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

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

HRVATSKO DRUŠTVO ZA KLINIČKU MIKROBIOLOGIJU
HRVATSKOG LIJEČNIČKOG ZBORA
SEKCIJA ZA REZISTENCIJU NA ANTIBIOTIKE
CROATIAN SOCIETY FOR CLINICAL MICROBIOLOGY
OF THE CROATIAN MEDICAL ASSOCIATION
SECTION FOR ANTIBIOTIC RESISTANCE

Osjetljivost i rezistencija bakterija na antibiotike u Republici Hrvatskoj u 2022.g.

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AUTORI / *AUTHORS*

Izv. prof. prim. dr. sc. Arjana Tambić Andrašević, dr. med., FESCMID
Dr. sc. Ljiljana Žmak, dr. med.
Dr. sc. Mihaela Obrovac, dr. med.
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Prof. prim. dr. sc. Suzana Bukovski, dr. med.
Josip Ujević, mag. biol. mol.
Sandra Lucić, mag. MLD
Irena Groš, mag. MLD

UREDNICA / *EDITOR*

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

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

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In memoriam

Prim. dr. sc. TERA TAMBIĆ, dr. med.
(28. listopada 1930. – 16. rujna 2022.)

Tera Tambić je rođena u obitelji Franje i Ane Kovač, 28. listopada 1930. u Belišću. Nakon školovanja u Osijeku i Križevcima, upisala je Medicinski fakultet u Zagrebu. Nekoliko godina po završetku fakulteta radila je kao liječnik obiteljske medicine, što je značajno odredilo njen pristup medicini i znanosti orjentiranoj individualnom čovjeku.

Specijalizaciju iz mikrobiologije započela je 1960-tih godina na Hrvatskom zavodu za javno zdravstvo. U okviru specijalizacije s posebnim je interesom sudjelovala u terenskim istraživanjima krpeljnog encefalitisa na Braču. Karijeru je nastavila u Klinici za zarazne bolesti, gdje uz veliku podršku profesora Frana Mihaljevića osniva i razvija laboratorij za kliničku mikrobiologiju. Uz profesora Mihaljevića sudjeluje na velikim vizitama, na kojima stječe veliko kliničko iskustvo i mogućnost ispoljavanja svoje profesionalne težnje da individualnim pristupom svakom pacijentu mikrobiološku dijagnostiku učini brzom i svrsishodnom. Posebno unaprijeđuje dijagnostičke postupke za dokazivanje bakterija u krvi i likvoru, te značajno unaprjeđuje dijagnostiku urinarnih infekcija. Također, sudjeluje u osnivanju i radu prve Komisije za suzbijanje i sprječavanje hospitalnih infekcija i izradi prvog hrvatskog Protokola za kontrolu bolničkih infekcija, 1967.g. po uzoru na američki pravilnik iz 1966.g.

Uz podršku profesora Mihaljevića, tijekom 1970-tih u dva navrata boravi na stručnom usavršavanju u St. Thomas' Hospital u Londonu, gdje ima prilike proširiti saznanja o suvremenoj dijagnostici te kontroli bolničkih infekcija. U nastavku njene karijere, veliku ulogu ima profesor Ian Phillips, voditelj Odjela za mikrobiologiju klinike St. Thomas', jedan od osnivača i prvih predsjednika Europskog društva za kliničku mikrobiologiju i infektologiju (ESCMID). Suradnja prim. dr. sc. Tere Tambić s profesorom Ianom Phillipsom je uvelike doprinjela razvoju kliničke mikrobiologije u Hrvatskoj. Prim. dr. sc. Tera Tambić je imala želju svoje znanje stečeno u inozemstvu podijeliti s drugim kolegicama i kolegama, po uzoru na zapadnoeuropsku mikrobiologiju približiti mikrobiologe i kliničare, ubrzati dijagnostiku i individualizirati interpretaciju mikrobioloških nalaza. Prim. dr. sc. Tera Tambić je, stoga, svoje napore za unaprjeđenje struke usmjerila na rad Hrvatskog društva za medicinsku mirobiologiju pri Hrvatskom liječničkom zboru želeći naglasiti potrebu za povezivanjem liječnika mikrobiologa s kolegama liječnicima drugih specijalnosti. Kao predsjednica društva, prim. dr. sc. Tera Tambić je održavala redovite stručne sastanke koncipirane tako da o istoj temi govori liječnik mikrobiolog i liječnik kliničar, što je bio lijepi začetak suradnje kakvu danas njegujemo. Prim. dr. sc. Tera Tambić je progovarala i kroz brojne stručno znanstvene sastanke koje je organizirala, od kojih se svojim značajem i aktualnošću teme posebno izdvajaju »Simpozij o bakterijama roda Staphylococcus«, održan na Plitvicama 1988. godine, te svakako Prvi hrvatski kongres kliničke mikrobiologije, održan 1987. Prim. dr. sc. Tera Tambić je uhodala redovito održavanje ovog kongresa svake tri godine. Bitna značajka ovih kongresa je bila multidisciplinarnost, a rado su ga posjećivali i brojni kolege iz cijele tadašnje Jugoslavije. Ponosni smo na ovakvu tradiciju i sretni da je naš kongres ove godine doživio svoje 13. izdanje i kao što znamo, evoluirao u zajednički kongres hrvatskih mikrobiologa i infektologa, danas poznati CROCMID.

Uz područje kontrole bolničkih infekcija i antibiotske terapije, posebno područje interesa dr. Tere Tambić je bilo dijagnostika i terapija infekcija mokraćnih puteva. Iz tog područja dr. Tera Tambić je objavila značajne radove, održala brojna predavanja, te doktorirala pod mentorstvom profesora Radonića. Za zasluge u unaprijeđenju dijagnostike infekcija mokraćnih puteva prim. dr. sc. Tera Tambić je dobila počasnu titulu specijaliste nefrologa.

Veliki izazov za prim. dr. sc. Teru Tambić je bilo osnivanje mikrobiološkog laboratorija u Općoj bolnici "Sveti Duh", bolnici s brojnim kirurškim odjelima, odjelima intenzivne medicine i rizičnim pacijentima gdje izazovi kliničke mikrobiologije dolaze do punog izražaja. U ovoj bolnici je 1973. godine osnovala Zavod za kliničku mikrobiologiju i bolničke infekcije te pronašla brojne bliske suradnike među kolegama različitih struka.

Iako je razvoj struke bio prioritet u njenom djelovanju, prim. dr. sc. Tera Tambić je uvelike zadužila ne samo hrvatsku već i svjetsku javnost svojim znanstvenim radom na istraživanjima koja su dovela do otkrića novog antibiotika, popularnog azitromicina. Danas rijetko tko u svijetu zna da je azitromicin originalni hrvatski proizvod jer je ubrzo nakon registracije lijeka patent preuzela velika američka tvrtka, a još manje ljudi, pa čak i hrvatskih mikrobiologa, zna da je prva ključna istraživanja s tada nepoznatim makrolidskim molekulama, kao vanjski suradnik Plive, obavljala prim. dr. sc. Tera Tambić, te da je upravo ona, od svih ponuđenih molekula, izdvojila DCH3 molekulu kao onu na kojoj vrijedi provoditi daljnja istraživanja. Prim. dr. sc. Tera Tambić je sudjelovala u prvim istraživanjima učinkovitosti i farmakokinetike azitromicina i bila joj je osobita čast predstaviti novi antibiotik na Svjetskom kongresu kemoterapije, International Congress of Chemotherapy, 1975. u Londonu.

Baveći se antimikrobnom terapijom u praksi, prim. dr. sc. Teri Tambić nije promaklo da rezistencija bakterija na antibiotike počinje predstavljati sve veći problem. Već za rana je počela upozoravati na nužnost racionalne primjene antibiotika i na opasnost od širenja rezistencije te je 1984.g. organizirala Prvi hrvatski simpozij o rezistenciji na antibiotike, koji se od tada održava redovito svake tri godine i prati aktualnosti na tom dinamičnom području.

Odlazak u mirovinu za prim. dr. sc. Teru Tambić nije značio prestanak rada i djelovanja za unaprijeđenje struke. Kao član Hrvatske akademije medicinskih znanosti i znanstvena tajnica Akademije u četiri mandata, angažirala se na osuvremenjavanju rada Akademije, organizirala znanstvena predavanja i podržavala rad čelništva Akademije. U okrilju Akademije našla je stimulirajuće okruženje za osnivanje Odbora za praćenje rezistencije bakterija na antibiotike u Republici Hrvatskoj, što je jedna od prvih inicijativa na nacionalnoj razini na području kontrole širenja rezistencije. Slične međunarodne inicijative uslijedile su nekoliko godina kasnije te je Odbor pod vodstvom prim. dr. sc. Tere Tambić proširio svoje aktivnosti na bogatu međunarodnu suradnju. Za izniman doprinos medicini, prim. dr. sc. Teri Tambić dodijeljen je naziv Laureata Hrvatske akademije medicinskih znanosti.

Neprekinuti rad Odbora je najbolji izraz zahvale našoj dragoj prim. dr. sc. Teri Tambić, prvoj predsjednici i doživotnoj počasnoj predsjednici našeg Odbora.

Izv. prof. dr. sc. Arjana Tambić Andrašević, dr. med.
Predsjednica
Odbor za praćenje rezistencije

Prim. Marina Payerl Pal, dr. med.
Tajnica
Odbor za praćenje rezistencije

In memoriam

Prim. TERA TAMBIĆ, MD, PhD
(28th October 1930 – 16th September 2022)

Tera Tambić was born in the family of Franjo and Ana Kovač on October 28, 1930 in Belišće. After ending school in Osijek and Križevci, she attended the School of Medicine at the University of Zagreb. After graduating, she worked as a general practitioner for several years, which significantly determined her approach to medicine and science oriented towards the individual patient.

She started training in microbiology in the 1960s at the Croatian Institute of Public Health. During her traineeship, she took great interest in field research on tick-borne encephalitis on Brač. She continued her career at the University hospital for Infectious Diseases, where, with the great support of Professor Fran Mihaljević, she founded and developed a laboratory for clinical microbiology. She participated in ward rounds led by professor Mihaljević, which enabled her to gain extensive clinical experience and provided the opportunity to develop rapid microbiological diagnostics with an individual approach to each patient. She greatly improved diagnostic procedures, especially the diagnostics of bloodstream infections and bacterial meningitis. Also, she took part in the establishment and work of the first Committee for infection prevention and control and participated in the development of the first Croatian by-law on nosocomial infections, developed in 1967, following the publication of the American guidelines in 1966.

With the support of Professor Mihaljević, during the 1970s, she visited St. Thomas' Hospital in London on two occasions, and that gave her the opportunity to expand her knowledge of modern diagnostics and hospital infection control. Her career was greatly influenced by Professor Ian Phillips, head of the Department of Microbiology at St. Thomas' Hospital, one of the founders and first presidents of the European Society for Clinical Microbiology and Infectious Diseases (ESCMID). Intense collaboration between Dr Tera Tambić and Professor Ian Phillips greatly contributed to the development of clinical microbiology in Croatia. Dr Tera Tambić always aspired to share her knowledge acquired abroad with other colleagues, to bring microbiologists and clinicians closer, following the example of Western European microbiology, to speed up diagnostics and to tailor the interpretation of microbiological findings to the individual patient. Dr Tera Tambić, therefore, streamlined her efforts to improve laboratory practice to the work of the Croatian Society for Medical Microbiology at the Croatian Medical Association, wanting to emphasize the need to connect microbiologists with colleagues in other specialties. As the president of the society, Dr Tera Tambić held regular meetings designed so that a microbiologist and a clinician speak on the same topic, which was a nice beginning of the multidisciplinary collaboration we have today. Dr Tera Tambić was active in organizing numerous scientific meetings, of which the »Symposium on staphylococci«, held in Plitvice in 1988, and especially the First Croatian Congress of Clinical Microbiology, held in 1987, stand out due to their significance and clinical impact. Dr Tera Tambić ensured that this congress continued to be held regularly every three years. An important feature of these congresses was their multidisciplinary approach, and it was readily visited by many colleagues from all over what was Yugoslavia at the time. We are proud of this tradition and happy that this year our congress was held for the 13th time and that it evolved into a joint congress of the Croatian clinical microbiologists and infectious diseases doctors, a congress also known today as CROCMID.

In addition to the area of hospital infection control and antibiotic therapy, the special field of interest of Dr Tera Tambić was the diagnosis and therapy of urinary tract infections. In this field, Dr Tera Tambić published significant research studies, held numerous lectures, and obtained her PhD degree under the mentorship of Professor Radonić. For her merits in improving the diagnosis of urinary tract infections Dr Tera Tambić received the honorary title of consultant nephrologist.

A big challenge for Dr Tera Tambić was to establish a microbiology laboratory at the "Sveti Duh" General Hospital, a hospital with numerous surgical departments, intensive care units and high-risk patients. In 1973, she founded the Department of Clinical Microbiology and Hospital Infections in this hospital which led to the fruitful collaboration with many colleagues of different specialities.

Although the development of the professional affairs was her priority, Dr Tera Tambić greatly indebted not only the Croatian but also the world public with her scientific work on research that led to the discovery of a new antibiotic, the azithromycin. Today, hardly anyone in the world knows that azithromycin is an original Croatian product, because shortly after the drug's registration, the patent was taken over by a large American company, and even fewer people, be it even Croatian microbiologists, know that the first key research with then-unknown macrolide molecules, was performed by Dr Tera Tambić, who was collaborating with Pliva at the time. She was the one to single out the DCH3 molecule as the one worth conducting further research on. Dr Tera Tambić participated in the first studies on the effectiveness and pharmacokinetics of azithromycin and had the honour of presenting this new antibiotic at the International Congress of Chemotherapy in London in 1975.

Dealing with antimicrobial therapy in practice, Dr Tera Tambić did not miss the fact that antibiotic resistance is becoming a growing problem. Already early on, she began to warn about the need for the rational use of antibiotics and the danger of the spread of resistance, and in 1984 she organized the First Croatian Symposium on Antibiotic Resistance, which has been held regularly every three years since then.

Retirement did not stop Dr Tera Tambić working on improving professional affairs. As a member of the Croatian Academy of Medical Sciences and the scientific secretary of the Academy for four mandates, she contributed to the modernization of the Academy, organized scientific lectures and supported the work of the Executive board. In the auspices of the Academy, she found a stimulating environment for the establishment of the Croatian Committee for Antibiotic Resistance Surveillance, which is one of the first initiatives at the national level in the field of controlling the spread of resistance. Similar international initiatives followed a few years later, and the Committee under the leadership of Dr Tera Tambić expanded its activities towards more intensive international cooperation. For the outstanding contribution to medicine Dr Tera Tambić was awarded the title of Laureate of the Croatian Academy of Medical Sciences.

The continuous work of the Committee is the best token of gratitude to our dear Dr Tera Tambić, the first president and lifetime honorary president of our Committee.

Assoc. prof. Arjana Tambić Andrašević, MD, PhD
President
Committee for Antibiotc Resistance Surveillance

Prim. Marina Payerl Pal, MD
Honorary Secretary

SADRŽAJ / *TABLE OF CONTENTS*

PREDGOVOR:

U 2022.g. smo još uvijek krenuli s opterećenjem pandemije SARS-CoV-2, no procijepljenost stanovništva i zdravstvenih djelatnika, kao i velik udio stanovnika koji su infekciju preboljeli normalizirao je situaciju u zdravstvu. Osobna zaštitna oprema se počela racionalnije koristiti, a pritisak terminalno bolesnih pacijenata je popustio te se smanjio i broj bolnički stečenih infekcija. Aktivnosti Odbora za praćenje rezistencije bakterija na antibiotike opisane u poglavljima ove publikacije su se i u ovoj pandemijskoj godini nesmetano odvijale, a druženje na zajedničkim skupovima se intenziviralo. Normalizacija situacije u zdravstvu i društvu u cjelini omogućila je povratak organiziranja stručno znanstvenih sastanaka u živo, pa su u području antimikrobne rezistencije 2022. godinu obilježila dva važna sastanka u Hrvatskoj, 4. zajednički kongres mikrobiologa i infektologa, CROCMID 2022 (13. hrvatski kongres kliničke mikrobiologije i 10. hrvatski kongres o infektivnim bolestima) te europski tečaj ESCMID Postgraduate Educaton Course "Clinical microbiology testing in settings with limited resources and high prevalence of AMR: the role of diagnostic stewardship", oba održana u listopadu u Šibeniku. Potrošnja antibiotika u sektorima medicine, veterine i okoliša posredno i neposredno utječe na razvoj rezistencije u medicinski važnih bakterija. Stručnjaci ovih različitih sektora dobro surađuju u Hrvatskoj, prvenstveno u sklopu zajedničkog rada u Interdisciplinarnoj sekciji za kontrolu rezistencije na antibiotike (ISKRA), a tradicionalni simpozij povodom obilježavanja Europskog dana i Svjetskog tjedna svjesnosti o antimikrobnim lijekovima u studenom, ove je godine bio posvećen popularizaciji upravo ovog principa jedinstvenog zdravstva (engl. „One health"). U podizanju svjesnosti o antibioticima među onima koji antibiotike propisuju i izdaju, ali i među građanima koji bi ih trebali vrlo odgovorno konzumirati, Hrvatska ima snažnu potporu Svjetske zdravstvene organizacije (WHO) i Europskog centra za prevenciju i kontrolu bolesti (ECDC), čije smjernice čine i osnovu Nacionalnog programa za kontrolu otpornosti bakterija na antibiotike. Hrvatska već dugo kontinuirano sudjeluje u europskim programima praćenja rezistencije i potrošnje antibiotika, a u 2022.g. međunarodne aktivnosti Hrvatske su bile pojačane kroz sudjelovanje Referentnog centra MZ za praćenje rezistencije bakterija na antibiotike u međunarodnim projektima EURGen-RefLabCap te Horizon 2020 projektima AmReSu i ECRAID Base. Iako se više od 90% antibiotika potroši izvanbolnički, posebno zabrinjava visoka potrošnja antibiotika posljednjeg izbora u bolničkim sredinama. Dugogodišnji napori da se bolnička potrošnja antibiotika poboljša uvođenjem timova za upravljanje antimikrobnom terapijom još uvijek nisu doveli do željenih rezultata te uvođenje ovih timova ostaje jedan od najvažnijih ciljeva Nacionalnog programa i u nadolazećem razdoblju.

U 2022. godini smo se s velikom tugom oprostili od prim. dr. sc. Tere Tambić, osnivačice, prve i počasne predsjednice Odbora za praćenje rezistencije bakterija na antibiotike. Njena vizija o standardizaciji rada laboratorija i prikupljanju pouzdanih podataka o rezistenciji bakterija na antibiotike povela nas je od prve zajedničke aktivnosti na nacionalnoj razini, kroz razne etape proširivanja opsega rada i sve intenzivnije međunarodne suradnje do razvoja snažne akademske zajednice koja se složno i kontinuirano prilagođava stalnim promjenama u području rezistencije na antibiotike te pruža pouzdane podatke na osnovi kojih se mogu planirati ostale aktivnosti kontrole širenja rezistencije. Zahvaljujem svima koji ovo nasljeđe cijene i svojim velikim zalaganjem provode.

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

PREFACE

The year 2022 was still marked with the burden of the SARS-CoV-2 pandemic, but the vaccination and a large proportion of the naturally immunized population, has normalized the situation in the health care. The irrational use of personal protective equipment improved and a decrease in terminally ill patients eased the pressure on intensive care unts which all resulted in the decrease of healthcare associated infections. The activities of the Croatian Committee for Antibiotic Resistance Surveillance, described in the chapters of this publication, continued uninterrupted during this pandemic year, and scientific communication intensified. The normalization of the situation in the health care and society as a whole enabled the return of face to face meetings, and in the field of antimicrobial resistance, the year 2022 was marked in Croatia by two important meetings, the 4th joint congress of clinical microbiology and infectious diseases, the CROCMID 2022 (13th Croatian Congress of Clinical Microbiology and the 10th Croatian Congress on Infectious Diseases) and the ESCMID Postgraduate Education Course "Clinical microbiology testing in settings with limited resources and high prevalence of AMR: the role of diagnostic stewardship", both held in October in Šibenik. Antibiotic consumption in the medical, veterinary, and environmental sectors directly and indirectly affects the development of resistance in medically important bacteria. Experts from these different sectors cooperate well in Croatia, primarily through the joint work in the Interdisciplinary Section for Control of Antibiotic Resistance (ISKRA). The traditional symposium marking European Day and World Antimicrobial Awareness Week in November this year was dedicated to the "One health" approach in fighting antimicrobial resistance. In raising awareness about antibiotics among those who prescribe and dispense antibiotics, but also among those who are supposed to consume them responsibly, Croatia has the strong support of the World Health Organization (WHO) and the European Centre for Disease Prevention and Control (ECDC). Also, the essential part of the Croatian National Program for the Antibiotic Resistance Control is based on the guidelines of these two institutions. For a long time, Croatia has continuously participated in European programs for antibiotic resistance and antibiotic consumption surveillance, and in 2022 Croatia's international activities were further expanded through the participation of the Croatian Reference Center for Antibiotic Resistance Surveillance in the international projects EURGen-RefLabCap and the Horizon 2020 projects AmReSu and ECRAID Base. Although more than 90% of antibiotics are consumed outside the hospital, the high consumption of antibiotics of last resort in hospital settings is of particular concern. Long-standing efforts to improve hospital antibiotic consumption by introducing antimicrobial stewardship teams have not yet led to the desired results, and the introduction of these teams remains one of the most important goals of the National Program in the coming period.

In 2022, with great sadness we parted from Dr Tera Tambić, founder, first and honorary president of the Croatian Committee for Antibiotic Resistance Surveillance. Her vision on the laboratory standardization and the need to collect reliable data on antibiotic resistance led us from the first joint activity at the national level, through various phases of expanding activities and intensifying international cooperation to the development of a strong academic community that harmoniously and continuously adapts to constant changes in the area of antibiotic resistance and provides reliable data on the basis of which other activities to control the spread of resistance can be planned. I would like to express my sincere thanks to everyone who appreciates this legacy and implements it with great commitment.

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

PRAĆENJE REZISTENCIJE NA ANTIBIOTIKE U HRVATSKOJ

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

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

ANTIBIOTIC RESISTANCE SURVEILLANCE IN CROATIA

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

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

REZISTENCIJA BAKTERIJSKIH IZOLATA U 2022. GODINI

ANTIBIOTIC RESISTANCE IN 2022

Arjana Tambić Andrašević
Sandra Lucić

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

UVOD

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

INTRODUCTION

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

MATERIJALI I METODE

Globalno praćenje rezistencije

U praćenje su uključeni svi izolati dogovorenih bakterijskih vrsta izolirani iz kliničkih materijala u razdoblju od 1.10. do 31.12.2022.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 31.12.2022. Podatke za 2022.g. podnijelo je 39 centara (popis u legendi za tablice), što obuhvaća >90% populacije u Hrvatskoj.

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

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

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

c. u ispitivanom razdoblju s dogovorenom paletom antibiotika testiraju se svi izolati iz kliničkih materijala ili 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 2022.g. korišteni su za testiranje i interpretaciju nalaza standardi europskog odbora, European Committee on Antimicrobial Susceptibility Testing (EUCAST) (Clinical Breakpoint Tables v. 12.0). U testiranju osjetljivosti na antibiotike većina laboratorija koristi disk difuzijsku metodu, a određivanje minimalnih inhibitornih koncentracija (MIK) se koristi za određivanje osjetljivosti anaerobnih bakterija, osjetljivosti na penicilin i ampicilin kod pneumokoka smanjene osjetljivosti na penicilin, osjetljivosti stafilokoka na glikopeptide te pseudomonasa i acinetobaktera na kolistin. Svake godine, na sastanku Odbora u prosincu komentiraju se i usvajaju promjene u EUCAST standardima za nadolazeću godinu. Već u 2019.g. su svi članovi Odbora trebali usvojiti novu interpretaciju S, I i R kategorija, što predstavlja najznačajniju izmjenu EUCAST standarda posljednjih godina. Od 2019.g. kategorija S znači "osjetljiv uz standardno doziranje", kategorija I "osjetljiv uz povećanu izloženost" te kategorija R "rezistentan". U 2021.g. EUCAST standardi su za neke kombinacije mikroorganizama i antibiotika uveli odvojenu interpretaciju za slučaj infekcije središnjeg živčanog sustava i slučaj ostalih infekcija. Dogovorno, za potrebe praćenja prijavljuje se interpretacija za "ostale (ne-meningitis) infekcije". U 2022.g. uvedeno je praćenje osjetljivosti *A.baumanii* i *P.aeruginosa* na cefiderokol, te enterobakterija na cefiderokol i imipenem / relebaktam. 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). Za određivanje MIK kolistina od 2017.g. usvojen je naputak EUCAST-a da se koristi mikrodilucija u bujonu (MICRONAUT MIC-Strip, Merlin Diagnostika; MIKROLATEST MIC, Erba Lachema). U skladu s upozorenjem EUCAST-a da je korištenje gradient strip testova nepouzdano u određivanju osjetljivosti pneumokoka na penicilin, posebno u izolata s rasponom MIK vrijednosti 0.5 – 2.0 mg/L, Odbor je preporučio testiranje osjetljivosti pneumokoka na penicilin metodom mikrodilucije u bujonu, no za sada uporaba mikrodilucije u bujonu nije obavezni uvjet za prijavljivanje vrijednosti MIK penicilina za potrebe praćenja rezistencije.

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

Ciljane studije

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

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

U sklopu European Antimicrobial Resistance Surveillance System (EARSS) projekta, a potom EARS-Net programa Odbor posebno obrađuje rezistenciju u invazivnih izolata (iz krvi i likvora) bakterijskih vrsta *S. pneumoniae*, *S. aureus, E. faecalis, E. faecium, E. coli*, *K. pneumoniae, P. aeruginosa* i *Acinetobacter baumannii*. Za ove izolate referentni centar (RC) za praćenje rezistencije prikuplja i obrađuje demografske podatke pacijenata, a u svrhu detaljnije analize izolati se šalju u Zavod za kliničku mikrobiologiju Klinike za infektivne bolesti "Dr. F. Mihaljević". RC za praćenje rezistencije šalje podatke o invazivnim izolatima u The European Surveillance System (Tessy) Europskog centra za kontrolu bolesti (engl. "European Centre for Disease Prevention and Control", ECDC). Podaci o invazivnim izolatima od početka praćenja do 2022.g. prikazani su u zasebnom poglavlju ove publikacije.

Od 2001.g., uključivanjem u europski projekt European Surveillance of Antimicrobial Consumption (ESAC), a potom i ESAC-Net, Hrvatska prati potrošnju antibiotika izraženu u definiranim dnevnim dozama na 1000 stanovnika dnevno (DDD/TID). Podaci o bolničkoj i izvanbolničkoj potrošnji antimikrobnih lijekova se također šalju u Tessy sustav ECDC-a. Podaci o potrošnji antibiotika u Hrvatskoj u 2022.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 2022. Data on group A streptococci, salmonellae, shigellae and anaerobic bacteria were reported for the whole year, from 1 January to 31 December 2022 due to the small number of isolates. In 2022 thirty-nine centres took part in antibiotic resistance surveillance (names of the centres are listed in the legend to the tables) which makes a catchment population of >90%.

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

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

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

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

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

Laboratories send their data for analysis to the Croatian Reference 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 2022 all laboratories used the European Committee on Antimicrobial Susceptibility Testing (EUCAST) standards for susceptibility testing (Clinical Breakpoint Tables v. 12.0). Disk diffusion method is the most widely used susceptibility testing method in Croatian laboratories and minimal inhibitory concentration (MIC) testing is used for testing susceptibility in anaerobic bacteria and for detection of penicillin and ampicillin resistance in penicillin non-wild type pneumococci, glycopeptide resistance in staphylococci and colistin resistance in pseudomonas and acinetobacter. Every year at the Croatian Committee for Antibiotic Resistance Surveillance meeting in December the EUCAST updates for the coming year are discussed and adopted. Since 2019 all Committee members are using the new interpretation of the S, I and R categories, which is the most significant change in EUCAST standards in recent years. From 2019 category "S" means "susceptible, standard dosing", category "I" "susceptible, increased exposure" and category "R" "resistant". In 2021 for some drug bug combinations EUCAST introduced separate interpretation for meningitis and other infections. For surveillance purpose it was agreed that interpretation for other (non-meningitis) infections will be reported. In 2022 it was agreed to introduce testing of *A.baumannii* and *P.aeruginosa* susceptibility to cefiderocol, and susceptibility of enterobacteria to cefiderocol and imipenem / relebactam. 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* were processed in the National Laboratory for Tuberculosis at the Croatian Public Health Institute. Resistance in *Mycobacterium tuberculosis* is described in a separate chapter of this publication.

Gonococci are included in antibiotic resistance surveillance since 2016. Data are 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 2022 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 2022 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 2022.g. sudjelovalo je 39 centara u Hrvatskoj. Prosječni rezultati za Hrvatsku i rezultati za pojedinačne centre prikazani su u tablicama i grafovima u daljnjem tekstu. Rezultati laboratorija koji su prijavili manje od 30 izolata pojedine bakterijske vrste smatraju se nepouzdanim podacima za taj centar, ali su uvršteni u tablice i uključeni su u zbirne rezultate za RH. Podaci o izolatima malo vjerojatnog fenotipa, koji nisu potvrđeni u RC za praćenje rezistencije, označeni su zvjezdicom kao nepotvrđeni i ne smatraju se važećima.

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

- BJ ZZJZ je za *C. jejuni* i *C. coli* prikazao rezultate za razdoblje od 1.10. – 31.12.2022.
- ČK ZZJZ je za *A. baumannii* prikazao rezultate za cijelu godinu
- DU ZZJZ je za *C. jejuni* i *C. coli* prikazao rezultate za razdoblje od 1.10. – 31.12.2022.
- GS ZZJZ je za sve vrste prikazao rezultate za cijelu godinu
- IG ZZJZ je za *E. faecium* prikazao rezultate za cijelu godinu
- KA OB je za *S. pneumoniae, E. faecium* i *H. influenzae* prikazala rezultate za cijelu godinu i za *C. jejuni* i *C. coli* rezultate za razdoblje od 1.10. – 31.12.2022.
- KC ZZJZ je za *C. jejuni* i *C. coli* prikazao rezultate za razdoblje od 1.10. – 31.12.2022.
- KR ZZJZ je za *E. faecium* i *H. influenzae* prikazao rezultate za cijelu godinu
- KT MAGD. je za *S. aureus*/MSSA, *S. aureus*/MRSA, *E. faecalis, E. faecium, E. coli, P. mirabilis, K. pneumoniae, Enterobacter* spp*., Klebsiella aerogenes, Serratia* spp. i *Citrobacter* spp., *P. aeruginosa* i *A. baumannii* prikazala rezultate za cijelu godinu
- OG OB je za *C. jejuni* i *C. coli* prikazao rezultate za razdoblje od 1.10. – 31.12.2022.
- OS NZZJZ je za *C. jejuni* i *C. coli* prikazao rezultate za razdoblje od 1.10. – 31.12.2022.
- PK OŽB je za *C. jejuni* prikazala rezultate za razdoblje od 1.10. – 31.12.2022.
- PŽ OŽB je za *C. jejuni* prikazao rezultate za razdoblje od 1.10. – 31.12.2022.
- PU NZZJZ je za *H. influenzae* i *A. baumannii* prikazao rezultate za cijelu godinu
- RI NZZJZ je za *C. jejuni* i *C. coli* prikazao rezultate za razdoblje od 1.10. – 31.12.2022.
- SK ZZJZ je za *C. jejuni* i *C. coli* prikazao rezultate za razdoblje od 1.10. – 31.12.2022.
- ST KBC je za *C. jejuni* i *C. coli* prikazao rezultate za razdoblje od 1.10. – 31.12.2022.
- ST NZZJZ je za *C. jejuni* prikazao rezultate za razdoblje od 1.10. – 31.12.2022.
- VK ZZJZ je za *S. pneumoniae, S. aureus/*MSSA, *S. aureus*/MRSA, *E. faecium, H. influenzae i A. baumannii* prikazao rezultate za cijelu godinu (izolati iz OŽB Vinkovci)
- ZG KBC je za *S. pneumoniae, S. aureus/*MSSA, *S. aureus*/MRSA i *H,.influenzae* prikazao rezultate za razdoblje od 3.10. do 3.1.2023*.,* za *E. faecalis* i E*. coli* za

razdoblje od 3.10 do 11.10.2022., za *E. faecium* i *A. baumannii* za razdoblje od 3.10. do 11.11.2022., za *P. mirabilis* za razdoblje od 3.10. – 19.10.2022., *K. pneumoniae* za razdoblje od 3.10 do 12.10.2022., *Enterobacter* spp*., Klebsiella aerogenes, Serratia* spp. i *Citrobacter* spp. i *P. aeruginosa* za razdoblje od 3.10. do 19.10.2022.

- ZG KBD je za *C. jejuni* prikazala rezultate za razdoblje od 1.10. – 31.12.2022.
- ZG KBCSM je za *C. jejuni* i *C. coli* prikazao rezultate za razdoblje od 1.10. – 31.12.2022.
- ZG KBM je za *S. pneumoniae* prikazala rezultate za cijelu godinu
- ZG KDB je za *A. baumannii* prikazala rezultate za cijelu godinu
- ZG NZZJZ je za *E. faecium* i *A. baumannii* prikazao rezultate za razdoblje od 3.10. do 31.12.2022., *E. coli* za razdoblje od 7.10. do 11.11.2022, *P. mirabilis*, *K. pneumoniae*, *Enterobacter* spp*., Klebsiella aerogenes*, *Serratia* spp*., Citrobacter* spp. za razdoblje od 7.11. do 25.11.2022. i *P. aeruginosa* za razdoblje od 3.10. do 25.11.2022.
- ZG KBSD je za *C. jejuni* prikazala rezultate za razdoblje od 1.10. – 31.12.2022.

Dva laboratorija su prijavila izolaciju šigela: RI NZZJZ *S. sonnei* (1) i ZG KIB *S. flexnerii* (1) i *S. sonnei* (2). Ukupno su tijekom 2022.g. izolirane četiri šigele.

U 2022.g. ukupno je obrađeno 1 043 anaerobne bakterije, *Cutibacterium acnes* (176); *Bacteroides* spp. (611); *Prevotella* spp. (156); *Fusobacterium necroforum* (28); *Clostridium perfringens* (72) iz 22 centra: ČK ZZJZ *Bacteroides* spp. (24); IG ZZJZ *Bacteroides* spp. (1); KA OB *Cutibacterium acnes* (4), *Bacteroides* spp. (21), *Prevotella* spp. (8), *Fusobacterium necroforum* (2), *Clostridium perfringens* (13); OG OB *Bacteroides* spp. (7); OS KBC *Cutibacterium acnes* (7), *Bacteroides* spp. (61), *Prevotella* spp. (41); PU NZZJZ *Bacteroides* spp. (6), *Clostridium perfringens* (2); PŽ OŽB *Bacteroides* spp. (6); RI KBC *Cutibacterium acnes* (7), *Bacteroides* spp. (60), *Prevotella* spp. (10), *Fusobacterium necroforum* (2), *Clostridium perfringens* (15); SB ZZJZ *Cutibacterium acnes* (1), *Bacteroides* spp. (5), *Clostridium perfringens* (2); SK ZZJZ *Cutibacterium acnes* (1), *Bacteroides* spp. (4); ST KBC *Cutibacterium acnes* (8), *Bacteroides* spp. (53) *Prevotella* spp. (9); *Clostridium perfringens* (8); ŠI ZZJZ *Cutibacterium acnes* (10), *Bacteroides* spp. (7), *Fusobacterium necroforum* (1); VK ZZJZ *Cutibacterium acnes* (1), *Bacteroides* spp. (5), *Clostridium perfringens* (2); VT ZZJZ *Bacteroides* spp. (2), *Prevotella* spp. (1); VŽ ZZJZ *Cutibacterium acnes* (16), *Bacteroides* spp. (42), *Prevotella* spp. (19), *Fusobacterium necroforum* (1), *Clostridium perfringens* (7); ZG KBD *Cutibacterium acnes* (16), *Bacteroides* spp. (30), *Prevotella* spp. (9), *Fusobacterium necroforum* (1), *Clostridium perfringens* (2); KBM *Cutibacterium acnes* (1), *Bacteroides* spp. (18), *Prevotella* spp. (5), *Clostridium perfringens* (11); ZG KBCSM *Cutibacterium acnes* (91), *Bacteroides* spp. (197), *Prevotella* spp. (43), *Fusobacterium necroforum* (16), *Clostridium perfringens* (5); ZG KIB *Cutibacterium acnes* (2), *Bacteroides* spp. (2), *Fusobacterium necroforum* (3); ZG HZJZ *Bacteroides* spp. (2), *Prevotella* spp. (1); ZG KDB *Bacteroides* spp. (20), *Prevotella* spp. (1); ZG KBSD *Cutibacterium acnes* (12), *Bacteroides* spp. (38), *Prevotella* spp. (9), *Fusobacterium necroforum* (2), *Clostridium perfringens* (2).

RESULTS

Thirty-nine centres took part in antibiotic resistance surveillance in Croatia in 2022. 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:

- BJ ZZJZ reported data for *C. jejuni* and *C. coli* for the period 1.10. – 31.12.2022.
- ČK ZZJZ reported data for *A. baumannii* for the whole year
- DU ZZJZ reported data for *C. jejuni* and *C. coli* for the period 1.10. – 31.12.2022.
- GS ZZJZ reported data for all species for the whole year
- IG ZZJZ reported data for *E. faecium* for the whole year
- KA OB reported data for *S. pneumoniae, E. faecium* and *H. influenzae* for the whole year and for *C. jejuni* and *C. coli* for the period 1.10. – 31.12.2022.
- KC ZZJZ reported data for *C. jejuni* and *C. coli* for the period 1.10. – 31.12.2022.
- KR ZZJZ reported data for *E. faecium* and *H. influenzae* for the whole year
- KT MAGD. reported data for *S. aureus/*MSSA, *S. aureus*/MRSA, *E. faecalis, E. faecium, E. coli, P. mirabilis, K. pneumoniae, Enterobacter* spp*., Klebsiella aerogenes, Serratia* spp. and *Citrobacter* spp*., P. aeruginosa.* and *A. baumannii* for the whole year
- OG OB reported data for *C. jejuni* and *C. coli* for the period 1.10. – 31.12.2022.
- OS NZZJZ reported data for *C. jejuni* and *C. coli* for the period 1.10. – 31.12.2022.
- PK OŽB reported data for *C. jejuni* for the period 1.10. – 31.12.2022.
- PŽ OŽB reported data for *C. jejuni* for the period 1.10. – 31.12.2022.
- PU NZZJZ reported data for *H. influenzae* and *A. baumannii* for the whole year
- RI NZZJZ reported data for *C. jejuni* and *C. coli* for the period 1.10. – 31.12.2022.
- SK ZZJZ reported data for *C. jejuni* and *C. coli* for the period 1.10. – 31.12.2022.
- ST KBC reported data for *C. jejuni* and *C. coli* for the period 1.10. – 31.12.2022.
- ST NZZJZ reported data for *C. jejuni* for the period 1.10. – 31.12.2022.
- VK ZZJZ reported data for *S. pneumoniae, S. aureus/*MSSA, *S. aureus*/MRSA, *E. faecium, H. influenzae* and *A. baumannii* for the whole year (isolates from OB Vinkovci)
- ZG KBC reported data for *S. pneumoniae, S. aureus/*MSSA, *S. aureus*/MRSA and *H. influenzae* for the period 3.10. – 3.1.2022., *E. faecalis and E. coli* for the period 3.10. – 11.10.2022*, E. faecium* and *A. baumannii* for the period 3.10. – 11.11.2022., *P. mirabilis* for the period 3.10. – 19.10.2022., *K. pneumoniae* for the period 3.10. – 12.10.2022., *Enterobacter* spp*., Klebsiella aerogenes, Serratia* spp. and *Citrobacter* spp*.,* and *P. aeruginosa* for the period 3.10. – 19.10.2022.
- ZG KBD reported data for *C. jejuni* for the period 1.10. – 31.12.2022.

- ZG KBCSM reported data for *C. jejuni* and *C. coli* for the period 1.10. – 31.12.2022.
- ZG KBM reported data for *S. pneumoniae* for the whole year
- ZG KDB reported data for *A. baumannii* for the whole year
- ZG NZZJZ reported data for *E. faecium* and *A. baumannii* for the period 3.10. – 31.12.2022., *E. coli* for the period 7.10. – 11.11.2022., *P. mirabilis, K. pneumoniae, Enterobacter* spp.*, Klebsiella aerogenes, Serratia* spp. and *Citrobacter* spp. for the period 7.11. – 25.11.2022. and *P. aeruginosa.* for the period 3.10. – 25.11.2021.
- ZG KBSD reported data for *C. jejuni* for the period 1.10. – 31.12.2022.

Two laboratories reported shigella isolates: RI NZZJZ *S. sonnei* (1) and ZG KIB *S. flexnerii* (1) and *S. sonnei* (2). Altogether four shigella isolates were reported in 2022.

In 2022 altogether 1 043 anaerobic bacteria were isolated, *Cutibacterium acnes* (176); *Bacteroides* spp. (611); *Prevotella* spp. (156); *Fusobacterium necroforum* (28); *Clostridium perfringens* (72). They were isolated in 22 centers: ČK ZZJZ *Bacteroides* spp. (24); IG ZZJZ *Bacteroides* spp. (1); KA OB *Cutibacterium acnes* (4), *Bacteroides* spp. (21), *Prevotella* spp. (8), *Fusobacterium necroforum* (2), *Clostridium perfringens* (13); OG OB *Bacteroides* spp. (7); OS KBC *Cutibacterium acnes* (7), *Bacteroides* spp. (61), *Prevotella* spp. (41); PU NZZJZ *Bacteroides* spp. (6), *Clostridium perfringens* (2); PŽ OŽB *Bacteroides* spp. (6); RI KBC *Cutibacterium acnes* (7), *Bacteroides* spp. (60), *Prevotella* spp. (10), *Fusobacterium necroforum* (2), *Clostridium perfringens* (15); SB ZZJZ *Cutibacterium acnes* (1), *Bacteroides* spp. (5), *Clostridium perfringens* (2); SK ZZJZ *Cutibacterium acnes* (1), *Bacteroides* spp. (4); ST KBC *Cutibacterium acnes* (8), *Bacteroides* spp. (53) *Prevotella* spp. (9); *Clostridium perfringens* (8); ŠI ZZJZ *Cutibacterium acnes* (10), *Bacteroides* spp. (7), *Fusobacterium necroforum* (1); VK ZZJZ *Cutibacterium acnes* (1), *Bacteroides* spp. (5), *Clostridium perfringens* (2); VT ZZJZ *Bacteroides* spp. (2), *Prevotella* spp. (1); VŽ ZZJZ *Cutibacterium acnes* (16), *Bacteroides* spp. (42), *Prevotella* spp. (19), *Fusobacterium necroforum* (1), *Clostridium perfringens* (7); ZG KBD *Cutibacterium acnes* (16), *Bacteroides* spp. (30), *Prevotella* spp. (9), *Fusobacterium necroforum* (1), *Clostridium perfringens* (2); KBM *Cutibacterium acnes* (1), *Bacteroides* spp. (18), *Prevotella* spp. (5), *Clostridium perfringens* (11); ZG KBCSM *Cutibacterium acnes* (91), *Bacteroides* spp. (197), *Prevotella* spp. (43), *Fusobacterium necroforum* (16), *Clostridium perfringens* (5); ZG KIB *Cutibacterium acnes* (2), *Bacteroides* spp. (2), *Fusobacterium necroforum* (3); ZG HZJZ *Bacteroides* spp. (2), *Prevotella* spp. (1); ZG KDB *Bacteroides* spp. (20), *Prevotella* spp. (1); ZG KBSD *Cutibacterium acnes* (12), *Bacteroides* spp. (38), *Prevotella* spp. (9), *Fusobacterium necroforum* (2), *Clostridium perfringens* (2).

DISKUSIJA

Epidemija SARS-CoV-2 virusa je značajno utjecala na pojavnost respiratornih infekcija poglavito tijekom 2020.g. kad su držanje socijalne distance i ostale protuepidemijske mjere bile najrigoroznije. Sukladno tome, u 2020.g. je bio zabilježen značajno manji broj respiratornih patogena, no u 2021.g., uz ublažavanje protuepidemijskih mjera, broj prijavljenih pneumokoka i hemofilusa, ali ne i streptokoka grupe A, se opet povećao i gotovo dostigao brojnost registriranu u predepidemijsko doba. U 2022.g. nakon dvogodišnjeg razdoblja niskih stopa sterptokoknih infekcija svjedočili smo naglom porastu prijavljenih streptokoka grupe A (12.341 u 2019.g., 4.553 izolata u 2020.g., 2.570 izolata u 2021.g., te 8.978 izolata u 2022.g.). Dinamika učestalosti streptokoknih infekcija se bolje očitava u usporedbi sezona jesen / zima te usporedba predpandemijske sezone 2018./19. i postpandemijske 2022./23. pokazuje da je ove sezone došlo do porasta incidencije streptokoknih infekcija čak i u odnosu na predpandemijsko razdoblje (podaci Klinike za infektivne bolesti). Srećom, stope rezistencije nisu porasle, već su se, naprotiv, smanjile i za makrolide u 2022.g. iznose 6% (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 nešto niža negoli prethodnih godina (konstitutivna 1% u 2022.g., 5% u 2021.g., 4% u 2020.g.; inducibilna 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, *Haemophilus influenzae* i *Moraxella catarrhalis* se smatraju respiratornim patogenima, no često se nalaze i kao dio fiziološke mikrobiote gornjih dišnih puteva u zdravih ljudi ili tijekom virusne infekcije gornjih dišnih puteva. Izolati pneumokoka i hemofilusa opisani u ovom poglavlju potječu pretežno iz briseva nazofarinksa koji pokazuju nisku specifičnost i osjetljivost i ne preporučuju se kao uzorci za dijagnosticiranje etiologije infekcija gornjih dišnih puteva, no mogu poslužiti za epidemiološko istraživanje osjetljivosti ovih bakterijskih vrsta na antibiotike. Neinvazivni pneumokoki često pokazuju veće stope rezistencije negoli invazivni izolati. Rezistencija invazivnih pneumokoka opisana je u poglavlju o invazivnim izolatima i mjerodavnija je kao putokaz za primjenu antimikrobne terapije. Praćenje stopa rezistencije ukupnih pneumokoka omogućuje, međutim, uočavanje bitnih trendova u širenju rezistencije. U Hrvatskoj je rezistencija pneumokoka na penicilin za sada još uvijek niska (5% u 2022.g. 4% u 2021.g., 3% u 2020.g., 2019.g. i 2018.g., 2% u 2017.g.) i parenteralni penicilin je još uvijek lijek izbora u liječenju pneumokoknih pneumonija. Empirijsko liječenje pneumonije treba, međutim, započeti višim dozama penicilina kako bi se učinkovito djelovalo na pneumokoke koji pokazuju osjetljivost samo uz povećanu izloženost penicilinu. Do 2019.g. takvi izolati su se nazivali intermedijarnima, no od 2019.g. EUCAST je pojam intermedijarne osjetljivosti zamijenio pojmom osjetljivosti uz povećanu izloženost, sugerirajući da su i takvi izolati podložni liječenju ispitivanim antibiotikom, samo uz povećano izlaganje, što se u slučaju parenteralnog penicilina lako postiže povećanjem doze. Udio pneumokoka osjetljivih na penicilin uz povećanu

izloženost u 2022.g. iznosi 13% i nešto je niži od stopa zadnjih godina (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 2022.g. iznosi 18% što je podjednako prošlogodišnjoj stopi (20%). 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 2022.g., 97% svih pneumokoka ima MIK penicilina ≤2.0 mg/L i reagirat će na dozu od 6x2.4g (6x4MIU), 95% pneumokoka ima MIK penicilina ≤1.0 mg/L i reagirat će na dozu od 4x2.4g (4x4MIU) ili 6x1.2g (6x2MIU), a 92% pneumokoka ima MIK penicilina ≤0.5 mg/L i reagirat će na dozu od 4x1.2g (4x2MIU). Ove stope su podjednake prošlogodišnjima. Zbog povoljnijih farmakodinamskih osobina i dobre djelotvornosti na pneumokoke i hemofiluse, amoksicilin/ampicilin se češće od penicilina upotrebljava kao prva linija u liječenju upale uha, sinuitisa i pneumonija. U 2022.g. je bilo 92% osjetljivih pneumokoka koji su dostupni liječenju standardnom dozom oralnog amoksicilina (3x500mg) i parenteralnog ampicilina (3x2g), što je podjednako prijašnjim stopama (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 kao i prošle godine obuhvatiti 95% pneumokoka (95% u 2021.g. i 2022.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) te u ovogodišnjoj publikaciji nije više uvršten graf s prikazom raspona MIK-ova ampicilina / amoksicilina. Iz istog razloga stopa izolata obuhvaćenih parenteralnim ampicilinom je identična stopi za oralni amoksicilin i izgleda nešto niža u odnosu na prethodne godine kad je za parenteralni ampicillin vrijedila za jedno razrjeđenje viša granična MIK vrijednost. Osjetljivost na parenteralni ampicillin uz pojačano doziranje (4x2g) ove godine tako iznosi 95%, a prethodnih godina, uz nešto višu graničnu vrijednost za rezistentne izolate, je iznosila 98% u 2021.g., 97% u 2020.g., 2019.g. i 2018.g. U 2022.g. su još uvijek svi laboratoriji testirali osjetljivost na ampicillin / amoksicilin paralelno disk difuzijskom metodom i određivanjem MIK-ova. Kako su obje metode pokazale visoku podudarnost ubuduće će se službeno koristiti disk difuzijska metoda i u ovoj publikaciji su objavljeni rezultati dobiveni tom metodom. Amoksicilin / ampicillin je i nadalje vrlo dobra opcija i za oralnu i za parenteralnu empirijsku terapiju respiratornih bakterijskih infekcija. Usprkos povećane potrošnje makrolida u 2021.g., rezistencija pneumokoka na makrolide je niža negoli prethodnih godina (24% u 2022.g., 28% u 2021.g., 29% u 2020.g., 31% u 2019.g., 32% u 2018.g.). Rezistencija na ko-trimoksazol pokazuje daljnji trend pada (43% u 2010.g., 35% u 2011.g., 29% u 2012.g., 27% u 2013.g., 29% u 2014.g., 26% u 2015.g., 23% u 2016.g., 22% u 2017.g., 20% u 2018.g., 17% u 2019.g. i 2020.g., 14% u 2021.g., 13% u 2022.g.). Rezistencija na i tetraciklin također pokazuje blagi trend pada (15% u 2022.g., 17% u 2021.g., 16% u 2020.g., 18% u 2019.g., 19% u 2018.g., 28% u 2010.g.). Otpornost pneumokoka na respiratorne kinolone je još uvijek niska (1%) no ovi antibiotici se ne bi smjeli široko upotrebljavati u empirijskoj terapiji respiratornih infekcija.

Broj izolata *H.influenzae* se u 2022.g. vratio na razinu blizu onoj u predpandemijsko vrijeme (1.158 izolata u 2022.g., 942 izolata u 2021.g., 434 izolata u 2020.g., 1.305 izolata u 2019.g.). Rezistencija na amoksicilin je u 2022.g. bila slična prošlogodišnjim stopama (14% u 2014.g., 20% u 2015.g., 24% u 2016. i 2017.g., 22% u 2018.g., 25% u 2019.g. te 22% u 2020.g., 20% u 2021.g., 22% u 2022.g.). Prelaskom na EUCAST standarde detektiramo više izolata s graničnom rezistencijom na ampicilin, uzrokovanom promjenom ciljnih PBP molekula, što ponekad dovodi, možda, i do precjenjivanja rezistencije. Prema EUCAST standardima i za osjetljive hemofiluse potrebne su više doze

oralnog amoksicilina (3x750mg tj. 3x1g) i oralnog cefuroksima (2x500mg). Iz tog razloga parenteralni pripravci amoksicilina /ampicilina sa ili bez inhibitora imaju kategorije „S“ i „R“ a pareneteralni cefuroksim „S”, „I” i „R”, dok njihovi oralni pripravci mogu imati samo kategorije „I“ i „R“. Rezistencija na ko-trimoksazol (20%) je slična stopama rezistencije prethodnih godina, a rezistencija na ceftriakson nije uočena.

Staphylococcus aureus je glavni uzročnik infekcija kože i mekih tkiva i kao takav ujedno i najčešći uzročnik infekcija kirurških rana. Rezistencija na penicillin se proširila još 1940-tih godina i danas su još samo rijetki izolati osjetljivi na penicilin. Osim uobičajene rezistencije na penicilin te umjerenih stopa rezistencije na makrolide (17%) i klindamicin (14%) meticilin senzitivni *Staphylococcus aureus* (MSSA) sojevi ne pokazuju značajnije stope rezistencije na druge antistafilokokne antibiotike. Od 2021.g. se uvelo testiranje osjetljivosti stafilokoka na tetraciklin i rezistencija na tetraciklin kod MSSA iznosi 4% u obje godine praćenja. Stečena rezistencija na kinolone kod MSSA je niska (2%) no i kod osjetljivih izolata, samo se od moksifloksacina može očekivati osjetljivost uz standardno doziranje, dok ciprofloksacin i levofloksacin djeluju samo ako se primjenjuju u višoj dozi. Meticilin rezistentni *Staphylococcus aureus* (MRSA) sojevi su rezistentni na sve beta-laktamske antibiotike (osim novijih cefalosporina, ceftarolina i ceftobiprola), a često pokazuju križnu rezistenciju i na druge klase antibiotika. Nakon 2008.g. uočen je trend pada udjela MRSA sojeva i najniže stope (12%) su zabilježene 2013. i 2014.g., no od 2015.g. stopa MRSA opet počinje rasti, a nagli skok je, nažalost, zabilježen 2020.g. i još više u 2021.g. (25% u 2007. g., 26% u 2008. g., 21% u 2009. g., 16% u 2010. g., 14% u 2011. g., 13% u 2012. g., 12% u 2013.g. i 2014.g., 14% u 2015.g., 16% u 2016.g., 15% u 2017.g., 16% u 2018.g. i 2019.g., 21% u 2020.g., 27% u 2021.g.). U 2022.g. trend porasta stopa je, srećom, zaustavljen, stopa MRSA iznosi 21%, ali povoljno je i da je prijavljen manji ukupan broj izolata MRSA (955 izolata u 2022.g., 1.238 u 2021.g., 699 u 2020.g., 784 u 2019.g.). Istovremeno, prijavljen je oko 10% veći broj izolata MSSA u odnosu na prethodnu godinu. Udio MRSA sojeva rezistentnih na klindamicin (77%) je niži u odnosu na prošlu godinu (87%), prvenstveno na račun sojeva s inducibilnom rezistencijom na klindamicin (17% u 2022.g., 29% u 2021.g., 28% u 2020.g., 29% u 2019.g., 26% u 2018.g., 32% u 2017.g., 28% u 2016.g., 21% u 2015.g., 16% u 2014.g.). Rezistencija MRSA na gentamicin (10%) je nešto niža negoli prethodne godine i potvrđuje trend pada rezistencije (91% u 2006.g., 81% u 2009.g., 77% u 2010.g., 69% u 2011.g., 64% u 2012.g., 59% u 2013.g., 43% u 2014.g., 38% u 2015.g., 32% u 2016.g., 23% u 2017.g., 18% u 2018.g. i 2019.g., 13% u 2020.g. i 2021.g.). Rezistencija na linezolid i vankomicin nije uočena. Udio izolata s MIK-om vankomicina od 2.0 mg/L je podjednak prethodnim godinama (11% u 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 viša negoli prethodne godine (11% u 2022.g., 5% u 2021.g.), a udio izolata koje treba liječiti višim dozama je podjednak (8% u 2022.g., 9% u 2021.g.). U slučaju pneumonije, na ceftarolin je rezistentno 19% izolata, što je porast u odnosu na prethodnu godinu (14%). Stopa rezistencije na ko-trimoksazol je nešto viša negoli prethodne dvije godine (7% u 2022.g., 5% u 2021.g. i 2020.g.), a rezistencija na tetraciklin, čije praćenje je uvedeno 2021.g., iznosi 10% za obje godine praćenja i nije značajno viša od stopa rezistencije kod MSSA. Rezistencija na rifampicin je i dalje niska (4%), no ovaj antibiotik se ne preporuča u monoterapiji stafilokoknih infekcija zbog visokog udjela rezistentnih mutanti u populaciji.

Enterokoki su prirodno rezistentni na mnoge grupe antibiotika, a gotovo svi izolati *Enterococcus faecium* pokazuju rezistenciju na ampicilin. Svi enterokoki pokazuju urođenu rezistenciju niskog stupnja na aminoglikozide, ali se aminoglikozidi kod divljih tipova enterokoka još uvijek mogu upotrebljavati u terapiji kombiniranoj s ampicilinom ili glikopeptidima u svrhu postizanja sinergističkog učinka. Kod sojeva visoko rezistentnih na aminoglikozide, ovi se antibiotici ne mogu upotrebljavati niti u kombiniranoj terapiji. Udio sojeva s visokom rezistencijom na aminoglikozide iznosi 23%

za *E. faecalis* i 38% za *E .faecium*, što je slično kao i prethodnih godina. Rezistencija na vankomicin je još uvijek rijetka u *E. faecalis* (<1%), dok rezistencija na vankomicin u *E. faecium* pokazuje trend porasta s naglim skokom u 2021.g. (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.). Porast rezistencije na vankomicin uočava se od 2015.g., kad se vankomicin rezistentni *E. faecium* (VRE) izolati počinju s većom učestalošću javljati u raznim regijama Hrvatske, a ne samo u zagrebačkim bolnicama kao što je to bilo u početku. U 2021.g., uz porast stope rezistencije na vankomicin uočen je i porast ukupnog broja *E.faecium* u odnosu na prethodnu godinu, ali i na predepidemijsko razdoblje. U 2022.g. se zadržala i visoka stopa rezistencije na vankomicin i visoki apsolutni broj takvih izolata, veći negoli u predpandemijsko doba (1.271 izolata u 2022.g., 1.242 izolata u 2021.g., 859 izolata u 2020.g., 1.074 izolata u 2019.g.). Istovremeno, ukupan broj izolata *E. faecalis* je podjednak broju izolata u predpandemijskoj godini (5.502 u 2022.g., 5.419 u 2021.g., 3.764 u 2020.g., 5.264 u 2019.g). U 2014.g. EUCAST je uveo testiranje osjetljivosti enterokoka na kinolone, s tim da se disk difuzijom testira osjetljivost na norfloksacin kao indikator osjetljivosti na ciprofloksacin i levofloksacin. Kinoloni su namijenjeni liječenju enterokoknih infekcija, samo ako se radi o nekompliciranim infekcijama mokraćnog sustava. Rezistencija na kinolone u *E. faecalis* i *E. faecium* podjednaka je stopama prethodnih godina (22% i 75% u 2017.g., 22% i 84% u 2018.g., 22% i 85% u 2019.g., 23% i 81% u 2020.g., 23% i 87% u 2021.g., 22% i 86% u 2022.g.). Za nekomplicirane uroinfekcije koje urokuje *E. faecalis* može se koristiti i nitrofurantoin na koji ovaj uzročnik pokazuje nisku rezistenciju (2%).

Escherichia coli je najčešći uzročnik infekcija mokraćnog sustava (IMS), a ostale enterobakterije češće uzrokuju komplicirane IMS ili infekcije raznih sustava povezane s bolničkom skrbi. S obzirom da su enterobakterije dio fiziološke mikrobiote često su izložene primjeni antibiotika, a širenje jednom nastalih mutanti teško je uočiti i kontrolirati. Broj prijavljenih izolata *E.coli* je u pandemijskoj 2020.g. bio znatno niži od uobičajenog, no u 2021.g. broj prijavljenih izolata je bio sličan, a u 2022.g. i veći negoli u predepidemijskom razdoblju (21.770 izolata u 2022.g., 18.825 u 2021.g., 12.912 u 2020.g., 20.284 u 2019.g.), što govori u prilog da se dijagnostička aktivnost za bakterijske infekcije, reducirana u početku covid epidemije, brzo povratila. Od početka praćenja *E. coli* pokazuje visoku rezistenciju na ampicilin, koja i u 2022.g. iznosi 46%, slično kao i prethodnih godina. Amoksicilin s dodatkom klavulanske kiseline, međutim, pokazuje dobru djelotvornost jer klavulanska kiselina uspješno blokira beta-laktamaze širokog spektra i većinu beta-laktamaza proširenog spektra (engl. "extended spectrum beta-lactamases, ESBL"). Kombinacija s klavulanskom kiselinom, međutim, ograničava primjenu amoksicilina u visokim dozama, kakve su često potrebne kod ozbiljnih sistemnih infekcija. U 2014.g. EUCAST je po prvi puta razdvojio interpretaciju osjetljivosti na amoksicilin s klavulanskom kiselinom ovisno o tome radi li se o nekompliciranoj IMS ili drugim oblicima infekcije. Nakon te podjele, stope rezistencije su ostale podjednake odnosno pokazuju blagi trend porasta, ako se interpretiraju za primjenu kod nekompliciranih IMS (7% u 2013.g. i 2014.g., 9% u 2015.g., 10% u 2016.g., 2017.g., 2018.g. i 2019.g., 11% u 2020.g., 12% u 2021.g., 10% u 2022.g.) 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.). U 2022.g. se zaustavio trend laganog porasta rezistencije te su se stope vratile na vrijednosti u predpandemijskoj godini. Od 2020.g. u EUCAST standardima za enterobakterije se uvela posebna interpretacja osjetljivosti na parenteralni i oralni cefuroksim s tim da za oralnu primjenu postoje kategorije „S" i „R" ali se preporuča samo za nekomplicirane uroinfekcije, dok se parenteralni cefuroksim može primjenjivati i za sistemne infekcije ali samo u višoj dozi te za parenteralni cefuroksim postoje samo kategorije „I" i „R". Rezistencija na cefuroksim je slična prošlogodišnjoj (11% u 2022.g., 10% u 2021.g., 11% in 2020). Rezistencija na cefalosporine treće generacije (9% do 10%) je slična

prošlogodišnjim stopama (8% do 11%). Novi pripravci cefalosporina s inhibitorima beta-laktamaza, ceftazidim / avibaktam i ceftalozan / tazobaktam te imipenema s inhibitorom beta-laktamaza relebaktamom 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 (3% rezistentnih izolata). U 2022.g. su izolati enterobakterija po prvi puta testirani na cefiderokol, i rezistencija *E.coli* na ovaj antibiotik iznosi 2%. Rezistencija na ciprofloksacin je 2017.g. dosegla 20%, ali od tada stagnira i ovogodišnja stopa se ne razlikuje bitno od prošlogodišnjih stopa (14% u 2012. i 2013.g., 17% u 2014.g., 18% u 2015.g., 19% u 2016.g., 20% u 2017.g. i 2018.g., 19% u 2019.g., 18% u 2020.g., 19% u 2021.g., 18% u 2022.g.). Stope rezistencije na ko-trimoksazol (26%), gentamicin (10%), amikacin (1%), nitrofurantoin (3%), fosfomicin (1%) i nitroksolin (<1%) su jednake 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 2022.g. iznosi za ampicilin 46%, za ko-amoksiklav 24%, za piperacilin/tazobaktam 2%, za cefalosporine 3. i 4. generacije od 9% za cefepim do 17% za cefiksim, što je slično prošlogodišnjim stopama. I u 2022.g. registrirana je niska rezistencija na nove cefalosporine u kombinaciji s inhibitorima beta-laktamaza, ceftazidim / avibaktam (1% u 2018.g., 2019.g., 2020.g. i 2021.g., <1% u 2022.g.), ceftalozan / tazobaktam (10% u 2018.g., 9% u 2019.g., 8% u 2020.g., 7% u 2021.g., 6% u 2022.g.). Stope rezistencije na ciprofloksacin (27%), gentamicin (22%), amikacin (10%) i ko-trimoksazol (40%) su također slične ili jednake prošlogodišnjima. Zbog svoje urođene otpornosti na kolistin, tigeciklin te niže osjetljivosti na imipenem *Proteus mirabilis* i drugi *Proteus* spp. bi u budućnosti mogli predstavljati sve veći problem, naročito kod uroloških bolesnika i infekcija povezanih s bolničkom skrbi. Rezistencija na novi antibiotik cefiderokol, prvi put testiran u 2022.g. je 1%.

Klepsijele i enterobakteri često uzrokuju infekcije povezane s bolničkom skrbi te već dugi niz godina pokazuju visoke stope rezistencije. *Klebsiella pneumoniae* je prirodno rezistentna na ampicilin no rezistencija na ostale beta-laktame je stečena uslijed dugotrajnog izlagnja antibioticima. Stope rezistencije na cefalosporine treće i četvrte generacije (38% za cefepim do 40% za ceftriakson i cefiksim) su nešto niže negoli prošlogodišnje, ali i dalje više negoli u predepidemijskoj godini (41% do 43% u 2021.g., 35% do 38% u 2019.g.). I rezistencija na ko-amoksiklav (38% u 2018.g. i 2019.g., 45% u 2020.g., 43% u 2021.g., 41% u 2022.g.) ceftolozan / tazobaktam (20% u 2018.g. i 2019.g., 25% u 2020.g., 23% u 2021.g. i 2022.g.) te piperacilin / tazobaktam (19% u 2018.g., 21% u 2019.g., 27% u 2020.g., 31% u 2021.g., 30% u 2022.g.) je slična prošlogodišnjim stopama. Rezistencija na ceftazidim / avibaktam je i dalje vrlo niska (2% u 2018.g., 2019.g., 2020.g., 1% u 2021.g., 2% u 2022.g.) te je ovaj antibiotik, sa svojom djelotvornošću na sojeve koji proizvode ESBL i AmpC betalaktamaze, ali i velik dio karbapenemaza (KPC, OXA-48), najučinkovitiji beta-laktam kod klepsijela. Rezistencija na nove beta-laktame, cefiderokol i imipenem / relebaktam, iznosi 7% i 11%. Nakon što je broj klepsijela rezistentnih na karbapeneme po prvi puta u 2014.g. dosegao razinu vidljivu kao postotak rezistencije na imipenem i meropenem (1%), te su stope u 2019.g. narasle na 5% i 6%, a u pandemijskoj 2020.g. na 7% i 16% uz dodatno 8% i 2% izolata osjetljivo uz povećanu izloženost („I" kategorija). Te razine su ostale slične i u 2021.g. (8% i 14% rezistentnih te 4% i 2% osjetljivih uz povećanu izloženost) i 2022.g. (9% i 13% rezistentnih te 4% i 3% osjetljivih uz povećanu izloženost). Ukupan broj izoliranih klebsijela je, međutim, nastavio rasti (5.864 izolata u 2019.g., 4.244 izolata u 2020.g., 5.601 izolata u 2021.g., 6.245 izolata u 2022.g.) što ukazuje na još veće širenje na

karbapeneme rezistentnih izolata. Rezistencija na ciprofloksacin (40%), gentamicin (26%), amikacin (7%) i ko-trimoksazol (38%) pokazuje stope slične prošlogodišnjima.

Enterobakteri, citrobakteri i seracije čine grupu enterobakterija koje prirodno posjeduju inducibilne cefalosporinaze i s izuzetkom *Citrobacter koseri* pokazuju rezistenciju ne samo na ampicilin već i na ko-amoksiklav i cefalosporine prve generacije. Od 2019.g. *Enterobacter aerogenes* je preimenovan u *Klebsiella aerogenes* no ta vrsta se i nadalje analizira unutar ove grupe enterobakterija 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 koji stabilno hiperproduciraju AmpC cefalosporinaze i time uvjetuju rezistenciju i na cefalosporine treće generacije. Udio derepresiranih mutanti rezistentnih na cefalosporine treće i četvrte generacije (10% za cefepim do 27% za cefiksim) je u okvirima stopa registriranih prošlih godina (16% do 32% u 2017.g., 10% do 25% u 2018.g., 12% do 26% u 2019.g., 12% do 28% u 2020.g., 10% do 28% u 2021.g.), a i rezistencija na karbapeneme, koja je postala vidljiva 2013.g. (1%), ostala je gotovo jednaka (1% rezistentnih i 1% osjetljivih uz povećano izlaganje za imipenem i 1% rezistentnih za meropenem, 5% rezistentnih za ertapenem) i u 2022.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 u 2022.g. stopa rezistencije u enterobaktera (11% u 2018.g. i 2019..g., 8% u 2020.g. i 2021.g., 7% u 2022.g.) je ipak nešto niža od stopa rezistencije na cefepim (10% u 2018.g., 12% u 2019.g. i 2020.g., 10% u 2021.g. i 2022.g.) i piperacilin / tazobaktam (9% u 2018.g., 10% u 2019.g. i 2020.g., 13% u 2021.g. i 2022.g.). Stope rezistencije na ciprofloksacin (10%), gentamicin (8%), amikacin (1%) i ko-trimoksazol (11%) su identične prošlogodišnjima, a rezistencija na nove beta-laktame, cefiderokol i imipenem / relebaktam iznosi 2%.

Multiplorezistentni *Pseudomonas aeruginosa*, poglavito sojevi rezistentni na karbapeneme, već dugi niz godina predstavljaju jedan od najvećih problema rezistencije u Hrvatskoj. Rezistencija na imipenem i meropenem je u 2020.g. značajno porasla, no nije nastavila rasti u 2021.g. i 2022.g. (17% u 2018.g., 18% u 2019.g., 23% i 22% u 2020.g., 20% i 21% u 2021.g., 21% i 18% u 2022.g.). Ni rezistencija na nove cefalsosporine s inhibitorom, ceftazidim / avibaktam (4% u 2018.g., 6% u 2019.g., 7% u 2020.g., 6% u 2021.g. i 2022.g.) i ceftalozan / tazobaktam (4% u 2018.g., 6% u 2019.g., 7% u 2020.g., 5% u 2021.g. i 2022.g.) se ne povećava, a rezistencija na cefiderokol koji je po prvi puta uključen u praćenje u 2022.g. iznosi 1%. Rezistencija na piperacilin / tazobaktam (10% u 2019.g., 12% u 2020.g., 9% u 2021.g., 10% u 2022.g.), ceftazidim (16% u 2019.g., 21% u 2020.g., 15% u 2021.g., 17% u 2022.g.) i cefepim (13% u 2019.g., 16% u 2020.g., 13% u 2021.g., 15% u 2022.g.) je nakon porasta u 2020.g. ponovno došla na stope slične onima u predepidemijskom razdoblju. Rezistencija na ciprofloksacin (24% u 2019.g. i 2020.g, 20% u 2021.g., 25% u 2022.g.) je ponovno porasla, a na amikacin je ista kao prethodne godine (6%). Od 2020.g. EUCAST standardi ne predviđaju testiranje *P. aeruginosa* na gentamicin jer smatraju da ovaj antibiotik nije djelotvoran za pseudomonasne infekcije. Za aminoglikozide se općenito preporuča da se za infekcije izvan urotrakta koriste samo u kombinaciji s drugim antibioticima. Opće je poznato da se za liječenje pseudomonasnih infekcija koriste više doze antibiotika što je od 2020.g. jasno iskazano u EUCAST standardima kao nepostojanje „S" kategorije (osjetljiv uz standardno doziranje) kod pseudomonasa za mnoge antibiotike (ceftazidim, cefepim, piperacilin/tazobaktam, imipenem, ciprofloksacin). Za testiranje osjetljivosti na kolistin potrebno je učiniti test mikrodilucije u bujonu, što je bitno zahtjevnije i skuplje od testiranja disk difuzijom te se u ovom slučaju odstupa od pravila da se u razdoblju praćenja rezistencije svi izolati testiraju na sve antibiotike i na kolistin se testiraju samo

multiplo, poglavito na karbapeneme rezistentni sojevi. Podatak o rezistenciji na kolistin kod *P.aeruginosa* se, stoga, ne može uspoređivati sa stopama rezistencije na druge antibiotike, ali omogućuje praćenje kolistinske rezistencije u subpopulaciji multiplorezistentnih pseudomonasa. U 2021.g. ta je stopa bila značajno viša negoli prethodnih godina, ali se u 2022.g. vratila na 3% (3% u 2019.g. i 2020.g., 8% u 2021.g., 3% u 2022.g.).

Rezistencija na karbapeneme kod *Acinetobacter baumannii* se u Hrvatskoj naglo proširila od 2008.g. i u 2022.g. su se zadržale visoke stope rezistencije na imipenem i meropenem (90% i 91%). Najdrastičniji učinak epidemije COVID-19 na širenje rezistencije se u Hrvatskoj, ali i velikom broju drugih europskih zemalja, ogledao u povećanom ukupnom broju prijavljenih izolata acinetobaktera rezistentnog na karbapeneme, no u 2022.g. su se apsolutni brojevi srećom ipak smanjili (1.740 izolata u 2019.g., 2.087 izolata u 2020.g., 2.582 izolata u 2021.g., 1.605 u 2022.g.), što je vjerojatno posljedica smanjenog pritiska na liječenje u jedinicama intenzivne njege i racionalizacije uporabe osobne zaštitne opreme, u prvom redu rukavica, pri njezi oboljelih od COVID-a. Prema EUCAST standardima ne postoje jasni dokazi o učinkovitosti ampicilin/sulbaktama na acinetobaktere, no kako je to jedan od rijetkih antibiotika koji još pokazuju djelotvornost *in vitro*, ovaj antibiotik se u Hrvatskoj testira i interpretira prema američkim standardima. Rezistencija i osjetljivost uz povećanu izloženost za ampicilin/sulbaktam kontinuirano pokazuju visoke stope (40% i 16% u 2018.g., 34% i 20% u 2019.g., 31% i 18% u 2020.g., 32% i 23% u 2021.g., 29% i 26% u 2022.g.). Kao i kod pseudomonasa, kolistin se testira samo kod na karbapeneme rezistentnih izolata, no kako već nekoliko godina takvi izolati čine >90% ukupnih acinetobaktera, može se smatrati da se kolistin testira na skoro svim izolatima i stope kolistinske rezistencije se mogu uspoređivati sa stopama za ostale antibiotike. Stope rezistencije acinetobaktera na kolistin su još uvijek niske (2% u 2020.g., 1% u 2021.g. i 2022.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.). ESBL sojevi su i dalje rijetki među salmonelama i u 2022.g. rezistencija na ceftazidim i ceftriakson je iznosila 2% i 1%. Rezistencija na ko-amoksiklav (7%) je slična, a na ko-trimoksazol (4%) identična prošlogodišnjim stopama. Zabrinjava, međutim, nagli skok rezistencije salmonela na ciprofloksacin. Do 2013.g. osjetljivost salmonela na ciprofloksacin na razini Hrvatske je bila 100%, a rezistencija na nalidiksičnu kiselinu, koja je bolji pokazatelj niske razine rezistencije na kinolne je bila do 2%. Od 2014.g. EUCAST je uveo preciznije testiranje osjetljivosti na kinolone (ciprofloksacin) preko pefloksacinskog diska što je vjerojatno utjecalo na registriranje stopa rezistencije na ciprofloksacin od 2% u 2014.g., no i od tada rezistencija na ciprofloksacin ima tenddenciju blagog porasta, a u 2022.g. je naglo skočila u mnogim regijama i na nacionalnoj razini (4% u 2015.g., 3% u 2016.g., 4% u 2017.g., 2018.g. i 2019.g., 5% u 2020.g., 4% u 2021.g., 18% u 2022.g.). Ujedno se u 2022.g. ukupan broj izolata vratio na vrijednosti u predepidemijsko doba, nakon dvije godine rjeđeg izoliranja salmonela, vjerojatno zbog ograničenja društvenih aktivnosti u doba epidemije (2.031 izolata u 2019.g., 1.169 izolata u 2020.g., 1.278 izolata u 2021.g., 1.858 izolata u 2022.g.)

Osjetljivost u *Campylobacter coli* i *Campylobacter jejuni* se prati od 2013.g. Trend porasta rezistencije na ciprofloksacin se u 2019.g. zaustavio, ali je rezistencija u 2022.g. ponovno nešto viša negoli prethodnih godina (u 2015.g. 52% i 50%, u 2016.g. 60% obje vrste, u 2017.g. 69% i 66%, u 2018.g. 78% i 76%, u 2019.g. 71% i 75%, u 2020.g. 74% i 71%, u 2021.g. 77% obje vrste, u 2022.g. 79% i 82%). 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 *C. coli* i <1% za *C. jejuni*) je i dalje niska. Nakon zaustavljanja trenda porasta rezistencije na tetraciklin u

2020.g., u 2022.g. su ponovno registrirane više stope rezistencije i u *C.coli* i u *C.jejuni* (35% i 30% u 2017.g., 41% i 36% u 2018.g., 46% i 42% u 2019.g., 35% i 41% u 2020.g., 33% i 28% u 2021.g., 37% i 43%).

U 2022.g. izolirane su samo četiri šigele iz dva laboratorija. Sva tri *S. sonnei* izolata su bila osjetljiva na ampicilin, ko-amoksiklav, ceftazidim, ceftriakson i ciprofloksacin, a jedan od tih izolata je bio rezistentan na ko-trimoksazol. *S. flexneri* izolat je bio rezistentan na ampicilin i osjetljiv na druge antibiotike.

S obzirom da je u 2022.g. EUCAST uveo odvojenu interpretaciju za različite anaerobne bakterijske vrste, od ove godine se prikazuju rezultati za vrste koje imaju specifičnu interpretaciju. Kako je velik broj anaerobnih bakterija ostao bez specifične interpretacije, u ovoj godini je prijavljeno znatno manje anaerobnih bakterijskih izolata (427 u 2022., 1.234 u 2021.). Rezistencija na penicilin je izražena u *Prevotella* spp. (57%) i *Fusobacterium necrophorum* (22%), rezistencija na metronidazol je bila izražena u *Fusobacterium necrophorum* (22%) i *Clostridium perfringens* (25%), a na klindamicin je u svih bakterijskih vrsta rezistencija iznosila iznad 20%. Rezistencija na amoksicilin s klavulanskom kiselinom nije testirana zbog nepostojanja EUCAST standarda za interpretaciju, a rezistencija na piperacilin/tazobaktam i meropenem je u svih vrsta niska (<5%).

DISCUSSION

The SARS-CoV-2 virus epidemic has significantly influenced the incidence of respiratory tract infections, especially during the year 2020 when social distancing and other anti-epidemic measures were most rigorous. Consequently, a significantly lower number of respiratory pathogens was recorded in 2020, and in 2021 the number of isolates increased close to the pre-epidemic values for haemophilus and pneumococci but not for group A streptococci (GAS). In 2022, after a two year period of very low incidence of GAS, we have witnessed a sudden increase in GAS isolates (12.341 in 2019, 4.553 in 2020, 2.570 in 2021, and 8.978 in 2022). Dynamics of streptococcal infections is even better presented if autumn / winter seasons are compared for pre-pandemic 2018 / 19 and post-pandemic 2022 / 23 seasons. Comparing calendar years did not suggest higher incidence in 2022 compared to 2019 but comparing autumn / winter seasons suggests high increase in the post-pandemic season compared to both pandemic and pre-pandemic period (oral communication, data for the University Hospital for Infectious Diseases). Luckily, resistance rates did not increase, on the contrary, macrolide resistance rate (6%) decreased compared to the previous years (10% in 2021, 8% in 2020, 9% in 2019, 10% in 2018, 7% in 2017 and 2016, 9% in 2015 and 2014, 10% in 2013, 9% in 2012, 7% in 2011, 8% in 2010, 9% in 2009, 13% in 2008). Resistance to clindamycin is also somewhat lower than in the previous years (constitutive 3% in 2022, 5% in 2021, 4% in 2020; inducible 1% in 2022, 3% in 2021 and 2020). According to the EUCAST standards, isolates with inducible clindamycin resistance used to be reported as susceptible to clindamycin with a warning to avoid prolonged therapy but since 2014 these isolates are reported as resistant to clindamycin with a note that clindamycin may still be used for short-term therapy or less severe skin and soft tissue infections. Clindamycin is recommended for use in combination with penicillin for treating severe necrotizing infections as it blocks toxin synthesis and has a more rapid antibacterial effect than beta-lactams. The clinical importance of inducible clindamycin resistance in combination treatment of severe streptococcal infections is not well studied but considering the rapid spread of such infections it is probably wise to add clindamycin to initial treatment even for infections caused by GAS with inducible clindamycin resistance. Penicillin resistance in beta-haemolitic streptococci is not yet described so penicillin remains the first drug of choice in the treatment of streptococcal infections.

Pneumococci, *Haemophilus influenzae* and *Moraxella catarrhalis* are classified as respiratory pathogens but are frequently found as part of the normal microbiota of the upper respiratory tract in healthy individuals or during a viral upper respiratory tract infection. Most of the pneumococcal and haemophilus isolates reported in this chapter originate from nasopharyngeal swabs and aspirates, samples that are not adequate for the diagnostics of bacterial upper respiratory infections but can be used for surveillance studies to estimate antimicrobial resistance rates in these pathogens. Non-invasive pneumococci often have higher resistance rates than invasive isolates. Resistance in invasive isolates is described in a separate chapter of this publication and is more relevant for choosing adequate empirical antibiotic therapy. Resistance rates in all site isolates are, however, important for epidemiological surveillance and can indicate trends in antibiotic resistance. In Croatia, penicillin resistance in pneumococci is still low (5% in 2022, 4% in 2021, 3% in 2020., 2019, and 2018, 2% in 2017) and parenteral penicillin is still a drug of first choice for treating pneumococcal pneumonia. Empirical therapy of pneumonia should, however, include higher penicillin dosing to achieve efficacy against pneumococci susceptible only with increased exposure. Until 2019 such isolates were categorised as intermediate but in 2019 EUCAST changed the term intermediate into susceptible, increased exposure, suggesting that these isolates are still treatable with the tested antibiotic but exposure to the drug should be increased. In case of pneumococci and penicillin this could be easily achieved by increasing the penicillin dosing. The rate of penicillin susceptible, increased exposure pneumococcal isolates in 2022 was 13%

which is somewhat lower compared to the rates recorded in previous years (16% in 2021, 21% in 2020 and 2019, 17% in 2018, 21% in 2017). Infections caused by penicillin susceptible, increased exposure pneumococci cannot be treated with oral penicillin and in case they involve central nervous system (CNS) they cannot be treated with parenteral penicillin either. Resistance to penicillin in case of CNS infections or other infections if treated with oral penicillin is 18% in 2022 which is similar as last year (20%). However, pneumonia caused by pneumococci that are penicillin susceptible increased exposure can still be treated with parenteral penicillin if dosing is adjusted to the minimal inhibitory concentration (MIC) of the isolate. According to the MIC range of pneumococci isolated in 2022, 97% of pneumococci have penicillin MIC ≤2.0 mg/L and will be covered by 6x2.4g (6x4MIU) dosing, 95% have penicillin MIC ≤1.0 mg/L and will be covered by 4x2.4g (4x4MIU) or 6x1.2g (6x2MIU) dosing and 92% have penicillin MIC ≤0.5 mg/L and will be covered by 4x1.2g (4x2MIU) dosing. These values are similar to the last year rates. Due to the better pharmacodynamic characteristics and good activity against pneumococci and haemophilus amoxicillin / ampicillin is used as a first line treatment of acute otitis media, sinusitis and pneumonia more frequently than penicillin. In 2022, 92% of pneumococci were treatable with standard dosing of oral amoxicillin (3x500mg) and parenteral ampicillin (3x2g) which is similar to the previous rates (90% in 2021, 87% in 2020 and 2019, 90% in 2018). Increased dose of oral amoxicillin includes 3x750mg or 3x1000mg (formulation available at the market) and covers 95% of pneumococci, same as the last year (95% in 2022 and 2021, 92% in 2020, 93% in 2019, 94% in 2018). In 2022 EUCAST decreased the MIC breakpoint between susceptible increased exposure and resistant categories for parenteral ampicillin and made it identical to the breakpoint for oral amoxicillin. For this reason, interpretation of susceptibility to parenteral ampicillin and oral amoxicillin became identical and simpler to discuss so in this year publication there was no more a need to present a graph with ampicillin MIC distributions. For this same reason, susceptibility increased exposure for parenteral ampicillin seems to be somewhat lower (95%) than in previous years when higher MIC breakpoint was applied (98% in 2021, 97% in 2020, 2019 and 2018). In 2022 all laboratories tested susceptibility to ampicillin / amoxicillin by disk diffusion and by MIC method in parallel. As both methods showed high degree of concordance, we decided to include disk diffusion results in this and future reports. In conclusion, oral and parenteral amoxicillin / ampicillin are still suitable first line antibiotics for empirical therapy of respiratory tract infections. In spite of the increased macrolide consumption in 2021, macrolide resistance in pneumococci is lower than in the previous years (24% in 2022, 28% in 2021, 29% in 2020, 31% in 2019, 32% in 2018). Resistance to co-trimoxazole is showing further decrease (43% in 2010, 35% in 2011, 29% in 2012, 27% in 2013, 29% in 2014, 26% in 2015, 23% in 2016, 22% in 2017, 20% in 2018, 17% in 2019 and 2020, 14% in 2021, 13% in 2022). Resistance to tetracycline also shows a mildly decreasing trend (15% in 2022, 17% in 2021, 16% in 2020, 18% in 2019, 19% in 2018, 28% in 2010). Resistance of pneumococci to respiratory quinolones is still low (<1%) but these drugs should not be widely used in empiric therapy of respiratory tract infections.

In 2022, the number of *H.influenzae* isolates returned to the values close to the pre-pandemic period (1.158 in 2022, 942 in 2021, 434 in 2020, 1.305 in 2019). In 2022, resistance to ampicillin was similar as in the last few years (14% in 2014, 20% in 2015, 24% in 2016 and 2017, 22% in 2018, 25% in 2019, 22% in 2020, 20% in 2021, 22% in 2022). When switching to EUCAST standards we started to detect more isolates with borderline resistance mediated by modification of the target PBP molecules, which possibly leads to a slight overestimation of clinical resistance. EUCAST standards imply that even susceptible isolates need to be treated with higher doses of oral amoxicillin (3x750mg or 3x1000mg) and oral cefuroxime (2x500mg). For this reason, parenteral amoxicillin / ampicillin with or without inhibitors has categories "S" and "R", while their oral preparations can only have categories "I" and "R". Similarly, there are “S”, “I” and “R” categories for parenteral cefuroxime, but only “I” and “R” categories for oral

cefuroxime. Resistance to co-trimoxazole (20%) is similar to resistance rates in previous years, and resistance to ceftriaxone has not been observed.

Staphylococcus aureus is the main cause of skin and soft tissue infections and as such is also the most common cause of surgical site infections. Penicillin resistance spread back in the 1940s and today only a few penicillin-susceptible isolates remain. Apart from the common resistance to penicillin and moderate rates of resistance to macrolides (17%) and clindamycin (14%), methicillin-susceptible *Staphylococcus aureus* (MSSA) strains show no significant rates of resistance to other antistaphylococcal antibiotics. Since 2021 susceptibility testing to tetracycline was introduced and resistance in MSSA was found to be 4% in both years of surveillance. Acquired resistance to quinolones in MSSA is low (2%), but even in susceptible isolates only moxifloxacin is expected to be effective with standard dosing while ciprofloxacin and levofloxacin work only if used at a higher dose. Methicillin-resistant *Staphylococcus aureus* (MRSA) strains are resistant to all beta-lactam antibiotics (except newer cephalosporins, ceftaroline, and ceftobiprole), and often show cross-resistance to other classes of antibiotics. After 2008 a decreasing trend in MRSA rates was observed and the lowest rates (12%) were recorded in 2013 and 2014, but since 2015 the MRSA rate started to rise again, and a sudden increase was unfortunately recorded in 2020 and again in 2021 (25% in 2007, 26% in 2008, 21% in 2009, 16% in 2010, 14% in 2011, 13% in 2012, 12 % in 2013 and 2014, 14% in 2015, 16% in 2016, 15% in 2017, 16% in 2018 and 2019, 21 % in 2020, 27% in 2021). In 2022 the increasing trend seems to be ended with MRSA rate being 21%, but even better result is that the total number of MRSA isolates reported was lower (955 in 2022, 1.238 in 2021, 699 in 2020, 784 in 2019). At the same time the number of MSSA isolates reported increased by approx. 10%. The proportion of MRSA strains resistant to clindamycin (77%) is somewhat lower that in the last year (87%) and this is mostly due to the decreased rate of isolates with inducible resistance to clindamycin (17% in 2022, 29% in 2021, 28% in 2020, 29% in 2019, 26% in 2018, 32% u 2017, 28% in 2016, 21% in 2015, 16% in 2014). MRSA resistance to gentamicin (10%) is somewhat lower than in the last year and still in line with the decreasing trend (91% in 2006, 81% in 2009, 77% in 2010, 69% in 2011, 64% in 2012, 59% in 2013, 43% in 2014, 38% in 2015, 32% in 2016, 23% in 2017, 18% in 2018 and 2019, 13% in 2020 and 2021, 10% in 2022). Resistance to linezolid and vancomycin was not observed. The proportion of isolates with MIC of 2.0 mg / L is similar as in the previous years (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). MRSA resistance to ceftaroline is higher than in the last year (11% in 2022, 5% in 2021), and the proportion of isolates that should be treated with higher doses is similar (8% in 2022, 9% in 2023). In case of pneumonia, 19% of isolates are considered ceftaroline resistant which is an increase compared to the last year (14%). Resistance to co-trimoxazole is somewhat higher (7% in 2022, 5% in 2021 and 2020) and resistance to tetracycline, surveillance of which was introduced in 2021, is 10% for both years of surveillance and not very different from the rates seen in MSSA. Resistance to rifampicin is still low (4%), but this antibiotic should not be used as monotherapy as the rate of mutants in the population is high.

Enterococci are naturally resistant to many antibiotic classes, and almost all isolates of *Enterococcus faecium* show resistance to ampicillin. All enterococci show innate low-grade resistance to aminoglycosides, but aminoglycosides in wild-type enterococci can still be used in therapy combined with ampicillin or glycopeptides to achieve a synergistic effect. In strains highly resistant to aminoglycosides, these antibiotics cannot be used even in combination therapy. The proportion of strains with high level resistance to aminoglycosides is 23% for *E.faecalis* and 38% for *E.faecium* which is similar to the rates observed last year. Vancomycin resistance is still rare in *E. faecalis* (<1%), while vancomycin resistance in *E. faecium* shows an increasing trend with a sudden raise in 2021 (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). An increase in

vancomycin resistance has been observed since 2015, when vancomycin-resistant *E. faecium* (VRE) isolates began to occur with greater frequency in various regions of Croatia, and not only in Zagreb hospitals as it was in the beginning. In 2021 along with the raise in resistance rates, the raise in total numbers of *E.faecium* was observed as compared to the previous year but also in comparison with the pre-pandemic period. In 2022 vancomycin resistance rate and apsolute number of isolates remained high and above the pre-pandemic values (1.271 isolates in 2022, 1.242 isolates in 2021, 859 isolates in 2020, 1.074 isolates in 2019). At the same time, total number of *E. faecalis* isolates remained almost the same as in the pre-pandemic period (5.502 in 2022, 5.419 in 2021, 3.764 in 2020, 5.264 in 2019). In 2014 EUCAST has introduced susceptibility testing of enterococci to quinolones using norfloxacin as an indicator of susceptibility to ciprofloxacin and levofloxacin. Quinolones are intended to treat enterococcal infections only in case of uncomplicated urinary tract infections. Resistance to quinolones in *E. faecalis* and *E. faecium* is similar to the rates of previous years (22% and 75% in 2017, 22% and 84% in 2018, 22% and 85% in 2019, 23% and 81% in 2020, 23% and 87% in 2021, 22% and 86% in 2022). For uncomplicated urinary tract infections caused by *E. faecalis*, nitrofurantoin can also be used and resistance to this antibiotic is still low (2%).

Escherichia coli is the most common pathogen causing urinary tract infections (UTI) and other enterobacteriaceae are more common in complicated UTI or health care associated infections affecting different organ systems. As part of human microbiota enterobacteriaceae are frequently exposed to antibiotics and once the resistant mutants emerge they are difficult to spot and control. The number of reported *E.coli* isolates in the pandemic 2020 was significantly lower than usual, but the number of reported isolates was in 2021 similar and in 2022 even bigger compared to the pre-epidemic period (21.770 isolates in 2022, 18.825 in 2021, 12.912 in 2020, 20.284 in 2019), which indicates that diagnostics for bacterial infections has recovered after being reduced at the beginning of the covid epidemic. Since the early days of surveillance, *E. coli* has shown high resistance to ampicillin, which in 2022 is 46%, similar to previous years. Amoxicillin with the addition of clavulanic acid, however, shows good efficacy because clavulanic acid successfully blocks broad-spectrum beta-lactamases and most extended-spectrum beta-lactamases ("extended spectrum beta-lactamases, ESBL"). The combination with clavulanic acid, however, limits the use of amoxicillin in high doses, which are often needed in serious systemic infections. In 2014 for the first time, EUCAST introduced different interpretation of amoxicillin/clavulanic acid susceptibility for uncomplicated UTI and for other infections. After this differentiation, resistance rates did not change significantly if interpretation for uncomplicated UTI is applied (7% in 2013 and 2014, 9% in 2015, 10% in 2016, 2017, 2018 and 2019, 11% in 2020, 12% in 2021, 10% in 2022) but following the change of standards the rates applicable to other infections turned out much higher and expressed a slightly increasing trend (16% in 2014 and 2015, 15% in 2016, 2017 and 2018, 16% in 2019, 19% in 2020, 22% in 2021, 16% in 2022). In 2022 the resistance rate decreased to the pre-epidemic value. In 2020 EUCAST standards for enterobacteria introduced a separate interpretation of susceptibility to parenteral and oral cefuroxime, with categories "S" and "R" being applicable for oral cefuroxime which is recommended for use in uncomplicated urinary tract infections only. Parenteral cefuroxime can be used for systemic infections but only at a higher dose and therefore for parenteral cefuroxime there are only categories "I" and "R". Resistance to cefuroxime is similar to the last year (11% in 2022, 10% in 2021, 11% in 2020). Resistance to third-generation cephalosporins (9% to 10%) is similar to last year's rates (8% to 11%). New cephalosporins with beta-lactamase inhibitors, ceftazidime / avibactam and ceftalozane / tazobactam and a new combination of imipenem with relebactam show high efficiency against ESBL strains and the resistance of *E.coli* to these antibiotics is <1% and 1%, which is identical to the efficacy of carbapenems (<1% of resistant isolates) and slightly better than the efficacy of piperacillin / tazobactam (3% of resistant isolates). In 2022 susceptibility testing to cefiderocol was introduced and resistance rate of 2% was

recorded. Resistance to ciprofloxacin is 2017 reached 20%, but since then it has stagnated and this year's rate does not differ significantly from last year's rate (14% in 2012 and 2013, 17% in 2014, 18% in 2015, 19% in 2016, 20% in 2017 and 2018, 19% in 2019, 18% in 2020, 19% in 2021, 18% in 2022). Resistance rates to co-trimoxazole (26%), gentamicin (10%), amikacin (1%), nitrofurantoin (3%), fosfomycin (1%) and nitroxoline (<1%) are the same or similar as last year's rates.

Proteus mirabilis still causes predominantly community-acquired infections and should naturally be a bacterial species well-susceptible to all beta-lactam antibiotics directed at gram-negative bacteria. Unfortunately, resistance to beta-lactam antibiotics has already reached high rates and in 2022 resistance is 46% for ampicillin, 24% for co-amoxiclav, 2% for piperacillin/tazobactam, 9% (cefepime) to 17% (cefixime) for the 3rd and 4th generation cephalosporins, which is similar to last year's rates. In 2022 resistance is still low for the new cephalosporin combinations with beta-lactamase inhibitors, ceftazidime / avibactam (1% in 2018, 2019, 2020 and 2021, <1% in 2022), ceftalozane / tazobactam (10% in 2018, 9% in 2019, 8% in 2020, 7% in 2021, 6% in 2022). Rates of resistance to ciprofloxacin (27%), gentamicin (22%), amikacin (10%) and co-trimoxazole (40%) are also similar or equal to last year rates. Due to their innate resistance to colistin, tigecycline and lower susceptibility to imipenem, *Proteus mirabilis* and other *Proteus* spp. could represent an increasing problem in the future, especially in urological patients and infections associated with hospital care. Resistance to the new antibiotic cefiderocol, for the first time tested in 2022, is 1%.

Klebsiella spp. and *Enterobacter* spp. usually cause healthcare associated infections and for many years demonstrate high rates of resistance. *K.pneumoniae* has innate resistance to ampicillin but resistance to other beta-lactams is acquired due to high antibiotic exposure. Third- and fourth-generation cephalosporin resistance rates (38% for cefepime to 40% for ceftriaxone and cefixime) are somewhat lower than last year but still higher than in the pre-pandemic period (41% to 43% in 2021, 35% to 38% in 2019.g.). Also, resistance to co-amoxiclav (38% in 2018 and 2019, 45% in 2020, 43% in 2021, 41% in 2022), ceftolozane / tazobactam (20% in 2018 and 2019, 25% in 2020, 23% in 2021 and 2022), and piperacillin / tazobactam (19% in 2018, 21% in 2019, 27% in 2020, 31% in 2021, 30% in 2022.g.) is similar to last year's rates. Ceftazidime / avibactam still shows very low resistance (2% in 2018, 2019, 2020, 1% in 2021, 2% in 2022) and with its effectiveness against strains producing ESBL, AmpC beta-lactamase and a large number of carbapenemases (KPC, OXA-48), it remains the most effective beta-lactam for treatment of klebsiella infections. Resistance rates for the new beta-lactams cefiderocol and imipenem / relebactam are 7% and 11%. The number of carbapenem-resistant *K.pneumoniae* isolates reached the level visible as a percentage of resistance to imipenem and meropenem (1%) for the first time in 2014, the rates in 2019 increased to 5% and 6% and in 2020 there was a sudden increase in carbapenem resistance and rates reached 7% and 16% with an additional 8% and 2% isolates being susceptible at increased exposure ("I" category). These rates remained similar in 2021 (8% and 14% resistant and 4% and 2% susceptible with increased exposure) and in 2022 (9% and 13% resistant and 4% and 3% susceptible with increased exposure). However, the total number of *Klebsiella* isolates continued increasing (5.864 isolates in 2019, 4.244 isolates in 2020, 5.601 isolates in 2021, 6.245 isolates in 2022) suggesting the further spread of carbapenem resistant isolates. Resistance to ciprofloxacin (40%), gentamicin (26%), amikacin (7%) and co-trimoxazole (38%) shows rates similar to the last year values.

Enterobacter spp., *Citrobacter* spp. and *Searratia* spp. form a group of enterobacteriaceae which poses innate inducible cephalosorinases and with the exception of *Citrobacter koseri* demonstrate resistance not only to ampicillin but to co-amoxiclav and 1st generation cephalosporins as well. In 2019 *Enterobacter aerogenes* was renamed into *Klebsiella aerogenes* and this species continues to be discussed here within this group of

Enterobacterales. Cefuroxime is marginally active against these bacteria and EUCAST standards do not include cefuroxime interpretation for this group of enterobacteria. Wild type isolates are susceptible to the 3rd generation cephalosporins but resistant derepressed mutants that hyperproduce AmpC cephalosporinases often emerge during therapy with these agents. The proportion of derepressed mutants resistant to third- and fourth-generation cephalosporins (10% for cefepime to 27% for cefixime) is within the limits of the rates registered in previous years (16% to 32% in 2017, 10% to 25% in 2018, 12% to 26% in 2019, 12% to 28% in 2020, 10% to 28% in 2021), and resistance to carbapenems, which became visible for the first time in 2013 (1%), remained almost the same in 2022 (1% resistant and 1% susceptible increased exposure to imipenem and 1% resistant to meropenem, 5% resistant to ertapenem). Ceftalozan / tazobactam is primarily expected to be an advantage in the treatment of infections caused by pseudomonas and ESBL-producing enterobacteria, which are more common among *K.pneumoniae* and *E.coli* isolates than among Enterobacter group, and the ceftolozane / tazobactam resistance rate in Enterobacter group (11% in 2018 and 2019, 8% in 2020 and 2021, 7% in 2022) is similar to the rate of resistance to cefepime (10% in 2018, 12% in 2019 and 2020, 10% in 2021 and 2022) and piperacillin / tazobactam (9% in 2018, 10% in 2019 and 2020, 13% in 2021 and 2022). Resistance rates to ciprofloxacin (10%), gentamicin (8%), amikacin (1%) and co-trimoxazole (11%) are identical to the last year rates. Resistance rate to the new beta-lactam antibiotics, cefiderocol and imipenem / relebactam is 2%.

Multiply resistant *Pseudomonas aeruginosa*, especially carbapenem resistant isolates, have been one of the biggest resistance problems in Croatia for many years. Resistance to imipenem and meropenem increased significantly in 2020 but did not continue to raise in 2021 and 2022 (17% in 2018, 18% in 2019, 23% and 22% in 2020, 20% and 21% in 2021, 21% and 18% in 2022). Resistance to the new cephalosporin combinations with an inhibitor, ceftazidime / avibactam (4% in 2018, 6% in 2019, 7% in 2020, 6% in 2021 and 2022) and ceftalozane / tazobactam (4% in 2018, 6% in 2019, 7% in 2020, 5% in 2021 and 2022) also did not increase further and resistance to cefiderocol, first tested in 2022, is 1%. Resistance to piperacillin / tazobactam (10% in 2019, 12% in 2020, 9% in 2021, 10% in 2022), ceftazidime (16% in 2019, 21% in 2020, 15 % in 2021, 17% in 2022) and cefepime (13% in 2019, 16% in 2020, 13% in 2021, 15% in 2022), after the increase in 2020, came back to rates similar to those in the pre-epidemic period. Resistance to ciprofloxacin (24% in 2019 and 2020, 20% in 2021, 25% in 2022) is further increasing and resistance to amikacin (6%) is the same as last year. From 2020 EUCAST standards do not include testing of *P. aeruginosa* for gentamicin because this antibiotic is not effective for pseudomonas infections. For aminoglycosides, it is generally recommended that they should be used only in combination with other antibiotics for infections outside the urinary tract. It is common knowledge that higher doses of antibiotics are used to treat pseudomonas infections, and since 2020 this is clearly stated in EUCAST standards as for pseudomonas there is no "S" category (susceptible, standard dosage) for many antibiotics (ceftazidime, cefepime, piperacillin / tazobactam, imipenem, ciprofloxacin). Colistin susceptibility testing requires the use of a broth microdilution test, which is significantly more demanding and expensive than disk diffusion testing, and therefore the rule to test all isolates to all antibiotics under surveillance, in this case is modified and only multiply, in particular carbapenem resistant isolates are tested with colistin. Therefore, the data on resistance to colistin in *P.aeruginosa* cannot be compared with the rates of resistance to other antibiotics, but these data still enable the monitoring of colistin resistance in the subpopulation of multiply resistant pseudomonas isolates. In 2021 this rate was significantly higher than in previous years but in 2022 the colistin resistance rate is back to 3% (3% in 2019 and 2020, 8% in 2021, 3% in 2022).

Carbapenem resistance in *A. baumannii* has rapidly spread throughout Croatia since 2008 and in 2022 resistance rates to imipenem and meropenem (91% and 92%) are still extremely high and similar to the last year results. The most drastic impact of COVID-19

pandemic on the spread of resistance in Croatia, but many other European countries as well, is the sudden increase in total number of carbapenem resistant *Acinetobacter* spp. Luckily, in 2022, this number decreased (1.740 isolates in 2019, 2.087 isolates in 2020, 2.582 isolates in 2021, 1.830 isolates in 2022), which is probably a consequence of a reduced number of severely ill patients and the reduced pressure on the intensive care units but also of a more rational use of personal protective equipment, especially gloves, when caring for COVID-19 patients. According to the EUCAST guidelines there is no sufficient evidence that acinetobacter is a good target for ampicillin/sulbactam. However, this is one of the rare antibiotics that still demonstrate *in vitro* activity against acinetobacter in Croatia, so in Croatia, American standards are used to test and interpret susceptibility of acinetobacter to ampicillin / sulbactam. Resistance and susceptibility with increased exposure are still high for ampicillin / sulbactam (40% and 16% in 2018, 34% and 20% in 2019, 31% and 18% in 2020, 32% and 23% in 2021, 37% and 22% in 2022). As with pseudomonas, colistin is tested only on carbapenem-resistant isolates, but since for several years such isolates constitute >90% of the total acinetobacter isolates, it can be considered that colistin is tested on almost all isolates and the rates of colistin resistance can be compared with the rates for other antibiotics. Acinetobacter resistance rates to colistin are still low (2% in 2020, 1% in 2021 and 2022).

Ampicillin resistance in salmonellae exceeded 10% in 2014 (14% in 2014, 16% in 2015, 14% in 2016, 13% in 2017, 15% in 2018, 16% in 2019, 19% in 2020 and 2021, 16% in 2022). ESBL isolates are still rare among salmonellae and in 2022 resistance to ceftazidime and ceftriaxone was 2% and 1%. Resistance to co-amoxiclav (7%) is similar and to co-trimoxazole (4%) identical to the last year values. However, the sudden increase in ciprofloxacin resistance is concerning. Until 2013 the susceptibility of salmonella to ciprofloxacin at the national level was 100%, and the resistance to nalidixic acid, which was considered to be a better indicator of a low level of resistance to quinolones, was up to 2%. Since 2014 EUCAST introduced the use of pefloxacin disk as a better indicator of susceptibility to the quinolones (ciprofloxacin) which probably influenced the recording of a ciprofloxacin resistance rate of 2% in 2014. The mildly increasing trend was further recorded in the years that followed and in 2022 resistance rates increased significantly in many regions and at the national level (4% 2015, 3% in 2016, 4% in 2017, 2018 and 2019, 5% in 2020, 4% in 2021, 18% in 2022). In the two pandemic years low numbers of salmonella were reported, probably due to the limited social gatherings, but in 2022, the total number of salmonella isolates returned to the pre-pandemic values (2.031 isolates in 2019, 1.169 isolates in 2020, 1.278 isolates in 2021, 1.858 isolates in 2022).

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

In 2022, only four shigella isolates from two laboratories were reported. All the three *S. sonnei* isolates were susceptible to ampicillin, co-amoxiclav, ceftazidime, ceftriaxone and ciprofloxacin, and one of the isolates was resistant to co-trimoxazole. *S. flexneri* isolate was resistant to ampicillin and susceptible to other antibiotics.

In 2022, EUCAST introduced separate interpretation of susceptibility results for different anaerobic bacterial species, and hence, since this year results are presented for the anaerobic species that have designated species specific interpretation. As many of the anaerobic species do not have species specific interpretation, this year significantly fewer anaerobic isolates were reported (427 in 2022, 1.234 in 2021). Resistance to penicillin was high in *Prevotella* spp. (57%) and *Fusobacterium necrophorum* (22%), resistance to metronidazole was high in *Fusobacterium necrophorum* (22%) and *Clostridium perfringens* (25%), and clindamycin resistance exceeded 20% in all anaerobic species. Susceptibility to amoxicillin plus clavulanic acid was not tested due to the lack of the EUCAST standard for interpretation, and resistance to piperacillin/tazobactam and meropenem was low for every species (<5%).

LEGENDA ZA TABLICE */ LEGEND TO TABLES*:

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

* uključuje podatke i za: Opću bolnicu Zabok

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

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

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

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

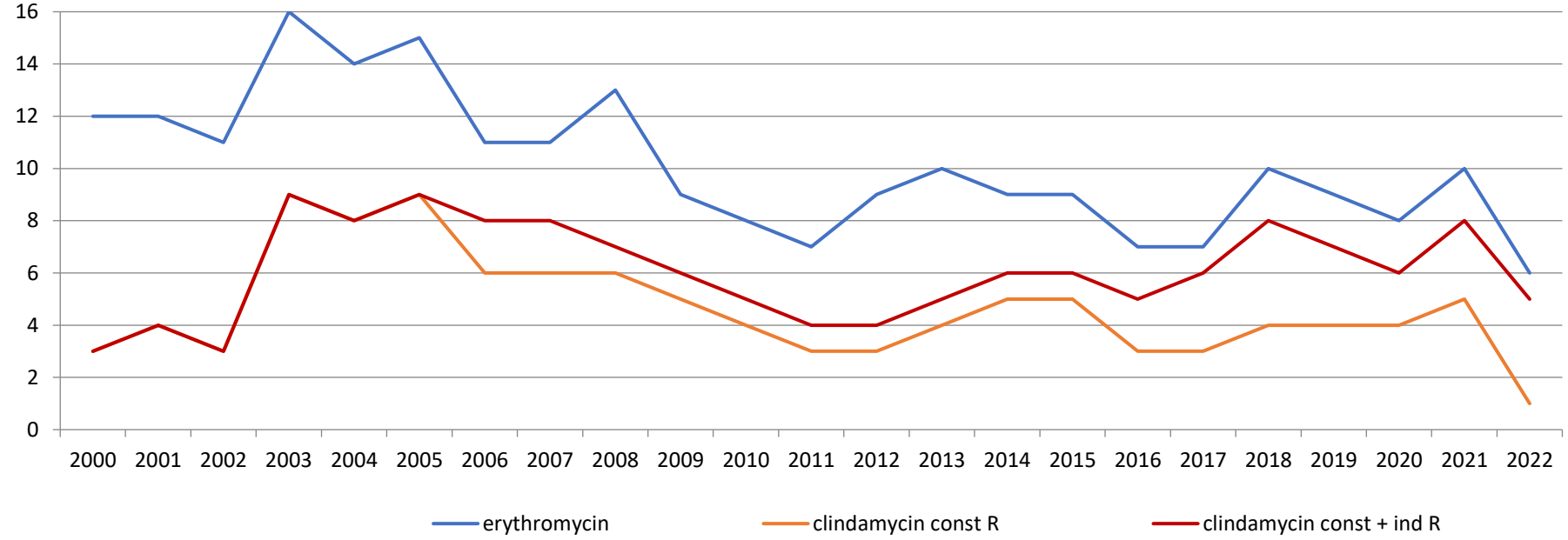
ANTIBIOTICI / *ANTIBIOTICS*:

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

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

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

rezistencija na antibiotike u RH / *antibiotic resistance in Croatia*, 2000. - 2022.



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

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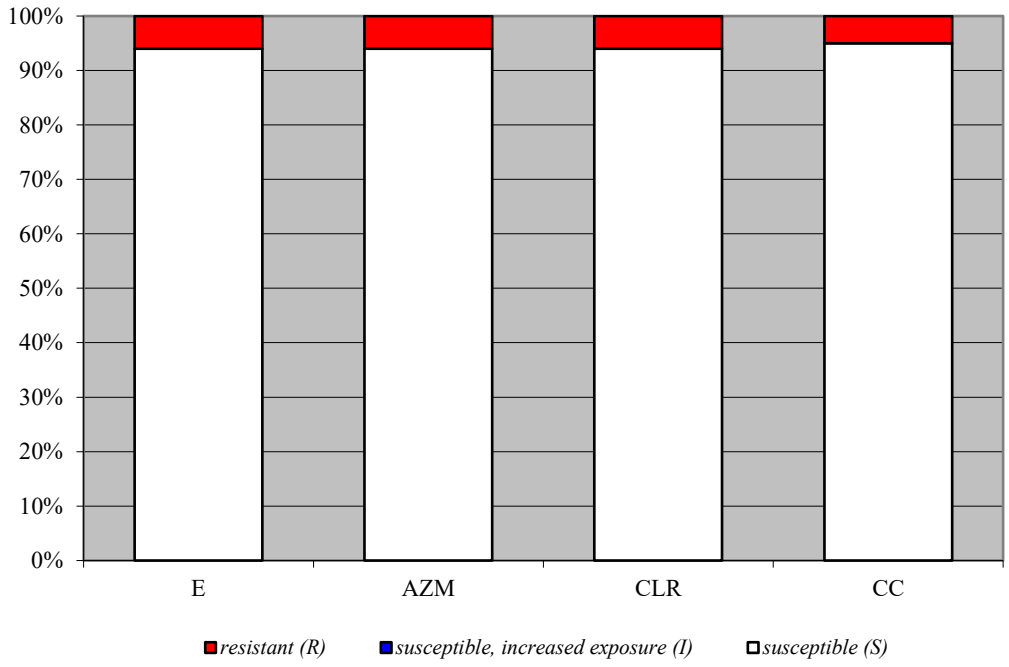
Beta-hemolitički streptokok grupe A / *Group A streptococcus*

rezistencija na antibiotike u razdoblju od 1.01.- 31.12.2022., zbirni prikaz izolata iz 39 centara u RH /
antibiotic resistance for the period 1.01. - 31.12.2022, summary results for the isolates from 39 centers in Croatia

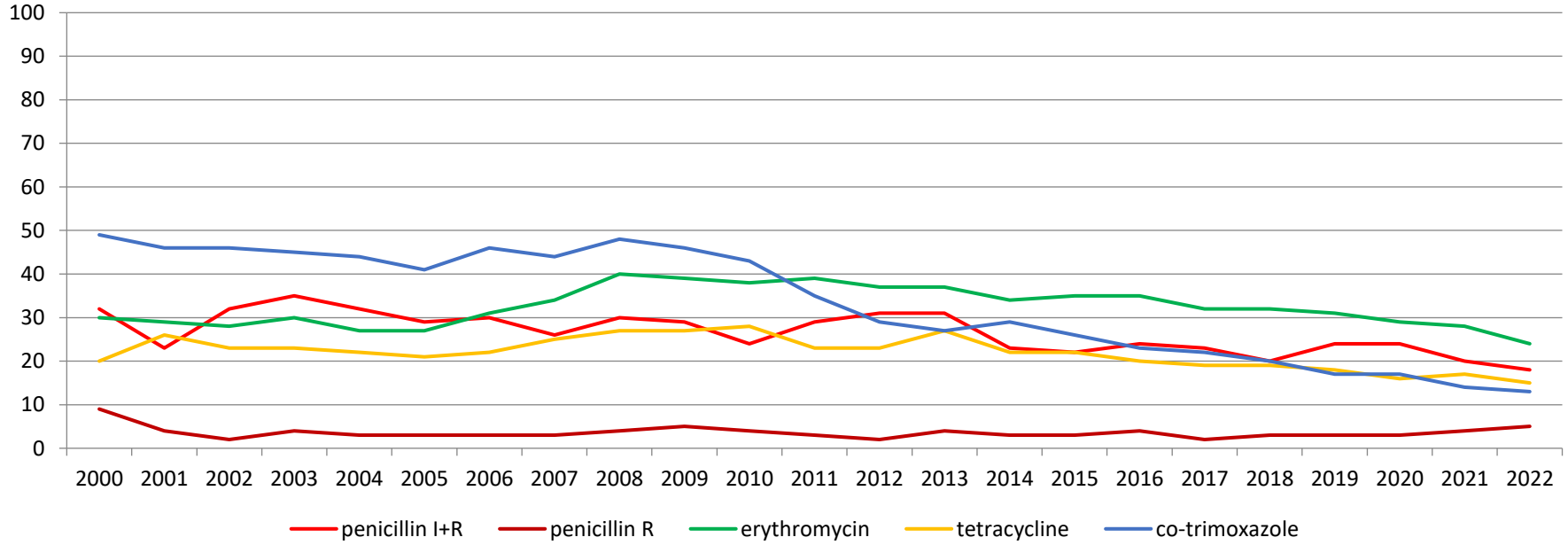
ANTIBIOTIK / *ANTIBIOTIC*	**Broj izolata** / *No. of isolates*	**% rezistentnih (R) (% osjetljivih uz povećanu izloženost (I)) izolata** / *% of resistant (R) (% of susceptible, increased exposure (I)) isolates*	**Raspon lokalnih rezultata*** / *Range of local results**
Erythromycin	8 978	6 (0)	0 (0) - 24 (0)
Azithromycin	8 978	6 (0)	0 (0) - 24 (0)
Clarythromycin	8 978	6 (0)	0 (0) - 24 (0)
Clindamycin	8 982	5 (0)	0 (0) – 22 (0)
constitutive		1	0 - 18
inducible		3	0 - 21

*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. - 2022.



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

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Streptococcus pneumoniae

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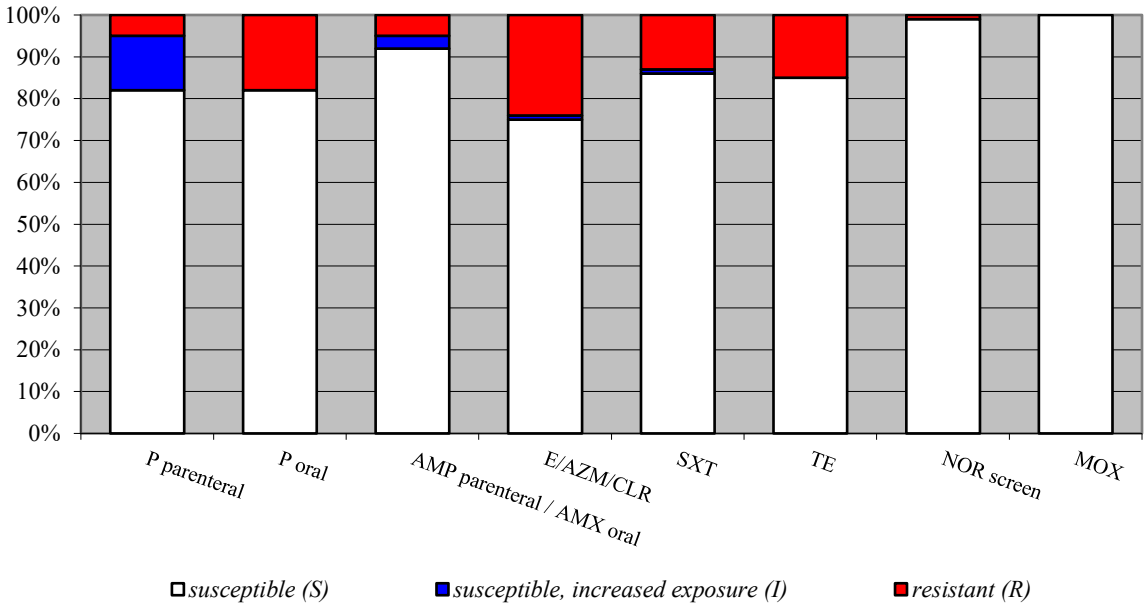
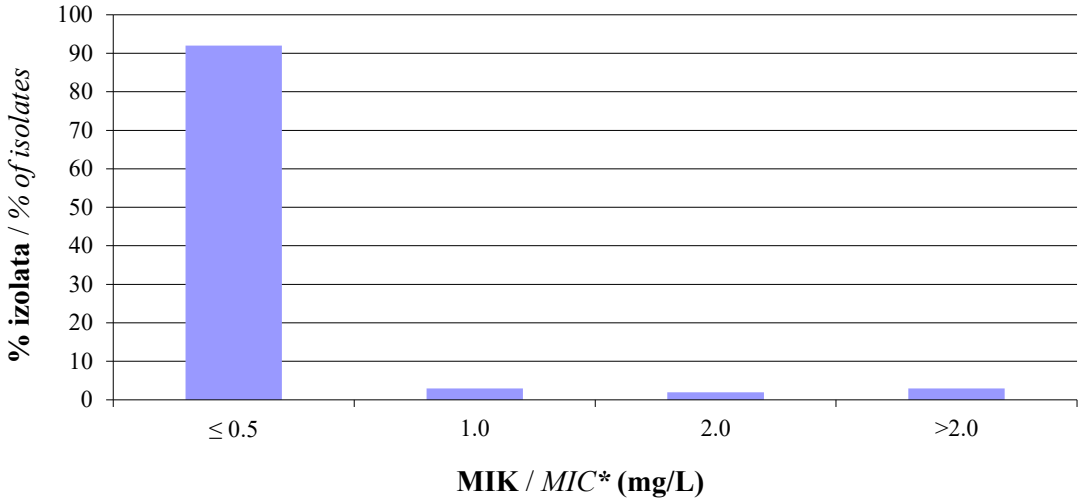
ANTIBIOTIK / *ANTIBIOTIC*	**Broj izolata** / *No. of isolates*	**% rezistentnih (R) (% osjetljivih uz povećanu izloženost (I)) izolata** / *% of resistant (R) (% of susceptible, increased exposure (I)) isolates*	**Raspon lokalnih rezultata*** / *Range of local results**
Penicillin $_{\text{parenteral}}$	1 360	5 (13)	0 (0) - 8 (4)
Penicilin $_{\text{oral}}$	1 360	18 (0)	0 (0) - 42 (0)
Ampicillin $_{\text{parenteral}}$ **/ Amoxicillin** $_{\text{oral}}$	1 125	5 (3)	0 (0) - 21 (7)
Erythromycin/Azithromycin/ Clarythromycin	1 366	24 (1)	0 (0) - 54 (3)
Co-trimoxazole	1 363	13 (1)	0 (0) - 28 (18)
Tetracycline	1 184	17 (2)	0 (0) – 30 (0)
Norfloxacin $_{\text{screen}}$	1 309	1 (0)	0 (0) - 7 (0)
Moxifloxacin	1 329	1 (0)	0 (0) - 13 (0)

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



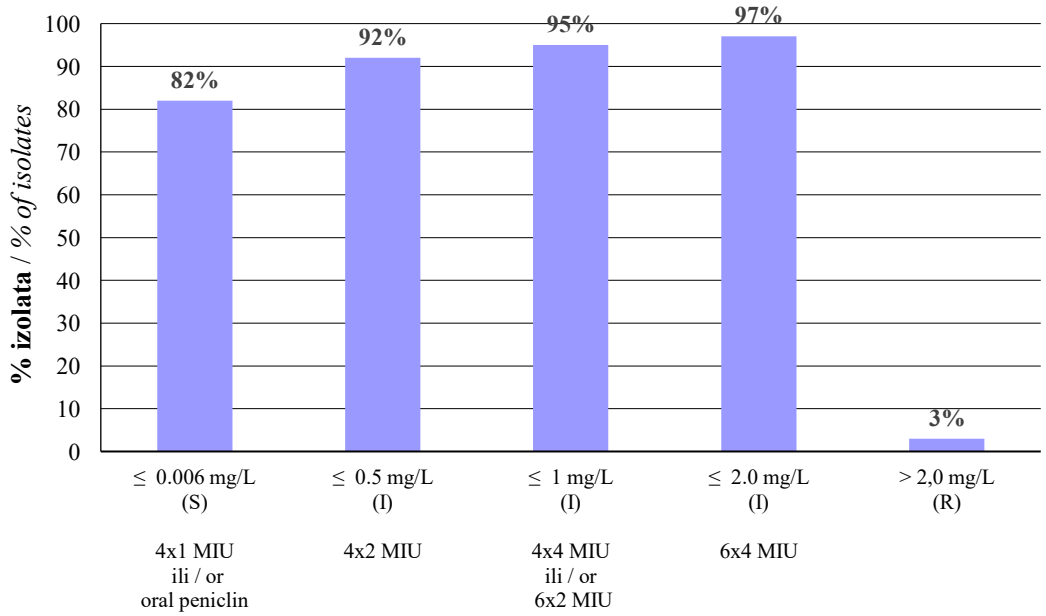
Streptococcus pneumoniae

Distribucija MIK-ova penicilina, (1 244 *S. pneumoniae* izolata) /
Penicillin MIC distribution, (1 244 S. pneumoniae isolates), 1.10. – 31.12.2022.



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

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



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Odbor za praćenje rezistencije bakterija na antibiotike u RH
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Staphylococcus aureus / MSSA

rezistencija na antibiotike u razdoblju od 1.10.- 31.12.2022.,
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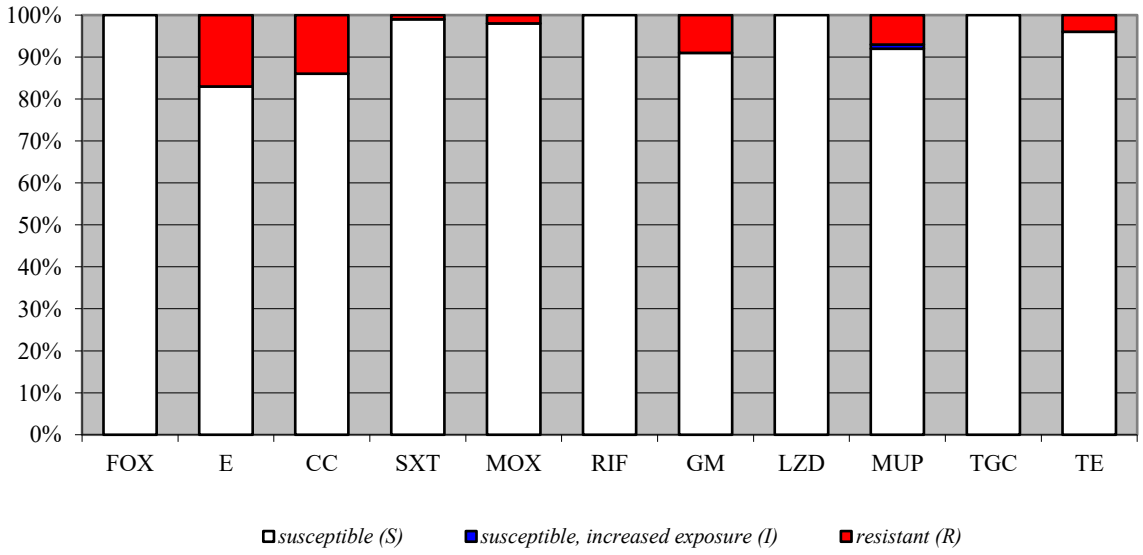
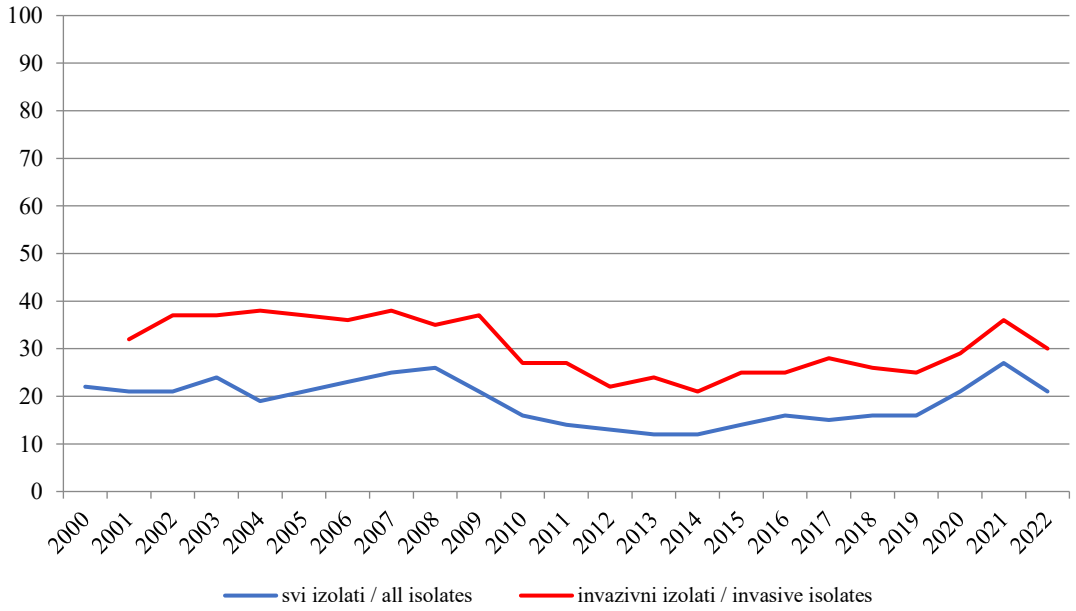
ANTIBIOTIK / *ANTIBIOTIC*	**Broj izolata** / *No. of isolates*	**% rezistentnih (R) (% osjetljivih uz povećanu izloženost (I)) izolata** / *% of resistant (R) (% of susceptible, increased exposure (I)) isolates*	**Raspon lokalnih rezultata*** / *Range of local results**
Cefoxitin/			
Methicillin	3 695	0 (0)	0 (0) - 0 (0)
Erythromycin	3 646	17 (0)	6 (0) - 29 (0)
Clindamycin	3 646	14 (0)	6 (0) – 27 (0)
constitutive		8	0 - 19
inducible		6	0 - 25
Co-trimoxazole	3 651	1 (0)	0 (0) – 5 (0)
Moxifloxacin	3 362	2 (0)	0 (0) - 23 (0)
Rifampicin	3 415	0 (0)	0 (0) - 2 (0)
Gentamicin	3 649	9 (0)	0 (0) - 36 (0)
Linezolid	3 434	0 (0)	0 (0) - 0 (0)
Mupirocin	3 278	7 (1)	0 (0) - 23 (0)
Tigecycline	3 290	0 (0)	0 (0) – 2 (0)
Tetracycline	2 866	4 (0)	0 (0) - 15 (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*

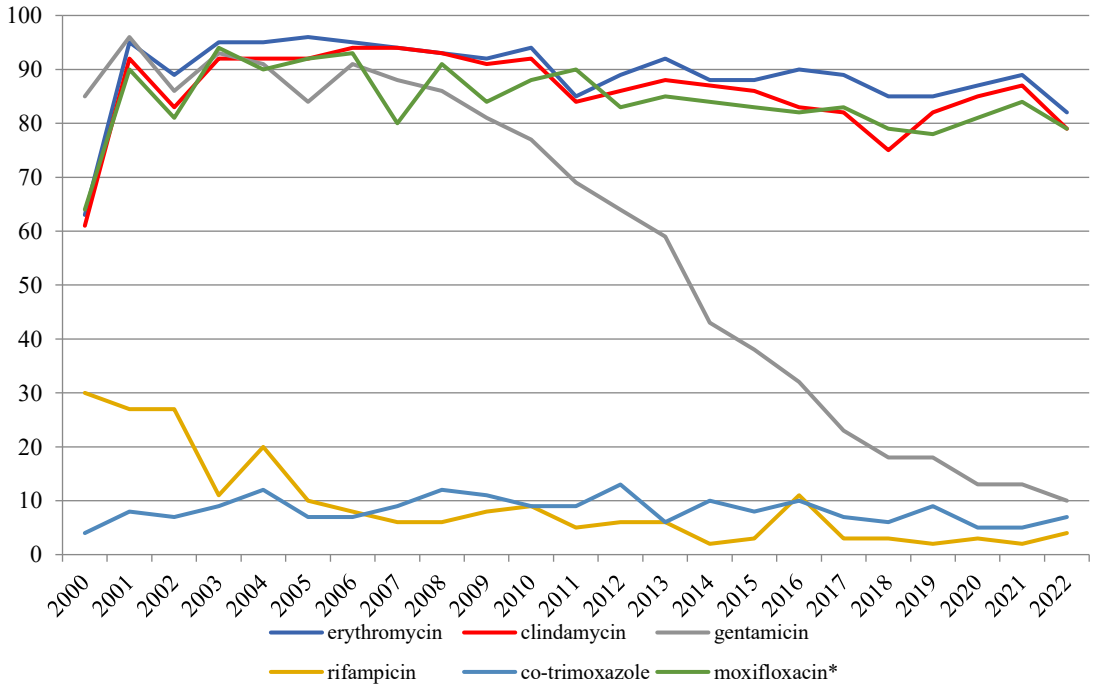


Staphylococcus aureus / MRSA

Methicillin resistant *Staphylococcus aureus* (MRSA) – stope / *rates*, 2000. - 2022.



rezistencija na antibiotike u RH /*resistance to antibiotics in Croatia*, 2000. - 2022.



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

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Croatian Committee for Antibiotic Resistance Surveillance

Staphylococcus aureus / MRSA

rezistencija na antibiotike u razdoblju od 1.10. - 31.12.2022.,
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Cefoxitin/ Methicillin	955	100 (0)	100 (0) - 100 (0)
Ceftaroline	738	11 (8)	0 (0) - 28 (6)
Erythromycin	939	82 (0)	58 (0) - 90 (0)
Clindamycin	939	79 (0)	58 (0) - 61 (0)
constitutive		17	6 - 79
inducible		60	0 - 57
Co-trimoxazole	924	7 (0)	0 (0) - 50 (0)
Moxifloxacin	829	79 (0)	50 (0) - 93 (0)
Rifampicin	860	4 (0)	0 (0) - 25 (0)
Gentamicin	939	10 (0)	0 (0) - 25 (0)
Linezolid	910	0 (0)	0 (0) - 0 (0)
Mupirocin	824	11 (0)	0 (0) - 50 (0)
Tigecycline	845	2 (0)	0 (0) - 13 (0)
Tetracycline	758	10 (0)	5 (0) - 25 (0)
Vankomicin	862	0 (0)	0 (0) - 0 (0)

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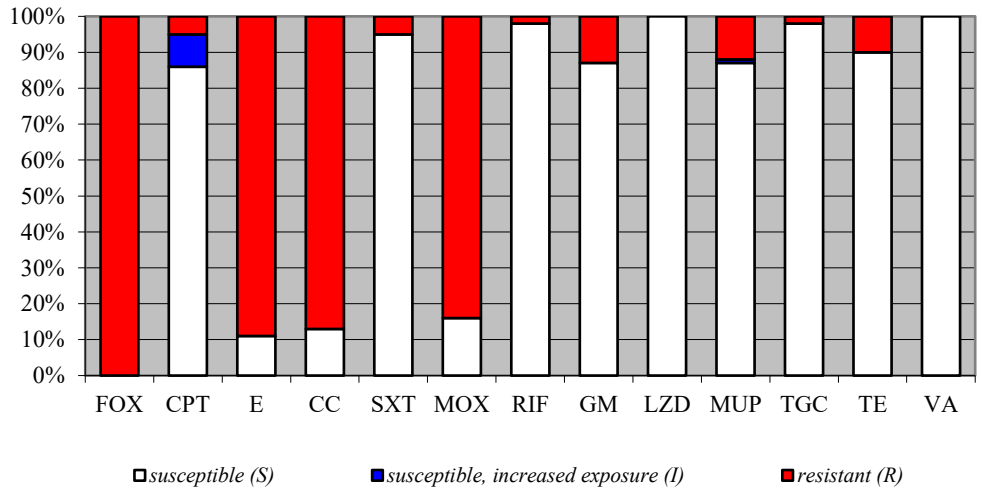
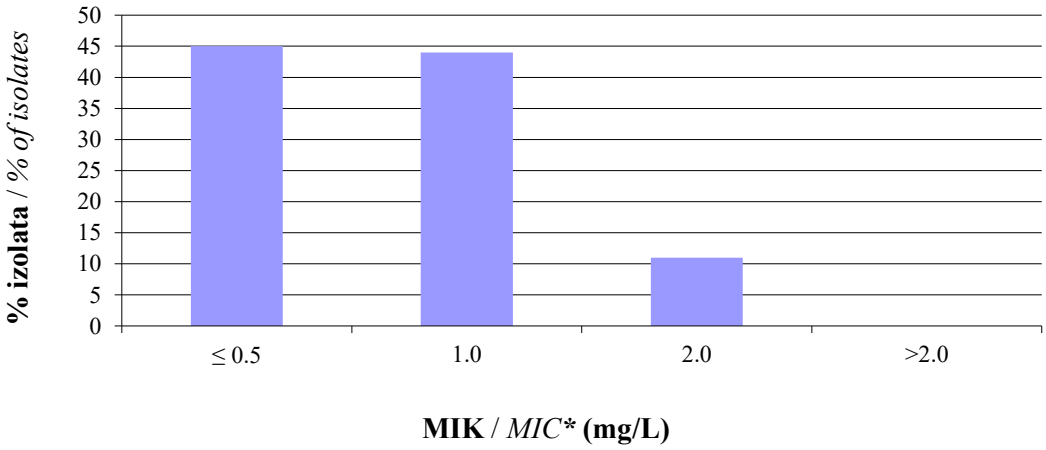
results from the centers with small number of isolates (<30) were not taken into consideration



Staphylococcus aureus / MRSA

Distribucija MIK-ova vankomicina, (862 MRSA izolata) /
Vancomycin MIC distribution, (862 MRSA isolates), 1.10. – 31.12.2022.



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

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Enterococcus faecalis

rezistencija na antibiotike u razdoblju od 1.10. - 31.12.2022.,
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ANTIBIOTIK / *ANTIBIOTIC*	**Broj izolata** / *No. of isolates*	**% rezistentnih (R) (% osjetljivih uz povećanu izloženost (I)) izolata** / *% of resistant (R) (% of susceptible, increased exposure (I)) isolates*	**Raspon lokalnih rezultata*** / *Range of local results**
Ampicillin	5 502	2 (0)	0 (0) - 30 (0)
Gentamicin	5 259	23 (0)	3 (0) - 45 (0)
Vancomycin	5 493	0 (0)	0 (0) - 4 (0)
Nitrofurantoin	5 386	2 (0)	0 (0) - 12 (0)
Norfloxacin $_{\text{screem}}$	5 154	22 (0)	0 (0) - 44 (0)
Linezolid	5 120	0 (0)	0 (0) - 0 (0)

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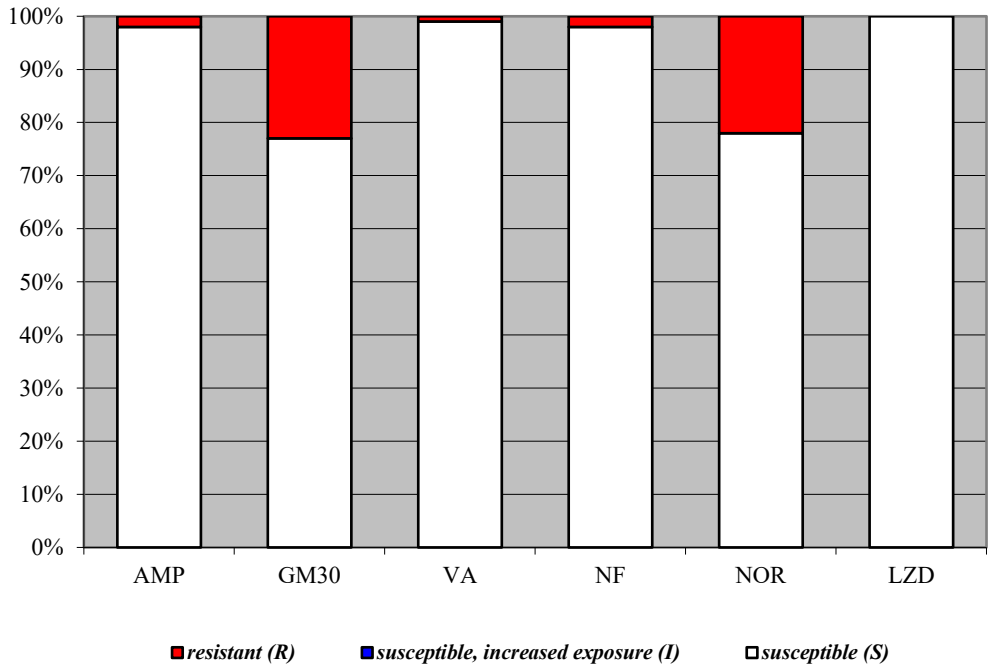
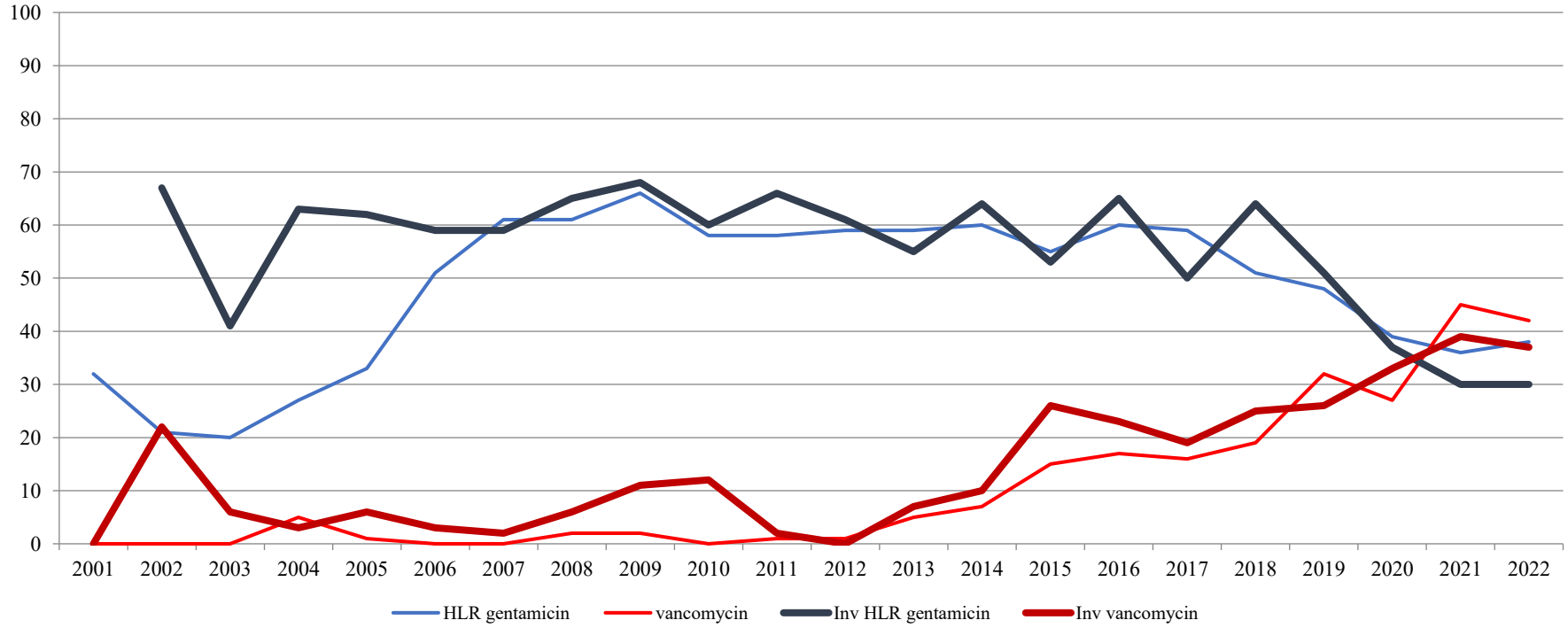


Enterococcus faecium

rezistencija na antibiotike u RH / *resistance to antibiotics in Croatia*, 2001. - 2022.



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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ANTIBIOTIK / *ANTIBIOTIC*	**Broj izolata** / *No. of isolates*	**% rezistentnih (R) (% osjetljivih uz povećanu izloženost (I)) izolata** / *% of resistant (R) (% of susceptible, increased exposure (I)) isolates*	**Raspon lokalnih rezultata*** / *Range of local results**
Ampicillin	1 271	94 (0)	22 (0) - 100 (0)
Gentamicin	1 179	38 (0)	22 (0) - 55 (0)
Vancomycin	1 286	42 (0)	3 (0) - 78 (0)
Norfloxacin	1 181	86 (0)	25 (0) - 100 (0)
Linezolid	1 214	2 (0)	0 (0) – 5 (0)

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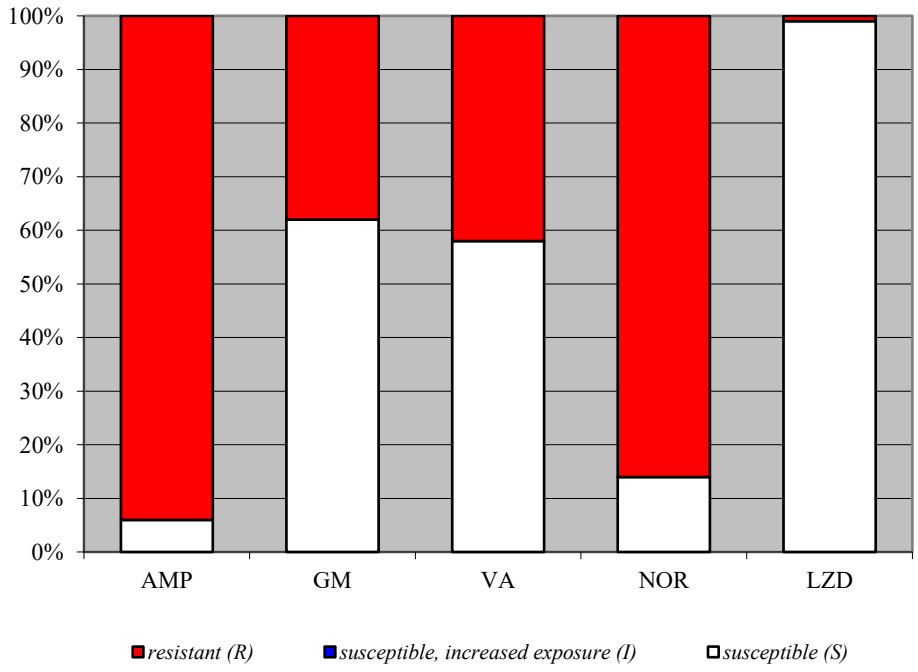
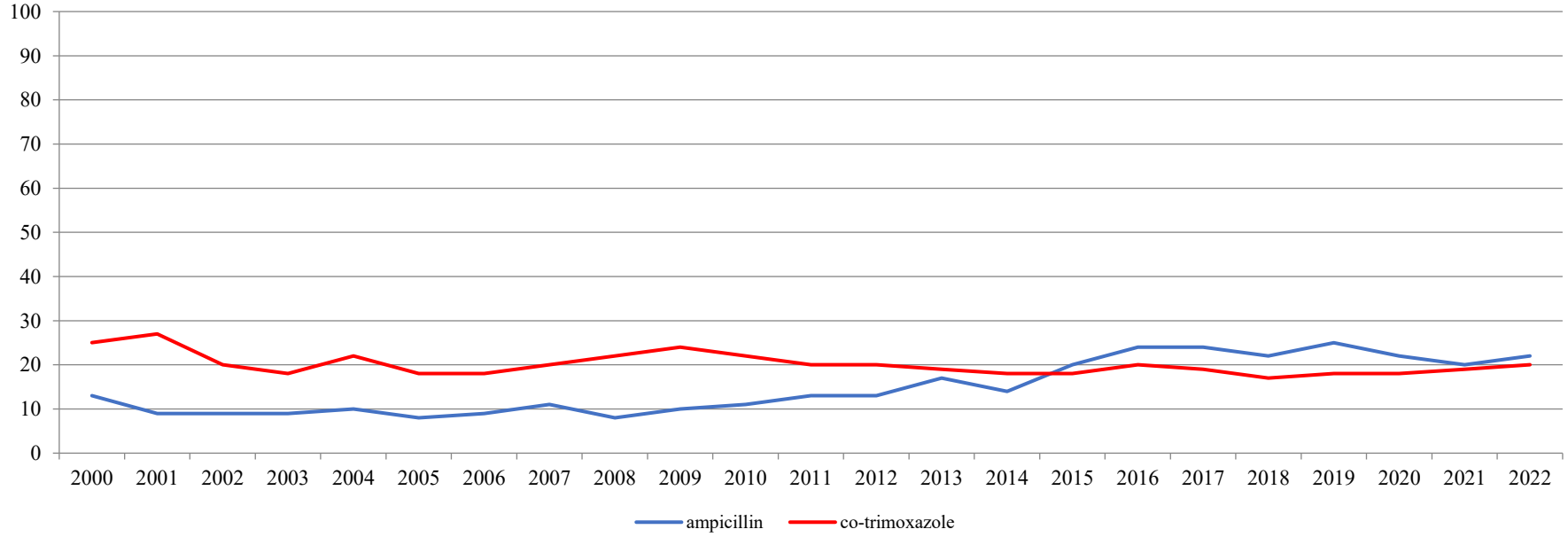
results from the centers with small number of isolates (<30) were not taken into consideration



Haemophilus influenzae

rezistencija na antibiotike u RH / *resistance to antibiotics in Croatia*, 2000. - 2022.



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Haemophilus influenzae

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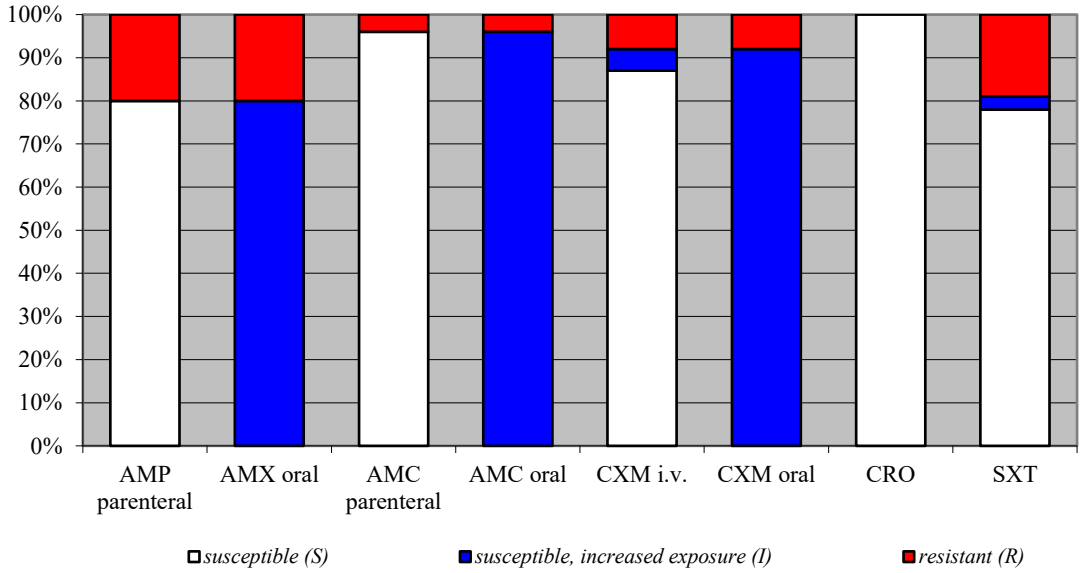
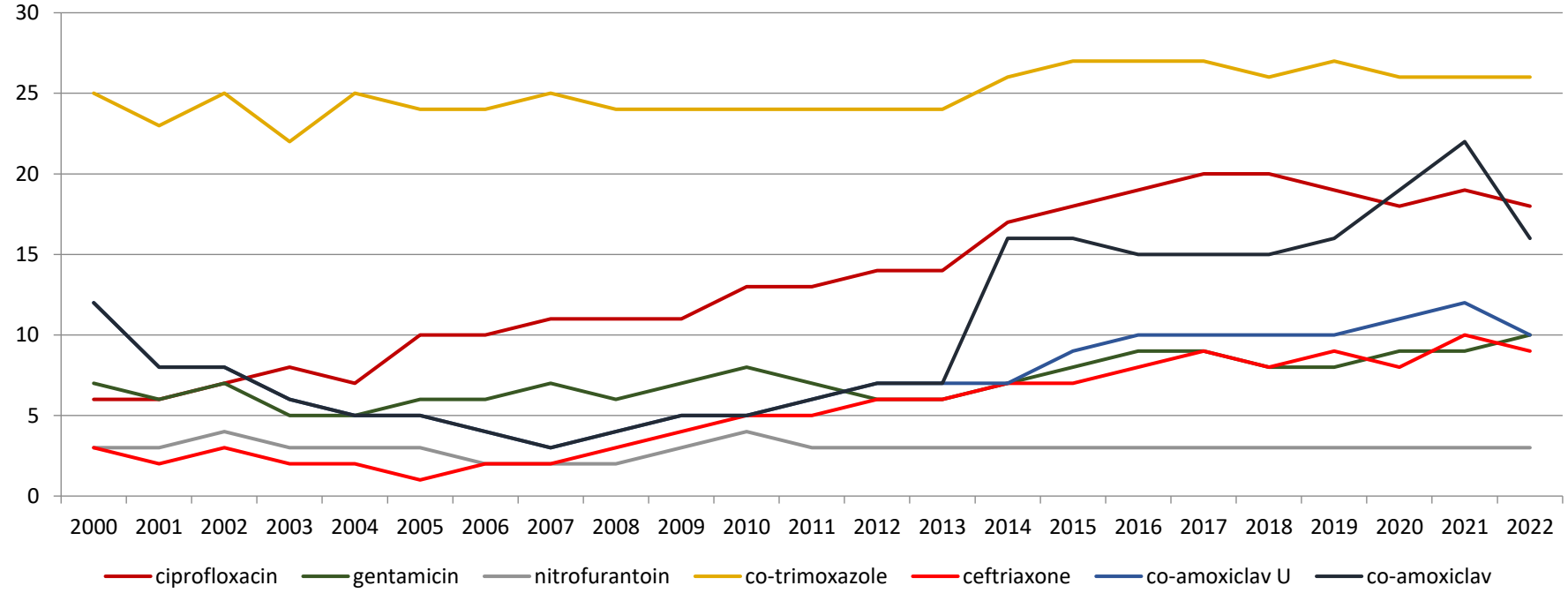
Ampicillin parenteral	1 158	22 (0)	0 (0) - 41 (0)
Amoxicillin oral	1 158	23 (77)	0 (100) – 64 (36)
Amoxicillin + clav. acid parenteral	1 155	7 (0)	0 (0) - 16 (0)
Amoxicillin + clav. acid oral	1 155	8 (92)	0 (100) – 28 (72)
Cefuroxime parenteral	1 163	9 (2)	0 (0) - 21 (5)
Cefuroxime oral	1 160	10 (90)	0 (100) - 30 (70)
Ceftriaxone	1 102	0 (0)	0 (0) - 7 (0)
Co-trimoxazole	1 159	20 (1)	0 (0) - 46 (0)

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



Escherichia coli

rezistencija na antibiotike u RH / *resistance to antibiotics in Croatia*, 2000. - 2022.



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

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

Escherichia coli

rezistencija na antibiotike u razdoblju od 1.10. - 31.12.2022.,
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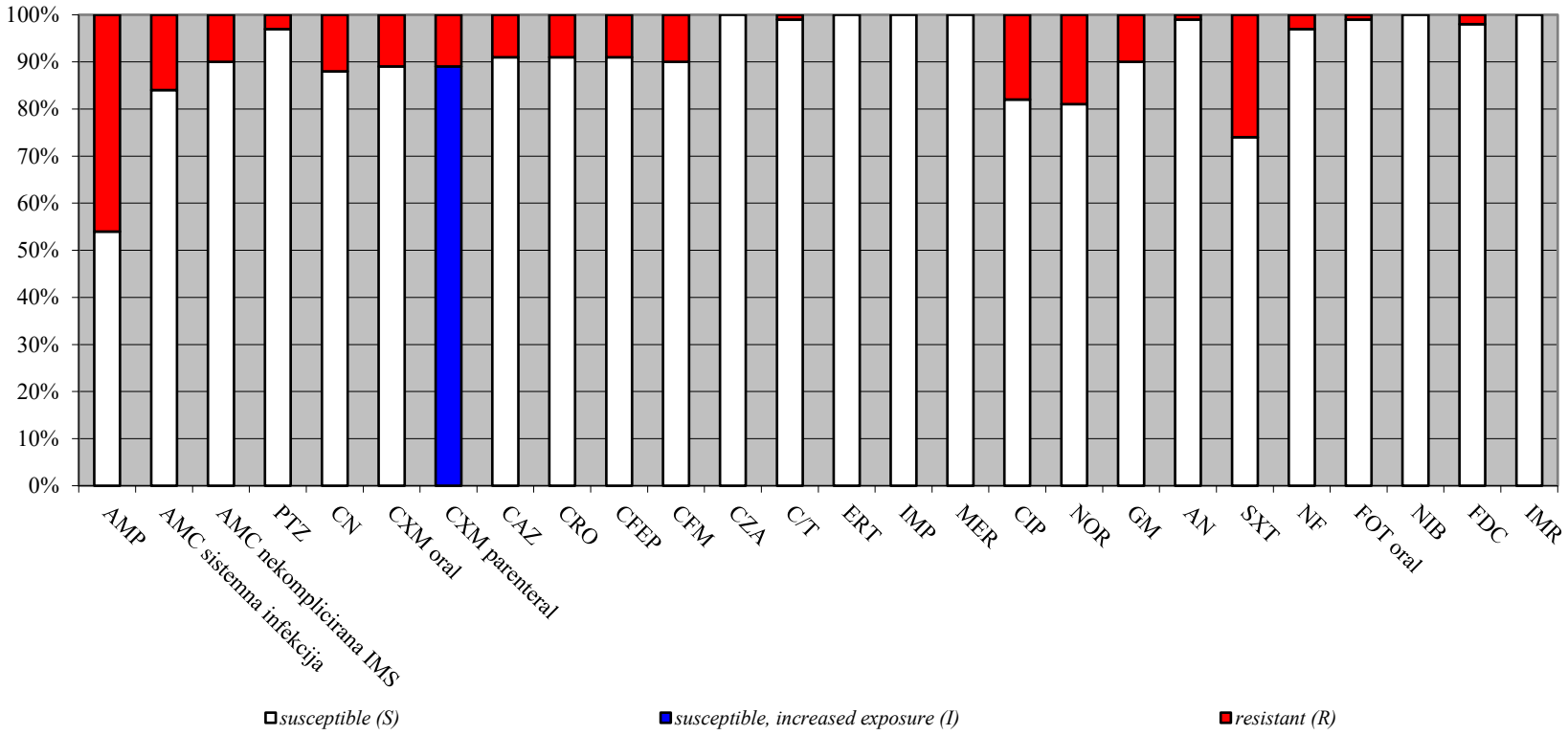
ANTIBIOTIK / *ANTIBIOTIC*	**Broj izolata /** *No. of isolates*	**% rezistentnih (R) (% osjetljivih uz povećanu izloženost (I)) izolata /** *% of resistant (R) (% of susceptible, increased exposure (I)) isolates*	**Raspon lokalnih rezultata* /** *Range of local results**
Ampicillin	21 770	46 (0)	1 (0) - 61 (0)
Amoxicillin + clav. acid sistemna infekcija	20 683	16 (0)	5 (0) - 39 (0)
Amoxicillin + clav. Acid nekomplicirana IMS	21 487	10 (0)	5 (0) - 29 (0)
Piperacillin + tazobactam	20 877	3 (0)	0 (0) - 15 (0)
Cephalexin	21 038	12 (0)	4 (0) - 22 (0)
Cefuroxime oral	21 633	11 (0)	4 (0) - 22 (0)
Cefuroxime parenteral	21 725	11 (89)	4 (96) – 22 (78)
Ceftazidime	21 648	9 (0)	0 (0) - 17 (4)
Ceftriaxone	21 668	9 (0)	3 (0) - 17 (0)
Cefepime	20 872	9 (0)	0 (0) – 41 (3)
Cefixime	20 934	20 (0)	5 (0) – 20 (0)
Ceftazidime + avibactam	19 727	0 (0)	0 (0) – 1 (0)
Ceftolozane + tazobactam	19 289	1 (0)	0 (0) – 10 (0)
Ertapenem	20 884	0 (0)	0 (0) - 2 (0)
Imipenem	20 658	0 (0)	0 (0) - 1 (1)
Meropenem	20 885	0 (0)	0 (0) - 5 (0)
Ciprofloxacin	21 007	18 (0)	7 (5) - 51 (4)
Norfloxacin	21 271	19 (0)	7 (0) - 31 (0)
Gentamicin	21 721	10 (0)	4 (0) - 20 (0)
Amikacin	21 636	1 (0)	0 (0) - 21 (0)
Co-trimoxazole	21 668	26 (0)	16 (0) - 36 (0)
Nitrofurantoin	21 314	3 (0)	0 (0) - 22 (0)
Fosfomycin oral	20 594	1 (0)	0 (0) - 6 (0)
Nitroxolin	19 639	0 (0)	0 (0) - 2 (0)
Cefiderocol	14 779	2 (0)	0 (0) – 7 (0)
Imipenem + relebactam	15 789	0 (0)	0 (0) – 7 (0)

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

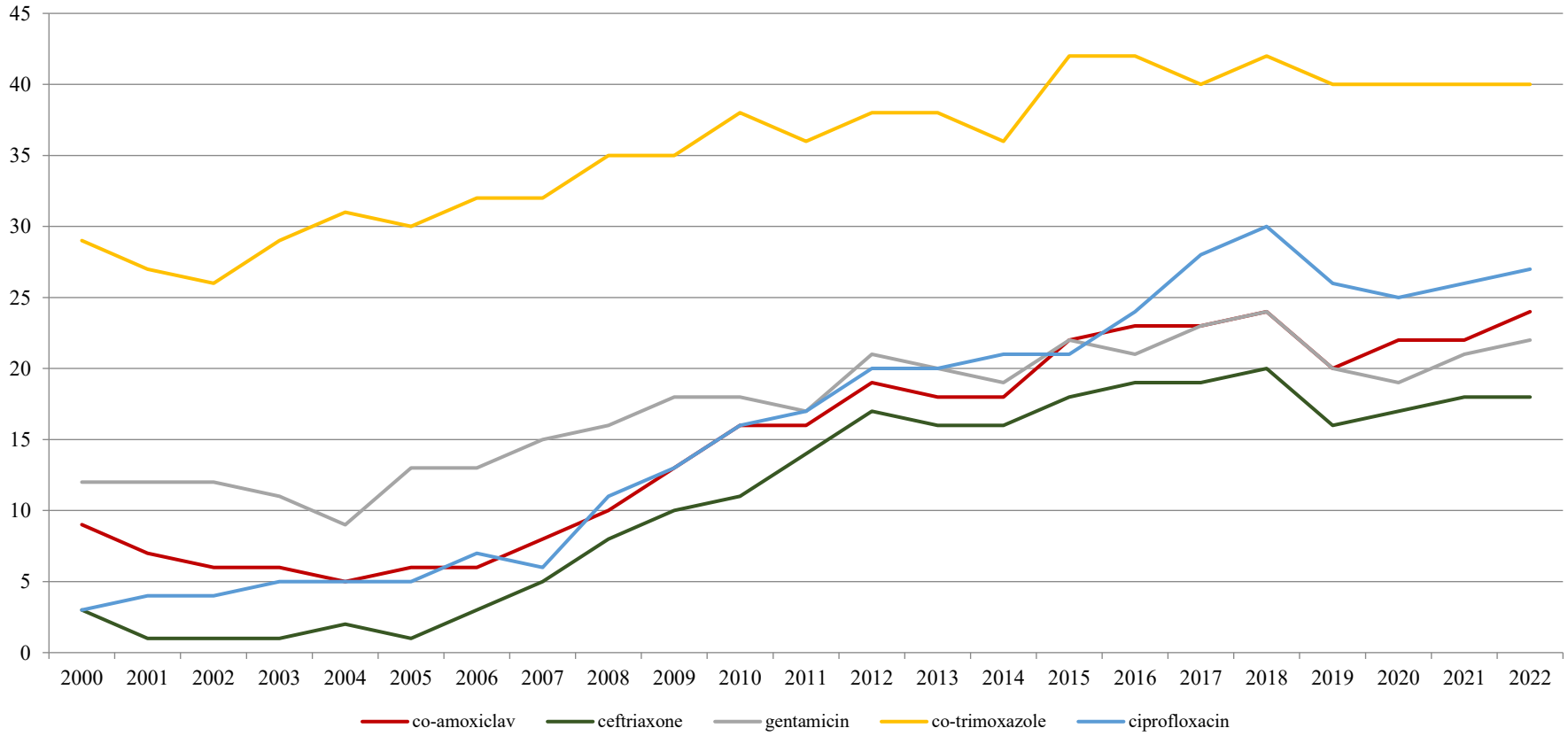
Escherichia coli

osjetljivost na antibiotike u RH / *sensitivity to antibiotics in Croatia*, 1.10. – 31.12.2022



Proteus mirabilis

rezistencija na antibiotike u RH / *resistance to antibiotics in Croatia*, 2000. – 2022.



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Croatian Committee for Antibiotic Resistance Surveillance

Proteus mirabilis

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Ampicillin	4 250	46 (0)	30 (0) - 76 (0)
Amoxicillin + clav. acid	4 251	24 (0)	4 (0) - 67 (0)
Piperacillin + tazobactam	4 105	2 (0)	0 (0) - 9 (0)
Cephalexin	4 078	23 (0)	4 (0) - 59 (0)
Cefuroxime $_{\text{oral}}$	4 191	21 (0)	4 (0) - 59 (0)
Cefuroxime $_{\text{parenteral}}$	4 249	21 (78)	0 (0) – 59 (41)
Ceftazidime	4 201	16 (0)	0 (0) - 59 (0)
Ceftriaxone	4 204	18 (0)	2 (0) – 59 (0)
Cefepime	4 097	9 (3)	1 (0) - 28 (5)
Cefixime	4 037	17 (0)	2 (0) - 59 (0)
Ceftazidime + avibactam	3 841	0 (0)	0 (0) – 7 (0)
Ceftolozane + tazobactam	3 742	6 (0)	0 (0) – 21 (0)
Ertapenem	4 105	0 (0)	0 (0) – 4 (0)
Meropenem	4 102	0 (0)	0 (0) – 2 (0)
Ciprofloxacin	4 099	27 (1)	6 (0) – 63 (0)
Norfloxacin	4 098	27 (0)	0 (0) – 63 (0)
Gentamicin	4 249	22 (0)	7 (0) – 41 (0)
Amikacin	4 184	10 (0)	0 (0) – 39 (0)
Co-trimoxazole	4 201	40 (0)	20 (0) – 69 (0)
Cefiderocol	2 956	1 (0)	0 (0) – 4 (0)

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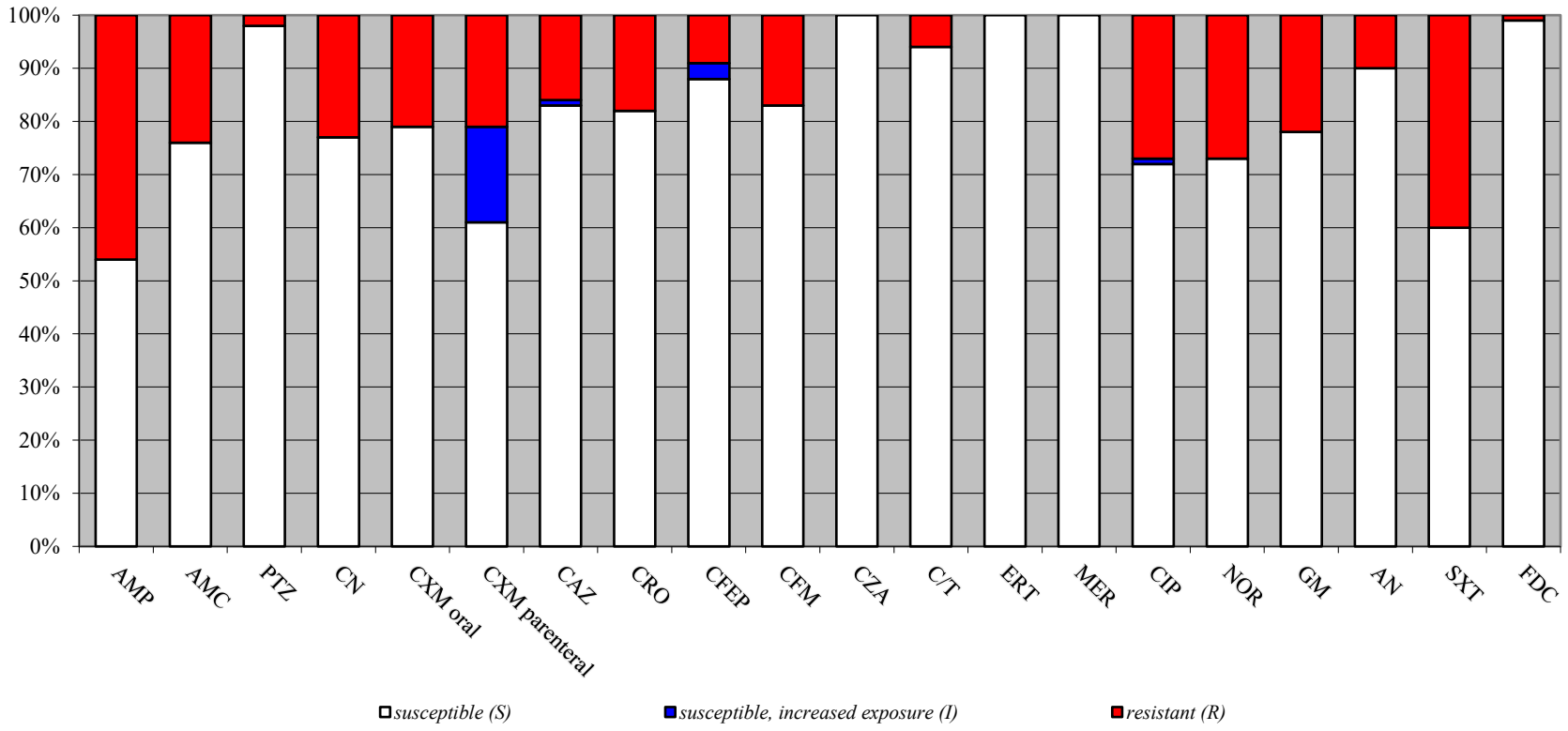
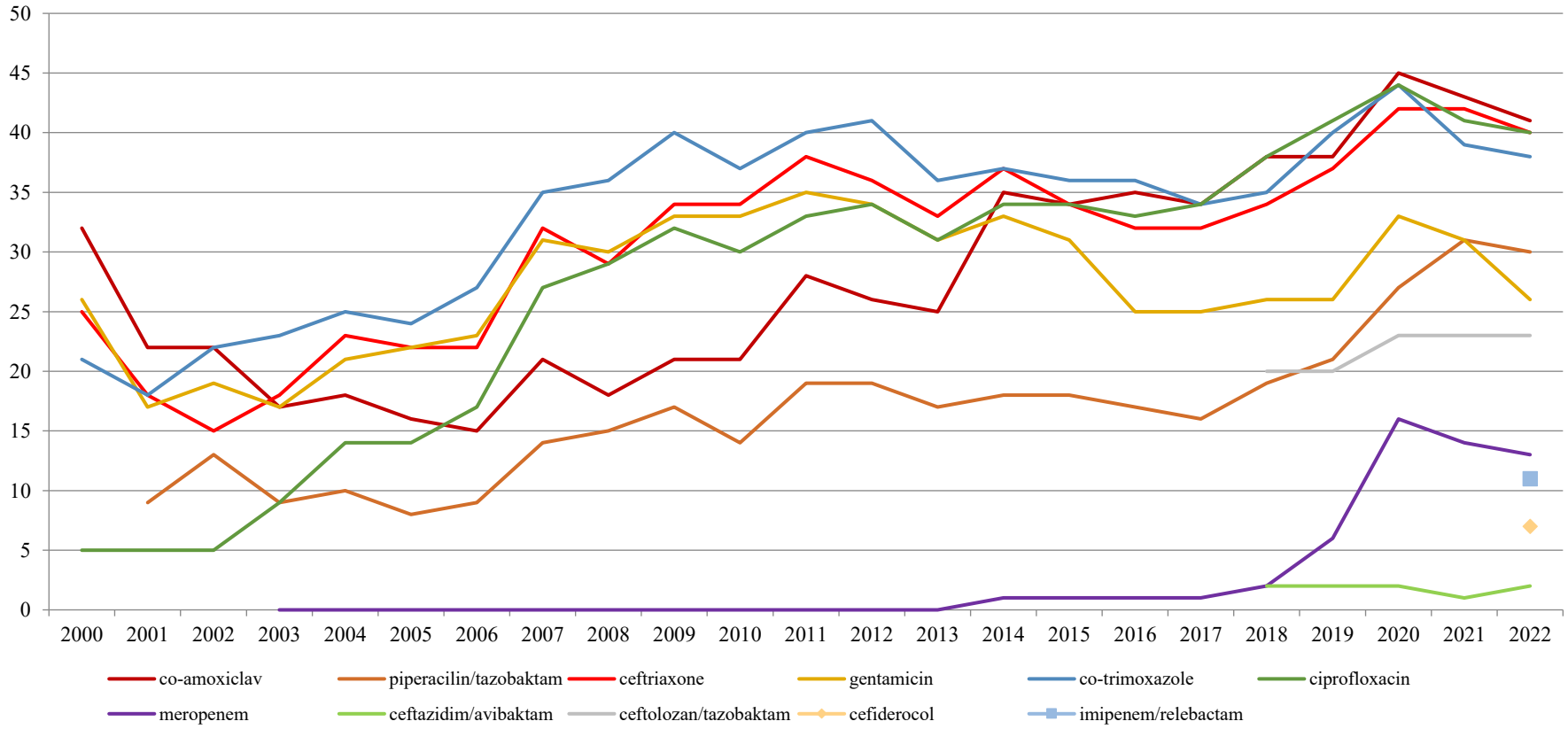
Proteus mirabilis

osjetljivost na antibiotike u RH / *sensitivity to antibiotics in Croatia*, 1.10. – 31.12.2022.



Klebsiella pneumoniae

rezistencija na antibiotike u RH /*resistance to antibiotics in Croatia*, 2000. - 2022.



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Klebsiella pneumoniae

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Ampicillin	6 245	100 (0)	100 (0) – 100 (0)
Amoxicillin + clav. acid	6 247	41 (0)	14 (0) – 63 (0)
Piperacillin + tazobactam	5 949	30 (1)	5 (0) – 53 (0)
Cephalexin	5 972	43 (0)	16 (0) – 64 (0)
Cefuroxime oral	6 139	41 (0)	17 (0) – 63 (0)
Cefuroxime parenteral	6 247	42 (58)	16 (84) – 63 (37)
Ceftazidime	6 158	39 (0)	13 (0) – 61 (1)
Ceftriaxone	6 159	40 (0)	13 (0) – 63 (0)
Cefepime	5 945	38 (1)	11 (0) – 65 (0)
Cefixime	5 931	40 (0)	13 (0) – 63 (0)
Ceftazidime + avibactam	5 498	2 (0)	0 (0) – 17 (0)
Ceftolozane + tazobactam	5 357	23 (0)	0 (0) – 56 (0)
Ertapenem	5 960	21 (0)	0 (0) – 41 (0)
Imipenem	5 875	9 (4)	0 (0) – 23 (4)
Meropenem	5 964	13 (3)	0 (0) – 33 (2)
Ciprofloxacin	5 966	40 (1)	14 (0) – 68 (1)
Norfloxacin	5 847	40 (0)	14 (0) – 70 (0)
Gentamicin	6 243	26 (0)	5 (0) – 54 (0)
Amikacin	6 186	7 (0)	0 (0) – 30 (0)
Co-trimoxazole	6 150	38 (1)	16 (0) – 60 (0)
Ceficerocol	4 330	7 (0)	0 (0) – 16 (0)
Imipenem + relebactam	4 650	11 (0)	0 (0) – 38 (0)

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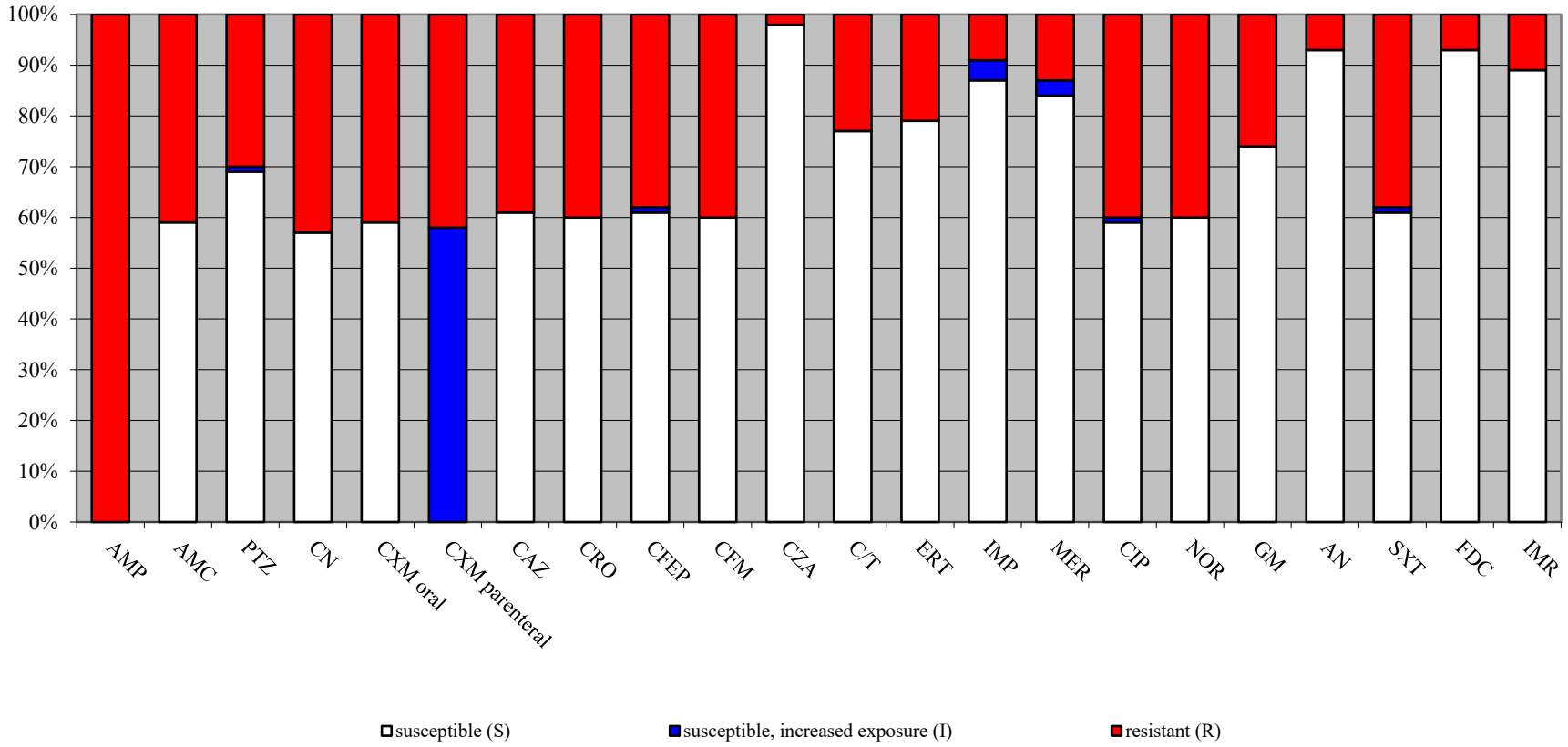
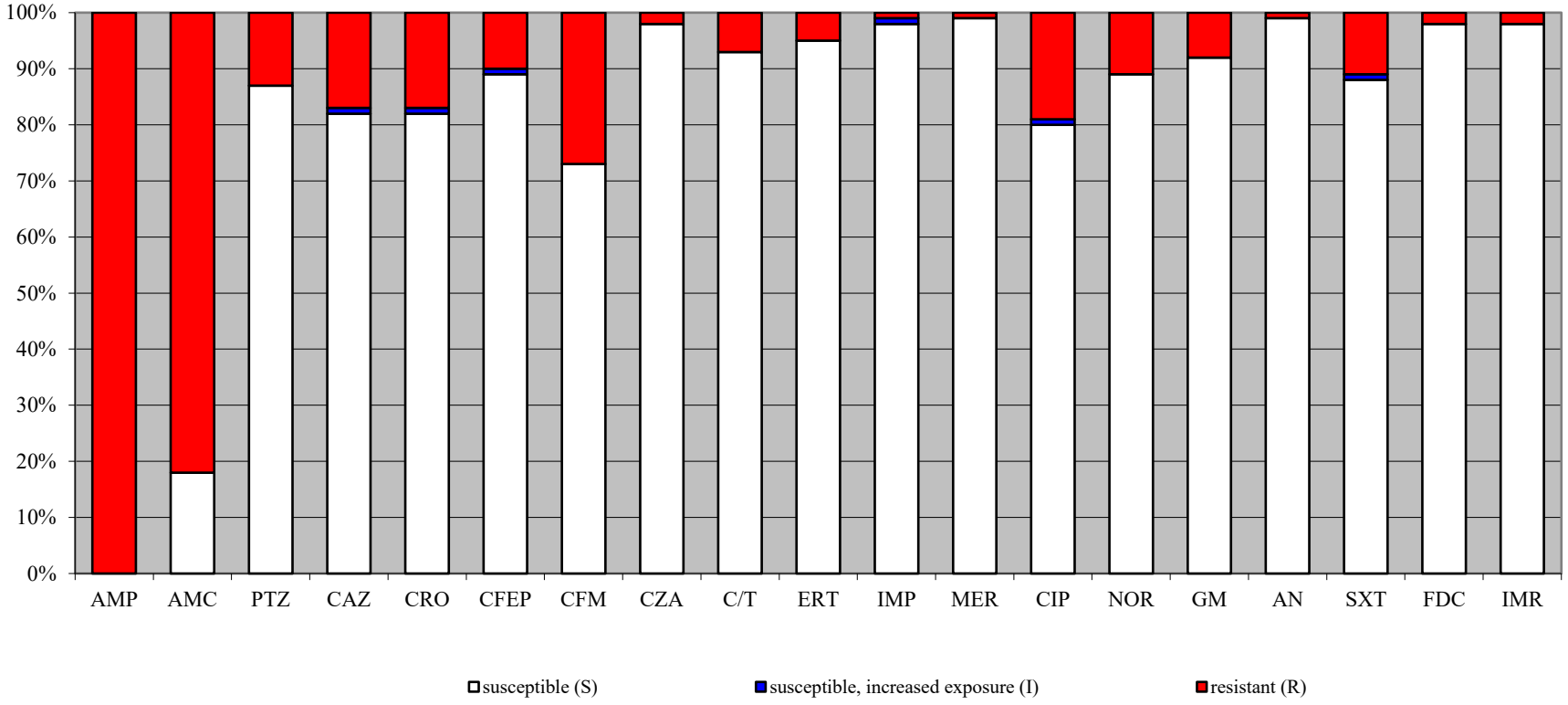
Klebsiella pneumoniae

osjetljivost na antibiotike u RH / *sensitivity to antibiotics in Croatia*, 1.10. – 31.12.2022.



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

osjetljivost na antibiotike u RH / *sensitivity to antibiotics in Croatia,* 1.10. – 31.12.2022.



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

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Ampicillin	3 668	100 (0)	100 (0) - 100 (0)
Amoxicillin + clav. acid	3 668	82 (0)	58 (0) - 100 (0)
Piperacillin + tazobactam	3 658	13 (0)	2 (0) - 54 (0)
Ceftazidime	3 661	17 (1)	6 (0) - 67 (0)
Ceftriaxone	3 663	17 (1)	4 (0) - 59 (3)
Cefepime	3 657	10 (1)	0 (0) - 49 (5)
Cefixime	3 528	27 (0)	10 (0) - 80 (0)
Ceftazidime + avibactam	3 419	2 (0)	0 (0) - 27 (0)
Ceftolozane + tazobactam	3 313	7 (0)	0 (0) – 30 (0)
Ertapenem	3 651	5 (0)	0 (0) – 24 (0)
Imipenem	3 630	1 (1)	0 (0) - 7 (0)
Meropenem	3 652	1 (0)	0 (0) - 7 (5)
Ciprofloxacin	3 658	10 (1)	3 (0) - 27 (5)
Norfloxacin	3 566	11 (0)	3 (0) - 64 (0)
Gentamicin	3 667	8 (0)	1 (0) - 46 (0)
Amikacin	3 612	1 (0)	0 (0) - 14 (0)
Co-trimoxazole	3 649	11 (0)	1 (0) - 66 (0)
Cefiderocol	2 698	2 (0)	0 (0) – 18 (9)
Imipenem + relebactam	2 933	2 (0)	0 (0) – 7 (0)

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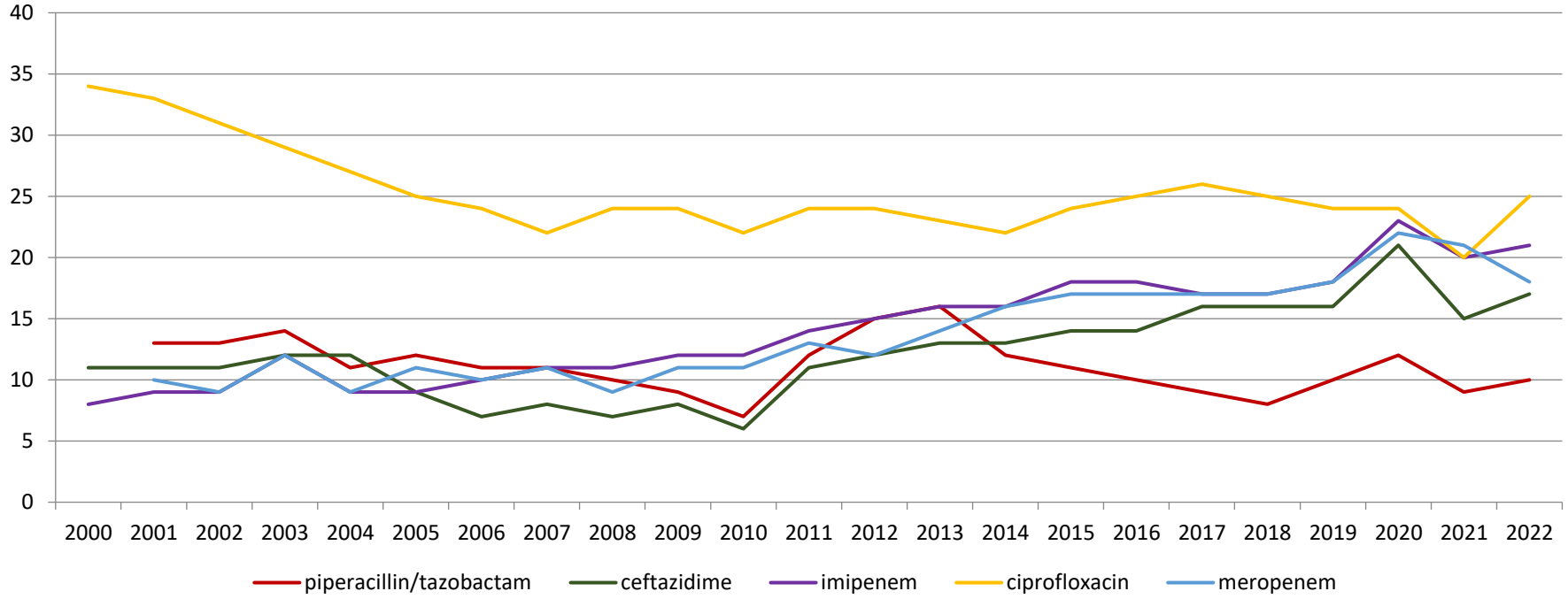
Pseudomonas aeruginosa

rezistencija na antibiotike u RH / *resistance to antibiotics in Croatia*, 2000. - 2022.



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Pseudomonas aeruginosa

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Piperacilin + tazobaktam	4 190	10 (89)	0 (100) - 31 (69)
Ceftazidim	4 190	17 (82)	3 (97) - 51 (49)
Cefepim	4 192	15 (84)	1 (99) - 39 (61)
Ceftazidime + avibactam	3 677	6 (0)	0 (0) – 23 (0)
Ceftolozane + tazobactam	3 643	5 (0)	0 (0) – 21 (0)
Cefiderocol	4 244	25 (75)	0 (0) – 8 (5)
Imipenem	4 110	21 (78)	3 (97) - 47 (53)
Meropenem	4 151	18 (5)	0 (0) - 47 (1)
Ciprofloxacin	4 244	25 (75)	3 (97) - 44 (56)
Amikacin	4 156	6 (0)	0 (0) - 21 (0)
Colistin	969	3 (0)	0 (0) - 13 (0)

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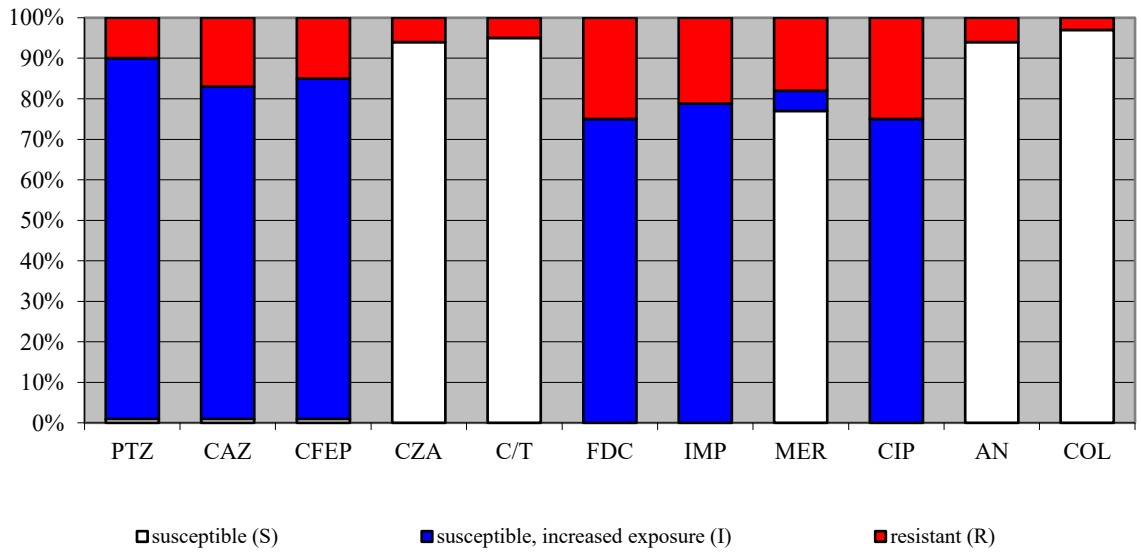
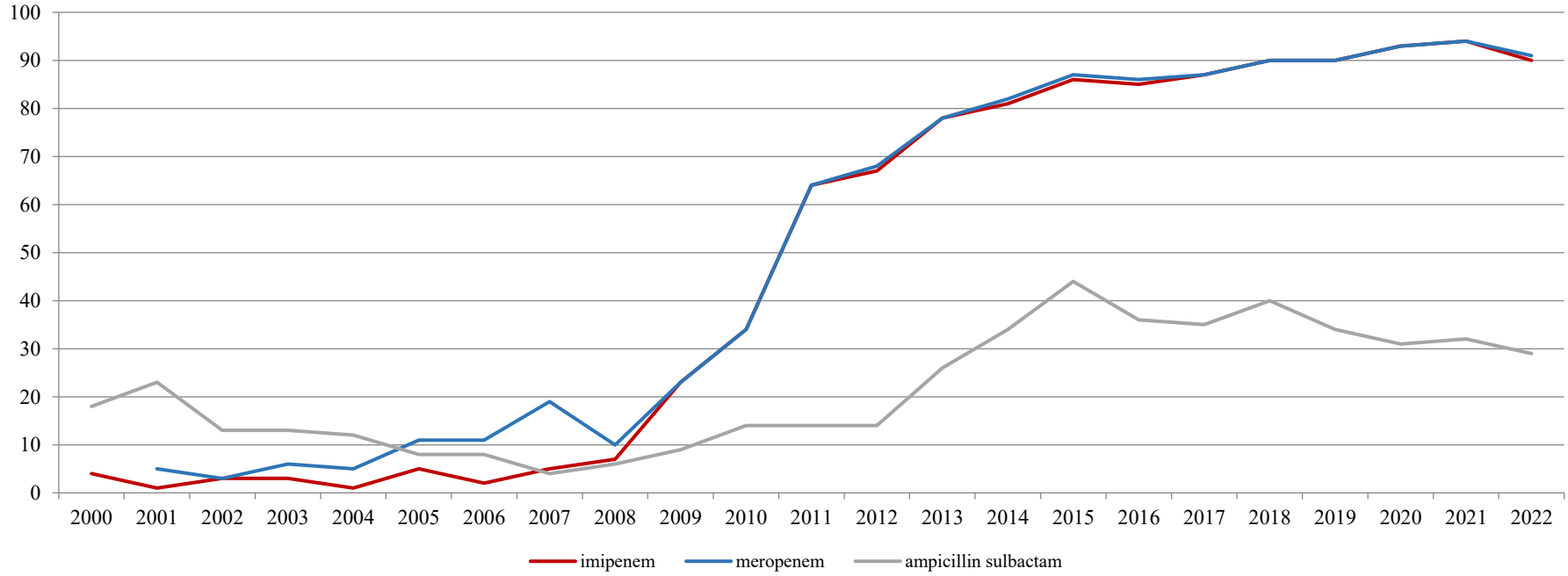


Acinetobacter baumannii

rezistencija na antibiotike u RH / *resistance to antibiotics in Croatia*, 2000. - 2022.



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Acinetobacter baumannii

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Ampicillin + sulbactam	1 605	29 (26)	0 (100) - 69 (19)
Meropenem	1 654	91 (0)	74 (0) - 99 (0)
Imipenem	1 626	90 (1)	74 (0) - 99 (0)
Ciprofloxacin	1 654	92 (8)	74 (26) - 100 (0)
Gentamicin	1 654	87 (0)	68 (0) - 100 (0)
Amikacin	1 653	83 (0)	56 (0) - 99 (0)
Co-trimaxazole	1 618	74 (1)	40 (0) - 100 (0)
Colistin	1 352	1 (0)	0 (0) - 6 (0)
Cefiderocol	1 139	1 (0)	0 (0) – 11 (0)

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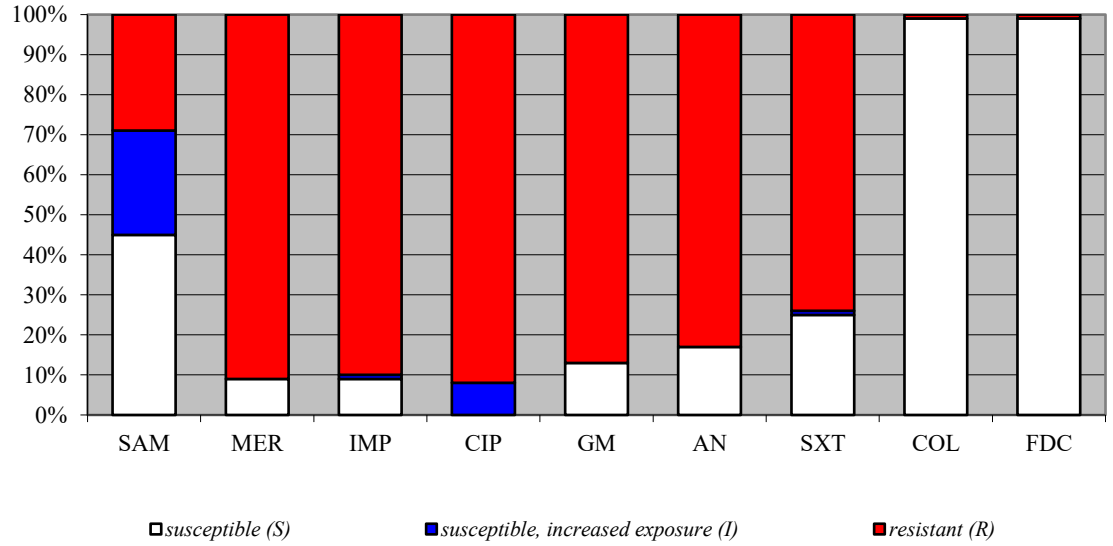

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Salmonella spp.

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Ampicillin	1 858	16 (0)	0 (0) - 51 (0)
Amoxicillin + clav. acid	1 857	7 (0)	0 (0) - 66 (0)
Ceftazidim	1 856	2 (1)	0 (0) - 12 (0)
Ceftriaxone	1 857	1 (1)	0 (0) - 20 (12)
Ciprofloxacin	1 825	18 (0)	0 (0) - 66 (0)
Co-trimoxazole	1 858	4 (0)	0 (0) - 12 (0)

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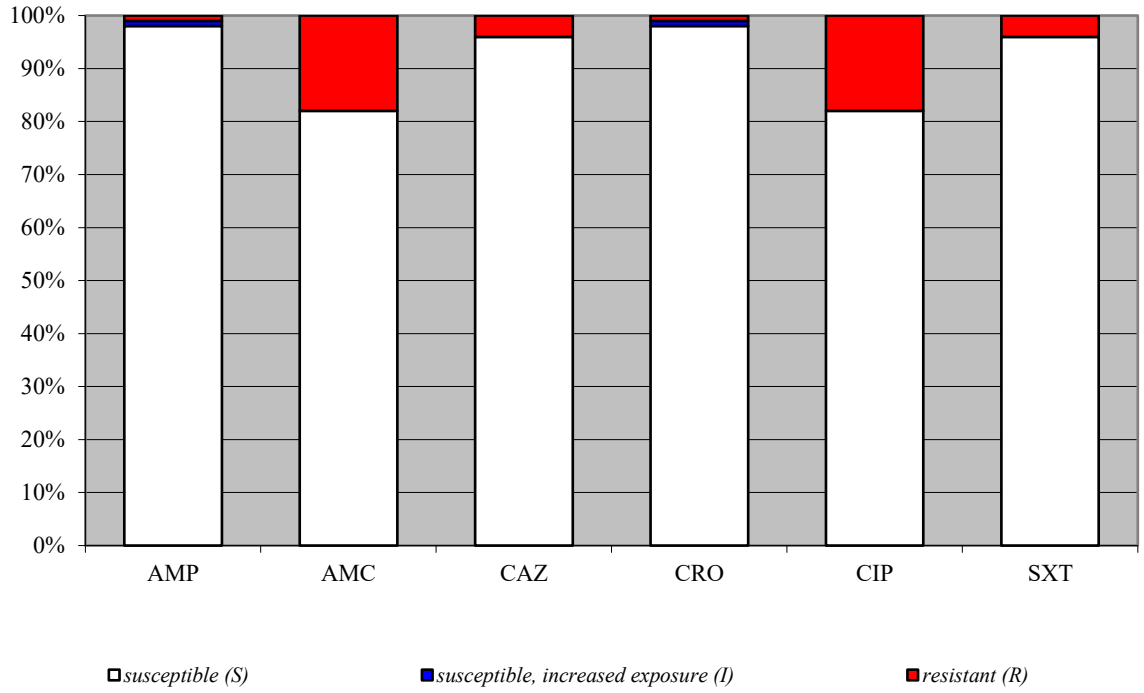

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Campylobacter jejuni

rezistencija na antibiotike u razdoblju od 1.01.- 31.12.2022.,
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antibiotic resistance for the period 1.01. - 31.12.2022,
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Ciprofloxacin	2 262	72 (18)	64 (36) - 95 (5)
Erythromicin	2 263	0 (0)	0 (0) - 8 (0)
Tetracycline	2 258	43 (0)	27 (0) - 56 (0)

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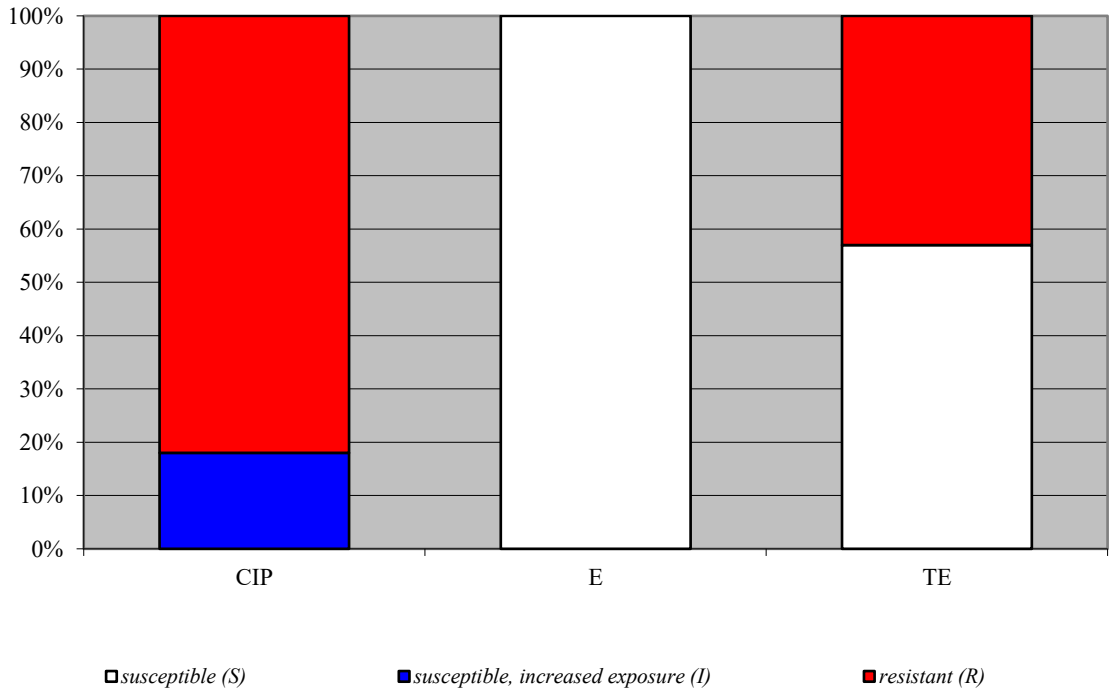

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Campylobacter coli

rezistencija na antibiotike u razdoblju od 1.01. - 31.12.202.,
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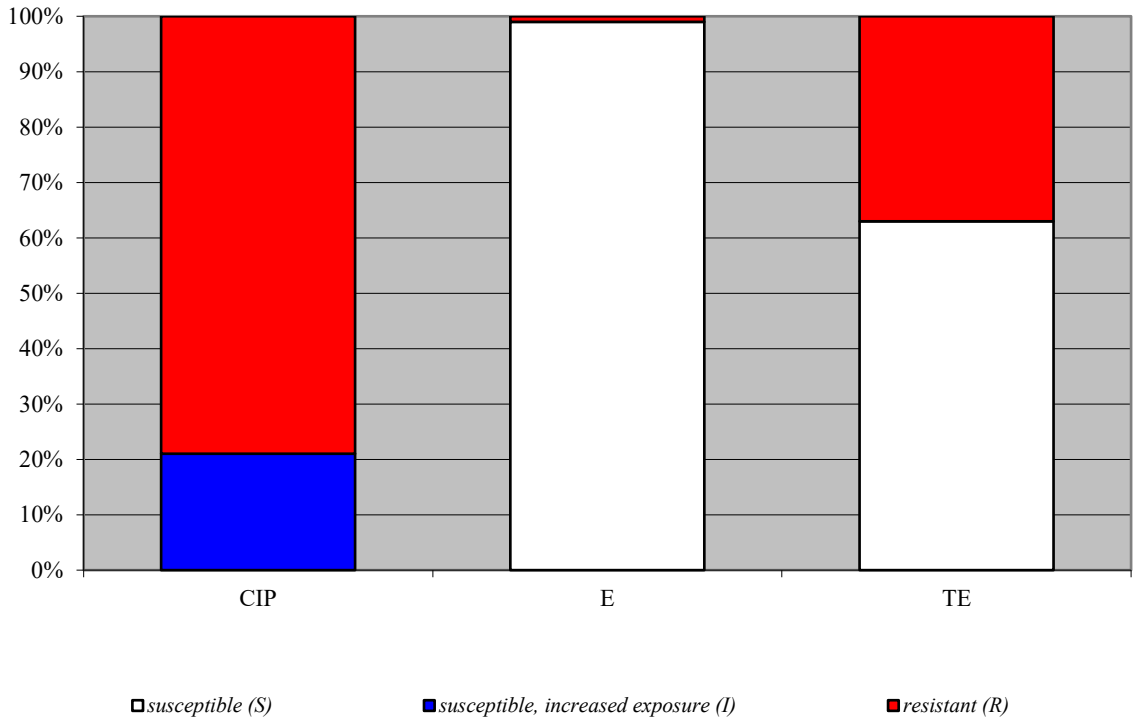
summary results for the isolates from 39 centers in Croatia

ANTIBIOTIK / ANTIBIOTIC	**Broj izolata** / No. of isolates	**% rezistentnih (R) (% osjetljivih uz povećanu izloženost (I)) izolata** / *% of resistant (R) (% of susceptible, increased exposure (I)) isolates*	**Raspon lokalnih rezultata*** / Range of local results*
Ciprofloxacin	594	79 (21)	64 (36) - 87 (13)
Erythromicin	594	1 (0)	0 (0) - 4 (0)
Tetracycline	593	37 (0)	22 (0) - 52 (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



Shigella spp.

rezistencija na antibiotike u RH / *antibiotic resistance in Croatia*, 01.01. – 31.12.2022.*

***Shigella* spp.**	**AMP**			**AMC**			**CAZ**			**CRO**			**CIP**			**SXT**			**AZM**		
	No	S	**R**	No	S	**R**	No	S	**R**	No	S	**R**	No	S	**R**	No	S	**R**	No	WT**	**Non WT****
Shigella sonnei	3	3	**0**	3	3	**0**	3	3	**0**	3	3	**0**	3	3	**0**	3	2	**1**	3	2	**1**
Shigella flexneri	1	0	**1**	1	1	**0**	1	1	**0**	1	1	**0**	1	1	**0**	1	1	**0**	1	0	**1**
UKUPNO / *TOTAL*	4	3	**1**	4	4	**0**	4	4	**0**	4	4	**0**	4	4	**0**	4	3	**1**	**4**	**2**	**2**

*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*

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

Anaerobne bakterije / *Anaerobes*

rezistencija na antibiotike u RH / *antibiotic resistance in Croatia*, 01.01. – 31.12.2022.

Anaerobne bakterije / *Anaerobes*	**P**			**PTZ**			**MEM**			**CC**			**MTZ**			**VA**		
	No	S %	**R %**	No	S %	**R %**	No	S %	**R %**	No	S %	**R %**	No	S %	**R %**	No	S %	**R %**
Cutibacterium acnes	176	99	**1**	84	100	**0**	86	99	**1**	173	72	**28**	-	-	**-**	81	100	**0**
***Bacteroides* spp.**	-	-	**-**	409	94	**6**	393	96	**4**	611	59	**41**	610	92	**8**	-	-	**-**
***Prevotella* spp.**	155	43	**57**	111	99	**1**	111	99	**1**	156	49	**51**	155	92	**8**	-	-	**-**
Fusobacterium necrophorum	27	78	**22**	12	100	**0**	11	100	**0**	28	79	**21**	27	78	**22**	-	-	**-**
Clostridium perfringens	69	96	**4**	69	100	**0**	50	100	**0**	72	56	**44**	68	65	**25**	64	98	**2**
UKUPNO / *TOTAL*	427	77	**23**	685	96	**4**	651	96	**4**	1040	61	**39**	860	91	**9**	145	99	**1**

OSJETLJIVOST *M. TUBERCULOSIS* U HRVATSKOJ U 2022. GODINI

SENSITIVITY OF M. TUBERCULOSIS IN CROATIA, 2022

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 2022. godini

Za analizu podataka o bakteriološkoj dijagnostici tuberkuloze (TBC) u Hrvatskoj u 2022. godini koristio se „Upitnik o radu TBC laboratorija u 2022. godini“. U prošloj godini, radi i dalje iznimne situacije uzrokovane COVID-19 pandemijom, dijagnostika tuberkuloze provodila se u 13 laboratorija organiziranih na tri razine. Ukupno je pregledano 24 243 kliničkih uzoraka na TBC što je porast od 9% od broja uzoraka iz 2021. godine. Iako je preporučeni minimalni godišnji broj uzoraka za obradu na mikobakterije 2000, samo četiri je laboratorija u 2022. obradilo više od 2000 uzoraka. Nadalje, svi laboratoriji iz naše mreže još uvijek ne koriste tekuće podloge za sve uzorke nego samo za paucibacilarne ili izvanplućne uzorke. U 4% uzoraka kultivacijom je otkriven *M. tuberculosis*, a raspon pozitivnih kultura među laboratorijima se kretao od 0,5 do 18,8%. Ukupno je izolirano 1 268 sojeva mikobakterija.

Tijekom 2022. godine genotipiziran je 182 izolat *M. tuberculosis* iz cijele Hrvatske. U skladu s očekivanim, M. tuberculosis je najčešće izoliran iz plućnih uzoraka, a među 10 (5,5%) izvanplućnih bakteriološki dokazanih slučajeva TBC najčešća je bila limfoglandularna TBC (N=4), TBC pleure (N=2), tkiva (N=2), TBC središnjeg živčanog sustava (N=1) te TBC rane (N=1).

Tijekom 2022. godine iz humanih kliničkih materijala nije izoliran *M. bovis*, niti *M. bovis – BCG* soj. 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 2022. godini od uvjetno patogenih spororastućih mikobakterija najviše je izoliran *M. avium* (66 izolata), *M. xenopi* (54 izolata), te *M. intracellulare* (50 izolata). Od brzorastućih mikobakterija najveći broj izolata odnosio se na *M. fortuitum* (23 izolata), a slijede ga *M. chelonae* sa 22 izolata i *M. abscessus* sa 10 izolata. *M. gordonae* kao saprofitna mikobakterija je identificiran u 15,1% izolata NTM. Najčešće se radi o kontaminaciji uzoraka, slučajnim nalazima i prolaznim kolonizacijama. U 2022. godini su otkrivene 82 osobe sa zadovoljenim mikrobiološkim kriterijima za dijagnozu mikobakterioze (dva i više izolata, ili izolat iz asp. bronha). Kod 24 bolesnika izoliran je *M. xenopi*, a slijede ga *M. avium* koji je izoliran kod 18 bolesnika te *M. intracellulare* kod 10 bolesnika i *M. gordonae* kod osam bolesnika.

Nastavljen je izrazito povoljan trend broja rezistentnih sojeva *M. tuberculosis*. Od 963 testiranih sojeva samo je 23 (2,4%) bilo rezistentno na prvu liniju antituberkulotika, a otkriveni su kod sedam bolesnika s rezistentnom tuberkulozom. Među bolesnicima s rezistentnim oblikom tuberkuloze, njih šest (85,7%) je imalo monorezistenciju (četiri na streptomicin i dva na izonijazid), a jedan pacijent je imao zarazu polirezistentnim sojem (rezistencija na rifampicin, etambutol i pirazinamid).

Mycobacteria isolated in Croatia in 2022

In 2022, due to the COVID-19 pandemic, the TB diagnostics was performed in 13 laboratories, organized at three levels. To analyze data on tuberculosis (TB) bacteriological diagnostics, the "Questionnaire on the work of TB laboratories in 2022" was used. A total of 24 243 clinical samples were analyzed for tuberculosis, which is 9% more than the number of samples in 2021. The number of processed samples was still under the recommended minimum of 2000 samples in a total of nine laboratories. Furthermore, all laboratories still don't use liquid mediums for all samples, but only for paucibacillar or extrapulmonary samples. In 4% of samples, cultivation detected mycobacteria and the range of positivity of cultivation in different laboratories was from 0.5 to 18.8%. A total of 1 268 mycobacterial isolates were cultivated.

During 2022, a total of 182 M. tuberculosis isolates were genotyped. As expected, M. tuberculosis was most frequently isolated from pulmonary samples. Among bacteriologically confirmed extrapulmonary TB (N=10; 5.5%), the most frequent forms were lymphoglandular TB (N=4), pleural TB (N=2), tissue TB (N=2), central nervous system TB (N=1), and wound TB (N=1). There were no M. bovis strains or M. bovis - BCG strains isolated.

Although M. tuberculosis remained the predominant mycobacterium with 963 (75.9%) isolates, the number of nontuberculous mycobacteria (NTM) is still high, accounting for 23.9% of all isolates in 2022. 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 2022 prevailed isolates of M. avium (N=66), M. xenopi (N=54), and M. intracellulare (N=50), while in the rapidly growing group the most commonly isolated species were M. fortuitum (N=23), M. chelonae (N=22) and M. abscessus (N=10). M. gordonae, a saprophytic mycobacterium, was identified in 15,1% of all NTM isolates. In most cases, the isolation was the result of specimen contamination, accidental finding and transient colonization.

In 2022, a total of 82 cases that fulfilled the microbiological criteria for mycobacteriosis (two or more isolates or isolate from bronh. aspirate) were documented. M. xenopi was isolated in 24 patients, M. avium in 18 patients, M. intracellulare in 10, and M. gordonae in eight patients.

The number of resistant M. tuberculosis strains and, by extension, number of resistant TB cases has demonstrated a continuous low number of new cases. Of the 963 tested M. tuberculosis strains, only 23 (2.4%) were resistant to antituberculotic drugs, isolated in seven patients with resistant TB. Among patients with resistant TB, six patients (85.7%) were infected with monoresistant strains (four to streptomycin and two to isoniazid), while one patient had infection with a poliresistant strain (resistant to rifampicin, pyrazinamide and ethambutol).

Tablica / *Table* **1.**
Mikobakterije izolirane u Hrvatskoj, 2012. – 2022. /
Mycobacteria strains isolated in Croatia, 2012-2022

Godina	Ukupno mikobakterija	*M. tuberculosis*		*M. bovis*		Netuberkulozne mikobakterije	
		Broj	%	*M. bovis*	BCG soj	Broj	Broj
2012.	2108	1807	85,7	1	6	294	14
2013.	2153	1748	81,2	-	1	402	18,8
2014.	1969	1541	78,3	-	1	423	21,5
2015.	1880	1505	80,1	-	6	375	19,9
2016.	2021	1587	78,5	-	5	428	21,2
2017.	1596	1246	78,1	-	2	350	21,9
2018.	1689	1387	82,1	-	2	302	17,9
2019.	1751	1281	73,2	4	2	464	26,5
2020.	1081	855	79,1	-	9	217	20
2021.	1009	799	79,2	-	1	209	20,7
2022.	1268	963	75,9	-	**1**	304	23,9

Tablica / *Table* **2.**
Netuberkulozne mikobakterije (NTM) izolirane u Hrvatskoj u 2022. /
Nontuberculous mycobacteria (NTM) isolated in Croatia in 2022

	Vrsta	Broj	%
Uvjetno patogene mikobakterije	*M. avium*	66	21,7
	M. xenopi	54	17,8
	M. intracellulare	50	16,4
	M. kansasii	7	2,3
	M. scrofulaceum	2	0,7
	M. chimaera	1	0,3
	M. gastri	1	0,3
	M. fortuitum	23	7,6
	M. chelonae	22	7,2
	M. abscessus	10	3,3
	M. mucogenicum	7	2,3
	M. celatum	2	0,7
	M. marinum	1	0,3
Saprofitne mikobakterije	*M. gordonae*	46	15,1
	Mycobacterium spp.	12	3,9
Ukupno		**304**	**100**

Tablica / *Table* **3.**
Bolesnici s rezistentnom tuberkulozom u Hrvatskoj, 2022. /
Resistant tuberculosis in Croatia, 2022

	Broj / *Number*	**%**
Ukupno bolesnika / *Patients total*	**7**	**100**
Monorezistencija / *Monoresistance*		
S	4	57,1
H	2	28,6
Polirezistencija / Poliresistance		
REZ	1	14,3

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

OSJETLJIVOST GONOKOKA U HRVATSKOJ U 2022

SENSITIVITY OF GONOCOCCI IN CROATIA IN 2022

Blaženka Hunjak
Tatjana Unukić
Andrea Babić-Erceg

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

Antimikrobna rezistencija u gonokoka izoliranih Hrvatskoj u 2022. godini

Godine 2022. koja je, na sreću, obilježena postepenim završtekom COVID-19 pandemije, zaprimili smo ukupno 17 sojeva *Neisseria gonorrhoeae* (NG) na razini RH, iako smatramo da ovaj broj izolata ne pokazuje realnu sliku prijave NG. I dalje nam je cilj dosegnuti rezultate iz 2019. god. kada smo sakupili više od 70 NG izolata iz cijele RH. Ove godine je ponovo na razini EU aktiviran Projekt Euro – GASP, koji prati rezistenciju i učestalost NG, zajedno s epidemiološkim podacima. U svjetlu razvoja rezistencije u NG kao modela razvoja antimikrobne rezistencije (AMR) prikazujemo dobivene rezultate.

U HZJZ i dalje dolaze viabilni izolati NG, ali u manjem broju, te je retestiranje vrlo zahtjevno ili čak nemoguće, obzirom na zahtjevni transport i osjetljivost izolata. Većinom dolaze samo tablični pikazi. Broj dobivenih izolata, za 2015. god. bio je 15, u 2016.- 35, u 2017. - 36, u 2018. godini - 46, u 2019. - 73, u 2021. - 26 i 2022., je prijavljeno 17 izolata. U Tablici 1. navedene su vrijednosti gradijenata koje pokazuje rezultate testiranja metodom E-testa i disk difuzije.

Rezultati osjetljivosti za 2022. su kako slijedi (Tablica 2):

- na penicilin je bilo 8 (57,1%) osjetljivih, 6 (42,9%) umjereno osjetljivih, te niti jedan rezistentni izolat,
- na ceftriakson su svi izolati, od ukupno 17 testiranih , svi (100%) bili osjetljivi,
- na cefixim su svi testirani izolati; 16(100%), bili osjetljivi,
- na ciprofloksacin je bilo osjetjivih 8 (47,1%), jedan (5,9%) umjereno rezistentan, te 8 (47,1%) rezistentnih izolata.

Može se ponovo naglasiti da za gentamicin i dalje nema gradijenta za testiranje, ali se preporuča testiranje kako bi se ispitala djelotvornost gentamicina za slučaj ograničenog izbora terapije, kao i testiranje na tetraciklin. Osjetljivost na spektinomicin u RH i dalje provjeravamo, ali na spektinomicin rezistencija nije ustanovljena niti kod jednog testiranog izolata.

Antimicrobial resistance in gonococci isolated in Croatia in 2022.

In 2022, which, fortunately, was marked by the gradual end of the COVID-19 pandemic, we received a total of 17 strains of Neisseria gonorrhoeae (NG) at the level of the Republic of Croatia, although we believe that this number of isolates does not show a realistic picture of NG reporting. Our goal is still to reach the results from 2019. when we collected more than 70 NG isolates from all over the Republic of Croatia. This year, the Euro-GASP Project was activated again at the EU level, which monitors the resistance and frequency of NG, together with epidemiological data. In light of the development of resistance in NG as a model for the development of antimicrobial resistance (AMR), we present the obtained results.

Viable NG isolates still arrive at the CIPH; but in smaller numbers, and retesting is very demanding or even impossible, given the demanding transport and sensitivity of the isolates. Most of them only come with written results in forms. Number of obtained isolates, for 2015. was 15, in 2016 - 35, in 2017 - 36, in 2018 - 46, in 2019 - 73, in 2021 - 26 and in 2022, 17 isolates were reported. Table 1 lists the values of the gradients that show the results of the E-test and disk diffusion tests.

The sensitivity results for 2022 are as follows (Table 2):

- to penicillin there were 8 (57.1%) sensitive, 6 (42.9%) moderately sensitive, and not a single resistant isolate,

- all isolates, out of a total of 17 tested, were all (100%) sensitive to ceftriaxone,

- all isolates tested on cefixime; 16 (100%), were sensitive,

- 8 (47.1%) were susceptible to ciprofloxacin, one (5.9%) was moderately resistant, and 8 (47.1%) were resistant isolates.

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

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

Tablica 1. Minimaln inhibitorne koncentracije ispitivanih antibiotika za sojeve *N. gonorrhoeae* u Hrvatskoj te rezultati Nitocefinskog testa, 2022.

Ustanova	Penicilin MIK* (mg/L)			Ceftriakson MIK* (mg/L)			Cefixim MIK* (mg/L)			Ciprofloxacin MIK* (mg/L)			Azithromycin*** MIK* (mg/L)	Tetracycline MIK* (mg/L)			Spektinomycin MIK* (mg/L)			Nitrocefin
	S	I	R	S	I	R	S	I	R	S	I	R		S	I	R	S	I	R	
HZJZ (Zagreb)																				
1.	**/	**/	**/	0,004			0,016					2	0,016			64	0,064			**NEG**
2.	**/	**/	**/	0,003			0,016					1	0,016	0,5			1,5			**NEG**
3.	**/	**/	**/	0,094			0,047					8	0,75			4	8			/
4.		0,38		0,012			0,016					4	0,19		1		4			**NEG**
5.		0,125		0,003			0,016					4	0,25		1		6			/
KZIB																				
1.	0,032			0,002			50mm◦					0,38	0,023	0,047			**/	**/	**/	/
2.	0,016			<0,002			50mm◦			0,032			<0,016	<0,016			**/	**/	**/	/
3.		0,094		0,023			44mm◦			<0,003			0,19			8	**/	**/	**/	/
4.	0,032			<0,002			60mm◦			<0,002			0,032	0,125			**/	**/	**/	/
5.	0,064			<0,002			50mm◦			<0,002			0,125	0,023			**/	**/	**/	/
6.	0,023			<0,002			52mm◦			<0,002			0,064	0,094			**/	**/	**/	/
7.	0,006			<0,002			50mm◦			<0,002			<0,016	<0,016			**/	**/	**/	/
8.	0,032			<0,002			50mm◦				0,064		<0,016	0,125			**/	**/	**/	/
NZJZ Primorsko - goranska županija																				
1.	0,064			0,016			0,125					0,25	0,125	0,19			0,094			**NEG**
ZZJZ Varaždinske županije																				
1.		0,125		0,002			**/	**/	**/	0,002			0,032	**/	**/	**/	**/	**/	**/	**NEG**
ZZJZ Šibensko-kninske županije																				
1.		0,38		0,006			0,023					1	**/	**/	**/	**/	**/	**/	**/	**NEG**
2.		0,19		0,002			0,002			0,002			0,125	**/	**/	**/	**/	**/	**/	**NEG**

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

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

***Azitromicin se uvijek koristi zajedno s drugim učinkovitim sredstvom. Prilikom ispitivanja stečenog mehanizma rezistencije, ECOFF je 1 mg/L (EUCAST 2020.)

◦ metoda disk difuzije

Tablica 2. / *Table 2*. **Osjetljivost sojeva N. gonorrhoeae na antibiotike u Hrvatskoj, 2022.** / *Antimicrobial susceptibility of N. gonorrhoeae strains to antibiotics in Croatia, 2022*

Ustanova	Penicilin MIK* (mg/L)				Ceftriakson MIK* (mg/L)				Cefixim MIK* (mg/L)				Ciprofloxacin MIK* (mg/L)				Tetracycline MIK* (mg/L)				Spektinomycin MIK* (mg/L)			
	UK***	S (%)	I (%)	R (%)	UK***	S (%)	I (%)	R (%)	UK***	S (%)	I (%)	R (%)	UK***	S (%)	I (%)	R (%)	UK***	S (%)	I (%)	R (%)	UK***	S (%)	I (%)	R (%)
HZJZ (Zagreb)	**2**	0	2 (100)	**0**	**5**	5 (100)	0	**0**	**5**	5 (100)	0	**0**	**5**	0	0	**5 (100)**	**5**	1 (20)	2 (40)	**2 (40)**	**5**	5 (100)	0	**0**
KZIB	**8**	7 (87,5)	1 (12,5)	0	**8**	8 (100)	0	**0**	**8**	8 (100)	0	**0**	**8**	6 (75)	1 (12,5)	**1 (12,5)**	**8**	7 (87,5)	0	**1 (12,5)**	**/	**/	**/	**/
NZJZ Primorsko - goranska županija	**1**	1 (100)	0	**0**	**1**	1 (100)	0	**0**	**1**	1 (100)	0	**0**	**1**	0	0	**1 (100)**	**1**	1 (100)	0	**0**	**1**	1 (100)	0	**0**
ZZJZ Varaždinske županije	1	0	1 (100)	0	**1**	1 (100)	0	**0**	**/	**/	**/	**/	**1**	1 (100)	0	**0**	**/	**/	**/	**/**	**/**	**/	**/	**/**
ZZJZ Šibensko-kninske županije	2	0	2 (100)	0	**2**	2 (100)	0	**0**	**2**	2 (100)	0	**0**	**2**	1 (50)	0	**1 (50)**	**/	**/	**/	**/**	**/	**/	**/	**/**
UKUPNO:	**14**	8 (57,1)	6 (42,9)	**0**	**17**	17 (100)	0	**0**	**16**	16 (100)	0	0	**17**	8 (47,1)	1 (5,9)	**8 (47,1)**	**14**	9 (64,3)	2 (14,3)	**3 (21,4)**	**6**	6 (100)	0	**0**

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

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

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

PRAĆENJE REZISTENCIJE NA ANTIBIOTIKE U INVAZIVNIH IZOLATA

ANTIBIOTIC RESISTANCE SURVEILLANCE IN INVASIVE ISOLATES

Silvija Šoprek Strugar
Arjana Tambić Andrašević

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

Važnost praćenja rezistencije u invazivnih izolata

Sustavno praćenje rezistencije na antibiotike na europskoj razini započelo je 1999.g. u okviru "European Antimicrobial Resistance Surveillance System" (EARSS) projekta. Za prioritete u praćenju odabrano je u početku šest bakterijskih vrsta *S. aureus, E. faecalis, E. faecium, S. pneumoniae* i *E. coli*, od 2005.g. dodano je praćenje rezistencije u *K. pneumoniae* i *P. aeruginosa*, a od 2013.g. započeto je i praćenje rezistencije u *Acinetobacter* spp. S obzirom na različitu praksu uzimanja uzoraka i interpretaciju nalaza u različitim zemljama, a s ciljem da bi se osigurala usporedivost i pouzdanost rezultata iz različitih zemalja, odlučeno je da se u praćenju na europskoj razini uzmu u obzir samo invazivni izolati (iz hemokultura i likvora). S obzirom da je interpretacija nalaza ovih bakterija u hemokulturi i likvoru u svim laboratorijima jednaka, njihovo kliničko značenje je neupitno.

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

Unatoč nekim izazovima, kao što je mali broj invazivnih izolata u nekim centrima što otežava analizu na razini pojedinih centara, te činjenica da se prikupljanjem podataka samo iz prvih izolata novi mehanizmi rezistencije ne moraju javiti u hemokulturi ili likvoru, sudjelovanje u europskoj mreži omogućuje Hrvatskoj usporedbu s drugim zemljama te raspolaganje s vrijednim podacima o rezistenciji među invazivnim izolatima. Masovno praćenje rezistencije opisano u prvom poglavlju ove publikacije i ciljano praćenje invazivnih izolata dobro se nadopunjuju i predstavljaju dobru kombinaciju za praćenje rezistencije u Hrvatskoj na nacionalnoj i lokalnoj razini.

Rezultati praćenja rezistencije u invazivnih izolata

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

U sklopu EARS-Net programa, u Referentni centar za praćenje rezistencije bakterija na antibiotike se nastavlja slati i prikupljati svi invazivni izolati *S. pneumoniae, S. aureus, E. faecalis, E. faecium, E. coli, K. pneumoniae, P. aeruginosa, Acinetobacter* spp., praćeni sa svrhom retestiranja izolata s rijetkim fenotipom i eventualne daljnje obrade. Tijekom 2022.g. prikupljeno je 89 izolata *S. pneumoniae,* 1054 izolata *E. coli*, 394 izolata *K. pneumoniae*, 696 izolata *S. aureus,* 365 izolata enterokoka (288 *E. faecalis* i 137 *E. faecium* izolata), 282 izolata *P. aeruginosa*, te 308 izolata *Acinetobacter* spp. (Tablica 1).

U 2022. godini primijećen je kontinuirani rast broja laboratorija koji prijavljuju podatke o izolatima unutar nacionalne mreže. Međutim, zabilježen je nešto manji broj izolata u usporedbi s prethodnom godinom (3188 izolata u 2022.g.; 3706 izolata u 2021.g.). U Tablici 1. prikazani su brojevi laboratorija i broj prikupljenih invazivnih izolata pojedinih vrsta.

Značajan porast broja prijavljenih invazivnih izolata *Acinetobacter* spp., *S. aureus*, enterokoka i *K. pneumoniae* primijećen je tijekom 2020. i 2021. godine, ali taj trend je zaustavljen u 2022. godini. Svi navedeni izolati, osobito *Acinetobacter* spp., bilježe značajan pad, pri čemu je broj *Acinetobacter* spp. izolata smanjen za polovicu (308 izolata u 2022.g.; 640 izolata u 2021. g. Ovaj pad broja navedenih izolata povezan je sa završetkom pandemije SARS-CoV-2, što je dovelo do stabilizacije zdravstvenog

sustava. Posljedično, zaustavilo se širenje tipičnih bolničkih patogena, osobito *Acinetobacter* spp., koji je često prisutan u bolničkim okruženjima.

Sličan ali ne tako drastičan pad se primijećuje i kod ostalih spomenutih vrsta, S. aures, enterokoke i K. pneumoniae.

U 2022.g. uz zabilježen pad broja prijavljenih izolata S. aureus, bilježimo i nešto niže stope MRSA izolata (30% MRSA u 2022.g.; 36% u 2021.g). Međutim, iako je došlo do pada u stopi MRSA izolata, još uvijek se suočavamo s izrazito visokim stopama invazivnih MRSA sojeva, što predstavlja zabrinjavajući trend.

Unatoč padu u usporedbi s podacima iz prošle godine, zabilježene stope glikopeptidne rezistencije u E.faecium predstavljaju visoke i zabrinjavajuće stope (37% u 2022.g.; 39% u 2021.g.). U usporedbi s prošlogodišnjim podacima, u 2022.g. zabilježene su ponovno niže razine rezistencije na glikopeptide kod E. faecalis (1% u 2022.g.; 3% u 2021. godini). Stope visoke rezistencije na aminoglikozide u 2022.g. ne pokazuju znatnija odstupanja prema prošlogodišnjim podacima, ali su i dalje visoke.

Primijećen kontinuirani trend rasta stopa rezistencije u svim klasama antibiotika među invazivnim izolatima K. pneumoniae bilježimo do 2022. godine, kada se napokon zaustavlja, te se u 2022.g. uočava blagi pad stopa rezistencije u svim klasama antibiotika. Do sad najzabrinjavajući sojevi K. pneumoniae, otporni na karbapeneme (imipenem i/ili meropenem), zabilježili su stopu rezistencije čak od 28% tijekom 2021.g.. Međutim, u 2022. godini primjetan je pad, sa stopama rezistencije u padu te bilježimo 23% takvih izolata. Dodatnih 5% izolata K. pneumoniae osjetljivo je na iste uz povećanu dozu antibiotika. Sveukupno 28% invazivnih izolata K. pneumoniae predstavlja i dalje velik izazov u liječenju i odabiru otpimalne antibiotske terapije.

U invazivnim izolatima P. aeruginosa se i dalje primjećuje trend smanjenja stopa rezistencije u skupini aminoglikozida, dok se gotovo u svim ostalim skupinama antibiotika bilježi porast stopa rezistencije.

Stopa rezistencije E. coli na 3. generaciju cefalosporina nije se bitno mijenjala u odnosu na prošlu godinu (17%). Podaci pokazuju da je rezistencija u toj klasi antibiotika i dalje pretežno uzrokovana proizvodnjom beta-laktamaza proširenog spektra (engl. „extended spectrum beta-lactamases“, ESBL). Prema prikupljenim podacima tijekom posljednjih nekoliko godina, primjećuje se povećanje udjela ESBL sojeva među izolatima E. coli, dosežući najvišu zabilježenu razinu od 30% u 2022. godini.Stopa rezistencije na kinolone iznosi 31%.

U odnosu na pandemijske godine SARS-CoV-2, broj prijavljenih izolata S. pneumoniae sada je stabiliziran (n = 89). Među invazivnim izolatima pneumokoka, neosjetljivost na penicillin i dalje pokazuje trend smanjenja, te u 2022.g. iznosi 18%. Nastavljamo također pratiti trend pada stopa rezistencije na macrolide (24% u 2021.g.; 40% u 2020.g.; 30% u 2019.g.).

Stope rezistencije detaljno su prikazane u Tablici 2.

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

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

Impact of antibiotic resistance surveillance in invasive isolates

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 regarding the type of departments, it was decided, starting from 2020, to present data exclusively for intensive care units (ICU), resulting in a change in the format of the former Tables 3 and 4, which previously displayed demographic information for patients and the origin of samples.
Within the framework of the EARS-Net program, the Reference Center for Antibiotic Resistance Surveillance continues to receive and collect all invasive isolates of *S. pneumoniae, S. aureus, E. faecalis, E. faecium, E. coli, K. pneumoniae, P. aeruginosa*, and *Acinetobacter* spp., to retest isolates with rare phenotypes and further analysis. During 2022, a total of 89 isolates of *S. pneumoniae*, 1054 isolates of *E. coli*, 394 isolates of *K. pneumoniae*, 696 isolates of *S. aureus*, 365 isolates of enterococci (288 *E. faecalis* and 137 *E. faecium* isolates), 282 isolates of *P. aeruginosa*, and 308 isolates of *Acinetobacter* spp. were collected (Table 1).

In 2022, a continuous increase in the number of laboratories submitting isolate data within the national network was observed. However, there was a slightly smaller number of isolates compared to the previous year (3188 isolates in 2022; 3706 isolates in 2021). Table 1. shows the number of laboratories and the number of collected invasive isolates for each species.

The substantial increase in reported invasive isolates of *Acinetobacter* spp., *S. aureus*, enterococci, and *K. pneumoniae*, which was observed in 2020 and 2021, was stopped in 2022. All mentioned isolates, especially *Acinetobacter* spp., experienced a notable decline, with the number of *Acinetobacter* spp. isolates reduced by half (308 isolates in 2022; 640 isolates in 2021). This decrease in the number of isolates is linked to the conclusion of the SARS-CoV-2 pandemic, which resulted in the stabilization of the healthcare system and consequently, the cessation of the spread of typical hospital pathogens, particularly *Acinetobacter* spp., which is commonly present in hospital settings.

A similar but not as drastic decline is also observed in other mentioned species, such as *S. aureus*, enterococci, and *K. pneumoniae*.

In 2022, alongside the recorded decrease in the number of reported *S. aureus* isolates, we also note slightly lower rates of MRSA isolates (30% MRSA in 2022; 36% in 2021). However, despite the decrease in MRSA rates, we still face significantly high rates of invasive MRSA strains, posing a concerning trend.

Despite a decrease compared to data from the previous year, the recorded rates of glycopeptide resistance in *E. faecium* remain high and concerning (37% in 2022; 39% in 2021). However, in comparison to last year's data, lower levels of glycopeptide resistance in E. faecalis were recorded in 2022 (1% in 2022; 3% in 2021). The rates of high resistance to aminoglycosides in 2022 show no significant deviation from last year's data but remain consistently high.

We have observed a continuous trend of increasing resistance rates in all classes of antibiotics among invasive isolates of *K. pneumoniae*, up until the year 2022 when it finally ceases, when a slight decline in resistance rates in all antibiotic classes is noted. Previously, the most concerning strains of *K. pneumoniae*, resistant to carbapenems (imipenem and/or meropenem), exhibited a resistance rate of as high as 28% during 2021. However, in 2022, a decline has been evident, with resistance rates decreasing and recording 23% for such isolates. An additional 5% of *K. pneumoniae* isolates are susceptible to the same antibiotics at an increased dosage. Overall, 28% of invasive *K. pneumoniae* isolates continue to pose a significant challenge in treatment and the selection of optimal antibiotic therapy.

In invasive isolates of *P. aeruginosa*, there continues to be a decreasing trend in the rates of resistance in the aminoglycoside group, while almost all other antibiotic groups show an increase in resistance rates.

The resistance rate of *E. coli* to 3rd generation cephalosporins has not significantly changed compared to the previous year (17%). The data indicate that resistance in this class of antibiotics is still predominantly caused by extended-spectrum beta-lactamase (ESBLs) production. According to the collected data over the past few years, there is an increase in the proportion of ESBL strains among *E. coli* isolates, reaching the highest recorded level of 30% in 2022. The resistance rate to quinolones is 31%.

Compared to the pandemic years of SARS-CoV-2, the number of reported *S. pneumoniae* isolates has now stabilized (n = 89). Among invasive pneumococcal isolates, reduced susceptibility to penicillin continues to show a decreasing trend and is at 18% in 2022.

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.-2022. /
Number of laboratories and number of isolates reported for the period 2001-2022

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

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

Tablica 3. / *Table 3.*
Prikaz gram-pozitivnih invazivnih izolata u 2022.g. prema demografskim podacima pacijenata /
Selected details on gram-positive invasive isolates from the reporting period 2022

	S.pneumoniae		***S.aureus***		***Enterococcus* spp.**	
	n=89		**n=696**		**n=365**	
	% tot	**% PNPS**	**% tot**	**% MRSA**	**% tot**	**% VRE**
UZORAK ***SAMPLE***						
Krv / Blood	99	18	99	30	99	14
Likvor / CSF	1	100	<1	0	<1	67
SPOL ***GENDER***						
M	63	18	66	27	64	14
Ž / F	37	21	33	34	36	14
Nepoznato / Unknown	0	0	1	50	0	0
DOB ***AGE***						
0-4	16	21	2	0	5	17
5-19	3	0	1	0	<1	0
20-64	33	55	27	20	25	15
>65	48	19	70	34	69	13
Nepoznato / Unknown	0	0	0	0	0	0
ODJEL ***DEPARTMENT***						
Intenzivna / ICU	16	14	16	30	21	15

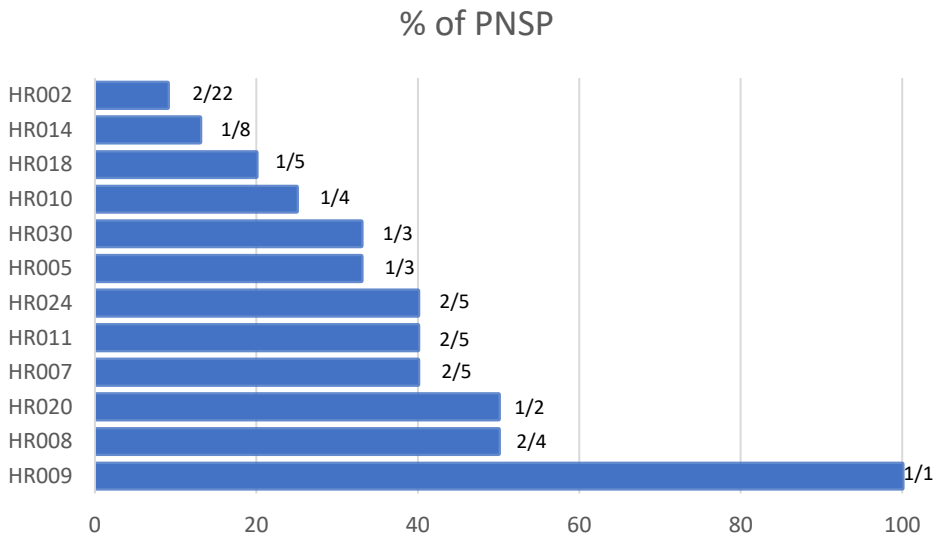
PNSP=Penicillin Non-Susceptible *S. Pneumoniae* MRSA=Methicillin Resistant *S.aureus* VRE=Vancomycin Resistant Enterococcus

Tablica 4. / *Table 4.*
Prikaz gram-negativnih invazivnih izolata u 2022.g. prema demografskim podacima pacijenata /
Selected details on gram-negative invasive isolates from the reporting period 2022

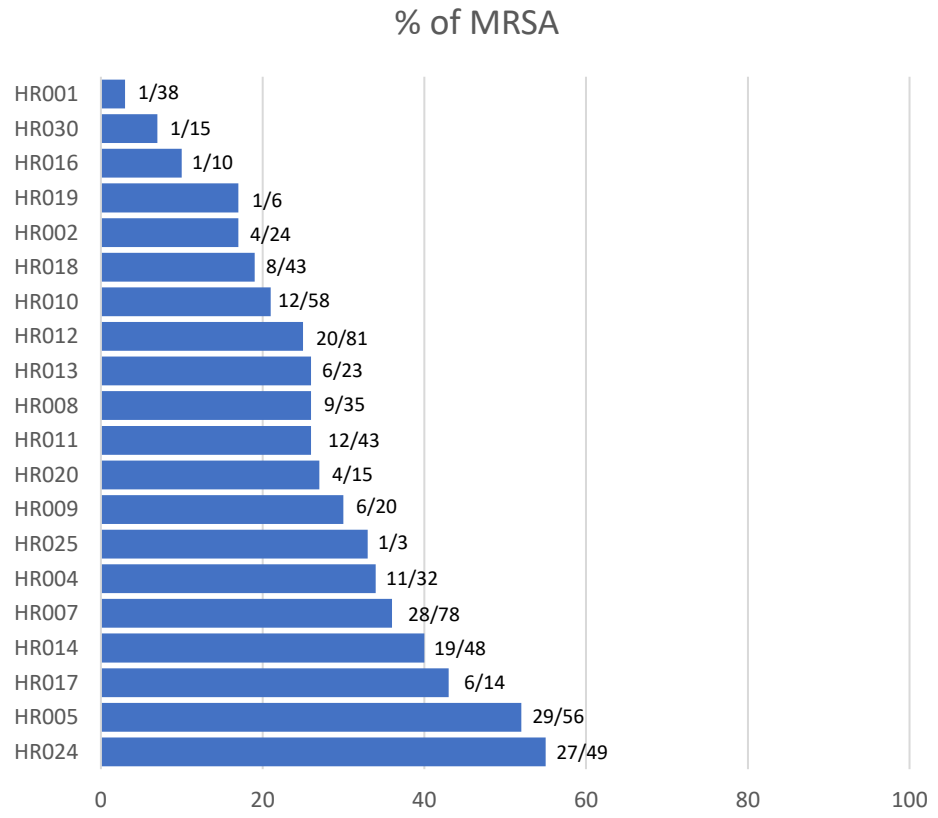
	E. coli			*Acinetobacter* spp.		*K.pneumoniae*		*P.aeuroginosa*	
	n=1054			n=308		n=394		n=282	
	% tot	% FREC	% CREC	% tot	% CRA	% tot	% CRKP	% tot	% CRPA
UZORAK ***SAMPLE***									
Krv / Blood	99	30	17	99	97	99	54	99	65
Likvor / CSF	<1	0	0	1	100	1	33	1	33
SPOL ***GENDER***									
M	45	38	18	68	97	63	55	65	20
Ž / F	55	25	15	31	98	37	53	34	29
Nepoznato / Unknown	0	0	0	1	100	<1	100	<1	100
DOB ***AGE***									
0-4	4	5	5	2	100	7	45	1	40
5-19	<1	20	0	1	0	0	0	1	50
20-64	24	26	12	38	96	32	48	38	23
>65	71	34	19	61	98	61	59	58	22
Nepoznato / Unknown	<1	0	0	0	0	0	0	0	0
ODJEL ***DEPARTMENT***									
Intenzivna / ICU	7	29	14	57	98	20	66	31	25

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.

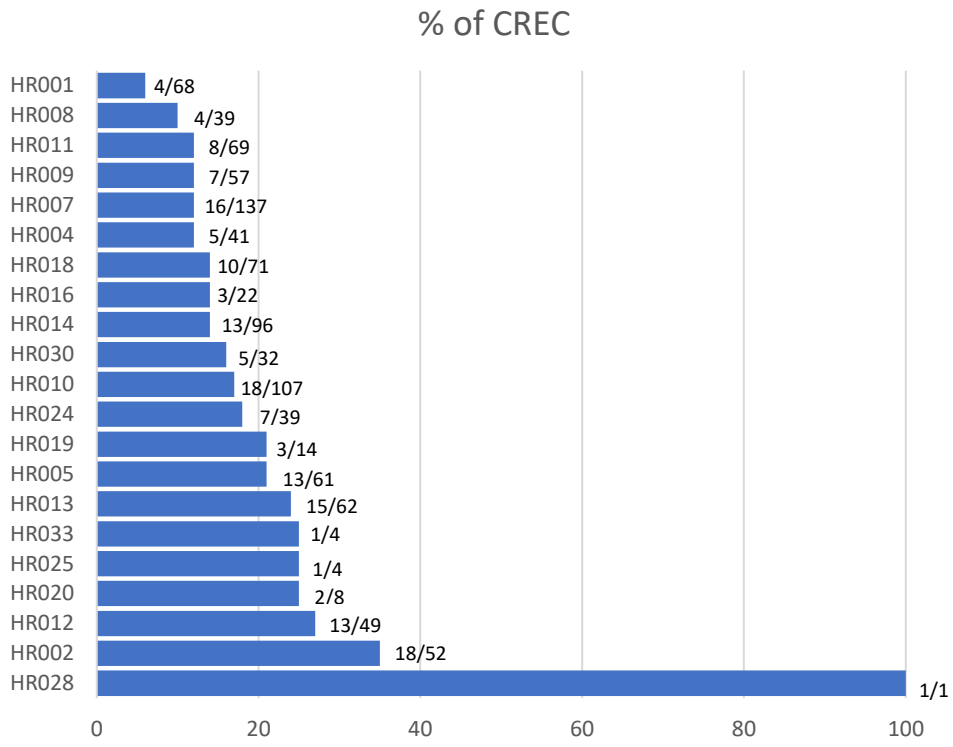
Slika 1. / *Figure 1.*
Udio (%) izolata *S. pneumoniae* smanjene osjetljivosti na penicilin (PNSP) po centrima / *Proportion (%) of penicillin non-susceptible S. pneumoniae (PNSP) by center*



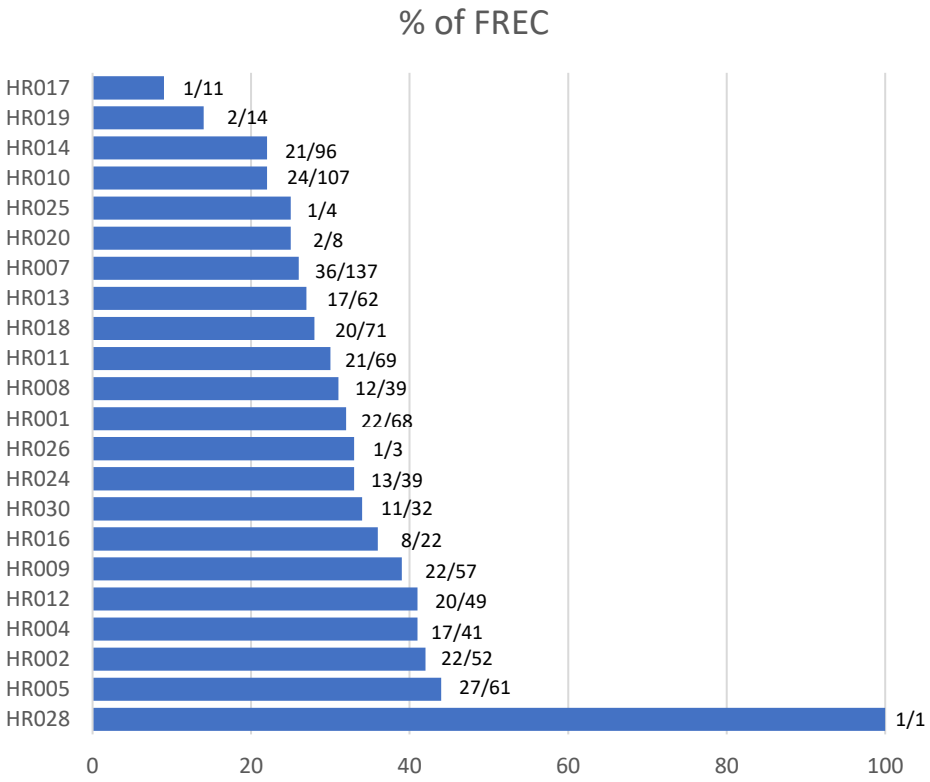
Slika 2. / *Figure 2.*
Udio (%) MRSA izolata po centrima / *Proportion (%) of MRSA isolates by center*



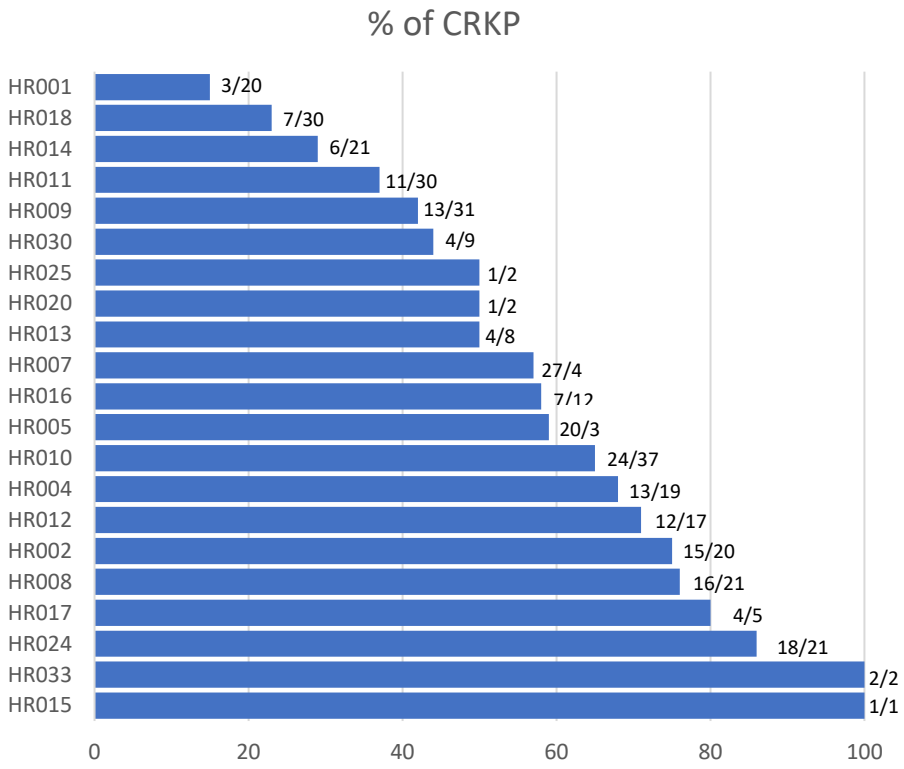
Slika 3. / *Figure 3.*
Udio (%) ceftazidim rezistentnih izolata *E. coli* (CREC) po centrima /
Proportion (%) of ceftazidime resistant E. coli isolates (CREC) by center



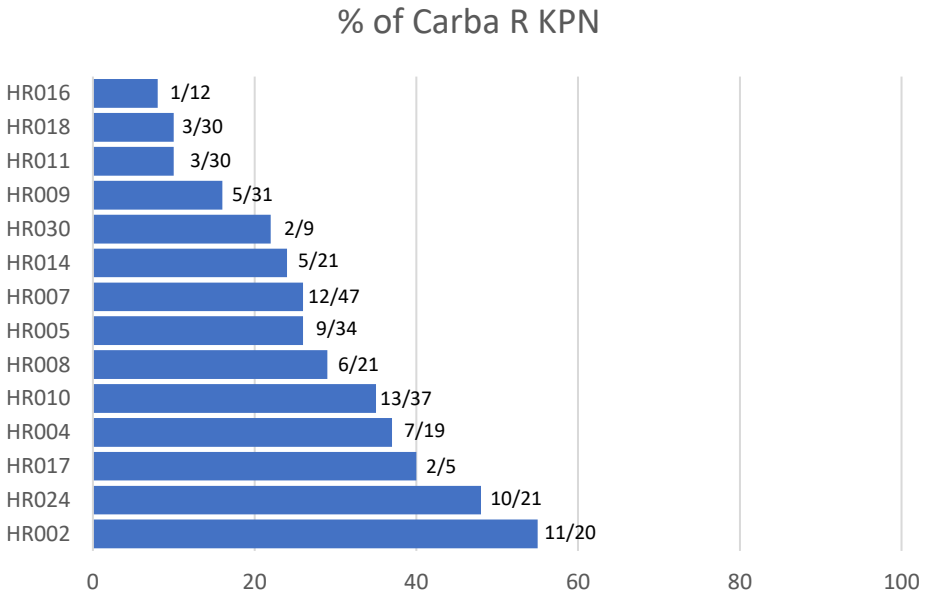
Slika 4. / *Figure 4.*
Udio (%) fluorokinolon rezistentnih izolata *E. coli* (FREC) po centrima /
Proportion (%) of fluoroquinolone resistant E.coli isolates (FREC) by center



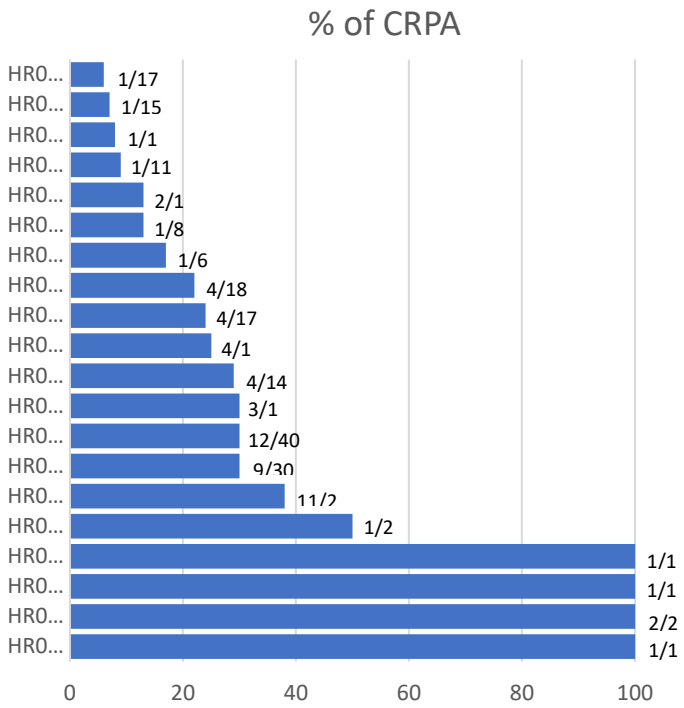
Slika 5. / *Figure 5.*
Udio (%) ceftazidim rezistentnih izolata *K. pneumoniae* (CRKP) po centrima /
Proportion (%) of ceftazidime resistant K. pneumoniae (CRKP) by center



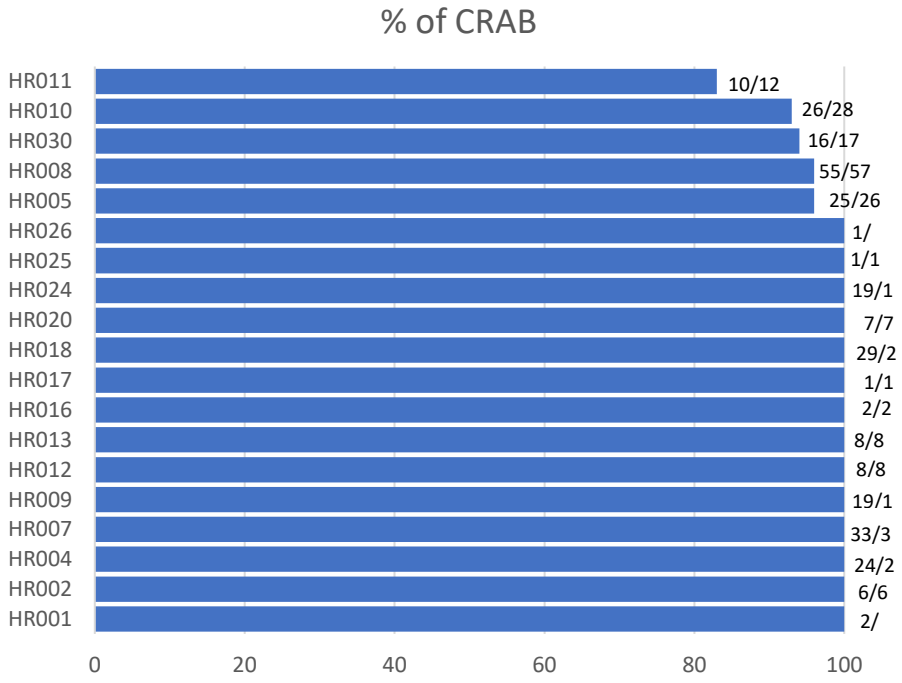
Slika 6. / *Figure 6.*
Udio (%) karbapenem rezistentnih izolata *K. pneumoniae* (Carb R KP) po centrima /
Proportion (%) of carbapenem resistant K. pneumoniae (Carb R KP) by center



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 2022. GODINI

DISTRIBUTION OF CANDIDA SPECIES AND ANTIFUNGAL SUSCEPTIBILITY IN PATIENTS WITH CANDIDEMIA IN CROATIA, 2022

Sanja Pleško
Zoran Herljević
Violeta Rezo Vranješ
Marko Siroglavić
Ivana Mareković

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

UVOD

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

Klinički zavod za kliničku i molekularnu mikrobiologiju Kliničkog bolničkog centra Zagreb 2018. godine stekao je naziv Centra izvrsnosti za laboratorijsku mikologiju Europske konfederacije za medicinsku mikologiju te od početka 2019. godine uz podršku Odbora za praćenje rezistencije započeo s prikupljanje izolata *Candida* spp. kod bolesnika s kandidemijom. Svi mikrobiološki laboratoriji u Hrvatskoj pozvani su po izolaciji *Candida* spp. u hemokulturi bolesnika poslati u Centar izvrsnosti te ispuniti obrazac na mrežnoj stranici Centra izvrsnosti fungi.kbc-zagreb.hr koji sadrži podatke o samom izolatu, primjenjenim metodama identifikacije i ispitivanja osjetljivosti na antifungalne lijekove kao i kliničkim karakteristikama bolesnika. U Centru izvrsnosti se svaki poslani izolat identificira te se ispituje njegova osjetljivost na antifungalne lijekove referentnom metodom mikrodilucije u bujonu (prema CLSI smjernicama). U ovom izvješću prikazani su podaci o učestalosti vrsta *Candida* spp. i osjetljivosti na antifungalne lijekove u 2022. godini.

Učestalost vrsta *Candida* spp.

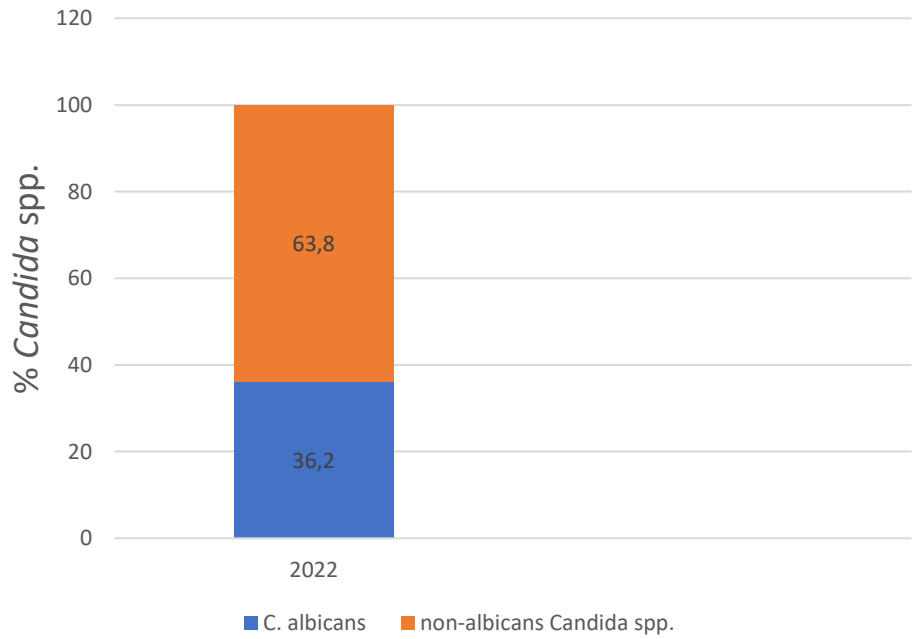
Za vrijeme ovog razdoblja ukupno je prikupljeno i analizirano 185 izolata *Candida* spp. Učestalost pojedinih *Candida* spp. prikazana je u Tablici 1. Usporedbom podataka iz 2021. (215 izolata) godine bilježi se pad broja analiziranih izolata no važno je istaknuti da u 2022. godini nismo dobili podatke iz dva velika klinička centra.

Najčešće prisutne vrste *Candida* spp. u 2022. godini bile su *C. parapsilosis* kod 36,2% (67/185), *C. albicans* kod 36,2% (67/215), i *C. glabrata* kod 15,1% (28/185) bolesnika s kandidemijom.

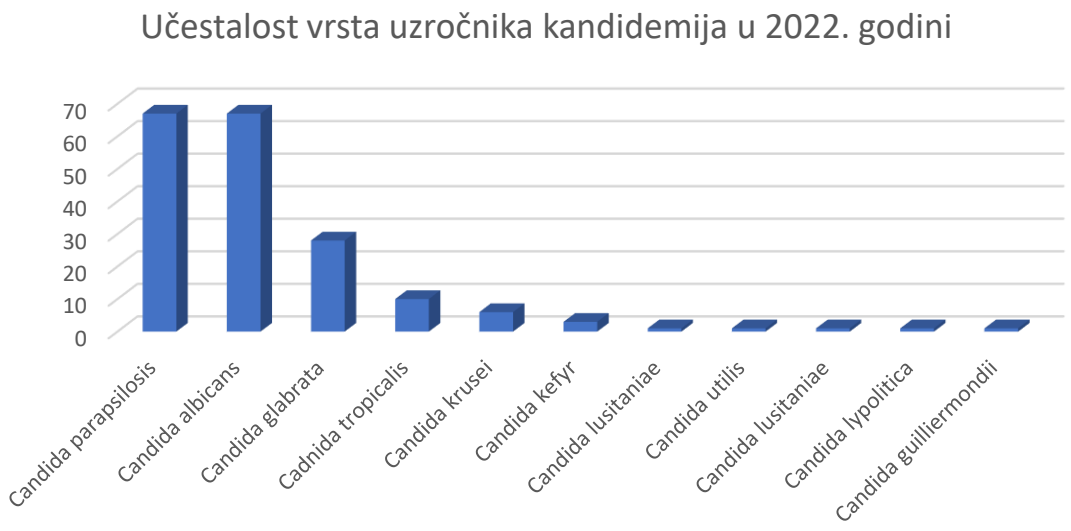
Tablica 1. */ Table 1.*
Učestalost pojedinih vrsta *Candida* spp. kod bolesnika s kandidemijom u Hrvatskoj u 2022. godini */ Incidence of different Candida spp.in patients with candidemia in Croatia in 2022*

Vrsta *Candida* spp.	**N (%)**
Candida parapsilosis	67 (36,2)
Candida albicans	67 (36,2)
Candida glabrata	28 (15,1)
Candida krusei	6(3,24)
Candida lusitaniae	1 (0,54)
Cadnida tropicalis	10 (5,41)
Candida utilis	1(0,54)
Candida kefyr	3 (1,62)
Candida lypolitica	1 (0,54)
Candida guilliermondii	1 (0,54)
UKUPNO	**185**

Slika 1. */ Figure 1.*
Udio *C. albicans* i non-albicans vrsta u 2022. godini među izolatima bolesnika s kandidemijom u Hrvatskoj / *Proportion of C. albicans and non-albicans species in 2022*



Slika 2. */ Figure 2.*
Učestalost vrsta uzročnika kanidemija u 2022. godini */ Proportion of Candida spp. causing candidemia in 2022.*



Udio *C. albicans* i non-albicans vrsta u 2022. godini među izolatima bolesnika s kandidemijom prikazan je na slici 1. Iz analiziranih podataka se vidi da je *C. parapsilosis*

jednako zastupljena vrsta kao i *C. albicans* (dijele prvo mjesto) u Hrvatskoj što je posebno zabrinjavajuće obzirom na visoki postotak stečene rezistencije *C. parapsilosis* na flukonazol. Slijedeća vrsta po učestalosti je *C. glabrata.*

Rezultati našeg praćenja s dostupnim podacima pokazali su da je za razliku od 2021. jednaka učestalost kandidemija uzrokovanih *C. albicans* i *C. parapsilosis*, a slijedeća po učestalosti je *C. glabrata.* Udio *C. parapsilosis* je manji u odnosu na 2021. godinu kad je bila na prvom mjestu, a u 2022. godini dijeli prvo mjesto s *C. albicans*, ali ovi su podaci još uvijek zabrinjavajući. Navedeni podaci imaju kliničku važnost budući *C. parapsilosis* i *C. glabrata* imaju manju osjetljivost na ehinokandine odnosno azole.

Osjetljivost na antifungalne lijekove

Osjetljivost vrsta *Candida* spp. u Hrvatskoj u 2022. godini na amfotericin B, kaspofungin, mikafungin, anidulafungin i flukonazol prikazana je na grafikonu 3., 4., 5., 6. i 7.

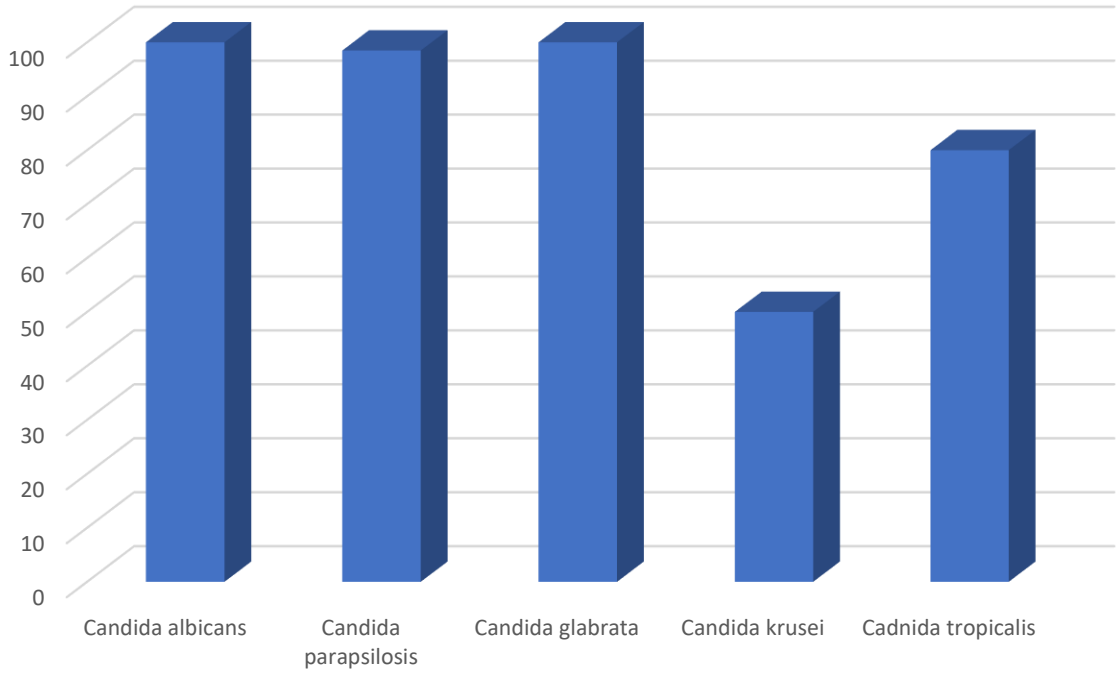
Osjetljivost na amfotericin B bila je 100% za *C. albicans i , C. glabrata i C. tropicalis* 80%, a za *C. krusei* 50%%. *C. parapsilosis* na amfotericin bila je 98,48% (slika 3).

Osjetljivost uzročnika kandidemija na ehinokandine je još uvijek vrlo visoka, što je i očekivano. Svi uzročnici kandidemija za koje postoje granične vrijednosti za interpretaciju u CLSI smjernicama bili su 100% osjetljivi na kaspofungin i mikafungin, na anidulafungin osjetljivost C. parapsilosis je bila 98,44% dok su svi drugi uzročnici kadndidemija za za koje postoje granične vrijednosti za interpretaciju u CLSI smjernicama su bili 100% osjetljivi. (grafikon 4,5,6). *C. albicans* je osjetljiva na flukonazol u 97,01% ispitivanih izolata što govori u prilog potrebe testiranja osjetljivosti klinički značajnih izolata *C. albicans* na antifungike, 80% izolata *C. tropicalis* u je bilo osjetljivo na flukonazol. Ono što posebno zabrinjava je da su izolati *C. parapsilosis* (koja je intrinzički osjetljiva na flukonazol za razliku od *C.*

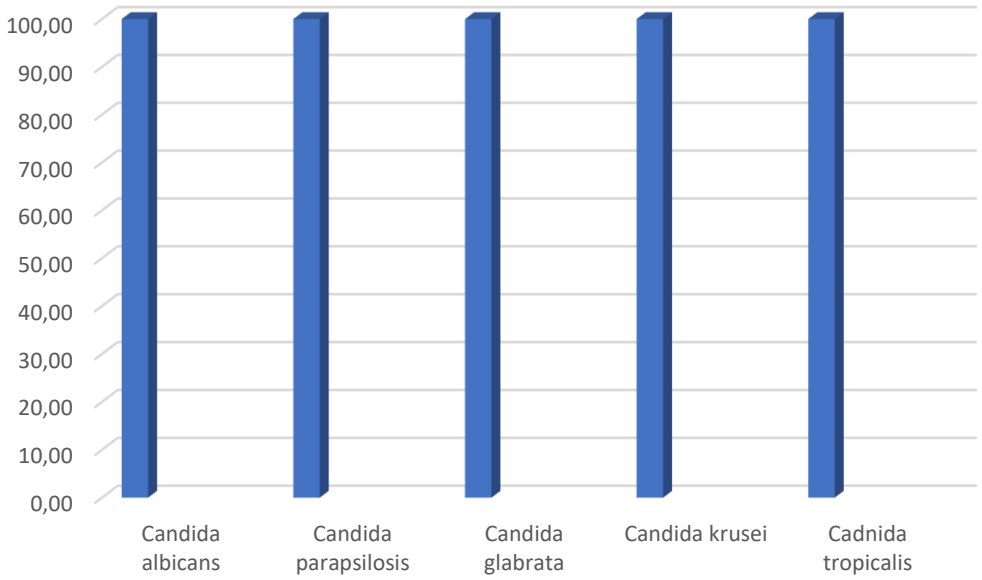
glabrata i C. krusei) nažalost je u velikom broju slučajeva razvila rezistenciju pa je u 2022. godini bila osjetljiva u 18,18% slučajeva, a 2021. u 20%, što znači da je rezistencija porasla za. C. *parapsilosis* dijeli prvo mjesto s *C. albicans* po učestalost kao uzročnik kandidemija i stoga je taj podatak vrlo zabrinjavajući.

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

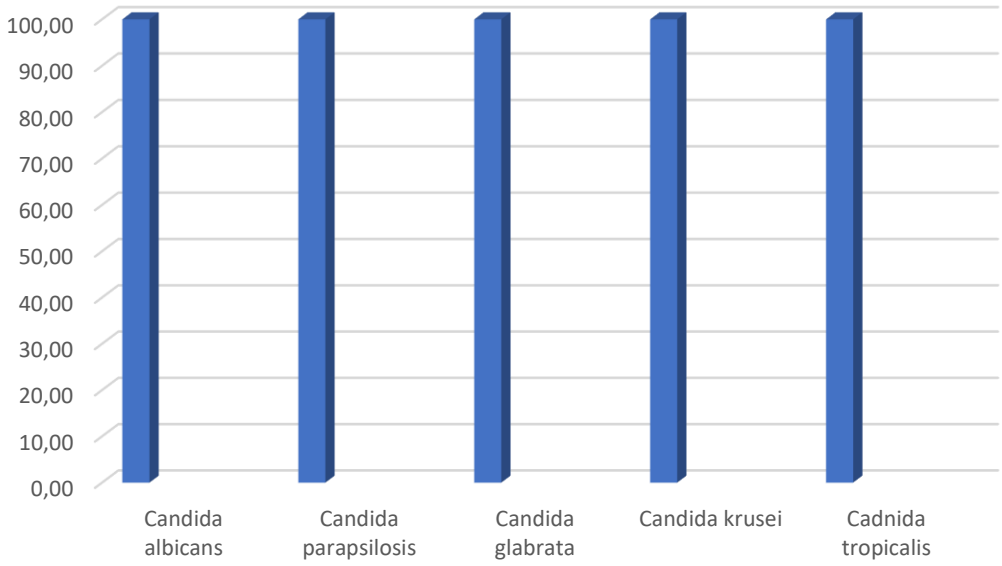
Slika 3. / *Figure 3.*
Osjetljivost vrsta *Candida* spp. u Hrvatskoj u 2022. godini na amfotericin B / *Candida spp. susceptibility to amphotericin B in Croatia in 2022*



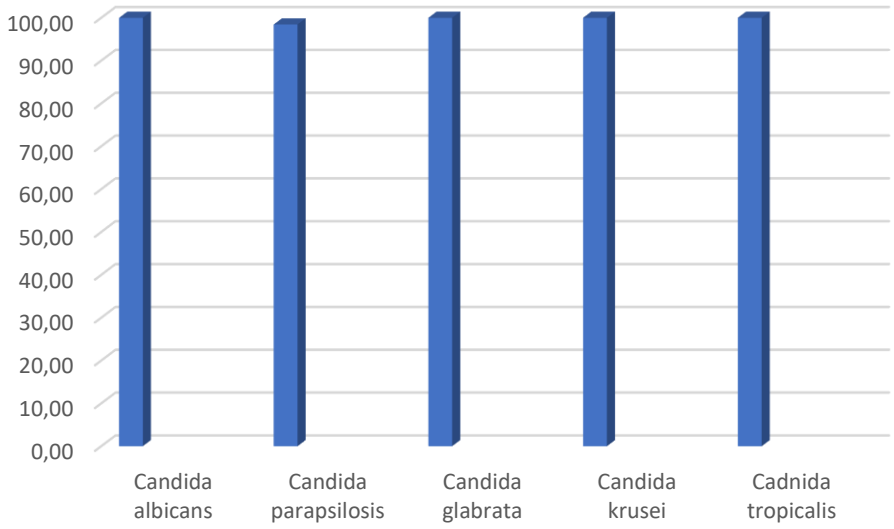
Slika 4. / *Figure 4.*
Osjetljivost vrsta *Candida* spp. u Hrvatskoj u 2022. godini na kaspofungin / *Candida spp. susceptibility to caspofungin in Croatia in 2022*



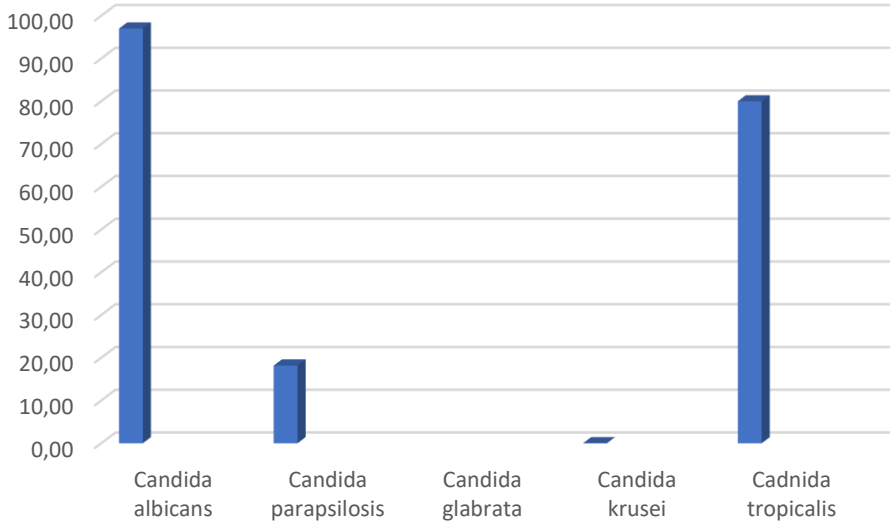
Grafikon 5. / *Figure 5.*
Osjetljivost vrsta *Candida* spp. u Hrvatskoj u 2022. godini na mikafungin / *Candida spp. susceptibility to micafungin in Croatia in 2022*



Slika 6. / *Figure 6.*
Osjetljivost vrsta *Candida* spp. u Hrvatskoj u 2022. godini na anidulafungin / *Candida spp. susceptibility to anidulafungin in Croatia in 2022*



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



INTRODUCTION

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

Department for Clinical and Molecular Microbiology, University Hospital Centre Zagreb in 2018 became ECMM Excellence Centre for Medical Mycology and from January 2019 with the support of Croatian Committee for Antibiotic Resistance Surveillance started collecting *Candida* spp. isolates from blood cultures. All microbiological laboratories in Croatia were invited after isolation of *Candida* spp. from blood culture to send the isolate to Excellence Centre and fulfil the form on the Excellence Centre website fungi.kbc-zagreb.hr. This form contains the data about the isolate, identification methods and methods used to determine isolate antifungal susceptibility as well as clinical data about the patient. In Excellence Centre every isolate was reidentified and then susceptibility testing was performed using microdilution method according to CLSI guidelines. This report contains the data about incidence of different *Candida* species and susceptibility to antifungal agents in year 2022.

Incidence of different *Candida* species

During 2022 185 isolates of *Candida* spp. were collected and analysed. The incidence of different *Candida* species is shown in Table 1. Compared to data from year 2021 (215 isolates) with year 2022 (185 isolates) there was decrease in number of candidemia, but we have to emphasize that we didn't receive any data in 2022 from two big University Centres.

The most common *Candida* spp. in year 2022 were *C. parapsilosis* in 36,2% (67/185), *C. albicans* in 36,2% (67/185) and *C. glabrata* in 15.1% (28/185) patients with candidemia.

Distribution of *C. albicans* and non-albicans species among candidemia isolates in year 2022 is shown on Figure 1. Our data documented that *C. parapsilosis* as common speces as *C. albicans* and they share first place among isolates from patients with candidemia. They are followed by *C. glabrata* on the third place. Results of our surveillance on available data documented that in the contrast to year 2021 the incidence of *C. albicans* and C. parapsilosis among patients with candidemia are the same. Those results are clinically important considering the fact that *C. parapsilosis* and *C glabrata* have reduced susceptibility to echinocandins or azoles.

Antifungal susceptibility

Antifungal susceptibility of *Candida* spp. in Croatia in year 2022 to amphotericin B, caspofungin, micafungin, anidulafungin and fluconazole is shown in Figure 3,4,5,6 and 7.

Susceptibility to amphotericin B was 100% for *C. albicans, C. glabrata,* for *C. tropicalis* was 80% *for C. parapsilosis* 98,48%, and for *C. krusei* was 50%. (Figure 3).

As expected, echinocandins showed excellent efficiency against *Candida* isolates. All *Candida* spp. that has breakpoints for interpretation in CLSI guidelines isolated from blood cultures were 100% susceptible on caspofungin and micafungin. For anidulafungin susceptibility of *C. parapsilosis* was 98,44% and all other *Candida* spp. that have breakpoints for interpretation in CLSI guidelines isolated from blood cultures were 100% susceptible. (figure 4,5,6)

Susceptibility to fluconazole was 97,01% in *C. albicans* and we must emphasize susceptibility testing clinically important *C. albicans* isolates. *C. tropicalis* showed susceptibility of 80%. Isolates of *C. parapsilosis* (that is in the contrast to *C. glabrata* and *C. krusei* intrinsically susceptible to fluconazole) developed resistance in large number of isolates unfortunately; in 2022

susceptibility was 18,18%compared to 20% in previous year as *C. parapsiolosis* shares first place with *C. albicans as* frequent etiological cause of candidemia, this result is rather alarming.

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

POTROŠNJA ANTIBIOTIKA U HRVATSKOJ
ANTIBIOTIC CONSUMPTION IN CROATIA

Marina Payerl Pal
Damjan Debelec

Arjana Tambić Andrašević

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

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

Izvanbolnička potrošnja antibiotika

Potrošnja antibiotika u Hrvatskoj kontinuirano se prati od 2001. godine u skladu s 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.

Podatke o potrošnji antibiotika Hrvatska dostavlja u europsku mrežu za praćenje potrošnje antibiotika The European Surveillance of Antimicrobial Consumption Network (ESAC-Net), što joj omogućava usporedbu potrošnje antibiotika sa svim ostalim zemljama uključenim u mrežu preko platforme za unos podataka, The European Surveillance System (TESSY).

Od 2012. godine ambulantna potrošnja antibiotika prati se iz dva izvora, putem veledrogerija i putem crvenih recepata dobivenim od HZZO-a. Od početka praćenja potrošnje 2001. do 2011. godine potrošnja se temeljila samo na podacima dobivenim iz veledrogerija. Podaci dobiveni putem HZZO-a su službeni podaci o ambulantnoj potrošnji antibiotika za Republiku Hrvatsku koji se dostavljaju u TESSY.

Iz godine u godinu se prati razlika u potrošnji antibiotika ovisno o izvoru podataka (tablica 3; slika 2). Potrošnja temeljena na podacima veledrogerija je nešto viša u usporedbi s podacima dobivenim od HZZO-a. Razlika u potrošnji u 2022. godini od 2,6 DDD/TID je znatno viša u odnosu na prethodnu godinu (1,4 DDD/TID). Razlika je uočljiva u svim klasama antibiotika, a i nadalje je najveća u klasi penicilina i klasi makrolid-linkozamid-streptogramin (tablica 4; slika 3). Kod klase penicilina (J01C) uočava se najveća razlika (1,42 DDD/TID), što je dvostruko više u odnosu na prethodnu godinu kada je iznosila 0,68 DDD/TID. U skupini makrolid-linkozamid (J01F) je razlika 0,47 DDD/TID, što je više u odnosu na prethodnu godinu (0,29 DDD/TID). I kod ostalih klasa antibiotika uočavaju se razlike, ali znatno manje (tablica 4; slika 3). Navedene razlike mogu se objasniti podizanjem antibiotika na privatni recept, što neće biti zabilježeno u HZZO-u te direktno putem snabdjevanja ambulanti s antibioticima iz veledrogerija, posebno za potrebe parenteralne terapije.

Na slici 1 prikazana je ambulantna potrošnja antibiotika kroz prethodne 22 godine praćenja čije kretanje je detaljno obrazloženo u prethodnim godinama. U ovoj publikaciji posebno se osvrćemo na posljednje tri godine, koje je obilježila pandemija COVID-a. U 2020. godini zabilježena je najniža ambulantna potrošnja antibiotika (14,05 DDD/TID) od kada se prati potrošnja, kao odraz provođenja strogih protuepidemijskih mjera tijekom pandemije uzrokovane SARS CoV-2 virusom. Već iduće godine 2021., usprkos trajanju pandemije, ali uz oslabljene protuepidemijske mjere, ambulantna potrošnja antibiotika je porasla (16,22 DDD/TID), ali nije dosegla vrijednosti godina prije pandemije. 2022. godine prati se daljnji porast potrošnje koji iznosi 18,18 DDD/TID, što je najviša vrijednost koju smo zabilježili u zadnjih deset godina.

Ambulantnu potrošnju možemo analizirati putem određenih indikatora. Jedan od njih je omjer potrošnje širokospektralnih penicilina, beta-laktama s inhibitorima, cefalosporina II. i III. generacije, makrolida (osim eritromicina) i fluorokinolona (J01 (CR+DC+DD+FA-FA01)+MA) i potrošnje širokospektralnih penicilina bez inhibitora (amoksicilina), uskospektralnih penicilina, cefalosporina I. generacije i eritromicina (J01 (CA+CE+CF+DB+FA01). U 2022. godini prekinut je nepovoljan trend rasta omjera te on iznosi 5,3, što je niže u odnosu na prethodne dvije godine (6,4; 5,7) (tablica 5; slika 4). To ukazuje na smanjenje potrošnje širokospektralnih antibiotika u ukupnoj ambulantnoj potrošnji te veću primjenu uskospektralnih antibiotika, a time i na smanjen nepovoljan utjecaj na bakterijsku floru i poticanje rezistencije.

U 2022. godini nastavljen je trend porasta potrošnje širokospektralnih penicilina bez inhibitora (J01CA), što je pozitivan pokazatelj s obzirom da je amoksicilin namijenjen za empirijsku primjenu kod infekcija gornjeg dišnog sustava i sumnje na bakterijsku infekciju (npr. *otitis media*), u skladu s ISKRA smjernicama. Međutim za skupinu širokospektralnih penicilina s inhibitorima beta-laktamaza (J01CR) također se nastavlja rast potrošnje, za što nema uporišta u smjernicama. Zabilježena je najviša potrošnja u zadnjih deset godina, koja s približila na 6 DDD/TID (Tablica 1). Omjer potrošnje širokospektralnih penicilina s inhibitorima beta-laktamaza (J01CR) i širokospektralnih penicilina bez inhibitora (J01CA) u zadnje dvije godine je identičan (iznosi 4,2), što je više u odnosu na prethodne dvije godine, kada je iznosio 3,9 u 2020. i 3,2 u 2019. godini.

Kod penicilina uskog spektra (J01CE) bilježi se blagi porast (0,25 DDD/TID) u odnosu na prethodnu godinu (0,21 DDD/TID), dok je potrošnja beta-laktamaza rezistentnih penicilina (J01CF) posljednjih šest godina bez promjena (0,01 DDD/TID) (Tablica 1).

Klasa cefalosporina bilježi porast potrošnje svih generacija, što je nastavak prošlogodišnjeg trenda. Najviše je porasla potrošnja cefalosporina 2. generacije (za 0,15 DDD/TID).

Porast potrošnje uočava se kod svih ostalih klasa antibiotika (sulfonamidi + trimetoprim, makrolidi i linkozamidi te fluorokinoloni), osim kod aminoglikozida (J01G), čija je ambulantna potrošnja u svim godinama vrlo mala i bilježi pad u 2022. godini, kao i klasa tetraciklina, čija je potrošnja niža u odnosu na prethodnu godinu (tablica 1). +Potrošnja nitrofuantoina (J01XE) i dalje nastavlja rasti te je u 2022. godini, po prvi puta, iznad jedan (1,04 DDD/TID). Potrošnja fosfomicina (J01XX) na istom je nivou kao i prethodne godine (0,09 DDD/TID).

Ambulantna potrošnja u Hrvatskoj u 2022. godini je najviša u posljednjih deset godina i iznosi 18,18 DDD/TID, što je 90,18% ukupne potrošnje antibiotika u Hrvatskoj.

U tablici 6 i na slici 5 poredani su antibiotici prema učestalosti potrošnje - "top lista" najpropisivanijih antibiotika, i ovaj puta prvih 6 antibiotika, obzirom da se zadnja dva izmjenjuju i vrlo su slični po potrošnji. Poredak prva četiri antibiotika ostao je identičan kao i prethodne godine (koamoksiklav, azitromicin, cefuroksimaksetil, amoksicilin). Na peto mjesto ponovno se vratio nitrofurantoin (1,04 DDD/TID), koji je po prvi puta premašio 1 DDD/TID u potrošnji, kojeg na šestom mjestu slijedi doksiciklin (0,94 DDD/TID).

Potrošnja antibiotika po kvartalima još uvijek nije tipična, kao u godinama prije COVID pandemije, kada su prvi i četvrti kvartal bilježili veću potrošnju od drugog i trećeg kvartala. U 2022. godini potrošnja u prva tri kvartala je prilično ujednačena (4,54; 4,10; 4,02) dok je u četvrtom kvartalu najviša i iznosi 5,52 DDD/TID (tablica 7; slika 6).

Kao i prethodne godine među prvih deset dijagnoza po učestalosti za koje se propisuju antibiotici su tri dijagnoze koje se odnose na infekcije mokraćnih puteva (upala mokraćnog mjehura, cistitis (N30); infekcija urinarnog trakta lokacija neoznačena (N39.0), drugi poremaćaji urinarnog sustava (N39) (tablica 8; slika 7). Ostalih sedam dijagnoza se odnose na dišni sustav, akutna upala ždrijela (J02); akutna upala sinusa (J01), akutna upala tonzila (J03), akutna upala gornjeg dišnog sustava (J06), akutni bronhitis (J20), nesupurativna upala srednjeg uha (H65) te akutna respiratorna bolest uzrokovana 2019-noCoV (U07.1). Iako se radi o dijagnozi bolesti koja je uzrokovana virusom nalazi se na 10. mjestu po učestalosti dijagnoza za koju su se propisivali antibiotici.

Upala mokraćnog mjehura (cistitis) je vodeća dijagnoza za propisivanje antibiotika u izvanbolničkoj populaciji, kao i prethodnih godina za koju se potrošilo najviše antibiotika 1,95 DDD/TID. Za tri dijagnoze koje se odnose na infekcije mokraćnog sustava među prvih deset dijagnoza za koje se propisuju antibiotici, ukupno je potrošeno 2,97 DDD/TID (u prošloj godini 2,863). Na respiratorne infekcije (sedam dijagnoza među deset za koje se koriste antibiotici) je ukupno potrošeno znatno više, 4,97 DDD/TID, što je nešto manje nego prethodne godine (5,843 DDD/TID). Ovakav omjer potrošnje

ukazuje da se antibiotici znatno više koriste za liječenje respiratornih infekcija, koje su znatno češće uzrokovane virusima na koje antibiotici ne djeluju, što ukazuje na nepotrebnu primjenu antibiotika.

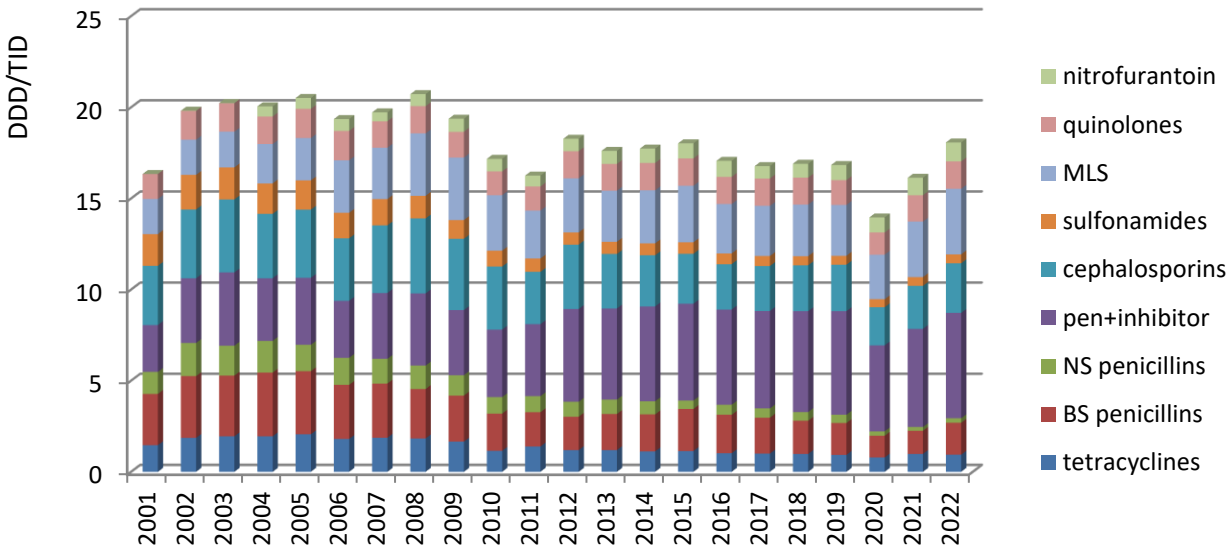
U 2022. godini ambulantna potrošnja antibiotika je porasla u odnosu na godinu prije i iznosi 18,18 DDD/TID, što je najviša vrijednost u zadnjih deset godina. Udio ambulantne potrošnje u ukupnoj potrošnji iznosi 90,2%, što je uobičajeni udio osim u prethodnoj godini kada je iznosio nešto manje od 90% (89,36%).

Klasa penicilina je, kao i do sada, najzastupljenija u ambulantnoj potrošnji antibiotika (42,8%). Porasla je potrošnja svih klasa antibiotika, osim aminoglikozida i tetraciklina. Među klasom penicilina najveći porast je zabilježen kod kombinacije penicilina s inhibitorima (J01CR), dok je kod klase cefalosporina najveći porast potrošnje uočen za 2.generaciju cefalosporina (tablica 1). Nastavlja se trend rasta potrošnje nitrofurantoina (0,68; 0,76; 0,83; 0,83; 0,96; 1,04 DDD/TID) u zadnjih pet godina, što je povoljan pokazatelj s obzirom da je cistitis vodeća dijagnoza za propisivanje antibiotika u izvanbolničkoj praksi.

Indikator potrošnje antibiotika koji pokazuje omjer potrošnje širokospektralnih antibiotika u odnosu na uskospektralne pao je u odnosu na godinu prije čime je zaustavljen negativan trend potrošnje širokospektralnih antibiotika (tablica 5, slika 4). Ipak, omjer potrošnje širokospektralnih penicilina s inhibitorima beta-laktamaza (J01CR) i širokospektralnih penicilina bez inhibitora (J01CA) u zadnje dvije godine je identičan (iznosi visokih 4,2), što 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 u odnosu na prethodne godine, dok su infekcije dišnog sustava najzastupljenije dijagnoze (7 od 10) među prvih deset za koje se propisuju antibiotici.

Slika 1. */ Figure 1.*
Ambulantna potrošnja antibiotika (DDD/TID) u Hrvatskoj, 2001 – 2022. */ Ambulatory antibiotic consumption (DDD/TID) in Croatia, 2001 – 2022*



Outpatient Antibiotic Consumption

The consumption of antibiotics in Croatia has been continuously monitored since 2001 in compliance with internationally recognized standards set by European Surveillance of Antibiotic Consumption (ESAC). Outpatient and hospital antibiotic consumption have been tracked separately. Data on the use of antibiotics is collected from the Croatian Health Insurance Fund (CHIF) in accordance with the Anatomical Therapeutic Chemical (ATC) classification of drugs at the 5th level, while consumption itself is on the 4th and 3rd levels of the ATC classification. The use of antibiotics is expressed in defined daily doses (DDDs) per 1000 inhabitants per day (DDD/TID). Each antibiotic has a prescribed defined daily dose according to the Collaborating Centre for Drug Statistics Methodology (Oslo, Norway). The denominator for calculating antibiotic consumption is the size of the population. According to the latest 2021 Census, the population of Croatia is 3,871,833.

Croatia submits antibiotic consumption data to the European Surveillance of Antimicrobial Consumption Network (ESAC-Net), enabling the comparison of the obtained data with other countries through The European Surveillance System (TESSy) data entry platform.

Since 2012, outpatient antibiotic consumption data has been collected from two sources: pharmaceutical wholesalers and CHIF reimbursement data. From the start of monitoring in 2001 until 2011, consumption was based solely on the data obtained from pharmaceutical wholesalers. However, CHIF reimbursement data are the official data on outpatient antibiotic consumption for the Republic of Croatia, which are submitted to TESSy.

Variations in consumption arising from different source of data have been monitored over the years as well (Table 3; Figure 2), showing that consumption based on pharmaceutical wholesalers' data is slightly higher when compared to the one obtained from CHIF. However, in 2022 this difference was 2.6 DDDs/TID, which was significantly higher than that in the previous year (1.4 DDDs/TID). This disparity is evident in all antibiotic classes, the most considerable continuing to be in the penicillin class and the macrolide-lincosamide-streptogramin class (Table 4; Figure 3). The largest difference of 1.42 DDDs/TID was observed in the penicillin class (J01C), which doubled from the previous year (0.68 DDD/TID). In the macrolide-lincosamide class (J01F), it was 0.47 DDD/TID, which was higher than the year before (0.29 DDD/TID). Variations are also noticeable in other antibiotic classes, but they are considerably smaller (Table 4; Figure 3). These differences can be explained by patients choosing to purchase antibiotics with private prescriptions, which are not recorded by CHIF, and by direct supply of parenteral antibiotics from wholesalers to primary care.

Figure 1 shows ambulatory antibiotic consumption over the past 22 years of surveillance, its trends detailed in previous years. This paper focuses on the last three years, marked by the COVID-19 pandemic. 2020 saw the lowest outpatient antibiotic consumption (14.05 DDDs/TID) since monitoring began, reflecting strict anti-epidemic measures in place during the pandemic of SARS-CoV-2 virus. The following year, 2021, despite the ongoing pandemic but with weakened anti-epidemic measures, outpatient antibiotic consumption increased (16.22 DDDs/TID) yet did not reach the levels of pre-pandemic years. In 2022, further consumption increase is observed, reaching 18.18 DDDs/TID, the highest value recorded in the past decade.

Outpatient consumption of antibiotics can be analyzed with specific indicators. One of them is the ratio of consumption of broad-spectrum penicillins, beta-lactamase with inhibitors, cephalosporins of the 2nd and 3rd generations, macrolides (except erythromycin), and fluoroquinolones (J01 (CR+DC+DD+FA-FA01)+MA) and consumption of broad-spectrum penicillins without inhibitors (amoxicillin), narrow-spectrum penicillins, 1st generation cephalosporins, and erythromycin (J01 (CA+CE+CF+DB+FA01). In 2022, the unfavorable trend of the consumption ratio was interrupted at 5.3, which was lower if compared to the previous two years (6.4; 5.7) (Table 5; Figure 4). This indicates a reduction in the share

of broad-spectrum antibiotics in overall outpatient consumption and a greater use of narrow-spectrum antibiotics, thereby lessening their adverse impact on bacterial flora and development of resistance.

In 2022, the trend of increased usage of broad-spectrum penicillins without inhibitors (J01CA) continued, which is a positive indicator given that amoxicillin is intended for empirical use in upper respiratory tract infections and suspected bacterial infections (e.g. *otitis media*), following the guidelines provided by ISKRA (The Interdisciplinary Section for Antibiotic Resistance Control). However, the group of broad-spectrum penicillins with beta-lactamase inhibitors (J01CR) was also on the rise, which is not stipulated by the guidelines. The highest consumption in the last ten years was recorded, reaching around 6 DDDs/TID (Table 1). The consumption ratio of broad-spectrum penicillins with beta-lactamase inhibitors (J01CR) to broad-spectrum penicillins without inhibitors (J01CA) in the last two years was identical (at 4.2), which was higher than in the previous two, when it was 3.9 in 2020 and 3.2 in 2019.

In the case of narrow-spectrum penicillins (J01CE), there was a slight increase (0.25 DDD/TID) in comparison with the previous year (0.21 DDD/TID), while the consumption of beta-lactamase-resistant penicillins (J01CF) remained unchanged for the past six years (0.01 DDD/TID) (Table 1).

Consumption of all generations of cephalosporins grew, thus continuing the trend from 2021, with second-generation cephalosporins seeing the highest increase (0.15 DDD/TID).

There was a rise in the use of all other antibiotic classes (sulfonamides + trimethoprim, macrolides and lincosamides, and fluoroquinolones), except for aminoglycosides (J01G), which have very low outpatient consumption throughout the years and saw a decline in 2022, as well as the tetracycline class, which were used less frequently than in 2021 (Table 1).

The consumption of nitrofurantoin (J01XE) continued to rise and in 2022, for the first time, exceeded 1 (1.04 DDD/TID), whereas fosfomycin (J01XX) remained at the same level as the year before (0.09 DDD/TID).

Ambulatory antibiotic consumption in 2022 was the highest in the last ten years, amounting to 18.18 DDDs/TID, which accounted for 90.18% of the total use of antibiotics in Croatia.

In Table 6 and Figure 5, antibiotics are ranked by consumption frequency - a "top list" of the most commonly prescribed ones. This time, the first 6 antibiotics are listed, as the last two alternate and have very similar consumption rates. The order of the first four antibiotics remained the same as in the previous year (co-amoxiclav, azithromycin, cefuroxime axetil, amoxicillin). Nitrofurantoin returned to the fifth place (1.04 DDD/TID), exceeding 1 DDD/TID in consumption for the first time, followed by doxycycline in the sixth place (0.94 DDD/TID).

Quarterly consumption reports are still not common, as they were in the years before the COVID pandemic, when the first and fourth quarters had higher consumption than the second and third ones. In 2022, consumption in the first three quarters was fairly consistent (4.54, 4.10, 4.02), while in the fourth quarter it peaked at 5.52 DDDs/TID (Table 7; Figure 6).

As in 2021, among the ten most frequent diagnoses for which antibiotics were prescribed, three are related to urinary tract infections (bladder inflammation, cystitis (N30); urinary tract infection - site not specified (N39.0), and other disorders of the urinary system (N39) (Table 8; Figure 7). The remaining seven relate to the respiratory system: acute pharyngitis (J02); acute sinusitis (J01), acute tonsillitis (J03), acute upper respiratory tract infection (J06), acute bronchitis (J20), non-suppurative inflammation of the middle ear (H65), and acute respiratory illness due to 2019-nCoV (U07.1). Although caused by a virus, it was the 10th most common diagnosis for which antibiotics were prescribed.

As in the previous years, bladder inflammation (cystitis) was the most common diagnosis for antibiotic prescription in outpatient environment, consuming 1.95 DDD/TID. Among the top ten diagnoses, a total of 2.97 DDDs/TID was consumed by the three related to urinary tract infections (compared to 2.863 in

the year before). The other seven were respiratory infections which consumed a much higher total of 4.97 DDDs/TID, but still slightly less than the previous year (5.843 DDDs/TID). This consumption ratio indicates that antibiotics are significantly more used for treating respiratory infections, which are frequently of viral origin and therefore not an indication for antibiotic therapy.

In 2022, ambulatory use of antibiotics increased compared to the previous year, amounting to 18.18 DDDs/TID, the highest value in the last ten years. Its share in total consumption was 90.2%, which is the usual percentage, excluding 2021 when it was slightly below 90% (89.36%). The penicillin class remained the most represented in outpatient antibiotic consumption (42.8%). There was a rise in the use of all classes of antibiotics, except aminoglycosides and tetracyclines. Within the penicillin class, the largest increase was observed in the use of combinations of penicillin with inhibitors (J01CR), while in the cephalosporin class, the same applied for the 2nd generation cephalosporins (Table 1). The trend of increasing nitrofurantoin consumption (0.68; 0.76; 0.83; 0.83; 0.96; 1.04 DDD/TID) over the past five years continued, which is a favourable indicator considering the fact that cystitis is the leading diagnosis for outpatient antibiotics prescribing.

The consumption indicator showing the ratio of broad-spectrum antibiotics to narrow-spectrum ones decreased when compared to the previous year, thus stopping the negative trend of using broad-spectrum antibiotics (Table 5, Figure 4). However, the ratio between broad-spectrum penicillins with beta-lactamase inhibitors (J01CR) and broad-spectrum penicillins without inhibitors (J01CA) over the last two years remained identical (high at 4.2), indicating a fourfold increase in the use of co-amoxiclav rather than amoxicillin in primary healthcare.

Co-amoxiclav was the leading antibiotic in outpatient antibiotic consumption, reaching its highest value in the past few years, while respiratory infections were the most common diagnoses (7 out of 10) among the top ten for which antibiotics were prescribed.

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

ATC šifra ATC code	ANTIBIOTIK ANTIBIOTIC	2012 *	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
J01AA	Tetraciklini Tetracylines	1,19	1,19	1,12	1,14	1,02	1,00	0,98	0,93	0,79	0,98	0,94
J01CA	Penicilini širokog spektra Broad spectrum penicillins	1,83	1,98	2,03	2,31	2,11	1,97	1,82	1,75	1,19	1,27	1,75
J01CE	Penicilini uskog spektra Narrow spectrum penicillins	0,82	0,79	0,72	0,46	0,55	0,51	0,48	0,45	0,24	0,21	0,25
J01CF	Beta-laktamaza rezistentni penicilini Beta-lactamase resistant penicillins	0,00	0,00	0,00	0,01	0,00	0,01	0,01	0,01	0,01	0,01	0,01
J01CR	Kombinacije s beta-laktamaza inhibitorima Combinations with inhibitors	5,09	5,00	5,20	5,31	5,22	5,34	5,53	5,68	4,72	5,38	5,78
J01DB	Cefalosporini I gen. Cephalosporins	0,79	0,77	0,72	0,66	0,60	0,47	0,38	0,35	0,27	0,29	0,36
J01DC	Cefalosporini II gen. Cephalosporins	1,95	1,77	1,85	1,85	1,69	1,67	1,73	1,72	1,38	1,46	1,61
J01DD	Cefalosporini III gen. Cephalosporins	0,79	0,45	0,24	0,23	0,20	0,33	0,41	0,49	0,44	0,61	0,75
J01EE	Sulfonamides + trimethoprim	0,67	0,67	0,65	0,63	0,59	0,55	0,50	0,49	0,44	0,48	0,49
J01F	Macrolides, lincosamides	2,97	2,80	2,91	3,10	2,71	2,75	2,83	2,79	2,44	3,05	3,60
J01G	Aminoglikozidi Aminoglycosides	0,00	0,00	0,04	0,01	0,00	0,01	0,01	0,004	0,003	0,003	0,002
J01MA	Fluorokinoloni Fluoroquinolones	1,49	1,47	1,50	1,50	1,49	1,50	1,48	1,36	1,22	1,44	1,50
J01XE	Nitrofurantoin	0,68	0,72	0,79	0,83	0,88	0,68	0,76	0,83	0,83	0,96	1,04
J01XX	Fosfomycin	-	-	-	-	0,004	0,05	0,08	0,08	0,08	0,09	0,09
UKUPNO TOTAL		**18,3**	**17,6**	**17,8**	**18,0**	**17,1**	**16,8**	**17,0**	**16,9**	**14,1**	**16,2**	**18,2**

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

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

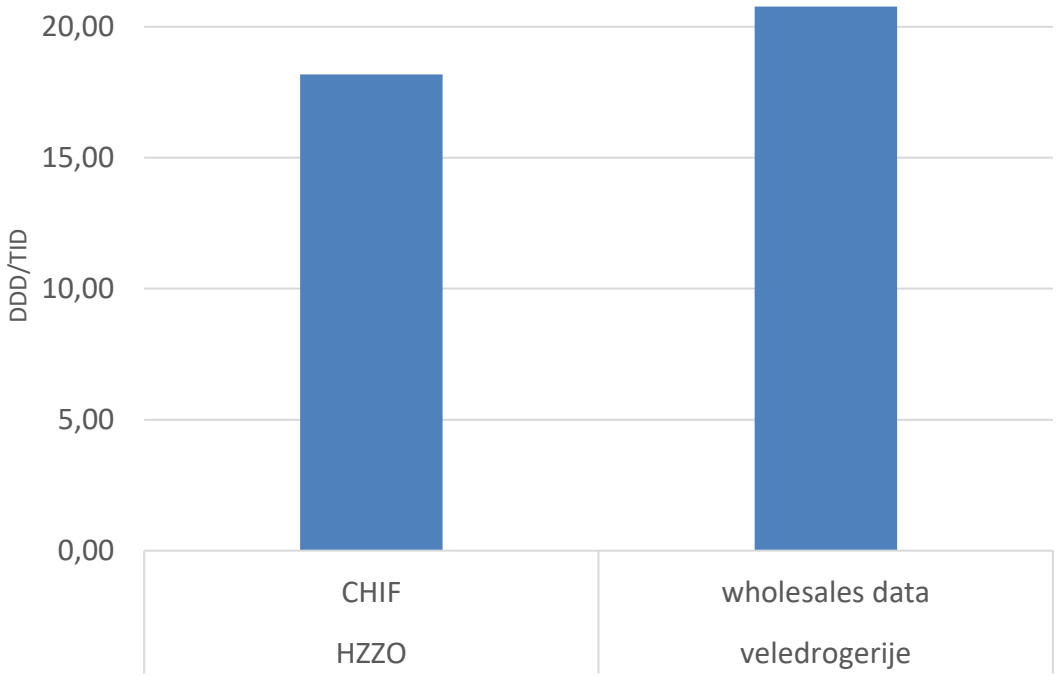
ATC šifra ATC code	ANTIBIOTIK ANTIBIOTIC	2012**	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
J01AA	Tetraciklini Tetracylines	0,06	0,05	0,04	0,04	0,04	0,04	0,03	0,04	0,03	0,03	0,03
J01CA	Penicilini širokog spektra Broad spectrum penicillins	0,03	0,04	0,02	0,02	0,03	0,02	0,02	0,02	0,02	0,02	0,03
J01CE	Penicilini uskog spektra Narrow spectrum penicillins	0,03	0,03	0,02	0,02	0,02	0,02	0,02	0,02	0,01	0,01	0,01
J01CF	Beta-laktamaza rezistentni penicilini Beta-lactamase resistant penicillins	0,04	0,03	0,03	0,03	0,03	0,04	0,04	0,04	0,03	0,03	0,04
J01CR	Kombinacije s beta-laktamaza inhibitorima Combinations with inhibitors	0,40	0,35	0,37	0,38	0,37	0,38	0,40	0,42	0,33	0,40	0,42
J01DB	Cefalosporini I gen. Cephalosporins	0,10	0,08	0,09	0,10	0,10	0,10	0,09	0,10	0,08	0,09	0,10
J01DC	Cefalosporini II gen. Cephalosporins	0,23	0,21	0,20	0,17	0,19	0,20	0,20	0,20	0,15	0,16	0,15
J01DD + J01DE	Cefalosporini III + IV gen. Cephalosporins	0,16	0,15	0,18	0,18	0,16	0,17	0,16	0,17	0,19	0,24	0,24
J01DH	Carbapenems	0,05	0,05	0,06	0,06	0,06	0,08	0,07	0,08	0,09	0,12	0,12
J01EE	Sulfonamides + trimethoprim	0,06	0,04	0,05	0,04	0,04	0,04	0,04	0,04	0,03	0,03	0,04
J01F	Macrolides, lincosamides	0,16	0,15	0,14	0,15	0,15	0,16	0,16	0,18	0,19	0,21	0,21
J01G	Aminoglikozidi Aminoglycosides	0,11	0,10	0,10	0,10	0,09	0,09	0,09	0,09	0,07	0,08	0,09
J01MA	Fluorokinoloni Fluoroquinolones	0,19	0,19	0,20	0,21	0,21	0,23	0,24	0,24	0,20	0,24	0,24
J01XA	Glycopeptides	0,03	0,03	0,03	0,04	0,03	0,04	0,05	0,05	0,05	0,07	0,07
J01XD	Metronidazole	0,07	0,08	0,09	0,10	0,10	0,11	0,15	0,12	0,10	0,12	0,12
J01XE	Nitrofurantoin	0,02	0,01	0,02	0,01	0,01	0,01	0,01	0,01	0,01	0,02	0,02
J01XX	Fosfomycin	-	-	-	-	0,00 1	0,02	0,02	0,02	0,02	0,04	0,04
UKUPNO TOTAL		**1,75**	**1,58**	**1,65**	**1,70**	**1,65**	**1,74**	**1,80**	**1,85**	**1,61**	**1,93**	**1,98**

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

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

	HZZO CHIF	veledrogerije wholesales data
DDD	25798290,76	29488834,15
DDD/TID	18,18	20,78

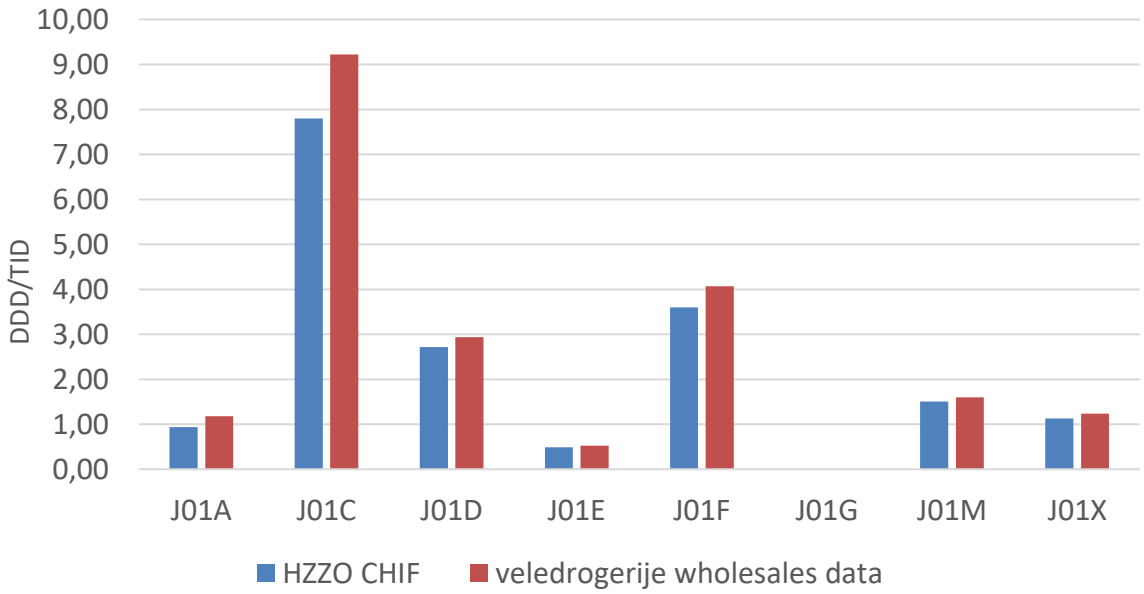
Slika 2. */ Figure 2.*
Ambulantna potrošnja antibiotika (DDD/TID) usporedba podataka HZZO i veledrogerija / *Ambulatory antibiotic consumption (DDD/TID) comparison between CHIF data and wholesales data*



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

DDD/TID	HZZO CHIF	veledrogerije wholesales data
J01A	0,94	1,18
J01C	7,80	9,22
J01D	2,72	2,94
J01E	0,49	0,53
J01F	3,60	4,07
J01G	0,00	0,01
J01M	1,50	1,60
J01X	1,13	1,24

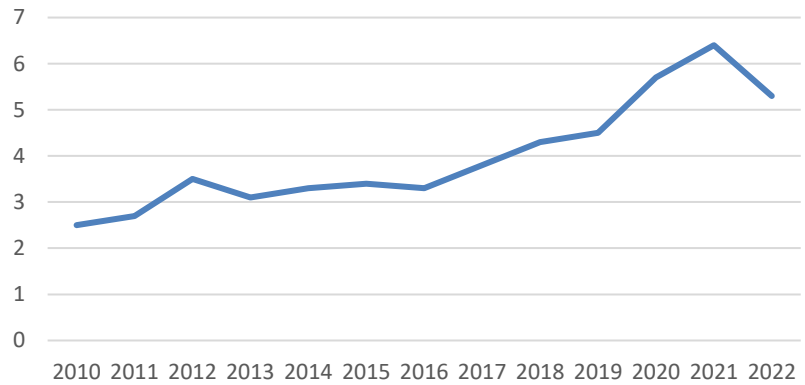
Slika 3. */ Figure 3.*
Ambulantna potrošnja antibiotika (DDD/TID) po klasama, usporedba podataka HZZO i veledrogerija */ Ambulatory antibiotic consumption* (DDD/TID) *by class, comparison between CHIF data and wholesales data*



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 2010-2022 / *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 2010-2022*

	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

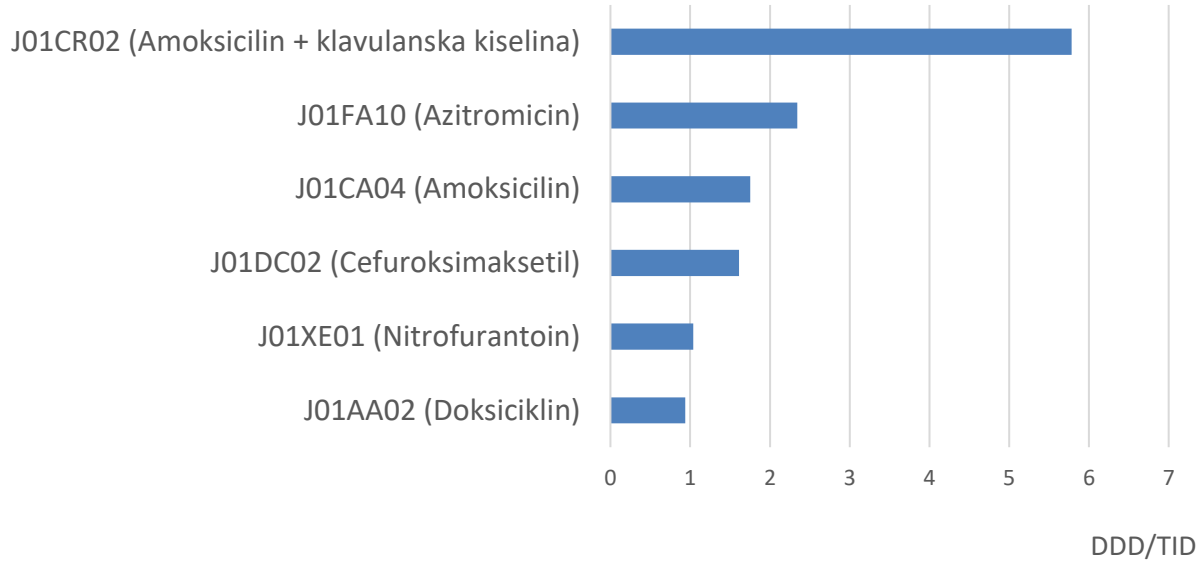
Slika 4. / *Figure 4.*
Omjer izvanbolničke potrošnje izražene u DDD na tisuću stanovnika na dan, penicilina širokog spektra, cefalosporina, makrolida (osim eritromicina) i fluorokinolona i potrošnje izražene u DDD na tisuću stanovnika na dan, penicilina uskog spektra, cefalosporina i eritromicina u razdoblju 2010-2022 / *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 2010-2022*



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

Klasa / class	DDD/TID
J01CR02 (Amoksicilin + klavulanska kiselina)	5,78
J01FA10 (Azitromicin)	2,34
J01CA04 (Amoksicilin)	1,75
J01DC02 (Cefuroksimaksetil)	1,61
J01XE01 (Nitrofurantoin)	1,04
J01AA02 (Doksiciklin)	0,94

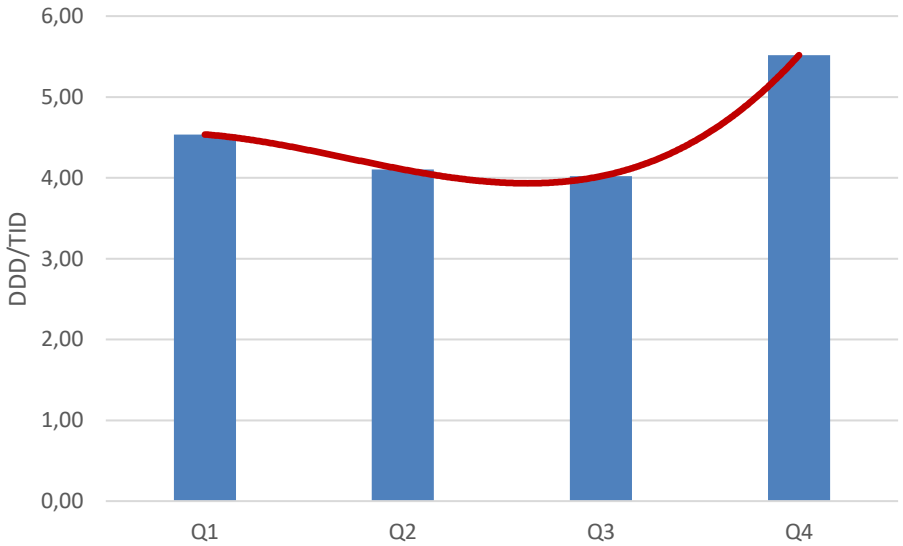
Slika 5. */ Figure 5.*
Ambulantna potrošnja antibiotika („top 6“ antibiotika – DDD/TID), izvor podataka – HZZO /
Ambulatory antibiotic consumption („top 6“antibiotics- DDD/TID); origin of data-CHIF



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

kvartal	DDD/TID
I	4,54
II	4,10
III	4,02
IV	5,52

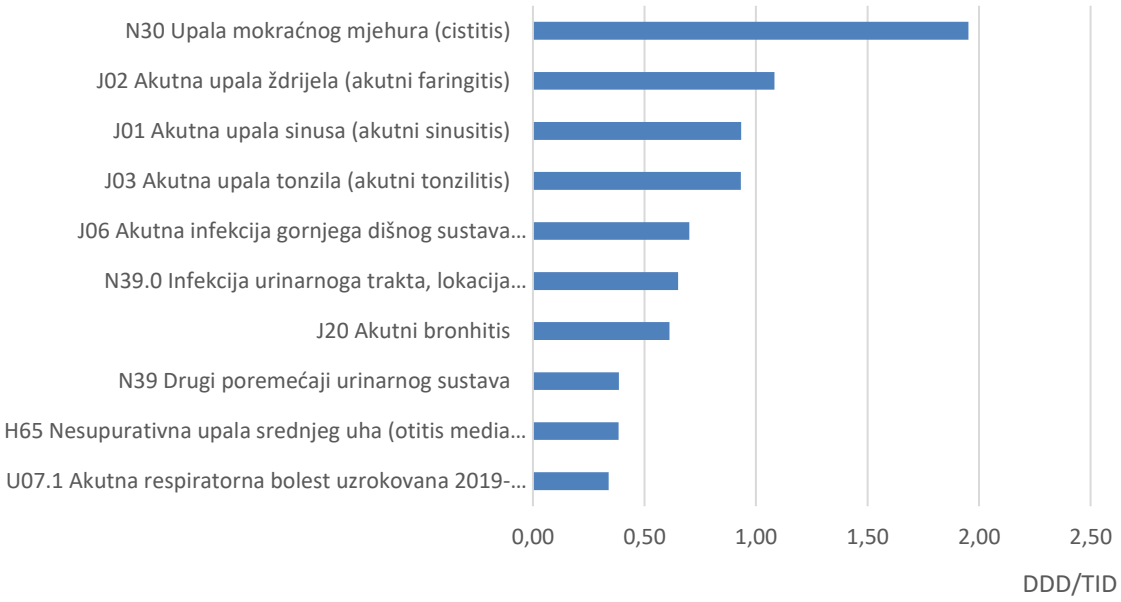
Slika 6. */ Figure 6.*
Ambulantna potrošnja antibiotika po kvartalima – DDD/TID, izvor podataka – HZZO / *Ambulatory antibiotic consumption – by quarters DDD/TID; origin of data-CHIF*



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)	1,95
J02 Akutna upala ždrijela (akutni faringitis)	1,08
J01 Akutna upala sinusa (akutni sinusitis)	0,93
J03 Akutna upala tonzila (akutni tonzilitis)	0,93
J06 Akutna infekcija gornjega dišnog sustava multiplih i nespec.	0,70
N39.0 Infekcija urinarnoga trakta, lokacija neoznačena	0,65
J20 Akutni bronhitis	0,61
N39 Drugi poremećaji urinarnog sustava	0,39
H65 Nesupurativna upala srednjeg uha (otitis media nonsuppurativa)	0,38
U07.1 Akutna respiratorna bolest uzrokovana 2019-noCoV	0,34

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



Potrošnja antibiotika u hrvatskim bolnicama

Od samog početka praćenja potrošnje antibiotika bolnička potrošnja se prati odvojeno od ambulantne potrošnje. Do 2011. godine bolnička potrošnja antibiotika se pratila putem podataka dobivenih od veledrogerija. Djelovanjem Interdisciplinarne sekcije za kontrolu rezistencije (ISKRA) pri Ministarstvu zdravstva od 2011. godini 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 dostavljaju se u europski program praćenja potrošnje ESAC-Net (tablica 2).
Podatke o potrošnji antibiotika bolnice dostavljaju u paketima ili komadima uz administrativne podatke o broju bolničkoopskrbnih dana (BOD) i broju primitaka za čitavu bolnicu 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 prati bolnička potrošnja 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 2022. godini razlika je iznosila 0,51 DDD/TID, dok je u prethodnoj godini bila 0,35 DDD/TID, a što je najveća razlika od kada se bolnička potrošnja prati iz oba izvora (tablica 9; slika 8).

Šezdesetosam bolnica je poslalo podatke o potrošnji antibiotika u 2022. 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, iako je to najpoželjniji način dostave podataka. Nakon obrade podataka svaka bolnica je dobila svoje obrađene podatke na provjeru, što je uobičajena praksa u svim prethodnim godinama.
Bolnička potrošnja antibiotika nastavila je s trendom rasta bez obzira na način prikazivanja, odnosno na korišteni denominator. Ako se potrošnja izračunava u DDD/1000 stanovnika/dan (DDD/TID) iznosi 1,98 (tablica 2), što je najviše do sada. Ako je bolnička potrošnja antibiotika izražena u DDD/100 bolničkoopskrbnih dana (DDD/100 BOD), također se već devetu godinu za redom potrošnja povećava te ima linearan trend porasta (tablica 10, slika 9).

Porast ukupne bolničke potrošnje rezultat je porasta potrošnje klase penicilina (penicilina širokog spektra, beta-laktamaza rezsitentnog penicilina, te kombinacije penicilina s beta laktamaza inhibitorima) skupine sulfonamida s trimetoprimom te aminoglikozida (tablica 2, tablica 11, slika 10). Pozitivno je to da je kod skupine cefalosporina potrošnja kao i prethodne godine, bez porasta, kao i kod skupine „ostalih“ antibiotika (glikopeptidi, polimiksini, ostali: linezolid, daptomicin, fosfomicin) kod koje se bilježi blagi pad potrošnje. Za makrolide i fluorokinolone potrošnja je ostala na istom nivou.

Rang lista vodećih pet antibiotika u bolničkoj potrošnji ostala je ista kao i prethodne godine s malim razlikama u potrošnji zadnje dvije godine. Ko-amoksiklav čvrsto drži vodeću poziciju (8,26 DDD/100 BOD), s najvišom potrošnjom do sada (8,07 DDD/100 BOD u 2021.). Na drugom mjestu je ceftriakson, koji je zaustavio rast pa je potrošnja nešto niža u odnosu na godinu prije (4,41 u odnosu na 4,62 DDD/100 BOD).
Na trećem mjestu je cefuroksimaksetil s nešto nižom potrošnjom (3,39 DDD/100 BOD u odnosu na 3,69 DDD/100 BOD), na četvrtom ciprofloksacin s gotovo identičnom potrošnjom (3,19 DDD/100 BOD u

odnosu na 3,18 DDD/100 BOD prethodne godine) te azitromicin na petom mjestu s gotovo istom potrošnjom (2,90 DDD/100 BOD u odnosu na 2,89 DDD/BOD) (tablica 12; slika 11).

Vodećih pet antibiotika u bolničkoj potrošnji ostalo je na istim pozicijama, a ko-amoksiklav je je zabilježio najveću potrošnju do sada.

Kao indikator bolničke potrošnje antibiotika prati se udio potrošnje rezervnih antibiotika glikopeptida (J01XA), cefalosporina III. generacije (J01DD), cefalosporina IV. generacije (J01DE), monobaktama (J01DF), karbapenema (J01DH), fluorokinolona (J01MA), polimiksina (J01XB), piperacilin+tazobaktama (J01CR05), linezolida (J01XX08), tedizolida (J01XX11) i daptomicina (J01XX09) u ukupnoj bolničkoj potrošnji. U 2022. godini došlo je do smanjenja udjela na 38,9%. Time je zaustavljen trend neprekidnog povećanja udjela rezervnih antibiotika u ukupnoj potrošnji u zadnjih pet godina praćenja (tablica 13, slika 12).

Sve **kliničke ustanove**, njih trinaest je dostavilo podatke o potrošnji antibiotika (tablica 14, slika 13). Raspon potrošnje antibiotika u 2022. godini kretao se od 26,19 do 138,50 DDD/100 BOD (tablica 15; slika 14). Raspon potrošnje je očekivano velik, jer se radi o kliničkim ustanovama s različitim odjelima i kazuistikom.

Kod četiri kliničke ustanove (K 01; K 03; K 04; K 08) uočava se pad potrošnje antibiotika, što je dvostruko manje u odnosu na prethodnu godinu, kada je pad zabilježen kod 8 bolnica.. Kod pet kliničkih ustanova došlo je do porasta potrošnje (K 02; K 06; K 09, K 13; K 14), dok je kod 4 kliničke ustanove (K 05; K07; K11, K 15) razlika u potrošnji manja od jednog DDD na 100 BOD u zadnje dvije godine.

U 2022. godini 22 **opće bolnice** su dostavile svoje podatke koji su međusobno usporedivi obzirom da se radi o najhomogenijoj skupini bolnica. Potrošnja antibiotika se kretala u širokom rasponu od 48,27 do 95,55 DDD/100 BOD (tablica 16), što upućuje da i dalje postoje velike razlike u praksi propisivanja antibiotika među bolnicama usprkos sličnoj strukturi njihovih odjela i usluga koje pružaju.

Kod 12 bolnica bilježi se pad potrošnje antibiotika (O 03; O 07; O 08; O 10; O 11; O 14; O 17; O 18; O 20; O 21; O 22; O 24), što je identično prethodnoj godini (tablica 17.).

Kod 6 bolnica uočava se porast potrošnje (O 02; O 05; O 09; O 12; O15; O 19), a kod četiri nema razlika većih od 1 DDD/100 BOD (O 01; O 04; O 13; O 23) u zadnje dvije godine.

Na slici 15 je prikazana potrošnja u općim bolnicama prema pojedinim klasama antibiotika u 2022. godini. U tablici 17 i na slici 16 prikazana je potrošnja u općim bolnicama u petogodišnjem periodu što svakoj bolnici daje mogućnost praćenja vlastitih trendova potrošnje.
Opće bolnice O 02; O 09; O 13 te O 19 bilježe kontinuirani trend porasta potrošnje antibiotika u zadnje tri godine, a naročito je to uočljivo kod opće bolnice 09 kod koje je potrošnja u zadnjih šest godine porasla za 19,35 DDD/100 BOD, dok se u bolnici O 07 potrošnja vratila na razdoblje prije pandemije, a nakon što je u 2020 i 2021. bilježila veliki skok u potrošnji.

Manji je broj bolnica s nižom potrošnjom, u rasponu potrošnje od 41-50 DDD/100 BOD (4) u odnosu na prethodnu godinu (5). U sedam bolnica potrošnja se kretala između 51 i 60 DDD/100 BOD, što je više u odnosu na prethodnu godinu kada su se u tom rasponu nalazilo pet bolnica. Četiri bolnice su u skupini bolnica s potrošnjom od 61 do 70 DDD/100 BOD, kao i u skupini od 71 do 80 DDD/100 BOD. Potrošnja u dvije opće bolnice se kretala između 81 do 90 DDD/100 BOD-a dok je u jednoj bolnici zabilježena potrošnja od 95,55 DDD/100 BOD, što je gotovo dvostruko više u odnosu na potrošnju u bolnici s najnižom potrošnjom.

Potrošnja antibiotika u **psihijatrijskim bolnicama** kreće se od 0,65 do 15,71 DDD/100 BOD (tablica 18). Na slici 17 prikazana je potrošnja po klasama antibiotika u psihijatrijskim bolnicama. U 2022. godini u dvije psihijatrijske bolnice (P 07; P 08) uočava se porast potrošnje, dok je u tri bolnice (P 01; P

03; P04) potrošnja u padu. Kod četiri bolnice (P 02; P 05; P 06; P 09) nema promjena u potrošnji većoj od 1 DDD/100 BOD. U tablici 19 i na slici 18 prikazana je potrošnja u psihijatrijskim bolnicama u zadnjih šest godina s uočljivim trendovima potrošnje. Psihijatrijska ustnova P 01 nakon značajnog porasta potrošnje u 2021. godini ponovno je vratila potrošnju na vrijednosti slične godinama prije. Posebno je uočljiv trend porast potrošnje psihijatrijske ustanove P 09 u zadnje tri godine, s najvišom potrošnjom u 2022. godini. U prethodnoj godini, najveći skok u potrošnji zabilježen je kod psihijatrijske ustanove P 07, i to za 5,3 DDD/100 BOD. Psihijatrijska ustanove P 02 prekinula je kontinuirani uzlazni trend potrošnje nakon prethodnih godina.

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 9,35 do 80,08 DDD/100 BOD. Dvije bolnice bilježe porast potrošnje (S03; S 13). Pet bolnica (S 01; S 02; S 18; S 21; S 23) bilježi pad potrošnje, dok kod tri bolnice (S 04; S 19; S 22) nema razlika većih od 1 DDD/100 BOD (tablica 21; slika 20).

U skupini specijalnih bolnica namijenjenih rehabilitaciji kretanje potrošnje antibiotika je značajno niže i kreće se od 0,69 do 9,59 DDD/100 BOD (tablica 21; slika 20), dvije bolnice imaju zabilježen porast potrošnje (S 06; S 14). Samo kod specijalne bolnice S 07 zabilježen je pad potrošnje, dok je kod svih ostalih potrošnja ujednačena s prethodnom godinom i ne odstupa više ili manje od 1 DDD/100 BOD.

Na slici 19 prikazana je potrošnja antibiotika po klasama u 2022. godini. U tablici 21 i na slici 20 prikazana je potrošnja u specijalnim bolnicama u zadnjih šest godina.

Iako se u bolnicama propisuje oko 10% ukupne potrošnje antibiotika, struktura potrošnje je bitno drugačija od ambulantne što ima osobit značaj na nastanak i širenje rezistentnih bakterijskih sojeva i klonova. U „zatvorenom" bolničkom sustavu velik broj pacijenata dobiva antibiotsku terapiju, što povećava selektivni pritisak antibiotika na bakterijsku populaciju. Osim toga sve je veći udio starijeg stanovništva s brojnim kroničnim bolestima, koji se učestalo hospitaliziraju, što olakšava daljnju kolonizaciju višestrukootpornim bakterijskim sojevima i širenje tih sojeva unutar bolničkih ustanova, a često i razmijenjivanje takvih sojeva s domovima za starije i nemoćne u koje se ti pacijenti vraćaju.

U Hrvatskoj linearno raste bolnička potrošnja zadnjih devet godina. U 2022. godini porast ukupne potrošnje je posljedica kontinuiranog rasta potrošnje skupine penicilina (J01C). Zaustavljen je porast potrošnje skupine „ostalih" (J01X) u kojoj se nalaze rezervni antibiotici (osim metronidazola), tako da njihov udio u ukupnoj potrošnji bilježi pad u zadnjoj godini praćenja bolničke potrošnje antibiotika.

Još uvijek u hrvatskim bolnicama nije zaživjelo rukovođeno propisivanje antibiotika, što je preduvjet za kontroliranu i racionalnu primjenu antibiotika.

Antibiotic Consumption in Croatian Hospitals

Since the very beginning of surveillance, antibiotic consumption in hospitals has been tracked separately from the one in outpatient setting. Until 2011 it was monitored through the data obtained from pharmaceutical wholesalers. However, following the involvement of the Interdisciplinary Section for Resistance Control (ISKRA) at the Ministry of Health in 2011, all hospitals have been providing antibiotic consumption data from their pharmacies as well. As a result, the use of antibiotics in hospitals has been comprised from two sources since then (both wholesalers and hospital pharmacies). The data obtained from hospital pharmacies are submitted to the European Surveillance of Antimicrobial Consumption Network (ESAC-Net) program (Table 2).

Hospitals provide consumption data in packages or units along with administrative information about the number of Bed Days (BDs) and the number of admissions both for the entire hospital and separately for intensive care units (ICU) by types (mixed, surgical, internal, paediatric). Starting in 2011, usage of antibiotics in day hospitals has also been included in hospital consumption monitoring, and their Days of Therapy have been added to the denominator along with BDs.

The above-mentioned data is gathered in accordance with the Anatomical Therapeutic Chemical (ATC) classification at the fifth level and is presented at the 3rd and 4th levels.

Hospital consumption data is expressed in Defined Daily Doses per 1000 inhabitants per day (DDD/TID) (Table 2).

However, since 2011, when hospital consumption started being tracked through the data from hospital pharmacies and when administrative data for each hospital in Croatia became available, hospital antibiotic consumption can also be measured in DDD/BDs. This way of expressing consumption has significant advantages over DDD/TIDs because it is more objective, precise, and allows detailed analysis by specific classes and types of antibiotics at the national level, as well as individually for each hospital.

Table 9 and Figure 8 juxtapose the data obtained from both sources since 2014. A higher consumption was recorded based on data obtained from hospital pharmacies (except in 2015) which resulted in an increased difference in consumption favoring hospitals. In 2022, this difference was 0.51 DDD/TID, while in the previous year it was 0.35 DDD/TID, which is the largest difference since hospital consumption has been monitored from both sources (Table 9; Figure 8).

Sixty-eight hospitals provided data on antibiotic consumption in 2022. All hospitals submitted their data electronically to iskra.antibiotici@gmail.com. Just like in previous years, only 4 hospitals directly exported data from their pharmacy programs, even though this is the preferred method of data delivery. After processing, each hospital received its data for verification, which was a common practice in all previous years.

Hospital antibiotic consumption continued its upward trend regardless of the presentation method or the denominator used. If calculated in Defined Daily Doses per 1000 inhabitants per day (DDD/TID), it amounted to 1.98 (Table 2), which was the highest consumption so far. If expressed in DDDs per 100 Bed Days (DDD/100 BDs), it had been increasing for the ninth consecutive year, following a linear upward trend (Table 10, Figure 9).

The rise in overall usage of antibiotics in hospitals is a result of growth in consumption of penicillin class antibiotics (broad-spectrum penicillins, beta-lactamase resistant penicillins, and combinations of penicillins with beta-lactamase inhibitors), sulfonamide group with trimethoprim, and aminoglycosides (Table 2, Table 11, Figure 10). The consumption of cephalosporin group of antibiotics remained favourable – the same as in 2021, which also applies to the "other" antibiotics group (glycopeptides,

polymyxins, others: linezolid, daptomycin, fosfomycin), where a slight decrease in usage was noted. Consumption levels for macrolides and fluoroquinolones remained the same.

The ranking of the top five antibiotics used in hospitals remained the same as in 2021, while there were minor differences in the two preceding years. Co-amoxiclav kept its leading position (8.26 DDD/100 BDs), culminating in 2021 (8.07 DDD/100 BDs). In the second place was ceftriaxone, which ceased to grow and as a result had slightly lower consumption than the year before (4.41 compared to 4.62 DDD/100 BDs).

Ranking third is cefuroxime axetil with slightly lower usage (3.39 DDD/100 BDs compared to 3.69 DDDs/100 BDs), the fourth is ciprofloxacin with almost identical consumption of 3.19 DDDs/100 BDs compared to 3.18 DDDs/100 BDs in the previous year, and the same applies to azithromycin in the fifth place, with only a minor difference in the last two years (2.90 DDDs/100 BDs compared to 2.89 DDDs/100 BDs) (Table 12; Figure 11).

The top five antibiotics used in hospitals kept the same positions, with co-amoxiclav recording the highest consumption to date.

The share of reserve antibiotics in overall hospital usage is monitored as an indicator. These include glycopeptides (J01XA), third-generation cephalosporins (J01DD), fourth-generation cephalosporins (J01DE), monobactams (J01DF), carbapenems (J01DH), fluoroquinolones (J01MA), polymyxins (J01XB), piperacillin+tazobactam (J01CR05), linezolid (J01XX08), tedizolid (J01XX11), and daptomycin (J01XX09). In 2022, this share dropped to 38.9%, thus interrupting the trend of their continuous increase in overall hospital consumption observed over the past five years of monitoring (Table 13; Figure 12).

All **clinics**, thirteen of them, provided their antibiotic consumption data (Table 14; Figure 13) which in 2022 ranged from 26.19 to 138.50 DDDs/100 BDs (Table 15; Figure 14). This wide range was to be expected, given the diverse clinical departments and caseloads in these institutions.

The number of clinics that reported a drop in consumption was four (K 01; K 03; K 04; K 08) - a half from the previous year. In five clinics there was an increase (K 02; K 06; K 09, K 13; K 14), while in the remaining four (K 05; K 07; K 11, K 15), the difference in consumption was less than one DDD per 100 BDs over the last two years.

In 2022, 22 **general hospitals** provided their data, which was mutually comparable since it is the most homogeneous group of hospitals. Antibiotic consumption ranged widely, from 48.27 to 95.55 DDDs/100 BDs (Table 16), indicating significant variation in antibiotic prescribing practices among hospitals despite their similar departmental structures and services provided.

In twelve hospitals, antibiotic consumption decreased (O 03; O 07; O 08; O 10; O 11; O 14; O 17; O 18; O 20; O 21; O 22; O 24), just as it did in 2021. (Table 17).

On the other hand, consumption increased in six hospitals (O 02; O 05; O 09; O 12; O 15; O 19), while in four there were no differences greater than 1 DDD/100 BDs (O 01; O 04; O 13; O 23) over the last two years.

Figure 15 displays antibiotic consumption in general hospitals by specific antibiotic classes in 2022. Table 17 and Figure 16 show the same but over a five-year period, allowing each hospital to track its own consumption trends. General hospitals O 02; O 09; O 13, and O 19 showed a continuous rising trend in the usage of antibiotics over the last three years. General hospital O 09 saw a notable consumption increase of 19.35 DDDs/100 BDs in the last six years. In hospital O 07, consumption returned to pre-pandemic levels after significant jumps in 2020 and 2021.

The number of hospitals with lower usage of antibiotics is smaller, ranging from 41-50 DDD/100 BDs in 4 of them compared to the previous year when there were 5. In seven hospitals, the consumption varied between 51 and 60 DDDs/100 BDs, which is higher than in 2021 when there were five hospitals in this span. Four hospitals comprised the group with values from 61 to 70 DDDs/100 BDs, as well as the group from 71 to 80 DDDs/BBDs. The usage of antibiotics in two general hospitals ranged from 81 to 90 DDDs/100 BDs, while in one hospital, consumption of 95.55 DDDs/100 BDs was recorded, which is almost double the value of the hospital with the lowest consumption.

Usage of antibiotics in **psychiatric hospitals** ranged from 0.65 to 15.71 DDDs/100 BDs (Table 18). Figure 17 details consumption by class of antibiotics. In 2022, there was an increase in two psychiatric hospitals (P 07; P 08), while three (P 01; P 03; P04) saw a decrease. In four hospitals (P 02; P 05; P 06; P 09), there were no changes in consumption greater than 1 DDD/100 BDs. Table 19 and Figure 18, cover the period of past six years and there are some noticeable trends in consumption. Psychiatric institution P 01, after a significant increase in 2021, returned its consumption to values similar to previous years. Particularly notable is the rising consumption trend in hospital P 09 in the last three years, reaching the peak in 2022. In the previous year, P 07 recorded a surge in consumption by 5.3 DDDs/100 BDs. Psychiatric institution P 02 interrupted its continuous upward consumption trend seen in previous years.

Specialty hospitals are divided into two main groups based on their focus, and they exhibit large variations in the use of antibiotics. The first group comprises 10 hospitals dedicated to treatment (acute/chronic), while the second group includes 14 institutions for rehabilitation (Table 20; Figure 19). In the first group, consumption ranges from 9.35 to 80.08 DDDs/100 BDs. Two hospitals saw an increase in consumption (S03; S 13), five hospitals (S 01; S 02; S 18; S 21; S 23) a decrease, while in three hospitals (S 04; S 19; S 22) there were no differences greater than 1 DDD/100 BDs (Table 21; Figure 20).

In the group of specialty hospitals dedicated to rehabilitation, antibiotic usage is significantly lower, ranging from 0.69 to 9.59 DDDs/100 BDs (Table 21; Figure 20). Two hospitals recorded an increase in consumption (S 06; S 14). Only in hospital S 07, there was a decrease in usage, while in all the other hospitals consumption equalled previous year, with discrepancy of about 1 DDD/100 BDs.

Figure 19 details consumption in specialty hospitals by classes of antibiotics in 2022. Table 21 and Figure 20 show their consumption trends over the last six years.

Although hospitals account for around 10% of the total use of antibiotics, the consumption structure differs significantly from the outpatient setting. This has implications for the emergence and spread of resistant bacterial strains and clones. In the “closed” hospital setting, a large number of patients receive antibiotic therapy, thus increasing selective pressure on bacterial population. Moreover, a growing share of aging population with numerous chronic diseases is more frequently hospitalized, facilitating further colonization with multidrug-resistant bacterial strains and their spread not only within hospitals, but often extending to nursing homes where these patients return.

In Croatia, hospital antibiotic consumption has been linearly increasing over the last nine years. In 2022, the rise in overall consumption was due to the continuous growth in the use of the penicillin group (J01C). The increase in the usage of the "other" group (J01X), which includes reserve antibiotics (except metronidazole), was halted. Consequently, their share in total consumption decreased in the last year of hospital antibiotic consumption monitoring.

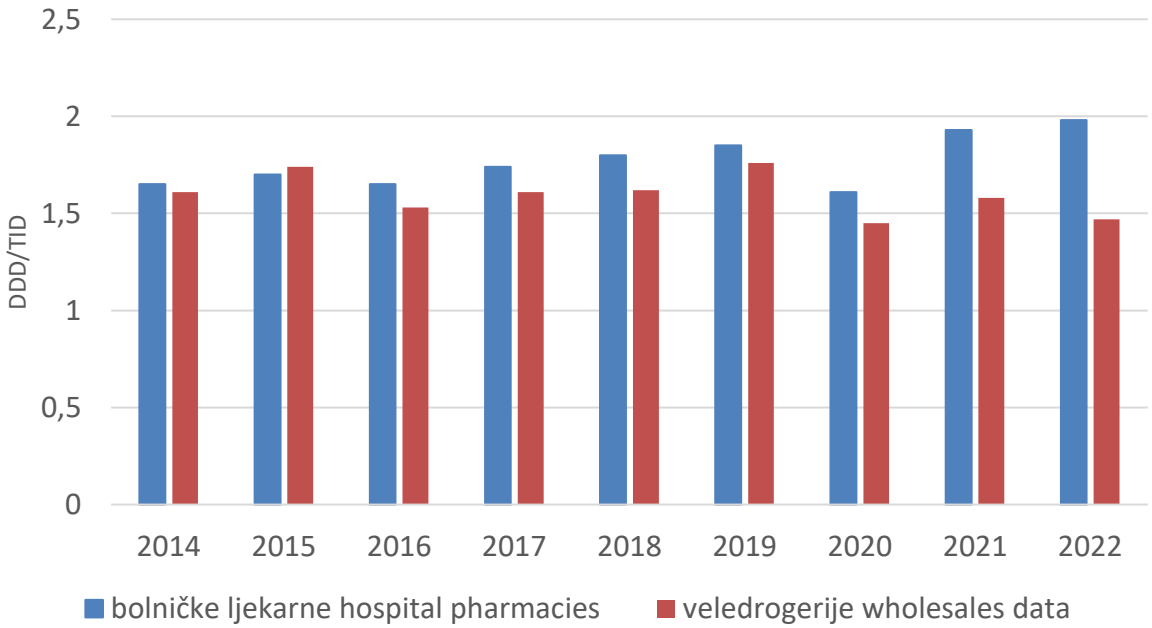
Antibiotic stewardship is still not fully established in Croatian hospitals, which is a prerequisite for controlled and rational use of antibiotics.

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

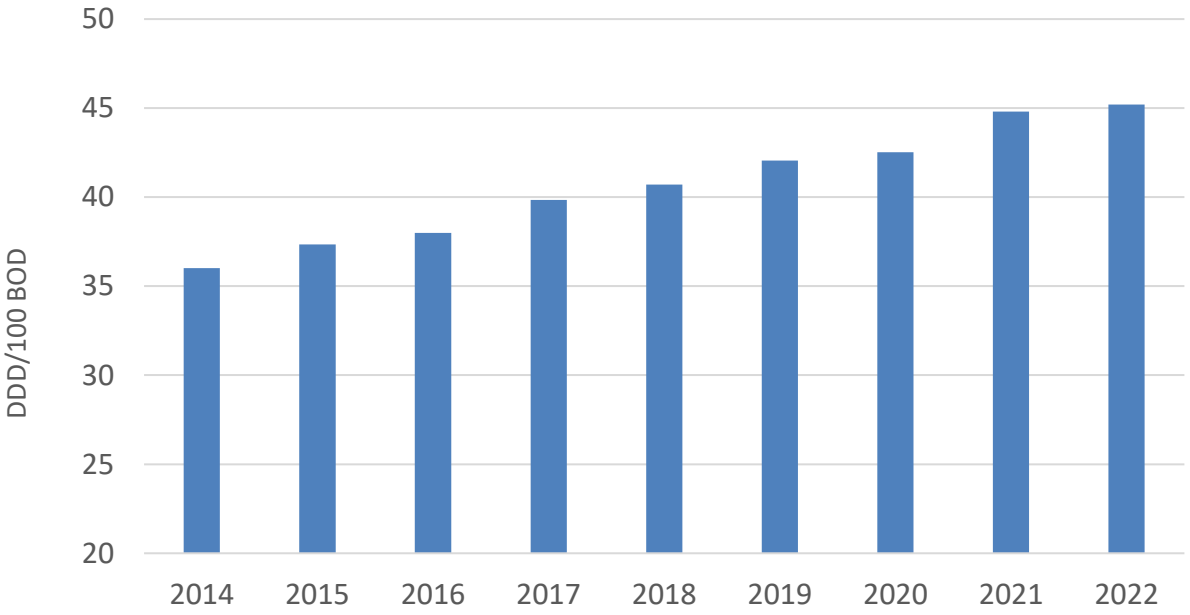
Slika 8. */ Figure 8.*
Bolnička potrošnja antibiotika (DDD/TID) usporedba podataka bolničkih ljekarni i veledrogerija */ Hospital antibiotic consumption (DDD/TID) comparison between hospital pharmacy data and wholesales data*



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

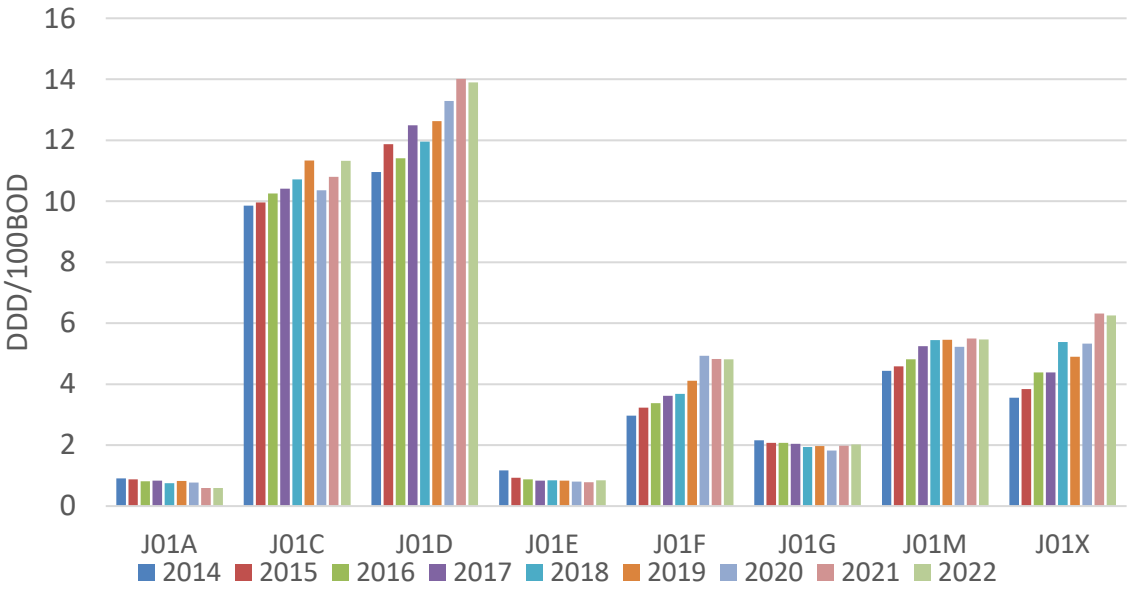
Slika 9. */ Figure 9.*
Bolnička potrošnja antibiotika (DDD/100 BOD) / *Hospital antibiotic consumption (DDD/100 BD)*



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

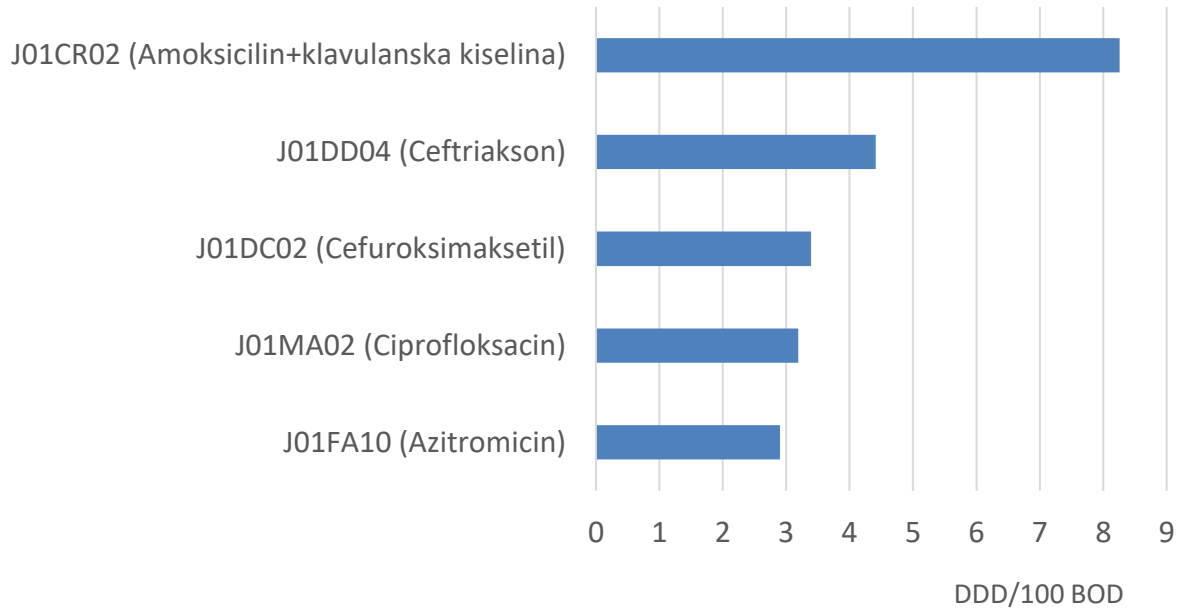
Slika 10. */ Figure 10.*
Bolnička potrošnja antibiotika (DDD/100 BOD) po klasama, izvor podataka – bolničke ljekarne /
Hospital antibiotic consumption (DDD/100 BD) by class, origin of data - hospital pharmacies



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

Klasa / class	DDD/100 BOD / *DDD/100 BD*
J01CR02 (Amoksicilin+klavulanska kiselina)	8,26
J01DD04 (Ceftriakson)	4,41
J01DC02 (Cefuroksimaksetil)	3,39
J01MA02 (Ciprofloksacin)	3,19
J01FA10 (Azitromicin)	2,90

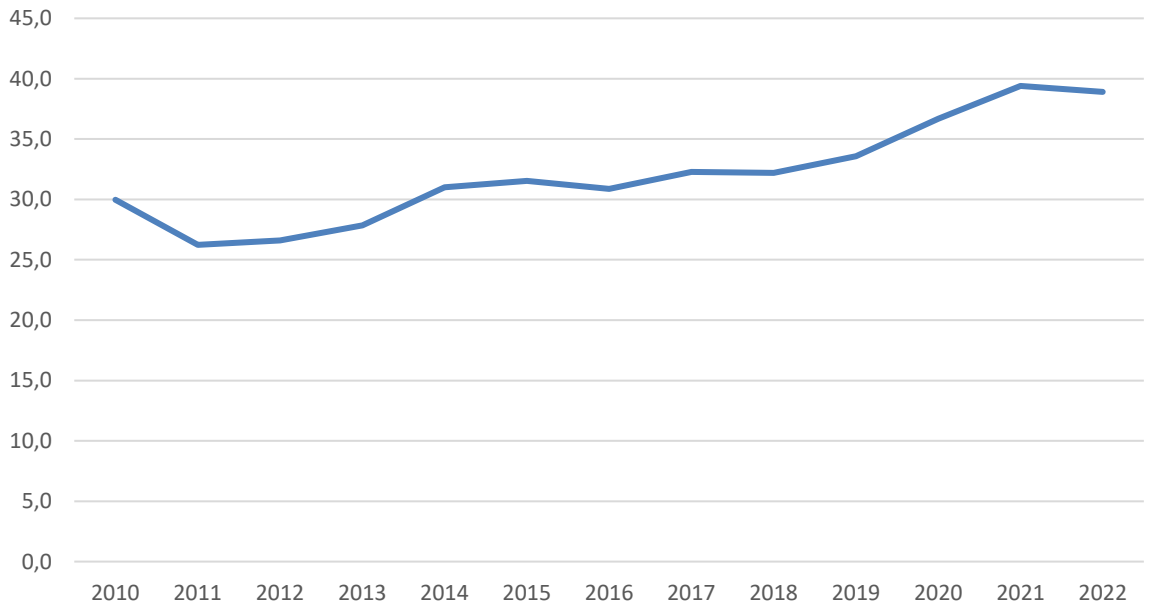
Slika 11. */ Figure 11.*
Bolnička potrošnja antibiotika „top 5“ antibiotika – DDD/100 BOD, izvor podataka – bolničke ljekarne / *Hospital antibiotic consumption „top 5“antibiotics – DDD/100 BD; origin of data - hospital pharmacies*



Tablica 13. / *Table 13.*
Udio potrošnje glikopeptida* (J01XA), cefalosporina III. generacije* (J01DD), cefalosporina IV. generacije* (J01DE), monobaktama* (J01DF), karbapenema* (J01DH), fluorokinolona* (J01MA), polimiksina* (J01XB), piperacilin+tazobaktama* (J01CR05), linezolida* (J01XX08), tedizolida* (J01XX11) i daptomicina* (J01XX09) u odnosu na ukupnu potrošnju antibiotika za sistemsku upotrebu u bolnicama izražen kao DDD na tisuću stanovnika na dan u razdoblju 2010-2022 / *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) 2010-2022*

	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

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 2010-2022 / *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) 2010-2022*

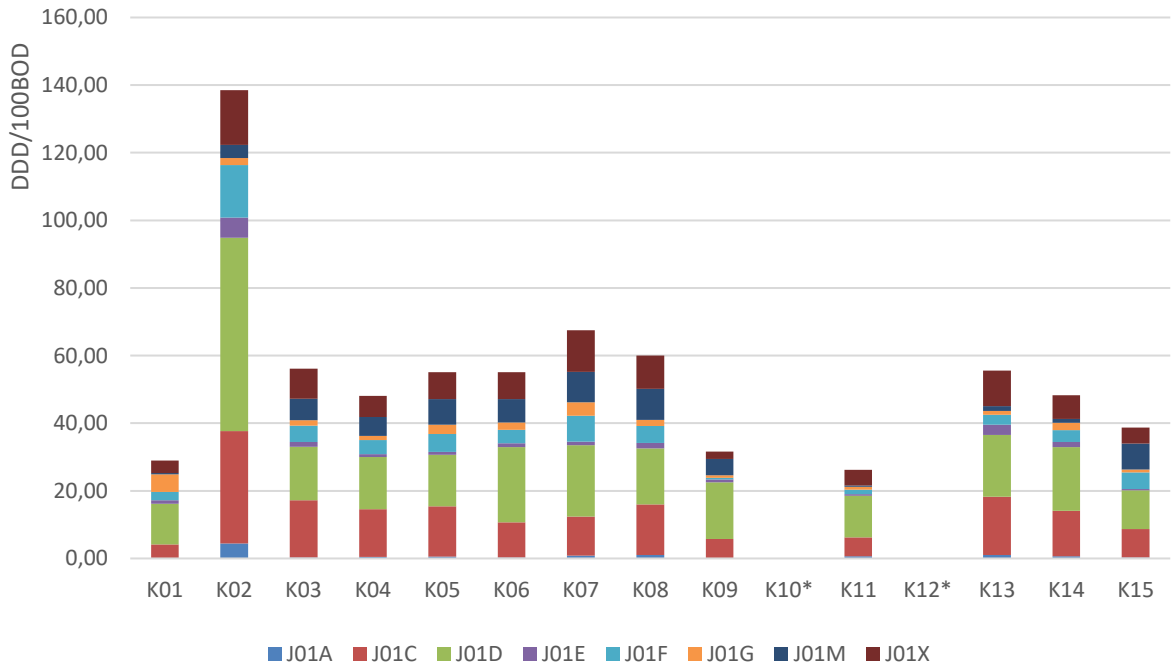


Tablica 14. */ Table 14.*
Kliničke ustanove - potrošnja antibiotika 2022. **/** *Clinical insitutions – antibiotic consumption in 2022*

	DDD/100 BOD, DDD/100 BD								
USTANOVA INSTITUTION	UKUPNO TOTAL	J01A	J01C	J01D	J01E	J01F	J01G	J01M	J01X
K 01	28,97	0,05	4,10	12,02	1,02	2,44	5,29	0,34	3,72
K 02	138,50	4,42	33,27	57,19	5,91	15,57	2,04	3,94	16,16
K 03	56,11	0,26	16,99	15,80	1,40	4,83	1,63	6,31	8,90
K 04	48,05	0,44	14,11	15,44	0,83	4,22	1,17	5,59	6,25
K 05	55,08	0,51	14,89	15,26	0,88	5,27	2,71	7,60	7,94
K 06	55,12	0,31	10,38	22,27	1,12	3,97	2,21	6,85	8,01
K 07	67,51	0,85	11,49	21,14	1,01	7,74	3,94	8,97	12,36
K 08	60,02	1,03	14,92	16,58	1,67	4,97	1,80	9,19	9,86
K 09	31,57		5,79	16,71	0,89	0,50	0,69	4,83	2,16
K 10*									
K 11	26,19	0,61	5,66	12,30	0,41	1,35	0,87	0,36	4,63
K 12*									
K 13	55,53	1,03	17,25	18,28	2,99	2,94	1,15	1,41	10,48
K 14	48,23	0,67	13,41	18,82	1,57	3,47	2,15	1,20	6,95
K 15	38,76	0,28	8,43	11,42	0,38	4,91	0,92	7,67	4,74

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

Slika 13. **/** *Figure 13.*
Kliničke ustanove - potrošnja antibiotika 2017-2022. **/** *Clinical insitutions – antibiotic consumption in 2017-2022*



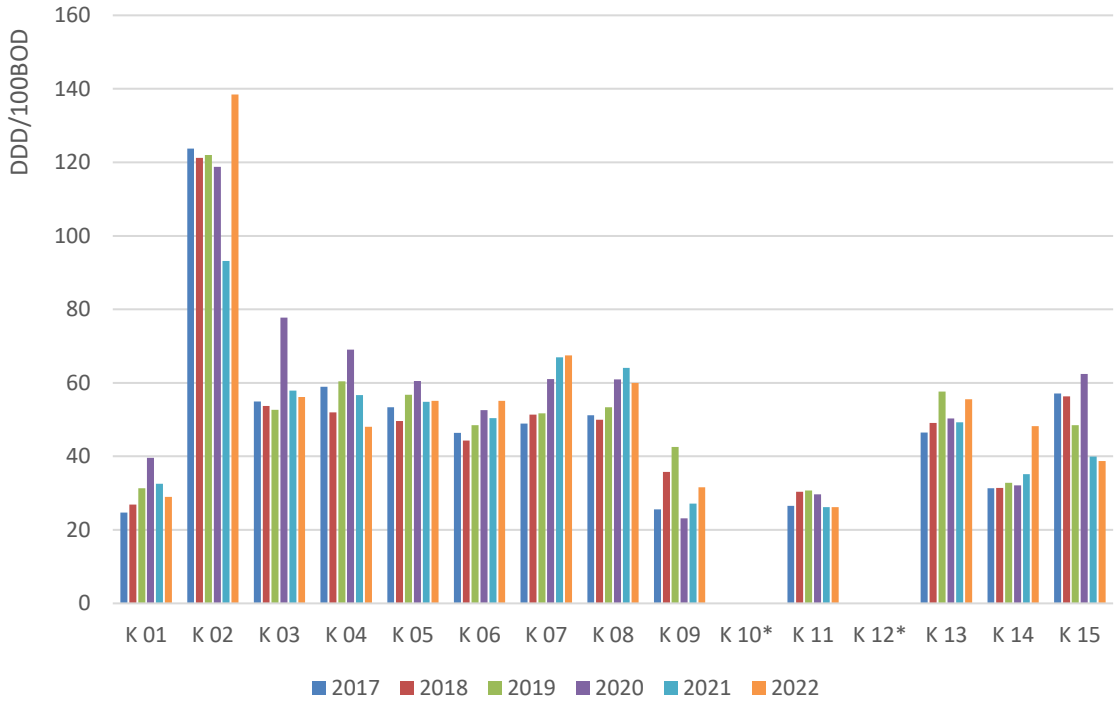
Tablica 15. */ Table 15.*

Kliničke ustanove - potrošnja antibiotika 2017-2022. */ Clinical insitutions – antibiotic consumption in 2017-2022*

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

* 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.-2022. */ Clinical insitutions – antibiotic consumption in 2017-2022*

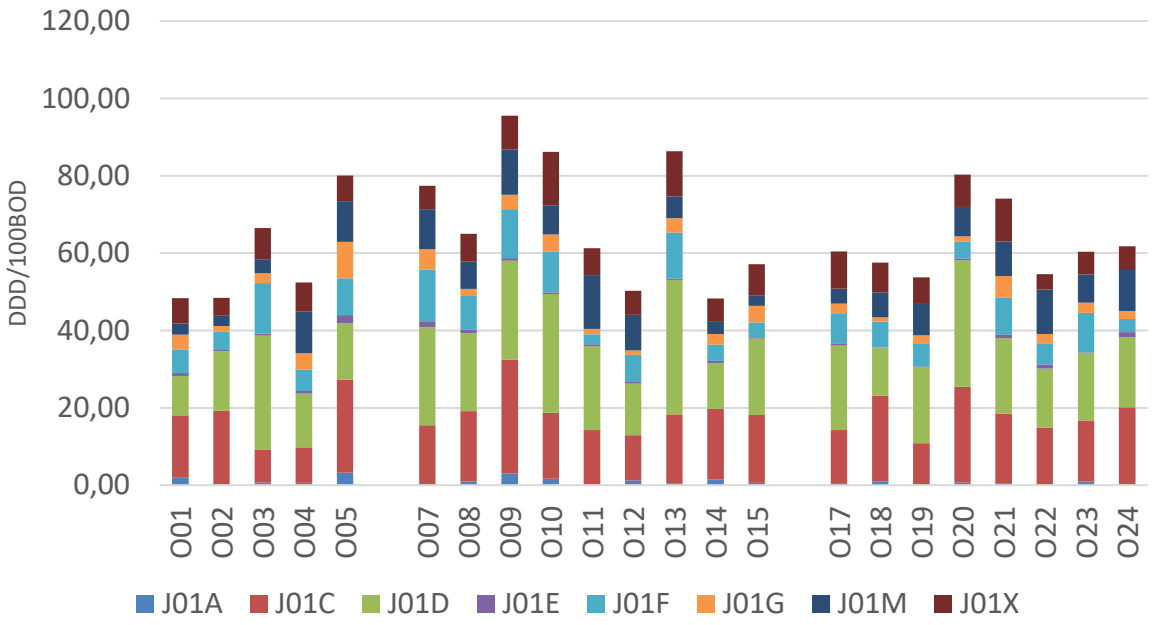


Tablica 16. */ Table 16.*
Opće bolnice - potrošnja antibiotika 2022. **/** *General hospitals – antibiotic consumption in 2022*

USTANOVA INSTITUTION	UKUPNO TOTAL	DDD/100 BOD, DDD/100 BD							
		J01A	J01C	J01D	J01E	J01F	J01G	J01M	J01X
O 01	48,36	1,91	16,14	10,20	0,72	6,09	3,81	2,98	6,52
O 02	48,46	0,22	19,01	15,40	0,35	4,69	1,48	2,66	4,65
O 03	66,48	0,65	8,43	29,55	0,49	13,14	2,53	3,47	8,23
O 04	52,37	0,62	9,16	13,91	0,62	5,57	4,27	10,73	7,48
O 05	80,08	3,21	24,01	14,68	2,03	9,57	9,37	10,41	6,79
O 06*									
O 07	77,38	0,13	15,36	25,28	1,63	13,31	5,26	10,42	5,99
O 08	64,95	0,95	18,19	20,15	0,95	8,71	1,80	7,04	7,16
O 09	95,55	3,03	29,39	25,63	0,65	12,68	3,70	11,66	8,81
O 10	86,15	1,70	17,03	30,72	0,36	10,52	4,47	7,57	13,77
O 11	61,27	0,21	14,00	21,76	0,42	2,59	1,44	13,89	6,96
O 12	50,26	1,23	11,73	13,29	0,42	7,05	1,17	9,14	6,23
O 13	86,37	0,47	17,85	34,72	0,37	11,88	3,73	5,63	11,71
O 14	48,27	1,47	18,26	11,85	0,57	4,21	2,69	3,20	6,02
O 15	57,11	0,57	17,56	19,77	0,33	3,86	4,31	2,70	8,02
O 16**									
O 17	60,42	0,38	13,88	21,83	0,61	7,78	2,48	3,85	9,61
O 18	57,53	0,97	22,13	12,39	0,11	6,69	1,08	6,44	7,70
O 19	53,74	0,29	10,53	19,63	0,26	5,94	2,06	8,13	6,89
O 20	80,25	0,70	24,72	32,66	0,43	4,37	1,42	7,63	8,32
O 21	74,11	0,52	17,94	19,56	0,95	9,45	5,65	8,92	11,14
O 22	54,58	0,28	14,58	15,32	1,05	5,45	2,37	11,53	4,00
O 23	60,39	0,96	15,80	17,36	0,19	10,20	2,67	7,32	5,88
O 24	61,77	0,19	19,94	18,08	1,36	3,36	2,12	10,60	6,11

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

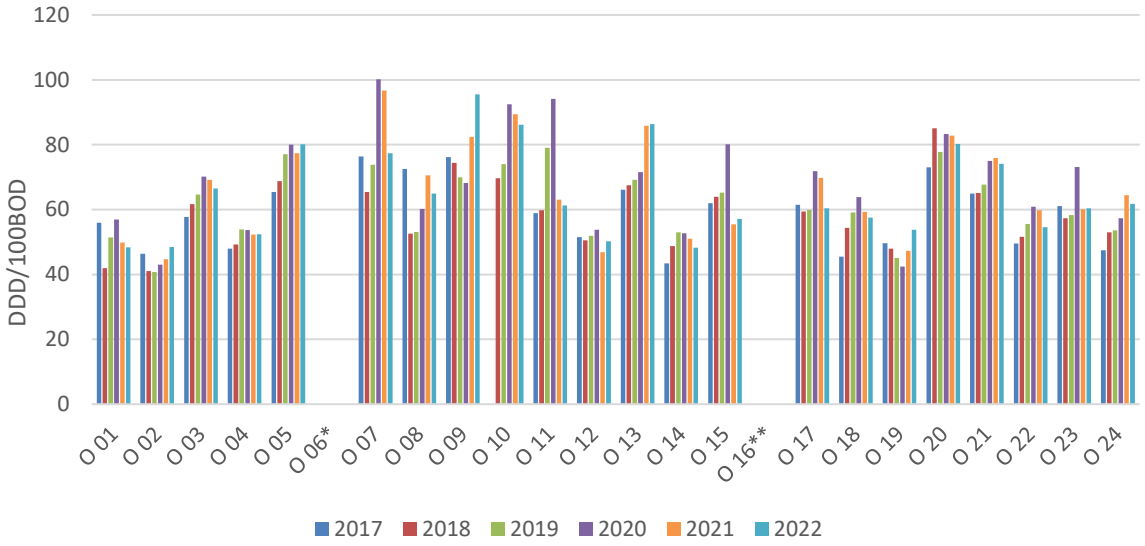
Slika 15. */ Figure 15.*
Opće bolnice - potrošnja antibiotika 2022. / *General hospitals – antibiotic consumption* 2022



Tablica 17. */ Table 17.*
Opće bolnice - potrošnja antibiotika 2017-2022. **/** *General hospitals – antibiotic consumption in 2017-2022*

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

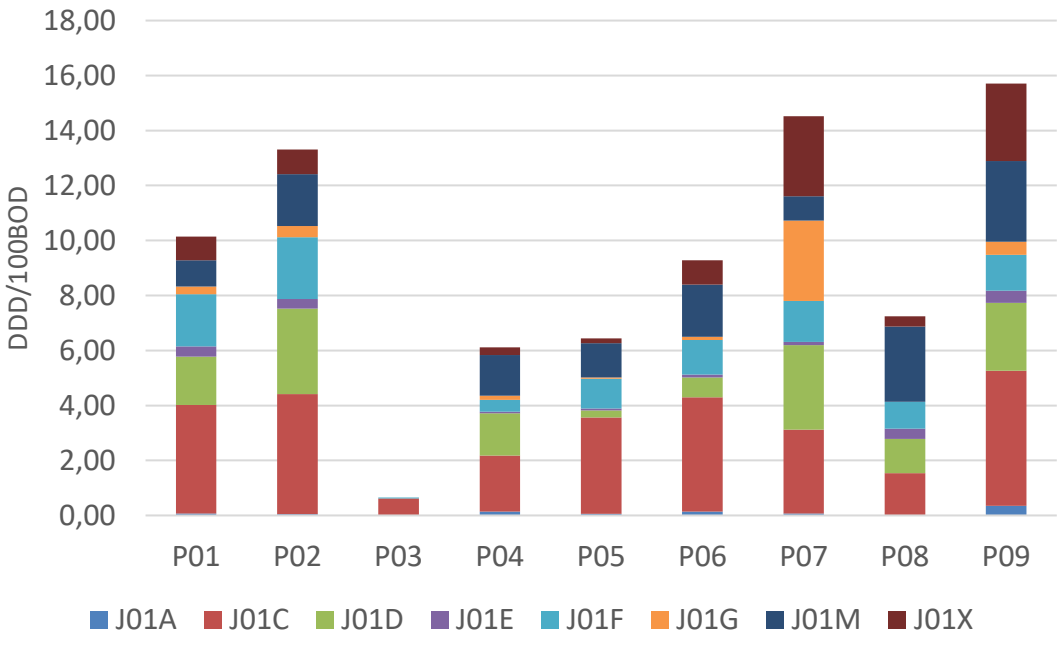
Slika 16. */ Figure 16.*
Opće bolnice - potrošnja antibiotika 2017-2022. */ General hospitals – antibiotic consumption 2017-2022*



Tablica 18. */ Table 18.*
Psihijatrijske ustanove - potrošnja antibiotika 2022. */ Psychiatric institutions – antibiotic consumption in 2022*

USTANOVA INSTITUTION	DDD/100 BOD, DDD/100 BD								
	UKUPNO / TOTAL	J01A	J01C	J01D	J01E	J01F	J01G	J01M	J01X
P 01	10,14	0,07	3,95	1,76	0,38	1,89	0,28	0,96	0,85
P 02	13,31	0,05	4,36	3,11	0,35	2,25	0,41	1,88	0,90
P 03	0,65		0,62			0,03			
P 04	6,12	0,14	2,03	1,54	0,06	0,43	0,15	1,48	0,29
P 05	6,44	0,06	3,50	0,26	0,07	1,09	0,04	1,24	0,18
P 06	9,28	0,14	4,16	0,73	0,10	1,26	0,11	1,90	0,88
P 07	14,52	0,07	3,04	3,08	0,12	1,49	2,92	0,88	2,92
P 08	7,25		1,54	1,24	0,38	0,97		2,74	0,38
P 09	15,71	0,35	4,92	2,47	0,44	1,30	0,49	2,92	2,82

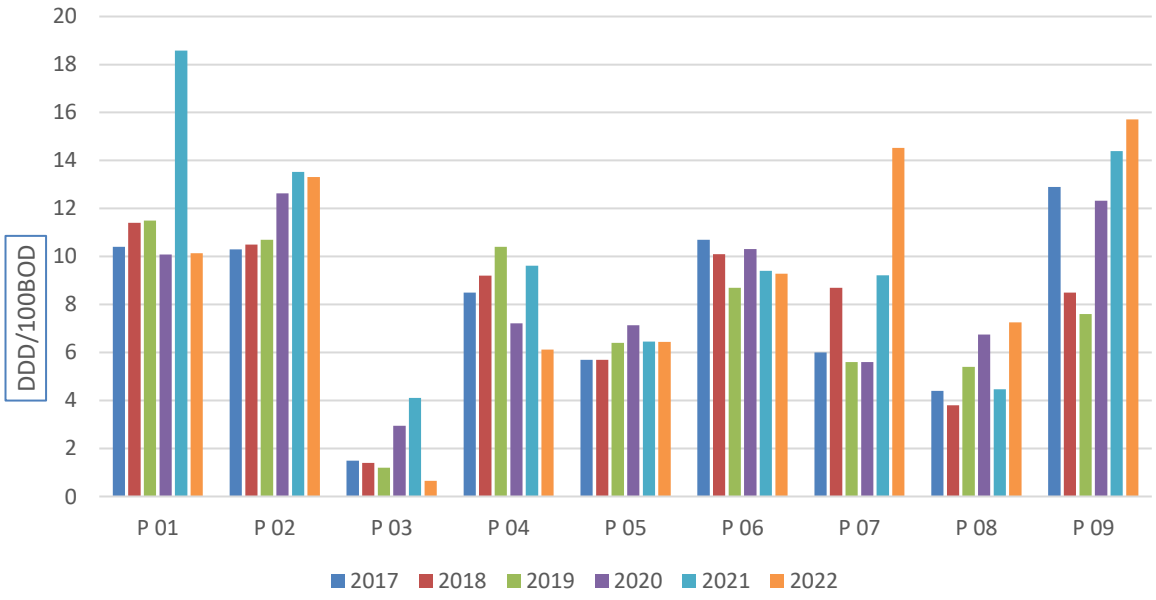
Slika 17. */ Figure 17.*
Psihijatrijske ustanove - potrošnja antibiotika 2022. */ Psychiatric institutions – antibiotic consumption 2022*



Tablica 19. */ Table 19.*
Psihijatrijske ustanove - potrošnja antibiotika 2017-2022. */ Psychiatric institutions – antibiotic consumption in 2017-2022*

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

Slika 18. */ Figure 18.*
Psihijatrijske ustanove - potrošnja antibiotika 2017-2022. */ Psychiatric institutions – antibiotic consumption 2017-2022*

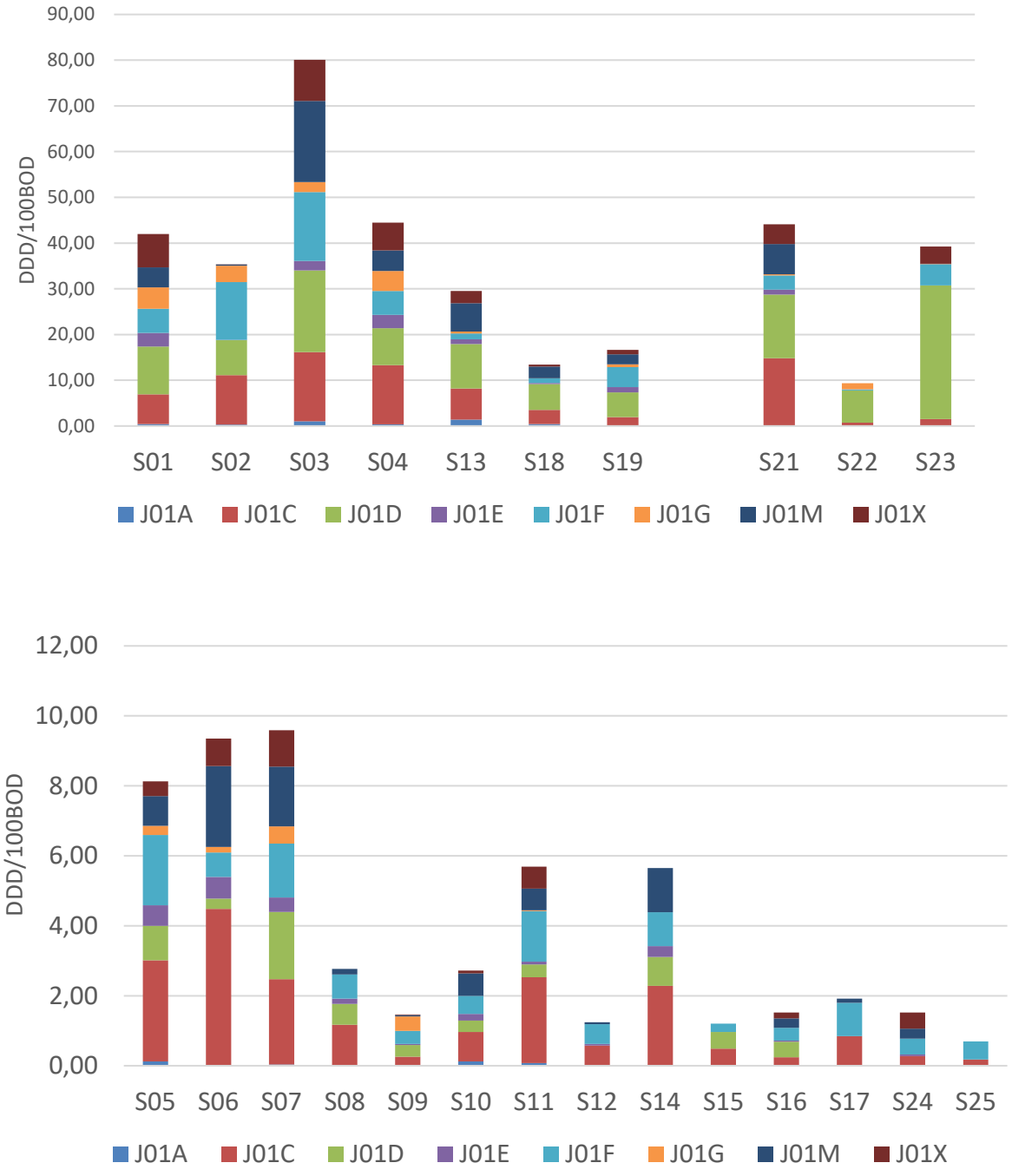


Tablica 20. */ Table 20.*
Specijalne bolnice - potrošnja antibiotika 2022. **/** *Specialty hospitals – antibiotic consumption in 2022*

	DDD/100 BOD, DDD/100 BD								
USTANOVA INSTITUTION	UKUPNO TOTAL	J01A	J01C	J01D	J01E	J01F	J01G	J01M	J01X
S 01	41,98	0,44	6,48	10,46	2,97	5,30	4,69	4,37	7,27
S 02	35,35	0,32	10,81	7,68	0,04	12,61	3,60	0,22	0,07
S 03	80,08	1,02	15,12	17,91	2,04	15,10	2,18	17,75	8,97
S 04	44,46	0,37	12,96	8,09	2,90	5,22	4,37	4,48	6,08
S 13	29,52	1,41	6,81	9,68	1,05	1,26	0,44	6,19	2,67
S 18	13,40	0,44	3,07	5,69	0,25	1,01	0,03	2,55	0,37
S 19	16,67	0,11	1,84	5,41	1,12	4,39	0,62	2,19	0,98
S 20*									
S 21	44,11		14,86	13,89	1,11	3,06	0,28	6,57	4,34
S 22	9,35		0,70	7,07		0,26	1,32		
S 23	39,28		1,53	29,23		4,62	0,04	0,06	3,79
S 05	8,13	0,13	2,89	0,98	0,59	2,01	0,26	0,85	0,42
S 06	9,35		4,48	0,29	0,62	0,70	0,16	2,31	0,79
S 07	9,59	0,04	2,44	1,93	0,41	1,54	0,50	1,70	1,04
S 08	2,77		1,17	0,60	0,15	0,69		0,15	
S 09	1,47		0,26	0,34	0,03	0,37	0,42	0,04	0,02
S10	2,72	0,12	0,84	0,33	0,19	0,52		0,64	0,08
S11	5,69	0,07	2,46	0,36	0,08	1,44	0,03	0,61	0,63
S12	1,24		0,57		0,05	0,56		0,05	
S14	5,65		2,28	0,83	0,31	0,97		1,26	
S15	1,21		0,49	0,48		0,24			
S16	1,52		0,24	0,45	0,03	0,37		0,27	0,17
S17	1,92		0,85			0,95		0,12	
S24	1,52		0,28		0,04	0,46		0,28	0,46
S25	0,69		0,18			0,52			

Slika 19. / *Figure 19.*

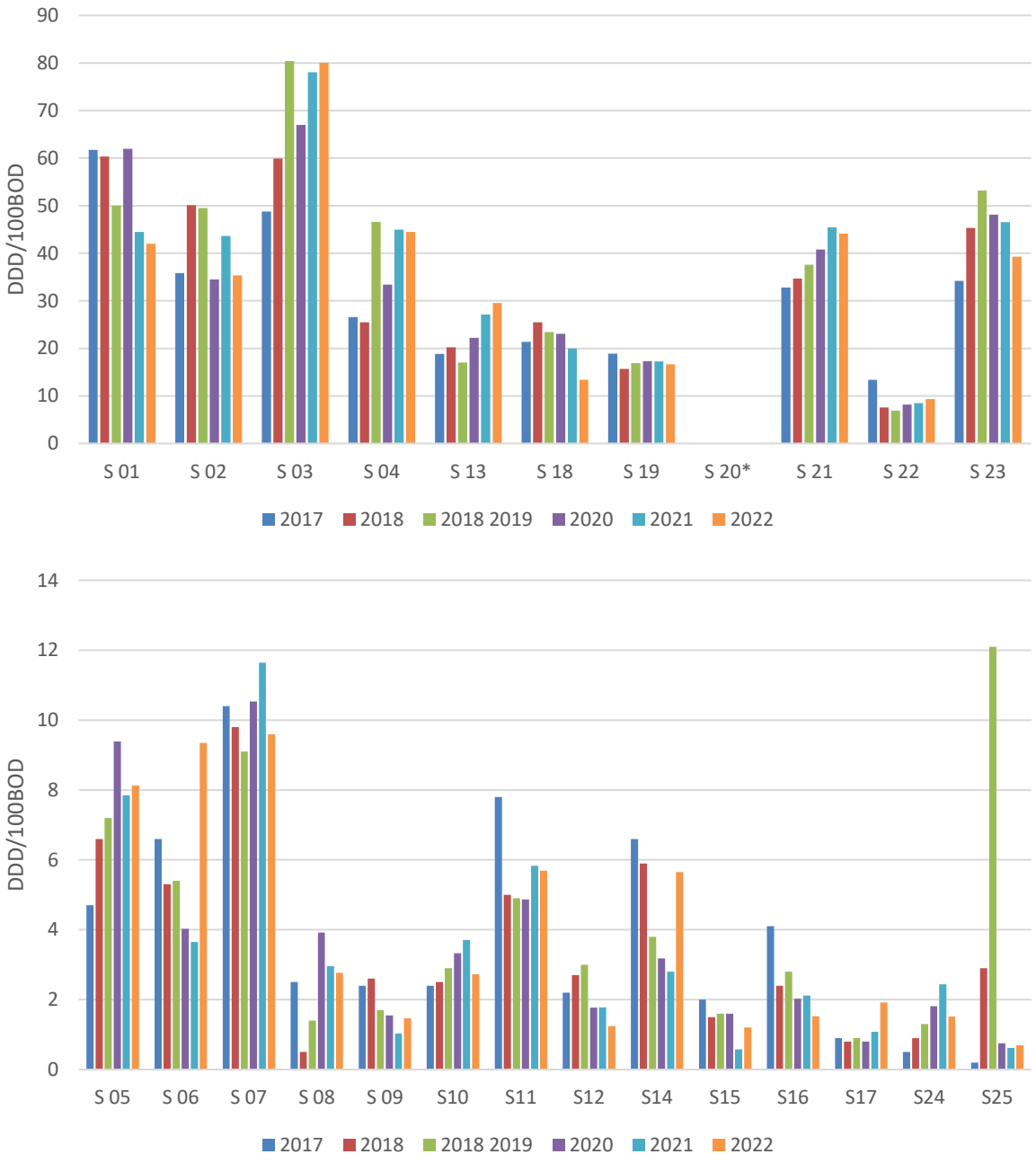
Specijalne bolnice - potrošnja antibiotika 2022. / *Specialty hospitals – antibiotic consumption 2022*



Tablica 21. */ Table 21.*
Specijalne bolnice - potrošnja antibiotika 2017-2022. **/** *Specialty hospitals – antibiotic consumption in 2017-2022*

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

Slika 20. / *Figure 20.*
Specijalne bolnice - potrošnja antibiotika 2017-2022. / *Specialty hospitals – antibiotic consumption 2017-2022*



ATK KLASIFIKACIJA ANTIBIOTIKA:
ATC CLASSIFICATION OF ANTIBIOTICS

J01A – TETRACIKLINI / *TETRACYCLINES*

J01B – AMFENIKOLI / *AMPHENICOLS*

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

J01D – ß LAKTAMI – 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*