25 mg/L), cefiksim (MIC 0,5 mg/L), azitromicin (MIC >256 mg/L), ciprofloksacin (MIC 8,0 mg/L) i tetraciklin (MIC 16,0 mg/L) . Izolati su bili osjetljivi na spektinomicin (MIC 8,0 mg/L). MIK-ovi bili su niski za gentamicin (MIC 2,0 mg/L) i ertapenem (MIC 0,016 mg/L). MIk-ovi penicilina bili su različiti za dva izolata: MIC za faringealni izolat >32 mg/L, pozitivan na beta-laktamazu i MIC za uretralni izolat 0,25 mg/L, negativan na beta-laktamazu, što implicira mogući gubitak plazmida. Rezultati testiranja uretre i farinksa bili su negativni nakon liječenja ceftriaksonom 1 g IM.

Zbog navedenoga , istražuje se i dalje potencijal i gentamicina za upotrebu u liječenju NG, kako bi ustanovili da li će gentamicin u budućnosti biti jedna od opcija za liječenje, da te da li eventualno dolazi u obzir kao mogući budući lijek za gonoreju.

Od preporuka i novih lijekova ponovo skrećemo pažnju na zoliflodacin. In vitro aktivnost zoliflodacina testirana je na panelu od 986 izolata N. gonorrhoeae prikupljenih od muškaraca u Nanjingu u Kini u periodu od 2014. do 2018. Svi izolati bili su osjetljivi na spektinomicin, ali rezistentni na ciprofloksacin s MIK-om zoliflodacina od ≤0,002 do 0,25 mg/l uz značajan godišnji pad postotka izolata s nižim MIK-om zoliflodacina.

Smjernice CDC-a i dalje preporučuju jednu intramuskularnu dozu ceftriaksona od 500 mg za nekompliciranu gonoreju ili jednu intramuskularnu dozu gentamicina od 240 mg i jednu oralnu dozu od 2 g azitromicina za pacijente s alergijom na cefalosporin. Kontrola uspješnosti liječenja preporučuje se svim pacijentima s faringealnom gonorejom jedan do dva tjedna nakon završetka terapije.

Prema podacima Projekta Euro – GASP , u 2020. otkriven je samo jedan izolat s rezistencijom na ceftriakson (MIC=0,25 mg/L) i to u Belgiji. Izolat je imao MIC azitromicina na epidemiološkoj granici za azitromicin (ECOFF) (MIC=1 mg/L) i bio je otporan na ciprofloksacin (MIC>32 mg/L). Rezultati Euro-GASP 2020. otkrili su ukupno 0,5% izolata gonokoka s rezistencijom na cefiksim (MIC>0,125 mg/L), što je značajno smanjenje u odnosu na 0,9% izolata zabilježenih 2019. (p=0,02), broj zemalja koje su prijavile bilo kakve rezistentne izolate također se smanjio s prethodno stabilnih četrnaest na šest.
Od siječnja 2019., granična točka kliničke rezistencije Europskog odbora za ispitivanje osjetljivosti na antimikrobna sredstva (EUCAST) za azitromicin od MIC>0,5 mg/L zamijenjena je vrijednošću ECOFF od MIC>1 mg/L. Nakon značajnog povećanja udjela izolata iznad azitromicina ECOFF 2018. (7,6%) i 2019. (10,1%), udio je ostao stabilan na 11,0% u 2020. U 2020. 21 zemlja zabilježila je barem jedan izolat s MIC-om iznad azitromicin ECOFF (MIC >1 mg/L) u usporedbi s 24 zemlje u 2019., 25 zemalja u 2018., 21 u 2017. i 20 zemalja u 2016. Udio izolata koji pokazuju otpornost na ciprofloksacin ostao je na konstantnoj razini s onom zabilježenom 2019. (57,3%) na 57,7% u 2020. godini.
Iako je dvojna rezistencija na azitromicin i ceftriakson rijetka, više od 10% izolata imalo je MIC azitromicina iznad ECOFF-a što, u kombinaciji s kontinuiranim otkrivanjem rezistencije na ceftriakson, ostaje zabrinjavajuće i ugrožava učinkovitost trenutno vrlo učinkovitog režima dvojne terapije (ceftriakson plus azitromicin) i monoterapija visokim dozama ceftriaksona koju su usvojile neke europske zemlje. Iako se razina rezistencije na cefiksim značajno smanjila, rezistenciju na cefiksim treba pomno pratiti, posebno zato što se sojevi gonokoka koji su rezistentni i na cefiksim i na ceftriakson nastavljaju međunarodno širiti. Nastavak aktivnosti praćenja antimikrobne osjetljivosti osigurane kvalitete, zajedno s razvojem alternativnih gonokoknih režima, ključan je kako bi se osiguralo da gonoreja ostane infekcija koja se može liječiti.
Od početka uključivanja RH u Euro-GASP (krajem 2014.) pokušava se u javnosti propagirati važnost praćenja učetalosti NG, a od 2015, uključeno je praćenje AMR NG u godišnje izvješće o rezistenciji u Publikaciju Odbora za praćenje antimikrobne rezistencije u RH. Izolati NG iz svih laboratorija koji sudjeluju u praćenju, šalju se na Odjel za bakteriologiju Službe za mikrobiologiju HZJZ-a. U HZJZ se provodi i potvrđuje identifikacija NG metodama kultivacije, molekularnom metodom PCR na uređaju ABI Prism sequence detection system 7000 (Applied Biosystems, USA) metodom Real time – PCR (prema J Clin Microbiol. Nov 2005; 43(11): 5653–5659. doi: 10.1128/JCM.43.11.5653-5659.2005), te se provodi testiranje osjetjivosti na antibiotike (metoda E-test).
U HZJZ i dalje dolaze viabilni izolati NG ili podaci o osjetljivosti na NG (obzirom na zahtjevni transport i osjetljivost izolata) iz mikrobioloških laboratorija u RH koji sudjeluju u praćenju rezistencije. Prati se porast broja dobivenih izolata, te je tako za 2015. god zaprimljeno podataka za 15, u 2016. g. za 35, u 2017. za 36, u 2018. godini za 46, u 2019. godini 73 izolata, a u 2021. godini za 26 izolata . U Tablici 1. navedene su vrijednosti gradijenata koje pokazuje rezultate testiranja metodom E-testa I disks difuzije.

Na žalost u odnosu na a 2019. god. kada je testirano je 73 soja, u 2021. bilo je svega 26 izolata , što je pad od 47 izolata, ali je više nego za 2020 . god., kada nismo zaprimili niti jedan izolat.
Rezultati osjetljivosti za 2021. u usporedbi sa 2019 su kako slijedi (Tablica 2):

- za 2021. na penicilin je bilo 7 (29,2%) osjetljivih, 14 (58,3%) umjereno osjetljivih, i 3 (12,5%) rezistentnih izolata; u usporedbi s 2019., kada je na na penicilin je bilo 38,6% osjetljivih, 46.3% umjereno osjetljivih, i 14.9% rezistentnih izolata
- za 2021. na ceftriakson nije niti kod jednog od ukupno 26 izolata ustanovljena rezistencija, kao niti 2019, 2018, god., za razliku od podataka za 2017. kada je u samo jednog izolata ustanovljena rezistencija.
- za 2021. na cefixim nije niti kod jednog od ukupno 24 testirana izolata ustanovljena rezistencija, za razliku od 2019 kada je na cefixim ustanovljena rezitencija u samo jednog izolata, što je manje u odnosu na 2018 god. (5,3%) ili 2017. kada je bilo 6,9% rezistentnih izolata.
- za 2021. na ciprofloksacin je bilo 19 (76%) rezistentnih izolata , za razliku od 2019., kada je bilo 66.7% rezistentnih izolata, što je porast i u odnosu na 2018. , kada je bilo 58,7% ili 2017. sa 42,4% rezistentna izolata.

Obzirom da se azitromicin po smjernicama koristi uvijek zajedno s drugim učinkovitim sredstvom, a prilikom ispitivanja stečenog mehanizma rezistencije, ECOFF je 1 mg/L (EUCAST 2020.), za 2019. godinu nisu interpretirani rezultati testiranja osjeljivosit za azitromicin, iako su testiranja provedena, te je bilježena vrijednost MIK-a. (Tablica 1.). Može se kazati da za gentamicin i dalje nema gradijenta za testiranje, ali se preporuča testiranje kako bi se ispitala djelotvornost gentamicina za slučaj ograničenog izbora terapije. Iako je azitromicin u RH dostupan i postignuta je dobra suradljivost pacijenata, azitromicin se više ne preporuča samostalno za testiranje, jer se prema iskustvima daje uvijek u kombinaciji s još jednim antibiotikom. Spektinomicin u RH i dalje nije dostupan, ali postoji mogućnost da se u budućnosti uvede, te je potrebno provjeravati njegovu djelotvornost. U 2021. g. na spektinomicin rezistencija nije ustanovljena niti kod jednog testiranog izolata.

Antimicrobial resistance in gonococci isolated in Croatia in 2021

In 2021, which was also marked by the COVID-19 pandemic, we were somewhat more successful in collecting Neisseria gonorrhoeae (NG) isolates at the level of the Republic of Croatia, although our goal is to reach the results of 2019. when we collected more than 70 NG isolates from all over the Republic of Croatia. However, it is clear to us that not only the employees of HZJZ, but also other institutions are still largely involved in corona diagnostics. Last year, in this publication, we described reports of recent literature in this area, because NG is a very good model for monitoring the progression of resistance and the development of multiple resistant bacteria. In light of the development of resistance in NG as a model for the development of antimicrobial resistance (AMR), we present a few more interesting cases from abroad and some results of the EURO-GASP Project, which monitors resistance and frequency of NG, together with epidemiological data.

The French National Reference Centre of bacterial STI reports a new case of multidrug-resistant Neisseria gonorrhoeae (NG) urogenital infection with ceftriaxone resistance in a heterosexual couple in south-East France, suffering from vaginitis for the female and urethritis for the male. The female patient's history revealed that the N. gonorrhoeae F92 isolate was likely transmitted by the patient's husband who had urethritis upon returning from business trips to Vietnam and Switzerland. Both patients had been symptomatic since May. The first episode was diagnosed by PCR alone on the vaginal swab without culture for the female patient who has been treated by ceftriaxone 1 g single dose. Efficacy of treatment had been controlled by a test of cure which was negative. The male patient was treated outside France. The culture on vaginal swab for the female patient was positive after a second episode . The F92 N. gonorrhoeae isolate showed resistance to ceftriaxone (MIC 0.5 mg/L), cefixime (MIC 2 mg/L), tetracycline (MIC 4 mg/L) and ciprofloxacin (MIC > 32 mg/L). The isolate remained susceptible to spectinomycin (MIC 16 mg/L) and to azithromycin (MIC 0.5 mg/L). It also had a low MIC of gentamicin (MIC 8 mg/L). The female patient was treated by azithromycine 2 g single dose.

Whole genome sequencing of the N. gonorrhoeae F92 isolate identified MLST1901, new NG-MAST (porB 2553, tbpB 2459) and NG-STAR233-like. Resistance to extended-spectrum cephalosporins was conferred by a mosaic penA-60.001-like allele, encoding a mosaic penicillin-binding protein 2. The isolate F92 appeared to be distinct from the successful clone FC428, the two isolates F90 and F91 found in France in 2017 and 2019 and had a low genetic proximity with the N. gonorrhoeae F89 isolate.

Another interesting case also testifies to the development of multiple resistance of gonococcal isolates. A case of XDR N. gonorrhoeae was identified in a UK resident who acquired the infection in Thailand. The case is a heterosexual male in his 40s who had sexual contact in Phuket. The patient developed urethral symptoms in Thailand and was treated there by oral cefixime and azithromycin. His symptoms persisted, and procedure of diagnostc was continued in the UK. Cultures were positive from both urethral and pharyngeal swabs. Both isolates were resistant to ceftriaxone (MIC 0.25 mg/L), cefixime (MIC 0.5 mg/L), azithromycin (MIC >256 mg/L), ciprofloxacin (MIC 8.0 mg/L) and tetracycline (MIC 16.0 mg/L). Both were susceptible to spectinomycin (MIC 8.0 mg/L). MICs were low for gentamicin (MIC 2.0 mg/L) and ertapenem (MIC 0.016 mg/L). The penicillin MICs were different for the two isolates: pharyngeal isolate MIC >32 mg/L, beta-lactamase positive and urethral isolate MIC 0.25mg/L, beta-lactamase negative, implying possible loss of a plasmid.

Urethral and pharyngeal test-of-cure were negative after treatment with ceftriaxone 1g IM. The case did not have any sexual partners in the UK. Unfortunately, there are no contact details available for the partner in Thailand.

Because of the above written, the potential of gentamicin for use in the treatment of N. gonorrhoeae is still being investigated, in order to determine whether gentamicin will be a treatment option, and whether it could possibly come into consideration as a possible future complete cure for gonorrhea.

From recommendations and new drugs, we again turn our attention to zoliflodacin. The in vitro activity of zoliflodacin was tested on a panel of 986 N. gonorrhoeae isolates collected from men in

Nanjing, China, from 2014 to 2018. All isolates were susceptible to spectinomycin but resistant to ciprofloxacin with zoliflodacin MICs of ≤0.002 to 0.25 mg/l with a significant annual decrease in the percentage of isolates with a lower MIC of zoliflodacin.

CDC guidelines continue to now recommend a single 500 mg intramuscular dose of ceftriaxone for uncomplicated gonorrhea or a single 240 mg intramuscular dose of gentamicin and a single 2 g oral dose of azithromycin for patients with cephalosporin allergy. Control of treatment success is recommended for all patients with pharyngeal gonorrhea one to two weeks after the end of therapy.

According to data of EURO-Gasp, in 2020, only one isolate with resistance to ceftriaxone (MIC=0.25 mg/L) was detected, in Belgium. The isolate had an azithromycin MIC at the azithromycin epidemiological cut-off (ECOFF) (MIC=1 mg/L) and was ciprofloxacin resistant (MIC>32 mg/L). The Euro-GASP 2020 results revealed a total of 0.5% of gonococcal isolates with resistance to cefixime (MIC>0.125 mg/L), which was a significant decrease from the 0.9% of isolates recorded in 2019 (p=0.02), the number of countries reporting any resistant isolates also decreased from a previously stable fourteen to six.

Since January 2019, the European Committee on Antimicrobial Susceptibility Testing (EUCAST) clinical resistance breakpoint for azithromycin of MIC>0.5 mg/L has been replaced with an ECOFF value of MIC>1 mg/L. After the significant increases in the proportion of isolates above azithromycin ECOFF in 2018 (7.6%) and 2019 (10.1%), the proportion remained stable at 11.0% in 2020. In 2020, 21 countries recorded at least one isolate with an MIC above the azithromycin ECOFF (MICs >1 mg/L) compared to 24 countries in 2019, 25 countries in 2018, 21 in 2017 and 20 countries in 2016, respectively. The proportion of isolates showing ciprofloxacin resistance remained at a level constant with that observed in 2019 (57.3%) at 57.7% in 2020.

Although dual azithromycin and ceftriaxone resistance is rare, over 10% of isolates had and azithromycin MIC above the ECOFF that, combined with the continued detection of ceftriaxone resistance, remains a concern and threatens the effectiveness of the currently highly effective dual-therapy regimen (ceftriaxone plus azithromycin) and high-dose ceftriaxone monotherapy adopted by some European countries. Even though the level of resistance to cefixime has significantly decreased, cefixime resistance needs to be monitored closely, particularly because gonococcal strains with resistance to both cefixime and ceftriaxone continue to spread internationally. The continuation of quality-assured antimicrobial susceptibility surveillance activities, along with the development of alternative gonococcal regimens, is essential to ensure gonorrhoea remains a treatable infection.

Since the beginning of the inclusion of the Republic of Croatia in Euro-GASP (at the end of 2014), attempts have been made to publicize the importance of monitoring the frequency of NG, and since 2015, the monitoring of AMR NG has been included in the annual report on resistance in the Publication of the Committee for Monitoring Antimicrobial Resistance in the Republic of Croatia. NG isolates from all laboratories participating in the monitoring are sent to the Department of Bacteriology of the Microbiology Service of the HZJZ. At the HZJZ, NG identification is carried out and confirmed by cultivation methods, molecular PCR method on the device ABI Prism sequence detection system 7000 (Applied Biosystems, USA) by Real time - PCR method (according to J Clin Microbiol. Nov 2005; 43(11): 5653–5659 doi: 10.1128/JCM.43.11.5653-5659.2005), and sensitivity testing to antibiotics (E-test method) is performed.
Viable isolates of NG or data on sensitivity to NG (given the demanding transport and sensitivity of isolates) continue to arrive at HZJZ from microbiological laboratories in the Republic of Croatia that participate in resistance monitoring. The increase in the number of obtained isolates is being monitored; so in 2015, data was received for 15, in 2016 for 35, in 2017 for 36, in 2018 for 46, in 2019 for 73 isolates, and in 2021. year for 24 isolates. Table 1 lists the values of the gradients that show the results of testing with the E-test and disk diffusion method.
Unfortunately, compared to and in 2019. when there were 73 strains, in 2021 there were only 26 isolates, which is a decrease of 47 isolates, but it is more than for 2020. yr., when we did not receive a single isolate.
The sensitivity results for 2021 compared to 2019 are as follows (Table 2):

In 2021, there were 7 (29.2%) susceptible, 14 (58.3%) moderately susceptible, and 3 (12.5%) resistant isolates to penicillin; compared to 2019, when there were 38.6% susceptible, 46.3% moderately susceptible, and 14.9% resistant isolates to penicillin

In 2021, resistance to ceftriaxone was not established in any of the 26 isolates, as well as in 2019, 2018, 2107. in contrast to the data for 2017, when resistance was found in only one isolate.

In 2021, resistance to cefixime was not found in any of the 24 isolates tested, in contrast to 2019, when resistance to cefixime was found in only one isolate, which is less than in 2018. (5.3%) or in 2017 when there were 6.9% of resistant isolates

In 2021, there were 19 (76%) resistant isolates to ciprofloxacin, in contrast to 2019, when there were 66.7% of resistant isolates, which is an increase compared to 2018, when it was 58.7%, or 2017 with 42 .4% of resistant isolates.

Given that, according to the guidelines, azithromycin is always used together with another effective agent, and when testing the acquired resistance mechanism, the ECOFF is 1 mg/L (EUCAST 2020), for the year 2019, the results for azithromycin were not interpreted, although the tests were carried out, and the MIK value was recorded. (Table 1).

It can be said that there is still no gradient to test for gentamicin, but testing is recommended to examine the efficacy of gentamicin in the event of a limited choice of therapy. Although azithromycin is available in the Republic of Croatia and good patient cooperation has been achieved, azithromycin is no longer recommended alone for testing, because according to experience, it is always given in combination with another antibiotic. Spectinomycin is still not available in the Republic of Croatia, but there is a possibility that it will be introduced in the future, and it is necessary to check its effectiveness. In 2021, spectinomycin resistance was not found in any of the tested isolates.

Tablica 1. Osjetljivost sojeva N. gonorrhoeae na antibiotike u RH, sa vrijednostima ispitivanja MIC-a metodom E-test
Izuzeci: osjetljivost ispitivana i metodom disk – difuzije
Table 1. Susceptibility testing of N. gonorrhoeae strains to antibiotics in Croatia, with MIC gradient band (E-test)
Exceptions: sensitivity testing by disk - diffusion methods

Ustanova	Penicilin MIK* (mg/L)			Ceftriakson MIK* (mg/L)			Cefiximi MIK* (mg/L)			Ciprofloxacin MIK* (mg/L)			Azithromycin*** MIK* (mg/L)	Tetracycline MIK* (mg/L)			Spektinomycin MIK* (mg/L)			Nitrocefin
	S	I	R	S	I	R	S	I	R	S	I	R		S	I	R	S	I	R	
HZJZ Zagreb																				
1.		0,125		0,002			0,016					1,5	0,125			1	1,5			/**
2.			1,5	0,002			/**	/**	/**			0,016	0,023	/**	/**	/**	0,064			**POZ**
3.		0,25		0,012			0,016			/**	/**	/**	0,125		0,75		4			**NEG**
NZJZ Štampar																				
1.		0,125		0,012			0,016					0,75	0,25	0,38			/**	/**	/**	**NEG**
2.	0,047			0,003			<0,016			<0,002			0,023	0,38			/**	/**	/**	**NEG**
3.		0,064		0,002			0,047					1	6	0,19			/**	/**	/**	**NEG**
4.		0,125		0,008			<0,016			0,003			1	0,25			/**	/**	/**	**NEG**
5.			3	0,012			0,064					1	4			8	/**	/**	/**	**POZ**
6.	0,032			<0,016			0,016					0,75	0,5			16	/**	/**	/**	**NEG**
7.		0,094		<0,016			0,032					4	1,5		1		/**	/**	/**	**NEG**
8.		0,38		0,016			0,047					1,5	>256	0,5			/**	/**	/**	**NEG**
9.		0,094		0,008			0,047					3	1,5		1		/**	/**	/**	**NEG**
10.		0,19		0,016			0,094					1,5	0,5	0,38			/**	/**	/**	**NEG**
11.		0,19		0,008			0,047					24	1,5			2	/**	/**	/**	**NEG**
12.		0,094		0,008			0,032					1	0,25	0,5			/**	/**	/**	**NEG**
13.	0,032			0,003			0,016			0,003			0,047	0,19			/**	/**	/**	**NEG**
KZIB																				
1.		0,064		<0,002			60mm◦					1,5	<0,023	0,25			/**	/**	/**	/
2.	0,047			0,006			50mm◦					1	0,009	0,038			/**	/**	/**	/
3.			>32	≤0,016			50mm◦					1	≤0,016	0,5			/**	/**	/**	**POZ**
KBC Split																				
1.		0,094		0,003			/**	/**	/**	<0,002			0,5	0,25			/**	/**	/**	/
NZJZ Primorsko - goranska županija																				
1.	0,047			0,125			0,125					0,75	16	0,125			/**	/**	/**	**NEG**
2.	0,094			0,002			0,016					0,75	0,25	0,094			/**	/**	/**	**NEG**
3.	0,012			0,002			0,016					0,125	0,125	0,016			0,125			**NEG**

ZZJZ Međimurske županije-Čakovec																			
1.	/**	/**	/**	0,012			0,032					1,5	32			24	4			**NEG**
ZZJZ Šibensko-kninske županije																			
1.	/**	/**	/**	0,003			0,016			0,002			0,5			1,5	/**	/**	/**	**NEG**
Zagreb-privatna poliklinika																			
1.		0,25		0,004			0,016					2	0,094			2	4			/

*MIK =Minimalna inhibiotrna koncentracija antibiotika određena metodom eksponencijalnog gradijenta (E-test)
**/ = Zbog tehničkih razloga nije bilo moguće provesti testiranje osjetljivost izolata na dotični antibiotic
***Azitromicin se uvijek koristi zajedno s drugim učinkovitim sredstvom. Prilikom ispitivanja stečenog mehanizma rezistencije, ECOFF je 1 mg/L (EUCAST 2020.)
◦ metoda disk difuzije

Tablica 2. Osjetljivost sojeva N. gonorrhoeae na antibiotike u Hrvatskoj, 2021.
Table 2. Antimicrobial susceptibility of N. gonorrhoeae strains to antibiotics in Croatia. 2021.

Ustanova	Penicilin MIK* (mg/L)				Ceftriakson MIK* (mg/L)				Cefixim MIK* (mg/L)				Ciprofloxacin MIK* (mg/L)				Tetracycline MIK* (mg/L)				Spektinomycin MIK* (mg/L)			
	UK***	S (%)	I (%)	R (%)	UK***	S (%)	I (%)	R (%)	UK***	S (%)	I (%)	R (%)	UK***	S (%)	I (%)	R (%)	UK***	S (%)	I (%)	R (%)	UK***	S (%)	I (%)	R (%)
HZJZ Zagreb	**3**	0	2 (66,7)	**1 (33,3)**	**3**	3 (100)	0	**0**	**2**	2 (100)	0	**0**	**2**	0	0	**2 (100)**	**2**	0	1 (50)	**1 (50)**	**3**	3 (100)	0	**0**
NZJZ Štampar	**13**	3 (23,1)	9 (69,2)	**1 (7,7)**	**13**	13 (100)	0	**0**	**13**	13 (100)	0	**0**	**13**	3 (23,1)	0	**10 (76,9)**	**13**	8 (61,5)	2 (15,4)	**3 (23,1)**	**/	**/	**/	**/
KZIB	**3**	1 (33,3)	1 (33,3)	1 (33,3)	**3**	3 (100)	0	**0**	**3**	3 (100)	0	**0**	**3**	0	0	**3 (100)**	**3**	3 (100)	0	**0**	**/	**/	**/	**/
KBC Split	**1**	0	1 (100)	**0**	**1**	1 (100)	0	**0**	**/	**/	**/	**/	**1**	1 (100)	0	**0**	**1**	1 (100)	0	**0**	**/	**/	**/	**/
NZJZ Primorsko - goranska županija	**3**	3 (100)	0	**0**	**3**	3 (100)	0	**0**	**3**	3 (100)	0	**0**	**3**	0	0	**3 (100)**	**3**	3 (100)	0	**0**	**1**	1 (100)	0	**0**
ZZJZ Međimurske županije-Čakovec	**/	**/	**/	**/	**1**	1 (100)	0	**0**	**1**	1 (100)	0	**0**	**1**	1 (100)	0	**0**	**1**	0	0	**1 (100)**	**1**	1 (100)	0	**0**
ZZJZ Šibensko-kninske županije	**/	**/	**/	**/	**1**	1 (100)	0	**0**	**1**	1 (100)	0	**0**	**1**	1 (100)	0	**0**	**1**	0	0	**1 (100)**	**/	**/	**/	**/
Zagreb- privatna poliklinika	**1**	0	1 (100)	**0**	**1**	1 (100)	0	**0**	**1**	1 (100)	0	**0**	**1**	0	0	**1 (100)**	**1**	0	0	**1 (100)**	**1**	1 (100)	0	**0**
UKUPNO	**24**	7 (29,2)	14 (58,3)	**3 (12,5)**	**26**	26 (100)	0	**0**	**24**	24 (100)	0	0	**25**	6 (24)	0	**19 (76)**	**25**	15 (60)	3 (12)	**7 (28)**	**6**	3 (100)	0	**0**

*MIK = Minimalna inhibiotrna koncentracija antibiotika određena metodom eksponencijalnog gradijenta (E-test)
**/ = Zbog tehničkih razloga nije bilo moguće provesti testiranje osjetljivost izolata na dotični antibiotik
***UK = ukupan broj sojeva ispitane osjetljivosti na određeni antibiotik

POGLAVLJE / CHAPTER 4.

PRAĆENJE REZISTENCIJE NA ANTIBIOTIKE U INVAZIVNIH IZOLATA

ANTIBIOTIC RESISTANCE SURVEILLANCE IN INVASIVE ISOLATES

Silvija Šoprek
Arjana Tambić Andrašević

Klinika za infektivne bolesti "Dr. Fran Mihaljević", Zagreb
Referentni centar za praćenje rezistencije bakterija na antibiotike Ministarstva zdravlja RH
University Hospital for Infectious Diseases "Dr. Fran Mihaljević", Zagreb
Reference Centre for Antibiotic Resistance Surveillance of the Croatian Ministry of Health

Važnost praćenja rezistencije u invazivnih izolata

Sustavno praćenje rezistencije na antibiotike na europskoj razini započelo je 1999.g. u okviru European Antimicrobial Resistance Surveillance System (EARSS) projekta. Za prioritete u praćenju odabrano je u početku šest bakterijskih vrsta *S. aureus, E. faecalis, E. faecium, S. pneumoniae* i *E. coli*, od 2005.g. dodano je praćenje rezistencije u *K. pneumoniae* i *P. aeruginosa*, a od 2013.g. započeto je i praćenje rezistencije u *Acinetobacter* spp. S obzirom na različitu praksu uzimanja uzoraka i interpretaciju nalaza u različitim zemljama odlučeno je da se u praćenju na europskoj razini u obzir uzimaju samo invazivni izolati (iz hemokultura i likvora). Interpretacija nalaza ovih bakterija u hemokulturi i likvoru je u svim laboratorijima jednaka i njihovo kliničko značenje je neupitno. S obzirom na već postojeću mrežu mikrobioloških laboratorija u okviru Odbora za praćenje rezistencije na antibiotike, Hrvatska se spremno uključila u EARSS projekt od samog početka, a nakon što je Hrvatska postala članicom Europske unije hrvatski podaci su uključeni u EARS-Net program Europskog centra za prevenciju i kontrolu bolesti (engl. "European Center for Disease Prevention and Control", ECDC). Nedostatak praćenja rezistencije samo u invazivnih izolata je mali broj izolata u nekim centrima što onemogućuje analizu na razini pojedinih centara te činjenica da se prvi izolati s novim mehanizmima rezistencije ne moraju javiti u hemokulturi ili likvoru. Prednost sudjelovanja u europskoj mreži je mogućnost uspoređivanja s drugim zemljama te raspolaganje podacima o rezistenciji među invazivnim izolatima. Masovno praćenje rezistencije opisano u prvom poglavlju ove publikacije i ciljano praćenje invazivnih izolata dobro se nadopunjuju i predstavljaju dobru kombinaciju za praćenje rezistencije u Hrvatskoj na nacionalnoj i lokalnoj razini.

Rezultati praćenja rezistencije u invazivnih izolata

Tijekom niza godina podaci o izolatima su prikupljani putem papirnatih obrazaca u Referentnom centru za praćenje rezistencije bakterija na antibiotike, u Klinici za infektivne bolesti „Dr. Fran Mihaljević", gdje su centralno upisivani te statistički obrađivani. Do reorganizacije u prikupljanju podataka dolazi tijekom 2020.g., kada se prema dogovoru službeno prelazi na elektronsko slanje podataka, te se od 2021.g. podaci šalju i prikupljaju samo u elektronskom obliku. Zbog često insuficijentnih podataka o vrsti odjela, od 2020.g. odlučeno je prikazivati podatke samo za jedinice intezivne njege (ICU) što je promijenilo izgled tablice 3 i 4 u kojoj su prikazani demografski podaci za pacijente i porijeklo uzoraka.

U sklopu EARS-Net programa, u Referentni centar za praćenje rezistencije bakterija na antibiotike se šalju i prikupljaju svi invazivni izolati *S. pneumoniae, S. aureus, E. faecalis, E. faecium, E. coli, K. pneumoniae, P. aeruginosa, Acinetobacter* spp., praćeni sa svrhom retestiranja izolata s rijetkim fenotipom i eventualne daljnje obrade. Tijekom 2021.g. prikupljeno je 93 izolata *S. pneumoniae,* 988 izolata *E. coli*, 482 izolata *K. pneumoniae*, 786 izolata *S. aureus*, 433 izolata enterokoka (271 *E. faecalis* i 162 *E. faecium* izolata), 284 izolata *P. aeruginosa*, te 640 izolata *Acinetobacter* spp. (Tablica 1).

U 2021.g. bilježimo veći broj laboratorija koji su prijavili svoje izolate, te je posljedično prikupljen značajno veći broj izolata nego prethodnih godina (3706 izolata 2021.g.; 2821 izolat 2017.g.). Zamijećen pad prijavljenih izolata tijekom 2020.g i 2021.g. predstavlja izolirani fenomen direktno povezan s organizacijsko-logističkim poteškoćama tijekom pandemije izazvane uzročnikom SARS-CoV-2. Broj laboratorija i broj prikupljenih invazivnih izolata pojedinih vrsta prikazani su u Tablici 1.

Značajan porast broja prijavljenih invazivnih izolata *Acinetobacter* spp., *S.aureus*, enterokoka te *K. pneumoniae,* zabilježen u 2020.g., nastavlja se i tijekom 2021.g. Većina navedenih izolata predstavlja tipične bolničke patogene pa dodatno zabrinjava činjenica da je povećan njihov udio i u jedinicama intenzivne njege.

Zapaža se izraziti skok u broju prijavljenih izolata *Acinetobacter* spp. (225 u 2020.g; 640 u 2021.g.) što se može objasniti olakšanim širenjem *Acinetobacter* spp. unutar kohortiranih pacijenata inficiranih sa SARS-CoV-2, a istom pridonosi i veći broj laboratorija koji su tijekom 2021.g prijavili svoje podatke. Rezistencija *Acinetobacter* spp. na karbapeneme je pri tome izuzetno visoka (>99%). Porast broja izolata *Acinetobacter* spp. u jedinicama za intenzivnu njegu (ICU), prvotno primijećen tijekom pandemijskog razdoblja se i dalje nastavlja, pa u 2021.g. imamo 75% izolata *Acinteobacter* spp. iz ICU (40% izolata iz ICU 2019).

Sličan fenomen se primijećuje i kod izolata *S. aures*, gdje se broj prijavljenih izolata gotovo udvostručio tijekom dvogodišnjeg razdoblja pandemije, pa u 2021.g. bilježimo 786 prijavljenih izolata *S. aureus*.
Nažalost povećanje broja prijavljenih izolata *S. aureus* slijedi i veći broj prijavljenih MRSA izolata, te se u 2021.g. suočavamo sa zabrinjavajuće visokim stopama invazivnih MRSA sojeva (36%), što su najviše zabilježene stope u zadnjih 10 godina. Povećan udio MRSA (27%) je registriran i kod ukupnog broja izoliranih stafilokoka iz svih uzoraka (Poglavlje 1).

Trend glikopeptidne rezistencije u *Enterococcus faecium* je i dalje prisutan s kontinuiranim rastom stopa rezistencije (39% u 2021.g., 33% u 2020.g.). Rezistencija na glikopeptide kod *E. faecalis* je nešto viša nego prijašnjih godina (3%). Stope visoke rezistencije na aminoglikozide su i dalje visoke u *E. faecalis izolata* dok se kod izolata *E.faecium* zadnjih godina primjećuje trend pada rezistencije na tu skupinu antibiotika s najniže zabilježenim stopama ikad (30%).

Trend porasta stopa rezistencije kod invazivnih izolata *K.pneumoniae* uočen je u svim klasama antibiotika osim u aminoglikozida gdje su stope rezistencije stabilne zadnjih nekoliko godina (oko 40%). Nažalost stope rezistencije na karbapeneme ne pokazuju tendenciju stabilizacije dosadašnjeg trenda porasta, dapače, 2021.g. bilježimo značajan skok u rastu stopa rezistencije na tu skupinu antibiotika. Gledajući izolate rezistentne na karbapeneme (imipenem i/ili meropenem), stope rezistencije dosežu čak 28%, dok je dodatnih 7% izolata *K.pneumoniae* osjetljivo na iste uz povećanu dozu antibiotika. Sveukupno 34% invazivnih izolata *K.pneumoniae* predstavlja velik izazov u liječenju i odabiru otpimalne antibiotske terapije.

Invazivni izolati *P.aeruginosa* ne pokazuju značajnijih odstupanja prema dosadašnjim stopama rezistencije, osim u skupini aminoglikozida gdje se i dalje nastavlja trend pada stopa rezistencije.

Stopa rezistencije *E. coli* na 3. generaciju cefalosporina nije se bitno mijenjala u odnosu na prošlu godinu (18%). Podaci pokazuju da je rezistencija u toj klasi antibiotika i dalje pretežno uzrokovana proizvodnjom beta-laktamaza proširenog spektra (engl. „extended spectrum beta-lactamases“, ESBL). Rezistencija na kinolone je 29%.

Broj prijavljenih izolata *S. pneumoniae* u 2021.g. je veći u odnosu na pandemijske godine SARS-CoV-2, kako zbog većeg broja laboratorija koji prijavljuju svoje podatke tako i zbog novih epidemioloških mjera koje su dovele do normalizacije u cirkulaciji respiratornih patogena. Neosjetljivost na penicilin među invazivnim izolatima pneumokoka u 2021.g. je 19%, što je najniža vrijednost zadnjih 10tak godina. Stopa rezistencije na makrolide je u značajnom padu s obzirom na dosadašnje godine (24% u 2021.g.; 40% u 2020.g.; 30% u 2019.g.).

Stope rezistencije detaljno su prikazane u Tablici 2.

Demografski podaci za pacijente i porijeklo uzoraka prikazani su u Tablicama 3 i 4.

Zastupljenost rezistentnih izolata u pojedinim centrima prikazana je na Slikama 1- 8.

Impact of antibiotic resistance surveillance in invasive isolates

Systematic antibiotic resistance surveillance at the European level started with the European Antimicrobial Resistance Surveillance System (EARSS) project in 1999. At the beginning six bacterial species were selected as a priority for resistance surveillance, namely *S. aureus, E. faecalis, E. faecium, S. pneumoniae* and *E. coli*. In 2005 *K. pneumoniae* and *P. aeruginosa* and in 2013 *Acinetobacter* spp. were added in resistance surveillance. Considering that there is a wide variation in sampling and interpretation of results among different countries it was decided that only invasive isolates (from bloodcultures and cerebrospinal fluid, CSF) will be included in the European surveillance. Interpretation of bacterial growth in blood and CSF is unique for the species tested in all laboratories and the clinical significance of these findings is not questionable. Thanks to the already existing network of microbiology laboratories within the Croatian Committee for Antibiotic Resistance Surveillance, Croatia readily joined EARSS at the very beginning of the project and when Croatia joined European Union, Croatian data were included into EARS-Net program of the European Centre for Disease Prevention and Control (ECDC). The limitation of antibiotic resistance surveillance in invasive isolates only, is that some centres may have too few isolates to enable analysis at the local level and first isolates with novel resistance mechanisms do not necessarily appear in blood or CSF. Participation in the European surveillance network offers many advantages such as a possibility of comparing data with other countries and having information about resistance in invasive isolates. Therefore mass surveillance as described in chapter 1 of this publication and focused study of resistance in invasive isolates provide a good combination for surveillance of antimicrobial resistance at local and national level in Croatia.

Results of the antibiotic resistance surveillance in invasive isolates

Over a number of years, data on isolates were sent on paper forms and processed in the Reference Centre for Antibiotic Resistance Surveillance. The reorganization of data collection will take place during 2020, when, according to the agreement, laboratories will officially start sending data through electronic databases. For laboratories that were not able to report data electronically, the possibility of sending data on the paper forms was still an option. From 2021 data is sent and collected only in electronic form. Due to the frequently missing data on sample origin (department and location), from 2020 it was decided to display data separately for Intensive Care Units (ICU) only, which changed the layout of Tables 3 and 4.

All isolates of species included in EARS-Net program are sent to the Reference Centre for Antibiotic Resistance Surveillance, with a purpose of retesting and further analysis of isolates with unusual phenotype. During 2021, 93 isolates of *S. pneumoniae*, 988 isolates of *E. coli*, 482 isolates of *K. pneumoniae*, 786 isolates of *S.aureus*, 433 enterococcal isolates (271 *E. faecalis* and 162 *E. faecium* isolates), 284 isolates of *P.aeruginosa* and 640 isolates of *Acinetobacter* spp. were collected (Table 1).

We are recording a larger number of laboratories reporting their isolates to Reference Center in 2021. Accordingly, a significantly higher number of isolates was collected than in previous years (3706 isolates in 2021; 2821 isolates in 2017). Decline observed in number of reported isolates during 2020 and 2021 is probably isolated phenomenon directly linked to variety of difficulties connected with SARS-CoV-2 pandemic that affected all parts of health care system. The number of laboratories and the number of collected invasive isolates of individual species are shown in Table 1.

A significant increase in the number of reported invasive isolates of *Acinetobacter* spp., *S.aureus*, enterococcus and *K. pneumoniae*, recorded in 2020, continues in 2021. As the majority of the listed

isolates represent typical hospital pathogens, the fact there is an increase in the proportion of them originating from intensive care units arises an additional concern.

The number of invasive *Acinetobacter* spp. isolates almost tripled comparing to last years data, and is the highest ever (640). The observed increase can be partially explained with the larger number of laboratories reporting data and by the facilitated spread of *Acinetobacter* spp. within cohorted COVID patient. Almost all reported isolates of *Acinetobacter* spp. are resistant to carbapenems, consequently the carbapenem resistance rates are extremely high (>99%). Especially worrying is the high proportion of *Acinetobacter* spp. isolates with the origin from intensive care units (ICU). As much as 74% of isolates originate from ICU.

A similar phenomenon is observed with *S. aures* isolates, where the number of reported isolates almost doubled during the two-year period of the pandemic, with 786 reported S. aureus isolates in 2021. Unfortunately, the larger number of reported *S. aureus* isolates is followed by the increase of MRSA isolates, and in 2021. we are facing alarmingly high rates of invasive MRSA strains (36%), which are the highest recorded rates in the last 10 years. An increased proportion of MRSA (27%) was also registered in the total number of isolated staphylococci from all samples (Chapter 1).

The increasing trend in glycopeptide resistance in *Enterococcus faecium* is still present with a continuous increase in resistance rates (39% in 2021, 33% in 2020), while glycopeptide resistance in *E. faecalis* is slightly higher than in previous years (3%). High rates of aminoglycoside resistance remain high in *E. faecalis*, while a decreasing trends can be observed in *E.faecium* isolates, with the lowest rates ever recorded (30%).

The trend of increasing resistance rates in invasive isolates of K.pneumoniae is still present in all classes of antibiotics except aminoglycosides, where resistance rates have been stable for the last few years (around 40%). Unfortunately, the resistance rates to carbapenems continue to increase. Looking at isolates resistant to carbapenems (imipenem and/or meropenem), the resistance rates reach as high as 28%, with 7% of isolates sensitive to carabapenems with an increased dose. Overall, 34% of invasive *K.pneumoniae* isolates present a major challenge for treatment due to very few antibiotics left as treatment options.

There are no significant changes in resistance rates of *P.aeruginosa* isolates. A trend of decreasing resistance rates in the group of aminoglycosides is still present.

The resistance of *E. coli* to the 3rd generation cephalosporins did not change significantly compared to last year (18%). The data show that resistance in this class of antibiotics is still predominantly caused by the production of extended spectrum beta-lactamases (ESBLs). Resistance to quinolones is 29%.

The number of reported isolates of *S. pneumoniae* in 2021 is higher compared to the SARS-CoV-2 pandemic years, both due to a greater number of laboratories reporting their data and due to new epidemiological measures that led to normalization in the circulation of respiratory pathogens. Reduced susceptibility to penicillin among invasive pneumococcal isolates in 2021 is 19% which is the lowest rate observed in the last 10 years. The macrolides resistance rate significantly decreased compared to previous years (24% in 2021; 40% in 2020; 30% in 2019).

Resistance rates are in detail shown in Table 2.

Demographic patient data and sample origin data are shown in Table 3 and 4.

Proportion of resistant isolates by laboratory centre is shown in Figures 1- 8.

Tablica 1. / *Table 1.*
Broj laboratorija i izolata prijavljenih u razdoblju od 2001.-2021. /
Number of laboratories and number of isolates reported for the period 2001-2021

Godina	*S. pneumoniae*		*S. aureus*		*E.coli*		*Enterococcus* spp.		*K .pneumoniae*		*P. aeruginosa*		*Acinetobacter spp.*	
	Lab	Izolati / Isolates	Lab	Izolati/ Isolates	Lab	Izolati/ Isolates	Lab	Izolati/ Isolates	Lab	Izolati/ Isolates	Lab	Izolati/ Isolates	Lab	Izolati / Isolate
2001	10	20	14	149	13	182	7	33	0	0	0	0		
2002	14	90	14	279	15	490	13	96	0	0	0	0		
2003	12	88	14	360	16	570	11	101	0	0	0	0		
2004	12	103	13	392	14	535	11	115	0	0	0	0		
2005	15	129	17	354	16	638	11	120	14	112	10	72		
2006	14	116	17	391	17	780	16	178	15	205	15	170		
2007	15	136	15	375	17	852	13	174	17	279	16	189		
2008	13	100	18	474	17	915	16	232	17	333	14	221		
2009	14	100	14	463	16	911	20	223	16	318	15	212		
2010	11	103	15	363	16	897	12	176	16	286	15	217		
2011	16	127	14	451	16	1007	15	244	14	314	15	265		
2012	11	98	17	412	17	921	14	219	15	344	14	204		
2013	16	119	21	533	20	1066	17	250	19	396	19	256	13	114
2014	17	131	19	514	20	1104	18	226	18	341	18	251	16	170
2015	15	126	16	516	18	1062	16	308	17	395	17	267	17	203
2016	17	156	18	476	18	1078	14	288	17	339	16	269	14	188
2017	13	132	18	540	19	1201	17	272	19	319	17	249	17	215
2018	17	147	18	471	19	1263	16	220	19	350	17	210	14	160
2019	16	156	15	374	19	1145	17	206	17	341	15	192	16	151
2020	12	55	19	424	19	828	16	250	16	270	18	165	14	225
2021	17	93	22	786	22	988	21	433	20	482	19	284	21	640

Tablica 2. / *Table 2.*
Udio izolata rezistentnih i osjetljivih uz povećanu izloženost na antibiotike izražen u postocima / *Proportion of antibiotic resistant and susceptible, increased exposure isolates in percent*

PATOGEN / PATHOGEN	ANTIBIOTICI/ Antimicrobial classes	2009 %	2010 %	2011 %	2012 %	2013 %	2014 %	2015 %	2016 %	2017 %	2018 %	2019 %	2020 %	2021 %
S. pneumoniae	Penicillin R	6	7	1	1	4	1	1	1	1	1	2	1	0
	Penicillin I+R	19	21	18	23	27	26	20	22	21	20	20	24	19
	Macrolides R	8	29	24	28	34	28	19	33	37	33	30	40	24
S. aureus	Oxacillin/Met R	37	27	27	22	24	21	25	25	28	26	25	29	36
E. coli	Aminopenicillin R	55	55	55	52	54	54	56	57	59	58	57	58	57
	Aminoglycoside R	8	6	7	7	7	10	12	14	16	14	13	15	14
	Fluoroquinolone R	16	17	20	17	21	20	25	28	30	30	27	30	29
	3. gen Cef R	5	8	7	8	9	11	13	12	16	14	15	17	18
	ESBL			9	7	9	11	13	14	16	15	17	16	25
E. faecalis	Aminopenicillins R		5	1	5	9	6	4	7	5	3	2	4	6
	HL Aminoglycoside R	36	37	33	39	35	33	35	33	32	34	24	38	43
	Glycopeptides R	<1	<1	1	<1	<1	0	0	0	<1	2	2	1	3
E. faecium	Aminopenicillin R		82	98	98	90	94	97	98	96	98	94	99	96
	HL Aminoglycoside R	68	60	66	61	55	64	53	65	50	64	51	37	30
	Glycopeptides R	11	12	2	0	7	10	26	23	19	25	26	33	39
K. pneumoniae	Aminoglycoside R	47	49	43	45	51	48	40	31	28	33	40	38	42
	Fluoroquinolone R	51	48	43	43	45	46	50	44	50	49	59	54	60
	3. gen Cef R	53	56	50	44	50	48	46	42	41	42	51	52	58
	ESBL			51	52	50	48	47	46	41	43	51	52	62
	Carbapenems I+R			<1	<1	1	2	3	2	5	7	16	19	34
	Carbapenem R			0	0	0	0	0	0	0	2	12	19	28
P. aeruginosa	Piperacillin R		23											
	Piperacllin/ Tazobactam R		16	23	18	23	32	25	20	16	11	14	10	13
	Ceftazidime R	11	12	17	14	20	28	20	23	21	19	20	19	20
	Carbapenems R	31	26	30	21	25	35	37	41	30	27	23	30	31
	Aminoglycoside R	37	26	34	26	24	37	34	32	27	23	20	10	9
	Fluoroquinolones R	29	27	34	24	23	28	37	38	39	29	26	23	23
A. baumannii	Carbapenems R					91	88	89	95	96	95	93	96	99

Tablica 3. / *Table 3.*
Prikaz gram-pozitivnih invazivnih izolata u 2021.g. prema demografskim podacima pacijenata /
Selected details on gram-positive invasive isolates from the reporting period 2021

	S.pneumoniae		***S.aureus***		***Enterococcus* spp.**	
	n=98		**n=786**		**n=433**	
	% tot	**% PNPS**	**% tot**	**% MRSA**	**% tot**	**% VRE**
UZORAK ***SAMPLE***						
Krv / Blood	96	18	99	30	99	14
Likvor / CSF	4	50	<1	25	<1	0
SPOL ***GENDER***						
M	52	19	62	33	63	14
Ž / F	41	20	38	38	36	15
Nepoznato / Unknown	0	0	<1	100	<1	0
DOB ***AGE***						
0-4	12	27	3	25	3	7
5-19	<1	0	<1	0	<1	0
20-64	41	16	34	30	33	9
>65	45	21	63	38	63	17
Nepoznato / Unknown	1	0	0	0	0	0
ODJEL ***DEPARTMENT***						
Intenzivna / ICU	20	26	25	49	40	17

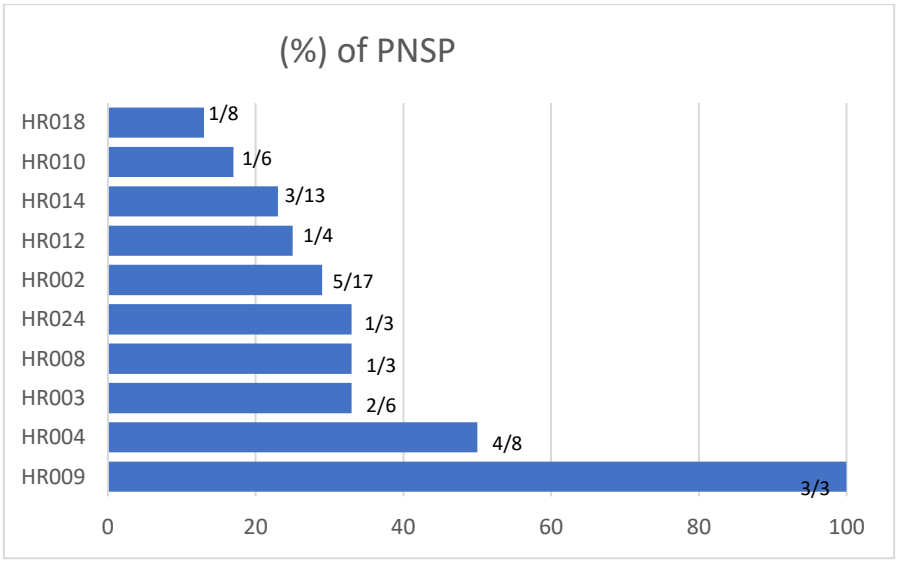
PNSP=Penicillin Non-Susceptible *S. Pneumoniae* MRSA=Methicillin Resistant *S.aureus* VRE=Vancomycin Resistant Enterococcus

Tablica 4. / *Table 4.*
Prikaz gram-negativnih invazivnih izolata u 2021.g. prema demografskim podacima pacijenata / *Selected details on gram-negative invasive isolates from the reporting period 2021*

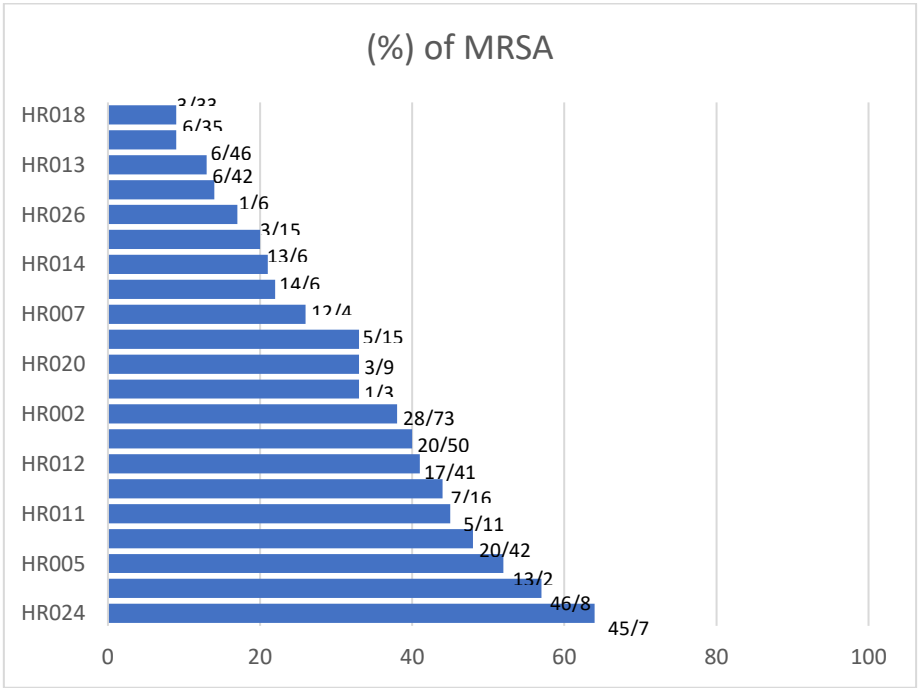
	E. coli			***Acinetobacter* spp.**		***K.pneumoniae***		***P.aeuroginosa***	
	n=828			**n=225**		**n=270**		**n=165**	
	% tot	**% FREC**	**% CREC**	**% tot**	**% CRA**	**% tot**	**% CRKP**	**% tot**	**% CRPA**
UZORAK *SAMPLE*									
Krv / Blood	99	28	16	99	96	99	51	100	30
Likvor / CSF	<1	0	0	1	100	1	100	0	0
SPOL *GENDER*									
M	44	34	18	73	97	53	55	64	29
Ž / F	54	23	14	26	95	43	46	36	32
Nepoznato / Unknown	2	28	28	1	100	4	64	0	0
DOB *AGE*									
0-4	3	4	0	<1	50	4	50	1	100
5-19	<1	0	0	<1	100	<1	100	1	0
20-64	28	24	12	38	97	31	55	40	37
>65	68	32	19	59	97	65	49	58	24
Nepoznato / Unknown	<1	<1	<1	<1	100	0	0	0	0
ODJEL *DEPARTMENT*									
Intenzivna / ICU	5	35	19	73	100	16	40	32	34

FREC=Fluoroquinolone Resistant *E.coli* CREC=3rd gen. Cepfalosporine Resistant *E.coli* CRKP=3rd gen. Cepfalosporine Resistant *K. pneumoniae* CRPA=Carbapenem Resistant *P. aeruginosa* CRA=Carbapenem Resistant *Acinetobacte*r spp.

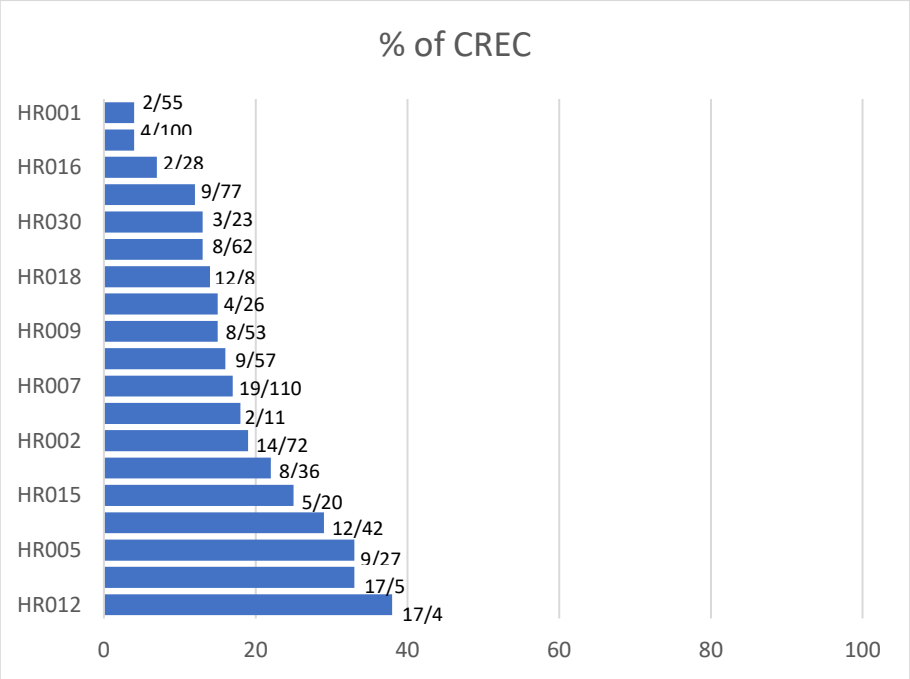
Slika 1. / *Figure 1.*
Udio (%) izolata *S. pneumoniae* smanjene osjetljivosti na penicilin (PNSP) po centrima /
Proportion (%) of penicillin non-susceptible S. pneumoniae (PNSP) by center



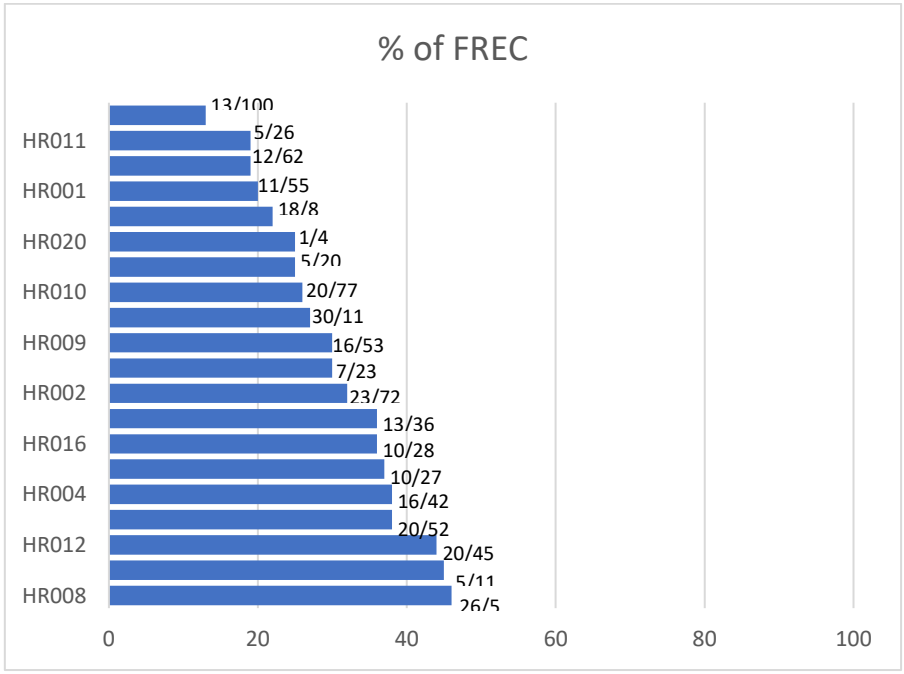
Slika 2. / *Figure 2.*
Udio (%) MRSA izolata po centrima /
Proportion (%) of MRSA isolates by center



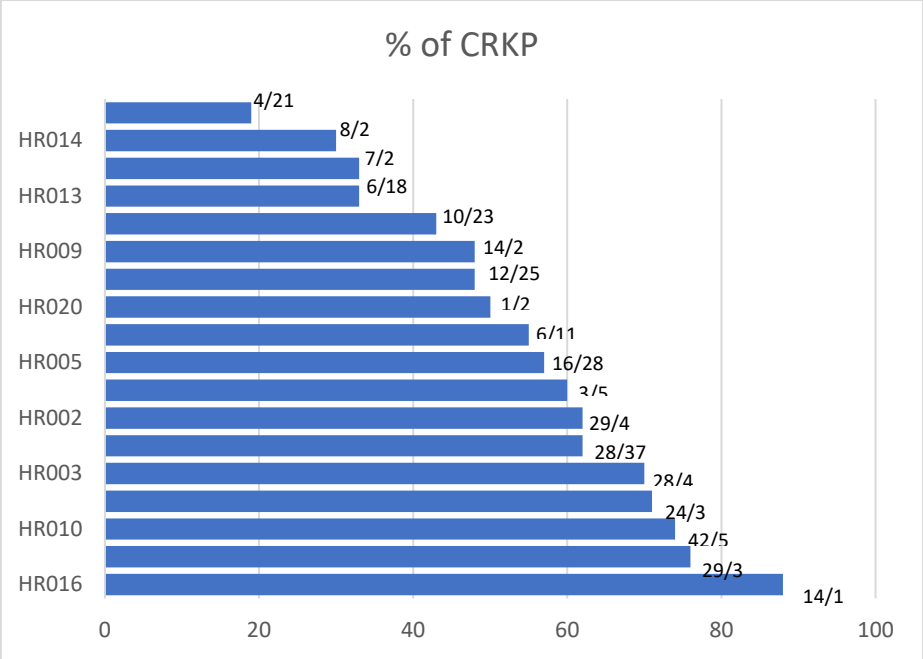
Slika 3. / *Figure 3.*
Udio (%) ceftazidim rezistentnih izolata *E. coli* (CREC) po centrima /
Proportion (%) of ceftazidime resistant E. coli isolates (CREC) by center



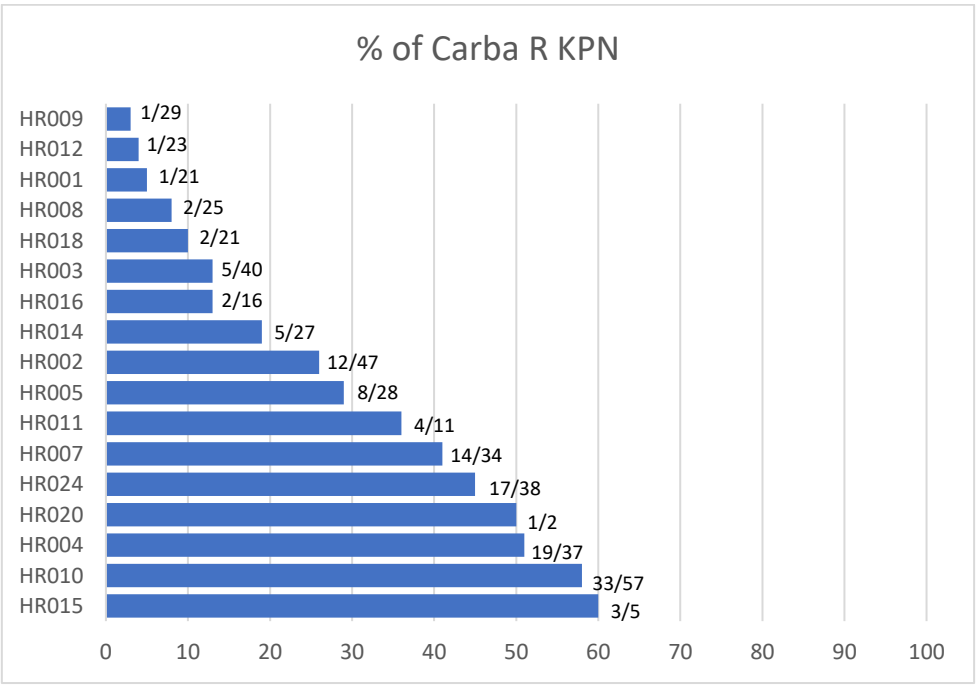
Slika 4. / *Figure 4.*
Udio (%) fluorokinolon rezistentnih izolata *E. coli* (FREC) po centrima /
Proportion (%) of fluoroquinolone resistant E.coli isolates (FREC) by center



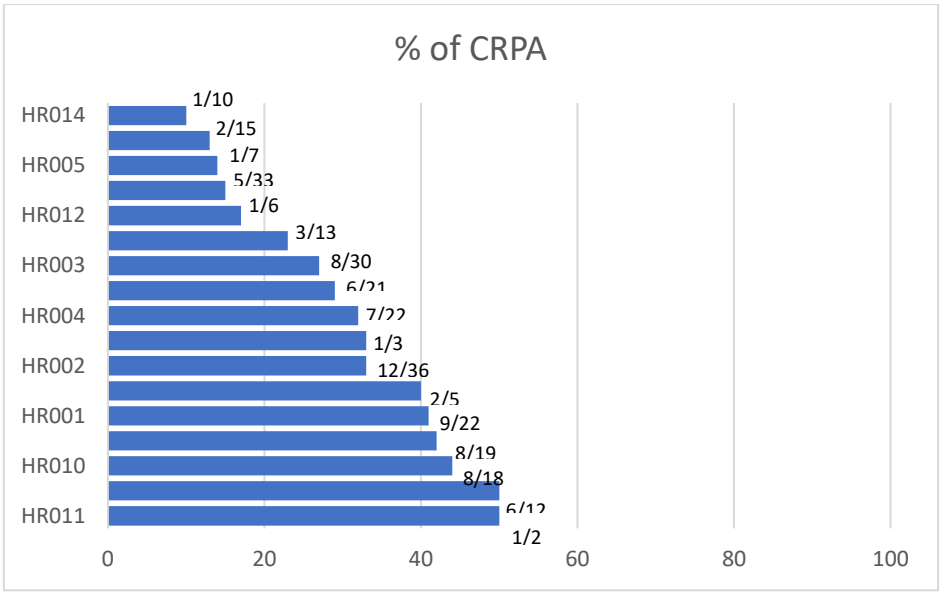
Slika 5. / *Figure 5.*
Udio (%) ceftazidim rezistentnih izolata *K. pneumoniae* (CRKP) po centrima /
Proportion (%) of ceftazidime resistant K. pneumoniae (CRKP) by center



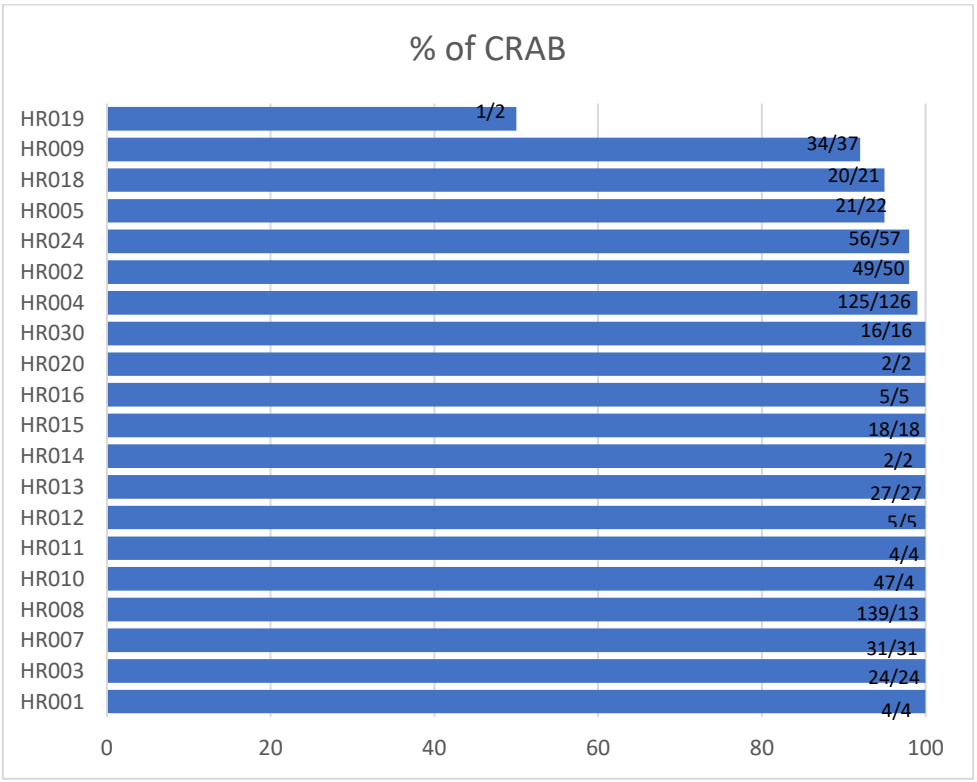
Slika 6. / *Figure 6.*
Udio (%) karbapenem rezistentnih izolata *K. pneumoniae* (Carb R KP) po centrima /
Proportion (%) of carbapenem resistant K. pneumoniae (Carb R KP) by center



Slika 7. / *Figure 7.*
Udio (%) karbapenem rezistentnih izolata *P. aeruginosa* (CRPA) po centrima /
Proportion (%) of carbapenem resistant P. aeruginosa (CRPA) by center



Slika 8. / *Figure 8.*
Udio (%) karbapenem rezistentnih izolata *Acinetobacter* spp. po centrima /
Proportion (%) of carbapenem resistant Acinetobacter spp. by center



POGLAVLJE / CHAPTER 5.

UČESTALOST VRSTA *CANDIDA* SPP. I OSJETLJIVOST NA ANTIFUNGALNE LIJEKOVE KOD BOLESNIKA S KANDIDEMIJOM U HRVATSKOJ U 2021. GODINI

DISTRIBUTION OF CANDIDA SPECIES AND ANTIFUNGAL SUSCEPTIBILITY IN PATIENTS WITH CANDIDEMIA IN CROATIA, 2021

Sanja Pleško
Zoran Herljević
Violeta Rezo Vranješ
Marko Siroglavić
Ivana Mareković

Klinički bolnički centar Zagreb
Klinički zavod za kliničku i molekularnu mikrobiologiju
Centar izvrsnosti za laboratorijsku mikologiju Europske konfederacije za medicinsku mikologiju
University Hospital Centre Zagreb
Department for Clinical and Molecular Microbiology Excellence Centre for Medical Mycology of European Confederation of Medical Mycology (ECMM)

Učestalost vrsta *Candida* spp. i osjetljivost na antifungalne lijekove kod bolesnika s kandidemijom u Hrvatskoj u 2021. godini

Distribution of *Candida* species and antifungal susceptibility in patients with candidemia in Croatia, 2021

Sanja Pleško, Zoran Herljević, Violeta Rezo Vranješ, Marko Siroglavić, Ivana Mareković

Klinički bolnički centar Zagreb
Klinički zavod za kliničku i molekularnu mikrobiologiju
Centar izvrsnosti za laboratorijsku mikologiju Europske konfederacije za medicinsku mikologiju

Uvod

Posljednjih desetak godina u svijetu je je došlo do porasta incidencije kandidemija ovisno o geografskom položaju i populaciji bolesnika. Prema posljednjim procjenama u svijetu se godišnje zabilježi oko 700 000 slučajeva invazivne kandidoze. Brojna do sada provedena epidemiološka istraživanja iz mnogih europskih zemalja pokazala su različitost i potrebu za praćenjem učestalosti pojedinih vrsta *Candida* spp. i njihove osjetljivosti na antifungalne lijekove. Poznavanje navedenih podataka temelj je pri odlučivanju o empirijskom liječenju, profilaksi te mjerama prevencije i kontrole infekcija.

Klinički zavod za kliničku i molekularnu mikrobiologiju Kliničkog bolničkog centra Zagreb 2018. godine stekao je naziv Centra izvrsnosti za laboratorijsku mikologiju Europske konfederacije za medicinsku mikologiju te od početka 2019. godine uz podršku Odbora za praćenje rezistencije započeo s prikupljanje izolata *Candida* spp kod bolesnika s kandidemijom. Svi mikrobiološki laboratoriji u Hrvatskoj pozvani su po izolaciji *Candida* spp. u hemokulturi bolesnika poslati u Centar izvrsnosti te ispuniti obrazac na mrežnoj stranici Centra izvrsnosti fungi.kbc-zagreb.hr koji sadrži podatke o samom izolatu, primjenjenim metodama identifikacije i ispitivanja osjetljivosti na antifungalne lijekove kao i kliničkim karakteristikama bolesnika. U Centru izvrsnosti se svaki poslani izolat identificira te se ispituje njegova osjetljivost na antifungalne lijekove referentnom metodom mikrodilucije u bujonu (prema CLSI smjernicama). U ovom izvješću prikazani su podaci o učestalosti vrsta *Candida* spp. i osjetljivosti na antifungalne lijekove u 2021. godini.

Učestalost vrsta *Candida* spp.

Za vrijeme ovog razdoblja ukupno je prikupljeno i analizirano 215 izolata *Candida* spp. Učestalost pojedinih *Candida* spp prikazana je u Tablici 1. Usporedbom podataka iz 2019. (154 izolata) godine i 2020. (136 izolata) bilježi se značajan porast analiziranih izolata (oko 40%)

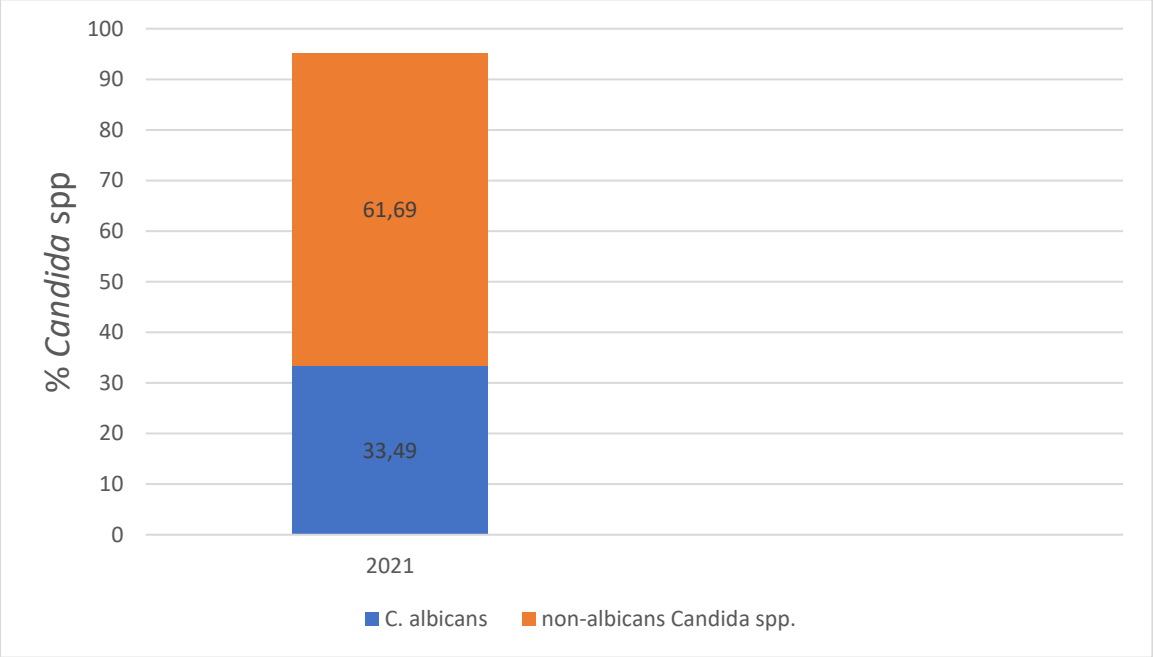
Najčešće prisutne vrste *Candida* spp u 2021. godini bile su *C. parapsilosis* kod 37.20% (80/215), *C. albicans* kod 33,49% (72/215), i *C. glabrata* kod 18.14% (39/215) bolesnika s kandidemijom .

Tablica 1. Učestalost pojedinih vrsta *Candida* spp. kod bolesnika s kandidemijom u Hrvatskoj u 2021. godini

Table 1. Incidence of different *Candida* spp.in patients with candidemia in Croatia in 2021

Vrsta *Candida* spp.	**2021 N (%)**
Candida parapsilosis	80 (37,20)
Candida albicans	72 (33,49)
Candida glabrata	39 (18,14)
Candida krusei	4 (1,86)
Candida lusitaniae	5 (2,33)
Cadnida tropicalis	5 (2,33)
Candida dubliniensis	3 (1,39)
Saccharomyces cerevisiae	1 (0,47)
Candida kefyr	1 (0,47)
Candida lypolitica	1 (0,47)
Candida guilliermondii	2 (0,93)
UKUPNO	215

Grafikon 1. Udio *C. albicans* i non-albicans vrsta u 2021. godini među izolatima bolesnika s kandidemijom u Hrvatskoj
Figure 1. Proportion of *C. albicans* and non-albicans species in 2021



Grafikon 2. Učestalost vrsta uzročnika kanidemija u 2021. godini
Figure 2. Proportion of *Candida* spp causing candidemia in 2021.

Udio *C. albicans* i non-albicans vrsta u 2021. godini među izolatima bolesnika s kandidemijom prikazan je na Grafikonu 1. Iz analiziranih podataka se vidi da je *C. parapsilosis* najzastupljenija vrsta u Hrvatskoj što je posebno zabrinjavajuće obzirom na visoki postotak stečene rezistencije *C. parapsilosis* na flukonazol. Druga po učestalosti je *C. albicans* , a slijedi je *C. glabrata.*

Rezultati našeg praćenja pokazali su da se udio *C. albicans* među izolatima bolesnika s kandidemijom u Hrvatskoj smanjio na manje od 33,49% u korist non-albicans *Candida* spp. i da se taj udio u usporedbi s 2020. godine smanjio za 3,27%. Ovi podaci imaju kliničku važnost budući *C. parapsilosis* i *C. glabrata* imaju manju osjetljivost na ehinokandine odnosno azole. Ovakva distribucija *Candida* spp. karakteristična je za južnu Europu te iako njeno tumačenje još uvijek nije do kraja poznato, pretpostavlja se da je posljedica klimatskih utjecaja, načina primjene antifungalnih lijekova s posebnim naglaskom na način provođenja mjera prevencije i kontrole infekcija.

Osjetljivost na antifungalne lijekove

Osjetljivost vrsta *Candida* spp u Hrvatskoj u 2021. godini na amfotericin B, kaspofungin, mikafungin, anidulafungin i flukonazol prikazana je na grafikonu 3., 4., 5., 6 i 7.

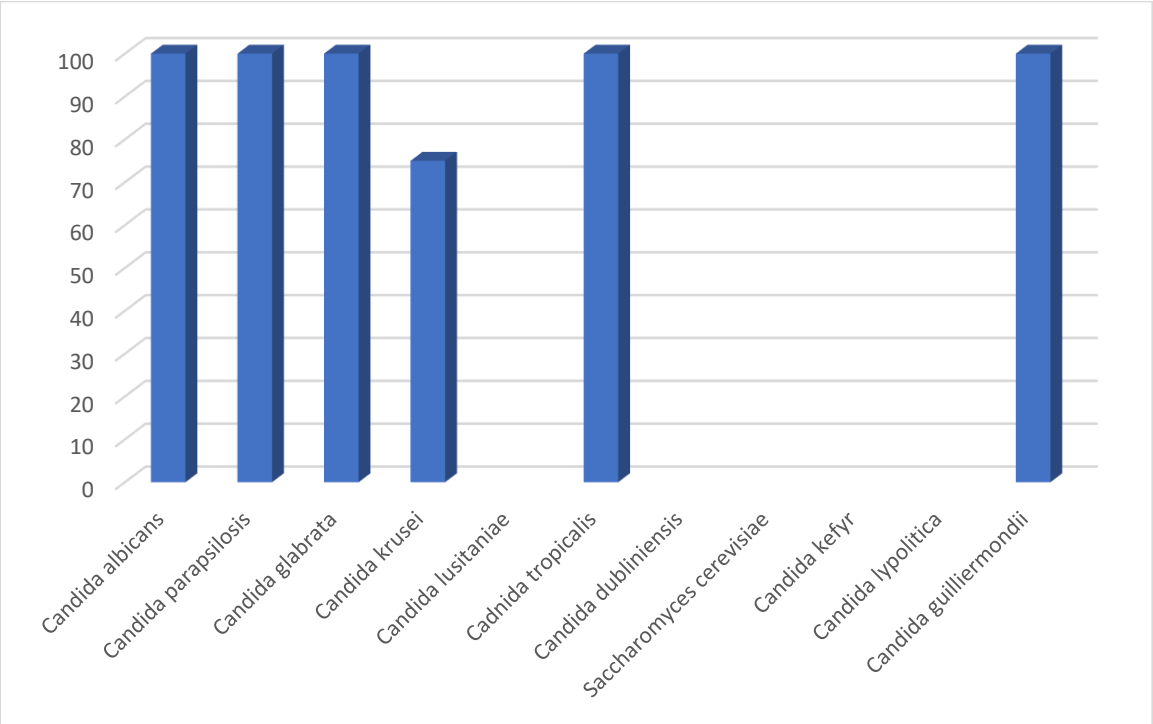
Osjetljivost na amfotericin B bila je 100% za *C. albicans, C. parapsilosis, C. glabrata i C. tropicalis, C. guilliermondii* a za *C. krusei* 75%. (grafikon 3).

Osjetljivost uzročnika kandidemija na ehinokandine je još uvijek vrlo visoka, što je i očekivano. Osjetljivost na kaspofungin izolata *C. albicans* u 2021. bila je 100%. Izolati *C. parapsilosis* izolirani iz hemokultura su 96,25% osjetljivi na kaspofungin,a slično i izolati *C. glabrata* 97,37%, *C. tropicalis, C. krusei i C. guilliermondii* 100%. (grafikon 4). Mikafungin je pokazao sličnu učinkovitost pa su tako izolati *C. albicans* 2021. godine bili osjetljivi 100% . Izolati *C. parapsilosis* izolirani iz hemokultura su 2021 godine bili 96,25% osjetljivi. Izolati *C. glabrata* bili su osjetljivi 97,3%, a *C. tropicalis, C. krusei i C. guilliermondi* 100 (grafikon 5). Anidulafungin također pokazuje vrlo sličnu djelotvornost na uzročnike kandidemija pa su tako izolati *C. albicans* bili osjetljivi na anidulafungin u 2021. godine 98,59%. S druge strane izolati *C. parapsilosis* su bili osjetljivi 80%, a *C. glabrata* 97,37%. Izolati, *C. krusei, C. tropicalis i C. guilliermondii* su bili osjetljivi 100%. (grafikon 6)

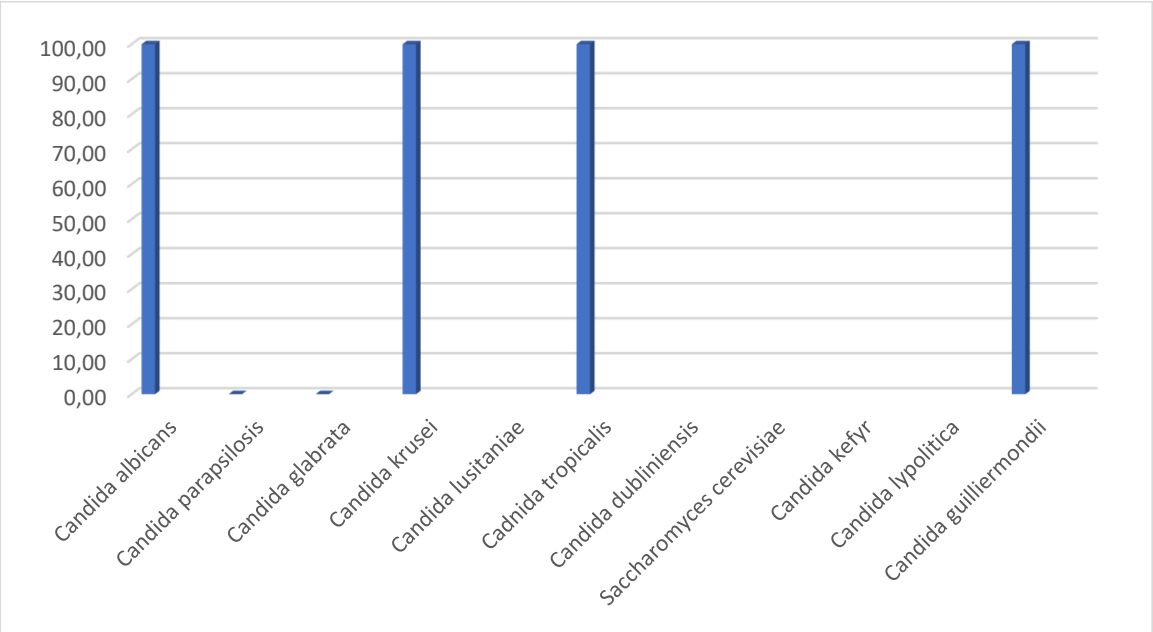
C. albicans je osjetljiva na flukonazol u 100% ispitivanih izolata, 100% izolata *C. tropicalis* u je bilo osjetljivo na flukonazol. Ono što posebno zabrinjava je da su izolati *C. parapsilosis* (koja je intrinzički osjetljiva na flukonazol za razliku od *C. glabrata i C. krusei*) nažalost je u velikom broju slučajeva razvila rezistenciju pa je u 2021. godini bila osjetljiva u 20% slučajeva, a 2020. u 26,32%, što znači da je rezistencija porasla za 6,32%. C. *parapsilosis* izbila na prvo mjesto uzročnika kandidemija, taj je podatak vrlo zabrinjavajući.

Kao što je i za očekivati nije bilo osjetljivih izolata vrsta *C. glabrata* i *C. krusei* na flukonazol obzirom na to da je *C. glabrata* intrinzički smanjene osjetljivosti na flukonazol i vrlo brzo postaje rezistentna, a *C. krusei* intrinzički rezistentna na flukonazol (grafikon 7).

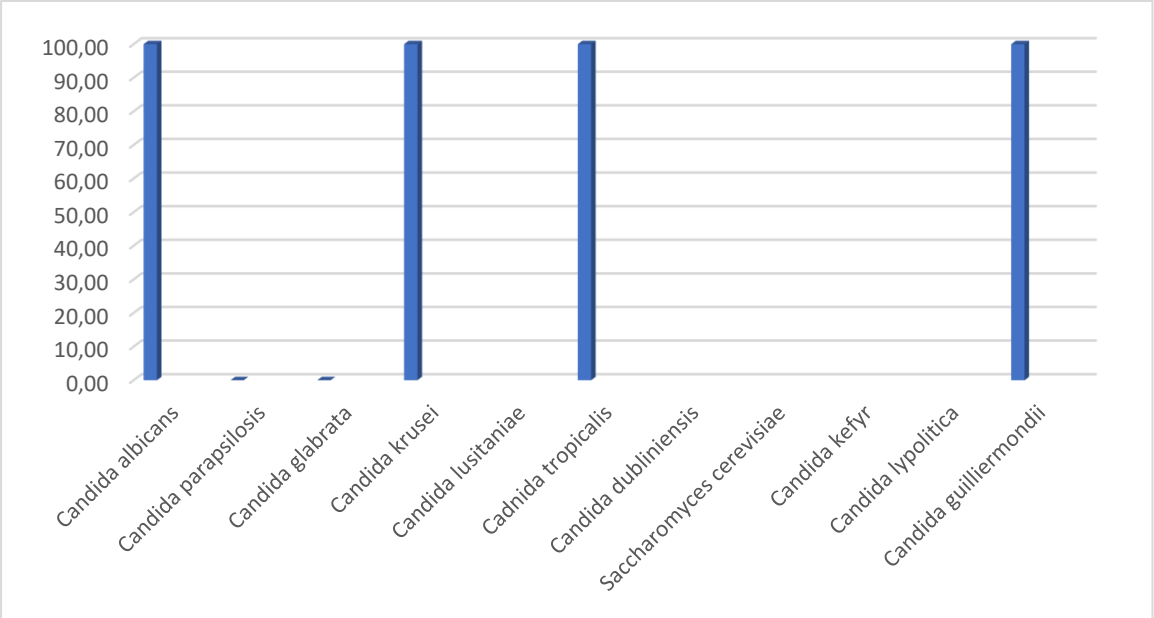
Grafikon 3. Osjetljivost vrsta *Candida* spp. u Hrvatskoj u 2021. godini na amfotericin B
Figure 3. *Candida* spp susceptibility to amphotericin B in Croatia in 2021



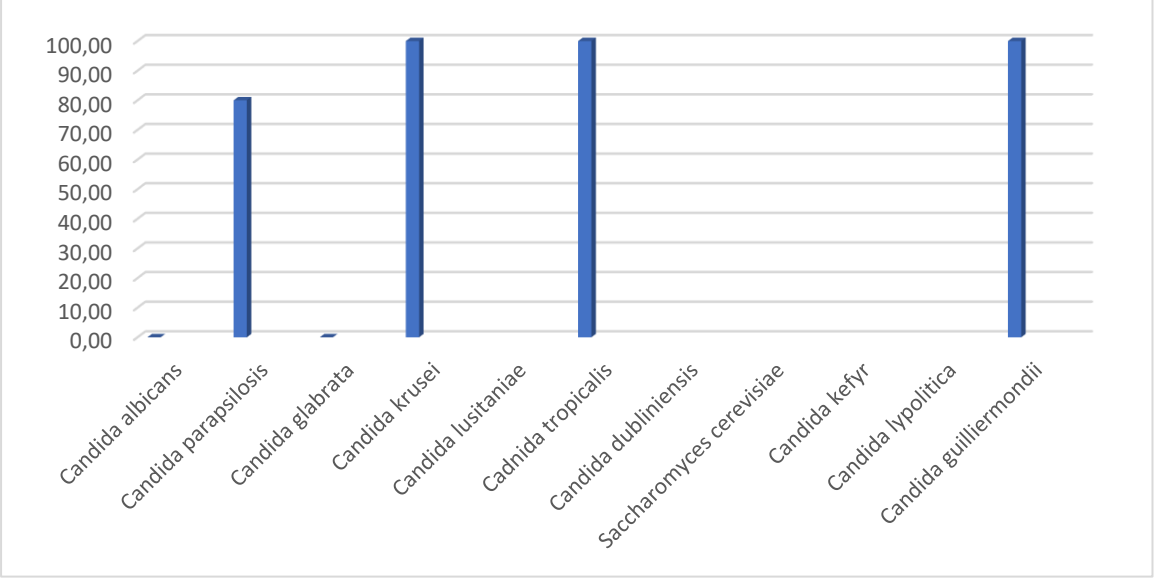
Grafikon 4. Osjetljivost vrsta *Candida* spp. u Hrvatskoj u 2021. godini na kaspofungin
Figure 4. *Candida* spp susceptibility to caspofungin in Croatia in 2021



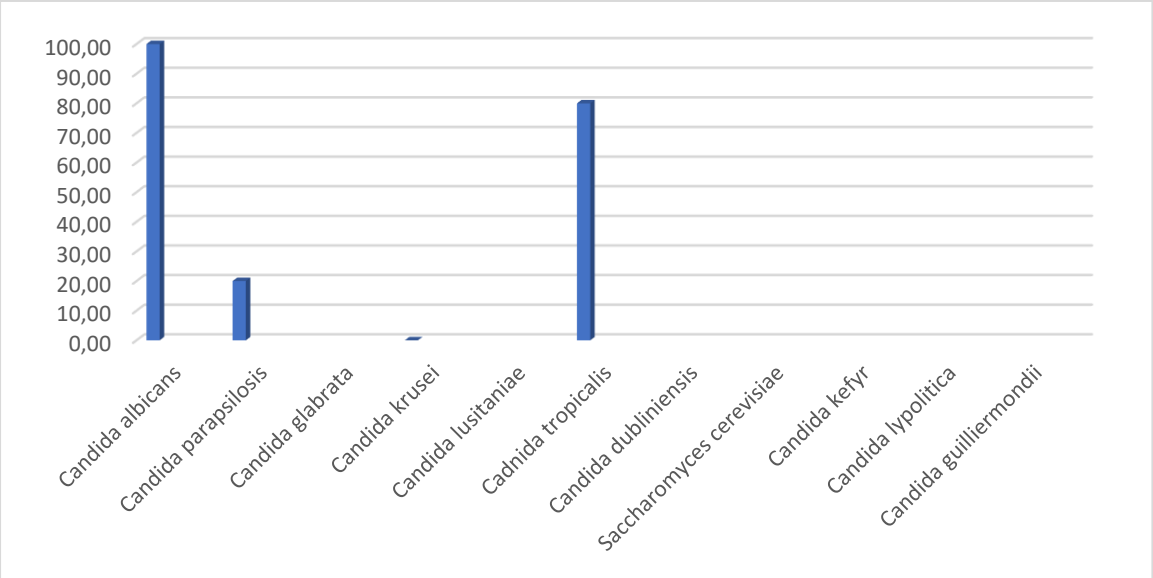
Grafikon 5. Osjetljivost vrsta *Candida* spp. u Hrvatskoj u 2021. godini na mikafungin
Figure 5. *Candida* spp susceptibility to micafungin in Croatia in 2021



Grafikon 6. Osjetljivost vrsta *Candida* spp. u Hrvatskoj u 2021. godini na anidulafungin
Figure 6. *Candida* spp susceptibility to anidulafungin in Croatia in 2021



Grafikon 7. Osjetljivost vrsta *Candida* spp. u Hrvatskoj u 2021. godini na flukonazol
Figure 7. *Candida* spp susceptibility to fluconazol in Croatia in 2021



Distribution of *Candida* species and antifungal susceptibility in patients with candidemia in Croatia, 2021

Sanja Pleško, Zoran Herljević, Violeta Rezo Vranješ, Marko Siroglavić, Ivana Mareković

University Hospital Centre Zagreb
Department for Clinical and Molecular Microbiology
Excellence Centre for Medical Mycology of European Confederation of Medical Mycology (ECMM)

Introduction

The global incidence of candidemia has increased in the last decade and is dependent upon geographical location and patient population. Recent global estimates have suggested that around 700,000 cases of invasive candidiasis occur annually. Many epidemiological studies from European countries demonstrated difference in the *Candida* species distribution and antifungal susceptibility and emphasized the necessity for surveillance. These data are essential for making choice of empirical therapy, prophylaxis and prevention and infection control measures

Department for Clinical and Molecular Microbiology, University Hospital Centre Zagreb in 2018 became ECMM Excellence Centre for Medical Mycology and from January 2019 with the support of Croatian Committee for Antibiotic Resistance Surveillance started collecting *Candida* spp. isolates from blood cultures. All microbiological laboratories in Croatia were invited after isolation of *Candida* spp from blood culture to send the isolate to Excellence Centre and fulfil the form on the Excellence Centre website fungi.kbc-zagreb.hr. This form contains the data about the isolate, identification methods and methods used to determine isolate antifungal susceptibility as well as clinical data about the patient. In Excellence Centre every isolate was reidentified and then susceptibility testing was performed using microdilution method according to CLSI guidelines. This report contains the data about incidence of different *Candida* species and susceptibility to antifungal agents in year 2021.

Incidence of different *Candida* species

During 2021 215 isolates of *Candida* spp. were collected and analysed. The incidence of different *Candida* species is shown in Table 1. In 2021 was observed significant increase of number of isolates (215) compared to 2020 (136 isolates). That increase is around 40%.

The most common *Candida* spp. in year 2021 were *C. parapsilosis* in 37,20% (80/215), *C. albicans* in 33.49% (72/215) and *C. glabrata* in 18.14% (39/215) patients with candidemia.

Distribution of *C. albicans* and non-albicans species among candidemia isolates in year 2021 is shown on Figure 1. Our data documented that *C. parapsilosis* was the for the first time became most common species isolated from blood cultures in Croatia in 2021, On the second place is *C. albicans* followed by *C. glabrata* on the third place. Results of our surveillance documented that the incidence of *C. albicans* among patients with candidemia decreased on 33,49% and non-albicans isolates increased and compared to 2020 that proportion decreased for 3,27%. Those results are clinically important considering the fact that *C. parapsilosis* and *C glabrata* have reduced susceptibility to echinocandins or azoles. That kind of distribution is characteristic for South Europe and is presumed that it is influenced by climatic influences, use of antifungal agents and and emphasized on adherence to prevention and infection control measures.

Antifungal susceptibility

Antifungal susceptibility of *Candida* spp. in Croatia in year 2021 to amphotericin B, caspofungin, micafungin, anidulafungin and fluconazole is shown in Figure 3,4,5,6 and 7.

Susceptibility to amphotericin B was 100% for *C. albicans, C. parapsilosis, C. glabrata, C. tropicalis and C. guilliermondii* and for *C. krusei* was 75%. (Figure 3).

As expected, echinocandins showed excellent efficiency against *Candida* isolates. Susceptibility to caspofungin of *C. albicans* isolates in 2021 was 100%. *C. parapsilosis* isolates from blood cultures showed 96,25% susceptibility to caspofungin, as well as isolates of *C. glabrata* 97,37%, *C. tropicalis, C. krusei. and C. guilliermondii* showed 100% susceptibility (Figure 4). Micafungin showed similar activity because C. *albicans* isolates in year 2021 showed susceptibility of 100%. *C. parapsilosis* isolates from blood cultures demonstrated susceptibility of 96,25%. Isolates of *C. glabrata* were susceptible in 97,3%, *C. tropicalis, C. krusei* and and *C. guilliermondii* were 100% susceptible to micafungin (Figure 5). Anidulafungin showed very similar efficacy and susceptibility of 98,59% in year 2021 among isolates of *C. albicans*. On the other hand, *C. parapsilosis* isolates showed susceptibility of 80% in year 2021 and *C. glabrata* 97,37%. Isolates of, *C. tropicalis, C. krusei C. guilliermondii* were 100% susceptible to anidulafungin (Figure 6)

Susceptibility to fluconazole was 100% in *C. albicans. C. tropicalis* showed susceptibility of 100%. Isolates of *C. parapsilosis* (that is in the contrast to *C. glabrata* and *C. krusei* intrinsically susceptible to fluconazole) developed resistance in large number of isolates unfortunately; in 2021 susceptibility was 20%. and that is 6,32% resistance increase compared to previous year. As *C. parapsiolosis* is the most frequent etiological cause of candidemia, this result is rather alarming.

As expected, there were no susceptible isolates of *C. glabrata* and *C. krusei* to fluconazole (Figure 7).

POTROŠNJA ANTIBIOTIKA U HRVATSKOJ
ANTIBIOTIC CONSUMPTION IN CROATIA

Marina Payerl Pal
Damjan Debelec

Arjana Tambić Andrašević

Zavod za javno zdravstvo Međimurske županije, Čakovec
Public Health Institute Međimurje County, Čakovec

Klinika za infektivne bolesti "Dr. F. Mihaljević"
University Hospital for Infectious Diseases "Dr. F. Mihaljević"

Izvanbolnička potrošnja antibiotika

Potrošnja antibiotika u Hrvatskoj se prati od 2001. godine u skladu s međunarodno priznatim European Surveillance of Antibiotic Consumption (ESAC) standardima, odvojeno ambulantna i bolnička potrošnja. Podaci o potrošnji antibiotika se prikupljaju od Hrvatskog zavoda za zdravstveno osiguranje (HZZO) u skladu s Anatomsko-Terapijsko-Kemijskom klasifikacijom lijekova (ATK klasifikacija). Za izračun potrošnje antibiotika potrebno je poznavati definiranu dnevnu dozu (DDD) za svaki pojedini antibiotik u skladu s Kolaborativnim centrom za statistiku (Oslo, Norveška). Za preračunavanje potrošnje antibiotika koristi se broj stanovnika kao denominator.
Potrošnja antibiotika iskazuje se u definiranim dnevnim dozama (DDD) na 1000 stanovnika po danu (DDD/TID) na 3. i 4. nivou ATK klasifikacije.
Hrvatska je uključena u europsku mrežu praćenja potrošnje antibiotika the European Surveillance of Antimicrobial Consumption Network (ESAC-Net), što joj omogućava usporedbu potrošnje antibiotika sa svim ostalim zemljama uključenim u mrežu preko platforme za unos podataka, The European Surveillance System (TESSY).

Do 2011. godine ambulantna potrošnja antibiotika temeljila se na podacima dobivenim putem veledrogerija, a od 2012. godine podatke o ambulantnoj potrošnji antibiotika dobivamo od Hrvatskog zavoda za zdravstveno osiguranje (HZZO). Od tada smo nastavili s praćenjem potrošnje iz dva izvora u svim narednim godinama. Podaci dobiveni putem HZZO-a se temelje na crvenim receptima te se od 2012. godine koriste kao službeni podaci Republike Hrvatske koji se dostavljaju u TESSY. Rezultati se razlikuju ovisno o izvoru podataka (tablica 3; slika 2) na način da je potrošnja temeljena na podacima veledrogerija nešto viša u usporedbi s podacima dobivenim od HZZO-a. Razlika u potrošnji u 2021. godini od 1,41 DDD/TID je viša u odnosu na prethodnu godinu (1,27 DDD/TID). Razlika je uočljiva u svim klasama antibiotika, s tim da je i nadalje najveća u klasi penicilina i klasi makrolid-linkozamid-streptogramin (tablica 4; slika 3). Kod klase penicilina (J01C) uočava se najveća razlika (0,68 DDD/TID), što je više u odnosu na prethodnu godinu kada je iznosila 0,50 DDD/TID. U skupini makrolid-linkozamid (J01F) je razlika 0,29 DDD/TID, što je vrlo slično prethodnoj godini (0,30 DDD/TID). I kod ostalih klasa antibiotika uočavaju se razlike, ali znatno manje (tablica 4; slika 3). Navedene razlike mogu se objasniti podizanjem antibiotika na privatni recept, što neće biti zabilježeno u HZZO-u te direktno snabdjevanje ambulanti s antibioticima iz veledrogerija, posebno za potrebe parenteralne terapije.

Potrošnja antibiotika u Hrvatskoj, prema prije spomenutoj metodologiji, se prati od 2001. godine (slika 1). Na slici 1 uočavaju se dva „vala“ potrošnje. Prvi „val“ od 2001. do 2011. godine u kojem se koristi isti denominator prema popisu stanovništva iz 2001. godine (4 555 219 stanovnika) potrošnja se kreće oko 20 DDD/TID . Skok potrošnje između 2001. i 2002. godine sa 16,5 na 19,9 DDD/TID može se objasniti promjenom formulacije koamoksiklava (2x1.2 g umjesto dotadašnjih 3x0.625g) iako se broj propisanih doza nije bitno mijenjao. Pad u ambulantnoj potrošnji u 2010. i 2011. godini uz isti denominator vjerojatno je posljedica smanjenog broja stanovnika, što se je utvrdilo popisom stanovništva 2011. godine (4 284 889), a nije posljedica smanjenog propisivanja antibiotika. U drugom „valu“ potrošnje, kojeg pratimo na slici 1, oslanjamo se na podatke popisa stanovništva iz 2011. godine. U tom drugom desetogodišnjem razdoblju potrošnja se kretala između 17-18 DDD/TID do 2020. kada je pala na najnižu vrijednost od početka praćenja potrošnje od 14,05 DDD/TID. Radi se o pandemijskoj godini s promijenjenim načinom života koji je nametnula prisutnost i širenje SARS-CoV-2 virusa te uvedenim epidemiološkim mjerama, koje su utjecale na smanjenu incidenciju respiratornih infekcija te posljedično i na manje propisivanje antibiotika u 2020. godini. Međutim, u 2021. godini bilježi se ponovno povećanje ambulantne potrošnje antibiotika, koja iznosi 16,22 DDD/TID, što je još uvijek ispod razine potrošnje u vrijeme prije pandemije. I 2021. godina je pandemijska godina u kojoj se bilježe 4. i 5. valovi pandemije SARS-CoV-2 virusa te provođenje prilično restriktivnih epidemioloških mjera u svakodnevnom životu.

Analizom određenih indikatora kvalitete propisivanja antibiotika, kao što je omjer potrošnje širokospektralnih penicilina, beta-laktama s inhibitorima, cefalosporina II. i III. generacije,

makrolida (osim eritromicina) i fluorokinolona (J01 (CR+DC+DD+FA-FA01)+MA) i potrošnje širokospektralnih penicilina bez inhibitora (amoksicilina), uskospektralnih penicilina, cefalosporina I. generacije i eritromicina (J01 (CA+CE+CF+DB+FA01) uočava se nastavak nepovoljnog trenda (tablica 5; slika 4). Omjer potrošnje širokospektralnih antibiotika naspram antibiotika užeg spektra iznosi 6,4, što ukazuje na veliku primjenu antibiotika širokog spektra (tablica 5; slika 4), s vrlo vjerojatnim utjecajem na pojavu i širenje rezistencije među bakterijama.

U 2021. godini, zaustavljen je trend pada potrošnje širokospektralnih penicilina (J01C), kojeg pratimo od 2015. godine, što je povoljan pokazatelj. Međutim, za skupinu širokospektralnih penicilina s inhibitorima beta-laktamaza , nakon prošlogodišnjeg pada u potrošnji, bilježi se značajan skok sa 4,72 na 5,38 DDD/TID, što je nepovoljan pokazatelj. Kod penicilina uskog spektra (J01CE) bilježi se lagani pad, dok je potrošnja beta-laktamaza rezistentnih penicilina (J01CF) posljednjih pet godina stabilna, bez promjena (0,01 DDD/TID).

Za razliku od prethodne godine, kada je uočen pad potrošnje, kod klase cefalosporina se prati porast potrošnje svih generacija (1.,2.,3.), od kojih je najviše porasla potrošnja treće generacije (J01DD) za 0,17 DDD/TID.

Porast potrošnje uočava se kod svih ostalih klasa antibiotika (sulfonamidi + trimetoprim, makrolidi i linkozamidi te fluorokinoloni), osim kod aminoglikozida (J01G), čija je ambulantna potrošnja vrlo mala i ne odstupa u potrošnji u odnosu na prethodnu godinu (0,003 DDD/TID).

U zadnjih pet godina nitrofurantoin (J01XE) kontinuirano bilježi porast potrošnje, koja u 2021. iznosi najviše do sada 0,96 DDD/TID. Pozitivan trend bilježi se i kod fosfomicina (J01XX) čija potrošnja je blago porasla u odnosu na prethodne godine. Ti podaci ohrabruju i govore u prilog liječenja urinarnih infekcija, koje su najčešće izvanbolničke bakterijske infekcije, u skladu s nacionalnim smjernicama za liječenje urinarnih infekcija.

Ambulantna potrošnja u Hrvatskoj u 2021. godini iznosi 16,22 DDD/TID, što je 89,36% ukupne potrošnje antibiotika u Hrvatskoj. Ukazuje to na sve veći udio bolničke potrošnje antibiotika (10,6%) u ukupnoj potrošnji antibiotika. Do sada, tijekom praćenja potrošnje antibiotika, udio bolničke potrošnje nije prelazio 10%.

U tablici 6 i na slici 5 poredani su antibiotici prema učestalosti potrošnje - "top lista" najpropisivanijih antibiotika, ovaj puta prvih 6 antibiotika, obzirom da su zadnja dva vrlo slična po potrošnji. Poredak prva četiri antibiotika ostao je identičan kao i prethodne godine (koamoksiklav, azitromicin, cefuroksimaksetil, amoksicilin). Na peto mjesto se probio doksiciklin (0,98 DDD/TID) s malom prednošću pred nitrofurantoinom (0,96 DDD/TID), koji je potisnut na šesto mjesto, odnosno zamijenili su 5. i 6. mjesto u odnosu na prethodnu godinu.

Promijenila se tipična slika potrošnje po kvartalima (tablica 7; slika 6) na način da je potrošnja u prva tri kvartala podjednaka (3,58; 3,67; 3,83 DDD/TID), dok je u četvrtom kvartalu najviša i iznosi 5,15 DDD/TID. Porast potrošnje u četvrtom kvartalu je vjerojatno posljedica iznimno velikog broja oboljelih od COVID-19 bolesti te češće uporabe antibiotika u liječenju ne samo komplikacija virusne infekcije, već i drugih infekcija virusne etiologije, čestih u zimskim mjesecima. U prethodnim godinama uočljiva je tipična slika s višom potrošnjom u 4. i 1. kvartalu, za razliku od 2. i 3. kvartala, kao posljedica češće primjene antibiotika tijekom hladnijih mjeseci kada su respiratorne infekcije češće.

Među prvih deset dijagnoza po učestalosti za koje se propisuju antibiotici su tri dijagnoze koje se odnose na infekcije mokraćnih puteva (upala mokraćnog mjehura; infekcija urinarnog trakta, lokacija neoznačena; drugi poremaćaji urinarnog sustava) (tablica 8; slika 7). Ostalih sedam dijagnoza se odnose na dišni sustav (akutna upala sinusa; akutna upala ždrijela, akutna upala tonzila, akutna upala gornjeg dišnog sustava, akutni bronhitis, periapikalni apsces bez sinusa). Iako se ne

radi o dijagnozi bakterijske infekcije, U07.1 akutna respiratorna bolest uzokovana 2019-noCoV, nalazi se na 8.mjestu po učestalosti dijagnoza za koju su se propisivali antibiotici.

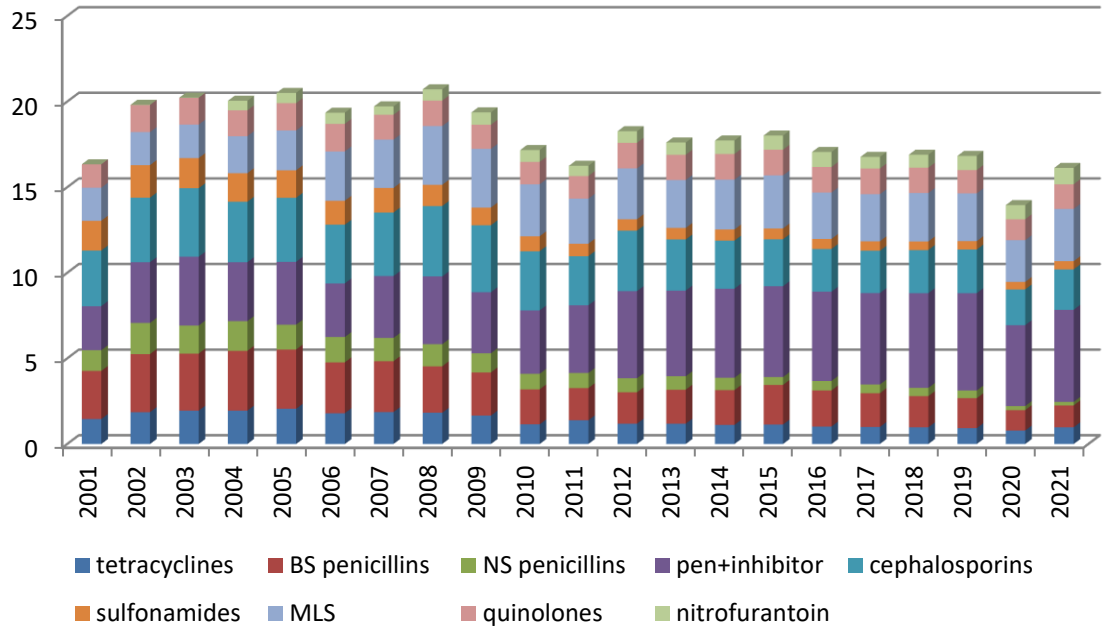
Upala mokraćnog mjehura je vodeća dijagnoza za propisivanje antibiotika u izvanbolničkoj populaciji, kao i prethodne godine. Među prvih deset dijagnoza nalaze se još dvije koje se odnose na liječenje infekcija mokraćnog sustava (infekcija urinarnog trakta; drugi poremećaji urinarnog sustava), za koje se ukupno potrošilo 2,863 DDD/TID. Ostalih sedam vodećih dijagnoza za koje se propisuju antibiotici su dijagnoze iz područja respiratornog sustava, što pokazuje da se antibiotici i dalje često neopravdano propisuju u liječenju, dominantno virusnih infekcija, kod izvanbolničke populacije. U 2021. godini u Hrvatskoj je zabilježen vrlo mali broj oboljelih od gripe pa time i značajno manji broj potencijalnih bakterijskih komplikacija koje bi zahtijevale uporabu antibiotika. Za liječenje pacijanata s dijagnozom infekcije respiratornog sustava, među prvih deset vodećih dijagnoza, potrošeno je 5,843 DDD/TID, što je dvostruko više nego za liječenje infekcija mokraćnog sustava, koje su najčešće izvanbolničke bakterijske infekcije.

U 2021. godini ambulantna potrošnja antibiotika porasla je u odnosu na godinu prije, ali je ostala niža u odnosu na razdoblje prije pandemije (do 2019.). U 2021. godini po prvi puta se koristio novi denominator prema popisu stanovništva iz 2021. godine. Udio ambulantne potrošnje antibiotika iznosio je manje od 90% (89,36%). Klasa penicilina je, kao i do sada, najzastupljenija u ambulantnoj potrošnji antibiotika (42,36%). Porasla je potrošnja svih klasa antibiotika, osim aminoglikozida. Među klasom penicilina najveći porast je zabilježen kod kombinacije penicilina s inhibitorima (J01CR), dok je kod klase cefalosporina najveći porast potrošnje uočen za 3.generaciju cefalosporina (tablica 1). Nastavlja se trend rasta potrošnje nitrofurantoina (0,68; 0,76; 0,83; 0,83; 0,96 DDD/TID) u zadnjih pet godina, što je povoljan pokazatelj.

Nažalost, indikator potrošnje antibiotika koji pokazuje omjer potrošnje širokospektralnih antibiotika u odnosu na uskospektralne je vrlo nepovoljan. U odnosu na prethodnu godinu je još porastao (6,4 u 2021.; 5,7 u 2020.) (tablica 5, slika 4).

Koamoksiklav ostaje i dalje vodeći antibiotik po potrošnji kao što je i u svim prethodnim godinama, a infekcije dišnog sustava najzastupljenije dijagnoze (7 od 10) među prvih deset za koje se propisuju antibiotici.

Slika 1. */ Figure 1.*
Ambulantna potrošnja antibiotika (DDD/TID) u Hrvatskoj, 2000 - 2021.
Ambulatory antibiotic consumption (DDD/TID) in Croatia, 2000 – 2021



Outpatient Antibiotic Consumption

The consumption of antibiotic in Croatia has been monitored since 2001 in accordance with the internationally recognised European Surveillance of Antibiotic Consumption (ESAC) standards, with outpatient and inpatient consumption being tracked separately. Data on antibiotic consumption are collected from the Croatian Health Insurance Fund (CHIF) in accordance with the Anatomical Therapeutic Chemical (ATC) classification. For the calculation of antibiotic consumption, it is necessary to know the defined daily dose (DDD) for each individual antibiotic in accordance with the Collaborative Centre for Statistics (Oslo, Norway). The population number as a denominator is used for the calculation of antibiotic consumption. Antibiotic consumption is expressed in defined daily doses (DDD) per 1.000 inhabitants daily (DDD/TID) at the third and fourth level of the ATC classification system. Croatia is a part of the European Surveillance of Antimicrobial Consumption Network (ESAC-Net), which enables it to compare its antibiotic consumption with all other countries in the network through the data sharing platform European Surveillance System (TESSY).

Until 2011, outpatient antibiotic consumption monitoring was based on data received from wholesale pharmacies. Since 2012, data have been obtained from the Croatian Health Insurance Fund (CHIF). From that point, we continued monitoring the consumption from two sources in all subsequent years. The data obtained from CHIF are based on red prescription sheets, which have been used as official data of the Republic of Croatia since 2012 and fed into TESSY. The results vary depending on the data source (Table 3, Figure 2) – the consumption based on wholesale data is somewhat higher compared to data obtained from CHIF. The difference in the consumption in 2021 of 1.41 DDD/TID is higher compared to the previous year (1.27 DDD/TID). The difference is noticeable in all classes of antibiotics, with the highest consumption in the penicillin and macrolide-lincosamide-streptogramin classes (Table 4; Figure 3). In the penicillin class (J01C), the difference is the greatest (0.68 DDD/TID), which is higher compared to the previous year, when it was 0,50 DDD/TID. In the macrolide-lincosamide group (J01F), the difference is 0.29 DDD/TID, which is very similar to the previous year (0.30 DDD/TID). In other classes of antibiotics there are also some differences, but substantially smaller ones (Table 4; Figure 3). Those difference can be explained by the antibiotics being acquired through private prescriptions, which is not recorded by CHIF, as well as direct supply of clinics with antibiotics from wholesale pharmacies, particularly for parenteral therapy purposes.

Antibiotic consumption in Croatia has been tracked since 2001 (Figure 1) according to the aforementioned methodology. Figure 1 shows two “waves” of consumption. In the first “wave”, from 2001 to 2011, in which the same denominator according to the 2001 population census is used (4.555.219 inhabitants), the consumption is around 20 DDD/TID. The consumption hike between 2001 and 2002 from 16.5 to 19.9 DDD/TID can be explained by the change of co-amoxiclav formulation (2 x 1.2 g instead of 3 x 0.625 g previously), even though the number of prescribed doses did not change significantly. The drop in the outpatient consumption in 2010 and 2011 with the same denominator is most likely a consequence of the population decline as determined in the 2011 census (4.284.889), and not reduced antibiotic prescription. In the second “wave” of consumption, which is shown on Figure 1, we rely on the data from the 2011 population census. In that second 10-year period, the consumption was 17-18 DDD/TID until 2020, when it fell to the lowest value of 14.05 DDD/TID since the beginning of the consumption tracking. It was the year of the pandemic forcing an altered lifestyle with the presence and spread of the SARS-CoV-2 virus, along with the epidemiological measures that had an impact on the reduced incidence of respiratory infections and consequently fewer antibiotic prescriptions in 2020. However, in 2021, an increase in the outpatient consumption of antibiotics was again recorded (16.22 DDD/TID), which was still below the consumption level in the pre-pandemic period. The year 2021 was the year of the pandemic as well, with the fourth and fifth waves of the SARS-CoV-2 virus pandemic as well as the implementation of particularly stringent epidemiological measures in day-to-day life.

An analysis of certain indicators of antibiotic prescription quality, such as the ratio of consumption of wide-spectrum penicillins, beta-lactames with inhibitors, 2nd- and 3rd-generation cephalosporins,

macrolides (apart from erythromycin) and fluoroquinolones (J01 (CR+DC+DD+FA-FA01)+MA) against the consumption of wide-spectrum penicillin without inhibitors (amoxicilin), narrow-spectrum penicillins, first generation cephalosporins without inhibitors and erythromycin (J01 (CA+CE+CF+DB+FA01) demonstrates a continuation of the unfavourable trend (Table 5; Figure 4). The ratio of the consumption of wide-spectrum antibiotics to narrow-spectrum antibiotics is 6.4, which indicates a large application of wide-spectrum antibiotics (Table 5, Figure 4), with a very likely impact on the appearance and spread of resistance among bacteria.

In 2021 saw the discontinuation of the downward trend in the consumption of wide-spectrum penicillins (J01C), tracked since 2015, which is a favourable indicator. However, for the group of wide-spectrum penicillins with beta-lactamase inhibitors, after last year's drop in the consumption, there is a significant leap from 4.72 to 5.38 DDD/TID, which is not a favourable indicator. As regards narrow-spectrum penicillins (J01CE), there is a slight drop, while the consumption of beta lactamase resistant penicillins (J01CF) has been stable for the last five years, without changes (0.01 DDD/TID).

Unlike in the previous year, when a drop in the consumption was detected, the consumption increase for all generations (first, second, third) is tracked in the cephalosporin class, out of which the consumption of the third generation (J01DD) saw the most growth, by 0.17 DDD/TID.

The increase in the consumption is seen in all other classes of antibiotics (sulfonamides + trimethoprim, macrolides and lincosamides as well as fluoroquinolones), except in aminoglycosides (J01G), whose outpatient consumption is rather small and does not deviate from the previous year’s consumption (0.003 DDD/TID).

In the past five years, there has been a continuous increase in nitrofurantoin (J01XE) consumption, which in 2021 amounted to 0.96 DDD/TID, the highest ever. Another positive trend was recorded for fosfomycin (J01XX), whose consumption grew slightly compared to the previous years. Such data are encouraging and paint a positive picture of the treatment of urinary infections, which are the most frequent outpatient bacterial infections, in accordance with the national guidelines for urinary infection treatment.

Outpatient consumption in Croatia amounted to 16.22 DDD/TID in 2021, which is 89.36% of the total antibiotic consumption in Croatia. It points to the growing proportion of intpatient antibiotic consumption (10.6%) in the total antibiotic consumption. To date, during the tracking of antibiotic consumption, the proportion of intpatient consumption has not exceeded 10%.

Table 6 and Figure 5 present a line-up of antibiotics according to the frequency of their consumption – it is the “top list” of the most prescribed antibiotics, this time the top six antibiotics, since the last two are very similar with regard to their consumption. The ranking of the first four antibiotics remained identical as in the previous year (co-amoxiclav, azithromycin, cefuroximaxetil, amoxicillin). Doxycycline moved up to the fifth place (0.98 DDD/TID), with a small advantage over nitrofurantoin (0.96 DDD/TID), which was brought down to the sixth place, i.e. the fifth and sixth antibiotics switched places compared to the previous year.

The typical consumption distribution by quarters changed (Table 7; Figure 6) so that the consumption in the first three quarters is roughly the same (3.58; 3.67; 3.83 DDD/TID), while in the fourth quarter it is the highest, amounting to 5.15 DDD/TID. The consumption hike in the fourth quarter is likely a consequence of a very large number of COVID-19 infections as well as a more frequent use of antibiotics in the treatment of not only complications from viral infections, but also other infections of viral aetiology, which are common in the winter months. In the previous years, there is the typical distribution with a higher consumption in the fourth and first quarters, unlike the second and third quarters, as a consequence of a more frequent application of antibiotics during the colder months, when there is a higher incidence of respiratory infections.

The top ten most frequent diagnoses for which antibiotics are prescribed includes three diagnoses relating to urinary tract infections (bladder infections; urinary tract infections with site not specified; other urinary system disorders) (Table 8; Figure 7). Other seven diagnoses concern the respiratory system (acute sinus infection; acute throat infection, acute tonsil infection, acute upper respiratory system infection, acute bronchitis, periapical abscess without sinus). Even through it is not a bacterial infection, U07.1 as an acute respiratory disease caused by 2019-noCoV holds the eight place when it comes to the frequency of diagnoses for which antibiotics are prescribed.

Urinary bladder infection is the leading diagnosis for the prescription of antibiotics in the outpatient population, which was also the case in the previous year. Among the top ten diagnoses there are two more that concern the treatment of urinary tract infections (urinary tract infection; other urinary system disorders), for which a total of 2.863 DDD/TID were spent. The other seven leading diagnoses for which antibiotics are prescribed are diagnoses from the area of the respiratory system, which shows that antibiotics continue to be prescribed without justification in the treatment of predominantly viral infections in the outpatient population. In 2021, very few incidences of flu were recorded, which led to a significantly smaller number of potential bacterial infections that would require the use of antibiotics. For the treatment of patients diagnosed with a respiratory system infection, among the top ten leading diagnoses, 5.843 DDD/TID were spent, which is twice as much as for the treatment of urinary system infections, which are the most frequent outpatient bacterial infections.

In 2021, outpatient antibiotic consumption increased compared to the previous year, but remained lower compared to the pre-pandemic period (until 2019). The 2021 saw the first use of the denominator according to the 2021 population census. The proportion of outpatient antibiotic consumption amounted to less than 90% (89.36%). As before, the penicillins class was the most prevalent in the outpatient antibiotic consumption (42.36%). The consumption of all classes of antibiotics increased, with the exception of aminoglycosides. In the penicillins class, the largest increase was recorded in the combinations of penicillins with inhibitors (J01CR), while in the cephalosporins class the greatest increase in consumption was recorded for the 3rd generation of cephalosporins (Table 1). The upwards trend of nitrofurantoin consumption (0.68; 0.76; 0.83; 0.83; 0.96 DDD/TID) has been ongoing in the past few years, which is a favourable indicator.

Unfortunately, the antibiotic consumption indicator that shows the proportion of the consumption of wide-spectrum antibiotics compared to narrow-spectrum antibiotics is quite unfavourable. Compared to the previous year, it grew still (6.4 in 2021; 5.7 in 2020) (Table 5, Figure 4).

Co-amoxiclav remains the leading antibiotic when it comes to consumption just like in all previous years, while respiratory system infections are still the most prevalent diagnoses (7 out of 10) among the top ten diagnoses for which antibiotics are prescribed.

Tablica 1. / *Table 1.*
Izvanbolnička potrošnja antibiotika (DDD/TID)
Ambulatory antibiotic consumption (DDD/TID)

ATC šifra / ATC code	ANTIBIOTIK / ANTIBIOTIC	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021
J01AA	Tetraciklini Tetracylines	1,39	1,19	1,19	1,12	1,14	1,02	1,00	0,98	0,93	0,79	0,98
J01CA	Penicilini širokog spektra Broad spectrum penicillins	1,88	1,83	1,98	2,03	2,31	2,11	1,97	1,82	1,75	1,19	1,27
J01CE	Penicilini uskog spektra Narrow spectrum penicillins	0,88	0,82	0,79	0,72	0,46	0,55	0,51	0,48	0,45	0,24	0,21
J01CF	Beta-laktamaza rezistentni penicilini Beta-lactamase resistant penicillins	0,00	0,00	0,00	0,00	0,01	0,00	0,01	0,01	0,01	0,01	0,01
J01CR	Kombinacije s beta-laktamaza inhibitorima Combinations with inhibitors	3,95	5,09	5,00	5,20	5,31	5,22	5,34	5,53	5,68	4,72	5,38
J01DB	Cefalosporini I gen. cephalosporins	0,84	0,79	0,77	0,72	0,66	0,60	0,47	0,38	0,35	0,27	0,29
J01DC	Cefalosporini II gen. cephalosporins	1,26	1,95	1,77	1,85	1,85	1,69	1,67	1,73	1,72	1,38	1,46
J01DD	Cefalosporini III gen. Cephalosporins	0,77	0,79	0,45	0,24	0,23	0,20	0,33	0,41	0,49	0,44	0,61
J01EE	Sulfonamides + trimethoprim	0,73	0,67	0,67	0,65	0,63	0,59	0,55	0,50	0,49	0,44	0,48
J01F	Macrolides, lincosamides	2,63	2,97	2,80	2,91	3,10	2,71	2,75	2,83	2,79	2,44	3,05
J01G	Aminoglikozidi Aminoglycosides	0,01	0,00	0,00	0,04	0,01	0,00	0,01	0,01	0,004	0,003	0,003
J01MA	Fluorokinoloni Fluoroquinolones	1,32	1,49	1,47	1,50	1,50	1,49	1,50	1,48	1,36	1,22	1,44
J01XE	Nitrofurantoin	0,60	0,68	0,72	0,79	0,83	0,88	0,68	0,76	0,83	0,83	0,96
J01XX	Fosfomycin	-	-	-	-	-	0,004	0,05	0,08	0,08	0,08	0,09
UKUPNO / TOTAL		**16,5**	**18,3**	**17,6**	**17,8**	**18,0**	**17,1**	**16,8**	**17,0**	**16,9**	**14,1**	**16,2**

* Do 2012.g. izvor podataka su bile veledrogerije, počevši s 2012.g. izvor podataka je Hrvatski zavod za zdravstveno osiguranje / Until 2012 wholesalers were the source of data and starting with 2012 Croatian Health Insurance Fund data are used
Do 2012.g. korišten je popis stanovništva iz 2001., počevši s 2012.g. korišten je popis iz 2011/ The Croatian Bureau of Statistics, Census 2001was used until 2012 and starting with 2012 Census 2011 was used

Tablica 2. /*Table 2.*
Bolnička potrošnja antibiotika (DDD/TID)
Hospital antibiotic consumption (DDD/TID)

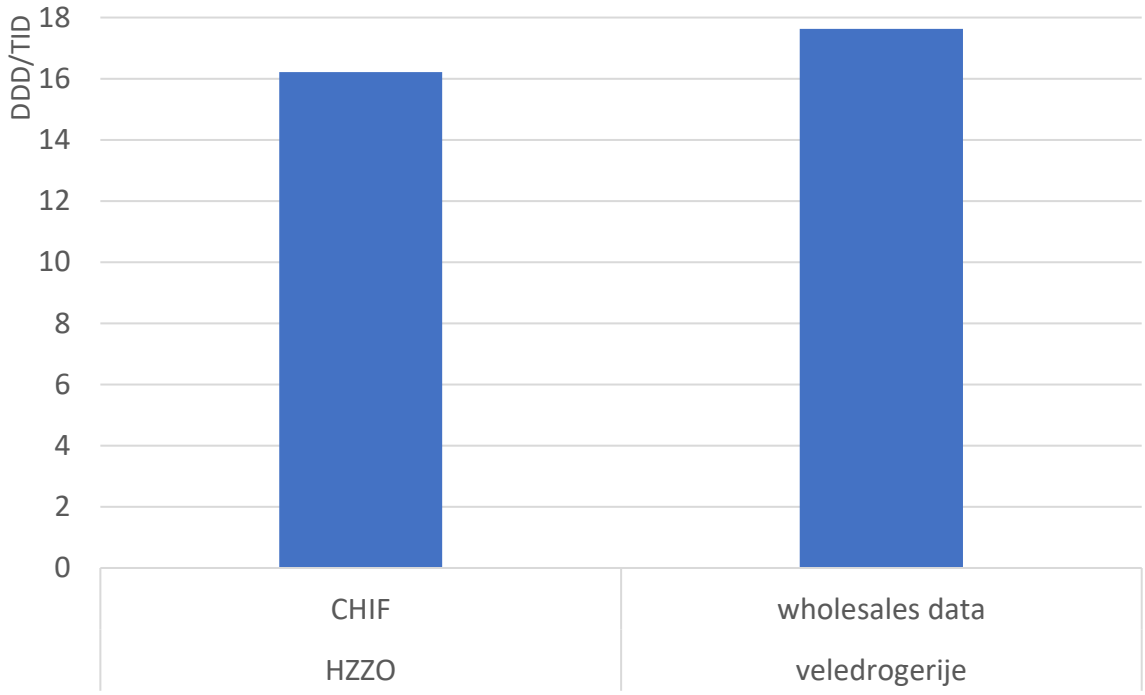
ATC šifra ATC code	ANTIBIOTIK ANTIBIOTIC	2011	2012 **	2013	2014	2015	2016	2017	2018	2019	2020	2021
J01AA	Tetraciklini Tetracylines	0,06	0,06	0,05	0,04	0,04	0,04	0,04	0,03	0,04	0,03	0,03
J01CA	Penicilini širokog spektra Broad spectrum penicillins	0,03	0,03	0,04	0,02	0,02	0,03	0,02	0,02	0,02	0,02	0,02
J01CE	Penicilini uskog spektra Narrow spectrum penicillins	0,03	0,03	0,03	0,02	0,02	0,02	0,02	0,02	0,02	0,01	0,01
J01CF	Beta-laktamaza rezistentni penicilini Beta-lactamase resistant penicillins	0,03	0,04	0,03	0,03	0,03	0,03	0,04	0,04	0,04	0,03	0,03
J01CR	Kombinacije s beta-laktamaza inhibitorima Combinations with inhibitors	0,35	0,40	0,35	0,37	0,38	0,37	0,38	0,40	0,42	0,33	0,40
J01DB	Cefalosporini I gen. cephalosporins	0,20	0,10	0,08	0,09	0,10	0,10	0,10	0,09	0,10	0,08	0,09
J01DC	Cefalosporini II gen. cephalosporins	0,21	0,23	0,21	0,20	0,17	0,19	0,20	0,20	0,20	0,15	0,16
J01DD + J01DE	Cefalosporini III + IV gen. cephalosporins	0,15	0,16	0,15	0,18	0,18	0,16	0,17	0,16	0,17	0,19	0,24
J01DH	Carbapenems	0,04	0,05	0,05	0,06	0,06	0,06	0,08	0,07	0,08	0,09	0,12
J01EE	Sulfonamides + trimethoprim	0,04	0,06	0,04	0,05	0,04	0,04	0,04	0,04	0,04	0,03	0,03
J01F	Macrolides, lincosamides	0,14	0,16	0,15	0,14	0,15	0,15	0,16	0,16	0,18	0,19	0,21
J01G	Aminoglikozidi Aminoglycosides	0,12	0,11	0,10	0,10	0,10	0,09	0,09	0,09	0,09	0,07	0,08
J01MA	Fluorokinoloni Fluoroquinolones	0,19	0,19	0,19	0,20	0,21	0,21	0,23	0,24	0,24	0,20	0,24
J01XA	Glycopeptides	0,03	0,03	0,03	0,03	0,04	0,03	0,04	0,05	0,05	0,05	0,07
J01XD	Metronidazole	0,06	0,07	0,08	0,09	0,10	0,10	0,11	0,15	0,12	0,10	0,12
J01XE	Nitrofurantoin	0,01	0,02	0,01	0,02	0,01	0,01	0,01	0,01	0,01	0,01	0,02
J01XX	Fosfomycin	-	-	-	-	-	0,001	0,02	0,02	0,02	0,02	0,04
UKUPNO TOTAL		**1,69**	**1,75**	**1,58**	**1,65**	**1,70**	**1,65**	**1,74**	**1,80**	**1,85**	**1,61**	**1,93**

* Do 2012.g. korišten je popis stanovništva iz 2001, počevši s 2012.g. korišten je popis iz 2011/ The Croatian Bureau of Statistics, Census 2001was used until 2012 and starting with 2012 Census 2011 was used

Tablica 3. */Table 3.*
Ambulantna potrošnja antibiotika (DDD/TID) usporedba podataka HZZO i veledrogerija
Ambulatory antibiotic consumption (DDD/TID) comparison between CHIF data and wholesales data

	HZZO CHIF	veledrogerije wholesales data
DDD	23 024 194,27	25 022 699,81
DDD/TID	16,22	17,63

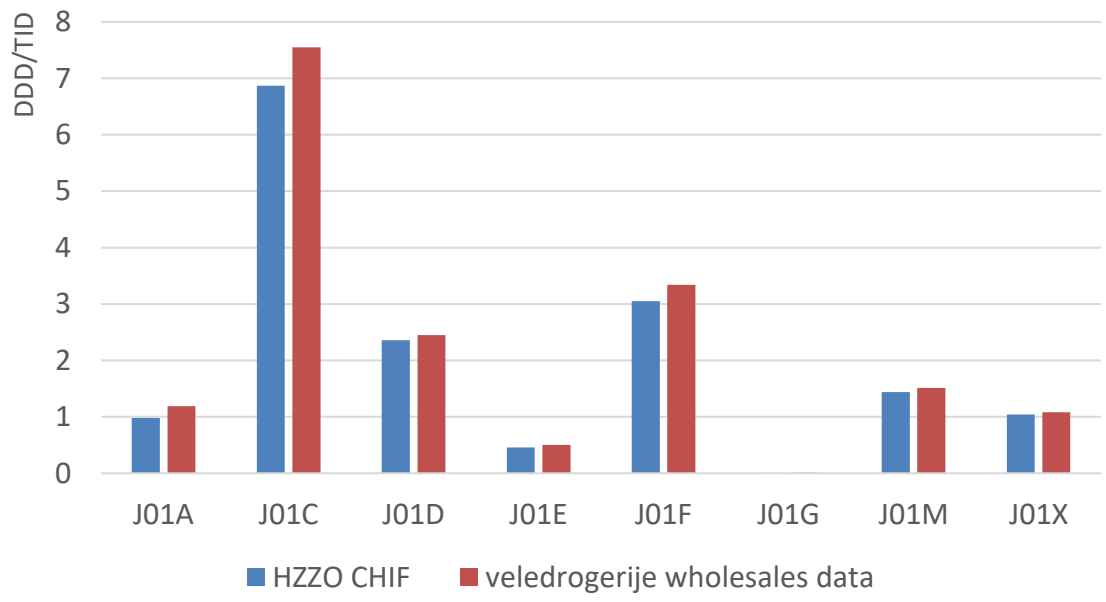
Slika 2. */ Figure 2.*
Ambulantna potrošnja antibiotika (DDD/TID) usporedba podataka HZZO i veledrogerija
Ambulatory antibiotic consumption (DDD/TID) comparison between CHIF data and wholesales data



Tablica 4. / *Table 4.*
Ambulantna potrošnja antibiotika (DDD/TID) po klasama, usporedba podataka HZZO i veledrogerija
Ambulatory antibiotic consumption (DDD/TID) by class, comparison between CHIF data and wholesales data

DDD/TID	HZZO CHIF	veledrogerije wholesales data
J01A	0,98	1,19
J01C	6,87	7,55
J01D	2,36	2,45
J01E	0,46	0,50
J01F	3,05	3,34
J01G	0,003	0,007
J01M	1,44	1,51
J01X	1,04	1,08

Slika 3. / *Figure 3.*
Ambulantna potrošnja antibiotika (DDD/TID) po klasama, usporedba podataka HZZO i veledrogerija
Ambulatory antibiotic consumption (DDD/TID) *by class, comparison between CHIF data and wholesales data*



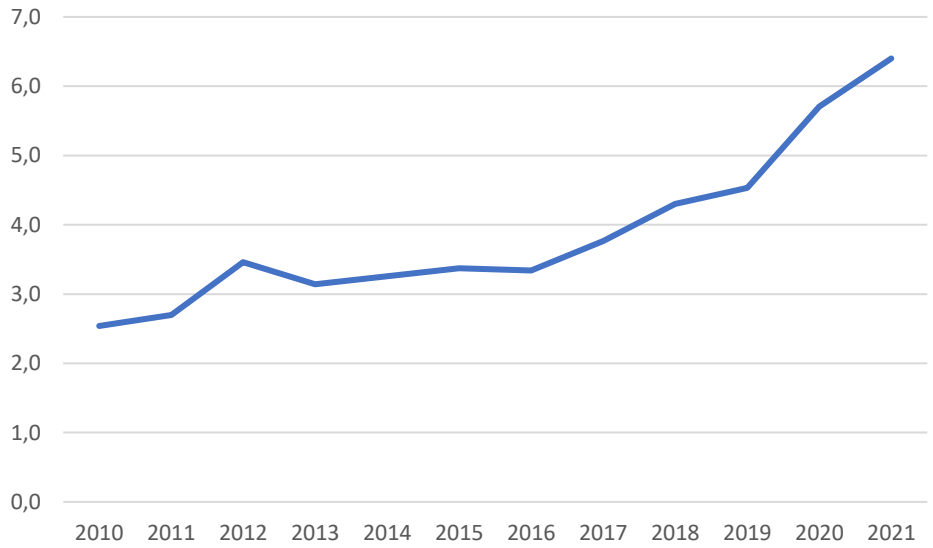
Tablica 5./ *Table 5.*
Omjer izvanbolničke potrošnje izražene u DDD na tisuću stanovnika na dan, penicilina širokog spektra, cefalosporina, makrolida (osim eritromicina) i fluorokinolona i potrošnje izražene u DDD na tisuću stanovnika na dan, penicilina uskog spektra, cefalosporina i eritromicina u razdoblju 2010-2021/
The ratio of consumption of broad-spectrum penicillins, cephalosporins, macrolides (except erythromicin) and fluoroqinolones to the consumption of narrow-spectrum penicillins, cephalosporins and erythromicin expressed as DDD per 1000 inhabitants per day in the community 2010-2021

	Omjer potrošnje antibiotika
2010	2,5
2011	2,7
2012	3,5
2013	3,1
2014	3,3
2015	3,4
2016	3,3
2017	3,8
2018	4,3
2019	4,5
2020	5,7
2021	6,4

Slika 4./ *Figure 4.*

Omjer izvanbolničke potrošnje izražene u DDD na tisuću stanovnika na dan, penicilina širokog spektra, cefalosporina, makrolida (osim eritromicina) i fluorokinolona i potrošnje izražene u DDD na tisuću stanovnika na dan, penicilina uskog spektra, cefalosporina i eritromicina u razdoblju 2010-2021/

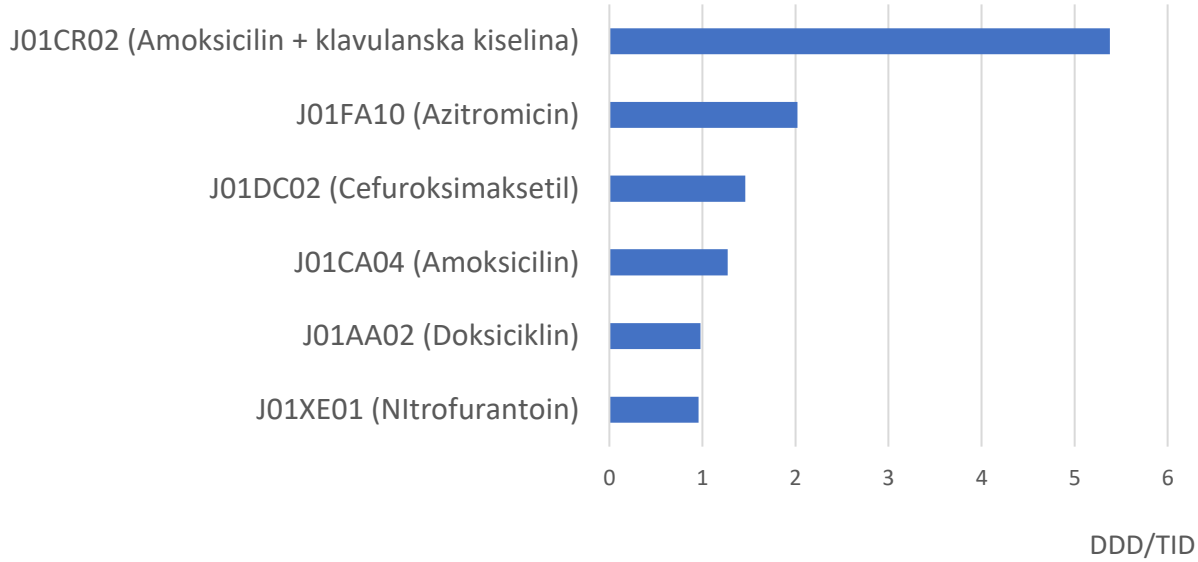
The ratio of consumption of broad-spectrum penicillins, cephalosporins, macrolides (except erythromicin) and fluoroqinolones to the consumption of narrow-spectrum penicillins, cephalosporins and erythromicin expressed as DDD per 1000 inhabitants per day in the community 2010-2021



Tablica 6. / *Table 6.*
Ambulantna potrošnja antibiotika („top 6“ antibiotika – DDD/TID), izvor podataka - HZZO
Ambulatory antibiotic consumption („top 6“antibiotics- DDD/TID); origin of data - CHIF

klasa	DDD/TID
J01CR02 (Amoksicilin + klavulanska kiselina)	5,38
J01FA10 (Azitromicin)	2,02
J01DC02 (Cefuroksimaksetil)	1,46
J01CA04 (Amoksicilin)	1,27
J01AA02 (Doksiciklin)	0,98
J01XE01 (Nitrofurantoin)	0,96

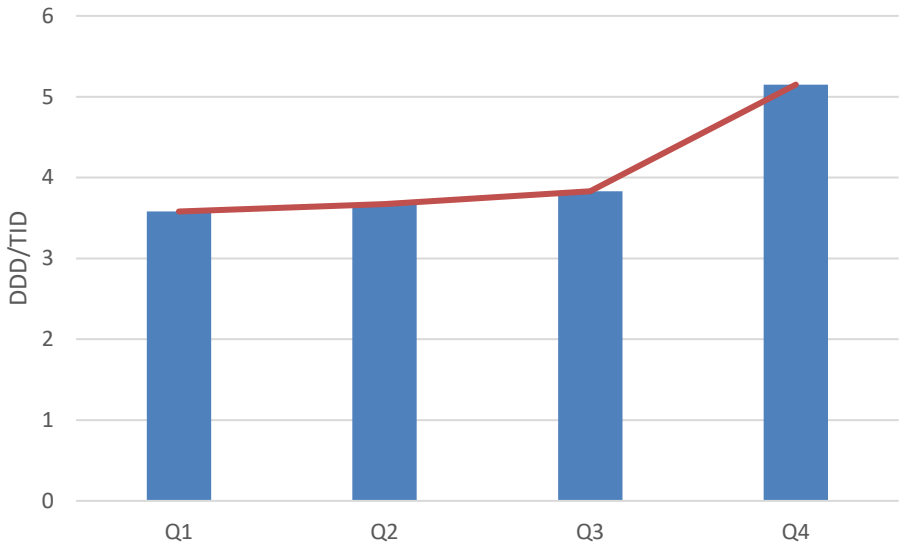
Slika 5. */ Figure 5.*
Ambulantna potrošnja antibiotika („top 6“ antibiotika – DDD/TID), izvor podataka – HZZO
Ambulatory antibiotic consumption („top 6“antibiotics- DDD/TID); origin of data-CHIF



Tablica 7. */ Table 7.*
Ambulantna potrošnja antibiotika po kvartalima – DDD/TID, izvor podataka - HZZO
Ambulatory antibiotic consumption – by quarters DDD/TID; origin of data-CHIF

kvartal	DDD/TID
I	3,58
II	3,67
III	3,83
IV	5,15

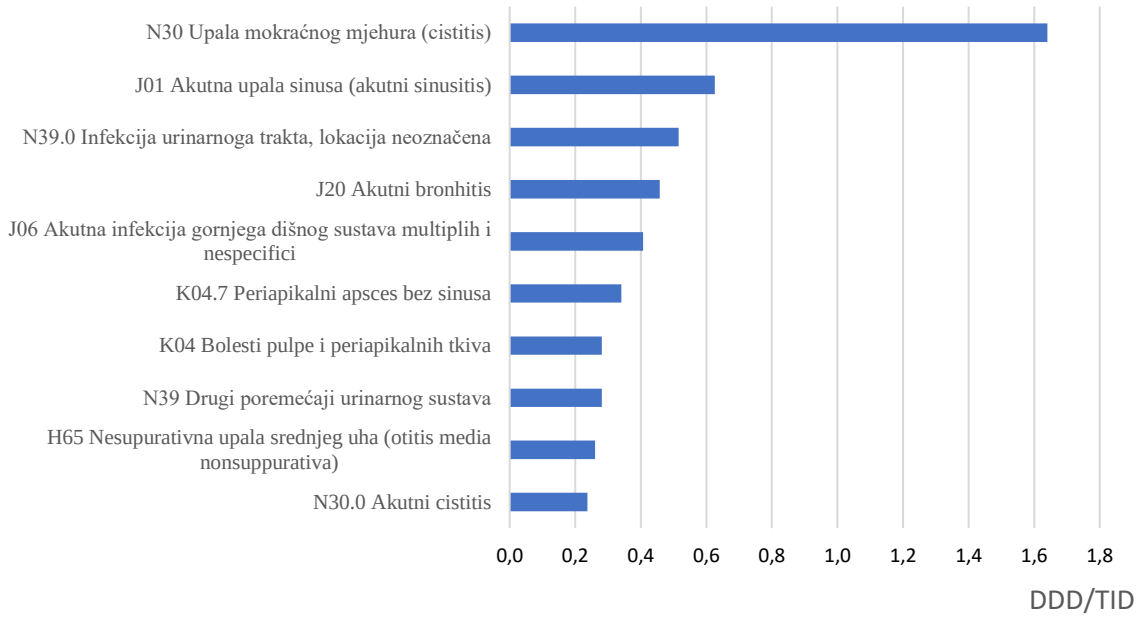
Slika 6. */ Figure 6.*
Ambulantna potrošnja antibiotika po kvartalima – DDD/TID, izvor podataka – HZZO
Ambulatory antibiotic consumption – by quarters DDD/TID; origin of data-CHIF



Tablica 8. */ Table 8.*
Ambulantna potrošnja antibiotika „top 10“ dijagnoza – DDD/TID, izvor podataka - HZZO
Ambulatory antibiotic consumption „top 10“diagnosis – DDD/TID, origin of data-CHIF

11	DDD/TID
N30 Upala mokraćnog mjehura (cistitis)	1,895
J01 Akutna upala sinusa (akutni sinusitis)	0,767
J02 Akutna upala ždrijela (akutni faringitis)	0,733
J03 Akutna upala tonzila (akutni tonzilitis)	0,642
N39.0 Infekcija urinarnoga trakta, lokacija neoznačena	0,624
J06 Akutna infekcija gornjega dišnog sustava multiplih i nespecifici	0,483
J20 Akutni bronhitis	0,480
U07.1 Akutna respiratorna bolest uzrokovana 2019-noCoV	0,396
N39 Drugi poremećaji urinarnog sustava	0,344
K04.7 Periapikalni apsces bez sinusa	0,342

Slika 7. */ Figure 7.*
Ambulantna potrošnja antibiotika „top 10“ dijagnoza – DDD/TID, izvor podataka - HZZO
Ambulatory antibiotic consumption „top 10“diagnosis – DDD/TID, origin of data-CHIF



Potrošnja antibiotika u hrvatskim bolnicama

Bolnička potrošnja antibiotika prati se odvojeno od ambulantne potrošnje od 2001. godine kada je započelo praćenje potrošnje. Do 2010. godine podaci o bolničkoj potrošnji antibiotika prikupljali su se samo iz veledrogerija. Nakon toga podaci se dobivaju iz dva izvora, veledrogerija i bolničkih ljekarni.
Od 2010. godine službeni podaci o bolničkoj potrošnji antibiotika, koji se šalju u europski program praćenja potrošnje (ESAC-Net) su oni koje dobivamo od bolničkih ljekarni (tablica 2). Podaci o potrošnji antibiotika se dobivaju u paketima ili komadima. Svaka bolnica dostavlja i administrativne podatke o broju bolničkoopskrbnih dana (BOD) i broju primitaka odvojeno za čitavu bolnicu te za jedinice intenzivnog liječenja (JIL) po vrstama (mješoviti, kirurški, internistički, pedijatrijski). Od 2011. godine u praćenje bolničke potrošnje uključena je i potrošnja antibiotika u dnevnim bolnicama, a denominatoru su uz bolničke dane pridruženi terapijski dani dnevne bolnice.
Podaci o potrošnji antibiotika prikupljaju se na petoj razini ATK klasifikacije, a izražavaju na 3. ili 4. razini.
Podaci o bolničkoj potrošnji iskazuju se u DDD/1000 stanovnika po danu (DDD/TID) (tablica 2). Obzirom da sve bolnice u Republici Hrvatskoj (68) dostavljaju svoje podatke, podaci o potrošnji antibiotika se mogu izraziti u DDD/100 BOD. Takav način prikazivanja potrošnje je objektivniji, precizniji i omogućava detaljnu analizu po pojedinim klasama i vrstama antibiotika na nacionalnom nivou, ali i posebno za svaku bolnicu.

U tablici 9 i na slici 8 usporedno su prikazani podaci od 2014. godine dobiveni iz oba izvora. Svake godine potrošnja iz bolničkih ljekarni je nešto viša u odnosu na podatke dobivene iz veledrogerija, osim u 2015. godini kada je potrošnja antibiotika izračunata prema podacima dobivenim od veledrogerija za 0,04 DDD/100 BOD bila viša. Razlika potrošnje u 2021. godini, iznosi najviše do sad (0,35 DDD/TID) tijekom praćenja u korist podataka dobivenih iz bolničkih ljekarni. Taj podatak je dvostruko viši od prethodne godine, kada je razlika iznosila 0,16 DDD/TID (tablica 9; slika 8).

Za 2021. godinu sve bolnice (ukupno 68) su poslale podatke o bolničkoj potrošnji antibiotika. Uobičajeni način slanja podataka je elektronskim putem na adresu iskra.antibiotici@gmail.com. Poželjno je slanje podataka direktno eksportom iz ljekarničkih programa, što su učinile samo 4 bolnice.

Prema ustaljenoj praksi, nakon obrade podataka o potrošnji antibiotika, dobiveni rezultati se šalju na kontrolu i konačnu potvrdu svakoj bolnici.
Iako je bolnička potrošnja antibiotika izražena u DDD/TID 2021. godine bila niža u odnosu na godinu prije (tablica 2), to se nije potvrdilo i u prikazu potrošnje izražene u DDD na 100 BOD (tablica 10, slika 9), koji realnije prikazuju potrošnju antibiotika, obzirom da je denominator broj bolničkih dana. Trend bolničke potrošnje pokazuje kontinuirani rast od 2014. godine, a u 2021. je dosegnuo najvišu razinu do sada od 44,81 DDD/BOD (tablica 10, slika 9).

U 2021. zabilježena je najviša potrošnja antibiotika ako ju izrazimo na 1000 stanovnika po danu, obzirom da je promijenjen denominator u skladu s popisom stanovništva iz 2021. godine.

U 2021. godini raste potrošnja klase penicilina (J01C), cefalosporina (J01D), aminoglikozida (J01G), kinolona (J01M) i klase ostali antibiotici (J01X). Klasa ostali antibiotici bilježi i najveći porast, za 0,99 DDD/BOD u prošloj godini (tablica 11, slika 10). Klasu ostali antibiotici čine većinom rezervni antibiotici (glikopeptidi, polimiksini, ostali: linezolid, daptomicin, fosfomicin), osim derivata imidazola.
Pad potrošnje bilježi se kod klase tetraciklina (J01A), klase sulfonamidi s trimetoprimom (J01E), te klase makrolid-linkozamid-streptogramin (J01F).

Antibiotici koji zauzimaju vodećih pet mjesta po potrošnji u bolnicama ostali su isti kao i prethodne godine. Ko-amoksiklav učvrstio je svoju poziciju na prvom mjestu s još višom potrošnjom (8,07 DDD/100 BOD) u odnosu na godinu prije (7,71 DDD/100 BOD). Na drugom mjestu je ceftriakson s nešto višom potrošnjom (4,62 DDD/100 BOD) u odnosu na godinu prije (4,06 DDD/100 BOD). Na trećem mjestu je cefuroksimaksetil s nešto nižom potrošnjom (3,69 DDD/100 BOD u odnosu na 3,98 DDD/100 BOD), na četvrtom ciprofloksacin s gotovo identičnom potrošnjom (3,18 DDD/100 BOD u odnosu na 3,19 DDD/100 BOD prethodne godine) te azitromicin na petom mjestu s nešto nižom potrošnjom (2,89 DDD/100 BOD) u odnosu na godinu ranije (3,07 DDD/100 BOD (tablica 12; slika 11).

Kao indikator potrošnje antibiotika prati se udio potrošnje rezervnih antibiotika glikopeptida (J01XA), cefalosporina III. generacije (J01DD), cefalosporina IV. generacije (J01DE), monobaktama (J01DF), karbapenema (J01DH), fluorokinolona (J01MA), polimiksina (J01XB), piperacilin+tazobaktama (J01CR05), linezolida (J01XX08), tedizolida (J01XX11) i daptomicina (J01XX09) u ukupnoj bolničkoj potrošnji, koji je najveći u zadnjih 12 godina i iznosi 39,4 % (tablica 13, slika 12). Prošle godine taj udio je iznosio 36,7%.

Sve **kliničke ustanove**, njih trinaest je dostavilo podatke o potrošnji antibiotika (tablica 14, slika 13). Raspon potrošnje antibiotika u 2021. godini kretao se od 26,17 do 93,21 DDD/100 BOD. U odnosu na prethodnu godinu u 2021. godini raspon potrošnje antibiotika je sužen, jer je porasla potrošnja u bolnici s najnižom potrošnjom i pala u bolnici s najvišom potrošnjom (tablica 15; slika 14). Raspon potrošnje je očekivano velik, jer se radi o kliničkim ustanovama s različitom kazuistikom.

Kod četiri kliničke ustanove (K 07; K 08; K 09; K 14) uočava se porast potrošnje antibiotika, što je dvostruko manje u odnosu na prethodnu godinu. Kod osam kliničkih ustanova došlo je do pada potrošnje (K 01; K 02; K 03; K 04, K 05; K 06; K 11; K15), dok je u jednoj kliničkoj ustanovi (K 13) razlika u potrošnji manja od jednog DDD na 100 BOD u dvije zadnje godine. U klinici 15 bilježi se drastičan pad potrošnje (39,97 DDD/BOD) u odnosu na godinu ranije kada je potrošnja iznosila 62,38 DDD/100 BOD.

Za 2021. godinu 22 **opće bolnice** su dostavile svoje podatke koji su međusobno usporedivi obzirom da se radi o najhomogenijoj skupini bolnica. Potrošnja antibiotika se kretala u širokom rasponu od 44,71 do 96,75 DDD/100 BOD (tablica 16) , što se ne bi moglo objasniti razlikama u tipu bolnica, obzirom da su to sve opće bolnice sa sličnim odjelima.

Na slici 15 je prikazana potrošnja u općim bolnicama prema pojedinim klasama antibiotika u 2021. godini. U tablici 17 i na slici 16 prikazana je potrošnja u općim bolnicama u petogodišnjem periodu što svakoj bolnici daje mogućnost praćenja vlastitih trendova potrošnje.
Opće bolnice O 08; O 13; O 21 te O 24 bilježe kontinuirani porast potrošnje antibiotika u petogodišnjem razdoblju. Opća bolnica O 02 je bolnica s najnižom potrošnjom antibiotika kroz godine, ali s blagom tendencijom porasta potrošnje.

Kod 6 općih bolnica uočava se trend porasta potrošnje (O 02; O 08; O 09; O 13; O 19; O 24) u odnosu na prethodnu godinu, dok je kod 12 bolnica uočen pad potrošnje (O 01; O 05; O 07; O10; O11; O 12; O 14; O15; O 17; O18; O22; O23), a kod četiri bolnice nema razlike u potrošnji veće od 1 DDD/100BOD (O 03; O 04; O20; O21).
U pet bolnica potrošnja se kretala između 40 i 50 DDD/100 BOD, što je bolje u odnosu na prethodnu godinu kada su se u tom rasponu nalazile samo dvije bolnice. Pet bolnica se nalazi u skupini bolnica s potrošnjom od 51 do 60 DDD/100 BOD, 5 bolnica je u skupini od 61 do 70 DDD/100 BOD. Potrošnja u dvije opće bolnice se kretala između 71 do 80 DDD/100 BOD-a. Čak četiri bolnice su zabilježile potrošnju veću od 81 DDD/ 100 BOD, dok je u jednoj bolnici zabilježena potrošnja od 96,75 DDD/100 BOD, što je više nego dvostruko u odnosu na potrošnju u bolnici s najnižom potrošnjom.

Potrošnja antibiotika u **psihijatrijskim bolnicama** kreće se od 4,11 do 18,58 DDD/100 BOD (tablica 18). Na slici 17 prikazana je potrošnja po klasama antibiotika u psihijatrijskim bolnicama. U 2021. godini u pet psihijatrijskih bolnica (P 01; P 03; P 04; P 07; P 09) uočava se porast potrošnje, dok je u jednoj bolnici (P 08) potrošnja u padu. Kod tri bolnice (P 02; P 05; P 06) nema promjena u potrošnji većoj od 1 DDD/100 BOD. U tablici 19 i na slici 18 prikazana je potrošnja u psihijatrijskim bolnicama u zadnjih pet godina s uočljivim trendovima potrošnje. Kontinuirani porast potrošnje uočava se kod psihijatrijske ustanove P 02.

Specijalne bolnice su podijeljene u dvije velike grupe s obzirom na njihov profil rada i kao takve bilježe veliki raspon u potrošnji antibiotika. U prvoj skupini nalazi se 10 bolnica, koje su namijenjene liječenju (akutnom/kroničnom), dok je u drugoj skupini 14 ustanova namijenjeno rehabilitaciji (tablica 20; slika 19). U prvoj skupini ustanova raspon potrošnje antibiotika se kreće od 8,46 do 78,06 DDD/100 BOD. Pet bolnica (S 02; S 03; S 04; S 13; S 21) bilježe porast potrošnje (tablica 21; slika 20).
U skupini specijalnih bolnica namijenjenih rehabilitaciji kretanje potrošnje antibiotika je značajno niže, od 0,58 do 11,64 DDD/100 BOD (tablica 21; slika 20) te svega jedna ima zabilježen porast potrošnje (S 07). Kod jedne specijalne bolnice (S 05) zabilježen je pad potrošnje, dok je kod svih ostalih potrošnja ujednačena s prethodnom godinom i ne odstupa više ili manje od 1 DDD/100 BOD.
Na slici 19 prikazana je potrošnja antibiotika po klasama u 2021. godini. U tablici 21 i na slici 20 prikazana je potrošnja u specijalnim bolnicama u zadnjih pet godina.
Nastavlja se linearan rast bolničke potrošnje antibiotika koja je u 2021. godini zabilježila najvišu vrijednost od 44,81 DDD/100 BOD. Najveći udio u potrošnji čine cefalosporini s 31%, čija potrošnja je porasla u odnosu na godinu prije. Slijede ih penicilini s udjelom od 24%. Na trećem mjestu je klasa ostalih antibiotika s udjelom od 14%, kod koje je zabilježen i najviši porast potrošnje u odnosu na godinu prije za 0,99 DDD/100 BOD.

Udio potrošnje rezervnih antibiotika u ukupnoj bolničkoj potrošnji raste iz godine u godinu, te je u 2021. godini nadmašio prethodnu godinu kada se njihov porast dijelom mogao pripisati velikom udjelu teških COVID-19 pacijenata liječenih u jedinicama intenzivnog liječenja koji su razvili bakterijske infekcije povezane sa zdravstvenom skrbi. U 2021. godini udio u potrošnji rezervnih antibiotika iznosi gotovo 40% (39,4%).

Očigledno je pandemija COVID-19 i u 2021. godini utjecala na ukupnu bolničku potrošnju kao i na strukturu potrošnje antibiotika u kojoj se posebno ističe kontinuirani rast potrošnje rezervnih antibiotika.

Antibiotic consumption in Croatian hospitals

Inpatient antibiotic consumption has been tracked separately from outpatient consumption since 2001, when consumption tracking started. Until 2010, data on inpatient antibiotic consumption were collected only from wholesale pharmacies. Afterwards, data were obtained from two sources – wholesales data and hospital pharmacies.

Since 2010, official data on antibiotic consumption sent to the European Surveillance on Antimicrobial Consumption (ESAC-Net) have been those that we obtain from hospital pharmacies (Table 2). Antibiotic consumption data are obtained in packages or pieces. Every hospital also delivers administrative data on bed days (BD) and number of admissions separately for the entire hospital as well as the intensive care units by types (mixed, surgical, intern, pediatrics). Since 2011, inpatient consumption has involved the consumption of antibiotics in day care, while day care therapy days have been added to the denominator along with the hospital days.

Antibiotic consumption data are collected at the fifth level of the ATC classification, and are expressed at the third or fourth level.
Inpatient consumption data are expressed in defined daily doses per 1000 inhabitants daily (DDD/TID) (Table 2). As all hospitals in the Republic of Croatia (68) submit their data, antibiotic consumption data may be expressed in defined daily doses per 100 bed days (DDD/100 BD). Such a manner of expressing consumption is more objective, more precise and enables a detailed analysis per individual antibiotic classes and types at the national level, but also for each hospital separately.

Table 9 and Figure 8 show in parallel the data from 2014 obtained from both sources. Each year, the consumption from hospital pharmacies is somewhat higher compared to the data obtained from wholesale pharmacies, except in 2015, when antibiotic consumption calculated according to the data from wholesale pharmacies was higher by 0.04 DDD/100 BD. The difference in the consumption in 2021 is the largest ever (0.35 DDD/TID) since the beginning of tracking in favour of the data obtained from hospital pharmacies. The figures are twice as high compared to those from the previous year, when the difference was 0.16 DDD/TID (Table 9; Figure 8).

For 2021, all hospitals (68 in total) send their inpatient antibiotic consumption data. The usual way to collect data is electronicaly via the e-mail address iskra.antibiotici@gmail.com. The preferred method of data submission is a direct export from the pharmacy software, which only four hospitals did.

According to the usual practice, the results obtained are sent to each hospital for control and final confirmation following antibiotic consumption data processing.

Even though inpatient antibiotic consumption expressed in DDD/TID was lower in 2021 compared to the previous year (Table 2), this was not confirmed by the overview of the consumption expressed in DDD per 100 BD (Table 10, Figure 9), which show antibiotic consumption more realistically, with regard to the number of hospital days as the denominator. The inpatient consumption trend shows a continuous growth since 2014, and in 2021 it reached the highest level so far – 44.81 DDD/BD (Table 10; Figure 9).

In 2021, the highest antibiotic consumption was recorded if expressed per 1,000 inhabitants daily as the denominator has been changed in accordance with the 2021 population census.

The year 2021 saw the increase in the consumption of penicillins (J01C), cephalosporins (J01D), aminoglycosides (J01G), quinolones (J01M) and other antibacterials (J01X). The largest increase is in the other antibacterials class, by 0.99 DDD/BD in the previous year (Table 11, Figure 10). The

other antibiotics class is comprised mostly of reserve antibiotics (glycopeptides, polymyxins, others: linezolid, daptomcyin, phosphomycin), except imidazole derivatives.
A drop has been recorded in the consumption of the tetracyclines (J01A), sulphonamides and trimethoprim (J01E) and macrolides-lincosamides and streptogramin class (J01F).

The top five antibiotics in terms of inpatient consumption have remained the same as in the previous year. Co-amoxiclav has consolidated its top position with an even higher consumption (8.07 DDD/100 BD) compared to the previous year (7.71 DDD/100 BD). Ceftriaxone comes second with a slightly higher consumption (4.62 DDD/100 BD) compared to the previous year (4.06 DDD/100 BD). Cefuroximaxetil comes third, with a slightly lower consumption (3.69 DDD/100 BD) compared to the previous year (3.98 DDD/100 BD), while ciprofloxacin comes fourth with a nearly identical consumption (3.18 DDD/100 BD compared to 3.19 DDD/100 BD from the previous year), with azithromycin in the fifth place with a somewhat lower consumption (2.89 DDD/100 BD) compared to the previous year (3.07 DDD/100 BD) (Table 12; Figure 11).

The indicator of antibiotic consumption is the proportion of the consumption of reserve antibiotics glycopeptide (J01XA), third generation cephalosporins (J01DD), fourth generation cephalosporins (J01DE), monobactams (J01DF), carbapenems (J01DH), fluoroquinolones (J01MA), polymyxin (J01XB), piperacillin+tazobactam (J01CR05), linezolid (J01XX08), tedizolid (J01XX11) and daptomycin (J01XX09) in the total inpatient consumption, which is the highest in the past 12 years, amounting to 39.4% (Table 13, Figure 12). In the previous year, the proportion was 36,7%.

All **clinical institutions**, thirteen of them, submitted their antibiotic consumption data (Table 14, Figure 13). Antibiotic consumption in 2021 ranged from 26.17 to 93.21 DDD/100 BD. Compared to the previous year (2021), the antibiotic consumption range is somewhat more narrow due to an increased consumption in the hospital with the lowest consumption and drop decreased consumption in the hospital with the highest consumption (Table 15; Figure 14). The consumption range is as high as was expected because the involved clinical institutions have different casuistics.

In four clinical institutions (K 07; K 08; K 09; K 14), there is an increase in the consumption of antibiotics, which is half as much as in the previous year. In eight clinical institutions (K 01; K 02; K 03; K 04, K 05; K 06; K 11; K 15) the consumption dropped, while in one clinical institution (K 13) the difference in the consumption is less than 1 DDD/100 BD in the past two years. Clinic 15 recorded a drastic drop in the consumption (39.97 DDD/100 BD) compared to the previous year, when the consumption was 62.38 DDD/100 BD.

For 2021, 22 **general hospitals** submitted their data, which are comparable with one another since it is the most homogeneous group of hospitals. Antibiotic consumption ranged from 44.71 to 96.75 DDD/ 100 BD (Table 16), which could not be explained by the differences in the types of hospitals since all of them are general hospitals with similar wards.

Figure 15 shows the consumption in general hospitals according to individual antibiotic classes in 2021. Table 17 and Figure 16 show the consumption in general hospitals in a five-year period, which enables each hospital to track its own consumption trends.

General hospitals O 08, O 13, O 21 and O 24 recorded a continuous increase in their antibiotic consumption in the five-year period. General hospital O 02 is a hospital with the lowest antibiotic consumption through the years, but with a slight upward tendency.

In six general hospitals there is an upward trend of consumption (O 02; O 08; O 09; O 13; O 19; O 24) compared to the previous year, in twelve general hospitals the consumption dropped (O 01; O 05; O 07; O10; O11; O 12; O 14; O15; O 17; O18; O22; O23), while in four general hospitals there is no difference in consumption larger than 1 DDD/100 BD(O 03; O 04; O20; O21).

In five hospitals, the consumption ranged between 40 and 50 DDD/100 BD, which is more compared to the previous year, when only two hospitals were in the same range. Five hospitals are in the group of hospitals with the consumption of 51-60 DDD/100 BD, and five hospitals are in the 61-70 DDD/100 BD group. The consumption in two general hospitals ranged between 71 and 80 DDD/100 BD. As many as four hospitals recorded a consumption of more than 81 DDD/100 BD, while in one hospital as much as 96.75 DDD/100 BD was recorded, which is more than a double compared to the figure in the hospital with the lowest consumption.

Antibiotic consumption in **psychiatric hospitals** ranges from 4.11 to 18.58 DDD/100 BD (Table 18). Figure 17 shows the consumption by antibiotic classes in psychiatric hospitals. In 2021, in five psychiatric hospitals (P 01; P 03; P 04; P 07; P 09) there was an increase in the consumption, while in one hospital (P 08) the consumption dropped. In three hospitals (P 02; P 05; P 06), there was no changes in the consumption greater than 1 DDD/100 BD. Table 19 and Figure 18 show the consumption in psychiatric hospitals in the past five years with noticeable consumption trends. A continuous increase in the consumption is seen in the psychiatric institution P 02.

Specialised hospitals are divided into two large groups with regard to their patient profile; as such, they have recorded a wide range of antibiotic consumption. The first group contains ten hospitals intended for treatment (acute/chronic), while the second group contains fourteen institutions for rehabilitation (Table 20; Figure 19). In the first group, the consumption ranges from 8.46 to 78.06 DDD/100 BD. In five hospitals (S 02; S 03; S 04; S 13; S 21), there was an increase in the consumption (Table 21; Figure 20).

In the group of specialised hospitals intended for rehabilitation, antibiotic consumption is significantly lower, ranging from 0.58 to 11.64 DDD/100 BD (Table 21; Figure 20), and only one of them recorded a consumption increase (S 07). One specialised hospital (S 05) recorded a consumption decrease, while in all others the consumption was equal to that in the previous year, not deviating from 1 DDD/100 BD.

Figure 19 shows the consumption of antibiotic by classes in 2021. Table 21 and Figure 20 show consumption in specialised hospitals in the past five years.

There is a continuation of the linear growth of inpatient antibiotic consumption, which was the highest in 2021, standing at 44.81 DDD/100 BD. Cephalosporins constitute the greatest proportion in the consumption (31%) as their consumption grew compared to the previous year. They are followed by penicillins (24%). Other antibacterials come third (14%) and also display the greatest consumption increase compared to the previous year, by 0.99 DDD/100 BD.

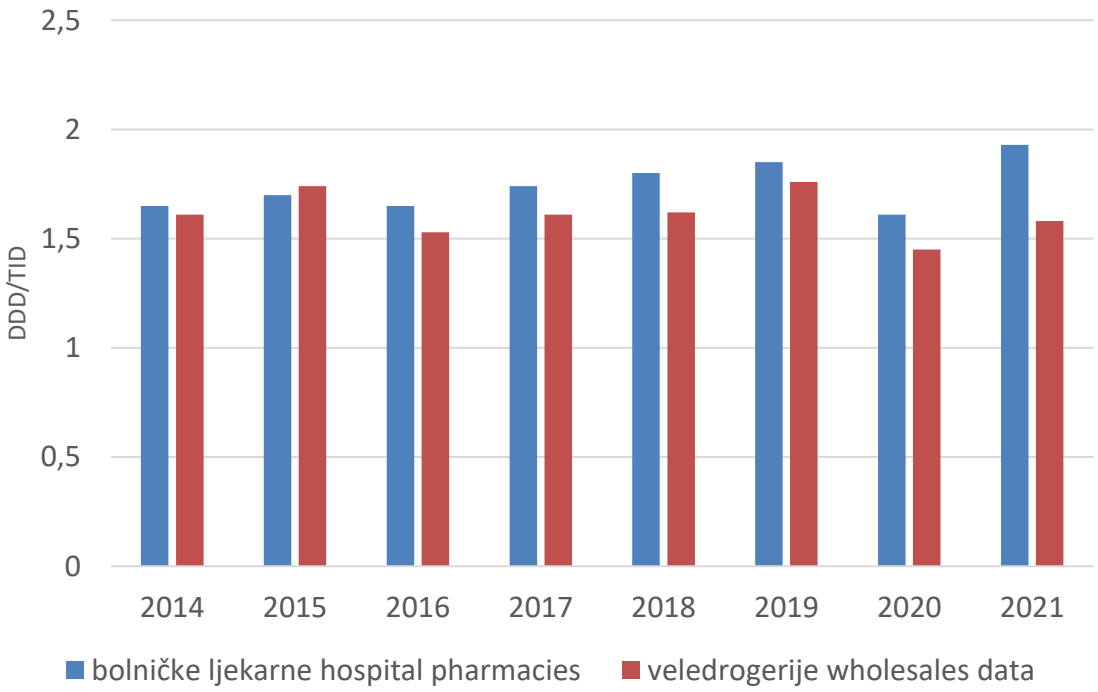
The proportion of the consumption of reserve antibiotics in the total inpatient consumption grows year by year. In 2021, it exceeded the previous year, when the increase could partly be ascribed to a large proportion of severe COVID cases in patients treated in intensive care units, with bacterial healthcare - associated infections. In 2021, the proportion in the consumption of reserve antibiotics amounted to nearly 40% (39.4%).

It is obvious that, in 2021, the COVID-19 pandemic again affected the total inpatient consumption as well as the structure of antibiotic consumption, where the continuous increase in the consumption of reserve antibiotics is particularly emphasized.

Tablica 9. /*Table 9.*
Bolnička potrošnja antibiotika (DDD/TID) usporedba podataka bolničkih ljekarni i veledrogerija /
Hospital antibiotic consumption (DDD/TID) comparison between hospital pharmacy data and wholesales data

godina year	bolničke ljekarne hospital pharmacies	veledrogerije wholesales data
2014	1,65	1,61
2015	1,70	1,74
2016	1,65	1,53
2017	1,74	1,61
2018	1,80	1,62
2019	1,85	1,76
2020	1,61	1,45
2021	1,93	1,58

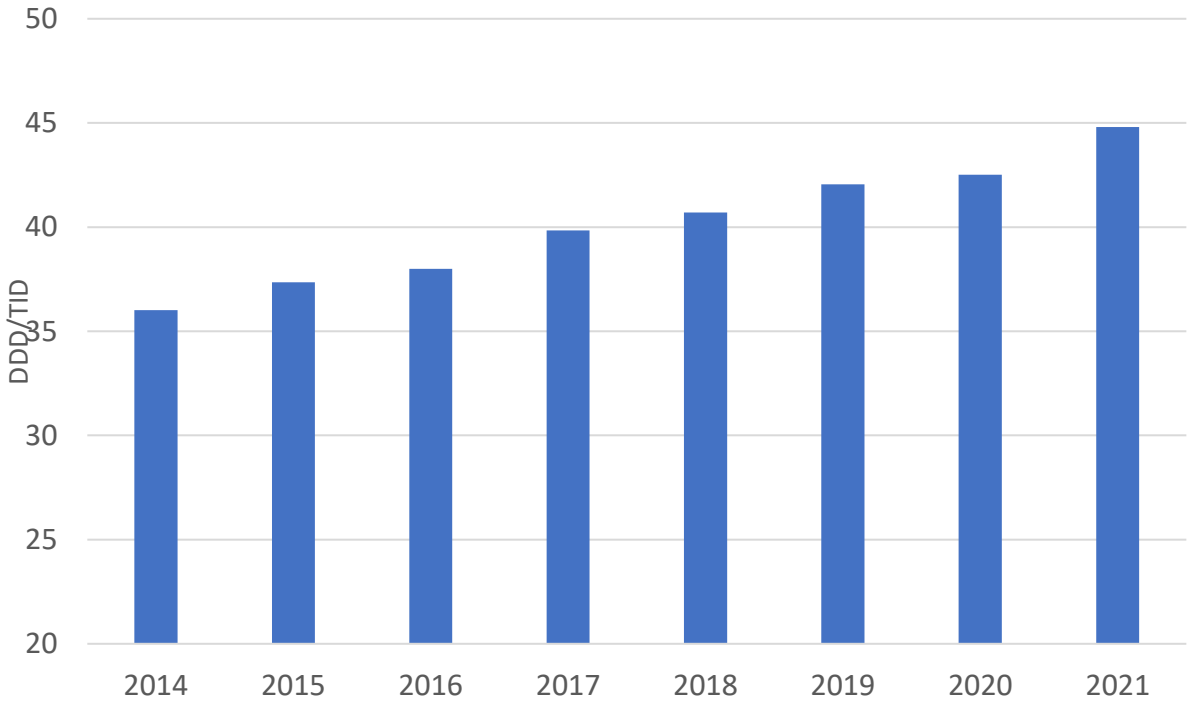
Slika 8. */ Figure 8.*
Bolnička potrošnja antibiotika (DDD/TID) usporedba podataka bolničkih ljekarni i veledrogerija /
Hospital antibiotic consumption (DDD/TID) comparison between hospital pharmacy data and wholesales data



Tablica 10. */ Table 10.*
Bolnička potrošnja antibiotika (DDD/100 BOD)
Hospital antibiotic consumption (DDD/100 BD)

Godina / *year*	DDD/100 BOD / *DDD/100 BD*
2014	36,01
2015	37,35
2016	37,99
2017	39,84
2018	40,70
2019	42,05
2020	42,52
2021	44,81

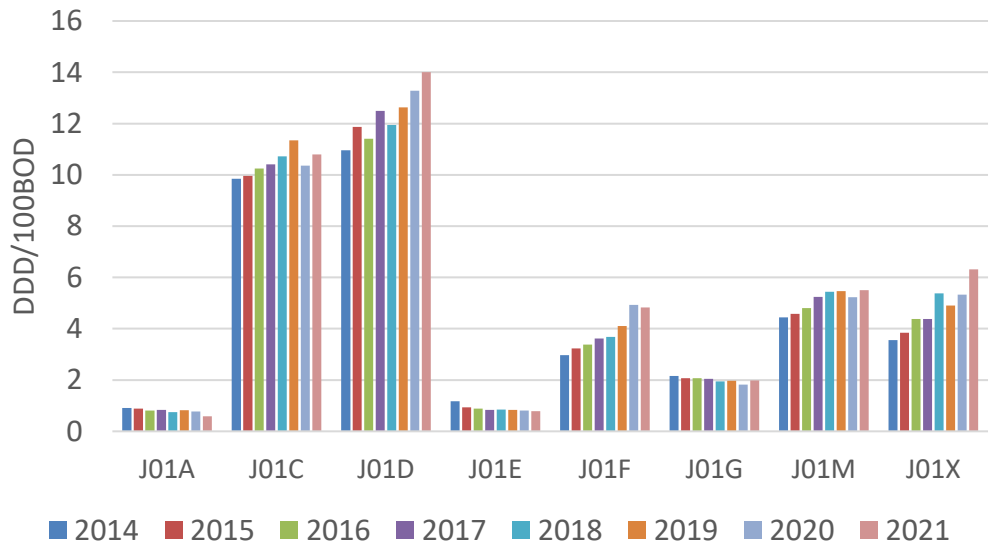
Slika 9. */Figure 9.*
Bolnička potrošnja antibiotika (DDD/100 BOD)
Hospital antibiotic consumption (DDD/100 BD)



Tablica 11. */ Table 11.*
Bolnička potrošnja antibiotika (DDD/100 BOD) po klasama, izvor podataka – bolničke ljekarne/
Hospital antibiotic consumption (DDD/100 BD) by class, origin of data - hospital pharmacies

Klasa / *class*		Godina / *year*						
	2014	2015	2016	2018	2018	2019	2020	2021
J01A	0,91	0,88	0,81	0,83	0,75	0,82	0,77	0,59
J01C	9,85	9,96	10,25	10,41	10,72	11,34	10,36	10,80
J01D	10,96	11,87	11,41	12,49	11,95	12,63	13,29	14,01
J01E	1,17	0,93	0,88	0,83	0,85	0,83	0,81	0,78
J01F	2,97	3,23	3,38	3,62	3,68	4,11	4,93	4,83
J01G	2,16	2,07	2,07	2,04	1,94	1,97	1,82	1,98
J01M	4,44	4,58	4,81	5,24	5,44	5,46	5,22	5,50
J01X	3,55	3,84	4,38	4,38	5,38	4,90	5,33	6,32

Slika 10. */ Figure 10.*
Bolnička potrošnja antibiotika (DDD/100 BOD) po klasama, izvor podataka – bolničke ljekarne/
Hospital antibiotic consumption (DDD/100 BD) by class, origin of data - hospital pharmacies



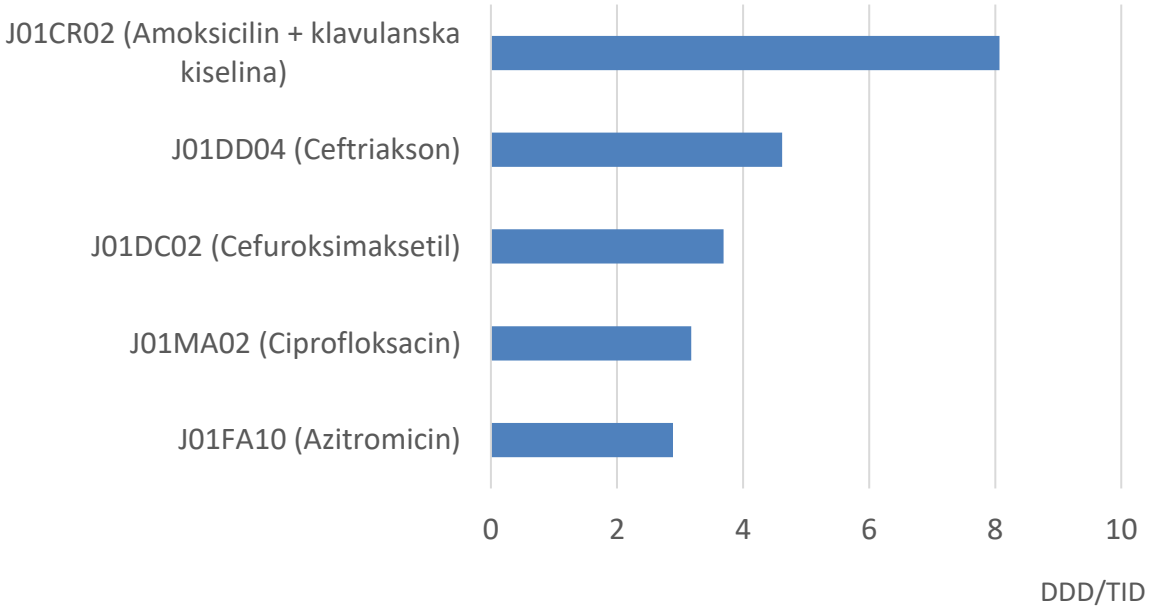
Tablica 12. */ Table 12.*
Bolnička potrošnja antibiotika „top 5“ antibiotika – DDD/100 BOD, izvor podataka – bolničke ljekarne /
Hospital antibiotic consumption „top 5“antibiotics – DDD/100 BD; origin of data - hospital pharmacies

klasa	DDD/100 BOD
J01CR02 (Amoksicilin+klavulanska kiselina)	8,07
J01DD04 (Ceftriakson)	4,62
J01DC02 (Cefuroksimaksetil)	3,69
J01MA02 (Ciprofloksacin)	3,18
J01FA10 (Azitromicin)	2,89

Slika 11. */ Figure 11.*

Bolnička potrošnja antibiotika „top 5“ antibiotika – DDD/100 BOD, izvor podataka – bolničke ljekarne /

Hospital antibiotic consumption „top 5“antibiotics – DDD/100 BD; origin of data - hospital pharmacies



Tablica 13./ *Table 13.*

Udio potrošnje glikopeptida* (J01XA), cefalosporina III. generacije* (J01DD), cefalosporina IV. generacije* (J01DE), monobaktama* (J01DF), karbapenema* (J01DH), fluorokinolona* (J01MA), polimiksina* (J01XB), piperacilin+tazobaktama* (J01CR05), linezolida* (J01XX08), tedizolida* (J01XX11) i daptomicina* (J01XX09) u odnosu na ukupnu potrošnju antibiotika za sistemsku upotrebu u bolnicama izražen kao DDD na tisuću stanovnika na dan u razdoblju 2010-2021/

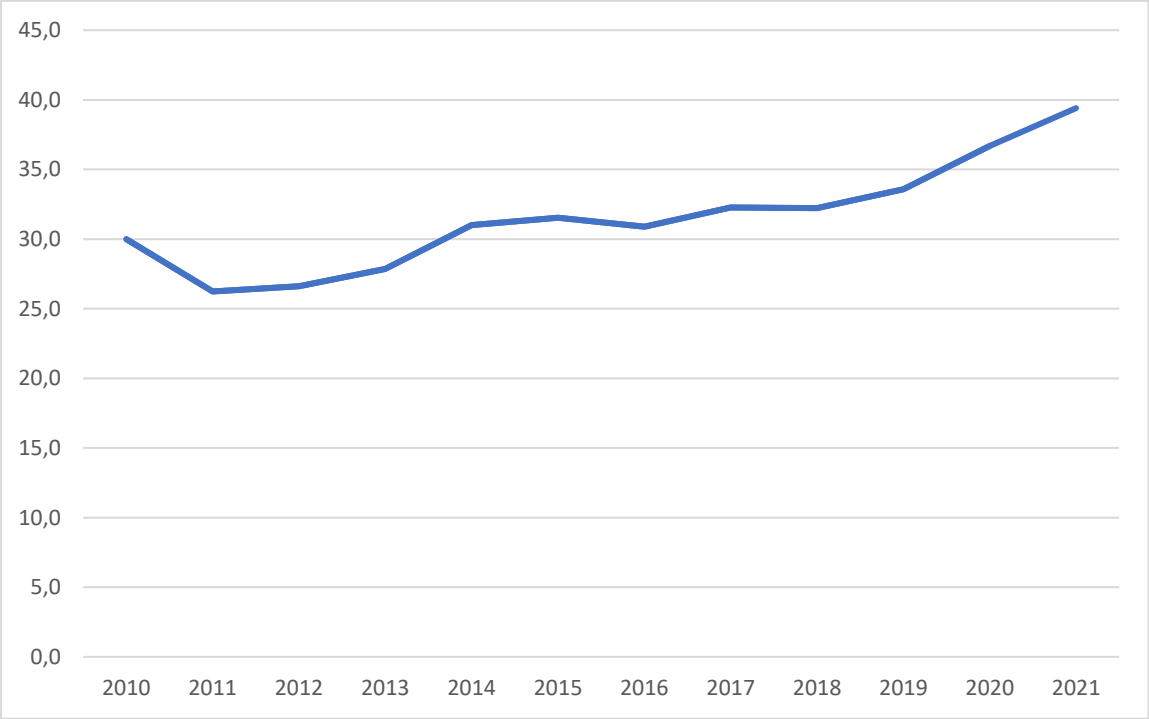
The proportion of glycopeptides (J01XA), third-generation cephalosporin*s (J01DD), fourth-generation cephalosporins*, (J01DE), monobactams* (J01DF), carbapenems* (J01DH), fluoroquinolones* (J01MA), polymyxins* (J01XB), piperacillin and tazobactam* (J01CR05), linezolid* (J01XX08), tedizolid* (J01XX11) and daptomycin* (J01XX09) consumption out of total consumption of antibacterials for systemic use in the hospital (DDD/ TID) 2010-2021*

	Udio potrošnje rezervnih* antibiotika u ukupnoj bolničkoj potrošnji %
2010	30,0
2011	26,2
2012	26,6
2013	27,9
2014	31,0
2015	31,5
2016	30,9
2017	32,3
2018	32,2
2019	33,6
2020	36,7
2021	39,4

Slika 12./ *Figure 12.*

Udio potrošnje glikopeptida* (J01XA), cefalosporina III. generacije* (J01DD), cefalosporina IV. generacije* (J01DE), monobaktama* (J01DF), karbapenema* (J01DH), fluorokinolona* (J01MA), polimiksina* (J01XB), piperacilin+tazobaktama* (J01CR05), linezolida* (J01XX08), tedizolida* (J01XX11) i daptomicina* (J01XX09) u odnosu na ukupnu potrošnju antibiotika za sistemsku upotrebu u bolnicama izražen kao DDD na tisuću stanovnika na dan u razdoblju 2010-2021/

The proportion of glycopeptides (J01XA), third-generation cephalosporins (J01DD), fourth-generation cephalosporins, (J01DE), monobactams (J01DF), carbapenems (J01DH), fluoroquinolones (J01MA), polymyxins (J01XB), piperacillin and tazobactam (J01CR05), linezolid (J01XX08), tedizolid (J01XX11) and daptomycin (J01XX09) consumption out of total consumption of antibacterials for systemic use in the hospital (DDD/ TID) 2010-2021

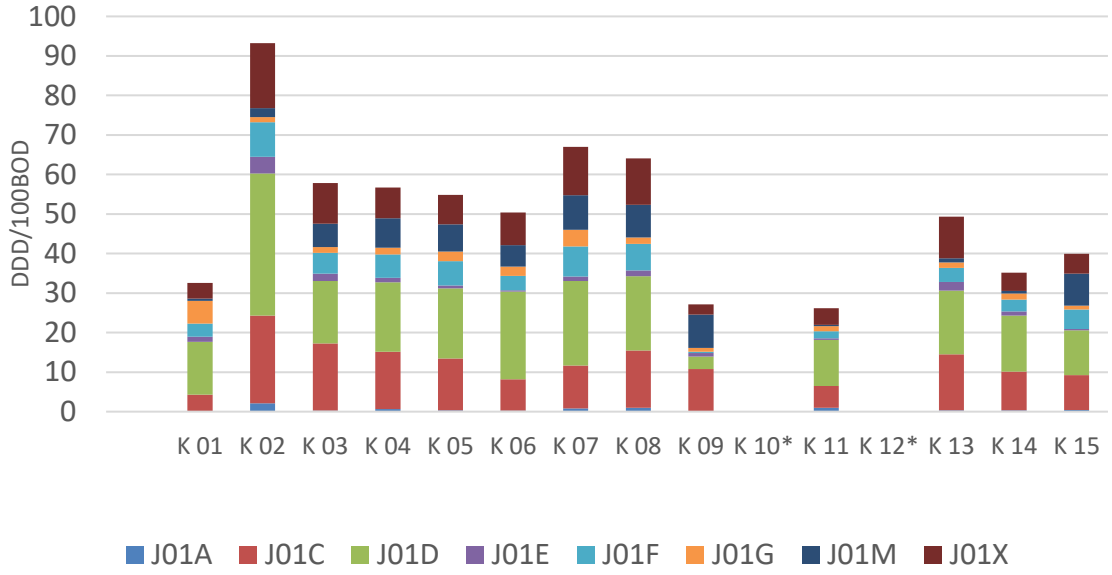


Tablica 14. */ Table 14.*
Kliničke ustanove - potrošnja antibiotika 2021.
Clinical insitutions – antibiotic consumption in 2021

	DDD/100 BOD, DDD/100 BD								
USTANOVA INSTITUTION	UKUPNO TOTAL	J01A	J01C	J01D	J01E	J01F	J01G	J01M	J01X
K 01	32,53	0,05	4,21	13,44	1,23	3,35	5,71	0,60	3,94
K 02	93,21	2,08	22,20	35,99	4,20	8,74	1,29	2,32	16,39
K 03	57,86	0,24	16,98	15,87	1,80	5,32	1,42	5,93	10,30
K 04	56,69	0,66	14,47	17,63	1,09	5,95	1,65	7,49	7,74
K 05	54,86	0,36	13,13	17,71	0,72	6,16	2,45	6,82	7,51
K 06	50,39	0,21	7,97	22,19	0,31	3,64	2,34	5,46	8,28
K 07	66,95	0,78	10,91	21,33	1,17	7,62	4,18	8,75	12,22
K 08	64,08	0,95	14,51	18,80	1,44	6,76	1,60	8,30	11,73
K 09	27,13	0,10	10,69	3,17	0,88	0,35	0,91	8,41	2,63
K 10*									
K 11	26,17	0,97	5,54	11,63	0,39	1,81	1,32	0,28	4,23
K 12*									
K 13	49,30	0,29	14,18	16,14	2,17	3,56	1,44	1,05	10,47
K 14	35,18	0,35	9,81	14,16	1,04	3,02	1,49	0,67	4,63
K 15	39,97	0,37	8,84	11,40	0,30	4,94	0,99	8,09	5,04

* bolnice koje su ušle u sastav drugih kliničkih ustanova / these hospitals merged in other clinical hospitals

Slika 13. */figure 13.*
Kliničke ustanove - potrošnja antibiotika 2017.-2021.
Clinical insitutions – antibiotic consumption in 2017-2021

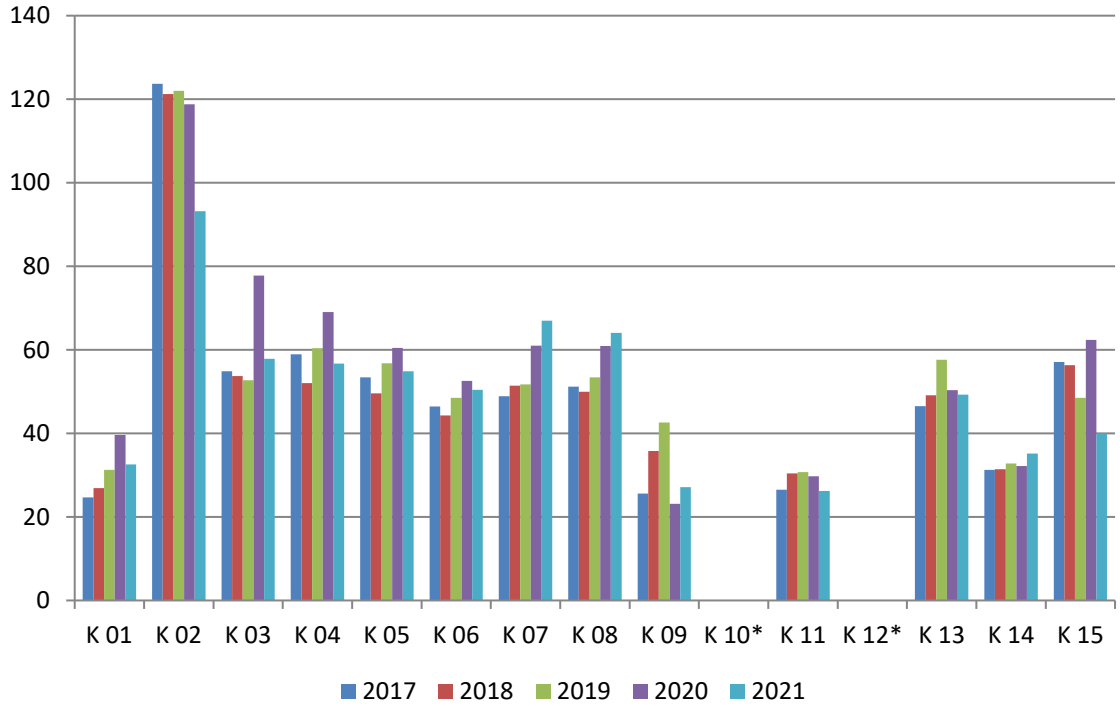


Tablica 15. */ table 15.*
Kliničke ustanove - potrošnja antibiotika 2017-2021.
Clinical insitutions – antibiotic consumption in 2017-2021

	DDD/100 BOD, DDD/100BD				
USTANOVA INSTITUTION	2017	2018	2019	2020	2021
K 01	24,7	26,9	31,3	39,64	32,53
K 02	123,7	121,2	122,0	118,77	93,21
K 03	54,9	53,7	52,7	77,76	57,86
K 04	58,9	52,0	60,4	69,01	56,69
K 05	53,4	49,6	56,8	60,47	54,86
K 06	46,4	44,3	48,5	52,54	50,39
K 07	48,9	51,4	51,7	61,03	66,95
K 08	51,2	50,0	53,4	60,94	64,08
K 09	25,6	35,8	42,6	23,12	27,13
K 10*					
K 11	26,5	30,4	30,7	29,71	26,17
K 12*					
K 13	46,5	49,1	57,6	50,34	49,30
K 14	31,3	31,4	32,8	32,15	35,18
K 15	57,1	56,3	48,5	62,38	39,97

* bolnice koje su ušle u sastav drugih kliničkih ustanova / these hospitals merged in other clinical hospitals

Slika 14. / *figure 14.*
Kliničke ustanove - potrošnja antibiotika 2017.-2021.
Clinical insitutions – antibiotic consumption in 2017-2021

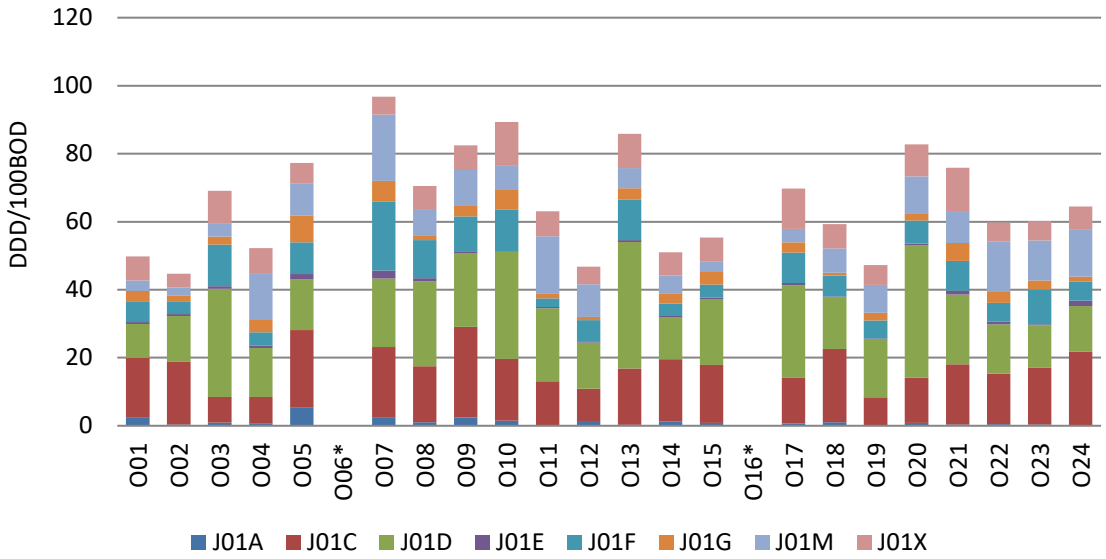


Tablica 16. */Table 16.*
Opće bolnice - potrošnja antibiotika 2021.
General hospitals – antibiotic consumption in 2021

USTANOVA INSTITUTION	UKUPNO TOTAL	DDD/100 BOD, DDD/100 BD							
		J01A	J01C	J01D	J01E	J01F	J01G	J01M	J01X
O 01	49,81	2,33	17,60	10,04	0,54	5,91	3,18	3,17	7,05
O 02	44,71	0,36	18,60	13,32	0,58	3,59	1,76	2,45	4,03
O 03	69,12	0,90	7,61	31,73	0,83	12,21	2,32	3,94	9,59
O 04	52,26	0,75	7,71	14,40	0,78	3,83	3,85	13,54	7,38
O 05	77,31	5,46	22,66	14,85	1,68	9,32	7,89	9,34	6,10
O 06*									
O 07	96,75	2,33	20,83	20,13	2,38	20,29	6,01	19,49	5,29
O 08	70,51	1,03	16,44	25,01	0,93	11,22	1,21	7,88	6,80
O 09	82,43	2,47	26,63	21,57	0,46	10,41	3,36	10,29	7,25
O 10	89,37	1,49	18,20	31,50	0,24	12,21	5,88	6,92	12,93
O 11	63,03	0,00	13,10	21,43	0,35	2,57	1,33	16,96	7,30
O 12	46,83	1,09	9,84	13,50	0,42	6,25	0,91	9,64	5,17
O 13	85,86	0,24	16,61	37,17	0,60	11,93	3,29	5,95	10,07
O 14	50,97	1,22	18,38	12,17	0,54	3,68	2,83	5,37	6,78
O 15	55,40	0,89	17,03	19,32	0,45	3,80	3,93	2,98	6,99
O 16**									
O 17	69,77	0,63	13,60	27,09	0,66	8,96	2,99	3,93	11,90
O 18	59,29	1,06	21,55	15,20	0,17	6,12	0,88	7,17	7,13
O 19	47,27	0,14	8,23	17,18	0,17	5,21	2,32	8,15	5,86
O 20	82,76	0,81	13,27	38,92	0,56	6,80	2,17	10,82	9,41
O 21	75,84	0,35	17,71	20,54	1,15	8,69	5,27	9,15	12,98
O 22	59,77	0,49	14,85	14,53	0,82	5,43	3,20	14,84	5,61
O 23	60,10	0,41	16,67	12,49	0,24	10,16	2,78	11,75	5,61
O 24	64,46	0,17	21,59	13,40	1,64	5,63	1,42	13,73	6,88

*premještena u skupinu specijalnih bolnica / transferred to the group of specialized hospitals
**premještena u skupinu kliničkih bolnica / transferred to the group of clinical hospitals

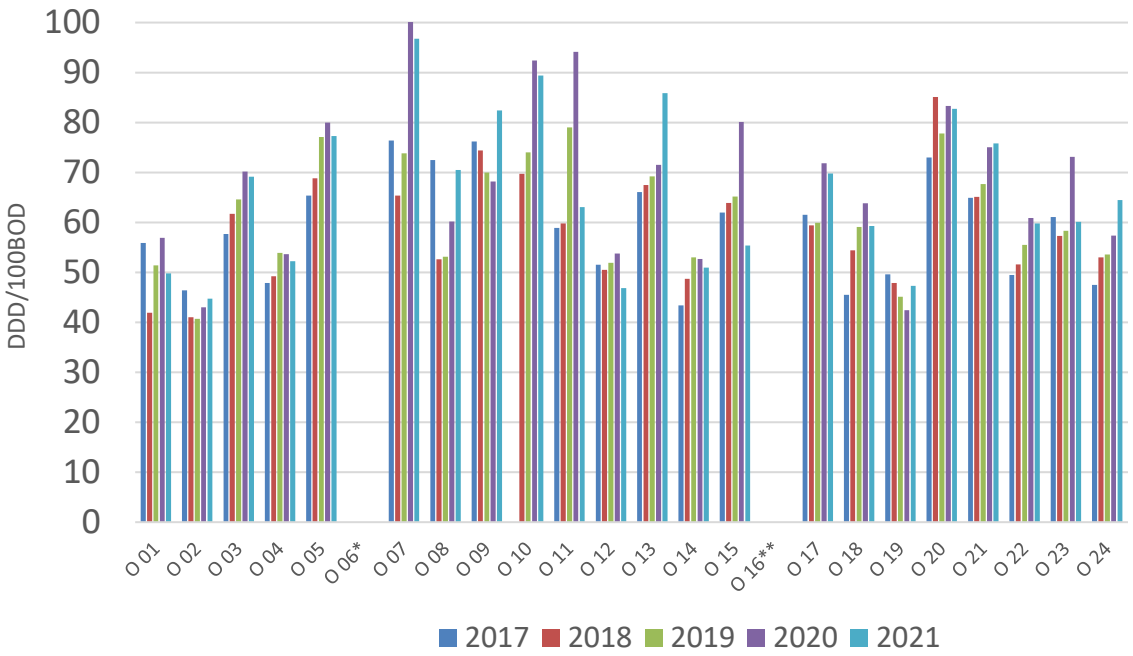
Slika 15. */Figure 15.*
Opće bolnice - potrošnja antibiotika 2021.
General hospitals – antibiotic consumption 2021



Tablica 17. */Table 17.*
Opće bolnice - potrošnja antibiotika 2017.-2021.
General hospitals – antibiotic consumption in 2017-2021

USTANOVA INSTITUTION	DDD/100 BOD, DDD/100 BD				
	2017	2018	2019	2020	2021
O 01	55,9	41,9	51,4	56,92	49,81
O 02	46,4	41,0	40,7	42,98	44,71
O 03	57,7	61,7	64,6	70,15	69,12
O 04	47,9	49,2	53,9	53,66	52,26
O 05	65,4	68,8	77,1	79,98	77,31
O 06*					
O 07	76,4	65,4	73,8	100,11	96,75
O 08	72,5	52,6	53,1	60,18	70,51
O 09	76,2	74,4	70,0	68,19	82,43
O 10		69,7	74,0	92,41	89,37
O 11	58,9	59,8	79,0	94,17	63,03
O 12	51,5	50,5	51,9	53,77	46,83
O 13	66,1	67,5	69,2	71,55	85,86
O 14	43,4	48,7	53,0	52,65	50,97
O 15	62,0	63,9	65,2	80,11	55,40
O 16**					
O 17	61,5	59,4	59,9	71,87	69,77
O 18	45,5	54,4	59,1	63,85	59,29
O 19	49,6	47,9	45,1	42,42	47,27
O 20	73,0	85,1	77,8	83,33	82,76
O 21	64,9	65,1	67,7	75,03	75,84
O 22	49,5	51,6	55,5	60,88	59,77
O 23	61,1	57,3	58,3	73,12	60,10
O 24	47,5	53,0	53,6	57,34	64,46

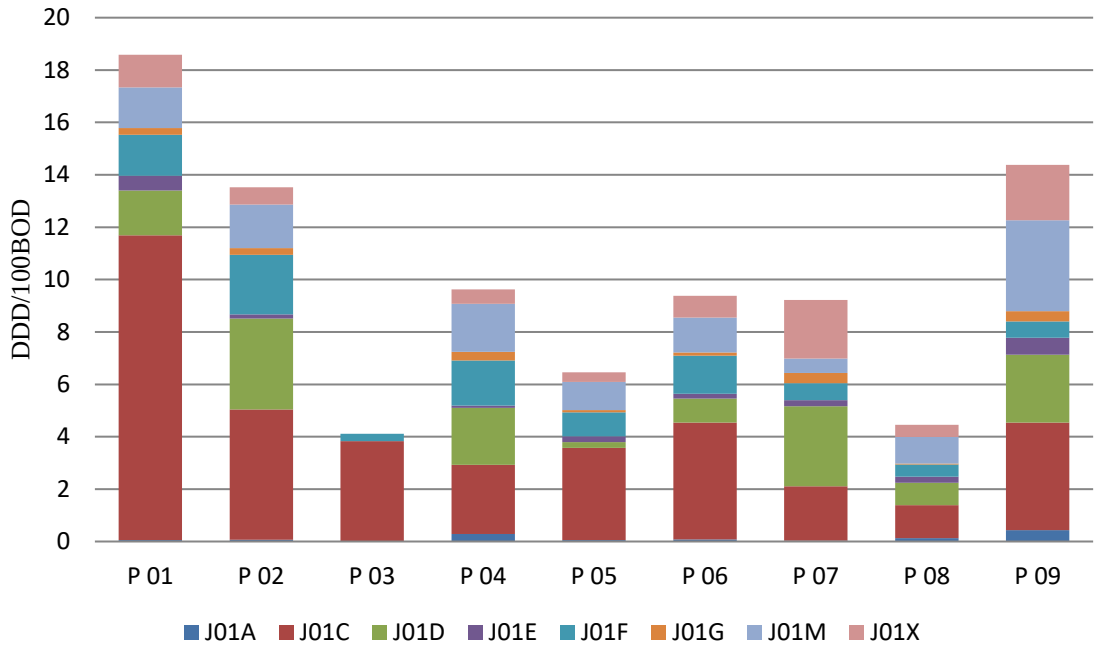
Slika 16. */ Figure 16.*
Opće bolnice - potrošnja antibiotika 2017.-2021.
General hospitals – antibiotic consumption 2017-2021



Tablica 18. */Table 18.*
Psihijatrijske ustanove - potrošnja antibiotika 2021.
Psychiatric institutions – antibiotic consumption in 2021

USTANOVA INSTITUTION	DDD/100 BOD, DDD/100 BD								
	UKUPNO / TOTAL	J01A	J01C	J01D	J01E	J01F	J01G	J01M	J01X
P 01	18,58	0,06	11,63	1,71	0,56	1,57	0,25	1,56	1,24
P 02	13,53	0,07	4,97	3,47	0,16	2,28	0,25	1,66	0,67
P 03	4,11	0,00	3,83	0,00	0,00	0,28	0,00	0,00	0,00
P 04	9,62	0,29	2,64	2,17	0,09	1,72	0,33	1,83	0,56
P 05	6,46	0,06	3,51	0,23	0,22	0,91	0,09	1,07	0,37
P 06	9,40	0,08	4,46	0,92	0,18	1,46	0,12	1,33	0,83
P 07	9,22	0,03	2,08	3,05	0,24	0,65	0,38	0,55	2,24
P 08	4,47	0,13	1,26	0,85	0,23	0,47	0,04	1,01	0,47
P 09	14,39	0,44	4,10	2,59	0,65	0,62	0,39	3,47	2,12

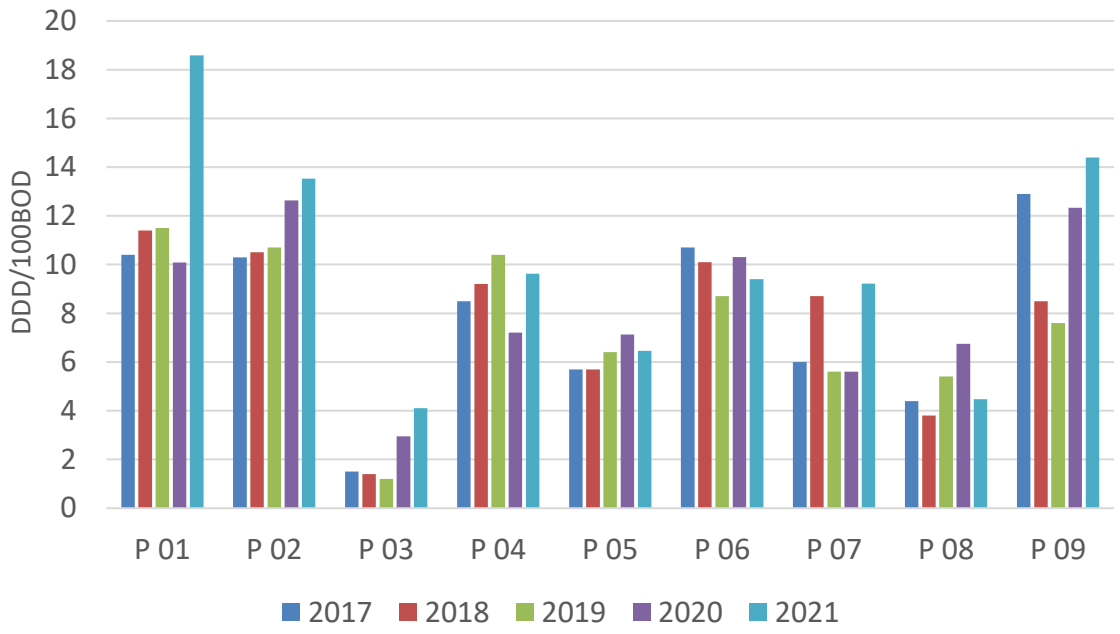
Slika 17. /*Figure 17.*
Psihijatrijske ustanove - potrošnja antibiotika 2021.
Psychiatric institutions – antibiotic consumption 2021



Tablica 19. /*Table 19.*
Psihijatrijske ustanove - potrošnja antibiotika 2017.-2021.
Psychiatric institutions – antibiotic consumption in 2017-2021

USTANOVA INSTITUTION	DDD/100 BOD, DDD/100 BD				
	2017	2018	2019	2020	2021
P 01	10,4	11,4	11,5	10,08	18,58
P 02	10,3	10,5	10,7	12,63	13,53
P 03	1,5	1,4	1,2	2,95	4,11
P 04	8,5	9,2	10,4	7,21	9,62
P 05	5,7	5,7	6,4	7,13	6,46
P 06	10,7	10,1	8,7	10,31	9,40
P 07	6,0	8,7	5,6	5,60	9,22
P 08	4,4	3,8	5,4	6,75	4,47
P 09	12,9	8,5	7,6	12,33	14,39

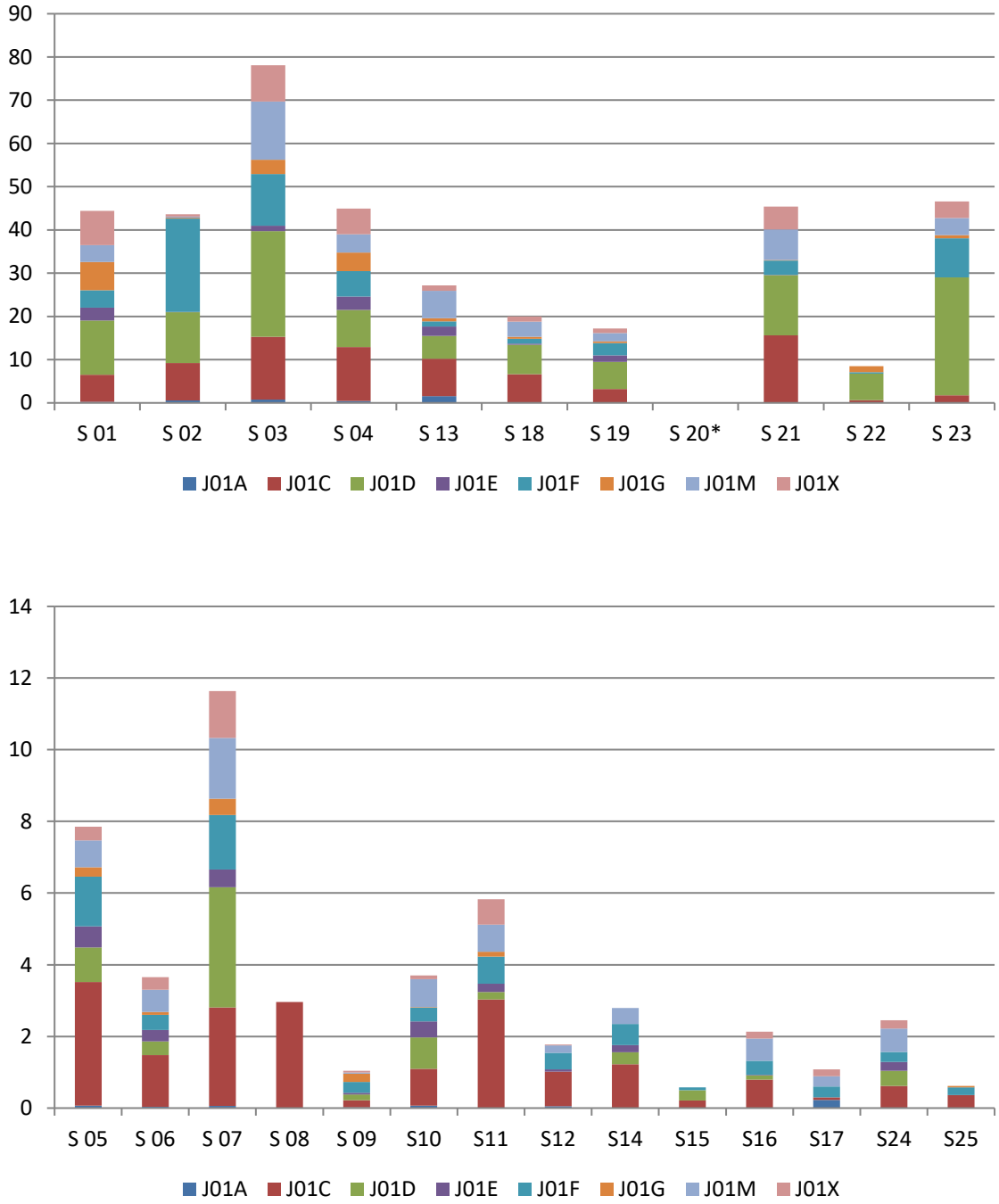
Slika 18. / *Figure 18.*
Psihijatrijske ustanove - potrošnja antibiotika 2017.-2021.
Psychiatric institutions – antibiotic consumption 2017-2021



Tablica 20. */Table 20.*
Specijalne bolnice - potrošnja antibiotika 2021.
Specialised hospitals – antibiotic consumption in 2021

	DDD/100 BOD, DDD/100 BD								
USTANOVA NSTITUTION	UKUPNO TOTAL	J01A	J01C	J01D	J01E	J01F	J01G	J01M	J01X
S 01	44,45	0,26	6,22	12,58	2,99	3,99	6,58	3,87	7,95
S 02	43,61	0,54	8,65	11,81	0,01	21,60	0,23	0,28	0,49
S 03	78,06	0,78	14,52	24,45	1,20	11,96	3,31	13,46	8,40
S 04	44,96	0,42	12,51	8,57	3,11	5,90	4,29	4,22	5,93
S 13	27,14	1,55	8,66	5,28	2,16	1,24	0,72	6,29	1,25
S 18	19,96	0,07	6,57	6,82	0,26	1,13	0,47	3,47	1,17
S 19	17,24	0,11	3,07	6,28	1,56	2,79	0,41	1,93	1,08
S 20*									
S 21	45,42	0,00	15,61	13,94	0,10	3,27	0,16	7,02	5,31
S 22	8,46	0,13	0,52	6,12	0,00	0,36	1,33	0,00	0,00
S 23	46,56	0,00	1,77	27,24	0,00	9,03	0,73	3,99	3,80
S 05	7,85	0,07	3,45	0,96	0,59	1,39	0,26	0,75	0,38
S 06	3,65	0,04	1,44	0,38	0,32	0,42	0,08	0,62	0,35
S 07	11,64	0,06	2,75	3,35	0,50	1,52	0,45	1,70	1,31
S 08	2,96	0,00	2,96	0,00	0,00	0,00	0,00	0,00	0,00
S 09	1,03	0,02	0,20	0,16	0,05	0,30	0,23	0,03	0,05
S10	3,71	0,07	1,03	0,87	0,45	0,38	0,02	0,78	0,10
S11	5,83	0,00	3,03	0,21	0,23	0,76	0,13	0,76	0,71
S12	1,78	0,05	0,97	0,00	0,06	0,46	0,00	0,21	0,02
S14	2,80	0,00	1,22	0,34	0,20	0,59	0,00	0,44	0,00
S15	0,58	0,00	0,21	0,29	0,00	0,08	0,00	0,00	0,00
S16	2,12	0,00	0,79	0,12	0,02	0,39	0,00	0,62	0,19
S17	1,08	0,23	0,07	0,00	0,00	0,30	0,00	0,29	0,19
S24	2,44	0,00	0,62	0,42	0,25	0,28	0,00	0,65	0,23
S25	0,62	0,00	0,36	0,00	0,00	0,22	0,04	0,00	0,00

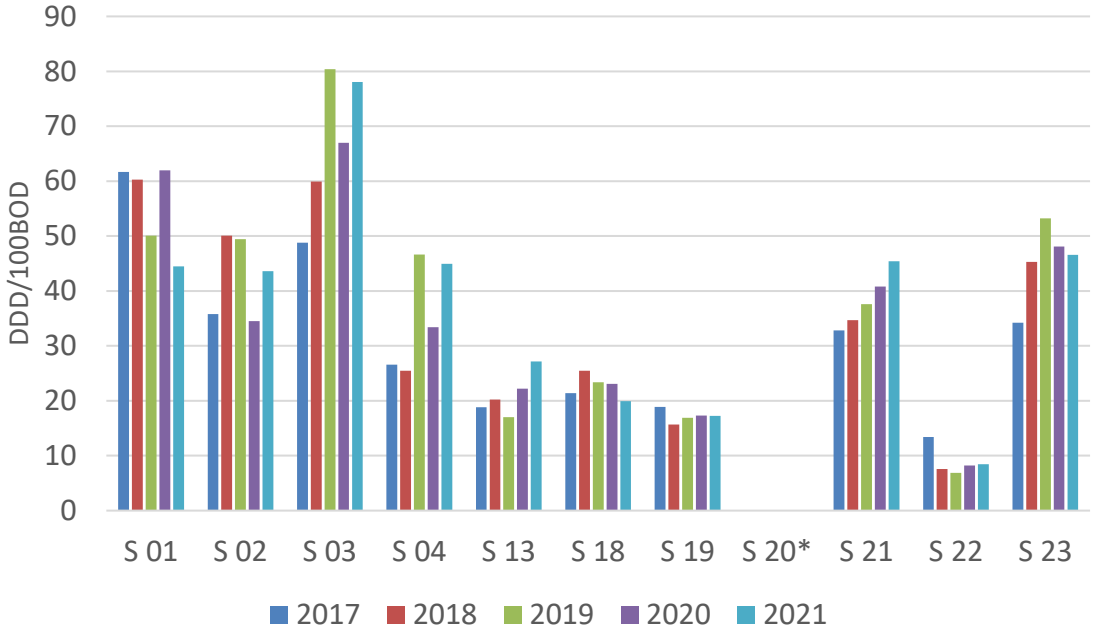
Slika 19. / *Figure 19.*
Specijalne bolnice - potrošnja antibiotika 2021.
Specialised hospitals – antibiotic consumption 2021

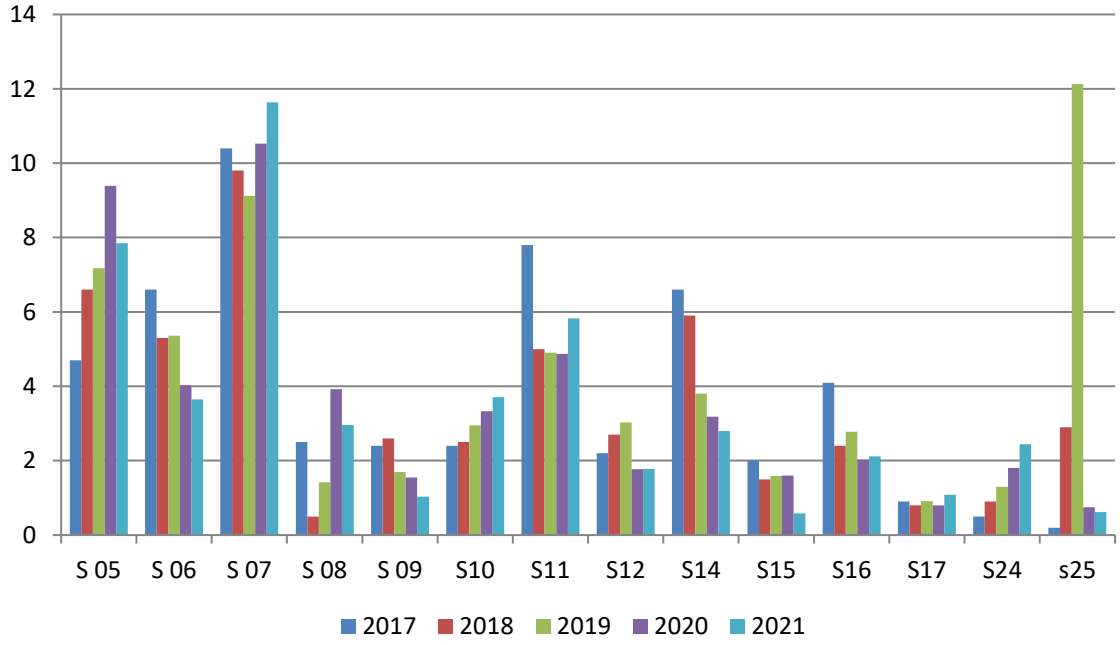


Tablica 21. */Table 21.*
Specijalne bolnice - potrošnja antibiotika 2017.-2021.
Specialised hospitals – antibiotic consumption in 2017-2021

	DDD/100 BOD, DDD/100 BD				
USTANOVA INSTITUTION	2017	2018	2019	2020	2021
S 01	61,7	60,3	50,0	61,95	44,45
S 02	35,8	50,1	49,5	34,51	43,61
S 03	48,8	59,9	80,4	66,98	78,06
S 04	26,6	25,5	46,6	33,38	44,96
S 13	18,8	20,2	17,0	22,21	27,14
S 18	21,4	25,5	23,4	23,09	19,96
S 19	18,9	15,7	16,9	17,29	17,24
S 20*					
S 21	32,8	34,7	37,6	40,79	45,42
S 22	13,4	7,6	6,9	8,21	8,46
S 23	34,2	45,3	53,2	48,08	46,56
S 05	4,7	6,6	7,2	9,39	7,85
S 06	6,6	5,3	5,4	4,03	3,65
S 07	10,4	9,8	9,1	10,53	11,64
S 08	2,5	0,5	1,4	3,92	2,96
S 09	2,4	2,6	1,7	1,55	1,03
S10	2,4	2,5	2,9	3,33	3,71
S11	7,8	5,0	4,9	4,87	5,83
S12	2,2	2,7	3,0	1,77	1,78
S14	6,6	5,9	3,8	3,18	2,80
S15	2,0	1,5	1,6	1,60	0,58
S16	4,1	2,4	2,8	2,03	2,12
S17	0,9	0,8	0,9	0,80	1,08
S24	0,5	0,9	1,3	1,81	2,44
S25	0,2	2,9	12,1	0,75	0,62

Slika 20. / *Figure 20.*
Specijalne bolnice - potrošnja antibiotika 2017.-2021.
Specialised hospitals – antibiotic consumption 2017-2021





ATK KLASIFIKACIJA ANTIBIOTIKA:
ATC CLASSIFICATION OF ANTIBIOTICS

J01A – TETRACIKLINI / *TETRACYCLINES*

J01B – AMFENIKOLI / *AMPHENICOLS*

J01C – ßLAKTAMI – PENICILINI / *ß LACTAM-PENICILLINS*

J01D – ßLAKTAMI – CEFALOSPORINI / *ß LACTAM-CEPHALOSPORINS*

J01E – SULFONAMIDI I TRIMETOPRIM / *SULFONAMIDES AND TRIMETHROPIM*
J01F – MAKROLIDI, LINKOZAMIDI I STREPTOGRAMIN / *MACROLIDES, LINCOZAMIDES AND STREPTOGRAMIN*

J01G – AMINOGLIKOZIDI / *AMINOGLYCOSIDES*

J01M – KINOLONI /*QUINOLONES*
J01 X – OSTALI (GLIKOPEPTIDI, POLIMIKSIN, METRONIDAZOL, NITROFURANTOIN) / *OTHERS (GLYCOPEPTIDES, POLYMYXIN, METRONIDASOLE, NITROFURANTOIN*