AKADEMIJA MEDICINSKIH ZNANOSTI HRVATSKE
KOLEGIJ JAVNOG ZDRAVSTVA
ODBOR ZA PRAĆENJE REZISTENCIJE BAKTERIJA NA ANTIBIOTIKE U REPUBLICI HRVATSKOJ
ACADEMY OF MEDICAL SCIENCES OF CROATIA
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
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SECTION FOR ANTIBIOTIC RESISTANCE

Osjetljivost i rezistencija bakterija na antibiotike u Republici Hrvatskoj u 2024. g.

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PREDGOVOR:

U 2024.g. smo ušli svjesni konkretnih ciljeva koje nam je za 2030.g. postavila Europska komisija: smanjiti ukupnu potrošnju antibiotika u humanoj medicini za 9%; povećati udio usko spektralnih antibiotika tako da barem 65% primijenjenih antibiotika bude iz grupe „Access" prema AWaRe klasifikaciji antibiotika; smanjiti za 6% incidenciju bakterijemija uzrokovanih bakterijom *Staphylococcus aureus* rezistentnom na meticilin (MRSA); zadržati incidenciju bakterijemija uzrokovanih bakterijom *Escherichia coli* rezistentnom na cefalosporine 3. generacije na istoj razini; smanjiti za 4% incidenciju bakterijemija uzrokovanih bakterijom *Klebsiella pneumoniae* rezistentnom na karbapeneme. Kao referentna godina, u odnosu na koju se navode tražene vrijednosti smanjenja potrošnje antibiotika i incidencije bakterijemija, odabrana je predpandemijska 2019.g. Činjenica je da je u mnogim europskim zemljama, a nažalost i u Hrvatskoj, tijekom pandemije COVID-19 došlo do porasta incidencije infekcija uzrokovanih rezistentnim bakterijama, prvenstveno onih uzrokovanih karbapenem rezistentnim *Acinetobacter baumannii* i karbapenem rezistentnom *Klebsiella pneumoniae*. Nakon pandemije broj izolata *A. baumannii* se vratio približno na vrijednosti prije pandemije, no broj prijavljenih *K. pneumoniae* izolata rezistentnih na karbapeneme je nastavio rasti. Iako je ove godine prijavljeno nešto manje bakterijemija uzrokovanih ovim uzročnicima, stope rezistencije su veće i među invazivnim izolatima. Nažalost, nakon pandemije, potrošnja antibiotika i u ambulantnom i u bolničkom sektoru pokazuje zabrinjavajući trend porasta. Podaci kontinuiranog praćenja rezistencije i potrošnje antibiotika izneseni u ovoj publikaciji trebali bi biti podloga za intervencije na nacionalnoj i lokalnoj razini. Na nacionalnoj razini u 2024.g. je održano nekoliko značajnih sastanaka. Na „11. hrvatskom simpoziju o rezistenciji na antibiotike", održanom u ožujku u Zagrebu, uz prezentiranje aktualne situacije s rezistencijom u Hrvatskoj i svijetu dominirale su teme o intervencijama usmjerenim na optimiziranje uporabe antibiotika, od smjernica i indikatora racionalne primjene antibiotika do elemenata programa upravljanja antimikrobnom terapijom (engl. „antimicrobial stewardship", AMS). Na simpozij su kao predavači bili pozvani i gosti iz zemalja koje imaju uhodane AMS programe, koji su s nama podijelili iskustva u organiziranju ovih programa u lokalnim sredinama. U lipnju je održana prva „Škola antimikrobne terapije" u Trakošćanu, za koju se nadamo da će evoluirati u kontinuirano, iznimno potrebno, nacionalno događanje. Na jesen je u Zagrebu održan simpozij „Stiže zima" s prikladnom temom respiratornih infekcija te je tradicionalno održan „Simpozij povodom obilježavanja Europskog dana (EAAD) i Svjetskog tjedna (WAAW) svjesnosti o antimikrobnim lijekovima". Okrugli stol ovogodišnjeg EAAD / WAAW simpozija bio je posvećen unaprjeđenju dodiplomske edukacije u području praktične primjene antibiotika, jer se principi AMS moraju usvajati već na toj razini. U kontroli širenja rezistencije na antibiotike iznimno je važna suradnja između humane i veterinarske medicine unutar jedinstvenog zdravstva. Važna tema na „7. hrvatskom veterinarskom kongresu", održanom u listopadu u Dubrovniku bila je upravo antimikrobna rezistencija. Na lokalnoj razini, u mnogim zdravstvenim ustanovama, nažalost, još uvijek nedostaju AMS programi i A-timovi koji bi organizirano provodili optimalizaciju primjene antibiotika u praksi.

Arjana Tambić Andrašević

Predsjednica Odbora za praćenje rezistencije bakterija na antibiotike u RH

PREFACE:

In 2024, we entered the year aware of the specific goals set for us by the European Commission for 2030: to reduce the overall consumption of antibiotics in human medicine by 9%; to increase the proportion of narrow-spectrum antibiotics so that at least 65% of antibiotics used belong to the "Access" group according to the WHO AWaRe classification; to reduce by 6% the incidence of bloodstream infections caused by methicillin-resistant Staphylococcus aureus (MRSA); to maintain the incidence of bloodstream infections caused by Escherichia coli resistant to third-generation cephalosporins at the same level; and to reduce by 4% the incidence of bloodstream infections caused by Klebsiella pneumoniae resistant to carbapenems. The reference year against which the required reductions in antibiotic consumption and bacteremia incidence are measured is the pre-pandemic year 2019. The fact is that in many European countries, including unfortunately Croatia, the COVID-19 pandemic led to an increase in the incidence of infections caused by resistant bacteria, primarily those caused by carbapenem-resistant *Acinetobacter baumannii* and carbapenem-resistant *Klebsiella pneumoniae*. After the pandemic, the number of *A. baumannii* isolates returned to approximately pre-pandemic levels, but the number of reported *K. pneumoniae* isolates resistant to carbapenems continued to rise. Although this year slightly fewer bacteremias caused by these pathogens were reported, resistance rates are higher, even among invasive isolates. Unfortunately, after the pandemic, antibiotic consumption in both outpatient and hospital sectors has shown an alarming upward trend. The continuous surveillance data on resistance and antibiotic consumption presented in this publication should serve as a basis for interventions at the national and local levels. At the national level, several important meetings were held in 2024. At the "11th Croatian Symposium on Antibiotic Resistance," held in March in Zagreb, alongside presentations of the current resistance situation in Croatia and worldwide, the main topics focused on interventions aimed at optimizing antibiotic use — from guidelines and indicators of rational antibiotic use to elements of antimicrobial stewardship (AMS) programs. Guest speakers from countries with well-established AMS programs were invited to share their experiences in organizing such programs in local healthcare settings. In June, the first "School of Antimicrobial Therapy" was held in Trakošćan, which we hope will evolve into a continuous and much-needed national event. In autumn, the "Winter is Coming" symposium was held in Zagreb, focusing on respiratory infections, along with the traditional "Symposium marking the European Antibiotic Awareness Day (EAAD) and the World Antimicrobial Awareness Week (WAAW)." The round table at this year's EAAD/WAAW symposium was dedicated to improving undergraduate education in the practical application of antibiotics, since AMS principles must be adopted already at that level. In controlling the spread of antibiotic resistance, cooperation between human and veterinary medicine within the framework of One Health is of utmost importance. A key topic at the "7th Croatian Veterinary Congress," held in October in Dubrovnik, was precisely antimicrobial resistance. At the local level, many healthcare institutions still unfortunately lack AMS programs and dedicated antimicrobial teams ("A-teams") that would systematically implement antibiotic use optimization in 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. donio 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 Academy of Medical Sciences of Croatia. 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 fields 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

POGLAVLJE / *CHAPTER* **1**.

REZISTENCIJA BAKTERIJSKIH IZOLATA U 2024. GODINI

ANTIBIOTIC RESISTANCE IN 2024

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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 The European Committee on Antimicrobial Susceptibility Testing (EUCAST) i na godišnjem 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 i 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 anual meeting. Due to the regular Committee meetings and NAC activity a high level of interlaboratory standardization is achieved and the external quality assessment (EQA) results demonstrate high reproducibility of collected 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.

MATERIJAL I METODE

Globalno praćenje rezistencije

U praćenje su uključeni svi izolati dogovorenih bakterijskih vrsta izolirani iz kliničkih materijala u razdoblju od 1.10. do 31.12.2024.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 31.12.2024. Podatke za 2024.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. Ako broj testiranih izolata za određeni antibiotik odstupa više od 30% rezultati za taj antibiotik se ne prikazuju u tablici. 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 2024.g. korišteni su za testiranje i interpretaciju nalaza standardi europskog odbora, European Committee on Antimicrobial Susceptibility Testing (EUCAST) (Clinical Breakpoint Tables v. 14.0). U testiranju osjetljivosti na antibiotike većina laboratorija koristi disk difuzijsku metodu, a određivanje minimalnih inhibitornih koncentracija (MIK) se koristi za određivanje 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 2024.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 2024.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 2024. Data on group A streptococci, salmonellae, shigellae and anaerobic bacteria were reported for the whole year, from 1 January to 31 December 2024 due to the small number of isolates. In 2024 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. If the number of isolates tested for a certain antibiotic deviates for >30% from the number of isolates tested to most antibiotics, results for this antibiotic are not presented. 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 2024 all laboratories used the European Committee on Antimicrobial Susceptibility Testing (EUCAST) standards for susceptibility testing (Clinical Breakpoint Tables v. 14.0). Disk diffusion method is the most widely used susceptibility testing method in Croatian laboratories and minimal inhibitory concentration (MIC) testing is used 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 2024 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 2024 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 2024.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 *E. faecium* i *A. baumannii* prikazao rezultate za cijelu godinu
- KA OB je za *S. pneumoniae, S. aureus*/MSSA, *S. aureus*/MRSA, *E. faecalis, E. faecium* i *H. influenzae* prikazala rezultate za cijelu godinu
- KC ZZJZ je za *E. faecium* i *H. influenzae* prikazao rezultate za cijelu godinu
- KR ZZJZ je za *E. faecium* prikazao rezultate za cijelu godinu
- PK OŽB je za BHS-A prikazao rezultate za razdoblje od 1.10. do 31.12.2024.
- SB NZZJZ je za *S. pneumoniae* prikazao rezultate za cijelu godinu
- ŠI ZZJZ je za *A. baumannii* 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)
- ZD ZZJZ je za *S. pneumoniae, E. faecalis, E. faecium* i *H. influenzae* prikazao rezultate za cijelu godinu
- ZG KBC je za *E. faecalis* i *K. pneumoniae* prikazao rezultate za razdoblje od 1.10. do 13.10.2024., za *Enterobacter* spp*., Klebsiella aerogenes, Serratia* spp. i *Citrobacter* spp. prikazao rezultate za razdoblje od 1.10 do 16.10.2024., za *E. faecium* za razdoblje od 1.10. do 23.10.2024., za *E. coli* za razdoblje od 1.10 do 6.10.2024, za *P. mirabilis i P. aeruginosa* za razdoblje od 1.10. – 20.10.2024.
- ZG NZZJZ je za *E. faecalis* prikazao rezultate za razdoblje od 1.10. do 11.10.2024., za *E. coli* za razdoblje od 14.10. do 18.10.2024., za *P. mirabilis*, *K. pneumoniae*, *Enterobacter* spp*., Klebsiella aerogenes*, *Serratia* spp. i *Citrobacter* spp za razdoblje od 14.10. do 28.10.2024., za *P. aeruginosa* i *A. baumannii* za razdoblje od 1.10. do 13.12.2024.

Pet laboratorija je prijavilo izolaciju šigela: ČK ZZJZ *S. flexneri* (3); ST NZZJZ *S. boydii* (2); ZG KBC *S. boydii* (1), ZG KBCSM *S. flexneri* (1) i ZG KIB *S. sonnei* (7), *S. flexneri* (4). Ukupno je tijekom 2024.g. izolirano 18 šigela.

U 2024.g. ukupno je obrađeno 1 882 anaerobnih bakterija, *Cutibacterium acnes* (354); *Bacteroides* spp. (1010); *Prevotella* spp. (390); *Fusobacterium necroforum* (15); *Clostridium perfringens* (113)

iz 23 centara: ČK ZZJZ *Bacteroides* spp. (60), *Cutibacterium acnes* (2), *Prevotella* spp. (12), *Clostridium perfringens* (6); DU ZZJZ *Bacteroides* spp. (1); KA OB *Cutibacterium acnes* (13), *Bacteroides* spp. (28), *Prevotella* spp. (16), *Fusobacterium necroforum* (2), *Clostridium perfringens* (8); KC ZZJZ *Bacteroides* spp. (8), *Clostridium perfringens* (3); OG OB *Cutibacterium acnes* (1), *Bacteroides* spp. (2), *Clostridium perfringens* (2); OS KBC *Cutibacterium acnes* (30), *Bacteroides* spp. (126), *Prevotella* spp. (80), *Fusobacterium necroforum* (3), *Clostridium perfringens* (3); PU NZZJZ *Bacteroides* spp. (17), *Prevotella* spp. (1), *Clostridium perfringens* (2); RI KBC *Bacteroides* spp. (48), *Prevotella* spp. (3), *Clostridium perfringens* (4); SB ZZJZ *Cutibacterium acnes* (7), *Bacteroides* spp. (8), *Prevotella* spp. (3); ŠI ZZJZ *Cutibacterium acnes* (7), *Bacteroides* spp. (10), *Prevotella* spp. (11); SK ZZJZ *Cutibacterium acnes* (6), *Bacteroides* spp. (10), *Fusobacterium necroforum* (2), *Clostridium perfringens* (7); ST KBC *Cutibacterium acnes* (8), *Bacteroides* spp. (54), *Prevotella* spp. (16), *Clostridium perfringens* (11); VK ZZJZ *Bacteroides* spp. (3), *Prevotella* spp. (2), *Fusobacterium necroforum* (1), *Clostridium perfringens* (6); VT ZZJZ *Bacteroides* spp. (1), *Clostridium perfringens* (1); VŽ ZZJZ *Cutibacterium acnes* (19), *Bacteroides* spp. (74), *Prevotella* spp. (27), *Clostridium perfringens* (4); ZG HZJZ *Prevotella* spp. (3); ZG KBC *Cutibacterium acnes* (105), *Bacteroides* spp. (168), *Prevotella* spp. (79), *Fusobacterium necroforum* (2), *Clostridum perfringens* (21); ZG KBD *Cutibacterium acnes* (28), *Bacteroides* spp. (64), *Prevotella* spp. (4), *Clostridum perfringens* (17); KBM *Cutibacterium acnes* (2), *Bacteroides* spp. (37), *Prevotella* spp. (1), *Clostridium perfringens* (5); ZG KBCSM *Cutibacterium acnes* (115), *Bacteroides* spp. (273), *Prevotella* spp. (121), *Fusobacterium necroforum* (4), *Clostridium perfringens* (12); ZG KIB *Cutibacterium acnes* (3), *Bacteroides* spp. (9), *Prevotella* spp. (1), *Clostridium perfringens* (1); ZG KBSD *Cutibacterium acnes* (5), *Bacteroides* spp. (9), *Fusobacterium necroforum* (1), *Prevotella* spp. (8); ZG LABPLUS *Cutibacterium acnes* (3), *Prevotella* spp. (2).

RESULTS

Thirty-seven centers took part in antibiotic resistance surveillance in Croatia in 2024. 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 *E. faecium* and *A. baumannii* for the whole year
- KA OB reported data for *S. pneumoniae, S. aureus*/MSSA, *S. aureus*/MRSA, *E. faecalis, E. faecium* and *H. influenzae* for the whole year
- KC ZZJZ reported data for *E. faecium* and *H. influenzae* for the whole year
- KR ZZJZ reported data for *E. faecium* for the whole year
- PK OŽB reported data for BHS-A for the period 1.10.-31.12.2024.
- SB ZZJZ reported data for *S. pneumoniae* for the whole year
- ŠI ZZJZ reported data for *A. baumannii* 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 GH Vinkovci)
- ZD ZZJZ reported data for *S. pneumoniae, E. faecalis, E. faecium* and *H. influenzae* for the whole year
- ZG KBC reported data for *E. faecalis* and *K. pneumoniae* for the period 1.10. – 13.10.2024., for *Enterobacter* spp., *Klebsiella aerogenes, Serratia* spp. and *Citrobacter* spp reported data for the period 1.10. – 16.10.2024., for *E. faecium* for the period 1.10. – 23.10.2024., for *E. coli* for the period 1.10. – 6.10.2024., for *P. mirabilis* and *P. aeruginosa* for the period 1.10. – 20.10.2024.
- ZG NZZJZ reported data for *E. faecalis* for the period 1.10. – 11.10.2024., for *E. coli* for the period 14.10. – 18.10.2024., for *P. mirabilis, K. pneumoniae, Enterobacter* spp., *Klebsiella aerogenes, Serratia* spp. and *Citrobacter* spp. for the period 14.10. – 28.10.2024., for *P. aeruginosa* and *A. baumannii* for the period 1.10. – 13.12.2024.

Five laboratories reported shigella isolates: ČK ZZJZ *S. flexnerii* (3); ST NZZJZ *S. boydii* (2); ZG KBC *S. boydii* (1); ZG KBCSM *S. flexnerii* (1) i ZG KIB *S. flexnerii* (4), *S. sonnei* (7). Altogether 18 shigella isolates were reported in 2024.

In 2024 altogether 1 840 anaerobic bacteria were isolated, *Cutibacterium acnes* (354); *Bacteroides* spp. (973); *Prevotella* spp. (390); *Fusobacterium necroforum* (15); *Clostridium perfringens* (109).

They were isolated in 23 centers: ČK ZZJZ *Bacteroides* spp. (60), *Cutibacterium acnes* (2), *Prevotella* spp. (12), *Clostridium perfringens* (6); DU ZZJZ *Bacteroides* spp. (1); KA OB *Cutibacterium acnes* (13), *Bacteroides* spp. (28), *Prevotella* spp. (16), *Fusobacterium necroforum* (2), *Clostridium perfringens* (8); KC ZZJZ *Bacteroides* spp. (8), *Clostridium perfringens* (3); OG OB *Cutibacterium acnes* (1), *Bacteroides* spp. (2), *Clostridium perfringens* (2); OS KBC *Cutibacterium acnes* (30), *Bacteroides* spp. (126), *Prevotella* spp. (80), *Fusobacterium necroforum* (3), *Clostridium perfringens* (3); PU NZZJZ *Bacteroides* spp. (17), *Prevotella* spp. (1), *Clostridium perfringens* (2); RI KBC *Bacteroides* spp. (48), *Prevotella* spp. (3), *Clostridium perfringens* (4); SB ZZJZ *Cutibacterium acnes* (7), *Bacteroides* spp. (8), *Prevotella* spp. (3); SK ZZJZ *Cutibacterium acnes* (6), *Bacteroides* spp. (10), *Prevotella* spp (11); ST KBC *Cutibacterium acnes* (8), *Bacteroides* spp. (54), *Prevotella* spp. (16), *Clostridium perfringens* (11); ŠI ZZJZ *Cutibacterium acnes* (7), *Bacteroides* spp. (10), *Prevotella* spp. (11); SK ZZJZ *Cutibacterium acnes* (6), *Bacteroides* spp. (10). *Fusobacterium necroforum* (2), *Clostridium perfringens* (7); VŽ ZZJZ *Cutibacterium acnes* (19), *Bacteroides* spp. (74), *Prevotella* spp. (27), *Clostridium perfringens* (4); ZG HZJZ *Prevotella* spp. (3), ZG KBC *Cutibacterium acnes* (105), *Bacteroides* spp. (168), *Prevotella* spp. (79), *Fusobacterium necroforum* (2), *Clostridium perfringens* (21); ZG KBD *Cutibacterium acnes* (28), *Bacteroides* spp. (64), *Prevotella* spp. (4), *Clostridum perfringens* (17); KBM *Cutibacterium acnes* (2), *Bacteroides* spp. (37), *Prevotella* spp. (1), *Clostridium perfringens* (5); ZG KBCSM *Cutibacterium acnes* (115), *Bacteroides* spp. (273), *Prevotella* spp. (121), *Fusobacterium necroforum* (4), *Clostridium perfringens* (12); ZG KIB *Cutibacterium acnes* (3), *Bacteroides* spp. (9), *Prevotella* spp. (1)., *Clostridium perfringens* (1); ZG KBSD *Cutibacterium acnes* (5), *Bacteroides* spp. (9), *Fusobacterium necroforum* (1), *Prevotella* spp. (8); ZG LABPLUS *Cutibacterium acnes* (3), *Prevotella* spp. (2).

DISKUSIJA

Poremećaj u incidenciji respiratornih patogena uvjetovan epidemijom SARS-CoV-2 virusa, bio je znatno kraći za *Streptococcus pneumoniae* i *Haemophilus influenzae* negoli za streptokok grupe A (BHS-A) koji je nakon izuzetno niske incidencije tijekom 2020. i 2021.g. pokazao nagli porast u 2022.g., a visoke razine su se zadržale i u 2023.g. U 2024.g. broj izolata BHS-A je ipak počeo opadati, ali je još uvijek iznad vrijednosti 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., 16.567 u 2024.g.). Promjene u incidenciji su još uočljivije ako se uspoređuju sezone jesen / zima negoli kad se uspoređuju kalendarske godine (podaci Klinike za infektivne bolesti). Srećom, porast incidencije BHS-A nije bio praćen porastom rezistencije, već su stope rezistencije na makrolide u razdoblju veće incidencije postale niže i iznose 5% u 2024.g. i 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 2024.g. i 2023.g., 1% u 2022.g., 5% u 2021.g., 4% u 2020.g.; inducibilna 1% u 2024.g. i 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 nisu pogodan uzorak za etiološku dijagnostiku respiratornih infekcija jer nalazi pokazuju slabu korelaciju s kliničkom slikom, no mogu poslužiti kao uzorci 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 (5% u 2024.g., 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 i 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 sličan prošlogodišnjem (16% u 20124.g., 15% 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 2024.g. iznosi 21% što je nešto više od prošlogodišnje stope (18%). 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 2024.g., 96% svih pneumokoka ima MIK penicilina ≤2.0 mg/L i reagirat će na dozu od 6x2.4g (6x4MIU), 93% pneumokoka ima MIK penicilina ≤1.0 mg/L i reagirat će na dozu od 4x2.4g (4x4MIU) ili 6x1.2g (6x2MIU), a 90% pneumokoka ima MIK penicilina ≤0.5 mg/L i reagirat će na dozu od 4x1.2g (4x2MIU). Ove stope su slične 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 2024.g. je bilo 89% osjetljivih pneumokoka koji su dostupni liječenju standardnom dozom oralnog amoksicilina (3x500mg) i parenteralnog ampicilina (3x2g), što je podjednako prijašnjim stopama (92% u 2023.g. i 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 93% pneumokoka (94% u 2023.g., 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 tri godine (93% u 2024.g., 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 u tom razdoblju bila nešto niža, ali je u 2024.g. zabilježen lagani porast (26% u 2024.g., 24% u 2023.g. i 2022.g., 28% u 2021.g., 29% u 2020.g., 31% u 2019.g., 32% u 2018.g.). Općenito, u 2024.g. se bilježi blagi porast rezistencije pneumokoka na ne-betalaktamske antibiotike. Trend pada rezistencije na ko-trimoksazol se, nažalost, zaustavio i u 2024.g. ponovo prelazi 20% (23% u 2024.g., 17% u 2023.g., 13% u 2022.g., 14% u 2021.g., 17% u 2019.g. i 2020.g., 20% u 2018.g., 22% u 2017.g., 23% u 2016.g., 26% u 2015.g., 29% u 2014., 27% u 2013.g., 29% u 2012.g., 35% u 2011.g., 43% u 2010.g.). Rezistencija na tetraciklin, koja je također pokazivala blagi trend pada, ponovno je viša od 20% (21% u 2024.g., 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% na moksifloksacin) i ovi antibiotici se ne bi smjeli široko upotrebljavati u empirijskoj terapiji respiratornih infekcija.

Amoksicilin je prvi lijek izbora za liječenje respiratornih infekcija kod kojih se računa da bi uzročnik mogao biti i *Haemophilus influenzae*. Rezistencija na amoksicilin je u 2024.g. bila slična prošlogodišnjim stopama (20% u 2024.g., 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.). Dodavanje klavulanske kiseline značajno pospješuje učinkovitost amoksicilina na *H. influenzae*. Rezistencija na ko-amoksiklav iznosi 7%, identično kao i prošle godine. Korištenjem EUCAST standarda detektira se 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 (20%) je slična stopama rezistencije prethodnih godina, a rezistencija na ceftriakson je <1%.

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 (20%) i klindamicin (16%), 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 četiri godine praćenja. Stečena rezistencija na kinolone kod MSSA je niska (3%), 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 2024.g. stopa MRSA je identična onoj u 2023.g. (19% u 2024.g. i 2023.g., 21% u 2022.g.). Ukupan broj izolata MRSA je niži negoli na početku pandemije, ali još uvijek viši negoli prije pandemije (997 izolata u 2024.g., 960 izolata u 2023.g., 955 izolata u 2022.g., 1.238 u 2021.g., 699 u 2020.g., 784 u 2019.g.). Jedan od ciljeva koje je Europska komisija zadala Hrvatskoj za ostvariti do 2030.g. je smanjenje MRSA bakterijemija u odnosu na 2019.g. Ako ne dođe do smanjenja ukupnih MRSA izolata, bit će teško ostvariti ovaj zadani cilj. Udio MRSA sojeva rezistentnih na klindamicin (81%) je nešto viši od prošlogodišnjeg (77%), a naročito raste postotak sojeva s inducibilnom rezistencijom na klindamicin (34% u 2024.g., 21% u 2023.g.). Rezistencija MRSA na gentamicin je slična vrijednostima zabilježenima prethodnih godina, 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., 12% u 2024.g.). Rezistencija na linezolid i vankomicin nije uočena. Udio izolata s MIK-om vankomicina od 2.0 mg/L je nešto viši negoli prethodnih godina (16% u 2024.g., 12% u 2023.g., 11% u 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 slična kao prethodnih godina (8% u 2024.g., 10% u 2023.g., 11% u 2022.g., 5% u 2021.g.), ali je udio izolata koje treba liječiti višim dozama nešto viši

(12% u 2024.g., 8% u 2023.g. i 2022.g., 9% u 2021.g.). U slučaju pneumonije, na ceftarolin je rezistentno 20% izolata. Stopa rezistencije na ko-trimoksazol je jednaka prošlogodišnjoj (6% u 2024.g. i 2023.g., 7% u 2022.g., 5% u 2021.g. i 2020.g.), a rezistencija na tetraciklin, čije praćenje je uvedeno 2021.g., iznosi 11% slično kao i u prve tri godine praćenja (10% u 2023.g., 2022.g. i 2021.g.) i nije značajno viša od stopa rezistencije kod MSSA (4%). Rezistencija na rifampicin je i dalje niska (3%), 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 težih infekcija. Kod sojeva visoko rezistentnih na aminoglikozide, ovi se antibiotici ne mogu upotrebljavati niti u kombiniranoj terapiji. Udio sojeva s visokom rezistencijom na aminoglikozide iznosi 24% za *E. faecalis* i 47% 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 (54%), i ponovno u porastu (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., 54% u 2024.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. Nažalost, uz povišenje stope rezistencije u 2024.g., zabilježen je ponovno i značajan porast ukupnog broja izolata (1.527 izolata u 2024.g., 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* ne pokazuje velike oscilacije osim pada u prvoj pandemijskoj godini (5.947 u 2024.g., 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). Testiranje osjetljivosti na norfloksacin disk difuzijom, služi 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 (24% i 88% u 2024.g., 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 (2%).

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 razdoblju prije epidemije (23.307 izolata u 2024.g., 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 je dijagnostička aktivnost za bakterijske infekcije, bila reducirana samo u prvoj godini COVID epidemije. Od početka praćenja, *E. coli* pokazuje visoku rezistenciju na

ampicilin, koja i u 2024.g. iznosi 50%, slično kao i prethodnih godina. Kod osjetljivih izolata, oralni amoksicilin se može koristiti u standardnoj dozi samo ako se radi o nekompliciranoj IMS. Kod kompliciranih IMS, oralni amoksicilin se mora koristiti u višim dozama, a kod infekcija izvan urotrakta amoksicilin se za osjetljive izolate može koristiti samo u kombinaciji s drugom učinkovitom terapijom. Amoksicilin s dodatkom klavulanske kiseline pokazuje puno veću djelotvornost jer klavulanska kiselina uspješno blokira beta-laktamaze širokog spektra i većinu beta-laktamaza proširenog spektra (engl. "extended spectrum beta-lactamases, ESBL"). 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., 13% u 2024.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. i 2024.g.). I za amoksicilin s klavulanskom kiselinom vrijedi pravilo da se oralni pripravak primjenjuje u višim dozama ako se radi o kompliciranoj IMS, odnosno u kombinaciji s drugom učinkovitom terapijom ako se radi o infekcijama izvan urotrakta. Oralni pripravak cefuroksima se preporuča samo za nekomplicirane uroinfekcije. Kod osjetljivih izolata, u toj indikaciji, može se primjenjivati u standardnoj dozi te za oralnu primjenu kod nekompliciranih IMS postoje kategorije „S" i „R". Parenteralni cefuroksim se 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 slična prošlogodišnjoj (12% u 2024.g., 11% u 2023.g. i 2022.g., 10% u 2021.g., 11% u 2020.g.). Rezistencija na cefalosporine treće generacije (9% do 11%) je jednaka prošlogodišnjim stopama. To je bitno jer je jedan od ciljeva koje je Hrvatskoj postavila Europska komisija za ispunjenje do 2030.g., održavanje incidencije bakterijemija uzrokovanih izolatima *E. coli* rezistentnima na treću generaciju cefalosporina na razini incidencije 2019.g. 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 je od početka praćenja niska (1% u 2024.g., 2% u 2023.g. i 2022.g.). Rezistencija na ciprofloksacin je 2017.g. dosegla 20%, ali od tada stagnira i ovogodišnja stopa se ne razlikuje bitno od prošlogodišnjih stopa (19% u 2024.g i 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 (29%), gentamicin (11%), amikacin (2%), nitrofurantoin (3%), fosfomicin (5%) i nitroksolin (<1%) su slične ili jednake 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 2024.g. iznosi za ampicilin 47%, za ko-amoksiklav 24%, za piperacilin/tazobaktam 3%, za cefalosporine 3. i 4. generacije od 11% za cefepim do 20% za ceftriakson i cefiksim, što je isto ili

slično prošlogodišnjim stopama. Rezistencija na meropenem je <1%. I u 2024.g. registrirana je niska rezistencija na nove cefalosporine u kombinaciji s inhibitorima beta-laktamaza, ceftazidim / avibaktam (1% u 2024.g. i 2023.g., <1% u 2022.g., 1% u 2021.g., 2020.g., 2019.g. i 2018.g.), ceftalozan / tazobaktam (7% u 2024.g., 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 gentamicin (24%) i amikacin (12%) su jednake prošlogodišnjima, a na ciprofloksacin (30%) i ko-trimoksazol (44%) su nešto 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 kao i prošle godine 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 (41% za cefepim, ceftazidim i ceftriakson te 42% za cefiksim) su nešto više od prošlogodišnjih (38% do 39% u 2023.g., 38% do 40% u 2022.g., 41% do 43% u 2021.g., 35% do 38% u 2019.g.). I stope rezistencije na ko-amoksiklav (45% u 2024.g., 41% u 2023.g. i 2022.g., 43% u 2021.g., 45% u 2020.g., 38% u 2019.g. i 2018.g.) ceftolozan / tazobaktam (25% u 2024.g., 23% u 2023.g., 2022.g. i 2021.g., 25% u 2020.g., 20% u 2019.g. i 2018.g.) te piperacilin / tazobaktam (34% u 2024.g., 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 nešto više negoli prošle godine. Rezistencija na ceftazidim / avibaktam je i dalje niska, no ipak viša negoli prošlih godina (3% u 2024.g., 1% u 2023.g., 2% u 2022.g., 1% u 2021.g., 2% u 2020.g., 2019.g., 2018.g.). Ovaj antibiotik je i nadalje, zbog svoje djelotvornosti na sojeve koji proizvode ESBL i AmpC betalaktamaze, te velik dio karbapenemaza (KPC, OXA-48), najučinkovitiji beta-laktam kod klepsijela. Rezistencija na cefiderokol (9% u 2024.g., 7% u 2023.g. i 2022.g.) i imipenem / relebaktam (16% u 2024.g., 12% u 2023.g., 11% u 2022.g.) je, također, nešto viša negoli prethodnih godina. 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), a u 2024.g. su najviše do sada (13% i 18% rezistentnih te 4% i 3% osjetljivih uz pojačanu izloženost). Ukupan broj izoliranih klebsijela je, također narastao (7.912 u 2024.g., 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 upućuje na mogućnost da je opterećenje infekcijama uzrokovanim klepsijelama rezistentnima na karbapeneme u porastu i da se udaljujemo od cilja koji je pred Hrvatsku postavila Europska komisija, a koji se odnosi na smanjenje incidencije infekcija krvotoka uzrokovanih klepsijelama rezistentnima na karbapeneme do 2030.g. za 5% u odnosu na predepidemijske vrijednosti iz 2019.g. Rezistencija na ciprofloksacin (43%), gentamicin (28%), amikacin (12%) i ko-trimoksazol (43%) je također nešto viša negoli prethodne godine.

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 23% za cefiksim) je u okvirima stopa registriranih prošlih godina (10% do 26% 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, 8% rezistentnih za ertapenem) i u 2024.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 (8% u 2024.g., 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 2024.g., 2023.g., 2022.g. i 2021., 12% u 2020.g. i 2019.g., 10% u 2018.g.,) pa i piperacilin / tazobaktam (14% u 2024.g., 13% u 2023.g., 2022.g. i 2021.g., 10% u 2020.g. i 2019.g., 9% u 2018.g.). Stope rezistencije na ciprofloksacin (11%), gentamicin (9%), amikacin (2%) i ko-trimoksazol (13%) su neznatno više od prošlogodišnjih, a rezistencija na nove beta-laktame, cefiderokol i imipenem / relebaktam iznosi 4% i 3%.

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 nešto viša negoli prethodne godine (20% i 17% u 2024.g., 18% i 16% u 2023.g., 21% i 18% u 2022.g., 20% i 21% u 2021.g., 23% i 22% u R2020.g., 18% u 2019.g., 17% u 2018.g.). Rezistencija na nove cefalsosporine s inhibitorom, ceftazidim / avibaktam (6% u 2024.g., 2023.g., 2022.g. i 2021.g., 7% u 2020.g., 6% u 2019.g., 4% u 2018.g.) i ceftalozan / tazobaktam (5% u 2024.g., 2023., 2022.g. i 2021.g., 7% u 2020.g., 6% u 2019.g., 4% u 2018.g.) se ne mijenja proteklih godina, kao niti rezistencija na cefiderokol koja iznosi 2%. Rezistencija na piperacilin / tazobaktam (11% u 2024.g., 8% u 2023.g., 10% u 2022.g., 9% u 2021.g., 12% u 2020.g., 10% u 2019.g.), ceftazidim (16% u 2024.g., 15% u 2023.g., 17% u 2022.g., 15% u 2021.g., 21% u 2020.g., 16% u 2019.g.,) i cefepim (15% u 2024.g., 13% u 2023.g., 15% u 2022.g., 13% u 2021.g., 16% u 2020.g., 13% u 2019.g.) je također nešto viša negoli prethodne godine. Rezistencija na ciprofloksacin (23% u 2024.g. i 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 nešto viša negoli prethodne godine (8% u 2024.g., 6% u 2023.g.). 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

difuzijskom metodom 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 sojevi rezistentni na karbapeneme. 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 pseudomonasa rezistentnih na karbapeneme. Nakon porasta rezistencije na kolistin u 2021.g. i povratka na niže vrijednosti, ponovno je zabilježena nešto veća stopa rezistencje (4% u 2024.g., 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 2024.g. su se zadržale visoke stope rezistencije na imipenem i meropenem (90% na oba karbapenema). Nakon drastičnog povećanja broja ukupnih pa time i na karbapeneme rezistentnih izolata tijekom epidemije COVID-19, od 2022.g. su se ukupni brojevi prijavljenih acinetobaktera počeli smanjivati, no u 2024.g. ponovno bilježimo veći broj izolata (2.087 izolata u 2024.g., 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.). 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, a u kliničkoj praksi se za liječenje infekcija uzrokovanih acinetobakterom primjenjuje u visokim dozama. Rezistencija i osjetljivost uz povećanu izloženost za ampicilin/sulbaktam kontinuirano pokazuju visoke stope (31% i 18% u 202.g., 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 izolata rezistentnih na karbapeneme, 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 (2% u 2024.g., 1% u 2023.g., 2022.g. i 2021.g., 2% u 2020.g.). Rezistencija na cefiderokol je porasla (6% u 2024.g., 2% u 2023.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., 14% u 2024.g.). Rezistencija na ko-amoksiklav (6%) je identična prošlogodišnjoj vrijednosti. ESBL sojevi su i dalje rijetki među salmonelama i u 2024.g. rezistencija na ceftazidim i ceftriakson je iznosila 1%, jednako kao i prethodne godine. Rezistencija na ko-trimoksazol (3%) je nešto niža negoli prethodne godine, a posebno je dobra vijest da je rezistencija na ciprofloksacin nakon dvogodišnjeg razdoblja vrlo visokih vrijednosti ponovno znatno niža (8% u 2024.g., 28% 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.). Vjerojatno se radilo o prolaznom kolanju rezistentnog soja unešenog nekom namirnicom, jer ovo prolazno povećanje rezistencije nije bilo povezano s povećanom primjenom ciprofloksacina ni u humanoj medicini niti u veterini, niti su u tom razdoblju zabilježene povećane stope rezistencije na ciprofloksacin u veterinarskom sektoru (podaci Hrvatskog veterinarskog instituta).

Osjetljivost u *Campylobacter coli* i *Campylobacter jejuni* se prati od 2013.g. Kod obje vrste je zaustavljen trend porasta rezistencije na ciprofloksacin (u 2024.g. 78% i 70%, 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, a rezistencija na tetraciklin je u *C.coli* nešto niža, a u *C.jejuni* nešto viša negoli prethodne godine (43% i 49% u 2024.g., 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 2024.g. izolirano je 17 šigela iz pet laboratorija: *Shigella sonnei* (7 izolata), *Shigella flexneri* (8 izolata), *Shigella boydii* (2 izolata). Rezistencija je zabilježena na sve testirane antibiotike, a posebno zabrinjava 100% rezistencija *S. sonnei* na ampicilin, ceftriakson, ciprofloksacin i ko-trimoksazol.

U 2024. godini je prijavljeno 1 882 anaerobnih bakterijskih izolata, najviše *Bacteroides* spp. (1 010) i *Prevotela* spp. (390) iz 23 centara. Rezistencija je ukupno najviša na klindamicin (47%), a najniža na meropenem (3%) i piperacilin/tazobaktam (8%).

DISCUSSION

Disruption in the incidence of respiratory pathogens caused by the SARS-CoV-2 epidemic was considerably shorter for *Streptococcus pneumoniae* and *Haemophilus influenzae* than for group A streptococcus (GAS), which, after an exceptionally low incidence during 2020 and 2021, showed a sharp increase in 2022, with high levels persisting throughout 2023. In 2024, the number of GAS isolates began to decline, but it still remains above the pre-epidemic levels (12.341 in 2019; 4.553 in 2020; 2.570 in 2021; 8.978 in 2022; 19.005 in 2023; and 16.567 in 2024). Changes in incidence are even more pronounced when comparing autumn/winter seasons rather than calendar years (data from the University Hospital for Infectious Diseases). Fortunately, the increase in GAS incidence was not accompanied by a rise in resistance; on the contrary, macrolide resistance rates were lower during the period of higher incidence: 5% in 2024 and 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. Clindamycin resistance has also remained low (constitutive: 2% in 2024 and 2023, 1% in 2022, 5% in 2021, 4% in 2020; inducible: 1% in 2024 and 2023, 3% in 2022, 3% in 2021 and 2020). According to EUCAST standards, isolates with inducible resistance were, up to 2014, reported as *susceptible to clindamycin* with a note recommending avoidance of prolonged therapy of severe infections with clindamycin. Since 2014, such isolates have been interpreted as *resistant to clindamycin* with the note that clindamycin may still be used for short-term therapy or for the treatment of mild skin and soft tissue infections. Clindamycin is recommended in combination therapy with penicillin for severe necrotizing infections, as it acts faster than beta-lactams and inhibits toxin synthesis. The impact of inducible resistance on combination therapy efficacy has not been specifically studied; however, given the acute phase of necrosis spread in such infections, it is probably advisable to include clindamycin at the start of therapy even when the infection is caused by a streptococcus showing inducible clindamycin resistance. Resistance to penicillin among beta-hemolytic streptococci has still not been reported, and penicillin remains the first-line treatment for streptococcal infections.

Streptococcus pneumoniae, *Haemophilus influenzae*, and *Moraxella catarrhalis* are considered respiratory pathogens, but they are also often found as part of the normal microbiota of the upper respiratory tract in healthy individuals or during viral upper respiratory tract infections. The pneumococcal and *H. influenzae* isolates described in this chapter originate predominantly from nasopharyngeal swabs, which are not suitable for etiological diagnosis of respiratory infections due to their weak correlation with clinical presentation. However, such samples can serve for epidemiological surveillance of antibiotic susceptibility in these bacterial species, bearing in mind that non-invasive pneumococci often show higher resistance rates than invasive isolates. Resistance of invasive pneumococci is discussed in the chapter on invasive isolates and is more relevant for guiding antimicrobial therapy. Nevertheless, monitoring overall pneumococcal resistance allows observation of significant trends in resistance spread. In Croatia, pneumococcal resistance to penicillin remains low (5% in 2024, 3% in 2023, 5% in 2022, 4% in 2021, 3% in 2020, 2019, and 2018, and 2% in 2017), and parenteral penicillin continues to be the treatment of choice for pneumococcal pneumonia. Empirical treatment of pneumonia, however, should begin with higher penicillin doses to effectively cover pneumococci that are susceptible only with increased exposure to penicillin. Until 2019, such isolates were described as *intermediate*, but since 2019, EUCAST replaced the term with *susceptible, increased exposure*, indicating that these isolates can still be treated with the tested antibiotic, provided higher exposure is achieved, something easily done by increasing the penicillin dose. The proportion of pneumococci susceptible with increased exposure

to penicillin is similar to the previous year (16% in 2024, 15% in 2023, 13% in 2022, 16% in 2021, 21% in 2020 and 2019, 17% in 2018, 21% in 2017). Infections caused by pneumococci requiring increased penicillin exposure cannot be treated with oral penicillin and, in the case of central nervous system (CNS) infections, not even with parenteral penicillin. Resistance of pneumococci to penicillin in CNS infections or when treated with oral preparations in 2024 was 21%, slightly higher than the previous year's 18%. Pneumonias caused by isolates requiring increased penicillin exposure can be treated with parenteral penicillin at doses adjusted to the pathogen's minimal inhibitory concentration (MIC). According to 2024 MIC data, 96% of all pneumococci have a penicillin MIC ≤2.0 mg/L (responsive to 6×2.4 g or 6×4 MIU dosing), 93% have MIC ≤1.0 mg/L (responsive to 4×2.4 g or 6×1.2 g dosing), and 90% have MIC ≤0.5 mg/L (responsive to 4×1.2 g dosing). These rates are similar to those of the previous year. Due to favorable pharmacodynamic properties and good activity against pneumococci and *H. influenzae*, amoxicillin/ampicillin is more commonly used than penicillin as first-line therapy for otitis media, sinusitis, and pneumonia. In 2024, 89% of pneumococci were susceptible to standard doses of oral amoxicillin (3×500 mg) or parenteral ampicillin (3×2 g), similar to previous years (92% in 2023 and 2022, 90% in 2021, 87% in 2020 and 2019, 90% in 2018). With higher oral amoxicillin doses (3×750 mg or 3×1000 mg), 93% of pneumococci can be effectively covered (94% in 2023, 95% in 2022 and 2021, 92% in 2020, 93% in 2019, 94% in 2018). In 2022, EUCAST tightened breakpoints for parenteral ampicillin, aligning them with those for oral amoxicillin. This simplified susceptibility interpretation (categories now match for oral and parenteral forms), though it may have slightly lowered the proportion of isolates susceptible to parenteral ampicillin with enhanced dosing (4×2 g) over the last three years (93% in 2024, 94% in 2023, 95% in 2022, 98% in 2021, 97% in 2020, 2019, and 2018). The presented data clearly show that amoxicillin/ampicillin remains an excellent option for both oral and parenteral empirical therapy of bacterial respiratory tract infections where pneumococcus is the main expected pathogen. Despite the increased use of macrolides during the COVID-19 epidemic, pneumococcal resistance to macrolides was slightly lower in that period, though a modest increase was recorded in 2024 (26% in 2024, 24% in 2023 and 2022, 28% in 2021, 29% in 2020, 31% in 2019, 32% in 2018). Overall, a mild increase in pneumococcal resistance to non–beta-lactam antibiotics was noted in 2024. The downward trend in resistance to co-trimoxazole unfortunately stopped, and in 2024 it again exceeded 20% (23% in 2024, 17% in 2023, 13% in 2022, 14% in 2021, 17% in 2019 and 2020, 20% in 2018, 22% in 2017, 23% in 2016, 26% in 2015, 29% in 2014, 27% in 2013, 29% in 2012, 35% in 2011, 43% in 2010). Tetracycline resistance, which had also been slowly declining, has again risen above 20% (21% in 2024, 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 fluoroquinolones remains low (1% to moxifloxacin), but these antibiotics should not be widely used for empirical treatment of respiratory infections.

Amoxicillin is the first-line treatment for respiratory infections in which *Haemophilus influenzae* is considered a possible pathogen. Resistance to amoxicillin in 2024 was similar to the rates recorded in previous years (20% in 2024, 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, and 14% in 2014). The addition of clavulanic acid significantly enhances the efficacy of amoxicillin against *H. influenzae*. Resistance to co-amoxiclav is 7%, identical to the previous year. When applying EUCAST standards, a higher number of isolates with borderline ampicillin resistance are detected, caused by alterations in target PBP molecules, which may occasionally lead to an overestimation of resistance. According to EUCAST, even for susceptible *H. influenzae* isolates, higher doses of oral amoxicillin (3×750 mg or 3×1 g) and oral cefuroxime (2×500 mg) are required. For this reason, parenteral formulations of amoxicillin/ampicillin with or without a β-lactamase inhibitor are categorized as "S" and "R",

parenteral cefuroxime with “S”, “I”, and “R”, but their oral counterparts may only be categorized as “I” and “R”. Resistance to co-trimoxazole (20%) remains comparable to previous years, and resistance to ceftriaxone is <1%.

Staphylococcus aureus is the main causative agent of skin and soft tissue infections and, as such, also the most common cause of surgical wound infections. Resistance to penicillin emerged as early as the 1940s, and today only rare isolates remain susceptible to it. Apart from the expected resistance to penicillin and moderate resistance rates to macrolides (20%) and clindamycin (16%), methicillin-susceptible *Staphylococcus aureus* (MSSA) strains do not show significant resistance to other antistaphylococcal antibiotics. Testing for tetracycline susceptibility was introduced in 2021, and resistance among MSSA has remained stable at 4% throughout the four years of monitoring. Acquired fluoroquinolone resistance among MSSA is low (3%), but even for susceptible isolates, only moxifloxacin can be expected to be effective at standard doses, while ciprofloxacin and levofloxacin are effective only when administered at higher doses.

Methicillin-resistant *Staphylococcus aureus* (MRSA) strains are resistant to all beta-lactam antibiotics (except the newer cephalosporins, ceftaroline and ceftobiprole) and often show cross-resistance to other antibiotic classes. After 2008, a downward trend in MRSA prevalence was observed, reaching the lowest levels (12%) in 2013 and 2014. However, since 2015, MRSA rates began to rise again, with a sharp increase noted in 2020 and an even greater one 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, and 27% in 2021). In 2022, the upward trend fortunately stopped, and in 2024 the MRSA rate remained identical to that in 2023 (19% in both 2024 and 2023, 21% in 2022). The total number of MRSA isolates is lower than at the start of the pandemic but still higher than before it (997 isolates in 2024, 960 in 2023, 955 in 2022, 1,238 in 2021, 699 in 2020, and 784 in 2019). One of the goals set by the European Commission for Croatia to achieve by 2030 is the reduction of MRSA bacteremia cases relative to 2019. If the total number of MRSA isolates does not decrease, achieving this target will be difficult. The proportion of MRSA strains resistant to clindamycin (81%) is somewhat higher than last year (77%), with a marked increase in isolates showing inducible clindamycin resistance (34% in 2024, 21% in 2023). Resistance to gentamicin among MRSA is similar to previous years, though a long-term downward trend is evident (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% in 2023, 12% in 2024). No resistance to linezolid or vancomycin has been detected. The proportion of isolates with a vancomycin MIC of 2.0 mg/L is somewhat higher than in previous years (16% in 2024, 12% in 2023, 11% in 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). Resistance of MRSA to ceftaroline is similar to previous years (8% in 2024, 10% in 2023, 11% in 2022, 5% in 2021), though the share of isolates requiring higher dosing is slightly increased (12% in 2024 vs. 8% in 2023 and 2022, 9% in 2021). In cases of pneumonia, 20% of isolates are resistant to ceftaroline. Resistance to co-trimoxazole remains unchanged from last year (6% in 2024 and 2023, 7% in 2022, 5% in 2021 and 2020), and resistance to tetracycline, monitored since 2021, is 11%, similar to previous years (10% in 2023, 2022, and 2021), and not significantly higher than in MSSA (4%). Resistance to rifampicin remains low (3%), though this antibiotic is not recommended for monotherapy of staphylococcal infections due to the high proportion of resistant mutants in the bacterial population.

Enterococci are naturally resistant to many classes of antibiotics, and nearly all *Enterococcus faecium* isolates are resistant to ampicillin. All enterococci exhibit intrinsic low-level resistance to

aminoglycosides, but wild-type strains can still be treated using combination therapy with ampicillin or glycopeptides to achieve synergistic effects in severe infections. In strains with high-level aminoglycoside resistance, these antibiotics cannot be used even in combination therapy. The proportion of strains with high-level aminoglycoside resistance is 24% for *E. faecalis* and 47% for *E. faecium*, similar to previous years. Resistance to vancomycin remains rare in *E. faecalis* (<1%), while vancomycin resistance in *E. faecium* is high (54%) and again increasing (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, 54% in 2024). The increase in vancomycin resistance has been observed since 2015, when vancomycin-resistant *E. faecium* (VRE) isolates began appearing more frequently across different regions of Croatia, rather than being confined to hospitals in Zagreb as before. In 2021, along with a rise in vancomycin resistance rates, an increase in the total number of *E. faecium* isolates was also recorded compared with both the previous year and the pre-pandemic period. Unfortunately, in 2024, resistance rates rose again, accompanied by a significant increase in the total number of isolates (1.527 in 2024, 1.152 in 2023, 1.271 in 2022, 1.242 in 2021, 859 in 2020, and 1.074 in 2019). The total number of *E. faecalis* isolates shows little fluctuation except for a decline during the first pandemic year (5.947 in 2024, 5.260 in 2023, 5.502 in 2022, 5.419 in 2021, 3.764 in 2020, and 5.264 in 2019). Testing susceptibility to norfloxacin by disk diffusion serves as an indicator of susceptibility to ciprofloxacin and levofloxacin. Fluoroquinolones are used to treat enterococcal infections only in cases of uncomplicated urinary tract infections. Resistance to fluoroquinolones remains much lower in *E. faecalis* than in *E. faecium* and is similar to previous years (24% and 88% in 2024, 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 infections caused by *E. faecalis*, nitrofurantoin may be used, as this pathogen shows low resistance (2%).

Escherichia coli is the most common cause of urinary tract infections (UTIs), while other Enterobacterales species more frequently cause complicated UTIs or various types of healthcare-associated infections. Since Enterobacterales are part of the physiological microbiota, they are often exposed to antibiotic use, and the spread of mutants, once they emerge, is difficult to detect and control. The number of reported *E. coli* isolates was significantly lower than usual in the pandemic year 2020, but since 2021 the number of reported isolates has returned to pre-pandemic levels (23,307 isolates in 2024, 20,349 in 2023, 21,770 in 2022, 18,825 in 2021, 12,912 in 2020, 20,284 in 2019), suggesting that diagnostic activity for bacterial infections was reduced only during the first year of the COVID-19 pandemic. From the beginning of monitoring, *E. coli* has shown a high rate of resistance to ampicillin, which in 2024 remained at 50%, similar to previous years. In susceptible isolates, oral amoxicillin can be used at a standard dose only for uncomplicated UTIs. For complicated UTIs, oral amoxicillin must be used in higher doses, and for infections outside the urinary tract, amoxicillin can only be used in combination with another effective therapy. Amoxicillin combined with clavulanic acid shows much higher efficacy because clavulanic acid successfully inhibits broad-spectrum beta-lactamases and most extended-spectrum beta-lactamases (ESBLs). In 2014, EUCAST for the first time differentiated the interpretation of susceptibility to amoxicillin–clavulanic acid depending on whether it was used for uncomplicated UTIs or other types of infections. After this distinction, resistance rates remained similar or showed a slight upward trend when interpreted for use in uncomplicated UTIs (7% in 2013 and 2014, 9% in 2015, 10% in 2016–2019, 11% in 2020, 12% in 2021, 10% in 2022, 11% in 2023, 13% in 2024), but increased substantially after the change in standards when interpreted for use in other infections, and they are showing a further mild upward trend in subsequent years (16% in 2014–2015, 15% in 2016–2018, 16% in 2019, 19% in 2020, 22% in 2021, 16% in 2022, 18% in 2023 and 2024). For

amoxicillin–clavulanic acid, the same rule applies: the oral formulation should be used in higher doses for complicated UTIs, or in combination with another effective therapy for infections outside the urinary tract. Oral cefuroxime is recommended only for uncomplicated UTIs and can be used at standard doses for that indication, with "S" and "R" susceptibility categories defined for oral use. Parenteral cefuroxime can be used for systemic infections, but only at higher doses, and only "I" and "R" categories apply for parenteral use. Resistance to cefuroxime was similar to last year (12% in 2024, 11% in 2023 and 2022, 10% in 2021, 11% in 2020). Resistance to third-generation cephalosporins (9–11%) was also unchanged compared to last year. This is important because one of the targets set by the European Commission for Croatia to achieve by 2030 is maintaining the incidence of *E. coli* bacteremia resistant to third-generation cephalosporins at the 2019 level. New beta-lactam/beta-lactamase inhibitor combinations, ceftazidime/avibactam and ceftolozane/tazobactam, show high activity against ESBL-producing *E. coli* strains, with resistance rates of <1% and 1%, respectively, similar to the efficacy of carbapenems with or without inhibitors (<1% resistant isolates) and slightly better than piperacillin/tazobactam (4% resistant isolates). *E. coli* isolates were tested for the first time in 2022 against cefiderocol, and resistance has remained low (1% in 2024, 2% in 2023 and 2022). Resistance to ciprofloxacin reached 20% in 2017 but has since stabilized, with the current rate similar to previous years (19% in 2024 and 2023, 18% in 2022, 19% in 2021, 18% in 2020, 19% in 2019, 20% in 2017–2018, 19% in 2016, 18% in 2015, 17% in 2014, 14% in 2013 and 2012). Resistance rates to co-trimoxazole (29%), gentamicin (11%), amikacin (2%), nitrofurantoin (3%), fosfomycin (5%), and nitroxoline (<1%) were similar or identical to last year's. Given these low resistance rates, nitrofurantoin, oral fosfomycin, and nitroxoline remain the first-line drugs for uncomplicated UTIs.

Proteus mirabilis still causes predominantly community-acquired infections and should, by nature, remain well-susceptible to beta-lactam antibiotics active against Gram-negative bacteria. Unfortunately, resistance to beta-lactams has already reached high levels: in 2024, resistance was 47% for ampicillin, 24% for co-amoxiclav, 3% for piperacillin/tazobactam, and between 11% (cefepime) and 20% (ceftriaxone and cefixime) for third- and fourth-generation cephalosporins, similar to last year's values. Resistance to meropenem remained <1%. Low resistance rates were again observed in 2024 for the new beta-lactam/beta-lactamase inhibitor combinations ceftazidime/avibactam (1% in 2024 and 2023, <1% in 2022, 1% in 2021–2019 and 2018) and ceftolozane/tazobactam (7% in 2024, 8% in 2023, 6% in 2022, 7% in 2021, 8% in 2020, 9% in 2019, 10% in 2018). Resistance rates to gentamicin (24%) and amikacin (12%) were the same as last year, while those to ciprofloxacin (30%) and co-trimoxazole (44%) were slightly higher. Because of its intrinsic resistance to colistin and tigecycline and reduced susceptibility to imipenem, *Proteus mirabilis* (and other *Proteus* spp.) could become an increasing problem in the future, especially among urological patients and in healthcare-associated infections. Resistance to the new antibiotic cefiderocol, first tested in 2022, remained at 2%, the same as last year.

Klebsiella and *Enterobacter* species frequently cause healthcare-associated infections and have shown high levels of antibiotic resistance for many years. *Klebsiella pneumoniae* is naturally resistant to ampicillin, but resistance to other beta-lactams is acquired through prolonged exposure to antibiotics. Resistance rates to third- and fourth-generation cephalosporins (41% for cefepime, ceftazidime, and ceftriaxone, and 42% for cefixime) were slightly higher than last year (38–39% in 2023, 38–40% in 2022, 41–43% in 2021, and 35–38% in 2019). Resistance to co-amoxiclav (45% in 2024, 41% in 2023 and 2022, 43% in 2021, 45% in 2020, 38% in 2019 and 2018), ceftolozane/tazobactam (25% in 2024, 23% in 2023–2021, 25% in 2020, 20% in 2019 and 2018), and piperacillin/tazobactam (34% in 2024, 32% in 2023, 30% in 2022, 31% in 2021, 27% in 2020,

21% in 2019, 19% in 2018) also increased slightly compared to the previous year. Resistance to ceftazidime/avibactam remains low, though slightly higher than in previous years (3% in 2024, 1% in 2023, 2% in 2022, 1% in 2021, and 2% in 2020–2018). This antibiotic continues to be the most effective beta-lactam against *Klebsiella* species because of its activity against ESBL- and AmpC-producing strains, as well as many carbapenemase producers (KPC, OXA-48). Resistance to cefiderocol (9% in 2024, 7% in 2023 and 2022) and imipenem/relebactam (16% in 2024, 12% in 2023, 11% in 2022) also showed a slight increase compared to previous years. After the proportion of carbapenem-resistant *K. pneumoniae* isolates first became visible in 2014 (1% resistance to imipenem and meropenem), the rates rose to 5% and 6% in 2019, and sharply increased in 2020 (7% and 16%, with an additional 8% and 2% isolates classified as "I" – susceptible with increased exposure). These levels remained similar in 2021 (8% and 14% resistant, 4% and 2% "I"), 2022 (9% and 13% resistant, 4% and 3% "I"), and 2023 (11% and 16% resistant, 4% and 2% "I"), but reached their highest levels in 2024 (13% and 18% resistant, 4% and 3% "I"). The total number of *Klebsiella* isolates also increased (7,912 in 2024, 6,557 in 2023, 6,245 in 2022, 5,601 in 2021, 4,244 in 2020, 5,864 in 2019), suggesting a growing burden of carbapenem-resistant *Klebsiella* infections and a deviation from the European Commission's target for Croatia - a 5% reduction in the incidence of bloodstream infections caused by carbapenem-resistant *Klebsiella* by 2030 compared with pre-pandemic levels from 2019. Resistance to ciprofloxacin (43%), gentamicin (28%), amikacin (12%), and co-trimoxazole (43%) also increased slightly compared to the previous year.

Enterobacter, Citrobacter, and *Serratia* species form a group of Enterobacterales that naturally possess inducible cephalosporinases and, with the exception of *Citrobacter koseri*, are resistant not only to ampicillin but also to co-amoxiclav and first-generation cephalosporins. Since 2019, *Enterobacter aerogenes* has been reclassified as *Klebsiella aerogenes*, but it continues to be analyzed within this group due to its similar intrinsic resistance profile to beta-lactams. Cefuroxime has only marginal activity against these Enterobacterales, and according to EUCAST standards, there is no clinical breakpoint for this antibiotic for this bacterial group. Wild-type strains are susceptible to third-generation cephalosporins, but during cephalosporin therapy, derepressed mutants that stably hyperproduce AmpC cephalosporinases can be selected, leading to resistance to third-generation cephalosporins. The proportion of derepressed mutants resistant to third- and fourth-generation cephalosporins (10% for cefepime up to 23% for cefixime) remained within the range of previous years (10–26% in 2023 and 2022, 10–28% in 2021, 12–28% in 2020, 12–26% in 2019, 10–25% in 2018, 16–32% in 2017). Resistance to carbapenems, first observed in 2013 (1% for imipenem and meropenem), has also remained nearly unchanged (1% resistant and 1% "I" for imipenem and meropenem, 8% resistant to ertapenem) in 2024. Ceftolozane/tazobactam is primarily expected to have advantages in treating infections caused by *Pseudomonas* and ESBL-producing Enterobacterales, which are more frequent among *K. pneumoniae* and *E. coli* than among Enterobacter species. Nevertheless, resistance rates among Enterobacterales (8% in 2024, 7% in 2023–2022, 8% in 2021–2020, 11% in 2019–2018) were slightly lower than for cefepime (10% in 2024–2021, 12% in 2020–2019, 10% in 2018) and piperacillin/tazobactam (14% in 2024, 13% in 2023–2022–2021, 10% in 2020–2019, 9% in 2018). Resistance rates to ciprofloxacin (11%), gentamicin (9%), amikacin (2%), and co-trimoxazole (13%) were slightly higher than last year, while resistance to the new beta-lactams, cefiderocol and imipenem/relebactam, was 4% and 3%, respectively.

Multidrug-resistant *Pseudomonas aeruginosa*, particularly carbapenem-resistant strains, have long represented one of the most serious resistance challenges in Croatia. Resistance to imipenem and meropenem increased slightly compared to last year (20% and 17% in 2024, 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–inhibitor combinations, ceftazidime/avibactam (6% in 2024–2021, 7% in 2020, 6% in 2019, 4% in 2018) and ceftolozane/tazobactam (5% in 2024–2021, 7% in 2020, 6% in 2019, 4% in 2018), has remained stable, as has resistance to cefiderocol (2%). Resistance to piperacillin/tazobactam (11% in 2024, 8% in 2023, 10% in 2022, 9% in 2021, 12% in 2020, 10% in 2019), ceftazidime (16% in 2024, 15% in 2023, 17% in 2022, 15% in 2021, 21% in 2020, 16% in 2019), and cefepime (15% in 2024, 13% in 2023, 15% in 2022, 13% in 2021, 16% in 2020, 13% in 2019) was also slightly higher than last year. Resistance to ciprofloxacin (23% in 2024–2023, 25% in 2022, 20% in 2021, 24% in 2020–2019) remained stable, while resistance to amikacin increased slightly (8% in 2024, 6% in 2023). Since 2020, EUCAST standards no longer recommend testing *P. aeruginosa* for gentamicin, as this antibiotic is considered ineffective against *Pseudomonas* infections. In general, aminoglycosides are recommended only in combination therapy for infections outside the urinary tract. It is well known that higher antibiotic doses are used for *Pseudomonas* infections, which EUCAST has reflected since 2020 by removing the "S" (susceptible at standard dosing) category for many antibiotics (ceftazidime, cefepime, piperacillin/tazobactam, imipenem, ciprofloxacin). Testing for colistin susceptibility requires broth microdilution, which is technically demanding and costly compared to disk diffusion; therefore, in surveillance programs, only carbapenem-resistant isolates are tested for colistin. As a result, colistin resistance rates cannot be directly compared with those for other antibiotics but do allow for monitoring within the carbapenem-resistant *Pseudomonas* subpopulation. After a rise in colistin resistance in 2021 followed by a decrease, a slight increase was again observed this year (4% in 2024, 2% in 2023, 3% in 2022, 8% in 2021, 3% in 2020 and 2019).

Carbapenem resistance in *Acinetobacter baumannii* has spread rapidly in Croatia since 2008, and in 2024 resistance rates to imipenem and meropenem remained very high (90% for both carbapenems). After a sharp increase in the total number of isolates — and consequently carbapenem-resistant isolates — during the COVID-19 pandemic, the overall number of reported *Acinetobacter* isolates began to decline from 2022. However, in 2024 the number increased again (2.087 isolates in 2024, 1.603 in 2023, 1.605 in 2022, 2.582 in 2021, 2.087 in 2020, and 1.740 in 2019). According to EUCAST standards, there is no clear evidence of the clinical efficacy of ampicillin/sulbactam against *Acinetobacter*, but since this is one of the few antibiotics still showing in vitro activity, it continues to be tested and interpreted in Croatia according to U.S. (CLSI) standards. In clinical practice, high doses of ampicillin/sulbactam are used to treat *Acinetobacter* infections. Resistance and susceptibility with increased exposure have consistently shown high rates (31% and 18% in 2024, 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 in carbapenem-resistant isolates. However, since for several years these isolates have accounted for around or more than 90% of all *Acinetobacter* isolates, it can be considered that nearly all isolates are tested for colistin, and thus colistin resistance rates can be compared with those for other antibiotics. Resistance to colistin remains low (2% in 2024, 1% in 2023–2021, 2% in 2020). Resistance to cefiderocol increased (6% in 2024, 2% in 2023).

Resistance of *Salmonella* spp. to ampicillin first exceeded 10% in 2014 (14% in 2014, 16% in 2015, 14% in 2016, 13% in 2017, 15% in 2018, 16% in 2019, 19% in 2020–2021, 16% in 2022, 17% in 2023, and 14% in 2024). Resistance to co-amoxiclav (6%) was identical to last year's value. ESBL-producing strains remain rare among *Salmonella* spp., and in 2024 resistance to ceftazidime and ceftriaxone was 1%, the same as in the previous year. Resistance to co-trimoxazole (3%) was slightly lower than last year, and notably, resistance to ciprofloxacin, which had been very high for

two years, dropped significantly (8% in 2024, 28% in 2023, 18% in 2022, 4% in 2021, 5% in 2020, 4% in 2019–2017, 3% in 2016, and 4% in 2015). It is likely that this temporary increase was due to the circulation of a resistant strain introduced via contaminated food, as the spike in resistance was not associated with increased use of ciprofloxacin in either human or veterinary medicine, nor were higher rates of ciprofloxacin resistance observed in the veterinary sector during that period (dana from the Croatian Veterinary Institute).

Susceptibility of *Campylobacter coli* and *Campylobacter jejuni* has been monitored since 2013. In both species, the upward trend in ciprofloxacin resistance appears to have stabilized (78% and 70% in 2024; 83% and 81% in 2023; 79% and 82% in 2022; 77% for both 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 in 2016; 52% and 50% in 2015). Since 2021, EUCAST has removed the "S" category (susceptible at standard dosing), indicating that infections caused by *Campylobacter* spp., even by susceptible isolates, should be treated with higher doses of ciprofloxacin. Resistance to erythromycin (1% for both species) remains low. Resistance to tetracycline was slightly lower in *C. coli* and slightly higher in *C. jejuni* compared to last year (43% and 49% in 2024, 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 2024, 17 *Shigella* isolates were reported from five laboratories: *Shigella sonnei* (7 isolates), *Shigella flexneri* (8 isolates), and *Shigella boydii* (2 isolates). Resistance was detected to all tested antibiotics, and of particular concern is the 100% resistance of *S. sonnei* to ampicillin, ceftriaxone, ciprofloxacin, and co-trimoxazole.

In 2024, 1,882 anaerobic bacterial isolates were reported, mainly *Bacteroides* spp. (1.010 isolates) and *Prevotella* spp. (390 isolates) from 23 centers. Overall resistance was highest to clindamycin (47%) and lowest to meropenem (3%) and piperacillin/tazobactam (8%).

LEGENDA ZA TABLICE */ TABLE LEGENDS*:

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 bolnica Karlovac, Karlovačka županija
KA ZZJZ	ZZJZ Karlovačke županije, Karlovac
KC ZZJZ	ZZJZ Koprivničko-križevačke županije, Koprivnica
KR ZZJZ[a]	ZZJZ Krapinsko-zagorske županije, Krapina
NG OB	Opća bolnica 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[b]	ZZJZ Varaždinske županije, Varaždin
ZD ZZJZ	ZZJZ Zadarska županije, Zadar
ZG HZJZ	Hrvatski zavod za javno zdravstvo, Zagreb
ZG KBC[c]	Klinički bolnički centar „Zagreb“, Zagreb
ZG KBCSM[d]	Klinički bolnički centar „Sestre milosrdnice“, Zagreb
ZG KBD	Klinička bolnica „Dubrava“, Zagreb
ZG KBM[e]	Klinička bolnica „Merkur“, Zagreb
ZG KBSD	Klinička bolnica „Sveti Duh“, Zagreb
ZG KDB	Klinika za dječje bolesti Zagreb, Zagreb
ZG KIB[f]	Klinika za infektivne bolesti „Dr. Fran Mihaljević“, Zagreb
ZG LAB PLUS	Poliklinika LabPlus, Zagreb
ZG NZZJZ	Nastavni ZZJZ grada Zagreba, Zagreb

a) uključuje podatke i za: Opću bolnicu Zabok
b) uključuje podatke i za: Bolnicu za plućne bolesti i TBC, Klenovnik
c) uključuje podatke i za: Kliniku za plućne bolesti “Jordanovac”, Zagreb
d) uključuje podatke i za: Institut za tumore i Kliniku za traumatologiju, Zagreb
e) uključuje podatke i za: Sveučilišnu kliniku za dijabetes, endokrinologiju i bolesti metabolizma “Vuk Vrhovac”, Zagreb
f) uključuje podatke i za: Kliniku za kardiovaskularne bolesti „Magdalena“, Krapinske Toplice, Specijalna bolnica Akromion i Kliniku za psihijatriju Vrapče

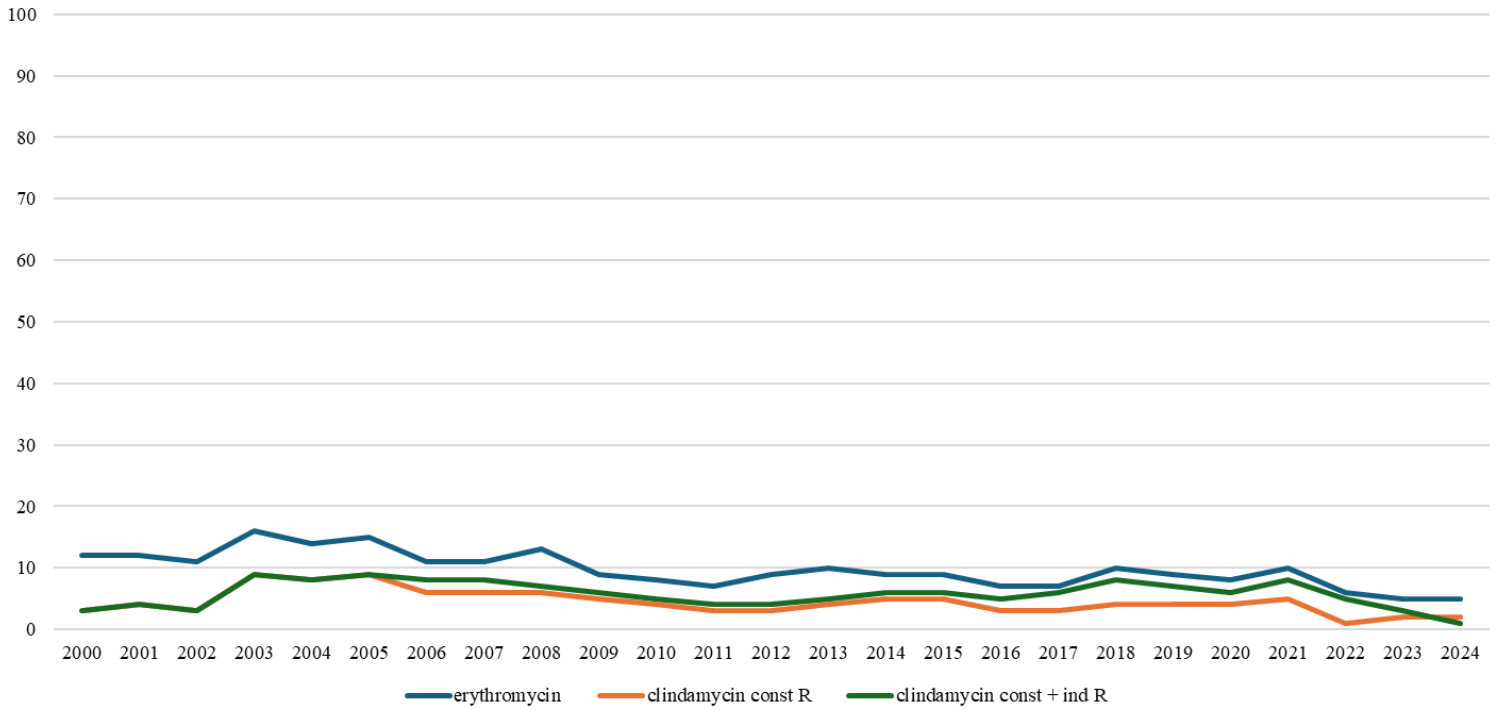
ANTIBIOTICI / *ANTIBIOTICS*:

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 / % *resistance*

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

rezistencija na antibiotike u RH / *antibiotic resistance in Croatia*, 2000. - 2024.



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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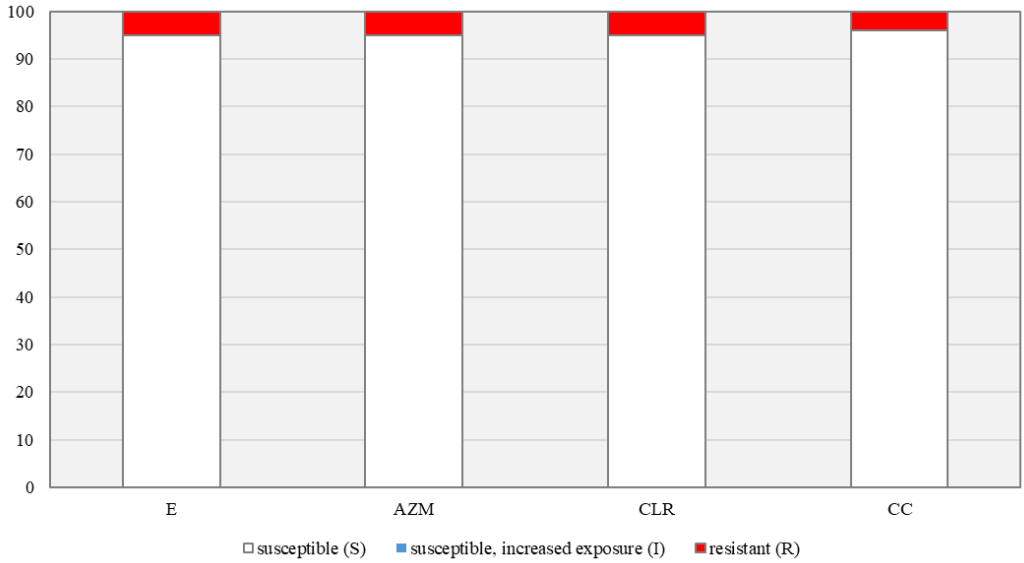
Croatian Committee for Antibiotic Resistance Surveillance

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

rezistencija na antibiotike u razdoblju od 1.01.- 31.12.2024., zbirni prikaz izolata iz 37 centara u RH /
antibiotic resistance for the period 1.01. - 31.12.2024, summary results for the isolates from 37 centers in Croatia

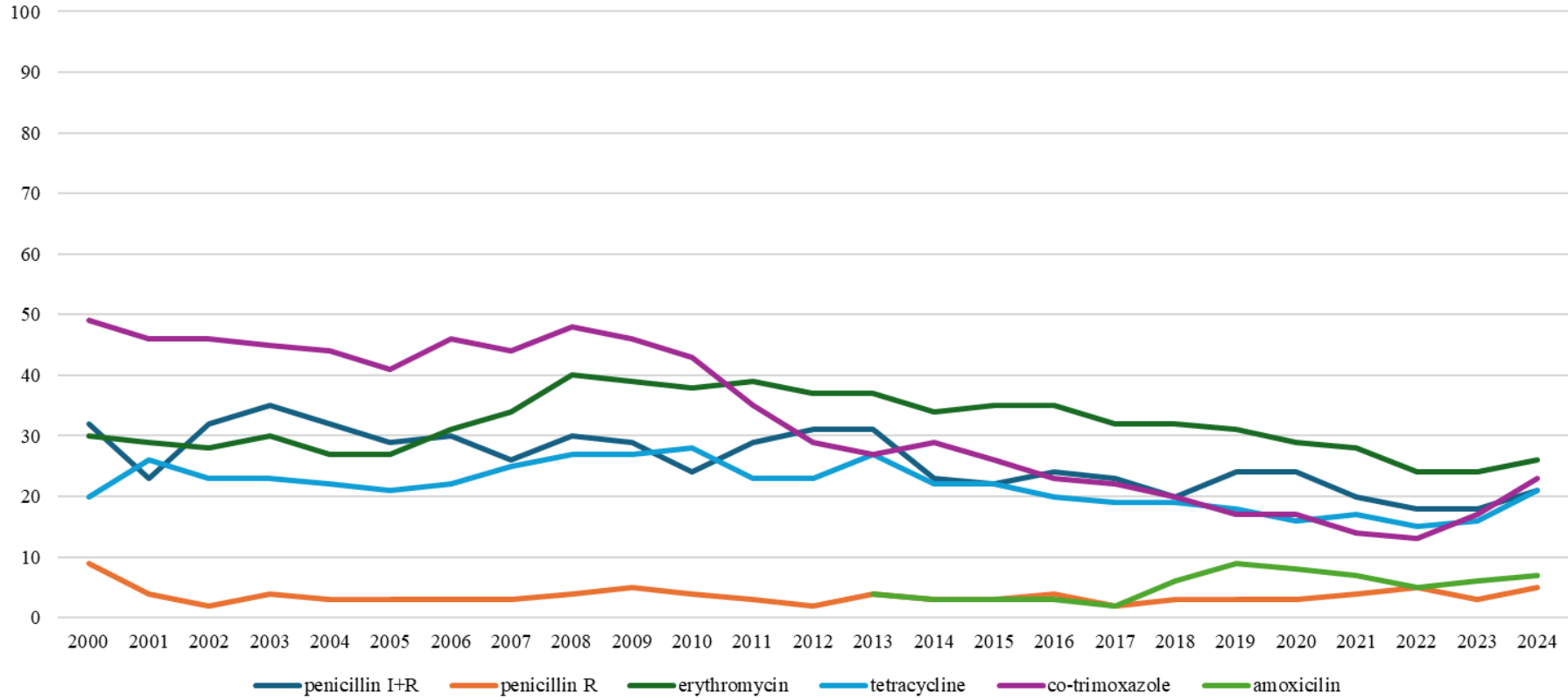
ANTIBIOTIK / *ANTIBIOTIC*	**Broj izolata** / *No. of isolates*	**% rezistentnih (R) (% osjetljivih uz povećanu izloženost (I)) izolata** / *% of resistant (R) (% of susceptible, increased exposure (I)) isolates*	**Raspon lokalnih rezultata*** / *Range of local results**
Erythromycin	17 203	5 (0)	0 (0) - 13 (0)
Azithromycin	17 203	5 (0)	0 (0) - 13 (0)
Clarythromycin	17 203	5 (0)	0 (0) - 13 (0)
Clindamycin	17 201	4 (0)	0 (0) - 16 (0)
constitutive		2	0 - 16
inducible		1	0 - 8

*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. - 2024.



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

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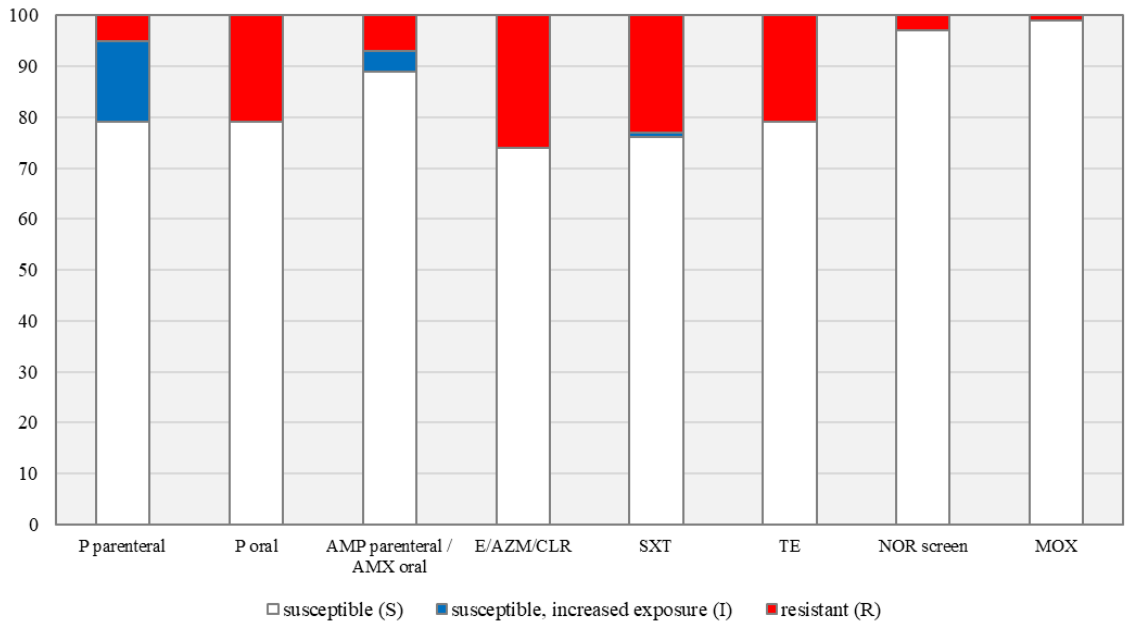
Streptococcus pneumoniae

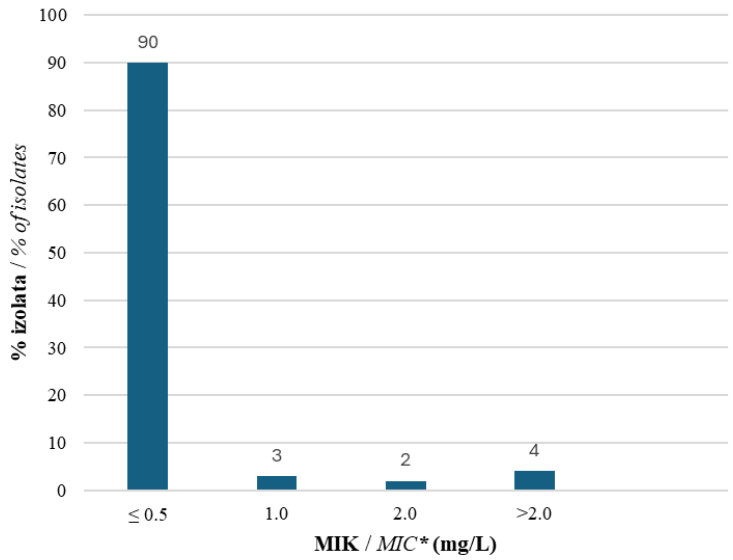
rezistencija na antibiotike u razdoblju od 1.10.- 31.12.2024.,
zbirni prikaz izolata iz 37 centara u RH /
antibiotic resistance for the period 1.10. - 31.12.2024,
summary results for the isolates from 37 centers in Croatia

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 $_{\text{parenteral}}$	1 379	5 (16)	0 (2) - 11 (26)
Penicilin $_{\text{oral}}$	1 379	21 (0)	2 (0) - 43(0)
Ampicillin $_{\text{parenteral}}$ **/ Amoxicillin** $_{\text{oral}}$	1 400	7 (4)	0 (0) - 16 (5)
Erythromycin/Azithromycin/ Clarythromycin	1 403	26 (0)	7 (0) - 50 (0)
Co-trimoxazole	1 400	23 (1)	10 (0) - 40 (0)
Tetracycline	1 197	21 (0)	3 (0) - 58 (3)
Norfloxacin $_{\text{screen}}$	1 318	3 (0)	0 (0) - 39 (0)
Moxifloxacin	1 377	1 (0)	0 (0) - 5 (0)



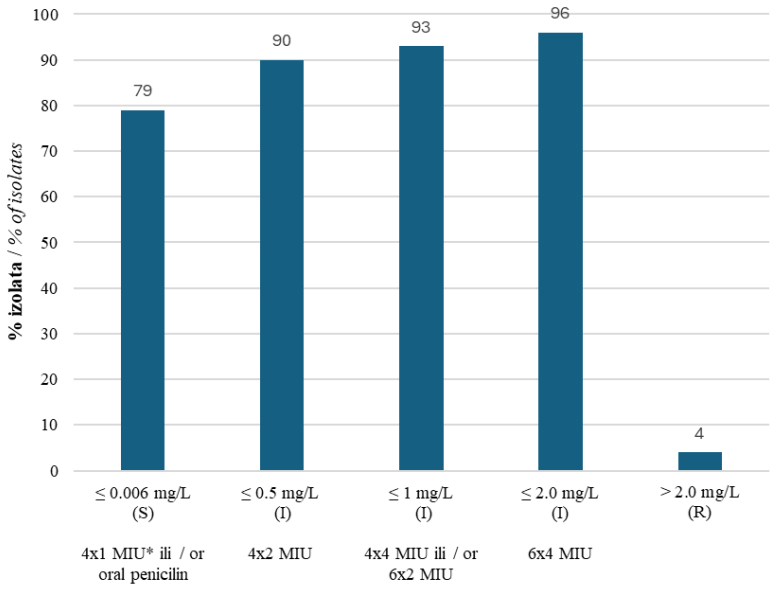
Streptococcus pneumoniae

Distribucija MIK-ova penicilina, (1 334 *S. pneumoniae* izolata) /
Penicillin MIC distribution, (1 334 S. pneumoniae isolates), 1.10. – 31.12.2024.



*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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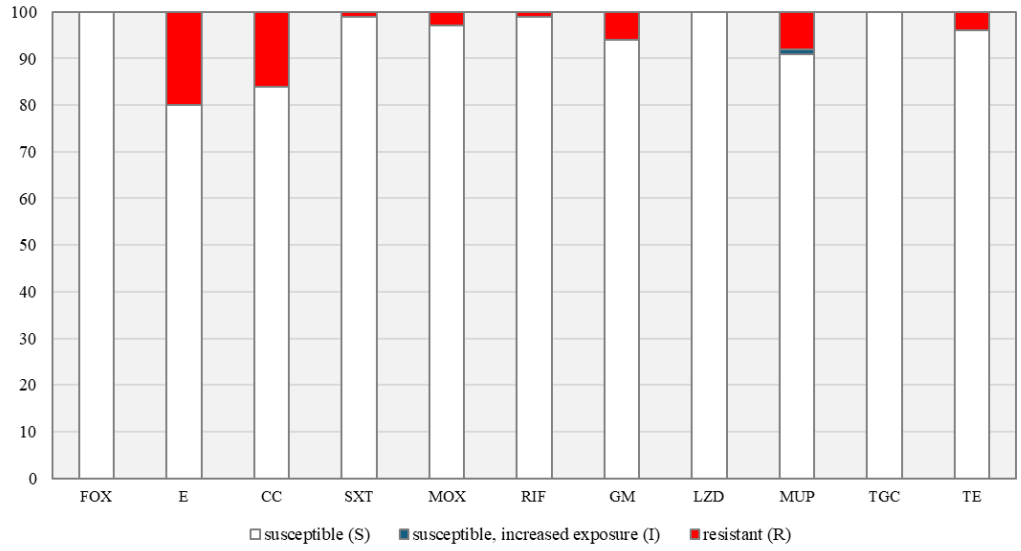
Croatian Committee for Antibiotic Resistance Surveillance

Staphylococcus aureus / MSSA

rezistencija na antibiotike u razdoblju od 1.10.- 31.12.2024.,
zbirni prikaz izolata iz 37 centara u RH /
antibiotic resistance for the period 1.10. - 31.12.2024,
summary results for the isolates from 37 centers in Croatia

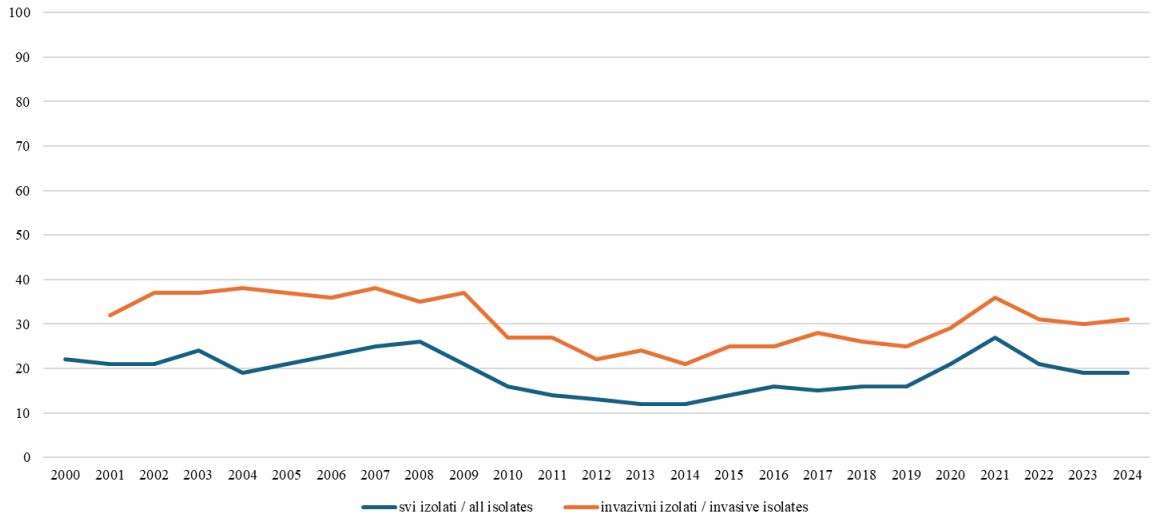
ANTIBIOTIK / *ANTIBIOTIC*	**Broj izolata /** *No. of isolates*	**% rezistentnih (R) (% osjetljivih uz povećanu izloženost (I)) izolata /** *% of resistant (R) (% of susceptible, increased exposure (I)) isolates*	**Raspon lokalnih rezultata* /** *Range of local results**
Cefoxitin/ Methicillin	4 310	0 (0)	0 (0) - 0 (0)
Erythromycin	4 158	20 (0)	8 (0) - 38 (0)
Clindamycin	4 160	16 (0)	0 (0) – 32 (0)
constitutive		8	0 - 23
inducible		8	0 – 18
Co-trimoxazole	4 141	1 (0)	0 (0) – 8 (0)
Moxifloxacin	4 106	3 (0)	0 (0) - 16 (0)
Rifampicin	3 952	1 (0)	0 (0) - 3 (0)
Gentamicin	4 148	6 (0)	2 (0) - 15 (0)
Linezolid	4 046	0 (0)	0 (0) - 0 (0)
Mupirocin	3 785	8 (1)	0 (0) - 21 (0)
Tigecycline	3 878	0 (0)	0 (0) – 13 (0)
Tetracycline	3 742	4 (0)	0 (0) - 21 (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

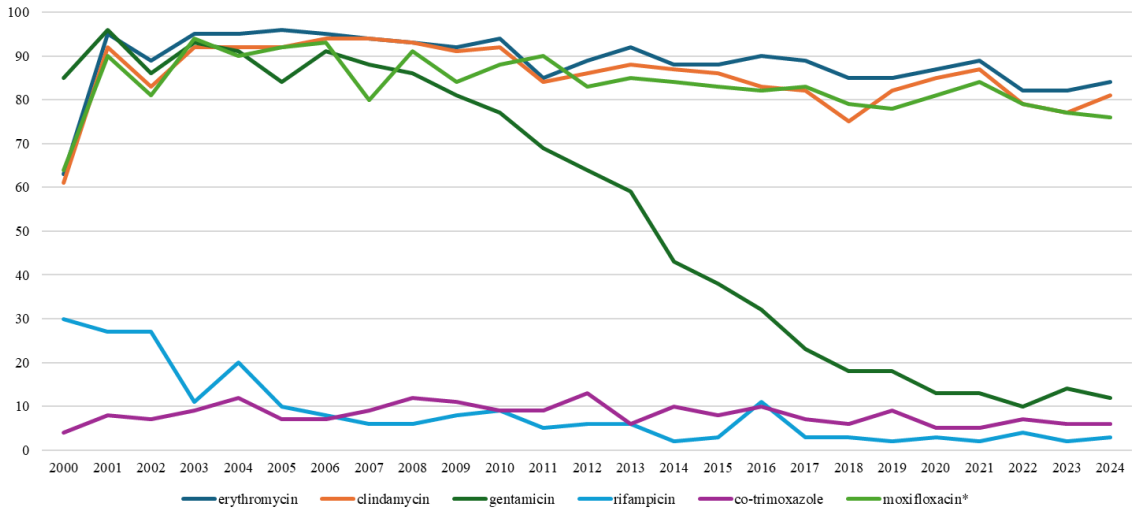


Staphylococcus aureus / MRSA

Methicillin resistant *Staphylococcus aureus* (MRSA) – stope / *rates*, 2000. - 2024.



rezistencija na antibiotike u RH /*resistance to antibiotics in Croatia*, 2000. - 2024.



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

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Staphylococcus aureus / MRSA

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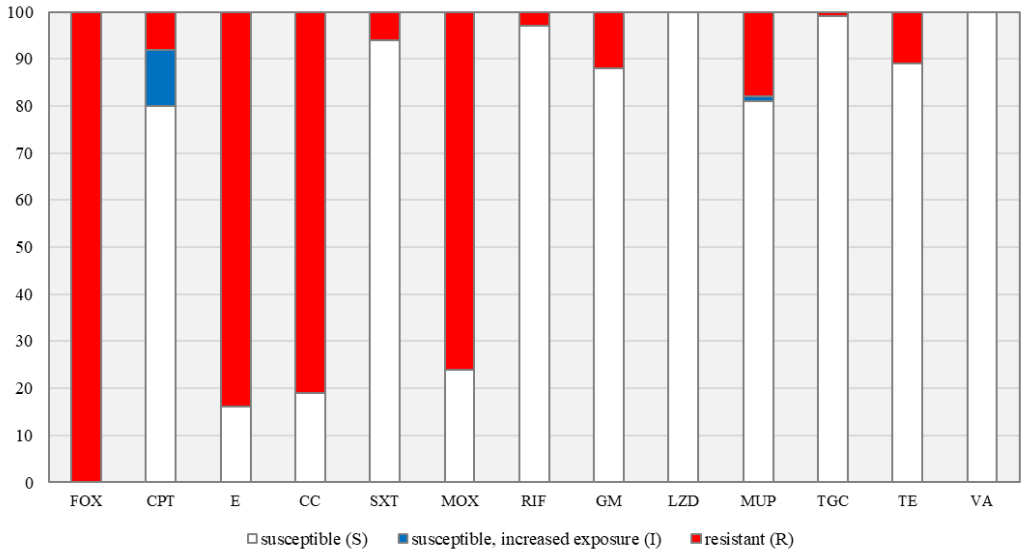
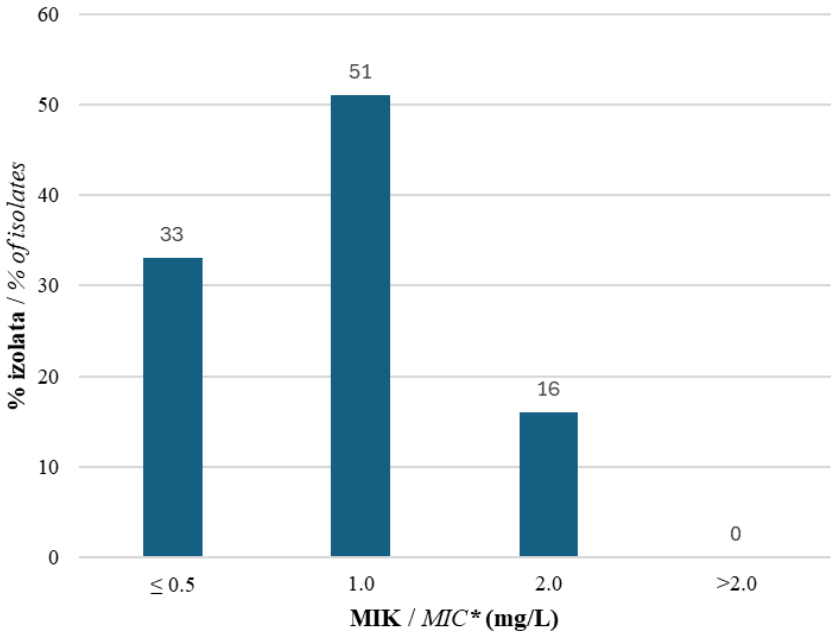
Cefoxitin/ Methicillin	997	100 (0)	100 (0) - 100 (0)
Ceftaroline	842	8 (12)	0 (0) - 18 (0)
Erythromycin	990	84 (0)	74 (0) - 100 (0)
Clindamycin	990	81 (0)	74 (0) - 90 (0)
constitutive		45	4 - 88
inducible		34	0 – 88
Co-trimoxazole	985	6 (0)	0 (0) - 13 (0)
Moxifloxacin	946	76 (0)	6 (0) - 94 (0)
Rifampicin	950	3 (0)	0 (0) - 4 (0)
Gentamicin	985	12 (0)	2 (0) - 24 (0)
Linezolid	981	0 (0)	0 (0) - 0 (0)
Mupirocin	891	18 (1)	0 (0) - 49 (4)
Tigecycline	929	1 (0)	0 (0) - 3 (0)
Tetracycline	892	11 (0)	0 (0) - 21 (0)
Vankomicin	867	0 (0)	0 (0) - 0 (0)

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



Staphylococcus aureus / MRSA

Distribucija MIK-ova vankomicina, (867 MRSA izolata) /
Vancomycin MIC distribution, (867 MRSA isolates), 1.10. – 31.12.2024.



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

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Enterococcus faecalis

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Ampicillin	5 947	2 (0)	0 (0) - 13 (0)
Gentamicin	5 487	24 (0)	3 (0) - 52 (0)
Vancomycin	5 950	0 (0)	0 (0) - 3 (0)
Nitrofurantoin	5 818	2 (0)	0 (0) - 22 (0)
Norfloxacin $_{\text{screen}}$	5 788	24 (0)	4 (0) - 40 (0)
Linezolid	5 652	0 (0)	0 (0) – 4 (0)

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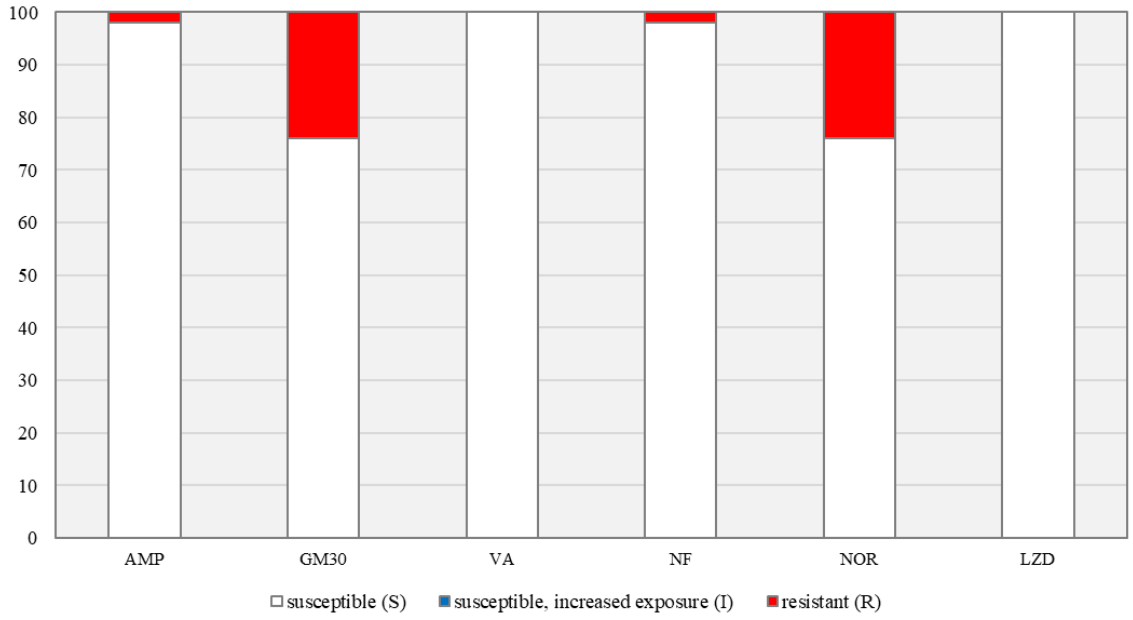
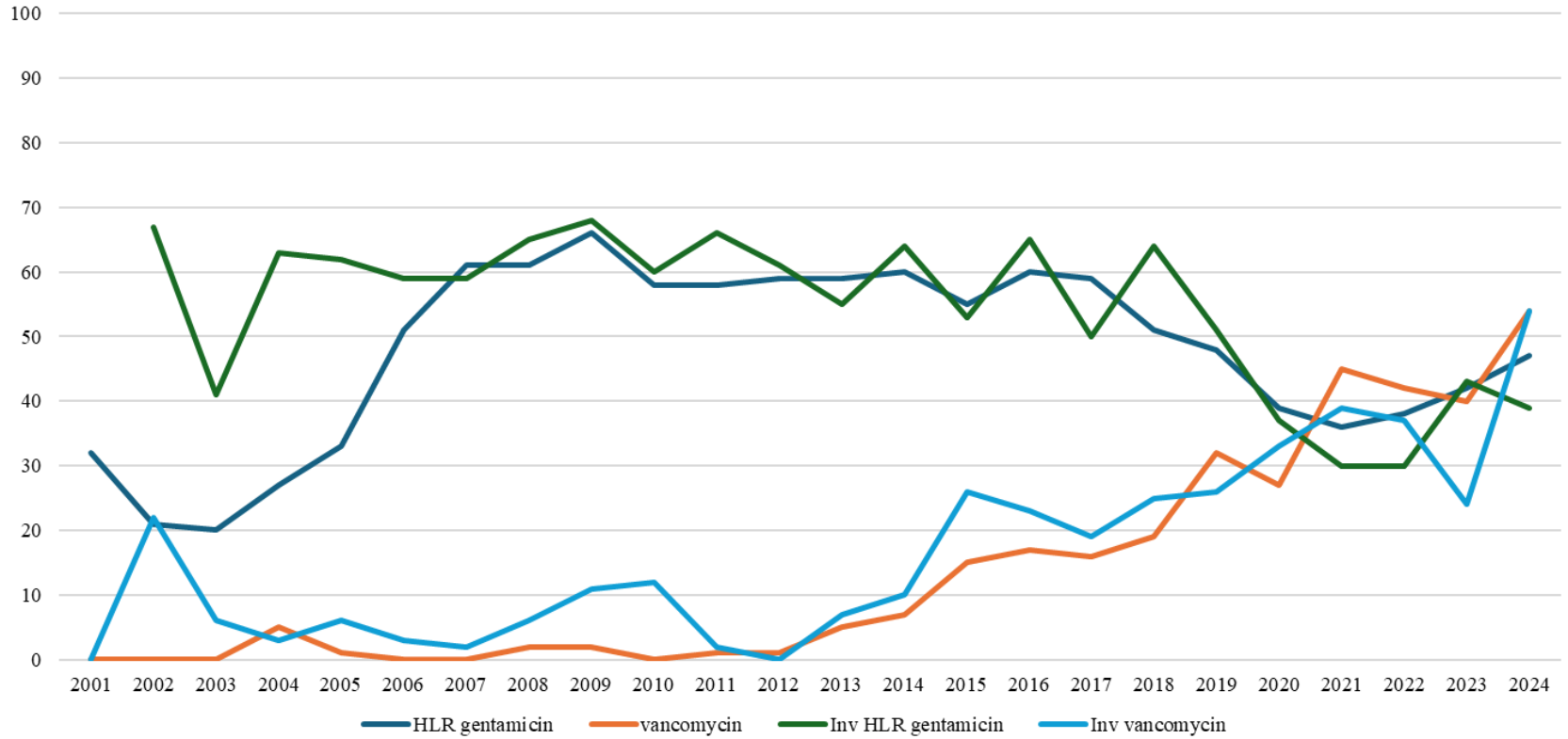


Enterococcus faecium

rezistencija na antibiotike u RH / *resistance to antibiotics in Croatia*, 2001. - 2024.



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	1 527	95 (0)	86 (0) - 100 (0)
Gentamicin	1 455	47 (0)	26 (0) - 70 (0)
Vancomycin	1 547	54 (0)	6 (0) - 92 (0)
Norfloxacin	1 458	88 (0)	0 (0) - 100 (0)
Linezolid	1 448	0 (0)	0 (0) – 2 (0)

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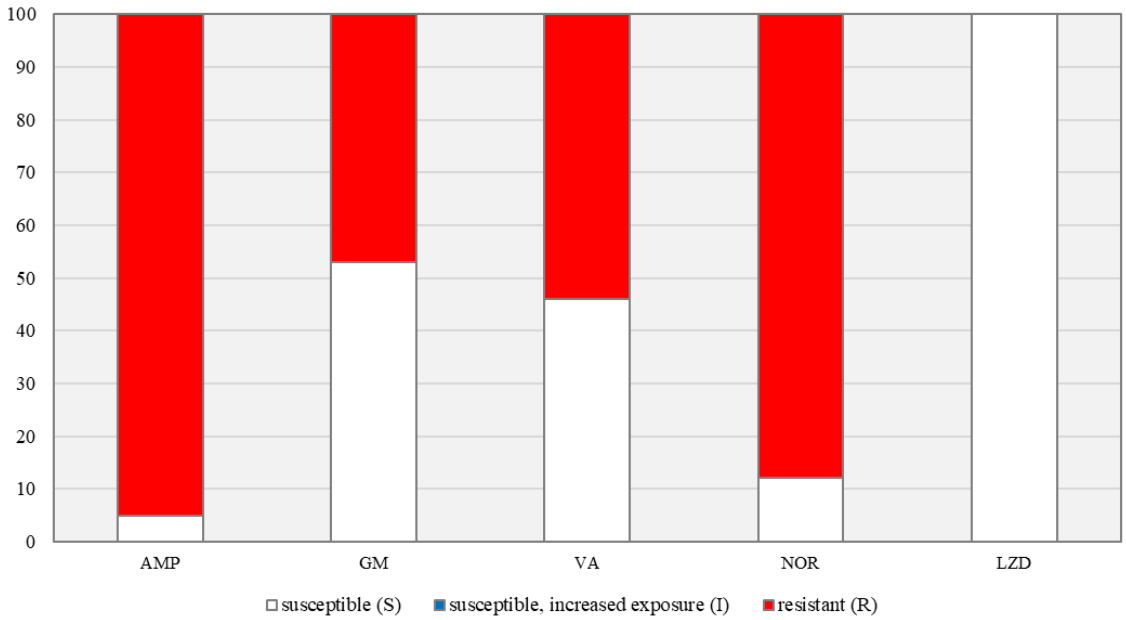
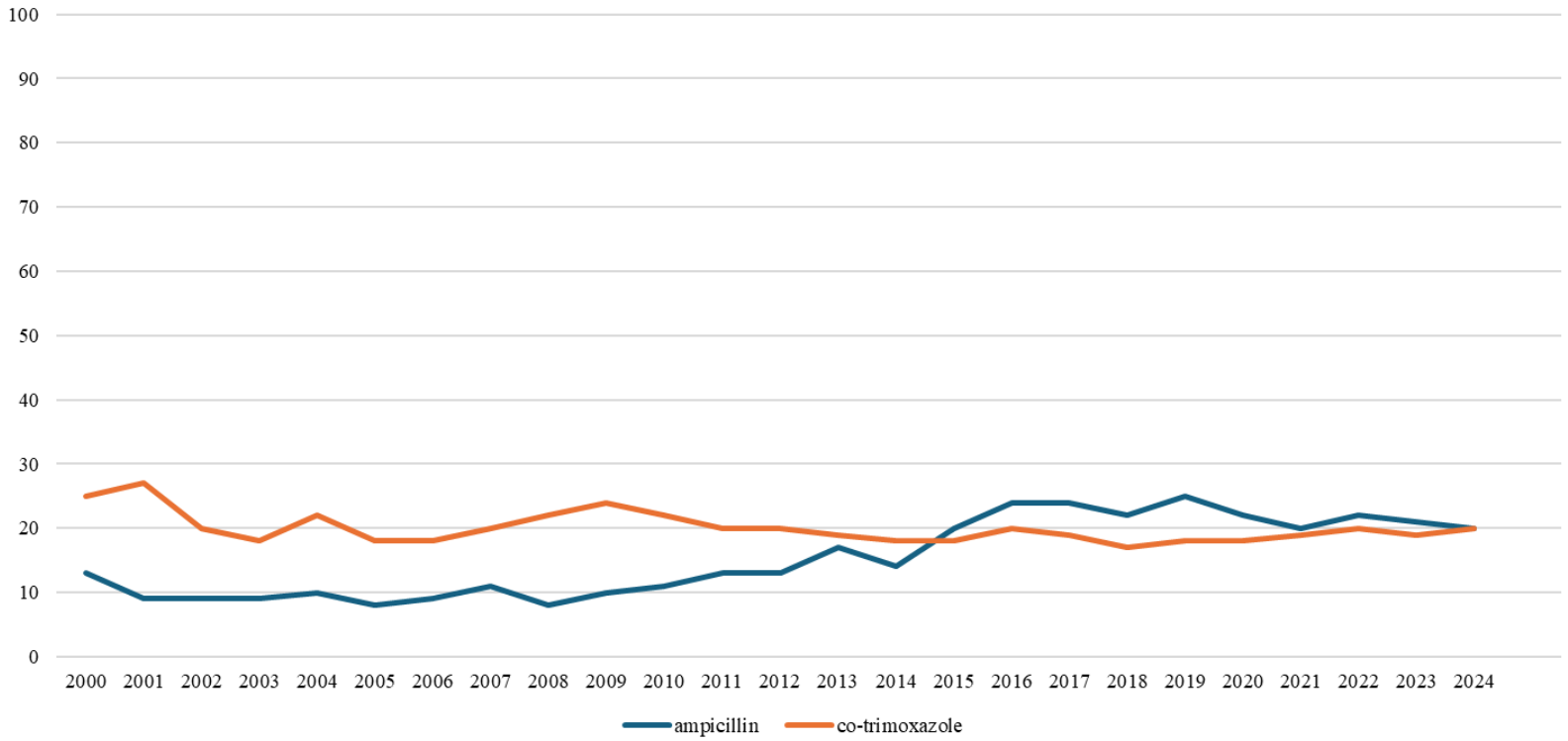


Haemophilus influenzae

rezistencija na antibiotike u RH / *resistance to antibiotics in Croatia*, 2000. - 2024.



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Haemophilus influenzae

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Ampicillin parenteral	1 089	20 (0)	5 (0) - 39 (0)
Amoxicillin oral	1 089	20 (80)	0 (95) – 45 (55)
Amoxicillin + clav. acid parenteral	1 089	7 (0)	0 (0) – 23 (0)
Amoxicillin + clav. acid oral	1 089	7 (93)	0 (100) – 23 (77)
Cefuroxime parenteral	1 090	10 (2)	0 (0) - 35 (0)
Cefuroxime oral	1 090	12 (88)	0 (100) - 35 (65)
Ceftriaxone	1 042	0 (0)	0 (0) - (0)
Co-trimoxazole	1 092	20 (1)	9 (0) - 33 (1)

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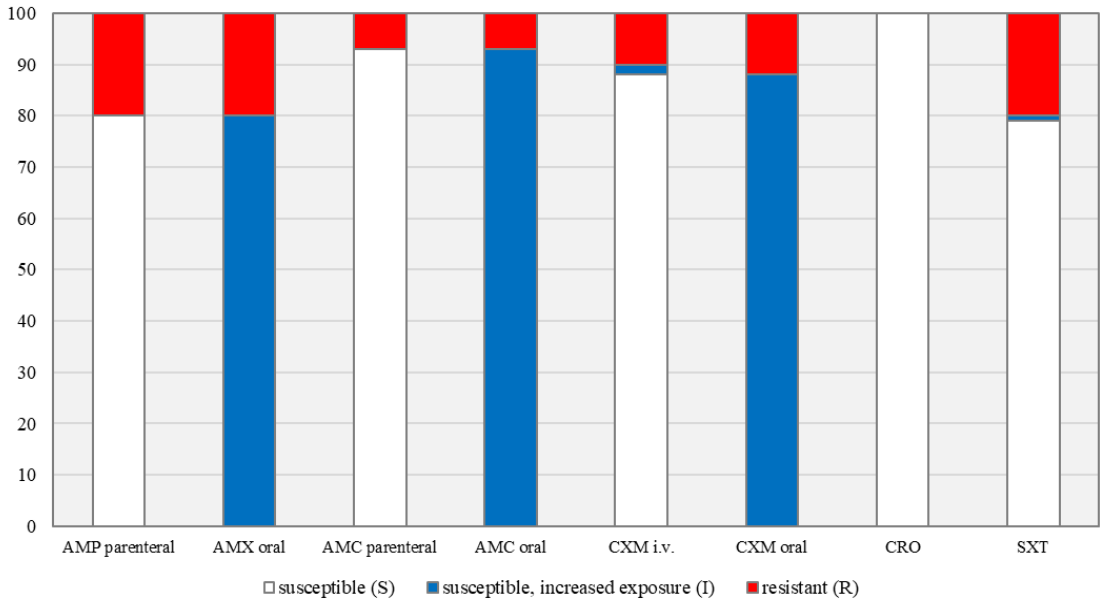
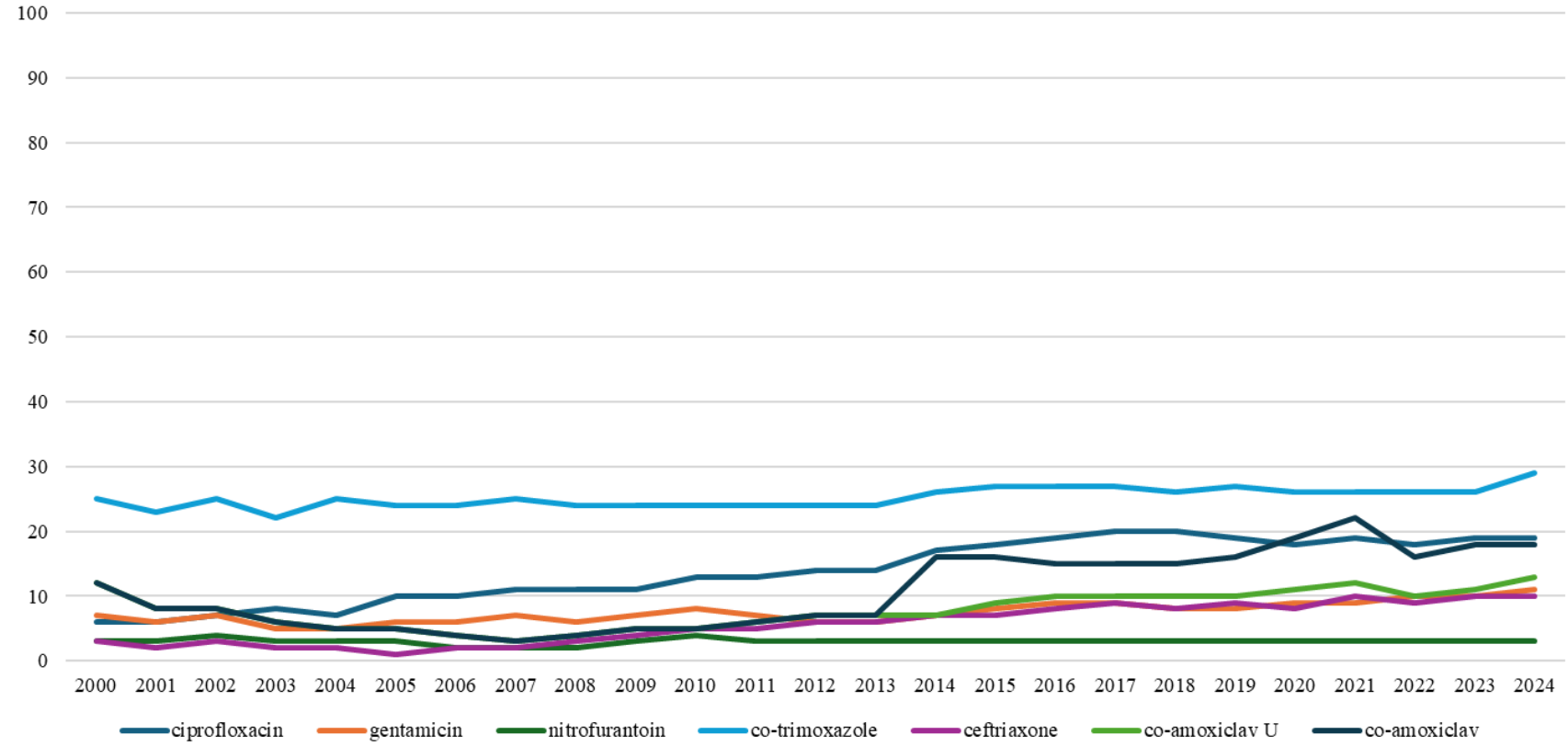


Escherichia coli

rezistencija na antibiotike u RH / *resistance to antibiotics in Croatia*, 2000. - 2024.



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

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Escherichia coli

rezistencija na antibiotike u razdoblju od 1.10. - 31.12.2024., zbirni prikaz izolata iz 37 centara u RH /
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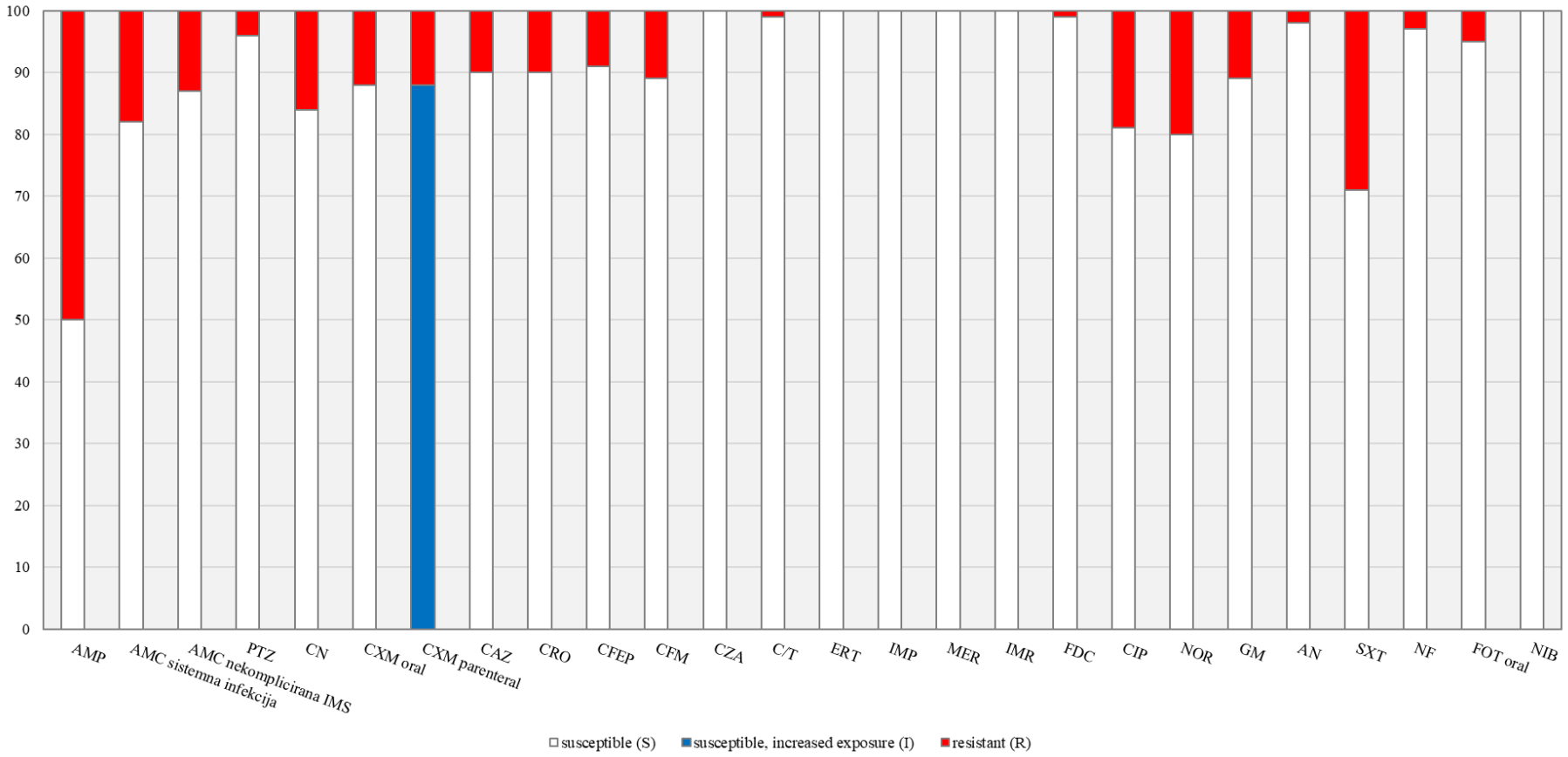
Ampicillin	23 307	50 (0)	35 (0) - 64 (0)
Amoxicillin + clav. acid sistemna infekcija	22 523	18 (0)	4 (0) - 38 (0)
Amoxicillin + clav. Acid nekomplicirana IMS	23 232	13 (0)	3 (0) - 36 (0)
Piperacillin + tazobactam	22 560	4 (0)	0 (0) - 20 (0)
Cephalexin	22 288	16 (0)	7 (0) - 84 (0)
Cefuroxime oral	23 182	12 (0)	2 (0) - 24 (0)
Cefuroxime parenteral	23 182	12 (88)	2 (98) – 24 (76)
Ceftazidime	23 257	10 (0)	0 (0) - 20 (1)
Ceftriaxone	23 258	10 (0)	0 (0) - 20 (0)
Cefepime	22 559	9 (0)	0 (0) – 18 (0)
Cefixime	22 541	11 (0)	3 (0) – 20 (0)
Ceftazidime + avibactam	20 968	0 (0)	0 (0) – 1 (0)
Ceftolozane + tazobactam	20 685	1 (0)	0 (0) – 3 (0)
Ertapenem	22 564	0 (0)	0 (0) - 2 (0)
Imipenem	20 987	0 (0)	0 (0) - 2 (0)
Meropenem	21 604	0 (0)	0 (0) - 1 (0)
Imipenem + relebactam	20 676	0 (0)	0 (0) – 6 (0)
Cefiderocol	20 324	1 (0)	0 (0) – 9 (0)
Ciprofloxacin	22 609	19 (0)	11 (3) - 37 (0)
Norfloxacin	22 890	20 (0)	10 (0) - 37 (0)
Gentamicin	23 307	11 (0)	5 (0) - 19 (0)
Amikacin	23 300	2 (0)	0 (0) - 10 (0)
Co-trimoxazole	23 252	29 (0)	6 (0) - 42 (0)
Nitrofurantoin	22 894	3 (0)	0 (0) - 12 (0)
Fosfomycin oral	22 870	5 (0)	0 (0) - 37 (0)
Nitroxolin	21 696	0 (0)	0 (0) - 1 (0)

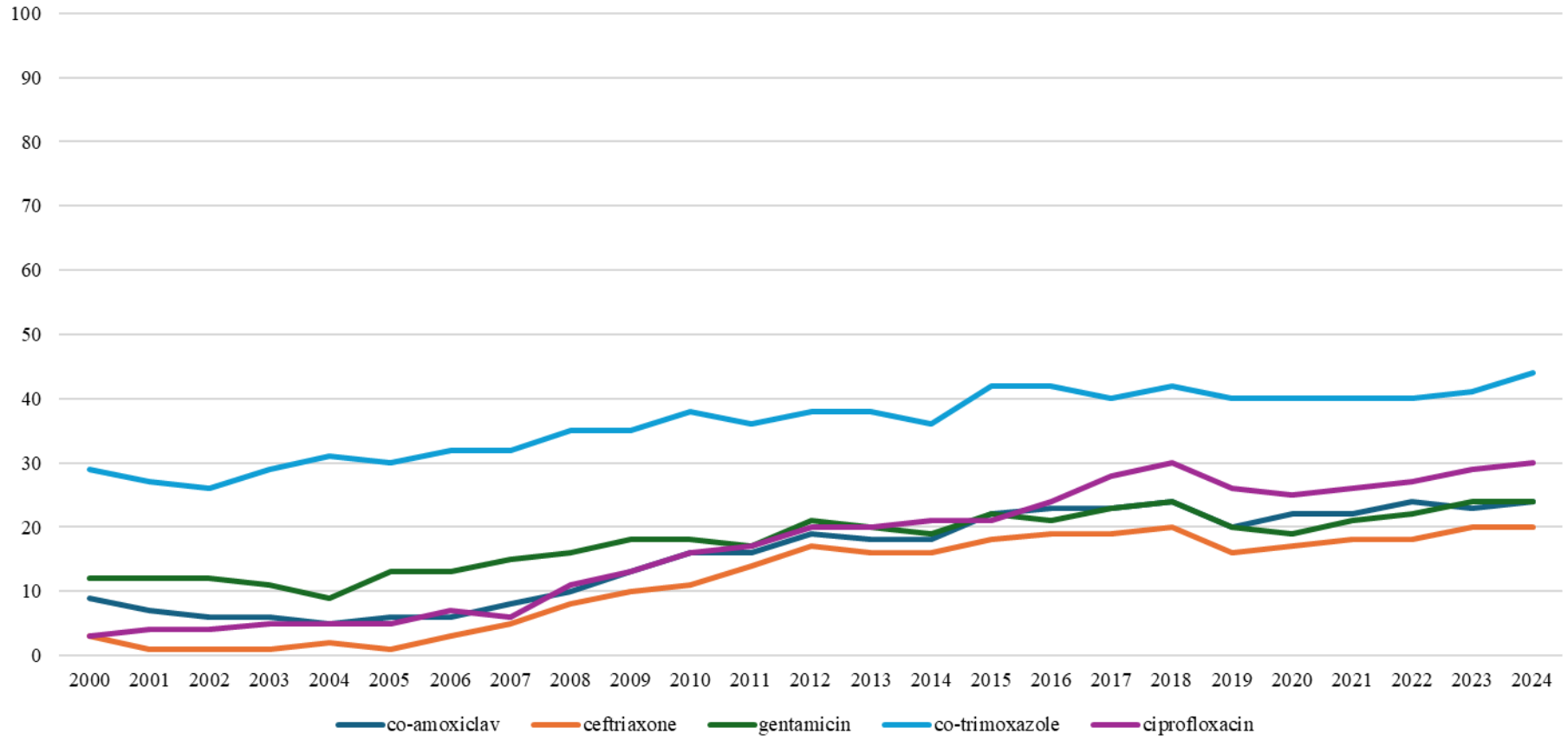
Escherichia coli

osjetljivost na antibiotike u RH / *sensitivity to antibiotics in Croatia*, 1.10. – 31.12.2024.



Proteus mirabilis

rezistencija na antibiotike u RH / *resistance to antibiotics in Croatia*, 2000. – 2024.



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Proteus mirabilis

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Ampicillin	4 550	47 (0)	24 (0) - 83 (0)
Amoxicillin + clav. acid	4 547	24 (0)	7 (0) - 69 (0)
Piperacillin + tazobactam	4 470	3 (0)	0 (0) - 35 (0)
Cephalexin	4 358	24 (0)	7 (0) - 65 (0)
Cefixime	4 398	20 (0)	6 (0) - 63 (0)
Cefuroxime $_{\text{oral}}$	4 533	23 (0)	3 (0) - 65 (0)
Cefuroxime $_{\text{parenteral}}$	4 533	23 (77)	3 (97) - 65 (35)
Ceftazidime	4 505	18 (1)	0 (0) - 58 (0)
Ceftriaxone	4 506	20 (0)	0 (0) - 65 (0)
Cefepime	4 421	11 (4)	0 (0) - 29 (25)
Ceftazidime + avibactam	4 188	1 (0)	0 (0) - 19 (0)
Ceftolozane + tazobactam	4 164	7 (0)	0 (0) – 24 (0)
Cefiderocol	4 068	2 (0)	0 (0) – 4 (0)
Ertapenem	4 431	1 (0)	0 (0) – 3 (0)
Meropenem	4 388	0 (0)	0 (0) – 3 (0)
Ciprofloxacin	4 432	30 (1)	3 (0) – 65 (2)
Norfloxacin	4 457	31 (0)	3 (0) – 67 (0)
Gentamicin	4 549	24 (0)	6 (0) – 58 (0)
Amikacin	4 477	12 (0)	0 (0) – 46 (0)
Co-trimoxazole	4 518	44 (0)	12 (0) – 63 (0)

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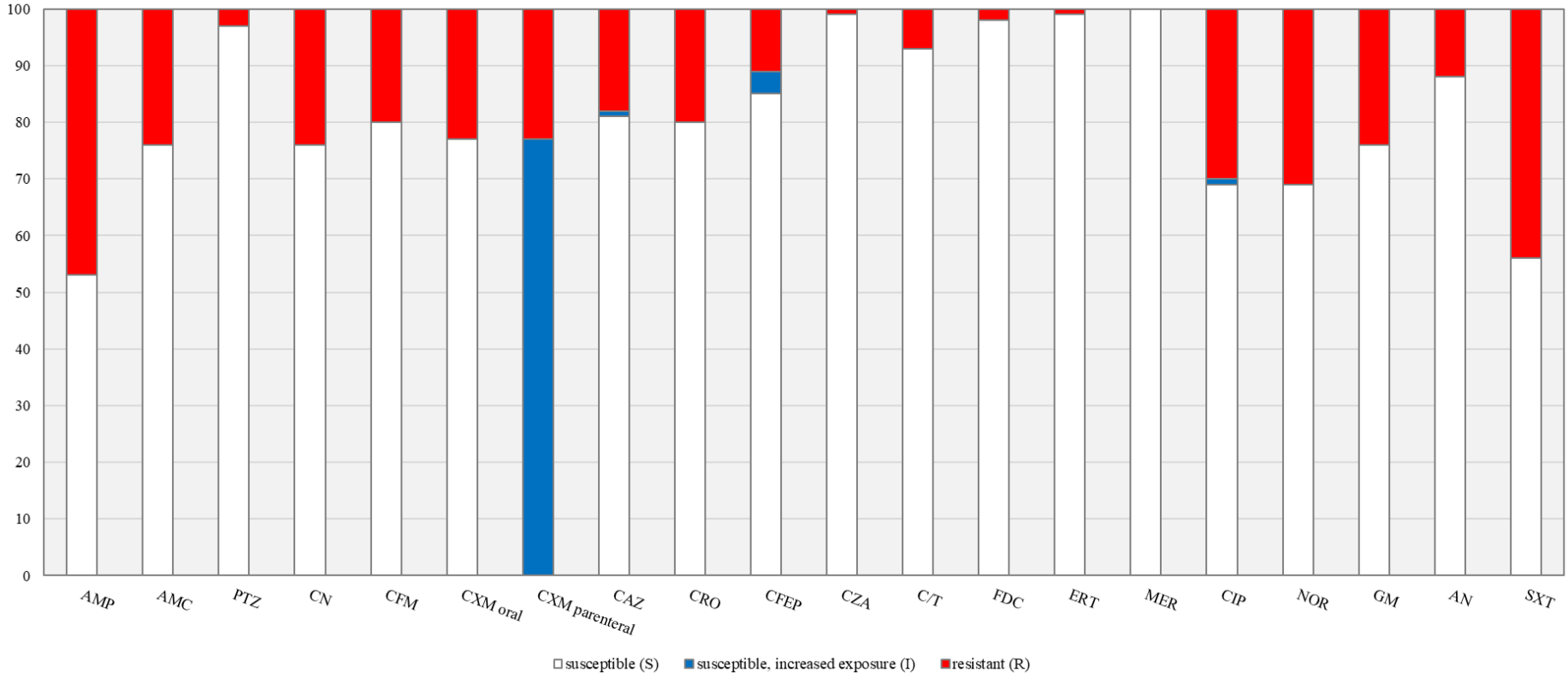
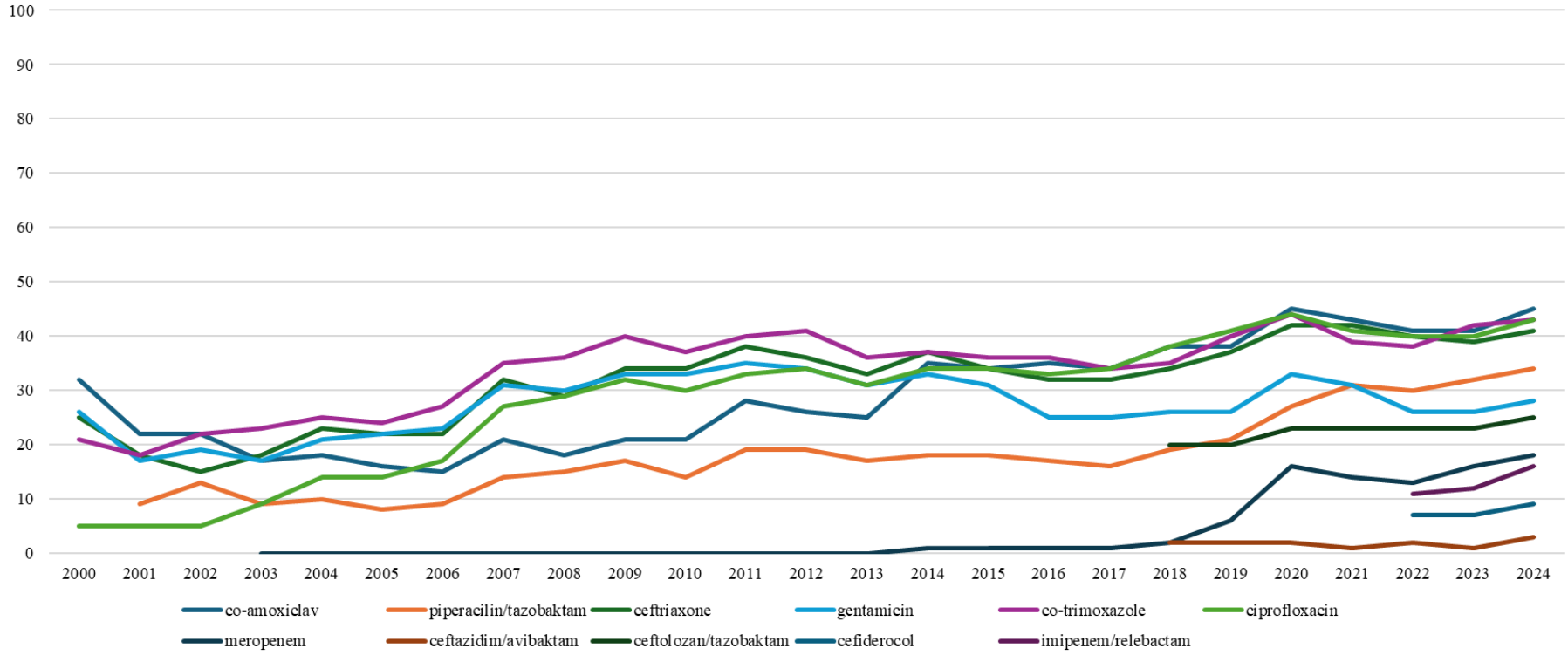
Proteus mirabilis

osjetljivost na antibiotike u RH / *sensitivity to antibiotics in Croatia*, 1.10. – 31.12.2024.



Klebsiella pneumoniae

rezistencija na antibiotike u RH /*resistance to antibiotics in Croatia*, 2000. - 2024.



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Klebsiella pneumoniae

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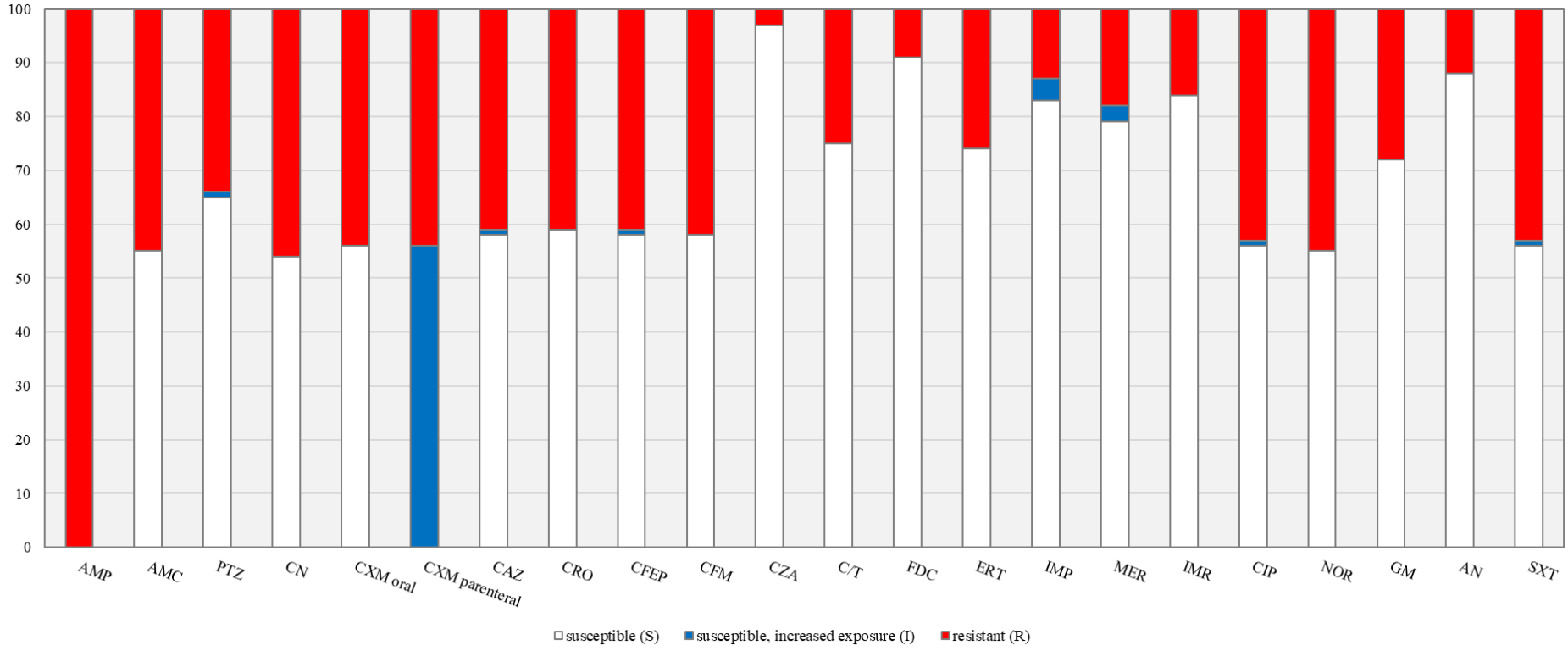
Ampicillin	7 912	100 (0)	100 (0) - 100 (0)
Amoxicillin + clav. acid	9 911	45 (0)	11 (0) - 75 (0)
Piperacillin + tazobactam	7 599	34 (1)	7 (1) - 72 (0)
Cephalexin	7 552	46 (0)	9 (91) - 76 (0)
Cefuroxime oral	7 863	44 (0)	9 (0) - 76 (0)
Cefuroxime parenteral	7 863	44 (56)	9 (91) – 76 (24)
Ceftazidime	7 846	41 (1)	6 (12) - 76 (0)
Ceftriaxone	7 841	41 (0)	3 (3) - 76 (0)
Cefepime	7 596	41 (1)	7 (0) – 76 (0)
Cefixime	7 605	42 (0)	13 (0) – 76 (0)
Ceftazidime + avibactam	7 405	3 (0)	0 (0) – 15 (0)
Ceftolozane + tazobactam	7 176	25 (0)	2 (0) – 64 (0)
Ertapenem	7 631	26 (0)	4 (0) -58 (0)
Imipenem	7 361	13 (4)	0 (0) - 37 (0)
Meropenem	7 576	18 (3)	0 (0) - 45 (7)
Imipenem + relebactam	7 190	16 (0)	0 (0) – 38 (0)
Cefiderocol	7 072	9 (0)	0 (0) – 37 (0)
Ciprofloxacin	7 518	43 (1)	3 (6) - 78 (1)
Norfloxacin	7 542	45 (0)	9 (0) - 80 (0)
Gentamicin	7 920	28 (0)	3 (0) - 50 (0)
Amikacin	7 948	12 (0)	0 (0) - 32 (0)
Co-trimoxazole	7 827	43 (1)	6 (0) - 66 (0)

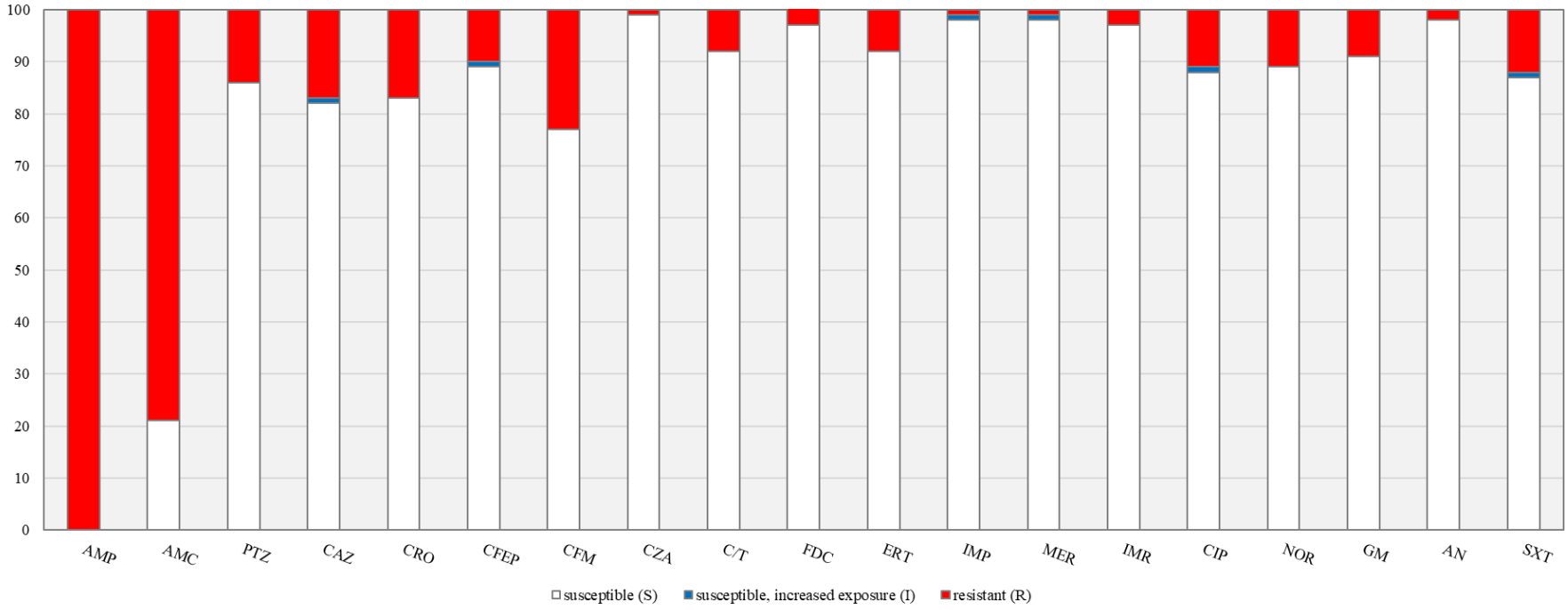
Klebsiella pneumoniae

osjetljivost na antibiotike u RH / *sensitivity to antibiotics in Croatia*, 1.10. – 31.12.2024.



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

osjetljivost na antibiotike u RH / *sensitivity to antibiotics in Croatia,* 1.10. – 31.12.2024.



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

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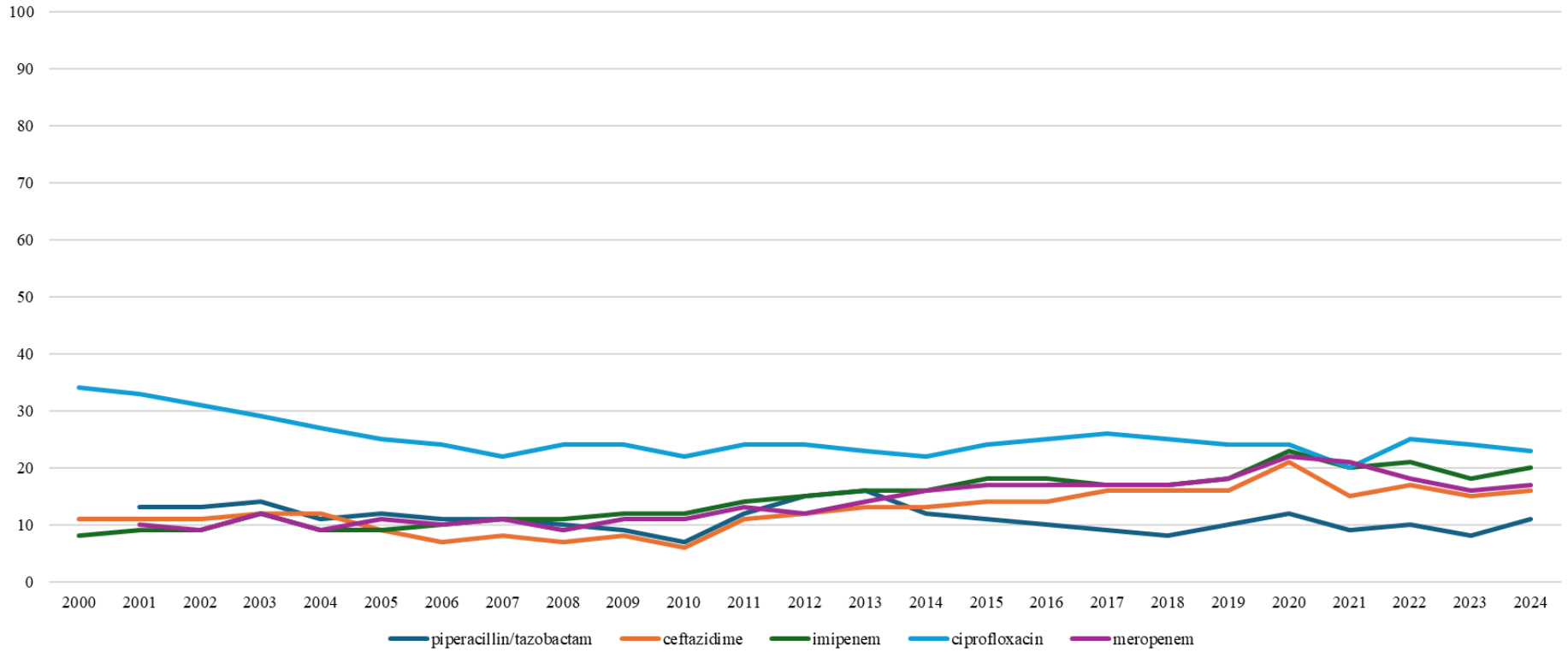
Ampicillin	4 182	100 (0)	100 (0) - 100 (0)
Amoxicillin + clav. acid	4 192	79 (0)	57 (0) - 100 (0)
Piperacillin + tazobactam	4 186	14 (0)	3 (0) - 32 (3)
Ceftazidime	4 128	17 (1)	4 (3) - 44 (0)
Ceftriaxone	4 128	17 (0)	5 (1) - 42 (0)
Cefepime	4 186	10 (1)	0 (0) - 32 (0)
Cefixime	3 962	23 (0)	9 (0) - 74 (0)
Ceftazidime + avibactam	3 906	1 (0)	0 (0) - 12 (0)
Ceftolozane + tazobactam	3 852	8 (0)	0 (0) – 27 (0)
Cefiderocol	3 675	4 (0)	0 (0) – 27 (0)
Ertapenem	4 188	8 (0)	0 (0) – 29 (0)
Imipenem	3 942	1 (1)	0 (0) – 29 (0)
Meropenem	4 156	1 (1)	0 (0) – 12 (2)
Imipenem + relebactam	3 842	3 (0)	0 (0) – 40 (0)
Ciprofloxacin	4 176	11 (1)	3 (1) - 37 (0)
Norfloxacin	3 827	11 (0)	3 (0) - 37 (0)
Gentamicin	4 192	9 (0)	0 (0) - 32 (0)
Amikacin	4 132	2 (0)	0 (0) - 14 (0)
Co-trimoxazole	4 111	13 (1)	5 (0) - 37 (0)

Pseudomonas aeruginosa

rezistencija na antibiotike u RH / *resistance to antibiotics in Croatia*, 2000. - 2024.



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Pseudomonas aeruginosa

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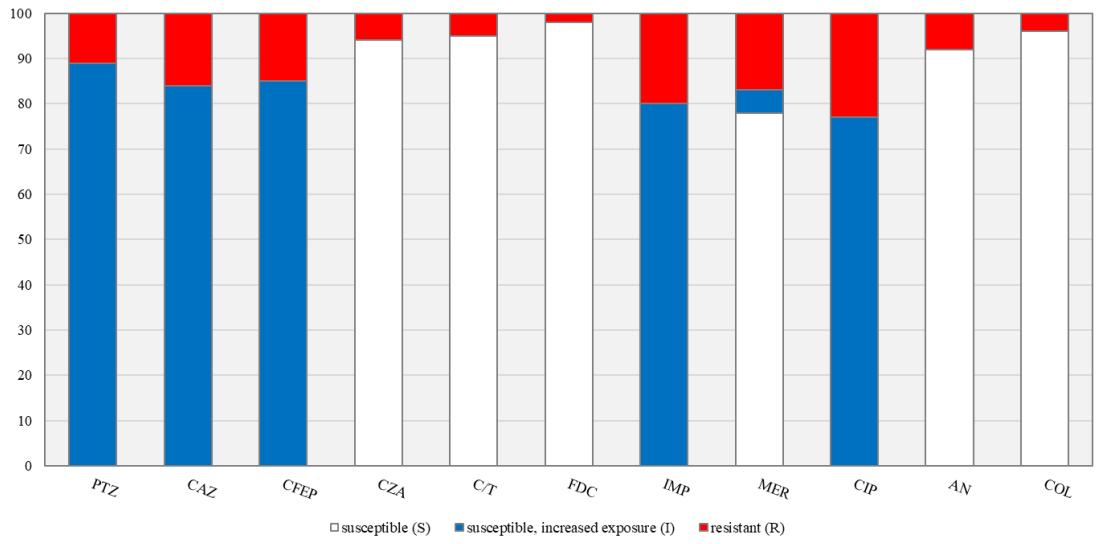
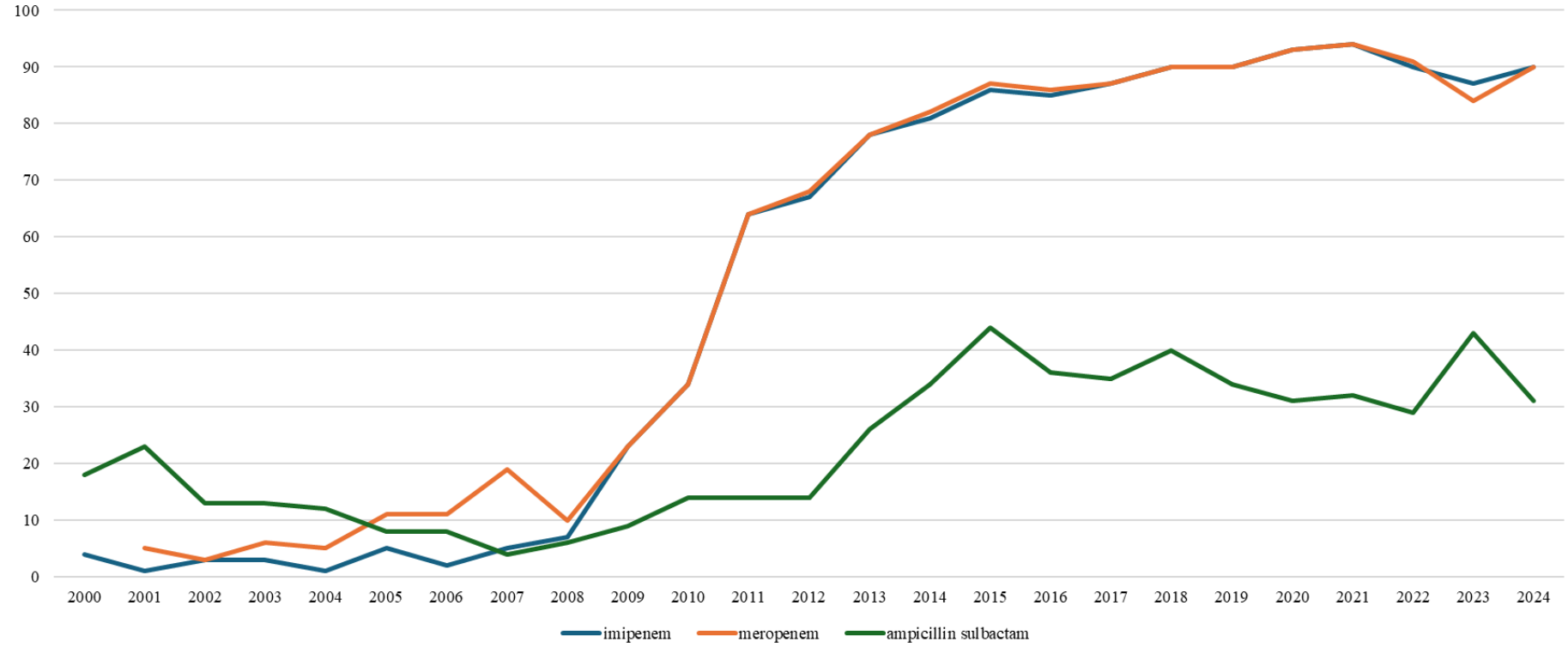
Piperacilin + tazobaktam	4 684	11 (89)	2 (98) - 26 (74)
Ceftazidim	4 679	16 (84)	3 (97) - 60 (40)
Cefepim	4 684	15 (85)	3 (97) - 46 (34)
Ceftazidime + avibactam	4 368	6 (0)	0 (0) – 24 (0)
Ceftolozane + tazobactam	4 342	5 (0)	0 (0) – 22 (0)
Cefiderocol	4 151	2 (0)	0 (0) – 5 (0)
Imipenem	4 486	20 (80)	5 (95) - 53 (47)
Meropenem	4 673	17 (5)	2 (2) - 44 (46)
Ciprofloxacin	4 681	23 (77)	4 (96) - 37 (63)
Amikacin	4 589	8 (0)	0 (0) - 28 (0)
Colistin	1 072	4 (0)	0 (0) - 18 (0)



Acinetobacter baumannii

rezistencija na antibiotike u RH / *resistance to antibiotics in Croatia*, 2000. - 2024.



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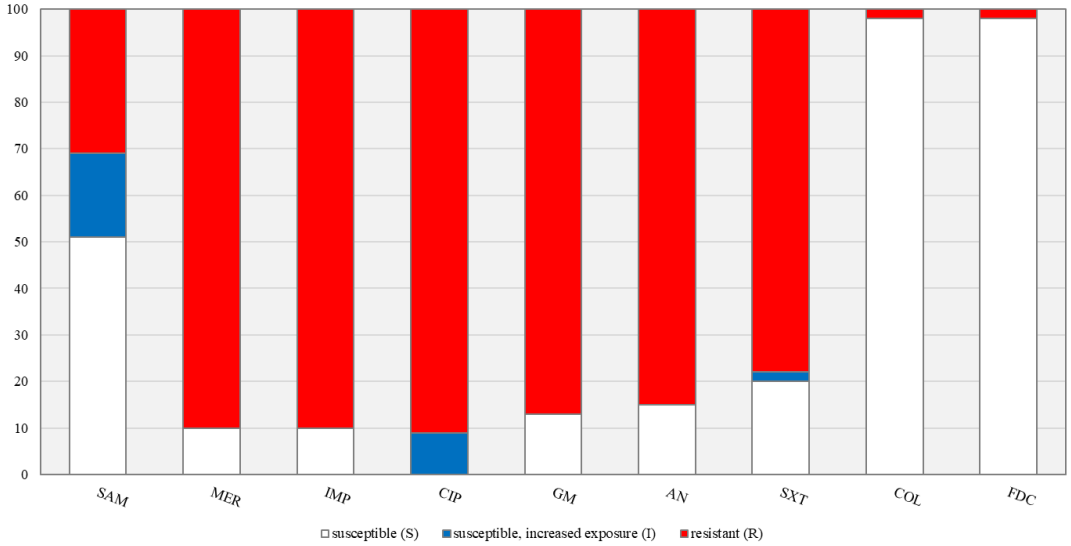
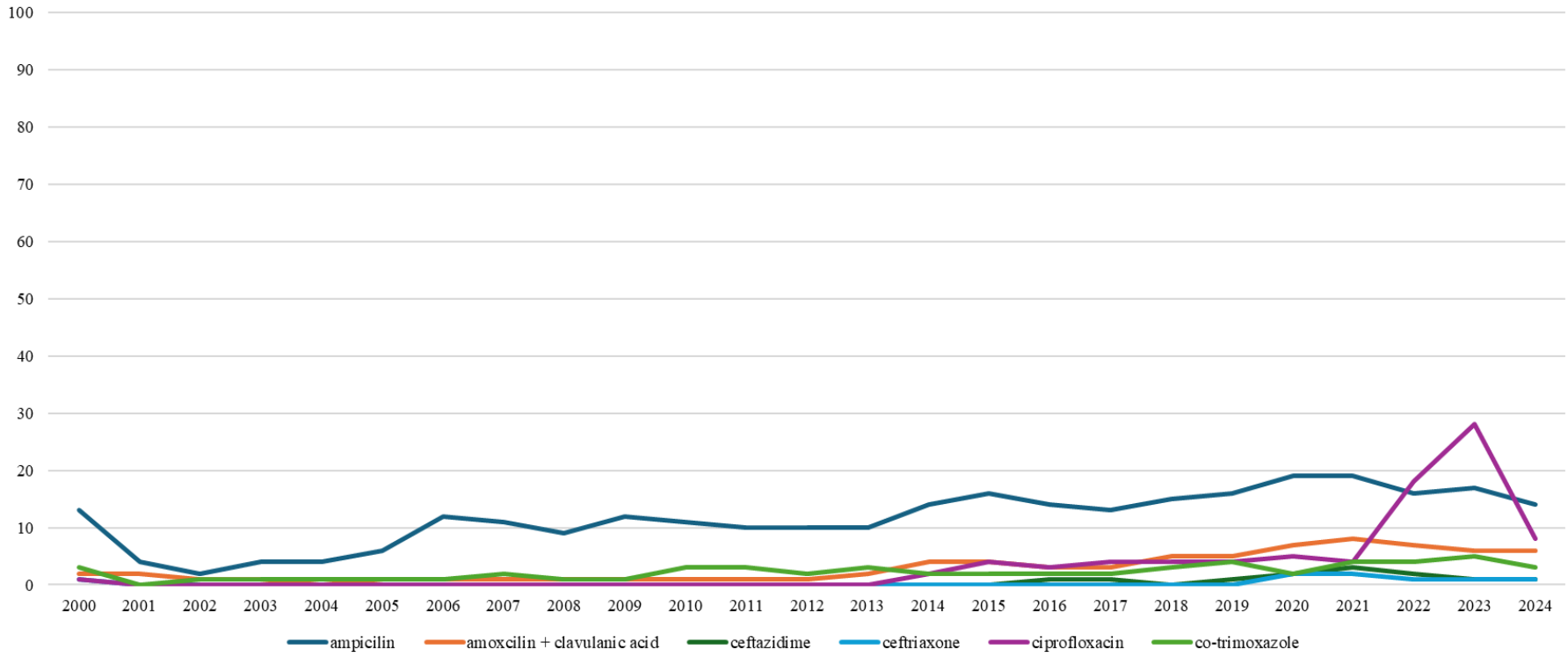
Ampicillin + sulbactam	2 027	31 (18)	2 (7) - 97 (3)
Meropenem	2 087	90 (0)	82 (1) - 100 (0)
Imipenem	2 014	90 (0)	82 (0) - 100 (0)
Ciprofloxacin	2 085	91 (9)	82 (18) - 100 (0)
Gentamicin	2 087	87 (0)	70 (0) - 100 (0)
Amikacin	2 087	85 (0)	67 (0) - 100 (0)
Co-trimaxazole	2 023	78 (2)	51 (1) - 100 (0)
Colistin	1 806	2 (0)	0 (0) - 10 (9)
Cefiderocol	1 782	2 (0)	0 (0) – 4 (0)

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



Salmonella spp.

rezistencija na antibiotike u RH / *resistance to antibiotics in Croatia*, 2000. - 2024.



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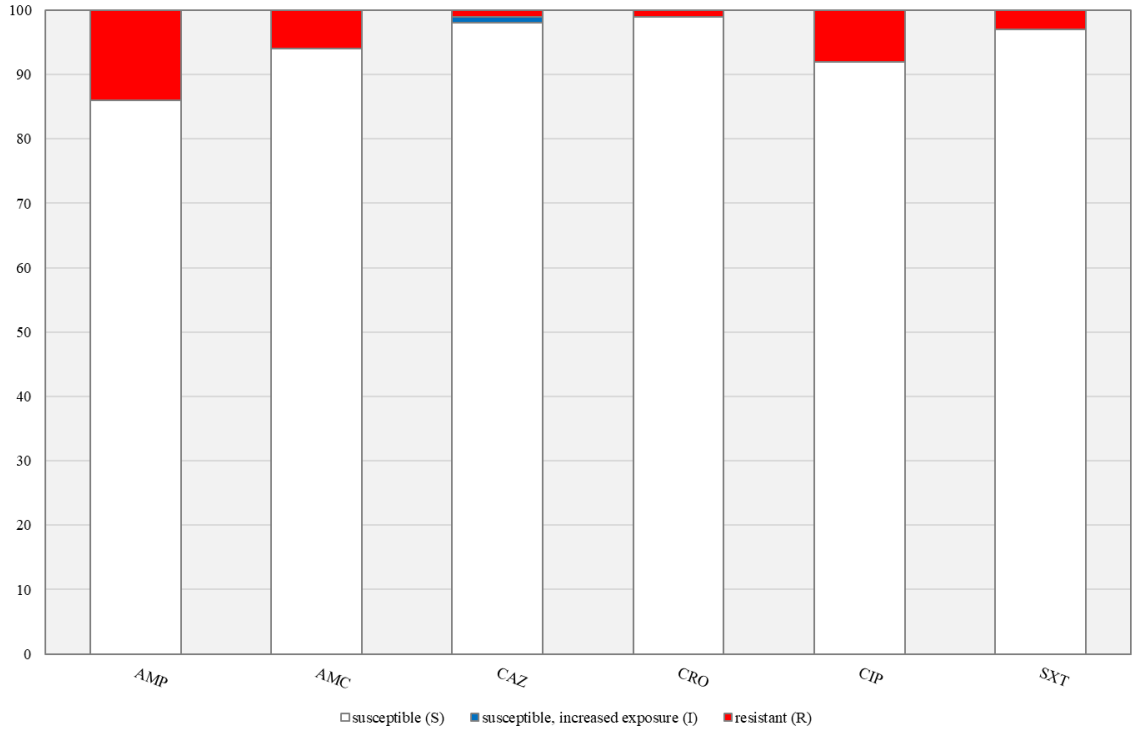
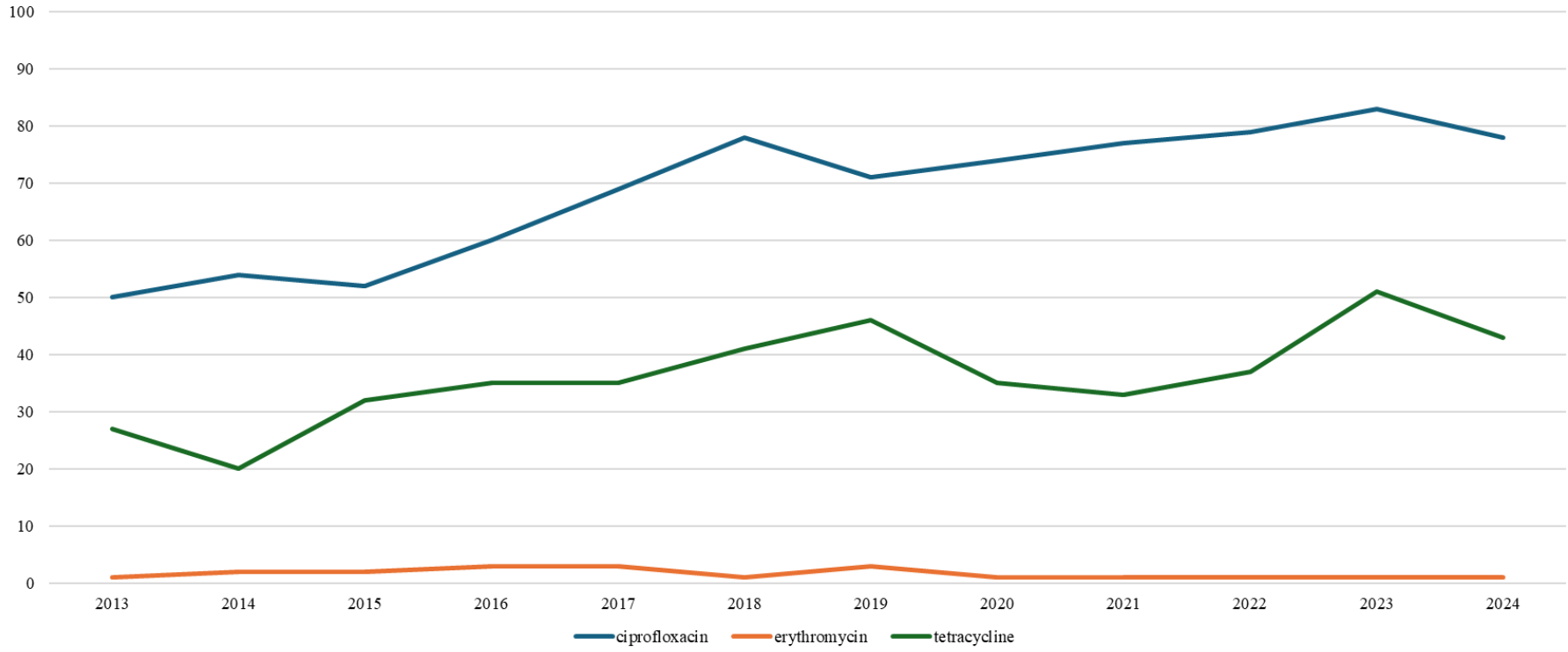
Ampicillin	2 170	14 (0)	0 (0) - 37 (0)
Amoxicillin + clav. acid	2 168	6 (0)	0 (0) - 30 (0)
Ceftazidim	2 170	1 (1)	0 (0) - 12 (2)
Ceftriaxone	2 168	1 (0)	0 (0) - 7 (4)
Ciprofloxacin	2 168	8 (0)	0 (0) - 21 (0)
Co-trimoxazole	2 170	3 (0)	0 (0) - 10 (0)



Campylobacter coli

rezistencija na antibiotike u RH / *resistance to antibiotics in Croatia*, 2013. - 2024.



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ANTIBIOTIK / ANTIBIOTIC	**Broj izolata** / No. of isolates	**% rezistentnih (R) (% osjetljivih uz povećanu izloženost (I)) izolata** / *% of resistant (R) (% of susceptible, increased exposure (I)) isolates*	**Raspon lokalnih rezultata*** / Range of local results*
Ciprofloxacin	472	78 (22)	69 (31) - 87 (13)
Erythromicin	472	1 (0)	0 (0) - 9 (0)
Tetracycline	472	43 (0)	36 (0) - 64 (0)

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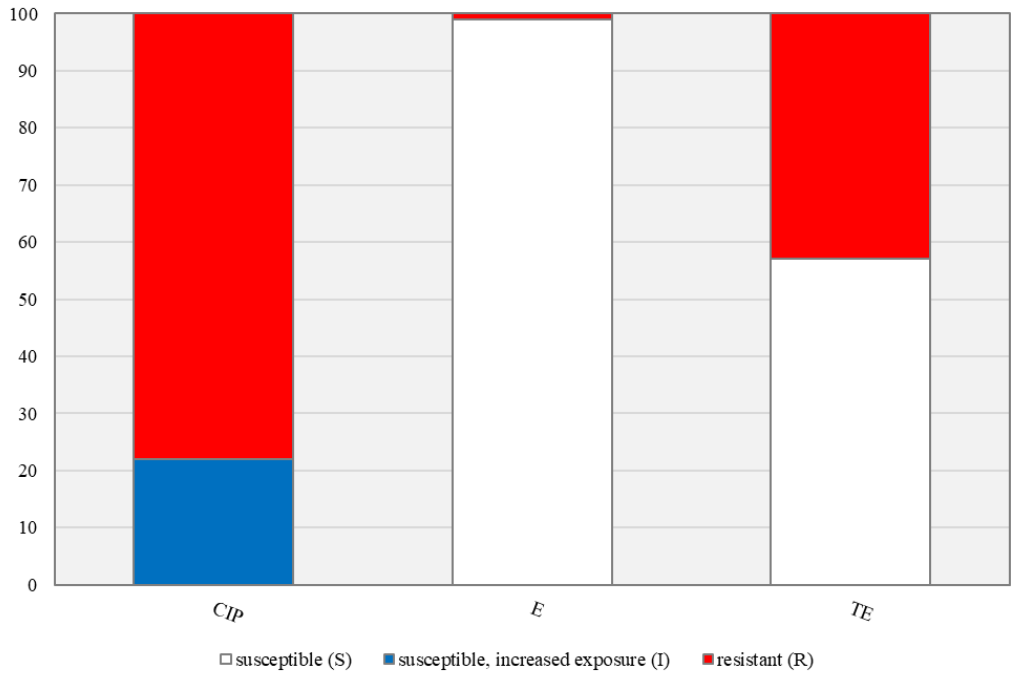
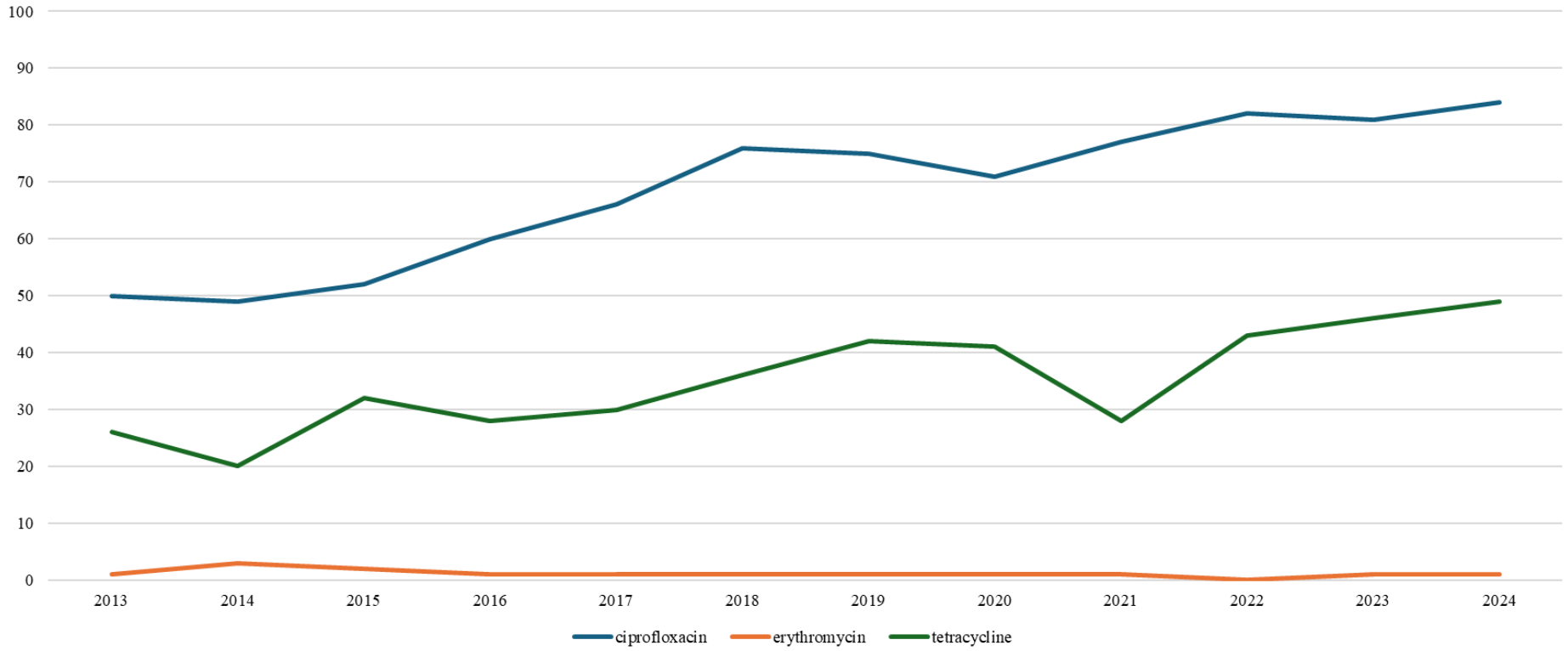


Campylobacter jejuni

rezistencija na antibiotike u RH / *resistance to antibiotics in Croatia*, 2013. - 2024.



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ANTIBIOTIK / *ANTIBIOTIC*	**Broj izolata** / *No. of isolates*	**% rezistentnih (R) (% osjetljivih uz povećanu izloženost (I)) izolata** / *% of resistant (R) (% of susceptible, increased exposure (I)) isolates*	**Raspon lokalnih rezultata*** / *Range of local results**
Ciprofloxacin	3 005	84 (16)	69 (31) - 97 (3)
Erythromicin	3 005	1 (0)	0 (0) - 2 (0)
Tetracycline	3 002	49 (0)	28 (0) - 57 (0)

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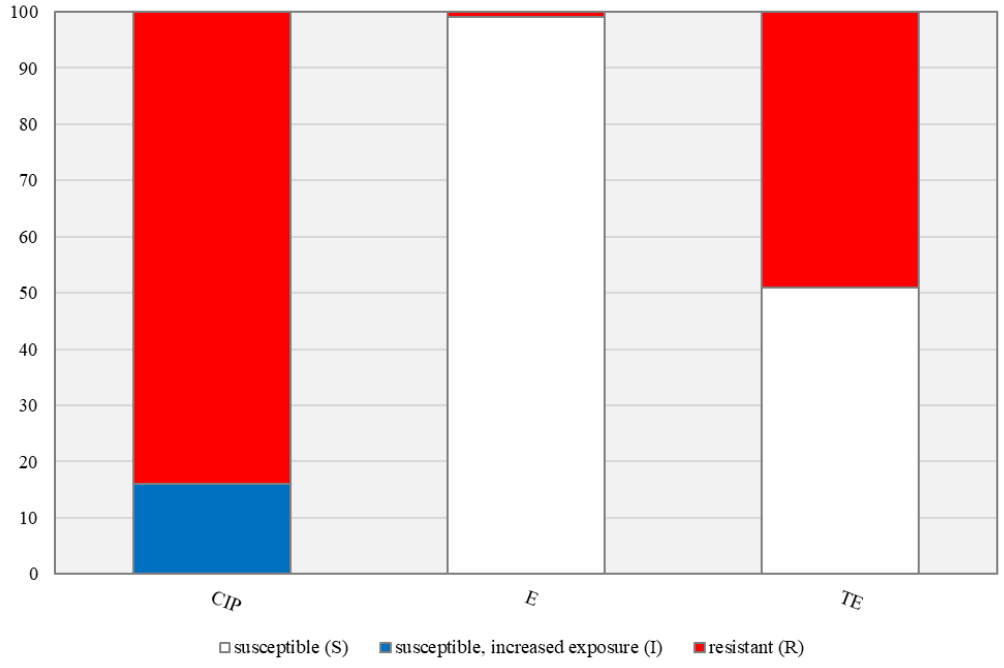

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Shigella spp.

rezistencija na antibiotike u RH / *antibiotic resistance in Croatia*, 01.01. – 31.12.2024.*

***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*	7	0	**7**	7	6	**1**	7	2	2	**3**	7	0	**7**	7	0	**7**	7	0	**7**	7	1	**6**
Shigella flexneri*	8	3	**5**	8	4	**4**	8	7	0	**1**	8	7	**1**	8	5	**3**	8	6	**2**	7	7	**0**
Shigella boydii*	2	0	**2**	2	1	**1**	2	2	0	**0**	3	3	**0**	3	2	**1**	3	2	**1**	0	0	**0**
UKUPNO / *TOTAL*	17	3	**14**	17	11	**6**	17	11	2	**4**	18	10	**8**	18	7	**11**	18	8	**10**	**14**	**8**	**6**

*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. – 31.12.2024.

Anaerobne bakterije / *Anaerobes*	**P**			**AMC**			**CRO**			**PTZ**			**ERT**			**MER**			**VA**			**CC**			**LZD**			**MTZ**		
	No	S %	**R %**	No	S %	**R %**	No	S %	**R %**	No	S %	**R %**	No	S %	**R %**	No	S %	**R %**	No	S %	**R %**	No	S %	**R %**	No	S %	**R %**	No	S %	**R %**
Cutinacterium acnes	351	98	**2**	351	99	**1**	331	100	**0**	351	100	**0**	350	99	**1**	348	100	**0**	351	100	**0**	354	81	**19**	266	100	**0**			
Bacteroides spp.				1042	64	**36**				1010	86	**14**				1007	95	**5**				1009	49	**51**				1003	90	**10**
Prevotella spp.	387	30	**70**	384	65	**35**				385	98	**2**	363	98	**2**	365	98	**2**				387	40	**60**				385	87	**13**
Fusobacterium necrophorum *	15	67	**33**	15	87	**13**				15	87	**13**	15	87	**13**	15	87	**13**				15	73	**27**				14	64	**36**
Clostridium perfrigens	113	96	**4**	112	96	**4**				113	96	**4**	113	98	**2**	113	100	**0**	113	97	**3**	113	45	**55**				112	86	**14**
UKUPNO / *TOTAL*	866	67	**33**	1904	73	**27**	331	100	**0**	1874	92	**8**	841	98	**2**	1848	97	**3**	464	99	**1**	1878	53	**47**	266	99	**1**	1514	89	**11**

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

POGLAVLJE / *CHAPTER* **2**.

OSJETLJIVOST *M. TUBERCULOSIS* U HRVATSKOJ U 2024. GODINI

SENSITIVITY OF M. TUBERCULOSIS IN CROATIA, 2024

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 2024. GODINI

Za analizu podataka o bakteriološkoj dijagnostici tuberkuloze (TBC) u Hrvatskoj u 2024. godini koristio se „Upitnik o radu TBC laboratorija u 2024. godini“. U prošloj godini dijagnostika tuberkuloze provodila se u 12 laboratorija organiziranih na tri razine. Ukupno je pregledano 27.169 kliničkih uzoraka na TBC što je porast od 1,7% od broja uzoraka iz 2023. godine. Iako je preporučeni minimalni godišnji broj uzoraka za obradu na mikobakterije 2000, samo četiri je laboratorija u 2024. 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 izvan plućne uzorke. U 4,0% uzoraka kultivacijom je otkriven *M. tuberculosis*, a raspon pozitivnih kultura među laboratorijima se kretao od 0,8 do 16,2%. Ukupno je izolirano 1.439 sojeva mikobakterija.

Tijekom 2024. godine genotipizirano je 229 izolata *M. tuberculosis* iz cijele Hrvatske. U skladu s očekivanim, *M. tuberculosis* je najčešće izoliran iz plućnih uzoraka, a među 32 (14,0%) izvanplućnih bakteriološki dokazanih slučajeva TBC najčešća je bila limfoglandularna TBC (N=12), TBC pleure (N=5) i TBC središnjeg živčanog sustava (N=2). Kod čak šest pacijenata nađena je diseminirana tuberkuloza.

Tijekom 2024. godine iz humanih kliničkih materijala nije izoliran *M. bovis*, ali je izolirano osam *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 2024. godini od uvjetno patogenih spororastućih mikobakterija najviše je izoliran *M. aviumi* (77 izolata), *M. xenopi* (53 izolata), te *M. intracellulare* (41 izolat). Od brzorastućih mikobakterija najveći broj izolata odnosio se na *M. fortuitum* (37 izolata), a slijede ga *M. chelonae* sa 18 izolata i *M. mucogenicum* sa devet izolata. *M. gordonae* kao saprofitna mikobakterija je identificiran u 16,5% izolata NTM. Najčešće se radi o kontaminaciji uzoraka, slučajnim nalazima i prolaznim kolonizacijama. U 2024. godini su otkriveno je 85 osobe sa zadovoljenim mikrobiološkim kriterijima za dijagnozu mikobakterioze (dva i više izolata, ili izolat iz asp. bronha). Kod 25 bolesnika izoliran *je M. xenopi*, a slijede ga *M. avium* koji je izoliran kod 21 bolesnika te *M. intracellulare* kod 11 bolesnika.

Nažalost, i 2024. godine izoliran je veliki broj rezistentnih sojeva. Od 1099 testiranih sojeva njih 53 (8,7%) bilo je rezistentno na prvu liniju antituberkulotika, a otkriveni su kod 17 bolesnika s rezistentnom tuberkulozom. Među bolesnicima s rezistentnim oblikom tuberkuloze, njih 12 je imalo monorezistenciju na jedan od antituberkulotika prve linije, troje pacijenata imalo je zarazu polirezistentnim sojem te dvoje pacijenata je imalo MDR soj.

MYCOBACTERIA ISOLATED IN CROATIA IN 2024

In 2024, 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 2024" was used. A total of 27,169 clinical samples were analyzed for tuberculosis, which is 1,7% more than the number of samples in 2023. 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 4.0% of samples, cultivation detected mycobacteria and the range of positivity of cultivation in different laboratories was from 0.8 to 16,2%. A total of 1,439 mycobacterial isolates were cultivated.

During 2024, a total of 229 M. tuberculosis isolates were genotyped. As expected, *M. tuberculosis* was most frequently isolated from pulmonary samples. Among bacteriologically confirmed extrapulmonary TB (N=32; 14.0%), the most frequent forms were lymphoglandular TB (N=12), pleural TB (N=5) and TB of the central nervous system (N=2). Disseminated tuberculosis was found in as many as six patients. During 2024, no *M. bovis* was isolated from human clinical materials, but eight *M. bovis* - BCG strains were isolated. Although *M. tuberculosis* remained the predominant mycobacterium with 1099 (76.4%) isolates, the number of nontuberculous mycobacteria (NTM) is still high, accounting for 23.6% of all isolates in 2024. 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 2024 prevailed isolates of *M. avium* (N=77), *M. xenopi* (N=53), and *M. intracellulare* (N=41), while in the rapidly growing group the most commonly isolated species were *M. fortuitum* (N=37), *M. chelonae* (N=18) and M. mucogenicum (N=9). M. gordonae, a saprophytic mycobacterium, was identified in 16,5% of all NTM isolates. In most cases, the isolation was the result of specimen contamination, accidental finding and transient colonization.

In 2024, a total of 85 cases that fulfilled the microbiological criteria for mycobacteriosis (two or more isolates or isolate from bronh. aspirate) were documented. M. xenopi was isolated in 25 patients, M. avium in 21 patients, M. intracellulare in 11 patients.

Unfortunately, the number of resistant strains remained high. Out of 1099 strains tested, 53 (8.7%) were resistant to the first line of antituberculosis drugs, and were detected in 17 patients with resistant tuberculosis. Among the patients with a resistant form of tuberculosis, 12 had monoresistance, three patients had infection with a polyresistant strain and two with an MDR strain.

Tablica / *Table* **1**.
Mikobakterije izolirane u Hrvatskoj, 2014. – 2024. /
Mycobacteria strains isolated in Croatia, 2014-2024

Godina	Ukupno mikobakterija	*M. tuberculosis*		*M. bovis*		Netuberkulozne mikobakterije	
		Broj	%	*M. bovis*	BCG soj	Broj	%
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
2024.	1439	1099	76,4	-	8	340	23,6

Tablica / *Table* **2**.
Netuberkulozne mikobakterije (NTM) izolirane u Hrvatskoj u 2024. /
Nontuberculous mycobacteria (NTM) isolated in Croatia in 2024

		Vrsta - *Species*	**Broj** - *No.*	**%**
UVJETNOPATOGENE MIKOBAKTERIJE - *Facultatively pathogenic*	sporog rasta - *slow growth*	*M. avium*	77	22,6
		M. xenopi	53	15,6
		M. intracellulare	41	12,1
		M. kansasii	15	4,4
		M. chimaera	6	1,8
		M. malmoense	4	1,2
	brzog rasta - *fast growth*	*M. fortuitum*	37	10,9
		M. chelonae	18	5,3
		M. abscessus	9	2,6
		M. mucogenicum	9	2,6
		M. celatum	1	0,3
		M. lentiflavum	1	0,3
		M. setense	1	0,3
SAPROFITNE MIKOBAKTERIJE - *Saprophytic mycobacteria*		*M. gordonae*	56	16,5
		Mycobacterium spp.	12	3,5
UKUPNO - *Total*			**340**	**100**

Tablica / *Table* **3**.
Bolesnici s rezistentnom tuberkulozom u Hrvatskoj, 2024. /
Resistant tuberculosis in Croatia, 2024

	Antibiotik - *Antibiotic*	**Broj** - *No.*	**%**
MONOREZISTENCIJA – *Monoresistance*	H	5	29,4
	S	4	23,5
	R	2	11,8
	E	1	5,9
POLIREZISTENCIJA – *Polyresistance*	H, S	2	11,8
	H, S, PAS	1	5,9
MULTIREZISTENCIJA – *Multiresistance*	H, R	1	5,9
	H, R, Eth	1	5,9
UKUPNO – *Total*		**17**	**100**

Legenda - *Key*:
R – rifampicin, S – streptomicin, H – izoniazid, Z – pirazinamid, E – etambutol, Eth – etionamid, PAS - para-aminosalicilna kiselina

POGLAVLJE / *CHAPTER* **3**.

OSJETLJIVOST GONOKOKA U HRVATSKOJ U 2024

SENSITIVITY OF GONOCOCCI IN CROATIA IN 2024

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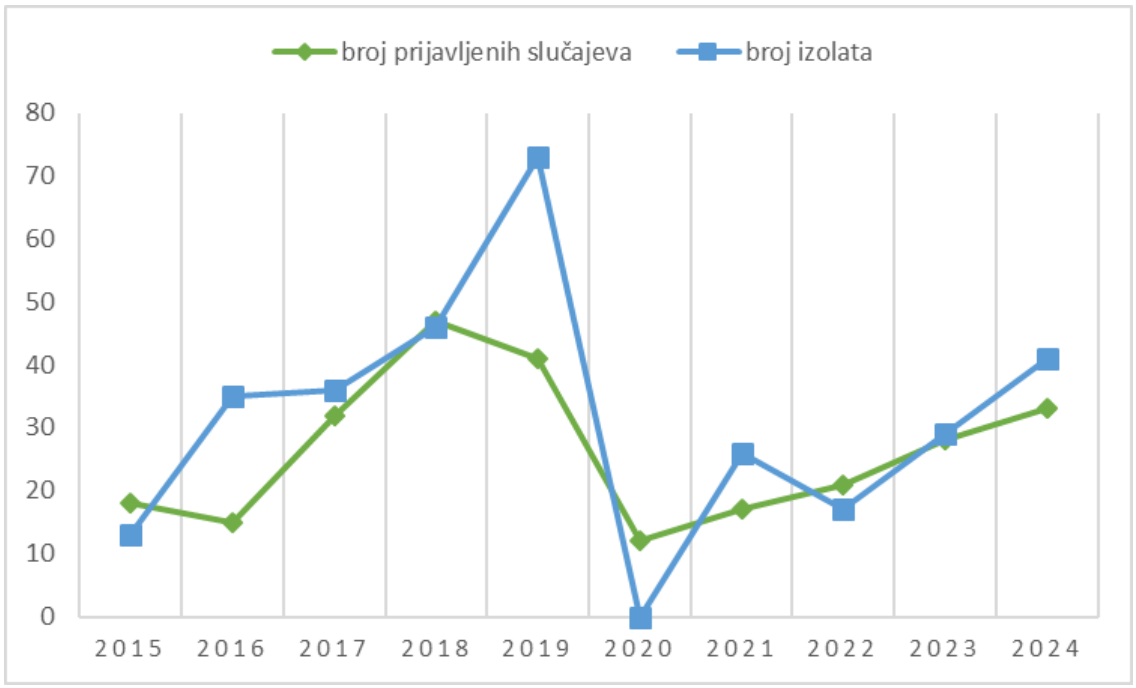
ANTIMIKROBNA REZISTENCIJA U GONOKOKA IZOLIRANIH U HRVATSKOJ U 2024. GODINI

Tijekom 2024. godine nastavljena je provedba Europskog programa za nadzor antimikrobne rezistencije gonokoka – Euro-GASP (European Gonococcal Antimicrobial Surveillance Programme), koji provodi Europski centar za prevenciju i kontrolu bolesti (ECDC), a u kojem Republika Hrvatska (RH) sudjeluje već deset godina. Cilj projekta je praćenje učestalosti i obrazaca antimikrobne rezistencije kod izolata *Neisseria gonorrhoeae* (NG), u kombinaciji s prikupljanjem relevantnih epidemioloških podataka.

Tijekom desetogodišnjeg razdoblja (2015.–2024.) zabilježene su oscilacije u broju prijavljenih slučajeva gonoreje (epidemiološki podaci) i u broju izolata NG (mikrobiološki podaci) (Slika 1).

Broj prijavljenih slučajeva epidemiološkoj službi postupno je rastao do 2019. godine, nakon čega je u 2020. zabilježen pad, vjerojatno povezan s pandemijom COVID-19 i otežanim pristupom zdravstvenoj skrbi, ali i vjerojatno zbog potprijavljivanja. Od 2021. nadalje bilježi se blagi, ali kontinuirani porast broja prijava. Sličan obrazac uočen je i u broju izolata NG: porast do 2019., potom nagli pad u 2020. te postupni oporavak u narednim godinama. Uočeni trendovi mogu odražavati kombinirani utjecaj više čimbenika – promjenjive incidencije gonoreje u populaciji, dostupnosti zdravstvene skrbi i testiranja, dijagnostičke i laboratorijske prakse te kapaciteta nadzora sustava, osobito u pandemijskim i postpandemijskim godinama.

Slika 1. Gonoreja u RH (2015.–2024.) – Broj prijavljenih slučajeva i izolata *N. gonorrhoeae*
Figure 1. Gonorrhoea in Croatia (2015-2024) – Number of reported cases and N. gonorrhoeae isolates



U Hrvatski zavod za javno zdravstvo (HZJZ) dostavljaju se izolati s pratećim obrascima s podacima o rezultatima osjetljivosti NG. Zbog osjetljivosti izolata na transportne uvjete i posljedičnog gubitka vijabilnosti, dostava izolata za potrebe retestiranja postaje sve rjeđa. Kako bi se osigurala kvaliteta i usporedivost rezultata, laboratorij redovito sudjeluje u programima vanjske procjene kvalitete (EQA, *external quality assessment*).

Obrazci su prikupljeni iz sljedećih ustanova: Nastavni zavod za javno zdravstvo „Dr. Andrija Štampar", Zagreb; Klinika za infektivne bolesti „Dr.Fran Mihaljević", Zagreb; Zavod za javno zdravstvo Međimurske županije, Čakovec; Nastavni zavod za javno zdravstvo Splitsko-dalmatinske županije, Split; Zavod za javno zdravstvo Šibensko-kninske županije, Šibenik; Nastavni zavod za javno zdravstvo Primorsko-goranske županije, Rijeka; te Hrvatski zavod za javno zdravstvo, Zagreb.

U Tablici 1. prikazane su vrijednosti minimalnih inhibicijskih koncentracija (MIK) dobivene gradijentnom difuzijskom metodom (E-test), kao i rezultati ispitivanja osjetljivosti primjenom disk difuzijske metode.

Rezultati ispitivanja antimikrobne osjetljivosti izolata za 2024. prikazani su u Tablici 2.

U 2024. godini testiran je 41 izolat NG. Rezistencija na penicilin zabilježena je u tri izolata (7,3%), a nitrocefin test je bio pozitivan u 12 izolata (30,7%). Rezistencija na ceftriakson zabilježena je u jednom (2,4%), a na cefiksim u dva izolata (4,9%). Visoka razina rezistencije zabilježena je na ciprofloksacin, s 29 rezistentnih izolata (70,7%), dok je od 37 testiranih tetraciklin bio rezistentan kod 21 izolata (56,8%). Azitromicin je testiran u 41 izolatu, od kojih je sedam (17,1%) imalo MIK vrijednosti >1 mg/L. Prema standardima Europskog odbora za ispitivanje antimikrobne osjetljivosti (EUCAST; ECOFF = 1 mg/L), ovi nalazi ukazuju na moguću prisutnost stečenog mehanizma

rezistencije. Gentamicin je testiran u četiri izolata, s rasponima MIK vrijednosti od <0,016 - 1,5 mg/L. Gentamicin je uključen u protokole testiranja osjetljivosti u okviru ključnih međunarodnih programa nadzora rezistencije gonokoka, poput Euro-GASP (ECDC, Stockholm), EGASP (WHO, Ženeva) i GRASP (UK). Također je uključen u terapijske smjernice CDC-a i IUSTI-ja (2000.) u kombinaciji s azitromicinom za liječenje gonokokne infekcije kada ceftriakson nije opcija. Stoga je važno kontinuirano praćenje osjetljivosti na gentamicin, iako je klinička interpretacija podataka ograničena zbog izostanka definiranih graničnih vrijednosti prema EUCAST-u. Spektinomicin, iako i dalje nije dostupan kao registrirani lijek na hrvatskom tržištu, također je bio uključen u ispitivanje osjetljivosti, pri čemu rezistencija nije zabilježena.

Usporedbom rezultata ispitivanja antimikrobne osjetljivosti izolata gonokoka iz 2023. i 2024. godine uočeni su trendovi koji su prikazani na Slici 2.

Penicilin: I dalje relativno niska rezistencija, uz blagi porast u 2024.

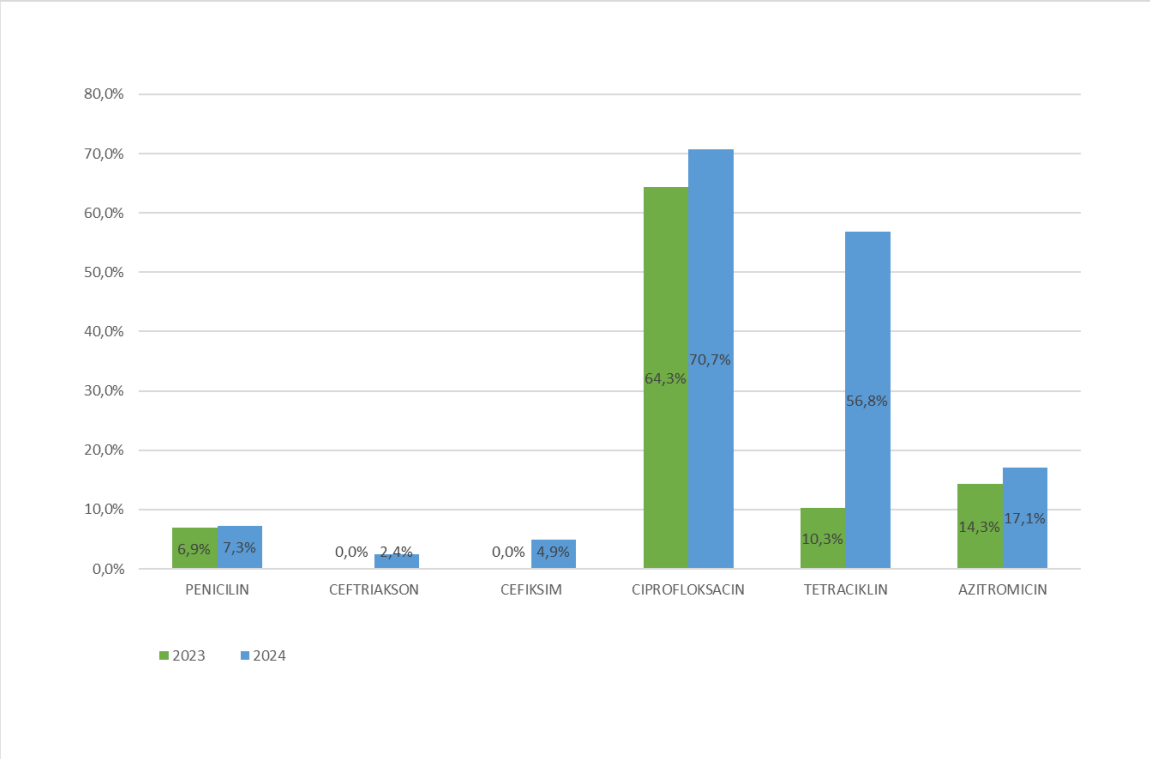
Cefalosporini (cetriakson i cefiksim)**:** U 2024. godini, detektirana je rezistencija na ceftriakson u jednom izolatu (MIK 0,19 mg/L; 2,4%) dok je rezistencija na cefiksim otkrivena u dva izolata (4,9%), što zahtijeva posebnu pozornost i naglašava potrebu za kontinuiranim praćenjem. U desetogodišnjem praćenju, rezistencija na ceftriakson zabilježena je još samo 2017. godine (1 izolat; MIK 0,38 mg/L; 2,8%). Rezistencija na cefiksim kretala se u razdoblju 2015.-2019. između 17,2% i 1,5%, dok u razdoblju 2021.-2023. nije bilo zabilježenih rezistentnih izolata. Sada je, nažalost, ponovo potvrđena pojava rezistentnih sojeva na cefiksim.

Ciprofloksacin: Visoka i dalje rastuća rezistencija

Tetraciklini: Rezistencija na tetraciklin porasla je s 10,3% (2023.) na 56,8% (2024.).

Azitromicin: MIK vrijednosti >1 mg/L (ECOFF) zabilježene su u 2023. godini u 14,3% izolata, a u 2024. u 17,1% izolata, što ukazuje na blagi porast u odnosu na prethodnu godinu.

Slika 2. Udio rezistentnih izolata *Neisseria gonorrhoeae* u RH u 2023. i 2024. godini
Figure 2. Proportion of resistance of Neisseria gonorrhoeae isolates in Croatia in 2023 and 2024



Bez obzira na mali broj testiranih izolata, rezultati ukazuju na nepovoljne trendove u antimikrobnoj rezistenciji gonokoka u RH. Najznačajniji nalaz u 2024. godini bila je pojava rezistencije na cefalosporine (ceftriakson i cefiksim). Međutim, zbog gubitka vijabilnosti izolata, rezistencija nije mogla biti potvrđena jer nije bilo moguće provesti fenotipsko retestiranje (određivanje MIK vrijednosti), niti genotipsku analizu metodom cjelogenomskog sekvenciranja (WGS, *Whole Genome Sequencing*). Slični slučajevi zabilježeni su u međunarodnim nadzorima uključujući Euro-GASP, UK GRASP i EGASP, koji povremeno prijavljuju "pretpostavljenu rezistenciju" na ceftriakson i cefiksim kada izolati nisu mogli biti potvrđeni zbog gubitka vijabilnosti ili graničnih MIK vrijednosti.

Nastavlja se dugogodišnji trend visoke, a ujedno i rastuće rezistencije na ciprofloksacin, što onemogućava njegovu upotrebu u empirijskom liječenju gonokoknih infekcija. Također, globalni podaci ukazuju na visoku i postojanu razinu rezistencije NG na ciprofloksacin, čak i u regijama s smanjenom primjenom ovog antibiotika, što sugerira dugotrajnu stabilnost mutacije u genu *gyr*A povezanu s rezistencijom.

Nadalje, zabrinjava i značajan porast rezistencije na tetraciklin u 2024.godini, što se djelomično može objasniti promjenom EUCAST kriterija, odnosno ukidanjem kategorije „osjetljiv uz povećanu izloženost" (I). Dodatno, ovakav porast može biti posljedica selekcijskog pritiska njegove primjene u drugim indikacijama ili horizontalnog prijenosa gena rezistencije, a djelomično i širenja rezistentnih sojeva povezano s primjenom doksiciklinske postekspozicijske profilakse (DoxyPEP, *Doxycycline Post-Exposure Prophylaxis*). Međutim, u RH trenutačno nema dostupnih podataka koji bi potvrdili ili odbacili utjecaj DoxyPEP-a na rizik od razvoja rezistencije na tetraciklin. Važno je

naglasiti da su Europska komisija i ECDC u izvještaju iz lipnja 2023. prepoznali DoxyPEP kao moguću strategiju za smanjenje incidencije spolno prenosivih infekcija među muškarcima koji imaju spolne odnose s muškarcima, uz naglasak na potrebu daljnjeg praćenja i evaluacije njezinih učinaka na javno zdravlje. Ovakav stav ukazuje na značaj DoxyPEP-a u javnozdravstvenim strategijama na razini EU, ali i na potrebu za oprezom zbog mogućeg doprinosa selekciji rezistentnih sojeva.

U 2024. godini u RH zabilježen je blagi porast broja izolata s MIK vrijednostima azitromicina >1 mg/L (ECOFF), što je u skladu s podacima Euro-GASP programa (ECDC). Međutim, takav trend ima klinički značaj jer povećava rizik od terapijskih neuspjeha pri empirijskoj primjeni kombinirane terapije (ceftriakson + azitromicin).

Također, u 2024. godini 29,2% izolata NG pokazuje rezistenciju na dva, a 14,6% na tri antimikrobna lijeka što predstavlja značajan porast u odnosu na 2023. godinu kada je 10,3 % izolata bilo rezistentno na dva, a 6,8% na tri antimikrobna lijeka.

Posebno zabrinjava širenje sojeva rezistentnih na ključne lijekove – ceftriakson, cefiksim i azitromicin – budući da upravo oni čine temelj empirijskog liječenja gonoreje. Takvi izolati već su prijavljeni u nekoliko zemalja, uključujući Australiju, Japan, Kinu i dijelove Europe.

Zbog iznimne sposobnosti *Neisseria gonorrhoeae* da brzo razvija rezistenciju na više klasa antibiotika, liječenje višestrukorezistentnih sojeva predstavlja rastući izazov. Stoga postoji hitna potreba za novim terapijama uključujući zoliflodacin koji je u fazi III ispitivanja, te za razvojem cjepiva kao dugoročnog rješenja.

Zaključno, 2024. godine u RH zabilježeni su nepovoljni trendovi rezistencije gonokoka, uključujući visoku rezistenciju na ciprofloksacin, značajan porast rezistencije na tetraciklin i blagi porast broja izolata s MIK vrijednosima azitomicina iznad ECOFF-a. Posebno zabrinjava sporadična pojava rezistencije na cefalosporine, koja zbog gubitka vijabilnosti izolata nije mogla biti potvrđena. Ovi nalazi naglašavaju potrebu za sveobuhvatnim i kontinuiranim mikrobiološkim i epidemiološkim nadzorom kroz Euro-GASP, kako bi se bolje razumjeli mehanizmi i širenje rezistencije u populaciji te omogućila pravovremena prilagodba terapijskih smjernica.

ANTIMICROBIAL RESISTANCE IN GONOCOCCAL ISOLATES IN CROATIA IN 2024

In 2024, the implementation of the European Gonococcal Antimicrobial Surveillance Program (Euro-GASP), coordinated by the European Center for Disease Prevention and Control (ECDC), continued, in which the Republic of Croatia has participated for ten years. The aim of the project is to monitor the prevalence and patterns of antimicrobial resistance (AMR) in *Neisseria gonorrhoeae* (NG) isolates, combined with the collection of relevant epidemiological data.

Over the ten-year period (2015–2024), fluctuations were observed in the number of reported gonorrhoea cases (epidemiological data) and in the number of NG isolates (microbiological data). (Figure 1).

The number of cases reported to the epidemiological service gradually increased until 2019, followed by a decline in 2020, most likely related to the COVID-19 pandemic and the associated reduced access to healthcare, but also probably due to underreporting. Since 2021, a slight but continuous increase in the number of notifications has been recorded. A similar pattern was observed in the number of NG isolates: an increase until 2019, a sharp decline in 2020, and a gradual recovery in subsequent years. These trends may reflect the combined influence of several factors – changing incidence of gonorrhoea in the population, availability of healthcare and testing, diagnostic and laboratory practices, and the capacity of the surveillance system, particularly during the pandemic and post-pandemic years.

Isolates of NG, accompanied by reporting forms with susceptibility results, are submitted to the Croatian Institute of Public Health (CIPH). Due to the sensitivity of isolates to transport conditions and the consequent loss of viability, the submission of isolates for retesting purposes has become increasingly rare. To ensure the quality and comparability of results, the laboratory regularly participates in external quality assessment (EQA) programs.

The isolates and forms were collected from the following institutions: Teaching Institute of Public Health "Dr. Andrija Štampar", Zagreb; Clinic for Infectious Diseases "Dr. Fran Mihaljević", Zagreb; Institute of Public Health of Međimurje County, Čakovec; Teaching Institute of Public Health of Split-Dalmatia County, Split; Institute of Public Health of Šibenik-Knin County, Šibenik; Teaching Institute of Public Health of Primorje-Gorski Kotar County, Rijeka; and the Croatian Institute of Public Health, Zagreb.

Table 1 shows the values of minimal inhibitory concentration (MIC) obtained using the gradient diffusion method (E-test), as well as the results of susceptibility testing performed using the disk diffusion method.

The antimicrobial susceptibility results of isolates for 2024 are presented in Table 2.

In 2024, 41 NG isolates were tested. Resistance to penicillin was observed in three isolates (7.3%), and the nitrocefin test was positive in 12 isolates (30.7%). Resistance to ceftriaxone was detected in one isolate (2.4%), and to cefixime in two isolates (4.9%). High-level resistance was observed for ciprofloxacin, with 29 resistant isolates (70.7%), while out of 37 isolates tested for tetracycline, 21 (56.8%) were resistant. Azithromycin was tested in 41 isolates, of which seven (17.1%) had MIC values >1 mg/L. According to the European Committee on Antimicrobial Susceptibility Testing (EUCAST; ECOFF = 1 mg/L), these findings suggest the possible presence of an acquired resistance mechanism.

Gentamicin was tested in four isolates, with MIC values ranging from <0.016 to 1.5 mg/L. Gentamicin is included in susceptibility testing protocols within key international gonococcal resistance surveillance programs, such as Euro-GASP (ECDC, Stockholm), EGASP (WHO, Geneva), and GRASP (UK). It is also incorporated into CDC and IUSTI therapeutic guidelines (2000) in combination with azithromycin for the treatment of gonococcal infection when ceftriaxone is not an option. Therefore, continued monitoring of gentamicin susceptibility is important, although clinical interpretation of the data remains limited due to the absence of defined breakpoints by EUCAST.

Spectinomycin, although still not available as a registered drug in the Croatian market, was also included in susceptibility testing, and no resistance was detected.

Comparison of antimicrobial susceptibility results of gonococcal isolates from 2023 and 2024 revealed trends presented in Figure 2.

Penicillin: Resistance remained relatively low, with a slight increase observed in 2024.

Cephalosporins (ceftriaxone and cefixime): In 2024, resistance to ceftriaxone was detected in a single isolate (MIC 0.19 mg/L; 2.4%), while resistance to cefixime was identified in two isolates (4.9%). These findings warrant particular attention and underscore the need for continuous surveillance. Over a ten-year monitoring period, ceftriaxone resistance had previously been recorded only in 2017 (1 isolate; MIC 0.38 mg/L; 2.8%). Cefixime resistance ranged from 1.5% to 17.2% between 2015 and 2019, with no resistant isolates detected from 2021 to 2023. Unfortunately, resistant strains to cefixime have now re-emerged.

Ciprofloxacin: Resistance remains high and continues to increase.

Tetracyclines: Tetracycline resistance rose from 10,3% in 2023 to 56.8% in 2024.

Azithromycin: MIC values >1 mg/L (ECOFF) were recorded in 14.3% of isolates in 2023 and 17.1% in 2024, indicating a slight increase compared to the previous year. Despite the small number of tested isolates, the results indicate unfavourable trends in gonococcal antimicrobial resistance in Croatia. The most significant finding in 2024 was the emergence of resistance to cephalosporins (ceftriaxone and cefixime). However, due to the loss of isolate viability, resistance could not be confirmed, as neither phenotypic retesting (MIC determination) nor genotypic analysis by whole genome sequencing (WGS) could be performed.

Similar cases have been reported in international surveillance programs, including Euro-GASP, UK GRASP, and EGASP, which occasionally report "presumed resistance" to ceftriaxone and cefixime when isolates could not be confirmed due to loss of viability or borderline MIC values.

A long-standing trend of high and increasing resistance to ciprofloxacin continues, precluding its use in empirical treatment of gonococcal infections. Global data also indicate a high and persistent level of *Neisseria gonorrhoeae* resistance to ciprofloxacin, even in regions with reduced use of this antibiotic, suggesting long-term stability of the resistance-associated gyrA gene mutation.

Furthermore, a notable increase in tetracycline resistance was observed in 2024, which can be partially attributed to changes in EUCAST criteria, specifically the removal of the "susceptible, increased exposure" (I) category. This increase may also result from selective pressure due to tetracycline use in other indications, horizontal transfer of resistance genes, or the spread of resistant strains associated with doxycycline post-exposure prophylaxis (DoxyPEP). However, no data are currently available in Croatia to confirm or exclude the impact of DoxyPEP on tetracycline

resistance development. It is important to emphasize that in a report from June 2023, the European Commission and the ECDC recognized DoxyPEP as a possible strategy for reducing the incidence of sexually transmitted infections among men who have sex with men, emphasizing the need for further monitoring and evaluation of its effects on public health. This position indicates the importance of DoxyPEP in public health strategies at the EU level, but also the need for caution due to the possible contribution to the selection of resistant strains.

In 2024, a slight increase in the number of isolates with azithromycin MIC values >1 mg/L (ECOFF) was recorded in the Republic of Croatia, which is in line with data from the Euro-GASP program (ECDC). However, such a trend has clinical significance because it increases the risk of therapeutic failures in the empirical use of combination therapy (ceftriaxone + azithromycin).

In 2024, 29.2% of *Neisseria gonorrhoeae* isolates exhibited resistance to two antimicrobials, and 14.6% to three, representing a significant increase compared to 2023, when 10.3% of isolates were resistant to two and 6.8% to three antimicrobials.

Particularly concerning is the spread of strains resistant to key drugs—ceftriaxone, cefixime, and azithromycin—as these form the cornerstone of empirical gonorrhoea treatment. Such isolates have already been reported in several countries, including Australia, Japan, China, and parts of Europe.

Due to the remarkable ability of *N. gonorrhoeae* to rapidly develop resistance across multiple antibiotic classes, treating multidrug-resistant strains represents a growing challenge. This underscores the urgent need for novel therapies, including zoliflodacin, currently in phase III trials, and the development of a vaccine as a long-term solution.

In conclusion, 2024 in Croatia was marked by unfavourable trends in gonococcal resistance, including high ciprofloxacin resistance, a significant increase in tetracycline resistance, and a slight rise in the number of isolates with azithromycin MIC values above the ECOFF. Of particular concern is the sporadic occurrence of cephalosporin resistance, which could not be confirmed due to loss of isolate viability. These findings highlight the necessity for comprehensive and continuous microbiological and epidemiological surveillance through Euro-GASP, to better understand resistance mechanisms and dissemination in the population, and to enable timely adaptation of treatment guidelines.

Tablica 1. Osjetljivost sojeva *N. gonorrhoeae* na antibiotike u RH, sa vrijednostima ispitivanja MIK-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	Penicillin			Ceftriaxone			Cefixime			Ciprofloxacin			Azithromycin			Tetracycline			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			0.002			45mm**					3	0.25			0.5					
	2	0.047			<0,016			40mm**			<0,002			0.064			0.125					
	3	0.047			0.002			45mm**					0.38	<0,016			0.19					
	4		0.5		0.003			45mm**					1.5	0.064					8			
	5	0.023			<0,016			36mm**					0.25	0.25			0.125					
	6		0.094		<0,016			40mm**			<0,002			0.064			0.38					
	7		0.094		0.002			38mm**					1	0.038			0.038					
	8			1	0.008			32mm**					1.5	0.032					8			
	9		0.094		<0,002			50mm**					0.5	0.016					32			
	10	0.064			0.012			37mm**					0.75	0.125			0.25					
	11		0.5		0.004			36mm**					1.5	0.016					12			
	12		0.7		0.016			39mm**					1	0.016					6			
ZG HZJZ	1		0.38		0.047			0.016					0.75	0.19					16	2		
	2	cef.neg.					0.19			0.75			0.064	0.016								
	3		0.125		0.008			0.064					3	0.064					1	6		
	4		0.19		0.094					2			2			3						
ZG NZJZ	1			1.5	0.008			0.047					1.5	0.125					12			
	2		0.19		0.004			<0,016			0.008					1.5			1.5			
	3		0.125		0.006			<0,016					4			2			0.75			
	4		0.094		0.023			<0,016					>32	1					1			
	5	0.064			<0,002			<0,016			<0,002			0.75					0.75			
	6		0.094		0.003			<0,016					0.75	1			0.25					
	7		0.75		0.004			0.04					1.5	0.125					12			
	8		0.38		0.006			0.016			0.003			0.38					1			
	9		0.125		0.006			<0,016			<0,002			0.25					0.75			
	10	0.064			<0,002			<0,016			<0,002					1.5	0.38					
	11	0.047			<0,002			<0,016			<0,002			0.5					1			
	12			4	0.004			<0,016					0.75	0.094					8			
	13		0.094		<0,002			<0,016					1.5			1.5	0.25					
	14		0.75		0.008			0.032					2	0.125					24			
	15		0.094		0.002			<0,016					4	0.064					0.75			
	16		0.094		0.004			<0,016					4			2	0.38					
	17		0.23		<0,002			<0,016					4	0.064			0.38					
MĐ ZZJZ	1		0.125		0.003			<0,016					1.5	<0,016					16	2		
SD NZJZ	1	0.064			0.003			0.016					4	0.094						6		
ŠK ZZJZ	1	0.064			0.002			0.002			0.002			0.05								
PG NZJZ	1	<0,002			<0,002			<0,016			<0,002			<0,016			<0,016			<0,064		
	2		0.094		<0,002			0.016					0.5	0.75			0.19			4		
	3		0.094		0.002			<0,016			0.023					<256	0.064			1.5		
	4		0.25		0.002			0.016					1	0.016					12	1		
	5	0.002			0.002			0.016			0.125			0.064			0.016			0.064		
UKUPNO (%)	**41***	12 (30)	25 (62,5)	**3 (7,5)**	40 (97,6)	/	**1 (2,4)**	39 (95,1)	/	**2 (4,9)**	12 (29,3)	/	**29 (70,7)**	34 (82,9)	/	**7 (17,1)**	16 (43,2)	/	**21 (56,8)**	9 (100)	/	/

* Iako je u praćenje uključeno 41 izolat, nije bilo moguće provesti testiranje svih izolata na sve antibiotike zbog tehničkih razloga / Although 41 isolates were included in the monitoring, it was not possible to test all isolates against all antibiotics due to technical reasons

**Ispitivanje je provedeno disk difuzijom / The testing was performed using the disk diffusion method

Tablica 2. Osjetljivost sojeva *N. gonorrhoeae* na antibiotike u Hrvatskoj, 2024.

Table 2. Antimicrobial susceptibility of N. gonorrhoeae strains to antibiotics in Croatia, 2024.

Ustanova	Penicillin MIK* (mg/L)				Ceftriaxone MIK* (mg/L)				Cefixime MIK* (mg/L)			
	UK***	S (%)	I (%)	R (%)	UK***	S (%)	I (%)	R (%)	UK***	S (%)	I (%)	R (%)
HZJZ Zagreb	4	1 (25)	3 (75)	0	4	3 (75)	0	1 (25)	4	2 (50)	0	2(50)
NZJZ A.Štampar	17	3 (17,6)	12 (70,6)	2 (11,8)	17	17 (100)	0	0	17	17 (100)	0	0
KZIB F.M. Zagreb	12	5 (41,7)	6 (50)	1 (8,3)	12	12 (100)	0	0	12	12 (100)	0	0
ZZJZ Međimurske županije	1	0	1 (100)	0	1	1 (100)	0	0	1	1 (100)	0	0
NZJZ Splitsko-dalmatinske županije	1	1 (100)	0	0	1	1 (100)	0	0	1	1 (100)	0	0
ZZJZ Šibensko-kninske županije	1	1 (100)	0	0	1	1 (100)	0	0	1	1 (100)	0	0
NZJZ Primorsko-goranske županije	5	2 (40)	3 (60)	0	5	5 (100)	0	0	5	5 (100)	0	0
UKUPNO	41	13 (31,7)	25 (61)	3 (7,3)	41	40 (97,6)	0	1 (2,4)	41	39 (95,1)	0	2 (4,9)

Ustanova	Ciprofloxacin MIK* (mg/L)				Tetracycline MIK* (mg/L)				Spectinomycin MIK* (mg/L)			
	UK***	S (%)	I (%)	R (%)	UK***	S (%)	I (%)	R (%)	UK***	S (%)	I (%)	R (%)
HZJZ Zagreb	4	0	0	4 (100)	2	0	0	2 (100)	2	2 (100)	0	0
NZJZ A.Štampar	17	6 (35,3)	0	11 (64,7)	17	5 (29,4)	0	12 (70,6)	**/	**/	**/	**/
KZIB F.M. Zagreb	12	2 (20)	0	10	12	7 (63,6))	0	5 (41,7)	**/	**/	**/	**/
ZZJZ Međimurske županije	1	0	0	1 (100)	1	0	0	1 (100)	1	1 (100)	0	0
NZJZ Splitsko-dalmatinske županije	1	0	0	1 (100)	**/	**/	**/	**/	1	1 (100)	0	0
ZZJZ Šibensko-kninske županije	1	1 (100)	0	0	**/	**/	**/	**/	**/	**/	**/	**/
NZJZ Primorsko-goranske županije	5	3 (60)	0	2 (40)	5	4 (80)	0	1 (20)	5	5 (100)	0	0
UKUPNO	41	12 (29,3)	0	29 (70,7)	37	16 (43,2)	0	21 (56,8)	9	9 (100)	0	0

*MIK (Minimalna inhibitorna koncentracija antibiotika) određena je gradijentnom difuzijskom metodom (E-test) / The minimum inhibitory concentration of the antibiotic was determined using the gradient diffusion method (E-test); **/ = Iz tehničkih razloga nije bilo moguće ispitati osjetljivost izolata na navedeni antibiotic / Due to technical reasons, it was not possible to test the susceptibility of the isolates to the given antibiotic;
***UK = Ukupan broj sojeva kod kojih je ispitana osjetljivost na određeni antibiotik / Total number of strains tested for susceptibility to a given antibiotic

POGLAVLJE / *CHAPTER* **4.**

PRAĆENJE REZISTENCIJE NA ANTIBIOTIKE U INVAZIVNIH IZOLATA

ANTIBIOTIC RESISTANCE SURVEILLANCE IN INVASIVE ISOLATES

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VAŽNOST PRAĆENJA REZISTENCIJE U INVAZIVNIH IZOLATA

Sustavno praćenje rezistencije na antibiotike na europskoj razini započelo je 1999.g. u okviru "European Antimicrobial Resistance Surveillance System" (EARSS) projekta. Za prioritete u praćenju odabrano je u početku šest bakterijskih vrsta *S. aureus, E. faecalis, E. faecium, S. pneumoniae* i *E. coli*, od 2005.g. dodano je praćenje rezistencije u *K. pneumoniae* i *P. aeruginosa*, a od 2013.g. započeto je i praćenje rezistencije u *Acinetobacter* spp. S obzirom na različitu praksu uzimanja uzoraka i interpretaciju nalaza u različitim zemljama, 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.

Važno je istaknuti da se od tada standardi prijavljivanja, protok informacija te tehnički okvir i format dostave podataka nisu znatno mijenjali. Sustav se u proteklim godinama pokazao stabilnim i funkcionalnim, ali zahtijeva kontinuirano praćenje kvalitete i dosljednosti unosa podataka iz svih uključenih laboratorija.

U okviru EARS-Net programa, Referentni centar za praćenje rezistencije bakterija na antibiotike nastavlja primati i prikupljati sve invazivne izolate vrsta Streptococcus pneumoniae, *Staphylococcus aureus*, *Enterococcus faecalis*, *Enterococcus faecium*, *Escherichia coli*, *Klebsiella*

pneumoniae, *Pseudomonas aeruginosa* i *Acinetobacter* spp., sa svrhom retestiranja izolata s rijetkim fenotipom te njihove eventualne daljnje obrade. Tijekom 2024.g. prikupljeno je 216 izolata *S. pneumoniae,* 1127 izolat *E. coli*, 533 izolata *K. pneumoniae*, 653 izolata *S. aureus,* 372 izolata enterokoka (231 *E. faecalis* i 141 *E. faecium* izolata), 247 izolata *P. aeruginosa*, te 214 izolata *Acinetobacter* spp. (Tablica 1).

S obzirom na dosadašnje iskustvo i trendove iz prethodnih godina, vidljivo je smanjenje odaziva laboratorija uključenih u sustav praćenja rezistencije. Dok je tijekom 2023. godine podatke prijavljivalo čak 26 laboratorija, u 2024. godini potpune i tehnički ispravne podatke dostavilo je njih 21. Ovakav pad odaziva upućuje na potrebu podizanja svijesti o važnosti redovitog i potpunog prijavljivanja podataka, kao i o njihovom značaju za nacionalni sustav praćenja antimikrobne rezistencije. Bez dodatnog jačanja sustavne podrške i aktivnog uključivanja svih laboratorija, može doći do iskrivljene slike o stvarnom opsegu i trendovima rezistencije u zemlji.

Manji odziv laboratorija odrazio se i na ukupan broj prijavljenih izolata, koji je u padu u odnosu na prethodne godine. Tijekom 2024. godine prijavljeno je ukupno 3.261 izolat. Zahvaljujući suradnji s Referentnim centrom za praćenje rezistencije bakterija na antibiotike, ukupan broj prijavljenih izolata naknadno je korigiran naviše, ponajprije zbog uočene znatne razlike u prijavljenom broju izolata Streptococcus pneumoniae. Nakon uključivanja dodatnih podataka o pneumokokima, ukupan broj prijavljenih izolata korigiran na 3.362.

Putem Referentnog centra zaprimljeno je 216 izolata pneumokoka, dok je kroz redoviti EARS-Net sustav elektroničkim putem prijavljen gotovo dvostruko manji broj. Ovo je prvi put da je usporednom analizom uočen tako izražen nesrazmjer između dvaju izvora podataka. Iako su se i ranijih godina provodile provjere između baza podataka Referentnog centra i EARS-Net sustava, dosad nisu zabilježena značajnija odstupanja.

Vjeruje se da sličan obrazac podprijavljivanja postoji i kod drugih bakterijskih vrsta koje se prate u okviru nacionalnog sustava nadzora. Ova zapažanja dodatno naglašavaju važnost dosljednog, potpunog i pravovremenog unosa podataka od strane svih laboratorija, kako bi prijavljene stope rezistencije i ukupan broj izolata vjerno odražavali stvarno stanje te predstavljali pouzdanu osnovu za praćenje trendova i kreiranje empirijske antimikrobne terapije na nacionalnoj razini.

U Tablici 1. prikazani su brojevi laboratorija i broj prikupljenih invazivnih izolata pojedinih vrsta.

Iako se u 2024. godini ukupan broj prijavljenih izolata, kao i većine praćenih bakterijskih vrsta, smanjio, bilježi se porast udjela izolata *Streptococcus pneumoniae*, pri čemu broj prijavljenih izolata u 2024. godini iznosi 2016. Također, u 2024. godini raste udio pneumokoka s neosjetljivošću na penicilin. Ukupno 20% izolata pokazuje smanjenu osjetljivost (I+R) na penicilin, dok je 1% sojeva po prvi put kategorizirano kao potpuno rezistentno (R). Ovi podaci predstavljaju porast u odnosu na 2023. godinu, kada je ukupna stopa neosjetljivosti iznosila 13%, što upućuje na ponovni porast udjela neosjetljivih sojeva unatoč smanjenom ukupnom broju prijavljenih izolata.

Istodobno, nakon višegodišnjeg trenda smanjenja, u 2024. godini zabilježen je blagi porast rezistencije na makrolide, koja sada iznosi 19%, unatoč većem broju prijavljenih izolata u odnosu na prethodne godine.

Tijekom 2024. godine po prvi je put uvedeno praćenje osjetljivosti pneumokoka na cefalosporine treće generacije, pri čemu je kao predstavnik ove skupine antibiotika odabran ceftriakson. Zabilježeni su i sojevi s reduciranom osjetljivošću (I+R) na ceftriakson, u udjelu od 1% ukupno

ispitanih izolata za 2024. godinu. Radi usporedbe i potpunijeg uvida u trendove, podaci su naknadno retrospektivno prikupljeni i za prethodno petogodišnje razdoblje.

Dobiveni nalazi ukazuju na potrebu za daljnjim praćenjem i potvrdom kroz referentno retestiranje, s ciljem preciznijeg određivanja njihova epidemiološkog značaja i mogućeg utjecaja na kreiranje empirijske antimikrobne terapije.

U 2024. godini, uz primijećeno smanjenje ukupnog broja prijavljenih izolata *Staphylococcus aureus*, stope meticilin-rezistentnih sojeva (MRSA) ostaju stabilne kroz promatrano razdoblje (31% u 2024., 30% u 2023. te 31% u 2022. godini), bez značajnijih odstupanja u trendu.

Unutar roda *Enterococcus* nastavljaju se izražene razlike u obrascima rezistencije između vrsta *E. faecium* i *E. faecalis*. Kod *E. faecium* posljednjih se godina bilježio stabilan porast udjela glikopeptidno rezistentnih izolata (35–40%), no tijekom 2024. godine zabilježen je izrazito nepovoljan skok, pri čemu je stopa rezistencije porasla na 54%. Istodobno, visoka razina rezistencije na aminoglikozide održava se stabilno visokom, uz udio rezistentnih izolata od 39% u 2024. godini. Nasuprot tome, kod *E. faecalis* stope rezistencije na glikopeptide ostaju niske (2% u 2024.), dok se kod visoke rezistencije na aminoglikozide bilježi postupni trend smanjenja – 2024. godine zabilježena je najniža vrijednost od početka praćenja (29%). Unatoč zamijećenom padu, i dalje se radi o visokim stopama rezistencije koje predstavljaju značajan terapijski izazov.

U usporedbi s 2023. godinom, kada je ukupna stopa neosjetljivosti (I+R) iznosila 34%, u 2024. se, unatoč značajnom smanjenju broja prijavljenih izolata *Klebsiella pneumoniae*, bilježi daljnji porast rezistencije na karbapeneme u invazivnih sojeva. Ukupna stopa neosjetljivih izolata (I+R) porasla je na 37%, dok udio potpuno rezistentnih (R) sojeva doseže 31% među invazivnim izolatima, što potvrđuje nastavak nepovoljnog trenda rasta karbapenem-rezistentnih sojeva.

Istodobno, i u ostalim skupinama antibiotika bilježi se kontinuirani porast stopa rezistencije. Udio ESBL-pozitivnih izolata doseže 65%, što se podudara s visokom stopom rezistencije na cefalosporine treće generacije (62%). Rezistencija na kinolone također je u porastu, dosežući najvišu vrijednost do sada – 62%, dok se stope rezistencije na aminoglikozide kroz posljednje godine zadržavaju na stabilno povišenim razinama (oko 40%), s 42% zabilježenih u 2024. godini.

Kod invazivnih izolata *Escherichia coli* u 2024. godini bilježi se nastavak stabilnih trendova rezistencije u svim praćenim skupinama antibiotika, bez značajnijih odstupanja u odnosu na prethodne godine. Stope rezistencije na treću generaciju cefalosporina ostaju nepromijenjene u odnosu na prethodnu godinu (20%), dok rezistencija na aminoglikozide iznosi 19%, pokazujući kroz godine blagi, ali kontinuirani trend porasta. Rezistencija na kinolone također se zadržava na razini sličnog opsega kao i prethodnih godina, iznoseći 28% u 2024. godini (30% u 2023.).

Kao i ranijih godina, rezistencija na treću generaciju cefalosporina pretežno je povezana s proizvodnjom beta-laktamaza proširenog spektra (engl. *extended-spectrum beta-lactamases* – ESBL), što potvrđuje trajnu prisutnost ovog mehanizma rezistencije u populaciji invazivnih *E. coli* sojeva.

Kod tipično bolničkog patogena *Acinetobacter* spp. u 2024. godini primjećuje se također manji broj prijavljenih izolata u odnosu na prethodne godine. Iako su u 2024. zabilježene nešto niže stope rezistencije u usporedbi s ranijim razdobljem, one i dalje ukazuju na izrazito visok stupanj rezistencije na karbapeneme (93% u 2024.). Dodatni uvid u osjetljivost na druge skupine antibiotika pokazuje da problem nije ograničen samo na karbapeneme – u više od 95% izolata zabilježena je

visoka rezistencija i na ostale ključne antibiotike, što potvrđuje da se radi o visoko rezistentnim MDR sojevima.

Kod invazivnih izolata *Pseudomonas aeruginosa* u 2024. godini nisu zabilježena značajnija odstupanja u odnosu na dosadašnje podatke. Najniže stope rezistencije zabilježene su za piperacilin/tazobaktam (15%) te za amikacin (7%), dok se u ostalim skupinama antibiotika stope rezistencije zadržavaju iznad 20% – za ceftazidim 24%, karbapeneme 34% i fluorokinolone 27%.

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.

It is important to highlight that since the last structural revision, the reporting standards, data flow, and technical format of data submission have not changed significantly. Over the past years, the system has proven to be stable and functional; however, continuous monitoring of data quality and consistency of submissions from all participating laboratories remains essential.

Within the EARS-Net programme, the National Reference Centre for Antibiotic Resistance Surveillance continues to receive and collect all invasive isolates of *Streptococcus pneumoniae, Staphylococcus aureus, Enterococcus faecalis, Enterococcus faecium, Escherichia coli, Klebsiella*

pneumoniae, Pseudomonas aeruginosa, and *Acinetobacter spp.* for the purpose of retesting isolates with rare phenotypes and conducting further analyses where indicated.

During 2024, a total of 216 *S. pneumoniae*, 1,127 *E. coli*, 533 *K. pneumoniae*, 653 *S. aureus*, 372 enterococcal isolates (231 *E. faecalis* and 141 *E. faecium*), 247 *P. aeruginosa*, and 214 *Acinetobacter spp.* isolates were collected (Table 1).

Based on previous experience and long-term trends, a decrease in the number of laboratories actively participating in resistance surveillance is evident. While in 2023 as many as 26 laboratories reported data, in 2024 only 21 laboratories submitted complete and technically valid datasets. This decline highlights the need to raise awareness of the importance of regular and comprehensive data reporting and its critical role in the national antimicrobial resistance (AMR) surveillance system. Without further strengthening of systemic support and the active engagement of all laboratories, there is a risk of distortion in the true national picture and trends of resistance.

The lower number of reporting laboratories was also reflected in the total number of submitted isolates, which declined compared to previous years. During 2024, a total of 3,261 isolates were reported. Based on the review of national data obtained from the National Reference Centre for Antibiotic Resistance Surveillance, the reported figure was adjusted upward primarily due to significant discrepancies in the number of *Streptococcus pneumoniae* isolates reported. After inclusion of additional data on pneumococcal isolates, the total number was adjusted to 3,362. A total of 216 pneumococcal isolates were received through the Reference Centre, while the routine EARS-Net electronic reporting system contained nearly half that number. This is the first time such a pronounced discrepancy between the two data sources has been identified through comparative analysis. Although cross-checks between the Reference Centre and EARS-Net databases have been performed in previous years, no major deviations were observed until now. It is believed that a similar pattern of underreporting may exist for other bacterial species included in the national surveillance programme. These findings further emphasize the importance of consistent, complete, and timely data entry by all laboratories to ensure that reported resistance rates and isolate counts accurately reflect the true epidemiological situation and provide a reliable basis for monitoring trends and guiding empirical antimicrobial therapy at the national level.

Proportion of pneumococcal isolates showing reduced susceptibility to penicillin increased. Overall, 20% of isolates exhibited decreased susceptibility (I+R) to penicillin, while 1% were classified as resistant. These data represent an increase compared to 2023, when the overall non-susceptibility rate was 13%, indicating a renewed rise in the proportion of non-susceptible strains despite the lower total number of reported isolates. Macrolide resistance reached 19% in 2024, slightly higher than the 16% recorded in the previous year. During 2024, monitoring of pneumococcal susceptibility to third-generation cephalosporins was introduced for the first time, with ceftriaxone selected as the representative agent for this antibiotic group. Isolates showing reduced susceptibility (I+R) to ceftriaxone were identified, representing 1% of all tested isolates in 2024. For comparative purposes and a more comprehensive trend analysis, retrospective data were also added for the previous five-year period.

In 2024, despite the observed decrease in the total number of *Staphylococcus aureus* isolates, the proportion of methicillin-resistant strains (MRSA) remained stable throughout the reporting period—31% in 2024, 30% in 2023, and 31% in 2022—without significant deviation in the overall trend.

Within the *Enterococcus* spp., notable differences in resistance profiles between *E. faecium* and *E. faecalis* persist. In *E. faecium*, a gradual upward trend in glycopeptide resistance observed over the past several years culminated in 2024 with a sharp and concerning rise, as resistance rates reached 56%. At the same time, high-level aminoglycoside resistance remained consistently elevated, affecting 39% of isolates in 2024. Conversely, in *E. faecalis*, glycopeptide resistance remained low (2% in 2024), while a gradual decline was observed in high-level aminoglycoside resistance, reaching its lowest value since the beginning of surveillance (29% in 2024). Despite this decline, resistance rates remain high and continue to pose a significant therapeutic challenge.

Compared with 2023, when the overall rate of non-susceptibility (I+R) among *Klebsiella pneumoniae* invasive isolates was 34%, 2024 data indicate a continued increase in carbapenem resistance despite a substantial reduction in the total number of reported isolates. The overall proportion of non-susceptible isolates (I+R) rose to 37%, while the proportion of resistant (R) isolates reached 31% among invasive strains—confirming the ongoing unfavourable trend in the prevalence of carbapenem-resistant *K. pneumoniae*. Simultaneously, resistance continued to increase across other antibiotic groups. The proportion of ESBL-positive isolates reached 65%, corresponding to the high resistance rate to third-generation cephalosporins (62%). Fluoroquinolone resistance also continued to rise, reaching its highest recorded level to date (62%), while aminoglycoside resistance remained stably elevated at approximately 40%, with 42% reported in 2024.

Among invasive *Escherichia coli* isolates, resistance trends in 2024 remained stable across all monitored antibiotic groups, with no major deviations from previous years. Resistance to third-generation cephalosporins remained unchanged compared with 2023 (20%), while aminoglycoside resistance was 19%, showing a mild but steady upward trend over recent years. Fluoroquinolone resistance remained at a comparable level to previous years (28% in 2024 vs. 30% in 2023). As in previous years, resistance to third-generation cephalosporins is predominantly associated with the production of extended-spectrum β-lactamases (ESBLs), confirming the persistent presence of this resistance mechanism among invasive E. coli isolates.

For the typical hospital pathogen *Acinetobacter* spp., 2024 data show a further decrease in the total number of reported isolates compared with previous years. Although slightly lower resistance rates were observed compared to earlier periods, the level of carbapenem resistance remains extremely high (93% in 2024). Additional susceptibility testing to other antibiotic groups confirmed that the problem is not limited to carbapenems—over 95% of isolates showed resistance to multiple key antibiotics, confirming the circulation of highly resistant MDR strains.

Among invasive *Pseudomonas aeruginosa* isolates, no significant changes were observed in 2024 compared with previous years. The lowest resistance rates were recorded for piperacillin/tazobactam (15%) and amikacin (7%), while resistance rates for other antibiotic groups remained above 20%—24% for ceftazidime, 34% for carbapenems, and 27% for fluoroquinolones.

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.-2024.** / *Number of laboratories and number of isolates reported for the period 2001-2024*

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
2024	20	216	22	653	22	1127	21	372	22	533	19	247	17	214

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 %	2024 %
S. pneumoniae	Penicillin R	6	7	1	1	4	1	1	1	1	1	2	1	0	0	0	1
	Penicillin I+R	19	21	18	23	27	26	20	22	21	20	20	24	19	18	13	20
	Ceftriaxone I+R												0	3	1	3	1
	Macrolides R	8	29	24	28	34	28	19	33	37	33	30	40	24	27	16	19
S. aureus	Oxacillin/Met R	37	27	27	22	24	21	25	25	28	26	25	29	36	31	30	31
E. coli	Aminopenicillin R	55	55	55	52	54	54	56	57	59	58	57	58	57	56	57	58
	Aminoglycoside R	8	6	7	7	7	10	12	14	16	14	13	15	14	16	18	19
	Fluoroquinolone R	16	17	20	17	21	20	25	28	30	30	27	30	29	31	30	28
	3. gen Cef R	5	8	7	8	9	11	13	12	16	14	15	17	18	17	20	20
	ESBL			9	7	9	11	13	14	16	15	17	16	25	30	27	29
E. faecalis	Aminopenicillins R		5	1	5	9	6	4	7	5	3	2	4	6	3	3	2
	HL Aminoglycoside R	36	37	33	39	35	33	35	33	32	34	24	38	43	37	28	29
	Glycopeptides R	<1	<1	1	<1	<1	0	0	0	<1	2	2	1	3	1	<1	2
E. faecium	Aminopenicillin R		82	98	98	90	94	97	98	96	98	94	99	96	93	91	93
	HL Aminoglycoside R	68	60	66	61	55	64	53	65	50	64	51	37	30	30	43	39
	Glycopeptides R	11	12	2	0	7	10	26	23	19	25	26	33	39	37	24	54
K. pneumoniae	Aminoglycoside R	47	49	43	45	51	48	40	31	28	33	40	38	42	43	38	42
	Fluoroquinolone R	51	48	43	43	45	46	50	44	50	49	59	54	60	55	57	62
	3. gen Cef R	53	56	50	44	50	48	46	42	41	42	51	52	58	55	55	62
	ESBL			51	52	50	48	47	46	41	43	51	52	62	64	54	65
	Carbapenems I+R			<1	<1	1	2	3	2	5	7	16	19	34	28	34	37
	Carbapenem R			0	0	0	0	0	0	0	2	12	19	28	23	27	31
P. aeruginosa	Piperacillin R		23														
	Piperacllin/ Tazobactam R		16	23	18	23	32	25	20	16	11	14	10	13	13	11	15
	Ceftazidime R	11	12	17	14	20	28	20	23	21	19	20	19	20	24	21	24
	Carbapenems R	31	26	30	21	25	35	37	41	30	27	23	30	31	35	29	34
	Aminoglycoside R	37	26	34	26	24	37	34	32	27	23	20	10	9	8	10	7
	Fluoroquinolones R	29	27	34	24	23	28	37	38	39	29	26	23	23	29	33	27
A. baumannii	Carbapenems R					91	88	89	95	96	95	93	96	99	99	97	93

Tablica 3. / *Table 3.* **Prikaz gram-pozitivnih invazivnih izolata u 2024.g. prema demografskim podacima pacijenata** / *Selected details on gram-positive invasive isolates from the reporting period 2024*

	S.pneumoniae		***S.aureus***		***Enterococcus* spp.**	
	n=216		**n=653**		**n=372**	
	% tot	**% PNPS**	**% tot**	**% MRSA**	**% tot**	**% VRE**
UZORAK ***SAMPLE***						
Krv / Blood	93	16	99	29	99	20
Likvor / CSF	7	18	<1	0	<1	0
SPOL ***GENDER***						
M	48	18	61	31	63	22
Ž / F	35	28	39	30	37	18
Nepoznato / Unknown	17	11	<1	0	0	0
DOB ***AGE***						
0-4	10	41	2	15	3	33
5-19	2	40	1	0	<1	0
20-64	37	8	31	22	29	28
>65	35	31	66	36	67	18
Nepoznato / Unknown	16	11	0	0	0	0
ODJEL ***DEPARTMENT***						
Intenzivna / ICU	NA	NA	10	37	10	22

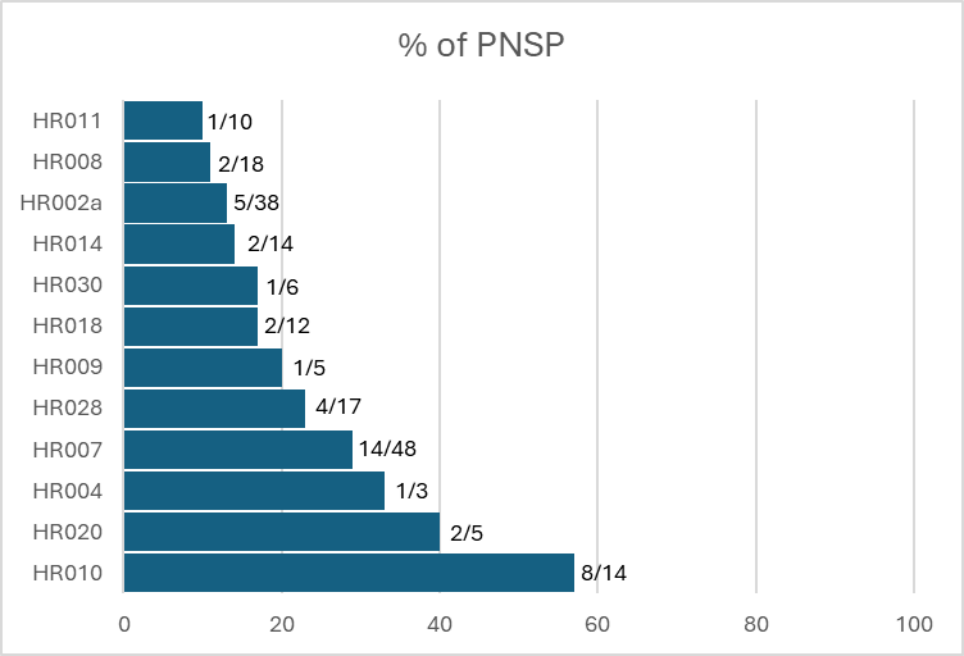
PNSP=Penicillin Non-Susceptible *S. Pneumoniae* MRSA=Methicillin Resistant *S.aureus* VRE=Vancomycin Resistant Enterococcus
NA=non-applicable

Tablica 4. / *Table 4.* **Prikaz gram-negativnih invazivnih izolata u 2024. g. prema demografskim podacima pacijenata** / *Selected details on gram-negative invasive isolates from the reporting period 2024*

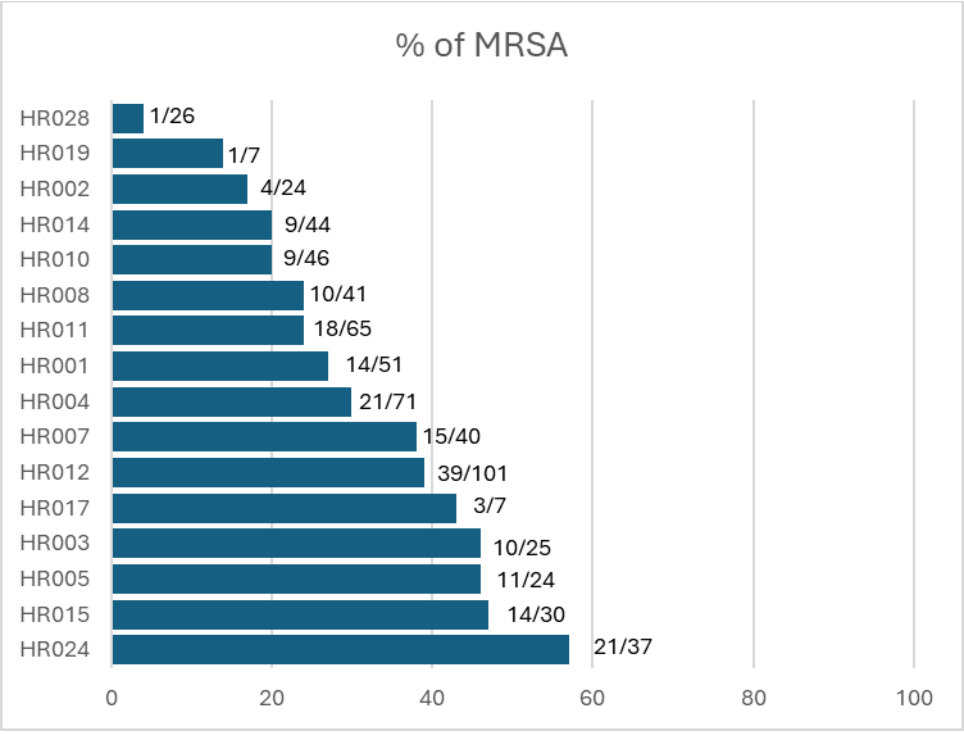
	E. coli			*Acinetobacter* spp.		*K.pneumoniae*		*P.aeuroginosa*	
	n=1127			n=235		n=533		n=235	
	% tot	% FREC	% CREC	% tot	% CRA	% tot	% CRKP	% tot	% CRPA
UZORAK ***SAMPLE***									
Krv / Blood	99	27	18	99	93	99	62	99	27
Likvor / CSF	<1	0	0	1	100	1	100	1	0
SPOL ***GENDER***									
M	58	24	13	59	92	59	63	69	28
Ž / F	42	34	24	40	94	40	61	31	23
Nepoznato / Unknown	0	0	0	1	0	<1	100	0	0
DOB ***AGE***									
0-4	3	3	3	<1	<1	50	50	2	0
5-19	<1	0	13	0	0	<1	60	1	25
20-64	25	21	16	37	93	34	64	38	36
>65	71	30	19	62	93	62	61	63	22
Nepoznato / Unknown	<1	0	0	0	0	0	0	0	0
ODJEL ***DEPARTMENT***									
Intenzivna / ICU	4	31	22	44	96	19	73	25	81

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.

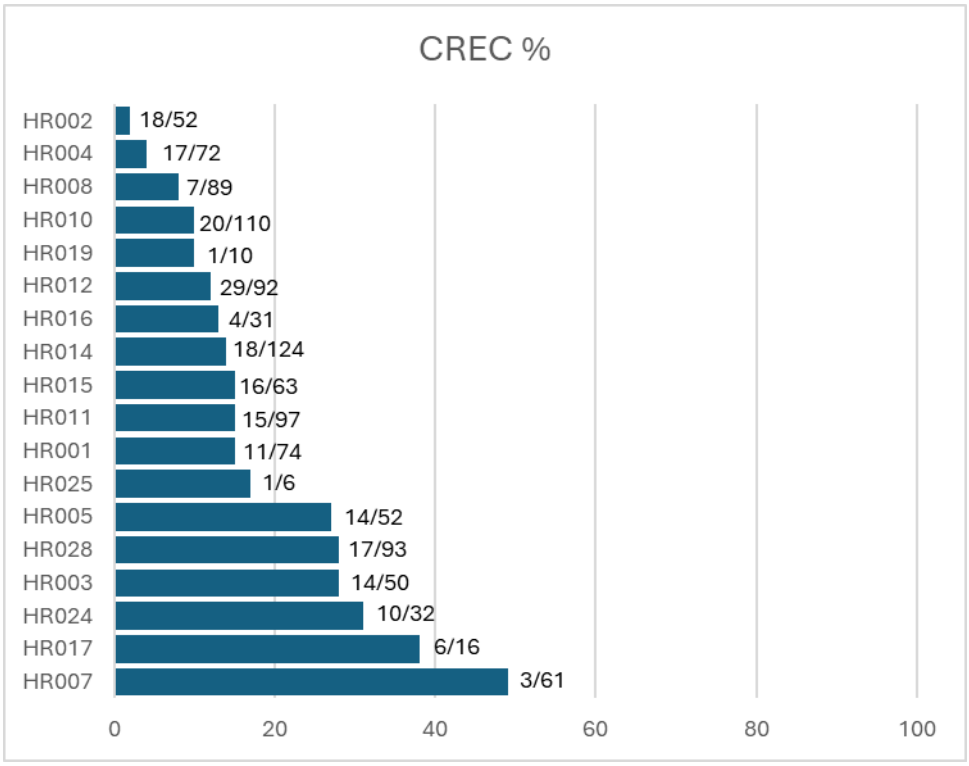
Slika 1. / *Figure 1.***Udio (%) izolata *S. pneumoniae* smanjene osjetljivosti na penicilin (PNSP) po centrima** / *Proportion (%) of penicillin non-susceptible S. pneumoniae (PNSP) by center*



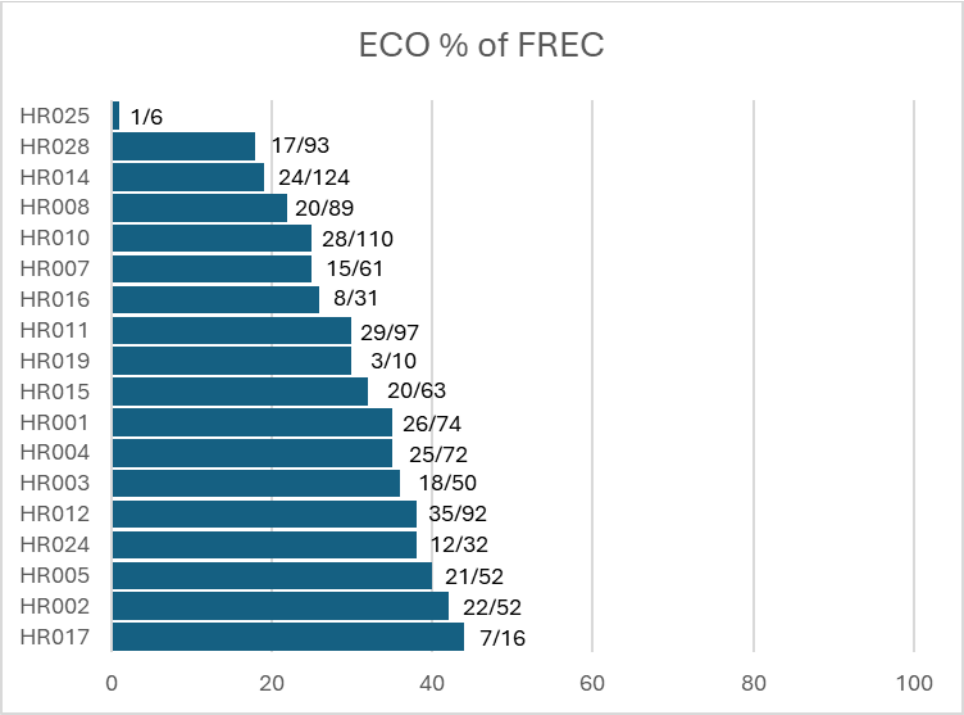
Slika 2. / *Figure 2.* **Udio (%) MRSA izolata po centrima** / *Proportion (%) of MRSA isolates by center*



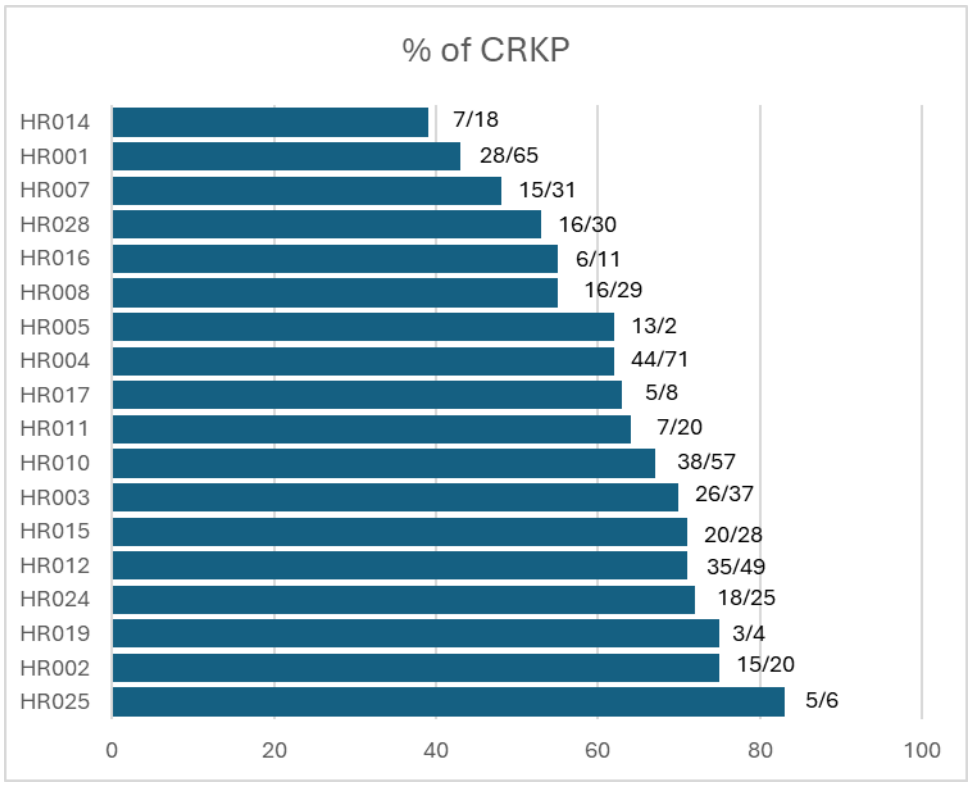
Slika 3. / *Figure 3.* **Udio (%) ceftazidim rezistentnih izolata *E. coli* (CREC) po centrima** / *Proportion (%) of ceftazidime resistant E. coli isolates (CREC) by center*



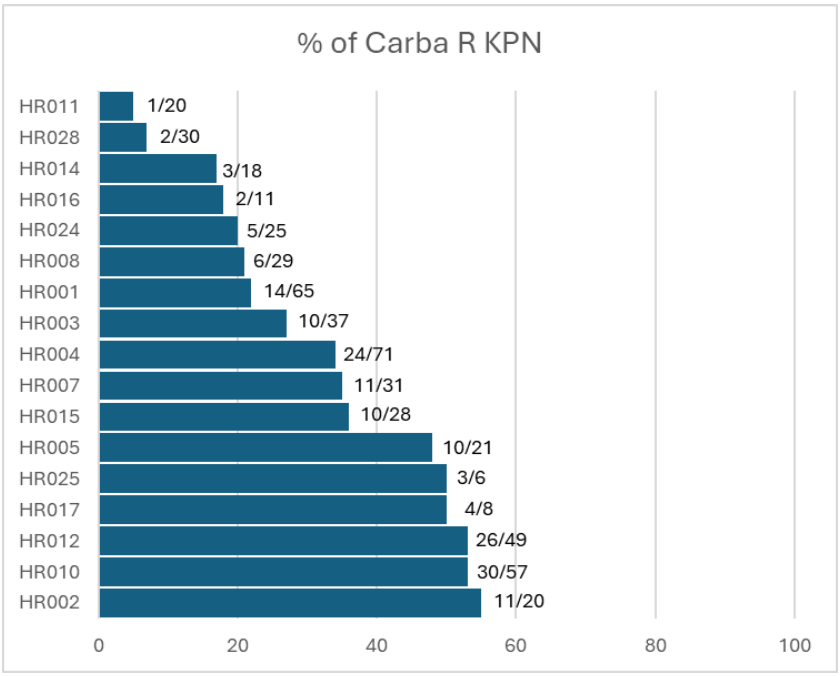
Slika 4. / *Figure 4.* **Udio (%) fluorokinolon rezistentnih izolata *E. coli* (FREC) po centrima** / *Proportion (%) of fluoroquinolone resistant E.coli isolates (FREC) by center*



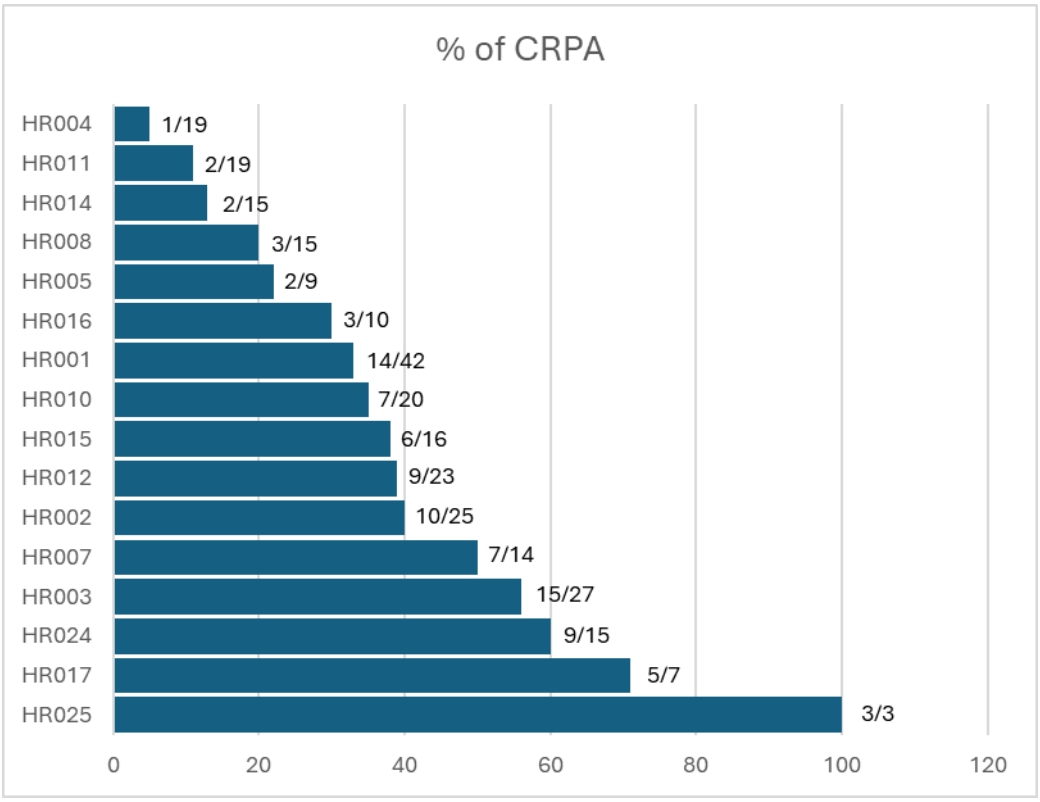
Slika 5. / *Figure 5.* **Udio (%) ceftazidim rezistentnih izolata *K. pneumoniae* (CRKP) po centrima** / *Proportion (%) of ceftazidime resistant K. pneumoniae (CRKP) by center*



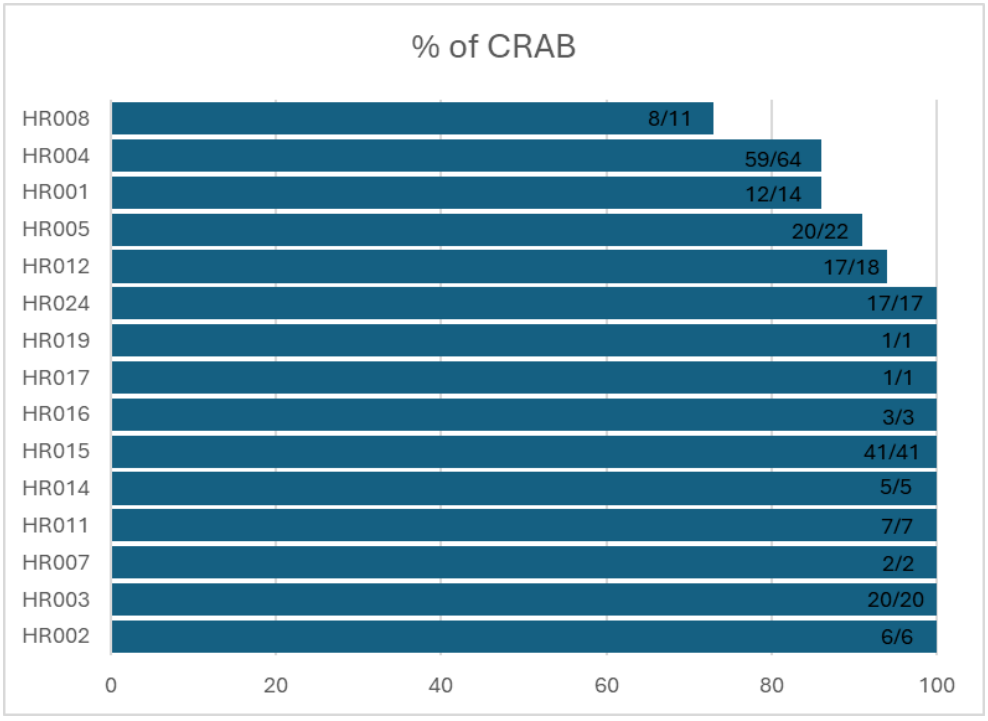
Slika 6. / *Figure 6.* **Udio (%) karbapenem rezistentnih izolata *K. pneumoniae* (Carb R KP) po centrima** / *Proportion (%) of carbapenem resistant K. pneumoniae (Carb R KP) by center*



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 2024. GODINI

DISTRIBUTION OF CANDIDA SPECIES AND ANTIFUNGAL SUSCEPTIBILITY IN PATIENTS WITH CANDIDEMIA IN CROATIA, 2024

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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. Od 2023. godine zbog kibernetičkih prijetnji mrežna stranica nije više u funkciji. 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 2024. godini.

UČESTALOST VRSTA *CANDIDA* SPP.

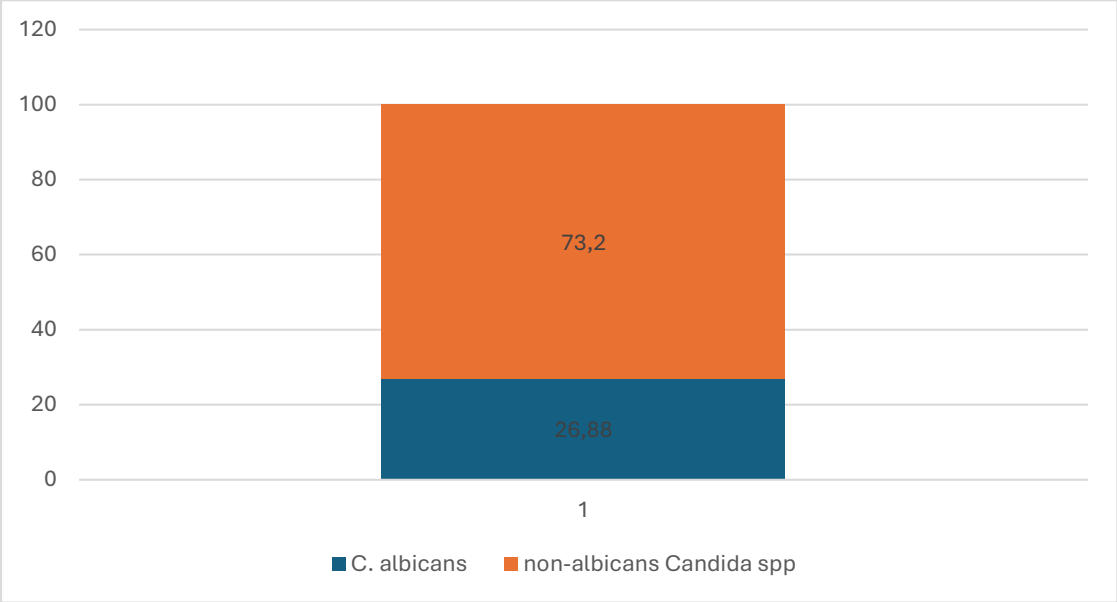
Za vrijeme ovog razdoblja ukupno je prikupljeno i analizirano 160 izolata *Candida* spp. Učestalost pojedinih *Candida* spp. prikazana je u Tablici 1. Usporedbom podataka iz 2023. (162 izolata) godine nema značajne razlike u broju zaprimljenih izolata.

Najčešće prisutne vrste *Candida* spp. u 2024. godini bile su *C. parapsilosis* kod 40% (64/160), *C. albicans* kod 26,87% (43/160),a osim bitnog pada udjela C. albicans u odnosu na prethodnu godinu i bilježi se kao treći po učestalosti uzročnik *C. glabrata* kod 25,62% (41/160) bolesnika s kandidemijom što gotovo da predstavlja izjednačenje po učestalosti *C. albicans* i *C. glabrata*.

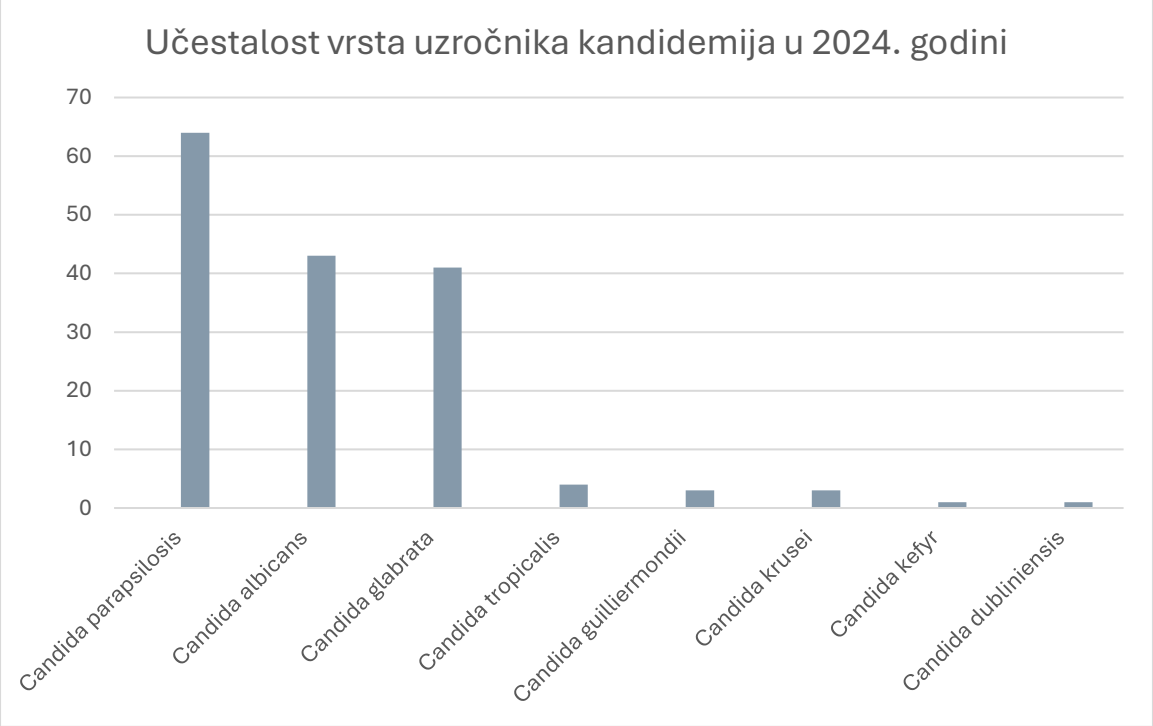
Tablica 1. */ Table 1.* **Učestalost pojedinih vrsta *Candida* spp. kod bolesnika s kandidemijom u Hrvatskoj u 2024. godini /** *Incidence of different Candida spp.in patients with candidemia in Croatia in 2024*

Vrsta *Candida* spp.	**N (%)**
Candida parapsilosis	64 (40)
Candida albicans	43 (26,88)
Candida glabrata	41(25,63)
Candida tropicalis	4 (2,5)
Candida krusei	3(1,88)
Candida kefyr	1 (0,62)
Cadnida dubliniensis	1(0,62)
Candida guillermondii	1(0,62)
UKUPNO	**160**

Slika 1. */ Figure 1.* **Udio *C. albicans* i non-albicans vrsta u 2024 godini među izolatima bolesnika s kandidemijom u Hrvatskoj /** *Proportion of C. albicans and non-albicans species in 2024*



Grafikon 2. / *Figure 2*. **Učestalost vrsta uzročnika kanidemija u 2024. Godini** / *Proportion of Candida spp. causing candidemia in 2024.*



Udio *C. albicans* i non-albicans vrsta u 2024. godini među izolatima bolesnika s kandidemijom prikazan je na Grafikonu 1. Iz analiziranih podataka se vidi da je *C. parapsilosis* daleko najzastupljenija vrsta u Hrvatskoj, odmah iza je *C. albicans* u vrlo sličnom postotku kao *C. glabrata* što je posebno zabrinjavajuće obzirom na visoki postotak stečene rezistencije *C. parapsilosis* na flukonazol, kao i urođene smanjene osjetljivosti *C. glabrata* na flukonazol.

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 2024. godini na amfotericin B, kaspofungin, mikafungin, anidulafungin i flukonazol prikazana je na grafikonu 3., 4., 5., 6. i 7.

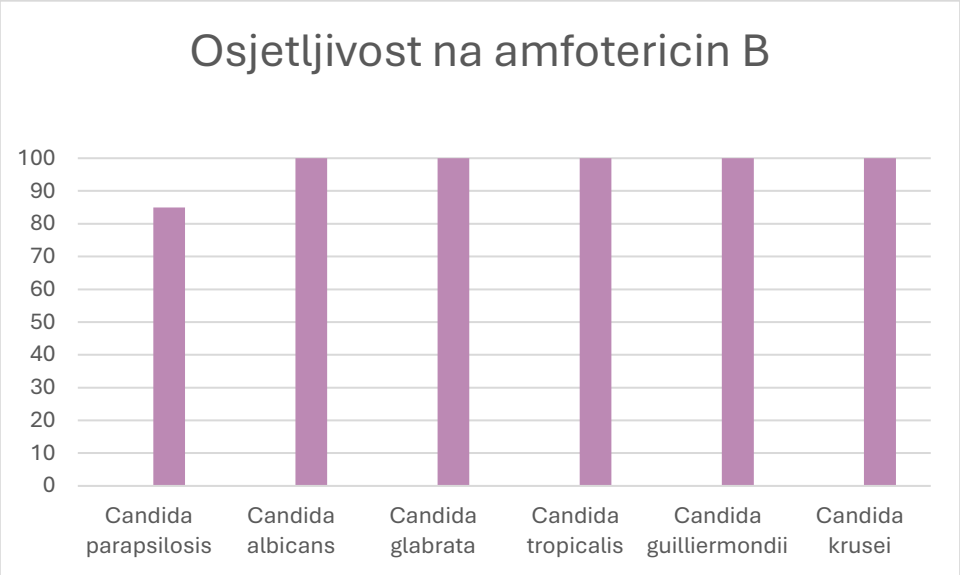
Osjetljivost na amfotericin B bila je 100% za *C. albicans, C. parapsilosis, C. tropicalis, C. glabratu, Candida guilliermondii, C. krusei, a za Candidu parapsilosis* 85%. (grafikon 3).

Osjetljivost uzročnika kandidemija na ehinokandine je još uvijek vrlo visoka, što je i očekivano. Osjetljivost na kaspofungin svih izolata *Candida* spp koji su uzrokovali kadidemije. u 2024. bila je 100% kao I na mikafungin. Izolati *C. parapsilosis* izolirani iz hemokultura su bili 82% osjetljivi na anidulafungin, a svi ostali izolati 100%. (grafikon 4,5 i 6)).

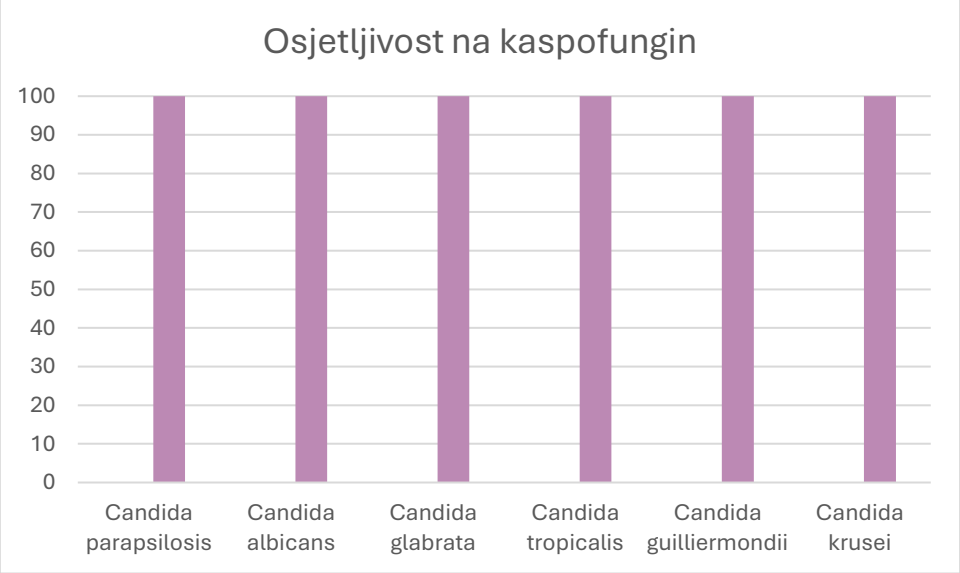
C. albicans i *C. tropicalis* su osjetljiva na flukonazol u 100% ispitivanih izolata. Ono što posebno zabrinjava je da su izolati *C. parapsilosis* (koja je intrinzički osjetljiva na flukonazol za razliku od *C. glabrata i C. krusei*) nažalost je u velikom broju slučajeva razvila rezistenciju pa je u 2024. godini bila osjetljiva u 28% 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. (grafikon 7).

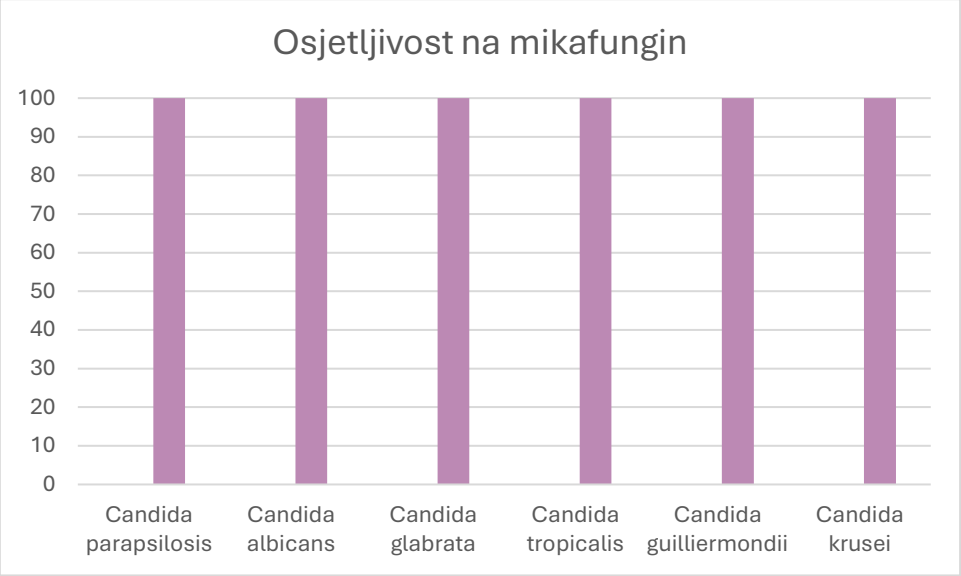
Grafikon 3. / Figure 3. **Osjetljivost vrsta *Candida* spp. u Hrvatskoj u 2024. godini na amfotericin B /** *Candida* spp. susceptibility to amphotericin B in Croatia in 2024



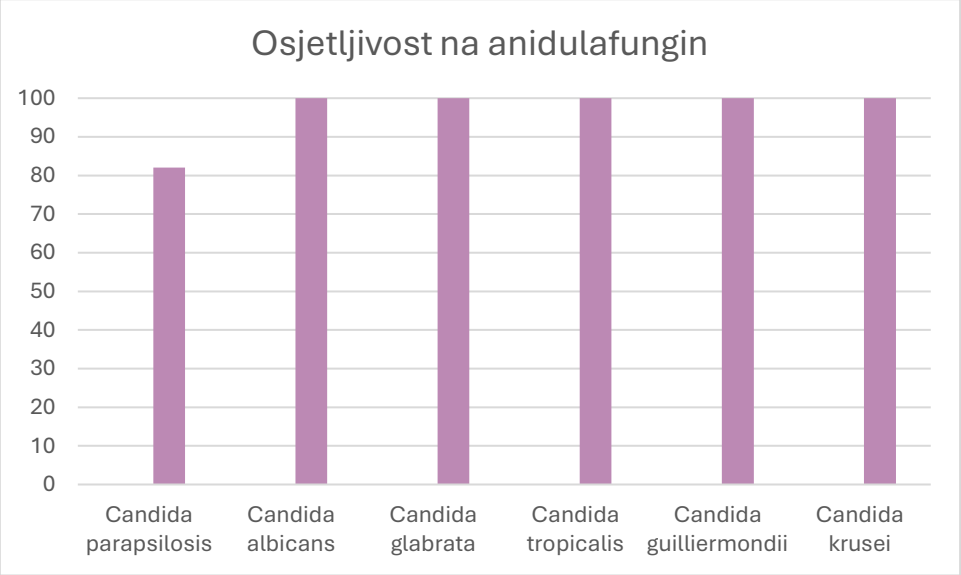
Grafikon 4. / *Figure 4.* **Osjetljivost vrsta *Candida* spp. u Hrvatskoj u 2024. godini na kaspofungin** / Candida spp. susceptibility to caspofungin in Croatia in 2024



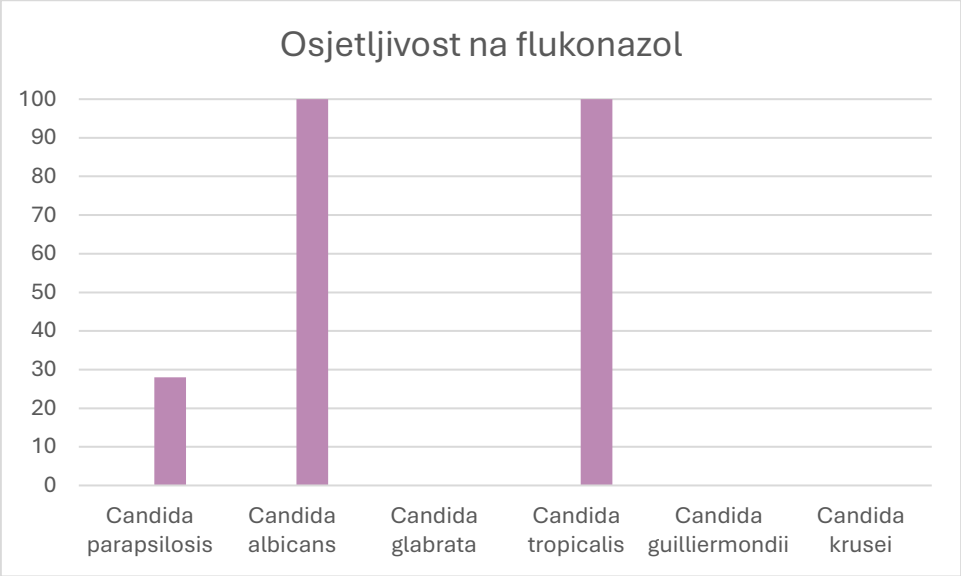
Grafikon 5. Osjetljivost vrsta *Candida* spp. u Hrvatskoj u 2024. godini na mikafungin
Figure 5. *Candida* spp. susceptibility to micafungin in Croatia in 2024



Grafikon 6. Osjetljivost vrsta *Candida* spp. u Hrvatskoj u 2024. godini na anidulafungin
Figure 6. *Candida* spp susceptibility to anidulafungin in Croatia in 2024



Grafikon 7. Osjetljivost vrsta *Candida* spp. u Hrvatskoj u 2024. godini na flukonazol
Figure 7. *Candida* spp susceptibility to fluconazol in Croatia in 2023



INTRODUCTION

The global incidence of candidemia has increased over the last decade and varies depending on 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 have demonstrated differences in the distribution of Candida species and antifungal susceptibility, emphasizing 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. Since 2023, the website has been out of service due to cyber threats.

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 2024 160 isolates of *Candida* spp. were collected and analysed. The incidence of different *Candida* species is shown in Table 1. Comparing the data from 2023, there where no significant difference in the number of received and tested isolates.

The most common *Candida* spp. in the year 2024 were *C. parapsilosis* in 40% (64/160), *C. albicans* in 26,87% (43/160), and *C. glabrata* in 25,62% (41/160) patients with candidemia. This results, which almost equates *C. albicans* with *C. glabrata.*

The distribution of *C. albicans* and non-albicans species among candidemia isolates in the year 2024 is shown in Figure 1.*C. parapsilosis* is far most common isolate followed by *C. albicans* and *C. glabrata* . Those results are clinically important because *C. parapsilosis* and *C glabrata* have reduced susceptibility to azoles. That kind of distribution is characteristic of South Europe and is presumed to be influenced by climatic influences, the use of antifungal agents, and emphasized adherence to prevention and infection control measures.

ANTIFUNGAL SUSCEPTIBILITY

The susceptibility of Candida spp. species in Croatia in 2024 to amphotericin B, caspofungin, micafungin, anidulafungin and fluconazole is shown in graphs 3, 4, 5, 6 and 7.

Sensitivity to amphotericin B was 100% for C. albicans, C. parapsilosis, C. tropicalis, C. glabrata, Candida guilliermondii, C. krusei, and for Candida parapsilosis 85%. (graph 3).

The susceptibility of candidemia causative agents to echinocandins is still very high, which is expected. The susceptibility to caspofungin of all Candida spp. isolates that caused candidemia in 2024 was 100% as well as to micafungin. C. parapsilosis isolates isolated from blood cultures were 82% susceptible to anidulafungin, and all other isolates were 100%. (Figure 4, 5 and 6)).

C. albicans and C. tropicalis are susceptible to fluconazole in 100% of tested isolates. What is particularly worrying is that isolates of C. parapsilosis (which is intrinsically susceptible to fluconazole, unlike C. glabrata and C. krusei) unfortunately developed resistance in a large number of cases, so in 2024 it was susceptible in 28% of cases.

As expected, there were no susceptible isolates of C. glabrata and C. krusei to fluconazole, given that C. glabrata is intrinsically less susceptible to fluconazole and quickly becomes resistant, and C. krusei is intrinsically resistant to fluconazole. (Figure 7).

POGLAVLJE / *CHAPTER* **6**.

POTROŠNJA ANTIBIOTIKA U HRVATSKOJ
ANTIBIOTIC CONSUMPTION IN CROATIA

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IZVANBOLNIČKA POTROŠNJA ANTIBIOTIKA

Praćenje potrošnje antibiotika u Hrvatskoj kontinuirano se provodi od 2001. godine sukladno međunarodno priznatim European Surveillance of Antibiotic Consumption (ESAC) standardima. Odvojeno se prate ambulantna i bolnička potrošnja antibiotika.

Podaci o potrošnji antibiotika se prikupljaju od Hrvatskog zavoda za zdravstveno osiguranje (HZZO) 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). Svaki antibiotik ima propisanu definiranu dnevnu dozu u skladu s Kolaborativnim centrom za statistiku (Oslo, Norveška). Denominator za preračunavanje potrošnje antibiotika je broj stanovnika. Prema zadnjem popisu stanovnika iz 2021. godine broj stanovnika u Hrvatskoj iznosi 3 871 833.

Od ove 2025. godine, podaci o potrošnji antibiotika se unose u EpiPulse Cases (EPC), koji je zamijenio dosadašnju platformu za unos podataka The European Surveillance System (TESSY). Sve zemlje Europske unije unose svoje podatke o potrošnji u EPC te je moguće vršiti usporedbu potrošnje antibiotika i indikatora potrošnje Hrvatske s drugim zemljama.

Podaci o potrošnji antibiotika koji su dobiveni od Hrvatskog zavoda za zdravstveno osiguranje (HZZO) koriste se kao službeni podaci za ambulantnu potrošnju od 2012. godine. Od početka praćenja, 2001. godine pa do 2011. godine koristili su se samo podaci dobiveni putem veledrogerija. Od 2012. godine prati se potrošnja antibiotika iz oba izvora.

Koristeći podatke iz oba izvora, iz godine u godinu, se prati razlika u potrošnji antibiotika ovisno o izvoru podataka (tablica 3; slika 2).

Prema podacima veledrogerija potrošnja antibiotika je viša za 2,78 DDD/TID u odnosu na podatke iz HZZO-a, što je manja razlika u odnosu na godinu prije, kada je ona iznosila 3,14 DDD/TID. Razlika je uočljiva kod svih klasa antibiotika, a i nadalje je najveća u klasi penicilina (1,58 DDD/TID) i klasi makrolid-linkozamid-streptogramin (0,71 DDD/TID) (tablica 4; slika 3). Razlozi toj neusklađenosti između podataka dobivenih iz dva izvora su propisivanje antibiotika od strane liječnika u privatnom sektoru (neizdavanje „crvenog recepta") i moguće snabdjevanje ambulanti s određenim antibioticima direktno putem veledrogerija.

Na slici 1 prikazana je ambulantna potrošnja antibiotika kroz prethodne 24 godine praćenja, a o čemu je bila riječ u prethodnim publikacijama. Ovom prilikom osvrnula bih se na zabrinjavajući trend, koji se uočava od 2020. godine, kada je zabilježena najniža ambulantna potrošnja (14,05 DDD/TID), u vrijeme pandemije uzrokovane SARS CoV-2 virusom. Od te godine ambulantna potrošnja antibiotika bilježi uzlazni trend iz godine u godinu (16,22; 18,18; 19,14). U 2024. godini zabilježena je najviša ambulantna potrošnja antibiotika od 19,78 DDD/TID.

U 2024. godini nastavljen je trend porasta potrošnje širokospektralnih penicilina bez inhibitora (J01CA), što smatramo pozitivnim pokazateljem s obzirom da je amoksicilin namijenjen za empirijsku primjenu kod infekcija gornjeg dišnog sustava i sumnje na bakterijsku infekciju (npr. *otitis media*) kao prvi lijek izbora, što je u skladu s ISKRA smjernicama, kao i prema The Access, Watch, Reserve (AWaRe) klasifikaciji i smjernicama. Nažalost, nastavlja se rast potrošnje širokospektralnih penicilina s inhibitorima beta-laktamaza (J01CR) za što nema uporišta u smjernicama. Zabilježena je najviša potrošnja do sada (tablica 1). Omjer potrošnje

širokospektralnih penicilina s inhibitorima beta-laktamaza (J01CR) i širokospektralnih penicilina bez inhibitora (J01CA) iznosi 3,9 što je gotovo identično godini ranije kada je iznosio 4,0. Taj podatak ukazuje da nema promjena u empirijskom propisivanju penicilinske skupine antibiotika te da se i dalje, kao vodeći antibiotik, koristi kombinacija penicilina s beta-laktamaza inhibitorima, što nije potrebno niti stručno opravdano s obzirom da se najčešće radi o respiratornim infekcijama koje su uzrokovane virusima, a ako su uzrokovane bakterijama najčešće se ne radi o uzročnicima koji produciraju beta-laktamaze.

Kod penicilina uskog spektra (J01CE) bilježi se značajniji porast (0,37 DDD/TID) u odnosu na prethodnu godinu (0,18 DDD/TID), dok je potrošnja beta-laktamaza rezistentnih penicilina (J01CF) u zadnje dvije godine identična (0,02) i viša u odnosu na niz prethodnih godina (0,01 DDD/TID) (tablica 1). Uskospektralni penicilini (J01 CE i J01 CF) zajedno čine samo 4,4 % ukupne potrošnje peniciliske klase antibiotika. Usprkos tim pozitivnim pokazateljima u potrošnji uskospektralnih penicilina i potrošnji penicilina širokog spektra (J01CA), njihov udio u penicilinskoj skupini antibiotika iznosi svega 24%, dok dvije trećine, odnosno 76% čini potrošnja širokospektralnih antibiotika s inhibitorima (J01CR).

Kod klase cefalosporina u 2024. godini nema značajnijih promjena u potrošnji u odnosu na prethodnu godinu.

Blagi porast potrošnje uočava se kod klasa tetraciklina (1,02; 1,06) i sulfonamida + trimetoprim (0,52; 0,54), dok je nešto veći kod makrolida i linkozamida (3,70; 3,87). Nakon 4 godine kontinuiranog trenda porasta potrošnje fluorokinolona u 2024. godini bilježi se pad u potrošnji sa 1,51 na 1,45 DDD/TID (tablica 1).

Potrošnja nitrofurantoina (J01XE) nastavlja s rastom, kao i potrošnja fosfomicina (J01XX) (tablica 1), što je pozitivan pokazatelj, ako imamo u vidu da su urinarne infekcije najčešće izvanbolničke, bakterijske infekcije.

Analizirajući jedan od ambulantnih indikatora potrošnje, a to je omjer širokospektralnih penicilina, beta-laktama s inhibitorima, cefalosporina II. i III. generacije, makrolida (osim eritromicina) i fluorokinolona (J01 (CR+DC+DD+FA-FA01)+MA) i potrošnje širokospektralnih penicilina bez inhibitora (amoksicilina), uskospektralnih penicilina, cefalosporina I. generacije i eritromicina (J01 (CA+CE+CF+DB+FA01) uočava se pad sa 6,2 na 5,7, što je povoljnije u odnosu na prethodne godine, ali još uvijek ukazuje na velik udio u potrošnji širokospektralnih antibiotika, što značajno pridonosi poticanju rezistencije (tablica 5; slika 4) .

Rang lista najpropisivanijih ambulantnih antibiotika (6 vodećih) prikazana je u tablici 6 i na slici 5. Poredak prva dva (koamoksiklav i azitromicin) je identičan prethodnoj godini. Promjena je na trećoj poziciji, na kojoj je amoksicilin umjesto cefuroksima koji je zauzeo 4. mjesto, odnosno ta dva antibiotika su zamijenila mjesta u odnosu na prethodnu godinu. Poredak na petom i šestom mjestu je identičan kao i prethodne godine (nitrofurantoin, doksiciklin).

Kvartalna potrošnja antibiotika je još jedan indikator ambulantne potrošnje. U 2024. godini pokazuje se potpuno neuobičajena slika potrošnje antibiotika po kvartalima. Tipična slika potrošnje po kvartalima je slika „ljuljačke", na kojoj je veća potrošnja u prvom i zadnjem kvartalu, dok je u drugom i trećem ona niža. U 2024. godini, najviša je potrošnja antibiotika zabilježena u trećem kvartalu (jesenski), za koji je uz drugi kvartal (proljetni) uobičajeno najniža potrošnja antibiotika tijekom godine. U odnosu na godinu prije u 1. kvartalu je potrošnja porasla za 0,09, a u trećem,

očekivano s najnižom potrošnjom, porasla je čak za 1,5 DDD/TID. U četvrtom kvartalu se bilježi pad za 0,38 DDD/TID u odnosu na prethodnu godinu (tablica 7; slika 6).

„Top 10" dijagnoza za koju su bili propisani antibiotici identična je listi od prethodne godine za prvih 9 dijagnoza. Jedina razlika je na desetom mjestu na kojem se, umjesto dijagnoze periapikalni apsces (K04.7), nalazi dijagnoza J018 pneumonija, nespecificiranog uzročnika. Na prvom mjestu, kao i prethodnih godina, po propisivanju antibiotika se nalazi dijagnoza upala mokraćnog mjehura (N30), što je očekivano s obzirom da je to najčešća izvanbolnička bakterijska infekcija. Još su dvije dijagnoze iz područja mokraćnog sustava (N39.0 i N39) među prvih deset dijagnoza. Ostalih sedam dijagnoza se odnose na dišni sustav: akutna upala ždrijela (J02), akutna upala tonzila (J03), akutna upala sinusa (J01), akutna upala gornjeg dišnog sustava (J06), akutni bronhitis (J20), nesupurativna upala srednjeg uha (H65) te pneumonija, nespecifiranog uzročnika (J18).

Za liječenje infekcija mokraćnog sustava potrošeno je 2,88 DDD/TID (prošle godine 2,97 DDD/TID), dok je za respiratorne infekcije potrošeno više antibiotika u odnosu na prethodnu godinu (5,33 DDD/TID; 4.97 DDD/TID).

Uočava se velika potrošnja antibiotika za liječenje respiratornih infekcija, gotovo dvostruko veća nego za liječenje infekcija urinarnog sustava, što ukazuje na često nepotrebnu primjenu s obzirom da su respiratorne infekcije, osobito gornjeg dijela dišnog sustava najčešće uzrokovane virusima na koje antibiotici ne djeluju.

U 2024. godini ambulantna potrošnja je najviša u zadnjih jedanaest godina i iznosi 19,78 DDD/TID, s kontinuiranim trendom porasta potrošnje od 2020. godine. Udio ambulantne potrošnje u ukupnoj potrošnji iznosi 90%.

Klasa penicilina je, kao i do sada, najzastupljenija u ambulantnoj potrošnji antibiotika (44,0 %). Slijede ju makrolidi s 20% te skupina cefalosporina s 14%, zatim fluorokinoloni sa 7%, skupina ostali sa 6% te sulfonamidi+trimetoprim i tetraciklini s 5% u ukupnoj ambulantnoj potrošnji antibiotika.

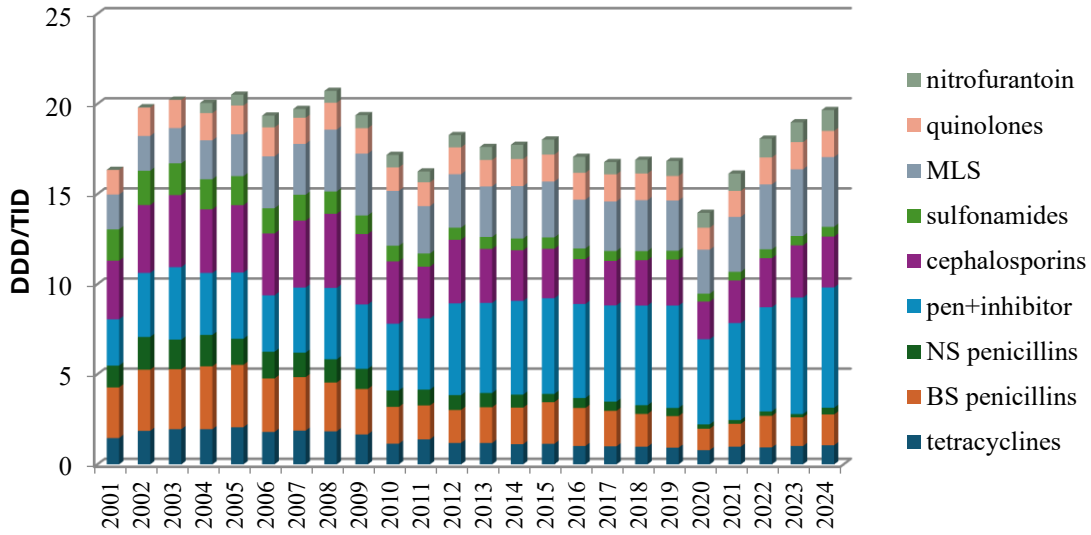
U 2024. godini porasla je potrošnja skupine tetraciklina. U skupini penicilina porasla je potrošnja penicilina širokog spektra, penicilina uskog spektra te kombinacije penicilina s beta-laktamaza inhibitorima. U prošloj godini bilježi se pad u potrošnji cefalosporina 1. generacije, dok su 2. i 3. generacija ostale na vrlo sličnom nivou potrošnje. Porasla je potrošnja skupine sulfonamida s trimetoprimom, skupine makrolida i linkozamida te skupina ostali, među kojima se prati povećana potrošnja nitrofurantoina i fosfomicina. Zabilježen je pad u potrošnji fluorokinolona (tablica 1).

Indikator potrošnje antibiotika koji pokazuje omjer potrošnje širokospektralnih antibiotika u odnosu na uskospektralne iznosi 5,7 što je niže u odnosu na godinu ranije, ali još uvijek ukazuje na gotovo 6 puta veću potrošnju širokospektralnih antibiotika u odnosu na uskospektralne (tablica 5, slika 4). Omjer potrošnje širokospektralnih penicilina s inhibitorima beta-laktamaza (J01CR) i širokospektralnih penicilina bez inhibitora (J01CA) iznosio je 3,9, što je gotovo identično podatku iz 2023. godine (4,0) te ukazuje na četverostruko češću primjenu ko-amoksiklava u odnosu na amoksicilin u primarnoj zdravstvenoj zaštiti.

Koamoksiklav je vodeći antibiotik u ambulantnoj potrošnji, s najvišom vrijednošću (6,68 DDD/TID) do sada u praćenju ambulantne potrošnje, a infekcije dišnog sustava su najzastupljenije dijagnoze (7 od 10) među prvih deset za koje se propisuju antibiotici, što samo ukazuje na njegovu neopravdanu primjenu.

U današnje vrijeme snažnog razvoja mikrobiološke dijagnostike u smislu brzine, preciznosti i olakšane identifikacije bakterijskih uzročnika i gena rezistencije potrebno je više nego ikad istovremeno primjenjivati dijagnostički „stewardship“, kako bi se antibiotici, barem u većini slučajeva, koristili za liječenje samo bakterijskih infekcija uz rukovođenu primjenu antibiotika u primarnoj zdravstvenoj zaštiti, a da odabrani antibiotik bude u skladu sa stručnim smjernicama za liječenje određenih kliničkih entiteta.

Slika 1. */ Figure 1.* **Ambulantna potrošnja antibiotika (DDD/TID) u Hrvatskoj, 2001 – 2024.** */ Ambulatory antibiotic consumption (DDD/TID) in Croatia, 2001 – 2024*



OUTPATIENT ANTIBIOTIC CONSUMPTION

Antibiotic consumption monitoring has been conducted continuously since 2001, in accordance with internationally recognized ESAC (European Surveillance of Antibiotic Consumption) standards. Usage of antibiotics in outpatient and hospital environments is monitored separately.

Data on the use of antibiotics is collected from the Croatian Health Insurance Fund (CHIF) in compliance 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 same classification. Antibiotic consumption is expressed in Defined Daily Doses (DDDs) per 1,000 inhabitants per day (DDD/TID). Each antibiotic has a prescribed daily dose assigned by the Collaborating Centre for Statistics (Oslo, Norway). The number of inhabitants is used as a denominator for calculating antibiotic consumption. According to the most recent Census of 2021, Croatia has the population of 3,871,833.

As of 2025, consumption data is entered into EpiPulse Cases (EPC) which has replaced The European Surveillance System (TESSy) data entry platform. Since all European Union member states enter their respective consumption data into EPC, Croatia is able to compare its antibiotic usage as well as consumption indicators with other EU countries.

Antibiotic consumption data obtained from the Croatian Health Insurance Fund (CHIF) has been used as the official data on outpatient consumption since 2012. At the beginning of monitoring, from 2001 to 2011, only the data provided by pharmaceutical wholesalers was used. Since 2012, however, data on the usage of antibiotics has been collected from both of these sources, which has enabled monitoring of differences in the consumption arising from the source of data over the years (Table 3; Figure 2).

According to data provided by pharmaceutical wholesalers, consumption is higher by 2.78 DDD/TID when compared to the CHIF data, which is a smaller discrepancy than 3.14 DDD/TID recorded a year earlier. The discrepancy is evident across all antibiotic classes and remains highest in the penicillin class (1.58 DDD/TID) and the macrolide-lincosamide-streptogramin class (0.71 DDD/TID) (Table 4; Figure 3). The reasons for the disparity between the two data sources are following: prescribing of antibiotics by physicians in private healthcare sector (without issuing “red prescriptions”) as well as possible direct supply of certain antibiotics to outpatient clinics via wholesale pharmacies.

Figure 1 shows outpatient antibiotic consumption over the past 24 years, which has been addressed in previous publications. This time, I would like to draw attention to a worrying trend observed since 2020 and the SARS CoV-2 virus pandemic, when the lowest outpatient consumption was recorded (14.05 DDD/TID). Ever since, there has been an upward trend in ambulatory consumption year after year (16.22; 18.18; 19.14). It peaked in 2024 when the highest outpatient antibiotic consumption value of 19.78 DDD/TID was recorded.

2024 also saw continuation of the increased usage of broad-spectrum penicillins without inhibitors (J01CA), which we consider a positive indicator, given that amoxicillin is empirically used as the first-line therapy for upper respiratory tract infections and suspected bacterial infections (e.g. *otitis media*), in accordance with the ISKRA guidelines as well as The Access, Watch, Reserve (AWaRe) classification and recommendations. Unfortunately, the consumption of broad-spectrum penicillins with beta-lactamase inhibitors (J01CR) also continued to rise, which is unsupported by the

guidelines. The highest consumption to date was recorded (Table 1). The ratio of the consumption of broad-spectrum penicillins with beta-lactamase inhibitors (J01CR) to broad-spectrum penicillins without inhibitors (J01CA) is 3.9, which is almost identical to the previous year's ratio of 4.0. This indicates that there was no change in empirical prescribing of the penicillin class, and that combination of penicillins with beta-lactamase inhibitors remains the leading antibiotic, which is neither necessary nor professionally justified, since most respiratory infections are viral in origin or, if bacterial, are seldom caused by beta-lactamase-producing pathogens.

There has been a significant rise (0.37 DDD/TID) in the consumption of narrow-spectrum penicillins (J01CE) compared to the previous year (0.18 DDD/TID), while the usage of beta-lactamase-resistant penicillins (J01CF) remained the same over the last two years (0.02), but higher than it had been in the several preceding years (0.01 DDD/TID) (Table 1). Narrow-spectrum penicillins (J01CE and J01CF) together account for only 4.4% of the overall consumption of penicillin group of antibiotics. Despite these positive indicators in the usage of both narrow-spectrum and broad-spectrum penicillins (J01CA), their share in the penicillin class is just 24%, while two-thirds, or 76%, comprise broad-spectrum antibiotics with inhibitors (J01CR).

In the cephalosporin class, there were no significant changes in consumption in 2024, compared to the year before.

There was a slight growth in the usage of tetracyclines (1.02; 1.06) and sulfonamides+trimethoprim (0.52; 0.54), while it was more substantial for macrolides and lincosamides (3.70; 3.87). After 4 years of continuous upward trend in consumption of fluoroquinolones, 2024 saw a decline from 1.51 to 1.45 DDD/TID (Table1).

The consumption of nitrofurantoin (J01XE) and fosfomycin (J01XX) continued to grow (Table 1), which is a positive indicator considering the fact that urinary tract infections are the most common outpatient bacterial infections.

Analysing one of the outpatient consumption indicators – the ratio of broad-spectrum penicillins, beta-lactams with inhibitors, II and III generation of 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 erytromycin (J01 (CA+CE+CF+DB+FA01) - a decline in consumption was noticed, from 6.2 to 5.7, which is an improvement on previous years, but nevertheless indicates a large share of broad-spectrum penicillins in overall consumption, thus significantly contributing to the development of antimicrobial resistance (Table 5, Figure 4).

Table 6 and Figure 5 show the ranking of the six most frequently prescribed ambulatory antibiotics. The first two (co-amoxiclav and azithromycin) retained their positions from the previous year. A change occurred in the third place where amoxicillin replaced cefuroxime pushing it to the fourth place, having basically switched places compared to the preceding year. The fifth and sixth positions remained the same (nitrofurantoin and doxycycline).

Another indicator of ambulatory antibiotic usage is their quarterly consumption, which in 2024 was unprecedented. The typical quarterly pattern resembles a "swing", where higher consumption is recorded in the first and last quarter, and lower in the second and third. In 2024 however, the highest consumption was recorded in the third (autumn) quarter which typically has the lowest consumption values, along with the second (spring) quarter. Compared to the previous year, consumption in the first quarter increased by 0.09 DDD/TID while in the third – where the lowest usage was expected

– it surged by 1.5 DDD/TID. The fourth quarter recorded a drop by 0.38 DDD/TID in relation to the year before (Table 7; Figure 6).

The ranking of the "Top 10" diagnoses for which antibiotics were prescribed remained almost identical to the preceding year, with the only change happening in the tenth place where J018 (pneumonia, unspecified organism) replaced diagnosis K04.7 (perapical apscess). In the first place, as in previous years, was bladder inflammation (N30), being the most common outpatient bacterial infection. There were two more diagnoses related to urinary tract (N39.0 and N39) among the leading ten. The remaining seven were respiratory tract infections: acute pharyngitis (J02), acute tonsillitis (J03), acute sinusitis (J01), acute upper respiratory tract infection (J06), acute bronchitis (J20), non-suppurative otitis media (H65) and pneumonia, unspecified organism (J18). Antibiotics used for treating urinary tract infections amounted to 2.88 DDD/TID (unlike 2.97 DDD/TID the year before), whereas more antibiotics were used for respiratory infections (5.33 DDD/TID) than in the preceding year (4.97 DDD/TID).

As seen, a large amount of antibiotics is used for treating respiratory infections – almost double that used for infections of urinary tract – indicating their often unnecessary use in light of the fact that respiratory infections, particularly those of the upper tract, are most commonly caused by viruses against which antibiotics are ineffective.

In 2024 outpatient antibiotic consumption reached its highest level in the last eleven years, amounting to 19.78 DDD/TID, with a consistent upward trend observed since 2020. Antibiotics used in ambulatory setting accounted for 90% of the total consumption.

The penicillin class, as in previous years, remained the most represented in outpatient use (44%). It was followed by macrolides at 20%, cephalosporins at 14%, fluoroquinolones at 7%, the "other"group at 6% and finally sulfonamides+trimethoprim and tetracyclines each comprising 5% of the total outpatient antibiotic consumption.

In 2024, the consumption of tetracyclines increased. Within the penicillin group, higher usage was recorded for both broad-spectrum and narrow-spectrum penicillins, as well as combinations of penicillins with beta-lactamase inhibitors. On the other hand, there was a decrease in the consumption of first-generation cephalosporins, whereas the use of their second and third generation remained mostly unchanged. Furthermore, an increase was recorded in the consumption of sulfonamides with trimethoprim, the macrolide and lincosamide group as well as the "other" group, within which higher use of nitrofurantoin and fosfomycin was noted. There was a decrease in the consumption of fluoroquinolones (Table 1).

The indicator of antibiotic consumption that reflects the ratio of broad-spectrum to narrow-spectrum antibiotics remained 5.7, lower than the year before, but still indicative of six times greater usage of broad-spectrum antibiotics in relation to narrow-spectrum ones (Table 5, Figure 4). The ratio between the consumption of broad-spectrum penicillins with beta-lactamase inhibitors (J01CR) and those without inhibitors (J01CA) was 3.9, almost identical to 2023 when it was 4.0, which shows that co-amoxiclav is used approximately four times more often than amoxicillin in primary healthcare.

The fact that co-amoxiclav is the most commonly used antibiotic in outpatient setting – reaching its record high of 6.68 DDD/TID since monitoring began, combined with predominance of respiratory tract infections among indications for antibiotic prescribing (7 out of 10), highlights the extent of its inappropriate use.

Nowadays, when microbiological diagnostics is making rapid advances in terms of speed, accuracy, and ease of identifying bacterial pathogens and resistance genes, it is more imperative than ever to implement diagnostic ”stewardship” so as to use antibiotics, at least in most of the cases, exclusively for treating bacterial infections, with guided prescribing (“antimicrobial stewardship”) in primary healthcare, so that the chosen antibiotic is in line with professional guidelines for the treatment of specific clinical entities.

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

ATC šifra ATC code	ANTIBIOTIK ANTIBIOTIC	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024
J01AA	Tetraciklini Tetracylines	1,12	1,14	1,02	1,00	0,98	0,93	0,79	0,98	0,94	1,02	1,06
J01CA	Penicilini širokog spektra Broad spectrum penicillins	2,03	2,31	2,11	1,97	1,82	1,75	1,19	1,27	1,75	1,59	1,71
J01CE	Penicilini uskog spektra Narrow spectrum penicillins	0,72	0,46	0,55	0,51	0,48	0,45	0,24	0,21	0,25	0,18	0,37
J01CF	Beta-laktamaza rezistentni penicilini Beta-lactamase resistant penicillins	0,00	0,01	0,00	0,01	0,01	0,01	0,01	0,01	0,01	0,02	0,02
J01CR	Kombinacije s beta-laktamaza inhibitorima Combinations with inhibitors	5,20	5,31	5,22	5,34	5,53	5,68	4,72	5,38	5,78	6,46	6,68
J01DB	Cefalosporini I gen. Cephalosporins	0,72	0,66	0,60	0,47	0,38	0,35	0,27	0,29	0,36	0,39	0,32
J01DC	Cefalosporini II gen. Cephalosporins	1,85	1,85	1,69	1,67	1,73	1,72	1,38	1,46	1,61	1,60	1,59
J01DD	Cefalosporini III gen. Cephalosporins	0,24	0,23	0,20	0,33	0,41	0,49	0,44	0,61	0,75	0,92	0,91
J01EE	Sulfonamides + trimethoprim	0,65	0,63	0,59	0,55	0,50	0,49	0,44	0,48	0,49	0,52	0,54
J01F	Macrolides, lincosamides	2,91	3,10	2,71	2,75	2,83	2,79	2,44	3,05	3,60	3,70	3,87
J01G	Aminoglikozidi Aminoglycosides	0,04	0,01	0,00	0,01	0,01	0,004	0,003	0,003	0,002	0,02	0,002
J01MA	Fluorokinoloni Fluoroquinolones	1,50	1,50	1,49	1,50	1,48	1,36	1,22	1,44	1,50	1,51	1,45
J01XE	Nitrofurantoin	0,79	0,83	0,88	0,68	0,76	0,83	0,83	0,96	1,04	1,10	1,16
J01XX	Fosfomycin	-	-	0,004	0,05	0,08	0,08	0,08	0,09	0,09	0,11	0,12
UKUPNO TOTAL		**17,8**	**18,0**	**17,1**	**16,8**	**17,0**	**16,9**	**14,0**	**16,2**	**18,1**	**19,1**	**19,7**

* 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., od 2022. koriste se podaci iz popisa 2021./ The Croatian Bureau of Statistics, Census 2001was used until 2012 and starting with 2012 Census 2011 was used, starting 2022 census 2021 was used

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

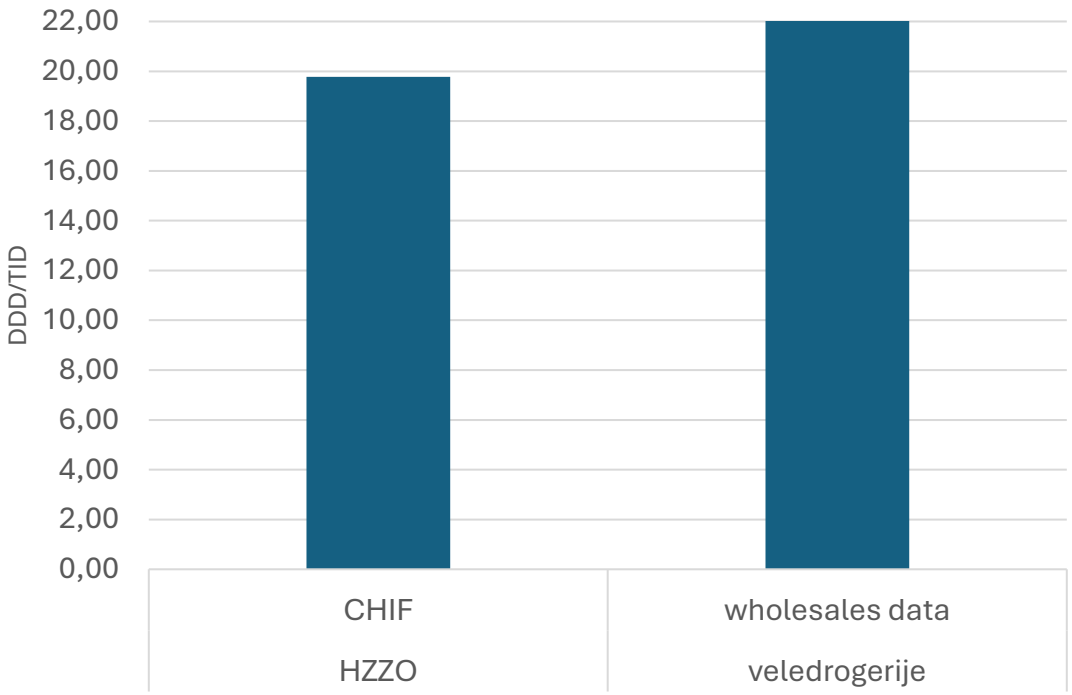
ATC šifra ATC code	ANTIBIOTIK ANTIBIOTIC	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024
J01AA	Tetraciklini Tetracylines	0,04	0,04	0,04	0,04	0,03	0,04	0,03	0,03	0,03	0,03	0,03
J01CA	Penicilini širokog spektra Broad spectrum penicillins	0,02	0,02	0,03	0,02	0,02	0,02	0,02	0,02	0,03	0,02	0,02
J01CE	Penicilini uskog spektra Narrow spectrum penicillins	0,02	0,02	0,02	0,02	0,02	0,02	0,01	0,01	0,01	0,02	0,01
J01CF	Beta-laktamaza rezistentni penicilini Beta-lactamase resistant penicillins	0,03	0,03	0,03	0,04	0,04	0,04	0,03	0,03	0,04	0,04	0,05
J01CR	Kombinacije s beta-laktamaza inhibitorima Combinations with inhibitors	0,37	0,38	0,37	0,38	0,40	0,42	0,33	0,40	0,42	0,43	0,44
J01DB	Cefalosporini I gen. Cephalosporins	0,09	0,10	0,10	0,10	0,09	0,10	0,08	0,09	0,10	0,11	0,12
J01DC	Cefalosporini II gen. Cephalosporins	0,20	0,17	0,19	0,20	0,20	0,20	0,15	0,16	0,15	0,15	0,14
J01DD + J01DE	Cefalosporini III + IV gen. Cephalosporins	0,18	0,18	0,16	0,17	0,16	0,17	0,19	0,24	0,24	0,27	0,29
J01DH	Carbapenems	0,06	0,06	0,06	0,08	0,07	0,08	0,09	0,12	0,12	0,13	0,14
J01EE	Sulfonamides + trimethoprim	0,05	0,04	0,04	0,04	0,04	0,04	0,03	0,03	0,04	0,04	0,04
J01F	Macrolides, lincosamides	0,14	0,15	0,15	0,16	0,16	0,18	0,19	0,21	0,21	0,22	0,23
J01G	Aminoglikozidi Aminoglycosides	0,10	0,10	0,09	0,09	0,09	0,09	0,07	0,08	0,09	0,09	0,09
J01MA	Fluorokinoloni Fluoroquinolones	0,20	0,21	0,21	0,23	0,24	0,24	0,20	0,24	0,24	0,25	0,25
J01XA	Glycopeptides	0,03	0,04	0,03	0,04	0,05	0,05	0,05	0,07	0,07	0,07	0,07
J01XD	Metronidazole	0,09	0,10	0,10	0,11	0,15	0,12	0,10	0,12	0,12	0,14	0,15
J01XE	Nitrofurantoin	0,02	0,01	0,01	0,01	0,01	0,01	0,01	0,02	0,02	0,02	0,02
J01XX	Fosfomycin	-	-	0,00 1	0,02	0,02	0,02	0,02	0,04	0,04	0,05	0,06
UKUPNO TOTAL		**1,65**	**1,70**	**1,65**	**1,74**	**1,80**	**1,85**	**1,61**	**1,93**	**1,98**	**2,08**	**2,18**

** Do 2012.g. korišten je popis stanovništva iz 2001, počevši s 2012.g. korišten je popis iz 2011, od 2022. koriste se podaci iz popisa 2021 / The Croatian Bureau of Statistics, Census 2001was used until 2012 and starting with 2012 Census 2011 was used, starting 2022 census 2021 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	28079064,70	32025744,12
DDD/TID	19,78	22,56

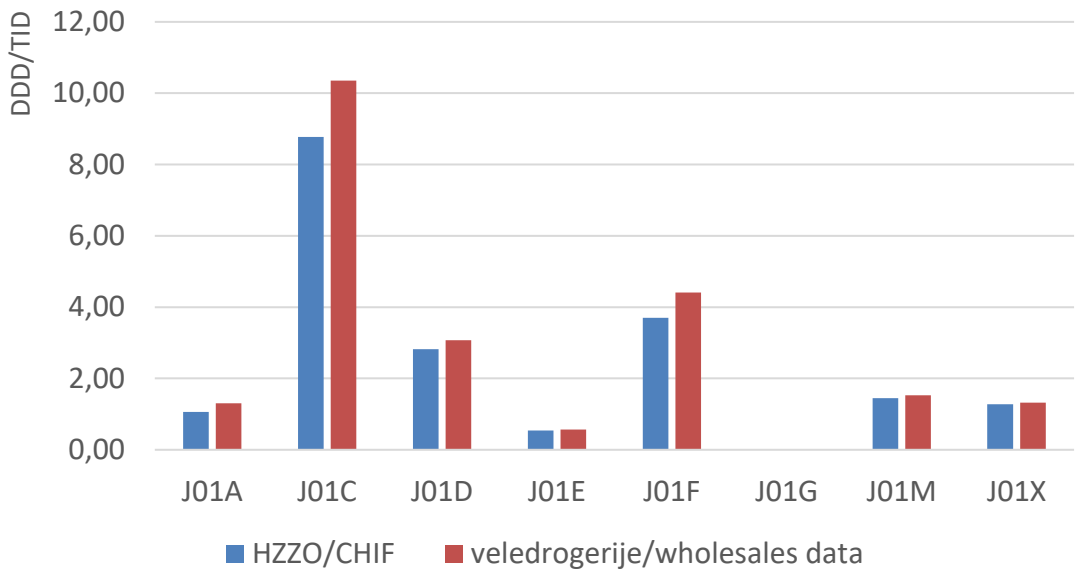
Slika 2. */ Figure 2.*
Ambulantna potrošnja antibiotika (DDD/TID) usporedba podataka HZZO i veledrogerija
Ambulatory antibiotic consumption (DDD/TID) comparison between CHIF data and wholesales data



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	1,06	1,30
J01C	8,77	10,35
J01D	2,82	3,07
J01E	0,54	0,57
J01F	3,70	4,41
J01G	0,00	0,01
J01M	1,45	1,53
J01X	1,28	1,32

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 2010-2024/

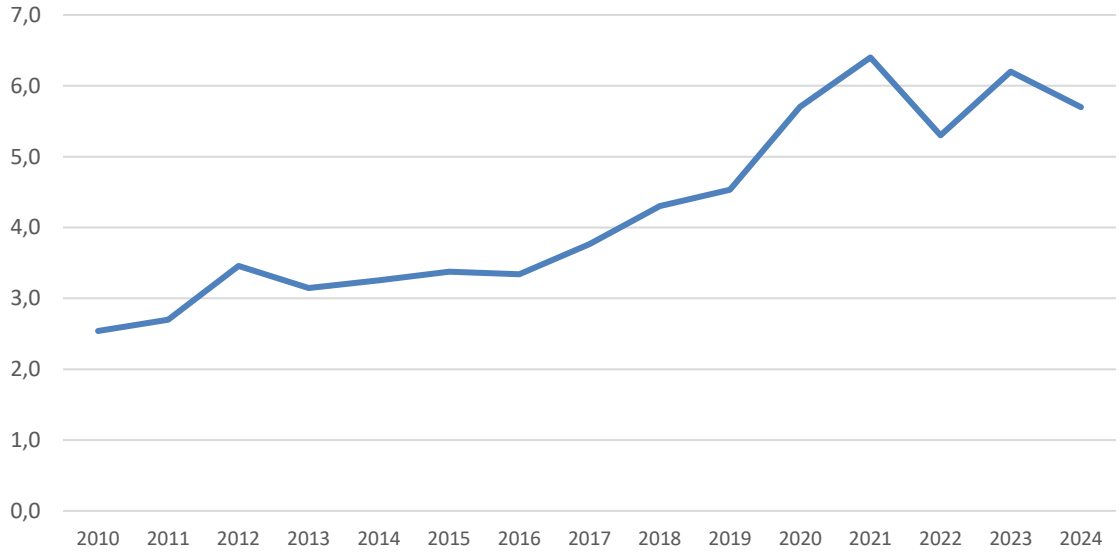
The ratio of consumption of broad-spectrum penicillins, cephalosporins, macrolides (except erythromicin) and fluoroqinolones to the consumption of narrow-spectrum penicillins, cephalosporins and erythromicin expressed as DDD per 1000 inhabitants per day in the community 2010-2024

	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
2024	5,7

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 2010-2024/

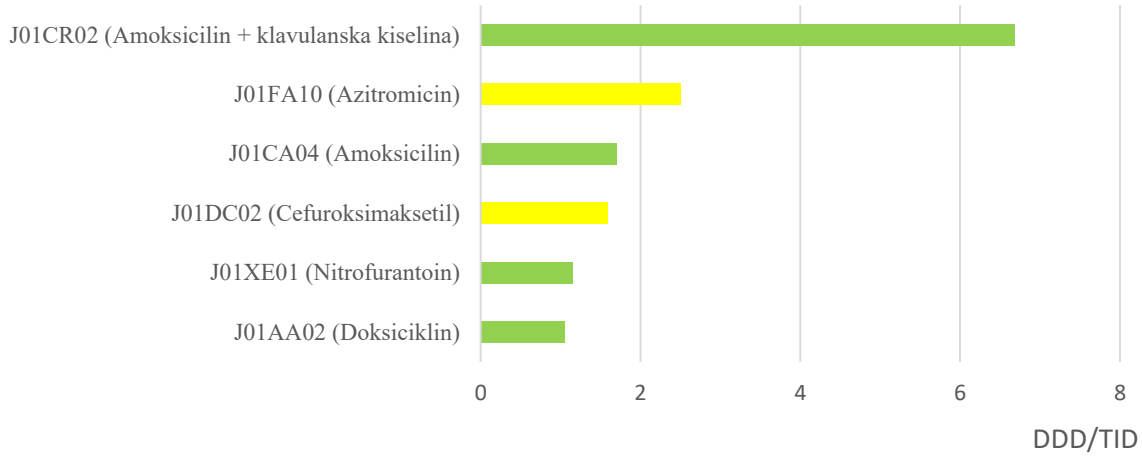
The ratio of consumption of broad-spectrum penicillins, cephalosporins, macrolides (except erythromicin) and fluoroqinolones to the consumption of narrow-spectrum penicillins, cephalosporins and erythromicin expressed as DDD per 1000 inhabitants per day the community 2010-2024



Tablica 6. / *Table 6.*
Ambulantna potrošnja antibiotika („top 6“ antibiotika – DDD/TID), izvor podataka – HZZO Zeleno polje označava antibiotik iz skupine “Access”, žuto polje označava antibiotik iz skupine “Watch”/
Ambulatory antibiotic consumption („top 6“antibiotics- DDD/TID); origin of data – CHIF Green field indicates an antibiotic from the group Access, yellow field indicates an antibiotic from the group Watch

Klasa / class	DDD/TID
J01CR02 (Amoksicilin + klavulanska kiselina)	6,68
J01FA10 (Azitromicin)	2,51
J01CA04 (Amoksicilin)	1,71
J01DC02 (Cefuroksimaksetil)	1,59
J01XE01 (Nitrofurantoin)	1,16
J01AA02 (Doksiciklin)	1,06

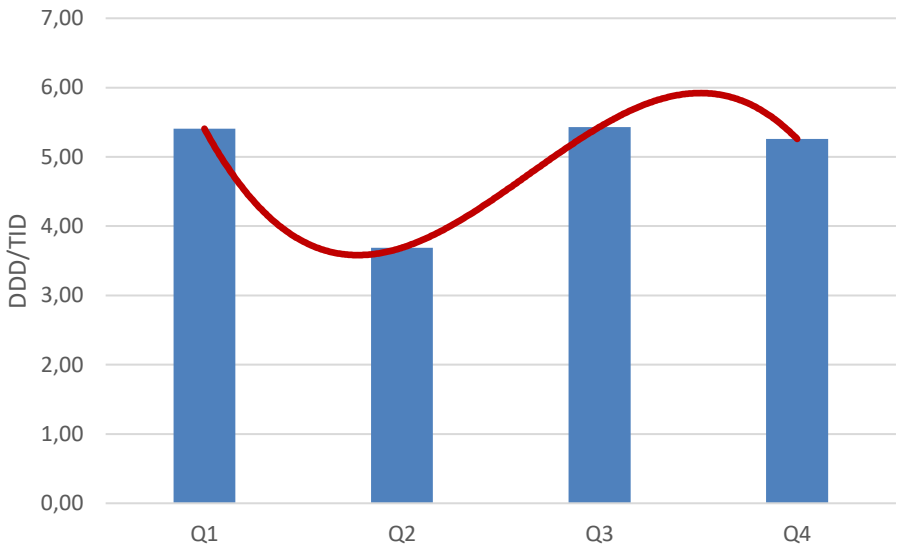
Slika 5. */ Figure 5.*
Ambulantna potrošnja antibiotika („top 6“ antibiotika – DDD/TID), izvor podataka – HZZO Zelena traka označava antibiotik iz skupine Access, žuta traka označava antibiotik iz skupine Watch/
Ambulatory antibiotic consumption („top 6“antibiotics- DDD/TID); origin of data-CHIF Green bar indicates an antibiotic from the group Access, yellow bar indicates an antibiotic from the group Watch



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	5,41
II	3,69
III	5,43
IV	5,26

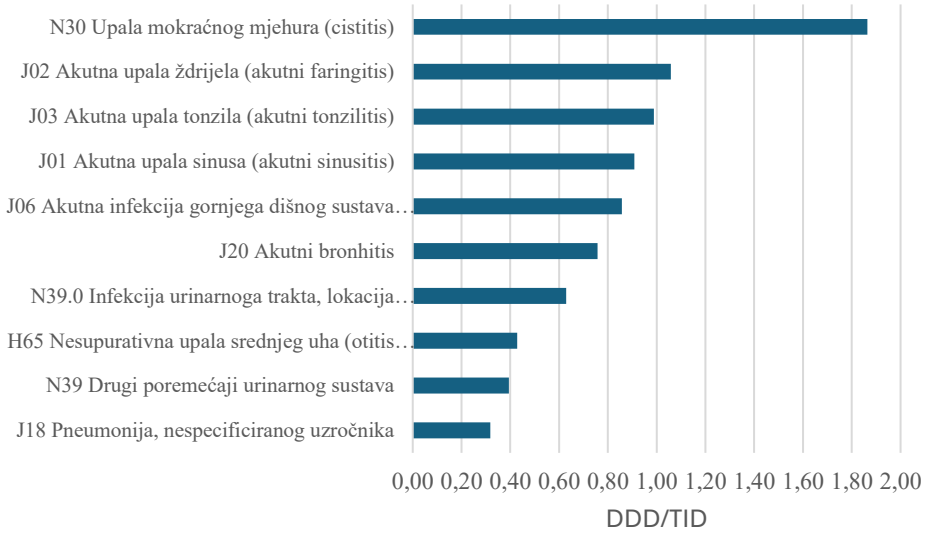
Slika 6. / *Figure 6.*
Ambulantna potrošnja antibiotika po kvartalima – DDD/TID, izvor podataka – HZZO
Ambulatory antibiotic consumption – by quarters DDD/TID; origin of data-CHIF



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)	1,86
J02 Akutna upala ždrijela (akutni faringitis)	1,06
J03 Akutna upala tonzila (akutni tonzilitis)	0,99
J01 Akutna upala sinusa (akutni sinusitis)	0,91
J06 Akutna infekcija gornjega dišnog sustava multiplih i nespecifici	0,86
J20 Akutni bronhitis	0,76
N39.0 Infekcija urinarnoga trakta, lokacija neoznačena	0,63
H65 Nesupurativna upala srednjeg uha (otitis media nonsuppurativa)	0,43
N39 Drugi poremećaji urinarnog sustava	0,39
J18 Pneumonija, nespecificiranog uzročnika	0,32

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



POTROŠNJA ANTIBIOTIKA U HRVATSKIM BOLNICAMA

Bolnička potrošnja antibiotika se prati odvojeno od ambulantne potrošnje. Do 2011. godine bolnička potrošnja antibiotika se pratila samo putem podataka dobivenih od veledrogerija. Zahvaljujući osnutku i radu Interdisciplinarne sekcije za kontrolu rezistencije (ISKRA) pri Ministarstvu zdravstva od 2011. godine sve bolničke ustanove dostavljaju potrošnju antibiotika iz svojih ljekarni, tako da se od tada bolnička potrošnja antibiotika prati iz dva izvora (veledrogerije, bolničke ljekarne).

Podaci dobiveni putem bolničkih ljekarni, kao službeni podaci o bolničkoj potrošnji antibiotika dostavljaju se u europski program praćenja potrošnje EpiPulse od ove godine, što je zamijena za TESSY. (tablica 2).

Vezano uz metodologiju rada podatke o potrošnji antibiotika bolnice dostavljaju u paketima ili komadima uz administrativne podatke o broju bolničkoopskrbnih dana (BOD) i broju primitaka za čitavu bolnicu i 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).

Od 2011. godine, od kada se bolnička potrošnja prati putem podataka dobivenih iz bolničkih ljekarni i od kada se dobivaju administrativni podaci za svaku bolnicu u Hrvatskoj, bolnička potrošnja antibiotika se može iskazivati i u DDD/BOD, što ima velike prednosti u odnosu na iskazivanje prema broju stanovnika (DDD/TID). Takav način prikazivanja potrošnje je objektivniji, precizniji i omogućava detaljnu analizu po pojedinim klasama i vrstama antibiotika na nacionalnom nivou, ali i posebno za svaku bolnicu.

U tablici 9 i na slici 8 usporedno su prikazani podaci od 2014. godine dobiveni iz oba izvora. 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 2024. godini razlika je iznosila najviše do sada 0,75 DDD/TID, što je značajno više od prethodne godine kada je iznosila 0,37 DDD/TID (tablica 9; slika 8). S obzirom da se svi antibiotici koji se koriste u bolnicama dobivaju putem veledrogerija teško je objasniti ovu razliku, koja se prvi puta značajnije povećala u 2021. godini na 0,35 DDD/TID i zadržala ili porasla svake godine do 2024. godine, ovisno o izvoru podataka.

Šezdesetosam bolnica je poslalo podatke o potrošnji antibiotika u 2024. godini. Sve bolnice su poslale podatke elektronskim putem na adresu iskra.antibiotici@gmail.com. Kao i prethodnih godina samo 4 bolnice su direktno eksportirale podatke iz ljekarničkih programa. Obrađeni podaci o potrošnji antibiotika se dostavljaju svakoj bolnici na provjeru prije nego se koriste kao službeni podaci za tu godinu.

Bolnička potrošnja antibiotika najviša je do sada bez obzira na denominator. Izražena u DDD/TID iznosi 2,18. Prije pandemije uzrokovane SARS CoV-2 virusom bolnička potrošnja se kretala između 1,65 do 1,8 DDD/TID. Najniža vrijednost potrošnje zabilježena je 2020. godine u jeku pandemije (1,61 DDD/TID) (tablica 2). Bolnička potrošnja antibiotika izražena u DDD/100 BOD

kontinuirano pokazuje trend porasta od 2014. godine, s najvišom vrijednošću prošle godine od 45,77 DDD/100BOD (tablica 10, slika 9).

U bolničkoj potrošnji se uočava porast potrošnje klase cefalosporina (J01D) i klase „ostali" (J01X). Od 2021. uočava se blagi pad potrošnje kinolona (tablica 11, slika 10).

Rang lista vodećih pet antibiotika u bolničkoj potrošnji nešto je promijenjena u poretku antibiotika, ali su svi antibiotici isti kao i prethodne godine. Ko-amoksiklav i dalje čvrsto drži vodeću poziciju (7,80 DDD/100BOD), iako s nešto manjom potrošnjom u odnosu na prethodnu godinu (8,11 DDD/100 BOD). Na drugom mjestu je ceftriakson, čija potrošnja je porasla u odnosu na godinu prije (4,98 u odnosu na 4,73 DDD/100BOD). Na trećem mjestu je došlo do promjene. Umjesto cefuroksimaksetila nalazi se metronidazol, koji se sa petog mjesta preselio na treće i bilježi veću potrošnju (3,11 DDD/100BOD) u odnosu na 3,02 DDD/100BOD godinu ranije). Zbog manje potrošnje cefuroksimaksetila u 2024. godinu (2,90 DDD/100BOD, godinu ranije 3,15 DDD/100BOD) on se preselio na četvrto mjesto, dok je ciprofloksacin također pao s četvrtog na peto mjesto zbog nešto niže potrošnje (2,86 u odnosu na 3,12 DDD/BOD) (tablica 12; slika 11).

Koristan indikator bolničke potrošnje antibiotika je 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 2024. godini došlo je do porasta udjela na 40,2%, što ukazuje na povećanje potrošnje širokospektralnih antibiotika (tablica 13, slika 12).

Trinaest **kliničkih ustanova** je dostavilo podatke o potrošnji antibiotika (tablica 14, slika 13). Raspon potrošnje antibiotika u 2024. godini kretao se od 24,09 do 176,31 DDD/100BOD (tablica 15; slika 14). Raspon potrošnje je očekivano velik, jer se radi o kliničkim ustanovama s različitim vrstama odjela i raznolikom kazuistikom.

Kod tri kliničke ustanove (K06; K11; K13) uočava se pad potrošnje antibiotika što je pad za jednu kliniku u odnosu na četiri prošle godine. Isto kao i u 2024. godini, kod pet kliničkih ustanova došlo je do porasta potrošnje (K01; K02; K04; K09; K14). Značajno je porasla potrošnja u klinici K09 (za 10,25 DDD/100BOD) i K14 (za čak 13,32 DDD/100BOD), dok je kod 5 kliničkih ustanova (K03; K05; K07, K08, K15) razlika u potrošnji manja od jednog DDD na 100 BOD u zadnje dvije godine. Kod više klinika se uočava trend porasta potrošnje antibiotika iz godine u godinu (K01; K02; K05;), ali kod dvije klinike je to osobito izraženo (K09; K14) koje bilježe skok za više od 10 DDD/100BOD. Kao dobar primjer istaknula bi kliniku 11 koja bilježi nisku potrošnju kroz godine s trendom smanjivanja potrošnje. Silazni trend u potrošnji antibiotika uočava se i kod klinike 15.

U 2024. godini 22 **opće bolnice** su dostavile svoje podatke koji su međusobno usporedivi s obzirom da se radi o najhomogenijoj skupini bolnica. Potrošnja antibiotika se kretala u širokom rasponu od 41,79-96,74 DDD/100BOD (tablica 16, slika 15), što ukazuje na velike razlike u propisivanju antibiotika među bolnicama usprkos sličnoj strukturi njihovih odjela i usluga koje pružaju.

Kod 6 bolnica bilježi se pad potrošnje antibiotika (O08; O09; O14; O17 ; O21; O24), dok je lani zabilježen kod 10 bolnica (tablica 17).

Dvostruko se povećao broj bolnica kod kojih se bilježi porast potrošnje, sa 6 na 12 bolnica. To su: O01; O02; O03; O04; O07; O11; O13; O15; O18; O20; O22; O23), a kod četiri nema razlika većih od 1 DDD/100BOD (O05; O10; O12; O19) u zadnje dvije godine.

Na slici 15 je prikazana potrošnja u općim bolnicama prema pojedinim klasama antibiotika u 2024. godini. U tablici 17 i na slici 16 prikazana je potrošnja u općim bolnicama u zadnjih osam godina što svakoj bolnici daje mogućnost praćenja vlastitih trendova potrošnje.

Opće bolnice O01; O02; O04; O07; O11; O13; O15; O18; O20; O22; O23 bilježe kontinuirani trend porasta potrošnje antibiotika u zadnje tri godine. Bolnica O15 bilježi najveći porast potrošnje u odnosu na prethodnu godinu za 12,53 DDD/100BOD.

Bolnica 014 u svim godinama praćenja potrošnje pokazuje uravnoteženu potrošnju s najmanje oscilacija kroz godine i trendom pada potrošnje u zadnjih šest godina, što je dobar primjer koji ukazuje na dobro upravljanje antibioticima u toj bolničkoj sredini.

Svega dvije bolnice imaju potrošnju u rasponu potrošnje od 41-50 DDD/100BOD, kao što je bilo i u prethodnoj godini. U osam bolnica potrošnja se kretala između 51 i 60 DDD/100BOD, što je identično prethodnoj godini. Pet bolnica je u skupini bolnica s potrošnjom od 61 do 70 DDD/100BOD, a tri u skupini od 71 do 80 DDD/100BOD. Potrošnja u tri opće bolnice se kretala između 81 do 90 DDD/100 BOD-a dok je u bolnici O13 zabilježena potrošnja od 96,74 DDD/100BOD, što je dvostruko više u odnosu na potrošnju u bolnici s najnižom potrošnjom (O19).

Potrošnja antibiotika u **psihijatrijskim bolnicama** kreće se od 0,98 do 17,54 DDD/100BOD (tablica 18). Na slici 17 prikazana je potrošnja po klasama antibiotika u psihijatrijskim bolnicama. U 2024. godini u tri psihijatrijske bolnice (P02; P04; P07) uočava se porast potrošnje, dok je u dvije bolnice (P 05; P06) potrošnja u padu. Kod četiri bolnice (P01; P03; P08; P09) nema promjena u potrošnji većoj od 1 DDD/100BOD. U tablici 19 i na slici 18 prikazana je potrošnja u psihijatrijskim bolnicama u zadnjih osam godina s uočljivim trendovima potrošnje. Psihijatrijska ustnova P02 bilježi najveći porast potrošnje za 2,57 DDD/100BOD, dok je najveći pad uočen kod psihijatrijske ustanove P06 za 5 DDD/100BOD.

Specijalne bolnice su podijeljene u dvije velike grupe 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 12,22 do 75,30 DDD/100 BOD. Dvije bolnice bilježe porast potrošnje (S22; S23). Četiri bolnice (S01; S02; S03; S04) bilježe pad potrošnje, dok kod četiri bolnice (S13; S18: S19; S21) 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 0,63 do 6,60 DDD/100BOD (tablica 21; slika 20). Niti jedna bolnica ne bilježi porast potrošnje, tri bolnice imaju nižu potrošnju, dok 11 bolnica nema razlike u potrošnji veće od 1,00 DDD/100BOD.

Na slici 19 prikazana je potrošnja antibiotika po klasama u 2024. godini. U tablici 21 i na slici 20 prikazana je potrošnja u specijalnim bolnicama u zadnjih osam godina.

Potrošnja antibiotika u bolničkom sustavu u Hrvatskoj iznosi 10% ukupne potrošnje antibiotika. Ipak, indikatori koje pratimo brinu. Na prvom mjestu je bolnička potrošnja antibiotika, koja je najveća od početka praćenja. Uz uočljive promjene u kretanju bolničke potrošnje antibiotika kroz godine praćenja, uočljiv je kontinuirani trend porasta potrošnje bez obzira na način prikazivanja potrošnje, odnosno na denominator (TID ili 100 BOD) koji se koristi za izračun potrošnje. Među prvih pet najpropisivanijih antibiotika u hrvatskim bolnicama tri su iz skupine „Watch": cefriakson, cefuroksimaksetil, ciprofloksacin. Udio potrošnje rezervnih antibiotika u ukupnoj potrošnji iznosi

40,2%, što je najviše do sada. Ciljevi Europske komisije (EK) su jasno definirani u pogledu potrošnje antibiotika do 2030. godine. Pokazatelji potrošnje antibiotika u Hrvatskoj odmiču se od postavljenih ciljeva.

Jedino koordiniranim aktivnostima svih u zdravstvenom sustavu na području bolničke higijene, na području pravilnog propisivanja antibiotika te brzom, točnom i pouzdanom mikrobiološkom dijagnostikom možemo promijeniti smjer. Praćenje antimikrobne rezistencije bakterija na antibiotike i praćenje potrošnje antibiotika uspostavljeni su u Hrvatskoj niz godina. Da bismo mogli napredovati i doseći ciljeve Europske komisije do 2030. godine (smanjenje ukupne potrošnje antibiotika na 17,1 DDD/TID, povećanje udjela antibiotika u skupini „Access" na ≥ 65%) imperativ je uspostavljanje rukovođenog propisivanja antibiotika u svakoj bolnici i u izvanbolničkoj praksi propisivanja antibiotika.

ANTIBIOTIC CONSUMPTION IN CROATIAN HOSPITALS

Antibiotic consumption in hospitals is monitored separately from the one in outpatient environment. Up to 2011 it was tracked exclusively through data obtained from pharmaceutical wholesalers, but ever since the Interdisciplinary Section for Resistance Control (ISKRA) was established within the Ministry of Health in 2011, all hospitals submit consumption data obtained through their pharmacies. In that way, use of antibiotics in hospitals is tracked via two sources – wholesale and hospital pharmacies.

Data obtained through hospital pharmacies is the official data on consumption of antibiotics in hospitals, and as such is submitted to the European consumption surveillance portal EpiPulse which replaced TESSy as of this year (Table 2).

As far as methodology is concerned, hospitals submit consumption data in packages or units along with administrative data on the number of hospital bed days (BDs) and the number of admissions both for the entire hospital as well as separately for intensive care units (ICUs) by type (mixed, surgical, internal medicine, paediatric). From 2011, the monitoring of hospital consumption has also included the 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 in accordance with the ATC classification at the fifth level and displayed at the third and fourth levels.

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

From 2011, the use of antibiotics in hospitals has been monitored through data provided by both hospital pharmacies and administrative data for each hospital in Croatia. This means that consumption can also be expressed in more advantageous DDD/BDs, since it is more objective and precise than DDD/TID, enabling detailed analysis of consumption by classes and kinds of antibiotics on national level, as well as separately for each hospital.

Table 9 and Figure 8 juxtapose data obtained from both sources since 2014. Based on the data from hospital pharmacies, higher consumption was recorded (except in 2015) as well as an increased difference in consumption favouring hospitals. In 2024, this difference was the highest so far, amounting to 0.75 DDD/TID, which is considerably more than the year before when it was 0.37 DDD/TID (Table 9; Figure 8). Bearing in mind that all antibiotics used in hospitals are supplied by pharmaceutical wholesalers, it is hard to explain this discrepancy which increased significantly for the first time in 2021 at 0.35 DDD/TID, and ever since either grew or remained stable up to 2024, depending on the source of data.

Sixty-eight hospitals submitted data on antibiotic consumption in 2024 electronically to iskra.antibiotici@gmail.com. As in previous years, only 4 hospitals exported data directly from their pharmacy programs. Processed data is later returned to each hospital for checking before being used as the official data for that year.

Consumption of antibiotics in hospitals reached its highest point ever, regardless of the denominator. Expressed in DDD/TID, it amounted to 2.18. Prior to SARS CoV-2 pandemic, it ranged from 1.65 to 1.8 DDD/TID. During the pandemic, in 2020, the lowest value ever was recorded (1.61 DDD/TID) (Table 2). Usage of antibiotics in hospitals, expressed in DDD/100 BDs, grew steadily from 2014, reaching its peak last year at 45.77 DDD/100 BDs (Table 10; Figure 9).

Hospital consumption saw an increase in cephalosporin class (J01D) and the "other" class (J01X). Since 2021, there has been a slight decline in the usage of quinolones (Table 11; Figure 10).

The ranking of the top five antibiotics somewhat changed from the year before. Co-amoxiclav continued to hold the leading position with 7.80 DDD/100BDs, a slightly lower value than the previous year (8.11 DDD/100 BDs). In the second place was cefriaxone, whose consumption increased in comparison with the preceding year (4.98 vs 4.73 DDD/100 BDs). There was a change in the third place: instead of cefuroxime axetil, there was metronidazole which jumped from the fifth into the third place, having recorded higher consumption (3.11 DDD/100 BDs) than the year before (3.02 DDD/100 BDs). 2024 saw a decline in the usage of cefuroxime axetil (2.90 from previous 3.15 DDD/100 BDs) so it dropped into the fourth place, thus pushing ciprofloxacin down into the fifth position (2.86 from 3.12 DDD/100 BDs) (Table 12; Figure 11).

Useful indicator of usage of reserve antibiotics is the proportion of glycopeptides (J01XA), third-generation cephalosporins (J01DD), fourth generation cephalosporins (J01DE), monobactams (J01DF), carbapenems (J01DH), flouroquinolones (J01MA), polymyxins (J01XB), piperacillin+tazobactam (J01CR05), linezolid (J01XX08), tedizolid (J01XX11), and daptomycin (J01XX09) consumption out of total hospital consumption. In 2024, their share increased to 40.2%, reflecting higher usage of broad-spectrum antibiotics (Table 13; Figure 12).

Thirteen **clinics** submitted their antibiotic consumption data (Table 14; Figure 13), which in 2024 varied from 24.09 to 176.31 DDD/100 BDs (Table 15, Figure 14). Such a wide range was to be expected, as these are clinics with different kinds of departments and casuistry.

Three clinics (C06; C11; C13) showed decrease in antibiotic consumption, unlike the year before when there were four. As in 2024, five clinics (C01; C02; C04; C09; C14) saw increased use of antibiotics, the most prominent growth being at clinics C09 (by 10.25 DDD/100 BDs) and C14 (by even 13.32 DDD/100 BDs). At five clinics (C03; C05; C07; C08; C15) the difference in consumption was below 1 DDD per 100 BDs over the past two years. An upward trend in consumption has been noticed at more clinics over the last few years (C01; C02; C05), but it was most pronounced at two of them (C09; C14) where it surged by more than 10 DDD/100 BDs. On the other hand, there is a praiseworthy example of clinic C11 where consumption has been in decline over the years, just as at clinic C15 which also recorded a downward trend in the usage of antibiotics.

In 2024, 22 **general hospitals** submitted their consumption data, which is commensurable since this is the most homogeneous group of hospitals. Their use of antibiotics ranged widely from 41.79 to 96.74 DDD/100 BDs (Table 16, Figure 15), which reflects significant variations in antibiotic prescribing practices among the hospitals, despite similar structure of their departments and services they provide.

6 hospitals recorded a decrease in the use of antibiotics (G08; G09; G14; G17; G21; G24) while there were 10 the year before (Table 17).

The number of hospitals with higher consumption doubled, from 6 to 12. These are G01; G02; G03; G04; G07; G11; G13; G15; G18; G20; G22; G23, while in the remaining four (G05; G10; G12; G19) the difference was less than 1 DDD/ 100 BDs over the last two years.

Figure 15 shows consumption in general hospitals by individual classes of antibiotics in 2024. Table 17 and Figure 16 show their usage in general hospitals over the past eight years, allowing each hospital to track its own consumption trends.

General hospitals G01; G02; G04; G07; G11; G13; G15; G18; G20; G22; G23 have recorded a steady upward trend in the use of antibiotics over the past three years. Hospital G15 saw the highest increase in consumption compared to the year before – by 12.53 DDD/100 BDs.

Hospital G14 has shown the most consistent consumption with least oscillations through all the years of monitoring, with a downward trend noticeable over the last six years, which reflects good antibiotic stewardship in that particular hospital.

As in the preceding year, only two hospitals show a consumption range between 41 and 50 DDD/100 BDs. In eight of them the usage varied from 51 to 60 DDD/100 BDs, the same as the year before. Five hospitals make up the group with consumption range between 61 and 70 DDD/100 BDs, while there are three within 71-80 DDD/100 BDs span. Furthermore, in three hospitals the usage fluctuated between 81 and 90 DDD/100 BDs, whereas hospital G13 recorded 96.74 DDD/100 BDs, the double that of the hospital G19 with the lowest consumption noted.

As far as **psychiatric hospitals** are concerned, antibiotic consumption ranged from 0.98 to 17.54 DDD/100 BDs (Table 18). Figure 17 details the usage by classes of antibiotics. In 2024, three psychiatric hospitals (P02; P04; P07) saw a rise in consumption unlike hospitals P05 and P06 where there was a decline. In four other hospitals (P01; P03; P08; P09) there were no greater changes than 1 DDD/100 BDs. Table 19 and Figure 18 show the usage of antibiotics in psychiatric hospitals over the past eight years, with some noticeable consumption trends. Hospital P02 recorded the largest increase – that of 2.57 DDD/100 BDs, while P06 saw the biggest drop in consumption, by 5 DDD/100 BDs.

Specialty hospitals are divided into two large groups based on their focus, and as such, they show large variations in the use of antibiotics. The first group consists of 10 hospitals dedicated to treatment (acute/chronic), while the second includes 14 rehabilitation facilities (Table 20; Figure 19). In the first group, the range of antibiotic consumption varied from 12.22 to 75.30 DDD/100 BDs. Two (S22; S23) recorded an increase, four a decrease (S01; S02; S03; S04) and in the remaining four (S13; S18; S19; S21) there were no differences in consumption exceeding 1 DDD/100 BDs (Table 21; Figure 20).

In the group consisting of rehabilitation facilities, antibiotic use was significantly lower, ranging from 0.63 to 6.60 DDD/100 BDs (Table 21; Figure 20). None of these hospitals saw a rise in consumption: it was lower in three of them, while in the remaining 11 dissimilarity was less than 1 DDD/100 BDs.

Figure 19 details usage of antibiotics by class in 2024. Table 21 and Figure 20 show consumption in specialty hospitals over the past eight years.

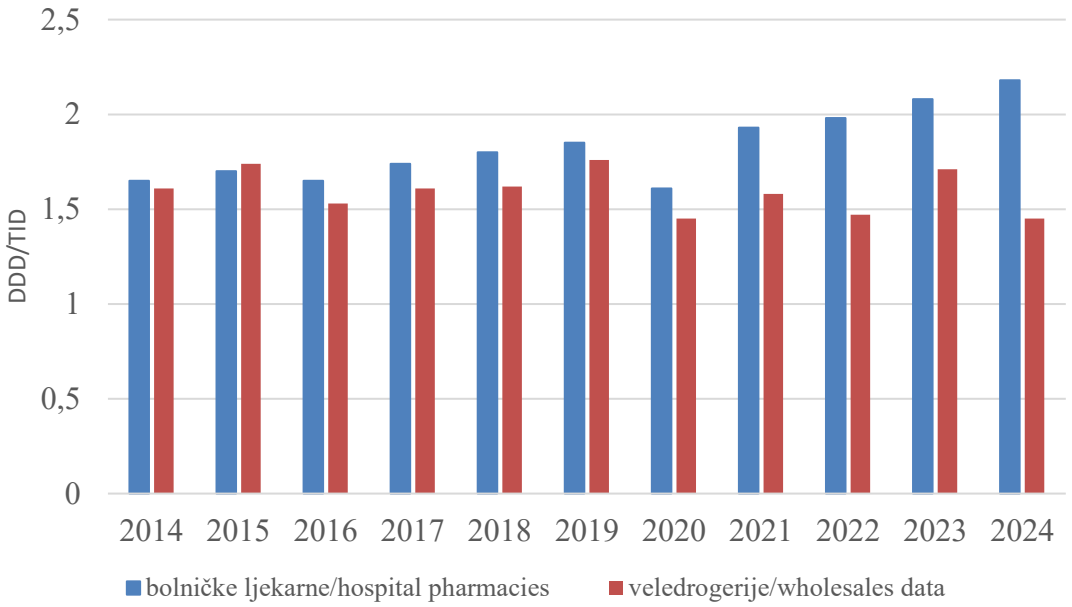
Amount of antibiotics used in Croatian hospitals accounts for 10% of their total consumption. Nevertheless, the indicators that we are monitoring are unsettling. Firstly, hospital antibiotic consumption is at its highest level since the monitoring started. Besides noticeable fluctuations in consumption levels over the years, there is a distinctive, consistently upward trend in the use of antibiotics, regardless of the way it is expressed, i.e. a denominator used in calculations (TID or 100 BDs). Among five most frequently prescribed antibiotics in Croatian hospitals, three are from the "Watch" group: cefriaxone, cefuroxime axetil and ciprofloxacin. The share of reserve antibiotics in overall consumption reached 40.2%, the highest value ever. The aims set by the European Commission (the EC) regarding consumption of antibiotics are clearly defined by 2030. However, indicators of their usage in Croatia are deviating from these targets.

This can be changed only through coordinated action across the healthcare system, encompassing hospital hygiene, appropriate antibiotic prescribing, as well as rapid, accurate and reliable microbiological diagnostics. Monitoring of both antimicrobial resistance in bacteria and antibiotic consumption has been conducted in Croatia for many years. In order to make progress and meet the European Commission targets by 2030 – reducing total antibiotic consumption to 17.1 DDD/TID and increasing the share of antibiotics in the "Access" group to ≥ 65% - it is essential to implement antibiotic stewardship in every hospital as well as in outpatient setting.

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
2024	2,18	1,45

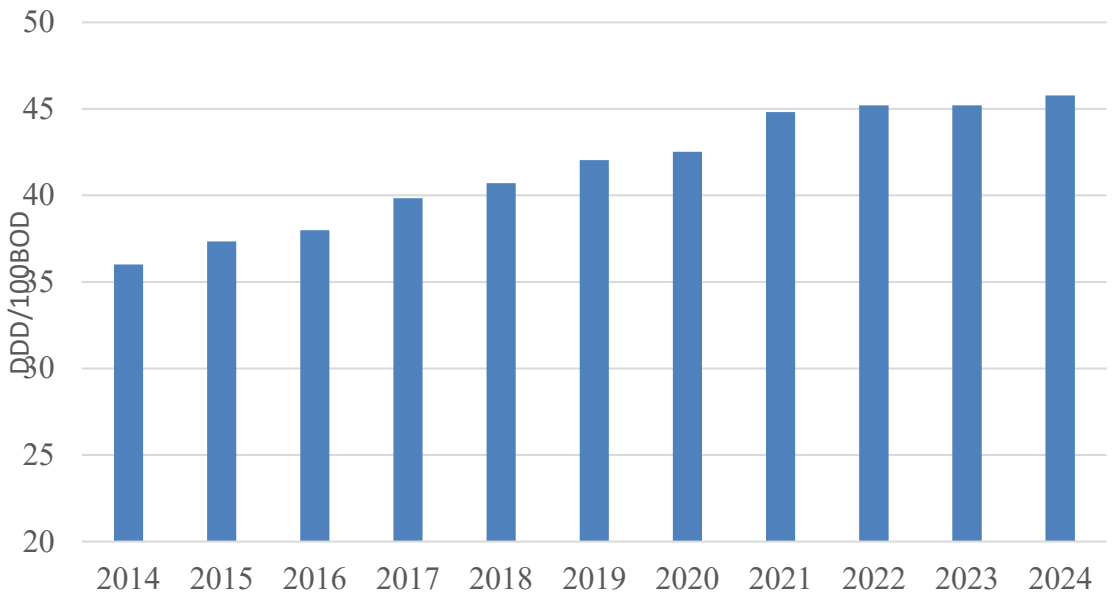
Slika 8. */ Figure 8.*
Bolnička potrošnja antibiotika (DDD/TID) usporedba podataka bolničkih ljekarni i veledrogerija/
Hospital antibiotic consumption (DDD/TID) comparison between hospital pharmacy data and wholesales data



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

Godina / *year*	DDD/100 BOD / *DDD/100 BD*
2014	36,01
2015	37,35
2016	37,99
2017	39,84
2018	40,70
2019	42,05
2020	42,52
2021	44,81
2022	45,20
2023	45,20
2024	45,77

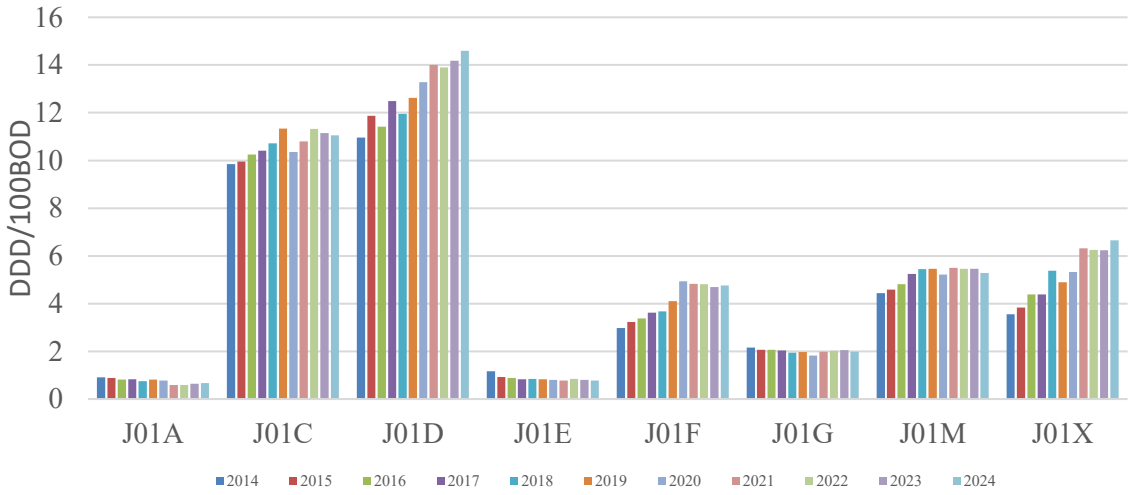
Slika 9. */ Figure 9.*
Bolnička potrošnja antibiotika (DDD/100 BOD)
Hospital antibiotic consumption (DDD/100 BD)



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	2024
J01A	0,91	0,88	0,81	0,83	0,75	0,82	0,77	0,59	0,59	0,65	0,67
J01C	9,85	9,96	10,25	10,41	10,72	11,34	10,36	10,80	11,32	11,14	11,05
J01D	10,96	11,87	11,41	12,49	11,95	12,63	13,29	14,01	13,90	14,17	14,59
J01E	1,17	0,93	0,88	0,83	0,85	0,83	0,81	0,78	0,84	0,80	0,78
J01F	2,97	3,23	3,38	3,62	3,68	4,11	4,93	4,83	4,81	4,69	4,76
J01G	2,16	2,07	2,07	2,04	1,94	1,97	1,82	1,98	2,02	2,05	1,99
J01M	4,44	4,58	4,81	5,24	5,44	5,46	5,22	5,50	5,46	5,46	5,28
J01X	3,55	3,84	4,38	4,38	5,38	4,90	5,33	6,32	6,25	6,24	6,65

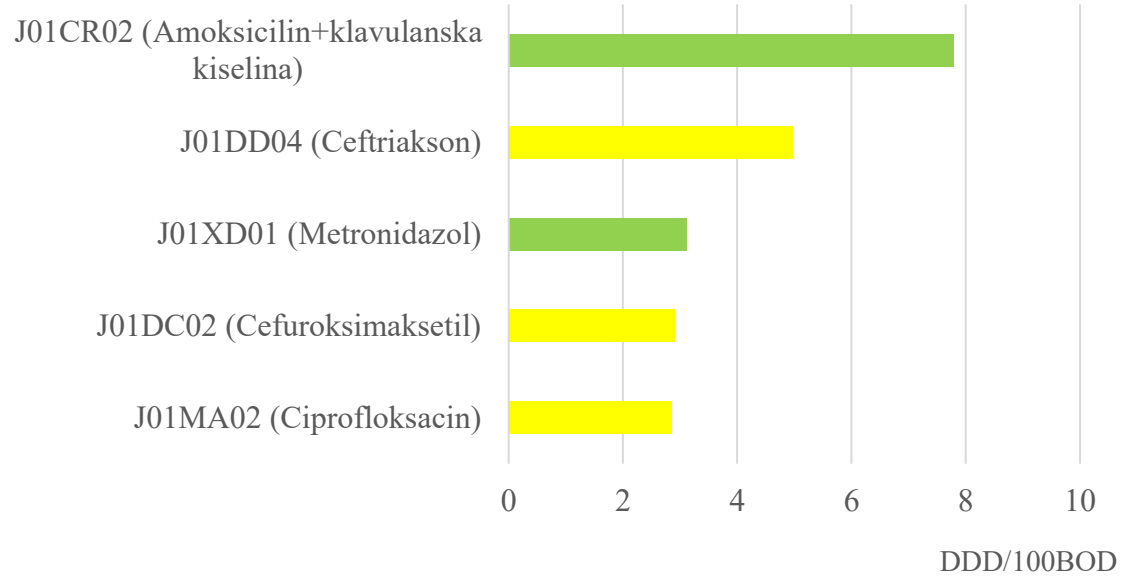
Slika 10. */ Figure 10.*
Bolnička potrošnja antibiotika (DDD/100 BOD) po klasama, izvor podataka – bolničke ljekarne/
Hospital antibiotic consumption (DDD/100 BD) by class, origin of data - hospital pharmacies



Tablica 12. */ Table 12.*
Bolnička potrošnja antibiotika „top 5“ antibiotika – DDD/100 BOD, izvor podataka – bolničke ljekarne, zeleno polje označava antibiotik iz skupine “Access”, žuto polje označava antibiotik iz skupine“Watch”/
Hospital antibiotic consumption „top 5“antibiotics – DDD/100 BD; origin of data - hospital pharmacies, green field indicates an antibiotic from the group Access, yellow field indicates an antibiotic from the group Watch

Klasa / class	DDD/100 BOD / *DDD/100 BD*
J01CR02 (Amoksicilin+klavulanska kiselina)	7,80
J01DD04 (Ceftriakson)	4,98
J01XD01 (Metronidazol)	3,11
J01DC02 (Cefuroksimaksetil)	2,90
J01MA02 (Ciprofloksacin)	2,86

Slika 11. */ Figure 11.*
Bolnička potrošnja antibiotika „top 5“ antibiotika – DDD/100 BOD, izvor podataka – bolničke ljekarne / zelena traka označava antibiotik iz skupine “Access”, žuta traka označava antibiotik iz skupine“Watch”/
Hospital antibiotic consumption „top 5“antibiotics – DDD/100 BD; origin of data - hospital pharmacies, green bar indicates an antibiotic from the group Access, yellow bar indicates an antibiotic from the group Watch



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 2010-2024/

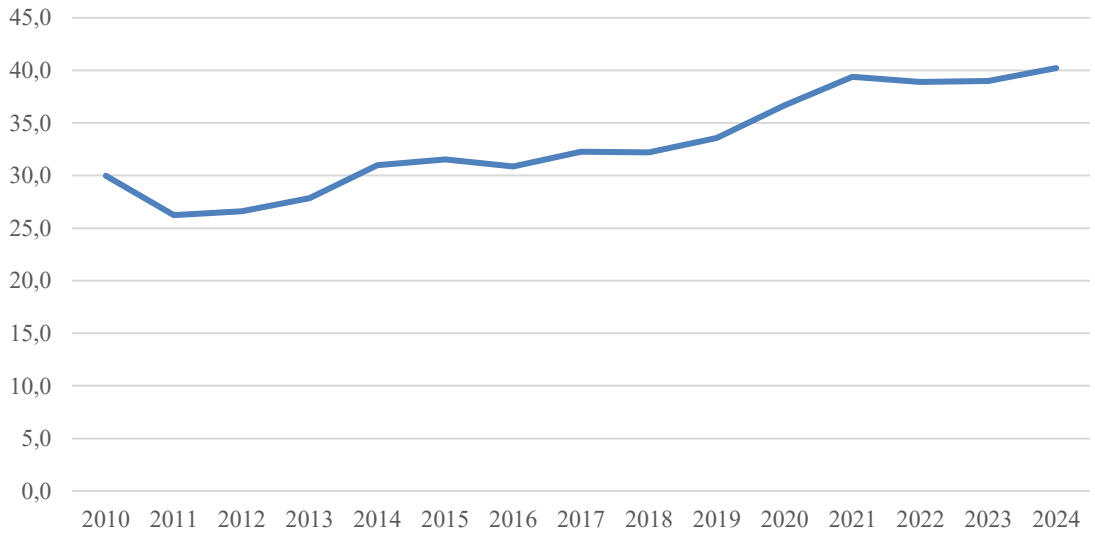
The proportion of glycopeptides (J01XA), third-generation cephalosporin*s (J01DD), fourth-generation cephalosporins*, (J01DE), monobactams* (J01DF), carbapenems* (J01DH), fluoroquinolones* (J01MA), polymyxins* (J01XB), piperacillin and tazobactam* (J01CR05), linezolid* (J01XX08), tedizolid* (J01XX11) and daptomycin* (J01XX09) consumption out of total consumption of antibacterials for systemic use in the hospital (DDD/ TID) 2010-2024*

	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
2024	40,2

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 2010-2024/

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) 2010-2024

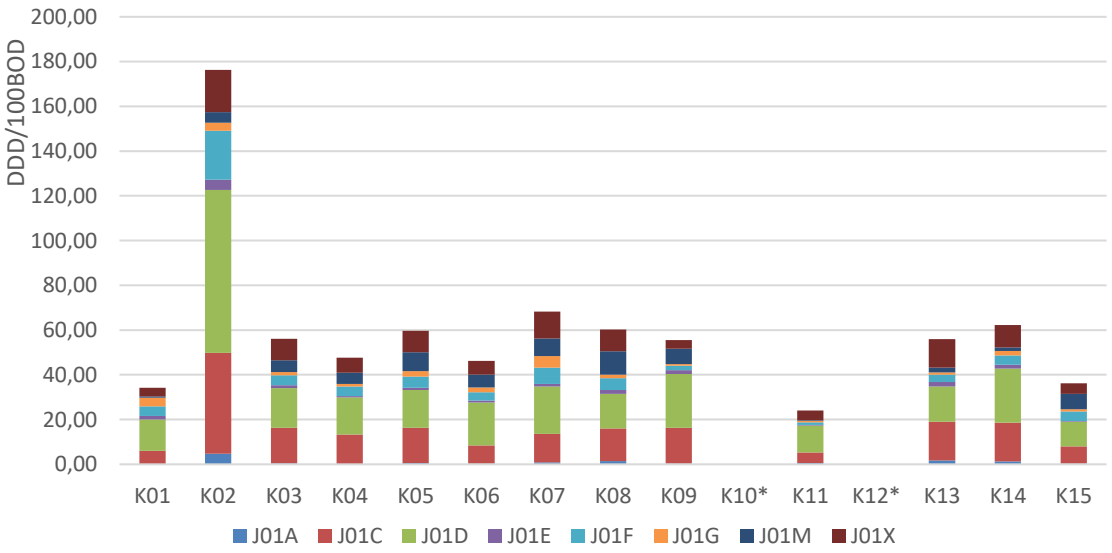


Tablica 14. */ Table 14.*
Kliničke ustanove - potrošnja antibiotika 2024. /
Clinical insitutions – antibiotic consumption in 2024

	DDD/100 BOD, DDD/100 BD								
USTANOVA INSTITUTION	UKUPNO TOTAL	J01A	J01C	J01D	J01E	J01F	J01G	J01M	J01X
K 01	34,27	0,05	6,02	13,93	1,67	4,20	3,96	0,52	3,93
K 02	176,31	4,79	44,98	72,83	4,57	21,94	3,56	4,80	18,85
K 03	56,08	0,40	15,92	17,69	1,27	4,53	1,34	5,34	9,59
K 04	47,64	0,13	13,21	16,51	0,66	4,33	1,14	4,96	6,70
K 05	59,73	0,65	15,67	16,91	0,93	4,99	2,46	8,50	9,62
K 06	46,24	0,27	8,14	19,24	0,84	3,73	2,11	5,77	6,13
K 07	68,25	0,87	12,67	21,26	1,07	7,39	5,13	7,87	11,99
K 08	60,25	1,42	14,59	15,49	1,66	5,39	1,54	10,38	9,77
K 09	55,48	0,23	16,11	24,08	1,61	2,08	0,72	6,89	3,76
K 10*									
K 11	24,09	0,52	4,79	12,00	0,29	1,10	0,72	0,26	4,41
K 12*									
K 13	56,02	1,65	17,41	15,77	1,94	3,32	1,02	2,11	12,80
K 14	62,24	1,22	17,42	24,12	1,67	4,28	1,95	1,60	9,97
K 15	36,14	0,30	7,67	11,10	0,32	4,23	1,01	6,79	4,72

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

Slika 13. */ Figure 13.*
Kliničke ustanove - potrošnja antibiotika 2024. /
Clinical insitutions – antibiotic consumption in 2024

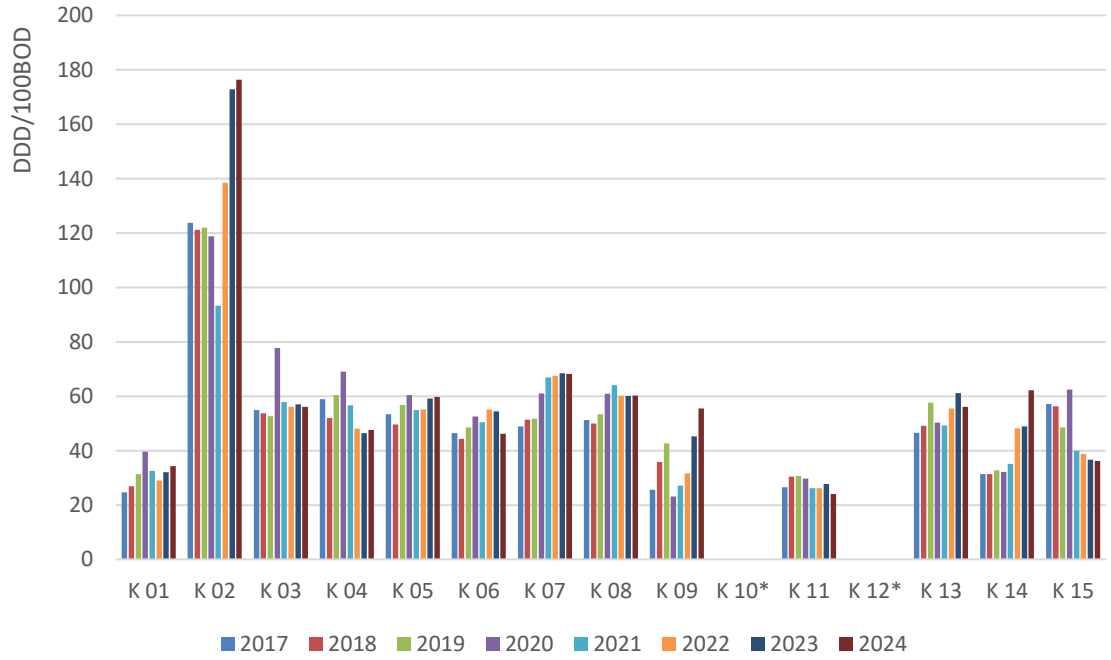


Tablica 15. */ Table 15.*
Kliničke ustanove - potrošnja antibiotika 2017-2024. /
Clinical insitutions – antibiotic consumption in 2017-2024

	DDD/100 BOD, DDD/100BD							
USTANOVA INSTITUTION	2017	2018	2019	2020	2021	2022	2023	2024
K 01	24,7	26,9	31,3	39,64	32,53	28,97	32,08	34,27
K 02	123,7	121,2	122,0	118,77	93,21	138,50	172,81	176,31
K 03	54,9	53,7	52,7	77,76	57,86	56,11	57,06	56,08
K 04	58,9	52,0	60,4	69,01	56,69	48,05	46,43	47,64
K 05	53,4	49,6	56,8	60,47	54,86	55,08	59,13	59,73
K 06	46,4	44,3	48,5	52,54	50,39	55,12	54,47	46,24
K 07	48,9	51,4	51,7	61,03	66,95	67,51	68,39	68,25
K 08	51,2	50,0	53,4	60,94	64,08	60,02	60,06	60,25
K 09	25,6	35,8	42,6	23,12	27,13	31,57	45,23	55,48
K 10*								
K 11	26,5	30,4	30,7	29,71	26,17	26,19	27,68	24,09
K 12*								
K 13	46,5	49,1	57,6	50,34	49,30	55,53	61,16	56,02
K 14	31,3	31,4	32,8	32,15	35,18	48,23	48,92	62,24
K 15	57,1	56,3	48,5	62,38	39,97	38,76	36,62	36,14

* 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.-2024. /
Clinical insitutions – antibiotic consumption in 2017-2024

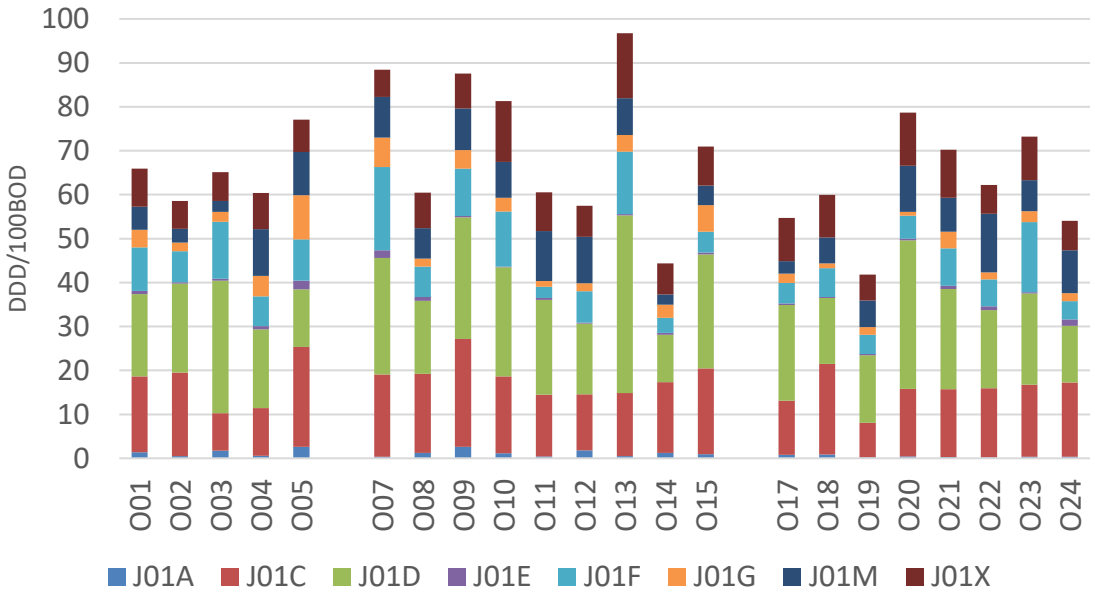


Tablica 16. */ Table 16.*
Opće bolnice - potrošnja antibiotika 2024. /
General hospitals – antibiotic consumption in 2024

USTANOVA INSTITUTION	UKUPNO TOTAL	DDD/100 BOD, DDD/100 BD							
		J01A	J01C	J01D	J01E	J01F	J01G	J01M	J01X
O 01	65,95	1,34	17,30	18,70	0,77	9,89	4,00	5,27	8,69
O 02	58,54	0,48	19,06	20,19	0,30	7,12	1,91	3,19	6,29
O 03	65,09	1,74	8,49	30,19	0,44	12,96	2,29	2,49	6,50
O 04	60,37	0,58	10,87	17,87	0,75	6,78	4,69	10,61	8,23
O 05	77,04	2,59	22,75	13,14	1,94	9,40	10,09	9,80	7,33
O 06*									
O 07	88,41	0,36	18,70	26,57	1,73	18,95	6,68	9,24	6,19
O 08	60,48	1,23	18,01	16,57	0,89	6,90	1,84	6,96	8,08
O 09	87,58	2,59	24,61	27,62	0,33	10,75	4,26	9,48	7,96
O 10	81,34	1,15	17,50	24,81	0,21	12,46	3,19	8,15	13,88
O 11	60,56	0,43	14,08	21,55	0,40	2,56	1,30	11,38	8,85
O 12	57,46	1,84	12,75	16,05	0,27	7,13	1,81	10,57	7,05
O 13	96,74	0,50	14,35	40,46	0,30	14,17	3,78	8,38	14,79
O 14	44,38	1,26	16,10	10,72	0,47	3,46	2,93	2,33	7,12
O 15	70,95	0,90	19,57	25,97	0,41	4,75	6,00	4,48	8,88
O 16**									
O 17	54,70	0,81	12,27	21,80	0,40	4,66	2,11	2,81	9,84
O 18	59,95	0,83	20,65	14,98	0,25	6,52	1,15	5,86	9,71
O 19	41,79	0,22	7,87	15,34	0,29	4,37	1,74	6,10	5,86
O 20	78,66	0,42	15,41	33,78	0,37	5,22	0,88	10,52	12,05
O 21	70,24	0,27	15,46	22,83	0,68	8,57	3,76	7,72	10,95
O 22	62,21	0,24	15,71	17,75	0,89	6,14	1,59	13,29	6,59
O 23	73,22	0,37	16,37	20,74	0,35	15,94	2,44	7,09	9,91
O 24	54,03	0,37	16,92	12,87	1,44	4,21	1,79	9,77	6,68

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

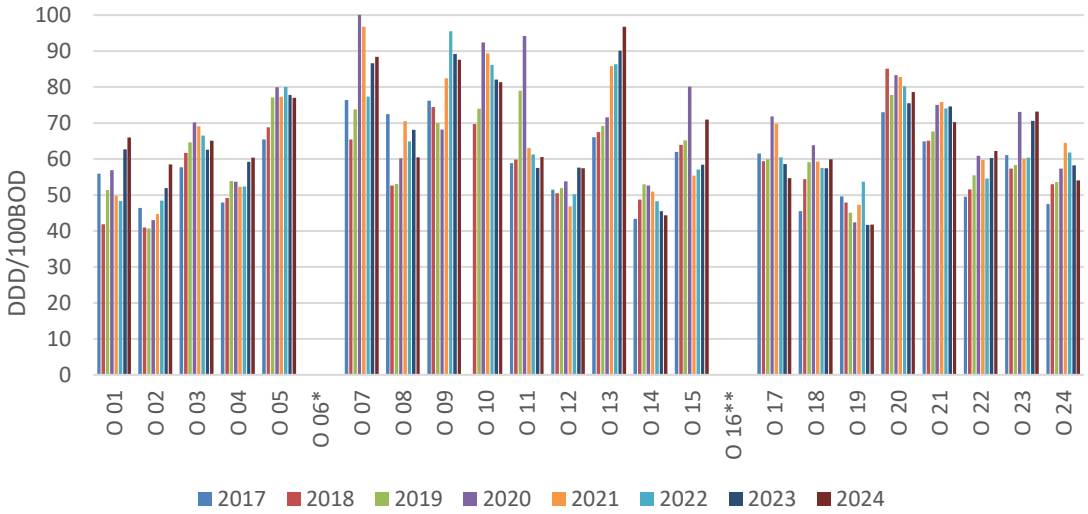
Slika 15. */ Figure 15.*
Opće bolnice - potrošnja antibiotika 2024. /
General hospitals – antibiotic consumption 2024



Tablica 17. */ Table 17.*
Opće bolnice - potrošnja antibiotika 2017.-2024. /
General hospitals – antibiotic consumption in 2017-2024

USTANOVA INSTITUTION	DDD/100 BOD, DDD/100 BD							
	2017	2018	2019	2020	2021	2022	2023	2024
O 01	55,9	41,9	51,4	56,92	49,81	48,36	62,69	65,95
O 02	46,4	41,0	40,7	42,98	44,71	48,46	51,90	58,54
O 03	57,7	61,7	64,6	70,15	69,12	66,48	62,64	65,09
O 04	47,9	49,2	53,9	53,66	52,26	52,37	59,17	60,37
O 05	65,4	68,8	77,1	79,98	77,31	80,08	77,83	77,04
O 06*								
O 07	76,4	65,4	73,8	100,11	96,75	77,38	86,65	88,41
O 08	72,5	52,6	53,1	60,18	70,51	64,95	68,12	60,48
O 09	76,2	74,4	70,0	68,19	82,43	95,55	89,19	87,58
O 10	0,00	69,7	74,0	92,41	89,37	86,15	82,09	81,34
O 11	58,9	59,8	79,0	94,17	63,03	61,27	57,53	60,56
O 12	51,5	50,5	51,9	53,77	46,83	50,26	57,62	57,46
O 13	66,1	67,5	69,2	71,55	85,86	86,37	90,06	96,74
O 14	43,4	48,7	53,0	52,65	50,97	48,27	45,48	44,38
O 15	62,0	63,9	65,2	80,11	55,40	57,11	58,42	70,95
O 16**								
O 17	61,5	59,4	59,9	71,87	69,77	60,42	58,61	54,70
O 18	45,5	54,4	59,1	63,85	59,29	57,53	57,47	59,95
O 19	49,6	47,9	45,1	42,42	47,27	53,74	41,69	41,79
O 20	73,0	85,1	77,8	83,33	82,76	80,25	75,48	78,66
O 21	64,9	65,1	67,7	75,03	75,84	74,11	74,57	70,24
O 22	49,5	51,6	55,5	60,88	59,77	54,58	60,25	62,21
O 23	61,1	57,3	58,3	73,12	60,10	60,39	70,64	73,22
O 24	47,5	53,0	53,6	57,34	64,46	61,77	58,22	54,03

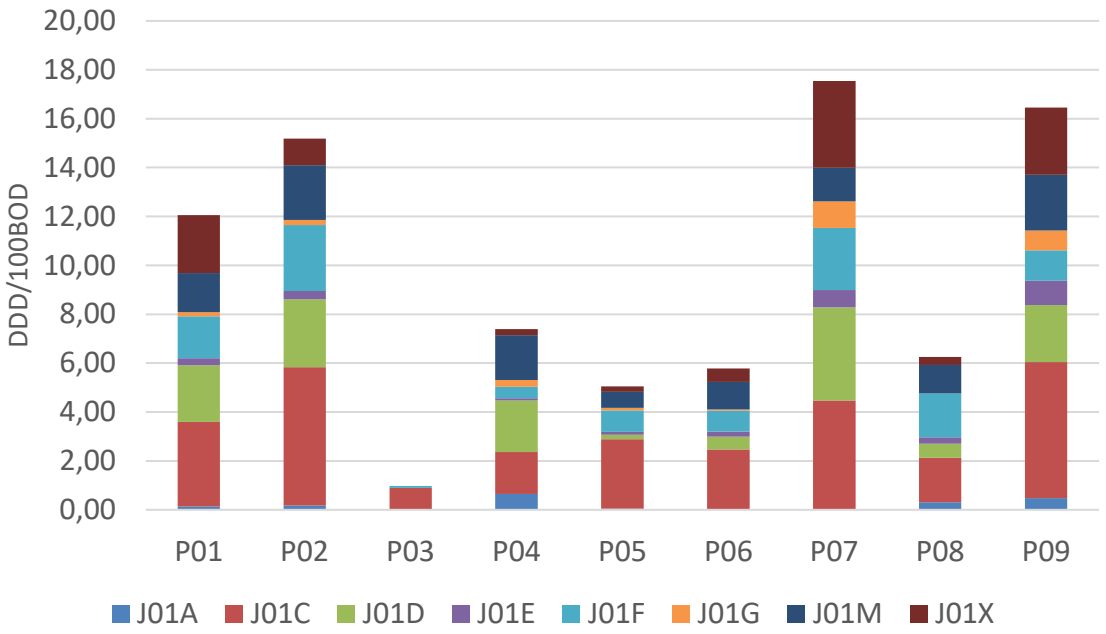
Slika 16. */ Figure 16.*
Opće bolnice - potrošnja antibiotika 2017.-2024. /
General hospitals – antibiotic consumption 2017-2024



Tablica 18. */ Table 18.*
Psihijatrijske ustanove - potrošnja antibiotika 2024. /
Psychiatric institutions – antibiotic consumption in 2024

USTANOVA INSTITUTION	DDD/100 BOD, DDD/100 BD								
	UKUPNO / TOTAL	J01A	J01C	J01D	J01E	J01F	J01G	J01M	J01X
P 01	12,05	0,13	3,47	2,31	0,30	1,72	0,17	1,59	2,37
P 02	15,19	0,18	5,66	2,78	0,33	2,70	0,22	2,24	1,09
P 03	0,98		0,89			0,09			
P 04	7,39	0,65	1,71	2,11	0,09	0,47	0,27	1,84	0,24
P 05	5,05	0,04	2,85	0,18	0,12	0,88	0,10	0,65	0,23
P 06	5,78	0,04	2,43	0,53	0,20	0,86	0,05	1,12	0,55
P 07	17,54		4,47	3,82	0,70	2,54	1,08	1,39	3,54
P 08	6,25	0,31	1,81	0,58	0,27	1,79		1,16	0,33
P 09	16,45	0,48	5,57	2,33	0,99	1,24	0,81	2,28	2,74

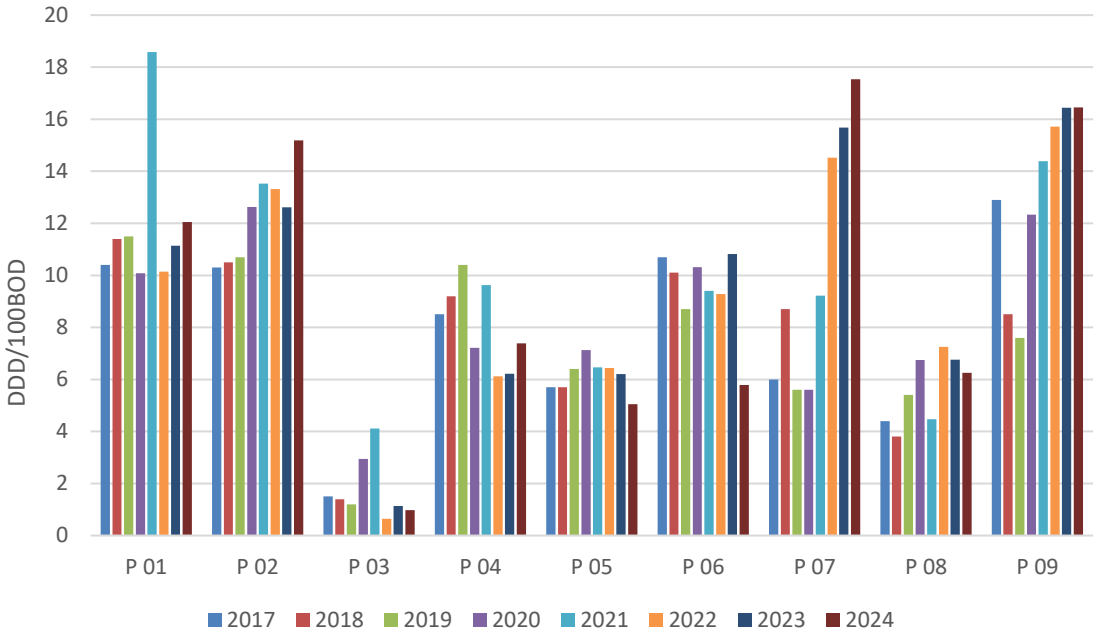
Slika 17. / *Figure 17.*
Psihijatrijske ustanove - potrošnja antibiotika 2024. /
Psychiatric institutions – antibiotic consumption 2024



Tablica 19. / *Table 19.*
Psihijatrijske ustanove - potrošnja antibiotika 2017.-2024. /
Psychiatric institutions – antibiotic consumption in 2017-2024

USTANOVA INSTITUTION	DDD/100 BOD, DDD/100BD							
	2017	2018	2019	2020	2021	2022	2023	2024
P 01	10,4	11,4	11,5	10,08	18,58	10,14	11,13	12,05
P 02	10,3	10,5	10,7	12,63	13,53	13,31	12,62	15,19
P 03	1,5	1,4	1,2	2,95	4,11	0,65	1,13	0,98
P 04	8,5	9,2	10,4	7,21	9,62	6,12	6,22	7,39
P 05	5,7	5,7	6,4	7,13	6,46	6,44	6,21	5,05
P 06	10,7	10,1	8,7	10,31	9,40	9,28	10,82	5,78
P 07	6,0	8,7	5,6	5,60	9,22	14,52	15,68	17,54
P 08	4,4	3,8	5,4	6,75	4,47	7,25	6,76	6,25
P 09	12,9	8,5	7,6	12,33	14,39	15,71	16,44	16,45

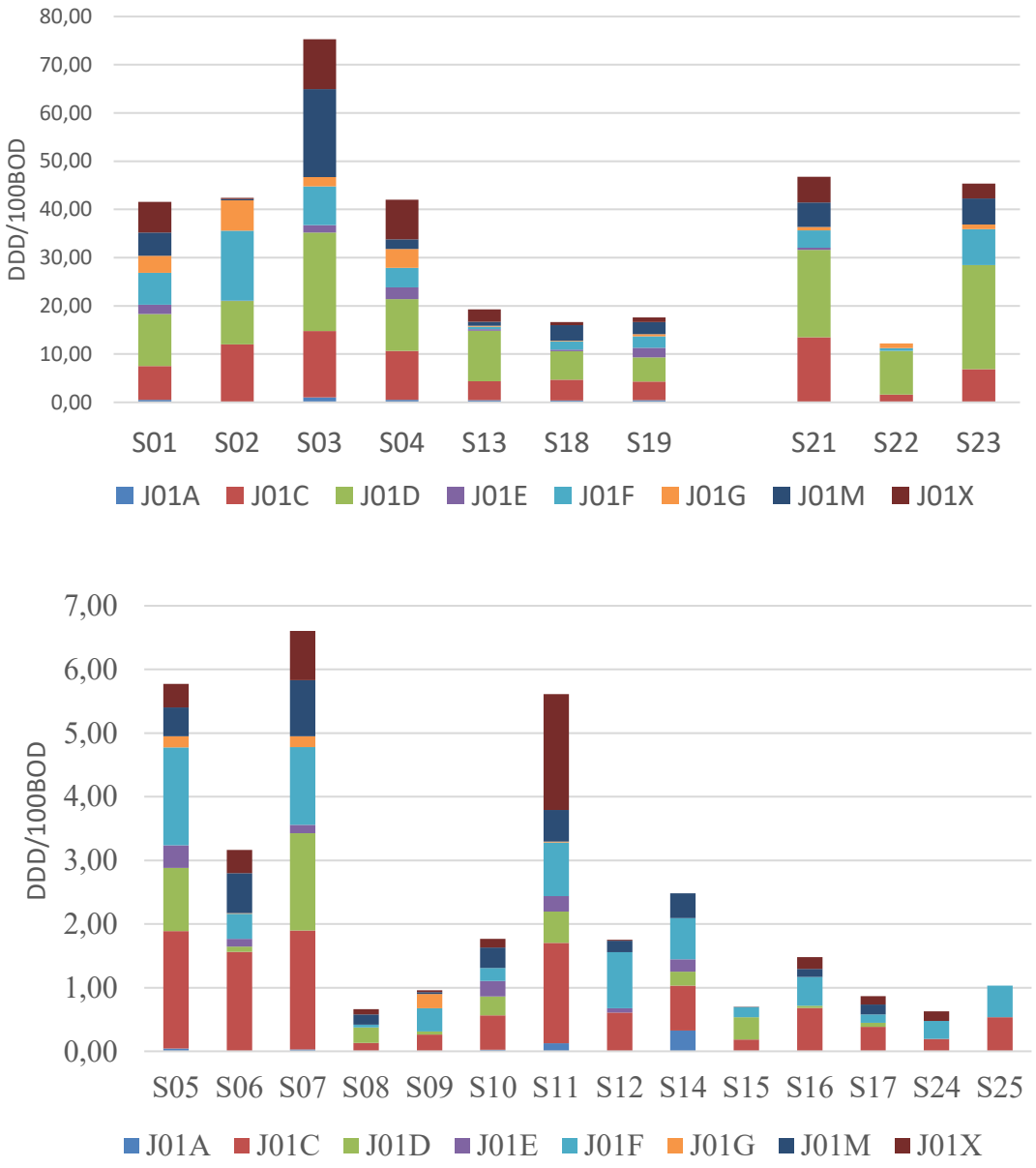
Slika 18. / *Figure 18.*
Psihijatrijske ustanove - potrošnja antibiotika 2017.-2024. /
Psychiatric institutions – antibiotic consumption 2017-2024



Tablica 20. */ Table 20.*
Specijalne bolnice - potrošnja antibiotika 2024. /
Specialty hospitals – antibiotic consumption in 2024

	DDD/100 BOD, DDD/100 BD								
USTANOVA INSTITUTION	UKUPNO TOTAL	J01A	J01C	J01D	J01E	J01F	J01G	J01M	J01X
S 01	41,55	0,52	7,03	10,75	1,96	6,57	3,53	4,88	6,32
S 02	42,42		12,02	8,98	0,04	14,58	6,27	0,22	0,30
S 03	75,30	1,06	13,73	20,45	1,51	8,02	1,94	18,23	10,37
S 04	41,99	0,55	10,10	10,73	2,48	4,01	3,94	1,98	8,19
S 13	19,31	0,45	3,92	10,45	0,36	0,48	0,19	0,83	2,62
S 18	16,61	0,38	4,32	5,92	0,29	1,78	0,07	3,26	0,59
S 19	17,62	0,46	3,87	5,02	1,94	2,39	0,45	2,52	0,96
S 20*									
S 21	46,76		13,48	18,15	0,40	3,64	0,70	5,06	5,32
S 22	12,22		1,60	9,05		0,60	0,97		
S 23	45,35		6,87	21,58		7,46	1,01	5,36	3,08
S 05	5,77	0,04	1,84	0,99	0,36	1,54	0,17	0,45	0,37
S 06	3,16		1,56	0,08	0,12	0,39	0,01	0,63	0,36
S 07	6,60	0,03	1,87	1,52	0,13	1,22	0,17	0,88	0,77
S 08	0,66		0,13	0,24		0,05		0,16	0,08
S 09	0,96		0,26	0,05		0,37	0,22	0,03	0,03
S10	1,77	0,02	0,54	0,29	0,24	0,21		0,32	0,14
S11	5,61	0,12	1,58	0,49	0,24	0,84	0,02	0,49	1,82
S12	1,75		0,61		0,07	0,88		0,18	0,02
S14	2,48	0,33	0,71	0,22	0,20	0,65		0,39	
S15	0,70		0,18	0,35		0,16			0,01
S16	1,48		0,68	0,04		0,45		0,12	0,18
S17	0,87		0,39	0,06		0,13		0,15	0,13
S24	0,63		0,19			0,28			0,15
S25	1,03		0,54			0,50			

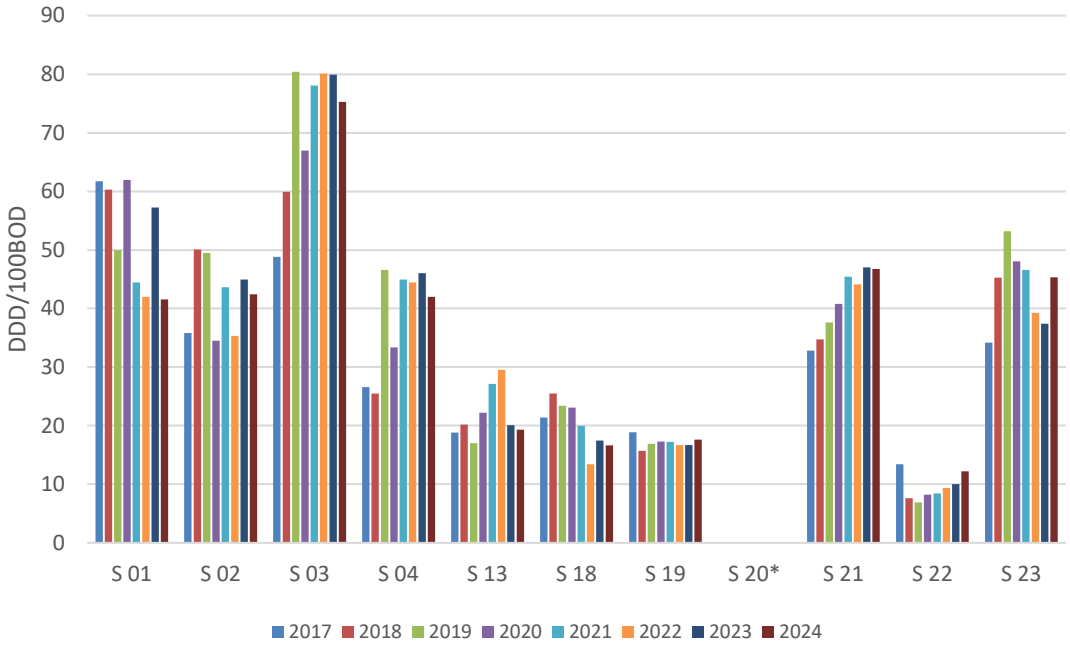
Slika 19. / *Figure 19.*
Specijalne bolnice - potrošnja antibiotika 2024. /
Specialty hospitals – antibiotic consumption 2024

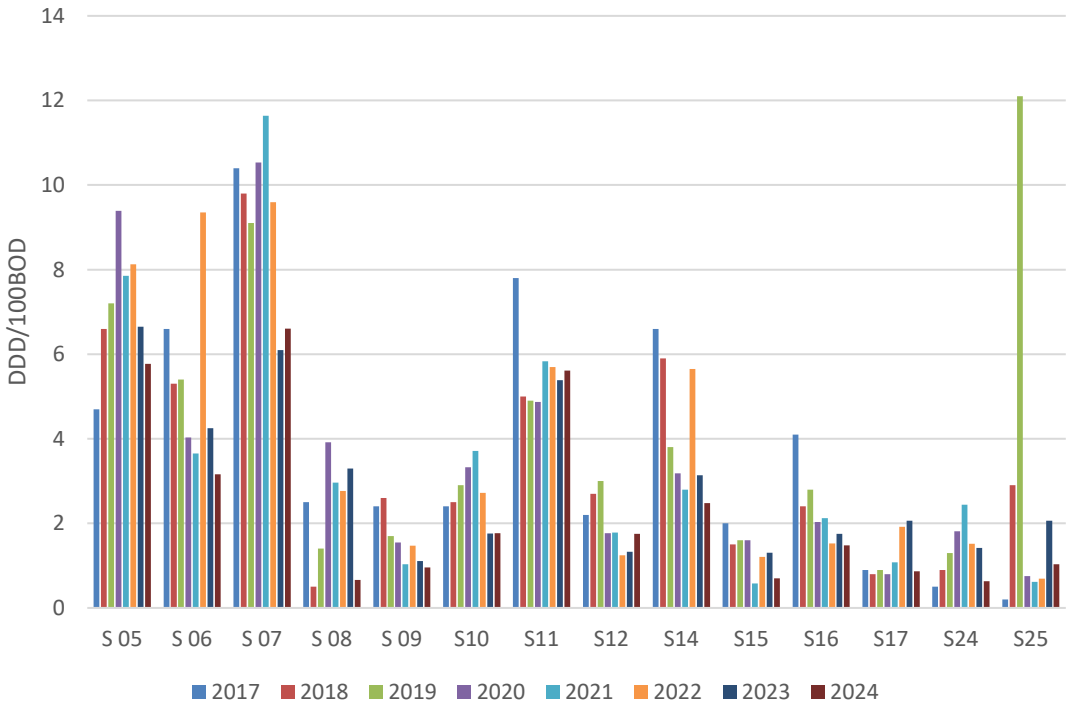


Tablica 21. */ Table 21.*
Specijalne bolnice - potrošnja antibiotika 2017.-2024. /
Specialty hospitals – antibiotic consumption in 2017-2024

	DDD/100 BOD, DDD/100 BD							
USTANOVA INSTITUTION	2017	2018	2019	2020	2021	2022	2023	2024
S 01	61,7	60,3	50,0	61,95	44,45	41,98	57,27	41,55
S 02	35,8	50,1	49,5	34,51	43,61	35,35	44,93	42,42
S 03	48,8	59,9	80,4	66,98	78,06	80,08	79,90	75,30
S 04	26,6	25,5	46,6	33,38	44,96	44,46	46,01	41,99
S 13	18,8	20,2	17,0	22,21	27,14	29,52	20,09	19,31
S 18	21,4	25,5	23,4	23,09	19,96	13,40	17,48	16,61
S 19	18,9	15,7	16,9	17,29	17,24	16,67	16,69	17,62
S 20*								
S 21	32,8	34,7	37,6	40,79	45,42	44,11	47,00	46,76
S 22	13,4	7,6	6,9	8,21	8,46	9,35	10,03	12,22
S 23	34,2	45,3	53,2	48,08	46,56	39,28	37,43	45,35
S 05	4,7	6,6	7,2	9,39	7,85	8,13	6,65	5,77
S 06	6,6	5,3	5,4	4,03	3,65	9,35	4,25	3,16
S 07	10,4	9,8	9,1	10,53	11,64	9,59	6,10	6,60
S 08	2,5	0,5	1,4	3,92	2,96	2,77	3,29	0,66
S 09	2,4	2,6	1,7	1,55	1,03	1,47	1,11	0,96
S10	2,4	2,5	2,9	3,33	3,71	2,72	1,76	1,77
S11	7,8	5,0	4,9	4,87	5,83	5,69	5,38	5,61
S12	2,2	2,7	3,0	1,77	1,78	1,24	1,33	1,75
S14	6,6	5,9	3,8	3,18	2,80	5,65	3,14	2,48
S15	2,0	1,5	1,6	1,60	0,58	1,21	1,31	0,70
S16	4,1	2,4	2,8	2,03	2,12	1,52	1,75	1,48
S17	0,9	0,8	0,9	0,80	1,08	1,92	2,06	0,87
S24	0,5	0,9	1,3	1,81	2,44	1,52	1,42	0,63
S25	0,2	2,9	12,1	0,75	0,62	0,69	2,07	1,03

Slika 20. / *Figure 20.*
Specijalne bolnice - potrošnja antibiotika 2017.-2024. /
Specialty hospitals – antibiotic consumption 2017-2024





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

Svjetska zdravstvena organizacija priredila je AWaRe klasifikaciju antibiotika 2017. godine s ciljem pravilne uporabe antibiotika. Antibiotici su podijeljeni u tri skupine, „Access", „Watch" i „Reserve" prema utjecaju pojedinih antibiotika i klasa antibiotika na antimikrobnu otpornost s naglaskom na važnost njihove pravilne primjene. Antibiotici koji pripadaju pojedinoj skupini su obilježeni različitim bojama, pa tako oni u skupini „Access" su zelene boje, u skupini „Watch" su žuti, a iz skupine „Reserve" su crveni. Zadnja revizija antibiotika u skladu s AWaRe klasifikacijom antibiotika je bila 2023. godine te se u 2025. godini očekuje nova.

AWaRe klasifikacija antibiotika je dostupna na linku: https://www.who.int/publications/i/item/WHO-MHP-HPS-EML-2023.04.

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, fenoksimetilpenicilin, 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. Antibiotici iz te skupine pružaju najbolju terapijsku vrijednost uz najniži potencijal za razvoj rezistencije.

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. Većina tih antibiotika je nova. Njihova uporaba namijenjena je za posebno odabrane pacijente koji se liječe od životno ugrožavajućih infekcija uzrokovanih s multirezistentnim uzočnicima. 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.

AWaRe klasifikacija antibiotika je koristan alat za praćenje potrošnje antibiotika, jer daje mogućnost analize potrošnje u skladu s podjelom antibiotika i praćenje ostvarenja postavljenih ciljeva Europske unije (EU) vezanih uz potrošnju antibiotika.

Prvi cilj članica 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 s 21,2 DDD/TID, a u 2024. potrošnja antibiotika je porasla i iznosi 21,96 DDD/TID (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 i iznosio je 60,71% , a u 2024. godini je gotovo identičan prethodnoj godini sa 61% (tablica 23 i slika 21).

U 2024. godini uočljiv je porast udjela antibiotika iz skupine „Reserve” u odnosu na godinu prije, a posebno u odnosu na 2019. godinu (0,41%; 0,33%; 0,17%).

AWaRe klasifikacija antibiotika je pomoć za praćenje potrošnje antibiotika i praćenje učinaka politika upravljanja kojima je za cilj optimizirati upotrebu antibiotika i kontrolirati antimikrobnu otpornost. Mnogo aktivnije i s većim angažmanom svih stručnjaka na svim razinama je potrebno djelovati u smjeru ostvarivanja zacrtanih ciljeva.

ANTIBIOTIC CONSUMPTION IN CROATIA ACCORDING TO THE AWARE CLASSIFICATION

The World Health Organization developed the AWaRe classification of antibiotics in 2017 with the aim of promoting their proper use. Antibiotics are categorized into three groups – "Access", "Watch" and "Reserve" – based on the impact of both individual antibiotics and their classes on development of antimicrobial resistance and emphasizing the significance of their proper usage. Each group of antibiotics is colour-coded: those in the "Access" group are green, "Watch" are yellow, and "Reserve" ones are red. The last revision of antibiotics in accordance with the AWaRe classification was in 2023, so a new one is expected in 2025.

The AWaRe classification of antibiotics is available at https://www.who.int/publications/i/item/WHO-MHP-HPS-EMI-2023.04

The **"Access"** group currently includes 87 antibiotics intended for the treatment of 25 most common infections. These antibiotics must be available, affordable and of assured quality. The most commonly used ones are β-lactam antibiotics, penicillins (ampicillin, amoxicillin, co-amoxiclav, benzylpenicillin, phenoxymethylpenicillin, procaine benzylpenicillin, cloxacillin), as well as cephalosporins, of which only cefazolin and cephalexin from 1st generation of cephalosporins are in this group. Other frequently used antibiotics in this category include clindamycin, metronidazole, nitrofurantoin, gentamicin, and doxycycline. Antibiotics in the "Access" group combine best therapeutic value with the lowest risk of resistance development.

The **"Watch"** group comprises 147 antibiotics, most of which are of critical importance and as such are recommended exclusively 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 last-resort options, primarily in hospitals. Most of these antibiotics are new and intended for selectively chosen patients who are being treated for life-threatening infections caused by multidrug-resistant pathogens. In Croatia, the most commonly used antibiotics from this group are colistin, polymyxin B, intravenous fosfomycin, linezolid, and newer generation beta-lactam antibiotics with beta-lactamase inhibitors.

The AWaRe classification is a useful tool for monitoring antibiotic consumption, as it enables its analysis in accordance with antibiotic classes and facilitates tracking of progress made towards consumption goals set by the European Union (the EU).

The first goal for European Union (EU) member states is to reduce total antibiotic usage by 20% until 2030. For Croatia, this would mean an overall consumption 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 levels were not maintained in 2023, when Croatia exceeded the EU average with an overall consumption of 21.2 DDD/TID. In 2024, antibiotic consumption increased even further and reached 21.96 DDD/TID (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% and remained almost unchanged in 2024, at 61% (Table 23; Figure 21).

2024 saw a noticeable increase in the share of "Reserve" antibiotics when compared to the year before, and especially to 2019 (0.41%; 0.33%; 0.17%).

The AWaRe classification of antibiotics is designed as a tool for monitoring antibiotic consumption and tracking the effects of stewardship policies aimed at optimizing antibiotic use and controlling antimicrobial resistance.

Achieving the set targets requires increased and more active engagement of professionals at all levels.

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

DDD/TID	2019.	2023.	2024.	2030.
Hrvatska	18,8	21,2	21,96	17,1
EU	19,9	20,07	20,00	15,9

Tablica 23. / *Table 23.*
Udio potrošnje antibiotika u Hrvatskoj iz skupine "Access" (%) /
Portion of "Access" antibiotics (%) in Croatia

GODINA	2019.	2023.	2024.	2030.
% „Access"	62,73	60,71	61,0	65,0

Slika 21. / *Figure 21*
Ukupna potrošnja antibiotika u Hrvatskoj u skladu s AWaRe klasifikacijom 2024. (%) /
Total antibiotic consumption in Croatia in accordance with the AWaRe classification 2024 (%)