HRVATSKA AKADEMIJA MEDICINSKIH ZNANOSTI
KOLEGIJ JAVNOG ZDRAVSTVA
ODBOR ZA PRAĆENJE REZISTENCIJE BAKTERIJA NA ANTIBIOTIKE U REPUBLICI HRVATSKOJ
CROATIAN ACADEMY OF MEDICAL SCIENCES
PUBLIC HEALTH COLLEGIUM
COMMITTEE FOR ANTIBIOTIC RESISTANCE SURVEILLANCE IN CROATIA

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

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Osjetljivost i rezistencija bakterija na antibiotike u Republici Hrvatskoj u 2023.g.

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PREDGOVOR:

U 2023.g. je vidljivo da je prekinut trend porasta nekih multiplorezistentnih uzročnika, uočen tijekom pandemije COVID-19, no za neke uzročnike se apsolutni brojevi izolata i stope rezistencije još nisu vratili na vrijednosti u vrijeme prije pandemije COVID-19. U svojoj rezoluciji od lipnja 2023., Europska komisija je postavila konkretne ciljeve smanjenja potrošnje antibiotika i smanjenja stopa rezistencije do 2030.g. u Europi, prema kojima je svaka zemlja članica EU, dobila proporcionalno određene ciljeve. Od pet usvojenih ciljeva, Hrvatskoj će najteže biti suočiti se sa zahtjevom smanjenja incidencije na karbapeneme rezistentne *K. pneumoniae*, čije su stope naglo narasle tijekom pandemije, a očekivano smanjenje se uspoređuje s vrijednostima prije pandemije, tj. podacima iz 2019.g. Za smanjenje stopa rezistencije i incidencije infekcija uzrokovanih multiplorezistentnim uzročnicima bit će potrebno pojačati naše napore u području prevencije i kontrole infekcija te uvesti i provoditi programe upravljanja antimikrobnom terapijom. S obzirom da je velik broj naših bolnica trenutno u rekonstrukciji, prilika je to da se poboljša infrastruktura koja će podržavati lakše provođenje standardnih mjera predostrožnosti i mjera izolacije, kao što je npr. povećani udio smještaja bolesnika u jednokrevetnim sobama. S druge strane potrebno je racionalizirati potrošnju antibiotika u izvanbolničkom i bolničkom sektoru za što su potrebni intenzivniji napori u edukaciji, od dodiplomske nastave do edukacije samih edukatora, usmjereni prvenstveno protiv prakticiranja defenzivne medicine u kojoj se rješenja traže u širokoj primjeni široko spektralnih antibiotika. Racionalizaciju primjene antibiotika treba pratiti i brza mikrobiološka dijagnostika, za koju danas postoje brojne tehnološke mogućnosti. Treba, ipak, imati na umu da je osim tehnoloških mogućnosti bitno osigurati i dostupnost izrade i interpretacije mikrobioloških testova sve dane u tjednu, a za životno ugrožene pacijente i 24/7 kako bi rezultati testiranja pravodobno usmjeravali liječenje bolesnika. U 2023.g. održan je jubilarni X. tečaj o testiranju osjetljivosti na antibiotike, kojem je ove godine glavna tema bila upravo upravljanje antimikrobnom terapijom i mikrobiološkom dijagnostikom od indikacije za mikrobiološko testiranje do interpretacije nalaza. U borbi protiv širenja rezistencije na antibiotike Hrvatska sudjeluje u inicijativama Svjetske zdravstvene organizacije (WHO) i Europskog centra za prevenciju i kontrolu bolesti (ECDC) te je tako i u 2023.g., u studenom, organiziran tradicionalni simpozij povodom obilježavanja Europskog dana i Svjetskog tjedna svjesnosti o antimikrobnim lijekovima. Bila je to prilika prokomentirati situaciju u Hrvatskoj i predstaviti ciljeve koje je Europska komisija postavila za Europu i pojedinačne zemlje članice. Ostvarivanje tih ciljeva ovisi o zajedničkim naporima mnogih sudionika u sektoru humane i veterinarske medicine. Raspolaganje pouzdanim podacima o potrošnji antibiotika i stopama rezistencije prvi je korak u kontroli širenja rezistencije, a pred svima nama je vrlo zahtjevan izazov provođenja intervencija sa ciljem mijenjanja kliničke prakse.

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

PREFACE

In 2023, it is evident that the increasing trend for some multidrug-resistant pathogens, observed during the COVID-19 pandemic, has been interrupted, but for some pathogens the absolute numbers of isolates and resistance rates have not yet returned to the values before the COVID-19 pandemic. In its resolution from June 2023, the European Commission set specific goals for reducing the consumption of antibiotics and reducing resistance rates by 2030 in Europe, according to which each EU member state received proportionally determined goals. Of the five adopted goals, it will be the most difficult for Croatia to face the requirement to reduce the incidence of carbapenem-resistant *K. pneumoniae*, the rates of which increased sharply during the pandemic, and the expected reduction is compared with the values before the pandemic, i.e. data from 2019. To reduce the resistance rates and the incidence of infections caused by multidrug-resistant pathogens, it will be necessary to strengthen our efforts in the area of infection prevention and control and to introduce and implement antimicrobial stewardship programs. Given that a large number of our hospitals are currently undergoing reconstruction, this is an opportunity to improve the hospital infrastructure that will support better compliance with standard and isolation precautions, such as, for example, an increased proportion of patients' accommodation in single rooms. On the other hand, it is necessary to optimize antibiotic consumption in outpatient and hospital settings. This requires more intensive efforts in education, from undergraduate education to the education of educators, directed primarily against practicing defensive medicine which typically leads to the widespread use of broad-spectrum antibiotics. The optimization of the antibiotic use should be accompanied by rapid microbiological diagnostics, for which there are numerous technological possibilities today. It should, however, be kept in mind that, in addition to technological possibilities, it is also important to ensure the availability of microbiological testing and results interpretation every day of the week, and for severely ill patients 24/7, so that the test results can guide patient management in a timely manner. In 2023, the jubilee 10th Course on antibiotic susceptibility testing was held, the main topic of which was specifically antimicrobial and diagnostic stewardship focusing on sample processing from the indication for testing to the interpretation of findings. In the fight against the spread of antibiotic resistance, Croatia participates in the initiatives of the World Health Organization (WHO) and the European Center for Disease Prevention and Control (ECDC). In line with international initiatives, a traditional Symposium to mark the European Antimicrobial Awareness Day and the World Antimicrobial Awareness Week was organized in November 2023. This was an opportunity to discuss the situation in Croatia and to present the goals that the European Commission has set for Europe and individual member states. Achieving these goals depends on the joint efforts of many actors in the human and veterinary medicine sector. Having reliable data on antibiotic consumption and resistance rates is the first step in controlling the spread of resistance, and we all are facing the very demanding challenge of implementing interventions aimed at changing clinical practice.

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

PRAĆENJE REZISTENCIJE NA ANTIBIOTIKE U HRVATSKOJ

- Praćenje rezistencije na antibiotike na nacionalnoj razini je u Hrvatskoj započelo 1996. g. osnivanjem **Odbora za praćenje rezistencije bakterija na antibiotike** pri Akademiji medicinskih znanosti Hrvatske. Odbor je u početku prikupljao podatke iz 17 centara odabranih da geografski predstavljaju pouzdan uzorak za Hrvatsku, no s vremenom su se Odboru priključili gotovo svi mikrobiološki laboratoriji u zemlji tako da podaci pokrivaju više od 90% hrvatske populacije. Sudjelovanje u radu Odbora je započeto na dobrovoljnoj bazi, no nakon pristupanja Europskoj uniji sudjelovanje u nacionalnom praćenju rezistencije postaje i obveza. Standardizacija rada mikrobioloških laboratorija prepoznata je kao prioritet od samog početka rada Odbora te su kao obavezni standardi unutar hrvatske mreže praćenja prihvaćeni američki Clinical and Laboratory Standards Institute (CSLI) standardi do 2010.g., a od 2011.g. svi su hrvatski laboratoriji usvojili standarde europskog odbora The European Committee on Antimicrobial Susceptibility Testing (EUCAST).
- **The European Committee on Antimicrobial Susceptibility Testing (EUCAST)** je odbor osnovan unutar Europskog društva kliničke mikrobiologije i infektologije (The European Society of Clinical Microbiology and Infectious Diseases, ESCMID) sa ciljem harmonizacije metodologije testiranja osjetljivosti na antibiotike među europskim zemljama, no EUCAST standardi su sve više prihvaćeni i na drugim kontinentima. Kada je EUCAST 2010.g. donijeo jedinstvene europske standarde za disk difuzijsku metodu, hrvatski laboratoriji su, zahvaljujući dobro uhodanoj mreži Odbora za praćenje rezistencije, lako usvojili nove europske standarde i sinkronizirano 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 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 Susceptibility 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 2023. GODINI

ANTIBIOTIC RESISTANCE IN 2023

Arjana Tambić Andrašević
Sandra Lucić

Klinika za infektivne bolesti "Dr. Fran Mihaljević"
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UVOD

Od početka praćenja svi laboratoriji koji sudjeluju u nacionalnom praćenju rezistencije obavezni su pridržavati se opisane metodologije prijavljivanja, primjenjivati iste standarde u testiranju osjetljivosti i sudjelovati u vanjskoj kontroli kvalitete. Prelaskom europskog projekta European Antimicrobial Resistance Surveillance System (EARSS) u EARS-Net program Europskog centra za prevenciju i kontrolu bolesti, praćenje rezistencije na nacionalnoj razini postalo je obavezno u svim zemljama članicama Europske unije pa tako, od ulaska u Europsku uniju, i u Hrvatskoj. Povjerenstvo za metodologiju određivanja osjetljivosti na antibiotike (nacionalno povjerenstvo za antibiotike, engl. „national antibiotic committee", NAC) je tijelo pri Odboru za praćenje rezistencije koje prati novosti u standardima European Committee on Antimicrobial Susceptibility Testing (EUCAST) i na zimskom sastanku Odbora donosi preporuke o standardima važećim za narednu godinu. Zahvaljujući redovitim sastancima Odbora i djelovanju nacionalnog povjerenstva za antibiotike postignut je visok stupanj standardizacije u među laboratorijskom 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. Premda se na lokalnoj razini podaci mogu analizirati po izolatu, manjak ovakve organizacije praćenja je da na nacionalnoj razini, nije moguće analizirati podatke prema demografskim osobinama pacijenata, vrsti uzorka ili pratiti križnu rezistenciju. Za sada ovaj oblik praćenja, međutim, omogućuje uključivanje velikog broja izolata iz mnogih centara, što stope rezistencije čini vjerodostojnijima te omogućuje pravodobno otkrivanje sojeva s rijetkim mehanizmima rezistencije.

INTRODUCTION

From the very beginning of the surveillance program all laboratories that participate in the antibiotic resistance surveillance network are obliged to adhere to the specified surveillance methodology, comply with the same sensitivity testing standards and take part in the external quality assurance scheme (EQAS). Following transition of the European Antimicrobial Resistance Surveillance System (EARSS) project into the EARS-Net program of the European Center for Disease Prevention and Control (ECDC) antimicrobial resistance (AMR) surveillance at the national level became obligatory for all European Union Member States including Croatia. Croatian national antibiotic committee (NAC) for susceptibility testing methodology is a subcommittee of the Committee for antibiotic resistance surveillance and it closely follows developments within the European Committee on Antimicrobial Susceptibility Testing (EUCAST) and updates national susceptibility testing standards accordingly every year at the Committee winter meeting. Due to the regular Committee meetings and NAC activity a high level of interlaboratory standardization is achieved and the EQAS results demonstrate high reproducibility of delivered resistance data. Although this chapter reports aggregated national resistance data, these data represent a compilation of isolate based data analysed at the level of a local laboratory and great attention is given to exclude copy isolates and to test all isolates to all the antibiotics of the well-defined panel throughout the surveillance period. Thus, while it is possible to analyse isolate based data at the local level the pitfall of this surveillance scheme is that at the national level, data cannot be analysed by patient demographic data, sample type or cross-resistance. For the moment, however, this is the only feasible scheme that ensures collection of data for a large number of clinical isolates from a large number of centers which makes resistance rates representative and enables 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 31.12.2023.g. Rezultati za izolate streptokoka grupe A, salmonela, šigela i anaerobnih bakterija prikupljali su se, zbog malog broja izolata, tijekom cijele godine, od 1.1. do 31.12.2023. Podatke za 2023.g. podnijelo je 37 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 prvih 100 uzastopnih izolata

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

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

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

Tijekom 2023.g. korišteni su za testiranje i interpretaciju nalaza standardi europskog odbora, European Committee on Antimicrobial Susceptibility Testing (EUCAST) (Clinical Breakpoint Tables v. 13.0). 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. U 2019.g. je usvojena nova interpretacija S, I i R kategorija, što predstavlja najznačajniju izmjenu EUCAST standarda posljednjih godina. Od 2019.g. kategorija S znači ”osjetljiv uz standardno doziranje”, kategorija I ”osjetljiv uz povećanu izloženost” te kategorija R ”rezistentan”. U 2021.g. EUCAST standardi su za neke kombinacije mikroorganizama i antibiotika uveli odvojenu interpretaciju za slučaj infekcije središnjeg živčanog sustava i slučaj ostalih infekcija. Dogovorno, za potrebe praćenja prijavljuje se interpretacija za ”ostale (ne-meningitis) infekcije”. Od 2022.g. za anaerobe je dostupno testiranje disk difuzijskom metodom uz različite interpretacije za pojedine bakterijske vrste te se od 2022.g. rezistencija pratiti

odvojeno prema vrstama: *Bacteroides* spp., *Prevotella* spp., *Fusobacterium necrophorum*, *Clostridium perfringens*, *Cutibacterium acnes*.

Minimalne inhibitorne koncentracije (MIK) se određuju korištenjem gradijent testova (Etest, bioMérieux; MIC Test Strip, Liofilchem). Od 2017.g. usvojen je naputak EUCAST-a da se za određivanje MIK kolistina koristi mikrodilucija u bujonu (MICRONAUT MIC-Strip, Merlin Diagnostika; MIKROLATEST MIC, Erba Lachema). U skladu s upozorenjem EUCAST-a da je korištenje gradijent strip testova nepouzdano u određivanju osjetljivosti pneumokoka na penicilin, posebno u izolata s rasponom MIK vrijednosti 0.5 – 2.0 mg/L, Odbor je preporučio testiranje osjetljivosti pneumokoka na penicilin metodom mikrodilucije u bujonu, no za sada uporaba mikrodilucije u bujonu nije obavezni uvjet za prijavljivanje vrijednosti MIK penicilina za potrebe praćenja rezistencije.

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

Ciljane studije

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

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

U sklopu European Antimicrobial Resistance Surveillance System (EARSS) projekta, a potom EARS-Net programa Odbor posebno obrađuje rezistenciju u invazivnih izolata (iz krvi i likvora) bakterijskih vrsta *S. pneumoniae*, *S. aureus, E. faecalis, E. faecium, E. coli*, *K. pneumoniae, P. aeruginosa* i *Acinetobacter baumannii*. Za ove izolate referentni centar (RC) za praćenje rezistencije prikuplja i obrađuje demografske podatke pacijenata, a u svrhu detaljnije analize izolati se šalju u Zavod za kliničku mikrobiologiju Klinike za infektivne bolesti "Dr. F. Mihaljević". RC za praćenje rezistencije šalje podatke o invazivnim izolatima u The European Surveillance System (Tessy) Europskog centra za kontrolu bolesti (engl. "European Centre for Disease Prevention and Control", ECDC). Podaci o invazivnim izolatima od početka praćenja do 2023.g. prikazani su u zasebnom poglavlju ove publikacije.

Od 2001.g., uključivanjem u europski projekt The 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 2023.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 2023. Data on group A streptococci, salmonellae, shigellae and anaerobic bacteria were reported for the whole year, from 1 January to 31 December 2023 due to the small number of isolates. In 2023 thirty-seven 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 to 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 Center 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 Centre. The alert microorganisms include the following:

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

In 2023 all laboratories used the European Committee on Antimicrobial Susceptibility Testing (EUCAST) standards for susceptibility testing (Clinical Breakpoint Tables v. 13.0). Disk diffusion method is the most widely used susceptibility testing method in Croatian laboratories and minimal inhibitory concentration (MIC) testing is used for testing susceptibility in anaerobic bacteria and for detection of penicillin and ampicillin resistance in penicillin non-wild type pneumococci, glycopeptide resistance in staphylococci and colistin resistance in pseudomonas and acinetobacter. Every year at the Croatian Committee for Antibiotic Resistance Surveillance meeting in December the EUCAST updates for the coming year are discussed and adopted. Since 2019 the new interpretation of the S, I and R categories is in use, which represents the most significant change in EUCAST standards in recent years. From 2019 category "S" means "susceptible, standard dosing", category "I" "susceptible, increased exposure" and category "R" "resistant". In 2021 for some drug bug combinations EUCAST introduced separate interpretation for meningitis and other infections. For surveillance purposes it was agreed that interpretation for other (non-meningitis) infections will be reported. In 2022 disk diffusion testing standards became available for anaerobic bacteria with distinct interpretation for different species, so in 2022 separate reporting was introduced for the following species: *Bacteroides* spp., *Prevotella* spp., *Fusobacterium necrophorum*, *Clostridium perfringens*, *Cutibacterium acnes*.

Minimal inhibitory concentrations are determined by gradient tests (Etest, bioMérieux; MIC Test Strip, Liofilchem). In 2017 the EUCAST recommendation to use microbroth dilution for testing colistin MIC (MICRONAUT MIC-Strip, Merlin Diagnostika; MIKROLATEST MIC, Erba Lachema) was adopted. In line with the EUCAST warning that the use of gradient strip tests is unreliable in determining the susceptibility of pneumococci to penicillin, especially in isolates with a MIC range of 0.5 - 2.0 mg / L, the Committee recommended penicillin susceptibility testing in pneumococci to be done by broth microdilution method, but as for now, the use of broth microdilution is not mandatory for reporting the penicillin MIC values for surveillance purpose.

Bacterial species and antibiotics tested are listed in tables.

Focused studies

Data on *M. tuberculosis* was 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 analysed 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 Centre for Disease Control (ECDC) surveillance network. Data on invasive isolates from the beginning of surveillance until 2023 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 2023 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 Centre Zagreb for retesting and data analysis. Results are presented in a special chapter of this publication.

REZULTATI

U praćenju rezistencije u 2023.g. sudjelovalo je 37 centara u Hrvatskoj. Prosječni rezultati za Hrvatsku i rezultati za pojedinačne centre prikazani su u tablicama i grafovima u daljnjem tekstu. Rezultati laboratorija koji su prijavili manje od 30 izolata pojedine bakterijske vrste smatraju se nepouzdanim podacima za taj centar, ali su uvršteni u tablice i uključeni su u zbirne rezultate za RH. Podaci o izolatima malo vjerojatnog fenotipa, koji nisu potvrđeni u RC za praćenje rezistencije, označeni su zvjezdicom kao nepotvrđeni i ne smatraju se važećima.

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

- ČK ZZJZ je za *A. baumannii* prikazao rezultate za cijelu godinu
- IG ZZJZ je za *S. aureus*/MSSA, *S. aureus*/MRSA, *E. faecium* i *A. baumannii* prikazao rezultate za cijelu godinu
- KA OB je za *S. pneumoniae, S. aureus*/MSSA i *S. aureus*/MRSA prikazala rezultate za cijelu godinu
- KR ZZJZ je za *E. faecium* i *H. influenzae* prikazao rezultate za cijelu godinu
- SB NZZJZ je za *S. pneumoniae i H. influenzae* prikazao rezultate za cijelu godinu
- ST NZZJZ je za BHS-A prikazao rezultate za cijelu godinu
- VK ZZJZ je za *S. aureus*/MSSA, *S. aureus*/MRSA, *E. faecium, H. influenzae i A. baumannii* prikazao rezultate za cijelu godinu (izolati iz OŽB Vinkovci)
- ZG KBC je za *S. pneumoniae, S. aureus*/MSSA, *S. aureus*/MRSA, *H. influenzae* i *A. baumannii* prikazao rezultate za razdoblje od 2.10. do 2.1.2023., za *E. faecalis, K. pneumoniae* i *Enterobacter* spp., *Klebsiella aerogenes, Serratia* spp. i *Citrobacter* spp. prikazao rezultate za razdoblje od 2.10 do 16.10.2023., za *E. faecium* za razdoblje od 2.10. do 5.11.2023., za *E. coli* za razdoblje od 2.10 do 9.10.2023, za *P. mirabilis i P. aeruginosa* za razdoblje od 2.10. – 23.10.2023.
- ZG KBM je za *S. pneumoniae* prikazala rezultate za cijelu godinu
- ZG KDB je za *A. baumannii* prikazala rezultate za cijelu godinu
- ZG NZZJZ je za *S. aureus*/MSSA, *S. aureus*/MRSA, *E. faecium* i *A. baumannii* prikazao rezultate za razdoblje od 2.10. do 31.12.2023., *E. coli* za razdoblje od 16.10. do 20.10.2023, *P. mirabilis*, *K. pneumoniae*, *Enterobacter* spp., *Klebsiella aerogenes*, *Serratia* spp., *Citrobacter* spp. za razdoblje od 16.10. do 27.10.2023. i *P. aeruginosa* za razdoblje od 2.10. do 12.12.2023.

Šest laboratorija je prijavilo izolaciju šigela: ČK ZZJZ *S. flexnerii* (8); KR ZZJZ *S. flexnerii* (3); KA ZZJZ *S. flexnerii* (1); ŠI ZZJZ *S. sonnei* (1); ZG KIB *S. flexnerii* (3), *S. sonnei* (11) i ZG NZZJZ *S. sonnei* (3). Ukupno su tijekom 2023.g. izolirano 30 šigela.

U 2023.g. ukupno je obrađeno 1 541 anaerobnih bakterija, *Cutibacterium acnes* (318); *Bacteroides* spp. (875); *Prevotella* spp. (212); *Fusobacterium necroforum* (13); *Clostridium perfringens* (96) iz 19 centara: ČK ZZJZ *Bacteroides* spp. (28), *Prevotella* spp. (2), *Clostridium perfringens* (2); KA OB *Cutibacterium acnes* (10), *Bacteroides* spp. (24), *Prevotella* spp. (7), *Fusobacterium necroforum* (3), *Clostridium perfringens* (5); OG OB *Bacteroides* spp. (10), *Clostridium perfringens* (2); OS KBC *Cutibacterium acnes* (16), *Bacteroides* spp. (71), *Prevotella* spp. (49), *Clostridium perfringens* (6); PU NZZJZ *Bacteroides* spp. (19), *Clostridium perfringens* (2); RI KBC *Cutibacterium acnes* (7),

Bacteroides spp. (29), *Prevotella* spp. (5), *Clostridium perfringens* (11); SB ZZJZ *Cutibacterium acnes* (5), *Bacteroides* spp. (4), *Prevotella* spp. (1); SK ZZJZ *Cutibacterium acnes* (2), *Bacteroides* spp. (11), *Clostridium perfringens* (4); ST KBC *Cutibacterium acnes* (7), *Bacteroides* spp. (66), *Prevotella* spp. (16), *Clostridium perfringens* (13); ŠI ZZJZ *Cutibacterium acnes* (15), *Bacteroides* spp. (15), *Prevotella* spp. (3); VK ZZJZ *Cutibacterium acnes* (1), *Bacteroides* spp. (5), *Prevotella* spp. (2); VŽ ZZJZ *Cutibacterium acnes* (15), *Bacteroides* spp. (74), *Prevotella* spp. (26), *Fusobacterium necroforum* (3), *Clostridium perfringens* (2); ZG KBC *Cutibacterium acnes* (95), *Bacteroides* spp. (145), *Prevotella* spp. (46), *Clostridum perfringens* (19); ZG KBD *Cutibacterium acnes* (34), *Bacteroides* spp. (43), *Prevotella* spp. (8), *Clostridum perfringens* (14); KBM *Cutibacterium acnes* (3), *Bacteroides* spp. (19), *Prevotella* spp. (3), *Clostridium perfringens* (7); ZG KBCSM *Cutibacterium acnes* (92), *Bacteroides* spp. (253), *Prevotella* spp. (25), *Fusobacterium necroforum* (6), *Clostridium perfringens* (5); ZG KIB *Bacteroides* spp. (6), *Fusobacterium necroforum* (1), *Clostridium perfringens* (1); ZG KDB *Bacteroides* spp. (5), *Clostridium perfringens* (3); ZG KBSD *Cutibacterium acnes* (16), *Bacteroides* spp. (48), *Prevotella* spp. (19).

RESULTS

Thirty-seven centers took part in antibiotic resistance surveillance in Croatia in 2023. 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 centres expanded surveillance to the whole year and some centres reported different surveillance periods for various reasons. Deviations from official surveillance periods were reported as follows:

- ČK ZZJZ reported data for *A. baumannii* for the whole year
- IG ZZJZ reported data for *S. aureus/*MSSA, *S. aureus*/MRSA*, E. faecium* and *A. baumannii* for the whole year
- KA OB reported data for *S. pneumoniae, S. aureus/*MSSA and *S. aureus*/MRSA for the whole year
- KR ZZJZ reported data for *E. faecium* and *H. influenzae* for the whole year
- SB ZZJZ reported data for *S. pneumoniae* and *H. influenzae* for the whole year
- ST NZZJZ reported data for BHS-A for the whole year
- VK ZZJZ reported data for *S. aureus/*MSSA, *S. aureus*/MRSA, *E. faecium, H. influenzae* and *A. baumannii* for the whole year (isolates from OB Vinkovci)
- ZG KBC reported data for *S. pneumoniae, S. aureus/*MSSA, *S. aureus*/MRSA, *H. influenzae* and *A. baumannii* for the period 2.10. – 2.1.2023., for *E. faecalis, K. pneumoniae and Enterobacter* spp.*, Klebsiella aerogenes, Serratia* spp. and *Citrobacter* spp. for the period 2.10. – 16.10.2023*,* for *E. faecium* for the period 2.10. – 5.11.2023., for *E. coli* for the period 2.10. – 9.10.2023., for *P. mirabilis* and *P. aeruginosa* for the period 2.10. – 23.10.2023.
- ZG KBM reported data for *S. pneumoniae* for the whole year
- ZG KDB reported data for *A. baumannii* for the whole year
- ZG NZZJZ reported data for *S. aureus/*MSSA, *S. aureus*/MRSA *, E. faecium* and *A. baumannii* for the period 2.10. – 31.12.2023., *E. coli* for the period 16.10. – 20.10.2023., *P. mirabilis, K. pneumoniae, Enterobacter* spp.*, Klebsiella aerogenes, Serratia* spp. and *Citrobacter* spp. for the period 16.10. – 27.10.2023. and *P. aeruginosa* for the period 2.10. – 12.12.2023.

Six laboratories reported shigella isolates: ČK ZZJZ *S. flexnerii* (8); KR ZZJZ *S. flexnerii* (3); KA ZZJZ *S. flexnerii* (1); ŠI ZZJZ *S. sonnei* (1); ZG KIB *S. flexnerii* (3), *S. sonnei* (11) and ZG NZZJZ *S. sonnei* (3). Altogether 30 shigella isolates were reported in 2023.

In 2023 altogether 1 541 anaerobic bacteria were isolated, *Cutibacterium acnes* (317); *Bacteroides* spp. (875); *Prevotella* spp. (212); *Fusobacterium necroforum* (11); *Clostridium perfringens* (126). They were isolated in 19 centers: ČK ZZJZ *Bacteroides* spp. (28), *Prevotella* spp. (2), *Clostridium perfringens* (2); KA OB *Cutibacterium acnes* (10), *Bacteroides* spp. (24), *Prevotella* spp. (7), *Fusobacterium necroforum* (3), *Clostridium perfringens* (5); OG OB *Bacteroides* spp. (10), *Clostridium perfringens* (2); OS KBC *Cutibacterium acnes* (16), *Bacteroides* spp. (71), *Prevotella* spp. (49),

Clostridium perfringens (6); PU NZZJZ *Bacteroides* spp. (19), *Clostridium perfringens* (2); RI KBC *Cutibacterium acnes* (7), *Bacteroides* spp. (29), *Prevotella* spp. (5), *Clostridium perfringens* (11); SB ZZJZ *Cutibacterium acnes* (5), *Bacteroides* spp. (4), *Prevotella* spp. (1); SK ZZJZ *Cutibacterium acnes* (2), *Bacteroides* spp. (11), *Clostridium perfringens* (4); ST KBC *Cutibacterium acnes* (7), *Bacteroides* spp. (66), *Prevotella* spp. (16), *Clostridium perfringens* (13); ŠI ZZJZ *Cutibacterium acnes* (15), *Bacteroides* spp. (15), *Prevotella* spp. (3); VK ZZJZ *Cutibacterium acnes* (1), *Bacteroides* spp. (5), *Prevotella* spp. (2); VŽ ZZJZ *Cutibacterium acnes* (14), *Bacteroides* spp. (74), *Prevotella* spp. (26), *Fusobacterium necroforum* (3), *Clostridium perfringens* (2); ZG KBC *Cutibacterium acnes* (95), *Bacteroides* spp. (145), *Prevotella* spp. (46), *Clostridum perfringens* (19); ZG KBD *Cutibacterium acnes* (34), *Bacteroides* spp. (43), *Prevotella* spp. (8), *Clostridum perfringens* (14); KBM *Cutibacterium acnes* (3), *Bacteroides* spp. (19), *Prevotella* spp. (3), *Clostridium perfringens* (7); ZG KBCSM *Cutibacterium acnes* (92), *Bacteroides* spp. (253), *Prevotella* spp. (25), *Fusobacterium necroforum* (6), *Clostridium perfringens* (5); ZG KIB *Bacteroides* spp. (6), *Fusobacterium necroforum* (1), *Clostridium perfringens* (1); ZG KDB *Bacteroides* spp. (5), *Clostridium perfringens* (3); ZG KBSD *Cutibacterium acnes* (16), *Bacteroides* spp. (48), *Prevotella* spp. (19).

DISKUSIJA

Utjecaj epidemije SARS-CoV-2 virusa na pojavnost bakterijskih respiratornih patogena se osjetio i u 2023.g. Dok su se *Streptococcus pneumoniae* i *Haemophilus influenzae* postupno vratili na razine prije epidemije, streptokok grupe A je nakon izuzetno niske incidencije tijekom 2020. i 2021.g. pokazao nagli porast u 2022.g., a u 2023.g. incidencija je uvelike nadišla i onu iz razdoblja prije epidemije (12.341 u 2019.g., 4.553 izolata u 2020.g., 2.570 izolata u 2021.g., 8.978 izolata u 2022.g. te 19.005 u 2023.g.). Nagli porast je još uočljivi ako se uspoređuju sezone jesen / zima negoli kad se uspoređuju kalendarske godine (podaci Klinike za infektivne bolesti). Stope rezistencije su i u 2023.g. ostale niže negoli u predepidemijskom razdoblju i za makrolide iznose 5% u 2023.g., 6% u 2022.g., 10% u 2021.g., 8% u 2020.g., 9% u 2019.g., 10% u 2018.g., 7% u 2017.g. i 2016.g., 9% u 2015.g. i 2014.g, 10% u 2013.g., 9% u 2012. g., 7% u 2011.g., 8% u 2010.g., 9% u 2009.g., 13% u 2008.g. Rezistencija na klindamicin je također ostala niska (konstitutivna 2% u 2023.g., 1% u 2022.g., 5% u 2021.g., 4% u 2020.g.; inducibilna 1% u 2023.g., 3% u 2022.g., 3% u 2021.g. i 2020.g.). Prema EUCAST standardima izolati s inducibilnom rezistencijom su se do 2014.g. izdavali kao osjetljivi na klindamicin uz upozorenje da se izbjegava dugotrajnija terapija teških infekcija klindamicinom, a od 2014.g. se takvi izolati interpretiraju kao rezistentni na klindamicin uz opasku da se klindamicin još uvijek može primijeniti u kratkotrajnom liječenju ili u liječenju blažih infekcija kože i mekih tkiva. Klindamicin se preporuča 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. Rezistencija na penicilin u beta-hemolitičkih streptokoka i nadalje nije opisana te je ovaj antibiotik prvi lijek izbora u liječenju streptokoknih infekcija.

Pneumokoki, *H. influenzae* i *Moraxella catarrhalis* se smatraju respiratornim patogenima, no često se nalaze i kao dio fiziološke mikrobiote gornjih dišnih puteva u zdravih ljudi ili tijekom virusne infekcije gornjih dišnih puteva. Izolati pneumokoka i hemofilusa opisani u ovom poglavlju potječu pretežno iz briseva nazofarinksa koji pokazuju nisku specifičnost i osjetljivost i ne preporučuju se kao uzorci za dijagnosticiranje etiologije infekcija gornjih dišnih puteva, no mogu poslužiti za epidemiološko istraživanje osjetljivosti ovih bakterijskih vrsta na antibiotike s tim da se treba imati na umu da neinvazivni pneumokoki često pokazuju veće stope rezistencije negoli invazivni izolati. Rezistencija invazivnih pneumokoka opisana je u poglavlju o invazivnim izolatima i mjerodavnija je kao putokaz za primjenu antimikrobne terapije. Praćenje stopa rezistencije ukupnih pneumokoka omogućuje, međutim, uočavanje bitnih trendova u širenju rezistencije. U Hrvatskoj je rezistencija pneumokoka na penicilin za sada još uvijek niska (3% u 2023.g., 5% u 2022.g. 4% u 2021.g., 3% u 2020.g., 2019.g. i 2018.g., 2% u 2017.g.) i parenteralni penicilin je još uvijek lijek izbora u liječenju pneumokoknih pneumonija. Empirijsko liječenje pneumonije treba, međutim, započeti višim dozama penicilina kako bi se učinkovito djelovalo na pneumokoke koji pokazuju osjetljivost samo uz povećanu izloženost penicilinu. Do 2019.g. takvi izolati su se nazivali intermedijarnima, no od 2019.g. EUCAST je pojam intermedijarne osjetljivosti zamijenio pojmom osjetljivosti uz povećanu izloženost, sugerirajući da su i takvi izolati podložni liječenju ispitivanim antibiotikom, samo uz povećano izlaganje, što se u slučaju parenteralnog penicilina lako postiže povećanjem doze. Udio pneumokoka osjetljivih na penicilin uz povećanu izloženost je nešto niži u zadnje dvije godine (14% u 2023.g., 13% u 2022.g., 16% u 2021.g., 21% u 2020.g. i 2019.g., 17% u 2018.g., 21% u 2017.g.). Infekcije uzrokovane pneumokokima koji zahtjevaju povećanu izloženost penicilinu nisu dostupne liječenju oralnim penicilinom, a u slučaju kad zahvaćaju središnji živčani sustav

(SŽS) ni parenteralnim penicilinom. Otpornost pneumokoka na penicilin u slučaju infekcije SŽS ili liječenja drugih infekcija oralnim pripravkom u 2023.g. iznosi 18% što je identično prošlogodišnjoj stopi. Pneumonije uzrokovane izolatima koji zahtjevaju povećanu izloženost penicilinu se mogu liječiti parenteralnim penicilinom u dozama prilagođenima visini minimalnih inhibitornih koncentracija (MIK) uzročnika. Prema rasponu MIK-ova penicilina registriranih u 2023.g., 98% svih pneumokoka ima MIK penicilina ≤2.0 mg/L i reagirat će na dozu od 6x2.4g (6x4MIU), 96% pneumokoka ima MIK penicilina ≤1.0 mg/L i reagirat će na dozu od 4x2.4g (4x4MIU) ili 6x1.2g (6x2MIU), a 93% 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, sinuitisa i pneumonija. U 2023.g. je bilo 92% osjetljivih pneumokoka koji su dostupni liječenju standardnom dozom oralnog amoksicilina (3x500mg) i parenteralnog ampicilina (3x2g), što je podjednako prijašnjim stopama (92% u 2022.g., 90% u 2021.g., 87% u 2020.g. i 2019.g., 90% u 2018.g.). Povećanim doziranjem oralnog amoksicilina od 3x750mg ili 3x1000mg (pripravak dostupan na tržištu) može se slično kao i prošlih godina obuhvatiti 94% pneumokoka (95% u 2022.g. i 2021.g., 92% u 2020.g., 93% u 2019.g., 94% u 2018.g.). U 2022.g. EUCAST je pooštrio granične vrijednosti za parenteralni ampicillin i izjednačio ih s vrijednostima za oralni amoksicilin. Iz tog razloga interpretacija osjetljivosti na ampicillin i amoksicilin je jednostavnija (katogorije osjetljivosti se podudaraju za oralni i parenteralni pripravak), ali treba uzeti u obzir mogućnost da je to utjecalo na nešto niže stope izolata osjetljivih na parenteralni ampicillin uz pojačano doziranje (4x2g) u posljednje dvije godine (94% u 2023.g, 95% u 2022.g., 98% u 2021.g., 97% u 2020.g., 2019.g. i 2018.g.). Iz prikazanih rezultata je vidljivo da je amoksicilin / ampicillin i nadalje vrlo dobra opcija i za oralnu i za parenteralnu empirijsku terapiju respiratornih bakterijskih infekcija gdje se kao glavni uzročnik očekuje pneumokok. Usprkos povećane potrošnje makrolida tijekom epidemije COVID-19, rezistencija pneumokoka na makrolide je ostala niža u zadnje dvije godine (24% u 2023.g. i 2022.g., 28% u 2021.g., 29% u 2020.g., 31% u 2019.g., 32% u 2018.g.). Trend pada rezistencije na ko-trimoksazol se, nažalost, zaustavio (43% u 2010.g., 35% u 2011.g., 29% u 2012.g., 27% u 2013.g., 29% u 2014.g., 26% u 2015.g., 23% u 2016.g., 22% u 2017.g., 20% u 2018.g., 17% u 2019.g. i 2020.g., 14% u 2021.g., 13% u 2022.g., 17% u 2023.g.). Rezistencija na tetraciklin, koja je također pokazivala blagi trend pada, stagnira (16% u 2023.g., 15% u 2022.g., 17% u 2021.g., 16% u 2020.g., 18% u 2019.g., 19% u 2018.g., 28% u 2010.g.). Otpornost pneumokoka na respiratorne kinolone je još uvijek niska (1%) no ovi antibiotici se ne bi smjeli široko upotrebljavati u empirijskoj terapiji respiratornih infekcija.

Broj izolata *H.influenzae* se nakon 2022.g. vratio na razinu blizu onoj u predpandemijsko vrijeme (1.156 izolata u 2023.g., 1.158 izolata u 2022.g., 942 izolata u 2021.g., 434 izolata u 2020.g., 1.305 izolata u 2019.g.). Rezistencija na amoksicilin je u 2023.g. bila slična prošlogodišnjim stopama (21% u 2023.g., 22% u 2022.g., 20% u 2021.g., 22% u 2020.g., 25% u 2019.g., 22% u 2018.g., 24% u 2016. i 2017.g., 20% u 2015.g., 14% u 2014.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 oralnog amoksicilina (3x750mg tj. 3x1g) i oralnog cefuroksima (2x500mg). Iz tog razloga parenteralni pripravci amoksicilina /ampicilina sa ili bez inhibitora imaju kategorije „S“ i „R“ a pareneteralni cefuroksim „S”, „I” i „R”, dok njihovi oralni pripravci mogu imati samo kategorije „I“ i „R“. Rezistencija na ko-trimoksazol (19%) je slična stopama rezistencije prethodnih godina, a rezistencija na ceftriakson nije uočena.

Staphylococcus aureus je glavni uzročnik infekcija kože i mekih tkiva i kao takav ujedno i najčešći uzročnik infekcija kirurških rana. 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 (18%) i klindamicin (15%), meticilin senzitivni *Staphylococcus aureus* (MSSA) sojevi ne pokazuju značajnije stope rezistencije na druge antistafilokokne antibiotike. Od 2021.g. se uvelo testiranje osjetljivosti stafilokoka na tetraciklin i rezistencija na tetraciklin kod MSSA iznosi 4% u sve tri godine praćenja. Stečena rezistencija na kinolone kod MSSA je niska (2%), no i kod osjetljivih izolata samo se od moksifloksacina može očekivati osjetljivost uz standardno doziranje, dok ciprofloksacin i levofloksacin djeluju samo ako se primjenjuju u višoj dozi. Meticilin rezistentni *Staphylococcus aureus* (MRSA) sojevi su rezistentni na sve beta-laktamske antibiotike (osim novijih cefalosporina, ceftarolina i ceftobiprola), a često pokazuju križnu rezistenciju i na druge klase antibiotika. Nakon 2008.g. uočen je trend pada udjela MRSA sojeva i najniže stope (12%) su zabilježene 2013. i 2014.g., no od 2015.g. stopa MRSA opet počinje rasti, a nagli skok je, nažalost, zabilježen 2020.g. i još više u 2021.g. (25% u 2007. g., 26% u 2008. g., 21% u 2009. g., 16% u 2010. g., 14% u 2011. g., 13% u 2012. g., 12% u 2013.g. i 2014.g., 14% u 2015.g., 16% u 2016.g., 15% u 2017.g., 16% u 2018.g. i 2019.g., 21% u 2020.g., 27% u 2021.g.). U 2022.g. trend porasta stopa je, srećom, zaustavljen, a u 2023.g. stopa MRSA je i nešto niža (19% u 2023.g., 21% u 2022.g.). Povoljno je i da je ukupan broj izolata MRSA prestao rasti (960 izolata u 2023.g., 955 izolata u 2022.g., 1.238 u 2021.g., 699 u 2020.g., 784 u 2019.g.). Udio MRSA sojeva rezistentnih na klindamicin (77%) je podjednak prošlogodišnjem. Rezistencija MRSA na gentamicin (14%) je nešto viša negoli prethodne godine, ali dugoročno se uočava trend pada rezistencije (91% u 2006.g., 81% u 2009.g., 77% u 2010.g., 69% u 2011.g., 64% u 2012.g., 59% u 2013.g., 43% u 2014.g., 38% u 2015.g., 32% u 2016.g., 23% u 2017.g., 18% u 2018.g. i 2019.g., 13% u 2020.g. i 2021.g., 10% u 2022.g., 14% u 2023.g.). Rezistencija na linezolid i vankomicin nije uočena. Udio izolata s MIK-om vankomicina od 2.0 mg/L je podjednak prethodnim godinama (11% u 2023.g. i 2022.g., 10% u 2021.g., 5% u 2020.g., 14% u 2019.g., 10% u 2018.g., 9% u 2017.g., 8% u 2016.g., 7% u 2015.g., 16% u 2014.g., 20% u 2013.g.). Rezistencija MRSA na ceftarolin je podjednaka kao prethodne godine (10% u 2023.g., 11% u 2022.g., 5% u 2021.g.), a jednak je i udio izolata koje treba liječiti višim dozama (8% u 2023.g. i 2022.g., 9% u 2021.g.). U slučaju pneumonije, na ceftarolin je rezistentno 18% izolata. Stopa rezistencije na ko-trimoksazol je slična prošlogodišnjoj (6% u 2023.g., 7% u 2022.g., 5% u 2021.g. i 2020.g.), a rezistencija na tetraciklin, čije praćenje je uvedeno 2021.g., iznosi 10% za sve tri godine praćenja i nije značajno viša od stopa rezistencije kod MSSA (4%). Rezistencija na rifampicin je i dalje niska (2%), no ovaj antibiotik se ne preporuča u monoterapiji stafilokoknih infekcija zbog visokog udjela rezistentnih mutanti u populaciji.

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 23% za *E. faecalis* i 42% za *E .faecium*, što je slično kao i prethodnih godina. Rezistencija na vankomicin je još uvijek rijetka u *E. faecalis* (<1%). Rezistencija na vankomicin u *E. faecium* je visoka, ali nakon trenda porasta i naglog skoka u 2021.g. u zadnje dvije godine stagnira (1% u 2012.g., 5% u 2013.g., 7% u 2014.g., 15% u 2015.g., 17% u 2016.g., 16% u 2017.g., 18% u 2018.g., 32% u 2019.g., 27% u 2020., 45% u 2021.g., 42% u 2022., 40% u 2023.g.). Porast rezistencije na vankomicin uočava se od 2015.g., kad se vankomicin rezistentni *E. faecium* (VRE) izolati počinju s većom učestalošću javljati u raznim regijama Hrvatske, a ne samo u zagrebačkim bolnicama kao što je to bilo u

početku. U 2021.g., uz porast stope rezistencije na vankomicin uočen je i porast ukupnog broja *E.faecium* u odnosu na prethodnu godinu, ali i na predepidemijsko razdoblje. U 2023.g. se zadržala visoka stopa rezistencije na vankomicin, ali ukupni broj izolata se smanjuje i približava predpandemijskim vrijednostima (1.152 izolata u 2023.g., 1.271 izolata u 2022.g., 1.242 izolata u 2021.g., 859 izolata u 2020.g., 1.074 izolata u 2019.g.). Ukupan broj izolata *E. faecalis* nije pokazivao velike oscilacije osim pada u prvoj pandemijskoj godini (5.260 u 2023.g., 5.502 u 2022.g., 5.419 u 2021.g., 3.764 u 2020.g., 5.264 u 2019.g). 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 je znatno niža u *E. faecalis* negoli u *E. faecium* i podjednaka je stopama prethodnih godina (23% i 85% u 2023.g., 22% i 86% u 2022.g., 23% i 87% u 2021.g., 23% i 81% u 2020.g., 22% i 85% u 2019.g., 22% i 84% u 2018.g., 22% i 75% u 2017.g.). Za nekomplicirane uroinfekcije koje urokuje *E. faecalis* može se koristiti i nitrofurantoin na koji ovaj uzročnik pokazuje nisku rezistenciju (1%).

Escherichia coli je najčešći uzročnik infekcija mokraćnog sustava (IMS), a ostale enterobakterije češće uzrokuju kompliciranе IMS ili infekcije raznih sustava povezane s bolničkom skrbi. S obzirom da su enterobakterije dio fiziološke mikrobiote često su izložene primjeni antibiotika, a širenje jednom nastalih mutanti teško je uočiti i kontrolirati. Broj prijavljenih izolata *E.coli* je u pandemijskoj 2020.g. bio znatno niži od uobičajenog, no od 2021.g. broj prijavljenih izolata se ponovno vratio na vrijednosti registrirane u predepidemijskom razdoblju (20.349 izolata u 2023.g., 21.770 u 2022.g., 18.825 u 2021.g., 12.912 u 2020.g., 20.284 u 2019.g.), što govori u prilog da se dijagnostička aktivnost za bakterijske infekcije, reducirana u početku covid epidemije, brzo povratila. Od početka praćenja, *E. coli* pokazuje visoku rezistenciju na ampicilin, koja i u 2023.g. iznosi 47%, slično kao i prethodnih godina. Amoksicilin s dodatkom klavulanske kiseline, međutim, pokazuje dobru djelotvornost jer klavulanska kiselina uspješno blokira beta-laktamaze širokog spektra i većinu beta-laktamaza proširenog spektra (engl. "extended spectrum beta-lactamases, ESBL"). Kombinacija s klavulanskom kiselinom, međutim, ograničava primjenu amoksicilina u visokim dozama, kakve su često potrebne kod ozbiljnih sistemnih infekcija. U 2014.g. EUCAST je po prvi puta razdvojio interpretaciju osjetljivosti na amoksicilin s klavulanskom kiselinom ovisno o tome radi li se o nekompliciranoj IMS ili drugim oblicima infekcije. Nakon te podjele, stope rezistencije su ostale podjednake odnosno pokazuju blagi trend porasta, ako se interpretiraju za primjenu kod nekompliciranih IMS (7% u 2013.g. i 2014.g., 9% u 2015.g., 10% u 2016.g., 2017.g., 2018.g. i 2019.g., 11% u 2020.g., 12% u 2021.g., 10% u 2022.g., 11% u 2023.g.) no znatno su se povisile nakon promjene standarda uz lagani trend porasta u sljedećim godinama, ako se interpretiraju za primjenu kod ostalih infekcija (16% u 2014. i 2015.g., 15% u 2016.g., 2017.g. i 2018.g., 16% u 2019.g., 19% u 2020.g., 22% u 2021.g., 16% u 2022.g., 18% u 2023.g.). Od 2020.g. u EUCAST standardima za enterobakterije se uvela 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 cefuroksim je identična prošlogodišnjoj (11% u 2023.g. i 2022.g., 10% u 2021.g., 11% in 2020). Rezistencija na cefalosporine treće generacije (9% do 11%) je slična prošlogodišnjim stopama (9% do 10%). 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, sa i bez inhibitora (<1% rezistentnih izolata) i nešto bolje od učinka piperacilin / tazobaktama (4% rezistentnih izolata). U 2022.g. su izolati enterobakterija po prvi puta testirani na cefiderokol, i rezistencija *E.coli* na ovaj antibiotik u obje godine praćenja iznosi 2%.

Rezistencija na ciprofloksacin je 2017.g. dosegla 20%, ali od tada stagnira i ovogodišnja stopa se ne razlikuje bitno od prošlogodišnjih stopa (19% u 2023.g., 18% u 2022.g., 19% u 2021.g., 18% u 2020.g., 19% u 2019.g., 20% u 2017.g. i 2018.g., 19% u 2016.g., 18% u 2015.g., 17% u 2014.g., 14% u 2013. i 2012.g.). Stope rezistencije na ko-trimoksazol (26%), gentamicin (10%), amikacin (1%), nitrofurantoin (3%) i nitroksolin (<1%) su jednake, a na fosfomicin (3%) slične prošlogodišnjim stopama. S obzirom na niske stope rezistencije, nitrofurantoin, oralni fosfomicin i nitroksolin su prvi lijek izbora za nekomplicirane IMS.

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 2023.g. iznosi za ampicilin 47%, za ko-amoksiklav 23%, za piperacilin/tazobaktam 3%, za cefalosporine 3. i 4. generacije od 11% za cefepim do 20% za ceftriakson, što je slično prošlogodišnjim stopama. I u 2023.g. registrirana je niska rezistencija na nove cefalosporine u kombinaciji s inhibitorima beta-laktamaza, ceftazidim / avibaktam (1% u 2023.g., <1% u 2022.g., 1% u 2021.g., 2020.g., 2019.g. i 2018.g.), ceftalozan / tazobaktam (8% u 2023.g., 6% u 2022.g., 7% u 2021.g., 8% u 2020.g., 9% u 2019.g., 10% u 2018.g.). Stope rezistencije na ciprofloksacin (29%), gentamicin (24%), amikacin (12%) i ko-trimoksazol (41%) su neznatno više od prošlogodišnjih. 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. Rezistencija na novi antibiotik cefiderokol, prvi put testiran u 2022.g. je 2%.

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 (38% za cefepim do 39% za ceftazidim, ceftriakson i cefiksim) su slične prošlogodišnjima (38% do 40% u 2022.g., 41% do 43% u 2021.g., 35% do 38% u 2019.g.). I stope rezistencije na ko-amoksiklav (41% u 2023.g. i 2022.g., 43% u 2021.g., 45% u 2020.g., 38% u 2019.g. i 2018.g.) ceftolozan / tazobaktam (23% u 2023.g., 2022.g. i 2021.g., 25% u 2020.g., 20% u 2019.g. i 2018.g.) te piperacilin / tazobaktam (32% u 2023.g., 30% u 2022.g., 31% u 2021.g., 27% u 2020.g., 21% u 2019.g., 19% u 2018.g.) su slične prošlogodišnjima, no općenito rezistencija na beta-laktamske antibiotike je i dalje viša negoli u predepidemijskim godinama. Rezistencija na ceftazidim / avibaktam je i dalje vrlo niska (1% u 2023.g., 2% u 2022.g., 1% u 2021.g., 2% u 2020.g., 2019.g., 2018.g.) te je ovaj antibiotik, sa svojom djelotvornošću na sojeve koji proizvode ESBL i AmpC betalaktamaze, ali i sojeve koje proizvode velik dio karbapenemaza (KPC, OXA-48), najučinkovitiji beta-laktam kod klepsijela. Rezistencija na nove beta-laktame, cefiderokol i imipenem / relebaktam, iznosi 7% i 12%, slično kao i prethodne godine (7% i 11%). Nakon što je broj klepsijela rezistentnih na karbapeneme po prvi puta u 2014.g. dosegao razinu vidljivu kao postotak rezistencije na imipenem i meropenem (1%), te su stope u 2019.g. narasle na 5% i 6%, a u pandemijskoj 2020.g. na 7% i 16% uz dodatno 8% i 2% izolata osjetljivo uz povećanu izloženost („I" kategorija). Te razine su ostale slične i u 2021.g. (8% i 14% rezistentnih te 4% i 2% osjetljivih uz povećanu izloženost), 2022.g. (9% i 13% rezistentnih te 4% i 3% osjetljivih uz povećanu izloženost) i 2023.g. (11% i 16% rezistentnih te 4% i 2% osjetljivih uz povećanu izloženost). Ukupan broj izoliranih klebsijela je ostao sličan prošlogodišnjim vrijednostima (6.557 u 2023.g., 6.245 izolata u 2022.g., 5.601 izolata u 2021.g., 4.244 izolata u 2020.g., 5.864 izolata u 2019.g.) što ukazuje da se širenje na karbapeneme rezistentnih izolata nije smanjilo nakon epidemije COVID-19. Upravo je to najveći izazov za timove za kontrolu bolničkih infekcija i timove za upravljanje antibioticima jer se sukladno europskoj inicijativi od Hrvatske očekuje da do 2030.g. smanji incidenciju infekcija krvotoka uzrokovanih na

karbapeneme rezistentnim klepsijelama za 5% u odnosu na predepidemijske vrijednosti iz 2019.g., što iznosi više od 50% u odnosu na sadašnju situaciju. Rezistencija na ciprofloksacin (40%), gentamicin (26%), amikacin (9%) i ko-trimoksazol (42%) pokazuje stope jednake ili slične prošlogodišnjima.

Enterobakteri, citrobakteri i seracije čine grupu enterobakterija koje prirodno posjeduju inducibilne cefalosporinaze i s izuzetkom *Citrobacter koseri* pokazuju rezistenciju ne samo na ampicilin već i na ko-amoksiklav i cefalosporine prve generacije. Od 2019.g. *Enterobacter aerogenes* je preimenovan u *Klebsiella aerogenes* no ta vrsta se i nadalje analizira unutar ove grupe enterobakterija s obziorm na zajednički profil urođene rezistencije na beta-laktame. 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 koje stabilno hiperproduciraju AmpC cefalosporinaze i time uvjetuju rezistenciju i na cefalosporine treće generacije. Udio derepresiranih mutanti rezistentnih na cefalosporine treće i četvrte generacije (10% za cefepim do 27% za cefiksim) je u okvirima stopa registriranih prošlih godina (10% do 27% u 2023.g. i 2022.g., 10% do 28% u 2021.g., 12% do 28% u 2020.g., 12% do 26% u 2019.g., 10% do 25% u 2018.g., 16% do 32% u 2017.g.), a i rezistencija na karbapeneme, koja je postala vidljiva 2013.g. (1% za imipenem i meropenem), ostala je gotovo jednaka (1% rezistentnih i 1% osjetljivih uz povećano izlaganje za imipenem i meropenem, 7% rezistentnih za ertapenem) i u 2023.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 stopa rezistencije je i u enterobaktera (7% u 2023.g. i 2022.g., 8% u 2021.g. i 2020.g., 11% u 2019.g. i 2018..g.) ipak nešto niža od stopa rezistencije na cefepim (10% u 2023.g., 2022.g. i 2021., 12% u 2020.g. i 2019.g., 10% u 2018.g.,) pa i piperacilin / tazobaktam (14% u 2023.g., 13% u 2022.g. i 2021.g., 10% u 2020.g. i 2019.g., 9% u 2018.g.). Stope rezistencije na ciprofloksacin (9%), gentamicin (8%), amikacin (1%) i ko-trimoksazol (12%) su slične ili jednake prošlogodišnjima, a rezistencija na nove beta-laktame, cefiderokol i imipenem / relebaktam iznosi 3% i 2%.

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. porasla, no poslije toga nije nastavila rasti i vraća se na vrijednosti razdoblja prije epidemije (18% i 16% u 2023.g., 21% i 18% u 2022.g., 20% i 21% u 2021.g., 23% i 22% u 2020.g., 18% u 2019.g., 17% u 2018.g.). Ni rezistencija na nove cefalsosporine s inhibitorom, ceftazidim / avibaktam (6% u 2023.g., 2022.g. i 2021.g., 7% u 2020.g., 6% u 2019.g., 4% u 2018.g.) i ceftalozan / tazobaktam (5% u 2023., 2022.g. i 2021.g., 7% u 2020.g., 6% u 2019.g., 4% u 2018.g.) se ne povećava, a rezistencija na cefiderokol iznosi 2%. Rezistencija na piperacilin / tazobaktam (8% u 2023.g., 10% u 2022.g., 9% u 2021.g., 12% u 2020.g., 10% u 2019.g.), ceftazidim (15% u 2023.g., 17% u 2022.g., 15% u 2021.g., 21% u 2020.g., 16% u 2019.g.,) i cefepim (13% u 2023.g., 15% u 2022.g., 13% u 2021.g., 16% u 2020.g., 13% u 2019.g.) je nakon porasta u 2020.g. ponovno došla na stope slične onima u razdoblju prije epidemije. Rezistencija na ciprofloksacin (24% u 2023.g., 25% u 2022.g., 20% u 2021.g., 24% u 2020.g. i 2019.g.) je slična prethodnim godinama, a na amikacin je ista kao prethodne godine (6%). Od 2020.g. EUCAST standardi ne predviđaju testiranje *P. aeruginosa* na gentamicin jer smatraju da ovaj antibiotik nije djelotvoran za pseudomonasne infekcije. Za aminoglikozide se općenito preporuča da se za infekcije izvan urotrakta koriste samo u kombinaciji s drugim antibioticima. Opće je poznato da se za liječenje pseudomonasnih infekcija koriste više doze antibiotika što je od 2020.g. jasno iskazano u EUCAST standardima kao nepostojanje „S" kategorije (osjetljiv uz standardno doziranje) kod pseudomonasa za mnoge antibiotike (ceftazidim, cefepim,

piperacilin/tazobaktam, imipenem, ciprofloksacin). Za testiranje osjetljivosti na kolistin potrebno je učiniti test mikrodilucije u bujonu, što je bitno zahtjevnije i skuplje od testiranja disk difuzijom te se u ovom slučaju odstupa od pravila da se u razdoblju praćenja rezistencije svi izolati testiraju na sve antibiotike i na kolistin se testiraju samo multiplo, poglavito na karbapeneme rezistentni sojevi. Podatak o rezistenciji na kolistin kod *P.aeruginosa* se, stoga, ne može uspoređivati sa stopama rezistencije na druge antibiotike, ali omogućuje praćenje kolistinske rezistencije u subpopulaciji multiplorezistentnih pseudomonasa. Nakon porasta rezistencije na kolistin u 2021.g. ta se stopa vratila na niske vrijednosti (2% u 2023.g., 3% u 2022.g., 8% u 2021.g., 3% u 2020.g. i 2019.g.).

Rezistencija na karbapeneme kod *Acinetobacter baumannii* se u Hrvatskoj naglo proširila od 2008.g. i u 2023.g. su se zadržale visoke stope rezistencije na imipenem i meropenem (87% i 84%). Nakon drastičnog povećanja broja na karbapeneme rezistentnih izolata tijekom epidemije COVID-19, od 2022.g. su se ukupni brojevi prijavljenih acinetobaktera srećom ipak počeli smanjivati (1.603 izolata u 2023.g., 1.605 izolata u 2022.g., 2.582 izolata u 2021.g., 2.087 izolata u 2020.g., 1.740 izolata u 2019.g.), što je vjerojatno posljedica smanjenog pritiska na liječenje u jedinicama intenzivne njege i racionalizacije uporabe osobne zaštitne opreme, u prvom redu rukavica, pri njezi oboljelih od COVID-a. 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 kontinuirano pokazuju visoke stope (43% i 17% u 2023.g., 9% i 26% u 2022.g., 32% i 23% u 2021.g., 31% i 18% u 2020.g., 34% i 20% u 2019.g., 40% i 16% u 2018.g.). Kao i kod pseudomonasa, kolistin se testira samo kod na karbapeneme rezistentnih izolata, no kako već nekoliko godina takvi izolati čine oko ili više od 90% ukupnih acinetobaktera, može se smatrati da se kolistin testira na skoro svim izolatima i stope kolistinske rezistencije se mogu uspoređivati sa stopama za ostale antibiotike. Stope rezistencije acinetobaktera na kolistin su još uvijek niske (1% u 2023.g., 2022.g. i 2021.g., 2% u 2020.g.).

Rezistencija salmonela na ampicilin je 2014.g. prešla 10% (14% u 2014.g., 16% u 2015.g., 14% u 2016.g., 13% u 2017.g., 15% u 2018.g., 16% u 2019.g., 19% u 2020.g. i 2021.g., 16% u 2022.g., 17% u 2023.g.). ESBL sojevi su i dalje rijetki među salmonelama i u 2023.g. rezistencija na ceftazidim i ceftriakson je iznosila 2% i 1%, jednako kao i prethodne godine. Rezistencija na ko-amoksiklav (7%) je identična, a na ko-trimoksazol (6%) slična prošlogodišnjim stopama. Zabrinjava, međutim, rezistencija na ciprofloksacin koja je 2022.g. naglo skočila, a visoke vrijednosti su se zadržale i u 2023.g. (25% u 2023.g., 18% u 2022.g., 4% u 2021.g., 5% u 2020.g., 4% u 2019.g., 2018.g. i 2017.g., 3% u 2016.g., 4% u 2015.g.). Ujedno se od 2022.g. ukupan broj izolata vraća na vrijednosti u predepidemijsko doba, (1.795 izolata u 2023.g., 1.858 izolata u 2022.g., 1.278 izolata u 2021.g., 1.169 izolata u 2020.g., 2.031 izolata u 2019.g., 1.832 izolata u 2018.g.).

Osjetljivost u *Campylobacter coli* i *Campylobacter jejuni* se prati od 2013.g. Kod obje vrste zabrinjava trend porasta rezistencije na ciprofloksacin (u 2023.g. 83% i 81%, u 2022.g. 79% i 82%, u 2021.g. 77% obje vrste, u 2020.g. 74% i 71%, u 2019.g. 71% i 75%, u 2018.g. 78% i 76%, u 2017.g. 69% i 66%, u 2016.g. 60% obje vrste, u 2015.g. 52% i 50%). Od 2021.g. EUCAST je ukinuo mogušnost izdavanja „S" kategorije (osjetljivost uz standardno doziranje), ukazujuću na potrebu da se i infekcije uzrokovane osjetljivim izolatima kampilobaktera moraju liječiti višim dozama ciprofloksacina. Rezistencija na eritromicin (1% za obje vrste) je i dalje niska, no rezistencija na tetraciklin pokazuje trend porasta i u *C.coli* i u *C.jejuni* (51% i 47% u 2023.g., 37% i 43% u 2022.g., 33% i 28% u 2021., 35% i 41% u 2020.g., 46% i 42% u 2019.g., 41% i 36% u 2018.g., 35% i 30% u 2017.g.).

U 2023.g. izolirano je 30 šigela iz šest laboratorija. Izolati *S. sonnei* su jedino na ko-amoksiklav bili 100% osjetljivi, dok su na ostale antibiotike bili pretežno rezistentni. Rezistencija je bila nešto manje izražena u izolata *S. flexneri*, u kojih je osjetljivost na beta-laktame (osim ampicilina) i azitromicin bila visoka, ali na ko-trimoksazol i ciprofloksacin znatno snižena.

U 2023. godini je prijavljeno 1 541 anaerobnih bakterijskih izolata, najviše *Bacteroides* spp. (875) i *Cutibacterium acnes* (318) iz 19 centara. Rezistencija je ukupno najviša na klindamicin (47%), a najniža na meropenem (3%) i piperacilin/tazobaktam (5%).

DISCUSSION

Impact of the SARS-CoV-2 epidemic on the occurrence of bacterial respiratory pathogens was still remarkable in 2023. While *Streptococcus pneumoniae* and *Haemophilus influenzae* gradually returned to the pre-pandemic levels, group A streptococci (GAS) increased suddenly in 2022, after a two year period of very low incidence. In 2023 the incidence of GAS infections has greatly exceeded that of the pre-epidemic period (12.341 in 2019, 4.553 in 2020, 2.570 in 2021, 8.978 in 2022 and 19.005 u 2023). A sharp increase of GAS is even more obvious when autumn / winter seasons rather than calendar years are compared (oral communication, data for the University Hospital for Infectious Diseases). Resistance rates remained lower also in 2023, and are for macrolides 5% in 2023, 6% in 2022, 10% in 2021, 8% in 2020, 9% in 2019, 10% in 2018, 7% in 2017 and 2016, 9% in 2015 and 2014 10% in 2013, 9% in 2012, 7% in 2011, 8% in 2010, 9% in 2009, and 13% in 2008. Resistance to clindamycin also remained low (constitutive 2% in 2023, 1% in 2022, 5% in 2021, 4% in 2020; inducible 1% in 2023, 3% in 2022, 3% in 2021 and 2020). did not increase, on the contrary, macrolide resistance rate (6%) decreased compared to the previous years (10% in 2021, 8% in 2020, 9% in 2019, 10% in 2018, 7% in 2017 and 2016, 9% in 2015 and 2014, 10% in 2013, 9% in 2012, 7% in 2011, 8% in 2010, 9% in 2009, 13% in 2008). Resistance to clindamycin is also somewhat lower than in the previous years (constitutive 3% in 2022, 5% in 2021, 4% in 2020; inducible 1% in 2022, 3% in 2021 and 2020). According to the EUCAST standards, isolates with inducible clindamycin resistance used to be reported 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. Penicillin resistance in beta-haemolitic streptococci is not yet described so penicillin remains the first drug of choice in the treatment of streptococcal infections.

Pneumococci, *Haemophilus influenzae* and *Moraxella catarrhalis* are classified as respiratory pathogens but are frequently found as part of the normal microbiota of the upper respiratory tract in healthy individuals or during a viral upper respiratory tract infection. Most of the pneumococcal and haemophilus isolates reported in this chapter originate from nasopharyngeal swabs and aspirates, samples that are not adequate for the diagnostics of bacterial upper respiratory infections but can be used for surveillance studies to estimate antimicrobial resistance rates in these pathogens. Non-invasive pneumococci often have higher resistance rates than invasive isolates. Resistance in invasive isolates is described in a separate chapter of this publication and is more relevant for choosing adequate empirical antibiotic therapy. Resistance rates in all site isolates are, however, important for epidemiological surveillance and can indicate trends in antibiotic resistance. In Croatia, penicillin resistance in pneumococci is still low (3% in 2023, 5% in 2022, 4% in 2021, 3% in 2020., 2019, and 2018, 2% in 2017) and parenteral penicillin is still a drug of first choice for treating pneumococcal pneumonia. Empirical therapy of pneumonia should, however, include higher penicillin dosing to achieve efficacy against pneumococci susceptible only with increased exposure. Until 2019 such isolates were categorised as intermediate but in 2019 EUCAST changed the term intermediate into susceptible, increased exposure, suggesting that these isolates are still treatable with the tested antibiotic but exposure to the drug should be increased. In case of pneumococci and penicillin this could be easily achieved by increasing the penicillin dosing. The rate of penicillin susceptible, increased exposure pneumococcal isolates is somewhat lower in

the past two years (14% in 2023, 13% in 2022, 16% in 2021, 21% in 2020 and 2019, 17% in 2018, 21% in 2017). Infections caused by penicillin susceptible, increased exposure pneumococci cannot be treated with oral penicillin and in case they involve central nervous system (CNS) they cannot be treated with parenteral penicillin either. Resistance to penicillin in case of CNS infections or other infections if treated with oral penicillin is 18% in 2023 which is identical to last year's rate. However, pneumonia caused by pneumococci that are penicillin susceptible increased exposure 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 2023, 98% of pneumococci have penicillin MIC ≤2.0 mg/L and will be covered by 6x2.4g (6x4MIU) dosing, 96% have penicillin MIC ≤1.0 mg/L and will be covered by 4x2.4g (4x4MIU) or 6x1.2g (6x2MIU) dosing and 93% have penicillin MIC ≤0.5 mg/L and will be covered by 4x1.2g (4x2MIU) dosing. These values are similar to last year's rates. Due to the better pharmacodynamic characteristics and good activity against pneumococci and haemophilus amoxicillin / ampicillin is used as a first line treatment of acute otitis media, sinusitis and pneumonia more frequently than penicillin. In 2023, 92% of pneumococci were treatable with standard dosing of oral amoxicillin (3x500mg) and parenteral ampicillin (3x2g) which is similar to the previous rates (92% in 2022, 90% in 2021, 87% in 2020 and 2019, 90% in 2018). Increased dose of oral amoxicillin includes 3x750mg or 3x1000mg (formulation available at the market) and covers 94% of pneumococci, similarly as in previous years (95% in 2022 and 2021, 92% in 2020, 93% in 2019, 94% in 2018). In 2022 EUCAST decreased the MIC breakpoint between susceptible increased exposure and resistant categories for parenteral ampicillin and made it identical to the breakpoint for oral amoxicillin. For this reason, interpretation of susceptibility to parenteral ampicillin and oral amoxicillin became identical and simpler to discuss but it should be taken into consideration that this change might have had an impact on slightly lower susceptibility, increased exposure rates for parenteral ampicillin in the past two years (94% in 2023, 95% in 2022, 98% in 2021, 97% in 2020, 2019 and 2018). The surveillance results imply that oral and parenteral amoxicillin / ampicillin are still suitable first line antibiotics for empirical therapy of respiratory tract infections. In spite of the increased macrolide consumption during the COVID-19 epidemic, macrolide resistance in pneumococci is lower in the past two years (24% in 2023 and 2022, 28% in 2021, 29% in 2020, 31% in 2019, 32% in 2018). The trend of decreasing resistance to co-trimoxazole has, unfortunately, stopped (43% in 2010, 35% in 2011, 29% in 2012, 27% in 2013, 29% in 2014, 26% in 2015, 23% in 2016, 22% in 2017, 20% in 2018, 17% in 2019 and 2020, 14% in 2021, 13% in 2022, 17% in 2023). Resistance to tetracycline, which also showed a slight downward trend, is stagnating (16% in 2023, 15% in 2022, 17% in 2021, 16% in 2020, 18% in 2019, 19% in 2018, 28% in 2010). Resistance of pneumococci to respiratory quinolones is still low (1%) but these drugs should not be widely used in empirical therapy of respiratory tract infections.

Since 2022, the number of *H.influenzae* isolates returned to the values close to the pre-pandemic period (1.156 in 2023, 1.158 in 2022, 942 in 2021, 434 in 2020, 1.305 in 2019). In 2023, resistance to ampicillin was similar as in the last few years (21% in 2023, 22% in 2022, 20% in 2021, 22% in 2020, 25% in 2019, 22% in 2018, 24% in 2016 and 2017, 20% in 2015, 14% in 2014). 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) and oral cefuroxime (2x500mg). For this reason, parenteral amoxicillin / ampicillin with or without inhibitors has categories "S" and "R", and parenteral cefuroxime „S", „I" and „R", while their oral preparations can only have categories "I" and "R". Resistance to co-trimoxazole (19%) is similar to resistance rates in previous years, and resistance to ceftriaxone has not been observed.

Staphylococcus aureus is the main cause of skin and soft tissue infections and as such is also the most common cause of surgical site 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 (18%) and clindamycin (15%), methicillin-susceptible *Staphylococcus aureus* (MSSA) strains show no significant rates of resistance to other antistaphylococcal antibiotics. Since 2021 susceptibility testing to tetracycline was introduced and resistance in MSSA was found to be 4% in all the three years of surveillance. Acquired resistance to quinolones in MSSA is low (2%), but even in susceptible isolates only moxifloxacin is expected to be effective with standard dosing while ciprofloxacin and levofloxacin work only if used at a higher dose. Methicillin-resistant *Staphylococcus aureus* (MRSA) strains are resistant to all beta-lactam antibiotics (except newer cephalosporins, ceftaroline, and ceftobiprole), and often show cross-resistance to other classes of antibiotics. After 2008 a decreasing trend in MRSA rates was observed and the lowest rates (12%) were recorded in 2013 and 2014, but since 2015 the MRSA rate started to rise again, and a sudden increase was unfortunately recorded in 2020 and again in 2021 (25% in 2007, 26% in 2008, 21% in 2009, 16% in 2010, 14% in 2011, 13% in 2012, 12 % in 2013 and 2014, 14% in 2015, 16% in 2016, 15% in 2017, 16% in 2018 and 2019, 21 % in 2020, 27% in 2021). In 2022 the increasing trend was luckily ended with MRSA rate being even lower in 2023 (19% in 2023, 21% in 2022). It is also favourable that the total number of MRSA isolates has stopped rising (960 isolates in 2023, 955 in 2022, 1.238 in 2021, 699 in 2020, 784 in 2019). The proportion of MRSA strains resistant to clindamycin (77%) is the same as last year. MRSA resistance to gentamicin (14%) is somewhat higher than in the last year but in the long term there is still a decreasing trend (91% in 2006, 81% in 2009, 77% in 2010, 69% in 2011, 64% in 2012, 59% in 2013, 43% in 2014, 38% in 2015, 32% in 2016, 23% in 2017, 18% in 2018 and 2019, 13% in 2020 and 2021, 10% in 2022, 14% u 2023). Resistance to linezolid and vancomycin was not observed. The proportion of isolates with vancomycin MIC of 2.0 mg / L is similar as in the previous years (11% in 2023 and 2022, 10% in 2021, 5% in 2020, 14% in 2019, 10% in 2018, 9% in 2017, 8% in 2016, 7% in 2015, 16% in 2014, 20% in 2013). MRSA resistance to ceftaroline is the similar as the previous year (10% in 2023, 11% in 2022, 5% in 2021), and the proportion of isolates that should be treated with higher doses is similar (8% in 2023 and 2022, 9% in 2021). In case of pneumonia, 18% of isolates are considered resistant to ceftaroline. Resistance to co-trimoxazole is similar as in the previous years (6% in 2023, 7% in 2022, 5% in 2021 and 2020) and resistance to tetracycline, surveillance of which was introduced in 2021, is 10% for all the three years of surveillance and not very different from the rates seen in MSSA (4%). Resistance to rifampicin is still low (2%), but this antibiotic should not be used as monotherapy as the rate of mutants in the population is high.

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 23% for *E.faecalis* and 42% for *E.faecium* which is similar to the rates observed in the previous years. Vancomycin resistance is still rare in *E. faecalis* (<1%) but high in *E. faecium* (40%). After a sudden raise in 2021, vancomycin resistance in *E. faecium* is stagnating (1% in 2012, 5% in 2013, 7 % in 2014, 15% in 2015, 17% in 2016, 16% in 2017, 18% in 2018, 32% in 2019, 27% in 2020, 45% in 2021, 42% in 2022, 40% in 2023). An increase in vancomycin resistance has been observed since 2015, when vancomycin-resistant *E. faecium* (VRE) isolates began to occur with greater frequency in various regions of Croatia, and not only in Zagreb hospitals as it was in the beginning. In 2021 along with the raise in resistance rates, the raise in total numbers of *E.faecium* was observed as compared to the previous year but also in comparison with the pre-pandemic

period. In 2023 vancomycin resistance rate remained high, but the absolute number of isolates is decreasing and approaching the pre-pandemic values (1.152 isolates in 2023, 1.271 isolates in 2022, 1.242 isolates in 2021, 859 isolates in 2020, 1.074 isolates in 2019). Total number of *E. faecalis* isolates did not demonstrate high variations except a decrease in the first pandemic year (5.260 in 2023, 5.502 in 2022, 5.419 in 2021, 3.764 in 2020, 5.264 in 2019). 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 is significantly lower in *E. faecalis* than in *E. faecium* and is similar to the rates in previous years (23% and 85% in 2023, 22% and 86% in 2022, 23% and 87% in 2021, 23% and 81% in 2020, 22% and 85% in 2019, 22% and 84% in 2018, 22% and 75% in 2017). For uncomplicated urinary tract infections caused by *E. faecalis*, nitrofurantoin with low resistance rate (1%) can also be used.

Escherichia coli is the most common pathogen causing urinary tract infections (UTI) and other enterobacteriaceae are more common in complicated UTI or health care associated infections affecting different organ systems. As part of human microbiota enterobacteriaceae are frequently exposed to antibiotics and once the resistant mutants emerge they are difficult to spot and control. The number of reported *E.coli* isolates in the pandemic 2020 was significantly lower than usual, but since 2021 the number of reported isolates reached again the values recorded in the pre-pandemic period (20.349 isolates in 2023, 21.770 in 2022, 18.825 in 2021, 12.912 in 2020, 20.284 in 2019), which indicates that diagnostics for bacterial infections has recovered quickly after being reduced at the beginning of the covid epidemic. Since the early days of surveillance, *E. coli* has shown high resistance to ampicillin, which in 2022 is 47%, similar to previous years. Amoxicillin in combination with clavulanic acid, however, shows good efficacy because clavulanic acid successfully blocks broad-spectrum beta-lactamases and most extended-spectrum beta-lactamases ("extended spectrum beta-lactamases, ESBL"). The combination with clavulanic acid, however, limits the use of amoxicillin in high doses, which are often needed in serious systemic infections. In 2014 for the first time, EUCAST introduced different interpretation of amoxicillin/clavulanic acid susceptibility for uncomplicated UTI and for other infections. After this differentiation, resistance rates did not change significantly if interpretation for uncomplicated UTI is applied (7% in 2013 and 2014, 9% in 2015, 10% in 2016, 2017, 2018 and 2019, 11% in 2020, 12% in 2021, 10% in 2022, 11% in 2023) but following the change of standards the rates applicable to other infections turned out much higher and expressed a slightly increasing trend (16% in 2014 and 2015, 15% in 2016, 2017 and 2018, 16% in 2019, 19% in 2020, 22% in 2021, 16% in 2022, 18% u 2023). In 2020 EUCAST standards for enterobacteria introduced 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. 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 cefuroxime is identical as last year (11% in 2023 and 2022, 10% in 2021, 11% in 2020). Resistance to third-generation cephalosporins (9% to 11%) is similar to last year's rates (9% to 10%). New cephalosporins with beta-lactamase inhibitors, ceftazidime / avibactam and ceftalozane / tazobactam show high efficiency against ESBL strains and the resistance of *E.coli* to these antibiotics is <1% and 1%, which is identical to the efficacy of carbapenems with or without inhibitor (<1% of resistant isolates) and slightly better than the efficacy of piperacillin / tazobactam (4% of resistant isolates). Susceptibility testing to cefiderocol was introduced in 2022 and resistance rate of 2% was recorded in both years. Resistance to ciprofloxacin reached 20% in 2017, but since then it has stagnated and this year's rate does not differ significantly from last year's rate (19% in 2023, 18% in 2022, 19% in 2021, 18% in 2020, 19% in 2019, 20% in 2017 and 2018, 19% in 2016, 18% in 2015, 17% in 2014, 14% in 2013 and 2012).

Resistance rates to co-trimoxazole (26%), gentamicin (10%), amikacin (1%), nitrofurantoin (3%), and nitroxoline (<1%) are the same and to fosfomycin (3%) similar as last year's rates. Due to the low resistance rates nitrofurantoin, oral fosfomycin and nitroxoline are the first line antibiotics for uncomplicated UTI.

Proteus mirabilis still causes predominantly community-acquired infections and should naturally be a bacterial species well-susceptible to all beta-lactam antibiotics directed at gram-negative bacteria. Unfortunately, resistance to beta-lactam antibiotics has already reached high rates and in 2023 resistance is 47% for ampicillin, 23% for co-amoxiclav, 3% for piperacillin/tazobactam, 11% (cefepime) to 20% (ceftriaxone) for the 3rd and 4th generation cephalosporins, which is similar to last year's rates. In 2023 resistance is still low for the new cephalosporin combinations with beta-lactamase inhibitors, ceftazidime / avibactam (1% in 2023, <1% in 2022, 1% in 2021, 2020, 2019 and 2018), ceftalozane / tazobactam (8% in 2023, 6% in 2022, 7% in 2021, 8% in 2020, 9% in 2019, 10% in 2018). Rates of resistance to ciprofloxacin (29%), gentamicin (24%), amikacin (12%) and co-trimoxazole (41%) are slightly higher than last year. Due to their innate resistance to colistin, tigecycline and lower susceptibility to imipenem, *Proteus mirabilis* and other *Proteus* spp. could represent an increasing problem in the future, especially in urological patients and infections associated with hospital care. Resistance to the new antibiotic cefiderocol, for the first time tested in 2022, is 2%.

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 (38% for cefepime to 39% for ceftazidime, ceftriaxone and cefixime) are similar to the last year’s rates (38% to 40% in 2022, 41% to 43% in 2021, 35% to 38% in 2019.g.). Also, resistance to co-amoxiclav (41% in 2023 and 2022, 43% in 2021, 45% in 2020, 38% in 2019 and 2018), ceftolozane / tazobactam (23% in 2023, 2022 and 2021, 25% in 2020, 20% in 2019 and 2018), and piperacillin / tazobactam (32% in 2023, 30% in 2022, 31% in 2021, 27% in 2020, 21% in 2019, 19% in 2018) is similar to last year's rates and in general resistance to beta-lactams is still higher than in pre-pandemic period. Ceftazidime / avibactam still shows very low resistance (1% in 2023, 2% in 2022, 1% in 2021, 2% in 2020, 2019 and 2018) and with its effectiveness against strains producing ESBL, AmpC beta-lactamases and a large number of carbapenemases (KPC, OXA-48), it remains the most effective beta-lactam for treatment of klebsiella infections. Resistance rates for the new beta-lactams cefiderocol and imipenem / relebactam are 7% and 12% similar as last year (7% and 11%). The number of carbapenem-resistant *K.pneumoniae* isolates reached the level visible as a percentage of resistance to imipenem and meropenem (1%) for the first time in 2014, the rates in 2019 increased to 5% and 6% and in 2020 there was a sudden increase in carbapenem resistance and rates reached 7% and 16% with an additional 8% and 2% isolates being susceptible at increased exposure (“I” category). These rates remained similar in 2021 (8% and 14% resistant and 4% and 2% susceptible with increased exposure), in 2022 (9% and 13% resistant and 4% and 3% susceptible with increased exposure) and in 2023 (11% and 16% resistant and 4% and 2% susceptible with increased exposure). The total number of *Klebsiella* isolates remained similar as last year (6.557 isolates in 2023, 6.245 in 2022, 5.601 in 2021, 4.244 in 2020, 5.864 in 2019) suggesting the continuous spread of carbapenem resistant isolates after the COVID-19 epidemic. The control of carbapenem resistant klebsiellas represents the major challenge for infection control and antimicrobial stewardship teams as by 2030, Croatia is expected to reduce bloodstream infections caused by carbapenem resistant klebsiellas by 5% compared with the incidence reported in the pre-pandemic 2019 year, which is equal to a reduction of >50% of current values. Resistance to ciprofloxacin (40%), gentamicin (26%), amikacin (9%) and co-trimoxazole (42%) shows rates similar to the last year’s values.

Enterobacter spp., *Citrobacter* spp. and *Searratia* spp. form a group of enterobacteriaceae which poses innate inducible cephalosorinases and with the exception of *Citrobacter koseri* demonstrate resistance not only to ampicillin but to co-amoxiclav and 1st generation cephalosporins as well. In 2019 *Enterobacter aerogenes* was renamed into *Klebsiella aerogenes* and this species continues to be discussed here within this group of *Enterobacterales*. Cefuroxime is marginally active against these bacteria and EUCAST standards do not include cefuroxime interpretation for this group of enterobacteria. Wild type isolates are susceptible to the 3rd generation cephalosporins but resistant derepressed mutants that hyperproduce AmpC cephalosporinases often emerge during therapy with these agents. The proportion of derepressed mutants resistant to third- and fourth-generation cephalosporins (10% for cefepime to 27% for cefixime) is within the limits of the rates registered in previous years (10% to 27% in 2023 and 2022, 10% to 28% in 2021, 12% to 28% in 2020, 12% to 26% in 2019, 10% to 25% in 2018, 16% to 32% in 2017.g.) and resistance to carbapenems, which became visible for the first time in 2013 (1% for imipenem and meropenem), remained almost the same in 2023 (1% resistant and 1% susceptible increased exposure to imipenem and meropenem, 7% resistant to ertapenem). Ceftalozan / tazobactam is primarily expected to be advantageous in the treatment of infections caused by pseudomonas and ESBL-producing enterobacteria, which are more common among *K.pneumoniae* and *E.coli* isolates than among Enterobacter group. However, the ceftolozane / tazobactam resistance rate is also in Enterobacter group (7% in 2023 and 2022, 8% in 2021 and 2020, 11% in 2019 and 2018) somewhat lower than the rate of resistance to cefepime (10% in 2023, 2022 and 2021, 12% in 2020 and 2019, 10% in 2018,) and piperacillin / tazobactam (14% in 2023, 13% in 2022 and 2021, 10% in 2020 and 2019, 9% in 2018). Resistance rates to ciprofloxacin (9%), gentamicin (8%), amikacin (1%) and co-trimoxazole (12%) are similar or identical to the last year's rates. Resistance rate to the new beta-lactam antibiotics, cefiderocol and imipenem / relebactam is 3% and 2%.

Multiply resistant *Pseudomonas aeruginosa*, especially carbapenem resistant isolates, have been one of the biggest resistance problems in Croatia for many years. Resistance to imipenem and meropenem increased significantly in 2020 but did not continue to raise and is now back to the pre-pandemic rates (18% and 16% in 2023, 21% and 18% in 2022, 20% and 21% in 2021, 23% and 22% in 2020, 18% in 2019, 17% in 2018). Resistance to the new cephalosporin combinations with an inhibitor, ceftazidime / avibactam (6% in 2023, 2022 and 2021, 7% in 2020, 6% in 2019, 4% in 2018) and ceftalozane / tazobactam (5% in 2023, 2022 and 2021, 7% in 2020, 6% in 2019, 4% in 2018) also did not increase further and resistance to cefiderocol, first tested in 2022, is 2%. Resistance to piperacillin / tazobactam (8% in 2023, 10% in 2022, 9% in 2021, 12% in 2020, 10% in 2019), ceftazidime (15% in 2023, 17% in 2022, 15% in 2021, 21% in 2020, 16% in 2019) and cefepime (13% in 2023, 15% in 2022, 13% in 2021, 16% in 2020, 13% in 2019), after the increase in 2020, came back to rates similar to those in the pre-epidemic period. Resistance to ciprofloxacin (24% in 2023, 25% in 2022, 20% in 2021, 24% in 2020 and 2019) is similar and resistance to amikacin (6%) is the same as last year. Since 2020 EUCAST standards do not include testing susceptibility of *P. aeruginosa* to 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 for many antibiotics higher dosing is used to treat pseudomonas infections, and since 2020 this is clearly stated in EUCAST standards as for pseudomonas there is no "S" category (susceptible, standard dosage) for many antibiotics (ceftazidime, cefepime, piperacillin / tazobactam, imipenem, ciprofloxacin). Colistin susceptibility testing requires the use of a broth microdilution test, which is significantly more demanding and expensive than disk diffusion testing, and therefore the rule to test all isolates to all antibiotics under surveillance, in this case is modified and only multiply, in particular carbapenem resistant isolates are tested with colistin. Therefore, the data on resistance to colistin in

P.aeruginosa cannot be compared with the rates of resistance to other antibiotics, but these data still enable the monitoring of colistin resistance in the subpopulation of multiply resistant pseudomonas isolates. In 2021 this rate was significantly higher than in previous years but afterwards the colistin resistance rate is back to lower rates (2% in 2023, 3% in 2022, 8% in 2021, 3% in 2020 and 2019).

Carbapenem resistance in *A. baumannii* has rapidly spread throughout Croatia since 2008 and in 2023 resistance rates to imipenem and meropenem (87% and 84%) are still extremely high. After the drastic increase of the number of resistant isolates during the COVID-19 pandemic, the total number of isolates started to decrease since 2022 (1.603 isolates in 2023, 1.605 in 2022, 2.582 in 2021, 2.087 in 2020, 1.740 in 2019), which is probably a consequence of a reduced number of severely ill patients and the reduced pressure on the intensive care units but also of a more rational use of personal protective equipment, especially gloves, when caring for COVID-19 patients. 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 (43% and 17% in 2023, 9% and 26% in 2022, 32% and 23% in 2021, 31% and 18% in 2020, 34% and 20% in 2019, 40% and 16% in 2018). As with pseudomonas, colistin is tested only on carbapenem-resistant isolates, but since for several years such isolates constitute >90% of the total acinetobacter isolates, it can be considered that colistin is tested on almost all isolates and the rates of colistin resistance can be compared with the rates for other antibiotics. Acinetobacter resistance rates to colistin are still low (1% in 2023, 2022 and 2021, 2% in 2020).

Ampicillin resistance in salmonellae exceeded 10% in 2014 (14% in 2014, 16% in 2015, 14% in 2016, 13% in 2017, 15% in 2018, 16% in 2019, 19% in 2020 and 2021, 16% in 2022, 17% in 2023). ESBL isolates are still rare among salmonellae and in 2023 resistance to ceftazidime and ceftriaxone was 2% and 1%, same as last year. Resistance to co-amoxiclav (7%) is identical and to co-trimoxazole (6%) similar to the last year's values. However, the sudden increase in ciprofloxacin resistance since 2022 is concerning as rates remained high in 2023 (25% in 2023, 18% in 2022, 4% in 2021, 5% in 2020, 4% in 2019, 2018 and 2017, 3% in 2016, 4% in 2015). Since 2022 the total number of isolates came back to the pre-pandemic values (1.795 isolates in 2023, 1.858 isolates in 2022, 1.278 isolates in 2021, 1.169 isolates in 2020, 2.031 isolates in 2019, 1.832 isolates in 2018).

Susceptibility rates in *Campylobacter coli* and *Campylobacter jejuni* were first reported in 2013. Increasing trend of resistance to ciprofloxacin in both species is concerning (83% and 81% in 2023, 79% and 82% in 2022, 77% for both species in 2021, 74% and 71% in 2020, 71% and 75% in 2019, 78% and 76% in 2018, 69% and 66% in 2017, 60% for both species in 2016, 52% and 50% in 2015). In 2021 EUCAST excluded the "S" category (susceptible, standard dosing) for ciprofloxacin suggesting that even infections caused by wild type campylobacter isolates should be treated with higher dosing. Resistance to erythromycin (1% for both species) is still low but resistance to tetracycline shows increasing trend in both, *C.coli* and *C.jejuni* (51% and 47% in 2023, 37% and 43% in 2022, 33% and 28% in 2021, 35% and 41% in 2020, 46% and 42% in 2019, 41% and 36% in 2018, 35% and 30% in 2017).

In 2023, 30 shigella isolates were reported by six laboratories. *S. sonnei* isolates demonstrated 100% susceptibility to co-amoxiclav only, while they were predominantly resistant to other antibiotics. Resistance was slightly less pronounced in *S. flexneri* isolates, in which susceptibility to beta-lactams (except ampicillin) and azithromycin was high, but to co-trimoxazole and ciprofloxacin significantly decreased.

In 2023, 1.541 anaerobic bacterial isolates were reported, mostly *Bacteroides* spp. (875) and *Cutibacterium* acnes (318) from 19 centers. Resistance is overall highest to clindamycin (47%), and lowest to meropenem (3%) and piperacillin / tazobactam (5%).

LEGENDA ZA TABLICE */ LEGEND TO TABLES*:

Šifra / *code*	**USTANOVE** / *CENTERS*
BJ ZZJZ	ZZJZ Bjelovarsko-bilogorske županije, Bjelovar
ČK ZZJZ	ZZJZ Međimurske županije, Čakovec
DU ZZJZ	ZZJZ Dubrovačko-neretvanske županije, Dubrovnik
GS ZZJZ	ZZJZ Ličko-senjske županije, Gospić
IG ZZJZ	ZZJZ Zagrebačke županije, Ivanić Grad
KA OB	Opća bolinica Karlovac, Karlovačka županija
KA ZZJZ	ZZJZ Karlovačke županije, Karlovac
KC ZZJZ	ZZJZ Koprivničko-križevačke županije, Koprivnica
KR ZZJZ*	ZZJZ Krapinsko-zagorske županije, Krapina
NG OB	Opća bolnia Nova Gradiška, Brodsko-posavska županija
OG OB	Opća bolnica i bolnica branitelja Domovinskog rata Ogulin, Karlovačka županija
OS KBC	Klinički bolnički centar «Osijek», Osijek
OS NZZJZ	Nastavni ZZJZ Osječko-baranjske županije, Osijek
PK OŽB	Opća županijska bolnica, Pakrac i bolnica hrvatskih veterana
PU NZZJZ	Nastavni ZZJZ Istarske županije, Pula
PŽ OŽB	Opća županijska bolnica Požega, Požeško-slavonska županija
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 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 i Kliniku za traumatologiju, Zagreb

****** uključuje podatke i za: Kliniku za kardiovaskularne bolesti „Magdalena", Krapinske Toplice

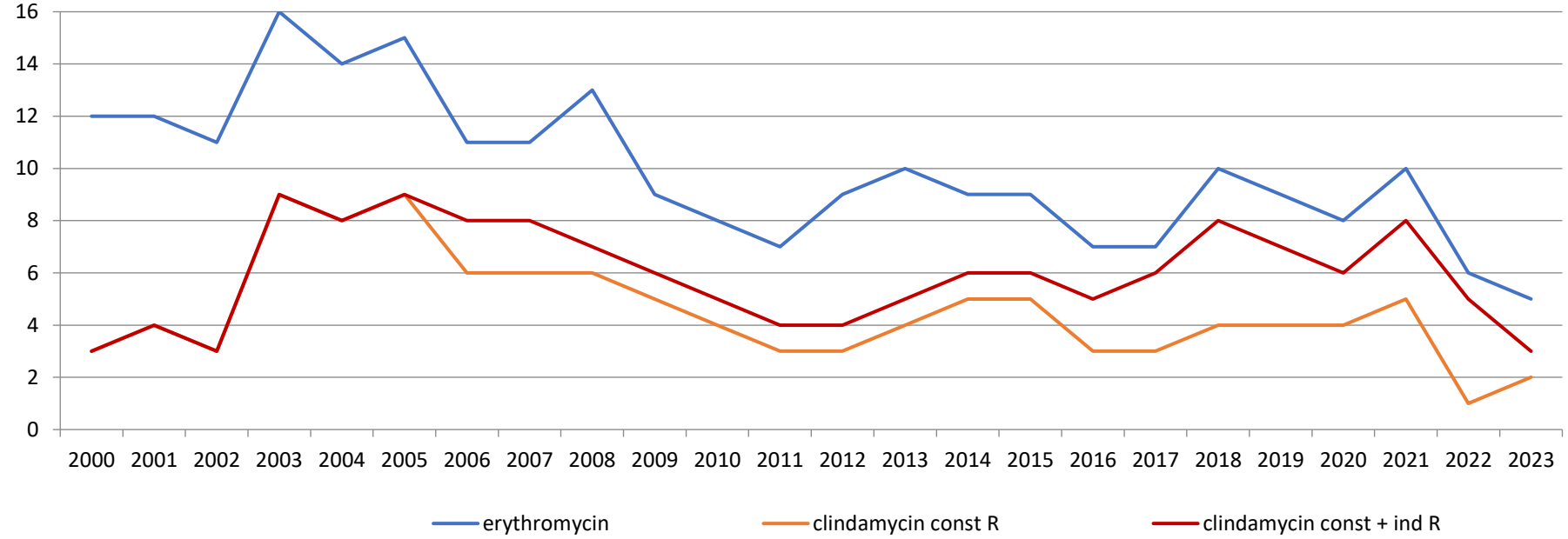
ANTIBIOTICI / *ANTIBIOTICS*:

P **parenteral**	*penicillin* parenteral
P **oral**	*penicillin* oral
AMP	*ampicillin*
AMP **parenteral**	*ampicillin* parenteral
AMX **oral**	*amoxicillin* oral
AMC	*amoxicillin + clavulanic acid*
AMC **u**	*amoxicillin + clavulanic acid* **uncomplicated urinary tract infection**
SAM	*ampicillin + sulbactam*
FOX	*cefoxitin*
CN	*cefalexin (I. gen. cephalosporins)*
CXM	*cefuroxime (II. gen. cephalosporins)*
CXM **parenteral**	*cefuroxime parenteral*
CXM **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 **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 **oral**	*fosfomycn* oral
NIB	*nitroxolin*
FDC	*cefiderocol*
IMR	*imipenem/relebactam*

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. - 2023.



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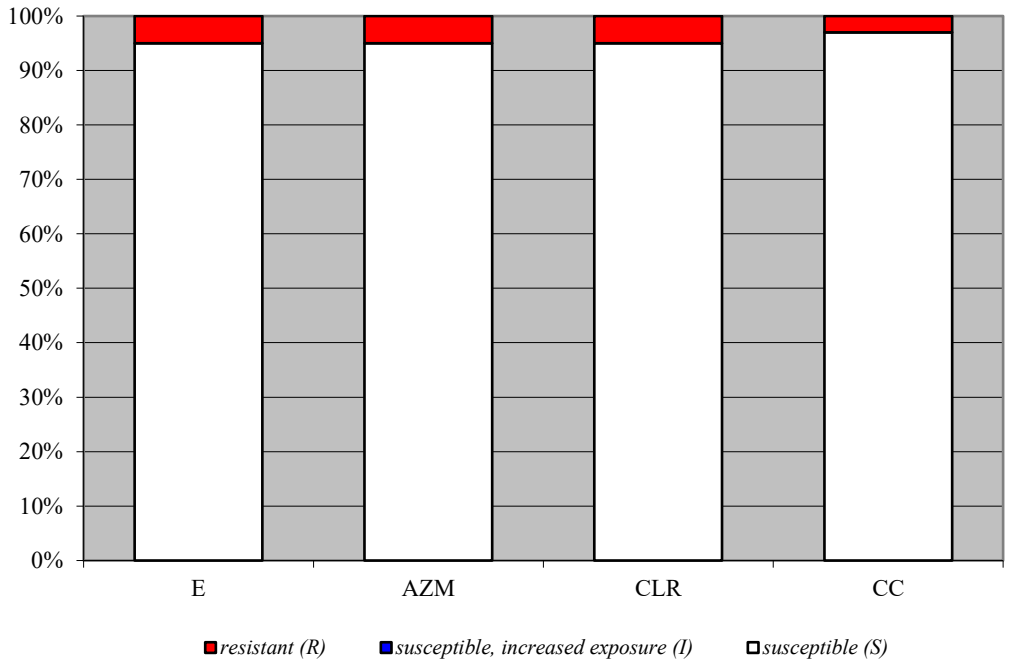
Beta-hemolitički streptokok grupe A / *Group A streptococcus*

rezistencija na antibiotike u razdoblju od 1.01.- 31.12.2023., zbirni prikaz izolata iz 37 centara u RH /
antibiotic resistance for the period 1.01. - 31.12.2023, summary results for the isolates from 37 centers in Croatia

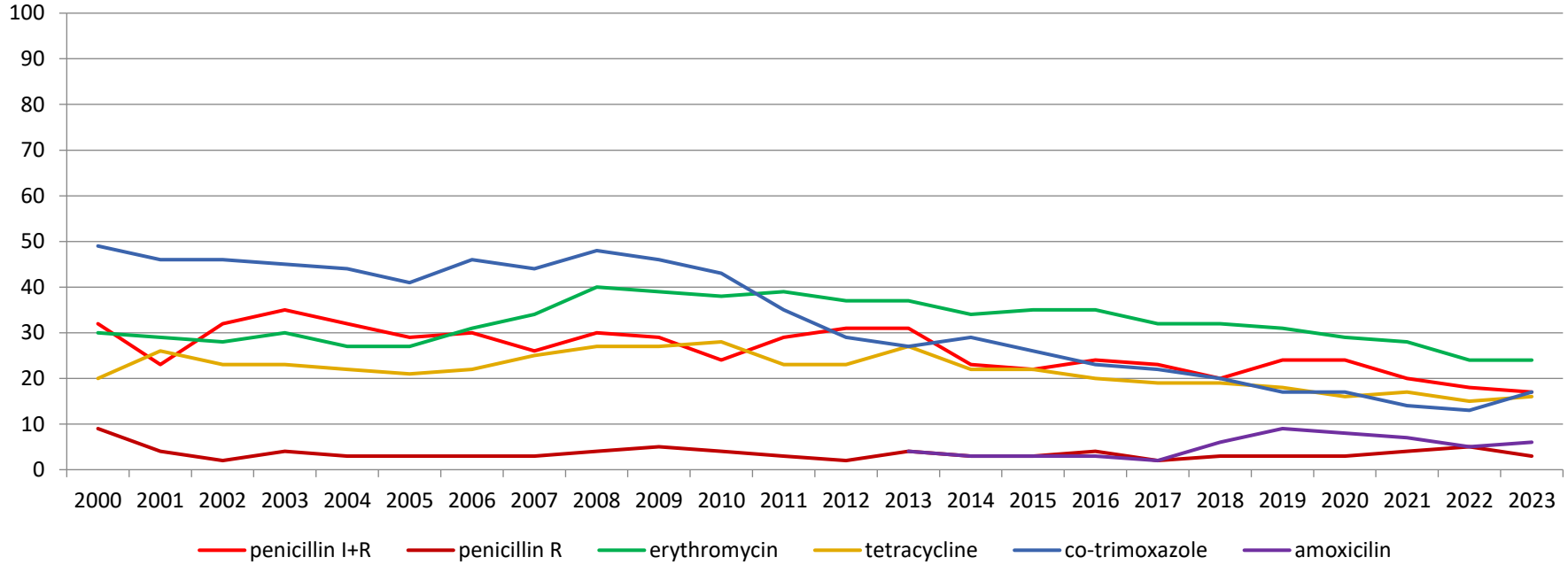
ANTIBIOTIK / *ANTIBIOTIC*	**Broj izolata** / *No. of isolates*	**% rezistentnih (R) (% osjetljivih uz povećanu izloženost (I)) izolata** / *% of resistant (R) (% of susceptible, increased exposure (I)) isolates*	**Raspon lokalnih rezultata*** / *Range of local results**
Erythromycin	19 005	5 (0)	0 (0) - 16 (0)
Azithromycin	19 005	5 (0)	0 (0) - 16 (0)
Clarythromycin	19 005	5 (0)	0 (0) - 16 (0)
Clindamycin	19 003	3 (0)	0 (0) – 16 (0)
constitutive		2	0 - 11
inducible		1	0 - 6

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



Streptococcus pneumoniae

rezistencija na antibiotike u RH / *resistance to antibiotics in Croatia*, 2000. - 2023.



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

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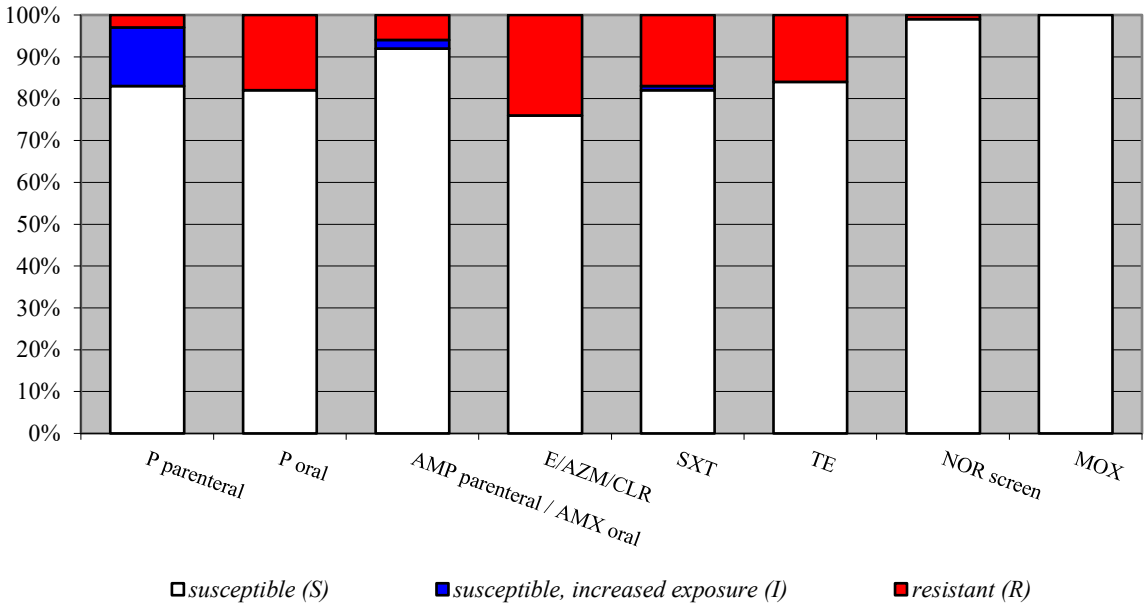
Streptococcus pneumoniae

rezistencija na antibiotike u razdoblju od 1.10.- 31.12.2023.,
zbirni prikaz izolata iz 37 centara u RH /
antibiotic resistance for the period 1.10. - 31.12.2023,
summary results for the isolates from 37 centers in Croatia

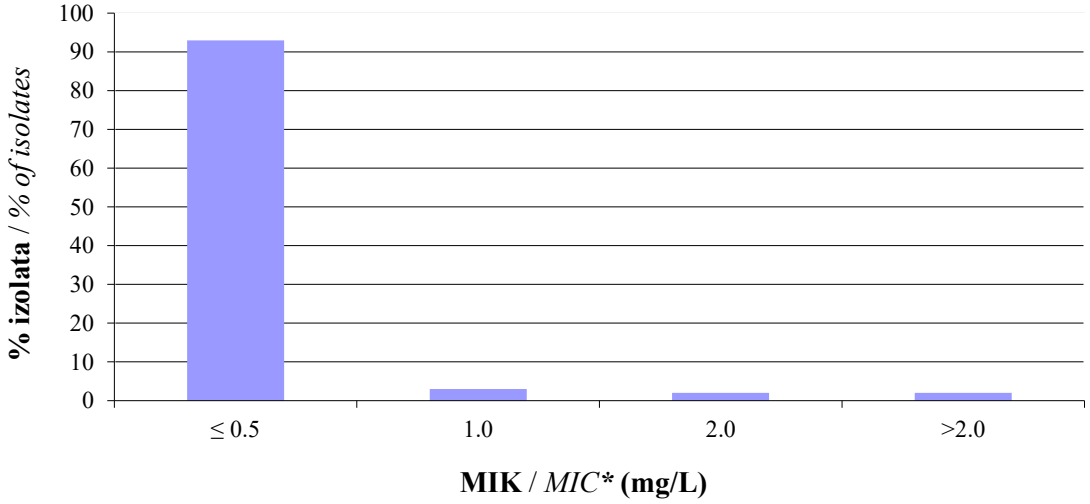
ANTIBIOTIK / *ANTIBIOTIC*	**Broj izolata** / *No. of isolates*	**% rezistentnih (R) (% osjetljivih uz povećanu izloženost (I)) izolata** / *% of resistant (R) (% of susceptible, increased exposure (I)) isolates*	**Raspon lokalnih rezultata*** / *Range of local results**
Penicillin $_{\text{parenteral}}$	1 632	3 (14)	0 (0) - 13 (26)
Penicilin $_{\text{oral}}$	1 632	18 (0)	0 (0)- 61(0)
Ampicillin $_{\text{parenteral}}$ **/ Amoxicillin** $_{\text{oral}}$	1 619	6 (2)	0 (0) - 19 (7)
Erythromycin/Azithromycin/ Clarythromycin	1 636	24 (0)	0 (0) - 62 (0)
Co-trimoxazole	1 636	17 (1)	0 (0) - 44 (0)
Tetracycline	1 456	16 (0)	0 (0) – 34 (0)
Norfloxacin $_{\text{screen}}$	1 544	1 (0)	0 (0) - 3 (0)
Moxifloxacin	1 620	0 (0)	0 (0) - 3 (0)

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



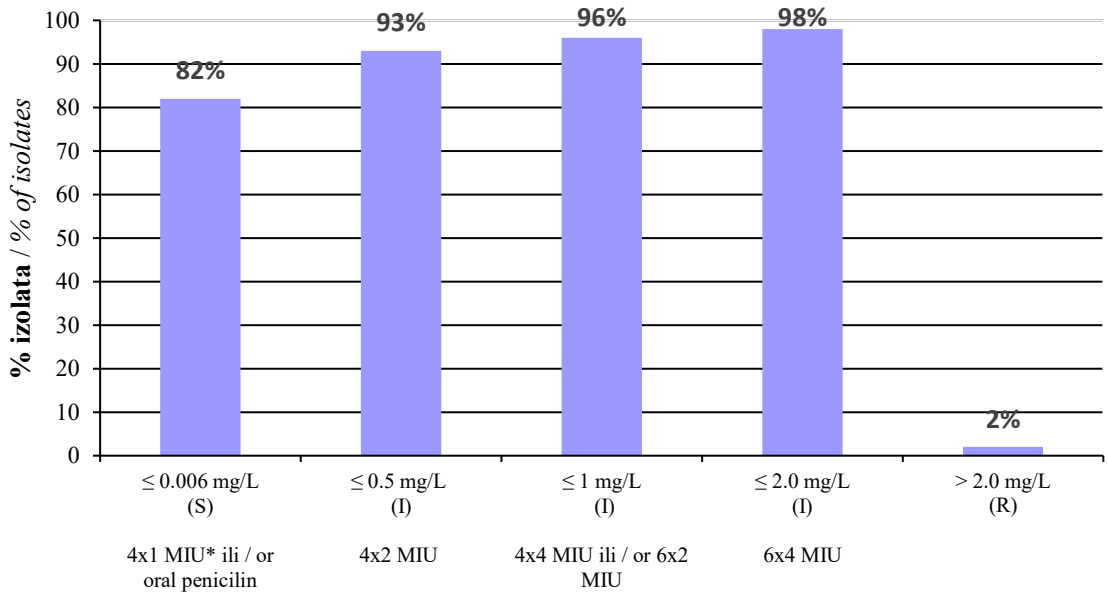
Streptococcus pneumoniae

Distribucija MIK-ova penicilina, (1 634 *S. pneumoniae* izolata) /
Penicillin MIC distribution, (1 634 S. pneumoniae isolates), 1.10. – 31.12.2023.



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

Udio pneumokoka podložnih liječenju različitim dozama penicilina
Rates of pneumococcal isolates treatable with different penicilin dosing



*MIU = milijun međunarodnih jedinica / *MIU = million international units*

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Staphylococcus aureus / MSSA

rezistencija na antibiotike u razdoblju od 1.10.- 31.12.2023.,
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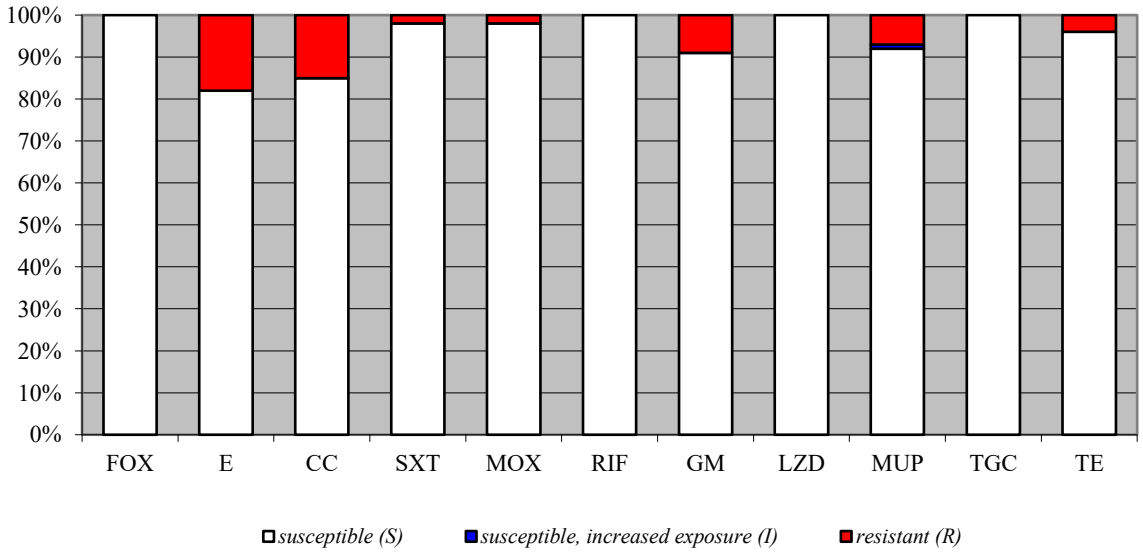
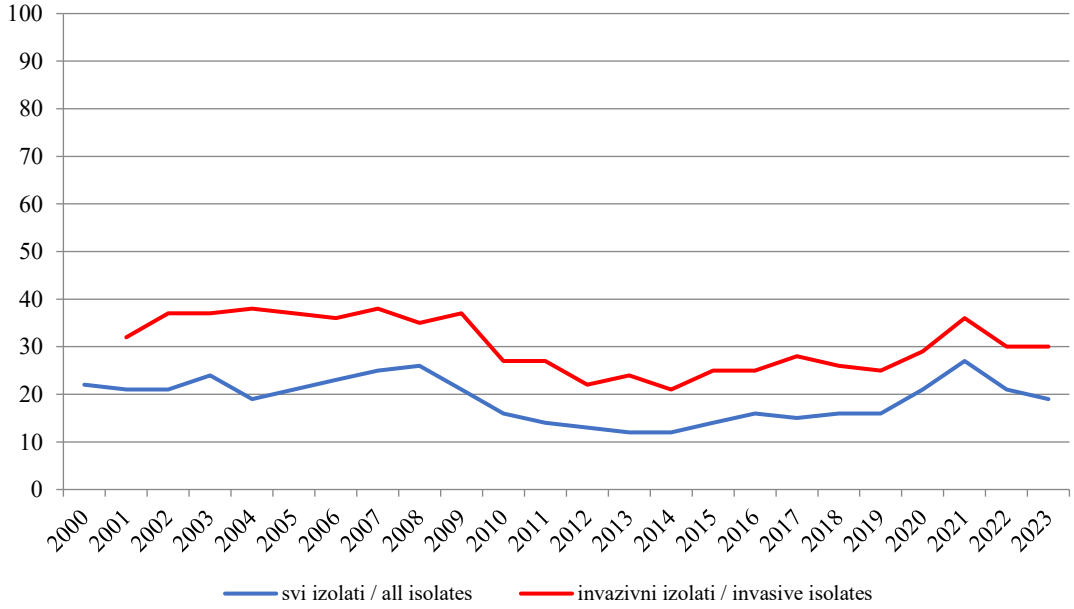
ANTIBIOTIK / *ANTIBIOTIC*	**Broj izolata** / *No. of isolates*	**% rezistentnih (R) (% osjetljivih uz povećanu izloženost (I)) izolata** / *% of resistant (R) (% of susceptible, increased exposure (I)) isolates*	**Raspon lokalnih rezultata*** / *Range of local results**
Cefoxitin/ Methicillin	4 144	0 (0)	0 (0) - 0 (0)
Erythromycin	4 061	18 (0)	10 (0) - 32 (0)
Clindamycin	4 061	15 (0)	5 (0) – 23 (0)
constitutive		7	0 - 19
inducible		8	0 - 14
Co-trimoxazole	4 057	2 (0)	0 (0) – 9 (0)
Moxifloxacin	3 885	2 (0)	0 (0) - 14 (0)
Rifampicin	3 861	0 (0)	0 (0) - 3 (0)
Gentamicin	4 067	7 (0)	2 (0) - 43 (0)
Linezolid	3 971	0 (0)	0 (0) - 0 (0)
Mupirocin	3 781	7 (1)	0 (0) - 43 (2)
Tigecycline	3 831	0 (0)	0 (0) – 1 (0)
Tetracycline	3 675	4 (0)	0 (0) - 25 (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*

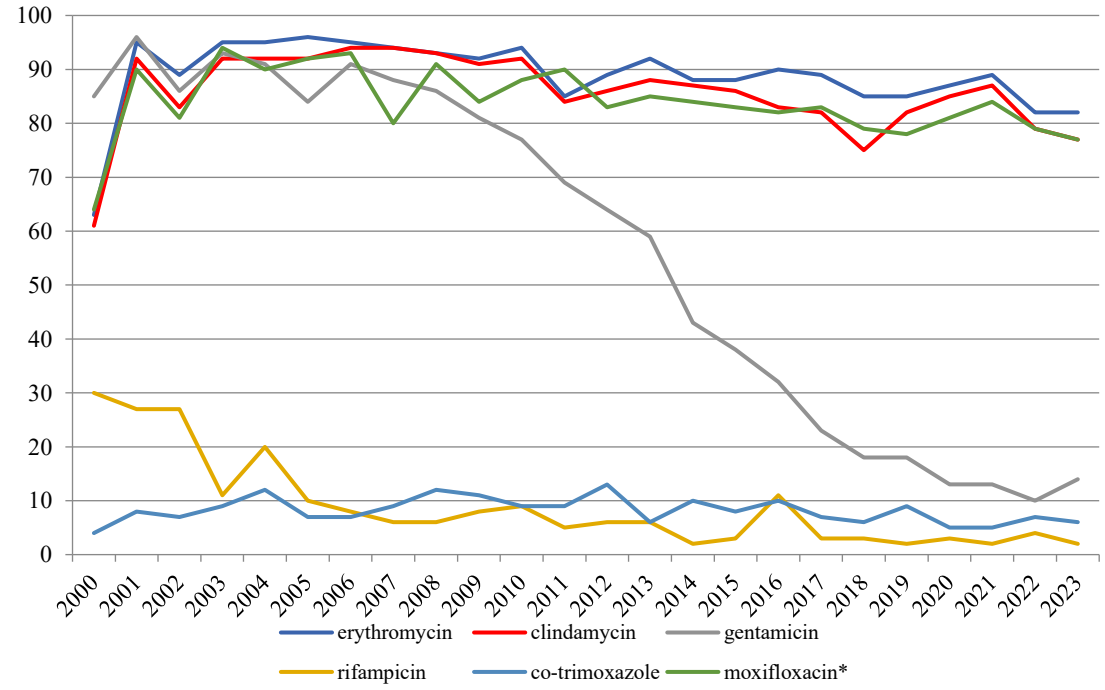


Staphylococcus aureus / MRSA

Methicillin resistant *Staphylococcus aureus* (MRSA) – stope / *rates*, 2000. - 2023.



rezistencija na antibiotike u RH /*resistance to antibiotics in Croatia*, 2000. - 2023.



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

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Staphylococcus aureus / MRSA

rezistencija na antibiotike u razdoblju od 1.10. - 31.12.2023.,
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Cefoxitin/ Methicillin	960	100 (0)	100 (0) - 100 (0)
Ceftaroline	745	10 (8)	0 (0) - 42 (30)
Erythromycin	946	82 (0)	60 (0) - 96 (0)
Clindamycin	946	77 (0)	60 (0) - 96 (0)
constitutive		55	18 - 83
inducible		21	0 - 68
Co-trimoxazole	937	6 (0)	0 (0) - 19 (0)
Moxifloxacin	893	77 (0)	50 (0) - 97 (0)
Rifampicin	909	2 (0)	0 (0) - 8 (0)
Gentamicin	946	14 (0)	0 (0) - 24 (0)
Linezolid	925	0 (0)	0 (0) - 0 (0)
Mupirocin	856	13 (2)	0 (0) - 40 (3)
Tigecycline	871	2 (0)	0 (0) - 11 (0)
Tetracycline	855	10 (0)	3 (0) - 21 (0)
Vankomicin	799	0 (0)	0 (0) - 0 (0)

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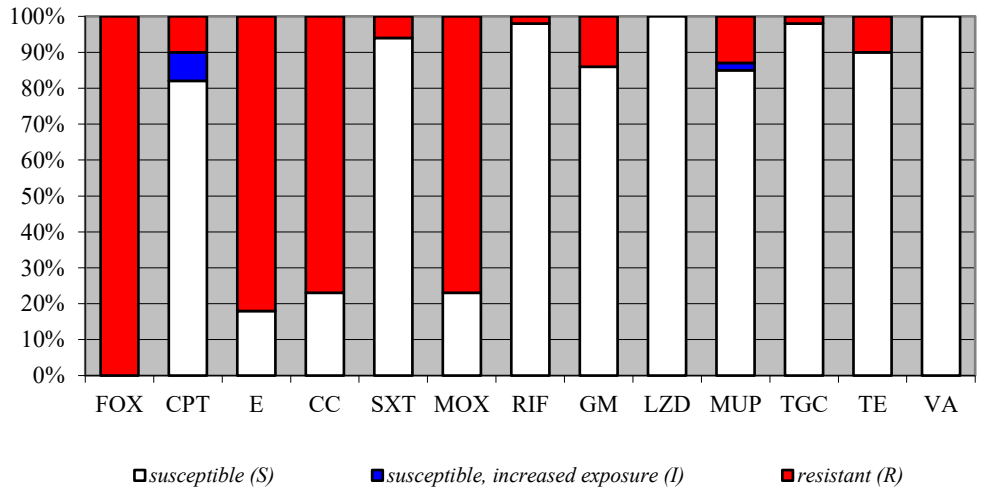
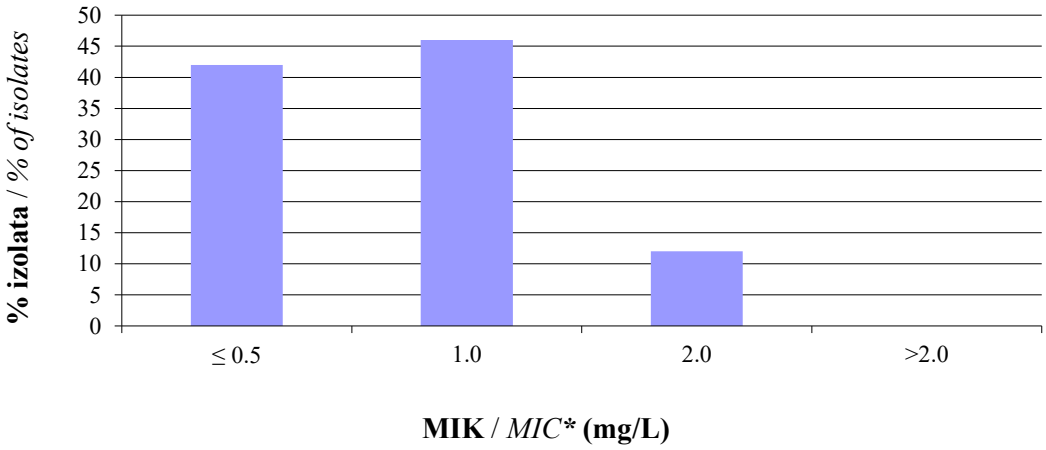


Staphylococcus aureus / MRSA

Distribucija MIK-ova vankomicina, (800 MRSA izolata) /
Vancomycin MIC distribution, (800 MRSA isolates), 1.10. – 31.12.2023.



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

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Enterococcus faecalis

rezistencija na antibiotike u razdoblju od 1.10. - 31.12.2023.,
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Ampicillin	5 260	1 (0)	0 (0) - 25 (0)
Gentamicin	4 992	23 (0)	5 (0) - 45 (0)
Vancomycin	5 276	0 (0)	0 (0) - 3 (0)
Nitrofurantoin	5 162	1 (0)	0 (0) - 13 (0)
Norfloxacin $_{\text{screem}}$	5 171	23 (0)	2 (0) - 46 (0)
Linezolid	5 006	0 (0)	0 (0) - 1 (0)

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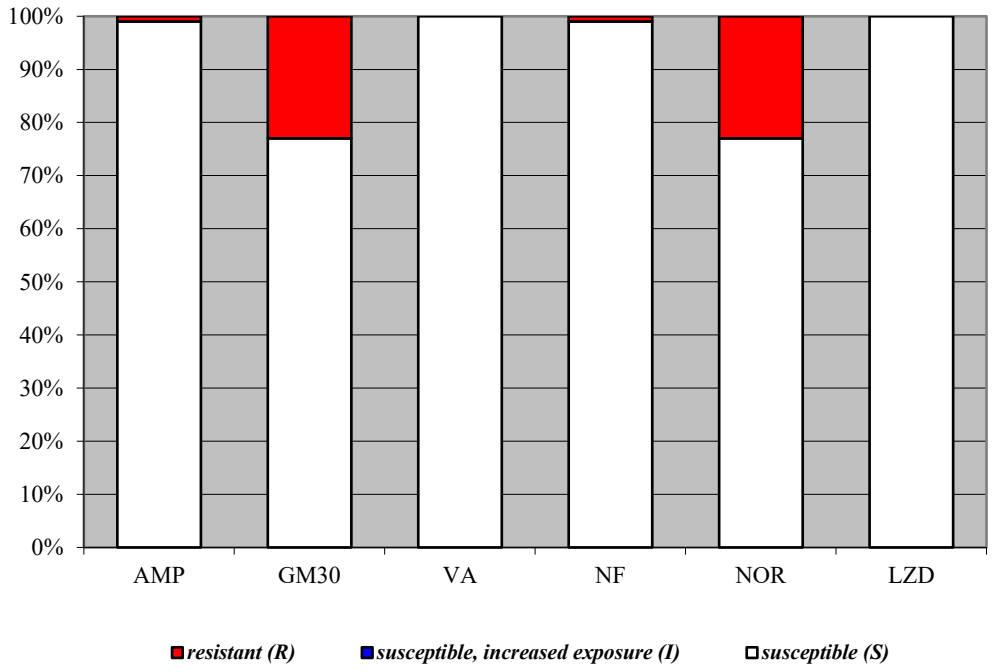
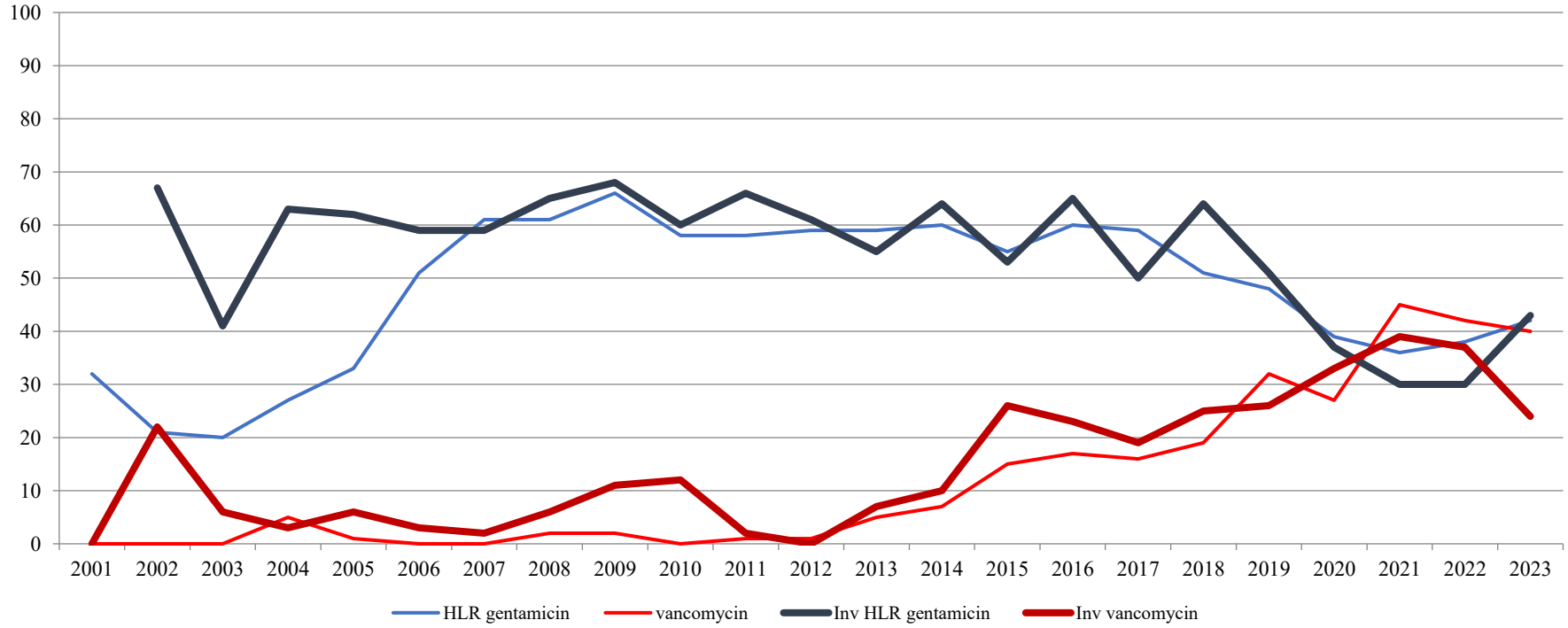


Enterococcus faecium

rezistencija na antibiotike u RH / *resistance to antibiotics in Croatia*, 2001. - 2023.



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

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Enterococcus faecium

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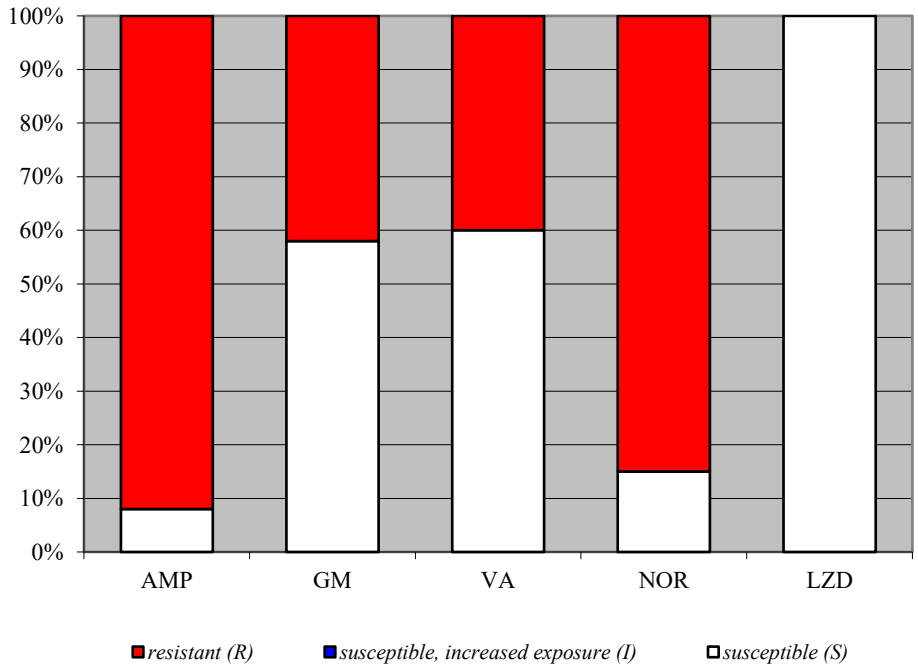
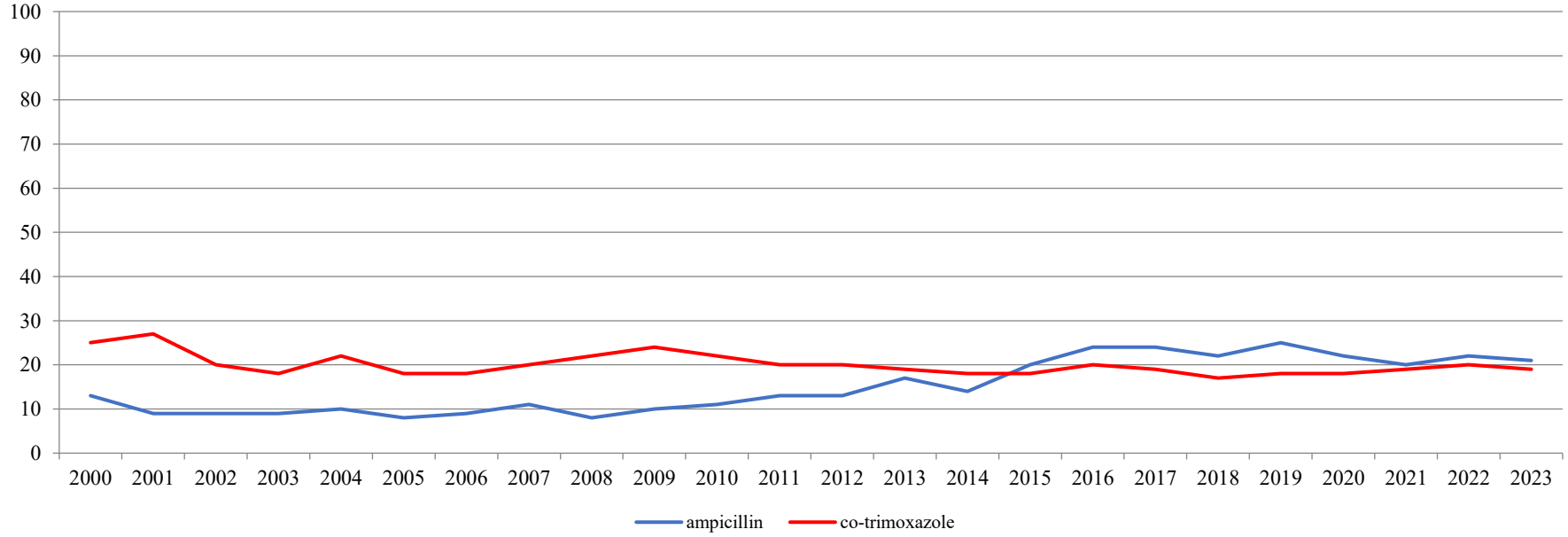
Ampicillin	1 152	92 (0)	74 (0) - 100 (0)
Gentamicin	1 097	42 (0)	20 (0) - 58 (0)
Vancomycin	1 169	40 (0)	6 (0) - 84 (0)
Norfloxacin	1 095	85 (0)	68 (0) - 99 (0)
Linezolid	1 118	0 (0)	0 (0) – 2 (0)

*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



Haemophilus influenzae

rezistencija na antibiotike u RH / *resistance to antibiotics in Croatia*, 2000. - 2023.



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Haemophilus influenzae

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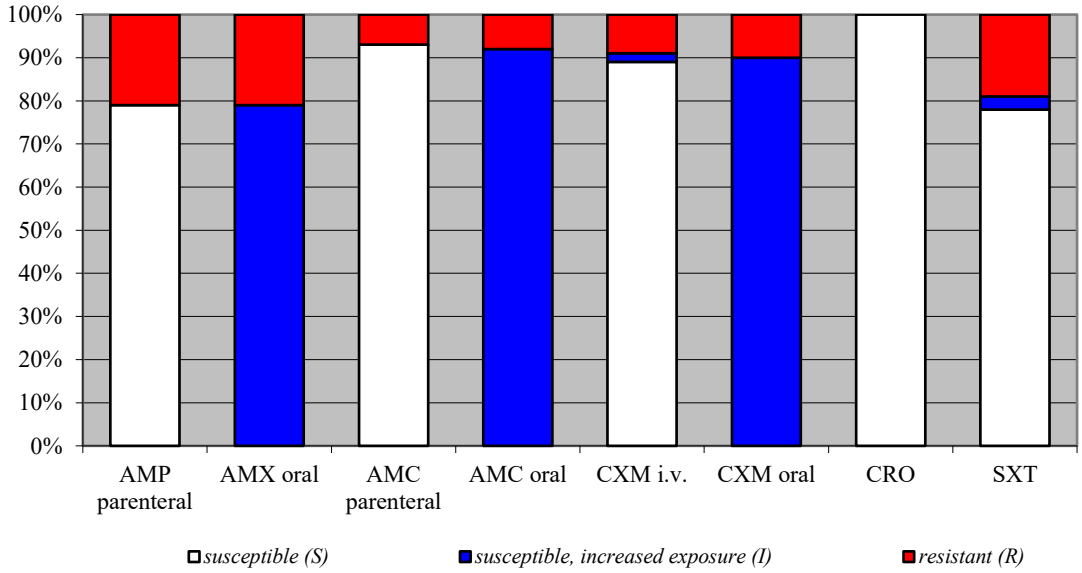
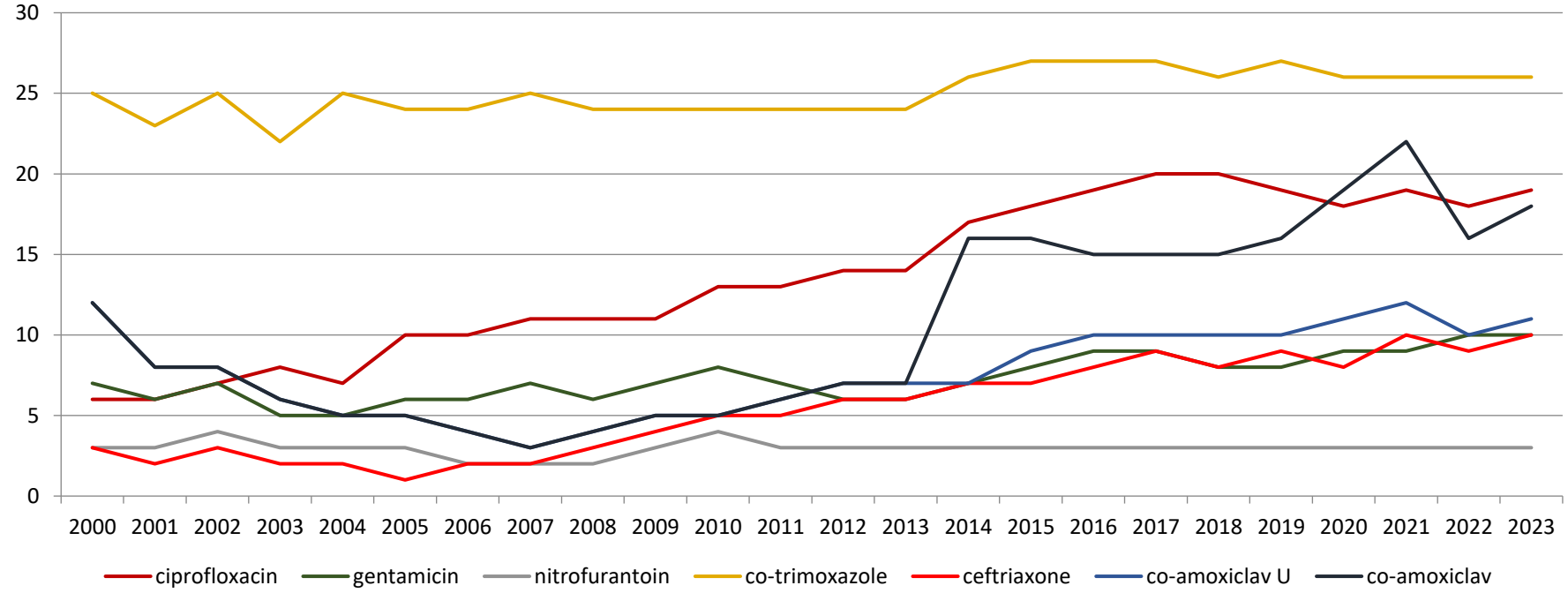
ANTIBIOTIK / *ANTIBIOTIC*	**Broj izolata** / *No. of isolates*	**% rezistentnih (R) (% osjetljivih uz povećanu izloženost (I)) izolata** / *% of resistant (R) (% of susceptible, increased exposure (I)) isolates*	**Raspon lokalnih rezultata*** / *Range of local results**
Ampicillin parenteral	1 156	21 (0)	0 (0) - 36 (0)
Amoxicillin oral	1 156	21 (79)	0 (100) – 36 (64)
Amoxicillin + clav. acid parenteral	1 152	7 (0)	0 (0) – 28 (0)
Amoxicillin + clav. acid oral	1 152	8 (92)	0 (100) – 31 (69)
Cefuroxime parenteral	1 157	9 (2)	0 (0) - 31 (0)
Cefuroxime oral	1 157	10 (90)	0 (100) - 31 (69)
Ceftriaxone	1 095	0 (0)	0 (0) - 3 (0)
Co-trimoxazole	1 156	19 (3)	0 (0) - 39 (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



Escherichia coli

rezistencija na antibiotike u RH / *resistance to antibiotics in Croatia*, 2000. - 2023.



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. - 31.12.2023.,
zbirni prikaz izolata iz 37 centara u RH /
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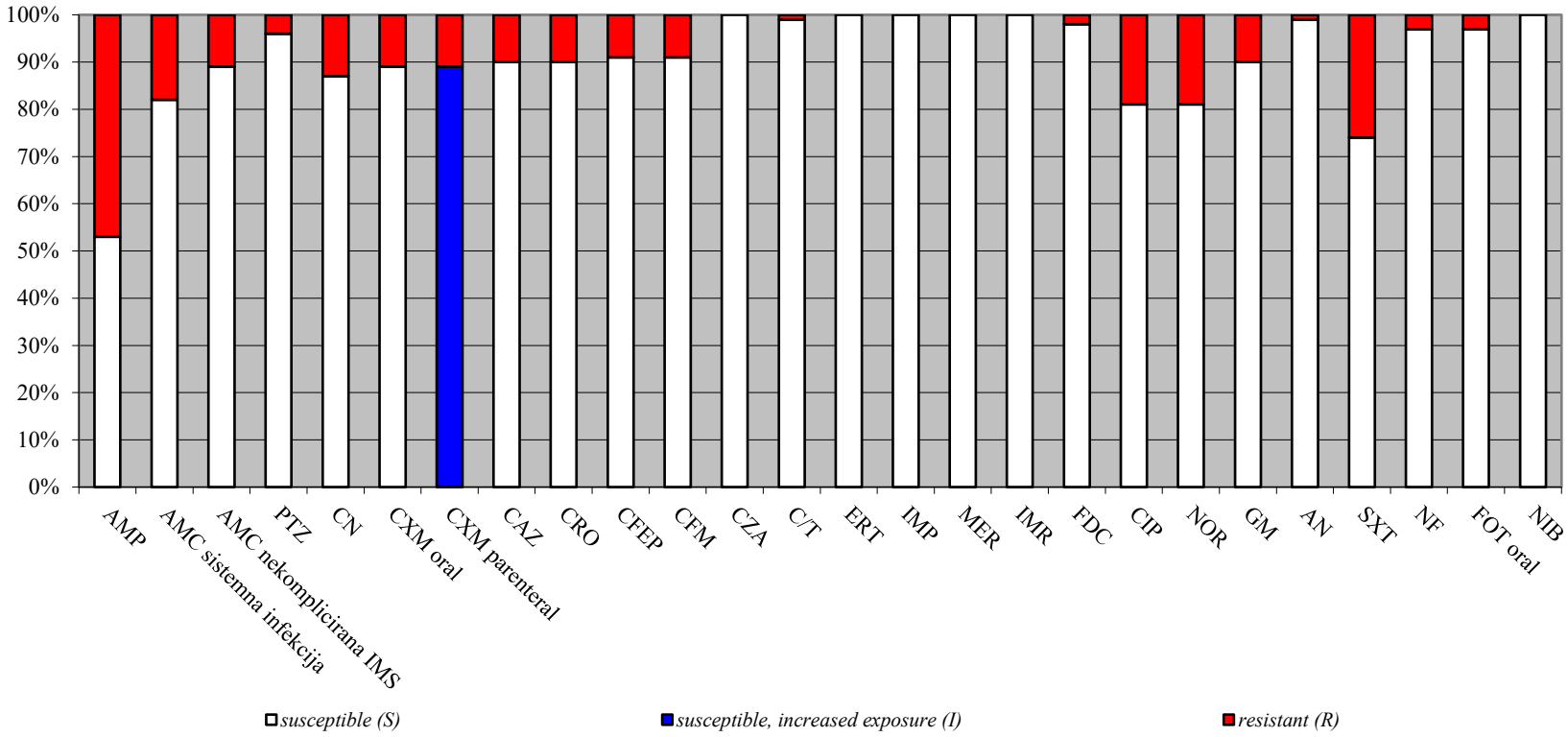
ANTIBIOTIK / *ANTIBIOTIC*	**Broj izolata** / *No. of isolates*	**% rezistentnih (R) (% osjetljivih uz povećanu izloženost (I)) izolata** / *% of resistant (R) (% of susceptible, increased exposure (I)) isolates*	**Raspon lokalnih rezultata*** / *Range of local results**
Ampicillin	20 349	47 (0)	36 (0) - 62 (0)
Amoxicillin + clav. acid sistemna infekcija	20 260	18 (0)	2 (0) - 48 (0)
Amoxicillin + clav. Acid nekomplicirana IMS	20 313	11 (0)	1 (0) - 35 (0)
Piperacillin + tazobactam	20 342	4 (0)	0 (0) - 25 (0)
Cephalexin	19 392	13 (0)	5 (0) – 24 (0)
Cefuroxime oral	20 220	11 (0)	3 (0) - 22 (0)
Cefuroxime parenteral	20 220	11 (89)	3 (97) – 22 (78)
Ceftazidime	20 288	10 (0)	1 (0) - 21 (0)
Ceftriaxone	20 287	10 (0)	0 (0) - 21 (0)
Cefepime	20 309	9 (0)	0 (0) – 24 (0)
Cefixime	19 697	11 (0)	1 (0) – 21 (0)
Ceftazidime + avibactam	19 381	0 (0)	0 (0) – 7 (0)
Ceftolozane + tazobactam	19 382	1 (0)	0 (0) – 3 (0)
Ertapenem	20 307	0 (0)	0 (0) - 3 (0)
Imipenem	19 948	0 (0)	0 (0) - 0 (0)
Meropenem	20 306	0 (0)	0 (0) - 1 (0)
Imipenem + relebactam	19 363	0 (0)	0 (0)- 10(0)
Cefiderocol	18824	2 (0)	0 (0)-10 (0)
Ciprofloxacin	20 302	19 (0)	9 (1) - 36 (2)
Norfloxacin	19 997	19 (0)	12 (0) - 37 (0)
Gentamicin	20 349	10 (0)	5 (0) - 22 (0)
Amikacin	20 341	1 (0)	0 (0) - 8 (0)
Co-trimoxazole	20 288	26 (0)	3 (0) - 35 (0)
Nitrofurantoin	20 057	3 (0)	1 (0) - 24 (0)
Fosfomycin oral	19 530	3 (0)	0 (0) - 14 (0)
Nitroxolin	18 565	0 (0)	0 (0) - 1 (0)

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

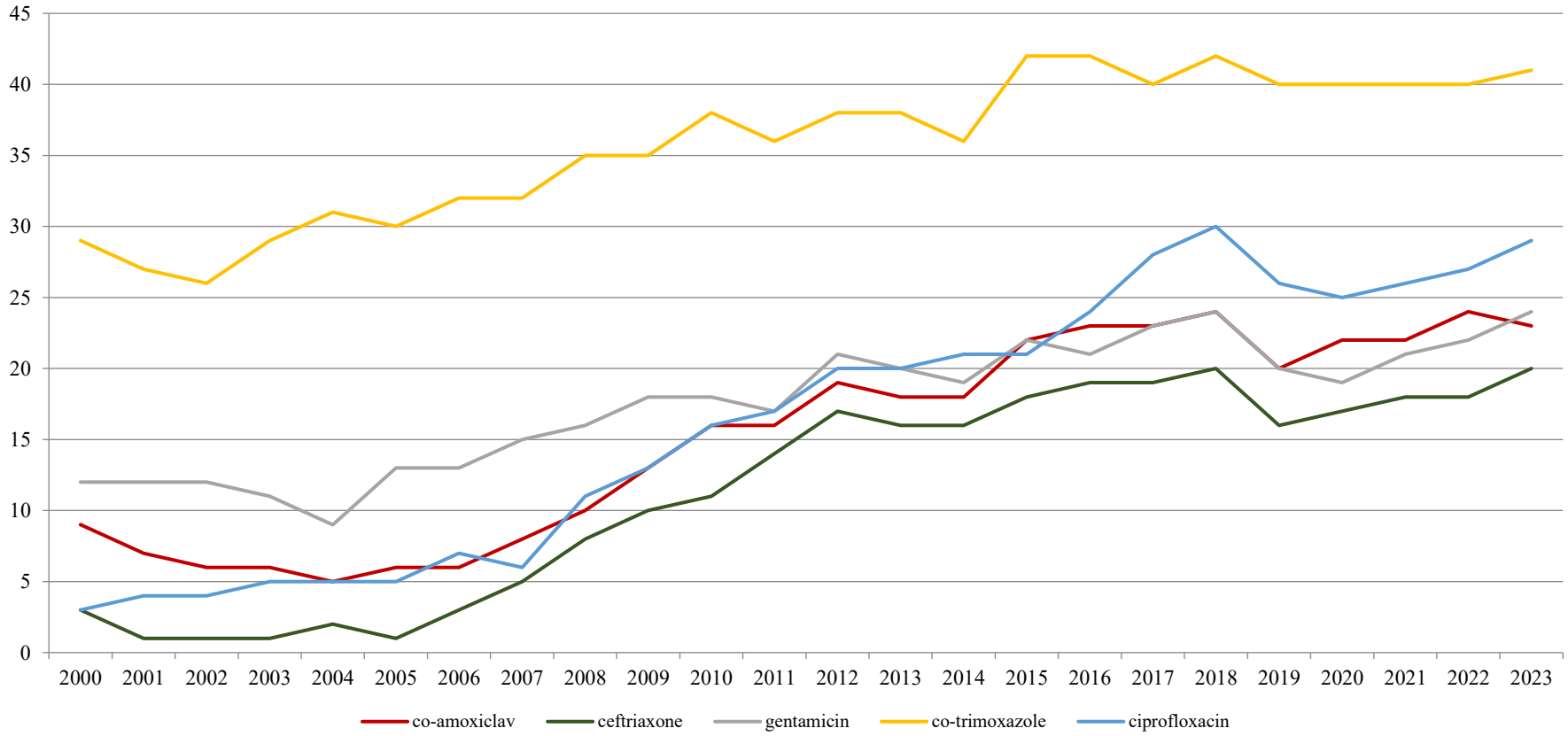
Escherichia coli

osjetljivost na antibiotike u RH / *sensitivity to antibiotics in Croatia*, 1.10. – 31.12.2023.



Proteus mirabilis

rezistencija na antibiotike u RH / *resistance to antibiotics in Croatia*, 2000. – 2023.



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Proteus mirabilis

rezistencija na antibiotike u razdoblju od 1.10. - 31.12.2023.,
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Ampicillin	4 090	47 (0)	20 (0) - 78 (0)
Amoxicillin + clav. acid	4 097	23 (0)	4 (0) - 71 (0)
Piperacillin + tazobactam	3 954	3 (0)	0 (0) - 19 (0)
Cephalexin	3 773	24 (0)	3 (0) - 64 (0)
Cefixime	3 825	18 (0)	0 (0) - 64 (0)
Cefuroxime $_{\text{oral}}$	3 923	22 (0)	3 (0) - 62 (0)
Cefuroxime $_{\text{parenteral}}$	3 923	22 (78)	3 (0) - 62 (38)
Ceftazidime	3 943	17 (1)	0 (0) - 60 (0)
Ceftriaxone	3 944	20 (0)	0 (0) - 60 (0)
Cefepime	3 956	11 (5)	0 (0) - 35 (0)
Ceftazidime + avibactam	3 732	1 (0)	0 (0) - 8 (0)
Ceftolozane + tazobactam	3 720	8(0)	0 (0) – 26 (0)
Cefiderocol	3 574	2 (0)	0 (0)- 10 (0)
Ertapenem	3 957	0 (0)	0 (0) – 6 (0)
Meropenem	3 959	0 (0)	0 (0) – 3 (0)
Ciprofloxacin	3 958	29 (1)	0 (0) – 67 (0)
Norfloxacin	3 879	29 (0)	0 (0) – 67 (0)
Gentamicin	3 981	24 (0)	0 (0) – 55 (0)
Amikacin	3 930	12 (0)	0 (0) – 43 (0)
Co-trimoxazole	3 957	41 (0)	10 (0) – 63 (0)

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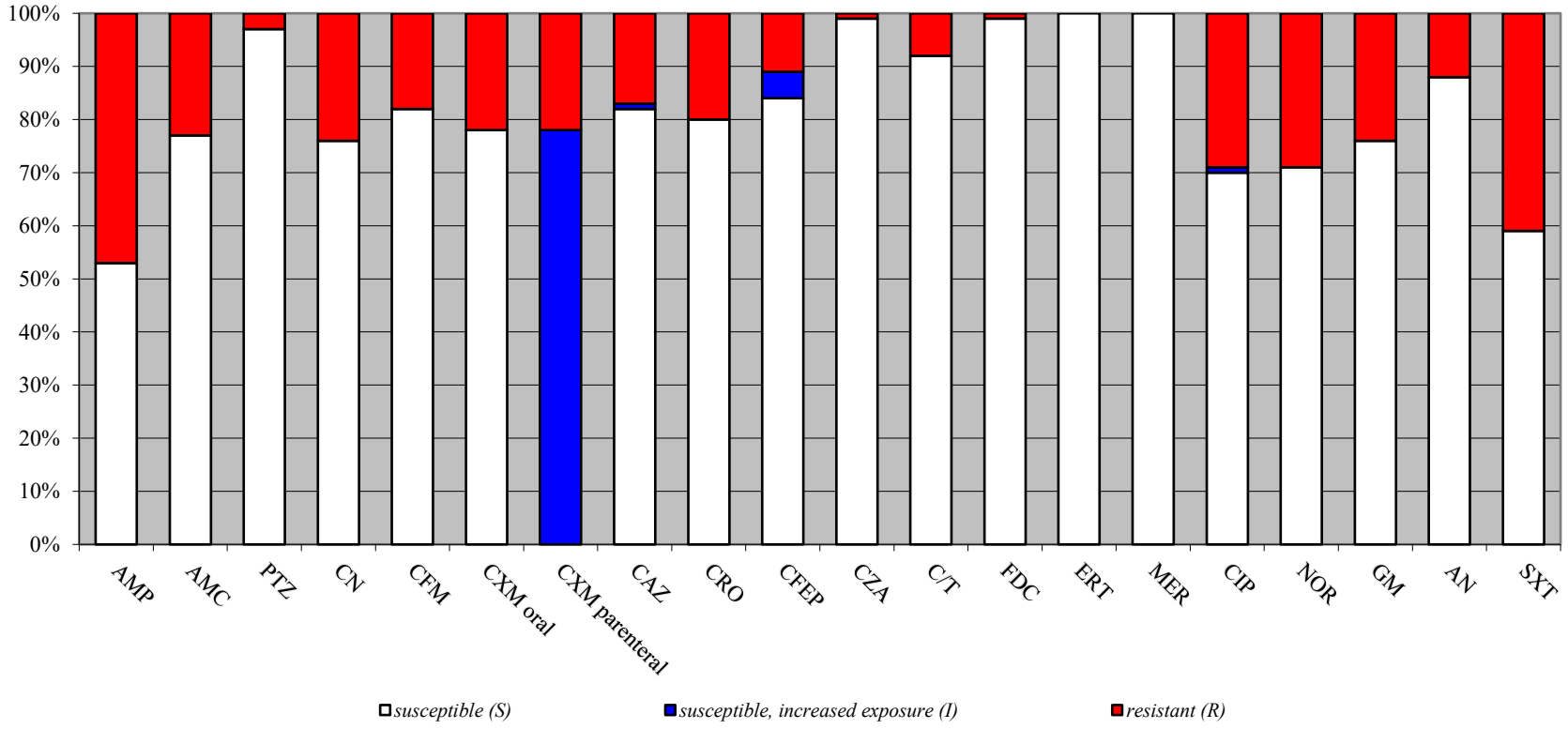
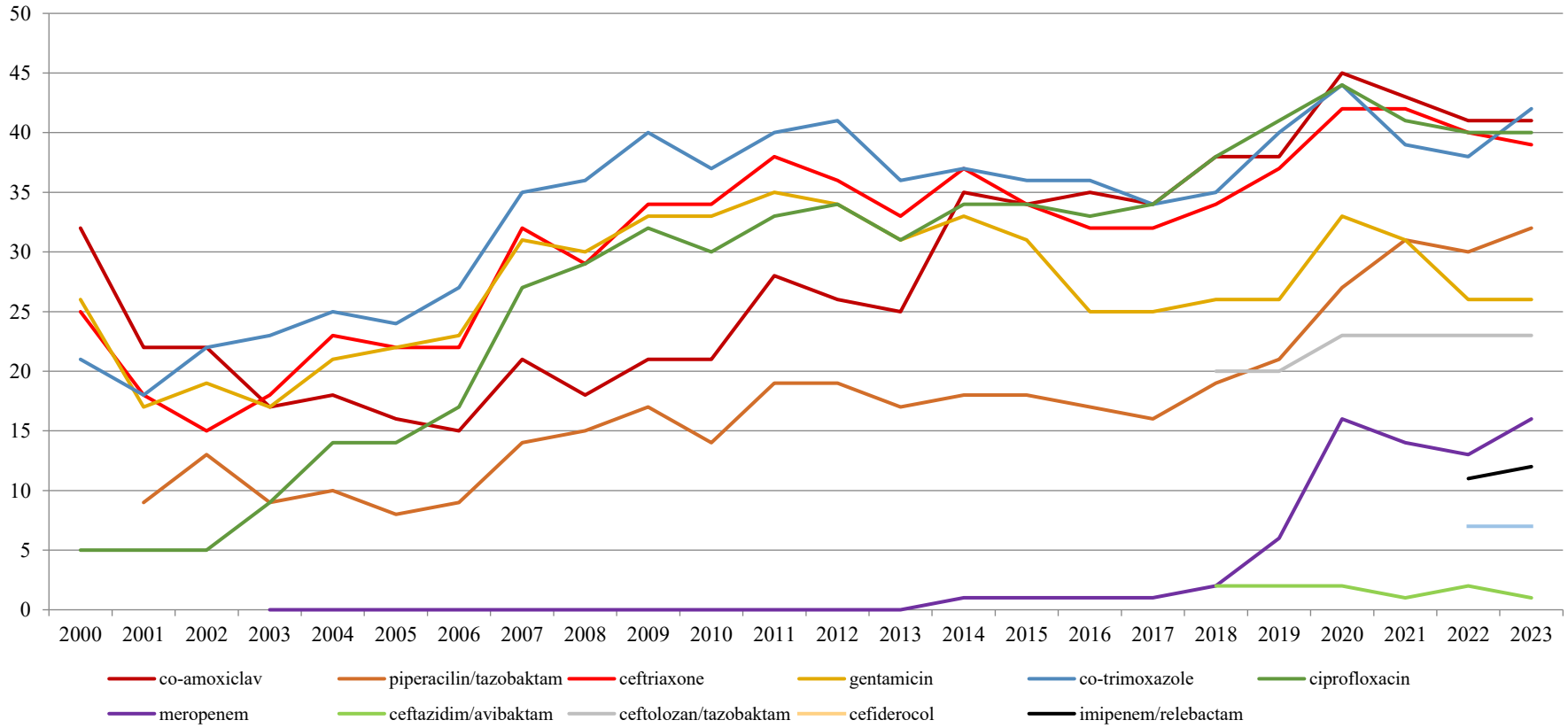
Proteus mirabilis

osjetljivost na antibiotike u RH / *sensitivity to antibiotics in Croatia*, 1.10. – 31.12.2023.



Klebsiella pneumoniae

rezistencija na antibiotike u RH /*resistance to antibiotics in Croatia*, 2000. - 2023.



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Klebsiella pneumoniae

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Ampicillin	6 557	100 (0)	100 (0) – 100 (0)
Amoxicillin + clav. acid	6 541	41 (0)	7 (0) – 66 (0)
Piperacillin + tazobactam	6 548	32 (0)	3 (0) – 60 (0)
Cephalexin	6 207	42 (0)	13 (0) – 65 (0)
Cefuroxime oral	6 449	41 (0)	16 (0) – 65 (0)
Cefuroxime parenteral	6 449	41 (59)	16 (84) – 65 (35)
Ceftazidime	6 504	39 (0)	7 (0) – 65 (0)
Ceftriaxone	6 507	39 (0)	10 (0) – 65 (0)
Cefepime	6 544	38 (1)	6 (0) – 63 (1)
Cefixime	6 351	39 (0)	8 (0) – 65 (0)
Ceftazidime + avibactam	6 223	1 (0)	0 (0) – 5 (0)
Ceftolozane + tazobactam	6 169	23 (0)	0 (0) – 49 (0)
Cefiderocol	5 988	7 (0)	0 (0) – 16 (0)
Ertapenem	6 543	24 (0)	1 (0) – 48(0)
Imipenem	6 349	11 (4)	0 (0) – 29 (3)
Meropenem	6 548	16 (2)	0 (0) – 39 (0)
Imipenem + relebactam	6 094	12 (0)	0 (0) – 39 (2)
Ciprofloxacin	6 536	40 (1)	14 (0) – 69 (0)
Norfloxacin	6 322	42 (0)	14 (0) – 71 (0)
Gentamicin	6 553	26 (0)	4 (0) – 47 (0)
Amikacin	6 553	9 (0)	0 (0) – 27 (0)
Co-trimoxazole	6 498	42 (1)	18 (0) – 63 (0)

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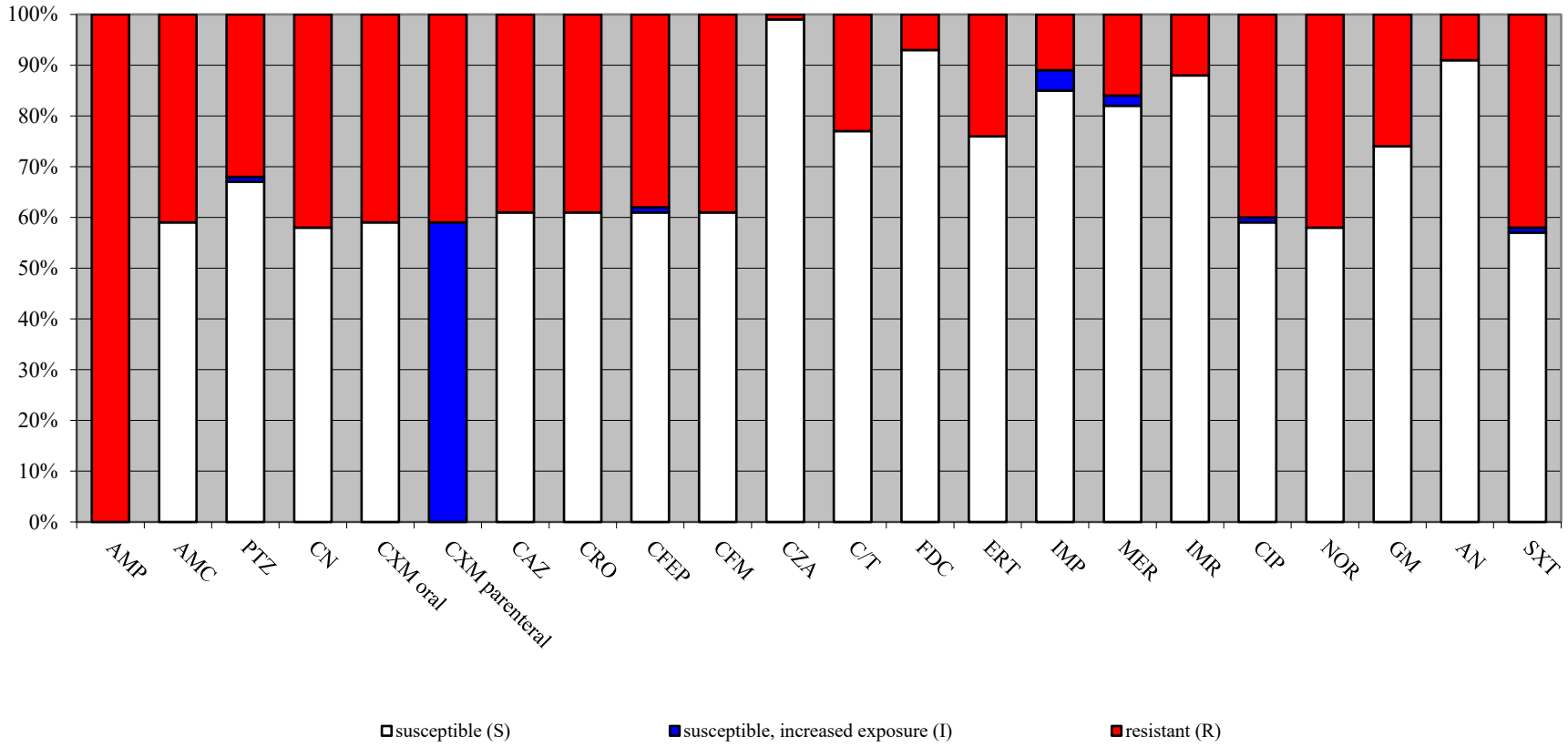
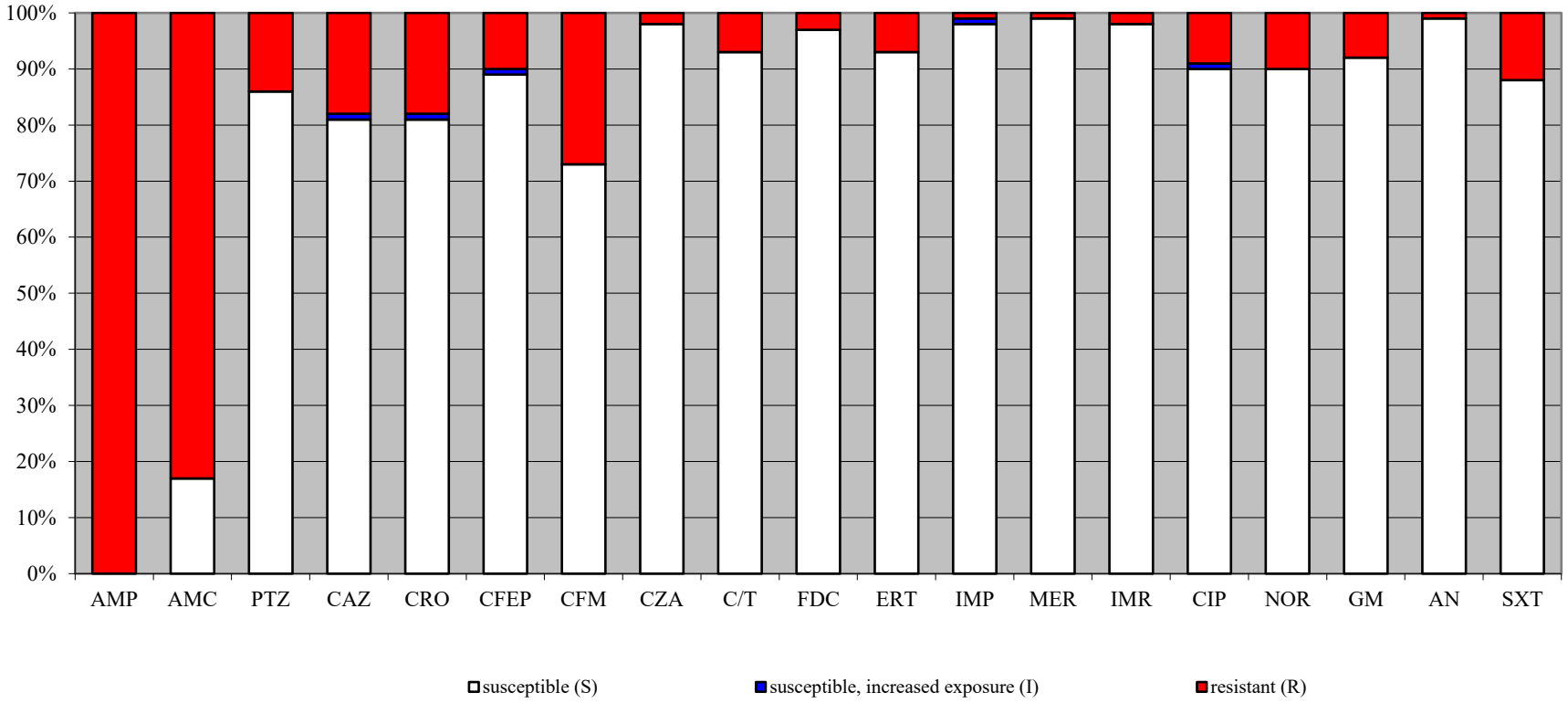
Klebsiella pneumoniae

osjetljivost na antibiotike u RH / *sensitivity to antibiotics in Croatia*, 1.10. – 31.12.2023.



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

osjetljivost na antibiotike u RH / *sensitivity to antibiotics in Croatia,* 1.10. – 31.12.2023.



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

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Ampicillin	3 639	100 (0)	100 (0) - 100 (0)
Amoxicillin + clav. acid	3 640	83 (0)	54 (0) - 100 (0)
Piperacillin + tazobactam	3 636	13 (0)	0 (0) - 40 (3)
Ceftazidime	3 610	17 (1)	6 (1) - 46 (3)
Ceftriaxone	3 610	17 (1)	6 (0) - 51 (3)
Cefepime	3 638	9 (1)	0 (0) - 51 (3)
Cefixime	3 481	26 (0)	10 (0) - 79 (0)
Ceftazidime + avibactam	3 433	2 (0)	0 (0) - 11 (0)
Ceftolozane + tazobactam	3 427	7 (0)	0 (0) – 19 (0)
Cefiderocol	3 321	3 (0)	0 (0) – 9 (0)
Ertapenem	3 637	7 (0)	0 (0) – 26 (0)
Imipenem	3 588	1 (1)	0 (0) – 6 (2)
Meropenem	3 637	1 (1)	0 (0) – 3 (1)
Imipenem + relebactam	3 368	2 (0)	0 (0) – 7 (0)
Ciprofloxacin	3 638	9 (1)	2 (1) - 32 (0)
Norfloxacin	3 526	10 (0)	3 (0) - 32 (0)
Gentamicin	3 640	8 (0)	1 (0) - 29 (0)
Amikacin	3 577	1 (0)	0 (0) - 7 (0)
Co-trimoxazole	3 610	12 (0)	2 (0) - 39 (0)

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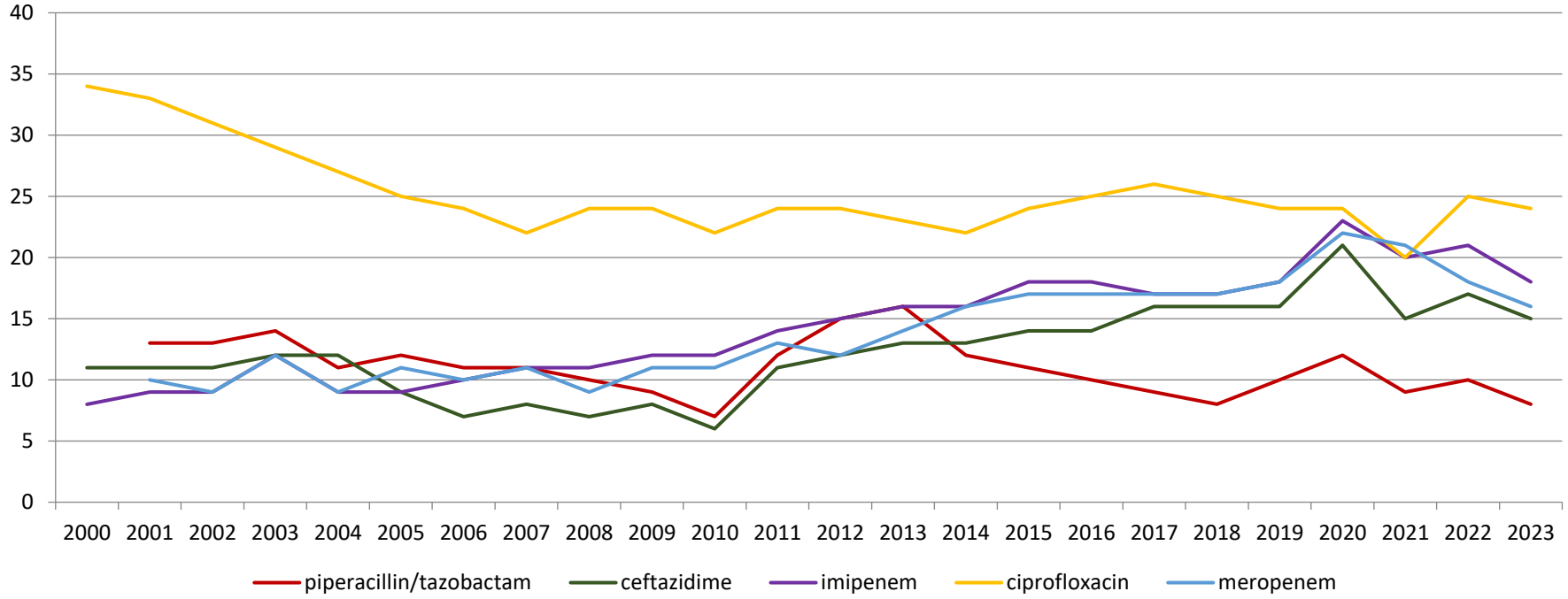
Pseudomonas aeruginosa

rezistencija na antibiotike u RH / *resistance to antibiotics in Croatia*, 2000. - 2023.



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Pseudomonas aeruginosa

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Piperacilin + tazobaktam	4 303	8 (92)	0 (100) - 21 (79)
Ceftazidim	4 300	15 (85)	1 (99) - 51 (49)
Cefepim	4 302	13 (87)	1 (99) - 33 (67)
Ceftazidime + avibactam	3 962	6 (0)	0 (0) – 32 (0)
Ceftolozane + tazobactam	4 014	5 (0)	0 (0) – 14 (0)
Cefiderocol	3 678	2 (0)	0 (0) – 7 (0)
Imipenem	4 145	18 (82)	3 (97) - 46 (54)
Meropenem	4 302	16 (5)	1 (9) - 41 (5)
Ciprofloxacin	4 301	24 (76)	5 (95) - 51 (49)
Amikacin	4 204	6 (0)	0 (0) - 23 (0)
Colistin	799	2 (0)	0 (0) - 13 (0)

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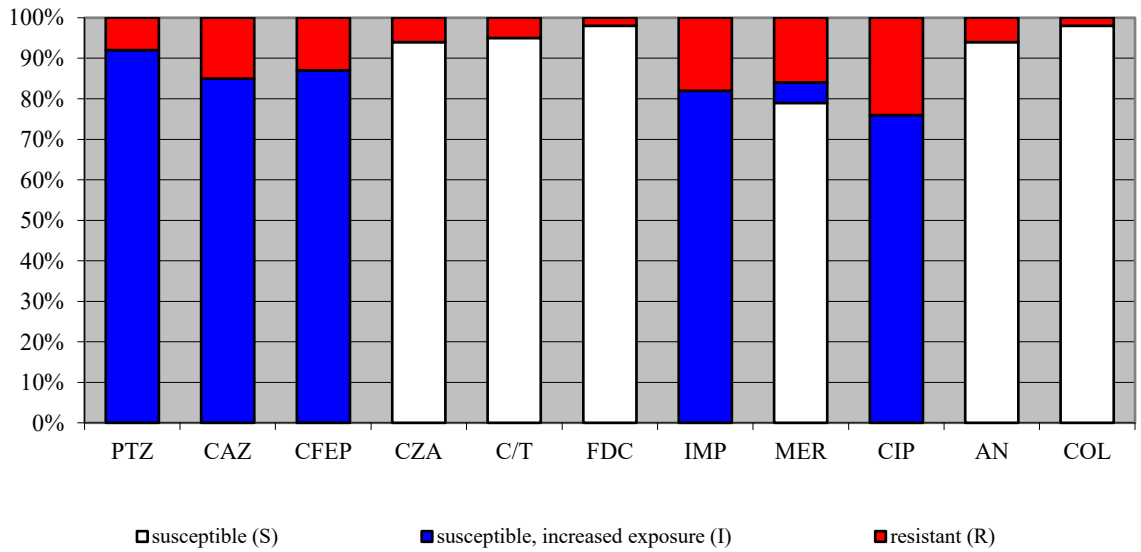
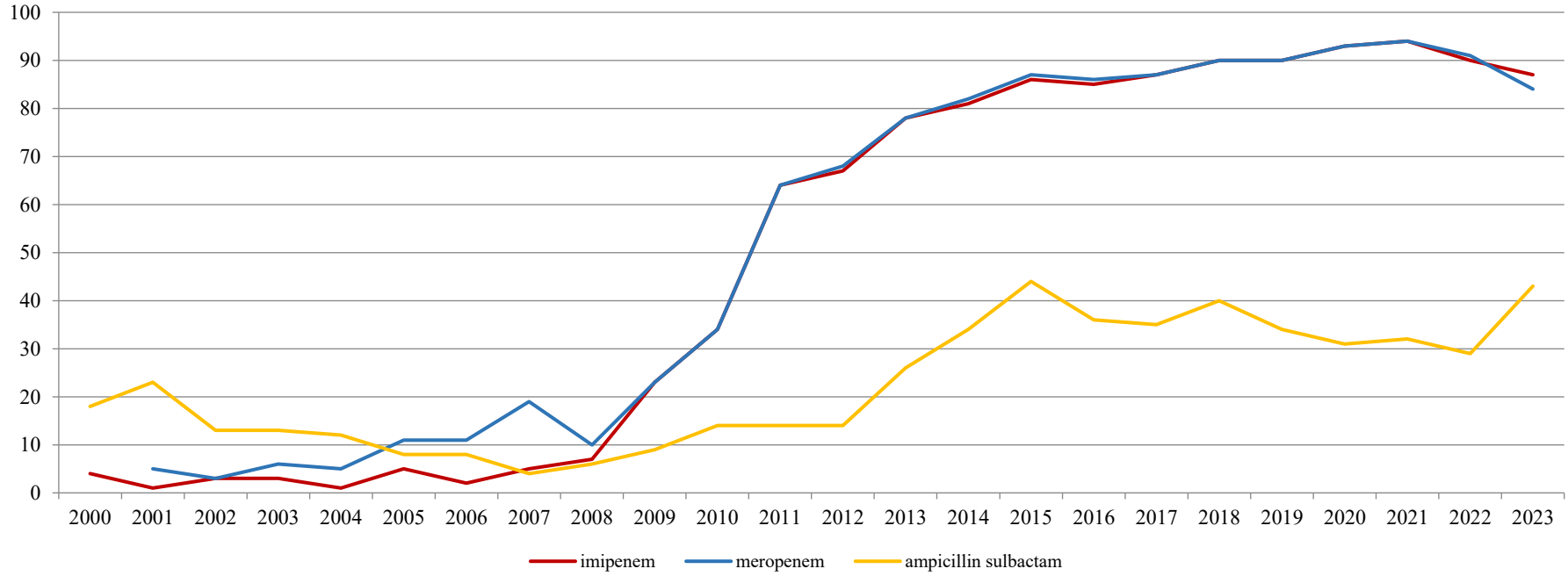


Acinetobacter baumannii

rezistencija na antibiotike u RH / *resistance to antibiotics in Croatia*, 2000. - 2023.



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Acinetobacter baumannii

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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 + sulbactam	1 563	41 (17)	4 (12) - 91 (0)
Meropenem	1 625	87 (1)	64 (8) - 100 (0)
Imipenem	1 564	87 (1)	64 (6) - 100 (0)
Ciprofloxacin	1 628	90 (10)	62 (38) - 100 (0)
Gentamicin	1 624	85 (0)	60 (0) - 100 (0)
Amikacin	1 626	82 (0)	56 (0) - 100 (0)
Co-trimaxazole	1 585	80 (2)	56 (4) - 100 (0)
Colistin	1 294	1 (0)	0 (0) - 6 (0)
Cefiderocol	1 354	2 (0)	0 (0) – 20 (0)

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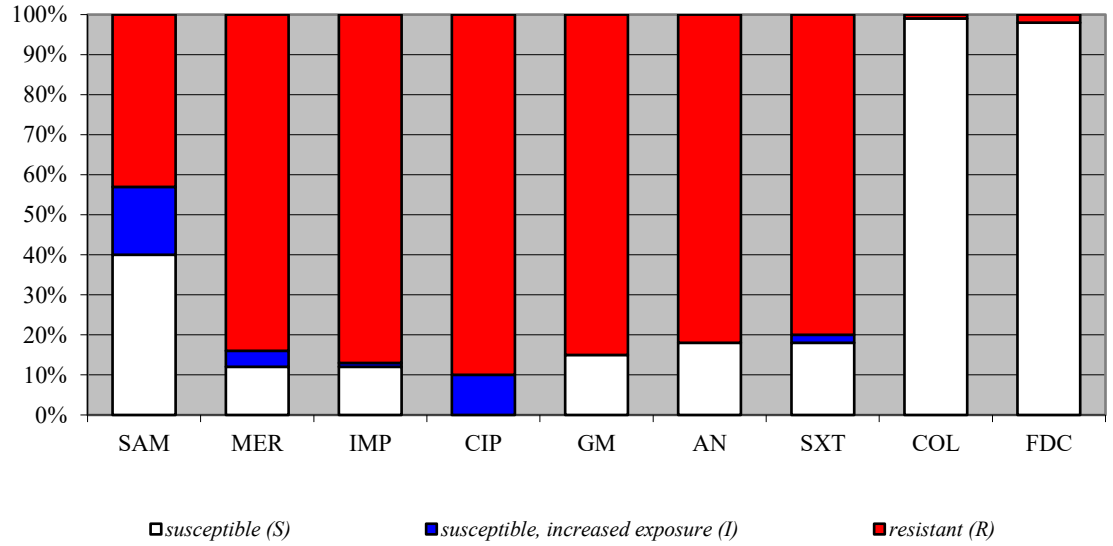
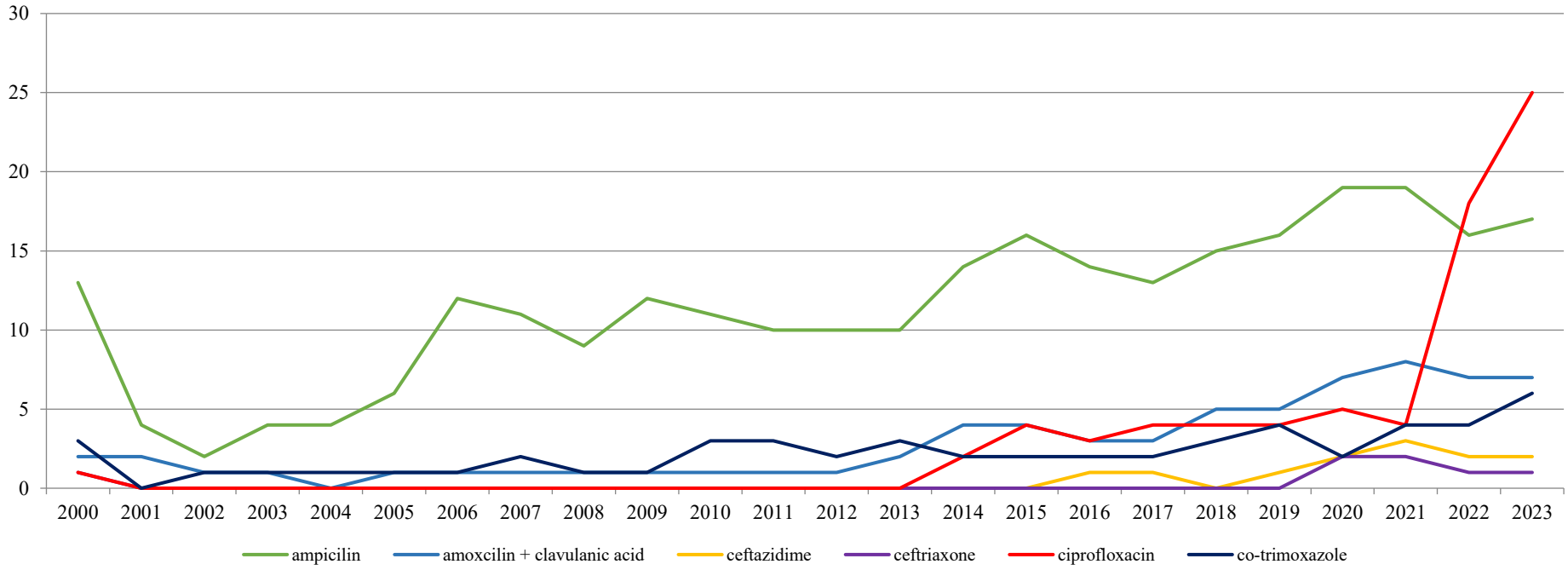


Salmonella spp.

rezistencija na antibiotike u RH / *resistance to antibiotics in Croatia*, 2000. - 2023.



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Salmonella spp.

rezistencija na antibiotike u razdoblju od 01.01. - 31.12.2023.,
zbirni prikaz izolata iz 37 centara u RH /
antibiotic resistance for the period 01.01. - 31.12.2023.,
summary results for the isolates from 37 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	1 795	16 (0)	0 (0) - 31 (0)
Amoxicillin + clav. acid	1 792	6 (0)	0 (0) - 28 (0)
Ceftazidim	1 792	2 (1)	0 (0) - 12 (0)
Ceftriaxone	1 792	1 (0)	0 (0) - 8 (4)
Ciprofloxacin	1 776	25 (0)	0 (0) - 46 (0)
Co-trimoxazole	1 793	6 (0)	0 (0) - 16 (0)

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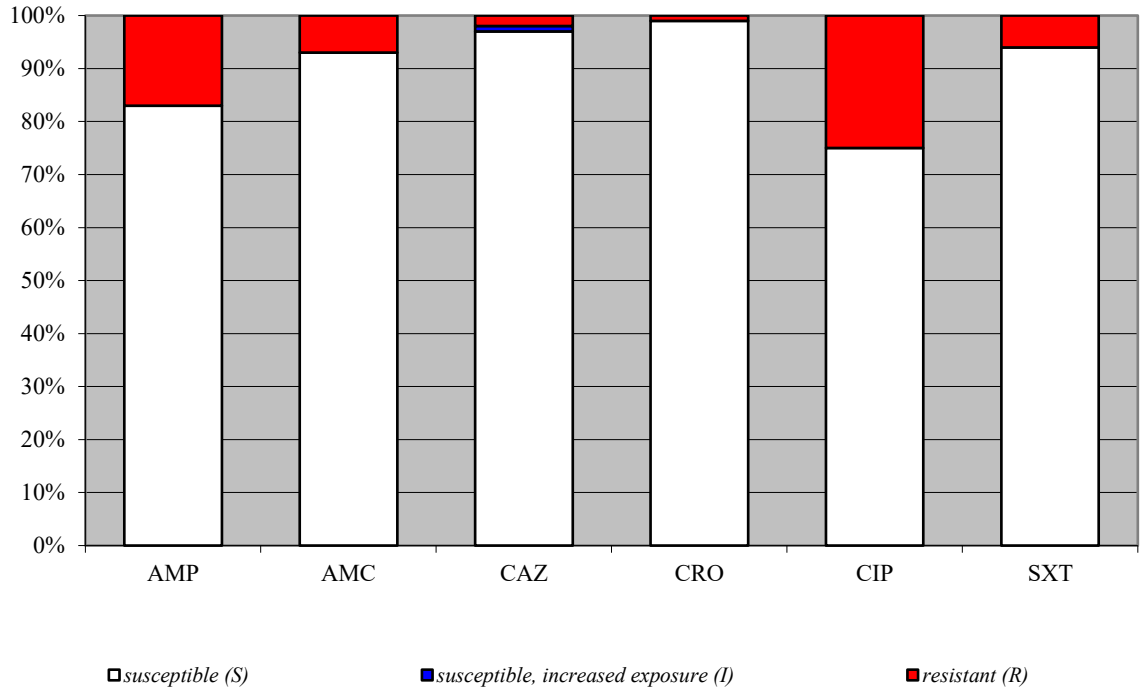
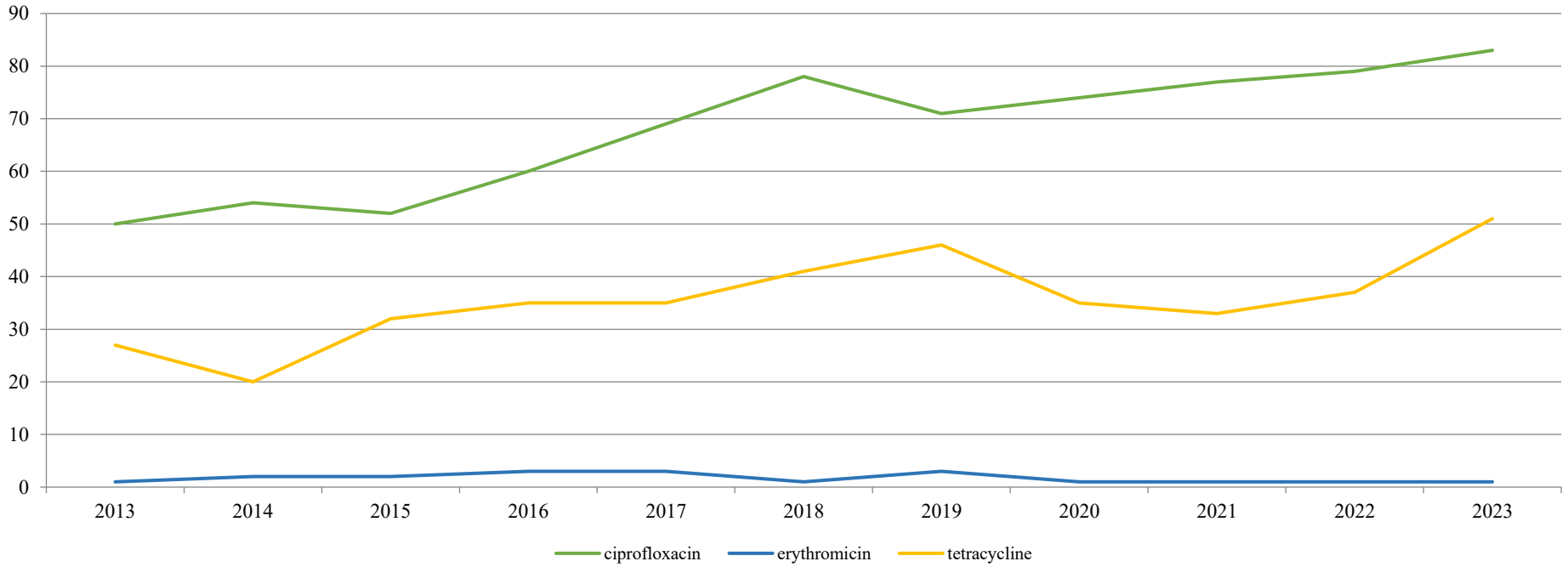


Campylobacter coli

rezistencija na antibiotike u RH / *resistance to antibiotics in Croatia*, 2013. - 2023.



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Campylobacter coli

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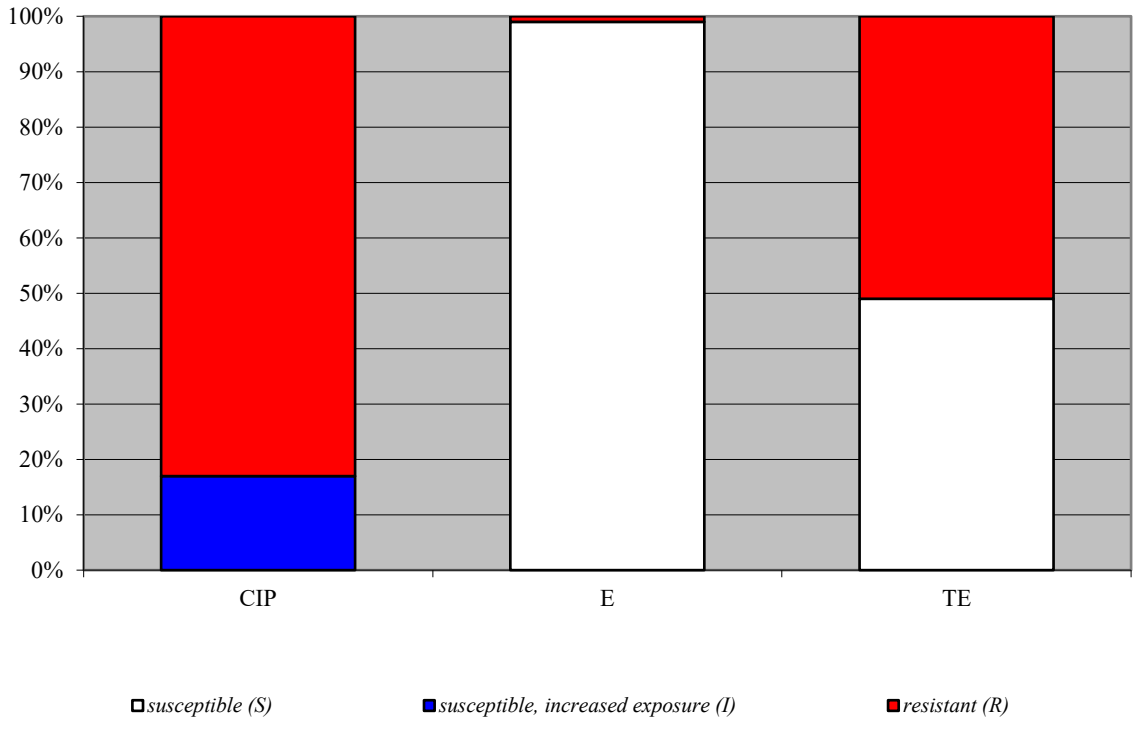
summary results for the isolates from 37 centers in Croatia

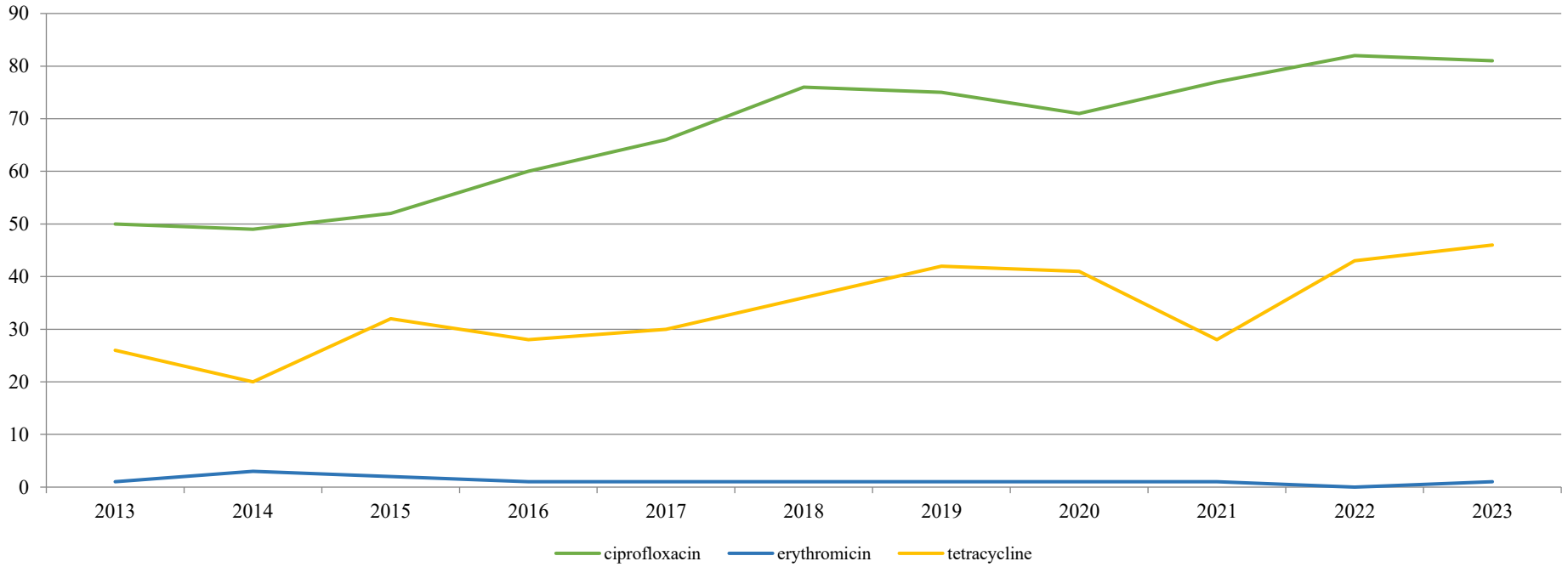
ANTIBIOTIK / ANTIBIOTIC	**Broj izolata** / No. of isolates	**% rezistentnih (R) (% osjetljivih uz povećanu izloženost (I)) izolata** / *% of resistant (R) (% of susceptible, increased exposure (I)) isolates*	**Raspon lokalnih rezultata*** / Range of local results*
Ciprofloxacin	454	83 (17)	77 (23) - 94 (6)
Erythromicin	454	1 (0)	0 (0) - 2 (0)
Tetracycline	452	51 (0)	33 (0) - 65 (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



Campylobacter jejuni

rezistencija na antibiotike u RH / *resistance to antibiotics in Croatia*, 2013. - 2023.



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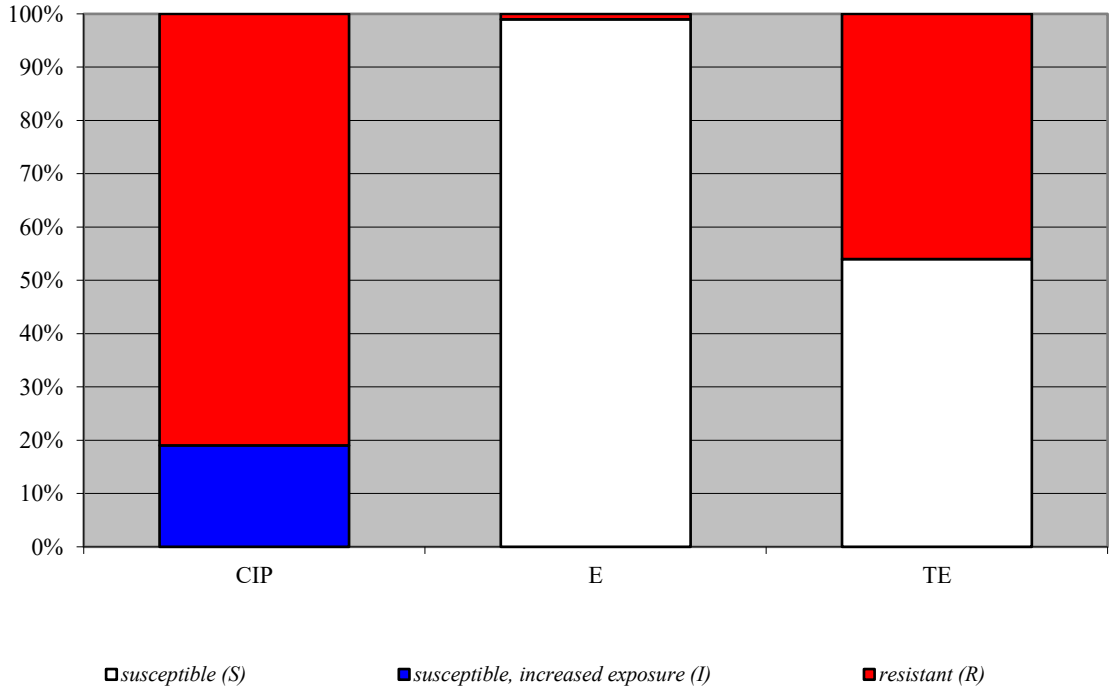
Odbor za praćenje rezistencije bakterija na antibiotike u RH
Croatian Academy of Medical Sciences, Public Health Collegium
Croatian Committee for Antibiotic Resistance Surveillance

Campylobacter jejuni

rezistencija na antibiotike u razdoblju od 1.01.- 31.12.2023.,
zbirni prikaz izolata iz 37 centara u RH /
antibiotic resistance for the period 1.01. - 31.12.2023,
summary results for the isolates from 37 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	3 136	81 (19)	46 (54) - 91 (9)
Erythromicin	3 136	1 (0)	0 (0) - 21 (0)
Tetracycline	3 126	46 (0)	18 (0) - 55 (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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Shigella spp.

rezistencija na antibiotike u RH / *antibiotic resistance in Croatia*, 01.01. – 31.12.2023.*

***Shigella* spp.**	**AMP**			**AMC**			**CAZ**				**CRO**			**CIP**			**SXT**			**AZM**		
	No	S	**R**	No	S	**R**	No	S	I	**R**	No	S	**R**	No	S	**R**	No	S	**R**	No	WT**	**Non WT****
Shigella sonnei*	15	2	**13**	13	13	**0**	11	5	2	**4**	12	3	**9**	15	4	**11**	15	0	**15**	12	12	**10**
Shigella flexneri*	15	1	**14**	15	14	**1**	15	15	0	**0**	15	15	**0**	15	9	**6**	15	9	**6**	8	8	**0**
UKUPNO / *TOTAL*	30	3	**27**	28	27	**1**	26	20	2	**4**	27	18	**9**	30	13	**17**	30	9	**21**	**20**	**10**	**10**

*zbog malog broja izolata prikazani su apsolutni brojevi, a ne postoci / *due to the low number of isolates, apsolute numbers are presented, not percentages*
** WT = divlji tip / *wild type*

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Anaerobne bakterije / *Anaerobes*

rezistencija na antibiotike u RH / *antibiotic resistance in Croatia*, 01.01. – 31.12.2023.*

Anaerobne bakterije / *Anaerobes*	**P**			**PTZ**			**MEM**			**CC**			**MTZ**			**VA**		
	No	S %	**R %**	No	S %	**R %**	No	S %	**R %**	No	S %	**R %**	No	S %	**R %**	No	S %	**R %**
Cutibacterium acnes	311	97	**3**	289	100	**0**	299	100	**0**	314	78	**22**				308	100	**0**
***Bacteroides* spp.**				864	94	**6**	868	96	**4**	873	49	**51**	856	92	**8**			
***Prevotella* spp.**	201	38	**62**	207	95	**5**	207	99	**1**	212	38	**62**	203	91	**9**			
Fusobacterium necrophorum*	13	62	**38**	12	100	**0**	11	100	**0**	13	62	**38**	13	85	**15**			
Clostridium perfringens	95	91	**9**	96	96	**4**	96	100	**0**	96	42	**58**	93	87	**13**	96	100	**0**
UKUPNO / *TOTAL*	620	76	**24**	1468	95	**5**	1481	97	**3**	1508	53	**47**	1165	91	**9**	404	100	**0**

*zbog malog broja izolata prikazani su apsolutni brojevi, a ne postoci / *due to the low number of isolates, apsolute numbers are presented, not percentage*

OSJETLJIVOST *M. TUBERCULOSIS* U HRVATSKOJ U 2023. GODINI

SENSITIVITY OF M. TUBERCULOSIS IN CROATIA, 2023

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

Mikobakterije izolirane u Hrvatskoj u 2023. godini

Za analizu podataka o bakteriološkoj dijagnostici tuberkuloze (TBC) u Hrvatskoj u 2023. godini koristio se „Upitnik o radu TBC laboratorija u 2023. godini“. U prošloj godini, radi prestanka rada pojedinih laboratorija tijekom COVID-19 pandemije te privremenog zatvaranja pojedinih laboratorija radi obnove nakon potresa, dijagnostika tuberkuloze provodila se u 12 laboratorija organiziranih na tri razine. Ukupno je pregledano 26 704 kliničkih uzoraka na TBC što je porast od 9% od broja uzoraka iz 2022. godine. Iako je preporučeni minimalni godišnji broj uzoraka za obradu na mikobakterije 2000, samo četiri laboratorija je u 2023. obradilo 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 4,3% uzoraka kultivacijom je otkriven *M. tuberculosis*, a raspon pozitivnih kultura među laboratorijima se kretao od 1,4 do 18,0%. Ukupno je izolirano 1485 sojeva mikobakterija.

Tijekom 2023. godine genotipiziran je 232 izolat *M. tuberculosis* iz cijele Hrvatske. U skladu s očekivanim, *M. tuberculosis* je najčešće izoliran iz plućnih uzoraka, a među 33 (14,3%) izvanplućnih bakteriološki dokazanih slučajeva TBC najčešća je bila limfoglandularna TBC (N=9), TBC pleure (N=9) i osteoartikularna TBC (N=2). Kod čak šest pacijenata nađena je diseminirana tuberkuloza.

Tijekom 2023. godine iz humanih kliničkih materijala nije izoliran *M. bovis*, ali su izolirana tri *M. bovis* – BCG soja. Nastavlja se trend visokog omjera izolata NTM i broja mogućih bolesnika s mikobakteriozom. 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 2023. godini od uvjetno patogenih spororastućih mikobakterija najviše je izoliran *M. xenopi* (73 izolata), *M. avium* (69 izolata) te *M. intracellulare* (34 izolata). Od brzorastućih mikobakterija najveći broj izolata odnosio se na *M. fortuitum* (41 izolat), a slijede ga *M. chelonae* sa 18 izolata i *M. mucogenicum* sa 10 izolata. *M. gordonae* kao saprofitna mikobakterija je identificiran u 14,5% izolata NTM. Najčešće se radi o kontaminaciji uzoraka, slučajnim nalazima i prolaznim kolonizacijama. U 2023. godini su otkrivene 72 osobe sa zadovoljenim mikrobiološkim kriterijima za dijagnozu mikobakterioze (dva i više izolata, ili izolat iz asp. bronha). Kod 21 bolesnika izoliran je *M. xenopi*, a slijede ga *M. avium* koji je izoliran kod 18 bolesnika te *M. intracellulare* kod osam bolesnika i *M. gordonae* kod osam bolesnika.

Nažalost, primijećen je uzlazni trend izolacije rezistentnih sojeva. Od 1137 testiranih sojeva njih 84 (7,4%) bilo je rezistentno na prvu liniju antituberkulotika, a otkriveni su kod 18 bolesnika s rezistentnom tuberkulozom, što je gotovo trostruki porast od broja iz 2022. godine. Među bolesnicima s rezistentnim oblikom tuberkuloze, njih 17 (94,4%) je imalo monorezistenciju (11 izonijazid, četiri na streptomicin i dva na pirazinamid), a jedan pacijent je imao zarazu polirezistentnim sojem (rezistencija na izonijazid i streptomicin).

Mycobacteria isolated in Croatia in 2023

In 2023, due to the shutdown of certain laboratories during the COVID-19 pandemic and the temporary closure of certain laboratories for reconstruction after the earthquake, tuberculosis diagnostics were carried out in 12 laboratories organized on three levels. To analyze data on tuberculosis (TB) bacteriological diagnostics, the "Questionnaire on the work of TB laboratories in 2023" was used. A total of 26704 clinical samples were analyzed for tuberculosis, which is 9% more than the number of samples in 2022. The number of processed samples was still under the recommended minimum of 2000 samples in a total of eight laboratories. Furthermore, all laboratories still don't use liquid media for all samples, but only for paucibacillar or extrapulmonary samples. In 4.3% of samples, cultivation detected mycobacteria and the range of positivity of cultivation in different laboratories was from 1.4 to 18.0%. A total of 1,485 mycobacterial isolates were cultivated.
During 2023, a total of 232 *M. tuberculosis* isolates were genotyped. As expected, *M. tuberculosis* was most frequently isolated from pulmonary samples. Among bacteriologically confirmed extrapulmonary TB (N=33; 14.3%), the most frequent forms were lymphoglandular TB (N=9), pleural TB (N=9) and osteoarticular TB (N=2). Disseminated tuberculosis was found in as many as six patients. During 2023, no *M. bovis* was isolated from human clinical materials, but three *M. bovis* - BCG strains were isolated. 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 2023 prevailed isolates of *M. xenopi* (N=73), *M. avium* (N=69), and *M. intracellulare* (N=34), while in the rapidly growing group the most commonly isolated species were *M. fortuitum* (N=41), *M. chelonae* (N=18) and *M. mucogenicum* (N=10). *M. gordonae*, a saprophytic mycobacterium, was identified in 14,5% of all NTM isolates. In most cases, the isolation was the result of specimen contamination, accidental finding and transient colonization.

In 2023, a total of 72 cases that fulfilled the microbiological criteria for mycobacteriosis (two or more isolates or isolate from bronh. aspirate) were documented. *M. xenopi* was isolated in 21 patients, *M. avium* in 18 patients, *M. intracellulare* in eight, and *M. gordonae* in eight patients.
Unfortunately, an upward trend in the isolation of resistant strains has been observed. Out of 1137 strains tested, 84 of them (7.4%) were resistant to the first line of antituberculosis drugs, and were detected in 18 patients with resistant tuberculosis, which is almost a threefold increase from the number in 2022. Among patients with resistant TB, 17 patients (94.4%) were infected with monoresistant strains (11 to isoniazid, four to streptomycin and two to pyrazinamide), while one patient had infection with a poliresistant strain (isoniazid and streptomycin).

Tablica / *Table* **1.**
Mikobakterije izolirane u Hrvatskoj, 2013. – 2023. /
Mycobacteria strains isolated in Croatia, 2013-2023

Godina	Ukupno mikobakterija	*M. tuberculosis*		*M. bovis*		Netuberkulozne mikobakterije	
		Broj	%	*M. bovis*	BCG soj	Broj	%
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	-	2	350	21,9
2018.	1689	1387	82,1	-	2	302	17,9
2019.	1751	1281	73,2	4	2	464	26,5
2020.	1081	855	79,1	-	9	217	20
2021.	1009	799	79,2	-	1	209	20,7
2022.	1268	963	75,9	-	1	304	23,9
2023.	1485	1137	76,6	-	3	345	23,2

Tablica / *Table* **2.**
Netuberkulozne mikobakterije (NTM) izolirane u Hrvatskoj u 2023. /
Nontuberculous mycobacteria (NTM) isolated in Croatia in 2023

	Vrsta	Broj	%
Uvjetno patogene mikobakterije	*M. avium*	69	20,0
	M. xenopi	73	21,2
	M. intracellulare	34	9,9
	M. kansasii	18	5,2
	M. celatum	1	0,3
	M. intermedium	2	0,6
	M. fortuitum	41	11,9
	M. chelonae	18	5,2
	M. abscessus	5	1,4
	M. mucogenicum	10	2,9
	M. neoaurum	8	2,3
Saprofitne mikobakterije	*M. gordonae*	50	14,5
	Mycobacterium spp.	16	4,6
Ukupno		**304**	**100**

Tablica / *Table* **3.**
Bolesnici s rezistentnom tuberkulozom u Hrvatskoj, 2023. /
Resistant tuberculosis in Croatia, 2023

		BROJ - *No.*	**%**	
UKUPNO BOLESNIKA - *Patients total*		**18**	**100**	
MONOREZISTENCIJA - *Monoresistance*				
	H	11	61,1	
	S	4	22,2	
	Z	2	11,1	
POLIREZISTENCIJA - *Polyresistance*				
	HS	1	5,6	
Legenda - Key: R - rifampicin S – streptomicin H – izoniazid Z - pirazinamid E - etambutol				

OSJETLJIVOST GONOKOKA U HRVATSKOJ U 2023

Blaženka Hunjak
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Antimikrobna rezistencija u gonokoka izoliranih Hrvatskoj u 2023. godini

Godine 2023. bila je nešto uspješnija u odnosu na 2022.godinu u pogledu praćenje antimikrobne rezistencije (AMR) u gonokoka i sakupljanja izolata *Neisseria gonorrhoeae* (NG) na razini Republike Hrvatske (RH). Tijekom 2023. god. sakupljeni su podaci za ukupno 29 izolata NG.

Uzorci su dobiveni iz slijedećih ustanova: NZJZ A.Štampar, Zagreb, KZIB "Dr.Fran Mihaljević", Zagreb, NZZJZ Osječko-baranjske županije, ZZJZ Karlovačke županije, ZZJZ Virovitičko-podravske županije te Hrvatski zavod za javno zdravstvo (HZJZ) Zagreb.

Cilj nam ostaje, barem dosegnuti, ili ako je moguće premašiti, rezultate iz 2019. god., kada smo sakupili više od 70 NG izolata iz cijele RH.

Sa završetkom pandemije korona virusom, intenziviralo se praćenje AMR NG, te se nastavlja Projekt na razini Europske Unije (EU), EURO – Gasp, koji prati rezistenciju i učestalost NG, zajedno s epidemiološkim podacima. Nadalje, izuzetno važnim se postavlja i novi cilj; ne samo praćenje AMR i učestalosti NG, te epidemiološka povezanost izolata s različitih geografskih područja, nego se inzistira i na molekularnoj metodologiji praćenja AMR i analize cijelog genoma metodom sekvenciranja cijelog genoma *(*engl.*Whole Genome Seqencing; WGS*), u svrhu boljeg praćenja i bržeg ustanovljavanja AMR. Do ove godine, izolati su slani na WGS u inozemstvo, a ove ćemo godine (2024.god.) prvi puta pokušati izvesti WGS u RH i to u HZJZ, koji je pojačao svoja znanja u području molekularne dijagnostike, ne samo u tehničkom smislu (oprema), nego i obrazovanosti medicinsko laboratorijskog osoblja. Stoga su na novom sastaku o Projektu EURO - Gasp, pod naslovom: EURO - Gasp, koordinacijski sastanak, u virtualnom okruženju, koji je održan 17. studenoga 2023.god., postavljeni ciljevi za nadolazeće razdoblje (2023-2027):

- nadzor nad AMR NG

- godišnje praćenje testiranja osjetljivosti na antimikrobne lijekove za 2023.god., svih izolata sakupljenih kroz EURO – Gasp

- osiguravanje provjere rada kvalitete laboratorija kroz Vanjsku kontrolu, praćenu od strane ECDC-a,

- molekularna tipizacija NG i implementacija u strategiju ECDC-a za molekurnu tipizaciju

- sekvenciranje cijelog genoma NG u svrhu boljeg praćenja i bržeg ustanovljavanja NG AMR u 2023. god., kod što više izolata

- vanjska kontrola kvalitete i uporaba bioinformatičkog triasa za cijeli genom

- uspostava mreže sekvenciranja cijelog genoma NG, te uspostava elektronskog sustava mreže laboratorija u svrhu povratnih informacija u vezi poboljšanja kvalitete i izvedbe metode

- osiguranje kapaciteta za edukaciju osoblja i povećanje tehničkih kapaciteta koji će pojačati aktivnosti za sve spolno prenosive infekcije (SPI), s naglaskom na molekularnu tipizaciju

Nadalje, o važnosti praćenja razvoja rezistencije u NG kao modela razvoja AMR, dobiveni su novi zadaci za HZJZ od Europskog centra za kontrolu i prevenciju bolesti (ECDC). Sve to, u svrhu poboljšanja objedinjavanja rezultata praćenja NG, propisivanja antibiotika za gonoreju u ambulantama Opće medicine, te pokušaja dobivanja strukturiranih podataka iz cijele RH elektronskim putem, kako bi se lakše, brže i učinkovitije mogli usporediti svi podaci na razini EU. To je zadatak HZJZ-a za predstojeće razdoblje, a već je započeo tijekom 2024., što govori o velikom interesu na nivou EU, ali i šire, o važnosti praćenja NG i AMR u NG.

Bakterija NG je vrlo dobar model praćenja napredovanja rezistencije i razvitka višestruko otpornih bakterija, te nam razvoj rezistencije u NG može poslužiti kao model razvoja AMR za druge bakterije. Prema epidemiološkim izvještajima, gonoreja je i dalje druga najčešća SPI bakterijskog podrijetla današnjice.

Praćenje učestalosti infekcija uzrokovanih bakterijom NG, važan je i javno zdravstveni problem, kao i točno procjenjivanje podataka o rezistenciji gonokoka na antimikrobne lijekove, zbog moguće pojave višestruko otpornih bakterija. Zabrinjava činjenica da se gonokok u posljednje vrijeme posebice širi u populaciji mladih muškaraca homoseksualca (engl. *Men who have sex with men*, MCM). Nadalje, činjenice su da, gonokokna infekcija utječe nepovoljno na tijek trudnoće i novorođenčad, ne izaziva zaštitni imunitet, te istovremeno može pospješiti i ubrzati širenje infekcije uzrokovane virusom humane imunodeficijencije.

U HZJZ i dalje dolaze viabilni izolati NG, ali u manjem broju, te je retestiranje vrlo zahtjevno ili čak nemoguće, obzirom na zahtjevni transport i osjetljivost izolata. Većinom dolaze samo tablični prikazi.

Broj dobivenih izolata za 2015. god., bio je 15; 2016. – 35; 2017. – 36; 2018. – 46; 2019. – 73; 2021. – 26; 2022. – 17 izolata; 2023. – 29 izolata. U Tablici 1. navedene su vrijednosti gradijenata koje pokazuje rezultate testiranja metodom E-testa i disk difuzije.

Rezultati osjetljivosti za 2023. su kako slijedi (Tablica 2):

- na penicilin je bilo 2 (6,9%) rezistentnih izolata, od ukupno 29,
- na ceftriakson su svi izolati (100%), od ukupno 29 testiranih, bili osjetljivi,
- na cefixim su svi testirani izolati – 27 (100%), bili osjetljivi,
- na ciprofloksacin je bilo 18 (64,29%) rezistentnih izolata, od ukupno 28 testiranih,
- na tetraciklin je bilo 3 (10,34%) rezistentnih izolata, od ukupno 29 testiranih,

Možemo naglasiti, kao i prošlih godina, da za gentamicin nema gradijenta za testiranje, ali se preporuča testiranje, kako bi se ispitala djelotvornost gentamicina za slučaj ograničenog izbora terapije. Na žalost, iako se testiranje na tetraciklin preporuča zbog istih razloga kao i za gentamicin, testiranje na tetraciklin pokazalo je ove godine prvi put, rezistenciju u čak 10,34% izolata NG u RH u 2023., prema nama dostupnim podacima. Na spektinomicin, koji nije na našem tržištu, rezistencija nije ustanovljena niti kod jednog testiranog izolata u RH. Naravno, svjesni smo činjenice, da se radi o vrlo malom broju izolata. Između ostalog, brine nas i nesrazmjer između prijavljenih podataka o učestalosti NG prema podacima epidemiologa u HZJZ-u, i mikrobioloških podataka.

Nadalje, zabrinjava brzi razvoj i širenje otpornosti u NG, na nivou EU, na donedavno djelotvorne kinolone, cefalosporine treće generacije, ali i makrolide, što ograničava mogućnost liječenja. Na sreću, prema nama dostupnim podacima za 2023. god. u RH, na cefalosporine treće generacije, nema razvoja rezistencije. Jedan od specifičnih ciljeva nadzora SPI u EU je otkrivanje i praćenje učestalosti gonokoka i osjetljivosti na antibiotike, povezano s epidemiološkim obilježjima, kako bi se pridonijelo učinkovitim kliničkim smjernicama dijagnostike gonoreje i osigurala odgovarajuća terapija.

U zaključku, može se ponovo naglasiti da još uvijek ne postoji gradijent za određivanje vrijednosti testova osjetljivosti na antibiotike za gentamicin, ali se preporuča testiranje za ispitivanje učinkovitosti gentamicina u slučaju ograničenog izbora terapije, kao i testiranje na tetraciklin. Još uvijek

provjeravamo osjetljivost na spektinomicin u RH, ali niti kod ijednog testiranog izolata, nije utvrđena rezistencija na spektinomicin.

Viabilni NG izolati ipak stižu u HZJZ - ali u manjem broju (uvođenje sve više molekularnih testova za identifikaciju: npr.*Multiplex STD PCR* – mogući problem?). Retestiranje NG je vrlo zahtjevno ili čak nemoguće, s obzirom na zahtjevan transport i osjetljivost izolata. Većina podataka o NG dolazi samo s upisanim rezultatima na obrascima.

Obaveza nam ostaje kontinuirano otkrivati rezistenciju na ceftriakson, jer ukoliko praćenje AMR u NG pokaže porast rezistencije na cefalosporine treće generacije, posebno na ceftriakson, ovakav tip rezistencije zabrinjava, jer može ugroziti trenutno vrlo učinkovit režim dvojne terapije (ceftriakson plus azitromicin) i monoterapiju visokim dozama ceftriaksona koje su usvojile neke europske zemlje.

Iako se razina rezistencije na cefiksim značajno smanjila u EU, AMR je potrebno pomno pratiti, posebno zato što se gonokokni sojevi otporni i na cefiksim i na ceftriakson i dalje otkrivaju u i izvan EU/EEA.

Nastavak aktivnosti praćenja AMR, zajedno s razvojem alternativnih režima za liječenje gonoreje, ključni su, kako bi se osiguralo da gonoreja ostane infekcija koja se može jednostavno, učinkovito, brzo i uspješno izliječiti.

Antimicrobial resistance in gonococci isolated in Croatia in 2023

In 2023, we were more successful than in 2022 in terms of monitoring antimicrobial resistance (AMR) in gonococci and collecting *Neisseria gonorrhoeae* (NG) isolates at the level of the Republic of Croatia (RH). During 2023, data was collected for a total of 29 isolates.

Data on NG isolates were obtained from the following institutions: NZJZ A. Štampar, Zagreb, KZIB "Dr. Fran Mihaljević", Zagreb, NZJZ Osijek-Baranja County, ZZJZ Virovitica - Podravska County and Croatian Institute of Public Health (CIPH), Zagreb.

Our goal is, at least reach, or if possible, exceed the results from 2019, when we collected more than 70 NG isolates from all over the RH.

With the end of the corona virus pandemic, the monitoring of AMR NG was intensified, and the project at the level of the European Union (EU), which monitors the resistance and frequency of NG, continues, also epidemiological data including. Furthermore, a new goal is set as extremely important; on the molecular methodology of monitoring AMR resistance and analysis of the entire NG genome using the Whole Genome Sequencing (WGS) method, for the purpose of better monitoring and faster establishment of AMR in NG. Until this year, the isolates were sent for WGS abroad, and this year (2024) we will try to perform WGS in the Republic of Croatia for the first time, in CIPH, which has strengthened its knowledge in the field of molecular diagnostics, not only in the technical equipment, but also the education of medical laboratory staff. Therefore, at the new meeting on the *EURO - Gasp Project*, entitled: *EURO - Gasp*, coordination meeting, in a virtual environment, which was held on November 17, 2023, the goals for the coming period (2023-2027) were set:

- Surveillance of NG antimicrobial susceptibility.
- Annual AST testing of 2023 isolates.
- Provision of an external quality assessment (EQA) scheme for susceptibility testing of NG

gonorrhoeae.

- Molecular typing of NG and implementation of the ECDC strategy for

molecular typing for surveillance of NG.

- WGS 2023 survey.
- External quality assessment (EQA) and bioinformatic ring trial for whole genome

sequencing of N. gonorrhoeae.

- WGS “wetlab” EQA – feedback on performance and quality.
- Provision of training and capacity building activities in STI laboratory diagnostics, NG

gonorrhoeae susceptibility testing and molecular typing including whole genome sequencing.

Furthermore, on the importance of monitoring the development of resistance in NG as a model for the development of AMR, new tasks for CIPH were obtained by European Centre for Prevention and Disease Control (ECDC). All this, for the purpose of improving the harmonisation of the results of monitoring NG, prescribing antibiotics for gonorrhoea in General Medicine Offices in Republic of Croatia (RC), and trying to obtain structured data, from the entire RC, electronically, so that all data at the EU level could be compared more easily, quickly and efficiently. This is the task of the CIPH for the upcoming period. It has already started during 2024, which proves the great interest at the EU level, but also more broadly, of the importance of monitoring NG and AMR in NG.

The NG bacteria is a very good model for monitoring the progress of AMR and the development of multiple resistant bacteria, and the development of resistance in NG can serve as a model for the

development of AMR for other bacteria. According to epidemiological reports, gonorrhoea is still the second most common STI of bacterial origin today.

Monitoring the frequency of infections caused by NG bacteria is also an important public health problem, as is the accurate assessment of data on the resistance of gonococci to antimicrobial drugs, due to the possible emergence of multi-resistant bacteria. The fact that gonococcal infection has recently spread especially among the population of young homosexual men (*Men who have sex with men, MCM*) is worrying. Furthermore, the facts are that gonococcal infection adversely affects the course of pregnancy and newborns, does not induce protective immunity, and at the same time can promote and accelerate the spread of infection caused by the human immunodeficiency virus.

Viable NG isolates still arrive at the CIPH, but in lower numbers, and retesting is very demanding or even impossible, given the demanding transport and sensitivity of the isolates. Most of them only come in the forms.

The number of isolates obtained in 2015 was 15; in 2016 – 35; in 2017 – 36; in 2018 – 46; in 2019 – 73; in 2021 – 26; in 2022 – 17 isolates; in 2023 – 29 isolates. Table 1 lists the values of the gradients that show the results of the E-test and disk diffusion tests.

The sensitivity results for 2023 are as follows (Table 2):

- there were 2 (6.9%) isolates resistant to penicillin, out of a total of 29,
- all isolates (100%), out of a total of 29 tested, were sensitive to ceftriaxone,
- all isolates were tested on cefixime - 27(100%), were sensitive,
- there were 18 (64.29%) resistant isolates to ciprofloxacin, out of a total of 28 tested,
- there were 3 (10.34%) resistant isolates to tetracycline, out of a total of 29 tested.

It can be stressed, as in previous years, that there is no gradient for antibiotic susceptibility testing to test for gentamicin, but testing is recommended to test the effectiveness of gentamicin in the event of a limited choice of therapy. Unfortunately, although tetracycline testing is recommended for the same reasons as for gentamicin, tetracycline testing, however, it showed resistance in as many as 10.34% of NG isolates in the Republic of Croatia in 2023, according to the data available to us. Resistance to spectinomycin, which is not on our market, was not found in any tested isolate in the Republic of Croatia. Of course, we are aware of the fact that this is a very small number of isolates. Among other things, we are concerned about the disparity between reported epidemiological data on the frequency of NG and microbiological data.

Furthermore, the rapid development and spread of resistance in NG, at the EU level, to quinolones, third - generation cephalosporins, and macrolides, which were effective until recently, is of greatest concern, which limits the possibility of treatment. Fortunately, according to the data available to us for 2023. in the Republic of Croatia, there is no development of resistance to cephalosporins of the third generation. One of the specific objectives of STI surveillance in the EU is to detect and monitor gonococcal frequency and antibiotic susceptibility, linked to epidemiological features, in order to contribute to effective clinical guidelines for the diagnosis of gonorrhoea and ensure appropriate therapy.

As a conclusion, it can be stressed that there is still no gradient for antimicrobial testing for gentamicin, but testing is recommended to examine the efficacy of gentamicin in the possible situation of a limited choice of therapy, as well as testing for tetracycline. We are still checking the sensitivity to spectinomycin in the Republic of Croatia, but spectinomycin resistance has not been established in any of the tested isolates.

Viable NG isolates still arrive at the CIPH - but in smaller numbers (*Multiplex STD PCR* – possible problem?). Retesting is very demanding or even impossible, given the demanding transport and sensitivity of the isolates. Most of them we only become, with written results in forms.

Combined with the continued detection of ceftriaxone resistance, AMR in NG, this remains a concern and may threaten the currently highly - effective dual-therapy regimen (ceftriaxone plus azithromycin) and high-dose ceftriaxone monotherapy adopted by some European countries.

Even though the level of resistance to cefixime has significantly decreased in EU, this needs to be monitored closely, particularly because gonococcal strains with resistance to both cefixime and ceftriaxone continue to be detected in and outside the EU/EEA.

The continuation of quality- assured antimicrobial susceptibility surveillance activities, along with the development of alternative gonococcal regimens, is essential to ensure gonorrhoea remains a treatable infection.

Tablica 1. Osjetljivost sojeva N. gonorrhoeae na antibiotike u RH, sa vrijednostima ispitivanja MIC-a metodom E-test
Izuzeci: osjetljivost ispitivana i metodom disk – difuzije

Table 1. Susceptibility testing of N. gonorrhoeae strains to antibiotics in Croatia, with MIC gradient band (E-test)
Exceptions: sensitivity testing by disk - diffusion methods

Ustanova	Izolat	Penicilin			Ceftriaxon			Cefixim			Ciprofloxacin			Azithromycin			Tetracyclin			Spectinomycin		
		S	I	R	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R
ZG KIB	1	0,064			0,004			35mm**					3	0,33			0,25					
	2		0,125		0,004			46mm**					2	0,125			0,5					
	3	0,064			0,002			48mm**					1	0,064			0,25					
	4	0,032			0,002			45mm**					0,75	0,125			0,5					
	5		0,125		0,004			50mm**			0,004			0,19					1			
	6	0,047			<0,002			46mm**				0,064				>256	0,19					
	7	0,064			0,004			44mm**					0,75	0,5			0,19					
	8	0,032			<0,002			50mm**					0,75	0,094			0,064					
	9		0,19		0,004			35mm**					1	0,094			0,5					
	10	0,012			<0,002			45mm**					0,5	0,032			0,5					
	11	0,012			<0,002			45mm**					2	0,064			0,125					
	12	**0,032**			**<0,002**			**45mm****					**1**	**0,125**			**0,25**					
ZG HZJZ	1	0,012			0,003			0,016			0,002					>256	0,094			0,5		
	2		0,19		0,012			0,047					6	0,023				1		0,75		
ZG NZZJZ	1		0,125		0,004			<0,016				0,032		1			0,38					
	2		0,125		0,008			0,016			<0,002			0,19			0,9					
	3		0,125		<0,002								2				0,125					
	4	0,064			<0,002			<0,016			0,003			0,5			0,5					
	5	0,046			0,002			<0,016			<0,002			0,25			0,25					
	6		0,25		0,003			<0,016					3			1,5		0,75				
	7		0,19		0,008			<0,016					8			1,5		0,75				
	8		0,125		0,003			<0,016					1	1			0,5					
	9			16	0,006			0,023					0,75	0,25					24			
	10		0,125		<0,002			<0,016			<0,002			0,094			0,5					
	11	0,064			0,002			0,016			<0,002			0,75			0,5					
	12		0,38		0,008			<0,016					4	0,38				0,75				
OS NZZJZ	1		0,094		0,008								0,38	0,094					6			
KA ZZJZ	1			>32	0,012			0,023					2	0,047					3	6		
VT ZZJZ	1	0,094			0,094			0,023			0,008			0,023			0,38			0,75		
UKUPNO (%)	**29***	14 (48,28)	13 (48,82)	**2 (6,9)**	29 (100)	/	/	27 (100)	/	/	8 (27,6)	2 (6,9)	**19 (65,5)**	24 (85,7)	/	**4 (14,3)**	21 (72,4)	4 (13,8)	**4 (13,8)**	4 (100)	/	/

* iako je u praćenje uključeno 29 izolata, nije bilo moguće provesti testiranje svih izolata na sve antibiotike zbog tehničkih razloga.

**ispitivanje je provedeno disk difuzijom

Tablica 2. Osjetljivost sojeva *N. gonorrhoeae* na antibiotike u Hrvatskoj, 2023.
Table 2. Antimicrobial susceptibility of N. gonorrhoeae strains to antibiotics in Croatia, 2023.

Ustanova	Penicilin MIK* (mg/L)				Ceftriakson MIK* (mg/L)				Cefixim MIK* (mg/L)			
	UK***	S (%)	I (%)	R (%)	UK***	S (%)	I (%)	R (%)	UK***	S (%)	I (%)	R (%)
HZJZ Zagreb	**2**	1 (50)	1 (50)	**0**	**2**	2 (100)	0	**0**	**2**	2 (100)	0	**0**
NZJZ A.Štampar	**12**	3 (25)	8 (66,67)	**1 (8,33)**	**12**	12 (100)	0	**0**	**11**	11 (100)	0	**0**
KZIB F.M. Zagreb	**12**	9 (75)	3 (25)	0	**12**	12 (100)	0	**0**	**12**	12 (100)	0	**0**
NZZJZ Osječko-baranjske županije	**1**	0	1 (100)	**0**	**1**	0	1 (100)	**0**	**/	**/	**/	**/
ZZJZ Karlovačke županije	**1**	0	0	**1 (100)**	**1**	1 (100)	0	**0**	**1**	1 (100)	0	**0**
ZZJZ Virovitičko-podravske županije	**1**	1 (100)	0	**0**	**1**	1 (100)	0	**0**	**1**	1 (100)	0	**0**
UKUPNO	**29**	14 (48,28)	13 (44,88)	**2 (6,9)**	**29**	28 (96,55)	1 (3,45)	**0**	**27**	27 (100)	0	0

Ustanova	Ciprofloxacin MIK* (mg/L)				Tetracycline MIK* (mg/L)				Spektinomycin MIK* (mg/L)			
	UK***	S (%)	I (%)	R (%)	UK***	S (%)	I (%)	R (%)	UK***	S (%)	I (%)	R (%)
HZJZ Zagreb	**2**	1 (50)	0	1 (50)	**2**	1 (50)	1 (50)	**0**	**2**	2 (100)	0	**0**
NZJZ A.Štampar	**12**	5 (41,67)	1 (8,33)	**6 (50)**	**12**	8 (66,67)	3 (25)	**1 (8,33)**	**/	**/	**/	**/
KZIB F.M. Zagreb	**12**	1 (50)	1 (50)	**10 (83,33)**	**12**	11 (91,67)	1 (8,33)	**0**	**/	**/	**/	**/
NZZJZ Osječko-baranjske županije	**/	**/	**/	**/	**1**	0	0	**1 (100)**	**/	**/	**/	**/
ZZJZ Karlovačke županije	**1**	0	0	**1 (100)**	**1**	0	0	**1 (100)**	**1**	1 (100)	0	**0**
ZZJZ Virovitičko-podravske županije	**1**	1 (100)	0	**0**	**1**	1 (100)	0	**0**	**1**	1 (100)	0	**0**
UKUPNO	**28**	8 (28,57)	2 (7,14)	18 (64,29)	**29**	21 (72,41)	5 (17,24)	**3 (10,34)**	**4**	4 (100)	0	**0**

*MIK = Minimalna inhibiotrna koncentracija antibiotika određena metodom eksponencijalnog gradijenta (E-test)

**/ = Zbog tehničkih razloga nije bilo moguće provesti testiranje osjetljivost izolata na dotični antibiotik

***UK = ukupan broj sojeva ispitane osjetljivosti na određeni antibiotik

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, a s ciljem da bi se osigurala usporedivost i pouzdanost rezultata iz različitih zemalja, odlučeno je da se u praćenju na europskoj razini uzmu u obzir samo invazivni izolati (iz hemokultura i likvora). S obzirom da je interpretacija nalaza ovih bakterija u hemokulturi i likvoru u svim laboratorijima jednaka, njihovo kliničko značenje je neupitno.

Hrvatska se od samog početka aktivno uključila u EARSS projekt, s obzirom na već postojeću mrežu mikrobioloških laboratorija u okviru Odbora za praćenje rezistencije na antibiotike. Nakon što je postala članicom Europske unije, hrvatski su podaci uključeni u EARS-Net program Europskog centra za prevenciju i kontrolu bolesti (engl." European Center for Disease Prevention and Control", ECDC).

Unatoč nekim izazovima, kao što je mali broj invazivnih izolata u nekim centrima što otežava analizu na razini pojedinih centara, te činjenica da se prikupljanjem podataka samo iz prvih izolata novi mehanizmi rezistencije ne moraju javiti u hemokulturi ili likvoru, sudjelovanje u europskoj mreži omogućuje Hrvatskoj usporedbu s drugim zemljama te raspolaganje s vrijednim 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

Podaci se o izolatima šalju i prikupljaju u elektronskom obliku u Referentnom centru za praćenje rezistencije bakterija na antibiotike, u Klinici za infektivne bolesti „Dr. Fran Mihaljević", te se statistički obrađuju. Do reorganizacije u prikupljanju podataka došlo je tijekom 2020.g., kada se prema dogovoru službeno prelazi na elektronsko slanje podataka. Kako je primijećeno da se učestalo pojavljuje problem insuficijentnih podataka o vrsti odjela, od 2020.g. odlučeno je prikazivati podatke samo za jedinice intezivne njege (ICU) što je rezultiralo promjenom izgleda nekadašnjih Tablica 3. i 4. u kojima su prikazani demografski podaci za pacijente i porijeklo uzoraka.

U okviru EARS-Net programa, Referentni centar za praćenje rezistencije bakterija na antibiotike nastavlja primati i prikupljati sve invazivne izolate vrsta *S. pneumoniae, S. aureus, E. faecalis, E. faecium, E. coli, K. pneumoniae, P. aeruginosa* i *Acinetobacter* spp., sa svrhom retestiranja izolata s rijetkim fenotipom i eventualne daljnje obrade. Tijekom 2023.g. prikupljeno je 136 izolata *S. pneumoniae,* 1431 izolat *E. coli*, 643 izolata *K. pneumoniae*, 862 izolata *S. aureus,* 420 izolata enterokoka (258 *E. faecalis* i 162 *E. faecium* izolata), 404 izolata *P. aeruginosa*, te 278 izolata *Acinetobacter* spp. (Tablica 1).

Na temelju podataka iz 2023.g., evidentno je da broj laboratorija koji prijavljuju podatke o izolatima unutar nacionalne mreže nastavlja rasti. Od 39 mikrobioloških laboratorija u okviru Odbora za praćenje rezistencije na antibiotike, 26 je prijavilo svoje podatke o invazivnim izolatima za 2023.g. Broj prijavljenih izolata u 2023.g. povećan je gotovo za trećinu u odnosu na prijašnje godine (4174 izolata u 2023.g, 3188 izolata u 2022.g.).
U Tablici 1. prikazani su brojevi laboratorija i broj prikupljenih invazivnih izolata pojedinih vrsta.

Analizom ukupnog broja prijavljenih izolata u 2023.g., uočavamo porast broja izolata svih praćenih vrsta, osim tipično bolničkog patogena *Acinetobacter* spp., kod kojeg broj prijavljenih izolata i dalje opada, ali stope rezistencije na karbapeneme ostaju i dalje izuzetno visoke, 97%. Najznačajniji porast zabilježen je kod izolata *S. aureus*, *K. pneumoniae* i *P. aeruginosa*, gdje je broj prijavljenih izolata najveći u posljednjih deset godina.

Broj prijavljenih izolata *S. pneumoniae* se vratio na razine zabilježene prije pandemije COVID-19. Broj izolata neosjetljivih na penicilin nastavlja opadati, pri čemu je u 2023.g. zabilježena stopa od 13%. Nastavljamo pratiti trend smanjenja stopa rezistencije na makrolide, pri čemu je 2023. g. zabilježena najniža stopa rezistencije u posljednjih deset godina, koja iznosi 16%.

U 2023.g. osim primijećenog porasta broja prijavljenih izolata *S. aureus*, nema znatnih promjena u stopama MRSA izolata (30% MRSA u 2023.g.; 31% u 2022.g).

Iako smo posljednjih godina svjedočili rastu glikopeptidne rezistencije kod izolata *E. faecium* s vrlo visokim stopama rezistencije, u 2023. g. zabilježen je pad na 24% takvih izolata, što predstavlja značajan pad u odnosu na 37% u 2022. g. i 39% u 2021. g. Istovremeno, stope rezistencije na glikopeptide kod izolata *E. faecalis* ostale su stabilne i niske, ispod 1%. Stope visoke rezistencije na aminoglikozide su kod izolata *E. faecalis* pokazale su značajan pad u 2023. g. (28% u 2023.g., 37% u 2022.g.). Nasuprot tome, kod *E. faecium* zabilježen je porast stopa rezistencije na ovu klasu antibiotika, sa 30% u 2022. g. na 43% u 2023. g.

Uz povećanje ukupnog broja prijavljenih invazivnih izolata *K. pneumoniae*, nastavlja se trend rasta broja izolata otpornih na karbapeneme (imipenem i/ili meropenem), pri čemu je stopa rezistencije u 2023. g. dostigla 27%. Dodatnih 7% izolata *K. pneumoniae* osjetljivo je na karbapeneme uz povećanu dozu primijenjenog antibiotika. Sveukupno 34% invazivnih izolata *K. pneumoniae* predstavlja i dalje velik izazov u liječenju i odabiru otpimalne antibiotske terapije. Kod ostalih grupa praćenih antibiotika nisu uočena značajnija odstupanja.

Kod invazivnih izolata *P. aeruginosa* nisu zabilježena značajna odstupanja od dosadašnjih podataka. Uočene su nešto niže stope rezistencije u usporedbi s prošlom godinom u svim praćenim grupama antibiotika, osim u skupini kinolona, gdje se već nekoliko godina bilježi porast rezistencije, te u 2023.g. bilježimo 33% invazivnih izolata *P.aeruginosa* rezistentnih na kinolone.

Kod invazivnih izolata *E. coli* prati se trend porasta stopa rezistencije na treću generaciju cefalosporina, koja je dostigla 20% u 2023. godini, kao i na aminoglikozide, sa zabilježenom stopom rezistencije od 18% u istoj godini. Podaci ukazuju na to da je rezistencija na treću generaciju cefalosporina i dalje pretežno uzrokovana proizvodnjom proizvodnjom beta-laktamaza proširenog spektra (engl. „extended spectrum beta-lactamases“, ESBL). Stopa rezistencije na kinolone iznosi 30%.

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

The Antimicrobial Resistance Surveillance System (EARSS) project was initiated in 1999. Initially, six bacterial species were selected as monitoring priorities: *S. aureus, E. faecalis, E. faecium, S. pneumoniae, and E. coli*. In 2005, monitoring of resistance in *K. pneumoniae* and *P. aeruginosa* was added, and in 2013, monitoring of *Acinetobacter* spp. resistance commenced. To ensure comparability and reliability of results across different countries, the surveillance at the European level only considered invasive isolates (from blood cultures and cerebrospinal fluid), given the varying practices in sampling and interpretation of findings.

Since the interpretation of these bacterial isolates in blood cultures and cerebrospinal fluid is consistent in all laboratories, their clinical significance is unquestionable. Croatia actively engaged in the EARSS at the very beginning of the project, thanks to the already existing network of microbiology laboratories within the Croatian Committee for Antibiotic Resistance Surveillance. Upon becoming a member of the European Union, Croatian data were included in the EARS-Net program of the European Centre for Disease Prevention and Control (ECDC).

Despite certain challenges, such as the limited number of invasive isolates in some centres, which may which complicates the analysis at individual levels, and the fact that collecting data solely from the first isolates might not capture new resistance mechanisms that could emerge in blood cultures or cerebrospinal fluid, participation in the European network enables Croatia to compare data with other countries and access valuable information on resistance among invasive isolates. The comprehensive monitoring of resistance described in the first chapter of this publication and the targeted surveillance of invasive isolates complement each other, providing a robust approach for monitoring resistance in Croatia at both national and local levels.

Results of the antibiotic resistance surveillance in invasive isolates

Data on isolates are sent and collected electronically at the Reference Center for Antibiotic Resistance Surveillance located at the Clinic for Infectious Diseases "Dr. Fran Mihaljević," and are subjected to statistical analysis. A reorganization in data collection occurred during 2020 when it was agreed to officially transition to electronic data submission. Due to the frequent occurrence of insufficient data 2020, to present data exclusively for intensive care units (ICU), resulting in a change in the format of the former Tables 3 and 4, which previously displayed demographic information for patients and the origin of samples.
Within the framework of the EARS-Net program, the Reference Center for Antibiotic Resistance Surveillance continues to receive and collect all invasive isolates of *S. pneumoniae, S. aureus, E. faecalis, E. faecium, E. coli, K. pneumoniae, P. aeruginosa*, and *Acinetobacter* spp., to retest isolates with rare phenotypes and further analysis. During 2022, a total of 89 isolates of *S. pneumoniae*, 1054 isolates of *E. coli*, 394 isolates of *K. pneumoniae*, 696 isolates of *S. aureus*, 365 isolates of enterococci (288 *E. faecalis* and 137 *E. faecium* isolates), 282 isolates of *P. aeruginosa*, and 308 isolates of *Acinetobacter* spp. were collected (Table 1).

Based on data from 2023, it is evident that the number of laboratories reporting data on isolates within the national network continues to grow. Out of 39 microbiological laboratories in the Antibiotic Resistance Monitoring Committee, 26 reported their data on invasive isolates for 2023. The number of reported isolates in 2023 increased by one-third compared to previous years (4174 isolates in 2023, 3188 isolates in 2022). Table 1. shows the number of laboratories and the number of collected invasive isolates of various species.

In analyzing the total number of reported isolates for 2023, we observe an increase in isolates across all monitored species, with the exception of *Acinetobacte*r spp., a typical hospital pathogen, where the number of reported isolates continues to decline, while resistance rates to carbapenems remain exceptionally high at 97%. The most significant increase was noted for isolates of *S. aureus*, *K. pneumoniae*, and *P. aeruginosa*, where the number of reported isolates is the highest in the last ten years.

The number of reported *S. pneumoniae* isolates has returned to pre-COVID-19 pandemic levels. The number of penicillin non-susceptible isolates continues to decrease, with a rate of 13% recorded in 2023. We are also monitoring the trend of decreasing macrolide resistance rates, with 2023 marking the lowest resistance rate in the past ten years at 16%.
In 2023, aside from the observed increase in the number of reported *S. aureus* isolates, there were no significant changes in the rates of MRSA isolates (30% MRSA in 2023; 31% in 2022).

Although we have witnessed an increase in glycopeptide resistance among E. faecium isolates with very high resistance rates in recent years, the rate dropped to 24% in 2023. This represents a significant decrease compared to 37% in 2022 and 39% in 2021. Meanwhile, glycopeptide resistance rates among E. faecalis isolates remained stable and low, below 1%. The rates of high resistance to aminoglycosides among E. faecalis isolates showed a significant decrease in 2023 (28% in 2023, down from 37% in 2022). In contrast, resistance rates to this class of antibiotics increased among E. faecium isolates, rising from 30% in 2022 to 43% in 2023.

Along with the increase in the total number of reported invasive *K. pneumoniae* isolates, the trend of rising numbers of carbapenem-resistant isolates (imipenem and/or meropenem) continues, with a resistance rate reaching 27% in 2023. An additional 7% of *K. pneumoniae* isolates are susceptible, increased exposure to carbapenems. Overall, 34% of invasive *K. pneumoniae* isolates remain a significant challenge in treatment and the selection of optimal antibiotic therapy. No significant changes have been observed in the resistance rates of other monitored antibiotic groups.

For *P. aeruginosa* isolates, resistance rates have remained consistent with previous data, showing no significant deviations. Slightly lower resistance rates were observed compared to the previous year in all monitored antibiotic groups, except for quinolones. Quinolone resistance has been rising for several years, reaching 33% of invasive *P. aeruginosa* isolates in 2023.

Invasive *E. coli* isolates show a trend of increasing resistance rates to third-generation cephalosporins, reaching 20% in 2023, and to aminoglycosides, with a recorded resistance rate of 18% in the same year. Data indicate that resistance to third-generation cephalosporins is still predominantly caused by the production of extended-spectrum beta-lactamases (ESBL). The resistance rate to quinolones is 30%.

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.-2023. /
Number of laboratories and number of isolates reported for the period 2001-2023

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
2021	17	93	22	786	22	988	21	433	20	482	19	284	21	640
2022	20	89	23	696	25	1054	22	365	23	394	22	282	21	308
2023	19	136	26	862	26	1431	26	420	23	643	21	404	20	278

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

PATOGEN / PATHOGEN	ANTIBIOTICI/ Antimicrobial classes	2009 %	2010 %	2011 %	2012 %	2013 %	2014 %	2015 %	2016 %	2017 %	2018 %	2019 %	2020 %	2021 %	2022 %	2023 %
S. pneumoniae	Penicillin R	6	7	1	1	4	1	1	1	1	1	2	1	0	0	0
	Penicillin I+R	19	21	18	23	27	26	20	22	21	20	20	24	19	18	13
	Macrolides R	8	29	24	28	34	28	19	33	37	33	30	40	24	27	16
S. aureus	Oxacillin/Met R	37	27	27	22	24	21	25	25	28	26	25	29	36	31	30
E. coli	Aminopenicillin R	55	55	55	52	54	54	56	57	59	58	57	58	57	56	57
	Aminoglycoside R	8	6	7	7	7	10	12	14	16	14	13	15	14	16	18
	Fluoroquinolone R	16	17	20	17	21	20	25	28	30	30	27	30	29	31	30
	3. gen Cef R	5	8	7	8	9	11	13	12	16	14	15	17	18	17	20
	ESBL			9	7	9	11	13	14	16	15	17	16	25	30	27
E. faecalis	Aminopenicillins R		5	1	5	9	6	4	7	5	3	2	4	6	3	3
	HL Aminoglycoside R	36	37	33	39	35	33	35	33	32	34	24	38	43	37	28
	Glycopeptides R	<1	<1	1	<1	<1	0	0	0	<1	2	2	1	3	1	<1
E. faecium	Aminopenicillin R		82	98	98	90	94	97	98	96	98	94	99	96	93	91
	HL Aminoglycoside R	68	60	66	61	55	64	53	65	50	64	51	37	30	30	43
	Glycopeptides R	11	12	2	0	7	10	26	23	19	25	26	33	39	37	24
K. pneumoniae	Aminoglycoside R	47	49	43	45	51	48	40	31	28	33	40	38	42	43	38
	Fluoroquinolone R	51	48	43	43	45	46	50	44	50	49	59	54	60	55	57
	3. gen Cef R	53	56	50	44	50	48	46	42	41	42	51	52	58	55	55
	ESBL			51	52	50	48	47	46	41	43	51	52	62	64	54
	Carbapenems I+R			<1	<1	1	2	3	2	5	7	16	19	34	28	34
	Carbapenem R			0	0	0	0	0	0	0	2	12	19	28	23	27
P. aeruginosa	Piperacillin R		23													
	Piperacllin/ Tazobactam R		16	23	18	23	32	25	20	16	11	14	10	13	13	11
	Ceftazidime R	11	12	17	14	20	28	20	23	21	19	20	19	20	24	21
	Carbapenems R	31	26	30	21	25	35	37	41	30	27	23	30	31	35	29
	Aminoglycoside R	37	26	34	26	24	37	34	32	27	23	20	10	9	8	10
	Fluoroquinolones R	29	27	34	24	23	28	37	38	39	29	26	23	23	29	33
A. baumannii	Carbapenems R					91	88	89	95	96	95	93	96	99	99	97

Tablica 3. / *Table 3.*
Prikaz gram-pozitivnih invazivnih izolata u 2023.g. prema demografskim podacima pacijenata /
Selected details on gram-positive invasive isolates from the reporting period 2023

	S.pneumoniae		***S.aureus***		***Enterococcus* spp.**	
	n=136		**n=862**		**n=420**	
	% tot	**% PNPS**	**% tot**	**% MRSA**	**% tot**	**% VRE**
UZORAK ***SAMPLE***						
Krv / Blood	90	14	99	28	99	9
Likvor / CSF	10	0	<1	0	1	0
SPOL ***GENDER***						
M	54	11	62	29	65	11
Ž / F	45	15	38	25	34	6
Nepoznato / Unknown	1	0	<1	0	1	0
DOB ***AGE***						
0-4	10	29	2	0	6	15
5-19	3	25	1	7	1	0
20-64	37	4	33	22	24	15
>65	50	15	64	32	69	7
Nepoznato / Unknown	0	0	0	0	0	0
ODJEL ***DEPARTMENT***						
Intenzivna / ICU	18	8	13	34	16	12

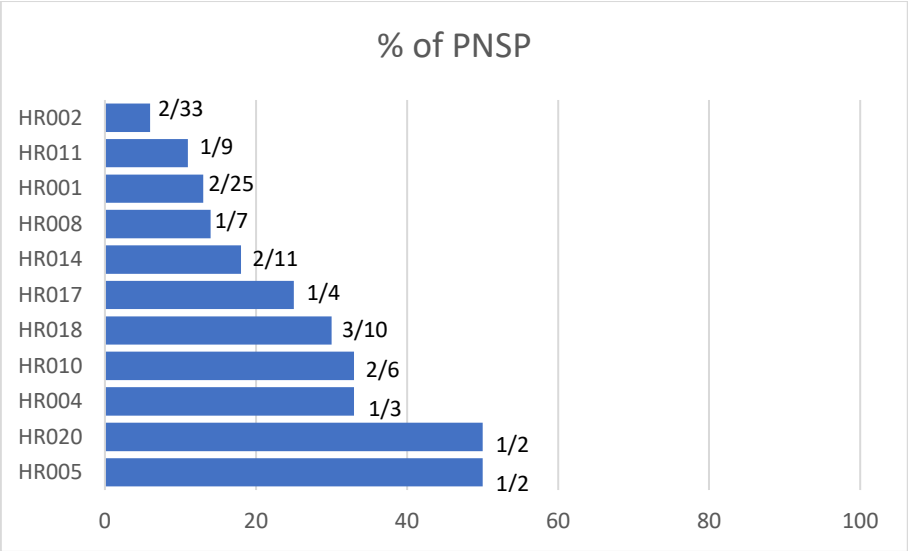
PNSP=Penicillin Non-Susceptible *S. Pneumoniae* MRSA=Methicillin Resistant *S.aureus* VRE=Vancomycin Resistant Enterococcus

Tablica 4. / *Table 4.*
Prikaz gram-negativnih invazivnih izolata u 2023. g. prema demografskim podacima pacijenata /
Selected details on gram-negative invasive isolates from the reporting period 2023

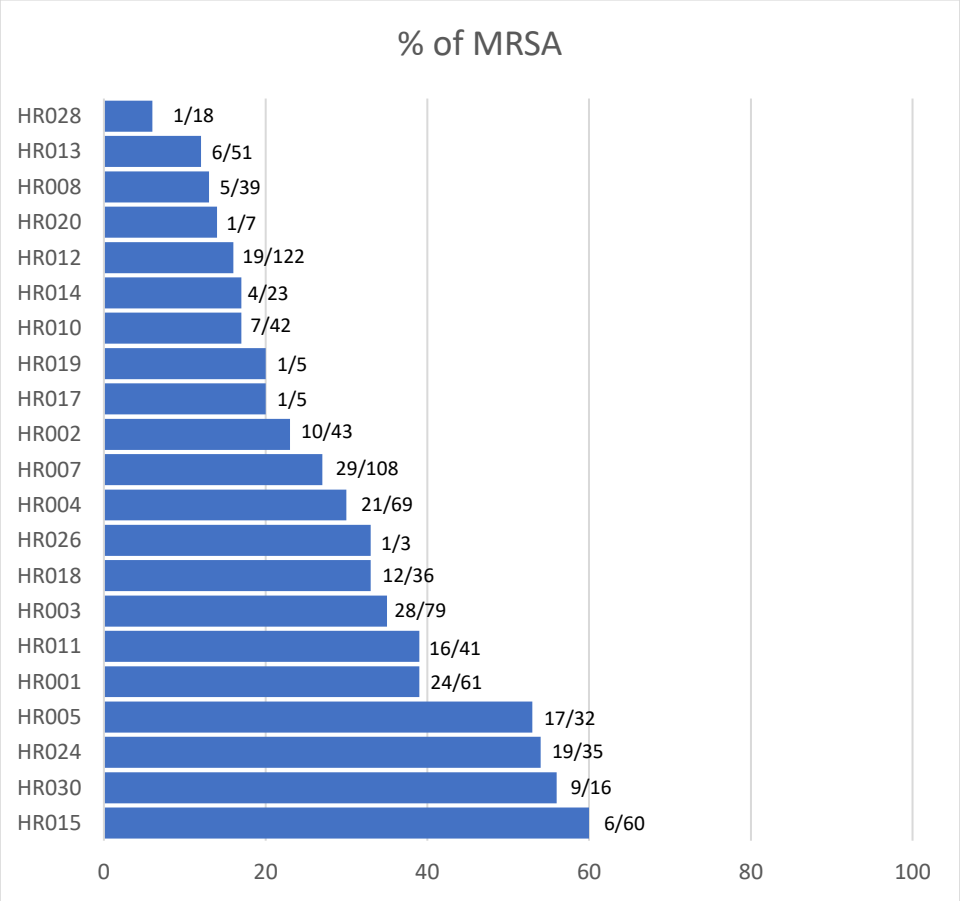
	E. coli			*Acinetobacter* spp.		*K.pneumoniae*		*P.aeuroginosa*	
	n=1431			n=278		n=643		n=404	
	% tot	% FREC	% CREC	% tot	% CRA	% tot	% CRKP	% tot	% CRPA
UZORAK ***SAMPLE***									
Krv / Blood	99	30	19	98	96	99	53	99	30
Likvor / CSF	0	0	0	2	100	1	50	1	67
SPOL ***GENDER***									
M	43	35	21	64	98	61	57	64	30
Ž / F	56	25	17	36	92	39	46	35	31
Nepoznato / Unknown	1	20	0	0	0	<1	100	<1	100
DOB ***AGE***									
0-4	3	5	8	<1	100	4	13	<1	0
5-19	<1	20	0	1	100	<1	40	3	36
20-64	26	27	18	33	95	35	54	37	36
>65	70	11	20	65	96	60	55	59	27
Nepoznato / Unknown	<1	0	0	0	0	0	0	0	0
ODJEL ***DEPARTMENT***									
Intenzivna / ICU	7	23	23	47	95	19	42	33	36

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.

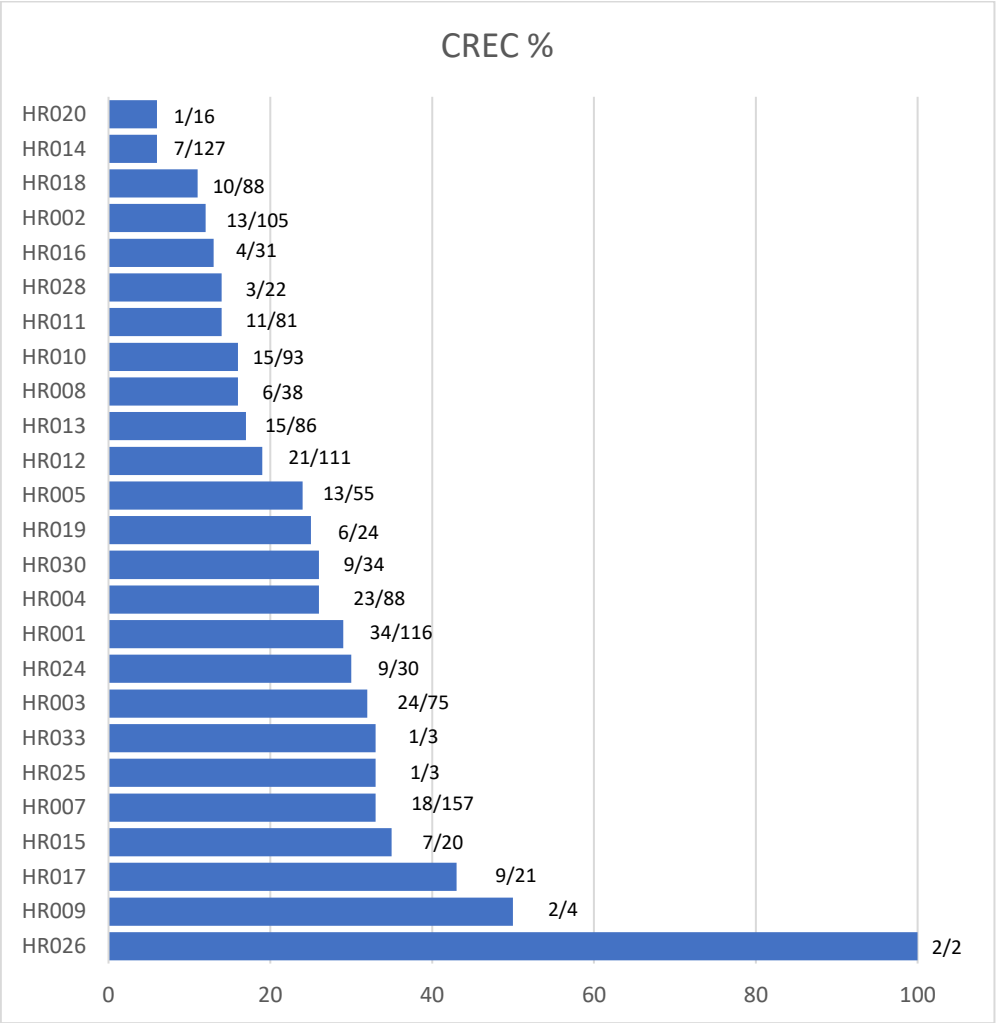
Slika 1. / *Figure 1.*
Udio (%) izolata *S. pneumoniae* smanjene osjetljivosti na penicilin (PNSP) po centrima / *Proportion (%) of penicillin non-susceptible S. pneumoniae (PNSP) by center*



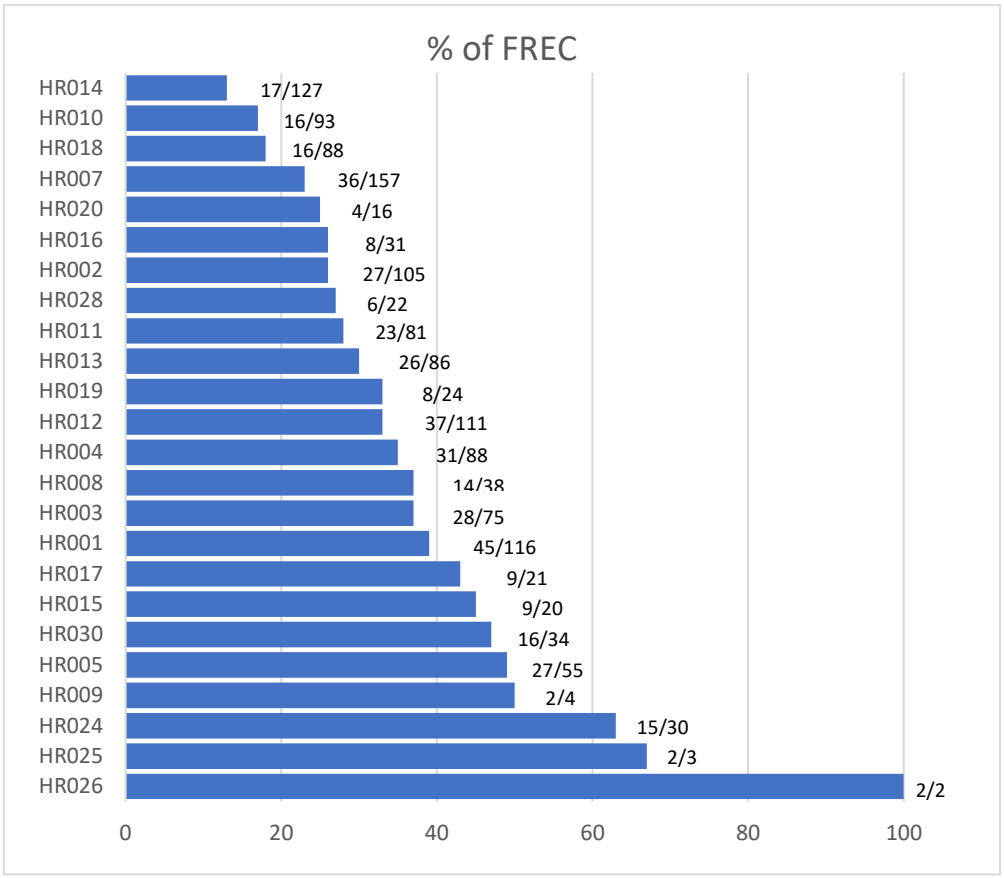
Slika 2. / *Figure 2.*
Udio (%) MRSA izolata po centrima / *Proportion (%) of MRSA isolates by center*



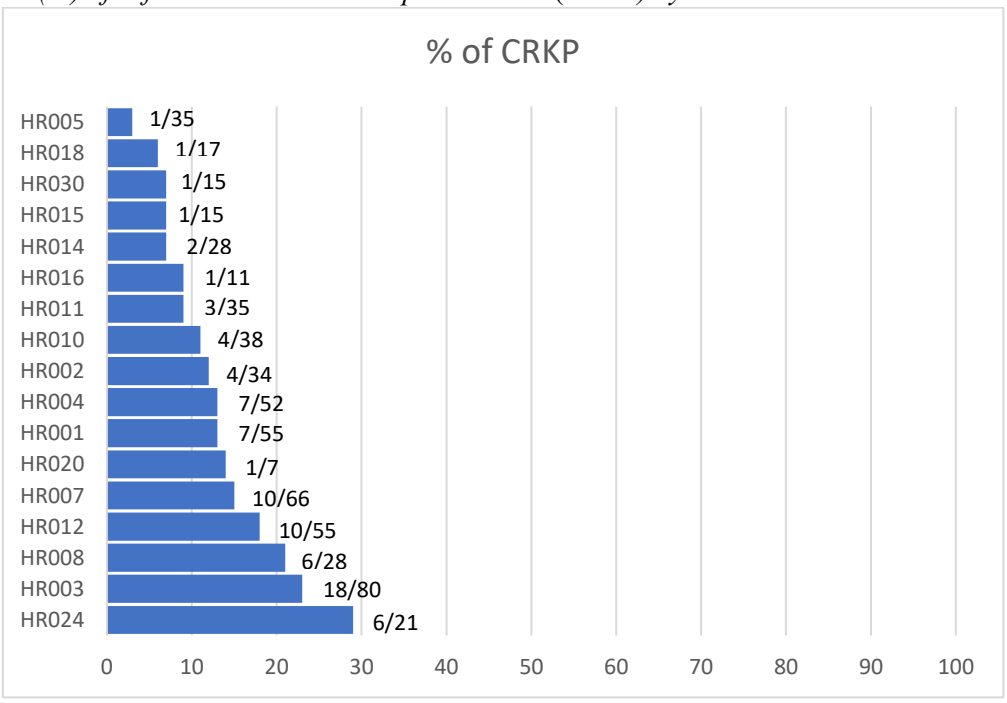
Slika 3. / *Figure 3.*
Udio (%) ceftazidim rezistentnih izolata *E. coli* (CREC) po centrima /
Proportion (%) of ceftazidime resistant E. coli isolates (CREC) by center



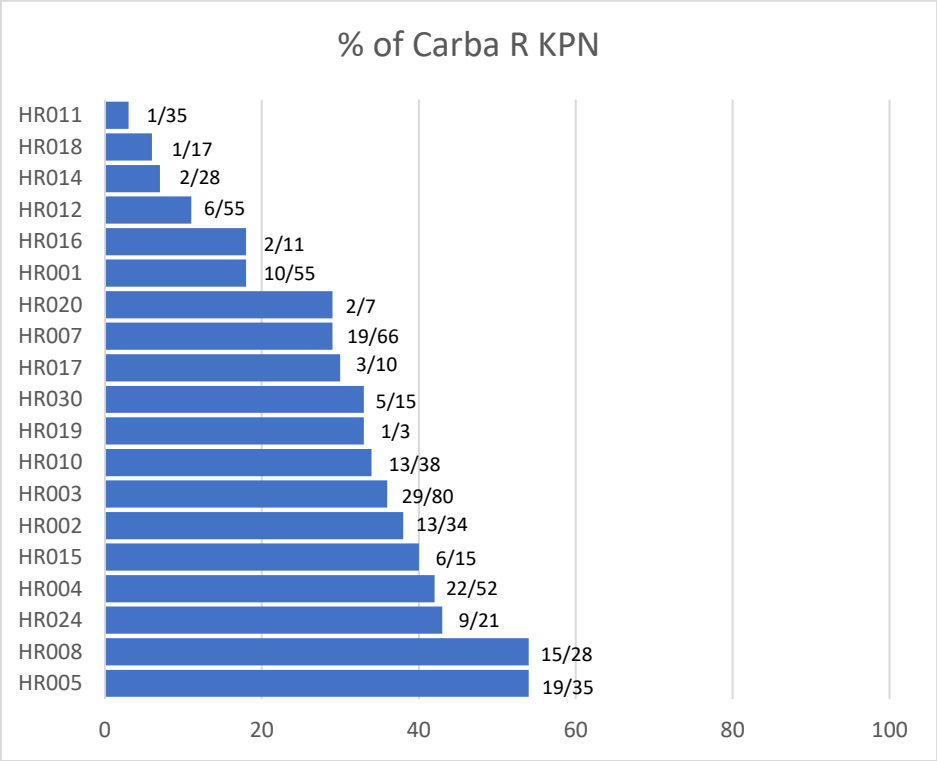
Slika 4. / *Figure 4.*
Udio (%) fluorokinolon rezistentnih izolata *E. coli* (FREC) po centrima /
Proportion (%) of fluoroquinolone resistant E.coli isolates (FREC) by center



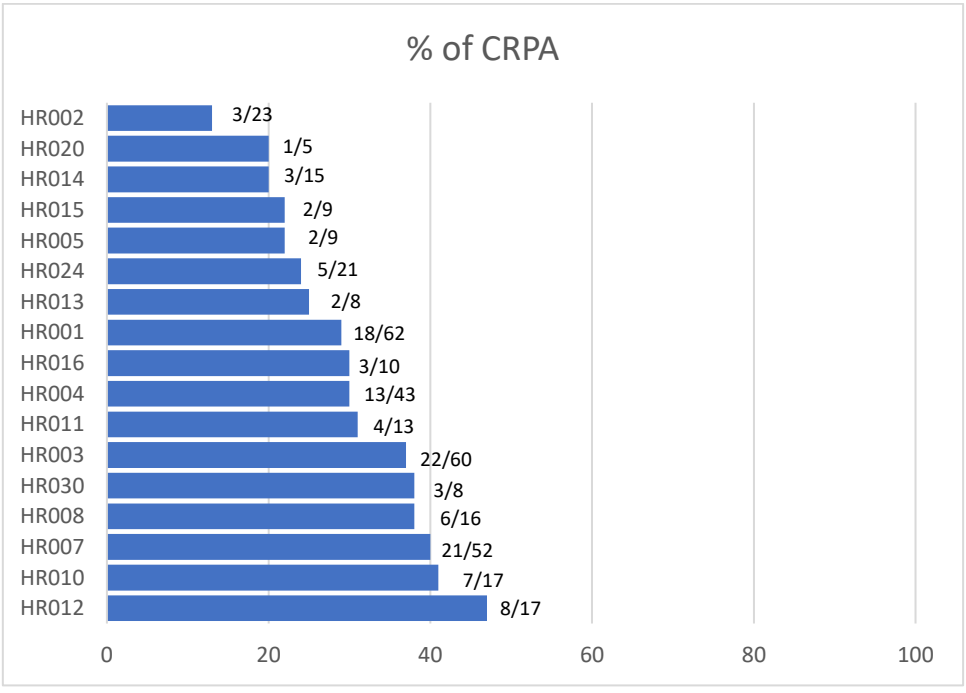
Slika 5. / *Figure 5.*
Udio (%) ceftazidim rezistentnih izolata *K. pneumoniae* (CRKP) po centrima /
Proportion (%) of ceftazidime resistant K. pneumoniae (CRKP) by center



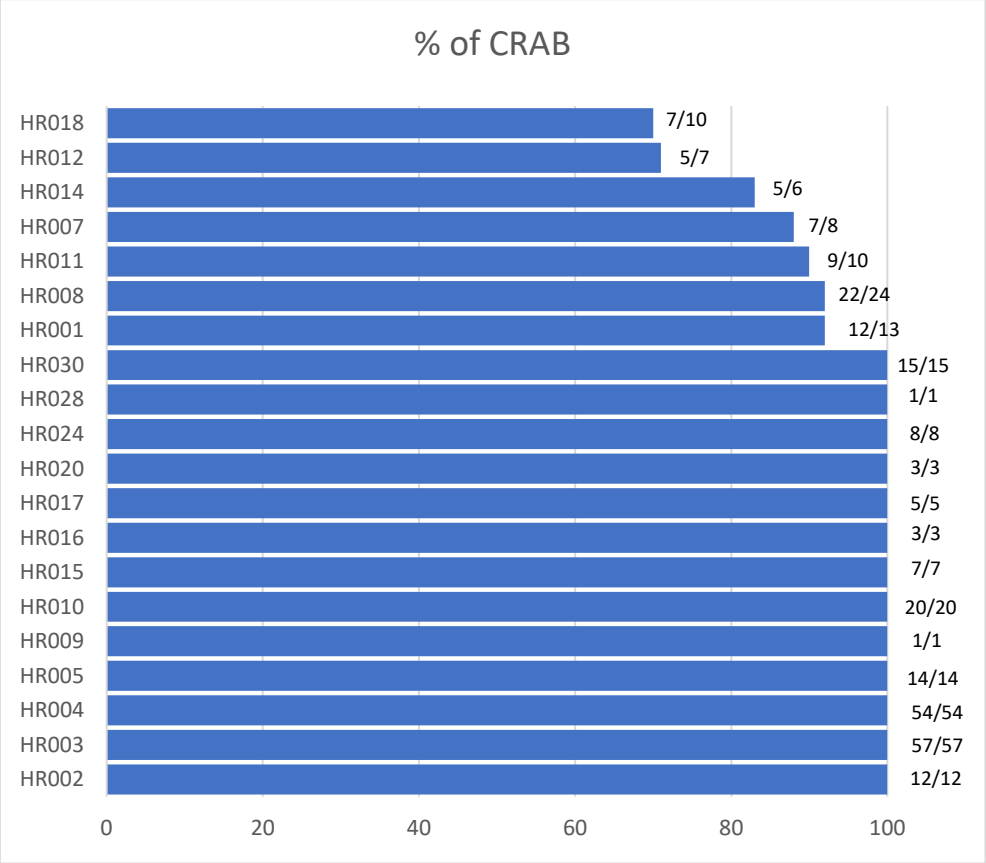
Slika 6. / *Figure 6.*
Udio (%) karbapenem rezistentnih izolata *K. pneumoniae* (Carb R KP) po centrima /
Proportion (%) of carbapenem resistant K. pneumoniae (Carb R KP) by center



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 2023. GODINI

DISTRIBUTION OF CANDIDA SPECIES AND ANTIFUNGAL SUSCEPTIBILITY IN PATIENTS WITH CANDIDEMIA IN CROATIA, 2023

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UVOD

Posljednjih 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 2023. godini.

Učestalost vrsta *Candida* spp.

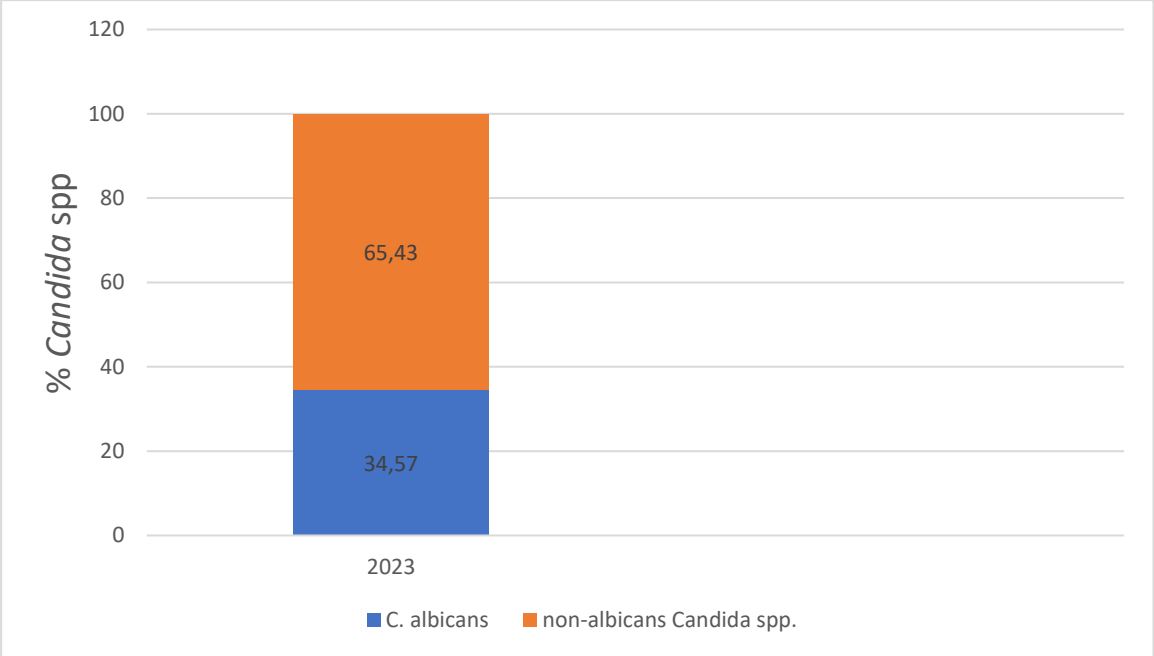
Za vrijeme ovog razdoblja ukupno je prikupljeno i analizirano 162 izolata *Candida* spp. Učestalost pojedinih *Candida* spp. prikazana je u Tablici 1. Usporedbom podataka iz 2022. (185 izolata) godine bilježi se pad broja analiziranih izolata no važno je istaknuti da u 2023. godini nismo dobili podatke iz dva velika klinička centra.

Najčešće prisutne vrste *Candida* spp. u 2023. godini bile su *C. albicans* kod 34,57% (56/162), *C. parapsilosis* kod 32,72% (53/162), , i *C. glabrata* kod 27,78% (45/162) bolesnika s kandidemijom.

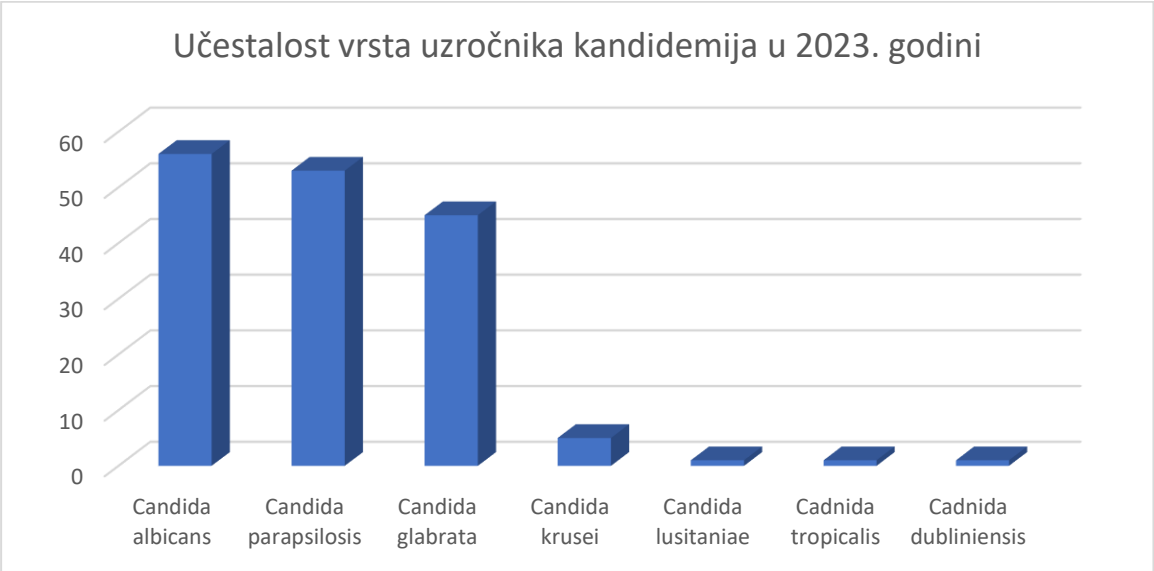
Tablica 1. */ Table 1.*
Učestalost pojedinih vrsta *Candida* spp. kod bolesnika s kandidemijom u Hrvatskoj u 2023. godini / *Incidence of different Candida spp.in patients with candidemia in Croatia in 2023*

Vrsta *Candida* spp.	**N (%)**
Candida albicans	56 (34,57)
Candida parapsilosis	53 (32,72)
Candida glabrata	45(27,78)
Candida krusei	5(3,09)
Candida lusitaniae	1 (0,62)
Cadnida tropicalis	1 (0,62)
Cadnida dubliniensis	1(0,62)
UKUPNO	**162**

Slika 1. */ Figure 1.*
Udio *C. albicans* i non-albicans vrsta u 2023 godini među izolatima bolesnika s kandidemijom u Hrvatskoj / *Proportion of C. albicans and non-albicans species in 2023*



Grafikon 2. Učestalost vrsta uzročnika kanidemija u 2023. godini
Figure 2. Proportion of *Candida* spp. causing candidemia in 2023.

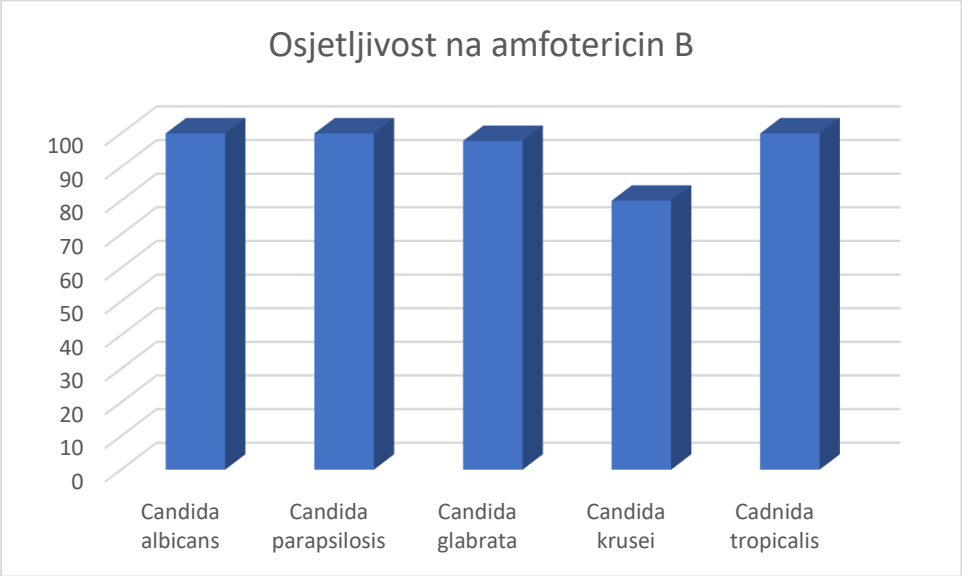


Udio *C. albicans* i non-albicans vrsta u 2023. godini među izolatima bolesnika s kandidemijom prikazan je na Grafikonu 1. Iz analiziranih podataka se vidi da je *C. albicans* najzastupljenija vrsta u Hrvatskoj, ali odmah iza je *C. parapsilosis* što je posebno zabrinjavajuće obzirom na visoki postotak stečene rezistencije *C. parapsilosis* na flukonazol. Vrlo je zabrinjavajući gotovo dvostruki skok *C. glabrata* posebice uzimajući u obzir njezinu urođenu smanjenu osjetljivost na azole.
Ovi podaci imaju kliničku važnost budući *C. parapsilosis* i *C. glabrata* imaju manju osjetljivost na ehinokandine odnosno azole. Ovakva distribucija *Candida* spp. karakteristična je za južnu Europu te iako njeno tumačenje još uvijek nije do kraja poznato, pretpostavlja se da je posljedica klimatskih utjecaja, načina primjene antifungalnih lijekova s posebnim naglaskom na način provođenja mjera prevencije i kontrole infekcija.

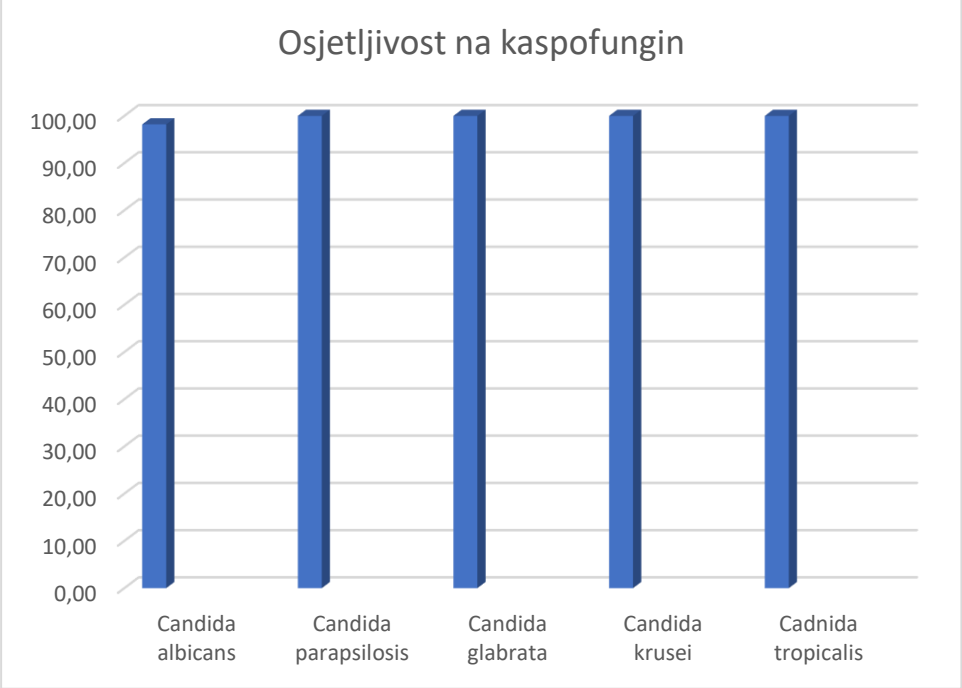
Osjetljivost na antifungalne lijekove

Osjetljivost vrsta *Candida* spp u Hrvatskoj u 2023. godini na amfotericin B, kaspofungin, mikafungin, anidulafungin i flukonazol prikazana je na grafikonu 3., 4., 5., 6. i 7.
Osjetljivost na amfotericin B bila je 100% za *C. albicans, C. parapsilosis, C. tropicalis,* a za *C. glabratu* 97,78% i *C. krusei* 80%. (grafikon 3).
Osjetljivost uzročnika kandidemija na ehinokandine je još uvijek vrlo visoka, što je i očekivano. Osjetljivost na kaspofungin izolata *C. albicans* u 2023. bila je 98,21%. Izolati *C. parapsilosis* izolirani iz hemokultura su 100% osjetljivi na kaspofungin,a slično i izolati *C. glabrata*, *C. tropicalis, C. krusei* 100%. (grafikon 4). Mikafungin je pokazao sličnu učinkovitost pa su tako izolati *C. albicans* 2023. godine bili osjetljivi 98,21% . Izolati *C. parapsilosis* izolirani iz hemokultura su 2021 godine bili 98,21% osjetljivi. Izolati *C. glabrata* bili su osjetljivi 100%, a *C. tropicalis i C. krusei* 100% (grafikon 5). Anidulafungin također pokazuje vrlo sličnu djelotvornost na uzročnike kandidemija pa su tako izolati *C. albicans* bili osjetljivi na anidulafungin u 2023. godine 98,21%. S druge strane izolati *C. parapsilosis* su bili osjetljivi 79,25%, a *C. glabrata* 100% (grafikon 6).
C. albicans je osjetljiva na flukonazol u 100% ispitivanih izolata. 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 2023. godini bila osjetljiva u 22,64% slučajeva.
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. Analizirali smo jedan izolat *C. tropicalis* koji je bio intermedijaran na flukonazol (grafikon 7).

Grafikon 3. Osjetljivost vrsta *Candida* spp. u Hrvatskoj u 2023. godini na amfotericin B
Figure 3. *Candida* spp. susceptibility to amphotericin B in Croatia in 2023

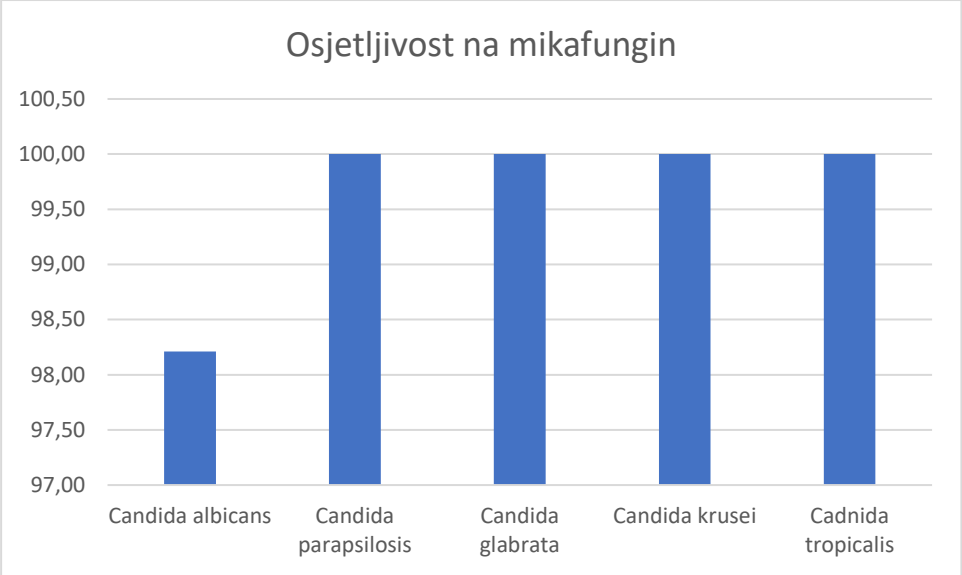


Grafikon 4. Osjetljivost vrsta *Candida* spp. u Hrvatskoj u 2023. godini na kaspofungin
Figure 4. *Candida* spp. susceptibility to caspofungin in Croatia in 2023

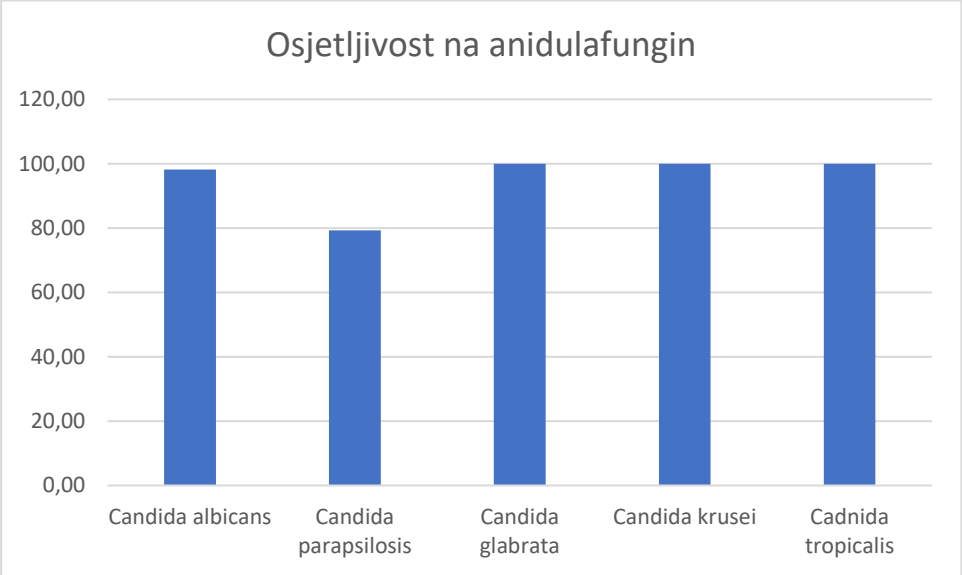


c

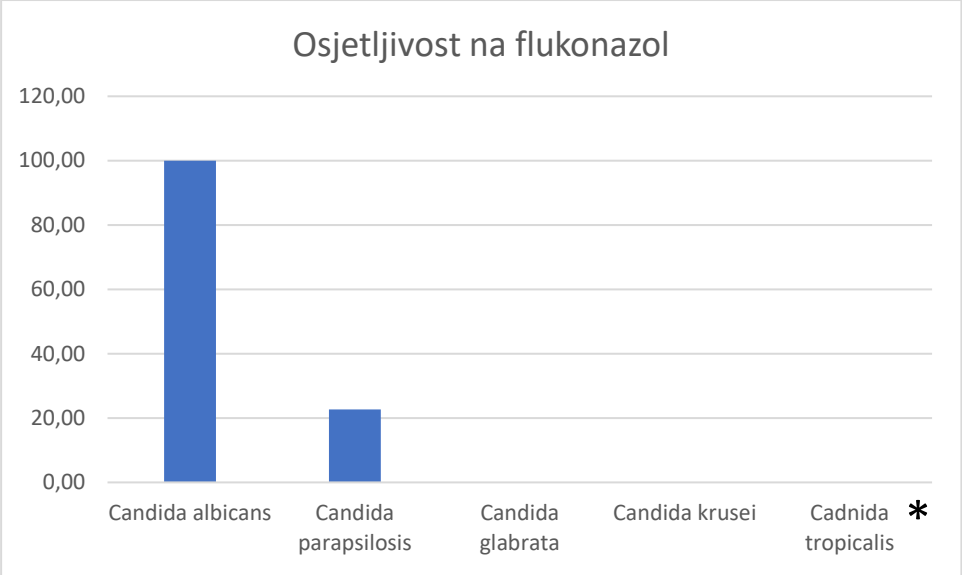
Grafikon 5. Osjetljivost vrsta *Candida* spp. u Hrvatskoj u 2023. godini na mikafungin
Figure 5. *Candida* spp. susceptibility to micafungin in Croatia in 2023



Grafikon 6. Osjetljivost vrsta *Candida* spp. u Hrvatskoj u 2023. godini na anidulafungin
Figure 6. *Candida* spp susceptibility to anidulafungin in Croatia in 2023



Grafikon 7. Osjetljivost vrsta *Candida* spp. u Hrvatskoj u 2023. godini na flukonazol
Figure 7. *Candida* spp susceptibility to fluconazol in Croatia in 2023



* Radi se o samo jednom izolatu *C. tropicalis* koji je bio I na flukonazol

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 differences in the *Candida* species distribution and antifungal susceptibility and emphasized the necessity for surveillance. These data are essential for choosing empirical therapy, prophylaxis, 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 the Croatian Committee for Antibiotic Resistance Surveillance started collecting *Candida* spp. isolates from blood cultures. All microbiological laboratories in Croatia were invited after the isolation of *Candida* spp from blood culture to send the isolate to the Excellence Centre and fulfill the form on the Excellence Centre website fungi.kbc-zagreb.hr. This form contains the data about the isolate, identification methods, methods used to determine isolate antifungal susceptibility as well as clinical data about the patient. In the Excellence Centre every isolate was reidentified and then susceptibility testing was performed using the microdilution method according to CLSI guidelines. This report contains the data about the incidence of different *Candida* species and susceptibility to antifungal agents in the year 2023.

Incidence of different *Candida* species

During 2023 162 isolates of *Candida* spp. were collected and analysed. The incidence of different *Candida* species is shown in Table 1. Comparing with the data from 2022 in 2023 was observed a significant decrease of the number of isolates (162) compared to 2022 (185 isolates). We have to emphasize that some big hospitals didn't participate in isolate collection.

The most common *Candida* spp. in the year 2023 were *C. albicans* in 34,57% (56/162), *C. parapsilosis* in 32.72% (53/162), and *C. glabrata* in 27.78% (45/162) patients with candidemia.

The distribution of *C. albicans* and non-albicans species among candidemia isolates in the year 2023 is shown in Figure 1.*C. albicans* is again the most common isolate followed by *C. parapsilosis* and *C. glabrata* was in the third place. Those results are clinically important because *C. parapsilosis* and *C glabrata* have reduced susceptibility to echinocandins or azoles. That kind of distribution is characteristic of South Europe and is presumed that it is influenced by climatic influences, the use of antifungal agents and emphasized adherence to prevention and infection control measures.

Antifungal susceptibility

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

Susceptibility to amphotericin B was 100% for *C. albicans, C. parapsilosis, C. glabrata, C. tropicalis* and for *C. glabrata* 97,78% and *C. krusei* was 80%. (Figure 3).

As expected, echinocandins showed excellent efficiency against *Candida* isolates. Susceptibility to caspofungin of *C. albicans* isolates in 2023 was 98,21%. *C. parapsilosis, C. glabrata, C. tropicalis, C, krusei* isolates from blood cultures showed 100% susceptibility to caspofungin, (Figure 4). Micafungin showed similar activity because C. *albicans* isolates in the year 2023 showed a susceptibility of 98,21%. *C. parapsilosis* isolates from blood cultures demonstrated a susceptibility of 96,25%. Isolates of *C. glabrata*, *C. tropicalis* and *C. krusei* were 100% susceptible to micafungin *(Figure 5*). Anidulafungin showed very similar efficacy and susceptibility of 98,59% in the year 2021 among isolates of *C. albicans*. On the other hand, *C. parapsilosis* isolates showed susceptibility of 79,25% in the year 2023 and *C. glabrata* 100%. Isolates of*, C. tropicalis* and *C. krusei* were 100% susceptible to anidulafungin (Figure 6).

Susceptibility to fluconazole was 100% in *C. albicans. C. tropicalis* wasn't susceptible to fluconazole but was just one isolate that was intermediate to fluconazole. Isolates of *C. parapsilosis* (that is in contrast to *C. glabrata* and *C. krusei* intrinsically susceptible to fluconazole) developed resistance in the large number of isolates unfortunately; in 2023 susceptibility was 22,64%.

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

POGLAVLJE / CHAPTER 6.

POTROŠNJA ANTIBIOTIKA U HRVATSKOJ
ANTIBIOTIC CONSUMPTION IN CROATIA

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Izvanbolnička potrošnja antibiotika

Hrvatska je uključena u praćenje potrošnje antibiotika od samog početka 2001. godine u okviru mreže praćenja European Surveillance of Antibiotic Consumption (ESAC) i u skladu s njezinim standardima.
Podaci za ambulantnu potrošnju antibiotika se prikupljaju iz Hrvatskog zavoda za zdravstveno osiguranje (HZZO) i putem veledrogerija te za bolničku potrošnju iz bolničkih ljekarni i veledrogerija. U skladu s tim odvojeno se prikazuju ambulantna i bolnička potrošnja antibiotika.
Podaci o potrošnji antibiotika se prikupljaju u skladu s Anatomsko-Terapijsko-Kemijskom klasifikacijom lijekova (ATK klasifikacija) na 5. razini, a potrošnja se prikazuje na 4. i 3. nivou ATK klasifikacije.
Potrošnja antibiotika se izražava u definiranim dnevnim dozama (DDD) na 1000 stanovnika po danu (DDD/TID). ATK/DDD index se ažurira svake godine i dostupan je na stranicama Kolaborativnog centra za statistiku i metodologiju Svjetske zdravstvene organizacije (SZO) (http://www.whocc.no/atc_ddd_index).
Ambulantna potrošnja antibiotika se izražava na 1000 stanovnika po danu (DDD/1000/dan). Broj stanovnika koji se koristi kao denominator kod izračuna potrošnje iznosi 3 871 833 u skladu s popisom stanovništva Hrvatske iz 2021. godine. Bolnička potrošnja antibiotika se iskazuje u DDD na 1000 stanovnika po danu (TID) i u DDD na 100 bolničkoopskrbnih dana (DDD/100 BOD).
Sudjelovanjem u europskoj mreži za praćenje potrošnje (ESAC-Net), što je ujedno i obveza svake zemlje, članice Europske unije Hrvatskoj daje mogućnost usporedbe potrošnje s drugim zemljama koje su uključene u mrežu preko platforme za unos podataka, The European Surveillance System (TESSY).
Iako se ambulantna potrošnja antibiotika prati iz dva izvora, od 2012. godine službeni podaci o ambulantnoj potrošnji su oni dobiveni od HZZO-a putem crvenih recepata. Koristeći dva izvora podataka za praćenje ambulantne potrošnje uočavaju se i razlike u potrošnji, ovisno o izvoru (tablica 3: slika 2). Veća potrošnja se uočava kod podataka dobivenih iz veledrogerija. U 2023. godini razlika u odnosu na podatke dobivene putem HZZO-a iznosi 3,14 DDD/TID, što je za 0,54 DDD/TID više u odnosu na godinu prije (2,6 DDD/TID).

Razlika se uočava u svim klasama antibiotika. Najveća razlika je, kao i prethodnih godina kod klase penicilina (1,78 DDD/TID) i klase makrolid-linkozamid-streptogramin (0,52 DDD/TID) (tablica 4; slika 3). Razlike su veće u odnosu na prethodnu godinu (1,42 DDD/TID; 0,47 DDD/TID). I kod ostalih klasa antibiotika uočavaju se razlike, ali su one znatno manje (tablica 4; slika 3). Razlozi tome su propisivanje antibiotika od strane liječnika u privatnim zdravstvenim ustanovama, što nije evidentirano putem crvenog recepta, a time niti zabilježeno u HZZO-u. Još jedan razlog je direktno snabdjevanje ambulanti s antibioticima iz veledrogerija, posebno za potrebe parenteralne terapije. To je moguće objašnjenje za skupinu cefalosporina, posebno treću generaciju (ceftriakson) i aminoglikozide (gentamicin), čija potrošnja je porasla čak deset puta u odnosu na prethodnu godinu.

Na slici 1 prikazani su rezultati kontinuiranog praćenja ambulantne potrošnje antibiotika u Hrvatskoj od 2001. godine, koji pokazuju značajne oscilacije u tom dvadesettrogodišnjem periodu. Oscilacije su odraz promjene numeratora (broj potrošenih DDD), ponekad, iako rijetko, promjene formulacije antibiotika (pr. koamoksiklav 2002. godine kojem je povećana koncentracija amoksicilina u dnevnoj dozi) te denominatora, odnosno nazivnika, a to je broj stanovnika. U skladu s popisom stanovnika, svakih deset godina taj broj se mijenja. U Hrvatskoj se bilježi trend smanjivanja broja stanovnika, time i denominatora, što se odražava i na iskazanu potrošnju antibiotika.
Od zadnjeg popisa stanovništva (2021. godine) bilježi se trend porasta ambulantne potrošnje izražen u DDD/TID kontinuirano od 2021., 2022. i 2023. (16,22; 18,18; 19,14). U 2023. godini ambulantna potrošnja antibiotika je najviša do sada u zadnjih desetak godina.

U 2023. godini uočava se negativan trend jednog od indikatora potrošnje antibiotika koji se iskazuje kroz omjer izvanbolničke potrošnje izražene u DDD na tisuću stanovnika na dan (DDD/TID) širokospektralnih penicilina, beta-laktama s inhibitorima, cefalosporina II. i III. generacije, makrolida (osim eritromicina) i fluorokinolona (J01 (CR+DC+DD+FA-FA01)+MA) i potrošnje širokospektralnih penicilina bez inhibitora (amoksicilina), uskospektralnih penicilina, cefalosporina I. generacije i eritromicina (J01 (CA+CE+CF+DB+FA01) (tablica 5; slika 4). Omjer potrošnje iznosi 6,2 , što ukazuje

na porast potrošnje antibiotika širokog spektra u odnosu na uski spektar, za razliku od prošle godine kada se taj omjer smanjio u odnosu na godinu ranije.

U 2023. godini je porasla potrošnja tetraciklina, nakon sedam godina ponovno je viša od 1 DDD/TID (1,02). Nažalost, nije se nastavio trend porasta potrošnje širokospektralnih penicilina bez inhibitora (J01CA). Taj porast je prošle godine bio ohrabrujući i potaknuo je očekivanje da će se nastaviti, kako bi se potrošnja širokospektralnih penicilina bez inhibitora barem približila potrošnji širokospektralnih penicilina s inhibitorom s obzirom da su to antibiotici koji se empirijski preporučuju za liječenje infekcija gornjeg dišnog sustava u skladu s ISKRA smjernicama. Nažalost bilježi se najviša potrošnja (6,46 DDD/TID) i veliki porast potrošnje (za 0,68 DDD/TID) skupine širokospektralnih penicilina s inhibitorima beta-laktamaza (J01CR).

Omjer potrošnje širokospektralnih penicilina s inhibitorima beta-laktamaza (J01CR) i širokospektralnih penicilina bez inhibitora (J01CA) iznosi 4,0, što je nešto niže u odnosu na prethodne dvije godine kada je iznosio 4,2.

Penicilin uskog spektra (J01CE i J01CF) su vrlo skromno zastupljeni u ukupnoj potrošnji antibiotika te čine najmanji udio u potrošnji penicilinske skupine antibiotika (2,4%).
Penicilini uskog spektra (J01CE) bilježe pad potrošnje (s 0,25 DDD/TID u 2022. na 0,18 DDD/TID u 2023.), dok je potrošnja beta-laktamaza rezistentnih penicilina (J01CF) zabilježila porast, odnosno najvišu potrošnju do sada (0,02 DDD/TID) (Tablica 1).

Kod klase cefalosporina (J01D) bilježi se porast potrošnje 1. i 3. generacija, dok kod 2. generacija nema značajnijih promjena.
U 2023. godini je porasla potrošnja sulfonamida + trimetoprim (J01EE), makrolida i linkozamida (J01F), aminoglikozida (J01G) te nitrofurantoina (J01XE) i fosfomicina (J01XX). Potrošnja kinolona (J01M) je na gotovo istoj razini kao i prošle godine.

Ambulantna potrošnja antibiotika je najviša u zadnjih desetak godina u Hrvatskoj i iznosi 19,14 DDD/TID, što čini 90,2 % ukupne potrošnje antibiotika u Hrvatskoj.

U tablici 6 i na slici 5 poredani su antibiotici prema učestalosti potrošnje - “top lista” najpropisivanijih antibiotika. Antibiotici koji se nalaze među prvih šest su isti i poredani na isti način kao i prethodne godine. Na prvom mjestu je i dalje koamoksiklav, slijede ga azitromicin, cefuroksim i amoksicilin. Na petom mjestu je nitrofurantoin s nešto višom potrošnjom (1,10 DDD/TID) te doksiciklin (1,02 DDD/TID), kojem je također porasla potrošnja iznad 1 DDD/TID.

Još jedan od indikatora ambulantne potrošnje antibiotika je potrošnja po kvartalima, koja u zemljama s niskom potrošnjom antibiotika, kao na primjer Nizozemska, ne bilježi značajne razlike. Međutim, kod nas je uočljivo viša potrošnja u zimskim mjesecima godine, odnosno u prvom i zadnjem kvartalu godine (5,32; 4,25; 3,93; 5,64) (tablica 7; slika 6).

Rang lista prvih deset dijagnoza za koje se ambulantno propisuju antibiotici gotovo je identična prethodnoj godini. Na prvom mjestu je upala mokraćnog mjehura (cistitis) (N30). Za liječenje pacijenata s tom dijagnozom potrošnja iznosi 1,96 DDD/TID, gotovo identično kao i prošle godine (1,95 DDD/TID). Još dvije dijagnoze, koje se tiču infekcija urinarnog trakta, se nalaze među prvih deset, a to su infekcije urinarnog trakta, lokacija neoznačena (N 39.0) te drugi poremećaju urinarnog sustava (N 39). Za liječenje infekcija pod tim dijagnozama potrošnja antibiotika iznosi 1,07 DDD/TID. Ukupna potrošnja antibiotika za liječenje infekcija urinarnog trakta iznosi 3,03 DDD/TID, što je nešto više od lani kada je iznosila 2,97 DDD/TID).
Ostale dijagnoze za koje se propisuju antibiotici među prvih deset se odnose na infekcije respiratornog sustava. Redom na drugom mjestu je akutna upala ždrijela (akutni faringitis) (J02), zatim akutna upala tonzila (akutni tonzilitis) (J03), akutna upala sinusa (akutni sinusitis) (J01), akutna infekcija gornjega dišnog sustava (J06) te na šestom mjestu akutni bronhitis (J20). Na osmom mjestu je nesupurativna upala srednjeg uha (H 65) te na desetom periapikalni apsces (K04.7). Potrošnja antibiotika za liječenje

infekcija s tim dijagnozama, među prvih deset, iznosi 5,56 DDD/TID, što je porast u odnosu na prošlu godinu (4,97 DDD/TID) (tablica 8, slika 7).
„Top 10“ dijagnoze, za koje se ambulantno troši najviše antibiotika, ukazuju da se trećina odnosi na liječenje urinarnih infekcija, a dvije trećine na respiratorne infekcije. Izuzetno nepovoljan omjer ukazuje na nepravilno, često neopravdano liječenje respiratornih infekcija antibioticima, usprkos tome što su većinom uzrokovane virusima.

U 2023. pratimo nastavak rasta ambulantne potrošnje antibiotika. U 2023. godini potrošnja je najviša u zadnjih petnaest godina praćenja.
Udio ambulantne potrošnje u ukupnoj potrošnji iznosi 90,2%. što je uobičajeni udio u skladu s podjelom između ambulantne i bolničke potrošnje.

U ambulantnoj potrošnji antibiotika poredak klasa sukladno potrošnji je sljedeći: klasa penicilina je visoko na prvom mjestu (8,25 DDD/TID), slijede ju makrolidi i linkozamidi s 3,7 DDD/TID. Na trećem mjestu po potrošnji su cefalosporini s 2,91 DDD/TID. Na četvrtom mjestu su kinoloni s 1,51 DDD/TID, slijedi skupina ostali J01X s 1,21, tetraciklini J01A s 1,02 DDD/TID te na posljednjem su sulfonamidi s trimetoprimom (0,52 DDD/TID).

Klasa penicilina je, kao i do sada, najzastupljenija u ambulantnoj potrošnji antibiotika (43 %). Porast potrošnje je zabilježen kod svih klasa, osim kinolona koji su se zadržali na prošlogodišnjim vrijednostima. Kod klase penicina uočava se pad potrošnje širokog spektra penicilina J01CA te penicilina uskog spektra (J01CE). Pozitivan je trend porasta potrošnje beta-laktamaza rezistentnih penicilina (J01CF), koji su prvi lijek izbora za liječenje infekcija uzrokovanih sa *S. aureusom*. Loš pokazatelj je kontinuirani trend porasta potrošnje kombinacije amoksicilina i inhibitora beta-laktamaza, koji je premašio 6 DDD/TID i iznosi 6,46, a što je do sada najviša vrijednost (tablica 1).

Nastavlja se trend rasta potrošnje nitrofurantoina (0,68; 0,76; 0,83; 0,83; 0,96; 1,04; 1,10 DDD/TID) zadnjih godina, što je povoljan pokazatelj s obzirom da je cistitis vodeća dijagnoza za propisivanje antibiotika u izvanbolničkoj praksi te je njegova primjena u skladu s nacionalnim smjernicama za propisivanje antibiotika.

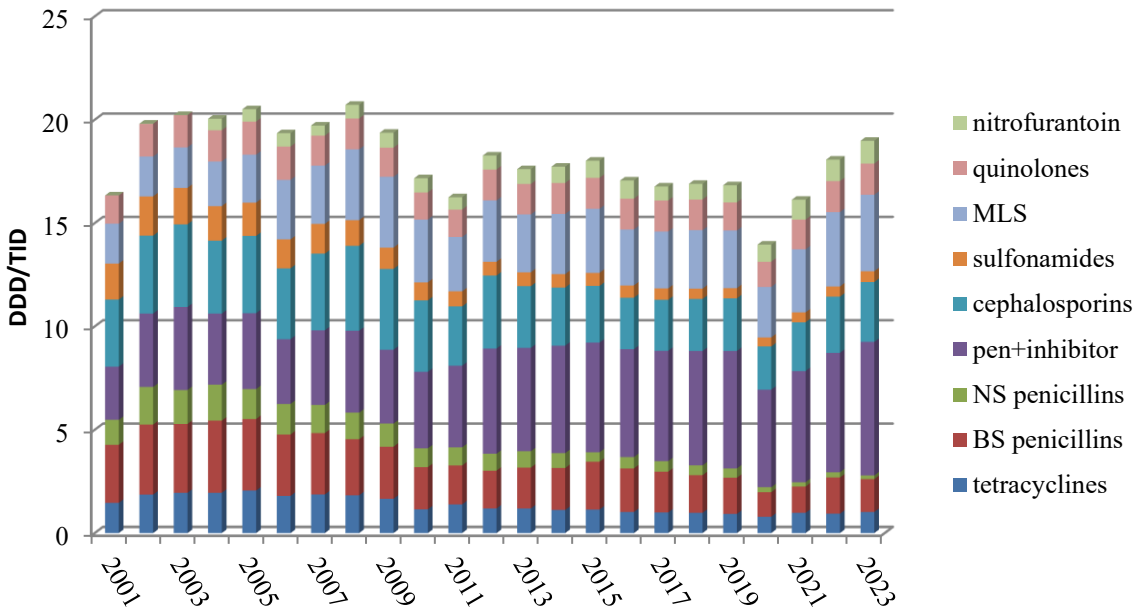
Indikator potrošnje antibiotika koji pokazuje omjer potrošnje širokospektralnih antibiotika u odnosu na uskospektralne nakon kratkotrajnog silaznog trenda prošle godine (5,3), ponovno je porastao (6,2) (tablica 5, slika 4).

I dalje je omjer potrošnje širokospektralnih penicilina s inhibitorima beta-laktamaza (J01CR) i širokospektralnih penicilina bez inhibitora (J01CA) iznosi četiri, odnosno nije se značajnije promjenio u odnosu na prethodne godine kada je iznosio 4,2.

2023. godinu karakterizira porast ambulantne potrošnje antibiotika na vrijednost 19,14 DDD/TID, što je i najviša potrošnja u zadnjih niz godina. Udio ambulantne potrošnje uobičajeno iznosi preko 90 % (90,2%) u ukupnoj potrošnji antibiotika. Vodeća klasa antibiotika s najvećim udjelom u potrošnji su penicilini s 43 %. Koamoksiklav je vodeći antibiotik u ambulantnoj potrošnji s višom vrijednošću potrošnje u odnosu na prethodnu godinu. Četiri puta manje se trošilo penicilina širokog spektra bez inhibitora (amoksicilin/ampicilin) u odnosu na koamoksiklav, dok najmanji udio u potrošnji te skupine antibiotika čine uskospektralni beta laktamskih antibiotici. Druga najzastupljenija skupina antibiotika u ambulantnoj potrošnji su makrolidi i linkozamidi (19 %), dok su na trećem mjestu ostali betalaktamski antibiotici (cefalosporini) s udjelom od 15 %. U toj skupini se bilježi porast 3. i 4. generacije cefalosporina.
Upala mokraćnog sustava je infekcija za koju se propisuje najviše antibiotika. Potrošnja nitrofurantoina zadnje tri godine je u porastu (0,96; 1,04; 1,10 DDD/TID. Infekcije dišnog sustava najzastupljenije su dijagnoze (7 od 10) među prvih deset za koje se propisuju antibiotici. U zimskim mjesecima godine bilježi se značajno viša potrošnja antibiotika nego u proljetno-ljetnim mjesecima, što ukazuje na veliku potrošnju antibiotika za liječenje respiratornih infekcija koje su većinom uzrokovane virusima.

Indikator potrošnje antibiotika koji pokazuje omjer potrošnje širokospektralnih antibiotika u odnosu na uskospektralne ponovno je porastao nakon prošle godine, kada je, nakon nekoliko, godina zabilježen pad.

Slika 1. */ Figure 1.*
Ambulantna potrošnja antibiotika (DDD/TID) u Hrvatskoj, 2001 – 2023.
Ambulatory antibiotic consumption (DDD/TID) in Croatia, 2001 – 2023



Outpatient Antibiotic Consumption

Croatia has been involved in monitoring antibiotic consumption from the very beginning in 2001, as part of the European Surveillance of Antibiotic Consumption (ESAC) network and in compliance with its standards.

Data on outpatient antibiotic consumption is collected from the Croatian Health Insurance Fund (CHIF) and through wholesale pharmacies, while on hospital consumption from both hospital and wholesale pharmacies. Therefore, outpatient and hospital antibiotic consumption are presented separately.

Data on the use of antibiotics is collected in accordance with the Anatomical Therapeutic Chemical (ATC) classification of drugs at the 5th level, while consumption itself is presented at the 4th and 3rd levels of the ATC classification.

The use of antibiotics is expressed in defined daily doses (DDDs) per 1,000 inhabitants per day (DDD/TID). The ATC/DDD index is updated annually and is available on the website of the WHO Collaborating Centre for Drug Statistics Methodology (http://www.whocc.no/atc_ddd_index).

Outpatient antibiotic consumption is expressed per 1,000 inhabitants per day (DDD/1000/day). The number of inhabitants used as the denominator for calculating consumption is 3,871,833, according to the Croatian census of 2021. Hospital antibiotic consumption is expressed both in DDD per 1,000 inhabitants per day (TID) and in DDD per 100 hospital bed days (DDD/100 BDs).

By participating in the European Surveillance of Antimicrobial Consumption Network (ESAC-Net), which is an obligation of every European Union member state, Croatia is able to compare its consumption with other countries included in the network through The European Surveillance System (TESSy) data entry platform.

Although outpatient antibiotic consumption data is collected from two sources, since 2012 the official data on outpatient consumption has been that obtained from the CHIF reimbursement data. Variations in consumption arising from different sources of data are apparent, as shown in Table 3; Figure 2. Higher consumption is observed in data provided by pharmaceutical wholesalers. In 2023, this difference, when compared to data obtained from the CHIF, was 3.14 DDD/TID, which is 0.54 DDD/TID more than in the previous year (2.6 DDD/TID).

This disparity is evident across all classes of antibiotics, the largest being, as in previous years, in the penicillin class (1.78 DDD/TID) and the macrolide-lincosamide-streptogramin class (0.52 DDD/TID) (Table 4; Figure 3), where it is considerable when compared to the previous year (1.42 DDD/TID; 0.47 DDD/TID). Variations are also noticeable in other classes of antibiotics, but they are significantly smaller (Table 4; Figure 3). The reasons for this include the prescribing of antibiotics by doctors in private healthcare facilities, which is not recorded through red prescriptions and therefore not registered by the CHIF. Another reason is the direct supply of antibiotics to outpatient clinics from wholesale pharmacies, particularly for parenteral therapy needs. This may explain the increase in the consumption of cephalosporins, especially third generation (ceftriaxone), and aminoglycosides (gentamicin), whose consumption increased tenfold compared to the previous year.

Figure 1 shows the results of continuous monitoring of outpatient antibiotic consumption in Croatia since 2001, revealing significant fluctuations over this twenty-three-year period. These fluctuations reflect changes in the numerator (the number of DDDs consumed), and sometimes, though rarely, alterations in antibiotic formulation (e.g., co-amoxiclav in 2002, when the concentration of amoxicillin in the daily dose was increased), and the denominator, which is the size of population. According to the census, this number changes every ten years. Croatian population has been in decline, which affects the recorded consumption of antibiotics.

However, since the last census (2021), there has been a continuous upward trend in ambulatory consumption expressed in DDD/TID in 2021, 2022, and 2023 (16.22; 18.18; 19.14). In 2023, outpatient antibiotic consumption reached its highest value recorded in the past decade.

In 2023, a negative trend was observed in one of the indicators of antibiotic consumption, expressed as the ratio of outpatient consumption in DDD per thousand inhabitants per day (DDD/TID) of broad-spectrum penicillins, beta-lactams with inhibitors, second and third-generation cephalosporins, macrolides (except erythromycin), and fluoroquinolones (J01 (CR+DC+DD+FA-FA01)+MA) to the consumption of broad-spectrum penicillins without inhibitors (amoxicillin), narrow-spectrum penicillins, first-generation cephalosporins, and erythromycin (J01 (CA+CE+CF+DB+FA01) (Table 5; Figure 4). This consumption ratio amounted to 6.2, indicating an increase in the usage of broad-spectrum antibiotics compared to narrow-spectrum ones, unlike the previous year when this ratio decreased compared to the year before.

In 2023, the consumption of tetracyclines grew, exceeding 1 DDD/TID (1.02) for the first time in seven years. Unfortunately, the trend of increased usage of broad-spectrum penicillins without inhibitors (J01CA) did not continue. In the previous year this increase was encouraging and led to the expectation that it would persist, so that the consumption of broad-spectrum penicillins without inhibitors might at least approach the usage of broad-spectrum penicillins with inhibitors, given that these antibiotics are empirically recommended for the treatment of upper respiratory tract infections, in accordance with the guidelines provided by ISKRA (The Interdisciplinary Section for Antibiotic Resistance Control). Unfortunately, the group of broad-spectrum penicillins with beta-lactamase inhibitors (J01CR) recorded highest consumption value of 6.46 DDD/TID, which is a significant increase of 0.68 DDD/TID.

The ratio of the consumption of broad-spectrum penicillins with beta-lactamase inhibitors (J01CR) to broad-spectrum penicillins without inhibitors (J01CA) was 4.0, which is slightly lower compared to the previous two years when it was 4.2.

The share of narrow-spectrum penicillins (J01CE and J01CF) in the overall antibiotic consumption was 2.4%, the smallest in the penicillin group of antibiotics. Narrow-spectrum penicillins (J01CE) show a decrease in consumption (from 0.25 DDD/TID in 2022 to 0.18 DDD/TID in 2023), while the usage of beta-lactamase-resistant penicillins (J01CF) increased, reaching its highest level to date (0.02 DDD/TID) (Table 1).

In the cephalosporin class (J01D), there was an increase in the consumption of 1st and 3rd generations, while there were no significant changes for 2nd generation. In 2023, the consumption of sulfonamides + trimethoprim (J01EE), macrolides and lincosamides (J01F), aminoglycosides (J01G), and nitrofurantoin (J01XE) and fosfomycin (J01XX) increased. The usage of quinolones (J01M) remained at almost the same level as the year before.

In 2023 outpatient antibiotic consumption in Croatia reached its highest level in the last ten years, amounting to 19.14 DDD/TID, which accounted for 90.2% of the total use of antibiotics in Croatia.

In Table 6 and Figure 5, antibiotics are ranked according to their consumption frequency – a "top list" of the most commonly prescribed ones. The top six did not change and they retained the same order of frequency as the year before. Co-amoxiclav remained in the first place, followed by azithromycin, cefuroxime, and amoxicillin. In the fifth place was nitrofurantoin, with slightly higher consumption (1.10 DDD/TID), and doxycycline (1.02 DDD/TID), whose consumption also rose above 1 DDD/TID.

Another indicator of ambulatory use of antibiotics is quarterly consumption, which does not show significant differences in countries with low antibiotic consumption, such as the Netherlands. However, in our country, usage of antibiotics is noticeably higher in the winter months, i.e., in the first and last quarter of the year (5.32; 4.25; 3.93; 5.64) (Table 7; Figure 6).

The ranking of the top ten diagnoses for which antibiotics were prescribed in outpatient setting is almost identical to the one in previous year. In the first place is bladder inflammation (cystitis) (N30), the treatment of which amounts to 1.96 DDD/TID of antibiotics, nearly identical to the year before (1.95 DDD/TID). Two other diagnoses related to urinary tract infections are among the top ten: urinary tract infection, site not specified (N39.0), and other disorders of the urinary system (N39). Antibiotics used for treating infections under these diagnoses amounted to 1.07 DDD/TID. The total consumption of antibiotics for treating urinary tract infections was 3.03 DDD/TID, which is slightly higher than the year before when it was 2.97 DDD/TID.

Other diagnoses among the leading ten for which antibiotics were prescribed relate to respiratory tract infections. In the second place is acute pharyngitis (J02), followed by acute tonsillitis (J03), acute sinusitis (J01), acute upper respiratory tract infection (J06), and in the sixth place is acute bronchitis (J20). The eighth is non-suppurative otitis media (H65), and the tenth is periapical abscess (K04.7). The consumption of antibiotics for treating infections with these diagnoses, among the top ten, amounts to 5.56 DDD/TID, which is an increase compared to the preceding year (4.97 DDD/TID) (Table 8, Figure 7).

These "Top 10" diagnoses for which antibiotics were most commonly prescribed in outpatient settings indicate that one-third of the consumption related to the treatment of urinary infections, while two-thirds were used for respiratory ones. This extremely unfavourable ratio indicates improper, often unjustified, treatment of respiratory infections with antibiotics, despite the fact that they are mostly caused by viruses.

In 2023 usage of antibiotics in ambulatory setting continued to rise, reaching its highest level in the last fifteen years of monitoring.

Outpatient consumption accounted for 90.2% of the total antibiotic use, which is a typical proportion reflecting the division between outpatient and hospital consumption.

In outpatient setting, the ranking of antibiotic classes according to their usage is as follows: the penicillin class holds the top spot (8.25 DDD/TID), followed by macrolides and lincosamides with 3.7 DDD/TID. Cephalosporins are in third place with 2.91 DDD/TID. Quinolones are fourth with 1.51 DDD/TID, followed by the "other J01X" group with 1.21 DDD/TID, tetracyclines (J01A) with 1.02 DDD/TID, and lastly, sulfonamides with trimethoprim (0.52 DDD/TID).

The penicillin class remains the most represented in ambulatory usage with 43%. An increase in consumption was recorded across all classes except quinolones, which remained at previous year's levels. Within the penicillin class, there is a decline in the use of broad-spectrum penicillins (J01CA) and narrow-spectrum penicillins (J01CE). A positive trend is the increase in the consumption of beta-lactamase-resistant penicillins (J01CF), which are the first-line treatment for infections caused by *S. aureus*. However, there is a worrying trend in the continued rise in the use of the amoxicillin and beta-lactamase inhibitor combination, which exceeded 6 DDD/TID, reaching 6.46, the highest value recorded to date (Table 1).

The trend of increasing nitrofurantoin consumption has continued over recent years (0.68; 0.76; 0.83; 0.83; 0.96; 1.04; 1.10 DDD/TID), which is a favourable indicator, given that cystitis is the leading diagnosis for prescribing antibiotics in outpatient practice, and its use aligns with national guidelines for antibiotic prescribing.

The indicator of antibiotic consumption showing the ratio of broad-spectrum to narrow-spectrum antibiotic use increased again after a brief downward trend the year before (from 5.3 to 6.2) (Table 5, Figure 4).

The ratio of broad-spectrum penicillins with beta-lactamase inhibitors (J01CR) to broad-spectrum penicillins without inhibitors (J01CA) remained at 4, indicating no significant change compared to previous years when it was 4.2.

The year 2023 is characterized by an increase in outpatient antibiotic consumption to 19.14 DDD/TID, the highest level in recent years. Ambulatory consumption , as usual, accounts for over 90% (90.2%) of total antibiotic use. The leading class of antibiotics with the largest share in consumption is penicillins at 43%, with co-amoxiclav retaining the top position in outpatient environment, with higher usage than the previous year. Broad-spectrum penicillins without inhibitors (amoxicillin/ampicillin) were used four times less than co-amoxiclav, while narrow-spectrum beta-lactam antibiotics have the smallest share in this group’s consumption. The second most represented group in outpatient setting is the one of macrolides and lincosamides (19%), followed by other beta-lactam antibiotics (cephalosporins) with a

15% share. In this group, there was an increase in the consumption of 3rd and 4th generation cephalosporins.

Urinary tract infections were the leading cause for which antibiotics were prescribed. Nitrofurantoin consumption has been increasing over the past three years (0.96; 1.04; 1.10 DDD/TID). Respiratory tract infections were the most common diagnoses (7 out of top 10) for which antibiotics were prescribed. In the winter months, antibiotic consumption was significantly higher than in the spring-summer months, indicating substantial use of antibiotics for treating respiratory infections, which are mostly caused by viruses.

The indicator of antibiotic consumption, which shows the ratio in use of broad-spectrum to narrow-spectrum antibiotics, increased again after 2022, when a decrease was recorded for the first time in several years.

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

ATC šifra ATC code	ANTIBIOTIK ANTIBIOTIC	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023
J01AA	Tetraciklini Tetracylines	1,19	1,12	1,14	1,02	1,00	0,98	0,93	0,79	0,98	0,94	1,02
J01CA	Penicilini širokog spektra Broad spectrum penicillins	1,98	2,03	2,31	2,11	1,97	1,82	1,75	1,19	1,27	1,75	1,59
J01CE	Penicilini uskog spektra Narrow spectrum penicillins	0,79	0,72	0,46	0,55	0,51	0,48	0,45	0,24	0,21	0,25	0,18
J01CF	Beta-laktamaza rezistentni penicilini Beta-lactamase resistant penicillins	0,00	0,00	0,01	0,00	0,01	0,01	0,01	0,01	0,01	0,01	0,02
J01CR	Kombinacije s beta-laktamaza inhibitorima Combinations with inhibitors	5,00	5,20	5,31	5,22	5,34	5,53	5,68	4,72	5,38	5,78	6,46
J01DB	Cefalosporini I gen. Cephalosporins	0,77	0,72	0,66	0,60	0,47	0,38	0,35	0,27	0,29	0,36	0,39
J01DC	Cefalosporini II gen. Cephalosporins	1,77	1,85	1,85	1,69	1,67	1,73	1,72	1,38	1,46	1,61	1,60
J01DD	Cefalosporini III gen. Cephalosporins	0,45	0,24	0,23	0,20	0,33	0,41	0,49	0,44	0,61	0,75	0,92
J01EE	Sulfonamides + trimethoprim	0,67	0,65	0,63	0,59	0,55	0,50	0,49	0,44	0,48	0,49	0,52
J01F	Macrolides, lincosamides	2,80	2,91	3,10	2,71	2,75	2,83	2,79	2,44	3,05	3,60	3,70
J01G	Aminoglikozidi Aminoglycosides	0,00	0,04	0,01	0,00	0,01	0,01	0,004	0,003	0,003	0,002	0,02
J01MA	Fluorokinoloni Fluoroquinolones	1,47	1,50	1,50	1,49	1,50	1,48	1,36	1,22	1,44	1,50	1,51
J01XE	Nitrofurantoin	0,72	0,79	0,83	0,88	0,68	0,76	0,83	0,83	0,96	1,04	1,10
J01XX	Fosfomycin	-	-	-	0,004	0,05	0,08	0,08	0,08	0,09	0,09	0,11
UKUPNO TOTAL		**17,60**	**17,80**	**18,00**	**17,10**	**16,80**	**17,00**	**16,94**	**14,05**	**16,22**	**18,18**	**19,14**

* 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)

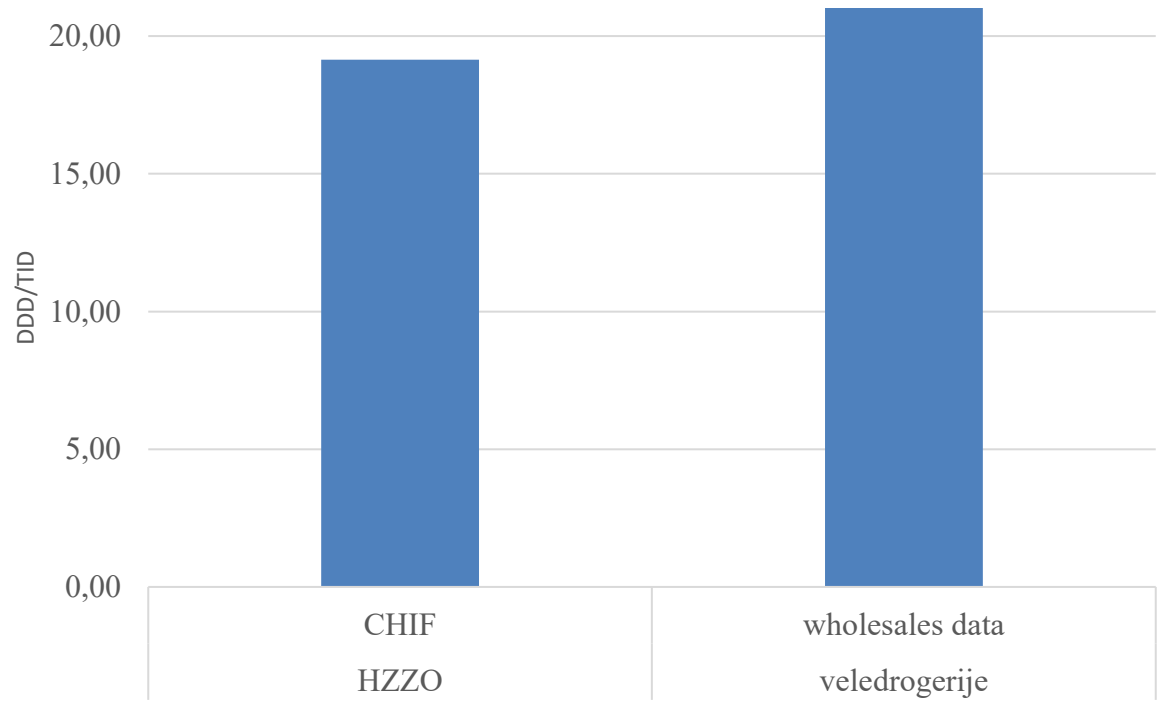
ATC šifra ATC code	ANTIBIOTIK ANTIBIOTIC	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023
J01AA	Tetraciklini Tetracylines	0,05	0,04	0,04	0,04	0,04	0,03	0,04	0,03	0,03	0,03	0,03
J01CA	Penicilini širokog spektra Broad spectrum penicillins	0,04	0,02	0,02	0,03	0,02	0,02	0,02	0,02	0,02	0,03	0,02
J01CE	Penicilini uskog spektra Narrow spectrum penicillins	0,03	0,02	0,02	0,02	0,02	0,02	0,02	0,01	0,01	0,01	0,02
J01CF	Beta-laktamaza rezistentni penicilini Beta-lactamase resistant penicillins	0,03	0,03	0,03	0,03	0,04	0,04	0,04	0,03	0,03	0,04	0,04
J01CR	Kombinacije s beta-laktamaza inhibitorima Combinations with inhibitors	0,35	0,37	0,38	0,37	0,38	0,40	0,42	0,33	0,40	0,42	0,43
J01DB	Cefalosporini I gen. Cephalosporins	0,08	0,09	0,10	0,10	0,10	0,09	0,10	0,08	0,09	0,10	0,11
J01DC	Cefalosporini II gen. Cephalosporins	0,21	0,20	0,17	0,19	0,20	0,20	0,20	0,15	0,16	0,15	0,15
J01DD + J01DE	Cefalosporini III + IV gen. Cephalosporins	0,15	0,18	0,18	0,16	0,17	0,16	0,17	0,19	0,24	0,24	0,27
J01DH	Carbapenems	0,05	0,06	0,06	0,06	0,08	0,07	0,08	0,09	0,12	0,12	0,13
J01EE	Sulfonamides + trimethoprim	0,04	0,05	0,04	0,04	0,04	0,04	0,04	0,03	0,03	0,04	0,04
J01F	Macrolides, lincosamides	0,15	0,14	0,15	0,15	0,16	0,16	0,18	0,19	0,21	0,21	0,22
J01G	Aminoglikozidi Aminoglycosides	0,10	0,10	0,10	0,09	0,09	0,09	0,09	0,07	0,08	0,09	0,09
J01MA	Fluorokinoloni Fluoroquinolones	0,19	0,20	0,21	0,21	0,23	0,24	0,24	0,20	0,24	0,24	0,25
J01XA	Glycopeptides	0,03	0,03	0,04	0,03	0,04	0,05	0,05	0,05	0,07	0,07	0,07
J01XD	Metronidazole	0,08	0,09	0,10	0,10	0,11	0,15	0,12	0,10	0,12	0,12	0,14
J01XE	Nitrofurantoin	0,01	0,02	0,01	0,01	0,01	0,01	0,01	0,01	0,02	0,02	0,02
J01XX	Fosfomycin	-	-	-	0,001	0,02	0,02	0,02	0,02	0,04	0,04	0,05
UKUPNO TOTAL		**1,58**	**1,65**	**1,70**	**1,65**	**1,74**	**1,80**	**1,85**	**1,61**	**1,93**	**1,98**	**2,08**

** 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	27160086,44	31628065,06
DDD/TID	19,14	22,28

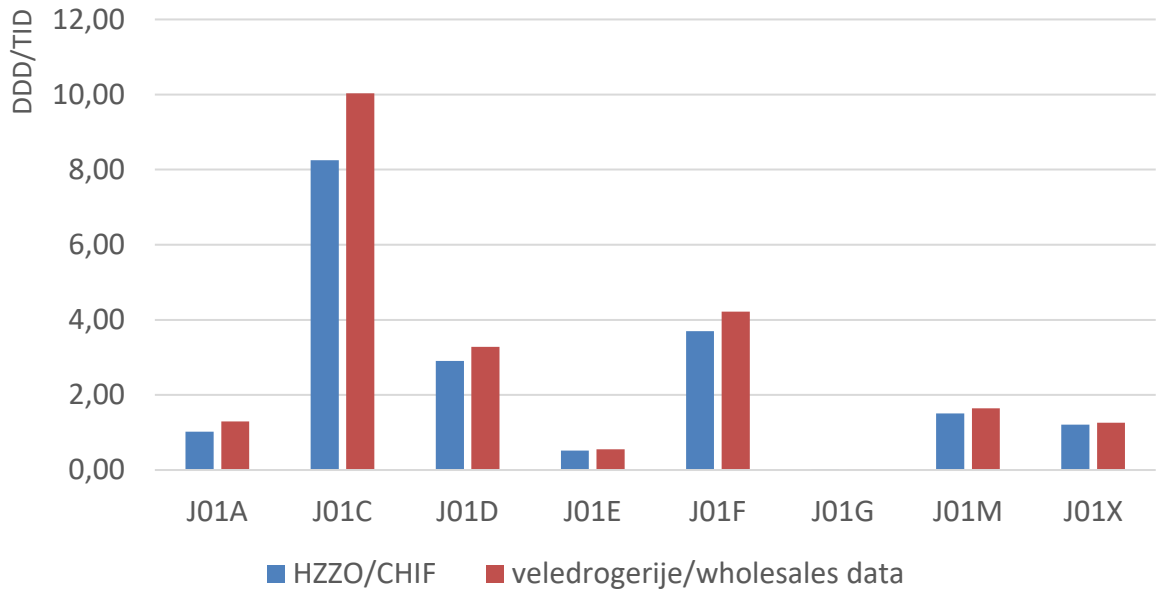
Slika 2. */ Figure 2.*
Ambulantna potrošnja antibiotika (DDD/TID) usporedba podataka HZZO i veledrogerija
Ambulatory antibiotic consumption (DDD/TID) comparison between CHIF data and wholesales data



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	1,02	1,29
J01C	8,25	10,03
J01D	2,90	3,28
J01E	0,52	0,55
J01F	3,70	4,22
J01G	0,02	0,01
J01M	1,51	1,64
J01X	1,21	1,26

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

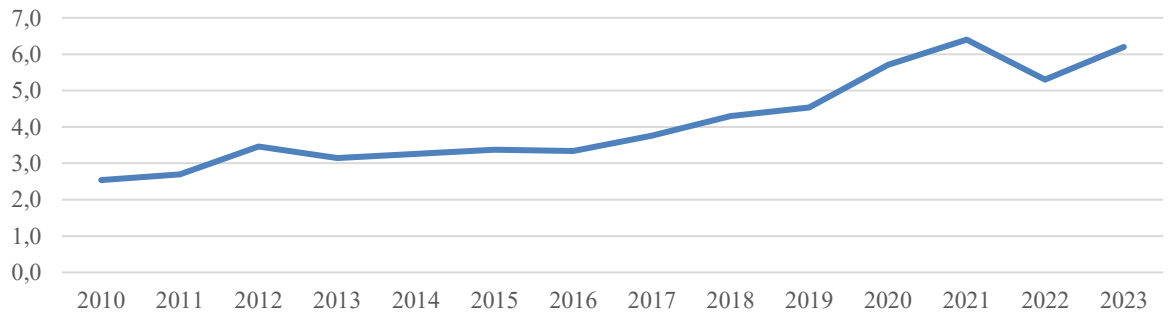


Tablica 5./ *Table 5.*
Omjer izvanbolničke potrošnje izražene u DDD na tisuću stanovnika na dan, penicilina širokog spektra, cefalosporina, makrolida (osim eritromicina) i fluorokinolona i potrošnje izražene u DDD na tisuću stanovnika na dan, penicilina uskog spektra, cefalosporina i eritromicina u razdoblju 2010-2023/
The ratio of consumption of broad-spectrum penicillins, cephalosporins, macrolides (except erythromicin) and fluoroqinolones to the consumption of narrow-spectrum penicillins, cephalosporins and erythromicin expressed as DDD per 1000 inhabitants per day in the community 2010-2023

	Omjer potrošnje antibiotika
2010	2,5
2011	2,7
2012	3,5
2013	3,1
2014	3,3
2015	3,4
2016	3,3
2017	3,8
2018	4,3
2019	4,5
2020	5,7
2021	6,4
2022	5,3
2023	6,2

Slika 4./ *Figure 4.*
Omjer izvanbolničke potrošnje izražene u DDD na tisuću stanovnika na dan, penicilina širokog spektra, cefalosporina, makrolida (osim eritromicina) i fluorokinolona i potrošnje izražene u DDD na tisuću stanovnika na dan, penicilina uskog spektra, cefalosporina i eritromicina u razdoblju 2010-2023/

The ratio of consumption of broad-spectrum penicillins, cephalosporins, macrolides (except erythromicin) and fluoroqinolones to the consumption of narrow-spectrum penicillins, cephalosporins and erythromicin expressed as DDD per 1000 inhabitants per day the community 2010-2023

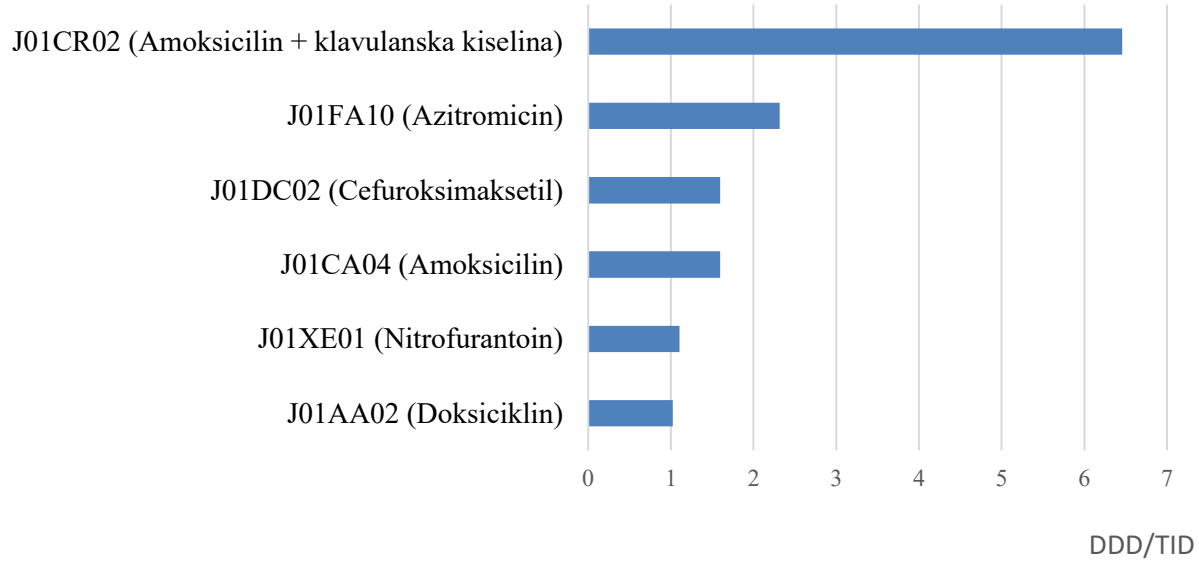


Tablica 6. / *Table 6.*

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

Klasa / class	DDD/TID
J01CR02 (Amoksicilin + klavulanska kiselina)	6,46
J01FA10 (Azitromicin)	2,31
J01DC02 (Cefuroksimaksetil)	1,60
J01CA04 (Amoksicilin)	1,59
J01XE01 (Nitrofurantoin)	1,10
J01AA02 (Doksiciklin)	1,02

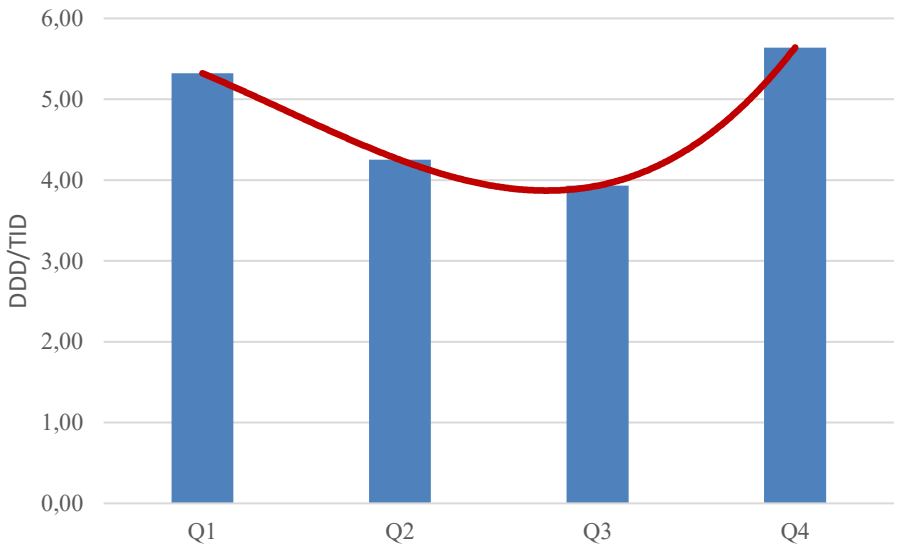
Slika 5. */ Figure 5.*
Ambulantna potrošnja antibiotika („top 6“ antibiotika – DDD/TID), izvor podataka – HZZO
Ambulatory antibiotic consumption („top 6“antibiotics- DDD/TID); origin of data-CHIF



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

kvartal	DDD/TID
I	5,32
II	4,25
III	3,93
IV	5,64

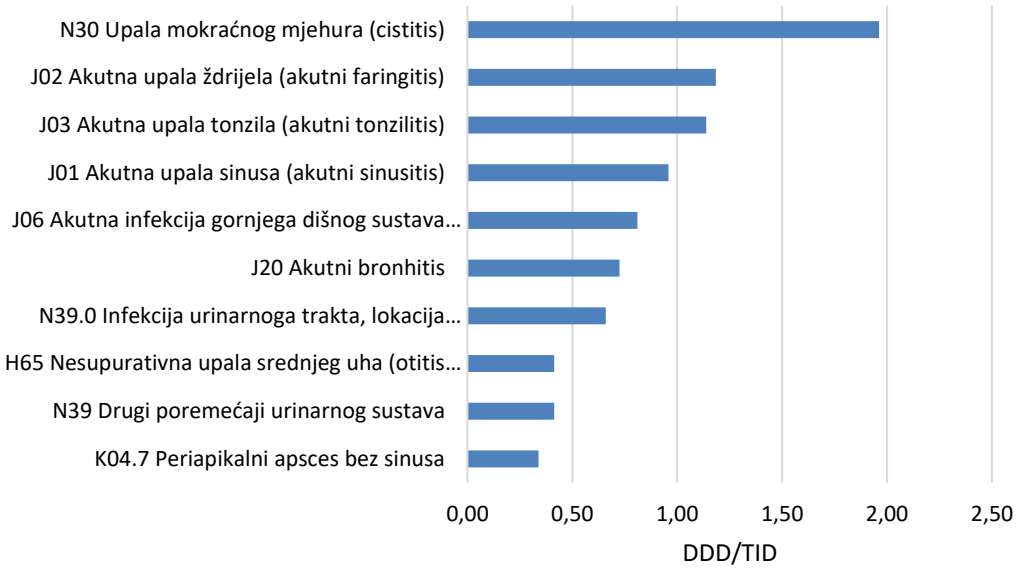
Slika 6. */ Figure 6.*
Ambulantna potrošnja antibiotika po kvartalima – DDD/TID, izvor podataka – HZZO
Ambulatory antibiotic consumption – by quarters DDD/TID; origin of data-CHIF



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)	1,96
J02 Akutna upala ždrijela (akutni faringitis)	1,18
J03 Akutna upala tonzila (akutni tonzilitis)	1,14
J01 Akutna upala sinusa (akutni sinusitis)	0,96
J06 Akutna infekcija gornjega dišnog sustava multiplih i nespecifici	0,81
J20 Akutni bronhitis	0,72
N39.0 Infekcija urinarnoga trakta, lokacija neoznačena	0,66
H65 Nesupurativna upala srednjeg uha (otitis media nonsuppurativa)	0,41
N39 Drugi poremećaji urinarnog sustava	0,41
K04.7 Periapikalni apsces bez sinusa	0,34

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

Potrošnja antibiotika u hrvatskim bolnicama ima dugu tradiciju i prati se odvojeno od ambulantne potrošnje. Od 2011. godine bolnička potrošnja se prati iz dva izvora, podataka dobivenih od veledrogerija te, zahvaljujući Interdisciplinarnoj sekciji za kontrolu rezistencije (ISKRA) pri Ministarstvu zdravstva i iz bolničkih ljekarni.
Podaci dobiveni putem bolničkih ljekarni dostavljaju se u europski program praćenja potrošnje ESAC-Net (tablica 2).
Podatke o potrošnji antibiotika bolnice dostavljaju u paketima ili komadima uz administrativne podatke o broju bolničkoopskrbnih dana (BOD) i broju primitaka za čitavu bolnicu te odvojeno za jedinice intenzivnog liječenja (JIL) po vrstama (mješoviti, kirurški, internistički, pedijatrijski). Od 2011. godine u praćenje bolničke potrošnje uključena je i potrošnja antibiotika u dnevnim bolnicama, a denominatoru su uz bolničke dane pridruženi terapijski dani dnevne bolnice.
Podaci o potrošnji antibiotika prikupljaju se u skladu s ATK klasifikacijom na petoj razini, a prikazuju na 3. i 4. razini.
Podaci o bolničkoj potrošnji iskazuju se u DDD/1000 stanovnika po danu (DDD/TID) (tablica 2).

Zahvaljujući prikupljanju podataka o potrošnji antibiotika putem bolničkih ljekarni te istovremeno prikupljanju administrativnih podataka o broju bolničkoopskrbnih dana (BOD), u mogućnosti smo iskazivati potrošnju i u DDD/100 BOD. Na taj način pokazatelji potrošnje su precizniji, što omogućava minuciozno praćenje potrošnje za svaku bolnicu, ali i kretanje ukupne potrošnje, i potrošnje po klasama i podskupinama unutar klase na nacionalnom nivou.

U tablici 9 i na slici 8 usporedno su prikazani podaci od 2014. godine dobiveni iz oba izvora. Bilježi se veća potrošnja prema podacima dobivenim iz bolničkih ljekarni (osim u 2015. godini) i porast razlike u potrošnji u korist bolničke potrošnje prema podacima dobivenim iz bolničkih ljekarni. U 2023. godini razlika je iznosila 0,37 DDD/TID, što je manje u odnosu na prethodnu godinu kada je utvrđena najveća razlika koja je iznosila 0,51 DDD/TID (tablica 9; slika 8).

Šezdesetosam bolnica je poslalo podatke elektronskim putem na adresu iskra.antibiotici@gmail.com o potrošnji antibiotika u 2023. godini. Kao i prethodnih godina samo 4 bolnice su direktno eksportirale podatke iz ljekarničkih programa. Prema ustaljenoj praksi, a nakon obrade podataka svaka bolnica je dobila svoje obrađene podatke za prethodnu godinu na provjeru i usporedbu s prethodnim godinama.

Bolnička potrošnja antibiotika porasla je u odnosu na prethodne godine. Po prvi puta iznosi više od 2,00 (2,08 DDD/TID) (tablica 2), kada se izražava u DDD na 1000 stanovnika po danu. Iskazana na 100 BOD-a, odnosno kada se kao denominator koriste administrativni podaci bolnica (broj bolničkih dana) ne bilježi se porast, već je vrijednost bolničke potrošnje identična prošlogodišnjoj vrijednosti (45,20 DDD/100 BOD) (tablica 10, slika 9).

S obzirom na identičnu bolničku potrošnju antibiotika iskazanu u DDD/100 BOD ne uočavaju se značajne razlike niti u potrošnji pojedinih klasa antibiotika u zadnje dvije godine (tablica 2). Najveća razlika se uočava kod klase cefalosporina (J01D).

Vodeća klasa u bolničkoj potrošnji antibiotika su cefalosporini s udjelom od 32 %, sljede ju penicilini (24,5 %), zatim fluorokinoloni (12 %). Slična fluorokinolonima po udjelu u bolničkoj potrošnji je skupina makrolida+linkozamida (10,6 %). Aminoglikozidi su na petom mjestu s udjelom od 4,3 %. Slijede ih sulfonamidi +trimetoprim (1,9 %), zatim tetraciklini (1,4 %) kod kojih nema promjena.

Rang lista vodećih pet antibiotika u bolničkoj potrošnji ostala je ista kao i prethodne godine s malim razlikama u potrošnji zadnje dvije godine. Koamoksiklav i dalje čvrsto drži vodeću poziciju s 8,11 DDD/100 BOD, što je nešto manje u odnosu na prošlu godinu (8,26 DDD/100 BOD). Na drugom mjestu je ceftriakson, čija je potrošnja porasla u odnosu na prethodnu godinu (4,73 DDD/100 BOD u usporedbi s 4,41 DDD/100 BOD u 2022. godini).

Na trećem mjestu je cefuroksimaksetil kojem potrošnja i dalje pada (3,15 DDD/100BOD) u odnosu na prijašnje godine (3,39 DDD/100 BOD u 2022.u odnosu na 3,69 DDD/100 BOD 2021.), na četvrtom ciprofloksacin s nešto nižom potrošnjom (3,12 DDD/100 BOD) u odnosu na godinu prije (3,19 DDD/100 BOD. Na petom mjestu je metronidazol s potrošnjom od 3,02 DDD/100 BOD, umjesto azitromicina, koji je pao po potrošnji ispod petog mjesta. (tablica 12; slika 11).

Kao indikator bolničke potrošnje antibiotika prati se udio potrošnje rezervnih antibiotika glikopeptida (J01XA), cefalosporina III. generacije (J01DD), cefalosporina IV. generacije (J01DE), monobaktama (J01DF), karbapenema (J01DH), fluorokinolona (J01MA), polimiksina (J01XB), piperacilin+tazobaktama (J01CR05), linezolida (J01XX08), tedizolida (J01XX11) i daptomicina (J01XX09) u ukupnoj bolničkoj potrošnji. U 2023. godini udio je ostao gotovo isti 39 %, kao i prethodne godine (38,9 %) te je time zaustavljen trend kontinuiranog povećanja udjela rezervnih antibiotika u ukupnoj potrošnji u zadnjih pet godina praćenja (tablica 13, slika 12).

Sve **kliničke ustanove**, njih trinaest je dostavilo podatke o potrošnji antibiotika (tablica 14, slika 13). Raspon potrošnje antibiotika u 2023. godini kretao se od 27,68 (K11) do 172,81 DDD/100 BOD (K02), što je značajnije veći raspon nego u prošloj godini, kada se kretao od 26,19 do 138,50 DDD/100 BOD (tablica 15; slika 14). S ozirom da se radi o vrlo različitim kliničkim ustanovama, od kojih su neke specijalizirane, na primjer samo za kirurške zahvate, a neke samo za liječenje infektivnih bolesnika, odnosno treće su mješovitog tipa, raspon potrošnje je očekivano velik.

Kod šest kliničkih ustanova (K 01; K 02; K 05; K 09; K 11; K13) uočava se porast potrošnje antibiotika. Od tih šest kliničkih ustanova kod tri ustanove (02, 09 i 13) se prati kontinuirani porast potrošnje kroz godine. Kod kliničke ustanove K 02 bilježi se veliki skok u potrošnji u zadnjoj godini za 34,31 DDD/100 BOD u odnosu na prethodnu godinu. I kod K 09 uočen je velik skok u potrošnji antibiotika (za 13,7 DDD/100 BOD). Samo kod dvije kliničke ustanove došlo je do pada potrošnje (K 04; K 15), od kojih je uočljiv nastavak pada potrošnje za ustanovu K04. Kod pet kliničkih ustanova (K03; K06; K07; K08; K14) nema značajnijih promjena u potrošnju, odnosno razlika u potrošnji je manja od jednog DDD na 100 BOD u zadnje dvije godine.

U 2023. godini 22 **opće bolnice** su dostavile svoje podatke o potrošnji antibiotika. S obzirom da je ta grupa bolnica slična po djelokrugu rada i vrstama odjela, rezultati su međusobno usporedivi. Potrošnja antibiotika se kretala u širokom rasponu od 41,69 do 90,06 DDD/100 BOD (tablica 16), što je slično rezultatima prethodne godine. Veliki raspon, više nego dvostruko između bolnice s najnižom potrošnjom (O19) i bolnice s najvišom potrošnjom (O13) ukazuje na velike razlike u praksi propisivanju antibiotika.

Kod 10 bolnica bilježi se pad potrošnje antibiotika (O03; O05; O09; O10; O11; O14; O17; O19; O20; O24), što je za dvije bolnice manje nego u prethodnoj godini.

Kod čak 10 bolnica uočava se porast potrošnje (lani kod šest) (O01; O02; O04; O07; O08; O12; O13; O15; O22; O23), a kod dvije nema razlika većih od 1 DDD/100 BOD (O18; O21) u zadnje dvije godine (tablica 17.).

Na slici 15. je prikazana potrošnja u općim bolnicama prema pojedinim klasama antibiotika u 2023. godini. U tablici 17. i na slici 16. prikazana je potrošnja u općim bolnicama u zadnjih sedam godina što svakoj bolnici daje mogućnost praćenja vlastitih trendova potrošnje. Ističe se bolnica O13 kod koje se vidi kontinuirani trend porasta potrošnje kroz godine. Kod opće bolnice O02 bilježi se kontinuirani trend porasta potrošnje antibiotika u zadnje četiri godine. Nakon dostizanja visokih vrijednosti potrošnje (u 2022. godini 95,55 DDD/100 BOD) bolnica 09 je zaustavila trend porasta potrošnje, koji je bio uočen prošlih godina.
Najveći broj općih bolnica (9) bilježi potrošnju u rasponu od 51-60 DDD/100 BOD. Samo dvije bolnice (O14 i O19) bilježe potrošnju manju od 50 DDD/100 BOD, dok se četiri bolnice nalaze u krugu onih s najvišom potrošnjom (O07; O09; O10; O13), što je dvostruko više nego prošle godine.

Izdvajaju se bolnice O01 koja je u 2023. zabilježila značajan porast potrošnje čak za 14,33 DDD/100 BOD te bolnica O19 kod koje se uočava značajan pad potrošnje za 12,05 DDD/100 BOD.

Potrošnja antibiotika u **psihijatrijskim bolnicama** kreće se od 1,13 do 16,44 DDD/100 BOD (tablica 18). Na slici 17 prikazana je potrošnja po klasama antibiotika u psihijatrijskim bolnicama. U dvije bolnice (P06; P07) bilježi se porast potrošnje (za 1,54 i 1,16 DDD/100 BOD) u odnosu na prethodnu godinu. Kod svih ostalih bolnica (P 01; P 02; P 03; P 04; P 05; P08; P09) nema promjena u potrošnji većoj od 1 DDD/100 BOD. Radi se o skupini bolnica kod kojih je potrošnja antibiotika prilično stabilna.

U tablici 19 i na slici 18 prikazana je potrošnja u psihijatrijskim bolnicama u zadnjih sedam godina s uočljivim trendovima potrošnje. Psihijatrijske ustanove P 07 i P 09 nastavljaju s uzlaznim trendom potrošnje.

Specijalne bolnice su podijeljene u dvije velike skupine s obzirom na njihov sadržaj rada i kao takve bilježe velike raspone u potrošnji antibiotika. U prvoj skupini nalazi se 10 bolnica, koje su namijenjene liječenju (akutnom/kroničnom), dok je u drugoj skupini 14 ustanova namijenjeno rehabilitaciji (tablica 20; slika 19). U prvoj skupini ustanova raspon potrošnje antibiotika se kreće od 10,03 do 79,90 DDD/100 BOD. Pet bolnica (prošle godine samo dvije bolnice) bilježi porast potrošnje (S 01; S 02; S 04; S 18; S 21). Samo dvije bolnice (S 13; S 23) bilježe pad potrošnje, dok kod tri bolnice (S 03; S 19; S 22) nema razlika većih od 1 DDD/100 BOD (tablica 21; slika 20).

U skupini specijalnih bolnica namijenjenih rehabilitaciji kretanje potrošnje antibiotika je značajno niže i kreće se od 1,11 do 6,65 DDD/100 BOD (tablica 21; slika 20). Samo bolnica S25 ima zabilježen porast potrošnje, dok je pad zabilježen kod 4 bolnice (S 05; S06; S07; S14). Kod svih ostalih potrošnja je ujednačena s prethodnom godinom i ne odstupa više ili manje od 1 DDD/100 BOD.

Na slici 19. prikazana je potrošnja antibiotika po klasama u 2023. godini. U tablici 21. i na slici 20. prikazana je potrošnja u specijalnim bolnicama u zadnjih sedam godina.

Bolnička potrošnja antibiotika u Hrvatskoj je velika. Po prvi puta je premašila 2,0 DDD/100 BOD. Iako čini manje od 10 % ukupne potrošnje, bolnička potrošnja pojedinih klasa i podskupina se značajno razlikuje od ambulantne potrošnje. Izražena u DDD na 100 BOD bolnička potrošnja antibiotika bilježi istu vrijednost zadnje dvije godine, dok izražena na 1000 stanovnika po danu je porasla u odnosu na prošlu godinu (2,08 DDD/TID u odnosu na 1,98 DDD/TID), što ukazuje na važnost denominatora i posebno naglašava vrijednost ovakvog načina praćenja bolničke potrošnje antibiotika, kojim je omogućeno precizno uočavanje promjena u bolničkoj potrošnji.

Najveći porast potrošnje se bilježi u klasi cefalosporina. Blaži porast se uočava u klasi tetraciklina i aminoglikozida. Kod ostalih klasa su manje razlike u potrošnji zadnje dvije godine.

Osobito je dobar pokazatelj prestanak rasta potrošnje skupine J01X (ostali) u kojoj se nalaze uglavnom rezervni antibiotici, a koja je zadnjih godina kontinuirano rasla.

U bolničkoj potrošnji antibiotika najzastupljenija klasa su cefalosporini i to 3. i 4. generacija cefalosporina. Koamoksiklav je antibiotik na prvom mjestu po potrošnji, a slijedi ga ceftriakson. Cefuroksimaksetil, ciprofloksacin i metronidazol podjednako su zastupljeni na trećem, četvrtom i petom mjestu po potrošnji.

Praćenjem potrošnje antibiotika na nivou pojedine bolnice uočavaju se velike razlike u praksi propisivanja antibiotika, kao i velike razlike u trendovima potrošnje antibiotika u pojedinim bolnicama. Za neke bolnice uočava se kontinuirani trend porasta potrošnje kroz godine. Sve to govori u prilog tome da još uvijek nije zaživjelo rukovođeno propisivanje antibiotika. Da bi ostvarili ciljeve koji su postavljeni na nivou Europe do 2030. godine potrebno je smanjiti rezistenciju bakterija na antibiotike (MRSA iz primarno sterilnih materijala za 15 %, *E. coli* rezistentne na treću generaciju cefalosporina iz krvi za 10 % te za 5 % reducirati pojavnost infekcija krvi uzrokovane s enterobakterijama rezistentnim

na karbapeneme), i ukupnu potrošnju antibiotika za 20 %. Pri odabiru antibiotika za liječenje koristiti antibiotike iz skupine „Acess" s udjelom 65 %. Da bismo to ostvarili nužno je provoditi propisivanje antibiotika u skladu s dobrom praksom, koja podrazumijeva implementaciju rukovođenog propisivanja antibiotika (*antibiotic stewardship*).

Antibiotic Consumption in Croatian Hospitals

Antibiotic consumption in Croatian hospitals has a long tradition and is monitored separately from the one in outpatient setting. Since 2011, hospital consumption has been tracked from two sources: data obtained from pharmaceutical wholesalers and, owing to the Interdisciplinary Section for Resistance Control (ISKRA) within the Ministry of Health, from hospital pharmacies.

Data obtained through hospital pharmacies is submitted to the European Surveillance of Antimicrobial Consumption Network (ESAC-Net) (Table 2).

Hospitals submit antibiotic consumption data in packages or units along with administrative data on the number of hospital bed days (BDs) and the number of admissions for the entire hospital, as well as separately for intensive care units (ICUs) by type (mixed, surgical, internal medicine, paediatric). Since 2011, the monitoring of hospital consumption has also included usage of antibiotics in day hospitals, and their Days of Therapy have been added to the denominator alongside hospital bed days.

Antibiotic consumption data is collected according to the ATC classification at the fifth level and displayed at the third and fourth levels

Hospital consumption data is expressed in DDD/1,000 inhabitants per day (DDD/TID) (Table 2).

Having at our disposal two kinds of data -that on antibiotic consumption obtained from hospital pharmacies and administrative data on the number of hospital bed days (BDs) - we are able to express consumption in DDD/100 BDs. This provides more accurate usage indicators, enabling detailed monitoring of consumption for each hospital, as well as tracking not only overall consumption trends, but also usage of antibiotics by classes and subclasses on national level.

Table 9 and Figure 8 juxtapose the data obtained from both sources since 2014. Higher consumption is recorded based on data from hospital pharmacies (except in 2015), which resulted in an increased difference in consumption favouring hospitals. In 2023, this difference was 0.37 DDD/TID, which is lower than the previous year, when the highest difference of 0.51 DDD/TID was recorded (Table 9; Figure 8).

Sixty-eight hospitals submitted data on antibiotic consumption in 2023 electronically to iskra.antibiotici@gmail.com. As in previous years, only 4 hospitals directly exported data from their pharmacy programs. Following established practice, after processing, each hospital received its processed data for the previous year for review and comparison with preceding period.

Hospital antibiotic consumption increased when compared to previous years. For the first time, it exceeded 2.00 (2.08 DDD/TID) (Table 2) when calculated in DDD per 1,000 inhabitants per day. However, when expressed per 100 BDs, using hospital administrative data (number of hospital days) as the denominator, there was no increase, with the hospital consumption value remaining identical to the previous year's value (45.20 DDD/100 BDs) (Table 10, Figure 9).

Since hospital antibiotic consumption expressed in DDD/100 BDs remained the same, there have been no significant changes in the usage of specific antibiotic classes in the last two years (Table 2). The most noticeable difference is observed in the cephalosporin class (J01D).

The leading class in hospital antibiotic consumption are cephalosporins with a share of 32%, followed by penicillins (24.5%), and then fluoroquinolones (12%). Similar to fluoroquinolones in terms of hospital consumption share is the macrolides + lincosamides group (10.6%). Aminoglycosides are in fifth place with a share of 4.3%, followed by sulfonamides + trimethoprim (1.9%), and then tetracyclines (1.4%), which have not changed.

The ranking of the top five antibiotics used in hospitals remained the same as the year before, with minor differences in consumption in the two preceding years. Co-amoxiclav continues to hold the leading position with 8.11 DDD/100 BDs, which is slightly lower value than the previous year (8.26 DDD/100 BDs). In the second place is ceftriaxone, whose consumption increased when compared to the previous year (4.73 DDD/100 BDs as opposed to 4.41 DDD/100 BDs in 2022).

Ranking third is cefuroxime axetil, whose consumption continues to decline (3.15 DDD/100 BDs) if compared to previous years (3.39 DDD/100 BDs in 2022, 3.69 DDD/100 BDs in 2021). Ciprofloxacin is in the fourth place, with slightly lower consumption (3.12 DDD/100 BDs) compared to the previous year (3.19 DDD/100 BDs). In the fifth place is metronidazole with 3.02 DDD/100 BDs, replacing azithromycin which fell below the fifth place in terms of consumption (Table 12; Figure 11).

The share of reserve antibiotics in overall hospital consumption is monitored as an indicator. These include glycopeptides (J01XA), third-generation cephalosporins (J01DD), fourth-generation cephalosporins (J01DE), monobactams (J01DF), carbapenems (J01DH), fluoroquinolones (J01MA), polymyxins (J01XB), piperacillin+tazobactam (J01CR05), linezolid (J01XX08), tedizolid (J01XX11), and daptomycin (J01XX09). In 2023, this share remained almost the same at (39%) as the year before (38.9%), thus halting the trend of their continuous increase in total hospital consumption over the past five years of monitoring (Table 13, Figure 12).

All **clinics**, thirteen of them, submitted their antibiotic consumption data (Table 14, Figure 13) which in 2023 varied from 27.68 (C11) to 172.81 DDD/100 BDs (C02). This is a significantly wider range than in the previous year, when it extended from 26.19 to 138.50 DDD/BDs (Table 15; Figure 14). Nevertheless, it was to be expected, given that these are very different clinics, some of which are specialized, for example, only for surgical procedures, some only for treating infectious diseases, while others are of mixed type.

Six clinics (C01; C02; C05; C09; C11; C13) showed an increase in antibiotic consumption. In three of them (02, 09, and 13) there has been a continuous rise in the use of antibiotics over the years. Clinic C02 recorded a considerable jump in consumption last year, with an increase of 34.31 DDD/100 BDs compared to year before. C09 also showed a significant growth in the use of antibiotics (13.7 DDD/100 BDs). Only two clinics saw a decrease in consumption (C04; C15), with this decline continuing over the years at C04. At five clinics (C03; C06; C07; C08; C14), there were no significant changes in consumption, with differences being less than one DDD per 100 BDs over the past two years.

In 2023, 22 **general hospitals** submitted their antibiotic consumption data. Since this group of hospitals is similar in terms of scope of work and types of departments, the results are comparable. The use of antibiotics ranged widely from 41.69 to 90.06 DDD/100 BDs (Table 16), which is similar to the previous year's results. Such a wide range, which is more than double between the hospital with the lowest consumption (G19) and the one with the highest (G13) is indicative of significant variations in antibiotic prescribing practices among the hospitals.

In 10 hospitals, a decrease in antibiotic consumption was recorded (G03; G05; G09; G10; G11; G14; G17; G19; G20; G24), which is two hospitals fewer than the year before.

Conversely, there was a rise in consumption in 10 hospitals (from six the year before) – in G01; G02; G04; G07; G08; G12; G13; G15; G22; G23, while in the remaining two (G18; G21) the difference was less than 1 DDD/100 BD over the last two years (Table 17).

Figure 15 shows antibiotic consumption in general hospitals by individual antibiotic classes in 2023. Table 17 and Figure 16 show consumption in general hospitals over the past seven years, allowing each hospital to track its own consumption trends. General hospital G13 stands out, showing a continuous increase in consumption over the years. Hospital G02 has also recorded a steady growth in the use of antibiotics over the past four years. Finally, after reaching high consumption values of 95.55 DDD/100 BDs in 2022, hospital G09 halted the upward consumption trend observed in previous years.

In the largest number of general hospitals (9 of them) consumption varied within the range of 51-60 DDD/100 BDs. In only two of them (G14 and G19) it was below 50 DDD/100 BDs, while four hospitals are among those with the highest consumption recorded (G07; G09; G10; G13), which is twice as many as in the preceding year. Hospitals G01 and G19 stand out, with G01 recording a significant increase in the usage of antibiotics in 2023 - by 14.33 DDD/100 BDs, unlike G19 which saw a considerable decline of 12.05 DDD/100 BDs.

Antibiotic consumption in **psychiatric hospitals** ranged from 1.13 to 16.44 DDD/100 BDs (Table 18). Figure 17 details the usage by antibiotic classes. Two hospitals (P06; P07) recorded an increase in consumption (by 1.54 and 1.16 DDD/100 BDs) when compared to the previous year. In all the other hospitals (P01; P02; P03; P04; P05; P08; P09), there were no changes in consumption greater than 1 DDD/100 BD. This group of hospitals has a relatively stable antibiotic consumption.

Table 19 and Figure 18 cover the period of past seven years with some noticeable consumption trends. Psychiatric institutions P07 and P09 continue to show an upward trend in consumption.

Specialty hospitals are divided into two large groups based on their focus and as such, they exhibit large variations in the use of antibiotics. The first group consists of 10 hospitals dedicated to treatment (acute/chronic), while the second group includes 14 institutions for rehabilitation (Table 20; Figure 19). In the first group, the range of antibiotic consumption varied from 10.03 to 79.90 DDD/100 BDs. Five hospitals (unlike two the year before) recorded an increase in consumption (S01; S02; S04; S18; S21). Only two hospitals (S13; S23) saw a decrease, while in three hospitals (S03; S19; S22) there were no differences greater than 1 DDD/100 BDs (Table 21; Figure 20).

In the group of specialty hospitals dedicated to rehabilitation, antibiotic usage is significantly lower, ranging from 1.11 to 6.65 DDD/100 BDs (Table 21; Figure 20). Only hospital S25 recorded an increase in consumption, while a decrease was observed in four hospitals (S05; S06; S07; S14). In all the other hospitals, consumption remained consistent with the previous year, with deviations not exceeding 1 DDD/100 BDs.

Figure 19 details antibiotic consumption by class in 2023. Table 21 and Figure 20 show consumption in specialty hospitals over the past seven years

Hospital antibiotic consumption in Croatia is high. For the first time, it exceeded 2.0 DDD/100 BDs. Although it accounts for less than 10% of total use of antibiotics, hospital consumption of certain classes and subgroups significantly differs from that in outpatient setting. Expressed in DDD per 100 BD, hospital antibiotic consumption remained the same over the past two years; however, when expressed per 1000 inhabitants per day, it increased compared to the previous year (2.08 DDD/TID as opposed to 1.98 DDD/TID), highlighting the importance of the denominator and especially emphasizing the value of this method of monitoring which allows for precise detection of changes in hospital antibiotic consumption.

The largest increase in consumption was recorded in the class of cephalosporins. A slight growth was observed in the classes of tetracyclines and aminoglycosides. For other classes, the differences in consumption over the last two years were minor.

A particularly positive indicator is the cessation of growth in the usage of the J01X group (the “other”), which mainly includes reserve antibiotics, and which have been increasing steadily in recent years.

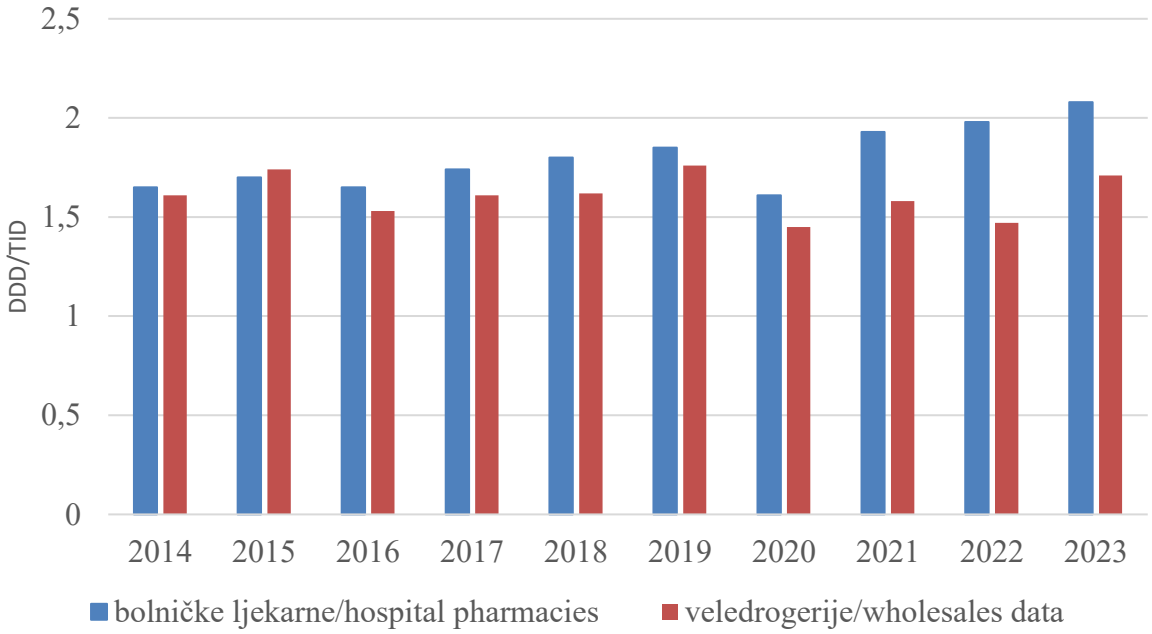
In hospital antibiotic consumption, the most represented class are cephalosporins, specifically 3rd and 4th generation. Co-amoxiclav is the leading antibiotic in terms of consumption, followed by ceftriaxone. Cefuroxime axetil, ciprofloxacin, and metronidazole are ranked third, fourth, and fifth having similar consumption values.

Monitoring antibiotic consumption at the level of individual hospitals reveals significant differences in prescribing practices as well as in consumption trends. Some hospitals have shown a continuously growing trend in consumption over the years. All of this indicates that antibiotic stewardship is still not widely adopted. To achieve the goals set at the European level by 2030, which include reducing bacterial resistance to antibiotics (MRSA from primary sterile sites by 15%, *E. coli* resistant to third-generation cephalosporins in blood by 10%, and a 5% reduction in the incidence of bloodstream infections caused by carbapenem-resistant Enterobacteriaceae), as well as reducing overall antibiotic consumption by 20%, it is necessary to prescribe antibiotics from the 'Access' group, with a target of 65%. In order to achieve this, it is essential to implement antibiotic prescribing in line with best practices, which involves the implementation of antibiotic stewardship.

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

godina year	bolničke ljekarne hospital pharmacies	veledrogerije wholesales data
2014	1,65	1,61
2015	1,70	1,74
2016	1,65	1,53
2017	1,74	1,61
2018	1,80	1,62
2019	1,85	1,76
2020	1,61	1,45
2021	1,93	1,58
2022	1,98	1,47
2023	2,08	1,71

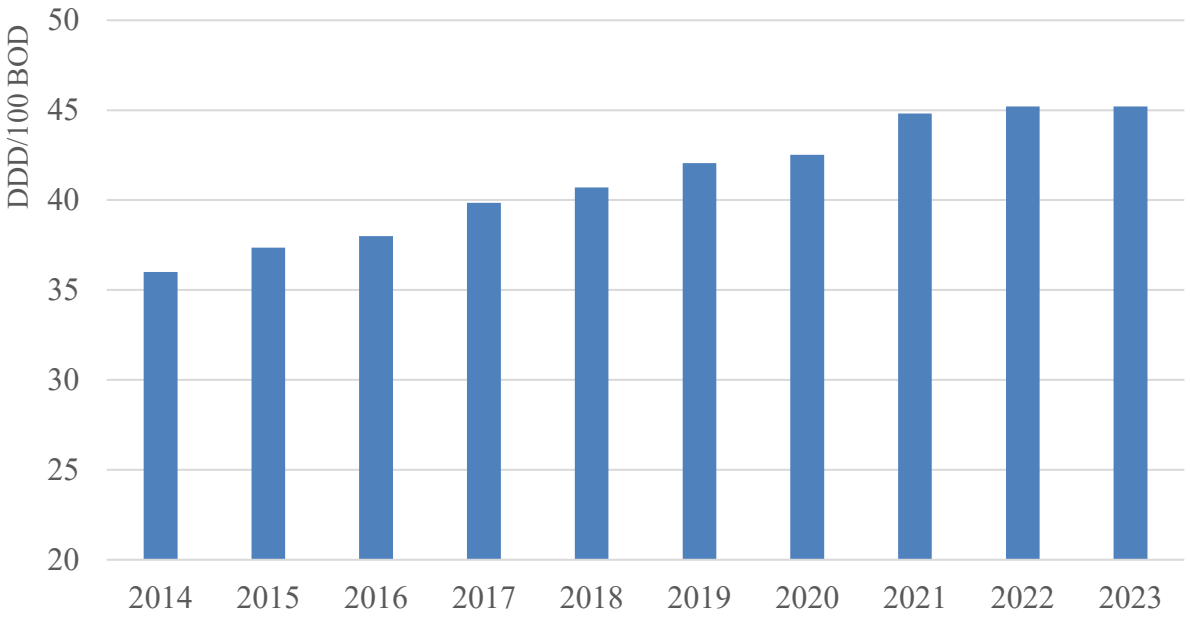
Slika 8. */ Figure 8.*
Bolnička potrošnja antibiotika (DDD/TID) usporedba podataka bolničkih ljekarni i veledrogerija/
Hospital antibiotic consumption (DDD/TID) comparison between hospital pharmacy data and wholesales data



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

Godina / *year*	DDD/100 BOD / *DDD/100 BD*
2014	36,01
2015	37,35
2016	37,99
2017	39,84
2018	40,70
2019	42,05
2020	42,52
2021	44,81
2022	45,20
2023	45,20

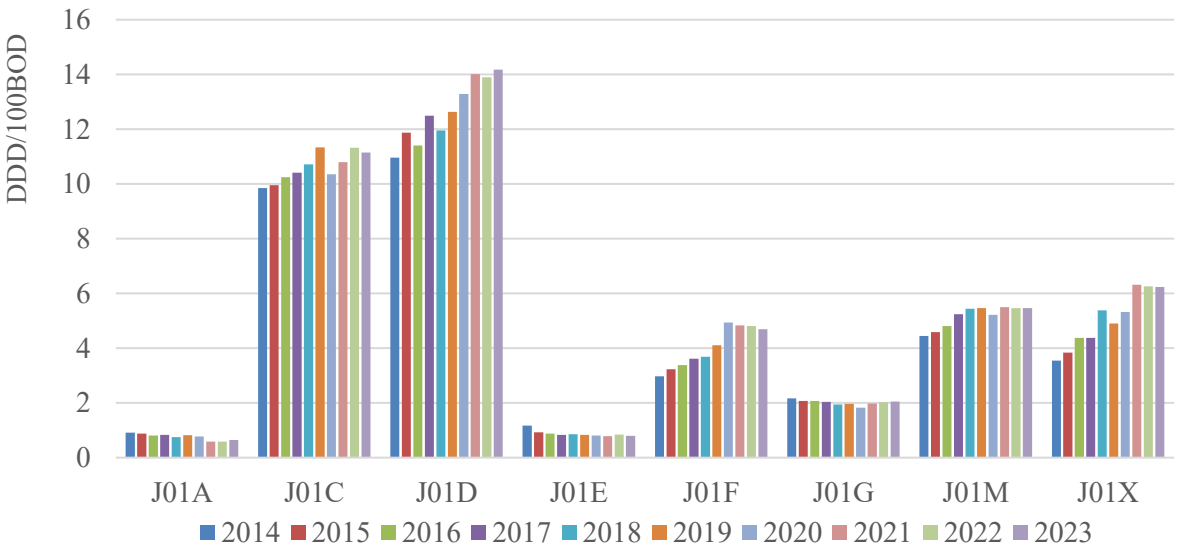
Slika 9. */Figure 9.*
Bolnička potrošnja antibiotika (DDD/100 BOD)
Hospital antibiotic consumption (DDD/100 BD)



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

Klasa / *class*	Godina / *year*									
	2014	2015	2016	2018	2018	2019	2020	2021	2022	2023
J01A	0,91	0,88	0,81	0,83	0,75	0,82	0,77	0,59	0,59	0,65
J01C	9,85	9,96	10,25	10,41	10,72	11,34	10,36	10,80	11,32	11,14
J01D	10,96	11,87	11,41	12,49	11,95	12,63	13,29	14,01	13,90	14,17
J01E	1,17	0,93	0,88	0,83	0,85	0,83	0,81	0,78	0,84	0,80
J01F	2,97	3,23	3,38	3,62	3,68	4,11	4,93	4,83	4,81	4,69
J01G	2,16	2,07	2,07	2,04	1,94	1,97	1,82	1,98	2,02	2,05
J01M	4,44	4,58	4,81	5,24	5,44	5,46	5,22	5,50	5,46	5,46
J01X	3,55	3,84	4,38	4,38	5,38	4,90	5,33	6,32	6,25	6,24

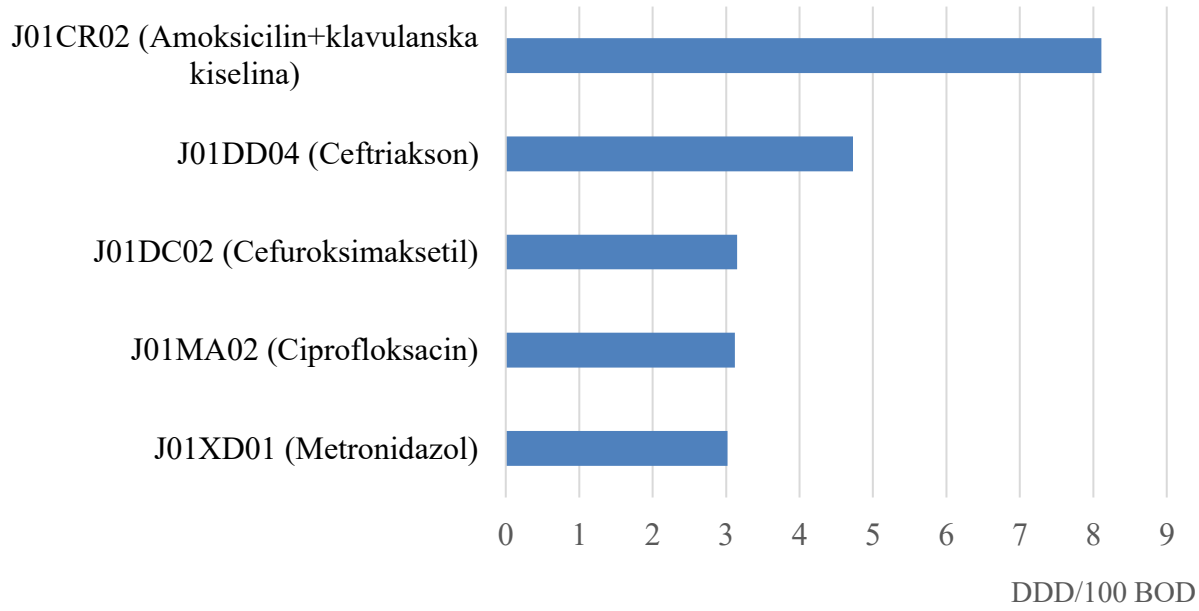
Slika 10. */ Figure 10.*
Bolnička potrošnja antibiotika (DDD/100 BOD) po klasama, izvor podataka – bolničke ljekarne/
Hospital antibiotic consumption (DDD/100 BD) by class, origin of data - hospital pharmacies



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

Klasa / class	DDD/100 BOD / *DDD/100 BD*
J01CR02 (Amoksicilin+klavulanska kiselina)	8,11
J01DD04 (Ceftriakson)	4,73
J01DC02 (Cefuroksimaksetil)	3,15
J01MA02 (Ciprofloksacin)	3,12
J01XD01 (Metronidazol)	3,02

Slika 11. */ Figure 11.*
Bolnička potrošnja antibiotika „top 5“ antibiotika – DDD/100 BOD, izvor podataka – bolničke ljekarne /
Hospital antibiotic consumption „top 5“antibiotics – DDD/100 BD; origin of data - hospital pharmacies



Tablica 13./ *Table 13.*

Udio potrošnje glikopeptida* (J01XA), cefalosporina III. generacije* (J01DD), cefalosporina IV. generacije* (J01DE), monobaktama* (J01DF), karbapenema* (J01DH), fluorokinolona* (J01MA), polimiksina* (J01XB), piperacilin+tazobaktama* (J01CR05), linezolida* (J01XX08), tedizolida* (J01XX11) i daptomicina* (J01XX09) u odnosu na ukupnu potrošnju antibiotika za sistemsku upotrebu u bolnicama izražen kao DDD na tisuću stanovnika na dan u razdoblju 2010-2023/

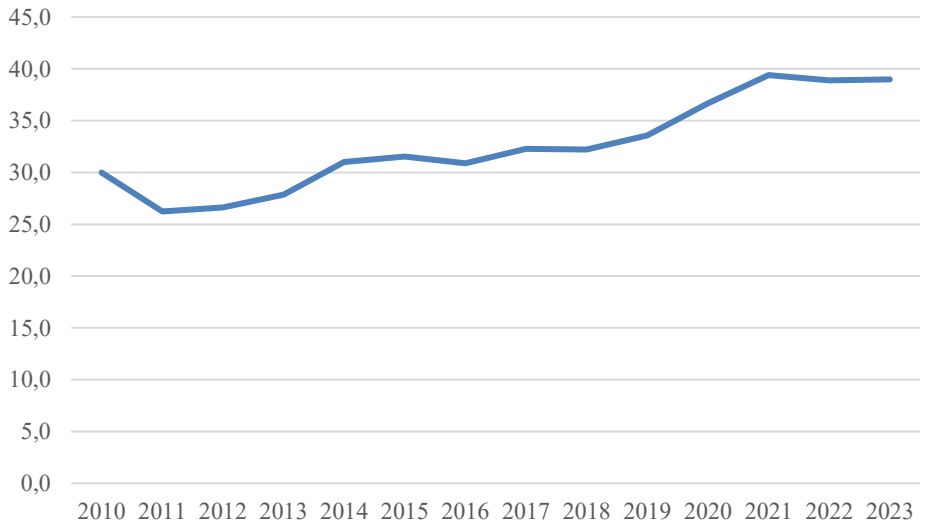
The proportion of glycopeptides (J01XA), third-generation cephalosporin*s (J01DD), fourth-generation cephalosporins*, (J01DE), monobactams* (J01DF), carbapenems* (J01DH), fluoroquinolones* (J01MA), polymyxins* (J01XB), piperacillin and tazobactam* (J01CR05), linezolid* (J01XX08), tedizolid* (J01XX11) and daptomycin* (J01XX09) consumption out of total consumption of antibacterials for systemic use in the hospital (DDD/ TID) 2010-2023*

	Udio potrošnje rezervnih* antibiotika u ukupnoj bolničkoj potrošnji %
2010	30,0
2011	26,2
2012	26,6
2013	27,9
2014	31,0
2015	31,5
2016	30,9
2017	32,3
2018	32,2
2019	33,6
2020	36,7
2021	39,4
2022	38,9
2023	39,0

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 2010-2023/

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) 2010-2023

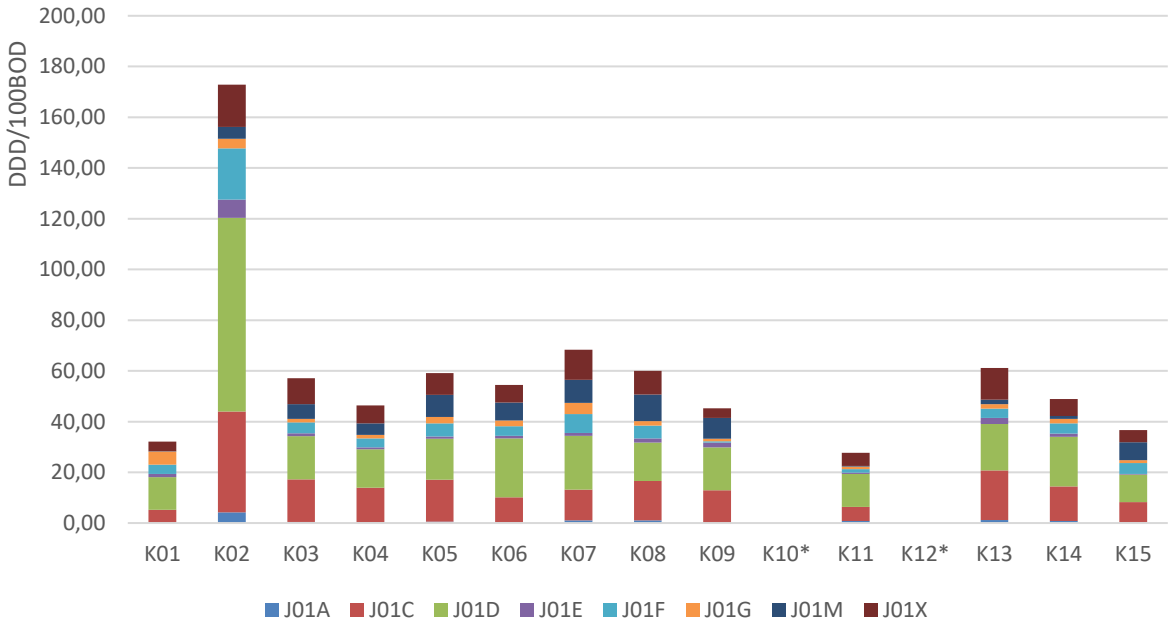


Tablica 14. */ Table 14.*
KLINIČKE USTANOVE - POTROŠNJA ANTIBIOTIKA 2023.
CLINICAL INSITUTIONS – ANTIBIOTIC CONSUMPTION IN 2023

	DDD/100 BOD, DDD/100 BD								
USTANOVA INSTITUTION	UKUPNO TOTAL	J01A	J01C	J01D	J01E	J01F	J01G	J01M	J01X
K 01	32,08	0,00	5,28	12,80	1,23	3,66	5,19	0,19	3,72
K 02	172,81	4,25	39,74	76,31	7,30	20,09	3,79	4,66	16,67
K 03	57,06	0,48	16,69	17,04	1,15	4,31	1,36	5,85	10,18
K 04	46,43	0,36	13,64	15,06	0,76	3,59	1,30	4,62	7,10
K 05	59,13	0,52	16,58	16,18	0,80	5,21	2,49	8,74	8,61
K 06	54,47	0,27	9,82	23,24	1,04	3,73	2,33	7,13	6,89
K 07	68,39	1,03	12,16	21,18	1,17	7,45	4,44	9,09	11,86
K 08	60,06	1,11	15,46	15,12	1,64	5,16	1,77	10,44	9,37
K 09	45,23	0,00	12,89	16,96	1,92	0,46	1,04	8,17	3,79
K 10*									
K 11	27,68	0,79	5,54	13,02	0,46	1,44	1,08	0,24	5,11
K 12*									
K 13	61,16	1,18	19,60	18,25	2,42	3,66	1,74	1,75	12,56
K 14	48,92	0,75	13,68	19,58	1,28	4,02	1,75	1,18	6,68
K 15	36,62	0,19	8,05	10,82	0,35	4,26	1,18	7,07	4,71

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

Slika 13. */Figure 13.*
KLINIČKE USTANOVE - POTROŠNJA ANTIBIOTIKA 2017.-2023.
CLINICAL INSITUTIONS – ANTIBIOTIC CONSUMPTION IN 2017-2023

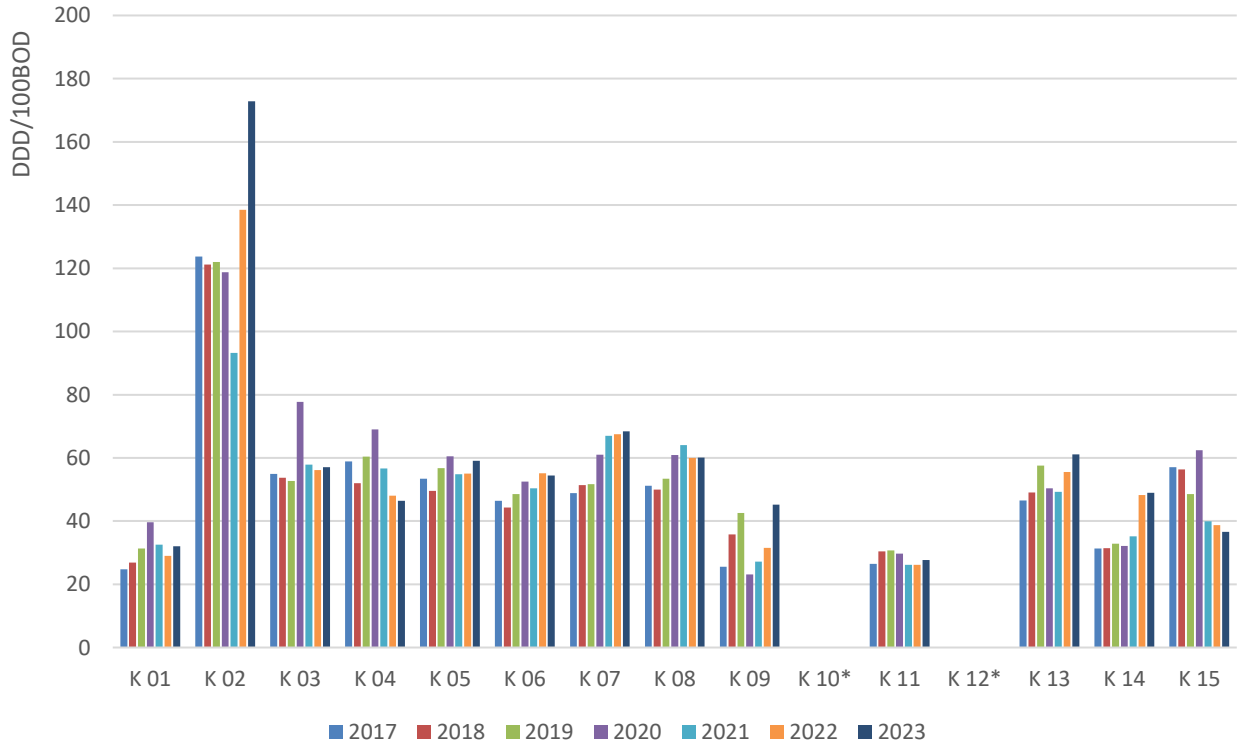


Tablica 15. */ Table 15.*
KLINIČKE USTANOVE - POTROŠNJA ANTIBIOTIKA 2017-2023.
CLINICAL INSITUTIONS – ANTIBIOTIC CONSUMPTION IN 2017-2023

	DDD/100 BOD, DDD/100BD						
USTANOVA INSTITUTION	2017	2018	2019	2020	2021	2022	2023
K 01	24,7	26,9	31,3	39,64	32,53	28,97	32,08
K 02	123,7	121,2	122,0	118,77	93,21	138,50	172,81
K 03	54,9	53,7	52,7	77,76	57,86	56,11	57,06
K 04	58,9	52,0	60,4	69,01	56,69	48,05	46,43
K 05	53,4	49,6	56,8	60,47	54,86	55,08	59,13
K 06	46,4	44,3	48,5	52,54	50,39	55,12	54,47
K 07	48,9	51,4	51,7	61,03	66,95	67,51	68,39
K 08	51,2	50,0	53,4	60,94	64,08	60,02	60,06
K 09	25,6	35,8	42,6	23,12	27,13	31,57	45,23
K 10*							
K 11	26,5	30,4	30,7	29,71	26,17	26,19	27,68
K 12*							
K 13	46,5	49,1	57,6	50,34	49,30	55,53	61,16
K 14	31,3	31,4	32,8	32,15	35,18	48,23	48,92
K 15	57,1	56,3	48,5	62,38	39,97	38,76	36,62

* 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.-2023.
CLINICAL INSITUTIONS – ANTIBIOTIC CONSUMPTION IN 2017-2023

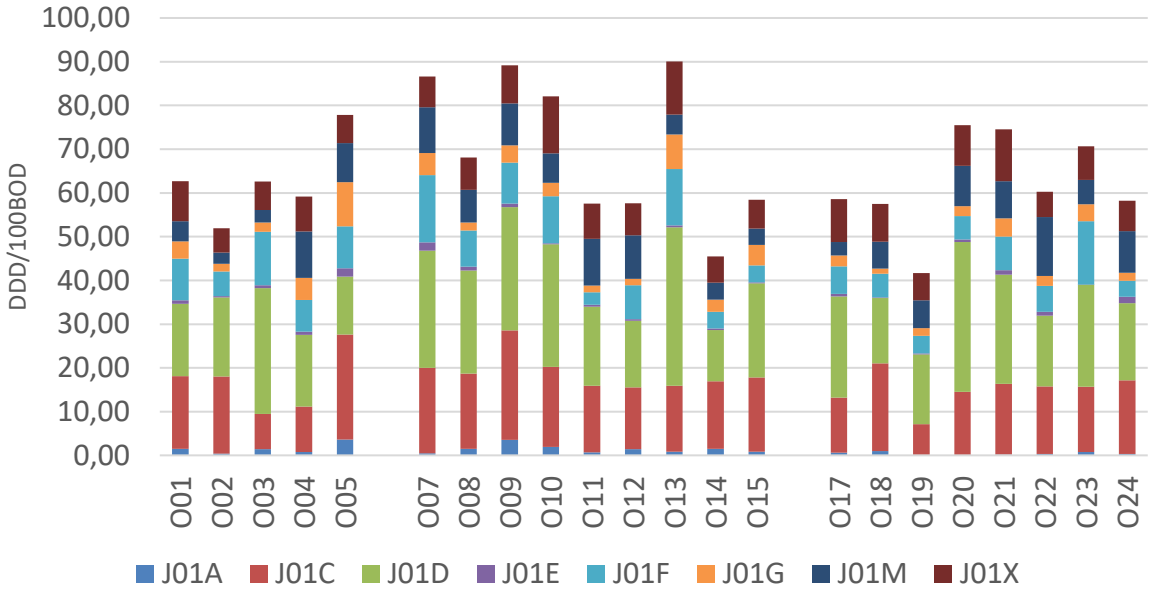


Tablica 16. */Table 16.*
OPĆE BOLNICE - POTROŠNJA ANTIBIOTIKA 2023.
GENERAL HOSPITALS – ANTIBIOTIC CONSUMPTION IN 2023

USTANOVA INSTITUTION	UKUPNO TOTAL	DDD/100 BOD, DDD/100 BD							
		J01A	J01C	J01D	J01E	J01F	J01G	J01M	J01X
O 01	62,69	1,48	16,66	16,54	0,78	9,54	3,95	4,60	9,15
O 02	51,90	0,37	17,67	18,07	0,32	5,60	1,79	2,53	5,55
O 03	62,64	1,41	8,05	28,80	0,65	12,21	2,10	2,86	6,56
O 04	59,17	0,77	10,42	16,37	0,70	7,30	5,02	10,65	7,95
O 05	77,83	3,65	23,99	13,21	1,92	9,57	10,10	8,97	6,42
O 06*									
O 07	86,65	0,50	19,55	26,79	1,90	15,35	5,04	10,49	7,04
O 08	68,12	1,47	17,20	23,60	0,86	8,28	1,81	7,48	7,43
O 09	89,19	3,53	25,03	28,17	0,84	9,39	3,93	9,61	8,70
O 10	82,09	1,90	18,34	28,01	0,19	10,79	3,10	6,73	13,02
O 11	57,53	0,69	15,25	18,08	0,44	2,82	1,57	10,65	8,03
O 12	57,62	1,39	14,18	15,21	0,37	7,77	1,46	9,90	7,34
O 13	90,06	0,87	15,06	36,22	0,39	12,92	7,91	4,51	12,18
O 14	45,48	1,48	15,47	11,67	0,37	3,81	2,81	3,90	5,97
O 15	58,42	0,81	16,98	21,51	0,26	3,87	4,71	3,69	6,58
O 16**									
O 17	58,61	0,58	12,59	23,15	0,57	6,34	2,46	3,06	9,85
O 18	57,47	0,99	20,07	14,95	0,11	5,45	1,16	6,14	8,60
O 19	41,69	0,10	7,06	15,91	0,24	4,01	1,80	6,30	6,26
O 20	75,48	0,12	14,37	34,32	0,59	5,33	2,26	9,20	9,29
O 21	74,57	0,18	16,20	24,95	0,99	7,68	4,22	8,49	11,86
O 22	60,25	0,31	15,44	16,20	0,85	5,93	2,29	13,50	5,74
O 23	70,64	0,75	14,96	23,30	0,05	14,50	3,87	5,57	7,65
O 24	58,22	0,32	16,82	17,65	1,50	3,67	1,83	9,50	6,94

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

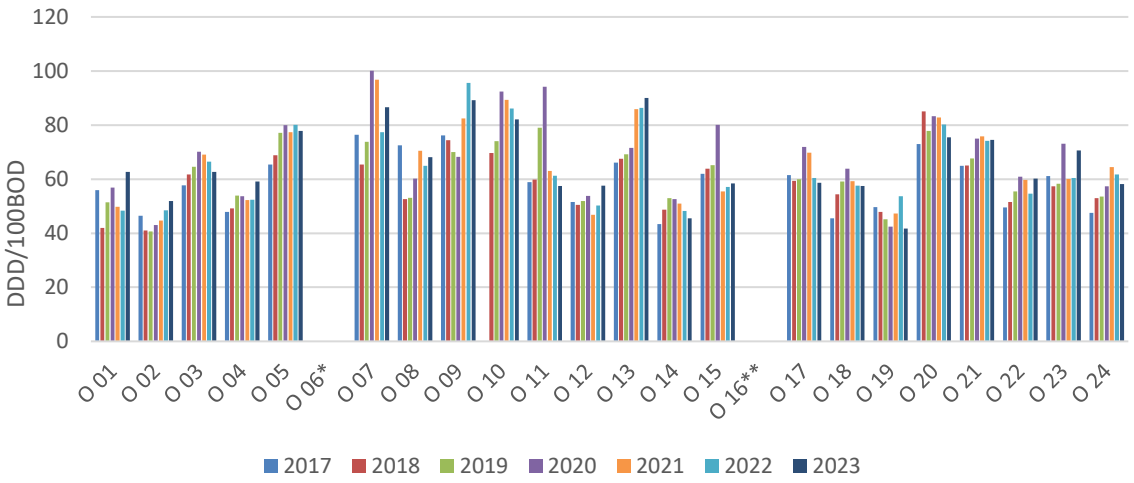
Slika 15. */Figure 15.*
OPĆE BOLNICE - POTROŠNJA ANTIBIOTIKA 2023.
GENERAL HOSPITALS – ANTIBIOTIC CONSUMPTION 2023



Tablica 17. */Table 17.*
OPĆE BOLNICE - POTROŠNJA ANTIBIOTIKA 2017.-2023.
GENERAL HOSPITALS – ANTIBIOTIC CONSUMPTION IN 2017-2023

USTANOVA INSTITUTION	DDD/100 BOD, DDD/100 BD						
	2017	2018	2019	2020	2021	2022	2023
O 01	55,9	41,9	51,4	56,92	49,81	48,36	62,69
O 02	46,4	41,0	40,7	42,98	44,71	48,46	51,90
O 03	57,7	61,7	64,6	70,15	69,12	66,48	62,64
O 04	47,9	49,2	53,9	53,66	52,26	52,37	59,17
O 05	65,4	68,8	77,1	79,98	77,31	80,08	77,83
O 06*							
O 07	76,4	65,4	73,8	100,11	96,75	77,38	86,65
O 08	72,5	52,6	53,1	60,18	70,51	64,95	68,12
O 09	76,2	74,4	70,0	68,19	82,43	95,55	89,19
O 10	0,00	69,7	74,0	92,41	89,37	86,15	82,09
O 11	58,9	59,8	79,0	94,17	63,03	61,27	57,53
O 12	51,5	50,5	51,9	53,77	46,83	50,26	57,62
O 13	66,1	67,5	69,2	71,55	85,86	86,37	90,06
O 14	43,4	48,7	53,0	52,65	50,97	48,27	45,48
O 15	62,0	63,9	65,2	80,11	55,40	57,11	58,42
O 16**							
O 17	61,5	59,4	59,9	71,87	69,77	60,42	58,61
O 18	45,5	54,4	59,1	63,85	59,29	57,53	57,47
O 19	49,6	47,9	45,1	42,42	47,27	53,74	41,69
O 20	73,0	85,1	77,8	83,33	82,76	80,25	75,48
O 21	64,9	65,1	67,7	75,03	75,84	74,11	74,57
O 22	49,5	51,6	55,5	60,88	59,77	54,58	60,25
O 23	61,1	57,3	58,3	73,12	60,10	60,39	70,64
O 24	47,5	53,0	53,6	57,34	64,46	61,77	58,22

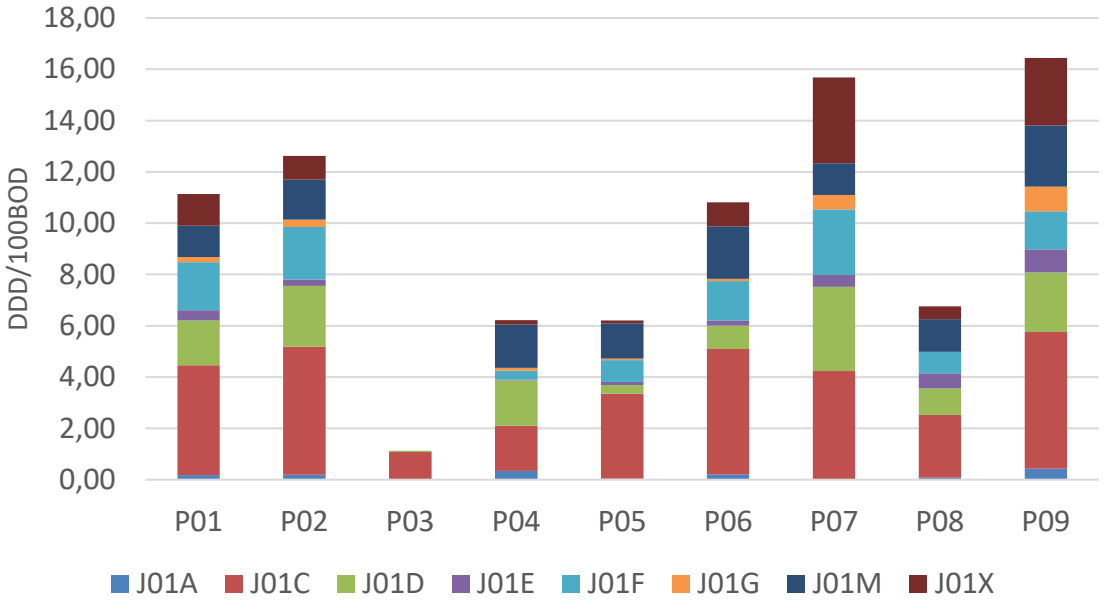
Slika 16. */ Figure 16.*
OPĆE BOLNICE - POTROŠNJA ANTIBIOTIKA 2017.-2023.
GENERAL HOSPITALS – ANTIBIOTIC CONSUMPTION 2017-2023



Tablica 18. */Table 18.*
PSIHIJATRIJSKE USTANOVE - POTROŠNJA ANTIBIOTIKA 2023.
PSYCHIATRIC INSTITUTIONS – ANTIBIOTIC CONSUMPTION IN 2023

USTANOVA INSTITUTION	DDD/100 BOD, DDD/100 BD								
	UKUPNO / TOTAL	J01A	J01C	J01D	J01E	J01F	J01G	J01M	J01X
P 01	11,13	0,18	4,28	1,75	0,40	1,86	0,20	1,22	1,24
P 02	12,62	0,19	4,99	2,38	0,25	2,04	0,28	1,57	0,92
P 03	1,13	0,00	1,08	0,05	0,00	0,00	0,00	0,00	0,00
P 04	6,22	0,34	1,76	1,77	0,03	0,34	0,12	1,68	0,18
P 05	6,21	0,04	3,30	0,33	0,14	0,85	0,06	1,38	0,11
P 06	10,82	0,21	4,89	0,91	0,20	1,53	0,09	2,04	0,94
P 07	15,68	0,00	4,24	3,28	0,46	2,56	0,56	1,23	3,35
P 08	6,76	0,08	2,44	1,04	0,58	0,83	0,00	1,27	0,50
P 09	16,44	0,43	5,33	2,31	0,90	1,48	0,96	2,39	2,63

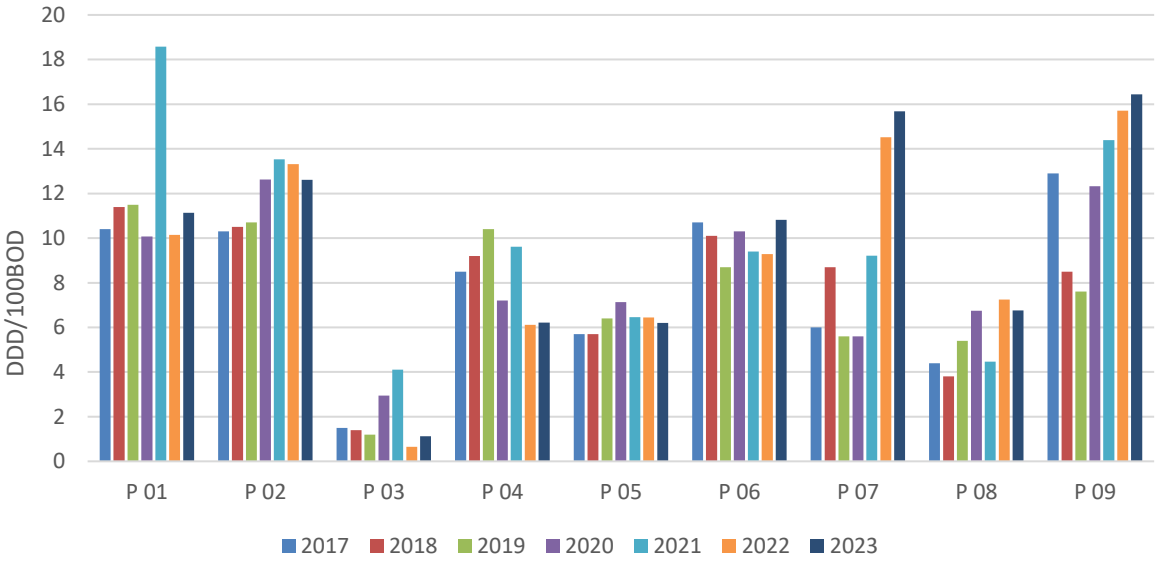
Slika 17. */Figure 17.*
PSIHIJATRIJSKE USTANOVE - POTROŠNJA ANTIBIOTIKA 2023.
PSYCHIATRIC INSTITUTIONS – ANTIBIOTIC CONSUMPTION 2023



Tablica 19. */Table 19.*
PSIHIJATRIJSKE USTANOVE - POTROŠNJA ANTIBIOTIKA 2017.-2023.
PSYCHIATRIC INSTITUTIONS – ANTIBIOTIC CONSUMPTION IN 2017-2023

USTANOVA INSTITUTION	DDD/100 BOD, DDD/100BD						
	2017	2018	2019	2020	2021	2022	2023
P 01	10,4	11,4	11,5	10,08	18,58	10,14	11,13
P 02	10,3	10,5	10,7	12,63	13,53	13,31	12,62
P 03	1,5	1,4	1,2	2,95	4,11	0,65	1,13
P 04	8,5	9,2	10,4	7,21	9,62	6,12	6,22
P 05	5,7	5,7	6,4	7,13	6,46	6,44	6,21
P 06	10,7	10,1	8,7	10,31	9,40	9,28	10,82
P 07	6,0	8,7	5,6	5,60	9,22	14,52	15,68
P 08	4,4	3,8	5,4	6,75	4,47	7,25	6,76
P 09	12,9	8,5	7,6	12,33	14,39	15,71	16,44

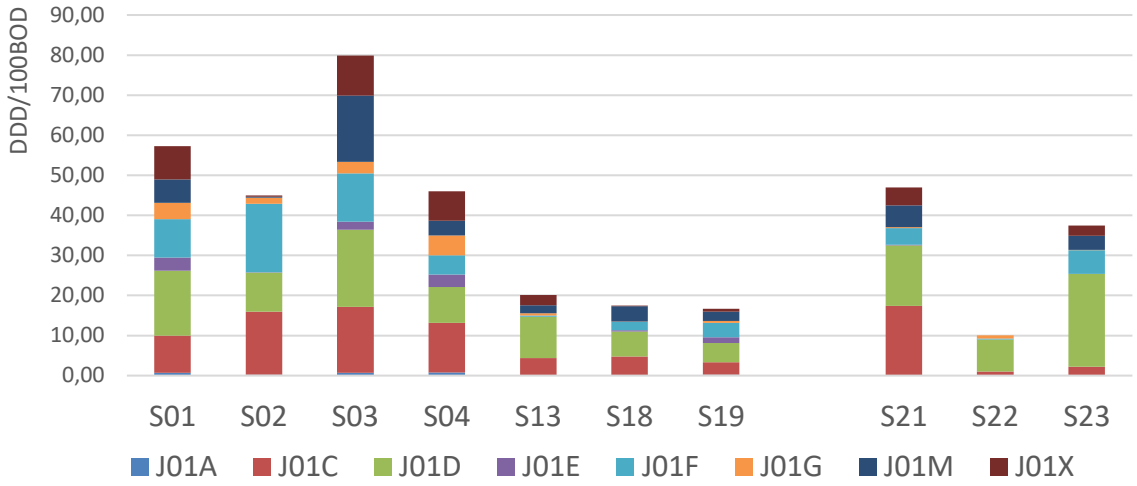
Slika 18. / *Figure 18.*
PSIHIJATRIJSKE USTANOVE - POTROŠNJA ANTIBIOTIKA 2017.-2023.
PSYCHIATRIC INSTITUTIONS – ANTIBIOTIC CONSUMPTION 2017-2023

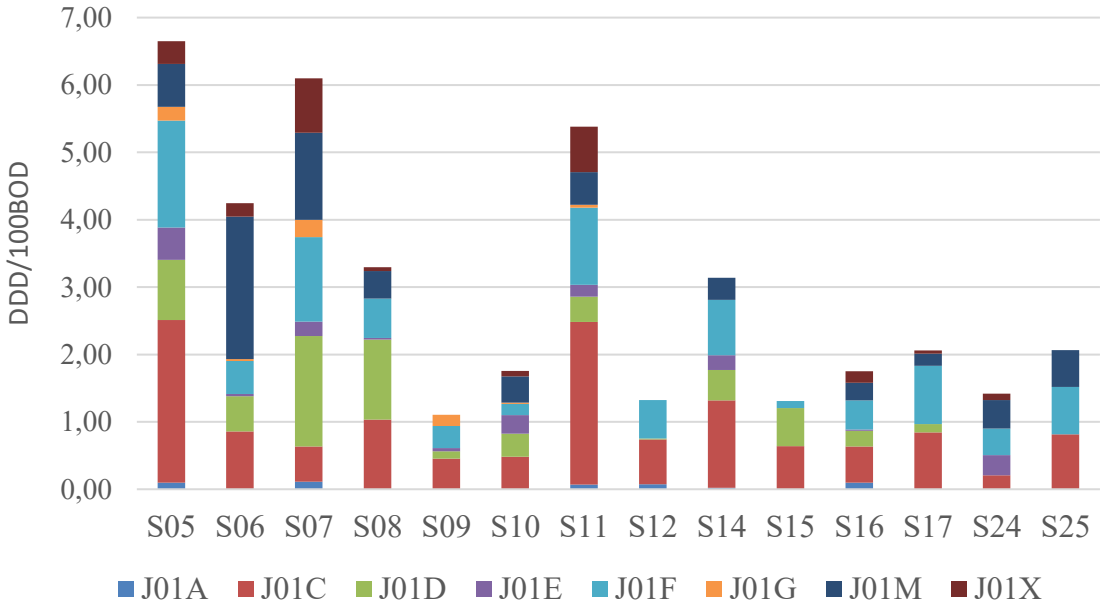


Tablica 20. */Table 20.*
SPECIJALNE BOLNICE - POTROŠNJA ANTIBIOTIKA 2023.
SPECIALTY HOSPITALS – ANTIBIOTIC CONSUMPTION IN 2023

	DDD/100 BOD, DDD/100 BD								
USTANOVA INSTITUTION	UKUPNO TOTAL	J01A	J01C	J01D	J01E	J01F	J01G	J01M	J01X
S 01	57,27	0,70	9,25	16,25	3,24	9,57	4,07	5,87	8,31
S 02	44,93	0,24	15,69	9,79	0,04	17,17	1,46	0,24	0,31
S 03	79,90	0,67	16,50	19,28	1,98	12,03	2,90	16,57	9,98
S 04	46,01	0,76	12,44	8,92	3,10	4,76	4,97	3,66	7,40
S 13	20,09	0,00	4,35	10,36	0,00	0,29	0,55	1,99	2,56
S 18	17,48	0,13	4,68	6,23	0,25	2,08	0,07	3,89	0,14
S 19	16,69	0,21	3,15	4,78	1,42	3,62	0,46	2,30	0,74
S 20*									
S 21	47,00	0,00	17,38	15,12	0,20	4,09	0,26	5,43	4,53
S 22	10,03	0,00	1,02	8,01	0,00	0,22	0,78	0,00	0,00
S 23	37,43	0,00	2,21	23,17	0,00	5,94	0,04	3,56	2,51
S 05	6,65	0,10	2,42	0,89	0,48	1,59	0,21	0,63	0,34
S 06	4,25	0,00	0,85	0,52	0,03	0,49	0,03	2,11	0,20
S 07	6,10	0,11	0,53	1,64	0,21	1,26	0,26	1,29	0,81
S 08	3,29		1,04	1,19	0,02	0,59		0,41	0,06
S 09	1,11		0,45	0,11	0,05	0,33	0,17		
S10	1,76		0,48	0,34	0,28	0,17	0,02	0,39	0,08
S11	5,38	0,07	2,41	0,38	0,18	1,14	0,04	0,48	0,68
S12	1,33	0,07	0,67	0,01		0,57			
S14	3,14	0,02	1,30	0,45	0,22	0,82		0,33	
S15	1,31		0,64	0,56		0,10			
S16	1,75	0,10	0,54	0,23	0,02	0,43		0,26	0,17
S17	2,06		0,84	0,12		0,87		0,18	0,05
S24	1,42		0,21		0,30	0,39		0,42	0,10
S25	2,07		0,81			0,70		0,55	

Slika 19. / *Figure 19.*
SPECIJALNE BOLNICE - POTROŠNJA ANTIBIOTIKA 2023.
SPECIALTY HOSPITALS – ANTIBIOTIC CONSUMPTION 2023

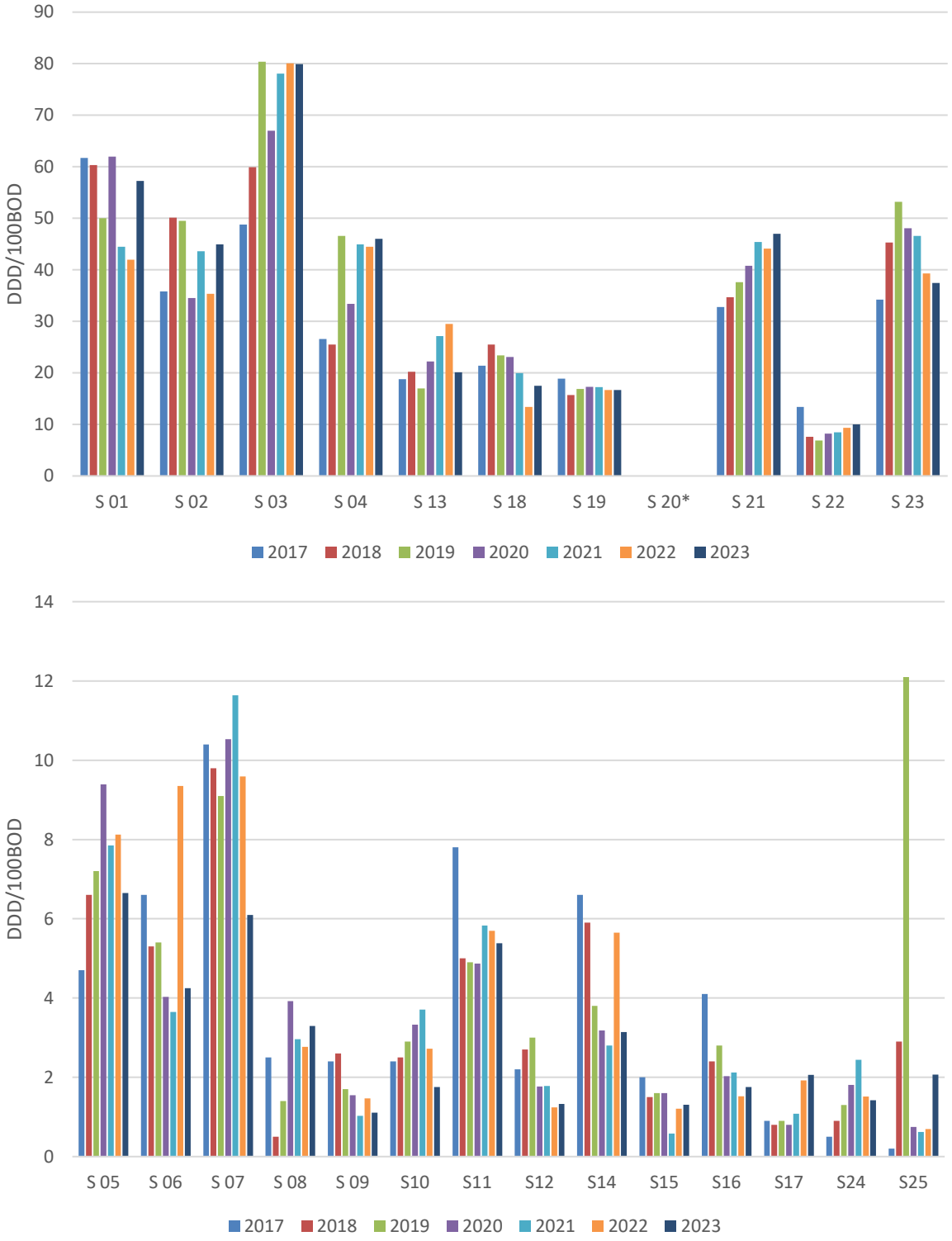




Tablica 21. */Table 21.*
SPECIJALNE BOLNICE - POTROŠNJA ANTIBIOTIKA 2017.-2023.
SPECIALTY HOSPITALS – ANTIBIOTIC CONSUMPTION IN 2017-2023

	DDD/100 BOD, DDD/100 BD						
USTANOVA INSTITUTION	2017	2018	2019	2020	2021	2022	2023
S 01	61,7	60,3	50,0	61,95	44,45	41,98	57,27
S 02	35,8	50,1	49,5	34,51	43,61	35,35	44,93
S 03	48,8	59,9	80,4	66,98	78,06	80,08	79,90
S 04	26,6	25,5	46,6	33,38	44,96	44,46	46,01
S 13	18,8	20,2	17,0	22,21	27,14	29,52	20,09
S 18	21,4	25,5	23,4	23,09	19,96	13,40	17,48
S 19	18,9	15,7	16,9	17,29	17,24	16,67	16,69
S 20*							
S 21	32,8	34,7	37,6	40,79	45,42	44,11	47,00
S 22	13,4	7,6	6,9	8,21	8,46	9,35	10,03
S 23	34,2	45,3	53,2	48,08	46,56	39,28	37,43
S 05	4,7	6,6	7,2	9,39	7,85	8,13	6,65
S 06	6,6	5,3	5,4	4,03	3,65	9,35	4,25
S 07	10,4	9,8	9,1	10,53	11,64	9,59	6,10
S 08	2,5	0,5	1,4	3,92	2,96	2,77	3,29
S 09	2,4	2,6	1,7	1,55	1,03	1,47	1,11
S10	2,4	2,5	2,9	3,33	3,71	2,72	1,76
S11	7,8	5,0	4,9	4,87	5,83	5,69	5,38
S12	2,2	2,7	3,0	1,77	1,78	1,24	1,33
S14	6,6	5,9	3,8	3,18	2,80	5,65	3,14
S15	2,0	1,5	1,6	1,60	0,58	1,21	1,31
S16	4,1	2,4	2,8	2,03	2,12	1,52	1,75
S17	0,9	0,8	0,9	0,80	1,08	1,92	2,06
S24	0,5	0,9	1,3	1,81	2,44	1,52	1,42
S25	0,2	2,9	12,1	0,75	0,62	0,69	2,07

Slika 20. / *Figure 20.*
SPECIJALNE BOLNICE - POTROŠNJA ANTIBIOTIKA 2017.-2023.
SPECIALTY HOSPITALS – ANTIBIOTIC CONSUMPTION 2017-2023



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*

Potrošnja antibiotika u Hrvatskoj u skladu s AWaRe klasifikacijom

Odbor stručnjaka Svjetske zdravstvene organizacije razvio je AWaRe klasifikaciju antibiotika 2017. godine s ciljem podrške u upravljanju antibioticima na lokalnoj, nacionalnoj i globalnoj razini.

Antibiotici su podijeljeni u tri grupe, „Access", „Watch" i „Reserve" prema utjecaju pojedinih antibiotika i klasa antibiotika na antimikrobnu rezistenciju uz naglasak na važnost njihove pravilne primjene.

U skupini **„Access"** trenutno je 87 antibiotika koji su namijenjeni za liječenje 25 najčešćih infekcija. Radi se o antibioticima koji moraju biti dostupni, pristupačni i sigurne kvalitete. Najčešći koje koristimo iz te grupe su ß-laktamski antibiotici, penicilini (ampicilin, amoksicilin, ko-amoksiklav, benzilpenicilin, fenoksimetil penicilin, prokain benzilpenicilin, kloksacilin) te cefalosporini, od kojih su u toj skupini samo cefazolin i cefaleksin iz 1. generacije cefalosporina. Ostali antibiotici koji se češće koriste, a pripadaju toj skupini su klindamicin, metronidazol, nitrofurantoin, gentamicin i doksiciklin.

U skupini **„Watch"** je uključeno 147 antibiotika, od kojih je većina kritično važnih, koji se preporučuju samo za specifične, ograničene indikacije. To je skupina s najvišim potencijalom za razvoj rezistencije bakterija na antibiotike. U toj skupini su, uz ostale, piperacilin+tazobaktam, svi cefalosporini 2., 3. i 4. generacije, makrolidi (azitromicin, klaritromicin), kinoloni, meropenem i vankomicin.

U skupini **„Reserve"** je 29 antibiotika, koji se koriste kao posljednja linija obrane, uglavnom isključivo u bolnici. Najčešće primjenjivani antibiotici kod nas, iz te skupine, su kolistin, polimiksin B, fosfomicin i.v., linezolid te beta-laktamski antibiotici s inhibitorima beta-laktamaza novije generacije.

Svake dvije godine AWaRe klasifikacija antibiotika se obnavlja, i dostupna je na linku: https://www.who.int/publications/i/item/WHO-MHP-HPS-EML-2023.04

AWaRe klasifikacija antibiotika je osmišljena kao alat za praćenje potrošnje antibiotika i praćenje učinaka politika upravljanja kojima je za cilj optimizirati upotrebu antibiotika i kontrolirati antimikrobnu otpornost. Kao početna godina od koje se prate postavljeni ciljevi je 2019. godina, godina prije pandemije uzrokovane SARS CoV-2 virusom.

Prvi cilj članica Europske unije (EU) do 2030. godine je smanjenje ukupne potrošnje antibiotika za 20%, što bi za Hrvatsku značilo ukupnu potrošnju od 17,1 DDD/TID u ciljnoj godini. Hrvatska u 2019. godini ima nižu ukupnu potrošnju antibiotika u odnosu na prosjek EU (18,8 vs.19,9 DDD/TID). Nažalost, takve vrijednosti nisu zadržane u 2023. godini, kada je Hrvatska po ukupnoj potrošnji nadmašila prosjek EU (Tablica 22.).

Drugi cilj je vezan uz primjenu antibiotika u skladu s AWaRe klasifikacijom, prema kojoj bi udio antibiotika iz skupine „Access" trebao biti najmanje 65 %. U 2019. godini ukupna potrošnja antibiotika iz skupine „Access" iznosila je 62,73%, dok je u 2023. godini udio smanjen na 60,71% (Slika 21. i Slika 22.).

I ove brojke i postoci ukazuju da je potrebno intenzivirati napore za primjenu rukovođenog propisivanja antibiotika u primarnoj zdravstvenoj zaštiti i u bolnici kako bi dosegli postavljene ciljeve.

Antibiotic consumption in Croatia according to the AWaRe classification

The World Health Organization's Expert Committee developed the AWaRe classification of antibiotics in 2017 to support management of prescribing antibiotics at local, national, and global levels. Antibiotics are divided into three groups: 'Access,' 'Watch,' and 'Reserve,' based on the impact of individual antibiotics and antibiotic classes on antimicrobial resistance, with emphasis on the importance of their proper use.

The **'Access'** group currently includes 87 antibiotics intended for the treatment of 25 most common infections. These are antibiotics that must be available, affordable, and of safe quality. The most commonly used antibiotics from this group include β-lactam antibiotics, penicillins (ampicillin, amoxicillin, co-amoxiclav, benzylpenicillin, phenoxymethylpenicillin, procaine benzylpenicillin, cloxacillin), and cephalosporins, of which only cefazolin and cephalexin from 1st generation of cephalosporins are in this group. Other frequently used antibiotics in this group include clindamycin, metronidazole, nitrofurantoin, gentamicin, and doxycycline.

The **'Watch'** group contains 147 antibiotics, most of which are critically important and recommended only for specific, limited indications. This group has the highest potential for the development of bacterial resistance to antibiotics. It includes, among others, piperacillin+tazobactam, all 2nd, 3rd, and 4th generation cephalosporins, macrolides (azithromycin, clarithromycin), quinolones, meropenem, and vancomycin.

The **'Reserve'** group includes 29 antibiotics, which are used as the last line of defence, primarily in hospitals. In our country, the most commonly used antibiotics from this group are colistin, polymyxin B, fosfomycin IV, linezolid, and newer generation beta-lactam antibiotics with beta-lactamase inhibitors.

The AWaRe classification of antibiotics is updated every two years and is available at the link: https://www.who.int/publications/i/item/WHO-MHP-HPS-EML-2023.04

The AWaRe classification of antibiotics is designed as a tool for monitoring antibiotic consumption and tracking the effects of management policies aimed at optimizing antibiotic use and controlling antimicrobial resistance. The baseline year for tracking the established objectives is 2019, the year preceding the SARS-CoV-2 pandemic.

The first goal for European Union (EU) member states is to reduce total antibiotic consumption by 20% until 2030, which would mean for Croatia an overall usage of 17.1 DDD/TID in the target year. In 2019, Croatia had a lower total antibiotic consumption compared to the EU average (18.8 vs. 19.9 DDD/TID). Unfortunately, these values were not maintained in 2023, when Croatia exceeded the EU average in overall consumption (Table 22).

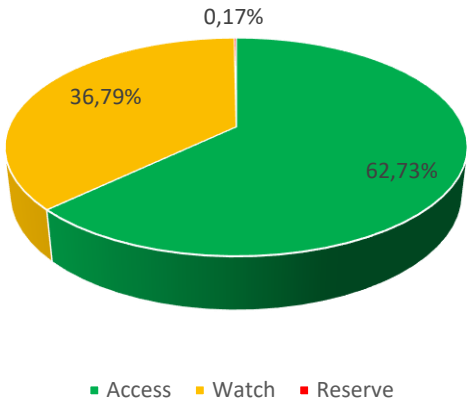
The second goal relates to the use of antibiotics according to the AWaRe classification, where the share of antibiotics from the 'Access' group should be at least 65%. In 2019, the total consumption of 'Access' antibiotics was 62.73%, while in 2023, this share decreased to 60.71% (Figures 21 and 22).

These figures and percentages indicate that efforts need to be intensified to implement antibiotic stewardship both in primary healthcare and hospitals in order to reach the set objectives.

Tablica 22. / *Table 22.*
Ukupna potrošnja antibiotika izražena u DDD/TID
Total antibiotic consumption DDD/TID

DDD/TID	2019.	2023.	2030.
Hrvatska	18,8	21,2	17,1
EU	19,9	20	15,9

Slika 21. / *Figure 21.*
Ukupna potrošnja antibiotika u skladu s AWaRe klasifikacijom 2019. (%)
Total antibiotic consumption in accordance with the AWaRe classification 2019 (%)



Slika 22. / *Figure 22.*
Ukupna potrošnja antibiotika u skladu s AWaRe klasifikacijom 2023. (%)
Total antibiotic consumption in accordance with the AWaRe classification 2023 (%)