AKADEMIJA MEDICINSKIH ZNANOSTI HRVATSKE
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CROATIAN ACADEMY OF MEDICAL SCIENCES
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KLINIKA ZA INFEKTIVNE BOLESTI "DR. F. MIHALJEVIĆ"
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REFERENCE CENTER FOR ANTIBIOTIC RESISTANCE SURVEILLANCE, CROATIAN MINISTRY OF HEALTH

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PREDGOVOR:

Godinu 2020. je u mnogim aspektima života, a pogotovo u pitanju zdravlja i organizacije zdravstvenog sustava, obilježila epidemija SARS-CoV-2. Glasnogovornica Europskog centra za prevenciju i kontrolu bolesti (European Center for Disease Prevention and Control, ECDC) je izjavila da je pandemija bolesti COVID-19 velika pošast za čovječanstvo, no da ECDC rezistenciju bakterija na antibiotike smatra još većom, iako puno tišom, prijetnjom za čovječanstvo. Stručnjaci koji se u rutini učestalo susreću s izazovima u liječenju pacijenata oboljelih od infekcija uzrokovanih multiplorezistentnim bakterijama su toga svjesni, no treba uložiti mnogo u edukaciju i podizanje svijesti da svatko, ponaosob, tko sudjeluje u propisivanju, izdavanju ili konzumiranju antibiotika treba dati svoj doprinos u racionalizaciji primjene i očuvanju djelotvornosti antibiotika. Već dugo se kontroli širenja rezistencije pristupa s pozicije jedinstvenog zdravstva (engl. „One health approach“) gdje se prepoznaje važnost kontrole uporabe antibiotika i širenja rezistencije ne samo u sektoru humane medicine, već i u veterinarskom sektoru i okolišu. Kroz blisku suradnju u okviru Interdisciplinarne sekcije za kontrolu rezistencije na antibiotike (ISKRA-e) sve više izmjenjujemo podatke o rezistenciji i potrošnji antibiotika u raznim sektorima i sve smo više svjesni ekološke povezanosti s brojnim mogućim rezervoarima rezistentnih gena. Ipak, rezistencija na antibiotike koji su zadnja linija terapije životnougrožavajućih infekcija, najviše je posljedica velike uporabe antibiotika u humanoj medicini i suboptimalne kontrole širenja rezistentnih uzročnika prvenstveno u bolničkoj sredini. Praćenje rezistencije i potrošnje antibiotika je osnova međunarodne, pa tako i hrvatske nacionalne strategije za kontrolu širenja rezistencije te rezultati prikazani u ovoj publikaciji pružaju osnovu za daljnje aktivnosti predviđene nacionalnim programom kao što je edukacija i podizanje svijsnosti o situaciji u lokalnoj sredini, pisanje smjernica za racionalnu uporabu antibiotika te planiranje istraživanja i intervencija u području kontrole širenja rezistencije na antibiotike. Mnogi od rezultata prikazanih u ovoj publikaciji se mogu naći i u sklopu međunarodnih izvješća o rezistenciji i potrošnji antibiotika u Europskoj uniji, što omogučuje dobru suradnju s drugim zemljama. Ipak, prvenstveno se nadamo da će ovi podaci mnogima pomoći u primjeni antibiotika u svakodnevnom radu te da će sve više jačati svijest da kod svake individualne antimikrobne terapije treba misliti na dobrobit pojedinca koji ju konzumira, ali i budućih pacijenata koji će tražiti pomoć liječnika.

Mnogi stručnjaci su sudjelovali u prikupljanju podataka, analizi rezultata i nastanku ove publikacije te im se svima iskreno zahvaljujem na uloženom trudu i želji da daju svoj doprinos kontroli širenja rezistencije.

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

PREFACE

The year 2020 was marked by the SARS-CoV-2 epidemic in many aspects of life, especially in terms of health and the organization of the health care system. A spokeswoman for the European Center for Disease Prevention and Control (ECDC) said the COVID-19 pandemic was a major calamity for mankind, but that ECDC saw antibiotic resistance in bacteria as an even greater, albeit much quieter, threat to mankind. Experts who frequently face challenges in the treatment of patients with infections caused by multiply-resistant bacteria are aware of this, but much should be invested in educating and raising awareness that everyone involved in prescribing, dispensing or consuming antibiotics should contribute to optimizing the use and preserving the effectiveness of antibiotics. For a long time, the one health approach to controlling resistance recognizes the importance of controlling the use of antibiotics and spreading resistance not only in the human medicine sector, but also in the veterinary sector and the environment. Through close cooperation within the Interdisciplinary Section for the Control of Antibiotic Resistance (ISKRA), we are increasingly exchanging data on antibiotic resistance and consumption in various sectors and are increasingly aware of the ecological significance of many resistant genes reservoirs. However, resistance to antibiotics which are the last line of therapy for life-threatening infections, is mostly due to the extensive use of antibiotics in human medicine and suboptimal control of the spread of resistant pathogens, primarily in hospital settings. Antibiotic resistance and consumption surveillance is the basis of the international and Croatian national strategy for controlling the spread of resistance, and the results presented in this publication provide a basis for further activities envisaged by the national program such as education and awareness raising on resistance in the local environment, guidelines development and planning research and intervention activities. Many of the results presented in this publication can also be found in international reports on antibiotic resistance and consumption in the European Union, which allows for good cooperation with other countries. Nevertheless, we primarily hope that these data will help many in dealing with antibiotics in their daily practice with increasing awareness that whenever an antibiotic is prescribed to an individual, we should think of patients who will seek medical care in the future as well.

Many experts have participated in data collection, analysis of results and the creation of this publication, and I sincerely thank them all for their efforts and desire to contribute to controlling the spread of resistance.

Arjana Tambić Andrašević
President of the Committee for Antibiotic Resistance Surveillance in Croatia

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 Sensitivity 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 2020. GODINI

ANTIBIOTIC RESISTANCE IN 2020

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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 for Antimicrobial Sensitivity 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 sensitivity testing methodology is a subcommittee of the Committee for antibiotic resistance surveillance and it closely follows developments within the European Committee for Antimicrobial Sensitivity Testing (EUCAST) and updates national sensitivity 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 exclusion of copy isolates and testing of all isolates to the well defined panel of antibiotics 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 31.12.2020.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 31.12.2020. Podatke za 2020.g. podnijelo je 38 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 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 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. enterobakterije rezistentne ili osjetljive uz pojačanu izloženost na bilo koji od karbapenema (ertapenem, meropenem, imipenem)

Tijekom 2020.g. korišteni su za testiranje i interpretaciju nalaza standardi europskog odbora, European Committee for Antimicrobial Sensitivity Testing (EUCAST) standardi (Breakpoint Table 10.0). 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 2020.g. većina promjena se odnosila na dosljedno prikazivanje I kategorije kod kombinacija bakterijske vrste i antibiotika kod kojih nema S već postoji samo I kategorija.

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 uporaba mikrodilucije u bujonu nije bila obavezni uvjet za prijavljivanje vrijednosti MIK penicilina Odboru u 2020.g.

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 2020.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 2020.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, 2020. Data on group A streptococci, salmonellae, shigellae and anaerobic bacteria are collected throughout the year, from 1 January to 31 December, 2020 due to the small number of isolates. In 2020 thirty-eight centers took part in antibiotic resistance surveillance (names of the centers 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. enterobacterales resistant or susceptible increased exposure to any carbapenem (ertapenem, meropenem, imipenem)

In 2020 all laboratories used EUCAST standards for susceptibility testing (Breakpoint Table 10.0). Disk diffusion method is the most widely used sensitivity 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-susceptible pneumococci, glycopeptide resistance in staphylococci and colistin resistance in pseudomonas and acinetobacter. Every year at the Committee for Antibiotic Resistance Surveillance meeting in December the EUCAST updates for the coming year are discussed and adopted. Already in 2019 all Committee members were to adopt a 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 "sensitive to standard dosing", category "I" "sensitive to increased exposure" and category "R" "resistant". In 2020 most of the changes were related to the consistent interpretation of an "I" category for drug bug combinations where there is no "S" but only "I" category.

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 by broth microdilution method, but the use of broth microdilution was not mandatory for reporting the penicillin MIC values in 2020.

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 2020 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 2020 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 2020.g. sudjelovalo je 38 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 *E. faecalis* i *A. baumannii* prikazao rezultate za cijelu godinu
- GS ZZJZ je za sve vrste prikazao rezultate za cijelu godinu
- KA ZZJZ je za *S. pneumoniae* prikazao rezultate za cijelu godinu
- PU ZZJZ je za *H. influenzae* prikazao rezultate za cijelu godinu
- RI KBC je za *H. influenzae* prikazao rezultate za cijelu godinu
- SB ZZJZ je za *H. influenzae* prikazao rezultate za cijelu godinu
- VK ZZJZ je za *S. pneumoniae, S. aureus*/MSSA, *S. aureus*/MRSA, *H. influenzae i A. baumannii* prikazao rezultate za cijelu godinu (izolati iz OŽB Vinkovci)
- ZD ZZJZ je za *E. faecium, H. influenzae* i *A. baumannii* prikazao rezultate za cijelu godinu
- ZG KBC je za *E. faecalis* prikazao rezultate za razdoblje od 2.10. do 8.11.2020., za *E. coli, K. pneumoniae* i *P. aeruginosa* za razdoblje od 2.10. do 23.10.2020, a za *P. mirabilis, , Enterobacter* spp., *Klebsiella aerogenes, Serratia* spp. i *Citrobacter* spp. za razdoblje od 2.10. do 8.11.2020.
- ZG KBCSM je prikazao rezultate za anerobne bakterije za razdoblje od 1.10. do 31.12.2020.
- ZG KIB je za *H. influenzae* prikazala rezultate za cijelu godinu
- ZG NZZJZ je za *E. faecalis, E. faecium, E. coli, P. mirabilis, K. pneumoniae, Enterobacter* spp., *Klebsiella aerogenes, Serratia* spp., *Citrobacter* spp, *P. aeruginosa* i *A. baumannii* prikazao rezultate za razdoblje od 2.11. do 13.11.2020.

Dva laboratorija su prijavila izolaciju šigela: OG OB *Sh. boydii* (1) i ZG KIB *Sh. flexnerii* (1); Ukupno su tijekom 2020.g. izolirane 2 šigele.

U 2020.g. ukupno je obrađeno 944 anaerobnih bakterija, 450 gram-pozitivnih i 494 gram-negativnih iz 27 centara: ČK ZZJZ gram-pozitivni anaerobi (48), gram-negativni anaerobi (31); DU ZZJZ gram-pozitivni anaerobi (3), gram-negativni anaerobi (2); KA ZZJZ gram-pozitivni anaerobi (2), gram-negativni anaerobi (1); KC ZZJZ gram-pozitivni anaerobi (4), gram-negativni anaerobi (1); KT MAGD. gram-pozitivni anaerobi (2); OG OB gram-pozitivni anaerobi (1), gram-negativni anaerobi (2); OS KBC gram-pozitivni anaerobi (7), gram-negativni anaerobi (79); OS ZZJZ gram-pozitivni anaerobi (2), gram-negativni anaerobi (2); PK OŽB gram-pozitivni anaerobi (2), gram-negativni anaerobi (2); PU ZZJZ gram-pozitivni anaerobi (2), gram-negativni anaerobi (11); RI KBC gram-pozitivni anaerobi (32), gram-negativni anaerobi (60); SB ZZJZ gram-pozitivni anaerobi (11), gram-negativni anaerobi (6); SK ZZJZ gram-pozitivni anaerobi (2), gram-negativni anaerobi (2); ST KBC gram-pozitivni anaerobi (55), gram-negativni anaerobi (62); ŠI ZZJZ gram-pozitivni anaerobi (20), gram-negativni anaerobi (13); VK

ZZJZ gram-pozitivni anaerobi (3), gram-negativni anaerobi (5); VT ZZJZ gram-pozitivni anaerobi (1), gram-negativni anaerobi (2); VŽ ZZJZ gram pozitivni anaerobi (68), gram-negativni anaerobi (59); ZD ZZJZ gram-pozitivni anaerobi (33), gram-negativni anaerobi (52); ZG KBD gram-pozitivni anaerobi (8), gram-negativni anaerobi (1); ZG KBM gram-pozitivni anaerobi (16), gram-negativni anaerobi (25); ZG KBCSM gram-pozitivni anaerobi (64), gram-negativni anaerobi (28); ZG KZT gram-pozitivni anaerobi (1); ZG KIB gram-pozitivni anaerobi (9), gram-negativni anaerobi (2); ZG HZJZ gram-pozitivni anaerobi (5); ZG KDB gram-pozitivni anaerobi (14), gram-negativni anaerobi (12); ZG KBSD gram-pozitivni anaerobi (35), gram-negativni anaerobi (34).

RESULTS

Thirty-eight centers took part in antibiotic resistance surveillance in Croatia in 2020. 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 *E. faecalis* and *A. baumannii* for the whole year
- GS ZZJZ reported data for all species for the whole year
- KA ZZJZ reported data for *S. pneumoniae* for the whole year
- PU ZZJZ reported data for *H. influenzae* for the whole year
- RI KBC reported data for *H. influenzae* for the whole year
- SB ZZJZ reported data for *H. influenzae* for the whole year
- VK ZZJZ reported data for *S. pneumoniae, S. aureus*/MSSA, *S. aureus*/MRSA, *H. influenzae* and *A. baumannii* for the whole year (isolates from OB Vinkovci)
- ZD ZZJZ reported data for *E. faecium, H. influenzae* and *A. baumannii* for the whole year
- ZG KBC reported data for *E. faecalis* for the period 2.10. – 8.11.2020., *E. coli, K. pneumoniae* i *P. aeruginosa* for the period 2.10. – 23.10.2020., and *P. mirabilis,, Enterobacter* spp., *Klebsiella aerogenes, Serratia* spp. and *Citrobacter* spp.for the period 2.10. – 8.11.2020.
- ZG KBCSM reported data for anaerobic bacteria for the period 1.10. – 31.12.2020.
- ZG KIB reported data for *H. influenzae* for the whole year
- ZG NZZJZ reported data for *E. faecalis, E. faecium, E. coli, P. mirabilis, K. pneumoniae, Enterobacter* spp., *Klebsiella aerogenes, Serratia* spp., *Citrobacter* spp, *P. aeruginosa.* and *A. baumannii* for the period 2.11. – 13.11.2020.

Two laboratories reported shigella isolates: OG OB *Sh. boydii* (1) i ZG KIB *Sh. flexnerii* (1); Altogether 2 shigella isolates were reported in 2020.

In 2020 altogether 944 anaerobic bacteria were isolated, 450 gram-positives and 494 gram-negatives. They were isolated in 27 centers: ČK ZZJZ gram-positive anaerobes (48), gram-negative anaerobes (31); DU ZZJZ gram-positive anaerobes (3), gram-negative anaerobes (2); KA ZZJZ gram-positive anaerobes (2), gram-negative anaerobes (1); KC ZZJZ gram-positive anaerobes (4), gram-negative anaerobes (1); KT MAGD. gram-positive anaerobes (2); OG OB gram-positive anaerobes (1), gram-negative anaerobes (2); OS KBC gram-positive anaerobes (7), gram-negative anaerobes (79); OS ZZJZ. gram-positive anaerobes (2), gram-negative anaerobes (2); PK OŽB gram-positive anaerobes (2), gram-negative anaerobes (2); PU ZZJZ gram-positive anaerobes (2), gram-negative anaerobes (11); RI KBC gram-positive anaerobes (32), gram-negative anaerobes (60); SB ZZJZ gram-positive anaerobes (11), gram-negative anaerobes (6); SK ZZJZ gram-positive anaerobes (2), gram-negative anaerobes (2); ST KBC gram-positive

anaerobes (55), gram-negative anaerobes (62); ŠI ZZJZ gram-positive anaerobes (20), gram-negative anaerobes (13); VK ZZJZ gram-positive anaerobes (3), gram-negative anaerobes (5); VT ZZJZ gram-negative anaerobes (1), gram-negative anaerobes (2); VŽ ZZJZ gram-positive anaerobes (68), gram-negative anaerobes (59); ZD ZZJZ gram-positive anaerobes (33), gram-negative anaerobes (52); ZG KBD gram-positive anaerobes (8), gram-negative anaerobes (1); ZG KBM gram-positive anaerobes (16), gram-negative anaerobes (25); ZG KBCSM gram-positive anaerobes (64), gram-negative anaerobes (28); ZG KZT gram-positive anaerobes (1); ZG KIB gram-positive anaerobes (9), gram-negative anaerobes (2); ZG HZJZ gram-positive anaerobes (5); ZG KDB gram-positive anaerobes (14), gram-negative anaerobes (12); ZG KBSD gram-positive anaerobes (35), gram-negative anaerobes (34).

DISKUSIJA

Epidemija SARS-CoV-2 virusa je značajno utjecala na učestalost respiratornih patogena. U 2020. godini prijavljeno je 4553 izolata streptokoka grupe A (u 2019.g. 12341), 765 pneumokoka (u 2019.g. 1613) te 434 *Haemophilus influenzae* (u 2019.g. 1305). To je vjerojatno posljedica manje incidencije izvanbolničkih infekcija gornjih dišnih puteva u doba držanja većeg socijalnog razmaka i smanjenog vremena provođenja u kolektivima, ali i manje medikalizacije ovih većinom samoograničavajućih infekcija. Ograničavanje odlazaka liječniku na klinički ozbiljnije infekcije te smanjeno uzimanje uzoraka gornjeg dišnog sustava za bakteriološku obradu u ovome slučaju je praksa koju treba podržati i bez restrikcija nametnutih pojavom epidemije COVID-19.

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 2020.g. (8%) je podjednaka stopama uočenim zadnjih godina (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 identična prošlogodišnjim stopama (konstitutivna 4%, inducibilna 3%). 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. Brisevi nazofarinksa, stoga, pokazuju nisku specifičnost i osjetljivost, često zavode u kliničkom rasuđivanju i ne preporučuju se kao uzorci za dijagnosticiranje etiologije infekcija gornjih dišnih puteva. U Hrvatskoj se brisevi nazofarinksa sve manje uzimaju, čemu doprinose i smjernice Hrvatskog društva za kliničku mikrobiologiju, te se broj prijavljenih pneumokoka i hemofilusa sve više smanjuje. Izolati pneumokoka i hemofilusa opisani u ovom poglavlju potječu, ipak, još uvijek pretežno iz briseva nazofarinksa i predstavljaju pretežno kolonizirajuću mikrobiotu. 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. Stope rezistencije ukupnih pneumokoka imaju, međutim, epidemiološko značenje jer ukazuju na trendove u širenju rezistencije. U Hrvatskoj je rezistencija pneumokoka na penicilin za sada još uvijek niska (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 2020.g. iznosi 21% i u razini je stopa zadnjih godina (21% u 2019, 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 2020.g. iznosi, dakle, 24%. Međutim, pneumonije uzrokovane izolatima koji zahtjevaju povećanu izloženost penicilinu se mogu liječiti parenteralnim penicilinom u dozama prilagođenima visini minimalnih inhibitornih koncentracija (MIK). Prema rasponu MIK-ova penicilina registriranih u 2020.g., 97% 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 90% 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 2019.g. je bilo 87% osjetljivih pneumokoka koji su dostupni liječenju standardnom dozom amoksicilina od 3x500mg, što je podjednako prijašnjim stopama (87% u 2019.g., 90% u 2018.g.). Povećanim doziranjem oralnog amoksicilina od 3x750mg ili 3x1000mg (pripravak dostupan na tržištu) može se obuhvatiti 92% pneumokoka (93% u 2019.g., 94% u 2018.g.), a parenteralnom primjenom ampicilina 97% izolata (97% u 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 2020..g. četiri laboratorija nisu udovoljila zahtjevu da se u 2019.g. osjetljivost na ampicilin / amoksicilin testira istovremeno i disk difuzijom i određivanjem minimalnih inhibitornih koncentracija (MIK). Zbirni podaci na nacionalnoj razini se nešto, 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 (29%), ko-trimoksazol (17%) i tetraciklin (16%) je slična prošlogodišnjim stopama (31%, 17% i 18%). 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.). 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 je, nažalost, zadnjih godina prešla 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 (18%) 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 (15%) i klindamicin

(11%) meticilin senzitivni *Staphylococcus aureus* (MSSA) sojevi ne pokazuju značajnije stope rezistencije na druge antistafilokokne antibiotike. Stečena rezistencija na kinolone kod MSSA je manja od 10% no i kod osjetljivih izolata 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. (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.). Ukupan broj MRSA izolata je podjednak broju prijavljenih prošle godine, no udio u ukupnom broju stafilokoka je znatno viši što se uočava i kod multiplorezistentnih izolata drugih bakterijskih vrsta. Udio MRSA sojeva s inducibilnom rezistencijom na klindamicin (30%) 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.). Rezistencija MRSA na gentamicin (13%) je u daljnjem padu (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.). Rezistencija na linezolid i vankomicin nije uočena. Distribucija MIK-ova vankomicina pokazuje pomak prema nižim vrijednostima MIK-a. Udio izolata s MIK-om od 2.0 mg/L je iznosio 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. i 20% u 2013.g. Rezistencija MRSA na ceftarolin je 7%, a još 11% izolata treba liječiti višim dozama. U slučaju pneumonije na ceftarolin je rezistentno 18% izolata.

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 39% za *E.faecium*. Rezistencija na vankomicin je još uvijek rijetka u *E.faecalis* (<1%), dok rezistencija na vankomicin u *E. faecium* pokazuje nešto nižu stopu negoli prethodne godine (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.). 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 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* (81%) podjednaka je stopama prethodnih godina (22% i 75% u 2017.g., 22% i 84% u 2018.g., 22% i 85% u 2019.g.). Za nekomplicirane uroinfekcije koje urokuje *E. faecalis* može se koristiti i nitrofurantoin na koji ovaj uzročnik pokazuje nisku rezistenciju (2%).

Escherichia coli je najčešći uzročnik infekcija mokraćnog sustava (IMS), a ostale enterobakterije češće uzrokuju komplicirane 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. Od početka praćenja *E. coli* pokazuje visoku rezistenciju na ampicilin, koja i u 2020.g. iznosi 51%, 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 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.) no znatno su se povisile 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.). 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 nekomplicirane 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 cefalosporine treće generacije (7% do 9%) je slična prošlogodišnjim stopama (8% 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 (2% rezistentnih izolata). Rezistencije na kinolone se zadržala na prošlogodišnjim stopama (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.). Stope rezistencije na ko-trimoksazol (26%), gentamicin (9%), amikacin (1%), nitrofurantoin (3%), fosfomicin (1%) i nitroksolin (1%) su slične ili 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 2020.g. iznosi za ampicilin 47%, za ko-amoksiklav 22%, za piperacilin/tazobaktam 1%, za cefalosporine 3. i 4. generacije od 9% za cefepim do 17% za ceftriakson, 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. i 2020.g.), ceftalozan / tazobaktam (10% u 2018.g., 9% u 2019.g., 8% u 2020.g.). Stope rezistencije na ciprofloksacin (25%), gentamicin (19%), amikacin (9%) 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 do 43% za cefiksim) su više negoli prošle godine (35% do 38% u 2019.g.), a povećala se i rezistencija na ko-amoksiklav (38% u 2018.g. i 2019.g., 45% u 2020.g.). Povećala se i rezistencija na ceftolozan / tazobaktam (20% u 2018.g. i 2019.g., 25% u 2020.g.) i piperacilin / tazobaktam (19% u 2018.g., 21% u 2019.g., 27% u 2020.g.), a ceftazidim / avibaktam i dalje pokazuje vrlo nisku rezistenciju (2% u 2018.g., 2019.g., 2020.g.). 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 2020.g. na 7% i 16% uz dodatno 8% i 2% izolata osjetljivo uz povećanu izloženost („I" kategorija). Trenutno je ceftazidim / avibaktam sa svojom djelotvornošću na sojeve koji proizvode ESBL i AmpC

betalaktamaze, ali i velik dio karbapenemaza (KPC, OXA-48), najučinkovitiji beta-laktam kod klepsijela.

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 (12% 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.), a i rezistencija na karbapeneme, koja je postala vidljiva 2013.g. (1%), ostala je jednaka (1% rezistentnih i 1% osjetljivih uz povećano izlaganje za imipenem i meropenem, 6% rezistentnih za ertapenem) i u 2020.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, no može se uočiti da je stopa rezistencije u enterobaktera (11% u 2018.g. i 2019..g., 8% u 2020.g.) nešto niža od stopa rezistencije na cefepim (10% u 2018.g., 12% u 2019.g. i 2020.g.) i piperacilin / tazobaktam (9% u 2018.g., 10% u 2019.g. i 2020.g.). Stope rezistencije na ciprofloksacin (13%), gentamicin (11%), amikacin (2%) i ko-trimoksazol (15%) su iste ili slične prošlogodišnjima.

U 2020.g. je uočen smanjen broj prijavljenih izolata svih enterobakterija, no broj nije toliko manji kao za respiratorne patogene i vjerojatno je više odraz smanjene dijagnostičke aktivnosti, negoli smanjenog poboljevanja od bakterijskih infekcija tijekom COVID-19 epidemije. Kod *K. pneumoniae* je, nažalost, u ovom razdoblju uočen i nagli porast rezistencije na većinu antibiotika, a najviše zabrinjava nagli porast rezistencije na karbapeneme, što je vjerojatno odraz širenja rezistentnih klonova u bolničkoj sredini.

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 (17% u 2018.g., 18% u 2019.g., 23% i 22% u 2020.g.). Rezistencija na piperacilin / tazobaktam (10% u 2019.g., 12% u 2020.g.) te nove cefalsosporeine ceftazidim / avibaktam i ceftalozan / tazobaktam (4% u 2018.g., 6% u 2019.g., 7% u 2020.g. za oba antibiotika) je u blagom porastu. Rezistencija na ceftazidim (16% u 2019.g., 21% u 2020.g.) i cefepim (13% u 2019.g., 16% u 2020.g.) je dosta porasla. Rezistencija na ciprofloksacin (24%) i amikacin (7%) je jednaka kao prošle 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).

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 (93%), 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.). U 2020.g. jedino se broj izolata *A. baumannii* povečao u odnosu na prethodnu godinu (1740 izolata u 2019.g. i 2087 izolata u 2020.g.), što je, nažalost, slično kao i porast rezistentnih klepsijela, odraz slabije primjene standardnih mjera i mjera kontaktne izolacije za multiplorezistentne bakterije u tijeku epidemije COVID-19.

Osjetljivost na kolistin se može ispitati samo određivanjem minimalnih inhibitornih koncentracija te se osjetljivost na kolistin zasada određuje samo kod pseudomonasa i acinetobaktera rezistentnih na karbapeneme. Rezistencija na kolistin je registrirana u 3% na karbapenem rezistentnih *P.aeruginosa* i 2% na karbapenem rezistentnih acinetobaktera.

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.). ESBL sojevi su i dalje rijetki među salmonelama i u 2020.g. rezistencija na ceftazidim i ceftriakson je iznosila 2%. Rezistencija na ko-amoksiklav (7%), ko-trimoksazol (2%) i ciprofloksacin (5%) je identična ili slična prošlogodišnjim stopama. Do 2013.g. osjetljivost salmonela na ciprofloksacin na razini Hrvatske je bila 100%, a na nalidiksičnu kiselinu, koja je bolji pokazatelj niske razine rezistencije na kinolne, do 2%. Od 2014.g. EUCAST je uveo 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.).

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%). Rezistencija na eritromicin (1% za obje vrste) je i dalje niska, a porast rezistencije na tetraciklin se zaustavio u 2020.g. (35% i 30% u 2017.g., 41% i 36% u 2018.g., 46% i 42% u 2019.g., 35% i 41%).

Tijekom 2020.g. registrirana su samo dva izolata šigela, svaki u po jednom centru. Jedan izolat *Shigella boydii* je izoliran u OB Ogulin i bio je osjetljiv na sve testirane antibiotike osim ampicilina. Jedan izolat *Shigella flexneri* je izoliran u Klinici za infektivne bolesti i bio je osjetljiv na sve testirane antibiotike osim ko-trimoksazola.

Među gram-negativnim anaerobima rezistencija je visoka na penicilin (84%) i klindamicin (36%), a kod gram-pozitivnih anaeroba rezistencija je visoka na metronidazol (49%) te klindamicin (19%). Rezistencija na ko-amoksiklav, piperacilin/tazobaktam i ertapenem je niska (<10%).

DISCUSSION

The SARS-CoV-2 virus epidemic significantly affected the incidence of respiratory pathogens. In 2020 fewer isolates were reported, 4553 isolates of group A streptococci (12341 in 2019), 765 pneumococci (1613 in 2019) and 434 *Haemophilus influenzae* (1305 in 2019). This is probably due to the lower incidence of community-acquired upper respiratory tract infections at the time of keeping a greater social distance and reduced time spent in collectives, but also due to less medicalization of these mostly self-limiting infections. Restricting doctor visits to clinically more severe infections and reducing upper respiratory tract sampling for bacteriological examination is a practice that should be supported even without the restrictions imposed by the COVID-19 outbreak.

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 to macrolides in GAS in 2020 (8%) does not differ significantly from the rates recorded in the previous years (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, and 13% in 2008). Resistance to clindamycin is identical to the rates in the previous year (constitutive 4% and inducible 3%). 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. Nasopharyngeal swabs have, therefore, low sensitivity and specificity, they can be misleading in clinical judgement and they are not recommended as samples for diagnosing aetiology of upper respiratory tract infections. In Croatia nasopharyngeal swabs are becoming less popular as diagnostic tool and their use is discouraged in guidelines of the Croatian Society of Clinical Microbiology so the number of reported pneumococcal and haemophilus isolates is decreasing. Most of the pneumococcal and haemophilus isolates reported in this chapter are still from nasopharyngeal swabs and aspirates and therefore mostly represent colonizing microbiota. 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 (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 2020 was 21% which is similar to the rates recorded in previous years (21% in 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, 24% in 2020. 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 2020, 97% 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 90% have penicillin MIC ≤0.5 mg/L and will be covered by 4x1.2g (4x2MIU) dosing. 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 2020, 87% of pneumococci were treatable with standard oral amoxicillin dosing of 3x500mg which is similar to the previous rates (87% in 2019, 90% in 2018). Increased dose of 3x750mg or 3x1000mg (formulation available at the market) covers 92% of pneumococci (93% in 2019, 94% in 2018) and parenteral ampicillin covers 97% (97% in 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 2020 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. Pneumococcal resistance rates to macrolides (29%), co-trimoxazole (17%) and tetracycline (16%) are similar to the last year rates (31%, 17% and 18%). 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). In 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%).

Ampicillin resistance in *H.influenzae* is, unfortunately, over 20% in the past few years (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 (18%) 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 (15%) and clindamycin (11%), methicillin-susceptible *Staphylococcus aureus* (MSSA) strains show no significant rates of resistance to other antistaphylococcal antibiotics. Acquired resistance to quinolones in MSSA is less than 10%, but in susceptible isolates

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 (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). In 2020, the total number of MRSA isolates is similar to the number reported last year, but the share in the total number of staphylococci is significantly higher, which is also observed for multi-resistant isolates of other bacterial species. The proportion of MRSA strains with inducible resistance to clindamycin (30%) 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). MRSA resistance to gentamicin (13%) is further declining (91% in 2006, 81% in 2009, 77% in 2010, 69% in 2011, 64% in 2012). g., 59% in 2013, 43% in 2014, 38% in 2015, 32% in 2016, 23% in 2017, 18% in 2018 and 2019). Resistance to linezolid and vancomycin was not observed. The distribution of vancomycin MIC shows a shift toward lower MIC values. The share of isolates with MIC of 2.0 mg / L was 5% in 2020, 14% in 2019, 10% in 2018, 9% in 2017, 8% in 2016. g., 7% in 2015, 16% in 2014. and 20% in 2013. MRSA resistance to ceftaroline is 7%, and another 11% of isolates should be treated with higher doses. In the case of pneumonia, 18% of isolates are ceftaroline resistant.

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 39% for *E.faecium*. Vancomycin resistance is still rare in *E. faecalis* (<1%), while vancomycin resistance in *E. faecium* shows a slightly lower rate than in the previous year (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). 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 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* (81%) is similar to the rates of previous years (22% and 75% in 2017, 22% and 84% in 2018, 22% and 85% in 2019). For uncomplicated urinary tract infections caused by *E. faecalis*, nitrofurantoin can also be used and resistance to this antibiotic is still low (2%).

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. From the very beginning of surveillance resistance to ampicillin in *E. coli* is high and in 2019 it is 51%, similar as in the previous years. Amoxicillin with clavulanic acid, on the other hand, is still highly effective as clavulanic acid successfully blocks broad spectrum beta-lactamases and most extended spectrum beta-lactamases (ESBL). However, addition of clavulanic acid restricts the use of higher amoxicillin dosing which is often required in severe infections. In 2014 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, 2017, 2018 and 2019, 11% in 2020) but did change significantly if using breakpoints for other infections (16% in 2014 and 2015, 15% in 2016, 2017 and 2018, 16% in 2019, 19% in 2020). 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 third-generation cephalosporins (7% to 9%) is similar to last year's rates (8% to 9%). New cephalosporin with beta-lactamase inhibitors, ceftazidime / avibactam and ceftolozane / tazobactam show high efficacy on ESBL strains and *E. coli* resistance to these antibiotics is <1% and 1%, which is equivalent to the effect of carbapenems (<1% of resistant isolates) and slightly better than the effect of piperacillin / tazobactam (2% resistant isolates). Resistance to quinolones remained at last year's rates (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). Resistance rates to co-trimoxazole (26%), gentamicin (9%), amikacin (1%), nitrofurantoin (3%), fosfomycin (1%), and nitroxoline (1%) are similar to or equal to last year's rates.

Proteus mirabilis is still predominately a community acquired pathogen and wild type organisms are susceptible to all beta-lactams designed for gram-negatives. Unfortunately, acquired resistance to beta-lactam antibiotics is high with rates of 47% for ampicillin, 22% for co-amoxiclav, 1% for piperacillin / tazobactam, 9% (cefepime) to 17% (ceftriaxone) for 3rd and 4th generation cephalosporins, which is similar to last year's rates. Resistance is equal to or slightly lower than last year for new cephalosporins combined with beta-lactamase inhibitors, ceftazidime / avibactam (1% in 2018, 2019 and 2020), ceftolozane / tazobactam (10% in 2018, 9% in 2019, 8% in 2020). Resistance rates to ciprofloxacin (25%), gentamicin (19%), amikacin (9%) and co-trimoxazole (40%) are also similar to or equal to last year results. Due to their innate resistance to colistin, tigecycline, and lower susceptibility to imipenem, *Proteus mirabilis* and other *Proteus* spp. could become a growing problem in the future, especially in urological patients and healthcare associated infections.

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 to 43% for cefixime) are higher than last year (35% to 38% in 2019), and co-amoxiclav resistance has increased as well (38% in 2018 and 2019, 45% in 2020). Resistance to ceftolozane / tazobactam (20% in 2018 and 2019, 25% in 2020) and piperacillin / tazobactam also increased (19% in 2018, 21% in 2019). , 27% in 2020) but ceftazidime / avibactam still shows very low resistance (2% in 2018, 2019, 2020). 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). Currently, ceftazidime / avibactam, with its efficacy on strains producing ESBL and AmpC beta-lactamases, but also some important carbapenemases (KPC, OXA-48), is the most effective beta-lactam in *K.pneumoniae*.

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 (12% for cefepime to 28% for cefixime) is within the rates registered in previous years (16% to 32% in 2017, 10% to 25% in 2018. , 12% to 26% in 2019), and resistance to carbapenems, which first became visible in 2013 (1%), remained the same (1% resistance and 1% susceptibility increased exposure to imipenem and meropenem, 6% resistance to ertapenem). Ceftolozane / tazobactam is primarily expected to have an advantage in the treatment of infections caused by pseudomonas and ESBL-producing enterobacteria, which is more commonly seen in *K. pneumoniae* and *E. coli* than in enterobacter group, and the ceftolozane / tazobactam resistance rate in Enterobacter group (11% in 2018 and 2019, 8% in 2020) seem to be slightly lower than the rates of resistance to cefepime (10% in 2018, 12% in 2019 and 2020) and piperacillin / tazobactam (9% in 2018, 10% in 2019 and 2020). The rates of resistance to ciprofloxacin (13%), gentamicin (11%), amikacin (2%) and co-trimoxazole (15%) are the same or similar to last year values.

In 2020 a reduced number of isolates was reported for all enterobacteria, but the numbers did not decrease as much as for respiratory pathogens and this decrease is probably more a reflection of reduced diagnostic activity than reduced morbidity from bacterial infections during the COVID-19 epidemic. In *K. pneumoniae*, unfortunately, a sudden increase in resistance to most antibiotics was observed during this period, and the most worrying is the sudden increase in resistance to carbapenems, which is probably a reflection of the spread of resistant clones in the hospital environment.

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 (17% in 2018, 18% in 2019, 23% and 22% in 2020). Resistance to piperacillin / tazobactam (10% in 2019, 12% in 2020) and new cephalosporin / beta-lactamase inhibitor combinations, ceftazidime / avibactam and ceftolozane / tazobactam is slightly increasing (4% in 2018, 6% in 2019, 7 % in 2020 for both antibiotics). Resistance to ceftazidime (16% in 2019, 21% in 2020) and cefepime (13% in 2019, 16% in 2020) has increased significantly. Resistance to ciprofloxacin (24%) and amikacin (7%) is the same as last 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).

Carbapenem resistance in *A. baumannii* has rapidly spread throughout Croatia since 2008 and in 2020 resistance rates to imipenem and meropenem (93%) 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). In 2020 only the number of *A. baumannii*

isolates increased compared to the previous year (1740 isolates in 2019 and 2087 isolates in 2020), which is, similar to the increase in resistant klebsiella, a reflection of poor compliance with standard precautions and contact isolation measures during the COVID-19 epidemic.

Susceptibility to colistin can only be detected by MIC test, so it is determined only in pseudomonas and acinetobacter isolates resistant to carbapenems. Colistin resistance has been recorded in 3% of carbapenem resistant *P.aeruginosa* and 2% of carbapenem resistant *A.baumannii*.

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). ESBL isolates are still rare among salmonellae and in 2020 resistance to ceftazidime and ceftriaxone was 2%. Resistance to co-amoxiclav (7%), co-trimoxazole (2%) and ciprofloxacin (5%) is still low and identical or similar to the rates recorded in the previous year. Until 2013 susceptibility of salmonellae to ciprofloxacin in Croatia was 100% with 2% resistance to nalidixic acid, which is an indicator of low level resistance to quinolones. 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).

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). Resistance to erythromycin (1% for both species) is still low and the increasing trend in tetracycline resistance seems to be stopped in 2020 (35% and 30% in 2017, 41% and 36% in 2018, 46% and 42% in 2019, 35% and 41% in 2020).

During 2020, only two shigella isolates were reported. One *Shigella boydii* isolate susceptible to all antibiotics except ampicillin was reported in the General Hospital Ogulin. One *Shigella flexneri* isolate susceptible to all antibiotics except co-trimoxazole was reported in the University Hospital for Infectious Diseases.

Among gram-negative anaerobes resistance is high to penicillin (84%) and clindamycin (36%), and in gram-positive anaerobes high resistance is recorded for metronidazole (49%) and for clindamycin (19%). 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
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
NG OB	Opća bolnica Nova Gradiška, Brodsko-posavska županija
OG OB	Opća bolnica Ogulin, Karlovačka županija
OS KBC	Klinički bolnički centar «Osijek», Osijek
OS ZZJZ	ZZJZ Osječko-baranjske županije, Osijek
PK OŽB	Opća županijska bolnica, Pakrac i bolnica hrvatskih veterana
PU ZZJZ	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

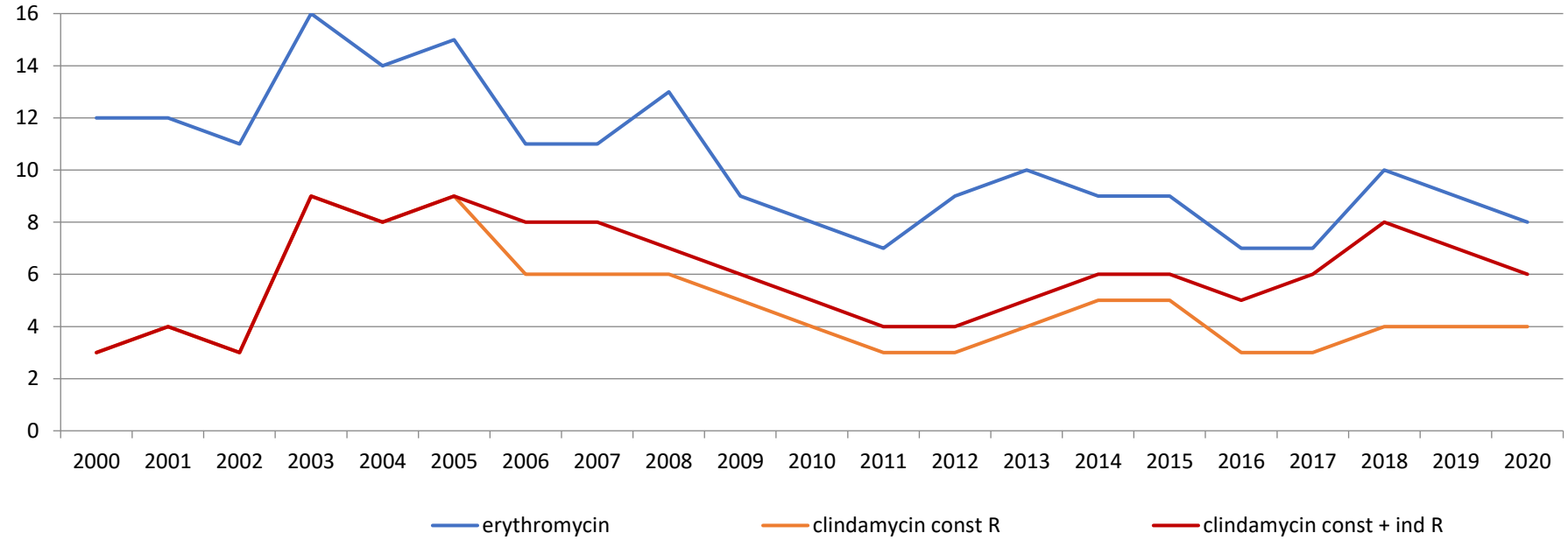
ANTIBIOTICI / *ANTIBIOTICS*:

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. - 2020.



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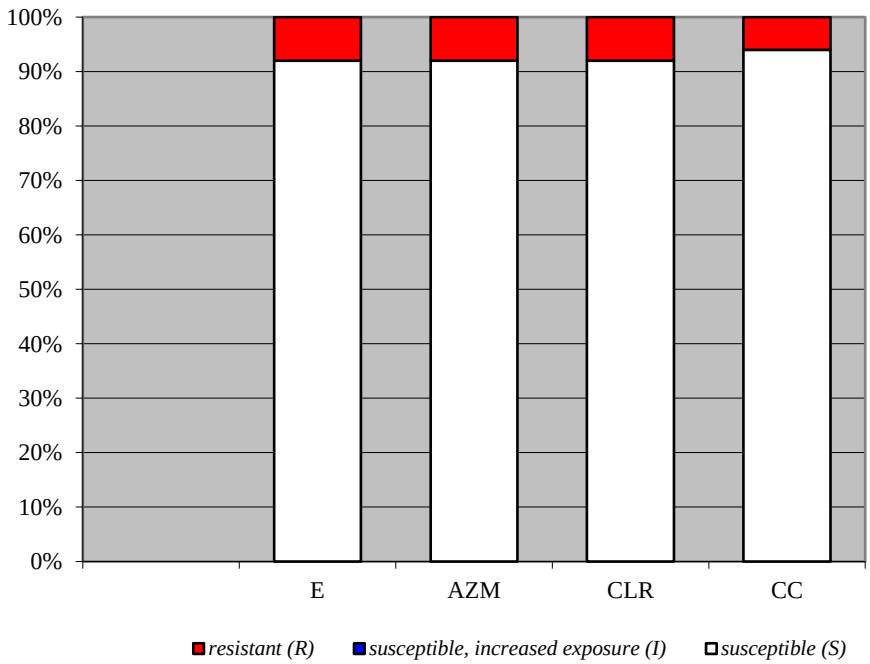
Beta-hemolitički streptokok grupe A / *Group A streptococcus*

rezistencija na antibiotike u razdoblju od 1.01.- 31.12.2020., zbirni prikaz izolata iz 38 centara u RH /
antibiotic resistance for the period 1.01. - 31.12.2020, summary results for the isolates from 38 centers in Croatia

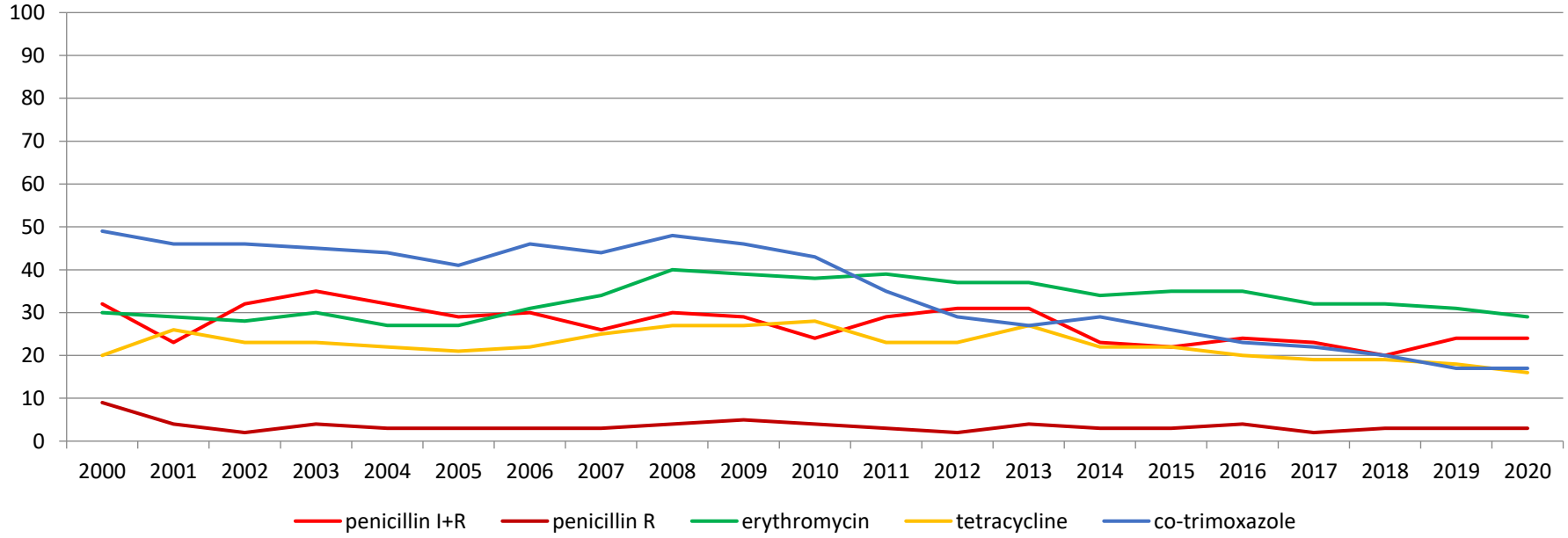
ANTIBIOTIK / *ANTIBIOTIC*	**Broj izolata** / *No. of isolates*	**% rezistentnih (R) (% osjetljivih uz povećanu izloženost (I)) izolata** / *% of resistant (R) (% of susceptible, increased exposure (I)) isolates*	**Raspon lokalnih rezultata*** / *Range of local results**
Erythromycin	4 553	8 (0)	0 (0) - 27 (0)
Azithromycin	4 553	8 (0)	0 (0) - 27 (0)
Clarythromycin	4 553	8 (0)	0 (0) - 27 (0)
Clindamycin	4 555	7 (0)	0 (0) - 12 (0)
constitutive		4	0 - 12
inducible		3	0 - 10

*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. - 2020.



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

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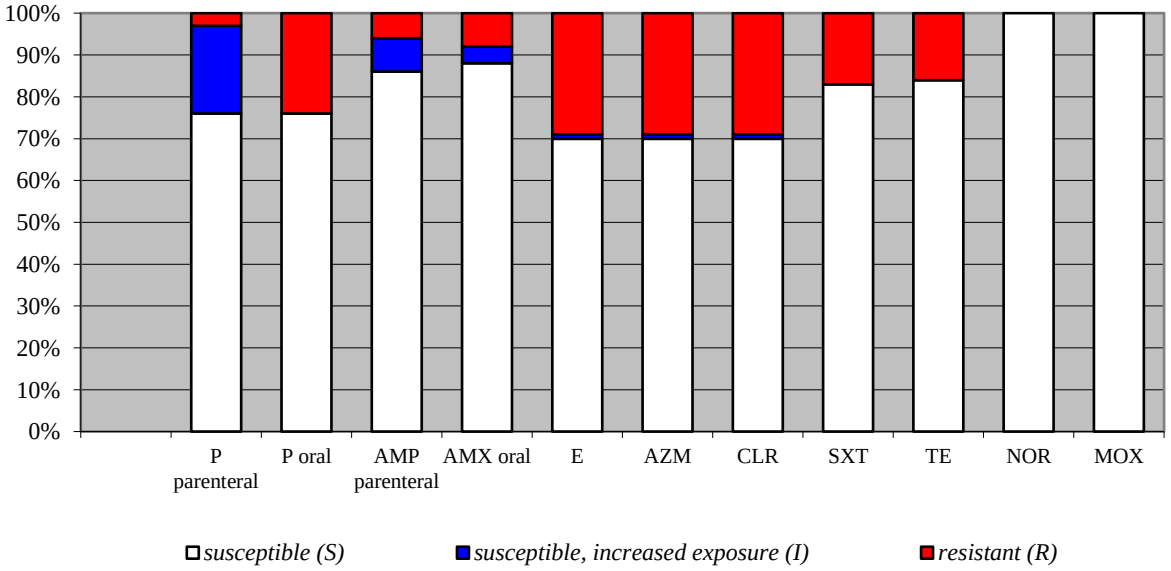
Streptococcus pneumoniae

rezistencija na antibiotike u razdoblju od 1.10.- 31.12.2020.,
zbirni prikaz izolata iz 38 centara u RH /
antibiotic resistance for the period 1.10. - 31.12.2020,
summary results for the isolates from 38 centers in Croatia

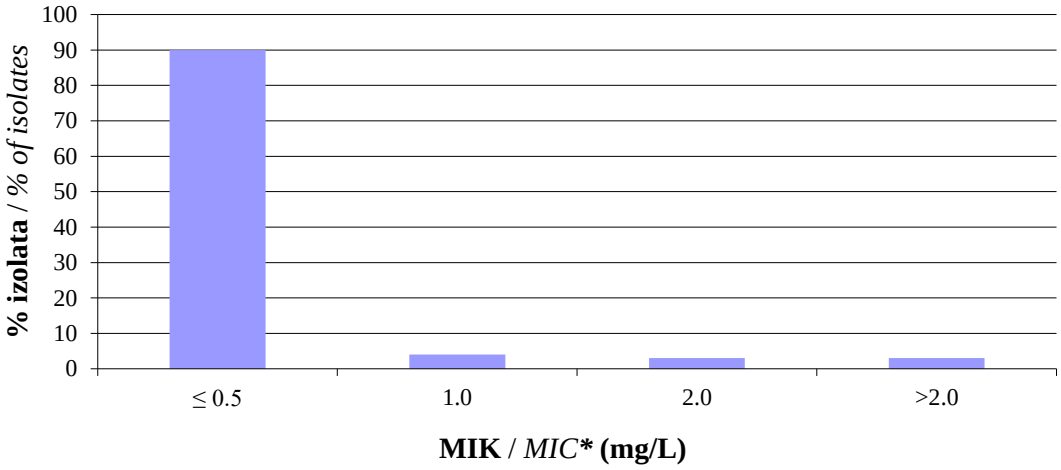
ANTIBIOTIK / *ANTIBIOTIC*	**Broj izolata** / *No. of isolates*	**% rezistentnih (R) (% osjetljivih uz povećanu izloženost (I)) izolata** / *% of resistant (R) (% of susceptible, increased exposure (I)) isolates*	**Raspon lokalnih rezultata*** / *Range of local results**
Penicillin $_{\textbf{parenteral}}$	647	3 (21)	0 (0) - 10 (6)
Penicilin $_{\textbf{oral}}$	647	24 (0)	5 (0) - 48 (0)
Ampicillin $_{\textbf{parenteral}}$	684	8 (6)	0 (0) - 28 (9)
Amoxicillin $_{\textbf{oral}}$	679	8 (4)	0 (0) - 37 (0)
Erythromycin/Azithromycin/ Clarythromycin	686	29 (1)	5 (0) - 46 0)
Co-trimoxazole	686	17 (0)	5 (0) - 46 (0)
Tetracycline	619	16 (0)	0 (0) - 28(0)
Norfloxacin	669	0 (0)	0 (0) - 5 (0)
Moxifloxacin	638	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



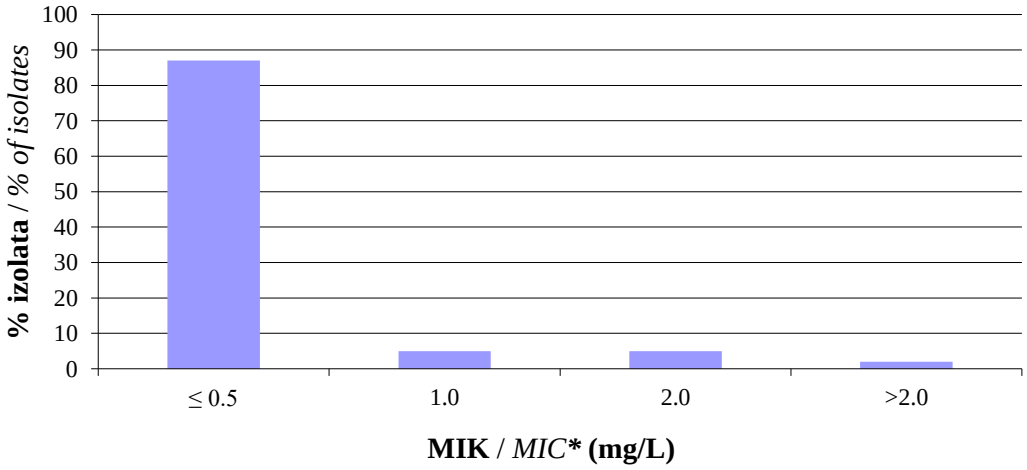
Streptococcus pneumoniae

Distribucija MIK-ova penicilina, (686 *S. pneumoniae* izolata) /
Penicillin MIC distribution, (686 S. pneumoniae isolates), 1.10. – 31.12.2020.



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

Distribucija MIK-ova ampicilina, (566 *S. pneumoniae* izolata) /
Ampicillin MIC distribution, (566 S. pneumoniae isolates), 1.10. – 31.12.2020.



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

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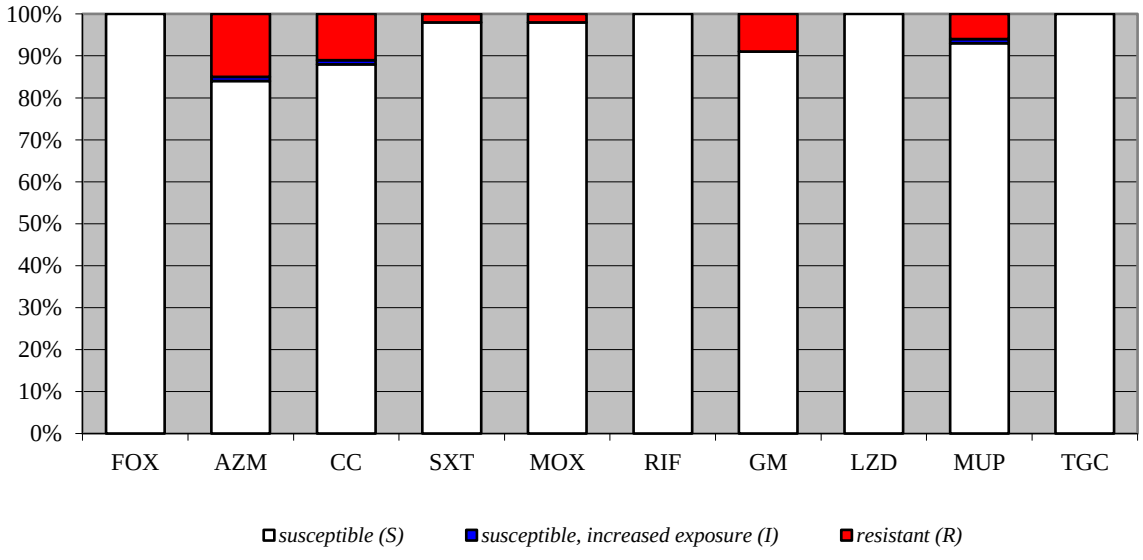
Staphylococcus aureus / MSSA

rezistencija na antibiotike u razdoblju od 1.10.- 31.12.2020.,
zbirni prikaz izolata iz 38 centara u RH /
antibiotic resistance for the period 1.10. - 31.12.2020,
summary results for the isolates from 38 centers in Croatia

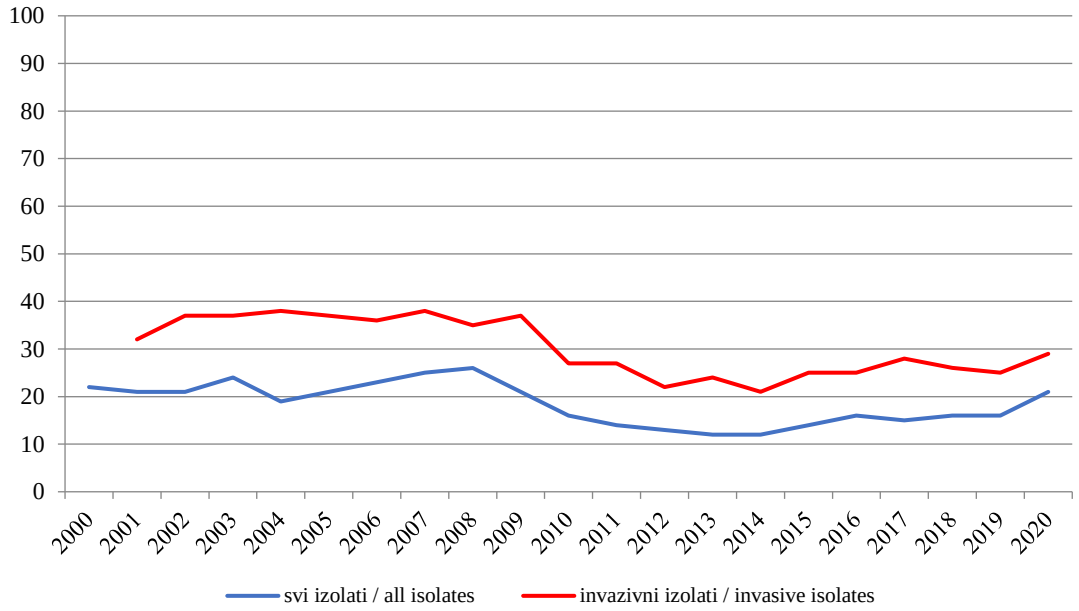
ANTIBIOTIK / *ANTIBIOTIC*	**Broj izolata** / *No. of isolates*	**% rezistentnih (R) (% osjetljivih uz povećanu izloženost (I)) izolata** / *% of resistant (R) (% of susceptible, increased exposure (I)) isolates*	**Raspon lokalnih rezultata*** / *Range of local results**
Cefoxitin/ Methicillin	2 593	0 (0)	0 (0) - 0 (0)
Azithromycin	2 524	15 (1)	3 (0) - 32 (0)
Clindamycin	2 539	11 (1)	3 (0) – 26 (0)
constitutive		6	0 - 15
inducible		5	0 - 16
Co-trimoxazole	2 527	2 (0)	0 (0) – 12 (0)
Moxifloxacin	2 466	2 (0)	0 (0) - 5 (0)
Rifampicin	2 445	0 (0)	0 (0) - 3 (0)
Gentamicin	2 537	9 (0)	0 (0) - 32 (0)
Linezolid	2 494	0 (0)	0 (0) - 0 (0)
Mupirocin	2 232	6 (1)	0 (2) - 13 (0)
Tigecycline	2 279	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*

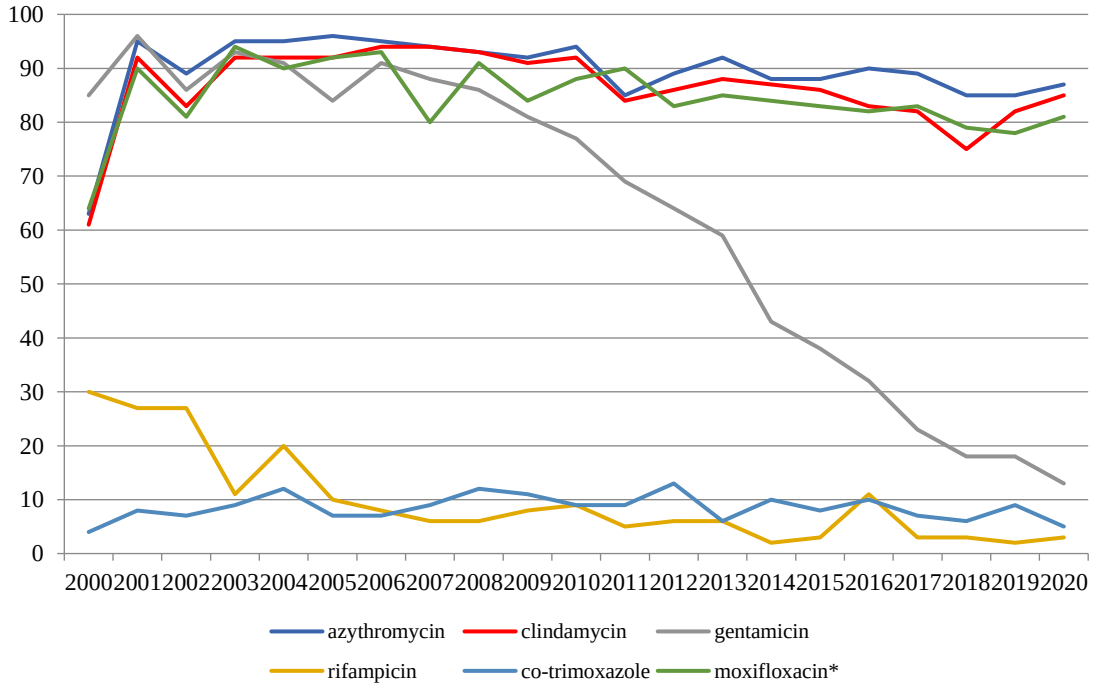


Staphylococcus aureus / MRSA

Methicillin resistant *Staphylococcus aureus* (MRSA) – stope / *rates*, 2000. - 2020.



rezistencija na antibiotike u RH /*resistance to antibiotics in Croatia*, 2000. - 2020.



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

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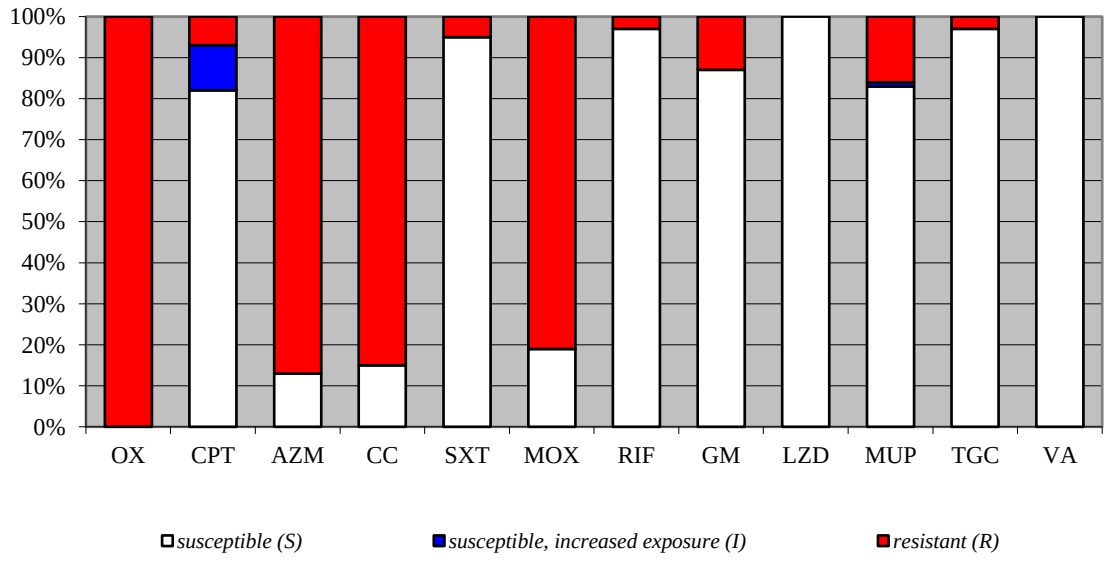
Staphylococcus aureus / MRSA

rezistencija na antibiotike u razdoblju od 1.10. - 31.12.2020.,
zbirni prikaz izolata iz 38 centara u RH /
antibiotic resistance for the period 1.10. - 31.12.2020,
summary results for the isolates from 38 centers in Croatia

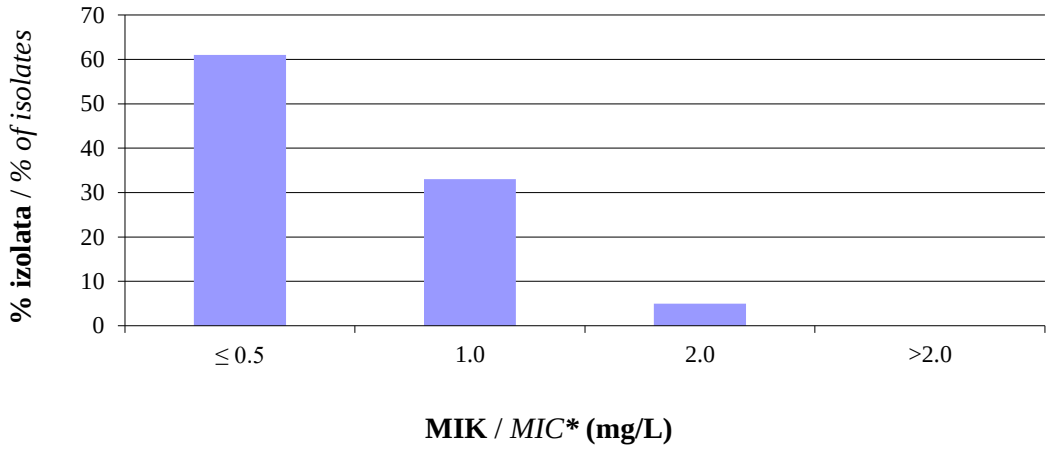
ANTIBIOTIK / *ANTIBIOTIC*	**Broj izolata** / *No. of isolates*	**% rezistentnih (R) (% osjetljivih uz povećanu izloženost (I)) izolata** / *% of resistant (R) (% of susceptible, increased exposure (I)) isolates*	**Raspon lokalnih rezultata*** / *Range of local results**
Cefoxitin/ Methicillin	699	100 (0)	100 (0) - 100 (0)
Ceftaroline	583	7 (11)	0 (5) – 41 (10)
Azithromycin	698	87 (0)	77 (0) - 96 (0)
Clindamycin	698	80 (0)	69 (3) - 100 (0)
constitutive		52	0 - 77
inducible		28	14 - 69
Co-trimoxazole	697	5 (0)	0 (0) - 11 (0)
Moxifloxacin	670	81 (0)	77 (0) - 98 (0)
Rifampicin	691	3 (0)	0 (0) - 5 (0)
Gentamicin	699	13 (0)	0 (0) - 30 (0)
Linezolid	698	0 (0)	0 (0) - 0 (0)
Mupirocin	617	16 (1)	0 (0) - 72 (0)
Tigecycline	639	3 (0)	0 (0) - 0 (0)
Vankomicin	615	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



Staphylococcus aureus / MRSA

Distribucija MIK-ova vankomicina, (615 MRSA izolata) /
Vancomycin MIC distribution, (615 MRSA isolates), 1.10. – 31.12.2020.



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

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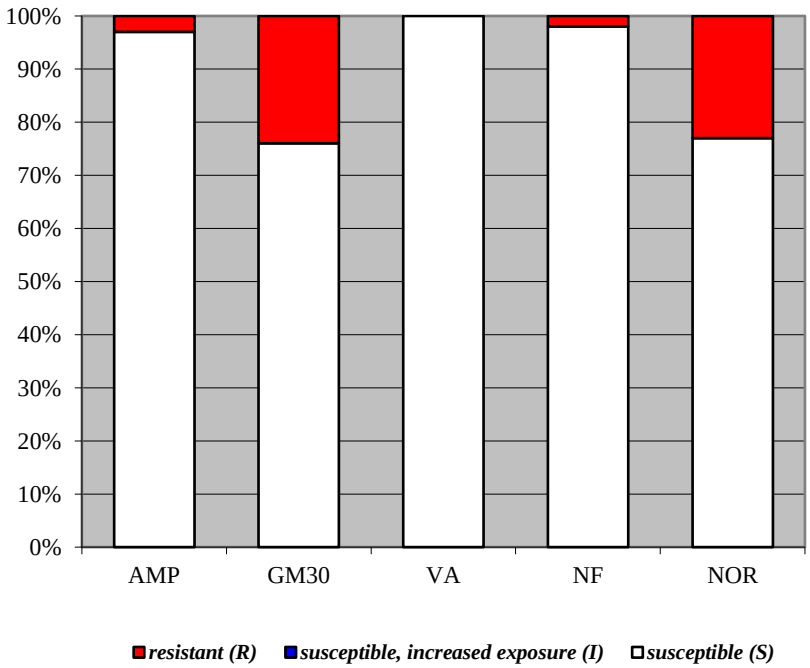
Enterococcus faecalis

rezistencija na antibiotike u razdoblju od 1.10. - 31.12.2020.,
zbirni prikaz izolata iz 38 centara u RH /
antibiotic resistance for the period 1.10. - 31.12.2020,
summary results for the isolates from 38 centers in Croatia

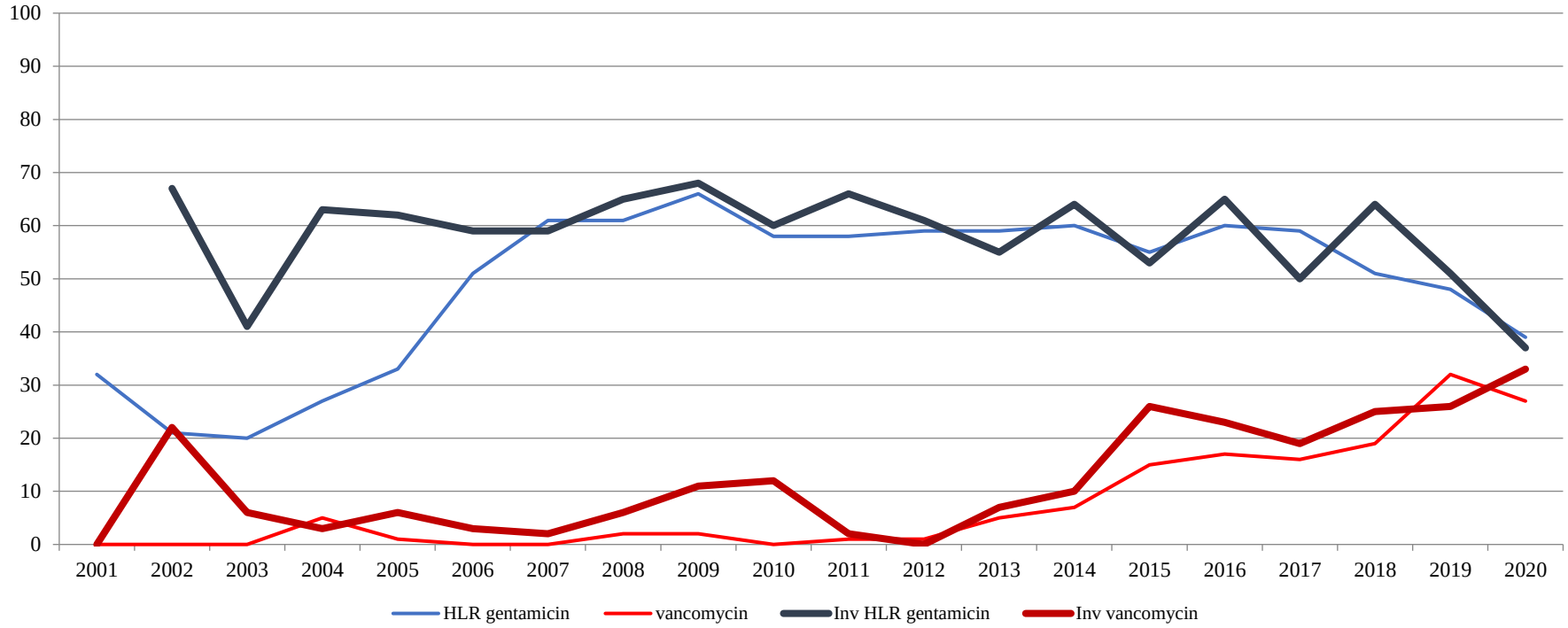
ANTIBIOTIK / *ANTIBIOTIC*	**Broj izolata /** *No. of isolates*	**% rezistentnih (R) (% osjetljivih uz povećanu izloženost (I)) izolata /** *% of resistant (R) (% of susceptible, increased exposure (I)) isolates*	**Raspon lokalnih rezultata* /** *Range of local results**
Ampicillin	3 764	3 (0)	0 (0) - 45 (0)
Gentamicin	3 748	24 (0)	0 (0) - 62 (0)
Vancomycin	3 764	0 (0)	0 (0) -2 (0)
Nitrofurantoin	3 714	2 (0)	0 (0) - 10 (0)
Norfloxacin	3 644	23 (0)	4 (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



Enterococcus faecium

rezistencija na antibiotike u RH / *resistance to antibiotics in Croatia*, 2001. - 2020.



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

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Enterococcus faecium

rezistencija na antibiotike u razdoblju od 1.10. - 31.12.2020.,
zbirni prikaz izolata iz 38 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**
Ampicillin	859	92 (0)	37 (0) - 100 (0)
Gentamicin	860	39 (0)	4 (0) - 60 (0)
Vancomycin	858	27 (0)	2 (0) - 54 (0)
Norfloxacin	826	81 (0)	8 (0) - 97 (0)

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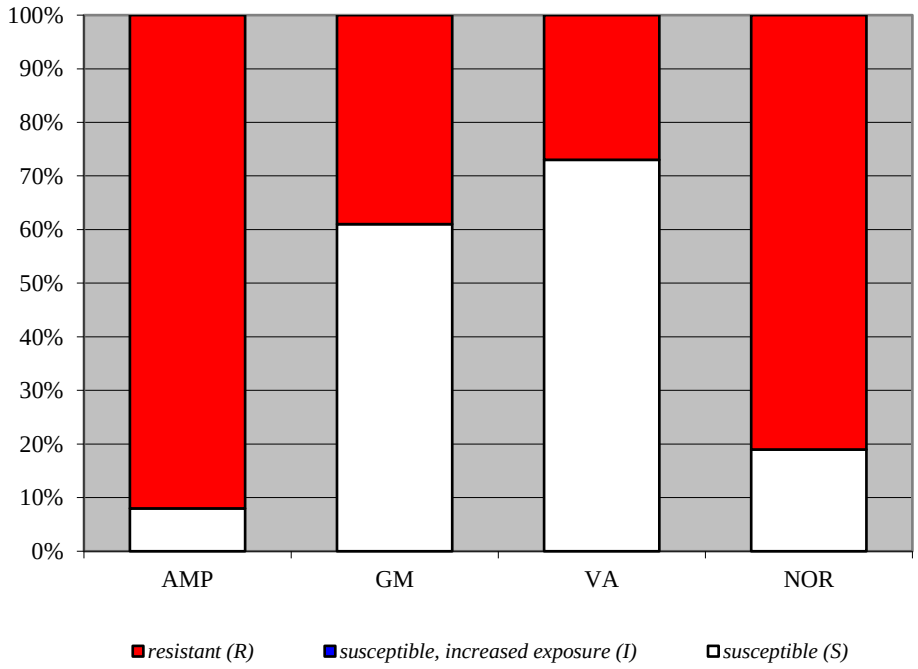
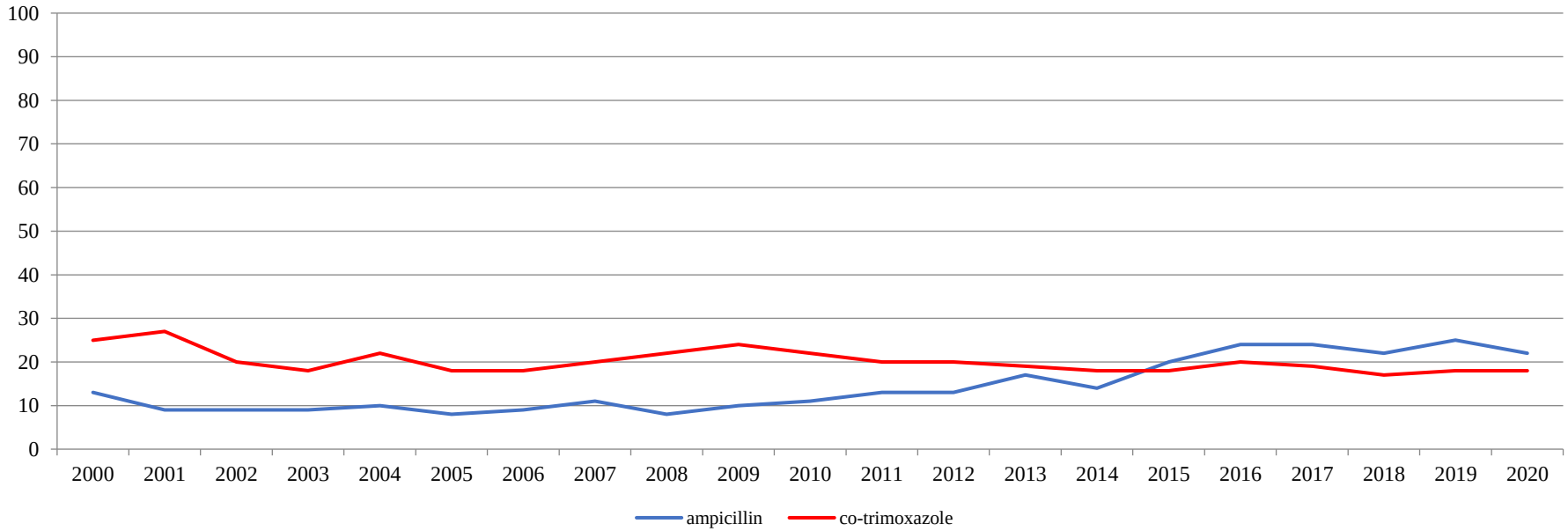


Haemophilus influenzae

rezistencija na antibiotike u RH / *resistance to antibiotics in Croatia*, 2000. - 2020.



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Haemophilus influenzae

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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	434	22 (0)	3 (0) - 25 (0)
Ampicillin oral	434	22 (78)	3 (0) – 25 (0)
Amoxicillin + clav. acid parenteral	431	2 (0)	0 (0) - 10 (0)
Amoxicillin + clav. acid oral	431	3 (97)	0 (100) – 10 (90)
Cefuroxime parenteral	432	11 (6)	0 (3) - 43 (7)
Cefuroxime oral	432	17 (83)	3 (97) - 50 (50)
Ceftriaxone	420	0 (0)	0 (0) - 0 (0)
Co-trimoxazole	427	18 (0)	13 (0) - 27 (0)

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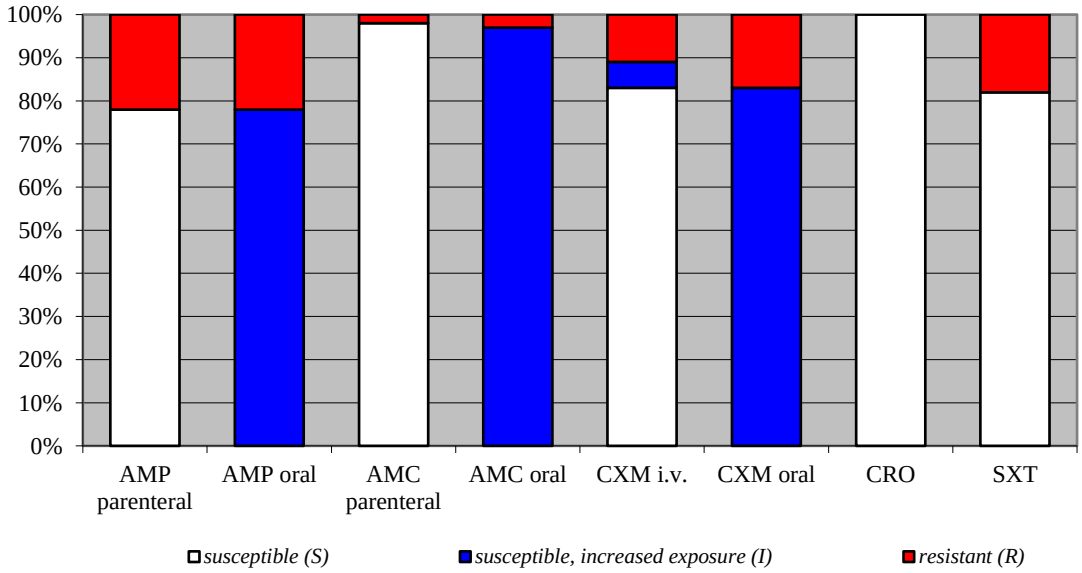
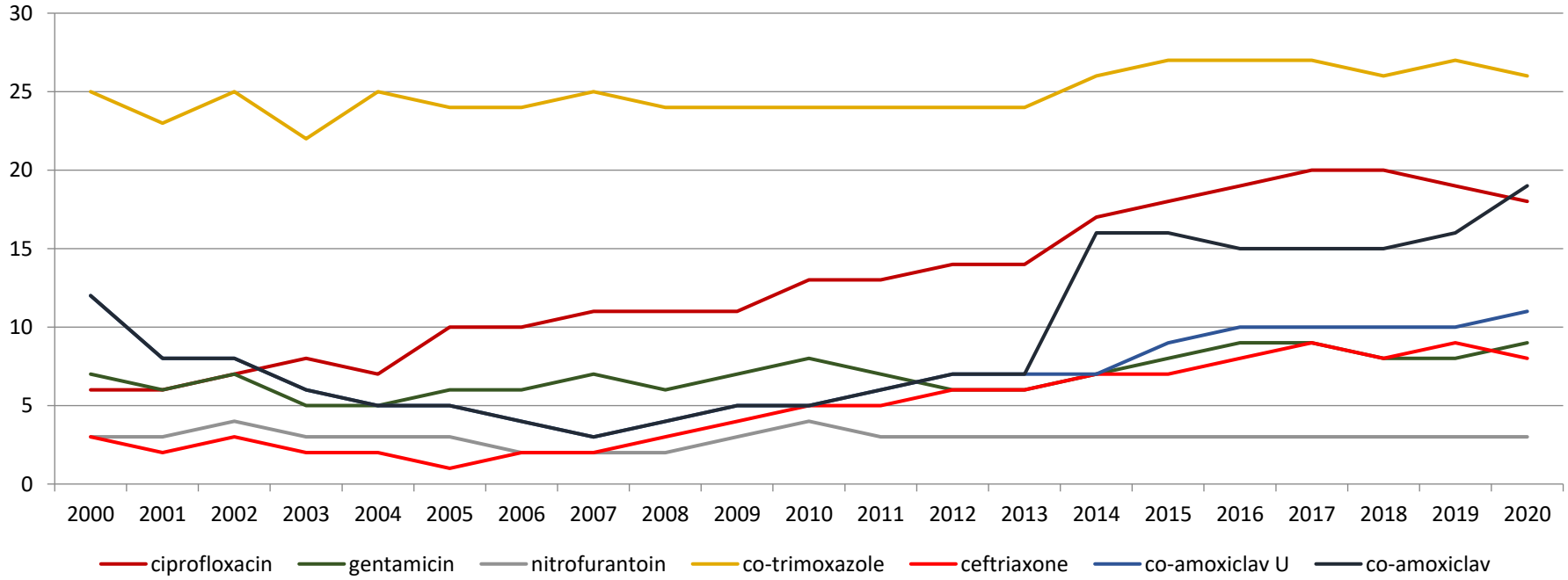


Escherichia coli

rezistencija na antibiotike u RH / *resistance to antibiotics in Croatia*, 2000. - 2020.



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

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Escherichia coli

rezistencija na antibiotike u razdoblju od 1.10. - 31.12.2020.,
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antibiotic resistance for the period 1.10. - 31.12.2020,
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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	12 912	51 (0)	37 (0) - 71 (0)
Amoxicillin + clav. acid sistemna infekcija	12 332	19 (0)	0 (0) - 36 (0)
Amoxicillin + clav. acid nekomplicirana IMS	12 796	11 (0)	3 (0) - 22 (0)
Piperacillin + tazobactam	12 868	2 (1)	0 (0) - 34 (1)
Cephalexin	12 597	12 (0)	6 (0) - 32 (0)
Cefuroxime oral	12 874	11 (0)	5 (0) - 32 (0)
Cefuroxime parenteral	12 422	10 (90)	0 (0) – 32 (0)
Ceftazidime	12 911	8 (0)	1 (0) - 24 (0)
Ceftriaxone	12 902	8 (0)	1 (0) - 24 (0)
Cefepime	12 869	7 (0)	0 (0) – 20 (1)
Cefixime	12 633	9 (0)	4 (0) – 20 (0)
Ceftazidime + avibactam	11 873	0 (0)	0 (0) – 4 (0)
Ceftolozane + tazobactam	11 755	1 (0)	0 (0) – 9 (0)
Ertapenem	12 872	0 (0)	0 (0) - 2 (0)
Imipenem	12 845	0 (0)	0 (0) - 1 (1)
Meropenem	12 849	0 (0)	0 (0) - 1 (1)
Ciprofloxacin	12 896	18 (0)	8 (0) - 37 (0)
Norfloxacin	12 855	18 (0)	8 (0) - 37 (0)
Gentamicin	12 906	9 (0)	0 (0) - 20 (0)
Amikacin	12 636	1 (0)	0 (0) - 1 (0)
Co-trimoxazole	12 884	26 (0)	16 (0) - 43 (0)
Nitrofurantoin	12 758	3 (0)	0 (0) - 6 (0)
Fosfomycin	12 692	1 (0)	0 (0) - 4 (0)
Nitroxolin	11 794	1 (0)	0 (0) - 6 (0)

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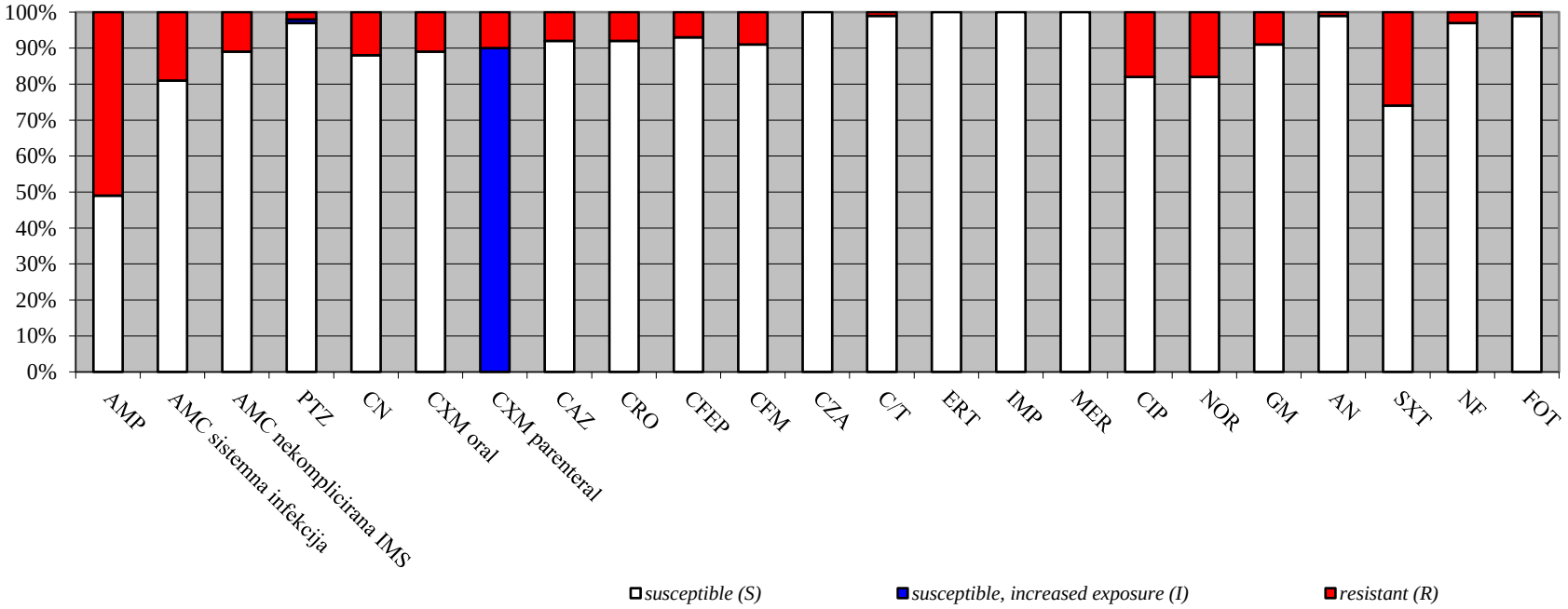
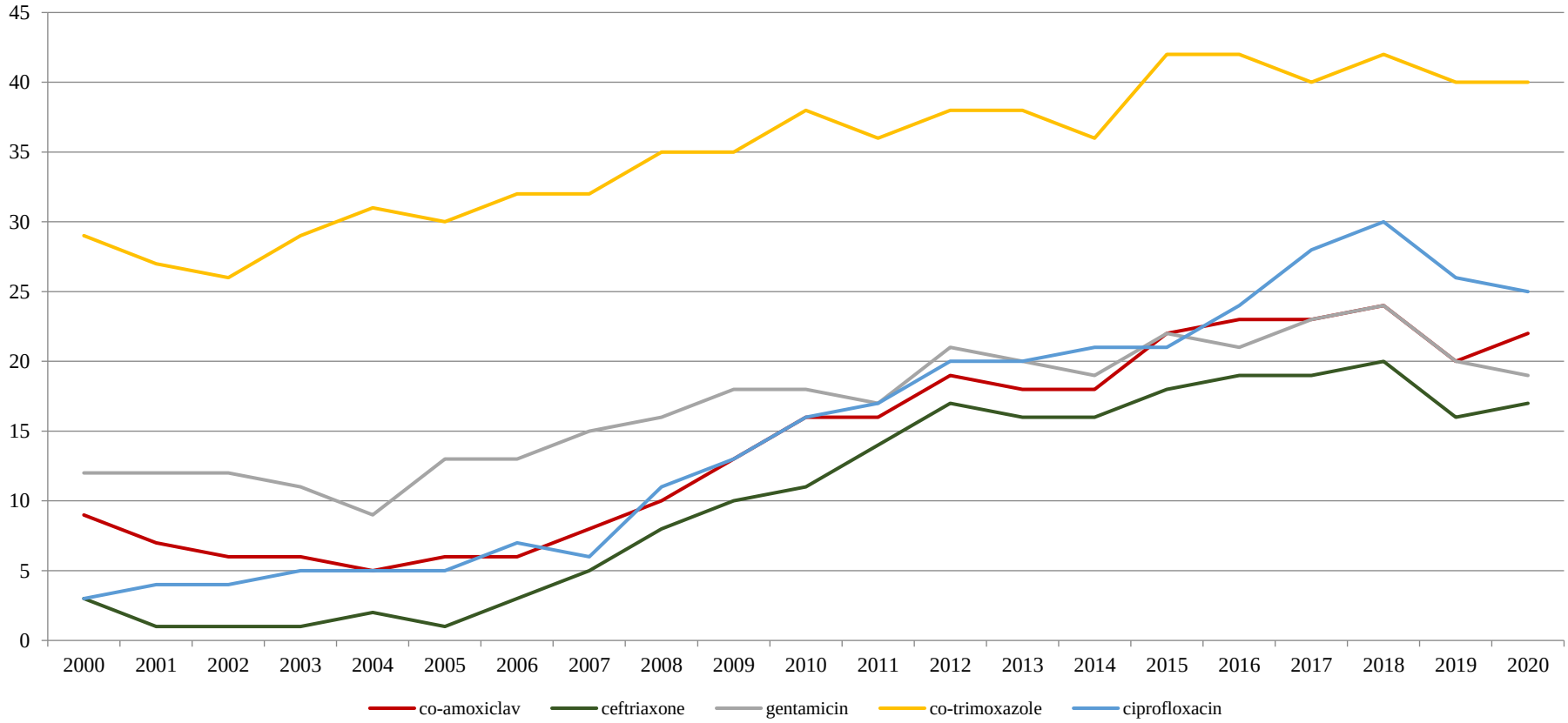
Escherichia coli

osjetljivost na antibiotike u RH / *sensitivity to antibiotics in Croatia*, 1.10. – 31.12.2020.



Proteus mirabilis

rezistencija na antibiotike u RH / *resistance to antibiotics in Croatia*, 2000. – 2020.



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Proteus mirabilis

rezistencija na antibiotike u razdoblju od 1.10. - 31.12.2020.,
zbirni prikaz izolata iz 38 centara u RH /
antibiotic resistance for the period 1.10. - 31.12.2020,
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Ampicillin	3 114	47 (0)	22 (0) - 69 (0)
Amoxicillin + clav. acid	3 121	22 (0)	5 (0) - 42 (0)
Piperacillin + tazobactam	3 093	1 (0)	0 (0) - 10 (0)
Cephalexin	3 097	22 (0)	0 (0) - 51 (0)
Cefuroxime $_{\textbf{oral}}$	3 097	20 (0)	0 (0) - 51 (0)
Cefuroxime parenteral	3 042	20 (80)	0 (100) – 51 (49)
Ceftazidime	3 117	16 (0)	1 (1) - 33 (0)
Ceftriaxone	3 117	17 (0)	4 (0) – 33 (0)
Cefepime	3 093	9 (2)	0 (0) - 26 (0)
Cefixime	3 075	16 (0)	0 (0) - 31 (0)
Ceftazidime + avibactam	2 962	1 (0)	0 (0) – 5 (0)
Ceftolozane + tazobactam	2 935	8 (0)	0 (0) – 20 (0)
Ertapenem	3 100	0 (0)	0 (0) – 3 (0)
Meropenem	3 093	0 (0)	0 (0) – 2 (0)
Ciprofloxacin	3 111	25 (1)	0 (0) – 51 (0)
Norfloxacin	3 103	25 (0)	0 (0) – 51 (0)
Gentamicin	3 114	19 (0)	3 (0) – 34 (0)
Amikacin	3 077	9 (0)	0 (0) – 23 (0)
Co-trimoxazole	3 109	40 (0)	8 (0) – 63 (0)

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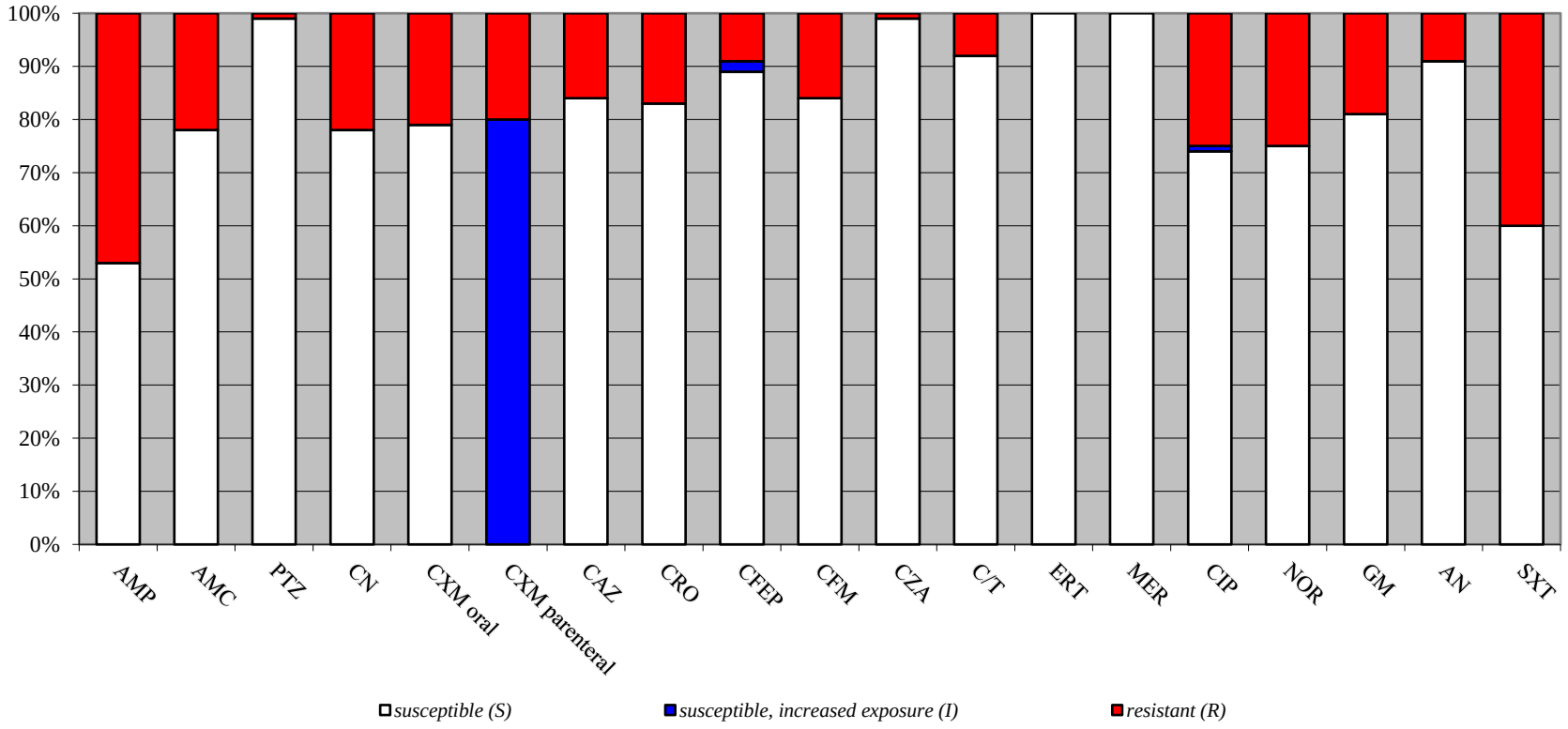
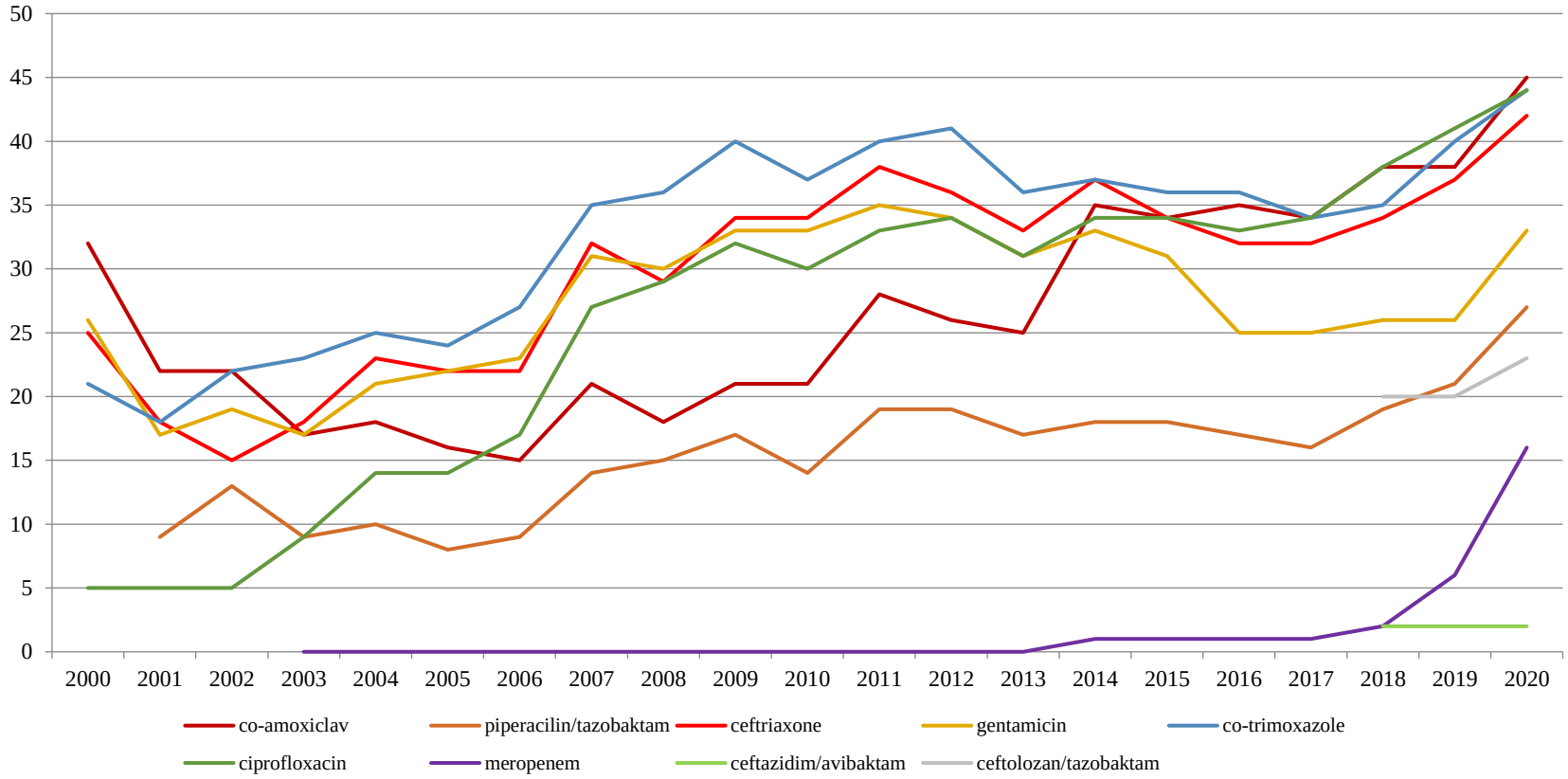
Proteus mirabilis

osjetljivost na antibiotike u RH / *sensitivity to antibiotics in Croatia*, 1.10. – 31.12.2020.



Klebsiella pneumoniae

rezistencija na antibiotike u RH /*resistance to antibiotics in Croatia*, 2000. - 2020.



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Klebsiella pneumoniae

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Ampicillin	4 244	100 (0)	100 (0) - 100 (0)
Amoxicillin + clav. acid	4 242	45 (0)	16 (0) - 79 (0)
Piperacillin + tazobactam	4 236	27 (3)	0 (0) - 72 (0)
Cephalexin	4 160	47 (0)	0 (0) - 96 (0)
Cefuroxime $_{oral}$	4 213	46 (0)	14 (0) - 96 (0)
Cefuroxime $_{parenteral}$	4 224	44 (56)	1 (99) – 96 (4)
Ceftazidime	4 252	42 (1)	12 (0) - 85 (0)
Ceftriaxone	4 250	42 (0)	13 (0) - 84 (0)
Cefepime	4 235	41 (1)	12 (0) - 84 (0)
Cefixime	4 161	43 (0)	15 (0) - 91 (0)
Ceftazidime + avibactam	4 079	2 (0)	0 (0) – 5 (0)
Ceftolozane + tazobactam	4 037	23 (0)	0 (0) – 73 (0)
Ertapenem	4 228	22 (0)	0 (0) – 71 (0)
Imipenem	4 228	7 (8)	0 (0) – 29 (20)
Meropenem	4 234	16 (2)	0 (0) - 62 (0)
Ciprofloxacin	4 242	44 (1)	21 (0) - 90 (0)
Norfloxacin	4 206	45 (0)	21 (0) - 90 (0)
Gentamicin	4 243	33 (0)	5 (0) - 83 (0)
Amikacin	4 204	7 (0)	0 (0) – 29 (0)
Co-trimoxazole	4 226	44 (0)	15 (0) - 93 (0)

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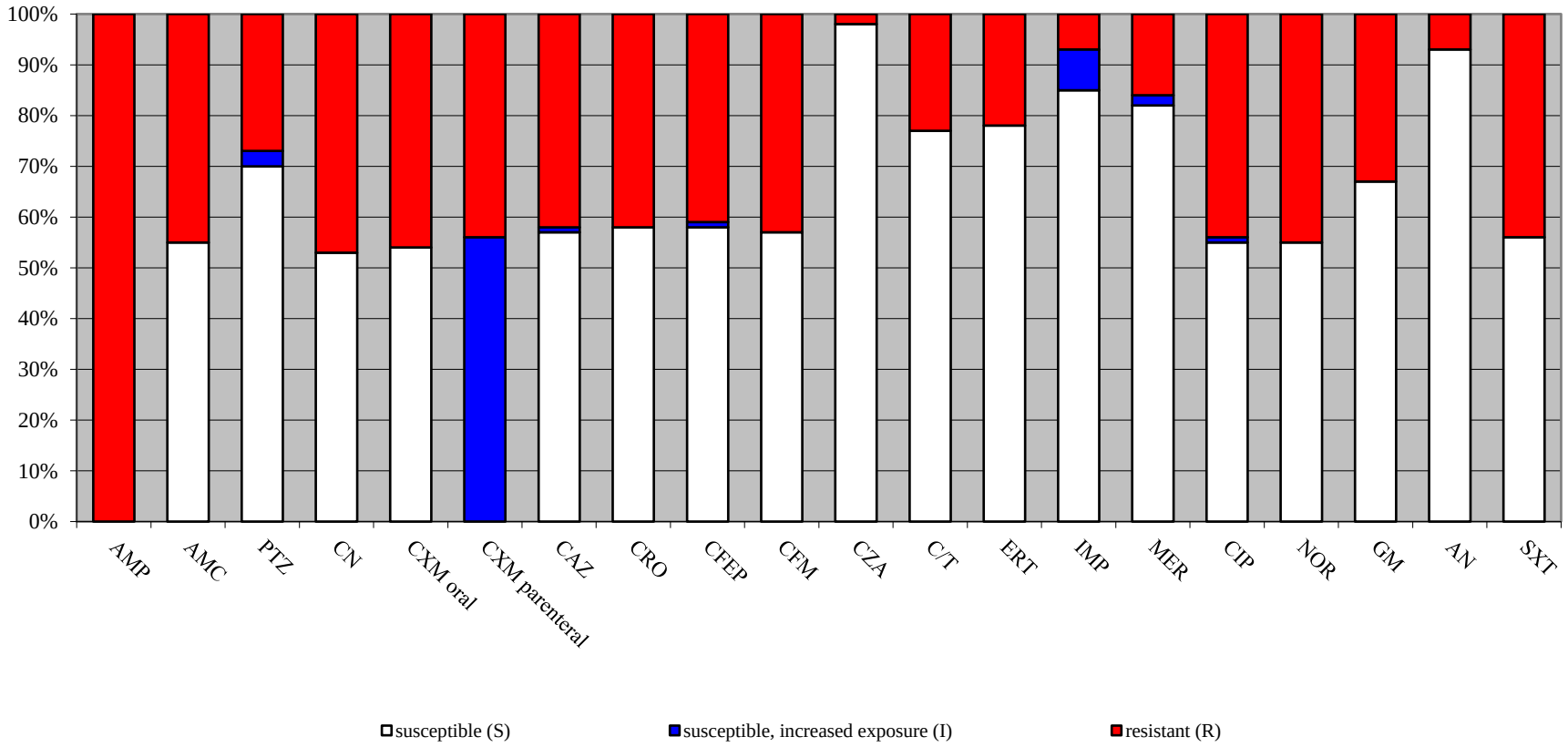
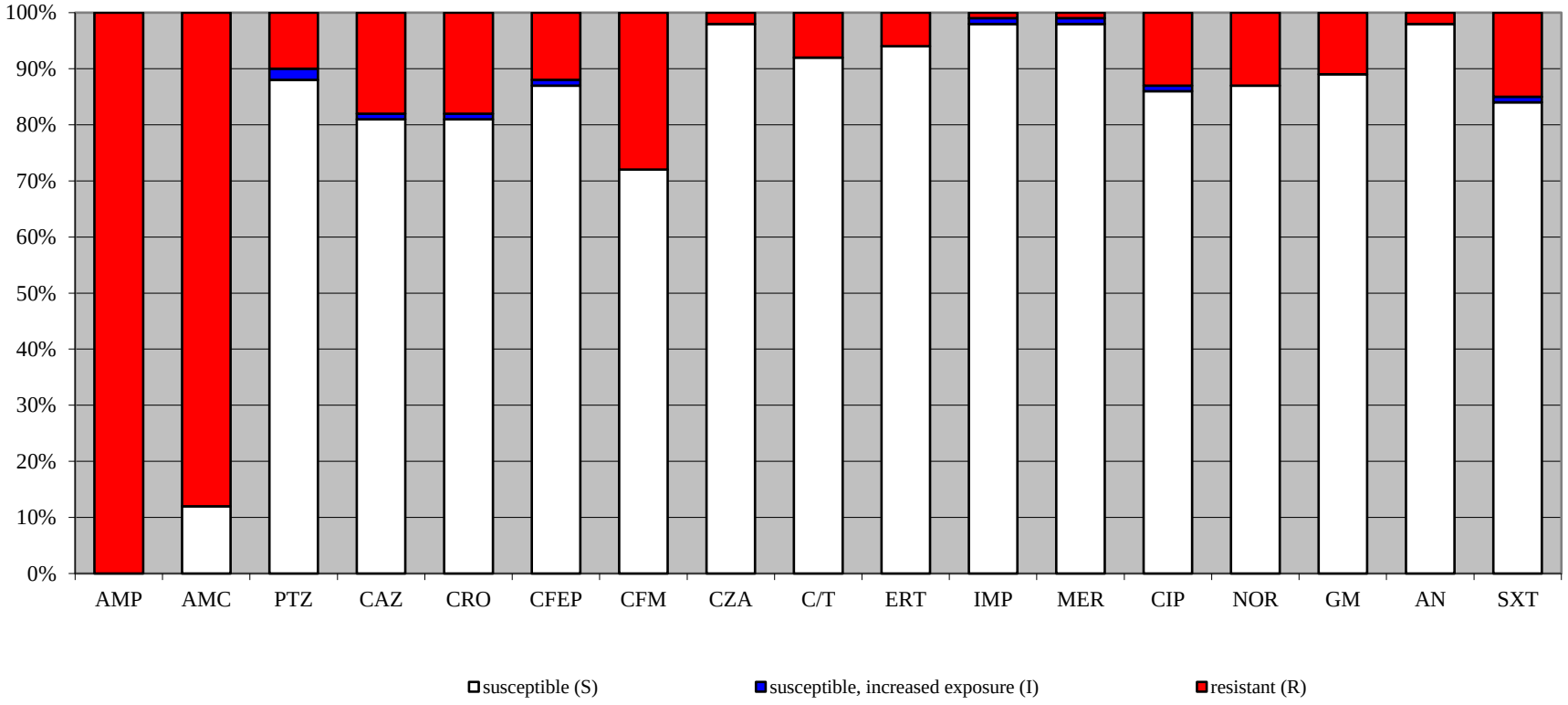
Klebsiella pneumoniae

osjetljivost na antibiotike u RH / *sensitivity to antibiotics in Croatia*, 1.10. – 31.12.2020.



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

osjetljivost na antibiotike u RH / *sensitivity to antibiotics in Croatia,* 1.10. – 31.12.2020.



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

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Ampicillin	2 726	100 (0)	100 (0) - 100 (0)
Amoxicillin + clav. acid	2 736	88 (0)	63 (0) - 100 (0)
Piperacillin + tazobactam	2 713	10 (2)	4 (0) - 31 (0)
Ceftazidime	2 732	18 (1)	4 (4) - 33 (0)
Ceftriaxone	2 729	18 (1)	6 (0) - 36 (0)
Cefepime	2 712	12 (1)	1 (1) - 24 (0)
Cefixime	2 656	28 (0)	10 (0) – 64 (0)
Ceftazidime + avibactam	2 590	2 (0)	0 (0) – 6 (0)
Ceftolozane + tazobactam	2 552	8 (0)	0 (0) – 17 (0)
Ertapenem	2 703	6 (0)	0 (0) – 18 (0)
Imipenem	2 708	1 (1)	0 (0) - 18 (0)
Meropenem	2 713	1 (1)	0 (0) - 6 (0)
Ciprofloxacin	2 710	13 (1)	0 (9) - 27 (0)
Norfloxacin	2 644	13 (0)	4 (0) - 31 (0)
Gentamicin	2 726	11 (0)	5 (0) - 29 (0)
Amikacin	2 703	2 (0)	0 (0) - 20 (0)
Co-trimoxazole	2 690	15 (1)	3 (0) - 38 (0)

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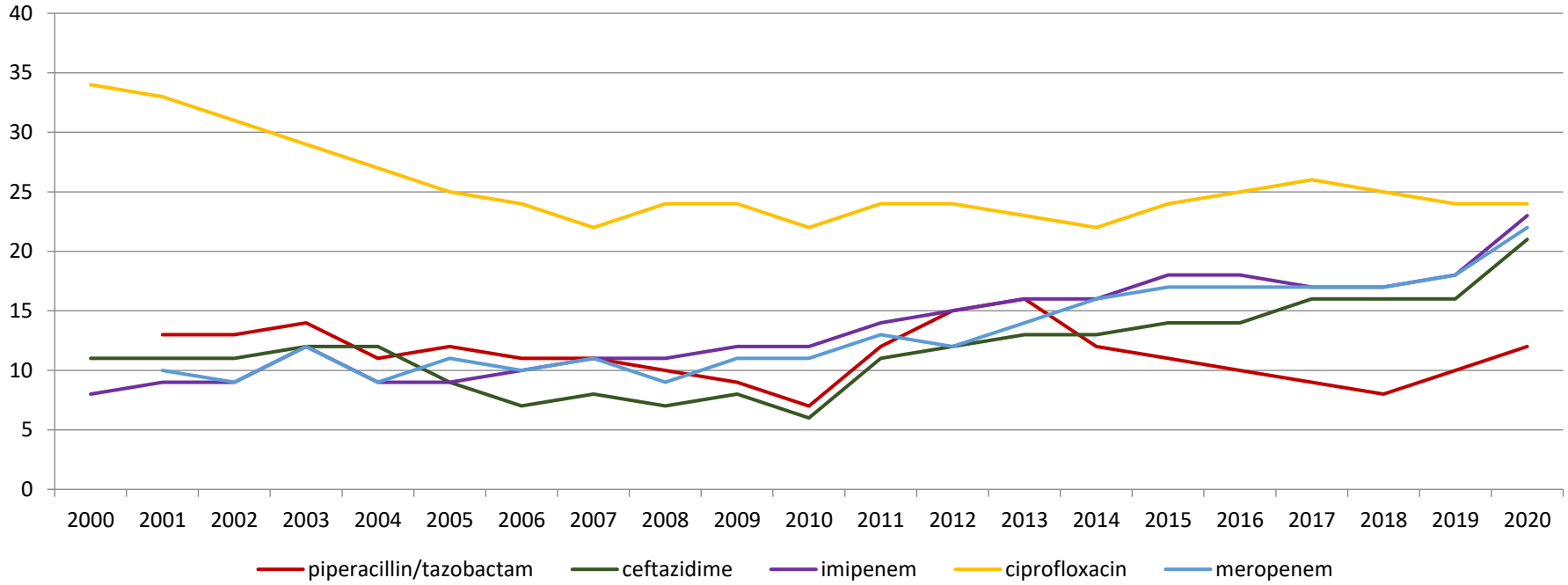
Pseudomonas aeruginosa

rezistencija na antibiotike u RH / *resistance to antibiotics in Croatia*, 2000. - 2020.



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Pseudomonas aeruginosa

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Piperacilin + tazobaktam	3 000	12 (87)	2 (98) - 59 (41)
Ceftazidim	2 297	21 (79)	2 (98) - 64 (36)
Cefepim	3 002	16 (83)	4 (96) - 45 (55)
Ceftazidime + avibactam	2 816	7 (0)	0 (0) – 32 (0)
Ceftolozane + tazobactam	2 869	7 (0)	0 (0) – 20 (0)
Imipenem	3 014	23 (76)	6 (94) - 48 (52)
Meropenem	3 016	22 (7)	0 (0) - 42 (5)
Ciprofloxacin	3 003	24 (75)	11 (89) - 39 (61)
Amikacin	2 975	7 (0)	0 (0) - 16 (0)
Colistin	625	3 (0)	0 (0) - 18 (0)

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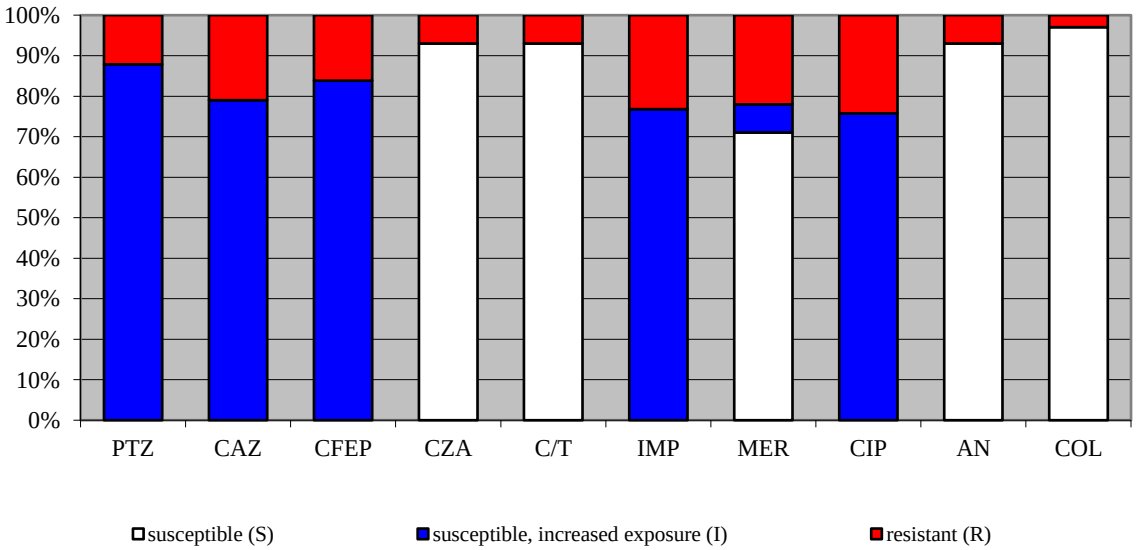
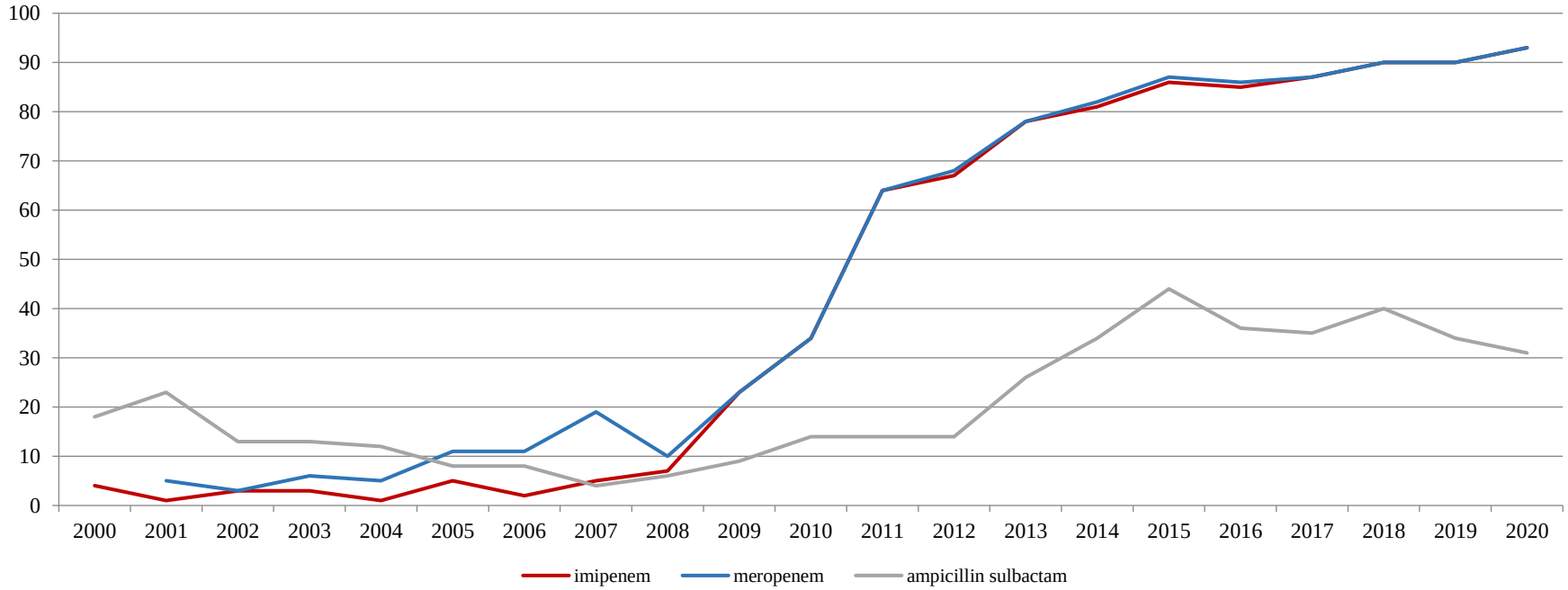


Acinetobacter baumannii

rezistencija na antibiotike u RH / *resistance to antibiotics in Croatia,* 2000. - 2020.



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Acinetobacter baumannii

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antibiotic resistance for the period 1.10. - 31.12.2020, summary results for the isolates from 38 centers in Croatia

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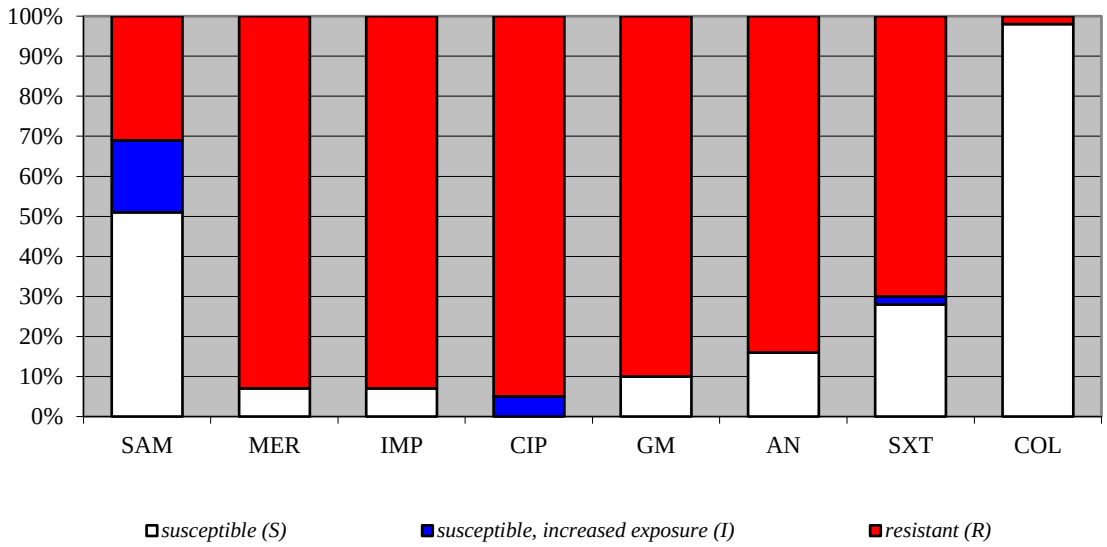
Ampicillin + sulbactam	2 060	31 (18)	5 (6) - 85 (0)
Meropenem	2 064	93 (0)	75 (0) - 100 (0)
Imipenem	2 066	93 (0)	75 (0) - 100 (0)
Ciprofloxacin	2 087	95 (5)	80 (0) - 100 (0)
Gentamicin	2 058	90 (0)	68 (0) - 100 (0)
Amikacin	2 052	84 (0)	75 (0) - 100 (0)
Co-trimaxazole	1 964	70 (2)	43 (0) - 99 (0)
Colistin	1 681	2 (0)	0 (0) - 17 (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

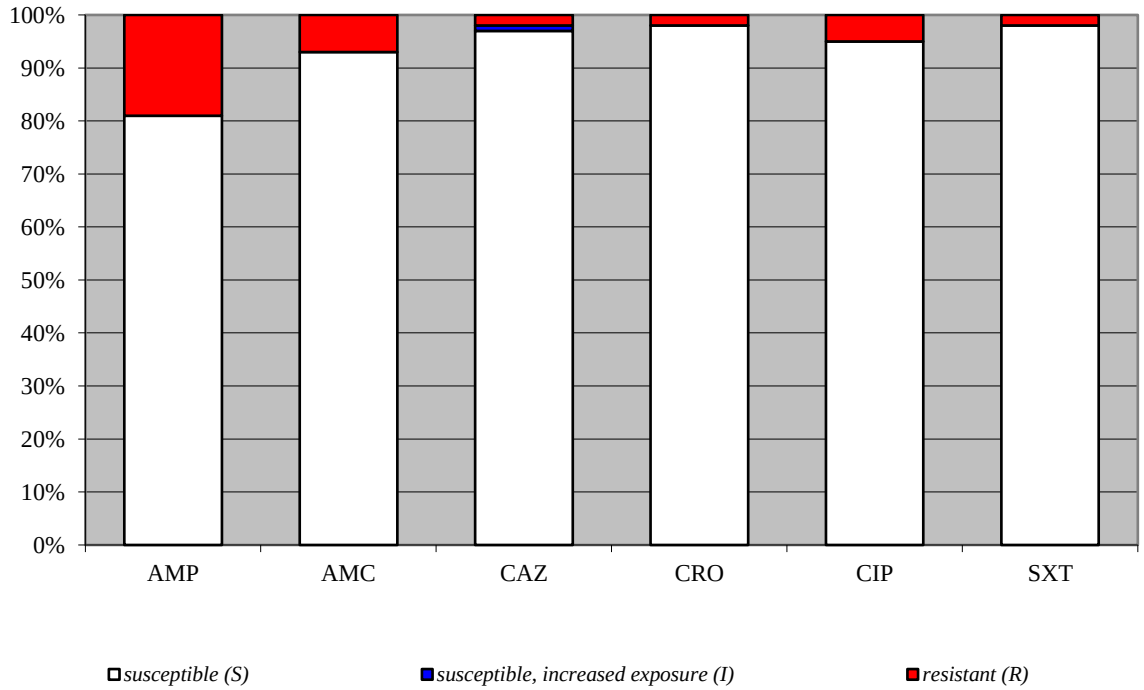


Salmonella spp.

rezistencija na antibiotike u razdoblju od 01.01. - 31.12.2020., zbirni prikaz izolata iz 38 centara u RH /
antibiotic resistance for the period 01.01. - 31.12.2020, summary results for the isolates from 38 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	1 169	19 (0)	0 (0) - 55 (0)
Amoxicillin + clav. acid	1 169	7 (0)	0 (0) - 41 (0)
Ceftazidim	1 169	2 (1)	0 (0) - 24 (8)
Ceftriaxone	1 169	2 (0)	0 (0) - 31 (6)
Ciprofloxacin	1 163	5 (0)	0 (0) - 20 (0)
Co-trimoxazole	1 168	2 (0)	0 (0) - 10 (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



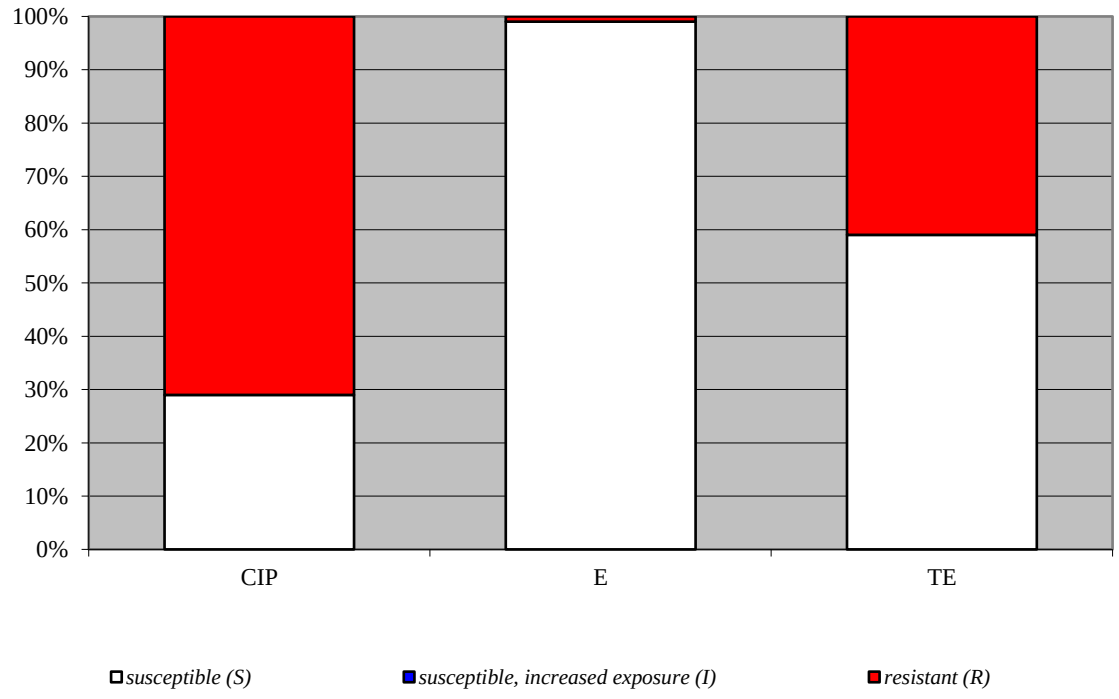
Odbor za praćenje rezistencije bakterija na antibiotike u RH
Croatian Academy of Medical Sciences, Public Health Collegium
Croatian Committee for Antibiotic Resistance Surveillance

Campylobacter jejuni

rezistencija na antibiotike u razdoblju od 1.01.- 31.12.2020.,
zbirni prikaz izolata iz 38 centara u RH /
antibiotic resistance for the period 1.01. - 31.12.2020,
summary results for the isolates from 38 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**
Ciprofloxacin	1 609	71 (0)	42 (0) - 92 (0)
Erythromicin	1 609	1 (0)	0 (0) - 3 (0)
Tetracycline	1 600	41 (0)	25 (0) - 84 (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



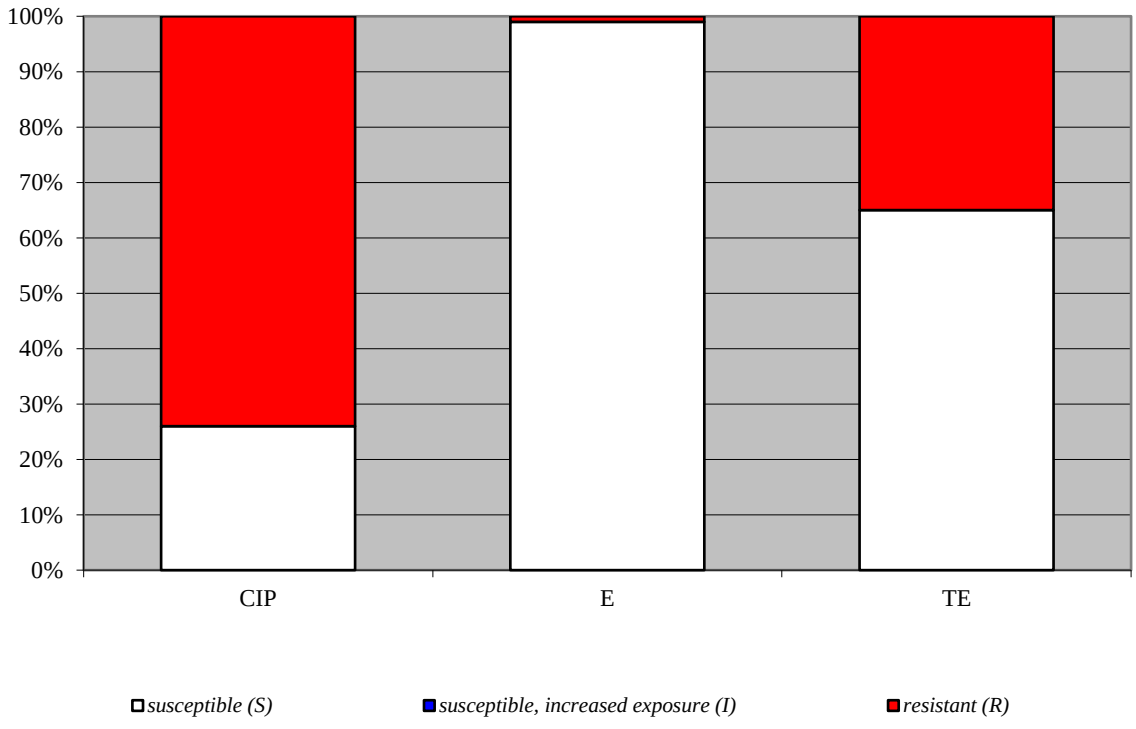
Akademija medicinskih znanosti Hrvatske, Kolegij za javno zdravstvo
Odbor za praćenje rezistencije bakterija na antibiotike u RH
Croatian Academy of Medical Sciences, Public Health Collegium
Croatian Committee for Antibiotic Resistance Surveillance

Campylobacter coli

rezistencija na antibiotike u razdoblju od 1.01. - 31.12.2020.,
zbirni prikaz izolata iz 38 centara u RH /
antibiotic resistance for the period 1.01. - 31.12.2020,
summary results for the isolates from 38 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*
Ciprofloxacin	465	74 (0)	50 (0) - 85 (0)
Erythromicin	465	1 (0)	0 (0) - 2 (0)
Tetracycline	461	35 (0)	24 (0) - 44 (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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Croatian Committee for Antibiotic Resistance Surveillance

Anaerobne bakterije / *Anaerobes*

rezistencija na antibiotike u RH / *antibiotic resistance in Croatia*, 01.01. – 31.12.2020.

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*	450	1	**9**	447	0	**1**	341	0	**0**	428	0	**1**	448	0	**49**	449	0	**19**
Gram negativni anaerobi /*Gram-negative Anaerobes*	494	1	**84**	494	2	**11**	373	3	**5**	580	0	**1**	493	0	**15**	493	0	**36**
UKUPNO / *TOTAL*	944	1	**48**	941	1	**6**	714	2	**2**	908	0	**1**	941	0	**31**	942	0	**28**

OSJETLJIVOST *M. TUBERCULOSIS* U HRVATSKOJ U 2020. GODINI

SENSITIVITY OF M. TUBERCULOSIS IN CROATIA, 2020

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

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Mikobakterije izolirane u Hrvatskoj u 2020. 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 cijela 2020. godina bila pandemijska godina. Premda se epidemiološki podaci još obrađuju, do sada je u prošloj godini prijavljeno 188 novooboljelih, što daje stopu učestalosti od 4,6/100.000, dok je u 2019. godini stopa učestalosti iznosila 7,5/100.000 stanovnika.

Za analizu podataka o bakteriološkoj dijagnostici TBC u Hrvatskoj u 2020. godini koristio se „Upitnik o radu TBC laboratorija u 2020. 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 22.100 kliničkih uzoraka na TBC što je pad od gotovo 40% u odnosu na broj uzoraka iz 2019. godine. Iako je preporučeni minimalni godišnji broj uzoraka za obradu na mikobakterije 2000, samo četiri laboratorija u 2020. 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 3,9% uzoraka kultivacijom je otkriven *M. tuberculosis*, a raspon pozitivnih kultura među laboratorijima se kretao od 0,3 do 14,4%. Ukupno je izolirano 1.081 soj mikobakterija (Tablica 1).

Tijekom 2020. godine genotipizirano je 170 izolata *M. tuberculosis* iz cijele Hrvatske. U skladu s očekivanim, *M. tuberculosis* je najčešće izoliran iz plućnih uzoraka, a među a među 9 (5,3%) izvanplućnih bakteriološki dokazanih slučajeva TBC najčešća je bila TBC tkiva (koji nisu svrstani u druge grupe) (N=5), limfoglandularna TBC (N=2), te slijede TBC pleure (N=1) i urogenitalnog sustava (N=1).
Tijekom 2020. godine iz humanih kliničkih materijala nije izoliran *M. bovis*, dok je *M. bovis* – BCG soj izoliran kod tri pacijenta (9 izolata).

Među 1.081 izoliranih sojeva mikobakterija, *M. tuberculosis* i dalje dominira s 855 (79,1%) izolata. Udio netuberkuloznih mikobakterija (NTM) među izoliranim mikobakterijama smanjio se u odnosu na 2019. godinu, sa 26,5% na 20,0%. 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 2020. godini od uvjetno patogenih spororastućih mikobakterija najviše je izoliran *M. xenopi* (44 izolata), *M. avium* (22 izolata) te *M. intracellulare* (21 izolat) (Tablica 2.). Od brzorastućih mikobakterija najveći broj izolata odnosio se na *M. fortuitum* (23 izolata), a slijede ga *M. chelonae* sa 13 izolata i *M. abscessus* sa 10 izolata. *M. gordonae* kao saprofitna mikobakterija je identificiran u 24% izolata NTM. Najčešće se radi o kontaminaciji uzoraka, slučajnim nalazima i prolaznim kolonizacijama. U 2020. godini je otkriveno 48 osoba sa zadovoljenim mikrobiološkim kriterijima za dijagnozu mikobakterioze (dva i više izolata, ili izolat iz asp. bronha). Kod 15 bolesnika izoliran je *M. xenopi*, a slijede ga *M.*

intracellulare i *M. gordonae* koji su izolirani kod po sedam bolesnika, te *M. avium* kod šest te *M. fortuitum* kod četiri.
Nastavljen je izrazito povoljan trend broja rezistentnih sojeva *M. tuberculosis*. Od 855 testiranih sojeva samo je 41 (4,8%) bilo rezistentno na prvu liniju antituberkulotika, a otkriveni su kod devet bolesnika s rezistentnom tuberkulozom (Tablica 3.). Među bolesnicima s rezistentnim oblikom tuberkuloze, njih osam (88,9%) je imalo monorezistentni oblik, dok je jedan izolat multirezistentan.

Mycobacteria isolated in Croatia in 2020

Data from the Tuberculosis Registry of the Epidemiology Service of the Croatian Institute of Public Health indicate a decline in the number of tuberculosis patients (TB). However, it should be taken into account that the whole of 2020 was a pandemic year. Although epidemiological data are still being processed, 188 new cases have been reported so far in the last year, which gives an incidence rate of 4.6 / 100,000, while in 2019 the incidence rate was 7.5 / 100,000 inhabitants.

To analyze data on TB bacteriological diagnostics, the "Questionnaire on the work of TB laboratories in 2020" 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 22,100 clinical samples were examined for TB, which is a decrease of almost 40% compared to the number of samples in 2019. Although the recommended minimum annual number of samples to be processed for mycobacteria is 2000, only four laboratories in 2020 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 3.9% of samples, *M. tuberculosis* was detected by cultivation, and the range of positive cultures among laboratories ranged from 0.3 to 14.4%. A total of 1,081 strains of mycobacteria were isolated (Table 1).

During 2020, 170 isolates of *M. tuberculosis* were genotyped. As expected, *M. tuberculosis* was most often isolated from lung samples, and among 9 (5.3%) extrapulmonary bacteriologically confirmed cases of TB, the most common was tissue TB (not classified in other groups) (N = 5), lymphoglandular TB (N = 2), followed by pleural TB (N = 1) and urogenital TB (N = 1).
During 2020, *M. bovis* was not isolated from human clinical samples, while *M. bovis* - BCG strain was isolated in three patients (9 isolates).

Among 1,081 isolated strains of mycobacteria, *M. tuberculosis* still dominates with 855 (79.1%) isolates. The number of non-tuberculous mycobacteria (NTM) among isolated mycobacteria decreased compared to 2019, from 26.5% to 20.0%. 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 2020 prevailed isolates of *M. xenopi* (44 isolates), *M. avium* (22 isolates) and *M. intracellulare* (21 isolates) (Table 2). In the rapidly growing group the most commonly isolated species were *M. fortuitum* (23 isolates), followed by *M. chelonae* with 13 isolates and *M. abscessus* with 10 isolates. *M. gordonae* as a saprophytic mycobacterium was identified in 24% of NTM isolates. In most cases, the isolation was the result of specimen contamination, accidental finding and transient colonization. In 2020, a total of 48 cases fulfilled the microbiological criteria for mycobacteriosis (two or more isolates). *M. xenopi* was isolated in 15 patients, followed by *M. intracellulare* and *M. gordonae*, which were isolated in seven patients each, *M. avium* in six and *M. fortuitum* in four.

The number of resistant *M. tuberculosis* strains and, by extension, number of resistant TB cases has demonstrated a continuous favorable trend. Of the 855 strains tested, only 41 (4.8%) were resistant to

first-line antituberculotics, and were detected in nine patients with resistant tuberculosis (Table 3). Among patients with the resistant form of tuberculosis, eight (88.9%) had the monoresistant form, while one isolate was multiresistant.

Tablica / *Table* **1.**
Mikobakterije izolirane u Hrvatskoj, 2010. – 2020. /
Mycobacteria strains isolated in Croatia, 2010-2020

Godina	Ukupno mikobakterija	*M. tuberculosis*		*M. bovis*		Netuberkulozne mikobakterije	
		Broj	%	*M. bovis*	BCG soj	Broj	%
2010.	2712	2283	84,2	-	1	429	15,8
2011.	2351	2000	85,0	-	4	347	14,8
2012.	2108	1807	85,7	1	6	294	14,0
2013.	2153	1748	81,2	-	1	402	18,8
2014.	1969	1541	78,3	-	1	423	21,5
2015.	1880	1505	80,1	-	6	375	19,9
2016.	2021	1587	78,5	-	5	428	21,2
2017.	1596	1246	78,1	-	4	350	21,9
2018.	1689	1387	82,1	-	1	302	17,9
2019.	1751	1281	73,2	4	1	464	26,5
2020.	1081	855	79,1	-	9	217	20,0

Tablica / *Table* **2.**
Netuberkulozne mikobakterije (NTM) izolirane u Hrvatskoj u 2020. /
Nontuberculous mycobacteria (NTM) isolated in Croatia in 2020

	Vrsta	**Broj**	**%**
Uvjetno patogene mikobakterije	*M. xenopi*	44	20,3
	M. avium	22	10,1
	M. intracellulare	21	9,7
	M. chimaera	1	0,5
	M. kansasii	10	4,6
	M. fortuitum	23	10,6
	M. chelonae	13	6,0
	M. abscessus	10	4,6
	M. mucogenicum	7	3,2
Saprofitne mikobakterije	*M. gordonae*	52	24,0
	Mycobacterium sp.	14	6,5
Ukupno		**217**	**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

OSJETLJIVOST GONOKOKA U HRVATSKOJ U 2020

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Antimikrobna rezistencija u gonokoka - Kvartalni sažetak (prosinac 2020. - veljača 2021.) publikacija iz Europe i svijeta povezanih s promjenom obrazaca rezistencije kod Neisseria gonorrhoeae

Godine 2020. koja je obilježena COVID-19 pandemijom, na žalost, nismo uspjeli sakupiti izolate Neisseria gonorrhoeae (NG) na razini RH, kao prošlih godina, zbog velike uključenosti svih djelatnika HZJZ-u dijagnostiku. Iako smo tijekom 2019. god. sakupili više od 70 NG izolata iz cijele RH, taj trend je prekinut, te bismo ga željeli nastaviti tijekom 2021.

U ovom izvješću stoga, prenosimo informacije i pregled literature koje dobivamo na kvartalnoj razini iz Europskog centra za kontrolu i prevenciju bolesti (ECDC), a odnose se na podatke o rezistenciji NG na globalnom nivou, trendove razvoja rezistencije i aktualne protokole izvođenja testova osjetljivosti i preporučenu terapiju.

Izabrali smo najaktualnije izvješće o kvartalu od prosinca 2020.-veljače 2021, te prikazali i popis aktualne literature koja može pojasniti navedenu problematiku.

U ovom tromjesečju objavljena je jedna publikacija vezana za gonokoknu antimikrobnu rezistenciju (AMR) u Španjolskoj. Uočeno je da je rezistencija na ceftriakson i cefiksim niska (0,2%, odnosno 1,7%) s 12,1% rezistentnih na azitromicin i 56,2% rezistentnih na ciprofloksacin među 2574 izolata Neisseria gonorrhoeae prikupljenih u deset bolnica u Španjolskoj od travnja 2018. do rujna 2019. Izolati su također testirani na gentamicin i fosfomicin s vrijednostima MIC50 i MIC90 od 4 i 8 mg / L, odnosno 24 i 48 mg / L.

Globalno je objavljena publikacija o 540 izolata N. gonorrhoeae prikupljenih iz osam kineskih provincija u 2018. godini, koja je identificirala meropenem kao potencijalno mogući lijek za liječenje izuzetno rezistentnih sojeva N. gonorrhoeae. Minimalne inhibitorne koncentracije (MIC) za meropenem, fosfomicin, berberin hidroklorid i doksiciklin utvrđene su metodom agar dilucije. Svi izolati pokazali su MIC ≤ 0,125 mg / l za meropenem, uključujući 24 izolata smanjene osjetljivosti na ceftriakson. U drugoj studiji iz Kine, molekularnom epidemiologijom 909 izolata N. gonorrhoeae prikupljenih između 2014. i 2018. u Shenzenu te prethodno ispitane osjetljivosti, Kina je identificirala MLST ST7365 i ST7360 kao povezane sa smanjenom osjetljivošću na ceftriakson. Druga genetska studija iz Indianapolisa u SAD-u identificirala je 14 visoko rezistentnih izolata N. gonorrhoeae na azitromicin među 1016 izolata prikupljenih u jednoj klinici između 2017. i 2018. Genomska analiza tih izolata pokazala je visok stupanj genetske povezanosti sugerirajući održivi prijenos soja unutar Indianapolisa. Molekularnom epidemiologijom sojeva povezanih s uočenim porastom rezistencije na azitromicin u Njemačkoj sa 4,3% u 2016. na 9,2% u 2018. godini utvrđeno je da je pretežno uzrokovana klonalnim širenjem NG-MAST G12302.

Istražen je potencijal gentamicina za upotrebu u liječenju N. gonorrhoeae u Novom Južnom Walesu. Od 2768 izolata N. gonorrhoeae prikupljenih u Novom Južnom Walesu između 2015. i 2020., srednja vrijednost MIC-a za gentamicin iznosila je 4 mg / L, što upućuje da će gentamicin u budućnosti biti opcija za liječenje. U ovom su tromjesečju identificirana još dva potencijalna kandidata za buduća liječenja; utvrđeno je da natrijev tetrafenilborat pokazuje visoku baktericidnu aktivnost i specifičnost protiv N. meningitidis i N. gonorrhoeae dok na druge blisko srodne vrste komenzala, kao što je N. lactamica, manje utječe čak i pri pet puta višim dozama. Testiranjem pet kliničkih i jednog kontrolnog WHO soja pokazalo se da novi spojevi N- (1,3,4-oksadiazol-2-il) benzamida HSGN-237 i HSGN-238 djeluju snažno protiv N. gonorrhoeae. Budući rad će biti usmjeren na razvoj manje hidrofobnih analoga ovih spojeva koji poboljšavaju MIC u prisutnosti seruma. Također je objavljen pregled s naglaskom na antivirulentne terapijske mogućnosti liječenja gonoreje koje se mogu koristiti kao dodatak antibioticima ili kao pomoć pri pročišćavanju imunološkog sustava domaćina.

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.

U ovom su kvartalu objavljene dvije publikacije s ažuriranim CDC smjernicama za liječenje gonoreje. Nove smjernice sada 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. Objavljen je i pregled baze podataka korištene za informiranje o europskim smjernicama za liječenje gonoreje 2020. Studija slučaja iz Nevade, SAD, dokumentirala je prvu identifikaciju N. gonorrhoeae koja u sebi sadrži mozaični alel PenA60 koji smanjuje osjetljivost na ceftriakson u Sjedinjenim Državama. Soj je izoliran iz kulture uretre muškog heteroseksualca u listopadu 2019. godine koji je uspješno izliječen s 250 mg intramuskularnog ceftriaksona uz 1 g azitromicina oralno. U prosincu 2019. u Južnoj Nevadi nisu otkriveni daljnji slučajevi N. gonorrhoeae koja nosi penA60, niti bilo koji daljnji slučaj u nacionalnom GISP projektu s izolatima prikupljenim u 2019.

Važnost problema širenja izolata NG naglašava i činjenica da je Vlada Velike Britanije najavila financiranje dodatnih 1,5 milijuna funti na 3,5 milijuna funti za potporu Global Antibiotic Research and Development Partnership (GARDP) u razvoju i dostupnosti zoliflodacina kao lijeka za gonoreju.

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Antimicrobial resistance in Neisseria gonorrhoae - Quarterly summary (December 2020 – February 2021) publications from Europe and globally related to changing resistance patterns in Neisseria gonorrhoeae

In the 2020, marked by the COVID-19 pandemic, unfortunately, we were unable to collect NG isolates in Croatia due to the high involvement of all CIPH laboratory staff in resolving the corona diagnostics. Although during 2019 were collected more than 70 isolates from all over the Republic of Croatia, this trend has been interrupted, and we would like to continue it during 2021.

In this report, therefore, we would like to transfer the information we receive on a quarterly basis from the EDCD, relating to data on NG resistance globally, resistance development trends, and current protocols for performing susceptibility tests and recommended therapy. In this quarter, one publication related to gonococcal antimicrobial resistance (AMR) in Spain was published. Ceftriaxone and cefixime resistance were observed to be low (0.2% and 1.7% respectively) with 12.1% resistant to azithromycin and 56.2% resistant to ciprofloxacin amongst the 2574 Neisseria gonorrhoeae isolates collected at ten hospitals in Spain between April 2018 to September 2019. Isolates were also tested with gentamicin and fosfomycin with MIC50 and MIC90 values of 4 and 8 mg/L and 24 and 48 mg/L respectively.

Globally there was a publication on 540 N. gonorrhoeae isolates collected from eight Chinese provinces in 2018 which identified meropenem as a potential treatment option for extensively resistant N. gonorrhoeae strains. The minimum inhibitory concentrations (MICs) to meropenem, fosfomycin, berberine hydrochloride, and doxycycline were determined using the agar dilution method. All isolates showed the MIC ≤0.125 mg/L to meropenem including 24 ceftriaxone-decreased susceptibility isolates.

In another study from China, the molecular epidemiology of 909 previously susceptibility tested N. gonorrhoeae isolates collected between 2014 and 2018 in Shenzen, China identified MLST ST7365 and ST7360 as associated with decreased susceptibility to ceftriaxone. Another genetic study in Indianapolis, USA identified 14 high-level azithromycin resistant N. gonorrhoeae isolates amongst 1016 isolates collected at a single clinic between 2017 and 2018. Genomic analysis of these isolates suggested a high-degree of genetic relatedness suggesting sustained transmission of the strain within Indianapolis. The molecular epidemiology of strains associated with the observed azithromycin resistance increase in Germany from 4.3% in 2016 to 9.2% in 2018 was investigated and found to be predominately caused by the clonal spread of NG-MAST G12302.

The potential for gentamicin to be utilised for N. gonorrhoeae treatment in New South Wales was investigated. Of 2768 N. gonorrhoeae isolates collected in New South Wales between 2015 and 2020 the median gentamicin MIC was 4 mg/L suggesting gentamicin is a viable future treatment option. Two other potential candidates for future treatment were identified this quarter; sodium tetraphenylborate was found to display high bactericidal activity and specificity against both N. meningitidis and N. gonorrhoeae with other closely related commensal species such as N. lactamica, to be less affected even at 5-fold higher doses. Novel N-(1,3,4-oxadiazol-2-yl) benzamides compounds HSGN-237 and HSGN-238 have been demonstrated to potent activity against N. gonorrhoeae by testing of five clinical and one WHO control strain. Future work will be focused on developing less hydrophobic analogs of these compounds that improve MICs in the presence of serum. There was also a review published focusing on anti-virulence therapeutic options for gonorrhoea treatment which could be used as antibiotic adjuvants or used to assist in host immune system clearance.

The in vitro activity of zoliflodacin was tested against a panel of 986 N. gonorrhoeae isolates collected from men in Nanjing, China between 2014 and 2018. All isolates were susceptible to spectinomycin but resistant to ciprofloxacin with the MICs of zoliflodacin from ≤0.002 to 0.25 mg/liter with the percentage of isolates with lower zoliflodacin MICs significantly declining annually.

Two publications on the CDCs updated gonorrhoea treatment guidelines were published this quarter. The new guidelines now recommend a single 500 mg intramuscular dose of ceftriaxone for uncomplicated gonorrhoea or a single 240 mg intramuscular dose of gentamicin and a single 2 g oral dose of azithromycin for patients with a cephalosporin allergy. Test of cure is recommended for all patients with pharyngeal gonorrhoea one to two weeks post-treatment. A background review for the evidence base used to inform the 2020 European gonorrhoea treatment guidelines was also published.

A case study from Nevada, USA documented the first identification of N. gonorrhoeae harbouring a mosaic penA60 allele conferring reduced susceptibility to ceftriaxone in the United States. The strain was isolated from a urethral culture from a male heterosexual in October 2019 who was successfully treated with 250 mg intramuscular ceftriaxone plus 1 g oral azithromycin. No further cases of penA60 harbouring N. gonorrhoeae were identified in Southern Nevada in December 2019 nor any further cases detected in the nationwide GISP project with isolates collected in 2019. The importance of the problem of AMR in NG and urgent need for development of new drugs, is stressed with the fact the UK government has announced an additional £1.5 million of funding to add to the £3.5 million to support the Global Antibiotic Research and Development Partnership (GARDP) in the development and availability of zoliflodacin as a treatment for gonorrhoea.

POGLAVLJE / CHAPTER 4.

PRAĆENJE REZISTENCIJE NA ANTIBIOTIKE U INVAZIVNIH IZOLATA

ANTIBIOTIC RESISTANCE SURVEILLANCE IN INVASIVE ISOLATES

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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

U 2020.g. prikupljeno je otprilike 25% manje izolata nego prijašnjih godina. Razlog tome su vjerojatno različite organizacijsko-logističke poteškoće koje je sa sobom donijela pandemija izazvana uzročnikom SARS-CoV-2. Zbog preopterećenja mikrobioloških laboratorija, moguće je da nisu svi invazivni izolati prijavljeni, no u različitim fazama pandemije bila je iz epidemioloških razloga smanjena aktivnost u bolnicama, što je rezultiralo i manjim brojem dijagnosticiranih bakterijemija. Usprkos svemu, prijavljen je reprezentativan broj izolata iz većine laboratorija u Hrvatskoj. Broj laboratorija i broj prikupljenih invazivnih izolata pojedinih vrsta prikazani su u Tablici 1.

Po prvi puta su podaci o izolatima za 2020.g. slani u Referentni centar za praćenje rezistencije bakterija na antibiotike, u Klinici za infektivne bolesti, u elektronskom obliku, a za laboratorije koji to nisu bili u mogućnosti izvesti, ostavljena je mogućnost slanja podataka u obliku formulara. Podaci koji su poslani na formularima obrađeni su u Referentnom centru za praćenje rezistencije na antibiotike zajedno sa svim pristiglim elektronskim bazama podataka. 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 Referentni centar za praćenje rezistencije bakterija na antibiotike se šalju i prikupljaju svi invazivni izolati praćeni u sklopu EARS-Net programa sa svrhom retestiranja izolata s rijetkim fenotipom i eventualne daljnje obrade. Tijekom 2020.g. prikupljeno je 55 izolata *S. pneumoniae,* 828 izolata *E. coli,* 270 izolata *K. pneumoniae*, 424 izolata *S. aureus,* 250 izolata enterokoka (162 *E. faecalis* i 88 *E. faecium* izolata), 165 izolata *P. aeruginosa*, te 225 izolata *Acinetobacter* spp. (Tablica 1).

Iako u 2020.g. bilježimo manji broj ukupno prijavljenih invazivnih izolata, broj prijavljenih invazivnih izolata *Acinetobacter* spp. je najveći ikad (225). Zabilježeni porast se vjerojatno može objasniti olakšanim širenjem *Acinetobacter* spp. unutar kohortiranih pacijenata inficiranih sa SARS-CoV-2. Rezistencija *Acinetobacter* spp. na karbapeneme je pri tome i dalje izuzetno visoka (96%). Izrazito je

zabrinjavajući porast izolata *Acinetobacter* spp. u jedinicama za intenzivnu njegu (ICU) odakle potječe čak 73% izolata, što je očigledan porast s obzirom na podatke iz prijašnjih godina (40% izolata iz ICU 2019).

Slična situacija se primijećuje i kod izolata *S. aures*. Broj prijavljenih izolata *S. aureus* je veći nego prijašnjih godina (424 u 2020.g; 374 u 2019.g.), a slijedi ga i veći broj prijavljenih MRSA izolata, što je rezultiralo većim udjelom MRSA izolata nego prošle godine (29% u 2020.g; 25% u 2019.g.). Povećan udio MRSA (21%) je registriran i kod ukupnog broja izoliranih stafilokoka iz svih uzoraka (Poglavlje 1).

Trend porasta glikopeptidne rezistencije u *Enterococcus faecium* je i dalje prisutan s najvišom stopom rezistencije do sada (33%), dok je rezistencija na glikopeptide kod *E. faecalis* slična kao i prijašnjih godina (1%). Stope visoke rezistencije na aminoglikozide su i dalje visoke u obje vrste *Enterococcus* spp.

Kod invazivnih izolata *P.aeruginosa* primijećena su dva zanimljiva trenda zadnjih godina. Prvi trend je vezan za pad broja prijavljenih izolata *P. aeruginosa*, koji doseže svoj minimun 2020.g. (165), dok je drugi vezan za pad stopa rezistencije u svim klasama praćenih antibiotika. Iako se radi o trendovima uočenim tijekom nekoliko zadnjih godina, potreban je oprez u interpretaciji pada broja izolata u 2020.g. s obzirom da su podaci za neke od laboratorija u 2020.g. insuficijentni.

Trend porasta stopa rezistencije kod invazivnih izolata *K.pneumoniae* uočen je u svim klasama antibiotika osim u aminoglikozida gdje se stope rezistencije kreću oko 40% zadnjih nekoliko godina. Najviše zabrinjava stopa rezistentnih izolata na karbapeneme (imipenem i/ili meropenem) koja i dalje raste (19% u 2020.g., 12% u 2019.g.).

Stopa rezistencije *E. coli* na 3. generaciju cefalosporina nije se bitno mijenjala u odnosu na prošlu godinu (17%). 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 31%, nešto viša nego prošle godine (27%).

Pad u broju prijavljenih izolata je posebno očit kod invazivnih izolata *S. pneumoniae* kojih je tri puta manje nego prijašnjih godina (55 izolata 2020.g., 156 izolata 2019.g.). Različiti mogući razlozi se spominju u literaturi a osnovni razlog je vjerojatno smanjena cirkulacija respiratornih patogena zbog epidemioloških mjera usmjerenih na kontrolu širenja SARS-CoV-2. Među prijavljenim izolatima se ne primjećuje bitan odmak od dosadašnjih stopa rezistencije, ali je rezistencija na ključne antibiotike ipak nešto viša. Neosjetljivost na penicilin među invazivnim izolatima pneumokoka u 2020.g. (24%) je nešto viša od prošlogodišnje stope neosjetljivosti (20%), dok je stopa rezistencije na makrolide najviša ikad zabilježena (40%).

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

Number of isolates collected and referred to Reference Center in 2020 has fallen by 25%. The reasons are probably linked to variety of difficulties connected with SARS-CoV-2 pandemic that affected all parts of health care system. There was an obvious work overload for microbiology laboratories so probably not all invasive isolates were reported to the surveillance network and also in some phases of pandemic hospital activities were reduced for epidemiological reasons, which resulted in a smaller number of diagnosed bacteraemia cases. Regardless, a representative number of isolates from most laboratories in Croatia were reported. The number of laboratories reporting and the number of invasive isolates collected are shown in Table 1.

For the first time, data on isolates for 2020 was sent to the Reference Centre for Antibiotic Resistance Surveillance at the University Hospital for Infectious Diseases electronically, and for laboratories that were not able to report data electronically, the possibility of sending data on the paper forms was still an option. The data sent on forms were processed in the Reference Centre for Antibiotic Resistance Surveillance and combined with electronic databases. 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 2020, 55 isolates of *S. pneumoniae*, 828 isolates of *E. coli*, 270 isolates of *K. pneumoniae*, 424 isolates of *S.aureus*, 250 enterococcal isolates (162 *E. faecalis* and 88 *E. faecium* isolates), 165 isolates of *P.aeruginosa* and 225 isolates of *Acinetobacter* spp. were collected (Table 1).

Although in 2020 a total number of reported invasive isolates is smaller, the number of invasive *Acinetobacter* spp. isolates is the highest ever (225). The observed increase can probably be explained by the facilitated spread of *Acinetobacter* spp. within cohorted COVID patients. The resistance of *Acinetobacter* spp. to carbapenems is still extremely high (96%). Especially worrying is the increase in the number of *Acinetobacter* spp. isolates in intensive care units (ICU). As much as 73% of isolates originate from ICU, which is an obvious increase compared to data from previous years (40% of isolates from ICU in 2019).

A similar situation is observed with *S. aureus* isolates. The number of reported *S. aureus* isolates is higher than in previous years (424 in 2020; 374 in 2019), and in adition MRSA rates increased (29% in 2020; 25% in 2019). An increased proportion of MRSA (21%) was also registered in the total number of staphylococci isolated from all samples (Chapter 1).

The increasing trend in glycopeptide resistance in *Enterococcus faecium* is still present with the highest resistance rate to date (33%), while glycopeptide resistance in *E. faecalis* is similar to previous years (1%). High rates of aminoglycoside resistance remain high in both species of *Enterococcus* spp.

Two interesting trends have been observed in invasive isolates of *P. aeruginosa* in recent years. First trend relates to the decrease in the number of reported isolates of *P. aeruginosa* which reaches its minimum in 2020 (165) and second trend is related to the decrease in resistance rates for all classes of antibiotics. Although these are trends observed over the last few years, caution is needed in interpreting the decreasig numbers of isolates in 2020 given that the data for some of the laboratories are incomplete for 2020.

The increasing resistance trends in invasive *K. pneumoniae* isolates have been observed in all classes of antibiotics except aminoglycosides where resistance rates have been around 40% in the last few years. Of most concern is the rate of carbapenem-resistant isolates (imipenem and / or meropenem) which continues to rise (19% in 2020, 12% in 2019).

The resistance of *E. coli* to the 3rd generation cephalosporins did not change significantly compared to last year (17%). 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 31%, higher than last year (27%).

The decrease in the number of reported isolates is particularly evident in invasive *S. pneumoniae* isolates and the number of isolates reported in 2021 is three times lower than in previous year (55 isolates in 2020, 156 isolates in 2019). There are various possible reasons for this decrease discussed in the literature and the main reason is probably the reduced transmission of respiratory pathogens due to epidemiological measures aimed at controlling the spread of SARS-CoV-2. There is no significant change in resistance rates for most antibiotics, but resistance to key antibiotics is slightly higher. Reduced susceptibility to penicillin among invasive pneumococcal isolates in 2020 (24%) is slightly higher than last year's rate (20%), and the macrolide resistance rate is the highest ever recorded (40%).

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.-2020. /
Number of laboratories and number of isolates reported for the period 2001-2020

Godina	*S. pneumoniae*		*S. aureus*		*E. coli*		*Enterococcus* spp.		*K. pneumoniae*		*P. aeuroginosa*		*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

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	2007 %	2008 %	2009 %	2010 %	2011 %	2012 %	2013 %	2014 %	2015 %	2016 %	2017 %	2018 %	2019 %	2020 %
S. pneumoniae	Penicillin R	1	4	6	7	1	1	4	1	1	1	1	1	2	1
	Penicillin I+R	18	17	19	21	18	23	27	26	20	22	21	20	20	24
	Macrolides R	8	14	8	29	24	28	34	28	19	33	37	33	30	40
S. aureus	Oxacillin / Met R	38	35	37	27	27	22	24	21	25	25	28	26	25	29
E. coli	Aminopenicillins R	51	53	55	55	55	52	54	54	56	57	59	58	57	58
	Aminoglycosides R	6	6	8	6	7	7	7	10	12	14	16	14	13	15
	Fluoroquinolones R	13	15	16	17	20	17	21	20	25	28	30	30	27	30
	3. gen Cef R	3	4	5	8	7	8	9	11	13	12	16	14	15	17
	ESBL					9	7	9	11	13	14	16	15	17	16
E. faecalis	Aminopenicillins R	2	5		5	1	5	9	6	4	7	5	3	2	4
	HL Aminoglycosides R	37	46	36	37	33	39	35	33	35	33	32	34	24	38
	Glycopeptides R	<1	<1	<1	<1	1	<1	<1	0	0	0	<1	2	2	1
E. faecium	Aminopenicillins R	78	79		82	98	98	90	94	97	98	96	98	94	99
	HL Aminoglycosides R	59	65	68	60	66	61	55	64	53	65	50	64	51	37
	Glycopeptides R	2	6	11	12	2	0	7	10	26	23	19	25	26	33
K. pneumoniae	Aminoglycosides R	38	51	47	49	43	45	51	48	40	31	28	33	40	38
	Fluoroquinolones R	34	44	51	48	43	43	45	46	50	44	50	49	59	54
	3. gen Cef R	40	54	53	56	50	44	50	48	46	42	41	42	51	52
	ESBL					51	52	50	48	47	46	41	43	51	52
	Carbapenems I+R					<1	<1	1	2	3	2	5	7	16	19
	Carbapenem R					0	0	0	0	0	0	0	2	12	19
P. aeruginosa	Piperacillin R	30	34		23										
	Piperacillin / Tazobactam R				16	23	18	23	32	25	20	16	11	14	10
	Ceftazidime R	14	13	11	12	17	14	20	28	20	23	21	19	20	19
	Carbapenems R	26	30	31	26	30	21	25	35	37	41	30	27	23	30
	Aminoglycosides R	40	39	37	26	34	26	24	37	34	32	27	23	20	10
	Fluoroquinolones R	30	33	29	27	34	24	23	28	37	38	39	29	26	23
A. baumannii	Carbapenems R							91	88	89	95	96	95	93	96

Tablica 3. / *Table 3.*
Prikaz gram-pozitivnih invazivnih izolata u 2020.g. prema demografskim podacima pacijenata / *Selected details on gram-positive invasive isolates from the reporting period 2020*

	S.pneumoniae		***S.aureus***		***Enterococcus* spp.**	
	n=55		**n=424**		**n=250**	
	% tot	**% PNPS**	**% tot**	**% MRSA**	**% tot**	**% VRE**
UZORAK ***SAMPLE***						
Krv / Blood	91	14	99	99	99	13
Likvor / CSF	9	0	<1	<1	<1	0
SPOL ***GENDER***						
M	53	10	61	31	71	10
Ž / F	44	17	38	26	27	18
Nepoznato / Unknown	3	0	1	50	2	25
DOB ***AGE***						
0-4	25	7	1	0	2	0
5-19	4	0	4	14	<1	100
20-64	38	5	34	25	30	12
>65	33	27	62	33	67	13
Nepoznato / Unknown	0	0	0	0	0	0
ODJEL ***DEPARTMENT***						
Intenzivna / ICU	18	10	12	34	23	16

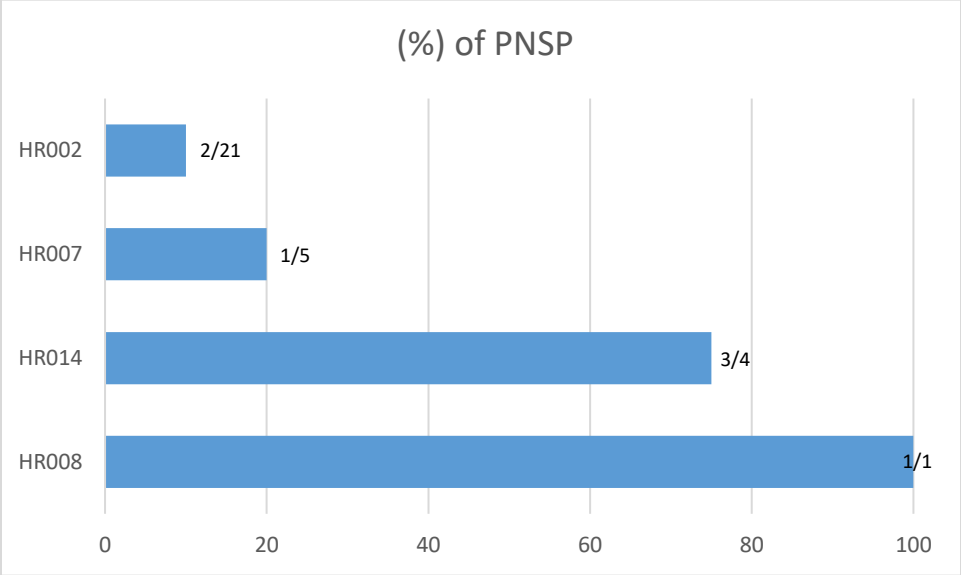
PNSP=Penicillin Non-Susceptible *S. Pneumoniae* MRSA=Methicillin Resistant *S.aureus* VRE=Vancomycin Resistant Enterococcus

Tablica 4. / *Table 4.*
Prikaz gram-negativnih invazivnih izolata u 2020.g. prema demografskim podacima pacijenata
/ Selected details on gram-negative invasive isolates from the reporting period 2020

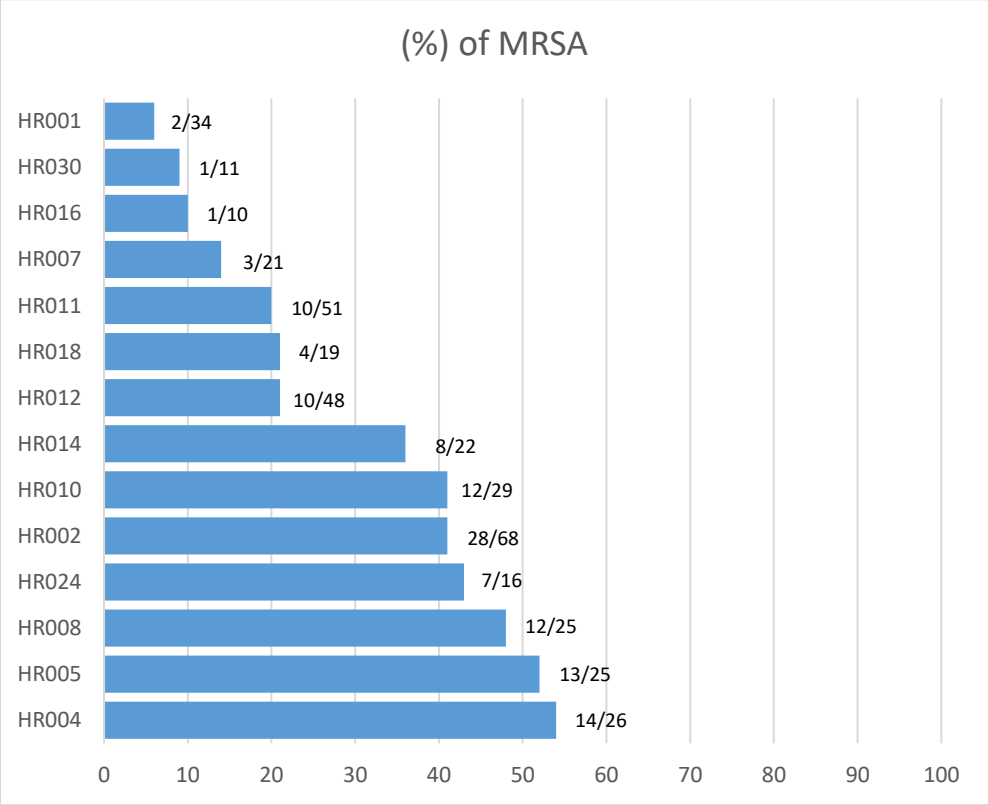
	E. coli			*Acinetobacter* spp.		*K.pneumoniae*		*P.aeuroginosa*	
	n=828			n=225		n=270		n=165	
	% tot	% FREC	% CREC	% tot	% CRA	% tot	% CRKP	% tot	% CRPA
UZORAK ***SAMPLE***									
Krv / Blood	99	28	16	99	96	99	51	100	30
Likvor / CSF	<1	0	0	1	100	1	100	0	0
SPOL ***GENDER***									
M	44	34	18	73	97	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.

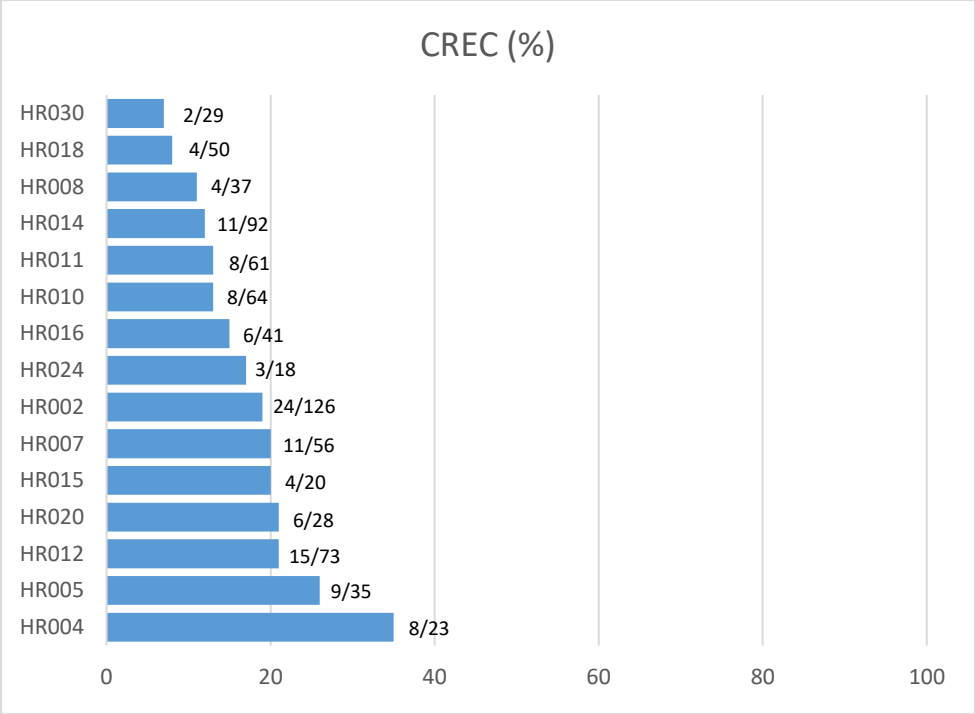
Slika 1. / *Figure 1.*
Udio (%) izolata *S. pneumoniae* smanjene osjetljivosti na penicilin (PNSP) po centrima /
Proportion (%) of penicillin non-susceptible S. pneumoniae (PNSP) by center



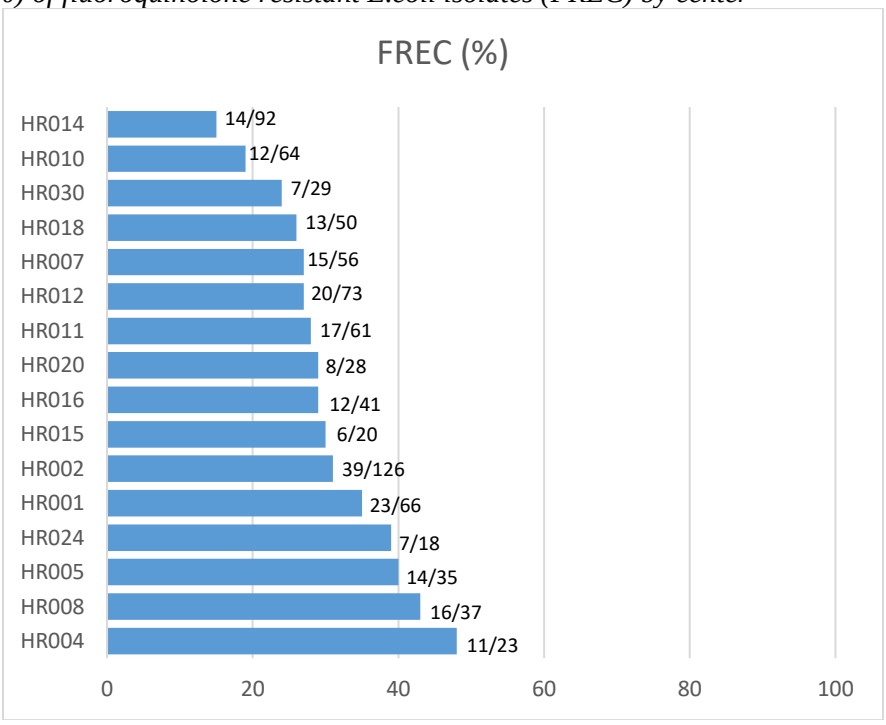
Slika 2. / *Figure 2.*
Udio (%) MRSA izolata po centrima /
Proportion (%) of MRSA isolates by center



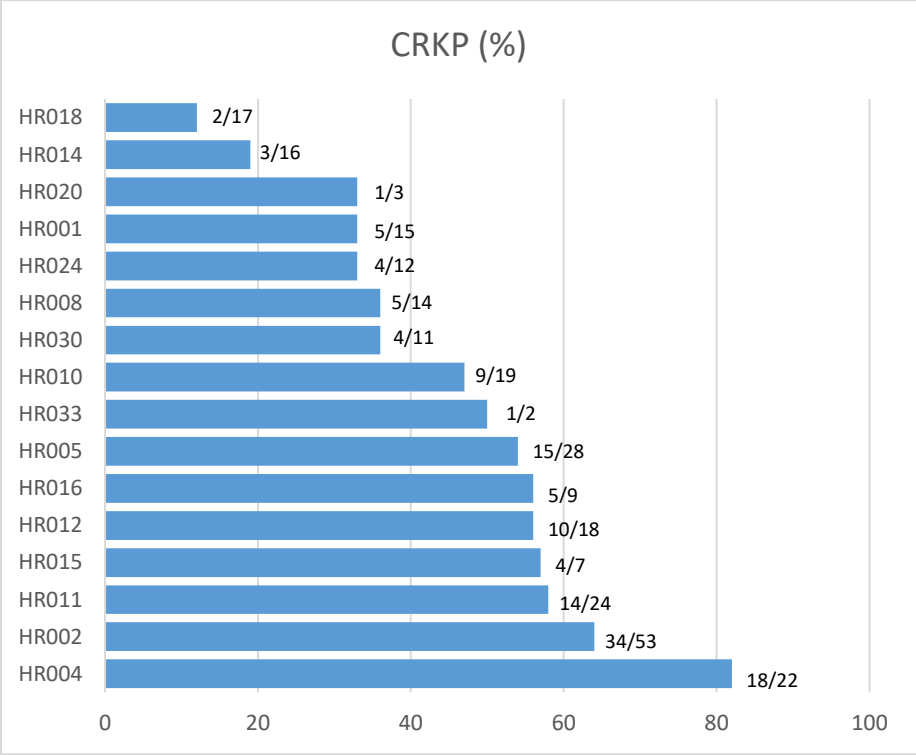
Slika 3. / *Figure 3.*
Udio (%) ceftazidim rezistentnih izolata *E. coli* (CREC) po centrima /
Proportion (%) of ceftazidime resistant E. coli isolates (CREC) by center



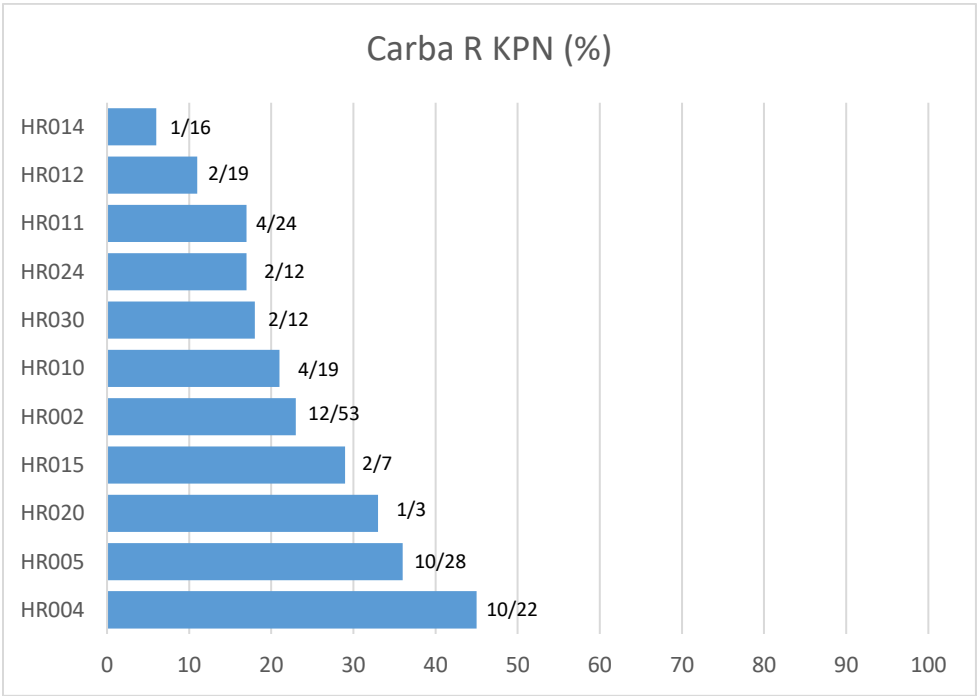
Slika 4. / *Figure 4.*
Udio (%) fluorokinolon rezistentnih izolata *E. coli* (FREC) po centrima /
Proportion (%) of fluoroquinolone resistant E.coli isolates (FREC) by center



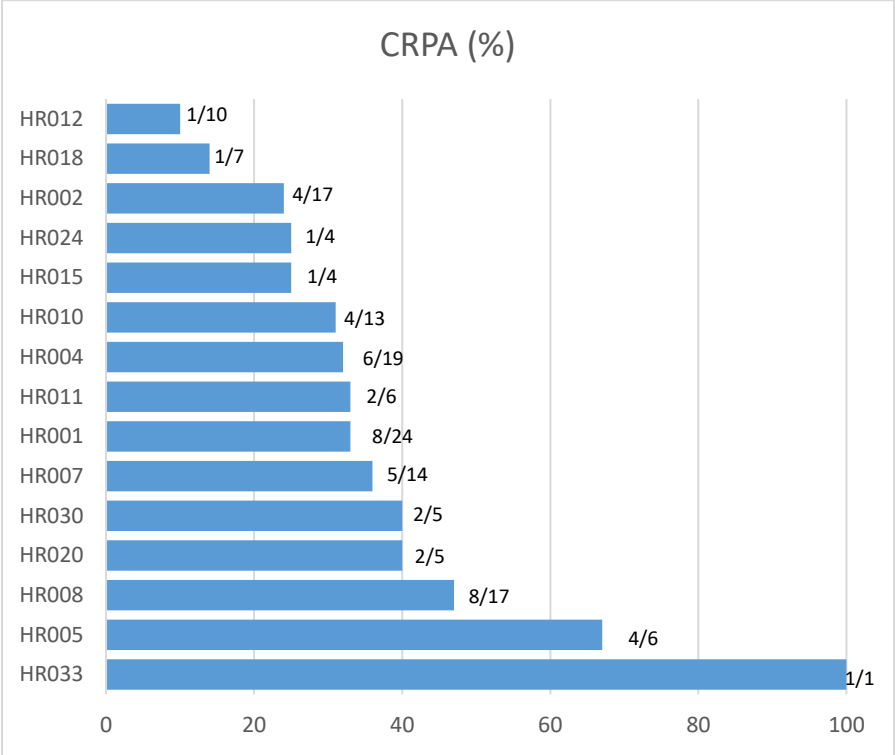
Slika 5. / *Figure 5.*
Udio (%) ceftazidim rezistentnih izolata *K. pneumoniae* (CRKP) po centrima /
Proportion (%) of ceftazidime resistant K. pneumoniae (CRKP) by center



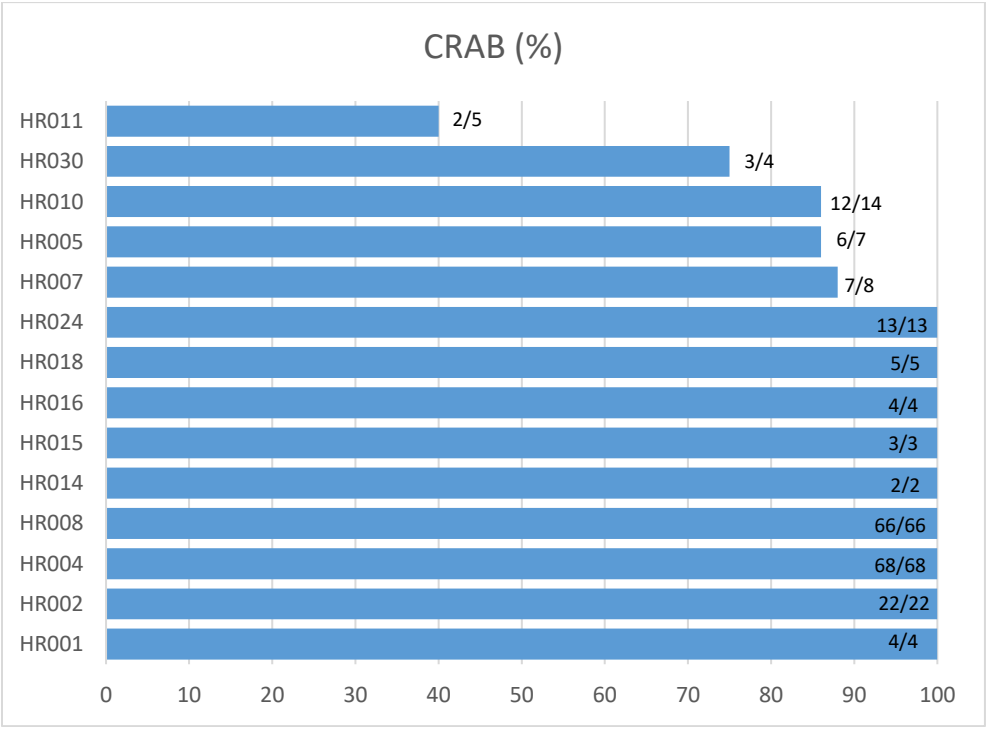
Slika 6. / *Figure 6.*
Udio (%) karbapenem rezistentnih izolata *K. pneumoniae* (Carb R KP) po centrima /
Proportion (%) of carbapenem resistant K. pneumoniae (Carb R KP) by center



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 2019. I 2020. GODINI

DISTRIBUTION OF CANDIDA SPECIES AND ANTIFUNGAL SUSCEPTIBILITY IN PATIENTS WITH CANDIDEMIA IN CROATIA, 2019-2020

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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 2019. i 2020. godini

Distribution of *Candida* species and antifungal susceptibility in patients with candidemia in Croatia, 2019-2020

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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 2019. i 2020. godini.

Učestalost vrsta *Candida* spp.

Za vrijeme dvogodišnjeg razdoblja ukupno je prikupljeno i analizirano 154 izolata *Candida* spp. u 2019. i 136 izolata u 2020. godini. Učestalost pojedinih *Candida* spp prikazana je u Tablici 1.

Najčešće prisutne vrste *Candida* spp u 2019. godini bile su *C. albicans* kod 38.31% (59/154), *C. parapsilosis* kod 33.77% (52/154) i *C. glabrata* kod 18.18% (28/154) bolesnika s kandidemijom a u 2020. godini *C. albicans* kod 36.76% (50/136), *C. parapsilosis* kod 27.94% (38/136) i *C. glabrata* kod 27% (19.85) bolesnika s kandidemijom.

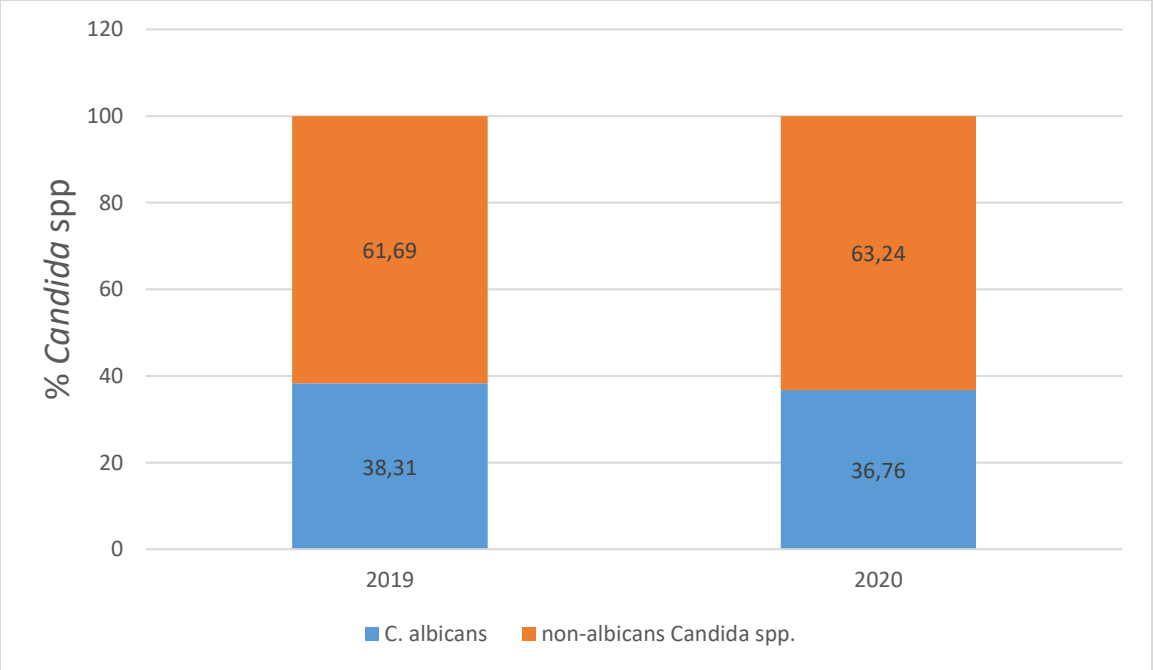
Tablica 1. Učestalost pojedinih vrsta *Candida* spp. kod bolesnika s kandidemijom u Hrvatskoj u 2019. i 2020. godini

Table 1. Incidence of different Candida spp.in patients with candidemia in Croatia in 2019 and 2020

Vrsta *Candida* spp.	2019 N (%)	2020 N (%)
Candida albicans	59 (38.31)	50 (36.76)
Candida parapsilosis	52 (33.77)	38 (27.94)
Candida glabrata	28 (18.18)	27 (19.85)
Candida krusei	7 (4.54)	9 (6.62)
Candida lusitaniae	4 (2.60)	2 (1.48)
Cadnida tropicalis	2 (1.30)	6 (4.41)
Candida dubliniensis	1 (0.65)	2 (1.48)
Candida fabianii	1 (0.65)	1 (0.73)
Candida kefyr	0	1 (0.73)
Candida methapsilosis	0	0
UKUPNO	154	136

Grafikon 1. Udio *C. albicans* i non-albicans vrsta u 2019. i 2020. godini među izolatima bolesnika s kandidemijom u Hrvatskoj

Figure 1. Proportion of C. albicans and non-albicans species in 2019 and 2020



Udio *C. albicans* i non-albicans vrsta u 2019. i 2020. godini među izolatima bolesnika s kandidemijom prikazan je na Grafikonu 1. Iako je *C. albicans* bila najzastupljenija vrsta u Hrvatskoj u 2019. i 2020. godini, postoji visoka učestalost *C. parapsilosis* na drugome mjestu koju slijedi *C. glabrata.* Rezultati našeg praćenja pokazali su da se udio *C. albicans* među izolatima bolesnika s kandidemijom u Hrvatskoj smanjio na manje od 50% (*shift*) u korist non-albicans *Candida* spp. i da se taj udio između 2019. i 2020. godine smanjio za 1.55%. 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 i načina provođenja mjera prevencije i kontrole infekcija.

Osjetljivost na antifungalne lijekove

Osjetljivost vrsta *Candida* spp u Hrvatskoj u 2019. i 2020. godini na amfotericin B, kaspofungin, mikafungin, anidulafungin i flukonazol prikazana je na grafikonu 2., 3., 4., 5. i 6.

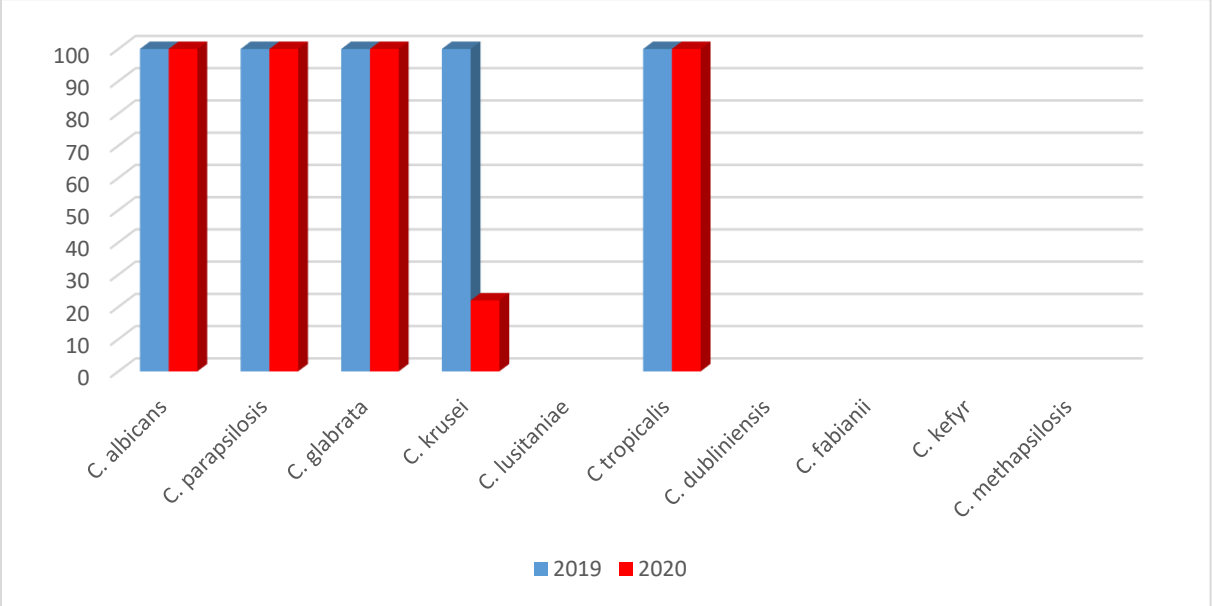
Osjetljivost na amfotericin B bila je 100% za *C. albicans, C. parapsilosis, C. glabrata i C. tropicalis,* a za *C. krusei* je 100% bila u 2019, a 22% u 2020. godini. Rezistencija *C. krusei* na amfotericin B nije ništa neuobičajeno no radi se o malom broju izolata , sveukupno 7 u 2019. godini i 9 u 2020. godini pa je na osnovu ovih podataka teško govoriti o značajnom porastu rezistencije *C. krusei* na amfotericin B (grafikon 2).

Ehinokandini pokazuju visoku djelotvornost na uzročnike kandidemija što je i očekivano. Osjetljivost na kaspofungin izolata *C. albicans* 2019. godine bila je 96, 61% , a u 2020. godini 100%. Izolati *C. parapsilosis* izolirani iz hemokultura su 2019. i 2020. godine bili 100% osjetljivi na kaspofungin, kao i izolati *C. glabrata, C. tropicalis,* i *C. krusei.* (grafikon 3). Mikafungin je pokazao sličnu djelotvornost pa su tako izolati *C. albicans* 2019. godine bili osjetljivi 96, 55% , a u 2020. godini 100%. Izolati *C. parapsilosis* izolirani iz hemokultura su 2019. godine bili 94,23% osjetljivi, a 2020. 100%. Izolati *C. glabrata, C. tropicalis,* i *C. krusei* bili su u obje godine 100% osjetljivi na mikafungin (grafikon 4). Anidulafungin pokazuje vrlo sličnu djelotvornost na uzročnike kandidemija pa su tako izolati *C. albicans* bili osjetljivi na anidulafungin 2019. i 2020. godine 98%. S druge strane izolati *C. parapsilosis* su 2019. bili osjetljivi 92%, a 2020. godine 84,21%. U obje godine su na anidulafungin izolati *C. glabrata, C. tropicalis,* i *C. krusei* osjetljivi 100%. (grafikon 5)

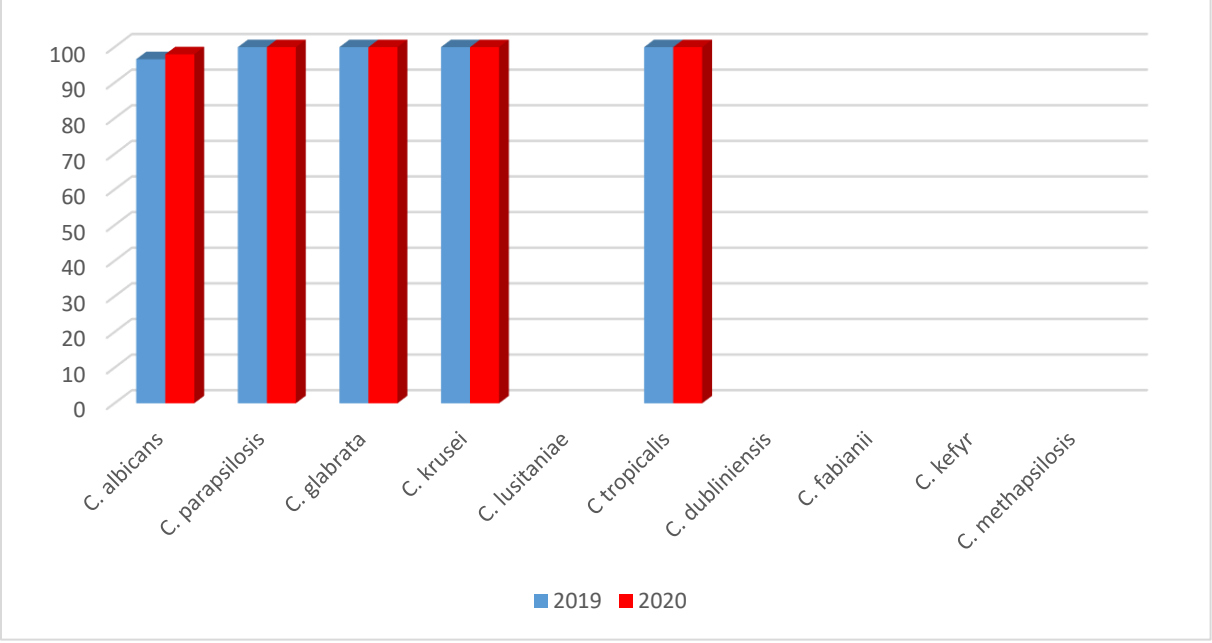
C. albicans je osjetljiva na flukonazol u obje godine u 98% ispitivanih izolata, 100% izolata *C. tropicalis* u 2019., no u 2020. 80% *C. tropicalis* je bilo osjetljivo na flukonazol. Ono što posebno zabrinjava je da su izolati *C. parapsilosis* (koja je intrinzički osjetljiva na flukonazol za razliku od *C. glabrata i C. krusei*) nažalost je u velikom broju slučajeva razvila rezistenciju pa je u 2019. godini bila osjetljiva u 23,3% slučajeva, a 2020. u 26,32%, a obzirom da je C. *parapsilosis* druga vrsta po učestalosti 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 6).

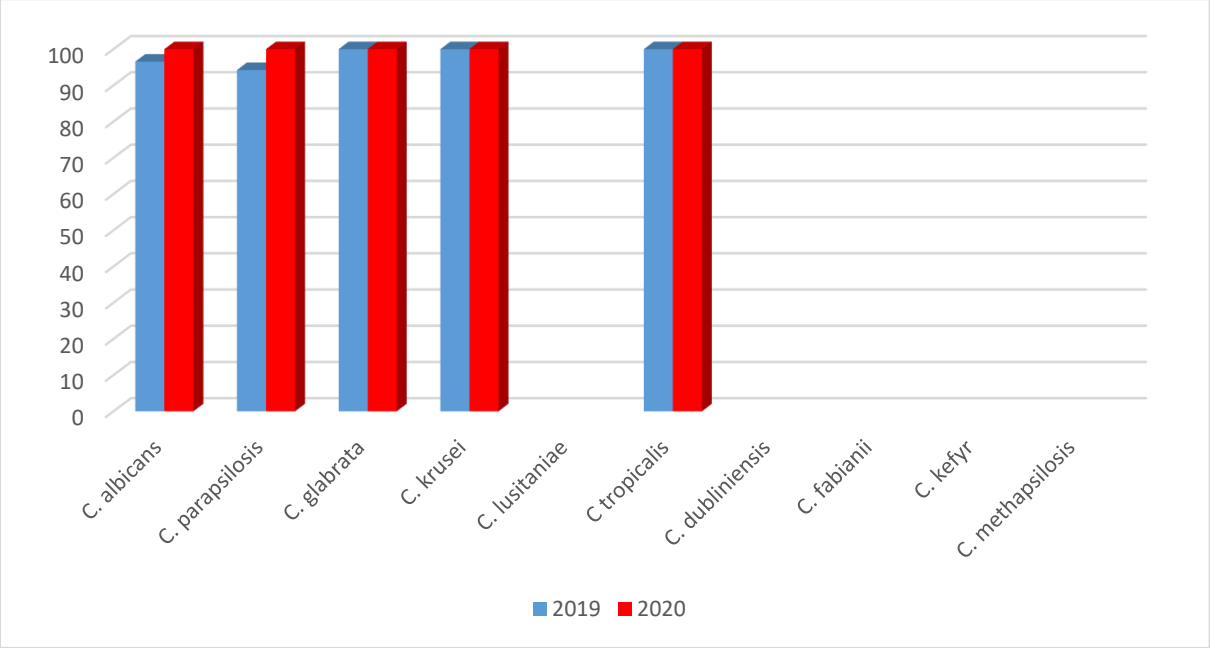
Grafikon 2. Osjetljivost vrsta *Candida* spp. u Hrvatskoj u 2019. i 2020. godini na amfotericin B
Figure 2. Candida spp susceptibility on amphotericin B in Croatia in 2019 and 2020



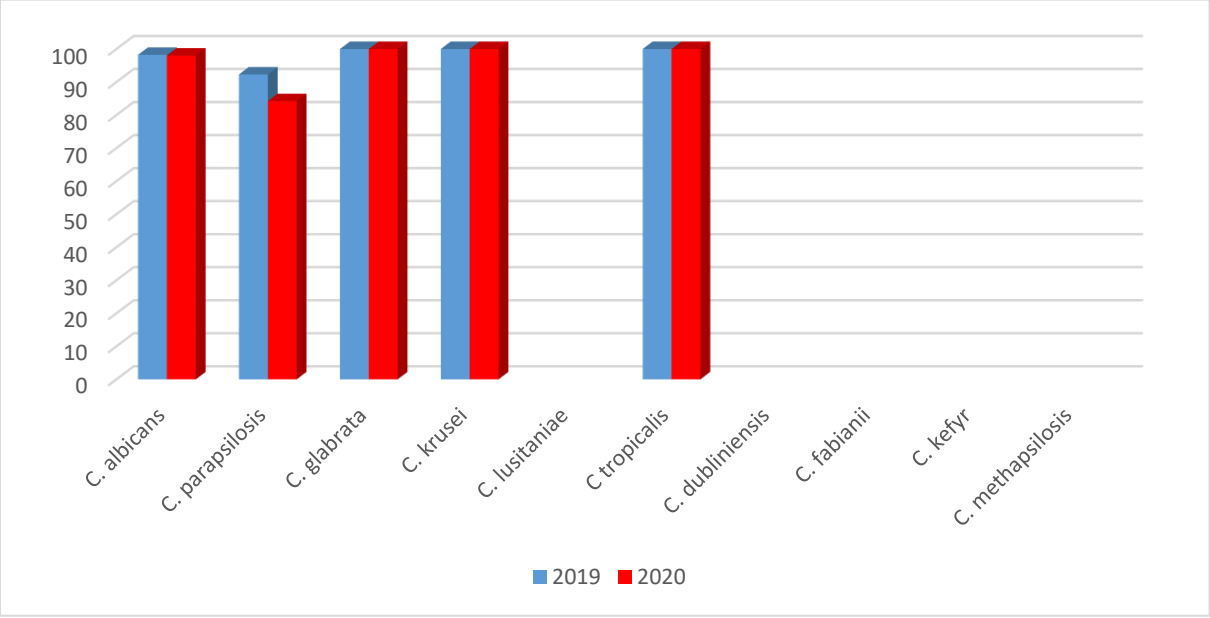
Grafikon 3. Osjetljivost vrsta *Candida* spp. u Hrvatskoj u 2019. i 2020. godini na kaspofungin
Figure 3. Candida spp susceptibility on caspofungin in Croatia in 2019 and 2020



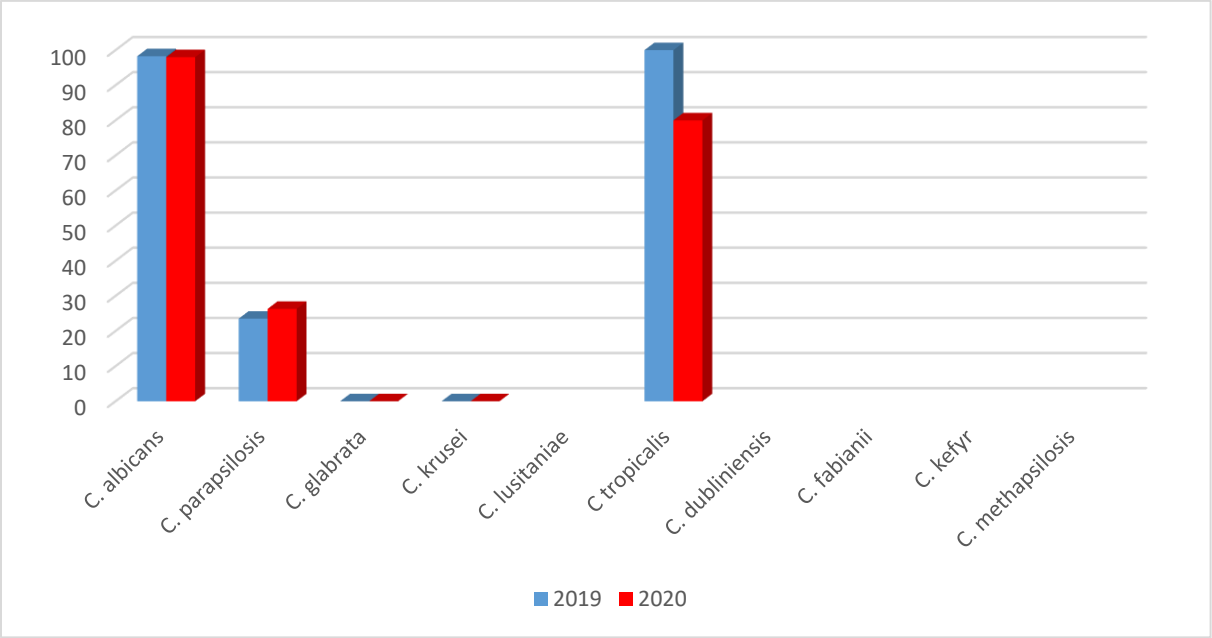
Grafikon 4. Osjetljivost vrsta Candida spp. u Hrvatskoj u 2019. i 2020. godini na mikafungin
Figure 4. Candida spp susceptibility to micafungin in Croatia in 2019 and 2020



Grafikon 5. Osjetljivost vrsta *Candida* spp. u Hrvatskoj u 2019. i 2020. godini na anidulafungin
Figure 5. Candida spp susceptibility to anidulafungin in Croatia in 2019 and 2020



Grafikon 6. Osjetljivost vrsta *Candida* spp. u Hrvatskoj u 2019. i 2020. godini na flukonazol
Figure 6. Candida spp susceptibility to fluconazol in Croatia in 2019 and 2020



Distribution of *Candida* species and antifungal susceptibility in patients with candidemia in Croatia, 2019-2020

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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 2019 and 2020.

Incidence of different *Candida* species

During two-year period 154 isolates of *Candida* spp. in year 2019 and 136 isolates in year 2020 were collected and analysed. The incidence of different *Candida* species is shown in Table 1.

The most common *Candida* spp. in year 2019 were *C. albicans* in 38.31% (59/154), *C. parapsilosis* in 33.77% (52/154) and *C. glabrata* in 18.18% (28/154) patients with candidemia and in year 2020 *C. albicans* in 36.76% (50/136), *C. parapsilosis* in 27.94% (38/136) and *C. glabrata* in 27% (19.85) patients with candidemia.

Distribution of *C. albicans* and non-albicans species among candidemia isolates in year 2019 and 2020 is shown on Figure 1. Although *C. albicans* was the most common species isolated from blood cultures in Croatia in 2019 and 2020, there is high percentage of *C. parapsilosis* on the second place followed by *C. glabrata*. Results of our surveillance documented that the incidence of *C. albicans* among patients with candidemia decreased below 50% (shift) and non-albicans isolates increased. Those results are clinically important considering the fact that *C. parapsilosis* and *C glabrata* have reduced susceptibility on 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 adherence to prevention and infection control measures.

Antifungal susceptibility

Antifungal susceptibility of *Candida* spp. in Croatia in year 2019 and 2020 to amphotericin B, caspofungin, micafungin, anidulafungin and fluconazole is shown in Figure 2,3,4,5 and 6.

Susceptibility to amphotericin B was 100% for *C. albicans*, *C. parapsilosis, C. glabrata* and *C. tropicalis* and for *C. krusei* was 100% in year 2019 and 22% in year 2020. Resistance of *C. krusei* to amphotericin B is not uncommon but it should be noticed that there was a total of seven and nine isolates in year 2019 and 2020, respectively. Thus, considering small number of isolates it is difficult to conclude about resistance increase (Figure 2).

As expected, echinocandins showed excellent efficiency against *Candida* isolates. Susceptibility to caspofungin of *C. albicans* isolates in 2019 was 96, 61% and in 2020 100%. *C. parapsilosis* isolates from blood cultures showed 100% susceptibility to caspofungin, as well as isolates of *C. glabrata*, *C. tropicalis,* and *C. krusei*. (Figure 3). Micafungin showed similar activity because C. *albicans* isolates showed susceptibility of 96, 55% and 100% in 2019 and 2020, respectively. *C. parapsilosis* isolates from blood cultures demonstrated susceptibility of 94,23% in 2019 and 100% in 2020. Isolates of *C. glabrata, C. tropicalis,* and *C. krusei* were in both years 100% susceptible to micafungin (Figure 4). Anidulafungin showed very similar efficacy and susceptibility of 98% in year 2019 and 2020 among isolates of *C. albicans*. On the other hand, *C. parapsilosis* isolates showed susceptibility of 92% and 84,21% in year 2019 and 2020, respectively. In both years *C. glabrata, C. tropicalis,* and *C. krusei* were 100% susceptible to anidulafungin (Figure 5)

Susceptibility to fluconazole was 98% in *C. albicans* in both, 2019 and 2020. *C. tropicalis* showed susceptibility of 100% in 2019, but in 2020 80% of *C. tropicalis* isolates were susceptible to fluconazole. 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 2019 susceptibility was 23,3% and in 2020 26,32%. As *C. parapsiolosis* is the second most frequent etiological cause of candidemia, this result is rather alarming.

As expected, there were no susceptible isolates of *C. glabrata* and *C. krusei* on fluconazole (Figure 6).

POGLAVLJE / CHAPTER 6.

POTROŠNJA ANTIBIOTIKA U HRVATSKOJ
ANTIBIOTIC CONSUMPTION IN CROATIA

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Izvanbolnička potrošnja antibiotika

Hrvatska prati potrošnju antibiotika od 2001. godine u skladu s međunarodno priznatim European Surveillance of Antibiotic Consumption (ESAC) standardima. Podaci o potrošnji antibiotika prikupljaju se, koristeći Anatomsko-Terapijsko-Kemijsku klasifikaciju (ATK klasifikacija) i definirane dnevne doze (DDD) u skladu s metodologijom razvijenom u suradnji s kolaborativnim centrom za statistiku (Oslo, Norveška). Kao denominator se koristi broj stanovnika te se potrošnja iskazuje u definiranim dnevnim dozama (DDD) na 1000 stanovnika po danu (DDD/TID) na 3. i 4. nivou ATK klasifikacije.

DDD je jedinica mjere potrošnje lijekova, odnosno prosječna doza održavanja lijeka pri njegovoj glavnoj indikaciji kod odraslog bolesnika. Koristeći ATK klasifikaciju i DDD moguće je agregirati antibiotike različitih proizvođača (tvorničkih naziva) koji se razlikuju u pakiranju te jačini aktivne supstance. Dobiveni podaci su usporedivi longitudinalno kroz godine na nacionalnoj razini, ali i između zemalja uključenih u program praćenja potrošnje antibiotika, the European Surveillance of Antimicrobial Consumption Network (ESAC-Net) i pripadajuću platformu za unos podataka, The European Surveillance System (TESSY).

DDD pojedinih lijekova se mogu promijeniti bilo zbog promjene glavne indikacije za primjenu ili nekih drugih razloga. U tom slučaju podaci prikupljeni u prethodnim godinama zahtijevaju prilagodbu prema zadnjim izmjenama DDD/ATK.
Potrošnja antibiotika se prati odvojeno za ambulantnu i bolničku potrošnju i izražava se u DDD na 1000 stanovnika po danu (DDD/TID).

Do 2011. godine ambulantna potrošnja antibiotika temeljila se na podacima dobivenim putem veledrogerija, a od 2012. godine praćenje potrošnje započelo je i putem HZZO-a, odnosno iz dva izvora što se nastavilo i 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 nešto 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 (1,27 DDD/TID) je približna (1,24 DDD/TID) prethodnoj godini. Razlika je uočljiva u svim klasama antibiotika, s tim da je najveća u klasi penicilina i klasi makrolid-linkozamid-streptogramin (tablica 4; slika 3). Kod klase penicilina (J01C) uočava se najveća razlika (0,50 DDD/TID), što je manje u odnosu na prethodnu godinu (0,70 DDD/TID). U skupini makrolid-linkozamid (J01F) je razlika 0,30 DDD/TID, što je nešto više nego prethodne godine (0,22 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). U longitudinalnom praćenju se uočavaju dva veća pomaka u izvanbolničkoj potrošnji antibiotika. U 2002. godini je uvedena nova formulacija koamoksiklava u primjenu (2x1.2 g umjesto dotadašnjih 3x0.625g) što je, uz istu vrijednost DDD, dovelo do skoka u ukupnoj potrošnji u odnosu na 2001. godinu (sa 16,5 na 19,9 DDD/TID) iako se broj propisanih doza nije bitno mijenjao. Do 2010. potrošnja se kretala oko 20 DDD/TID kad je pala na 17,2 DDD/TID u 2010. i 16.50 DDD/TID u 2011. što vjerojatno nije posljedica manjeg propisivanja po glavi stanovnika, već korištenja istog denominatora (4 555 219 stanovnika) kroz 10 godina prema popisu stanovništva iz 2001. godine. Od 2012. godine se koristi novi denominator (4 284 889) prema popisu stanovništva iz 2011. godine što je dovelo do pouzdanijih rezultata barem na početku

desetogodišnjeg razdoblja koje se oslanja na popis stanovništva iz 2011. godine. U tom razdoblju potrošnja se kretala između 17,00 i 18,00 DDD/TID, a u 2019. godini je iznosila 16,94 DDD/TID.

U 2020. godini potrošnja iznosi 14,05 DDD/TID, što je najniža potrošnja od početka praćenja potrošnje antibiotika 2001. godine. Pad u potrošnji antibiotika može se tumačiti značajnom promjenom u načinu života u 2020. godini obzirom na pandemiju uzrokovanu SARS-CoV-2 virusom. Promijenjeni režim života, ograničavanje kretanja stanovnika u Hrvatskoj, smanjeni boravak djece u predškolskim i školskim ustanovama, rad od kuće i druge preporučene epidemiološke mjere doprinio je nižoj incidenciji respiratornih bolesti i smanjenom propisivanju antibiotika.

Međutim, analizom drugih indikatora kvalitete propisivanja antibiotika, a to je omjer potrošnje 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 (amoksicilina), uskospektralnih penicilina, cefalosporina I. generacije i eritromicina (J01 (CA+CE+CF+DB+FA01) uočava se nepovoljan trend (tablica 5; slika 4). Kretanje potrošnje ukazuje na porast potrošnje širokospektralnih antibiotika u odnosu na uskospektralne, što sigurno utječe na pojavu i širenje rezistencije bakterija na antibiotike. Takav nepovoljan omjer potrošnje udvostručio se u zadnjih 10 godina od 2,5 na 5,7 (tablica 5; slika 4).

Širokospektralni penicilinski antibiotici, J01CA (amoksicilin) nastavljaju sa silaznim trendom potrošnje od 2015. godine (2,31; 2,11; 1,97; 1,82 DDD/TID) te bilježe najnižu vrijednost u 2020. godini 1,19 DDD/TID. Međutim, po prvi puta i kombinacija širokospektralnih antibiotika s inhibitorima betalaktamaza, J01CR (najzastupljeniji ko-amoksiklav) pokazuje pad potrošnje (tablica 1; slika 1).

Uskospektralni penicilini, J01CE nastavljaju s trendom pada potrošnje, dok se to ne uočava kod beta-laktamaza rezistentnih penicilina, J01F koji su zadržali istu potrošnju kao i prethodnih godina usprkos ukupnom padu potrošnje antibiotika.

Kod klase cefalosporina prati se trend pada potrošnje svih generacija (1., 2. i 3.), što je vidljivo i kod ostalih klasa (sulfonamidi +trimetoprim, makrolidi i linkozamidi, aminoglikozidi i fluorokinoloni).

Dobar pokazatelj je taj da je usprkos padu ukupne ambulantne potrošnje, potrošnja nitrofurantoina (0,83 DDD/TID) i fosfomicina (0,08 DDD/TID) na razini kao i prethodne godine, što govori u prilog tome da je došlo do pada potrošnje antibiotika koji se koriste za liječenje respiratornih infekcija ali ne i do pada potrošnje antibiotika koji se koriste u liječenju izvanbolničkih urinarnih infekcija.

Ambulantna potrošnja u Hrvatskoj čini 90% ukupne potrošnje, što odgovara podacima u prethodnim godinama.

U tablici 6 i na slici 5 poredani su antibiotici prema učestalosti izvanbolničke potrošnje - "top lista" najpropisivanijih antibiotika. U 2020. godini je došlo do promjene u poretku na način da je azitromicin sa 4. mjesta skočio na drugo mjesto prema učestalosti propisivanja u primarnoj zdravstvenoj zaštiti, odmah iza ko-amoksiklava. Doksiciklin nije više među prvih pet najpropisivanijih antibiotika, a na peto mjesto se popeo nitrofurantoin. Cefuroksimaksetil ostao je na trećem mjestu, kao i prethodne godine, dok je amoksicilin pao na četvrto mjesto.

Potrošnja antibiotika po kvartalima je uobičajena. Najviša potrošnja se bilježi u prvom (4,60 DDD/TID) i četvrtom (3,94 DDD/TID) kvartalu (tablica 7; slika 6), što ukazuje na neopravdano visoko povećanu potrošnju antibiotika u zimskim mjescima, što je vidljivo u velikoj razlici u potrošnji između 1. i 2. kvartala koja iznosi 2,00 DDD/TID. Iako su

respiratorne infekcije učestalije u zimskim mjesecima najčešće su uzrokovane virusima na koje antibiotici ne djeluju i nepotrebno se koriste.

Među prvih deset dijagnoza po učestalosti za koje se propisuju antibiotici je šest dijagnoza koje se odnose na dišni sustav (akutna upala sinusa; akutni bronhitis, akutna infekcija gornjeg dišnog sustava, …) (tablica 8; slika 7). Iako je upala mokraćnog mjehura (N30) vodeća dijagnoza za propisivanje antibiotika, kao i prethodne godine, što je i očekivano, jer se radi o najčešćoj izvanbolničkoj bakterijskoj infekciji, još uvijek se neopravdano troši velik broj antibiotika za liječenje infekcija dišnog sustava. Top lista najčešće propisanih antibiotika ne korelira s top listom dijagnoza za koje se propisuju antibiotici.

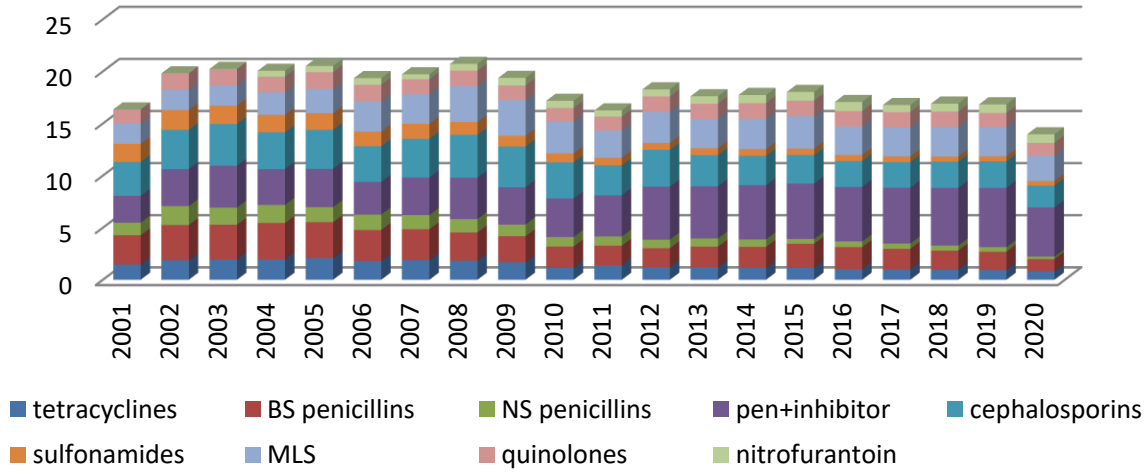
2020. godina, obzirom na pandemiju uzrokovanu SARS-CoV-2 virusom, bila je specifična po mnogočemu, što se je odrazilo i na potrošnju antibiotika. Zabilježen je značajan pad ukupne ambulantne potrošnje antibiotika (14,05 DDD/TID), odnosno potrošeno je 2,9 DDD/TID manje od prethodne godine (16,94). Zadnjih deset godina nije bilo značajnije oscilacija u ambulantnoj potrošnji antibiotika i ona se kretala od 16,50 do 18,30 DDD/TID. Sukladno ukupnom padu potrošnje uočava se pad potrošnje svih klasa antibiotika.

Ipak, indikator potrošnje antibiotika koji pokazuje omjer potrošnje širokospektralnih antibiotika u odnosu na uskospektralne je vrlo nepovoljan. Unazad jedanaest godina se udvostručio.

Ohrabruje ista razina potrošnje nitrofurantoina kao i prethodne godine, koji se koristi u liječenju nekompliciranih urinarnih infekcija, a koje su prve na top listi najčešćih dijagnoza za koje se propisuju antibiotici. Inače niska potrošnja izoksazoilskog penicilina zadržala je svoju razinu potrošnje, što također govori u prilog prepoznavanja tog antibiotika za liječenje bakterijskih infekcija, poglavito stafilokoknih, u ambulantnoj primjeni.

Udio ambulantne potrošnje i dalje iznosi 90% ukupne potrošnje antibiotika. Potrošnja širokospektralnih antibiotika (9,81 DDD/TID) značajno nadmašuje potrošnju uskospektralnih antibiotika (1,72 DDD/TID), odnosno omjer potrošnje iznosi 5,7 u 2020. godini u odnosu na prethodnu godinu kada je iznosio 4,5. Vodeći antibiotik po potrošnji i dalje je ko-amoksiklav.

Slika 1. */ Figure 1.*
Ambulantna potrošnja antibiotika (DDD/TID) u Hrvatskoj, 2000 - 2020.
Ambulatory antibiotic consumption (DDD/TID) in Croatia, 2000 – 2020



Outpatient Antibiotic Consumption

Standardized surveillance of antibiotic consumption in Croatia started in 2001 within the European Surveillance of Antibiotic Consumption (ESAC) and according to international ESAC standards. Data on consumption are collected in accordance with the Anatomical Therapeutic Chemical (ATC) classification and are published on the fourth and third level. Data are expressed in defined daily doses (DDD) in accordance with methodology of Norwegian Institute of Public Health from Oslo. The Census of 2011 was used as a denominator and data on antibiotic consumption are expressed in defined daily doses per 1000 inhabitants daily (DDD/TID).

DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults. DDDs provide a fixed unit of measurement regardless of package size and strength of active substance. By applying DDD it is possible to make international comparisons of antibiotic consumption. However, DDDs sometimes need to be reviewed because dosages and indications for use may change over time and that reflects on data on total antibiotic consumption.

Data on consumption are expressed in defined daily doses per 1000 inhabitants daily (DDD/TID), separately for hospital and outpatient consumption.

Up until 2011 wholesales data was the basis for outpatient consumption analysis. Since 2012 data has been collected from two sources (wholesales data and Croatian Health Insurance Fund, CHIF reimbursement data). CHIF reimbursement data are considered as the official national data. There is a difference in antibiotic consumption depending on the source of the data (Table 3, Figure 2), being slightly higher when based on wholesales data, rather than the one provided by CHIF. Thus, in 2020 the difference in consumption was 1.27 DDD/TID, which is slightly higher than in 2019 when it was 1.24 DDD/TID. The biggest difference can be observed in the penicillins class (J01C) and in the macrolides-lincosamides class (J01F) (Table 4; Figure3). In the penicillins class the difference is 0.50 DDD/TID. In other groups of antibiotics there are also some discrepancies in data on consumption but they are not as significant (Table 4, Figure 3). All antibiotics in Croatia are reimbursed but some patients choose to purchase antibiotics with private prescriptions which may create differences in the obtained consumption data. Another reason may be direct supply of mostly parenteral antibiotics in primary care offices which however is not a very common practice.

Standardized surveillance of antibiotic consumption in Croatia started in 2001 according to international ESAC standards (Table 1). In 2002 there were some changes in DDDs for amoxicillin-clavulanic acid (from 3x0.625g to 2x1.2 g) with an impact on total antibiotic consumption. Up until 2010 outpatient antibiotic consumption amounted to 20 DDD/TID while in 2011 it amounted to 17.2 DDD/TID. Until 2012 the Census of 2001 (4 555 219 people) was used as a denominator, and since 2012 a denominator has been the Census of 2011 (4 284 889) indicating a decrease in the number of inhabitants. Since 2011 outpatient antibiotic consumption ranges from 17 DDD/TID to 18 DDD/TID, and in 2019 it was 16.94 DDD/TID.

In 2020 outpatient antibiotic consumption amounted to 14.05 DDD/TID and was the lowest ever, probably because of the impact of the COVID-19 pandemic. Emergency lockdowns and school closures were initiated in Croatia, resulting in a decrease in incidence of respiratory tract infections and consequently antibiotic consumption.

The ratio between the consumption of broad-spectrum antibiotics, beta-lactams with inhibitors, second and third generation of cephalosporins, macrolides and fluoroquinolones and the consumption of narrow-spectrum antibiotics, first generation of cephalosporins and erythromycin is one of the

indicators to measure the quality of antimicrobial stewardship. There has been an increase in use of broad-spectrum antibiotics and its direct side effect is antibiotic resistance (Table 5; Figure 4).

Since 2015 there has been a continuous decrease in consumption of broad-spectrum penicillins (J01CA) (2.31; 2.11; 1.97; 1.82), being the lowest in 2020 – 1.19 DDD/TID. Moreover, for the first time ever the consumption of the class J01CR (combinations with inhibitors) declined (Table1; Figure 1).

The use of narrow-spectrum penicillins (JO1CE) shows a decreasing trend while prescribing of beta-lactamase resistant penicillins (J01CF) was similar to the one recorded in the previous years.

The consumption of the first, second and the third generation of cephalosporins is also falling. The other groups of antibiotics also show a decreasing trend in consumption (sulfonamides+trimethoprim, macrolides/lincosamides, aminoglycosides and fluoroquinolones).

The use of nitrofurantoin (J01XE) and fosfomycin was similar to the previous years (0.83 DDD/TID for nitrofurantoin and 0,08 DDD/TID for fosfomycin).

In 2020, outpatient antibiotic consumption accounted for 90% of total antibiotic consumption, which is similar to the one recorded in the previous years. Table 6 and Figure 5 show the consumption of the most frequently used antibiotics ("the top list"). In 2020 the most common were broad-spectrum penicillins with inhibitors, then azythromycin, cefuroxime axetil, amoxicillin and nitrofurantoin. In 2019 azythromycin was in the fourth and doxycycline in the fifth place.

Antibiotic consumption analyzed quarterly was the same as in the previous years. It was higher in the first (4.60 DDD/TID) and the last (3.94 DDD/TID) quarter (Table 7; Figure 6), reflecting higher incidence of respiratory tract infections. The difference in consumption in the first and second quarter was 2.00 DDD/TID, which is perturbing since respiratory tract infections are mostly of viral origin and therefore not frequently an indication for antibiotic therapy

Table 8 and Figure 7 show ten most frequent diagnosis used for prescribing antibiotics. Six of these are respiratory tract infections (sinusitis, bronchitis, acute respiratory tract infection …). In the first place are, however, urinary tract infections (N30) which are the most common bacterial infections requiring medical care and antibiotic treatment. The list of the most frequently used antibiotics does not match with the most frequent indications for their prescribing.

The coronavirus pandemic had an impact on the use of antibiotics. In 2020 there was a noticeable drop in total antibiotic consumption (14.05 DDD/TID in 2020 compared to 16.94 DDD/TID in 2019) as well as in the consumption of all classes of antibiotics. However, over the last ten years there were no significant oscillations in outpatient antibiotic consumption, which ranged from 16.50 DDD/TID to 18.30 DDD/TID.

The ratio of the consumption of broad-spectrum antibiotics to the consumption of narrow-spectrum antibiotics is one of the indicators for measuring the quality of antimicrobial stewardship. The situation in Croatia is unsatisfactory, due to an increasing trend in the use of broad-spectrum antibiotics, while the consumption of narrow-spectrum antibiotics has been decreasing over the last eleven years.

Nitrofurantoin is the first-line therapy for the treatment of uncomplicated lower urinary tract infections and its consumption in 2020 was similar to the previous year. Beta-lactamase resistant penicillin (J01CF) is active against penicillinase-producing strains of *Staphylococcus aureus*. Its consumption was similar to the year before.

The outpatient antibiotic consumption still accounts for 90% of total antibiotic consumption. The consumption of broad-spectrum antibiotics (9.81 DDD/TID) significantly surpasses the use of narrow-spectrum antibiotics (1.72 DDD/TID), which means the ratio is 5.7 while in 2019 it was 4.5. In 2020 the most commonly used were still broad-spectrum penicillins with inhibitors (co-amoxiclav).

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
JO1AA	Tetraciklini Tetracylines	1,39	1,19	1,19	1,12	1,14	1,02	1,00	0,98	0,93	0,79
JO1CA	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
JO1CE	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
JO1CF	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
JO1CR	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
JO1DB	Cefalosporini I gen. cephalosporins	0,84	0,79	0,77	0,72	0,66	0,60	0,47	0,38	0,35	0,27
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
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
JO1EE	Sulfonamides + trimethoprim	0,73	0,67	0,67	0,65	0,63	0,59	0,55	0,50	0,49	0,44
JO1F	Macrolides, lincosamides	2,63	2,97	2,80	2,91	3,10	2,71	2,75	2,83	2,79	2,44
JO1G	Aminoglikozidi Aminoglycosides	0,01	0,00	0,00	0,04	0,01	0,00	0,01	0,01	0,004	0,003
JO1MA	Fluorokinoloni Fluoroquinolones	1,32	1,49	1,47	1,50	1,50	1,49	1,50	1,48	1,36	1,22
JO1XE	Nitrofurantoin	0,60	0,68	0,72	0,79	0,83	0,88	0,68	0,76	0,83	0,83
J01XX	Fosfomycin	-	-	-	-	-	0,004	0,05	0,08	0,08	0,08
UKUPNO TOTAL		**16,50**	**18,30**	**17,60**	**17,80**	**18,00**	**17,10**	**16,80**	**17,00**	**16,94**	**14,05**

* 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)

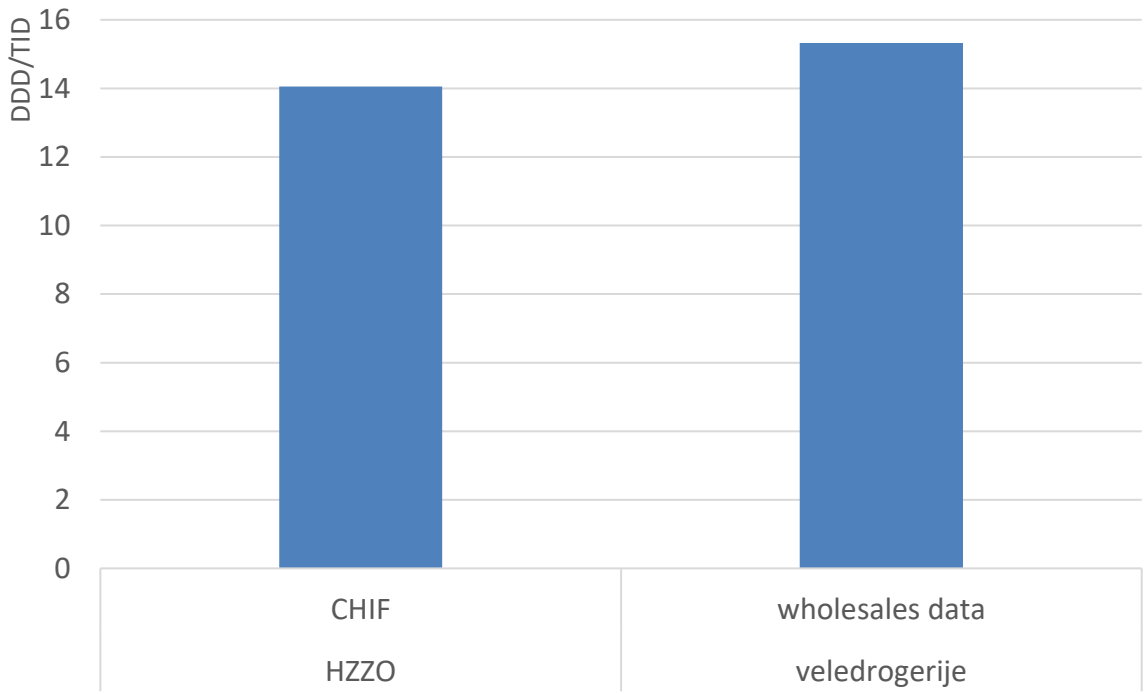
ATC šifra ATC code	ANTIBIOTIK ANTIBIOTIC	2011	2012 *	2013	2014	2015	2016	2017	2018	2019	2020
JO1AA	Tetraciklini Tetracylines	0,06	0,06	0,05	0,04	0,04	0,04	0,04	0,03	0,04	0,03
JO1CA	Penicilini širokog spektra Broad spectrum penicillins	0,03	0,03	0,04	0,02	0,02	0,03	0,02	0,02	0,02	0,02
JO1CE	Penicilini 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
JO1CF	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
JO1CR	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
JO1DB	Cefalosporini I gen. cephalosporins	0,20	0,10	0,08	0,09	0,10	0,10	0,10	0,09	0,10	0,08
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
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
JO1DH	Carbapenems	0,04	0,05	0,05	0,06	0,06	0,06	0,08	0,07	0,08	0,09
JO1EE	Sulfonamides + trimethoprim	0,04	0,06	0,04	0,05	0,04	0,04	0,04	0,04	0,04	0,03
JO1F	Macrolides, lincosamides	0,14	0,16	0,15	0,14	0,15	0,15	0,16	0,16	0,18	0,19
JO1G	Aminoglikozidi Aminoglycosides	0,12	0,11	0,10	0,10	0,10	0,09	0,09	0,09	0,09	0,07
JO1MA	Fluorokinoloni Fluoroquinolones	0,19	0,19	0,19	0,20	0,21	0,21	0,23	0,24	0,24	0,20
JO1XA	Glycopeptides	0,03	0,03	0,03	0,03	0,04	0,03	0,04	0,05	0,05	0,05
JO1XD	Metronidazole	0,06	0,07	0,08	0,09	0,10	0,10	0,11	0,15	0,12	0,10
JO1XE	Nitrofurantoin	0,01	0,02	0,01	0,02	0,01	0,01	0,01	0,01	0,01	0,01
JO1XX	Fosfomycin	-	-	-	-	-	0,001	0,02	0,02	0,02	0,02
UKUPNO TOTAL		**1,69**	**1,75**	**1,58**	**1,65**	**1,70**	**1,65**	**1,74**	**1,80**	**1,85**	**1,61**

* 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	21 975 227,27	23 961 301,69
DDD/TID	14,05	15,32

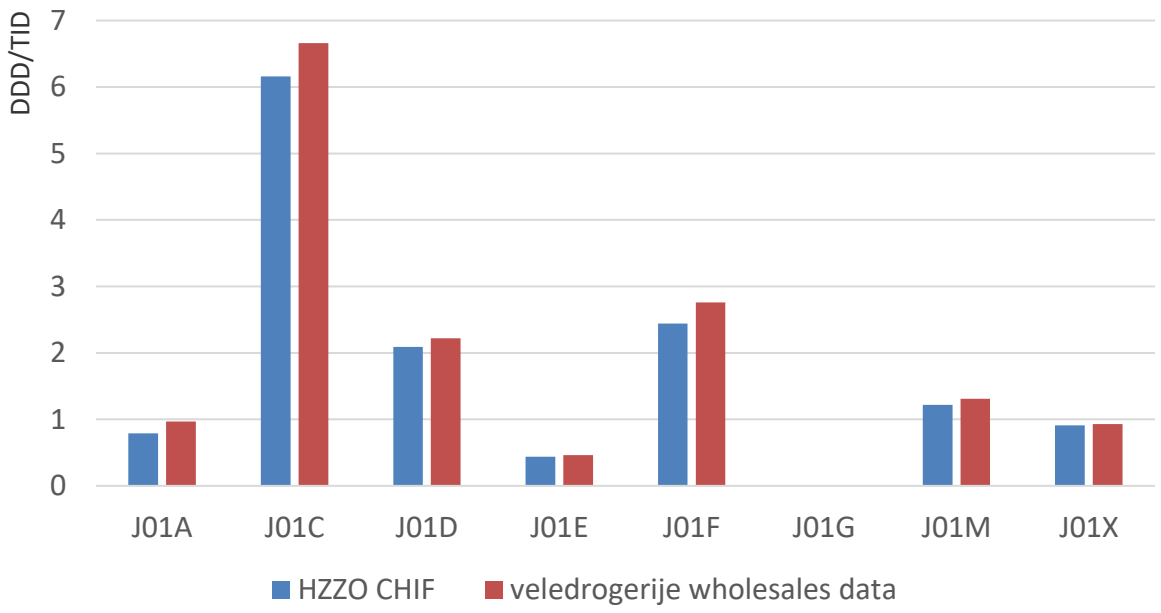
Slika 2. */ Figure 2.*
Ambulantna potrošnja antibiotika (DDD/TID) usporedba podataka HZZO i veledrogerija
Ambulatory antibiotic consumption (DDD/TID) comparison between CHIF data and wholesales data



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	0,79	0,97
J01C	6,16	6,66
J01D	2,09	2,22
J01E	0,44	0,46
J01F	2,44	2,76
J01G	0,003	0,01
J01M	1,22	1,31
J01X	0,91	0,93

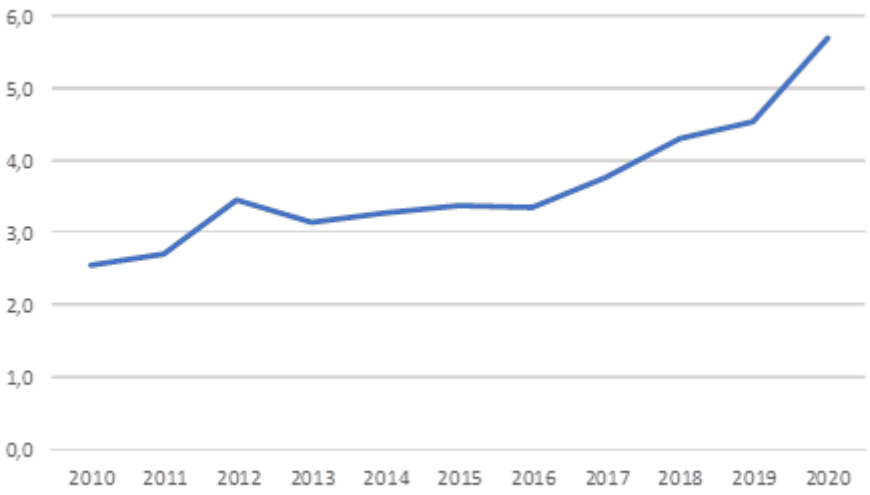
Slika 3. / *Figure 3.*
Ambulantna potrošnja antibiotika (DDD/TID) po klasama, usporedba podataka HZZO i veledrogerija
Ambulatory antibiotic consumption (DDD/TID) *by class, comparison between CHIF data and wholesales data*



Tablica 5. / *Table 5.*
Omjer izvanbolničke potrošnje beta – laktama s inhibitorima, cefalosporina 2. i 3. generacije, makrolida (osim eritromicina) i fluorokinolona i potrošnje penicilina uskog spektra, penicilina širokog spektra, cefalosporina 1. generacije i eritromicina u razdoblju 2010.- 2020.; izražene u DDD na tisuću stanovnika na dan /
The ratio between the ambulatory consumption of beta-lactams with inhibitors, 2nd and 3rd generation cephalosporins, macrolides and fluoroquinolones to the consumption of narrow-spectrum penicillin, broad-spectrum penicillins, 1 st generation cephalosporins and erythromicin, 2010 – 2020; expressed as DDD per 1000 inhabitants per day

	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

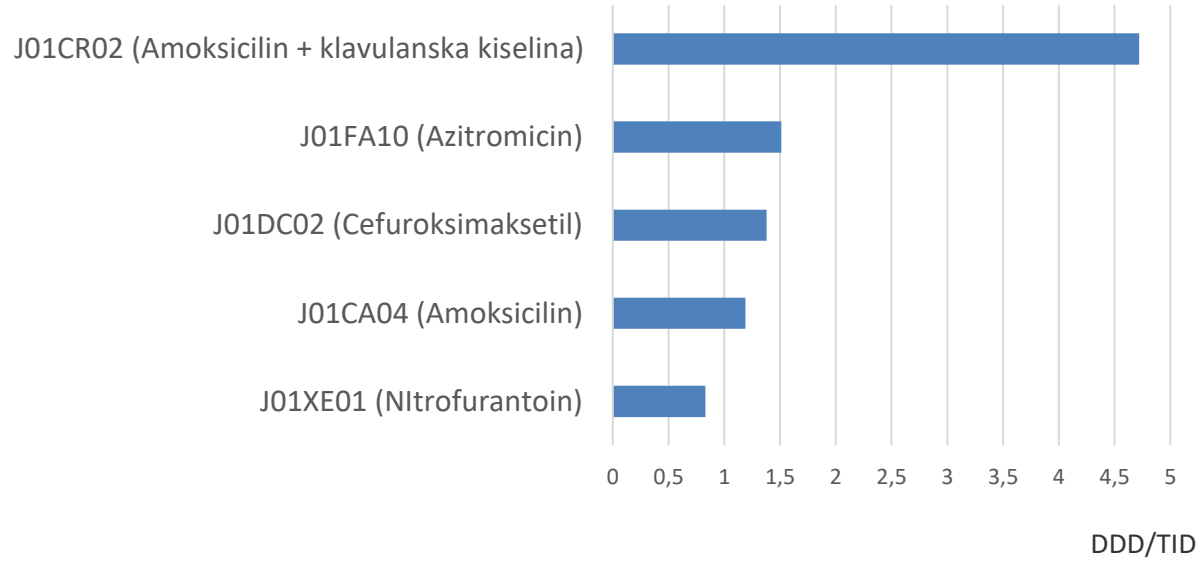
Slika 4. / *Figure 4.*
Omjer izvanbolničke potrošnje beta – laktama s inhibitorima, cefalosporina 2. i 3. generacije, makrolida (osim eritromicina) i fluorokinolona i potrošnje penicilina uskog spektra, penicilina širokog spektra, cefalosporina 1. generacije i eritromicina u razdoblju 2010.- 2020.; izražene u DDD na tisuću stanovnika na dan /
The ratio between the ambulatory consumption of beta-lactams with inhibitors, 2nd and 3rd generation cephalosporins, macrolides and fluoroquinolones to the consumption of narrow-spectrum penicillin, broad-spectrum penicillins, 1 st generation cephalosporins and erythromicin, 2010 – 2020; expressed as DDD per 1000 inhabitants per day



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

klasa	DDD/TID
J01CR02 (Amoksicilin + klavulanska kiselina)	4,72
J01FA10 (Azitromicin)	1,51
J01DC02 (Cefuroksimaksetil)	1,38
J01CA04 (Amoksicilin)	1,19
J01XE01 (Nitrofurantoin)	0,83

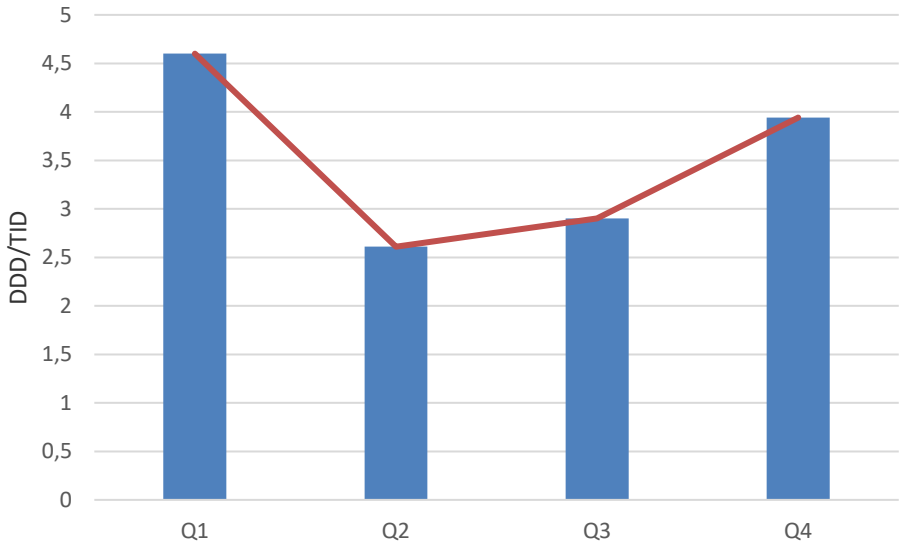
Slika 5. */ Figure 5.*
Ambulantna potrošnja antibiotika („top 5“ antibiotika – DDD/TID), izvor podataka – HZZO
Ambulatory antibiotic consumption („top 5“antibiotics- DDD/TID); origin of data-CHIF



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	4,60
II	2,61
III	2,90
IV	3,94

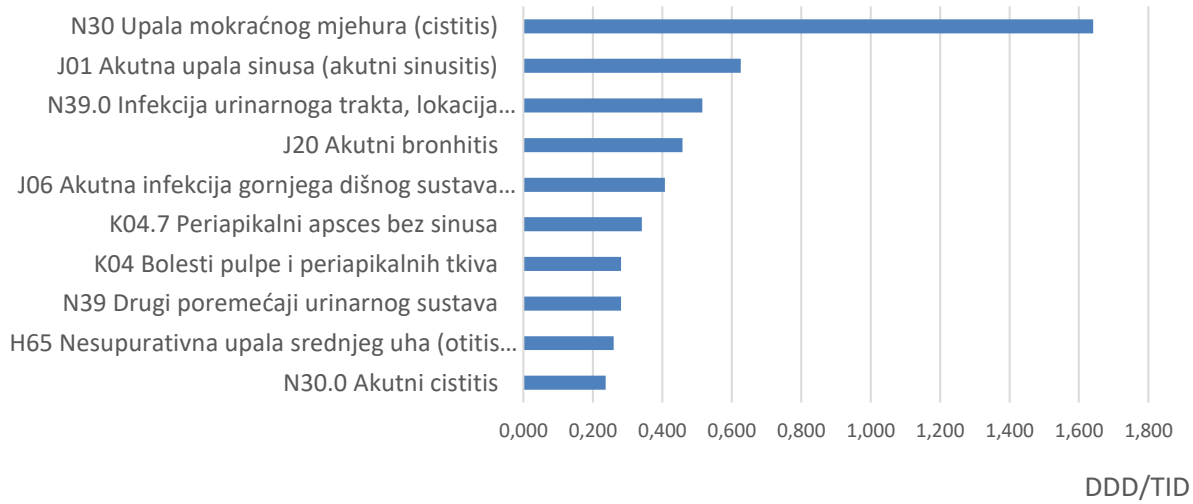
Slika 6. */ Figure 6.*
Ambulantna potrošnja antibiotika po kvartalima – DDD/TID, izvor podataka – HZZO
Ambulatory antibiotic consumption – by quarters DDD/TID; origin of data-CHIF



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

MKB dijagnoza	DDD/TID
N30 Upala mokraćnog mjehura (cistitis)	1,641
J01 Akutna upala sinusa (akutni sinusitis)	0,626
N39.0 Infekcija urinarnoga trakta, lokacija neoznačena	0,516
J20 Akutni bronhitis	0,458
J06 Akutna infekcija gornjega dišnog sustava multiplih i nespecificificiranih lokalizacija	0,407
K04.7 Periapikalni apsces bez sinusa	0,341
K04 Bolesti pulpe i periapikalnih tkiva	0,281
N39 Drugi poremećaji urinarnog sustava	0,281
H65 Nesupurativna upala srednjeg uha (otitis media nonsuppurativa)	0,260
N30.0 Akutni cistitis	0,237

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 (tablica 2). Do osnutka Interdisciplinarne sekcije za kontrolu rezistencije na antibiotike (ISKRA) 2006. godine podaci su prikupljani samo putem veledrogerija, dok se od tada dobivaju iz dva izvora. Do 2010.g. kao službeni podaci RH korišteni su podaci dobiveni putem veledrogerija, a počevši od 2010.g. službenim podacima, koji su naznačeni u Tablici 2 i koji se šalju u europski program praćenja potrošnje (ESAC-Net) se smatraju podaci iz bolničkih ljekarni. 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 praćenju bolničke potrošnje uključena je i potrošnja antibiotika u dnevnim bolnicama, a denominatoru su uz bolničke dane pridruženi terapijski dani dnevne bolnice.

Izražavanje potrošnje na 100 BOD-a (DDD/100BOD) uz uobičajeno prikazivanje na 1000 stanovnika po danu (DDD/TID) daje precizniji uvid u potrošnju antibiotika i mogućnost detaljnije analize po pojedinim klasama i vrstama antibiotika, kako na nacionalnom nivou, tako i za svaku bolnicu posebno.

Bolnička potrošnja antibiotika u 2020. godini izražena u DDD/TID prikazana je u tablici 2., za što je korišten denominator prema popisu stanovništva iz 2011.godine. 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 2020. godini iznosi 0,16 DDD/TID u korist podataka dobivenih iz bolničkih ljekarni, što je više od prethodne godine, kada je razlika iznosila 0,09 DDD/TID (tablica 9; slika 8).

Za 2020. 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.

Nakon obrade podataka o bolničkoj potrošnji antibiotika i administrativnih podataka za svaku bolnicu (bolničkoopskrbni dani, broj primitaka) podaci se vraćaju svakoj bolnici na provjeru i potvrdu zajedno s podacima o ukupnoj potrošnji i prema klasama antibiotika u prethodnim godinama za usporedbu. 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.

Iako je bolnička potrošnja antibiotika po glavi stanovnika u 2020. bila niža negoli prethodnih godina (Tablica 2), bolnička potrošnja antibiotika izražena u definiranim dnevnim dozama na 100 bolničkoopskrbnih dana (DDD/100BOD) kontinuirano, i to linearno raste, tako da je u 2020. godini zabilježena najviša potrošnja do sada 42,52 (tablica 10; slika 9). Manja bolnička potrošnja izračunata na broj stanovnika uz povećanu potrošnju izraženu na BOD je vjerojatno odraz manje aktivnosti bolnica tijekom pandemije.

U 2020. godini, po prvi puta, tijekom praćenja bilježi se pad u potrošnji penicilinske skupine betalaktamskih antibiotika (J01C) (tablica 11; slika 10). Pad u potrošnji se bilježi i kod skupine tetraciklina (J01A), kotrimoksazola (J01E), aminoglikozida (J01G) te kinolona (J01M). Značajan porast potrošnje se uočava kod klase cefalosporina (J01D), klase makrolid-linkozamid-streptogramin te klase ostali (J01X).

Vodeći antibiotik po potrošnji i dalje je ko-amoksiklav, dok se redoslijed ostalih antibiotika promijenio. Na drugo mjesto se pozicionirao ceftriakson, koji je u prethodnoj godini bio na četvrtom mjestu. S drugog na treće mjesto je pao cefuroksimaksetil, dok je ciprofloksacin na četvrtom mjestu (prošle je godine bio na trećem). Metronidazol nije više na listi među prvih pet antibiotika u bolničkoj potrošnji. Njegovo mjesto zauzeo je azitromicin. (tablica 12; slika 11).

Jedan od indikatora kvalitete propisivanja antibiotika u bolnici je udio bolničke 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) izražen kao DDD na tisuću stanovnika na dan u odnosu na ukupnu bolničku potrošnju. Na tablici 13 i slici 12 uočava se rast udjela potrošnje rezevnih antibiotika, koji u 2020. godini iznosi 36,7%.

Sve **kliničke ustanove**, njih trinaest je dostavilo podatke o potrošnji antibiotika (tablica 14, slika 13). Raspon potrošnje antibiotika u 2020. godini kretao se od 23,12 do 118,77 DDD/100BOD. Tako širok raspon u potrošnji se očekuje s obzirom na različite profile tih ustanova (tablica 15; slika 14).

Kod osam kliničkih ustanova (K 01; K 03; K 04; K 05; K 06; K 07; K 08; K 15) uočava se porast potrošnje antibiotika u odnosu na prethodnu godinu, što je identičan broj kao i u prethodnoj godini.

Tri klinike (K 02; K 09; K 13) bilježe pad potrošnje antibiotika, dok se kod dvije klinike (K 11; K 14) ne uočava bitna razlika u potrošnji (manje od 1 DDD/100BOD u dvije godine).

Klinika 9, koja je u prethodnim godinama bilježila kontinuirani porast potrošnje (25,6; 35,8; 42,6 DDD/100BOD) u 2020. godini bilježi najnižu potrošnju u zadnje četiri godine (23,12 DDD/100 BOD), što je povezano s njezinom specijaliziranošću za pružanje određene vrste medicinskih postupaka i liječenja te u uvjetima pandemije nametnutom promjenom svog osnovnog rada.

Za 2020. godinu 22 **opće bolnice** su dostavile svoje podatke koji se mogu međusobno uspoređivati obzirom da je to najhomogenija skupina bolnica. Potrošnja antibiotika se kretala u širokom rasponu od 42,42 do 100,11 DDD/100BOD, što je ujedno i najveći raspon do sada zabilježen (57,69 DDD/100BOD).

Na slici 15 je prikazana potrošnja u općim bolnicama prema pojedinim klasama antibiotika u 2020. godini. U tablici 17 i na slici 16 prikazana je potrošnja u općim bolnicama u četvorogodišnjem periodu s mogućnošću praćenja trendova potrošnje. Kod 18 općih bolnica (82%) uočava se trend porasta potrošnje (O 01;O 02;O 03; O 05; O 07; O 08; O 10; O 11; O12; O 13; O 15; O 17; O 18; O 20; O 21; O 22; O 23; O 24) u odnosu na prethodnu godinu, dok je kod samo dvije bolnice (O 09; O 19) (9%) zabilježen pad potrošnje, a kod dvije bolnice nema razlike u potrošnji veće od 1 DDD/100BOD (O 04; O 14) (9%). Svega dvije bolnice troše između 40 i 50 DDD/100 BOD, kao i prethodne godine. Sedam bolnica više od 51, a manje od 60 (prošle godine 10 bolnica), dok tri bolnice troše u rasponu od 61-70 DDD/100 BOD (prošle godine pet). Čak šest bolnica troši iznad 71 DDD/100 BOD, a manje od 80, dok četiri bolnice troše više od 80 DDD/100 BOD, a jedna čak i preko 100, što nije zabilježeno u prethodnim godinama.

Potrošnja antibiotika u **psihijatrijskim bolnicama** kreće se od 2,95 do 12,63 DDD/100 BOD (tablica 18). Na slici 17 prikazana je potrošnja po klasama antibiotika u psihijatrijskim bolnicama. U 2020. godini u pet psihijatrijskih bolnica (P 02; P 03; P 06; P 08; P 09) uočava se porast potrošnje, dok je u dvije bolnice potrošnja u padu (P 01; P 04). Kod dvije bolnice (P 05; P 07) nema promjena u potrošnji u zadnje dvije godine većoj od 1 DDD/100BOD. U tablici 19 i na slici 18 prikazana je potrošnja u psihijatrijskim bolnicama u zadnje četiri godine s vidljivim trendovima potrošnje.

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. U prvoj skupini ustanova raspon potrošnje antibiotika se kreće od 8,21 do 66,98 DDD/100 BOD. Četiri bolnice (S 01; S 13; S 21; S 22) bilježe porast potrošnje (tablica 20; slika 19).

U skupini specijalnih bolnica namijenjenih rehabilitaciji kretanje potrošnje antibiotika je značajno niže, od 0,75 do 10,53 DDD/100 BOD (tablica 20; slika 19) te svega dvije imaju zabilježen porast potrošnje (S 05; S 08). Na slici 19 prikazana je potrošnja antibiotika po klasama u 2020. godini. U tablici 21 i na slici 20 prikazana je potrošnja u specijalnim bolnicama u zadnje četiri godine. Uočava se veliki skok u potrošnji u 2019. godini kod bolnice S 25, koji je u 2020. ponovno pao na vrijednosti slične prijašnjim godinama.

Potrošnja antibiotika u bolnicama izražena na BOD, linearno raste, te je u 2020. godini dosegnula najvišu vrijednost. Usprkos različitim nastojanjima, brojnim stručnim aktivnostima na različitim razinama ne uspijeva se zaustaviti trend povećane bolničke potrošnje antibiotika u Hrvatskoj. Posebno se uočava trend porasta pojedinih klasa. Klasa cefalosporina koja čini 30% ukupne bolničke potrošnje, bilježi trend porasta s najvišom vrijednošću potrošnje do sada. Klasa ostalih antibiotika, koju čine najvećim dijelom rezervni antibiotic, je treća po udjelu u bolničkoj potrošnji antibiotika.

Udio potrošnje rezervnih antibiotika u ukupnoj bolničkoj potrošnji raste iz godine u godinu, uz značajan porast upravo u 2020. godini, što se dijelom može pripisati velikom udjelu teških COVID pacijenata liječenih u jedinicama intenzivnog liječenja koji su razvili bakterijske infekcije povezane sa zdravstvenom skrbi. Potrošnja antibiotika generira rezistenciju, posebno određeni antibiotici s velikim potencijalom za razvoj rezistencije. Rukovođeno propisivanje antibioticima imperativ je koji treba zaživjeti u našim bolnicama.

Antibiotic consumption in Croatian hospitals

Antibiotic consumption in Croatian hospitals has been monitored separately from that in outpatient setting since 2001 (Table 2). Since 2006, when the Interdisciplinary Section for Antibiotic Resistance Control was established, antibiotic consumption has been monitored using two sources of data, hospital pharmacies and wholesales data, while up until then only wholesales data was available for surveillance. Since 2010 hospital pharmacies' data has been considered the official national data in Croatia and has been entered into a template table, which matches the ESAC-Net template (Table 2). To calculate hospital antibiotic consumption, it is necessary to obtain essential administrative data (number of bed days, total number of admissions and number of admissions in intensive care units, mixed, surgical, intern, pediatrics). Since 2011 antibiotics used in day hospitals have been included in overall hospital antibiotic consumption and the number of therapy days in day hospitals was added to the number of hospital bed days as a denominator.

Consumption data is usually expressed in defined daily doses per 1000 inhabitants daily (DDD/TID) but can also be expressed in defined daily doses per 100 bed days (DDD/100BD), which is a more reliable indicator as it enables more detailed and precise surveillance of antibiotic prescribing, not only for individual hospitals but also on the national level.

The overview of the hospital consumption in 2020 is shown in Table 2. Data from Census 2011 has been used as a denominator. Table 9 and Figure 8 show parallel data on antibiotic use gathered from both wholesale and hospital pharmacies since 2014. Unlike the numbers obtained from wholesale pharmacies, the data from hospital pharmacies shows an annual increase in antibiotic consumption since 2014 (except in 2015 when wholesales data indicate higher consumption). As in previous years, the data obtained for 2020 does not entirely match, depending on which source it comes from (0.16 DDD/TID in 2020 and 0.09 DDD/TID in 2019) (Table 9; Figure 8).

In 2020 all hospitals (68) sent their data on antibiotic consumption electronically to iskra.antibiotici@gmail.com . Although it is preferrable to send data directly from pharmacy information systems, only four hospitals used this method. After processing, each hospital received the processed data to check and compare with the results from previous years. Since 2011 antibiotics used in day hospitals have been included in overall hospital antibiotic consumption and the number of day hospital therapy days was added to the number of hospital bed days as a denominator.

In 2020 the hospital antibiotic consumption expressed in defined daily doses per 1000 inhabitants daily (DDD/TID) was lower then in the previous years (Table 2), but the hospital antibiotic use expressed in defined daily doses per 100 bed days amounted to 42.52 (Table 10, Figure 9), and is the highest ever. The difference in consumption expressed in defined daily doses per 1000 inhabitants daily and defined doses per 100 bed days is probably due to the impact of the pandemic on hospitals.

In 2020 for the first time there was a decrease in the use of beta-lactam antibiotics (J01C) (Table 11, Figure 10), as well as tetracyclins (J01A), sulfonamides (JO1E), aminoglycosides (J01G) and quinolones. However, there was an increase in consumption of cephalosporins (J01D), macrolide/linkosamides (J01F), and the category "other" (J01X).

Leading in its consumption is amoxicillin+clavulanic acid, followed by ceftriaxone and cefuroxime axetil, with ciprofloxacin and azitromicin ranked behind. In 2019 there were some differences in consumption of the most frequent antibiotics - ceftriaxone was in the fourth and metronidazole in the fifth place of the most commonly used antibiotics (Table 12; Figure 11).

Consumption of antibiotics on the "reserve list" can be one of the quality indicators to measure the appropriateness of antibiotic use. Data on prescribing of "reserve antibiotics" is shown in Table 13

and Figure 12 (glycopeptides JO1XA; third and fourth generation of cephalosporins JO1DD, JO1DE; monobactams J01DF; carbapenems J01DH; fluoroqinolones J01MA; polymyxins J01XB; piperacillin+tazobactam J01CR05; linezolid J01XX08; tedizolid J01XX11; daptomycin J01XX09). They account for 36.7% of total antibiotic consumption in 2020.

Thirteen tertiary care hospitals supplied data on their antibiotic consumption (Table 14; Figure 13) which ranges from 23.12 to 118.77 DDD/100 BD. The discrepancies in consumption reflect different hospital institution profiles (Table 15; Figure 14).

In eight clinics (K 01; K 03; K 04; K 05; K 06; K07; K 08; K 15) there has been an increase in use of antibiotics, while only three record a decrease (K 02; K 09; K 13). In two clinics (K 11; K14) there has been no difference in consumption in the last two years (less than 1 DDD/BD). In the previous years one clinic (K 09) showed an increasing trend in antibiotic consumption (25.6; 35.8; 42.6 DDD/100 BD) which, however, dropped to its lowest ever in 2020 due to the impact of coronavirus pandemic.

22 general hospitals sent their data on antibiotic consumption in 2020. This group, consisting of general hospitals, is the most homogeneous group, so the data on antibiotic prescribing can be easily compared. Antibiotic consumption in general hospitals ranges from 42.42 to 100.11 DDD/100 BD (the difference of 57.69 DDD/100BD is the largest ever). Figure 15 shows consumption by classes of antibiotics. Table 17 and Figure 16 show antibiotic use over the last four years. In 18 general hospitals (82%) there has been an increase in antibiotic consumption (O 01; O 02; O 03; O 05; O 07; O 08; O 10; O 11; O 12; O 13; O15; O17; O 18; O 20; O 21: O 22; O 23; O 24), while in only two of them (9%) there has been a decrease (O 09; O 19). In two hospitals (9%) there have been no oscillations in consumption over the last two years (O 04; O 14). There are only two hospitals with a consumption range from 40 to 50 DDD/100 BD. In seven hospitals it ranges from 51 to 60 DDD/100 BD. Three general hospitals have a consumption range from 61 to 70 DDD/100 BD, six from 71 to 80 DDD/100 BD, four over 80 DDD/100 BD and in only one hospital consumption reached over 100DDD/100BD, which is the highest ever.

Antibiotic consumption in psychiatric hospitals ranges from 2.95 to 12.63 DDD/100 BD (Table 18). Figure 17 shows antibiotic use by classes. In 2020, five psychiatric hospitals registered an increase in consumption (P 02; P 03; P 06; P08; P 09), while two hospitals recorded a decreasing trend (P 01; P 04). In two hospitals (P 05; P07) there have been no oscillations in antibiotic consumption in the last two years. Table 19 and Figure 18 show the frequency of prescribing antibiotics in psychiatric hospitals over the last four years.

Specialized hospitals are divided into two large groups with regard to their patient profile, and they are characterized by a wide span of antibiotic consumption. In the first group there are 10 hospitals where acute/chronic patients are treated, while the other consists of 14 rehabilitation facilities. The first group has the consumption range from 8.21 to 66.98 DDD/100 BD. Four hospitals (S 01; S 13; S 21; S 22) registered an increase in antibiotic consumption (Table 20; Figure 19). In the other group, the range is from 0.75 to 10.53 DDD/100 BD (Table 21; Figure 20) and only two hospitals registered an increase in consumption (S 05; S 08). Figure 19 shows consumption by classes of antibiotics. Table 21 and Figure 20 show antibiotic prescribing over the last four years. In 2019 one hospital (S 25) had the highest increase in consumption but in 2020 its consumption dropped to the level similar to previous years.

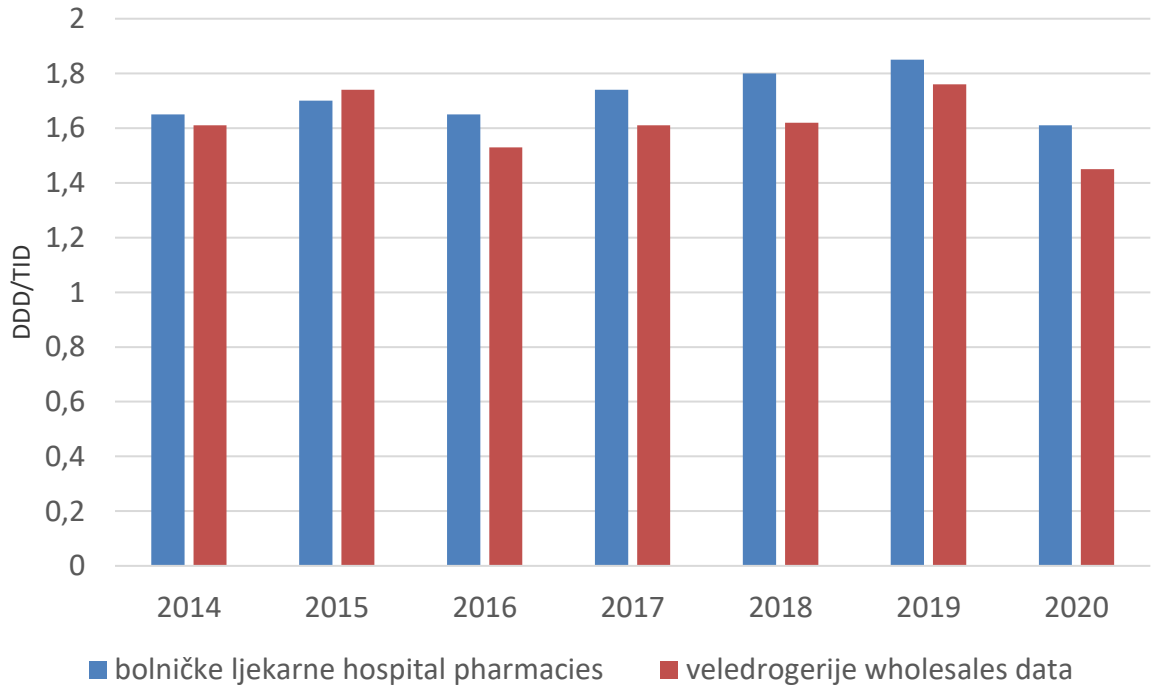
There has been a linear increase in hospital antibiotic consumption which peaked in 2020. In 2020 there was the highest ever increase in prescribing of cephalosporins (which make up 30% of total consumption). Antibiotics classified as “other” were in the third place, which is quite perturbing since this category contains reserve antibiotics. Generally, there has been an increasing trend in antibiotic consumption in Croatia, including the rise in the use of reserve antibiotics, which peaked in 2020 because of the global pandemic of coronavirus. It led to

prolonged ICU hospitalization and extensive use of antimicrobial drugs in order to fight secondary bacterial infections. Since antibiotic consumption leads to developing resistance to them, it is vital to implement antibiotic stewardship in all hospitals as soon as possible.

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

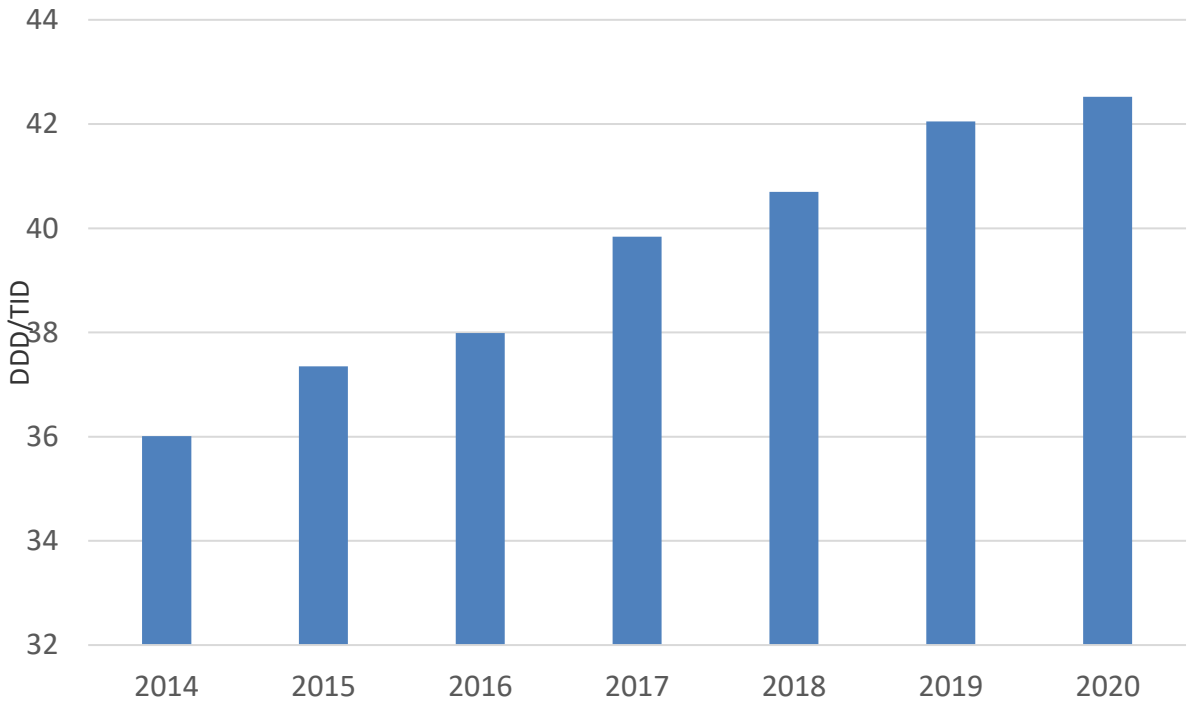
Slika 8. / *Figure 8.*
Bolnička potrošnja antibiotika (DDD/TID) usporedba podataka bolničkih ljekarni i veledrogerija /
Hospital antibiotic consumption (DDD/TID) comparison between hospital pharmacy data and wholesales data



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

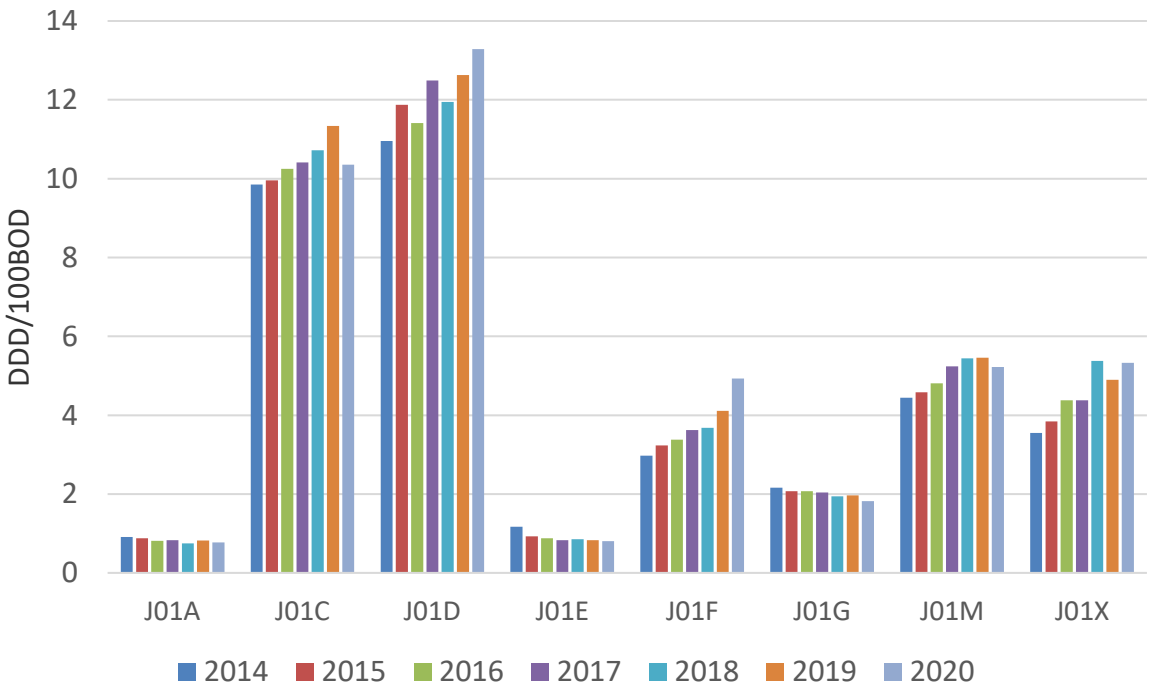
Slika 9. */ Figure 9.*
Bolnička potrošnja antibiotika (DDD/100BOD)
Hospital antibiotic consumption (DDD/100 BD)



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
J01A	0,91	0,88	0,81	0,83	0,75	0,82	0,77
J01C	9,85	9,96	10,25	10,41	10,72	11,34	10,36
J01D	10,96	11,87	11,41	12,49	11,95	12,63	13,29
J01E	1,17	0,93	0,88	0,83	0,85	0,83	0,81
J01F	2,97	3,23	3,38	3,62	3,68	4,11	4,93
J01G	2,16	2,07	2,07	2,04	1,94	1,97	1,82
J01M	4,44	4,58	4,81	5,24	5,44	5,46	5,22
J01X	3,55	3,84	4,38	4,38	5,38	4,90	5,33

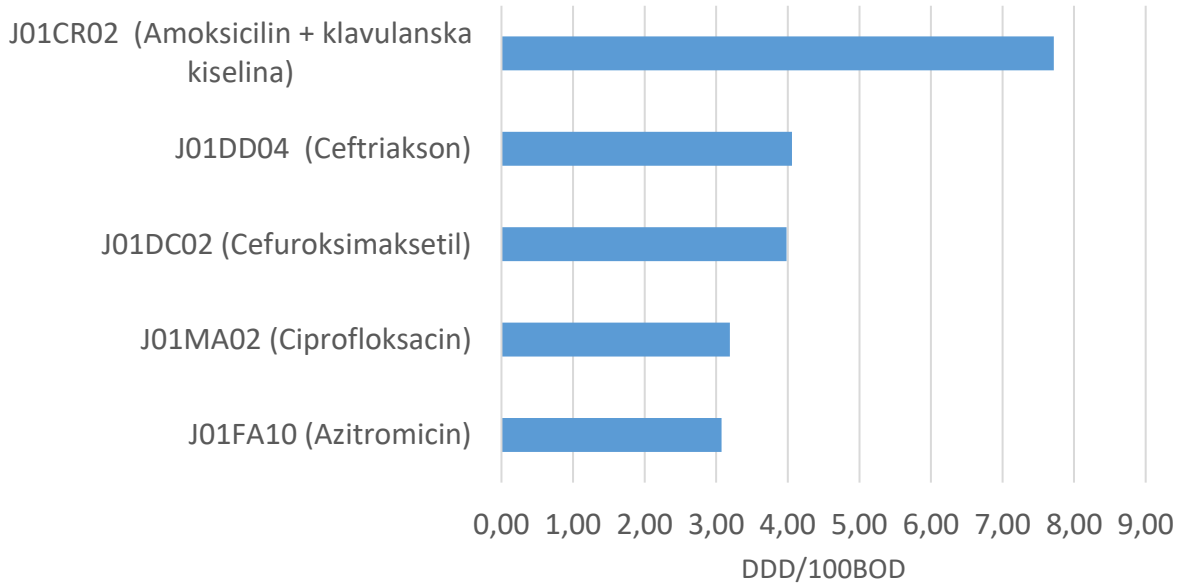
Slika 10. */ Figure 10.*
Bolnička potrošnja antibiotika (DDD/100 BOD) po klasama, izvor podataka – bolničke ljekarne/
Hospital antibiotic consumption (DDD/100 BD) by class, origin of data - hospital pharmacies



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

klasa	DDD/100BOD
J01CR02 (Amoksicilin + klavulanskakiselina)	7,71
J01DD04 (Ceftriakson)	4,06
J01DC02 (Cefuroksimaksetil)	3,98
J01MA02 (Ciprofloksacin)	3,19
J01FA10 (Azitromicin)	3,07

Slika 11. */ Figure 11.*
Bolnička potrošnja antibiotika „top 5“ antibiotika – DDD/BOD, izvor podataka – bolničke ljekarne /
Hospital antibiotic consumption „top 5“antibiotics – DDD/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 2010-2020/

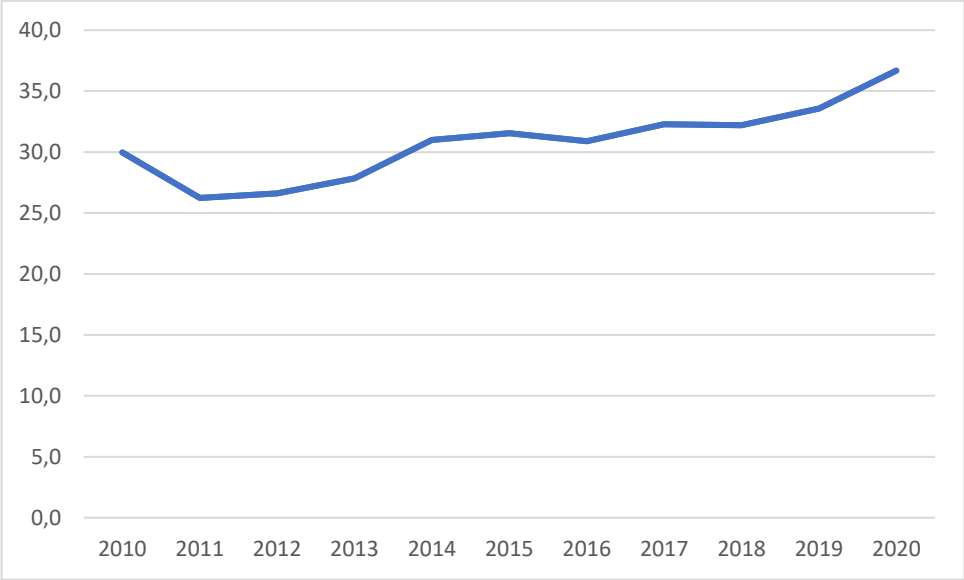
The proportion of glycopeptides (J01XA), third-generation cephalosporin*s (J01DD), fourth-generation cephalosporins*, (J01DE), monobactams* (J01DF), carbapenems* (J01DH), fluoroquinolones* (J01MA), polymyxins* (J01XB), piperacillin and tazobactam* (J01CR05), linezolid* (J01XX08), tedizolid* (J01XX11) and daptomycin* (J01XX09) consumption out of total consumption of antibacterials for systemic use in the hospital (DDD/ TID) 2010-2020*

	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

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 2010-2020/

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) 2010-2020

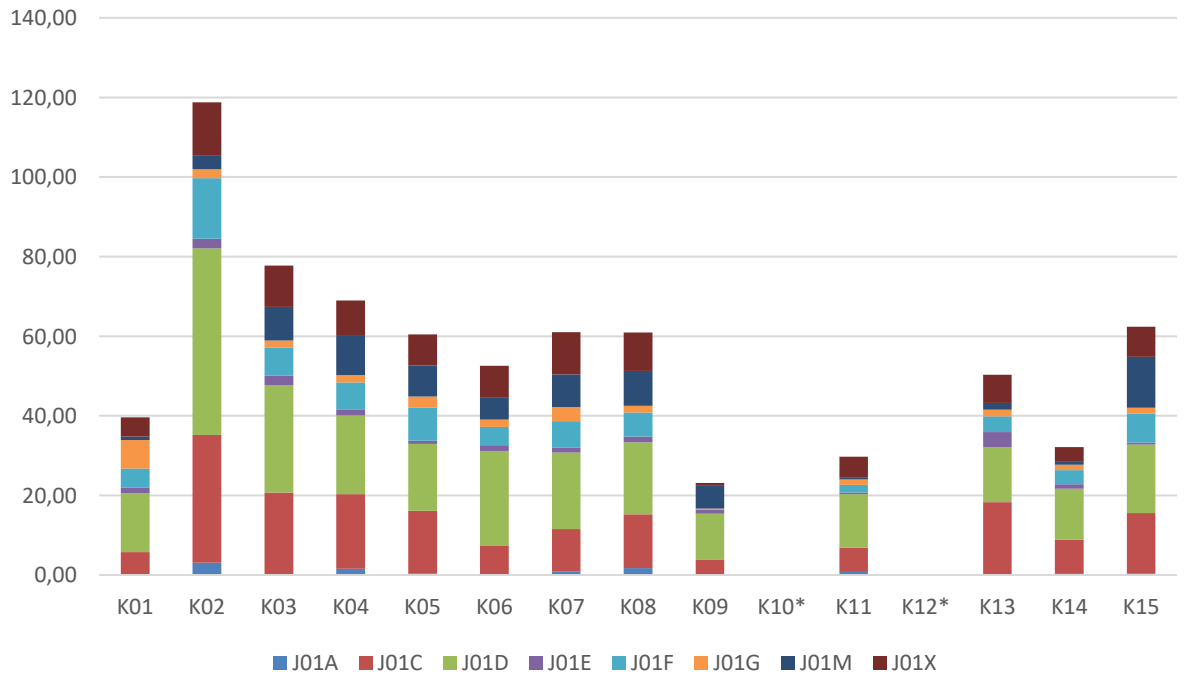


Tablica 14. */ Table 14.*
KLINIČKE USTANOVE - POTROŠNJA ANTIBIOTIKA 2020.
CLINICAL INSITUTIONS – ANTIBIOTIC CONSUMPTION IN 2020

	DDD/100 BOD, DDD/100BD								
USTANOVA INSTITUTION	UKUPNO TOTAL	JO1A	JO1C	JO1D	JO1E	JO1F	JO1G	JO1M	JO1X
K 01	39,64	0,14	5,60	14,81	1,44	4,79	7,16	0,83	4,86
K 02	118,77	3,12	32,06	46,90	2,42	15,20	2,25	3,53	13,29
K 03	77,76	0,23	20,46	27,07	2,29	7,08	1,81	8,48	10,36
K 04	69,01	1,57	18,78	19,75	1,51	6,77	1,84	10,09	8,70
K 05	60,47	0,46	15,67	16,86	0,80	8,28	2,82	7,77	7,83
K 06	52,54	0,24	7,20	23,77	1,44	4,61	1,82	5,47	8,00
K 07	61,03	0,88	10,70	19,22	1,22	6,67	3,50	8,18	10,66
K 08	60,94	1,71	13,57	18,09	1,42	6,06	1,66	8,76	9,67
K 09	23,12		3,88	11,50	1,04	0,14	0,13	5,70	0,74
K 10*									
K 11	29,71	1,03	5,82	13,49	0,37	1,95	1,35	0,57	5,13
K 12*									
K 13	50,34	0,07	18,20	13,89	3,74	3,93	1,76	1,65	7,10
K 14	32,15	0,29	8,59	12,79	1,17	3,47	1,44	0,72	3,69
K 15	62,38	0,48	15,05	17,28	0,47	7,31	1,43	12,81	7,55

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

Slika 13. */ Figure 13.*
KLINIČKE USTANOVE - POTROŠNJA ANTIBIOTIKA 2007.-2020.
CLINICAL INSITUTIONS – ANTIBIOTIC CONSUMPTION IN 2007-2020

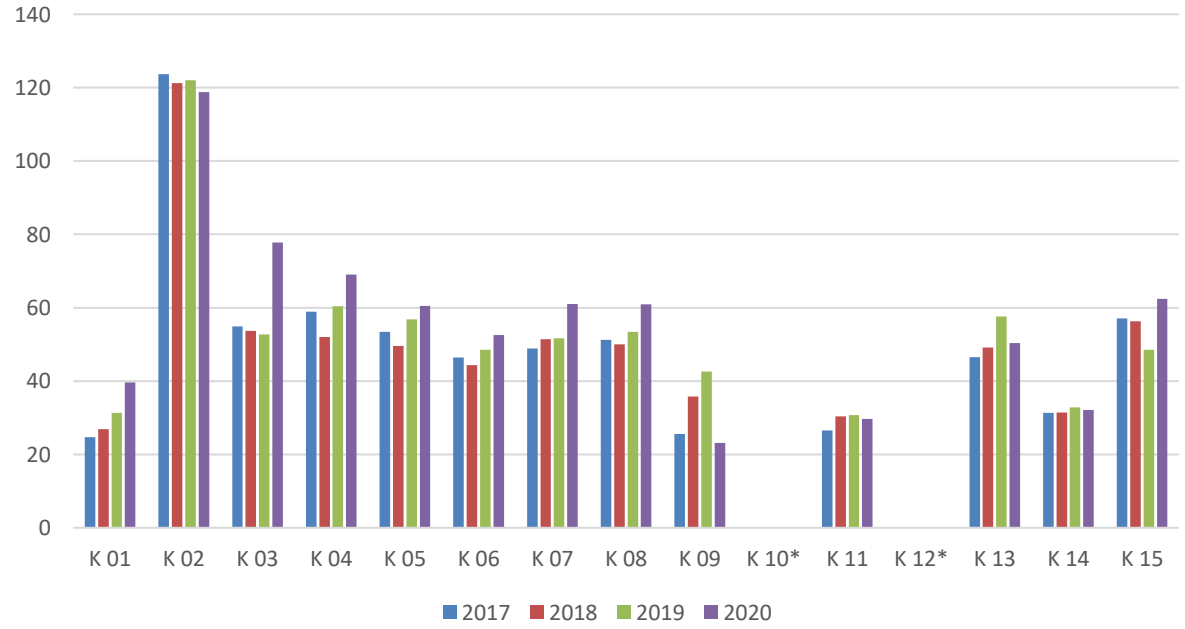


Tablica 15. */ Table 15.*
KLINIČKE USTANOVE - POTROŠNJA ANTIBIOTIKA 2017-2020.
CLINICAL INSITUTIONS – ANTIBIOTIC CONSUMPTION IN 2017-2020

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

* 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.-2020.
CLINICAL INSITUTIONS – ANTIBIOTIC CONSUMPTION IN 2017-2020

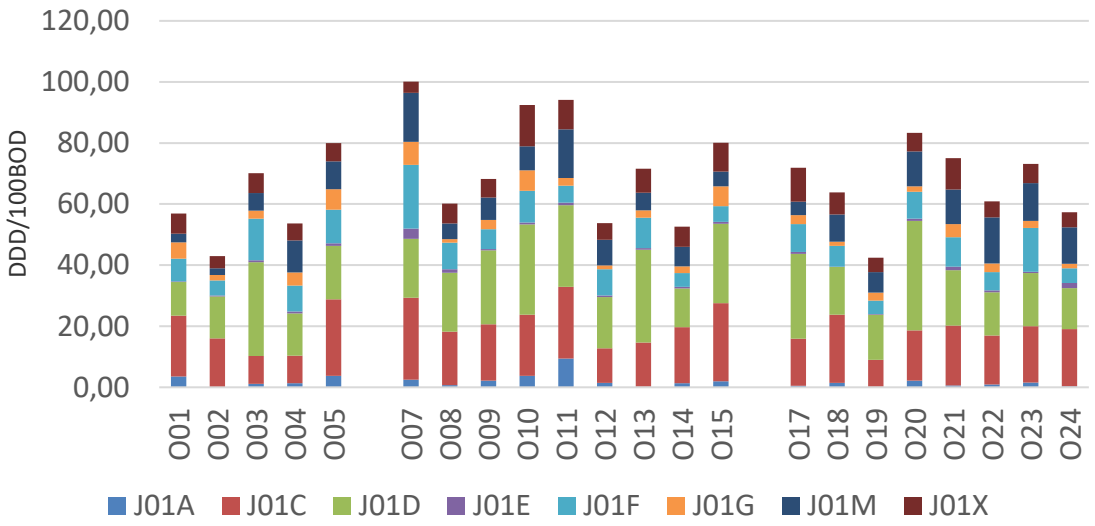


Tablica 16. */ Table 16.*
OPĆE BOLNICE - POTROŠNJA ANTIBIOTIKA 2020.
GENERAL HOSPITALS – ANTIBIOTIC CONSUMPTION IN 2020

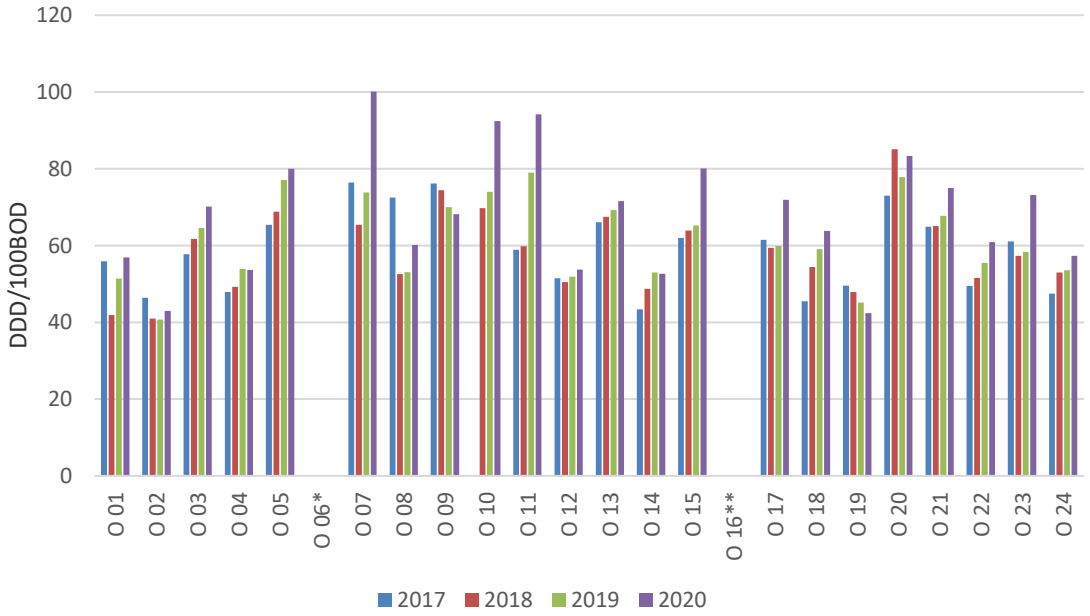
USTANOVA INSTITUTION	UKUPNO TOTAL	DDD/100 BOD, DDD/100 BD							
		JO1A	JO1C	JO1D	JO1E	JO1F	JO1G	JO1M	JO1X
O 01	56,92	3,55	19,88	11,00	0,29	7,41	5,31	2,88	6,60
O 02	42,98	0,13	15,90	13,71	0,32	4,91	1,75	2,29	3,97
O 03	70,15	1,10	9,19	30,69	0,63	13,58	2,63	5,84	6,49
O 04	53,66	1,35	9,01	13,85	0,61	8,51	4,26	10,46	5,61
O 05	79,98	3,76	25,04	17,54	0,81	11,03	6,67	9,10	6,03
O 06*									
O 07	100,11	2,46	26,83	19,30	3,35	20,86	7,58	16,09	3,63
O 08	60,18	0,76	17,41	19,34	1,15	8,67	1,16	5,21	6,48
O 09	68,19	2,19	18,41	24,28	0,43	6,44	3,02	7,37	6,06
O 10	92,41	3,80	19,96	29,61	0,60	10,38	6,68	7,94	13,45
O 11	94,17	9,43	23,44	26,76	0,82	5,59	2,54	15,91	9,67
O 12	53,77	1,44	11,35	16,76	0,52	8,60	1,21	8,36	5,51
O 13	71,55	0,20	14,41	30,42	0,50	9,97	2,43	5,74	7,86
O 14	52,65	1,35	18,36	12,61	0,62	4,50	2,12	6,48	6,61
O 15	80,11	2,00	25,59	25,94	0,66	5,17	6,47	4,87	9,42
O 16**									
O 17	71,87	0,51	15,36	27,85	0,61	9,16	2,87	4,45	11,06
O 18	63,85	1,44	22,34	15,65	0,10	6,83	1,32	8,87	7,31
O 19	42,42	0,23	8,75	14,82	0,16	4,46	2,59	6,68	4,72
O 20	83,33	2,20	16,50	35,85	0,69	8,80	1,74	11,44	6,12
O 21	75,03	0,58	19,61	18,11	1,21	9,68	4,21	11,36	10,27
O 22	60,88	0,93	16,00	14,15	0,68	5,90	2,90	15,03	5,28
O 23	73,12	1,51	18,53	17,38	0,39	14,40	2,28	12,42	6,21
O 24	57,34	0,30	18,81	13,34	1,67	4,84	1,48	11,96	4,94

*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 2020.
GENERAL HOSPITALS – ANTIBIOTIC CONSUMPTION 2020



Slika 16. / *Figure 16.*
OPĆE BOLNICE - POTROŠNJA ANTIBIOTIKA 2017.-2020.
GENERAL HOSPITALS – ANTIBIOTIC CONSUMPTION 2017-2020



Tablica 17. / *Table 17.*

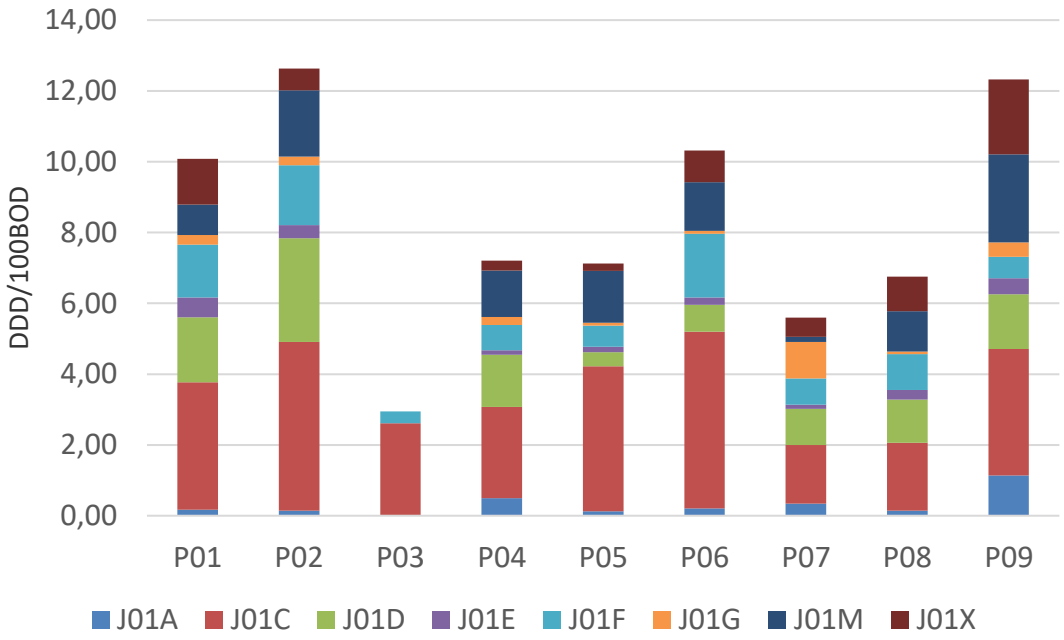
OPĆE BOLNICE - POTROŠNJA ANTIBIOTIKA 2017.-2020.
GENERAL HOSPITALS – ANTIBIOTIC CONSUMPTION IN 2017-2020

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

Tablica 18. */ Table 18.*
PSIHIJATRIJSKE USTANOVE - POTROŠNJA ANTIBIOTIKA 2020.
PSYCHIATRIC INSTITUTIONS – ANTIBIOTIC CONSUMPTION IN 2020

USTANOVA INSTITUTION	DDD/100 BOD, DDD/100BD								
	UKUPNO / TOTAL	JO1 A	JO1 C	JO1 D	JO1 E	JO1 F	JO1 G	JO1 M	JO1 X
P 01	10,08	0,17	3,60	1,84	0,55	1,50	0,27	0,86	1,29
P 02	12,63	0,14	4,77	2,93	0,37	1,69	0,24	1,88	0,61
P 03	2,95	0,00	2,61	0,00	0,00	0,34	0,00	0,00	0,00
P 04	7,21	0,49	2,58	1,47	0,12	0,72	0,22	1,31	0,28
P 05	7,13	0,12	4,10	0,40	0,15	0,60	0,08	1,46	0,21
P 06	10,31	0,21	4,99	0,76	0,22	1,79	0,08	1,37	0,90
P 07	5,60	0,34	1,66	1,01	0,12	0,74	1,03	0,14	0,55
P 08	6,75	0,14	1,91	1,22	0,28	1,01	0,08	1,14	0,97
P 09	12,33	1,14	3,57	1,54	0,46	0,60	0,41	2,48	2,12

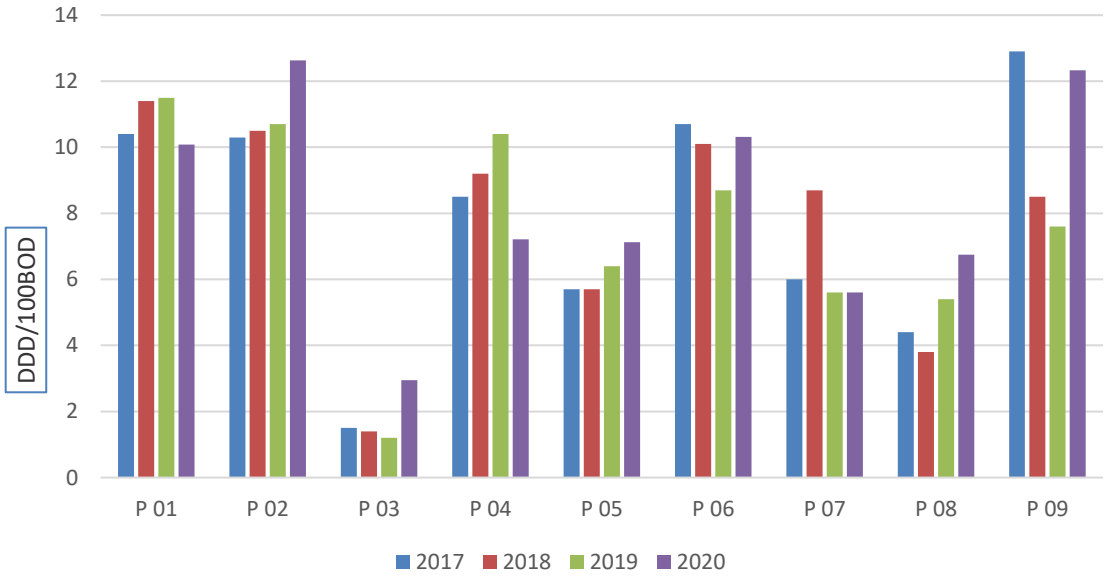
Slika 17. / *Figure 17.*
PSIHIJATRIJSKE USTANOVE - POTROŠNJA ANTIBIOTIKA 2020.
PSYCHIATRIC INSTITUTIONS – ANTIBIOTIC CONSUMPTION 2020



Tablica 19. / *Table 19.*
PSIHIJATRIJSKE USTANOVE - POTROŠNJA ANTIBIOTIKA 2017.-2020.
PSYCHIATRIC INSTITUTIONS – ANTIBIOTIC CONSUMPTION IN 2017-2020

USTANOVA INSTITUTION	DDD/100 BOD, DDD/100BD			
	2017	2018	2019	2020
P 01	10,4	11,4	11,5	10,08
P 02	10,3	10,5	10,7	12,63
P 03	1,5	1,4	1,2	2,95
P 04	8,5	9,2	10,4	7,21
P 05	5,7	5,7	6,4	7,13
P 06	10,7	10,1	8,7	10,31
P 07	6,0	8,7	5,6	5,60
P 08	4,4	3,8	5,4	6,75
P 09	12,9	8,5	7,6	12,33

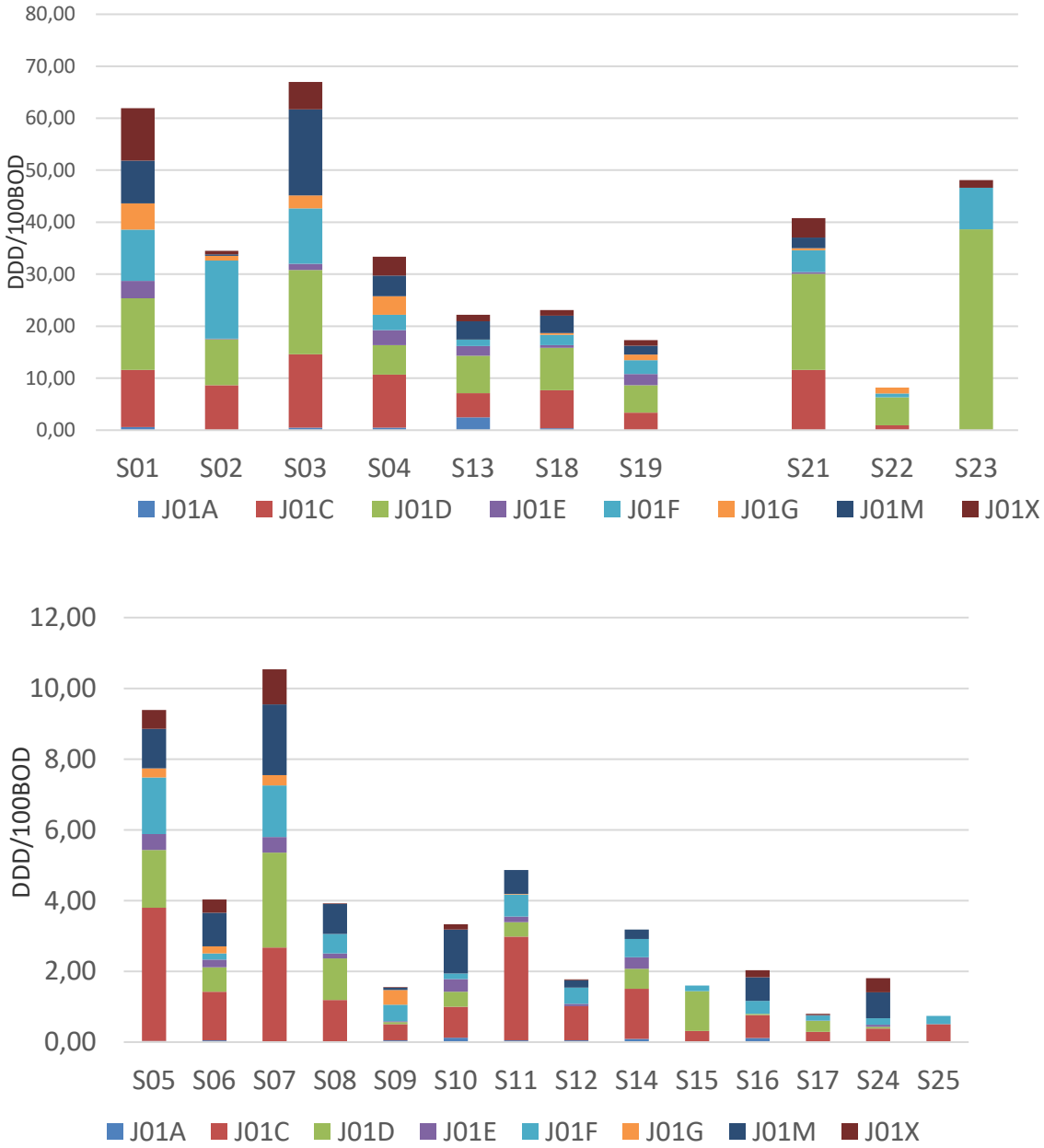
Slika 18. / *Figure 18.*
PSIHIJATRIJSKE USTANOVE - POTROŠNJA ANTIBIOTIKA 2017.-2020.
PSYCHIATRIC INSTITUTIONS – ANTIBIOTIC CONSUMPTION 2017-2020



Tablica 20. */ Table 20.*
SPECIJALNE BOLNICE - POTROŠNJA ANTIBIOTIKA 2020.
SPECIALISED HOSPITALS – ANTIBIOTIC CONSUMPTION IN 2020

	DDD/100 BOD, DDD/100 BD								
USTANOVA NSTITUTION	UKUPNO TOTAL	JO1A	JO1C	JO1D	JO1E	JO1F	JO1G	JO1M	JO1X
S 01	61,95	0,58	11,04	13,77	3,35	9,82	5,07	8,20	10,11
S 02	34,51	0,00	8,64	8,87	0,08	15,03	0,91	0,27	0,71
S 03	66,98	0,47	14,14	16,19	1,18	10,68	2,48	16,56	5,28
S 04	33,38	0,46	10,21	5,66	2,92	2,93	3,57	3,96	3,67
S 13	22,21	2,48	4,65	7,16	1,89	1,24	0,04	3,46	1,29
S 18	23,09	0,34	7,36	8,13	0,53	1,97	0,34	3,33	1,09
S 19	17,29	0,00	3,37	5,30	2,11	2,71	1,08	1,70	1,03
S 20*									
S 21	40,79	0,05	11,56	18,46	0,37	4,20	0,40	2,04	3,73
S 22	8,21	0,00	0,93	5,40	0,00	0,73	1,16	0,00	0,00
S 23	48,08	0,00	0,00	38,63	0,00	8,02	0,00	0,00	1,43
S 05	9,39	0,03	3,76	1,63	0,45	1,61	0,25	1,11	0,54
S 06	4,03	0,05	1,37	0,69	0,22	0,17	0,20	0,95	0,37
S 07	10,53	0,00	2,67	2,68	0,44	1,46	0,29	1,99	0,99
S 08	3,92	0,00	1,19	1,18	0,14	0,55	0,00	0,84	0,02
S 09	1,55	0,05	0,46	0,06	0,02	0,47	0,41	0,07	0,01
S10	3,33	0,12	0,88	0,43	0,36	0,16	0,00	1,23	0,16
S11	4,87	0,05	2,93	0,41	0,16	0,62	0,02	0,67	0,00
S12	1,77	0,05	0,97		0,06	0,46		0,21	0,02
S14	3,18	0,09	1,42	0,56	0,33	0,52		0,27	
S15	1,60		0,32	1,12		0,16			
S16	2,03	0,12	0,65	0,04		0,36		0,67	0,20
S17	0,80		0,29	0,31	0,01	0,14		0,02	0,03
S24	1,81		0,38	0,05	0,06	0,18		0,74	0,40
S25	0,75		0,51			0,24			

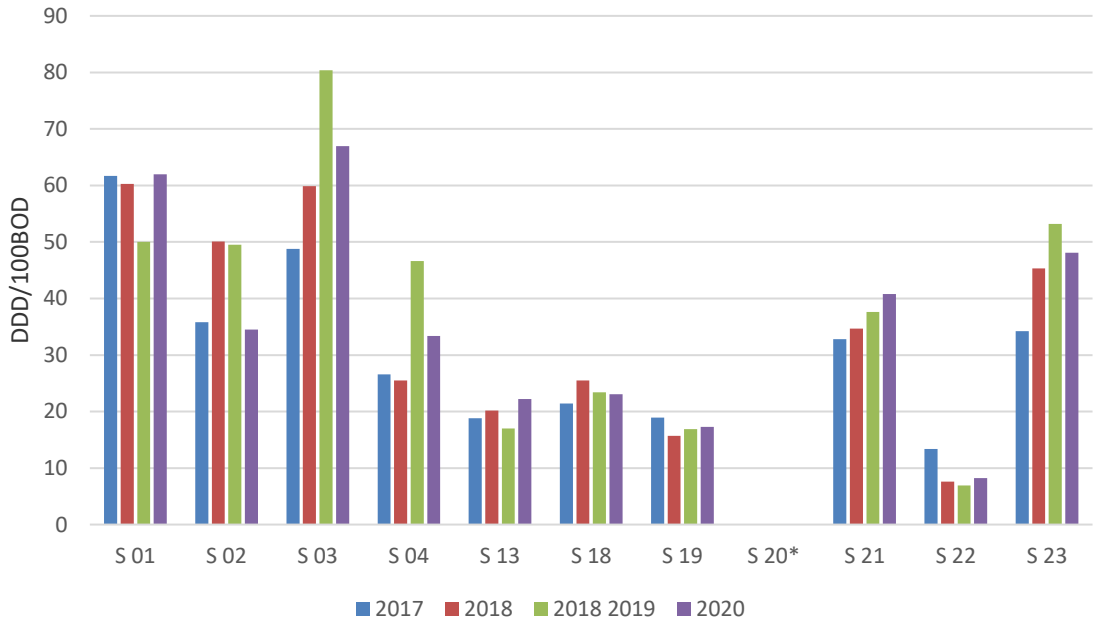
Slika 19. / *Figure 19.*
SPECIJALNE BOLNICE - POTROŠNJA ANTIBIOTIKA 2020.
SPECIALISED HOSPITALS – ANTIBIOTIC CONSUMPTION 2020

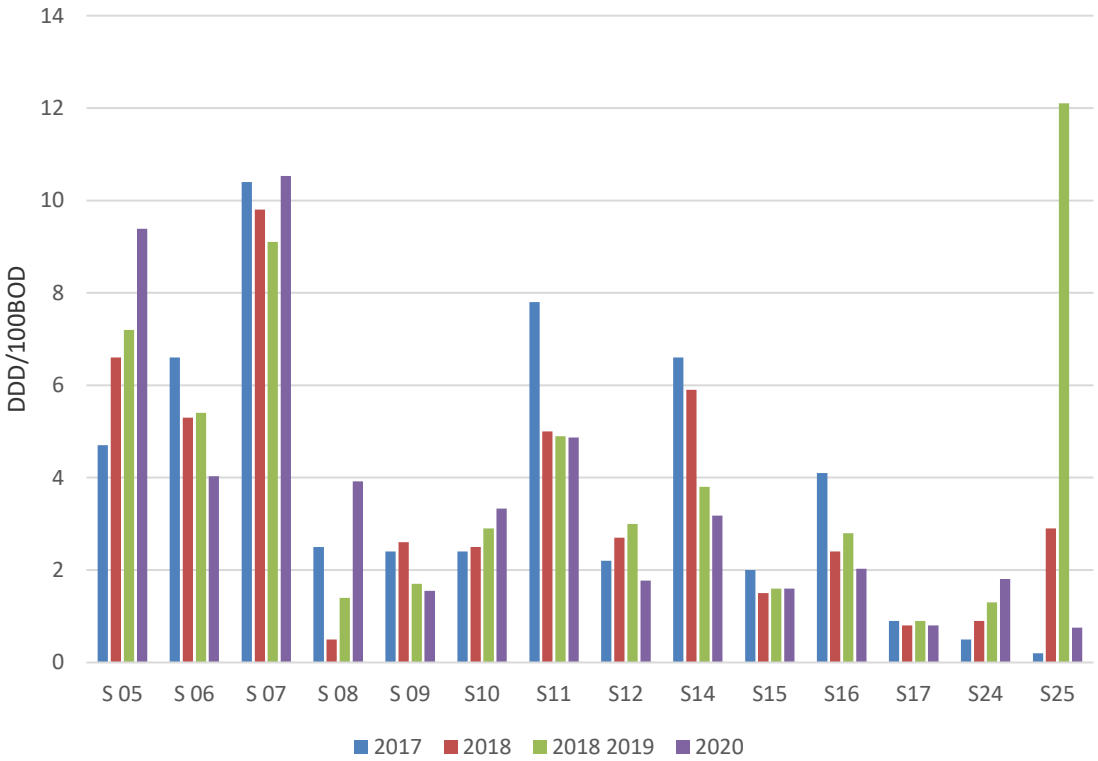


Tablica 21. */ Table 21.*
SPECIJALNE BOLNICE - POTROŠNJA ANTIBIOTIKA 2017.-2020.
SPECIALISED HOSPITALS – ANTIBIOTIC CONSUMPTION IN 2017-2020

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

Slika 20. / *Figure 20.*
SPECIJALNE BOLNICE - POTROŠNJA ANTIBIOTIKA 2017.-2020.
SPECIALISED HOSPITALS – ANTIBIOTIC CONSUMPTION 2017-2020





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*